2020 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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Area No. 8102
Fiscal Year: 2019-2023
https://www.hyper-adapt.org/

Contents

Program Overview and Activities of Steering Committee

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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. New members of publicly projects join the program from April, 2020 (Fig. 1); A05 group (15 projects): Izumi, Amemori, Matsumoto, K. Kobayashi, Abe, Hida, Miyawaki, Maeda, Kondo, Osu, Takeuchi, Fujiyama, Masamizu, Higo, and Yoshida. B05 group (11 projects): Hayashibe, Nozaki, Ogihara, Nambu, Y. Kobayashi, Hasegawa, Nomura, Sakamoto, Sakurada, Inamura, and Kanazawa). 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

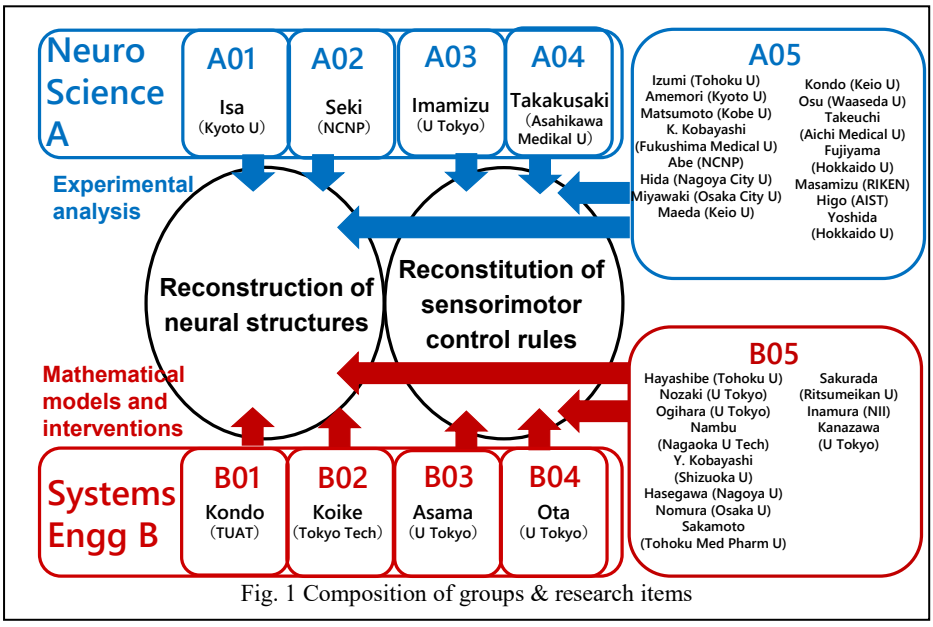

Fig. 1 Composition of groups & research items

methods.

III. Group Members

Members of the management group consists of one principal investigator (Ota), three funded co-investigators (Isa, Kondo, and Funato), and fifteen co-investigators (Seki, Imamizu, Takakusaki, Koike, Asama, Naito, Hanakawa, Izawa, Tsutsui, Aizawa, Chiba, Wen, An, and Yozu).

IV. Activities

Following events were held by management group.

A. Activities organized by the project

- 4th management meeting
Date: May 15th, 2020. 12:00-13:00
Place: Online
Contents: members of the management group discussed about the operation method, symposiums, and counterplans against Covid-19, etc.

- 1st public symposium
Date: Oct. 10th, 2020. 12:00-12:50
Place: Online
Contents: The theme was "Hyper-adaptation in a post-coronavirus society". The symposium focused on the decline in motor functions due to the restricted activities caused by the corona disaster, the resulting maladaptation in the body-brain relationship, and the prospects for solutions. After an overview by Ota, seven lectures were given by Isa, Takakasagi, Tsutsui, Maeda, Asama, and Hanakawa, followed by a panel discussion on the theme of post-corona and hyper-adaptation.

- 5th management meeting
Date: Oct. 10th, 2020. 12:00-12:50
Place: Online
Contents: members of the management group discussed about the operation method, symposiums, publications, etc.

- B group meeting
Date: Nov. 7th, 2020. 10:00-17:00
Place: Online
Contents: A group meeting was held for the purpose of exchange within and outside Group B. After an explanation of the purpose of the meeting by the group leader (Kondo), group members took presentations of their researches and research plans. The meeting was attended by more than 45 researchers at all times, and active discussions were held.

- A group meeting
Date: Nov. 13th and Nov. 14, 2020.
Place: Online
Contents: A group meeting was held for the purpose of exchange within and outside Group A. 24 group members gave 10-minute presentation and 10-minute Q&A sessions in blocks of 3 members each. A "virtual coffee break" using the Zoom's breakout room function of Zoom was held between each block. Through the meeting, active exchanges took place.

- 2st plenary conference
Date: March 5th - 6th, 2021
Place: Online
Contents: summary of the researches in the year was presented by project representative and researchers in the project.

- 6rd management meeting
Date: Marge 5th, 2021. 11:40-13:00
Place: Online
Contents: members of the management group discussed about the operation method, management of International symposium, etc.

B. Activities for publications

- Newsletters
We published two newsletters on May, 2020 and on Jan, 2021. Th newsletters are published from the following website.
https://www.hyper-adapt.org/newsletter/

V. 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. Organizing International Workshop

On July 18, 2020, we held an online workshop at the international conference EMBC2020. Prof. Ota, Prof. Takakusagi, Prof. Chiba, Prof. Shirafuji, Prof. Hayashi, and Prof. An participated in the workshop, and presented their researches and had discussions with the participants.

B. Literature Study Group

A study session on "Control and Adaptation of Body Movements" by Koji Ito was held from October to November 2020. Each chapter was explained and discussed by young researchers in the research field. The materials and movies of the workshop are shared on the website of the research area, and we are trying to expand the common knowledge base.

C. Organizing Speciall Issue in International Journal

We planned a special issue on our field, "Hyper-Adaptability for Overcoming Body-Brain Dysfunction," in Advanced Robotics, an international journal published by the Robotics Society of Japan. We have received submissions from inside and outside the field, and we are preparing for publication in July 2021.

D. Information Sharing Infrastructure using Slack

We have started to use Slack to promote discussion and information sharing among young researchers in this area, and plan to expand it to the entire area in the next year.

VI. Future Perspective

As main activities of the next fiscal year, the management group plans an International symposium on May 2021 (online) and 3rd plenary conference on March 2022.

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.

Group A02 (Seki) investigated the adaptation of the central nervous system to the acute change of the body schema by cross union surgery of forearm muscles in the macaque monkeys. They clarified that the muscle synergies once switch soon after the surgery, but later changes again to the original one. In collaboration with the Group B, they are analyzing the phenomenon from the viewpoint of the cost function.

Group A03 (Imamizu, Tsutsui) is trying to understand mechanisms in which motivation and body cognition facilitate motor learning in challenging situations, and to develop the methods for facilitating motor learning through artificial control of motivation and body cognition. Imamizu and colleagues demonstrated that the short-term learning efficiency is enhanced by the sense of agency in the preceding trials compared with the cases without it. Tsutsui and colleagues used the transcranial magnetic stimulation and suppressed the local brain activity in the frontal cortex and investigated the effects on the performance in the motor learning task. They found that suppression of the anterior cingulate cortex caused deterioration of the task performance caused by decline of motivation.

Group A04 (Takakusaki and Hanakawa) is investigating how the change in the dynamics of brain activity caused by the dynamic change in the neurotransmitter systems such as dopamine and acetylcholine/ For that purpose, Takakusaki and colleagues set up the experimental system to analyze the shift of the center of the gravity of cats during the reaching movements. Hanakawa and colleagues are developing the experimental system to measure the brain activity and \dynamics of their connectivity using the simultaneous recordings of the electroencephalography and fMRI.

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

Shin-ichi Izumi “Elucidation of the hyper-adaptation mechanism of upper limb recovery in stroke patients”
Kenichi Amemori “Synchronization of neural oscillation among primate limbic structures and the striatum during recovery from anxiety like state”
Riki Matsumoto “Mechanism of hyper-adaptivity of the human premotor area: electrophysiological connectome analysis with electrocorticogram”
Kazuto Kobayashi “Neural circuit rearrangement mechanisms underlying the recovery from learning deficits in Parkinson’s disease model animals”
Mitsunari Abe “Development of non-invasive brain stimulation techniques that can induce recruitment of the corticospinal motor indirect pathway during acquisition of hand motor skills”
Hideki Hida “Analysis of motor control system in the recovery of forelimb function by rehabilitation after intracerebral hemorrhage”
Hiroyuki Miyawaki “Regulatory mechanisms of inter-regional network changes underlying hyper-adaptation from mal-adaptation state caused by fear memory”
Takaki Maeda “Facilitating hyper-adaptation in neurological and psychiatric diseases through improving precision on the sense of agency”
Takahiro Kondo “The role of inhibitory neurons related to skilled hand movements after spinal cord injury
Rieko Osu “Activating preference network for affected side by neural and behavioral modulation”
Kosei Takeuchi “Hyper-adaptability from inducing synapse connection regulation of extracellular matrix. – Spinal cord injury and AI-based motion capture-“
Fumino Fujiyama “Reconstruction of basal ganglia by aging and neurodegenerative disease”
Yoshito Masamizu “Development of techniques to improve brain functions by using hyper-adaptability”
Noriyuki Higo “Adaptive mechanism occurring in both hemispheres after unilateral brain damage”
Masatoshi Yoshida “Animal model of unilateral spatial neglect in marmosets”

III. ACTIVITIES

He whole Group A meeting was held on November 13 (Sat) – 14 (Sun) by online with Zoom software.

IV. Future Plan

We will soon organize the 1st Group A 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 existence of disinhibition interhemispheric pathway in the monkeys with spinal cord injury using electrophysiology and aged humans using fMRI. We are also studying the involvement of dopamine system in the global disinhibition in 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 record the movement-related activity in the sensorimotor cortices and the cortical and muscle responses to electrical stimulation through the cortical electrodes longitudinally before after the spinal cord injury in monkey to clarify the mechanism of disinhibition across the large-scaled brain network. In rodents, Aizawa Group will perform the activity measurement and optogenetical stimulation of monoaminergic systems including dopaminergic and serotonergic neurons, to supply the information about the global disinhibition in the cortex. In humans, Naito Group will capture the chronic disinhibitory state of the aged people by fMRI and propose the effective training methods of the brain to improve the rain functioms using the disinhibitory state as a measure of progression of aging-related frailty.

III. Research Topics

A. Global dinsinhibition after spinal cord injury in monkeys

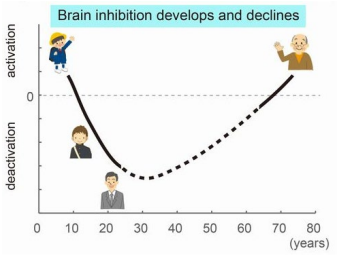
As reported in the last year, in a macaque monkey with sub-hemisection at the mid-cervical level, dropped from 100% to 0%, but success ratio of the immature grasping guided by the slit edge recovered to around 90 % in 1-2 months. We used direct electrical stimulation with ECoG electrodes to investigate the connectivity between motor-related areas and muscles for the affected side before and after the sub-hemisection. Fig.1 shows the induced muscle twitches in the affected forelimb by the electrical stimulation of contralesional PM. Muscle twitches started being induced in proximal muscles from the contralesional PM/M1 after around Day 16. Twitch responses gradually spread from the proximal to distal muscles including digits almost simultaneously as the monkey started grasping. Similar results were confirmed in the 2nd monkey. Furthermore, we confirmed that interhemispheric inhibitory interaction in the intact state was changed to interhemispheric facilitation during the recover. These results suggested that global disinhibition spread across a large cortical network along with the recovery.

[1] 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*, in press.
[2] Koshimizu Y, Isa K, Kobayashi K, **Isa T** (2021) Double viral vector technology for selective manipulation of neural pathways with higher level of efficiency and safety. *Gene Therapy*, doi: 10.1038/s41434-020-00212-y.
[3] 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*, doi: 10.1093/cercor/bhaa399.
[4] Takakuwa N, Isa K, Onoe H, Takahashi J, **Isa T** (2020) Contribution of the pulvinar and lateral geniculate nucleus to the control of visually guided saccades in blindsight monkeys. *Journal of Neuroscience*, JN-RM-2293-20. doi: 10.1523/JNEUROSCI.2293-20.2020.
[5] Tokuoka K, Kasai M, Kobayashi K, **Isa T** (2020) Anatomical and electrophysiological analysis of cholinergic projections from the parabigeminal nucleus to the superficial superior colliculus. *Journal of Neurophysiology,* 124(6):1968-1985.
[6] Chen C-Y, Matrov D, Veale R, Onoe H, Yoshida M, Miura K, **Isa T** (2020) Properties of visually-guided saccadic behavior and bottom-up attention in marmoset, macaque, and human. *Journal of Neurophysiology*, 125:437-457.
[7] Isa K, Sooksawate T, Kobayashi K, Kobayashi K, Redgrave P, **Isa T** (2020) Dissecting the tectal output channels for orienting and defense responses. *eNeuro*, 7(5): ENEURO.0271-20.2020.
[8] Vancraeyenest P, Arsenault JT, Li X, Zhu Q, Kobayashi K, Isa K, **Isa T**, Vanduffel W (2020) Selective mesoaccumbal pathway inactivation affects

motivation but not reinforcement-based learning in macaques. *Neuron*, 108:568-581.
[9] Suzuki M, Onoe K, Sawada M, Takahashi N, Higo N, Murata Y, Tsukada H, **Isa T**, Onoe H, Nishimura Y (2020) The ventral striatum is a key node of cortical reorganization required for functional recovery of finger dexterity after spinal cord injury in monkeys. *Cerebral Cortex,* 30: 3259-3270.

B. Visualization of development and age-related deterioration of human interregional inhibitory systems using negative BOLD as an indicator (Naito and Asada)

In collaboration with Asada group (Osaka University), Naito group (NICT, CiNet) visualized development and age-related deterioration of human interregional inhibitory systems using Negative BOLD, which can be measured by functional MRI, as an index during a right-hand motor task. In young adults, we identified interhemispheric inhibition in the hand section of the ipsilateral (right) motor cortex, cross-somatotopic inhibition in the feet and face sections, crossmodal inhibition in visual and auditory cortices, as well as inhibition in the default mode network. We found that over a lifespan, all of these inhibitions develop from childhood to adulthood and diminishing or disappearing with age (Figure from Morita et al. 2021). Regarding the interhemispheric inhibition, we found that inhibition of the hand/arm section of the ipsilateral (right) motor cortex during a right hand movement was associated with right hand\finger dexterity, and that elementary school children with more developed the inhibition had more developed right hand/finger dexterity as assessed by the peg test (Naito et al. 2020). In contrast, in the elderly, the inhibition of the hand/arm section of the ipsilateral (right) motor cortex was attenuated or lost, and this was related to their deterioration in right hand/finger dexterity. We further found 2-months bilateral digital training could improve this inhibition, which in turn improved their hand/finger dexterity.



[1] Naito E, Morita T and Asada M Importance of the primary motor cortex in development of human hand/finger dexterity. Cerebral Cortex Communications 1: 1-12, https://doi.org/10.1093/texcom/tgaa085, 2020.

[2] Morita T, Asada M and Naito E Examination of the development and aging of brain deactivation using a unimanual motor task. Advanced Robotics accepted 2021.

C. Elaboration of the rodent model of hyper-addaptation and a role of dopamine

Aizawa group (Hiroshima University) addressed a role of extracellular dopamine in modification of the mice behavior to adapt to the tail suspension condition. Mice exhibited alternation between despair and struggling behaviors under the tail suspension stress (Cui et al., 2020). Upon real-time measurement of extracellular dopamine in the nucleus accumbens, transient decrease of the extracellular dopamine release was observed immediately before the transition to the struggling from despair state. To address a causal effect of dopamine dip in the nucleus accumbens on initiation of struggling, optogenetic suppression of the accumbal dopamine was performed in collaboration with Isa group. Results showed that photoinhibition of the accumbal dopamine release induced struggling under the tail suspension stress. Consistent with this, knocking out of the dopamine type 1 receptor in the region also facilitated the struggling behavior, suggesting that the dopaminergic modulation in the nucleus accumbens has an instructive role in stress coping behavior for adaptation under the acute stress.

The group also established an experimental setup to enable physiological analysis on interhemispheric inhibition as a basis of global disinhibition suggested in hyper-adapting brain in human and non-human primate model in Isa and Naito group, based on the electrophysiological recording of the murine cortical activity (Aizawa et al., 2020). Furthermore, mouse model of systemic inflammation was analyzed to address the mechanism underlying hyper-adaptation to the global stress such as systemic inflammation (Kikutani et al., 2020; Giga et al., 2020).

[1] Giga H, Ji B, Kikutani K, Fukuda S, Kitajima T, Katsumata S, Matsumata M, Suhara T, Yamawaki S, Shime N, Hosokawa K, Aizawa H. Pharmacological and Genetic Inhibition of Translocator Protein 18 kDa Ameliorated Neuroinflammation in Murine Endotoxemia Model. Shock. 2020 *in press*

[2] Kikutani K, Giga H, Hosokawa K, Shime N, Aizawa H. Microglial translocator protein and stressor-related disorder. Neurochem Int. 2020 Nov;140:104855.

[3] Ito H, Nozaki K, Sakimura K, Abe M, Yamawaki S, Aizawa H. Activation of proprotein convertase in the mouse habenula causes depressive-like behaviors through remodeling of extracellular matrix. Neuropsychopharmcology. 2021 46(2):442-454.

[4] Cui W, Aida T, Ito H, Kobayashi K, Wada Y, Kato S, Nakano T, Zhu M, Isa K, Kobayashi K, Isa T, Tanaka K, Aizawa H. Dopaminergic Signaling in the Nucleus Accumbens Modulates Stress-Coping Strategies during Inescapable Stress. J Neurosci. 2020 Sep 16;40(38):7241-7254.

[5] Aizawa H, Sun W, Sugiyama K, Itou Y, Aida T, Cui W, Toyoda S, Terai H, Yanagisawa M, Tanaka K. Glial glutamate transporter GLT-1 determines susceptibility to spreading depression in the mouse cerebral cortex. Glia. 2020 68(12):2631-2642.

IV. Future Perspective

Isa Group aim will publish an article on the current results, and will work on the more fundamental neuronal mechanisms of global dininhibition in collaboration with Aizawa group. Naito Group will conduct additional experiments to summarize our findings in the elderly, and at the same time, in collaboration with the Asada group, will attempt to develop a mathematical model of the development and deterioration of E/I balance.
Aizawa group would analyze roles of monoamines in the interhemispheric inhibition and adaptation to the global stress using neuropharmacology and optogenetics based on the findings they acquired in this fiscal year.

Annual report of research project A02

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***Abstract*—In the FY2020, our experimental studies were basically halted under the effect of the Covid-19. However, we've made significant progresses for data analysis as well an writing manuscripts.**

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 Topics

A. Data Analysis

After completing the behavioural and electromyography (EMG) recordings in a second monkey which underwent a procedure of cross-connecting the forearm tendons of the flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) and which lasted from December to March of the last year, we focused on the analysis of the collected data (n=2).

We first analysed the behavioural data recorded by two high-speed cameras from two different angles by calculating the times required for reaching and grasping each of the four objects. For monkey A, data from 40 days before surgery to 3 months after surgery, and for monkey B, data from 3 days before surgery and 2 months after surgery were taken into account. In both monkeys A and B, reaching and grasping times were temporarily and significantly prolonged after surgery, however, recovered to preoperative times about 30 days after surgery (early phase), and changes thereafter were gradual (late phase). These results strongly suggest that the central nervous system adaptation to functional muscle repositioning, introduced by tendon cross-transfer surgery, should be complete within about one month after surgery. Therefore, as an index for the adaptive evaluation of the nervous system, we analysed the electromyographic activity of the rearranged muscles and the changes over time in muscle synergies including non-relocated muscles.

In each case, recovery was evaluated by cross-correlation analysis between the pre-operative recordings of EMG/muscle synergy and the same muscle for each post-operative measurement date. Firstly, as a result we found that the decrease in the mutual correlation coefficient in the major muscle synergies of the rearranged as well as the non-relocated muscles became the largest at the same time as the recovery of the above evaluated behavioural index. On the other hand, the intercorrelation coefficients with the repositioned muscle and muscle synergy were maximized at the same time. Therefore, the tendon transfer procedure revealed that the re-positioned muscle exhibits the temporal activity of the original muscle activity/muscle synergy at its new destination. This phenomenon was observed in both the FDS and EDC muscles, suggesting that the central nervous system uses a strategy to swap the activity of the repositioned flexor and extensor muscles and flexor/extensor synergy, thereby improving the behavioural performance.

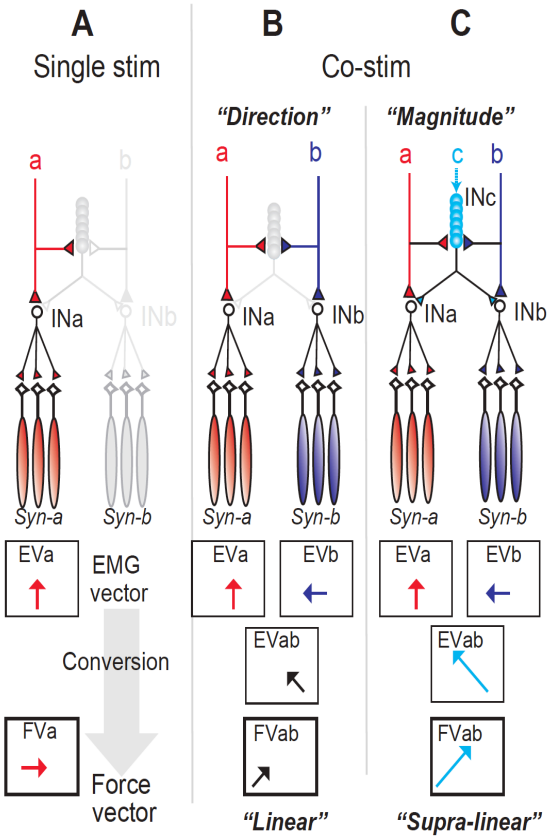
However, the cross-correlation coefficients of EMG activity and synergy of the repositioned muscles, which had once decreased, increased again in the two monkeys about 60 days after surgery and returned to their preoperative values. This trend was observed in both the FDS and EDC muscles, indicating a two-stage adaptation of the central nervous system in which muscle activity and muscle synergy are "replaced" in the first early phase and then "restored" in the second late phase. Next, more detailed movement observations were made to investigate the functional significance of the late phase adaptation. An ataxic movement patterns, which were not observed preoperatively, were observed up to the late phase adaptation, but disappeared after the late phase. These results suggest that the changes in motor control strategies in the central nervous system during the early phase are not optimal from the point of view of smooth execution of movements, and that before the late phase, ataxic control strategies were used to achieve successful movements, probably at a high cost.

Therefore, it was considered that the smooth movement was achieved by returning to the conventional/original control *style/strategy* instead of using the temporarily adopted control *style/strategy*. In the future, quantitative evaluation of the above-mentioned cost and further analysis of the difference between the two control systems (late phase and the control) will be necessary.

B. Modular organization of spinal motor output

The human hand has 27 muscles and 18 joints, which our nervous system is able to coordinate for complex movements. However, the number of combinations -- or degrees of freedom -- is so large that attempting to artificially replicate this control and adjustment of muscle activity during movement in real time taxes even a modern supercomputer. While the method used by the central nervous system to reduce this complexity is still being intensely studied, the "motor module" hypothesis is one possibility. Under the motor module hypothesis, the brain recruits interneuronal modules in the spinal cord rather than recruiting individual muscles directly to create movement; wherein different modules can be combined to create specific movements. Nearly 40 years ago, research in frogs showed that simultaneously recruiting two modules of neurons controlling leg muscles created the same pattern of motor activity that represents a "linear summation" of the two component patterns.

In this paper, we attempted to determine if this motor control method is also present in the primate spinal cord. If validated, it would provide new insight into the importance of spinal interneurons in motor activity and lead to new ideas in movement disorder treatments and perhaps even a method to "reanimate" a limb post-spinal injury. We implanted a small array of electrodes into the cervical spinal cord in three macaque . Under anesthesia, different groups of interneurons were recruited individually using a technique called intraspinal microstimulation (ISMS). We found that, as in the frog leg, the force direction of the arm at the wrist during dual-site simulation was equal to the linear summation of the individually recruited outputs. However, unlike the frog leg, the force magnitude output could be many times higher than that expected from a simple linear summation of the individual outputs. When we examined the muscle activity, they found that this supralinear summation was in a majority of the muscles, particularly in the elbow, wrist, and finger.



This is a very interesting finding for two reasons. First, it demonstrates a particular trait of the primate spinal cord related to the increased variety of finger movements. Second, we now have direct evidence primates can use motor modules in the spinal cord to control arm movement direction and force magnitude efficiently and independently.

In effect, using paired stimulation in the primate spinal cord not only directly activate two groups of interneurons, INa and INb, which recruit their target muscle synergies, Syn-a and Syn-b, to set the arm trajectory, but can also activate a third set of interneurnons that can adapt the motor activity at the spinal level to change the force of the movement, group INc. This would let the brain plan the path the arm should take while the spinal cord adapts the muscle activity to make sure that path happens. One example of this "plan and adapt" approach to motor control is the deceptively simple act of drinking from a can of soda. The brain can predetermine the best way to lift the can to your mouth for a sip, but the actual amount of soda in the can -- and therefore the can's weight -- is perhaps unknown. Once your brain has determined the trajectory the can should take -- in this case INa and INb -- the amount of force needed to complete that action can be modulated separately in INc, rather than redetermining which sets of muscles will be needed.

This study experimentally proves for the first time that primate arm movements may be efficiently controlled by motor modules present in the spinal cord. Based on the results of this research, it is expected that the analysis and interpretation of human limb movements based on the motor module hypothesis will further advance in the future.

IV. Future Perspective

We are preparing to start the planned experiment again. We will address neural representation of the early and late adaptation.

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Annual report of research project A03

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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 relationships between sense of agency (a sense that "I am the one causing an action," which is an aspect of body cognition) and motor learning in several experiments, 2) revealing fundamental mechanisms of sense of agency, 3) establishing a standard procedure to evaluate the motivational level of animals (monkeys), and 4) specifying a brain region in the cerebral cortex responsible for motivation.**

I. Introduction

Previous studies in neuroscience and psychology have investigated how feedback information from the external world (such as motor error and reward prediction error) contribute to motor learning. Recently, by contrast, many researchers have interest in the contribution of internal information, such as motivation and body cognition, to motor learning. For instance, the level of 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 (Mr. Tanaka and Imamizu) and Prof. Izawa of the B03-group started an experiment, investigating how self-attribution of the movement facilitates motor learning in the last fiscal year. They collected data from 20 participants in this fiscal year. They revealed that the self-attribution of actions in the preceding trial significantly facilitates a short-term efficacy of learning rate in the next trial (Fig. 1).

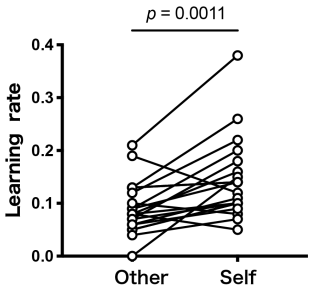

Fig. 1 Difference in learning rate due to action attribution

2) Sense of agency and control as a reward: A group of the principal investigator (Mr. Tanaka, Dr. Ohata, and Imamizu) and Prof. Izawa of the B03-group started a psychological experiment examining if successful manipulation of an object gives a performer a subjective reward. Participants moved a cursor to the left or right target. A variance of a noise imposed to the cursor was different between the left and right movements. They investigated if participants preferred the action with small noise (high controllability) even when the rewards for the left and right actions were equalized to each other. In collaboration with Prof. Tsutsui (co-investigator), they also designed an experiment to investigate a change in neural signatures of motivation (activity of neurons in the medial and dorsal prefrontal regions) according to the controllability of devices.

3) Relationship between sensitivity to controllability and efficacy of motor learning: The principal investigator and Prof. Wen of the B03 group investigated the individual difference in sensitivity to change in controllability of an object. They found that an individual's sensitivity to increasing control is correlated with his/her efficacy in motor learning. The principal investigator revealed that an increase in proprioceptive acuity, which is essential for the perception of controllability, facilitates motor learning effectiveness [1].

B. Understanding mechanisms of sense of agency

1) Sense of agency over speech: It has been suggested that deficits in the sense of agency over speech lead to auditory hallucinations. However, little is known about the agency over speech. A group of the principal investigator (Dr. Ohata and Imamizu) has investigated a sense of agency during a naturalistic speech paradigm. They found a critical role of the sign of self in acoustic quality, as well as action-outcome causality, in the sense of agency over speech.

2) Cognitive psychological approach to sense of agency: A group of the principal investigator (Dr. Ohata and Imamizu) and Prof. Wen of the B03-group investigated cognitive mechanisms

of sense of agency. They established a two-stage model of active sensing of control difference [2]. They also found a categorial information processing in the perception of control [3].

3) Mathematical model of sense of agency: The principal investigator, Prof. Kondo and Dr. Yano of the B01-group, and Dr. Maeda of the B05-8 established a statistical learning model in the sense of agency. They revealed that the sense of agency could be formalized as the likelihood of an internal model of the environment [4].

4) Brain network related to individual differences in the sense of agency: The principal investigator, Dr. Yamashita, and Dr. Maeda of the B05-8 found that networks including the caudate nucleus and the right parietal regions are associated with the individual difference in the sense of agency. The principal investigator and Dr. Yamashita published a paper on a fundamental method for investigating brain networks. [5].

C. Understanding the brain mechanisms of motivation

1) Establishing a methodology of evaluating the level of motivation in animals (monkeys): A group of co-investigator Tsutsui and his colleague (Dr Nakamura) has established a standardized method of evaluating the level of motivation of a mokey, by using a modified Brainkman Board Test. This procedure enables the evaluation of motivation with small number of trials and short time duration [6].

2) Evaluating the effect of repetitive transcranial magnetic stimulation (rTMS) on the cortical excitability and electrocorticogram signals as a mean of neural intervention: A group of co-investigator Tsutsui and his colleague (Dr Nakamura) has studied the impact of rTMS on the cortical excitability indicated by motor evoked potentials (MEP) and the electrocorticogram (ECoG) signals. Stimulation frequency conditions were set in a parametrical manner (0.5, 1, 2, 5, 10, and 20 Hz). Out of these conditions, 1Hz rTMS induced largest inhibitory effect on the cortical excitability, accompanied by the decrease of the power of relative low frequency bands (theta, alpha, and beta) in the ECoG signal, whereas 10 or 20 Hz rTMS induced largest excitatory effect on the cortical excitability, accompanied by the increase of the gamma frequency band in the ECoG signal. Thus, we found that 1 Hz and 10 or 20 Hz, respectively would be the optimum rTMS frequency for inhibitory and facilitatory neural interventions, and that changes of ECoG signals can be indications of the efficacy of rTMS interventions on the stimulated brain area [7].

