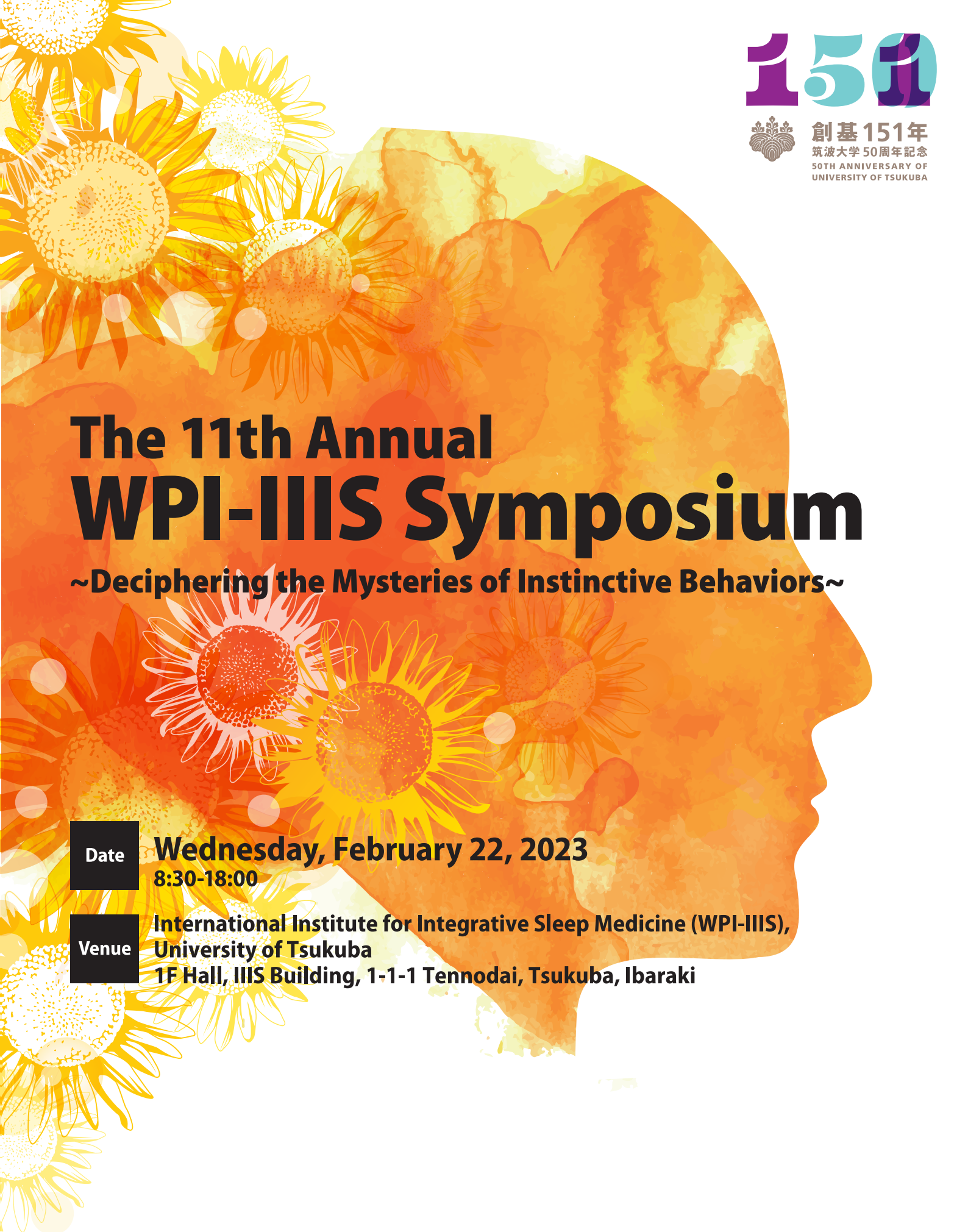


創基151年
筑波大学50周年記念
50TH ANNIVERSARY OF
UNIVERSITY OF TSUKUBA

The 11th Annual
WPI-IIIS Symposium

~Deciphering the Mysteries of Instinctive Behaviors~

Date Wednesday, February 22, 2023
8:30-18:00

Venue International Institute for Integrative Sleep Medicine (WPI-IIIS),
University of Tsukuba
1F Hall, IIIS Building, 1-1-1 Tennodai, Tsukuba, Ibaraki

