Information for Attendees

1. Registration

Nov. 17 (Sun.)
Time: 13:00
Nov. 18 (Mon.)
Time: 8:30
Nov. 19 (Tue.)
Time: 9:00

2. Venue information

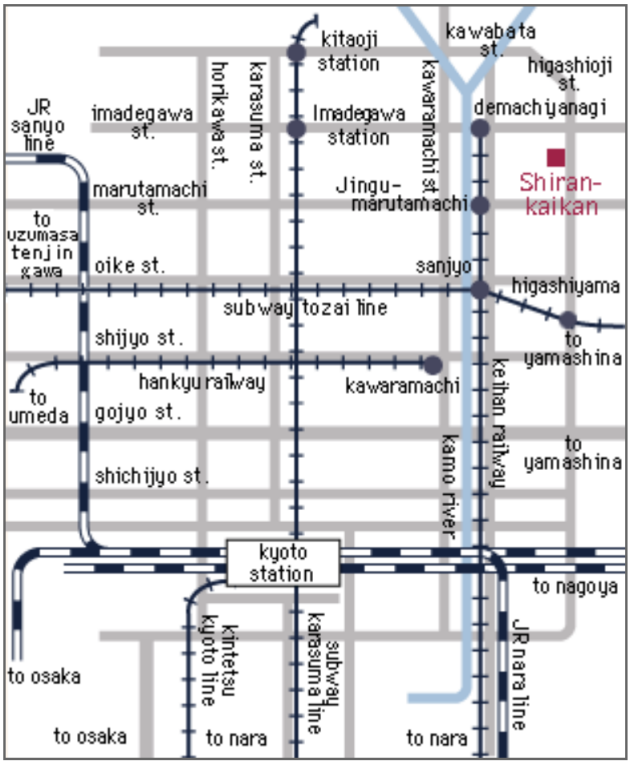
Shirankaikan, Kyoto Univ. Medical School Area, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Access

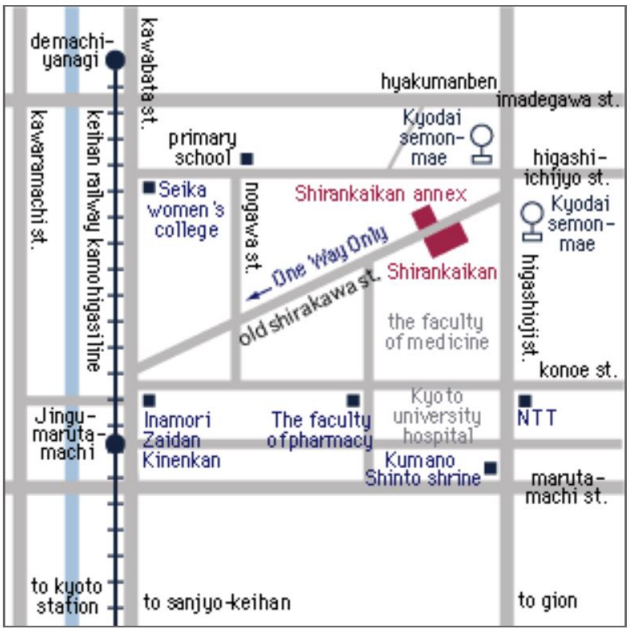
Nearest station	Time required
Kyoto Station (JR)	30-40 min by bus
Kawaramachi Station (Hankyu Railway)	15-25 min by bus
Imadegawa Station (Kyoto City Subway)	10-15 min by bus
Demachi-Yanagi Station (Keihan Railway)	15 min on foot
Kyodai Seimon Mae (Kyoto City Bus)	2 min on foot

MAP

KYOTO CITY MAP



LOCAL MAP



3. Eating and Drinking

Eating and drinking are prohibited in Inamori Hall. We will prepare your lunch on Nov. 18 (Sun.) and 19 (Mon.) in Yamauchi Hall.

4. Cloakroom

Cloakroom is not prepared.

5. Smoking

Smoking is forbidden in the venue.

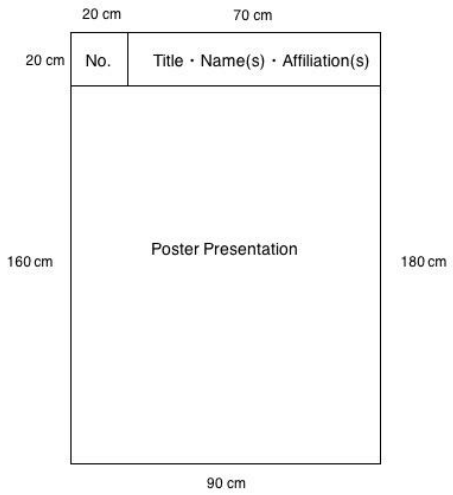
Information for Presenters

Information for Lectures and Symposium presenters

1) The language to be used for presentation is English.
2) Please prepare PC by yourself.
3) Venue: Inamori Hall.
4) We use HDMI and VGA D-sub 15-pin male connection to data projections. If your laptop has no output for them, bring an appropriate connector converter of your own.
5) Screen size is 1280px × 800px.
6) Be sure to bring your own AC adapter for power supply and to disable screensavers and power-saving mode prior to your presentation.
7) Please check the operation before presentation.
8) For your oral presentations excluding special lectures you have 25 minutes followed by 5 minutes for Q&A. The oral presentation will be accurately timed, so make sure you finish in time.

Poster Presentaions

1) Poster presentations should also be made in English.
2) Venue: Yamauchi Hall.
3) The display and removal times are follows:
   <u>Display from 12:00 on Nov. 18</u>
   <u>Removal 17:00 – 17:30 on Nov. 19</u>
   Poster remaining after the removal time will be disposed of by the Secretariat.
4) Each poster is tagged with the number in the left upper corner (20 cm wide × 20 cm wide) of the panel. Attach your poster to the corresponding panel as shown on the figure.



Program Timetable

17 Nov	18 Nov	19 Nov
	8:30 Reception	**9:00 Reception**
	9:00-11:00 Session 2 Mathematical Model of Brain （Coffee Break） **11:10-12:00** Special Lecture	**9:30-11:30** Session 4 Challenging Epilepsy
13:00 Reception	**12:00-13:10** Lunch on Poster	**11:30-13:00** Lunch on Poster
13:25 Opening Remarks **13:30-16:15** Session 1 Basal Ganglia （Coffee Break） **16:30-17:30** Special Lecture	**13:10-15:10** Session 3 Dynamics of Mind/Brain I （Coffee Break） **15:30-17:00** Session 3 Dynamics of Mind/Brain II （Break） **17:10-18:10** Session 3 Dynamics of Mind/Brain II **18:30-20:45** Information Exchange Meeting	**13:00-15:00** Session 5 There's Something about Motor Cortex （Coffee Break） **15:15-16:45** Session 6 Brain Imaging and Oscillation **16:45** Closing Remarks

Program

Sun. Nov. 17, 2019

Inamori Hall

13:30 – 18:30

Session 1

Basal Ganglia: Normal and Pathological Functions

Session chairs:
Atsushi Nambu (National Institute for Physiological Sciences)
Ritsuko Hanajima (Tottori University)

13:30-14:00

Oscillations in Movement Disorders: What has it changed?
◎ José Obeso (HM CINAC, CEU-San Pablo University)

14:00-14:30

Dynamic properties of the cortex-BG loop: a phylogenic Approach
◎ Thomas Boraud (Université de Bordeaux, CHU Bordeaux)

14:30-15:00

Monitoring and updating of action selection through direct and indirect pathways in the dorsomedial striatum
◎ Minoru Kimura (Tamagawa University)

15:00-15:15

Coffee Break

15:15-15:45

Abnormal information processing through the cortico-basal ganglia pathways is responsible for parkinsonian symptoms
◎ Satomi Chiken, Atsushi Nambu
(National Institute for Physiological Sciences)

15:45-16:15

Excitability changes in the human motor cortex in the basal ganglia disorders
◎ Ritsuko Hanajima[1], Yoshikazu Ugawa[2]
([1]Tottori University, [2]Fukushima Medical University)

16:15 – 16:30

Break

16:30 – 17:30

Special Lecture

Synergies of modern brain imaging and mathematics enable clinical translation

◎Viktor Jirsa (Aix Marseille Université)

Session chairs (commentators):
Akio Ikeda (Kyoto University)
Ichiro Tsuda (Chubu University)

Mon. Nov. 18, 2019

Inamori Hall

9:00 – 11:00

Session 2

Mathematical Model of Brain

Session chairs:
Katsunori Kitano (Ritsumeikan University)
Kenji Morita (University of Tokyo)

9:00-9:30

Uniting the many and the few: Reconciling the Kuramoto and HKB models of biological coordination

◎Scott Kelso (Florida Atlantic University, Ulster University)

9:30-10:00

Origin of transient beta band oscillations in the basal ganglia

◎Arvind Kumar

(KTH Royal Institute of Technology, Science for Life Laboratories)

10:00-10:30

Harnessing High-Dimensionality of Brain Data

◎Kazuyuki Aihara (University of Tokyo)

10:30-11:00

An exploration of the principle of functional differentiation in the brain: mathematical models

◎Ichiro Tsuda (Chubu University)

11:00-11:10

Coffee Break

11:10 – 12:00

Special Lecture

Oscillations: Good and Bad

◎Mark Hallett (National Institute of Health)

Session chairs (commentators):
Tatsuya Mima (Ritsumeikan University)
Keiichi Kitajo (National Institute for Physiological Sciences)

12:00-13:10

Lunch on Poster

Yamauchi Hall

13:10 – 15:10

Session 3

Dynamics of Mind / Brain I: Consciousness

Session chairs:
Tatsuya Mima (Ritsumeikan University)
Keiichi Kitajo (National Institute for Physiological Sciences)

13:10-13:40

The flexible nature of executive functions emerges through neuronal dynamics in the prefrontal cortex

◎Kazuhiro Sakamoto[1], Hajime Mushiake[2]

([1]Tohoku Medical and Pharmaceutical University, [2]Tohoku University)

13:40-14:10

Opponent neurochemical and functional processing in NREM and REM sleep in visual learning

◎Yuka Sasaki[1, 2], Takeo Watanabe[1, 2]

([1]Brown University, [2]ATR)

14:10-14:40

Identifying the neural substrate of consciousness from first principles

◎Shuntaro Sasai (University of Wisconsin-Madison)

14:40-15:10

Eye movements and visual salience in schizophrenia

◎Masatoshi Yoshida

(National Institute for Physiological Sciences, Graduate University for Advanced Studies (SOKENDAI))

15:10-15:30

Coffee Break

15:30 – 18:10

Session 3

Dynamics of Mind / Brain II: Plasticity

Session chairs:
Yoshikazu Ugawa (Fukushima Medical University)
Kenji Kansaku (Dokkyo Medical University)

15:30-16:00

Transcranial application of static magnetic field over the human cortex modulate neural oscillations

◎Antonio Oliviero (Hospital Nacional de Parapléjicos)

16:00-16:30

Optogenetic stimulus-triggered acquisition of resilience

◎Ko Matsui (Tohoku University)

16:30-17:00
Motor effects and clinical use of oscillatory transcranial brain stimulation
◎Satoko Koganemaru (Dokkyo Medical University)

17:00-17:10
Break

17:10-17:40
Cortical mechanisms of tongue motor functions in humans: MEG and tDCS studies
◎Hitoshi Maezawa[1,2], Tatsuya Mima[3], Michael A. Nitsche[1]
([1] Leibniz Research Center for Working Environment and Human Factors,
[2] Osaka University, [3] Ritsumeikan University)

17:40-18:10
Manipulating sensorimotor cortical oscillation for promoting post-stroke recovery
◎Junichi Ushiba (Keio University)

18:30-20:45
Information exchange meeting
Yamauchi Hall

Tue. Nov 19, 2019

Inamori Hall

9:30 – 11:30

Session 4

Challenging Epilepsy

Session chairs:
Atsuo Fukuda (Hamamatsu Medical University)
Masao Matsuhashi (Kyoto University)

9:30-10:00

Translational Neuroscience: from bifurcations to personalized medicine
◎Viktor Jirsa (Aix Marseille Université)

10:00-10:30

Epileptogenesis as revealed by wide-band ECoG analyses
◎Riki Matsumoto[1], Takayuki Kikuchi[2], Akio Ikeda[2]
([1]Kobe University, [2]Kyoto University)

10:30-11:00

Significance of epileptic high-frequency oscillations on electroencephalogram in pediatric epileptic encephalopathy
◎Katsuhiro Kobayashi (Okayama University)

11:00-11:30

Mathematical Model of High Frequency Oscillations in Epilepsy
◎Takao Namiki[1], Ichiro Tsuda[2]
([1]Hokkaido University, [2]Chubu University)

11:30-13:00

Lunch on Poster

Yamauchi Hall

13:00 – 15:00

Session 5

There's Something about Motor Cortex

Session chairs:
Hajime Mushiake (Tohoku University)
Hiroyuki Ito (Kyoto Sangyo University)

13:00-13:30

Tremor and the cerebellum
◎John Rothwell, N Grossman, S Schreglmann (University College London)

13:30-14:00

Spatiotemporal dynamics of beta oscillation phase in the monkey motor cortex
◎Hidenori Watanabe[1,2], Kazutaka Takahashi[1], Hajime Mushiake[2]

([1]The University of Chicago, [2]Tohoku University)

14:00-14:30

Cortical oscillatory network for recovery from spinal cord injury

◎Tadashi Isa (Kyoto University)

14:30-15:00

Intensity matters to TBS

◎Masashi Hamada[1], Sasaki T[1], Ugawa Y[2]

([1]University of Tokyo, [2]Fukushima Medical University)

15:00-15:15

Coffee Break

15:15 – 16:45

Session 6

Brain Imaging and Oscillation

Session chairs:

Shozo Tobimatsu (Kyushu University)

Manabu Honda (National Center of Neurology and Psychiatry)

15:15-15:45

Exploring human brain researches using simultaneous EEG-fMRI recording

◎Takashi Hanakawa[1,2], Kenji Yoshinaga[1]

([1]National Center of Neurology and Psychiatry, [2] Kyoto University)

15:45-16:15

The origin of default-mode network

◎Takuya Hayashi (RIKEN)

16:15-16:45

Restoring lost voluntary limb control using neural oscillations

◎Yukio Nishimura (Tokyo Metropolitan Institute of Medical Science)

Abstracts

Oscillations in Movement Disorders: What has it changed?

Jose A. Obeso
(HM CINAC, Mostoles and CEU-San Pablo University Madrid, Spain;
CIBERNED, Instituto Carlos III, Madrid, Spain）

Initial neurophysiological studies of the basal ganglia consisted in classic recordings of single cell neuronal activities. These showed that basal ganglia output nuclei, i.e. the subthalamic nucleus and globus pallidus pars interna, fired at a higher and hyper-synchronous fashion. Such data formed the basis for the highly influential pathophysiological Basal Ganglia Model that has persisted, with some variations, until today. It was also considered a "firing rate" model whereby the *parkinsonian state* was associated with *increased* mean firing frequency whereas the *dyskinetic state* was associated with *decreased* mean neuronal firing activity. In parallel, the *direct* striato-pallidal projection was associated with reducing neuronal activity in the output of the basal ganglia and thus, facilitating movement; on the other hand, the *indirect* pathway (including the *hyperdirect* cortico-subthalamic projection) was associated with increasing output activity which stop movement. This relatively simple understanding has received over the years many criticisms but also relevant support like studies in mice with selective activation of the direct/indirect projection by optogenetics respectively associated with movement facilitation and inhibition, and particularly in Parkinson´s disease (PD) the clinical benefit of functional neurosurgery of the subthalamic nucleus and globus pallidus pars interna (GPi). However, the "firing rate" model failed to explain some prevailing observations among which how ablation of the GPi in PD abolished (rather than enhanced) dyskinesias and benefited parkinsonism.

The idea that *oscillatory* basal ganglia-cortical activity rather than firing rate was important and underlying the pathophysiology of movement disorders then became important as it was recognized that the *parkinsonian state* was associated with predominant beta band (16 Hz) and also 300 Hz peak activity in the output basal ganglia nuclei, and *dyskinesias* was accompanied by a peak in theta activity. This was extended also to PD patients with abnormal behavior, like impulse control disorders. Abnormal oscillations allow to understand brain disorders as a "*circuitopathy"* rather than simple neuronal activity and was a step forward in understanding pathophysiology of movement disorders.