3) Finding the cortical area responsible for the generation of motivation: A group of co-investigator Tsutsui and his colleague (Dr Nakamura) has studied whether the motivation measured by the modified Brinkman Board Test can be altered by an inhibitory neural intervention of 1 Hz rTMS targeting various regions of the frontal cortex. It was found that the inhibition of neural activity of the subgenual or pregenual anterior cingulate cortex alters the performance, whereas the inhibition of any other regions of the frontal cortex does not. The observed change of performance was that the monkeys completed less number of sessions in the “difficult” condition, whereas no change was observed in the “easy” condition. (Task difficulty was manipulated by changing the width of the food well on the board.) The result indicates the critical involvement of the subgenual or pregenual anterior cingulate cortex in the generation of motivation. Furthermore, in addition to the change of performance in Brinkman Board Test, those monkeys showed reduced sociability and increase of blood cortisol level, which can be indications of a mild depressive state [8].

IV. Future Perspective

We made advances in the investigation of the relationship between the sense of agency and motor learning. Our experiments have demonstrated that a sense of agency facilitates motor learning. We also revealed fundamental mechanisms of sense of agency in cognitive framework and brain networks. Concerning motivation, we have established a methodology of evaluating the level of motivation in animals (monkeys), and specified the brain area critically involved in the generation of motivation. In collaboration with Prof. Izawa of the B03-group, we will investigate neural and psychological mechanisms in which sense of agency plays a role of a reward in motor learning in monkey and human experiments.

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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 second year, Takakusaki and colleagues examined the role of the parietal cortex in the optimization of predictive postural control during multi-task voluntary movements (from gaze fixation in quiet standing to postural preparation and forelimb reaching) in the cat. Hanakawa and colleagues used a simultaneous EEG-fMRI for evaluating a dynamic profile of functional connectivity between distinct neural networks. They also examine neuro-melanin 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 [1]. 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

Takakusaki (a principal investigator) and his colleagues in AMU aim to verify the mechanisms of optimal postural control during voluntary movements in experimental animals (cats) with and without damages in DA/ACh systems. In the first year (2019), we established paradigms of postural control of the cat that has learned the "multitask voluntary movements" from quiet standing with fixed gaze position to forelimb reaching to the target in various conditions (Fig.1). In the 2020 year, we employed this experimental paradigm to examine the role of the parietal cortex in the manner of optimization in postural control preceding the forelimb reaching movement. For this, muscimol (10 μg/μl, per site), one of $GABA_A$-agonist, was microinjected into the various areas of the posterior parietal cortex (PPC) so that the target areas were inactivated. Then, changes in the center of vertical pressure of the cat was measured before, during, and after achievement of the reaching.

Hanakawa (a research collaborator) and his colleagues in Kyoto University/NCNP have performed clinical studies. In the academic year 2019-2023, 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 PADNI [1] which is a longitudinal cohort study involving healthy elderly people as well as patients with PD and AD. In this year they developed a method to examine relationship between cognitive functions and dynamic profiles of functional connectivity among distinct neural networks (simultaneous EEG-fMRI) of elder subjects in a comprehensive manner so that they provide necessary data for modelling to engineering research groups. The Hanakawa lab also started a basic research on neuromelanin MRI to assess DA production in the substantia nigra (SN) in addition to DA transporter (DAT) SPECT for evaluating the activity of the DA system.

III. Research Topics

A. Role of the parietal cortex in the optimal postural control

Takakusaki group established an experimental system for examination of the visuomotor multi-tasks of the cat. (Fig. 1A). The center of vertical pressure (CVP), which was calculated from the ground reactive force exerted on each limb, was used as a parameter of postural changes. As shown in Fig.1Ba, 0.2~0.4 s after gazing at the target, the cat started to change posture (●), which shifted CVP with a speed of 0.2~0.6 m/s (●), and then, the cat lifted its left forelimb, which reached the target of 0.1~0.2 s later (●). Fig.1Ca shows changes in CVP throughout the task. When the cat gazed at the target (◈), the CVP moved forward about 20 mm from the reference coordinates (○), and before lifting the forelimbs (◈), it moved about 30 mm to the right. However, the CVP hardly moves from the forelimb lift to the end of reaching (◈). Namely, the optimal postural control that precedes the voluntary movement is considered to be "predicting and generating the postural state of the end of the goal-directed movement before starting." We also observed that muscimol injection into the medial PPC prolonged postural control time, decreased CVP velocity, reduced the CVP shift between the states, and restricted the distribution range of coordinates of each state (Fig. 1Bb, Cb). Muscimol injections into the medial PPC, on the other hand,

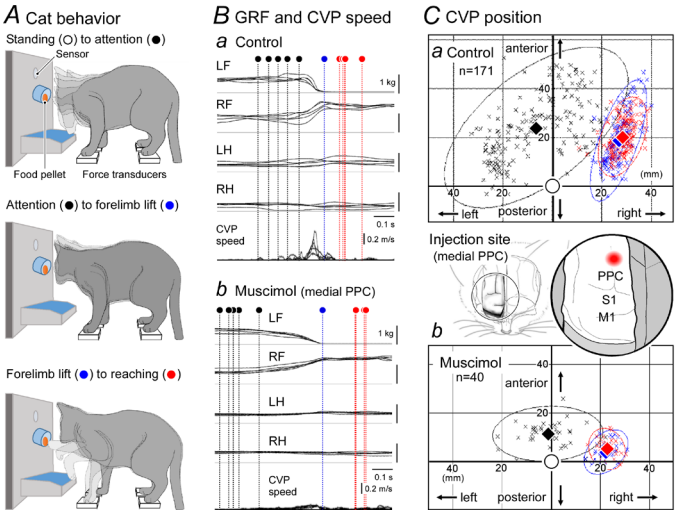

Fig. 1. Forelimb reaching task in the cat.

See text for details. M1; primary motor cortex, S1; primary sensory cortex, PPC; posterior parietal cortex.

increased the frequency of target gaze and increased the time required for reaching. Therefore, the medial part of the PPC may be involved in preceding postural control, and the lateral part may contribute to the accurate control of forelimb reaching movements.

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

Yoshinaga and Hanakawa have been working on developing simultaneous EEG-fMRI and MEG [2] 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 and retrieved the default mode network, dorsal attention network, salience network, and central executive network. Inter-network correlation of fMRI time-series (functional connectivity, FC) was assessed for each time window, yielding dynamic changes of FC. Yoshinaga et al. found at least two internetwork states: a dense FC condition and a sparse FC condition (Fig. 2).

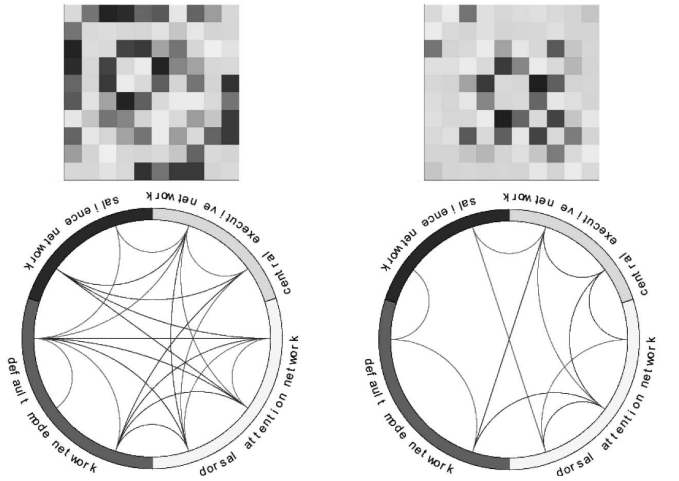

Fig. 1. Dense and sparse states of functinal connectivity across default mode network, salience network, dorsal attentional network, and central executive network.

Yoshinaga et al. applied this analysis to the previous data of the PADNI study [1]. Yoshinaga et al. compared the dynamic network states among patients with Parkinson's disease, those with dementia with Lewy bodies (DLB) and healthy elderly participants. Yoshinaga et al. found that patients with DLB tended to show the sparse FC condition.

C. *DA imaging in humans*

The Hanakawa lab has continued to use neuromelanin MRI for the potential assessment of DA synthesis in the substantia nigra, in addition to dopamine transporter (DAT) SPECT for the potential assessment of presynaptic DA terminals in the striatum. The team has also aimed to combine the MRI method with the histochemical assessment in specimen. In this year, by utilizing a few structural MRIs, the team has discovered a synthesized MRI contrast image, which potentially reflects substantia nigra and fibers connecting between the substantial nigra and other basal ganglia nuclei.

IV. Future Perspective

Takakusaki's group found that the PPC was involved in the optimal control of preceding posture adjustment and goal-directed movements. Considering that degeneration of the parietal cortex in AD in which cholinergic function is impaired, the present findings suggest that postural dysregulation that depends on higher brain function is one of the major causes of the frequent falls in AD. From the next fiscal year onward, they will employ pharmacological and optogenetic approaches combined with neurophysiological techniques to examine cortical and subcortical mechanisms of optimal control of preceding postural adjustment with respect to the role of the DA-ACh systems. Hanakawa's group developed simultaneous EEG-fMRI measurements for evaluating a dynamic profile of functional connectivity alongside standard fMRI technique in PD [3]. They plan to apply this method to 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 substantia nigra, basic studies will be conducted in parallel.

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Annual report of research project A05-1

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***Abstract*—This study aims to elucidate the hyper-adaptation mechanism of upper limb recovery in stroke patients. We longitudinally investigate relationship among frequency of upper limb use, body-specific attention and brain activities in stroke patients by using accelerometers, psychophysical methods, and fMRI, respectively. We expect the elucidation of the adaptation mechanism underlying upper limb recovery after stroke could contribute to understanding the hyper-adaptation mechanism of body-brain system. This year, we enrolled 30 patients with stroke, and analyzed the measured data in the subacute phase and measured the longitudinal data until the chronic phase.**

I. Introduction

The most common disability after stroke is upper limb 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 [1]. Upper limb paralysis affects the activities of daily living and significantly impairs the quality of life[2].

In order to establish effective rehabilitation for upper limb paralysis, various treatment techniques based on plastic changes in the central nervous system have been developed so far. For example, CI therapy, which encourages the use of the paretic upper limb in daily life by restraining the non-paretic upper limb and overcomes the learned non-use of the paretic hand[3], repetitive facilitation exercises, action observation, brain- computer interface (BCI), virtual reality (VR), kinesthetic illusion induced by visual stimulation (KiNvis), robotic training, neuromuscular electrical stimulation, and noninvasive brain stimulation have been reported [4]. 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[5]. In order to overcome these problems, we have participated in the scientific research on innovative areas " Understanding brain plasticity on body representations to promote their adaptive functions: Embodied-brain systems science" (2014-2018) as leader of the rehabilitation medicine group. And 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[6]. 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 frequency of upper limb use and brain activity.

II. Aim of the Group

This study aims to elucidate the hyper-adaptation mechanism of upper limb recovery in stroke patients. We longitudinally investigate relationship among frequency of upper limb use, body-specific attention and brain activities in stroke patients by using accelerometers, psychophysical methods, and fMRI, respectively. We expect the elucidation of the adaptation mechanism underlying upper limb recovery after stroke could contribute to understanding the hyper-adaptation mechanism of body-brain system.

III. Research Topics

The study design was a longitudinal prospective observational study. The subjects were 30 patients with subacute stroke whose general condition had stabilized after 2 weeks of onset. The measurement time points were initial (after enrollment), 2 weeks, 1 month, 2 months, 6 months, and 1 year. The Fugl-Meyer Assessment (FMA) was used to evaluate clinical upper limb function, and the Action Research Arm Test (ARAT) was used to evaluate the ability to manipulate objects. The frequency of upper limb use in daily life was measured using an activity meter with a built-in 3-axis accelerometer (wearable activity meter ActiGraph Link, GT9X Acti Japan Co). The accelerometers were worn on both wrists (Fig. 1A). The measurement period was 3 days, and the daily wearing time was from waking up to going to bed. The accelerometers were removed when the subjects were wet, such as when bathing. We measured the body-specific attention of the paretic hand in a visual stimulus detection task as an index reflecting body consciousness [6]. To examine the amount of body-specific attention to the paretic hand, we defined the amount of body-specific attention to the paretic hand calculated by subtracting the average reaction time for the paretic hand from that for the dummy hand (Fig. 1B). Brain activity was confirmed by fMRI. The motor task consisted of finger flexion and extension at a rate of 1 Hz. 30-second block design was used (30-second rest, 30-second hand movement). Three conditions were performed: paretic hand, non-paretic hand, and both hands. The images were analyzed

using SPM12 (Statistical Parametric Mapping: Wellcome Trust Center for Neuroimaging, University College London, UK), a functional brain image analysis software, in a MATLAB environment. Individual and group analyses were performed using the preprocessed data (Fig. 1C).

For rehabilitation during the study period, the usual occupational and physical therapies were performed according to the general condition (early mobilization, ADL training, self-management guidance). The content and amount of upper extremity exercises were controlled using a standardized upper extremity program Graded Repetitive Arm Supplementary Program (GRASP) for one hour per day[7].

A. Changes of function, frequency of upper limb use, and body consciousness in subacute stroke patients.

First, data were analyzed to determine the relationship between paretic upper limb function (FMA, ARAT), frequency of upper limb use (activity meter), and changes in body-specific attention, a marker of body consciousness, in patients with subacute stroke.

Results showed that paretic upper limb function improved up to 2 months and was maintained up to 6 months. The frequency of upper extremity use and body-specific attention increased up to 1 month, and the change was gradual up to 6 months. There was a positive correlation between the amount of change in body-specific attention and the amount of change in the frequency of upper limb use.

B. Changes of brain functional and structural networks in subacute stroke patients.

Second, functional brain imaging was used to examine changes in brain activity regions during paretic hand movements. In order to align the lesion side of the stroke patients, the functional and structural images taken were flipped for 2nd level analysis. The extensive brain activity including the contralesional hemisphere, which was observed in the early stage during paretic hand movement, gradually localized to the hand region.

Diffusion tensor imaging (DTI) was performed during the acquisition of functional brain images to evaluate the status of structural networks including corticospinal tracts due to brain damage. TBSS was performed to confirm the changes of white matter fibers in the whole brain. We also performed ROI analysis using regions of interest, which are considered to be important for recovery after brain injury. DTI analysis has been the subject of various discussions regarding damaged brains, and we aimed to establish an optimal analysis method. In the future, we will analyze the correlation between the obtained functional and structural image data and the behavioral indices at each period.

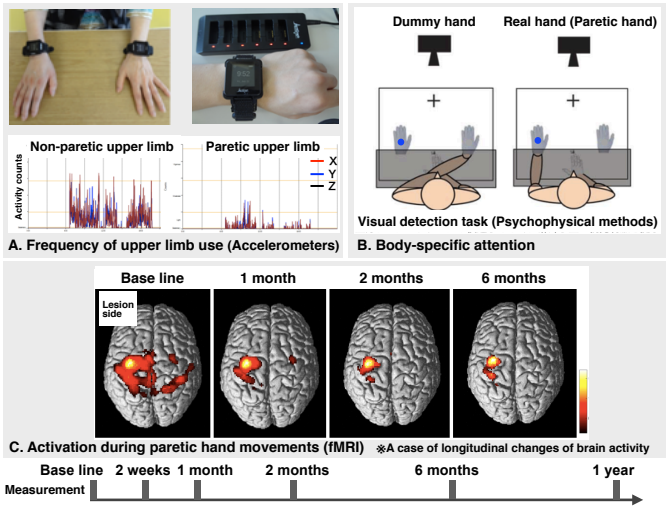

Fig.1. Overview of this study. A : Wristwatch type 3-axis accelerometers (right) were worn on both wrists (left) , and the time series data of bilateral arm activities were recorded (bottom). B : When a blue stimulus was presented on the dummy hand or the paretic hand, the subject quickly pressed a button with the non-paretic hand and the reaction time (RT) was measured. we defined the amount of body-specific attention as calculated by subtracting the RT for the paretic hand from that for the dummy hand. C : Brain activities during the paretic hand movement were recorded using fMRI. Changes of the brain activity were found in a representative case from baseline to 6 months after the enrollment.

IV. Future Perspective

In the recovery process of paretic upper limb, body-specific attention was found to be related to frequency of upper limb use. We believe that the results will contribute to the construction of rehabilitation strategies to enhance body consciousness and frequency of upper limb use according to the stage and condition of stroke. In the next year, we will analyze the correlation between the brain functional and structural networks and behavioral indices of stroke patients.

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Annual report of research project A05-2

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***Abstract*— Clinical studies have shown that patients with anxiety disorders exhibited coactivation of limbic cortices and basal ganglia. We hypothesized that excessive synchronization of the neural oscillations of the cortical-striatal network could be involved in the induction of the abnormal anxiety states. To investigate this, we will produce a monkey model of an anxiety disorder using the electrical stimulation of the striatum. Using a multi-site neural recording method, we will simultaneously record neural activity in the network of the limbic cortex and striatum. We will analyze how the activities of each region synchronized during the pathologically anxiety state and recovery phases.**

I. Introduction

The functional alterations in the state of anxiety disorders should be correlated with the abnormal communication in the limbic structures. We hypothesized that excessive synchronization of neural oscillations in the limbic system could be correlated with excessive anxiety-like states. To investigate this hypothesis, we will record the neural oscillations from the multiple structures of the limbic cortex and basal ganglia. Then we analyze whether the synchronous activities among those structures changes depending on the pathologically anxiety-like state and the recovery phase.

II. Aim of the Group

First, the specific objective of this research item is to clarify the differences in neural activity between pACC and subgenual cingulate cortex (SCC). We further focus on the synchronization of the local field potentials (LFPs), which have been recorded by the representative regions using the multi-site recording method. We will clarify whether the neural oscillations recorded from the pACC and SCC can synchronize. We adopted the approach-avoidance decision-making task to quantitatively analyze the anxiety-like state of macaque monkeys. We then have found that the electrical microstimulation of the striatum can induce pessimistic decision making resembling the anxiety-like state [1, 2]. The striatal beta oscillation could be categorized into two major groups (Ap and Av groups), and the oscillation intensity of the Av group was correlated with the induced anxiety-like state.

III. Research Topics

Three specific results of this year's project are listed below. We provide a summary for each section.

A. Anatomy of an anxiety-related network originating from the pACC

First, we asked humans to perform a conflict task similar to that of macaque monkeys and examined neural responses by fMRI. We found that neural activity related to the approach-avoidance conflict was similar between macaques and humans in various brain areas, including the pACC [3]. These results suggest that the network originating from the pACC is common between humans and macaques. We found that the pACC sends projection to the striatal striosome compartment [4]. We further found that the pACC and other anxiety-related structure projects to the amygdala (Fig. 1)and construct a reciprocally connected network. We summarize these results (Fig. 2) and submitted to a journal [5].

Fig. 1. pACC projections to the amygdala.

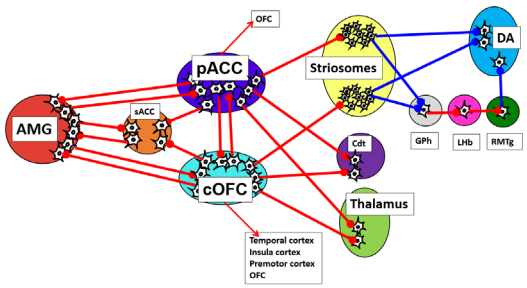

Fig. 2. The connection originating from the pACC and cOFC could consists anxiety network.

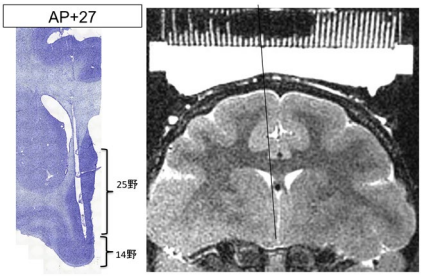

Fig. 3. Simultaneous recording from pACC, SCC, and striatum was confirmed.

B. *Construction of an experimental system from the ventromedial prefrontal cortex*

Second, we have recorded from the SCC [6], which is the critical target of deep brain stimulation (DBS) to treat major depression. We also have simultaneously recorded from the pACC. We thus investigated the relationship between the pACC and the SCC by focusing on the two areas' synchronous activities (i.e., coherence). We further recorded the LFPs in the striatum. The results were analyzed and published in a journal [7]. The synchronization of the beta oscillations in each area can be examined by analyzing coherence. We will induce a pessimistic state by striatal stimulation and examine whether the coherence intensity changes with the change of the emotional states. If the membrane potential in the two regions oscillates synchronously, then the influence of spikes in one region to the other becomes more effective (communication through coherence hypothesis)[8]. We will examine whether the induction of anxiety can change the coherence between the two areas. This year, we confirmed the positions of the electrodes by histological examination. We confirmed that the electrodes had been properly inserted into the SCC (Fig. 3).

C. *Discovery of un-uniform inverse correlation between striatal dopamine concentration and beta oscillations*

Dopamine depletion in the brain is known to cause Parkinson's disease, associated with movement and mood disorders. In the patients with Parkinson's disease, an increase in the magnitude of the beta-range neural oscillations in the striatum of the basal ganglia was observed. It is thus assumed that the beta magnitude in the striatum is inversely correlated with the dopamine concentration. We performed simultaneous recordings of the beta-range neural oscillations and dopamine signals using Fast scan cyclic voltammetry (FSCV) while monkeys performed a behavioral task. We found that the inverse correlation between beta waves and dopamine appeared depending on the task context, showing a more complex feature than the previous assumption. The inverse correlation between beta oscillation and dopamine was not uniform. This new finding is expected to provide a new guideline for diagnosing and treating Parkinson's disease. We recently published these results[9].

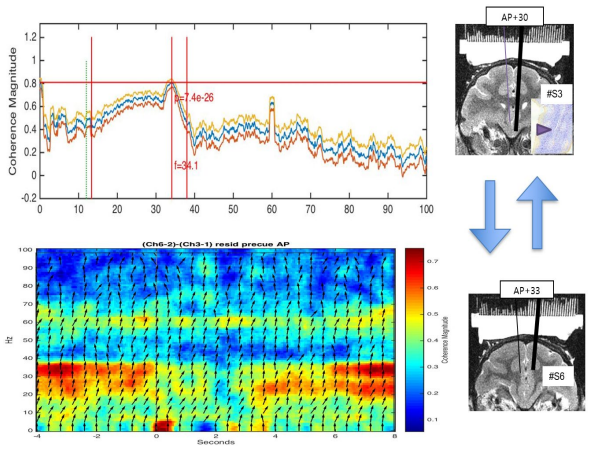

Fig. 4. Example of coherence between SCC and pACC. We will investigate the relationship between anxiety induction and coherence in detail.

IV. Future Perspective

Finally, we will summarize the results of this year's research and provide an outlook for the next year and beyond. We calculated the degree of synchronization by calculating the coherence between the pACC and the LFP of the SCC and found that there is particularly strong synchronization (coherence) in the high-beta band (Fig. 4). We will continue to analyze these data and further elucidate how the correlation between pACC and SCC changes when anxiety is induced.

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Annual report of research project A05-3

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***Abstract*—In order to elucidate the Hyper-Adaptabiility 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, we make 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 extract structural features such as cluster coefficient or centrality, and attempt to clarify modifications of the connectome by epilepsy pathology or variations by different strategies for higher-order motor tasks.**

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 research area "Embodied-Brain Systems Science," we delineated the neural basis and compensation mechanism of praxis or sense of agency (SoA) embodied in the ventral frontal lobe and the parietal lobe as physicians contributing to epilepsy surgery. In the present research area, "Hyper-Adaptability," for investigating the acute and subacute (hyper) adaptation at the network level, we 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.

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.

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, we make 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 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 clarify how the brain hyper-adapts to the intervention to the premotor cortex, we investigate the impact of high-frequency electrical stimulation and brain surgery on hyper-adaptation. We apply high-frequency electrical stimulation to the cortex for clinical functional cortical mapping. Stimulation of the premotor areas affects the execution of higher-order motor tasks to a variable degree. To investigate the immediate modulation, we use this opportunity to study the relationship between the mode of behavioral impairment and network impairment by combining quantitative motion analysis and ECoG signal analysis during stimulation.

III. Research Topics

We have carried out the following three research projects.

A. Electrophysiological connectome of individual patient and patients group

With subdural electrodes (more than 100 electrodes per one patient), ECoG was recorded during motor tasks such as simple movements (face, hands, shoulders, feet) and higher-order motor tasks such as tool-use pantomime, reach to grasp movements, finger movements, and Go / NoGo tasks. The cortical brain rhythms, ranging from infraslow to high gamma activity, was explored and referred to as a localizer together with the anatomical information of the electrodes. In the NoGo task, task-specific event-related potentials (ERPs) were recorded mainly in the medial frontal lobe and the dorsal premotor area [1]. Next, low-frequency electrical stimulation was applied through all electrodes, and the cortico-cortical evoked potential (CCEP) recorded via intercortical

connections was used as an indicator of effective connection. Electrophysiological connectomes were created in each patient.

CCEP during the inferior frontal gyrus stimulation showed a connectivity gradient. Pars Orbitalis and Pars Opercularis stimulation elicited responses at the antero-inferior part of the temporal lobe & angular gyrus, and the posterior part of the temporal lobe & supramarginal gyrus, respectively, while Pars Triangularis stimulation showed an intermediate connectivity pattern between the two. [2].

The part of the ventral premotor area (negative motor area [NMA]) was known to show a negative motor response (arrests of repetitive movement of the tongue, hands, and feet stops) upon ECS. In NMA, we showed significantly larger outbound connections compared to the primary motor cortex and the language areas [3]. In addition, we investigated how epilepsy modulated brain networks, and revealed strengthened connectivity in epileptic regions and weakened connectivity in non-epileptic regions [4]. In the future, we will compare individual connectome with group data to clarify the transformation of connectome due to epilepsy pathology and strategies. Besides, as a leading-expert in CCEP, the PI wrote reviews and textbook chapters on intraoperative CCEP function mapping [5] [6] .

B. Disturbance of network by high-frequency electrical stimulation and disability of higher-order motor function

In the Go / NoGo task, high frequency stimulation tended to impair NoGo task performance when the stimulated electrodes had broader CCEP connectivity. It was suggested that disturbance of the NoGo task is caused by its impact to the whole network including the cortical regions other than the stimulated area.

In addition, by carefully removing stimulus artifacts of high-frequency stimuli, we were able to detect intrastimulus discharges (ISD) that were induced in the remote cortical regions by ECS of the premotor area. ISD appeared within the range of physiological CCEP connectivity, but only a small number of electrodes with ISD did show a negative motor response upon ECS [7]. We will identify the mode of network disturbance caused by ECS in the premotor area by incorporating ECS-induced ISD and CCEP connectome database. We then compare the network disturbance with the degree of task impairment by combining subject's introspection and quantitative behavior analyses in order to clarify the dynamics of the brain to the acute intervention. We attempt to generalize the brain dynamics to ECS by performing the similar analyses in the language or visual-related tasks (preliminary reports [8,9]).

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

This prospective study is not well performed this year due to COVID-19 pandemic. 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 excluding the resection area 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 elucidate "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, we focused on the human premotor area and constructed preliminary electro-physiological connectomes related to the premotor area to elucidate the network characteristics. Although it may be difficult to recruit patients due to the COVID-19 pandemic, we plan to recruit five patients prospectively. We also retrospectively incorporate 20 patients in whom higher motor-related cortical rhythm measurements and comprehensive CCEP evaluations were available. We will continue the aforementioned research plans in the next year. Findings obtained in clinical systems neuroscience would contribute to delineate the "hyper-adaptability" mechanism as an essential reference for model construction/verification and network modification by rehabilitation intervention.

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A05-4 Neural circuit rearrangement mechanisms underlying the recovery from learning deficits in Parkinson's disease model animals

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Abstract—**Model rats for Parkinson's disease generated by degeneration of nigrostriatal dopamine neurons impairs the acquisition of sensory discrimination learning, but the impairment is recovered gradually through the continuous trials. To understand this recovery mechanism, our research group aims to address the role of dopaminergic neuronal pathway originating from the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) in the learning recovery.**

I. Introduction

Neural circuits in the central nervous system show a dynamic rearrangement in response to impairment or injury of the brain regions and play a key role in the recovery and compensation from the disturbed functions. The rearrangement of the network is an important strategy for animal's adaptation to compensate and restore the impaired functions. Although the study of the mechanism underlying network rearrangement has been performed by using models impaired motor functions, the mechanism for improving learning and cognitive dysfunctions remains still unknown. Our research group has been investigating the neural mechanism of cortico-basal ganglia network that controls the acquisition and performance of stimulus-response association during operant learning. Especially, the learning deficits caused by impaired dorsal striatal function were recovered gradually by continuous task trials, and this recovery is dependent on the function of the nucleus accumbens (NAc). These findings suggest the possibility that dysfunction in the dorsal striatum in Parkinson's disease may be compensated by the neural circuit mediated through the NAc. Model rats for Parkinson's disease generated by pharmacological disruption of nigrostriatal dopamine neurons impairs the acquisition of sensory discrimination learning, but the impairment is recovered gradually through the continuous trials. So far, one mechanism that explains this recovery is considered to be originated from regeneration of nerve fibers from the nigrostriatal system. In this study, our group will examine the possibility that the NAc circuit may be involved in the restoration of the learning deficits in Parkinson's disease model animals during the repetitive task trials.

II. Aim of the Group

In this study, our group focusses on dopamine system originating from the ventral tegmental area (VTA) and projecting to the NAc and to investigate the role of VTA-NAc dopamine pathway in the learning recovery by using the technique of pathway-specific manipulation of neural activity. To address this issue, a chemogenetic strategy is necessary to suppress or stimulate the activity of specific neuronal types during the process of learning recovery. Generally, a mutant form of metabotropic receptors is used for chemogenetic strategy, but this procedure requires endogenous second messenger systems, which may lead to different responses among individual neuronal types. Therefore, our group tried to use a chemogenetic approach with ionotropic receptors. For inhibitory ionotropic receptors, glutamate-chloride ionic channels that are stimulated by a specific ligand ivermectin are known to be useful to suppress the activity of target neurons. In contrast, because a stimulatory ionotropic receptor system that can induce a behavioral response has not yet been developed, our group tried to establish this new approach. Next, a transgenic rat strain that expresses Cre recombinase in specific ell types is necessary to manipulate the activity of the VTA-NAc dopamine system. Our group aimed to generate knock-in rats, in which Cre transgene is introduced into the gene encoding tyrosine hydroxylase (TH) by using the genome editing technique.

