Poster Session Abstracts

The Joint Symposium of WPI-IIIS, Ph.D. Program in Humanics,
and 36th Takamine Conference
Fusion of Biomedical and Physical/Informational Sciences in Neurobiology

Data Blitz by Poster Presenters	**15:40 – 16:10**
Poster Session	**16:10 – 16:50**

Poster list

P01

Analysis of gait motion change by intervention using robot suit HAL in acute and chronic stage myelopathy patients decompression surgery

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The ossification of the Posterior Longitudinal Ligament (OPLL) is a degenerative spine disease that can cause motor disorder. Even after appropriate surgical decompression, there are some residual motor impairments could be left. The Hybrid Assistive Limb (HAL) is a wearable powered suit to assist and support users voluntary control of hip and knee joint motion by detecting bioelectric signals from surface of their skin and from force/pressure sensors in the shoes during their movement. In the current study, the HAL intervention was applied to 5 acute and 7 chronic phase of OPLL patients who generated myelopathy after decompression surgery, and their gait before and after intervention was compared.There were significant improvements in gait speed, cadence, stride length, swing time. Peak comparison of joint angles of leg was used to evaluate the limb movement during the gait; Range of movement (ROM) of hip joints, knee joints, foot joints, and toe lift have increased significantly, and double knee action has appeared after HAL intervention. ROM of Elevation angle in thigh, shank, and foot has enlarged increased significantly. Improvement in all the angles above except ROM of foot joint was observed for the chronic patients. HAL training enable patients to do repetitive training without giving stress on knee joints, so that lead them to learn and control knee muscles correctly. Importantly, instead of gaining knee hypertension that is common gait impairment for OPLL, double knee action has appeared after the HAL intervention and it leads to smoother and healthier gait motion.

P02

Maladaptation in a redundant motor task is caused by history dependency of error-backpropagation capability

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A fundamental, yet poorly understood problem in human motor learning – as well as motor recovery – is redundancy: the dimensionality of the cortical representation of motor commands is far larger than that of the end-effector. However, traditional motor adaptation studies rely on experimental paradigms that do not take redundancy into account.

A computational theory called distal-learning predicts that the brain learns a structure of how to transform a visual error in the task space into an appropriate motor adaptation signal (called error-backpropagation) simultaneously with the learning of a controller.

We examine this prediction in a redundant motor task. We define two perpendicular control environments, A and B, in a multidimensional motor command space (task-relevant motor commands in A are task-irrelevant in B, and vice-versa), using hand gestures (acquired with a 14-DOF data glove) to control a cursor in a 2D screen. Subjects experience either control environment A for two days (AA group, N = 4) or A on day one and B on day two (AB group, N = 4). Learning to manipulate the cursor progressed well on both conditions and days, but AB group subjects could not adequately learn the error-backpropagation structure of B on day two, which goes against the prediction of the distal-learning theory.

Our result suggests that forming the error-backpropagation structure is strongly influenced by the previous experience on a different control environment, which may lead to maladaptation in a redundant motor learning problem such as motor recovery after stroke.

P03

Optimizing learning rate by meta-learning to maximize reward in visuomotor learning

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Both human and animals accelerate learning in a variety of tasks and environments, yet its underlying mechanism is unclear. In machine learning, regulation of learning rate is achieved by reinforcement meta-learning to maximize reward. If the same algorithm underlies regulation of motor learning rate, the relationship between motor learning and reward should determine how a learner changes learning rate. Here, we implemented a reinforcement meta-learning problem in a visuomotor arm-shooting task. Specifically, human participants first observed sensory prediction error induced by rotation of cursor feedback during movement in one trial, and then the degree of learning from the error (aftereffect) was evaluated with monetary feedback in subsequent trials. By manipulating the relationship between learning and reward, we demonstrated that learning was accelerated over training when fast learning yielded more reward compared to when fast learning yielded less reward (p = .01), and the effect remained transiently after reward was removed (p = .04). The results support regulation of motor learning rate by reinforcement learning, suggesting that people optimize learning rate by learning (meta-learning) to maximize reward. As growing evidence from neuroimaging research suggests that the cerebellum is sensitive to not only sensory error for motor learning but also reward, we speculate that the cerebellum may interact with the reinforcement learning system (e.g., cortico-basal ganglia) for tuning motor learning rate and increasing reward from the environment.

P04

Sensorimotor Learning from Out-of-Body Viewpoint via the Avatar in Virtual Reality

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It is effective to use mental imagery for or see one's own body movement in order to improve motor skills. This perspective is stated as an out-of-body viewpoint. Recently engineers implemented new devices by which it is possible to obtain visual feedback of the user's posture and body movement (i.e. "self-image") via the avatar in a virtual reality (VR) environment [Hamanishi et al., 2019]. This system has an advantage in monitoring the self-image on using mirrors or video recording since it can provide online visual feedback from free viewpoint. However, it remains unclear how and to what extent the out-of-body viewpoint contributes to sensorimotor learning. Here we devised a novel visuomotor adaptation task in the VR space where the participants observed a self-body motion from the out-of-body viewpoint (i.e. the third-person perspective) via the avatar. In addition, we asked the participants to conduct another cognitive task measuring the individual's ability to take other's point of view (Spatial Perspective Taking, SPT). Estimating parameters involved in the state-space model for sensorimotor learning based on the dual-rate learning process (Smith et al., 2006), we examined the relations of each parameter and the performance of the cognitive task. The results indicated that in the computational model SPT was important for processing errors, but not for learning or retention factors.

