2022 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 A05-9

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)

Annual report of research project B03

Principal investigator, Hajime ASAMA (Professor, The University of Tokyo)

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

- 4th plenary conference
Date: July 19, 2022 9:00-18:00
July 20, 2022 9:00-15:45
Place: Hagi-Hall, Tohoku University
Contents: The 4th Plenary Meeting of the Hyper-adaptability Area was held as the first meeting after the addition of researchers in the second phase of the A05 group. For the purpose of mutual understanding and for future collaboration, all the principal investigators and funded co-investigators gave oral presentation about their research. In addition, poster session was held in conjunction with the meeting. There were 100 registrants and 47 posters were presented. This was the first on-site meeting after the kick-off symposium, and both the oral presentations and the poster session were very heated.

- 9th management meeting
Date: July 20, 2022 12:10-13:10
Place: Hagi-Hall, Tohoku University
Contents: members of the management group discussed about the operation method, symposiums, etc.

- The 2nd open symposium
Date: Oct 16, 2022 9:00-14:40
Place: Osaka International Convention Center
Contents: The "Hyper-adaptability" open symposium was held as a co-sponsored symposium at the 20th Annual Meeting of the Japan Society of Physical Therapy. Following a special

lecture by A01 Isa on " Hyper-adaptability in the process of functional recovery after brain and spinal cord injury," A02 Seki, B02 Funato, A04 Takakusaki, and B01 Chiba presented the latest research results in the morning symposium on "Muscle Synergy and Gait" and A03 Imamizu, B03 Izawa, and A03 Tsutsui in the afternoon symposium on "Motor Learning and Functional Recovery. The latest research results were explained in an easy-to-understand manner to the audience, which consisted mainly of therapists. Of the 2,360 on-site participants at the conference, more than half attended the " Hyper-adaptability" symposium. In the symposium, there were many questions from the audience. In the general discussion, researchers and therapists had a heated debate on how the findings of fundamental research should be applied to rehabilitation.

- 10th management meeting
Date: Oct 16, 2022 15:00-16:00
Place: Osaka International Convention Center
Contents: members of the management group discussed about the operation method, management of symposium, etc.

- 5th plenary conference
Date: March 3th - 4th, 2023
Place: Takeda Hall, The University of Tokyo.
Contents: summary of the researches in the year was presented by project representative and researchers in the project.

- 11th management meeting
Date: March 8th, 2022. 12:20-13:20
Place: Hongo Campus, The University of Tokyo
Contents: members of the management group discussed about the operation method, management of symposium in the next year, etc.

B. Journal Special Issue / Organized Session

- Journal Special Issue: Journal of Robotics and Mechatronics
Special Issue on “Special Issue on Systems Science of Hyper-Adaptability” was organized in Journal of Robotics and Mechatronics, Vol. 34, no. 4. 14 papers were published.

- Journal Special Issue: Journal of The Society of Instrument and Control Engineers
Special Issue on “System Theoretical Approaches to Understanding Hyper-Adaptability in the Human Body and Brain” was organized in Journal of The Society of Instrument and Control Engineers, Vol. 61, no. 4. 9 papers were published.

- OS: RSJ2022 (40th Annual Conference of the Robotics Society of Japan)
Date: September 6th and 9th, 2022
Contents: Nine researches presented at a symposium on “Hyper-adaptability” on Sep. 6th. Open forum “Hyper-adaptability in Rehabilitation Prompted by Robotics” composed with four lectures and panel discussion was held on Sep. 9th.

- OS: MHS 2022 (33rd International Symposium on Micro-NanoMechatronics and Human Science)
Date: November 28th, 2022
Contents: eight researches including two keynote talks were presented at a symposium on “Hyper-adaptability”. Moreover, B05-2 Ogihara presented his researches as a plenary lecture.

- OS: Next Generation Brain Project, Winter symposium
Date: December 14th, 2022
Contents: An organized symposium with Seven researches and panel discussion were held.

- OS: 35th SICE Symposium on Decentralized Autonomous Systems.
Date: January 22nd-23id, 2023
Contents: 14 researches were presented at a symposium on “Hyper-adaptability”.

- OS: The 100th Annual Meeting of the Physiological Society of Japan
Date: March 15th, 2023
Contents: Symposium of “Surprise-induced brain hyper-adaptability” is organized.

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. Study Session

In this year, three study sessions were held from Sep. to Oct. 2022 to deepen the understanding of network analysis, a method used by many researchers in this research area, and young researchers (Isao Nambu (Nagaoka University of Technology), Reona Yamaguchi (Kyoto University), Kenji Yoshinaga (Kyoto University), Megumi Miyashita (Tokyo University of Agriculture and Technology) and Jihoon Park (NICT) provided explanations and discussions. The materials and videos of the workshop are available on the website and Slack, and we are striving to expand the common knowledge.

B. Data Sharing withing research field

To promote joint research between Group A, which handles biological data obtained from humans and experimental animals, and Group B, which takes a systems science-based approach, this year we established a framework for sharing cortical EEG, electromyography, and movement data recorded by a monkey model of spinal cord injury within the field.

V. Future Perspective

We plan to conduct the following activities of the next fiscal year:
- 2nd international symposium on October, 2023
- fiscal year-end plenary conference on March, 2024.

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 (Neurosciences) 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 the researches 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. In the nonhuman primate studies, Isa and colleagues clarified the changes in excitatory and inhibitory connectives associated with disinhibition after spinal cord injury. Naito and colleagues investigated hyper-adaptation in the brain of a wheelchair race-top Paralympians. Aizawa and colleagues tested cellular mechanism underlying the interhemispheric inhibition in mice.

Group A02 (Seki) aimed to investigate the mode of adaptation of neural function to rapid musculoskeletal structural modification from the viewpoint of reconstructing the biological structure of hyper-adaptation and to elucidate the principles behind this process. This year, based on the analysis of the tendon replacement model of the extensor digitorum and flexor digitorum superficialis, we confirmed that the adaptation mechanism to the body modification consists of two stages. Among them, it was shown that the improvement of motor function after the initial adaptation is brought about by the temporary replacement of muscle synergy, while the subsequent recovery may be attributed to other factors.

Group A03 (Imamizu and Tsutusi) conducted manipulative studies to uncover mechanisms by which a sense of agency and emotion facilitate motor learning. In human experiments, fMRI brain activity was measured to investigate how parameters of brain stimulation cause changes in activity. We conducted psychological experiments and showed that synchrony between action and consequence plays a key role in the sense of agency in a novel learning task. In monkey experiments, we studied the different roles of prefrontal subregions in the generation and modulation of motivation, by TMS neural interventions. We have established a system to study sense of agency in monkeys in collaboration with an external research group.

Group A04 (Takakusaki, Hanakawa) investigated the role of dopamine (DA) in the alteration of the brain network dynamics associated with posture-gait control (animal experimentation) and the higher-order executive function (human experiments). Takakusaki and colleagues revealed that the midbrain DA neurons contributed to the regulation of postural muscle tone by acting on the pedunculopontine tegmental nucleus (PPN) neurons, possibly via the reticulospinal pathways. Hanakawa and colleagues succeeded in explaining a synthetic MRI contrast using multiple histological contrasts, including tyrosine hydroxylase (TH) staining.

In addition, 16 members (below) joined as the A05 group, who were selected through the applications.

Yuichi Takeuchi "A closed-loop brain stimulation for reinforcing hyper-adaptability" A technology with discriminative cross-spectral factor analysis (a machine learning technology focusing on oscillatory brain activities) has been developed to decode seizure susceptibility from large-scale electrophysiological recordings of cerebral activities during the interictal period of a rat model of epilepsy. It was successful in five out of six cases.

Shinichi Izumi "Comprehensive understanding of the mechanisms of adaptive changes in brain, body consciousness and arm use underlying upper limb recovery in stroke patients" conducted a longitudinal study using fMRI and DTI to elucidate the relationship between arm use and brain function and structure underlying upper limb recovery after stroke. As a result, they found that different brain regions and neural pathways were associated with arm use and functional recovery.

Rie Kimura "Elucidation of neural circuits for optimal adaptation to the external environment." We aim to understand the neural basis of optimal adaptation to the external environment by examining the visual responses in multidimensional brain systems. This year, we observed behavioral-level adaptations to a variety of visual stimuli.

Akihiro Funamizu "Neural substrate of unified learning theory for adaptive behavior" We hypothesize that multiple-behavioral strategies are driven by a unique learning algorithm in the brain. To understand the algorithm, we used head-fixed mice and performed a behavioral task which required multiple strategies. We also developed a setup for recording the neural activity of mice during the task.

Riki Matsumoto "Mechanism of Hyper-Adaptability of the human premotor area: electrophysiological connectomes analysis with electrocorticogram" In the Go/No-Go task, task performance was more impaired upon high frequency electrical cortical stimulation (HFECS), when more CCEP responses were observed within the task-activated cortical region. This suggests HFECS exerts its effect at the network-level via electrophysiological connections.

Yoko Yazaki-Sugiyama "Enhanced neuronal circuits for vocal learning with extensive experiences during development" Zebra finches learn to sing by listening and memorizing, then mimicking a tutor's song (TS) during development. We found the transient axonal projections from the neuronal TS ensembles in higher auditory forebrain, NCM into song motor control site, HVC. Enriched learning experiences retained NCM connectivity to HVC into adulthood.

Hiroyuki Miyawaki, "Regulatory mechanisms of inter-regional network changes underlying hyper-adaptation from mal-adaptation state caused by fear memory." investigated local and inter-regional network dynamics that support extinction learning of learned fear by using multi-regional large-scale electrophysiological recordings on freely moving rodents. The study revealed that activities of extinction-related neuronal ensembles were enhanced prior to extinction learning.

Takaki Maeda advanced clinical studies of cognitive rehabilitation for mental illnesses including schizophrenia, ASD, ADHD and eating disorders in order to tune up precision of SoA. We tried to show whether this rehabilitation method could improve spatial SoA in addition to temporal SoA.

Tomohiko Takei "Adaptive mechanisms for perturbations in the neural manifold" We recorded and analyzed frontal-parietal cortical activity in a monkey performing a context-dependent feedback motor task and showed that the orthogonalization of neural dimensions during the preparation and response periods, suggesting a flexible preparation of motor responses.

Hironobu Osaki, "Spatio-temporal modulation of disinhibition for super-recovery from motor dysfunction in the chronic phase of stroke" Group A05-11 (Osaki) aims to develop a method of neural modulation to enhance functional recovery from cortical infarction. To quantitatively monitor the functional recovery of mice's behavior, we developed a behavioral monitoring system that can also record and modulate neural activity.

Rieko Osu "Hyper adaptive changes in spatial recognition Using Augmented reality (AR)" We constructed a system to present all spaces in the right space that are not ignored in patients with hemispatial neglect. We also designed a task to test the characteristics of attention in patients with hemispatial neglect.

Kosei Takeuchi "Creation of hyper-adaptability by synthetic organizers and micro-environmental control of neural reconstruction" aimed to induce hyper-adaptation and recovery by combining the synthetic synapse connector in the process of recovery from brain and spinal cord injury. We show that maintaining inhibitory-synapses to prevent disinhibition delays recovery by the newly created inhibitory-synapse connector.

Tatsuya Mima "Brain reorganization in stroke patients with hyper-recovery by measuring EEG modulation induced by static and dynamic magnetic fields." As an example of hyperadaptation, we plan to elucidate brain reorganization in hyper-recovered stroke survivors using EEG modulation induced by brain stimulation. In FY2022, we established an experimental environment that enables stable measurement of TMS-EEG, and completed the study in healthy volunteers."

Atsushi Nambu "Brain adaptation after limb loss" examined plastic changes in the primary motor cortex (M1) using a Japanese monkey who accidentally lost its forelimb. The M1 region corresponding to the lost forelimb shrunk while the whole forelimb region remained intact.

Noriyuki Higo "Adaptive mechanism occurring in both hemispheres after unilateral brain damage" VBM and histochemical analyses were performed in macaques with focal infarcts in the unilateral internal capsule. During the period of motor recovery, gray matter volume and dendritic arborization of pyramidal cells were increased in the ventral premotor cortex of the hemisphere contralateral to the infarcts.

Osamu Yokoyama "Functional reorganization of motor and somatosensory cortices during recovery of motor functions after the loss of peripheral sensory inputs" Transecting the dorsal rootlets of the monkey cervical cord caused impairments of, in addition to somatosensory function, motor function in the upper limb, which recovered in about 2 weeks. High-gamma activity in the primary motor and somatosensory cortex during movement execution increased immediately after injury and decreased with functional recovery.

III. ACTIVITIES

From October 31, 2022, the data obtained in the A01 Group are shared by the whole "Hyper-adaptation" research groups including Group B to facilitate the collaborative researches foe development of mathematical models and examination of connectivity analysis.

IV. FUTURE PLAN

Group A should further facilitate discussion among the A01-05 groups and summarize the "Hyper-adaptation" –related phenomenon observed across the electrophysiological and molecular levels and promote the collaboration with 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 changes in excitatory and inhibitory connectives associated with disinhibition after spinal cord injury, hyper-adaptation in the brain of a wheelchair race-top Paralympians 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, and that the diffuse projection systems such as monoaminergic neurons would be involved in the process. 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 across the large-scaled brain network in the macaque model of recovery from the spinal cord injury or lesion of the primary visual cortex. 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-Asada 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. Global disinhibition after partial spinal cord injury in monkeys (Isa)

In our previous experiment, we investigated the recovery process of motor function after sub-hemisection at the C4/C5 segment in macaque monkeys. We found that monkeys experienced severe paralysis in the affected forelimb soon after the sub-hemisection, however, through intensive training and electrical stimulation to motor related areas, the reaching and grasping movements considerably recovered. We also tested the interhemispheric interaction from ipsilesional premotor cortex (PM) to contralesional primary cortex (M1) by a conditioning paradigm. We found that the effect of conditioning stimulus was inhibitory before the lesion as has been reported in human studies, however, the effect was switched to facilitation during the earlier stage of recovery. 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 sever impairment. Granger causality can assess the directionality of the connectivity between each brain area, but the polarity of the connectivity among brain regions associated with excitation-inhibition balance is still unclear. In this year, we investigated 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, LiNGAM (linear non-Gaussian acyclic model). We applied LiNGAM to brain activity at each frequency band before and after spinal cord injury. In this analysis, we focused on pathway from ipsilesional PM to contralesional M1 which showed remarkable disinhibition by a conditioning paradigm after the lesion. As for the excitatory connectivity, there were no significant difference in early and late phases of recovery compared with preoperative stage. However, intensity of inhibitory connectivity significantly decreased in in early and late phases of recovery. These results indicated that reduction of inhibitory connectivity induce disinhibition associated with motor recovery from spinal cord injury.

[1] Sawamura M, Onoe H, Tsukada H, Uemura N, Isa K, Isa T, Takahashi R. “α-synuclein propagation via olfactory pathway induces olfactory bulb atrophy and widespread glucose hypometabolism in a non-human primate model. (P1-1.Virtual),” Neurology, 98 (18 Supplement) 2422. 2022.

[2] Tsujihana K, Tanegashima K, Santo Y, Yamada H, Akazawa S, Nakao R, Tominaga K, Saito R, Nishito Y, Hata RI, Nakamura T, Murai I, Kono Y,

Sugawa M, Tanioka M, Egawa G, Doi M, Isa T, Kabashima K, Hara T, Okamura H. “Circadian protection against bacterial skin infection by epidermal CXCL14-mediated innate immunity,” Proc. Natl. Acad. Sci. U. S. A., 119 (25):e2116027119. doi: 10.1073/pnas.2116027119. 2022.
[3] Yamauchi K, Okamoto S, Ishida Y, Konno K, Hoshino K, Furuta T, Takahashi M, Koike M, Isa K, Watanabe M, Isa T, Hioki H. “Fluorochromized tyramide-glucose oxidase as a multiplex fluorescent tyramide signal amplification system for histochemical analysis,” Sci. Rep., 12 (1):14807. doi: 10.1038/s41598-022-19085-9. 2022.
[4] Isa T, Tohyama T, Kinoshita M. “Phylogenetic view of the compensatory mechanisms in motor and sensory systems after neuronal injury,” Curr. Res. Neurobiol., 3:100058. doi: 10.1016/j.crneur.2022.100058. 2022.
[5] Umeda T, Isa T, Nishimura Y. “Temporal dynamics of the sensorimotor convergence underlying voluntary limb movement,” Proc. Natl. Acad. Sci. U. S. A., 119 (48):e2208353119. doi: 10.1073/pnas.2208353119. 2022.
[6] Janssen P, Isa T, Lanciego J, Leech K, Logothetis N, Poo MM, Mitchell AS. “Visualizing advances in the future of primate neuroscience research,” Curr. Res. Neurobiol., 4:100064. doi: 10.1016/j.crneur.2022.100064. 2022
[7] Takakuwa N, Isa K, Yamaguchi R, Onoe H, Takahashi J, Yoshida M, Isa T. “Protocol for making an animal model of "blindsight" in macaque monkeys,” STAR Protoc. 4 (1):101960. doi: 10.1016/j.xpro.2022.101960. 2022.

B. *Elucidation of hyper-adaptation in the brain of a wheelchair race-top Paralympians and verification of differences between younger and older adults in the disinhibition patterns of ipsilateral sensorimotor regions during complex hand movements (Naito, Asada, Nakano)*

In collaboration with Asada group (Osaka Univ), Naito group (NICT, CiNet) has used functional MRI to elucidate hyper-adaptation phenomena observed in the brain of a wheelchair racing top Paralympian. The foot section of the motor cortex (M1) is normally inhibited during hand movements, but in this athlete, the foot section was activated during hand movements (Morita et al. Front Syst Neurosci 2022). In addition, hand proprioceptive information processing was enhanced in this athlete, and the action inhibition network functioned in a characteristic manner to prevent occurrence of actual movement during passive hand movements (Morita t al. Brain Science 2022). Furthermore, the transcallosal fibers between the left and right M1 were well developed, and the bilateral motor cortices were active even during right hand movements, suggesting that the motor control of the right hand was in a bilateral control mode in this athlete. With regard to complex hand movements, in collaboration with Nakano group (Kyoto Tachibana Univ), we found, unlike younger adults, involuntary electromyograms from the resting left hand during right hand finger complex movements in older adults. During complex hand movements, we found activations in the ipsilateral sensorimotor cortices in younger adults. But among these cortices, the dorsal premotor cortex (PMd) consistently increased functional coupling with multiple contralateral sensorimotor areas, and the PMd was more strongly recruited in individuals with less dexterous performance. The ipsilateral M1 remained inhibited during complex as well as simple hand movements in younger adults, whereas this inhibition disappeared during complex movements in older adults, suggesting that this may be closely related to the appearance of involuntary muscle activity in their left relaxed hand.

[8] Morita T, Hirose S, Kimura N, Takemura H, Asada M, Naito E. Hyper-Adaptation in the Human Brain: Functional and Structural Changes in the Foot Section of the Primary Motor Cortex in a Top Wheelchair Racing Paralympian. Front Syst Neurosci. 16:780652. doi: 10.3389/fnsys.2022.780652. 2022
[9] Morita T, Naito E. Facilitation of Hand Proprioceptive Processing in Paraplegic Individuals with Long-Term Wheelchair Sports Training. Brain Sci. 12(10):1295. doi: 10.3390/brainsci12101295. 2022

C. *Analysis of the cellular mechanism underlying the interhemispheric inhibition and adaptive behaviors using mice (Aizawa)*

Aizawa group analyzed murine neural activity with optogenetics in the cerebral cortex to address a cellular mechanism underlying the interhemispheric inhibition which was altered in the monkey and human with hyper-adaptation as revealed by Isa and Naito-Asada-Nakano groups. Topical cortical application of $GABA_A$ receptor agonist increased transiently firing rate in a significant proportion of the presumptive fast spiking neurons in the contralateral primary motor cortex. Those neurons were also activated by cholinergic antagonist, suggesting a role of acetylcholine system in modulation of interhemispheric inhibition. On the other hand, the group examined mouse model of local cerebral infarction and sepsis in which the interplay between hemispheres were reported to be altered. Mice gradually developed reduction of inhibitory effect of the callosal inputs from contralesional side in association with lateralization of forelimb use after local cortical infarction. Mice after sepsis exhibited long-lasting behavioral impairments (Kikutani et al., Shock, 2023).

[10] Kikutani K, Hosokawa K, Giga H, Ota K, Matsumata M, Zhu M, Takemoto H, Ji B, Ohshimo S, Shime N, Aizawa H. “GENETIC DELETION OF TRANSLOCATOR PROTEIN EXACERBATES POST-SEPSIS SYNDROME WITH ACTIVATION OF THE C1Q PATHWAY IN SEPTIC MOUSE MODEL,” Shock., 59 (1):82-90. doi: 10.1097/SHK.0000000000002030. 2023.

IV. Future Perspective

In the next fiscal year, Isa group will summarize the mechanism od disinhibition associated with functional recovery and publish those papers. In addition, we will clarify the molecular system for the disinhibition collaborating with Aizawa group.

Naito-Asada-Nakano group will publish several papers on the results of our work to date. Based on the results, we will construct computational model that can explain the principles of facilitation and inhibition between bilateral motor cortices and propose a new rehabilitation method using these principles, and verify the effectiveness of the method. Aizawa group will identify specific cell type responsible for interhemispheric inhibition and propose a novel method to modulate the interhemispheric inhibition via manipulation of cholinergic system using mouse model.

A02 Annual report of research project

Kazuhiko SEKI
National Institute of Neuroscience, NCNP

Abstract—**In the FY2022, the aim of our research group was to 1) confirm the previous result about the EMG changes to tendon-transfer surgery, 2) visualize the functionality of muscle and tendon after the surgery, and 3) to evaluate the sensory prediction error by measuring the extent of sensory gating during movement.**

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 this fiscal year, we are preparing the paper about the research results on the muscle relocation surgery obtained up to the last fiscal year. Right now, we are about to finish the final draft. In addition, research results on muscle synergy analysis during rehabilitation trials for stroke patients have been published in a paper (Ref. 1). Other progress was made in 1) the follow-up experiments to confirm changes in muscle synergy after repositioning surgery, 2) research to visualize tendon gliding and repositioned muscle function before and after surgery using ultrasound measurements, and 3) the development of a method to quantify sensory prediction errors in the cortex after tendon transfer surgery. Below, we report the results of our research item by item.

1) Adaptation of muscle activities after the tendon-transfer surgery (confirmation in the third monkey)

As a treatment to regain lost muscle function, tendons of an injured muscle may be replaced with tendons of another healthy muscle, and this is called a tendon transfer. Sometime after tendon transfer, the patient becomes able to move the replaced muscle freely and adaptive changes are expected to occur in the nervous system during this process, but the adaptive mechanisms remain unexplained.

In this study, in order to clarify the adaptation process after tendon transfer, we replaced EDC and FDS tendons in the macaque monkey and measured the task before and after replacing for about 8 months. By using this data and analyzing the changes in EMG and muscle synergy after the replacement, we investigated what kind of adaptation process is manifested in the nervous system.

Macaque monkeys were trained to perform a precision grasping task, and EMG was measured by inserting wire electrodes directly into the muscles. A comparison of EDC and FDS muscle activity before and after tendon transfer revealed that while EDC showed a tendency for the activity to change after tendon transfer and then return to the same as before, FDS showed no change in activity pattern or peak timing at any period after tendon transfer.

Moreover, to investigate the nature of the changes in the coordinated activity of muscle groups due to tendon transfer, We performed muscle synergy analysis using non-negative matrix factorization on the EMG data sets of all 14 muscles measured and extracted two synergies: extensor synergy consisting of EDC and its cooperating muscles, and flexor synergy consisting of FDS and its cooperating muscles. Observing changes in the spatial and temporal patterns of these synergies, we find that regarding the spatial pattern, while there was no major change in the composition of synergy, there was a long-term change in the projection ratio to each muscle, regarding the temporal pattern, changes similar to the activity of EDC and FDS were shown.

These results suggest that the changes in muscle activity in EDC and FDS occurred at a synergistic level and that these synergies were integrated through long-term adaptation after tendon transfer.

2) Development of technology for image visualization of gliding and function of the transferred muscles and tendons.

Various tendon transfer techniques have been used to treat nerve palsy and traumatic myotendinous defects, but the mechanisms of the nervous system in postoperative functional conversion remain unclear. We have been studying the adaptive function of the nervous system after tendon transfer using an electrophysiological macaque forearm tendon transfer model. We developed a method to evaluate transition tendon sliding using direct muscle stimulation.

Cross-tendon transfer of the flexor digitorum superficialis (FDS) and extensor digitorum commonus (EDC) of the macaque forearm was performed; the proximal FDS transection was transferred directly to the EDC and the proximal EDC transection was sutured to the distal FDS transection via a plantar tendon harvested from the lower extremity as a graft tendon, After 1-week cast immobilization plus upper extremity trunk immobilization, postoperative evaluation of migration of the transition tendon by muscle stimulation was performed at 1, 3, 5, 9, 15 and 19 weeks. The target muscle was stimulated with a stimulator (DS8R, Digitimer), the intramuscular tendon was identified by ultrasound image B-mode, the M-mode wave derived from the tendon was extracted, and the amplitude, duration, and area of the waveform were measured. The movement of the index and middle finger during muscle stimulation was captured by two cameras, and the three-dimensional coordinates were reconstructed and quantified by the DLT method.

Results indicated that the M-mode waveform increased with stimulation intensity, and the area of the M-mode waveform during 50 mA stimulation was almost constant over time, indicating that constant muscle contraction was obtained with direct muscle stimulation. Finger movements showed IP joint flexion with EDC stimulation and MP joint extension with FDS stimulation, confirming the continuity of the transition tendon until the final evaluation.

When studying changes in the nervous system induced by tendon transfer, it is necessary to demonstrate objectively that the effect of tendon transfer is sustained. The method developed in this study was able to objectively demonstrate the continuity and sliding state of tendons by quantifying finger movements under constant muscle contraction induced by external stimuli.

3) Extraction of sensory prediction errors represented at the central nervous system in monkeys performing voluntary movements.

Our sensory systems respond not only to external sensory information but also to self-generated information caused by our movement. For example, we feel less when we move. This phenomenon is known as sensory attenuation. Although the sensory attenuation of cutaneous afferent input to the CNS is well documented, that of a proprioceptive afferent signal is not. Furthermore, it is unclear if the comparable modulation of afferent sensory input could also be triggered by the non-overt motor events, e.g., action observation. To address these questions, we recorded somatosensory-evoked potentials (SEPs) from Brodman's area 3a (BA3a) by applying electrical stimuli to a cuff electrode implanted in the deep radial nerve (DR: muscle afferent of wrist extensor) (DR-SEPs) and that from BA3b from the superficial radial nerve(SR: cutaneous afferent from wrist dorsum)(SR-SEPs) while monkeys performed reaching and grasping movements (self-movement: SM) (n=2), or observed a person sitting in front of the monkeys and performing the same task (action observation: AO)(n=1).

During SM, we found that the size of DR-SEPs ($p < 0.01$), not only the SR-SEP ($p < 0.01$), was significantly suppressed in the movement phase compared to the pre-movement control period (inter-trial interval; t-test). Therefore, we conclude that the cortical SEPs evoked by muscle and cutaneous afferents show sensory attenuation during movement execution. Interestingly, we also found two contrasting results between DR- and SR-SEP's modulation during the SM and AO tasks. First, while the onset of DR-SEP attenuation started after the movement initiation, for SR-SEP attenuation started before movement onset in the SM task ($p < 0.01$). Second, while we found no difference in the size of DR-SEPs during the task, the size of SR-SEPs was consistently larger throughout the AO task; this was also a more significant pre-movement control period during the SM task, both compared with the inter-task interval period. These differences between DR-SEPs and SR-SEPs suggest the differential source of sensory gain modulation to the primary sensory cortex's proprioceptive and cutaneous sensory input. While the sensory attenuation of the proprioceptive input could be driven robustly by the efference copy of volitional motor command, the cutaneous signal could be more flexibly modulated depending on its value for current and future movement.

IV. Future Perspective

In addition to the above, we are continuing to develop evaluation techniques for cortical activity plasticity using ECOG electrodes this year. After the technology is established, we will identify the neural factors of rearranged muscle control using methods such as cortico-cortical coherence and cortico-muscular coherence.

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.

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) We measured fMRI brain activity while manipulating a sense of agency (a sense that "I am the one causing an action", which is an aspect of body cognition) and found that activity was modulated in regions related to the sense of agency when a relationship between sensorimotor information and the sense of agency was modulated. We provided a basis for manipulating the sense of agency to facilitate motor learning. 2) We showed how a sense of agency is established in a novel learning situation where the outcome of the action cannot be predicted. 3) We performed a neurotracing study visualizing the connectivity between two important regions for emotional regulation, ventral medial frontal cortex and amygdala, and identified a previously unknown projection linking between the shallow layers of the pregenual anterior cingulate cortex (pgACC) and the basolateral amygdala (BLA). This unique circuit, a cortico-basal ganglia projection starting in shallow layers, is expected to play a special role in regulating emotion and generating motivation. 4) We performed a psychophysical experiment on monkeys to confirm that they possess "sense of agency" similar to humans, using a virtual-reality system inducing temporal delays to the visual feedback of one's hand action.**

I. Introduction

Previous studies in neuroscience and psychology have investigated how feedback from the external world (such as motor error and reward prediction error) contribute 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 a 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. Manipulation of a sense of agecy wiih brain stimulation

A group of the principal investigator (Hiromitsu, Asai and Imamizu) continued experiments on manipulating the sense of agency using high-definition transcranial alternating current stimulation (HD-tACS). Participants moved a cursor with a joystick to follow a target trajectory. The cursor movement was mixed with the other's pre-recorded movement at a specific ratio (10, 50 or 90%). After the movement, participants rated how much the cursor movement resembled their own movement (agency rating). They hypothesized that the neural connection between the right inferior parietal lobe (rIPL) and the right inferior frontal gyrus (rIFG) contributes to agency judgments. Based on this hypothesis, they conducted experiments in which the connection between the two regions was modulated by electronic stimulation. They found that anti-phase stimulation of the regions altered the correlation between cursor-joystick distance (≒ prediction error) and agency judgments compared to in-phase stimulation and no stimulation (Fig. 1A). This year, they measured fMRI brain activity while participants performed the same task. This replicated last year's behavioral results (Fig. 1B). They found that activity decreased in rIPL and increased in rIFG compared to the in-phase and no-stimulation conditions (Fig. 1C). In addition, they confirmed that anti-phase stimulation specifically increased activity in the

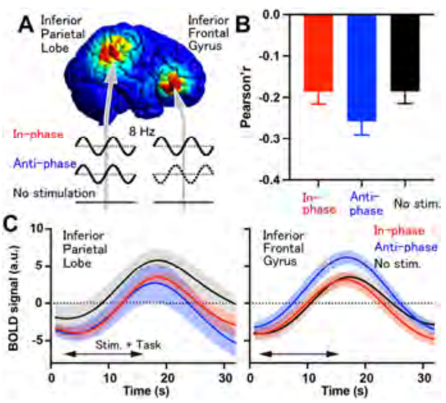


Fig. 1 Manipulation of prediction error - agency rating correlation by brain stimulation. (A) Stimulation details. (B) Changes in prediction error - agency rating correlation. (C) Changes in BOLD signal by stimulation method.

two regions during the task-free resting state. Furthermore, separate stimulation of the rIPL or rIFG did not cause a significant change in the correlation, suggesting that simultaneous stimulation is critical for the change.

B. Formation of sense of agency in novel learning stiutation

A comparator model, a representative model of agency, assumes that a difference between action outcome prediction and sensory feedback (prediction error) is critical for agency. However, it is difficult to predict action outcome in a novel learning situation, which is what the hyper-adaptation project assumes. How is the sense of agency formed in the novel situation? A group of the principal investigator (Takumi Tanaka and Imamizu) had participants learn to control a cursor in a novel rule in which the cursor position was determined by the 1st and 2nd components derived from principal component analysis of joint sensor values of a data glove. They examined changes in the sense of agency with the novel learning task and found that 1) synchrony between the action and its outcome is important for the sense of agency at the early stage of learning, and 2) the sense of agency is determined by the prediction error as learning progresses and the outcome becomes predictable.

C. Towards the identification of the neural cirtuit involved in the regulation of emotion and motivation

The group lead by co-investigator Tsutsui have demonstrated that suppression of neuronal activity in the ventral medial frontal cortex (vMFC) in monkeys induced depression-like symptoms. To investigate the details of the projections from the vMFC to amygdala, they injected a retrograde viral tracer (AAV-retro) into the amygdala. As a result, it was confirmed that deep cells in the subgenual anterior cingulate cortex (sgACC) send strong projections to the basolateral nucleus (BLA) and basomedial nucleus (BMA) of the amygdala. And furthermore, it was found for the first time, that the superficial layer of the pregenual anterior cingulate cortex (pgACC) sends projections to BLA. This unique circuit, a cortico-basal ganglia projection starting in shallow layers, is expected to play a special role in regulating emotion and generating motivation.

D. Sense of agency in monkeys

The group lead by co-investigator Tsutsui conducted the following research in collaboration with Dr. Kasahara's group at Sony CSL. They have developed a virtual reality (VR) system that makes it possible to add temporal or spatial displacement to the movement of the hand (visual feedback) projected on the display while making the monkey perform reaching movements. They conducted a psychophysical examination to test monkeys' sense of agency by having them pick up small pieces of potatoes regularly placed on a board using a device. First, when a bee was used as a startle stimulus and the bee was superimposed on the displayed hand, the subject immediately withdrew the hand and followed the movement of the bee by the eyes. The heart rate showed a significant increase with the appearance of bees. When the monkey's hand was not visible on the screen, the bee's appearance did not increase the heart rate. This suggests that the subject recognizes the hand projected on the screen as its own hand. Next, when a time delay was added to the hand movements displayed on the screen, we found that there was no significant effect on the hand movements with a short delay time, but the movement started to slow down when the delay exceeded a certain period of time. This result can be considered to reflect the status of the sense of agency that it is maintained when the delay applied to visual feedback related to movement is shorter than a certain time, but the sense of agency is lost when the delay exceeds the threshold. was taken. The above psychophysical experiments suggest that monkeys may have a sense of agency similar to humans.

E. Publications of research activityies

A group of the principal investigator published their study on the sense of agency over speech in Psychological Science and issued a press-release [1]. They published their study on the neural basis for flexible switching of driving skills [2]. The group lead by co-investigator Tsutsui published their study inducing depression in monkeys by inhibiting the neural activity of the ventral medial frontal cortex by low-frequency rTMS [3].

IV. Future Perspective

We made progress in developing a method to facilitate motor learning by manipulating the sense of agency by finding changes in brain activity due to stimulation, regional specificity in stimulation-evoked activity, and the importance of simultaneous stimulation of the two regions. We obtained an important clue to understanding the role of a sense of agency in hyper-adaptation by finding a process of agency formation during a novel learning situation. Furthermore, we could establish the basis of research for studying sense of agency in monkeys. Concerning motivation, we identified a new projection circuit which is expected to play an important role in the regulation of emotion and motivation.

References

[1] Ohata, R., Asai, T., Imaizumi, S., Imamizu, H. (2022) My voice, therefore I spoke: The sense of agency over speech is enhanced by hearing self-voice, ***Psychological Science***. 33(8), pp. 1226–1239.

[2] Ohata, R., Ogawa, K., & Imamizu, H. (2022). Neuroimaging Examination of Driving Mode Switching Corresponding to Changes in the Driving Environment. ***Frontiers in Human Neuroscience***, 16, e788729.