III. Research Topics

A. Develpmeent of stimulatory ionotropic chemogeenetic strategy: Drosophila ionotropic recepors (IRs) belong to the glutmate receptor superfamily, and IR84a and IR8a subunits form the functional complex showing an excitatory respnse to specific ligands, such as phenylacetoaldehyde and phenylacetate. In this technoloy, IR84a/IR8a complex is expressed in neurons of interet and injection of a specific liand into the brain region induces the activation of the target neurons (Fig. 1A). Transgeic mice were generated that carry GFP-IR84a-2A-IR8a gene cassette under the contrrol of TH gene promoter. Transgene expresson was detected in the locus

coeruleus (LC) of the transgenic mice by immuno-histochemistry and in situ hybridization methods. Brain slices through the LC were pepared and used for in vitro electrophysiology. The applicaton of phenylacetate solution (0.1%) induced the increased firing frequency and elevated membrane potential in LC neurons of the transgenic mice (Fig. 1B). In the in vivo electrophysology, pneumatic injection of phenylacette solution into the LC caused an increase in firing activity in LC neurons of the transgenic animals (Fig. 1C). In addition, the microdialysis experiment indicated that microinjection of phenylacetate into the LC stimulated the release of noradrenaline in nerve terminal regions of the LC in the transgenics. Furthermore, conditioned mice with taste version were used for taste reactivity test, in which conditioned stimulus (CS: sucrose solution) is intraorally injected through the cathether. Microinjection of phenylacetate into the LC markedly shortened the latency to express aversive behavior to the CS in the transgenic mice (Fig. 1D), indicating that the stimulation of LC actvity enhances the rerieval process of conditioned taste avesion memory. These results highlight that our ionotropic chemogenetic strategy with IRs enable to stimulate the activity of target neurons expressing IR84a/IR8a complex, resulting in the chaned behavioral response (reference 1).

B. Generation of knock-in rats expressing Cre recombinase in dopamine neurons: The gene cassette contaning 2A-Cre-poly A signal was introduced beween the C-terminal amino acid and stop codon in te rat TH gene by using a modified genome editing termed the Combi-CRISPR method. Guide RNA, edited DNA, ans Cas 9 were introduced into rat fertilized eggs with electroporation, which were implanted into pseudopregnant females. The offspring with a knock-in mutation were ideentified with polymerase chain reaction (reference 2). Expression pattern of Cre recombinase transgene was analyzed by immunohistochemistry with anti-Cre antibody. Cre transgene was detected in dopamine neurons in the substantia nigra and VTA as well as noradrenline neurons in the LC of the knock-in transgenic rats. When viral vectors that expres GFP dependent on Cre-loxP recombination were injected into the brain rgions, expression of GFP transgene was observed in dopamine and noadrenaline neurons in the knock-in rats. These data indicte that the knock-in rat stran will be useful to introduce the transgenes appropriate for the control of neuronal activity into dopamine neuons by using the viral vector system.

IV. Future Perspective

Our research group successfully developed a new strategy for stimulatory ionotropic chemogenetic tool with insect IRs and generated the knock-in rat strain that expressed Cre transgene in dopamine neurons. These resources are necessary for studying the role of VTA-NAc dopamine system in the recovery from learning deficits in Parkinson's disease model. Subsequently, our group will produce a disease model with the TH-Cre knock-in rats and manipulate the activity of VTA-NAc dopamine neurons with stimulatory and inhibitory chemogenetic approaches to examine the involvement of VTA-NAc dopamine system in the behavioral recovery in animal models.

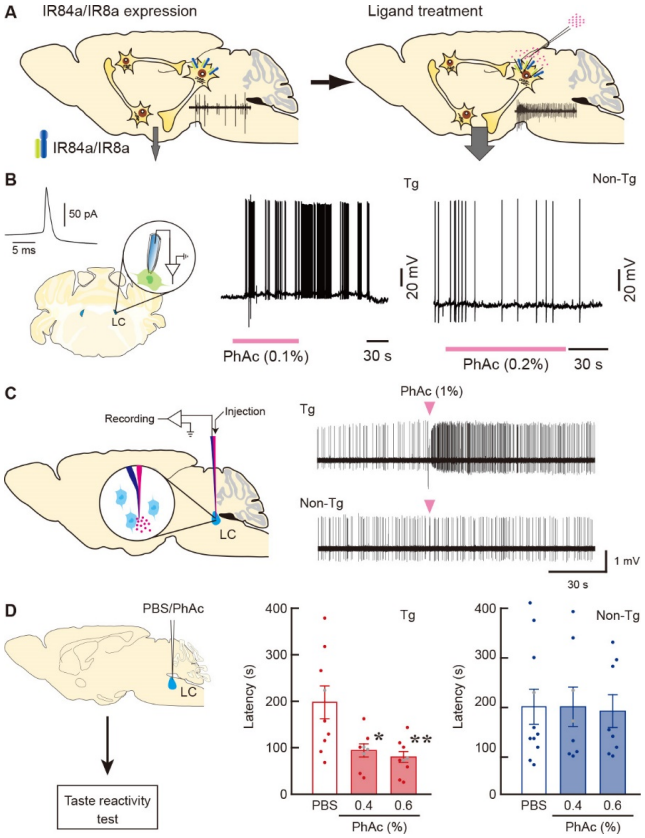

Figure 1. Stimultory ionotropic chemogenetic approach. (A) Experimental strategy. (B) Slice electrophysiology. (C) In vivo electrophysiology. (D) Effect of ligand injection on the retrievl process of conditioned tast aversion task. (modified from reference 1)

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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. Hand movement is controlled mainly by the two corticospinal pathways: the direct and indirect pathway which exert monosynaptic or polysynaptic control from M1s over spinal motoneurons. When the direct pathway was lesioned, the indirect pathway played a role in functional recovery of the impaired hand movements. Our motivation is to develop the neurorehabilitative protocols to increase recruitment of the indirect pathway in functional recovery in patients who disable to perform fractionated hand movements. Repetitive brain stimulation protocols alter corticospinal conductivity. Our long-term goal is to develop the brain stimulation techniques that enable to optimize recruitment of the indirect pathway during execution of hand movements. During the period of fiscal year 2020, we have finished development of the cortico-spinal functional magnetic resonance (cs-fMRI) techniques to observe activation of the indirect pathway. We are also developing the novel techniques to estimate change in conductivity of the indirect pathway after the brain stimulation protocols.**

I. Introduction

Recent studies in non-human primates indicated involvement of the indirect pathway during dexterous hand movement. No studies so far demonstrated recruitment of the indirect pathway during hand movements in humans. We estimated recruitment of the direct and indirect pathway during right-hand movement (RHM) and left-hand movement (LHM) using cs-fMRI. We measured neuronal activity in M1 and spinal cord at the segments where motoneurons innervating hand muscles reside. We assumed the direct and indirect model that exerted multi-synaptic influences from primary motor cortex to the spinal cord (Figure 1). Our results suggested involvement of the indirect pathway during LHM but not during RHM. We will observe the effects of repetitive brain stimulation on the indirect pathway using cs-fMRI techniques. The effects of several brain stimulation protocols will be compared with respect to the following questions. Will the stimulation protocols increase recruitment of the indirect pathway during LHM? Will the stimulation protocol alter conductivity in the indirect pathway? To address the two questions, we decided to improve the cs-fMRI techniques.

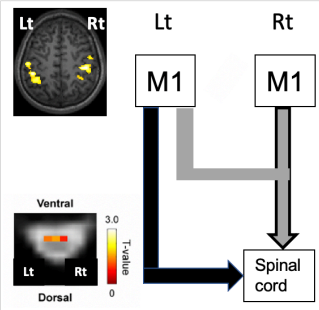

Fig1. The indirect pathway model during LHM. We measured activity in bilateral M1 and the spinal cord. We constructed the direct and indirect pathway model that conveys the monosynaptic inputs from M1 contralateral to the moving hand (black-colored) or integrates signals from bilateral M1s onto the spinal cord (gray-colored). We simulated if the indirect pathway may explain activity in the spinal cord.

Abbreviations: Left=Lt, Right=Rt

II. Aim of the Group

Our goal is to determine the brain stimulation protocol that can induce the greatest recruitment of the indirect pathway during LHM. To compare the effects of several brain stimulation protocols on the indirect pathway, we will employ the cs-fMRI techniques. In this fiscal year 2020, we have developed the modified version of the cs-fMRI techniques.

III. Research Topics

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

A. Dvelopment of the modified version of the cs-fMRI techniques.

As we described in the introduction, we had developed the cs-fMRI techniques. We measured activity in M1 and the spinal cord only, as depicted in Fig.1. Note that the indirect pathway includes relay circuits in the brainstem and the spinal cord at the cervical segments C3-C4 that likely serve integration of the signals from bilateral M1s. We did not observe activity in the brainstem and the spinal cord. To visualize activity in the brain, brainstem and the spinal cord. We modified the MRI scanning protocol to cover all of the three regions. We also 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. Here we presented the result of single subject's data (Fig. 2).

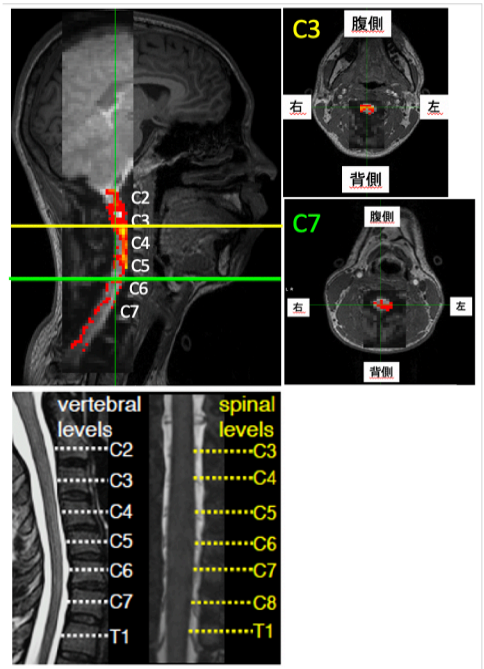

Figure 2. Statistical parametric mapping in the entire cervical spinal cord. We performed statistical parametric mapping to explore active regions during LHM relative to rest (left panel, upper). Anatomical landmarks of C2-C7 indicates vertebral levels in the cervical spinal cord. Note the difference 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).

B. Development of the novel techniques to estimate conductivity between M1, brainstem and the spinal cord.

In the conventional techniques, we computed conductivity with use of input and output activity. There are no non-invasive techniques to record neuronal activity in the spinal cord in humans. We decided to develop the techniques to estimate conductivity in the indirect pathway. In this experimental setting, we will give test pulses of brain stimulation, measure evoked activity in the brainstem and the spinal cord at the cervical segments C3-C4, and compute conductivity with use of the input and output measurements. To achieve this project, we need to integrate brain stimulation and cs-fMRI techniques. We also need to synchronize the timing of test pules of brain stimulation and fMRI scanning. We have experiences to accomplish integration of the brain stimulation and fMRI techniques. We are preparing to reconstruct this system.

IV. Future Perspective

In this fiscal year 2020, we have developed the cs-fMRI techniques to estimate activity and conductivity in the indirect pathway. We conducted a pilot study, analyzed data and discussed the expected results. In the next fiscal year 2021, we will perform a main experiment using the techniques that we developed.

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A05-6 Analysis of motor control system in the recovery of forelimb function by rehabilitation after intracerebral hemorrhage

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***Abstractt*—In the FY2020, we established the methods for our project such as multi-electrode analysis from the cerebellum and double-virus infection into dentate nucleus and red nucleus, showing that we are ready to analysis for our project in near future.**

I. INTRODUCTION

Constraint-induced movement therapy (CIMT) is known as an effective rehabilitation by forcing the use of damaged forelimb after the cerebrovascular disorder. Using model rats that show relatively big motor deficits with a small hemorrhage near the internal capsule (ICH), we are challenging to clarify the mechanism of forced-limb use (FLU) that represents CIMT in rats. We revealed that FLU after ICH improves the recovery of disturbed forelimb function by ICH, cortico-rubral pathway is involved in the functional recovery by FLU, and cortico-reticular pathway has a potential to substitute the recovery of cortico-rubral pathway when needed. However, dynamic change of the adaptive mechanism via the cerebellum in the functional recovery by FLU is still unknown.

II. AIM OF THE GROUP

The final purpose of our project is to analyze adaptive mechanism of motor control system in the cerebellum on the recovery process of the rehabilitation after cerebral hemorrhage by the selective blockade in the recurrence pathways among the red nucleus, the olive nucleus and the cerebellum with double virus-vector infection method.

The purpose of this year for our final purpose is 1) to confirm both inputs and outputs in the red nucleus (parvocellular part) that is supposed to be related to functional recovery by the rehabilitation, 2) to investigate if we can successfully detect the electric response from the cerebellum nucleus (dentate nucleus) and Purkinje cell using the multi-electrode analysis, and 3) to establish our experimental system for the final purpose including the availability of double virus-infection method into the red nucleus.

III. RESEARCH TOPICS

The results of our experiment in this year were shown as follows.

A. Confirmation of the inputs and the outputs in the red nucleus parvocellular part

We inject a retrograde tracer Mini-Ruby into two places of the red nucleus at first and examined the stainability of the cerebellar nucleus of contralateral side of the cerebellum, ipsilateral side of the cingulate gyrus and ipsilateral side of the motor area.

Although Mini-Ruby-positive cells were detected in the dentate nucleus, the interposed nucleus, and the fastigial nucleus of the cerebellum, no significant difference in the positive cells was shown between three groups of sham group, ICH group, and ICH + FLU group. In other words, it was revealed that the tracer infusion should be limited near the parvocellular part of the red nucleus.

We next performed to inject Mini-Ruby into red nucleus parvocellular part and the biotin dextran amine (BDA) into the dentate nucleus of the cerebellum.

Limited detection of Mini-Ruby-positive cells was observed in contralateral side of dentate nucleus with the injection into a place (A: -5.2mm, L: 1.6mm, V: 7.5mm) of the red nucleus (Figure 1). In addition, the injection of an anterograde tracer BDA into the dentate nucleus resulted in BDA-positive fibers in the contralateral side of red nucleus. Furthermore, Mini-Ruby-positive cell bodies were shown in the purkinje cell layer by the injection into the dentate nucleus.

From the above results, neural network of Purkinje cell - dentate nucleus - red nucleus parvocellular part was confirmed.

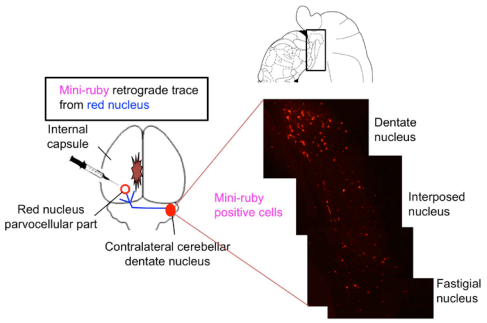

Figure 1 Retro-tracing of cerebellum nucleus by Mini-Ruby injection into the red nucleus

B. *Investigation of successful detection of the electric response fron the cerebellum nucleus (dentate nucleus)*

To measure the changes of electrical response in the motor control system by the rehabilitation after ICH, we challenged to detect electrical response in the Purkinje cell of control rat with the multi-channel electrode method as the pre-stage. (Solages et al, Neuron 2008)

As a result, we was able to record the spikes in the cerebellar cortex that is related to forelimb movement in anesthesia condition. In addition, we revealed that each response of simple spike and the complex spike was detected by spike analysis of the recorded spikes (Figure 2). In other words, we were ready to measure the changes of electrical response in the cerebellum Purkinje cell by the rehabilitation after ICH with multi-channel electrode method.

On the other hand, we are now trying to investigate the electrical response in the dentate nucleus of the cerebellum.

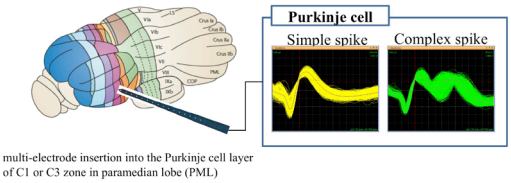

Figure 2 Spike detection in the Purkinye cell and spike sorting

C. *Confirmation of experimental plan for double virus infection method*

To block neuronal network between dentate nucleus and red nucleus parvocellular part selectively with double-virus infection method, we discussed the virus information with Associate Professor Kenta Kobayashi of Natl. Inst. for Physiological Sci. (research cooperator of this project) and decided a future experiment plan as follows: adenoassociated virus vector (AAV-DJ-EF1-DIO-hM4D(Gi)-mCherry) should be injected into the dentate nucleus with retrovirus vector (FuGE-MCSV-Cre) injection into red nucleus parvocellular part.

Using AAV-DJ vector (there is no DREDD system) developing only EGFP in response to Cre, we are now examining optimization of the quantity of infusion of the virus vector to a cerebellum dentate nucleus.

IV. FUTURE PERSPECTIVE

To analyze adaptive mechanism of motor control system in the cerebellum on the recovery process of the rehabilitation after ICH, we performed 1) to confirm both inputs and outputs in the red nucleus (parvocellular part), 2) to investigate if we can successfully detect the electrical response from the cerebellum nucleus (dentate nucleus) using the multi-electrode analysis, and 3) to establish our experimental plan for the final purpose including the availability of double virus-infection method into the red nucleus and dentate nucleus.

Following to the optimization of virus infusion, we will confirm the loss-of-function of DREADD system with double-virus infection method in the group of ICH + FLU. We also evaluate forelimb motor function by pellet reaching test.

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A05-7 Dynamics of Inter-regional networks underlying hyper-adaptation from fear induced mal-adaptation states

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***Abstract*—Animals that have experienced strong aversive experiences fall into mal-adaptation states in which they cannot take adaptive behaviors due to the fearful memories. Through the following hyper-adaptation process, the animals recover their adaptive behaviors. Accumulating evidence suggests that multiple brain regions such as amygdala, ventral hippocampus, and prefrontal cortex are involved in the fear memory related transitions to the mal-adaptation states and ones to the hyper-adaptation states, but it is still elusive how inter-regional networks change through these state transitions. Furthermore, it is barely known what kind of network activities regulates the changes. To elucidate these points, we performed simultaneous large-scale electrophysiological recording in the amygdala, ventral hippocampus, and prelimbic cortex of fear-conditioned rats. We found that amygdala–prelimbic cortex and ventral hippocampus–prelimbic cortex cell ensemble pairs coactivated in post- but not in pre-conditioning non-rapid eye movement sleep epochs. We also observed that these inter-regional coactivations were hosted by fast network oscillations. These findings suggest fast oscillation may regulate inter-regional communications that are crucial for the transition to mal-adaptation states. Further studies are warranted to elucidate how inter-regional ensemble coactivations are involved in the hyper-adaptation process.**

I. Introduction

Fear conditioning is a well-established animal model of human post-traumatic stress disorder (PTSD). Fear-conditioned animals are in mal-adaptation states where the animals cannot take adaptive behavior due to their fearful memories. On the other hand, extinction learning provokes a hyper-adaptation process in which animals recover normal behavior by acquiring new memory that suppress fear responses while fearful memories themselves are maintained [1]. The acquisition and extinction of fear memories involve the amygdala, ventral hippocampus, and prefrontal cortex [2]. However, it is still elusive how inter-regional networks across these regions change through transitions to mal-adaptation states and ones to hyper-adaptation states and how these changes are regulated. Revealing these points would provide fundamental information for developing cure methods of memory and emotion related mental disorders such as PTSD and anxiety disorders.

II. Aim of the Group

This research project aims to clarify changes in inter-regional brain networks which supports hyper-adaptation from fear memory induced mal-adaptation. Furthermore, this project also tries to reveal regulation mechanisms underlying the changes in the inter-regional networks. To obtain these goals, first, we elucidate what changes in the process of mal-adaptation, then try to understand the compensation mechanism that enables hyper-adaptation. In this year, we focused on the transition to mal-adaptation states, and we aimed to clarify the dynamics of inter-regional networks during the mal-adaptation process and network mechanisms that support the dynamics.

III. Research Topics

A. Simultaneous recording from three brain regions using multi-regional large-scale electrophysiology

By performing multi-regional large-scale electrophysiological recordings on freely moving rats, we obtained spike activities of hundreds of neurons and local field potentials (LFPs) from basolateral amygdala (BLA), ventral hippocampus CA1 region (vCA1), prelimbic cortex layer 5 (PL5) in the prefrontal cortex (Fig.1). Neuronal activities were continuously recorded for 17 hours, during which fear conditioning, context and cue retention test, extinction learning, and test for retention of extinction were administrated. To reduce electrical noise, we used stimulation through eyelid electrodes as the unconditioned stimulus [3].

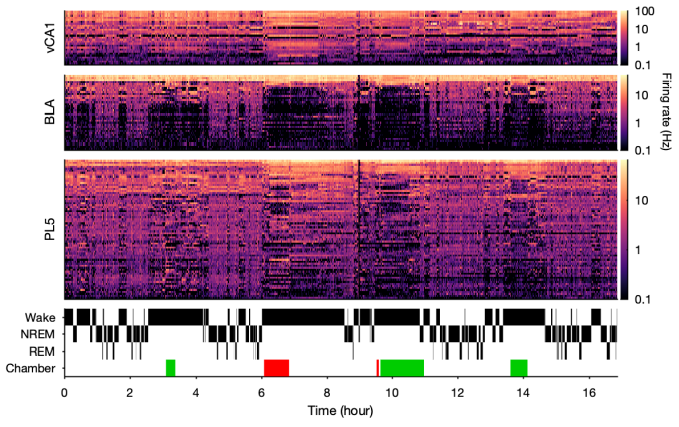

Fig. 1. A representative example of continuous large-scale electrophysiological recording from vCA1, BLA, and PL. Firing rates of simultaneously recorded neurons were calculated in 10-s bins. Each row represents each cell. Hypnograms and timing of behavioral experiments were shown on the bottom.

B. *The inter-regional synchronous activity emerged in sleep periods following fear conditioning*

To evaluate inter-regional interactions of local cell ensembles, we first determined cell ensembles in BLA, vCA1, and PL5 during fear conditioning periods by using independent component analyses and estimated instantaneous ensemble activation strength of the identified ensembles in pre- and post-conditioning sleep periods [4]. Next, we evaluated inter-regional interactions of the cell ensemble activations by performing cross-correlogram analyses. We found that subsets of BLA–PL5 and vCA1–PL5 ensemble pairs coactivated significantly in post-conditioning non-rapid eye movement sleep (NREM) epochs (Fig. 2). In contrast, we observed virtually no significant coactivations in pre-conditioning NREM epochs. These results indicate BLA–PL5 and vCA1–PL5 synchronous activity emerged after the transition to the fear-induced mal-adaptation states.

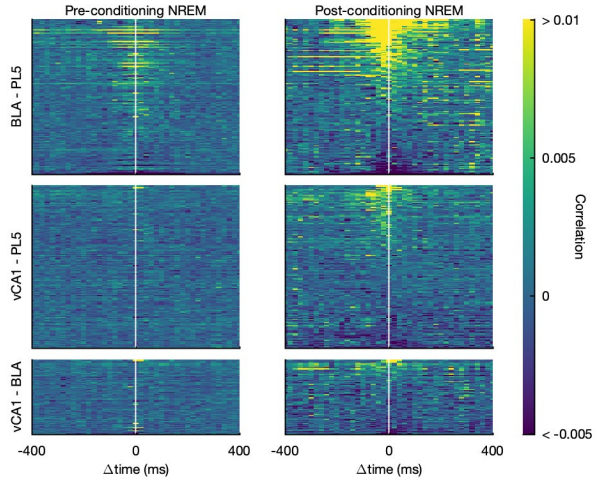

Fig. 2. Cross-correlograms across instantaneous activation strength of cell ensembles in different brain regions during pre- and post-conditioning NREM. Each row represents each ensemble pair.

C. *Fast oscillations on the local field potentials hosted inter-regional ensemble coactivation*

Next, we sought network activity patterns during which the ensemble coactivation among vCA1, BLA, and PL5 occurred. First, we obtained instantaneous coactivation strength as products of z-scored instantaneous activation strength with optimal time shift which was determined based on the peak time point of the cross-correlogram, then individual coactivation events were detected by thresholding the instantaneous reactivation strength traces. To examine whether characteristic network activity patterns are associated with the inter-regional ensemble coactivations, coactivation event-triggered averages of LFP wavelet power were obtained (Fig. 3). At the BLA–PL5 and vCA1–PL5 coactivation, strong peaks around 100 – 300 Hz were observed on BLA and vCA1 wavelet power, respectively. These peaks presumably reflect amygdalar high frequency oscillations (HFOs) [5] and hippocampal sharp-wave ripples (SWRs) [6]. Consistent with these observations, HFO- and SWR-peak triggered average of ensemble coactivation strength showed transient enhancement around time 0. These results imply that fast network oscillations such as HFOs and SWRs are tightly related to inter-regional synchronous ensemble actives that emerged after the transition to the mal-adaptation states.

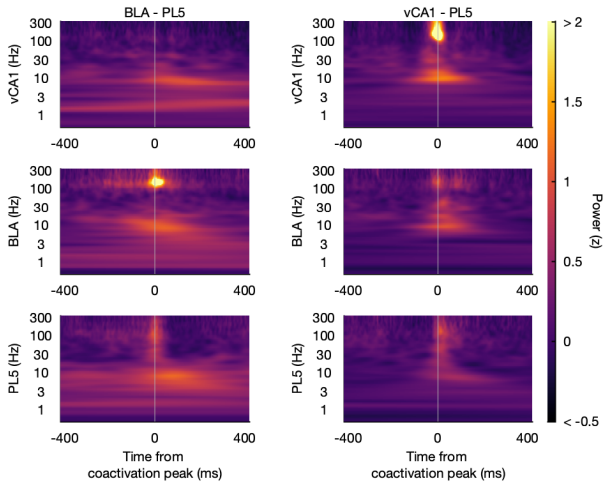

Fig. 3. BLA–PL5 and vCA1–PL5 coactivation triggered average of LFP wavelet power. Wavelet powers were z-scored within each frequency scale.

IV. Future Perspective

In this year, we revealed that inter-regional coactivations of cell ensembles emerged after the transition to the mal-adaptation states. Furthermore, our results indicate that fast network oscillations such as HFOs and SWRs are involved in the inter-regional coactivations of cell ensembles. So far, we performed pair-wise analyses of cell ensemble interactions, but we will analyze how interactions among three brain regions change to obtain a comprehensive understanding of inter-regional network dynamics associated with transitions to mal-adaptation states. Furthermore, we will analyze network changes induced by extinction learning and compare them with ones caused by fear-conditioning to clarify what kind of compensation enable hyper-adaptation.

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Annual report of research project A05-8

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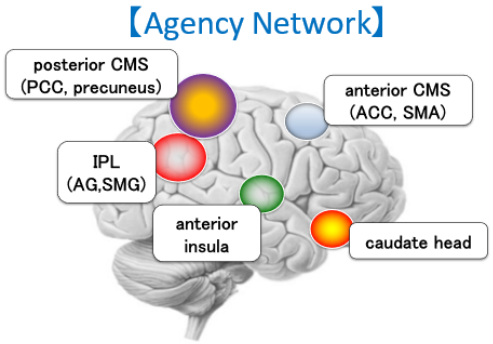
Abstract

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. Our main achievements in this fiscal year are as follows. 1) We revealed a Statistical Learning Model of the Sense of Agency, 2) We showed the time window for sense of agency in school-age children is different from that in young adults, 3) We found the altered sense of agency in children with developmental coordination disorder, 4) We developed a method for cognitive rehabilitation of SoA (Agency Tuning).

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". 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.



PLoS ONE 8(8):e72267,2013.
Front. Psychiatry 10:171,2019.

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 hypothesize that this tuning of SoA could reorganize neural systems and achieve hyper-adaptation of patients with those illnesses in their living environment.

III. Research Topics

A. Statistical Learning Model of the Sense of Agency

Humans have a natural tendency to generate prediction models of the environment and adapt their models according to changes in the environment. The SoA is associated with the degree of the adaptation of the prediction models, e.g., insufficient adaptation causes low predictability and lowers the SoA over the environment. Thus, identifying the mechanisms behind the adaptation process of a prediction model related to the SoA is essential for understanding the generative process of the SoA. In the first half of the current study, we constructed a mathematical model in which the SoA represents a likelihood value for a given observation (sensory feedback) in a prediction model of the environment and in which the prediction model is updated according to the likelihood value. From our mathematical model, we theoretically derived a testable hypothesis that the prediction model is updated according to a Bayesian rule or a stochastic gradient. In the second half of our study, we focused on the experimental examination of this hypothesis. In our experiment, human subjects were repeatedly asked to observe a moving square on a computer screen and press a button after a beep sound. The button press resulted in an abrupt jump of the moving square on the screen. Experiencing the various stochastic time intervals between the action execution (button-press) and the consequent event (square jumping) caused gradual changes in the subjects' degree of their SoA. By comparing the above theoretical hypothesis with the experimental results, we concluded that the update (adaptation) rule of the prediction model based on the SoA is better described by a Bayesian update than by a stochastic gradient descent [1].

B. The time window for sense of agency in school-age children is different from that in young adults

This study investigated the difference in the time window of sense of agency between school-age children (N = 94, aged 6–12 years) and young adults (N = 30, aged 21–23 years) by using an agency attribution task and international standardized manual dexterity test. The results showed that the time window for sense of agency was significantly shorter in children compared to young adults. In addition, there was a significant correlation between the time window for sense of agency and manual dexterity only in children. The present

results suggested that sensory-motor function greatly contributes to sense of agency in school-age children [2].

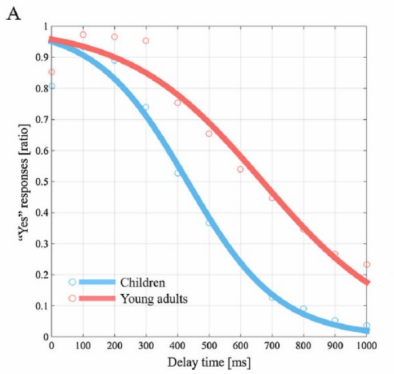


Fig.2 Different SoA between children and adults

C. *Altered sense of agency in children with developmental coordination disorder*

There is increasing evidence that children with developmental coordination disorder (DCD) have deficits in sensory-motor integration, but it is unclear whether the SoA generated by sensory-motor integration is altered. Aims: To investigate whether there is a difference in the time window for SoA between children with DCD and typically developing (TD) children. Methods and Procedures: An agency attribution task was used to quantitatively measure and compare the time window for SoA in 15 children with DCD and 46 children in the TD group. Variables that correlated with the time window for SoA were also examined in both groups of children. Outcomes and Results: The time window for SoA was significantly extended in children with DCD compared to TD children. The time window for SoA in TD children was significantly associated with manual dexterity, whereas the time window for SoA in children with DCD was significantly associated with depressive tendency. Conclusions and Implications: The time window for SoA is altered in children with DCD. The present results suggest that there may be a bidirectional relationship between an internal model deficit and depressive tendency and SoA in children with DCD [3].

Moreover, Previous studies have suggested that children with DCD rely heavily on vision to perform movements, which may contribute to their clumsy movements. However, few studies have objectively and quantitatively investigated the perceptual biases of children with DCD. A visual-tactile temporal order judgment (TOJ) task was used to measure and compare the perceptual biases of 19 children with DCD and 19 age- and sex-matched typically developing children. The point of subjective equality, which demonstrates when "visual first" and "tactile first" judgment probabilities are equal (50%), obtained by analyzing the results of the visual tactile TOJ task, was used as an indicator of perceptual biases. Further, variables (age and manual dexterity in all participants; motor function, autism spectrum disorder and attention deficit hyperactivity disorder traits, and depressive symptoms in children with DCD) associated with perceptual biases were examined with correlation analysis. Children with DCD had significantly stronger visual bias than typically developing children. Overall correlation analysis showed that increased visual bias was significantly correlated with poor manual dexterity. Children with DCD had a strong visual bias, which was associated with poor manual dexterity [4].

