2019 Annual report

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

Program Director: Jun Ota (The University of Tokyo)

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https://www.hyper-adapt.org/

Contents

Program Overview and Activities of Steering Committee

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

I. Purpose of the Research Project

With coming of a super-aging society in Japan, we are facing the urgent problems of sensory-motor impairments, declining higher-order brain functions, cognitive impairment, loss of motivation, and mood disorders caused by aging, and in turn extreme decline of bodily and neurological functions. All of these problems have a common source: inability to adapt appropriately to a brain-body system changed with aging and impairments.

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

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

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

II. Content of the Research Project

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

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

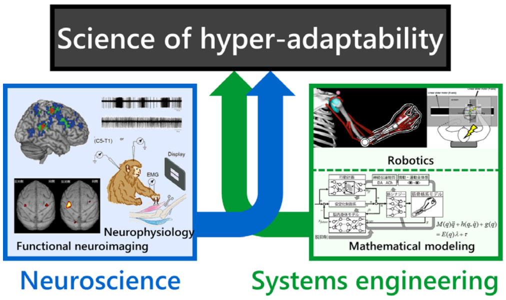

Fig. 1 Whole constitution of the project

Expected Research Achievements and Scientific Significance

The following research achievements and scientific significance can be expected in the research project:

1. Systematization of “science of hyper-adaptability” by elucidating its underlying neural mechanisms and through its computational modelings
2. Construction of mathematical modeling (gray-box model), which can describe brain functions by integrating multi-modal experimental data such as electrophysiology, brain imaging, and behavior.
3. Construction of a comprehensive theory that can explain adaptation principle from its neural entity to its neural computation principle.

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, Yano, Wen, An, and Yozu).

IV. ACTIVITIES

Following events were held by management group.

A. Activities organized by the project

- 1st management meeting
Date: July 17th, 2019. 17:00-19:00
Place: The university of Tokyo
Contents: members of the management group discussed about the operation method, persons in charge of the project symposiums, publications, supports for the activities, etc.

- 2nd management meeting
Date: September 20th, 2019. 12:00-13:00
Place: The university of Tokyo
Contents: members of the management group discussed about the operation method, management of 1st plenary conference, organization of young researches group, etc.

- Kickoff symposium
Date: September 20th, 2019. 13:30-16:00
Place: Ito hall, the university of Tokyo
Consents: kickoff symposium of the project. Project representative (Ota), group A representative (Isa), and group B representative (Kondo) introduced the overview of the area and research groups. Project representative (Ota) explained about public offering. More than 100 people participated in the symposium and shared various opinions.

- 1st plenary conference
Date: March 4th - 6th, 2020
Place: Iwate
Contents: summary of the researches in the year was presented by project representative and researchers in the project.

- 3rd management meeting
Date: Marge 6th, 2020. 11:30-12:30
Place: Iwate
Contents: members of the management group discussed about the operation method, management of 2nd plenary conference, etc.

B. Activities in academic societies

- Next generation brain project winter Symposium
Date: December 18th -20th, 2019.
Place: Hitotsubashi hall, Hitotsubashi University
Contents: project representative (Ota) presented about the overview of the project. Information about the project was also published with poster.

- 32th distributed autonomous system symposium OS
Date: January 25th - 26th, 2020.
Place: Shibaura institute of technology
Contents: Project organized an OS named "hyper-adaptability" in distributed autonomous system symposium organized by SICE. Nine researches presented in the OS.

C. Other activities

- Construction of the project homepage
The management group constructed a project homepage for publication and for sharing the project information.
URL: https://www.hyper-adapt.org/

- Organization of young researchers' group
We organized a young researchers' group for the sake of the communication among young researchers in the project and for their supports. Details are described below.

- Establishment of international collaboration program
In order to support the international collaboration of project researchers, the management group established a financial support program for international collaboration.

V. ACTIVITES BY YOUNG RESEARCHERS

This program promotes activities of young researchers chaired by Dr. Qi An (The University of Tokyo). The followings are the list of them:

A. Kick-off meeting for young researchers

On November 21, 2019, a kick-off meeting for young researchers was held at the Hongo Campus of the University of Tokyo. In this meeting, the activities of the future young researcher associations will be confirmed to have research exchange meetings, literature study sessions, lecturers inviting senior researchers, and gathering important literature in the related field to be disseminated throughout all the member in this research area.

B. 1st research exchange meeting

A research exchange meeting was held on January 26, 2020, in conjunction with the 32nd Autonomous Decentralized System Symposium. Ten researchers participated in this meeting. The presentations briefly introduce their own research first and Dr. Qi An gave a talk about effects of cognition and emotion on the rehabilitation of hemiplegic patients.

C. First literature study session (planned)

On March 26-27, 2020, a study session on “Computational Neuroscience” by Hirokazu Tanaka was held at Hongo Campus of the University of Tokyo. Ten researchers from inside and outside the field participated and learned about a systematic approach to neuroscience.

VI. FUTURE PERSPECTIVE

As main activities of the next fiscal year, the management group plans a 2nd plenary conference on May 2020 in Tokyo, a public symposium on July 2020 and 3rd plenary conference on March 2021.

Group A. Research Report FY2019

Principal Investigator: Tadashi Isa
Kyoto University, Graduate School of Medicine, WPI-ASHBi

I. AIM OF THE GROUP

Group A aims at clarifying how the process of "reconstruction of biostructures" and "restructuring of action principles" are involved in the hyper-adaptation process following the neural injuries, aging, reformation of the body structure, painful learning process or malfunction of neurotransmitter systems through experimental studies on animals or humans.

Group A01 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 experimental studies on rodents, nonhuman primates and humans.

Group A02 will investigate the adaptation of neural systems to the change in skeleton-muscular structures and its underlying principles.

Group A03 will study how the body recognition and emotion systems promote the hyper-adaptation, that is, the motor learning under difficult condition such as change in the body frame.

Group A04 will test the working hypothesis that "restructuring of action principles" against the change in the brain dynamics accompanying depletion of neurotransmitters such as dopamine and acetylcholine in aging or neurodegenerative disorders will induce hyper-adaptation.

II. MEMBERS OF THE GROUP

A01: "Elucidation of the hyper-adaptation mechanism by reconstruction of biostructures and challenges for prevention of decline in latent adaptive capacity"
PI: Tadashi Isa (Kyoto Univ)
Collaborator 1: Eichi Naito (CiNet)
Collaborator 2: Hidenori Aizawa (Hiroshima Univ)

A02: "Elucidating the neural mechanism of hyper-adaptation to the change in skeleton-muscular structures"
PI: Kazuhiko Seki (NCNP)

A03: "Mechanisms of body cognition and emotion inducing hyper-adaptability"
PI: Hiroshi Imamizu (Tokyo Univ)
Collaborator: Ken-Ichiro Tsutsui (Tohoku Univ)

A04: "Alteration of brain dynamics as underlying mechanisms of hyper-adaptability in neurotransmitter disorders"
PI: Kaoru Takakusaki (Asahikawa Medical univ)
Collaborator: Takashi Hanakawa (Kyoto Univ/NCNP)

III. RESEARCH ACTIVITY

[Group A01] (1) Date: 2019/09/06, Place: Kyoto Univ, Discussion on measurement of monoamine release in the brain with voltammetry. Participants: Isa, Onoe, Yamaguchi and Aizawa.

(2) Date: 2019/11/09, Place: Science Council of Japan (Tokyo), Discussion on the hyper-adaptation in para-athletes. Participants: Isa, Naito.

[Group A02] (1) Date: 2019/12/18, Place: Univ of Electro-Communications. Discussion on analysis method on EMG data obtained from cross-union experiments in monkeys and the current results, etc. Participants: Seki, Funato, Uchida, Kondo, Yano, Ishitsubo, Naganuma, Tsuchiya.

[GroupA03] (1) Date: 2019/08/02, Place: Tohoku Univ, Discussion on how to measure the subjective sense and will in animal experiments. Participants: Tsutsui, Nakamura, Izawa, Ohata, Imamizu.

(2) Date: 2019/10/21, Web meeting. Discussion on how to understand the subjective sense and will in the hierarchical order as recognition of controllability and possibility of investigating their influence on ordinary motor learning and difficult motor learning by adding perturbation at various levels, etc. Participants: Tsutsui, Nakamura, Izawa, Ohata, Tanaka, Kikuchi, Imamizu.

(3) Date: 2019/12/24, Web meeting. Discussion on how to construct the experimental paradigm to understand the structural learning about the controllability of the systems from the viewpoint of will and subjective sense. Participants: Tsutsui, Nakamura, Izawa, Ohata, Tanaka, Imamizu.

(4) Date: 2020/1/17, Web meeting. Discussion on how to investigate how recognition of controllability is generalized between decision making and motor learning. Participants: Izawa, Ohata, Imamizu.

