2023 Annual report

"Hyper-adaptability for overcoming body-brain dysfunction: Integrated empirical and system theoretical approaches"

Program Director: Jun Ota (The University of Tokyo)

HYPER-ADAPTABILITY

Grant-in-Aid for Scientific Research on Innovative Areas
(Research in a proposed research area), supported by Japan Society for the
Promotion Science (JSPS), and The Ministry of Education, Culture, Sports,
Science and Technology (MEXT), Japan

Area No. 8102
Fiscal Year: 2019-2023
https://www.hyper-adapt.org/

Contents

Annual report of research project A05-8

Principal Investigator, Hiroyuki MIYAWAKI (Lecturer, Osaka Metropolitan University)

Annual report of research project A05-9

Principal Investigator, Takaki MAEDA (Lecturer, Keio University)

Annual report of research project A05-10

Principal Investigator, Tomohiko TAKEI (Associate Professor, Brain Science Institute, Tamagawa University)

Annual report of research project A05-11

Principal Investigator, Hironobu OSAKI (Program-Specific Associate Professor, Doshisha University)

Annual report of research project A05-12

Principal Investigator, Rieko OSU (Professor, Waseda University)

Annual report of research project A05-13

Principal Investigator, Kosei TAKEUCHI (Professor, Aichi Medical University)

Annual report of research project A05-14

Principal Investigator, Tatsuya MIMA (Professor, Ritsumeikan University)

Annual report of research project A05-15

Principal Investigator, Atsushi NAMBU (Professor, National Institute for Physiological Sciences)

Annual report of research project A05-16

Principal Investigator, Noriyuki HIGO (Group Leader, National Institute of Advanced Industrial Science and Technology)

Annual report of research project A05-17

Principal Investigator, Osamu YOKOYAMA (Senior Researcher, Tokyo Metropolitan Institute of Medical Science)

Activities of Group B (Mathematical Model)

Leader of Group B, Toshiyuki KONDO
(Professor, Tokyo University of Agriculture and Technology)

Annual report of research project B01

Principal investigator, Toshiyuki KONDO
(Professor, Tokyo University of Agriculture and Technology)

Annual report of research project B02

Principal investigator, Yasuharu KOIKE (Professor, Tokyo Institute of Technology)

X00 Program Overview and Activities of Steering Committee

Jun Ota
Research into Artifacts, Center for Engineering (RACE), School of Engineering, the University of Tokyo

I. Purpose of the Research Project

In Japan, where the population is rapidly aging at an unprecedented pace, brain and motor dysfunction, such as stroke and spinal cord injuries and frailty, which is decline of bodily and neurological functions, are rapidly increasing. Here, there is a common source where we ourselves cannot adapt well to these changes in the body-brain system.

The human body has a high degree of redundancy. For example, "when a hand is paralyzed by a spinal cord injury, the ipsilateral motor cortex immediately joins its control by reactivating its pre-existing neural pathway, which is normally suppressed and preserved in the course of development" (Isa, 2019).

In light of such facts, we believe that clarifying the brain's "hyper-adaptability" may resolve the abovementioned issues.

The goal of our research project is to elucidate the neural and computational principles of hyper-adaptability in which the brain manages impairment of brain functions by linking neuroscience with systems engineering in order to comprehensively understand acute/chronic impairments and disorders, and the principle of frailty.

II. Content of the Research Project

When a person experiences acute/chronic impairment or disorder due to aging, the brain reorganizes neural networks by disinhibiting pre-existing neural network that is normally suppressed and searching for latent but available network that has long been unutilized through course of evolution and development. We call this process of functional compensation as "reconstruction of neural structure", i.e. a neural entity that achieves hyper-adaptability. In order to implement practical functions to this reconstituted neural network, the network should acquire a new control policy of motor effectors based on precise recognition of the present states of the brain and the body. Here, the brain has to activate the new network by repeatedly performing neural computations and updates the network based on prediction error. We call this learning cycle in a new control space as "reconstitution of sensorimotor control rules", i.e. neural computation principle that enables hyper-adaptability.

In order to verify the hypotheses described above, knowledge of neuroscience is essential. However, with only the "bottom-up" approach relying on experiments and analyses, it would be difficult to clarify hyper-adaptability that is manifested by systematic behavior of a neural network. Therefore, we apply an interdisciplinary approach that integrates the mathematical modeling technology of systems engineering with neuroscience (Fig. 1). We adopt two new analytical approaches: (a) Robotic-interventional neuroscience, i.e. combinatory use of well-controlled robotic technologies and biological approaches of viral vector, optogenetics, chemogenetics and brain stimulation. This allows verification of cause-effect relationship of neural activity and its generated functions and behaviors. (b) Function-oriented neural encoding, which constitutes a model that may incorporate any knowledge of brain functions into gray-box modeling or hypothesizes the structure of a model based on statistical methods.

III. Activities

Following events were held by management group.

A. Activities organized by the project

- The 2nd international symposium HypAd2023
Date: October 28, 2023
October 29, 2023
Place: Kyoto University Centennial Clock Tower Memorial Hall
Contents: the 2nd International Symposium (HypAd2023) was held with full local participation. The symposium invited Prof. Andrea d'Avella (University of Messina, Italy), Prof. Steven Cramer (University of California, Los Angeles, USA), Prof. Grégoire Courtine and Prof. Jocelyne Bloch (Swiss Federal Institute of Technology, Lausanne, Switzerland), and Diego Torricelli of the Cajal Institute, Spain to give invited lectures at the site. In addition, 14 members of the planning group and some members of the subscribed research groups presented their research results. There were also 60 poster presentations from inside and outside of the project, and active discussions took place. Total number of participants was 120.

- 12th management meeting
Date: October 28, 2023, 12:15 - 1:00 p.m.
Place: Kyoto University Clock Tower Conference Room
Content: members of the management group discussed about the management of the project, plenary conference, public symposiums, and other meetings.

- 2nd evaluation committee meeting
Date: October 29, 2023, 17:00-18:00

Place: Kyoto University Clock Tower Conference Room
Contents: under the participation of evaluation committee members Prof. Ugawa and Prof. Kitazawa, and external evaluation committee member Prof. d'Avella, the status and results of project activities were explained, evaluated by each evaluation committee member, and opinions were exchanged.

- 6th plenary conference
Date: March 1 - March 2, 2024
Place: Hiroshima University, Kasumi Campus
Contents: summary of the research in the year was presented by project representative and researchers in the project.

- 13th management meeting
Date: March 1, 2024, 12:00-13:00
Location: Hiroshima University, Kasumi Campus
Content: members of the management group discussed about the management of the project, about the public symposium in the next year, etc.

B. Organized Session

- OS: IEEE-EMBC 2023 (45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society)
Date: July 27, 2023
Location: International Convention Centre, Sydney, Australia.
Contents: A Mini-Symposium was held at IEEE-EMBC 2023, and five researchers were presented, including four members from the project and one invited researcher.

- OS: The 60th Annual Conference of the Japanese Association of Rehabilitation Medicine
Date: July 30, 2023
Place: Fukuoka International Congress Center, Fukuoka, Japan
Contents: A joint symposium "Hyper-adaptation in Rehabilitation" was held on June 30. Five researchers presented and a panel discussion was held.

- OS: The 46th Annual Meeting of the Japan Neuroscience Society
Date: August 1, 2023
Place: Sendai International Center, Miyagi Prefecture
Contents: A symposium, "New Horizons of Hyper-adaptation," was held on August 1st and five researchers presented their research.

- Research Meeting: 37th Basal Ganglia Research Meeting
Location: Art Hotel Asahikawa, Hokkaido
Date: August 19 and August 20, 2023
Conents: on August 19 and 20, a research meeting about basal ganglia research was held, and two special lectures and a symposium were held.

- OS: MHS 2023 (34th International Symposium on Micro-NanoMechatronics and Human Science)
Date: November 20, 2023
Place: Noyori Conference Hall, Nagoya University
Contents: symposium "Hyper-Adaptability" was held. One plenary talk by B05-5 Kobayashi, and 5 talks including one keynote talk were presented.

- OS: The 36th Symposium on Autonomous Decentralized Systems
Date: February 16 - 17, 2024
Place: Tokyo University of Agriculture and Technology, Koganei Campus
Contents: OS "Hyper-adaptation" was held and presentations from project members were made.

IV. Activities By Young Researchers

The Young Scientists' Group, chaired by Dr. Qi An (The University of Tokyo), has been organized to promote the activities of young scientists in this field. This year's activities are listed below.

A. Workshop and Organized Session

A special session was held on July 27, 2023 at IEEE EMBC2023 (Sydney, Australia). Prof. Jun Ota, Prof. Hiroshi Imamizu, Prof. Victor Barradas, Prof. Qi An, Prof. Lingbin Bian attended the session and the results were presented and discussed actively.

On November 01, 2023, a workshop was held jointly with Moonshot Goal 3 (“Development of Awareness AI Robot System to Promote Proactive Behavior Change”) at the University of Tokyo. Prof. Jun Ota, Prof. Arito Yozu, Prof. Qi An, and Dr. Kohei Kaminishi attended the workshop. Presentations and discussions were held on diagnostic techniques and modeling of Parkinson's disease.

Organized session about hyper-adaptability was held on February 16-17, 2024 at The 36th Symposium on Distributed Autonomous Systems (Tokyo University of Agriculture and Technology). There were 12 presentations, mainly from within the field, and research results were presented and actively discussed.

B. Research Meeting

On October 27, 2023, a meeting of the Young Researchers was held at Kyoto University. About 20 young researchers participated in the meeting. They presented their research and discussed about important factors to promote phenomena of hyper-adaptability.

In addition, on February 29, 2024, a meeting of the Young Researchers was held in Hiroshima, and many young researchers participated and exchanged their views on hyper-adaptability phenomena.

V. Future Perspective

The third public symposium is scheduled to be held in Tokyo in September 2024.

Annual report of “Financial support for International Collaboration and Human Resource Development”

Jun Ota
Research into Artifacts, Center for Engineering (RACE), School of Engineering, the University of Tokyo

I. Introduction

The "Financial support for International Collaboration and Human Resource Development" program for hyper-adaptability provided support for activities in line with the following objectives.

a. To improve the level of research in the field of hyper-adaptation and increase its global presence through discussions and joint research by inviting prominent overseas researchers or by staying at overseas research institutes of the project members.

To enable members of the hyper-adaptability project to interact with world-class researchers so that they can make their research widely known to the public. Through these activities, we aim to form the basis for building an international network. In addition, we will support the writing of jointly authored papers through collaborative research. Spread the research content of the project throughout the world. Activities aimed at getting members to invite others to their conferences, etc.

b. Develop hyper-adaptability human resources through mutual exchange between the Neuroscience and Systems Engineering laboratories.

Aiming to develop human resources with knowledge in both neuroscience and systems engineering, researchers in each area will spend a short period of time in the laboratory of the other area to gain an understanding of its contents.

II. Support for Activities in FY2023

In FY2023, support was provided for the following three activities.

Type: Invitation of overseas researchers
Applicant: B03 Qi An (Graduate School of Frontier Sciences, The University of Tokyo)
Description: Dr. Juan Moreno of the Caja Institute (Spain) was invited as the international support. Dr. Moreno is a leading researcher in the field of neurorehabilitation in Europe, and has a great experience in functional electrical stimulation and exoskeletal robotic rehabilitation. During his stay in Japan, we exchanged opinions on diagnostic techniques in daily life space, which is particularly important for Parkinson's disease. As a result, we have devised a joint research project on diagnostic technology using a shoe-type force sensor developed by our laboratory, which will be carried out in the future.

Type: Invitation of overseas researchers
Applicant: B02 Yasuharu Koike (Institute of Innovative Research, Tokyo Institute of Technology)
Description: Dr. BIAN LINGBIN from Shanghai University of Science and Technology was invited to IEEE EMBC 2023 held in Sydney from July 24 to 27 to give a talk on "Bayesian community detection for brain states and transitions using functional He discussed the latest results of fMRI analysis, and also discussed the analysis of hyperadaptive brain activity. We also invited Dr. Nicolas Schwighofer of the University of Southern California to Tokyo Tech to collaborate on a model of brain motor control and learning. We discussed computational models that reproduce the results of psychophysical experiments on arm movements.

Type: Invitation of overseas researchers
Applicant: B03 Jun Izawa (Institute of Systems and Information Engineering, University of Tsukuba)
Contents: From 2023/10/22 to 10/30, we invited Dr. Lucas Dal'Bello, a young researcher from Fondazione Santa Lucia in Italy, to conduct joint research discussions at the University of Tsukuba. This was followed by a presentation and discussion at the 2nd International Symposium Hyper-Adaptability 2023, hosted by Kyoto University. He presented the results of our collaboration about hyper-adaptability in the symposium.

Group A: Neuroscience

Tadashi Isa, Professor, Kyoto University
isa.tadashi.7u@kyoto-u.ac.jp

I. Aim of the Group

The traditional motor control research field has worked on the adaptation mechanism of the neural systems. “Hyper-adaptation” operates as the biological responses to the severe acute insults such as brain and spinal cord injury or chronic dysfunctions of the brain and spinal cord caused by aging and frailty, far beyond the ordinary adaptation. The Group A (Neuroscience) will aim at clarifying the mechanism of “Reconstruction of neural structures” and “Reconstruction of sensorimotor control rules” associated with Hyper-adaptation through experimental studies mostly in the field of neurosciences. However, just looking at the experimental data, it is difficult to get insight into the principles of the neural system operation underlying the obtained data. Therefore, the Group A will promote research in collaboration with the Group B (Systems engineering) from the start of designing the experiments.

II. Members

Group A01 (Isa, Naito, Aizawa, Asada, Nakano) aimed at revealing the global “disinhibition” associated with the recovery from brain and spinal cord injury (experiments on nonhuman primates), or aging (experiments on humans) and at elucidating its neuronal mechanisms in rodents. Isa group showed that decrease of inhibitory connectives among brain areas induced the disinhibition associated with recovery after spinal cord injury in monkeys. Naito group conducted visualization of trainability and plasticity of interhemispheric inhibition between left and right motor cortices. Aizawa group tested dynamics of acetylcholine released into the extracellular space when the hyperadaptive reorganization of the nervous structure upon large-scale brain injury.

Group A02 (Seki) In the final fiscal year of 2023, we advanced the publication of research results on muscle relocation surgery obtained up to the previous year and submitted them to academic journals, but they have not yet been accepted. Currently, based on comments from reviewers, the manuscript is being thoroughly revised, enabling new interpretations of the experimental results. Furthermore, this fiscal year has seen progress in research on rehabilitation for stroke, a concrete example of these adaptive changes in clinical settings.

Group A03 (Imamizu, Tsutsui) In the human study, we clarified the formation process of "sense of agency" in motor learning that is so novel that the outcome cannot be predicted, which is assumed in hyper-adaptation. In addition, we found the right hemispheric dominance in the induction of the sense of agency by brain stimulation. In the monkey study, we identified the emotional signal flowing from the cingulate to MI cortex before the onset of task-related hand movement.

Group A04 (Takakusaki, Hanakawa) In the 5 years of research, animal experiments by the Takakusaki group revealed that dopamine (DA) facilitated the actions of the cholinergic system that regulated the activity of the brainstem-spinal postural control systems. This mechanism may enhance α-band activity that promotes task-relevant neural circuit generation. Through clinical studies, the Hanakawa group advanced technology to examine the state of DA in human brains, revealing that the dynamics of brain circuits may be altered in association with DA-reduced states in patients with Parkinson's disease, dementia with Lewy bodies, and their prodromal stage.

Report of A05 group

Yuichi Takeuchi “A closed-loop brain stimulation for reinforcing hyper-adaptability” This project achieved control of pathological fear of rat PTSD model, control of depression-like behavior of rats, and improvement of cognitive function of Alzheimer’s disease model mice by using novel time-targeted brain stimulation technologies.

Shinichi Izumi “Comprehensive understanding of the mechanisms of adaptive changes in brain, body consciousness and arm use underlying upper limb recovery in stroke patients” We found that different brain regions and nerve fibers were associated with arm use and functional recovery in stroke patients. Furthermore, we found that facilitation of imitative movement in patients with chronic hemiplegia triggered by illusory ownership.

Rie Kimura “Elucidation of neural circuits for optimal adaptation to the external environment.” I aim to understand the neural basis of optimal adaptation to the external environment by examining the visual responses in multidimensional brain systems. This year, I prepared to analyze the neural basis of the differences in adaptation to the diversity of visual information by stress loading dependent on the difficulty of tasks or by producing an animal model of autism by administration of valproic acid.

Akihiro Funamizu “Neural substrate of unified learning theory for adaptive behavior” This study hypothesizes that the brain has one learning rule to achieve various behavioral strategies. We investigated the neural substrate of learning rule by modeling the choice behavior of mice with artificial neural network. We also recorded the dopamine changes in nucleus accumbens with fiber bundle imaging during a task.

Yoko Yazaki-Sugiyama “Enhanced neuronal circuits for vocal learning with extensive experiences during development” We have submitted our manuscript reporting the finding of developmentally transient neuronal projections from zebra finch auditory to motor cortex (in revision). We further developed our study to understand how this transient projection alters its timing of disconnections based on early auditory experiences.

Riki Matsumoto “Mechanism of Hyper-Adaptability of the human premotor area: electrophysiological connectomes analysis with electrocorticogram” We created an electrophysiological connectome library from comprehensive CCEP measurements, visualized the brain networks involved in speech of apraxia, and analyzed the CCEP connectome for latent circuits during recovery, suggesting the possibility of hyperadaptation by the premotor cortex. We also revealed alterations in the connectome in epilepsy pathology, and suggested that decreased CCEP network density is associated with poor postoperative outcome in epilepsy surgery.

Hiroyuki Miyawaki, "Regulatory mechanisms of inter-regional network changes underlying hyper-adaptation from mal-adaptation state caused by fear memory." By using multi-regional, large-scale electrophysiological recording techniques, we analyzed the network dynamics that support the extinction learning of fear memories and found that local activity patterns coactivating with patterns in other brain regions tend to be maintained after extinction learning.

Takaki Maeda "Research on developing a cognitive rehabilitation method for neurological and psychiatric diseases thorough improving precision on the sense of agency" Aberrant sense of agency (SoA) in patients with schizophrenia has been considered due to temporal delays in sensory-motor prediction signals. We demonstrated this hypothesis via computational modeling using a recurrent neural network expressing the sensory-motor prediction process. (Okimura et al., 2023). Moreover, we have developed methods for cognitive rehabilitation of SoA in order to tune up precision of SoA. We showed different patterns of learning of internal prediction models for agency judgment between normal controls and patients with schizophrenia (in preparation).

Tomohiko Takei "Adaptive mechanisms for perturbations in the neural manifold" We recorded and analyzed the low-dimensional structure of the fronto-parietal cortical activity in a monkey performing a context-dependent adaptive feedback motor task and suggested that the activity in the dorsal premotor cortex may be responsible for the adaptive switching of low dimensional neural subspaces.

Hironobu Osaki, "Spatio-temporal modulation of disinhibition for super-recovery from motor dysfunction in the chronic phase of stroke" We used a rodent infarct model and monitored a motor function and neural activity before and after motor cortex infarction. We also monitored the effect of optogenetic motor cortex inhibition on motor function. An increase of the falling time of forelimb and a change injoint angle after the infarction were successfully observed.

Rieko Osu "Hyper adaptive changes in spatial recognition Using Augmented reality (AR)" Using augmented reality (AR) technology, we developed a system that projects the entire visual space, including the left visual space, which is often missed by patients with hemispatial neglect, in their right visual field. The effectiveness of the system was confirmed through feasibility tests on patients with hemispatial neglect. In addition, experiments with healthy participants showed that self-generated movement enhanced attention to the direction of movement. These results lead to the development of attention promotion training in hemispatial neglect.

Kosei Takeuchi "Creation of hyper-adaptability by synthetic organizers and micro-environmental control of neural reconstruction" We conclusively demonstrated, using a rodent model, that synthetic synaptic connectors facilitate functional recovery even in the chronic phase following spinal cord injury. Additionally, we identified the impact of novel next-generation synaptic connectors, including inhibitory synapses or neurotrophic factor connectors, on post-injury physiological functions. The findings highlight the potential of these interventions as new tools for promoting hyper-adaptation beyond injury recovery, showcasing their applicability in motor function analysis.

Tatsuya Mima "Brain reorganization in stroke patients with hyper-recovery by measuring EEG modulation induced by static and dynamic magnetic fields." We discovered that tSMS, one of the noninvasive brain stimulation methods clinically applied in humans, can induce intrinsic plasticity mediated by Cl- channels. This contributes to the elucidation of the physiological mechanisms of adaptability and hyper-adaptability phenomena. The results of TMS/tSMS-EEG in healthy subjects to measure functional neural networks with good temporal resolution are in submission. Clinical research is underway to apply this method to hyper-recovered stroke survivors.

Atsushi Nambu "Brain adaptation after limb loss" We observed how a somatotopic representation in the cerebral cortex was reorganized in macaque monkeys who lost their forelimbs accidentally. In the motor cortices, the area previously representing a lost distal forelimb shrunk, while that in the somatosensory cortex was rather preserved. This discrepancy between the motor and somatosensory cortices might be the basis of phantom limb, the sensation that an amputated limb is still attached.

Noriyuki Higo "Adaptive mechanism occurring in both hemispheres after unilateral brain damage" We examined the molecular and brain activity changes that occur during motor recovery in macaques with focal infarcts in the unilateral internal capsule. At the period of motor recovery, there was an increase in excitatory synapse markers and a change in hemodynamics during grasping in the ventral premotor cortex.

Osamu Yokoyama "Functional reorganization of motor and somatosensory cortices during recovery of motor functions after the loss of peripheral sensory inputs" During the recovery of motor function in monkeys whose upper limb somatosensory input was impaired by dorsal root transection of the cervical spinal cord, we found frequency-band-dependent changes in the activity levels of the primary motor and somatosensory cortices, and in the flow of information between these regions.

III. ACTIVITIES

To summarize the results, Group A meeting was held on January 17 (Wed) in 2024 at center for information and neural networks.

IV. FUTURE PLAN

We will summarize our results and focus on publishing papers. At the same time, we will continue to facilitate the collaboration with the members of Group B.

A01 Annual report of research project

Tadashi Isa, Professor, Kyoto University
Eiichi Naito, General manager, CiNet
Hidenori Aizawa, Professor, Hiroshima University
Minoru Asada, Professor, Osaka University
Hideki Nakano, Associate professor, Kyoto Tachibana University

***Abstract*— We have demonstrated the polarity of the connectivity associated with disinhibition after spinal cord injury, visualization of trainability and plasticity of interhemispheric inhibition between left and right motor cortices and cellular mechanism underlying the interhemispheric inhibition in mice.**

I. Introduction

The A01 Group will examine the hypothesis that disinhibition across the large-scaled network of the brain is the basis of hyper-adaptation by "reconstruction of biostructures" by fusion and further development of our current researches. Our previous researches have shown that the brain is equipped with the global disinhibition mechanisms and in case of spinal cord injury, the mechanism is triggered to recruit the latent circuit for functional recovery. However, details of the underlying neural mechanism are still elusive. On the other hand, human studies suggested that such disinhibition mechanism is declined as aging, which may be related to the difficulty in recovery for the aged people. This research group will study these issues and wish to propose the strategies to prevent the decline in latent adaptive capacity.

II. Aim of the Group

The A01 Group will aim at clarifying the mechanism of disinhibition through experiments on rodents, nonhuman primates and humans, and proposing the effective strategies to promote functional recovery to overcome frailty in the aged people. Isa Group will clarify the mechanism of disinhibition in brain network associated with recovery from the spinal cord injury or lesion of the primary visual cortex in macaque monkeys. In rodents, Aizawa Group will perform the activity measurement and optogenetical stimulation of monoaminergic systems including dopaminergic and serotonergic neurons, to supply the information about the global disinhibition in the cortex. In humans, Naito Group will capture the chronic disinhibitory state of the aged people by fMRI and propose the effective training methods to improve the brain functions using the disinhibitory state as a measure of progression of aging-related frailty.

III. Research Topics

A. *Cortical connectivity associated with recovery from spinal cord injury by statistical causal search with LiNGAM (Isa)*

Our previous study showed that drastic motor recovery was observed after subhemisection spinal cord injury in macaques that received a combination of intensive training and cortical electrical stimulation. We also found that disinhibition occurred globally and nonspecifically across wide cortical areas in both hemispheres, and effect of interhemispheric interaction from ipsilesional premotor cortex (PM) to contralesional primary cortex (M1) became inhibition to facilitation by using a conditioning paradigm. According to these results, we hypothesized that the change of excitation-inhibition balance is considered as neural basis of plastic changes which can improve the recover from severe impairment. On the other hand, Granger causality can assess the directionality of the connectivity between each brain area, polarity of the connectivity among brain regions associated with excitation-inhibition balance is still unclear. The aim of this study is to reveal the polarity of the connectivity associated with the motor recovery after spinal cord injury by using a novel causal inference model based on a statistical causal discovery method (linear non-Gaussian acyclic model, LiNGAM). First, we conducted the physiological validation to the connectivity predicted by the LiNGAM. In this validation, we blocked interhemispheric pathway unidirectionally and reversibly that is known to work mainly as inhibition and analyzed brain activity using LiNGAM. In fact, we confirmed that only inhibitory connectivity was significantly decreased after the blockade, and polarity of connectivity predicted by LiNGAM was demonstrated to reflect physiological relevance. Next, we tested the polarity change of connectivity in cortical network associated with recovery from spinal cord injury. In the early stage of recovery, there were no significant changes in excitatory connectivity. On the other hand, intensity of inhibitory connectivity in α band significantly decreased in the pathway from ipsilesional PM to ipsilesional M1, recurrent circuit of ipsilesional PM, and recurrent circuit of contralesional M1. These results suggested that global disinhibition associated with recovery was induced mainly by the reduction of inhibitory connectivity.

[1] Sasaki R, Ohta Y, Onoe H, Yamaguchi R, Miyamoto T, Tokuda T, Tamaki Y, Isa K, Takahashi J, Kobayashi K, Ohta J, Isa T. Balancing risk-return decisions by manipulating the mesofrontal circuits in primates. Science 383, 55-61. DOI:10.1126/science.adj6645, 2024

[2] Yamaguchi R, Ueno S, Kawasaki T, Chao Z C, Mitsuhashi M, Isa K, Takei T, Kobayashi K, Takahashi J, Onoe H, Isa T. Global disinhibition and corticospinal plasticity for drastic recovery after spinal cord injury. bioRxiv, 2023.2003.2015.532773. DOI:10.1101/2023.03.15.532773, 2023

[3] Mitsuhashi, M., Yamaguchi, R., Kawasaki, T., Ueno, S., Sun, Y., Isa, K., Takahashi, J., Kobayashi, K., Onoe, H., Takahashi R, Isa T. State-dependent role of interhemispheric pathway for motor recovery in primates. bioRxiv, 2023.2004.2023.538021. DOI:10.1101/2023.04.23.538021, 2023

B. *Visualization of trainability and plasticity of interhemispheric inhibition between left and right motor cortices and verification of the effects of excitation/inhibition balance on network structure and function (Naito, Asada, Nakano)*

Using MRI, Naito group (NICT, CiNet) discovered a hyper-adaptation phenomenon in the brain of a top wheelchair racing Paralympian in which interhemispheric facilitation, rather than the interhemispheric inhibition typically seen in typically developing individuals, developed through long-term bimanually synchronized upper-limb training for wheelchair racing since childhood (Morita et al. 2023). Based on this finding, in collaboration with Nakano group (Kyoto Tachibana Univ), we found that training one hand to move passively in synchronization with the voluntary movement of the other hand can effectively induce the muscle activity of the passive hand. In addition, using right finger simple and complex motor tasks, we found that young adults exhibit interhemispheric inhibition during a simple task, but during a complex task, mainly the ipsilateral premotor cortex complements complex movement by increasing functional coupling with the contralateral sensorimotor cortices. On the other hand, older adults chronically disinhibit interhemispheric inhibition even during the simple task, and are unable to adopt strategies for interhemispheric functional coupling and complementation during the complex task (Miura et al., in prep). Asada group (Osaka Univ) tested the effects of the disturbance in the balance between excitation and inhibition (E/I balance) of the nervous system (which can be assumed in older brains) on general network structure and function, using a spiking neural network model. Increasing the E/I ratio locally strengthened excitatory coupling throughout the network, reduced the complexity of neural activity, and decreased information transfer between groups of neurons in response to an external input (Park et al. 2023). The higher E/I ratio due to chronic disinhibition in older adults may decline information-processing capacity in their aging brains.

[4] Morita T, Takemura H, and Naito E Functional and structural properties of interhemispheric interaction between bilateral precentral hand motor regions in a top wheelchair racing Paralympian. Brain Sciences 13(5), 715; https://doi.org/10.3390/brainsci13050715, 2023.

[5] Park JH, Kawai Y, and Asada M Spike timing-dependent plasticity under imbalanced excitation and inhibition reduces the complexity of neural activity. Frontiers in Computational Neuroscience, 17:1169288, 2023.

C. *Neural circuit mechanism underlying interhemispheric inhibition and its modulation using mouse model (Aizawa)*

Aizawa group (Hiroshima University) addressed a mechanism underlying interhemispheric inhibition and its alteration as a neural basis of hyperadaptability using mouse motor cortex. Upon activation of the unilateral motor cortex via optogenetic stimulation, the extracellular field response in the contralateral motor cortex turned out to reflect an extent of interhemispheric inhibition. This approach enabled the group to unravel a novel role of acetylcholine to modulate the interhemispheric inhibition so far. Based on this finding, the group addressed 1. interhemispheric interaction of spiking activities across hemisphere of mice engaging in forelimb-reaching task and 2. an effect of pharmacological activation and inhibition of the cholinergic transmission on this interaction. Results showed that correlative activity of neurons across hemispheres emerged upon use of unilateral forelimb for reaching movement. Specifically, excitatory neurons in the motor cortex contralateral to the moving forelimb started to be correlated negatively with the excitatory neurons in the ipsilateral motor cortex, while they exhibited positive correlation with the inhibitory neurons in the ipsilateral motor cortex. Since such correlative activities in the pairs of neurons across hemisphere was not observed during resting state, it is suggested to be involved with sharpening the unilateral activation of the cortical hemisphere. Interestingly, positive correlation of spiking activity between the contralateral excitatory neurons and ipsilateral inhibitory neurons were up- and down-regulated by the antagonist and agonist for the muscarinic cholinergic transmission, respectively. In line with this, gene and protein expression analyses revealed that M2 muscarinic acetylcholine receptor was specifically expressed in the parvalbumin-expression inhibitory neuron in the deep cortical layer. The group published a paper showing a novel method examining those cells in the three dimensional space in the brain (Kasaragod and Aizawa, 2023) and submitted an article summarizing the physiological results on cholinergic modulation of the interhemispheric interaction between murine motor cortices (Handa et al., 2024).

[6] Kasaragod DK, Aizawa H. Deep ultraviolet fluorescence microscopy of three-dimensional structures in the mouse brain. Sci Rep 26;13(1):8553; https://doi.org/10.1038/s41598-023-35650-2, 2023

[7] Handa T, Zhang Q, Aizawa H. Cholinergic modulation of interhemispheric inhibition in the mouse motor cortex. bioRxiv https://doi.org/10.1101/2024.02.05.579044, 2024

IV. Future Perspective

As for the monkey experiment, we will publish the papers for the mechanism of disinhibition associated with functional recovery and connectivity analysis using LiNGAM. In addition, we will clarify the molecular system for the connectivity predicted by LiNGAM collaborating with Aizawa group. Focusing mainly on interhemispheric inhibition between the left and right motor cortices, we have visualized hyper-adaptation phenomena associated with special training, flexible interhemispheric functional complementation in younger brains, and chronic disinhibition and difficulty in interhemispheric functional complementation in aging brains. We also showed the possibility that higher E/I ratio due to chronic disinhibition may decline information-processing capacity in aging brains. In the future, we will verify the effectiveness of the new training developed based on these findings in rehabilitation settings. For the mouse study, we will reveal dynamics of acetylcholine released into the extracellular space when the hyperadaptive reorganization of the nervous structure upon large-scale brain injury. This approach leads to a proposal of a novel method to induce hyperadaptation via modulation of cholinergic neurotransmission.

A02 Annual report of research project

Kazuhiko SEKI
National Institute of Neuroscience, NCNP

Abstract—**In the FY2023, the aim of our research group was mainly to summarize the experimental and modeling result. In addition, we made significant progress in research on rehabilitation for stroke, a concrete example of hyper-adaptive changes in clinical settings.**

I. Introduction

From the cradle to the grave, the musculoskeletal structure of the human body changes continuously. It can change with a prolonged time constant in a predictive manner, following a biological process of development and aging. It also could change immediately without any prediction, like a traffic accident and some disease. Notably, we can spend our daily life by using this changing body structure, with the aid of practice or rehabilitation therapy occasionally. This is a clear example that our central nervous system (CNS) could adapt and keep communicating with our body by making adaptive changes corresponding to the change of bodily structure predictably or unpredictably. So far, however, it is not established how the CNS adapts to the continuously changing body and what is the trigger of its adaptation.

II. Aim of the Group

We will address the CNS mechanism of "hyper-adaptation" corresponding to the ever-changing musculoskeletal structure by establishing novel animal models and cutting-edge technology. By developing the muscle relocation model, where the association of muscle activity and its physical action will be surgically or ontogenetically manipulated, we will investigate how the CNS acquire a control strategy of their body de novo. We will implement novel neurophysiological tools for assessing the hyper-adaptation occurring in the multiple levels of the CNS, from the spinal cord, brain stem, and cerebral cortex.

III. Research Results

In the final fiscal year of 2023, we advanced the publication of research results on muscle relocation surgery obtained up to the previous year and submitted them to academic journals, but they have not yet been accepted. Currently, based on comments from reviewers, the manuscript is being thoroughly revised, enabling new interpretations of the experimental results. Furthermore, this fiscal year has seen progress in research on rehabilitation for stroke, a concrete example of these adaptive changes in clinical settings. Below, we report these research outcomes.

1. <u>Development of Primate Model Animals of Stroke</u>

1) Creation of a Cerebral Cortex Injury Model in Monkeys

We have used the photothrombosis method to locally induce ischemic cerebral cortex injuries in the motor areas of the brain in common marmosets. After all experiments were completed, the brain injury sites for each of the four animals were confirmed by perfusion-fixing the animals and performing immunostaining on brain slices. As a result, cortical injuries were observed in motor-related areas such as the primary motor cortex, pre-motor cortex, and supplementary motor area in all animals.

2)Recovery of Motor Function after Cerebral Cortex Injury

The overall body movement within the cage and the feeding behavior using the paralyzed limb were recorded with a video camera from before the cerebral cortex injury until 8 weeks after the injury. The overall body movement was evaluated by scoring specific items. The feeding behavior was assessed by installing an acrylic board in the animal's cage and placing feed at a fixed point on the board, requiring the paralyzed limb to perform upper limb reaching and grasping movements. Moreover, reaching and grasping movements were evaluated separately based on kinematic indicators used for stroke patients with hemiplegia. The indicators for grasping movements included the grasping time, i.e., the time from the start of finger flexion until the feed was grasped, and the maximum distance between the thumb and index finger at maximum extension, i.e., the maximum joint distance between the thumb and index finger before finger flexion began.

Consistent motor function impairments were confirmed among the animals. Flaccid paralysis was observed in all animals the day after cortical injury induction. Feeding behavior with the paralyzed limb was impossible until 2 weeks after the cortical injury. Afterward, recovery of motor function was confirmed in all individuals, and feeding behavior with the paralyzed limb became possible at 4 weeks after the injury. However, indicators of reaching and grasping movements were significantly worsened in all animals compared to before the injury. The animal model we developed excels in reproducibility and similarity to humans in terms of the degree of motor function impairment. Furthermore, recovery of most motor functions was observed within 4 weeks after the cortical injury, similar to the most dramatic recovery of motor function occurring within a month in stroke patients with hemiplegia.

The subsequent recovery process showed consistent recovery in overall body movement and grasping movement among animals. However, a different recovery process was observed for reaching movement, differing from overall body movement and grasping movement. The angular error in movement direction immediately after movement onset, an indicator of feedforward control, recovered in some individuals from 4 to 8 weeks after the injury, while others showed no change or even worsened. Similarly, trends were observed in the peak number of movement direction speeds, an indicator of feedback control.

3)Neural Plasticity Changes Underlying Motor Function Recovery

The factors that cause different recovery processes depending on the type of movement and animal relate to the coordination of muscle activity and the structure of the central nervous system. For example, grasping strength requires the coordination of muscles by interneurons in the spinal cord and mainly arises from the contribution of subcortical areas, whereas upper limb reaching movements based on visual information depend on the cerebral cortex and the frontal-parietal lobe network. Therefore, it is considered that the recovery of movements involving subcortical regions occurs quickly after cortical injury, while recovery of cortex-dependent movements is slow. This indicates that the recovery process varies depending on how the injury site and changes in neural plasticity affect motor control.

2. Reevaluation of the Method for Assessing the Effects of Stroke Rehabilitation Using Muscle Synergy Analysis

The Fugl-Meyer Assessment (FMA) is a representative evaluation of motor function impairment recovery after stroke. In the FMA, patients perform various daily activities, and medical professionals score the completion of each activity. Although FMA is widely used in clinical settings due to its effectiveness, the movements used for evaluation are empirically selected by experts, and there has been little research verifying the validity of FMA itself from the perspective of recovery mechanisms such as changes in neural activity. Therefore, this study analyzed patients' muscle activity during FMA evaluation movements and assessed the changes in muscle activity accompanying recovery from the perspective of muscle synergy.

1)Muscle Synergy Constituting FMA: Standard Synergy

The muscle activity of 41 sites was measured in stroke patients (20) and healthy individuals (7) during 37 upper body FMA evaluation movements, and muscle synergy analysis was conducted. Initially, the muscle synergy of healthy individuals was estimated, and 13 types of muscle synergies common to the 7 subjects were identified. This indicates that the muscle activity during the 37 FMA evaluation movements is composed of combinations of these 13 types of muscle synergy (hereafter referred to as standard synergy). Upon examining the muscles with high weights in each muscle synergy, it was found that each standard synergy is composed of muscle groups from various body parts, such as the upper arm, forearm, fingers, chest, abdomen, and posterior trunk.

When investigating which standard synergy each of the 37 tasks is composed of based on muscle activity during each task, it was observed that the standard synergies related to the upper arm, forearm, and fingers sequentially activate, and the standard synergy corresponding to the posterior trunk activates in all movements.

Looking at the activity of the posterior trunk in stroke patients, it was found that mild patients had increased activity in the standard synergy of the posterior trunk compared to healthy individuals, whereas severe patients had decreased activity. These results suggest that activity in the posterior trunk is important in all upper body movements, and severe patients who could not perform tasks well might have been unable to use their trunk effectively.

2)Changes in Muscle Synergy in Stroke Patients

Next, to examine the correlation between FMA scores and changes in muscle synergy, the correlation between the standard synergy and each patient's muscle synergy was calculated. It was found that mild patients had a one-to-one correspondence between the standard synergy and the patient's muscle synergy, but as severity increased, this correspondence broke down, and each patient's muscle synergy was composed of multiple fused standard synergies. Therefore, to examine the relationship between the fusion of standard synergy and the severity of the patient, the degree of fusion of standard synergy was plotted against FMA scores, and it was found that patients with lower FMA scores (higher severity) had a higher degree of fusion. In severe patients with significant functional decline, unnecessary muscle synergies activated simultaneously (fused) instead of being given individual motor commands for each standard synergy, reflecting this property of the nervous system in FMA scores.

3)Simplification of Tasks by Reevaluating FMA

The relationship between the degree of synergy fusion and patient severity (FMA scores) is derived from a series of muscle activities in all FMA tasks, but by dividing muscle activity by task, a similar relationship can be found for each of the 37 FMA tasks. By examining whether a significant relationship between synergy fusion degree and severity is observed in each task (i.e., muscle activity), it is possible to assess whether each task reflects the relationship between patient severity and synergy change. Analysis showed that 26 out of 37 tasks had a significant relationship between severity and synergy fusion degree ($P<0.01$), whereas the remaining 11 movements had a relatively low relationship ($P>0.01$). This indicates that from the perspective of synergy, there are effective and ineffective tasks in using FMA to evaluate patient recovery, suggesting the possibility of simplifying the number of FMA tasks to about 26.

IV. FUTURE PERSPECTIVE

The analysis of the muscle relocation model has made it possible to quantitatively demonstrate the hyper-adaptive function inherent in the central nervous system of primates. Going forward, it will be necessary to evaluate the neural plasticity at the cellular level that underlies this phenomenon.

REFERENCES

[1] Funato T, Hattori N, Yozu A, An Q, Oya T, Shirafuji S, Jino A, Miura K, Martino G, Berger D, Miyai I, Ota J, Ivanenko Y, d'Avella A, Seki K: Muscle synergy analysis yields an efficient and physiologically relevant method of assessing stroke. Brain Communications 4(4), 2022, fcac200.

[2] Kosugi A, Saga Y, Kudo M, Koizumi M, Umeda T, Seki K: Time course of recovery of different motor functions following a reproducible cortical infarction in non-human primates. Front Neurol. 2023; 14: 1094774

A03 Annual report of research project

Hiroshi Imamizu[1] and Ken-Iichiro Tsutsui[2]
[1]Graduate school of Humanities and Sociology, The University of Tokyo
[2]Graduate school of Life Sciences, Tohoku University

***Abstract*— Our research project aims to elucidate the neural mechanisms by which body cognition and positive emotions, such as motivation, facilitate motor learning in challenging situations ("hyper-adaptation"). Our main achievements during the year were: 1) Psychological experiments revealed a formation process of a sense of agency (a sense that "I am the one causing an action," which is an aspect of body cognition) in line with the acquisition of an internal model for motor apparatus (Imamizu). 2) Non-invasive brain stimulation of frontoparietal connections in the left and right hemispheres revealed a right hemispheric dominance in the formation of the sense of agency (Imamizu). 3) Through electro-encephalogram (EEG) recording experiments in monkeys, we identified the neural activity that may be reflecting the process by which emotion and motivation influence motor function (Tsutsui). 4) Through neurotracing experiments in monkeys, we identified parallelly organized subsystems linking different part of ACC and subcortical areas, such as amygdala, nucleus accumbens, and periaqueduct gray (PAG), which may be differentially involved in the control of mood and emotion. (Tsutsui).**

I. Introduction

Previous studies in neuroscience and psychology have investigated how feedback from the external world (such as motor error and reward prediction error) contributes to motor learning. By contrast, many researchers have recently been interested in the contribution of internal information, such as motivation and body cognition, to motor learning. For instance, a patient's motivation affects the recovery of motor functions after the spinal cord injury and the sense of agency increases during motor learning. However, little is known about the theoretical framework and neurophysiological mechanisms in which motivation and body cognition facilitate motor learning. We expect that investigation of such mechanisms leads to developing methods for inducing efficient motor learning even in challenging situations.

II. Aim of the Group

Our aims are 1) understanding mechanisms in which motivation and body cognition facilitate motor learning in challenging situations and 2) developing methods for facilitating motor learning through artificial control of motivation and body cognition. Our research activity will contribute to understanding the "hyper-adaptability" and future development of the methods for inducing and facilitating it.

III. Research Topics

A. The formation process of agency in novel motor learning

The comparator model proposes that the difference between "prediction of action-outcome" and "sensory feedback" (prediction error) is important in determining the sense of agency. However, it is difficult to predict the action outcome in the case which is assumed in hyper-adaptation. The principal investigators (Takumi Tanaka and Imamizu) applied principal component analysis to multiple joint sensor values measured with a data glove. They examined changes in the sense of agency in a novel learning task in which the first and second components manipulate the cursor position on a screen (Fig. 1A). During the course of learning, the sense of agency was examined under various conditions. The results revealed that 1) before learning the "internal model" for predicting the action outcome, synchronization between the cursor and own motion is important to gain a sense of agency over the cursor, and 2) as the internal model is acquired, the difference between the predicted and actual motion direction of the cursor (prediction error) is important for the formation of a sense of agency (Fig. 1B). In addition, the principal investigators (Chiyohara and Imamizu) clarified the role of short-term memory of proprioceptive sensation, which is important for body perception, in motor learning [1].

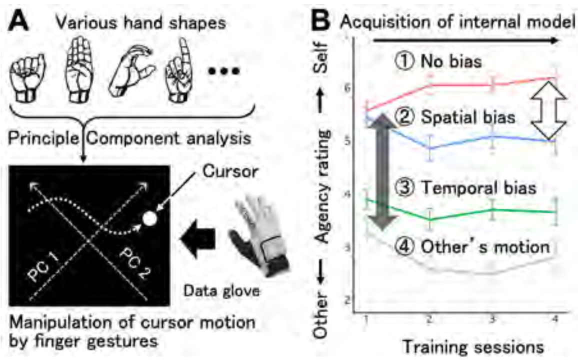


Fig. 1 (A) A novel learning task. We measured various hand shapes and applied principal component analysis to the sensor values. Participants manipulated the cursor with the first and second components. (B) Changes in the sense of agency examined under four different conditions during the learning process. The black arrows indicate the difference between the cases in which there is synchrony between the cursor and hand movements (conditions 1 and 2) and those in which there is not (conditions 3 and 4). The white arrows indicate the difference between the cases with (1) and without (2) spatial bias. In the early stages of learning, the presence or absence of synchrony causes differences in the sense of agency, but in the later stages, spatial misalignment (prediction error) begins to affect the agency.

B. Hemispheric dominance in the neural basis for sense of agency

Hiromitsu, Asai, and Imamizu have previously shown that the relationship between prediction error and sense of agency changes when brain stimulation (transcranial anti-synchronous AC stimulation) is applied to the connection between the inferior parietal lobule and inferior frontal gyrus in the right hemisphere. To investigate left-right differences in the neural basis of the sense of agency based on prediction error, we applied the same type of brain stimulation to the left hemisphere. We examined how the prediction error-sense-of-agency correlations changed from the baseline condition without stimulation. The results showed that the relationship between prediction error and sense of agency changed less than when the right hemisphere connections were stimulated (Fig. 2). This result indicates that the mechanism by which the sense of agency is formed based on prediction error is right-hemisphere dominant.

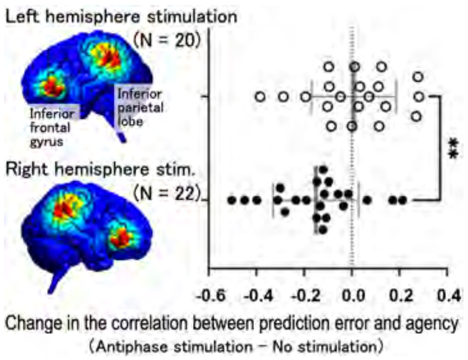


Fig. 2 Effects of interventions in the inferior parietal lobule-inferior frontal gyrus of the left and right hemispheres on the relationship between prediction error and sense of agency. Correlation values show the change from no stimulation to anti-synchronous stimulation. **: P = 0.0064, t(40) = 2.88.

C. Neural processes through which the emotion and motivation affect the motor function

Tsutsui and his colleagues have shown that the medial frontal cortex and dorsolateral prefrontal cortex play an important role in controlling mood, emotion, and motivation. However, it remains unclear how such information related to internal states influences motor output. We conducted an experiment in which monkeys performed a Pavlovian probabilistic conditioning task in which the same movement (the movement of releasing the hand from a hold key) resulted in a different outcome (juice or saline) in each trial. Prior to the "go" cue for the movement, a cue stimulus indicating the possible outcome of the movement was presented. There were five progressive conditions in which either favorable or unfavorable outcome was delivered (favorable outcome: unfavorable outcome = 100%: 0%, 75%: 25%, 50%: 50%, 25%: 75%, 0%: 100%). Electroencephalogram (EEG) was recorded during the task performance. We found differential neural signals preceding the onset of the movement, in the midline (Fz, Cz) and in the contralateral side (C_3) of the hand use, preferentially greater for either favorable or unfavorable outcome. Furthermore, the functional connectivity of the midline and lateral electrodes became significantly higher at this period. As the sources of the signals observed in the midline and lateral electrodes can be estimated as the medial frontal cortex and the lateral motor cortices, the observed neural activity may reflect the neural process of emotional and motivational information influencing the motor function.

D. Organization of the neural circuits connecting Anterior Cingulate Cortex (ACC), amygdala, nucleus accumbens, and periaqueductal gray (PAG)

The anterior cingulate cortex (ACC), which is a part of the medial frontal cortex and surrounds the corpus callosum, is known to have various functions related to cognition and emotion. It can be subdivided into several areas, such as pregenual, subgenual, and dorsal anterior cingulate cortex (pg, sg, and d-ACC), however their functional segregations largely remain unknown. Here we conducted neural tracing experiments to examine projections from these regions to the amygdala, nucleus accumbens, and periaqueductal gray (PAG). When we locally injected adeno-associated virus (AAV), an anterograde viral tracer, into the dACC, pgACC, and sgACC, we found that they all project to the amygdala, nucleus accumbens, and PAG, but to their different subregions. Thus, it was indicated that the neural circuits connecting the ACC, amygdala, nucleus accumbens, and PAG are separately and parallelly organized, presumably having different contributions in the regulation of mood an emotion, as well as their integration with cognition.

IV. Future Perspective

In the first stage of hyper-adaptation (reconstruction of neural structure), the synchrony between motor commands and their consequences is important, and in the latter stage (reorganization of sensorimotor control rules), the prediction error is important. The right hemisphere stimulation was found to be a key factor in the manipulation of the sense of agency by brain stimulation. These results are expected to clarify the mechanism of the formation process of the sense of agency in motor learning and to contribute to the efficient manipulation of the sense of agency. Regarding the relationship between motivation and motor function, it was suggested that input from the medial frontal cortex to the motor cortex may be involved in regulating motor function according to emotion. Additionally, the ACC, which belongs to the medial frontal cortex, has been indicated to be a part of multiple parallel circuits connecting its subregions to the amygdala, nucleus accumbens, and PAG, each of which has a different role in regulating mood, emotion, and motivation. By investigating the interactions between these areas, we will be able to uncover the mechanism by which motivation promotes motor function and motor learning.

References

[1] Chiyohara, S., Furukawa, J., Noda, T., Morimoto, J. & Imamizu, H. (2023). Proprioceptive short-term memory in passive motor learning. ***Scientific Reports***, 13(1), e20826.

A04 Annual report of research project

Kaoru Takakusaki[1], Takashi Hanakawa[2]

[1]Department of physiology, Division of Neuroscience, Asahikawa Medical University (AMU)

[2] Kyoto University Graduate School of Medicine

***Abstract*— Our research projects aimed at testing the hypothesis that the alteration of neural dynamics following abnormal DA or ACh neurotransmissions may lead to the change of the "rule of the conduct" as one of the mechanisms of "hyper-adaptation." In the fifth year, we performed animal experiments and human clinical studies. Takakusaki and colleagues have examined the role of midbrain DA-ACh interaction acting on the posture-gait control system in the brainstem-spinal cord in the cat. Hanakawa and colleagues have been developing simultaneous EEG-fMRI to evaluate a dynamic profile of functional connectivity between distinct neural networks in elders relating to DA content and Aβ accumulation. These studies will clarify the relationship across cognitive functions, neural network dynamics, and neurotrans-mitters underlying hyper-adaptation generation.**

I. Introduction

Age-related decreases in neurotransmitters such as dopamine (DA) and acetylcholine (ACh) in the brain are associated with the pathogenesis of Parkinson's disease (PD) and Alzheimer's disease (AD), which impair motor and higher brain functions. [1, 2]. To overcome the decline in the brain and bodily functions of these diseases, it is necessary to understand how the above neurotransmitters control motor and higher brain functions. It is also required to elucidate the mechanism of hyper-adaptation that works under the reduction of these neurotransmitters.