The 11th Annual
WPI-IIIS Symposium
~Deciphering the Mysteries of Instinctive Behaviors~

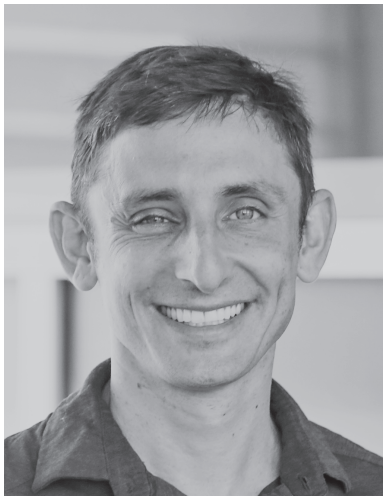
Date : **Wednesday, February 22, 2023, 8:30 – 18:00**

Venue : **1F Hall, IIIS Building, University of Tsukuba**

Time Table

Opening | MC: Mayumi Kimura (WPI-IIIS, University of Tsukuba)				
8:30 - 8:45	Welcome	**Masashi Yanagisawa**	Director, WPI-IIIS, University of Tsukuba	
	Opening Address 1	**Akira Ukawa**	WPI Academy Director, JSPS	
	Opening Address 2	**Noriko Osumi**	WPI Academy Officer / Vice President, Tohoku University	
Session 1 | Chair: Yu Hayashi (WPI-IIIS, University of Tsukuba)				
8:45 - 9:25	The evolution of sleep loss in Mexican cavefish	**Alex Keene**	Texas A&M University	Page 4
9:25 - 10:05	Metabolic control of sleep	**Anissa Kempf**	University of Basel	Page 5
10:05 - 10:20	Break			
Session 2 | Chair: Arisa Hirano (WPI-IIIS, University of Tsukuba)				
10:20 - 11:00	Sleep duration, sleep quality and energy metabolim	**Esra Tasali**	University of Chicago	Page 6
11:00 - 11:40	Sleep and circadian rhythm disruption: from genes and environment to behaviour	**Stuart Peirson**	University of Oxford	Page 7
11:40 - 11:55	Lunch Preparation / Break			
Session 3 | Chair: Kaspar Vogt (WPI-IIIS, University of Tsukuba)				
11:55 - 12:35	Rapid eye movement sleep is initiated by basolateral amygdala dopamine signaling in mice	**Emi Hasegawa**	Kyoto University	Page 8
12:35 - 13:15	Midbrain circuits linking social stress and sleep	**Xiao Yu**	Chinese Academy of Sciences, Shanghai	Page 9
13:15 - 13:55	Hypothalamic neural circuit mechanism controlling female reproductive behaviors	**Sayaka Inoue**	Stanford University	Page 10
13:55 - 14:05	Photo / Break			
Poster Session | Chair: Shoi Shi (WPI-IIIS, University of Tsukuba)				
14:05- 14:45	Data Blitz			Page 14-15
14:45 - 16:00	Poster Presentation			Page 14-15
Session 4 | Chair: Sakiko Honjoh (WPI-IIIS, University of Tsukuba)				
16:00 - 16:40	The mechanisms and meaning of sleep homeostasis	**Vladyslav Vyazovskiy**	University of Oxford	Page 11
16:40 - 17:20	Towards cortex-wide volumetric recording of neuroactivity at cellular resolution	**Alipasha Vaziri**	The Rockefeller University	Page 12
17:20 - 18:00	A signaling pathway for transcriptional regulation of daily sleep amount in mice	**Qinghua Liu**	National Institute of Biological Sciences, Beijing	Page 13
18:00	Closing			

The evolution of sleep loss in Mexican cavefish



Alex Keene

Texas A & M University, USA

ABSTRACT

Sleep is nearly ubiquitous throughout the animal kingdom, yet its duration and timing varies dramatically between species. We have developed the Mexican tetra, Astyanax mexicanus as a model to study evolved changes in sleep, and how naturally occurring genetic variation encodes for sleep differences between individuals. These fish exist as eyed-surface populations that inhabit the rivers of northeast Mexico and multiple blind cave populations that have converged on sleep loss. We have identified neuromodulators that contribute to the evolution of sleep loss in A. mexicanus cavefish including upregulation of the wake-promoting neuropeptide Hypocretin/Orexin. In addition, we have developed transgenic and gene-editing methodology in this emergent model system allowing for systematic investigation of the genes and neurons regulating evolved differences in sleep. Systematic analysis has identified convergence on wide-spread neuroanatomical differences between surface fish and cavefish including hypothalamic expansion that is accompanied by increased sleep intensity. Current studies seek to identify how naturally occurring genetic variation contributes do these phenotypes. Investigating the mechanisms of sleep loss in Mexican cavefish has potential to provide insights into the variation in sleep need throughout the animal kingdom. Further, the resources developed to study sleep can be broadly applied to study other cavefish associated traits including obesity, diabetes, and dysregulation of stress response.