Currently, we are interested in the role of cortical oscillatory activity driving and influencing striatal and subthalamic physiological states and perhaps playing a causal role in the origin of focal dopaminergic motor deficit in PD. Thus, we postulate that increased coupling of slow cortical oscillations during sleep and enhanced beta activity during awakening may lead to enhanced striatal synchronous activity, glutamatergic hyperactivity, Calcium efflux, and ultimately synaptic changes associated with synuclein release and impairment of pre-synaptic dopaminergic terminals (Foffani & Obeso, Neuron, 2018). Thus, oscillatory activity may be not only relevant in terms of understanding clinical manifestations (i.e. pathophysiology) but also the onset of nigro-striatal neurodegeneration in PD (i.e. etiopathogenic).

Dynamic properties of the cortex-BG loop: a phylogenic Approach

Thomas Boraud[1,2]

([1]Institut des Maladies Neurodégénératives, Université de Bordeaux, CNRS, UMR 5293, Bordeaux, France. [2]CHU Bordeaux, 33000, Bordeaux, France.)

The dorsal pallium (cortex in mammals) makes a loop circuit with the basal ganglia and the thalamus known to control and adapt behavior but the who's who of the functional roles of these structures and their dynamic properties are still debated. Current theories propose a hierarchical organization on the top of which stands the cortex to which the subcortical structures are sub-ordinated. In particular, habits formation has been proposed to reflect a switch from conscious on-line control of behavior by the cortex, to a fully automated subcortical control. We proposed to revalue the function of the network in light of the current experimental evidence concerning the anatomy and physiology of the basal ganglia-cortical circuits in vertebrates and how oscillation regime can be generated in the network. After reminding the state of the art concerning the anatomical architecture of the network and the underlying dynamic processes, we summarize the evolution of the anatomical and physiological substrate of skill learning and performance among vertebrates and the associated dynamical states. It allowed us to propose a minimal computational framework where this hypothesis can be explicitly implemented and tested. Our model predicts that early vertebrates that are deprived of a proper cortex should be able to perform associative learning but could not automatize. We validated this hypothesis in Pleurodeles Waltl, rats and primates. We showed that this pallium/cortex is not necessary for a dopaminergic dependent operant learning but is important to develop proper habits. It also has implication concerning the condition in which oscillations can be generated and the role of the different cortico-sub cortical pathways in the generation of physiological and pathological oscillations.

Monitoring and updating of action selection through direct and indirect pathways in the dorsomedial striatum

Minoru Kimura

(Brain Science Institute, Tamagawa University)

Accumulating evidence revealed that the basal ganglia play indispensable roles for decision and action selection through their links to wide cortical areas, midbrain dopamine and thalamus, and that their dysfunction causes neurological disorders including Parkinson's disease. However, roles of central processing circuits in the basal ganglia, direct- and indirect-pathways with differential dopamine innervation, are still enigmatic. We investigated signal processing through direct and indirect pathways in the dorsomedial striatum (DMS), a subsystem of basal ganglia known for goal-directed behavior. Rats adapted to select higher-value option between push or pull of a lever (push 80% vs. pull 20% or vice versa). We found that both optogenetically and electrophysiologically identified direct pathway neurons (dSPNs) and indirect pathway neurons (iSPNs) were activated similarly after GO signal, but oppositely after outcome tones: activation by reward in dSPNs, activation by noreward in iSPNs (Figure 1).

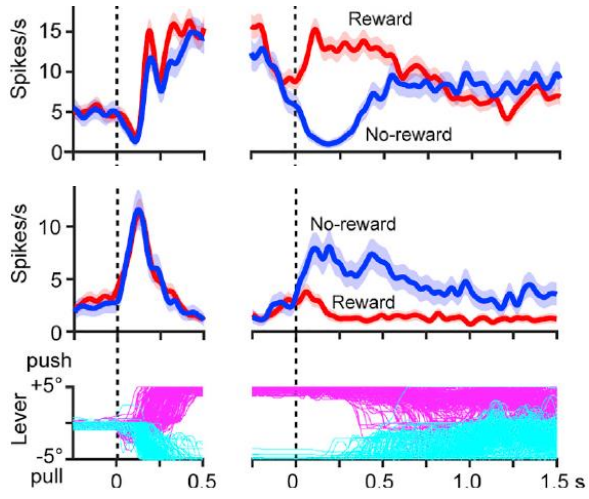


Figure 1 Representative activities of dSPN (top panel), iSPN (middle) and superimposed traces of lever movement (bottom), which are aligned at GO signal and at outcome tones (interrupted lines).

Discharge increases after GO signal and after outcome tones had preference to either push or pull and the preference of outcome response was the same as that of GO responses in most of (2/3) both dSPN and iSPNs. This suggested neuronal coding of which action let to reward (dSPNs) and to no-reward (iSPNs). Multiple Linear Regression analysis showed a tendency of outcome coding of dSPNs to stay selecting rewarded action again, whereas, that of iSPNs actually encode switch selection in the next trials.

Finally, we tested whether dSPNs and iSPNs are causally related to these functions by manipulating outcome signals of dSPNs and iSPNs. Light stimulation (1-ms duration, 5-ms interval, 5-10 mW, 76 pulses) of dSPNs during reward tone, but not noreward tone, decreased probability to switch and enhanced probability to stay in the next selection. In contrast, iSPN activation during noreward tone, but not reward tone, facilitated switch indeed.

Our data reveal that direct and indirect pathways in the DMS play major roles in goal-directed monitoring and updating of action selection in a complementary manner.

Supported by KAKENHI (JP26290009, JP15K14320, JP26112005, JP26250009 JP15H05873), AMED (JP18dm0207043, JP18dm0207050) and Tamagawa BSI (S1311013)

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1) Nonomura S et al., Neuron. 99:1302-1314 (2018)

Abnormal information processing through the cortico-basal ganglia pathways is responsible for parkinsonian symptoms

Satomi Chiken, Atsushi Nambu

(Division of System Neurophysiol, National Institute for Physiological Sciences)

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms, such as bradykinesia, rigidity, tremor, depression, and autonomic dysfunctions. Progressive loss of nigrostriatal dopaminergic neurons has been proposed to cause abnormal neuronal activities in the basal ganglia, such as spontaneous firing rate and pattern changes, and result in PD symptoms. However, the exact pathophysiology of PD still remains unclear. To elucidate pathophysiological mechanism underlying PD symptoms, we have analyzed neuronal activities in primate and rodent models of PD. In PD monkeys generated by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; dopaminergic neurotoxin) treatment exhibited obvious motor symptoms such as akinesia and rigidity. In normal monkeys, motor cortical stimulation, which mimics cortical excitation initiating voluntary movements, induces a triphasic response composed of early excitation, inhibition, and late excitation in the internal segment of the globus pallidus (GPi), the output station of the basal ganglia. On the other hand, in PD monkeys, cortically evoked inhibition, which is mediated by the cortico-striato-GPi *direct* pathway, was strongly diminished without apparent changes in spontaneous firing rate and patterns in the GPi. These results suggest that interruption of information flow through the cortico-striato-GPi *direct* pathway, which initiates movements, is responsible for PD symptoms and that spontaneous activity changes are an epiphenomenon (Figure 1). Similar activity changes were also observed in PD rodents. In this talk, we will discuss pathophysiological mechanisms underlying PD symptoms based on abnormal information processing through the cortico-basal ganglia pathways.

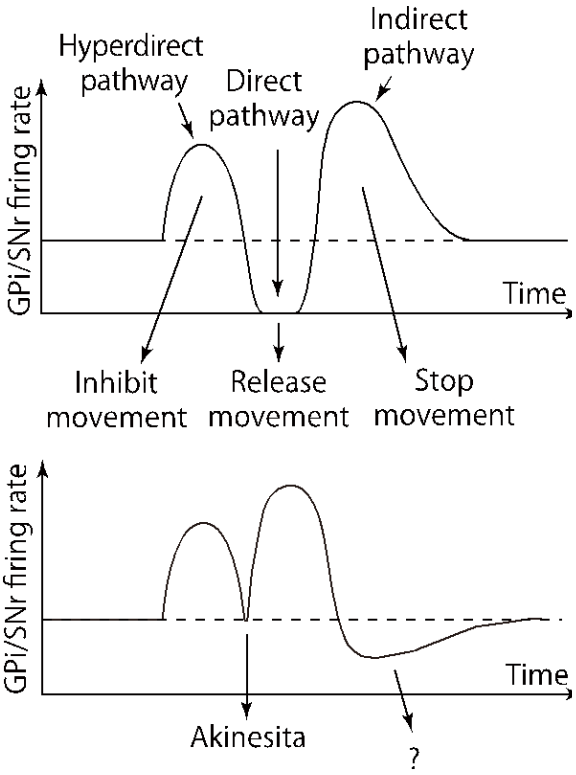

Figure 1. Pathophysiology of Parkinson's disease.

Excitability changes in the human motor cortex in the basal ganglia disorders

Ritsuko Hanajima[1], Yoshikazu Ugawa[2]
([1]Division of Neurology, Department of Brain and Neurosciences,
Faculty of Medicine, Tottori University
[2]Department of Neuro-Regeneration, Fukushima Medical University)

Transcranial magnetic stimulation (TMS) is a non-invasive tool to study cortical excitability of the human primary motor cortex (M1). To study cortical excitability changes in the basal ganglia disorders, such as Parkinson's disease (PD) or focal hand dystonia (FHD), several kinds of TMS technique have been applied. Here, we review the previous reports about cortical excitability changes in the basal ganglia disorders using paired pulse TMS and our recently developed triad-conditioning transcranial magnetic stimulation (TMS) technique.

Paired pulse TMS is used to study cortical $GABA_A$ inhibition function within M1. When conditioning stimuli below the motor threshold (MT) are applied 1-5ms prior to test stimuli, motor evoked potentials (MEPs) are significantly diminished (short interval intracortical inhibition: SICI). In both PD and FHD, this inhibition is reduced which could be due to abnormal inputs from the basal ganglia.

The triad-conditioning TMS aimed to investigate the intrinsic rhythm of M1. TMS was applied over the M1 to study its frequency dependency. In the intervention condition, the subthreshold, same intensity three conditioning stimuli separated by a certain interval (5 to 100 ms, i.e. 10 to 200 Hz) were given prior to the supra-threshold test stimulus. In the control condition, the test stimulus was given alone. MEPs were compared between the two conditions. In healthy volunteers, triad-conditioning stimuli at an interval of 25ms induced MEP facilitation, whereas the other intervals triad-conditioning stimuli induced no facilitation. This frequency dependent facilitation may reflect some intrinsic rhythm of M1 (25ms, i.e. 40Hz). In Parkinson's disease (PD), triad-conditioning stimuli at ISI of 25ms evoked no facilitation and triad-conditioning TMS at ISIs of 30, and 40 and 50 ms (20–33 Hz) significantly smaller in PD patients at Off state. The size ratio at 50 ms seemed to be normalized by L-dopa (On state) and the degree of MEP size ratio at 50ms significantly correlated with the UPDRS III score. Triad conditioning TMS experiment may enable us to investigate an intrinsic rhythm of M1 in humans.

The combination of SICI and triad stimulation TMS has shown several functional abnormalities of M1 in basal ganglia disorders.

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1) Ridding MC et al. (1995) Ann Neurol.37: 181-8.
2) Hanajima, R. et al. (1996) J Neurol Sci. 140, 109-16
3) Hanajima, R. et al. (2008) Clin Neurophysiol. 119, 1400-7
4) Hanajima, R. et al. (2009) Brain Res.1296, 15-23
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Synergies of modern brain imaging and mathematics enable clinical translation

Viktor Jirsa
(Aix Marseille Université)

Pattern formation in physics, biology and chemistry is based on dynamic principles of self-organization. Pattern formation phenomena in brain research are no exception and form the basis of our current understanding of cognitive brain functions. Perception and motor behavior emerge together with neuroelectrical and chemical activity, but so do epilepsy and neurodegenerative diseases. This pattern formation in the brain results from the interaction of billions of neurons over several time and space scales, but is typically measured in humans only on very large scales such as in magnetic resonance imaging or electroencephalography (EEG). In order to bridge the gap to clinical applications, it is therefore essential to model the traverse of scales using computer simulations and advanced mathematics, supported by individual state-of-the-art brain imaging. This combination allows to create autonomous brain models of individual patients and to test concrete clinical questions, possibly even to develop new therapies. Especially in epilepsy, these modern approaches are applied and enable the development of novel surgical interventions.

Uniting the many and the few: Reconciling the Kuramoto and HKB models of biological coordination

J.A. Scott Kelso[1,2]

[1]Center for Complex Systems and Brain Sciences, Florida Atlantic University, USA and
[2]Intelligent Systems Research Centre, Ulster University, Derry ~ Londonderry, N. Ireland

Prolegomenon: *As the Organizers of this conference so deeply intuit, nonlinear oscillations, neural and otherwise, are crucial to an integrative understanding of human nature. Evidence comes from the ubiquitous cyclicity of living things at all scales, essential to multiple biological functions, including the sensory, motor, cognitive, emotional and social functions of human brains. Over 40 years ago, my colleagues and I, following A.S. Iberall's "Homeokinetics" (e.g. Soodak & Iberall, 1978) pursued the idea that biological control and regulation is governed by ensembles of loosely coupled limit cycle oscillators whose stability is modulated both chemically and electrically. The nonlinear oscillator was identified as an elementary unit of action. When coupled together such units form functional synergies or coordinative structures (e.g. Kelso, 2012). The contribution herein generalizes this proposal and elucidates its foundational character for understanding the lawful basis of coordination in complex, biological systems, viz. Coordination Dynamics.*

Coordination, from cells to brains to society, is a ubiquitous feature of all living things. Existing theoretical models of coordination--from bacteria to brains--focus on systems with very large numbers of elements ($N \rightarrow \infty$) or systems with just a few elements coupled together (typically N=2). Both approaches have proceeded largely independent of each other. Can they be reconciled, and if so, how? It turns out, as the poet Robert Frost intimated, the secret to their unification sits in the middle. Recent joint experimental, theoretical and computational modeling of intermediate sized ensembles proves to be the key to reconciling large- and small-scale theories of coordination (Zhang, Beetle, Kelso & Tognoli, 2019). Results indicate that observed phenomena such as disorder-order transitions, multistability, metastability and order-to-order phase transitions figure prominently across all scales of observation, attesting to the importance of multi-scale, multi-level approaches. By focusing on the in between, it has proved possible to marry two well-known models of large- and small-scale coordination: one based on statistical mechanics (Kuramoto) and the other on nonlinear dynamics (extended HKB). Models of the many and the few, previously quite unconnected, are thereby united in a single formulation. The research has led to novel topological methods to handle high dimensional dynamics and has implications for the design of (bio-rhythm inspired) computers.

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Zhang, M., Beetle, C., Kelso, J.A.S., & Tognoli, E. (2019). Connecting empirical phenomena and theoretical models of biological coordination across scales. *J. Royal Society Interface* 16: 20190360.http://dx.doi.org/10.1098/rsif.2019.0360

Origin of transient beta band oscillations in the basal ganglia

Arvind Kumar[1,2]

([1]Division of Comutational Science and Technology, KTH Royal Institute of Technology, Stockholm Sweden. [2]Science for Life Laboratories, Stockholm, Sweden)

Basal ganglia (BG) are composed of the striatum, globus pallidus externa (GPe), globus pallidus interna (GPi) and subthalamic nucleus (STN). Dynamic interactions among these nuclei are crucial for a variety of cognitive and motor tasks and learning. BG function is often described in terms of the interaction among the direct, indirect and hyper-direct pathway. The neuromodulator dopamine plays an important role in controlling the interactions among these pathways. Lack of dopamine most prominently leads to Parkinson's disease (PD). Appearance of PD is associated with the emergence of many changes in the neurons, synapses and network activity dynamics such as: (1.) emergence of 15-30Hz (beta-band) oscillation (2.) increased synchrony in the STN and GPe neurons (3.) increased bursting in the GPe, GPi and STN neurons (4.) increased variability of GPi neurons (5.) Increased activity of D2 type striatal projection neurons (6.) increased (decreased) excitability of D2 (D1) type striatal projection neurons, (7.) weakened cortical input & cortico-striatal synapses on D1 type striatal neurons, (8.) reduced diversity and flexibility of neuronal activity in the striatum.

In my talk I will explore how these various signatures of PD are inter-related. In particular, I will focus on transient beta oscillations (beta bursts). I will isolate the effect of changes in the firing rates, synchrony and spike patterns (e.g. spike bursts) on the emergence of transient beta oscillations. I will show that changes in the firing rate of D2 type striatal projection neurons is sufficient to unleash oscillations in the STN-GPe network. In addition, we found that an increase in synchrony in the striatal neurons can induce transient beta oscillation bursts without any appreciable change in the firing rate of the striatal neurons.