[3] Nakamura S, Kishimoto Y, Sekino M, Nakamura M, Tsutsui KI. (2022) Depression induced by low-frequency repetitive transcranial magnetic stimulation to ventral medial frontal cortex in monkeys. ***Exp Neurol.*** 357:114168

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 fourth 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 dopa-mine (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. For this purpose, we performed animal experiments and human clinical studies in this 4th (FY 2002) year. Animal experimentation with cats and rats has been made to explore the brainstem-spinal cord posture-gait control mechanisms by the interaction between midbrain DA-ACh systems. In human clinical studies, we developed measurement procedures of brain network dynamics related to DA decrease and Aβ accumulation. Further, we started to provide human data for constructing mathematical models.

II. Aim of the Group

Takakusaki's group has been in charge of the animal experiment to evaluate the functions of ACh and DA systems in the cognitive-motor linkage. Using decerebrate cats as experimental animals, DA-ACh interactions between the substantia nigra pars compacta (SNc), and the pedunculo-pontine nucleus (PPN) in the midbrain have been tested on how it modulated posture-gait control mechanisms in the brainstem-spinal cord.

Hanakawa's 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 [3] which is a longitudinal study involving healthy elderly people as well as patients with PD and AD. They also have developed an advanced method to analyze relationship between cognitive functions and dynamic profiles of functional connectivity among distinct neural networks. The Hanakawa lab also started basic research on neuromelanin MRI to assess DA production in the substantia nigra (SN) in addition to DA transporter (DAT) SPECT for evaluating the activity of the DA system.

III. Research Topics

The following points are the major achievements.

A. *Posture-gait control by the midbrain DA system acting on the brainstem* *(Takakusaki; Asahikawa)*

Figures 1A and 2A schematically illustrate the working hypotheses for the contribution of DA system to posture and locomotor, respectively. The SNc-DA neurons and the PPN-ACh neurons have a mutual interaction in the midbrain. The acute decerebrate cat, where the forebrain was disconnected from the midbrain, exhibited tonic contractions of the hindlimb extensor (soleus) muscles due to decerebrate rigidity so that it maintained an upright standing posture (Fig.1B, left). However, microinjection of DA into the unilateral PPN abolished bilateral soleus muscle activity leading to muscular atonia (Fig.1B, right). On the other hand, to block the inhibitory effect from the substantia nigra par reticulata (SNr) to the PPN, muscimol (GABA-A receptor agonist) was microinjected in the SNr, resulting in an increase in the activity of the PPN-ACh neuron which was accompanied by muscle tone suppression and rapid eye movements (REMs) (Fig. 1C).

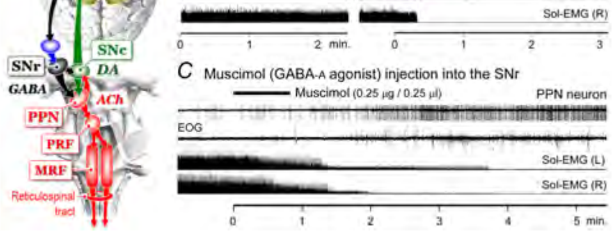


Figure 1; DA and GABA effects on PPN postural control system

Glutaminergic (Glu) neurons in the cuneiform nucleus and a part of the PPN constitute the mesencephalic locomotor region (MLR). A few minutes after DA microinjection into this area, the decerebrate cat exhibited spontaneous locomotion. The locomotor pattern was changed according to the treadmill's speed from walking to galloping (Fig.2B). These results suggest that the DA pathway projecting to the PPN area, including the MLR, acts on ACh and Glu neurons to regulate postural muscle tone and locomotion, respectively.

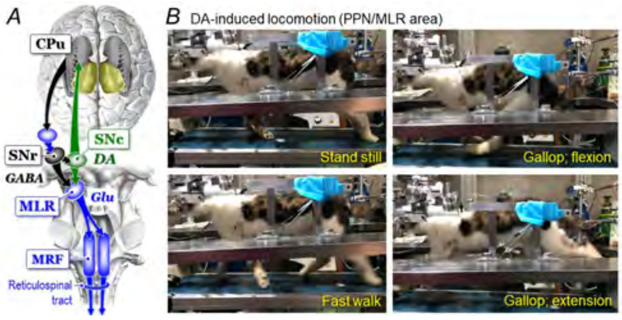


Figure 2; DA effects on MLR locomotor control system

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

Hanakawa and colleagues use non-invasive measurements brain dynamics using fMRI and EEG to elucidate dynamic adaptation mechanisms of human brain to physiological and pathological DA reduction. This year, as development of basic methodology, they developed simultaneous EEG-fMRI technology, which allowed them to investigate dynamic changes of the basal ganglia-cortical circuits in a mu-rhythm based brain-computer interface (BCI) task [4]. Increased activity in the putamen was observed during successful than unsuccessful BCI performance. Moreover, during successful than unsuccessful BCI performance, the striatum more effectively communicated with the globus pallidum, thalamus, and motor cortices. This study indicated the basal ganglia, which is under the strong influence of DA, play a pivotal role in modulating mu-rhythm via the basal ganglia-cortical circuits, thereby influencing BCI performance. We previously reported impaired BCI performance in patients with PD. Patients with PD often show characteristic gait disturbance called freezing of gait (FOG). FOG is an episode during which a patient cannot walk as if the feet are glued to the floor especially on the initiation of walking or turning. It is known that the phenomenon of FOG is strongly influenced by sensory stimuli in the environment, emotion, and attention. Using resting-state fMRI, Hanakawa's group studied network correlates of FOG [5]. They found that FOG scores were correlated with connectivity of subcortical motor network, emotional network involving the amygdala, and fronto-parietal network underlying cognition and attention. The group was able to estimate the degree of FOG or presence of FOG using a set of those connectivity. Hanakawa's group also published a collaborative study with Dr. Abe at National Center of Neurology and Psychiatry [6].

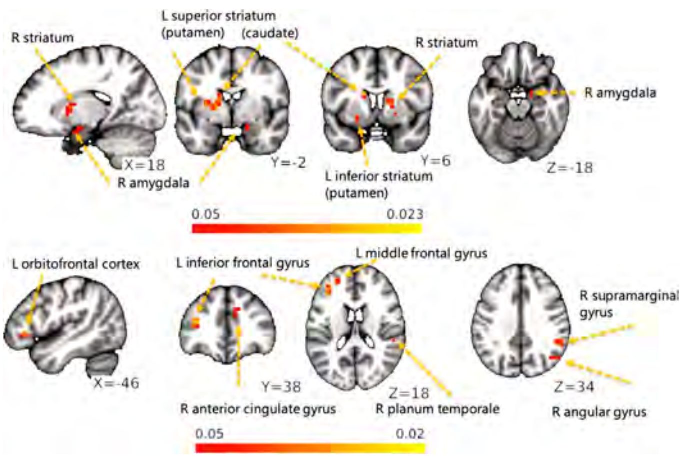


Figure 3; Network correlates of freezing of gait in Parkinson's disease

IV. Future Perspective

In the next fiscal year, the Takakusaki group will continue animal experiments to ensure the results of this year's research, in addition to examination of the mechanism of posture and walking by the ACh and DA systems projecting to the forebrain. Specifically, we will use molecular genetically encoding techniques involving the ACh and DA systems to verify whether the cortico-reticular pathway, which connects the cerebral cortex and the brainstem, plays a crucial role in the cognitive aspect of posture-gait control. Hanakawa group will continue to elucidate dynamic changes of brain circuits in association with dopamine reduced states in humans. They will also advance technology to examine the state of dopamine in human brains.

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 3^{rd} Series. 2023 (in press)

[3] Wakasugi N and Hanakawa T: It is time to study overlapping molecular and circuit pathophysiologies in Alzheimer's disease and Lewy body disease spectrums. Front Systems Neurosci 15:777706, 2021. 2021.11.18 doi.org/10.3389/fnsys.2021.777706

[4] Kasahara K, DaSalla CS, Honda M, Hanakawa T: Basal ganglia-cortical connectivity underlies self-regulation of brain oscillations in humans. Commun Biol 5(1):712, 2022. doi.org/10.1038/s42003-022-03665-6

[5] Togo H, Nakamura T, Wakasugi N, Takahashi Y, Hanakawa T: Interactions across emotional, cognitive, and motor networks underlying the freezing of gait. Neuroimage: Clin. 2023. doi.org/10.1016/j.nicl.2023.103342

[6] Takasawa E, Abe M, Chikuda H, Hanakawa T: A computational model based on corticospinal functional MRI revealed asymmetrically organized motor corticospinal networks in humans. Commun Biol 5(1):664, 2022 doi.org/10.1038/s42003-022-03615-2

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 four 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, Identification of a brain activity that maintains positive mood in rats; C, Establishment of a decoding and quantification system of seizure susceptibility from large-scale electrophysiological brain activity recordings during interictal states of epileptic rats; D, Preparation of a recording and real-time intervention system for 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]

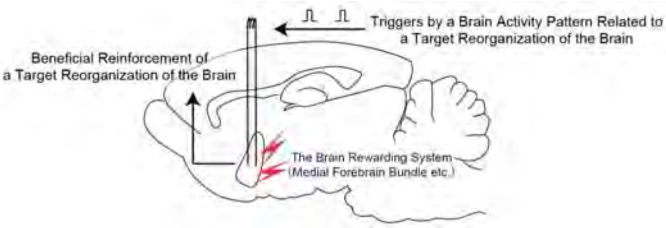


Fig. 1. A closed-loop brain stimulation for reinforcing hyper-adaptability [4]

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, identify brain activity related to depression-like symptoms, decipher brain activity patterns that explain seizure susceptibility in epilepsy, and implement a recording and real-time intervention system for a mouse model of Alzheimer's disease [5].

III. RESEARCH TOPICS

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

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]

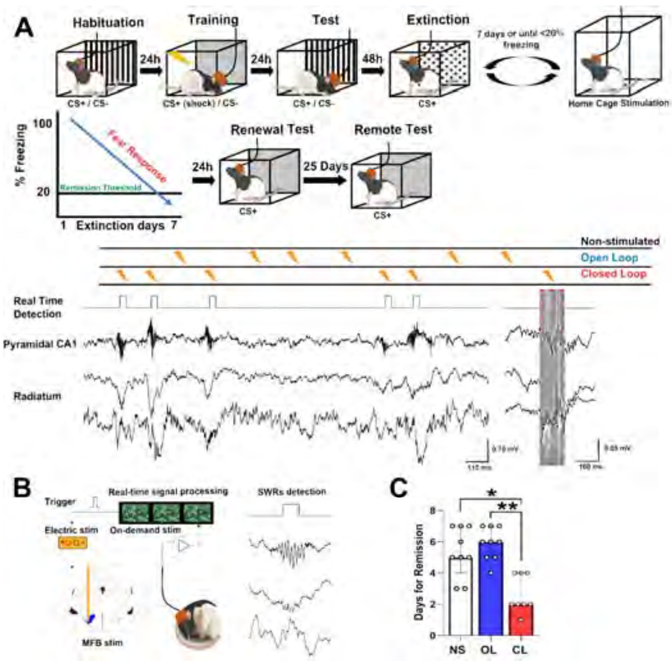


Fig. 2. Hippocampal Sharp Wave-Ripple-triggered stimulation of the reward system in the brain during the sleep after extinction training reinforces extinction of a fear memory. [6] A: Experimental schedule and a recording and stimulation systems of the hippocampus and the medial forebrain bundle. B: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

B. Identification of a brain activity that maintains positive mood in rats

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 pisiform cortices was related to the maintenance of positive mood as measured by the performance on a sucrose preference test. [7]

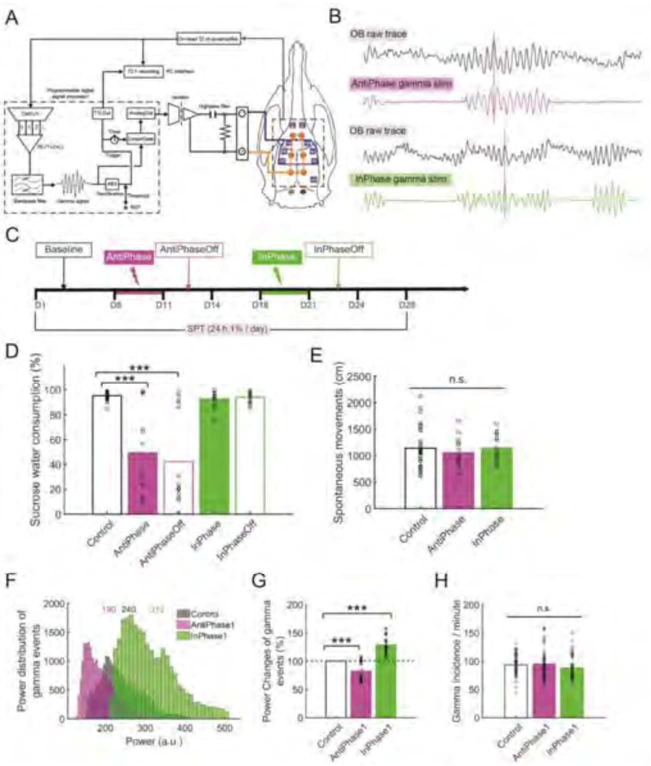


Fig. 3. Gamma frequency functional couplings between the olfactory bulb and the piriform cortex mainteins hednic mood in rats. [7] A, B: A closed-loop electrical stimulation system of the piriform cortex in real-time gamma band oscillatory activity patterns in the olfactory bulb. C: Experimental schedule. 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. Establishment of a quantification system of seizure susceptibility from large-scale brain activity recordings

If seizure susceptibility of epilepsy can be decoded in real-time from ongoing brain activities, it will be possible to selectively reinforce the brain states with lower seizure susceptibility. Toward this goal, we here developed a technology of decoding and quantifying seizure susceptibility from large-scale electrophysiological brain activity recordings during the interictal period using Cross-Spectral Factor Analysis (CSFA) [8], a machine learning algorithm focusing on inter-reginal oscillatory brain activities (Fig. 4).

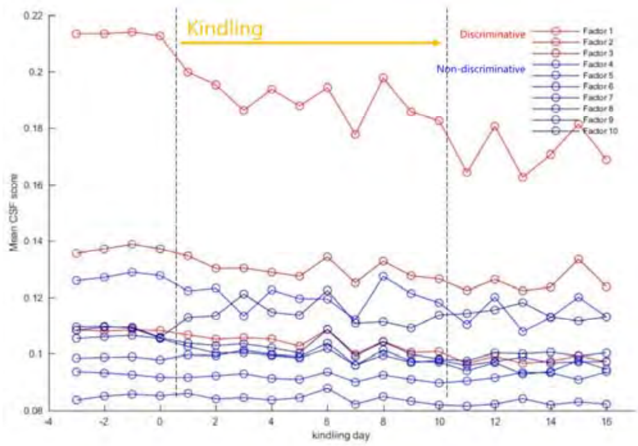


Fig. 4. Quantification of seizure susceptibility by large-scale brain activity recordings and a machine learning technology. A coefficient of the first cross-spectral factor (a multi-regional brain activity pattern) decreased during the daily electrical stimulation of the hippocampal commissure, which inversely correlates with seizure susceptibility.

IV. Future Perspective

We have achieved a control of pathological fear memory with a time targeted stimulation of the brain reward system during this fiscal year. Similar strategy will be employed to control epilepsy, Alzheimer's disease, and depression in the next fiscal year.

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 to reduce pathologic fear," *bioRxiv*, 2022.07.24.501314, July 2022.

[7] Q. Li †, Y. Takeuchi †, J. Wang, *et al*., "Reinstating olfactory bulb derived limbic gamma oscillations alleviates depression," *bioRxiv*, 2022.02.01.478683, February 2022.

[8] Y. Takeuchi, "Development of on-demand interventions of epileptic seizures and a quantitative method of seizure susceptibility," *Medical Science Digest*, vol. 46, pp. 118-121, February 2020.

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. In addition, to understand the relationship between amount of limb use and body consciousness in the physically disabled, we measured body-specific attention to prosthetic foot in lower limb amputees and found a use-dependent increase in body-specific attention during the process of gait acquisition. 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 of the paretic hand 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 physically disabled persons, using the findings of stroke and amputation patients as a clue. 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]. 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

1) 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. 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) In addition, the aim of this study is to clarify the relationship between amount of limb use and body consciousness in the physically disabled, we measured body-specific attention to prosthetic foot in lower limb amputees and investigate the changes in body-specific attention during the process of gait acquisition. 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 of the paretic hand 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 , 2 weeks, 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. Use-dependent increase in attention to the prosthetic foot in patients with lower limb amputation

Although body-specific attention to hands and feet has been studied in healthy subjects[3], it is unclear how body-specific attention to the prosthetic foot changes during the process of gait acquisition in lower-limb amputees. It is possible that amputees who successfully use their prostheses pay more attention to their prostheses. We aimed to longitudinally measure body-specific attention to the prosthetic foot in amputees beginning to practice walking rehabilitation with a prosthesis and to examine its relationship to walking ability. The study subjects were 11 lower-limb amputees. Body-specific attention was measured using a visual detection task. In the initial phase of walking rehabilitation, the index of attention to the prosthetic foot was lower than that to the healthy leg. However, at the final stage, there was no significant difference between the two attention indices. Correlation analysis revealed that the longer the prosthetic foot was used, the higher the body-specific attention to the prosthetic foot. These findings suggest that once a person gains the ability to walk with a prosthetic foot, attention is directed to the prosthesis in the same way as to the healthy lower limb. The participants also commented that once they were able to walk independently, the prosthetic foot felt as if it were part of their body. These findings suggest that the use of a prosthetic foot causes the integration of visual information about the prosthesis and movement, resulting in subjective embodiment. [4]

C. 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. In addition, to better understand the relationship between amount of limb use and body consciousness in the physically disabled, we measured body-specific attention to prosthetic foot in patients with lower limb amputation and found an increase in use-dependent body-specific attention during the gait acquisition process. 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 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.-I. Izumi, "Time-dependent decline of body-specific attention to the paretic limb in chronic stroke patients," *Neurology*, vol. 91, pp. e751-758, 2018

[2] R. Otaki *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.

[3] N. Aizu *et al.*, "Body-Specific Attention to the Hands and Feet in Healthy Adults," *Front. Syst. Neurosci.*, vol. 15, Jan. 2022

[4] N. Aizu, Y. Oouchida, K. Yamada, K. Nishii, and I. Shin-Ichi, "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

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. Furthermore, they perceive fluorescent lights as flickering and painful. 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. Furthermore, the neurons fired more strongly in correct-choice than in incorrect-choice trials at low contrast. They efficiently represented low-contrast orientations. Even the primary visual 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 contrast of external visual input is now evident [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 adaptive mechanism is modified by different levels of adaptation, stress load, and developmental characteristics in autism. We seek 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 presented rats with various visual stimuli and observed their visual adaptation to the stimuli. First, using the touchscreen operant platform, freely moving rats learned a visual discrimination task to distinguish between vertical and horizontal gratings. Then, the visual stimuli were randomly rotated while maintaining the 90-degree difference in tilt between the two gratings. The rats selected the discrimination behavior depending on whether the presented stimulation was closer to the vertical or horizontal grating; at a rotation of 45 degrees, the orientation was exactly between the vertical and horizontal gratings, so the behavior selection was at chance level. However, up to approximately a 30-degree rotation, they could select the vertical behavior if it was closer to the vertical grating. In contrast, when the two gratings were rotated gradually and continuously, keeping the 90-degree difference in tilt between the two gratings, the correct answer could still be obtained in many sessions, even after a 90-degree rotation or a reversal, in as short a period as one session. When rotated randomly, rats, of course, chose the behavior before such a large rotation and could not select the correct behavior. However, when the visual stimulation was rotated continuously, rats were able to select the behavior after such a large rotation. Next, in the experiment in which head-restrained rats perform visual discrimination, the difficulty level was much higher for the reasons described in the next chapter, and the rats could not adapt to the large rotation angle as in the touchscreen experiment. However, a similar trend was observed in the head-fixed condition. Rats were able to adapt to larger rotation angles to some extent in a shorter period (one session) when visual stimulation was rotated gradually and continuously than when the stimulation was rotated randomly. At this time, when neuronal activities were recorded from the primary visual cortex, some neurons were observed that maintained relatively stable visual responses to vertical and horizontal gratings even after continuous rotation and large rotation angles. Whether this is the neural basis of perception adapted to the continuous rotation of visual stimulation needs further verification.

We are currently conducting experiments to determine whether this perceptual adaptation to the rotation of visual stimuli is dependent on the degree of stress load, i.e., the difficulty of the task. In addition, we are preparing to perform large-scale multi-unit recording using the Neuropixels probe to simultaneously record the firing activity of multiple neurons across multiple brain regions and to perform widefield calcium imaging of multiple brain regions by expressing the fluorescent calcium probe GCaMP specifically at the recording time with the Tet-On system.

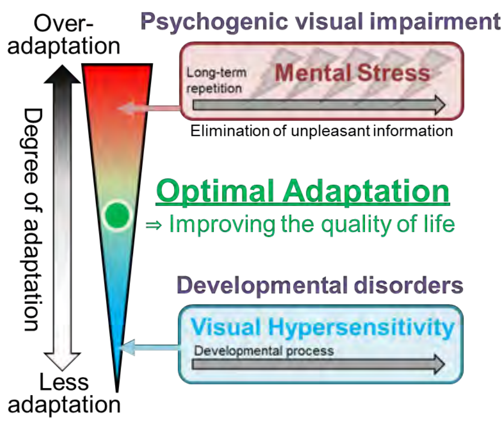


Fig. 1. Schematic diagram of optimal adaptation to the external environment.

IV. Future Perspective

This year, we started our research and have not yet produced many results; however, we have introduced a new experimental system in which freely moving rats perform a visual discrimination task using a touchscreen operant experimental apparatus. However, to accurately determine the parameters of the visual stimuli to be presented, it is effective to conduct experiments in a head-fixed condition where the distance between the eyes and the monitor can be kept constant. Head fixation also facilitates recording of neural activity. However, if we want to present visual stimuli to the receptive field at the recording location, only one visual stimulation can be presented, and two gratings cannot be compared simultaneously. In addition, different symmetrical movements must be made in response to each stimulation. For these reasons, the difficulty of conducting experiments in the head-fixed condition is greatly increased. To observe the adaptation to rotation of visual stimuli in a convenient manner, experiments using the touchscreen operant platform would be effective. In the next year, we will use this experimental system to examine how the adaptation alters to the changes in visual stimulation in rats subjected to stress or in autism models created by the administration of valproic acid to pregnant animals. Furthermore, by large-scale multi-unit recording and widefield calcium imaging, which will be set up this year, we aim to elucidate the neural basis of 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.

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. The neural mechanism of implementing multiple strategies is still unclear at least in a single neuron level because a precise neural recording and manipulations often require experiments with animals. Here we perform a neural recording in head-fixed mice during a strategy-switching task to investigate the neural substrate of model-free and inference-based strategy. We propose an AI (artificial intelligence) -based approach to investigate the relationship between the algorithms of brain and AI. Our study potentially proposes an idea that the brain learns multiple strategies with learning rules and switches the strategy with non-linear neuronal circuits.**

I. Introduction

Recent studies propose that the brain has multiple behavior strategies in parallel and selects the strategy in a context-dependent manner [Ref.1]. In a field of engineering, behavioral strategy is divided into model-free strategy, which decides choices based on direct experiences of choice and reward (habitual behavior), and inference-based strategies, which estimates a hidden context based on observed sensory inputs to make flexible choices.

Because of the simplicity of behavioral tasks and the related models, previous studies often investigate the neural mechanism of model-free strategy [Ref.2]. In contrast, the inference-based strategy is mainly tested with human experiments [Ref.3]. The human experiments use sophisticated behavioral tasks to separate the model-free and inference-based strategies [Ref.1,4], although human studies are sometimes difficult to investigate the detail neuronal circuits because of the methodological constrains.

Recent studies used rodents and started to investigate the neural mechanism of inference-based or model-based strategies [Ref.5-7]. These studies used optogenetics or pharmacological tools to inactivate a specific brain region and found that the hippocampus or medial frontal cortices are necessity for the inference-based strategy. However, the neural representations of inference-based strategy and of strategy switching are still unclear.

This study performs a behavioral task in head-fixed mice to dissociate the model-free and inference-based strategies. During a strategy switching task, we record the neural activity of mice to investigate the neural correlates of the two strategies. Because this study is still ongoing, we need to inform that the manuscript does not include the specific aims and the target brain regions.

II. Aim of the Group

We propose a unified learning theory for model-free and inference-based strategies, and investigate the neural implementation of the theory by recording the neural activity of mice. We construct an artificial neural network with the behavioral and neural data to model the strategy switching in the brain.

III. Research Topics

We summarize the three achievements in this year as follows:

A. Strategy-switching task in head-fixed mouse

We developed a strategy switching behavioral task to dissociate the model-free and inference-based strategies. Mice were head-fixed and placed on a spherical treadmill. We presented a sound stimulus with various frequencies. When the sound frequency was low (5-10 kHz, state L), mice required to lick a left spout to get a reward of sucrose water. A high-frequency sound (20-40 kHz, state H) provided the reward by licking the right spout. The state (L or H) of each trial was determined with a transition probability (P) and the tone frequency of previous trial [Ref.8]: the state was flipped in every trial with the probability of P. Reinforcement leaning theory shows that the probability (P) can dissociate the model-free and inference-based strategies:

- Repeat condition (P = 0.2): Maximize the reward by repeating the rewarded choice in a previous trial: model-free strategy.

- Zigzag condition (P = 0.9): Estimate the hidden state (L or H) from the observed sensory inputs and outcomes. Maximize the reward by mainly making an opposite choice from a previous trial. For example, when the previous state is L, the probability of receiving a reward at right choice is 80 % in the next trial (state H): inference-based strategy.

We continue to perform the strategy-switching task since our different research project. In this year, we performed the repeat and switch conditions in separate groups of mice. To maximize the reward amounts in both the conditions, mice not only required to making choices based on the tone frequencies but biasing the choices depending on the transition probability. We analyzed the mice choices with a psychometric function and found that mice biased the choices based on the transition probability. The acquisition of behavioral biases was faster in the repeat than in zigzag conditions (**Fig. 1**). This result

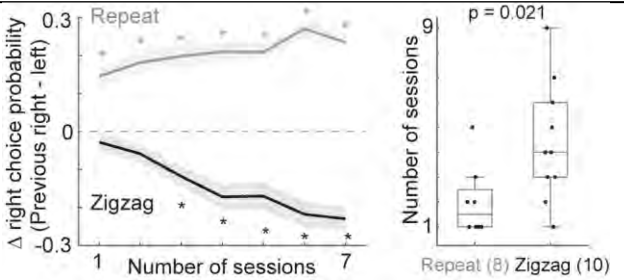


Fig. 1. Faster learning of behavioral biases in repeat than in zigzag conditions
Left: Learning curve of behavioral biases. Means and standard errors (* $p < 0.01$ in Wilcoxon signed rank test).
Right: Number of sessions to achieve the behavior biases. Parentheses show the number of mice. The acquisition of condition-dependent behavioral biases was faster in the repeat than in zigzag conditions (Mann-Whitney U-test).

suggests that the behavioral strategy in each condition was different.

B. Behavioral modeling

We analyzed the choice behavior of mice with a model-free reinforcement learning (RL) model and a state-transition model. This analysis used the data between the first and seven sessions (days) from introducing the transition probability in both conditions (P = 0.2 or 0.9). The model-free RL updates the expected reward for each choice (action value) based on the direct experiences of choices and outcomes. In contrast, the state-transition model estimates the transition probability (P) from the experiences. Based on the estimated P, the model decided choices.

In the repeat condition, the mice choices matched to the model-free RL than the transition model on average. In contrast, the choices in zigzag condition were fit to the transition model. These results suggest that different behavioral strategies were used in the repeat and zigzag conditions.

In addition, we modeled the mice choices with an artificial neural network, i.e., recurrent neural network (RNN) with Long Short Term Memory (LSTM). We trained the RNN with simulated behavioral data and updated the connections with an Advantage Actor-Critic (A2C). The RNN succeeded in modeling the behavioral biases in both the repeat and zigzag conditions. In this year, we are investigating whether the RNN can simulate the faster learning in the repeat than in zigzag conditions.

C. Setup for neural recording

We are introducing a fiber bundle imaging for neural recording. This method uses GCaMP [Ref.9] or G-protein-coupled receptor-activation-based (GRAB) sensors [Ref.9] to image the temporal changes of neural activity or neuromodulators. We plan to simultaneously images the activity of 4 to 6 brain regions. So far, we finished setting up the rig and prepared the AAV virus for neural imaging. We are currently setting up the surgery for recording.

IV. Conclusion

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

In this year, we performed the strategy-switching task to separate the model-free and inference-based strategy in head-fixed mice. We analyzed the choice behavior in the repeat and zigzag conditions and found that (i) the learning of behavioral biases was faster in repeat than in zigzag conditions and (ii) the choice behavior in repeat and zigzag conditions were fit to a model-free RL model and state-transition model, respectively. These results suggest that the behavioral strategy was different in each task condition. In addition, an artificial neural network succeeded in modeling the behavioral biases of mice in both task conditions. Next, we are going to investigate whether an artificial neural network models the different learning speeds of mice in the repeat and zigzag conditions.

Currently, we are setting up a fiber bundle imaging to record the neural activity during the task. With this method, we are going to simultaneously image the activity of multiple brain regions for understanding a unified learning theory of model-free and inference-based strategies.

References

[1] 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.

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

[3] 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.

[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] 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.

[10] 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. Moreover, 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 in this study, we try to identify the timeline of axonal retraction which are suggested from the transient NCM-HVC projections. We also will try to investigate the underlying neuronal mechanism for persistence of neuronal connection with enriched experiences in juveniles. 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. Identifying the timeline of axonal retraction

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 different ages were exposed to TS playback concurrent with DOX in drinking water to induce EYFP expression only in TS-responsive neurons. We found TS-responsive NCM neurons projected their axons densely into the HVC still in juveniles at 70 DPH, in contrast, in slightly older juveniles (80 DPH) axonal projection from TS-responsive NCM neurons were sparce (Fig. 1). We found the song of juveniles became stereotyped (less variable in the sequence in repetition) between 70-80 DPH, suggesting correlation of NCM-HVC neuronal connection with song maturation. We will apply this timeline in the experiments described in the following sections.

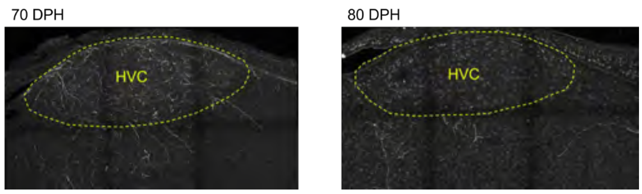


Fig. 1: Axonal projections in the song motor region, HVC from TS-responsive NCM neurons. Abundant axonal projections were observed in the HVC in the juveniles which were injected with AAV-cFOS-TetOn-EYFP-PEST and provided TS playback with DO water at 70 DPH, while fewer axons observed in juveniles which were exposed to TS playback at slightly older age, 80 DPH.

B. Establishing in vivo imaging system for axonal retraction

We have been suggesting axonal retraction from the TS-responsive NCM neurons from the HVC by comparing confocal images from the juveniles at 60 DPH and 90 DPH. To confirm the phenomena of "axonal retraction" we have tried to establish long-term time lapse in vivo imaging system in zebra finch brain. Adult zebra finches were injected with AAV for expressing GFP in HVC neurons. A cranial window was chronically established by placing a cover glass and sealed to the scull on top of HVC. We then periodically examined HVC neurons which expressed GFP under dissection microscope (Fig. 2). We successfully imaged HVC neurons, including their axons, stably for more than two weeks in vivo. Our experiment, shown in the previous section *A*, suggest axonal retraction from NCM TS-responsive neurons happening between 70 and 80 DPH. We will express GFP in the TS-responsive NCM neurons by using AAV as described in the previous section, and track their axonal projection in the HVC those period under confocal microscope in coming years. We will simultaneously monitor song maturation to see the correlation between song stabilization and axonal retraction.

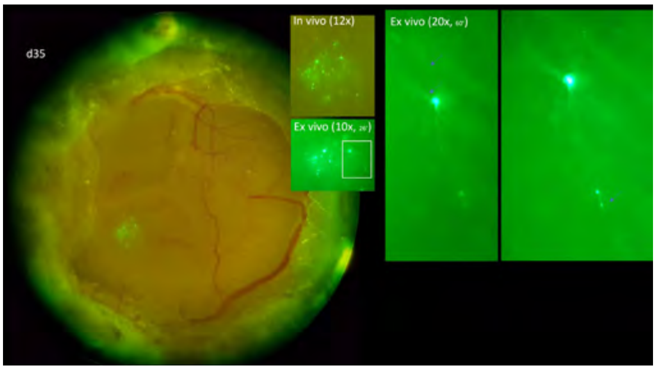


Fig. 2: In vivo imaging of HVC neurons expressing GFP with AAV injections using dissection microscope. HVC neurons and their axons were periodically examined through cranial window.

C. *Establishing in vivo imaging system for axonal retraction*

Our recent study revealed retained axonal projection in HVC from TS-responsive NCM neurons in adults which had enriched song learning experiences. Those birds were fostered to a Bengalese finch pair starting just after hatching (0-2 DPH) for 30 days. Then, they were isolated for another 30 days after which they were exposed to a conspecific zebra finch tutor for 30 days. Under this paradigm, juveniles memorized and copied two TS sequentially, transiently learning from a Bengalese foster father and quickly re-learning from the zebra finch second tutor. So, it has yet to be clarified which experience, exposing to tutors and learned songs of other bird species, or learned songs in the extended developmental learning period with social isolation, caused persistence of axonal projection into adulthood. To examine which experience is critical for retention of neuronal projections, we have started raising zebra finch juveniles with varies rearing conditions; 1) sequential tutoring with two conspecific (zebra finch) tutors, 2) sequential tutoring with two tutors without isolation in between, 3) single tutored with heterospecific (Bengalese finch) foster parents.

Persistent neuronal connection with enriched experiences during juvenile period suggests increased song neuronal circuit capacity. We further will investigate the possibility of recovering song re-learning in adults, implicating possibilities of enhanced recovering ability during rehabilitation after injury.

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. Enriched experiences might enhance neuronal circuit capacity. Our future experiments in coming years would tell us the exact timeline of axonal projection and retraction subserving for vocal learning, as well as the underlying neuronal mechanism for enhanced neuronal circuits with experiences. Novel approach for supporting rehabilitation for recovering from injury are expect to be suggested.

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. We record electrocorticogram (ECoG) in epilepsy patients who undergo intracranial electrode implantation in the frontal and parietal lobes for preoperative evaluation of epilepsy surgery. We probe neural signatures of higher-order motor control by recording wide-band ECoG activities during higher-order motor tasks. To understand the brain network associated with motor control and hyper-adaptive reorganization, we made 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 investigated the associations of performance impairment by electrical cortical stimulation and CCEP spatial distribution during the Go-NoGo task. We also elucidated that the CCEP late-latency potentials (N2 responses) were correlated with the functional connectivity in the Human Connectome Project database. We proceed with EEG or ECoG network analysis using a time-varying graphical lasso.**

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 partial 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. In Year 2022, because of the ongoing COVID-19 pandemic that prevented us from recruiting many patients, we focused on making the electrophysiological connectome by means of cortico-cortical evoked potentials (CCEPs) since the understanding of the macroscopic human brain connectome is essential to tangle the hyperadaptability of the premotor area and human brain in general. This fiscal year, we studied the relationship between the CCEP distribution and the performance of Go/No-Go task that emerges during ECS, and the relationship between the effective connectivity of CCEP and the resting-state functional connectivity of the Human Connectome Project (HCP) database. For inter-group collaboration, we collaborated with Group B and utilized the Time -Varying Graphical Lasso (TVGL) to analyze the scalp and intracranial EEG recordings.

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 and 1062.