[GroupA04] (1) Date: 2019/07/24, Place: Tokyo Univ, Joint meeting of A04 and B04. Discussion on mathematical modeling of postural control during standing. Participants: Takakusaki, Ota, Asama, Uenishi.

(2) Date: 2019/08/09, Place: Tokyo Univ. Joint meeting of A04 and B04. Discussion on the mathematical modeling of central mechanism of postural control. Participants: Takakusaki, Ota, Uenishi.

(3) Date: 2019/09/10, Place: Asahikawa Medical Univ. Jpint meeting of A04 and B01. Central mechanism of postural disturbance of Parkinson disease patients.

(4) Date: 2019/11/21, Place: Tokyo Univ. Joint meeting of A04 and B04. Presentation and general discussion on the research plan during the next 5 years. Participants: Takakusaki, Hanakawa, Ota, Yotsu, Nakajima, Takahashi, Yoshinaga, Higashiguchi, Shirafuji, Omura, Uenishi, Ishii.

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

***Abstract*—The Group A01 will try to test the hypothesis that disinhibition across wide brain areas underlies the hyper-adaptation process against the neural injuries or frailty. For this purpose, Isa Group works on the recovery after the spinal cord injury in the macaque monkeys, Naito Group works on the neuroimaging during performance of motor tasks in aged people, and Aizawa Group works on the diffuse projection systems such as dopaminergic and serotonergic systems as the possible neural substrate of the global disinhibition in mice.**

I. INTRODUCTION

The A01 Group will examine the hypothesis that disinhibition across the large-scaled network of the brain is the basis of hyper-adaptation by “reconstruction of biostructures” by fusion and further development of our current researches. Our previous researches have shown that the brain is equipped with the global disinhibition mechanisms and in case of spinal cord injury, the mechanism is triggered to recruit the latent circuit for functional recovery, and that the diffuse projection systems such as monoaminergic neurons would be involved in the process. However, details of the underlying neural mechanism 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 with demonstration of the frailty in the aged people. Isa Group will record the movement-related activity in the sensorimotor cortices with electrocorticography (ECoG) and the electromyogram (EMG), and the cortical and muscle responses to electrical stimulation through the ECoG 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. METHODS

In Isa’s Group study, A male macaque monkey (*Macaca fuscata*) was trained to reach, grasp and retrieve a small piece of sweet potato through a narrow vertical slit using both the index finger and thumb. Then, a pair of 18-channel ECoG electrodes were chronically implanted on bilateral PM/M1/S1. We made sub-hemisection at C4/C5 and longitudinally monitored the cortical activity during a reach and grasp task, and applied direct electrical stimulation through the ECoG electrodes to probe the connectivity between motor-related areas and muscles before and after the sub-hemisection (up to 5 months postoperatively).

Naito’s Group conducted fMRI experiments and measured brain activity when right-handed healthy old adults (n = 50; aged 65-78 years) and right-handed healthy young adults (n = 30; aged 20-27 years) experienced illusory movement of right hand. They also evaluated the right hand dexterity of patients using a standard peg test.

Aizawa Group developed the methods to record the extracellular dynamics of dopamine and serotonin, and examined how their experimental manipulation affects the brain activity and behavior of the animals to investigate whether dopamine and/or serotonin underlies the global disinhibition for hyper-adaptation. They conducted 1) development of electro-chemical technique to record the extracellular release of dopamine and serotonin with high sensitivity and speed, 2) investigation of the effect of manipulating the dopaminergic system on the brain activity and behavior of mice, and 3) development of local infarction model animals using photo-active dyes in the head-fixed mice and evaluation of feasibility of the animal model by combining the photo-imaging of neural activity.

IV. Research Topics

A. Global dinsinhibition after spinal injury in monkeys

Preoperatively, success ratio of precision grips was nearly 100 %. On day 32 post-injury, success ratio of the grasping guided by the slit edge reached 41.5 % and then saturated around 90 % from day 40 post-injury. On the other hand, precision grip did not completely recover and success ratio of the precision grip had been 0 % from the lesion. These results indicate that the dexterous finger movements did not fully recover after the sub-hemisection. 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. These results suggested that disinhibition spread in contralesional cortical network along with the recover

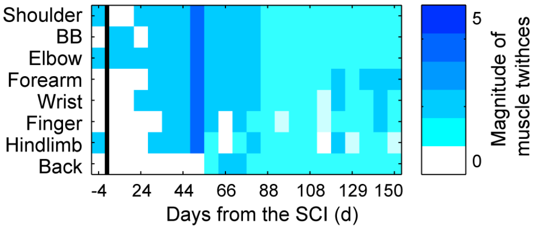

Fig.1 Muscle twiches in various body parts by contralesional PM stimulation.

B. fMRI investigation of lacking of ipsilateral motor deactivation in the healthy elderly and its relation with aging-related decline in hand dexterity

Naito Group found significant deactivation in the hand section of the ipsilateral (right) motor cortex (M1) during motor illusion in young group. In contrast, such ipsilateral deactivation generally reduced in old adults and some of them showed ipsilateral activation rather than deactivation. When we examined brain regions wherein activity is correlated with the peg test performance, we found that activity in the hand section of the ipsilateral M1 was significantly correlated with the performance, and that the M1 was the only region showing such correlation in the entire brain (see figure below). Namely, older adults with higher right-hand dexterity (shorter time required to complete peg test) showed ipsilateral M1 deactivation, whereas those with lower right-hand dexterity

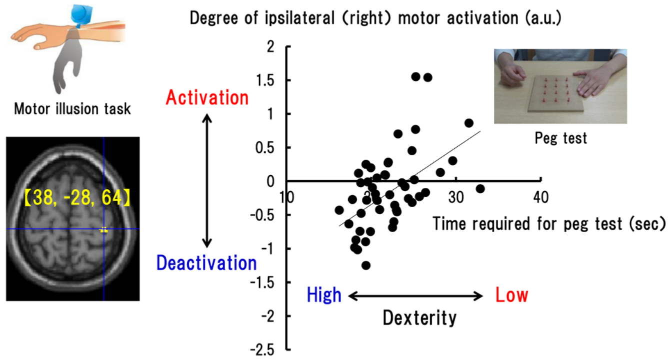

Fig.2 Relation between ipsilateral M1 activity and score of Peg-test.

showed ipsilateral activation rather than deactivation (Fig.2). These results suggested that lack of ipsilateral M1 deactivation in the elderly may disturb and deteriorate their digital dexterity.

C. Sensitive quantification of extracellular monoamines in rodents

Aizawa group addressed the involvement of monoaminergic systems as a basis of global disinhibition for hyper-adaptation by analyzing dynamics of extracellular monoamines in the rodent brain. Carbon fiber microelectrode was used to record the oxidative peak of current intensity peculiar to the monoamines following the adsorption of positively charged monoamines by application of negative ramping potential through the electrodes placed in the multiple brain regions (Fast scan controlled adsorption voltammetry, FSCAV). Electrodes, calibrated sensitivity in vitro, were able to monitor the ambient level of extracellular dopamine in the regions such as somatosensory cortex, dorsal and ventral striatum and olfactory tubercle as shown below. Furthermore, FSCAV revealed that the dopamine reuptake inhibitor (nomifensine) consistently increased extracellular level of dopamine in those brain regions, providing the pharmacological evidence supporting the advantage of the current technology. Interestingly, behavioral analyses unraveled the mice with excessive extracellular dopamine with nomifensine exhibited the increased locomotor activity, anxious and hedonic behaviors suggesting the modulation of global cerebral activity.

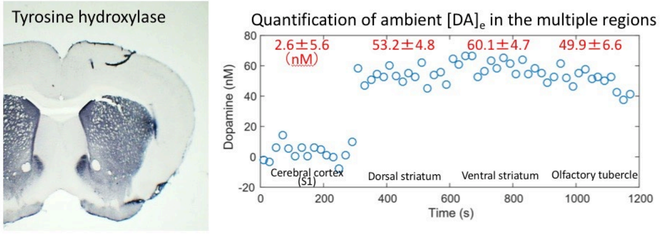

Fig.3 Highly sensitive measurement ofdopamine release in multiple regions.