Metabolic control of sleep

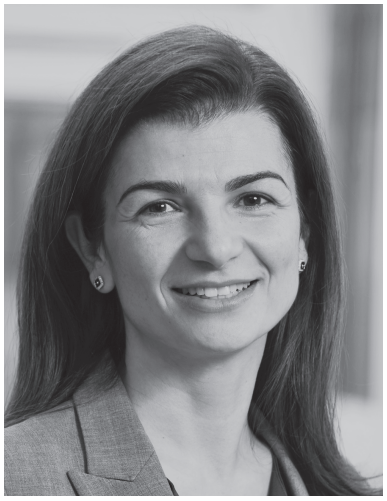
Anissa Kempf

University of Basel, Switzerland

ABSTRACT

Sleep is essential, yet its function remains one of biology's biggest mysteries. A short or poor night of sleep is usually followed by longer and/or deeper periods of sleep. The existence of such a compensatory mechanism suggests that our brain can monitor the amount of waking time and trigger corrective action if needed. In the fly brain, this behavioural change is reflected in electrical changes of sleep-promoting neurons that project to a region of the fly brain referred to as the dorsal fan-shaped body (dFB). Previous work has shown that dFB neurons of sleep-deprived flies are more excitable than those of rested flies. This suggests that the excitability state of dFB neurons tracks the sleep need of the fly: as sleep need builds up, dFB neurons upregulate their excitability, and as sleep debt gets cleared, it reverts back to baseline. Understanding what modulates the excitability of dFB neurons will undoubtedly inform us about the molecular basis of sleep need. Here, I will show that mitochondrial metabolism plays a key role in this process: dFB neurons track their redox state to form a biochemical memory of sleep need and to adjust their excitability state accordingly. Uncovering the molecular basis of sleep homeostasis might shed light onto one of biology's biggest mysteries: the function of sleep.

Sleep duration, sleep quality and energy metabolism



Esra Tasali

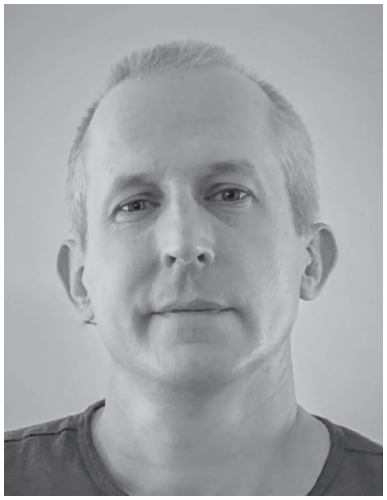
University of Chicago

ABSTRACT

Sleep has been recognized as an important contributor to metabolic health. Insufficient sleep duration and reduced sleep quality are associated with impairments in energy metabolism. Insufficient sleep duration has been associated with an increased risk for obesity and diabetes. Sleep apnea is a highly common sleep disorder. It has been strongly linked to adverse metabolic (e.g., impaired glucose metabolism) and cardiovascular outcomes. This talk will review the clinical and experimental human studies linking reduced sleep duration/quality to impairments in energy metabolism, discuss potential underlying mechanisms, and provide highlights from interventional human studies aiming to improve sleep patterns and metabolic outcomes.