The mission of A04 item is to examine the mechanisms of alteration of dynamic brain activities accompanying changes in the dynamics of DA and ACh. The 5th year (2023) worked on animal experiments where the role of ACh-DA interactions in the regulation of brainstem-spinal cord pathways' activity in postural control and on human studies where the measurement of brain network dynamics related to DA decrease and Aβ accumulation. These findings further assisted in developing mathematical models.

II. Aim of the Group

Takakusaki group conducted animal experiments in decerebrate cats to investigate the role of the interaction of the DA and ACh systems between the substantia nigra pars compacta (SNc) and the pedunculopontine nucleus (PPN) at the midbrain in the control of brainstem-spinal cord postural control systems.

Hanakawa group has been conducting clinical studies. They aim at discovering relationship among brain functions and dynamics of brain activity-connectivity in association with senescence. To this end, the Hanakawa lab will take advantages of the PADNI cohort, which is a longitudinal study involving healthy elderly people as well as patients with PD and AD. They are also involved in a cohort study about isolated REM behavioral disorder (iRBD), which is regarded as prodromal PD accompanying subclinical DA deficiency. The Hanakawa group is also working on improving DA transporter (DAT) SPECT technology for evaluating the activity of the DA system in humans.

III. Research Topics

The following points are the major achievements.

A. *Role of the DA-ACh interaction in the control of brainstem-spinal pathways* (Takakusaki; Asahikawa)

The role of DA projections in the PPN area was elucidated in decerebrate cats of how micro-injection DA into the PPN modulated the activities of the reticulo- and vestibulo-spinal tracts. The PPN, pontomedullary reticular formation (PMRF), and lateral vestibular nucleus (LVN) were stimulated (Fig.1A). The stimuli activated the reticulospinal and vestibulospinal tracts to elicit a mixture of excitatory (blue) and inhibitory (red) effects on motoneurons as monitored by the ventral root potentials (VRPs) (upper row in Fig.1B). Injecting a small amount of DA into the PPN amplified both the excitatory and inhibitory effects by each stimulus (bottom row in Fig.1B). Observation of an extended period showed 10-14Hz (a-band) oscillation time-locked to the PMRF stimulation after DA injection (Fig.1B, upper and lower right). These results indicate that the DA projection to the PPN-ACh neurons activates postural control systems to generate rhythmic α-band activity

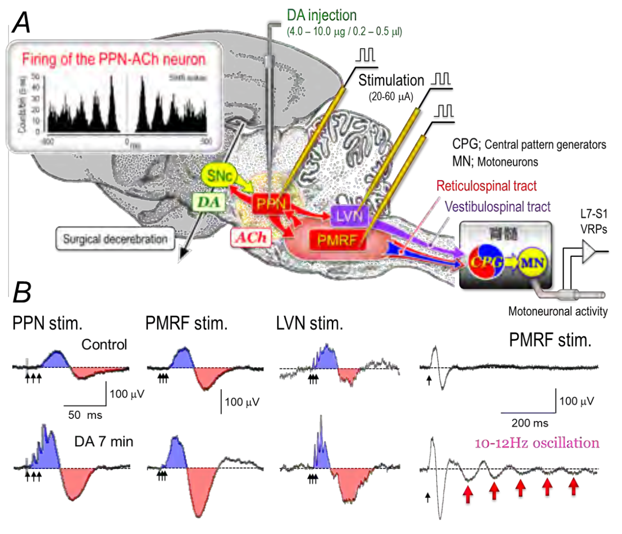


Figure 1. Effects of PPN-DA injection on brainstem-spinal cord pathways

in motoneurons. The PPN-ACh neurons exhibit α-band activity (Fig.1A inset), which maintains the whole brain activity in the α-band (α-wave in EEG and physiological tremor, Fig.2).

The DA system may, thus, enhance the PPN-ACh system's activity to entrain neural activity of diverse areas into the α band, facilitating plastic brain network generation.

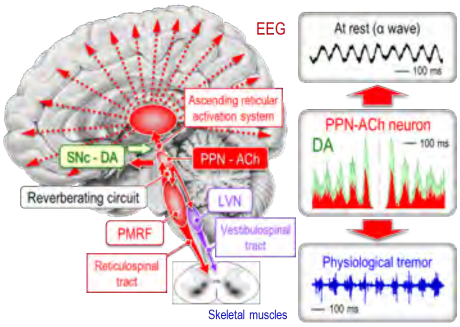


Figure 2. Role of DA-ACh interaction

B. *Non-invasice multimodal measurement of dynamic changes of brain activity and connectivity and DA imaging in humans* (Hanakawa, Kyoto)

In patients with PD and iRBD who have DA deficiency, Hanakawa and colleagues used neuroimaging technology such as fMRI to investigate dynamic adaptive changes of the cortico-basal ganglia circuits under the strong influence of DA. They also develop DAT SPECT technology for evaluating the activity of the DA system in patients. This year, the group used DAT SPECT data collected at four clinical centers from healthy aged persons and patients with PD and examined the effects of inter-site differences in striatal DAT uptake in the form of specific binding ratio. The group observed substantial inter-site differences in SBR. Although a statistical method called ComBat was able to remove the inter-site differences, this method showed limitation in terms of quantitativity. Hence, the study recommended the calibration across the SPECT scanners using a phantom and standardization of operations whenever possible [3]. A study analyzed a clinical dataset from prospective PADNI and found pronounced mild behavioral impairment in patients with both the reduction of DA and the deposition of Aβ [4]. PADNI consists of both prospective and retrospective cohorts. Some patients with PD in the retrospective PADI underwent a motion analysis during stance and gait. Such data were used for a simulation study by the B04 group [5]. This simulation analysis will use DAT data to link between a parameter in the simulation and whereabouts of the DA deficiency in the brain.

The J-PPMI is a longitudinal cohort study that recruits patients with iRBD. iRBD draws recent attention as a prodromal stage of α-synucleinopathy such as PD and dementia with Lewy bodies [6]. The group computed functional connectivity from resting-state fMRI data collected from iRBD patients in the J-PPMI cohort and healthy aged controls and then tested whether FC carried information to discriminate between iRBD and controls. They retrieved 8646-dimensional FC, used the random forest for dimensional reduction and weight computation, and made a classifier using either the logistic regression or the support vector machine. the results showed that the classifier with FC was able to differentiate iRBD and HC at accuracy around 70% (area under the curve of receiver-operator characteristic curve). Furthermore, the FCs adapted by the classifier were correlated with measures of motor disturbance and cognitive impairment in iRBD [7]. The group went on analyzing dynamic FC and performing topology analysis based on a graph theory. The group also reported that macrostructural neuroplasticity of the cerebellum underlies motor recovery after stroke [8].

IV. Summary of the Projects

In the past 5 years of research, the Takakusaki group found that the ACh system in the brainstem regulated the activity of the brainstem-spinal cord postural control systems in which the excitability was facilitated by the DA system. This DA-ACh interaction may enhance α-band activity in the postural control system which promotes task-relevant neural circuit generation. Hanakawa group developed methods to assess the integrity of DA system in humans. They performed many studies about dynamics of the brain with DA reduction and identified network properties that may serve imaging biomarkers of DA depleted conditions.

References

[1] Takakusaki K, Takahasi M, Noguchi T, Chiba R. Neurophysiological mechanisms of gait disturbance in advanced Parkinson's disease patients Neurol Clin Neurosci 2022. DOI: 10.1111/ncn3.12683

[2] Takakusaki K. Gait control by the frontal lobe. Chapter 5. Motor System Neuromuscular Disorders, Vol 1. in Handbook of Clinical Neurology 3rd Series. 2023 (in press)

[3] Wakasugi N, Takano H, Abe M, Sawamoto N, Murai T, Mizuno T, Matsuoka T, Yabe H, Matsuda H, Hanakawa T, PADNI: Harmonization of Dopamine Transporter SPECT Imaging Improves Segregation between Patients with Parkinson's disease and Healthy Elderlies in Multicenter Cohort Studies. Front Neurol (in press)

[4] Matsuoka T, Oya N, Narumoto J, Morii-Kitani F, Niwa F, Mizuno T, Akazawa K, Yamada K, Abe M, Takano H, Wakasugi N, Shima A, Sawamoto N, Ito H, Toda W, Hanakawa T, Parkinson's and Alzheimer's disease Dimensional Neuroimaging Initiative: Contribution of Alzheimer's disease and Lewy body disease pathologies on the mild behavioral impairment. Int J Geriatr Psychiatry 38(9):e5993, 2023.

[5] Omura Y, Togo H, Kaminishi K, Hasegawa T, Chiba R, Yozu A, Takakusaki K, Abe M, Takahashi Y, Hanakawa T, Ota J: Analysis of Stooped Posture in Patients with Parkinson's Disease Using a Computational Model Considering Muscle Tones. Front Comp Neurosci 17:1218707, 2023.

[6] Nishikawa N, Murata M, Hatano T, Mukai Y, Saito Y, Sakamoto T, Hanakawa T, Kamei Y, Tatsumori H Hatano K, Matsuda H, Taruno Y, Sawamoto N, Kajiyama Y, Ikenaka K, Kawabata K, Nakamura T, Iwaki H, Kadotani H, Sumi Y, Inoue Y, Hayashi T, Ikeuchi T, Shimo Y, Mochizuki H, Watanabe H, Hattori N, Takahashi Y, Takahashi R, the Japan Parkinson's Progression Markers Initiative (J-PPMI) study group: An observational study on idiopathic rapid eye movement sleep behavior disorder in Japan. Parkinson Relat Disord 103: 129-135, 2022.

[7] Matsushima T, Yoshinaga K, Wakasugi N, Togo H, Hanakawa T, Japan Parkinson's Progression Markers Initiative (J-PPMI) study group. Functional connectivity-based classification of rapid eye movement sleep behavior disorder. Sleep Med 115:5-13, 2024.

[8] Hanakawa T, Hotta F, Nakamura T, Shindo K, Ushiba N, Hirosawa M, Yamazaki Y, Sato Y, Takai S, Mizuno K, Liu M: Cerebellar neuroplasticity correlated with motor recovery after stroke. Neurorehab Neural Repair 37(11-12):775-785, 2023.

A05-1 Annual report of research project

Yuichi Takeuchi
Faculty of Pharmaceutical Sciences, Hokkaido University

***Abstract*— We develop a brain stimulation technology that reinforces a target brain state by precisely timed stimulation of the brain reward system toward beneficial reorganization of the neural circuit in the brain to control brain disorders. Toward the goal, the following three research milestones have been achieved during this fiscal year: A, Control of pathological fear memory of rats by time targeted stimulation of the brain reward system; B, Control of depression-like behaviors in rats; C, Improvement of Alzheimer's disease model mice.**

I. Introduction

Neurological diseases such as epilepsy and Alzheimer's disease and psychiatric disorders such as depression and post-traumatic stress disorder (PTSD) are often drug resistant. Induction of network reorganization in the brain by deep brain stimulation may be effective in controlling such drug-resistant brain diseases. [1] However, when the brain network reorganization is properly induced, it may work beneficially, such as recovery of disorders, whereas when it is improperly induced, it may produce undesirable results, such as no recovery of disorders or a condition like phantom limb pain, for example. However, few methods are known to properly reinforce and induce network reorganization in the brain. Therefore, it is necessary to develop a new technology that appropriately guides brain network reorganization via time targeted stimulation of the brain rewarding system by the combination of our time targeted brain stimulation technology [2] and stimulation of the reward system in the brain [3] (Fig. 1). [4]

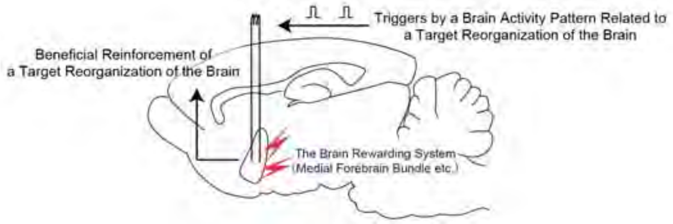


Fig. 1. A closed-loop brain stimulation for reinforcing hyper-adaptability [4]

II. Aim of the Group

Therefore, the aim of this group was set as "Development of a method to enhance brain network reorganization by time targeted stimulation the reward system in the brain". Specifically, we aim to control disease-like symptoms in animal models of epilepsy, Alzheimer's disease, depression, and PTSD by reinforcing specific brain states between ongoing brain activities. In this fiscal year, we aimed to develop a technology to control PTSD-like symptoms and depression-like symptoms, and to recover cognitive deficits in dementia animal models such as Alzheimer's disease [5].

III. Research Topics

A. Control of pathological fear memory of rats by time-targeted stimulation of the brain reward system

Rats that had been fear conditioned with sound and plantar electrical stimulation (CS+ US+) were trained to erase their fear memories in a sound-only environment (CS+ US-). The brain rewarding system of those rats were then stimulated by timings triggered by hippocampal Sharp Wave / Ripples (SWRs) during the sleep after the extinction training. The group that received SWR-triggered stimulation of the brain reward system decreased freezing responses (fear) significantly more efficiently than the no-stimulus group (Fig. 2). [6]

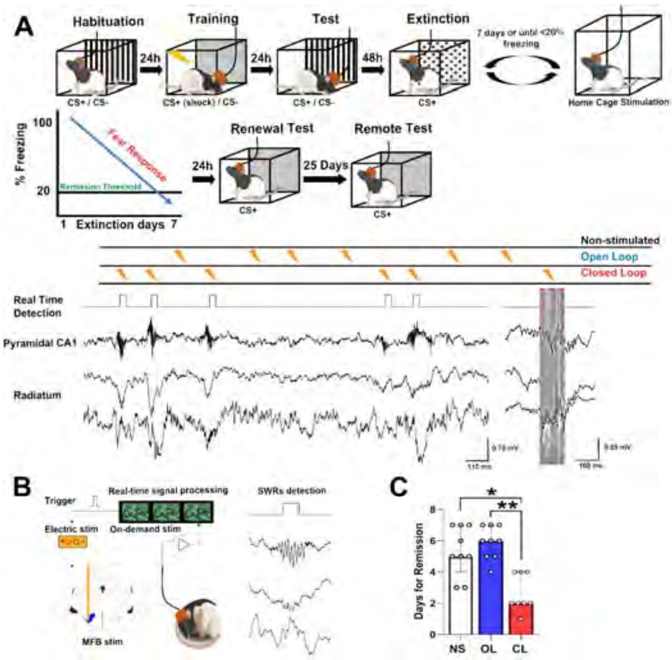


Fig. 2. Hippocampal Sharp Wave-Ripple-triggered stimulation of the reward system in the brain during the sleep after extinction training reinforces extinction of a fear memory. [6] A: Experimental schedule and a recording and stimulation systems of the hippocampus and the medial forebrain bundle. B: A closed-loop medial forebrain bundle stimulation system. C: Days for 80% remission of freezing behaviors.

B. Control of depression-like behaviors by time-targeted deep brain stimulation

Olfactory bulbectomized rats have been used as a model of depression because they show depression-like symptoms such as decreased performance in sucrose preference tests (reflecting anhedonia). However, it is unclear whether brain damage, inflammation, or changes in brain activity associated with olfactory bulbectomy produce these depression-like symptoms. Therefore, we here implemented a real-time electrical stimulation system of the bilateral piriform cortices with waveforms of gamma frequency oscillation patterns in the olfactory bulb in real time to bidirectionally manipulate the functional coupling int the gamma band frequency between the olfactory blub and the piriform cortices. We found that the gamma frequency coupling between the olfactory bulb and piriform cortices was related to the maintenance of positive mood as measured by the performance on a sucrose preference test. Furthermore, we have successfully alleviated depression-like symptoms by time targeted stimulation of the piriform cortices via increasing their gamma frequency coupling with the olfactory bulb. [7]

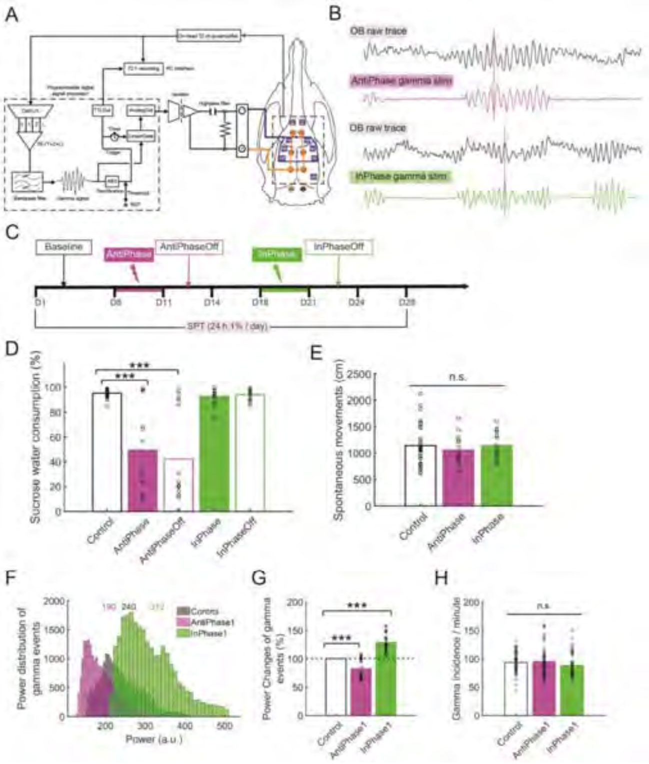


Fig. 3. Gamma frequency functional couplings between the olfactory bulb and the piriform cortex mainteins hednic mood in rats. [7] A, B: A closed-loop electrical stimulation system of the piriform cortex in real-time gamma band oscillatory activity patterns in the olfactory bulb. C: Experimental schedule. D: Performances of the sucrose preference test. E: Locomotion. F–H: Bilateral modulation of gamma oscillatory activities in the piriform cortex by the closed-loop stimulation.

C. *Alleviation of deficit of cognitive functions of Alzheimer's model mice by time targeted stimulation of the brain reward system*

We have experimentally addressed the hypothesis that cognitive functions impaired by Alzheimer's disease or other diseases can be improved by enhancing γ-frequency brain activity in the cerebral cortex and hippocampus, which have been reported to be involved in cognitive functions. We employed humanized amyloid precursor protein knock-in mice, which carries mutations derived from a familial Alzheimer's disease patient. [5] First, we confirmed that γ-frequency brain activities in the cerebral cortex and hippocampus decreased in the model mice with a decrease in cognitive function as assessed by the Y-maze test. In the model mice, we stimulated the rewarding brain system triggered by γ-frequency brain activity. As a result, γ-frequency brain activity in the cortex and hippocampus of APP mice was increased and their performance in the Y-maze test was improved (n = 2).

IV. Future Perspective

We have achieved control of pathological fear memory and improvement of cognitive functions of rodents by time targeted stimulation technologies of the brain reward system. We have also alleviated depression-like behaviors of rodents by time-targeted deep brain stimulation. Regarding the improvement of cognitive functions by time-targeted stimulation of the brain rewarding system, there is still room for further investigation of more efficient stimulation conditions, etc. Thus, further research is needed.

References

[1] Y. Takeuchi, A. J. Nagy, L. Barcsai, *et al*., "The medial septum as a potential target for treating brain disorders associated with oscillopathies," *Front. Neural Circuits*, vol. 15, pp. 701080, July 2021.

[2] Y. Takeuchi and A. Berényi, "Oscillotherapeutics – Time-targeted interventions in epilepsy and beyond," *Neurosci. Res.*, vol. 152, pp. 87-107, March 2020.

[3] H. Norimoto and Y. Ikegaya, "Visual cortical prosthesis with a geomagnetic compass restores spatial navigation in blind rats ," *Curr. Biol.*, vol 25, pp. 1091-1095, April 2015.

[4] K. Hara and Y. Takeuchi, " Time-targeted stimulation of the brain rewarding system as a novel brain disorder treatment," *Medical Science Digest*, *in press*.

[5] T. Saito, Y. Matsuba, N. Mihira, *et al*., "Single App knock-in mouse models of Alzheimer's disease," *Nat. Neurosci.*, vol. 17, pp. 661-663, May 2014.

[6] R. O. Sierra, L. K. Pedraza, L. Barcsai, *et al*., "Closed-loop brain stimulation augments fear extinction in male rats," *Nat. Commun.*, vol. 14, 3972, July 2023.

[7] Q. Li †, Y. Takeuchi †, J. Wang, *et al*., "Reinstating olfactory bulb-derived limbic gamma oscillations alleviates depression-like behavioral deficits in rodents," *Neuron*, vol. 111, pp. 2065-2075, July 2023.

A05-2 Annual report of research project

Shin-Ichi Izumi
Graduate School of Biomedical Engineering, Tohoku University

Abstract—**This study aims to comprehensively understand the mechanism of adaptive changes in brain, real-world arm use and body consciousness underlying upper limb (UL) recovery in stroke patients. In this study, we longitudinally investigate plastic changes in function and structure of the brain in stroke patients using fMRI and DTI. In addition, we measure real-world arm use and UL function by using accelerometers and Fugl-Meyer Assessment (FMA), respectively, to elucidate the relationship among them. We expect to investigate the neural basis of hyper-adaptation in the rehabilitation of stroke UL paralysis and to contribute to the elucidation of the relationship between behavioral execution and neural reorganization. The results revealed that different brain regions and neural pathways were associated with the recovery of use behavior and function. These findings provide new insights into the relationship between use behavior and brain function and structure, and may contribute to the development of rehabilitation strategies to promote real-world arm use after stroke. Furthermore, we examined the effect of a sense of body ownership, one of body consciousness, on the motor imitation training in stroke patients, and found that the increase in sense of body ownership facilitated the effect of imitation training. We believe that these results contribute to a multifaceted understanding of the relationship between body consciousness and motor function in stroke patients. We have also made steady progress in the publication of the above research results.**

I. Introduction

The most common disability after stroke is UL paralysis occurring on the contralateral side of unilateral cerebral hemisphere injury, and more than 80% of stroke patients experience this condition in the acute phase and more than 40% have residual disability in the chronic phase. In order to establish effective rehabilitation for UL paralysis, various treatment techniques based on plastic changes in the central nervous system have been developed so far. However, the pathophysiology and recovery process of stroke hemiplegia are diverse, and the therapeutic effects vary widely among individuals, reflecting this. No standard has been established to indicate which treatment technique should be applied to each individual patient. The combination of various therapeutic techniques has also been studied, but the optimal type and timing of combination is not clear. In order to overcome these problems, we have been working to understand the adaptive mechanisms of the neural basis that mediates between the brain and the body and to develop rehabilitation treatment based on body consciousness. In this study, we developed a method to quantify body-specific attention as a marker of body consciousness, and found that body-specific attention was lower in chronic stroke patients with longer time since stroke onset and lower hand function [1]. This is the first finding to measure learned non-use in chronic stroke patients from the aspect of body consciousness. Furthermore, the relationship between body-specific attention, real-world arm use, and UL function from subacute to the chronic phase was clarified [2]. We also successfully quantified body-specific attention in the lower limb as well as the upper limb, and reported the relationship between the different roles of limb functions and body-specific attention [3]. In addition, to better understand the relationship between limb use and body awareness in the physically disabled, we measured body-specific attention to prosthetic legs in lower limb amputees and revealed a use-dependent increase in body-specific attention during the gait acquisition process [4]. These studies have provided important insights into the relationship between body-specific attention to limbs and the amount of limb use. However, it is not clear the relationship between the real-world arm use and brain function and structure. In addition, the relationship between limb use and body-specific attention in the physically disabled and the effects of enhance of a sense of body ownership, one of body consciousness, on upper limb motor function have not been fully investigated.

II. Aim of the Group

This study aims to comprehensively understand the mechanism of adaptive changes in the brain, real-world arm use and body consciousness underlying upper limb (UL) recovery in stroke patients. 1) We longitudinally investigate plastic changes in function and structure of the brain in stroke patients using fMRI and DTI. In addition, we measure real-world arm use and UL function by using accelerometers and Fugl-Meyer Assessment (FMA), respectively, to elucidate the relationship among them. 2) Furthermore, we elucidate the effect of enhance of body ownership, on the effect of motor imitation training in stroke patients, and investigate that the increase in sense of body ownership facilitated the effect of imitation training.

III. Research Topics

A. Relationship between the real-world arm use and plastic changes in the brain in stroke patients: A longitudinal study.

We conducted a longitudinal observational study of 25 patients with first-ever subacute stroke. Measurements were taken at baseline, 1 month, 2 months, and 6 months after enrollment. Real-world arm use was measured using accelerometers on both wrists. UL function was measured using the Fugl–Meyer Assessment (FMA). Brain function was measured by functional magnetic resonance imaging (fMRI) to determine brain activity during paretic hand movements, and diffusion tensor imaging (DTI) to determine fractional anisotropy (FA) values for brain structures, and the relationship between changes in each index was examined. Results showed that real-world arm use and UL function improved up to 6 months. The amount of change in arm use during the period of greatest improvement was correlated with activity in the posterior parietal lobe. Furthermore, the ratio of FA values of the injured to the uninjured side of the superior longitudinal fasciculus (FA ratio) was correlated with the final (6 months) real-world arm use. Final UL function was correlated with activity of the injured primary motor cortex and FA ratio of the corticospinal tract. The posterior parietal lobe and connecting nerve pathway in the frontal and parietal lobes were identified as brain regions associated with arm use during UL recovery after stroke, revealing that different brain regions and neural pathways are associated with use behavior and functional recovery. These results provide new insights into the relationship among arm use and brain functions and structures.

B. Effectof a sense of body ownership on motor imitation practice in stroke patients: Virtual hand illusion (VHI) using a head-mounted display

In post stroke rehabilitation, encouraging the use of the paretic limb in daily life is one of the vital issues. The settled a sense of body ownership toward the paralyzed body part is considered to promote increased arm use of the paretic limb and to prevent learned non-use. Therefore, in addition to traditional methods, there is a growing need for novel interventions using neurorehabilitation techniques that induce self-body recognition. Present study aimed to investigate whether the illusory experience of the patients' ownership alterations for their paretic hand causes facilitation in the motor output of succeeding imitation movements, and an experiment combining a modified version of the rubber hand illusion (RHI) with imitation training by presenting a pre-recorded video stream through a head-mounted display was conducted in 13 patients with chronic hemiplegia. A larger imitation movement of the paretic hand was observed in the illusion induced condition, indicating that the feeling of ownership toward the observing limb is conducive to the induction of intrinsic potential for motor performance. This type of training, which utilizes subjective experience to enhance the sense of body ownership toward the observing body part, may contribute to the development of new rehabilitation methods in post stroke rehabilitation.

IV. Future Perspective

In the recovery process of paretic UL, we found that different brain regions and neural pathways are associated with use behavior and functional recovery in stroke patients. These results provide new insights into the relationship between use behavior and brain, and may contribute to the development of new rehabilitation strategies to promote real-world arm use after stroke. Furthermore, we examined the effect of sense of body ownership on the motor imitation training, and found that an increase in body ownership in the paretic hand facilitated the effectiveness of imitation movements. We believe that these findings will contribute to the construction of rehabilitation strategies to enhance body awareness and increase motor function and arm use after stroke. In addition, our previous studies have revealed a use-dependent increase in body-specific attention during the process of gait acquisition with prostheses after lower limb amputation. We believe that these results contribute to a multifaceted understanding of the relationship between body awareness, function, and behavior in the physically disabled, using the findings of stroke patients and amputees as a clue.

In the future, we will investigate the neural basis of body-specific attention and use-behavior in more detail, and clarify the long-term changes in the brain functional and structural networks during the recovery process of stroke patients.

References

[1] N. Aizu, Y. Oouchida, and S. Izumi, "Time-dependent decline of body-specific attention to the paretic limb in chronic stroke patients," *Neurology*, vol. 91, pp. e751-758, 2018, doi: 10.1212/WNL.0000000000006030.

[2] R. Otaki, Y. Oouchida, N Aizu, T Sudo, H Sasahara, Y Saito, S Takemura, S. Izumi *et al.*, "Relationship Between Body-specific attention to a Paretic Limb and Real-World Arm Use in Stroke Patients: A Longitudinal Study," *Front. Syst. Neurosci.*, vol. 15, 2022, doi: 10.3389/fnsys.2021.806257.

[3] N. Aizu, R. Otaki, K. Nishii, T. Kito, R Yao, K Uemura, S. Izumi, K. Yamada *et al.*, "Body-Specific Attention to the Hands and Feet in Healthy Adults," *Front. Syst. Neurosci.*, vol. 15, Jan. 2022, doi: 10.3389/FNSYS.2021.805746/FULL.

[4] N. Aizu, Y. Oouchida, K. Yamada, K. Nishii, and I. S. Izumi, "Use-dependent increase in attention to the prosthetic foot in patients with lower limb amputation," *Sci. Rep.*, vol. 12, no. 1, p. 12624, Dec. 2022, doi: 10.1038/S41598-022-16732-Z.

[5] K. Ataka, T. Sudo, R. Otaki, E. Suzuki, and S. Izumi, "Decreased Tactile Sensitivity Induced by Disownership: An Observational Study Utilizing the Rubber Hand Illusion," *Front. Syst. Neurosci.*, vol. 15, Jan. 2022, doi: 10.3389/FNSYS.2021.802148/FULL.

[6] N. Aizu, T. Sudo, Y. Oouchida, and S. Izumi, "Facilitation of imitative movement in patients with chronic hemiplegia triggered by illusory ownership," *Sci. Rep.*, vol. 13, no. 1, Dec. 2023, doi: 10.1038/S41598-023-43410-5.

A05-3 Annual report of research project

Rie Kimura
International Research Center for Neurointelligence, Institutes for Advanced Study, The University of Tokyo

***Abstract*— Blindly over-adapting or failing to adapt to the external environment often leads to mental and physical illnesses and, in many cases, a decline in our quality of life (QOL). Optimal adaptation is thought to be essential to improving QOL. Using rats performing visual discrimination tasks, we aim to clarify how the adaptation to changes in visual stimulation is influenced by mental stress and developmental disorders. By examining the visual responses in the multidimensional brain systems across multiple regions, we aim to understand the neural basis of optimal adaptation to the external environment.**

I. INTRODUCTION

To adapt and live with stress in a flood of information, people occasionally eliminate unpleasant information, whether consciously or unconsciously. This is also true for sensory perception; people may adapt and perceive unpleasant sensory information by attenuating it. Over-adaptation can result in psychogenic sensory impairments. Despite the inability to detect organic abnormalities, in the case of vision, psychogenic visual impairment can result in reduced visual acuity and visual field defects due to psychological causes. In contrast, in autism spectrum disorders, which are characterized largely by impaired social skills and limited behavior and interests, sensory hypersensitivity or hypoesthesia is often observed. In the case of visual hypersensitivity, people with autism perceive sunlight as dazzling and blank in front of their eyes. It is thought that the brain is unable to regulate and adapt its neural activity to allow for comfortable perception. In both instances, they have problems adapting to the external environment. Over-adaptation to the external environment is a problem, but so is failing to adapt. Moderate adaptation to the external environment is thought to be important for improving quality of life. Filtering in the thalamus [1] is thought to play an important role in the representation of sensory information during adaptation to stress [2]. During acute stress, the brain is thought to increase sensory responses and represent more information from the external environment. However, when stress is repeatedly applied over a long period of time, the prefrontal cortex and other areas are activated by anticipating the stress event, and conversely, sensory responses are thought to be attenuated [3]. On the other hand, it has been reported that the effects of inhibition against excitation are weakened within the neural circuits in autism [4, 5] and that additional weight is given to bottom-up input rather than top-down prediction [6]. In addition, neural connections within the anterior and dorsomedial nuclei of the thalamus, which performs an important function during the aforementioned stress adaptation, are reduced [7, 8]. This area is known to project sensory and association areas such as the primary visual cortex and prefrontal cortex [9]. In contrast, long-range connections among these regions are increased [7, 8]. Consequently, different brain regions become active simultaneously, increasing excitability and causing sensory hypersensitivity [7].

We previously trained head-restrained rats to discriminate between vertical and horizontal gratings in a visual discrimination task. After achieving high correct percentages, lower-contrast stimuli were also presented. We performed multiple single-unit recordings from deep layers of the primary visual cortex of trained rats during this task. We found that the number of low contrast–preferring neurons, which responded more strongly to low-contrast stimuli than high-contrast stimuli, increased after learning. Even the primary sensory cortex, which is thought to represent the external world faithfully, can represent low-contrast information well enough as a population by creating a new function that fires strongly with weak input. Adaptation to changes in the visual contrast has been observed [10]. However, there is less systematic understanding of how neural circuits and sensory responses in the brain adapt depending on the degree of adaptation at the perceptual level. We have yet to understand the neural basis of optimal adaptation to the external environment.

II. AIM OF THE GROUP

In this study, we will determine how the brain adapts to changes in the external environment, especially when presented with a variety of different visual stimuli, and how this adaptation mechanism is modified by different levels of adaptation, stress load, and developmental characteristics in autism. We aim to understand how changes in neural activity across multiple dimensions within single neurons, neuronal pairs in single brain regions, multiple neurons, and multiple brain regions result in optimal adaptations to the external environment at the perceptual level.

III. RESEARCH TOPICS

This year, we first examined how visual discrimination is affected by stress loading depending on the difficulty of tasks. Using the touchscreen operant platform, freely moving rats were trained to discriminate between vertical and horizontal gratings. The stimuli were then rotated while maintaining the 90-degree difference in tilt between the two gratings. Two blocks were switched at regular intervals: an easy block with a small rotation angle and a low-stress condition, and a difficult block with a large rotation angle and a high-stress condition. The easy and difficult blocks were explicitly distinguished by presenting a pure tone of a different frequency simultaneously with the visual stimuli. We observed that the percentage of correct responses differed between the easy and difficult blocks, even when the task was of the same difficulty level. We hypothesized that the balance of various influences, such as attention, stress, novelty, degree of boredom, experience of reference trials, and satiety, would change depending on the difficulty of tasks, thereby affecting the correct response rate for visual discrimination. This may be related to the characteristics of psychogenic visual impairment, for example, difficulty in reading a question text during an exam or difficulty in seeing when trying to concentrate. In the future, we would like to understand the neural basis that influences visual discrimination by collecting the number of data and analyzing the various effects separately.

Next, to investigate the effects of developmental characteristics of autism, which is known to cause sensory hypersensitivity problems in many cases, on visual discrimination, we created a rat model of autism by injecting valproic acid, an antiepileptic drug, into pregnant rats. Objects and new rats were placed in two of the three compartments, and the contact time was measured. The control group showed long contact with the new rat. On the other hand, the valproic acid-treated group stayed in the middle compartment more frequently, without much contact with either the rats or the objects. Thus, as in many previous reports, a decrease in sociality was observed in the valproic acid-treated rats. In the future, we would like to perform a visual discrimination task using these rats and record neural activities.

The brain makes predictions based on past experience when processing input sensory information and outputting behavior. It is known that the brain initially faithfully represents information from the external world, but as it learns, it builds internal predictive models about the input information and increases top-down inputs related to prediction, expectation, and attention from higher brain regions [11]. Therefore, we first examined the involvement of top-down inputs related to visual perception using normal rats. The rats were repeatedly exposed to a discrimination task using the orientation of the gratings after switching from a black screen to a gray Cue screen. At Cue, some neurons in the primary visual cortex (V1) showed gradually increasing activity, i.e., a predictive signal. In contrast to previous reports, this was observed to the same extent before and after learning in high contrast–preferring neurons. In contrast, the predictive signal was almost nonexistent in the anesthetized rats, suggesting that the predictive signal is generated by top-down modulation, as in previous reports. We believe that the increased attentional state of the rats makes a lower-order prediction of the upcoming presentation of the gratings even before learning. However, the coherence between the local field potential (LFP) in the secondary motor cortex (M2) [12], considered as one of the top-down sources, and the LFP in V1 during the grating presentation was increased by learning. Furthermore, we calculated Granger causality of the interaction between M2 and V1: top-down causality from the LFP of M2 to V1 became higher during Cue presentation, both before and after learning. However, after learning, causality was again stronger during the presentation of the low-contrast gratings. Next, bottom-up causality from V1 to M2 remained low before learning, but increased after learning during the presentation of the low-contrast gratings. In summary, after learning, the top-down modulation from M2 to V1 and the bottom-up modulation from V1 to M2 were enhanced in both directions during low-contrast and low-visibility stimuli. After learning, the top-down and bottom-up interactions between higher-order brain regions and lower-order sensory cortices were altered in response to external input, leading to more refined predictions.

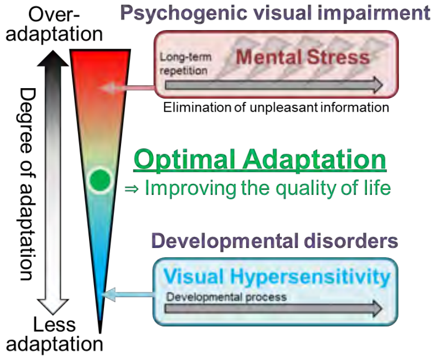


Fig. 1. Schematic diagram of optimal adaptation to the external environment.

IV. Future Perspective

Although we were unable to understand the neural basis of moderate adaptation during this year, we are now ready to develop experiments of stress load and developmental characteristics of autism. In the future, we will use these experimental systems to confirm differences in adaptation to a variety of visual stimuli, record neural activity, and discuss moderate adaptation.

References

[1] M. M. Halassa, and S. Kastner, “Thalamic functions in distributed cognitive control,” *Nat Neurosci,* vol. 20, no. 12, pp. 1669-1679, Dec, 2017.

[2] 岡本 泰昌, “ストレスを感じる前頭前野―ストレス適応破綻の脳内機構―,” *日本薬理学雑誌,* vol. 126, no. 3, pp. 194-198, 2005.

[3] K. Onoda, Y. Okamoto, K. Shishida, A. Hashizume, K. Ueda, A. Kinoshita, H. Yamashita, and S. Yamawaki, “Anticipation of affective image modulates visual evoked magnetic fields (VEF),” *Exp Brain Res,* vol. 175, no. 3, pp. 536-43, Nov, 2006.

[4] C. E. Robertson, and S. Baron-Cohen, “Sensory perception in autism,” *Nat Rev Neurosci,* vol. 18, no. 11, pp. 671-684, Nov, 2017.

[5] O. Yizhar, L. E. Fenno, M. Prigge, F. Schneider, T. J. Davidson, D. J. O'Shea, V. S. Sohal, I. Goshen, J. Finkelstein, J. T. Paz, K. Stehfest, R. Fudim, C. Ramakrishnan, J. R. Huguenard, P. Hegemann, and K. Deisseroth, “Neocortical excitation/inhibition balance in information processing and social dysfunction,” *Nature,* vol. 477, no. 7363, pp. 171-8, Jul 27, 2011.

[6] E. Pellicano, and D. Burr, “When the world becomes 'too real': a Bayesian explanation of autistic perception,” *Trends Cogn Sci,* vol. 16, no. 10, pp. 504-10, Oct, 2012.

[7] C. Gernert, P. Falkai, and C. M. Falter-Wagner, “The Generalized Adaptation Account of Autism,” *Front Neurosci,* vol. 14, pp. 534218, 2020.

[8] D. Tomasi, and N. D. Volkow, “Reduced Local and Increased Long-Range Functional Connectivity of the Thalamus in Autism Spectrum Disorder,” *Cereb Cortex,* vol. 29, no. 2, pp. 573-585, Feb 1, 2019.

[9] T. E. Behrens, H. Johansen-Berg, M. W. Woolrich, S. M. Smith, C. A. Wheeler-Kingshott, P. A. Boulby, G. J. Barker, E. L. Sillery, K. Sheehan, O. Ciccarelli, A. J. Thompson, J. M. Brady, and P. M. Matthews, “Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging,” *Nat Neurosci,* vol. 6, no. 7, pp. 750-7, Jul, 2003.

[10] R. Kimura, and Y. Yoshimura, “The contribution of low contrast-preferring neurons to information representation in the primary visual cortex after learning,” *Sci Adv,* vol. 7, no. 48, pp. eabj9976, Nov 26, 2021.

[11] H. Makino, and T. Komiyama, “Learning enhances the relative impact of top-down processing in the visual cortex,” *Nat Neurosci,* vol. 18, no. 8, pp. 1116-22, Aug, 2015.

[12] S. Manita, T. Suzuki, C. Homma, T. Matsumoto, M. Odagawa, K. Yamada, K. Ota, C. Matsubara, A. Inutsuka, M. Sato, M. Ohkura, A. Yamanaka, Y. Yanagawa, J. Nakai, Y. Hayashi, M. E. Larkum, and M. Murayama, “A Top-Down Cortical Circuit for Accurate Sensory Perception,” *Neuron,* vol. 86, no. 5, pp. 1304-16, Jun 3, 2015.

A05-4 Neural substrate of unified learning theory for adaptive behavior

Akihiro Funamizu
Institute for Quantitative Biosciences, the University of Tokyo

***Abstract*— Our brain has multiple strategies and selects the strategy in a context dependent manner. Previous studies investigate the neural mechanism of multiple strategies in humans and find parallel neural circuits for multiple strategies. However, the neural circuits of multiple strategies are still unclear at least in a single neuron level, as precise neural recording and manipulations are required with animal experiments. Here we perform a multi-strategy task in head-fixed mice to investigate the neural substrate of model-free and inference-based strategy. We propose an AI (artificial intelligence) -based approach to model the relationship between the algorithms of brain and AI. During the task, we record the dopamine changes in nucleus accumbens with fiber bundle imaging. Our study potentially proposes an idea that the brain learns multiple behavioral strategies with one learning rule and switches the strategy with a non-linear neuronal circuit.**

I. Introduction

The brain has multiple behavioral strategies in response to one sensory stimulus and selects the strategy depending on a context. In control theory, behavioral strategies are categorized into a model-free (habit), which is based on direct experiences of choices and outcomes, and an inference-based (or model-based), which infers a hidden context from sensory inputs to realize flexible behavior.

Previous neuroscience studies often focus on the model-free strategy, primarily due to the simple behavior tasks and modeling [Ref.1]. Conversely, the inference strategy is often tested in human experiment [Ref.2]. Through sophisticated experimental designs, human studies find the parallel neural pathways for model-free and inference-based strategies [Ref.3,4]. However, due to the limitation of neural manipulations and recording in humans, the detail neural circuits for inference-based strategies are still unclear.

Recently, rodent studies investigated the brain regions essential for inference behavior [Ref.5-7]. These studies used the optogenetics and pharmacological tools for neural silencing and found that the hippocampus and prefrontal cortex are necessity for inference-based strategy. Nonetheless, the neural representation of inference-based strategy and of strategy switching are still unknown. The learning phase of inference strategy remains unclear.

Here we propose a behavioral task that required switching the behavioral strategies in head-fixed mice. We model the mouse behavior with an artificial neural network to predict the circuits executing multiple strategies. At the same time, we record the dopamine activity of mice during the task. Due to the current research phase, we did write the detail methods and results on this abstract.

II. Aim of the Group

We propose a unified learning theory for model-free and inference-based strategies and investigate their neural implementations in mice. We build an artificial neural network (ANN) with the behavioral data to model the strategy switching in the brain. We then compare the neural activity of mice with the activity of ANN.

III. Research Topics

We summarize the two achievements in this year as follows:

A. Modeling mouse choice behavior with recurrent neural network

Last year, we performed a "multi-strategy behavioral task" that segregates habitual and inference-based behavior. The task presented sound stimuli with various frequencies to head-fixed mice. The mice received a water reward by selecting either the left or right spout, depending on the low or high frequency (L, H) of sound. The task switched the sound stimulus (L or H) with a transition probability of p [Ref.8]. We set the probability at p=0.2 or p=0.8 (repeating or alternating condition) to differentiate between the habitual or inference-based behaviors, respectively. Mice properly biased the choices based on the transition probability in both the conditions. The acquisitions of proper choice biases were faster in the repeating than in the alternating conditions.

We continued to perform the behavioral task in mice since our different research projects. In this year, we modeled the choice behavior of mice in the repeating and alternating conditions with a Continuous-time Recurrent Neural Network (CT-RNN) (**Fig. 1a**) [Ref.9]. The learning rule of the RNN was the Advantage Actor-Critic (A2C) in a reinforcement learning. The RNN consisted of 100 nodes. The inputs of the RNN were the sound frequency in current trial, the choice and outcome in previous trial. The output of RNN was the choice in the current trial.

We first trained the RNN with simulated data solving the multi-strategy task. The RNN achieved the 100% success rate in both the repeating and alternating conditions. These results indicate that the RNN was properly trained in this study. When we added a noise in the activity of each unit, the RNN biased the outputs (choices) depending on the transition probabilities

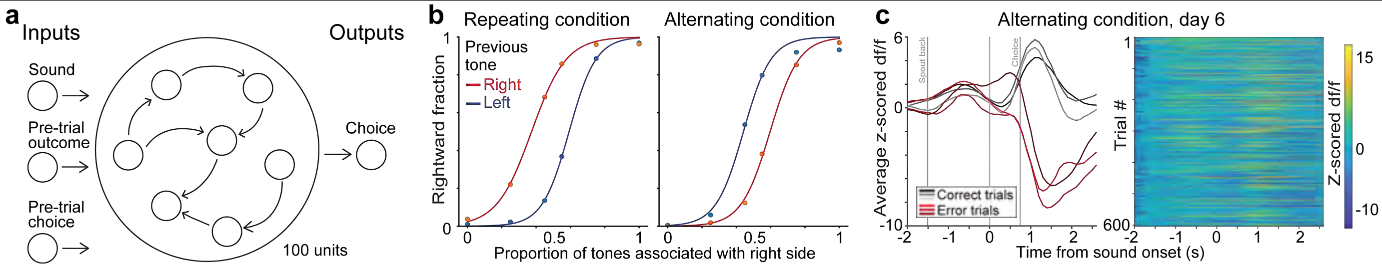


Fig. 1. Behavioral modeling and dopamine-activity recording during multi-strategy task in head-fixed mice.
a. Scheme of continuous-time recurrent neural network (CT-RNN). The inputs of RNN were the current-trial sound inputs, previous outcomes, and previous choices. The outputs of RNN were the left or right choice in the current trial.
b. Simulation of choice behavior with RNN. RNN succeeded to model the proper choice biases in both the repeating and alternating conditions depending on the transition probability of sound category.
c. Imaging of dopamine activity. Right: the dopamine activity was aligned at sound onset and averaged across trials in different sounds and choices. Left: Z-scored df/f in each trial. Colormap was scaled between 5% and 95% percentile of df/f.

of repeating and alternating conditions (**Fig. 1b**). Additionally, by adjusting some parameters within the RNN (the details of which are not written in this abstract), the RNN was able to replicate the difference in learning speed of the mice between the two task conditions.

B. Imaging of dopamine activity during task

We measured the dopamine activity during the task with a fiber bundle imaging. This method, using GCaMP [Ref.9] or G-protein-coupled receptor-activation-based (GRAB) sensors [Ref.10], enables imaging of neuronal activity or changes in neuromodulators. This study used the dopamine sensor, dLight (AAV5-CAG-dLight1.1), to measure the dopamine activity from the Orbitofrontal Cortex (OFC), Nucleus Accumbens (NAcc), and Ventral Tegmental Area (VTA). We now mainly focus on the NAcc for dopamine measurement (**Fig. 1c**).

This study imaged the dopamine activity in the NAcc while the mice gradually achieved the proper choice biases in the multi-strategy task. We found that the traces of dopamine in the NAcc depended on the bias-acquisition phase.

IV. Future Perspective

We summarize the achievements in this fiscal year and briefly explain the plan for the next year.

This year, we performed the "multi-strategy task" for head-fixed mice that we had previously constructed. We modeled the mice choice behavior using a continuous-time Recurrent Neural Network (CT-RNN). First, the RNN solved the behavioral task with 100% accuracy, indicating that the training of the RNN in this study was appropriate. In addition, by (i) adding noise to the activity of the RNN units and (ii) adjusting other parameters, the RNN reproduced the choice biases in the repeating and alternating conditions of mice and the difference in learning speed between the two task conditions.

During the multi-strategy task, we measured the dopamine activity in the NAcc with fiber bundle imaging. We found that the dopamine activity was dynamically changed during the acquisition phase of choice biases.

Next year, we will continue measuring the dopamine activity of NAcc with the fiber bundle imaging and analyze the data. We will investigate the relationship between the activity of RNN units and the dopamine activity of mice. We will submit the results obtained in this study to an international journal.

References

[1] W. Schultz, P. Dayan, and P.R. Montague, "A neural substrate of prediction and reward," Science, vol. 275(5306), pp. 1593-9, Mar 1997.

[2] A.N. Hampton, P. Bossarerts, and J.P. O'Doherty, "The role of the ventromedial prefrontal cortex in abstract state-based inference during decision making in humans," J Neurosci, vol. 36(32), pp. 8360-7, Aug 2006.

[3] N.D. Daw, S.J. Gershman, B. Seymour, P. Dayan, R.J. Dolan, "Model-based influences on humans' choices and striatal prediction errors," Neuron, vol. 69(6), pp. 1204-15, Mar 2011.

[4] J. Glascher, N.D. Daw, P. Dayan, J.P. O'Doherty, "States versus rewards: dissociable neural prediction error signals underlying model-based and model-free reinforcement learning," Neuron, vol. 66(4), pp. 585-95, May 2010.

[5] K.J. Miller, M.M. Botvinick, C.D. Brody, "Dorsal hippocampus contributes to model-based planning," Nat Neurosci, vol. 20(9), pp. 1269-76, Sep 2017.

[6] P. Vertechi, E. Lottem, D. Sarra, B. Godinho, I. Treves, T. Quendera, M.N.O. Lohuis, Z.F. Mainen, "Inference-Based Decisions in a Hidden State Foraging Task: Differential Contributions of Prefrontal Cortical Areas," Neuron, vol. 106(1), pp. 166-76.e6, Apr 2020.

[7] T. Akam, I. Rodrigues-Vaz, I. Marcelo, X. Zhang, M. Pereira, R.F. Oliveira, P. Dayan, R.M. Costa, "The anterior cingulate cortex predicts future states to mediate model-based action selection," Neuron, vol. 109(1), pp. 149-163.e7, Jan 2021.

[8] A. Hermoso-Mendizabal, A. Hyafil, P.E. Rueda-Orozco, S. Jaramillo, D. Robbe, J. de la Rocha, "Response outcomes gate the impact of expectations on perceptual decisions," Nat Commu, vol. 11(1), 1057, Feb 2020.

[9] G.R. Yang, X.J. Wang, "Artificial Neural Networks for Neuroscientists: A Primer", Neuron, vol.107(6), pp.1048-70, Sep 2020.

[10] T.L. Daigle, L. Madisen, T.A. Hage, M.T. Valley, U. Knoblich, R.S. Larsen, et al., "A Suite of Transgenic Driver and Reporter Mouse Lines with Enhanced Brain-Cell-Type Targeting and Functionality," Cell, vol. 174(2), pp. 465-80, Jul 2018.

[11] T. Patriarchi, J.R. Cho, K. Merten, M.W. Howe, A. Marley, W.H. Xiong, et al., "Ultrafast neuronal imaging of dopamine dynamics with designed genetically encoded sensors," Science, vol. 360(6396), eaat4422, Jun 2018.