P05

MC-SleepNet: Large-scale Sleep Stage Scoring in Mice by Deep Neural Networks

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Automated sleep stage scoring for mice is in high demand for sleep research, since manual scoring requires considerable human expertise and efforts. The existing automated scoring methods do not provide the scoring accuracy required for practical use. In addition, the performance of such methods has generally been evaluated using rather small-scale datasets, and their robustness against individual differences and noise has not been adequately verified. This research proposes a novel automated scoring method named "MC-SleepNet", which combines two types of deep neural networks. Then, we evaluate its performance using a large-scale dataset that contains 4,200 biological signal records of mice. The experimental results show that MC-SleepNet can automatically score sleep stages with an accuracy of 96.7% and kappa statistic of 0.94. In addition, we confirm that the scoring accuracy does not significantly decrease even if the target biological signals are noisy. These results suggest that MC-SleepNet is very robust against individual differences and noise. To the best of our knowledge, evaluations using such a large-scale dataset (containing 4,200 records) and high scoring accuracy (96.7%) have not been reported in previous related studies.

P06

Characterization of sleep architecture in CDKL5 knockout mice

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CDKL5 deficiency disorder (CDD) is a devastating X-linked neurodevelopmental disorder caused by pathogenic mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene. Patients with CDD display a variety of clinic symptoms that include early-onset refractory seizures in the first months of life, developmental delay, intellectual and motor disabilities, cortical visual impairment, and autistic-like symptoms. The majority (>86%) of patients have severe sleep problems, which greatly affect the quality of life for patients and their families. To gain insight into the pathogenesis of CDKL5-related diseases, several CDKL5-deficient mouse models have been generated. These mice recapitulated many aspects of human CDD symptoms, and exhibited impaired learning and memory, motor and visual dysfunction, and autistic-like phenotypes. However, little is known about their sleep phenotypes. We characterized baseline sleep/wake patterns and recovery sleep following sleep deprivation in adult *Cdkl5* knockout male mice and their wild-type (WT) littermates by electroencephalography and electromyography. CDKL5-null mice exhibited increased sleep latency, less overall sleep time, shorter sleep episode duration and frequent awakenings compared to WT mice which resemble sleep disturbances observed in human CDD patients. Our results suggest that the *Cdkl5* knockout mouse model may be a useful genetic model for studying sleep disruptions in CDD patients.

P07

Increased non-REM sleep in mice expressing mutant *Sik3* in postnatal neurons using newly developed *Synapsin1*^{CreERT2} mice

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Sleep amount is regulated in a homeostatic manner so that the drive for sleep become stronger after sleep deprivation. Despite empirical evidence of homeostatic regulation of sleep, the molecular and neural mechanism determine sleep need or sleep amount remains unknown. Recently, we identified a gain-of-function *Sleepy* mutation in salt-inducible kinase 3 (SIK3) that increases the sleep need and time spent in non-REM sleep. The *Sleepy* mutant mice investigated in previous studies systemically expressed the mutant allele of *Sik3* in the germline. Therefore, it remained to be elucidated whether neurons or other types of cells are responsible for the increased non-REM sleep. Additionally, we could not deny the possibility that mutant *Sik3* expression in the fetal brain decides the time spent in non-REM sleep in adult mice.

Here, we investigated sleep/wake behavior in mice expressing *Sleepy* mutant *Sik3* in postnatal neurons. We newly generated *Synapsin1*^{CreERT2} mice to manipulate a target gene in the neurons after tamoxifen administration. Histological examination of *Synapsin1*^{CreERT2} mice showed tamoxifen induced recombination in neurons and a few peripheral tissues. *Synapsin1*^{CreERT2} mice were then crossed with *Sik3*$^{flox/+}$ mice, which express *Sleepy* mutant *Sik3* in a Cre-dependent manner. EEG/EMG-based sleep staging of *Synapsin1*^{CreERT2}*; SIK3*$^{flox/+}$ mice revealed that tamoxifen-treated *Synapsin1*^{CreERT2}*; SIK3*$^{flox/+}$ mice exhibited increased non-REM sleep compared to control mice. Our results demonstrated that the mutant SIK3 regulates sleep amount by acting in postnatal neurons.