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 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. We also studied the relationship between CCEP distribution and performance on the Go/No-Go task during ECS, that between effective connectivity (CCEP) and resting-state functional connectivity (fMRI) in the Human Connectome Project (HCP) database. 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.

III. RESEARCH TOPICS

We have carried out the following three research projects.

A. Relationship between CCEP Distribution and Task Performance during High-Frequency Cortical Electrical Stimulation (ECS) in Go-NoGo Task

ECS is the gold standard mapping technique for clinically identifying functional brain localization, but the extent to which brain networks are involved with this technique has not been clarified.

In five patients with drug-resistant refractory epilepsy who underwent invasive presurgical evaluation with intracranial electrodes, we performed a Go/No-Go task and delineated areas with No-Go specific ERPs. ECS was applied to cortical areas with No-Go specific ERPs, and No-Go performance was evaluated. We compared the CCEP network from the stimulus site and the No-Go ERP network. As the more CCEP responses were observed within the No-Go ERP network, the poorer No-Go performance was induced by ECS. This suggests that, although ECS is a method for functional localization, ECS is likely to impact on the electrically connected network. Future studies are needed to elucidate whether the ECS effect is weighted at the stimulus site or equally across the network nodes [1].

B. Comparison of effective connectivity by CCEP and functional connectivity in the HCP database, and alteration of connectivity in the diseased brain

The CCEP distribution showed that the anterior part of the precuneus has connections with the lateral premotor cortex, the posterior part with the occipital lobe, and the posterior cingulate gyrus firmly with the medial frontal lobe, suggesting that these regions are involved in different ways in motor and visual functions [2]. In addition, we clarified the dynamics of cortical interactions in visual recognition of object category (living vs. non-living) by means of event-related causality analysis on ECoG high gamma activities. Specifically, we revealed that significantly stronger neural propagation occurs among sites within the ventral temporal lobe at early latencies, around 250 ms, for living objects compared to non-living objects [3]. We also compared effective connectivity by CCEP and functional connectivity in the HCP database using resting state fMRI, and found a strong correlation between N2 potentials in CCEP and functional connectivity [4]. In terms of brain plasticity, the relationship between epileptogenicity and brain network alterations in the epileptic brain showed that network alterations were observed in areas with severe epileptogenicity but less so in areas with mild epileptogenicity (Togo et al., to be presented at the 64th Annual Meeting of the Japanese Society of Neurology).

C. Intracranial EEG network during supraventricular EEG during sleep and reaching and grasping movements using TVGL

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. We will continue to brush up on the analysis method and increase the number of cases to see if it is possible to identify sleep stages and reaching and grasping movements from the viewpoint of the network.

IV. FUTURE PERSPECTIVE

In the present investigations, because of the COVID-19 pandemic, we had to change our original plan to recruit patients for the prospective study. Instead, by using the large retrospective CCEP data and some prospective data, we focused on the human premotor area and constructed electrophysiological or CCEP connectomes related to the premotor area to elucidate the network characteristics at both individual and group levels. We proceeded to analyze the relationship between high-frequency electrical cortical stimulation and the distribution of CCEP, its correlation with functional connectivity by fMRI, and its alteration by epileptic pathology. In the next fiscal year, we plan to carry out our original proposal, namely, simulate the postoperative CCEP connectome by using the CCEP connectomic data to clarify the network-level Hyper-Adaptivity. We plan to compare the network changes to the movement disability after surgery and its recovery, and try to extract the "hyper-adaptive" indicators. We also plan to keep collaborating with theory group B to seek for constructing mathematical model of hyper-adaptation.

References

[1] 林 梢，武山 博文，十河 正弥ら. Go/No-Go 課題を用いた脳機能局在と CCEP の関連性について. 超適応夏の全体会議, 7/19-20, 2022

[2] 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

[3] 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.

[4] 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)

A05-8 Annual report of the research project

Hiroyuki Miyawaki
The Osaka Metropolitan University

***Abstract*— Animals that have undergone traumatic experiences develop maladaptive states in which they are unable to take adaptive behavior due to fearful memories, and the following fear-extinction learning induces hyper-adaptation that enables the animals to regain their capacity for adaptive behaviors. Multiple brain regions, including the amygdala, ventral hippocampus, and prefrontal cortex, are known to be involved in fear-related mal-adaptation and hyper-adaptation, yet the changes in local and inter-regional networks remain to be fully understood. To shed light on this issue, we conducted multi-regional large-scale electrophysiological recordings in fear-conditioned rats and analyzed the dynamics of neuronal ensemble activity across the sessions for fear-conditioning, extinction learning, and testing retention of extinction. Our findings revealed that while a significant fraction of neuronal ensembles remained active throughout these sessions, new neuronal ensembles emerged during the session for extinction learning and persisted to ones for testing retention of extinction. Notably, within the prelimbic cortex, ensembles that were active during extinction learning and retention of extinction enhanced activity during sleep prior to the extinction learning. Further research will elucidate the dynamics of the local and global networks that underlie fear-extinction.**

I. Introduction

For animals, fear of situations associated with harmful stimuli is an important ability for survival. However, an excessive manifestation of fear can impede adaptive behavior, a condition referred to as post-traumatic stress disorder (PTSD) in humans, which has a profound impact on daily life. Fear conditioning and its extinction learning have been intensively studied as animal models of the development and treatment of PTSD. Previous studies have demonstrated that fear extinction is not a process of forgetting, but rather a hyper-adaptation process in which adaptive behaviors are regained while fear memories persist [1]. The amygdala, ventral hippocampus, and prefrontal cortex have been identified as crucial structures in the regulation of fear conditioning and extinction learning [2]. However, the dynamic changes that occur in the networks among these brain regions during the transition from mal-adaptation to hyper-adaptation states and the underlying mechanisms of regulation remain to be elucidated. Understanding these elements will provide insight into the pathophysiology of memory- and emotion-related disorders, including PTSD and anxiety disorders.

II. Aim of the Group

This research project endeavors to shed light on changes in local and inter-regional brain networks that underlie the hyper-adaptation from mal-adaptation states associated with fear and the neuronal mechanisms that govern these changes. In the brain, information is represented as the activity of "neuronal ensembles," which are relatively small groups of neurons that exhibit synchronous activation [3]. Previous research within this project has revealed that the local neuronal ensembles become activated synchronously across multiple brain regions following fear memory acquisition [4]. On the other hand, it has also been suggested that the neuronal ensembles detected during fear-conditioning exist even before fear-conditioned learning [4]. In light of these findings, this year we aim to determine the nature of the neuronal ensembles that are active during extinction learning and when the activities of the extinction-related neuronal ensembles commence.

III. Research Topics

A. Identification of the neuronal ensembles emerged during extinction learning.

By using multi-regional large-scale electro-physiological recordings on fear-conditioned rats, we simultaneously recorded the activity of neurons in the basolateral lateral amygdala (BLA), ventral hippocampal CA1 region (vCA1), and prefrontal cortex layer 5 (PL5). During these recordings, we conducted fear-conditioning, extinction learning, and test for retention of extinction were conducted [4]. To identify the neuronal ensembles, we applied independent component analysis (ICA) on the z-scored spike count matrixes obtained from these behavioral tasks. Ensemble detection was done in each brain region separately. The similarities of the resulting neuronal ensembles between extinction learning and the other two behavioral tasks were evaluated with the cosine similarity of the ICA basis vectors (Fig. 1). Considered ensembles were

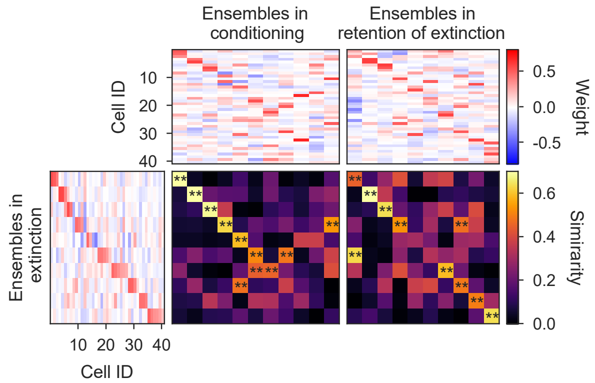


Fig. 1. Examples of cosine similarity among PL5 neuronal ensembles detected during fear conditioning, extinction learning, and test for retention of extinction.

considered to be similar if their cosine similarity was significantly higher than the shuffle surrogates.

Based on the presence of similar ensembles during fear conditioning and the retention of extinction test, we classified the neuronal ensembles detected during extinction learning as "Maintained" (ensembles that had similar ensembles during both fear conditioning and the retention of extinction test), "Terminated" (ensembles that had similar ensembles only during fear conditioning), “Initiated” (ensembles that had similar ensembles only during retention of extinction test), or “Transient” (ensembles that had no similar ensembles). Our analysis revealed a significant difference in the fraction of each class in the PL5 compared to the BLA and vCA1 ($p<0.01$, chi-square test with Bonferroni correction; Fig. 2).

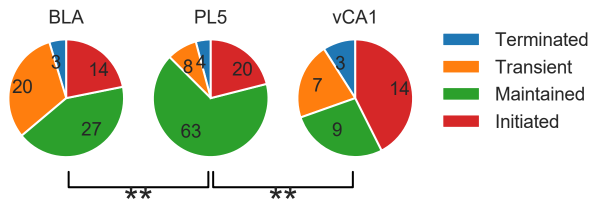


Fig. 2. Fraction of extinction-related neuronal ensemble classes identified in the BLA, PL5, and vCA1.

B. Dynamics of extinction-related neuronal ensembles during sleep.

During sleep, especially during non-REM sleep, the neuronal ensemble activity observed during wakefulness is reactivated, which is believed to play a role in modifying brain network dynamics [5]. Therefore, we examined whether the neuronal ensembles of each class were activated during non-REM sleep before and after the behavioral task (Fig. 3). We found that the Maintained and Terminated ensembles in PL5, which were detected during both fear conditioning and extinction learning, increased activation rate following fear conditioning (Fig. 3). The change in Maintained class was statistically significant ($p < 0.01$, Steel-Dwass test). Interestingly, a similarly significant change was also observed in the Initiated class, despite its absence during fear conditioning ($p < 0.01$, Steel-Dwass test). These findings suggest that the PL5 neuronal ensemble activity involved in extinction learning and its retention is elevated during sleep prior to the actual learning process.

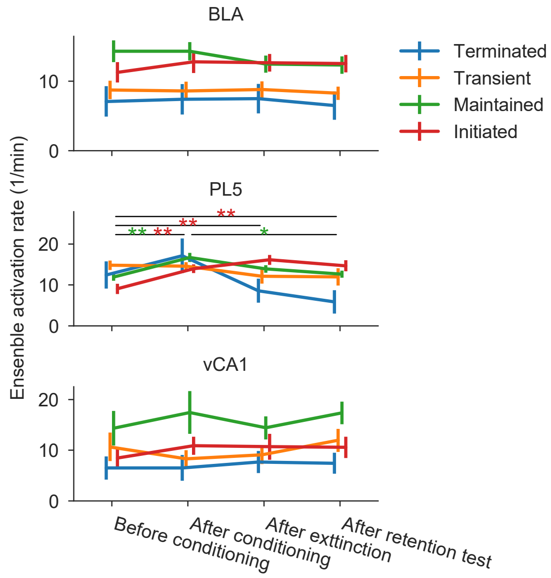


Fig. 3. Activation event rate of extinction-related neuronal ensembles during non-REM sleep preceding and following behavioral task.

IV. Future Perspective

This year, our research has focused on the dynamics of neuronal ensembles related to extinction. Of particular interest is the finding from PL5 ensembles, which indicates that the pre-extinction activity of neuronal ensembles influences their activity during extinction learning. In the future, we plan to examine the cross-regional interactions of these ensembles to gain a deeper understanding of the neural activities that facilitate extinction learning. This work is expected to contribute to the advancement of our knowledge on the neural basis of hyper-adaptation.

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.

[5] Diekelmann S, and Born J. *The memory function of sleep*. Nat. Rev. Neurosci. 2010;**11**(2): p114-26.

A05-9 Annual report of research project

Takaki Maeda, Oi Hiroki
Department of Neuropsychiatry, Keio University School of Medicine

Abstract

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. Actually, we have developed digital applications for cognitive rehabilitation of SoA in order to tune up precision of SoA. Our main achievements in this fiscal year are as follows. 1) We have developed a new SoA experiment task which was introduced spatial biases compared to the former task using temporal biases. 2) We have released the new digital application for agency tuning for artists and athletes: the *Agency Tuner for artists* in US and Poland as well as Japan [1]. The application is created in order to use rehabilitation for patients with occupational dystonia, so-called the yips. 3) In order to evaluate effects of cognitive rehabilitations of SoA, we developed a new application for monitoring trends of mood swing [2].

I. Introduction

We have studied pathophysiology of neurological and psychiatric illnesses from the stand of the SoA. Moreover, we have tried to establish the method to recover from those illness through reorganization of neural systems on the SoA. Actually, we have developed several digital applications for cognitive rehabilitation on the SoA and other mental state including mood swing.

II. Aim of the Group

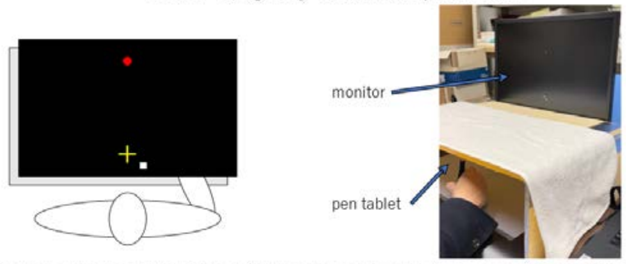
Digital applications have high potential to improve neural dysfunction through cognitive rehabilitations from the standpoint of accessibility & availability. In the future, we intend to develop these applications as digital drugs in clinical practice of neurology and psychiatry. Moreover, we have developed the new sense of agency task using spatial biases. And, we have started a research whether cognitive rehabilitations using these applications could be useful to generalize and tune up precision of SoA even in the SoA task using spatial biases.

III. Research Topics

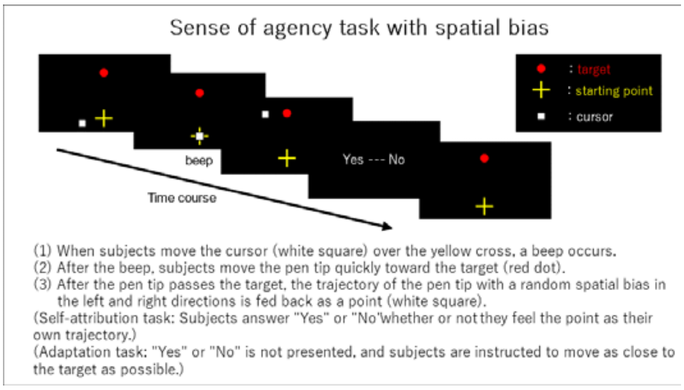
A. The new sense of agency task using spatial biases

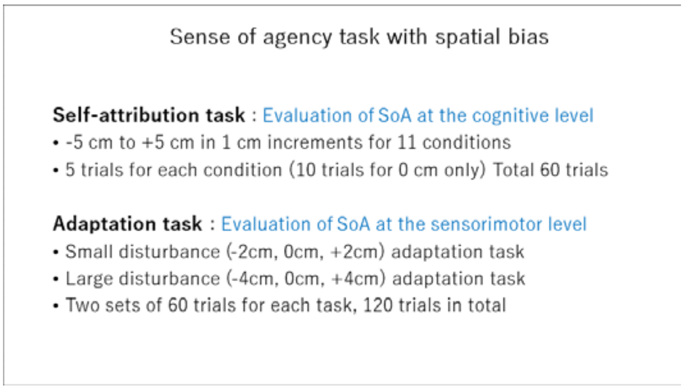
SoA experiments are mainly divided into two types: experiments introducing a temporal bias and experiments introducing a spatial bias. This year, we have developed SoA experiments that introduce a spatial bias. In the spatial bias task, subjects reach the cursor toward the target, but then receive visual feedback of their trajectory with a random spatial bias in the left-right direction. We conduct two types of tasks: a self-attribution task and an adaptation task. In the self-attribution task, SoA at the cognitive level is evaluated based on self-attribution judgments, and in the adaptation task, SoA at the sensorimotor level is evaluated based on adaptation rates. In the self-attribution task, we expect to understand the relationship between time and space in SoA generation by comparing with the results of our previous experiments introducing temporal bias. In the adaptation task, healthy subjects show a higher adaptation rate when the spatial bias increases, but when the spatial bias increases beyond a certain level, they put more weight on their own proprioceptive sense and, conversely, show a lower adaptation rate. However, patients with schizophrenia are likely to relatively put more weight on external information due to the lower accuracy of their own proprioceptive sense (internal model). Therefore, the adaptation rate of patients is expected to increase even when the spatial bias increases above a certain level.

Sense of agency task with spatial bias



Subjects watch the monitor in front of them and move the cursor (white square) quickly from the starting point (yellow cross) to the target (red dot) by operating the pen in their hand. As soon as the subjects start moving the pen, the cursor disappears. As the pentip passes the target, the trajectory of the pen with spatial bias (white square) is visually fed back.

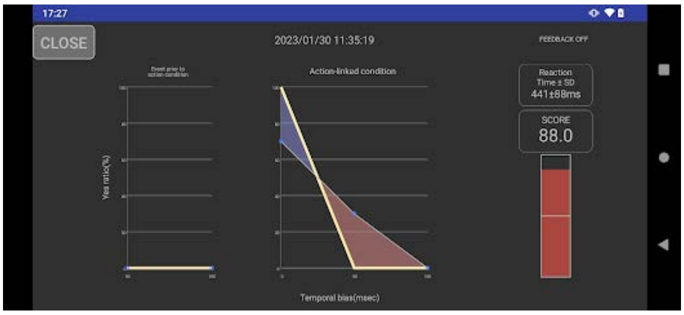




B. Develpopment of *the Agency Tuner for Artists*

We have studied pathophysiology of neurological and psychiatric illnesses from the stand of the SoA. We have developed methods for cognitive rehabilitation of SoA in order to tune up precision of SoA. We have released the application for agency tuning: the *Agency Tuner*, for general use in Japan. We hypothesize that this tuning of SoA could reorganize neural systems of SoA and achieve hyper-adaptation of patients with those illnesses in their living environment.

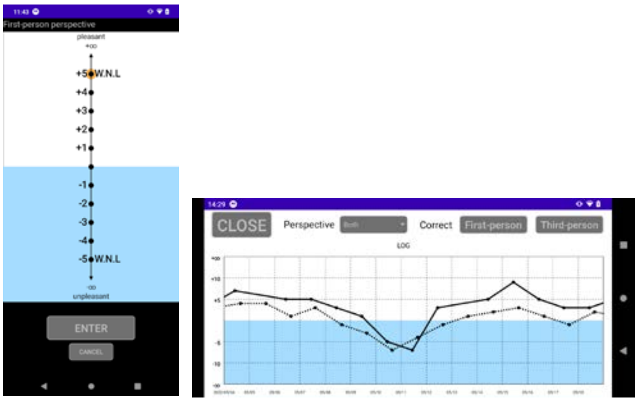
Furthermore, we have arranged the *Agency Tuner* in order to use this methodology for patients with occupational dystonia who are suffering from slump in their professional occupation including musician and athletes. This newly original application is designed to be hard to perform where users must to be highly attentive into the task, and result in the state of no-mindedness.



C. Develpopment of the Mood Swing Monitor

The mood is one of the most important metal state in human daily living. In order to evaluate effects of cognitive rehabilitations of SoA, we developed a new application for monitoring trends of mood swing.

Mood must be monitored form the longitudinal perspective, however, there have been no tool for daily monitoring and evaluating monitor in psychology and psychiatry. Monitoring trends of mood swing is methodologically useful to analyze in the computational neuroscience and psychiatry. we intend to use this new application for monitoring trends of mood swing for evaluating generalized effects of cognitive rehabilitation of SoA.



IV. Future Perspective

We have made advances in developing an original method for cognitive rehabilitation of the SoA: Agency Tuning for Artists, and the Mood Swing Monitor. We will advance clinical experiments of patients, and analyze their leaning processes of predictive models on the SoA for establishing feasible method of cognitive rehabilitation of the SoA, using these applications.

References

[1] Takaki Marda : 「AGENCY TUNER for Artists」 （APP on Google Play in JPN, US, Poland）, Feb 15, 2023.
https://play.google.com/store/apps/details?id=jp.art.re.agencytuner.blp&pli=1

[2] Takaki Maeda : 「Mood Swing Monitor」 （APP on Google Play and Apple Store in JPN, Poland, Turkey）, Nov 26, 2022～Mar 1, 2023.
https://play.google.com/store/apps/details?id=com.moodswingmonitor.blp&hl=jp&gl=jp
https://apps.apple.com/jp/app/mood-swing-monitor/id1658996068
（Japanese Patent-Pending 2022-158647: Shared Monitoring System）

A05-10 Annual report of research project

Tomohiko Takei, Akihiro Masaoka
Brain Science Institute, Tamagawa University

Abstract— **To elucidate the neural mechanisms of "Hyper-Adaptability" that occur during recovery from a large-scale restructure of the central nervous system (e.g., spinal cord injury) or musculoskeletal systems (e.g., tendon transfer), it is necessary to identify the flexibility and constraints of the adaptability of the central nervous system. This research project aims to identify low-dimensional spaces of a frontal-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 asked to perform a context-dependent feedback motor control task, and frontal-parietal cortical neural activity was recorded with Electrocorticogram (ECoG). The results showed that the neural subspaces for motor preparation and motor response were orthogonally arranged. This result was confirmed with the artificial neural network modelling which was trained to solved the similar behavioural task. These results suggests that segregation of neural subspaces for motor preparation and motor response is essential to achieve flexible feedback motor control.**

I. Introduction

In the mammalian central nervous system, acute and chronic injuries are known to 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].

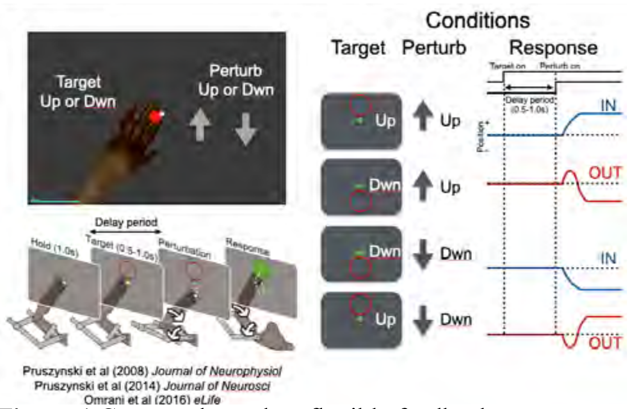


Figure 1 Context-dependent flexible feedback motor control task (INOUT task)

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 common motor learning tasks such as visuomotor rotation and force field adaptation tasks [4]. The coactivation pattern of this neuronal population is called the "neural manifold" and has been shown to be stable over a long term for years [5]. 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 [6]. 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 frontal-parietal cortical neural activity in monkeys to identify neural manifolds, as well as to understand neural dynamics during adaptive behavior based on neural manifolds. In particular, we will clarify what neural dynamics underlie the flexible feedback motor control by comparing the results of neural recordings with artificial neural circuit models.

III. Research Topics

A. Establishment of a technique for recording frontal-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 the task 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 start 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). One monkey that had completed training was implanted with electrodes of a 32-channel cortical electroencephalogram (ECoG). As a result, we succeeded in simultaneously recording the cortical activity of dorsal premotor, primary motor, primary somatosensory, and parietal 5 areas during the task.

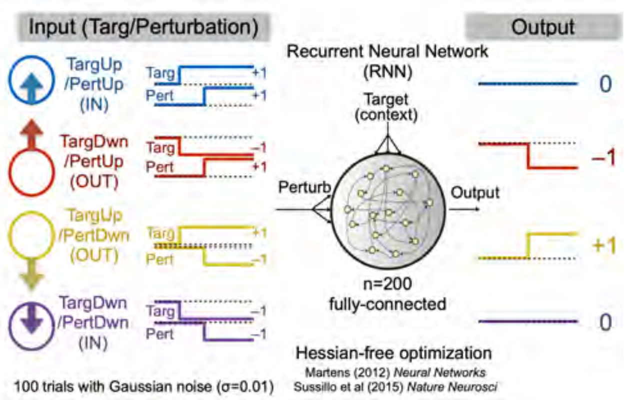


Figure 2 Artificial neural network model for a flexible feedback motor task.

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

We performed frequency decomposition with Wavelet transformation and dimensionality reduction with Principal Component Analysis on the ECoG signals during this task to examine the neural subspace during motor preparation and motor response. The results showed that the neural subspaces during motor preparation and motor response were orthogonal to each other in the neural space. This result was confirmed by building a recurrent neural network model that was trained to generate a similar input-output relation and finding that a similar orthogonality emerged in the trained network (Figure 2). This suggests that the orthogonality of the neural subspaces represents an important neural activity structure for flexible feedback motor control.

IV. Future Perspective

This year, we trained two monkeys in a flexible feedback response task and recorded fronto-parietal cortical activity (ECoG) in one monkey. The results revealed that the neural subspaces during motor preparation and motor response were orthogonal. This orthogonality was reproduced in the artificial neural network, suggesting that the orthogonality is an important feature for flexibly switching a feedback gain. In the next year, we plan to record frontal-parietal cortical potentials in one more individual to examine the homology and differences between individuals.

References

[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] 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.

A05-11 Annual report of research project

Hironobu Osaki
Doshisha University Graduate School of Brain Sciences

***Abstract*— During the acute phase of stroke, alterations in the central nervous system, such as disinhibition, would facilitate functional rapid recovery. During the chronic period, however, functional recovery becomes slower. Consequently, enhancing functional recovery during the chronic phase of stroke is crucial for improving rehabilitation outcomes. To establish a new strategy for accelerating the rate of recovery, we first created a macro Ca2+ imaging system in combination with a rodent motor task. Monitoring the behavior of mice before and after a motor cortex infarction allowed us to successfully examine the activity of the motor cortex. We have designed an X-Y galvo-controlled laser stimulation system of the motor cortex during behavior to regulate neural network activity. By utilizing these systems, we will attempt to identify the circuits that promote functional recovery during the chronic phase of stroke.**

I. INTRODUCTION

Cortical infarction induces loss of function, which will be partially recovered in the acute phase with the help of restored neural circuit compensations. These compensations are thought to be involved in the disinhibition of the whole brain network. In the primary motor cortex (M1) infarction, we have shown that such disinhibition disrupted sensory processing in the primary somatosensory cortex through the cortico-cortical network in the acute phase and recovered in the sub-acute phase of stroke [1]. Due to this disinhibition may recruit residual circuits may be activated to compensate for the function of the damaged brain area. In the chronic phase of stroke, these alterations and functional recovery, however, slow down and persist.

In this study, we use the rodent M1 infarction model. However, the network from M1 to spinal motoneuron is quite different between rodent and primate, including human [2]. For example, the rodent has no direct excitatory input from M1 to the spinal motoneuron, and this excitatory input increases according to the increase of the ability of fine hand movement [2]. Therefore, in rodents, most motor functions could be controlled indirectly by M1 but directly by the subcortical network that includes the brain stem [3].

II. AIM OF THE GROUP

Taking into account the differences between the neural networks of rodents and humans, our group focuses on the change of the neural network from the acute phase to the chronic phase of stroke and will attempt to identify the circuits that promote functional recovery. More specifically, we use a behavioral task that requires skilled motor behavior combined with Ca2+ imaging and electrophysiological recording. Using these systems, we will monitor the neural activity before and after M1 infarction. Our goal is to find the ways that neural circuit mechanisms to enhance functional recovery after an infarction.

III. RESEARCH TOPICS

A. Ladder rung walking task for monitoring M1 recovery after infarction

First, we developed a ladder-rung walking task, which is widely used to measure motor dysfunction after M1 infarction in rodents [4]. The movement of each limb is monitored by multiple cameras. Our custom program combined with Deeplabcut[5] automatically detects the limb falling. The M1 infarction was made by photothrombotic infarction previously reported [1]. After Rose Bengal was injected intraperitoneally, a green LED was illuminated on the M1. The size and position of infarction were controlled by the power of illumination and the position of optical fiber on the brain surface. We successfully observed the increase in the fall rate of the contralateral limbs to the M1 infarction. Using this index, we will examine recovery after M1 infarction.

Fig. 1. Falling limb detection in ladder rung walking task. The falling limb was detected by combining with pose tracking of limb position by DeepLabCut and each limb's speed, and distance from the ladder.

B. In vivo macro Ca^{2+} imaging system

Second, we developed in vivo macro Ca2+ imaging system and optogenetic laser stimulation system (Fig. 2, 3). This imaging system can observe the area 3 x 3 mm of Ca^{2+} signal (GCaMP6f) at 25 Hz for each 490 (blue) and 405 nm (violet). The 405 nm wavelength illumination was an isosbestic point of the GCaMP signal, which is thought of as Ca^{2+} independent fluorescence (⊿R). These signals are also included in the signal observed at 490 nm wavelength (⊿F), especially in macro-imaging. Therefore, we removed this noise from activity-dependent Ca^{2+} signal by the following equation. ⊿R was multiplied with **a** to fit with ⊿F[6].

$$\triangle Fc = \triangle F - a\triangle R \quad (1)$$

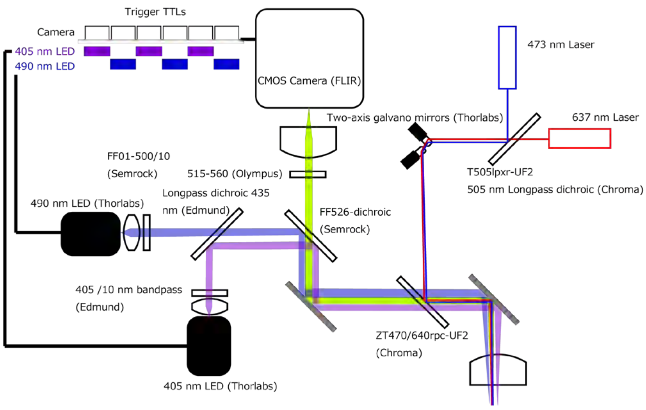


Fig. 2. System for macroscopy for GCaMP Ca^{2+} signal and optogenetics laser stimulation. Left, the unit for macro-imaging Ca^{2+} signal. Excitation LEDs (409 and 490 nm) were alternately controlled by TTL signals, which is also synchronized with CMOS camera shutter. Right, the light path for optogenetic activation and inhibition. The two wavelength lasers are combined with a dichroic filter and stimulate the specific region controlled by two-axis galvano mirrors. The optical fiber and the scan lens were not shown in this schema. The dichroic filter (ZT470/640rpc-UF2) is used during optical stimulation but removed during the imaging session.

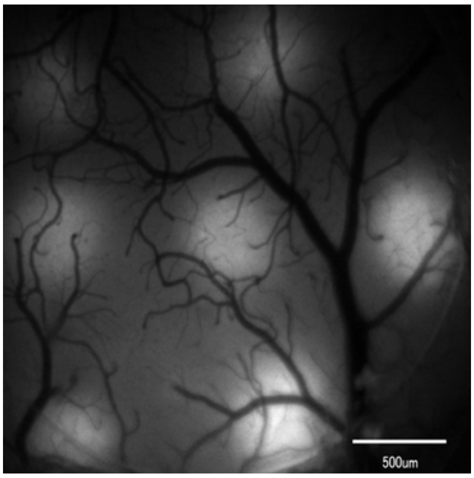


Fig. 3. Macroimaging of GCaMP6f signal in M1. Scale bar: 500μm。

This imaging and optogenetics stimulation system were modified from the system used in our system previously reported[7], showing the nociceptive region in the primary somatosensory cortex. This work was also supported by the area of Hyper-adaptability.

IV. Future Perspective

Using these systems, we will investigate the change in neural activity following the M1 infarction. We will also examine the specific circuit that induces functional recovery by optogenetic neural activity modulation. The Ca2+ imaging system can only detect the signal of neural activity from the brain surface. Therefore, we will also use an electrophysiological recording system and acquire the activity from the deeper brain, such as the deeper cortex, striatum, and thalamus in the next year. We aim to control neural activity and improve functional recovery during the chronic phase of stroke.

References

[1] Fukui, A., H. Osaki, Y. Ueta, K. Kobayashi, Y. Muragaki, T. Kawamata, and M. Miyata, *Layer-specific sensory processing impairment in the primary somatosensory cortex after motor cortex infarction.* Scientific reports, 2020. **10**(1): p. 3771.

[2] Lemon, R.N., *Descending pathways in motor control.* Annu Rev Neurosci, 2008. **31**: p. 195-218.

[3] Ruder, L., R. Schina, H. Kanodia, S. Valencia-Garcia, C. Pivetta, and S. Arber, *A functional map for diverse forelimb actions within brainstem circuitry.* Nature, 2021. **590**(7846): p. 445-450.

[4] Bechay, K.R., N. Abduljawad, S. Latifi, K. Suzuki, H. Iwashita, and S.T. Carmichael, *PDE2A Inhibition Enhances Axonal Sprouting, Functional Connectivity, and Recovery after Stroke.* J Neurosci, 2022. **42**(44): p. 8225-8236.

[5] Mathis, A., P. Mamidanna, K.M. Cury, T. Abe, V.N. Murthy, M.W. Mathis, and M. Bethge, *DeepLabCut: markerless pose estimation of user-defined body parts with deep learning.* Nat Neurosci, 2018. **21**(9): p. 1281-1289.

[6] Allen, W.E., I.V. Kauvar, M.Z. Chen, E.B. Richman, S.J. Yang, K. Chan, V. Gradinaru, B.E. Deverman, L. Luo, and K. Deisseroth, *Global Representations of Goal-Directed Behavior in Distinct Cell Types of Mouse Neocortex.* Neuron, 2017. **94**(4): p. 891-907 e6.

[7] Osaki, H., M. Kanaya, Y. Ueta, and M. Miyata, Distinct nociception processing in the dysgranular and barrel regions of the mouse somatosensory cortex. Nat Commun, 2022. **13**(1): p. 3622.

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. This year, we designed a task to discriminate the attentional network damaged in hemispatial neglect and developed an Augmented reality (AR) intervention system.**

I. Aim of the Group

A. Development of the Attention Network Assessment Method for hemispatial neglect

Psychological and neuroscientific findings indicate that there are two types of spatial attentional networks: those that work actively, such as selecting and focusing attention on an object (top-down attention network), and those that respond passively to suddenly appearing salient stimuli (bottom-up attention network). The former consists mainly of the prefrontal cortex of the bilateral hemispheres, including the frontal eye fields, and the posterior parietal lobes and is called the dorsal attentional network. The latter consists mainly of the insular cortex, temporal-parietal junction and inferior frontal gyrus in the right hemisphere and is called the ventral attentional network [1]. In hemispatial neglect, symptoms and the recovery process may also differ depending on which of these networks is damaged; Karnath et al [2] have shown that hemispatial neglect that persists into the chronic phase is confined to the damage in right temporal lobe. Deficit in bottom-up attention in hemispatial neglect due to damage to ventral attention network may have a poor prognosis, but may be unnoticed by the therapist or the patient, causing difficulties in life after discharge.

In clinical situations, the Behavioural Inattention Test (BIT) is commonly used to detect semi-lateral spatial neglect. The BIT consists of several desk tests, such as line bisection test, line cancellation test, and design copying test, but despite a negative BIT result for hemispatial neglect, neglect symptoms are sometimes observed in daily life situations, and not all neglect symptoms can be revealed by the BIT test. In recent years, the Posner cue paradigm, which applies psychological experiments, has been shown to be superior in detecting hemispatial neglect [3]. However, both of these assess disorders in a top-down attention and do not differentiate it from disorders in bottom-up attention. In the present study, therefore, the LANT (lateralised attention network test) paradigm [4], which can detect both bottom-up and top-down attention, was modified to adapt it to cases of patients with hemispatial neglect in order to detect which of the two networks is more impaired. By measuring gaze at the same time, the relationship between attention and gaze will also be investigated.