Such striatum induced oscillation are further modulated by spike bursts in the GPe and STN. We found that spike bursts affect beta oscillations in a network state-dependent manner and spike bursts in GPe always enhance oscillations while spike bursts in the STN can both enhance and suppress the oscillations depending on the bursting in the GPe. Finally, I will discuss how understanding of causal links among different signature of PD can help us identify more effect methods to restore a healthy activity dynamics in the BG and ameliorate the disease symptoms.

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Harnessing High-Dimensionality of Brain Data

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The brain is a typical example of complex systems with a huge number of elements. Therefore, we can simultaneously observe many variables in the brain. Usually, this kind of high-dimensionality causes difficulty of theoretical analysis named "the curse of high-dimensionality." However, we have been developing data analysis methods to exploit this high-dimensionality of the brain data, that is, the harness of high-dimensionality rather than the curse of high-dimensionality.

Another viewpoint of our theoretical analysis is to study not only functions of the normal brain that are an important target of the next-generation AI but also dysfunctions of the impaired brain[1)] that are essential to consider treatments of brain disorders.

First, I introduce DNB (Dynamical Network Biomarkers) theory on the basis of the viewpoints above. The DNB theory was proposed to detect early warning signals of transitions from healthy states to disease states[2)], and was recently shown to be effective for both acute and chronic diseases [3)]. This result seems to be useful because most brain disorders deteriorate over long periods like chronic diseases. On the other hand, such bifurcations as representational switching in the normal prefrontal cortex can be also detected by DNB[4),5)]. Further, since the energy landscape analysis with estimated Ising Hamiltonian related to spin representation of brain activity was developed by using fMRI data [6)], we might analyse global and near-global minima of such Ising Hamiltonian by our Coherent Ising Machines[7)-9)].

Second, I explain our RDE (Randomly Distributed Embedding) method [10)] to utilize high-dimensional brain data for predicting short-term evolution of activity at targeted ROIs in the brain.

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An exploration of the principle of functional differentiation in the brain: mathematical models

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One of the most striking features of the developing brain is the generation of functionally differentiated areas, while emerging interactions develop between networking areas. Functional differentiation is known as Brodmann areas or as a functional map in that different areas represent different cognitive and behavioral functions. Recently, the functional parcellation of the human neocortex was observed by means of the functional connectivity of the dynamics involved in the corresponding neural networks, and was shown to consist of finer areas compared with the functional map[1]. The finding of functional parcellation suggests that a self-organization of neural networks occurs rapidly, at least within a few seconds, under various constraints of behaviors. In this respect, we hypothesize the existence of a common principle of constrained self-organization in both functional differentiation and functional parcellation.

To clarify the neural mechanism of functional differentiation, we constructed a mathematical model of self-organization with constraints[2]. Casting different constraints, we investigated the mathematical structures embedded into the process of functional differentiation at various stages of neuronal development and obtained the following dynamic behaviors. We observed the genesis of a neuron-like dynamical system in the developmental process of coupled dynamical systems. We found the genesis of neuron-like units that respond specifically to sensory stimuli. We also detected the genesis of functional modules from randomly uniform networks of oscillations. In all cases, the appearance of chaos and chaotic itinerancy in the whole network plays an essential role in the generation of functional elements since differentiation via symmetry breaking is accelerated by the presence of chaos.

The differentiation of both sensorimotor systems and memory systems is also decisive for brain development. In this respect, we studied the neural networks of memory, and its dynamics. We found chaotic transitions between memories that were dynamically represented by attractors by introducing inhibitory neurons into the recurrent networks of excitatory neurons. This finding allowed the study of the dynamics of episodic memory formation in the hippocampus[3]. In the present talk, I will first describe a theoretical framework of self-organization with constraints. Next, I will deal with mathematical models at various levels of differentiation. Finally, I will discuss a mathematical structure, which may be embedded in the differentiation process.

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Oscillations: Good and Bad

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Oscillations are a critical language of the brain. They are responsible for many aspects of normal function, but they can go wrong or arise due to pathological processes. Oscillations range in frequency from about 0.0001 to 600 Hz and arise from brain networks and oscillatory properties of individual neurons.

Oscillations can be generated by the spinal cord such as the stepping generator. A fascinating slow pathological oscillator is responsible for periodic limb movements of sleep, one movement every 20 seconds. A critical brainstem oscillator is respiration. The basal ganglia in concert with the cortex generates a beta rhythm that seems to inhibit movement (which becomes problematic in Parkinson disease) and a gamma rhythm that facilitates movement.

The cortico-cerebello-thalamo-cortical loop is clearly critical for the fine control of movement. Interacting with this loop is the Guillain-Mollaret triangle which includes the spontaneously rhythmic inferior olivary nucleus. When this loop becomes unstable, tremor results and there can even be positive feedback that leads to a rapid, progressive increase in tremor (Hallett, 2014).

Cortical oscillations appear to be of two types. There are resting or idling rhythms such as the occipital alpha or the motor cortex mu, which has alpha and beta frequency components. When there is functional vision or movement, these rhythms decline. The beta component of the mu suggests it may be more than idling, it might be blocking. On the other hand, oscillations are also a mode of communication. In relation to the motor cortex, corticomuscular coherence is in multiple ranges, alpha, beta, and a smaller amount in gamma (Mima et al., 1999). However, identification of these rhythms appears to depend on a stable posture rather than more complex movement, so might be relevant in only simple conditions.

Cortico-cortical coherence seems important for communication. A proof of principle looked at the ability to perceive objects in the visual midline (Mima et al., 2001). Since the information of two halves of the object go to different hemispheres, there must be some synthesis to allow recognition. Coherence in the alpha range between the hemispheres between about 100 to 400 ms correlated with perception.

In a recent study (unpublished), we looked at cortico-cortical coherence in patients with writer's cramp while writing. We found a decrease of beta coherence between the motor cortices compared with normal controls. Since there is a strong interhemispheric inhibition, this finding might correlate with the phenomenon of mirror dystonia seen in these patients.

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The flexible nature of executive functions emerges through neuronal dynamics in the prefrontal cortex

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Executive functions are the cognitive processes necessary for planning goal-directed behavior in ever-changing environments[1]. For flexible adaptation to such environments, the prefrontal cortex (PFC) is thought to play a crucial role. In this paper, we point out three important neuronal properties in the monkey PFC that support this flexibility.

The path-planning task requires a subject to move a cursor to a final goal in a stepwise manner within a checkerboard-like maze (Fig. 1A). A group of neurons exhibited a shift of coded information by their activities from the final goal to the immediate goal of cursor movement. This shift was mediated by transient firing synchronization[2], and was predicted by the enhancement of the firing variability as a "critical fluctuation"[3], suggesting that the shift is caused by a *state transition of the network itself* (I) as a dynamical system. Recently, we found that the immediate goal was coded by axis tuned cells, which may indicate that the PFC codes relevant information in a *resource-saving* manner (II) [4].

In the study using a shape-manipulation task (Fig. 1B), we recorded local field potentials (LFPs) from a multi-contact electrode. A current source density analysis[5] and the time-frequency spectra of the LFPs[6] suggested that the PFC comprises column-like functional units of different properties, consistent with conventional anatomical studies. *Heterogeneity in the PFC network* (III) may contribute to the flexible emergence of operational information.

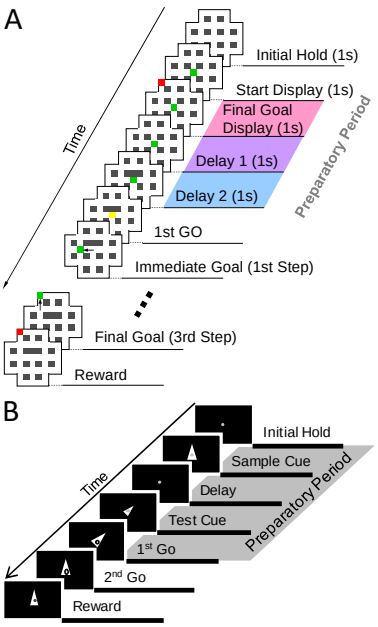

Figure 1 : The event sequences of (A) the path-planning task and (B) the shape- manipulation task

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Opponent neurochemical and functional processing in NREM and REM sleep in visual learning

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Sleep is beneficial for learning. However, whether NREM or REM sleep facilitates learning, whether the learning facilitation results from plasticity increases or stabilization and whether the facilitation results from learning-specific processing are all controversial.

Here, after training on a visual task we measured the excitatory and inhibitory neurochemical (E/I) balance[1,2], an index of plasticity in human visual areas, for the first time, while subjects slept. Offline performance gains of pre-sleep learning were associated with the E/I balance increase during NREM sleep, which also occurred without pre-sleep training. In contrast, increased stabilization was associated with decreased E/I balance during REM sleep only after pre-sleep training. These indicate that the above-mentioned issues are not matters of controversy but reflect opposite neurochemical processing for different roles in learning during different sleep stages: NREM sleep increases plasticity leading to performance gains independently of learning, while REM sleep decreases plasticity to stabilize learning in a learning-specific manner.

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Identifying the neural substrate of consciousness from first principles

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A major neuroscientific challenge is to identify the neural mechanisms support consciousness. Over the past hundred years, lesion, stimulation, and recording studies have accumulated evidence about the location of the neural substrate of consciousness (NSC). However, we still lack a full understanding of why certain brain areas, but not others, can support consciousness. In this talk, I will give an overview of our approach taking advantage of the theoretical framework provided by Integrated Information Theory (IIT) [1]. IIT is a theory of consciousness, which addresses the question from first principles — it derives the requirements for the physical substrate of consciousness from the essential properties of phenomenal experience, then it predicts that the physical substrate of consciousness is a maximum of integrated information. Our approach consists of two parts: (1) we test this IIT's prediction about the location of NSC with empirical data, then (2) we attempt to explain why the NSC is located where it is based on the relationship between integrated information and the anatomical connectivity. To test the prediction, we recently developed a practical method to approximate integrated information from functional neuroimaging time-series data and search for a maximum in high-dimensional settings. This method allowed us to identify the maximum of integrated information with voxel-wise functional magnetic resonance imaging (fMRI) data. I will introduce the method and results showing that a maximum of integrated information within the human brain indeed matches our best evidence concerning the location of the NSC, supporting the IIT's prediction. Then I will offer a graph-theoretical explanation for why the location of NSC can be a maximum of integrated information. We investigated how different wiring diagrams commonly found in the cerebral cortex, such as lattices and random networks, affect a network capacity for integrated information. We identified that the lattice-like architecture is more conducive to high integrated information compared to the random. A simulation of lattice vs random networks indicated that the strength of short-range connectivity is much higher in the lattice than in the random case. We estimated voxel-wise short-range connectivity strength from fMRI data and found that brain regions having stronger short-range connectivity correspond to the location of NSC. Based on these findings, I will argue that the ability of different brain regions to contribute or not to consciousness depends on graph-theoretical properties of their anatomical connectivity, which in turn determines their ability to support high integrated information.

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Eye movements and visual salience in schizophrenia

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Abnormality in eye movements during free-viewing is potentially an efficient biomarker for schizophrenia (Miura et.al. 2014; Morita et.al. 2016). We examined whether aberrant salience hypothesis (Kapur 2003; Howes and Murray 2014) explains the abnormalities in eye movements during free-viewing in schizophrenic subjects. We analyzed eye movement data obtained from 83 schizophrenic subjects and 252 healthy control subjects who viewed natural and/or complex images (n=56) for 8 seconds. We calculated the saliency map of the images (Yoshida et.al. 2012; Veale, Hafed and Yoshida 2017) and evaluated the time course of the salience value at the position of the gaze. We obtained evidence supporting aberrant visual salience during free-viewing in the schizophrenic subjects.

As a first step toward establishing "translatable" markers for schizophrenia, we measured eye movements from normal marmosets with the EyeLink 1000 Plus eye-tracker. The natural and/or complex images identical to those used for the human subjects were randomly presented for 8 seconds. In four marmosets, saccades were reliably detected and characterized as the mean saccade frequency and the main sequence relationship.

Then we evaluated a pharmacological model of schizophrenia in marmosets using intramuscular injection of ketamine at a sub-anesthetic dose. Since mismatch negativity (MMN) is a well-established brain marker for schizophrenia, we developed an experimental setup for simultaneous recording of eye movements and the MMN. For this purpose, silver-ball electrodes were epidurally implanted on the auditory cortices.

Then eye movements and LFPs were recorded during free-viewing of the identical images with tone stimuli (10% deviants and 90% standards). Ketamine (0.5 mg/kg) reduced the median amplitude of saccades and attenuated the MMN with a similar time course. These results suggest that free-viewing is a promising experimental paradigm for establishing "translatable markers" for schizophrenia in humans and in marmosets.

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Transcranial application of static magnetic field over the human cortex modulate neural oscillations

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Abstract The transcranial application of static magnetic field (tSMS) is able to interfere with brain functions. Static magnetic fields at intensity between 120 and 200 mT boosts the oscillatory activity at cortical level. The main effects are seen within the alpha band. tSMS is effective, extremely cheap and safe. People can be easily trained to apply tSMS. The device is portable and a treatment at the patient's house is easy as patients and/or caregivers can be trained easily to apply tSMS.

1. Introduction

Plasticity may provide the physiological basis for neuropsychiatric treatments and rehabilitation procedures. The neurophysiological techniques that can induce plasticity or simply modulate cortical excitability or produce interference with normal brain activity and behavior are known as neuromodulation techniques. Recently, it has been reported the possibility to obtain non- invasive neurmodulation using the transcranial application of static magnetic fields (tSMS) [1-3].

2.Material & Methods

Commercial neodymium magnets can be used to produce strong static magnetic fields that can be easly applied over the human cortex.

3.Results

tSMS is able to interfere with brain function. tSMS over the visual cortex boosts the oscillatory activity of the alpha band and have behavioural consequences [4]. It is effective, extremely cheap and safe [5]. Sensory functions and nociceptive system can be modulated by tSMS [6-7]. People and patients can be easily trained to apply tSMS. The device is portable and a treatment at the patient's house is available. It does not deliver currents to the brain. tSMS has not been tested in neuropsychiatric disorders, but it is promising due to the low-cost technology and its portability. At least in a lab environment, it has a perfect sham. The main disadvantage is that it is almost impossible to obtain individualized thresholds.

3. Discussion

tSMS is probably the easiest form to manipulate cortical activity in humans in a relatively focal manner. It is effective, extremely cheap and safe. As SMS does not deliver currents to the brain, all the regulatory pathways required to use it in clinical trials are easier and cheaper than the other NIBS techniques. For this reason, we think that translation for "bench to bedside" should be extremely quick.

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Conflict of interests. AO co-founded Neurek SL. a company with interests in tSMS and tDCS

Optogenetic stimulus-triggered acquisition of resilience

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Every science starts with observation. Analysis follows. What is required next is the experimental perturbation of the system. The "causal" relationships between the components that constitutes the system under study can only be extracted through such experimentations. Brain is a complex multicellular organism. Modern science believes that communication between these cells results in the creation of our mind. However, observation and analysis of the cellular signals are often not sufficient to really understand the principles that constitutes our mind.

Channelrhodopsin-2 and other light-sensitive proteins found in microorganism can genetically be expressed in mammalian brain cells. Scientists are now endowed with the power to optically control cell activity at will. This optogenetics technology has mostly been applied to reveal the transient nature of information transfer between neurons. However, using this technology in in vivo animals, we realized it could be used to pursue super long-term plasticity, which can occur over days and weeks.

Unlike the electrical circuit, the hardware of the brain is susceptible to change. In some models of epilepsy, repeated electrical brain stimulation can reassemble the circuitry and seizure can occur as an output in response to moderate stimulus as an input. Here, we report that optogenetic neuronal stimulation can also convert the rat brain initially to a state prone to hyperexcitability but subsequent stimulation produced a state that is resistant to seizure induction. Histochemical examinations showed that moderate astrocyte activation was coincident with the resilience acquisition. Administration of the adenosine A1 receptor antagonist instantly reverted the brain back to the hyperexcitable state, suggesting that the hyperexcitability was suppressed by the inhibitory transmitter, adenosine. Furthermore, increase in basal adenosine at hippocampus were confirmed using microdialysis technique. Daily neuron-to-astrocyte signaling likely prompted homeostatic increase in the endogenous actions of adenosine. Our data suggest that functional engineering of a long-term conversion of the brain circuit resilient to epilepsy is possible without exogenous drug administration.