D. *We developed a method for cognitive rehabilitation of SoA (Agency Tuning).*

We developed a method for cognitive rehabilitation of SoA (Agency Tuning) in order to tune up precision of SoA. We hypothesize that this tuning method of SoA could reorganize neural systems and achieve hyper-adaptation of patients with those illnesses in their living environment [5][6].

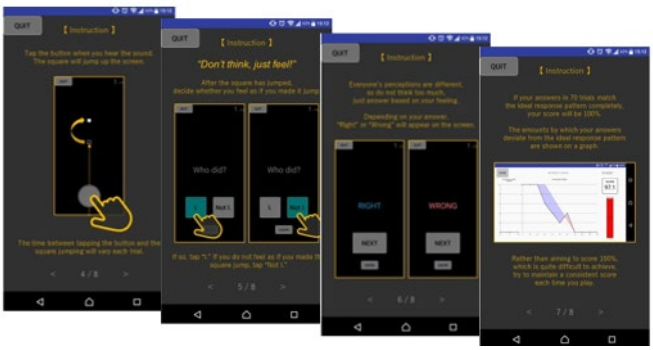


Fig.3 "Agency Tuner" for Agency Tuning

IV. Future Perspective

We have made advances in developing an original method for cognitive rehabilitation of the SoA. In the next fiscal year, 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.

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

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***Abstract*—This year's results can be divided into the following two major categories. (1) Establishment of a model of corticospinal tract injury in marmosets, (2) Establishment of a rehabilitation model, and establishment of an evaluation system for the model.**

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 central nervous system (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. Establishment of marmoset dexterous rehabilitation model

Although marmosets cannot perform the skilled precision grip, in which they pick up small objects with their thumb and index finger like macaque monkeys, they can perform the scissor grip, in which they forage by inserting their fingers into small gaps [3]. In this study, we developed a lever-pulling task for marmosets, referring to a study of squirrel monkeys in the same New World monkeys [4]. We analyzed the kinematics of the hand movements during the lever-pulling task using a high-speed camera, and found that there were differences in aiming and changes in finger angle in the case of small gaps.

B. Establishment of marmose tcorticospinal tract injury model

Second, we established a model of corticospinal tract injury at the level of the fourth cervical cord in marmosets. We found that the success rate of the marmosets in the lever-pulling task (described below) was 28.6% in the non-trained group (n=3). On the other hand, the success rate recovered to 94.2% in the rehabilitation group (n=2).

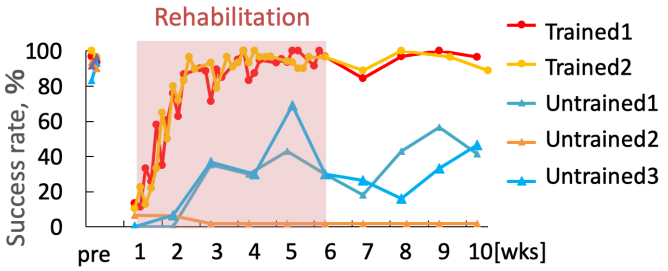

Fig. 1 Effect of rehabilitation in marmosets after injury

In these models, we performed intracortical microstimulation (ICMS) of the motor cortex and found that the motor map of the hand region expanded in the trained group, suggesting that rehabilitation after spinal cord injury causes functional reorganization of the marmoset brain (Fig. 2). Golgi staining was performed to verify the structural changes in the regions where these plasticities occurred, and dendrite elongation was observed in the regions where hand regions newly appeared in the rehabilitation group, suggesting that structural reorganization occurred (Fig. 3).

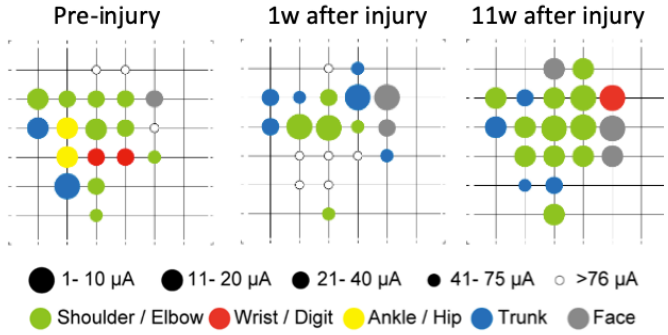

Fig. 2 The wrist/digit region appears after rehabilitation

IV. Future Perspective

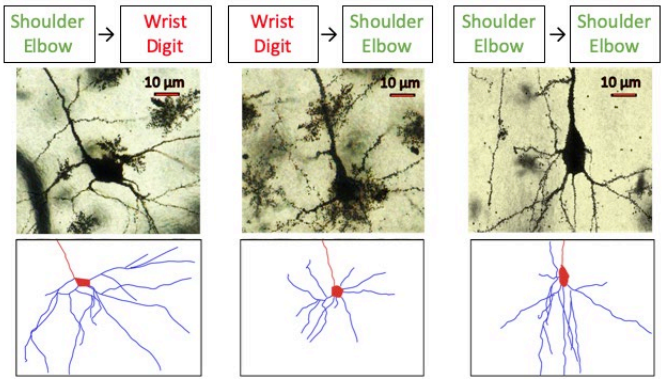

Fig. 3 Structural reorganization after injury

This year, we established a marmoset spinal cord injury model and a rehabilitation model, and verified the functional and structural reorganization in the motor cortex. In the next year, we will observe the activity of GABAergic neurons in the motor cortex by calcium imaging in this model, and follow the changes in spatiotemporal patterns of these neurons during the recovery of motor functions.

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A05-11 Activating neural circuits that prefer affected side of the body using neural modulation by brain stimulation and behavioral technique

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***Abstract*—Hand choices—deciding which hand to use to reach for targets—represent continuous, daily, unconscious decisions. The posterior parietal cortex (PPC) contralateral to the selected hand is activated during a hand-choice task, and disruption of left PPC activity with a single-pulse transcranial magnetic stimulation prior to the execution of the motion suppresses the choice to use the right hand but not vice versa. These findings imply the involvement of either bilateral or left PPC in hand choice. To determine whether the effects of PPC's activity are essential and/or symmetrical in hand choice, we increased or decreased PPC excitability in 16 healthy participants using transcranial direct current stimulation (tDCS; 10 min, 2 mA, 5 × 7 cm) and examined its online and residual effects on hand-choice probability and reaction time. After the right PPC was stimulated with an anode and the left PPC with a cathode, the probability of left-hand choice significantly increased and reaction time significantly decreased. However, no significant changes were observed with the stimulation of the right PPC with a cathode and the left PPC with an anode. These findings, thus, reveal the asymmetry of PPC-mediated regulation in hand choice.**

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 neuromodulation by non-invasive brain stimulation can implicitly change the probability of hand use [1].

II. Aim of the Research

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. [2] 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. [3] 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.

While single-pulse TMS provided causal evidence by disrupting an on-going neuronal process, it did not convey whether neuromodulatory changes in PPC excitability caused by plasticity such as long-term potentiation (LTP) or depression (LTD) affect the decision regarding hand choice. In recent years, tDCS has garnered attention as a tool to investigate a causal link between the behaviour and the neuronal activity of stimulated brain areas in neuroscience. In this study, 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.

III. Methods

Sixteen right-handed healthy participants were asked to reach a 4-cm-diameter target circle presented at one of nine positions on a semicircle situated approximately 27 cm away from the start position either with left or right hand as quickly as possible within 650 ms of target presentation (Fig 1).

Direct electrical current was delivered using a neuroConn DC Brain Stimulator Plus unit. Two stimulation conditions were assigned: (1) the left PPC was stimulated with a cathode and the right PPC with an anode (LCRA condition), and (2) the left PPC was stimulated with an anode and the right PPC with a cathode (LARC condition). A constant current of 2 mA was applied for a total of 10 min.

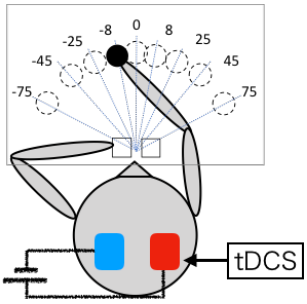

Figure 2 Setup

One block consisted of 108 unimanual reach trials (nine targets on the semicircle displayed 12 times) and 12 control trials presented in a pseudo-random order. The participants performed two blocks before (PRE), during (DURING), and after (POST) the stimulation (Fig 2).

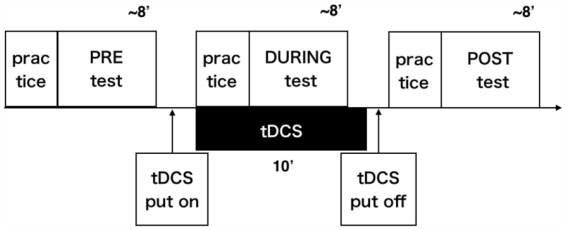

Figure 3 Procedure

IV. Resutls

A logistic function was fitted to the probability of right-hand choice and averaged across participants under the LCRA and LARC conditions. In the LCRA condition (Fig. 4A), the logistic function considerably moved toward the right in favour of the left-hand choice during and after the stimulation relative to before stimulation. In contrast, in the LARC condition (Fig. 4B), the logistic function did not significantly move during and after the stimulation.

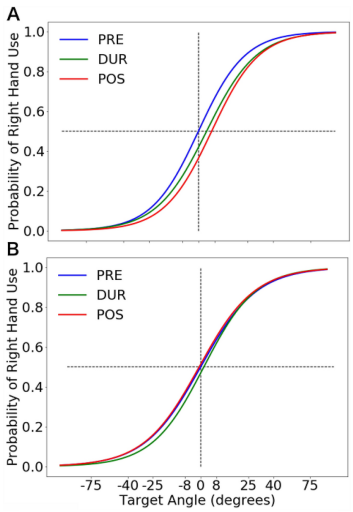

Figure 4 Logistic function fitted to the probability of right-hand choice

By fitting a logistic function to the choice probability data, we determined the point of subjective equality (PSE), i.e. the location at which the participants were estimated to be equally likely to use either the right or left hand. The change in PSE was significantly larger under the LCRA condition relative to the LARC condition after the stimulation. In contrast, the effect of stimulation was not significant under the LARC condition (Fig 5).

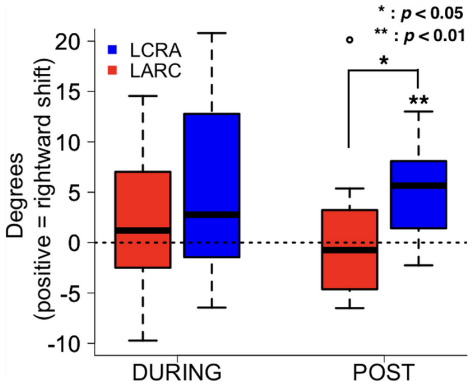

Figure 5 The change in point of subjective equality (PSE) relative to the PRE phase

V. Future Perspective

The present study demonstrated that the probability of left-hand choice increased and that of right-hand choice decreased significantly after stimulation under LCRA condition. 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.

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 10 min of tDCS increased the probability of left-hand choice subsequently. Therefore, we recommend continued development of our methods and their application to promote the use of paretic upper limbs in the rehabilitation of patients with stroke.

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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 results of this year are the following three items. 1. We demonstrated the unprecedented early recovery from acute and subacute phase of spinal cord injury(SCI) by a synthetic synapse organizer protein, CPTX. Moreover, we obtained the potential results of recovery from chronic phase where no effective therapeutic method has ever reported. 2. We applied the anti-sense oligo(ASO) of N-acetylgalactosaminyltransferase-1(T1), a key gene in CS biosynthesis into rodent SCI model. ASO improved the microenvironment for functional recovery. 3. We constructed the AI motion capture system to rigorously evaluate the recovery from SCI. We first tested an automatic measurement system for hind limb stepping (footfall analysis) of mouse. 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 inactivation of the regeneration inhibitor chondroitin sulfate (CS) to improve a fine regeneration environment for neural circuits and (2) the introduction of a synapse-forming factor synapse connector to artificially connect synapses. Furthermore, by combining these strategies with (3):rehabilitation, we aim the further functional improvement after injury. In particular, (1):we will try to reorganize the circuit using nucleic acid medicine for future clinical application. In (2):we plan to apply various epoch-making synaptic connectors to treat spinal cord injury. The technological purpose of this study is to establish a mouse physiology recovery evaluation system by introducing an AI trace system.

III. RESEARCH TOPICS

Followings are three outlines of this year's project.

A. Creation of artificial chimeric protein synaptic connector CPTX and application to spinal cord injury

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 spinal cord injury(Science. 2020) [1]. Although the effect of CPTX to Alzheimer's model mice and cerebellar ataxia is transient, CPTX permanently restored the motor function of SCI. These results indicate that CPTX is a powerful tool for physiological recovery by circuit reorganization and for future therapeutic applications [2] [3] .

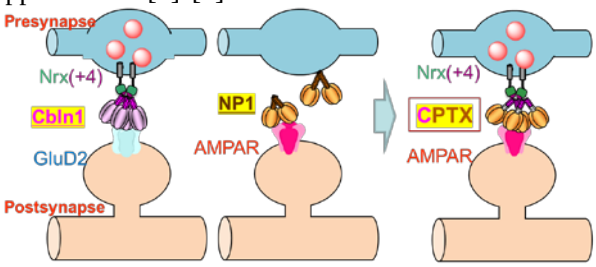

Fig.1 Synthetic synapse organizer(connector) "CPTX" (Science,2020)

CPTX is a novel synthetic molecule that crosslinks a presynaptic molecule (Nrx: neurexin) and a postsynaptic molecule (AMPAR: AMPA receptor). It was created as an artificial chimeric protein (CPTX) in the Cbln1 molecular region that binds to Nrx in the cerebellum and the NP1 molecular region that binds to AMPAR (Fig. 1).

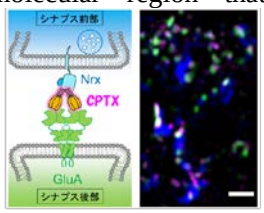

Fig 2. CPTX works with the synapse formation

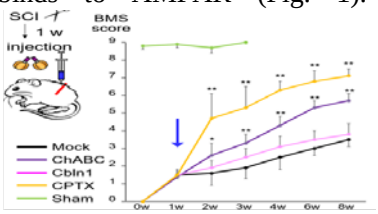

Fig.3 Application of CPTX for the subacute phase of SCI.

CPTX induces *de novo* synaptogenesis both *in vitro* and *in vivo*. The analysis of spinal cord tissue with a super-resolution microscope revealed that it surely localizes between pre and post synapses. These expression pattern suggest that CPTX recruit the adaptive neural circuits for functional recovery. Consistent with this idea, we found that mice treated with CPTX one week after injury (subacute post-injury) also showed dramatic recovery [1] (Fig. 3). In the future, we aim to dissect circuit reorganization and its adaptation to physiological functions. Furthermore, we aim to verify the spinal cord circuit with a new version of CPTX (which enables connections of inhibitory nerves, etc.).

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]. This year, we developed and applied an antisense oligo (ASO) for knocking down of CS expression in a tissue specific manner. Although the ASO sequence expected to be effective in mice and rats has already been found, it was confirmed that the mouse sequence ASO with the new chemical modification has a physiological recovery effect after spinal cord injury in mouse. In addition, we were able to show the possibility of the effect of using it in combination with CPTX. Currently, we are optimizing the appropriate administration timing and dose and try to generate a super-recover model with ASO.

C. Construction of AI trace system

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. This year, we first focused on the hind limb stepping down (footfall analysis), which was generally used for quantification of post-injury recovery. Since we had to rely on human evaluation, the automation and system evaluation were performed (Fig. 4).

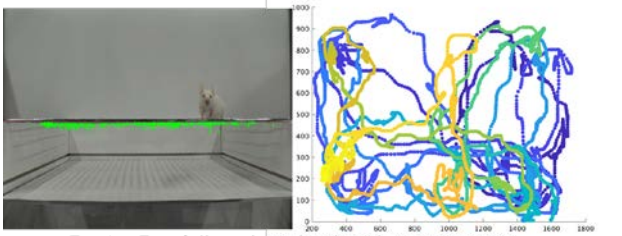

Fig.4 Footfall analysis by the AI-trace system

Mice in the process of recovery after spinal cord injury walk freely on the grid for a certain period, and the recorded movies from different angles were analyzed. The basement of the mouse tail is automatically tracked by AI to extract parameters of the total walking movement distance and speed (right). At the same time, the hind limbs dropped from the grid (left) has been automatically recognized and recorded. By combining these data, we succeeded in fully automating the footfall analysis. Now, it is possible to analysis our super-recover model to evaluate the degree of recovery over time and by the amount of administered drug. Furthermore, in the future, we plan to introduce rehabilitation and evaluate its effect with our collaborator, Dr. Yanagihara.

III. FUTUREU PERSPECTIVE

This year, we were able to obtain results of functional recovery from SCI through CPTX application. CPTX restored acute and sub-acute phase of SCI. We obtained the preliminary data that CPTX is also effective to chronic phase, which is beyond the initial plan. Since we have already prepared ASO for CS suppression, we will create a super-recovery model and expand the AI trace system in parallel. 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.

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A05-13 Reconstruction of Basal Ganglia by Aging and Neurodegenerative Disease

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***Abstract*—One of the inevitable changes faced by animals is the "aging" and the search for a desirable adaptation to the inevitable changes is an unavoidable problem in the aging society, which is becoming increasingly serious. Also, although "aging" is a risk factor for many neurodegenerative diseases, few studies have clearly delineated the relationship between aging and disease factors. Is the decline in neurotransmitters as a result of degeneration of certain nerve cells the only cause of neurodegenerative disease in older people? Or does the age-related decline in physical function affect the rearrangement of neural circuits? In other words, the possibility that neurons degenerate gradually over time and that the neural pathways may be rearranged to compensate for the effects of their slow decrease in dopamine has also been completely ignored. In this study, we investigate how the basal ganglia pathways are adaptively rearranged in young and old animals, isolating aging from neurotransmitter effects.**

II. Introduction

Frailty refers to a multifaceted situation in which not only physical functions such as the musculoskeletal system or cardiopulmonary function but also mental functions such as cognitive functions including decreased motivation are observed as a result of aging, and social life is generally impaired. In other words, with aging, both motor and brain functions are difficult to say as a result of either cause or effect, and they are impaired in a coordinated way. On the other hand, the incidence of many neurodegenerative diseases increases with age. For example, Parkinson's disease is caused by degeneration and loss of dopaminergic neurons in the substantia nigra of the midbrain, with incidence and prevalence increasing with age. However, the experimental animals used in most of the basic research to date are young adults, and the plasticity of neural pathways due to aging or changes in dopamine levels is not completely understood. To address this issue, we will explore how the basal ganglia pathway is adaptively rearranged, separating aging from neurotransmitter effects.

III. Aim of the Group

The aim of this study was to elucidate the anatomical and electrophysiological plasticity of the basal ganglia due to aging and the decrease in dopamine with aging.

IV. Research Topics

All experiment was conducted with research collaborators Dr. Fuyuki Karube, Dr. Yasuharu Hirai, and Ms. Fuko Kadono. The cooperation of Dept. Dermatology and Dept. Urology at the Hokkaido University was got for acquisition and clinical analysis of the aged mouse.

All researchers conduct appropriate animal experiments in compliance with the Animal Welfare and Management Law, related standards, etc., and with the principle of 3R (Replacement Reduction Refinement), which is the basic concept of animal welfare, and "National University Corporation Hokkaido University Rules on Animal Experimentation".

The following three results in this fiscal year are outlined.

A. Analysis of Motor Performance of Young and Aged Mice

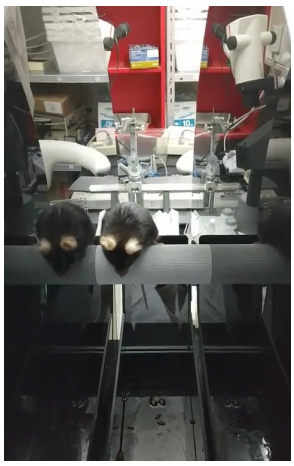

Fig1. motion analysis of mouse

Rotarod tests were performed to evaluate motor function (12-week-old male = 5; 60-70-week-old males = 4, females = 5). The rotarod test was conducted using a mouse rotarod device (MK -610 A, Muromachi), and the condition setting was made with reference to the mouse phenotype analysis protocol (Rota-rod test v1) of RIKEN BRC.

The running time of 60-week-old mice tended to be shorter than that of 12-week-old mice. However, since it cannot be ruled out that this difference may depend on weight gain, it is necessary to compare mice whose body weight has changed at the same age in the future. There is currently no significant difference between males and females, but the population needs to be increased.

B. Morphological Analysis of Young and Aged Mice

B-1. ***Subclass and distribution of dopamine neurons***

Dopamine neurons are subclassified biochemically and genetically into several subclasses. Are the subclasses of dopamine neurons that degenerate with Parkinson's disease or aging the same? Since the subclass that is preferentially denatured and lost by Parkinson's disease is known to be calbindin-negative dopamine neurons, we performed double immunostaining of calbindin and tyrosine hydroxylase (TH), a rate-limiting enzyme in the process of dopamine synthesis, in young and aged mice.

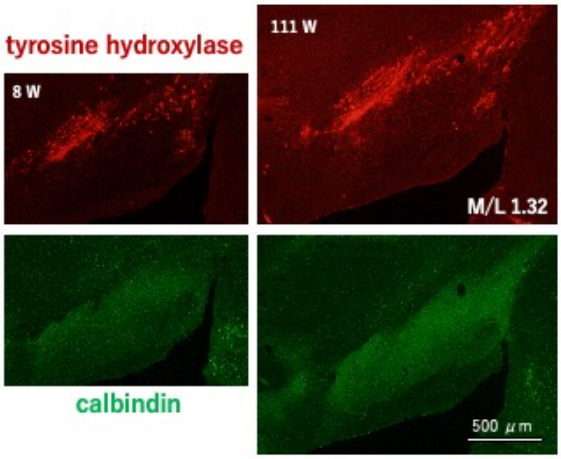

Fig.2 Dual immunohistochemistry of TH and calbindin in the midbrain substantia nigra

B-2. ***Dopaminergic terminals in the striatum***

We are now preparing to purchase cyclic voltammetry and measure dopamine levels electrochemically. However, we first observed dopamine projections from the substantia nigra of the midbrain to the striatum by immunostaining for TH. Calbindin immunohistochemistry was performed to visualize the patch (striosome) matrix compartments of the striatum.

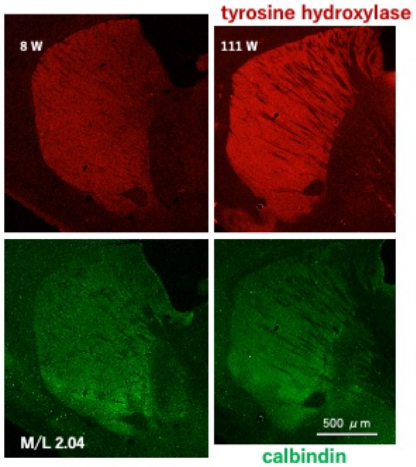

Fig.3 Dual immunohistochemistry of TH and calbindin in the striatum

V. Future Perspective

This year, due to the transfer of principal researcher and research collaborators from Doshisha University to Hokkaido University and restrictions on bringing in laboratory animals due to COVID-19, we spent a lot of time preparing the research environment and creating a valuable access route for aging animals. With the research environment finally in place, the following experiments will be conducted in next year (A) axon labeling detects age-altered neural projections, (B) confocal microscopic analysis reveals neurons with which these neural projections anatomically synapse; (C) changes in receptors at optically identified synaptic sites are confirmed by confocal microscopic analysis or electron microscopic analysis; and (D) anatomically identified synaptic connections are confirmed electrophysiologically by patch-clamp cell recordings using slice preparations. Thus, through this study, we plan to elucidate in detail the changes in neural pathways due to aging, from synapses to macroscopic levels.

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A05-14 Development of techniques to improve brain functions by using hyper-adaptability

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***Abstract*—Previous studies have mainly focused on the transplantation of cell suspension and have not established a method to create the neural circuit. In this study, the aim is to develop techniques to improve brain functions by using hyper-adaptability. In details, the transplantation of neuronal fibers could bypass the damaged areas of the brain. And then, we reveal the neural activity during the recovery of brain function with *in vivo* calcium imaging.**

I. Introduction

Transplantation of neural stem cell suspension is a useful method for the treatment of brain injury [1]. The transplanted neural stem cells could recover brain functions of the damaged area. Previous studies have mainly focused on the transplantation of cell suspensions and have not established a method to create the neural circuit. In this study, we aim to develop techniques to construct novel neural circuits.

II. Aim of the Group

The aim is to develop techniques to improve brain functions by using hyper-adaptability. In details, the transplantation of neuronal fibers could bypass the damaged area of the brain (Fig. 1, left). And then, we reveal the neural activity during the recovery of brain function with *in vivo* calcium imaging (Fig. 1, right).

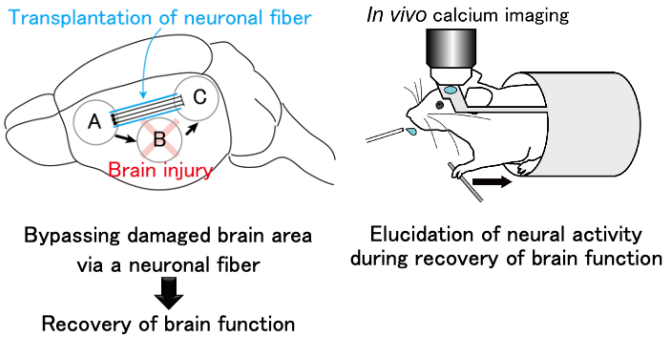

Fig. 1 Aim of the research

III. Research Topics

The significant results of this year are following two points.

A. Formation of neuronal fiber

We have established a system to produce a neuronal fiber with a double-coaxial laminar-flow microfluidic device [2]. The microfluidic device was fabricated by assembling pulled glass capillary tubes, rectangular glass tubes and connectors. The microfluidic device has a three-layer coaxial laminar flow (core stream, shell stream, and sheath stream). First, a core stream containing neuronal cells was surrounded by a shell stream of sodium alginate solution. Next, a calcium alginate shell is formed from the gelation reaction between sodium alginate and calcium chloride (Fig. 2). We investigated how long the neuronal fibers would survive. We also confirmed the spontaneous activity of the neuronal fiber with a calcium sensor. Fluorescence Changes of the calcium sensor is known to correlate with neural activity [3]. Furthermore, we confirmed what types of cells the fiber was composed of by immunostaining.

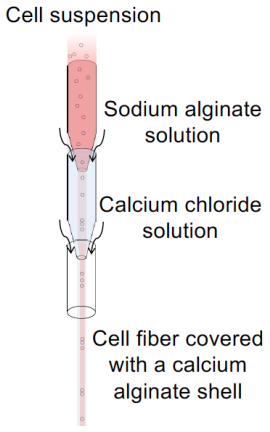

Fig. 2 Formation of a cell fiber with a microfluidic device

B. *Motor task*

We examined whether mice were able to perform motor tasks in the head-fixed condition (Fig. 3). In the future, we plan to examine whether damage to the cerebral cortex decreases the success rate and the number of successful trials in motor tasks.

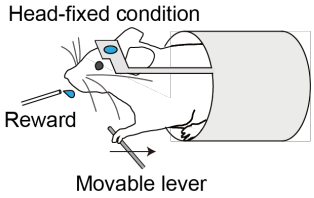

Fig. 3 Motor task

IV. Future Perspective

This year, we established a system to produce a neuronal fiber with a microfluidic device and examined whether mice were able to perform motor tasks in the head-fixed condition.

Next year, we plan to produce mice that have damage to the cerebral cortex. We examine whether the damage decreases the success rate and the number of successful trials in motor tasks. Next, we develop a system for transplanting neuronal fibers into the brain. Furthermore, we reveal the neural activity during brain function recovery with *in vivo* calcium imaging established in previous research [4]. We observe the neural activity of both a transplanted neuronal fiber and cerebral cortex with two-color calcium imaging of green and red calcium sensors. Calcium sensors are based on cpEGFP (circularly permuted enhanced green fluorescent protein) or cpRFP (circularly permuted red fluorescent protein), a calcium-binding protein (calmodulin), and a binding peptide (M13). In the presence of calcium, CaM undergoes a conformational change and associates with M13. The conformational change results in increased fluorescence brightness. [3, 5]. Using a glass window that we reported previously [6], we aim to observe the neuronal activity in the same population of neurons for a long time (Fig. 4).

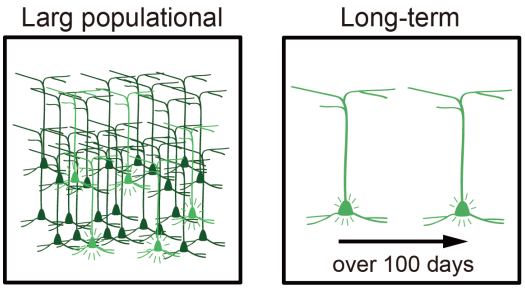

Fig. 4 Features of *in vivo* calcium imaging

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Annual report of research project A05-16

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Abstract*—In the present research project, we have investigated neuronal plastic changes, which underlie both motor recovery and pain syndromes after brain damage, using macaque models. In the studies reported here, we examined temporal changes of macrophages and microglia (MΦ/MG) after focal infarction of the internal capsule using a macaque model we recently established. Immunoreactivity for Iba1, a general marker for MΦ/MG, in the periinfarct core gradually increased from 0 days to 2–3 weeks after infarction, and the increased immunoreactivity continued at least until 6 months. We also found that Iba1-positive MΦ/MG transiently increased in layer V during several weeks after the infarction. Therefore, the time course of MΦ/MG activation differs between the perilesional area and the remote brain area where secondary damage occurs to tissue initially preserved after the infarct. Detailed analyses using the functional phenotype markers as well as cytokines released by cells with each phenotype suggest an anti-inflammatory role for activated MΦ/MG both in the periinfarct core during the chronic phase and in the primary motor cortex. In addition, to investigate changes in neuronal structures associated with central post-stroke pain (CPSP), we performed voxel-based morphometry (VBM) using T1-weighted magnetic resonance imaging and immunohistochemical analysis with our established CPSP monkey model. The present VBM analysis revealed a decrease in gray matter volume in the pain-related areas after weeks. Furthermore, immunohistochemical staining in the ipsilesional posterior insular cortex (ipsi-PIC), where the greatest reduction in gray matter volume was observed in the VBM result, displayed a significant reduction in both excitatory and inhibitory synaptic terminals compared to intact monkeys. Our results suggest that progressive changes in neuronal morphology, including synaptic loss in the ipsi-PIC, are involved in the pathogenesis of CPSP.