B. Development of AR-based intervention systems for hemispatial neglect

One of the clinically applied treatments for hemispatial neglect is prism adaptation, where prism glasses shift the visual space to the right by 10-15 degrees and patients adapt their movements under the shifted environment, which is known to sometimes improve the symptoms of hemispatial neglect after the glasses are removed [5]. Systems have also been proposed that use virtual reality (VR) to perform tasks under the shifted virtual environments to encourage attention to the left [6]. However, although prism glasses can manipulate real space, they have optical limitations, and VR is limited in its generalization to real space. In this regard, the use of AR, which is technologically advanced and offers improved resolution and real-time performance, could be a possible option. With AR, significant spatial transformations are possible, such as shifting the entire real space to the right space, where attention is allocated, and displaying it in real time. If the brain can hyper-adapt to an environment in which the entire real space is displayed in right space, it could be used by hemispatial neglect patients in their daily lives as glasses to correct visual space. They could also be used for recovery training, such as gradually returning the space presented in the right to the left and directing attention to the left.

II. Progress made ni this fiscal year

A. Development of the Attention Network Assessment Method for hemispatial neglect

To assess top-down and bottom-up attention simultaneously, we designed the task shown in Fig. 1. The task consists of a preceding cue stimulus (Fig. 1b) and a target stimulus (Fig. 1c). The cue stimulus directs passive attention to the left space or the right space or both and can detects bottom-up attention by its presence or absence. Target stimuli detect top-down attention by actively directing attention to the direction of an arrow that appears in the center in a Franker-type task consisting of congruent (adjacent arrows are the same direction with target arrow) and incongruent (adjacent arrows are the opposite direction with target arrow) stimuli. Reaction times and gaze to stimuli presented in left and right space are measured and quantitatively assessed to determine whether bottom-up or top-down attention results in shorter reaction times and guided gaze. In addition, stimulus locations were subdivided and presented in order to accommodate the visual space of hemispatial neglect (Fig. 1d).

In this fiscal year, we completed the development of the task has been completed and we plan to run a feasibility study on healthy participants and on patients with hemispatial neglect.

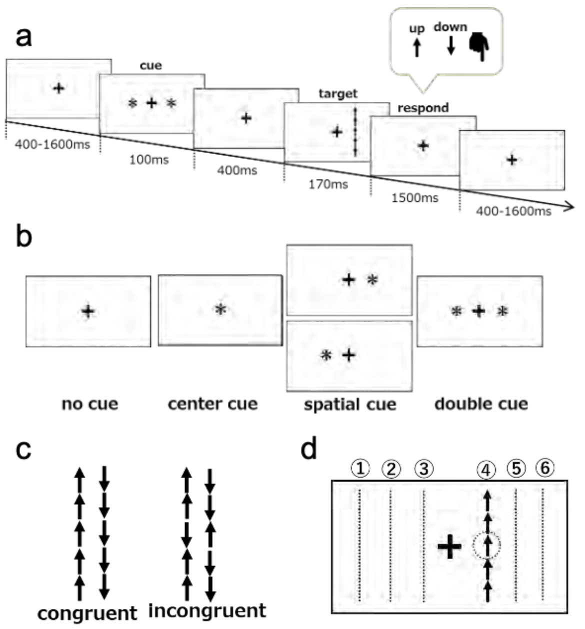


Fig. 1. Experimental paradigm

B. Development of AR-based intervention systems for hemispatial neglect

A system that transforms and presents real space using AR technology was developed: a special camera (ZED mini) was attached to the front of VR goggles (HTC VIVE pro eye) to capture images of the real world as seen by the subject, which was processed in real time and presented on the screen of the VR goggles (Fig. 2). In cases of hemispatial neglect, the subject did not perceive the left space, so information on the entire space, including the left space, was presented in the right visual field of each VR screen of the left and right eyes.

The development of the system was completed this year, and the wearing feeling of the system in patients with hemispatial neglect will be tested in the next step.

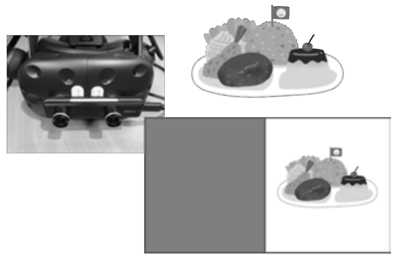


Fig. 2. Experimental paradigm

III. Future Perspective

We designed a task to discriminate the attention network damaged in hemispatial neglect and developed an AR-based intervention system this year. We will implemented and evaluated these system with patients with hemispatial neglect.

References

[1] M. Corbetta and G.L. Shulman, "Spatial neglect and attention networks," Annu Rev Neurosci, 34, pp. 569-99, 2011.

[2] H.O. Karnath, J. Rennig, L. Johannsen, and C. Rorden, "The anatomy underlying acute versus chronic spatial neglect: a longitudinal study," Brain, 134(Pt 3), pp. 903-12, 2011.

[3] J. Rengachary, G. d'Avossa, A. Sapir, G.L. Shulman, and M. Corbetta, "Is the posner reaction time test more accurate than clinical tests in detecting left neglect in acute and chronic stroke?," Arch Phys Med Rehabil, 90(12), pp. 2081-8, 2009.

[4] D.J. Greene, A. Barnea, K. Herzberg, A. Rassis, M. Neta, A. Raz, and E. Zaidel, "Measuring attention in the hemispheres: the lateralized attention network test (LANT)," Brain Cogn, 66(1), pp. 21-31, 2008.

[5] 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.

[6] 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.

A05-13 Annual report of reseach project

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

***Abstract*— In the treatment of spinal cord injury and traumatic brain injury, it is believed that adult nerve axons do not regenerate, and there is no fundamental treatment. Therefore, many attempts such as iPS cell transplantation are being tried for spinal cord injury treatment. The various trials to apply molecules that promote nerve axonal regeneration to drug discovery have also been made in model animals around the world. We develop applications to this problem by applying new concepts and methods of preserving lost circuits and exploiting latent circuits. Furthermore, we are trying to build a system that can estimate the functional recovery of model animals to humans using an AI learning system.**

One of the new methodologies is the application of synaptic connectors. Synapse connector "CPTX" is an synthetic chimeric protein inspired by a synaptic organizer "Cbln1", and has rapid and strong synaptic formation ability by cross-linking pre-and post-synaptic molecules. We have shown that this synaptic connector enables recovery from chronic-phase of spinal cord injury (chronic-SCI) models. This chronic phase was difficult despite various trials for recovery of SCI. In addition, a synaptic connector and a system for improving the regenerative environment that facilitates the hyper-adaptation have been prepared. In order to analyze the physiological recovery process by these interventions after SCI, we also proceeded with the constructions of AI systems that analyzes motor function in detail. Taking advantage of this result, we will challenge the control of inhibitory neuronal circuits using next generation- synaptic connectors.

I. INTRODUCTION

We attempt to establish the super-recovery mouse from SCI by inducing artificial synapse connect and providing extra cellular matrix field suitable for regeneration. This mouse will allow us to dissect the neural basis of adaptive circuits during recovery. To evaluate how the adaptive neural circuits generate the locomotory outputs, we are constructing the novel motion capture analysis system operated with AI algorithm. This system could detect and extract the behavioral elements specific to the super-recovery mouse. We aim that our AI motion capture system will become powerful and rigorous system for high-throughput analysis of rodent behaviors. This research consists of the principal investigator (Takeuchi), the research collaborators in our lab (Dr. Sasakura, Dr. Ikeno (Aichi medical Univ.). and the collaborators (Dr. Yuzaki (Keio Univ.), Dr. Yanagihara (University of Tokyo)).

II. AIM OF THE GROUP

The purpose of this research is to (1) further explore the function of synapse- connectors, and (2) simultaneously improve the regeneration environment by suppressing the expression of the regeneration-inhibitor chondroitin sulfate (CS). We propose a regeneration model from the subacute stage to the chronic stage, which has been difficult to treat until now. Furthermore, we will try to develop new synaptic-connectors and apply them to the spinal cord. The correlation with the physiological recovery process at that time will be examined with the aim of promoting the extraction of important factors and a versatile physiological function recovery evaluation system while promoting interventions such as rehabilitation.

III. RESEARCH TOPICS

A. The recovery of the chronic and sub-acute phase of SCI by CPTX

Our group (Takeuchi), Dr. Sasakura as a leading role of the project, has conducted studies of recovery from spinal cord injury using an artificial synaptic connector (named CPTX). As an international collaborative study with Oxford University & MRC Radu Aricescu in the United Kingdom and DZNE Alexander Dityatev in Germany, we reported that CPTX have outstanding property of restoring neurological function in Alzheimer's model mouse and cerebellar ataxia, and in SCI (Science. 2020) [1]. CPTX is a novel synthetic molecule that crosslinks a presynaptic molecule (Nrx: neurexin) and a postsynaptic molecule (AMPAR: AMPA receptor)(Fig1). It was created as an artificial chimeric protein (CPTX) in which Nrx binding domain of Cbln1 and AMPAR binding domain of NP1 are joined.

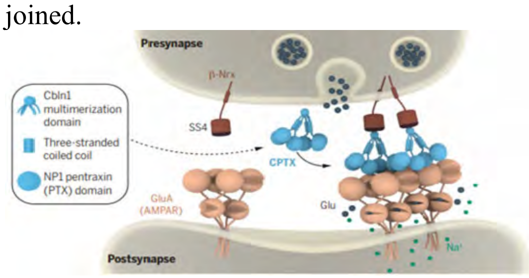


Fig1 Strategy of Synaptic connector

Last year, we tried if CPTX is effective to chronic phase of SCI. It is well known that recovery of chronic phase of SCI is extremely difficult. Despite the difficulty, majority of patients suffering from SCI are clinically chronic phase. CPTX restored the chronic phase of SCI. CPTX injection activated the hind leg movement within a few days, which otherwise showed the permanently poor movement.
Furthermore, from the design and synthesis of novel synaptic connectors (Fig. 2), we started to analyze spinal cord injury and motor function. In particular, we attempted to analyze new connectors that are more specific than CPTX for excitatory synaptic receptors and connectors for inhibitory nerves. At present, no drug that surpasses CPTX in terms of recovery function has been obtained, but one that enhances sensory receptor function has been obtained. In addition, we found that the recovery after spinal cord injury was delayed in connectors for inhibitory synapses. We believe that this is a delay in recovery due to the suppression of the disinhibition function, and we are proceeding with the investigation. From these, we showed that the new concept of neural circuit reorganization connection can be a powerful analytical tool [3]

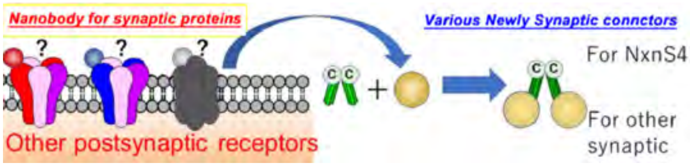


Fig2 Strategy for other synaptic connectors

B. Regenerative environment maintenance and super-recovery model by suppressing nerve regeneration inhibitors and analysis of sensory reception

The dramatic post-injury recovery of chondroitin sulfate (CS) KO mice, which is the greatest inhibitor of nerve regeneration after spinal cord injury, has demonstrated the effectiveness of its application [4] [5]. Aiming at clinical application, furthermore, for circuit formation and functional analysis, we have been developing antisense oligos (ASO) that can knock down the expression in a tissue site-specific manner, and have obtained effective ASOs by last year. We analyzed changes in sensory reception at synaptic connectors along with recovery by this ASO. It was clarified that ASO to chondroitin sulfate decreases pain reception, and that the above-mentioned synaptic connector CPTX does not increase sensory reception (lower pain threshold). Considering the application, it led to the fact that it is extremely effective without the possibility of causing allodynia.

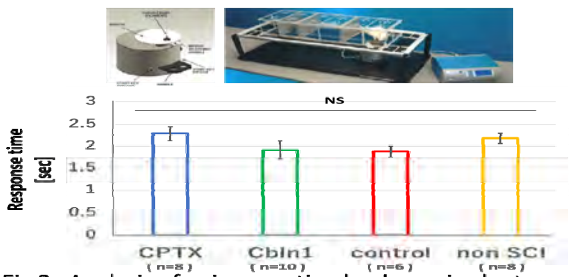


Fig 3 Analysis of pain reception by dynamic planters

C. Construction of AI trace system and capture of behavioral parameter in hyper-adaptability mouse

Using a super-recovery model after spinal cord injury, we are proceeding with thorough walking function analysis, such as the introduction of AI, in order to obtain the correlation of neural reorganization through quantitative motor function analysis and extraction of its factors.
From the analysis and comparative examination in various time series, we succeeded in extracting a characteristic recovery pattern in super recovery by inducing artificial synaptic connections by CPTX administration. In addition, we will analyze the application of analysis to chronic treatment, the effect of rehabilitation, and the motor function in disinhibition.

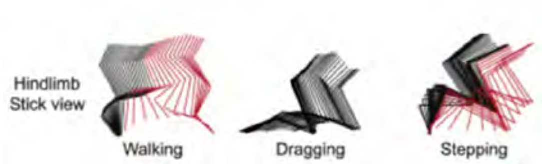


Fig 4 Analysis of Hindlimb movement by motion capture

III. Future perspective

In the application of synaptic connector CPTX to spinal cord injury, we obtained results such as adaptation to the chronic phase. It is now possible to extract important elements of physiological function recovery by AI tracing from this recovery process and analyze the correlation with the connection circuit. From these analyses, it is also becoming clear that "restoration of sensory reception" is important for improving physiological function [6]. The final goal of this research, the hyperadaptive function by "disinhibition", was analyzed from this spinal cord injury model using a novel synaptic connector, and an analysis was started to directly prove the function of the inhibitory circuit in physiological recovery. From the analysis of the correlation with physiological functions, we plan to proceed with the artificial intervention for hyperadaptation and its analysis.

References

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

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

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

[4] Takeuchi K. et al., Chondroitin sulphate N-acetylgalactosaminyl-transferase-1 inhibits recovery from neural injury. Nat. Comm. 4, 2740 (2014)

[5] Mercedes Balcells, “Two Proteins, One Stone” Science Translational Medicine 11:5, Issue 215, pp. 215ec203 (2014)

[6] 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 (2021)

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—**In FY2022, we established a methodology for simultaneous recording of transcranial magnetic stimulation (TMS) and electroencephalogram (EEG). To evaluate human functional neural networks noninvasively and quantitatively, multichannel EEG was continuously recorded while TMS was applied to the primary motor cortex (M1). TMS evoked potentials (TEP) obtained in contralateral M1 are thought to reflect interhemispheric inhibition (IHI). Therefore, IHI asymmetry has been considered a biomarker of poor recovery in previous studies of stroke patients. In FY2023, we plan to apply this methodology 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 FY2022 are as follows.
(1) We published several research papers on human motor control [1, 2].
(2) We published several case reports on the application of stroke rehabilitation methods to neuro-degenerative disorders [3, 4].
(3) We published review articles on "meta-plasticity" and "N-of-1 studies" which are related to hyper-adaptation [5, 6].
(4) The TMS-EEG method was studied on healthy subjects, and the recording and analysis method was established.
(5) We initiated 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).

II. Aim of the Group

The purpose of this study is to explore neural connections that are latent in healthy subjects but become active during the process of hyper-adaptation by measuring functional neural networks using TMS/tSMS-EEG and elucidating the specificity of neural network reconstruction in hyper-recovering individuals.

III. Research Topics

Two major specific results for FY2022 are listed below and outlined respectively.

A. Hyper-adaptation from the Perspective of N-of-1 Trials

The concept of evidence-based medicine (EBM) that dominates rehabilitation science today emphasizes statistical tests of average efficacy in a patient population. As a result, it has been difficult to conduct research on hyper-recovering individuals, who are highly singular. Therefore, this research project aims to conduct exploratory research to create "new questions and innovative working hypotheses" for brain reconstruction from single individualized data from the perspective of precision medicine and N-of-1 trials [7].

This can be paraphrased as a theoretical paradigm that emphasizes the perspective of "exception" and "minority" with respect to “hyper” in the concept of hyper-adaptation. In other words, we approach exceptional events such as hyper-adaptation and hyper-recovery from the viewpoint of individual case singularity (N-of-1), which does not fit into group averaging and standardization. For this reason, it is necessary to create experimental protococls that are strictly randomized and blinded, with controls set up within individual subjects. We formulated the methodology for applying such methods to clinical neuroscience research [5].

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).

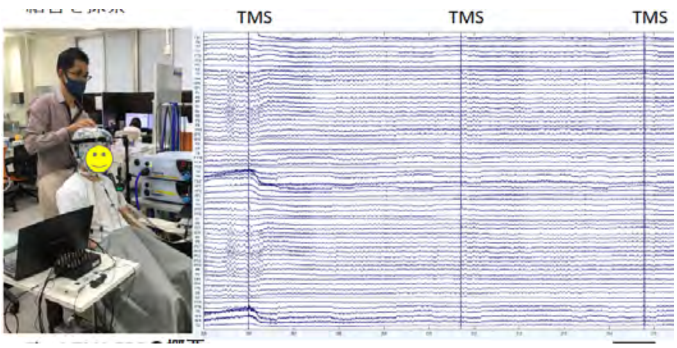


Figure 2: TMS-EEG recording (left) and raw EEG waveforms without pre-processing (right).

Ten right-handed healthy adults (22.2 ± 0.6 years old, 6 males) were recorded with a 64-channel EEG (sampling frequency: 5 kHz). The TMS was given by Magstim-200 and a figure-8 coil at the M1 of the right first dorsal interosseous muscle (n = 120). The intensity was set to the resting motor threshold.

EEG data were down-sampled to 1 kHz, formatted with respect to the global mean, and epoched for 1 second before and after TMS. Then, to remove artifacts due to TMS, artifact estimation and removal by signal source, removal of non-brain signal components by ICA method, and removal of AC noise components by band-stop filtering were performed, and then averaged.

As a result, we succeeded in detecting the following TEP components reported in previous studies: the largest positive potential, P30, at the left M1, the site where TMS was given, the negative potential, N45, found at contralateral M1, and N100, a negative potential widely found in the frontal and central regions.

The TEP obtained at contralateral M1 is thought to reflect interhemispheric inhibition (IHI). Therefore, asymmetry of IHI is a biomarker of poor recovery in previous studies on stroke victims [8]. There are also reports that alpha wave power induced in M1 by TMS, but not TEP, is a good biomarker that correlates with recovery [9]. As a next step, we plan to record these parameters in hyper-recovering stroke survivors.

IV. Future Perspective

In the first year of the study, we clarified the theoretical basis for the importance of studying "hyper-recovering" stroke survivors and established a method for analyzing TMS-EEG recordings in healthy subjects. In FY2023, we will analyze neural networks by TMS-EEG and tSMS-EEG in subjects who are hyper-recovering from stroke.

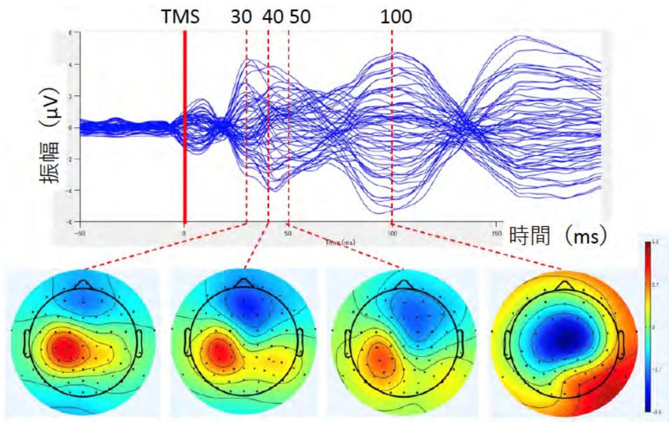


Figure 3: Superimposition of TEP waveforms in one subject (upper) and the scalp topography of TEP at 30, 40, 50 and 100 ms (lower).

References

[1] Shibata, S., Watanabe, T., Matsumoto, T., Yunoki, K., Horinouchi, T., Kirimoto, H., Zhang, J., Wang, H., Wu, J., Onishi, H., & Mima, T. (2022). Triple tSMS system ("SHIN jiba") for non-invasive deep brain stimulation: a validation study in healthy subjects. *Journal of NeuroEngineering and Rehabilitation*, 19(1), 129.

[2] Shibata, S., Watanabe, T., Otsuru, N., Onishi, H., Mima, T. (2023) Very low-frequency transcranial electrical stimulation over the primary motor area can influence the voluntary movement initiation in humans. *Brain Stimulation* 16(2): 442-444.

[3] Shima, A., Tanaka, K., Ogawa, A., Omae, W., Miyake, T., Nagamori, Y., Miyata, Y., Ohata, K., Ono, Y., Mima, T., Takahashi, R. *Koganemaru, S. (2023) Case Report: Backward gait training combined with gait-synchronized cerebellar transcranial alternating current stimulation in progressive supranuclear palsy. *Frontiers in Human Neuroscience-Brain Imaging and Stimulation* 17

[4] Shima, A., Miyake, T., Tanaka, K., Ogawa, A., Omae, E., Nagamori, Y., Miyata, Y., Ohata, K., Maki, T., Ono, Y., Mima, T., Takahashi, R. *Koganemaru, S. (2023) Case report: A novel approach of closed-loop brain stimulation combined with robot gait training in post-stroke gait disturbance. *Frontiers in Human Neuroscience-Brain Imaging and Stimulation* 17

[5] Mima, T., et al. (2022) How to perform N-of-1 trials? *The Japanese Journal of Rehabilitation Medicine* 59(11): 1111-1117.

[6] Mima, T. (2022) Meta-plasticity. *Journal of Clinical Rehabilitation* 31(6): 567-570.

[7] Mirza RD, Punja S, Vohra S, Guyatt G.(2017) The history and development of N-of-1 trials. *J R Soc Med*: 110(8): 330–340.

[8] Casula, E. P. et al. (2021) Evidence for interhemispheric imbalance in stroke patients as revealed by combining transcranial magnetic stimulation and electroencephalography. *Hum Brain Mapp*. 42:1343–1358.

[9] Pellicciari, M. C., et al. (2018) Dynamic reorganization of TMS-evoked activity in subcortical stroke patients. *NeuroImage*, 175: 365–378.

A05-15 Annual report of research project

Atsushi Nambu, Professor, National Institute for Physiological Sciences
Nobuhiko Hatanaka, Assistant Professor, National Institute for Physiological Sciences
Satomi Chiken, Assistant Professor, National Institute for Physiological Sciences
Pimpimon Nondhalee, NIPS Research Fellow, 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) indicate that the face region may have expanded to the lost hand region in the M1. However, such expansion of the face region could not be observed in the ICMS mapping on nonhuman primates. Studies on somatotopic differences between the healthy and affected sides after loss of the forelimb and hindlimb in the monkey M1 found that neuronal activity in the lost body part codes 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 lose 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.

On the other hand, 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 and the posterior bank of the central sulcus. 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 spino-thalamic 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 (Figure 1).

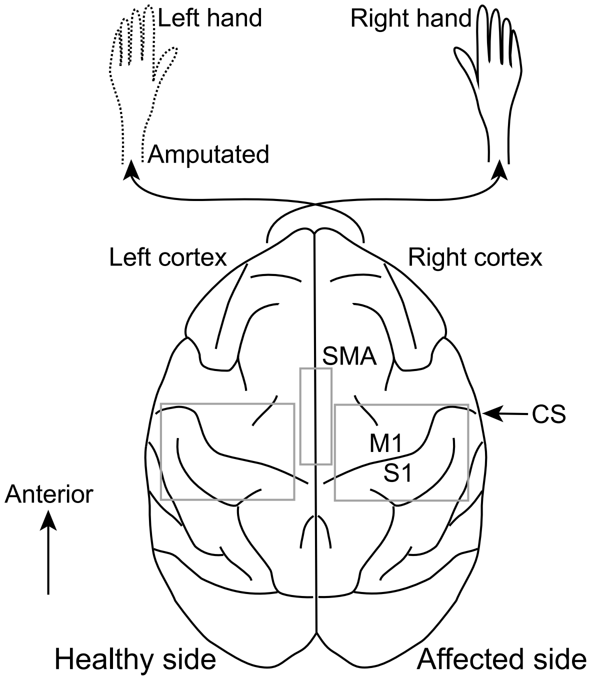


Figure 1. Somatotopic arrangements in the M1, SMA, and S1 of Japanese monkeys were examined by ICMS-evoked movement and somatosensory inputs under awake states, and their differences between healthy and affected sides were compared.

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: 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). 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. 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.

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. 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— **Compensatory plastic changes in the remaining intact brain regions are supposedly involved in functional recovery following stroke. Previously, a compensatory increase in cortical activation occurred in the ventral premotor cortex (PMv), which contributed to the recovery of dexterous hand movement in a macaque model of unilateral internal capsular infarcts. In this project, 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 a macaque model. We observed significant increases in the gray matter volume (GMV) and the dendritic arborization of layer V pyramidal neurons in the contralesional rostral PMv. Therefore, compensatory structural changes occur in the area during motor recovery following internal capsular infarcts, and the dendritic growth of pyramidal neurons is partially correlated with GMV increase. In addition, using a macaque model of central post-stroke pain (CPSP), we have confirmed the involvement of increased activity of the posterior insular cortex (PIC) and secondary somatosensory cortex (SII) to somatosensory stimuli in mechanical allodynia by a combination of imaging techniques with local pharmacological inactivation. However, it is unclear whether the same intervention would be effective for thermal hyperalgesia. Therefore, using the macaque model, we examined behavioral responses to thermal stimuli following pharmacological inactivation of the PIC/SII. Our data emphasize that increased activity in the PIC/SII after appearance of thalamic lesions can contribute to abnormal pain of multiple modalities and modulation of PIC/SII activity may be a therapeutic approach for thermal hyperalgesia.**

I. Introduction

When the brain is damaged, the function of the lost brain region is impaired, however, brain function can be restored through rehabilitative training. This is a typical example of "hyper-adaptivity" of the brain. Elucidating these changes will lead to innovative neurorehabilitation technologies that induce appropriate changes in the brain.

II. Aim of the Group

We have been studying the recovery process after damage to the primary motor cortex, which is the central region of motor output from the brain, using macaque monkeys, which have a similar brain and musculoskeletal structure to humans, as a model animal. As a result, it was found that flaccid paralysis occurs after primary motor cortex lesion, but rehabilitative training after lesion accelerates the recovery of precision grip [1]. In addition, our brain imaging analysis suggested that changes of brain activity occur in uninjured motor areas during recovery of precision grip after the primary motor cortex lesions [2]. However, clinically, cerebral hemorrhage or infarction in the subcortical white matter is often a problem. The purpose of this study is to gain knowledge that can be seamlessly applied to clinical practice by studying macaques that have created infarcts and hemorrhages in the subcortex.

III. Research Topics

A. Structural chnages after focal infarction of the macaque internal capsule

Structural changes in neurons are thought to underlie functional recovery and accompanying compensatory changes in brain activity after cerebral infarction. We therefore performed voxel-based morphometry (VBM) analysis using T1-weighted MRI and immunohistochemical staining in a previously established macaque model of internal capsular infarction [3]. Previous studies using functional near-infrared spectroscopy (fNIRS) to measure macaque motor cortex activity during grasping tasks have shown that before infarction, there was increased activity in the hand area of the primary motor cortex with the performance of grasping movements whereas increased activity in the ventral part of the premotor cortex was observed during functional recovery [4].

The results of VBM analysis suggested that gray matter increased in the ventral part of the contralateral premotor cortex during the period of motor function recovery after infarction (Fig. 1) [5].

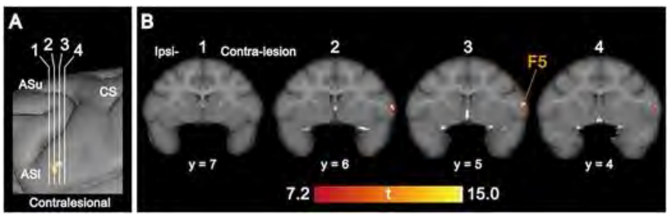


Fig. 1. Brain regions displaying a significant GMV increase post infarction. A) Vertical white lines indicate the location of the coronal slices displayed in B. B) Significant GMV increase is observed in the contra-F5 as one consecutive cluster with a maximum at the third slice (x, contra-ipsilateral = 24.0, y, rostrocaudal = 5.0, and z, dorsoventral = 4.0). The cluster-defining threshold is set at Puncorrected < 0.001, with an extent threshold Pcorrected < 0.05 (FWE correction). The scale bar indicates the T score. F5, ventral–rostral part of the premotor cortex; CS, central sulcus; ASu, upper limb of the arcuate sulcus; ASl, lower limb of the arcuate sulcus.

Immunohistochemical staining using SMI-32 antibody, which stains pyramidal cells, revealed degeneracy of pyramidal cells in layer V of the primary motor cortex in the ipsilateral hemisphere of the infarct. This may be due to retrograde neurodegeneration after the internal capsular infarction (Fig. 2). On the other hand, pyramidal cells in layer V of the ventral premotor cortex showed increased dendritic branching. These results suggest that compensatory structural changes in motor output cells in the ventral part of the contralateral premotor cortex are important for the recovery of motor function after infarction and that structural changes in dendrite projections underlie the GMV changes observed in the VBM analysis.

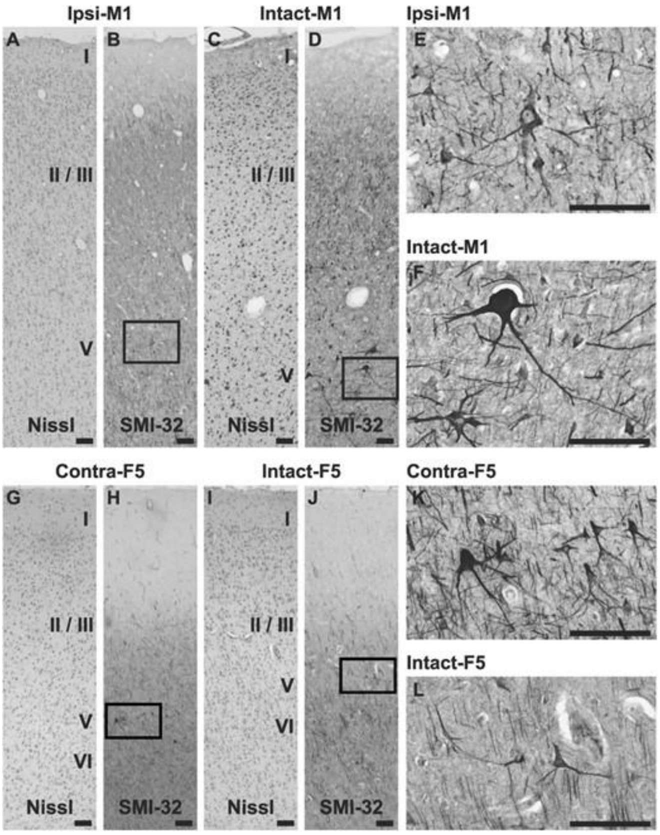


Fig. 2. IHC using SMI-32 antibody in M1 (A–F) and F5 (G–L). A, C, G, and I) Nissl-stained sections adjacent to the SMI-32 sections displayed in B, D, H, and J. E, F, K, and L) High magnification images of the pyramidal neurons in the layer V within the squares in B, D, H, and J, respectively. SMI-32-positive pyramidal neurons with smaller cell body are frequently observed in the layer V in the hand area of ipsi-M1, relative to that in the M1 of intact macaques. Contrarily, the neurons with extensive arborization are more frequently observed in the contra-F5 than in the intact F5. Scale bars: 100 μm.

B. Causality assessment of brain activity and pain in the macaque model of centrtal post stroke pain

Stroke lesions of somatosensory pathways are known to cause chronic pain called central post stroke pain (CPSP). Specifically, about 10% of all stroke patients experience allodynia, in which pain is produced by touch, and hyperalgesia, in which pain is more intense than normal pain stimuli. Brain imaging studies of CPSP patients and animal models have revealed maladaptive plasticity in pain-related brain regions as an underlying pathophysiological mechanism. Our previous studies in a macaque model of thalamic stroke have reported abnormal increase of brain activity and structural changes in areas called the posterior insular cortex and secondary somatosensory cortex [5, 6]. Furthermore, we have reported that pharmacological inactivation of these brain regions attenuates allodynia to mechanical stimuli. This year, we tested whether allodynia and hyperalgesia to thermal stimuli have a shared neural basis as a pathological mechanism by means of pharmacological inactivation experiments [7] and showed that administration of the GABA agonist muscimol to the posterior insular cortex and secondary somatosensory cortex in the macaque model reduced hyperalgesia to thermal stimuli (Fig. 3). These results suggest that there is a common neural basis for the abnormal pain evoked by tactile and thermal stimuli.

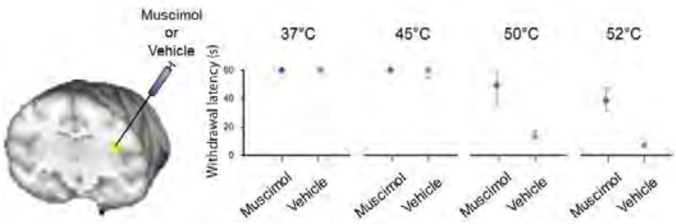


Fig. 3. Effect of PIC/SII inactivation on withdrawal latency. Withdrawal latencies (in sec) of the contra-lesion hand for each thermal stimuli after muscimol or vehicle injection. The withdrawal latencies for thermal stimulation (50-52°C) were increased compared to that after vehicle injection.

IV. Future Perspective

Studies in this project have elucidated some of the adaptive and nonadaptive changes that occur after subcortical stroke. Further cellular analysis will reveal the detailed mechanisms underlying the adaptive and nonadaptive changes.

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] Y. Murata, N. Higo, "Development and Characterization of a Macaque Model of Focal Internal Capsular Infarcts", PLoS ONE 11(5): e0154752,, 2016

[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. Nagasaka, I. Takashima, K. Matsuda, N. Higo, "Brain activity changes in a monkey model of central post-stroke pain". Exp Neurol 323, 113096, 2020

[6] K Nagasaka, K Nemoto, I Takashima, D Bando, K Matsuda, N Higo, "Structural Plastic Changes of Cortical Gray Matter Revealed by Voxel-Based Morphometry and Histological Analyses in a Monkey Model of Central Post-Stroke Pain", Cerebral Cortex, 31 (10), 4439-4449, 2021

[7] K. Nagasaka, I. Takashima, K. Matsuda, N. Higo, "Pharmacological inactivation of the primate posterior insular/secondary somatosensory cortices attenuates thermal hyperalgesia". Eur J Pain 26 (8), 1723-1731, 2022

A05-17 Annual report of research project

Osamu Yokoyama
Tokyo Metropolitan Institute of Medical Science

***Abstract*— Somatosensory functions play an important role in motor control. In the present study, we generated a monkey model of somatosensory impairment in which the input of somatosensory information to the central nervous system was selectively impaired by transection of the dorsal root entering the spinal cord. By longitudinally recording and analyzing neuronal activity in the motor cortex and the somatosensory cortex, we aimed to reveal the adaptive mechanism in the cerebral cortex that supports functional recovery from motor impairment caused by a lack of somatosensory input to the central nervous system. Immediately after transection of the dorsal root entering the cervical spinal cord, the motor performance of the upper limb was markedly impaired, and an increase in the high-gamma (80–120 Hz) activity was observed in the primary motor cortex and primary somatosensory cortex in relation to movement. Motor performance gradually recovered to the pre-lesion level in about 2 weeks, and high-gamma activity in the primary motor cortex and the primary somatosensory cortex also decreased to the pre-lesion level through a similar time course. These activity changes in the motor and somatosensory cortices may contribute to the recovery of motor function. These findings revealed an example of the way by which the cerebral cortex adapts to an abrupt loss of information by reorganizing its activity.**

I. Introduction

For at least the following two reasons, somatosensory information plays an important role not only in the sensory functions of perceiving the current state of one's own body and the external world, but also in motor control to accurately generate body movements. First, when the primary motor cortex generates motor commands, it is necessary to utilize somatosensory information such as the position of body parts, joint angles, and output forces. Second, during motor execution, spinal motor neurons receive sensory signals from peripheral sensory receptors in addition to descending motor command signals from the motor cortex, and integrate them to generate muscle activity [1]. Indeed, patients who cannot receive somatosensory information due to peripheral sensory neuropathy exhibit motor dysfunction in addition to somatosensory impairment [2–4]. Similarly, a monkey model of somatosensory impairment in which upper extremity somatosensory input to the central nervous system was impaired by transection of the dorsal root entering the cervical spinal cord exhibited motor deficits in the upper limb [5]. Such movement impairment in the lesioned monkeys recovers within weeks to months [5]. In the recovery process of motor function, the central nervous system must adapt to the abrupt loss of somatosensory information input that could have been received before the injury. However, the details of this adaptive process have not been well understood.