A05-5 Annual report of research project

Yoko Yazaki-Sugiyama
Neuronal Mechanism for Critical Period Unit, OIST Graduate University
WPI-IRCN, the University of Tokyo

***Abstract*— Like humans learning to speak, male zebra finches learn to sing by memorizing a tutor's song (TS) then vocally matching it in sequentially well-orchestrated auditory then sensorimotor developmental learning periods. Previous studies identified TS memory ensembles in the caudal nidopallium (NCM) which transiently project into the motor control region, HVC. Excessive song learning with sequential song learning from two tutors of different species yielded distinct neuronal ensembles for two song memories in the NCM, both of which retained connectivity to HVC into adulthood. Here we try to identify the axonal retraction timeline which support timely song learning. We further study the neuronal mechanism for persistence of neuronal connection with enriched experiences in juveniles. Increased neuronal circuit capacity may give rise a possibility or relearning in adulthood.**

I. Introduction

Like humans learning to speak, male zebra finches learn to sing by memorizing a tutor's song then vocally matching it in sequentially well-orchestrated auditory then sensorimotor developmental learning periods. Recently, we reported that a subset of neurons in the auditory phase is stored in the caudal nidopallium (NCM) exhibit highly-selective auditory responses to the playback of TS within some days after tutoring experiences (1,2). We found a transient neuronal projection into the motor control region, HVC, from TS responding NCM neurons during developmental song learning period. Moreover, enriched song learning experiences in juvenile period resulted in the retention of NCM projections in HVC into adulthood. Here in this FY, we identified the timeline of axonal retraction which are suggested from the transient NCM-HVC projections. We also investigated what time of song experiences regulate the maturation of NCM-HVC neuronal circuits and its modulations. Increase the capacity of neuronal circuits in adulthood with enriched experiences are suggested by human bilingual condition (3, 4), implicating a possibility of recovering learning ability in adults.

II. Research Topics

A. The timeline of NCM axonal disconnection and its relation with song maturation

In our recent research we found that NCM TS responding neurons project to the song motor control region, HVC in juveniles at 60 days post hatch (DPH) which were song vocal learning period, while not in the older juveniles which were at the end of song learning period (90 DPH), suggesting axon retraction happening between these period. Here we identified more exactly when axon retraction takes place especially regarding song learning. Zebra finches injected with the AAV-cFOS-TetOn-EYFP-PEST at 70, 80 or 90 DPH were exposed to TS playback concurrent with DOX in drinking water to induce EYFP expression in TS-responsive neurons. We found projection within HVC from the TS-responsive NCM neurons in 70 DPH juveniles were significantly higher than those in 80 or 90 DHP juveniles (Fig. 1). As zebra finch juveniles change

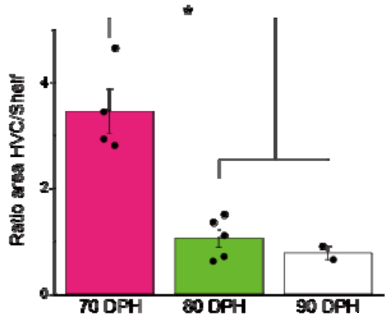


Fig. 1: Axonal projections in the song motor region, HVC from TS-responsive NCM neurons
The amount of axonal projection detected as GFP positive area, comparing to adjacent Shelf region, was significantly higher in the juveniles of 70DPH than those in juveniles of 80 or 90 DPH.

their songs by motor learning and gradually crystalize their songs by adults, we further analyzed the amount of song changes during the 10 days before sacrificing for the histological analysis by measuring the song similarity in between. Juveniles of 90 DPH barely changed their songs in the last 10 days as indicated in higher similarity between songs

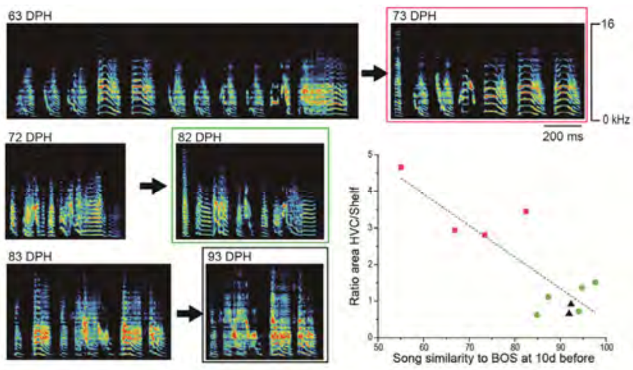


Fig. 2: NCM axonal projections in HVC correlate with song maturation
Sound spectrographs of songs at sacrificed day for histological analysis (right) and 10 days before (left). The amount of axonal projection in HVC shows negative correlation with the song similarity between songs in the last 10 days (linear regression, $r^2 = 0.71$).

recorded across 10 days, while juveniles of 70 DPH altered their songs. Interestingly, we found the negative correlation between the amount of song changes in the last 10 days and the amount of NCM projections in HVC, suggesting NCM-HVC projections are involved in song maturation (Fig 2).

B. Early experience dependent NCM-HVC circuit maturation

Our recent study revealed retained axonal projection in HVC from TS-responsive NCM neurons in adults which had enriched song learning experiences. To further investigated what kinds of and which time of song experiences regulate NCM-HVC neuronal circuit maturation and its modulations, we raised zebra finch juveniles with two tutors sequentially. They were raised by the first tutor (T1) and isolated with various timing and durations, then were exposed to the second tutor for two hours as indicated in Figure 3. The projections from the neurons in the NCM which were activated by the playback of the T1 songs and T2 singing of the second tutor (T2) were examined by using AAV (AAV-CFOS-TetOn-GFP & CFOS-TetOff-RFP) techniques.

Interestingly, with the song learning experiences from the T1, only a couple of hours exposure to T2 yielded axonal projections into HVC from the NCM activated by hearing of T2 singings, while those projections were not observed in the juveniles which were exposed to the T1 only the first 10 days of hatching and did not learn from them (Fig 3). Further investigation would tell us how NCM-HVC neuronal circuit maturation is determined by experiences and ultimately regulate song learning capacity.

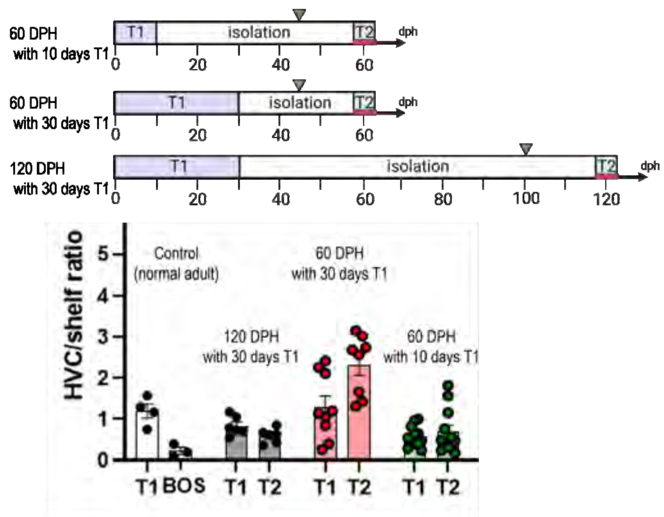


Fig. 3: Song learning experiences regulate NCM-HVC projections
Sequential song learning from two tutors with various timing and durations (top), and the amount of projections in HVC from the NCM neurons activated by the playback of the first tutor song (T1) and hearing of the second tutor singing (T2).

III. Future Perspective

Neuronal circuit reshaping with experiences during development has been well reported. Our studies, revealing transient neuronal projections subserving developmental auditory memory guided vocal learning, suggest novel concept of neuronal circuit rewiring for balancing acquiring new vocal patterns, while ensuring consistent motor patterns by limiting the temporal window of sensory-guided motor learning. We further suggest here that the early experiences might accelerate additional neuronal circuit wiring and enhance neuronal circuit capacity. Our future experiments in coming years would tell us how early experiences regulate interareal auditory-motor neuronal circuit maturate and underlaying molecular machinery.

Our research might help us to understand the neuronal mechanism for adult language learning of bilingual kids and to develop a new rehabilitation tools by using increased neuronal circuit capacities with training in early period.

References

[1] Yanagihara S. and Yazaki-Sugiyama Y. (2016) Auditory experience dependent cortical circuit shaping for memory formation in bird song learning. ***Nat. Commun***, doi: 10.1038/NCOMMS11946. (featured article)

[2] Katic K., Morohashi Y. and Yazaki-Sugiyama Y._Neural Circuit for Social Authentication in Song Learning. ***Nat. Commun*** (2022) 13(1):4442. doi: 10.1038/s41467-022-32207-1

[3] Pan, L., Ke, H. & Styles, S.J. Early linguistic experience shapes bilingual adults' hearing for phonemes in both languages. *Sci Rep* **12**: 4703, DOI: 10.1038/s41598-022-08557-7, (2022).

[4] Oh, J.S., Jun, S.A., Knightly, L.M. & Au T.K. Holding on to childhood language memory. *Cognition* **86**: B53-64, (2003).

A05-7 Annual report of research project

Riki Matsumoto
Division of Neurology, Kobe University Graduate School of Medicine

***Abstract*—To elucidate the Hyper-Adaptability mechanism of motor function under aging and pathological conditions, it is essential to understand the hyper-adaptability of the premotor cortex that integrates the information top-down from the prefrontal cortex and bottom-up from the parietal lobe. In this fiscal year, in order to understand the brain network associated with motor control and hyper-adaptive reorganization, we continued to construct an electrophysiological connectome using cortico-cortical evoked potentials (CCEPs) as an index of effective connectivity obtained by systemic evaluation of the whole implanted electrodes. We clarified the distinct CCEP connectivity patterns from each subregion of the medial parietal cortex. We also elucidated that the CCEP late-latency potentials (N2 responses) well correlated with the resting-state fMRI functional connectivity in the HCP database. From clinical point of view, we elucidated the CCEP connectivity changes associated with the epileptic network and those with supplementary motor area syndrome. We proceed with EEG or ECoG network analysis using a time-varying graphical lasso for sleep stating and understand the network dynamics during reach-to-grasp movement.**

I. Introduction

In order to elucidate the Hyper-Adaptability mechanism of motor function under aging and pathological condition, it is essential to understand hyper-adaptability of the premotor cortex that integrates the information top-down from the prefrontal cortex and bottom-up from the parietal lobe. For epilepsy surgery, it is crucial to fully resect the epileptic focus to cure the disease. At the same time, it is also important to preserve brain functions. As a part of presurgical evaluations for intractable focal epilepsy, patients undergo chronic implantation of subdural electrodes when the focus is not well determined by non-invasive evaluations or the focus is located around the important functional cortices. For functional mapping, we usually record neural activities (e.g., ERPs, high gamma activities) while patients complete a task, and then locate the cortex responsible for a particular task by delineating functional impairment during high-frequency electrical cortical stimulation (ECS). Although we apply various methods in epilepsy surgery, we still have difficulties in predicting the functional disabilities or recovery after resection surgery.

In the present research group "Hyper-Adaptability," for investigating the acute and subacute (hyper) adaptation at the network level, we aimed to investigate the impact of the resection of the premotor area by simulating the virtual lesion using the electrophysiological connectome and comparing it with the movement disability and its recovery after surgery. This fiscal year, we studied the relationship between the effective connectivity of CCEP and the resting-state functional connectivity of the Human Connectome Project (HCP) database and modification of the brain network in epilepsy patients. Additionally, we clarified the network pathophysiology of supplementary motor area (SMA) syndrome by longitudinal evaluation of the resting-state functional connectivity.

II. Aim of the Group/Methods

Subjects are patients with intractable partial epilepsy who underwent chronic subdural electrode implantation in the frontal & parietal areas for presurgical evaluations and gave written consent to the research protocols IRB#C533, 443, 1062, B230150, B230128.

In order to understand the brain network associated with motor control, we make an electrophysiological connectome by using CCEP as an index of effective connectivity, which were obtained by systemic stimulation and evaluation of the whole implanted electrodes. We have studied the differences in connectivity in the medial parietal lobe by CCEP, the association between effective connectivity of CCEP and resting-state functional connectivity in the Human Connectome Project (HCP) database, and the association between network alterations due to epilepsy pathology and seizure outcomes after focal resection. We also promote inter-group collaborative researches on the Time-Varying Graphical Lasso (TVGL) for analysis of intracranial and scalp EEG recordings with Group B. We published papers on the CCEP connectivity differences in the medial parietal lobe, and the dynamics of cortical interactions in visual recognition of object category (living vs. non-living) using ECoG high gamma activities.

III. Research Topics

We have carried out the following three research projects.

A. Comparison of effctive connectivity by CCEP with functional connectivity in the HCP database and exploration of brain connectivity alternation in patients with epilepsy

Using the CCEP, we showed differences in connectivity within the medial parietal lobe, with the anterior precuneus having connection with the premotor cortex, the posterior precuneus with the occipital lobe, and the posterior cingulate gyrus with the medial frontal lobe. These findings suggest that these regions are differentially involved in motor and visual functions [1]. We also clarified dynamics of the cortical interactions in visual recognition of object category - living vs. non-living. Specifically, we showed that the information processing within the posterior area of the basolateral temporal lobe is larger for living objects than non-living objects at around 250 ms after visual presentation [2]. Comparison between CCEP connectivity and HCP functional connectivity database revealed a strong correlation between CCEP N2 potentials and functional connectivity [3]. With regards to epileptogenicity, network alterations were observed in epileptic foci and areas with strong epileptogenicity (highly irritative area), but not in areas with weak epileptogenicity (less irritative area). [4].

B. Longitudinal functional connectivity assessment of motor compensatory mechanisms by human motor cortical network

In brain tumor neurosurgery, we experience patients who develop paresis despite preservation of motor evoked potentials originating from the primary motor cortex (M1) after removal of lesions in the premotor cortex (supplemental motor area (SMA) syndrome). The network alteration patterns underling SMA syndrome were investigated by longitudinal fMRI evaluation before and after surgery. We found that preserved anatomic connectivity but altered functional connectivity among cortical motor areas is involved in the development of SMA syndrome. Future studies are aimed at elucidating the hyperadaptation of cortical motor networks that play a role in the recovery process of SMA syndrome.

C. Application of new network analyses for evaluation of network dynamics using intracranial EEG and scalp EEG

Together with the Kondo and Nambu Groups of Group B, we are applying the TVGL technique to scalp EEG during sleep and intracranial EEG during reaching and grasping movements to analyze the brain network at each sleep stage and during reaching and grasping movements. Sleep staging is possible based on the network dynamics in the brain. We also elucidated network dynamics in the frontal and parietal lobes during reaching and grasping movements.

In addition, we developed a novel dimensionality compression algorithm (representational similarity learning) for multidimensional, graded representations, and clarified the gradients and dynamism of semantic representations in the human anterior temporal lobe [6]. We have clarified the electrophysiological network between cortices by measuring stimulus-evoked brain potentials using intracranial electrodes. For comprehensive understanding of the brain connectome, it is also very important to study how the white matter fibers connect to the cortices. To establish electrical tracing of the white matter fibers, we have refined the methods and reported the characteristics of the evoked waveforms in two international journals [7][8].

IV. Future Perspective

In this research project, we employed the large retrospective CCEP data and some prospective data to construct electrophysiological or CCEP connectomes related to the premotor area to elucidate the network characteristics at both individual and group levels. We investigated the effect of high-frequency electrical cortical stimulation based on the CCEP connectivity, its correlation with functional connectivity by fMRI, and its alteration by epileptic pathology. The electro-physiological CCEP connectome can contribute to individual patients for surgical strategy. At the group level, it is regarded as one of the gold standard references to validate the mathematical and analytic models and non-invasive connectome for the understanding hyper-adaptability of the human brain and its clinical application.

References

[1] Togo M, Matsumoto R, Usami K, et al. Distinct connectivity patterns in human medial parietal cortices: evidence from standardized connectivity map using cortico-cortical evoked potential. ***Neuroimage*** 2022;263:119639 DOI: 10.1016/j.neuroimage.2022.119639

[2] Usami K, Matsumoto R, Korzeniewska A, et al. The dynamics of cortical interactions in visual recognition of object category: living vs non-living. ***Cereb Cortex***. 2022 Nov 20:bhac456. doi: 10.1093/cercor/bhac456.

[3] 十河 正弥, 林 拓也, 麻生 俊彦ら. 皮質皮質間誘発電位(CCEP)の N2 電位は安静時 fMRI 機能的結合性と相関する：Human Connectome Project（HCP）データベースとの比較研究. 第 52 回臨床神経生理学会.2022/11/24-26. (口演)

[4] Togo M, Matsumoto R, Kobayashi K, et al. Network modification in irritative zones of epilepsy patients: a comparison of CCEP with HCP database. 第 64 回日本神経学会, 2023/5/31-6/3.

[5] Yamao, Sawamoto N, Kuieda T, et al. Changes in distributed motor network connectivity correlates with functional outcome after surgical resection of brain tumors. ***Neurosurgery open*** 4(1):e00028, March 2023. | DOI: 10.1227/neuprac.0000000000000028.

[6] Cox CR, , C.R., Rogers, T.T., Shimotake, A., et al. Representational similarity learning reveals a graded multidimensional semantic space in the human anterior temporal cortex. ***Imaging Neuroscience***, 2024, Advance Publication. https://doi.org/10.1162/imag_a_00093

[7] Rossel O, Schlosser-Perrin F, Duffau H, et al. Short-range axono-cortical evoked-potentials in brain tumor surgery: Waveform characteristics as markers of direct connectivity. ***Clin Neurophysiol.*** 2023 Sep;153:189-201. doi: 10.1016/j.clinph.2023.05.011.

[8] Schlosser-Perrin F, Rossel O, Duffau H, et al. The orientation of the stimulating bipolar probe modulates axono-cortical evoked potentials. ***Brain Stimul***. 16:1009-1011, 2023. doi: 10.1016/j.brs.2023.06.008. Epub 2023 Jun 15

A05-8 Annual report of research project

Hiroyuki Miyawaki
Osaka Metropolitan University

***Abstract*—Animals that have undergone traumatic experiences develop maladaptive states, characterized by an inability to exhibit adaptive behavior. Subsequent fear-extinction learning can induce a hyper-adaptive state that allows these animals to recover their capacity for adaptive behaviors. However, the neural mechanisms underlying these processes are not well understood. This study aimed to elucidate the changes in the inter-regional network during the transition to maladaptive states and into the hyper-adaptive states. Employing multi-regional large-scale electrophysiological recording techniques, we tracked the activity of neuronal cell ensembles in the ventral hippocampus, basolateral amygdala, and prefrontal cortex during fear conditioning and extinction learning. We found that the composition of coactivated pairs changed through extinction learning, although the fraction of significantly coactivated ensemble pairs remained similar. Furthermore, ensembles participating in inter-regional coactivation were more likely to be active in subsequent retention-of-extinction sessions. These results suggest a correlation between participation in inter-regional coactivity and the stability of cell ensembles. However, the causal relationship between the stability of cell ensembles and inter-regional coactivity remains to be elucidated. This aspect requires further exploration, particularly through the manipulation of inter-regional coactivity in future studies.**

I. Introduction

Aversion and fear responses to situations associated with harmful stimuli are crucial for the survival of animals. However, when the memory of fear is too strong, maladaptive behaviors such as showing fear responses even in safe environments can occur. In humans, such maladaptive states are known as Post-Traumatic Stress Disorder (PTSD), which impairs quality of daily life. The development and treatment of PTSD have been actively studied through animal models of fear conditioning and its extinction learning. Previous research suggests that the extinction of fear memories is not forgetting but rather a process of recovering adaptive behavior while retaining the memory of fear [1], which can be considered as a hyper-adaptation process. It has been clarified that brain regions such as the amygdala, ventral hippocampus, and prefrontal cortex play a crucial role in fear conditioning and extinction learning [2]. However, it remains unclear how the network between these brain regions changes during the transition from a maladaptive state caused by fear memory to a hyper-adaptive state and how these changes are controlled. Clarifying these points is expected to advance the understanding of the pathology and recovery processes of disorders related to memory and emotions such as PTSD and anxiety disorders, leading to insights for the development of effective treatments of these disorders.

II. Aim of the Group

This research aims to elucidate the changes that occur in the brain during the transition to a maladaptive state caused by fear memory and to clarify how these changes are overcame in process of hyper-adaptation. The representation of information in the brain is thought to be carried out by "cell ensemble," which are relatively small groups of cells that are synchronously activated, and the presence of cell ensembles has been reported in various brain regions such as the hippocampus, amygdala, and cerebral cortex [3]. Furthermore, this research project has revealed that the transition to a maladaptive state due to fear conditioning leads to inter-regional coactivation of cell ensemble [4]. In the previous year's research, it was revealed that new cell ensemble, are formed through the hyper-adaptation process (i.e. extinction learning), extinction learning. Building on this result, this year we focused on the changes in inter-regional coactivation of cell ensemble through extinction learning. The results imply that inter-regional coactivation may stabilize participating cell ensembles in the local circuits.

III. Research Topics

A. *Analysis of inter-regional coactivation of cell ensembles identified during extinction learning*

Using a multi-regional large-scale electrophysiological recording technique, which allows us to record activities of multiple neurons in various brain regions simultaneously from freely behaving rats, we recorded the activities of neurons in the basolateral amygdala (BLA), ventral hippocampus CA1 region (vCA1), and layer 5 of the prelimbic cortex (PL5). During these recordings, fear conditioning learning, extinction learning, and retention of extinction tests were conducted [4]. Furthermore, independent component analysis (ICA) was used to identify cell ensemble active during each of the behavioral session in each brain region. Previous studies have shown that among cell ensembles identified during fear conditioning, the proportion of inter-regional pairs which significantly coactivated were larger in post-learning sleep than pre-learning sleep [4]. The same analysis was performed on cell ensembles identified during extinction learning, but no significant change in the proportion of coactivated ensemble pairs was detected through extinction learning. (Fig.1; $p > 0.64$, Fisher's exact test). This suggests that, unlike fear conditioning learning, extinction learning does not enhance inter-regional coactivation.

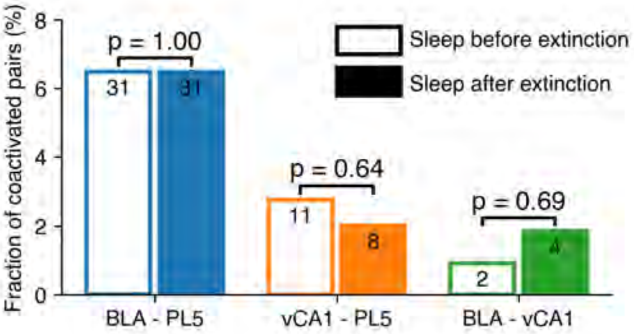


Fig. 1. The proportion of ensemble pairs showing significant coactivation during sleep before and after extinction learning.

Next, the pairs of cell ensembles that showed significant coactivation during post-extinction learning sleep were classified into two groups, those that had coactivated during pre-extinction learning sleep (preserved pairs) and those that had not (generated pairs). Although the proportion varied between region pairs, considerable fractions of pairs (25.8% to 75.0%) were categorized as the generated pairs (Fig. 2). This suggests that extinction learning causes a recombination of coactivated cell ensembles.

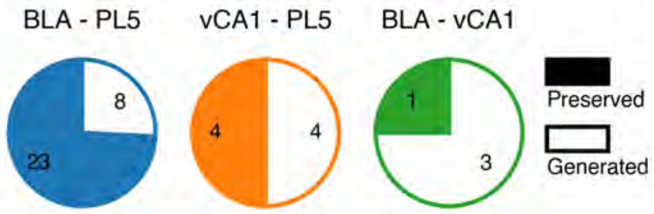


Fig. 2. The proportion of genereated and preserved pairs among coactivated ensemble pairs during sleep after extinction learning.

B. *Relationship between coactivation observed after extinction learning and the maintenance of cell ensembles*

Next, we examined the possibility that inter-regional coactivation of cell ensembles during post-extinction sleep may be related to whether the cell ensembles were maintained until the retention of extinction sessions. Cell ensembles detected during extinction learning were classified based on whether they showed synchronous activity with ensembles in other regions during post-extinction sleep, and the proportion of ensembles maintained until the retention of extinction sessions was calculated for each group (Fig. 3). The cell ensembles involved in coactivation were maintained more than those that did not have coactivation partner (p=0.03, Fisher's exact test). Similar trends were observed when examining individual brain regions separately. These results suggest that inter-regional coactivation may contribute to the stabilization of cell ensembles.

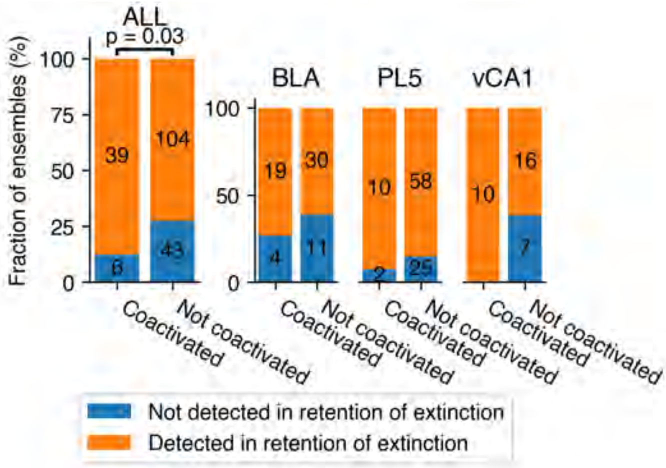


Fig. 3. The proportion of ensembles active during the extinction retention task, categorized by whether they showed synchronous activity during sleep after extinction learning.

IV. Future Perspective

This study revealed that although there was no change in the strength of inter-regional coactivation through the extinction learning of fear memory, there were changes in the components of the coactivations. Additionally, our results suggest that participation in inter-regional coactivation is related to the stability of cell ensembles. However, it is not clear whether stable cell ensembles are more likely to participate in synchronous activity or inter-regional coactivation stabilizes cell ensembles. In the future, we would like to clarify this point through intervention experiments on synchronous activity.

References

[1] Furini, C., J. Myskiw, and I. Izquierdo, *The learning of fear extinction.* Neurosci. Biobehav. Rev., 2014. **47**: p. 670-83.

[2] Tovote, P., J.P. Fadok, and A. Luthi, *Neuronal circuits for fear and anxiety.* Nat. Rev. Neurosci., 2015. **16**(6): p. 317-31.

[3] Tonegawa, S., Liu, X., Ramirez, S., and Redondo. R., *Memory engram cells have come of age.* Neuron, 2015. **87**(5): p 918-31

[4] Miyawaki, H., and Mizuseki, K., *De novo inter-regional coactivations of preconfigured local ensembles support memory.* Nat. Commun. 2022. **13**(1)**:** 1272.

A05-9 Annual report of research project

Takaki Maeda, Oi Hiroki, Tsukasa Okimuta
(Department of Neuropsychiatry, Keio University School of Medicine)
Yuichi Yamashita
(Department of Information Medicine,
National Institute of Neuroscience, National Center of Neurology and Psychiatry)

Our research project aims to reveal neural mechanisms of sense of agency (SoA). Moreover, we intend to study pathophysiology of neurological and psychiatric illnesses which show abnormal SoA. Then, we try to establish the method to recover from those illness through reorganization of neural systems on the SoA. We have studied methodology to intervene learning (updating) mechanisms of the internal prediction model for the SoA using original digital device and applications. Our approach is based on the basic premise that controllability is rewarding. Actually, we have developed experimental settings where temporal or spatial biases are introduced in order to make controllability ambiguous. Moreover, we designed experiments which evaluate hierarchical level (bottom-up ～ top-down process) of SoA emergence, and we have shown that pathophysiology of schizophrenia would be in the level of bottom up process.

I. Introduction

We have studied pathophysiology of neurological and psychiatric illnesses from the stand of the sense of agency(SoA). Our approach is based on the basic premise that controllability is rewarding. Actually, we have developed experimental settings where temporal or spatial biases are introduced in order to make controllability ambiguous. We have studied pathophysiology of mental illnesses including schizophrenia from the standpoint of hierarchical level (bottom-up～top-down process) of SoA emergence.

II. Aim of the Group

Our research project aims to reveal neural mechanisms of SoA. Moreover, we intend to study pathophysiology of neurological and psychiatric illnesses which show abnormal SoA. We have studied methodology to intervene learning (updating) mechanisms of the internal prediction model for the SoA using original digital device and applications.

III. Research Topics

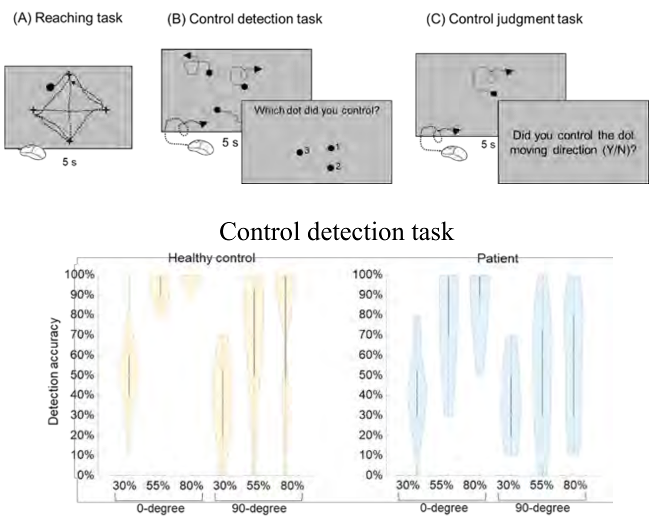
A. Aberrant sense of agency induced by delayed prediction signals in schizophrenia: a computational modeling study [1]

Aberrant sense of agency (SoA, a feeling of control over one's own actions and their subsequent events) has been considered key to understanding the pathology of schizophrenia. Behavioral studies have demonstrated that a bidirectional (i.e., excessive and diminished) SoA is observed in schizophrenia. Several neurophysiological and theoretical studies have suggested that aberrancy may be due to temporal delays (TDs) in sensory-motor prediction signals. Here, we examined this hypothesis via computational modeling using a recurrent neural network (RNN) expressing the sensory-motor prediction process. The proposed model successfully reproduced the behavioral features of SoA in healthy controls. In addition, simulation of delayed prediction signals reproduced the bidirectional schizophrenia-pattern SoA, whereas three control experiments (random noise addition, TDs in outputs, and TDs in inputs) demonstrated no schizophrenia-pattern SoA. These results support the TD hypothesis and provide a mechanistic understanding of the pathology underlying aberrant SoA in schizophrenia.

B. Hierarchical Components of Sense of Agency in Schizophrenia: From Motor Control to Self-Attribution [2]

The sense of agency refers to the feeling of initiating and controlling one's actions and their resulting effects on the external environment. Abnormal sense of agency has been reported in patients with schizophrenia. Previous studies have uncovered behavioural evidence of excessive self-attribution and, conversely, a reduction in sense of agency. This apparent paradox has yet to be fully resolved. In the current study, we employed three behavioural tasks utilising the same stimuli and experimental design to systematically evaluate multiple factors that influence sense of agency. These tasks included motor control, sensorimotor processing, and self-attribution. In all three tasks, participants' real-time mouse movements were combined with prerecorded other's motions with an angular bias of either 0 or 90 degrees. In the reaching task, participants were asked to move a dot to touch a target on the screen as frequently as possible. The control detection task required participants to identify one target dot among three moving dots whose motion incorporated a certain level of real-time mouse movement. In the control judgement task, participants made a binary yes/no response to indicate whether they felt they had control over the direction of one moving dot on the screen. The results indicated that patients with schizophrenia performed significantly worse on reaching and control detection tasks than healthy controls. However, their self-attribution judgement in the control judgement task was comparable to that of the healthy controls. The patient group seemed to retain the ability to evaluate the contingency between sensory and motor information; however, their capacity to use this sensorimotor information as a cue to detect control in a noisy environment was compromised. Subsequent cluster analysis revealed that the combined performance results of the three tasks accurately distinguished patients from healthy controls. To understand the interplay between the hierarchical 3 components of sense of agency, we propose that both top-down and bottom-up sensorimotor signals processing is involved. Patients with schizophrenia show notably stronger dysfunction in bottom-up processes than in top-down processes.

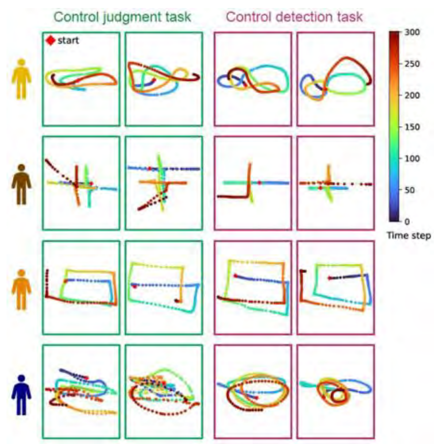
Fig.1. Motor Control Tasks



C. *The sense of agency from active causal inference* [3]

This study investigates the active component of the sense of agency (SoA) which is often overlooked in the literature, and posits that SoA is fundamentally an outcome of active causal inference regarding one's own actions and their impact on the environment. Participants engaged in tasks requiring control over visual objects via a computer mouse, with tasks designed to test their ability to judge control or detect controlled objects under varying noise conditions. Our findings reveal that participants actively formed high-level, low-dimensional action policies (plans) that were idiosyncratic across but consistent within individuals to effectively infer their degree of control in a noisy environment. Employing transformer-LSTM-based autoencoders, we captured these low-dimensional action plans and demonstrated that the geometrical and dynamical properties of these action plans could predict behavioural profiles in the tasks with remarkable accuracy. This suggests that participants' sense of control is shaped by actively altering action plans, viewed as generating causal evidence through intervention. Further, participants proactively expanded the diversity of their action plans, as measured by the dimensionality of the action plan distribution. It facilitates the exploration of the available action plan options while concurrently accumulating causal evidence for the inference process. Contrarily, patients with schizophrenia exhibited reduced action plan diversity, suggesting limited active control inference and impaired detection of self-relevant cues. Yet, their judgment responses closely matched predictions from the geometrical and dynamical aspects of their action plans, indicating that they adapt a proper decision boundary to optimise their active inference about their causal role in environmental changes. In conclusion, these findings expand our knowledge, offering a more comprehensive understanding of the sense of agency, deeply rooted in the process of active causal inference.

Fig.2. Motion trajectory during motor control tasks



IV. Future Perspective

We have shown that pathophysiology of schizophrenia would be in the level of bottom up process. Then, we would like to intervene learning (updating) mechanisms of the internal prediction model for the SoA in the level of bottom up process.

References

[1] Tsukasa Okimura et al. (2023). Aberrant sense of agency induced by delayed prediction signals in schizophrenia: a computational modeling study. Schizophrenia ;9(1):72.

[2] https://osf.io/preprints/psyarxiv/y3aes

[3] https://www.biorxiv.org/content/10.1101/2024.01.29.577723

A05-10 Annual report of research project

Tomohiko Takei, Akihiro Masaoka
Brain Science Institute, Tamagawa University

***Abstract*—"Hyper-Adaptability" is the extraordinary plasticity that animals show at a recovery from a large-scale restructure of the central nervous system (e.g., spinal cord injury) or musculoskeletal systems (e.g., tendon transfer). To elucidate the neural mechanisms for the hyper-adaptability, it is necessary to identify the flexibility and constraints of the adaptation in the central nervous system. This research project aims to identify low-dimensional spaces of a fronto-parietal cortical neural activity, which is called the "neural manifold", in monkeys performing a flexible feedback motor task to reveal the neural dynamics for adaptive motor behavior. Monkeys were trained to perform a context-dependent feedback motor control task, and fronto-parietal cortical neural activity was recorded with electrocorticogram (ECoG). The results showed that the context-dependent neural components are sustained over preparatory and response periods, while the response-dependent components emerged after the perturbation applied. Moreover, the context and response dependent components are separately represented in premotor cortex and motor-parietal network, respectively. These results suggests that context-dependent activity in premotor cortex switch the neural manifolds represented in motor-parietal network to achieve flexible feedback motor control.**

I. Introduction

In the mammalian central nervous system, acute and chronic injuries cause a large-scale neural network restructure, or "Hyper-Adaptability," that is beyond the extent of normal adaptation. For example, in monkeys hemiparalysed due to spinal cord injury, the ipsilateral motor cortex, which is normally inactive in healthy condition, is activated, and bilateral motor cortex takes place in a motor control of paralyzed hand that is different from the normal contralateral motor control [1,2]. It is also known that the visual cortex, which is normally inactivated by tactile stimulation, is activated when a visually impaired person performs Braille tactile reading [3]. What has become clear from the observation of these series of "Hyper-Adaptability" phenomena is that these large-scale plastic changes do not occur randomly in the central nervous system, but under certain constraints. For example, in the example of spinal cord injury, bilateral primary motor cortex is active in the early stages of recovery, but in the later stages, activity of primary motor cortex is again confined to the contralateral side [1].

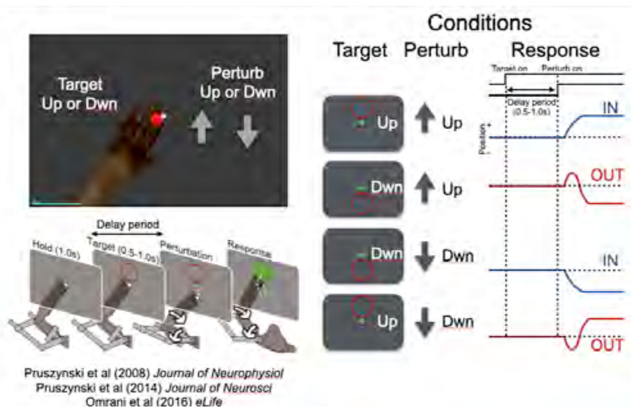


Figure 1 Context-dependent flexible feedback motor control task (INOUT task)

Recent studies have shown that the coactivation pattern of neuronal populations in the motor cortex (primary motor cortex and premotor cortex) remains largely unchanged when monkeys are subjected to standard motor learning tasks such as visuomotor rotation and force field adaptation tasks [4]. The coactivation pattern of neuronal population is called the "neural manifold" and has been shown to be stable over a long term for years [5] and across different behaviours [6]. This neural manifold constrains the adaptability of the central nervous system. Using a brain-computer interface (BCI), monkeys were trained to move a cursor by either activating motor cortex neurons with a different coactivation pattern than original manifold (out of manifold) or coactivating them within the original manifold (within manifold). The results showed that the within manifold condition can be learned in a few hours of training, whereas it requires a longer period of learning over several days for the out of manifold condition [7]. These findings suggest that (1) a stable neural manifold exists in the motor system, which enables stable but flexible motor control and motor learning, and (2) adaptation to deviate from this neural manifold requires a longer period of training to induce significant neural circuit restructure. Based on these findings, we hypothesized that "normal adaptation" occurs in existing neural manifolds, whereas "Hyper-Adaptability" requires restructuring of new neural manifolds".

II. Aim of the Group

The purpose of this research program is to establish a method for recording fronto-parietal cortical neural activity in monkeys to identify neural manifolds, as well as to understand neural dynamics during adaptive behavior based on neural manifolds.

III. Research Topics

A. *Establishment of a technique for recording fronto-parietal cortical activity in monkeys performing a flexible feedback motor task*

Two macaque monkeys were trained to perform a flexible feedback motor task in which motor response to a perturbation is needed to be changed in a context-dependent manner (INOUT task, Figure 1). By attaching an exoskeleton robot (KINARM) to the monkeys' arm, the kinematics of the shoulders and elbows were measured and the hand position was fed back online on a computer screen. The animal's feedback response was evaluated by applying a torque perturbation to the arm during the task. In each trial, a target was first presented as a contextual cue at one of the UP and DOWN locations. After a delay period, the monkey's arm was perturbed in one of the two directions (UP or DOWN). With the presentation of the perturbation, the initial target disappeared, and the monkey was required to make a quick reaching to the target in the presence of the perturbation. When the target direction and the perturbation directions are congruent, the monkey does not need to actively exert force because the monkey's arms are pushed toward the target direction (IN condition). On the other hand, when the target direction and the perturbation direction are opposite, the monkey needs to exert more force because it needs to reach the target against the perturbation (OUT condition). Thus, this task requires varying the response to the disturbance depending on the context (target location). Two monkeys that had completed training were implanted with electrodes of a 32-channel cortical electroencephalogram (ECoG). With these techniques, we succeeded in simultaneously recording the cortical activity of dorsal premotor (PMd), primary motor (M1), primary somatosensory (S1), and parietal area 5 (A5) during the task.

B. Identification of fronto-parietal cortical neural dynamics during a flexible feedback motor task

We applied frequency decomposition analysis to ECoG signals recorded from the monkey's fronto-parietal cortex during the INOUT task to examine the neural dynamics during motor preparation and during motor response. First, the results showed that the β-band (15-35 Hz) power of the PMd prominently changed in response to the target position during the preparation period after the target presentation (Fig. 2). Then, we further performed a low-dimensional decomposition analysis (demixed principal component analysis [8]), in which signal components dependending on the task parameters (target position and motor response) were extracted, and found that the target-dependent componts emerged during the motor preparation period and sustained to the response period, while the response-dependent component emerged after the perturbation was presented. Furthermore, the target-dependent components were mainly encoded in the PMd, whereas the response-dependent components involved the M1 and posterior parietal cortex (PPC). These results suggest that target-dependent cortical activity in the PMd switches the neural manifold of the M1-PPC to achieve the context-dependent feedback motor control.

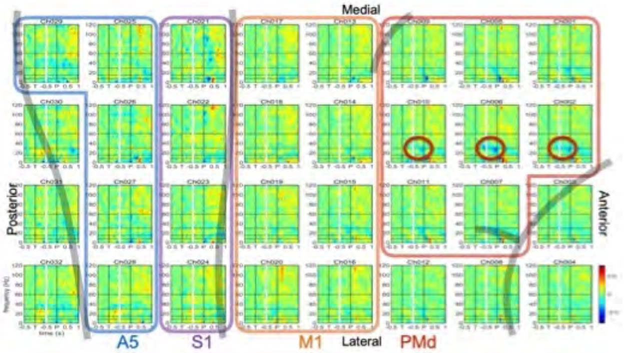


Figure 2 Neural dynamics of the fronto-parietal network during the INOUT task. PMd: dorsal premotor cortex; M1: primary motor cortex; S1: primary somatosensory cortex; A5: parietal area 5.

IV. Future Perspective

We trained a flexible feedback response task in two macaque monkeys and recorded fronto-parietal cortical activity (ECoG). The results showed that the target-dependent component mainly encoded in PMd sustained from preparatory and response periods, while the response-dependent components encoded inM1-PPC are emerged after the perturbation. These results suggest that motor responses to the sensory input (perturbation) are adaptively selected by switching neural manifolds in the neural activity space according to context, and are expected to provide fundamental insights for understanding the neural mechanisms of Hyper-Adaptability.

[1] Nishimura Y, Onoe H, Morichika Y, Perfiliev S, Tsukada H, Isa T (2007) Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury. Science (New York, NY) 318:1150–1155.

[2] Isa T (2016) Dexterous Hand Movements and Their Recovery After Central Nervous System Injury. Annu Rev Neurosci 42:1–21.

[3] Sadato N, Okada T, Honda M, Yonekura Y (2002) Critical Period for Cross-Modal Plasticity in Blind Humans: A Functional MRI Study. Neuroimage 16:389–400.

[4] Perich MG, Gallego JA, Miller LE (2018) A Neural Population Mechanism for Rapid Learning. Neuron 100:964-976.e7.

[5] Gallego JA, Perich MG, Chowdhury RH, Solla SA, Miller LE (2020) Long-term stability of cortical population dynamics underlying consistent behavior. Nature neuroscience 23:260–270.

[6] Gallego JA, Perich MG, Naufel SN, Ethier C, Solla SA, Miller LE (2018) Cortical population activity within a preserved neural manifold underlies multiple motor behaviors. Nature communications:1–13.

[7] Sadtler PT, Quick KM, Golub MD, Chase SM, Ryu SI, Tyler-Kabara EC, Yu BM, Batista AP (2014) Neural constraints on learning. Nature 512:423–426.

[8] Kobak D, Brendel W, Constantinidis C, Feierstein CE, Kepecs A, Mainen ZF, Qi X-L, Romo R, Uchida N, Machens CK (2016) Demixed principal component analysis of neural population data. Elife 5:e10989.

A05-11 Annual report of research project

Hironobu Osaki
Doshisha University

***Abstract*— Following cortical infarction, the activity of the remaining areas of the brain is upregulated. Such up-regulation is often considered necessary for functional recovery, but it does not always facilitate it. To investigate which areas aid in functional recovery and which do not, we analyzed the changes in cortical activity following cortical infarction. To study the change in cortical activity after cortical infarction, we have developed a macro Ca2+ imaging system to observe neural activity during a limb movement task in rodents. The movement of the forelimb was monitored and analyzed to reconstruct the estimation of the 3D position. The neural activity related to forelimb movement was successfully monitored. Optical stimulation controlled by a galvo-scanning system was used to modify the movement of a forelimb by optogenetically stimulating a forelimb region of the motor cortex. Furthermore, we investigated cognitive deficits in addition to motor function after cortical infarction. Our aim is to develop an effective modulation of brain activity after infarction by combining these strategies.**

I. Introduction

Functional recovery following cerebral cortex infarction is involved in compensatory mechanisms in the remaining neural circuits. For instance, when the primary motor cortex (M1) is damaged, the activity of the ipsilateral higher motor [1] and somatosensory [2] areas is increased. Furthermore, in cases of large infarctions, increased activity is often observed in the contralateral (healthy) hemisphere of the injured side.

Stimulating neuronal activity by a transcranial magnetic or an electrical stimulation of the injured hemisphere has been found to be effective, and optogenetics has shown promise in experimentally restoring function. The relationship between the increase in neural activity across multiple regions and functional recovery has not been fully explained. Studies using animal models of cortical infarction are needed to clarify this relationship. However, the relationship between the increase in neural activity in these different regions and functional recovery has not been fully elucidated. For example, in the primary motor cortex (M1), infarction causes a release of inhibition in the directly connected primary somatosensory cortex, resulting in a transient decrease in tactile information processing [2] and a decrease in sensory function. Thus, such non-specific post-infarct hyperactivity is not necessarily an effective change for functional recovery.

The results that optogenetic activation of peri-infarct region is effective for functional recovery [3], whereas activation of the healthy side prevents functional recovery of the damaged side [4], suggest that region-selective neuromodulation is beneficial for functional recovery after infarction. In addition to such region-selective activity control, it is expected that more effective methods for functional recovery will be found when stimulus timing and schedule are also investigated.

II. Aim of the Group

The aim of the group is to develop a method to promote functional recovery after cortical infarction by controlling specific neural circuits, focusing on functional changes in neural circuits from the acute to the chronic phase of stroke. Using an animal model of cortical infarction, we will perform functional imaging of neural activity during a ladder-rung task that requires fine motor skills, observe how M1 changes before and after motor cortex infarction. Based on these observation we will develop a new strategy to promote functional recovery after stroke.

III. Research Topics

A. Long-term Ca2+ imaging before and after infarction

We have developed an in vivo Ca2+ imaging system during the animal is walking on the ladder-rung. Using this system, we measured the behavior of an animal model of photothrombotic cortical infarction and performed macro-imaging of the surrounding area, including M1. Specifically, a photothrombotic infarction was created with Rose Bengal in M1 [Fig. 1], and activity during locomotion of the ipsilateral and contralateral M1 of the animal was measured by Ca2+ imaging during a ladder-rung task. The Ca2+ sensor, GCaMP6f, was expressed in M1 by injecting an adeno-associated virus vector into the target region, and the endogenous signal and other noise affecting the Ca2+ signal were corrected. In order to observe the changes in activity over several months, image registration was performed using the vessel pattern.

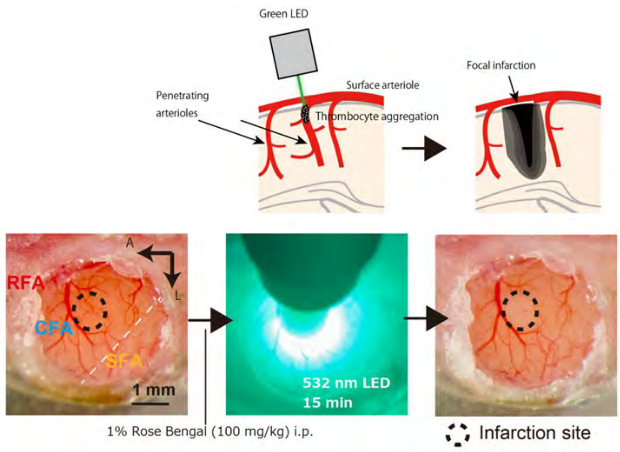


Fig. 1. Photothrombosis using Rose Bengal and green LED. SFA, sensory forelimb area; CFA, caudal forelimb area; RFA, rostoral forelimb area.

To quantitatively assess motor dysfunction after infarction, pose estimation was performed using DeepLabCut [5] and 3D limb position was reconstructed [Fig. 2]. Infarction in the M1 forelimb region resulted in falling of contralateral forelimb and reduction in joint angle.

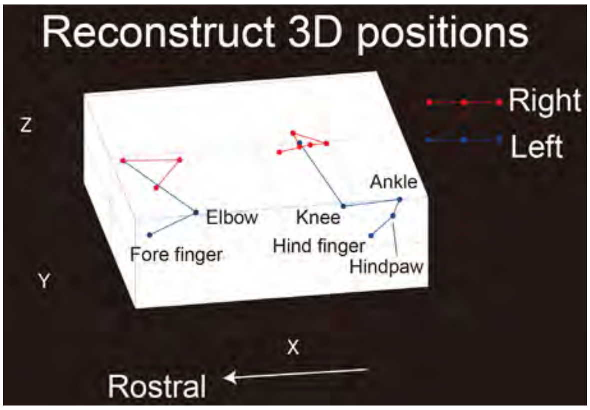


Fig. 2. Reconstruction of 3D positions from DeepLabCut

B. *Optogenetic neural modulation during behavioral task*

The system mentioned above can also control activity in specific brain regions by optogenetics controlled through X-Y Galvano-mirrors. We have confirmed that this system can control activity in motor-related regions and influence motor activity. We are currently using this system to identify brain regions that influence the long-term recovery process and to analyze the spatiotemporal stimulation patterns that are effective for recovery.

C. *Recovery process of attention disorder (collaboration with group B04)*

It has been suggested that the degree of functional recovery varies according to the location of the infarction. We investigated not only motor deficits but also cognitive deficits. Our group collaborated with group B04 (Ishii, Ibaraki Prefectural University of Health Sciences; Yozu, The University of Tokyo) by providing an analysis system, and investigated the relationship between the site of injury and the process of recovery from infarction.

The medial agranular cortex (AGm) is a region associated with several sensory areas and related to attention, and we have shown in rodent mice that damage to this region causes unilateral spatial neglect-like symptoms [6]. Because the AGm is a region with a longitudinal shape in the rostro-caudal direction, we created damage by photothrombosis and examined the recovery process to investigate the relationship between the position of damage and recovery. We found that the degree of recovery tended to be slower in the rostral AGm [7, under review]. In the present study, mice were asked to choose the direction of arms of 8 maze to estimate unilateral spatial neglect-like symptoms. Ishii and colleagues also summarized other methods for measuring spatial cognition in rodent models of unilateral neglect [8].