Session 2 **11:00 - 11:40**

Sleep and circadian rhythm disruption: from genes and environment to behaviour



Stuart Peirson

University of Oxford, UK

ABSTRACT

The 24h cycle of activity and sleep provides perhaps the most familiar example of circadian rhythms. In mammals, circadian activity rhythms are generated by a master biological clock located in the hypothalamic suprachiasmatic nuclei (SCN). This clock is synchronized (entrained) to the external light environment via light input from retinal photoreceptors. However, sleep is not a simple circadian output and also is regulated by a homeostatic process whereby extended wakefulness increases the need for subsequent sleep. As such, the amount and distribution of sleep depends upon the interaction between both circadian and homeostatic processes. To understand the complex genetic regulation of sleep, we have applied forward and reverse genetic approaches in mice. Firstly, using a forward genetic screen using behavioural sleep screening, we have identified a novel sleep mutant. In addition, using transcriptomic meta-analysis of sleep deprivation data, we have been able to identify novel sleep genes and subsequently verify sleep phenotypes. Finally, the light environment also exerts effects on sleep and circadian rhythms. The modern artificial light environment leads results in exposure to dim light on an evening (DLE), which causes a misalignment of normal sleep and circadian rhythms, with consequences for peripheral clocks, metabolism and cognitive behaviour.

Rapid eye movement sleep is initiated by basolateral amygdala dopamine signaling in mice

Emi Hasegawa

Kyoto University, Japan

ABSTRACT

Abstract: The sleep cycle is characterized by alternating non-rapid eye movement (NREM) and rapid eye movement (REM) sleeps. The mechanisms by which this cycle is generated are incompletely understood. We found that a transient increase of dopamine (DA) in the basolateral amygdala (BLA) during NREM sleep terminates NREM sleep and initiates REM sleep. DA acts on dopamine receptor D2 (Drd2)-expressing neurons in the BLA to induce the NREM-to-REM transition. This mechanism also plays a role in cataplectic attacks, which are a pathological intrusion of REM sleep into wakefulness, in narcoleptics. These results show a critical role of DA signaling in the BLA in initiating REM sleep and provide a neuronal basis for sleep cycle generation. Furthermore, this mechanism involved serotonergic neurons in the dorsal raphe and serotonin modulates DA signaling in the BLA to induce the NREM-to-REM transition.

Midbrain circuits linking social stress and sleep

Xiao Yu

Chinese Academy of Sciences, Shanghai, China

ABSTRACT

Stress correlates with an increased risk of clinical anxiety. Sleep has been suggested to be one of the mechanisms for alleviating the malign effects of stress. Nevertheless, the function and benefits of sleep are poorly understood. In mice, social defeat stress, an ethological model for psychosocial stress, induces sleep. Such sleep could enable resilience, but how stress promotes sleep is unclear. In this lecture, I will talk about how we discovered some key cells in the midbrain that regulate sleep in mice, and how these cells play an important role in mood control. I will substantially demonstrate the mechanisms underlying how stress-induced sleep was produced and how this sleep helps the mental processing of stressful events by discovering a specific circuit in the mouse midbrain dedicated to detecting stress and inducing restorative sleep. We found these specialized cells in the midbrain receive stress inputs from stress-detecting centers in the brain and induce sleep through the lateral hypothalamus. Stress-induced sleep generated by this pathway mitigated stress-induced anxiety, and alleviated stress levels, restoring mental and body functions. This discovery potentially provides a refined route for treating anxiety disorders, helping to understate the essential mechanisms of how sleep benefits in reducing anxiety in the brain, and strengthening the fundamental function of sleep.

Hypothalamic neural circuit mechanism controlling female reproductive behaviors

Sayaka Inoue

Stanford University, USA

ABSTRACT

Behaviors are associated to the internal physiological state. In many species, including mice, females dramatically change their sexual behaviors along the state of ovulation. Females of many species are sexually receptive exclusively during the estrus, ovulatory phase of the estrous cycle, while they are not receptive during other phases. Sex hormones such as estrogen and progesterone are required for both ovulation and female sexual behavior. Although central and peripheral mechanisms of ovulation is well characterized, neural circuit mechanisms underlying the estrus-associated change of the behavior is poorly understood. We have previously shown that progesterone receptor (PR) expressing neurons in the ventromedial hypothalamus (VMH) are essential for female sexual behavior. Targeted ablation of PR+ VMH neurons abolished female sexual behavior while it kept the estrous cycle intact. However, whether PR+ VMH neurons play a role in the estrus-associated change of female sexual behavior or they control the behavior independently from the estrus is unclear. We examined whether PR+ VMH neurons play a role in the estrus-associated change of female sexual behavior. We find that PR+ VMH neurons significantly strengthen their functional connections during estrus with the anteroventral periventricular nucleus. This cyclic increase in connectivity depends on estrogen signaling in PR+ VMH neurons. We further find that these projections are essential for female sexual receptivity during estrus because optogenetic inhibition of these connections abolishes female sexual behavior. These findings demonstrate that periodic remodeling in this behaviorally salient connections play a critical role in associating female sexual behavior with internal physiological state. We further identified a transcriptomically-defined homogeneous population expressing Cckar within the PR+ VMH population. The Cckar+ VMH neurons are the only neurons within the PR+ VMH neurons that regulate female sexual behavior. I will present these and recent findings to discuss hypothalamic circuit mechanisms that control the timing of female sexual behavior.