II. Aim of the Group

The aim of this study is to investigate reorganization of cerebral activity in the adaptive process during recovery of motor function after the loss of peripheral, somatosensory information.

III. Research Topics

After two Japanese macaques were trained on a reach-grasp task using the right upper limb, the dorsal roots that enter the right lower cervical spinal cord (C6–8), which is the transmission pathway for somatosensory signals from the right upper limb, were surgically transected. (Fig. 1 left). We confirmed that the response of the primary somatosensory cortex (somatosensory evoked potential) to peripheral (upper limb) electrical stimulation under anesthesia was attenuated after transection compared to before transection (Fig. 1, right).

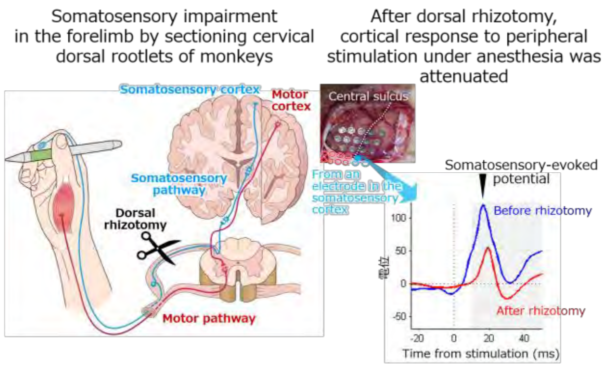


Fig. 1. (Left) A schema of the somatosensory and motor nerve pathways that convey somatosensory information and motor commands between the periphery and the central nervous system, and the position of the dorsal root transected in the present study. (Right) Somatosensory evoked potentials in the primary somatosensory cortex to stimulation of the adductor pollicis brevis muscle under anesthesia were attenuated after transection of the dorsal root (C6-C8) into the lower cervical spinal cord.

On the day after dorsal root transection, the animals were able to perform the reach-grasp task using the upper limb on the injured side, but the time taken to complete reaching movement was prolonged (Fig. 2). During the following days, the time taken to complete reaching movement gradually decreased, and returned to the pre-lesion level about 14 days after the transection (Fig. 2). In contrast, somatosensory evoked potentials to peripheral somatosensory stimuli had not recovered at that time. These results suggest that the animals regained motor performance through adaptive changes in the central motor control system in response to the abrupt loss of peripheral information that must have been received during voluntary movements.

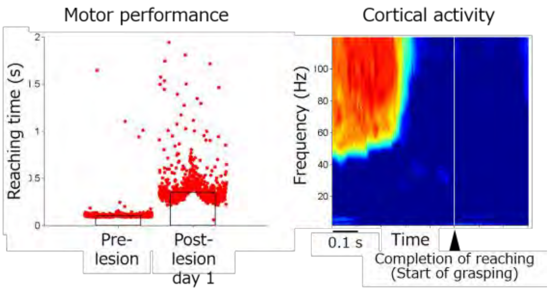


Fig. 2. (Left) Immediately after dorsal root transection, the time taken from the onset of movement to completion of reaching movement prolonged. (Right) Immediately after dorsal root transection, compared to before dorsal root transection, an activity increase in high-gamma band was observed at multiple sites in primary motor and primary somatosensory cortex (right; red indicates time and frequency of increased activity intensity).

Then, cortical electroencephalograms of the primary motor cortex and the primary somatosensory cortex during the reach-grasp task in the process of recovering motor performance after dorsal root transection were recorded from a sheet, multi-electrode array and analyzed. We found that, the day after transection, high gamma (80–120 Hz) activity in the primary motor cortex and the primary somatosensory cortex at initiating and executing reaching movement increased despite the attenuated inputs from the periphery. Then, the activity level gradually decreased with the recovery of motor performance and returned to the pre-lesion level (Fig. 2) in the time course similar to the reduction of time taken to complete reaching movement. These results suggest that the changes in high gamma activity may contribute to motor recovery from motor impairment caused by dorsal root transection.

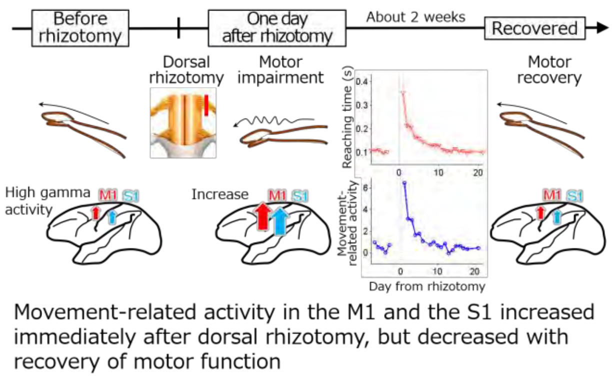


Fig. 3. Changes in motor performance and activity in the primary motor cortex and primary somatosensory cortex before and immediately after dorsal root transection, and during recovery of motor function.

IV. Future Perspective

We prepared a monkey model of somatosensory impairment by transecting cervical dorsal roots in two Japanese macaques. Motor function was impaired immediately after the lesion, but recovered in about 2 weeks. By longitudinally examining the activity of the primary motor cortex and the primary somatosensory cortex during the recovery of motor function, we succeeded in identifying a component of movement-related activity that covaried with the recovery of motor function. In the next year, in addition to the magnitude of brain activity in individual areas involved in motor and somatosensory functions, we will examine information flow between those areas by using mathematical methods such as Granger causal analysis. We will examine what changes in information flow account for the observed changes in the magnitude of brain activity after lesion and during recovery. We have already found a characteristic pattern of information flow between the primary motor cortex and the primary somatosensory cortex during voluntary movements in healthy, pre-injury monkeys [6]. By accumulating such findings, we will be able to gain a deeper understanding of the adaptation mechanism of cerebral activity to the abrupt loss of information input that is supposed to be received in the normal condition. It is also expected to lead to a more comprehensive understanding of the neural mechanisms that control voluntary movements from the perspective of the dynamics of the neural network consisting of both the motor control system and the somatosensory system.

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] 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.

[3] 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.

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

[5] 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.

[6] O. Yokoyama, M. Suzuki, and Y. Nishimura, "Motor stage- and frequency-dependent bidirectional information flows between the primary motor cortex and the primary somatosensory cortex during voluntary movements," The 16th annual meeting of the Japanese Society for Motor Control, 2022/08/26.

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, trying 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 the following four research projects. From this year, 10 new proposed research projects have joined the group. Please refer to the report of each research project for their research outcomes in the fiscal year.

Planned Research Groups

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

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

Research Outline: 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 latent structure in brain activity (EEG), and applied a weakly-coupled dynamic neuron model they proposed last year for data augmentation. (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 analyzed NIRS signals under an attention task (continuous performance test) for quantitative evaluation of human attention levels.

B02 Modeling of ultra-adaptive to body change

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

Research Outline: 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, (1) they constructed a musculoskeletal model of monkey to elucidate the adaptation mechanism after tendon transfer using dynamical simulation. (2) They experimentally confirmed that muscle synergy can be learned through motor learning while presenting similarities in muscle synergy.

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

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

Research Outline: 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.

In this year, (1) they proposed a computational model of hyper-adaptation mechanism for de-novo motor learning. (2) They investigated the effect of body cognition on muscle synergy. (3) They investigated the effect of a neuromodulation intervention based on the characteristics of the EEG power spectrum during motor learning. (4) They examined the changes in cerebral and cerebrum volumes in spinocerebellar degeneration patients. (5) They examined the subprocesses underlying the abnormality of sense of agency in Schizophrenia.

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)

Research Outline: 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 used a standing posture control model they previously proposed to analyze abnormal posture in patients with Parkinson's disease. (2) They constructed a regression model of 3D DAT-SPECT images. (3) They investigated cortical mechanisms during voluntary sway, and analyzed the effect of foot pain on posture during gait.

Proposed Research Groups

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

Principal investigator: Mitsuhiro Hayashibe (Tohoku U)
Principal investigator: Daichi Nozaki (U Tokyo)

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

Principal investigator: Naomichi Ogihara (U Tokyo)

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

Principal investigator: Hoshinori Kanazawa (U Tokyo)

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

Principal investigator: Isao Nambu (Nagaoka U of Tech)

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

Principal investigator: Yuichi Kobayashi (Shizuoka U)

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

Principal investigator: Michiteru Kitazaki (Toyohashi U Tech)

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)

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)

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

Principal investigator: Takeshi Sakurada (Seikei U)

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

Principal investigator: Yuki Ueyama (NDA Japan)

III. Activities

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

- November, 28th, 2022, HMS2022 Organized session (Nagoya University)
  After a COVID-19 infection, the international symposium was held as face-to-face style. Prof. Ogihara gave plenary talk. In the organized session, Prof. Izawa and Prof. Kutsuzawa gave keynote talks and 7 researchers in the research project presented their recent research results.
- January 22-23rd, 2022, Organized session at the symposium on Distributed Autonomous Systems (Online), 14 oral presentations.

IV. Future plan

Next fiscal year is the last year of the Hyper-adaptability research area. We proceed fruitful collaborations with Group A (Neuroscience group), continue deeper discussion on the research topics, and summarize the research outcomes in the planned and proposed research projects.

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) Probabilistic latent variable model for analyzing long-term multi-modal data, (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, and applied a weakly-coupled dynamic neuron model they proposed last year for data augmentation.

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). 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. As shown in Fig. 1, 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 (synergy). Moreover, they applied the EEG dataset of BCI Competition IV 2a (4-class motor imagery) to the weakly coupled neuron model they proposed last year, and developed a data augmentation technique based on the model. They confirmed that the classification accuracy using a convolutional neural networks (CNN) as a classifier was significantly improved by performing the data augmentation method (unpublished). Furthermore, they proposed a novel reinforcement learning algorithm, and confirmed the superior performance in black-box optimization tasks with constraints [1].

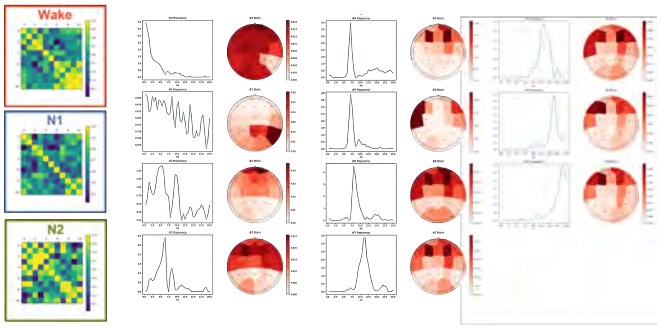


Fig. 1. Structural change of functional connectivity underlying in sleep EEG identified by using CP decomposition and TVGL.

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

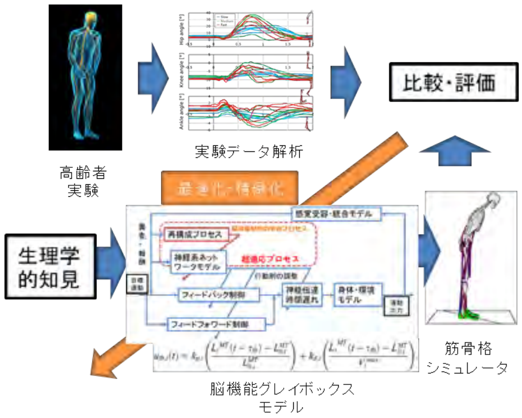


Fig. 2. Constructive modeling approach.

young and elderly subjects, based on the differences in the parameters of a simulator using a musculoskeletal model (Fig. 2).

Toward this goal, they constructed a three-dimensional computer model of gait initiation because modulation of the CoP's movement not only in the forward/backward direction but also in the left/right direction may cause falls. In order to construct the computer model, it is necessary to construct computer models of standing and gait.

They proposed a neural controller that enables three-dimensional gait. A three-dimensional model of standing posture are utilized that of previous studies. However, it is very difficult to design the activations of 70 muscles and obtain a reasonable gait because of the large number of parameters. Therefore, we 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, and then reducing the stiffness in turn. As a result, it was confirmed that the gait was within a reasonable range, although 500[Nm/rad] of stiffness was left at the hip joint and the waist joint. [2], [3]

They also proposed a neural controller for the gait initiation that links the above posture maintenance and gait. They confirmed that just switching from posture-maintaining control to gait control causes the model to fall. Therefore, the posture and timing of the switch were obtained by optimization. The evaluation index was the possibility of transitioning to gait. As a result, they obtained a solution that enabled a smooth transition. As a result of the analysis, it was observed that the CoP was moved to the supporting leg after being moved to the swing leg side. This may be an anticipatory postural adjustment to the gait motion, and it is interesting that this was observed even though the design was not intended for CoP movement but only for gait transition.

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 [5] [6] [7]. 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 [8]. 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. Future perspective

In consideration of future collaborations with neuroscience research groups, we proposed several methodologies for modeling the hyper-adaptability from both statistical and constructive modeling standpoints.

Next fiscal year, 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, Shiro Yano, and Toshiyuki Kondo, Evaluation of Safe Reinforcement Learning with CoMirror Algorithm in a Non-Markovian Reward Problem. In: Petrovic et al. (eds) Intelligent Autonomous Systems 17. *Lecture Notes in Networks and Systems*, vol 577. Springer, Cham. (2023)

[2] Hitohiro Etoh, Yuichiro Omura, Kohei Kaminishi, Ryosuke Chiba, Kaoru Takakusaki, and Jun Ota. (2022). Motion generation of anticipatory postural adjustments in gait initiation. the 2022 IEEE International Conference on Bioinformatics and Bioengineering (BIBE), Taichung, Taiwan (11/7, 2022).

[3] Hitohiro Etoh, Yuichiro Omura, Kohei Kaminishi, Ryosuke Chiba, Kaoru Takakusaki, and Jun Ota. Investigation of a method to extend a 2-dimensional gait to 3-dimensions in a human musculoskeletal model with 70 Muscles. Proc. The 33rd 2022 International Symposium on Micro-NanoMechatronics and Human Science (MHS2022), Nagoya, Japan (11/28, 2022).

[4] Saki Niiyama, Shiro Yano, and Toshiyuki Kondo, Cerebral Activity-Based Quantitative Evaluation for Attention Levels, *Journal of Robotics and Mechatronics*, Vol.34, No.4, pp.739–745, 2022

[5] Samirah Altukhaim, Toshiyuki Kondo, Yoshikatsu Hayashi, Enhancement of Sense of Ownership and Sense of Agency using Virtual Reality and Haptic Feedback, *Proceedings of the 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, Glasgow, UK, (7/11-15, 2022).

[6] Ozge Ozlem Saracbasi, William Seymour Harwin, Toshiyuki Kondo, Yoshikatsu Hayashi, Dual Instability against to Sequential Learning via Haptic Interaction, *Proceedings of the 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, Glasgow, UK, (7/11-15, 2022).

[7] Eiko Matsuda, Daichi Misawa, Shiro Yano, and Toshiyuki Kondo, Olfactory Cues to Reduce Retrograde Interference During the Simultaneous Learning of Conflicting Motor Tasks, *Journal of Robotics and Mechatronics*, Vol.34, No.4, pp. 746–755, 2022

[8] Naoya Yamamoto, Takato Matsumoto, Tamami Sudo, Megumi Miyashita, and Toshiyuki Kondo, Ring-shaped wearable device for logging finger usage in daily life, *Proceedings of the IEEE 2022 International Symposium on Micro-NanoMechatronics and Human Science (MHS2022)*, Nagoya, Japan (11/28, 2022).

B02 Annual report of research project

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

***Abstract*—We obtained the following two results.**

1. We constructed a musculoskeletal model of monkey for dynamical simulation of tendon transfer in monkeys.

2. We experimentally confirmed that muscle synergy can be learned through motor learning while presenting similarities in muscle synergy.

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. *Monkey musculoskeletal model for tendon transfer*

To investigate the neural adaptation mechanism after tendon transfer, our group constructs a simulation model that can reproduce the adaptation process after tendon transfer. Until last fiscal year, the effects of tendon transfer on muscle activity had been investigated using a musculoskeletal model on the musculoskeletal software OpenSIM[1]. Here, the musculoskeletal model used was created by scaling a human musculoskeletal model to monkey size, and there were problems with the muscle attachment positions and other differences from those of monkeys. This year, in collaboration with Prof. Ogihara of B05-2, we constructed a monkey musculoskeletal model on MuJoCo software, based on the monkey musculoskeletal model created by Prof. Ogihara, and created an environment that enables anatomically valid analysis of muscle activity.

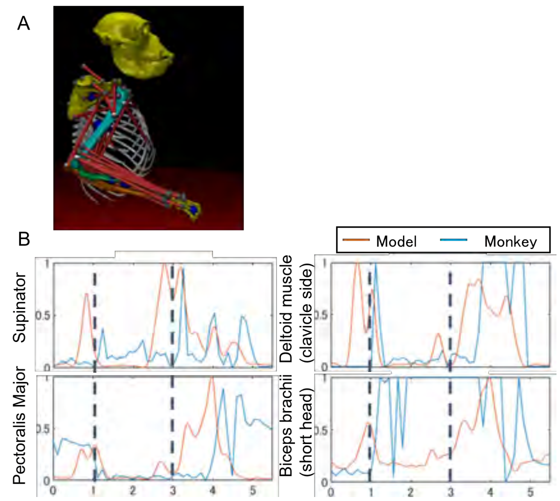


Fig. 1. A: Musculoskeletal model. B: Estimated muscle activities

Fig. 1A shows the monkey model constructed on MuJoCo. The skeletal system consists of the trunk, head, scapula, humerus, ulna, radius, and carpal bones. The skeleton has six degrees of freedom: three degrees of freedom in the shoulder joint (shoulder flexion, abduction, and external rotation), and one each in elbow flexion, forearm rotation, and wrist flexion. The number of muscles is 29, and they are arranged as red lines in Fig. 1A.

To validate the model, muscle activities were estimated from the measured monkey's grasping motion and compared to the measured muscle activities of the monkey. Fig. 1B shows the estimated muscle activities. In the grasping motion, the monkey extended their arms forward mainly around 1 s, reached the food around 3 s, and then carried the food to their mouth. The estimated results in Fig. 1B (red lines) show a pattern somewhat similar to the monkeys' measured muscle activities (blue lines), especially in the critical timing of the reaching and mouth-carrying motions. Thus, the constructed model was able to reproduce the characteristics of the monkey musculoskeletal model to some extent.

B. Motor Learning using muscle synergy similarity

When attempting to learn a new environment in a virtual surgery that involves muscle replacement, the correct solution may not be found through a trial-and-error search. Therefore, we investigated whether feedback of muscle synergy similarity could facilitate motor learning.

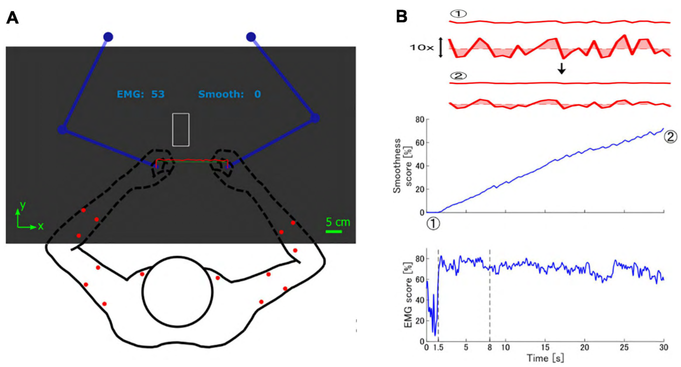


Fig. 2. Experimental Setup

Virtual task environment using KINARM is shown in Fig. 2(A). Participants held a pair of manipulanda (blue), and moved them to control the position of the polished object (red line). The main goal of the task was to smoothen the polished object by moving it against the grinder (white rectangle). Contact between both objects caused the manipulanda to generate forces simulating the contact interaction, which also changed the shape of the polished object. The EMG and smoothness scores were displayed above the task workspace. Red dots on the arms indicate the location of the EMG electrodes. In Fig. 2(B), deformation of the polished object by contact forces with the grinder. The polished object is shown with and without scaling in the vertical direction. The smoothness of the object was quantified as the area between the outline of the object and a horizontal line at the mean vertical position of all contact points. Smoothness and EMG similarity scores throughout a trial.

Figure 3 shows how the smoothness score and muscle synergy similarity score changed after five training sessions on different days for the group that received no feedback and the group that was presented with muscle synergy similarity to the expert's muscle synergy. The results show that smoothness scores were higher with or without presenting muscle synergy similarity, but muscle synergy similarity scores were significantly higher for the group that was given feedback. For the angle between the grinder and the object, the group that was presented with the muscle synergy similarity score was significantly smaller. This indicates that the force exerted is stable, or that the direction of exertion is such that the object is maintained horizontally. The smoothness of the object's surface can be confirmed by visual feedback, so the value is high regardless of the similarity of the muscle synergy, but the group displaying the similarity of the muscle synergy has a similar style to the skilled workers in terms of the way of applying force. This indicates that the group of participants

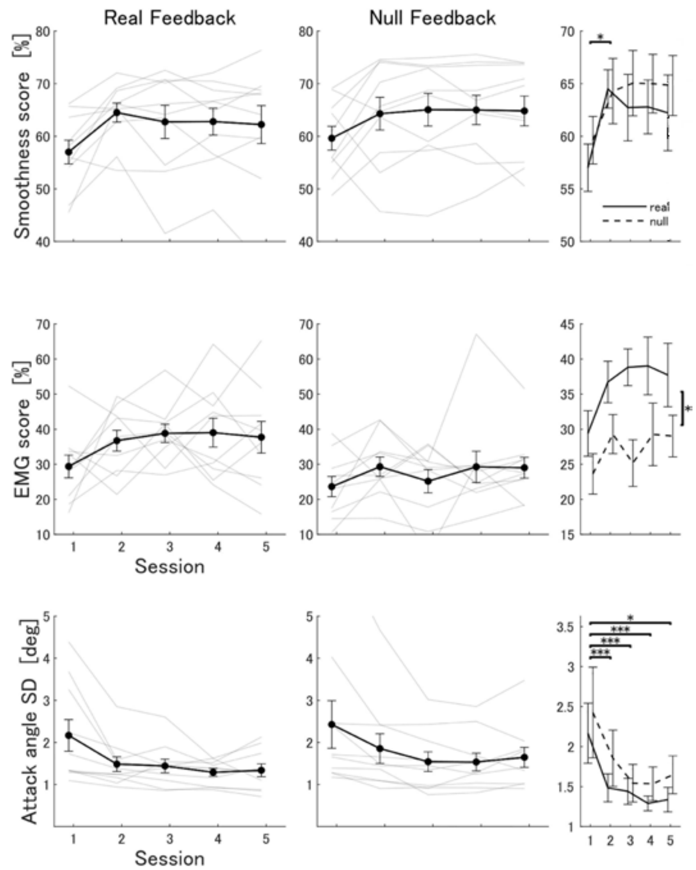


Fig. 3. Score change during training

who displayed the similarity of muscle synergy had a more similar style to the skilled workers, who were polishing a large quantity of products to provide a certain quality, and that they were able to learn how to apply force for that purpose as training for motor learning. In the future, we would like to investigate whether this kind of feedback is also effective for learning virtual surgery.

IV. Future Perspective

This year, to elucidate the adaptation mechanism after tendon transfer using dynamical simulation, we constructed a musculoskeletal model of monkey. We plan to use this model to approach the learning and control mechanisms that can reproduce adaptation after tendon transfer. In addition, we experimentally confirmed that muscle synergy can be learned through motor learning while presenting similarities in muscle synergy. From next fiscal year onwards, we plan to promote joint research with other groups.

References

[1] Uchida N., et al., Synergy Analysis of Musculoskeletal Model for Adaptation Mechanism of Monkey with Tendon Transfer, MHS 2021, MP2_1_3, 2021

[2] Victor R. Barradas and Woorim Cho and Yasuharu Koike, EMG space similarity feedback promotes learning of expert-like muscle activation patterns in a complex motor skill, Frontiers in Human Neuroscience, 16,2023

B03 Annual Report of Hyper-Adapt Project

ASAMA Hajime
The University of Tokyo

***Abstract*—B03 group aims to clarify the influence of body consciousness and emotion on the hyper-adaptation, and to establish mathematical model for hyper-adaptation which can quantitatively predict the state of body motor control ability. Furthermore, B03 group also aims to use the proposed mathematical model to develop and evaluate new methods for motor rehabilitation in future research. In the past year, we accomplished the following works: 1) We proposed a computational model of hyper-adaptation mechanism for de-novo motor learning. 2) We investigated the effect of body cognition on muscle synergy. 3) We investigated the effect of a neuromodulation intervention based on the characteristics of the EEG power spectrum during motor learning. 4) We examined the changes in cerebral and cerebrum volumes in spinocerebellar degeneration patients. 5) We examined the subprocesses underlying the abnormality of sense of agency in Schizophrenia.**

I. Introduction

B03 group focuses on the cognitive aspects such as body consciousness and emotion in the processes of hyper-adaptation. We aim to understand the processes of hyper-adaptation through a systematical approach, and to propose novel intervention methods that trigger hyper-adaptations via body consciousness and emotion. To do this, we aim to quantitatively measure the process of hyper-adaptation and establish a mathematical model, thereafter, develop a brain decoding method that can predict the semantic function. Moreover, we aim to develop a robotics platform for neural intervention, to further estimate our model-based intervention rehabilitation methods. In specific, we will examine the hyper-adaptation for post-stroke patients, and to model their motor recovery, and to examine the effect of model-based methods.

II. Aim of the Group

In B03 group, we aim to quantitatively measure body consciousness, emotion, and the hyper-adaptation of body motor control, establishing a mathematical model that is able to predict optimized intervention method for rehabilitation.

III. Research Topics

B03 accomplished the following studies in the past year.

A. A computational model of hyper-adaptation mechanism for de-novo motor learning

Last year, Izawa's group (University of Tsukuba) found that the participants can be categorized by one who exhibits hyper-adaptation and the other who does not exhibit hyper-adaptation when human participants adapt their motor control ability for novel body and task structures. They also found that the hyper-adaptation group exhibited a large motor command variance during the adaptation training. Thus, this year, Izawa's group developed the computational model to explain this hyper-adaptation phenomenon, given the hypothesis that large exploration is the clue to the hyper-adaptation ability[1]. The simple model was developed first, where the linear matrix gave the novel task structure. We proved that the covariance matrix of the exploration noise has to be a regular matrix and showed that the norm of the covariance matrix determined the learning speeds, which was confirmed via simple simulation experiments. Then, we developed the neural network model to explain previous reports of reach adaptation tasks, de novo learning tasks, and virtual surgery tasks and replicated these results with the model. Further, we found that the magnetic stimulation of the premotor cortex facilitates learning [2]. We also developed the hyper-adaptation model for rehabilitation where the recovery valley was overcome [3].

B. Investigation of the effect of body cognition on muscle synergy

An's (The University of Tokyo) research group has shown that there are four muscle synergies involved in human sit-to-stand motion: forward bending of the upper body, rising hip from a chair, extension of the whole body, and stabilization of posture. In addition to sensory information such as vision and vestibular sense, they newly investigated the effect of body cognition on human sit-to-stand motion, particularly on muscle synergy. To alter body cognition virtually, the participants were asked to perform the sit-to-stand motion while wearing an apparatus that restricted the range of motion of the knee joint, and the changes in standing motion caused by the apparatus were examined. As a result, it was found that restricting the range of motion of the joints increased the activity of muscle synergy 1 contributing to the forward bending of the upper body, as shown in Figure 1. This led to a strategy of more forward bending to generate momentum. At the same time, the activity of the muscle synergies 2 and 4 which contribute to rising hip and stabilization of posture decreased, compensating for the changes in the lower limbs by upper body movement. After removing the apparatus, the activity of muscle synergy returned to the same level as before wearing the apparatus, suggesting that the participants were able to adjust the activity of muscle synergy immediately in response to the changes in their own body [4].

C. The effect of neuromodulation intervention on motor learning

Asama, Wen, and Hamada's group (The University of Tokyo) investigated the effect of a neuromodulation intervention based on the characteristics of the EEG power spectrum on motor learning [5]. Transcranial alternating current stimulation of the gamma band was applied to the frontal and lateral parietal regions during hand motor learning in healthy participants to investigate its modulatory effects on the learning process. Contrary to the hypothesis, the stimulation group showed less proficiency in hand motor learning than the sham group. Intervention based on the EEG power spectrum related to motor learning was shown to be ineffective during motor learning, and further investigation of the timing and methods of intervention was found to be necessary.

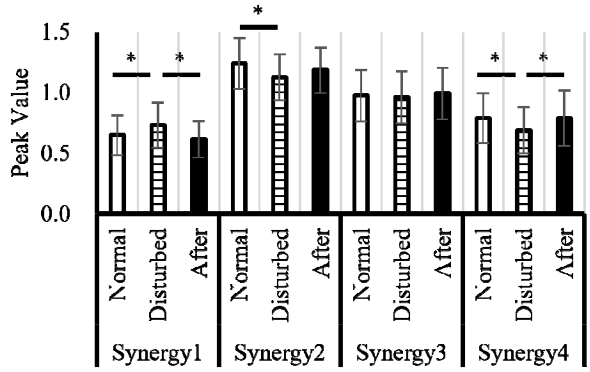


Figure 1. Changes of muscle synergy due to restriction of range of joint motion.

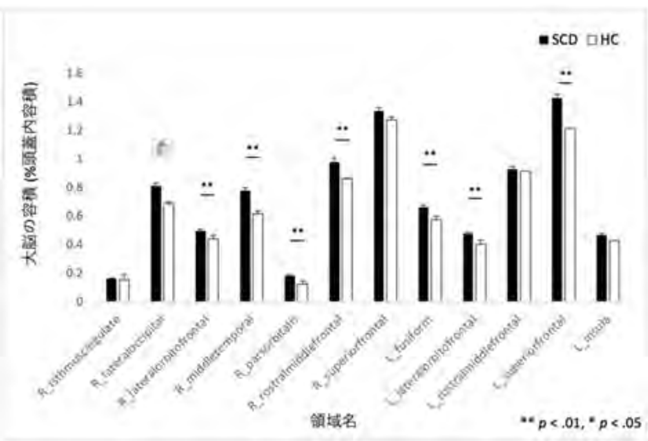


Figure 2. Comparison of cerebral volume in the patient group and the healthy group

D. The volumes of cerebral and cerebrum in spinocerebellar degeneration patients

Furthermore, Asama, Wen, and An's group identified regions that undergo plastic changes by calculating the cerebral volumes using brain structural image analysis to reveal how the motor control system impairment in spinocerebellar degeneration patients is compensated for in the cerebrum. The volume of the cerebellum in the patient group was found to have a significant negative correlation with the volume of the frontal and temporal regions of the cerebrum, and many of these regions were significantly increased compared to the healthy group [6] [7] (Fig. 2). These increased regions were considered to be responsible for compensating for the control system of the cerebellum.

E. The subcomponents underlying the abnormality in sense of agency in Schizophrenia

At last, Asama's group examined three subcomponents underlying the sense of agency in Schizophrenia by collaborating with Maeda's group in Keio University. It is known that patients with schizophrenia often show abnormal agency judgment. However, it is unclear whether such abnormal judgment is due to biased prior belief of impaired sensorimotor processes. The current study used three different tasks to target the agency judgment, control detection, and control planning, respectively. By analyzing the action plans in these tasks, we found that patients with schizophrenia are lack of action diversity, and their action plans were barely influenced by the sense of agency [8].

IV. Future Perspective

In the past year, we proposed the computational model of hyper-adaptation mechanism for de-novo motor learning. We examined the effect of body cognition on muscle synergy and the effect of brain simulation on motor learning. We also examined the neural and behavioral changes in different types of patients. Those results are useful for understanding the hyper-adaptation processes in both healthy people and patients.

References

[1] Dal'Bello, L.R., and Izawa, J. "Computational role of exploration noise in error-based de novo motor learning." Neural Networks 153 (2022): 349-372

[2] Sugiyama, T., Nakae, K., and Izawa, J. "Transcranial magnetic stimulation on the dorsal premotor cortex facilitates human visuomotor adaptation." NeuroReport 33.16 (2022): 723-727.

[3] Izawa, J. Higo, N., and Murata, Y. "Accounting for the valley of recovery during post-stroke rehabilitation training via a model-based analysis of macaque manual dexterity." Frontiers in rehabilitation sciences 3 (2022): 1042912.

[4] Yoshida, K., An, Q., Hamada, H., Yamakawa, H., Tamura, Y., Yamashita, A., and Asama, H. "Analysis of muscle activity of Sit-to-stand motion when knee movability is disturbed," Journal of Robotics and Mechatronics 34.4 (2022): 767-776.

[5] Hamada, H., Wen, W., Kawasaki, T., Yamashita, A. & Asama, H. "EEG Power Spectra Changes with the Proficiency of Motor Learning NEURO2022, Japan, 2022

[6] 濵田 裕幸, 菊地 豊, 温 文, 山下 淳, 淺間 一，脳構造画像解析に基づく脊髄小脳変性症患者の大脳による制御メカニズムの理解，第 40 回日本ロボット学会学術講演会，2022

[7] 濵田 裕幸, 菊地 豊, 温 文, 安 琪，山下 淳, 淺間 一，脳構造画像解析に基づく脊髄小脳変性症患者の大脳の制御システムの理解，第 35 回自律分散システム・シンポジウム，2022

[8] Chang, A. Y-C., Oi, H., Maeda, T. and Wen, W. "The sense of agency as active causal inference at an abstract action plan level". 第 35 回自律分散システム・シンポジウム，2022

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 24 co-investigators (Shirafuji, Kaminishi, Takamido, Hasegawa, Kohno, Kishimoto, Yuine, Ishibashi, Hamada, Miyata, Osaki, Kanaya, Kawano, Kanai, Omura, Etoh, Sonoda, Fujiwara, Huang, Makino, Orihara, Nishizawa, Ishikawa).

II. Research results and future plans

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 previously proposed a standing posture control model (with muscle tone and feedback control parameters as control parameters) that introduces control mimicking the descending tracts [1]. This year, we used this to analyze abnormal posture in patients with Parkinson's disease. To test the hypothesis that the abnormal posture is one of the postures in which the patient can stand with small sway, we went through the following process: 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 standing posture closer to the experimental results was achieved when the muscle tone was larger than the value equivalent to that of a normal subject (Fig. 1). In addition, the adjusted posture closest to the experimental results did not differ significantly from the experimental postural data (the difference in each joint angle was less than 5.2°), which supports the hypothesis.

