2021 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

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Principal Investigator, Hoshinori KANAZAWA
(Research Assistant Professor, The University of Tokyo)

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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

- International Symposium on Hyper-Adaptability HypAd 2021
Date: May 26th, 2021. 16:00-20:00
May 27th, 2021. 16:00-19:00
Place: Online
Contents: The 1st International Symposium on Hyper-Adaptation (HypAd2021) was held. Professor Andrea d'Avella of the University of Messina, Italy, gave an invited lecture entitled "Virtual surgeries to investigate motor learning and to enhance motor rehabilitation". The content of the lecture was related to the learning process after muscle rearrangement, which is also investigated as a model for hyper-adaptation in this field, and provided useful suggestions for the development of research in this field. In the talk session, the representatives of the planning groups reported on the progress, and in the poster session, the representatives of the subscribed research groups made presentations. Although the conference was limited to whom involved in the area, 161 people registered to attend and 58 poster presentations were made, making the conference a great success.

- 7th management meeting
Date: May. 27th, 2021. 10:30-12:00
Place: Online
Contents: members of the management group discussed about the operation method, symposiums, and counterplans against Covid-19, etc.

- B group meeting
Date: Sep. 7th, 2021. 13:00-15:10
Place: Online
Contents: Three talks by area researchers were given, focusing on research topics related to the promotion of Group B's overall research. The talks were: “Understanding hyper-adaptation using RNN model” by Q. An (Kyushu University), “Quantitative evaluation of posture control system based on motion measurement and system model of bipedal standing rats” by T. Funato (University of Electro-Communications), and "Study on identification of time-varying brain functional connectivity for clarification of hyper-adaptation" by I. Nambu (Nagaoka University of Technology).

- A group meeting
Date: Sep. 16th, 2021. 13:30-16:00
Place: Online
Contents: A group meeting was held for the purpose of exchange within and outside Group A. 22 group members gave presentation, and after the lectures, a social event using the virtual conference system oVice was held.

- 3rd plenary conference
Date: March 7th - 8th, 2022
Place: Online
Contents: summary of the researches in the year was presented by project representative and researchers in the project.

- 8th management meeting
Date: March 8th, 2022. 12:20-13:20
Place: Online
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: Advanced Robotics
Special Issue on “Hyper-adaptability for overcoming body-brain dysfunction” was organized in Advanced Robotics, Vol. 35, no. 13-14. Nine papers were published.

- OS: 44th Annual Meeting of the Japan Neuroscience Society
Date: July 28th, 2021
Contents: Five researches were presented at a symposium on “Hyper-adaptation in the brain”.
- OS: MHS 2021 (32nd International Symposium on Micro-NanoMechatronics and Human Science)
Date: December 6th, 2021
Contents: Seven researches including one keynote talk were presented at a symposium on “Hyper-adaptability”.

- OS: 51th Annual Meeting on the Japanese Society of Clinical Neurophysiology
Date: December 16th, 2021
Contents: Four researches were presented at a symposium on “Neurophysiology of Hyper-adaptability”.

- OS: 34th SICE Symposium on Decentralized Autonomous Systems.
Date: January 22th, 2022
Contents: Nine researches were presented at a symposium on “Hyper-adaptability”.

- OS: The 99th Annual Meeting of the Physiological Society of Japan
Date: March 18th, 2022
Contents: Symposium of “Physiology of hyper-adaptability” is organized.

C. Activities for publications

- Explanatory meeting for subscribed research groups
Explanatory meeting for subscribed research groups were held on Sep 7th, 2021, 15:30-15-50 and on Sep 16th, 2021, 13:00-13:20.

IV. Activities By Young Researchers

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

A. Study Session

In order to deepen the understanding of the analytical and experimental methods used in this field, the following three study sessions were held this year. The materials of the sessions are available on the website and Slack, and we are trying to expand the common knowledge base.
- Jun.-Jul. 2021 Study session of Winter's book “Biomechanics and Motor Control of Human Movement”.
- Dec. 2021: Study session on experimental methods in neuroscience (photogenetics, calcium imaging, chemical genetics)
-January-February 2022: Study group on electrophysiology

B. Lecture Meetings

We held three online lectures on emotion and motor control, which are important research topics in this field, inviting researchers from inside and outside the field, as follows
- Sep. 06, 2021 Prof. Ken-ichiro Tsutsui (Tohoku University)
- Sep 07, 2021 Prof. Taishin Nomura (Osaka University)
- October 07, 2021 Team Leader Wataru Sato (RIKEN)

C. Organizing Symposium

A joint symposium for young researchers was held at the Next Generation Brain Project Winter Symposium jointly with Grant-in-Aid for Scientific Research on Innovative Areas of “Brain Information Dynamics” and “Chronogenesis”. Two researchers from this area, Associate Professor Wen Wen and Assistant Professor Hoshinori Kanazawa, gave presentations, and a panel discussion was held with the participants.

V. Future Perspective

We plan to conduct the following activities of the next fiscal year:
- plenary conference including new publicly group members, in spring or summer, 2022,
- 2nd public symposium on October, 2022, and
- fiscal year-end plenary conference on March, 2023.

Group A: Neurosciences

Tadashi Isa, Professor, Kyoto University
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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) 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 that the interhemispheric interaction between the bilateral motor and premotor cortices switches from inhibitory to facilitatory during the recovery process from the subhemisection injury of the spinal cord. Naito and colleagues showed the decline of interhemispheric inhibition in aged subjects by measuring the negative BOLD signal of the fMRI.

The aim of **Group A02 (Seki)** was to evaluate the adaptation of the central nervous system to rapid changes in body structure by muscle rearrangement surgery in monkeys, whose musculoskeletal structure is similar to that of humans. In this year, we established the basic technology to intervene in the sensory prediction error, which is necessary to study the background mechanism of adaptation. Specifically, we aimed to establish a technique to introduce foreign genes into primates (marmosets) with high efficiency for specific types of sensory nerves.

Group A03 (Imamizu and Tsutusi) conducted studies on mechanisms which the sense of agency (the feeling that I am the source of the action) and motivation facilitate motor learning. A group of Imamizu conducted several psychological experiments showing that the sense of agency facilitates motor learning. They confirmed that a high-definition electric stimulation to the brain affects the sense of agency. A group of Tsutsui developed a device for investigating sense of agency and motivation commonly in humans and monkeys. They also established a long-lasting electrocorticogram recording method covering wide area of the monkey cerebral cortex.

Group A04 (Takakusaki, Hanakawa) researched changes in motor function (postural control) and brain network dynamics with aging. Based on animal experimentation, Takakusaki and colleagues suggested the possibility of the dysregulation of the reticulospinal and vestibulospinal tracts due to the degeneration of dopaminergic and cholinergic systems in Parkinson's disease (PD) induce antero-flexion posture. Hanakawa and colleagues compared the functional connectivity (FC) in major four (default mode, dorsal attention, salience, and central executive) network states in f-MRI of elders. They found the sparse FC condition in cognitively impaired PD and Alzheimer's disease but not in the healthy elderly and cognitively normal PD.

In addition, 15 members (below) joined as the A05 group, who were selected through the applications.

Shin-ichi Izumi "Title: Elucidation of the hyper-adaptation mechanism of upper limb recovery in stroke patients" Group A05-1 (Izumi) observed subacute stroke patients for 6 months and found that the frequency of use of the affected upper limb was related to its recovery and body-specific attention of the hemiplegic hand. The results suggest a relationship between use-dependent plastic changes and body representation.

Riki Matsumoto, "Mechanism of Hyper-Adaptivity of the human premotor area: electrophysiological connectome analysis with electrocorticogram" Electrophysiological connectome, namely, cortico-cortical evoked potential (CCEP) connectome was generated by means of systemic low-frequency electrical stimulation to all the implanted electrodes to record CCEP. The network analysis revealed that the higher-order motor area had significantly larger outbound connections compared to the primary motor cortex and the language areas.

Mitsunari Abe "Development of non-invasive brain stimulation techniques that can increase recruitment of the corticospinal motor indirect pathway during acquisition of hand motor skills" We discovered the corticospinal network in humans, operationally called *bilateral M1-network*, that integrated signals from bilateral primary motor cortices onto the spinal cord. We are developing the stimulation protocols that enable to increase recruitment of the *bilateral M1-network*. Our design is to induce neuronal plasticity in the relay neurons implemented in this network.

Hideki Hida " Analysis of the regulatory system change in functional recovery with the rehabilitation after stroke." He performed selective blockage in the cerebellum-rubral pathway using double-virus infection method and revealed that CNO treatment caused the inhibition of the functional recovery that is induced by forced-limb use after intracerebral hemorrhage, confirming the cerebellum-rubral pathway is involved in the functional recovery by the rehabilitation.

Hiroyuki Miyawaki, "Regulatory mechanisms of inter-regional network changes underlying hyper-adaptation from mal-adaptation state caused by fear memory." Group A05-7 investigated neuronal mechanisms of fear-memory related mal- and hyper-adaptation by performing multi-regional large-scale electrophysiology in freely moving rodents. The analyses revealed that inter-regional coactivation developed through the transition to the mal-adaptation state, and the coactivation accompanied fast network oscillations in the involved regions.

Takaki Maeda "Facilitating hyper-adaptation in neurological and psychiatric diseases through improving precision on the sense of agency" GroupA05-8 developed a method for cognitive rehabilitation of Sense of Agency(SoA) in order to tune up precision of SoA, and showed abnormal learning patterns in patients with psychiatric disorders including schizophrenia, ADHD and ASD.

Takahiro Kondo, "The role of inhibitory neurons related to skilled hand movements after spinal cord injury." To understand motor deficits and reconstruction after spinal cord injury, we analyzed joint movement coordination generated by the central nervous system. We found that the degree of impaired coordination in joint movements correlated with the degree of damage in the spinal cord.

Rieko Osu "Activating neural circuits that prefer affected side of the body using neural modulation by brain stimulation and behavioral technique" We showed that electrical stimulation on the wrist could modify the probability of hand choice during the reaching task. We demonstrated that the stroke patients' motivation for rehabilitation is extrinsic mainly rather than intrinsic. We developed a questionnaire to evaluate motivation for rehabilitation in subacute stroke patients.

Kosei Takeuchi "Hyper-adaptive function by microenvironment and synapse connection." We found that the synthetic synaptic organizer has a recovery effect even in the chronic-phase of spinal cord injury, and succeeded in extracting the physiological recovery process by AI-deep learning (with/B02:Yanagihara&Funato).

Noriyuki Higo "Adaptive mechanism occurring in both hemispheres after unilateral brain damage" We performed structural MRI VBM analysis and immunohistochemistry using SMI-32 antibody in a macaque model of internal capsular infarcts, and found increases in both gray matter volume and dendritic arborization of pyramidal neurons in the ventral premotor cortex of the contralesional hemisphere during the period of motor function recovery.

Masatoshi Yoshida, "Establishment and circuit manipulation of an animal model of unilateral spatial neglect in marmosets" To establish an animal model of unilateral spatial neglect by making lesions in the ventral attention network of common marmosets, 1) we identified area TPO using ECoG. 2) we evaluated saliency-guided eye movements during free-viewing, and 3) we measured Ca signals simultaneously from bilateral posterior parietal cortices.

III. ACTIVITIES

The whole Group A meeting was held on September 16 (Thu) in 2021, by online with Zoom software and the networking session by oVice software.

IV. FUTURE PLAN

We will soon organize the 1st whole group Meeting and facilitate the collaboration with the Group B members.

A01. Elucidation of the hyper-adaptation mechanism by reconstruction of biostructures and challenges for prevention of decline in latent adaptive capacity

Tadashi Isa, Professor, Kyoto University
Eiichi Naito, Research Manager, CiNet
Hidenori Aizawa, Professor, Hiroshima University
Minoru Asada, Professor, Osaka University

***Abstract*—We have demonstrated the critical role of interhemispheric inhibition in the monkeys with spinal cord injury using the pathway-selective manipulation, and in aged humans using fMRI. We are also studying the involvement of dopamine system in the global disinhibition I the rodent model.**

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 is 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)*

Previously we found that after the lesion of the corticospinal tract at the C4/C5 segments in macaques, the precision grip movements are once impaired but could recover in several weeks through rehabilitative trainings. Furthermore, we found that during the early stage of the recovery, the ipsilesional motor cortex increased its activity and contribute to recovery by reversible inactivation using microinjection of GABA receptor agonist muscimol (Nishimura et al. Science, 2007). Moreover, by multi-channel ECoG recordings from bilateral premotor (PM), primary motor and somatosensory cortex, we found that signal flow from the contralesional to ipsilesional PM is enhanced during the early recovery using Granger causality (GC) analysis (Chao et al. Cerebral Cortex 2019). To demonstrate that the direct callosal pathway from the contralesional PM to the ipsilesional PM is critical, we tried the pathway-selective blockade of the pathway. We injected AAV2retro-Cre into the ipsilesional PM and AAV2.1-DIO-hM4Di into the contralesional PM and administered DCZ to the monkey and confirmed that GC from the contralesional PM to ipsilesional PM was unidirectionally reduced and the pathway-selective blockade was successful. The selective blockade of the pathway was not effective during the intact state, but during the early stage of the recovery after the corticospinal tract lesion, the precision grip behavior was impaired by administration of DCZ. Thus, we could demonstrate the crucial role of the contralesional PM to ipsilesional caoolsal pathway is critical for the early stage recovery after the spinal cord injury.

[1] Suzuki M, Inoue K-I, Nakagawa H, Ishida H, Kobayashi K, Isa T, Takada M, Nishimura Y (2022) Multisynaptic pathway from the ventral midbrain to spinal motoneurons via the primary motor cortex in monkeys" *Journal of Physiology (London),* doi: 10.1113/JP282429..

[2] Isa K, Tokuoka K, Ikeda S, Karimi S, Kobayashi K, Sooksawate T, Isa T (2021) Amygdala underlies the environment-dependency of defense responses induced via superior colliculus. *Frontiers in Neural Circuits,* 15:768647. doi: 10.3389/fncir.2021.768647. eCollection 2021.

[3] Kasai M, Isa T (2021) Effects of light isoflurane anesthesia on organization of direction and orientation selectivity in the superficial layer of the mouse superior colliculus. *Journal of Neuroscience,* JN-RM-1196-21. doi: 10.1523/JNEUROSCI.1196-21.2021.

[4] Kato R, Zeghbib A, Redgrave P. Isa T (2021) Visual instrumental learning in blindsight monkeys. *Scientific Reports*, 11, 14819.

doi.org/10.1038/s41598-021-94192-7
[5] Zubair M, Murris S, Isa K, Onoe H, Koshimizu Y, Kobayashi K, Vanduffel W, Isa T (2021) Divergent whole brain projections from the ventral midbrain in macaque monkeys. *Cerebral Cortex*, bhaa399. doi: 10.1093/cercor/bhaa399.
[6] Takakuwa N, Isa K, Onoe H, Takahashi J, Isa T (2021) Contribution of pulvinar and lateral geniculate nucleus to the control of visually guided saccades in blindsight monkeys. *Journal of Neuroscience*, 41:1755-1768.
[7] Kato R, Hayashi T, Onoe K, Yoshida M, Tsukada H, Onoe H, Isa T, Ikeda T (2021) The posterior parietal cortex contributes to visuomotor processing for saccades in blindsight macaques. *Communications Biology*, 4(1):278. doi: 10.1038/s42003-021-01804-z.
[8] Isa T (2021) Double viral vector intersectional approaches for pathway-selective manipulation of motor functions and compensatory mechanisms. *Experimental Neurology,* 349:113959. doi: 10.1016/j.expneurol.2021.113959.
[9] Isa T, Yoshida M (2021) Neural mechanism of blindsight in a macaque model. *Neuroscience*, (Forefront review), 469: 138-161. https://doi.org/10.1016/j.neuroscience.2021.06.022
[10] Isa T, Marquez-Legorreta E, Grillner S, Scott EK (2021) The tectum/superior colliculus as the vertebrate solution for spatial sensory integration and action. *Current Biology* (review), 31(11):R741-R762.

B. Improved understanding of interhemispheric inhibitory mechanisms in human motor cortex and improvement of aging-degraded inhibitory system by training (Naito and Asada)

In collaboration with Asada group (Osaka University), Naito group (NICT, CiNet) has used functional MRI to facilitate understanding of the mechanism of interhemispheric inhibition in the human motor cortex. It has been proposed that the interhemispheric inhibition between the foot sections of the left and right motor cortices is weak or absent because humans walk bipedally. Although robust interhemispheric inhibition was not observed during motor execution of only one leg in young adults, significant interhemispheric inhibition was observed during kinesthesia information processing of one leg (Naito et al. Brain Science 2021). These results suggested that an interhemispheric inhibition mechanism also exists between the foot sections of the two motor cortices, and this inhibition is weakened during motor execution. As for age-degraded inhibitory system, we found that older adults with degraded inhibition in the hand section of the ipsilateral (right) motor cortex during right hand movements had poorer dexterity of the right hand/finger as assessed by a peg test. Then, we divided healthy older adults (65-78 years old) into two groups (bimanual and right-hand groups). The bimanual group underwent coordination training in which the left and right fingers performed different movements for two months, while the right-hand group underwent only right-handed training. Neither group was trained in the peg test itself, but after training, hand/finger dexterity improved in the bimanual group only. Furthermore, we found that those who improved their hand/finger dexterity well had suppressed activity in the ipsilateral motor cortex (Naito et al. Scientific Reports 2021). This study showed that age-degraded interhemispheric inhibitory system can be improved by coordination training, which also leads to improvement of hand/finger dexterity.

[1] Naito E, Morita T, Kimura N, and Asada M Existence of interhemispheric inhibition between foot sections of human primary motor cortices: Evidence from negative blood oxygenation-level dependent signal. Brain Sciences, 11, 1099. https://doi.org/10.3390/brainsci11081099, 2021.
[2] Naito E, Morita T, Hirose S, Kimura N, Okamoto H, Kamimukai C and Asada M Bimanual digit training improves right hand dexterity in older adults by reactivating declined ipsilateral motor-cortical inhibition. Scientific Reports, 11, Article number: 22696, 2021.

C. Modulatory mechanism underlying interhemiphespheric inhibition and adaptive behaviors of the animals using rodent model (Aizawa)

To address mechanism underlying modulation of the interhemispheric inhibition observed upon hyper-adaptation by Isa and Naito-Asada groups, Aizawa group (Hiroshima University) established an experimental paradigm combining electrophysiology and optogenetics in mice. Pharmacological examination in the mouse secondary motor cortex revealed that $GABA_B$ agonist and antagonist enhanced and suppressed the interhemispheric inhibition, respectively. Since cholinergic antagonist also enhanced the interhemispheric inhibition in the same region, suggesting that those neurotransmitter system could modulate the cerebral interaction between hemispheres. The group also examined the adaptive response of the murine cerebral cortex upon hyperactivation or ischemia as spreading depolarization (Terai et al., J Neurophysiol, 2021). For the behavioral assessment of the animals adapting to the stress, a novel IoT system reporting wheel-running activity of mice at home cage was developed (Zhu et al., eNeuro, 2021).

[1] Terai H, Gwedela MNV, Kawakami K, Aizawa H. Electrophysiological and pharmacological characterization of spreading depolarization in the adult zebrafish tectum. J Neurophysiol. 126(6):1934-1942. doi: 10.1152/jn.00343.2021, 2021.

[2] Zhu M, Kasaragod DK, Kikutani K, Taguchi K, Aizawa H. A Novel Microcontroller-Based System for the Wheel-Running Activity in Mice. eNeuro. 8(6) doi: 10.1523/ENEURO.0260-21.2021, 2021.

IV. Future Perspective

Isa group demonstrated the crucial role of the interhemispheric pathway from the contralesional premotor cortex to the ipsilesional premotor cortex in the recovery of precision grip behavior during the recovery from spinal cord injury in the macaque monkeys by the pathway-selective blocking technique.

Naito-Asada group has advanced the understanding of the interhemispheric inhibitory system in the human motor cortex, and shown that the aging-degraded inhibitory system can be improved by coordination training. In the next year, we will clarify the differences in the recruitment mode of ipsilateral motor cortex during complex hand movements between young and older adults, and summarize the hyperadaptive phenomena observed in the brain of a top wheelchair racing Paralympian with congenital paraplegia.

Aizawa group has begun to identify the neurotransmitter system modulating the interhemispheric inhibition for hyper-adaptation. Since the global neuromodulation could be based on diffuse modulatory system using dopamine and serotonin and hormones released by organs outside the brain, the group will apply the mouse model to address roles of those systems in modulation of the interhemispheric inhibition upon hyper-adaptation.

A02 Annual report of research project

Kazuhiko SEKI
National Institute of Neuroscience, NCNP

***Abstract*—In the FY2021, our research group aimed to establish an physiological way to manipulate sensory prediction error by artificially changing sensory feedback at specific peripheral afferent. As the first step, we developed a novel method to introduce marker gene into the specific type of peripheral afferent.**

I. Introduction

From the cradle to the grave, the musculoskeletal structure of the human body is changing continuously. It can change with a prolonged time constant with 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-adaptiation” corresponding to the ever-changing musculoskeletal structure by establishing the novel animal models and the cutting-edge technology. By developing the muscle relocation model, where the association of muscle activity and its physical action will be surgically or optogenetically manipulated, we will investigate how the CNS acquire control strategy of their body de novo. We will implement novel neurophysiological tools for assessing the hyper-adaptation occurring the multiple levels of the CNS, from the spinal cord, brain stem, and cerebral cortex.

III. Research Results

This year, we built a new experimental environment in order to proceed with the experiment more smoothly. Specifically, the introduction of an automatic behavior analysis system by machine learning and the introduction of a wireless EMG measurement system. Furthermore, in order to investigate the neural mechanism of muscle synergy plasticity, subdural electrodes were implanted and the experiment was continued. At the same time, we conducted research aimed at developing an animal model that can intervene in sensory prediction error, which is one of the driving factors of hyper-adaptation. The results of this research are reported below.

The aim of this subproject was to examine if the target specificity of AAV6 and AAV9 vectors to DRG neurons that relay nociceptive or other somatosensory signals, respectively (as established in rodent models), can be reproduced in nonhuman primates. We injected each of the vectors into the sciatic nerve in both the rat and common marmoset (a New World monkey) and compared their target specificity within DRG neurons.

Eight young male Jcl:Wistar rats (4 weeks old) and 12 adult common marmosets of either sex (four males and eight females) were used. In both the rat and marmoset, we found vigorous fluorescence in the ipsilateral sciatic nerve, DRGs, and spinal cord 4 weeks after vector injection (Fig. 1). This suggested that gene transfer to these regions was successfully achieved via anterograde transport from the sciatic nerve injection (Fig. 1A and B). We observed stronger fluorescence in the segments of L4 and L5 in the rat (Fig. 1C and D) and of L5 to L7 in the marmoset (Fig. 1E and F). This difference in the segmental distribution is considered reasonable for the species difference in sciatic nerve anatomy. In the spinal cord, we found strong expression of Green Fluorescent Protein (GFP) not only in the DRGs, but also in the dorsal lemniscus (Fig. 1C-F), where the proximal axon of DRG cells ascend toward the brainstem. However, limited fluorescence was observed for DRGs that did not accommodate sciatic nerve afferents (e.g., contralateral DRGs). This result indicated a lower off-target effect for intra-nerve induction.

We further confirmed DRG-cell specific transduction of the exogenous GFP gene by quantification of the vector genome copy number. Results are summarized in Fig. 1G. These results demonstrated that expression of GFP was highly

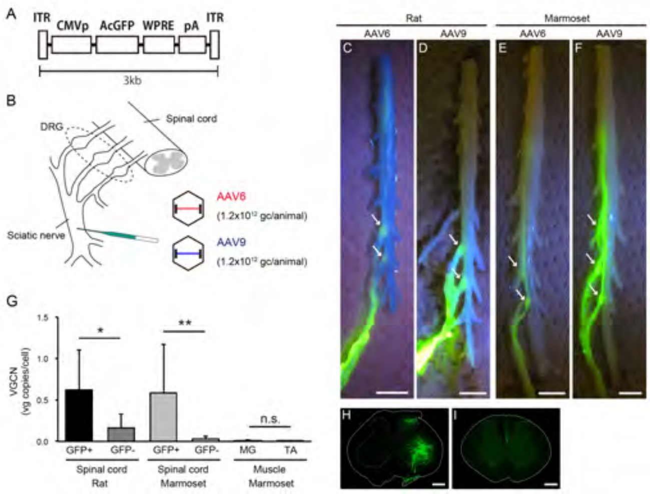

Fig. 1. Intra-nerve injections of AAV-GFP vectors in the rat and marmoset

specific to DRGs as well as to the spinal segments that innervated the nerve where the virus vector was injected, but without the off-target effect on tissues surrounding the site of injection (i.e., the muscles). Figure 2A-D show examples of immunostained sections containing DRG neurons transduced by AAV6 (A, C) and AAV9 (B, D) vectors in the rat (A, B) and marmoset (C, D). We immunostained with the antibodies, GFP (green) and neuron-sensitive marker (NeuN; red), to confirm successful gene delivery into DRG neurons. In these examples, we found a specific difference between the rat and marmoset. In the rat, the DRG neurons transduced by the AAV9 vector seemed to be larger than those transduced by the AAV6 vector. However, in the marmoset, this contrast was less dominant.

Next, we compared the target specificity of the AAV6 and AAV9 vectors in the rat and marmoset. Representative examples are shown in Figure 2E–L. For this analysis, we stained each DRG slice for NF200, a marker for myelinated primary afferents and DRG cells that convey somatosensory signals other than nociception, and peripherin, a marker for unmyelinated primary afferents and DRG cells that convey nociceptive signals38. Subsequently, we counted the DRG cells that exhibited double labeling for both GFP and NF200 or peripherin.

In the rat, we confirmed the specificity for nociceptive- and other somatosensory-related DRG neurons, as reported previously. For example, in the case of AAV6 vector injection, GFP-positive cells were found to be more frequently co-labeled for peripherin (Fig. 2F–F”) than for NF200 (Fig. 2E–E”; compare arrows in 2E” and F”). Conversely, in the case of AAV9 vector injection, the co-labeled cells were found more often for NF200 (Fig. 2G–G”) than for peripherin (Fig. 2H–H”) (compare arrows in Fig. 2G” and H”). Therefore, we successfully reproduced the previous findings in rodents. This confirmation is further supported by the transduction efficiency results (expressed as the ratio of NF200- or peripherin-labeled cells to GFP-labeled cells; Fig. 2M, left and N, left). We found that the AAV6 vector exhibited higher transduction efficiency

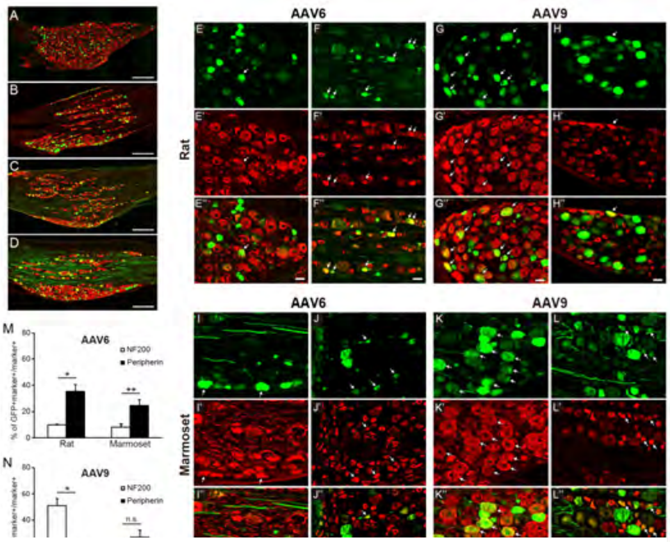

Fig. 2. Immunohistochemical evaluation and target-specific gene expression in DRG neurons in the rat and marmoset

into DRG neurons with unmyelinated fibers (peripherin labeled, Wilcoxon rank sum test, $p < 0.05$) and the AAV9 vector showed higher efficiency into DRG neurons with myelinated fibers (NF200 labeled, Wilcoxon rank sum test, $p < 0.05$).

To test whether the comparable target specificity of the AAV vectors to DRG neurons found in the rat is also represented in the marmoset, we repeated the equivalent examination in the marmoset and revealed two findings. First, in the case of AAV6 vector injection, we found that a proportion of the double-labeled cells was observed within peripherin-labeled cells (Fig. 2J–J”) more frequently than within NF200-labeled cells (Fig. 2I–I”). This profile was similar to the findings in the rat (Fig. 2E–F”). Further population analysis of the transduction efficiency of the AAV6 vector (Fig. 2M, right) confirmed that the target specificity of the AAV6 vector was biased toward peripherin- over NF200-labeled DRG neurons in both the rat and marmoset. Therefore, this result indicates that the target specificity of the AAV6 vector is represented in nonhuman primates as well as in rodents. Second, we found that the target specificity of the AAV9 vector in the marmoset was different from that in the rat. For example, the GFP transduction by AAV9 vector did not exhibit high preference to NF200-labeled cells, as was the case in the rat (compare Fig. 2G” and H”). Instead, we found a comparable number of NF200-labeled (Fig. 2K–K”) and peripherin-labeled (Fig. 2L–L”) cells (compare Fig. 2K” and L”) in the marmoset. Again, these results were supported by a population analysis (Fig. 2N): Although the AAV9 vector exhibited higher specificity to the NF200-labeled cells in the rat, the efficiency of transduction did not differ in the NF200- and peripherin-labeled cells in the marmoset (Wilcoxon rank sum test, $p > 0.05$).

Overall, we found that although the AAV6 vector displayed a comparable degree of target specificity (i.e., biased toward peripherin-labeled cells) in both the rat and marmoset, no clear target specificity of the AAV9 vector was detected in the marmoset, unlike in the rat, which showed specificity biased toward NF200-labeled cells.

IV. Future Perspective

Contrary to initial expectations, primates lost the selectivity of AAV9s to myelinated nerves. We need to further explore the optimal vector and/or promotor that is optimal to manipulate the activity of myelinated fiber for accessing the sensory prediction error. In the next fiscal year, we would like to continue the experiments which is currently ongoing, and clarify the neural basis behind the biphasic changes in muscle synergies by analyzing the ECoG signal.

References

[1] Kudo M, Wupuer S, Fujiwara M, Saito Y, Kubota S, Inoue K, , Takada M, Seki K: Specific gene expression in unmyelinated dorsal root ganglion neurons in nonhuman primates by intra-nerve injection of adeno-associated virus 6 vector. Molecular Therapy : Methods and Clinical Development, 6 Aug 2021

A03 Annual report of research project

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***Abstract*— Our research project aims to reveal neural mechanisms in which body cognition and positive emotion, such as motivation, facilitate motor learning in challenging situations ("hyper-adaptation"). Our main achievements in this fiscal year are 1) finding evidence that a sense of agency (a sense that "I am the one causing an action," which is an aspect of body cognition) facilitates motor learning in several behavioral experiments, 2) confirming that high-definition non-invasive brain stimulation can manipulate the relationship between sensorimotor information and the sense of agency, 3) identifying subregions of the frontal cortex to be involved in motivation by the non-invasive functional interventions in monkeys, 4) establishing a device for investigating sense of agency and motivation commonly in humans and monkeys, 5) establishing a long-lasting electrocorticogram recording method covering wide area of the monkey cerebral cortex.**

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. Relationship sense of agency and motor learning

1) Effect of sense of agency on motor learning: A group of the principal investigator (Tanaka and Imamizu) and Prof. Izawa of the B03-group have explored evidence that the sense of agency facilitates motor learning. They identified a relationship between spontaneous fluctuation in the sense of agency and efficiency in motor learning. In this fiscal year, they examined if the experimental manipulation of the sense of agency (self/other attribution of movements) affects the efficacy of short-term motor learning. Two participants sat side by side and moved a cursor to a target using a pen-tablet (Fig. 1A). In each trial, participants were instructed whether the cursor reflected their movement (self-condition) or the other's movement (other condition). The cursor movement was perturbed upward or downward by a computer. We estimated the effect of the perturbation on the performance in the subsequent trial as a short-term learning rate. As a result, the effect was significantly more significant in the self-condition than in the other condition (Fig. 1B). However, the effect was significantly greater than zero in the other condition. These results suggest that the sense agency causes a modulatory (but not decisive) impact on the learning efficacy.

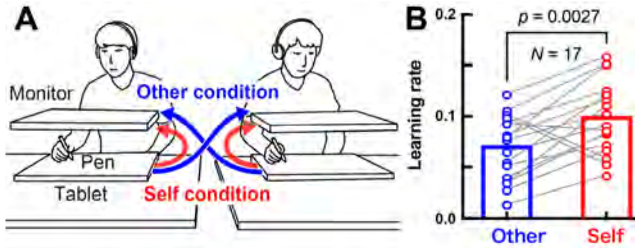

Fig. 1 Manipulation of self/other attribution by an instruction to participants (A) effect of the instruction (B)

2) Sensitivity to controllability and motor learning: A study on this topic was published by the group of the principal investigator Prof. Wen of the B03 [1].

B. The intervention of sense of agency with brain stimulation

A group of the principal investigator (Hiromitsu, Asai, and Imamizu) started experiments on the intervention of sense of agency with a high-definition transcranial alternating current stimulation (HD-tACS). They hypothesized that the neural connection between the right inferior parietal lobe (rIPL) and the right inferior frontal gyrus (rIFG) contributes to the judgment of a sense of agency. Participants moved a cursor with a joystick to trace a target trajectory. The cursor movement was mixed with the other's prerecorded movement with a specific ratio (10, 50, or 90%). After their movement, participants rated how much they felt the cursor movement seemed their own movement (agency rating) and how much the rating was confident (confidence). The alternating current was applied to the rIPL and rIFG during the movements under three conditions: In-phase, Anti-phase, and No stimulation, Fig 2A). As a result, we could not find a significant change in the relationship between the mix ratio of the other's movement and the agency ratio. However, a correlation became significantly more negative between the cursor-joystick distance (i.e., prediction error) and the agency rating in the anti-phase condition compared to the no-stimulation condition (Fig. 2B). It is known that an increase in the prediction error leads to a

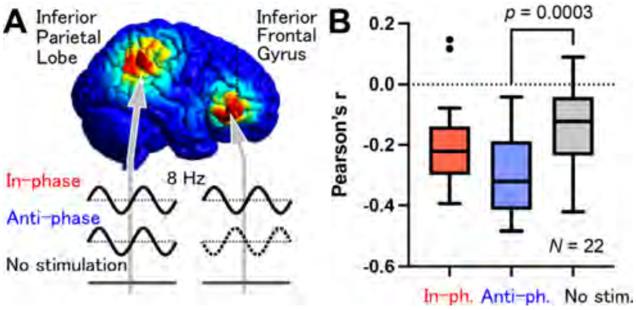

Fig. 2 Stimulation method (A) and effects (B)

decrease in the sense of agency (a negative correlation). The negative correlation was prominent in trials with high confidence in our data. These results suggest that the stimulation improved the agency rating based on the prediction error.

C. Basic studies on sense of agency

A principal investigator group (Ohata, Asai, Imaizumi, and Imamizu) wrote a paper on the sense of agency over speech, and the manuscript was accepted [2]. A review paper on the sense of agency co-authored with Prof. Wen of the B03 was accepted [3]. A group of the principal investigator developed a method to predict the effects of a robot rehabilitation from individuals' initial states [4]

D. Identificatin of motivation-related subareas in the frontal cortex by use of non-invasive functional interventions

The co-investigator group (Tsutsui and Nakamura) identified subregions in the frontal cortex to be involved in motivation by using repetitive transcranial magnetic stimulation (rTMS) as a means of neural intervention. To dissociate the factor of physiological drive, such as hunger, and cognitive motivation, behavioral performance in “competitive food picking task” was evaluated. After facilitating the neural activity of the dorsolateral prefrontal cortex (dlPFC), the stimulated monkey reached out more frequently to the food close to the competitor, and consequently obtained larger number of food pieces, while the performance under the non-competitive alone condition remained unchanged. After inhibiting the neural activity of the ventral medial frontal cortex (vMFC), the stimulated monkey reached out less frequently to the food close to the competitor, and consequently obtained larger number of food pieces, while the performance under the non-competitive alone condition remained unchanged. These results indicate the differential contribution of dlPFC and vMFC in cognitive motivation.

Fig. 3 The competitive food picking task. Off-line rTMS is applied to one monkey before the task performance.

E. Establishing a device for investigating sense of agency and motivation commonly in humans and monkeys

The co-investigator group (Tsutsui and Nakamura) have established a device for investigating sense of agency and motivation commonly in humans and monkeys. A subject sees his hands and target objects through a big LED screen; the graphics engine can generate and display spatial or time distortion to the visual image of the subject’s hands on the real time basis. This device is expected to change the subject’s sense of agency parametrically. We have confirmed that monkeys perform food picking through this system.

F. Establishing a long-lasting electrocorticogram recording method covering wide area of the monkey cerebral cortex

By the improvement of electrode design and surgery procedures, the co-investigator group (Tsutsui and Nakamura) have established an electrocorticogram recording methodology which enables stable recording from a wider area of the monkey cerebral cortex for a long period.

IV. FUTURE PERSPECTIVE

We made advances in developing a method to facilitate motor learning through manipulation of sense of agency by succeeding in facilitating motor learning due to experimental manipulation and intervention of the sense of agency by using non-invasive brain stimulation. We have identified multiple areas in the frontal cortex being involved in the control of cognitive motivation. We have established a methodological background to study sense of agency and motivation in a common behavioral paradigm.

REFERENCES

[1] Wen, W., Ishii, H., Ohata, R., Yamashita, A., Asama, H., Imamizu, H. (2021) Perception and control: individual difference in the sense of agency is associated with learnability in sensorimotor adaptation. ***Scientific Reports***, 11(1), e20542.

