【Grant-in-Aid for Transformative Research Areas（A)】

Section Ⅲ

Title of Project： Inducing lifelong plasticity (iPlasticity) by brain rejuvenation: elucidation and manipulation of critical period mechanisms

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【Purpose of the Research Project】

Brain function is greatly influenced by experience during postnatal development. Early in life, neural wiring is dramatically reorganized to reflect input from the environment in such “critical periods (CPs)” – restricted times during which plasticity of neuronal connectivity is particularly high. (Fig. 1). Salient CP experiences are etched into neural circuits that persist throughout life. For example, if juvenile animals are deprived of vision through one eye, that eye becomes virtually blind for the remainder of the animal’s life if not corrected during their CP. It is then anticipated that CP reopening in adulthood might enable recovery of impaired neural function or the acquisition of additional brain functionality. Indeed, recent studies have demonstrated the possibility to advance or delay CP onset as well as to reopen them in adulthood. (Fig. 1). Furthermore, after brain injury, neural circuit plasticity seems to be transiently enhanced to facilitate functional recovery, analogous to a “CP” seen in normal development. In our Transformative Research Area, we therefore redefine CP as a limited time window of elevated capacity for plasticity and reorganization of neural circuits potentially throughout life. We aim to deepen our understanding of the development of brain and mind by pursuing basic mechanisms of CPs and to induce lifelong plasticity (iPlasticity) by brain rejuvenation.

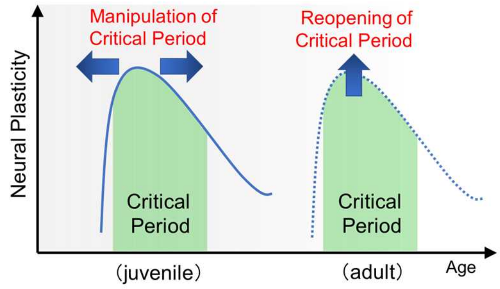

Figure 1. Critical Period and Its Manipulation and Reopening

【Content of the Research Project】

We established two research categories, A01: “Mechanisms of neural circuit reorganization in CPs during development” and A02: “Manipulation and reopening of CPs and mechanisms of CPs after brain injury”. In A01, the investigators will pursue the mechanisms of CPs in the developing nervous system in relation to synapse pruning, E/I balance (i.e., ratio of excitatory and inhibitory inputs) and social interaction. Masanobu Kano investigates how neural activity regulates synapse pruning during postnatal cerebellar development in mice. Mariko Miyata examines the difference between synapses that are strengthened and survive throughout life from those that are weakened and eventually eliminated by synapse pruning in the developing sensory thalamus. Kenichi Ohki investigates how neurons in the primary and higher visual cortices acquire response diversity during their CPs in developing mice. Motokazu Uchigashima examines structural plasticity of dendritic spines that leads to neural circuit reorganization in visual cortical neurons during the CP. Sho Tsuji performs quantitative analyses on the influence of language experience in the CP for native language acquisition in human infants.

In A02, investigators pursue how to manipulate timing and duration of CPs in the developing nervous system, how to reopen CPs in adulthood, and how to facilitate recovery from brain injury. Takao Hensch elucidates the mechanisms by which attention and arousal influence neural circuit plasticity during CPs and how to develop the means to reopen CPs in adult mice. Takashi Kanamaru theoretically investigates how neural networks acquire nonlinear dynamics such as stable attentional states during the CP. Takuya Takahashi measures the density and distribution of AMPA receptors and $GABA_A$ receptors and estimates the E/I balance in the human brain after stroke by using PET. Junichi Ushiba develops means to facilitate the formation of compensatory neural circuits in post-stroke subacute brains by using brain-machine interface (BMI) technology.

【Expected Research Achievements and Scientific Significance】

Our knowledge about the mechanisms of neural circuit reorganization during CPs of the developing nervous system will be greatly advanced. Discovery of the means to manipulate and reopen CPs may lead to novel therapy of neurodevelopmental disorders such as amblyopia, speech and hearing disorders. Developing effective rehabilitation procedures alongside methods for monitoring E/I balance in the human brain is expected to facilitate functional recovery after stroke. Furthermore, the outcome of our research area may give insights into infant care, education and clues to develop novel brain- inspired Artificial Intelligence.

【Key Words】

critical period: restricted time during which plasticity of neuronal connectivity is particularly high and neural wiring is reorganized to reflect input from the environment

【Term of Project】 FY2020-2024

【Budget Allocation】 1,247,500 Thousand Yen

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