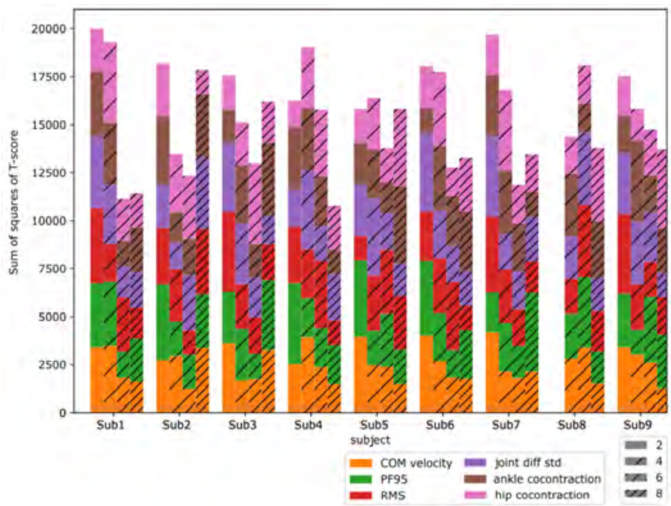


Fig. 1. Differences between simulation and experimental results for indices related to posture, sway, and co-contraction. In all participants' data, the differences were small when the muscle tone index, $\|\boldsymbol{u}_{ff}\|^2$, was as high as 6 or 8.

Dopamine transporter single-photon emission computed tomography (DAT-SPECT), which is used to diagnose Parkinson's disease, was also analyzed. The 3D information from DAT-SPECT is often reduced to a 1D scalar value. The relationship between DAT-SPECT and various motor symptoms has not been fully analyzed. Therefore, we developed a system that captures 3D DAT-SPECT information and examines the relationship between it and each motor symptom using deep learning technology. Using DAT-SPECT images as input, we constructed a model for regression analysis of scores related to each motor symptom, and visualized which parts of the image the model focused on (Fig. 2). In addition to improving the accuracy, we aim to describe the relationship between the neurotransmitter status and the behavior in combination with the model in the future.

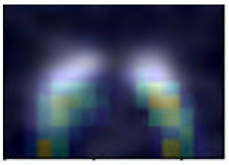


Fig. 2. Example of how the regression analysis model visualizes the regions around the striatum during the estimation of the muscle rigidity-related score. The closer the color is to red, the higher the degree of attention. The putamen (lower) was more important than the caudate nucleus (upper) in the analysis.

In addition, we attempted to characterize the postural sway of stroke patients by adjusting the parameters of the musculoskeletal model and the standing posture control model to reproduce the standing data of stroke patients and applying dimensionality reduction to these parameters [2]. As a result, differences in gain parameters related to whole-body extension were identified between stroke patients and young healthy subjects. These are necessary to maintain knee extension and whole-body balance while suppressing rapid extension of the lumbar region and ankles.

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 further understand this subject, we conducted a review of prior research on the subject of multitasking [3]. 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) [4]. However, our findings indicated the lack of a discernible effect of neurotransmitters on multitasking during static standing. 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 as a motor task, given its versatility in terms of task difficulty. We conducted a pre-patient study on healthy subjects before the patient subjects. Furthermore, as pain is often comorbid in Parkinson's disease, it still remains unclear how pain affects the postural and motor control. Therefore, we investigated the effects of pain on postural and motor performance in healthy subjects.

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 [5] 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 [4]. 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. Although prefrontal cortex activity is still under analysis, voluntary sway, in which movements are made in response to a specified frequency, can be interpreted as a multitasking task consisting of motor and cognitive tasks. In the future, we plan to investigate the effects of neurotransmitters on postural control by measuring voluntary sway in Parkinson's disease patients with diurnal fluctuations.

2) 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 [7]. 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.

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] 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.

[4] 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.

[5] T. Mori, T. Hasegawa, K. Kaminishi, R. Chiba, J. Ota, A. Yozu. Evaluation of voluntary sway during standing in human. Proceedings of the 34th SICE DAS Symposium. Online, 2022.

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

[7] K. Sonoda, T. Hasegawa, K. Kaminish, M. Osumi, M. Sumitani, R. Chiba, J. Ota, A. Yozu, Effects of plantar pain on gait. The 33rd 2022 International Symposium on Micro-NanoMechatronics and Human Science (MHS2022). Nagoya, 2022.

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

Mitsuhiro Hayashibe, Kyo Kutsuzawa
Tohoku University

***Abstract*—Neural integrators offer a promising model-free approach for handling high-dimensional control problems. It still remains an open problem on how we can create motor learning of modular structure and its generalization. In this study, we investigated neural integrators for inducing dynamic equilibrium for multi-limb multi-joint system and motor synergy generalization framework for unlearned motions.**

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 manipulator and environment is explicitly given. For the manipulation task, the dynamics conditions are always unknown. It still remains an open problem on how we can create human-like synergetic motion. This study provides neural integrator framework to induce dynamic equilibrium and motor synergy generalization framework.

II. Neural integrator to induce dynamic equilibrium

The synchronization phenomenon is common to many natural mechanical systems. Joint friction and damping in humans and animals are associated with energy dissipation. A coupled oscillator model is conventionally used to manage multiple joint torque generations to form a limit cycle in an energy dissipation system. The coupling term design and the frequency and phase settings become issues when selecting the oscillator model. The relative coupling relationship between oscillators needs to be predefined for unknown dynamics systems, which is quite challenging problem. We present a simple distributed neural integrators method to induce the limit cycle in unknown energy dissipation systems without using a coupled oscillator. The results demonstrate that synergetic synchronized oscillation could be produced that adapts to different physical environments. Finding the balanced energy injection by neural inputs to form dynamic equilibrium is not a trivial problem, when the dynamics information is not priorly known. The proposed method realized self-organized pattern generation to induce the dynamic equilibrium for different mechanical systems. The oscillation was managed without using the explicit phase or frequency knowledge. However, phase, frequency, and amplitude modulation emerged to form an efficient synchronized limit cycle [1]. This type of distributed neural integrator can be used as a source for regulating multi-joint coordination to induce synergetic oscillations in natural mechanical systems.

III. Motor Synergy Generalization

Humans can rapidly adapt to new situations, even though they have redundant degrees of freedom (d.f.). Previous studies in neuroscience revealed that human movements could be accounted for by low-dimensional control signals, known as motor synergies. Many studies have suggested that humans use the same repertories of motor synergies among similar tasks. However, it has not yet been confirmed whether the combinations of motor synergy repertories can be re-used for new targets in a systematic way. Here we show that the combination of motor synergies can be generalized to new targets that each repertory cannot handle. We use the multi-directional reaching task as an example. We first trained multiple policies with limited ranges of targets by reinforcement learning and extracted sets of motor synergies. Finally, we optimized the activation patterns of sets of motor synergies and demonstrated that combined motor synergy repertories were able to reach new targets that were not achieved with either original policies or single repertories of motor synergies [2]. We believe this is the first study that has succeeded in motor synergy generalization for new targets in new planes, using a full 7-d.f. arm model, which is a realistic mechanical environment for general reaching tasks.

IV. Conclusion

The first study gives inspiration on how neural integrators manage the amplitude, frequency, and phase modulation to the unknown dynamics [1]. The second study reveals that a linear combination of motor synergies extracted from multiple policies can be generalized to new targets. Notably, only with learning in horizontal and sagittal reaching, and totally new frontal reaching could be achieved through synergy generalization thanks to modularity advantage [2].

References

[1] M. Hayashibe and S. Shimoda, *Synergetic synchronized oscillation by distributed neural integrators to induce dynamic equilibrium in energy dissipation systems*, Scientific Reports, 12, 17163, 2022.
[2] K. Kutsuzawa and M. Hayashibe, *Motor synergy generalization framework for new targets in multi-planar and multi-directional reaching task*, Royal Society Open Science, vol. 9, 211721, 2022.

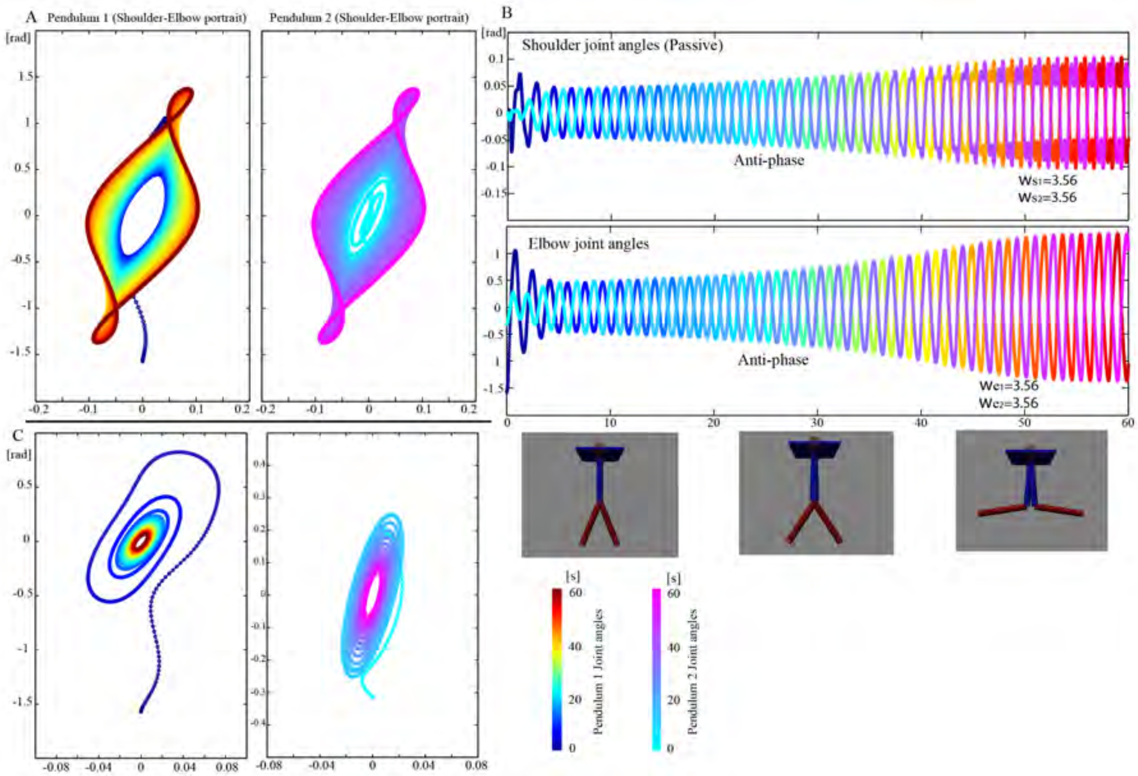


Fig. 1. (A) Phase portrait of two double pendulums connected to a common floating base. (B) The shoulder and the elbow move over time in anti-phase. When the common base was fixed, there was no interaction between the two pendulums. When the common base was floating, the pendulums achieved anti-phase oscillation instantly. This implies that "phase modulation" could be achieved with this method. (C) When neural integration was not used, the oscillation could not be sustained.

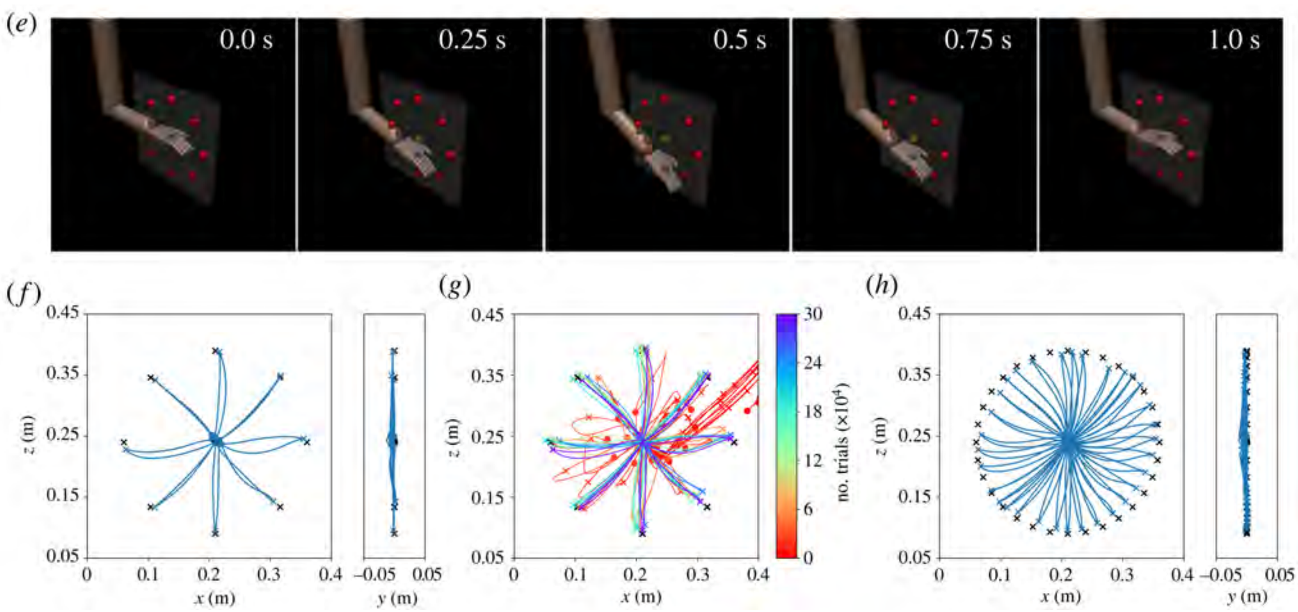


Fig. 2. Results in sagittal policies. (**E**) An example of snapshots in the sagittal targets. (**F**) Trajectories in the sagittal targets. (**G**) Learning progress. (**H**) Trajectories in the various targets with different θ, including unlearned ones.

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

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

Abstract— **It is generally accepted that the human musculoskeletal system is evolved in such a way that it facilitates generation of robust, energetically efficient bipedal locomotion. The fact that the human musculoskeletal system is morphologically adapted to generation of habitual bipedal locomotion possibly indicates that the human nervous system inherently possesses an ability to adaptively make use of such alteration of body structure and morphology to facilitate control and to reduce energetic cost of bipedal locomotion by hyper-adaptive reorganization of the locomotory nervous system. In this study, we attempt to elucidate such hyper-adaptive mechanism of human bipedal locomotion based on a neuro-musculoskeletal forward dynamic simulation.**

I. Introduction

For animals, locomotion is one of the most important bodily functions for their survival and reproductive success, i.e., escaping from predators, searching for food, and even meeting a mate and producing 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 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. Specifically, the evolutionary alterations of the hip and foot musculoskeletal structures (i.e., the bowl-like structure of the pelvis and longitudinal arch of the foot) are suggested to be the key for the acquisition of stable and efficient bipedal walking in humans.

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 ground reaction force 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 reticulospinal and 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].

The above nervous model incorporated the mathematical model of the CPG, but this is not sufficient to explain the mechanism of “hyper-adaptability”. The reticulospinal tract that involves in the control of muscle tone during postural and locomotor control, and the vestibulospinal tract responsible for vestibulospinal reflex necessary to maintain postural balance against external perturbations should be incorporated. Since reticulospinal tract neurons relay inputs from the mesencephalic locomotor region (MLR) to the CPG, we are modeling it such as to adjust muscle tones in response to changes in sensory information during locomotion. On the other hand, the vestibulospinal reflex is a reflex in which the vestibular organ senses the acceleration of the body due to external perturbations and adjusts the muscle tone of the limbs to maintain its body equilibrium. In this study, we hypothesize that the vestibular nucleus estimates the ground reaction force vector necessary to control trunk orientation in response to a perturbation based on information from the vestibular input and converts it to muscle torques and activations based on the transpose of the leg Jacobian matrix.

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. The simulated gait also captured the main features of the ground reaction force profiles in the Japanese macaque [6]. However, bipedal gait simulation based on a nervous model incorporating the reticulospinal and vestibulospinal tracts has not yet been realized. In the future, we intend to clarify the mechanism of "super-adaptation" associated with the alterations of the body structure by realizing the gait simulation incorporating the models of these descending tracts.

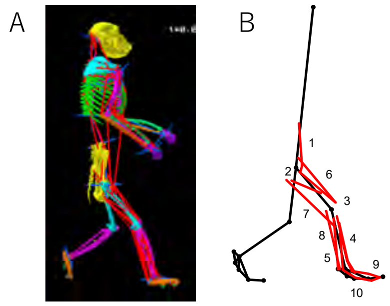


Fig. 1. Musculoskeleta model of the Japanese macaque. A: 3D whole-body model. B: 2D model used in the present study.

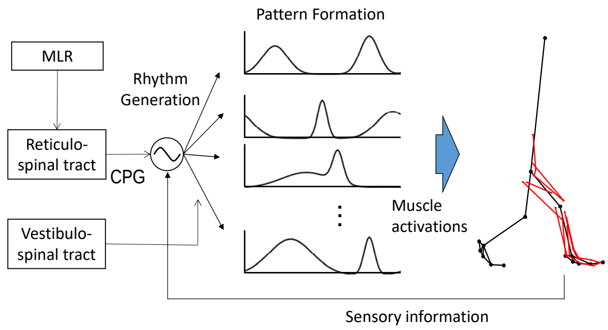


Fig. 2. Framework for the modeling of locomotor nervous system.

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.

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 often assumed that sensorimotor experiences evoked by infantile spontaneous movements have an essential role for development of sensorimotor coordination. We focus on analyzing sensorimotor data during such spontaneous movements in neonates and infants, to understand the specific functional recovery and compensatory processes that occur in early development. We collected and analyzed motion data from neonates and infants to identify a dynamic transition in sensorimotor interactions, such as "sensorimotor wandering," which emerged spontaneously in neonates and infants. In this year, we showed that neonates and infants learn patterns of sensorimotor interaction not only in the spatial direction but also in the temporal direction. We also developed a model to emerge muscle synergies in task-free movements, which enabled the verification of acquired muscle synergies contribution to developmental behavioral acquisition.

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 FY2022, we analyzed sensorimotor data during spontaneous movements in neonates and infants, and developed a model which generate self-organized muscle groups.

II. Aim of the Group

The specific aim of this research item 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. "Senseorimotor wandering" in neonates and infants

We has collected and analyzed motion data from neonates and infants before the emergence of intentional motor control, and has examined the spatial and temporal structuring of the relationship between muscle activity and proprioceptive inputs during their spontaneous movements. In this year, we adopted ensemble spectral clustering based on orthogonal non-negative matrix factorization (ortho-NMF), as the time-varying clustering methodology to analyze time-varying aspects of the information density of sensorimotor interactions. We determined the rank number based on the information criteria defined by Bai et al. To obtain the clusters at each time step, Ortho-NMF with k = 12 was iterated 10,000 times for calculating the information density of sensorimotor interactions considering Gaussian noise. We eventually, we conducted spectral clustering considering coincidence probability calculations and obtained 10,000 clustering results at each time step. Finally, we obtained 12 states and delineated a dynamic transition in sensorimotor interactions, expressing the spontaneous emergence of sensorimotor states, such as "sensorimotor wandering" in neonates and infants (Fig. 1).

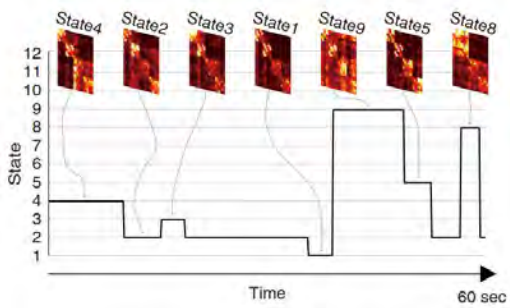


Fig.1 Example of transition of sensorimotor interactions.

To describe the developmental changes based on the properties of dynamic transition, we estimated group-level transition probabilities as a Markov chain (Fig. 2). The red dots in each transition probability matrix represent the points that exceeded the threshold generated by random permutation, indicating that when a participant is in one state, he or she then tends to transition to a certain state. To examine whether the transition probability matrix of neonate and infant group is far from random, we conducted the permutation test, in which the null hypothesis was that each matrix would have the same number of state transitions exceeding the threshold. These results clarified that the state transition of the infant group significantly differed from random (p=0.0210), whereas neonate group do not differ (p=0.6776).

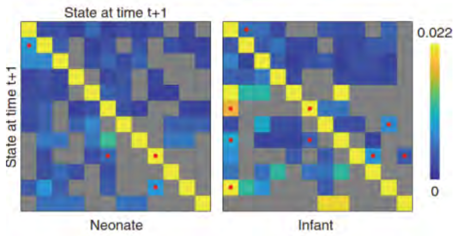


Fig.2 Transition matrix in sensorimotor interactions

Furthermore, we aimed to assess the presence of a temporal pattern in spontaneous sensorimotor interactions and associated age-related changes. With regard to temporal patterns, we defined the dyadic and triadic state sequences based on previous and subsequent sensorimotor states when state transitions occurred. The repetition ratio of each dyadic and triadic sequence pattern was calculated as the co-occurrence probability over the entire recording time and across participants. We consequently identified a higher co-occurrence probability of the dyadic and triadic state sequences in infants than in neonates.

These results indicates that infantile spontaneous movements, despite being task-free, structure and organize sensorimotor interactions in the entire body during early development.

B. NMF-based muscle synergy in spontaneous movement.

Major purpose of this project is to understand the specific functional recovery and functional compensatory processes that occur in early development. It requires a learning model that induces developmental change, as described in A, as a platform to enable this to be verified. In this year, we proposed a model for the acquisition of muscle synergy in task-free conditions such as infantile spontaneous movements. First, we input random muscle activity into an infant musculoskeletal model with 186 muscles throughout the body to generate spontaneous whole-body movements. We applied k-shape clustering or NMF to the resulting proprioceptive inputs and updated the weight matrices of network of muscle activities. Finally, the infant musculoskeletal model achieved muscle synergies (Fig3).

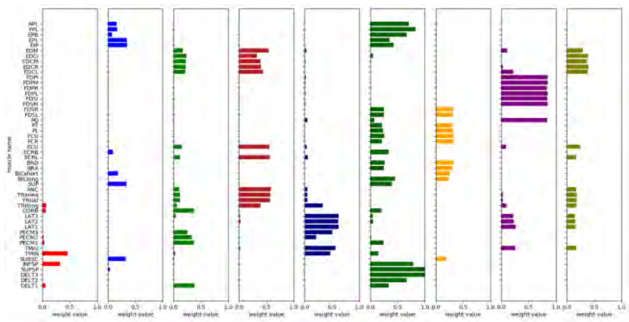


Fig.3 weight matrices of network of muscle activities

Subsequently, in order to confirm whether the acquired muscle synergies contribute to developmental behavioral acquisition, the learning of rolling over in reinforcement learning using Soft Actor Critic was verified. A comparison of learning performance with and without muscle synergies showed that while there was no learning at all when muscle synergies were not acquired (Figure 4, blue), rolling over could be learned after muscle synergies were acquired.

From these experiments, it has been demonstrated that sensorimotor learning through spontaneous movements in the early developmental stage would be acquired through relatively simple learning rules using task-free random movements, and the results can be utilized in later movements or behaviors.

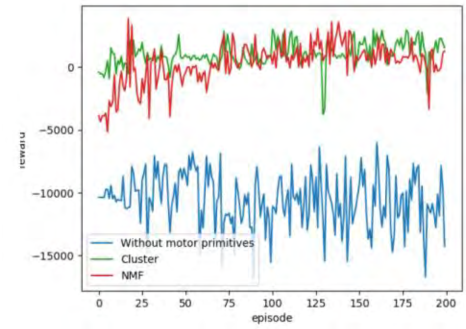


Fig.4 Comparison of rewards for learning to rolling over.

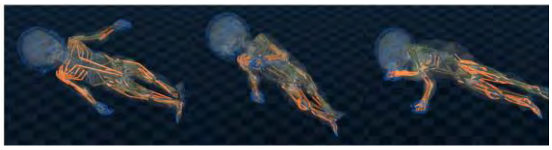


Fig.5 Examples of rolling over with muscle synergy..

IV. Future Perspective

This year, through the analysis of motor measurements in actual neonates and infants, we have shown that they learn patterns of sensorimotor interaction not only in the spatial direction but also in the temporal direction through task-free spontaneous movements in the early stages of development. In addition, using an infant musculoskeletal model, we have shown that they can acquire muscle synergies by learning the co-occurrence of random muscle activities during task-free spontaneous movements, and that the acquired muscle synergies can be used for specific learning. Next year, we will investigate how these learning processes are disrupted and how they can be improved in cases where abnormalities occur in the body or nervous system.

References

[1] Kanazawa, H., Yamada, Y., Tanaka, K., Kawai, M., Niwa, F., Iwanaga, K., & Kuniyoshi, Y. (2023). Open-ended movements structure sensorimotor information in early human development. Proceedings of the National Academy of Sciences, 120(1), e2209953120.

[2] Shinomiya Y, Kanazawa H, KimD, Kuniyoshi Y, Action acquisition of musculoskeltal infant agent using motor primitives and deep reinforcement learning, International Symposium on Adaptive Motion of Animals and Machines 2023 (submitted).

B05-4Annual report of research project

Isao Nambu
Nagaoka University of Technology

Abstract—**Functional connectivity is an important measure to evaluate relationship among different brain regions. While several recent studies suggest that neural population dynamics is represented as low-dimensional subspace, such the dynamic spaces are not investigated for functional connectivity yet. This study aims to develop a method to detect low-dimensional subspace for the functional connectivity. For this purpose, we examined the results using a method using auto-regressive models for electroencephalogram during reaching and a method using time-varying graphical lasso for electroencephalogram during sleep and electrocorticogram for reaching task. We found the possibility to detect dynamics related to the behavioral states in the low-dimensional subspace while many issues are to be solved**.

I. Introduction

There are various brain regions that communicates information among them to realize perception, behaviors, and so on. Functional connectivity is a measure to quantify the statistical dependence of time-series data among such multiple brain regions [1]. Therefore, functional connectivity is used to examine the relationship between multiple brain regions. Several functional connectivity methods have been proposed. However, it is difficult to interpret all relationships between multiple regions in a unified manner.

On the other hand, it has recently become clear that the neural representation of movements depends on the state in the low-dimensional space (Neural Manifold) consisting of neural populations [2]. For example, it has been suggested that in the motor cortex, the neural populations during motor planning and execution are represented in a low-dimensional space [2,3]. However, it is unclear how multiple brain regions are related to the movements and the relationships and interactions among these brain regions. If low-dimensional dynamics at the whole-brain level involving multiple brain regions can be clarified, we may be able to gain a deeper understanding of human movements, adaptation, and learning. Recently, studies have attempted to find the low dimensionality of functional connectivity for functional magnetic resonance imaging data [4,5]. Thus, it would be useful to elucidate the mechanism of functional connectivity if the dynamics can be examined in electroencephalogram or electrocorticogram with superior temporal resolution. In addition, changes in bilateral motor-related regions [6] are considered to be important in "hyper-adaptability," and it would be important to detect changes in dynamics of the bilateral motor-related regions. Therefore, in this study, we attempt to develop a method to identify the brain activity involved in movement as low-dimensional state-space dynamics and aim to elucidate the mechanism of "hyper-adaptability".

II. Aim of the Group

The purpose of this research is to develop a method to identify state-space representations for elucidating hyper-adaptability. We also aim to detect changes during hyper-adaptation by using the developed method to examine the dynamics in low-dimensional space, especially in bilateral motor-related regions. For this purpose, we continued to develop a method to find the low-dimensional subspace using directed graphs (AR-based method) for electroencephalogram (EEG) data during human reaching movements. Also, the low-dimensional spatial identification method using undirected graphs (TVGL-based method) was also examined on another data sets.

III. Research Topics

We examined two types of the methods as follows.

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

Continuing from the previous fiscal year, we studied a method that combines auto-regressive models (AR models) and the Kalman filter. This method incorporates a model of directed graphs that can clarify the directionality of functional connectivity. For directed graphs, we use the commonly used auto-regressive model. The coefficients of the autoregressive model are estimated using the Kalman filter. Distance was calculated from the coefficients obtained with these methods and then visualized using manifold learning.

An example of the results obtained from this method for EEG data during reaching movements [6] is shown in Fig. 1. Projection of the trial-averaged data onto a 2-dimensional or 3-dimensional space confirmed a smooth transition from the resting state to the execution state of the movements. This tendency became clearer when smoothing was applied, and the temporal changes in the low-dimensional space could be captured under limited conditions. This tendency was also observed in data from different subjects, but the trajectories in low-dimensional space showed different tendency. The temporal changes at different frequencies were also confirmed by using a band-pass filter with each specific frequency bands, suggesting transitions in multiple frequency bands. Therefore, it is considered necessary to further study the low dimensionality in different frequency bands.

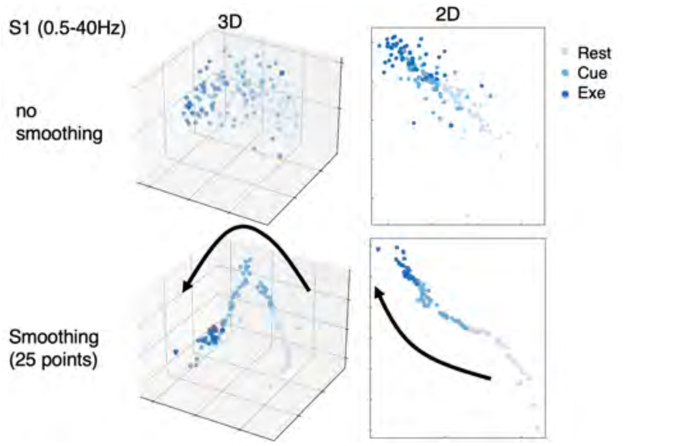


Fig. 1. An example of three-dimensional (left) and two-dimensional representation of the states using AR-based models for the reaching data. Upper figures show data without smoothing and lower figures show results with smoothing. Each color indicates different behavioral states (rest, cue, and exection).

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

Next, a low-dimensional visualization method using an non-directed graphical model was investigated. EEG and electrocorticogram (ECoG) are dynamically changing between regions from moment to moment. Therefore, it is desirable to construct a model that takes such dynamic nature into account. In a previous study, a stochastic graphical model, Time-Varying Graphical Lasso (TVGL) has been proposed [8]. In this study, we continued to investigate this method from the previous fiscal year. We applied it to different data sets (sleep EEG data and ECoG data.

For the sleep EEG data, we examined whether there were any changes related to sleep stage. It was confirmed that data at the same sleep stage but at different times were not confirmed to be in close states even in the low-dimensional space, suggesting rather reflecting the proximity of time. Therefore, it is considered necessary to consider the variation associated with time in the analysis.

Next, we also applied this method to the ECoG data during reaching and grasping movements. We found that a trend of gradual change from before to during the movements was observed in low-dimensional space. This tendency was particularly found in low-frequency bands such as theta and alpha bands. This suggests that a low-dimensional identification method using TVGL may be able to capture the low-dimensional dynamics of functional connectivity.

However, this is a preliminary study on a single subject. Further investigation for other data, parameter search, and examination of brain regions corresponding to low-dimensional space are needed.

IV. Future Perspective

In this study, we tried to develop a method to identify the low dimensional subspace for EEGs or ECoGs in humans. We tested two types of methods in this fascial year. We found a possibility that these methods can detect dynamics related to the task/behavioral states in the low-dimensional space. However, it is also observed temporal variations unrelated to the task states. In the next fiscal year, we will further examine such the methods specifically and apply it to data with bilateral motor-related areas for understanding of hyper-adaptability.

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] T. Semoto., I. Nambu., and Y. Wada. The Relationship Between the Movement Difficulty and Brain Activity Before Arm Movements. In *International Conference on Neural Information Processing*, pp. 522-529, 201

[8] 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.

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

Yuichi Kobayashi
Faculty of Engineering, Shizuoka University

***Abstract*—When partial dysfunction occurs in the human body or brain, it is possible to adaptively recover function by reusing previously acquired neural circuits. We propose a motor learning model that describes such an adaptive process. While our previous motor learning model that estimates the transformation of partial dependencies of motor systems is based on the feedback control mechanisms, this study also focuses on the process of acquiring the feedforward control. In addition to estimating the transformation of coefficient information in feedback control, by considering the transformation of feedforward terms, we aim to explain the process of reusing already acquired motor control information such as muscle synergy.**

I. Introduction

The human adaptive capacity encompasses the ability to dynamically recover functionality following partial impairments in the body or brain by reutilizing acquired neural pathways. For instance, it has been investigated that, as an alternative to neural circuitry, when one hand is paralyzed, it can be controlled through a distinct neural pathway [1].

We have constructed a motor learning model capable of explaining the aspect of ‘neural pathway reutilization,’ which has not been sufficiently represented in conventional human motor learning models. This model explains the process of reusing a portion of the acquired motor control model in response to situational demands. In upper limb motor control, there exist multiple causal (dependent) relationships, such as the kinematics that relate joint angles and hand position and the motion equations that relate joint torque and joint acceleration, among several sensor variables (proprioceptive information) with different modalities.

In the first stage of our research in the project, we proposed a model based on previous research results that estimates the dependency relationships between various sensor signals in motor control and automatically generates controllers [2]. We have developed a motor learning model that explains the process of reusing partial causal relationships in acquired controllers by introducing a mechanism for estimating transformations between mappings in the model [3].

On the other hand, in the process of motor learning and motor function recovery in living organisms, it is known that multiple muscles cooperate and activate together with a certain temporal pattern, a function called muscle synergy. Measuring the expression, generation, and recovery processes of muscle synergy is a powerful means of understanding the process of super-adaptation. Muscle synergy is thought to be

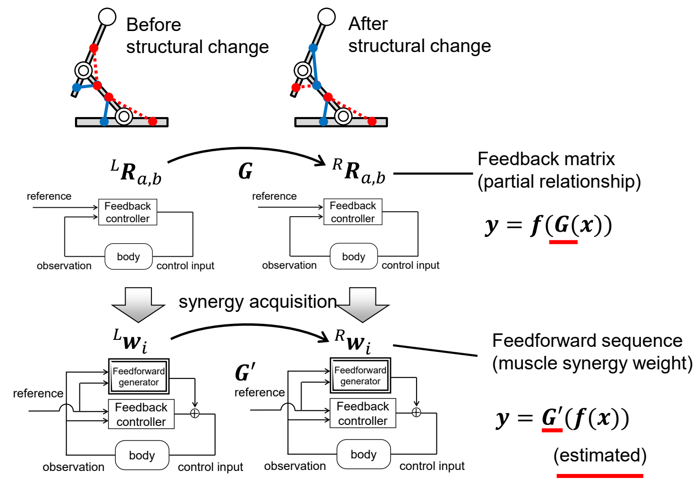


Fig. 1. Motor learning model of reuse of controller information including muscle synergy

acquired through repeated movements, and it is important to consider reusing knowledge about motor skills based on the acquisition of learning. In addition, both feedback (FB) control and feedforward (FF) control are used in human body control, and there are cases that suggest that by repeating movements, control can be switched from FB control to FF control, enabling unconscious control [4].

II. Aim of the Group

We propose an explainable motor learning model that extends our previously proposed feedback control-based knowledge reuse model to include the acquisition of feedforward time-series signals similar to muscle synergies. The generation of feedforward time-series control input based on the feedback control system is shown in the transition from the top to the bottom of Fig. 1. The reuse of motor information through variable transformation that we have previously proposed is represented by the left-to-right arrows in the top row. The left-to-right arrows in the bottom row represent the reuse process of acquired feedforward time-series signals through transformation. By considering the transformation that includes the acquisition of feedforward control, we can reproduce motor learning and adaptation processes, including the reuse of muscle synergies.