[2] Ohata, R., Asai, T., Imaizumi, S., Imamizu, H. (in press) My voice, therefore I spoke: The sense of agency over speech is enhanced by hearing self-voice, ***Psychological Science***.

[3] Wen, W. and Imamizu, H. (in press) The sense of agency in perception, behaviour, and human-machine interactions, ***Nature Reviews Psychology***.

[4] Takai, A., Lisi, G., Noda, T., Teramae, T., Imamizu, H., Morimoto, J. (2021) Bayesian Estimation of Potential Performance Improvement Elicited by Robot-Guided Training. ***Front Neurosci.***, 15, e704402.

A04. Alteration of brain dynamics as underlying mechanisms of hyper-adaptability in neurotransmitter disorders

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***Abstract* - The present research project (A04) is designed to test the hypothesis that the alteration of neural dynamics following abnormal DA or ACh neurotransmissions may lead to the change of "rule of the conduct" as an underlying mechanism of "hyper-adaptation". For this purpose, we employed both basic animal studies and clinical human studies in elder persons. In the third year, Takakusaki and colleagues has examined the role of brainstem ACh system and the brainstem-spinal cord pathways involved in postural control in the cat. Hanakawa and colleagues has been developing simultaneous EEG-fMRI for evaluating a dynamic profile of functional connectivity between distinct neural networks. They also examine neuromelanin MRI and DA transporter (DAT) SPECT for evaluation of dopamine systems. These studies will clarify relationship across cognitive functions, neural network dynamics and neurotransmitters underlying the generation of hyperadaptation.**

I. Introduction

The brain as a part of the body experiences various changes during senescence. Neurotransmitters such as dopamine (DA) and acetylcholine (ACh) are reduced by aging, resulting in Parkinson's disease (PD) and Alzheimer's disease (AD), respectively. The goal of this research project (A04) is elucidating brain-connectivity dynamics in the cortical and subcortical neural structures that underly the generation of hyperadaptation in elder persons due to decline of the above-mentioned neurotransmitters. To achieve the above goals, basic experiments in animals and clinical studies in humans are performed.

II. Aim of the Group

The Takakusaki group (PI; AMU) was in charge of animal experiments and examines the role of ACh and DA systems in executive posture-gait control. This year, we studied the postural control mechanism by the brainstem ACh system and the brainstem-spinal cord descending pathways. The reticulo-spinal tract (RST; load bearing) and vestibulospinal tract (VST; extending the body and balance control), which have antigravity capability, are crucial to maintaining the upright standing posture [1]. Because the brainstem ACh system is impaired in aging and neurodegenerative disorders, there is a need to formulate a working hypothesis that can explain the relationship between changes in the brainstem postural control system and those in postural deformities. We also attempt to afford substantial data to construct postural control mathematical models based on experimental findings.

Hanakawa (a research collaborator) and his colleagues in Kyoto University are 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 [2] which is a longitudinal study involving healthy elderly people as well as patients with PD and AD. They have started to acquire simultaneous EEG-fMRI from the participants of the PADN cohort. 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 [3] for evaluating the activity of the DA system. This year, they developed high-resolution MRI of the SN in the postmortem human brain.

III. Research Topics

A. Role of the brainstem ACh system in postural control

We examined functional connections between the pedunculopontine nucleus (PPN), the origin of the brainstem ACh systems, pontomedullary reticular formation (RF), and the lateral vestibular nucleus (LVN) in decerebrate cats. We observed that there are excitatory connections between the PPN muscle tone inhibitory area, where the ACh neurons exist, and the inhibitory region of the RF. Moreover, the PPN-ACh system excited more than half of the reticulospinal neurons and one-third of the vestibulospinal neurons. Therefore, both RST and VST can regulate postural muscle tone by the PPN-ACh system (Fig.1A). In PD, severe Lewy body pathology appears in the brainstem, including the PPN, RF, and LVN, in addition to the DA system. Together with this pathological nature, the present findings suggest that the impairment of the inhibitory RST and VST is more severe than the excitatory RST in PD. Therefore, we propose the working hypothesis that (1) the facilitation of the excitatory RST evokes co-contraction of extensor and flexor muscles, resulting in muscular rigidity, and (2) the decrease in VST activity causes flexion posture in PD (Fig.1B-C). We will prove this hypothesis by investigating the role of DA-ACh interaction at the brainstem in postural control. Moreover, there is a need to clarify how impairments in the cerebral cortex, basal ganglia, cerebellum, and limbic system in PD and AD disable postural control by acting on the brainstem posture control mechanisms.

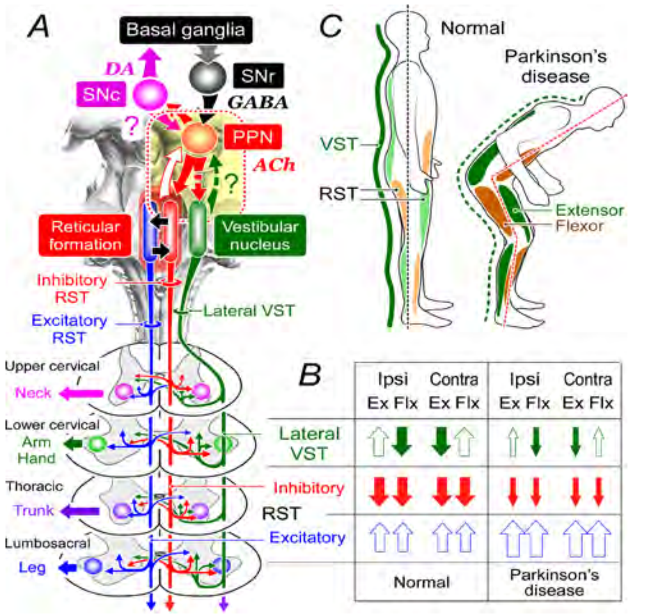

Fig. 1. Brainstem ACh system and brainstem-posture control mechanism

A; A hypothetical network of posture control by brainstem ACh system, RST, and VST. B-C. Activities in these descending tracts (B) and upright posture in normal and PD patients (C).

B. Non-invasice multimodal measurement of dynamic changes of brain activity and connectivity in humans

Yoshinaga (Kyoto University) and Hanakawa have been working on developing simultaneous EEG-fMRI and resting-state fMRI [4] to measure dynamic changes of brain activity and connectivity non-invasively in humans. This year, Yoshinaga et al. applied independent component analysis (ICA) to fMRI data from four groups: healthy elderly, cognitively normal patients with PD, cognitively impaired patients with PD symptoms, and patients with AD. Inter-network correlation of fMRI time-series (functional connectivity, FC) was retrieved from the default mode network, dorsal attention network, salience network, and central executive network. Dynamic changes of FC were assessed for each time window. Yoshinaga et al. found four internetwork states: a dense FC condition, a sparse FC condition and two intermediate conditions. Yoshinaga et al. compared the dynamic network states among the four groups. Yoshinaga et al. found that cognitively impaired patients with PD and AD, i.e., cognitively impaired elderly showed the sparse FC condition than the healthy elderly and cognitively normal PD (Fig. 2).

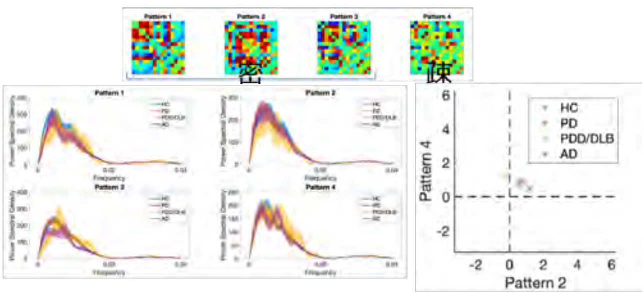

Figure 2: Comparison of 4 dFC patterns (dense, sparse, and two intermediate connections) across Healthy elderly (HC), Parkinson's disease (PD), PD with cognitive disturbance (PDD/DLB) and Alzheimer's disease (AD).

C. DA imaging in humans

The Hanakawa lab has continued to use neuromelanin MRI for the potential assessment of DA synthesis in the SN, in addition to DAT SPECT for the assessment of presynaptic DA terminals in the striatum in the elderly. The team has also aimed to combine the MRI method with the histochemical assessment in specimen. This year, the team has conducted high-resolution MRI of the midbrain including the SN, prompting the understanding of the MRI signals of SN (Fig. 3).

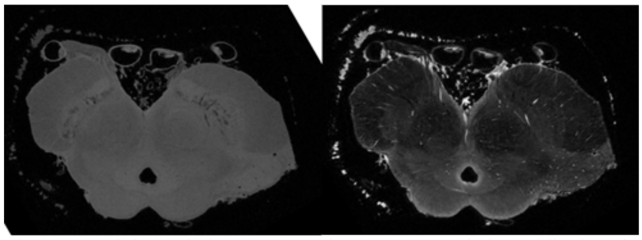

Figure 3: High-resolution T1W and T2W MRI of the midbrain of a postmortem human brain.

IV. Future Perspective

Takakusaki's group identified the basic principle of optimal postural control during voluntary movements [5]. In the next year, they will examine cortical and subcortical mechanisms of the optimal postural control concerning the function of the DA-ACh system. This year, Hanakawa's group advanced analysis technique for evaluating a dynamic profile of functional connectivity. They have also started to measure simultaneous EEG-fMRI from participants in the PADNI cohort study, while performing basic studies on this technique and DA imaging. In the PADNI cohort, DAT-SPECT will also be employed to detect a decrease in striatal DA. However, since many unclear points exist in the contrast expression in neuromelanin MRI, which is considered to reflect the production of DA in the SN, basic studies including postmortem studies, will be conducted in parallel.

References

[1] Takakusaki K, Takahasi M, Noguchi T, Chiba R. Neurophysiological mechanisms of gait disturbance in advance Parkinson's diseas. Neurol Clin Neurosci. (in press)

[2] N. Wakasugi N and T. Hanakawa: 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.

[3] J. Ikezawa, F. Yokoch, R. Okiyama, S. Kumada, M. Tojima, T. Kamiyama, T. Hanakawa, H. Matsuda H, F. Tanaka, Y. Nakata, E. Isozaki E: Is Generalized Dystonia Accompanied with Impairments of Dopaminergic System? Front Neurol 12:751434, 2021.

[4] 花川 隆：Q&A-神経科学の素朴な疑問: fMRI で測定されるゆっくりした脳活動の変動による脳領域間機能連関の神経基盤はどこまで解明されているのでしょう？Clin Neurosci 39(8): 1043, 2021.

[5] Takahasi M, Nakajima T, Takakusaki K. Preceding postural control during forelimb reaching movements in cats. Front Sys Neurosci 2022; 15:792665

A05-1Annual report of research project

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***Abstract*—This study aims to elucidate the hyper-adaptation mechanism of upper limb (UL) recovery in stroke patients. We expect the elucidation of the adaptation mechanism underlying UL recovery after stroke could contribute to understanding the hyper-adaptation mechanism of body-brain system. In this study, we measured the real-world arm use and body-specific attention longitudinally in subacute stroke patients using accelerometers and psychophysical methods, respectively, and investigated the relationship between them during the recovery process. The results showed a significant positive correlation between the amount of change in body-specific attention up to 1 month after enrollment and the long-term amount of change in real-world arm use up to 6 months after enrollment. This findings contribute to a new rehabilitation strategy to increase the real-world arm use. In addition, to understand the characteristics of this body-specific attention in more detail, we measured body-specific attention to the hands and feet in healthy subjects. As a result, we clarified the relationship between body-specific attention to the hands and feet and sensory-motor functions. Furthermore, we investigated the effect of a decrease in body ownership, one of the body consciousness, on sensory function (tactile sensitivity threshold). We found a significant negative correlation between loss of body ownership and tactile sensitivity threshold. These results contribute to a multifaceted understanding of the pathogenesis of UL paralysis in stroke patients from the perspective of body consciousness.**

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 with researchers in systems engineering and brain science to understand the adaptive mechanisms of the neural basis that mediates between the brain and the body (body representation in the brain) using mathematical models and to develop rehabilitation treatment based on these models. 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. However, it is not clear how body-specific attention changes from the onset of stroke to the chronic phase, and how it relates to the real-world arm use. In addition, the relationship between sensory-motor functions and body consciousness, including body-specific attention to hands and feet and a sense of body ownership, has not been fully elucidated.

II. AIM OF THE GROUP

1)This study aims to elucidate the hyper-adaptation mechanism of UL recovery in stroke patients. We longitudinally investigate relationship between real-world arm use and body-specific attention in stroke patients by using accelerometers and psychophysical methods, respectively. We expect the elucidation of the adaptation mechanism underlying UL recovery after stroke could contribute to understanding the hyper-adaptation mechanism of body-brain system. 2) In addition, the aim of this study is to clarify the characteristics of body-specific attention to the hands and feet, and the effects of loss of body ownership on sensory functions in healthy subjects. These will contribute to basic findings for understanding the pathology of hemiplegic stroke patients from various perspectives of body consciousness.

III. RESEARCH TOPICS

A. *Relationship between body-specific attention to a paretic limb and real-world arm use in stroke patients: A longitudinal study.*

We conducted a longitudinal prospective observational study of 25 patients with first-ever subacute stroke. Measurements were taken at baseline (T_{BL}), 2 weeks (T_{2w}), 1 month (T_{1M}), 2 months (T_{2M}), and 6 months (T_{6M}) after enrollment. UL function was measured using the Fugl–Meyer Assessment (FMA) and Action Research Arm Test. Real-world arm use was measured using accelerometers on both wrists. Body-specific attention was measured using a visual detection task. The UL function and real-world arm use improved up to T_{6M}. Longitudinal changes in body-specific attention were most remarkable at T_{1M}. Changes in body-specific attention up to T_{1M} correlated positively with changes in real-world arm use up to T_{6M}, and from T_{1M} to T_{6M}, and the latter more strongly correlated with changes in real-world arm use. Changes in real-world arm use up to T_{2M} correlated positively with changes in

FMA up to T_{2M} and T_{6M}. No correlation was found between body-specific attention and FMA scores. Thus, these results suggest that improved body-specific attention to the paretic limb during the early phase contribute to increase long-term real-world arm use, and that increased real-world use is associated with recovery of UL function. Our results may contribute to the development of rehabilitation strategies to enhance adaptive changes in body representation in the brain and increase real-world arm use after stroke. [2]

B. Body-specific attention to the hands and feet in healthy adults.

Body-specific attention to the hands has been examined but not to the feet. We aimed to confirm the existence of body-specific attention to the hands and feet, and examine its relation to motor and sensory functions from a behavioral perspective. The study included two groups of 27 right-handed and right-footed healthy adults, respectively. Visual detection tasks were used to measure body-specific attention. We measured reaction times to visual stimuli on or off the self-body and calculated the index of body-specific attention score to subtract the reaction time on self-body from that off one. Participants were classified into low and high attention groups based on each left and right body-specific attention index. For motor functions, Experiment 1 comprised handgrip strength and ball-rotation tasks for the hands, and Experiment 2 comprised toe grip strength involved in postural control for the feet. For sensory functions, the tactile thresholds of the hands and feet were measured. The results showed that, in both hands, the reaction time to visual stimuli on the hand was significantly lesser than that offhand. In the foot, this facilitation effect was observed in the right foot but not the left, which showed the correlation between body-specific attention and the normalized toe gripping force, suggesting that body-specific attention affected postural control. In the hand, the number of rotations of the ball was higher in the high than in the low attention group, regardless of the elaboration exercise difficulty or the left or right hand. However, this relation was not observed in the handgripping task. Thus, body-specific attention to the hand is an important component of elaborate movements. The tactile threshold was higher in the high than in the low attention group, regardless of the side in hand and foot. The results suggested that more body-specific attention is directed to the limbs with lower tactile abilities, supporting the sensory information reaching the brain. Therefore, we suggested that body-specific attention regulates the sensory information to help motor control. [3]

C. Decreased tactile sensitivity induced by disownership: An observational study utilizing the rubber hand illusion.

Long-term non-use of parts of the body due to physical dysfunction may disturb multisensory integration, resulting in a decreased sense of body ownership. The rubber hand illusion (RHI) is an experimental method of manipulating the sense of ownership (SoO). In this illusion, subjects feel as if the rubber hand in front of them were their own hand. The RHI elicits the disownership phenomenon; not only does the rubber hand feels like one's own hand, but one's own hand does not feel like one's own hand. The decrease of ownership of one's own body induced by the bodily illusion is accompanied by neurophysiological changes, such as attenuation of somatosensory evoked potential and decreases in skin temperature. If the loss of the SoO is associated with decreased neurophysiological function, the dysfunction of patients complaining of the loss of ownership can be exacerbated; appropriate rehabilitation prescriptions are urgently required. The present study attempted to induce a sense of disownership of subjects' own hands using the RHI and investigated whether the tactile sensitivity threshold was altered by disownership. Via questionnaire, subjects reported a decrease of ownership after the RHI manipulation; at the same time, tactile sensitivity thresholds were shown to increase in tactile evaluation using the Semmes-Weinstein monofilaments test. The tactile detection rate changes before and after the RHI were negatively correlated with the disownership-score changes. These results show that subjects' sense of disownership, that their own hands did not belong to them, led to decreases in tactile sensitivity. The study findings also suggest that manipulating of illusory ownership can be a tool for estimating the degree of exacerbation of sensory impairment in patients. Consideration of new interventions that optimize the sense of body ownership may contribute to new rehabilitation strategies for post-stroke sensory impairment. [4]

IV. Future Perspective

In the recovery process of paretic UL, body-specific attention was found to be related to real-world arm use. We believe that the results will contribute to the construction of rehabilitation strategies to enhance body consciousness and real-world arm use in stroke patients. In the future, we will investigate the neural basis of use-behavior and body-specific attention, and clarify the long-term changes in the brain functional and structural networks during the recovery process of stroke patients.

References

[1] N. Aizu, Y. Oouchida, and S. Izumi, "Time-dependent decline of body-speci fi c attention to the paretic limb in chronic stroke patients," *Neurology*, vol. 91, pp. e751-758, 2018.

[2] 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," *Front. Syst. Neurosci.*, vol. 15, 2022.

[3] 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," *Front. Syst. Neurosci.*, vol. 15, Jan. 2022.

[4] K. Ataka, T. Sudo, R. Otaki, E. Suzuki, and S.-I. Izumi, "Decreased Tactile Sensitivity Induced by Disownership: An Observational Study Utilizing the Rubber Hand Illusion," *Front. Syst. Neurosci.*, vol. 15, Jan. 2022.

A05-3Annual report of research project

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***Abstract*—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. 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. In order to understand the brain network associated with motor control and hyper-adaptic reorganization, we made an electrophysiological connectome by using cortico-cortical evoked potentials (CCEPs) as an index of effective connectivity, which were obtained by systemic evaluation of the whole implanted electrodes. We explored the network property of higher brain functions such as the premotor and language areas, and the effect of epilepsy upon the network integrity. For its clinical application, we validated the safety and feasibility of CCEP both for acute and chronic evaluations with intracranial electrodes, and proposed the intraoperative CCEP protocol.**

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 2021, because of the ongoing COVIC-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. We investigated the network characteristics proper to the higher brain functions and its plastic alternation due to pathology, namely, epilepsy.

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 extract structural features such as cluster coefficient or centrality, and attempt to clarify modifications of the connectome by epilepsy pathology or variations by different higher-order motor task strategies.

In order to delineate the mode of hyper-adaptability in each individual patient who underwent brain resection for epilepsy or tumor surgery, we need to establish the CCEP protocol under acute (intraoperative) and chronic evaluations with intracranial electrodes to make individual CCEP connectome. We validated the safety of CCEP investigation, and explored the effect of general anesthetics upon CCEP.

III. Research Topics

We have carried out the following three research projects.

A. Investigation of electrophysiological connectome to delineate network configuration proper to higher functions and its alternation due to pathology

Electrophysiological connectome, namely, CCEP connectome was generated by means of systemic low-frequency electrical stimulation to all the implanted electrodes to record CCEP. The network property of higher functions was investigated using the CCEP connectome, and the part of the findings (connectivity from the medial parietal cortices) is currently under review (Togo, Matsumoto et al.).

The part of the ventral premotor area (negative motor area [NMA]) is known to show a negative motor response (arrests of repetitive movement of the tongue, hands, and feet) upon ECS. In the group analysis of 8 patients, NMA showed significantly larger outbound connections compared to the primary motor cortex and the language areas while the language area showed larger inbound connections. With regards to pathology, namely, epilepsy, N1 inbound connections and N2 outbound connections were found to be altered within the epileptic focus.

We now have constructed the CCEP connectome based upon the data from 25 patients, and the network property and pathologic alternation will be presented in the coming annual meeting of the Japanese Society of Neurology in Spring, 2022 (Togo et al.). In the future, we will compare individual connectome with group data to clarify the transformation of connectome due to epilepsy pathology.

B. Validation of its safety and feasiblity under under general anethesia and proposal of CCEP protocol for clinical application of CCEP connectome

For clinical application of CCEP connectomic approach for hyper-adaptability, the safety is of utmost importance. A total of 1283 stimulation was analyzed in 29 consecutive patients who underwent chronic subdural electrode implantation and CCEP recording for the presurgical evaluation. Afterdischarges (ADs, 0.94%) and clinical seizures (0.39%) were rarely induced by low-frequency stimulation, and thus CCEP is regarded as a safe procedure. Although rare, the clinical seizure was more frequently triggered within the seizure onset zone. Stimulation intensity did not seem to be a risk factor of ADs and clinical seizures [4].

With regards to the effect of general anesthesia, the effect of propofol, the most common anesthetics we use for awake craniotomy, was systematically investigated in 14 patients who underwent intraoperative CCEP evaluation. The distribution of large CCEP response was marginally affected by propofol. The CCEP N1 amplitude increased from general anesthesia to awaking. These findings indicate that CCEP allows testing of the functional network such as dorsal language white matter pathway even under general anesthesia [5]. Taking account of these recent findings, we proposed the intraoperative CCEP protocol in an open-access manner [6, 7].

Besides, as a leading-expert in CCEP, the PI gave a talk in various domestic and international meetings on the concepts, development and future of CCEP [8-13], and wrote a chapter of the Handbook of Clinical Neurophysiology [14].

C. Modification of connectome by surgical resection and hyper-adaptability of network

This prospective study was not well performed due to ongoing COVID-19 pandemic in year 2021. When we have to resect a part of the premotor area due to clinical need for epilepsy or tumor surgery, we will reconstruct the premotor area connectome based on the comprehensive CCEP responses to simulate the structural changes in the network after resection. We then compare this simulation results with actual behavioral dysfunction that would occur immediately after surgery with potential subsequent recovery, and clarify the network-level hyper-adaptation by elucidating "hyper-adaptive" indicators that incorporate indexes such as cluster coefficient and centrality. Furthermore, based on comprehensive connectome information, we will promote collaborative researches with theory group B to seek for constructing mathematical model of hyper-adaptation after resection of the premotor area.

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 delineated network configuration proper to the premotor and other higher functional areas and their alteration due to epilepsy pathology. In the next grant application in this group, we plan to carry out the initial 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] Togo M, Matsumoto R, Nakae T, et al. Characteristics of intercortical networks created with late cortico-cortical evoked potential. ***62th JSN meeting,*** May 19, 2021. Candidate of the best presentation award.

[2] Togo M, Matsumoto R, Nakae T, et al. Connectivity strength modification in interareal cortical networks from the seizure onset zone: a cortico-coritical evoked potential study. ***JES54 meeting***, Sept.23, 2021

[3] Togo M, Matsumoto R, Nakae T, et al. Modification of effective connectivity strength in interareal cortical networks from the seizure onset zone: a cortico-cortical evoked potential study***. The 13th AOEC meeting,*** June 12, 2021.

[4] Kobayashi K, Matsumoto R, Usami K, et al. Cortico-cortical evoked potential by single-pulse electrical stimulation is a generally safe procedure. ***Clin Neurophysiol*** 132:1033-1040, 2021.

[5] Yamao Y, Matsumoto R, Kunieda T, et al. Effect of propofol on cortico-cortical evoked potentials: findings of intraoperative dorsal language pathway monitoring. ***Clin Neurophysiol*** 132:1919-1926, 2021.

[6] Yamao Y, Matsumoto R. Intraoperative cortico-cortical evoked potential recording for monitoring the arcuate fasciculus; Feasible under general anesthesia? ***Clin Neurophysiol*** S1388-2457(21)00737-9.

[7] Yamao Y, Matsumoto R, Kikuchi T, Yoshida K, Kunieda T, Miyamoto S. Intraoperative brain mapping by cortico-cortical evoked potential. ***Front Hum Neurosci***, 15:55, 2021. doi: 10.3389/fnhum.2021.635453

[8] 松本理器．皮質皮質間誘発電位：着想から臨床応用への道のり．**第 27 回日本脳神経モニタリング学会**，2021 年 7 月 3 日

[9] 松本理器．脳機能マッピングの過去･現在･未来．**15 回日本てんかん学会関東甲信越地方会**，2021 年 11 月 27 日

[10] 松本理器．皮質皮質感誘発電位(CCEP)：歴史と展望．**第 51 回日本臨床神経生理学会学術大会**，2021 年 12 月 16 日

[11] Matsumoto R. Intraoperative Brain Mapping by Cortico-Cortical Evoked Potential. O***N-LINE Meeting Spanish Society of Clinical Neurophysiology (SENFC 2021)***, Oct 16th, 2021

[12] Matsumoto R. Cortico-cortical evoked potential: its past, present and future. ***Grand Round, Cleveland Clinic Epilepsy Center***, June 4, 2021

[13] Matsumoto R. Physiology and pathology of the higher brain function: insights from intracranial EEG recordings. ***Chaucer Club (web seminar), MRC Cognition and Brain Sciences Unit.*** University of Cambridge, Apr 29, 2021

[14] Hallett M, DelRosso LM, Elble R, et al. (松本 9 番目) Chapter 1. Evaluation of movement and brain activity. ***Clinical Neurophysiology of Movement Disorders, 2nd Edition Handbook of Clinical Neurophysiology, Clin Neurophysiol*** 132:2608-2638. doi: 10.1016/j.clinph.2021.04.023. (review)

A05-5. Development of non-invasive brain stimulation techniques that can icrease recruitment of the corticospinal motor indirect pathway during acquisition of hand motor skills

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***Abstract*—Hand dexterity is a remarkable ability characterizing higher primates, including humans. Evidence from humans revealed that hand movement is controlled by primary motor cortices (M1s) in bilateral hemispheres. Our results suggested recruitment of the corticospinal networks between M1s and the spinal cord during hand movement that sends the influences from the contralateral M1 on the spinal cord (contralateral M1-SC network) or that converge the influences from bilateral M1s onto the spinal cord (bilateral M1s-SC network). It has been proposed that bilateral M1s-SC network may play a role in functional recovery of the impaired hand movements. Our motivation is to develop the non-invasive stimulation protocols to recruit the bilateral M1s-SC network in functional recovery in patients who disable to perform hand movements. During the fiscal year 2020-2022, we found that left-hand movement involved the bilateral M1s-SC network more than right-hand movement. Furthermore, we found higher neuronal activity in the spinal cord at the level of C3-C4 segments during left-hand movement. Previous evidence indicated that the propriospinal neurons located at the level of C3-C4 segments may serve functional recovery of the impaired hand movement. We hypothesized higher recruitment of the bilateral M1s-SC network by inducing the neuronal plasticity in the propriospinal neurons. We are developing the stimulation protocols that induce the timing-dependent plasticity in these neurons.**

I. Introduction

Human studies unveiled that hand movement involved not only contralateral M1 but also ipsilateral M1. A neurophysiological report suggested existence of the bilateral M1s-SC network in humans. However, no studies demonstrated whether right-hand movement or left-hand movement recruited the bilateral M1s-SC network. We thus developed the functional magnetic resonance imaging techniques which enabled simultaneous measurement of neuronal activity in M1 and spinal cord at the segments where motoneurons innervating hand muscles reside. During the fiscal year 2020-2022, we tested whether right-hand movement of left-hand movement involved the bilateral M1s-SC network. Our results suggested that left-hand movement more likely involved the bilateral M1s-SC network than right-hand movement. Furthermore, we found higher neuronal activity in the spinal cord at the level of C3-C4 segments during left-hand movement. We hypothesized increase of recruitment of the bilateral M1s-SC network by inducing long-term potentiation-like plasticity in the neurons at the level of C3-C4 segments. The stimulation protocols have been proposed that may induce plasticity in the propriospinal neurons, assumedly located at the level of C3-C4 segments. We assumed that the propriospinal neurons are implemented in bilateral M1s-SC network. We are constructing the experimental settings to test our hypothesis.

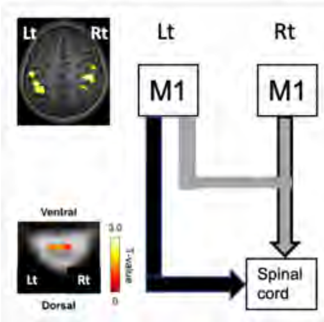

Fig1. The indirect pathway model during LHM. We measured activity in bilateral M1 and the spinal cord. We constructed the models of the contralateral M1 network (black-colored) and the bilateral M1s network (gray-colored). We tested whether right-hand movement or left-hand movement involved the contralateral M1 network or the the bilateral M1s network.

Abbreviations: Left=Lt, Right=Rt

II. Aim of the Group

Our long-term goal is to develop higher recruitment of the bilateral M1s-SC network by inducing the neuronal plasticity in the propriospinal neurons at the level of C3-C4 segments.

III. Research Topics

Here we described the following what we achieved and what we are preparing as follows.

A. Higher neuronal activity in the spinal cord at the level of C3-C4 segments during left-hand movement .

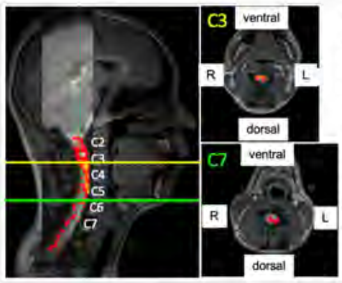

Figure 2. Statistical parametric mapping in the entire cervical spinal cord. We performed statistical parametric mapping to explore active regions during LHM relative to rest (left panel, upper). Anatomical landmarks of C2-C7 indicates vertebral levels in the cervical spinal cord. Note the difference between vertebral and spinal levels (left panel, lower). For example, motoneurons at the cervical segment C7 were localized at the vertebral level C8. We observed activity in not only C7 (see green line in upper, left panel. See also upper in right panel) but also C3-C4 (see yellow line in line in lower, right panel. See also lower in right panel).

Abbreviations: Left=Lt, Right=Rt

We examined whether right-hand movement or left-hand movement recruited the bilateral M1s-SC network. Our results suggested that left-hand movement more likely involved the bilateral M1s We constructed the bilateral M1s-SC network model in which influences from bilateral M1s modulated activity in the spinal cord (Fig. 1). Furthermore, we found higher neuronal activity in the spinal cord at the level of C3-C4 segments during left-hand movement than during right-hand movement (Fig. 2 and Fig. 3). Evidence from monkeys indicated the propriospinal neurons that relay signals from M1s. We interpreted recruitment of the neuronal activity in C3-C4 observed during left-hand movement.

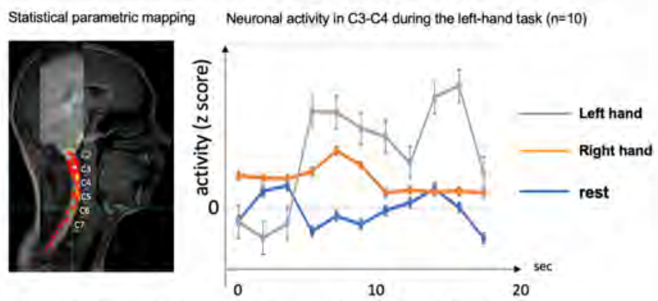

Figure 3: Statistical parametric mapping during left-hand movement. We observed neuronal activity in C3-C4 during right-hand movement, left-hand movement or rest. Plot data indicating activity during the 20-sec block were presented. We observed higher activity during left-hand movement than right-hand movement ($p = 0.011$) or rest ($p < 0.001$).

We developed the pipelines of the imaging data by using combination of the following widely distributed software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki [FSL], https://spinalcordtoolbox.com/en/stable/ [Spinal Cord Toolbox]). Now we achieved to perform statistical mapping analysis by voxel by voxel in the brain and the spinal cord.

B. Development of stimulation protocol that induce the timing-dependent plasticity in the propriosepinal neurons at the segment of C3-C4

We assumed that the propriospinal neurons are implemented in the bilateral M1-SC network. We designed the protocol that induces the timing-dependent plasticity in the propriospinal neurons. These neurons converge signals derived from M1s, and also integrate signals from M1 and afferents from peripheral neurons. Previous literatures observed modulation of motor evoked potentials when the double stimulation of the motor cortex and the peripheral nerve were applied. Notably this modulation was most evident when the peripheral stimulation was applied at the timing 7 ms before the cortical stimulation. These results suggested collision of stimulations from M1 and the peripheral nerve in the propriospinal neurons. We hypothesized the propriospinal neurons located at C3-C4 that are active using the double stimulation technique. We are preparing the experiential setting that enable measuring MRI activity in C3-C4 when the double stimulation technique is given.

IV. Future Perspective

In the fiscal year 2020-2022, we discovered evidence suggesting recruitment of neurons in C3-C4 during left-hand movement that are implemented in the bilateral M1-SC network. To facilitate the bilateral M1-SC network, we are on the way to develop the double stimulation protocols that induce plasticity in the propriospinal neurons located at the C3-C4 segment.

References

[1] Isa T, Kinoshita M, Nishimura Y. Role of Direct vs. Indirect Pathways from the Motor Cortex to Spinal Motoneurons in the Control of Hand Dexterity. Front Neurol. 2013;4:191.

[2] 高澤 英嗣, 阿部 十也, 飯塚 伯, 設楽 仁, 高岸 憲二, 筑田 博隆, 花川 隆. 脊椎疾患のニューロイメージングの近未来 脳脊髄機能的 MRI による皮質脊髄路の神経機能評価法とその展望. 日本整形外科学会雑誌 92(2) S335-S335 2018 年

[3] 高澤 英嗣, 阿部 十也, 飯塚 伯, 設楽 仁, 高岸 憲二, 花川 隆. 脳脊髄機能的 MRI による皮質脊髄路の機能評価法の開発. Journal of Spine Research 7(9) 1366-1372. 2016 年

[4] Hanakawa T, Mima T, Matsumoto R, Abe M, Inouchi M, Urayama S, Anami K, Honda M, Fukuyama H. Stimulus-response profile during single-pulse transcranial magnetic stimulation to the primary motor cortex. Cerebral Cortex. 19(11):2605-15. 2009.

[5] Abe M, Fukuyama H and Mima T. Water diffusion reveals networks that modulate multiregional morphological plasticity after repetitive brain stimulation. Proceedings of the National Academy of Sciences of the United States of America. 111(12):4608-13. 2014.

A05-6 The cerebellum–rubral pathway is involved in the function recovery by rehabilitation after intreacerebral hemorrhage

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***Abstract*— In the FY2021, we performed selective blockage in the cerebellum-rubral pathway using double-virus infection method, following to confirmation of optimum infection condition. In the skilled reaching test, CNO treatment caused the inhibition of the functional recovery that is induced by forced-limb use after intracerebral hemorrhage. The CNO effect to the cerebellum-rubral pathway is also supported by the electrophysiological analysis.**

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I. INTRODUCTION

To clarify the mechanism of CIMT that is used as a rehabilitation method after intracerebral hemorrhage (ICH), we have previously revealed that 1) forelimb motor function is recovered by forced-limb use (FLU) after ICH, 2) the cortico-rubral pathway has a causality to the functional recovery of FLU after ICH, and 3) the cortico-reticular pathway has a potency to substitute for the functional recovery by rehabilitation. In this study, using a rat ICH model, we are challenging to clarify motor regulatory mechanism of the cerebellum in the recovery by FLU.

II. AIM OF THE GROUP

The final purpose of our study is to clarify the mechanism of the recovered forelimb function by FLU after ICH using selective blockade in the cerebellum-rubral pathway.

As we could establish the efficient double-transfection into the cerebellum and the red nucleus in last year, we are challenging three projects as follows.

In ICH model rats that recovered forelimb function by FLU, 1) we transfect AAV-DJ-EF1-DIO-hM4D(Gi)-mCherry into the lateral nucleus of the cerebellum and FuGE-MCSV-Cre into the red nucleus parvocellular part, 2) we assessed forelimb function in the pellet reaching test with DREADD method by CNO, and 3) we measure the change of the nerve activity in the cerebellum-rubral pathway by multi-electrode electrode method as collaborating evidence for the inhibition by CNO.

III. RESEARCH TOPICS

A. Optimization of the double-virus infection method into the cerebellum – rubral pathway

To optimize the virus vector infusion method, we injected AAV-DJ-CAGGS-FLEX-EGFP into the cerebellum and FuG-E-MSCV-Cre into the red nucleus changing infusion conditions (quantity, the number of times, speed).

Confirming EGFP-positive cells as the marker which expression is induced by Cre, it was revealed that we can efficiently transfect the virus vectors into both the cerebellum and red nucleus road as shown in Table 1.

	both side	volume	AD	ML	DV	Vertical angle
Red Nucleus	1 area	0.8μℓ /4min	−5.2	±1.6	脳表 7.5	5 degree
Cerebellum	2 areas	0.6μℓ /3min	−11.0	±3.5	4.4	0 degree
			−11.4	±3.6	4.3	

Table 1 Virus infection condition into the cerebellum-rubral pathway

B. Evaluation of forelimb function under selective block in the cerebellum-rubral pathway using the DREADD method

After pre-training for 2 weeks in 6 weeks-old Wistar rat, FuG-E-MSCV-Cre was injected into the red nucleus at 8 weeks of age and then AAV-DJ-EF1-DIO-hM4D(Gi)-mCherry was injected into the lateral nucleus of cerebellum one week later.