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Motor effects and clinical use of oscillatory transcranial brain stimulation

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Oscillatory transcranial direct current stimulation (tDCS) is noninvasive methods of modulating brain activity. This approach can modulate intrinsic brain rhythmicity, thereby altering sensorimotor and cognitive functions.

Meanwhile, there has been no report of oscillatory tDCS on the repeated movements with regular rhythm such as gait. Those movements are considered to be based on oscillatory neuronal activities.

Now, we have investigated modulatory effects of the gait-combined oscillatory tDCS on gait function in both of healthy subjects and patients with gait dysfunction.

At first, we have investigated effects of the gait-combined oscillatory tDCS on the foot area of the primary motor cortex (M1 foot area) and gait parameters in healthy subjects. Subjects received the oscillatory tDCS over the right M1 foot area during gait with approximate frequency (not matched) of the individual gait cycle. As a result, gait speed and left leg stride length were significantly increased. In addition, the excitability increased in the corticospinal pathway of the left tibialis anterior muscle. Furthermore, the oscillatory tDCS entrained the gait cycle in some subjects. These findings suggest that the oscillatory tDCS during gait enhanced corticospinal activities driving flexor muscles during gait[1].

In the next step, we have investigated its effects in patients with gait dysfunction. Post-stroke patients with gait disturbance often show inadequate flexion of lower limb joints during the swing phase. Then, we have developed a closed-loop system using the oscillatory tDCS to target the swing phase activity in gait. In this system, the contact of the paretic foot triggers stimulation. We have investigated effects of this gait-synchronized closed-loop oscillatory tDCS over lesioned M1 foot area in post-stroke patients. As a result, it improved gait speed and balance parameters along with improved flexion of lower limb joints during the swing phase. Those findings suggested that oscillatory tDCS synchronized with gait rhythm could enhance M1 activities to improve gait function in post-stroke patients[2].

We consider that the oscillatory tDCS combined with rhythmic movements might be a powerful approach to enhance human motor function and treat motor dysfunction in patients with central nervous system disorders

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Cortical mechanisms of tongue motor functions in humans : MEG and tDCS studies

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The motor functions of the tongue are critical for human oral functions, such as swallowing, mastication. Fine tongue movements are in part controlled by cortical entrainment. We provide a overview of tongue motor functions in humans, based on the findings of recent magnetoencephalography (MEG) studies.

Previous MEG studies indicate that cortico-muscular coherence (CMC) reflects a bi-directional flow of information between the cortex and fingers. In our studies, CMC was demonstrated using whole-head MEG signals and EMG signals from both sides of the tongue. CMC was reflected over both hemispheres, for each side of the tongue, and at two frequency bands during isometric tongue protrusions: the β band at 15–35 Hz and a low-frequency band at 2–10 Hz. CMC at the β band mainly reflect the motor commands from the primary motor cortex (M1) to each side of the tongue, with contralateral dominance (1). Moreover, CMC at a low-frequency band mainly reflect proprioceptive afferent feedback from both sides of the tongue to the bilateral primary somatosensory cortex (2). This bidirectional flow of oscillatory information between the cortex and the tongue may be critical for sophisticated tongue movements.

We also provide a overview of a transcranial direct current stimulation (tDCS) technique for tongue motor functions (3). tDCS is a non-invasive tool for inducing cortical excitability changes. Since the tongue receives innervation from both sides of the hypoglossal nerve, we investigated the effects of anodal tDCS over the bilateral tongue M1 representation on tongue M1 excitability and tongue motor functions. We hypothesized improved stimulation efficacy by bilateral vs. unilateral stimulation.

Three stimulation sessions were conducted, namely 0.0833 mA/cm² tDCS for 20 min over the (1) bilateral (bi-tDCS) or (2) left (lt-tDCS) tongue M1 representation, and (3) sham stimulation. Motor evoked potentials (MEPs) for the bilateral tongue M1 representations were recorded from both sides of the tongue before and immediately, 30 min, and 60 min after tDCS. Maximum tongue forces were also evaluated.

Compared to sham stimulation, bi-tDCS and lt-tDCS induced significant elevations of bilateral tongue MEP amplitudes, as obtained by transcranial magnetic stimulation of the tDCS-treated hemisphere. Maximum tongue force was significantly larger in the bi-tDCS condition than in the lt-tDCS and sham conditions. Bilateral anodal tDCS over the tongue M1 representation enhances excitability of this area and motor functions of the tongue, suggesting that this technique might be clinically useful for treating tongue movement disorders.

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Manipulating sensorimotor cortical oscillation for promoting post-stroke recovery

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Cortical oscillation are well-known phenomena that characterize various information processing inside the brain. The sensorimotor rhythm (SMR) in the electroencephalogram (EEG) is one representative cortical oscillation that can observe over the sensorimotor cortex. EEG-SMR is derived as the closed-loop idling in the cortex-basal ganglia-thalamus circuit, thereby it is treated as a surrogate monitoring marker of the sensorimotor cortical activity.

For generation of physical movement, switching the sensorimotor cortex to the excitation state is needed. EEG-SMR should be desynchronized (namely, event-related desynchronization, ERD) to release the neurons from this entrapped oscillatory cargo, but EEG-SMR-ERD is less controlled due to disruption of the sensorimotor related neural circuitry. To initiate the process of functional remodeling in the remaining neural circuitry following stroke, training with the up-conditioning of EEG-SMR in the resting-state as well as the amplified regulation of the EEG-SMR-ERD has been proposed.

Brain-Computer Interface is a potential tool that enables users to monitor and manipulate EEG-SMR and its ERD in a neurofeedback manner. One challenge in this technology, however, is precise online detection of the EEG-SMR and its ERD. An overlapped 1-s sliding window has been often used to apply repeated fast Fourier Transform (FFT), but this technique often violate the precondition of the FFT; signal stationarity within a window and independency among the neighboring segmented signals. 1-s window contains 10 cycles of EEG-SMR, thereby the output signal was too much smoothed than the original envelope.

We recently developed a precise envelope detection of the ongoing EEG-SMR (Kato et al. 2018; Takahashi 2018). It is originally called "Locked-in Amplifier (LIA)" that has been deployed in the analogue electrical circuit, and is coded in the online software in this study.

LIA is consisted of online calculation of inner product between the signal and the trigonometric function of target frequency (Fig. 1). It is a mathematically same concept with FFT, but omitted calculation in the frequency regions, enabling fast estimation of the envelope and phase at a targeted frequency. The assessment identified that The delay time was significantly improved compared with those calculated by the conventional FFT (Fig. 2a). Coefficient of variance of the delay time was also reduced (b).

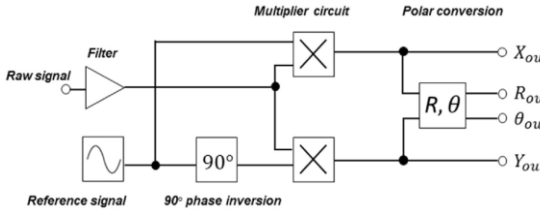

Fig. 1 Mathematical concept of LIA

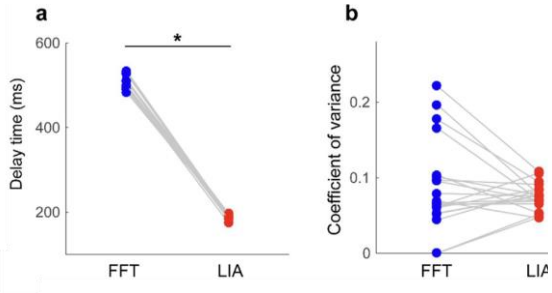

Fig. 2 Envelope detection by FFT and LIA

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Translational Neuroscience: from bifurcations to personalized medicine

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Over the past decade we have demonstrated that the fusion of subject-specific structural information of the human brain with mathematical dynamic models allows building biologically realistic brain network models, which have a predictive value, beyond the explanatory power of each approach independently. The network nodes hold neural population models, which are derived using mean field techniques from statistical physics expressing ensemble activity via collective variables. Our hybrid approach fuses data-driven with forward-modeling-based techniques and has been successfully applied to explain healthy brain function and clinical translation including stroke and epilepsy. Here we illustrate the workflow along the example of epilepsy: we reconstruct personalized connectivity matrices of human epileptic patients using Diffusion Tensor weighted Imaging (DTI). Subsets of brain regions generating seizures in patients with refractory partial epilepsy are referred to as the epileptogenic zone (EZ). During a seizure, paroxysmal activity is not restricted to the EZ, but may recruit other brain regions and propagate activity through large brain networks, which comprise brain regions that are not necessarily epileptogenic. The identification of the EZ is crucial for candidates for neurosurgery and requires unambiguous criteria that evaluate the degree of epileptogenicity of brain regions. Stability analyses of propagating waves provide a set of indices quantifying the degree of epileptogenicity and predict conditions, under which seizures propagate to non-epileptogenic brain regions, explaining the responses to intracerebral electric stimulation in epileptogenic and non-epileptogenic areas. These results provide guidance in the presurgical evaluation of epileptogenicity based on electrographic signatures in intracerebral electroencephalograms and have been validated in small-scale clinical trials. The example of epilepsy nicely underwrites the predictive value of personalized large-scale brain network models.

Epileptogenesis as revealed by wide-band ECoG analyses

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Technological developments of digital EEG enabled wide-band electrocorticographic (ECoG) recording for the invasive presurgical evaluation for epilepsy surgery. Wideband ECoG recording has provided a comprehensive approach to probe epileptogenicity by combining both infraslow (DC shift) and high (spontaneous and induced high frequency oscillations (HFOs)) ends of frequencies[1]. Regarding ictal ECoG recording, the co-occurrence of the ictal DC shift and HFOs seems to be a more sensitive surrogate biomarker of epileptogenicity since its spatial extent is generally smaller than that of the conventional seizure pattern[2]. The earlier occurrence of ictal DC shifts, compared with that of HFOs, would imply the active role of glia in seizure generation, and surgical removal of the cortical region with the core ictal DC shift resulted in better surgical outcome[3]. Pathological investigation of the cortical regions with ictal DC shifts showed the loss of Kir4.1 function in the astrocytes[4], supporting the active role of ictal DC shift in impaired potassium homeostasis and seizure generation. Cluster and logistic analysis of the ictal DC shift revealed two different types, rapid- and slow development patterns, probably due to the different degree of glial dysfunction[5]. The importance of co-occurrence of slow and high frequency activities is further endorsed by increased phase amplitude coupling and bidirectional information transfer between the two frequency activities[6].

Single pulse electrical stimulation (SPES) has been highlighted in the last decade since it can probe 1) seizure and functional brain networks, and 2) cortical excitability of the focus, namely, epileptogenicity (see ref 7 for review). Both early (i.e., cortico-cortical evoked potential (CCEP)) and delayed responses, and probably their HFO counterparts, are regarded as an interictal surrogate marker of epileptogenicity. Similar to the features of spontaneous pathological HFOs, the power of SPES-induced HFOs was greater in the epileptic focus than the cortices remote from the focus[8]. At the focus interictally, increased neuronal activity to the exogenous input such as SPES is followed by the decrease or inhibition of neuronal activities in an intensity dependent manner[9]. The suppression of neuronal activities, probably mediated by inhibitory interneurons, seems to be a target of neuromodulation, since 50 Hz stimulation of the focus resulted in the increase of low gamma at the phase of post-spike slow waves, associated with decreased number of interictal spikes and decrease HFO power at the phase of spikes[10].

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Significance of epileptic high-frequency oscillations on electroencephalogram in pediatric epileptic encephalopathy

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The electroencephalogram (EEG) indicates the functional state of the brain. High-frequency oscillations (HFOs) in the ripple (80–200/250Hz) and fast ripple (200/250–500/600 Hz) bands, as well as the ictal direct current (DC) shifts, have recently been attracting attention, and their recording has been enabled by advancements in digital EEG techniques (Figs. 1,2). The detection of HFOs was previously limited to intracranial EEG, but fast oscillations (FOs) in the gamma (40–80 Hz) and ripple bands can now be detected over the scalp. HFOs are recognized as related to epileptogenicity in intracranial EEG. In scalp EEG, FOs are also known to be related to epileptogenicity.

A large number of FOs are found in the scalp EEGs of pediatric epileptic encephalopathy represented by West syndrome.[1)] FOs are suggested to be a biomarker of the epileptogenic cortical region in epilepsy surgery. FOs are detectable even in idiopathic focal epilepsies, including benign epilepsy with centrotemporal spikes and Panayiotopoulos syndrome, which are not generally candidates for operation.[2)]

In epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) and related epileptic disorders, it was found that massive generation of epileptic FOs characterizes CSWS and might be closely related to the pathophysiology of this epileptic encephalopathy.[3)] Therefore, HFOs/FOs may provide clues to the pathophysiology of epilepsy and the relationship between HFOs and cognitive dysfunction.

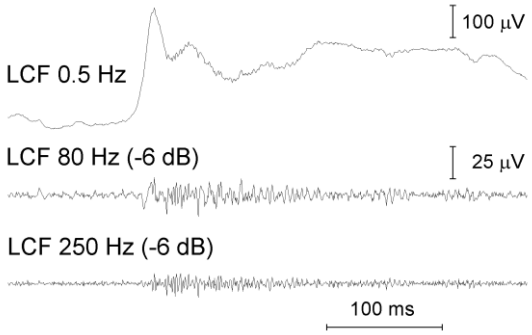

Figure 1: Representative epileptic HFOs embedded in a spike-wave-complex recorded from the hippocampus of a patient with mesial temporal lobe epilepsy. LCF: low-cut frequency filter

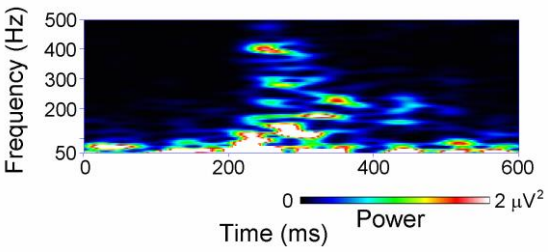

Figure 2: Time-frequency analysis of the HFOs shown in Fig. 1.
Spectral blobs indicate the detected HFOs.

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Mathematical Model of High Frequency Oscillations in Epilepsy

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From the viewpoint of mathematical modeling, the brain dynamics in epilepsy is an interesting phenomenon that includes two distinct dynamics of the interictal and ictal parts. In particular, the dynamics of the ictal onset consists of various oscillations and macroscopic DC shifts. The brain dynamics in epilepsy was characterized by analyzing wideband ECoG recorded datasets of epileptic patients at a 2,000 Hz sampling rate. The results showed strong autocorrelated behavior in the brain wave, x_t, for each dataset from the electrodes, and it was removed by determining the difference, $y_t = x_{t+1} - x_t$. During ictal onset, the anomalous high frequency oscillations (HFOs) were identified as shown in Figure 1. Each HFO continues for approximately 100 time steps.

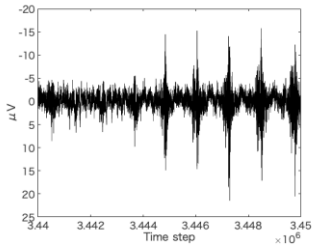

Figure 1 : Anomalous high frequency oscillations of approximately 10 μV amplitude for difference datasets y_t.

To characterize the HFOs, nonlinear time series analysis was applied to the anomalous HFO. First, plotting (y_t, y_{t+1}) on a graph showed torus-like behavior during the HFO, as shown in Figure 2. Second, on the torus-like dynamics, we transform the coordinate into the polar coordinate and the observation angle direction (θ_t). This resulted in a relationship between θ_t and θ_{t+1} by a function $\theta_{t+1} = T(\theta_t)$, as shown in Figure 3. We set the model equation $T(\theta_t) = c + \theta_t + r \sin^2(\pi\sqrt{\theta_t/\pi})$. The two parameters r and c were determined using the least square method.

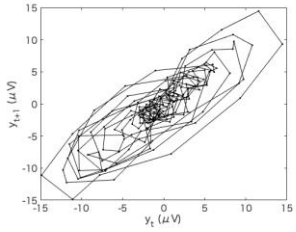

Figure 2: Result of plotting (y_{t+1}, y_t).

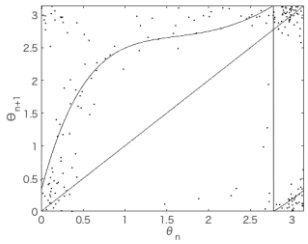

Figure 3. Dots: Result of plotting (θ_t, θ_{t+1}). Line: Graph of model $T(\theta_t)$.