I. Introduction

Neural plasticity after brain damage is crucial for functional recovery from deficits caused by brain damage. This plasticity is exploited by rehabilitation for stroke survivors. On the other hand, central post-stroke pain (CPSP) developed as a result of maladaptive plasticity after stroke in thalamus and other brain regions involved in somatosensory processing. CPSP is characterized by not only spontaneous pain but also evoked pain in which normally innocuous stimuli are perceived as painful, *i.e.*, allodynia, and it decreases the quality of life and frequently interferes with rehabilitation of the affected patients. Therefore, *Hyper-Adaptability* after brain damage has both good and bad sides.

II. Aim of the Group

So far, we have examined the process of functional recovery after brain injury in the macaque monkey, as it has cerebral and musculoskeletal structures in similar to those of humans. Our behavioral analyses suggested that recovery of dexterous hand movements can be induced by intensive postlesion training [1]. Moreover, 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]. The aim of the present research project is to investigate plastic changes of neuronal functions and structures in the macaque monkeys in which stoke was induced in the internal capsule or thalamus, by applying experimental design we have used for the primary motor cortex lesioned monkeys.

III. Research Topics

A. Time- and area-dependent macrophage/microglial responses after focal infarction of the macaque internal capsule

Inflammatory responses induced by macrophages/microglia (MΦ/MG), which are rapidly activated and proliferate after stroke, can impede functional recovery. It should be noted, however, that not all activated MΦ/MG are involved in the inflammatory response; in contrast to the pro-inflammatory M1 phenotype, the anti-inflammatory M2 phenotype may be responsible for tissue repair. Knowing the phenotype is therefore important to understanding the pathogenic role of MΦ/MG. We here examined temporal changes of MΦ/MG after focal infarction of the internal capsule using a macaque model we recently established [3]. Immunoreactivity for Iba1, a general marker for MΦ/MG, in the periinfarct core gradually increased from 0 days to 2–3 weeks after infarction, and the increased immunoreactivity continued at least until 6 months (Fig. 1); no study in rodents has reported increased Iba1-immunoreactive cells for so long.

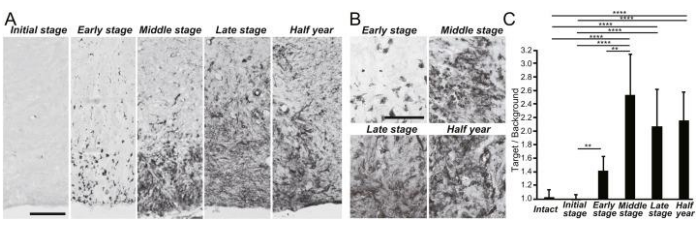

Fig. 1 Temporal changes of Iba1-immunoreactivity in the perilesional area. (A, B) Lower- (A) and higher- (B) magnification immunostaining images showing immunoreactivity of Iba1 in the periinfarct core from Early stage to Half year after infarction. (C) Quantitative analysis of Iba1 immunoreactivity in the periinfarct core. Iba1 immunoreactivity in the periinfarct core gradually increased from Initial stage to Middle stage. Although the immunoreactivity then decreased, it remained significantly elevated relative to the intact animals until Half year, the last time period assessed after infarction. **P < 0.01, ****P < 0.0001 (Kruskal–Wallis one-way analysis of variance and Dunn's post hoc test). Scale bars = 200 μm in A; 50 μm in B.

Retrograde atrophy / degeneration of neurons in layer V of the primary motor cortex, where the descending motor tract originates, was seen as secondary damage. Here we found that Iba1-positive MΦ/MG transiently increased in layer V during several weeks after the infarction (Fig. 2). Therefore, the time course of MΦ/MG activation differs between the perilesional area and the remote brain area where secondary damage occurs to tissue initially preserved after the infarct. Detailed analyses using the functional phenotype markers CD68, CD86, and CD206, as well as cytokines released by cells with each phenotype, suggest an anti-inflammatory role for activated MΦ/MG both in the periinfarct core during the chronic phase and in the primary motor cortex. We have published the results of this study in an international journal [4].

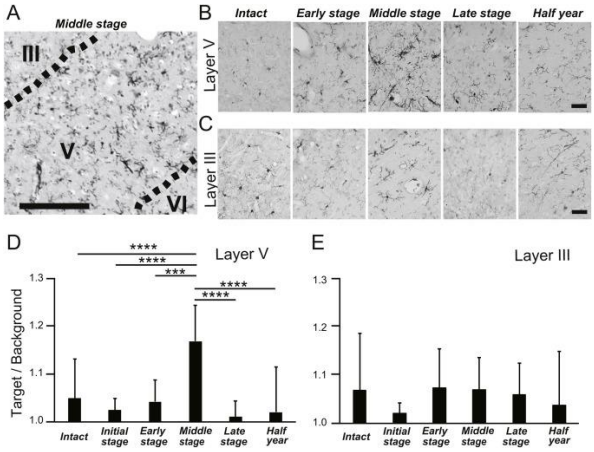

Fig. 2. Time-dependent changes of Iba1-immunoreactivity in the primary motor cortex. (A) Lower-magnification image of immunoreactivity for Iba1 at Middle stage. (B, C) Higher-magnification images of immunoreactivity for Iba1 in layers V (B) and III (C) in the intact tissue and at different time periods after infarction. (D, E) Quantitative analysis indicated that Iba1-immunoreactivity in layer V was significantly higher at Middle stage than in the intact animals and animals at other periods after infarction (D), whereas no increase was observed in layer III (E). ***P < 0.001, ****P < 0.0001 (Kruskal–Wallis one-way analysis of variance and Dunn's post hoc test). Scale bars = 200 μm in A; 50 μm in B, C.

B. Structural changes of cortical gray matter revealed by voxel-based morphometry and immunohistological analyses in a macaque CPSP model

Second, we investigated changes in neuronal structures associated with central post-stroke pain (CPSP). Several brain imaging studies among patients with CPSP demonstrate that the pathophysiological mechanism underlying this condition is the maladaptive plasticity of pain-related brain regions. However, little is known about the cellular basis of the plastic changes and how they are functionally related to pain. To elucidate these issues, we recently established a non-human primate model of CPSP based on the ventral posterolateral nucleus (VPL) of the thalamus using rhesus macaque monkeys [5]. The monkey model of CPSP faithfully reproduces late-onset allodynia / hyperalgesia observed among human patients. Moreover, using functional MRI in the macaque model, we previously reported increased cortical activity in the ipsilesional posterior insular cortex (ipsi-PIC) [6].

Here, we performed voxel-based morphometry (VBM) using T1-weighted magnetic resonance imaging and immunohistochemical analysis with the monkey model of CPSP. Several weeks after a hemorrhagic lesion to the unilateral ventral posterolateral nucleus of the thalamus, the monkeys exhibited behavioral changes that were interpreted as reflecting allodynia. The present VBM results revealed a decrease in gray matter volume in the pain-related areas after weeks rather than early periods. Furthermore, immunohistochemical staining in the ipsi-PIC, where the greatest reduction in gray matter volume was observed in the VBM result, displayed a significant reduction in both excitatory and inhibitory synaptic terminals. The results suggest that progressive changes in neuronal morphology are involved in the pathogenesis of CPSP.

IV. Future Perspective

We will investigate plastic changes of neuronal functions and structures in the macaque monkeys in which stoke was induced in the internal capsule. At present, we are applying VBM and immunohistochemical analyses to the macaques with internal capsular infarct.

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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 surgical lesions in the ventral attention network of common marmosets. In this fiscal year, we tried to establish 1) the target of the lesion, 2) how to evaluate their behavior and 3) how to measure the brain activity. For 1), we identified temporo-parieto-occipital association area using electrocorticogram (ECoG). For 2), we established the methods for eye-tracking during free-viewing. For 3), we succeeded in measuring Ca signals from the posterior parietal cortex.**

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 surgical 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 whole-cortex brain activity using a 96 channel ECoG electrode before and after the lesion and evaluate how the brain network is affected by the lesion. 3) 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. 4) 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 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.

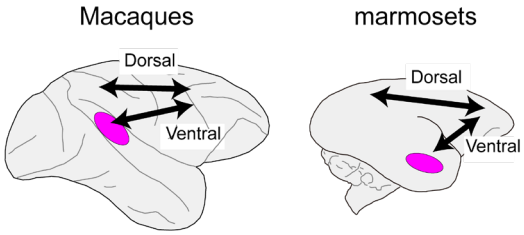

Fig. 1. Candidate of the lesion site

Our group selected as a candidate of the surgical lesion the temporo-parieto-occipital association area (rTPO) (Fig.1, right, magenta) [1], which is the homologous brain region to the human ventral attention network.

We also used a neurophysiological technique to find the homologous brain region to the human ventral attention network. We implanted 96-channel ECoG electrodes to marmosets [2] and measured brain activities during a visual mismatch task (Fig.2) to find brain regions associated with visual surprise.

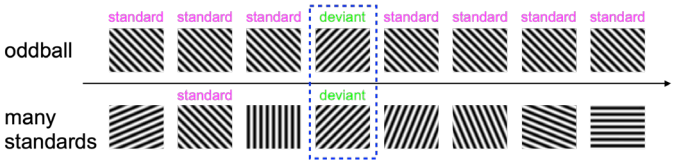

Fig. 2. Visual mismatch task

In the visual mismatch task (Fig.2), orientation grating stimuli were presented in front of marmosets with their head fixed. The stimulus sequence is composed of 300 repetitions of 0.5sec ON and 0.5sec OFF periods. 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 are able to evaluate which brain areas are associated with surprise. Using this method, we identified in the temporal association areas a brain area that is associated with surprise. Thus, we established how to identify the ventral attention network using a neurophysiological technique.

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, detection of saccades and the effect of ketamine on the saccade amplitudes (Fig. 3).

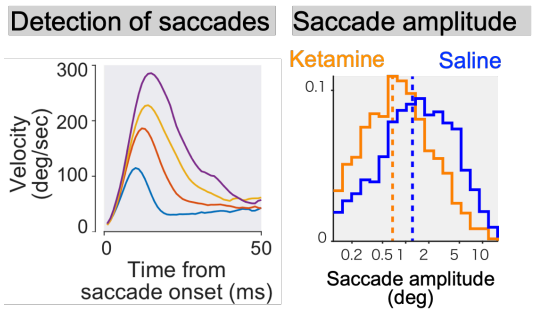

Fig. 3. Detection of saccades

In collaboration with Isa group in Kyoto University, we also found that the gazes during free-viewing of marmosets are attracted to visually salient stimuli [4], using a method developed for studying gazes of macaques [3].

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.

To understand the detailed brain mechanism of the neglect-like behavior, our group's strategy is to use marmosets and measure whole-cortical activities using 96-channel ECoG electrodes [2] and measure local circuit activities using an endoscope type Ca imaging system (nVoke, Inscopix).

Concerning the 96-channel ECoG recording, we succeeded in measuring activities not only during the visual mismatch task but also during free-viewing. We calculated the saccade-triggered averaging of the ECoG signals and found that saccade-related activities were found in the prefrontal cortex, the temporal association areas and the posterior parietal cortex (PPC). These activities showed selectivity to the directions of saccades.

Based on these findings, we decided to measure Ca signals from the PPC. By injecting adeno-associated virus AAV, the Ca sensor GCaMP6 was introduced in the PPC of a marmoset. The TET-off system specifically designed for marmosets [5] was used to amplify expression of GCaMP6. We succeeded in measuring Ca signals from the PPC of a marmoset (Fig. 4, left).

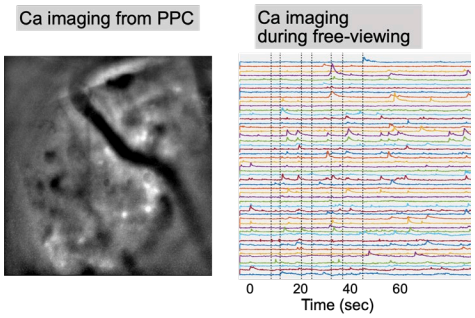

Fig. 4. Ca imaging from PPC

We measured Ca signals during free-viewing (Fig. 4, right) and identified signals related to stimulus onsets and saccade onsets.

IV. Future Perspective

In this fiscal year, we developed methods for establishing an animal model of USN using marmosets. From the next fiscal year onward, we will continue to add more experimental data for establishing methods to enable surgical lesions in marmosets.

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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.

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

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

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

In this fiscal year, (1) they proposed a combined use of tensor decomposition for dimensionality reduction and Time-Varying Graphical Lasso (TVGL) with Gaussian graphical model (GGM) for analyzing multimodal time-series data. (2) They improved the simulator to explain the changes of postural control in the dual task. (3) They found that a skill-level matching algorithm for adjusting the degrees of robotic intervention would be promising for enhancing the adaptabilit

B02 Modeling of ultra-adaptive to body change

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

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

In this fiscal year, (1) they estimated the muscle activities by inverse dynamics analysis from the measured human reaching motion, and simulated the reaching motion using the estimated muscle activities as control inputs. (2) They investigated the relationship between muscle activities and brain waves during finger movements, and identified the brain region relating finger movement direction.

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

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

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

In this fiscal year, (1) they developed VR motor rehabilitation system for stroke patients, and found visual intervention enhanced the sense of agency and showed positive effect on motor motivation. (2) They investigates the muscle activity of hemiplegic patients using surface electromyography. (3) They developed miniature robotic manipulandum for rodend studies.

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

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

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

In this fiscal year, (1) they investigated the role of arms in maintaining human standing posture. (2) They executed postural control experiments, and evaluated the role of neurotransmitters in the postural control with multitask. (3) They developed unilateral spatial neglect mouse model.

Proposed Research Groups

From this fiscal year, 11 proposed research projects joined the group. Please refer to the report of each research project for their concrete research outcomes.

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:

- July, 18th, 2020, IEEE EMBC2020 Workshop (Online)
  Due to the spread of COVID-19, the international workshop was held online. Prof. Ota and 5 researchers in the research project presented their recent research results and discussed.
- November 7th, 2020, Group B meeting (Online)
  The first Group B meeting was held online (Zoom). All the principal investigators and most of the co-investigators participated, thus approximately 45 people attended at all times, and deeper discussions were held, including future collaboration.

IV. Future plan

Towards the mid-term evaluation, in the next fiscal year, we summarize the research topics in the planned and subscription research projects by classifying the topics from the targeted subjects and the modeling methodologies points of view. Then we start deeper discussion on some of the topics. Moreover, we shall proceed fruitful collaborations with Group A (Neuroscience group).

Annual report of research project B01-1

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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 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 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.

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 multimodal 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, to quantify the long-term change of the extensive disinhibition structure in the brain, we develop a simultaneous analysis method by integrating muscle activities and cortical electroencephalography. (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 the collaborative motor learning experiments in healthy young and elderly. Based on the findings, we will develop appropriate visuomotor tasks

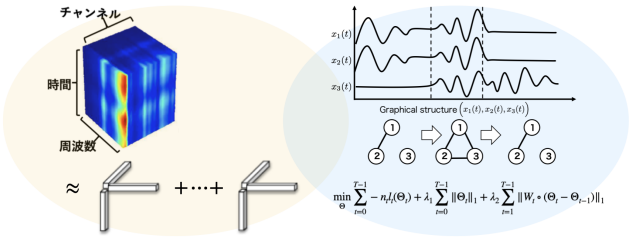

Fig. 1. Tensor decomposition and TVGL with GGM for brain modeling.

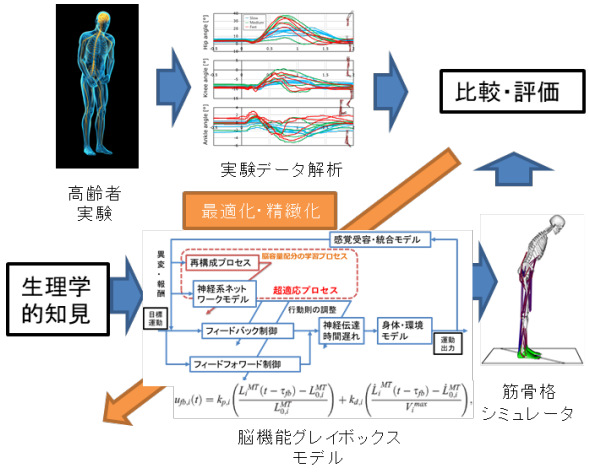

Fig. 2. Constructive modeling approach.

which can promote the reconstruction of neural structure in the brain, in collaboration with A01. By integrating these findings, 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 been developing 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. They proposed a combined use of tensor decomposition for dimensionality reduction and Time-Varying Graphical Lasso (TVGL) with Gaussian graphical model (GGM) for analyzing multimodal time-series data (Fig. 1). This year, they confirmed the applicability of the model by applying it to both artificial data [1] and sleep EEG (in preparation).

Moreover, in collaboration with the A03 group, they proposed a model of the Sense of Agency (SoA), and found that the adaptation process of the SOA model can be described by the Bayes' rule rather than the stochastic gradient descent (SGD) algorithm[2].

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.

We improved the simulator to explain the changes of postural control in the dual task for the above purpose. A computational simulation environment for gait was constructed in order to consider not only the standing posture but also the transition from standing to walking. This is because our hypothesis that "increasing muscle tone in elderly leads to a decreasing in motor function" is involved in walking. In the constructed simulation environment, it is possible to change the muscle tone in standing and gait. As a result, muscle tone was required for closing legs rather than opening legs in the standing posture, and the gait became irregular due to increasing muscle tone. These results show the validity of the computer model. It became possible to estimate the effect of hypertonia on postural and gait control.

In addition, as a preliminary experiment for the dual task, we conducted the dual task for 25 elderly in the Okoppe area in Hokkaido. The posture control task was to maintain the standing posture with open and closed legs, and the cognitive task was to repeatedly subtract from random numbers. As a result, we confirmed increasing of postural sway in the dual task, and also confirmed the precautions peculiar to the elderly in the protocol and instruction. Specifically, it may not be possible to maintain a standing posture with the closed legs, and it was necessary to simplify the instructions. This preliminary experiment enabled measurement experiments for the elderly, and was ready to collect knowledge for model construction and data for verification of models.

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

Prof. Kondo and his colleagues investigated cooperative motor learning tasks that can enhance their adaptability after the training with VR and haptic robot technologies. They found that a skill-level matching algorithm for adjusting the degrees of robotic intervention would be promising for enhancing the adaptability [3].

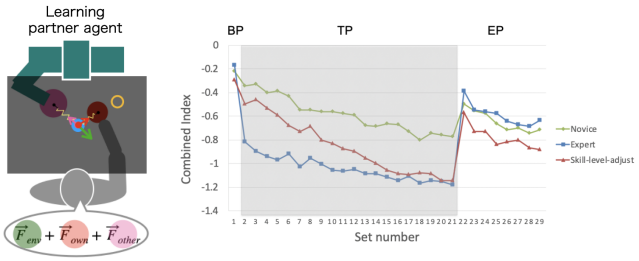

Fig. 3. Model-based robotic intervention for adaptability.

Moreover, 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) [4].

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. Moreover, we will continue to investigate the motor tasks that can induce "reconstruction of neural structure" with dis-inhibition in the brain of elderly people under the frailty state.

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Annual report of research project B02

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† The University of Electro-communications

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

1. The muscle synergies before and after the muscle rearrangement experiment of group A02 were analyzed and verified by a mathematical model. We also simulated exercise using an existing human upper limb musculoskeletal model.

2. 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.

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. Model of synergy change after tendon transfer

In collaboration with group A02, we investigated the recovery process after tendon transferring using two macaque monkeys. Tendons of the extensor and flexor finger muscles were transferred, and muscle activities were measured for two months. Then, we analyzed muscle synergies. The results of the analysis showed that time series of muscle synergies switched between the synergies for extensor and the synergies for flexor muscles after tendon transferring, and returned to their original relationships after approx. one month. During this duration, the structure of the muscle synergies hardly changed. In order to investigate the mechanism underlying the switching and returning of temporal synergies, we compared the measured muscle activities with the muscle activities explained by the muscle synergies. The results showed that the component explained by the existing synergies decreased during the process of switching and the component returned when the relationship of temporal synergies returned. This suggests that during the recovery process, strategies for muscle activities other than the existing synergies were explored, and that the original synergy structure was selected as the result of the exploration.

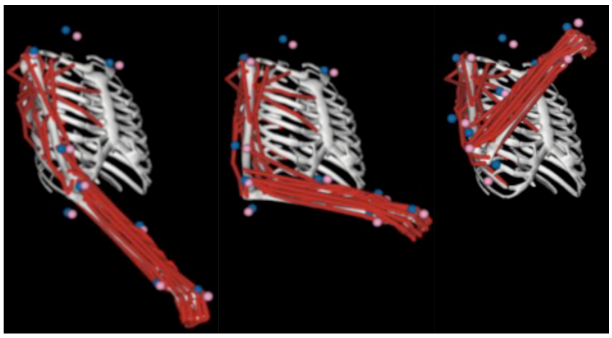

Fig. 1. Reaching motion of musculoskeletal model

To investigate the relationship between these changes in muscle synergies and the recovery of movement, we are constructing a dynamical model that can simulate movement from muscle activities. In order to construct a musculoskeletal model that can realize the reaching movement task of the upper limb performed in monkeys, we used an existing human upper limb musculoskeletal model [1] on the musculoskeletal simulation software OpenSim (Fig. 1). We estimated the muscle activities by inverse dynamics analysis from the measured human reaching motion, and simulated the reaching motion using the estimated muscle activities as control inputs. By fitting the physical parameters of this human musculoskeletal model with those of monkey skeleton, and adding necessary muscles, we construct a musculoskeletal model that can simulate the effects

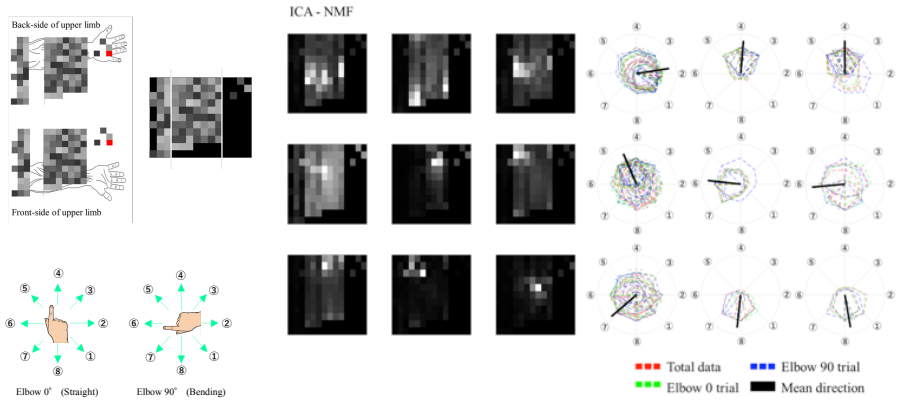

Fig. 2. Muscle synergy which related finger directon

of muscle transferring in monkeys.

B. Elucidation of reconstruction rule process by brain information decoding

For the purpose of confirming where muscle synergies are represented in the brain, muscle synergies calculated from electromyograms and source signals estimated from EEG using data obtained by simultaneously measuring movement-electromyogram-electroencephalograms during the finger motion task.

The surface EMG contains a mixture of superficial and deep muscle activity, but since finger movement is also related to the muscles in the deep part of the forearm, each muscle activity is analyzed separately. There is a need to. Independent component analysis was used to isolate muscle activity, and then nonnegative matrix factorization was used to determine muscle synergies [2].

In addition, the IC components related to the discrimination of movement were obtained from EEG signals by independent component analysis, and the region in the brain was calculated from the values of the independent components. Analysis of the weights of the decoder that identifies the direction of finger movement revealed that the right lingual gyrus, the left posterior cingulate, the left inferior temporal, and the right precuneus[3].

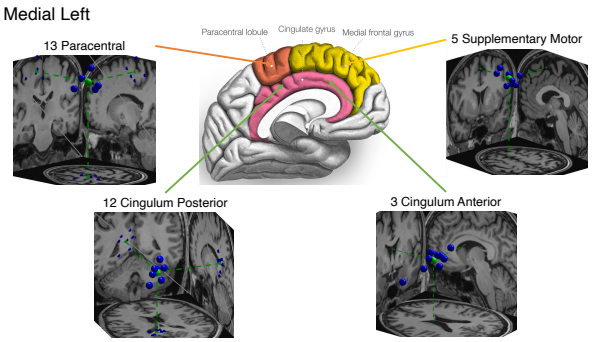

Fig. 3. Brain region of the ICs for identification of finger direction

From these results, task-related muscle synergies can be estimated at the finger movement level from the muscle activity obtained by the array electrodes, and the brain region related to work identification from the simultaneously measured EEG signals. Since it has become possible to estimate the brain region related to task identification from the EMG and EEG measured at the same time, it has become possible to analyze the acquisition process of muscle synergies from the EMG and EMG during tasks such as virtual surgery.

In addition, since the relationship between brain areas can be analyzed using fMRI. In order to clarify how much the brain region obtained this time is related during motor learning, it is necessary to identify the brain region by acquiring fMRI data during finger motor learning task.

IV. Future perspective

This year, we are conducting analysis of monkey finger movements in collaboration with group A02, as we did last year, and constructing a musculoskeletal model that realizes the reaching movement task of the upper limbs. In addition, we investigated which region of the brain is involved in finger movement and investigated the relationship with muscle synergies in humans.

From next fiscal year onwards, we plan to promote joint research with other groups.

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B03 Annual Report of Hyper-Adapt Project

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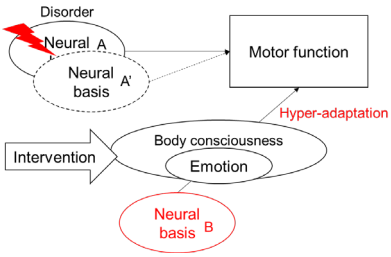
***Abstract*—B03 group aims to clarify the influence of body consciousness and emotion on the hyper-adaptation, and to establish mathematical model for hyper-adaptation which can quantitatively predict the state of body motor control ability. Furthermore, B03 group also aims to use the proposed mathematical 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 a method for motor rehabilitation focusing on body consciousness; 2) we developed an evaluation model to examine hemiplegic patients' recovery; 3) we developed a miniature robotic manipulandum for rodent studies.**

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. Development of VR-based rehabilitation system focusing on sense of agency

First, Asama and Wen's group (The University of Tokyo) proposed a VR-based motor rehabilitation system for stroke patients. Specifically, in the proposed task, participants were asked to perform vertical movements, which are very commonly used in motor rehabilitations (Fig. 2). The position of the actual hand was presented in virtual reality (VR). In the intervened condition, the hand position in VR was slightly modified to show better visual feedback (e.g., slightly higher when participants intended to reach a high position). This visual intervention significantly enhanced the sense of agency when moving one's arm [1], and also showed positive effect on motor motivation that was measure by the reaction time of muscle activities. Fig. 3 shows the model of the effect of visual modification on the sense of agency and motor intention. Visual intervention, which was consisted with one's motor intention, reduced prediction errors and enhanced the sense of agency, and through this, boosted motor intention.

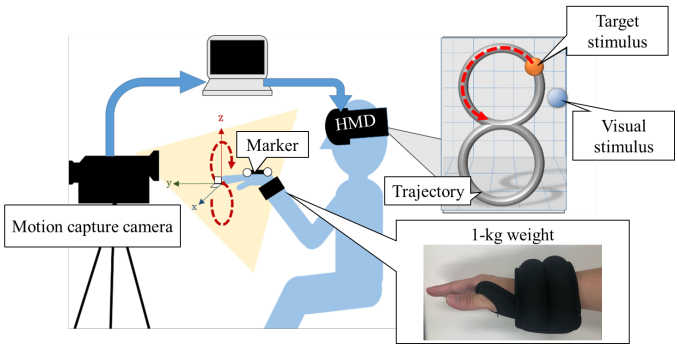


Fig. 2 The configuration of the VR-based motor rehabilitation system

We also collaborated with A03 group (Imamizu and Ohata) to examine the relationship between perceptual sensitivity to control change and the efficiency of motor learning. As a result, we found that people who are sensitive to the increase of control in environment also adapted faster in a motor learning task. On the other hand, the perceptual sensitivity to the decrease in control did not significantly correlate with the efficiency of motor learning. The results indicate that the processes underlying the increase and decrease of sense of

agency probably are partially independent from each other. Furthermore, those processes probably contribute differently to motor learning.

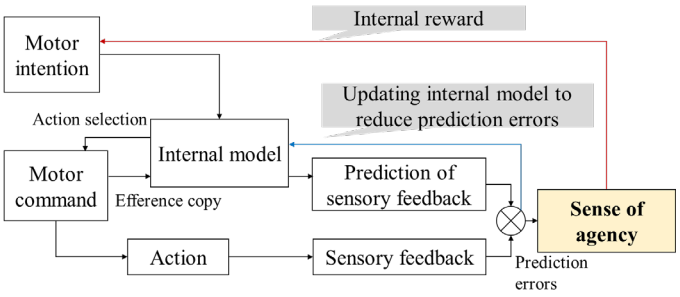


Fig. 3 The model showing the effect of visual modification on the sense of agency and motor intention

B. Evaluation for Recovery Process of Hemiplegic Patients

In Qi An's (Kyushu University) research group, we investigate the hyper-adaptation process of recovery in hemiplegic patients with impaired motor function. In our previous study, we found that the timing of muscle synergy activity improved before and after intervention by physical therapists when hemiplegic patients performed a standing movement. We also proposed an appropriate rehabilitation method for each patient based on the differences in the timing of muscle synergy activity [2]. Thus, it has been found that the timing of muscle synergy activity changes with the severity and functional recovery in hemiplegic patients.

However, it is thought that not only the timing of muscle activity but also the force exerted by the muscle changes during recovery in hemiplegic patients. To investigate the muscle activity of hemiplegic patients using surface electromyography, it is not possible to simply compare muscle potentials because the impedance of the skin and the point of application are different on different measurement days. In this study, we developed a method to estimate the muscle activity during sit-to-stand motion by optimization calculation from the joint torque calculated by inverse dynamics calculation. This method enables us to compare not only the timing of muscle activity but also the magnitude of force exerted by hemiplegic patients with different measurement dates. This result was presented at the International Conference on Neural Rehabilitation (ICNR2020) and received the Best Paper Award [3].

C. Development of the miniature robotic manipulandum for rodent studies on computational mechanisms of motor learning

Izawa (University of Tsukuba) found the change of the learning rate which is an essential component of the hyper-adaptability [4] in the collaboration with B04 group.

Then, to study neural background of such a hyper-adaptability, he developed the miniature robotic manipulandum for rodent studies. To understand how the computational process of motor recovery and motor learning was embedded in the neural mechanisms in the brain, intervention on the neural activities and measurement of neural activities are necessary. However, the empirical evidence of computational mechanisms of motor learning has been produced from human studies that take advantage of robotic devices. In the case of human studies, intervention to the neural processes and measurement of neural activities were technically challenging. Thus, here we aim to build a robotic device that can fit rodent studies where DNA techniques and neuroimaging techniques are established.

The developed manipulandum realizes 5mm-20mm reach movements in arbitral force environments, including the velocity and the position-dependent force fields and the channel force environment. The force sensor mounted on the end-effector provides us clues of the memory update process during the learning. Therefore, this device enables us to examine computational models of motor learning using rodents.