P08

Sleep/wakefulness in neuron type-specific SIK3-deficient mice

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Sleep is a fundamental behavior conserved from vertebrates to invertebrates. Although the two-process model has been proposed as a conceptual framework of sleep regulation, the molecular mechanism of sleep/wake regulation and neural substrate of sleep need remain unknown. SIK3 is a member of AMP-activated protein kinase (AMPK) family and is associated with sleep need. Gain-of-function *Sik3* gene mutant mice increase sleep need and time spent in NREM sleep. Almost all systemic SIK3-deficient mice die neonatally and very few survived mice suffered from several growth retardation and malnutrition, Thus, these mice are not suitable for the sleep/wake analysis.

Here, we examined whether neuronal SIK3-deficiency affects sleep/wakefulness and which neuronal groups are responsible for sleep/wake regulation using newly generated *Sik3-flox* mice. Pan-neuronal SIK3-deficient mice were healthy. We examined sleep/wakefulness through EEG/EMG analysis. We also examined circadian behavior using a running-wheel under the constant darkness. SIK3-deficiency in glutamatergic neurons resulted in decreased NREMS delta power and time spent in NREMS. SIK3-deficiency in GABAergic neurons prolonged the free-running period while delta power in NREMS was not affected. These results indicate that the neuronal group responsible for sleep regulation via SIK3 is different from those for circadian behavior.

P09

The role of SIK3 kinase activity in sleep/wakefulness

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The mouse pedigree, *Sleepy*, which has a splicing mutation in *Sik3* resulting in the skipping of exon 13, shows prolonged non-REM sleep time and increased sleep need. Since our results showed a hypomorphic *Sik3* mutation in mice and *Drosophila* resulted in a decrease in sleep time, the *Sleepy* mutation seems to be a gain-of-function allele. Moreover, it has been reported that SIK3 kinase activity is tightly linked with phosphorylation of Thr221 (T221) in the kinase domain T-loop of SIK3. Interestingly, the phosphorylation of T221 was increased in wild-type mice after sleep deprivation, suggesting that SIK3 kinase activity increases in mice which have a higher sleep need. However, whether the SIK3 kinase activity is involved in sleep regulation is still unknown.

Here, we investigated the role of SIK3 kinase activity in its phosphorylation status and established genetically modified $Sik3^{T221E}$ mice whose SIK3 is constitutively active. First, we examined the phosphorylation status and physical interaction of mutant SIK3 proteins using HEK293T cells. For further investigation, we have made $Sik3^{T221E}$ mice using CRISPR/Cas9 system. We confirmed the establishment of $Sik3^{T221E}$ mutant mice by dCAPS genotyping and direct sequencing.

P10

Sleep/wake behavior of mice lacking PKA phosphorylation site in SIK1 and SIK2

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We previously identified a kinase, SIK3, as an important sleep regulator through screening of randomly mutagenized mice. Mice that express mutant SIK3 lacking the 52 amino acids encoded by exon 13 showed a decrease in wake time and an increase in NREM sleep time. SIK3 is an AMPK-family protein kinase containing a well-conserved protein kinase A (PKA)-phosphorylation site, serine 551. The skipping of exon 13 results in a deletion of 52 amino acids including S551. Also, *Sik3 S551A* knock-in mice showed reduced total wake time and increased sleep need. These results suggest that PKA-SIK3 pathway is involved in the regulation of sleep/wake behavior.

The SIK family is composed of SIK1, SIK2, and SIK3. Importantly, an S551-equivalent serine residue is conserved at S577 in SIK1 and at S587 in SIK2. To examine whether the phosphorylation of S577 of SIK1 and S587 of SIK2 is required for proper sleep/wake behavior, we generated mutant mice in which SIK1 S577 and SIK2 S587 were substituted by alanine through the CRISPR/Cas9 method. Both *Sik1 S577A* mice and *Sik2 S587A* mice showed increased NREM sleep delta power, an index for sleep need to a smaller extent than *Sik3 S551A* mice. It can be explained by the lower expression of Sik1 and Sik2 than Sik3 in the brain. Furthermore, *Sik1 S577A* mice showed reduced wake time but showed normal circadian behavior and re-entrainment to a new circadian rhythm. These findings indicate the PKA recognition sites of SIK family are required for regulation of sleep need.

P11

Functional analysis of *SIK3* in *Drosophila*

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The amount of sleep is regulated by homeostasis, but the underlying molecular mechanism is still unclear. However, recent study identified *Sleepy1* mutation. *Sleepy1* mutation was discovered in an unbiased genetic screening of more than 8000 mice and was identified as an exon-skip mutation of *Sik3*, salt inducible kinase gene. This mutation dramatically increased total sleep time in mice (*Funato et al. Nature, 2016*). *Sik3* has a serine residue in the skipped exon, which is phosphorylated by PKA and conserved in *Drosophila*. In this study, we used phosphorylation-defective SIK3, in which the serine residue is substituted to an alanine residue (SIK3SA), in order to examine the function of SIK3 phosphorylation in sleep. Using GAL4-UAS system and GeneSwitch system, we found pan-neuronal over-expression of SIK3SA and conditional over-expression of SIK3SA increased sleep. The effects of this mutant gene were more remarkable in constant dark (DD) conditions, especially in subjective daytime, than in light-dark (LD) conditions. In order to localize where SIK3SA functions to regulate sleep, we expressed SIK3SA only in the subsets of neurons using various GAL4 drivers. Its over-expression in PDF neurons, which are master clock neurons also resulted in increase in sleep. These data indicate SIK3SA modulates sleep amount controlling the functions of PDF neurons. Next, we investigated SIK3 target genes and identified a novel sleep regulating gene. Overexpression of this gene in all neurons increased sleep. Now, we analyzed the detailed functions of this gene and interactions with *Sik3*.