IV. Future Perspective

We summarize the results of the project. This year, we were able to quantify the recovery process after infarction in terms of motor and cognitive deficits using the M1 and AGm animal models of cortical infarction, respectively. Each analysis is automated using a machine learning combined with proprietary algorithms. This allows for many validations to be performed in a short period of time without human error. Furthermore, the multiple validations will be useful in the development of more effective interventions for functional recovery in the future.

References

[1] Y. Murata, N. Higo, T. Hayashi, Y. Nishimura, Y. Sugiyama, T. Oishi, H. Tsukada, T. Isa, H. Onoe, Temporal Plasticity Involved in Recovery from Manual Dexterity Deficit after Motor Cortex Lesion in Macaque Monkeys, J. Neurosci. 35 (2015) 84–95.

[2] A. Fukui, H. Osaki, Y. Ueta, K. Kobayashi, Y. Muragaki, T. Kawamata, M. Miyata, Layer-specific sensory processing impairment in the primary somatosensory cortex after motor cortex infarction., Sci Rep-Uk 10 (2020) 3771.

[3] M.Y. Cheng, E.H. Wang, W.J. Woodson, S. Wang, G. Sun, A.G. Lee, A. Arac, L.E. Fenno, K. Deisseroth, G.K. Steinberg, Optogenetic neuronal stimulation promotes functional recovery after stroke, Proceedings of the National Academy of Sciences 111 (2014) 12913‐12918.

[4] A.R. Bice, Q. Xiao, J. Kong, P. Yan, Z.P. Rosenthal, A.W. Kraft, K.P. Smith, T. Wieloch, J.-M. Lee, J.P. Culver, A.Q. Bauer, Homotopic contralesional excitation suppresses spontaneous circuit repair and global network reconnections following ischemic stroke, ELife 11 (2022) e68852.

[5] A. Mathis, P. Mamidanna, K.M. Cury, T. Abe, V.N. Murthy, M. Mathis, M. Bethge, DeepLabCut: markerless pose estimation of user-defined body parts with deep learning, Nat Neurosci 21 (2018) 1281–1289.

[6] D. Ishii, H. Osaki, A. Yozu, K. Ishibashi, K. Kawamura, S. Yamamoto, M. Miyata, Y. Kohno, Ipsilesional spatial bias after a focal cerebral infarction in the medial agranular cortex: A mouse model of unilateral spatial neglect, Behav Brain Res 401 (2021) 113097.

[7] D. Ishii, H. Osaki, A. Yozu, T. Yamamoto, S. Yamamoto, M. Miyata, Y. Kohno, Role of the medial agranular cortex in unilateral spatial neglect, BioRxiv (2023) 2023.11.24.568203.

[8] D. Ishii, H. Osaki, A. Yozu, S. Yamamoto, Y. Kohno, The rodent model of unilateral spatial neglect and its clinical applications, J. Rehabilitation Neurosci. (2024) 241201.

A05-12 Annual report of research project Hyper adaptive changes in spatial recognition

Rieko Osu
Faculty of Human Sciences, Waseda University
Kento Hirayama, Yuki Ito
Graduate school of Human Sciences, Waseda University
Taiki Yoshida
Faculty of Rehabilitation, School of Health Sciences, Fujita Health University
David W Franklin
Department of Sport and Health Sciences, Technical University of Munich

***Abstract*—When the right hemisphere is damaged by stroke, hemispatial neglect, in which the person ignores the visual space on the left side of the body, appears with relatively high frequency, even if the vision is normal. It often improves within a few months, but in long-term residuals, the 'not noticing' of objects in the left space can interfere with daily life. Various interventions have been tried, but there is currently no definitive method. This study aims to gain insight into the methodology and neural mechanisms of spatial attention to help improve hemispatial neglect through hyper-adaptive interventions. Using augmented reality (AR) technology, we developed a system that projects the entire visual space, including the left visual space, which is often missed by patients with hemispatial neglect, in their right visual field. The effectiveness of the system was confirmed through feasibility tests on patients with hemispatial neglect. In addition, experiments with healthy participants showed that self-generated movement enhanced attention to the direction of movement. These results lead to the development of attention promotion training in hemispatial neglect.Introduction**

I. Aim of the Group

A. AR-based intervention systems for hemispatial neglect

Prism adaptation therapy is a well-established clinical intervention for addressing spatial neglect in patients who have suffered right hemisphere brain damage due to a stroke or similar conditions. This therapy involves the use of prism glasses to shift the visual field 10 to 15 degrees to the right, thereby assisting patients in adapting to this altered visual perspective. It has been observed that such adaptation can lead to significant improvements in symptoms of spatial neglect once the glasses are removed [1]. Moreover, virtual reality (VR) systems have been developed to augment rehabilitation by promoting attention to the left side of space, demonstrating the potential for technology-assisted interventions [2]. However, while prism glasses directly modify the perception of real space, they are constrained by optical limitations. Similarly, VR's applicability to real-world environments is limited, as it primarily functions within a virtual domain. In contrast, augmented reality (AR) technology, which has seen substantial advancements in resolution and real-time processing capabilities, offers a promising alternative. AR has the potential to transform the treatment of spatial neglect by shifting the entire real space into the patient's right visual field, thus enabling the real-time display and interaction within an adjusted spatial context. This novel approach could allow patients to hyper-adapt to a modified environment where real space is perceived predominantly in the right visual field, potentially facilitating the use of AR glasses as a daily aid for correcting spatial perception. Furthermore, AR technology could be leveraged for rehabilitation exercises that incrementally reintroduce stimuli to the left visual field, thereby training the patient's attention to shift leftward.

B. Inducing attention through movement

It has been reported that in healthy participants, combining self-generated movements with visual search reduces reaction time during visual search [3]. [4] compared the case in which pressing a button causes the circle on the display to move with the case in which the user only sees the circle move, and showed that the former, in which the user has a sense of manipulating the circle, shows enhancement of attention toward the direction of the circle's movement. On the other hand, it is not clear whether the same effect can be obtained in continuous movements such as those performed in daily life. Therefore, we examined the effects of continuous movements on spatial attention to the intended direction of movements in healthy participants. We also varied the sense of agency of the manipulated object and examined its effects on attention.

II. Results

A. AR-based intervention systems for hemispatial neglect

A presentation system was developed and tested in three patients with hemispatial neglect. Fig. 1 shows the actual images presented in the goggles and the eye movement during the presentation. In both presentations, most of the gaze were concentrated in the right from the center of the visual field. In other words, when the entire real space was presented in the right visual field, it was suggested that the gaze was also allocated to the left space in the real world. When patients were asked to response to the randomly presented target, the probability of finding the target was increased when the real space was presented in the right visual field than when it was presented in the full-visual field in the severely ill patient cases. The patient with mild neglect who already adapted to daily life performed well in both presentation conditions.

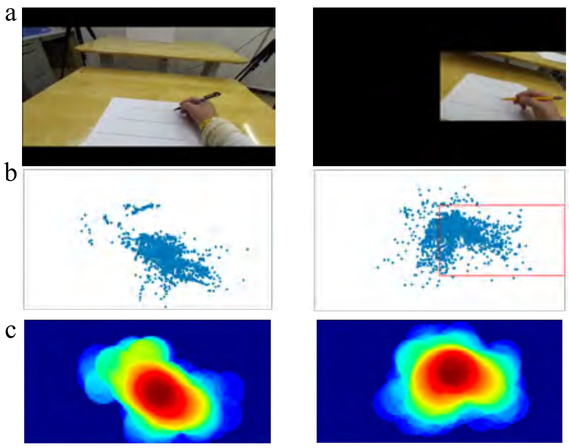


Fig. 1 The image in the goggles and the gaze
Left: Condition in which the entire visual space is presented in the full visual field. Right: condition in which the whole visual space was presented in the right visual field. a: images in the goggles. b, c: the gaze position in relation to the images in the goggles and its heat map during a whack-a-mole game.

One patient with severe neglect conducted a whack-a-mole game with wearing the goggle. It was observed that the patient was able to find and hit more moles in the left real space when the real space was presented in the right visual field. We plan to quantify and validate these performances in the future.

B. Inducing attention through movement

Participants performed a motor task in different conditions followed by a visual attention task. participants controlled a red circle on the screen by a computer mouse, while the sense of agency was manipulated to be high in the High condition, and low in the Low condition [5]. In the Passive condition, the participants watched the red circle movement of others recorded in advance. Participants also performed a control condition in which they did not perform any motor task (Attention condition). In the visual attention task, participants were instructed to quickly click the mouse (right click for right gap, left click for left gap) according to the gap of the target Landolt ring after 6 rings appeared (Fig. 2). Target positions were differentiated between trials in which the direction of movement in the preceding motor task and the target position coincided (D) and trials in which they did not (od), and labeled 1-3 in order of proximity of the target position from the fixation point.

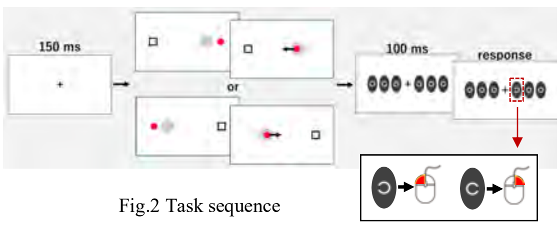


Fig.2 Task sequence

An ANOVA for reaction time in visual attention tasks with 6 target positions and 4 motor task conditions revealed that self-generated movements promoted attention to the spaces that do not coincide with the movement directions, compared to passive motion pursuit. It was also suggested that attention to the movement direction may be promoted when the sense of agency is low.

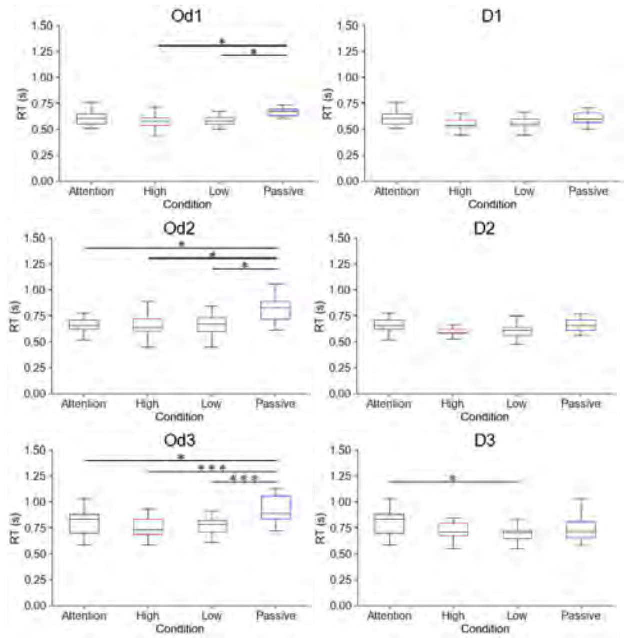


Fig.3 Comparison of reaction times between task conditions for each target location

III. Future Perspective

We conducted feasibility tests of the AR system and basic experiments on self-generated movement and attention. We plan to apply these to the rehabilitation of spatial neglect in the future.

References

[1] Y. Rossetti, G. Rode, L. Pisella, A. Farné, L. Li, D. Boisson, and M.-T. Perenin, "Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect," Nature, 395(6698), pp. 166-169, 1998.

[2] K. Yasuda, D. Muroi, M. Ohira, and H. Iwata, "Validation of an immersive virtual reality system for training near and far space neglect in individuals with stroke: a pilot study," Topics in Stroke Rehabilitation, 24(7), pp. 533-538, 2017.

[3] Y. Tamura, M. Egawa, S. Yano, T. Maeda, M. Kato, and H. Asama, "Activeness Improves Cognitive Performance in Human-Machine Interaction," Journal of Advanced Computational Intelligence and Intelligent Informatics, 17(3), pp. 425-432, 2013.

[4] R. Nakashima, "Beyond one's body parts: Remote object movement with sense of agency involuntarily biases spatial attention," Psychon Bull Rev, 26(2), pp. 576-582, 2019.

[5] W. Wen, N. Shimazaki, R. Ohata, A. Yamashita, H. Asama, and H. Imamizu, "Categorical Perception of Control," eNeuro, 7(5), 2020

A05-13 Annual report of reseach project

Kosei Takeuchi
Dept. of Medical Cell Biol., Sch. of Med., Aichi Medical University

***Abstract*— Spinal cord injury (SCI) causes permanent dysfunction in the body movement and sensation. It is well known that recovery becomes more difficult as time passes from injury. Even with the power of stem cell transplant, it is still hard to cure the late phase of SCI. Despite the difficulty, majority of patients suffering from SCI are clinically late phase. Thus, overcoming the late phase of SCI is an important mission. CPTX is the structurally guided synthetic peptide that joins the pre-synaptic neurexin and the post-synaptic AMPA receptors. We previously showed that CPTX recovered the early phase of SCI in mouse model. CPTX restored the behavioral deficiency of Ataxia and Alzheimer's mouse model as well. Therefore, CPTX is expected to be a promising medical agent to cure degenerated or injured CNS with novel concept.**

I. INTRODUCTION

Central nervous system injuries, especially spinal cord injuries, lack fundamental treatment methods. Currently, various regenerative medical treatments, including induced pluripotent stem cell (iPS) transplantation, are being attempted. However, the path towards therapeutic interventions through drug discovery remains challenging [1]. While advancements, particularly in Brain(Spine)-Computer(Machine) Interface, show promise in processing information from nerves and the spinal cord to guide recovery [2], numerous challenges persist. These include determining which neural circuits to intervene in, addressing issues such as allodynia that arise from sensory reception impairment in spinal cord injuries, and overcoming various obstacles.

Efforts towards clinical applications and attempts at different treatments raise questions about which circuits require regeneration enhancement and what artificial interventions, including rehabilitation, are both possible and effective. Understanding these aspects is a significant ongoing theme. Considering analyses and research in this context, exploring the possibility of achieving hyper-adaptation in physiological function recovery after spinal cord injuries is a major focus.

Spinal cord injury models prove to be highly effective analysis systems for exploring neural circuit reorganization and hyper-adaptive phenomena. Based on the regeneration and reorganization of neural circuits, our goal is to investigate hyper-adaptive mechanisms.

Inspired by synaptic organizers controlling synaptic formation, we have demonstrated spinal cord injury treatment and recovery through the creation and application of artificial synaptic connectors connecting excitatory synapses. Additionally, we are progressing in constructing a gene-regulation system to suppress the expression of nerve regeneration inhibitory factors and accelerate neural reorganization. Combining these efforts, we aim to build model systems that far surpass the physiological recovery speed and functional improvement of existing spinal cord injury mouse and rat models. We also strive to elucidate the correlation between adaptive interventions (such as rehabilitation) and circuit reorganization in the functional recovery process, along with understanding the mechanism of functional recovery through the control of inhibitory neurons.

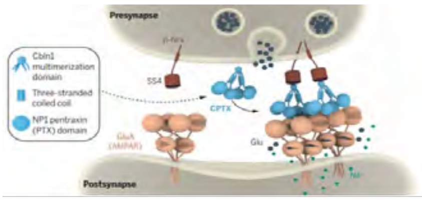


Fig1 Strategy of Synaptic connector

Alongside the rapid recovery model creation, we have established an analysis system incorporating AI motion capture for the analysis of the movement recovery process. This system helps identify distinctive behavioral changes and extract elements corresponding to neural reorganization and regeneration.

II. AIM OF THE GROUP

In this research project, our goals are to further explore the regenerative function of synaptic connector factors and propose a regenerative model from the subacute to chronic phase, traditionally considered difficult to treat. We also aim to progress with interventions like rehabilitation, correlating them with the physiological recovery process. The overarching objective is to advance a versatile physiological function recovery evaluation system and utilize AI machine learning to extract essential elements.

III. RESEARCH TOPICS

A. Application of the Synthetic Synaptic Connector CPTX to Subacute and Chronic Spinal Cord Injuries

CPTX possesses rapid and potent synaptic formation capabilities by bridging presynaptic molecules (Neuroligin) and postsynaptic molecules (AMPA receptors) (Science. 2020) [3]. (Refer to Fig.1)

Using CPTX, we have observed recovery in a mouse spinal cord injury model, even in the extremely challenging conditions of the subacute and chronic phases. This represents a groundbreaking recovery effect, especially considering the limited effectiveness seen in various previous treatment strategies. Furthermore, this effect persists even at the point of entry into the chronic phase, as evidenced in the mouse model six weeks post-injury (equivalent to approximately six months in human spinal cord injury timelines), where significant efficacy has been consistently demonstrated.

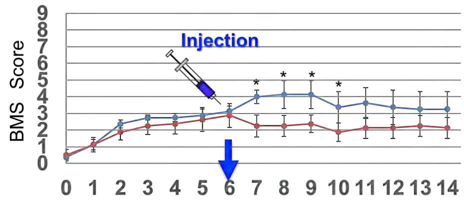


Fig 2 CPTX promotes recovery from chronic phase of SCI

When considering the application of the recovery process during the chronic and subacute phases, we thoroughly analyzed issues prevalent in human spinal cord injuries, such as the presence of allodynia (abnormal pain sensitivity). As a result, it was found that the expression of allodynia induced by CPTX administration did not occur. However, the recovery of tactile sensation in the paw following CPTX administration showed a clear trend of sensory improvement when compared to other drug administrations or natural recovery processes.

The remarkable recovery facilitated by CPTX after spinal cord injury is not only attributed to motor neurons and their functions but also considered a significant factor in the restoration of sensory functions in the paw. Looking ahead to the analysis, application, and development of "hyper-adaptation," it is suggested that beyond the analysis of motor physiological functions, understanding and assessing changes in the sensory functions (such as tactile stimulus perception in limbs and its recognition) is a crucial and important element. Connecting these analyses and changes to applications is essential for the comprehensive advancement of this field.

B. Motor Physiological Function Analysis from the Hyper-Recovery Model System through the Construction of an AI Tracing System

In the hyper-recovery process following spinal cord injury, we are advancing thorough analyses of quantitative motor function and the extraction of its factors using AI-integrated walking function analysis to gain correlations with neural reorganization.

In particular, within the physiological function recovery process, we have been extracting distinctive recovery patterns through CPTX administration to enhance treatment effects. Furthermore, we have analyzed the application of this to chronic phase treatment and the effects of rehabilitation. The construction of an AI-driven automatic analysis system has successfully extracted free-walking data of mice in dark conditions. Utilizing this system, we have successfully extracted elements of recovery through CPTX, introduced them into mice's voluntary rehabilitation, and are in the process of further enhancing recovery from the chronic phase.

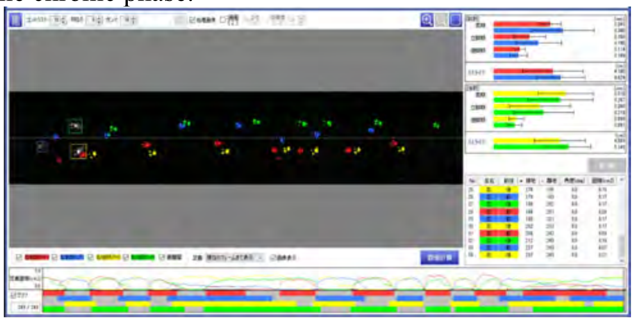


Fig 3 AI-driven analysis system for gait recovery through automatic extraction.

III. Future perspective

Regarding the application of the synaptic connector CPTX in spinal cord injuries, we have achieved notable results, particularly in its adaptation to the chronic phase and its correlation with sensory reception. By tracing AI through this recovery process, we have successfully extracted essential elements for physiological function recovery and developed the capability to analyze their correlation with connected circuits.

Furthermore, our analyses are indicating the increasing importance of "sensory reception recovery" in improving physiological functions [5]. Additionally, we are advancing the application of novel synaptic connectors and their use in neurological functional recovery, such as spinal cord injuries. With these novel synaptic connectors, we have established a system that, along with behavioral extraction using the AI machine learning system constructed in this study, allows us to explore how synaptic interventions impact the recovery process and how they connect with various physiological functions. Based on the correlation analyses with physiological functions, we plan to continue advancing artificial interventions and their analyses towards hyper-adaptation in the future.

References

[1] Christopher S. et.al., Traumatic spinal cord injury. Nature Reviews Disease Primers 3,: 17018 (2017)

[2] Lorach H et.al., Walking naturally after spinal cord injury using a brain–spine interface. Nature 618, 126–133 (2023)

[3] Suzuki K, Elegheert J, Song I, Sasakura H,et.al., A synthetic synaptic organizer protein restores glutamatergic neuronal circuits. Science 369 ;6507 : eabb4853 (2020)

[4] Patricia C. Salinas, Restoring neuron connections, Science. 369; 6507, 1052-1053.(2020)

[5] Habuchi H. et.al., Bone marrow derived mast cells injected into the osteoarthritic knee joints of mice induced spontaneous pain., PLoS One;16(6):e0252590(2022

A05-14 Brain reorganization in stroke patients with hyper-recovery by measuring EEG modulation induced by static and dynamic magnetic fields

Tatsuya MIMA, M.D., Ph.D.
Ritsumeikan University

***Abstract*— To promote research on hyper-adaptability, this study aims to measure functional neural networks using the TMS/tSMS-EEG method, which is a combination of noninvasive brain stimulation (NIBS) and EEG measurement, to elucidate the physiological mechanisms of NIBS and the specificity of neural network reconstruction in hyper-adaptive individuals. In FY2023, we discovered that tSMS, one of the NIBS clinically applied in humans, can induce intrinsic plasticity mediated by Cl- channels. This contributes to the elucidation of the physiological mechanisms of adaptability and hyper-adaptability phenomena. The results of TMS/tSMS-EEG in healthy subjects are in submission. Clinical research is underway to apply this method to hyper-recovered stroke survivors.**

I. Introduction

In this research project, we will treat the phenomenon that has been treated as a "miraculous healing" episode from stroke as a dramatic expression of hyper-adaptation, that is a reconfiguration of the brain's potential adaptive capacity. Then, from this perspective, we will conduct a clinical study of some exceptional stroke recoveries ("hyper-recovery"), focusing on the redundancy of neural networks. As a result, we aim to scientifically elucidate the so-called "miracles".

In this study, transcranial magnetic stimulation (TMS) will be given to measure functional neural networks in humans, and electroencephalography (EEG) will be recorded simultaneously. In addition to the TMS-EEG method, which measures EEG responses in real time to the application of dynamic electromagnetic field pulses, we will measure changes in EEG oscillatory responses to the application of a continuous magnetic field by transcranial static magnetic field stimulation (tSMS) in real time manner.

The main results in FY2023 are as follows.

(1) The physiological mechanism of transcranial static magnetic field stimulation (tSMS) was elucidated in an animal model [1].

(2) The results of clinical studies on stroke rehabilitation and Parkinson's disease were published [2, 3, 4].

(3) We showed the "N-of-1 study" as a method to elucidate individual differences in hyper-adaptability [5, 6, 7].

(4) The TMS-EEG method was studied on healthy subjects [8].

(5) We are doing a cross-disciplinary collaboration between medicine and engineering to develop a new method to use neurofeedback methods for rehabilitation of sensory disorders, with B05-09 (Prof. Sakurada) and a joint research on simultaneous measurement of tSMS with A05-12 (Prof. Osu).

II. Aim of the Group

The purpose of this study is to measure functional neural networks by TMS/tSMS-EEG to elucidate the physiological mechanisms of non-invasive brain stimulation, to reveal the specificity of neural network reconstruction in hyper-recovering individuals, and to explore neural connections that are latent in healthy individuals but are activated during the process of hyper-adaptability.

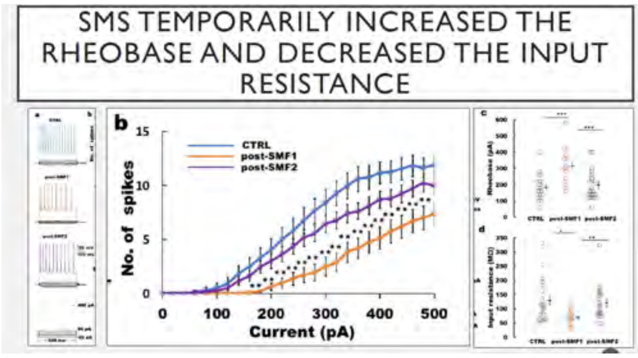
III. Research Topics

Two major specific results for FY2023 are listed below and outlined respectively.

A. Physiological Mechanism of tSMS

By placing a powerful neodymium magnet on the human head surface, tSMS can produce functional inhibition of the cortex directly below it. It has attracted attention as one of the safest noninvasive brain stimulation methods with no risk of epilepsy. However, the mechanism of its biological action was not known.

We showed that tSMS changes the intrinsic electrical properties of neurones (intrinsic or non-synaptic plasticity) by altering the activity of chloride (Cl−) channels in neurones. Our whole-cell current-clamp experiments show that exposure of mouse pyramidal neurones to a static magnetic field at a strength similar to human tSMS temporarily decreased their excitability and induced transient neuronal swelling, which was caused by a temporary increase in the membrane Cl− conductance acting as a shunt to offset membrane excitation. The Cl− channel blocker 4,4′-Diisothiocyano-2,2′-stilbenedisulfonic acid abolished the effects of tSMS; however, another blocker, 5-Nitro-2-(3-phenylpropylamino) benzoic acid, failed. A more selective blocker GlyH101, when applied, reversed the effects of tSMS. In addition, voltage clamp recordings revealed voltage dependence similar to SLC26A11 protein mediated currents.



These findings provide experimental evidence for the essential role of a specific Cl− channel in the neural effects of tSMS and advance our mechanistic understanding of non-invasive human neuromodulation.

Noninvasive brain stimulation methods in clinical application in humans are thought to induce synaptic plasticity by a mechanism similar to LTP/LTD. In contrast, we found that tSMS is based on intrinsic plasticity mediated by Cl- channels. This could be an important contribution to the understanding of the physiological mechanisms of adaptive and hyper-adaptive phenomena.

B. Establishment of TMS-EEG recording analysis method

To evaluate the functional neural network in humans non-invasively and quantitatively, TMS was given at the left primary motor xortex (M1) while multi-channel EEG recordings were continuously performed. The TMS-evoked potential (TEP), which is the change in the brain electric field induced by the eddy current pulse induced in the brain by the magnetic pulse, was recorded and analyzed using an EEG amplifier (BrainAmp) that can handle TMS artifacts and artifact elimination software (TESA).

In a study in healthy subjects, we investigated the neuromodulation elicited by tSMS using transcranial magnetic stimulation (TMS) in combination with simultaneous electroencephalography (EEG) to clarify the neurophysiological basis of tSMS [8]. 15 healthy subjects were tested with tSMS in the left primary motor cortex (M1) or sham stimulation was applied for 20 min. Single-shot TMS was given to left M1 before and after the intervention while EEG was recorded. 120 additions were made to record TEP.

The amplitude around P30 of the TEP in the left primary sensory-motor cortex (SM1) was significantly decreased after real TMS, while the amplitude around N60 of the TEP in the right SM1 was significantly increased after real TMS. Furthermore, the alpha power of the TMS-evoked oscillatory response (IOR) in left and right SM1 significantly decreased after real TMS.

TMS-EEG is a powerful tool for studying local and global cortical reactivity to external stimuli with high spatiotemporal resolution. P1 in the left M1 region has been reported to correlate positively with motor evoked potentials (MEPs) (Mäki, 2010), and the decrease in P1 amplitude on the stimulus side may reflect cortical inhibition by tSMS. The TEP obtained on the contralateral M1 is said to reflect interhemispheric inhibition (IHI). The increase in N1 amplitude in the right M1 region is thought to reflect a mediated effect through the corpus callosum.

Based on the results of the study in healthy subjects, recordings were made in two hyper-recovering stroke survivors and are now being analyzed. So far, the results show that on the affected side, P1 (P30) has disappeared and the amplitude of P45 is also reduced. These results suggest a decrease in cortical excitability.

IV. Future Perspective

In FY2023, the results of clinical research on the rehabilitation application of noninvasive brain stimulation methods (TMS, tSMS) to enhance recovery from stroke were published [2, 3, 4]. Especially for tSMS, a double-blinded prospective study revealed its clinical usefulness [3]. As a physiological mechanism of hyper-adaptability, plasticity at the level of networks and systems, rather than individual neurons or regions, is assumed to be important. To elucidate this, we first established a method for analyzing TMS-EEG recordings in healthy subjects, which is being submitted for publication in FY2023 [8]. We are currently analyzing the neural network of stroke survivors with hyper-recovery by TMS/tSMS-EEG methods.

References

[1] Sinha, A.*, Shibata, S.*, Takamatsu, Y.*, Akita,, T., Fukuda, A., Mima, T. (2024) Static magnetic field stimulation enhances shunting inhibition via a SLC26 family Cl− channel, inducing intrinsic plasticity. Journal of Neuroscience, in press.

[2] Nojima I, Horiba M, Sahashi K, Koganemaru S, Murakami S, Aoyama K, Matsukawa N, Ono Y, Mima T, Ueki Y, Gait-combined closed-loop brain stimulation can improve walking dynamics in Parkinsonian gait disturbances: a randomised-control trial. J Neurol Neurosurg Psychiatry 94(11): 938-944.

[3] Shimomura R, Shibata S, Koganemaru S, Minakuchi M, Ichimura S, Itoh A, Shimotake K, Mima T, (2023) Transcranial static magnetic field stimulation (tSMS) can induce functional recovery in patients with subacute stroke. Brain Stimulation 16(3): 933-935.

[4] Yukawa, Y., Shibata,S., Koganemaru, S., Minakuchi,M., Shimomura, R., Nakamura K., Mima, T. (2023) Low-frequency repetitive transcranial magnetic stimulation can alleviate spasticity and induce functional recovery in patients with severe chronic stroke: A prospective, non-controlled, pilot study. Heliyon 9: e15564

[5] Yamaoka, T., Takagi, Y., Shimomura, R., Murata, Y., Shimotake, K., Itoh, A., Mima, T., & Koganemaru, S. (2023). N-of-1 Trial of Electrical Sensory Stimulation Therapy on the Tibial Innervated Area during Gait in a Case of Post-stroke Sensory Disturbance. Progress in Rehabilitation Medicine 8: 20230018.

[6] Ogawa, A., Koganemaru, S., Takahashi, T., Takemura, Y., Irisawa, H., Goto, K., Matsuhashi, M., Mima, T., Mizushima, T., Kansaku, K. (2023) Swallow-related Brain Activity in Post-total Laryngectomy Patients: A Case Series Study. Progress in Rehabilitation Medicine 8: 20230026.

[7] Mima, T. (2023) The Personal can be Scientific: N-of-1 approach to hyper-adaptability. The 46th Annual Meeting of the Japan Neuroscience Society, Symposium: New horizon of Hyper-Adaptability 1st Aug., 2023. Sendai, Japan.

[8] Shibata, S., Onishi, H., Mima, T. (*in submission*) TMS-EEG signatures of the effects of transcranial static magnetic field stimulation (tSMS) on cortical excitability. *Scientific Report.*

A05-15 Annual report of research project

Atsushi Nambu, Resercher, National Institute for Physiological Sciences
Nobuhiko Hatanaka, Assistant Professor, National Institute for Physiological Sciences
Satomi Chiken, Assistant Professor, National Institute for Physiological Sciences

Abstract— **Our brain, especially somatomotor cortices, shows a somatotopic representation, a point-to-point correspondence of each body part to a specific brain region. The aim of this study is to investigate how such somatotopy is affected when the subjects lose their body parts. We perform physiological mappings of these cortical areas of adult Japanese monkeys in the awake state, who lost their left distal forelimbs accidentally in their childhood.**

I. Introduction

Somatotopy is a point-to-point correspondence of a part of the body to a specific region of the brain. In the cerebral cortex, there are several sensorimotor cortices, and they have their own somatotopic maps. The primary motor cortex (M1) is located in the precentral gyrus and the anterior bank of the central sulcus (CS) in humans and nonhuman primates. Hindlimb, trunk, upperlimb, and orofacial regions are arranged in the mediolateral direction. The intracortical microstimulation (ICMS) mapping revealed the fine somatotopic arrangement of the upper limb. Digit representations are surrounded by more proximal representations in the anterior bank of the CS and the precentral gyrus.

Much attention has been paid to how such somatotopy is affected when the subjects lose their body parts. Several lines of evidence have demonstrated small to large changes in somatotopy of the sensorimotor cortices. Clinical studies in humans using transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) indicated that the face region expanded to the lost hand region in the M1. However, such expansion of the face region was not observed in the ICMS mapping on nonhuman primates. Studies on somatotopic differences between the healthy and affected sides after loss of the forelimb or hindlimb in the monkey M1 found that neuronal activity in the lost body part coded the movements of the stump, a remaining part of the limb. The ICMS threshold to induce muscle movements was similar between the amputated and healthy sides or between the amputated and normal monkeys.

II. Aim of the Group

The aim of this group is how such somatotopy is affected when the subjects lost their body parts. Previous studies were acute and long (10-20 hours) experiments under general anesthesia with ketamine and xylazine or urethane. Application of general anesthesia increases the ICMS thresholds. Therefore, in the present study, we mapped somatotopy in chronic setup, recording neuronal activity under awake states without general anesthesia.

The supplementary motor area (SMA) is located on the medial wall anterior to the M1 leg region, and its somatotopy from face to leg is arranged antero-posteriorly. The distal-proximal segregation in the SMA was not clear. However, there are no reports about effects of the loss of body parts on the SMA somatotopy using electrophysiological approach. To address this question, we also investigated somatotopic changes after loss of the forelimb in the SMA as well as in the M1.

The somatosensory cortex (S1) located in the postcentral gyrus. It is well known that this cortical area plays a role in the somatosensory processing and sensorimotor integration. Further, recent physiological studies revealed that the S1 received efference copy from the M1 just before sensory feedbacks from the spinothalamic system. The S1 also showed a reorganization of the somatotopy; the face representation expanded into the former region of the amputated forelimb.

In this study, we tried to investigate differences of somatotopic arrangement in the M1, SMA, and S1 between healthy and affected sides by ICMS-evoked movement and somatosensory inputs under awake states using two Japanese monkeys who lost their left distal forelimbs accidentally in their childhood..

III. Research Topics

Somatotopic changes in the M1, SI, and SMA

The M1 occupies the surface area of the precentral gyrus and the anterior bank of the central sulcus. In the healthy cortical side, the somatotopic map of the M1 seems to be the same as that in normal monkeys. Somatotopy of the M1 was similarly represented in the both cortical sides of normal monkeys. On the other hand, in the affected cortical side, the cortical region that was supposed to represent the distal forelimb was lost, and instead represented the stump (Fig. 1):

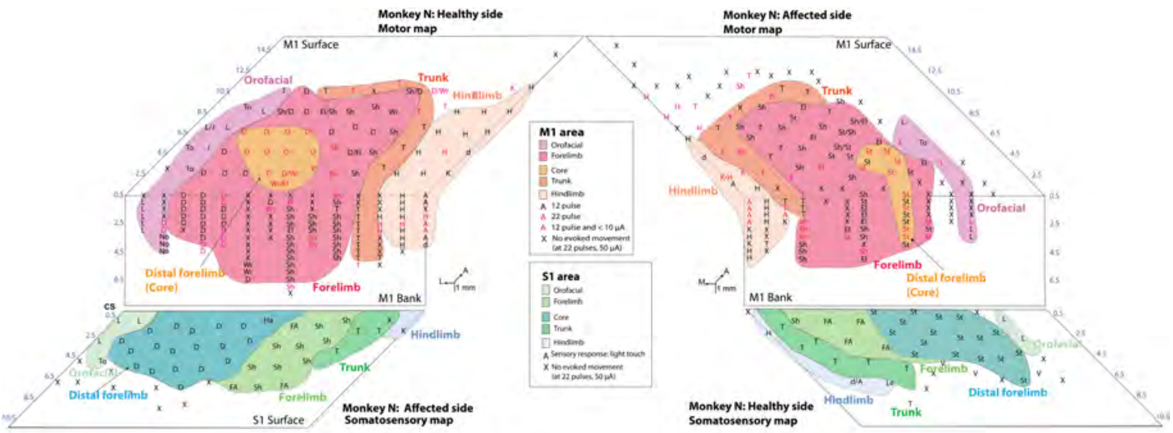


Figure 1. Somatotopic maps of the M1 and S1 in the healthy (left) and affected (right) hemispheres. **Upper**, M1 motor map representing body part movements evoked by ICMS. **Lower**, S1 somatosensory map representing body parts whose somatosensory stimulation evoked neuronal activity. Letters represent the following body parts: A, ankle; D, forelimb digits; d, hindlimb digits; El, elbow; FA, forearm; H, hip; J, jaw; K, knee; L, lip; Le, leg; No, nose; Sh, shoulder; St, stump; T, trunk; To, Tongue; Wr, wrist; X, no evoked movement or no somatosensory response.

Neurons in this region responded to the palpation of the stump, and ICMS in this region induced movements of the stump at threshold < 10 µA (core region, Fig. 1, orange). Therefore, the distal forelimb region in the M1 is considered to be substituted by the stump region. Other general somatotopic map of the M1, such as orofacial, proximal forelimb, trunk, and hindlimb regions, seems to be the same as that in the healthy sides. The core region in the affected side was smaller than that in the healthy side.

The S1 is located posteriorly to the CS. In the healthy side, the somatotopic arrangement of the S1 was similar to that reported previously. Somatotopy of the S1 was similarly represented in the both sides of normal monkeys. On the other hand, in the affected side, the stump region occupied some region in the forelimb region (Fig. 1). Therefore, the area that had been dedicated to the distal forelimb region was considered to be partly dedicated to the stump. Other body parts, such as orofacial, trunk, and hindlimb, are similarly represented as in the healthy side. The areas of the distal forelimb and total forelimb regions were compared between the affected and healthy sides. The distal forelimb region in the affected side was smaller than that in the healthy side, while the total forelimb regions showed inconsistent changes.

In the SMA, it is known that the orofacial, forelimb, trunk, and hindlimb regions are presented rostro-caudal direction in the mesial wall. In the healthy side, both motor and somatosensory examination identified the forelimb region between the orofacial and hindlimb/trunk regions. On the other hand, in the affected side, motor and somatosensory examination identified the forelimb regions, and most of the forelimb region represented the proximal forelimb, not the stump. The distal/stump and total forelimb regions in the SMA were compared between the affected and healthy sides. The stump region in the affected side was smaller than the distal forelimb region in the healthy side, while the total forelimb regions were similar between the affected and healthy sides.

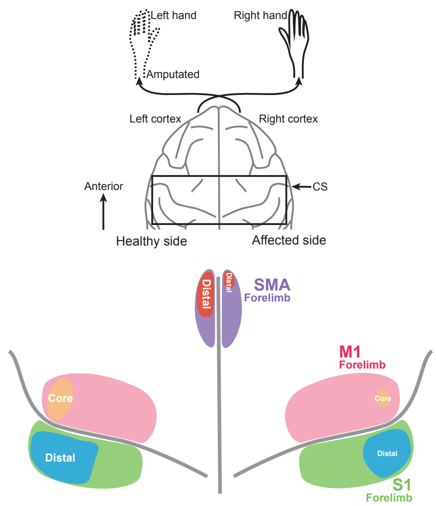


Figure 2. Summary diagram of the present study

IV. Future Perspective

We observed how a somatotopic representation in the cerebral cortex was reorganized in macaque monkeys who lost their forelimbs accidentally. In the motor cortices, the area previously representing a lost distal forelimb shrunk, while that in the somatosensory cortex was rather preserved (Fig. 2). This discrepancy between the motor and somatosensory cortices might be the basis of phantom limb, the sensation that an amputated limb is still attached. The knowledge on the reorganization of motor and somatosensory cortices is also important to develop a brain machine interface, especially a prosthetic hand controlled by brain activity.

A05-16 Annual report of research project

Noriyuki Higo
Human Informatics and Interaction Research Institute,
National Institute of Advanced Industrial Science and Technology (AIST)

*Abstract***— There are reports on compensatory plastic changes in the remaining intact brain which are involved in motor functional recovery following stroke. Functional brain imaging has revealed compensatory activation during movements following recovery; our brain imaging using functional near-infrared spectroscopy (fNIRS) suggested compensatory increase of brain activity in the rostral ventral premotor cortex (PMv) during voluntary movements after motor recovery. However, the mechanism by which structural plastic changes underlie functional reorganization is unclear. In this project, therefore, we investigated the structural plastic changes underlying functional changes together with voxel-based morphometry (VBM) analysis of magnetic resonance imaging data and immunohistochemical analysis using SMI-32 antibody in the macaque model of internal capsular infarcts. We observed significant increases in the gray matter volume (GMV) and the dendritic arborization of layer V pyramidal neurons in the contralesional rostral PMv. Immunohistochemical analysis also revealed increased immunoreactivity of brain-derived neurotrophic factor (BDNF) and vesicular glutamate transporter (VGLUT1) in the area. These results indicated that compensatory structural changes occur in the contralesional rostral PMv during motor recovery following internal capsular infarcts, and the dendritic growth and synaptic proliferation of pyramidal neurons may underlie the observed GMV increase. In addition, Our fNIRS data showed that response of oxyhemoglobin in the contralesional rostral PMv had changed in both strength and timing; the peak occurred significantly earlier after recovery from infarction than before infarction. Although it is not clear why these changes in response occurred, this result suggests that changes in strength and timing of oxyhemoglobin response as well as the activated area may be used as an indicator of functional compensations in the motor cortex after stroke.**

I. Introduction

Many previous reports have suggested that structural and functional changes in the brain in the residual regions are responsible for the recovery of brain function after brain damage. These changes are more dynamic than those in the healthy brain, and are a typical example of the "hyper-adaptive changes" in the brain. Elucidating these changes will lead to innovative neurorehabilitation technologies to assess and appropriately guide the brain to appropriate changes. The principal investigator of this project has been studying the adaptive changes that occur in the process of functional recovery after brain damage using macaques, which have similar brain and musculoskeletal structures to humans, as a model animal. We have elucidated that the recovery of "precision grasp" is accelerated by rehabilitation training [1] and that a change in brain activity compensates for the function of the damaged area [2]. Clinically, however, cerebral hemorrhages and infarcts that occur subcortically are often a problem.

II. Aim of the Group

By utilizing the macaque internal capsular infarction model, which has a clinical-like pathology, we aim to elucidate the functional and structural adaptation mechanisms of the brain during the process of motor function recovery, and to obtain knowledge that can be seamlessly applied to the rehabilitation of stroke patients. Using the obtained knowledge, we aim to develop a system to evaluate changes in brain activity during the rehabilitation process after stroke.

III. Research Topics

A. *Molecular chnages during motor recovery after focal infarction of the macaque internal capsule*

We established a technique to measure macaque motor cortex activity using functional near-infrared spectroscopy (fNIRS) [3] and measured motor cortex activity during a grasping task. The results showed that before the infarction, there was increased activity in the hand area of the primary motor cortex with the performance of grasping movements, whereas during functional recovery, there was increased activity in the rostral part of the ventral premotor cortex (PMv) [4]. We performed voxel-based morphometry (VBM) analysis using T1-weighted MRI and immunohistochemical staining to examine the structural changes underlying the functional changes. The results of VBM analysis suggested an increase in gray matter (GMV) in the rostral part of the contralateral PMv of the infarct during the period of motor recovery after cerebral infarction [5].

Immunohistochemical staining using SMI-32 antibody, which stains pyramidal cells, revealed increased dendritic branching in pyramidal cells in layer V of the infarct contralateral rostral PMv. Expression of brain-derived neurotrophic factor (BDNF), a neurotrophic factor involved in neuroplasticity, and vesicular glutamate transporter (VGLUT1), a marker of excitatory synapses, were also increased in the ventral part of the contralateral PMv of the infarct (Fig. 1). These experimental results suggest that compensatory structural changes in motor output cells in the rostral part of the contralateral PMv are important for motor function recovery after infarction and that structural changes in dendrites and excitatory synapses underlie the GMV changes observed in the VBM analysis.

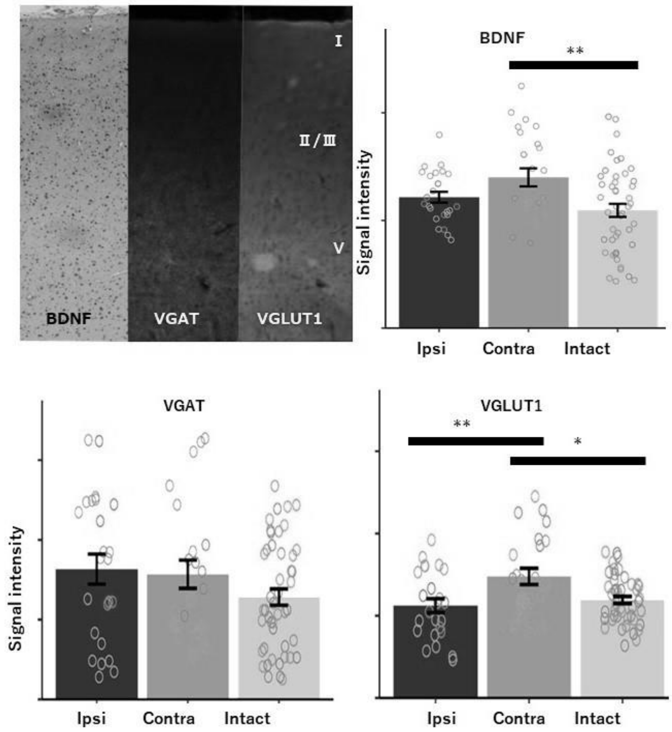


Fig. 1. Immunohistochemical analysis revealed increased immunoreactivity of brain-derived neurotrophic factor (BDNF) and vesicular glutamate transporter (VGLUT1), but not vesicular GABA transporter (VGAT) in pyramidal neurons in the contralesional rostral PMv..

B. fNIRS waveform changes and clinical application during the recovery process after internal capsular infarction

In the rostral PMv, where functional compensation by fNIRS was observed, characteristic changes in hemodynamics were observed. The oxyhemoglobin and deoxyhemoglobin changes seen during exercise before injury had a single peak or trough, and both had the same arrival time of about 5 seconds, whereas the arrival time of oxyhemoglobin was accelerated by more than 2 seconds in PMv after functional recovery, while the arrival time of deoxyhemoglobin was not accelerated. The opposite trends of oxy- and deoxyhemoglobin was lost (Fig. 2).

At this point, it is not possible to rationally explain why the hemodynamic changes specific to compensatory areas occur based on conventional neuroscience findings, but these results suggest the possibility of using changes in fNIRS waveforms as well as activation areas as indicators of functional compensations. Based on these findings, we are developing a system to extract brain signal features that correlate with the degree of recovery, and to predict recovery based on changes in these features over time. A prototype system for verification has been completed and is currently being tested on patients in collaboration with Ibaraki Prefectural University of Health Science, a clinical institution, and a related company (Fig. 2).

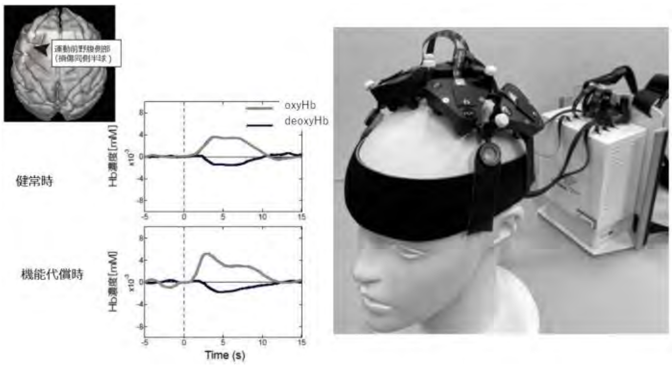


Fig. 2. Response of oxyhemoglobin (Oxy-Hb) in the contralesional rostral PMv had changed in both strength and timing; the peak occurred significantly earlier after recovery from infarction than before infarction. Based on these findings, we are developing a system to extract brain signal features that correlate with the degree of recovery and to predict recovery based on changes in these features over time. The right panel show a prototype system for verification in stroke patients.

IV. Future Perspective

The results of this year's study revealed functional and structural changes that occur in the rostral part of the ventral premotor cortex of the contralesional hemisphere during motor function recovery after internal capsular infarction. In addition to aiming for clinical application of our findings, we believe that analysis of the functional and structural changes in the neural network centered on the cerebral cortex is a future challenge for a more detailed understanding of the mechanism.

References

[1] Y. Murata, N. Higo, T. Oishi, A. Yamashita, K. Matsuda, M. Hayashi, S. Yamane, "Effects of motor training on the recovery of manual dexterity after primary motor cortex lesion in macaque monkeys", J Neurophysiol 99, pp. 773-786, 2008

[2] Y. Murata, N. Higo, T. Hayashi, Y. Nishimura, Y. Sugiyama, T. Oishi, H. Tsukada, T. Isa, H. Onoe, "Temporal plasticity involved in recovery from manual dexterity deficit after motor cortex lesion in macaque monkeys", J Neurosci 35, pp. 84-95, 2015

[3] T. Yamada, H. Kawaguchi, J. Kato, K. Matsuda, N. Higo, “Functional near-infrared spectroscopy for monitoring macaque cerebral motor activity during voluntary movements without head fixation”. Scientific Reports 8: 11941, 2018

[4] J. Kato, T. Yamada, H. Kawaguchi, K. Matsuda, N. Higo, “Functional near-infrared-spectroscopy-based measurement of changes in cortical activity in macaques during post-infarct recovery of manual dexterity.“, Scientific Reports, 10 (1), Article number: 6458, 1-12, 2020

[5] K. Matsuda, K. Nagasaka, J. Kato, I. Takashima, N. Higo, “Structural plasticity of motor cortices assessed by voxel-based morphometry and immunohistochemical analysis following internal capsular infarcts in macaque monkeys”, Cerebral Cortex Communications 3 (4), tgac046, 2022

A05-17 Annual report of research project

Osamu Yokoyama
Tokyo Metropolitan Institute of Medical Science

Abstract*— Somatosensory information plays an essential role in motor control. In this study, we induced somatosensory impairment in monkeys by transecting the dorsal roots of the spinal cord, which carry peripheral somatosensory information to the central nervous system. Motor function and neural activity in the cerebral motor and somatosensory cortices were longitudinally recorded and analyzed to elucidate the adaptive mechanisms of cortical activity that support functional recovery from motor impairments caused by a deficit of somatosensory input to the central nervous system. Immediately after the transection of the dorsal root in the cervical spinal cord, motor performance of the upper limb was impaired, and movement-related high-gamma and beta-band activity in the primary motor and primary somatosensory cortices and the flow of information in the beta band between these areas were significantly altered. Then, over a period of about two weeks, motor performance gradually recovered to a similar level as before the lesion, and over a similar time course, high gamma activity in the primary motor cortex and primary somatosensory cortex and the flow of information in the beta-band returned to a similar state as before the lesion. These changes in cerebral activity might contribute to the recovery of motor function. The results of this study reveal a process by which the cerebrum adapts to a deficit in somatosensory input from the periphery by dynamically reorganizing its activity.

I. Introduction

Somatosensory information plays an essential role not only in the sensory function itself, which perceives the state of one's own body and the external world, but also in the motor control, for at least two reasons. First, when the primary motor cortex generates motor commands, it must use somatosensory information such as the position of body parts, joint angles and output force. Second, during motor execution, spinal motor neurons receive sensory signals from peripheral sensory receptors in addition to descending motor commands from the cerebrum and integrate them to generate muscle activity [1,2]. Indeed, patients unable to receive somatosensory information due to peripheral sensory neuropathy have motor dysfunction in addition to somatosensory impairment [3-5]. Similarly, a monkey model of somatosensory impairment, in which the input of somatosensory information from the upper limb to the central nervous system is impaired by transection of the dorsal root of the cervical spinal cord, showed motor impairment of the upper limb [6]. The motor deficits in this somatosensory deficit model monkey recover over a period of weeks to months [6]. During this process of motor recovery, the central nervous system is assumed to adapt to the loss of somatosensory input. However, the details of this adaptation mechanism have remained unknown.