Results were not only obtained from a patient of epilepsy, but also from the ECoG datasets of five other patients. The details are shown in our presentation. We believe that our results contribute to both the theoretical and medical aspects of understanding epilepsy.

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Tremor and the cerebellum

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It is generally accepted that the cerebellum plays a role in sustaining patients with essential tremor and in patients with Parkinson's disease. Recently we have also shown, using eyeblink classical conditioning, that the cerebellum may also be implicated in some rarer forms of tremor such as Orthostatic Tremor (Antelmi et al., 2018) and the tremor of Motorneurone Disease (Latorrre et al., 2019). Here we test whether essential tremor can be suppressed to some extent by phase-locked transcranial electric stimulation over the cerebellum, and probe the possible mechanism of the effect.

Postural hand tremor was measured with an accelerometer attached to the dorsum of the hand, and was used in real-time to produce phase- locked transcranial alternating current (p-p max 2.7 mA) over the ipsilateral cerebellum using 6 different phase lags (0°, 60°, 120°, 180°, 240°, 300°). Stimulation was performed in blocks of 60s trials consisting of a 30s stimulation period (including 5s of ramp-up and 5s of ramp-down) and 15s stimulation-free periods before and after. We repeated the stimulation conditions four times in a double-blinded random order with a 30s rest interval between conditions and 5-10min rest interval between sessions of eight stimulation conditions.

Stimulation that was not phase-locked to the tremor had no significant effect on amplitude. In contrast, stimulation that was phase-locked to the tremor movement resulted in a significant reduction in the tremor amplitude that increased throughout the stimulation period and was sustained during the post stimulation period. The number of patients who showed a significant reduction in the tremor amplitude was significant during the second half of the stimulation and the post stimulation period, while the number of patients who showed a significant increase in the tremor amplitude was not significant.

We next tested whether it was possible to predict the magnitude of the stimulating effect from the characteristics of each individual's tremor. A feature-based statistical learning indicated that responders had a smaller amplitude, more regular, and more symmetric tremor than non-responders. Reduction in tremor amplitude appeared to be mainly due to a disruption of the temporal coherence of the tremor. Using a recent physiological model of neural activity in the cerebello-thalamo-cortical loop (Zhang & Santiello, 2019) we found that this could be explained as a decrease in the temporal coherence of tremor-related burst discharges in the deep cerebellar nuclei caused by dysregulation of complex spiking in Purkinje cells.

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Spatiotemporal dynamics of beta oscillation phase in the monkey motor cortex

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β oscillations (15~30 Hz) are ubiquitous in the motor cortex of the mammals. There has been, however, few attempts to analyze 3D spatiotemporal dynamics of neuronal activities at β band across the motor cortical areas. Previously we characterized horizontal dynamics of β oscillations from electrocorticogram (ECoG) recording by looking timings of phase locking to the instruction cues and movement onsets. Here, we implanted 3D electrode arrays into the primary motor cortex (M1) and the premotor cortex (PM) of a monkey and analyzed how site-dependent phase locking of β oscillations can be characterized in the surface and depth of motor-related cortices, and how the phase locking is related to behavioral events.

The monkey was trained to perform a reaching task with one arm. The monkey held the hand at the resting position for 2 seconds after a visual instruction target-cue randomly indicating one of the two target positions, then initiated reaching movement to the target after an acoustic go-cue. Two 128-channel electrode arrays (Matrix Array™, NeuroNexus, MI, US) were implanted in M1 and PM contralateral to the arm. Each array consisted of an ECoG grid (32 channels), and a 3D intracortical part (96 channels) having 12 needle probes horizontally spaced by 0.4mm with eight electrodes 0.2mm apart along each needle. A prominent β peak was identified at 22 Hz. To extract the amplitude and phase of the β band, a signal from each contact was bidirectionally filtered (20-24Hz), then Hilbert transformed. The Percent of Phase Locking (PPL) of β oscillations over trials was computed in relation to the instruction and go cues respectively. Significance of PPL in each channel was determined by application of resampling methods (randomized locking time, PPL value > mean + standard deviation; resampling of trails, $p>0.5$ as conservative threshold in each time step).

The PPL transiently increased among most channels around the reaching onsets, while the β amplitude decreased. The PPL in many channels occurred after instruction-cue as previously reported. Most channels showed statistically significant PPL after the instruction-cues and around reaching onsets. There is a temporal sequence of peak timing of the PPL across the M1 and PM area around the reaching on-sets. These results indicate that the temporal dynamics of the phase of β oscillation carry task-relevant information contained in instruction cue signals and about reaching.

Cortical oscillatory network for recovery from spinal cord injury

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The coricospinal tract (CST) is directly connected to the spinal motoneurons and it is believed to be the basis of dexterous hand movements in higher primates. However, previously, we have shown that precision grip could recover in a few weeks after transecting the CST axons in the dorsolateral funiculus at C4/C5 cervical segment in macaque monkeys[1]. We have been analyzing the neural mechanism of recovery in this spinal cord injury (SCI) model, in which the function of the direct cortico-motoneuronal pathway in the control of dexterous hand movements is compensated by other indirect pathways from the motor cortex to hand motoneurons. At the spinal level, the recovery is mediated by the propriospinal neurons in the mid-cervical segments[2),3)]. In addition, we have found that the large scaled cortical network is dynamically modified during the recovery. First, by using the positron emission tomography (PET), we found that bilateral sensori-motor cortices increased the activity during the early recovery stage (1 month after the SCI), and during the late stage of recovery (3-4 months), bilateral premotor cortex (PM) and contralesional primary motor cortex (M1) increased the activity. Reversible inactivation of these areas impaired the recovered precision grip, revealing that these cortical areas are causally involved in the recovery[4)]. More recently, we chronically implanted the multichannel electrocorticography (ECoG) electrodes on the bilateral PM, M1 and primary sensory cortices (15 ch electrodes on both ipsi- and contralesional sides, respectively) and made longitudinal recording of the activity of these areas before and after the SCI[5)]. Connectivity between pairs of cortical areas with ECoG recordings were evaluated by Granger causality (GC). The big data of GC between all the electrode pairs, across individual trials, different frequency domain, days before and after the SCI were processed by the parallel factor analysis (PARAFAC) and two major circuit components were obtained. One is the flow of the signals from the contralesional PM to M1 at the high γ–band active during the reach and grasp movements. This component was transiently increased soon after the SCI and quickly calmed down. The second component is the interhemispheric interaction from the contralesional PM to ipsilesional PM/M1 at low β to α–band and active before and during the movements. The amplitude of this component gradually increased and paralleled the whole recovery course. These results suggested that the enhanced activity of ipsilesional PM/M1 was derived from the contralesional PM/M1. The causal contribution of such interhemispheric interaction to the recovery will be discussed.

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Intensity matters to TBS

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BACKGROUND:

Responses to continuous theta burst stimulation (cTBS) applied to the human primary motor cortex are highly variable between individuals. However, little is known about how to improve the after-effects of cTBS by adjusting the protocol parameters.

OBJECTIVE:

We examined whether current directions adopted in the measurement of cortical motor excitability indexed as motor evoked potentials (MEPs) affect the responses to cTBS. We also tested whether the stimulus intensity of cTBS influences the after-effects.

METHODS:

Thirty-one healthy volunteers participated. The after-effects of cTBS with the conventional intensity of 80% of individual active motor threshold (AMT) (cTBS80%) were tested by measuring MEP amplitudes induced by not only posterior-anterior (PA) but also anterior-posterior (AP) and biphasic (PA-AP) currents. We also investigated cTBS with 65% AMT (cTBS65%) and 100% AMT (cTBS100%) in subjects who showed depression of MEP amplitudes after cTBS80%, as well as cTBS65% in subjects in whom facilitation of MEPs was induced by cTBS80%.

RESULTS:

Current directions in MEP measurement had no influence on the cTBS responses.

What we found in this study was that the intensity matters to TBS. That is, in subjects whose MEPs were depressed by cTBS80% (i.e. responder to conventional cTBS), increasing the intensity of cTBS (i.e. cTBS100%) partly induced MEP facilitation, while decreasing the intensity (i.e. cTBS65%) abolished the after-effects. Surprisingly, and perhaps most importantly, in non-responder to conventional cTBS (i.e. in subjects who showed MEP facilitation by cTBS80%), decreasing cTBS intensity (i.e. cTBS65%) partly induced MEP depression. That is , the non-responder became responder of cTBS when we reduce the intensity of cTBS.

CONCLUSIONS:

Stimulus intensity of cTBS influenced the responses to cTBS, and lowering stimulus intensity induced the expected after-effects of cTBS in some subjects. The results suggest that if you can't push it, pull it instead!

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Exploring human brain researches using simultaneous EEG-fMRI recording

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Because electroencephalography (EEG) and functional MRI (fMRI) have complementary characteristics for recording brain signals, simultaneous recording of EEG and fMRI is a powerful method for investigating human brain activity [1].

Thus far we have conducted simultaneous EEG and fMRI experiments to characterize whole-brain neural underpinnings of EEG oscillations such as occipital alpha rhythm [2] or sensorimotor rhythm (SMR) [3], to understand mechanisms of SMR-based brain machine interface, and to gain insight into pathophysiology of epilepsy. We were able to analyze both EEG and fMRI data after off-line and even on-line artifact removal and retrieve neuroscientifically reasonable results.

However, in these experiments, we cannot say we were completely satisfied with the quality of artifact removal on EEG. EEG signals recorded simultaneously with fMRI suffered from various artifacts such as MR-related artifacts (GA: gradient artifacts), cardiac-related artifacts (BCG: ballistocardiogram). Sufficient noise removal is required for data analysis of these EEG signals, while excessive noise removal can lead to considerable loss of brain signals of interest.

Hence, we have been exploring to investigate dynamics of spontaneous brain activity using the simultaneous EEG-fMRI recording. To achieve an optimal level of noise removal in this trade-off, we here proposed preprocessing pipeline for EEG signals recorded simultaneously with fMRI. In brief, we at first removed GA and BCG using the average artifact subtraction [3] and optimal basis set [4]. We then subtracted blink-related artifacts constructed by a combination of band-pass filter (0.1-8 Hz) and independent component analysis (filtered ICA). Residual stationary and non-stationary artifacts were removed using ICA and artifact subspace reconstruction [4], respectively. To validate this preprocessing, we compared flanker stimulus related potentials of EEG data preprocessed by the minimally required procedure (only GA/BCG removal and re-referencing) and this proposed pipeline. This analysis revealed that the proposed pipeline effectively removed EEG artifacts without attenuating actual brain responses (Figure 1).

We will continue our simultaneous EEG-fMRI recording during a flanker task to understand dynamics of brain networks.

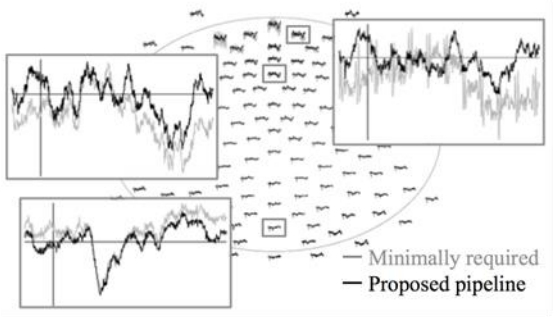

Figure 1. Flanker stimulus related potentials

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The origin of default-mode network

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The default mode network was discovered by using neuroimaging techniques in early 2000s. It is now commonly visualized by functional magnetic resonance imaging (fMRI) during at rest, which detects blood-oxygen level dependent (BOLD) signals synchronizing over remote brain areas at frequency of 0.005 to 0.01 Hz. The signal change may have its basis on spontaneous, oscillatory or fluctuating activity of neural populations, however, details on the origin of these dynamic activity have not been quantitatively investigated. Potential sources of the dynamics to be investigated may be amplitude of spontaneous neural activity in each brain area, variability in borders between brain areas, direct and indirect neural connection between areas, and efficiency and modulation of synaptic transmission between neural connections.

One of the issues in the default mode network science has been lack of basic research particularly in non-human primate (NHP) animals. Over a century, studies in NHP have provided the principle knowledge of brain organization such as cyto- and myeloarchitecture, connectivity and neural activity but mostly relying on the invasive techniques. Some fMRI studies localized neural functions but only in limited areas of cortex. The resultant functional maps are not easily captured as a homolog of those in human due to lack of knowledge on the cross-species similarity in brain organization characterized by FACT (function, architecture, connectivity and topology).

We have developed a system to obtain high-quality MRI data in two major NHP species in the neuroscience, macaque (Autio et al., 2019) and marmoset (Hori et al., in prep). A core technology is high-dimensional coils, which allow to detect radiofrequency (RF) by multiple elements (24-channel in macaque, 16-channel in marmoset) placed closely to the head surface. The coils are combined with a 3T MRI scanner, which was tuned for high gradient field and homogeneous RF transmission. In macaque, the structural image is obtained with 0.5mm isotropic resolution, and functional MRI with 1.25mm resolution, corresponding to the half of minimal cortical thickness and <5% of cortical thickness histogram, respectively. The fMRI data is obtained in high temporal resolution (~0.76 sec). We found the potential similarity in cortical myelin contrast in these species of human, macaque and marmoset, in which all species showed high myelin in sensorimotor and middle temporal (MT) areas and low in association areas. We also found putative homolog of default mode network and other resting-state network activities, which gave us insights on species similarity/difference. Future studies may inlude the fMRI data acquisition in awake conditions, cross-species registration based on FACT, and association of functional connectivity with neural connection and synaptic modulation.

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https://doi.org/10.1101/602979

Restoring lost voluntary limb control using neural oscillations

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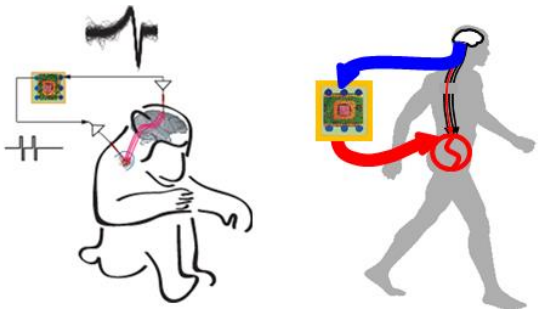
Regaining the function of an impaired limb is highly desirable in paralyzed individuals. One possible avenue to achieve this goal is to bridge the interrupted pathway between preserved neural structures and muscles using a brain-computer interface. Here I demonstrate an artificial neuronal connection (ANC) that bridges supra-spinal system and preserved spinal network beyond the lesion restore lost function. The ANC is produced by a computer interface that can detect the neural activity and converted in real-time to activity-contingent electrical stimuli delivered to nervous system.

A promising application is to bridge impaired biological connections. Mmonkeys with subcortical stroke were able to learn to use an artificial cortico-muscular connection (ACMC), which transforms cortical ocsillatory activity into electrical stimulation to the hand muscles, to regain volitional control of a paralysed hand. The ACMC induced an adaptive change of cortical activities throughout an extensive cortical area. In a targeted manner, modulating high-gamma activity became localized around an arbitrarily-selected cortical site controlling stimulation to the muscles. This adaptive change could be reset and localized rapidly to a new cortical site. Thus, ACMC impart new function for muscle control to a connected cortical sites and trigger cortical adaptation to regain impaired motor function after stroke.

ANC have clinical potential for restoring walking ability in patients with spinal cord injury (SCI). A clinical application of the ANC is the volitional walking could be restored by muscle-controlled non-invasive magnetic stimulation to lumbar spinal cord. Patients with severe SCI could control oscillated stimulation patterns of magnetic stimulation to lumbar locomotor circuits bellow the spinal lesion and regain voluntarily-controlled walking which initiate, stop walking and change the step cycles through ANC.

These paradigms have numerous potential applications, depending on the input signals, the computed transform and the output targets.