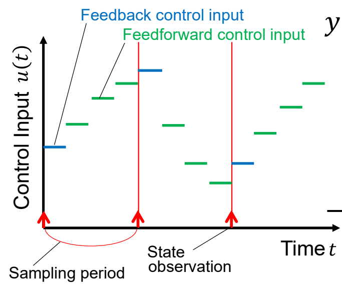


Fig. 2. Long period control

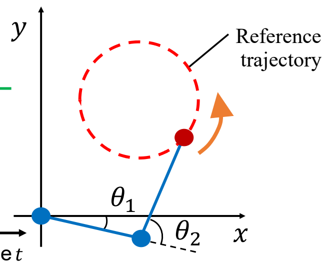


Fig. 3. 2-DoF manipulator motor learning

III. Research Topics

As an approach to constructing the motor learning model in Fig. 1, we conducted a more precise verification of the variable transformation proposed in [3] (the process from left to right in the upper row of the figure) and proposed a learning model that generates FF time series based on the FB control system (the process from the upper to the lower row in the figure).

A. Motor information transformation and reuse in feecback control system

In the motor learning method based on the algorithm [2] locally weighted regression is used to estimate the relationships between sensor variables. Based on this regression information, we proposed a variable transformation that can estimate the mirror relationship between the left and right arms using an adaptive grid distribution algorithm [3]. However, this algorithm has the problem that the representation freedom of variable transformations is high, and the search space becomes large for large-scale problems. To estimate variable transformations more efficiently with lower degrees of freedom, we proposed a method of estimating the relationship between local linear transformations in the form of transformation matrices, and verified it on a simple problem assuming the estimation problem of the mirror relationship of the left and right arm controllers [5].

B. Acquisition of feedforward sequence by extension of feedback control cycle

As a motor learning method for acquiring the time-series signal in FF control, we propose a learning process in which a person gradually becomes able to move smoothly by repeating the same movement. This is achieved by controlling with less FB information through repetition within a certain range of movement. In contrast to the conventional combination of FF control and FB control, which mainly focuses on control performance and robustness against disturbances, the main objective of this proposal is to reduce the frequency of FB control by adjusting FF control. To acquire such long-period control, we use a reinforcement learning, Blind Action Sequence Learning with EM (BASLEM) [6], which is state-independent and time-dependent.

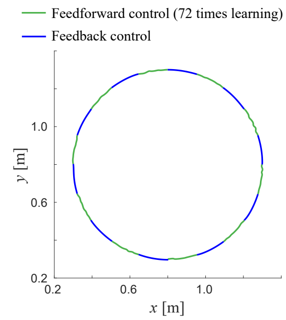


Fig. 4. Control result after learning

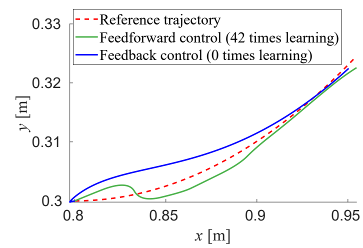


Fig. 5. Comparison of trajectories in the first section

By conducting 100 trial-and-error attempts on a 2-link manipulator control system for arc path tracking shown in Fig. 3, a long-period control was obtained, as shown in Fig. 4. The green area in the figure represents the interval controlled without state observation based on the FF time series. As shown in Fig. 5, which extracts the trajectory in some intervals, it was confirmed that the reference path was followed without degradation compared to when FB control was used.

IV. Future Perspectives

We proposed an explainable motor learning model that includes the reuse of knowledge, including the acquisition of time-series control signals such as muscle synergies in motor learning. We found that the motor learning model based on feedback control could represent the estimation of variable transformation with simpler calculations than before. In addition, we proposed a motor learning method called 'long-term potentiation of feedback control,' which made it possible to explain the process of 'becoming able to perform smooth and natural movements without conscious effort by repeating the movement.' In the future, we aim to verify these two achievements in more practical motor learning settings and develop a motor learning model that can be compared with biological experiments and knowledge.

References

[1] T. Isa, M. Mitsuhashi, R. Yamaguchi, Alternative routes for recovery of hand functions after corticospinal tract injury in primates and rodents, Current opinion in neurology, Vol.6, No.5, pp.836-843, 2019.

[2] 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.

[3] 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.

[4] X. Zhang, S. Wang, J. B. Hoagg, The Roles of Feedback and Feedforward as Humans Learn to Control Unknown Dynamic Systems, IEEE Transactions on Cybernetics, Vol. 48, No. 2, pp. 543–555, 2018.

[5] Yuichi Kobayasi and Sota Nakamura, Transfer of Partial Information of Motor Controller Based on Estimation of Coordinate Transformation Parameters, Proc. of The 33rd 2022 International Symposium on Micro-NanoMechatronics and Human Science, MA2-1-5, 2022.

[6] D. Nakano, S. Maeda and S. Ishii, Proposal of New Reinforcement Learning with a State-independent Policy, Trans. of the Institute of Systems, Control and Information Engineers, Vol. 27, No. 8, pp. 327–332, 2014.

B05-6 Annual report of research project

Michiteru Kitazaki
Toyohashi University of Technology

Abstract—**We have built a system for virtual eyes on the hand experiment, presented a demonstration exhibit and designed the experiment. For the system for virtual eyes on the back of the head, the experimental system was constructed, and data acquisition started; We found that the motor learning occurred, and the walking became smoother and faster during 10 days. In addition, experiments were conducted to verify the adaptability of humans for long-term learning of an impossible body with joints that bend in opposite directions, a virtual walking system with different directions of gaze, and a system where two people operate a single avatar.**

I. Introduction

Research on embodiment, such as the Rubber hand illusion, has developed in the aspect of body transformation using virtual reality (VR). By changing the appearance of avatars synchronized with body movements, it is possible to change the skin color, become a child's body, become transparent, make body parts scrambled, use one body for two people, and so on, and a sense of body ownership is induced in these avatars, changing attitudes and behavior to match the avatar's attributes (Fig. 1) [1-3]. However, in most studies, the body shape remains human and is typically manipulated by a single subject with a single avatar. In order to elucidate the limits and plasticity/adaptability of human body perception, further transformations of avatar shape and function need to be systematically investigated.

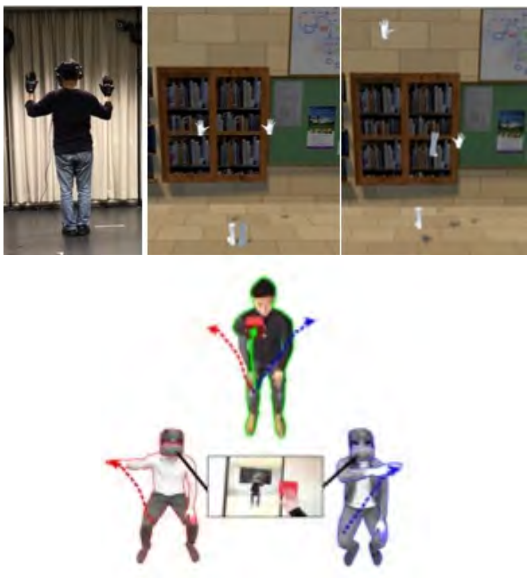


Fig. 1 Invisible body (top), and Shared body (bottom)

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 human'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 human's perception and behavior change with long-term adaptation. Specifically, bodies 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, are 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. 2).

Fig. 2 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 hand

In the VR space, a system was implemented and exhibited in which the left and right eyes (virtual cameras) were placed on the left- and right-hand controllers and could be moved freely by the left and right hands. When the binocular images were not fused, binocular rivalry occurred. However, when something was found and the eyes (i.e. hands) were moved to look that way, that field of vision became dominant and a consistent visual experience was obtained. When eye movements were measured, eye movements similar to the vestibular oculomotor reflex were observed when the hand, which is the eye, was moved [4].

B. 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 three 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. 3). 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.

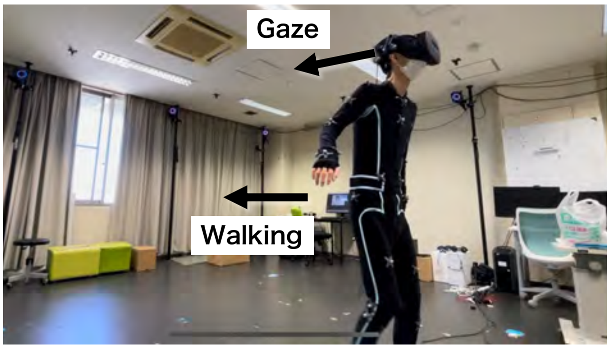


Fig. 3 Walking experiment with body with eyes behind the head.

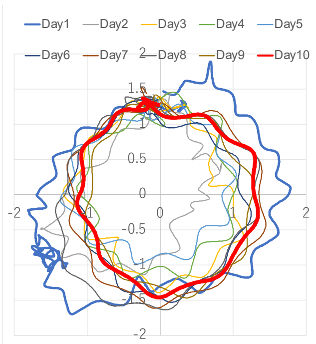


Fig. 4 Data on the walking trajectories of a participant in the experiment over a period of 10 days

For the participants' 10 days of circumferential walking, the walking trajectories became smoother as the days progressed (Fig. 4) and the walking time became shorter (faster walking speed); a similar trend was observed in the complex course walking task performed only on days 0 and 11. 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 or influenced by learning.

C. Adaptive learning for bodies with joints bent in opposite directions

An experiment was conducted by creating a body in which the elbow joints of the left and right arms were bent in 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 [5].

D. Virtual walking system with different avatar gaze direction from user's gaze direction

It is known that virtual walking experiences can be induced by presenting only foot vibrations and visual images without moving the legs in a sitting position. Our experiments showed that virtual walking experiences can be induced to some extent in a lying position on the back, where the direction of gaze in the VR space and the actual direction of gaze of the experimental participants are different [6].

IV. Future Perspective

For the two main experiments, a system was constructed for the eye on the hand experiment, a demonstration exhibition was held and a plan for the experiment was drawn up. For the eye on the back of the head experiment, the experimental system was constructed, and data acquisition was started. In addition, experiments were conducted to verify the adaptability of humans for long-term learning of an impossible body with joints that bend in opposite directions, a virtual walking system with a different direction of gaze, and a system where two people operate a single avatar [7]. In the next year, data acquisition and analysis will be carried out, and more detailed models will be built based on the data.

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] Onodera, R., Mimura, T., Hirose, S., Inoue Y., and Kitazaki, M. (2022). Espcape of eyes: Destruction of relationop between body and eyes, Annual Conference of Japan Virtual Reality Society, 1G-01, Sapporo.

[5] Hapuarachchi, H., Ishimoto, H., Sugimoto, M., Inami, M., and Kitazaki, M. (2022). Embodiment of an Avatar with Unnatural Arm Movements, 2022 IEEE International Symposium on Mixed and Augmented Reality (ISMAR), 17 – 21 October 2022, Singapore

[6] Nakamura, J., Ikei, Y., and Kitazaki, M. (2023). The Effect of Posture on Virtual Walking Experience Using Foot Vibrations. Augmented Humans 2023, 12-14 March 2023, Grasgow, UK.

[7] Hapuarachchi, H., Hagiwara, T., Ganesh, G., and Kitazaki, M. (2023). Effect of connection induced upper body movements on embodiment towards a limb controlled by another during virtual co-embodiment. PLoS One, 18(1): e0278022

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

Taishin Nomura
Osaka University

***Abstract*— Beta rebound, synchronous brain activities in the beta frequency band that appear after execution (Go) and/or suppression (No-Go) of movements, has been studied in the context of motor decision-making processes during upper limb voluntary movements. In the first stage of the Hyper-Adaptability project, we showed, for the first time, that there exists a beta rebound of electroencephalogram (EEG) activity during perturbed upright stance in response to a brief support-surface perturbation, using the perturbation-onset as a triggering event. Particularly, the long-lasting beta rebound appeared during a period of time when the postural state recovers slowly toward upright position along stable manifold of the unstable saddle-type upright equilibrium of the postural control system without active feedback control (OFF-period of the active control). Here, in the second stage of the project, we are examining whether a similar beta rebound can be observed during quiet stance. In this case, the "micro-recovery" is the target timing of our examination, during which the postural state recovers slowly toward upright position following the occurrence of the preceding micro-fall. As predicted by the the intermittent control hypothesis, we showed that EMG activity level of mediolateral gastrocnemius was low during the micro-recovery, implying that the postural state recovers during the OFF-period of the active control. Then, we are currently analyzing the Event-Related Spectral Perturbation map during the micro-recovery, using the onset of micro-fall as a triggering event. The interim result suggests the existence of beta rebound in the micro-fall during quiet stance.**

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 hypothesis [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 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 medial gastrocnemius 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 on Innovative Areas, 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) [4]. 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 [5]. 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 activity of the medial gastrocnemius [4].

In the second stage of this Research on Innovative Areas, we are investigating 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 repeats 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 thousands times throughout their developmental stage from infancy.

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 the mediolateral gastrocnemius 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.

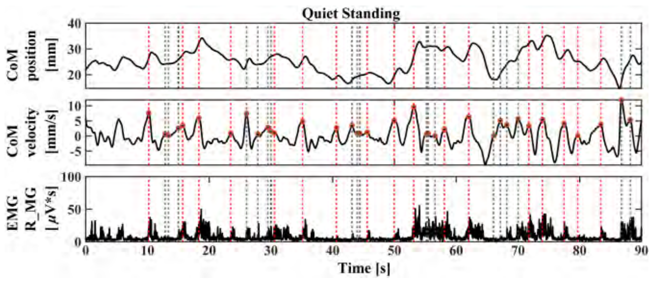


Fig. 1. Postural sway in anterior-posterior (AP) direction and the corresponding EMG activity of medial gastrocnemius during human quiet stance. Top, middle and bottom traces exemplify time series data of CoM-AP (center of pressure in AP direction) measured by a motion capture system, CoM velocity, and corresponding full-rectified and low-pass-filtered EMG from mediolateral gastrocnemius (MG), respectively. Vertical dotted lines indicate the sequence of micro-fall events.

Then, EMG and wavelet-transformed EEG time-frequency signals were averaged to obtain Event-Related Spectral Perturbation (ERSP) as shown in Fig. 2. In Fig. 2, activity of the medial gastrocnemius muscle increased with the occurrence of the micro-fall, but when the CoM started to show the micro-recovery, the activity of the medial gastrocnemius muscle decreased and formed a plateau waveform, which might correspond to the OFF-period of the intermittent control. Furthermore, ERS was confirmed in the β-band of ERSP during this OFF-period of the control.

IV. Future Perspective

The β-band ERS in Fig. 2 is considered to be β- rebound reflecting active postural monitoring during the micro-recovery process, although further careful examinations including statistical tests are necessary.

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] 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.

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

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

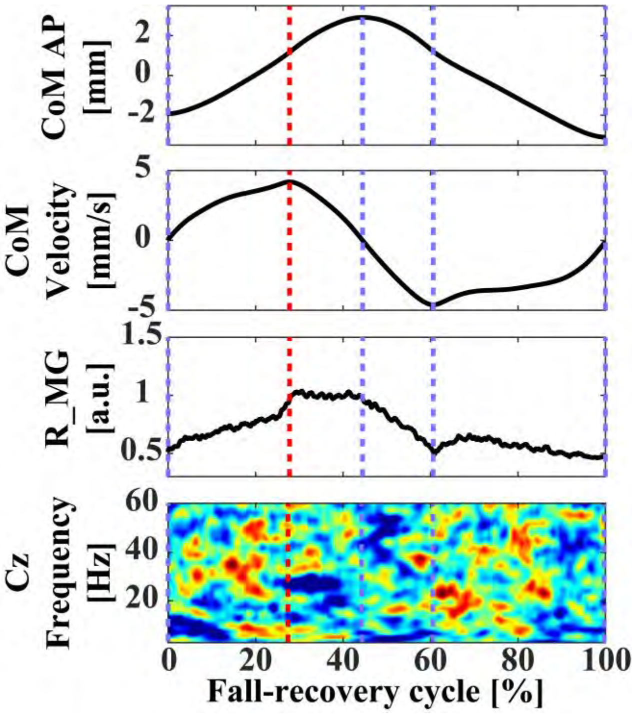


Fig. 2. Time-locked average of epochs for time series of CoM-AP, its velocity, rectified EMG of mediolateral gastrocnemius (MG), and wavelet-transformed EEG at Cz electrode (ERSP).

B05-8 Annual report of research project

Kazuhiro Sakamoto
Faculty of Medicine Tohoku Medial and Pharmaceutical University, Tohoku University Graduate School of Medicine

***Abstract*—Here, we developed a model for learning a two-target search task. In the task, the agent is required to gaze one of the four presented light spots. Two neighboring spots are served as the correct target alternately, and the correct target pair is switched after a certain number of consecutive successes. In order for the agent to obtain rewards with a high probability, it is necessary to make decisions based on the actions and results of the previous two trials. Our previous work achieved this by using a dynamic state space. However, to learn a task that includes events such as fixation to the initial central spot, the model framework should be extended. For this purpose, here we propose a "history-in-episode architecture." Specifically, we divide states into episodes and histories, and actions are selected based on the histories within each episode. The proposed model performed the task close to the theoretical optimum. The learning model including the proposed history-in-episode architecture and dynamic state scape provides a basis for hyper-adaptable learning systems to complex environments.**

I. Introduction

In the real world, the unexpected often occurs. An environment in which we cannot even define the probability space of what can happen is called an indefinite environment. To truly adapt to such new situations, it is necessary to proactively engage the world and generate the framework for adaptation itself. To elucidate the principle of proactive outreach to such an indefinite environment, Sakamoto et al. has constructed a reinforcement learning model that dynamically and autonomously defines the probability space or state space based on the criteria of experience saturation and action decision uniqueness[1][2]. However, the model is far from adequately reproducing the advanced adaptive abilities of primates.

II. Aim of the Group

In this research project, we aim to construct a learning model of higher-order brain functions, especially in the higher motor cortex, by extending the dynamic state-space reinforcement learning model described above. So far, we have developed a learning model based on a two-target search task (Fig. 1A). In this task, four light spots are presented in front of the animal's eyes, and the animal is rewarded for fixating on the correct target hidden in the spots. Two adjacent light spots are alternately used as the correct target (correct pair), but after a certain number of consecutive successes (exploitation phase), the correct pair is switched without informing the animal, and the animal has to search for a new correct pair (exploration phase). In the actual task, there were several events within a single trial (Fig. 1B). In the two-target search task, a fixation point first appeared, followed by four light spots around it. The disappearance of the fixation point in the center served a go signal, and the animal had to look at the correct light spot within a certain period of time to receive a reward. The question is how to handle the double time flow? That is, how to reconcile the learning of behavior based on the history of actions and their results across trials with the learning of behavior at each event within a trial? Reinforcement learning models basically determine the next action based on the previous state. To obtain a high correct response rate in the two-target search task, it is necessary to make decisions based on the actions and their results of the last two trials, but the subject has to fixate the center spot at the time physically just before shifting the gaze to the correct light spot.

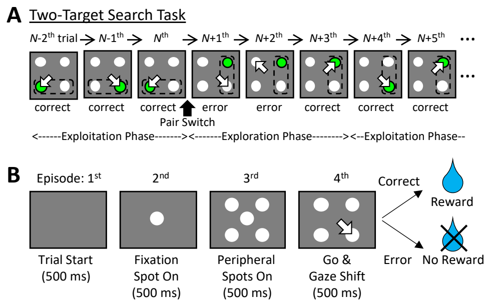


Fig. 1. Two target search task. (A) An illustration of a valid-pair switch. Green circle: correct target; arrow: choice (B) The event sequence of a trial.

III. Methods

To solve this problem, we devised a history-in-episode structure (Fig. 2)[3]. An episode here was specifically an event within a trial that was characterized by the presented stimulus. For example, an episode in which the subject was required to actually look at one of the four light spots was defined by the presentation of the four light spots (Go & Gaze-Shift episode). A memory set, i.e., a dynamically expanding and contracting Q-table, was assigned in response to each new presented stimulus (Fig. 2A). In the case of the two-target search task, the history of prior trials was traced back in the Go & Gaze-Shift episode, while in other episodes, the subject simply needed to fixate on the center and did not need to go back to the previous trial (Fig. 2B). Rewards were given only in Go & Gaze-Shift episodes, but behaviors in the preceding episodes were learned by handing over the reward prediction value.

IV. Research Topics

The results are shown in Fig. 3. As a comparison, we used a fixed 10-state model, i.e., a model in which the behavior was determined based on the action and the result (upper right, upper left, lower right, lower left, lower left, center) x (correct, error) of the previous trial in each episode, and a traditional SARSA model, i.e., a model with only one state in each episode. Although all models performed perfectly in the simplest task, in which one light point remained correct all the time (Fig. 3A), the SARSA model showed very low performance in the task in which two fixed light points alternated (Fig. 3B) and in the one-target search task, in which one light point was correct for a while and then switched to the other (Fig. 3C). In the two-target search task, the fixed 10-state model failed to show a high rate of correct responses (Fig. 3D).

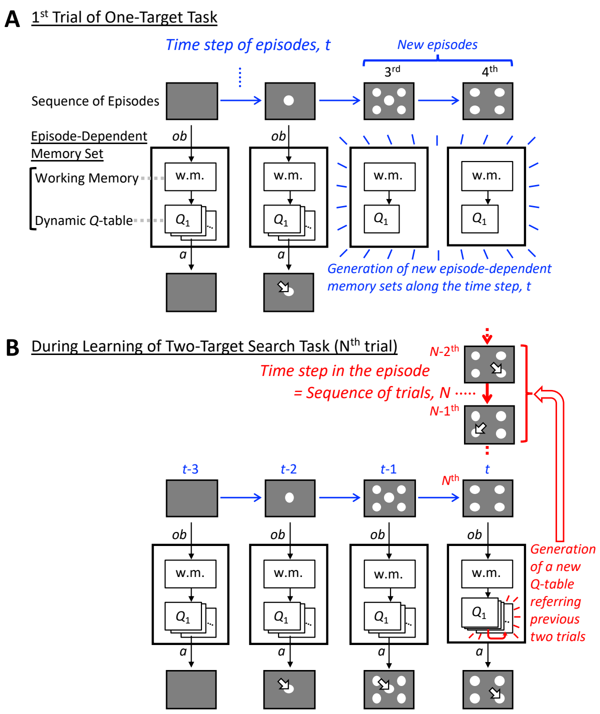


Fig. 2. Schematic diagram of model operations as training progresses. (A) The first trial of the one-target task after completion of the fixation task. Episode-dependent memory sets corresponding to task events 3 and 4 are newly generated. (B) While it is learning the two-target search task. The number of states in task event 4 is still increasing. w.m.: working memory; arrow: choice; ob: observation; a: action.

V. Future Perspective

This year, we added a history-in-episode structure to our previous dynamic state-space reinforcement learning model [1][2] and constructed a learning model that can make decisions based on the inter-trial history while learning actions at intra-trial events [3]. In the future, we plan to construct a model that can learn more advanced tasks including delay periods, but we have already obtained preliminary results [4][5]. Through these studies, we would like to construct a learning model that is hyper-adaptable to unexpected situations[6]. In addition, we would like to draw a novel picture of the brain that actively acts on an indefinite environment and achieves creative hyper-adaptation through elucidating and modeling of dynamic encoding of information in the prefrontal cortex [7][8][9][10].

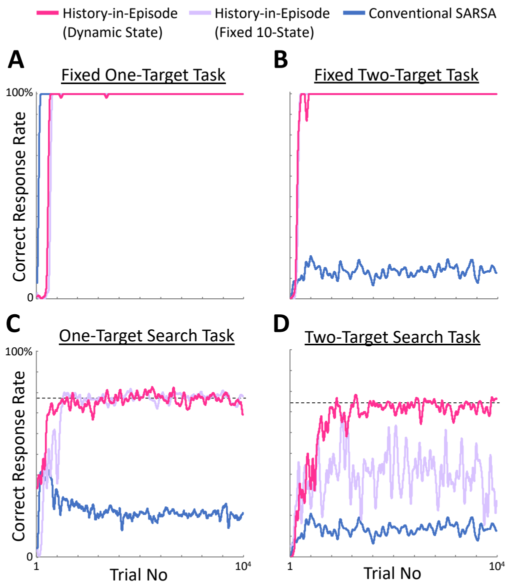


Fig. 3. Comparison of the performance on each task between models. (A) Evolution of the correct response rate in the fixed one-target task. (B) The fixed two-target task. (C) One-target search task. Dashed line: ideal performance. (D) Two-target search task. Dashed line: ideal performance.

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. (*references*)

[2] K. Sakamoto, T. Katakura, H. Mushiake, "Decision uniqueness and experience saturation define the appropriateness of state expansion: comparison between dynamic state space reinforcement learning model and Dirichlet models," NEURO2022, 3P-261, July 2022.

[3] K. Sakamoto, H. Yamada, N. Kawaguchi, Y. Furusawa, N. Saito, H. Mushiake, "Reinforcement Learning Model With Dynamic State Space Tested on Target Search Tasks for Monkeys: Extension to Learning Task Events," Front. Comput. Neurosci., vol. 16, 784604, June 2022.

[4] N. Tamura, H. Mushiake, K. Sakamoto, "A dynamic state-space reinforcement learning model explaining functional differentiation of higher motor areas in the cerebral cortex," IEICE Tech. Rep., vol. 122, NC2022-42, pp. 44-48, Sept. 2022.

[5] N. Tamura, H. Mushiake, K. Sakamoto, "A reinforcement learning model with dynamic state space reproduces functional differentiation between higher motor cortices," NEURO2022, 1P-310, July 2022.

[6] K. Sakamoto, "The brain beyond machine learning: Perspectives from neurophysiology and computational neuroscience of higher brain functions," APSIPA BioSiPS Workshop, Sept. 2022.

[7] K. Sakamoto, "Multidimensional analysis of extracellular potentials in the cerebral cortex," Nara Institute of Science and Technology, Information Science, Colloquium A, June 2022.

[8] K. Sakamoto, N. Saito, S. Yoshida, H. Mushiake, "A dynamic, economical, and robust coding scheme in the lateral prefrontal neurons of monkeys," The 29th International Conference on Neural Information Processing, p113, Nov. 2022.

[9] K. Sakamoto, N. Saito, S. Yoshida, H. Mushiake, "Increased firing variability may be an early warning signal of bifurcation in neuronal networks: Validation in action planning-related cells of monkey prefrontal cortex," Neuroscience 2022, 736.17, Nov. 2022.

[10] 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.

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 SSSEP, B) we improved the proposed neurofeedback training system, and C) we preliminarily examine the training effect based on SSVEP.**

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. Furthermore, we propose a model for the diversity of neural circuits acquired through neurofeedback training. 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. We adopt a training approach based on the outcome of "whether attention is focused or not" by indirectly estimating the attention state from the activity state of sensory areas, without explicitly setting a desired activity state for higher brain regions such as the prefrontal cortex and posterior parietal cortex, which are neural bases of attention function. Through this approach, we aim to demonstrate the effectiveness of an efficient neurofeedback training system that is independent of individual neural characteristics.

III. Research Topics

A. Body-specific attention training based on SSSEP

The attention to a specific body part is called body-specific attention. To train body-specific attention, we used a neurofeedback training system with SSSEP. Participants were randomly assigned to either a Real group (where feedback was based on their own brain activity) or a Sham group (where feedback was based on another person's pre-recorded brain activity, serving as a control group) and underwent 8 days of training. EEG electrodes were placed around the bilateral somatosensory cortexes, and mechanical vibration stimuli were presented to the fingertips of both hands (22Hz to the left hand, 25Hz to the right hand). During the presentation of these mechanical vibration stimuli, a fast Fourier transform was performed on a 5-second buffer of EEG data. The signal-to-noise ratio of the SSSEP was calculated as an indicator of the attention state (i.e., the strength of attention to the body part where the sensory stimulus was presented). During training, audio speakers were placed in front of the participants on both sides, and their volumes were determined based on the calculated signal-to-noise ratio. Participants were instructed to direct their attention to their left hand. When attention was appropriately directed to the left hand, an increase in SSSEP response (i.e., an increase in signal-to-noise ratio) was expected in the right somatosensory cortex, resulting in an increase in the volume of the left speaker. In addition, to evaluate the effects of neurofeedback training on behavior, the GoNogo task and Hand Choice task were performed before and after the training.

As a result of 8 days of neurofeedback training, a marked increase in the response from the right somatosensory cortex was observed in the Real group, as compared to the left somatosensory cortex. In contrast, no such neural modulation was observed in the Sham group. Regarding the evaluation tasks conducted before and after the neurofeedback training, a tendency for a reduction in reaction time to the Go signal presented to the left hand was observed only in the Real group in the GoNogo task after the training. Additionally, in the Hand choice task, an increase in the area where reaching movements were performed using the left hand (i.e., an increase in the frequency of using the left hand) was observed only in the Real group after the training (Fig. 1). These behavioral changes support that the acquired brain activity by the neurofeedback training contributes to improving attention function, demonstrating the effectiveness of the neurofeedback training system proposed in this study.

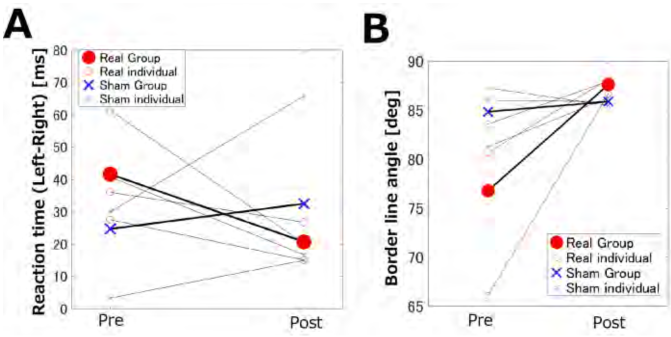


Fig. 1. Behavioral changes in SSSEP neurofeedback training.
A: GoNogo task. B: Hand choice task.

B. *Improvement of the proposed neurofeedback system*

We had been using a self-made vibration device with a brushless DC motor as an actuator to induce SSSEP. This device had the advantage of being noiseless but had also disadvantages such as being loud due to the sound of the motor and requiring a separate system for motor control. To address these issues, we adopted a more compact and easy-to-control haptic reactor as a new vibration stimulation device and used a microcontroller from the M5 Stack series for its control. As a result, the stimulus device became much more compact, and it became possible to present any vibration stimulus at a carrier frequency of around 200 Hz. Regarding the sensory stimulus setting during neurofeedback training, we had been using the same frequency throughout the entire training period. However, with this stimulus setting, it was not possible to exclude the possibility of adaptation or habituation to a specific frequency stimulus. Thus, we set different stimulus frequencies for each training day in new training protocols. Furthermore, based on the previous results, we attempted to reduce the burden on the trainees by shortening the training period from 8 days to 5 days.

C. *Spatial attention training based on SSVEP*

We conducted preliminary experiments on neurofeedback training using SSVEP for training spatial attention. Participants were assigned to the Real group and underwent 5 days of neurofeedback training. 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 (beta-band stimulation to the left visual field and alpha-band stimulation to the right visual field). Similar to the SSSEP training mentioned above, we estimated the attentional state based on the response of the sensory areas and provided feedback as the speaker volume. Participants were instructed to direct their attention to the left visual field. GoNogo and line bisection tasks were performed before and after neurofeedback training.

The results of the 5-day neurofeedback training revealed that the participants were divided into two groups: one group (participant No.1) had an amplified response in the right visual field, while the other group (participants No.2 and 3) had a decreased response. In terms of the training goal, the former was considered a success in neural modulation, while the latter was considered a failure. Next, in the GoNogo task, only participants who succeeded in neural modulation showed a decrease in reaction time. Furthermore, in the line bisection task, only participants who succeeded in neural modulation showed a shift in the midpoint position towards the left visual field, which was the target space for training (Fig. 2).

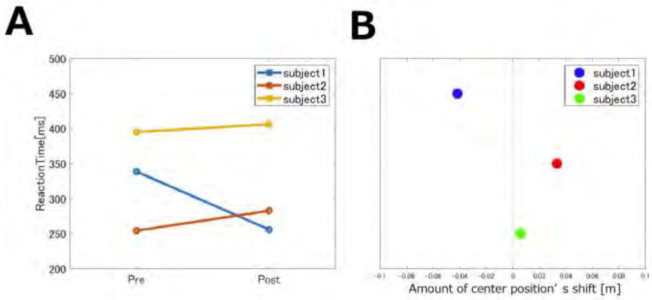


Fig. 2. Behavioral changes in SSVEP neurofeedback training.
A: GoNogo task. B: Line bisection task.

IV. Future Perspective

In B05-9, we confirmed the effectiveness of the proposed neurofeedback training system and made improvements to the system to achieve more efficient and effective training. While results supporting the training effect have been obtained, we have only evaluated the lower sensory areas that reflect attentional states. Therefore, in the next academic year, we conduct whole-brain measurements including the prefrontal cortex and the posterior parietal cortex to reveal the acquired neural circuits and their individual differences. Finally, we try to propose a model for the diversity of neural circuits acquired by the training system proposed in this study.

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.

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 using a visuomotor task. This fiscal year, we built the computational model and reproduced human behavior data in an exploratory task.**

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 built a reinforcement learning model that realizes exploratory adaptation, and reproduced behavioral data obtained in experiments.

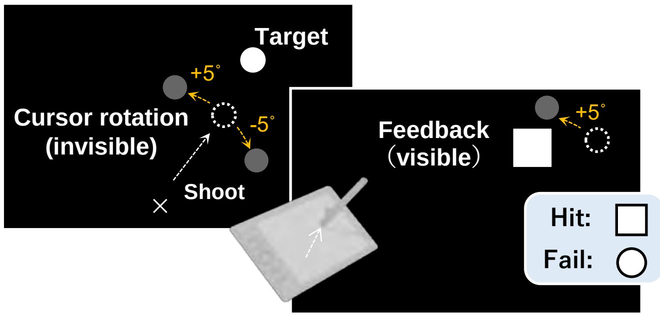


Fig. 1 Experimental task. The fixation cross was presented at the start position. The timing of the target presentation (white filled circle) was randomized across trials between 1 and 13 s with respect to the presentation of the fixation cross. Participants were asked to move a stylus pen tip (dashed 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.

III. Research Topics

We built a computational model to perform the reinforcement learning task and compared the simulation results with the results of previous experiments with human participants.

A. Experimental task

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. 1). 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.