P12

In vitro and in vivo pharmacology of small-molecule orexin receptor agonists for treatment of narcolepsy.

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Sleep/wakefulness is regulated by orexin, a neuropeptide produced by neurons exclusively localized in the lateral hypothalamus. Orexin deficiency causes narcolepsy-cataplexy characterized by excessive sleepiness, sleep/wake fragmentation and cataplexy. Orexin acts on two receptors, OX_1R and OX_2R, and OX_2R is the main receptor regulating sleep; the role of OX_1R is less clear. As orexin cannot pass the blood-brain barrier, the peptide is difficult to use as a clinical drug. Therefore, small-molecule orexin receptor agonists, especially OX_2R agonists, are expected to be a novel therapy for narcolepsy-cataplexy. We previously showed that YNT-185, an OX_2R-selective agonist, ameliorates narcolepsy-cataplexy symptoms in mouse models when peripherally (i.p.) administered. However, the effective dose of this compound for oral administration (p.o.) was too high.

Here we further optimized YNT-185 (EC_{50} for $OX_2R \approx 28$ nM) and produced 2 different types of agonists; a OX_2R-selective agonist, YNT-X (EC_{50} for $OX_2R \approx 1.1$ nM by Ca assay) and a OX_1R/OX_2R agonist, YNT-Y2 (EC_{50} for $OX_1R \approx 3.7$ nM, EC_{50} for $OX_2R \approx 0.9$ nM). Oral administration of these compounds increased wake time in wild-type mice in a dose-dependent manner. Their effective doses are several hundred times lower than YNT-185. These effects were not detected in orexin receptor-deficient mice. In addition, PO administration of YNT-Y2 ameliorated narcolepsy-cataplexy symptoms in orexin-deficient mice. Previous reports suggest the possibility that OX_1R signal may be important for consolidation of wakefulness. We will be able to dissect the role of orexin receptor subtypes in narcolepsy treatment by using these two types of orexin agonists.

P13

Roles of dopamine signaling in the amygdala in cataplexy

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Although the lack of orexin signaling causes the sleep disorder narcolepsy, the precise neural mechanisms by which orexin neurons prevent narcolepsy remain unclear. In a previous study, we found that targeted restoration of orexin receptor expression in the dorsal raphe nucleus (DR) and in the locus coeruleus (LC) of mice lacking both of orexin receptors inhibited cataplexy and pathological fragmentation of wakefulness (i.e., sleepiness), respectively. These results suggested that DR serotonergic (DR^{5HT}) and LC noradrenergic (LC^{NA}) neurons play differential roles in orexin neuron-dependent regulation of sleep/wakefulness. As a next step, we used optogenetic and chemogenetic approaches to demonstrate that DR^{5HT} neurons suppress cataplexy by reducing the activity of the basolateral/lateral amygdala that plays an important role in emotional processing, as consistent with the fact that strong emotion often triggers cataplexy. Our results suggest that the orexin neuron→DR^{5HT}→amygdala pathway is a critical circuit for preventing cataplexy. Furthermore, we identified a neuronal pathway that induces cataplexy when activated by optogenetic manipulation. We focused on the reward system dopamine from the fact that strong emotions, especially positive emotions, often cause cataplexy. The ventral tegmental area to amygdala pathway is a critical circuit for inducing cataplexy. We will discuss the role of this pathway in emotional processing as well as in REM-related muscle atonia.

P14

Delineation of Neural circuits that regulate Muscle Tone during REM sleep

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One of the hallmarks of REM sleep is bilateral muscle atonia. Cataplexy, a cardinal symptom of narcolepsy, is a sudden weakening of muscle tone triggered by strong emotions and considered to be a REM-related syndrome. However, the precise neuronal circuits that regulate REM atonia and cataplexy are unknown. The purpose of this study is to delineate neuronal circuits that evoke the REM atonia and examine whether this pathway is also involved in cataplexy or not. Recent studies in rodents showed that inhibitory neurons in the ventromedial medulla (VMM) are responsible for generating the muscle atonia during REM sleep. Consistently, we observed obvious increases in muscle tone and body movements during REM sleep in mice when we inhibited glycinergic neurons in the VMM (Gly^{VMM} neurons) by expression of tetanus toxin light chain. Furthermore, we also found that silencing Gly^{VMM} neurons significantly decreased both the duration and number of cataplexies in narcolepsy model mice. Rabies virus mediated retrograde tracing revealed that neurons located in the brainstem such as the sublaterodorsal tegmental nucleus (SLD) and the pontine reticular nucleus (Pn) make direct synaptic contacts with Gly^{VMM} neurons that send projection to the anterior horn of the spinal cord. We found that specific silencing of the glutamatergic neurons in the SLD ($Glut^{SLD}$) that project to the VMM resulted in REM sleep without atonia and decreased time spent in cataplexy in narcoleptic mice. These findings suggest that the $Glut^{SLD}$ →Gly^{VMM} pathways are common in REM atonia and cataplexy.