We evaluated skilled reaching test at 2-3 day just before ICH and at 12 day after ICH. The reaching test was also performed at 30 min after CNO treatment at 16 and 20 day after ICH, followed by the test at 28 day after ICH without CNO administration (Figure 1).

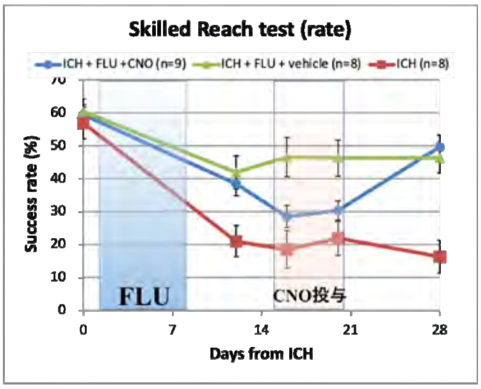

Figure 1. Selective blockade of the cerrebello-rubral pathway by CNO administration

As a result, it was revealed that the improvement effect of FLU after ICH on the forelimb function was disappeared by the CNO administration. In addition, the improvement effect by FLU was observed without CNO treatment at 28 day after ICH. On the other hand, the CNO action disappears three hours after the treatment, confirming that the improvement by FLU after ICH is related to the cerebellum-rubral pathway.

C. Confirmation of the electrophysiologicall response in the red nucleus to the stimulation in the lateral nucleus of the cerebellum

The technique of electrophysiological experiment and the analysis using the multi-point electrode probe were obtained in last year.

As the recovery effect by FLU after ICH is inhibited by the selective blockade in the cerebellum-rubral pathway, we are challenging the analysis of the response in the red nucleus against electric stimulation in the cerebellum as the collaborating evidence for the selective blockade.

The lateral nucleus of the cerebellum (AP: −13.2, ML:3.5, DV:4.5 with 20 degree angle posterior to vertical line) was stimulated by various condition (intensity: 10~200µA, duration: 0.1msec, interval: 3.3msec, 10 trains) .

Although both saline-treated control group and CNO-treated group is n=1, the field potential in the red nucleus against cerebellum stimulation was stable during 1 hour. On the other hand, about 35% decrease of the potential is shown at 30 mins after CNO administration.

Although it is necessary to increase the number of experiments, the electrophysiological collaborating evidence of the nerve block effect of the cerebellum-rubral pathway by CNO treatment could suppose collaborating evidence.

IV. Future Perspective

Finally, the results in FY2021I was summarized and our future plan was written as fokllows.

In this year, we revealed that forelimb functional recovery by FLU after ICH was significantly inhibited by selective blockade in the cerebellum-rubral pathway with CNO administration, which is shown by behavioral and electrophysiological experiments.

In the next year, we are planning to investigate the detail mechanism in motor regulatory system mediated by the cerebellum-rubral pathway, analyzing 1) time course of activation switch in the cerebellum-rubral pathway, 2) detailed forelimb movement by markerless method using DeepLabCut and its the relationship with the cerebellum-rubral pathway.

References

[1] C C Joyal, C Strazielle, R Lalonde Effects of dentate nucleus lesions on spatial and postural sensorimotor learning in rats. Behav Brain Res. 2001; 122(2): 131-37.

[2] A Ishida, K Kobayashi, Y Ueda, T Shimizu, N Tajiri, H Hida Dynamic Interaction between Cortico-Brainstem Pathways during Training-Induced Recovery in Stroke Model Rats. J Neurosci. 2019; 39(37), 7306-20..

A05-7Annual report of research project

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***Abstract*—Due to fearful memories of an excess aversive experience, animals fall into maladaptation states in which the animals take inadequate behaviors (e.g. freezing in safe environments). The animals recover adaptive behavior through the following hyper-adaptation process induced by extinction learning. It is well established that the amygdala is essential for fear-related maladaptation and hyper-adaptation. In addition, recent studies indicate other brain regions, such as the ventral hippocampus and prefrontal cortex, are also involved in the maladaptation and hyper-adaptation processes. However, it remains unclear how these brain regions interact with each other and whether the interaction changes with transitions to maladaptation or hyper-adaptation states. To investigate these points, we performed multi-regional large-scale electrophysiology in fear-conditioned rats. We found that cell-ensembles, groups of synchronously activated neurons, in the amygdala, ventral hippocampus, and prefrontal cortex are simultaneously activated during sleep periods following the fear-conditioning. Such synchronous activation was not detected in sleep preceding the conditioning. We also revealed that the triple-activation accompanies fast network oscillations in the involved regions. These findings suggest that the development of inter-regional interaction supports the transition to mal-adaptation states, and fast network oscillations may have important roles in the inter-regional interaction. Further studies are warranted to elucidate how inter-regional ensemble coactivations are involved in the maladaptation and hyper-adaptation process.**

I. Introduction

As a well-established animal model of human post-traumatic stress disorder (PTSD), Fear-conditioning has been intensively studied. Fear-conditioned animals are in maladaptation states where the animals take inadequate behaviors such as freezing in safe environments. The fear-conditioned animals recover their appropriate behavior through hyper-adaptation induced by extinction learning, whereas the fear memories themselves are maintained [1]. The acquisition and extinction of fear memories involve the amygdala, ventral hippocampus, and prefrontal cortex [2]. However, it remains unclear how inter-regional networks across these regions change through transitions to maladaptation/hyper-adaptation states and how these changes are regulated. Revealing these points would provide fundamental information on memory- and emotion-related mental disorders such as PTSD and anxiety disorders. Furthermore, the information would be crucial for developing neurophysiology-based cure procedures for these disorders.

II. Aim of the Group

This research project aims to clarify how inter-regional brain networks changes during hyper-adaptation from fear-memory induced maladaptation states. Furthermore, this project would also reveal regulation mechanisms underlying the changes in the inter-regional networks. To obtain these goals, we first elucidate how the network changes through the fear-memory-induced maladaptation, which would give an important clue to understand what is compensated through the hyper-adaptation process. In this year, we focused on the transition to maladaptation states, and we aimed to clarify the dynamics of inter-regional networks that involve multiple brain regions during the maladaptation process and its regulation mechanisms in each brain region.

III. Research Topics

A. Multi-regional large-scale electrophysiology in three brain regions and identification of cell ensembles

By utilizing multi-regional large-scale electrophysiological recordings on freely moving rats, we obtained spike activities of hundreds of neurons and local field potentials (LFPs) continuously for ~17 hours from basolateral amygdala (BLA), ventral hippocampus CA1 region (vCA1), prelimbic cortex layer 5 (PL5) in the prefrontal cortex (Fig. 1). During the recording, fear-conditioning and extinction-learning were performed in which electrical stimulation through eyelid electrodes was used as the unconditioned stimulus [3]. Then, we identified cell-ensembles in each brain region and their instantaneous activation strength based on independent component analyses (ICA) [4].

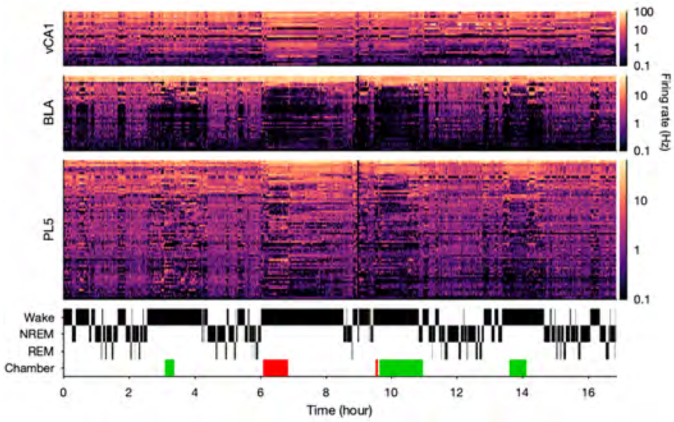


Fig. 1. A representative example of continuous large-scale electrophysiological recording from vCA1, BLA, and PL5.

B. Synchronized activation of cell-ensembles across three brain regions emerged after fear-conditioning.

We observed that cell-ensembles in vCA1, BLA, and PL5 were activated synchronously during sleep epochs following fear-conditioning (Fig. 2). To quantify this observation, we defined tripe cross-correlation (CCG) analysis by expanding CCG analyses (Fig 3). The subset of ensemble triplets showed a prominent peak on its triple CCG. The significance of the peak was examined with random shuffling analysis. This analysis revealed that the proportion of ensemble triplets with significant peaks on their triple CCG during non-rapid-eye-movement (NREM) sleep following the fear-conditioning was larger than those in NREM preceding the fear-conditioning. It indicates that ensembles in BLA, vCA1, and PL5 become activated synchronously through the transition to the fear-memory-induced maladaptation state.

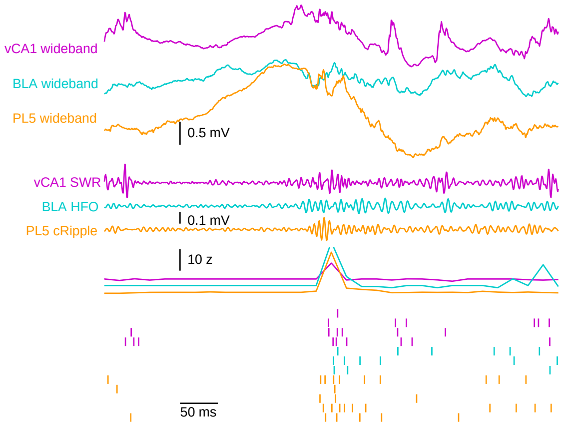
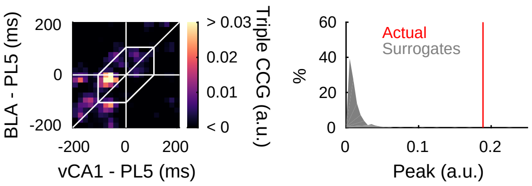


Fig. 2. Representative example of synchronous activation across three brain regions during NREM following fear-conditioning.



$$TripleCCG(\tau,\sigma) = \frac{1}{T}\sum_{t=1}^{T} f(t)g(t+\tau)h(t+\sigma)$$

Fig. 3. Example of triple-CCG analysis.

C. *Fast oscillations on the local field potentials hosted synchronous ensemble activation across three brain regions*

Next, we sought what kind of network activity patterns hosted the synchronous ensemble activation across the CA1, BLA, and PL5. First, we obtained instantaneous triple-activation strength as products of z-scored instantaneous activation strength with the optimal time shift, then individual triple-activation events were detected by thresholding the instantaneous triple-activation strength traces. To examine whether characteristic network activity patterns are associated with the identified tripe-activation events, event-triggered averages of LFP wavelet power were obtained (Fig. 4). The event-triggered average of wavelet power had strong peaks around 100 – 300 Hz in each brain region (Fig4), which corresponds to amygdalar high-frequency oscillations (HFOs) [5], hippocampal sharp-wave ripples (SWRs) [6], and cortical ripples (cRipples)[7]. These results imply the tight relationship between fast network oscillations, such as HFOs, SWRs, and cRipples, and inter-regional synchronous ensemble actives that emerged after the transition to the maladaptation states.

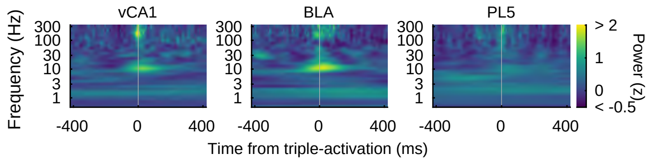


Fig. 4. BLA–CA1–PL5 triple-activation event-triggered average of LFP wavelet power in a representative animal.

IV. Future Perspective

In this year, we revealed that cell-ensembles in various brain regions started to activate synchronously after the transition to the maladaptation states. Furthermore, our results indicate that fast network oscillations, such as HFOs, SWRs, and cRipples are involved in the synchronous activations of cell-ensembles. As the next step, we would like to analyze network changes induced by extinction learning and compare them with ones caused by fear-conditioning to clarify compensation mechanisms that enable 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] Johansen, J.P., et al., *Neural Substrates for Expectation-Modulated Fear Learning in the Amygdala and Periaqueductal Gray.* Nat Neurosci, 2010. **13**(8): p. 979-86.

[4] Giri, B., et al., *Hippocampal Reactivation Extends for Several Hours Following Novel Experience.* J Neurosci, 2019. **39**(5): p. 866-875.

[5] Ponomarenko, A.A., T.M. Korotkova, and H.L. Haas, *High Frequency (200 Hz) Oscillations and Firing Patterns in the Basolateral Amygdala and Dorsal Endopiriform Nucleus of the Behaving Rat.* Behavioural Brain Research, 2003. **141**(2): p. 123-129.

[6] Buzsaki, G., *Hippocampal Sharp Wave-Ripple: A Cognitive Biomarker for Episodic Memory and Planning.* Hippocampus, 2015. **25**(10): p. 1073-188.

[7] Khodagholy, D., Gelinas, J.N., and Buzsáki, G. *Learning-Enhanced Coupling Between Ripple Oscillations in Association Cortices and Hippocampus*. Science 2017 **358**, 369-372.

Annual report of research project A05-8

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Abstract

Our research project aims to reveal neural mechanisms of sense of agency (SoA) from the standpoint of functional connectivity. Moreover, we intend to study pathophysiology of neurological and psychiatric illnesses from the stand of neural dysconnection. Then, we try to recover those illness through reorganization of neural systems on the SoA in order to facilitate hyper-adaptability to living environment. Actually, we have developed a method 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 showed abnormal learning patterns of prediction system in patients with psychiatric disorders including schizophrenia, ADHD and ASD. 2) We have released the application for agency tuning: the Agency Tuner, for general use in US as well as Japan [1]. 3) In order to evaluate hyper-adaptability, we reported passive way of measuring QOL/Well-Being levels using smartphone log [2].

I. Introduction

We aims to reveal neural mechanisms of sense of agency (SoA) from the standpoint of functional connectivity. Moreover, we intend to study pathophysiology of neurological and psychiatric illnesses from the stand of neural dysconnection. Then, we try to recover those illness through reorganization of neural systems on the SoA in order to facilitate hyper-adaptability to living environment.

We have reported neural substrates on the SoA as the "Agency Network" (Fig. 1). We expect that development of methods for reorganization of dysconnectivities of the "Agency Network" in neurological and psychiatric illnesses leads to the recovery from those illnesses.

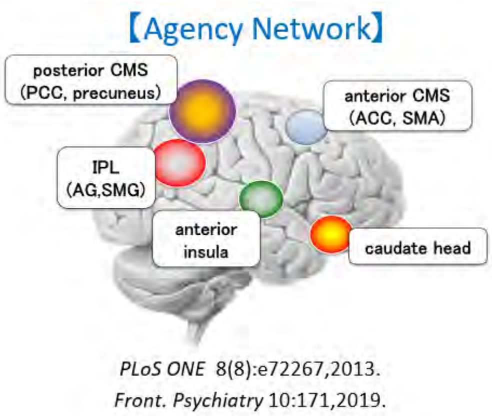

Fig.1 The Agency Network

II. Aim of the Group

Our research project aims to reveal neural mechanisms of sense of agency (SoA) . Moreover, we intend to study pathophysiology of neurological and psychiatric illnesses from the stand of neural disconnection. And then, we try to develop 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 (Fig. 2 and 3). We hypothesize that this tuning of SoA could reorganize neural systems and achieve hyper-adaptation of patients with those illnesses in their living environment.

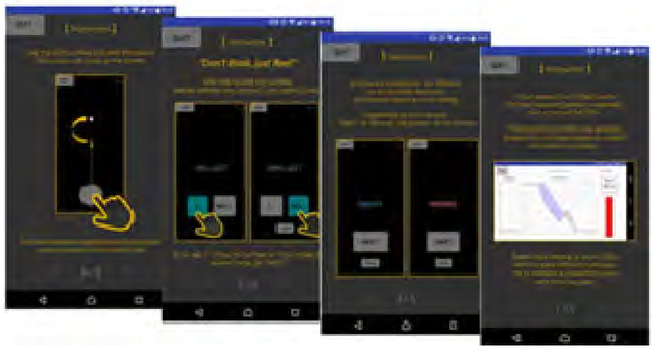

Fig.2 "Agency Tuner" for Agency Tuning

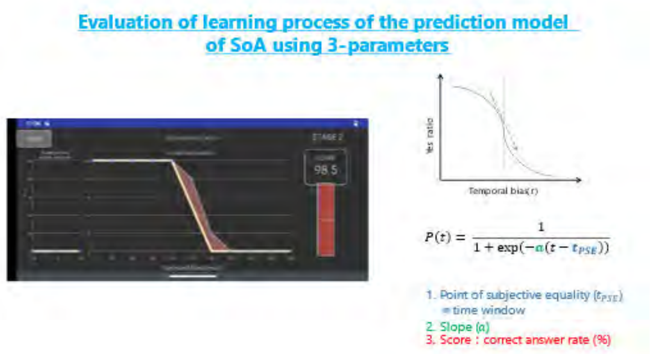

Fig.3 Evaluation of learning process of the prediction system of SoA

III. Research Topics

A. *Abnormal learning patterns of prediction system in patients with psychiatric disorders including schizophrenia, ADHD and ASD*

We showed abnormal learning patterns of prediction system in patients with psychiatric disorders including schizophrenia, ADHD and ASD (Fig4-6).

Fig.4 A trend graph of correct answer rate (%)
Schizophrenia
(chronic phase)

Fig.5 A trend graph of correct answer rate (%)
ADHD

Fig.6 A trend graph of correct answer rate (%)
ASD

B. Agency Tuning by "Agency Tuner" (on Google Play in US)

We have released the application for agency tuning: the Agency Tuner, for general use in US as well as Japan [1], in order to collaborate with US researchers.

C. Passive Way of Measuring QOL/Well-Being Levels Using Smartphone Log

In order to evaluate hyper-adaptability, we reported passive way of measuring QOL/Well-Being levels using smartphone log [2](Fig.7).

Research on mental health states involves paying increasing attention to changes in daily life. Researchers have attempted to understand such daily changes by relying on self-reporting through frequent assessment using devices (smartphones); however, they are mostly focused on a single aspect of mental health. Assessing the mental health of a person from various perspectives may help in the primary prevention of mental illness and the comprehensive measurement of mental health. In this study, we used users' smartphone logs to build a model to estimate whether the scores on three types of questionnaires related to quality of life and well-being would increase compared to the previous week (fluctuation model) and whether they would be higher compared to the average for that user (interval model). Sixteen participants completed three questionnaires once per week, and their smartphone logs were recorded over the same period. Based on the results, estimation models were built, and the F-score ranged from 0.739 to 0.818. We also analyzed the features that the estimation model emphasized. Information related to "physical activity," such as acceleration and tilt of the smartphone, and "environment," such as atmospheric pressure and illumination, were given more weight in the estimation than information related to "cyber activity," such as usage of smartphone applications. In particular, in the Positive and Negative Affect Schedule (PANAS), 9 out of 10 top features in the fluctuation model and 7 out of 10 top features in the interval model were related to activities in the physical world, suggesting that short-term mood may be particularly heavily influenced by subjective activities in the human physical world.

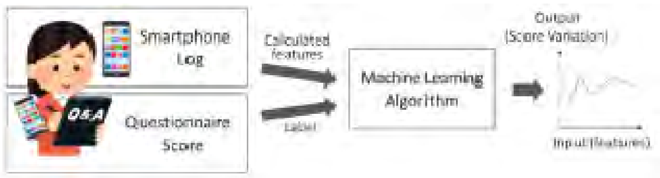

Fig.7

IV. Future Perspective

We have made advances in developing an original method for cognitive rehabilitation of the SoA: Agency Tuning. 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, and support patients with neurological and psychiatric illnesses for recovery, that is, hyper-adaptability to living environment.

References

[1] **Takaki Maeda** : "AGENCY TUNER"（APP on Google Play in US）, Aug, 2021.
https://play.google.com/store/apps/details?id=en.re.agencytuner.blp&hl=en&gl=US

[2] Wenhao Yao, Kohei Kaminishi , Naoki Yamamoto, Takashi Hamatani, Yuki Yamada, Takahiro Kawada, Satoshi Hiyama, Tsukasa Okimura, Yuri Terasawa, **Takaki Maeda**, Masaru Mimura and Jun Ota: Passive Way of Measuring QOL/Well-being Levels Using Smartphone Log. Frontier in Digital Health 2022.842460.
https://doi.org/10.3389/fdgth.2022.780566

A05-9 The role of inhibitory neurons related to skilled hand movements after spinal cord injury.

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***Abstract*—In this year, we established the analysis method in mouse and marmoset spinal cord injury (SCI) models. To understand motor deficits and reconstructive processes after SCI, we analyzed joint movement coordination patterns controlled by the central nervous system (CNS). As a result, we found that the degree of impaired coordination in joint movement correlated with the degree of histological damage in the spinal cord.**

I. Introduction

During the acquisition of new motor skills or during recovery after brain or spinal cord injury, the brain undergoes functional reorganization. GABA, an inhibitory neurotransmitter, is thought to play an important role in the regulation of this plasticity. It has been reported that during human motor learning, a decrease in GABA concentration in the early stages of learning is strongly correlated with the magnitude of subsequent learning [1]. In addition, it is known that functional reorganization occurs in the motor cortex after CNS disorders such as stroke and spinal cord injury [2], but little is known about the relationship between these changes and inhibitory control.

II. Aim of the Group

The specific purpose of this study is to observe the activity of GABAergic neurons in the motor cortex by calcium imaging using a marmoset spinal cord injury model, and to follow the changes in the spatiotemporal pattern of these neurons during motor function recovery.

III. Research Topics

A. Markerless analysis of hindlimb kinematics in spinal cord-injured mice through deep learning

Rodent models are commonly used to understand the underlying mechanisms of SCI. Kinematic analysis, an important technique to measure dysfunction of locomotion after SCI, is generally based on the capture of physical markers placed on bony landmarks. However, marker-based studies face significant experimental hurdles such as labor-intensive manual joint tracking, alteration of natural gait by markers, and skin error from soft tissue movement on the knee joint. Although the pose estimation strategy using deep neural networks can solve some of these issues, it remains unclear whether this method is adaptive to SCI mice with abnormal gait. In the present study, we developed a deep learning based markerless method of 2D kinematic analysis to automatically track joint positions. We found that a relatively small number (< 200) of manually labeled video frames was sufficient to train the network to extract trajectories. The mean test error was on average 3.43 pixels in intact mice and 3.95 pixels in SCI mice, which is comparable to the manual tracking error (3.15 pixels, less than 1 mm). Thereafter, we extracted 30 gait kinematic parameters and found that certain parameters such as step height and maximal hip joint amplitude distinguished intact and SCI locomotion [3].

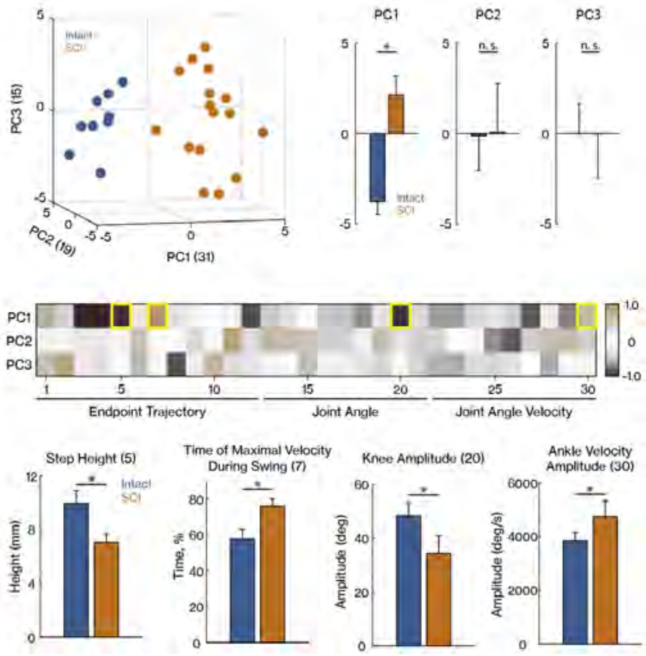

Fig. 1

B. Functional reorganization of locomotor kinematic synergies reflects the neuropathology in a mouse model of spinal cord injury

SCI disrupts motor commands to modular structures of the spinal cord, limiting the ability to walk. Evidence suggests that these modules are conserved across species from rodent to human and subserve adaptive walking by controlling coordinated joint movements (kinematic synergies). Since SCI causes uncoordinated joint movements of the lower limbs during walking, there may be a disorder of the modular structures that control them [4]. To gain insights into this complex process, we recorded the kinematics of intact and SCI mice when walking on a treadmill and applied principal component analysis to extract kinematic synergies. Most SCI mice walked stably on the treadmill, but their kinematic synergies were generally different from those of intact mice. We classified the kinematic synergies of SCI mice into three groups based on the similarity of the extracted first three synergy components. We found that these three groups had different degrees of spinal cord damage. This suggests that differences in kinematic synergies reflect underlying SCI neuropathology. These results may help guide the development of different rehabilitation approaches and future physiological experiments to understand the mechanisms of motor control and recovery [5].

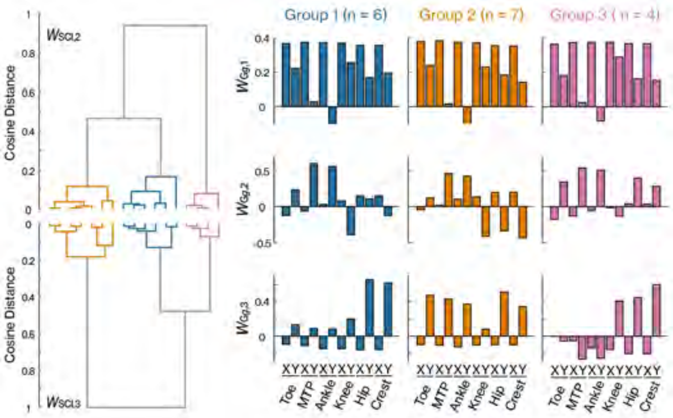

Fig. 2

C. Preserved Intersegmental Coordination During Locomotion after Cervical Spinal Cord Injury in Common Marmosets

It is known that primates including human regain some locomotor function after a partial spinal cord injury, but the locomotor pattern is different from before the injury. Although these observations have many implications for improving rehabilitative strategies, these mechanisms are not well understood. In this study, we used a common marmoset hemisection SCI model to examine temporal changes in locomotor pattern, in particular, intersegmental coordination of left hindlimb. Marmoset showed loss of detectable function in the left forelimb and hindlimb after left unilateral hemisection of cervical spinal cord. At two weeks after injury, weight-bearing of the left forelimb during locomotion was limited, but the left hindlimb was able to plantar step. Then marmosets showed gradual recovery in walking ability, but kinematics analysis showed differences in the endpoint trajectory and joint angle movement. Furthermore, intersegmental coordination in left hindlimb represented by planar covariation was preserved over time after the injury. Previous studies have reported that planar covariance is disrupted in patients with stroke or SCI, and that improvement in planarity correlates with recovery in walking ability after rehabilitation. In this study, quadrupedal marmosets were able to walk without loss of balance even after SCI; the different balance needs of bipedal and quadrupedal walkers may lead to differences in planar covariation. Our results show that planar covariation was preserved at all time points after the cervical unilateral hemisection [6].

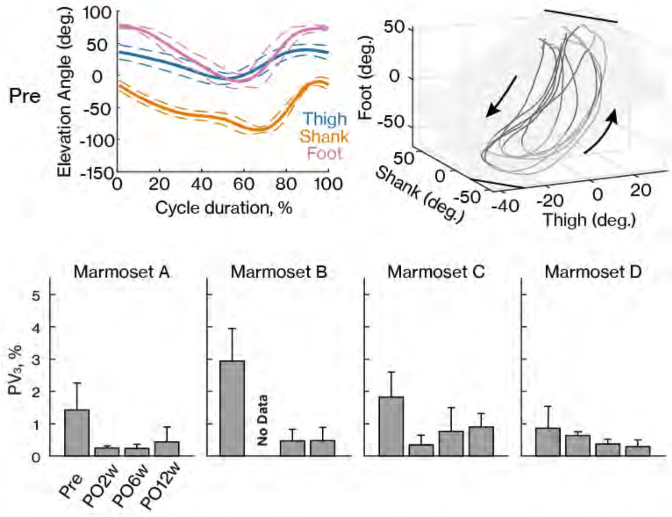

Fig. 3

IV. Future Perspective

This year, we established a gait analysis system in mice and marmoset spinal cord injury models, and reported it in a paper [3,5-6]. These analyses and the rehabilitation model established in the previous year will be used for further validation.

References

[1] J. Kolasinski, E. L. Hinson, A. P. Divanbeighi Zand, A. Rizov, U. Emir, and C. J. Stagg, "The dynamics of cortical GABA in human motor learning," J. Physiol. 2019 Jan;597(1):271-282.

[2] T. Isa, "Dexterous Hand Movements and Their Recovery After Central Nervous System Injury," Annu Rev Neurosci. 2019 Jul 8;42:315-335.

[3] Sato Y, Kondo T, Shinozaki M, Shibata R, Nagoshi N, Ushiba J, Nakamura M, Okano H, "Markerless analysis of hindlimb kinematics in spinal cord-injured mice through deep learning" Neurosci Res. 2021 Sep 8;S0168-0102(21)00203-0.

[4] Y P Ivanenko 1 , G Cappellini, I A Solopova, A A Grishin, M J Maclellan, R E Poppele, F Lacquaniti, "Plasticity and modular control of locomotor patterns in neurological disorders with motor deficits"

[5] Sato Y, Kondo T, Shibata R, Nakamura M, Okano H, Ushiba J,"Functional reorganization of locomotor kinematic synergies reflects the neuropathology in a mouse model of spinal cord injury" Neurosci Res. 2021 Dec 15:S0168-0102(21)00248-0.

[6] Sato Y, Kondo T, Uchida A, Sato K, Yoshino-Saito K, Nakamura M, Okano H, Ushiba J,"Preserved Intersegmental Coordination During Locomotion after Cervical Spinal Cord Injury in Common Marmosets" in press.

A05-11Annual report of research project

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Taiki Yoshida
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Abstract—**Hand choice is an unconscious decision that we frequently make in our daily lives. It has been shown that the probability of hand choice was biased by modulating neural activity in the posterior parietal cortex by magnetic or electrical stimulation using the transcranial magnetic stimulation or the transcranial direct current stimulation. However, the effect of transcutaneous electrical stimulation from peripheral body regions such as the wrist on hand selection has not been investigated. In this study, we focused on hand choice at the equilibrium point of the left and right-hand choice during a quick reach to a target in front of us and examined whether sensory stimulation by electrical stimulation to unilateral hand immediately before hand choice facilitates or inhibits subsequent hand choice. Electrical stimulation of the wrist significantly increased the choice of the stimulated hand. These results suggest that the prior sensory stimulation facilitates subsequent action selection.**

I. Introduction

To recover from the functional impairment caused by a stroke or other injury to the central nervous system and maintain its function, it is necessary not only to restore the function of the injured body part itself, but also to let the patients to pay attention to the affected side of the body and to develop a preference to actively use the affected body parts in daily life. In other words, it is important to improve the orientation and preference toward the body and space of the affected side of the body, which is often disliked or ignored. Therefore, this research project aims to clarify the method and mechanism to reveal and activate the neural circuits of preference to the affected side of the body using neuromodulation by brain stimulation, manipulation of space using VR technology, and manipulation of motivation.

This year, we tested if haptic electrical stimulation to wrist can implicitly change the probability of hand use.

II. Aim of the Group

Flexible adaptation to the outside world mandates appropriate action selection. Hand choice—deciding which hand to use to reach for targets—is an example of a daily unconscious action selection. Previous studies argued that the posterior parietal cortex (PPC) accumulates sensory information to evaluate the appropriate action selection and, thus, plays a critical role in this process. Fitzpatrick et al. [1] reported that while functional magnetic resonance imaging (fMRI) revealed bilateral increases in PPC activity during hand-choice tasks, this increase is enhanced in the PPC contralateral to the selected hand. Oliveira et al. [2] showed that the right-hand choice was suppressed following the disruption of the left PPC with single-pulse transcranial magnetic stimulation (TMS) just prior to the execution of the reach, but not vice versa, thus, indicating more dominant involvement of the left PPC in hand choice than the right PPC. In our study last year, we increased or decreased the cortical excitability of PPC using tDCS and examined its online and residual effects on the hand-choice probability and choice reaction time. The results demonstrated that the probability of left-hand choice increased and that of right-hand choice decreased significantly after stimulation when left PPC was stimulated with cathode and right PPC with anode. The decrease in the excitability of the left PPC and the increase in the excitability of the right PPC are essential to enhance left-hand choice [3]. Considering the clinical application to the stroke patients, however, tDCS is not a good solution to facilitate affected hand in daily life. Therefore, in the present study, we examined if the simple electrical stimulation to the wrist can bias the choice or not.

III. Research Topics

We recruited 14 right-handed healthy people to participate in this study. The Participants were asked to reach the target using eighter left or right hand as quickly and accurately as possible. The targets were presented at nine random positions on the semicircular (Fig. 1). We consisted of the psychometric function about the hand preference for each participant. We set the unilateral stimulus condition (right and left), the bilateral stimulus condition (as the control condition) and the no stimulus condition. The stimulation electrodes attached to each wrist (Fig. 1). The electrical stimulation was applied at target the target presentation (0 ms) or 300 ms, or 600 ms before target presentation randomly (Fig. 2).

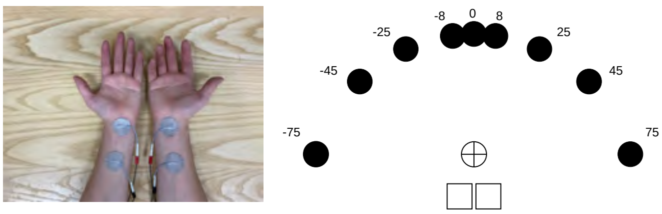

Fig. 2 stimulation site and target settings

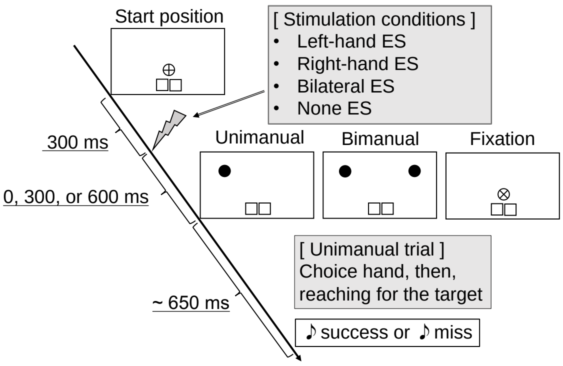

Fig. 2 procedure

Using logistic regression, we estimated the point of subjective equality (PSE): the virtual point at which participants would have an equal probability of using the right or the left hand for the reach. The effect of the stimulation condition of the PSE was investigated using one-way ANOVAs with repeated measures. Significant main effect was observed in the stimulation condition ($F\ (1,\ 10) = 11.3$, $P < 0.01$, partial $\eta 2 = 0.55$). Multiple comparisons between each pair of stimulation conditions showed that PSE in the left stimulation condition (PSE = 4.40°±10.46°) was significantly larger than that in the other stimulation conditions (adj $P < 0.05$), and PSE in the right stimulation condition (PSE = -2.04°±9.97°) was significantly smaller than that in the other stimulation conditions (adj $P < 0.05$). There was no significant difference between PSE in the bilateral stimulation condition and that in the no stimulation condition (adj P = 1.00). These results showed that the probability of hand choice was increased with the stimulated hand (Fig. 3).

Furthermore, to test the effect of the timing of the stimuli (0, 300, 600 ms) prior to the target presentation on the hand selection, the 90% confidence intervals of PSE for each stimulus timing were calculated with the bootstrap by 10000 resampling the data to compensate for the small number of data. The results showed that the closer the stimulus timing to the target presentation, the more likely the stimulated hand was chosen.

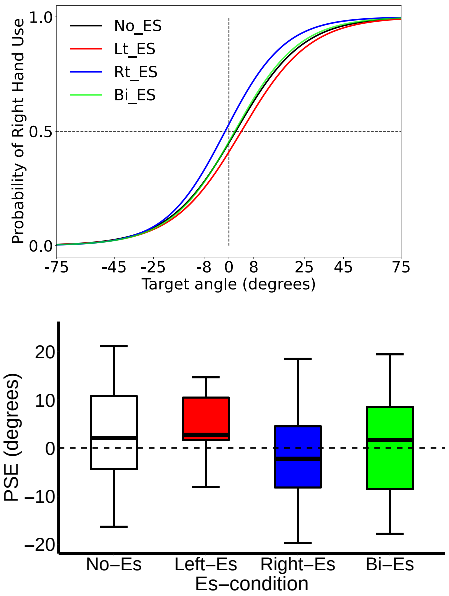

Fig. 4 choice probability and PSE
NoES: no stimulation LtES: left wrist stimulation, RtES: right wrist stimulation, BiEs: bilateral wrist stimulation

IV. Future Perspective

The present study demonstrated that the electrical stimulation of the wrist significantly increased the choice of the stimulated hand. These results suggest that the prior sensory stimulation facilitates subsequent action selection.

