R&D item

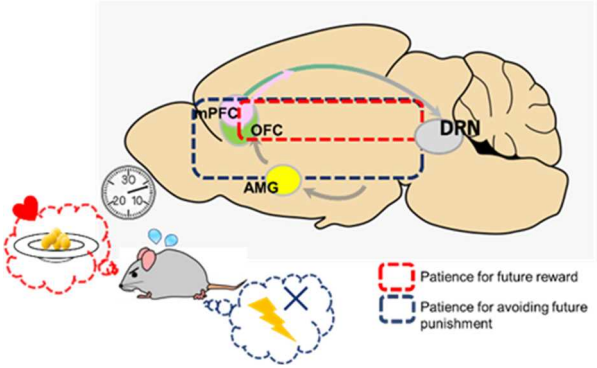
1. Serotonin subsystem for optimism and pessimism: observation and measurement

Progress until FY2023

1. Outline of the project

In this research topic, we focus on the dorsal raphe nucleus (DRN), which is the nucleus origin of serotonergic neurons, and the medial prefrontal cortex, orbitofrontal cortex, and amygdala, which are the projection sites of serotonergic neurons. These brain regions are known as the neural substrates that organize action selection and decision-making based on sensory input and are important for generating our mind. We use invasive methods (fiber photometry, fluorescence microscope camera), which are difficult for humans studies, for observation of neural activity in real time during reward acquisition or punishment avoidance behavior.

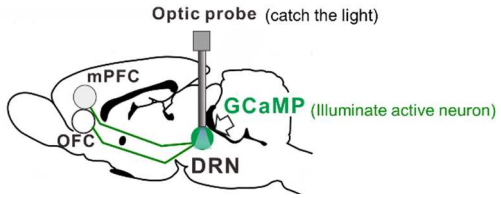
Our hypotheses: Different neural circuits including serotonin neurons contribute to patience behavior for reward acquisition and punishment avoidance.



2. Outcome so far

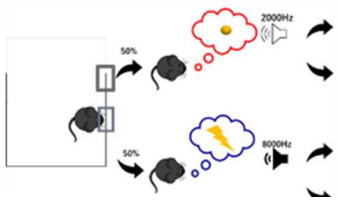
1.1 Observation of serotonergic activity in the DRN

In this study, we observed serotonin neural activity during mice performing a reward waiting task in which reward probability is changed from 25% to 100%. Serotonin neurons show increased activity during waiting for future reward and phasic increased activity to food presentation. We found that serotonin neural activity during waiting periods are modulated by reward probability. This discovery was made possible by combining the latest experimental techniques with behavioral tasks based on our original hypothesis, and is attracting attention from engineering and medical fields as a new role for serotonin.



Fiber photometry recording of serotonin neurons

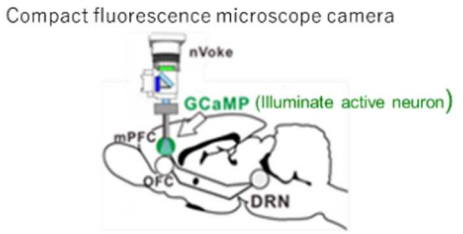
We also introduced reward acquisition/punishment avoidance task in which mice can acquire food in the future by waiting for a few seconds in a designated area (waiting excitedly) or avoid a weak foot shock (waiting helplessly because they do not want to feel pain). From the outside, mice seem to behave in the same way, but the purpose in their minds is different depending on the conditions. We are now observing serotonin neural activity in the DRN under each of these conditions.



Reward acquisition/ punishment avoidance task

1.3 Observation of neural activity in the brain region of serotonin projection

With fluorescence microscope camera, which weighs about 2 g and is attached to mouse's head, we observed hundreds of neural activities in orbitofrontal cortex and medial prefrontal cortex while the mouse performed the reward waiting task. Many neurons responded while waiting for delayed reward suggesting that they may be strongly influenced by serotonin input.



3. Future plans

We will clarify how serotonin neuronal activity in the DRN is expressed depending on whether the goal is to obtain reward or avoid punishment. Using a compact fluorescent microscope camera, we will clarify how the orbitofrontal cortex and medial prefrontal cortex neurons respond during the reward acquisition/punishment avoidance tasks.