P15

Abnormal Sleep and Cognitive ability in an *App* Knock-in Mouse Model of Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease. It is a slow progressing disease characterized by aggregation of amyloid-beta (Aβ) peptides. In addition to cognitive decline, AD patients often suffer from poor sleep. These symptoms not only affect their QOL but also those of the primary caregivers. Increasing studies support that sleep deficits can contribute to the progression of AD, consistent with the roles of sleep in memory and brain homeostasis. Thus, it is crucial to understand the underlying mechanisms of sleep disorders in AD.

Here, we unveil the sleep abnormalities exhibited by an AD mouse model. We chose the *App* knock-in mouse (Saito et al., Nature Neuroscience, 2014). In this AD mouse model, Aβ accumulates in a manner similar to human AD via mutation in the gene encoding amyloid-beta precursor protein (APP), and thus, various aspects of human AD are faithfully recapitulated. In these mice, at 6 months of age, when cognitive deficits become apparent, impairment in various aspects of the sleep architecture were detected. These phenotypes became more severe at 12 months of age. Consistent with the notion that sleep is important for memory consolidation, the AD mouse model also exhibited learning deficits. We expect that our results provide a starting point for addressing how sleep is impaired in AD and how it can affect cognitive functions.

P16

Slow Wave Sleep and Sleep Need Resolution

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Sleep is necessary for survival, however, its mechanisms are still not fully understood. In sleep, the brain generates slow electrical signals (1-4 Hz) that can be recorded in the electro-encephalogram (EEG); this slow wave activity (SWA) homeostatically increases with the duration of the waking time before sleep and decreases during sleep.

SWA is synchronous activity of cortical neurons during slow wave sleep (SWS), oscillating between silent OFF and active ON periods. During SWS ON periods, activity-dependent influx of calcium ions into neurons through voltage-gated calcium channels (VGCCs) is observed, but the function of this calcium influx is unclear.

We hypothesize that neuronal calcium influx is involved in resolving sleep need, visible as decreases in SWA during sleep. We used nifedipine, a common antihypertensive drug that readily penetrates the blood-brain barrier to block L-type VGCCs, responsible for a significant fraction of activity-dependent postsynaptic calcium influx in cortical neurons.

Nifedipine reduced EEG SWA for 1-2 h after subcutaneous injection in mice at the beginning of the light phase, when sleep need and SWA are highest. This decrease in SWA was followed by a rebound after the nifedipine-effect had worn off. Based on these results, we hypothesize that neuronal calcium influx contributes to sleep need resolution during SWA and that a significant fraction is contributed by L-type VGCCs.

P17

Neuronal activity of OFF period-like phase during optogenetically evoked cortical response in SWS

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Slow wave activity (SWA) during slow wave sleep (SWS), recorded from electroencephalograms (EEG) or local field potential (LFP) is a key indicator of sleep homeostasis and therefore it likely has a central role in sleep. It has been reported that SWA is not only spontaneously occurred but can also be induced by transcranial current stimulation (Marshall et al., *Nature*, 2006), magnetic stimulation (Massimini et al., *PNAS*, 2007), auditory stimulation (Tononi et al., *Medicamundi*, 2010), or electrical stimulation directly delivered to cortex (Vyazovskiy et al., *J Neurophysiol*. 2009). Here we investigated the cortical activity induced by brief optogenetic stimulation during SWS in mice and compared to the spontaneous OFF (silent) period of slow wave. The optogenetic stimulation triggered a biphasic response, a brief excitation followed by long silence of unit activity which was similar to the OFF period of SWA. However, the cortical neurons showed less excitability during the stronger evoked-silence period while larger excitation was observed during spontaneous OFF period compared to ON period. We further analyzed the neuronal activity of cortical neurons during the evoked response and found that the late silent period was most likely to be induced by the feedback inhibition which is triggered by the preceded brief excitation.