The results of the current study may be applied in the increase of paretic-hand use in patients with hemiparetic stroke whose quality of life is significantly diminished by stroke-induced difficulty in using paretic limbs effectively. Although rehabilitation has been demonstrated to improve limb function to some extent, patients often only use their non-paretic limbs after discharge. This learned non-use remains an unresolved issue in rehabilitative practice. The results of this study have demonstrated that simple, cheap, and easy to use electrical stimulation can bias the choice. We will continue development of our methods and their application to promote the use of paretic upper limbs in the rehabilitation of patients with stroke.

References

[1] A.M. Fitzpatrick, N.M. Dundon, and K.F. Valyear, "The neural basis of hand choice: An fMRI investigation of the Posterior Parietal Interhemispheric Competition model," Neuroimage, 185, 208-221, 2019.

[2] F.T. Oliveira, J. Diedrichsen, T. Verstynen, J. Duque, and R.B. Ivry, "Transcranial magnetic stimulation of posterior parietal cortex affects decisions of hand choice," Proc Natl Acad Sci U S A, 107, 17751-6, 2010.

[3] K. Hirayama, T. Koga, T. Takahashi, and R. Osu, "Transcranial direct current stimulation of the posterior parietal cortex biases human hand choice," Sci Rep, 11, 204, 2021.

A05-12 Hyper-adaptability from inducing synapse connection and regulation of extracelluar matrix.

- Spinal cord injury and AI-based motion capture -

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Abstract—The main results of this year are the following three items. 1) 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 demonstrated the significant recovery from chronic phase of spinal cord injury (SCI) by a synthetic synapse organizer protein, CPTX. Since such a robust recover from chronic phase of SCI has never been achieved, it is a great finding in our project. 2) Moreover, we obtained the results of recovery from acute or subacute phase of SCI by the application of anti-sense oligo (ASO) of N-acetylgalactosaminyl transferase-1(T1), a key gene in CS biosynthesis. ASO improved the microenvironment for functional recovery. 3)We constructed the AI motion capture system to rigorously evaluate the recovery from SCI. Using this system, we succeed in the characterization of the behavioral trait of CPTX induced hyper-adaptability. To summarize, it is now possible to guide the artificial super-adaptation of the neural circuit after the damage of the central nervous system, and to evaluate the behavioral outputs during the recovery.

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 aims of this research are (1) the remodeling of the regeneration field after spinal cord injury (SCI) by inactivating a regeneration inhibitor, Chondroitin sulfate (CS), (2) the re-construction of the functional circuits by introducing an artificial synapse-forming factor, synapse connector CPTX, and (3) the establishment of AI-based evaluation system to capture the parameters of hyper-adaptive animals in which rehabilitation is added to the administration of CS inhibitor and CPTX.

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].

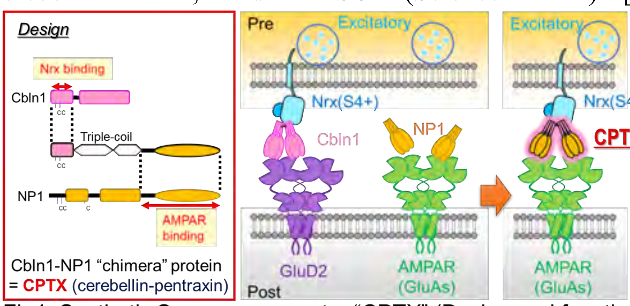

Fig1 Synthetic Synapse connector "CPTX" (Design and function)

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.

This 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. Thus, overcoming the chronic phase of SCI is an important mission. CPTX restored the chronic phase of SCI(Fig 2). CPTX injection activated the hind leg movement within a few days, which otherwise showed the permanently poor movement. At 2 weeks after injection, the effect of CPTX became maximum to the extent that some animals smoothly stepped. These results suggest that CPTX boost the dormant neural pathway into the active circuit. We are now attempting the more robust recovery combined with rehabilitation.

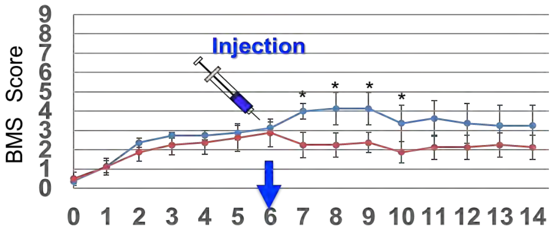

Fig 2 Administration in the chronic phase (6 weeks after SCI). Physiological function improves after SCI (BMS score)

B. Improvement of regeneration environment by suppression of nerve regeneration inhibitor chondroitin sulfate

We reported that chondroitin sulfate (CS) KO mice, which are the strongest inhibitors of nerve regeneration after spinal cord injury, show dramatic post-injury recovery [3]. CS is proposed to be one of the most ideal targets for SCI treatment [4]. Last year, we developed and applied an antisense oligo (ASO) for knocking down of CS expression in a tissue specific manner. This year, we applied ASOs to SCI animals and found that our oligos restored the locomotory function of acute and subacute phase of SCI.

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

We are promoting the introduction of AI into the evaluation of functional recovery to obtain the correlation between the quantitative motor function, nerve reorganization, and motor function of the super-recovery model after spinal cord injury. Last year, we first focused on the hind limb stepping down (footfall analysis), which was generally used for quantification of post-injury recovery. This year, we further promoted the system construction and the analysis to extract the characteristics of walking during the recovery process (Fig. 4). This research was a joint research with Professor Yanagihara in Tokyo university, who is also a research collaborator of the A05-12 group (and the B02 planning group), and it was supported by Professor Funato in university of Electro-communications of the B02 group.Two-dimensional position is calculated by DeepLabCut from the video data obtained by four high-speed cameras. This system enabled us to study the accurate tracking of motor function during recovery process. We succeeded in extracting the characteristic behavioral pattern during recovery process of hyper-adaptability mouse in which CPTX drive the remodeling of nervous circuit.

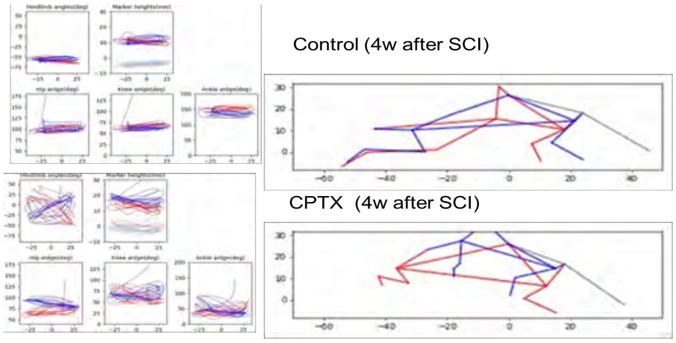

Fig3 Recovery process after spinal cord injury. Analysis by extracting various parameters such as hind leg movement angle and cycle

III. FUTUREU PERSPECTIVE

This year, we were able to obtain the results of functional recovery from chronic phase of SCI through CPTX application. We also showed that ASOs for knocking down of CS expression restored the locomotory function of acute and subacute phase of SCI. Since the time window and the mechanism of CPTX and ASOs for SCI recovery are different, the combination of both strategies would be useful. We succeed in the characterization of the behavioral trait of CPTX induced hyper-adaptability by AI trace. Development of next generation synapse connector that bridges inhibitory synapse is also in progress. Such novel tool combined with AI trace system will allow us to study super-adaptation and to conduct artificial intervention for functional recovery.

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)

A05-16Annual report of research project

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***Abstract*— In the present research project, we have investigated neuronal plastic changes, which underlie motor recovery after brain damage, using macaque models. In the studies reported here, we examined both functional and structural changes after focal infarction of the macaque internal capsule. Brain imaging using functional near-infrared spectroscopy (fNIRS) suggested compensatory increase of brain activity in the ventral premotor cortex during voluntary movements after motor recovery. Voxel-based morphometry (VBM) analysis using T1-weighted magnetic resonance imaging (MRI) and immunohistochemical staining using SMI-32 antibody suggested compensatory structural changes in pyramidal neurons in the ventral premotor cortex of the contralesional hemisphere. In the next step, we plan to elucidate the changes of neuronal projections that occur after brain damage. Specifically, we will perform diffusion tensor imaging (DTI) using MRI after recovery in order to clarify the projection changes underlying functional compensation. In addition, compensatory projection changes will be investigated at cellular level using anatomical tracers. We will also perform pharmacological inactivation experiments to investigate a causal relationship between the anatomical changes and functional recovery.**

I. Introduction

When the brain is damaged, such as in stroke patients, brain function is impaired. However, rehabilitation can induce dynamic plastic changes in the nervous system and restore lost brain functions. This is a typical example of "hyper-adaptivity" in 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, holding a small objects between the tips of the thumb and index finger [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. In this study, we will apply the experimental techniques we have used in the primary motor cortex injury model to macaque monkeys with focal infarction in the internal capsule where motor output fibers run, in order to obtain knowledge that can be seamlessly applied to clinical practice.

III. Research Topics

A. *Compensatory brain activity chnages after focal infarction of the macaque internal capsule*

We established a macaque monkey model with infarcts in the posterior internal capsule, which is a common site of stroke and involved in motor output from the cerebral cortex [3]. We also established a technique for measuring motor cortex activity in macaque monkeys using functional Near-Infrared Spectroscopy (fNIRS) [4], and measured motor cortex activity during a grasping task. Before infarction, there was an increase in activity in the hand region of the primary motor cortex, whereas during functional recovery, there was an increase in activity in the ventral premotor cortex (Fig. 1) [5]. The ventral premotor cortex in the cortex contralateral to infarcts plays a greater role in recovery when damage by stroke is more severe. When muscimol, a $GABA_A$ receptor agonist, was administered to the ventral premotor cortex of the hemisphere with elevated activity to temporarily inactivate the activity, the upper limb motor deficits recurred. This suggests that the area of increased activity may be involved in compensating for the function of the infarcted area. These results are consistent with the results of clinical studies reported in stroke patients, and also indicate that this experimental system is optimal for investigating the mechanism of functional recovery after stroke, as well as the possibility of developing technology for monitoring the recovery of brain function using fNIRS.

Compared to magnetic resonance imaging (MRI), fNIRS is less expensive and can measure brain activity during exercise without restraining the body, making it suitable for measuring brain activity during rehabilitation. On the other hand, it has a disadvantage that only brain surface activity can be measured due to its measurement principle. To solve this problem, we applied diffuse optical tomography (DOT) to the fNIRS data and tried to estimate three-dimensional images of the functional hemodynamic response [6]. In the intact macaque monkeys performing voluntary movements, the DOT analysis estimated the activity of motor-related cortical areas, including those in the brain sulci, and the temporal and spatial changes were consistent with previously known physiological findings (Fig. 2). By using this method with the fNIRS data, we can identify the changes in brain activity that occur during functional recovery after stroke in more detail.

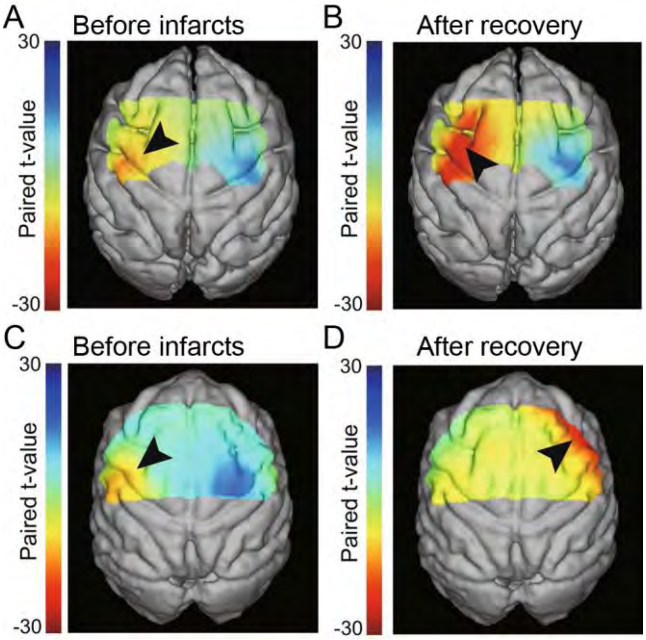

Fig. 1 fNIRS imaging of bain activation during voluntary hand movements before infarcts (A, C) and after motor recovery from the internal capsular infarcts in the macaque (B, D). Before infarcts, focal activation was observed in the hand area of the primary motor cortex (arrowhead in A, C). After motor recovery, increased activation of the premotor area was identified (arrowhead in B, D). The cortex contralateral to the stroke plays a greater role in recovery when lesions are more severe (D)..

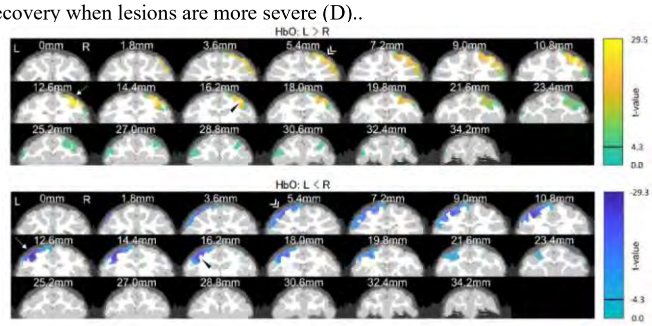

Fig. 2. Brain activation during voluntary hand movements in the inatact macaque. Color map of t-values (activated-area map) for HbO that exceeded th significance level of 0.5%. Plots are based on the reconstruction results using a DOT algorithm.

B. *Structural changes after focal infarction of the macaque internal capsule*

An appropriate structural basis is necessary for brain function to occur. Therefore, structural changes in neurons may underlie the compensatory changes in brain activity after infarcts in the internal capsule described above. Therefore, we performed voxel-based morphometry (VBM) analysis using T1-weighted MRI and immunohistochemistry using SMI-32 antibody to stain pyramidal cells in our established macaque model of capsular infarcts [3]. The VBM results suggested an increase in gray matter in the ventral premotor cortex of the contralesional hemisphere during the period of post-infarction motor function recovery. Immunohistochemical analysis showed shrinkage of pyramidal cells in layer V of the primary motor cortex of the ipsilesional hemisphere. This may be due to retrograde neurodegeneration after internal capsule infarction. On the other hand, pyramidal cells in layer V of the ventral premotor cortex showed an increase in dendritic arborization. These results suggest that compensatory structural changes in motor output cells in the contralesional ventral premotor cortex are involved in motor function recovery after capsular infarction, and that structural changes in dendrites underlie the signal changes observed in the VBM analysis.

IV. Future Perspective

Studies in this project have elucidated some of the functional and anatomical changes that occur during functional recovery after capsular infarctions. In the next step, we plan to elucidate the details of the anatomical changes that occur after brain damage at the neural circuit level. Specifically, we will perform diffusion tensor imaging (DTI) using MRI after recovery in order to clarify the projection changes underlying functional compensation. In addition, compensatory projection changes will be investigated at cellular level using anatomical tracers. In particular, we will focus on the projection pathways formed by the contralesional hemisphere to carry out the movements of the ipsilateral hand. We will also analyze the behavioral changes when the brain region where the new projection pathway is formed is inactivated to prove a causal relationship between the anatomical changes and functional recovery.

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

[5] 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

[6] R. Hayashi, O. Yamashita, T. Yamada, H. Kawaguchi, N. Higo, Diffuse optical tomography using fNIRS signals measured from the skull surface of the macaque monkey, Cerebral Cortex Communications, in pre

A05-17 Establishement and circuit manipulation of an animal model of ulateral spatial neglect in marmosets

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***Abstract*— Unilateral spatial neglect (USN) is a phenomenon characterized by an inability to response to the contralateral stimuli in patients with damages in the (mainly right) brain. Our group (A05-17) aims to establish an animal model of USN by making lesions in the ventral attention network of common marmosets. In this fiscal year, we tried to establish 1) the target and the method of the lesion, 2) how to evaluate their behavior and 3) how to measure the brain activity. For 1), we identified area TPO using ECoG. For 2), we established how to evaluate saliency-guided eye movements during free-viewing. For 3), we succeeded in measuring Ca signals simultaneously from bilateral posterior parietal cortices.**

I. Introduction

Unilateral spatial neglect (USN) is a phenomenon characterized by an inability to response to the contralateral stimuli in patients with damages in the (mainly right) brain. The mechanism of USN is still largely unknown but recent studies of human neuroimaging suggest that USN occurs as a consequence of imbalance in attentional networks. To understand the brain mechanism of USN, establishment of an animal model of USN is necessary. Our group (A05-17) started a project to establish an animal model of USN by making lesions in the ventral attention network of common marmosets.

II. Aim of the Group

The aims of the group are as follows. 1) Based on our previous findings using macaques, we will establish an animal model of USN by making a surgical lesion in the ventral attention network of common marmosets. 2) Then we will measure the neuronal activities using an endoscope-type Ca imaging system before and after the lesion and evaluate how the local circuits are affected by the lesion. 3) Then we will model these changes in the brain using a computational model. Finally, 4) based on the prediction made by the computational model, we will manipulate the brain circuit using electrical micro-stimulation, pharmacological technique, or optogenetics. Using this strategy, we expect that we are able to test whether and how the dorsal and ventral attention networks are causally involved in the symptoms of USN and to develop methods for functional recovery from USN.

III. Research Topics

A. the target and method of the lesion

Our previous findings using macaques succeeded in inducing neglect-like behavior in macaques by making a surgical lesion in the right superior temporal gyrus (rSTG) (Fig.1, left, magenta), which is the homologous brain region to the human ventral attention network.

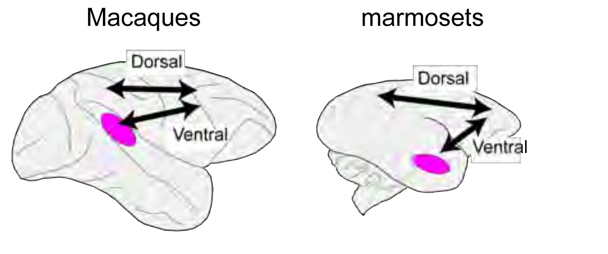

Fig. 1. Candidate of the lesion site

One of the candidates of the lesions is area TPO (Fig.1, right, magenta) because it is the homologous brain region to the human ventral attention network. To identify area TPO physiologically, we implanted 96-channel ECoG electrodes to marmosets [1] and measured brain activities during a visual mismatch task (Fig.2, left) and auditory mismatch task to find brain regions associated with surprise.

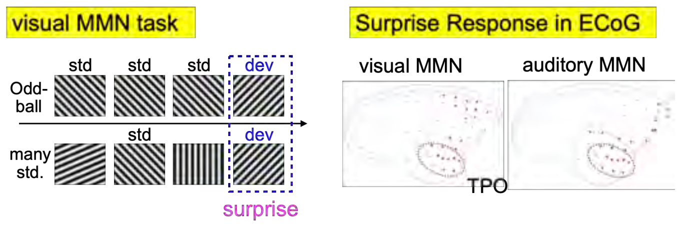

Fig. 2. Visual mismatch task

In the visual mismatch task (Fig.2, left), orientation grating stimuli were presented in front of marmosets with their head fixed. In the oddball condition (Fig.2, top), grating stimuli with 45-degree orientation were presented in 1/8 of ON periods and grating stimuli with 135-degree orientation were presented in 7/8 of ON periods. In many standards condition (Fig.2, bottom), grating stimuli with eight different orientations were randomly presented in equal probabilities (1/8). By comparing the responses to the deviant stimuli in both conditions, we identified area TPO that is associated with both visual and auditory surprise [3]. Thus, we established how to identify the ventral attention network using a neurophysiological technique.

As a method of the lesion, we choose injection of endothelin-1, which is reported to be effective in marmoset [2]. Currently, we are planning to start a lesion experiment in the late February.

B. how to evaluate their behavior

Our previous findings using macaques succeeded in identifying neglect-like behavior using eye-tracking technique during free-viewing, in which the gazes of the animals after the lesion showed biases gazes toward the right side of the screen, which is ipsilateral to the lesion in the right STG.

Our group measured eye movements during free-viewing in the head fixed condition and succeeded in simultaneous measurement of both eyes and evaluated saccade properties [4].

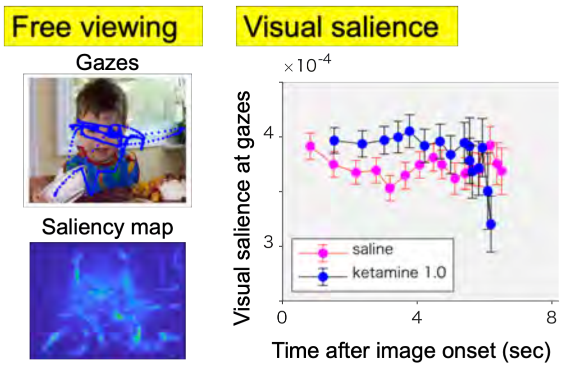

Fig. 3. Free-viewing task

We also found that the gazes during free-viewing of marmosets are attracted to visually salient stimuli, which was enhanced by subanesthetic dose of ketamine (Fig. 3) [5].

C. how to measure the brain activity

Our previous findings using macaques found that across-area correlation of BOLD signals (what is called 'functional connectivity') in resting-state fMRI changed across the time course of the brain lesion and functional recovery.

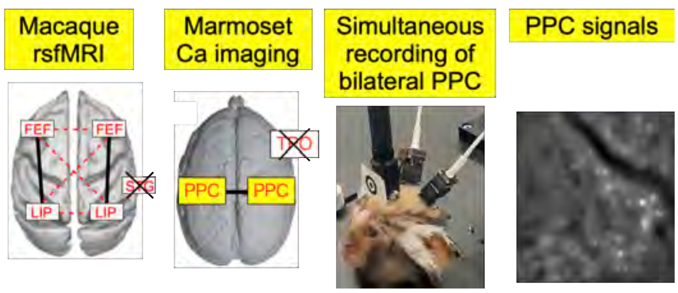

Fig. 4. Ca imaging from bilateral PPC

To understand the detailed brain mechanism of the neglect-like behavior, our group's strategy is to use marmosets and measure local circuit activities using an endoscope type Ca imaging system (nVoke, Inscopix).

In the last fiscal year, we injected adeno-associated virus (AAV) and introduced the Ca sensor GCaMP6 in the PPC of a marmoset. The TET-off system specifically designed for marmosets was used to amplify expression of GCaMP6. We succeeded in measuring Ca signals from the PPC of a marmoset during free-viewing.

In this fiscal year, we measured Ca signals form bilateral PPCs by using nVoke and nVista (Fig. 5). We identified visual responsive neurons (Fig. 5, left) and saccade-related neurons.

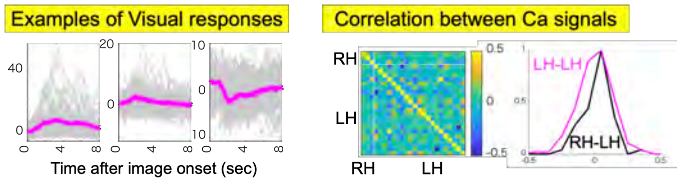

Fig. 5. Ca imaging from bilateral PPCs

We also evaluated correlation between the Ca signals during free-viewing (Fig. 5, right). Both correlations of the Ca signals within hemispheres and between hemispheres were weakly and positively correlated.

IV. Future Perspective

In this fiscal year, we developed methods for establishing and evaluating an animal model of USN using marmosets. We are ready to test these methods and plan to make a lesion in area TPO in this fiscal year.

References

[1] Komatsu, M., Kaneko, T., Okano, H., and Ichinohe, N. (2019). Chronic Implantation of Whole-cortical Electrocorticographic Array in the Common Marmoset. J. Vis. Exp. 221, 4–9.

[2] Matsui H., Komatsu M., Kaneko T., Okano H., Ichinohe N., Yoshida M. (2022) Visual and auditory mismatch negativities from whole-cortical electrocorticogram (ECoG) arrays in common marmosets. The 11th annual meeting of Japan marmoset society.

[3] Teo L, Bourne JA. (2014) A reproducible and translatable model of focal ischemia in the visual cortex of infant and adult marmoset monkeys. Brain Pathol. 24(5):459-74.

[4] Chen, C.-Y., Matrov, D., Veale, R.E., Onoe, H., Yoshida, M., Miura, K., and Isa, T. (2020). Properties of visually-guided saccadic behavior and bottom-up attention in marmoset, macaque, and human. J. Neurophysiol. 437–457.

[5] Zlata P., Komatsu M., Yamamori T., Yoshida M. (2022) The effect of ketamine on the saccadic amplitudes and pupil size during free-viewing of images in common marmosets. The 11th annual meeting of Japan marmoset society.

Group B: Systems engineering

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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 and 11 proposed research projects in 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.

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.

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.

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.

Proposed Research Groups

B05-1: Elucidation of the mechanism of motor synergy emergence in deep reinforcement learning

Principal investigator: Mitsuhiro Hayashibe (Tohoku U)

B05-2: Adaptation ability of human postural control system revealed by a closed-loop electrical muscle stimulation system

Principal investigator: Daichi Nozaki (U Tokyo)

B05-3: Mechanism underlying the hyper-adaptation of bipedal locomotion to the evolutionary change of the foot.

Principal investigator: Naomichi Ogihara (U Tokyo)

B05-4: Understanding neural manifold of the movements using human neuroimaging and non-invasive brain stimulation

Principal investigator: Isao Nambu (Nagaoka U of Tech)

B05-5: Development of motor learning model that can reuse partial dynamics based on estimation of transformation between mappings

Principal investigator: Yuichi Kobayashi (Shizuoka U)

B05-6: Shared-control of teleoperated robot maintaining operator's embodiment under intervention of AI

Principal investigator: Yasuhisa Hasegawa (Nagoya U)

B05-7: Systems engineering approach for understanding supraspinal mechanisms of the intermittent feedback control during human upright stance

Principal investigator: Taishin Nomura (Osaka U)

B05-8: A reinforcement learning model with dynamic state space that enables adaptation to indefinite environments

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

B05-9: Attention control training based on tailor-made neurofeedback system for facilitating motor learning in elderly

Principal investigator: Takeshi Sakurada (Ritsumeikan U)

B05-10: Modeling of the motor recovery process and optimization of rehabilitation strategy using VR

Principal investigator: Tetsunari Inamura (NII)

B05-11: Developmentalhyper-adaptability of sensorimotor dynamics under rapid growth

Principal investigator: Hoshinori Kanazawa (U Tokyo)

III. Activities

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

- September 7th, 2021, Group B meeting (Online)
  The Group B meeting was held online (Zoom). All the principal investigators and most of the co-investigators participated. Approximately 45 participants attended at all times, and held deep discussions including future collaboration.
- December, 7th, 2021, HMS2021 Organized session (Online)
  Due to the spread of COVID-19, the international symposium was held online. Prof. Hayashibe gave plenary talk. In the organized session, Dr. Kaminishi gave keynote talk and 6 researchers in the research project presented their recent research results.
- January 20-22nd, 2021, Organized session at the symposium on Distributed Autonomous Systems (Online), 9 oral presentations.

IV. Future plan

In the next fiscal year, we summarize the research topics in the planned and proposed research projects by classifying the topics from the targeted subjects and the modeling methodologies points of view. We continue deep discussion on the topics. Moreover, we shall proceed fruitful collaborations with Group A (Neuroscience group).

B01Annual report of research project

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***Abstract*— To understand the adaptability mechanism of a large-scale and complex network system such as the brain, constructive approach is indispensable, where a phenomenon can be modeled with the minimum degrees of freedom, and behavior of the model is verified by computer simulations. 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.**

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 that has long been unutilized through 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, we apply an interdisciplinary approach that integrates the mathematical modeling technology of systems engineering with neuroscience.

II. Aim of the Group

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.

The research group concretely performs the following three research topics. (1) By applying the probabilistic latent variable modeling methods to long-term multi-modal data such as monkey and human brain/muscle activities and behaviors provided from the groups A01/A02, we attempt to interpret/visualize the physiological structure behind these data (Fig. 1). In addition, we develop constructive models of brain networks, and evaluate their appropriateness through data assimilation approach. (2) To elucidate the deterioration mechanism of functional inhibition which seems different between young and elderly, we build a gray-box model of the brain network by considering the findings in clinical medicine such as resource allocation between motor and cognitive function, and by assuming unknown parameters such as resource limitation and inhibition strength (Fig. 2). By integrating this brain network model and musculoskeletal model, we construct a posture control simulator in cooperation with B04. We estimate unknown model parameters by incorporating the results of posture control experiments of human subjects. (3) By developing experimental systems that can arbitrarily change the relationship between the brain and body using VR/robot technology, we perform collaborative motor learning experiments in healthy young and elderly. According to the findings, we will develop appropriate visuomotor tasks which can promote the reconstruction of neural structure in the brain, in collaboration with A01.

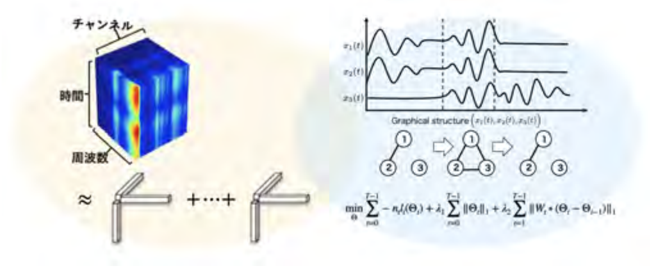

Fig. 1. Tensor decomposition and TVGL with GGM for brain modeling.

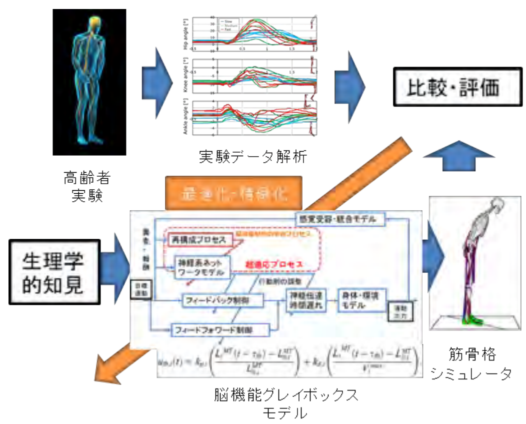

Fig. 2. Constructive modeling approach.

By integrating the knowledge, we aim to realize a model of hyper-adaptability that can estimate the reconstruction of neural structures in the process of recovery from a disorder or disease, and to obtain knowledge for effective treatment and training.

III. Research outcomes

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

Prof. Kondo (Tokyo University of Agriculture and Technology) 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, with respect to simultaneously observed EEG–EMG data. This year, they focused on the development of constructive models of brain networks and data assimilation. They proposed a Collective Almost Synchronization (CAS) model for predicting EEG time-series by using a weakly-coupled network of dynamical neurons (e.g., Hindmarsh-Rose model or Kuramoto model), and demonstrated that the network model can be used as a superior feature extraction model for EEG pattern classification [1]. Moreover, they proposed a novel reinforcement learning algorithm, and confirmed the superior performance in black-box optimization tasks with constraints [2]. Furthermore, to understand the relationship between brain activities and motor control, they analyzed EEG data measured during hand grasping movements under various experimental conditions (e.g., force levels, with/without visual feedback). As a result, they found that an EEG feature (event-related desynchronization, ERD) reflects the brain process for motor planning [3].

B. Integration of computational brain network and musculoskeletal models

Prof. Chiba (Asahikawa Medical University) and his colleagues put on the goal to estimate the factors which cause differences in results of dual task between young and elderly by differences of parameters in postural control simulator.

In this year, they focused on the motion at a gait initiation from a standing posture in order to see further differences in the elderly. It has been reported that the amount and time of center of pressure (CoP) movement at the gait initiation are shorter than those of healthy young people. They hypothesize that this is due to "increased muscle tone during standing posture and insufficient inhibition at the gait initiation".

They proposed a neural controller for standing posture and gait, and investigated its validity. By using of a musculoskeletal model to take into account the muscle tone, with parameter adjustment by optimization, appropriate standing posture and gait were achieved. In addition, when co-contractions of antagonist muscle groups were applied to simulate gait, falls due to stumbling were observed [4]. This indicates that falls in the elderly may be caused by the increased muscle tone.

They also proposed a neural controller for the gait initiation motion. It is confirmed that simple switching from standing postural control to gait control causes falls in computational simulations. Therefore, they proposed a motion of transition from a standing posture to a different posture and then switching to gait at an appropriate timing. The transition posture and the timing of the switch were obtained by optimization. As a result, a movement that leads to gait was obtained, although the forward tilt of the upper body was slightly large. In this motion, an approximate movement of the CoP mentioned above was observed. This may be an anticipatory postural adjustment to gait, and it is interesting that this was observed even though the motion design was not intended for the CoP movement.

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

Prof. Kondo and his colleagues investigated human–human cooperative motor learning experiments with VR and haptic robot technologies. They found that skill-level matching in the cooperative motor task would be significant for enhancing their adaptability to others [5], [6]. Moreover, they developed an immersive VR system for visuomotor adaptation experiment, and showed that enhanced visual feedback can facilitate impaired-side usage in simulated hemiplegic participants [7].

IV. 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. Moreover, we studied cooperative motor learning with robotic interventions, to identify motor tasks that can enhance adaptability.

Next fiscal year, we will continue to deepen the modeling methodology, and we further apply the models to actual neurophysiological data (data assimilation). 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] Nguyen T.M.P., Minh K.P., Hayashi, Y., Baptista, M.D.S., and Kondo, T., Collective Almost Synchronization Modeling Used for Motor Imagery EEG Classification, *Proc. the 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, Virtual Conference, (11/1-5, 2021).

[2] Miyashita, M., Kondo, T., and Yano, S., Reinforcement learning with constraint based on mirror descent algorithm, *Results in Control and Optimization*, 4, 100048, 2021.

[3] Nakayashiki, K., Tojiki, H., Hayashi, Y., Yano, S., and Kondo, T., Brain Processes Involved in Motor Planning Are a Dominant Factor for Inducing Event-Related Desynchronization, *Frontiers in Human Neuroscience*, 15:764281, 2021.

[4] Etoh H., Omura Y., Kaminishi K., Chiba R., Takakusaki K., Ota J., Proposal of a Neuromusculoskeletal Model Considering Muscle Tone in Human Gait, 2021 IEEE International Conference on Systems, Man, and Cybernetics (SMC), pp. 289-294, 2021, doi: 10.1109/SMC52423.2021.9658889.

[5] Nishimura, K., Saracbasi, O.O., Hayashi, Y., and Kondo, T., Cooperative Visuomotor Learning Experience with Peer Enhances Adaptability to Others, *Advanced Robotics*, 35, 13, pp.835–841, 2021

[6] Saracbasi, O.O., Harwin, W., Kondo, T., and Hayashi, Y., Mutual Skill Learning and Adaptability to Others via Haptic Interaction, *Frontiers in Neurorobotics*, 2021.

[7] Sakabe, N., Altukhaim, S., Hayashi, Y., Sakurada, T., Yano, S., and Kondo, T., Enhanced Visual Feedback Using Immersive VR Affects Decision Making regarding Hand Use with a Simulated Impaired limb, *Frontiers in Human Neuroscience*, 15:677578, 2021.

B02Annual 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. Muscle activity and brain waves during finger movement were measured at the same time, and the direction of movement was estimated using muscle synergies. In addition, the signal source was calculated from EEG, and the brain region which is related to the identification of the finger movement direction was searched. 2. We analyzed the muscle synergy before and after tendon transfer using a mathematical model. Results suggested that slow changes in muscle synergy and fast adaptation of temporal patterns caused the change in temporal patterns obsearved in the experiments.**

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. Muscloskeletal Model of Monkey with Tendon Transfer Analysis

We constructed a musculoskeletal model of the upper limb for investigating the changes in the nervous system associated with tendon transfer (Fig. 1). The model was constructed on the musculoskeletal simulation software OpenSim by scaling the human upper limb model MoBL-ARMS [1] to match the monkey's measurement data, and editing the skeleton and muscle attachment positions based on the monkey's anatomical data [2]. The motion data of the monkey's reaching movement was reproduced by the movements of the musculoskeletal model with inverse kinematics analysis. Then, the optimal muscle activities to reproduce the generated movements were estimated by inverse dynamics analysis and Static Optimization, and 41 muscle activities of the musculoskeletal model were estimated.

On the constructed musculoskeletal model, we replaced the extensor digitorum communis (EDC) and flexor digitorum superficialis (FDS) muscles involved in finger flexion and extension (similar to muscle reassignments performed in monkeys), and estimated muscle activity to reproduce the same motion data as before transferring using the model after transferring. Furthermore, we compared the muscle activity and the muscle synergy of the models before and after the reassignment. As a result, we found that the temporal pattern of activity in the musculoskeletal model did not change before and after the muscle transfer, but the combination of simultaneously activating muscles were changed (Fig. 2). This result was different from the experimental results of monkeys [3], in which the combination of muscles hardly changed after muscle transferring.

In the model, the optimal muscle activity in the standpoint

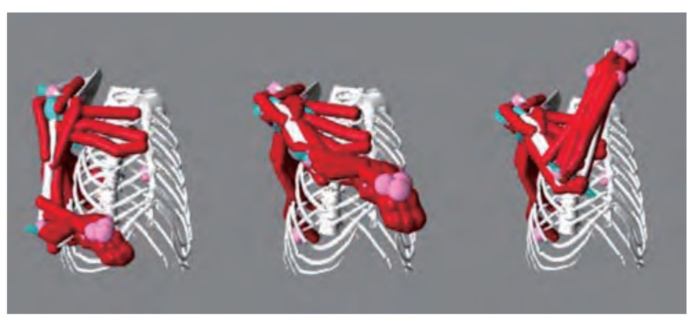

Fig. 1. Muscloskeletal model

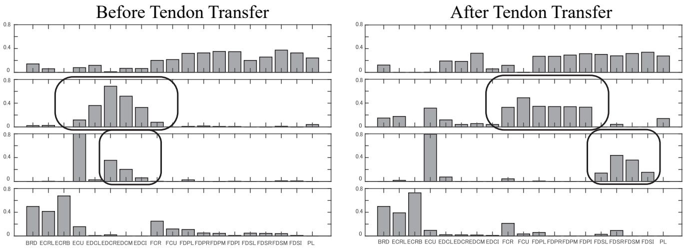

Fig. 2. Muscle synergies of the model before and after tendon transfer

of the mechanical features of the musculoskeletal system was estimated, whereas in the monkey, the neural structures of muscle synergy were involved in the muscle activity. Therefore, there is a difference in the presence or absence of neural demands (constraints) on the activity between the experiment and the model. In the future, we will explore the contribution of neural structures to muscle transfer by investigating the constraint that reproduce the experimental conditions using the model.