IV. Future Perspective

In the past year, we examined the role of body consciousness in motor rehabilitation. We also developed a method to quantitatively examine the recovery of hemiplegic patients. Further, we developed a miniature robotic manipulandum for rodent studies. In the next year, we plan to evaluation our rehabilitation system for stroke patient, to further examine the muscle synergies during the recovery of hemiplegic patients, and to apply the new miniature robotic manipulandum in computational research of motor learning.

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Annual report of research project B04

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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 13 co-investigators (Shirafuji, Kaminishi, Omura, Ishii, Hamada, Kohno, Kishimoto, Yuine, Ishibashi, Etoh, Miyata, Osaki, Kanaya).

II. Research Results and Future Plans

A. *Introduction of vestibulospinal tract-mimicking control into a model of nervous system postural control*

Ota et al. 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 plays an important role in human postural control. The vestibulospinal tract, along with the reticular spinal tract, which regulates muscle tone throughout the body, is responsible for postural control. We introduced control that mimics the vestibulospinal tract into the neural posture control model that we have developed, based on the following findings: 1) It projects to the entire spinal cord to coordinate muscle activations of the entire body; 2) It maintains the head in a stable vertical position by maintaining the body in a vertical position; 3) As an input, it receives mainly vestibular sensation in the vestibular nucleus in the brainstem; 4) As an output, it has an excitatory effect on extensors and an inhibitory effect on flexors (Fig. 1) [1]. We used this neural controller model to maintain the stance posture of a musculoskeletal model with 19 degrees of freedom and 94 muscles, and verified the validity of the neural controller model.

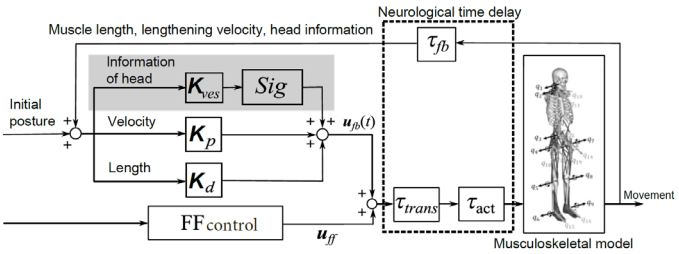

Fig. 1. The neural controller model with the control that mimics the vestibulospinal tract.

Fig. 2 shows the center of pressure velocity of the simulation results. In almost all muscle tone conditions, the value for the case with the vestibulospinal tract was smaller than the value for the case without the vestibulospinal tract. This is in line with the results of the experiment with patients with unilateral vestibular dysfunction, and confirms the validity of the controller model.

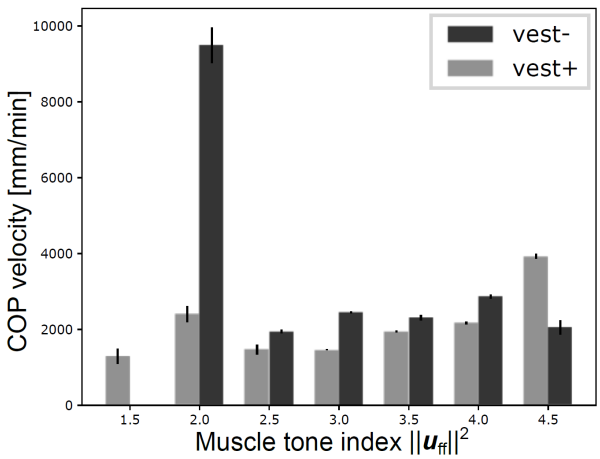

Fig. 2. Muscle tone index $||u_{ff}||^2$ and center of pressure velocity in the anterior-posterior direction. Black shows the results without vestibulospinal tract and gray shows the results with vestibulospinal tract.

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. In addition, we aim to describe the relationship between neurotransmitters, postural control mechanisms, and behavioral manifestations in conjunction with the results of human experiments.

Through musculoskeletal simulation, we are attempting to investigate the role of arms in maintaining human standing posture. Musculoskeletal models with/without arms were controlled using a neural controller model, and forward dynamics simulations were conducted to apply external forces to the models. As a result, the center of mass sway became smaller in the condition using the musculoskeletal model with arms, suggesting that the presence of arms contributes to the maintenance of standing posture [2].

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

Yozu et al. evaluate the role of neurotransmitters in postural control with multitask. In this year a) we designed a multitask protocol featuring a postural task and a cognitive task, b) we developed a system to measure kinematic and physiological responses during the tasks, and c) we measured patient with Parkinson's disease.

a) Designing of multitask featuring a postural task and a cognitive task

A multitask which could be performed by Parkinson's disease was designed. For a postural task, 30 seconds of quiet standing was adopted. For a cognitive task, an arithmetic task was adopted [3]. The participants were asked to recite serial subtractions by 7.

b) Development of a system to measure kinematic and physiological responses during the tasks

We developed a system to measure the posture, the center of pressure, and the surface electromyogram of the subjects. Center of pressure was measured using a stabilometer (Anima, Tokyo, Japan) with a sampling rate of 20 Hz. The surface electromyogram of 16 of the following muscles was measured by a wireless EMG system (Delsys, Tokyo, Japan): cervical paraspinal, sternocleidomastoid, lumbar paraspinal, gluteus maximus, quadriceps femoris, semitendinosus, tibialis anterior, and soleus (all bilaterally).

c) Measurements in patients with Parkinson's disease

To analyze the effect of multitask loading, participants were asked to perform i) standing task without arithmetic task, ii) multitask of the standing task and arithmetic task, and iii) only the standing task. Two Parkinson's disease patients was measured. They were measured before and after drug administration to evaluate the effect of dopamine on the multitask. As a result, there were fluctuation during one day, and center of pressure and electromyography changed partially concordantly. We are now submitting the result to an international journal.

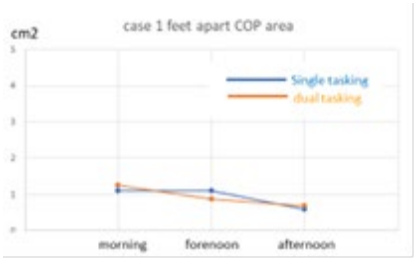

Fig.3 Fluctuation of the center of pressure in Parkinson's disease

C. Development of a Unilateral spatial neglect mouse model

Unilateral spatial neglect (USN) is a disorder of higher brain function that occurs after a brain injury, such as stroke, because patients with this condition often have other symptoms due to the presence of several brain lesions, it is difficult to evaluate the recovery mechanisms and effect of training on unilateral spatial neglect [4]. Yozu et al. induced a focal infarction in the right medial agranular cortex (AGm) of mice using photothrombosis, and created a mouse model of USN. After induction of cerebral infarction, USN was evaluated. The left-side selection rate was calculated as the symptom of USN. After the final evaluation of the USN (18 days after cerebral infarction), the brain was removed and cryosectioned (100 μm). The sections were stained with cresyl violet, and subsequently observed under a microscope to examine the infarct volumes, the extent of the lesions, and the centroid of the lesion area. The findings suggest that recovery from ipsilesional spatial bias requires neural plasticity within the anterior AGm. This conditional mouse model of ipsilesional spatial bias may be used to develop effective treatments for unilateral spatial neglect in humans.

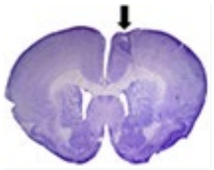

Fig.4. Development of infarction by photothrombosis

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

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***Abstract*—In this study, we apply Deep Reinforcement Learning for handling full-dimensional 7 degrees of freedom arm reaching, and demonstrate the relations among motion error, energy, and synergy emergence during the learning process, to reveal the mechanism of employing motor synergy. Although synergy information has never been encoded into the reward function, the synergy effect naturally emerges, leading to a similar situation as human motion learning. To the best of our knowledge, this is a pioneer study verifying synergy development in DRL for multi-directional reaching tasks.**

I. Introduction

In humans, our body has more degrees of freedom (DOF) than the number of dimensions of our task space performed in our daily life. This redundancy is advantageous because it enables us to execute a motor task by finding easier motor coordination considering our physical bio-mechanical conditions while maintaining a certain motion accuracy. Thus, humans can achieve highly coordinated and efficient movements in sophisticated ways with the complex musculoskeletal system. Elucidating control strategies that can overcome these complexities to reproduce neural control of human movement is a central issue in the field of human motor control.

Over the past few decades, several indexes are proposed for human movement optimization, for instance, by defining that the system accomplishes a task in minimum X, where X can be jerk, torque changes, motor command, or energy expenditure. In redundant manipulators, the model-based cost function is commonly adopted in the process of optimization. However, they basically rely upon the good knowledge of a physical inverse dynamics model or approximation-based model for precise control.

Due to the complex and nonlinear dynamic relationships among muscle activation, joint torques and joint motions, controlling human movements would appear to be a challenging task for the central nervous system (CNS). Indeed, researchers in the field of neuroscience have proven that the concept of motor synergy that organizes and simplifies upper-level tasks among a set of elemental controls exists within the CNSs.

By applying deep learning techniques in reinforcement learning (RL), i.e. deep reinforcement learning (DRL) offers a promising model-free approach for overcoming complex learning problems. It enables the robot to learn directly from the interaction with the environment. DRL has received increasing attention in robotics research and demonstrates its strength in obtaining the optimal policies for high dimensional humanoid robots. However, it should be pointed out that the current DRL algorithm does not account for synergetic motor behaviors, which can tend to produce unnatural and awkward control results.

In this study, we apply DRL for handling multi-directional reaching with full-dimensional arm, and demonstrate the relations among motion error, energy, and synergy emergence during the learning process, to reveal the mechanism of employing motor synergy [1]. We believe that a better understanding of how error-energy index is actually related to the synergy concept within deep reinforcement learning framework for multi-directional reaching would provide useful insights into improving DRL algorithm on managing the high dimensionality of motor control problems.

II. MATERIALS AND METHODS

A. Deep Reinforcement Learning Algorithm

RL enables an *agent* to learn optimal behaviours by trial-and-error interactions with its *environment*. The task in reinforcement learning can be described by the framework of infinite-horizon *Markov decision process* (MDP), characterized by the tuple $(\mathcal{S}, \mathcal{A}, p, r)$, comprising a *state* space $\mathcal{S} \in \mathbb{R}^n$ and a set of *actions* $\mathcal{A} \in \mathbb{R}^m$ available to the agent. The unknown state *transition probability* $p : \mathcal{S} \times \mathcal{A} \times \mathcal{S} \to [0, \infty)$ represents the probability density of the next state $s_{t+1} \in \mathcal{S}$ given the current state of an agent at time t: $s_t \in \mathcal{S}$ and action $a_t \in \mathcal{S}$, while the *reward function* $r : \mathcal{S} \times \mathcal{A} \to \mathbb{R}$ returns the immediate reward $r(a_t, s_t)$ to the agent after taking action a_t in state s_t. We use ρ_π to denote the trajectory distribution induced by a policy $\pi(a_t|s_t)$.

In this study, it is essential to choose a DRL algorithm that is capable of exploring an unknown environment stably and efficiently to solve complex robotics tasks [2]. The general goal in RL is to find a *policy* π that maximizes the agent's expected return as shown in (1). In contrast, soft actor-critic(SAC) is an algorithm that optimizes the stochastic policy. In particular, the objective of SAC is to find a policy by maximizing the agent's expected return in parallel to the expected entropy of the policy, π_{SAC} weighted by an entropy term α.

$$\pi = \text{argmax} \sum_{t=0}^{T} E_{(s_t,a_t)\sim\rho_\pi} [r(s_t, a_t)] \tag{1}$$

$$\pi_{SAC} = \text{argmax} \sum_{t=0}^{T} E_{(s_t,a_t)\sim\rho_{\pi_{SAC}}} [r(s_t, a_t) + \alpha \cdot H(\pi_{SAC}(\cdot|s_t))] \tag{2}$$

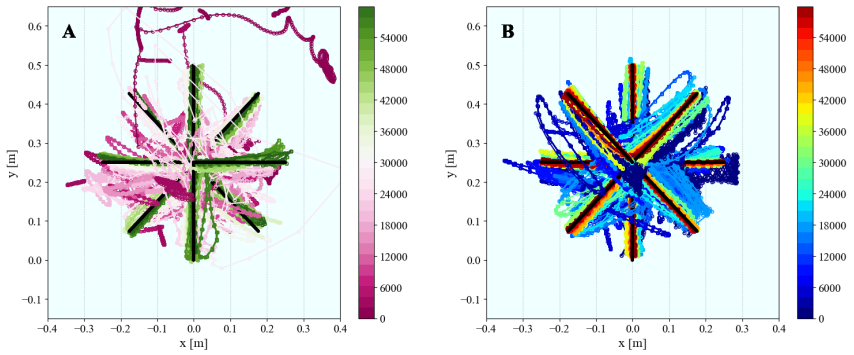

Fig. 1. Endpoint transition for multi-directional reaching. (A) with DRL algorithm, and (B) with DRL with feedback control.

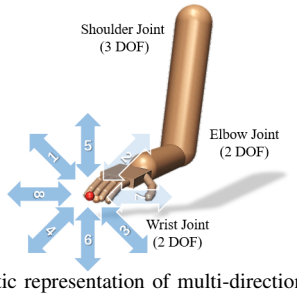

Fig. 2. Schematic representation of multi-directional reaching task.

III. EMERGENCE OF MOTOR SYNERGY

A. Simulated Agents

Our study is conducted on simulated agents using a simulation engine, called MuJoCo which is widely utilized for studying multi-joint mechanical system in the DRL community. We apply the proposed DRL control scheme on an anthropomorphic 7-DOF robotic arm to analyze the motion behaviors during the learning as depicted in Fig.2.

B. Motor Control Results

To evaluate the performance of the proposed method for the redundant robotic arm, the tracking result is firstly compared between DRL and DRL with feedback controller. Fig.1 illustrates the motor control result of endpoint transition (A) with DRL algorithm, and (B) with DRL with feedback control. A PiYG color map (ranging from purple to green) is used for DRL and a jet color map is used for PDRL, to illustrate sequential learning transition. It is interesting to see that DRL with feedback has less random exploration and better tracking performance. This phenomenon can be explained as the feedback control component may act as a supervised signal that guides the system to select an action toward that supervision. Hence, DRL with feedback can obtain feasible solutions faster without unnecessary random explorations.

C. Joint Synergy Analysis on Learned result

PCA is applied against Joint angles to estimate the matrix of joint synergies W and the matrix of activation signals C. After the joint synergies W and the activation signals C are gathered, the original control signals can be reconstructed with a certain degree of accuracy indicated by the R^2 metric.

Once the signals are collected from different training checkpoints of the policy, then the R^2 curves can be plotted for these checkpoints on the same diagram and associate each curve with different colors, as illustrated in Fig.3. The light blue curves correspond to the early phase of training, the purple curves and red curves correspond to the ending phase of the training. The R^2 accuracy varies based on the number of joint synergies used in the reconstruction and as the number of synergy components increases, the elevation of accuracy of reconstruction can be observed. It can be noticed that the synergy level of the curves generally rises towards the end of the training, as fewer synergy components are required to reach higher R^2 accuracy. This phenomenon is illustrated by the green arrows. These results indicate the interesting phenomenon that joint synergy is emerged in multi-directional reaching by using DRL algorithm [3].

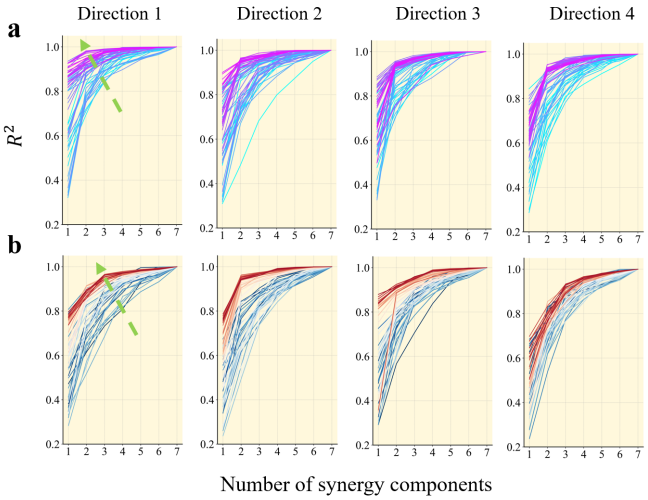

Fig. 3. Graph of R^2 accuracy vs the number of synergy components in multi-directional reaching. (*a*) with DRL, (*b*) with DRL with feedback control.

IV. Conclusion

We found that the reconstruction accuracy through synergy turns into high level during learning process. Future direction would be to extend this framework to other motor tasks.

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

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***Abstract*—This study aims to elucidate the ability of the human postural control system to adapt to a wide variety of dynamical environments. To this end, we propose a novel methodology to alter the dynamics of the body during quiet stance using closed-loop electrical muscle stimulation. Our idea is that the dynamics can be artificially altered if the ankle joint torque can be modulated by the electrical muscle stimulation depending on the position, velocity, and acceleration of the center of body mass. This year, we developed the system to validate this idea and obtained preliminary data showing how the human postural control system adapts to the change in postural dynamics.**

I. Introduction

Human has a remarkable ability to maintain unstable upright posture under a wide variety of environment. It is believed that this stability is achieved by the function of the postural control system to transform sensory information, including visual, vestibular, and proprioceptive signals, into an appropriate motor command [1]. However, little is known about how the adaptation process progresses, which might be partly because the conventional studies have limited to the methodologies to investigate spontaneous sway or the response to a transient perturbation to the vision and supporting surface.

In the study using the reaching experimental paradigm, the method to manipulate the dynamics using a robotic manipulandum has been widely used [2]. A considerable amount of knowledge has been accumulated as to how the adaptation process progresses from the viewpoint of behavior, neural representation, and computational mechanisms. In this project, we try to apply this powerful methodology to the study of the human postural control system.

II. Aim of the Group

The application of the system to alter the dynamics to postural control is not easy. For example, one can consider the perturbation methods, including exoskeleton robot [3], and pulling the body using a wire. However, these methods sometimes are quite expensive and the accurate manipulation of perturbation with the subtle postural sway information is difficult. Furthermore, the presence of the device could interfere with the postural dynamics itself. As a solution overcoming these problems, here, we propose that the tibialis anterior (TA) muscle can be utilized as a "natural" perturbation device. If we set up the electrical muscle stimulation (EMS) system to modulate the ankle joint torque with the COM position, velocity, and acceleration, the body dynamics can be artificially altered (Fig.1). This research project aims to develop the system to implement this idea and investigate how the postural control system adapts to novel dynamics imposed by this system. This year, we have developed the system and validated our idea. We also performed a preliminary experiment to impose novel body dynamics during quiet standing.

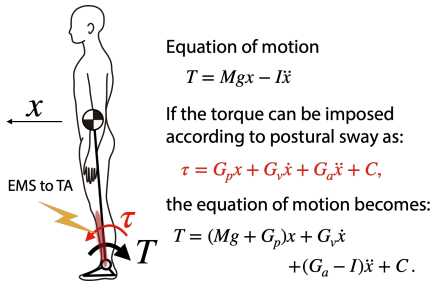

Fig.1 The dynamics of body can be artificially altered if the ankle dorsi-flexion torque is manipulated depending on the COM position, velocity, and acceleration.

III. Research Topics

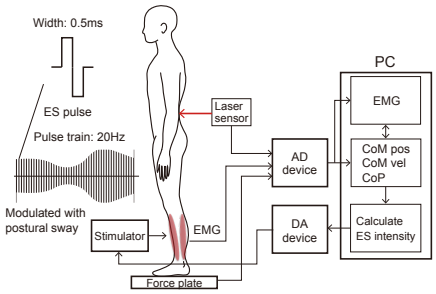

Fig.2 The closed-loop EMS system to alter the postural dynamics.

A. Development of the closed-loop EMS system

We measured the anterior-posterior displacement of COM using a laser displacement sensor (IL-2000, Keyence, Japan). This information was used to modulate the intensity of EMS (Isolator, ULI-100C-SI, Unique Medical, Japan) (Fig.2).

B. *Identification of the system to obtain the EMS pattern to produce arbitrary ankle joint torque*

The biphasic pulse (width 0.5msec) was used as EMS, and the frequency was maintained at 20 Hz to minimize the effect of fatigue [4]. First, the amplitude was sinusoidally modulated with various frequencies, and the resultant ankle joint (dorsiflexion) torque was measured (Fig.3). From the gain and phase of the relationship, the transfer function from the EMS to the ankle joint torque was identified. Then, the transfer function of the inverse system that transforms the ankle joint torque to the EMS intensity was obtained.

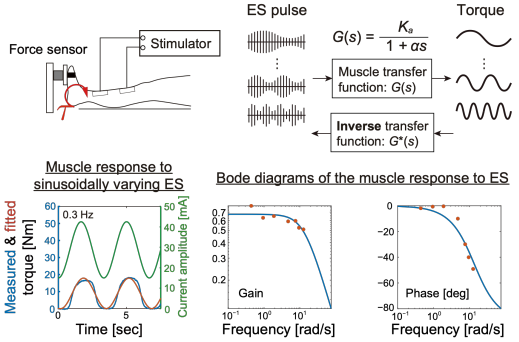

Fig.3 Identification of the transfer function from the EMS to the ankle joint torque. We measured the ankle joint torque when the EMS whose amplitude changed sinusoidally with various frequencies was applied to TA. The transfer function was identified from the gain and phase information.

Then, we validated if the EMS based on this transfer function can actually generate the ankle joint torque that changes with the COM position and velocity (Fig.4). More specifically, we constructed an idealistic ankle joint torque from the COM data collected from a participant. The EMS pattern was calculated using the transfer function of the inverse system. We directly measured the ankle joint torque when this EMS was applied to TA. The results indicate that the resultant ankle joint torque reasonably reproduced the ideal ankle joint torque pattern (Fig.4).

C. *Adaptation to a novel dynamical environment created by the closed-loop EMS system*

We performed a preliminary experiment that examined how the human postural control system adapted to novel dynamical environments created by the closed-loop EMS system. We imposed three different types of dynamics: the perturbation torque was modulated with the COM position, velocity, and both. During 7 minutes adaptation phase, we interleaved a forward perturbation to the ankle joint every 30 sec to see how the adaptation changed the response pattern. We observed the response to the forward perturbation changed depending on the imposed dynamics throughout the adaptation phase (Fig.5).

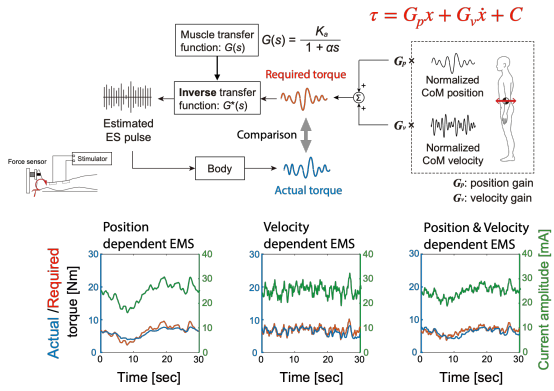

Fig.4 We validated if the EMS pattern obtained using the transfer function of the inverse system could produce the ideal ankle joint torque constructed from the COM data collected from a participants.

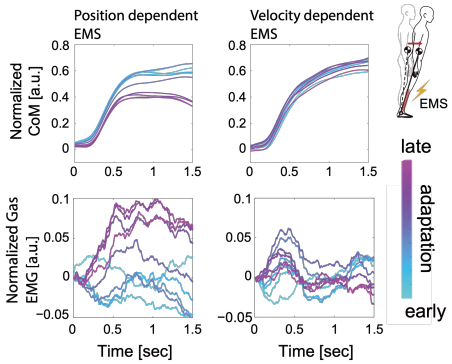

Fig.5 As the postural control system adapted to a novel dynamics, the response to the forward pertubation gradually changed and the changing pattern was specific to the imposed dynamics.

IV. Future Perspective

This year, we developed the new closed-loop EMS system. We plan to perform the adaptation experiment more systematically the next year. Furthermore, we will extend this closed-loop stimulation into the galvanic stimulation to investigate how the postural control system utilizes the vestibular sensory information for the postural adaptation.

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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 during the course 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

Japanese macaques generally have the ability to walk bipedally. Our group has been investigating bipedal locomotion in Japanese macaques as a way 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 seem to be 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 actually 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]. 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 (Fig. 2). 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.

We evaluated how virtual manipulation of foot morphology affects the kinematics, dynamics, and energetics of bipedal locomotion. 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.

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, such as the single-peaked vertical ground reaction force profile with a peak occurring in the early stance phase, the breaking peak magnitude being slightly larger than that for propelling, and the breaking period being shorter than the propelling period. Simulation framework successfully reproduced the basic kinematic and dynamic features of bipedal locomotion in the Japanese macaque.

When the foot morphology was altered (the calcaneal tuberosity was inferiorly translated), the vertical ground reaction force profile shifted from a single- to a double-peaked profile as in human walking. As the calcaneal point was inferiorly translated, the cost of transport gradually decreased compared with that of the original foot condition. The changes in the nervous system parameters due to the alteration of the foot morphology is currently under investigation.

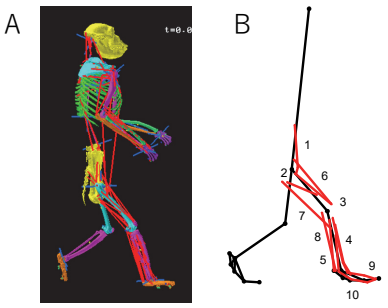

Fig. 1. Musculoskeleta model of the Japanese macaque. A: 3D whole-body model. B: 2D model used in the present study.

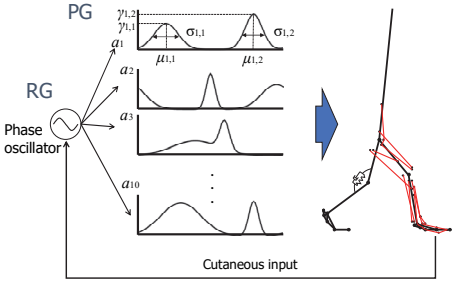

Fig. 2. Nervous system model.

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 understanding mechanisms of “hyper-adaptability” of bipedal locomotion.

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Annual report of research project B05-4

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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." In this year, I tried to develop a method to identify the low-dimensional state using combination of time-varying graphical lasso, calculating Kullback-Leibler divergence, and multi-dimensional scaling. The method worked for the simulated data with four dimensions. However, the distinct low dimensional representations for different tasks were not found in the public dataset measured by electroencephalogram, suggesting need for improving the method.

I. Introduction

Human movements vary across trials because of neural noises [1]. Recent studies suggest that such the variability of movements is derived from not only noises but also position or state in the low dimensional neural subspace composed from population of the neural activities (i.e., Neural manifold) in the phase of movement planning [2]. For example, in the experiment for the non-human primates, it has been suggested that the reaction time is determined depending on the state of the neural population of premotor cortex in the planning phase. From these results, it is hypothesized that movements are generated using dynamical systems whose inputs or initial position are state of the neural population in the planning [3]. Above mentioned neurophysiological studies (e.g. [2, 3]) showed the importance of identifying low dimensional subspaces. On the other hand, human neuroimaging studies have been reported that a relationship between several brain regions other than the motor cortex and errors or movement accuracy [4, 5]. However, it is unclear how these regions and connectivity between the regions are related to the movement variability and the errors. Also, it has been reported a possibility that human perception and behavioral performances are influenced by pre-stimulus activity or resting-state activity [6, 7]. While it remains unclear how these pre-stimulus activities influence perceptual and behavioral performances, it is hypothesized that low dimensional neural subspace in the planning is influence by the pre-stimulus activity. In addition, I think that such the different neural subspace representations are base of "hyper-adaptability." Therefore, in this study, I try to identify low dimensional neural subspace related to the movements in the whole-brain levels as state-space dynamics. Then, I would like to understand the mechanism of hyper-adaptability using non-invasive brain stimulation.

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. Furthermore, we are going to try to manipulate such a representation using a brain stimulation technique.

III. Research Topics

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

First, this study examined the method to identifying 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 first tried to identify the low dimensional subspace for EEG data using a method based on TVGL. Using TVGL, we obtained covariance matrices and precision matrices. Next, we calculated a distance matrix from the covariance matrices using Kullback-Leibler divergences and obtained distance (i.e., similarity) among the components.

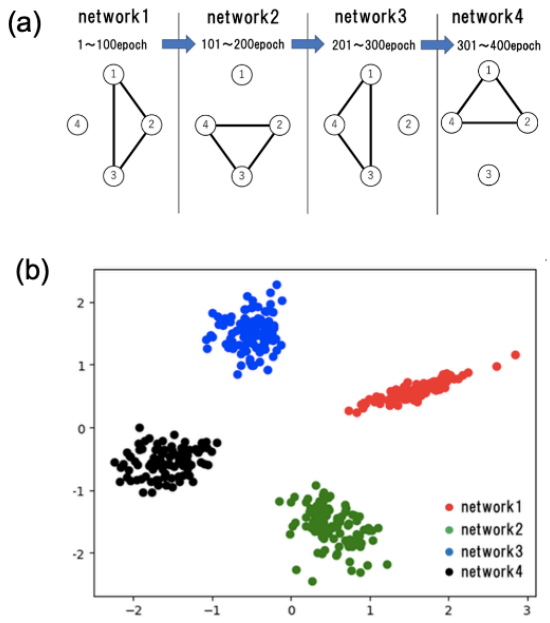

Fig. 1. The results of simulation.
(a) Simulation data and its structure. (b) A low-dimensional map for different network states.

Then, we used multidimensional scaling to visualize low dimensional subspace of the brain networks. Currently, we mapped the distance matrix into 2-D subspaces.

To evaluate this method, we first generated artificial data. The data had four variables that followed multi-variate gaussian distribution. Further, connectivity (or networks) of each variable changed depending on the time (Fig. 1A). We applied the above-mentioned method to identify low dimensional subspaces. The result showed that we could visualize the relationship or structure of the data that changes in every 100 epochs in the two-dimensional subspace (Fig. 1B).

Next, we applied this method to the real EEG data. In the present study, we used a public dataset for the brain-computer interfaces (BCI competition 2008 Graz A [10]). The task was four types of motor imagery (left-hand, right-hand, foot, tongue). We examined whether the proposed method detects changes in the data structures associated with tasks. The result showed that all the data seemed to be mixed and no distinct state was observed.

Taken together these results, a method that we evaluated was able to identify low dimensional subspace for the artificial data but not the real EEG data. This could be due to the complexity of the data or noises contained in the data, which may influence the precise estimation of the covariance matrix. Therefore, it is necessary to further develop a method to identifying low dimensional subspace precisely.

IV. Future Perspective

In this study, we tried to develop a method to identify the low dimensional subspace for EEGs in humans. We proposed a method by extending TVGL and applied it to artificial and real EEG data (BCI competition data) in this fascial year. The effectiveness of the proposed method for real EEG data is not verified. Therefore, further investigation into this issue is required. In the next fiscal year, we are planning to conduct an experiment with a task that generates variability, and manipulation of the state using brain stimulation. Also, collaboration with other groups is expected to deeply understand the low dimensional neural subspace and hyper-adaptability.

