DIVISION OF BRAIN CIRCUITS

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Various firing patterns of many cortical neurons represent information processing in the brain. The microarchitecture of synaptic connections control information processing in cortical circuits. The structure and location of synapses determine and modify the strength of this information processing. The aim of our laboratory is to reveal how information is formed, maintained, selected, and decoded in the brain at the levels of single cells and of single synapses. To do so, we mainly use two-photon microscopy that allows us to see fluorescence signals from deep within living tissue, developing novel photostimulation methods and animal behavioral tasks.

I. Development of novel techniques to photostimulate cortical neurons in vivo

We developed a method that uses Channelrhodopsin-2 (ChR2; blue-light-activated cation channel) for transcranial optogenetic stimulation. This method is based on scanning a light beam over the brain, thereby photostimulating ChR2-expressing neurons in intact mice. The laser illumination induced forelimb movement in two areas; rostral forelimb area (RFA) and caudal forelimb area (CFA). The motor forelimb areas determined by this photostimulation mapping corresponded to those determined by intracortical microstimulation (ICMS). We also revealed functional synaptic connections between RFA and CFA, by recording electrical signals in either area during the photostimulation mapping. In addition, we developed a method that uses Halorhodopsin (NpHR; yellow-light-activated chloride ion pump) for inactivating cortical neurons in vivo. Yellow light illumination on the cortical surface of NpHR transgenic mice inhibited the forelimb movement induced by ICMS in RFA. As these photostimulation methods were effective even to awake mice, these methods can be applied to the experiments described below.

II. Development of a novel operant task of head-restrained mice

To carry out two-photon calcium imaging while mice performed a self-initiated movement, we developed a head-restrained lever-pull task. Mice used the right forelimb to pull a lever for a given time and were rewarded with a water drop from a spout near the mouth, while simultaneously the lever was quickly pushed back to the wait position. Then, mice had to wait with the lever in the wait position for a while until the next trial. During the training sessions, task difficulty was increased by gradually increasing the lever-pull time. However, mice could increase or maintain the number of successful trials (>100) and the intertrial interval time decreased. After 8-9 training sessions, mice reliably performed this task. We are also improving this task for future research.

III. Spatio-temporal representation of motor information in the brain

The aim of this study is to reveal how voluntary movement is represented in cortical circuits. One of the most important problems in neuroscience is how a variety of spatio-temporally heterogeneous neural activity in the cortex emerges moment-by-moment at multiple stages of a movement. To reveal how their activities are organized in the local circuit, we carried out two-photon calcium imaging in the layer 2/3 RFA and CFA of mice performing the lever-pull task after the training sessions. We have found many types of neurons in the local circuit. We are now analyzing the activity, distribution, and connections of the cortical neurons involved in sequential motor phases. The activities of the cortical neurons will be modulated by using the optogenetic stimulation methods to clarify the direction of flow of motor information. Our results will provide insights into the principles of circuit operation and the cellular basis for recovery from brain cortical damage.

Publication List

〔Original papers〕

- Ako, R., Wakimoto, M., Ebisu, H., Tanno, K., Hira, R., Kasai, H., Matsuzaki, M., and Kawasaki, H. (2011). Simultaneous visualization of multiple neuronal properties with single-cell resolution in the living rodent brain. Mol. Cell. Neurosci. *48*, 246-257.
- Kanemoto, Y., Matsuzaki, M., Morita, S., Hayama, T., Noguchi, J., Senda, N., Momotake, A., Arai, T., and Kasai, H. (2011). Spatial distributions of GABA receptors and local inhibition of Ca^{2+} transients studied with GABA uncaging in the dendrites of CA1 pyramidal neurons. PLoS ONE *6*, e22652.
- Matsuzaki, M., Ellis-Davies, G.C.R., Kanemoto, Y., and Kasai, H. (2011). Simultaneous two-photon activation of presynaptic cells and calcium imaging in postsynaptic dendritic spines. Neural Syst. Circuits *1*, 2.
- Matsuzaki, M., and Kasai, H. (2011). Two-Photon Uncaging Microscopy. Cold Spring Harbor Protocols, pdb.prot5620.
- Noguchi, J., Nagaoka, A., Watanabe, S., Ellis-Davies, G.C.R., Kitamura, K., Kano, M., Matsuzaki, M., and Kasai, H. (2011). In vivo two-photon uncaging of glutamate revealing the structure-function relationships of dendritic spines in the neocortex of adult mice. J. Physiol. *589*, 2447-2457.

Note: Those members appearing in the above list twice under different titles are members whose title changed during 2011. The former title is indicated by an asterisk (*).