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Poster Session

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Cortico-striatal contributions to the basal ganglia

◎Hiromi Sano, Kenta Kobayashi, Satomi Chiken, Atsushi Nambu

(National Institute for Physiological Sciences)

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Inter-brain synchrony of neural oscillations: implications for the social basis of consciousness

◎Ana-Lucía Valencia[1, 2], Tom Froese[2]

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Optogenetic activation of the macaque motor cortex

◎Atsushi Nambu[1], Hidenori Watanabe[2], Hiromi Sano[1], Satomi Chiken[1], Kenta Kobayashi[1], Yuko Fukata[1], Masaki Fukata[1], Hajime Mushiake[2]

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Intracellular coupled feedback loops generate anti-phase oscillators of Drosophila circadian clocks

◎Md. Mamunur Rashid, Hiroyuki Kurata

(Kyushu Institute of Technology)

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Cortical excitability dynamically modulates in response to the exogenous stimuli at the epileptic focus: a single pulse electrical stimulation study at the site of stimulation

◎Shunsuke Kajikawa[1], Riki Matsumoto[2], Katsuya Kobayashi[3], Masao Matsuhahi[1], Tadashi Okada[1], Mayumi Otani[1], Masaya Togo[1], Yukihiro Yamao[1], Takayuki Kikuchi[1], Kazumichi Yoshida[1], Takeharu Kunieda[4], Ryosuke Takahashi[1], Akio Ikeda[1]

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Thalamocortical Axonal Activity in Motor Cortex Exhibits Layer-Specific Dynamics during Motor Learning

◎Yasuhiro R. Tanaka[1,2], Yasuyo H Tanaka[2], Yasuo Kawaguchi[3], Masanori Matsuzaki[2]

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Development and application of the multimodal ultra-thin endoscope for analyzing neuronal circuits in the deep brain region

◎Makoto Osanai[1, 2], Noriaki Ohkawa[3, 4], Yoshio Iguchi[5], Jun Yokose4, Shota Nakayama[4], Kaoru Inokuchi[4], Kazuto Kobayashi[5], Yoichi Haga[2], Hajime Mushiake[2]

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◎Yuchio Yanagawa (Gunma University)

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◎Adya Saran Sinha[1], Yasuyuki Takamatsu[2, 3], Tenpei Akita[1], Tatsuya Mima[2], Atsuo Fukuda[1]

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◎Song Ye[1], Keiichi Kitajo[2,3,4], Katsunori Kitano[1]

([1]Ritsumeikan University, [2]RIKEN Center for Brain Science, [3]National Institutes for Physiological Sciences, [4]The Graduate University for Advanced Studies (SOKENDAI))

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◎Toshihiko Aso

(RIKEN Center for Biosystems Dynamics Research）

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◎Hiroyoshi Inaba, Kohei Koide, Yuta Hattori, Hisaaki Namba, Hidekazu Sotoyama, Hiroyuki Nawa

(Niigata University）

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Intercortical network characteristics of seizure onset zone: a cortico-cortical evoked potential study

◎Masaya Togo[1], Riki Matsumoto[2], Nobutaka Mukae[3], Takuro Nakae[4], Katsuya Kobayashi[5], Kiyohide Usami[1], Takayuki Kikuchi[1], Akio Ikeda[1]

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The effect of transcranial static magnetic field stimulation over the premotor cortex or dorsolateral prefrontal cortex on reaction time

◎Nami Kubo[1], Daisuke Tsuru[1], XiaoXiao Chin[1], Tatsunori Watanabe[1], Tatsuya Mima[2], Hikari Kirimoto[1]

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The effects of transcranial static magnetic field stimulation over the supplementary motor area on the function of anticipatory postural adjustments

◎Daisuke Tsuru[1], Nami Kubo[1], Xiao Xiao Chin[1], Tatsunori Watanabe[1], Tatsuya Mima[2], Hikari Kirimoto[1]
([1]Hiroshima University, [2]Ritsumeikan University)

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Analysis of functions of the basal ganglia circuit using dopamine receptor and NMDA receptor mutant mice

◎Nae Saito[1], Kazuki Tainaka[1], Satomi Chiken[2], Satoshi Hara[3], Manabu Abe[1], Meiko Kawamura[1], Yoko Nabeshima[4], Yo-ichi Nabeshima[4], Shun Yamaguchi[5], Hiroshi Ichinose[3], Kenji Sakimura[1], Atsushi Nambu[2], Toshikuni Sasaoka[1]
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Behavioral oscillations in temporal attention

◎Tomoya Kawashima, Masamichi J Hayashi, Kaoru Amano
(National Institute of Information and Communications Technology)

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Information Theoretic Analysis of Epileptic Seizure in ECoG
- Cross Frequency Coupling and Information Transfer -

◎Hiroshi Yokoyama[1,7], Riki Matsumoto[2], Katsunori Kitano[3], Toshio Aoyagi[4] Masao Matsuhashi[4], Takayuki Kikuchi[4], Takeharu Kunieda[5], Akio Ikeda[4], Keiichi Kitajo[1,6,7]
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Cortico-striatal contributions to the basal ganglia

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The basal ganglia play important roles to regulate voluntary movements. Information for motor control is processing along the cortico-basal ganglia loop. The basal ganglia receive cortical inputs, process the information, and send it back to the cortex. In the current model of the basal ganglia, the striatum and subthalamic nucleus (STN) are inputs station of the basal ganglia and receive motor cortical inputs. Both of cortico-striatal and cortico-STN neurons are glutamatergic, and neither specific markers nor specific receptors are known. Therefore, it is difficult to selectively manipulate the input through cortico-striatal or cortico-STN neurons. To understand the functional differences between trans-striatal and trans-STN circuits, it is a key to examine how different information the cortex sends to the striatum and STN. In current our study, we applied optogenetics to reveal physiological and anatomical contributions of cortico-striatal neurons to the basal ganglia.

To express channelrhodopsin-2 (ChR2) in cortico-striatal neurons selectively, lentiviral vector termed neuron-specific retrograde gene transfer (NeuRet)[1)] was injected into the mouse striatum to express Cre recombinase in cortico-striatal neurons. Then, adeno-associated viral vector containing a double-floxed inverted open reading frame encoding ChR2 was injected into the motor cortex. ChR2 was expected to express specifically in cortico-striatal neurons and illumination of blue laser to the motor cortex has induced excitation in these neurons. Then we gave optical stimulation to the motor cortex and recorded neuronal activity in the external segment of the globus pallidus (GPe) and the substantia nigra pars reticulata (SNr), the relay and output nuclei of the basal ganglia, respectively. We observed triphasic response composed of early excitation, inhibition and late excitation. The early excitation and inhibition are mediated by cortico-STN-GPe/SNr and cortico-striato-GPe/SNr pathways, respectively[2, 3)]. These results suggest that cortico-STN as well as cortico-striatal projections were photo-stimulated. Nerve terminals of cortico-striatal neurons were visualized by ChR2, and found also in the STN. Our results suggest that cortico-striatal inputs are mediated by cortico-striatal neurons and collaterals of cortico-STN neurons.

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Inter-brain synchrony of neural oscillations: implications for the social basis of consciousness

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Cognitive processes require transient integration of several, widely distributed, and constantly interacting regions of the brain[1–3], achieved by the phase synchronization of neural oscillations. More specifically, coupled neural oscillations have been proposed to form the basis for the integration supporting the coherence of consciousness[2,4,5]. An open question would be whether similar forms of integration hold between two people in interaction.

A growing number of EGG-based hyperscanning studies have revealed that synchronous (phase coherent) oscillations appear across brains during social interaction. This synchrony is not attributable to a shared environment and selectively appears when cooperation, but not competition or individual task performance, is required[6]. This suggests that inter-brain synchrony is an emergent property of social dynamics, non-reducible to the activities of individual brains[7]. Furthermore, synchrony between brains is accompanied by subjective feelings of engagement, social connectedness, cooperativeness, and empathy[6].

The inter-personal nature of these findings fits particularly well with the enactive approach to cognitive science, which views the mind as arising through the dynamic of an organism acting in its environment; an environment that includes other beings with which an individual may interact and participate in dynamical, co-regulated, coupling[8]. This has implications for the concept of human nature.

We consider the possibility that, through mechanisms of neural synchrony between brains, the neural basis of consciousness could spatiotemporally extend beyond the limits of an individual brain into transient social collectives (during meaningful social interaction). Therefore, it is possible for individuals to form part of a larger co-regulated collective system, with its own coordination dynamics[9].

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Optogenetic activation of the macaque motor cortex

Atsushi Nambu[1], Hidenori Watanabe[4], Hiromi Sano[1], Satomi Chiken[1], Kenta Kobayashi[2], Yuko Fukata[3], Masaki Fukata[3], Hajime Mushiake[4]

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Optogenetics is a method to manipulate neuronal excitability by using genetically coded, light-gated ion channels or pumps in combination with light. Soon after introduction of optogenetics in 2002, it is widely used and has become one of indispensable tools to investigate the functions of the nervous system. Optogenetics has several advantages over classical tools, such as electrical stimulation and pharmacological manipulation, because it can excite or inhibit a specific population of neurons with high time resolution in the order of milliseconds. Optogenetics has been successfully used to modulate behaviors in rodents. However, its application in non-human primates is still rather limited. Optogenetic stimulation has been attempted to induce and/or modulate body and eye movements, which can be easily elicited by classical electrical intracortical microstimulation (eICMS) with weak currents. Eye movements can be successfully modulated by optogenetic activation or inactivation of the cerebral cortex. On the other hand, optogenetic stimulation of the motor cortices in monkeys failed to induce apparent body movements, although it activated or modulated cortical activity. This may be because opsins were not sufficiently expressed in neurons, and/or lights did not effectively penetrate the monkey brain tissue. Inducing movements by optogenetics is a very important next step in non-human primate research. In the present study, we have overcome these drawbacks by injection of effective viral vectors into the layer V of the identified primary motor cortex (M1) and by effective light delivery through optrodes that combine an optical fiber and recording and electrical stimulation electrodes. After these improvements, optogenetic intracortical microstimulation (oICMS) of the M1 successfully induced movements and muscle activity in the forelimb (Figure 1) that were comparable to those induced by eICMS. It also allowed us to record neuronal activity evoked by oICMS and compare the effects of oICMS and eICMS.

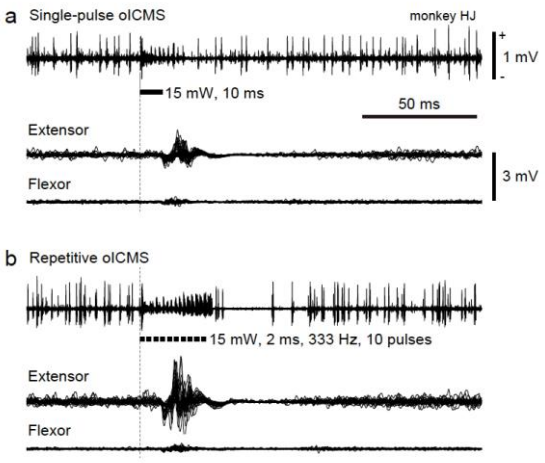

Figure 1. Simultaneously recorded M1 and muscle activities evoked by oICMS.

Intracellular coupled feedback loops generate anti-phase oscillators of *Drosophila* circadian clocks

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Keywords: Circadian rhythms, Coupled oscillator, Coupling strength, Coupling delay, Robustness

[Introduction]

Circadian rhythms are endogenous ~24 biological clocks, generated by interlocked transcriptional-translational negative feedback loops, provide robustness of oscillatory features such as phase, period and amplitude against external and internal variations. However, it remains unclear how these oscillatory features are simultaneously achieved. In this study, we investigated two distinct coupling networks of *Drosophila* circadian clocks; activator coupled oscillators (ACO) and repressor coupled oscillators (RCO). By examine the phase, period, and amplitude of the coupled oscillator, we identified two key parameters: "coupling strength" and "coupling delay" which play important roles in the robustness of oscillatory features.

[Biochemical network maps]

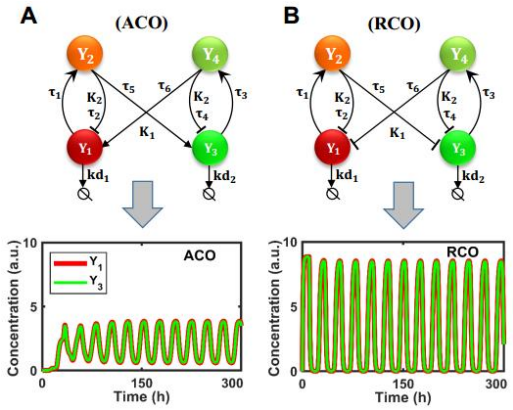

Fig. 1 The coupling structures of **ACO** and **RCO**

For considering oscillation dynamics, Hill-type delayed differential equations were employed for modeling. The ACO & RCO coupling has shown in Fig.1, where two negative feedback loops (PER-TIM: red colored & dCLK: green colored) are coupled through two mutual activators (Fig.1A) or repressors (Fig.1B), provides 24-hours oscillation.

[Results and Discussion]

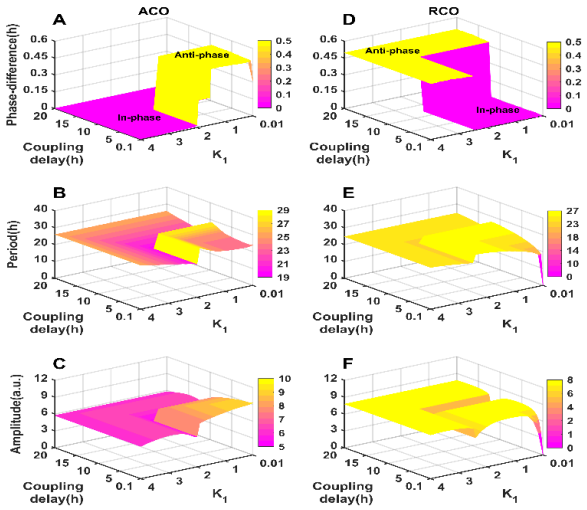

Fig. 2 The phase, period and amplitude dynamics

To assess stability of phase, period and amplitude, we varied two important parameters: the coupling strength (K_1) along with the coupling delay ($\tau_5 = \tau_6 = \tau$) simultaneously. Fig.2 shows the stability of phase, period and amplitude of ACO and RCO models. Both couplings show robust phase (Fig. 2A, D), where the period and amplitude robustness gained by RCO with different setting of coupling strength with coupling delays (Fig. 2E-F).

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Cortical excitability dynamically modulates in response to the exogenous stimuli at the epileptic focus: a single pulse electrical stimulation study at the site of stimulation.

Shunsuke Kajikawa[1], Riki Matsumoto[2], Katsuya Kobayashi[3], Masao Matsuhahi[4], Tadashi Okada[1], Mayumi Otani[1], Masaya Togo[1], Yukihiro Yamao[5], Takayuki Kikuchi[5], Kazumichi Yoshida[5], Takeharu Kunieda[6], Ryosuke Takahashi[1], Akio Ikeda[4]

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Introduction: Single pulse electrical stimulation (SPES) has been applied to study the functional brain and seizure networks as well as to study the cortical excitability at and around the epileptic focus. The latter could be further investigated by investigating high frequency activity (HFA) counterpart of the cortico-cortical evoked potential (CCEP). Here we overcame technical difficulties to investigate the neural responses at the site of stimulation to compare cortical excitability at the epileptic focus.

	Electrode type	Pulse width	Stimulation intensity and frequency	Stimulated electrode
Pt1 (BiTLE)	SEEG	0.3 ms	1, 4, 8 mA/0.5 Hz	Lt, Rt SOZ, control
Pt2 (BiTLE)	SEEG	0.4 ms	2, 4, 8 mA/0.5 Hz	Lt, Rt SOZ, 2 control
Pt3 (Lt TLE)	ECoG	0.3 ms	1, 2, 4, 8 mA/0.2 Hz	SOZ, control
Pt4 (Lt PLE)	ECoG	0.4 ms	2, 4, 8 mA/0.5 Hz	SOZ, irritative zone, control

Abbreviation: BiTLE: bitemporal epilepsy, Lt: left, PLE" parietal lobe epilepsy, Pt: patient, Rt: right, SOZ: seizure onset zone, TLE: temporal lobe epilepsy

Table1. Patient information

Methods: We recruited 4 patients with medically intractable partial epilepsy who underwent electrocorticography (ECoG) or stereo electroencephalography (SEEG) implantation for presurgical evaluation from December 2017 to July 2019 (IRB#C1212). SPES was delivered 60 times using a biphasic electrical pulse of 0.3 or 0.4 ms duration, when the patient was at rest and free of seizures. ECoG/SEEG was recorded with a DC EEG machine (gtec) at the sampling rate of 2400 Hz before and 2 ms after SPES using a special switching device (Miyuki Giken). SPES was delivered to the seizure onset zone (SOZ) and the control cortex at various intensities (Table 1). We averaged each stimulus epoch and performed short-time Fourier Transform (STFT) with a 100 ms window width (baseline -0.3~0.1 sec, analysis window 0-1.5 sec). We focused on the time frequency analysis after the timing of N1 (due to the artifacts) and analyzed the SPES-induced gamma (30-50 Hz), ripple (80-200 Hz), fast ripple (200-300 Hz) activities.

