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

Understanding primate serotonergic function in interaction with the extended Umwelt

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Purpose and Background of the Research

●Outline of the Research

Serotonin, a key neurotransmitter, plays multifaceted roles in emotion, cognition, and social behavior in rodents, providing insights into its potential functions in primates, including humans. However, a significant knowledge gap persists in our understanding of serotonin's involvement in the pathogenesis of neuropsychiatric diseases and the mechanisms underlying therapeutic interventions. This project seeks to bridge this gap by testing the hypothesis that serotonin is pivotal in reducing environmental uncertainty, thereby contributing to homeostasis within the primate Umwelt. We propose to investigate the neural underpinnings of serotonin's role using advanced chemogenetic technology to precisely manipulate serotonergic circuits.

Our approach encompasses two key investigative strands: ❶ the modulation of reward-based environmental information processing, and ❷ the utilization and manipulation of information within virtual reality settings. These dimensions will allow us to dissect the serotonergic network's influence on behavioral adaptation and neural representation. By juxtaposing the resulting data with observations from human subjects, both neurotypical and those undergoing serotonin-targeted therapies, we aim to construct a comprehensive model of serotonin function. This model will span the spectrum from normative brain function to the aberrations observed in disease states

Our research will provide groundbreaking insights into serotonin's role as a homeostatic regulator within the complex neural networks of primates and lay the groundwork for novel therapeutic strategies.

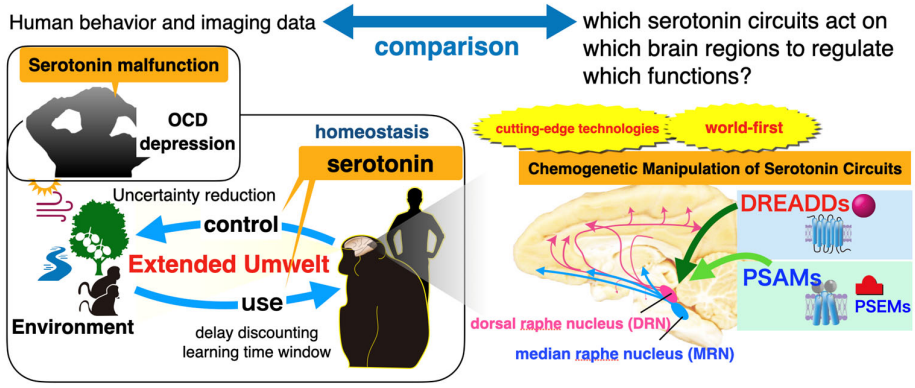

Figure 1. illustrates the proposed research methodology and expected outcomes.

●Background

We have reported that serotonin in macaques and humans plays an important role in regulating learning parameters for the use of environmental information, such as the value of rewards that can be obtained with a delay after an action (delay discounting) and how far back one learns from the past experiences (learning time window), which are crucial for maximizing the rewards obtained from the environment.

Alterations in these learning parameters have been shown to explain the repetitive compulsive behaviors seen in OCD patients, as well as the therapeutic effects of serotonin reuptake inhibitors, thus bridging the gap to clinical application.

As a breakthrough in understanding primate serotonin function, we have successfully suppressed serotonin-specific neural activity in primates using chemogenetic methods, enabling circuit-level intervention.

Expected Research Achievements

●Elucidation of the neural basis of primate serotonin function

First, we will construct a serotonin neural circuit map illustrating the brain regions projected from the dorsal raphe nucleus (DRN) and median raphe nucleus (MRN) in monkeys. Next, we will identify the causal role of serotonin in two aspects: ❶ use of reward information, and ❷ use/manipulation of environmental information unrelated to reward, by determining the changes in monkey behavior during chemogenetic manipulation of two serotonin pathways. We will then extract the brain networks associated with the behavioral changes due to serotonin neural manipulation and record neural activity from associated brain regions to clarify neural correlate of serotonin manipulation. Finally, we will compare the neural basis understood through serotonin manipulation in monkeys to the brain networks that reflect therapeutic effects on changes in learning parameters in human obsessive-compulsive disorder (OCD) (Figure 2).

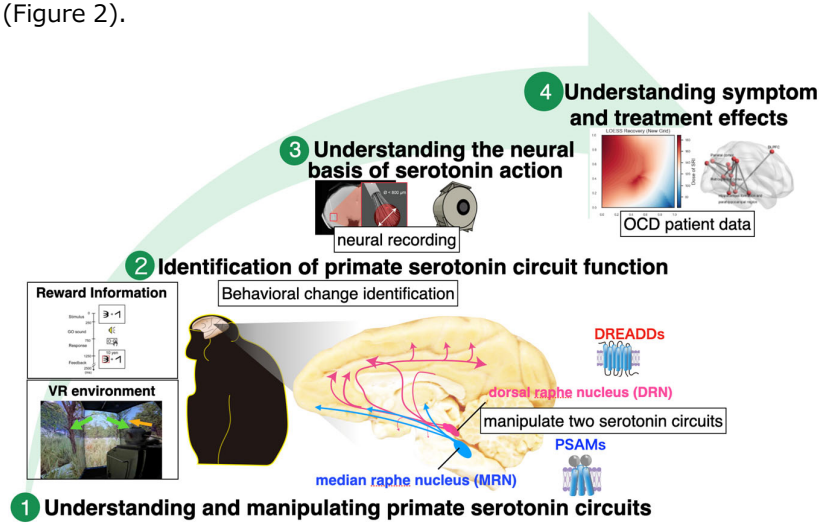

Figure 2. Diagram of the research plan

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