B. Analysis of adaptation process by gray box model

We examined how to adapt to multiple force fields using a gray box model that separately learns a forward model that predicts the future state of the body, a feedback controller that compensates for the difference between the motion target and the current state, and an inverse model that generates motor commands to stabilize the motion target[4]. Adapta-

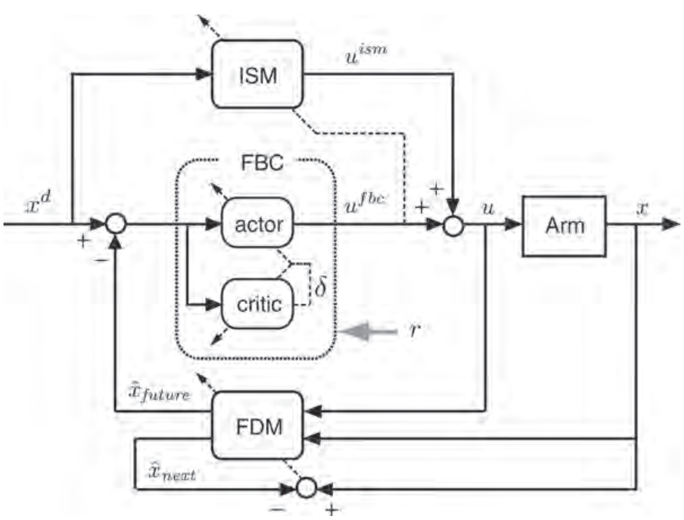

Fig. 3. Gray-box model for adaptation of force field

tion to a velocity-dependent force field, a position-dependent divergence force field, a velocity-dependent force field and a channel constraining the motion, and a velocity-dependent force field and a clamp at the end were simulated respectively, and the output of each module was compared before and after adaptation. After the adaptation, motion trajectories reproduced well the human motion trajectories and characteristics that have been investigated so far. An example for a channel constrainig adaptation is shown in Fig. 4. In this figure, after learning the velocity-dependent force field, the results were obtained by alternating between the channel and no channel conditions, and as in the human experiment, adaptation to the force field remained in the channel condition. The change

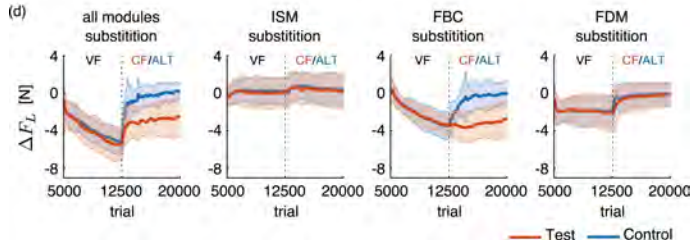

Fig. 4. Result of adaptation

in the output of each module was examined, and the output of the feedback controller was different between the two conditions. In addition, when compared with the condition of being clamped or not clamped at the end after the velocity-dependent force field, the output of the inverse model showed differences between the conditions when clamped at the end. Thus, we were able to simulate the process of adaptation to the force field and find the difference in the role of each module, which leads to a more detailed model.

IV. Future perspective

In this year, we used computer simulations to construct a musculoskeletal model that realizes muscle rearrangement in monkeys and to verify whether it can be adapted to multiple force fields. As a result, we confirmed that the muscle synergy is different from the actual experimental results in monkeys and that it can reproduce well the experimental results in humans.

We are planning to continue joint research with other groups in the next year and beyond.

References

[1] K. R. Saul, "Benchmarking of dynamic simulation predictions in two software platforms using an upper limb musculoskeletal model", Comput. Method Biomec, 18(13), 1445-58, 2015.

[2] N. Ogihara, H. Makishima, S. Aoi, Y. Sugimoto, K. Tsuchiya, M Nakatsukasa, "Development of an Anatomically Based Whole-Body Musculoskeletal Model of the Japanese Macaque (Macaca fuscata)", Am J Phys Anthropol, 139, 323-338, 2009.

[3] N. Uchida, R. Philipp, T. Oya, T. Funato, K. Seki. "Muscle synergy analysis of forearm muscles in macaque monkey after cross-transfer surgery", Neural Control of Movement Conference, 1-LB-106, 2019.

[4] H. Kambara, A. Takagi, H. Shimizu, T. Kawase, N. Yoshimura, N. Schweighofer, and Y. Koike, "Computational reproductions of external force field adaption without assuming desired trajectories", Neural Networks, vol. 139, no. July, pp. 179–198, 2021.

B03 Annual Report of Hyper-Adapt Project

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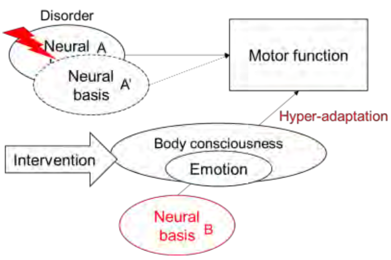
***Abstract*—B03 group aims to clarify the influence of body consciousness and emotion on the hyper-adaptation, and to establish mathematical model for hyper-adaptation which can quantitatively predict the state of body motor control ability. Furthermore, B03 group also aims to use the proposed mathematical 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 the Bayesian integration model for the sense of agency; 2) examined the relationship between body consciousness and slow/fast dynamics of motor learning; 3) we developed an evaluation model to examine hemiplegic patients' recovery.**

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

Figure 1 shows the outline of our approach. 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.



Component	Quantitative measures
Motor function	Muscle synergies, motor performance
Body consciousness	Decoding of sense of agency and ownership
Emotion	Emotion related physiological signals
Intervention	Skill abstraction using pressure sensor and motion capture
Neural basics	Brain activities (EEG)

Fig. 1 Processes of intervening hyper-adaptation via body consciousness and emotion, and quantitative measures.

III. Research Topics

B03 accomplished the following three studies in the past year.

A. *The Bayesian Integration Model for Sense of Agency*

First, Asama and Wen's group (The University of Tokyo) proposed the Bayesian integration model to explain the sense of agency, which is one of the most important aspects in body consciousness [1] (Fig. 2). We also designed a behavioral experiment to further verify this model and to determine the parameters. The Bayesian integration model suggest that humans have prior distributions regarding the sensory input at both the cognitive and sensorimotor level. When receiving actual sensory inputs, the probability of the self is calculated at both the cognitive and sensorimotor levels, and are integrated into the sense of agency with different weights. The weights for integration are considered to be related with the variance of the prior distribution. This model can well explain individual differences and other factors such as social influence. We conducted a behavioral experiment to find out the integration principle and to find out the method of describing individual difference with parameters of the model. The interim results confirmed the input at both levels, and highlighted the dominance of the sensorimotor level in the integration.

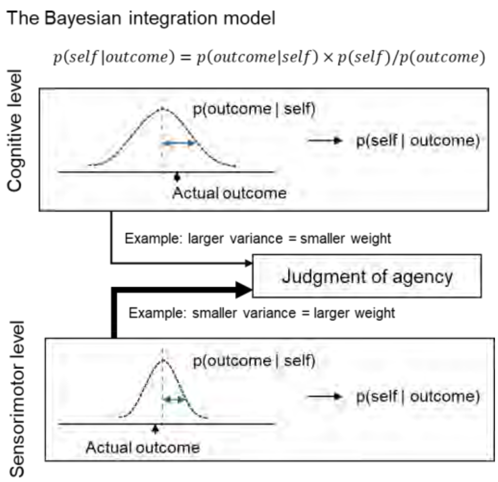


Fig. 2 The Bayesian integration model of the sense of agency

Furthermore, Asama and Wen's group examined the influence of self-voice on spatial localization [2]. This study focused on the influence of self-awareness on the perceptual processing of voice stimulus. The results showed that comparing to other-voice, the distance of the self-voice was over-estimated [2]. Moreover, this over-estimation effect of self-voice was correlated with participants' schizotypal scores, indicating the potential link between schizophrenia and the distortion in voice processing. People tend to over-estimate a distortion in their voice, and such distortion can be even magnified in schizophrenia. Further, B03 group is collaborating with A05-8 group on a schizophrenia study. This ongoing project sheds lights on the sub-processes underlying patients' sense of agency, and aims to design a novel diagnose for schizophrenia from the perspective of sense of agency.

At last, Asama and Wen's group investigated the characteristics of the EEG power spectrum during motor learning in order to construct a neuromodulation method to facilitate motor learning [3]. We measured the EEG during a hand motor learning task because we thought that understanding the changes in the EEG power spectrum during motor learning could identify the appropriate frequency bands and stimulation areas for neuromodulation intervention. Increased activity in the gamma band was observed in the frontal, lateral parietal, and occipital areas, and these areas were identified as candidates for neuromodulation intervention.

B. Bodily-self is composed of fast-self and slow-self

Motor recovery and motor learning are driven at least by two interacting systems with different dynamics: fast and slow systems. In the fast system, the memory is updated quickly but forgotten fast, whereas, in the slow system, it is updated gradually but sustained long. Since we are interested in how the bodily self which is composed of body ownership and agency, facilitates the hyper-adaptation phenomenon. To figure this out, Izawa (University of Tsukuba)'s group immerse the participant in VR space and ask them to manipulate the body of the avatar when the visual distortion of reach movement was inserted between the actual hand movement and the virtual body movement. Meanwhile, we asked them about feelings of body ownership and agency. We divided the participants into 3 groups. One group called 1PP-ipsi manipulated the right arm of the avatar with their right arm. 2nd group called 1PP-cont manipulated the left arm of the avatar by their left arm. 3rd called 3PP, is the same as 1PP-ipsi except that they view their avatar from the third-person perspective. By these manipulations, these groups exhibited different learning curvatures. We decomposed the body ownership and agency scores to slow and fast systems to determine how these learning speeds relate to body recognition. As a result, we found that the fast system drives the body ownership, but the slow system drives the agency. This suggests that the minimum unit of self is slow and fast selves [4]. In addition, we found that motor exploration is critical for de-novo learning, which appeared in neurorehabilitation [5].

C. Evaluation for Recovery Process of Hemiplegic Patients

An's group (Kyushu University) investigated the hyper-adaptation process of recovery in hemiplegic patients with impaired motor function. We hypothesized that there would be a difference between patients with better ADL ability and those with worse ADL ability at the time of hospital discharge. Patients within 3 months of onset of illness were divided into two groups, severe and moderate, based on FIM scores at discharge, and muscle synergy structures and kinematic indices of standing were compared.

Four muscle synergies were extracted from both severe and moderate groups, and it was found that these spatial patterns of muscle synergies (coordinated muscle activation) were similar in both groups. However, the peak of muscle synergy 3 contributing to body extension was later in the moderate group than in the severe group. This phenomenon is thought to be due to the fact that the moderate group used the paralyzed side, which lengthened the movement time and delayed the peak of muscle synergy 3.

Although there was no difference in motor function between the two groups by 3 months of stroke onset, the moderate group, which used the paralyzed side, recovered more ADL ability at the time of discharge. In other words, the use of the paralyzed limb in standing, especially from hip rise to body extension, resulted in better recovery of ADL ability by the time of hospital discharge [6]. This result is useful for promoting Hyper-Adaptation in functional recovery of hemiplegic patients.

IV. Future Perspective

In the past year, we proposed the computational model for the sense of agency, and designed a behavioral experiment to verify the model the determine the parameters. We also reported a novel effect of self-awareness on the spatial processes of voice, and revealed the link between this effect and the schizophrenia. We further collaborated with A05-8 group to design efficient diagnose focusing the sense of agency for schizophrenia. Furthermore, we examined the effect of body ownership on motor learning in a virtual reality experiment, to clarify the mechanism of slow and fast dynamics in motor learning. At last, we analyzed the muscle synergies of standing-up motion in paralyzed patients, found out significant differences in muscle synergies for patients with difference recoveries. Those results are useful for understanding the hyper-adaptation processes in hemiplegic patients.

References

[1] Wen, W. & Imamizu, H. "The sense of agency in perception, behaviour and human–machine interactions." Nature Reviews Psychology, (accepted).

[2] Wen, W., Okon, Y., Yamashita, A., & Asama, H. "The over-estimation of distance for self-voice versus other-voice." Scientific Reports, 2022, vol. 12, article no. 420.

[3] Hamada, H., Wen, W., Kawasaki, T., Yamashita, A. & Asama, H. "Characteristics of EEG Power SpectraInvolved in the Proficiency of Motor Learning." Proceedings of the 34th SICE DAS Symposium, Online, 2022.

[4] Ishikawa, R., Ayabe-Kanamura, S., & Izawa, J. "The role of motor memory dynamics in structuring bodily self-consciousness." iScience, 2021, 24.12: 103511.

[5] Dal'Bello, L. R. & Izawa, J. "Task-relevant and task-irrelevant variability causally shape error-based motor learning." Neural Networks 2021, 142: 583-596.

[6] Kogami, H., An, Q., Yang, N. Wang, R., Yoshida, K., Hamada, H., Yamakawa, H., Tamura, Y., Shimoda, S., Yamasaki, H., Sonoo, M., Alnajjar, F., Hattori, N., Takahashi, K., Fujii, T., Otomune, H., Miyai, I., Yamashita, A., & Asama, H. "Analysis of muscle synergy and kinematics in sit-to-stand motion of hemiplegic patients in subacute period." Advanced Robotics, 2021, vol. 35, pp. 867-87

B04Annual 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 20 co-investigators (Shirafuji, Kaminishi, Takamido, Omura, Ishii, Hamada, Kohno, Kishimoto, Yuine, Ishibashi, Etoh, Miyata, Osaki, Kanaya, Kawano, Kawai, Sonoda, Mori, Hasegawa, Makino).

II. Research results and future plans

A. *Verification of the influence of the control introduced into the neural controller model that mimics the descending pathways*

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

In this year, we aimed to introduce into our computational model a control that mimics the vestibulospinal tract, a descending tract that is responsible for postural control along with the reticulospinal tract, and studied the effect of its presence or absence [1]. We newly introduced control into the neural controller model that we have developed, based on the following findings: 1) It coordinates muscle activations of the entire body; 2) It maintains the body in a vertical position; 3) It receives mainly vestibular sensation in the vestibular nucleus in the brainstem; 4) It has an excitatory effect on extensors and an inhibitory effect on flexors (Fig. 1).

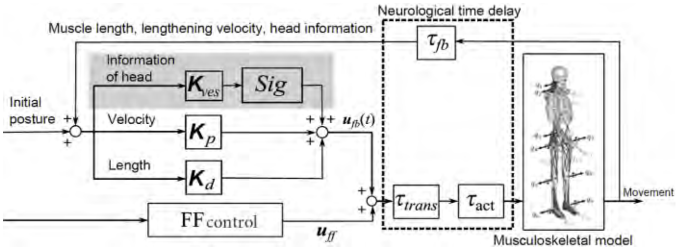


Fig. 1. The neural controller model with the control that mimics the vestibulospinal tract.

We performed simulations using the neural controller model and a musculoskeletal model with 19 degrees of freedom of joints and 94 muscles to maintain a standing posture. In almost all muscle tone conditions, the value of the center of foot pressure velocity in the case with the vestibulospinal tract was smaller than that in the case without the vestibulospinal tract (Fig. 2). This result is in line with the results of experiments on patients with unilateral vestibular dysfunction, and confirms the validity of the neural controller model.

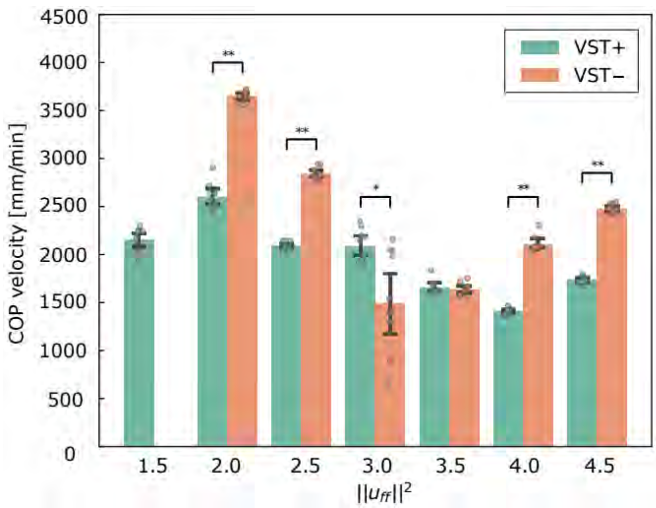


Fig. 2. Muscle tone index $||\boldsymbol{u}_{ff}||^2$ and center of pressure velocity in the anterior-posterior direction. Green shows the results without vestibulospinal tract and Orange shows the results with vestibulospinal tract. * $p < 0.05$, ** $p < 0.01$.

In addition, simulations using the neural controller model have confirmed the possibility that increased muscle tone in the reticulospinal tract leads to the bent posture seen in Parkinson's disease. In the future, we will use this neural controller model to represent diseases such as Parkinson's disease, in which the function of the descending tract is increased or decreased. We will also investigate the relationship between the model parameters and the visualized neurotransmitters in the brain and the characteristics of actual standing posture.

We analyzed the data of the standing posture maintenance experiment and tried to extract the important factors for modeling. We conducted an experiment in which participants were made to stand on a sliding table, and showed that muscle tone may affect the postural control strategy during posture recovery [2]. We also used machine learning methods to classify and cluster the standing data of stroke patients, and showed that the posture and the magnitude of sway may differ among the patients of subcategories of cerebral infarction and cerebral hemorrhage [3, 4].

B. Evaluation of the role of neurotransmitters in postural control with multitask

Yozu et al. evaluated the role of neurotransmitters in postural control with multitasking.

1) The effects of neurotransmitters on multitasking in patients with Parkinson's disease

Two Parkinson's disease patients were assessed. The participants were asked to perform (i) a standing task, (ii) a multitasking of the standing task and the arithmetic task, and (iii) the standing task. For the arithmetic task, the participants were asked to recite serial subtractions by seven. They were assessed before and after drug administration to evaluate the effect of dopamine on the multitasking test. As a result, there were fluctuations in symptoms over the course of one day, and the center of pressure and electromyography changed partially concordantly. Our results were accepted to an international journal [5].

2) Analysis of voluntary sway in standing posture in healthy individuals

We analyzed voluntary sway in a standing posture as a basic study aimed at elucidating postural control in Parkinson's disease patients. Ten healthy participants were included. We measured the joint angles of the trunk and lower limbs; the trajectory of the center of pressure; and the surface EMG of the trunk and lower limbs. The measurement condition was voluntary weight shifting in the anterior-posterior in a standing posture; the speed was divided into ten levels. As a result, we found that the joint angles of the trunk and knee used for postural control differed depending on the speed of weight shifting. We are preparing to submit to an international journal. We will analyze Parkinson's disease patients to evaluate the role of neurotransmitters in postural control.

C. Relationship between motor Functional Independence Measure gain and nonparalyzed side skeletal muscle mass change in rehabilitation after stroke

This study investigated the impact of control adaptation and physical recovery on stroke patients. We examined the relationship between skeletal muscle mass change on the nonparalyzed side and motor Functional Independence Measure (mFIM) gain in stroke patients. The group with maintenance of and gain in muscle mass on the nonparalyzed side at the time of discharge was defined as the maintenance and gain group (GG), and the group with a decrease in skeletal muscle mass on the nonparalyzed side at the time of discharge was defined as the loss group (LG), and mFIM gain was compared. Multiple regression analysis was performed with mFIM gain as the objective variable and hospitalization days, mFIM at admission, muscle mass at admission, and nonparalyzed side muscle mass as explanatory variables. In the multiple regression model, nonparalyzed side muscle mass was not significantly associated with mFIM gain. We found no relation between mFIM gain and the maintenance and gain or the loss of muscle mass on the nonparalyzed side during rehabilitation after stroke. It was assumed that poststroke functional recovery was not mainly due to a gain in muscle mass.

D. Development of a unilateral spatial neglect (USN) mouse model

Unilateral spatial neglect (USN) is a disorder of higher brain function that occurs after a brain injury, such as stroke. We induced a focal infarction in the right medial agranular cortex (AGm) of mice using photothrombosis and created a mouse model of USN. After the induction of cerebral infarction, USN was evaluated. The left-side selection rate was calculated as a symptom of USN. After the final evaluation of the USN (18 days after cerebral infarction), the brain was removed and cryosectioned. The sections were observed to examine the infarct volumes, the extent of the lesions, and the centroid of the lesion area. In addition, a ladder rung walking task was performed to evaluate motor function. The findings suggest that recovery from ipsilesional spatial bias requires neural plasticity within the anterior AGm. Motor function evaluation is currently under analysis. This conditional mouse model of ipsilesional spatial bias may be used to develop effective treatments for unilateral spatial neglect in humans.

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, accepted.

[2] K. Kaminishi, R. Chiba, K. Takakusaki, and J. Ota, "Increase in muscle tone promotes the use of ankle strategies during perturbed stance," Gait & Posture, vol. 90, pp. 67-72, 2021.

[3] D. Li, K. Kaminishi, R. Chiba, K. Takakusaki, M. Mukaino, and J. Ota, "Evaluating quiet standing posture of post-stroke patients by classifying cerebral infarction and cerebral hemorrhage patients," Advanced Robotics, vol. 35, no. 13-14, pp. 878-888, 2021.

[4] D. Li, K. Kaminishi, R. Chiba, K. Takakusaki, M. Mukaino, and J. Ota, "Evaluation of Postural Sway in Post-stroke Patients by Dynamic Time Warping Clustering," Frontiers in Human Neuroscience, vol. 15, 731677, 2021.

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

B05-1 Elucidation of the mechanism of motor synergy emergence in deep reinforcement learning

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***Abstract*—Deep reinforcement learning (DRL) offers a promising model-free approach for handling high-dimensional control problems. It still remains an open problem on how we can create human-like synergetic motion using learning algorithms. In this study, we apply DRL for managing full-dimensional arm manipulation. Although synergy information has never been encoded into the reward function, the synergy naturally emerges along with feedforward control, leading to a similar situation as human motion learning. To the best of our knowledge, this is a pioneer study demonstrating the error and energy optimization issue exists behind the motor synergy employment.**

I. Introduction

The ultimate goal for bionic arms is to realize human-like natural control. 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 in robotics and neuroscience. 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 or change with the contact situation and the hand load. Importantly, deriving a dynamics equation for a full-dimensional human arm is already challenging.

In order to manage a physically complex, high-dimensional problem, applying deep learning techniques to reinforcement learning (RL), i.e., deep reinforcement learning (DRL) offers a promising model-free approach. It enables the robot to learn directly from the interaction with the environment, based on the actions and states, instead of predefined dynamic conditions. DRL is gaining prominence in robotic research and has obtained impressive results for arm manipulation tasks. However, we should note that the current DRL algorithm does not account for synergetic behaviors, which can tend to produce unnatural and awkward control results even if we refer to learned motions available on OpenAI's website.

Previous method was not possible to apply to the full-dimensional reaching problem as the algorithm could not handle high-dimensional redundancy problems. We apply deep reinforcement learning for managing a full-dimensional arm manipulation, and then, verify the relations among motion error, energy, and synergy emergence in the learning process to reveal the mechanism of employing motor synergy.

To the best of our knowledge, it still remains an open problem on how we can create human-like synergetic reaching motion by using the DRL algorithm. This study provides the first demonstration that the error-energy optimization issue exists behind the motor synergy employment in full-dimensional arm manipulation.

II. PDRL Control Framework

Here, two types of DRL control are studied. When DRL was applied to the arm model, the action command was learned as an open-loop command to be given to the agent as shown by the blue line in Fig. 1(a). This is a standard style of DRL framework. Thus, the action from DRL can be considered as a feedforward signal. In addition, we study a second type of control, where DRL is applied while having a feedback control loop, represented by the other black lines. We name this second version as ”PDRL” which stands for a PD controller combined with a DRL controller.

For the neurological interpretation of the proposed control, we can basically apply the so-called internal model theory in the cerebellum. The climbing fiber input to the Purkinje cells carries error signals in the motor command coordinates, and their temporal waveforms can be well reproduced using the dynamics model. This neurological function corresponds to the DRL box that develops a predictive neural network with the state feedback during the learning process to form the feedforward signal. We can consider that the DRL box develops as an internal model. The contribution shift between the feedback and feedforward controls in the process of motor learning has been well demonstrated by obtaining the internal model in the cerebellum. Feedforward movements are generated without sensory feedback, showing the predictive nature of the given dynamics. Feedback control, in contrast, senses the state of the system and uses the information of error detection for modifying the current movement.

The control architecture is formulated as illustrated in the block diagram in Fig. 1(a), which comprises these separated elements in the loop.

- The feedback force error indicates the intention to track the target, which is represented by the direction toward the target, using the proportional (p) error between the target and current endpoint.
- The feedback force error is mapped into the joint space by using the Jacobian transpose of the arm.
- Here, local PD control mainly represents a local reflex loop as a function of the muscle spindles. This part helps to smoothly change the joint angle.
- The term displayed as the gray box corresponds to the action command from DRL algorithm.

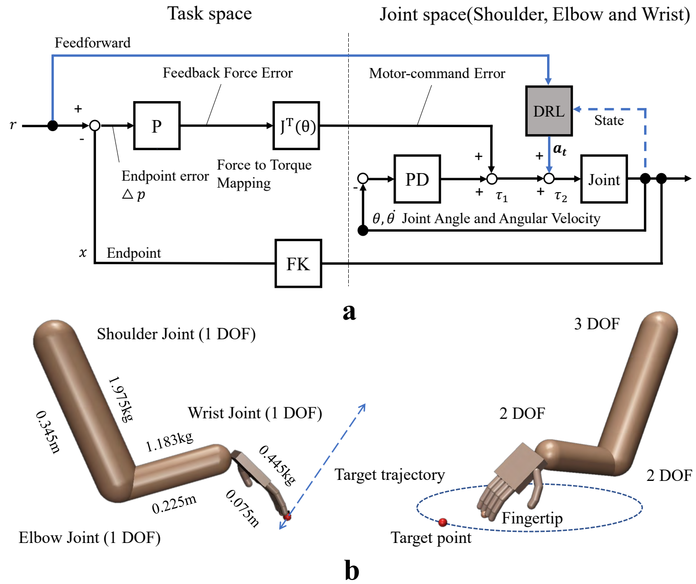

Fig. 1. a) Block diagram of motor learning, where P represents proportional, D represents derivative, and $\boldsymbol{a}_t$ is the action from DRL algorithm. b) The configuration of our simulated agents.

III. Motor Control Result

To evaluate the performance of the proposed scheme, the tracking result is compared among 1) PD feedback controller, 2) DRL, and 3) PDRL controller. PD feedback controller corresponds to the black lines in Fig. 1(a). DRL corresponds to the blue lines. PDRL controller involves all the lines.

Human motor control takes into account also the energy efficiency. A new measure is required to correctly evaluate the rate of motion accuracy per the energetic effort. We proposed previously a simple criterion to evaluate the coupled index over both error and energy. We name it as E-E index, which means 1/Error/Energy. It is simply the tracking accuracy rate per energy consumption.

Finally, we observe gradually optimized performance in the E-E index of both DRL and PDRL. The result of experiments assessing statistically the E-E index with PD, DRL and PDRL control are visualized in Fig. 2. All of the bar plots are generated by averaging the results of five experimental trials for 3- (Fig. 2(a)) and 7-DOF (Fig. 2(b)) agent. The standard deviation are added as error bars. As can be seen, with guidance from a feedback controller, the E-E index of PDRL is generally larger than that of DRL for all cases.

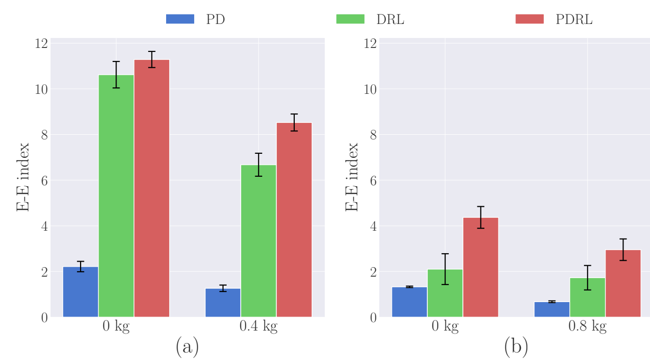

Fig. 2. Bar plots showing the result of the E-E index with PD, DRL and PDRL control under different hand load for (a) 3-DOF robotic arm case (b) 7-DOF robotic arm case.

IV. Conclusion

Automatic generation of human-like synergetic motion in high redundant 7 degrees of freedom is an unsolved issue by conventional approach. Although we did not explicitly encode the synergy between joints in our reward function, the synergy phenomenon naturally emerged during the learning process. The result implies that the error-energy optimization issue exists behind the synergy. The synergy may be a means for optimizing the error-energy criterion.

Moreover, the results of the proposed feedback-augmented DRL controller demonstrate better capability over DRL in terms of synergy development and error-energy index. This implies that feedback control can support the feedforward term development by avoiding unnecessary random exploration which leads to better search efficiency. We have also applied the concept to Soft Robot adaptation and Spiking Neural Network toward energy efficient motor control.

References

[1] J. Chai and M. Hayashibe, *Motor Synergy Development in High-Performing Deep Reinforcement Learning Algorithms*, IEEE Robotics and Automation Letters, vol.5, no.2, pp.1271–1278, 2020.

[2] J. Han, J. Chai and M. Hayashibe, *Synergy Emergence in Deep Reinforcement Learning for Full-dimensional Arm Manipulation*, IEEE Trans. on Medical Robotics and Bionics, vol.3, no.2, pp.498-509, 2021.

[3] T. Sugiyama, K. Kutsuzawa, D. Owaki and M. Hayashibe, *Individual Deformability Compensation of Soft Hydraulic Actuators through Iterative Learning-Based Neural Network*, Bioinspiration and Biomimetics, vol.16, 056016, 2021.

[4] K. Naya, K. Kutsuzawa, D. Owaki and M. Hayashibe, *Spiking Neural Network Discovers Energy-efficient Hexapod Motion in Deep Reinforcement Learning*, IEEE Access, Vol.9, pp.150345-150354, 2021.

B05-2 Adaptation ability of human postural control system revealed by a closed-loop electrical muscle stimulation system

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***Abstract*—Last year, we investigated how the postural control system adapts to a new dynamical environment using a closed-loop electrical muscle stimulation (EMS) system. This year, we pursued the possibility of the closed-loop EMS system to alter the human movement pattern through the adaptation process.**

I. Introduction

To artificially alter the dynamics of the human body during standing, we have developed an experimental system to impose ankle joint torque depending on the position and/or velocity of the center of body mass (CoM). Most importantly, our system does not use a special perturbation device but electrically stimulates the tibialis anterior muscle to generate the ankle joint torque (Fig.1A). Modulating the magnitude of electrical muscle stimulation (EMS) with the CoM measured by a laser displacement sensor enabled to alter the dynamics of the body. Furthermore, the postural control system develops the control strategy depending on the type of the imposed dynamics (Fig.1B).

II. Aim of the RESEARCH

Conventionally, a special device like a robotic manipulandum is necessary to investigate how the motor learning system adapts to a new dynamical environment. Thus, the target movement is restricted to a simple movement (e.g., reaching movement). Our method can remove this limitation and can be used to investigate the adaptation process of more complicated movements. This year, we performed new experiments using the closed-loop EMS system. We also tried to develop a new closed-loop EMS system to investigate the adaptation process and to alter the movement pattern.

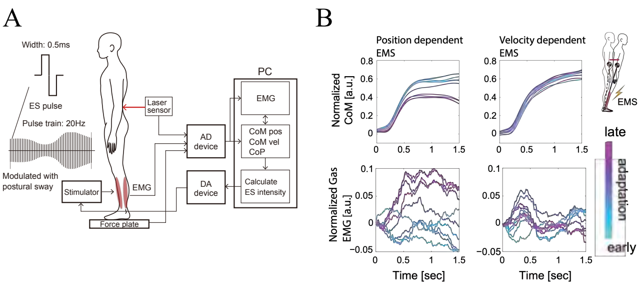

Fig.1 Experimental system to impose a new dynamical environment during standing posture using the electrical muscle stimulation (A). The postural response to a step perturbation while adapting the quiet stance to position and velocity dependent EMS (B).

III. Research Topics

A. Adaptation of reaching movement to EMS

The EMS was applied to the biceps brachii muscle during reaching movements. When the induced muscle contraction perturbs the movement in the subsequent trial in the direction opposite to the perturbation, it is evident that the motor system corrects the movement in the next trial in the direction opposite to the perturbation. Thus, in the present study, we focused on the movement correction induced by the unpredicted muscle contraction itself by constraining the hand trajectory with the error clamp method.

The EMS of about 20mA (2 biphasic pulses, pulse width:250μV, 100Hz) induced the maximal force of 4N at the handle. This force magnitude was comparable with the force field perturbation created by the ordinary robotic manipulandum. Importantly, since we used the error-clamp method, this force did not induce any movement error. Furthermore, the subjects were unable to tell the detail of the perturbation.

Nevertheless, in the subsequent error-clamp trial, we observed the force output at the handle directing in the direction opposite to the perturbation. This result indicates that, even when the perturbation did not induce any task-relevant movement error, the motor system detected the unpredicted muscle contraction and tried to correct the motor command.

B. Adaptation of walking movement to EMS

While the subject walked on a treadmill, the EMS was applied to the tibialis anterior (TA) and the biceps femoris (BF) during the swing and stance phase (biphasic pulse; pulse width: 500μV; 20Hz). The movement of the lower limb and the ground reaction force were measured by a motion capture system. We investigated how the walking movement pattern changed during 10 min walking under the presence of the EMS and how the adaptive change (i.e., aftereffect) persisted after the EMS was turned off.

In the initial EMS phase, not surprisingly, the EMS changed the movements around the joints spanned by the stimulated muscles (i.e., ankle joint by TA and knee joint by BF). The adaptation to the EMS did not restore the original walking movement pattern. Instead, the walking movement pattern converged to a new pattern while globally changing all lower limb joints movement patterns. Furthermore, such adaptive change persisted for a long time (~10 min) after the EMS was turned off.

These results indicate that there is no ideal lower limb movement pattern, and the motor system adopts different norms to be optimized. This study also implied that the EMS system developed here can alter the walking movement patterns without using expensive robotic devices [2].

C. *Adaptation of standing posture to galvanic vestibular stimulation*

The stability of standing posture is accomplished by multiple sensory information, including visual, vestibular, and proprioceptive information. However, it remains unknown how the sensory information of these different modalities is integrated to stabilize the standing posture.

This study investigated how proprioceptive and vestibular information is integrated to control standing posture by artificially creating a novel relationship between both information. To this end, we used galvanic vestibular stimulation (GVS): Applying weak electrical current through the electrodes placed behind both ears stimulates the vestibular organs and resultantly the body is swayed in the mediolateral (ML) direction. We tried to modulate the magnitude of GVS depending on the CoM velocity in the anterior-posterior (AP) direction measured with a laser displacement sensor.

In this experimental setup, the CoM velocity in the AP direction was always accompanied by the postural sway in the ML direction, for which the postural control system needs to compensate. When the 1cm/s velocity of the COM was set to induce 1mA GVS, the magnitude of GVS was restricted below 1.5mA and the subjects did not feel dizziness.

Maintaining the standing posture under the GVS might induce the following 3 possible adaptation responses. First, the postural control system ignored the GVS because the threat induced by the GVS was not critical. Second, the postural control system could try to reduce the AP sway to minimize the influence of GVS. Third, the postural control system could actively compensate for the ML sway by predicting the GVS associated with the AP sway. We are currently performing the experiment to examine which possibility is correct.

D. *Development of a system to modulate EMS with movement patterns*

The results of projects A and B described above strongly indicate that the EMS modulated with the movement could change the movement patterns through the motor adaptation process. We have developed an EMS system to alter the movement pattern, which is applicable for various movements, including throwing, walking, running, kicking, jumping.

We adopted a relatively inexpensive sensor (C-Stretch sensor, Kisco, Japan) to measure the angles of the upper and lower limbs. This sensor is stretchable and outputs the voltage signal depending on the stretching magnitude. We have succeeded in applying EMS without any delay.

IV. FUTURE PERSPECTIVE

The closed-loop EMS system can perturb the movement without using expensive special devices. This system is useful to investigate the adaptation of movements to a novel dynamical environment and to alter the movement pattern through the adaptation ability of the motor system. We need to verify the validity of this method further in future research by using the system that we have just finished developing (Research projects C and D).

REFERENCES

[1] “Balance, Gait, and Falls” Eds. Day B. L. and Lord S. R. Elsevier, 2018.