P18

Firing property of the neurons in the medulla involved in sleep/wake cycles and autonomic nervous system

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The medulla is well known for the center of the cardiovascular regulation. Besides that,
the medulla plays crucial roles in the promotion and the maintenance of rapid eye movement (REM) sleep. During REM sleep, blood pressure (BP) surges and rapid heart rate (HR) increases are observed due to the turbulence of the autonomic nervous system. However, it remains to be known how the neurons in the medulla regulate sleep/wake cycles and BP fluctuation during REM sleep.
We recorded single neuronal activity and BP in head-restrained and unanaesthetised rats during sleep/wake cycles. Of 115 neurons recorded, 75.7% (87/115) showed increased activity during REM sleep, REM sleep and waking, or Slow-wave sleep and REM sleep, which we term PS active neurons.
32.2 % of PS active neurons (28/87) started increasing their activity before the REM sleep onset. They are mainly located from central to the caudal medulla. The neurons in the caudal parts, which preceded the REM sleep onset, mostly showed phasic firing, whereas the neurons in the central parts showed tonic firing.
Of 87 PS active neurons, 32.2 % (28) showed firing in close relation with BP fluctuation during REM sleep, and 75 % of them (21/28) increased their firing rate before the BP fluctuation. These results suggest that neurons in the medulla are involved in the regulation of rapid BP increases during REM sleep.

P19

The adult-born neuron activity underlying memory consolidation during sleep

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Background: The hippocampus plays critical roles in memory consolidation during sleep, yet its responsible neural population is still unclear. In the hippocampus, the dentate gyrus (DG) continuously generate new neurons throughout life. These adult-born neurons (ABNs) are crucial for learning and memory retrieval, but their functions in sleep are completely unknown.

Method: We used the pNestin-CreER^{T2} driver mice to label and manipulate ABNs. Injection of an estrogen ligand, tamoxifen (TAM), to the mice induced recombination in the neural progenitor cells to express Halorhodopsin, a light-sensitive neuronal silencer, in DG. After TAM injection, we targeted different ages (~2, 4, and 10-week old) of the ABNs for silencing during each sleep stage.

Result: Light-induced silencing of the 4-week old ABN activity during sleep within the memory consolidation window impaired memory. It also led to elongation of ABN dendritic spine neck. Furthermore, no memory impairment was observed when ~2- or 10-week-old ABN activity was silenced in the same manner.

Conclusion: We provide causal evidence that the activity of the young ABNs is necessary for memory consolidation during sleep.

P20

Ensemble activities of adult-born neurons in memory consolidation during sleep

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The hippocampal dentate gyrus (DG) is one of the few brain regions that continue to produce new neurons throughout life. We showed that the adult-born neuron (ABN) activity during sleep is necessary for memory consolidation (Kumar et al., in revision). Here, we employ calcium imaging of ABNs under the free moving condition to reveal the mechanisms of memory consolidation during sleep. Under home cage conditions, ABNs display repetitive patterns of neuronal ensemble activities across sleep/wake periods. Interestingly, the ensemble activities are more frequent when the DG local field potential shows a synchronous oscillatory activity, theta oscillations. Theta oscillations play critical roles in the temporal coordination of neuronal activities (Buzsáki, Neuron 33: 325-40, 2002). We also examine the ensemble activities during encoding, consolidation, and retrieval periods of the contextual fear memory. We intend to show our most recent data at the presentation.

P21

The Effect of Olfactory Stimulation during REM Sleep on Dreams

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Dreams have been investigated, not only to clarify clinical problems such as possible associations between nightmares and depression, but also to understand fundamental processes such as mechanisms of memory or the purpose of rapid eye movement (REM) sleep. Compared with other sensory stimulations, olfactory stimuli may be able to be processed in the brain during dreaming, and without causing arousals. However, although olfactory perception shows large individual differences, these individual differences have not been considered. We therefore conducted two experiments to clarify if individual differences in odor perception affect dream emotionality after olfactory stimulation during REM sleep. Our investigation of the preference factor comprised Experiment 1. Study participants were divided into two groups according to each participant's individual preference for Phenylethyl alcohol (rose-like fragrance) odor, i.e. prefer or not-prefer groups. Each group was exposed to control and odor conditions. The goal of Experiment 2 was to investigate the effects of familiarity. There were two groups, i.e. familiar and unfamiliar groups. We observed effects of odor on dreams only in the prefer group (Experiment 1) and familiar group (Experiment 2). In addition, for both groups, dreams which occurred in odor conditions were more emotionally negative than those in control conditions.

P22

Effects of types of low intensity physical activity (exercise/housework) in the evening on sleep in older female adults

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Purpose: To examine different effects of exercise and housework on sleep quality in older female adults.

Methods: The present study was a randomized and 3-way crossover study. The participants were 10 healthy older females, and sleep was recorded polysomnographically. Three hours before bedtime, the participants were engaged in different types of lower intensity physical activity 30 minutes (exercise or housework) or sedentary activity (control). For the exercise, stepping exercise was conducted at 70 beats per minute while for the housework, housework was conducted on about 3 METs. Subjective sleep quality was investigated in the next morning using OSA-MA questionnaire.

Results: The deep body temperature was significantly elevated compared to the control after each activity (-0.2, +0.5, and +0.4℃, control, housework, and exercise, respectively). There is a significant difference in sleep latency (ANOVA P = 0.011) while there was no significant difference among the trials (14.2, 9.9, and 4.1 min for control, housework, and exercise, respectively). An increase in stage N3 by exercise and housework was observed during the first tertile of total sleep time (P < 0.001). Also, stage R was significantly longer in exercise than control and housework during the first tertile of total sleep time (P = 0.003). The total score of OSA-MA was significantly higher under exercise (91.0, 88.1, and 108.6 point for control, housework, and exercise, respectively).