IV. FUTURE PERSPECTIVE

In this fiscal year, Isa Group found that disinhibition occurred in the motor cortices in the recovery process, which would be a key mechanism for novel brain areas to be recruited to compensate for the impaired function. In next fiscal year, they will conduct the same experiment on the 2nd monkey and investigate the inter-individual difference and change in the brain activity and connectivity over time. Naito Group will subdivide the older adults into two groups, and to train each group with different type of motor training for several months. They then test if each training can effectively restore ipsilateral M1 deactivation and further reveal causal relationship between restoring of ipsilateral M1 deactivation and possible improvement of hand dexterity. Aizawa Group will analyze the dynamics of monoaminergic activation during hyper-adaptation to the neural circuit injury by applying the methods for measurement of the monoaminergic activation to the rodent model of stroke

Annual report of research project A02

Kazuhiko SEKI
National Institute of Neuroscience, NCNP

***Abstract*—In the FY2019, we established 1) the method to manipulate selectively the activity of somatosensory primary afferent by optogenetics, 2) the method to evaluate the sensorimotor function in freely behaving monkeys, and 3) the method to assess the activity of spinomuscular- and corticomuscular closed loops in monkeys performing motor task.The abstract goes here.**

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. Optogenetic manipulation of spinal reflex pathways from somatosensory primary afferents in rats.

Previously, fundamental structures and their mode of action in the spinal reflex circuit were determined by confirming their input-output relationship using electrophysiological techniques. In those experiments, the electrical stimulation of afferent fibres was used as a core element to identify different types of reflex pathways; however, a major disadvantage of this technique is its non-selectivity. In this study, we investigated the selective activation of large-diameter afferent by optogenetics combined with a virus vector transduction technique (injection via the sciatic nerve) in non-transgenic male Jcl:Wistar rats. We found that green fluorescent protein (GFP) gene transduction of rat dorsal root ganglion (DRG) neurons with a preference for medium-to-large-sized cells was achieved using adeno-associated virus 9 (AAV9) vector, compared with AAV6 vector (p=0.021). Furthermore, the optical stimulation of Channelrhodopsin 2 (ChR2) expressing DRG neurons (transduced by AAV9-expressing the ChR2 gene) produced compound action potentials in afferent nerves originating from fast-conducting nerve fibres. We also confirmed that physiological responses to different amplitudes were comparable between optogenetic and electrophysiological activation. However, the optically elicited responses had lower sensitivity with stimulus frequency, unlike electrically elicited responses. Finally, we showed that afferent volleys evoked by optical stimulation were sufficient to activate postsynaptic neurons in the spinal reflex arc. These results provide new insights for understanding the role of sensory afferent input to the central nervous system regarding behavioural control, and applicable to analyze the phenotype of the muscle relocation primate models. (Kubota et al. J. Physiol. 2019).

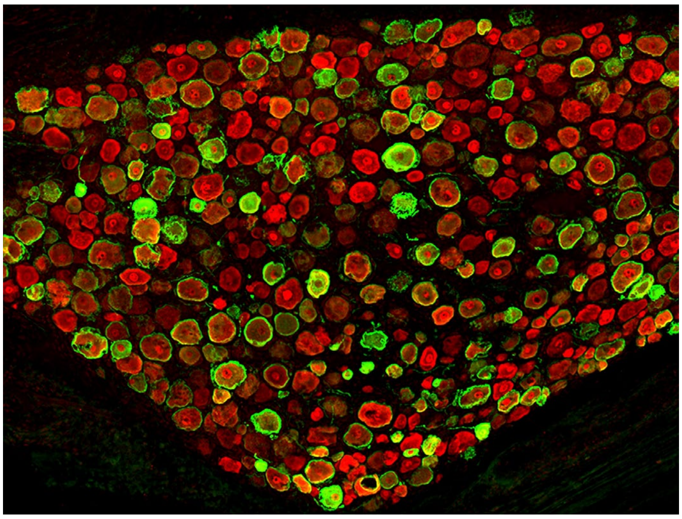

Fig.1. Part of yellow fluorescent protein (YFP) in the dorsal root ganglion (DRG) of the rat. Selective gene transduction (Channelrhodopsin 2, YFP) with a preference for medium-to-large-sized cells was achieved using the AAV 9.

B. Decoding of muscle activity from the sensorimotor cortex in freely behaving monkeys

In this study, we demonstrate accurate decoding of muscle activity from electrocorticogram (ECoG) signals in unrestrained, freely behaving monkeys. We recorded ECoG signals from the sensorimotor cortex as well as electromyogram signals from multiple muscles in the upper arm while monkeys performed two types of behaviors with no physical restraints, as follows:

forced forelimb movement (lever pulling task) and natural whole-body movement (free movement within the cage). As in previous reports using restrained monkeys, we confirmed that muscle activity during forced forelimb movement was accurately predicted from simultaneously recorded ECoG data. More importantly, we successfully demonstrated that accurate prediction of muscle activity from ECoG data was possible in monkeys performing natural whole-body movement. We found that high-gamma activity in the primary motor cortex primarily contributed to the prediction of muscle activity during natural whole-body movement as well as forced forelimb movement. In contrast, the contribution of high-gamma activity in the premotor and primary somatosensory cortices was significantly larger during natural whole-body movement, which suggests that activity in a larger area of the sensorimotor cortex was needed to predict muscle activity during natural whole-body movement. Based on this result, we now developing a method to assess the mechanism of sensory gain modulation of tendon relocation model in an free behaving setting. (Umeda et al. Neuroimage, 2019).

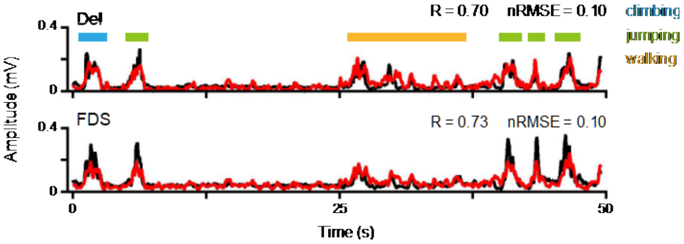

Fig.2. Reconstruction of shoulder (Del) and hand (FDS) muscle activities using ECoG signals.

C. *Distinct sensorimotor feedback loops for dynamic and static control of movement mediated by spinal and motor cortical neurons.*

Volitional limb motor control involves dynamic and static muscle actions. It remains elusive how such distinct actions are controlled through separated or shared neural circuits. In this study, we explored the potential separation for dynamic and static controls in the primate hand actions, by investigating the neuronal correlated activity between local field potentials (LFPs) of the spinal cord and the forelimb electromyographic activity (EMGs), and LFPs of the motor cortex and the EMGs during the performance of a precision grip in macaque monkeys. We analyzed neural coherence and information flows between LFPs from the spinal cord and the motor cortex, and EMG activity of the forearm, while the macaque monkey performed a precision grip task that involved the control of both dynamic grip and static hold. We found the emergence of significant spinomuscular and corticomuscular coherence as distinct time-frequency patterns relevant to the dynamic and static grip phases. Furthermore, directional information analyses indicated that spinal and cortical beta-range coherence comprised a reciprocal interaction with the muscles, with corresponding time lags for beta oscillations. Furthermore we showed that these two feedback loops (i.e., spinal local feedback vs. cortical divergent feedback loops) differ in the muscles involved. These results indicate that distinct sensorimotor feedback loops are engaged in the dynamic and static control of precision grip of primates. Therefore, a comparable behavioral task could be applied in the muscle relocation model to document the way their sensorimotor loop could change in the process of re-learning motor skill using de novo sensory prediction error. (Oya, Takei et.al. Communication Biology, 2020).

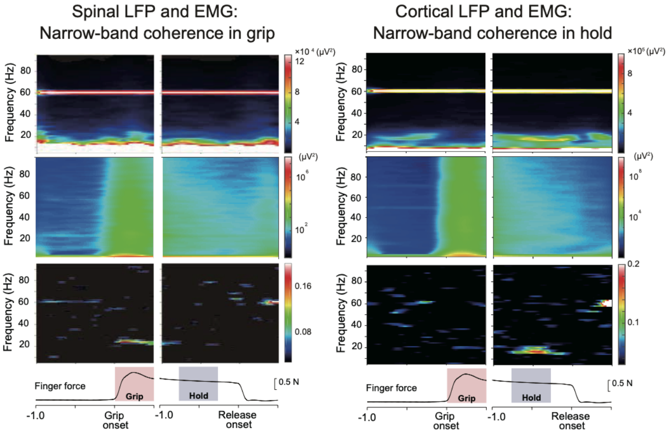

Fig.3. Power spectra of neural LFPs (top), EMGs (middle), and and their coherence between spinal β band (NB) LFP and AbPL (e), and cortical NB LFP and AbDM (f).

IV. FUTURE PERSPECTIVE

Along with the research described in above, we have improved the surgical technique for making the tendon relocation model monkeys and activity of more than ten muscles are recorded in ongoing experiments. We will also focus on the assessment of neuronal adaptation starting from FY2020.