[2] I. Cajigas, A. Koenig, G. Severin, M. Smith, and P. Bonato. “Robot-induced perturbations of human walking reveal a selective generation of motor adaptation”. Sci Robotics 2, eaam7749–10, 2017

B05-03: Mechanism underlying the hyper-adaptation of bipedal locomotion to the evolutionary change of the foot

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Abstract— **Foot is the most drastically altered part of the human body in the process of the human evolution. The fact that the human foot is highly specialized not only indicates that modification of the foot structure is essential for acquisition of stable, efficient bipedal locomotion, but also suggests that the human nervous system possesses an ability to adaptively reorganize itself so that the change in the body morphology can be recognized and effectively utilized to facilitate the control of bipedal locomotion. In this study, we try to elucidate such hyper-adaptive mechanism of human bipedal locomotion based on a neuro-musculoskeletal forward dynamic simulation.**

I. Introduction

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. Among these differences, those of the foot are particularly important, as it is the most distal segment of the body that directly interacts with the ground.

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 foot structure directly affect the way the foot 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 humanlike foot 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 foot structure to accomplish more stable, robust and efficient bipedal locomotion. If the neuronal mechanism underlying such "hyper-adaptability" of human locomotion to the change of the body structure 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

In this study, we aimed to clarify the neuronal mechanism underlying the "hyper-adaptability" of human locomotion to the alteration of the foot structure in a constructive approach using a forward dynamic simulation. Specifically, we analyzed the process of reorganization of the neural control system due to the alteration of the foot structure in a bipedal gait simulation of the Japanese macaque based on a neuro-musculoskeletal model.

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. The maximum forces of the muscles were assumed to be proportional to the physiological cross-sectional area (PCSA) of the corresponding muscle group.

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. Recent studies have suggested that 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 events. In addition, we assumed a simple feedback control for postural control of the trunk segment.

To generate bipedal walking, an appropriate activation pattern must be determined for each of the 10 muscles. In the present study, we used a genetic algorithm for tuning a total of 60 parameters defining the sequence of muscle activation patterns so as to minimize the gross metabolic cost of transport estimated based on the mechanical work done by the muscles and basal metabolic energy [6].

IV. Results and Discussions

The kinematics of the simulated bipedal locomotion in the Japanese macaque generally agreed with the measured data. The simulated gait also captured the main features of the ground reaction force profiles in the Japanese macaque. Simulation framework successfully reproduced the basic kinematic and dynamic features of bipedal locomotion in the Japanese macaque (Fig 2A) [6].

We evaluated how virtual manipulation of foot morphology affects the kinematics, dynamics, and energetics of bipedal locomotion (Fig 2B). Specifically, we investigated how the alteration of the foot from digitigrade to plantigrade by the inferior translation of the calcaneal tuberosity, which allows heel strike bipedal locomotion, affects the kinematics, dynamics, and energetics of bipedal locomotion in the Japanese macaque using computer simulation.

When the foot morphology was altered, the vertical ground reaction force profile shifted from a single- to a double-peaked profile as in human walking (Fig 2C). As the calcaneal point was inferiorly translated, the cost of transport gradually decreased compared with that of the intact condition. The double-peaked vertical ground reaction force profile is one of the most distinctive characteristics of human bipedal walking, and it is known to be functionally related to the energetic efficiency of walking. Our results therefore suggested that evolutionary changes in the foot morphology were important for the acquisition of human-like efficient bipedal walking [6].

V. Future Perspective

We constructed a computer simulation of bipedal locomotion in the Japanese macaque based on a neuromusculoskeletal model to evaluate how structural alteration of the foot affects kinematics, kinetics, and energetics of bipedal locomotion. The present nervous model incorporated only the mathematical model of the CPG, but this is not sufficient to explain the mechanism of “hyper-adaptability”. The reticulospinal tract that involves in postural control and locomotion, and the vestibulospinal tract responsible for vestibulospinal reflex necessary to maintain postural balance against external perturbations should be incorporated in the present nervous model towards deeper understanding mechanisms of “hyper-adaptability” of bipedal locomotion.

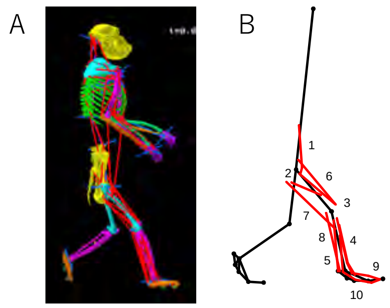

Fig. 1. Musculoskeleta model of the Japanese macaque. A: 3D whole-body model. B: 2D model used in the present study.

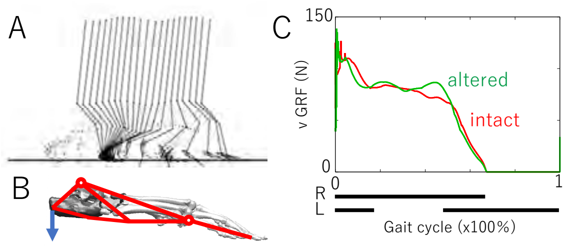

Fig. 2. Simulation results. A: Stick diagram of the simulated locomotion. B: Virtual alteration of foot morphology. C: Comparisons of the changes in vertical ground reaction force (vGRF).

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.

B05-4Annual report of research project

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***Abstract*—This project aims to find low-dimensional space in the brain networks and manipulate its state using non-invasive brain stimulation to understand the mechanism of the "hyper-adaptability." This year, we continued to develop a method to identify the low-dimensional state based on the time-varying graphical lasso. In addition, we tried to develop a method to find directed graph information using auto-regressive models and Kalman filter. We tested these two methods for different datasets**

I. Introduction

Recent studies suggest that the movement is represented by position or state in the low dimensional neural subspace composed of the population of the neural activities (i.e., Neural manifold) in the phase of movement planning and execution [1]. Neurophysiological studies (e.g. [1, 2]) showed the importance of identifying low dimensional subspaces. On the other hand, not only one or two motor-related areas but also several brain regions are involved in generating movements. However, it is unclear how these regions and the connectivity between the regions are related to the movement. It is hypothesized that low dimensional neural subspace in the planning/execution is influenced by multiple brain regions. In addition, we think that such different neural subspace representations are based on "hyper-adaptability." Therefore, in this study, we try to identify low dimensional neural subspace related to the movements in the whole-brain levels as state-space dynamics.

II. Aim of the Group

The purpose of this research is to examine neural representation (manifold) related to movement (variability) in humans. To achieve this purpose, we are going to conduct an EEG (electroencephalogram) experiment with motor tasks and identify the low-dimensional representation of EEG activity during the movements. Especially, we examined the effectiveness of the methods using the TVGL-based method and directed graph (AR-based method).

III. Research Topics

A. Development of the method to identifying low dimensional subspace for EEG data using TVGL-based method

First, this study examined the method to identify low dimensional subspace for the brain networks to understand hyper-adaptability. Specifically, we focused on the Electroencephalogram (EEG) data and examined a method using graphical models. In general, there are several ways to find connectivity between brain regions using EEG. For example, a method to calculate a correlation between regions or identify connectivity based on degrees of phase synchronization [8]. On the other hand, brain activity or EEG signals change dynamically, and connectivity between regions also changes depending on the time. Therefore, it is required to develop models that consider the dynamic property of the signals. In a previous study, Time-Varying Graphical Lasso (TVGL) has been proposed and applied to the resting-state brain activity measured by functional magnetic resonance imaging [9]. This is an extension of Graphical Lasso, which considers time-varying components and may capture dynamical connectivity between brain regions.

Therefore, in the present study, we tried to identify the low dimensional subspace for EEG data using a method based on TVGL, which was developed in the previous fiscal year. In this fiscal year, we continued to test the method for several datasets.

The first dataset was public datasets for the BCI competition IV [8]. In this dataset, data consists of trials with the four motor imagery tasks (left-hand, right-hand, foot, and tongue). When we applied the TVGL-based method to this dataset, the difference between the tasks seemed to be separated, indicating the possibility of visualization of the states. In addition, when we applied this to the data with resting and motor execution, the transitions from two states (from rest to left-hand task or from rest to right-hand task) were observed (Fig. 1). These results suggest a possibility that time-varying functional brain networks can be identified by this method.

Next, we also applied this method to data for the reaching experiment [9]. In this experiment, the subject performed the arm reaching movement for the target. Three types of target size were prepared and the subject was asked to reach the required target. Also, this data consists of rest, preparation (cue period), and execution period.

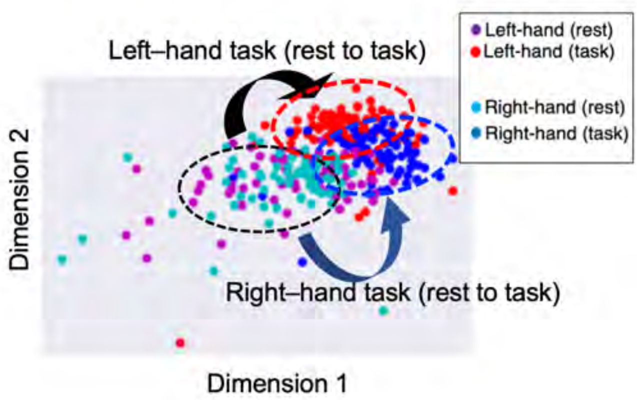

Fig. 1. Task transitions in the low dimensional states for BCI competition datasets.

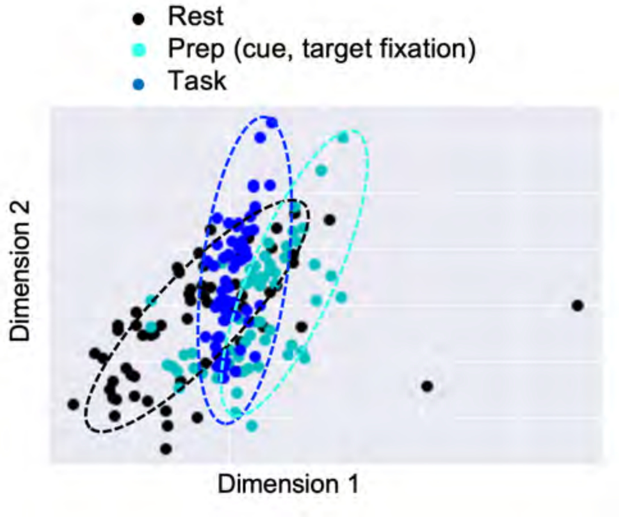

Fig. 2. Task transitions in the low dimensional states for the reaching data.

The result applying the TVGL-based method showed that preparation and execution data were largely overlapped in the low-dimensional space (Fig. 2) and transitions from rest to preparation or preparation to execution are not observed clearly.

B. *Development of the method to identifying low dimensional subspace for EEG data using AR-based method*

Next, we considered the method using a directed graph. In this study, we developed an auto-regressive (AR) model combined with a Kalman filter to identify low-dimensional space for EEG data.

The abovementioned TVGL-base method is a model to generate undirected graphs that have bidirectional connections between two nodes (i.e., two EEG channels). However, it is difficult to understand how information is transmitted between the regions. Therefore, here we considered AR models, which are commonly used to generate a directed graph. We also adopted the Kalman filter to find multiple weights of the AR models. After calculating the weight, the distances were calculated. The distances were used to identify the low-dimensional space using manifold learning.

The result for artificial data confirmed that this AR-based method can detect time-varying directed connectivity. Then we applied it to the reaching data described above. In the single-trial analysis, there is a possibility that resting and movement states can be separated in the low dimensional space (Fig. 3) while This result depended on the selection of manifold learning. On the other hand, preparation states are widely distributed and no clear separation was observed. Because this result was obtained from the single-trial analysis, we need to further examine the effectiveness of the AR-based method.

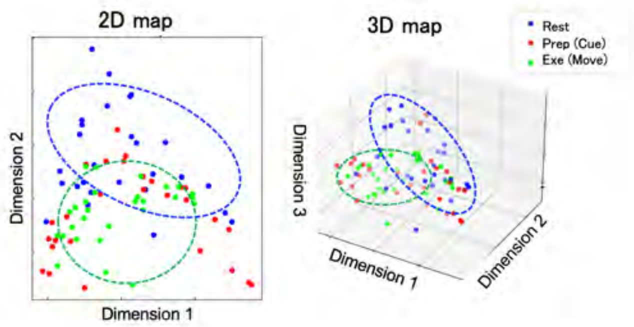

Fig. 3. Two-dimensional (left) and three-dimensional representation of the states using AR-based models for the reaching data.

IV. Future Perspective

In this study, we tried to develop a method to identify the low dimensional subspace for EEGs in humans. We proposed two methods by extending TVGL and AR models. The possibility of the proposed method for identifying low dimensional space for real EEG data is suggested. However, there are several issues to be examined in future works, including a comparison of the two methods. Therefore, further investigation into these methods is required. Also, collaboration with other groups is expected to deeply understand the low dimensional neural subspace and hyper-adaptability.

References

[1] 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.

[2] 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.

[3] N. Mizuguchi, S. Uehara, S. Hirose, S. Yamamoto, and E. Naito. Neuronal substrates underlying performance variability in well-trained skillful motor task in humans. Neural plasticity, 2016.

[4] R. L. Perri, M. Berchicci, G. Lucci, D. Spinelli, and F. Di Russo. "Why do we make mistakes? Neurocognitive processes during the preparation–perception–action cycle and error-detection". Neuroimage, vol. 113, pp. 320-328, 2015.

[5] H. Yokoyama., I. Nambu., J. Izawa, and Y. Wada. Alpha Phase Synchronization of Parietal Areas Reflects Switch-Specific Activity During Mental Rotation: An EEG Study. *Frontiers in human neuroscience*, vol. *12*, pp. 259, 2018.

[6] 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.

[7] M. Tangermann, "Review of the BCI competition IV", *Frontiers Neuroscience*, vol. 6, no. 55, pp. 1-31, 2012

[8] 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, 2018

B05-05 Development of motor learning model that can reuse partial dynamics based on estimation of transformation between mappings

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Abstract—**In this research, we aim to construct a model that can explain the reuse of partial control knowledge in human motor learning process. We developed a learning model based on the estimation of partial physical relationships of the target motor control system and a method for estimating the transformation between partial relations using the learning method. We assume that the task is to control the hand position of two arms with symmetrical kinematics. We proposed a motor learning framework that can explain the process of reusing partial information in the controllers of the left arm for recovery of the right arm controller. Assuming a twin-arm fingertip position control task with symmetrical kinematics, we proposed a motor learning framework that can account for the process of reusing partial information in the controllers of the left and right arms. It was shown that the coordinate transformation can be obtained by a distributed computation method.**

I. Introduction

Human adaptability includes the ability to adaptively regain function by reusing previously acquired neural circuits in the event of partial dysfunction of the body or brain. For example, as an example of neural circuit substitution, it has been shown that when one hand is paralyzed, that hand can be controlled by a different neural circuit than the normal one [1]. In order to explain the aspect of 'reuse of neural circuits,' which has not been adequately represented in previous models of human motor learning, this study constructs a motor learning model that can explain the process of reusing a part of the motor control model once it has been acquired, depending on the situation. In this study, we construct a motor learning model that can explain the process of reusing parts of a once-acquired motor control model according to the situation.

In the motor control of the upper limb shown in Fig.1, the state can be represented by multiple sensor variables (somatosensory information) with different modalities, such as muscle length, muscle contraction force, joint torque, joint angle, and hand position. Furthermore, there are several causal (dependency) relationships between these sensor variables, such as kinematics that relates joint angle and hand position, and equations of motion that relate joint angular torque and joint angular acceleration. In this research, we propose a model for automatically generating controllers by estimating dependencies among various sensor signals in motor control based on past research results [2], and develop a motor learning model that explains the process of reusing partial causal relationships in controllers acquired in the past by introducing a new mechanism called transformation estimation between mappings to the model.

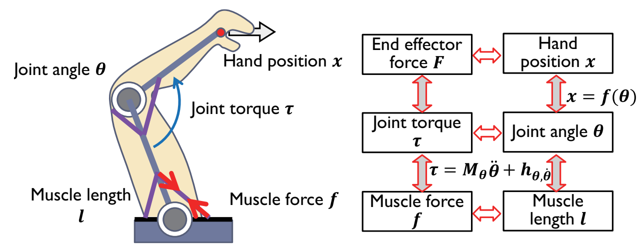

Fig. 1. An example of partial physical causality in human upper limb control

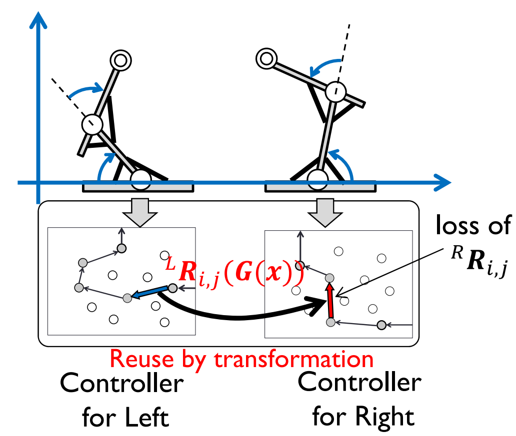

Fig. 2. Transformation estimation to discover the mirror image relationship between the left and right arms.

II. Achievements

As an example of motor function recovery through partial causal transformation, we consider a symmetrical 2-DOF arm as shown in Fig.2. The joint angles of the left arm and the right arm are defined symmetrically, with the direction in which the arm closes being positive and the direction in which it opens being negative. On the other hand, the hand positions are measured in a common Cartesian coordinate system. In this case, the two arms are mirror images of each other, and the hand positions for the same joint angle values of the left and right arms are represented by a relation with positive and negative inversions and offsets.

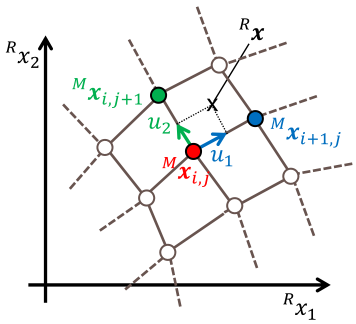

Fig. 3. Coordinate transformation estimation using adaptive grids.

In these left and right arms, a controller is constructed independently based on the method proposed in [2]. One of the partial physical causal relationships that is acquired and used in this controller is the relation of inverse differential kinematics (Jacobian inverse). There is a mirror image relationship between the left and right inverse differential kinematics (functions), which is represented by the transformation of the input $\boldsymbol{G}$. In other words, the problem of reusing the internal information of the controller is formulated as a problem of estimating the input transformation such that the two functions are matched. For the representation of the input transformations, we use an adaptive grid arrangement method as shown in Fig.3.

For a grid point position vector, we define an energy function and estimate the transformation such that the function matches after the input transformation by minimizing the energy function. To evaluate the agreement of the functions, the energy function is constructed as a sum of terms that evaluate the agreement of the zero-order and first-order local approximations of the functions, and a term corresponding to the regularization that evaluates the smoothness of the grid point arrangement. The minimization of this energy function corresponds to the estimation of the desired input transformation.

As a method for minimizing the energy function, we implemented the genetic algorithm (GA)[3]. The location information of the grid point group $\boldsymbol{X}$ is encoded as a gene, and multiple individuals are generated by random numbers. These individuals are selected based on the evaluation function $E(\boldsymbol{X})$, and the selected individuals are crossed and mutated to search for a better solution. As an example, we tested the matching of functions representing the kinematics of a two-degree-of-freedom manipulator.

Fig.4 shows how a two-dimensional grid starts from a random initial position and eventually finds the desired function matching. (a) in the figure shows the initial configuration of the grid and the configuration where the final matching should be done. In such a case where the grids have different orientations, the continuous variation of the gradient method alone cannot achieve proper matching because it is trapped in the local solution. It can be seen that the optimization by the proposed genetic algorithm succeeds in estimating the coordinate transformations that can perform proper matching for coordinate systems that are set in different directions at the beginning of the search.

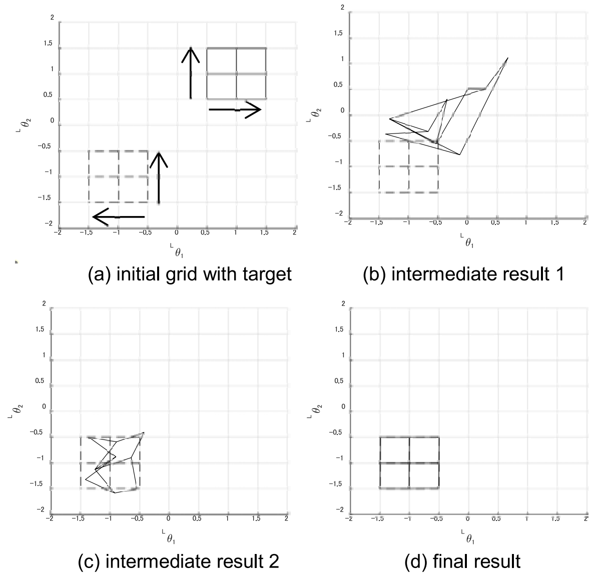

Fig. 4. Snapshots of grids for matching acquisition in GA evolution.

III. Summary and Future Plan

Aiming at a motor learning model that enables the reuse of the information of motor controllers in the motor learning process, we proposed a method for estimating the transformation between partial causal relations by matching functions with an adaptive grid. We proposed a method of mapping between coordinates using a distributed algorithm with nodes distributed in a grid, and an implementation method that searches for matching between functions while using the smoothness of the transformation as a regularization term by an energy function. As one of the implementation methods, we verified the optimization using the genetic algorithm and confirmed that the desired transformation can be estimated in the function matching problem that imitates the kinematics of left and right arms in a mirror image relationship.

In addition, we formulated the reuse of information in a motor controller from the viewpoint of feedback control, *i.e.*, 'input transformation of a function whose input is a state.' The construction of a model from such a perspective is also considered to be a future issue.

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

B05-6 Annual report of research project

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***Abstract*—The goal of this research is to enable an operator to enhance robotic embodiment through robot operation, which is under a shared control with an AI robot controller. As a result, the operator could operate skillful manipulation remotely, using the robot as if it were a part of his or her own body. In this year, we constructed an experimental environment to evaluate effects of intervention of the robot controller with AI on the operator's sense of agency under different auditory feedback conditions and then conducted experiments to evaluate them. In this environment, an operator sends motion commands to a robot for object handling through an intuitive teleoperation system with VR devices and then the robot controller adjusts the operator's commands to achieve a target task if necessary. Through experiments, we confirmed that auditory feedback during robot operation affects the operator's sense of agency when manipulation intervention occurs. It was also suggested that the simultaneous presentation of operator's sounds and sounds around the robot may obscure the judgment criteria related to the sense of agency.**

I. Introduction

Shared control is expected to reduce an operator's workload and improve safety in task execution with a tele-operated robot. This enables both real-time autonomous operation, in which the robot makes its own decisions and actions based on information obtained from the work site, and intelligent operation, in which the operator makes advanced cognitive and judgmental decisions based on the information from the work site. In addition, in order to ensure the execution of tasks and collision avoidance with obstacles, shared control is required, which gives strong authority to the robot side, such as shifting from human operation to autonomous operation by the robot.

On the other hand, the sense of immersion in the workspace is a major factor in the realization of the task, and further improvement in operability can be expected by promoting "robotic embodiment," in which the robot's motions can be planned and manipulated as if they were its own physical motions. One of the factors that promote this phenomenon is the sense of agency (the sense of recognition that the motion of the observed object is caused by himself or herself [1]). However, when manipulation intervention occurs, the sense of agency is expected to be degraded. Since this degradation is expected to cause the operator to feel uncomfortable and to lose motivation to work, it is necessary to realize new shared control that does not degrade the sense of agency.

II. Research topics

In this research, we will develop a manipulation interface for teleoperation of a robot arm which enables robot manipulation with self-agency while maximizing human adaptability without degrading robotic embodiment. Specifically, we will search for methods to suppress the cognitive functions that distinguish between self and other robot operations, as well as conditions that promote the adaptability of the robot operator. Based on these methods, we will develop a manipulation interface. Our goal is to develop a manipulation interface which enables the operator to manipulate the robot as if it were a part of his or her own body, while realizing skillful manipulation through the intervention of the robot controller.

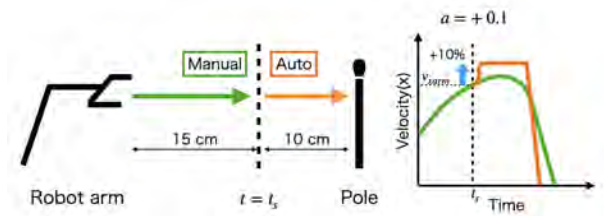
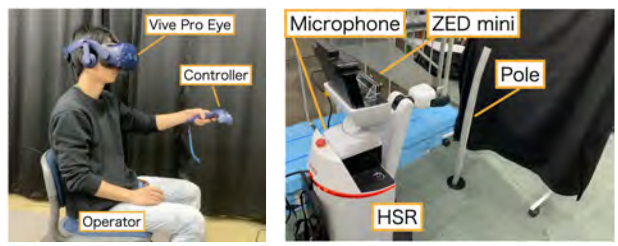


Fig. 1. Manipulation intervention to maintain or change arm velocity



(a) Operator (1F) (b) HSR (2F)

Fig. 2. Experimental environment

III. Achievements

A. Manipulation intervention using intuitive teleoperation system

In order to investigate the effect of manipulation intervention on the sense of agency during robotic teleoperation, we used an intuitive teleoperation system [2] that we have been developing. This system uses a VR device (HTC Vive Pro Eye) to remotely control TOYOTA HSR (Human Support Robot [3]). The position and posture of the operator's left hand are synchronized with the tip of HSR arm, and the head camera posture of HSR is controlled in real time to correspond to the operator's head posture. In addition, by presenting parallax images to the HMD, the system provides an immersive teleoperation experience.

A manipulation intervention to maintain or change the arm tip velocity of HSR and move it to the target position is introduced in this system. As shown in Fig. 1, when the

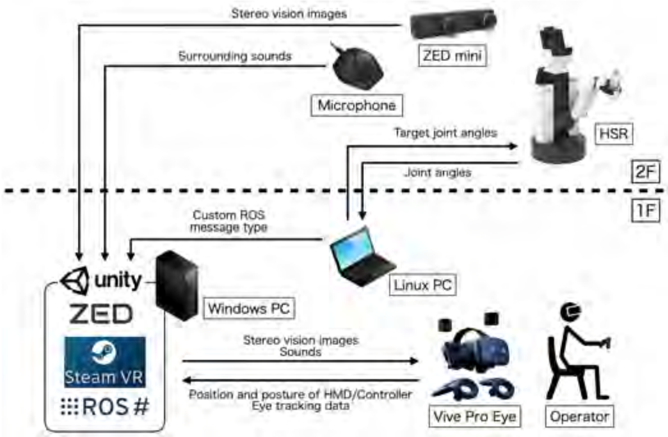


Fig. 3. System configuration for teleoperation between 1st and 2nd floors

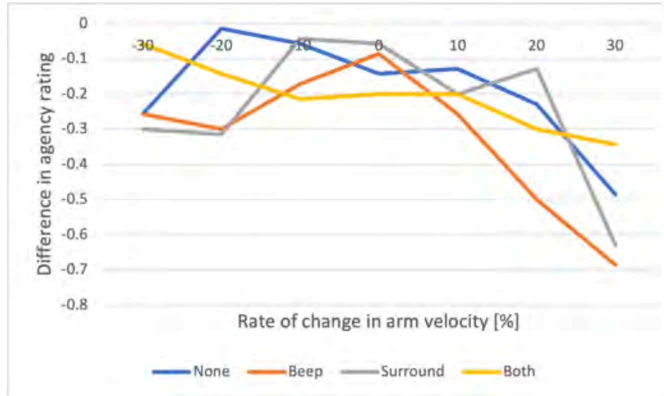


Fig. 4. Average of differences in agency ratings in each auditory feedback condition

distance between the arm tip and the target position becomes less than a certain value, the arm tip moves to the target position at a constant velocity automatically according to the equation (1).

$$x_{arm}(n) = x_{arm}(n-1) + v_{xarm}(t_s) \cdot (1+a) \cdot \Delta t_s, \quad (1)$$

where x_{arm} is the commanded position of the arm [m], v_{xarm} is the velocity of the arm in the depth direction [m/s], t_s is the start time of the correction [s], a is the rate of change in velocity, and Δt_s is the time required for one loop at the start of the correction [s].

B. Evaluation of the effect of auditory feedback on the sense of agency

We investigated the effects of manipulation interventions on the sense of agency under four different auditory feedback conditions. None: no sound is presented during operation. Beep: a sound source (monotone) is always played, and the pitch is changed according to the velocity of the controller in the depth direction. Surround: a microphone mounted on HSR collects sounds around the robot and plays them back. Both: both operation sounds and robot peripheral sounds are presented.

In this experiment, the operator tele-operated the robot on a different floor (Fig. 2). The system configuration of the inter-floor teleoperation is shown in Fig. 3.

In this experiment, HSR arm tip was remotely controlled only in the depth direction by seven subjects. The task was to move the arm from the initial arm position to a position where it could grasp a pole located 25 cm away in 3 seconds. The conditions with or without correction were changed randomly. For comparison, we changed a in seven steps ($a = 0, \pm 0.1, \pm 0.2, \pm 0.3$) in each auditory feedback condition.

The evaluation indices were the sense of agency toward arm manipulation and the awareness of correction. We asked the participants to rate on a 5-point scale after each trial whether their own operations were reflected in the movements of the robot arm. The experimental result is shown in Fig. 4.

In the None condition, the effect of weak manipulation intervention on the sense of agency was small, while in the Beep/Surround condition, the effect of manipulation intervention was large, and the sense of agency decreased significantly in the strong intervention condition.

In Both conditions, the decrease in the sense of agency was greater in the weak intervention condition than in the other conditions, but the decrease in the sense of agency was suppressed the most in the strong intervention condition. This result suggests that synchronization of visual and auditory stimuli and synchronization of motor and auditory stimuli may obscure the criteria for decreasing the sense of agency.

IV. Future Perspective

In this year's study, we introduced manipulation interventions to maintain or change the arm velocity under different auditory feedback conditions, and investigated the effects of these interventions on the sense of agency through the experiment. The experiment showed that the presentation of the robot arm movement sound and the controller operation sound did not suppress the decrease in the sense of agency caused by the strong intervention, and that the simultaneous presentation of both sounds may reduce the effect of the strong intervention.

In the future, we will redesign the type of sound and the presentation method according to the operator's operation, aiming for manipulation interventions that are hardly noticed by the operator.

References

[1] S. Gallagher, "Philosophical conceptions of the self: implications for cognitive science," *Trends in Cognitive Sciences*, vol. 4, no. 1, pp. 14–21, 2000.

[2] J. Nakanishi, S. Itadera, T. Aoyama, and Y. Hasegawa, "Towards the development of an intuitive teleoperation system for human support robot using a vr device," *Advanced Robotics*, vol. 34, no. 19, pp. 1239–1253, 2020.

[3] T. Yamamoto, K. Terada, A. Ochiai, F. Saito, Y. Asahara, and K. Murase, "Development of human support robot as the research platform of a domestic mobile manipulator," *ROBOMECH Journal*, vol. 6, no. 1, p. 4, 2019.

B05-7 Systems Engineering Approach for Understanding Neural Mechanisms of the Intermittent Control during Human Stance

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***Abstract*—Beta rebound after execution and/or suppression of movement has been studied in the context of motor decision-making processes. However, fewer study focused on the beta rebound during postural control in upright stance. Here, we examined beta rebound of electroencephalogram (EEG) activity during perturbed upright stance to investigate supraspinal contributions to postural stabilization. To this end, EEG signals were acquired from nine healthy young adults in response to a brief support-surface perturbation, together with the center of pressure, the center of mass and electromyogram (EMG) activities of ankle muscles. Event-related potentials (ERPs) and event-related spectral perturbations were computed from EEG data using the perturbation-onset as a triggering event. After short-latency ERPs, our results showed a decrease in high-beta band oscillations (event-related desynchronization), which was followed by a significant increase (event-related synchronization) in the same band, as well as a decrease in theta band oscillations. Unlike during upper extremity motor tasks, the beta rebound in this case was initiated before the postural recovery was completed, and sustained for as long as three seconds with small EMG responses for the first half period, followed by no excessive EMG activities for the second half period. We speculate that those novel characteristics of beta rebound might be caused by slow postural dynamics along a stable manifold of the unstable saddle-type upright equilibrium of the postural control system without active feedback control, but with active monitoring of the postural state, in the framework of the intermittent control.**

I. Introduction

In this study, we examined Event-Related Spectral Perturbations (ERSPs) during the long-lasting postural recovery process of upright equilibrium in response to small impulsive step-like support-surface perturbations. Particular interest was to investigate the timing and the duration of beta band Event-Related Desynchronization (ERD) and Event-related Synchronization (ERS) responses, and to quantify them. Because a postural recovery process from a perturbed posture to the upright equilibrium is transient, and it settles down eventually to the post-recovery equilibrium state, the post-recovery state could be regarded as a status quo for postural maintenance. Therefore, similarly to the studies for upper limbs (e.g., Engel and Fries 2010), we hypothesized that beta ERD during the recovery response and the subsequent post-movement (post-recovery) beta rebound (beta ERS) would be present in the EEG cortical activities following upright stance perturbations. If we could observe beta ERD and beta rebound as hypothesized, the next objective would be to clarify in the temporal profiles of the appearance of beta activities within the long-lasting biomechanical postural recovery response. In the simplest possible situation, beta ERD would appear persistently during the postural response while the muscles are active, and then a beta rebound would appear after the postural response is completed, i.e., as a post-movement rebound after a few seconds required for the upright posture to be fully recovered. This scenario is based on beta ERD and ERS during upper extremity tasks (Engel and Fries 2010), with possible variations in time intervals due to the longer-lasting postural response. However, if we observe beta ERD and ERS with qualitative differences in temporal characterizations from those during upper extremity tasks, they could lead to shedding new light on mechanistic causes of the beta rebound. Indeed, the final phase of the postural recovery has a particular meaning for the intermittent control hypothesis that has received attention in recent years (Bottaro et al. 2008; Asai et al. 2009; Suzuki et al. 2020). That is, the final phase of postural recovery takes place with a small postural tilt, during which, according to the intermittent control hypothesis, the active feedback control is switched off, and the postural state point approaches slowly the upright posture along a stable manifold of the unstable saddle-type upright equilibrium in the state space of postural control system. Because the switching action of the active feedback control, such as deciding to maintain the switch off or to turn the switch on, would involve active information processing, we expected to find cortical activities associated with it.

II. Aim of the Group

According to the intermittent control hypothesis, the central nervous system (CNS) inactivates (switches OFF) and activates (switches ON) the active contraction of medial gastrocnemius at a sequence of appropriate timings that depend on the state of posture (i.e., the tilt angle and angular velocity of the standing posture) as somatosensory information that is conveyed to the supraspinal brain with a large transmission delay time. That is, the active postural feedback control is switched OFF and ON alternately in accordance with time-delayed sensory information. In the intermittent control model, a timing of switch OFF the activation of gastrocnemius plays a key role for the postural stabilization. This seemingly paradoxical property allows the model to exhibit postural fluctuation with a long-range correlation. In other words, the core hypothesis of the intermittent control, in terms of its neural mechanisms, is an automated selection either activation (Go) or inactivation (NoGo) of the neural circuitry in the brainstem that innervates the medial gastrocnemius, depending on the mechanical state of upright posture. The cortico-basal ganglia loop is a core mechanism for such information processing, regulating activity of direct (corresponding to Go signal) and indirect (corresponding to NoGo signal) pathways.

The goal of 2021 was to characterize the beta rebound (beta ERS) that appears in response to a support surface perturbation during quiet stance. Beta rebound has been known for motor control of upper extremities, which appears after motor execution or suspension of motor execution (NoGo response in Go/NoGo tasks). Here, we hypothesize that the beta ERS for the postural recovery reflects a neural process for selecting either activation (Go) or inactivation (NoGo) of medial gastrocnemius along with active monitoring of the latest phase of the postural recovery, which might correspond to a processing of reafferent sensory motor information.

III. Research Topics

A. *The long-lasting beta rebound in the late phase of Postural Recovery in Response to a support-surface perturbation*

Standing posture, electromyography (EMG), and EEG signals were measured under the following two conditions: quiet standing (control) and support-surface perturbation (perturbed). Postural sway during quiet stance in the control condition was measured to determine the equilibrium posture with accompanied EEG signals (baseline EEG) to be compared with postural recovery process, particularly in the period a few seconds prior to each perturbation. We showed two novel event-related clusters of powers in ERSP for latencies longer than 1.0 s, which were the main findings of this study. One was the ERS at high-beta band (high-beta ERS, beta rebound), which appeared after the high-beta ERD (See Fig. 1). The high-beta ERS sustained over a relatively long duration with its peak latency located at about 3 s. The high-beta ERS was observed mainly at Cz electrode. The averaged powers across participants at the high-beta band in the latency of $1<t<4$ s were significantly greater than the resting potential, i.e., the beta rebound sustained for as long as three seconds. During the appearance of the high-beta ERS, the CoP and the CoM became close to each other in the very late phase of the recovery process. Comparison between ERSP and EMGs showed that activations of SO and MG muscles had become small compared to those of short latency (<0.3 s), but they were still slightly larger than those during quiet stance for the early period ($1<t<2.5$ s) of the high-beta ERS. However, activations of all muscles were the same as those during quiet stance for the later phase ($2.5<t<4$ s) of the high-beta ERS. That is, the high-beta ERS in its later phase was generated with no perturbation-induced excessive muscular activations.