The mechanisms and meaning of sleep homeostasis

Vladyslav Vyazovskiy

University of Oxford, UK

ABSTRACT

According to traditional view, the need for sleep accumulates during wakefulness and dissipates during sleep. Despite decades of research, it is still uncertain precisely which biological variables form the substrate of sleep need, what characteristics of wake challenge their stability, how information about sleep-wake history is integrated over time, and how sleep mediates the restoration of homeostasis. An even more fundamental question therefore remains whether homeostatic sleep regulation reflects an active process, dynamically shaping daily sleep architecture in response to a physiological need for the homeostatic regulation of specific variables, or whether it corresponds instead to an unknown innate time-keeping process which ensures only that a certain daily quota of sleep is obtained. While the earliest theories of sleep homeostasis supposed the existence of a single variable, termed Process S, which describes sleep drive at the global level, current views emphasise the importance of a local and activity-dependent component. Many candidate mechanisms have been proposed for the substrate of sleep homeostasis, including processes occurring at a cellular or local network level. These include the maintenance of cellular homeostasis, the replenishment of energy stores, the influence of sleep-related signalling molecules such as adenosine or cytokines, and the regulation of imbalanced synaptic strengths. The preference for global sleep, despite its fundamentally local mechanisms, may be evidence that sleep homeostasis ultimately does not serve a single specific local function. An alternative view is that the recent history of neuronal activity levels may regulate the local tendency to generate a signal (reflected in Process S) which is integrated over larger neuronal populations through intrinsic network mechanisms in order to produce a global sleep propensity signal that estimates the total time spent awake with great accuracy. This mechanism would enable the brain to enforce a daily quota of sleep, which could have many benefits at the physiological and ecological level, rather than to initiate sleep in response to the homeostatic need of one specific regulated variable.

Towards cortex-wide volumetric recording of neuroactivity at cellular resolution

Alipasha Vaziri

The Rockefeller University, USA

ABSTRACT

Understanding how sensory information is represented, processed and leads to generation of complex behavior is the major goal of systems neuroscience. However, the ability to detect and manipulate such large-scale functional circuits has been hampered by the lack of appropriate tools and methods that allow parallel and spatiotemporally specific manipulation of neuronal population activity while capturing the dynamic activity of the entire network at high spatial and temporal resolutions.

A central focus of our lab is the development and application of new optics-based neurotechnologies for large-scale, high-speed, and single-cell resolution interrogation of neuroactivity across model systems. Through these, we have consistently pushed the limits on speed, volume size, and depth at which neuronal population activity can be optically recorded at cellular resolution. Amongst others have demonstrated whole-brain recording of neuroactivity at cellular resolution in small model systems as well as more recently near-simultaneous recording from over 1 million neurons distributed across both hemispheres and different layers of the mouse cortex at cellular resolution.

I will present on our efforts on neurotechnology development and how the application of some of these optical neurotechnologies could enable solving a qualitatively new range of neurobiological questions that are beyond reach of current methods. Ultimately, our aim is to uncover some of the computational principles underlying representation of sensory information at different levels, its processing across the mammalian brain, and how its interaction with internal states generates behavior.