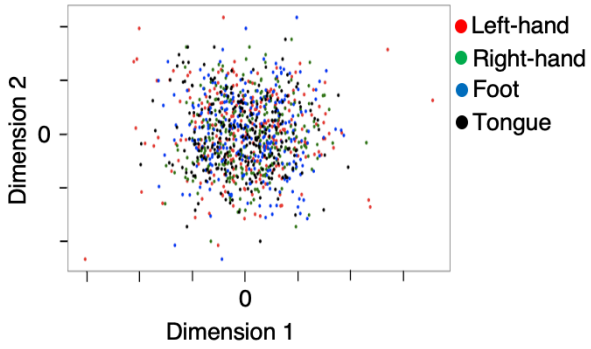

Fig. 2. The results of real EEG data. Each axis indcates dimension identified by multi-dimensional scaling. Each color indicates task-state, respectively.

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

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***Abstract*—In this study, we developed a motor learning model based on an estimation of partial dynamics of the target motor control system and a transformation estimation model between the partial dynamics. We show that it is possible to reconstruct the controller using the information of the other arm's controller when the controller of one arm is partially defective.**

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 was shown that when one hand is paralyzed, that hand can be controlled by a different neural circuit from the ordinary one [1]. There have been many studies on human motor learning models, such as the integration of multiple dynamics estimation models. However, the process of reuse and substitution of neural circuits has not been modeled yet. If we can develop such a model, we can expect to deepen our understanding of the human adaptation process and apply it to rehabilitation.

In this study, we aim to construct a motor learning model that can explain the process of reusing a part of a once-acquired motor control model according to the situation. We propose a model that automatically generates a controller by estimating the dependency among various sensor signals in motion control based on our past achievement [2], and develop a motion learning model that explains the process of reusing a part of dynamics in a previously acquired controller by introducing a new mechanism called transformation estimation among mappings to the model.

II. Achievements

There are mainly two achievements summarized as follows.

A. Construction of motor learning model based on estimation of partial dynamics

As a precondition for the proposed model, which is based on the estimation of transformations between mappings, we constructed and verified an algorithm that automatically generates a motion controller by estimating the relationships between observable sensor variables (mappings) as partial dynamics, unlike conventional motion learning models that focus only on the final input and output of the target system.

The structure of the musculoskeletal arm system targeted in this study is shown in Fig.1. The arm robot consists of three links and two joints, and the base link is fixed. Each joint is driven by two artificial muscles. In this study, the control input to the robot is the temperature of the muscles.

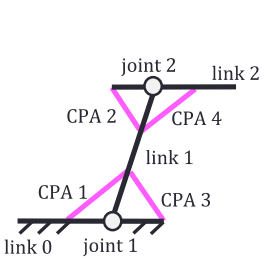

Fig. 1. Musculoskeletal arm model

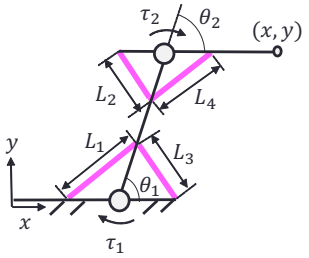

Fig. 2. Variables of manipulator

TABLE I
Sensor variables

$\dot{\boldsymbol{\theta}}$ [rad/s]	$\boldsymbol{d}_1 \in \mathbb{R}^2$	$\boldsymbol{\tau}$ [N/m]	$\boldsymbol{d}_7 \in \mathbb{R}^2$
$\dot{\boldsymbol{x}}$ [m/s]	$\boldsymbol{d}_2 \in \mathbb{R}^2$	$\dot{\boldsymbol{L}}$ [m/s]	$\boldsymbol{d}_8 \in \mathbb{R}^4$
$\boldsymbol{\theta}$ [rad]	$\boldsymbol{d}_3 \in \mathbb{R}^2$	$\boldsymbol{L}$ [m]	$\boldsymbol{d}_9 \in \mathbb{R}^4$
$\boldsymbol{x}$ [m]	$\boldsymbol{d}_4 \in \mathbb{R}^2$	$\ddot{\boldsymbol{L}}$ [m/s^2]	$\boldsymbol{d}_{10} \in \mathbb{R}^4$
$\ddot{\boldsymbol{\theta}}$ [rad/s^2]	$\boldsymbol{d}_5 \in \mathbb{R}^2$	$\boldsymbol{F}$ [N]	$\boldsymbol{d}_{11} \in \mathbb{R}^4$
$\ddot{\boldsymbol{x}}$ [m/s^2]	$\boldsymbol{d}_6 \in \mathbb{R}^2$	$\boldsymbol{T}$ [°C]	$\boldsymbol{d}_{12} \in \mathbb{R}^4$

The sensor variables are shown in TABLE I. $\boldsymbol{x}$,$\boldsymbol{\theta}$, $\boldsymbol{L}$, $\boldsymbol{\tau}$, $\boldsymbol{F}$, $\boldsymbol{T}$ denote the position of the end-effector, the angle of each joint, the length of the muscle, the joint torque, the muscle force, and the muscle temperature, respectively. The correspondence between each variable and the components of the robot is shown in Fig.2. To express the unknown structure of the robot, we assume that the physical meaning of each sensor variable is unknown. Therefore, each sensor variable such as $\boldsymbol{x}$, $\boldsymbol{\theta}$, etc. is treated as $\boldsymbol{d}_1$, $\boldsymbol{d}_2$. However, the relationship between the time derivatives of the variables $\boldsymbol{\theta}$, $\dot{\boldsymbol{\theta}}$, $\ddot{\boldsymbol{\theta}}$, etc. and the control input $\boldsymbol{\mu} = \boldsymbol{d}_{12} = \boldsymbol{T}$ are known. The goal of the arm robot is to generate a control law that leads the end-effector position $\boldsymbol{d}_{\text{target}} = \boldsymbol{d}_4 = \boldsymbol{x}$, to the target value $\boldsymbol{d}_{\text{des}}$.

We use mutual information to evaluate the relationship between sensor variables, define the weakness of the relationship as the cost, and search for the connection of variables with the minimum cost from the control target to the control input using the Dijkstra method. The connection of the variables is defined as a chain, and the feedback control is realized by the

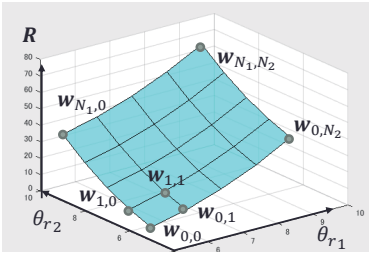

Fig. 3. A partial visualization of Jacobian in the state space with self-organizing elastic grid model.

control measure generation algorithm based on the chain. To generate the control law, we use locally linear approximation model. This local linear approximation model plays the role of the 'estimated partial dynamics' in this study.

B. Estimation of transformation between partial dynamics

Based on the above-motioned learning model, we proposed and constructed a model to estimate the transformation of the partial dynamics between the controllers of the two arms. The partial dynamics of the left and right arms are denoted as ${}^{L}\boldsymbol{R}_{i,j}$ (controller L) and ${}^{R}bmathR_{i,j}$ (controller R). Transformation between the partial dynamics is represented by

$$ {}^{R}\boldsymbol{R}_{i,j} \approx \boldsymbol{T}({}^{L}\boldsymbol{R}_{i,j}). \tag{1}$$

Fig.3 shows a visualization of a self-organizing elastic grid for estimating the transformation $\boldsymbol{T}$ between the left and right partial dynamics. This transformation estimation is represented by a group of nodes distributed in a grid defined in the variable space where the partial dynamics $\boldsymbol{R}$ are defined. Each node has a position in the space and holds a scale transformation coefficient between the left and right $\boldsymbol{R}$ at that position. If this transformation coefficient takes an appropriate value, the left and right $\boldsymbol{R}$ satisfy the relation (1). This matching is expressed as a cost function, and the matching problem is solved by minimizing the cost function using the gradient method.

Examples of numerical experiments assuming the disappearance of partial dynamics in the controller R are shown in Fig.4 and Fig.5. Assuming a case where ${}^{R}\boldsymbol{R}_{i,j}$ is not available, using ${}^{L}\boldsymbol{R}_{i,j}$ and estimated $\boldsymbol{T}$, ${}^{R}\boldsymbol{R}_{i,j}$ is substituted by $\boldsymbol{T}({}^{L}\boldsymbol{R}_{i,j})$. In the section labeled "ordinary control" in the figure, the reference trajectory of the hand position is followed by the acquired motion controller. In contrast, in the section labeled "partial disorder," due to the lack of proper control, whenever a hand position goes out of the specified area, the hand position is repositioned (reset). Therefore, we can see that resets occur frequently. It was confirmed that by using the controller with the partial dynamics substituted by $\boldsymbol{T}({}^{L}\boldsymbol{R}_{i,j})$, the control that follows the reference trajectory was recovered again.

III. Summary and Future Plan

The following results were obtained in this fiscal year:

- For two-arm systems with varying scales of link lengths, it was confirmed that an automatic control law generation algorithm based on the estimation of partial dynamics can generate a hand position controller for each arm.
- It was confirmed that appropriate motion control could be achieved by transforming the partial dynamics of the controller of the other arm when the information of the controller of one arm was lost by the transformation estimation between partial dynamics that could absorb the above-mentioned scale change.

In the future, the transformation estimation method implemented this year will be extended to be applicable to various transformations by referring to motion learning methods such as [4], and experiments on human motion learning will be conducted to verify the explainability of the proposed motion learning model.

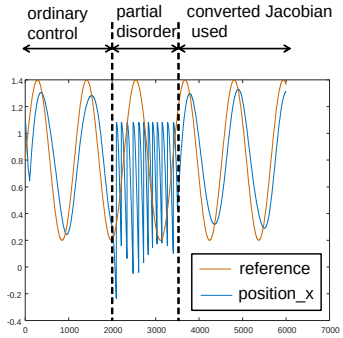

Fig. 4. Partial disorder and its recovery process based on conversion of Jacobian (x position).

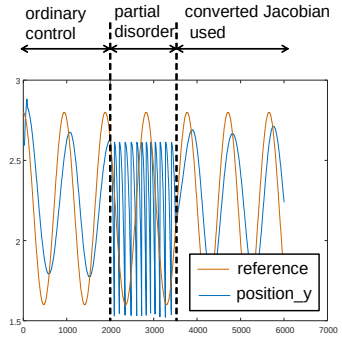

Fig. 5. Partial disorder and its recovery process based on conversion of Jacobian (y position).

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Annual report of research project B05-6

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***Abstract*—The goal of this research is to enable an operator to enhance embodiment of a robot 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 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 compete a target task if necessary. Through experiments, we confirmed that the operator's sense of agency tended to decrease when the robot controller intervened operator's manipulation. On the contrary, other results suggest that the sense of agency increases if the intervention from the AI robot controller is not conscious for the operator.**

I. Introduction

Shared control is a control approach in which a human and a machine work cooperatively, and each of them performs full operation process from perception to action in a consistent manner. It is expected to reflect the operator's intentions and achieve accurate operation, and has been applied to driving assistance for automobiles and rehabilitation robots.

However, if the operational intervention by the controller is different from the operator's intention, discomfort or sickness may occur. For example, it has been confirmed that sickness is induced by the operational intervention to avoid obstacles during the teleoperation of a robot with an automatic collision avoidance function. It is assumed that one of the reasons for this phenomenon is that the operator's sense of agency (the sense of recognizing that the motion of the observed object is caused by himself or herself[1]) is decreased when the manipulated object behaves differently from the operator's intention. Therefore, interventions which do not degrade operator's sense of agency are required.

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.

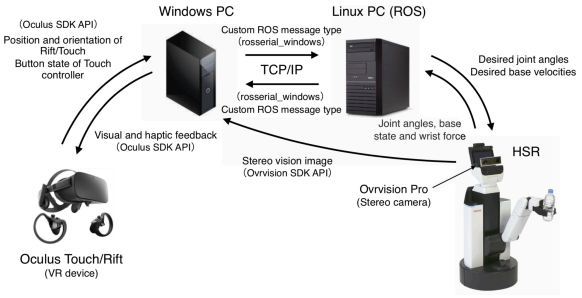


Fig. 1. Configuration of the teleoperation system with HSR and Oculus Rift /Touch[2]

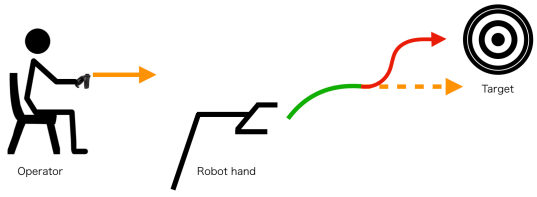


Fig. 2. Image of operational intervention: When the robot arm approaches near the target position, it moves there regardless of the operator's controller operation.

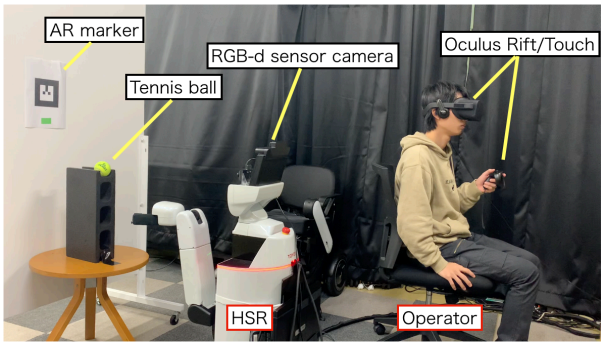


Fig. 3. The experiment to evaluate the Sense of Agency

III. Achievements

A. Manipulation intervention using the intuitive teleoperation system

To investigate the effect of manipulation intervention by a robot controller on robot teleoperation, we used the intuitive teleoperation system that has been developed in our laboratory[2].

The intuitive teleoperation system is a system for remotely controlling TOYOTA HSR (Human Support Robot) using VR

devices (head-mounted display and controller)(Fig. 1). In this system, the position and posture of the operator's left hand corresponds to the position and posture of the arm tip of HSR, and the position and posture of the operator's head corresponds to the position and posture of the head camera of the HSR, which are controlled in real time. In addition, the images from the binocular camera mounted on the robot's head are displayed on the head-mounted display, and the operator is presented with parallax images. This system allows the operator to teleoperate the robot with a sense of immersion.

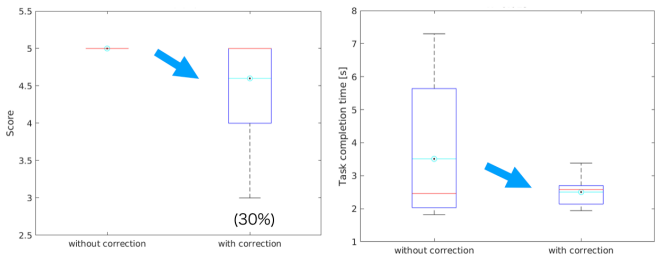
In this year, we introduced a function to support operations such as grasping an object by intervening to correct the arm tip position of HSR. When the distance between the arm tip and the target position becomes less than a certain value, the arm tip moves to the target position regardless of the operator's controller operation (Fig. 2). This correction is expected to improve the positioning accuracy of the arm, however, at the same time, it is also expected to reduce the operator's sense of agency. In order to achieve accurate manipulation without degrading the operator's sense of agency, it is necessary to clarify the relationship between the intervention in manipulation and the sense of agency.

B. Evaluation of the effect of manipulation intervention on the sense of agency

We conducted evaluation experiments to examine the effect of manipulation intervention on the operator's sense of agency in robotic teleoperation. The 3D camera on HSR's head recognized an AR marker on the wall, and placed a tennis ball at the target position based on the marker(Fig. 3). We set a task to move the robot arm to a position where it can grasp the ball, and randomly changed the conditions with and without correction. Two sets of 10 trials (5 trials for each condition) were performed per person.

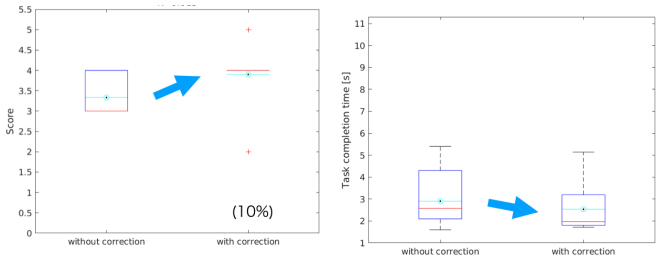
The evaluation indices were the sense of agency toward the arm manipulation, the time required to accomplish the task, and the time required to feel correction (discomfort), and we compared the results with and without correction. In oder to evaluate the sense of agency, we conducted a questionnaire survey after each trial and asked the participants to rate on a 5-point scale from 1 to 5 whether their own manipulations were reflected in the movements of the robot arm. In order to measure the time required to feel the correction (discomfort), the subjects were instructed to pull the trigger of the controller at the moment they felt the correction (discomfort).

As a comparison condition, we conducted an evaluation experiment by changing the intensity of the correction. The results of the comparison of subject A's sense of agency and task completion time in the conditions with and without correction are shown in Fig. 4. Although there are individual differences in the results, the correction tended to shorten the task completion time and decrease the sense of agency. However, in the case of subject B, when the rate of noticing the correction was low, the sense of agency was improved by the correction (Fig. 5).



(a) Score of questionnaire (b) Task completin time

Fig. 4. Experimental results of the subject A: With/without correction at gain K = 0.015, which determines the intensity of the correction. (Figures in parentheses indicate the percentage of times the trigger was pulled. Average value is calculated excluding outliers of task completion time.)



(a) Score of questionnaire (b) Task completin time

Fig. 5. Experimental results of the subject B: With/without correction at gain K = 0.015, which determines the intensity of the correction. (Figures in parentheses indicate the percentage of times the trigger was pulled. Average value is calculated excluding outliers of task completion time.)

IV. Future Perspective

In this year's study, we constructed an environment in which the operator can intervene in the teleoperation of the robot arm, and conducted an experiment to evaluate the effect of the intervention on the operator's sense of agency.

We found that the operator's sense of agency tended to decrease when the teleoperated robot arm underwent position correction. However, there were cases in which the sense of agency was improved by the correction when the rate of noticing the correction was low. This suggests that the positive task performance influenced the operator's sense of agency[3].

In the future, we plan to add more subjects, and to examine and evaluate intervention methods that take into account factors such as manipulation speed and trajectory.

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

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***Abstract*— The intermittent control is a novel hypothetical neural strategy for stabilizing upright posture during quiet stance. Although intermittency in the action of nonlinear postural controllers have been well established recently in the literature, and some studies are beginning to associate intermittency with a healthy control strategy and loss of intermittency with deterioration in postural function, it is still controversial whether such time-discontinuous, nonlinear controllers are more physiologically plausible compared to the traditional time-continuous linear controllers. Here, we are conducting a research to elucidate information processing in the central nervous system (CNS) as a neural basis of the intermittent control during quiet stance for providing supporting evidence for the intermittent control hypothesis.**

I. Introduction

It has been considered that the human quiet posture is stabilized by the tonic, i.e., continuous tension of the antigravity calf muscles and the associated high stiffness of the ankle joint with a help of spinal stretch reflex (continuous control model). Ten years ago, we proposed an intermittent control hypothesis that contradicts this traditional hypothesis [1]. In recent years, several research groups have announced the results of data assimilation based on our new hypothetical model with postural fluctuation data, showing that the new model can fit the data more accurately than the traditional model. In this study, bio-systems theory, measurement of postural dynamics in healthy people and patients with Parkinson's disease (PD), associated electroencephalograms (EEG) and electromyograms (EMG), data assimilation based on Bayesian inference, evaluation of cortico-spinal excitability by transcranial magnetic stimulations (TMS), and neuromodulation by repetitive transcranial magnetic stimulations (rTMS) are utilized. By integrating outcomes from those multi-modal information, we aim to elucidate the brain mechanism of the intermittent control during human upright standing.

II. Aim of the Group

According to the intermittent control hypothesis, the 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 first goal of year 2020 was to perform a data assimilation analysis using the intermittent control model and a number of postural sway data acquired from healthy young and elderly people and PD patients to demonstrate that the healthy strategy for postural stabilization is the intermittent control, and the intermittency is lost, leading to the continuous control, in PD patients.

The second goal of 2020 was to characterize a long latency and long-lasting event-related synchronization (ERS) at the beta band and accompanied an event-related desynchronization (ERD) at the theta band that appear in response to a support surface perturbation during quiet stance. Those novel EEG responses were found recently in our preliminary study for postural dynamics during standing. Similar beta ERS has been known for motor control of upper extremities, referred to as beta rebound, because it 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. In this year, we tried to establish a basis that are required to validate the hypothesis in 2021, using TMS and rTMS for evaluating and modulating cortical activity.

III. Research Topics

A. Data assimilation for postural sway data

The intermittent control model, which can also represent the traditional continuous control model for a specific choice of its parameter value, was assimilated into postural sway data during quiet stance acquired from hundreds of healthy people (young and elderly) as well as PD patients, using a method of Bayesian parameter inference [2].

Fig. 1 shows a set of posterior distributions of inferred parameter values for healthy people (upper panels) and PD patients (lower panels). The 6 graphs aligned at the bottom of each of upper and lower set of panels are the posterior distributions, in which the 3rd from the left is the one for the parameter ρ associated with the degree of intermittency in the active control. As can be confirmed in Fig. 1, ρ-values distributed around 0.5 for the healthy people, and they were close to 1.0 for the PD patients, implying that the upright posture of healthy people is stabilized by the intermittent control, whereas it is achieved rigidly by the continuous control [2].

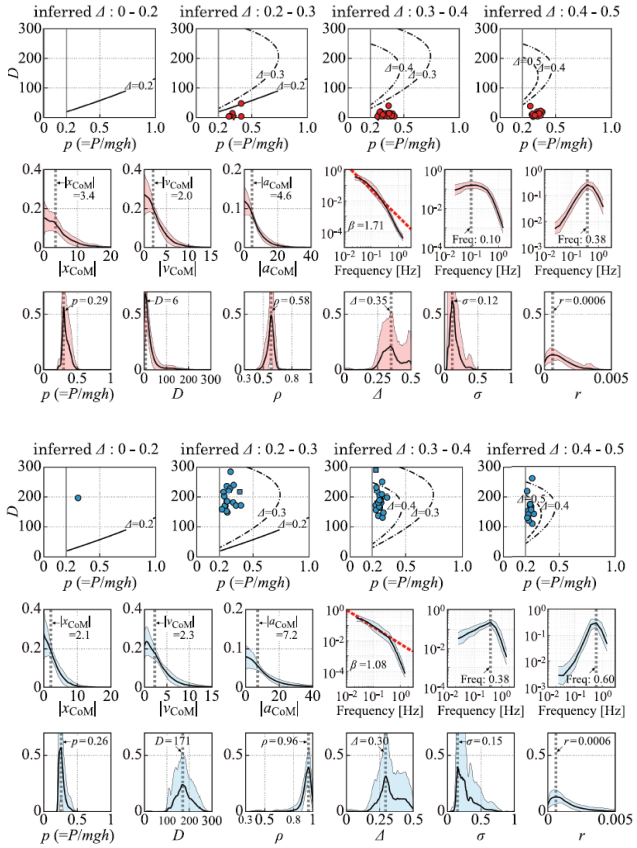

Figure 1. Upper: Posterior distributions of inferred parameters for healthy people. Lower: Posterior distributions of inferred parameters for PD patients. For the parameter ρ, ρ=1.0 represents the continuous control model, whereas ρ~0.5 represents a typical intermittent control model.

B. Beta ERD and ERS during postural recovery

A high-beta ERD followed by a high-beta ERS, as well as a theta ERD were characterized. Unlike in motor tasks of upper extremities, 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 and then with no excessive EMG activities for the second half period of the beta rebound. We speculate that those novel characteristics of the beta rebound might be caused by slow postural dynamics along a stable manifold of the unstable saddle-type upright equilibrium for the postural control system without active feedback control, but with active monitoring of the postural state, in the framework of the intermittent control.

Although the intermittent feedback is the involuntary control for automatic postural stabilization, selecting on or off of the switch is conceptually similar to the decision-making processes, which might generate the high-beta ERD and ERS as in the decision-making processes for selecting Go or NoGo actions in Go/NoGo tasks. Because selecting (or switching between) off and on requires a reliable estimate of the current state, active and continuous monitoring of the postural state plays an important role for achieving the intermittent postural control. Such active monitoring could also be a cause of the high-beta ERS, as suggested by previous studies such that the beta ERS represents a processing of afferent sensory information.

IV. Future Perspective

Causal relationship for the correlation between beta ERS and slow dynamics of the postural state along the stable manifold of the upright posture with switched-off feedback controller is necessary for validating the hypothesis. We are planning to utilize TMS and rTMS for evaluating and modulating cortical activity during the period of beta ERS.

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Annual report of research project B05-8

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***Abstract*—In this research, we studied the learning mechanism for adapting to an indefinite environment, where the possible states of the environment are not even determined, through the exploration-exploitation trade-off problem in reinforcement learning. In this year, we developed a prototype neural network reinforcement learning model that performs a target search task in which the exploration and exploitation trial periods appear alternately. In addition, through a meta-analysis of cognitive and behavioral tasks in mice with leptin-related gene mutations, we discussed the relationship between learning and memory, depression, and anxiety, and obtained a foothold for adapting the idea of "hyper-adaptability" to mental activity.**

I. Introduction

There are two kinds of uncertainty. One is like dice, where the state space is fixed, but which state is taken is probabilistic. The other is one in which even the state space is not fixed. The environment that contains the latter is called the indefinite environment. Living systems seem to have a much higher ability to adapt to an indefinite environment than existing machines.

Reinforcement learning brings a theoretical framework for acquiring the ability to adapt to the environment from only correct and incorrect information. One of the major problems in reinforcement learning is the exploration-exploitation trade-off problem (Sutton and Barto, 1998). In other words, the question is how to use the seemingly contradictory strategies of using previous experience (exploitation) or searching for new effective behaviors (exploration) in an ever-changing environment. Through this exploration-exploitation trade-off problem, we explore a framework for learning with high adaptability to an indefinite environment.

II. Aim of this Research

The specific purpose of this research item is to elucidate the neural mechanisms underlying the execution of a target search task (Kawaguchi et al., 2015) that we have previously used in physiological experiments in primates. In the task (one-target search task, Fig. 1), subjects are presented with four points while fixating on a fixed viewpoint, and are rewarded if they see one of the hidden targets. If the subject answers correctly for a specified number of trials in a row, another point becomes the hidden target without instructions. In this case, the subject searches for a new target through trial and error and correct and incorrect answers. In other words, the trial period of exploitation, in which the subject repeatedly looks at the found target to obtain the correct answer, and the trial period of exploration, in which the subject has to search for a new target, come alternately. Therefore, this task is suitable for dealing with the exploration-exploitation trade-off problem.

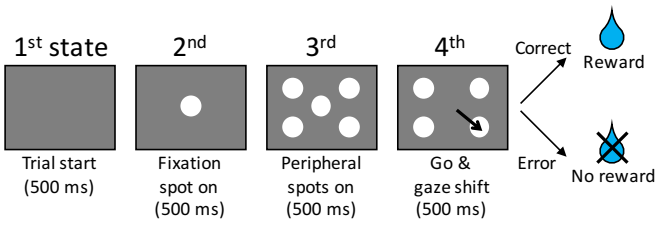

Fig. 1. The event sequence of the target search task.

III. Research Topics

A. *Prototype of a Newelnet Reinforcement Learning Model for Learning One-Target Search Tasks*

In this year, we have developed a prototype neural network reinforcement learning model that learns the one-target search task [1]. The neural network part consists of an input layer *I* and an output layer *O* (Fig.2A), and the softmax function determines the action based on the activity of the output layer.

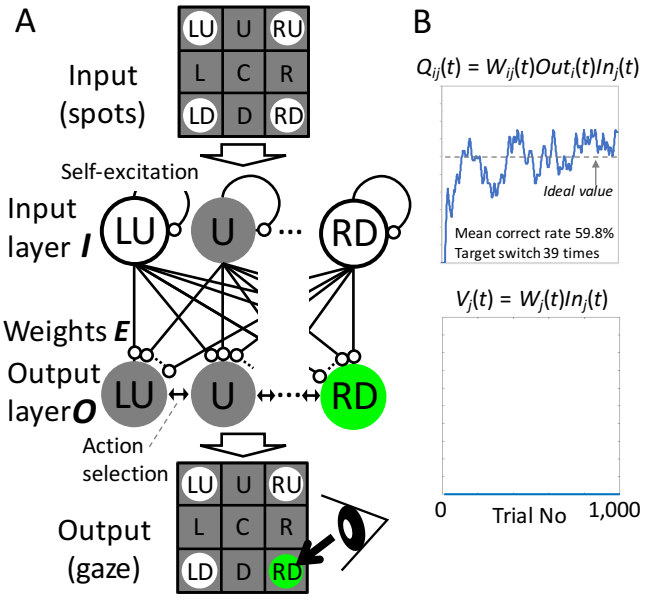

Fig. 2. Schematic view of the input–output part of the proposed model (A) and its performance (B).

The connection weights *E* between the input and output layers is changed based on the reward prediction error δ. However, by calculating the action value function *Q* required to calculate δ for the combination of input *In* and output *Out*, only a limited part of the connection weights is changed, and as a result, new targets can be found in a short time even if the target is changed repeatedly. (Fig. 2B up: *t* is the time step of the calculation, W

is the weight for Q or V calculation). However, when the value function is the state value function V, which is calculated only for the input, the modulated E is not limited, and as a result, the task is not learned correctly (Fig. 2B bottom).

B. A Meta-Analysis of Cognitive Behavioral Tasks in Leptin and Leptin Receptor Deficient Mice

The reward prediction error δ described above is thought to be carried by the activity of dopamine cells in the substantia nigra of the midbrain (Schultz et al., 1997). In addictions such as bulimia, the activity of these dopamine cells and the calculation of reward prediction error δ may be altered. Therefore, this year, we conducted a meta-analysis of 34 papers that met the criteria out of 54 papers obtained for cognitive and behavioral tasks in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice, which are known to be adipocyte-derived feeding activity inhibitory hormones [2].

Analysis revealed that these mutant mice showed significant abnormalities in performance compared to controls in memory-related tasks such as the Morris water maze task (Fig. 3A) and tasks used to assess depression-like behavior such as the tail suspension test. However, no significant changes were observed in tasks used to determine anxiety-like behavior, such as the elevated plus maze test (Fig. 3B).

Addiction is said to be related to anxiety, and the idea that it can be modeled a bias D in the reward prediction error δ calculation, as in

$$\delta(t) = \max\{ r(t) + \gamma Q(t+1) - Q(t) + D, D\},$$

where t is the time step in the calculation, r is the reward, γ is the discount rate, and Q is the behavioral value function (Redish, 2004). On the other hand, depression has recently been suggested to be associated with a decrease in the discount rate (Yoshida et al., 2019). In other words, in the above equation, δ related to the amount of neural network modulation associated with learning and memory, γ related to depression, and D related to anxiety are integrated as different contributions in one equation. Although some psychotropic drugs exhibit both anxiolytic and antidepressant effects, the discrepancy between depressive-like and anxiety-like behaviors in the genetically mutant mice dealt in this study suggests that these are closely related but different factors, and does not negate the above formulation. The results of this study provide a great suggestion for the application of the concept of "hyper-adaptability" in this area to higher brain functions and mental activities.