Results: When SPES was applied at a higher intensity, compared to the control cortex, SOZ stimulation revealed more prominent decrease, namely, neuronal inhibition in the gamma band (3 patients), the ripple band (all patients). The degree of inhibition tends to become less in stimulation at a lower stimulus intensity.

Conclusion: Our preliminary SPES study at the focus indicated that exogeneous input such as SPES could modulate the cortical excitability to suppress epileptic activities, which seems intensity-dependent. Further investigations including the behavior of the delayed response would further delineate the neural modulation by electrical stimuli.

Thalamocortical Axonal Activity in Motor Cortex Exhibits Layer-Specific Dynamics during Motor Learning.

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Through motor learning, animals acquire the skilled movements needed to accomplish their goals in everyday life effectively. In motor circuits, the dynamics of the neuronal ensemble in the primary motor cortex during motor learning require interactions with the basal ganglia and the cerebellum. The thalamus is the critical structure through which neural signals are transmitted from the basal ganglia and cerebellum to the motor cortex. To clarify the dynamics of neuronal activity transmitting the signals from subcortical structures to M1, we conducted two-photon calcium imaging of thalamocortical axonal activity in the motor cortex of mice learning a self-initiated lever-pull task. Through motor learning, the neural activity of thalamocortical axons became stable, and representation of the lever trajectories was improved. Layer 1 (L1) axons came to exhibit activity at lever-pull initiation and termination, while layer 3 (L3) axons did so at lever-pull initiation. We found that the sequence length in late sessions was longer in L1 than in L3. A more extended sequence in the L1 TC population activity implies that the population was engaged in lever pulls over a long time. Stimulation of the substantia nigra pars reticulata activated more L1 than L3 axons, whereas deep cerebellar nuclei (DCN) stimulation did the opposite. Lesions to either the dorsal striatum or the DCN impaired motor learning and disrupted temporal dynamics in both layers. Thus, layer-specific thalamocortical signals evolve with the progression of learning, which requires both the basal ganglia and cerebellar activities.

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Tanaka, Y.H., Tanaka, Y.R., Kondo, M., Terada, S.-I., Kawaguchi, Y., and Matsuzaki, M. (2018). Thalamocortical Axonal Activity in Motor Cortex Exhibits Layer-Specific Dynamics during Motor Learning. Neuron *100*, 244-258.e12.

Development and application of the multimodal ultra-thin endoscope for analyzing neuronal circuits in the deep brain region

Makoto Osanai[1,2], Noriaki Ohkawa[3,4], Yoshio Iguchi[5], Jun Yokose[4], Shota Nakayama[4], Kaoru Inokuchi[4], Kazuto Kobayashi[5], Yoichi Haga[6], Hajime Mushiake[2]

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Central nervous system has a hierarchical structure consisted with neurons, local neuronal circuits and large-scale network. To elucidate the function expression mechanisms of brain with hierarchical structure, we are developing the multimodal and multiscale brain function analysis concept. In this concept, a mesoscopic functional analysis tool which connects the analysis results obtained from in vivo and in vitro is important. Therefore, we are developing the multimodal ultra-thin endoscope (Fig 1). This endoscope system consisted with the ultra-thin fluorescence endoscope imaging system and the multi-electrode array on the zirconia tube, allowing simultaneous optical imaging and electrophysiological recording at deep brain region.

The fluorescence endoscope part had a diameter of 450 μm and a spatial resolution of about 2 μm. We succeeded multicellular activity recording in the hippocampus of Thy1-G-CaMP7 mouse using this endoscope (Fig 2).

The multi-electrode part had six electrodes around the end of the zirconia tube, which can be inserted the endoscope (figure 3). This multi-electrode can record the field potential from the rat brain (figure 3).

By combining an endoscope and multiple electrodes, we aim to elucidate the relationship between cellular activity and ensemble activity.

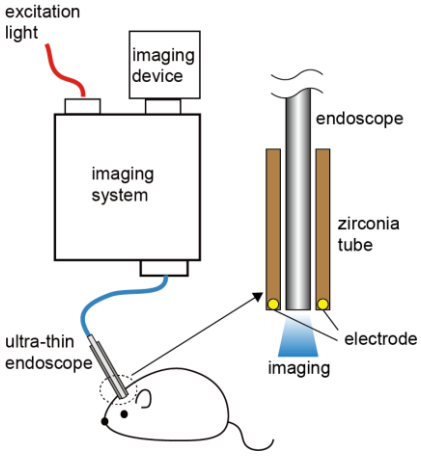

Figure 1: Schema of the multimodal endoscope. (Right panel) Probe of the endoscope.

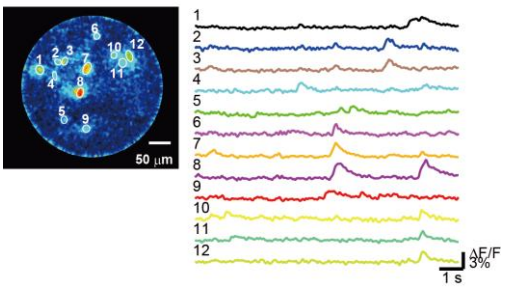

Figure 2: Multicellular activity recording from mouse hippocampal neurons.

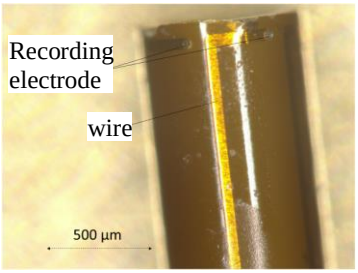

Figure 3: The multi-electrode array.

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Development of transgenic rodents for elucidating the role of GABA in neural oscillation

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GABA is a major inhibitory neurotransmitter in the adult mammalian CNS. GABA is implicated in pathophysiology of psychiatric disorders such as epilepsy, schizophrenia, autism spectrum disorder and anxiety disorder as well as neurological disorders such as Huntington disease and anti-GAD antibody encephalopathy. Cognitive dysfunction and neural oscillation impairments are found in patients with schizophrenia. High frequency oscillations were recorded on epileptic tissues of rats and humans. Glutamate decarboxylase (GAD) is the rate-limiting enzyme that catalyzes the production of GABA from glutamate. The two GAD isoforms, GAD65 and GAD67 are encoded by different *GAD2* and *GAD1* genes, respectively. These isoforms are distinguished by their molecular masses, their cofactor interaction and subcellular distribution. Recently Magri et al. reported patients from a schizophrenia family that was homozygous for a mutation in the *GAD1* gene (Magri et al. 2018). The GAD67 and/or GAD65 expression levels are decreased in cerebral cortex and hippocampus of patients with schizophrenia from the postmortem brain study (Akbarian & Huang, 2006). Anti-GAD antibody encephalitis consists of epilepsy, ataxia and cognitive dysfunction, and anti-GAD65 antibody is detected in serum of the patients. In order to clarify the role of GABA in oscillation and the relationship between GAD isoforms and pathophysiology of schizophrenia or epilepsy, we developed novel *Gad1* and *Gad2* knockout (KO) rats using genome editing technology, and characterized their phenotypes.

Gad2 KO rats exhibit epileptic seizures followed by death around the weaning period. The *Gad2* KO rats show abnormal EEG coincident with the seizures. These results suggest *Gad2* KO rats will be a useful model animal for epilepsy research and treatment.

Gad1 KO rats weigh less than their wild-type littermates at weaning stage, but achieve normal body size by adulthood. The *Gad1* KO rats are hypoactive in open field test, but change to hyperactive in a special environment such as forced swim test. They display deficits in spatial reference and working memory in Morris water maze and radial maze tests, respectively, suggesting that GAD67-mediated GABA plays an important role in cognitive function. EEG experiments will be performed to determine whether oscillation is impaired in *Gad1* KO rat brains.

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Static magnetic fields decrease excitability of pyramidal neurons by increasing membrane Cl^- conductance in the mouse motor cortex.

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Advances in technology have ushered in newer applications of electromagnetic fields in all spheres of life ranging from mobile technology to high resolution medical imaging using magnetic fields up to 7 Tesla(T).Previous reports suggested that exposure of normal human subjects to static magnetic fields (SMF) reduced neuronal excitability in their motor cortex. This effect persisted ~ 10 min after termination of the exposure (Oliviero et al., 2011).

Here, we investigated the excitability of motor cortical neurons exposed to SMF. Using acute brain slices (350μm thick) including the motor cortex from 3 weeks old C57BL/6J male mice; we examined in detail the effect of SMF exposure on the excitability of layer II/III pyramidal neurons in the motor cortex. SMF of 0.3 T was applied with a neodymium (NdFeB) magnet for 30 min. Following application of SMF, current clamp recordings were performed for evaluating both passive and active membrane properties at 10 min and 20 min respectively.

Using a standard low Cl^- (14 mM) patch pipette solution, we found that SMF exposure reduced membrane input resistance without affecting the resting membrane potential (RMP) at 10 min after the exposure in pyramidal neurons. This caused the increase in rheobase, minimum stimulation current required for eliciting an action potential (AP), and the decrease in frequency of APs in response to a given current stimulus. In addition, some neurons appeared to swell after the exposure. These effects were attenuated at 20 min. The AP waveform was, however, unchanged by the exposure. The swelling of neurons were thought to be associated with increase in Cl^- conductance and explain the reduction in input resistance. Therefore, to confirm we used a high Cl^- (154 mM) pipette solution and found that RMP was significantly depolarized at 10 min after SMF exposure. The increased rheobase and the decreased AP frequency were reproduced in this condition. However, the amplitude and the slope of upstroke of APs were reduced while the downstroke and half-width of APs were unchanged in this condition. These changes were found to be sensitive to the block of DIDS, a non-selective chloride channel blocker.

Together, these results strongly suggest that SMF temporarily suppresses the excitability of pyramidal neurons by enhancing the membrane Cl^- conductance of these neurons.

Reference:

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Information-theoretic approach to detect directional information flow in EEG signals induced by TMS

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Effective connectivity analysis has been widely applied to noninvasive recordings such as functional magnetic resonance imaging and electroencephalograms (EEGs). Previous studies have aimed to extract the causal relations between brain regions, but the validity of the derived connectivity has not yet been fully determined. This is because it is generally difficult to identify causality in the usual experimental framework based on observations alone. Transcranial magnetic stimulation (TMS) provides a framework in which a controllable perturbation is applied to a local brain region and the effect is examined by comparing the neural activity with and without this stimulation[1)]. This study evaluates two methods for effective connectivity analysis, symbolic transfer entropy (STE)[2)] and vector autoregression (VAR)[3)], by applying them to TMS-EEG data. In terms of the consistency of results from different experimental sessions, STE is found to yield robust results irrespective of sessions, whereas VAR produces less correlation between sessions. Furthermore, STE preferentially detects the directional information flow from the TMS target. Taken together, our results suggest that STE is a reliable method for detecting the effect of TMS, implying that it would also be useful for identifying neural activity during cognitive tasks and resting states.

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Origin of the slow oscillation lag structure in fMRI data

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Whether they are of neural or autoregulatory origin, fMRI signal response has been uniformly postulated to reflect increased cerebral blood flow (CBF) and eventual dilution of deoxy-hemoglobin (Hb), with additional minor CBV effects (Kim & Ress, 2016. NeuroImage). The spontaneous BOLD low-frequency oscillation (sLFO, < 0.1 Hz) encompassing multiple noise sources is a focus of recent studies on fMRI artifact (Tong 2017). Our hypothesis is that this sLFO originates from axial variation of the blood deoxy-Hb supply that has long been overlooked.

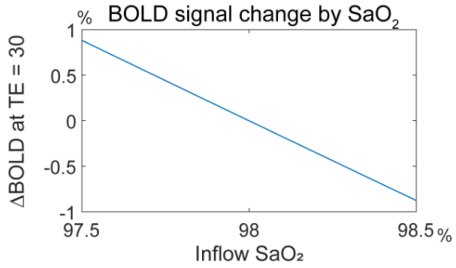

Figure 1 : Result X

A typical model of the BOLD signal change is

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1 - \left(\frac{CMRO_2}{CMRO_2|_0}\right)^{\beta}\left(\frac{CBV}{CBV_0}\right)\left(\frac{CBF}{CBF_0}\right)^{-\beta}\right)$$

$$M \equiv TE \cdot B_0 \cdot CBV_0 \cdot [deoxy\text{-}Hb]_{V0}^{\beta}$$

under the assumption of a negligible deoxy-Hb inflow. M is the factor for the BOLD susceptibility effect where B_0 is the magnetic field strength. Triggered by vasodilation of the arteriole, this effect is diminished by an inflow of fresh blood, which increases the MR signal. The baseline BOLD effect has been modeled in the formula of off-resonance frequency shift (δω):

$$\delta\omega = \gamma \cdot \frac{4}{3} \cdot \pi \cdot \Delta\chi_0 \cdot Hct \cdot OEF \cdot B_0$$

where γ is the gyromagnetic ratio (42.58 MHz/T), $\Delta\chi_0$ is the susceptibility difference between the fully oxygenated and fully deoxygenated blood, and Hct is the volume fraction of erythrocytes to the blood volume, typically around 40%. The oxygen extraction fraction (OEF) represents the only source of deoxy-Hb under the assumption of 100% oxygen saturation (SaO_2) in the inflow.

Thus the 100%-oxygenation assumption is firmly determining the current model. However, SaO_2 cannot reach 100% in room air in the first place. Besides, presence of axial inhomogeneity is compatible with various phenomena such as CO2 and pH fluctuations, since oxygen saturation of hemoglobin is sensitive to blood pH. Moreover, accompanying vaso- or flowmotion might also create Hct variation along the vessels that can directly cause deoxy-Hgb gradient. And most importantly it provides physiological account of the spontaneous low-frequency oscillations (sLFOs) and the "lag structure" embedded in fMRI data.

In this study, we conducted analyses furthering the hypothesis that the sLFO is not only largely of systemic origin, but also essentially intrinsic to blood, and hence behaves as a virtual tracer. By summing the small fluctuations of instantaneous phase differences between adjacent vascular regions, a velocity response to respiratory challenges was detected. Regarding the relationship to neurovascular coupling, removal of the whole lag structure resulted in a reduction of inter-individual variance while preserving the fMRI response. Examination of the T2* and S_0, or non-BOLD, components of the fMRI signal revealed that the lag structure is deoxy-hemoglobin dependent, while paradoxically presenting a signal-magnitude reduction in the venous side of the cerebral vasculature. More supporting evidence will be presented.

Ref. Aso, et al. (2019) "*Axial variation of deoxyhemoglobin density as a source of the low-frequency time lag structure in blood oxygenation level-dependent signals*". PLoS One

A schizophrenia rat model induced by an inflammatory cytokine exhibits abnormal beta synchronization to auditory steady-state stimuli

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(Dept of Molecular Neurobiology, Brain Research Institute, Niigata University)

Introduction

Abnormal neural oscillation has been suggested to cause deficits of attention and sensory processing seen in patients with schizophrenia. The gamma and beta frequency bands are considered relevant for these processing. schizophrenia is characterized by reduction in the auditory steady-state response (ASSR) to gamma frequency stimuli[1]. Moreover, some studies have shown abnormal increases in beta synchronization to beta frequency stimuli[2]. We have previously shown that perinatal administration of epidermal growth factor (EGF) induces schizophrenia-like cognitive, behavioral, and physiological abnormalities during the post-pubertal stages in various animals including rats[3,4]. In this study, we investigated whether this rat model shows impairment of the ASSR to gamma and beta frequency stimuli.

Methods

Electrocorticography electrodes were placed on the auditory and frontal cortices. Waveforms to auditory steady-state stimulation (20, 30, and 40 Hz clicks, 80 dB) were recorded under awake conditions. Event-related spectral perturbation (ERSP) and inter-trial phase coherence (ITPC) were calculated for each stimulation session.

Results

In the 20-Hz session, the ERSP and the ITPC recorded at the auditory cortex were increased in the EGF rats compared to controls in the beta frequency range. On the other hand, in the 40-Hz session, the ERSP and the ITPC were not different between groups in the gamma frequency range. The ASSR was not observed from the waveforms recorded in the frontal cortex in both groups. These results suggest that neonatal exposure to EGF results in abnormal increases in beta range auditory entrainment in the auditory cortex. Therefore, the abnormality may be a translational biomarker for schizophrenia common to humans and rodents.

