国際ワークショップのお知らせ

「記憶と認知の脳機構に関する最新の知見」
"Memory, Cognition, and the Brain State"

統合脳、理研脳科学総合研究センター、玉川大学ＣＯＥの共催で行ないます。
最先端の研究を、今注目を浴びている気鋭の研究者が語ります。是非参加してください。

日時：7 月 29 日（土）13:00-17:20
場所：玉川大学　大学研究室棟　B104 教室
　　（小田急線玉川学園駅下車、大学正門から 50m北進、左手）
July 29th (Sat) 13:00-17:20
Tamagawa University, University Research Building B104 (B1Floor)

【プログラム】
13:00-14:00 A. Grace, Interactions among prefrontal cortex, hippocampus, and amygdala in the control of motivated behavior

14:00-15:00 M. Walker, Tonic Inhibition in health and desease

Coffee break

15:20-16:20 S. Fusi, Learning and forgetting on multiple timescales: models and experiments

16:20-17:20 M. Wilson, Memory formation and reactivation in the hippocampus

################ Abstracts ############################

1) A. Grace
The limbic system consists of brain regions that regulate emotion and direct motivated behavior. This system is comprised of several interconnected regions, among these being the hippocampus, the amygdala, and the nucleus accumbens. The ventral hippocampal region is an area that is believed to control context-related behaviors, and in this

way provides a means for the organism to direct responses based on the context or setting in which the behavior is taking place. The amygdala is an area that is involved in controlling emotional expression, and shows activation whenever an organism is exposed to a stressful or threatening situation. The prefrontal cortex, being the highest neocortical region in the mammalian brain, exerts a potent regulatory influence over these systems, and in turn, is affected by the state of the limbic system. Each of these regions has overlapping projections within a brain area known as the nucleus accumbens. The dopamine neurotransmitter system exerts potent modulatory control over these afferent systems and the way that they interact within the accumbens. Through this interaction, there is a potent regulation of motivated behavior.

Using in vivo intracellular recordings in rats, we found that the hippocampus subiculum (the limbic portion of the hippocampus) provides a potent gating influence over the nucleus accumbens. Thus, the hippocampus drives accumbens neurons into a bistable activity pattern, in which the membrane is either in a hyperpolarized or "down" state, in which it is nonresponsive to inputs, or in a depolarized or "up" state and capable of being activated by inputs. When the hippocampus drives the accumbens into an "up" state, afferent drive from the prefrontal cortex is capable of causing these neurons to fire, which through a return feedback system projects back to the prefrontal cortex to "reinforce" a response pattern. In this way, the hippocampus provides a context-dependent gate over the way that the prefrontal cortex can modulate motivated behavior. The amygdala also has a potent excitatory input to the accumbens. In contrast to the hippocampus, the amygdala input is very brief, so any effect it has will be restricted to single events. Given that the amygdala is driven by emotional stimuli, it has the capacity to provide an emotional over-ride to motivated behavior when the organism is in a threatening situation.

The dopamine system exerts a powerful regulation over the inputs coming from these regions. When the dopamine system is in a low activity state (i.e., the neurons are firing in a single spike pattern), the constant tonic levels of dopamine in the accumbens act on dopamine D2 receptors to preferentially attenuate the input coming from the prefrontal cortex. In contrast, when there is a behaviorally salient event, the dopamine neurons fire bursts of spikes; this phasic dopamine input acts on dopamine D1 receptors to selectively potentiate the hippocampal drive. Therefore, when dopamine transmission is increased, there is a shift in the balance of the system away from prefrontal cortical control and toward limbic predominance. This interaction is reflected by its impact on goal-directed behavior. Thus, when the hippocampal input is pharmacologically disconnected from the accumbens, rats have a difficult time acquiring learned behavior.

However, if the prefrontal cortex is disconnected, the animals can learn a task rapidly; however, if the contingencies of the task are altered, the rats show perseveration ? i.e., they keep responding according to the old rules and fail to learn the new task.