Neural information processing to accomplish the postural recovery observed in this study can be interpreted according to the neuroanatomical model of higher-order regulation of postural control (Takakusaki et al, 2017). We associate such a neurophysiological interpretation with the long-lasting high-beta ERS (beta rebound) at the late phase of the postural recovery, in conjunction with the intermittent control model. Specifically, we speculate that the long-lasting high-beta ERS identified in this study, together with the theta ERD, are associated with the long-lasting neural expression of the body

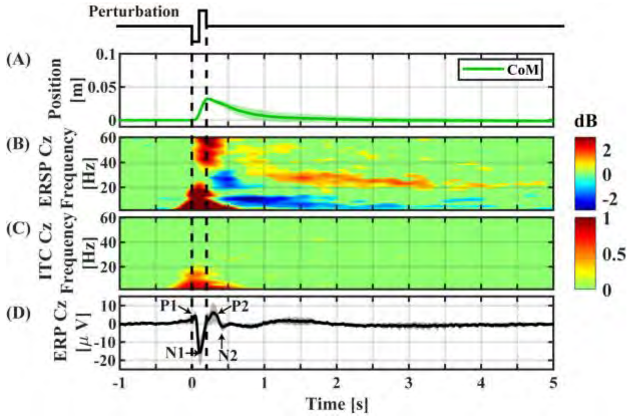

Fig. 1. Postural responses to the support-surface perturbation. (A) CoM position, (B) ERSP, (C) ITC, and (D) ERP at Cz electrode in resp.

schema of postural verticality at S1 and the posteroparietal cortex and a process of matching between the body schema and reafference of the postural state, where they are required to be long-lasting due to slow mechanical dynamics of postural recovery, perhaps along the stable manifold of the unstable saddle-type upright equilibrium point. That is, those circuitries might fulfill a role of active monitoring (including matching between the efference copy and the afference information) ongoingly, either with (middle phase of the recovery after the vestibular-spinal reflex) or without (late phase of the recovery) EMG outputs, in order to be always ready for switching ON or OFF the intermittent feedback controller.

IV. Future Perspective

It is expected that a similar beta rebound could be observed during quiet stance, because the intermittent control hypothesis claims that the active feedback is switched OFF during “micro postural recovery” from every “micro-fall” of postural sway.

References

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

[2] Bottaro, A., Yasutake, Y., Nomura, T., Casadio, M., and Morasso, P. (2008). Bounded stability of the quiet standing posture: An intermittent control model. *Hum. Mov. Sci*. 27, 473–495.

[3] Asai, Y., Tasaka, Y., Nomura, K., Nomura, T., Casadio, M., and Morasso, P. (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.

[4] Suzuki, Y., Nakamura, A., Milosevic, M., Nomura, K., Tanahashi, T., Endo, T., 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 Interdiscip. *J. Nonlinear Sci*. 30, 113140.

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

Annual report of research project B05-8

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***Abstract*—The real world is an indefinite environment in which the probability space is not specified in advance. Here, we developed a learning model in which the state space is expanded so that it refers to the arbitrary length of previous states, based on two criteria: experience saturation and decision uniqueness of action selection. The model was tested by a behavioral task called a two-target search task, and compared with ordinary infinite hidden Markov models (iHMMs). In contrast to the iHMMs, our model performed well by generating only necessary states with high reproducibility. The proposed model will serve as a basis hyper-adaptability to an indefinite environment by using these criteria defining the appropriateness of state expansion.**

I. Introduction

Uncertainty is classified into two types. The first is where the state of the environment is defined and fixed, and we can utilize this prior knowledge. The other is the case where even the state space is neither given nor hypothesized in advance. The latter type is defined as an indefinite environment, and adaptation to such an environment is a critical issue for living systems.

Reinforcement learning is a form of learning in which the agent learns to take an action in an uncertain environment based on the state at the previous time-step to maximize the cumulative reward. However, the current state of functions as prior knowledge in conventional reinforcement learning models. Therefore, they may not achieve high learning performance in indefinite environments.

II. Aim of this Research

Here, we propose a reinforcement learning model with a dynamic state space, and tested its performance by a two-target search taskm previously used in a physiological experiment with monkeys (Fig.1) [1,2]. Subjects were required to gaze at one spot from among four identical stimuli. If the correct spot (designated by green in Fig. 1) was selected, a reward was delivered. After training, the subjects learned to saccade alternately to two targets in a valid pair, and received a reward for several correct trials in a row (the exploitation phase). If the valid pair was changed without instruction, they started searching for a new valid pair after making errors (the exploration phase). In this task, by simply hypothesizing that the previous state is the previous trial, the agent cannot maximize the total reward. To do so, the agent must consider the two previous trials together as the previous state by itself.

III. Research Topics

Our proposed model is given no prior knowledge of the task structure other than the action of gazing at one of the four spots. Instead, it starts learning using the immediately preceding trial as the starting state, and expands and contracts the state space in the direction of previous trials based on the criteria of experience saturation and the decision uniqueness of the action selection (Fig. 2). These two criteria evaluate the magnitude of the change in Q-value with experience, and how close the Q-table is to a unique behavioral decision, respectively.

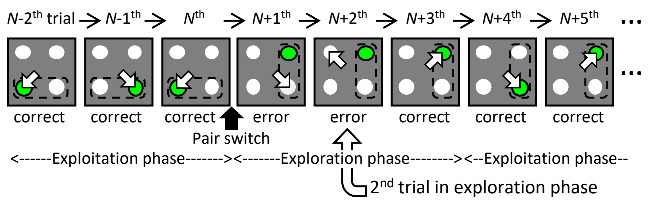

Fig. 1. Overview of the two-target search task. Schematic of several trials before and after a valid pair change. The pair change triggers the transition from the exploitation phase to the exploration phase. Dashed lines, empty arrows and green spots denote valid pairs, gazes and correct targets, respectively. Note that the subjects were not instructed to move their eyes by the green spot before gaze shift.

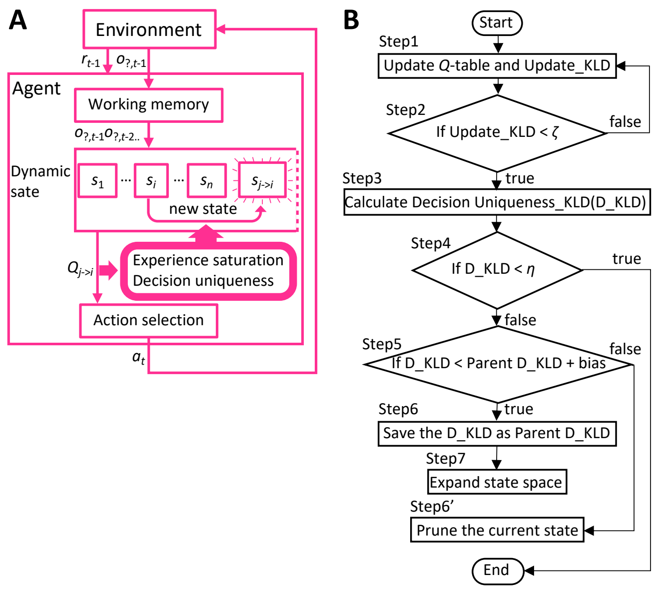

Fig. 2. Schematics of the proposed model. (A) Our dynamic state scheme hypothesizes that the agent receives only partial information from the environment. However, unlike POMDP, these observations are temporarily stored in working memory and serve to generate a new state not prepared a priori, based on the two criteria experience saturation and decision uniqueness. (B) Expansion and contraction of the state space. Flowchart of the expansion and contraction process.

The model not only achieved high performances (Fig. 3A), appropriate number of states (Fig.3B) and large number of valid pair switches (Fig. 3C) with a high reproducibility, which were comparable to the ideal model given prior knowledge of the task structure (data not shown), but also performed well on a task that was not envisioned when the models were developed (data not shown).

Furthermore, we compared the proposed model with infinite hidden Markov models (iHMMs) that dynamically generate states without prior knowledge by hierarchically using a Dirichlet process (Fig. 3D-F). In contrast to our model, these models generated too many states unnecessary to perform the behavioral task tested, and showed much less reproducibility.

These observations indicates that the two criteria included in the proposed model, decision uniqueness and experience saturation define the purpose of state expansion and the timing of state expansion, respectively. The proposed model is expected to be a basis of learning models that can adapt to an indefinite environment by including these criteria defining the appropriateness of state expansion.

In addition to above topic, "a prototype of a neural-net reinforcement learning model for learning one-target search Tasks" and "a meta-analysis of cognitive behavioral tasks in leptin and leptin receptor-deficient mice" reported last year were published in [3] and [4], respectively.

We also performed a time-frequency analysis of local field potential (LFP) recorded from the monkey lateral prefrontal cortex (lPFC) during the execution of a shape manipulation task. In the ventral part of the lPFC, θ-δ waves during the delay period changed in response to the transformed shape to be temporarily memorized. On the other hand, in the dorsal part, the γ wave in the shape presentation periods changed in response to the action-manipulation correspondence that switched every few dozen trials. These results suggest that the lPFC is functionally differentiated between ventral and dorsal parts, and that each region dynamically recruits information necessary for task execution via LFPs in different frequency bands [5].

IV. Future Perspective

One trial of the two-target search task includes multiple task events. Currently, we are developing a learning model that can learn appropriate actions for each task event as well as decision making based on the history of previous trials, and are submitting the first report. We are also developing a model that can learn delayed response tasks and can perform tasks that are characteristic of the frontal lobe, especially the premotor and supplementary motor areas. These preliminary results will be presented at next year's conference. Through developing this model, we want to pioneer a new field of computational higher-order dysfunction studies in the future.

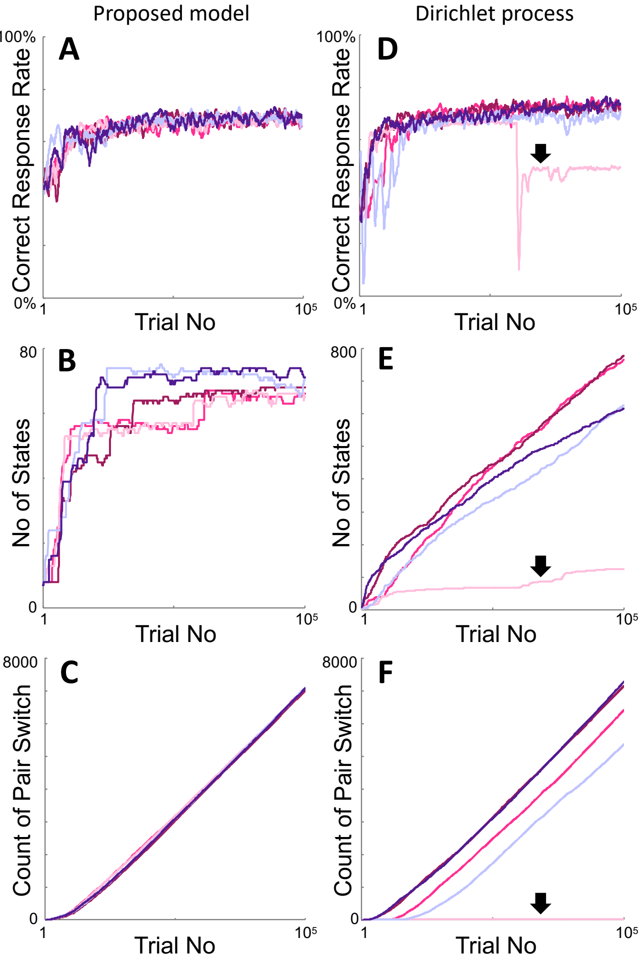

Fig. 3. Comparison of the proposed model and the iHMM in terms of the reproducibility of two-target search task learning. (A–C) Time courses of the correct response rate (A), increase in number of states (B), and increase in the cumulative number of target pair-switches (C) exhibited by the proposed model. (D–F) Identical plots of the Dirichlet process version of the iHMM. Black arrows indicate the same calculation of poor 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.

[2] K. Sakamoto, "The golden mean in dynamic reinforcement learning," The 31th Annual Conference of the Japanese Neural Network Society, P2-08, September, 2021.

[3] K. Sakamoto, H. Okuzaki, A. Sato, H. Mushiake, "Experience resetting in reinforcement learning facilitates exploration-exploitation transitions during a behavioral task for primates," bioRxiv 10.1101/2021.09.30. 462676, September 2021.

[4] T. Watanabe, K. Sakamoto, "Meta-analysis of cognitive and behavioral tests in leptin- and leptin receptor-deficient mice," Neurosci. Res., Vol. 170, pp. 217-325 September 2021.

[5] K. Sakamoto, N. Kawaguchi, H. Mushiake, "Multidimensional Analysis of Task Relevance of Theta Oscillations in Monkey Lateral Prefrontal Cortex during Shape Manipulation Task," The 44th Annual Meeting of the Japan Neuroscience Society, 3P-095, July, 2021.

B05-9 Annual report of research project

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***Abstract*—The research project B05-9 aims to establish tailor-made EEG-based neurofeedback (NF) training system to improve motor and cognitive functions by quantifying an individual's ability to control attention using brain activity. Furthermore, we try to demonstrate that a protocol considering individual cognitive traits contributes to the facilitation of NF training efficacy. The achievements in this year are as follows: 1) Our NF system successfully modulated somatosensory area activity through training over multiple days. Especially, we found such marked neuromodulation in individuals who had a higher cognitive ability for directing their attention to body movements. 2) With the neuromodulations in the somatosensory area, movement accuracy also improved during a rhythmic hand movement task. The current results suggested that tailor-made protocol is helpful to overcome individual differences in NF training efficacy.**

I. Introduction

In the previous academic year, we developed a noiseless vibrotactile stimulator for eliciting steady-state somatosensory evoked potentials in NF training and implemented a real-time estimation method of the individual attentional state. In this academic year, in order to demonstrate the usefulness of the NF training system, we evaluated neural activity change (i.e., neuromodulation) reflecting attention function improvement, and the effect of neuromodulation on motor function. Here, to achieve the improvement of the attention function, it is necessary to overcome the problem that NF training efficacy widely varies among individuals [1]. In this study, we focused on the individual differences in the ability to direct attention to body movements [2]-[4] as a factor that influence the NF training efficacy. By clarifying the relationship between individual differences in cognitive function and NF training efficacy, we try to propose a new training protocol that appropriately sets the goal of neural circuits to be re-constructed for each individual.

II. Aim of the Group

The present research aims to promote the reconstruction of an individual's neural circuit for attention control and facilitate the improvement of motor and cognitive functions through tailor-made NF training that shows the individual's estimated attention state in real-time. Furthermore, we aimed to identify the factor (i.e., explanatory variable) that determines the individual NF training efficacy, and to proposed a prediction model of NF training efficacy based on individual differences in the brain function characteristics. In this way, we try to individually realize the maximum improvement of brain function by a tailor-made protocol instead of a uniform protocol.

III. Research Topics

A. Individual differences in somatosensory responses in the proposed neurofeedback training

We used steady-state somatosensory evoked potentials (SSSEP) and steady-state visual evoked potentials (SSVEP) observed from the somatosensory and visual cortices to estimate individual attentional state during NF training. Here, we mainly report the findings regarding SSVEP responses.

We randomly assigned the participants to Real or Sham groups and the participants performed NF training seven days in total. Individuals in the Real group were received actual attentional state feedback based on their own SSSEP responses, and those in the Sham group were received dummy feedback based on the prerecorded SSSEP responses of another person, respectively. Electrodes for recording EEG were placed in the bilateral somatosensory area, and we measured SSSEP while presenting vibrotactile stimuli (Stimulus frequencies were 22Hz on left fingertips and 25Hz on right fingertips, respectively). For raw EEG data, we calculated frequency spectrum density by a fast Fourier transform applying to the buffered (5s) and filtered EEG signals. Then, the participant's attentional state (i.e., the strength of attention to vibrotactile stimuli) was quantified by calculating the signal-to-noise ratio of SSSEP. Speakers to present sounds reflecting the attentional state were placed in front of the participants, and the value of the signal-to-noise ratio of SSSEP was converted into the speaker volume. Note that, the strength of the attention to the left vibrotactile stimuli on the left hand was reflected as the volume of the left speaker, and that to the right hand was reflected as the volume of the right speaker, respectively. We required the participants to direct their attention to the left vibrotactile stimuli. In addition, the participants were also explained when the participants properly directed their attention to the left stimuli, the volume from the left speaker would be loud. If the proposed NF training system can improve the attention ability, it is expected that the SSSEP response in the right somatosensory area will be increased during the training process.

Figure 1 shows typical frequency spectrums in the bilateral somatosensory areas (Upper panels: left somatosensory area, Lower panels: right somatosensory area). The left, center, and right columns show an individual with higher attention ability to body movements (Real group), an individual with lower attention ability to body movements (Real group), and an individual in the Sham group, respectively. Large individual differences were observed in SSSEP response and its modulation. Specifically, in the individual with high attention ability, the 22Hz SSSEP response in the right somatosensory area was increased as expected. By contrast, in the left somatosensory area, decreased 25z SSSEP response was observed (Fig. 1a). On the other hand, the individual with low attention ability and that in the Sham group did not realize SSSEP modulation corresponding to the NF training purpose (Figs. 1bc). Based on the frequency spectrum shown in Fig. 1, Fig. 2 shows the changes in the signal-to-noise ratio of each individual.

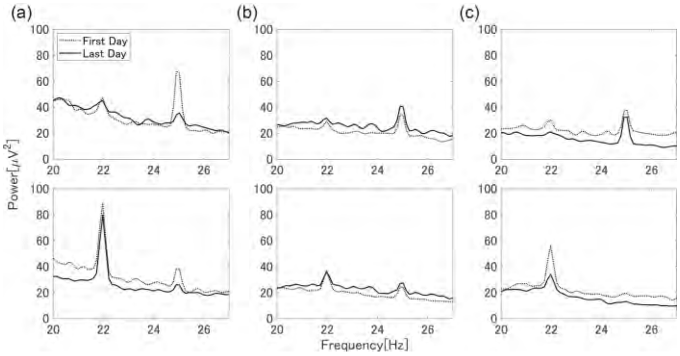

Fig. 1 Frequency spectrum of the SSSEP

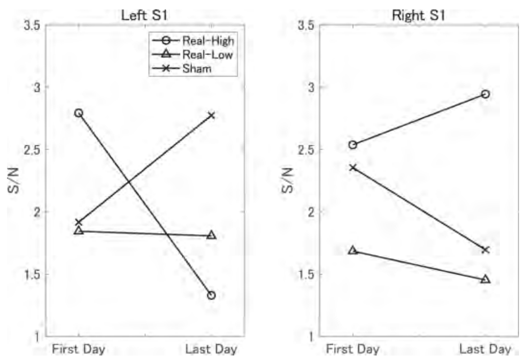

Fig. 2 Changes in SSSEP response in NF training

B. *NF training effect on motor function*

To evaluate the effect of improvement of attention ability by NF training on motor function, we prepared rhythmic and reciprocal reaching movement task before and after NF training. Participants held a digitizing pen on a drawing tablet with their right hand and were instructed to reciprocate the pen continuously on the longitudinal direction for 60s according to the sound presented at a constant rhythm (1Hz). Furthermore, they were also required to keep their movement amplitude constant. The participants performed the rhythmic reaching task with both the left and right hands, and the amplitude variability was evaluated for each hand. If the sensory sensitivity of the left hand is strengthened as the attention ability is improved by NF training, it is expected that the participants can easily maintain the movement amplitude, and as a result, the variability of movement amplitude becomes small (i.e., movement accuracy is improved).

Figure 3 shows the difference of movement amplitude variabilities evaluated before and after the NF training (after training minus before training). In the individual whose SSSEP response in the right somatosensory area was increased by NF training (individual corresponding to Fig. 1a), the amplitude variability reduced only in the left hand to be trained. On the other hand, for individuals who did not achieve the desired SSSEP responses (individuals corresponding to Figs. 1bc), no change in movement accuracy corresponding to the attention training to the left hand was observed.

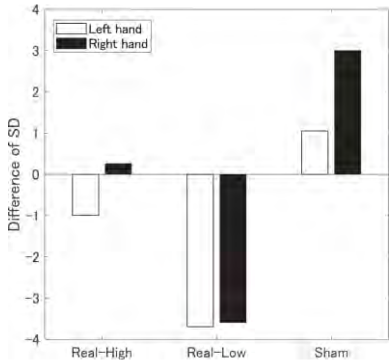

Fig. 3 Motor variability before and after NF training

IV. FUTURE PERSPECTIVE

In B05-9, we evaluated the SSSEP modulation in the somatosensory area associated with NF training and the effect of neuromodulation on motor function. As a result, we confirmed that individuals with higher attention ability to body movements were more likely to obtain the NF training efficacy. These findings indicate that the proposed NF training system may be useful for improving not only cognitive function but also motor function. Furthermore, we suggest the importance of a tailor-made training protocol that considers individual brain characteristics rather than traditional protocol with uniform training goals. However, we have not proposed a prediction model of NF training efficacy based on individual differences in brain function characteristics. In the future, we aim to propose a model for the purpose of maximizing the NF training efficacy by collecting further experimental data.

REFERENCES

[1] K.C. Kadosh, and G. Staunton, "A systematic review of the psychological factors that influence neurofeedback learning outcomes," NeuroImage, vol. 185, pp. 545-555, 2019.

[2] T. Sakurada, M. Hirai, and E. Watanabe, "Optimization of a motor learning attention directing strategy based on an individual's motor imagery ability," Experimental Brain Research, 234(1), pp.301-311, 2016.

[3] T. Sakurada, T. Nakajima, M. Morita, M. Hirai, E. Watanabe, "Improved motor peformance in patients with acute stroke using the optimal individual attentional strategy," Scientific Reports, Vol.7, 40592, 2017.

[4] T. Sakurada, M. Yoshida, and 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.

B05-10: Analysis of the effect of the successive illusory movement stimuli of the self-body for the adaptation ability

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***Abstract*— This study focuses on the optimal rehabilitation strategy for generating illusory visual stimuli in situations where the difference between the actual motion and the illusory-induced visual stimuli varies step by step over time. I discuss how to generate the illusory visual stimuli that have an intervention on proprioceptive sense, taking into account the learning effect on stimulus variability.**

I. INTRODUCTION

One of the problems in rehabilitation using visual stimuli that induce motion illusions (e.g., [1]) is that there are no clear criteria for judging how much difference should be incorporated into the images when creating illusion images that differ from reality. A significant induction effect can be expected if the difference is large, but it may adversely affect the sense of motion subjectivity and body possession. On the other hand, if the difference is slight, the sense of agency and body ownership are maintained, but the induction effect is not obtained.

In addition, it would be effective to dynamically vary the degree of difference in the illusory stimuli according to the situation, rather than just presenting the same degree of difference during the whole rehabilitation period. However, there is no specific adaptive model to determine the specific variation strategy.

II. AIM OF THE STUDY

This study focuses on the optimal strategy for generating illusory visual stimuli in a situation in which the difference between the actual motion and the illusion-induced visual stimuli is varied step by step over time.

This study aims to identify a suitable strategy for generating illusory visual stimuli that can maintain a large amount of intervention on the proprioceptive sense without adversely affecting the sense of agency and body ownership

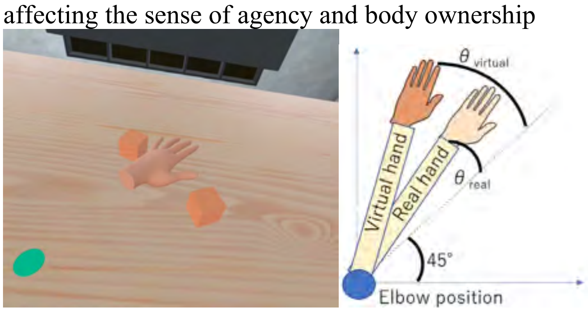

Fig.1: VR environment. The participants are asked to move their hand between two targets.

III. METHOD

As shown in Fig. 1, two targets are displayed on the desk in the VR environment. The participants are asked to slide the targets back and forth on the desk according to a metronome that sounds at 1 Hz. After 90 seconds, the screen goes dark to have a 20-second break. In the break time, participants are instructed to touch the target with their left hand, and the right hand is required to be placed symmetrically to the left hand.

Oculus Quest 2 is used as a device to present the VR environment. The position and the bending angle of fingers are measured, and the results are used to visualize the virtual hand of the left hand. The virtual hand of the left hand is displayed only during the left-right reciprocating motion, and the virtual hand is not shown during the 20-second break for measuring the proprioceptive sense. The virtual hand of the right hand is not displayed at all times. Here, during the left-right reciprocating motion, the actually measured forearm angle θ_{real} is exaggerated and adapted to the virtual hand angle θ_{virtual}, as shown in the right side of Figure 1.

The 90-second session is repeated 11 times. The exaggeration coefficients are varied for each session, as shown in Table 1. Two conditions were set up: Group A, in which the coefficients fluctuated from frequent to infrequent changes, and Group B, in which the coefficients changed from infrequent to frequent changes. At the end of 11 sessions, the subjects were asked to answer a questionnaire regarding the load on the VR experience based on VRNQ[2], the sense of agency, and the sense of body ownership.

Table 1: Exaggeration coefficiences through the experiment

session	1	2	3	4	5	6	7	8	9	10	11
GroupA	1.0	2.0	2.0	2.0	0.5	0.5	0.5	2.0	0.5	2.0	1.0
GroupB	1.0	2.0	0.5	2.0	0.5	2.0	0.5	2.0	2.0	2.0	1.0

IV. EVALUATION AND DISCUSSION

The following three parameters were used as indicators to express the subject's adaptive ability. 1) The drift of the proprioceptive sense of the left-hand position D(t) (the amount of drift between the target displayed in the VR and the actual position of the left hand.) 2) The drift of the proprioceptive sense of the right-hand position, D'(t) (the difference between the position of the target displayed for the left hand and the actual position of the right hand). 3) Adaptive inertia G(t) (cumulative difference between the position of the target and the position of the virtual hand at the moment the sound is played, i.e. at the moment when the target should be touched, during the first 5 seconds of each session.)

To exclude the learning effect that occurs throughout a session, I also considered the change in the exaggeration coefficient in each session, $C_{diff}(t)$, and the total amount of change in the exaggeration coefficient experienced up to that session, $C_{acc}(t)$. The relationship between $C_{diff}(t)$, the amount of drift change, $C_{diff}(t)$, and $C_{acc}(t)$ was investigated. Figure 2 shows the results for $D(t)$. Group A consisted of two subjects, and Group B consisted of three subjects.

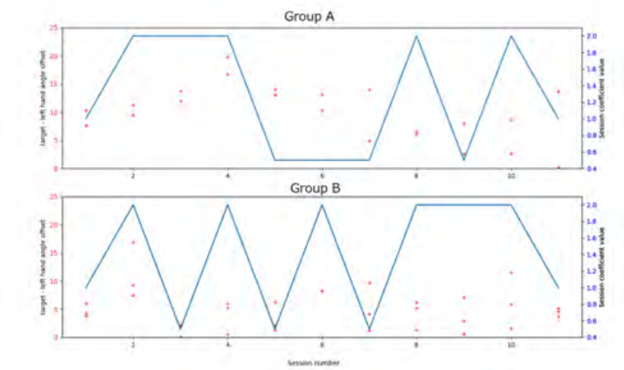

Fig. 2 : Drift of the proprioceptive sense for each session

$C_{diff}(t)$ and $C_{acc}(t)$ for groups A and B are as follows. If the coefficient changes from 0.5 to 2.0 from session t to t+1, it is interpreted as a two-step change, and $C_{diff}(t)$ is set to 2. If the coefficient changes from 1.0 to 0.5 or from 2.0 to 1.0, it is interpreted as a one-step change and $C_{diff}(t)$ is set to 1. $C_{acc}(t)$ is the accumulation of $C_{diff}(t)$ experienced up to time t.

Table 2: Change of the drift $D(t)$, change of the coefficience $C_{diff}(t)$, and accumulation of $C_{diff}(t)$, that is $C_{acc}(t)$

session	1	2	3	4	5	6	7	8	9	10
$D(t)$ A	2.19	2.46	5.41	4.67	1.95	3.12	4.76	2.9	0.43	3.71
$D(t)$ B	6.5	9.76	2.5	1.39	3.11	2.24	1.52	1.26	2.82	3.25
$C_{diff}(t)$A	1	0	0	2	0	0	2	2	2	1
$C_{acc}(t)$A	1	1	1	3	3	3	5	7	9	10
$C_{diff}(t)$B	1	2	2	2	2	2	2	0	0	1
$C_{acc}(t)$B	1	3	5	7	9	11	13	13	13	14

We can see that similar combinations of $C_{diff}(t)$ and $C_{acc}(t)$ values appear in the first and latter half of the session for Group A and Group B as shown by the gray area in Table 2. Therefore, by examining $D(t)$ at these two areas, we can cancel out the learning effect where the drift does not change with time and make a comparison. The following table shows the results of the average drift values of both groups A and B in the first half and the latter half.

In Group A, $D(t)$ for the first half decreased 3.94 degree to the latter half. In Group B, $D(t)$ for the first half decreased only 1.39 degrees to the latter half. The results suggest that the subjects in Group A were strongly affected on the proprioceptive sensation in the latter half of the session even learning effect is strong.

Although the small number of subjects does not allow for statistical discussion, the general trend suggests that Group A has a stronger ability to influence the amount of drift change, even when the learning effect is taken into account. In other words, starting from a situation in which the exaggeration coefficient fluctuates moderately, as in Group A, suggests that the degree of intervention on the proprioceptive sense is stronger than starting from a situation in which the exaggeration coefficient fluctuates violently, as in Group B. Although comparisons of individual differences must be made, when intervening with visual illusions using VR, it is suggested that the difference between the actual and the difference should be allowed to fluctuate gently and that presenting a large change in the difference will weaken the impact of the intervention.

Table 3: Drift of the proprioceptive sense at the first and latter half of the session

	First half (t: 3～5)	Latter half (t:7～9)
Group A	12.03	8.09
Group B	6.99	5.60

V. Future Perspective

Because of the delay in planning the subject experiments due to the COVID-19 disaster, only preliminary experimental results are reported in this document.

Thus, after increasing the number of subjects, I plan to conduct a comprehensive analysis that considers adaptive inertia, sense of agency and body ownership. I also plan to analyze the process of visual experience and the variation of adaptive capacity in VR.

References

[1] M. Okawada, F. Kaneko, K. Shindo, M. Yoneta, K. Sakai, K. Okuyama, K. Akaboshi, and M. Liu. "Kinesthetic Illusion Induced by Visual Stimulation Influences Sensorimotor Event-Related Desynchronization in Stroke Patients with Severe Upper-Limb Paralysis: A Pilot Study." Restorative Neurology and Neuroscience 38 (6): 455–65, 2021.

[2] P. Kurtesis, S. Collina, L. A. A. Doumas, and S. E. MacPherson. 2019. "Validation of the Virtual Reality Neuroscience Questionnaire: Maximum Duration of Immersive Virtual Reality Sessions Without the Presence of Pertinent Adverse Symptomatology." Frontiers in Human Neuroscience 13: 417.

B05-11. Developmental hyper-adaptability of sensorimotor dynamics under rapid growth

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***Abstract*— From early developmental phase, human infants exhibit complex and various spontaneous whole-body movements. It is often assumed that sensorimotor experiences evoked by such kinds of spontaneous movements have an essential role for development of sensorimotor coordination. In the same phase, they also exhibit acute physical growth, which would affect sensorimotor interactions. Although developmental changes of motor patterns have been well characterized, how a human infant develops their sensorimotor coordination in the midst of drastic changes remains unclear. Here, we conducted musculoskeletal dynamic simulation to understand how maximum muscle power and joint angle restriction affect to sensorimotor interaction during infantile spontaneous movement. Furthermore, we develop the soft skin and uterine model to simulate the physical interaction in twins.**

I. Introduction

It has been proposed that the mutual dynamics among brain-body-environment, induced by sensorimotor experience during early infancy, contributes to the development of human cognition and behavior in later life. While such a concept has been proposed for decades, it has not been concretely verified how sensory input and motor output are utilized for behavior acquisition in the early developmental stage, when the brain, body, and environment all show rapid and drastic changes.

In this project (B05-11), we aim to deepen the understanding of the mechanisms of developmental behavioral changes with rapid physical growth of the musculoskeletal body.

In FY2021, we conducted simulations of infantile spontaneous movement assuming for preterm infants with muscle weakness, hypertonia, and joint angle restriction to confirm the effects on the sensorimotor information structure. In addition, we developed the infant musculoskeletal model with soft tissues for the implementation of developmental simulation.

II. Aim of the Group

From early developmental phase, human infants exhibit complex and various spontaneous whole-body movements. It is often assumed that sensorimotor experiences evoked by such kinds of spontaneous movements have an essential role for maturation of sensorimotor modules. Although motor output patterns have been well characterized, whether and how a human infant acquires and augments these types of motor modules remains unclear. In addition, it is still unclear how neuronal disorders affects spontaneous movements and sensorimotor information structures in early development. In this project, we simulated the spontaneous movement using infantile musculoskeletal model and neural oscillators to make clear how muscle power and joint restriction affects sensorimotor information structures.

In this study, we investigate the developmental mechanism by combining measurements from experiments with actual infants and from physical dynamic simulations.

III. Research Topics

A. Sensorimotor information structure and neural disorder[1,2]

Infants with neuronal injury, preterm infants, and low-birth-weight infants sometimes have muscle weakness or joint angle restriction, which would affect sensorimotor experiences through early spontaneous movements. From preventive perspective, relaxations, passive joint movements, or stretches are provided in clinical care. However, it is unclear how such kinds of muscle abnormality and joint angle restriction during the early infancy affect the sensorimotor experience. Here, we examined the effects of muscle weakness and strengthening and joint angle restriction on sensorimotor information structure using musculoskeletal simulation.

First, we generated infantile whole-body spontaneous movements with neural oscillators applying α-motoneurons activities to each muscle of infantile musculoskeletal body model (gestational age: 32 weeks, number of skeletal muscles: 390, number of body parts: 21, number of joints: 20, number of degrees of freedom of joints: 36). Second, we examined the effect of increasing or decreasing the maximum muscle force for sensorimotor information structure. The standard muscle force (100%) was estimated based on the physiological cross-sectional area (6.3 kg/cm^2). The muscle force ratio was increased or decreased every 10% from 10% to 200% (Experiment (i)). Third, we examined the effect of joint angle restriction for sensorimotor information structure. The standard joint angle (100%) was defined based on the infant data. The joint angle was restricted every 2% from 0% to 40% (Experiment (ii)).

We calculated the correlation coefficients among muscle activities and proprioceptive inputs during spontaneous movement simulations for each of the conditions (Experiment

(i) and (ii)). Then, we estimated the number of coordinated muscle modules using an infinite relation model. Finally, we confirm how muscle power and joint restriction affects the number of coordinated muscle modules by approximated with cubic function.

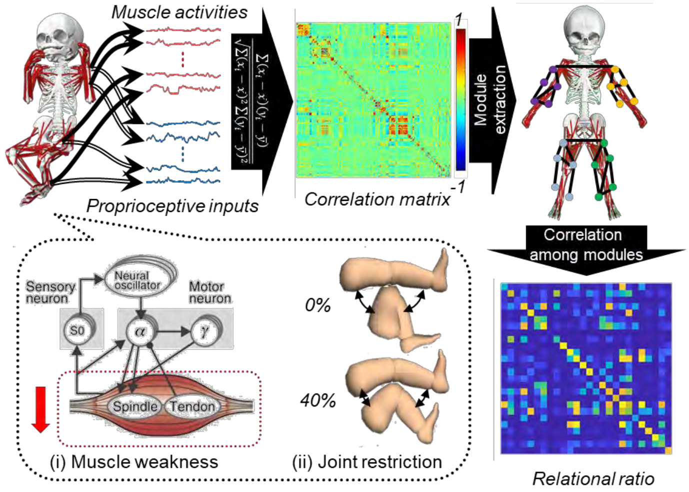

Fig. 1. Overview of module estimation in infantile spontaneous movement.

In experiment (i), we found that there are upward peaks of the number of coordinated muscle modules around 50% for both muscle activity and proprioceptive inputs (Fig. 2, top), indicating the existence of adequate muscle power to acquire the muscle modules. In experiment (ii), we found monotonic increase of the number of coordinated muscle modules for muscle activity, whereas upward peaks around 30% for proprioceptive inputs (Fig. 2, top), indicating the complex effects of joint restriction together with the adequate joint range.

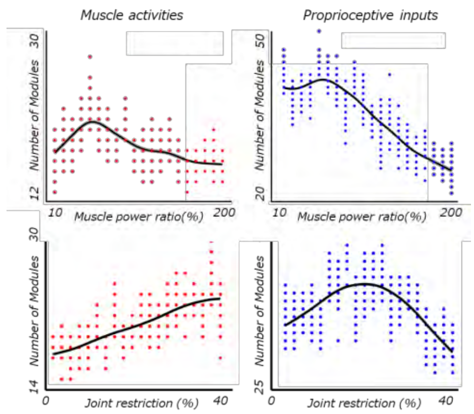

Fig. 2. Effect of muscle power (top) and joint restriction (bottom) on the number of coordinated muscle modules.

B. Development of the soft skin and uterine model[3]

The spontaneous movement simulations conducted in Section *A* employed a rigid skin model, which may not adequately reproduce the tactile sensory inputs of real fetuses and infants with soft skin. Therefore, we developed a flexible skin model and realistic 3D uterine model to simulate infantile sensorimotor interaction in a stretchy soft skin or uterine environment. Consequently, the implementation of the flexible skin model makes the tactile information received by the fetus more enrich, and realistic 3D uterine model enabled us to simulate interaction in twins (Fig. 2).

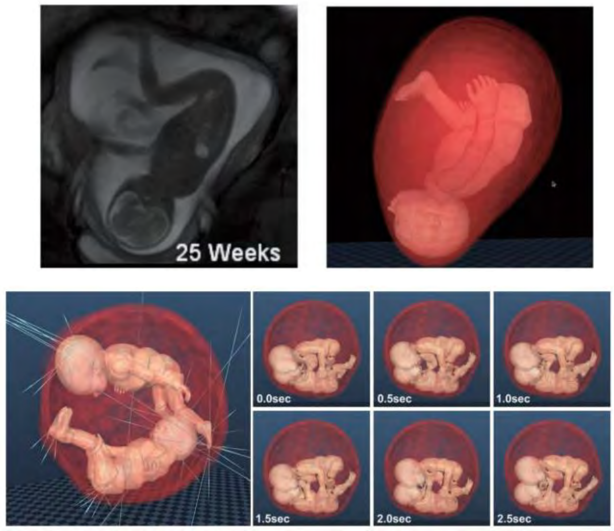

Fig. 3. Flexible uterus model (top) and twin model (bottom).