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Annual report of research project A03

Hiroshi Imamizu
Graduate school of Humanities and Sociology, The University of Tokyo

Abstract— **Our research project aims to reveal neural mechanisms in which body cognition and positive emotion, such as motivation, facilitate motor learning in challenging situation ("hyper-adaptation"). Our main achievements in this fiscal year are 1) finding a behavioral evidence that sense of agency (a sense that "I am the one causing an action," which is an aspect of body cognition) facilitates motor learning, 2) identification of neural correlates for a sense of control, which supports the sense of agency, by using fMRI, 3) establishing a behavioral paradigm for monkeys to study the motor learning process with the motivation factor monitored or controlled.**

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 interests 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 the development of 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) development of methods for facilitating motor learning through artificial control of motivation and body cognition. Our research activity will contribute to understanding mechanisms of the "hyper-adaptability" and future development of the methods for inducing and facilitating it.

III. RESEARCH TOPICS

A. Apprach to sense of agency and motor learning from behavioral experiments

1) Effect of sense of agency on motor learning: A group of the principal investigator (Masaru Tanaka and Hiroshi Imamizu) and Jun Izawa of the B03-group conducted a behavioral experiment. This experiment demonstrated that attribution of the observed movement to self, which is a fundamental process in the establishment of a sense of agency, facilitates motor learning. Specifically, participants moved a stylus on a pen-tablet to control a cursor on a screen placed over the tablet. Participants moved the cursor from the starting position to the target position located 15-cm to the right (Fig. 1). The cursor was presented as a feedback of the movement when it moved 15 cm in the right direction. The cursor position was artificially shifted by -2, 0 or +2 cm in the perpendicular direction to the start-target line (Fig. 1A). After the movement, participants reported whether the feedback reflected their movement (self-attribution of the movement) or not (non-self-attribution). As a result, we found that the participants biased their pen movements in the next trial toward the opposite direction to the shifted direction (Fig. 1B). Moreover, the bias was more significant after the self-attribution than the non-self-attribution. The bias reflects a learning rate between the trials. Thus, our results indicate that the attribution of the movement affects motor learning [1].

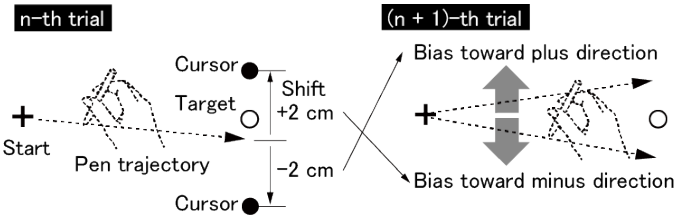

Fig. 1 Artificial shift of movement feedback and bias in the next trial

2) Mechanisms linking action to its consequence: A subjective compression of an interval between the intentional action and its consequence ("intentional binding") is often used as a measure of sense of agency. We found that subjective time globally shortens but locally elongates when the action and its consequences repeated several times, suggesting multiple timescales in the binding [2].

B. Neural basis for sense of agency (attributiono of movment to sef or other)

A group of the principal investigator (Ryu Ohata, Tomohisa Asai, and Hiroshi Imamizu) developed a decoding method to attribution of movement to self or other, which constitutes the fundamental technology for our project. This work was accepted as a research article [3].

C. Neural basis for sense of agency (controllability cognition)

A group of the principal investigator (Ryu Ohata and Hiroshi Imamizu), Wen Wen, and Hajime Asama of the B03-group measured brain response to change in the controllability of a manipulated object (i.e., a fundamental aspect of the sense of agency). Participants manipulated a joystick to move a cursor on a screen. While a participant was moving the cursor, we changed the cursor controllability by mixing the movement made by another participant with the participant's movement. We measured brain activity when the controllability increased or decreased. As a result, activity increased in the dorsolateral prefrontal cortex and the lateral cerebellum when the controllability increased (Fig. 2A). Activity decreased in the insula when the controllability decreased (Fig. 2B). The change in activity correlated with the rate of change in the controllability. Our result suggested different mechanisms underlying cognition of increase or decrease in controllability. This result indicates that we must change regions for brain stimulation according to an increase or decrease in the sense of agency to manipulate the sense of agency in our future studies.

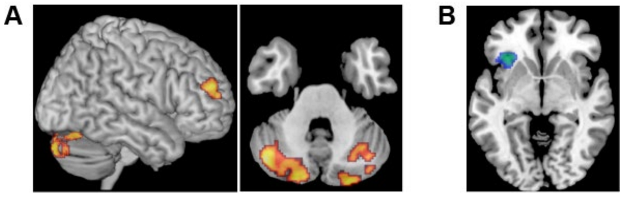

Fig. 2 Brain activity related to increase (A) or decrease (B) in controllability

D. Establishment of a behavioral paradigm for studying the motor learnng process with the motivation factor monitored or controlled

A group of the co-investigator (Ken-Ichiro Tsutsui and his colleagues) aimed to establish a behavioral paradigm to study the motor learning process with the motivation factor monitored or controlled. They modified the Brinkman board test (Fig. 3A) to have different levels of difficulty: wide slots for "easy" task (Fig. 3B) and narrow slots for "difficult" task (Fig. 3C).

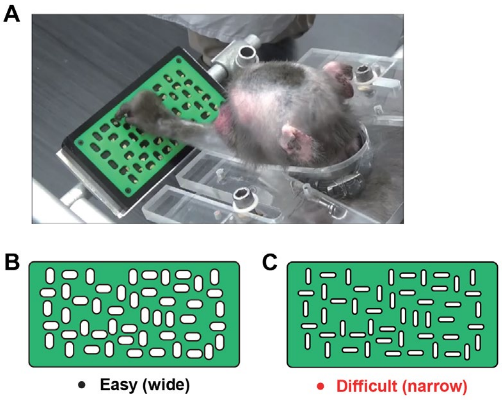

Fig. 3 Modified Brinkman board test

The original Brinkman board test is used for testing the manual dexterity. In this study, we aimed to modify this task so that it can evaluate the motor function while the motivation factor is being monitored or manipulated. We used pieces of sweet potato and tested the task performance of two Japanese monkeys (*Macaca fuscata*) under different levels of sensory specific satiety. In the "hungry" condition, the monkeys performed around 15-20 sessions of the "easy" task and around 10 sessions of the "difficult" task, until they stopped performing. (A completion of a board was counted as one session.) In the "satiated" conditions, we gave sweet potatoes to the monkeys before the task performance, in order to give sensory specific satiety. In the "moderately satiated" condition, the monkeys performed around 15-20 sessions of the "easy" task, but less than 5 sessions of the "difficult" task. In the "highly satiated" condition, the monkeys did not perform both the "easy" and "difficult" task. The time needed to complete a session for either "easy" or "difficult" task did not differ between the "hungry" and "moderately satiated" conditions. These results indicate that we can dissociate the motivation and motor factors by using the modified Brinkman test, in which the total number of session performed and the time spent to complete a session can be regarded as indices of motivation and motor factors, respectively. Furthermore, it was suggested that the motivation and the effort cost are in a non-linear relation in these monkeys, as the number of sessions performed was the same between "hungry" and "moderately satiated" conditions for the "easy" task, but smaller in "moderately satiated" condition for the "difficult" task.

IV. FUTURE PERSPECTIVE

We made advances in developing a behavioral paradigm to investigate the relationship between the sense of agency and motor learning, finding neural correlated for the cognition of controllability (as an aspect of the sense of agency) in humans, and a behavioral paradigm to study the motor learning process with the motivation factor monitored or controlled in monkeys. Besides these results, we continued intensive discussions for the paradigm shared with human and monkey experiments to investigate the effects of controllability cognition on motor learning. In the next fiscal year, we will establish an experimental paradigm with humans and monkeys.

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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 person. In this first year, we established methods of both studies. Takakusaki and colleagues established methods for evaluating optimal postural control in multitask voluntary movements (from gaze fixation in quite standing to postural preparation and forelimb reaching) in cats. This experimental system will be also applied to the model animals with damages in DA and ACh so that roles of these neurotransmitters in the alteration of optimal postural control during voluntary movements can be elucidated. Hanakawa and colleagues used a simultaneous EEG-fMRI for evaluating a dynamic profile of functional connectivity between distinct neural networks. They also started to examine neuromelanin MRI and DA transporter (DAT) SPECT for evaluation of dopamine systems. These studies will clarify relationship across cognitive functions, neural network dynamics and neuro-transmitters underlying the generation of hyper-adaptation.**

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. Single photon emission computed tomography (SPECT) with a DA transporter tracer (DAT) shows that DA nerve terminals are reduced 1-2% a year. Decreases in DA result in dysfunctions of multiple and parallel basal ganglia-cortical circuits, thereby affecting both motor and cognitive functions [1]. Furthermore, amyloid beta (Aβ), a key molecule of AD pathophysiology, accumulates over 10-20 years before manifestation of cognitive decline. A positron emission tomography (PET) with Aβ tracers indeed detects positive Aβ accumulation in the brain in 30% of cognitively normal elderly population [2]. Many factors may affect cognitive functions in elderly persons, influential factors such as DA and Aβ should ideally be measured for the assessment of cognitive functions.