Conclusion: Engaging in lower intensity of exercise and housework in the evening shows higher objective sleep quality compared to control. However, housework shows lower subjective sleep quality than exercise.

P23

Neural Mechanism for Hibernation

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Homeothermic animals, birds and mammals, consume a large portion of their body energy for heat production to maintain their body temperature (T_B) within a narrow range that is usually higher than the ambient temperature. However, some mammals actively lower T_B and reduce metabolic rate to conserve energy in order to survive food scarcity in wintertime. The physiological state of reduced metabolic rate and T_B in endothermic animals is known as hibernation. Hibernators return to normal condition without any obvious tissue damage. Although numerous studies have reported that hibernation are regulated by the central nervous system, neural mechanism of hibernation has remained totally unknown. Here, we found that neuroscientific manipulations of a novel genetically-defined neural population in the hypothalamus drive a long-lasting hypometabolic/hypothermic state (hibernation-like state) in mice which cannot have ability to hibernate. In this state, the mice show remarkable reductions in metabolic rate, heartbeat, ventilation and theoretical set-point T_B. With reduced these body functions, mice also demonstrate that their thermosensory and thermoregulatory systems remain functional, as well as examples of hibernator. In addition, mice spontaneously recovered from this state without obvious abnormalities, suggesting that the induced hypometabolic state are not passive, but actively regulated like hibernation. Our present finding sheds light on the mechanism of regulated hypometabolism, and can provide a key of developing a method to artificially induce a systemic hibernation-like hypometabolic state in non-hibernators including human being.

P24

Deciphering a novel neural circuit in the central amygdala implicated in regulation of social behavior

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The regulation of interpersonal distance i.e. social space plays a central role in social behavior, and intrusions into personal space often evoke negative emotion in social interactions. However, the neural mechanism regulating interpersonal distance remains unknown. Here, we identified a novel genetically-defined population of neurons that express neuropeptide B/W receptor 1 (Npbwr1 neurons) in the central nucleus of the amygdala (CeA) as an essential component for regulating interpersonal distance in mice. We generated *Npbwr1-iCre* knocked-in mice and used for various manipulation. Chemogenetic manipulation of Npbwr1 neurons in the CeA with excitatory and inhibitory DREADD (hM3Dq, hM4Di) bidirectionally modulated social interaction with a novel conspecific. To identify input and output architecture of Npbwr1 neurons, we took anterograde and retrograde tracing approach. Cell specific infection of Rabies virus (*SAD Δ G-GFP*) allowed us to visualize monosynaptic input neurons in the CA1, BNST, NAc and VTA. Cell specific infection of AAV carrying synaptophysin-mCherry identified the PBN, NTS and microcellular tegmentum (MiTg) as potential postsynaptic targets. Pathway specific manipulation of Npbwr1 neurons projecting MiTg modulated time of social interaction with a conspecific mouse. These results suggested that Npbwr1 neurons in the CeA projecting to the MiTg plays a crucial role in maintenance of interpersonal distance with between conspecifics. These findings shed light on the role of Npwbwr1 to regulate interpersonal distance showing a possibility to develop a new drug to treat the abnormal sociability sometimes seen in social phobia or adjustment disorder.

P25

Decoding the sexual behavior of male mice by capturing the dopamine dynamics / Development of the automated analyzing system for social behavior

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Sexual behavior is unsupervised innate behavior underlying reproductive success and widely observed in many species. In male rodents, sexual behavior is composed of two components: the appetitive and consummatory behaviors. The appetitive behavior reflects a motivational state and consists of searching and approaching a female. The appetitive behavior leads to the consummatory behaviors include mounting, intromission, and ejaculation. How the brain implements a sequential but complex sexual behavior is still unclear. Neuromodulator dopamine (DA) works as the most prominent reward and motivation related signals in the brain. Furthermore, DA is involved in cognitive and motor tasks. We hypothesize that DA signals in the Nucleus accumbense (NAc) modulates or controls the particular components of sexual behavior in the male mouse. Establishing a causal link between DA signaling and each male sexual behavior component, the measuring dopamine released with high spatiotemporal precision is necessary. Here, the in vivo fiber photometry system is used to measure dopamine dynamics in the NAc. Through measuring dopamine signaling in NAc during male mouse sexual behavior by combining fiber photometry and $GRAB_{DA}$, genetically encoded GPCR-activation-based-dopamine sensors, we observed characteristic dopamine signaling patterns depending on the region of NAc. During appetitive behaviors, DA release is transiently increased when a female mouse is introduced in a male mouse. During consummatory behaviors, especially during intromission and after ejaculation, two opposite patterns of DA release are observed: increased DA release or suppressed DA release.