II. Aim of the Group

The aim of this study was to elucidate the adaptation process of cortical activity that supports recovery of motor function by creating a monkey model of upper limb somatosensory impairment in which the input of somatosensory information from the upper limb to the central nervous system was selectively impaired by transection of the dorsal root of the spinal cord, and by longitudinally recording and analyzing the activity of the cerebral motor-related and somatosensory cortices during recovery of motor function.

III. Research Topics

After training two Japanese macaques in a reaching and grasping task and implanting a multi-electrode array on the surface of the upper limb region of the primary motor (M1), premotor and primary somatosensory (S1) areas of the left hemisphere of the brain, the dorsal roots in the right lower cervical cord (C6-8), the input pathway of somatosensory signals from the right upper limb to the spinal cord, was surgically transected (Fig. 1 left). We confirmed that the response of S1 (somatosensory evoked potentials) to peripheral (right upper limb) electrical stimulation under anesthesia was attenuated after the lesion compared to before the lesion (Fig. 1, right).

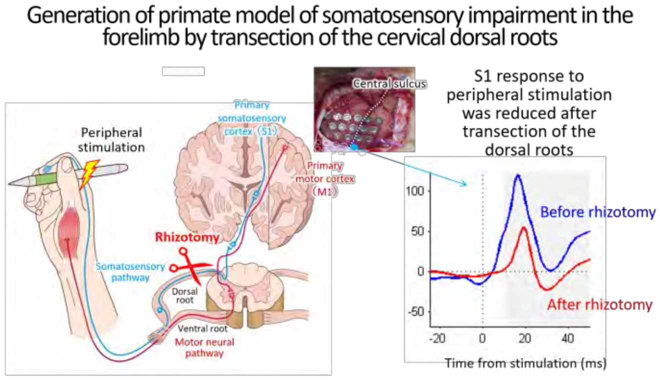


Fig. 1. (Left) Schematic representation of the somatosensory and motor nerve pathways that transmit somatosensory information and motor commands, respectively, between the periphery of the body and the central nervous system and the location of the dorsal root transection. (Right) The response of the primary somatosensory cortex (somatosensory evoked potentials) to stimulation of the adductor internus muscle under anesthesia was attenuated after transection of the dorsal roots (C6-C8) entering the lower cervical spinal cord.

The day after the dorsal root transection, the animals were able to perform the reaching and grasping task with the right upper limb, but the time required to complete the motor task was prolonged. Over the following days, the time required to complete the task gradually decreased, returning to a similar level as before the lesion approximately 14 days after the lesion (Fig. 2). When motor performance had recovered, somatosensory evoked potentials to peripheral somatosensory stimuli had not yet recovered. These results suggest that motor performance was recovered by adaptive changes in the central nervous system in response to the loss of somatosensory input associated with voluntary movements due to dorsal root transection.

We next analyzed electrocorticogram (ECoG) signals during the motor task, recorded from the motor-related and somatosensory cortices during recovery of motor performance. The results showed that on the day after the lesion, high gamma (80-120 Hz) activity in S1 and M1 immediately before the onset of reaching movements was increased compared with to pre-lesion levels. Furthermore, we used Granger causality analysis to examine the flow of information between brain regions and found that the flow of information in the beta band (15-30 Hz) from S1 to M1 during motor preparation and from M1 to S1 during motor initiation was reduced. Subsequently, it was found that the high gamma activity levels of S1 and M1 and the flow of information through the beta band from M1 to S1 gradually returned to similar levels as before the dorsal root transection as motor performance recovered (Fig. 2) [7]. The increase in cortical high gamma activity during motor initiation observed immediately after dorsal root transection might be a compensatory mechanism for reduced spinal reflexes to drive muscle activity. The flow of information from M1 to S1 during movement initiation, which was reduced by the dorsal root transection, might reflect efference copy, and the gradual re-establishment of the internal feed-forward model as motor function was restored and predictions were gradually made again. These adaptive changes in cortical activity are thought to provide the neural basis for the recovery of motor function from the motor impairment induced by dorsal root lesion.

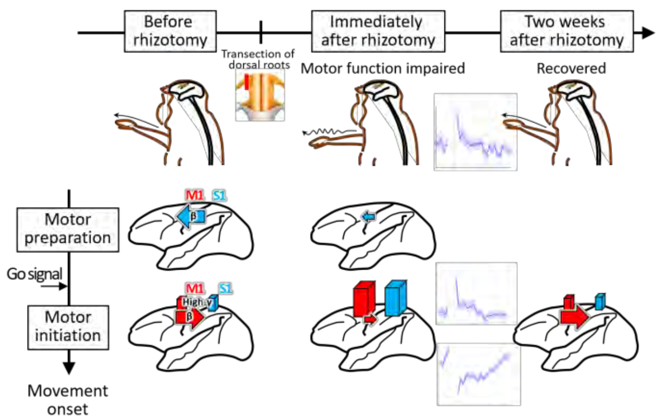


Fig. 2. Summary of changes in the magnitude of activity (bar graphs) and information flow (arrows) associated with voluntary movement in the primary motor cortex (M1) and primary somatosensory cortex (S1) before and after dorsal root transection and during recovery of motor function

IV. Future Perspective

In the present study, we generated monkeys with impairment in somatosensation in the upper limb by transection of the dorsal root of the spinal cord of the Japanese macaque, and examined longitudinal changes in activity in the cerebral motor and somatosensory cortices immediately after dorsal root transection and during recovery of motor function, to clarify changes in activity levels and information flow between brain regions during recovery of motor function. The results revealed changes in activity levels and information flows between brain regions associated with motor recovery. These results may reflect a process of rapid, large-scale adaptive change by the cerebrum to the new state created by the dorsal root transection, followed by a gradual reacquisition of predictive and control functions.

In the present study, the activity of only the motor and somatosensory cortices of the hemisphere ipsilateral to the injury was recorded and analyzed. Similar to the mechanism of motor recovery in the monkey model of spinal cord injury due to lateral corticospinal tract injury [8], the motor and somatosensory cortices of the hemisphere contralateral to the injury may also be involved in motor recovery. Reorganization of activity may also occur in other brain regions and subcortical structures such as the medulla and thalamus.

Further clarification of the whole aspect of cross-talk between motor and somatosensory neural circuits, including under normal conditions, is expected to lead to the development of new rehabilitation methods and neuroprosthetic methods to facilitate functional recovery after central nervous system injuries such as spinal cord injury and stroke.

References

[1] T. Umeda, T. Isa, and Y. Nishimura, “Temporal dynamics of the sensorimotor convergence underlying voluntary limb movement," Proc. Natl. Acad. Sci. USA, vol. 119 (48), e2208353119, 2022.

[2] T. Umeda, O. Yokoyama, M. Suzuki, M. Kaneshige, T. Isa, and Y. Nishimura, “Future spinal reflex is embedded in primary motor cortex output,” bioRxiv [preprint], 2023. doi: 10.1101/2023.06.19.545500

[3] J.C. Rothwell, M.M. Traub, B.L. Day, J.A. Obeso, P.K. Thomas, and C.D. Marsden, “Manual motor performance in a deafferented man,” Brain, vol. 105, pp. 515-542, 1982.

[4] N. Teasdale, R. Forget, C. Bard, J. Paillard, M. Fleury, and Y. Lamarre, “The role of proprioceptive information for the production of isometric forces and for handwriting tasks,” Acta Psychol (Amst), vol. 82, pp. 179-191, 1993.

[5] R. Forget, and Y. Lamarre, “Rapid elbow flexion in the absence of proprioceptive and cutaneous feedback,” Hum. Neurobiol., vol. 6, pp. 27-37, 1987.

[6] C. Darian-Smith, and M.M. Ciferri, “Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy,” J. Com. Neuro., vol. 491 (1), pp. 27-45, 2005.

[7] O. Yokoyama. Adaptive changes in cortical activity during recovery of motor function after transection of the dorsal roots in monkeys. The 53rd Annual Meeting of the Japanese Society of Clinical Neurophysiology, 1st December 2023.

[8] Y. Nishimura, H. Onoe, Y. Morichika, S. Perfiliev, H. Tsukada, and T. Isa, “Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury, ” Science, 318 (5853), pp. 1150-1155, 2007

Group B: Systems engineering

Toshiyuki Kondo
Tokyo University of Agriculture and Technology

I. Objective

Group B aims to understand the phenomenon of hyper-adaptability through computational modeling. In the research project, it has been expected that the systems engineering group mainly plays the following three roles:

- Promotion of understanding through computational modeling
- Development of intervention technology/strategies to clarify the causal relationship
- Proposal of novel research hypotheses to be investigated

To model the phenomenon observed in neuroscience and/or behavioral science, there are three types of modeling approaches; 1) white-box model, in which we hypothesize a mathematical expression according to the observation; 2) black-box model, where we assume a functional approximator such as artificial neural networks, and optimize its parameters via machine learning algorithms; and 3) gray-box model, a mixture of white and black box modelings. Especially in the hyper-adaptability project, we try to develop the methodology for function-oriented neural encoding using the gray-box modeling approach.

An important thing for understanding the phenomenon of hyper-adaptability is to try to investigate the causal relationship of neural activity and its generated functions and behaviors. For this aim, we propose robotic-interventional neuroscience, which realizes a model-based intervention using not only robotic technology, but also opto/chemo-genetics and brain stimulation technologies. In addition, the constructed model can be used to predict the behavior of target systems, and it is expected to offer novel research hypotheses to be investigated.

II. Members

To achieve the above mentioned research objective, we organized four planned and 10 proposed research projects. Please refer to the report of each research project for their research outcomes in the fiscal year.

Planned research projects

B01 Systems modelling of hyper-adaptation mechanism for reconstruction of neural structure

Principal investigator: Toshiyuki Kondo (TUAT), Funded co-investigators: Ryosuke Chiba (Asahikawa Med Univ), Megumi Miyashita (TUAT)

This research group aims to realize systems modeling of hyper-adaptability mechanism with functional dis-inhibition observed in the impaired brain, especially from the viewpoint of reconstruction of neural structure. To clarify the underlying adaptability mechanism of a large-scale and complex network system such as the brain, the constructive approach is indispensable, in which a phenomenon can be modeled with the minimum degrees of freedom, and behavior of the model is verified by computer simulations.

In this year, 1) they worked on the estimation of time-varying structure of latent variables embedded in brain activities (sleep-EEG and multi-unit recording data). 2) They proposed a method to search for parameters under conditions that facilitate gait by increasing the stiffness of each joint and search the parameters using an optimization method. 3) They developed a ring-shaped device to measure the finger usage in daily life of stroke patients, revealed that the correlation between the finger-usage rate and general clinical indices such as FMA-UE.

B02 Modeling of ultra-adaptive to body change

Principal investigator: Yasuharu Koike (Tokyo Tech), Funded co-investigator: Tetsuro Funato (UEC)

This research group aims at the modeling of the mechanism underlying the recovery of the motor function after the alteration of the body, especially from the viewpoint of the reconstruction of a neural structure in hyper-adaptability.

In this year, they obtained the following three results: 1) regression analysis of muscle activity and brain activity showed brain activity involved in muscle activity changes after tendon transfer. 2) Simulation of the monkey musculoskeletal system using reinforcement learning reproduced the learning process for motor acquisition. 3) They proposed a theoretical framework to explain differences in learning rates of inverse models with respect to learning of reaching movements.

B03 Systematic understanding and realization of hyper-adaptive phenomena focusing on cognition and emotion

Principal investigator: Hajime Asama (U Tokyo), Funded co-investigators: Jun Izawa (U Tsukuba), Wen Wen (Rikkyo U), and An Qi (U Tokyo)

This research group focuses on rehabilitation, the mechanism of hyper-adaptability is investigated from a systematical approach, and new rehabilitation methods are developed based on the investigation of effect of cognition and emotion on behavior adaptation and motor learning.

The achievements are summarized as follows: 1) Investigation of changes in the sense of agency in Parkinson's disease patients and compensatory mechanisms in the brain of patients with spinocerebellar degeneration, 2) Construction and demonstration of the computational theory of meta-learning, 3) Development of a predictive model for the sense of agency based on motion data using deep learning, 4) Construction of a movement function evaluation system to enhance user motivation.

B04 Modeling of hyper adaptability in human postural control considering the role of neurotransmitters

Principal investigator: Jun Ota (U Tokyo), Funded co-investigator: Arito Yozu (U Tokyo)

The research group aims to verify the following hypothesis from the viewpoint of reconstitution of sensorimotor control rules of the hyper-adaptation functions: Neurotransmitters (such as dopamine; DA), whose levels are reduced in patients with neurodegenerative disorders, adjust the activity levels in various brain areas and coupling strength between neuronal circuits as well as control the multitasking function.

In this year, 1) they analyzed the abnormal posture of Parkinson's disease patients using the standing posture control model developed in the previous year. 2) They analyzed DAT-SPECT images, and analyzed motor and neural activities under voluntary movements of Parkinson's disease patients.

Proposed research projects

B05-1: Motor learning of modularity in musculoskeletal models toward the emergernce of muscle synergy

Principal investigator: Mitsuhiro Hayashibe (Tohoku U)

A neural network model that can self-organize the automatic switching mechanism of human posture control mode according to the environment was constructed.

B05-2: A neural network model for hyper-adaptability of bipedal locomotion

Principal investigator: Naomichi Ogihara (U Tokyo)

To clarify the hyper-adaptability mechanism in bipedal locomotion to the alteration of the body structure, a gait simulation was constructed combining a 3D precise musculoskeletal model and a neural network model.

B05-3: Hyper-adaptation of bodily and neural sensorimotor information structures in early developmental stage

Principal investigator: Hoshinori Kanazawa (U Tokyo)

A motion generation model that can reproduce the actual motions of newborns and infants was proposed and used to show the sensory-motor information structure can be generated only through embodiment.

B05-4: Low-dimensional functional connectivity across bilateral motor-related areas for hyper-adaptability

Principal investigator: Isao Nambu (Nagaoka U of Tech)

A low-dimensional spatial identification method was applied to cortical EEG to investigate the low-dimensional dynamics of brain functional connectivity.

B05-5: Application of motor learning model for partial relationship reuse to reconstruction of muscle synergy

Principal investigator: Yuichi Kobayashi (Shizuoka U)

A mathematical model that can explain the "reuse of neural circuits" was investigated in the framework of reinforcement learning.

B05-6: Hierarchical understanging of adaptation to a new relationship between the eye and the body

Principal investigator: Michiteru Kitazaki (Toyohashi U Tech)

Adaptation to visuomotor disruption was investigated using immersive VR technology, found that the motor learning occurred in strategic and automatic levels after 10 days learning.

B05-7: Supraspinal mechanisms of the human upright postural control based on the EEG dynamics associated with micro-falls

Principal investigator: Taishin Nomura (Osaka U)

Neural mechanisms of postural stabilization was investigated through the EEG responses to micro-falls during human quiet stance.

B05-8: Higher brain functions as hyper-adaptability: an exploration of the principle of proactive outreach to an indefinite environment

Principal investigator: Kazuhiro Sakamoto (Tohoku Med and Pharma U)

A reinforcement learning model that dynamically and autonomously generates the probability or state space based on the criteria of experience saturation and decision uniqueness was developed.

B05-9: Individual differences in suitable neural circuits for attention control and its effect on motor control

Principal investigator: Takeshi Sakurada (Seikei U)

To realize neurofeedback training that takes into account individual differences in brain function, grouping subjects by attention level using SSVEP/SSSEP responses was investigated.

B05-10: Brain mechanisms for generating exploratory adaptation: Modeling the brain function based on meta-reinforcement learning

Principal investigator: Yuki Ueyama (NDA Japan)

DCM analysis was used to identify the brain networks in exploratory adaptation.

III. Activities

Activities mainly organized by the members of Group B are as follows:

- November, 20th, 2023, HMS2023 Organized session (Nagoya University)
  Prof. Kobayashi (B05-5) gave plenary talk. In the organized session, Prof. Nambu (B05-4) gave keynote talk and 5 researchers in Group B presented their recent research progress, and they deeply discussed.
- February 16-17rd, 2024, Organized session at the symposium on Distributed Autonomous Systems (Tokyo University of Agriculture and Technology), 13 oral presentations.

B01 Annual report of research project

Toshiyuki Kondo
Tokyo University of Agriculture and Technology
t_kondo@cc.tuat.ac.jp

Abstract— **This research project aims to realize systems modeling of hyper-adaptability mechanism with functional "dis-inhibition" observed in the impaired brain, especially from the viewpoint of reconstruction of neural structure. For this aim, we investigate (1) Tensor decomposition and probabilistic latent variable model for analyzing long-term brain activity, (2) Integration of computational brain network and musculoskeletal models, and (3) Motor learning experiments with VR/Robot technologies enhancing hyper-adaptability.**

I. Introduction

When a person experiences acute/chronic impairment or disorder due to aging, the brain reorganizes neural networks by dis-inhibiting pre-existing neural network that is normally suppressed and searching for latent but available network has not been utilized through the course of evolution and development. We call this functional compensation process as "reconstruction of neural structure", i.e. a neural entity that achieves hyper-adaptability.

In order to verify the hypotheses described above, knowledge in neuroscience is essential. However, with only the "bottom-up" approach relying on experiments and analyses, it would be difficult to clarify hyper-adaptability that is manifested by systematic behavior of a neural network. Therefore, this research project takes an interdisciplinary approach that integrates the mathematical modeling technology of systems engineering with neuroscience to understand the reconstruction of neural structure.

II. Research outcomes

A. Probabilistic latent variable model for analyzing long-term multi-modal data

Prof. Kondo (Tokyo University of Agriculture and Technology, TUAT), Dr. Miyashita (TUAT) and Dr. Yano (Toyota Motor Cooperation) have developed a statistical technique to quantify the time-varying structural change in the brain networks behind the hyper-adaptability. In this fiscal year, they worked on the estimation of latent structure in brain activity.

Specifically, the channel, frequency, and time components were obtained as a tensor by performing time-frequency analysis (the short-time Fourier transform) on the multi-channel time-series data of sleep EEG provided by Prof. Matsumoto (A05-7) [1]. After performing tensor decomposition (non-negative CP decomposition), the tensor were expressed as the sum of latent variables. The time component of the latent variables was divided by a pre-detedmined time window. For each time window, the correlation between the latent variables was calculated, and the dynamic structure of the latent variables was estimated by the Time-varying Graphical Lasso (TVGL) method. We can extract the relationship between latent variables as a graph structure specific to sleep stages, and visualize the characteristics of the dynamics as a combination of channels and frequency bands.

As shown in Fig. 1, we applied the method to multi-unit recording data of mice in action, which were provided by Prof. Aizawa (A01).

B. Integration of computational brain network and musculoskeletal models

Prof. Chiba (Asahikawa Medical University) and his colleagues is focusing on gait initiation to estimate differences in the brain networks of young and elderly people. It has been reported that the amount of movement of the Center of Pressure (CoP) and the time of movement of the CoP at the gait initiation in elderly are both shorter than those of healthy young adults. We hypothesize that this is due to "increased muscle tone during standing posture maintenance and insufficient inhibition during gait initiation. Their immediate goal is to estimate the factors that cause the difference between young and elderly subjects, based on the differences in the parameters using a musculoskeletal model (Fig. 2).

In the previous year, the stiffness of the hip and hip joints could not be completely set to zero in the musculoskeletal model. In other words, the results were the gaits with virtual aids in the simulations. Therefore, it was difficult to make comparisons with actual humans. In this fiscal year, we proposed a design method that enables the stiffness of all joints to be set to zero, and designed a controller which enables gait for several seconds. Based on this gait, we designed and analyzed a gait initiation motion.

We designed a gait and gait initiation motion for a body model with 70 muscles and 15 joint degrees of freedom in the lower limbs and trunk, a nerve transmission time of 20[ms], and motor noise, which enable a comparison with actual human. It is very difficult to design a controller under the above conditions and obtain a reasonable gait because of the large number of design parameters. We solved this problem by 1) assigning an feedforward (FF) controller and 2) applying a stepwise optimization method: 1) designing an FF controller without time delay and 2) designing an feedback (FB) controller with time delay to deal with noise. 2) In the design of each controller, optimization is done by fixing some of the degrees of freedom. The gait control parameters are obtained by using the optimal solution as

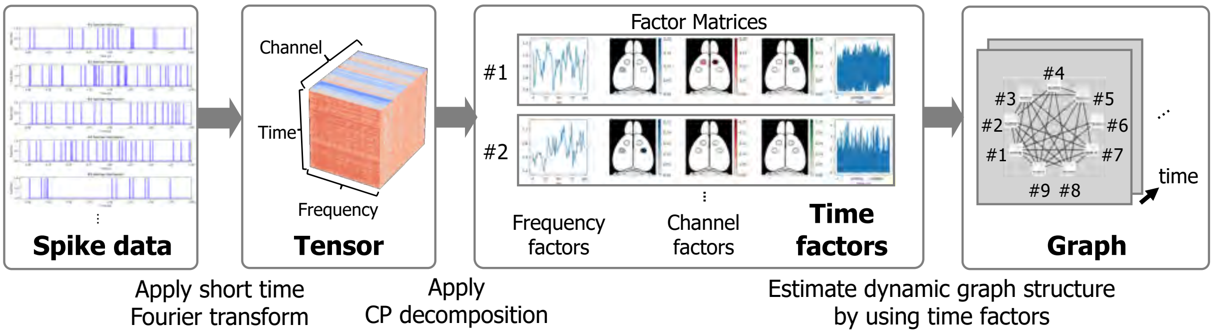


Fig. 1. Structural change in multi-unit recording data of mice in action identified by using Tensor decomposition and TVGL.

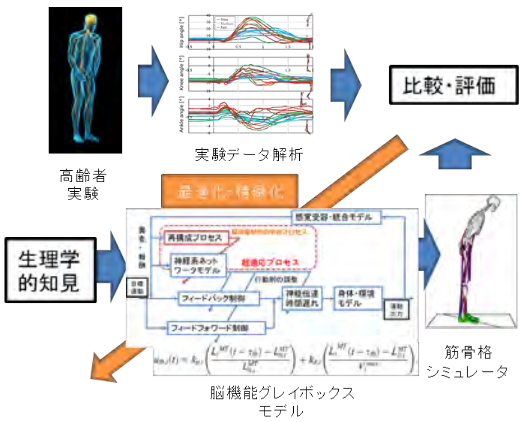


Fig. 2. Constructive modeling approach.

the initial values and releasing the fixed degrees of freedom sequentially. As a result, we confirmed to obtain a gait, although its gait is an outward pointing gait.

In addition, we designed a neural controller for gait initiation to enable the above gait from standing. We confirmed that just switching from posture-maintaining control to gait control alone would cause the model to fall down. Therefore, we designed the target posture and the timing of the switch in the gait start operation by optimization. As a result, we obtained a solution that enables the transition to gait. The analysis results showed that the CoP was moved to the supporting leg after being moved to the swinging leg side. This may be an anticipatory postural adjustment to the gait initiation. However, the model did not reach a sufficient velocity and fell at the fourth step. This means that the gait initiation may require different motions not only in the first step, but also after the second step [6].

C. Motor learning experiments with VR/Robot technologies enhancing hyper-adaptability

Prof. Kondo and his colleagues investigated motor learning experiments with VR and/or haptic robot technologies and motor function evaluation with brain signal analysis [2], [3]. In this fiscal year, they analyzed NIRS signals under an attention task (continuous performance test) for quantitative evaluation of human attention levels [4]. They found that high correlation between activity on the DLPFC related to executive function and the performance score.

Moreover, they developed a ring-shaped device and used it to measure the amount of finger usage in daily life of 20 stroke hemiplegic patients [5]. They investigated the correlation between the rate of finger usage on the paralyzed side and general clinical indeces (FMA-UE, ARAT, STEF, MAL). As a result, they confirmed that the measure correlated with the quantitative indices FMA-UE, ARAT, and STEF, but not with the qualitative index MAL.

III. Conclusions

As the final year of the project, we investigated usefulness of the proposed methodologies for modeling the hyper-adaptability in collaboration with neuroscience research groups.

In the future, we will continue to deepen the modeling methodology, and we further apply the models to actual neurophysiological data. Moreover, we will investigate the motor tasks that can induce ”reconstruction of neural structure” with dis-inhibition in the brain of elderly people under the frailty state.

References

[1] Megumi Miyashita, Toshiyuki Kondo, Analysis of data using tensor decomposition and time-varying graphical lasso, The 2nd International Symposium Hyper-adaptability, Kyoto, Japan, (10/28-29, 2023).

[2] Mizuki Miyazawa, Yoshikatsu Hayashi, Tamami Sudo, Megumi Miyashita and Toshiyuki Kondo, Hand Velocity in Passive Motor Experience affects Visuomotor Adaptation, *The 45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, Sydney, Australia, (7/24-27, 2023).

[3] Ozge Ozlem Saracbasi, William Harwin, Toshiyuki Kondo and Yoshikatsu Hayashi, Sequential Learning: A Pilot Hyperscanning Study, *The IEEE World Haptics 2023 conference*, Delft, Netherlands, (7/10-13, 2023).

[4] Saki Niiyama, Rie Yoshida, Tamami Sudo, Megumi Miyashita and Toshiyuki Kondo, Modulated Brain Networks via Motor Learning, *2023 International Symposium on Micro-NanoMechatronics and Human Science (MHS2023)*, Nagoya, Japan (11/20, 2023).

[5] Naoya Yamamoto, Takato Matsumoto, Tamami Sudo, Megumi Miyashita and Toshiyuki Kondo, Quantitative measurement of finger usage in stroke hemiplegia using ring-shaped wearable devices, *Journal of NeuroEngineering and Rehabilitation*, 20, 73, 2023.

[6] Ryosuke Chiba, Hitohiro Etoh, Kaoru Takakusaki, Kohei Kaminishi, Jun Ota, Generation of three-dimensional gait and gait initiation motion using a musculoskeletal model with 70 muscles, The 2nd International Symposium Hyper-adaptability, Kyoto, Japan, (10/28-29, 2023).

B02 Annual report of research project

Yasuharu Koike*, Tetsuro Funato†
* Tokyo Institute of Technology,
† The University of Electro-communications

***Abstract*—We obtained the following three results. 1. Regression analysis of muscle activity and brain activity showed brain activity involved in muscle activity changes after tendon transfer 2. Simulation of the monkey musculoskeletal system using reinforcement learning reproduced the learning process for motor acquisition. 3.We propose a theoretical framework to explain differences in learning rates of inverse models with respect to learning of reaching movements.**

I. Introduction

In this study, we conduct a modeling study of the recovery mechanism of the movement accompanying the body transformation.The nervous system adapts to the environment by repeating the optimization and learning of the control system in response to muscle tendon transformation. Here, humans and animal experiments reported the existence of discontinuous changes by reconstruction of muscle synergies. However, conventional system engineering approach using optimization and learning has paid little attention to the reconstruction of such a discontinuous structure, and almost no research has investigated its mechanism.

II. Objective

In this research, we study the modeling of the recovery mechanism of the movement accompanying the muscle tendon transformation. In order to model this process, we perform 1) construction of an experimental system to examine the effects of long-term physical transformation of a person by virtual surgery, 2) construction of a decoding method of brain and muscle activity, 3) construction of a musculoskeletal model that can reproduce the transformation. Through these studies, we will elucidate the mechanism of the hyperadaptive process for body transformation.

In addition, we will construct an experimental system that virtually realizes changes in motor functions associated with human body transformation using Virtual Reality, and a dynamic simulation environment. Through this, an experimental system that obtains biological information associated with long-term / short-term physical transformation and an information processing environment that handles the dynamic process of physical transformation are established.

III. Achievements

A. Analysis of Changes in Brain Activity in Monkeys after Tendon Transfer

Our previous studies about tendon transfer in Monkeys have shown stepwise changes of muscle usage in units of muscle synergies. This year, we studied changes in brain activity after tendon transfer by investigating the relationship between muscle activity and brain activity during this process [1].

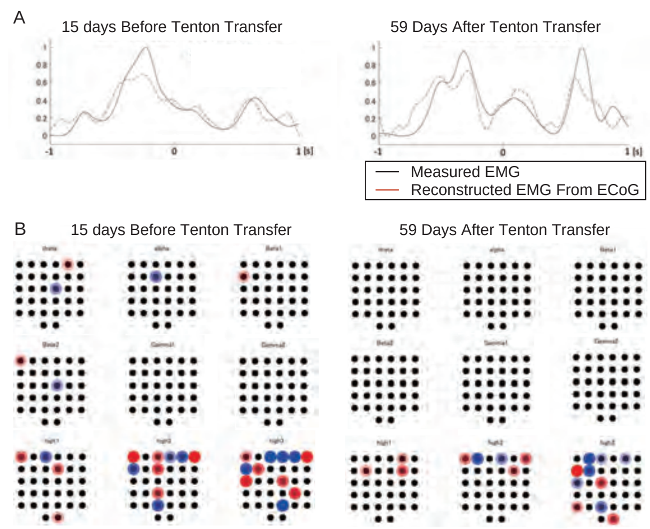


Fig. 1. Reconstruction of muscle activity from brain activity. Results of one trial each before and after tendon transfer are shown. A: Comparison of EMG reconstructed from ECoG and measured EMG. B: Brain regions within M1 used for reconstruction. Positive and negative contributions to the reconstruction are shown in red and blue, respectively.

We measured muscle activities (EMG) and brain activity (ECoG) during grasping movements in one macaque monkey with tendon transfer, where the two muscles used to flex and extend the fingers were replaced. Regression analysis between the measured EMG and ECoG was performed to determine which combination of brain regions and frequencies of brain activity constituted the muscle activity. In particular, regression analysis using sparse regression was conducted to identify factors that contribute to EMG above a certain level.

The results of sparse regression showed that muscle activity was reconstructed with high accuracy by a total of about 20 to 30 brain regions at three main high frequencies (Fig. 1). Furthermore, a comparison of the activity before and after tendon transfer showed that the trend of brain activity changed drastically approximately 3 months after tendon transfer as well as imediately after tendon transfer. This indicates that changes in brain activity associated with recovery occurs in a stepwise manner similar to muscle activity.

B. Reproduction of the motor reacquisition process using a monkey musculoskeletal model and reinforcement learning

To investigate motor recovery strategies after tendon transfer, we have constructed a monkey musculoskeletal muscle model on the musculoskeletal simulation software MuJoCo and investigated changes in muscle activity and muscle synergy before and after tendon transfer on the model.

This year, in order to reproduce the motor reacquisition process during recovery, we constructed a learning environment for reaching movements by reinforcement learning for the monkey musculoskeletal muscle model. We constructed a learning system using Deep Deterministic Policy Gradient (DDPG), a deep reinforcement learning method that can handle continuous state and action spaces, and trained it on a monkey musculoskeletal model constructed on MuJoCo. The results showed that it could reproduce the reaching behaviors of the monkey.

C. Theoretical limits on the speed of learning inverse models explain the rate of adaptation in arm reaching tasks

we use our theoretical framework to account for differences in the speed of learning in two previous studies. First, we address the speed of learning in visuomotor rotation experiments with different number of targets Second, we study a virtual surgery task, a type of musculoskeletal transformation in which the pulling forces of muscles in a mapping between muscle activations and end-point forces are changed, simulating tendon transfer surgeries.

Participants performed a reaching task using the trackpad of a laptop computer. Each experimental session was conducted on a different day.

Each trial began with the cursor at the center of the virtual environment. After a target appeared, participants quickly moved the cursor to the target. Participants only received visual feedback of the final position of the cursor. At the end of the trial, the cursor and the target disappeared, and participants returned the cursor to the center of the virtual environment. Only a circle indicating the distance of the cursor to the center was visible during this stage.

An essential aspect of human motor learning is the formation of inverse models, which map desired actions to motor commands. Inverse models can be learned by adjusting parameters in neural circuits to minimize errors in the performance of motor tasks through gradient descent. However, the theory of gradient descent establishes limits on the learning speed. Specifically, the eigenvalues of the Hessian of the error surface around a minimum determine the maximum speed of learning in a task. Here, we use this theoretical framework to analyze the speed of learning in different inverse model learning architectures in a set of isometric arm-reaching tasks.

$\boldsymbol{P}$ represents the forward physics of the task, and $\boldsymbol{m}$ is an N_m-dimensional motor command vector produced by the inverse model (joint torques, muscle activations or muscle synergy activations). Because the task is isometric, forces can be modeled as a linear function of the motor command $\boldsymbol{m}$, or the transformed motor command $\boldsymbol{\sigma}(\boldsymbol{m})$. We first consider the case in which the inverse model g^{-1} via a radial basis function (RBF) network. In the RBF network, the inverse model is given by:$g^{-1}(\boldsymbol{f}) = \boldsymbol{W}\boldsymbol{\phi}(\boldsymbol{f}) = \boldsymbol{m}$. where $\boldsymbol{W}$ is a matrix of weights, $\boldsymbol{\phi}$ is a vector of N^2 two-dimensional RBFs $\boldsymbol{\phi}(\boldsymbol{f})$ evaluated at $\boldsymbol{f}$

Learning in the isometric tasks aims to minimize the task performance error given by the cost function $J = \frac{1}{2}||\boldsymbol{f}_d - \boldsymbol{f}_r||^2$. The cost function can be approximated locally around its minimum as a second order Taylor expansion $J(\boldsymbol{w}) = J(\boldsymbol{w}^*) + \frac{1}{2}(\boldsymbol{w} - \boldsymbol{w}^*)^T \boldsymbol{H}(\boldsymbol{w} - \boldsymbol{w}^*)$ where $\boldsymbol{H}$ is the Hessian of J.

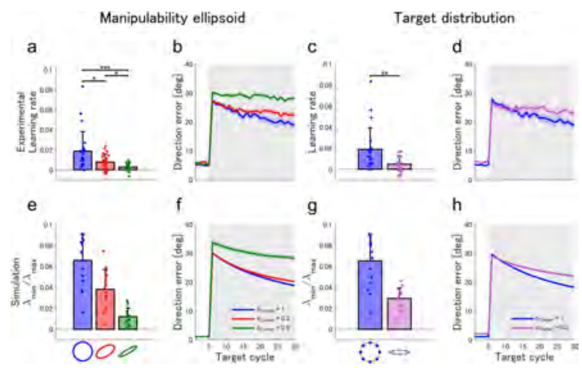


Fig. 2. Experimental and simulation results

Experimental and simulation results in the anisotropic scaling and anisotropic target distribution tasks. a. and c. Experimental learning rates in Experiment 1. e. Estimates of the slowest time constant of learning given by $\lambda_{Hmin}/\lambda_{Hmax}$ for the three scaling conditions in Experiment 1. f. Simulated mean error in initial direction during learning in the three scaling conditions in Experiment 1 (mean of the 15 simulated participants), and h. in Experiment 2.

In both simulated frameworks, the simulated learning curves in the compatible and incompatible surgeries closely match the learning curves observed experimentally after selecting an appropriate learning rate for each simulated subject.

IV. Conclusion

In the analysis of brain activity changes after muscle reconfiguration, investigating brain activity related to muscle activity generation through regression analysis has clarified the brain activity associated with changes in muscle activity after reconfiguration. In studies of monkey musculoskeletal simulations, it has become possible to replicate the learning process for reacquiring movement using reinforcement learning. Furthermore, a learning control model that replicates the learning speed of motor adaptation has been proposed.

References

[1] K. Himeji, T. Funato, R. Philipp, N. Ohta, T. Hara, K. Seki, Analysis of Brain Activity Changes in Monkeys during Motor Recovery after Muscle Reconfiguration, 36th Symposium on Autonomous Distributed Systems, 1A2-5, 2024.

[2] Victor R. Barradas and Yasuharu Koike and Nicolas Schweighofer, Theoretical limits on the speed of learning inverse models explain the rate of adaptation in arm reaching tasks, Neural Networks, 170, 376-389, 2024

B03 Annual report of research project

Hajime Asama
The University of Tokyo

***Abstract*— The aim of this research group is to elucidate the influence of body awareness and emotion on the acquisition process of hyper-adaptation, and to construct and validate a quantitative mathematical model capable of predicting changes in motor control. Additionally, we intend to propose and validate a model-based rehabilitation approach that facilitates function of hyper-adaptation through body awareness and emotion based on the mathematical model. The achievements of this year's study are summarized as follows: 1) Investigation of changes in the sense of agency in Parkinson's disease patients and compensatory mechanisms in the brain of patients with spinocerebellar degeneration, 2) Construction and demonstration of the computational theory of meta-learning, 3) Development of a predictive model for the sense of agency based on motion data using deep learning, 4) Construction of a movement function evaluation system to enhance user motivation.**

I. Introduction

The B03 project aims to propose new intervention methods from cognitive aspects such as body awareness and emotion to facilitate the acquisition of hyper-adaptation through body awareness and emotion. To quantitatively measure the hyper-adaptive process and construct mathematical models, we will develop brain decoding techniques and establish methods to quantitatively measure body awareness and emotion. Next, to validate the model-based rehabilitation approach, we will develop a robotic intervention platform. Specifically, in individuals with decreased motor function, we will quantitatively measure and model the hyper-adaptive process, propose and validate a model-based rehabilitation approach based on the mathematical model of hyper-adaptation, using a robotic intervention platform.

II. Aim of the Group

The specific aim of this research project is to construct a mathematical model capable of representing the reorganization processes of body awareness, emotion, and motor control laws during motor interventions, motor learning, and long-term learning processes. Based on this model, we aim to propose a model-based rehabilitation approach. Specifically, we will target clinical cases involving disorganization of body awareness and motor control, such as neurodegenerative diseases and schizophrenia, and construct models to investigate changes in the structure of the body and motor control laws.

III. Research Topics

A. *Change in sense of agency and hyper-adaptation in Patients with neurodegenerative disorders*

In Asama's group, we examine the relationship between the altered sense of agency in individuals with Parkinson's disease and the presence of micrographia. Forty-five patients with Parkinson's disease were included, and based on the characteristics of handwriting, they were categorized into groups: PM group (progressive micrographia), CM group (consistence micrographia), and without micrographia group. Performance on a task assessing the regularity in motor control contributing to the emergence of the sense of agency was compared among these groups. The results revealed that, compared to without micrographia group, the PM group showed a decrease in abilities related to regularity in motor control (Fig. 1). Our findings suggest the presence of an altered sense of agency underlying micrographia.

Furthermore, Asama's group investigated the changes in volume by structural imaging to clarify how the cerebrum compensates for the impaired motor control system observed in patients with spinocerebellar degeneration. Although our previous research has shown areas of increased cerebral volume in groups of patients, it was unclear whether there was a common pattern of increase in each area among patients. Therefore, to clarify the existence of patterns in volume increase, volumetric data of the cerebral cortex (68 regions) from 50 patients were subjected to principal component analysis for dimensionality reduction. Cluster classification based on the scores of each component was then performed. The results identified four clusters, with significant differences

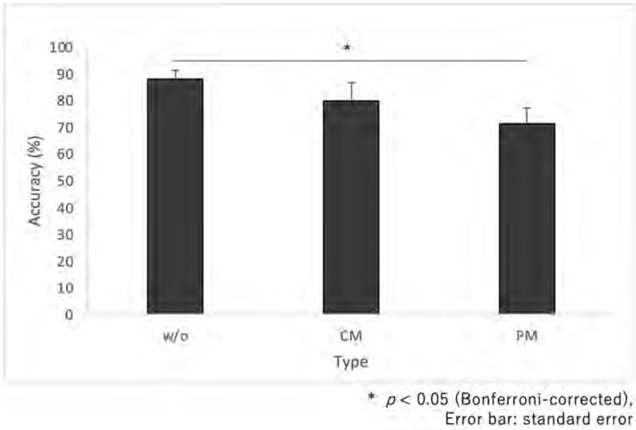


Fig. 1 Performance of each group in the task assessing the regularity of motor control

in motor function scores (SARA scores) observed between two of them [1]. The observed differences in motor function between these clusters suggest the presence of adaptive neural activity patterns or non-adaptive neural activity patterns governed by the cerebral cortex.

B. *The computational model of hyperadaptation as an adaptation of hyperparameters of motor adaptation*

If hyper-adaptation simply represents an excessive form of adaptive behavior, it risks undermining a healthy adaptive functions, leading to maladaptation. Both humans and animals possess an innate capability to adjust their adaptative processes to optimize the efficiency of their adaptation mechanisms. This capability, known as meta-learning, embodies the “learn-to-learn” process, often observed in our adaptive activities. Regarding motor adaptation, it is well-established that adaptation rates were altered in unstable environments, influenced by signals of reward and punishment, yet a computational model has not been proposed.

This year, we introduced a computational model for meta-learning motor skills grounded in an optimization principle (Fig. 2) [2]. This model accounts for various hyper-adaptation phenomena previously published. Moreover, we verified that existing models fail to interpret these phenomena. Our findings were further examined through a novel motor meta-learning task, wherein errors and rewards were presented in separate task trials. It was demonstrated that human participants could modulate both learning and retention by integrating rewards and errors across different trials, thereby supporting our computational model of motor meta-learning.

Previously, motor learning was conceptualized and modeled as a simple mechanism of reducing prediction errors in movement trajectories. The ecological rationale behind the reduction of trajectory errors by humans and animals remained vague. Our model, based on the optimization theory, prioritizes the maximization of rewards and minimization of punishments. This approach provides an ecological justification of the trajectory error minimization theory only when error minimization is linked to punishment minimization.

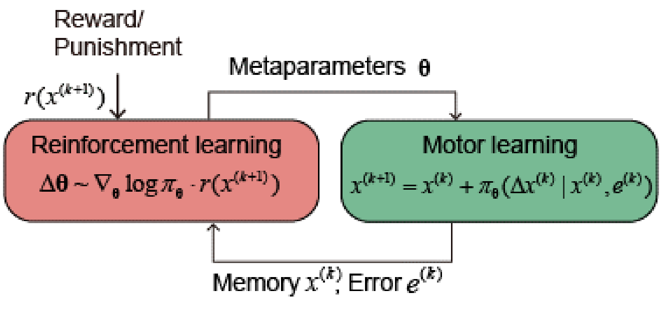


Fig. 2 Mode structure of meta-learning

C. *Verification of the active inference theory based on motion analysis using deep learning*

The Wen’s group has employed deep neural networks to learn the motion trajectories of mice on a two-dimensional plane, to analyze exploratory behaviors related to the sense of agency. Based on the information from the neurons in the hidden layer after learning, they calculated the similarities and differences between the trajectories drawn by the participants and those presented on the screen, thereby estimating the participants’ sense of movement agency with high accuracy [3]. Furthermore, this method accurately predicted the decline in control detection accuracy in patients with schizophrenia [4]. These results reveal that the reduction in the sense of agency in patients with schizophrenia is not merely due to changes at the perceptual or judgment levels, but to problems in generating behavioral strategies. Based on these findings, this study paves the way for a novel research approach that involves extracting and modeling information from behaviors that underlie the emergence of the sense of agency.

D. *Evaluation System of Motor Function*

With brain damage or aging, motor function declines, inhibiting daily life activities. In response, rehabilitation and daily exercise habits become crucial. Our research group focuses on human cognition and emotions, aiming to motivate individuals to engage in rehabilitation by presenting them with their own motor function.

This year, we targeted elderly individuals attending daycare and developed a system to estimate their muscle strength and balance capabilities using force sensors attached to assistive devices. We confirmed the system's ability to accurately estimate each parameter. By utilizing this system, we can measure the longitudinal changes in motor function without the need for sensor attachment and present these changes to users. This enables the convenient presentation of training effects in settings like daycare, potentially fostering increased motivation.

IV. Future Perspective

In the B03 project this year, we focused on investigating changes in motor agency perception in patients with neurodegenerative disorders and developing methods to infer these changes from movement data. Additionally, we proposed a computational model for meta-learning in motor tasks, constructing a new learning theory that surpasses traditional error minimization approaches. Furthermore, we proposed a system aimed at enhancing the motivation of individuals undergoing motor learning by developing a straightforward method for evaluating motor functions.

References

[1] Hamada, H., Kikuchi, Y., Wen, W., An Q., Yamashita, A., & Asama, H “Characteristics of Structural Changes in the Cerebrum of Patients with Spinocerebellar Degeneration,” Neuroscience 2023 (SfN2023), Washington D.C. (USA), November 2023.

[2] Sugiyama, Taisei, Nicolas Schweighofer, and Jun Izawa. "Reinforcement learning establishes a minimal metacognitive process to monitor and control motor learning performance." Nature Communications 14.1 (2023): 3988.

[3] A. Y. Chang, H. Oi, T. Maeda, and W. Wen, “The sense of agency from active causal inference,” bioRxiv, 2024, doi: 10.1101/2024.01.29.577723.

[4] H. Oi, W. Wen, A. Chang, H. Uchida, T. Maeda, and K. Hospital, “Hierarchical components of sense of agency in schizophrenia: From motor control to self-attribution,” PsyArXiv, 2023, doi: 10.31234/osf.io/y

B04 Annual report of research project

Jun Ota
Research into Artifact, Center for Engineering (RACE), School of Engineering, The University of Tokyo

I. Introduction

The study in this project aims to verify the following hypothesis for reconstitution of sensorimotor control rules of the hyper-adaptation functions: Neurotransmitters (such as dopamine; DA), whose levels are reduced in patients with neurodegenerative disorders, adjust the activity levels in various brain areas and coupling strength between neuronal circuits as well as control the multitasking function.

The term “multitasking function” denotes the ability to execute multiple tasks smoothly and simultaneously. To achieve this, we attempt to build a mathematical model that considers the role of neurotransmitters in posture control in co-operation with the A04 research group and other B01-B04 research groups. We address the study in three steps. 1) Verification of the role of neurotransmitters in posture control. The function necessary for multitasking is assumed to be impaired in patients with neurodegenerative disorders, such as Parkinson’s disease, and neuronal degeneration and abnormalities in neurotransmitters are thought to exist. To verify the role of the neurotransmitters in multitasking, we focus on neurotransmitters that may change in patients with Parkinson’s disease. 2) Development of a multitasking representation model that considers the role of neurotransmitters in posture control. A mathematical multitasking model will be developed to integrate information regarding neurotransmitters from a micro-viewpoint and information regarding behavioral and physiological reactions from a macro-viewpoint that appear to result from information processing. 3) Verification of this mathematical model using data obtained from humans.

Members of B04 group consists of a principal investigator (Ota), a funded co-investigator (Yozu), and 21 co-investigators (Shirafuji, Kaminishi, Takamido, Hasegawa, Kohno, Kishimoto, Yuine, Ishibashi, Hamada, Miyata, Kanaya, Osaki, Kawano, Kanai, Omura, Hou, Fujiwara, Makino, Nishizawa, Ishikawa).

II. Research results

A. Analysis of abnormal posture in Parkinson's disease using a computer model

Ota and colleagues build a mathematical model that considers the role of neurotransmitters in posture control with Prof. Takakusaki (A04) and Prof. Chiba (B01).

We have proposed a standing postural control model (with muscle tone parameters and feedback control parameters) that introduces control mimicking the reticulospinal and vestibulospinal tracts. In order to realize standing in abnormal posture with this control model, we analyzed abnormal posture of patients with Parkinson's disease: 1) Based on the postural data of patients, calculate the muscle tone parameters that allow the musculoskeletal model to stand; 2) After setting the muscle tone parameters, adjust the feedback control parameters and posture to reduce sway. The results showed that the muscle tone parameters that realize a Parkinson's patient-like standing posture were successfully estimated, and that a standing posture more similar to the experimental results was realized when the muscle tone was greater than the value equivalent to that of a normal person [1]. In addition, the hypothesis that "the patients exhibits abnormal posture because the sway in the abnormal posture is smaller than in the other postures in relation to the increase in muscle tone" was supported.

We also analyzed Dopamine transporter single-photon emission computed tomography (DAT-SPECT), which is used for the diagnosis of Parkinson's disease, and examined the relationship between the model control parameters. The relationship between DAT-SPECT and various motor symptoms has not been sufficiently analyzed. Therefore, we developed a system that captures 3D DAT-SPECT information and examines the relationship between DAT-SPECT and each motor symptom using deep learning technology. A model was constructed to regression analyze the scores associated with each motor symptom using DAT-SPECT images as input, and it was visualized which parts of the image the model focused on [2]. In the same way, it was shown that a neural network model using DAT-SPECT images as input can estimate the magnitude of the muscle tone parameters [3]. In the estimation, focus was placed on the area around the striatum, where DAT is thought to accumulate (Fig. 1), which is consistent with the existing findings. This provides a basis for describing the relationship between the state (quantity and distribution) of neurotransmitters in the brain and the behavioral and physiological responses that emerge. There is a possibility that this method can be applied to the pathological examination of diseases related to dopamine in the basal ganglia.

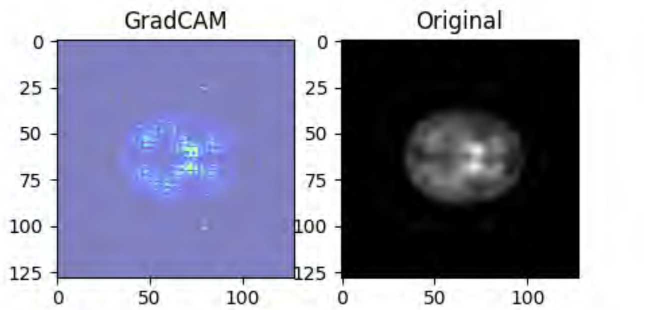


Fig. 1. Grad-CAM visualization of the estimated magnitude of the muscle tone parameters. The closer to the red color, the more attention was paid.

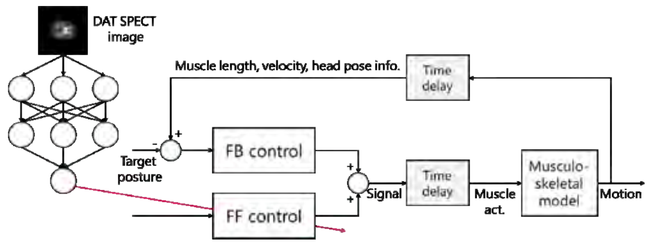


Fig. 2. Using brain imaging, a standing postural control model, and a musculoskeletal model, the behavioral-physiological responses that emerge from the neurotransmitter state are described.

B. Evaluation of the role of neurotransmitters in postural control while multitasking

Yozu et al. evaluated the role of neurotransmitters in postural control while multitasking. To understand this subject, we had conducted a review of prior research on the subject of multitasking [1]. Subsequently, we performed a preliminary study to assess the impact of neurotransmitters on multitasking in Parkinson's disease patients with diurnal fluctuations, in which we used a multi-task paradigm of static standing (motor task) and calculation (cognitive task) [2]. Our research thus far suggests that the impact of neurotransmitters on multitasking depends on the type and difficulty of the task. Therefore, we focused on voluntary sway and stepping as motor tasks, given their versatility in terms of task difficulty. This year, we have submitted a basic study about voluntary sway on healthy subjects [3] and conducted stepping study on the patient subjects. Furthermore, as pain is often comorbid in Parkinson's disease, we submitted the basic study which investigated the effects of pain on postural and motor performance in healthy subjects [4]. We also conducted more basic study on locomotion [5].