Based on the above considerations, 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 person due to decline of the above-mentioned neurotransmitters and molecule.

II. AIM OF THE GROUP

To achieve the above goals, basic experiments in animals and clinical researches in humans are performed.

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. Specifically, they examine 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. Either DA or ACh system is, then, manipulated by pharmacological and molecular-optogenetic techniques to examine the modification of postural control. Attempts are further made to determine the role of cortical (frontoparietal networks) and subcortical (cortico-brainstem-spinal pathways) mechanisms involved in these postural control processes [3-4] using electrophysiological and neuroanatomical techniques.

Hanakawa (a research collaborator) and his colleagues in Kyoto University and NCNP perform 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 (https://padni.org/), 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) [5] in addition to DA transporter (DAT) SPECT for evaluating the activity of the DA system.

III. RESEARCH TOPICS

The major results of this year are following three points.

A. *Multitasking experiment system for model animals*

Takakusaki's group constructed experimental system that requires cognitive-motor coordination of the cat during its execution of multitask voluntary movements. (Fig.1A). The cat has to keep standing posture on the narrow space beneath its feet. The cat gazes the target (attention) in front, then prepares its appropriate posture for reaching the target by either forelimb.

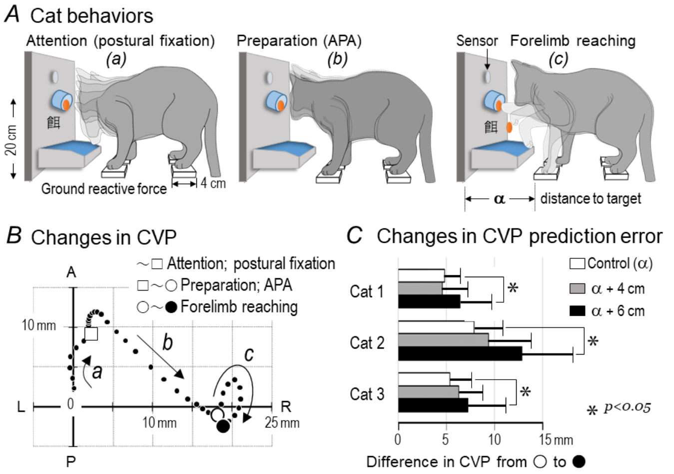

Fig. 1. Forelimb reaching task in the cat

The center of vertical pressure (CVP), which was calculated from ground reactive force exerted on each limb, was used as a parameter for posture control reflecting the center of gravity.

When the cat gazed the target, CVP position was fixed at (□) in Fig.1B. Until lifting up the left forelimb, CVP moved from □ to ○. During forelimb reaching, CVP further moved from ○ to ●, but the two CVP positions were very close. In 6 animals, there was no significant difference in coordinates of CVP at lifting (○) and reaching (●), indicating that the optimal CVP position was prepared in advance so that it maintained cat's posture during forelimb movements. It follows that the distance between the two CVP positions can be considered as "postural prediction error". When the distance of the cat and target was increased (Fig.1C), the prediction error (○ - ● distance) increased, indicating that voluntary movement is precedingly supported by postural adjustment that is optimal to the goal-directed action depending on the interaction between the cat and circumstance. Because injections of small amount of muscimol into the motor-related (4 and 6 areas) and parietal (5 and 7 areas) cortices altered the series of postural control during the task, such an optimal postural adjustment can be achieved by the operation of frontoparietal network [5].

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

Second, Hanakawa lab has worked on developing simultaneous EEG-fMRI recording to non-invasively measure dynamic changes of brain activity and connectivity in humans. By applying in-dependent component analysis (ICA) to fMRI data, the default mode network (DMN) and fronto-parietal network (FPN) were retrieved. Inter-network correlation of fMRI time-series (functional connectivity, FC) was assessed for each time window, resulting in the observation of dynamic changes of FC (Fig.2). Hanakawa lab is currently working on developing a method to integrate dynamics information from fMRI and EEG.

C. *Development and validation of DA imaging techniques*

Third, the Hanakawa lab has started to include neuromelanin MRI for the potential assessment of DA synthesis in the SN, in addition to DAT SPECT for the potential assessment of pre-synaptic DA terminals in the striatum (Fig.3). However, since how much of the neuromelanin MRI contrast really reflect DA synthesis remains controversial, this group is planning to combine the MRI method with the histochemical assessment in specimen. This year, necessary arrangement was made to make such an experiment possible.

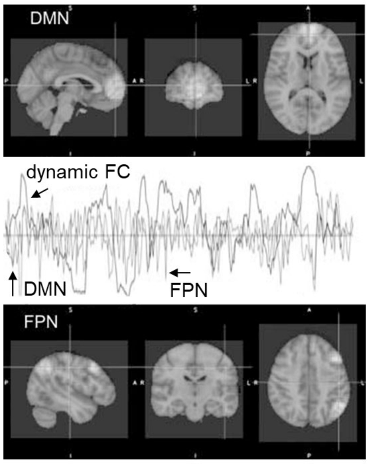

Fig.2. Dynamic relationship of functinal connectivity between DMN and FPN. (left).

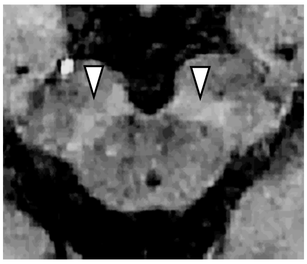

Fig.3. An example of neuromelanin MRI from a patient with PD

IV. FUTURE PERSPECTIVE

In this year, Takakusaki's group established an experimental system for measuring and evaluating optimal posture control during multitasking. Several animals were trained to stably perform the task. In future, they plan to identify cortical and sub-cortical mechanisms of optimal postural control using pharmacological and molecular-optogenetical methods combined with electrophysiological techniques, so that role of the DA-ACh systems in the generation of hyper-adaptable postural control mechanisms can be understood.

This year, Hanakawa's group developed simultaneous EEG-fMRI measurements for evaluating a dynamic profile of functional connectivity. They plan to apply this method to the PADNI cohort study, while repeating 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. In future, neuromelanin MRI measurement, which is thought to reflect DA production in the substantia nigra, will be further employed, assuming new subjects will be recruited.

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Group B: Systems engineering

Toshiyuki Kondo
Tokyo University of Agriculture and Technology

I. OBJECTIVE

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

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

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

An important thing for understanding the phenomenon of hyper-adaptability, trying to investigate the causal relationship of neural activity and its generated functions and behaviors. For this aim, we propose robotic-interventional neuroscience, which realizes a model-based intervention using not only robotic technology, but also opto/chemo-genetics and brain stimulation technologies.

In addition, the constructed model can be used to predict the behavior of target systems, and it is expected to offer novel research hypotheses to be investigated.

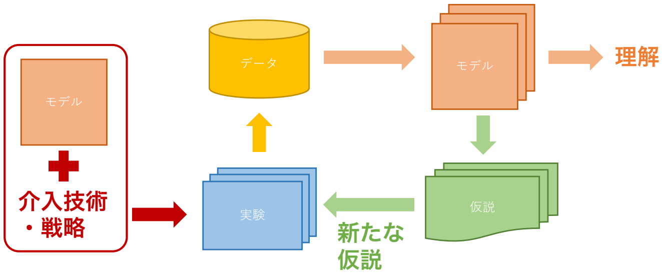

Fig. 1. Roles of systems engineering group.

II. MEMBERS

To achieve the above mentioned research objective, we organized the following four 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), Shiro Yano (TUAT)

Co-investigators: 2

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

B02 Modeling of ultra-adaptive to body change

Principal investigator: Yasuharu Koike (Tokyo Tech)

Funded co-investigator: Tetsuro Funato (UEC)

Co-investigators: 5

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

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

Principal investigator: Hajime Asama (U Tokyo)

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

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

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

Principal investigator: Jun Ota (U Tokyo)

Funded co-investigator: Arito Yozu (Ibaraki PUHS)

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.

III. ACTIVITIES

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

- September 13th, 2019, B01-B02-A02 meeting (NCNP)
- September 27th, 2019, B03-B04 meeting (Ibaraki PUHS)
- Nobember 21st, 2019, B04-A04 meeting (U Tokyo)
- December 18th, 2019, B01-B02-A02 meeting (UEC)
- January 25-26th, 2020, Organized session with SICE Technical Committee on Decentralized Autonomous Systems (SIT), 9 oral presentations.

Please refer the report of each research project for their concrete research outcomes.