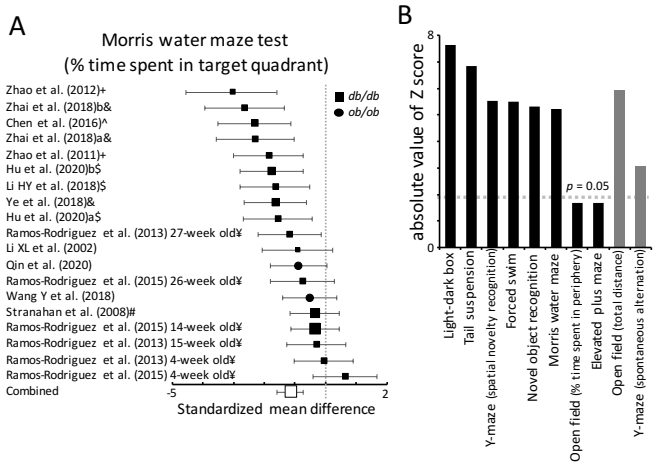

Fig. 3. Integrated behavioral measures obtained from behavioral tests analyzed. (A) The Morris water maze test. (B) Z scores in all tests analyzed.

C. The time-frequency pattern of local field potentials during action planning differs between dorsal and ventral lateral prefrontal cortex

In addition to the above, we conducted a time-frequency analysis of the local field potential (LFP) recorded from the monkey's prefrontal cortex during an action planning task (shape manipulation task). We found that in the ventral part of the brain, θ waves transiently intensified immediately after the start of the task and just before the presentation of the first shape, whereas in the dorsal part, θ waves transiently intensified just before the presentation of the second shape, when action planning became possible [3,4].

IV. Future Perspective

Based on this year's model that can perform the one-target search task, we will build a model that can perform a two-target search task (a task in which two of the four light points are targeted alternately) in the next year. At the same time, we will actively engage in intra-disciplinary exchange and joint research, which did not progress as expected in the corona disaster.

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Annual report of research project B05-9

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Abstract— **The research project B05-9 aims to establish a tailor-made EEG-based neurofeedback (NF) training system for the elderly to improve motor and cognitive functions by quantifying an individual's ability to control attention using brain activity. We try to demonstrate that the training considering individual differences can promote the functional network's reconstruction to control attention during motor tasks (i.e., hyper-adaptability) and that the reconstructed network leads to better motor performance. The achievements in this year are as follows: 1) We have built a noiseless sensory stimulator to induce EEG (steady-state somatosensory evoked potentials [SSSEP] and steady-state visual evoked potentials [SSVEP]) used for neurofeedback training. 2) We have developed the EEG processing algorithms for quantifying attentional states in real-time using the sensory evoked potential. 3) We have attempted to modulate (amplify) the corresponding EEG using this NF training system.**

I. Introduction

In this research project, we aim to demonstrate that a tailor-made NF training that matches each individual's attentional control ability can facilitate the reconstruction of neural circuit and to propose a prediction model for the training effect. Because previous training protocols for NF set consistent goals without considering differences in individual brain function, the conventional protocols cause large individual differences in the effect of training [1]. To overcome this issue, based on the individual differences in the optimal attentional strategy during motor tasks (i.e., Internal focus or External focus) and the somatosensory and visual cortexes' characteristics reflecting the individual optimal attentional strategy [4], we propose a new NF training protocol that appropriately sets the goals 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 a tailor-made NF training that shows the individual's estimated attention state in real-time (Fig. 1). Especially, we expect improvements in adaptation and motor learning abilities in the elderly after the NF training. To estimate the attention state, this NF training system focuses on the activities in the sensory areas instead of those in the prefrontal cortex and parietal association areas, which control attention. We also try to propose a prediction model of NF training effect based on individual differences in brain functions and to maximize improvement of brain functions under appropriate training protocols for individuals.

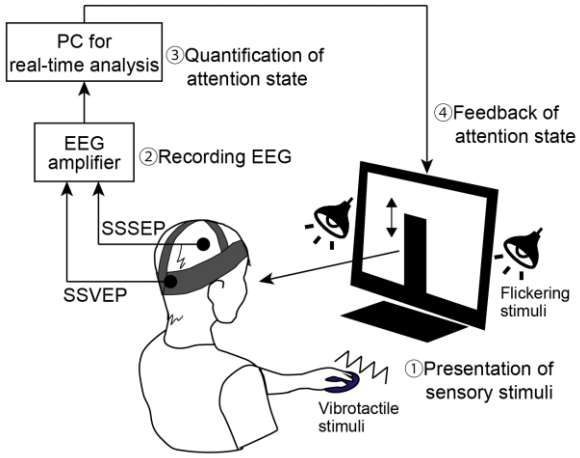

Fig. 1 EEG-based neurofeedback system

III. Research Topics

A. Development of noiseless stimulators

Steady-state somatosensory evoked potentials (SSSEP) and Steady-state visual evoked potentials (SSVEP) observed from the somatosensory and visual cortices, respectively, are used in the NF system in this study. For eliciting the SSSEP, we had developed a device capable of presenting any vibration frequency using a brushless direct current (DC) motor (Fig. 2). This vibrotactile stimulator has a mechanism converting the rotational motion of a DC-motor into a linear motion, and we succeeded in reducing the influence of electrical noise on the EEG signal. Meanwhile, for a visual stimulus to elicit SSVEP, we have also developed a device to control LEDs' flickering frequency from a computer.

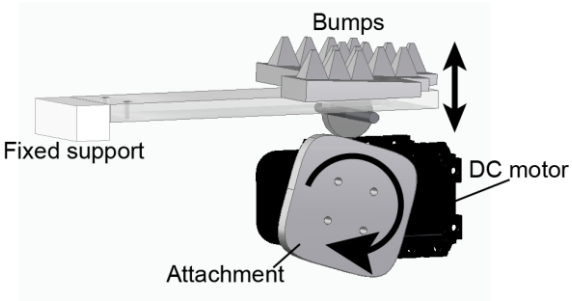

Fig. 2 Vibrotactile stimulator using a brushless DC motor

B. *Implementation of algorithms to estimate the attention state*

Top-down attention to sensory stimuli can increase the response of SSSEP and SSVEP. In other words, these evoked potentials reflect the cognitive processes for attention control. Therefore, in this NF training system, we applied the left and right somatosensory cortices for SSSEP recording and the left and right visual cortices for SSVEP recording, respectively. Regarding real-time analyses, EEG data from these low sensory cortices was buffered for several seconds and we applied FFT to detect SSSEPs or SSVEPs. Moreover, we implemented an algorithm to estimate the attention state based on the modulation of SSSEP or SSVEP intensity when individuals direct the attention to a sensory stimulus. Finally, the trainees themselves could recognize their own attention state by presenting the degree of modulation of the calculated SSSEP or SSVEP as auditory feedback.

Previous studies often used visual information for feedback modalities on attentional states. However, when using visual modality, it is difficult for the trainee to properly focus on sensory stimuli because attentional resources are devoted to feedback information. Thus, as a feedback modality suitable for this NF training system, we examine whether visual or auditory feedback modalities promote the effect of training.

C. *The modulation of brain activity using the NF system (SSSEP)*

Based on the NF training system with the algorithm estimating the attention state, we conducted a preliminary experiment to confirm the modulation of SSSEP responses. The NF training consisted of three days and SSSEP responses were evaluated before and after the training. EEG electrodes were placed on the left and right somatosensory cortices and vibrotactile stimuli with 22 Hz and 25 Hz were presented to the left and right fingers.

Figure 3 shows a typical result of the SSSEP response after the NF training. When calculating spectral power, a peak at 25 Hz in the left somatosensory cortex elicited by the stimulation on the right hand and a peak at 22 Hz in the right somatosensory cortex elicited by the stimulation on the left hand were observed. It was confirmed that these peaks were SSSEPs, and the corresponding EEGs were properly induced in this NF training system. Although an example in Figure 3 shows responses relatively expectedly in the preliminary study, some cases were observed no significant modulation in response strength after training during three days. Therefore, we examine whether individuals who failed to modulate brain activity by using SSSEP can be successfully trained using SSVEP. In addition, we focus on the relationship between individuals' ability to attention control and the NF training effect.

At present, participants performed the training under the condition that they monitored their own EEG (Real group). In the next step, to demonstrate the effectiveness of this NF training system, we prepare the control group (Sham group) that provides pseudo-feedback of other people's brain activity recorded in advance.

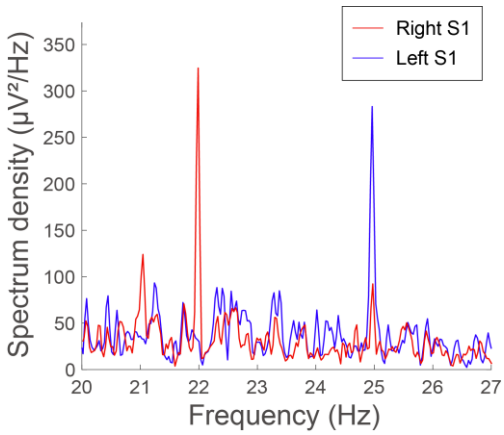

Fig. 3 SSSEP responses after NF training

IV. Future Perspective

In B05-9, we have developed a noiseless sensory stimulator for NF training and implemented a method to quantify the attention state in real-time. We also performed a preliminary experiment on the training for amplifying the response of SSSEP and SSVEP. In the next fiscal year, we try to evaluate whether motor learning can be promoted by modulating brain activity. Moreover, we aim to evaluate the training effect in both young and elderly populations and to propose a model for predicting the training effects to maximize individual brain functions' improvement.

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

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I. Introduction

Currently, rehabilitation for motor dysfunction has been a subjective and empirical decision-making process in which the patient works on a rehabilitation program according to a policy set by a physical therapist. The physical therapist observes the process and formulates a rehabilitation policy by estimating the recovery status of physical functions. This study aims to realize a system that optimizes the process of interaction between a physical therapist and patient and provides an optimal rehabilitation program according to the individual patient's condition. Suppose we can model the function f of the rehabilitation process $Y=f(X)$, which is to restore the motor function to state Y by applying the rehabilitation strategy f to the current motor function state X with motor disability. In that case, it will pave the way for optimizing a highly effective rehabilitation strategy. The purpose of this study is to clarify the methodology of modeling this rehabilitation strategy f.

II. Research Method

When the rehabilitation process is expressed as $Y=f(X)$, f cannot be obtained simply by mapping the relationship between X and Y using machine learning. Because f is the process of mid-to-long-term interaction between the physical therapist and the patient over weeks or months, and the physical therapist intends to transition X to the state of Y through trial and error.

The key idea to realize modeling is to record and create a database of the interaction process between physical therapists and patients. In conventional clinical practice, there is no time-series data in a form that can be subject to informatics analysis. However, rehabilitation histories in the form of subjective verbal expressions written in medical records remain. In this study, we collect data to model the rehabilitation process informatically by recording rehabilitation tasks (VR images and movement patterns) presented by physical therapists, patients' reactions to these tasks (body response movements and EMG signals), and evaluations by physical therapists over a long period. We will also test whether it is possible to optimize rehabilitation strategies based on the data.

Next, we aim to improve rehabilitation efficiency by considering the patient's cognitive and internal states. We introduce two intermediate parameters. The first parameter is the posture distribution θ_1, which increases the effectiveness of motor intervention rehabilitation. In other words, x is the accuracy of the sense of body ownership, which varies according to the different arm posture[1]. The second parameter θ_2 is an extension coefficient used in the VR movement induction function in KINVIS system[2] by Kaneko et al. Using these intermediate parameters, we model the rehabilitation strategy f in the form $Y=f(X; \theta_1, \theta_2)$ to establish an optimization method.

The research questions to be clarified are the following two points.

Q1) Is it possible to construct a rehabilitation strategy model that achieves effective motor function recovery by recording the rehabilitation process?

We hypothesize that the modeling of the relationship $Y=f(X)$ described above is possible only when the rehabilitation process is recorded over a med-to-long-term period. We will test this hypothesis by identifying f using machine learning under two conditions: one in which the patient's physical motor abilities and the stimulus pattern presented to the patient are recorded over a med-to-long-term period. Another condition does not use the patient's physical motor abilities and the stimulus pattern presented to the patient. We analyze the difference in accuracy between the two conditions.

Q2) Can the accuracy of modeling the rehabilitation process be improved by using intermediate parameters such as the accuracy of the sense of body ownership θ_1 and the expansion coefficient θ_2 in the VR movement induction function?

Even if the history of movement X and Y over the med-to-long-term period is used, it would not be easy to find an effective rehabilitation strategy. One factor is the lack of data that reflects the patient's cognitive internal state. Therefore, we introduce parameters related to the patient's cognitive state, such as the sense of body ownership and the augmentation coefficient, which generates visual stimuli by augmenting the actual motion in VR, and examine whether these parameters improve the accuracy of identifying f.

III. Model of the Rehabilitation Process

In modeling the rehabilitation process, we consider the relationship between the movement X and the intermediate parameters θ_1 and θ_2 for the rehabilitation task from two perspectives: the prediction problem to find X from θ_1 and θ_2, and the control problem to find θ_2 to optimize X. We propose a model for the prediction problem based on a probabilistic generative model framework as Fig.1. Because X is time-series data and Y has a similar characteristic of the probability distribution function.

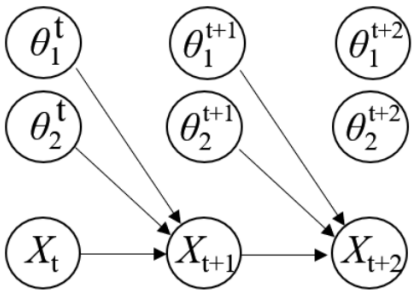

Fig. 1. A prediction model of X from hyper parameterof $\theta_1$andθ_2

Here, θ_1 is not easy to measure by sensors, and it requires several tens of minutes of subject experiments to obtain the distribution. Therefore, the distribution at time t should be used continuously, and the parameter should be updated immediately after the subject experiment is conducted.

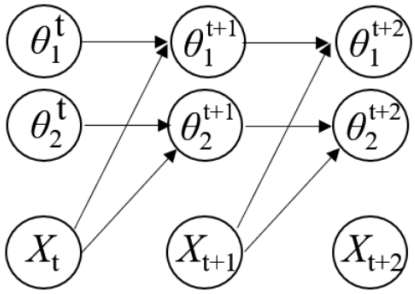

Fig. 2. An optimization model of θ from X

As shown in Fig. 2, we also prepare a model with different transition directions in the graph to infer $\theta_1\theta_2$ from the movement X. For the model learning, we use a probabilistic generative model[3][4] to predict time series data using probability distributions.

IV. Evaluation of the Proposed Model

One of the problems in using this model is determining the time range and sampling rate of the target time-series data. These settings vary depending on the focus target that captures short-term movement changes due to rehabilitation or rehabilitation effects over the med-to-long-term. The first way to evaluate the model is to automatically adjust the range of time series data to be trained from the viewpoint of slow dynamics and fast dynamics and consider the time range in which the model training is practical.

For the Research Question (Q2), we evaluate how the estimation accuracy varies depending on whether θ_1, a parameter with high measurement cost, is included in the model or not, and examine the contribution of θ_1 and the cost-effectiveness of how often it should be measured.

At present, we have only completed the investigation of the probabilistic generative model and the development of the experimental system using VR. We have not yet started the data collection and analysis of the subject experiments. We will continue to evaluate the model structure and the model learning method by conducting preliminary experiments on healthy subjects, since it is expected that the experiments on subjects in rehabilitation facilities will not proceed as planned due to the COVID-19 situation.

V. Conclusion and Future Works

Since the COVID-19 problem made it difficult to conduct experiments on subjects in rehabilitation facilities and hospitals this year, we developed an infrastructure system for conducting experiments using VR devices remotely. We have developed a cloud-based VR platform based on AWS [i] extending our previous research system on the sense of agency and sense of body ownership using VR[5]. This system enables subjects to wear HMD at home and gather with a physical therapist at a remote location in a VR space rehabilitation facility. Currently, we are operating this system as a robotics competition system[ii]. Although the system is used in a different domain from this hyper adapt project, the effectiveness of the system has been confirmed[6]. We also plan to use the cloud-type VR platform to cope with the COVID-19 situation.

We will soon start experiments on subjects using the above system to verify the accuracy of the prediction of movement X by the probabilistic generative model and the effectiveness of the optimization of the rehabilitation strategy.

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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 rapid 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 quantifiably estimated sensorimotor information of a human infant and constructed a musculoskeletal dynamic simulation to understand the mechanisms underlying early sensorimotor development with rapid physical growth.**

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 FY2020, we estimated the sensorimotor information structure in human neonates and infants during spontaneous movements. In addition, we constructed and modified the infant musculoskeletal model 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 this study, we collected detailed whole-body motion data from neonates and infants, and quantifiably estimated sensorimotor modules using musculoskeletal dynamic simulation.

In this project, we investigate the developmental mechanism by combining measurements from experiments with actual infants and from physical dynamic simulations (Fig. 1).

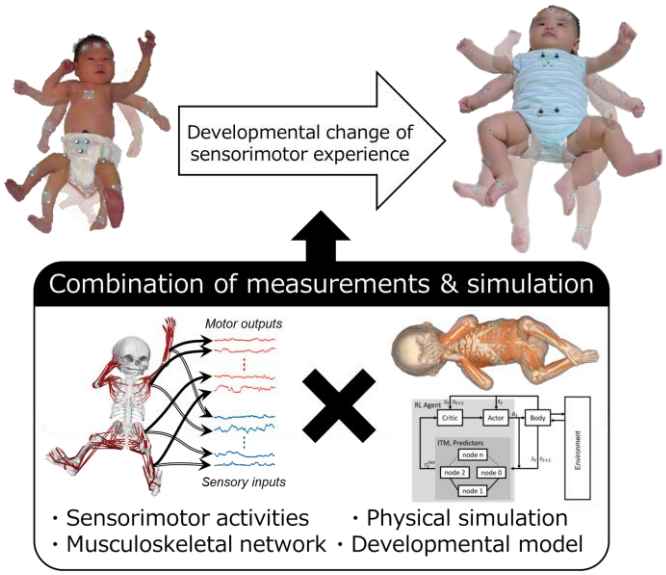

Fig. 1. Research overview

III. Research Topics

A. *Infantile sensorimotor information structure induced by spontaneous movements*

We first conducted a full-body motion capture of the spontaneous movements of 10 neonates (within seven days after birth) and 10 infants (three-months-old). A total of 144 muscle activities and proprioceptive sensory feedbacks were estimated by a musculoskeletal inverse dynamic simulation. Next, we quantified the sensorimotor interaction by calculating the information flow between all muscle pairs of motor activities and proprioceptive sensory inputs (Fig. 2, left). Finally, we identified sensorimotor modules and state transition among muscle activities and proprioceptive sensory inputs based on an Infinite Relational Model (Fig. 2, right). The results show that the infants have a larger number of modules than the neonates. Our results demonstrated a developmental increase in the sensorimotor modules, which is consistent with previous research that suggests the argumentation of motor modules in the early developmental phase [1, 2].

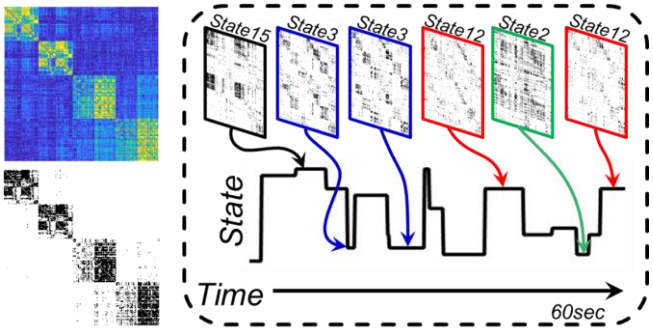

Fig. 2. sensorimotor interactions and state transition

B. Infantile musculoskeletal model

Although the above results suggest that sensorimotor information structure changes along with integration / separation during early infancy, mechanisms underlying these developmental changes remains unclear. To investigate the developmental mechanisms, we have developed fetus / infantile simulations using musculoskeletal models [3]. Here, we constructed a new infant musculoskeletal model based on an upper arm model (MoBL-ARMS Dynamic Upper Limb) and lower limb model (LaiArnold2017 model), adding inter-joint coordination and muscle constraint models. Furthermore, the model was built to be able to be used in the MuJoCo environment, enabling contact force calculations with multi-joints models. By introducing a neural oscillator model and a spinal reflex circuit to generate muscle activities, this infantile musculoskeletal model showed spontaneous movements (unpublished).

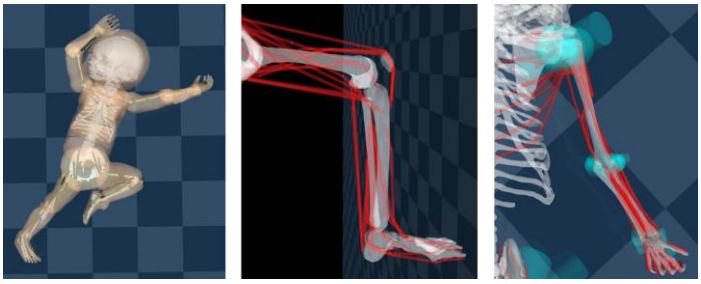

Fig. 3. Newborn and infant simulation on MuJoCo

IV. Future Perspective

In FY2020, we quantitatively analyzed sensorimotor information structure during spontaneous movements in human neonates and infants. In addition, we constructed an infant musculoskeletal model with inter-joint coordination and muscle constraint models. In the next year, we aim to investigate a learning model to explain the developmental changes of the sensorimotor information structure.

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2020

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14. Matsumoto R, Probing connectivity & epileptogenicity using cortico-cortical evokedpotential, 2nd Xuanwu Epilepsy & Brain Science International Forum, Online, China, 2020

Member List

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

Principal investigator	Jun Ota (Professor, The University of Tokyo)
Funded co-investigator	Tadashi Isa (Professor, Kyoto University)
Funded co-investigator	Toshiyuki Kondo (Professor, Tokyo University of Agriculture and Technology)
Funded co-investigator	Tetsuro Funato (Associate Professor, The University of Electro-Communications)
co-investigator	Eiichi Naito (Research Manager, NICT)
co-investigator	Hidenori Aizawa (Professor, Hiroshima University)
co-investigator	Kazuhiko Seki (Director, NCNP)
co-investigator	Hiroshi Imamizu (Professor, The University of Tokyo)
co-investigator	Ken-Ichiro Tsutsui (Professor, Tohoku University)
co-investigator	Kaoru Takakusaki (Professor, Asahikawa Medical University)
co-investigator	Takashi Hanakawa (Professor, Kyoto University)
co-investigator	Ryosuke Chiba (Associate Professor, Asahikawa Medical University)
co-investigator	Yasuharu Koike (Professor, Tokyo Institute of Technology)
co-investigator	Hajime Asama (Professor, The University of Tokyo)
co-investigator	Jun Izawa (Associate Professor, University of Tsukuba)
co-investigator	Wen Wen (Project Associate Professor, The University of Tokyo)
co-investigator	Qi An (Associate Professor, 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

Principal investigator	Tadashi Isa (Professor, Kyoto University)
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Funded co-investigator	Hidenori Aizawa (Professor, Hiroshima University)
Funded co-investigator	Minoru Asada (Specially Appointed Professor, Osaka University)
Co-investigator	Onoe Hirotaka (Project Professor, Kyoto University)
Co-investigator	Tomohiko Takei (Project Associate Professor, Kyoto University)
Co-investigator	Reona Yamaguchi (Project Assistant Professor, Kyoto University)
Co-investigator	Yusuke Yamamoto (PhD Student, Kyoto University)
Co-investigator	Toshinari Kawasaki (PhD Student, Kyoto University)
Co-investigator	Satoko Ueno (PhD Student, Kyoto University)
Co-investigator	Masahiro Mitsuhashi (PhD Student, Kyoto University)

Co-investigator	Tomoyo Morita (Specially Appointed Associate Professor, Osaka University)
Co-investigator	Satoshi Hirose (Researcher, NICT)
Co-investigator	Nodoka Kimura (Researcher, NICT)
Co-investigator	Miho Matsumata (Assistant Professor, Hiroshima University)
Co-investigator	Deepa Kamath Kasaragod (Assistant Professor, Hiroshima University)
Co-investigator	Takashi Handa (Assistant Professor, Hiroshima University)

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	Tatsuya Umeda (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	Yuki Hara (Lecturer, University of Tsukuba)

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

Principal investigator	Hiroshi Imamizu (Professor, The University of Tokyo)
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Co-investigator	Ryu Ohata (Researcher, The University of Tokyo)
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)

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	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)
Co-investigator	Sadaharu Miyazono (Lecturer, Asahikawa Medical 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 A05-1: Elucidation of the hyper-adaptation mechanism of upper limb recovery in stroke patients

Principal investigator	Shinichi Izumi (Professor, Tohoku University)
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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)

Research Project A05-2: Synchronization of neural oscillation among primate limbic structures and the striatum during recovery from anxiety like state.

Principal investigator	Kenichi Amemori (Associate Professor, Kyoto University)
Co-investigator	Oh Jungmin (Ph.D Student, Kyoto University)
Co-investigator	Satoko Amemori (Assistant Technical Staff, Kyoto University)

Research Project A05-3: Mechanism of Hyper-Adaptivity of the human premotor area: electrophysiological connectome analysis with electrocorticogram

Principal investigator	Riki Matsumoto (Professor, Kobe University)
Co-investigator	Akihiro Shimotoake (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, Kyoto University)

Research Project A05-4: Neural circuit rearrangement mechanisms underlying the recovery from learning deficits in Parkinson's disease model animals

Principal investigator　Kazuto Kobayashi (Professor, Fukushima Medical University)

Research Project A05-5: 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 (Section Chief, National Center of Neurology and Psychiatry)
Co-investigator　Kazumasa Uehara (Assistant Professor,
National Institute for Physiological Sciences)

Research Project A05-6: 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,
National Institute for Physiological Sciences)

Research Project A05-7: 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 A05-8: 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, National Center of Neurology and Psychiatry)
Co-investigator　Tsukasa Okimura (School of Medicine, Keio University)
Co-investigator　Hiroki Oi (School of Medicine, Keio University)

Research Project A05-9: 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 (Assistant Professor, 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)
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Co-investigator	Masashi Ikeno (Assistant Professor, Aichi Medical University)
Co-investigator	Yuki Morioka (Research Technician, Aichi Medical University)

Research Project A05-13: Reconstruction of Basal Ganglia by Aging and Neurodegenerative Disease

Principal investigator	Fumino Fujiyama (Professor, Hokkaido University)
Co-investigator	Huyuki Karube (Associate Professor, Hokkaido University)
Co-investigator	Yasuharu Hirai (Assistant Professor, Doshisya University)
Co-investigator	Fuko Kadono (Graduate Student, Hokkaido University)

Research Project A05-14: Development of techniques to improve brain functions by using hyper-adaptability

Principal investigator	Yoshito Masamizu (Deputy Team Leader, RIKEN)

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)

Co-investigator	Tamami Sudo (Assistant Professor, Tokyo University of Agriculture and Technology)

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	Natsue Yoshimura (Associate Professor, Tokyo Institute of Technology)
Co-investigator	Dai Yanagihara (Professor, The University of Tokyo)
Co-investigator	Shinya Aoi (Lecturer, Kyoto University)
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)
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Funded co-investigator	Wen Wen (Project Associate Professor, The University of Tokyo)
Funded co-investigator	Qi An (Associate Professor, Kyushu University)
Co-investigator	Masafumi Yano (Professor Emeritus, Tohoku University)
Co-investigator	Atsushi Yamashita (Associate Professor, The University of Tokyo)
Co-investigator	Hiroyuki Hamada (Project Assistant Professor, The University of Tokyo)
Co-investigator	Ningjia Yang (Researcher, The University of Tokyo)

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

Principal investigator	Jun Ota (Professor, The University of Tokyo)
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Co-investigator	Shohei Shirafuji (Assistant Professor, The University of Tokyo)
Co-investigator	Kohei Kaminishi (Postdoctoral Fellow, The University of Tokyo)
Co-investigator	Yuichiro Omura (Master's Student, The University of Tokyo)
Co-investigator	Daisuke Ishii (Assistant Professor, Ibaraki Prefectural University of Health Sciences)
Co-investigator	Hiroyuki Hamada (Assistant, Bunkyo Gakuin University)
Co-investigator	Yutaka Kohno (Professor, Ibaraki Prefectural University of Health Sciences)
Co-investigator	Hiroshi Kishimoto (Lecturer, Ibaraki Prefectural University of Health Sciences)
Co-investigator	Hiroshi Yuine (Assistant Professor, Ibaraki Prefectural University of Health Sciences)
Co-investigator	Kiyoshige Ishibashi (Ibaraki Prefectural University of Health Sciences)

Co-investigator	Hitohiro Etoh (Undergraduate Student, The University of Tokyo)
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)

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

Principal investigator	Mitsuhiro Hayashibe (Professor, Tohoku University)
Co-investigator	Kyo Kutsuzawa (Assistant Professor, Tohoku University)

Research Project B05-2: 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)
Co-investigator	Syota Hagio (Lecturer, Kyoto University)

Research Project B05-3: 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 B05-4: Understanding neural manifold of the movements using human neuroimaging and non-invasive brain stimulation

Principal investigator	Isao Nambu (Associate Professor, Nagaoka University of Technology)
Co-investigator	Yasuhiro Wada (Professor, Nagaoka University of Technology)
Co-investigator	Hiroshi Yokoyama (Project Assistant Professor, National Institute for Physiological Sciences)

Research Project B05-5: 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)

Research Project B05-6: 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 B05-7: 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	Akihiro Nakamura (PH.D Student, Osaka University)
Co-investigator	Matija Milosevic (Assistant Professor, Osaka University)
Co-investigator	Kimitaka Nakazawa (Professor, The University of Tokyo)
Co-investigator	Saburo Sakoda (Honorary Director, National Hospital Organization Osaka Toneyama Medical Center)
Co-investigator	Takuyuki Endo (Doctor, National Hospital Organization Osaka Toneyama Medical Center)

Research Project B05-8: 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)
Co-investigator	Hajime Mushiake (Professor, Tohoku University)
Co-investigator	Satoshi Zuguchi (PH.D Student, Tohoku University)

Research Project B05-9: 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)
Co-investigator	Fuminari Kaneko (Project Associate Professor, Keio University)

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

Principal investigator	Hoshinori Kanazawa (Research Assistant Professor, The University of Tokyo)
Co-investigator	Yasuo Kuniyoshi (Professor, The University of Tokyo)
Co-investigator	Dongmin Kim (Graduate Student, The University of Tokyo)
Co-investigator	Masahiko Kawai (Project Associate Professor, Kyoto University)