1) Analysis of cortical mechanisms during voluntary sway

Parkinson's disease causes postural instability; thus, it is important to understand postural instability, as it could potentially lead to patients falling. Patients with Parkinson's disease exhibits decreased forward center of pressure movement speed from the early stages of the disease (Hoehn and Yahr scale I~II). Therefore, we defined the task of moving the center of pressure in the anterior-posterior direction while adopting the standing posture as a voluntary sway and applied it as a motor task. The difficulty level of this task can be widely adjusted by increasing or decreasing the sway frequency. We developed a measurement system with voluntary sway; and before analyzing Parkinson's disease patients, we first measured heathy subject to clarify the changes in movement [3] and brain activity [6] as a result of changes in sway frequency. The postural analysis of voluntary sway in healthy individuals revealed that the joint angles of the trunk and knees varied depending on the speed of movement of the center of pressure. We also measured cerebral blood flow during voluntary sway using fNIRS. The results indicated that the primary motor cortex and supplementary motor area were continuously active during voluntary sway, whereas there was a peak of activity at the beginning of the walking motion.

2) Effects of dopamine on postural control during multitasking

To investigate the effects of dopamine on dual-task performance, we examined task performance and brain activity in Parkinson's disease patients in two states (ON and OFF). The task was a dual task consisting of arithmetic task and stepping. We compare the data of ON with that of OFF states, and also compare the data of single task with that of double task. The results are under analysis.

3) Analysis of the effect of foot pain on posture during gait

Pain is one of the non-motor symptoms in patients with Parkinson's disease, and it adversely affects a patient's quality of life and activities of daily livings; thus, it is an important symptom that should be addressed. Patients with Parkinson's disease often experience foot pain; however, the effect of pain on these patients' truncal posture during gait is unclear. Here, we analyzed the effects of pain on truncal posture in healthy subject. We induced pain during the stance phase, and measured data on trunk and lower limb joint angles, gait cycles, and foot pressure distribution. As a result, the anterior tilt of the trunk was observed. This study showed that experimentally induced plantar pain was associated with anterior trunk tilt [4]. When evaluating posture and movement in Parkinson's disease patients with comorbid pain, it might be necessary to consider the possible influence of pain on the anterior tilt of the trunk.

4) Development of an experimental setup on the origin of the multi task problems.

The problem of the multitasking is thought to be caused by the combination of the higher motor function of bipedal walking and the higher brain function of cognition. Therefore, we conducted basic research on crawling in order to develop an experimental system with more primitive postures and movements [5].

REFERENCES

[1] Y. Omura, K. Kaminishi, R. Chiba, K. Takakusaki and J. Ota, "A neural controller model considering the vestibulospinal tract in human postural control," Frontiers in Computational Neuroscience, vol. 16, 785099, 2022.

[2] K. Kaminishi, D. Li, R. Chiba, K. Takakusaki, M. Mukaino, and J. Ota, "Characterization of Postural Control in Post-Stroke Patients by Musculoskeletal Simulation," Journal of Robotics and Mechatronics, vol. 34, no. 6, pp. 1451-1462, 2022.

[3] Y. Omura, H. Togo, K. Kaminishi, T. Hasegawa, R. Chiba, A. Yozu, K. Takakusaki, M. Abe, Y. Takahashi, T. Hanakaaw, and J. Ota. Proceedings of the 36th SICE DAS Symposium, Tokyo, 2023.

[4] A. Yozu, J. Ota, T. Hanakawa, K. Takakusaki. Studies on dual tasking: review and their relevance in rehabilitation. The journal of the Japanese Society of Human Care and Network. 20, 103-106, 2022.

[5] A. Yozu, K. Kaminishi, D. Ishii, Y. Omura, A. Matsushita, Y. Kohno, R. Chiba, J. Ota, Effects of medication and dual tasking on postural sway in Parkinson's disease: A pilot case study. Advanced Robotics, 35. 889-897, 2021.

[6] T. Hasegawa, T. Mori, K. Kaminishi, R. Chiba, J. Ota, A. Yozu, "Effect of Sway Frequency on the Joint Angle and Center of Pressure in Voluntary Sway," J Mot Behav., vol. 55, no. 4, pp. 373-383, 2023.

[7] A. Yozu, K. Sonoda, T. Hasegawa, K. Kaminishi, M. Osumi,, M. Sumitani, R. Chiba, J. Ota, "Effect of experimentally induced plantar pain on trunk posture during gait," J Phys Ther Sci., vol. 35, no. 9, pp. 613-618, 2023.

[8] A. Yozu, T. Hasegawa, N. Ogihara, J. Ota, "Peak vertical ground force of hand-knee crawling in human adults," J Phys Ther Sci., vol. 35, no. 4, pp. 306-310, 2023..

[9] N. Orihara, T. Hasegawa, K. Kaminishi, R. Chiba, J. Ota, A. Yozu. Proceedings of the 35th SICE DAS Symposium. Osaka, 2023.

B05-1 Motor learning of modularity in musculoskeletal models toward the emergence of muscle synergy

Mitsuhiro Hayashibe
Tohoku University

***Abstract*—In the first phase of the project, research was conducted on the generation of synergy in redundant body models. In the second phase, we went one step further and studied learning that can self-organize the switching of synergy modules as an extension of synergy.**

I. Introduction

To perform an energetically efficient motion as in human control, the so-called mathematical optimization-based approach is a state-of-the-art approach for solving redundancy problems. Such an optimization approach can provide an optimal solution when the prior dynamics information of the articulated body and environment is explicitly given. For the most of human daily task, the dynamics conditions are often unknown and varying. It still remains an open problem on how we can create human-like synergistic motion in a self-organized manner to switch synergy modality. This study provides self-organized framework to induce adaptive motor synergy alternation corresponding to the given environment and the motion task.

II. Postural Synergy Alternation

A self-organized phenomenon in postural coordination is essential for understanding the auto-switching mechanism of in-phase and anti-phase postural coordination modes during standing and related supra-postural activities. Previously, a model-based approach was proposed to reproduce such self-organized phenomenon. However, if we set this problem including the process of how we establish the internal predictive model in our central nervous system, the learning process is critical to be considered for establishing a neural network for managing adaptive postural control. Particularly when body characteristics may change due to growth or aging or are initially unknown for infants, a learning capability can improve the hyper-adaptivity of human motor control for maintaining postural stability and saving energy in daily living. This study attempted to generate a self-organizing neural network that can adaptively coordinate the postural mode without assuming a prior body model regarding body dynamics and kinematics. Postural coordination modes are reproduced in head-target tracking tasks through a deep reinforcement learning algorithm. The transitions between the postural coordination types, i.e. in-phase and anti-phase coordination modes, could be reproduced by changing the task condition of the head tracking target, by changing the frequencies of the moving target. These modes are considered emergent phenomena existing in human head tracking tasks. Various evaluation indices, such as correlation, and relative phase of hip and ankle joint, are analyzed to verify the self-organizing neural network performance to produce the postural coordination transition between the in-phase and anti-phase modes. In addition, after learning, the neural network can also adapt to continuous task condition changes and even to unlearned body mass conditions keeping consistent in-phase and anti-phase mode alternation [1].

III. Walking Speed Generalization

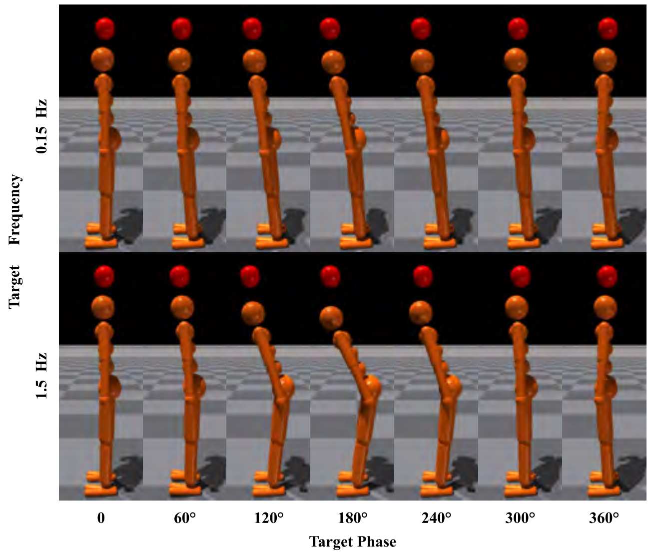
We humans can walk efficiently, sometimes slowly, sometimes quickly and at various speeds, sometimes unconsciously. However, there are still many unknowns about the mechanisms that produce energy-saving walking at such diverse speeds. Even for the same walking task, its muscle usage alters for slow, normal and fast speed thus its synergistic usage is systematically to be modulated. However, the existing reflex control modeling framework could not accurately change walking speed.

Our research group has focused on the human nervous system-based control known as reflex control and succeeded in reproducing variable speed walking through simulations using a musculoskeletal model that mimics humans [2]. We also developed an optimisation algorithm that extends the least-squares method and constructed a neural model that can realise more energy-efficient gait over a wide speed range. The analysis revealed that in reflex control, the neural circuits controlling the muscles that promote and inhibit swinging level of the swinging leg are an important factor in energy-saving gait. Simulation of a human-like musculoskeletal model varying its walking speed in response to an input target speed can be confirmed at Fig.2. Muscle usage alternation could be generated online depending on the given target speed.

IV. Conclusion

It has been demonstrated that the self-organisation phenomenon can be reproduced solely by motor experience and reinforcement learning, without the need for previously required prior body dynamics information. As the frequency of the motor task increases, the in-phase mode changes to an antiphase mode. This can be seen as a reproduction of the synergistic transition process between different synergy types.

Screenshots of learning tracking-balancing tasks at motion tracking frequency f of target point with regard to 0.15 $[Hz]$ and 1.5 $[Hz]$.



Evolution of correlation coefficient and relative phase influenced by different motion tracking frequencies f of the target point.

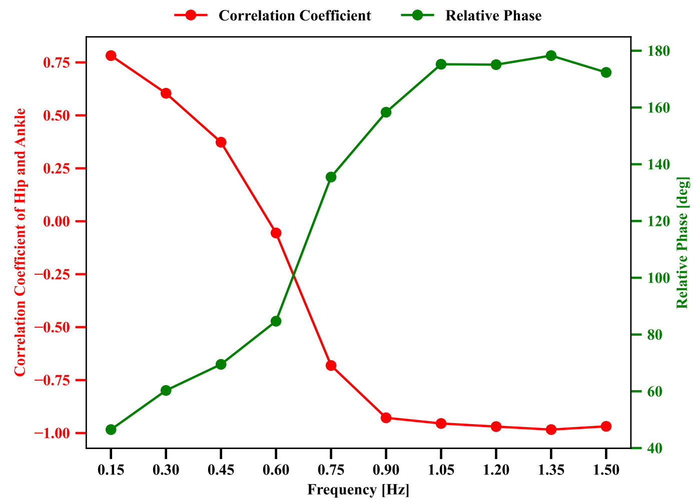


Fig. 1. Self-Organizing Neural Network for Reproducing Human Postural Synergy Alternation through Deep Reinforcement Learning

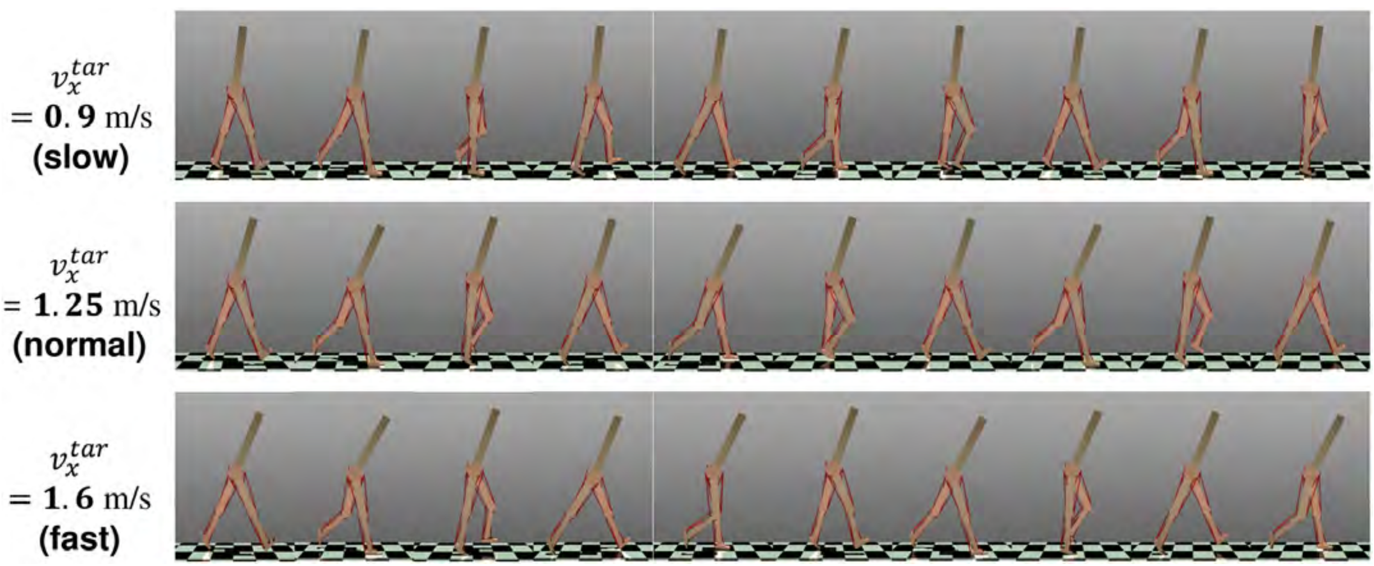


Fig. 2. Results of adaptive walking across a wide range of velocities in reflex-based musculoskeletal systems.

References

[1] K. Shen, G. Li, A. Chemori and M. Hayashibe, *Self-Organizing Neural Network for Reproducing Human Postural Mode Alternation through Deep Reinforcement Learning*, Scientific Reports, 13, 8966, 2023.

[2] S. Koseki, M. Hayashibe and D. Owaki, *Identifying essential factors for energy-efficient walking control across a wide range of velocities in reflex-based musculoskeletal systems*, PLOS Computational Biology, 20(1): e1011771, 2024.

B05-02: A neural network model for hyper-adaptability of bipedal locomotion

Naomichi Ogihara
Department of Biological Science, Graduate School of Sciences, The University of Tokyo

I. NTRODUCTION

Locomotion is one of the most important bodily functions for survival and reproductive success of humans. It encompasses actions such as evading predators, foraging for sustenance, and even seeking mates to propagate offspring. Locomotion is accomplished by the mechanical interaction of the musculoskeletal system with its inhabiting environment. Therefore, the morphology of the musculoskeletal system of an animal is shaped to adapt to its principal mode of locomotion. Humans are no exception. The human body has evolved over millions of years to adapt to the habitual bipedal locomotion.

Non-human primates can generally walk bipedally. Our group has been investigating bipedal locomotion in Japanese macaques to achieve a better understanding of the evolution of human bipedalism [1-4]. The acquisition of bipedal locomotion in an inherently quadrupedal primate could be regarded as a modern analogue for the evolution of bipedal walking, offering a living model for clarifying and reconstructing the evolution of bipedal locomotion. However, bipedal locomotion of Japanese macaques is different from that observed in humans. For example, the hip and knee joints are more flexed throughout the gait cycle, and macaques do not generally exhibit the characteristic double-peaked vertical ground reaction force (GRF) profile seen in humans. Such differences in kinematics and kinetics of bipedal walking between humans and nonhuman primates exist because of structural differences in the musculoskeletal system.

Bipedal walking is a mechanical phenomenon that moves the center of mass of the body from one place to the other by appropriately applying reaction forces acting from the ground to the feet. Therefore, the success or failure of bipedal walking depends on how the GRF are appropriately controlled. However, any changes of the musculoskeletal structure directly affect the way the body mechanically interacts with the ground, and should drastically alter coordinated dynamics of bipedal walking, more likely to disturb successful generation of stable bipedal locomotion. The fact that the selective pressure was applied to the human musculoskeletal structure during the evolution of human bipedal locomotion strongly indicates that the nervous system possesses an ability to spontaneously reorganize itself in such a way to adaptively make use of the morphological change in the body structure to accomplish more stable, robust and efficient bipedal locomotion. If the neuronal mechanism underlying such “hyper-adaptability” of human locomotion can be elucidated, the findings will not only contribute to clarifying the neural basis of the evolution of human bipedal locomotion, but also provides implications for effective therapeutic or rehabilitative interventions to restore walking ability in old adults who suffer from decline of bodily and neurological functions.

II. AIM OF THE GROUP

We aimed to clarify the neuronal mechanism underlying the “hyper-adaptability” of human locomotion to the alteration of the body structure in a constructive approach using a forward dynamic simulation. Specifically, we attempt to construct a model of locomotor nervous system incorporating the vestibulospinal tracts to realize stable, robust, and efficient bipedal locomotion while adaptively coping with the morphological change in the human body structure.

III. METHODS

A. *Musculoskeletal model*

We constructed a 2D musculoskeletal model of the bipedal Japanese macaque consisting of 9 links representing the HAT (head, arms, and trunk), thighs, shanks, and feet that are represented by two parts: a tarsometatarsal part and a phalangeal part based on our recently constructed anatomically based whole-body musculoskeletal model [5] (Fig. 1). Dimensions and inertial parameters of the limb segments were determined based on this 3D model. Here, we considered 10 principal muscle groups classified according to muscle disposition. Each muscle was modeled as a string connecting the origin and insertion points. The force generated by a muscle was calculated as the sum of the force generated by the contractile element due to the activation signal from the nervous system and the passive element parallel to the contractile element.

B. *Nervous model*

Animal locomotion is generally accepted as being produced by a rhythm-generating neuronal network in the spinal cord known as the central pattern generator (CPG), with locomotion evoked by stimulus input from the mesencephalic locomotor region in the brain stem. Such a spinal rhythm-generating neuronal network also seems to exist in primates and is hypothesized to contribute to the generation of actual locomotion. The CPG consists of two layers: a rhythm generation (RG) layer that generates oscillatory signals and a pattern generation (PG) layer that generates muscle activity patterns based on the phase signal from the RG layer. Therefore, in the present study, a mathematical model of the

CPG consisting of the RG and PG layers was constructed. The RG layer was modeled by two phase oscillators corresponding to the phase signals for the left and right legs. The PG layer then generated the activation pattern of each muscle represented by a combination of two Gaussian basis functions of the phase signal. The RG layer in the CPG is known to modulate its basic rhythm by producing phase shifts and rhythm resetting based on sensory information. To take this into account, we reset the oscillator phase based on foot–ground contact information. To generate bipedal walking, an appropriate activation pattern was determined for each of the 10 muscles such as to minimize the gross metabolic cost of transport estimated based on the mechanical work done by the muscles and basal metabolic energy by a genetic algorithm [6].

In addition, it is essential to incorporate the vestibulospinal tract, which plays a crucial role in the vestibulospinal reflex responsible for maintaining postural balance against external perturbations. This reflex involves the vestibular organ sensing the body's acceleration caused by external disturbances and adjusting the muscle tone in the limbs to preserve body equilibrium. In this study, we propose the hypothesis that the vestibular nucleus estimates the ground reaction force (GRF) vector needed to control trunk orientation in response to perturbations. This estimation is based on information from vestibular input and involves converting it into muscle torques and activations using the leg Jacobian matrix.

C. Whole-body angular momentum during bipedal walking

To elucidate how the locomotor nervous system stabilizes trunk rotation during bipedal walking by generating appropriate GRFs, we investigated the kinematics and GRFs during bipedal walking in Japanese macaques and humans. We estimated the position of the whole-body center of mass (COM) during walking and analyzed where the GRF vector passes relative to the COM. Additionally, for humans, we calculated changes in whole-body angular momentum around the COM during bipedal walking and analyzed the contribution of the GRFs to the control of rotational stability of the gait.

IV. Results and Discussions

The kinematics of the simulated bipedal locomotion in the Japanese macaque based on the CPG model generally agreed with the measured data (Fig. 1C). The simulated gait also captured the main features of the ground reaction force profiles in the Japanese macaque [6]. When the foot morphology was altered, the vertical GRF profile shifted from a single- to a double-peaked profile as in human walking, and the cost of transport decreased compared with that of the intact condition. Our results suggested that evolutionary changes in the foot morphology were important for the acquisition of human-like efficient bipedal walking [6].

Analysis of bipedal walking has shown that the GRF vector in Japanese macaques and humans does not pass through the COM but consistently falls above it [7] (Fig. 2A). This suggests that during bipedal walking, continuously generating active moments of forward or backward tilt around the COM by directing the GRF vector away from it contributes to the control of the whole-body angular momentum and, consequently, the rotational stability of walking (Fig. 2B).

Based on the findings, we constructed a neurocontrol model that passes GRFs above the COM in response to trunk segment angular acceleration, aiming to maintain the stability of forward and backward rotation of the body (Fig. 2C). Although the realization of bipedal walking generation based on the model of the vestibulospinal tract has not yet been achieved, we aim to advance the understanding of the mechanism of "hyper-adaptation" associated with the alterations of the body structure by realizing the gait simulation based on the vestibulospinal tract.

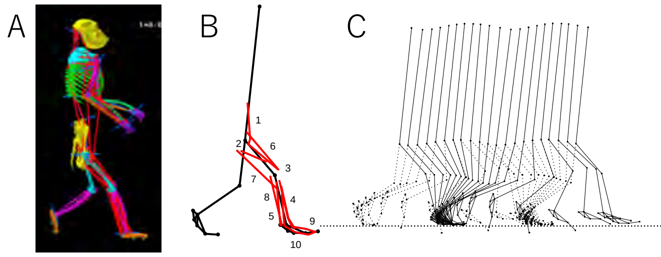


Fig. 1. Musculoskeleta model of the Japanese macaque. A: 3D whole-body model. B: 2D model used in the present study. C: Generated walking.

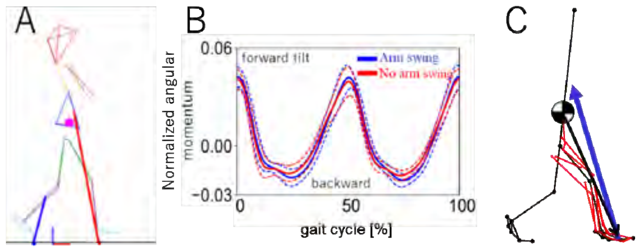


Fig. 2. Human gait kinematics and GRF (A), whole-body angular momentum (B), and the neurocontrol model of the vestibulospinal tract (C).

References

[1] Ogihara, N., Hirasaki, E., Kumakura, H., Nakatsukasa, M., 2007. Ground-reaction-force profiles of bipedal walking in bipedally trained Japanese monkeys. J. Hum. Evol. 53, 302–308.

[2] Ogihara, N., Makishima, H., Nakatsukasa, M., 2010. Three-dimensional musculoskeletal kinematics during bipedal locomotion in the Japanese macaque reconstructed based on an anatomical model-matching method. J. Hum. Evol. 58, 252–261.

[3] Ogihara, N., Kikuchi, T., Ishiguro, Y., Makishima, H., Nakatsukasa, M., 2012. Planar covariation of limb elevation angles during bipedal walking in the Japanese macaque. J. R. Soc. Interface. 9, 2181–2190.

[4] Ogihara, N., Hirasaki, E., Andrada, E., Blickhan, R., 2018. Bipedal gait versatility in the Japanese macaque (Macaca fuscata). J. Hum. Evol. 125, 2-14.

[5] Ogihara, N., Aoi, S., Sugimoto, Y., Tsuchiya, K., Nakatsukasa, M., 2011. Forward dynamic simulation of bipedal walking in the Japanese macaque: Investigation of causal relationships among limb kinematics, speed, and energetics of bipedal locomotion in a nonhuman primate. Am. J. Phys. Anthropol. 145, 568–580.

[6] Oku, H., Ide, N., Ogihara, N., 2021. Forward dynamic simulation of Japanese macaque bipedal locomotion demonstrates better energetic economy in a virtualised plantigrade posture, Commun. Biol., 4, 308.

[7] Negishi, T., Ogihara, N., 2023. Regulation of whole-body angular momentum during human walking, Sci. Rep., 13, 8000.

B05-3 Hyper adaptability of sensorimotor information structure in early human development

Hoshinori Kanazawa
Graduate School of Information Science and Technology, The University of Tokyo.

Abstract— It is well-known that neonates and infants exhibit a variety of spontaneous movements that are coordinated and structured, even in the absence of external stimuli. These movements, distinctive to early development, tend to disappear with the onset of voluntary movements such as reaching. Spontaneous movements and their developmental changes are believed to reflect the activity and maturation process of the central nervous system. Research involving the observation of spontaneous movements in human neonates and infants has investigated the patterns and coordination of limb movements. Here, we proposed a method for generating movements that can replicate those of actual neonates and infants. Furthermore, we demonstrated the sensorimotor information structure that can be produced solely through embodiment using this movement generation method. Our findings also suggest that in actual sensorimotor development, the structure derived from embodiment is influenced not only by neurological maturation but also by higher functions such as intention and curiosity.

I. Introduction

In cases of motor dysfunction or decline in higher brain function due to brain or body damage or aging, there are typically abnormal changes in neural activity and structure, which may be utilized for motor and behavioral control. Understanding the mechanisms underlying such changes is important. Adaptive processes involving function recovery or compensation that cannot be observed in adults are often reported in cases of physical impairment or neural damage during early development. B05-03 group focuses on sensorimotor responses and changes to dysfunctions occurring during the neonatal to infancy period, in order to construct a theory regarding "hyper-adaptation" to the transformation of the body and nervous system during early development.

In FY2023, to examine the influence of embodiment in behavioral development, we utilized infant musculoskeletal simulations to explore behaviors and sensorimotor information structures that arise solely from embodiment. We then compared these findings with actual neonates and infants.

II. Aim of the Group

The specific aim of this research is to examine the specific functional recovery and functional compensatory processes that occur in early development. We therefore investigated the developmental changes in sensorimotor interactions in neonates and infants, constructing models to explain these changes, and examining the changes and adaptations caused by dysfunction.

III. Research Topics

A. Generation of Spontaneous Movements in Early Development

It is known that neonates and infants perform a variety of coordinated and structured spontaneous movements in the absence of external stimuli [1]. These movements, specific to early development, tend to disappear with the onset of voluntary movements such as reaching. The central nervous system's activity and maturation process are believed to be reflected in these spontaneous movements and their developmental changes, with studies observing the movement patterns and coordination of limbs in human neonates and infants [2,3].

Our goal was to generate random movements while preserving the characteristic features of such specific spontaneous movements. Regarding the generation of random joint angles, we used the joint angles of 12 joints with 26 degrees of freedom (hands, elbows, shoulders, hips, knees, and ankles on both sides) from the whole-body movements of infants measured last year. We applied principal component analysis to the joint angles collected and analyzed in last year's study. By applying the surrogate method to the extracted principal components, we created random data that preserved the original data's frequency components and inter-joint relationships [4].

Neonatal and infant movements are often evaluated for their inter-joint coordination. The movements created by this method preserve this coordination, as well as amplitude and fundamental frequency, making it difficult to distinguish between the original data and the randomly generated data. This has potential applications in training for infant movement observation and abnormality detection.

B. Extraction of Sensorimotor Information Structure Dependent on Embodiment

The research group, led by the project leader, analyzed movement data from neonates and infants up to three months old who had not yet started voluntary movements in last year's study, examining the structuring of sensorimotor interactions occurring at that time [5]. This year, using the method of generating random movements while preserving the characteristics of actual infant movement data achieved in section A, we examined the role of embodiment in the structuring of sensorimotor information.

Specifically, our verification process involved the following steps: (1) Generating random joint angles using the surrogate method based on joint movements measured in previous studies, (2) Estimating proprioception and muscle activities through inverse dynamics analysis and muscle tension estimation using an infant musculoskeletal model, (3) Calculating the amount of information transmission between proprioception and muscle activities, (4) Extracting sensorimotor modules and calculating information transmission density, (5) Comparing with actual infant data.

The targeted sensorimotor modules are shown in Figure 1 (left), and in this study, we focused solely on the information density between the left and right arms and between the left and right legs (as indicated within the red frame in Figure 1, right).

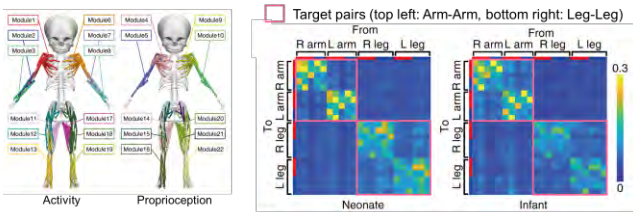


Fig.1 extracted modules and information density

As a result, when examining the information transmission density obtained, it was found that the surrogate data had an information density of about 1/2 to 1/10 compared to the actual movement data, but the general relative magnitude was preserved (Figure 2, upper panel). To better understand this relationship, we calculated the rank correlation of sensorimotor information density between surrogate and actual data (Figure 2, lower panel). We observed a certain degree of correlation, especially a higher correlation in the legs (Bootstrap 95%CI, arms: 0.22-0.44, legs: 0.53-0.67). However, there was no significant correlation with developmental changes, i.e., the differences between neonates and infants in the actual data (arms: -0.28 to 0.09, legs: -0.25 to 0.06). The blue dots indicate inter-limb information density, and the red dots indicate intra-limb information density, suggesting that information transmission across different body parts is less likely to occur.

The generated joint movements do not include coordination originating from the neural system, thus the calculated sensorimotor information structure depends solely on embodiment. The similarity of this information structure to that of actual neonates and infants suggests the influence of embodiment on the sensorimotor information structure during spontaneous movements. On the other hand, the lack of correlation with developmental changes implies that the development of sensorimotor information structure is attributable to the maturation of the neural system and voluntariness. It was found that even in early development, where spontaneous movements are task-free and without rewards or goals, spatial structuring based on embodiment is progressing [4].

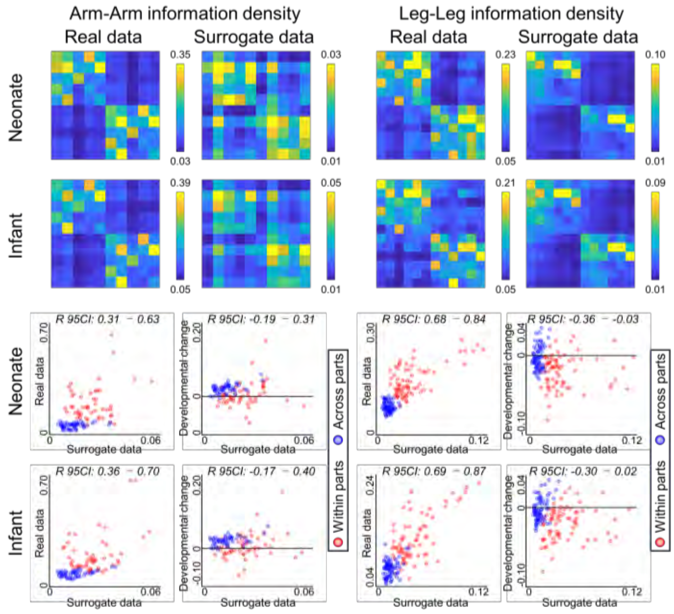


Fig.2 comparison of sensorimotor information density

IV. Conclusion

This year, we proposed a method for generating movements capable of replicating those of actual neonates and infants. Furthermore, by utilizing this movement generation, we demonstrated the sensorimotor information structure that can be produced solely through embodiment. In addition, our findings suggest that in actual sensorimotor development, the structure is influenced not only by embodiment but also by neural maturation and higher functions such as intention and curiosity.

References

[1] Hadders-Algra, M. (2018). Neural substrate and clinical significance of general movements: an update. Developmental Medicine & Child Neurology, 60(1), 39-46.

[2] De Vries, J. I., Visser, G. H., & Prechtl, H. F. (1982). The emergence of fetal behaviour. I. Qualitative aspects. Early human development, 7(4), 301-322.

[3] Kanemaru, N., Watanabe, H., & Taga, G. (2012). Increasing selectivity of interlimb coordination during spontaneous movements in 2-to 4-month-old infants. Experimental brain research, 218, 49-61.

[4] 金沢 星慶，國吉 康夫. 感覚運動発達における身体性の影響の検証. 日本赤ちゃん学会第 23 回学術集会，大阪，2023 年

[5] Kanazawa, H., Yamada, Y., Tanaka, K., Kawai, M., Niwa, F., Iwanaga, K., & Kuniyoshi, Y. (2023). Open-ended movements structure

B05-4 Annual report of research project

Isao Nambu
Nagaoka University of Technology

Abstract—**Functional connectivity is an important measure to evaluate relationship among different brain regions. The purpose of this study is to develop a method to identify low-dimensional representations of the functional connectivity and investigate time-varying network changes in such the low-dimensional space. We used a method using time-varying graphical lasso for electrocorticogram for reaching task. We found the possibility to detect dynamics related to the behavioral states in the low-dimensional subspace.**

I. Introduction

There are various parts of the brain that realize perception and behavior while exchanging information between these regions. Functional connectivity is an index that quantifies the statistical dependence of time-series data between such multiple brain regions and investigates the relationship between them [1]. However, since there are multiple brain regions, it is difficult to interpret all relationships in a unified manner.

In response to these problems, this study aims to elucidate the brain state of "hyper-adaptivity" by developing a method to identify brain activity involved in human movement as state-space dynamics at the whole brain level.

In recent years, it has been clarified that the representation of physical movement in the brain depends on the position in the low-dimensional state space (neural manifold) composed of neural activity groups during motor planning and execution [2]. For example, it has been suggested that neural activity groups may be represented in low-dimensional space in the motor cortex [2, 3], but it is not clear how multiple brain regions related to movement are related, and the relationships and interactions between them are not clear as well. If low-dimensional dynamics at the whole-brain level involving multiple brain regions are revealed, there is a possibility to gain a deeper understanding of human movement, adaptation, and learning. Recently, studies have attempted to reduce the dimensionality of brain functional connectivity in human functional magnetic resonance imaging data [4,5]. If we can investigate the dynamics of electroencephalogram (EEG) and electrocorticogram (ECoG) with good temporal resolution, it will be useful for elucidating the mechanism of brain functional connectivity. It is also interesting to view the changes in the dynamics of the bilateral motion-related region as a representation in low-dimensional space".

II. Aim of the Group

The purpose of this research is to develop a method for identifying the spatial representation of brain states for the elucidation of hyper-adaptation. In addition, we aim to detect changes during hyper-adaptation by investigating the dynamics in low-dimensional space, especially in the motion-related regions on both sides, using the developed method. method) on cortical EEG.

III. Research Topics

We examined two types of the methods as follows.

A. Development of the non-directed method to identifying low dimensional subspace for EEG data

This year, we examined the analysis of low-dimensional space visualization using undirected graphical models, which we have been working on continuously since last year, using electrocorticogram. In this method, dynamically changing brain functional coupling is described as Time-Varying Graphical Lasso (TVGL), a probabilistic graphical model using a Gaussian Markov probability field [7]. The distance matrix is calculated using KL-divergence for the accuracy matrix (covariance matrix) identified as the network, and analysis using multidimensional scaling is performed to represent time series with similar network patterns in low dimensions. Using this analysis, we analyzed human ECoG data. The data were obtained from the A05-3 group of Kobe University and were based on ECoG during reaching movements. A total of two subjects were analyzed. This study was conducted in collaboration with A05-3 Kobe University and B01 Tokyo University of Agriculture and Technology.

The result of this analysis showed that there was a gradual tendency to change from pre-movement to the time of execution in low-dimensional space (Fig.1). In the delta, theta, and alpha bands, the three-dimensional trajectories were observed to move apart from resting time to movements, while the trajectories tended to consolidate densely in the beta and low gamma bands. When checking the data of the other subject, it was confirmed that the trajectory was close to a circle in the high gamma band. These results suggest that the low-dimensional space identification method using TVGL may capture the low-dimensional dynamics of brain functional connectivity that may exhibit behaviors. In the future, it is necessary to search for parameters and study brain regions corresponding to low-dimensional spaces.

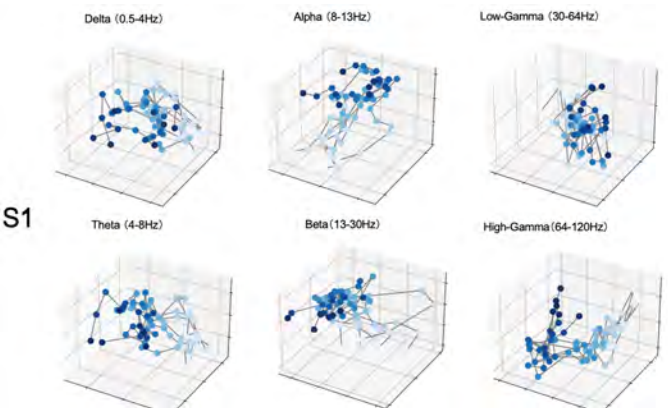


Fig. 1. An example of three-dimensional states using TVGL-based models for the reaching data. Each color represents different time points from rest (white), cue (light blue), and exection (blue).

B. *E/I balance estimation using data assimilation based method*

Next, in order to investigate disinhibition, which is one of the important mechanisms for achieving hyper-adaptation, we conducted an analysis using a method that can evaluate the balance between excitation and inhibition (E/I balance). Specifically, a method of estimating the activity of excitatory neurons and inhibitory neurons using data assimilation based on a neural mass model, thereby evaluating the E/I balance [8]. We investigated whether it is possible to determine the E/I balance from ECoG using this method. In this study, we analyzed a total of two channels near the left and right motor cortex, and we were able to observe different changes in the E/I balance in the left and right channels with the start of movement, suggesting that it may be possible to estimate the E/I balance that cannot be observed directly from ECoG. On the other hand, this study uses data assimilation of cortical brain signals from 1 Hz to 30 Hz after pre-processing. This is because the limit indicated by the model is considered to be 30 Hz or less. In addition, at present, we are conducting local analysis for each channel, and in the future, it is necessary to perform E/I balance analysis as a network.

IV. Future Perspective

In this study, we examined a low-dimensional spatial identification method using TVGL on cortical EEG data in order to clarify the low-dimensional spatial representation of brain functional connectivity. In addition, we clarified the possibility that a data assimilation method for estimating E/I balance can be used for the analysis of motor data such as cortical EEG. In the future, we aim to further investigate the possibility of a method that can be applied to data of various modalities and the low-dimensional dynamics of brain function connectivity.

References

[1] Makoto Fukushima, Functional Connectivity, Brain Science Dictionary doi: 10.14931/bsd.9954 (2021)

[2] J. A. Gallego, M. G. Perich, L. E. Miller and S. A. Solla, "Neural manifolds for the control of movement", Neuron, vol. 94, no. 5, pp. 978-984, 2017.

[3] K. V. Shenoy, M. T. Kaufman, M. Sahani and M. M. Churchland, "A dynamical systems view of motor preparation: Implications for neural prosthetic system design", Progr. Brain Res., vol. 192, pp. 33-58, Jan. 2011.

[4] J. Rué-Queralt et al., "Decoding brain states on the intrinsic manifold of human brain dynamics across wakefulness and sleep," Communications Biology 2021 4:1, vol. 4, no. 1, pp. 1-11, 2021/7// 2021, doi: 10.1038/s42003-021-02369-7.

[5] S. Gao, G. Mishne, and D. Scheinost, "Nonlinear manifold learning in functional magnetic resonance imaging uncovers a low-dimensional space of brain dynamics," *Hum Brain Mapp,* vol. 42, no. 14, pp. 4510-4524, Oct 1 2021, doi: 10.1002/hbm.25561.

[6] Z. C. Chao, M. Sawada, T. Isa, and Y. Nishimura, "Dynamic Reorganization of Motor Networks During Recovery from Partial Spinal Cord Injury in Monkeys," *Cereb Cortex,* vol. 29, no. 7, pp. 3059-3073, Jul 5 2019, doi: 10.1093/cercor/bhy172.

[7] B. Cai *et al*., "Capturing Dynamic Connectivity From Resting State fMRI Using Time-Varying Graphical Lasso," in *IEEE Transactions on Biomedical Engineering*, vol. 66, no. 7, pp. 1852-1862, July 2019.

[8] H. Yokoyama., and K. Kitajo, “A data assimilation method to track excitation-inhibition balance change using scalp EEG”. *Communications Engineering*, *2*(1), 92, 2023.

B05-5 Extension of motor learning model for reuse ofpartial relationship toward regeneration of muscle synergy

Yuichi Kobayashi
Faculty of Engineering, Shizuoka University

***Abstract*—Aiming to construct a model that can explain the process of partial control knowledge reuse in the human motor learning process, this study proposed a new method to model the process of acquiring feedforward control control from a motor control system that is mainly based on feedback control. Taking advantage of the property that repetitive motion learning by humans follows relatively close trajectories, we proposed a method to acquire feedforward control as a time series of signals using state-independent and time-dependent reinforcement learning. In particular, we showed that motor learning can be made more efficient by progressively acquiring the time series of control signals. We set up an upper limb motor control task and confirmed the effectiveness of the proposed feedforward control based on state-independent reinforcement learning in two types of paw tracking control: torque control and muscle drive control.**

I. Introduction

Human adaptability includes the ability to adaptively recover function in the event of partial dysfunction of the body or brain by reusing previously acquired neural circuits. Aiming to explain this aspect of 'neural circuit re-use' in motor control adaptation, the research group has proposed motor learning models that can explain the process of re-using parts of a motor control model once acquired, depending on the situation [1], [2]. The basis of these proposals is the automatic generation of feedback control laws proposed in [3], where the information to be reused corresponds to the feedback matrix in feedback control ($\boldsymbol{R}_{a,b}$ in the upper left and upper right of Fig. 1). However, the reuse of information in human motion control can occur not only in the feedback control system but also in the feedforward control component.

Therefore, in this study, the focus of attention in the human motor learning process is extended from the feedback control system to the process of transition from the feedback control system to the feedforward control system, as in the transition process from the upper left to the lower left in Fig. 1. FF control system can be regarded as a learning process that generates muscle synergy, and thus may contribute to modelling the adaptation process (corresponding to the transition from the lower left to the lower right in the figure), including the reuse of muscle synergy in response to changes in the body structure. As a process for this, a motor learning model for acquiring FF control while using the FB control system was proposed and validated.

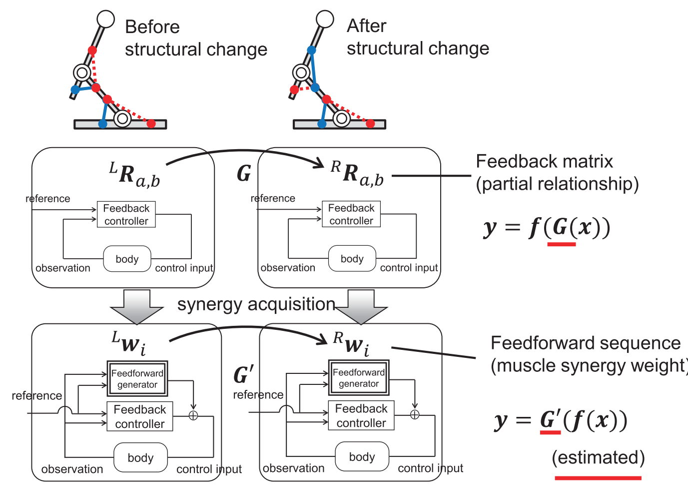


Fig. 1. Adaptation process to structural change of body through transition from FB control to FF control.

II. Achievements

Based on state-independent reinforcement learning (Blind Action Sequence Learning with EM, BASLEM), which is not based on the deviation between state observation and target, a motor learning model was proposed that can explain the gradual transition process from FB control to FF control in repeated movements. It was shown that FB control can be lengthened and control resources can be saved by allowing FF control to be acquired in upper limb motor control, which is mainly based on FB control. To improve the learning efficiency of the FF control acquisition method, we developed a learning model that can progressively change the FF learning interval while combining FB and FF control.

As a specific control object, a two-degree-of-freedom manipulator that imitates a human upper limb is considered. Two types of drive systems are considered for this manipulator: a model in which the joints are torque-controlled, and a model in which artificial muscles are placed at the joints. A progressive motion learning method was verified for the torque-controlled model. The state-independent reinforcement learning approach, on which the proposed method is based, was verified in a musculoskeletal model with artificial muscles attached to a 2-DOF manipulator (see Fig. 2).

Since BASLEM updates policy parameters simultaneously

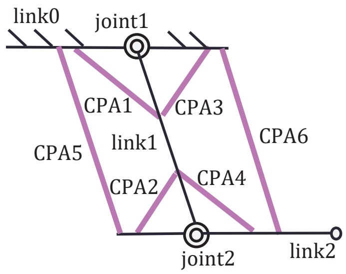


Fig. 2. Musculoskeletal arm with six muscles.

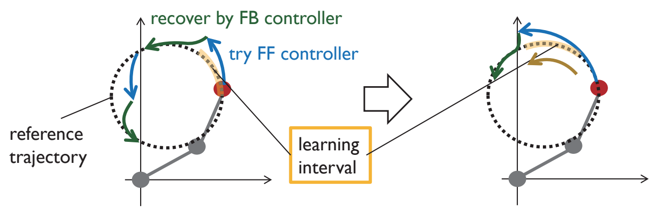


Fig. 3. Concept of gradual acquisition method of FF control through use with FB control system.

for the entire control time, it also updates parameters that have already been optimised, which can lead to inefficiency. In this study, we proposed a method to gradually change the learning range of BASLEM by utilising the property that the trajectory is constrained on the same trajectory by the FB control during iterative learning. The idea is shown in Fig. 3.

The trajectories before and after the learning are shown in Fig. 4 and Fig. 5, respectively. The FF control rate before learning was 44.4%, whereas the FF control rate after learning was 100%. Before learning, the reference trajectory could not be followed by the control using the initial policy parameters generated from the FB control when it entered the region where the disturbance was added. However, the trajectory was successfully followed after FF control was obtained.

The FF control acquisition learning of the musculoskeletal arm by BASLEM was verified by using a circular trajectory tracking task Fig. 6 shows the trajectories after FF control ac-

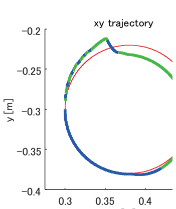


Fig. 4. Trajectory before learning.

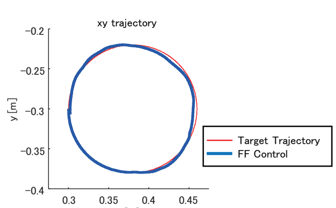


Fig. 5. Trajectory after FF control acquisition.

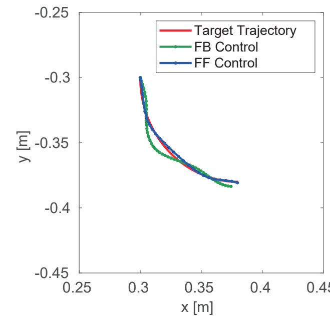


Fig. 6. Trajectories of FB control and after acquiring FF control in a circular trajectory tracking task with a musculoskeletal arm

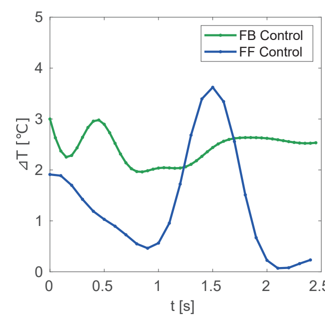


Fig. 7. Control input to CPA1.

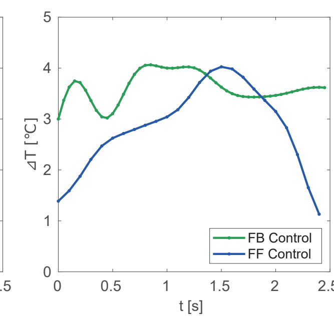


Fig. 8. Control input to CPA3.

heating temperature of the muscles corresponding to CPA1 and CPA3 in Fig. 2, respectively. Overall, it can be seen that the heating temperature of the muscles was reduced by learning.

III. Summary

To model the adaptation process including the acquisition of muscle synergy, we proposed a motor learning model in which the feed-forward controller is acquired by state-independent reinforcement learning through a combination with feedback control. The simulation results of the proposed method on a two-degree-of-freedom manipulator showed high tracking performance. Using this model, it is expected to verify that adaptive control is possible in humans through gradual acquisition to FF control. In application to musculoskeletal upperr limb control, the proposed learning method has successfully reduced the position error and the control input.

References

[1] S. Nakamura and Y. Kobayashi, A Grid-Based Estimation of Transformation of Partial Dynamics using Genetic Algorithm for Motor Learning, Proc. of The 32nd 2021 International Symposium on Micro-NanoMechatronics and Human Science, MP2-2-3, 2021.

[2] S. Nakamura, Y. Kobayashi and T. Matsuura, Grid-Based Estimation of Transformation Between Partial Relationships Using a Genetic Algorithm, Journal of Robotics and Mechatronics, Vol. 34, No. 4, pp. 786-794, 2022.

[3] Y. Kobayashi, K. Harada and K. Takagi, Automatic Controller Generation Based on Dependency Network of Multi-modal Sensor Variables for Musculoskeletal Robotic Arm, Robotics and Autonomous Systems, Vol. 118, pp. 55-65, 2019.

B05-6 Annual report of research project

Michiteru Kitazaki
Toyohashi University of Technology

***Abstract*—The system for virtual eyes on the back of the head was applied to test humans' adaptability to it. We found that the motor learning occurred in strategic and automatic levels after 10days learning. We identified temporal synchrony as a necessary factor for the embodiment of a biomechanically impossible body. We conducted experiments on shared-hand avatar. Finally, we developed and fundamentally evaluated a system that can amplify the direction of gaze with respect to head motion.**

I. Introduction

Research on the sense of body ownership and enbodiment uses virtual reality (VR), which focuses on the transformation of the body. By synchronizing body movements with those of avatars, we can perceive and manipulate avatars as our own bodies, even if they are different from our actual bodies. By embodying such avatars, it has been shown that attitudes and behaviors change according to the attributes of the avatar [1-3]. Systematically incorporating further transformations of body form and function is important for exploring the limits and plasticity of human body cognition.

II. Aim of the Group

We aim to modify the 'relationship between the eyes (visual sensors) and the body', intervene in the visual-motor cooperative relationship and elucidate how this changes people's perception and behavior. Normally, the human eyes are located in front of the head. This correspondence between body and sensory organs determines the hierarchical relationship between perception and environment. We manipulate the 'eye-body relationship' to clarify how people's perception and behavior change with long-term adaptation. Specifically, a body in which the relationship between the visual organ and the body is manipulated, such as a body with eyes behind the head and a body with eyes at the tips of the hands, is constructed using VR, and three different levels ('level of conscious action strategy', 'level of unconscious action' and 'level of perception') are focused on and clarified through psychophysical experiments and behavior analysis (Fig. 1).

Fig. 1 A body with eyes on the back of the head (left), and a body with eyes on the hand

III. Research Topics

A. A body with eyes on the back of the head

A body with eyes (virtual camera) behind the head was implemented in a VR space and tested on six experimental participants. The participants' body movements, including their heads, were measured with a motion capture system (Optitrack Primx22 12 camera). The viewpoint was set behind the head and visual stimuli were presented on a head-mounted display (HTC Vive Pro EYE) worn by the participants (Fig. 2). The experiment was conducted over 12 days: on days 0 and 11, participants performed two complex course walking tasks and a task where they had to walk to reach two locations and return to their initial location; on days 1-10, participants performed a daily task where they had to avoid a colliding wall, a straight walking task and a circular walking task, as well as reaching two different objects.