IV. FUTURE PLAN

In the next fiscal year, subscription research projects will join. Sooner we will have Group B meeting for deepening mutual understanding, will start 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

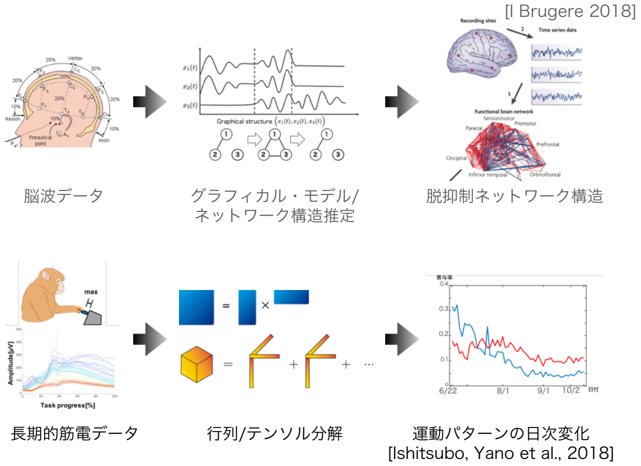

Fig. 1. Statistical modeling approach.

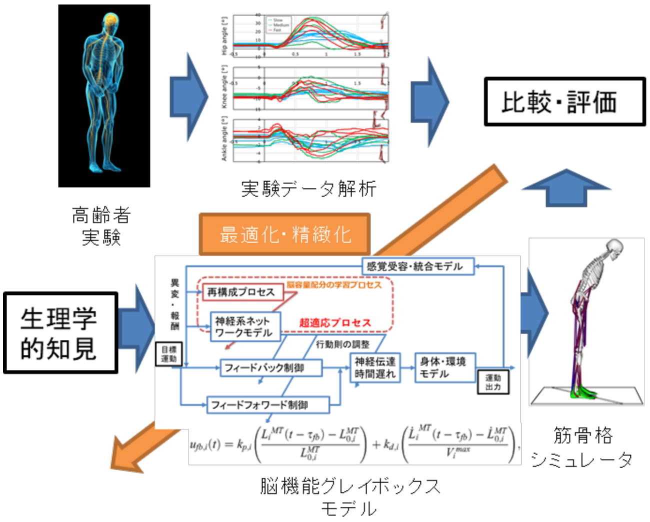

Fig. 2. Constructive modeling approach.

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 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. Yano (Tokyo University of Agriculture and Technology) and his colleagues develop a statistical tool to quantify the time varying structural shift behind the hyper-adaptability based on the simultaneously observed EMG-EEG data.

They proposed two novel analysis methods for EMG data which are the extended methods of the well-known synergy analysis method [1], [2]. The proposed method [1] analyses the long-term EMG data, which ranges from weeks to the months. The data consists of EMG time series data obtained by performing one training task multiple times. The method estimates the long-term adaptation effects on the muscle activity caused by the training. The second one [2] is also the extended method of the synergy analysis method. They combined Gaussian graphical models with standard synergy analysis and formulated network structure inference problem. It appears that different motion data contains different network structure, i.e. cooperative activity behind EEG data.

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 construct the experimental system and improve the simulator to explain the change of postural control in the dual task. The standing task and the cognitive task should be designed to show the effects of the dual task. With a preliminary experiment, we adopt a closed reg standing task which shows large sway. Also, we adopt a cognitive task in which subjects calculate by subtracting 7 from the given 3-digit integer. The postural control simulator is improved to be able to express the closed leg posture. By applying the nervous system control model, which includes the control of muscular tonus with musculoskeletal body model [3], we can investigate the effects of dual tasks on "muscular tonus".

We made an experiment on young healthy subjects in collaboration with the B04 research group. As the results, the sway in the open leg standing during dual tasks was reduced. We estimated the change of parameters using the proposed simulator. The results showed that the decrease in muscular tonus could lead to the increase of postural sway in open leg posture, and we showed the possibility that the muscular tonus cannot be reduced in the closed leg posture.

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

Prof. Kondo (Tokyo University of Agriculture and Technology) and his colleagues investigated cooperative motor learning tasks that can enhance their adaptability after the training using VR and/or haptic robot technologies. They found that a skill-level matching algorithm for adjusting the degrees of robotic motion intervention would be promising for enhancing learners adaptability (in preparation). Moreover, they developed a cooperative targets tracking task [4], and found that pairs of participants exchanged their motor intention using a kind of proto-language.

We also investigated the brain activity data obtained under a target tracking task [5]. We can discriminate the brain dynamics using an graph theory-based model. Different features were identified under three different conditions (movement only, visual observation only, visual pursuit movement).

IV. FUTURE PERSPECTIVE

From both statistical and constructive modeling standpoints, we have just started the discussion on the methodology for the modeling of hyper-adaptability. Moreover, we started searching for motor tasks that enhance learners adaptability.

In the next fiscal year, we will continue to deepen the modeling methodology, and furthermore we try to model neurophysiological data such as ECoG and EMG from neuroscience group. Moreover, we will continue to search for the motor tasks that 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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***Abstract*—We obtained the following three results. 1. In order to measure EMG signal efficiently, array EMG measuring device was developed and the relationship between the measured forces, movements and EMG signals was analyzed using a musculoskeletal model. 2. We analyzed the muscle synergy before and after tendon transfer using a mathematical model. Results suggested that slow changes in muscle synergy and fast adaptation of temporal patterns caused the change in temporal patterns obsearved in the experiments. 3. We analyzed the reconstruction rule using EEG, and found that the characteristics of the movement can be reproduced in the movement planning stage immediately before the movement by EEG, and that the information was the direction and distance of the movement, not the target position itself.**

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. Realization of human body transformation experiment by "virtual surgery"

"Virtual surgery" environment was conducted in which the relationship between human muscle activity and hand force was modeled, and changing the direction of the force generated by the experiment participants and the direction of the force realized on the screen. For this purpose, it is necessary to appropriately measure the muscle activity generated by the experiment participants. If electrodes can be quickly installed without using information on muscle anatomical locations, it will be easier to apply the same technique to patients in future rehabilitation. For this reason, using an aray electrode for EMG measuring, the relationship between forces and movements measured simultaneously with muscle activity obtained from 96-channel electrodes was calculated using a musculoskeletal model. As a result, when the electrodes are arranged in an array, not only surface muscle activity but also deep muscle activity can be measured, and the accuracy of torque and position estimation has been improved[1], [2].

B. Model of synergy change after tendon transfer

A02 group investigated the neural activities of monkeys in lever operating task, before and after transferring the flexor (EDC: extensor digitorum) and extensor (FDS: flexor digitorum superficialis) muscles of fingers. We collaborated with A02 group, analyzed the synergies of the measured muscles and calculated the correlation coefficient of the muscle synergies for over the four months of the experiment (Fig. 1AB, Synergy 1: mainly flexor muscles activities and Synergy 3: mainly extensor muscles activities). As a result, we found "the temporal coefficient of muscle synergies soon after the tendon transfer were different from those before the transfer, and they gradually returned" (see the report of A02 group). We assumed that the difference in the changing speed between muscle synergy and temporal coefficient caused this phenomenon, and analyzed the mechanism using a mathematical model.

Muscle synergy slowly changed with approximately two months after tendon transfer, and we assumed that the temporal coefficient adaptably generated for the achievement of the motion. In other words, muscle synergy slowly changes and the temporal coefficient can rapidly change for adaptation. Based on this assumption, we investigated the generated temporal patterns for the muscle synergies of each stage.

Now we consider the mathematical model of the above phenomenon. For the achievement of task, motion itself may change. But for the simplicity of model, the motion is supposed to be the same between before and after the tendon transfer. Then, we consider the temporal coefficient is determined so that the torque of before transfer is achieved with muscle condition of after transfer. jth joint torque τ_j can be represented as weighted sum of ith muscle activity m_i^j with contribution ratio to the torque a_i^j as follow.

$$\tau_j = a_1^j m_1^j + a_2^j m_2^j + \cdots + a_n^j m_n^j \tag{1}$$

Muscle activities are composed of muscle synergies.

$$\begin{bmatrix} m_1 & m_2 & \cdots & m_n \end{bmatrix} = \sum WH, \tag{2}$$

here, W is muscle synergy and H is temporal coefficient .