A signaling pathway for transcriptional regulation of daily sleep amount in mice

Qinghua Liu

National Institute of Biological Science, Beijing, China

ABSTRACT

Different mammals vary widely in daily sleep quotas, ranging from 2 to 5-h in giraffes to 18 to 22-h in koalas1,2, reflective of a specific homeostasis between sleep and wakefulness in each species. In mice and humans, sleep quantity of individuals is governed by genetic factors and exhibit age-dependent variations3,4. However, the core molecular pathways and effector mechanisms that regulate sleep quantity in mammals remain unclear. Here, we characterize a major signaling pathway for transcriptional regulation of sleep amount in mice by adeno-associated virus-mediated somatic genetics analysis5. Adult brain chimeric-knockout of LKB1 kinase, an activator of AMPK-related protein kinase SIK3/SLEEPY6-8, markedly reduces non-rapid eye movement sleep (NREMS) amount and delta power–a measure of sleep depth. Downstream of LKB1-SIK3 pathway, gain/loss-of-function of histone deacetylases HDAC4/5 in adult brain neurons causes bidirectional changes of NREMS amount and delta power. Phosphorylation of HDAC4/5 is regulated in relation to sleep need, and HDAC4/5 specifically regulate sleep amount in posterior hypothalamus. Genetic and transcriptomic studies reveal that HDAC4 cooperates with CREB in both transcriptional and sleep regulation. These findings introduce the concept of signaling pathways targeting transcription modulators to regulate daily sleep need and demonstrate the power of somatic genetics in mouse sleep research.

Poster Session

The 11th Annual WPI-IIIS Symposium

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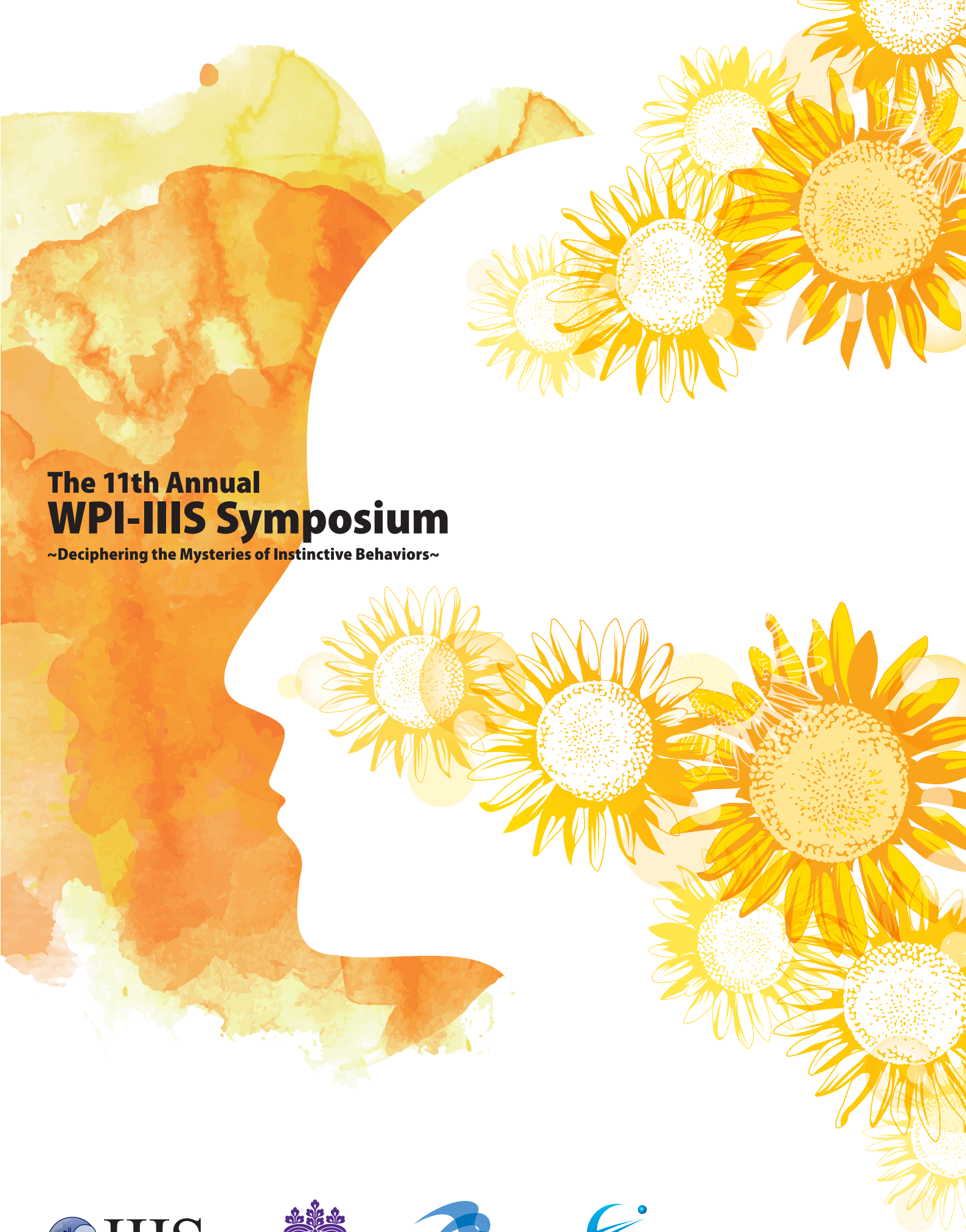
Data Blitz by Poster Presenters	**14:05 – 14:45**
Poster Presentation	**14:45 – 16:00**