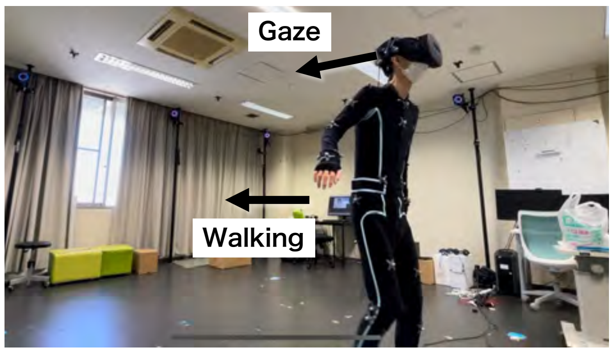


Fig. 2 Walking experiment with body with eyes behind the head.

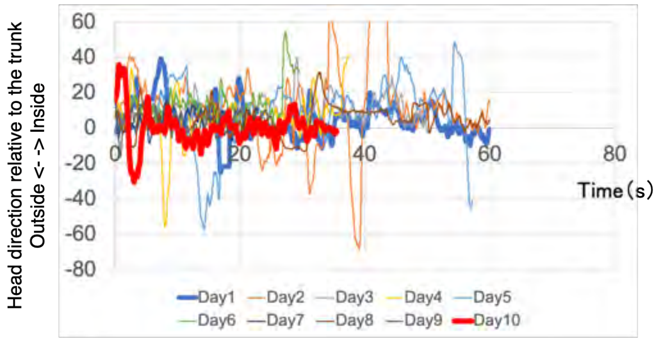


Fig. 3 Data of the head angle relative to the trunk over a period of 10 days

For the participants' 10 days of circumferential walking, the walking trajectories became smoother as the days progressed and the walking time became shorter. When changes in the direction of the head relative to the trunk were calculated, the difference between the trunk and head directions tended to become smaller and more stable as the days progressed. This suggests that the hierarchy of body movements is also acquired by learning.

B. *Adaptive learning for bodies with joints bent in opposite directions*

Experiments were performed by creating a body in which the elbow joints of the left and right arms were bent in (biomechanically impossible) opposite directions, and manipulating the direction of joint bending and the synchronization between the self-body movements and the avatar's movements. The results showed that adaptation did not occur for temporal asynchrony and the sense of body ownership was low, but for the joints that bend in the opposite direction, the body became self-embodied even after 10 min of learning. The findings were published in a journal [4].

C. *Virtual augmentation of visual field*

We have developed a system that can change the direction in which the viewer's gaze is directed depending on the amount of head rotation. By presenting images taken by a 360-degree camera in the direction of a virtual gaze with any gain based on the actual head direction, it is possible to observe directly behind the person even if the head is turned only 90 degrees to the side. With this system, it is possible to observe the entire environment with little physical effort.

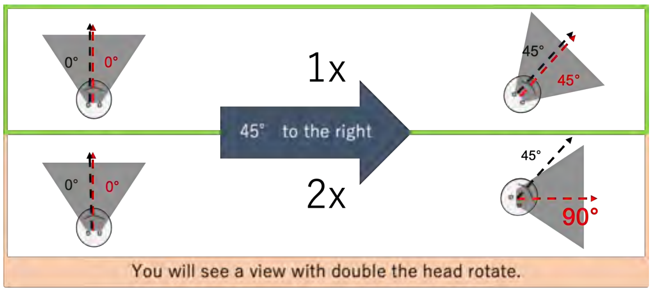


Fig. 4 Scheme of the system for augmentation of visual field

Fig. 5 A system that enables users to experience real images by attaching a 360-degree camera to an HMD (left). Actual use of the system (right).

IV. Future Perspective

We conducted an adaptation experiment to a system in which the eyes were facing the opposite direction to the head and identified changes in the level of implicit behavior in addition to changes in the level of strategic behavior. Temporal synchrony was identified as a requirement factor for the embodiment of the impossible body [4]. We also conducted experiments on the shared body of the hand and published articles [5,6]. Finally, we developed and fundamentally evaluated a system that can amplify the direction of gaze in a variable manner with respect to head motion.

References

[1] Kondo, R., Sugimoto, M., Minamizawa, K., Hoshi, T., Inami, M., and Kitazaki, M. (2018). Illusory body ownership of an invisible body interpolated between virtual hands and feet via visual-motor synchronicity, Scientific Reports, 8:7541

[2] Kondo, R., Tani, Y., Sugimoto, M., Inami, M., and Kitazaki, M. (2020). Scrambled body differentiates body part ownership from the full body illusion. Scientific Reports, 10:5274

[3] Hagiwara, T., Ganesh, Sugimoto, M., Inami, M., and Kitazaki, M. (2020) Individuals prioritize the reach straightness and hand jerk of a shared avatar over their own, iScience, 23(12): 101732

[4] Hapuarachchi, H., Ishimoto, H., Kitazaki, M., Sugimoto, M., Inami, M. (2023). Temporal visuomotor synchrony induces embodiment towards an avatar with biomechanically impossible arm movements, i-Perception, 14(6):20416695231211699

[5] Katsumata, Y., Inoue, Y., Toriumi, S., Ishimoto, H., Hapuarachchi, H., and Kitazaki, M. (2023). Shared avatar for hand movement imitation: Subjective and behavioral analyses. IEEE Access, 11, 96710-96717

[6] 勝俣安伸, 鳥海智志, 井上康之, Harin Hapuarachchi, 北崎充晃 (印刷中). 共有・結合した手による指リーチングにおける身体性と課題成績, 日本バーチャルリアリティ学会論文誌, 29(1), 1-11.

B05-7 Neural mechanisms of postural stabilization revealed by EEG responses to micro-falls during human quiet stance

Taishin Nomura
Osaka University

***Abstract*— Postural sway during quiet stance often exhibits a repetition of micro-fall and the subsequent micro-recovery. The classical view –that the quiet bipedal stance is stabilized by the ankle joint stiffness– has been challenged by paradoxical non-spring-like behaviors of calf muscles: gastrocnemius muscles are shortened and then lengthened, respectively, during the micro-fall and the micro-recovery. Here, we examined EEG based brain activity during quiet stance, and identified desynchronization and synchronization of beta oscillations that were associated, respectively, with the micro-fall and the micro-recovery. Based on a widely accepted scenario for beta-band desynchronization during movement and post-movement rebound in the control of discrete voluntary movement, our results reveal that the beta rebound can be considered as a manifestation of stop command to punctuate the motor control for every fall-recovery cycle. Namely, cortical interventions to the automatic postural control are discrete, rather than continuous modulations. The finding is highly compatible with the intermittent control model, rather than the stiffness control model.**

I. Introduction

It has been believed that the human upright posture is stabilized by the high stiffness of the ankle joint caused by the sustained activity of antigravity muscles and the spinal stretch reflex. Ten years ago, we challenged this dogma, and proposed the intermittent control model [1,2]. The intermittent control model switches off the ankle joint active torque intermittently in a state-dependent manner. It hypothesizes that the upright posture is stabilized by turning off the active control and exploits the passive posture recovery movement during the OFF-control period. It has been shown that the intermittent control model exhibits a much higher accuracy in model fitting of experimental postural sway data during quiet stance, compared to the conventional continuous stiffness control model [3]. In this study, electromyography of ankle muscles (EMG) and brain activity (EEG) related to neural control of posture were measured in addition to the posture sway during quiet stance. We aim to elucidate the brain mechanism of the intermittent control of standing posture. Elucidation of the functional meaning of the EEG of synchronous brain activity at beta-band (β-rebound) that appears when a voluntary movement is terminated or when movement execution is inhibited is one of the major issues in upper extremity movement-related EEG research [4]. There have been few studies related to β-rebound for automatic movements including stabilization of upright posture.

II. Aim of the Group

The intermittent postural control hypothesis claims that the upright posture is stabilized by inactivation (OFF) and activation (ON) of the mediolateral gastrocnemius muscle at a sequence of appropriate timings, based on the somatosensory information related to the postural state, i.e., the tilt angle and angular velocity of the standing posture, affected by the neural transmission time delay. The OFF/ON switching of the mediolateral gastrocnemius (MG) corresponds to the OFF/ON switching of the active feedback controller. In the intermittent control model, the timing of relaxation of the mediolateral gastrocnemius plays an important role in postural stabilization. In other words, in the intermittent control model, the upright posture is stabilized using passive posture recovery motions during the period when the active torque at the ankle joint is switched OFF. Owing to the paradoxical property that the posture is stabilized by muscle relaxation rather than muscle activation, the intermittent control model can generate postural fluctuations with long-term correlation exhibited by healthy young people. In other words, the essence of the intermittent control hypothesis is to determine whether the brain region that controls the MG muscle, i.e., the reticular formation in the brainstem receiving projections from the peduncle tegmental nucleus, is activated or inactivated depending on the postural state of the bodily mechanical system. Direct pathways (Go) and indirect pathways (No-Go) of the cortico-basal ganglia loop has been considered performing such information processing for voluntary movements.

In the first stage of this Research, we measured the standing postural response to a support-surface perturbation that moves a floor backward in a step function manner. It was clarified that Event Related Synchronization (ERS) in the high-frequency β band appears in the EEG in the vicinity of parietal association area with a long latency (about 1.5 seconds) and for a long time (about 3 seconds) [5]. The β-ERS that appears immediately after completion or cessation of voluntary movement of the upper extremities or fingers is called β-rebound or status quo [4]. It is also known that β-rebound appears at a timing similar to that of the Go response even for the case of the No-Go response in Go/No-Go tasks. Such β-rebound is thought to reflect motor control and brain activity based on sensory re-afferent information [6]. The β-rebound during perturbed stance that we have identified appeared when the standing posture, tilted forward by the backward floor motion, moves back to the upright position without using the active ankle joint torque. Since the muscle activation of the mediolateral gastrocnemius was small during this process, the corresponding postural recovery is determined passively solely by the bodily mechanics. Such β-rebound may reflect active postural monitoring associated with the ON/OFF selection process of motor commands for controlling the MG activity [4].

In the second stage of our Research, we investigated whether the β-rebound that appeared during the postural recovery process in response to the perturbation also appears during postural sway during quiet stance with no perturbation. Postural sway during quiet stance can be regarded as a stochastic process, in which a forward micro-fall followed by a micro-recovery repeat randomly. Micro-falls occur about once every second. Our brain responds appropriately to each micro-fall and maintains our stance. Thus, healthy adults are the experts in postural control who have been avoiding falls tens of thousand times across the lifespan.

III. Research Topics

Fig. 1 shows the anteroposterior variation of Center of Mass (CoM), which represents postural sway during quiet stance, and the corresponding EMG of MG muscle. A large number of vertical dotted lines in the figure represent the sequence of occurrences when the CoM toppling velocity attains a positive peak for every micro-fall. Using the onset of the forward micro-fall of the CoM, the micro-fall and subsequent micro-recovery processes were extracted as epochs. Then, EMG and wavelet-transformed EEG time-frequency signals were

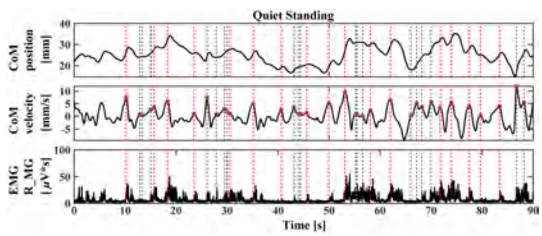


Fig. 1. Representative postural sway data in the anterior-posterior (AP) direction during stance with micro-falls. Top and middle panels show the CoM-position and the CoM-velocity time-series, respectively. The CoM-position on the top trace was represented with respect to the mean ankle joint position, i.e., the origin of the vertical axis was the mean ankle joint position. Bottom panel shows the EMG of MG from the right leg. Vertical dotted lines represent the micro-fall-peaks detected as the CoM-velocity positive peaks in CoM-velocity. EEG analyses were performed only for fall-recovery cycles associated with well-separated micro-fall-peaks that are represented by the vertical red dotted lines and the open black inverted triangles.

averaged to obtain Event-Related Spectral Perturbation (ERSP) as shown in Fig. 2. In Fig. 2, the MG activity increased with the occurrence of the micro-fall (ON-period), but when the CoM started to show the micro-recovery, the MG activity decreased and formed a plateau waveform, which might correspond to the OFF-period of the intermittent control. ERD and ERS were confirmed in the β-band of ERSP, respectively, during the ON- and OFF-periods of the control. Decrease and increase in the ERSP power for ERD and ERS were confirmed statistically.

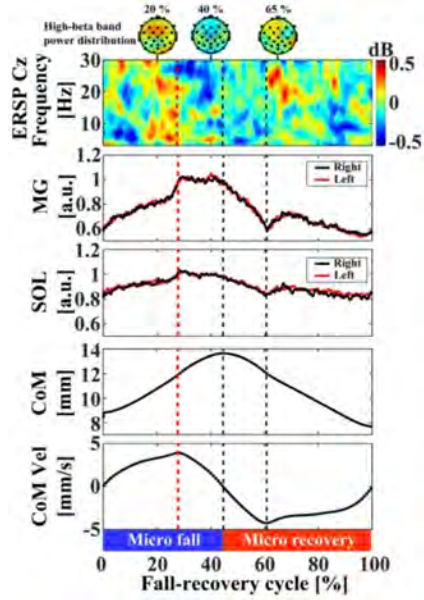


Fig. 2. Event-locked averages of EEG-ERSP, EMG of MG, SOL, the CoM-position in AP direction, and the corresponding CoM-velocity for the full fall-recovery cycle are shown in this order from the top to the bottom traces. 0% and 100% of the cycle were the beginning of the micro-fall and the end of the micro-recovery. The red dashed vertical line represents the micro-fall-peak, followed by two black dashed vertical lines. The first black dashed line represents the division between the micro-fall phase and the micro-recovery phase. The second black dashed line represents the micro-recovery-peaks defined by the negative peak of the CoM-velocity.

IV. Future Perspective

The β-band ERS in Fig. 2 is considered to be β-rebound that reflects the active postural monitoring during the micro-recovery process. It is likely that this beta-band activity is related to neural activities of the basal ganglia, as suggested by previous studies that identified attenuated beta-band desynchronization and synchronization in patients with Parkinson's disease during upper limb motor tasks. Moreover, the basal ganglia-cortical loop plays an important role in the action selection. Those evidences might support the idea that the beta-band desynchronization and synchronization we found in this study reflect the information processing required for the intermittent postural control.

References

[1] Bottaro, A.,et al. (2008) Bounded stability of the quiet standing posture: An intermittent control model. *Hum. Mov. Sci*. 27, 473–495.

[2] Asai, Y., et al. (2009) A Model of Postural Control in Quiet Standing: Robust Compensation of Delay-Induced Instability Using Intermittent Activation of Feedback Control. *PLOS ONE* 4, e6169.

[3] Suzuki, Y., et al. (2020) Postural instability via a loss of intermittent control in elderly and patients with Parkinson's disease: A model-based and data-driven approach. *Chaos* 30, 113140.

[4] Engel, A. K., and Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Curr. Opin. Neurobiol*. 20, 156–165.

[5] Nakamura, A., et al. (2021) Long- Lasting Event-Related Beta Synchronizations of EEG Activity in Response to Support-Surface Perturbations During Upright Stance. *Front. Syst. Neurosci.* 15:660434.

[6] Takakusaki K. (2017). Functional Neuroanatomy for Posture and Gait Control. *J. Mov. Disord*. 10, 1-17.

B05-8 Annual report of research project

Kazuhiro Sakamoto
Faculty of Medicine, Tohoku Medical and Pharmaceutical University

***Abstract*—We have previously proposed a model that learns by adaptively generating states in an environment where even the probability space is not determined. In this project, we proposed a model that not only enables learning of the action sequence task that has contributed to elucidating of functional differences between premotor and supplementary motor areas, but also provides computational interpretation of the neuronal activities. In future research, we hope to develop a model that emerges sequential actions as well, and build a computational theory of higher brain functions.**

I. Introduction

In the real world, the unexpected events often occurs. An environment in which even the probability space cannot be defined is called an indefinite environment. To adapt to such an environment, it is necessary to actively engage the world (proactive outreach) and generate the framework for adaptation. We have developed a reinforcement learning model that dynamically and autonomously generates the probability or state space based on the criteria of experience saturation and decision uniqueness[1][2]. However, the model is halfway to reproducing the highly adaptive abilities of primates.

II. Aim of the Group

To this purpose, here we developed a model[2] that can learn the action sequence task[3][4] (Fig. 1), which was used to elucidate the function of the monkey's higher motor cortices, specifically, the functional differentiation between the premotor and supplementary motor areas.

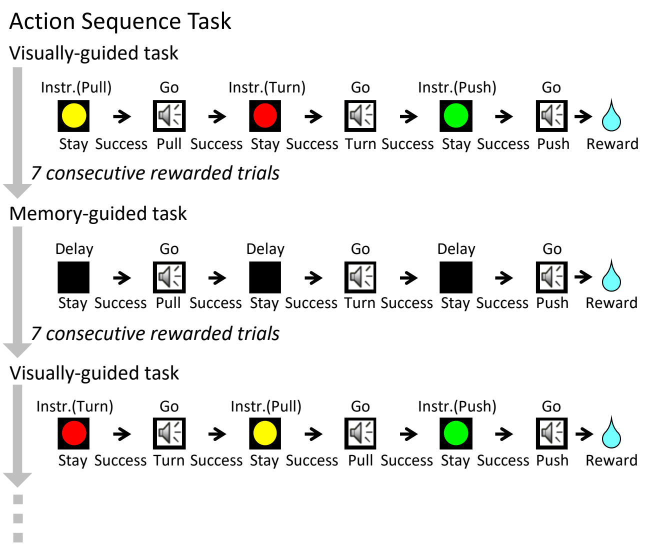


Fig. 1. Examples of trials in the action sequence task and block-wise changes.

In the task, the monkeys first performed a visually-guided task. They saw a signal that instructed them to perform one of three actions: Push, Pull, or Turn, and executed each instructed action when a go signal was delivered. In a certain block of trials, the same instruction signals were presented in the same order, and if the animals got seven consecutive trials correct, it was shifted to the memory-guided task. After seven consecutive correct trials, the task returned to the visually-guided task and animals were instructed to perform the actions in a different order.

III. The Model

The model generates different context-dependent learning sets for the different displays of the task. Each training set consists of a Sensory Information module and an Action-outcome History module. They are very similar, but use different cues in the dynamic generation of states, i.e., dynamically expanding the Q-table.

The Sensory Information module stores information about the previous contexts or displays. For example, in the case of the Go context, the current display, the previous Instruction display, and so on. Different instruction displays were retained as cues that distinguish different Instruction contexts (Fig. 2A).

In the other module, the histories of actions and outcomes were used as cues for state generation (Fig. 2B). The outcome cues are error, reward (Rwd.), and success without reward. The four action cues include Push, Pull, Turn, and Stay.

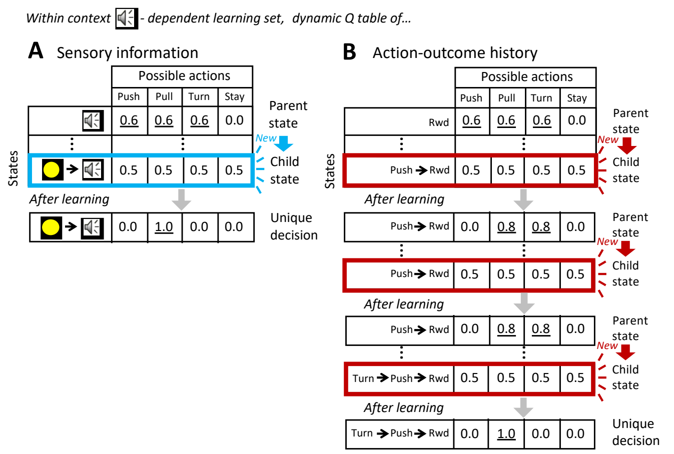


Fig. 2. Examples of extensions to the state or Q-table in the proposed model: A. Sensory information submodule; B. Action-outcome history submodule.

The expansion of the state space or Q-table was based on two criteria: Decision Uniqueness and Experience Saturation. Decision Uniqueness is the tendency to prefer a state with a small number of alternatives for action, specifically, three alternatives over four...one over two. Experience saturation is the criterion for whether a state has been experienced sufficiently, and actually monitors the change in the Q-table, and if the change is below a threshold, the experience in that state is considered saturated. Both quantities were evaluated in terms of Kullback-Leibler information.

IV. Results

The action sequence task requires the participants to perform three moves in sequence. The model learned the task quickly and showed a high rate of correct responses (Fig. 3A) and smooth sequence switches (Fig. 3B) after having previously learned a one-step and two-step tasks.

Physiological experiments have observed neuronal activities that are selective to a specific order of actions, for example, a cell that is active until the start of Push after the Pull action, or a cell that is active only at the beginning of a trial in which the Pull-Turn-Push action is to be performed [4]. If such cell activity is to be understood within the framework of the proposed model, it can be explained, for example, by the Q value of the action Pull in the state "Turn→Push→Rwd", i.e., "Turn was performed, followed by Push and Rwd was obtained". Plotting the Q value from the time this condition was identified to the time the Pull action was performed yields a time profile that closely resembles the neural activity actually observed in the supplementary motor area (figure not shown).

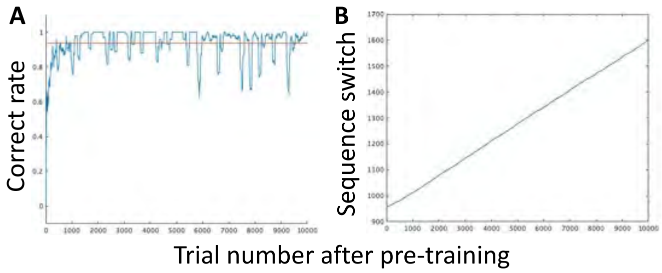


Fig. 3. Performance of the model. A. Correct rate. Red line: total mean. B. Switch of the sequence. The model has been pre-trained for 1,0000 trials for each of the 1- and 2-step tasks.

V. Future Perspective

In this study, we constructed a model that can learn the action sequence task used to elucidate functional differences between the premotor and supplementary motor areas of the cerebral cortex by learning the task with a module that extends the state based on sensory information and a module based on action-outcome in parallel. Furthermore, the actual neuronal activities were interpreted from the Q values of the model. The model is not only adaptable to indefinite environments by generating states by itself, but also opens the door to a computational understanding of the higher motor cortices.

For the two-target search task, which was the starting point for the development of this model, we also developed an apparatus for mice and a VR system [7]. These enabled us to perform the two-target search task on multiple animal species and to conduct a comprehensive experimental validation of the dynamic state-space reinforcement learning model.

Sequential actions should be emerged, not just learned. We have analyzed the prefrontal neuron activities involved in this process[8]. In addition, we have worked on solving the traveling salesman problem using the exclusive interaction between oscillators, where a city is regarded as a single oscillator [9-13]. In the latter, we showed by computer experiments that the system exhibits the shortest path solution in almost all cases if appropriate conditions are satisfied, and we have also developed its theoretical basis.

In future research, we hope to integrate this learning model with the oscillator system to build a novel computational model that can generate sequential actions for problem solving based on memory and experience and flexibly execute those actions at arbitrary rhythms and timings.

References

[1] T. Katakura, M. Yoshida, H. Hisano, H. Mushiake, K. Sakamoto, “Reinforcement learning model with dynamic state space tested on target search tasks for monkeys: self-determination of previous states based on experience saturation and decision uniqueness,” Front. Comput. Neurosci., Vol. 15, 784592, February 2022.

[2] K. Sakamoto, Kawaguchi, H. Mushiake, “Reinforcement Learning Model With Dynamic State Space Tested on Target Search Tasks for Monkeys: Extension to Learning Task Events,” Front. Behav. Neurosci., vol. 16, 750832, May 2022.

[3] H. Mushiake, M. Inase, and J. Tanji, Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements, J. Neurophysiol., vol.66, pp.705–718, 1991.

[4] J. Tanji, and K. Shima, Role for supplementary motor area cells in planning several movements ahead, Nature, vol.371, pp.413–416, 1994.

[5] N. Matsumoto, N.M.Tamura, H. Mushiake, K. Sakamoto, "Significance of single cell recording - Reverse engineering from supplementary motor cortex neuronal activity to reinforcement learning model -," IEICE Tech. Report,NC2023-25, 123(233) 1-5, Oct, 2023.

[6] K. Sakamoto, N. Matsumoto, N.M.Tamura, H. Mushiake, "A dynamic state-space reinforcement learning model explaining neuronal activities of the supplementary motor area in the cerebral cortex," 46th Annu. Meeting Jpn Neurosci. Soc., Aug 2, 2023.

[7] S. Zuguchi, K. Sakamoto, N. Katayama, H. Mushiake, "A high-speed measurement system for treadmill spherical motion in virtual reality for mice and a robust rotation axis estimation algorithm based on spherical geometry," IPSJ Trans. Bioinformatics, 16 1-12, Apr, 2023.

[8] K. Sakamoto, N. Saito, S. Yoshida, H. Mushiake, "A dynamic, economical, and robust coding scheme in the lateral prefrontal neurons of monkeys," Lec. Notes Comput. Sci., 13624 13-24, Apr, 2023.

[9] T. Kinugasa, F. Ono, K. Sakamoto, "Solving the traveling salesman problem using oscillator interaction," IEICE Tech. Report NC2023-23, 123(90) 149-152, Jun, 2023.

[10] F. Ono, T. Kinugasa, K. Sakamoto, Analytical Solution for the Exclusive Interactions between Three Kuramoto Oscillators," 33rd Annu. Meeting Jpn Neu. Network Soc., Sep 4, 2023.

[11] K. Sakamoto, T. Kinugasa, F. Ono,"Solving the traveling salesman problem using Kuramoto oscillators," 2023 Intl. Symp. Nonlinear Theory and Its Applications, 362-365, Sep, 2023.

[12] Writer’s Handbook. Mill Valley, CA: University Science, 1989.

B05-9 Annual report of research project

Takeshi Sakurada
Faculty of Science and Technology, Seikei University

***Abstract*— This study focuses on the neurofeedback training system for attention control. The achievements in this year are as follows: A) we demonstrated the training effect based on SSVEP, B) we optimized the vibrotactile stimulus for enhancing SSSEP responses, and C) we found the relationship between SSVEP responses and trainee fatigue.**

I. Introduction

In this research project, we aim to develop a tailor-made training system based on neurofeedback technique using sensory area activities, which is effective in improving attention function in young and older adults. In conventional neurofeedback training, a common goal (neural circuit to be obtained) is often set for the trainees [1]. However, in such training protocols, individual differences in brain function [2][3] are not considered, which increases the possibility that the training effect may not be sufficiently obtained [4]. To overcome these problems in neurofeedback training, we adopt a goal-free approach that does not explicitly set a desired activity for the brain region responsible for the targeted brain function. We expect that this approach promotes the activation of the neural circuits that each trainee is most likely to acquire, and ultimately aims to improve attention function and motor control ability efficiently.

II. Aim of the Group

The specific objective of this research project is to achieve improvement in cognitive and motor functions by using a neurofeedback training system that presents an individual's estimated attention state in real-time to promote the activation of the neural circuits. Regarding the estimation of attention state, we focus on Steady-State Somatosensory Evoked Potentials (SSSEP) in the somatosensory cortex or Steady-State Visual Evoked Potentials (SSVEP) in the visual cortex. These rhythmic EEGs have the property of amplifying the response by directing attention to sensory stimuli, so they are useful signals for estimating the attentional state in real-time [5]. In addition, in order to successfully train the proposed system, it is important to elicit SSSEP and SSVEP more robustly. Therefore, we tried to identify the appropriate carrier frequency for SSSEP response and the factors that influence the SSVEP response.

III. Research Topics

A. *Spatial attention training based on SSVEP*

The attention directed toward a specific location in external environments is called spatial attention. In order to train spatial attention, we conducted neurofeedback training using SSVEP. EEG electrodes were placed around the left and right visual areas, and flicker stimulation was presented to both visual fields from a high-frequency display. Participants were instructed to keep their gaze position fixed at the center of the display and direct their attention to the left visual field. During training, in order to exclude the influence of habituation to a stimulus with a specific frequency, the frequency of the flicker stimulus presented to the left visual field was randomly selected in the beta band. On the other hand, for the right visual field, a frequency in the alpha band was randomly selected.

The results of the 5-day neurofeedback training revealed that the participants were divided into two groups: four participants had an amplified response in the right visual cortex, while the others had a decreased response. Next, in the GoNogo task, only participants who succeeded in neural modulation showed a decrease in reaction time.

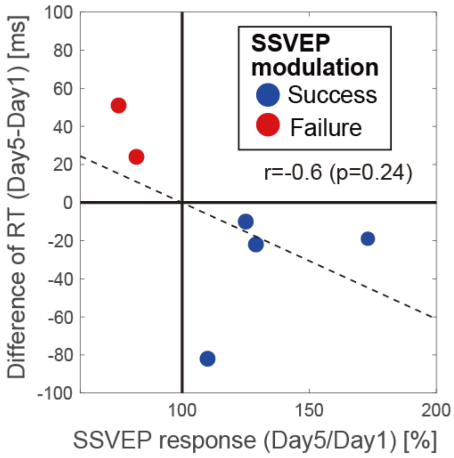


Fig. 1. Relationship between SSVEP modulation and behavioral change.

B. *Optimization of vibrotactile stimulation for SSSEP*

SSSEP is a rhythmic EEG elicited by vibrotactile stimulation with a certain frequency. As a mechanical vibration stimulus used to induce the SSSEP, we generated a low frequency (10 to 30Hz) stimulus by amplitude modulating a high frequency (100-300Hz) vibration. Here, the former high-frequency component is called the carrier frequency, and the latter low-frequency component is called the SSSEP frequency. Previous research has shown that vibration stimulation in the 20Hz range is the band that most strongly induces SSSEP [6]. On the other hand, regarding carrier frequency, there is no consistency in previous studies, and the relationship between SSSEP response and carrier frequency is unclear.

Therefore, we set various carrier frequencies and evaluated changes in the SSSEP response. As a result, when the carrier frequency was changed from 160Hz to 100Hz in 10Hz steps, the same response strength was maintained in the 160-120Hz band, even though the stimulus intensity weakened as the carrier frequency was lowered. Then, the response became significantly weaker at 110Hz/100Hz (p < 0.05, Fig. 2). This suggests that Meissner corpuscles, which are sensitive to frequencies below 160Hz (low response threshold), are involved in the SSSEP response. In the future, it is expected that by adopting vibration stimulation that takes into account the frequency characteristics of mechanoreceptors, it will be possible to establish a more robust neurofeedback training system using SSSEP.

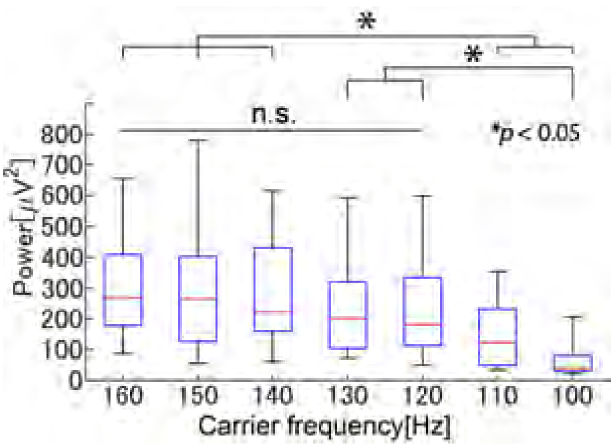


Fig. 2. Influence of carrier frequency on SSSEP responses.

C. *Individual difference factors in SSVEP response*

There are various factors that affect SSVEP responses and training effects. For example, factors such as arousal level, fatigue, and stress during training can have a large influence on performance on various tasks. We assumed that these factors cannot be ignored in neurofeedback training, we first attempted to estimate fatigue based on brain waves. There are various biological signals associated with fatigue and a relationship with brain waves has also been reported [7].

In the experiment, in parallel with the measurement of SSVEP during neurofeedback training, we evaluated the power in the α-θ band at C3/C4/F3/F4. As a result, it was confirmed that the SSVEP power tends to be amplified in trainees who had stronger alpha-theta band power (i.e., with higher fatigue during neurofeedback training: p = 0.0582, Fig. 3). Although these results seem contradictory, it is possible that the high fatigue level reflected a large amount of effort to the neurofeedback training.

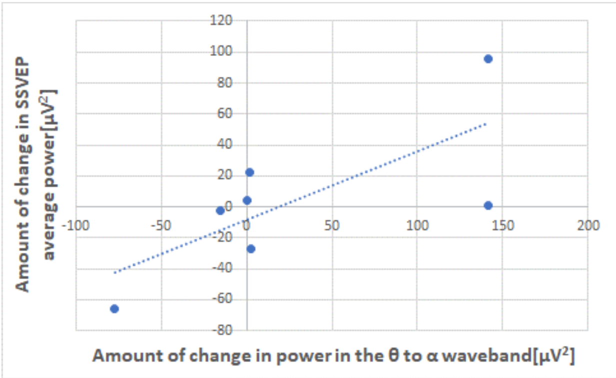


Fig. 3. Relationship between fatigue and SSVEP responses during neurofeedback training.

IV. FUTURE PERSPECTIVE

In B05-9, in addition to verifying the effectiveness of the neurofeedback training system proposed this year, we also began identifying the optimal stimulation format to more robustly induce the relevant brain waves and identifying factors that influence the training effect. Because we focused on improving the robustness of the system, we have not been able to obtain sufficient data (data from actual neurofeedback training) to demonstrate the effectiveness of neurofeedback training. We will continue to measure data including the control group (Sham group). Finally, we will show that it is effective for elderly people and stroke patients.

REFERENCES

[1] Y. Bagherzadeh, D. Baldauf, D. Pantazis and R. Desimone, “Alpha synchrony and the neurofeedback control of spatial attention,” Neuron, 105(3), pp. 577-587, 2020.

[2] O.M. Bazanova and D. Vernon, “Interpreting EEG alpha activity,” Neurosci Biobehav Rev, 44, pp. 94-110, 2013.

[3] T. Sakurada, M. Yoshida and K. Nagai, “Individual optimal attentional strategy in motor learning tasks characterized by steady-state somatosensory and visual evoked potentials,” Front Hum Neurosci, 15: 784292, 2022.

[4] O. Alkoby, A. Abu-Rmileh, O. Shriki and D. Todder, “Can we predict who will respond to neurofeedback? A review of the inefficacy problem and existing predictors for successful EEG neurofeedback learning,” Neuroscience, 378, pp. 155-164, 2018.

[5] T. Sakurada, Patent No. 7353632.

[6] S. Tobimatsu, Y.M. Zhang and M. Kato, “Steady-state vibration somatosensory evoked potentials: physiological characteristics and tuning function,” Clinical Neurophysiology, 110, pp. 1953-58, 1999.

[7] A. Craig, Y. Tran, N. Wijesuriya and H. Nguyen, “Regional brain wave activity changes associated with fatigue,” Psychophysiology, 49, pp. 574-582, 2012.

B05-10 Annual report of research project

Yuki Ueyama
Department of Mechanical Engineering, National Defense Academy of Japan

***Abstract*— As we acquired skills or adapted to new environments, we were able to do so with limited information through trial and error. In this study, we define the adaptation process based on exploratory behavior as "exploratory adaptation", which we hypothesize to be a computational mechanism of brain function involved in hyper-adaptation. The aim of this study is to elucidate the neural basis of the exploratory adaptation. We approach both the computational and the imaging analysis by building a model of exploratory adaptation based on meta-reinforcement learning and by performing fMRI experiments. This fiscal year, we identified neural circuits that enable the exploratory adaptation based on the fMRI data. In addition, we developed a method to facilitate the exploration of motion planning as a method to support the acquisition of complex motor skills.**

I. Introduction

We can efficiently adapt to the environment from the resulting limited information by adopting a trial-and-error behavior in unknown environments. For example, when we learn a skill such as riding a bicycle or adapting to a new environment, we search for the best strategy based on the limited information we receive as a result of our actions by repeating the actions in a trial-and-error fashion. In this study, we define "exploratory adaptation" as an adaptation mechanism based on such exploratory behavior, consider it as a computational mechanism of the brain that plays a role in super-adaptation, and aim to elucidate the neural basis of such exploratory adaptation. We model exploratory adaptation by an algorithm called meta-reinforcement learning [1], and approach the task from both computational and functional brain imaging perspectives by performing fMRI experiments using a simple motor learning task.

II. Aim of the Group

The aim of this study is to elucidate the neural basis of exploratory adaptation. In general, reward and sensory prediction are thought to be used in adaptive processes such as motor learning, but because many of the brain regions associated with them are common, their independent brain mechanisms and interactions remain unclear [2]. In this study, we used fMRI to measure brain activity during a rotational coordinate transformation task in visuomotor learning. Exploratory adaptation to tasks is modeled as meta-reinforcement learning, and brain activity is analyzed based on the model's estimation results to identify the brain network that enables exploratory adaptation.

This fiscal year, we identified neural circuits that enable the exploratory adaptation based on the fMRI data. In addition, we developed a method to facilitate the exploration of motion planning through augmented reality (AR) technology as a method to support the acquisition of complex skills in dart throwing performance.

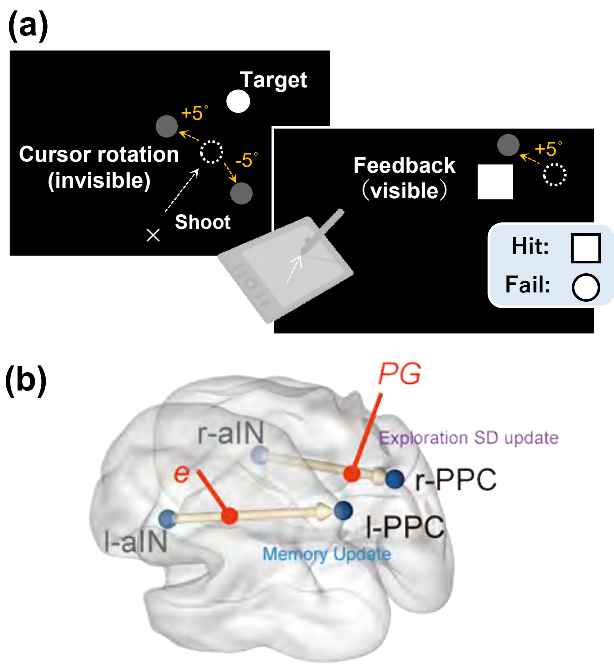


Fig. 1 fMRI study. (a) Experimental task. The fixation cross was presented at the start position. The timing of the target presentation (white filled circle) was randomized across trials between 1 and 13 s with respect to the presentation of the fixation cross. Participants were asked to move a stylus pen tip (dashed circle, invisible) from the start position to the center of the visual target within 1 s after target presentation. When the pen hit the target, participants received reward feedback (a filled white box explosion). Unbeknownst to the participants, the reward zone was shifted by ±5° in some of the trials. (b) Result of the Dynamic Causal Modeling analisys.

III. Research Topics

A. Neural connectivity for exploratory adaptation

We built a computational model to perform the reinforcement learning task and identified brain regions involved in changes in exploratory level and motor memory updating. In addition, we used the Dynamic Causal Modeling (DCM) analysis to identify the brain networks involved in exploratory adaptation.

The experimental task in this study was a reaching motion task in which the user manipulates the cursor on the screen by manipulating the stylus pen on the tablet and moves it in the presented target direction (Fig. 1a). In this task, participants cannot know the visual position of the cursor and perform the task using only the success or failure of the task given after each trial as a cue. The cursor is rotated +5° or –5° around the starting point every few trials, and this information is not known to the participants in advance. Therefore, the participants must learn the correct direction of movement by groping and changing the direction of movement of the stylus pen accordingly. In this experimental task, we define this process as exploratory adaptation.

According to the DCM analysis, the memory update and explanation level were found to affect the left and right anterior insula (aIN) and posterior parietal cortex (PPC), respectively (Fig. 1b).

B. Facilitating exploration in skill acquisition

The purpose of this study was to develop a method to assist subjects in the acquisition of motor skills. We then tested the effectiveness of an intervention using augmented reality (AR) technology on dart throwing performance.

We assumed that the acquisition of motor skills during dart throwing follows a computational model called the Planned Aim Point Correction (PAPC) model [3]. According to the PAPC model (Fig. 2a), the position $\mathbf{x}_t$ aimed at the target position $\mathbf{x}_d$ is affected by the motion noise represented by the planning noise $\mathbf{r}_t$ and the execution noise $\mathbf{n}_t$, and its action is determined by $\mathbf{z}_t$ as follows:

$$\mathbf{z}_t = \mathbf{x}_t + \mathbf{r}_t + \mathbf{n}_t \,. \quad (1)$$

To improve the performance, the error of $\mathbf{z}_t$ with respect to $\mathbf{x}_d$ is reduced, and the error correction is performed on the motion plan, which is the sum of the aimed position and the motion noise, by updating the aimed position $\mathbf{x}_{t+1}$ for the next trial using the follows:

$$\mathbf{x}_{t+1} = \mathbf{x}_t + \mathbf{r}_t + b \cdot (\mathbf{x}^d - \mathbf{z}_t) \,. \quad (2)$$

If the components of the motion noise, planning noise $\mathbf{r}_t$ and execution noise $\mathbf{n}_t$, are normally distributed and their standard deviations are σ_r and σ_n, respectively, then the fraction of planning noise in the motion noise is as follows:

$$w = \frac{\sigma_r^2}{\sigma_r^2 + \sigma_n^2} \,. \quad (3)$$

We conducted an experiment using the AR technology developed. According to the results, we confirmed that darting skills improved before and after the AR technology intervention (Fig. 2b). However, dart skills did not change during the AR intervention compared to the pre-intervention period. On the other hand, when the proportion of planning noise included in the motion noise was examined using equation (3), it was clear that the proportion of planning noise increased when the AR intervention was used, compared to before and after the intervention (Fig. 2c). It indicates that AR

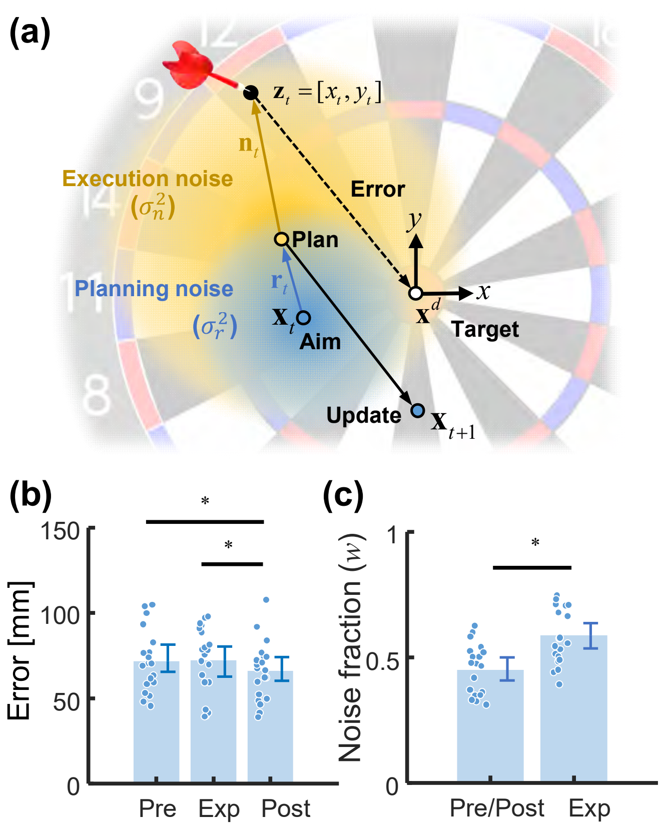


Fig. 2 Dart experiment. (a) Schematic illustration of the planned aim point correction (PAPC) model and the coordinate system. (b) Dart throwing accuracy shown as the mean error. The dots represent the data of individual participants, and the vertical bars are the 95% confidential intervals. (c) Motor noise fraction.

has been actively seeking to update the motor plan. Therefore, it is expected that the AR intervention can modulate planning noise and promote the acquisition of new skills.

IV. Future Perspective

This fiscal year, in addition to analyzing functional brain imaging data, we developed an assistive technology to facilitate the exploration for the next step in motor skill acquisition using AR technology.

Some of the results of this year's work, together with experimental data from previous years, have been published in a paper that has already been submitted for publication.

References

[1] A. Nagabandi, I. Clavera, S. Liu, RS. Fearing, P. Abbel, S. Levine, and C. Finn., Learning to Adapt in Dynamic, Real-World Environments through Meta-Reinforcement Learning, In 7th International Conference on Learning Representations (ICLR 2019), 2019.

[2] DJ. Palidis, JGA. Cashaback, and PL. Gribble., Neural signatures of reward and sensory error feedback processing in motor learning, Journal of Neurophysiology, vol. 121(4), pp. 1561-1574, 2019.

[3] R. J. van Beers, "Motor Learning Is Optimally Tuned to the Properties of Motor Noise," Neuron, vol. 63, no. 3, pp. 406 417, 2009.