The prefrontal cortex and hippocampus also show long-term plasticity in their interactions. Thus, high-frequency stimulation of the hippocampus induces long-term potentiation (LTP) of the hippocampal drive and long-term depression (LTD) of the prefrontal drive to the accumbens. In contrast, activation of the prefrontal input induces LTP in the prefrontal input and LTD in the hippocampal input. Therefore, these systems compete for influence over the accumbens. These types of plasticities also have a functional impact on the system. Thus, if a rat is treated repeatedly with cocaine, the system reacts in a similar manner as with stimulation of the hippocampus. As a result, following cocaine sensitization the rats exhibit perseverative behavior mediated by a hippocampal predominance. This could account for the highly focused drug-seeking behavior and the resistance to behavioral change in individuals that abuse cocaine. These types of complex system-wide interactions are believed to have important implications with respect to psychiatric disorders such as schizophrenia and drug abuse. The ability of the prefrontal cortex to elicit behavioral flexibility is an essential feature of its function; if this is disrupted by genetic predisposition to a disorder such as schizophrenia or by the influence of drug abuse, it will lock the individual into pathological behavioral states.

2) Matthew Walker

GABA is the major inhibitory neurotransmitter in the brain. It mediates it effect through ionotropic GABAA receptors and metabotropic GABAB receptors. There are a large variety of GABAA receptor subtypes in the central nervous system. These demonstrate different regional and subcellular expression. In addition, the receptors have very different properties with differing conductances, affinities for GABA and propensity to desensitize. Synaptic GABAA receptor mediated signaling provides a powerful means of regulating the temporal fidelity of excitatory transmission. Furthermore, GABAergic interneurones are necessary for the emergence of certain network oscillations, which may provide a context for network activity. In addition, extracellular GABA can tonically activate high-affinity, extrasynaptic GABAA receptors. Tonic currents are developmentally regulated, depend on synaptic and non-synaptic GABA release and are modulated by GABA uptake. Furthermore, the expression of these currents varies from

region to region and they demonstrate cell type specificity (e.g. interneuron versus pyramidal cell expression) that has important network implications.

Tonic GABAA receptor currents play critical roles in regulating neuronal and network excitability. More recently tonic currents have been shown to play a part in determining neuronal firing patterns, and modifying neuronal development. Such currents are dependent on both the expression of receptors and also the concentration of extracellular GABA. The latter can vary three-fold during changes in physiological state. Indeed, it is likely that tonic inhibition is a dynamic entity that may play a role in regulating memory, cognition and sleep. Furthermore, expression of the receptors that mediate tonic inhibition changes during the ovarian cycle, and this has been linked to changes in seizure susceptibility and anxiety. Tonic currents also show adaptive behaviour, increasing in pathological conditions such as epilepsy. Thus, tonic inhibition possesses both short-term and longer-term plasticity that can adapt in response to physiological and pathological change.

The multifarious role of GABAergic signalling has meant that it is the target for anaesthetic, sedative, anxiolytic and antiepileptic therapies. Additionally, the more complex role of GABAergic signalling in the regulation of memory and cognition has led to speculation that targeting GABAA receptors mediating tonic inhibtion may be an effective approach for enhancing memory and the treatment of conditions such as schizophrenia. The identification of compounds that target only specific GABAA receptor subtypes will hopefully lead to a pharmacological dissection of the different roles of synaptic/extrasynaptic GABAA receptor mediated signalling, and will open up the possibility of targeted therapies.

3) S. Fusi

Memories, maintained in patterns of synaptic connectivity, can be over-written and destroyed by ongoing plasticity arising from the storage of new memories. Such overwriting leads to forgetting and memory lifetimes that are only proportional to the logarithm of the number of synapses being used to store the memories (Amit Fusi 1994, Fusi 2002). This poor memory performance arises from imposing reasonable limits on the range of allowed synaptic efficacies because memories are destroyed when synapses reach the bounds on their strengths. We explore whether memory performance can be improved by allowing synapses to traverse a large number of states before reaching their bounds, or by changing the way in which these bounds are imposed. We show that the neither of these solutions affects the logarithmic dependence of memory capacity on the number of synapses used to store the memories. Changing this requires a more dramatic shift

in the way synapses store memories. We construct a model in which each synapse has a cascade of states with different levels of plasticity, connected by meta-plastic transitions. We show that such a model performs orders of magnitude better than alternative models which do not have meta-plasticity (Fusi, Drew, Abbott 2005). The mnemonic trace of cascade models decays with a power law, and hence it is scale invariant (in practice it decays with same law on all timescales).

What is the importance of scale invariance? We investigate this issue by analyzing and modeling an experiment performed on behaving monkeys in E.K. Miller's laboratory at MIT (Asaad, Rainer, Miller 1998). We show that there is direct evidence for learning on multiple timescales in the experimental data. The existence of these multiple learning components allows to solve the problem of fine tuning in models of decision making (Wang 2003). This last part of the work has been done in collaboration with X.-J. Wang (Yale) and W. Asaad and E.K. Miller (MIT).