IV. Future Perspective

In FY2021, we simulated infantile spontaneous movements with muscle hypotonia and hypertonia and joint restriction and developed soft tissue in dynamic bodily simulation. In the future, we aim to investigate a learning model to explain the developmental changes of the sensorimotor information structure.

References

[1] H. Kanazawa, D. Kim, Y. Kuniyopshi, Joint restriction affects to sensorimotor exeperiences during infantile spontaneous movements in musculoskeltal simulation study, in 8th Annual conference of Japanese Society of Pediatric Physical Therapy, Nov 2021 (in Japanese)

[2] H. Kanazawa, D. Kim, Y. Kuniyopshi, Muscle power affects to sensorimotor exeperiences during infantile spontaneous movements in musculoskeltal simulation study, in 8th Annual conference of Japanese Society of Pediatric Physical Therapy, Oct 2021 (in Japanese)

[3] Y. Yauso, H. Kanazawa, D. Kim, Human fetus simulation in Constructive Developmental Science, in 9th Society for New Fetal Medicine and Science, Nov 2021 (in Japanese)

List of Publications (2021)

Journal Papers

1. Dongdong Li, Kohei Kaminishi, Ryosuke Chiba, Kaoru Takakusaki, Masahiko Mukaino, Jun Ota, Evaluating quiet standing posture of post-stroke patients by classifying cerebral infarction and cerebral hemorrhage patients, Advanced Robotics, 35(1):1-11, 2021
2. Lin Chingszu, Ogata Taiki, Zhong Zhihang, Kanai-Pak Masako, Maeda Jukai, Kitajima Yasuko, Nakamura Mitsuhiro, Kuwahara Noriaki, & Ota Jun, Development of robot patient lower limbs to reproduce the sit-to-stand movement with correct and incorrect applications of transfer skills by nurses, Applied Sciences, 11(6), 2872, 2021
3. Nagasaka K, Nemolo K, Takashima I, Bando D, Matsuda K, Higo N, Structural plastic changes of cortical gray matter revealed by voxel-based morphometry and histological analyses in a monkey model of central post-stroke pain, Cereb Cortex, 31(10):4439-4449, 2021
4. H Kambara, H Ogawa, A Takagi, D Shin, N Yoshimura, Y Koike, Modulation of wrist stiffness caused by adaptation to stochastic environment, Advanced Robotics, 35(29):1-17, 2021
5. H Kambara, A Takagi, H Shimizu, T Kawase, N Yoshimura, Y Koike, Computational reproductions of external force field adaption without assuming desired trajectories, Neural Networks, 139, 179-198, 2021
6. Nishimura K, Saracbasi OO, Hayashi Y, Kondo T, Cooperative Visuomotor Learning Experience with Peer Enhances Adaptability to Others, Advanced Robotics, 35(13-14):1-7, 2021
7. Hiroki Kogami, Qi An, Ningjia Yang, Ruoxi Wang, Kazunori Yoshida, Hiroyuki Hamada, Hiroshi Yamakawa, Yusuke Tamura, Shingo Shimoda, Hiroshi Yamasaki, Moeka Sonoo, Fady Alnajjar, Noriaki Hattori, Koji Takahashi, Takanori Fujii, Hironori Otomune, Ichiro Miyai, Atsushi Yamashita, and Hajime Asama, Analysis of muscle synergy and kinematics in sit-to-stand motion of hemiplegic patients in subacute period, Advanced Robotics, 35(5):1-11, 2021
8. Kazunori Yoshida, Qi An, Hiroyuki Hamada, Hiroshi Yamakawa, Yusuke Tamura, Atsushi Yamashita, and Hajime Asama, Artificial Neural Network that Modifies Muscle Activity in Sit-to-Stand Motion Using Sensory Input, Advanced Robotics, 35(13-14):858-866, 2021
9. Amemiya K, Naito E, Takemura H, Age dependency and lateralization in the three branches of the human superior longitudinal fasciculus, Cortex, 139, 116-133, 2021

10. Oku H, Ide N, Ogihara N, Forward dynamic simulation of Japanese macaque bipedal locomotion demonstrates better energetic economy in a virtualised plantigrade posture, Communications Biology, 4(1):308, 2021

11. T Inoue, SI Terada, M Matsuzaki, J Izawa, A small-scale robotic manipulandum for motor control study with rodents, Advanced Robotics, 35(13-14):898-906, 2021

12. K Tanamachi, J Izawa, S Yamamoto, D Ishii, A Yozu, Y Kohno, Experience of after-effect of memory update reduces sensitivity to errors during sensory-motor adaptation task, Frontiers in Human Neuroscience, 15, 2021

13. Mads Lund Pedersen, Maria Ironside, Ken-Ichi Amemori, Callie M. McGrath, Min Su Kang, Ann M. Graybiel, Diego A. Pizzagalli, Michael J. Frank, Computational phenotyping of brain-behavior dynamics underlying approach-avoidance conflict in major depressive disorder, PLOS Computational Biology, 17(5), 2021

14. Helen N. Schwerdt, Dan J. Gibson, Kenichi Amemori, Lauren L. Stanwicks, Tomoko Yoshida, Michael J. Cima, Ann M. Graybiel, Chronic multi-modal monitoring of neural activity in rodents and primates, Proc. SPIE, Integrated Sensors for Biological and Neural Sensing, 2021

15. Zhihang Zhong, Chingszu Lin, Masako Kanai-Pak, Jukai Maeda, Yasuko Kitajima, Mitsuhiro Nakamura, Noriaki Kuwahara, Taiki Ogata, and Jun Ota, Multistream Temporal Convolutional Network for Correct/Incorrect Patient Transfer Action Detection Using Body Sensor Network, IEEE Internet of Things Journal, PP(99):1-1, 2021

16. Maruyama M, Yozu A, Okamoto Y, & Shiraki H, Relationship between total weight-bearing response of the navicular and talus bones and weight-bearing response of hindfoot valgus in normal foot arch, The Journal of Physical Fitness and Sports Medicine, 10(2), 75-84, 2021

17. Yozu A, Kaminishi K, Ishii D, Omura Y, Matsushita A, Kohno Y, Chiba R, Ota J, Effects of medication and dual tasking on postural sway in Parkinson’s disease: A pilot case study, Advanced Robotics, 35(13-14):889-897, 2021

18. Yamashita A, Sakai Y, Yamada T,Yahata N, Kunimatsu A, Okada N, Itahashi T, Hashimoto R, Mizuta H, Ichikawa N, Takamura M, Okada G, Yamagata H, Harada K, Matsuo K, Tanaka SC, Kawato M, Kasai K, Kato N, Takahashi H, Okamoto Y, Yamashita O, and Imamizu H, Common brain networks between major depressive-disorder diagnosis and symptoms of depression that are validated for independent cohorts, Frontiers in Psychiatry, 12, e667881, 2021

19. Dongting Tian, Shin-Ichi Izumi, Eizaburo Suzuki, Modulation of Interhemispheric Inhibition between Primary Motor Cortices Induced by Manual Motor Imitation: A Transcranial Magnetic Stimulation Study, Brain sciences , 11(2): 266-285, 2021

20. Naoko Sakabe, Samirah Altukhaim, Yoshikatsu Hayashi, Takeshi Sakurada, Shiro Yano, and Toshiyuki Kondo, Enhanced Visual Feedback Using Immersive VR Affects Decision Making regarding Hand Use with a Simulated Impaired limb, Frontiers in Human Neuroscience, 15, 677578, 2020

21. Soma S, Suematsu N, Sato A, Tsunoda K, Bramian A, Reddy A, Takabatake K, Karube F, Fujiyama F, Shimegi S, Acetylcholine from the nucleus basalis magnocellularis facilitates the retrieval of well-established memory, Neurobiology of Learning and Memory, 183, 107484, 2021

22. Ishii D, Ishibashi K, Yuine H, Takeda K, Yamamoto S, Kaku Y, Yozu A, Kohno Y, Contralateral and Ipsilateral Interactions in the Somatosensory Pathway in Healthy Humans, Frontiers in Systems Neuroscience, 15, 698758, 2021

23. Zhu M, Kasaragod DK, Kikutani K, Taguchi K, Aizawa H, A novel microcontroller-based system for the wheel-running activity in mice, eNeuro, 8(6), 0260-21, 2021

24. Megumi Miyashita, Toshiyuki Kondo, Shiro Yano, Reinforcement learning with constraint based on mirror descent algorithm, Results in Control and Optimization, 4, 100048, 2021

25. Ishii D, Ishibashi K, Takeda K, Yuine H, Yamamoto S, Kaku Y, Yozu A, Kohno Y, Interaction of the Left–Right Somatosensory Pathways in Patients With Thalamic Hemorrhage: A Case Report, Frontiers in Human Neuroscience, 15, 1 761186, 2021

26. Nakayashiki K, Tojiki H, Hayashi Y, Yano S and Kondo T, Brain Processes Involved in Motor Planning Are a Dominant Factor for Inducing Event-Related Desynchronization, Frontiers in Human Neuroscience, 15, 764281, 2021

27. Zhong Zhihang, Lin Chingszu, Kanai-Pak Masako, Maeda Jukai, Kitajima Yasuko, Nakamura Mitsuhiro, Kuwahara Noriaki, Ogata Taiki, & Ota Jun, Multistream temporal convolutional network for correct/incorrect patient transfer action detection using body sensor network, IEEE Internet of Things Journal, 8, 23, 2021

28. Tetsuro Funato, Yota Sato, Yamato Sato, Soichiro Fujiki, Shinya Aoi, Kazuo Tsuchiya, Dai Yanagihara, Quantitative evaluation of posture control in rats with inferior olive lesions, Scientific Reports, 11, 20362, 2021

29. Akira Konosu, Tetsuro Funato, Yuma Matsuki, Akihiro Fujita, Ryutaro Sakai, Dai Yanagihara, A model of predictive postural control against floor tilting in rats, Frontiers in Systems Neuroscience, 15(141), 2021

30. Saracbasi OO, Harwin W, Kondo T and Hayashi Y, Mutual Skill Learning and Adaptability to Others via Haptic Interaction, Frontiers in Neurorobotics, 15, 760132, 2021

31. Terai H, Gwedela MNV, Kawakami K, Aizawa H, Electrophysiological and pharmacological characterization of spreading depolarization in the adult zebrafish tectum, J Neurophysiol, 126(6), 1934-1942, 2021

32. Gwedela MNV, Terai H, Lampiao F, Matsunami K, Aizawa H, Anti-seizure effects of medicinal plants in Malawi on pentylenetetrazole-induced seizures in zebrafish larvae, J Ethnopharmacol, 284, 114763, 2021

33. Li D, Kaminishi K, Chiba R, Takakusaki K, Mukaino M, & Ota J, Evaluation of postural sway in post-stroke patients by dynamic time warping clustering, Frontiers in Human Neuroscience, 15, 731677, 2021

34. LR Dal'Bello, J Izawa, Task-relevant and task-irrelevant variability causally shape error-based motor learning, Neural Networks, 583-596, 2021

35. R Ishikawa, S Ayabe-Kanamaru, J Izawa, The Role of Motor Memory Dynamics in Structuring Bodily Self-Consciousness, iScience, 103511, 2021

36. Masahiro Hirai, Takeshi Sakurada, Jun Izawa, Takahiro Ikeda, Yukifumi Monden, Hideo Shimoizumi, Takanori Yamagata, Greater reliance on proprioceptive information during a reaching task with perspective manipulation among children with autism spectrum disorders, Scientific Reports, 11(1), 2021

37. Ueta Yoshifumi, Miyata Mariko, Electrophysiological and anatomical characterization of synaptic remodeling in the mouse whisker thalamus, STAR Protocols, 2(3), 100743-100743, 2021

38. Osaki Hironobu †, Kanaya Moeko, Ueta Yoshifumi, Miyata Mariko, Distinct nociresponsive region in mouse primary somatosensory cortex, bioRxiv, 2021

39. Saito T, Ogihara N, Takei T, Seki K, Musculoskeletal modeling and inverse dynamic analysis of precision grip in the Japanese macaque, Frontiers in Systems Neuroscience, 15, 774596, 2021

40. T Sugiyama, K Kutsuzawa, D Owaki, M Hayashibe, Individual Deformability Compensation of Soft Hydraulic Actuators through Iterative Learning-Based Neural Network, Bioinspiration & Biomimetics, 16, 56016, 2021

41. K. Naya, K. Kutsuzawa, D. Owaki, M. Hayashibe, Spiking Neural Network Discovers Energy-Efficient Hexapod Motion in Deep Reinforcement Learning, IEEE Access, 9, 150345 - 150354, 2021

42. Wen W, Ishii H, Ohata R, Yamashita A, Asama H, & Imamizu H, Perception and control: Individual difference in the sense of agency is associated with learnability in sensorimotor adaptation, Scientific Reports, 11, 20542, 2021

43. Nakamura A, Suzuki Y, Milosevic M, Nomura T, Long-Lasting Event-Related Beta Synchronizations of Electroencephalographic Activity in Response to Support-Surface Perturbations During Upright Stance: A Pilot Study Associating Beta Rebound and Active Monitoring in the Intermittent Postural Control, Frontiers in Systems Neuroscience, 15, 660434, 2021

44. Qi An, Ningjia Yang, Hiroshi Yamakawa, Hiroki Kogami, Kazunori Yoshida, Ruoxi Wang, Atsushi Yamashita, Hajime Asama, Shu Ishiguro, Shingo Shimoda, Hiroshi Yamasaki, Moeka Yokoyama, Fady Alnajjar, Noriaki Hattori, Kouji Takahashi, Takanori Fujii, Hironori Otomune, Ichiro Miyai, and Ryo Kurazume, Classification of Motor Impairments of Post-stroke Patients based on Force Applied to a Handrail, IEEE Transactions on Neural Systems and Rehabilitation Engineering, 29, 2399-2406, 2021

45. Kasai M, Isa T, Effects of light isoflurane anesthesia on organization of direction and orientation selectivity in the superficial layer of the mouse superior colliculus, Journal of Neuroscience, JN-RM-1196-21, 2021

46. Kato R, Zeghbib A, Redgrave P, Isa T, E Visual instrumental learning in blindsight monkeys, Scientific Reports, 11, 14819, 2021

47. Isa T, Yoshida M, Neural mechanism of blindsight in a macaque model, Neuroscience, (Forefront review), 469, 138-161, 2021

48. Isa T, Marquez-Legorreta E, Grillner S, Scott EK, The tectum/superior colliculus as the vertebrate solution for spatial sensory integration and action, Current Biology (review), 31(11), PR741-R762, 2021

49. Y Li, B Chen, N Yoshimura, Y Koike, Restricted Minimum Error Entropy Criterion for Robust Classification, IEEE TRANSACTIONS ON NEURAL NETWORKS AND LEARNING SYSTEMS, 9, 150345 – 150354, 2021

50. Z Qin, S Stapornchaisit, Z He, N Yoshimura, Y Koike, Multi–Joint Angles Estimation of Forearm Motion Using a Regression Model, frontiers in Neurorobotics, 15, 685961, 2021

51. Naito E, Morita T, Kimura N, and Asada M, Existence of interhemispheric inhibition between foot sections of human primary motor cortices: Evidence from negative blood oxygenation-level dependent signal, Brain Sciences, 11, 1099, 2021

52. Naito E, Morita T, Hirose S, Kimura N, Okamoto H, Kamimukai C and Asada M, Bimanual digit training improves right hand dexterity in older adults by reactivating declined ipsilateral motor-cortical inhibition, Scientific Reports, 11, 2021

53. Furuta T, Yamauchi K,OkamotoS, Takahashi M, Kakuta S, Ishida Y, Takenaka A, Yoshida A, Uchiyama Y, Koike M, Isa K, Isa T, Hioki H, Multi-scale light microscopy/electron microscopy neuronal imaging from brain to synapse with a tissue clearing method, Sca l eSF, iScience, 25(1), 103601, 2021

54. Yoshida T, Otaka Y, Osu R, Kumagai M, Kitamura S, & Yaeda J, T Motivation for Rehabilitation in Patients With Subacute Stroke: A Qualitative Study, Frontiers in Rehabilitation Sciences, 2, 2021

55. Kusano T, Kurashige H, Nambu I, Moriguchi Y, Hanakawa T, Wada Y, & Osu R, Wrist and finger motor representations embedded in the cerebral and cerebellar resting-state activation, Brain Struct Funct, 226(7), 2307-2319, 2021

56. Kita K, Furuya S, Osu R, Sakamoto T, & Hanakawa T, Aberrant Cerebello-Cortical Connectivity in Pianists With Focal Task-Specific Dystonia, Cereb Cortex, 31(10), 4853–4863, 2021

57. Ikegami T, Ganesh G, Gibo T L, Yoshioka T, Osu R, & Kawato M, Hierarchical motor adaptations negotiate failures during force field learning, PLoS Comput Biol, 17(4), e1008481, 2021

58. Hirayama K, Koga T, Takahashi,T, & Osu R, Transcranial direct current stimulation of the posterior parietal cortex biases human hand choice, Sci Rep, 11(1), 204, 2021

59. T Ohta Y, Guinto MC, Tokuda T, Kawahara M, Haruta M, Takehara H, Tashiro H, Sasagawa K, Onoe H, Yamaguchi R, Koshimizu Y, Isa K, Isa T, Kobayashi K, Akay YM, Akey M, Ohta J, Micro-LED Array-Based Photo-Stimulation Devices for Optogenetics in Rat and Macaque Monkey Brains, IEEE, 9, 127937, 2021

60. Cheung VCK, Seki K, Approaches to Revealing the Neural Basis of Muscle Synergies: A Review and A Critique, Journal of Neurophysiology, 17, 2021

61. Shimizu T, Murakoshi H, Matsumoto H, Ichino K, Hattori A, Ueno S, Ishida A, Tajiri N, Hida H., Tension sensor based on fluorescence resonance energy transfer reveals diameter-dependent mechanical fasctors during myelination, Frontiers Cell Neurosci, 15, 685044, 2021

62. Rogers T, Cox C, Lu Q, Shimotake A, Kikuch T, Kunieda T, Miyamoto S, Takahashi R, Ikeda A, Matsumoto R, Lambon-Ralph M, Evidence for a deep, distributed and dynamic code for animacy in human ventral anterior temporal cortex, eLife, 10, e66596, 2021

63. Yamao Y, Matsumoto R (CA), Kunieda T, Nakae T, Nishida S, Inano R, Shibata S, Kikuchi T, Arakawa Y, Yoshida K, Ikeda A, Miyamoto S., Supervised learning of mapping from sensor space to chained form for unknown non-holonomic driftless systems, Clin Neurophysiol, 132, 1919-1926, 2021

64. Sato N, Matsumoto R, Shimotake A, Matsuhashi M, Otani M, Kikuchi T, Kunieda T, Mizuhara H, Miyamoto S, Takahashi T, Ikeda A, Frequency-dependent cortical interactions during semantic processing: an electrocorticogram cross-spectrum analysis using a semantic space model, Cereb Cortex, 31, 4329-4339, 2021

65. Kobayashi K, Matsumoto R (CA), Usami K, Matsuhashi M, Shimotake A, Kikuchi T, Yoshida K, Kunieda T, Miyamoto S, Takahashi R, Ikeda A, Cortico-cortical evoked potential by single-pulse electrical stimulation is a generally safe procedure, Clin Neurophysiol, 132, 1033-1040, 2021

66. Yamao Y, Matsumoto R, Kikuchi T, Yoshida K, Kunieda T, Miyamoto S, Intraoperative brain mapping by cortico-cortical evoked potential, Front Hum Neurosci, 15(55), 2021

67. Ishioh M, Nozu T, Igarashi S, Tanabe H, Kumei S, Ohhira M, Takakusaki K, Okumura T, Activation of central adenosine A2B receptors mediate brain ghrelin-induced improvement of intestinal barrier function through the vagus nerve in rats, Exp Neurol, 341, 113708, 2021

68. Nozu T, Miyagishi S, Ishioh M, Takakusaki K, Okumura T, Phlorizin attenuates visceral hypersensitivity and colonic hyperpermeability in a rat model of irritable bowel syndrome, Biomed Pharmacother, 139, 111649, 2021

69. Nozu T, Miyagishi S, Nozu R, Ishioh M, Takakusaki K, Okumura T, EMA401, an angiotensin II type 2 receptor antagonist blocks visceral hypersensitivity and colonic hyperpermeability in rat model of irritable bowel syndrome, J Pharmacol Sci, 146(3), 121-124, 2021

70. Kaminishi K, Chiba R, Takakusaki K, Ota J, Increase in muscle tone promotes the use of ankle strategies during perturbed stance, Gait Posture, 90, 67-72, 2021

71. Li D, Kaminishi K, Chiba R, Takakusaki K, Mukaino M, Ota J, Evaluation of Postural Sway in Post-stroke Patients by Dynamic Time Warping Clustering, Front Hum Neurosci, 15, 731677, 2021

72. Sato Y, Kondo T, Shinozaki M, Shibata R, Nagoshi N, Ushiba J, Nakamura M, Okano H, Markerless analysis of hindlimb kinematics in spinal cord-injured mice through deep learning, Neurosci Res, 176, 49-56, 2021

73. Sato Y, Kondo T, Shibata R, Nakamura M, Okano H, Ushiba J, Functional reorganization of locomotor kinematic synergies reflects the neuropathology in a mouse model of spinal cord injury, in press, 2021

74. Takai A, Lisi G, Noda T, Teramae T, Imamizu H, and Morimoto J, Bayesian Estimation of Potential Performance Improvement Elicited by Robot-Guided Training, Frontiers in Neuroscience, e704402, 2021

75. Kazuhiro Sakamoto, Hidetake Okuzaki, Akinori Sato, Hajime Mushiake, Experience resetting in reinforcement learning facilitates exploration-exploitation transitions during a behavioral task for primates, bioRxiv, 462676, 2021

76. Morita T, Asada M, Naito E, Grey matter expansion of social brain networks in individuals high in public self-consciousness, Brain Sciences, 3, 374, 2021

77. 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, 2021

78. Higo N, Nonhuman primate models to explore the adaptive mechanisms after stroke, Frontiers in Systems Neuroscience, 15, 760311, 2021

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

80. 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

81. 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

82. 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

83. 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, in press, 2022

84. 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, 2022

85. 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, 2022

86. 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, 2022

87. 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, 2022

88. 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, 2022

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

90. Wen W. & Imamizu H, The role of the sense of agency in human perception, behavior, and human-machine interactions, Nature Reviews Psycholo, 1, 2022

91. 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, accepted, 2022

92. 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

93. 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

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

95. 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, 2022

96. 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, 2022

97. 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, accepted, 2022

98. Yamao Y, Matsumoto R, Intraoperative cortico-cortical evoked potential recording for monitoring the arcuate fasciculus; Feasible under general anesthesia?, Clin Neurophysiol, 133, 175-176, 2022

99. 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

100. 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

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

102. Obara K, Chiba R, Takahashi K, Matsuno T, Takakusaki K, Kee dynamics of the take-off and landing of the spike jump in volleyball players with patellar tendinopathy, J Phys Ther Sci, in press, 2022

103. Takakusaki K, Abnormality in neurotransmitters in Synucleinopathy and behavioral alteration in relation to awake-sleep states, Clin Neurphysiol, in press, 2022

104. Takakusaki K, Mirai T, Noguchi T, Chiba R, Neurophysiological mechanisms of gait disturbance in advanced Parkinson's disease, Neurology and Clinical Neuroscience, in press, 2022

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

International Conference

1. Imamizu, H. and Tsutsui, K, Neuroscientific approach to body cognition and emotion that induce "hyper-adaptability", The 1st International Symposium on Hype-Adaptability (HypAd2021), Online, 2021
2. Ohata R, Asai T, Imaizumi S, and Imamizu H, My voice therefore I spoke: Sense of agency over speech enhanced in hearing self-voice, The 1st International Symposium on Hype-Adaptability (HypAd2021), Online, 2021
3. Ohata R, Asai T, Imaizumi S, and Imamizu H, My voice therefore I spoke: Sense of agency over speech enhanced in hearing self-voice, The 2021 APS (Association for Psychological Science) Virtual Conference, Online, USA, 2021
4. Ota Jun, Science of hyper-adaptability: An Overview, Scientific Lectures in South China University of Technology, Online, China, 2021
5. K Kaminishi, Understanding the role of neurotransmitters in human postural control using a neuromusculoskeletal model, 32nd 2021 International Symposium on Micro-NanoMechatronics and Human Science, Online, 2021
6. Ota Jun, Hyper-adaptability for overcoming body-brain dysfunction and development of a new rehabilitation device, Workshop program KSU (King Saud University) & U Tokyo, Online, 2021
7. J Chai, M Hayashibe, Quantification of Joint Redundancy considering Dynamic Feasibility using Deep Reinforcement Learning, IEEE Int. Conf. on Robotics and Automation (ICRA2021), Online, 2021
8. L Guanda, J Shintake, M Hayashibe, Deep Reinforcement Learning Framework for Underwater Locomotion of Soft Robot, IEEE Int. Conf. on Robotics and Automation (ICRA2021), Online, 2021
9. J Chai, D Owaki, M Deep Reinforcement Learning with Gait Mode Specification for Quadrupedal Trot-Gallop Energetic Analysis, 43rd Annual International Conferences of the IEEE Engineering in Medicine and Biology Society (EMBC2021), Online, 2021
10. M Hayashibe, Motor Synergy Emergence in Redundancy through Deep Reinforcement Learning, 32nd 2021 International Symposium on Micro-NanoMechatronics and Human Science, Online, Japan, 2021
11. Isa T, Functional recovery after brain and spinal cord injuiries, JANUBET Primate Neurobiology School, Online, Japan, 2021
12. Isa T, How the brain works for recovery from spinal cord injury, Mongolian Neuroscience Society Meeting, Online, Mongol, 2021

13. Isa T, Neural circuit mechanism of functional recovery after brain and spinal cord injury, S.Hagiwara Memorial Lecture, Online, 2021

14. Naito E, Hyper-adaptation in a para-athlete, Hyper-adaptation in the brain The Symposium on 44th Annual Meeting of the Japan Neuroscience Society, Kobe, 2021

15. K Saitoh, I Nambu, Y Wada, The Effect of the Coefficient of Viscosity on the Reaching Movement in Virtual Space Using VR, Online, 2021

16. K Saitoh, I Nambu, Y. Wada, The Effect of the Rotary Inertia on the Reaching Movement in Virtual Space Using VR, 43rd Annual International Conferences of the IEEE Engineering in Medicine and Biology Society (EMBC2021), Online, 2021

17. D Nishiura, . Nambu, Y Maruyama, Y Wada, Improvement of human error prediction accuracy in single-trial analysis of electroencephalogram, 43rd Annual International Conferences of the IEEE Engineering in Medicine and Biology Society (EMBC2021), Online, 2021

18. M Yasuhara, I Nambu, Y Maruyama, Y. Wada, Decoding Individual Finger Movements from Single Trial EEG of Motor Execution and Imagery Using CNN, 43rd Annual International Conferences of the IEEE Engineering in Medicine and Biology Society (EMBC2021), Online, 2021

19. Seki K, Sensory gain modulation at the primate cuneate nucleus; top-down and bottom-up neural mechanisms, NCM2021, Online, 2021

20. Seki K, Elucidation of neural mechanisms of hyper-adaptabilityto body change, 1st International Symposium on Hyper-Adaptability, Online, 2021

21. Masaya Togo, Riki Matsumoto, Takuro Nakae, Katsuya Kobayashi, Kiyohide Usami, Akihiro Shimotake, Takayuki Kikuchi, Kazumichi Yoshida, Masao Matsuhashi, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda, Modification of effective connectivity strength in interareal cortical networks from the seizure onset zone: a cortico-cortical evoked potential study, 13th AOEC, Online, 2021

22. H Etoh, Y Omura, K Kaminishi, R Chiba, K Takakusaki, and J Ota, Proposal of a Neuromusculoskeletal Model Considering Muscle Tone in Human Gait, 2021 IEEE International Conference on Systems, Man, and Cybernetics (SMC), Online, Australia, 2021

23. S Nakamura and Y Kobayashi, A Grid-Based Estimation of Transformation of Partial Dynamics using Genetic Algorithm for Motor Learning, The 32nd 2021 International Symposium on Micro-NanoMechatronics and Human Science, Online, 2021

24. Isa T, Dynamics of global brain networks for recovery from spinal cord injury, The 7th CiNet Conference: New horizons in brain mapping, Online, 2022

25. Isa T, Induction of large-scaled adult brain plasticity for neuronal repair, The 25th Thai Neuroscience Society Conference 2022 (TNS25), Online, Thailand, 2022

Member List

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

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

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

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Funded co-investigator	Minoru Asada (Specially Appointed Professor, Osaka University)
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Co-investigator	Yasuharu Hirai (Assistant Professor, Doshisya University)
Co-investigator	Fuko Kadono (Graduate Student, Hokkaido University)

Research Project A02: Elucidation of neural mechanisms of super-adaptation to body change

Principal investigator	Kazuhiko Seki (Director, NCNP)
Co-investigator	Tomomichi Oya (Section Chief, NCNP)
Co-investigator	Roland Phillipp (Postdoctoral Fellow, NCNP)
Co-investigator	Amit Yaron (Postdoctoral Fellow, NCNP)
Co-investigator	Shinji Kubota (Postdoctoral Fellow, NCNP)
Co-investigator	Akito Kosugi (Postdoctoral Fellow, NCNP)
Co-investigator	Satomi Kikuta (Postdoctoral Fellow, NCNP)
Co-investigator	Yuki Hara (Lecturer, University of Tsukuba)
Co-investigator	Shiro Egawa (Special Postdoctoral Researcher, RIKEN)

Research Project A03: Mechanisms of body cognition and emotion inducing hyper-adaptability

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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)
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Co-investigator Tomohiro Noguchi (Lecturer, Asahikawa Medical University)
Co-investigator Toshi Nakajima (Assistant Professor, 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)
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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 Hiroki Togo (Postdoctoral fellow, NCNP)
Co-investigator Toma Matsushima (Undergraduate Student (Research Student), Tokyo University of Agriculture and Technology (NCNP))

Research Project A05-01: Elucidation of the hyper-adaptation mechanism of 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/Occupational therapist, Tohoku University)
Co-investigator Tamami Sudo (Researcher (Part-time Lecturer), Oouchi Hospital(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 A05-03: Mechanism of Hyper-Adaptivity of the human premotor area: electrophysiological connectome analysis with electrocorticogram

Principal investigator Riki Matsumoto (Professor, Kobe University)
Co-investigator Akihiro Shimotake (Assistant Professor, Kyoto University)
Co-investigator Takayuki Kikuchi (Assistant Professor, Kyoto University)
Co-investigator Kiyohide Usami (Assistant Professor, Kyoto University)
Co-investigator Hirofumi Takeyama (Assistant Professor, Kyoto University)
Co-investigator Masaya Togo (Assistant Professor, Kobe University)
Co-investigator Kozue Hayashi (Graduate Student, Kyoto University)
Co-investigator Kento Matoba (Graduate Student, Kobe University)

Research Project A05-05: Development of non-invasive brain stimulation techniques that can increase recruitment of the corticospinal motor indirect pathway during acquisition of hand motor skills.

Principal investigator Mitsunari Abe (Director, IBIC)
Co-investigator Kazumasa Uehara (Assistant Professor, NIPS)

Research Project A05-06: Analysis of motor control system in the recovery of forelimb function by rehabilitation after intracerebral hemorrhage

Principal investigator Hideki Hida (Professor, Nagoya City University)
Co-investigator Naoki Tajiri (Associate Professor, Nagoya City University)
Co-investigator Takeshi Shimizu (Lecturer, Nagoya City University)
Co-investigator Kenta Kobayashi (Associate Professor, NIPS)
Co-investigator Shinya Ueno (Assistant Professor, Nagoya City University)

Research Project A05-07: Regulatory mechanisms of inter-regional network changes underlying hyper-adaptation from mal-adaptation state caused by fear memory.

Principal investigator Hiroyuki Miyawaki (Assistant Professor, Osaka City University)

Research Project A05-08: Facilitating hyper-adaptation in neurological and psychiatric diseases thorough improving precision on the sense of agency

Principal investigator Takaki Maeda (Assistant Professor/Senior Assistant Professor, Keio University)
Co-investigator Yuichi Yamashita (Section Chief, NCNP)
Co-investigator Tsukasa Okimura (School of Medicine, Keio University)
Co-investigator Hiroki Oi (School of Medicine, Keio University)

Research Project A05-09: The role of inhibitory neurons related to skilled hand movements after spinal cord injury.

Principal investigator Takahiro Kondo (Assistant Professor, Keio University)
Co-investigator Yuta Sato (Ph.D Student, Keio University)

Research Project A05-11: Activating preference network for affected side by neural and behavioral modulation.

Principal investigator Rieko Osu (Professor, Waseda University)
Co-investigator Taiki Yoshida (Ph.D Student, Waseda University)
Co-investigator Kento Hirayama (Ph.D Student, Waseda University)

Research Project A05-12: Hyper-adaptability from inducing synapse connection and regulation of extracelluar matrix. -Spinal cord injury and AI-based motion capture-

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 Yuki Morioka (Research Technician, Aichi Medical University)

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: Animal model of unilateral spatial neglect in marmosets

Principal investigator Masatoshi Yoshida (Specially Appointed Associate Professor, Hokkaido University)
Co-investigator Hiroshi Matsui (Postdoctoral Fellow, Hokkaido University)
Co-investigator Polyakova Zlata (Postdoctoral Fellow, Hokkaido University)

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)
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Co-investigator Koji Ito (Emeritus Professor, Tokyo Institute of Technology)
Co-investigator Yoshikatsu Hayashi (Associate Professor, University of Reading)

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Research Project B02: Modeling of ultra-adaptive to body change

Principal investigator	Yasuharu Koike (Professor, Tokyo Institute of Technology)
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Co-investigator	Kazuo Tsuchiya (Emeritus Professor, Kyoto University)
Co-investigator	Soichiro Fujiki (Assistant Professor, Dokkyo Medical University)

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)
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Research Project B04: Modelling of hyper adaptability in human postural control considering the role of neurotransmitters

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Co-investigator	Tetsuya Hasegawa (Postdoctoral Fellow, The University of Tokyo)
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Co-investigator	Mariko Miyata (Professor, Tokyo Women's Medical University)
Co-investigator	Hironobu Osaki (Assistant Professor, Tokyo Women's Medical University)
Co-investigator	Moeko Kanaya (Assistant Professor, Tokyo Women's Medical University)
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Research Project B05-01: Elucidation of the mechanism of motor synergy emergence in deep reinforcement learning

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Research Project B05-02: Adaptation ability of human postural control system revealed by a closed-loop electrical muscle stimulation system

Principal investigator	Daichi Nozaki (Professor, The University of Tokyo)
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Research Project B05-03: Mechanism underlying the hyper-adaptation of bipedal locomotion to the evolutionary change of the foot.

Principal investigator	Naomichi Ogihara (Professor, The University of Tokyo)

Research Project B05-04: Understanding neural manifold of the movements using human neuroimaging and non-invasive brain stimulation

Principal investigator	Isao Nambu (Associate Professor, Nagaoka University of Technology)
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Co-investigator Hiroshi Yokoyama (Project Assistant Professor, NIPS)

Research Project B05-05: Development of motor learning model that can reuse partial dynamics based on estimation of transformation between mappings

Principal investigator Yuichi Kobayashi (Associate Professor, Shizuoka University)
Co-investigator Taisei Matsuura (Undergraduate Student, Shizuoka University)
Co-investigator Sota Nakamura (Undergraduate Student, Shizuoka University)

Research Project B05-06: Shared-control of teleoperated robot maintaining operator's embodiment under intervention of AI

Principal investigator Yasuhisa Hasegawa (Professor, Nagoya University)
Co-investigator Tomoya Morita (Nagoya University)

Research Project B05-07: Systems engineering approach for understanding supraspinal mechanisms of the intermittent feedback control during human upright stance

Principal investigator Taishin Nomura (Professor, Osaka University)
Co-investigator Yasuyuki Suzuki (Lecturer, Osaka University)
Co-investigator Matija Milosevic (Assistant Professor, Osaka University)
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Co-investigator Kimitaka Nakazawa (Professor, The University of Tokyo)
Co-investigator Saburo Sakoda (Honorary Director, National Hospital Organization Osaka Toneyama Medical Center)
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Research Project B05-08: A reinforcement learning model with dynamic state space that enables adaptation to indefinite environments

Principal investigator Kazuhiro Sakamoto (Associate Professor, Tohoku Medical and Pharmaceutical University)
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Co-investigator Satoshi Zuguchi (Ph.D Student, Tohoku University)

Research Project B05-09: Attention control training based on tailor-made neurofeedback system for facilitating motor learning in elderly

Principal investigator Takeshi Sakurada (Assistant Professor, Ritsumeikan University)

Research Project B05-10: Modeling of the motor recovery process and optimization of rehabilitation strategy using VR

Principal investigator	Tetsunari Inamura (Associate Professor, National Institute of Informatics)
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Research Project B05-11: Developmentalhyper-adaptability of sensorimotor dynamics under rapid growth

Principal investigator	Hoshinori Kanazawa (Research Assistant Professor, The University of Tokyo)
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