Poster List

#	Presenter	Title
1	**Yusuke Iino**	Synaptic plasticity in prefrontal cortex regulates sleep
2	**Ayako Imamura**	Both ablation and activation of POA cause sleep fragmentation
3	**Kseniia Prokofeva**	Regulation of Sleep and Wakefulness by Neuronal Circuits linking Ventrolateral Preoptic Nucleus and Lateral Hypothalamic Area
4	**Zhongwen Zhang**	Mechanism by which the BNST→DpMe pathway induces arousal
5	**Ruth Li**	Role of Gastrin-releasing hormones-producing neurons in regulation of the circadian rhythms
6	**Tohru Takahashi**	24 hours QIH induction by OPN4-based optogenetics
7	**Ai Miyasaka**	Male sexual behaviors are regulated by dopaminergic signaling in NAc in mice
8	**Susumu Umezawa**	Ventral tegmental area dopaminergic neurons mediate sleep reduction induced by ablation of the surrounding GABAergic neurons
9	**Koustav Roy**	Opto-chemical control of slow-wave sleep in the nucleus accumbens by a photoactivatable allosteric modulator of adenosine A2A receptors
10	**Rintaro Otani**	Development of photocaged drugs targeting adenosine 2A receptor
11	**Keita Kajino**	Design and synthesis of novel κ opioid receptor agonists with bicyclo [2.2.2] octane skeleton
12	**Kao Hashimoto**	Analysis of orexinergic function in chronic pain-like states
13	**Insung Park**	Orexin receptor antagonist modulates sleeping energy metabolism without overt effects on sleep architecture
14	**Yue Cao**	Does different-intensity exercise affect the rest-activity rhythms among older adults?
15	**Saki Tsumoto**	A Study on Automatic Sleep Analysis for a Variety of Sleep Patterns
16	**Javier Diaz**	Assessing Wakefulness Intensity as a Counterpart to Sleep Depth During the Sleep-Wake Cycle
17	**Zhiwei Fan**	Binaural beats at slow frequencies less than 1 Hz shorten the latency of slow-wave sleep
18	**Kazuki Sato**	Targeted memory reactivation during REM sleep selectively enhances brain responses to unpleasant images
19	**Hibiki Okamura**	Exploration of a novel mechanism of sleep regulation that depends on feeding condition
20	**Ami Kaneko**	Analysis of the mechanism of REM sleep with focus on Parkinson's disease
21	**Srinivasan Sakthivel**	Transient recruitment of adult-born neurons for fear memory consolidation in REM sleep
22	**Vergala Pablo**	CaliAli: neuronal tracing utilizing vasculature in calcium imaging
23	**Noriko Hotta-Hirashima**	Sex difference in sleep/wakefulness from infancy to adulthood in a hypersomnia model, Sleepy mutant mouse
24	**Liqin Cao**	Sleep disturbances in mice with a CDKL5 kinase-dead missense mutation, a novel mouse model of neurodevelopmental disorder
25	**Tomoyuki Fujiyama**	NALCN in the forebrain and pons-medulla regions have distinct roles in REM sleep regulation
26	**Minjeong Park**	Sleep/wake behavior of mice lacking PKA-phosphorylation sites of SIK3
27	**Tomohiro Kitazono**	Novel upstream and downstream pathways of SIK3 in the regulation of sleep and wakefulness
28	**Shinya Nakata**	Molecular mechanisms for sleep/wake regulation by SIK3 kinase signaling
29	**Fuyuki Asano**	SIK3-HDAC4 in the suprachiasmatic nucleus regulates the timing of arousal at the dark onset and circadian period in mice
30	**Kanako Iwasaki**	SIK3 regulates sleep amount through hypothalamic nuclei

MEMO



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