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Intercortical network characteristics of seizure onset zone: a cortico-cortical evoked potential study

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Introduction: The modification of epileptic activity on brain connectivity remains a matter of debate. Although some studies showed seizure onset zone (SOZ) evoked higher response amplitude in cortico-cortical evoked potential (CCEP) (Iwasaki et al., 2010), the study on the network characteristics are sparse (Keller et al.,2014). In the present study, we focused on the intercortical connectivity involving SOZ by means of CCEP with subdural grid electrodes.

Subjects and Methods: Subjects were 11 patients with intractable focal epilepsy who underwent implantation of intracranial electrodes in the inferior frontal area for presurgical evaluation (IRB#C1062, C1212).

Single-pulse electrical stimuli (1 Hz, pulse width 0.3 msec, 6-12 mA) were delivered to the whole neighboring pairs of electrodes in each patient. We extracted the responses with z-score of more than 6 and latency of less than 50 ms. Based on the results, we calculated an adjacency matrix and illustrating networks (Figure 1) and analyzed the normalized inbound/outbound connectivity in each electrode.

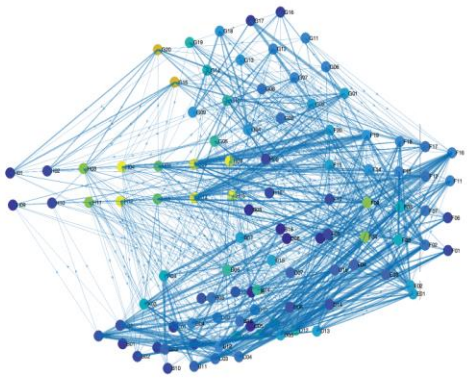

Figure 1: Intercortical network of CCEP responses in one patient

Results: SOZ did not show the significant differences in both indegree/outdegree compared to the non-SOZ (Figure 2). SOZ in each cortical parcellation such as the entorhinal cortex also did not show a significant difference in indegree/outdegree.

Conclusion: Connectivity analysis with CCEP responses did not show a significant difference in SOZ. The findings suggested epileptic activity does not affect the global intercortical network structures. Since we did not consider the amplitude of CCEP for the present analysis, modulation of the amplitude or the strength of connectivity is a subject of further investigation.

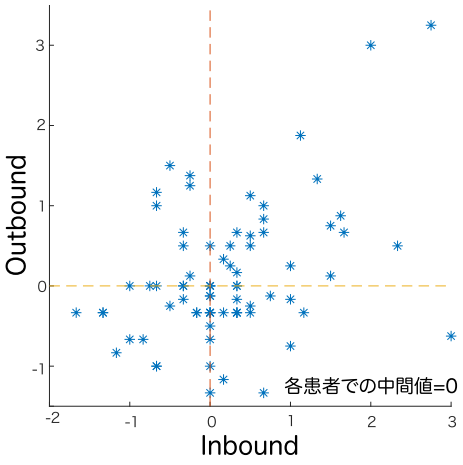

Figure 2: Indegree/outdegree of SOZ

References

The effect of transcranial static magnetic field stimulation over the premotor cortex or dorsolateral prefrontal cortex on reaction time

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Previous studies have reported that transcranial static magnetic field stimulation (tSMS) reduces excitability of the cortex such as the primary motor cortex (M1)[(1)] and the somatosensory cortex (S1)[(2)]. However, the effect of tSMS over the premotor cortex (PM) and dorsolateral prefrontal cortex (DLPFC) on cognitive process is still unclear. Given that the PM and DLPFC contribute to recognition and processing of sensory information, we investigated the effect of tSMS over the PM or DLPFC on the reaction time (RT) to a visual stimulus. Seventeen healthy volunteers completed two tasks: the simple RT task, in which they extended their wrist when the blue lamp lit up, and go/no-go (GNG) task, in which they extended their wrist when the blue lump lit up but hold the response when the red lamp lit up. For the simple RT task, tSMS or sham stimulation was applied to the PM (left, right or both hemisphere). For the GNG task, tSMS or sham stimulation was applied to DLPFC (F3 or F4 according to international 10-20 system). Each task was performed before, during and after 30 minutes application of tSMS. Figure 1 shows average RTs for each stimulation condition and time point. The 2-way ANOVA (stimulation condition × time) on the RT revealed no significant main effects or interaction. These results indicate that RT is not altered by tSMS applied over PM and DLPFC. Considering the various neural networks that are related to visuo-motor and cognitive processing, we suppose, even if tSMS have impaired the functions of the PM and DLPFC, the impairment might have been compensated by the other system. The effect of tSMS over the PM and DLPFC on RT may be apparent when more complex cognitive tasks are used.

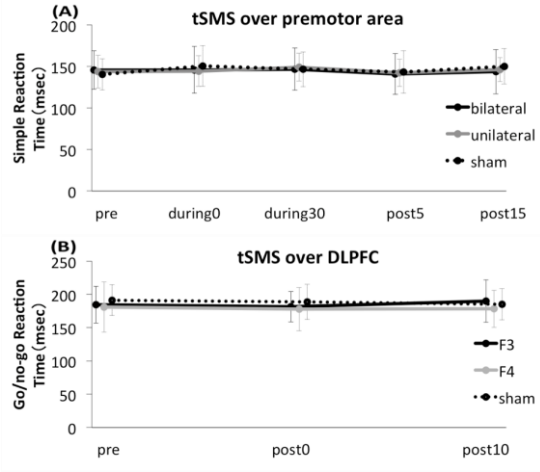

Figure 1. No change in RT was observed before and after tSMS in simple or go/no-go reaction time task.

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The effects of transcranial static magnetic field stimulation over the supplementary motor area on the function of anticipatory postural adjustments

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It has been demonstrated that transcranial static magnetic field stimulation (tSMS) can directly induce a reduction of cortical excitability in the motor [1)], somatosensory [2)], and visual systems of humans. However, the effect of tSMS over the supplementary motor area (SMA) is unclear. The SMA is suggested to contribute to the generation of anticipatory postural adjustments (APAs), which act to stabilize supporting body segments prior to movement. This study was performed to elucidate whether tSMS applied over the SMA modifies the function of APAs. tSMS and sham stimulations were applied over the SMA for 20 min in 18 healthy subjects. The subjects performed a self-paced rapid shoulder flexion task before, immediately, and 10 min after application of tSMS. Electromyographic (EMG) activity was recorded from the deltoid anterior (DEL_A), as the prime mover muscle, and biceps femoris (BF), as the postural muscle during the tasks. EMG latency difference (⊿EMG onset) between two muscles were calculated by subtracting the EMG burst onset of the BF from that of the DEL_A. Figure 1 shows the representative EMG waveforms before and 20 min after application of tSMS over the SMA. The ⊿EMG onset was significantly shortened after application of tSMS, but not after the sham stimulation. We demonstrated that tSMS over the SMA could inhibitively modulate the APAs function. tSMS may be an effective non-invasive brain stimulation tool to suppress excessive activity of the SMA, for example, in patients who have such neurological disorders as Parkinson's disease and Gilles de la Tourette syndrome.

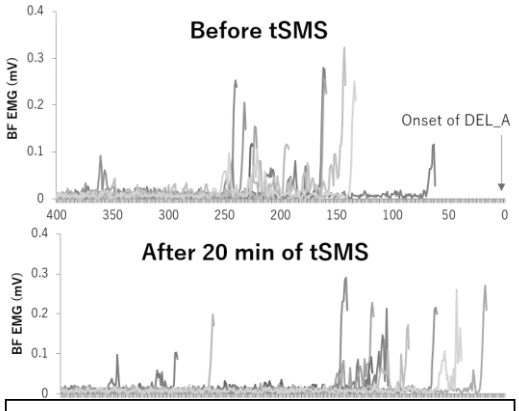

Fig. 1 Electromyography waveforms in the BF during a self-paced rapid shoulder flexion task for a representative case.

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Analysis of functions of the basal ganglia circuit using dopamine receptor and NMDA receptor mutant mice.

Nae Saito[1], Kazuki Tainaka[1], Satomi Chiken[2], Satoshi Hara[3], Manabu Abe[1], Meiko Kawamura[1], Yoko Nabeshima[4], Yo-ichi Nabeshima[4], Shun Yamaguchi[5], Hiroshi Ichinose[3], Kenji Sakimura[1], Atsushi Nambu[2], Toshikuni Sasaoka[1]

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Parkinson's disease (PD) is a neurological disorder that exhibits tremor, dyskinesia, rigidity and non-motor symptoms such as cognitive impairment and depression. PD is caused by impairment of dopaminergic neurotransmission due to degenerative loss of midbrain dopaminergic neurons. PD as well as Alzheimer's disease are fairly common in the elderly, and thus, elucidation of pathophysiology underlying symptoms of PD is urgent to develop better treatments and preventive measures. Midbrain dopaminergic neurons mainly project to the striatum, a main input station of the basal ganglia. In the striatum, there are two types of projection neurons: "direct pathway" neurons that express dopamine D1 receptors (D1R) and project to the internal segment of the globus pallidus and "indirect pathway" neurons that express dopamine D2 receptors (D2R) and project to the external segment of the globus pallidus. However, details of dopamine functions via D1R and D2R in information processing through the basal ganglia remain unclear.

To understand neural mechanisms of motor and non-motor symptoms of PD and the roles of dopamine in information processing through the basal ganglia, we developed novel D1R knockdown (KD) mice in which D1R expression can be reversibly regulated. Suppression of D1R expression using doxycycline (Dox) administration decreased their spontaneous motor activity and impaired their motor ability. It depressed neurotransmission through the direct pathway. A few days after termination of Dox administration, spontaneous motor activity temporarily increased by several times, and then returned to normal levels in a few days. To investigate the mechanism of such rebound motor activity, we analyzed contents of dopamine and various metabolites at several time points: before Dox administration, and just after and three days after termination of Dox administration for four weeks. In addition, we performed several behavior tests and observed the neural activity after passive avoidance test using the whole brain imaging technique using Arc-dVenus, D1RKD crossbred mice. When D1R expression was suppressed with Dox treatment, mice performed poorly on the passive avoidance test. Without Dox treatment, aversive stimuli caused high dVenus expression in the hippocampus and the cerebral cortex of Arc-dVenus D1RKD mice. However, Dox treatment decreased dVenus expression. These results suggest that D1R-mediated dopaminergic transmission is critical to aversive memory formation, specifically through influencing *Arc* expression in the cerebral cortex.

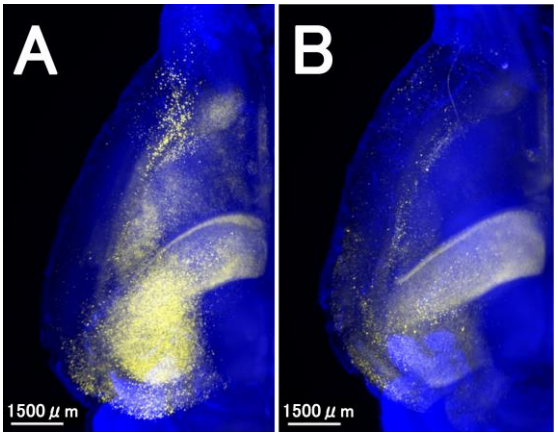

Figure1: The horizontal views of the 3D-reconstituted whole-brain images of Arc-dVenus D1RKD mice after delivery of electric footshock (left hemispheres of the brains are shown). (A) High dVenus signals were found in the hippocampus and the cerebral cortex of the mice without Dox treatment; (B) dVenus signals of mice with Dox treatment. Signals in the cerebral cortex were decreased. Nuclear staining is in blue.

Reference

1) Saito *et al*. Neurotransmission through dopamine D1 receptor is required for aversive memory formation and Arc activation in cerebral cortex. (Submitted)

Behavioral oscillations in temporal attention

Tomoya Kawashima, Masamichi J Hayashi, Kaoru Amano
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Recent studies have suggested that the visual inputs might be sampled at the theta-rhythmic cycle [1]. Typically, Landau and Fries [2] asked participants to detect a target presented within one of the two drifting gratings in the left and right visual fields. The flash event was used to attract attention to one of the locations. They evaluated the time course of detection accuracy as a function of the target timing with respect to the cue onset. Results showed behavioral oscillation: target detection in the same visual field as the flash was fluctuated at approximately 4 Hz. Thus, attention driven in a bottom-up fashion shows rhythmic sampling.

Here we examined whether rhythmic sampling also exists for top-down attention. Instead of just exposed by a cue to detect a target, we asked subjects to select two targets in succession, which is known to cause the attentional blink [3]. Thus, our participants had to attend the first target endogenously and then sample the second target.

31 and 30 (two were removed due to task performance) students participated in Experiment 1 and 2, respectively. In Experiment 1, they were asked to detect two successive targets (T1 and T2) with the masks, which is similar to the previous settings except that first event must be selected and two events were presented at the same location. In Experiment 2, to mainly test behavioral fluctuation of top-down attention, we presented T1 and T2 within the rapid serial visual presentation (RSVP) streams. The lag between T1 and T2 was set from 100 to 1000 ms in steps of 20 ms. The temporal profile of the accuracy was calculated as a function of T1-to-T2 lag.

Spectrum analysis showed that T2 detection accuracy fluctuated rhythmically in theta-cycle regardless of whether or not T1 was correctly reported in Experiment 1 (3.6–4.7 Hz for T2|T1 correct, and 2.5–4.0 Hz for T2|T1 error). Thus, we confirmed the rhythmic sampling even when two targets presented at the same place must be selected in succession.

Results in Experiment 2, where the targets were embedded in RSVP streams, revealed that T2 detection accuracy fluctuated in 7.2–9.1 Hz when T1 was correctly detected, and in 2.2–4.3 Hz and 5.8–6.6 Hz when T1 was missed. These results showed that, when top-down attention was required to ignore distractors and select targets, T2 detection performance fluctuated at faster cycle (about 8 Hz) when T1 was detected. This oscillatory property resembles alpha cycle (8–13 Hz), which plays a key role in sensory suppression in visual cortex [4]. In summary, we observed different frequency of rhythmic sampling of endogenously oriented attention which depends on the degree of top-down attention. Further works are needed to evaluate the underlining neural mechanisms.

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Information Theoretic Analysis of Epileptic Seizure in ECoG
- Cross Frequency Coupling and Information Transfer -

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Introduction

The purpose of this study is understanding how the neuronal information transfer during epileptic seizure is reflected in the oscillatory activity in brain wave. The studies on electrocorticography (ECoG) suggest that the interaction between slow and fast oscillations might be associated with the mechanism of the epileptic seizure [1, 2]. We hypothesized that the seizure-specific anomaly information transfer between slow and fast oscillations exists. In order to test this hypothesis, information theoretic analysis is useful. Applying the transfer-entropy (TE) analysis, we evaluate the directional information transfer between slow and fast oscillations in the ictal onset area.

Methods

Two patients, who underwent a pre-surgical evaluation for epilepsy with subdural electrodes, participated in this study. Phase-amplitude coupling (PAC) and TE analyses were applied to identify the following things: 1) frequency bands of coupling and, 2) directional cross-frequency information transfer.

Results and Discussions

As a result, the existence of the significant PAC between delta and HFO in the epileptogenic zone was found during 30s after the onset of the seizure. The delta-HFO coupling strength during the ictal state was drastically larger than the inter-ictal state in both patients. Interestingly, the bi-directional information transfer between delta phase and HFO amplitude-phase was increased during the ictal state, relative to the inter-ictal state. The results support our hypothesis that anomaly information transfer between slow and fast oscillations exists during epileptic seizure.

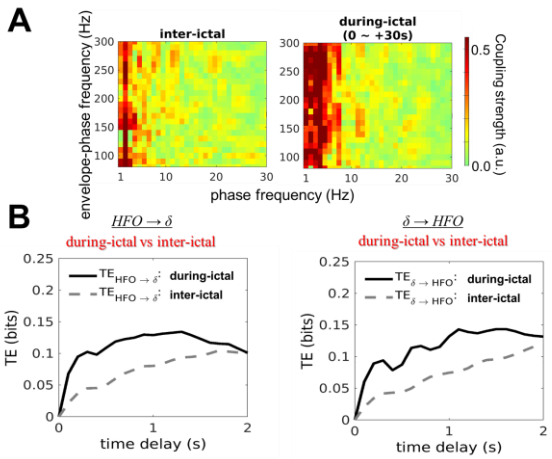

Figure 1: Typical result (Patient 1)
(A) PAC, (B) TE.

References

1) Edakawa et al, *Sci. Rep.* (2016)
2) Imamura et al, *Clin. Neurophysiol.* (2011)