We model the tendon transfer as a change of contribution ratio of muscle activity to the joint torque. Namely, tendon transfer of first and second muscle is represented as follow.

$$a_2^{j+} = a_1^j, a_1^{j+} = a_2^j \tag{3}$$

Temporal coefficient H is determined for matching the torque before and after tendon transfer, i. e., optimization that reducing the following evaluation function.

$$J = \sum \left(a^+ W^+ H^+ - aWH\right)^2 \tag{4}$$

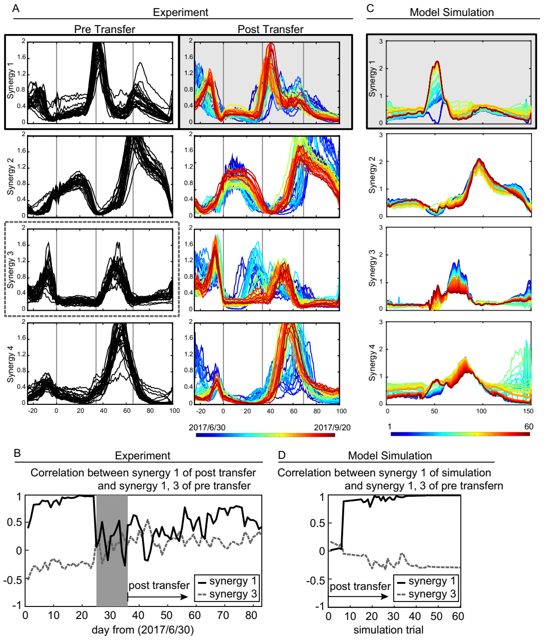
This optimization determines one optimal temporal pattern H^+ for each value of muscle synergies W^+. We investigated the change of temporal pattern H^+ with changing the value of muscle synergies W^+.

In the experiment, EMGs related to the finger movement were measured for 13 points, and the EDC and FDS were cross-transfered. Thus, the number of muscles for the model $n = 13$, and the contribution ratio a^j of EDC and FDS were exchanged. For simplicity, the number of joint was set 1 and the contribution ratio of each muscle a^j were set ECR=0.5, ECU=1, EDC=1, ED23=1, and 0 for the remaining muscles.

In order to calculate the optimal temporal patterns for the muscle-set after tendon transfer, the contribution ratio a were exchanged, and the activity level of EDC and FDS in muscle synergies were gradually exchanged with 60 steps. For each exchange level, the temporal coefficients were obtained as Fig. 1C. Fig. 1D shows the correlation coefficient of the temporal coefficient between before and after transfer. Temporal patterns of the initial phase (after exchange of a, no change in muscle synergies) were different from those of before transfer (low correlation coefficient), and the correlation coefficient gradually increased with the change in muscle synergies.

Our current model was rather simple, but the obtained phenomenon about the temporal coefficient were similar to that of the experiment. This result supported our assumption that the slow change in muscle synergy and fast change in temporal coefficient generated the change in the temporal patterns of the muscle synergies.

Fig. 1. Temporal coefficient of synergies in tendon transfer experiment and in simulation. A,C: temporal coefficients of synergies in pre and post tendon transfer(A) and those of simulation(C). B,D: correlation coefficient of synergies in the experiment (B) and simulation (D)



C. Elucidation of reconstruction rule process by brain information decoding

Focusing on muscle synergy, which is a cooperative structure between multiple muscle activities, among the characteristics of biological information, and examining the process of changes in the structure of muscle synergy, we clarify the restructuring rules of the biological structure. In order to confirm where and when this information is calculated in the brain, confirm whether the direction, distance, and target position of the movement can be estimated from the brain activity during exercise planning when reaching multiple targets did. As a result, the direction and distance of movement could not be estimated with high accuracy from all experimental participants[3].

IV. FUTURE PERSPECTIVE

This year, in cooperation with the A02 team, we started building a model that explains the data actually measured by the A02 team. Although it was a simple model, the results reproduced animal experiments. From next fiscal year onwards, we will improve the accuracy and promote modeling of super adaptation to body transformation.

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B03 Annual Report of Hyper-Adapt Project

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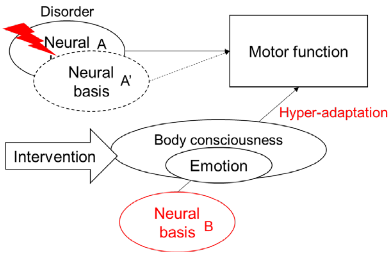
***Abstract*—B03 group aims to clarify the influence of body consciousness and emotion on the hyper-adaptation, and to establish mathematical model for hyper-adaptation which can quantitatively predict the state of body motor control ability. Furthermore, B03 group also aims to use the proposed mathematical model to develop and evaluate new methods for motor rehabilitation in future research. In the past year, we accomplished the following works: 1) we found out different mechanisms and neural basis for the perception of gaining and losing control; 2) we investigated the hyper-adaptation processes in post-stroke patients; 3) we examined the influence of body consciousness on motor learning.**

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 and cerebral palsy 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. Clarification of the mechanisms and neural basis of the sense of agency

First, B03 group (Asama and Wen) examined the mechanism for the sense of agency, proposing a novel mechanism of regularity detection, besides the traditional comparator mechanism [1]. Figure 2 shows the model considering the new regularity detection mechanism. Specifically, we designed a novel control detection task, in which the participants detected one target dot over which they had the sense of agency, among three moving dots. The actual control over the target dot was either nonlinearly disturbed by mixing other's motion, or linearly disturbed by applying an angular bias. The results from the motor control task showed that 60% of other's motion resulted in comparable amount of prediction errors with 90 degree angular bias. However, control detection accuracy was significantly lower in the former (nonlinearly disturbed) condition than the latter (linear disturbed) condition. This was because nonlinear disturbance produced prediction errors and impaired regularity at the same time, while linear disturbance only produced prediction errors but left regularity intact. In conclusion, we suggest that regularity detection is an important process that contributes to the sense of agency besides the traditional comparator mechanism.

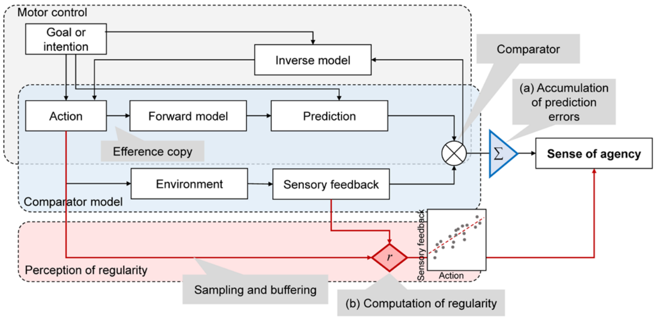


Fig. 2 The model of two separate contributions to the sense of agency

Second, we examined the hypothesis that there are distinct neural basis for perception of gaining and losing control, by collaborating with A03 group (Imamizu and Ohata). We found that the activities in the left cerebellum and the right dorsolateral prefrontal cortex positively correlated with the detection of an increase in control. In addition, we also found that the activity in the left anterior insula was negatively correlated with the detection of a decrease in control, while that in the bilateral frontoparietal regions was positively correlated. In short, our results clearly showed that the detection of gaining and losing control is linked to different brain mechanisms [2].

B. Evaluate Motor Impairment of Stroke Patients

In Qi An's (Co-PI) research group, we investigate adaptation process while post-stroke patients recover their motor function after stroke onset [3]. In particular, we focus on human sit-to-stand motion, which is important daily activity, and we clarify how muscle synergy structure is varied among patients who have different motor severity. We firstly measured motion and sEMG data from 33 post-stroke patients who stayed in Morinomiya hospital. These patients are divided into two groups based on Fugl-meyer assessment (FMA) score of lower limb; a severe group is defined as patients whose FMA score is less than 20 and a mild groups is defined as patients whose FMA score is not less than 20. Firstly, four muscle synergies were extracted from muscle activity of each trial of sit-to-stand motion. Next random forest model is used to develop motor impairment classifier. The model uses temporal features of muscle synergies to classify whether a trial of stroke patients sit-to-stand is evaluated as severely impaired or mildly impaired. As a result, the developed model could successfully classified motor impairment difference with 84.5%. Especially, we found that activation start, peak and end timing becomes earlier in mildly impaired group rather than severely impaired group. From this finding, it is indicated that activation timing of muscle synergy could be evaluation index of motor recovery and adaptation process in sit-to-stand motion of post-stroke patients. In our future study, we investigate how cognitive and emotion affect motor recovery of rehabilitation.

C. Experience of after-effect of memory update reduces sensitivity to errors during sensory-motor adaptation task

Izawa's group together with Dr. Yozu investigated the effect of recognition of aftereffect of learning in human sensory motor learning mechanism in order to study a theoretical background of hyper-adaptability. This is important for developing a theory that can be used to design and develop efficient neurorehabilitation strategy.

Motor learning is the updating of motor commands in response to a trajectory error induced by perturbations on the body or vision. The brain has a great capability to accelerate learning by increasing the sensitivity of this updating process to the perception of errors. Conventional theory suggests that the statistics of the perturbation and of the corresponding errors determine the sensitivity to errors. However, the potential effect of another type of error perception, a self-generated error as a result of motor command updates (i.e. an after-effect), on error sensitivity has not been considered yet. In this study, we dissociated the two kinds of errors by controlling the perception of the after-effect using a channel-force environment. One group experienced errors due to the after-effect of the learning process, while the other did not. We found that the participants who perceived the after-effect of the memory updates exhibited a significant decrease in error sensitivity, whereas the participants who did not perceive the after-effect did not show an increase or decrease in error sensitivity(Figure3).

