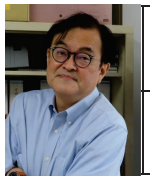
【Grant-in-Aid for Scientific Research (S)】

Elucidating the pathogenesis of and development of therapeutic strategies against the neuropsychiatric disorders in the primate models by utilizing the gene introduction and manipulation technologies



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Project Information	Project Number : 22H04992 Project Period (FY) : 2022-2026 Keywords : adult brain, plasticity, neuropsychiatric disorders, functional recovery, primate

Purpose and Background of the Research

●Outline of the Research

We will aim at (1) promoting the recovery of dexterous movements after spinal cord injury, (2) deciphering the mechanism and developing the therapeutic strategies against addition caused by impairment of healthy decision making, and (3) understanding the pathophysiology and developing the therapeutic therapies against the psychosis, all by inducing the massive plasticity of neural circuits in the adult primate brain by combining the selective stimulation of neural circuits, training and drug therapies.

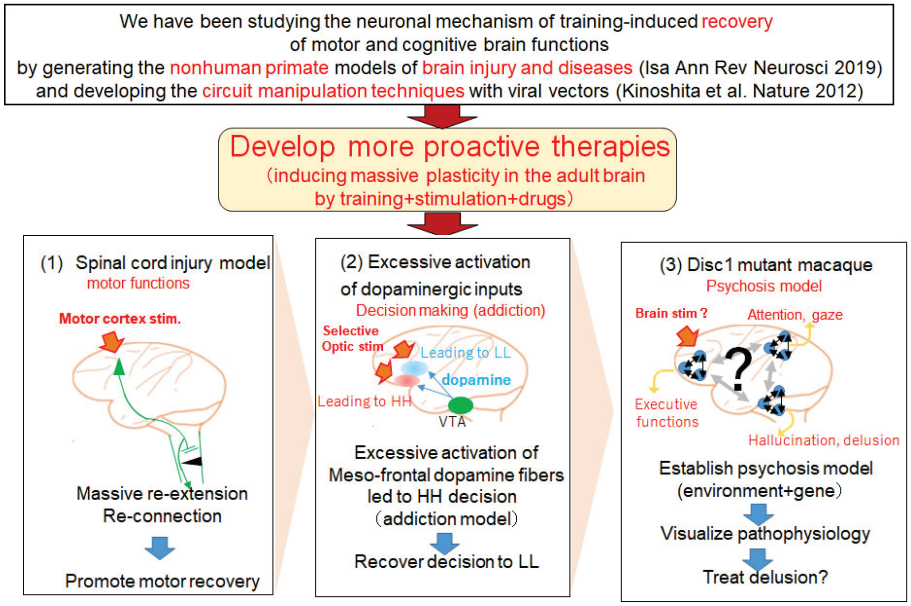

Figure 1. Three models of neuropsychatric disorders we tackle in this project

●Induction of massive plasticity in the adult brain will change the treatment of intractable neuropsychiatric disorders

We recently found in a macaque monkey model of subhemisection spinal cord injury that through intensive rehabilitative training and weekly extensive cortical stimulation through the chronically implanted electrocorticography electrodes, a large number of the corticospinal tract fibers originating from the contralesional motor cortex changed their course at the pyramidal decussation, descended in the contralesional lateral funiculus and reconnected to motoneurons after recrossing caudal to the lesion. We will apply this concept of massive plasticity in the adult brain to understand the mechanism and develop the therapeutic strategies against other neural disorders including addiction and psychosis in nonhuman primate models.

Expected Research Achievements

●Deciphering the mechanisms to induce the massive plasticity in the subhemisection spinal cord injury model

(1) We will clarify when the massive plasticity starts after the spinal cord injuries by injecting the anterograde neural tracers.

(2) We will clarify whether the corticospinal neurons with massive plasticity contributed to the recovery, by blocking transmission through these neurons with the double viral vector-based pathway-selective manipulation technique.

(3) We will clarify the change in the gene regulatory network in the corticospinal neurons that showed the massive plasticity by using the single nucleus RNA sequencing analysis.

(4) To examine whether the gene regulatory network revealed in (3) really contribute to the axonal re-routing the functional recovery, we will identify the hub-gene of the network and knock it down by expressing its shRNA by AAV in the contralesional motor cortex and test whether it perturbs the plasticity and recovery.

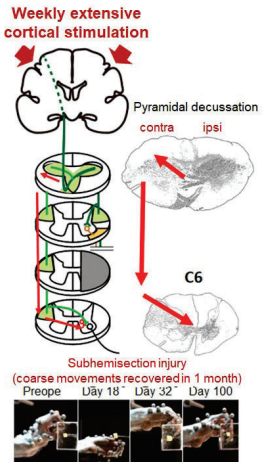

Figure 2 Induction of massive plasticity in the subhemisection spinal cord injury macaque model

●Shift if risk-dependent decision by excessive activation of meso-cortical dopamine fibers

While the monkey looks at a central fixation point, we present a pair of targets with different colors to the left and right, and require the monkey to shift the gaze to either of them. Each color is assigned with different reward probability and amount. For instance, selection of the red gives large reward in only 10% trials, the high risk-high return (HH) choice, while the blue is assigned with small reward in 90% trials, the low risk-low return (LL) choice. Optogenetic activation of dopaminergic inputs to the vlPFC shifted the monkey's decision to the HH mode both in the trial-by-trial basis and in a longer time course. Thus, excessive activation of mesofrontal dopaminergic fibers could underlie addiction such as gambling disorders. We also found activation of dopaminergic inputs to another frontal area reduced HH-preference, which might be a tool to treat the addictive behaviors including gambling disorders.

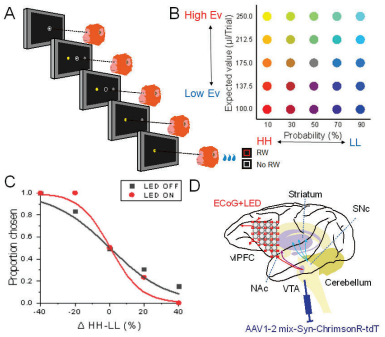

Figure 3 A. Decision task design. B. Assignment of reward probability and magnitude to the colors. C. Psychometric function. D. Design of optogenetic experiments. v

●Induction of psychosis in macaque monkeys with mutation of Disc-1 gene by genome editing technology to develop the therapeutic strategies

Disc1 is a hub gene of the interactome of a number of psychosis-related proteins. Therefore we expected that mutation of Disc-1 gene will cause dysfunction of a number of these proteins and induce psychosis phenotypes. We created Disc-1 mutant macaques in collaboration with Shiga University of Medical Sciences. We combine the social stress and drug administration analyze a variety of behaviors and brain activity of the mutant macaques, and gene expression of iPS cell-derived cell lines and brain organoids. Once we can establish the animals with psychosis phenotype, we will try to cure them by brain stimulation etc.

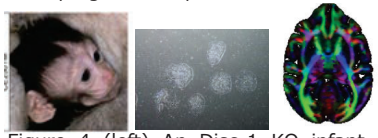

Figure 4 (left) An Disc-1 KO infant macaque. (middle) iPS cells derived from the Disc-1 mutant monkey. (right) diffusion tensor imaging of the macaque brain.

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