B. Computational model

We modeled the performance of the experimental task to a reinforcement learning using an actor-critical framework. The direction of cursor on the k-th trial is called by y_k, and is expressed as follows:

$$y_k = x_k + e_k + n_k + p_k, \tag{1}$$

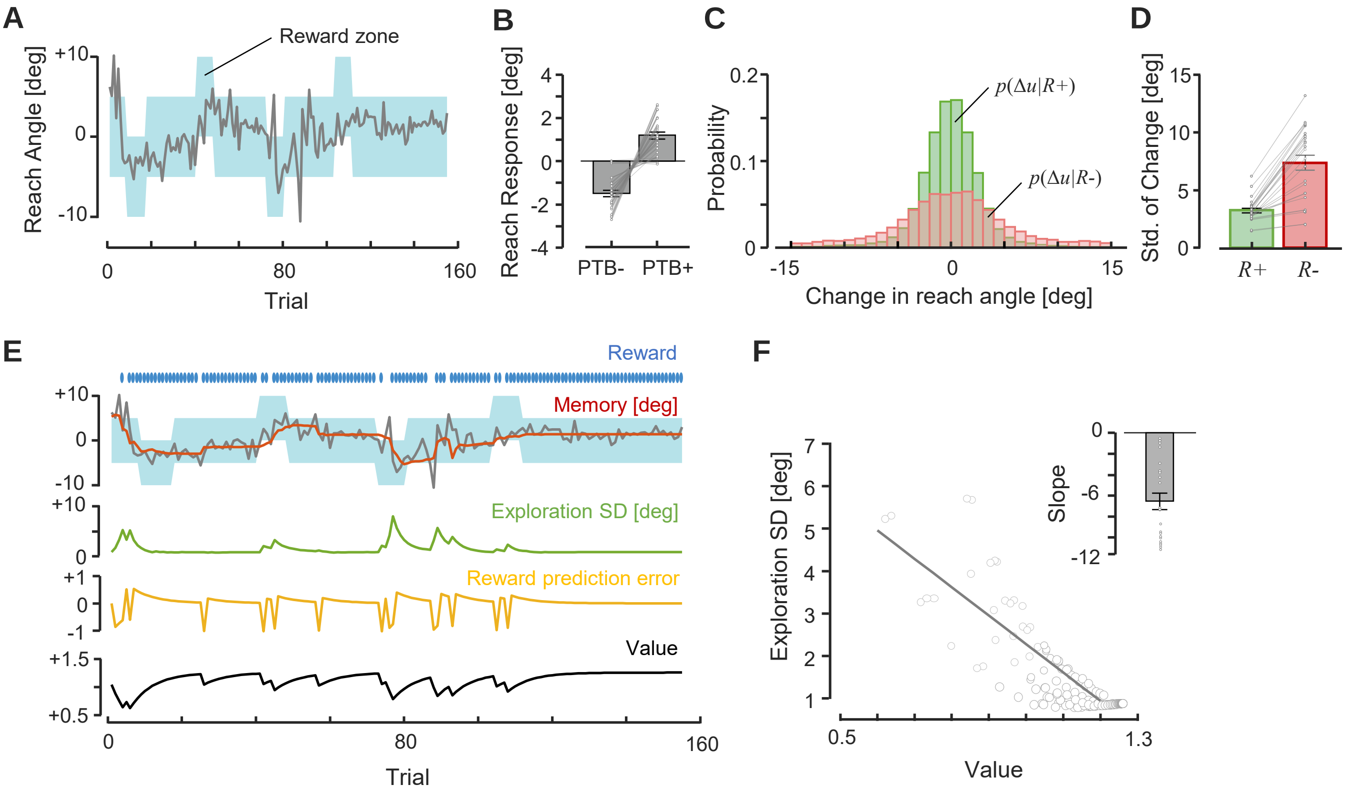


Fig. 2 Simulation result. Model simulation for behavioral data from participants (N = 25). The model adopted estimated hyperparameters that fit each participant's actual data. (A) The course of the reward zone angle over trials is indicated by the shaded area (cyan). The gray line is the reach angle of the simulated agent responding to the reward zone shift. (B) The average reach response across the simulated participants for + 5 degrees of rotation (PTB+) and –5 degrees of rotation (PTB–). (C) The histogram of the change in reach angle between n and n+1 trials after a successful trial (green, R+) and after an unsuccessful trial (R–). (D) The average of the change in reach angle for R+ and R– across the simulated participants. (E) The transition of the variables of the learning agent. From the top, Rewards, Memory, Exploration SD, Rewad precition error and Value over trials. (F) Control policy of Exploration SD. The scatter of Exploration SD over the values is plotted with the linear regression line. The bar graph in the upper right corner is the estimated slope value across the simulated participants.

where x_k is the motor memory, e_k is the exploration noise, n_k is the motor noise, and p_k is the perturbation of the cursor as an angle of rotation. Both the exploration noise and motor noise are assumed to be Gaussian noise, and exploratory adaptation is achieved by controlling the intensity of the exploration noise by its standard deviation (SD). The SD of the exploration noise is learned as well as the motor memory to maximize the reward by the reward prediction error δ_k, represented as follows:

$$\delta_k = r_{k+1} + \gamma \cdot V_{k+1} - V_k \,. \tag{2}$$

where r_{k+1}, and V_{k+1} are the reward and expected value function at trial k+1, respectively. In addition, γ is the discount rate, a hyperparameter unique to each participant, along with the learning rate required to update the motor memory and SD of the exploration noise.

We simulated the model using the hyperparameters obtained from the human experimental data, and the reproduced data fit the actual behavioral data with high accuracy.

IV. Future Perspective

During this fiscal year, we built a computational model and conducted simulations of human behavior in an experimental task for exploratory adaptation. 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.

In the next fiscal year, we will acquire imaging data through fMRI experiments and compare them with the model to elucidate the functional network structure of the brain to realize exploratory adaptation.

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.

List of Publications (2022)

Journal Papers

---

1. Hayashi R, Yamashita O, Yamada T, Kawaguchi H, Higo N, Diffuse optical tomography using fNIRS signals measured from the skull surface of the macaque monkey, Cerebral Cortex Communications, 3(1), tgab064, 2022

2. Miyawaki H, Mizuseki K, De novo inter-regional coactivations of preconfigured local ensembles support memory, Nature Communications, 1, 1272, 2022

3. Asai T, Hamamoto T, Kashihara S, and Imamizu H, Real-Time Detection and Feedback of Canonical Electroencephalogram Microstates: Validating a Neurofeedback System as a Function of Delay, Frontiers in Systems Neuroscience, e786200, 2022

4. Ohata R, Ogawa K, and Imamizu H, Neuroimaging Examination of Driving Mode Switching Corresponding to Changes in the Driving Environment, Frontiers in Human Neuroscience, e788729, 2022

5. Tokio Katakura, Mikihiro Yoshida, Haruki Hisano, Hajime Mushiake, Kazuhiro 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, Frontiers In Computational Neuroscience, 784592, 2022

6. Ogata K, Kadono F, Hirai Y, Inoue K, Takada M, Karube F, Fujiyama F, Conservation of the direct and indirect pathways dichotomy in mouse caudal striatum with uneven distribution of dopamine receptor D1- and D2-expressing neurons, Frontiers in Neuroanato, 16, 809446, 2022

7. R Otaki, Y Oouchida, N Aizu, T Sudo, H Sasahara, Y Saito, S Takemura, S Izumi, Relationship Between Body-specific attention to a Paretic Limb and Real-World Arm Use in Stroke Patients: A Longitudinal Study, Frontiers in Systems Neuroscience, 15, 806257, 2022

8. N. Aizu, R. Otaki, K. Nishii, T. Kito, R. Yao, K. Uemura, S. Izumi, K. Yamada, Body-Specific Attention to the Hands and Feet in Healthy Adults, Frontiers in Systems Neuroscience, 15, 805746, 2022

9. T. Sakurada, M. Yoshida, K. Nagai, Individual optimal attentional strategy in motor learning tasks characterized by steady-state somatosensory and visual evoked potentials, Frontiers in Human Neuroscience, 15, 784292, 2022

10. T. Sakurada, M. Matsumoto, S. Yamamoto, Individual sensory modality dominance as an influential

factor in the prefrontal neurofeedback training for spatial processing: a functional near-infrared spectroscopy study, Frontiers in Systems Neuroscience, 16, 774475, 2022

11. Yusuke Sekiguchi, Keita Honda, Shin-Ichi Izumi, Effect of Walking Adaptability on an Uneven Surface by a Stepping Pattern on Walking Activity After Stroke, Frontiers in Human Neuroscience, 15, 762223, 2022

12. Wen W, Okon Y, Yamashita A, & Asama H, The over-estimation of distance for self-voice versus other-voice, Scientific Reports, 12, 420, 2022

13. Wen W. & Imamizu H, The sense of agency in perception, behaviour and human–machine interactions, Nature Reviews Psycholo, 1, 211-222, 2022

14. Omura Y, Kaminishi K, Chiba R, Takakusaki K, and Ota, J, A Neural Controller Model Considering the Vestibulospinal Tract in Human Postural Control, Frontiers in Computational Neuroscience, 25, 16, 785099, 2022

15. K Ataka, T Sudo, R Otaki, E Suzuki, S Izumi, Decreased Tactile Sensitivity Induced by Disownership: An Observational Study Utilizing the Rubber Hand Illusion, Frontiers in Systems Neuroscience, 15, 802148, 2022

16. Isa K, Tokuoka K, Ikeda S, Karimi S, Kobayashi K, Sooksawate T, Isa T, Amygdala underlies the environment-dependency of defense responses induced via superior colliculus, Frontiers in Neural Circuits, 15, 768647, 2022

17. Isa T, Double viral vector intersectional approaches for pathway-selective manipulation of motor functions and compensatory mechanisms, Experimental Neurology, 3349, 1113959, 2022

18. Suzuki M, Inoue K, Nakagawa H, Ishida H, Kobayashi K, Isa T, Takada M, Nishimura Y, A multisynaptic pathway from the ventral midbrain toward spinal motoneurons in monkeys, Journal of Physiology, 600(7), 1731-1752, 2022

19. Hirayama K, Otaka Y, Kurayama T, Takahashi T, Tomita Y, Inoue S, Honaga K, Kondo K, & Osu R, Efficiency and Stability of Step-To Gait in Slow Walking, Frontiers in Human Neuroscience, 15, 779920, 2022

20. Togawa J, Matsumoto R, Usami K, Matsuhashi M, Inouchi M, Kobayashi K, Hitomi T, Nakae T, Shimotake A, Yamao Y, Kikuchi T, Yoshida K, Kunieda T, Miyamoto S, Takahashi R, Ikeda A, Enhanced phase-amplitude coupling of human electrocorticography in the posterior cortical region during rapid eye movement sleep, Cereb Cortex, 33(2), 486-496, 2022

21. Ito K, Nakamura T, Suzuki R, Negishi T, Oishi M, Nagura T, Jinzaki M, Ogihara N, Comparative functional morphology of human and chimpanzee feet based on three-dimensional finite element analysis, Frontiers in Bioengineering and Biotechnology, 9, 760486, 2022

22. Bohnen NI, Costa RM, Dauer WT, Factor SA, Giladi N, Hallett M, Lewis SJG, Nieuwboer A, Nutt JG, Takakusaki K, Kang UJ, Przedborski S, Papa SM; MDS-Scientific Issues Committee, Discussion of Research Priorities for Gait Disorders in Parkinson's Disease, Mov Disord, 37(2), 253-263, 2022

23. Takahashi M, Nakajima T, Takakusaki K, Preceding Postural Control in Forelimb Reaching Movements in Cats, Front Syst Neurosci, 15, 792665, 2022

24. Obara K, Chiba R, Takahashi K, Matsuno T, Takakusaki K, Knee dynamics of the take-off and landing of the spike jump in volleyball players with patellar tendinopathy, J Phys Ther Sci, 34(2), 103-109, 2022

25. Takakusaki K, Mirai T, Noguchi T, Chiba R, Neurophysiological mechanisms of gait disturbance in advanced Parkinson's disease patients, Neurology and Clinical Neuroscience, https://doi.org/10.1111/ncn3.12683, 2022

26. Sato Y, Kondo Y, Uchida A, Sato K, Yoshino-Saito K, Nakamura M, Okano H, Ushiba J, Preserved intersegmental coordination during locomotion after crvical spinal cord injury in common marmosets, Behav Brain Res, 425, 113816, 2022

27. Ohata, R., Asai, T., Imaizumi, S., and Imamizu, H., I Hear My Voice; Therefore I Spoke: The Sense of Agency Over Speech Is Enhanced by Hearing One's Own Voice, Psychological Science, 33(8), 1226-1239, 2022

28. Yihao Wu, Masahiko Morita, Jun Izawa, Reward prediction errors, not sensory prediction errors, play a major role in model selection in human reinforcement learning, Neural Networks, 154, 109-121, 2022

29. LR Dal'Bello, J Izawa, Computational role of exploration noise in error-based de novo motor learning, Neural Networks, 153, 349-372, 2022

30. Kasahara K, DaSalla CS, Honda M, Hanakawa T, Basal ganglia-cortical connectivity underlies self-regulation of brain oscillations in humans, Commun Biol, 5(1), 712, 2022

31. Takasawa E, Abe M, Chikuda H, Hanakawa T, A computational model based on corticospinal functional MRI revealed asymmetrically organized motor corticospinal networks in humans, 5(1), 664, 2022

32. Hosokawa T, Xu M, Katori Y, Yamada M, Aihara K, Tsutsui KI, Monkey Prefrontal Single-Unit Activity Reflecting Category-Based Logical Thinking Process and Its Neural Network Model, Journal of Neuroscience, 42(33), 6380-6391, 2022

33. Nakamura S, Kishimoto Y, Sekino M, Nakamura M, Tsutsui KI, Depression induced by low-frequency repetitive transcranial magnetic stimulation to ventral medial frontal cortex in monkeys, Experimental Neurology, Experimental Neurology, 357, 114168, 2022

34. Soccini Agata, Clocchiatti Alessandro, Inamura Tetsunari, Effects of frequent changes in extended self-avatar movements on adaptation performance, Journal of Robotics and Mechatronics, 34(4), 756-766, 2022

35. Tetsuro Funato, Noriaki Hattori, Arito Yozu, Qi An, Tomomichi Oya, Shouhei Shirafuji, Akihiro Jino, Kyoichi Miura, Giovanni Martino, Denise Berger, Ichiro Miyai, Jun Ota, Yury Ivanenko, Andrea d'Avella, Kazuhiko Seki, Muscle synergy analysis yields an efficient and physiologically relevant method of assessing stroke, Brain Communications, 4(4), fcac200, 2022

36. Sentong Wang, Kazunori Hase, Shunsuke Kita, Shinya Ogaya, Biomechanical effects of medial meniscus radial tears on the knee joint during gait: A concurrent finite element musculoskeletal framework investigation, Frontiers in Bioengineering and Biotechnology, 10, 957435, 2022

37. Naoki Aizu, Yutaka Oouchida, Kouji Yamada, Kazuhiro Nishii, Shin-Ichi Izumi, Use-dependent increase in attention to the prosthetic foot in patients with lower limb amputation, Scientific Reports, 12(10), 1295, 2022

38. Tomoyo Morita, Satoshi Hirose, Nodoka Kimura, Hiromasa Takemura, Minoru Asada, Eiichi Naito, Hyper-Adaptation in the Human Brain: Functional and Structural Changes in the Foot Section of the Primary Motor Cortex in a Top Wheelchair Racing Paralympian, Frontiers in Systems Neuroscience, 16, 780652, 2022

39. Tomoyo Morita, Eiichi Naito, Facilitation of Hand Proprioceptive Processing in Paraplegic Individuals with Long-Term Wheelchair Sports Training, Brain Sciences, 12(10), 1295, 2022

40. Kikutani K, Hosokawa K, Giga H, Ota K, Matsumata M, Zhu M, Takemoto H, Ji B, Oshimo S, Shime N, Aizawa H, Genetic deletion of translocator protein exacerbates post-sepsis syndrome with activation of the C1q pathway in septic mouse model, SHOCK, 59(1), 82-90, 2022

41. Sakamoto K, Yamada H, Kawaguchi N, Furusawa Y, Saito N, Mushiake H, Reinforcement Learning Model With Dynamic State Space Tested on Target Search Tasks for Monkeys: Extension to Learning Task Events, Frontiers in Computational Neuroscience, 16, 784604, 2022

42. Sakamoto K, Kawaguchi N, Mushiake H, Shape and Rule Information Is Reflected in Different Local Field Potential Frequencies and Different Areas of the Primate Lateral Prefrontal Cortex, Frontiers in Behavioral Neuroscience, 16, 750832, 2022

43. Nagasaka K, Takashima I, Matsuda K, Higo N, Pharmacological inactivation of the primate posterior insular/secondary somatosensory cortices attenuates thermal hyperalgesia, European Journal of Pain, 26(8), 1723-1731, 2022

44. Higo N, Motor cortex plasticity during functional recovery following brain damage, Journal of Robotics and Mechatronics, 34(4), 700-709, 2022
45. Matsuda K, Nagasaka K, Kato J, Takashima I, Higo N, 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
46. C. Zheng, G. Li, and M. Hayashibe, Joint Elasticity Produces Energy Efficiency in Underwater Locomotion: Verification with Deep Reinforcement Learning, Frontiers in Robotics and AI, 9, 957931, 2022
47. K. Kutsuzawa and M. Hayashibe, Motor synergy generalization framework for new targets in multi-planar and multi-directional reaching task, Royal Society Open Science, 9, 211721, 2022
48. M. Hayashibe and S. Shimoda, Synergetic synchronized oscillation by distributed neural integrators to induce dynamic equilibrium in energy dissipation systems, Scientific Reports, 12, 17163, 2022
49. C. Phunruangsakao, D. Achanccaray, S. Izumi, M. Hayashibe, Multibranch Convolutional Neural Network with Contrastive Representation Learning for Decoding Same Limb Motor Imagery Tasks, Frontiers in Human Neuroscience, 16, 1032724, 2022
50. 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, 34(6), 1451-1462
51. He Z, Qin Z, Koike Y., Continuous Estimation of Finger and Wrist Joint Angles Using a Muscle Synergy Based Musculoskeletal Model., Applied Sciences., 12(8), 3772, 2022
52. Cho W, Barradas VR, Schweighofer N, Koike Y., Design of an Isometric End-Point Force Control Task for Electromyography Normalization and Muscle Synergy Extraction From the Upper Limb Without Maximum Voluntary Contraction, Frontiers in Human Neuroscience, 16, 805452, 2022
53. Qin Z, He Z, Li Y, Saetia S, Koike Y., A CW-CNN regression model-based real-time system for virtual hand control, Front Neurorobot, 16, 1072365, 2022
54. Takeshi Sakurada, Ayaka Horiuchi, Takashi Komeda, Sensorimotor activities and their functional connectivity elicited by robot-assisted passive movements of lower limbs, Journal of Robotics and Mechatronics, 34(4), 777-785, 2022
55. T Sugiyama, K Nakae, J Izawa, Transcranial magnetic stimulation on the dorsal premotor cortex facilitates human visuomotor adaptation, NeuroReport, 33(16), 723-727, 2022
56. J Izawa, N Higo, Y Murata, Accounting for the valley of recovery during post-stroke rehabilitation training via a model-based analysis of macaque manual dexterity, Accounting for the valley of recovery

during post-stroke rehabilitation training via a model-based analysis of macaque manual dexterity, 3, 1042912, 2

57. Togo M, Matsumoto R(CA), Usami K, Kobayashi K, Takeyama H, Nakae T, Shimotake A, Kikuchi T, Yoshida K, Matsuhashi M, Kunieda T,, Distinct connectivity patterns in human medial parietal cortices: Evidence from standardized connectivity map using cortico-cortical evoked potential., Neuroimage, 263, 119639, 2022

58. Kimura N, Sato M, Kobayashi Y, Naito E, Augmented activity of the forearm extensor muscles induced by vibratory stimulation of the palm of the hand in individuals with subacute post-stroke hemiplegia, Brain Injury, 36(6), 782-791, 2022

59. 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, Cerebral Cortex, bhac456, 2022

60. Kimura N, Furuta T, Miura G, Naito E, Combining motor imagery and action observation with vibratory stimulation increases corticomotor excitability in healthy young adults, Journal of Behavioral and Brain Science, 12(5), 177-195, 2022

61. Morita T, Hirose S, Kimura N, Takemura H, Asada M, Naito E, Hyper-adaptation in the human brain: Functional and structural changes in the foot section of the primary motor cortex in a top wheelchair racing Paralympian, Frontier in Systems Neuroscience, 16, 780652, 2022

62. Morita T, Naito E, Facilitation of hand proprioceptive processing in paraplegic individuals with long-term wheelchair sports training, Brain Sciences, 12(10), 1295, 2022

63. Matsuda E, Misawa D, Yano S, and Kondo T, Olfactory Cues to Reduce Retrograde Interference During the Simultaneous Learning of Conflicting Motor Tasks, Journal of Robotics and Mechatronics, 34(4), 746-755, 2022

64. Saki Niiyama, Shiro Yano, and Toshiyuki Kondo, Cerebral Activity-Based Quantitative Evaluation for Attention Levels, Journal of Robotics and Mechatronics, 34(4), 739-745, 2022

65. S. Nakamura, Y. Kobayashi and T. Matsuura, Grid-Based Estimation of Transformation Between Partial Relationships Using a Genetic Algorithm, Journal of Robotics and Mechatronics, 34(4), 786-794, 2022

66. Takakuwa N, Isa K, Yamaguchi R, Onoe H, Takahashi J, Yoshida M, Isa T., Protocol for making an animal model of "blindsight" in macaque monkeys, STAR Protocols, 4(1), 101960, 2022

67. Umeda T, Isa T, Nishimura Y., Temporal dynamics of the sensorimotor convergence underlying voluntary limb movement., Proceedings of the National Academy of Sciences, 119(48), e2208353119, 2022

68. Isa T, Tohyama T, Kinoshita M., Phylogenetic view of the compensatory mechanisms in motor and sensory systems after neuronal injury., Current Research in Neurobiology, 3, 100058, 2022

69. Takeuchi Y, Li Q, Kawano T, Nagai J, Mima T, Editorial: Oscillotherapeutics – Toward real-time control of pathological oscillations in the brain, Frontiers in Behavioral Neurosci, 16, 1021616, 2022

70. Yunxiang Xia, Tatsuma Okazaki, Kenya Uemura, Shinichi Izumi, Implicit Body Representation of the Hand Enlarged by Repetitive Peripheral Magnetic Stimulation within the Boundary of a Real Hand, Applied Sciences, 12(10), 5250, 2022

71. Zhi-Ming Tang, Yutaka Oouchida, Meng-Xin Wang, Zu-Lin Dou, Shin-Ichi Izumi, Observing errors in a combination of error and correct models favors observational motor learning, BMC Neuroscience, 23(1), 4, 2022

72. Dongting Tian, Shin-Ichi Izumi, Transcranial Magnetic Stimulation and Neocortical Neurons: The Micro-Macro Connection., Frontiers in neuroscience, 16, 866245, 2022

73. Yunxiang Xia, Kento Tanaka1, Man Yang, Shinichi Izumi, Body representation underlies response of proprioceptive acuity to repetitive peripheral magnetic stimulation, Frontiers in Human Neuroscience, 16, 924123, 2022

74. Shibata, S., Watanabe, T., Matsumoto, T., Yunoki, K., Horinouchi, T., Kirimoto, H., Zhang, J., Wang, H., Wu, J., Onishi, H., Mima, T., Triple tSMS system ("SHIN jiba") for non-invasive deep brain stimulation: a validation study in healthy subjects, Journal of NeuroEngineering and Rehabilitation, 19(1), 129, 2022

75. Tetsunari Inamura, Digital Twin of Experience for Human-Robot Collaboration through Virtual Reality, International Journal of Automation Technology, 17(3), 2023

76. Yamao Y, Sawamoto N, Kuieda T, Inano R, Shibata S, Kikuchi T, Arawaka Y, Yoshida K, Matsumoto R, Ikeda A, Takahashi R, Fukuyama H, Miyamoto S, Changes in distributed motor network connectivity correlates with functional outcome after surgical resection of brain tumors., Neurosurgery Practice, 4(1), e00028, 2023

77. Makoto Ozawa, Yasuyuki Suzuki, Taishin Nomura, Stochastic Physiological Gaze-Evoked Nystagmus With Slow Centripetal Drift During Fixational Eye,Movements at Small Gaze Eccentricities., Stochastic Physiological Gaze-Evoked Nystagmus With Slow Centripetal Drift During Fixational Eye Movements at Small Gaze Eccentricities., 16, 842883, 2023

78. Harin Hapuarachchi, Takayoshi Hagiwara, Gowrishankar Ganesh, Michiteru Kitazaki, Effect of connection induced upper body movements on embodiment towards a limb controlled by another during virtual co-embodiment, PLOS ONE, 18(1), 2023

79. Kanazawa H, Yamada Y, Tanaka K, Kawai M, Niwa F, Iwanaga K, Kuniyoshi Y, Open-ended

movements structure sensorimotor information in early human development, Proceedings of the National Academy of Sciences, 120(1), e2209953120, 2023,

80. Barradas VR, Cho W, Koike Y, EMG space similarity feedback promotes learning of expert-like muscle activation patterns in a complex motor skill, Fronties in Human Neuroscience, 16, 805867, 2023

81. Shibata, S., Watanabe, T., Otsuru, N., Onishi, H., Mima, T., Very low-frequency transcranial electrical stimulation over the primary motor area can influence the voluntary movement initiation in humans, Brain Stimulation, 16(2), 442-444, 2023

82. Shima, A., Tanaka, K., Ogawa, A., Omae, W., Miyake, T., Nagamori, Y., Miyata, Y., Ohata, K., Ono, Y., Mima, T., Takahashi, R. *Koganemaru, S., Case Report: Backward gait training combined with gait-synchronized cerebellar transcranial alternating current stimulation in progressive supranuclear palsy, Frontiers in Human Neuroscience-Brain Imaging and Stimulation, 17, 1082555, 2023

83. Shima, A., Miyake, T., Tanaka, K., Ogawa, A., Omae, E., Nagamori, Y., Miyata, Y., Ohata, K., Maki, T., Ono, Y., Mima, T., Takahashi, R. *Koganemaru, S., Case report: A novel approach of closed-loop brain stimulation combined with robot gait training in post-stroke gait disturbance., Frontiers in Human Neuroscience-Brain Imaging and Stimulation, 17, 1082556, 2023

International Conference

1. Ohata, R., Uehigashi, Y., Asai, T., Imaizumi, S., and Imamizu, H., Prospective and retrospective inferences of hearing one's voice in the sense of agency over speech, The Federation of European Neuroscience Societies (FENS) Forum 2022, Paris, France, 2022

2. Tanaka, T. and Imamizu, H., The influence of changes in direction and velocity of feedback over the sense of control., The 22nd meeting of the European Society for Cognitive Psychology (ESCoP), Lille, France, 2022

3. Hapuarachchi, H., Ishimoto, H., Sugimoto, M., Inami, M., and Kitazaki, M., Embodiment of an Avatar with Unnatural Arm Movements, 2022 IEEE International Symposium on Mixed and Augmented Reality (ISMAR), Singapore, 2022

4. Hitohiro Etoh, Yuichiro Omura, Kohei Kaminishi, Ryosuke Chiba, Kaoru Takakusaki, and Jun Ota, Motion Planning of Anticipatory Postural Adjustments in Gait Initiation, 2022 The 22nd IEEE International Conference on BioInformatics and BioEngineering, Taiwan, 2022

5. Hitohiro Etoh, Yuichiro Omura, Kohei Kaminishi, Ryosuke Chiba, Kaoru Takakusaki, and Jun Ota, Investigation of a Method to Extend a 2-Dimensional Gait to 3-Dimensions in a Human Musculoskeletal Model with 70 Muscles, 33rd 2022 International Symposium on Micro-

NanoMechatronics and Human Science (From Micro & Nano Scale Systems to Robotics & Mechatronics Systems), Nagoya, 2022

6. Yuichiro Omura, Hiroki Togo, Kohei Kaminishi, Tetsuya Hasegawa, Ryosuke Chiba, Arito Yozu, Kaoru Takakusaki, Mitsunari Abe, Yuji Takahashi, Takashi Hanakawa, and Jun Ota, Muscle Tone in a Musculoskeletal Model to Represent the Abnormal Posture in Parkinson's Disease, 33rd 2022 International Symposium on Micro-NanoMechatronics and Human Science (From Micro & Nano Scale Systems to Robotics & Mechatronics Systems), Nagoya, 2022

7. Sakamoto K, Multidimensional analysis of extracellular potentials in the cerebral cortex, Nara Institute of Science and Technology, Information Science, Colloquium A, Nara, 2022

8. Sakamoto K, The Brain Beyond Machine Learning:Perspectives from Neurophysiology and Computational Neuroscience of Higher Brain Functions, APSIPA BioSiPS Workshop 2022, Kitami, 2022

9. Sakamoto K, Saito N, Yoshida S, Mushiake H, Increased firing variability may be an early warning signal of bifurcation in neuronal networks: Validation in action planning-related cells of monkey prefrontal cortex, Neuroscience 2022, San Diego, USA, 2022

10. Sakamoto K, Saito N, Yoshida S, Mushiake H, A dynamic, economical, and robust coding scheme in the lateral prefrontal neurons of monkeys, The 29th International Conference on Neural Information Processing, IIT Indore, India, 2022

11. Kim D, Kanazawa H, Kuniyoshi Y, Simulating a Human Fetus in Soft Uterus, IEEE International Conference on Development and Learning, ICDL, London, United Kingdom, 2022

12. Kim D, Kanazawa H, Kuniyoshi Y, Human fetus simulation in soft uterus environment, International Congress of Infant Studies (ICIS), Online, 2022

13. M.H. Ahmed, S. Shimoda, M. Hayashibe, Deep Reinforcement Learning Based Motion Synthesis for Prosthetic Elbow Motion Generation, The SICE Annual Conference 2022, Kumamoto, Japan, 2022

14. K. Tada, K. Kutsuzawa, D. Owaki, M. Hayashibe, Quantifying Motor and Cognitive Function of the Upper Limb Using Mixed Reality Smartglasses, 44th Annual Int. Conf. of the IEEE Engineering in Medicine and Biology Society, Glasgow, United Kingdom, 2022

15. K. Shen, A. Chemori, M. Hayashibe, Classification of Human Balance Recovery Strategies through Kinematic Motor Synergy Analysis, 44th Annual Int. Conf. of the IEEE Engineering in Medicine and Biology Society, Glasgow, United Kingdom, 2022

16. Sonoda,Kohta, Hasegawa,Tetsuya, Kaminisho,Kohei, Osumi,Michihiro, Sumitani,Masahiko, Chiba,Ryosuke, Ota,Jun, & Yozu,Arito, Effects of plantar pain on gait, The 33rd 2022 International Symposium on Micro-NanoMechatronics and Human Science (MHS2022), Nagoya, Japan, 2022

17. K. Kaminishi, Y. Omura, R. Chiba, K. Takakusaki, and J. Ota, Effects of Increased Arm Muscle Tone on Postural Recovery from External Forces: A simulation study, 2022 IEEE 22nd International Conference on Bioinformatics and Bioengineering (BIBE), Online, Taiwan, 2022

18. Matsumoto R, Physiology of the Cortico-Cortical Evoked Potential (Educational Course: Management of the Awake Patient Surgeries), 8th Congress of the International Society of Intraoperative Neurophysiology and Educational Course (ISIN2022), Online, USA, 2022

19. Matsumoto R, Brain Evoked Potentials in the context of Epilepsy and Beyond., Workshop on Brain Evoked Potentials in the context of Neurosurgery, Montpellier, France, 2022

20. Matsumoto R, Cortico-cortical evoked potential: its past, present and future, BCI&Neurotechnology Spring School, Online, Austria, 2022

21. Naoya Yamamoto, Takato Matsumoto, Tamami Sudo, Megumi Miyashita, and Toshiyuki Kondo, Ring-shaped wearable device for logging finger usage in daily life, IEEE 2022 International Symposium on Micro-NanoMechatronics and Human Science (MHS2022), Nagoya, Japan, 2022

22. Megumi Miyashita, Shiro Yano and Toshiyuki Kondo, Evaluation of Safe Reinforcement Learning with CoMirror Algorithm in a Non-Markovian Reward Problem, 17th International Conference on Intelligent Autonomous Systems (IAS-17), Zagreb, Croatia, 2022

23. Samirah Altukhaim, Toshiyuki Kondo, Yoshikatsu Hayashi, Enhancement of Sense of Ownership and Sense of Agency using Virtual Reality and Haptic Feedback, The 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS), Glasgow, UK, 2022

24. Ozge Ozlem Saracbasi, William Seymour Harwin, Toshiyuki Kondo, Yoshikatsu Hayashi, Dual Instability against to Sequential Learning via Haptic Interaction, The 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS), Glasgow, UK, 2022

25. Y. Kobayashi and S. Nakamura, Transfer of Partial Information of Motor Controller Based on Estimation of Coordinate Transformation Parameters, The 33rd 2022 International Symposium on Micro-NanoMechatronics and Human Science (MHS2022), Nagoya, Japan, 2022

26. Tadashi Isa, Roles of midbrain dopamine-related systems in motivation, decision and recovery after neuronal injuries, The 9th Annual Meeting of the Mongoloan Neuroscience Society, Ulaanbaatar, Mongolia, 2022

27. Tadashi Isa, Sensorimotor and cognitive functions of blindsight macaques, International school of neuroscience, Erice, Italy, 2022

28. Tadashi Isa, Visuomotor pathway and cognitive capacity of blindsight macaques, JANUBET Symposium, Kyoto, Japan, 2022

29. Sierra RO, Pedraza LK, Barcsai L, Peijin A, Kozák G, Takeuchi Y, Lőrincz M, Berényi A, Controlling pathologic fear expression through closed-loop brain stimulation, The 52nd SfN Annual Meeting, San Diego, U. S. A., 2022

30. Yoshida K, Chan M, Li Q, Pedraza L, Sierra R, Minami M, Berényi A, Takeuchi Y, Devinsky O, Buzsáki G, Berényi A, Reinstating olfactory bulb derived limbic gamma oscillations alleviates depression-like behavioral deficits in rodents, The 52nd SfN Annual Meeting, San Diego, U. S. A. 2022

31. Masaya Togo, Riki Matsumoto, Kiyohide Usami, Katsuya Kobayashi, Hirofumi Takeyama, Takuro Nakae, Akihiro Shimotake, Takayuki Kikuchi, Kazumichi Yoshida, Masao Matsuhashi, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda, Distinct connectivity patterns in human medial parietal cortices: evidence from standardized connectivity map using cortico-cortical evoked potential., American Epilepsy Society 2022, Nashville, USA, 2022

32. Matsumoto R, The value of Cortico-Cortical Evoked Potentials in a neurosurgical perspective (Keynote Lecture 2), International Symposium: Bridging Neurosciences and Neurosurgery - New Frontiers in Intraoperative Neurophysiology, Verona, Italy, 2023

33. Hapuarachchi, H., Ishimoto, H., Kato, Y., and Kitazaki, M., Embodiment of an Unnatural Avatar studied in VRChat Laboratory, 2023 the 7th International Conference on Virtual and Augmented Reality Simulations (ICVARS 2023), Sydney, Australia, 2023

34. Nakamura, J., Ikei, Y., and Kitazaki, M., The Effect of Posture on Virtual Walking Experience Using Foot Vibrations, Augmented Humans 2023, Glasgow, UK, 2023

35. Rie Kimura, Kenichi Ohki, Yumiko Yoshimura, Neuronal activity that allows us to perceive familiar images even at low contrast, 3rd International Symposium on Brain Information Dynamics 2023, Tokyo, Japan, 2023

36. Rie Kimura, Kenichi Ohki, Yumiko Yoshimura, A neural mechanism underlying the perception of low-contrast familiar objects, 5th Stockholm-Tokyo Workshop 2023, Tokyo, Japan, 2023

Member List

<u>Steering Committee (X00): Administrative research on hyper-adaptability for overcoming body-brain dysfunction</u>

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	Wen Wen (Project Associate Professor, The University of Tokyo)
co-investigator	Qi An (Associate Professor, The University of Tokyo)
co-investigator	Arito Yozu (Associate Professor, The University of Tokyo)

<u>Research Project A01: Elucidation of the hyper-adaptation mechanism by reconstruction of bio-structure and challenges for prevention of decline in latent adaptive capacity</u>

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)
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)
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	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)

<u>Research Project A02: Elucidation of neural mechanisms of super-adaptation to body change</u>

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)

<u>Research Project A03: Mechanisms of body cognition and emotion inducing hyper-adaptability</u>

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, 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	Kenji Yoshinaga (Postdoctoral fellow, NCNP)
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)

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, Aichi Medical 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	Soichiro Fujiki (Assistant Professor, Dokkyo Medical University)
Co-investigator	Wang Sentong (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	Wen Wen (Project Associate Professor, The University of Tokyo)
Funded co-investigator	Qi An (Associate Professor, The University of Tokyo)
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 (Project Assistant Professor, The University of Tokyo)
Co-investigator	Hoang Hiep Ly (Project Researcher, The University of Tokyo)
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)

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	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)

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	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)