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Here begins our new MIRAI
MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

R&D item

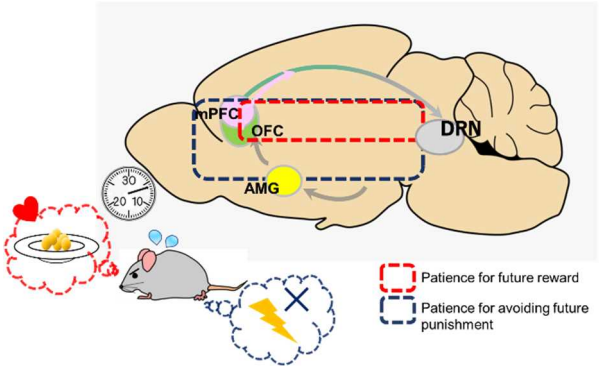
2. Serotonin subsystem for optimism and pessimism: Optogenetics

Progress until FY2023

1. Outline of the project

In this research topic, we directly control neural activity of behaving mice from the outside. Using genetically modified mouse, we use the latest technology called optogenetics, which manipulates neural activity by light, to explore optimism and pessimism in the mind. In the experiment, we examine how mice's behavior and neural activity in serotonin projection sites are affected, when light stimulus manipulates serotonergic neural activity while mice are working hard to achieve their future goals.

Our hypotheses: Different neural circuits including serotonin neurons contribute to patience behavior for reward acquisition and punishment avoidance

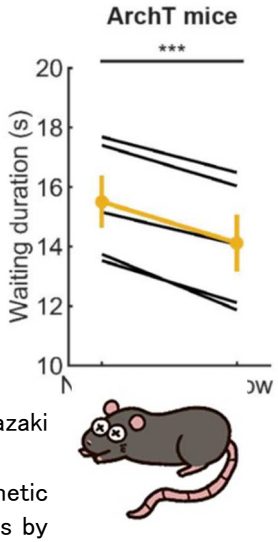


In this study, we focus on the dorsal raphe nucleus (DRN), which is the nucleus origin of serotonergic neurons, and the medial prefrontal cortex, orbitofrontal cortex, and amygdala, which are the projection sites of serotonergic neurons. These brain regions are known as the neural substrates that organize action selection and decision-making based on sensory input and are important for generating our mind. We will verify our original hypothesis with the latest technology and clarify the serotonergic neural mechanism that produces "I'm sure things will go well".

2. Outcome so far

2.1 Behavioral changes by serotonergic manipulation of DRN

In our previous research, when it was predicted that mice would be able to obtain rewards in the future by waiting without getting impatient, optogenetic activation of serotonin neurons during waiting for reward enabled them to wait longer (be patient) (Miyazaki et al., Curr Biol 2014).

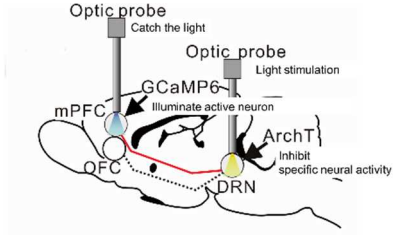


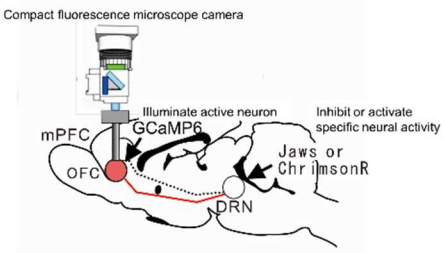
We also found that serotonin, which promotes patience, works differently in medial prefrontal cortex and orbitofrontal cortex (Miyazaki et. al., Sci Adv 2020).
We also confirmed optogenetic inhibition of serotonin neurons by using transgenic mice which selectively express ArchT on serotonin neurons (ArchT mice) during waiting for delayed reward shortened the waiting time (easily gave up) (Taira et al., bioRxiv 2024).

3. Future plans

2.2 Changes in neural activity by serotonin manipulation (excitation/inhibition)

In parallel with these experiments, we will investigate how serotonin neurons in DRN affects neural activity of serotonin projection sites to understand at the network level.





(MIYAZAKI Katsuhiko, MIYAZAKI Kayoko, OIST)

Japan Science and Technology Agency