Symposium 8: Novel brain functions revealed by precise measurement and manipulation of monoamine signals (Thu July 29, 16:40-18:40 JST)
Chair: Sho Yagishita (Univ of Tokyo, Japan)

16:40-17:10 Yuki Sugiura (School of Medicine, Keio University , Japan)
***In situ* imaging of monoamine localization and dynamics by mass spectrometry**

17:10-17:40 Rui Lin (National Institute of Biological Sciences, Beijing, China)
The raphe dopamine system controls the expression of incentive memory

17:40-18:10 Sho Yagishita (Graduate School of Medicine, The Univ of Tokyo, Japan)
Disinhibitory gating of discrimination learning and spine enlargement by dopamine D2 receptors in the nucleus accumbens

18:10-18:40 HyungGoo Kim (Center for Neuroscience Imaging Research (CNIR) and Department of Biomedical Engineering, Sungkyunkwan University, Korea)
Dopamine signals during spatial navigation

Symposium 8 Speaker 1

Yuki Sugiura
Lecturer
Keio University
Tokyo, Japan
yuki.sgi@keio.jp

In situ imaging of monoamine localization and dynamics by mass spectrometry

Due to recent technical advances in instrumentation and sample preparation protocols, current imaging mass spectrometry (IMS) is now able to visualize the localization of neurotransmitters, including monoamines. Although monoamine-producing neurons, as well as their projections and synapses, have been thoroughly characterized, localization and fluctuation of monoamines within these circuits remains unclear. We addressed this problem with generation of the *in situ* monoamine concentration maps obtained with IMS, which allow us to study fluctuations in local monoamine concentration in response to physiological stimuli, drug administration, and neurodegenerative disease progression. Our recent studies have shown that monoamines accumulate not only in cell bodies expressing enzymes that produce these transmitters (such as TH and TPH), but also in distant nerve terminals. This indicates that they are either actively transported along the axon or synthesized locally at the terminals. Furthermore, since the pharmacokinetics of exogenous drugs can also be visualized with IMS, the development of a method for simultaneous imaging of selective serotonin reuptake inhibitors (SSRIs) and monoamines could reveal where long-term SSRIs accumulate and how they affect local monoamine metabolism. I'll also show that how the stimulated immune metabolism alters brain monoamine signaling, by visualization of deficiency of the serotonin and dopamine in the brain, resulting in behavioral changes.

Symposium 8 Speaker 2

Rui Lin
Postdoc
National Institute of Biological Sciences
Beijing, China
linrui@nibs.ac.cn

The raphe dopamine system controls the expression of incentive memory

Memories of incentive stimuli that are either rewarding or aversive guide future behavioral choices, and their proper formation and expression are essential for animals' survival. Memory formation and expression are controlled by a distributed network that consists of multiple cortical and subcortical areas. These brain areas are subject to the regulation by the neuromodulatory systems, for example the dopamine (DA) system. In both invertebrates and vertebrates, DA fundamentally contributes to memory formation. In mammals, DA neurons in the canonical ventral tegmental area (VTA) of the midbrain are important for appetitive associative learning and the formation of reward memories. It remains unclear whether the VTA DA population and/or other DA populations outside the VTA are involved in memory expression. The dorsal raphe nucleus (DRN) harbors a major extra-VTA DA population. Recent progress suggests these neurons' involvement in arousal, social interaction, and fear response. However, little is known about their potential functions in memory expression. In this study, we use a combination of approaches to investigate the behavioral roles of DRN DA neurons in the expression of natural and drug memory. We found that the DRN DA population functions as an essential regulator of memory expression under normal conditions and in opioid addiction, and further identified a brainstem input to the DRN that is modified by opioid administration and is critical for the expression of reward memory.

Symposium 8 Speaker 3

Sho Yagishita
Lecturer
Department of Structural Physiology, School of Medicine, University of Tokyo
Tokyo, Japan
syagishita@m.u-tokyo.ac.jp

Disinhibitory gating of discrimination learning and spine enlargement by dopamine D2 receptors in the nucleus accumbens

Transient changes in dopamine activity in response to reward have been known to regulate reward-related learning. However, the cellular basis that detects the transient dopamine signaling has long been unclear. The striatum consists of two types of spiny-projection neurons (SPN), dopamine 1 receptor (D1R)-expressing and D2R-expressing SPNs. Previously, we characterized the role of dendritic spines of D1R-SPNs in the detection of a phasic burst of dopamine to regulate synaptic plasticity and reward-related learning. In contrast, the nature of D2R-dependent behaviors and the cellular mechanisms for detection of dopamine signaling has been unclear. The high affinity of D2R has implies that it has a role in the detection of decreases in dopamine concentration (DA dip) for punishment learning. We thus addressed the D2R function in plasticity and learning using optogenetic control of DA dips and inhibition of D2R signalling, both in vivo and in slice and found that D2R-SPNs detected DA dips for spine enlargement to refine the generalized reward learning formed by D1Rs. Moreover, we found that a repeated methamphetamine treatment, a model for psychosis, hindered the discrimination learning and a D2R antagonist restored it by enhancement of the plasticity, providing a novel view to understand psychotic symptoms of schizophrenia.

Symposium 8 Speaker 4

HyungGoo Kim
Assistant Professor
Center for Neuroscience Imaging Research (CNIR) and Department of Biomedical Engineering, Sungkyunkwan University)
Suwon, Korea
hyunggoo.r.kim@gmail.com

Dopamine signals during spatial navigation

Rapid phasic activity of midbrain dopamine neurons is thought to signal reward prediction errors (RPEs), resembling temporal difference errors used in machine learning. However, recent studies have reported slowly increasing dopamine signals in the ventral striatum during spatial navigation. It was proposed that the dopamine ramps represent state values. We developed experimental paradigms using virtual reality that disambiguate RPEs from values. In the virtual environment, we teleported animals or changed the speed of movement, which allowed us to examine dopamine circuit activity at various stages, from somatic spiking to the dopamine concentration in the ventral striatum. Our results demonstrate that ramping dopamine signals are consistent with RPEs rather than value. Dopamine ramps were typically not observed in the classical conditioning tasks using discrete sensory stimuli. What makes dopamine ramp? To address this issue, we used a moving-bar stimulus that indicates a gradual approach to a reward. We found that ramping dopamine signals can be driven by a dynamic stimulus without navigation components. The dopamine signals in the moving-bar tasks are also consistent with RPEs. We provide a unified computational understanding of rapid phasic and slowly ramping dopamine signals: dopamine neurons perform a derivative-like computation over values on a moment-by-moment basis.