【Grant-in-Aid for Scientific Research(S)】

Integrated Science and Innovative Science (Comprehensive fields)

Title of Project : Elucidation of neural mechanisms of primate cognitive memory using an integrated approach of magnetic resonance imaging and optogenetic manipulation

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Research Area : Comprehensive fields
Keyword : Cognitive neuroscience

【Purpose and Background of the Research】

Recent advances toward elucidating the network mechanisms of the primate cognitive memory system mostly focused on electrophysiological analyses of local neuronal circuits in the cerebral cortex. However, it is difficult to apply those approaches to the elucidation of brain-wide global network interactions. Functional magnetic resonance imaging (fMRI) has been one of the most powerful approaches in the whole-brain analysis, although fMRI can provide only correlative evidence. In the present study, we will combine the recently developed optogenetic manipulation method with fMRI in monkeys, aiming at obtaining causal evidence about global network interactions, particularly the interaction between the temporal cortex and prefrontal cortex in the retrieval of cognitive memory.

【Research Methods】

(1) Optogenetic manipulation of cortical neural circuit in monkeys

We will first develop a method of gene delivery that enables optogenetic excitation and/or inhibition of cortical neurons in monkeys. We will use lenti-viral vectors and AAV vectors (mostly AAV-5, AAV-8 and AAV-9) for gene delivery, and ChR2 and eNpHR for excitation and inhibition of cortical neurons, respectively. For circuit-specific gene delivery, we will examine an approach using the retrograde transport of modified lenti-viruses. Each of these techniques has been separately tested in rats in our laboratory, and an integration of these techniques in the monkey cerebral cortex is a challenge in this study. We will also develop a new minimally invasive optrode that enables the long-term exploration of deep brain structures in behaving monkeys for months.

(2) fMRI measurement of propagation of perturbation in cortical networks in monkeys

We have already established a whole-brain activity mapping method (BOLD activation mapping) using fMRI in monkeys. In this study, we aim to develop a new fMRI-based approach that quantitatively visualizes the propagation of perturbation that was initiated in a cortical area. We will first use a pharmacological perturbation that was caused by a local injection of a GABA agonist (muscimol) and analyze the dynamic change in the resting-state functional connectivity (rsFC). When an optogenetic manipulation method of monkey cortex becomes available (see above (1)), the pharmacological perturbation will be replaced by the optogenetic method that can control the origin of the perturbation more precisely.

(3) fMRI measurement of propagation of an optogenetic perturbation in monkeys performing cognitive memory tasks

By combining the achievements from (1) and (2), we will analyze the causal effect of optogenetic excitation and/or inhibition of the temporal association cortex and prefrontal cortex, both at the behavioral level and neural circuit level. We will train monkeys to perform two memory tasks: a serial probe recognition task and a recency judgment task. A standard BOLD activation analysis will be carried out while the monkeys perform the task, and the rsFC analysis will also be done in the monkeys. Then, ChR2 and eNpHR will be expressed in a hub-like cortical area that was activated by the tasks, and the causal effect of the optogenetic manipulation will be analyzed.

【Expected Research Achievements and Scientific Significance】

In this study, we combine the optogenetic manipulation of cortical neurons with 4.7 Tesla fMRI measurements and examine its global whole-brain effects in the monkey cerebral cortex. This approach will reveal causal mechanisms of cognitive memory both at the behavioral level and neural network level. The study will have profound impact in our understanding of how the primate cerebral cortex creates and retrieves declarative memory.

【Publications Relevant to the Project】

- Takeuchi, D., Hirabayashi, T., Tamura, K. and Miyashita, Y. : Reversal of interlaminar signal between sensory and memory processing in monkey temporal cortex. *Science* 331, 1443-1447, 2011.
- Matsui, T., Koyano, K.W., Koyama, M., Nakahara, K., Takeda, M., Ohashi, Y.,Naya,Y. and Miyashita, Y. : MRI-based localization of electrophysiological recording sites within the cerebral cortex at single voxel accuracy. ***Nature methods*** 4, 161-168, 2007.

【Term of Project】 FY2012-2016

【Budget Allocation】 167,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.physiol.m.u-tokyo.ac.jp/