R&D item

1． Establishment of a VR system to visualize brain function network dynamics

Progress until FY2023

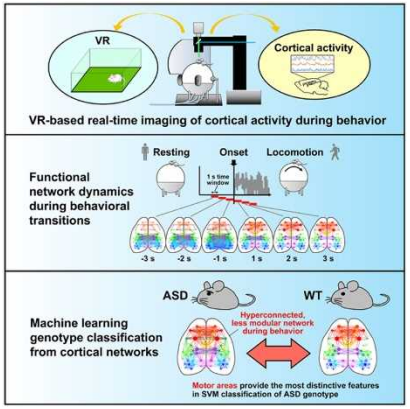
1. Outline of the project

In this R&D item, we will develop a virtual reality (VR) system that can visualize brain function network dynamics by providing various stimuli to mice in action. Furthermore, by combining two VR systems to form a metaverse space, we will quantify the "mental" state of mice when they communicate with other mice in a social environment as changes in their brain function networks.

Image of a mouse exploring a virtual space

2. Outcome so far

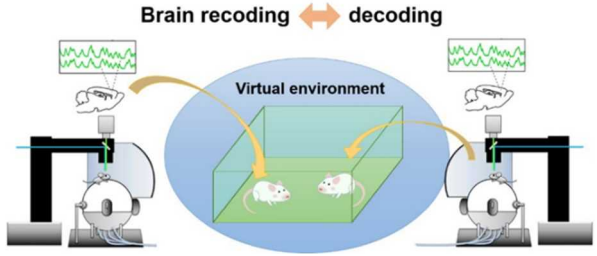
Based on the VR system for visual tasks that the Takumi Group has constructed, we have built a "multimodal VR system" that can provide other sensory information, such as whisker stimuli and odor stimuli, in an integrated and separated manner. The construction of a system that can visualize various sensory stimuli to mice in real-time is unique, and the results were published in Cell Reports, a leading international journal. Using visual stimulation, the system can record cortical neural activity in real-time as the mouse moves freely in a VR space. We succeeded in recording cortical neural network dynamics in response to mouse movements. Using machine learning, we could also predict mouse behavior from the images of the neural network dynamics. Furthermore, when we analyzed autism model mice, we found changes mainly in the motor system module. This suggests motor awkwardness in autism. Machine learning can also predict wild-type and autism models and is considered a fundamental technology for novel diagnostic methods.



We verified that test mice exhibit social interaction by displaying a mouse avatar in a section of the virtual space of a VR system and adding animations that mimic mouse movements and information on the odor of mouse urine. The control group was presented with an object model with added movements and odor information of neutrality. We analyzed the sensory input information (sociosensory stimuli) involved in social interaction based on the combination of visual, tactile, olfactory, and other stimuli.

We also built a machine learning model to predict the walking motion state of mice based on dynamic network information in the brain.

In addition, to investigate the social behavior of two mice in a virtual space, we constructed a prototype of an interactive social virtual reality (iSVR) system using two multimodal VR systems that can separate and integrate sensory stimuli. By linking the two VR systems on a computer, the two mice can actively and passively interact in a way closer to reality.



Interactive social virtual reality (iSVR) system

3. Future plans

Using this iSVR system, it will be possible to examine the functional cortical network and social behavioral phenotype of mice when they exhibit social interactions in a virtual space. In other words, brain activity and behavior can be recorded simultaneously by two individuals by synchronizing the VR system. This system is expected to reveal the dynamics of the brain functional network during social interactions, which have not been analyzed by conventional methods.

(TAKUMI Toru: Kobe University)

R&D item

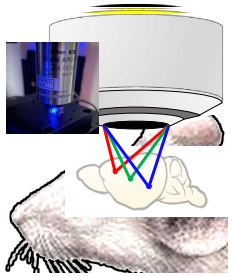
2. Optical manipulation of functional brain networks by optogenetics

Progress until FY2023

1. Outline of the project

In this R&D project, we use optogenetics, a technology to control neural activity with light, to induce changes in the brain function network artificially. By analyzing the changes in mouse behavior observed, we clarify how the functional brain network responds to changes in the "mind" and changes in behavior.

The elemental technology to be developed in this R&D project is a method of optical manipulation of the functional brain network by simultaneous optical stimulation of multiple brain points from the outside of the mouse cranium. For this purpose, we are constructing a holographic multi-point simultaneous cellular optical stimulation with a 3D measurement of brain shape and a 3D observation system.

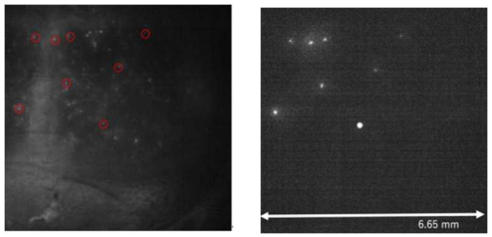


Overview of wide-field holographic microscopy covering the whole brain

2. Outcome so far

We have constructed a system that enables high-speed, three-dimensional observation of the brain by applying optical stimulation to precise areas based on brain geometry. Conventional optical light stimulation studies have been limited to small brain regions, but in this study, we constructed an experimental system that enables holographic light stimulation using a low-magnification objective lens to apply to the entire mouse cerebral cortex spanning 1 cm. Performance evaluation using fluorescent beads confirmed that the constructed system could cover a wide field of view of 6.6 mm and can also perform light illumination and fluorescent observation with a high spatial resolution of 20 μm.

Using this system, we also demonstrated that holographic light stimulation is possible through the skull by irradiating fluorescent beads applied to the skull of a mouse.



(Left) Fluorescent image of uniform illumination by LED light. Fluorescent images from individual fluorescent beads can be seen in the area circled in red. (Right) Multiple fluorescent beads were selected through the skull and simultaneously photostimulated using a hologram at the exact bead position. It can be seen that the beads were selectively and correctly photostimulated through the skull.

We also constructed a macro calcium imaging system for holographic optical stimulation of live mice using a low-magnification objective lens to detect the response to stimulation. We observed the reaction of the mouse cerebral cortex and confirmed that the system can detect the brain response to stimulation.

In order to irradiate neurons with sufficient light energy, a laser with an output of 300 mW and a wavelength of 473 nm was introduced. In addition, a multi-area and multi-spot irradiation function has been added to enable the simultaneous formation of multiple spot clumps in multiple locations for light stimulation over a wide area.

3. Future plans

We will develop a technology to manipulate the mouse cortical neural network. Namely, we will construct a holographic multi-point simultaneous cellular photostimulation and 3D observation system that simultaneously stimulates multiple points in the mouse cortex.

(MATOBA Osamu, TAKUMI Toru: Kobe University)