List of Publications (2023)

Journal Papers

---

1. Yamamoto, N., Matsumoto, T., Sudo, T., Miyashita, M., and Kondo, T., Quantitative measurement of finger usage in stroke hemiplegia using ring-shaped wearable devices, Journal of NeuroEngineering and Rehabilitation, Volume 20(73), 2023
2. Negishi, T., Ogihara, N., Regulation of whole-body angular momentum during human walking, Scientific Reports, Volume 13, 8000, 2023
3. Negishi, T., Ogihara, N., Functional signifcance of vertical free moment for generation of human bipedal walking, Scientific Reports, Volume 13, 6894, 2023
4. S. Koseki, K. Kutsuzawa, D. Owaki, M. Hayashibe, Multimodal Bipedal Locomotion Generation with Passive Dynamics via Deep Reinforcement Learning, Frontiers in Neurorobotics, Volume 16, 1054239, 2023
5. G. Li, J. Shintake and M. Hayashibe, Soft-Body Dynamics Induces Energy Efficiency in Undulatory Swimming: A Deep Learning Study, Frontiers in Robotics and AI, Volume 10, 1102854, 2023
6. M.H. Ahmed, J. Chai, S. Shimoda and M. Hayashibe, Synergy-Space Recurrent Neural Network for Transferable Forearm Motion Prediction from Residual Limb Motion, Sensors, Volume 23(9), 4188, 2023
7. M.H. Ahmed, K. Kutsuzawa and M. Hayashibe, Transhumeral Arm Reaching Motion Prediction through Deep Reinforcement Learning-based Synthetic Motion Cloning, Biomimetics, Volume 8(4), 367, 2023
8. A. Purnomo and M. Hayashibe, Sparse Identification of Lagrangian for Nonlinear Dynamical Systems via Proximal Gradient Method, Scientific Reports, Volume 13, 7919, 2023
9. K. Shen, G. Li, A. Chemori and M. Hayashibe, Self-Organizing Neural Network for Reproducing Human Postural Mode Alternation through Deep Reinforcement Learning, Scientific Reports,

   Volume 13, 8966, 2023
10. T. Sugiyama, K. Kutsuzawa, D. Owaki, M. Hayashibe, Latent Representation-based Learning Controller for Pneumatic and Hydraulic Dual Actuation of Pressure-driven Soft Actuators, Soft Robotics, 2023

11. Morita T, Takemura H, Naito E, Functional and structural properties of interhemispheric interaction between bilateral precentral hand motor regions in a top wheelchair racing Paralympian, Brain Sciences, Volume 13(5), 715, 2023

12. Yuanhao Li, Badong Chen, Yuxi Shi, Natsue Yoshimura, and Yasuharu Koike, Robust Sparse Brain Activity Decoding", IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, Volume 70(8), 2416-2429, 2023

13. Satoshi Zuguchi, Kazuhiro Sakamoto, Norihiro Katayama, Hajime Mushiake, A High-speed Measurement System for Treadmill Spherical Motion in Virtual Reality for Mice and a Robust Rotation Axis Estimation Algorithm Based on Spherical Geometry, IPSJ Transactions on Bioinformatics, Volume 16, 1-12, 2023

14. Kazuhiro Sakamoto, Naohiro Saito, Shun Yoshida, Hajime Mushiake, A Dynamic, Economical, and Robust Coding Scheme in the Lateral Prefrontal Neurons of Monkeys, Lecture Notes in Computer Science, Volume 13624, 13-24, 2023

15. Hamada H, Wen W, Kawasaki T, Yamashita A, Asama H, Characteristics of EEG power spectra involved in the proficiency of motor learning, Frontiers in Neuroscience, Volume 17, 2023

16. Suzuki, Y., Togame, K., Nakamura, A., Nomura, T., A Markov chain approximation of switched Fokker–Planck equations for a model of on–off intermittency in the postural control during quiet standing, Communications in Nonlinear Science and Numerical Simulation, Volume 126, 107488, 2023

17. Akihiro Nakamura, Ryota Miura, Yasuyuki Suzuki, Pietro Morasso, Taishin Nomura, Discrete cortical control during quiet stance revealed by desynchronization and rebound of beta oscillations, Neuroscience Letters, Volume 814, 137443, 2023

18. Li Q, Takeuchi Y, Wang J, Gellért L, Barcsai L, Pedraza LK, Nagy AJ, Kozák G, Nakai S, Kato S, Kobayashi K, Ohsawa M, Horváth G, Kékesi G, Lőrincz ML, Devinsky O, Buzsáki G, Berényi A, Reinstating olfactory bulb derived limbic gamma oscillations alleviates depression-like behavioral deficits in rodents, Neuron, Volume 111, 2065-2075, 2023

19. Sierra RO, Pedraza LK, Barcsai L, Peijin A, Li Q, Kozák G, Takeuchi Y, Nagy AJ, Lőrincz ML, Devinsky O, Buzsáki G, Berényi A, Closed-loop brain stimulation augments fear extinction in male rats, Nature Communications, Volume 14, 3972, 2023

20. Mishima, M.*, Hayashida, K.*, Fukasaku, Y., Ogata, R., Ohsawa, K., Iwai, K., Wen, W., Morioka, S., Adaptability of the sense of agency in healthy young adults in sensorimotor tasks for a short term, Behavioral Sciences, Volume 13(2), 132, 2023

21. Kosugi A, Saga Y, Kudo M, Koizumi M, Umeda T, Seki K, Time course of recovery of different motor

functions following a reproducible cortical infarction in non-human primates, Front Neurol. 2023; Frontiers in Neurology, Volume 14, 1094774, 2023

22. Tetsuya Hasegawa, Tomoki Mori, Kohei Kaminishi, Ryosuke Chiba, Jun Ota, Arito Yozu, Effect of Sway Frequency on the Joint Angle and Center of Pressure in Voluntary Sway, Journal of motor behavior, Volume 55(4), 373-383, 2023
23. Arito Yozu, Tetsuya Hasegawa , Naomichi Ogihara , Jun Ota, Peak vertical ground force of hand-knee crawling in human adults, Journal of physical therapy science, Volume 35(4), 306-310, 2023
24. Masayuki TETSUKA, Takeshi SAKURADA, Mayuko MATSUMOTO, Takeshi NAKAJIMA, Mitsuya MORITA, Shigeru FUJIMOTO and Kensuke KAWAI, Higher prefrontal activity based on short-term neurofeedback training can prevent working memory decline in acute stroke, Frontiers in Systems Neuroscience, Volume 17, 1130272, 2023
25. Kasaragod DK, Aizawa H., Deep ultraviolet fluorescence microscopy of three-dimensional structures in the mouse brain, Scientific Reports, Volume 13(1), 8553, 2023
26. Li WR, Nakano T, Mizutani K, Matsubara T, Kawatani M, Mukai Y, Danjo T, Ito H, Aizawa H, Yamanaka A, Petersen CCH, Yoshimoto J, Yamashita T., Neural mechanisms underlying uninstructed orofacial movements during reward-based learning behaviors, Current Biology, Volume 33(16), 3436-3451, 2023
27. Takakuwa N, Isa T, Visuomotor coordination and cognitive capacity in blindsight, Current Opinion in Neurobiology, Volume 82, 102764, 2023
28. Sawada M, Yoshino-Saito K, Ninomiya T, Oishi T, Yamashita T, Onoe H, Takada M, Nishimura Y, Isa T., Reorganization of Corticospinal Projections after Prominent Recovery of Finger Dexterity from Partial Spinal Cord Injury in Macaque Monkeys, eNeuro, Volume 10(8), 0209-23, 2023
29. Kimura R, Flexible information representation to stabilize sensory perception despite minor external input variations, Neuroscience Research, Volume 195, 1-8, 2023
30. Ueyama Y, Harada M, Augmented Reality-Based Trajectory Feedback Does Not Improve Aiming in Dart-Throwing, IEEE Access, Volume 11, 64738-64744, 2023
31. Katsumata, Y., Inoue, Y., Toriumi, S., Ishimoto, H., Hapuarachchi, H., and Kitazaki, M., Shared Avatar for Hand Movement Imitation: Subjective and Behavioral Analyses, IEEE Access, Volume 11, 96710 – 96717, 2023
32. Sano H, Nambu A, Behavioral effects of zonisamide on L-DOPA-induced dyskinesia in Parkinson's disease model mice, Front Aging Neurosci, Volume 15, 1221341, 2023
33. Rios A, Nonomura S, Kato S, Yoshida I, Matsushita N, Nambu A, Takada M, Hira R, Kobayashi K,

Sakai Y, Kimura M, Isomura Y, Reward experience uniformly modifies action-related activity and diversely modifies outcome-related activity in topographic nigral and striatal systems, Commun Biol, Volume 914, 2023

34. Abe Y, Yagishita S, Sano H, Sugiura Y, Dantsuji M, Suzuki T, Mochizuki A, Yoshimaru D, Hata J, Matsumoto M, Taira S, Takeuchi T, Okano H, Ohno N, Suematsu M Inoue T, Nambu A, Watanabe M, Tanaka KF, Shared GABA transmission pathology in dopamine agonist- and antagonist-induced dyskinesia, Cell Rep Med, Volume 4(10), 101208, 2023

35. Yoshida T, Otaka Y, Kitamura S, Ushizawa K, Kumagai M, Yaeda J, Osu R, Influence of motivation on rehabilitation outcomes after subacute stroke in convalescent rehabilitation wards, Frontiers in Neurology, Volume 14, 2023

36. Nozu T, Miyagishi S, Ishioh M, Takakusaki K, Okumura T, Imeglimin prevents visceral hypersensitivity and colonic hyperpermeability in irritable bowel syndrome rat model, J Pharmacol Sci, Volume 153(1), 26-30, 2023

37. Takakusaki K, Gait control by the frontal lobe (Review), Handb Clin Neurol, Volume 195, 103-126, 2023

38. Nozu T, Miyagishi S, Ishioh M, Takakusaki K, Okumura T Phlorizin attenuates postoperative gastric ileus in rats, Neurogastroenterol Motil, e14659, 2023

39. Harin Hapuarachchi, Hiroki Ishimoto, Michiteru Kitazaki, Maki Sugimoto, Masahiko Inami, Temporal visuomotor synchrony induces embodiment towards an avatar with biomechanically impossible arm movements, i-Perception, Volume 14, 1-17, 2023

40. Arito Yozu, Kohta Sonoda, Tetsuya Hasegawa, Kohei Kaminishi, Michihiro Osumi, Masahiko Sumitani, Ryosuke Chiba, Jun Ota, Effect of experimentally induced plantar pain on trunk posture during gait, Journal of physical therapy science, Volume 35(9), 613-618, 2023

41. C. Phunruangsakao, D. Achanccaray, S. Bhattacharyya, S. Izumi, M. Hayashibe, Effects of Visual-Electrotactile Stimulation Feedback on Brain Functional Connectivity during Motor Imagery Practice, Scientific Reports, Volume 13, 17752, 2023

42. Barradas, V. R., Koike, Y., Schweighofer, N., Theoretical limits on the speed of learning inverse models explain the rate of adaptation in arm reaching tasks, Neural Networks, Volume 170, 376-389, 2023

43. Li, Y., Chen, B., Wang, G., Yoshimura, N., Koike, Y., Partial maximum correntropy regression for robust electrocorticography decoding, Frontiers in Neuroscience, Volume 17, 2023

44. Sentong Wang, Kazunori Hase, Tetsuro Funato, Computational prediction of muscle synergy using a finite element framework for a musculoskeletal model on lower limb, Frontiers in Bioengineering and Biotechnology, Volume 11, 1130219, 2023

45. Matsugi A, Nishishita S, Bando K, Kikuchi Y, Tsujimoto K, Tanabe Y, Yoshida N, Tanaka H, Douchi S, Honda T, Odagaki M, Nakano H, Okada Y, Mori N, Hosomi K., Excessive excitability of inhibitory cortical circuit and disturbance of ballistic targeting movement in degenerative cerebellar ataxia, Scientific Reports, Volume 13(1), 13917, 2023

46. Nakano H, Murata S, Kodama T, Nakae H, Soma M., Effect of Rhythmic Finger Movement Training on Freezing of Gait and Electroencephalography Activity in People With Parkinson Disease :A Case Study, Topics in Geriatric Rehabilitation, Volume 39(3), 185-190, 2023

47. Sawai S, Fujikawa S, Ohsumi C, Ushio R, Tamura K, Yamamoto R, Kai Y, Murata S, Shima K, Nakano H., Effects of neurofeedback on standing postural control task with combined imagined and executed movements, Frontiers in Neurosciene, Volume 17, 1199398, 2023

48. Sawai S, Murata S, Fujikawa S, Yamamoto R, Nakano H., Effects of θ High Definition-Transcranial Alternating Current Stimulation in the Anterior Cingulate Cortex on the Dominance of Attention Focus in Standing Postural Control, Behavioral Sciences, Volume 13(6), 477, 2023

49. Sawai S, Murata S, Fujikawa S, Yamamoto R, Shima K, Nakano H., Effects of neurofeedback training combined with transcranial direct current stimulation on motor imagery: A randomized controlled trial, Frontiers in Neurosciene, Volume 17, 1148336, 2023

50. Nakano H, Matsugi A, Ito T, Oku K, Sakita M., Editorial: Pushing the limits of motor function recovery in rehabilitation: Basic to applied research based on neuroscience, Frontiers in Human Neuroscience, Volume 17, 1160632, 2023

51. Schlosser-Perrin F, Rossel O, Duffau H, Matsumoto R, Mandonnet E, Bonnetblanc F., The orientation of the stimulating bipolar probe modulates axono-cortical evoked potentials, Brain Stimul, Volume 16(4), 1009-1011, 2023

52. Rossel O, Schlosser-Perrin F, Duffau H, Matsumoto R, Mandonnet E, Bonnetblanc F., Short-range axono-cortical evoked-potentials in brain tumor surgery: Waveform characteristics as markers of direct connectivity, Clin Neurophysiol, Volume 153, 189-201, 2023

53. Eiro T, Miyazaki T, Hatano M, Nakajima W, Arisawa T, Takada Y, Kimura K, Sano A, Nakano K, Mihara T, Takayama Y, Ikegaya N, Iwasaki M, Hishimoto A, Noda Y, Miyazaki T, Uchida H, Tani H, Nagai N, Koizumi T, Nakajima S, Mimura M, Matsuda N, Kanai K, Takahashi K, Ito H, Hirano Y, Kimura Y, Matsumoto R, Ikeda A, Takahashi T., Dynamics of AMPA receptors regulate epileptogenesis in patients with epilepsy, Cell Rep Med, Volume 4(5), 101020, 2023

54. Usami K, Matsumoto R, Korzeniewska A, Shimotake A, Matsuhashi M, Nakae T, Kikuchi T, Yoshida K, Kunieda T, Takahashi R, Crone NE, Ikeda A, The dynamics of cortical interactions in visual recognition of object category: living vs non-living, Cereb Cortex, Volume 33(9), 5740-5750, 2023

55. Mizuseki, K., Miyawaki, H., Fast network oscillations during non-REM sleep support memory consolidation, Neuroscience Research, Volume 186, 3-12, 2023

56. Naoki Aizu, Tamami Sudo, Yutaka Oouchida, Shin-Ichi Izumi, Facilitation of imitative movement in patients with chronic hemiplegia triggered by illusory ownership, Scientific reports, Volume 13(1), 16143-16143, 2023

57. Saeka Tomatsu, GeeHee Kim, Shinji Kubota, Kazuhiko Seki, Presynaptic gating of monkey proprioceptive signals for proper motor action, Nature Communications, Volume 14, 6537, 2023

58. Y. Omura, H. Togo, K. Kaminishi, T. Hasegawa, R. Chiba, A. Yozu, K. Takakusaki, M. Abe, Y. Takahashi, T. Hanakawa, and J. Ota, Analysis of abnormal posture in patients with Parkinson's disease using a computational model considering muscle tones, Frontiers in Computational Neuroscience, Volume 17, 1218707， 2023

59. Ogawa A, Koganemaru S, Takahashi T, Takemura Y, Irisawa H, Goto K, Matsuhashi M, Mima T, Mizushima T, Kansaku K., Swallow-related Brain Activity in Post-total Laryngectomy Patients: A Case Series Study, Progress in Rehabilitation Medicine, Volume 8, 20230026, 2023

60. Yamaoka T, Takagi Y, Shimomura R, Murata Y, Shimotake K, Itoh A, Mima T, Koganemaru S., N-of-1 Trial of Electrical Sensory Stimulation Therapy on the Tibial Innervated Area during Gait in a Case of Post-stroke Sensory Disturbance., Progress in Rehabilitation Medicine, Volume 8,　20230018, 2023

61. Nojima I, Horiba M, Sahashi K, Koganemaru S, Murakami S, Aoyama K, Matsukawa N, Ono Y, Mima T, Ueki Y., Gait-combined closed-loop brain stimulation can improve walking dynamics in Parkinsonian gait disturbances: a randomised-control trial, J Neurol Neurosurg Psychiatry, Volume 94(11), 938-944, 2023

62. Shimomura R, Shibata S, Koganemaru S, Minakuchi M, Ichimura S, Itoh A, Shimotake K, Mima T., Transcranial static magnetic field stimulation (tSMS) can induce functional recovery in patients with subacute stroke, Brain Stimulation, Volume 16(3), 933-935, 2023

63. Sumiya Shibata, Satoko Koganemaru, Tatsuya Mima, Non-invasive Brain Stimulation in Post-stroke Dysphagia Rehabilitation: A Narrative Review of Meta-analyses in 2022, Progress in Rehabilitation Medicine, Volume 8, 1-10, 2023

64. Yukawa Y, Shibata S, Koganemaru S, Minakuchi M, Shimomura R, Nakamura K, Mima T., Low-frequency repetitive transcranial magnetic stimulation can alleviate spasticity and induce functional recovery in patients with severe chronic stroke: A prospective, non-controlled, pilot study, Heliyon, Volume 9(4), e15564, 2023

65. Ryota Shimomura*, Sumiya Shibata*, Satoko Koganemaru, Masatoshi Minakuchi, Sachimori Ichimura,

Akihiro Itoh, Katsumi Shimotake, Tatsuya Mima, Transcranial static magnetic field stimulation (tSMS) can induce functional recovery in patients with subacute stroke, Brain Stimulation, Volume 16(3), 933-935, 2023

66. Sumiya Shibata, Hirotaka Takahashi, Yu Miida, Tatsuya Mima, Hideaki Onishi, Priming effects of transcutaneous vagus nerve stimulation on the neuromodulation induced by transcranial static magnetic field stimulation in human motor cortex, Clinical Neurophysiology, Volume 154, 194-197, 2023

67. Takuya Matsumoto, Tatsunori Watanabe, Kanami Ito, Takayuki Horinouchi, Sumiya Shibata, Hiroshi Kurumadani, Toru Sunagawa, Tatsuya Mima, Hikari Kirimoto, Effect of transcranial static magnetic stimulation over unilateral or bilateral motor association cortex on performance of simple and choice reaction time tasks, Frontiers in Human Neuroscience, Volume 17, 1-10, 2023

68. Chiyohara S, Furukawa JI, Noda T, Morimoto J, Imamizu H., Proprioceptive short-term memory in passive motor learning, Scientific Reports, Volume 13(1), e20826, 2023

69. K. Tada, Y. Sorimachi, K. Kutsuzawa, D. Owaki, and M. Hayashibe, Integrated Quantitative Evaluation of Spatial Cognition and Motor Function with HoloLens Mixed Reality, Sensors, Volume 24(2), Volume 528, 2024

70. S. Koseki, M. Hayashibe, D. Owaki, Identifying essential factors for energy-efficient walking control across a wide range of velocities in reflex-based musculoskeletal systems, PLOS Computational Biology, Volume 20(1), e1011771, 2024

71. Konosu Akira, Matsuki Yuma, Fukuhara Kaito, Funato Tetsuro, Yanagihara Dai, Roles of the cerebellar vermis in predictive postural controls against external disturbances, Scientific Reports, Volume 14, 3162, 2024

72. Ueyama Y, Harada M, Basketball free-throw training with augmented reality-based optimal shot trajectory for novice shooters, Scientific Reports, Volume 14, 891, 2024

73. Matsugi A, Yoshida N, Nakano H, Okada Y., The Neurorehabilitation of Neurological Movement Disorders Requires Rigorous and Sustained Research, Journal of Clinical Medicine. Volume 13(3), 852, 2024

74. Cox CR, Rogers T, Shimotake A, Kikuchi T, Kunieda T, Miyamoto S, Takahashi R, Matsumoto R, Ikeda A, Lambon-Ralph MA., Representational similarity learning reveals a graded multidimensional semantic space in the human anterior temporal cortex, Imaging Neuroscience, early access, 2024

75. Adya saran Sinha*, Sumiya Shibata*, Yasuyuki Takamatsu*, Tenpei Akita, Atsuo Fukuda and Tatsuya Mima, Static magnetic field stimulation enhances shunting inhibition via a SLC26 family Cl－ channel, inducing intrinsic plasticity, Journal of Neuroscience, 2024

International Conference

1. Ryoya Kihara, Qi An, Kensuke Takita, Shu Ishiguro, Kazuto Nakashima, Ryo Kurazume, Analysis of Force Applied to Horizontal and Vertical Handrails with Impaired Motor Function, 2023 IEEE/SICE International Symposium on System Integration (SII), Atlanta USA, 2023
2. Koike, Y., Development of a musculoskeletal model that estimates muscle tension from electromyography, joint torque, impedance, and equilibrium position, ISB 2023 Congress XXIX Fukuoka, Japan, 2023
3. Kazuhiro Sakamoto, Nao Matsumoto, Naoki M.Tamura, Hajime Mushiake, A dynamic state-space reinforcement learning model explaining neuronal activities of the supplementary motor area in the cerebral cortex, The 46th Annual Meeting of the Japan Neuroscience Society Sendai, Japan, 2023
4. Takahashi, K., Inoue, Y. and Kitazaki, M., "Effects of Source Location, Loudness, and Understanding of Speech on Interpersonal Distance in a Virtual Environment", The 29th ACM Symposium on Virtual Reality Software and Technology (VRST), Christchurch, New Zealand, 2023
5. Haraguchi, G. and Kitazaki, M., Deforming Skin Illusion by Visual-tactile Stimulation, The 29th ACM Symposium on Virtual Reality Software and Technology (VRST), Christchurch, New Zealand, 2023
6. Xu Y, Yoshida K, Takeuchi Y, Toward non-invasive, precise control of internal organs via ultrasound neuromodulation of the autonomic nervous system, 9th Biomedical Imaging and Sensing Conference, Yokohama, Japan, 2023
7. Takeuchi Y, Closed-loop control of neurological and psychiatric disorders, Summer Program, Taipei Meicial University, Online, Japan, 2023
8. Taishin Nomura, control during human quiet stance: A greedy strategy for postural stabilization, The International Society for Postire and Gait World Congress 2023, Brisbane, Australia, 2023
9. Tomohiko Takei, Neural dynamics of motor cortex for flexible feedback motor control, The 8th CiNet Conference: Beyond Motor Control: Bridging the gap between action and perception, Suita, Japan, 2023
10. Ota, Jun, Science of Hyper-adaptability: An Introduction, 2023 45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Sydney, Australia, 2023
11. Tadashi Isa, Large-scaled adult brain plasticity for recovery from spinal cord injury, NIPS international symposium, Multi-disciplinary approach to understant neuronal network architecture to control motor actions, Okazaki, Japan, 2023
12. Tadashi Isa, Large-scaled adult brain plasticity for reovery after spinal cord injury, Neuro-BRB (Breach

the Research Barrier) 2023, Online, 2023

13. Tadashi Isa, Neural circuits and cognitive capacity underlying blindsight in monkeys, Systems Vision Science Summer School & Symposium, Online, 2023

14. Hiroshi Imamizu, Sense of agency facilitates motor learning, Sydney, Australia, 2023

15. D Kim, H Kanazawa, Y Kuniyoshi, Emergence of Reaching using Predictive Learning as Sensorimotor Development in Complex Dynamics, The 11th International Symposium on Adaptive Motion of Animals and Machines, Kobe, Japan, 2023

16. Y Shinomiya, H Kanazawa, D Kim, Y Kuniyoshi, Self-organized acquisition of muscle synergy and behavior with whole body musculoskeletal infant model, The 11th International Symposium on Adaptive Motion of Animals and Machines, Kobe, Japan, 2023

17. T Jülg, F Walter, D Kim, H Kanazawa, A Knoll, Y Kuniyoshi, Multi-Modal Representation Learning for Mapping Between Body Motion and Visual Imagery, The 11th International Symposium on Adaptive Motion of Animals and Machines, Kobe, Japan, 2023

18. Hoshinori Kanazawa, The Embodied Brain Model for Early Human Development, http://cyber.felk.cvut.cz/seminars/?event=1578, Prague, Czech, 2023

19. N Yoshida, H Kanazawa, Y Kuniyoshi, Homeostatic Reinforcement Learning through Soft Behavior Switching with Internal Body State, 2023 International Joint Conference on Neural Networks (IJCNN), Queensland, Australia, 2023

20. Nambu A, Somatotopic reorganization of the macaque sensorimotor cortex after accidental arm amputation, CIN-NIPS-Asia Pacific Systems Neuroscience Symposium, Tuebingen, Germany. 2023

21. Nambu A, In search of a unified view for the pathophysiology of movement disorders, 2023 IBAGS Conference, Stockholm, Sweden, 2023

22. Tomu Makino, Tetsuya Hasegawa, Shouhei Shirafuji, Jun Ota, Arito Yozu, Evaluation of the Giving-Way-Prevention Function of a Soft Exosuit Incorporating the Multi-articular Muscle Mechanism, The 34rd 2023 International Symposium on Micro-NanoMechatronics and Human Science (MHS2023), Nagoya, Japan, 2023

23. C. Herneth, M. Hayashibe, D. Owaki, Learnable Tegotae-based Feedback in CPGs with Sparse Observation Produces Efficient and Adaptive Locomotion, IEEE Int. Conf. on Robotics and Automation, London, United Kingdom, 2023

24. S. Koseki, M. Hayashibe, D. Owaki, Energy-Efficient Speed Control in a Reflex-based Bipedal Walking Model, Proc. of 11th Int. Symposium on Adaptive Motion of Animals and Mechanics, Kobe, Japan, 2023

25. L. Sulpice, D. Owaki, M. Hayashibe, Deep Reinforcement Learning for Tailorable Natural Quadruped Gait Generation, Proc. of 11th Int. Symposium on Adaptive Motion of Animals and Mechanics, Kobe, Japan, 2023

26. Barradas, V., Theoretical limits on the speed of learning inverse models explain the rate of adaptation in arm reaching tasks, IEEE EMBC2023, Sydney, Australia, 2023

27. Kazuhiro Sakamoto, Higher brain function research needs good questions and theories, NIPS workshop 2022 "Multi-disciplinary approach to understand neuronal network architecture for controlling motor actions", Okazaki, Japan, 2023

28. Kazuhiro Sakamoto, A Reinforcement Learning Model for Higher Motor Areas, The 2nd International Symposium “Hyper -Adaptability”, Kyoto, Japan, 2023

29. Kazuhiro Sakamoto, Tomoaki Kinugasa, Futo Ono, Solving the Traveling Salesman Problem using Kuramoto Oscillators, 2023 International Symposium on Nonlinear Theory and Its Applications, Catania, Italy, 2023

30. Murakami, T., and Kitazaki, M., Design of body transformation experience, ICAT-EGVE 2023, Dublin, Ireland, 2023

31. Matsumoto R., Mapping language network for presurgical evaluations of epilepsy and tumor surgery, BCI&Neurotechnology Spring School, Online, 2023

32. Matsumoto R., Cortico-cortical evoked potential for arcuate fasciculus monitoring, 5th Congress of Asia Oceanian Society of Intraoperative Neurophysiology Society (AOSIN2023), Taipei, Taiwan, 2023

33. Matsumoto R., Artifacts in EEG, Japan Epilepsy Society-Nihon Kohden Epilepsy Treatment Training Course in Indonesia, Online, 2023

34. Matsumoto R., Brain Potentials Evoked by Direct Electrical Stimulation for Better Guiding of Neurosurgery, Paris-Kobe workshop on Brain Evoked Potentials for Neurosurgery 2023, Paris, France, 2023

35. Matsumoto R., Evoked stimulation responses to guide surgical decisions, International Epilepsy Congress 2023, Dublin, Ireland, 2023

36. Matsumoto R., Neural basis of apraxia of speech: insights from the electrical cortical stimulation mapping and CCEP connectome, International Kobe-Cambridge Workshop for Neurobiology of Language and Related disorders, Kobe, Japan, 2023

37. Nakano H, Murata S, Sawai S, Fujikawa S, Yamamoto R, Shima K, Motor Imagery-based Neurofeedback Using Visual, Auditory, Vibrotactile, and Proprioceptive Senses: A Randomized Controlled Trial, 16th Asian Confederation for Physical Therapy Congress, Bangkok, Thailand, 2023

38. Nakano H, Nakagawa K, Nagashima M, Naito E, Improving paralyzed hand motor function in stroke patients with vibratory stimulation and mirror therapy, The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

39. Fujikawa S, Murata S, Sawai S, Yamamoto R, Shizuka Y, Goda A, Shiraiwa K, Horie J, Nakano H, Quantitative assessment of finger dexterity in older adults and relationship to physical function, The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

40. Sawai S, Murata S, Sakano Y, Fujikawa S, Yamamoto R, Shizuka Y, Nakano H, The dominance of attentional focus in standing postural control in the elderly, The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

41. Nakano H, Sawai S, Fujikawa S, Ohsumi C, Ushio R, Tamura K, Yamamoto R, Kai Y, Murata S, Shima K, Effects of neurofeedback on standing postural control task with combined imagined and executed movements: A randomized controlled trial, The Hong Kong Physiotherapy Association 60th Anniversary Conference, Hong Kong, China, 2023

42. Ryoji Otaki, Yutaka Oouchida, Naoki Aizu, Tamami Sudo, Hiroshi Sasahara, Yuki Saito, Sunao Takemura and Shin-Ichi Izumi, Functional and structural brain reorganization associated with real-world arm use underlying upper limb recovery after stroke: A longitudinal fMRI and DTI study The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

43. Seki K, Neural adaptation to a physically-modified body in non-human primates, The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

44. Philipp R, Uchida N, Ohta N, Oya T, Hara Y, Funato T, Seki K, Neural Adaptation in Response to Tendon Transfer in the Primate Forearm Part I: Amplitude and Temporal Features of EMG Patterns During a Grasping Movement, The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

45. Seki K, Centrally generated presynaptic inhibition selectively modulates proprioceptive and tactile reafferent signals at the spinal cord of behaving monkeys, Motor Control: Spinal Circuits and Beyond2023, St Andrews, Scotland, 2023

46. Seki K, "Muscle synergy analysis yields an efficient and physiologically relevant way of assessing stroke, 26th Thai Neuroscience Society International Conference, Bangkok, Thailand, 2023

47. R. Huang, K. Kaminishi, T. Hasegawa, A. Yozu, R. Chiba, and J. Ota, Estimation of center of pressure information by smartphone sensors for postural control training, 2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Sydney, Australia, 2023

48. Y. Omura, H. Togo, K. Kaminishi, T. Hasegawa, R. Chiba, A. Yozu, K. Takakusaki, M. Abe, Y. Takahashi, T. Hanakawa, and J. Ota, Analysis of the Relationship Between Muscle Tones and Abnormal Postures in a Computational Model, 2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Sydney, Australia, 2023

49. K. Kaminishi, Y. Omura, R. Chiba, K. Takakusaki, and J. Ota, Musculoskeletal simulation to investigate strategies for arm use during postural recovery, 2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Sydney, Australia, 2023

50. K. Kaminishi, M. Ishikawa, T. Hasegawa, R. Chiba, K. Takakusaki, and J. Ota, CNN-based analysis of the relationship between DAT SPECT and motor function in patients with Parkinson's disease, The 34th 2023 International Symposium on Micro-NanoMechatronics and Human Science (MHS2023), Nagoya, Japan, 2023

51. Y. Kobayashi, Proposal of Motor Learning Model toward Explainability of Adaptability in Multiple Levels, The 34th 2023 International Symposium on Micro-NanoMechatronics and Human Science (MHS2023), Nagoya, Japan, 2023

52. Rie Kimura, Yumiko Yoshimura, Kenichi Ohki, Visual information representation in V1 adapts to changes in the external environment after learning, The 2nd International Symposium Hyper-Adaptability, Kyoto, Japan, 2023

53. Matsumoto R., Accurate diagnosis of Drug-Resistant Epilepsy for new emerging therapies, 25th Cairo International Neurology Conference, Cairo, Egypt, 2024

Member List

Steering Committee (X00): Administrative research on hyper-adaptability for overcoming body-brain dysfunction

Principal investigator	Jun Ota (Professor, The University of Tokyo)
Funded co-investigator	Tadashi Isa (Professor, Kyoto University)
Funded co-investigator	Toshiyuki Kondo (Professor, Tokyo University of Agriculture and Technology)
Funded co-investigator	Tetsuro Funato (Associate Professor, The University of Electro-Communications)
co-investigator	Eiichi Naito (Director, CiNet)
co-investigator	Hidenori Aizawa (Professor, Hiroshima University)
co-investigator	Kazuhiko Seki (Director, NCNP)
co-investigator	Hiroshi Imamizu (Professor, The University of Tokyo)
co-investigator	Ken-Ichiro Tsutsui (Professor, Tohoku University)
co-investigator	Kaoru Takakusaki (Professor, Asahikawa Medical University)
co-investigator	Takashi Hanakawa (Professor, Kyoto University)
co-investigator	Ryosuke Chiba (Associate Professor, Asahikawa Medical University)
co-investigator	Yasuharu Koike (Professor, Tokyo Institute of Technology)
co-investigator	Hajime Asama (Professor, The University of Tokyo)
co-investigator	Jun Izawa (Associate Professor, University of Tsukuba)
co-investigator	Qi An (Associate Professor, The University of Tokyo)
co-investigator	Arito Yozu (Associate Professor, The University of Tokyo)
co-investigator	Wen Wen (Project Associate Professor, Rikkyo University)

Research Project A01: Elucidation of the hyper-adaptation mechanism by reconstruction of bio-structure and challenges for prevention of decline in latent adaptive capacity

Principal investigator	Tadashi Isa (Professor, Kyoto University)
Funded co-investigator	Eiichi Naito (Director, CiNet)
Funded co-investigator	Hidenori Aizawa (Professor, Hiroshima University)
Funded co-investigator	Minoru Asada (Specially Appointed Professor, Osaka University/ Vice President, International Professional University of Technology in Osaka)
Funded co-investigator	Hideki Nakano (Associate Professor, Kyoto Tachibana University)
Co-investigator	Hirotaka Onoe (Project-specific Professor, Kyoto University)
Co-investigator	Satoko Koganemaru (Program-specific Associate Professor, Kyoto University)
Co-investigator	Reona Yamaguchi (Project Assistant Professor, Kyoto University)
Co-investigator	Ryo Sasaki (Assistant Professor, Kyoto University)
Co-investigator	Atsushi Shima (Assistant Professor, Kyoto University)

Co-investigator	Kazuki Tanaka (Research Assistant, Kyoto University)
Co-investigator	Kaoru Isa (Technical Stuff, Kyoto University)
Co-investigator	Satoko Ueno (PhD Student, Kyoto University)
Co-investigator	Masahiro Mitsuhashi (PhD Student, Kyoto University)
Co-investigator	Saya Kitazume (Graduate Student, Kyoto University)
Co-investigator	Erika Omae (Graduate Student, Kyoto University)
Co-investigator	Yiping Sun (Research Student, Kyoto University)
Co-investigator	Tomoyo Morita (Senior Researcher, CiNet)
Co-investigator	Jihoon Park (Specially Appointed Assistant Professor, Osaka University / Researcher, CiNet)
Co-investigator	Tomohiko Takei (Associate Professor, Tamagawa University)
Co-investigator	Satoshi Hirose (Associate Professor, Otemon Gakuin University)
Co-investigator	Miho Matsumata (Assistant Professor, Hiroshima University)
Co-investigator	Deepa Kamath Kasaragod (Assistant Professor, Hiroshima University)
Co-investigator	Takashi Handa (Assistant Professor, Hiroshima University)
Co-investigator	Gen Miura (Graduate Student, Osaka University)
Co-investigator	Tomoya Furuta (Graduate Student, Osaka University)
Co-investigator	Tang Yandi (Graduate Student, Osaka University)
Co-investigator	Fumino Fujiyama (Professor, Hokkaido University)
Co-investigator	Huyuki Karube (Associate Professor, Hokkaido University)
Co-investigator	Yasuharu Hirai (Assistant Professor, Doshisya University)
Co-investigator	Fuko Kadono (Graduate Student, Hokkaido University)

Research Project A02: Elucidation of neural mechanisms of super-adaptation to body change

Principal investigator	Kazuhiko Seki (Director, NCNP)
Co-investigator	Shinji Kubota (Section Chief, NCNP)
Co-investigator	Yuki Hara (Orthopedic director, NCNP Hospital)
Co-investigator	Roland Phillipp (Postdoctoral Fellow, NCNP)
Co-investigator	Amit Yaron (Postdoctoral Fellow, NCNP)
Co-investigator	Akito Kosugi (Postdoctoral Fellow, NCNP)
Co-investigator	Satomi Kikuta (Postdoctoral Fellow, NCNP)
Co-investigator	Junichiro Yoshida (Postdoctoral Fellow, NCNP)
Co-investigator	Shun Nakamura (Undergraduate Student, NCNP)
Co-investigator	Shiro Egawa (Special Postdoctoral Researcher, RIKEN Center for Biosystems Dynamics Research)

Research Project A03: Mechanisms of body cognition and emotion inducing hyper-adaptability

Principal investigator	Hiroshi Imamizu (Professor, The University of Tokyo)
Funded co-investigator	Ken-Ichiro Tsutsui (Professor, Tohoku University)
Co-investigator	Ryu Ohata (Researcher, Karolinska Institutet)
Co-investigator	Kentaro Hiromitsu (Researcher, The University of Tokyo)
Co-investigator	Tomohisa Asai (Researcher, ATR)
Co-investigator	Hiroshi Kadota (Associate Professor, Kochi University of Technology)
Co-investigator	Shu Imaizumi (Assistant Professor, Ochanomizu University)
Co-investigator	Shinya Nakamura (Assistant Professor, Tohoku University)
Co-investigator	Shinya Ohara (Assistant Professor, Tohoku University)
Co-investigator	Takayuki Hosokawa (Associate Professor, Kawasaki University of Medical Welfare)
Co-investigator	Yu Takagi (Post-doctoral fellows, The University of Tokyo)
Co-investigator	Takumi Tanaka (Researcher, The University of Tokyo)

Research Project A04: Alteration of brain dynamics as underlying mechanisms of hyper-adaptability in neurotransmitter disorders

Principal investigator	Kaoru Takakusaki (Professor, Asahikawa Medical University)
Funded co-investigator	Takashi Hanakawa (Professor, Graduate School of Medicine, Kyoto University)
Co-investigator	Tomohiro Noguchi (Lecturer, Asahikawa Medical University)
Co-investigator	Mirai Takahashi (Visiting Assistant Professor, Asahikawa Medical University)
Co-investigator	Syusei Hukuyama (Assistant Professor, Asahikawa Medical University)
Co-investigator	Toshikatsu Okumura (Professor, Asahikawa Medical University)
Co-investigator	Tsukasa Nozu (Professor, Asahikawa Medical University)
Co-investigator	Seiji Matsumoto (Professor, Asahikawa Medical University)
Co-investigator	Hitoshi Sasajima (Lecturer, Asahikawa Medical University)
Co-investigator	Sadaharu Miyazono (Lecturer, Asahikawa Medical University)
Co-investigator	Tatsuya Umeda (Associate Professor, Kyoto University)
Co-investigator	Yoshifumi Mori (Associate Professor, Kyoto University)
Co-investigator	Kenji Yoshinaga (Associate Professor, Kyoto University)
Co-investigator	Tatsuhiro Nakamura (Project Researcher, Kyoto University)
Co-investigator	Yuki Oi (Graduate Student, Kyoto University)
Co-investigator	Masakazu Hirose (Graduate Student, Kyoto University)
Co-investigator	Toshi Nakajima (Associate Professor, University of Toyama)
Co-investigator	Hiroki Togo (Postdoctoral fellow, NCNP)
Co-investigator	Toma Matsushima (Undergraduate Student, Tokyo University of Agriculture and Technology / Research Student, NCNP)

Research Project A05-1: A closed-loop brain stimulation for reinforcing hyper-adaptability

Principal investigator Yuichi Takeuchi (Associate Professor, Hokkaido University)

Co-investigator Michele Chan (Specially Appointed Assistant Professor, Hokkaido University)

Research Project A05-2: Comprehensive understanding of the mechanism of adaptive changes in brain, body consciousness and arm use underlying upper limb recovery in stroke patients

Principal investigator Shinichi Izumi (Professor, Tohoku University)

Co-investigator Shintaro Seki (Part-time Lecturer, Tohoku University)

Co-investigator Ryoji Otaki (Ph.D Student, Tohoku University)

Co-investigator Tamami Sudo (Researcher, Oouchi Hospital / Part-time Lecturer, Tohoku University)

Co-investigator Ryuko Ishimoda (Assistant Technical Staff, Tohoku University)

Co-investigator Naoki Aizu (Assistant Professor, Fujita Health University)

Co-investigator Juan Wu (Graduate Student, Tohoku University)

Co-investigator Kouta Ataka (Graduate Student, Tohoku University)

Research Project A05-3: Elucidation of neural circuits for optimal adaptation to the external environment

Principal investigator Rie Kimura (Specially Appointed Assistant Professor, The University of Tokyo)

Research Project A05-4: Neural substrate of unified learning theory for adaptive behavior

Principal investigator Akihiro Funamizu (Lecturer, The University of Tokyo)

Co-investigator Maria Ines de Sa Ribeiro (Research Technician, The University of Tokyo)

Research Project A05-5: Enhanced neuronal circuits for vocal learning with extensive experiences during development

Principal investigator Yoko Yazaki-Sugiyama (Associate Professor, The Okinawa Institute of Science and Technology Graduate University / Project Associate Professor, The University of Tokyo)

Research Project A05-7: Mechanism of Hyper-Adaptivity of the human premotor area: electrophysiological connectomes analysis with electrocorticogram

Principal investigator Riki Matsumoto (Professor, Kobe University)

Co-investigator Takashi Sasayama (Professor, Kobe University)

Co-investigator Yosuke Fujimoto (Assistant Professor, Kobe University)

Co-investigator Masaya Togo (Assistant Professor, Kobe University)

Co-investigator Kento Matoba (Assistant Professor, Kobe University)

Co-investigator Takayuki Kikuchi (Lecturer, Kyoto University)

Co-investigator Akihiro Shimotake (Assistant Professor, Kyoto University)

Co-investigator Kiyohide Usami (Assistant Professor, Kyoto University)
Co-investigator Hirofumi Takeyama (Visiting researcher, Kyoto University)
Co-investigator Masamune kimura (Graduate Student, Kobe University)
Co-investigator Kozue Hayashi (Graduate Student, Kyoto University)

Research Project A05-8: Interregional brain network dynamics enabling hyper-adaptation from a fear-memory induced maladaptive state.

Principal investigator Hiroyuki Miyawaki (Lecturer, Osaka Metropolitan University)

Research Project A05-9: Research on developing a cognitive rehabilitation method for neurological and psychiatric diseases thorough improving precision on the sense of agency

Principal investigator Takaki Maeda (Lecturer, Keio University)
Co-investigator Yuichi Yamashita (Section Chief, National Center of Neurology and Psychiatry)
Co-investigator Tsukasa Okimura (School of Medicine, Keio University)
Co-investigator Hiroki Oi (School of Medicine, Keio University)

Research Project A05-10: Adaptive mechanisms for perturbations in the neural manifold.

Principal investigator Tomohiko Takei (Associate Professor, Brain Science Institute, Tamagawa University)
Co-investigator Akihiro Masaoka (Adjunct Research Fellow, Tamagawa University)

Research Project A05-11: Spatio-temporal modulation of disinhibition for super-recovery from motor dysfunction in the chronic phase of stroke

Principal investigator Hironobu Osaki (Program-Specific Associate Professor, Doshisha University)
Co-investigator Yoshito Masamizu (Professor, Doshisha University)
Co-investigator Kaneyasu Nishimura (Associate professor, Doshisha University)
Co-investigator Kotaro Tezuka (Graduate student, Doshisha University)

Research Project A05-12: Hyper adaptive changes in spatial recognition

Principal investigator Rieko Osu (Professor, Waseda University)
Co-investigator Kento Hirayama (Ph.D Student(Assistant), Waseda University)
Co-investigator Yuki Ito (Master Student, Waseda University)
Co-investigator Taiki Yoshida (Assistant Professor, Fujita Health University)
Co-investigator David Franklin (Prof. Dr., Technical University of Munich)

Research Project A05-13: Creation of hyper-adaptability by synthetic synaptic organizers and micro-environmental control of neural reconstruction

Principal investigator Kosei Takeuchi (Professor, Aichi Medical University)
Co-investigator Hiroyuki Sasakura (Assistant Professor, Aichi Medical University)
Co-investigator Masashi Ikeno (Associate Professor, Aichi Medical University)
Co-investigator Satoko hattori (Associate Professor, Aichi Medical University)
Co-investigator Yuki Morioka (Research Technician, Aichi Medical University)

Research Project A05-14: Brain reorganization in stroke patients with hyper-recovery by measuring EEG modulation induced by static and dynamic magnetic fields.

Principal investigator Tatsuya Mima (Professor, Ritsumeikan University)
Co-investigator Sumiya Shibata (Professor, Niigata University of Health and Welfare)
Co-investigator Satoko Koganemaru (Program-specific Associate Professor, Kyoto University)

Research Project A05-15: Brain adaptation after limb loss

Principal investigator Atsushi Nambu (Professor, National Institute for Physiological Sciences)
Co-investigator Nobuhiko Hatanaka (Assistant professor, National Institute for Physiological Sciences)
Co-investigator Satomi Chiken (Assistant professor, National Institute for Physiological Sciences)
Co-investigator Pimpimon Nondhalee (Research fellow, National Institute for Physiological Sciences)

Research Project A05-16: Adaptive mechanism occurring in both hemispheres after unilateral brain damage.

Principal investigator Noriyuki Higo (Group Leader, National Institute of Advanced Industrial Science and Technology)
Co-investigator Toru Yamada (Senior Researcher, National Institute of Advanced Industrial Science and Technology)
Co-investigator Hiroshi Kawaguchi (Senior Researcher, National Institute of Advanced Industrial Science and Technology)

Research Project A05-17: Functional reorganization of motor and somatosensory cortices during recovery of motor functions after the loss of peripheral sensory inputs

Principal investigator Osamu Yokoyama (Senior Researcher, Tokyo Metropolitan Institute of Medical Science)

Research Project B01: Systems modelling of hyper-adaptation mechanism for reconstruction of neural

structure

Principal investigator Toshiyuki Kondo (Professor, Tokyo University of Agriculture and Technology)
Funded co-investigator Ryosuke Chiba (Associate Professor, Asahikawa Medical University)
Funded co-investigator Megumi Miyashita (Assistant Professor, Tokyo University of Agriculture and Technology)
Co-investigator Koji Ito (Emeritus Professor, Tokyo Institute of Technology)
Co-investigator Shiro Yano (Visiting Associate Professor, Tokyo University of Agriculture and Technology)
Co-investigator Tamami Sudo (Assistant Professor, Tokyo University of Agriculture and Technology)
Co-investigator Yoshikatsu Hayashi (Associate Professor, University of Reading)
Co-investigator Tetsunari Inamura (Associate Professor, Principles of Informatics Research Division, National Institute of Informatics)
Co-investigator Fuminari Kaneko (Project Associate Professor, School of Medicine, Keio University)

Research Project B02: Modeling of ultra-adaptive to body change

Principal investigator Yasuharu Koike (Professor, Tokyo Institute of Technology)
Funded co-investigator TetsuroFunato (Associate Professor, The University of Electro Communications)
Co-investigator Natsue Yoshimura (Associate Professor, Tokyo Institute of Technology)
Co-investigator Victor Baradas (Project Assistant Professor, Tokyo Institute of Technology)
Co-investigator Dai Yanagihara (Professor, The University of Tokyo)
Co-investigator Shinya Aoi (Professor, Osaka University)
Co-investigator Kazuo Tsuchiya (Emeritus Professor, Kyoto University)
Co-investigator Hiroyuki Kanbara(Associate Professor, Tokyo Polytechnic University)
Co-investigator Soichiro Fujiki (Assistant Professor, Dokkyo Medical University)
Co-investigator Wang Sentong (Assistant Professor, Faculty of Science and Technology, Seikei University)
Co-investigator Akira Konosu (Project Researcher, The University of Electro-Communications)

Research Project B03: Systematic understanding and realization of hyper-adaptive phenomena focusing on cognition and emotion

Principal investigator Hajime Asama (Professor, The University of Tokyo)
Funded co-investigator Jun Izawa (Associate Professor, University of Tsukuba)
Funded co-investigator Qi An (Associate Professor, The University of Tokyo)
Funded co-investigator Wen Wen (Associate Professor, Rikkyo University)
Co-investigator Masafumi Yano (Professor Emeritus, Tohoku University)

Co-investigator Atsushi Yamashita (Professor, Graduate School of Frontier Sciences, The University of Tokyo)

Co-investigator Hiroyuki Hamada (Project Assistant Professor, The University of Tokyo)

Co-investigator Acer Chang (Assistant Professor, Rikkyo University)

Co-investigator Yukio Honda (Project Researcher, The University of Tokyo)

Co-investigator Ningjia Yang (Researcher, RIKEN)

Co-investigator Yutaka Kikuchi (Department Chief, Institute of Brain and Blood Vessels Mihara Memorial Hospital)

Co-investigator Yuta Okuda (Institute of Brain and Blood Vessels Mihara Memorial Hospital)

Co-investigator Dal'Bello Lucas (Researcher, Laboratory of Neuromotor Physiology, Fondazione Santa Lucia)

Research Project B04: Modelling of hyper adaptability in human postural control considering the role of neurotransmitters

Principal investigator Jun Ota (Professor, The University of Tokyo)

Funded co-investigator Arito Yozu (Associate Professor, The University of Tokyo)

Co-investigator Shohei Shirafuji (Assistant Professor, The University of Tokyo)

Co-investigator Kohei Kaminishi (Postdoctoral Fellow, The University of Tokyo)

Co-investigator Enrico Piovanelli (Postdoctoral Fellow, The University of Tokyo)

Co-investigator Ryota Takamido (Postdoctoral Fellow, The University of Tokyo)

Co-investigator Tetsuya Hasegawa (Postdoctoral Fellow, The University of Tokyo)

Co-investigator Yutaka Kohno (Professor, Ibaraki Prefectural University of Health Sciences)

Co-investigator Daisuke Ishii (Assistant Professor, Ibaraki Prefectural University of Health Sciences)

Co-investigator Hiroshi Kishimoto (Lecturer, Ibaraki Prefectural University of Health Sciences)

Co-investigator Hiroshi Yuine (Assistant Professor, Ibaraki Prefectural University of Health Sciences)

Co-investigator Kiyoshige Ishibashi (Ibaraki Prefectural University of Health Sciences)

Co-investigator Hiroyuki Hamada (Assistant, Bunkyo Gakuin University)

Co-investigator Mariko Miyata (Professor, Tokyo Women's Medical University)

Co-investigator Moeko Kanaya (Assistant Professor, Tokyo Women's Medical University)

Co-investigator Hironobu Osaki (Program-Specific Associate Professor, Doshisha University)

Co-investigator Michihiro Kawano (Professor, Saku University)

Co-investigator Yoshihide Kanai, (Lecturer, Saitama Medical University)

Co-investigator Yuichiro Omura (Ph.D Student, The University of Tokyo)

Co-investigator Hitohiro Etoh (Master Student, The University of Tokyo)

Co-investigator Xiyu Hou (Master Student, The University of Tokyo)

Co-investigator Kota Sonoda (Master Student, The University of Tokyo)
Co-investigator Yuhei Fujiwara (Graduate Student, The University of Tokyo)
Co-investigator Huang Rui (Graduate Student, The University of Tokyo)
Co-investigator Huyutake Makino (Master Student, The University of Tokyo)
Co-investigator Naoki Orihara (Undergraduate Student, The University of Tokyo)
Co-investigator Ritsuki Nishizawa (Undergraduate Student, The University of Tokyo)
Co-investigator Moichi Ishikawa (Undergraduate Student, The University of Tokyo)

Research Project B05-1: Motor learning of modularity in musculoskeletal models toward the emergence of muscle synergy

Principal investigator Mitsuhiro Hayashibe (Professor, Tohoku University)
Co-investigator Kyo Kutsuzawa (Assistant Professor, Tohoku University)
Co-investigator Ahmed Hannan (Ph.D Student, Tohoku University)
Co-investigator Li Guanda (Ph.D Student, Tohoku University)
Co-investigator Akito Fukunishi (Master Student, Tohoku University)
Co-investigator Taku Sugiyama (Master Student, Tohoku University)

Research Project B05-2: A neural network model for hyper-adaptability of bipedal locomotion

Principal investigator Naomichi Ogihara (Professor, The University of Tokyo)

Research Project B05-3: Hyper-adaptation of bodily and neural sensorimotor information structures in early developmental stage

Principal investigator Hoshinori Kanazawa (Research Assistant Professor, The University of Tokyo)
Co-investigator Yasuo Kuniyoshi (Professor, The University of Tokyo)
Co-investigator Masahiko Kawai (Project Associate Professor, Kyoto University)
Co-investigator Dongmin Kim (Graduate Student, The University of Tokyo)
Co-investigator Yohei Nomoto (Graduate Student, The University of Tokyo)
Co-investigator Akito Yoshida (Graduate Student, The University of Tokyo)
Co-investigator Yamato Shinomiya (Graduate Student, The University of Tokyo)

Research Project B05-4: Low-dimensional functional connectivity across bilateral motor-related areas for hyper-adaptability

Principal investigator Isao Nambu (Associate Professor, Nagaoka University of Technology)
Co-investigator Yasuhiro Wada (Professor, Nagaoka University of Technology)
Co-investigator Hiroshi Yokoyama (Project Assistant Professor, NIPS)

Research Project B05-5: Application of motor learning model for partial relationship reuse to reconstruction of muscle synergy

Principal investigator Yuichi Kobayashi (Associate Professor, Shizuoka University)
Co-investigator Sota Nakamura (Graduate student, Grauate school of Science and Technology, Shizuoka University)
Co-investigator Taisei Matsuura (Graduate student, Grauate school of Science and Technology, Shizuoka University)
Co-investigator Haruki Mamiya (Undergraduate Student, Grauate school of Science and Technology, Shizuoka University)
Co-investigator Izumi Wada (Undergraduate Student, Department of Mechanical Engineering, Faculty of Engineering, Shizuoka University)

Research Project B05-6: Hierarchical understanding of adaptation to a new relationship between the eye and the body.

Principal investigator Michiteru Kitazaki (Professor, Department of Computer Science and Engineering, Toyohashi University of Technology)

Research Project B05-7: Supraspinal mechanisms of the human upright postural control based on the EEG dynamics associated with micro-falls

Principal investigator Taishin Nomura (Professor, Osaka University)
Co-investigator Akihiro Nakamura (Graduate School of Engineering Science, Osaka University / Research Fellow, JSPS)
Co-investigator Yasuyuki Suzuki (Lecturer, Graduate School of Engineering Science, Osaka University)
Co-investigator Matija Milosevic (Assistant Professor, Graduate School of Engineering Science, Osaka University)
Co-investigator Kimitaka Nakazawa (Professor, The University of Tokyo)
Co-investigator Saburo Sakoda (Honorary Director, National Hospital Organization Osaka Toneyama Medical Center)
Co-investigator Takuyuki Endo (Doctor, National Hospital Organization Osaka Toneyama Medical Center)

Research Project B05-8: Higher brain functions as hyper-adaptability: an exploration of the principle of proactive outreach to an indefinite environment

Principal investigator Kazuhiro Sakamoto (Associate Professor, Faculty of Medicine, Tohoku Medical and Pharmaceutical University)
Co-investigator Yoshiya Matsuzaka (Professor, Faculty of Medicine, Tohoku Medical and Pharmaceutical University)
Co-investigator Hajime Mushiake (Professor, School of Medicine, Tohoku University)

Co-investigator Tadaho Nakamura (Associate Professor, Faculty of Medicine, Tohoku Medical and Pharmaceutical University)

Co-investigator Makoto Osanai (Professor, Graduate School of Medicine, Osaka University)

Co-investigator Satoshi Zuguchi (PH.D Student, School of Medicine, Tohoku University)

Research Project B05-9: Individual differences in suitable neural circuits for attention control and its effect on motor control.

Principal investigator Takeshi Sakurada (Associate Professor, Faculty of Science and Technology, Seikei University)

Co-investigator Shunsuke Taguchi (Undergraduate student, Faculty of Science and Technology, Seikei University)

Co-investigator Daisuke Nakajima (Undergraduate student, Faculty of Science and Technology, Seikei University)

Co-investigator Yuri Hayashi (Undergraduate student, Faculty of Science and Technology, Seikei University)

Research Project B05-10: Brain mechanisms for generating exploratory adaptation: Modeling the brain function based on meta-reinforcement learning

Principal investigator Yuki Ueyama (Associate Professor, National Defense Academy of Japan)

Co-investigator Hiroshi Imamizu (Professor, University of Tsukuba)

Co-investigator Jun Izawa (Associate Professor, University of Tsukuba)