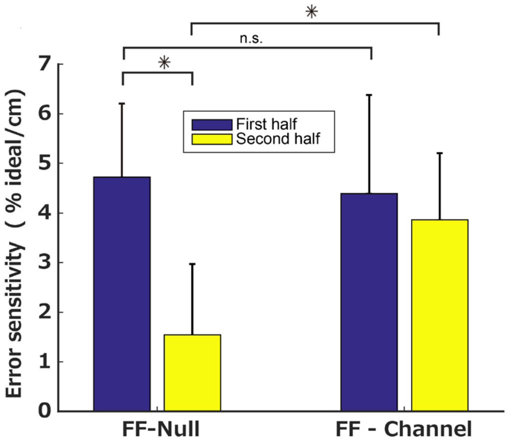


Fig. 3 Error sensitivity in each condition

This suggests that the perception of the after-effect of learning prevented participants from updating their motor commands and that both self-generated and externally induced errors modulate learning speed.

IV. FUTURE PERSPECTIVE

In the past year, we examined the mechanisms and neural basis of the sense of agency, attempted to quantitatively measure post-stroke patients' motor functions, and examined the influence of learning process on motor error detection. In the next year, we aim to further propose a model to explain the influence of emotion on body consciousness, and via it, on 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 five co-investigators (Shirafuji, Kaminishi, Omura, Ishii, and Hamada).

II. RESEARCH RESULTS AND FUTURE PLANS

A. *Reproduction of Abnormal Posture on a Mathematical Model*

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 fiscal year, we aimed to reproduce the abnormal posture peculiar to Parkinson's disease patients, on a mathematical model. Characteristics of Parkinson’s disease patients are abnormal posture and increased muscle tone. We reproduce the abnormalities with a neural controller model that considers muscle tone to obtain clues to elucidate the mechanism of posture control of Parkinson’s disease patients. Parkinson's disease patients show characteristic abnormal postures in the neck, such as antecollis. To express this posture, a musculoskeletal model with 19 joint degrees of freedom and 94 muscles was constructed by adding the joint degrees of freedom and muscles of the neck to an existing musculoskeletal model that focused on lower limbs. It is known that Parkinson’s disease patients have excessively increased muscle tone. Therefore, the constructed musculoskeletal model was controlled by using a neural controller model that models the reticulospinal tract that has the function to regulate muscle tone. A normal upright posture and an abnormal posture of a Parkinson's disease patient were given as target postures for the neural controller model, and control parameters were calculated by optimizations for each posture condition. As a result, the musculoskeletal model was successfully maintained his upright posture in both the upright posture and the abnormal posture conditions. The objective to reproduce the abnormal posture of Parkinson’s disease patients on a mathematical model was achieved [1]. Comparing the results of a comprehensive search for muscle tone that enables both an upright posture and an abnormal posture, we found that abnormal muscle posture requires greater muscle tone (Fig. 1). Because Parkinson's disease patients show increased muscle tone, so it is appropriate that increased muscle tone is simulated in abnormal postures. Furthermore, through calculations of muscle tone for each body part, increased muscle tone was observed especially at an ankle (Fig. 2). It has been reported that a healthy person controls his posture by the coordination of feedback gains and ankle stiffness for disturbances. We consider that Parkinson's disease patients take an abnormal posture to increase their ankle stiffness involuntarily and cannot coordinate their ankle stiffness and feedback gains, that cause postural control disorders. In the future, we introduce the vestibular spinal tract, which has the function of maintaining our body vertical, in the neural controller model, and aim to clarify the relationship between abnormal posture and abnormal postural control. In addition, we perform experiments with subjects to verify the built mathematical model.

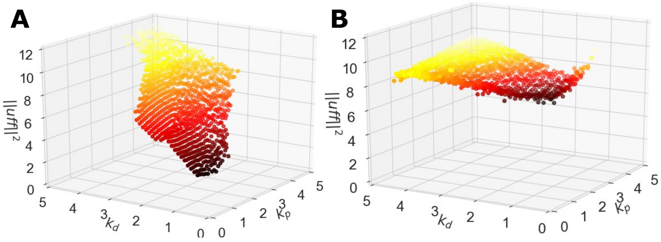

Fig. 1. Muscle tone that can maintain upright postures. (A) Normal posture. (B) Abnormal posture. The higher the values of the vertical axis, the larger muscle tone is.

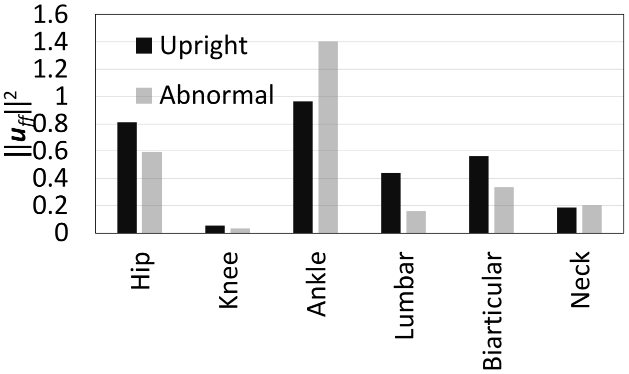

Fig. 2. Simulated muscle tone of each muscle group. The higher the values of the vertical axis, the larger muscle tone is. Black is for normal upright posture and gray is for abnormal upright posture.

Through musculoskeletal simulations and experiments with subjects, we investigated how muscle tone affects the response to external forces. Simulations suggest that increased muscle tone promotes the use of an ankle strategy, maintaining a standing posture based on the movement of ankle joints [2]. The simulation results were consistent with the experimental results [3], indicating the importance of muscle tone when we maintain an upright posture.

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 first year of the project, 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 stated measurements in healthy subjects and a patient with Parkinson’s disease.

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

A multitask which could be performed by aged subjects or patients with 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 [4, 5]. The participants were asked to recite serial subtractions by 7, starting from a randomly selected number between 300 and 900. The calculated result was reported at the end of the task to avoid the influence of articulation on postural sway [6].

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. Posture was recorded both anteriorly and laterally using video cameras. We applied markers to the head (Cz, according to International 10–20 System), external occipital protuberance, spinous process (C7), acromion (bilaterally), xiphoid process, anterior superior iliac spine (bilaterally), greater trochanter (bilaterally), knee (bilaterally), lateral malleolus (bilaterally), tuberosity of calcaneus (bilaterally), and fifth metatarsophalangeal joint (bilaterally). 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 healthy subjects and a patient 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. The reason we measured iii) only the standing task again was to evaluate the leaning effect of repeated measurement. We confirmed that measurements with healthy young adults and a Parkinson’s disease patient were stable in our experimental environment. Parkinson’s disease patient was measured before and after drug administration to evaluate the effect of dopamine on the multitask. In the next year, we are planning to measure large number of healthy adults and Parkinson’s disease patients. We are going to analyze the effect of dopamine with these data next year.

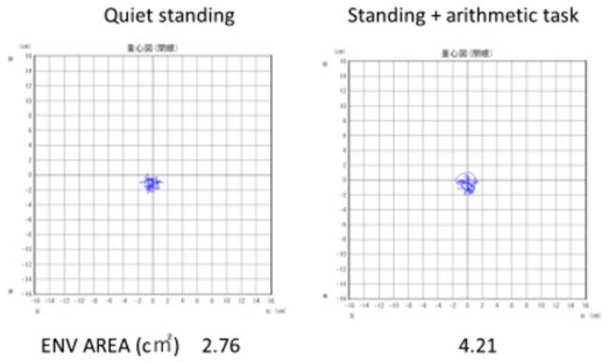

Fig. 3 Example data of center of pressure in healthy subject

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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)
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co-investigator	Wen Wen (Project Associate Professor, The University of Tokyo)
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Research Project A01: Elucidation of the hyper-adaptation mechanism by reconstruction of bio-structure and challenges for prevention of decline in latent adaptive capacity

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Co-investigator	Reona Yamaguchi (Project Assistant Professor, Kyoto University)
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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)

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

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Co-investigator	Amit Yaron (Postdoctoral Fellow, NCNP)
Co-investigator	Shinji Kubota (Postdoctoral Fellow, NCNP)
Co-investigator	Akito Kosugi (Postdoctoral Fellow, NCNP)
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Research Project A03: Mechanisms of body cognition and emotion inducing hyper-adaptability

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Research Project A04: Alteration of brain dynamics as underlying mechanisms of hyper-adaptability in neurotransmitter disorders

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

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

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

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

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