As a concurrent project, I'm developing an automated behavior analyzing system for identifying male sexual behavior.

P26

Neural dynamics of VTA dopaminergic neurons in female sexual behavior

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Dopamine has been thought to have a crucial role in sexual behavior in both male and female animals. However, the neural dynamics of VTA dopaminergic neurons in a female mouse during sexual behavior remain unclear. Here, we examined the neural activities of VTA dopaminergic neurons in a female mouse during sexual behavior. We used fiber photometry, which enables us to measure the bulk of neural activities of the genetically specific neural population with high temporal precisions. VTA dopaminergic neurons are labeled with a genetically encoded calcium indicator, GCaMP6s, by applying Cre-dependent GCaMP6s expressing AAV in Dopamine transporter (DAT)-Cre female mice. We discovered the dramatic surge of the neural activity of VTA dopaminergic neurons in the female mouse immediately after male mouse ejaculation. Although it is unclear the biological meaning of this surge of dopaminergic neurons activities in female mice during sexual behavior, we speculate that this would be related to social memory or recognition. Furthermore, the trigger of this rapid increase in neural activities is unknown. We are thinking several candidates; tactile or chemical input from sperm, ultrasonic vocalization of a male mouse.

P27

Novel neural circuits for innate fear induced defensive responses.

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Freezing has been recognized as a typical defensive behavior in predator related innate fear condition for many years. Besides freezing behavior, prey animals also show significant body temperature change as the physiological defensive strategy for survival when encountering their predators. But its neural mechanism is rarely studied before.

Here, we find predator odor 2MT induces potent freezing and hypothermia in mice and identify that external parabrachial nucleus (PBel) and their input to parasubthalamic nucleus (PSTh) contribute to 2MT induced innate fear responses. Optogenetic activation of fos expressed neurons in PBel, and their axon terminals in PSTh with CANE system induces both freezing and hypothermia in mice. Conversely, inhibition of Vglut2 positive neurons in PBel and PSTh with DREADD system attenuates 2MT induced freezing and hypothermia.

Moreover, we find hypothermia is regulated by the nucleus of solitary tract (NST) projecting PSTh neurons. Optogenetic activation of NST projecting neurons in PSTh induces hypothermia but not freezing, which hints that there exists another efferent brain region from PSTh for freezing regulating.

In conclusion, we identified novel neural circuits regulating predator odor induced freezing and hypothermia responses.

P28

The functional role of delta-opioid system on chronic exposure to social defeat stress

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Benzodiazepines, tricyclic antidepressants and SSRIs (Selective Serotonin Reuptake Inhibitors) are generally used for mood or anxiety disorder. However, these drugs need a long-term taking to obtain therapeutic effects, or often induce adverse effects. These evidences suggest the necessity for new attractive therapeutic targets in mood or anxiety disorder. Delta-opioid neurons exist in cortical and limbic structures, and produce unique emotional function in the brain. Here, we report delta-opioid neural function on exposure to chronic social defeat stress and delta-opioid receptor (DOR) agonist-induced therapeutic effectiveness on social defeat stress model. Chronic exposure to social defeat stress induced the depression-like behaviors characterized by anxiety, anhedonia and social avoidance behavior in normal mice. These behavioral changes following chronic social stress were recovered by repeated treatment of KNT-127, a selective DOR agonist. This recovery was observed from 3 days after KNT-127 treatment. In contrast to that, pre-treatment with NTI, a selective DOR antagonist, induced the exacerbation of depression-like behaviors following social stress in mice from the beginning of stress exposure, compared to pre-treatment with saline. These results suggest delta-opioid neural system plays a key role in stress defense mechanism in the brain and DOR agonist is expected to be a more effective drug than existing drugs.

P29

Signal dynamics corresponding to value-to-choice transformation in midbrain dopamine neurons and orbitofrontal neurons during economic decision-making in monkeys

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In economic decision-making, individuals first evaluate an option, and then decide to choose or not to choose the option based on its value. Although the cortical system, especially the orbitofrontal cortex (OFC) has been thought as the neural substrate of the transformation process from option's value information into animal's choice command, the whole picture of neural network remains unclear. Here we investigated the role of midbrain dopamine (DA) neuron, a key region for value-processing, and compared their role with that of the OFC. We recorded single-unit activity from DA and OFC neurons in monkeys performing an economic decision-making task. We found that both DA and OFC neurons represented diverse signals related not only to the option's value but also to the animal's choice; some neurons represented the value of the offered option, some represented whether the animal would choose or not choose the option, and some represented the value of the option only when the option was chosen by the monkey -we therefore called this activity pattern as *choice-dependent value* signal that was influenced by both value and choice. We next analyzed the time course of these signals and found that the order of signal representations in both regions corresponded to the value-to-choice transformation. Shortly after the onset of the option, the value signal rapidly appeared, which was followed by the choice-dependent value signal. The choice signal arose at last. Our findings provide evidence that not only cortical system but also the subcortical DA system may participate in value-to-choice transformation.