Multisensory object processing in a mouse model of Alzheimer's Disease

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Introduction

- Alzheimer's disease (AD) is the most common type of neurodegenerative disease characterized by an irreversible, progressive decline in multiple cognitive abilities.
- Certain perceptual capacities as well as high-order sensory processing deteriorate over the course of AD, yet the precise neural mechanisms by which this occurs are not well understood.
- Specifically, there is a lack of knowledge in the detailed patterns of neuronal circuitry underlying cross-modal object representation in AD.
- In this project, we aimed to use a miniature fluorescent endoscope (Miniscope) to measure neuronal activity patterns representing cross modal object representation in the perirhinal cortex of behaving mice using a mouse model of AD.
- To this end, we have assembled the Miniscopes and have begun using them to image cells of the hippocampus in awake mice.
- Data from the Miniscope recordings will be used to evaluate altered or disrupted sensory processing in transgenic AD mice.

Materials and Methods

- A transgenic mouse model of AD (3xTg-AD)[1] and non-transgenic control mice at the age of 6 - 8 months are used. For testing the Miniscope, another transgenic line (Scnn1a-Cre+Ai93 GCaMP6f) expressing genetically encoded calcium indicators was used.
- Animals will undergo three surgical procedures in order to prepare them for imaging with the Miniscope (Figure 1)[2,3].

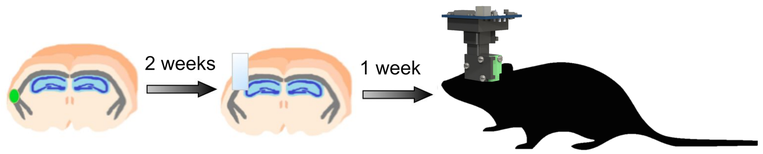


Figure 1. Schematic diagram of the experimental design. Mice undergo stereotactic injection of GCaMP6f virus in the perirhinal cortex (green region). Two weeks after surgery, a GRIN lens-microprism is implanted near the perirhinal cortex. After one week of recovery, a baseplate is cemented to the skull after adjusting the mounted Miniscope to a level at which clear focal plane and appropriate light intensity are achieved. The Miniscope can now be used to image cells.

- The Miniscope is used to record neural activity in awake, freely behaving animals (Figure 2)[3].

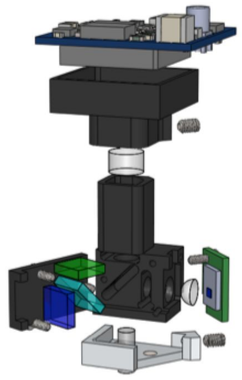
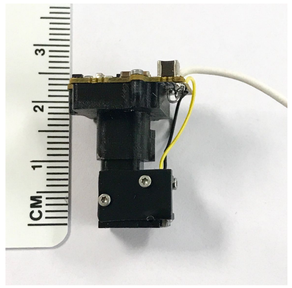


Figure 2. Parts configuration of the Miniscope. The Miniscope is a miniature fluorescence microscope used for wide-field calcium imaging to record neural activity in awake, freely behaving mice (www.miniscope.org). Based on a design conceived by Mark Schnitzer's Lab, the Miniscope can be easily assembled with an excitation light source (473nm LED), lenses for focusing light, a fluorescence sensor to detect emitted light, and lightweight body materials. The chronically implantable gradient refractive index (GRIN) lens allows optical access to the deep brain structures that are inaccessible to conventional two-photon imaging techniques.

Results

- We have assembled several Miniscopes to be used in imaging (Figure 3).
- The field of view is 700 by 450 micrometers.
- The imaging depth is limited to around 200 micrometers because as the imaging depth increases, the excitation light intensity decreases due to an increase in the scattering of emission light.

A)



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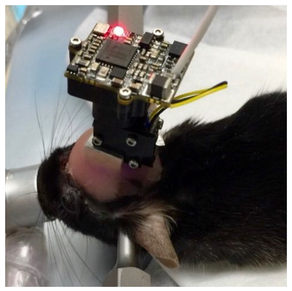
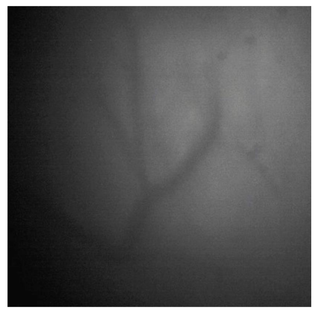


Figure 3. Miniscope assembly and use. A) A fully assembled Miniscope has a mass of 3 grams and is less than 2.5cm tall. It uses a single coaxial cable (the white cable attached to the top right) to carry power, control signals, and imaging data to data acquisition hardware and software. The data acquisition hardware is connected to a computer via a USB connection, enabling users to control/view Miniscope recordings on the computer. B) Initial testing of the Miniscope in an anesthetized transgenic mouse (Scnn1a-Tg3-Cre + Ai93 GCaMP6f). These animals have been genetically modified to express GFP-tagged calcium indicators, predominantly in excitatory neurons in cortical layer 4 and in restricted populations within the cortex, thalamus, and in cerebellum. For preliminary testing purpose, the GRIN lens was implanted above hippocampal CA1.

- The Miniscope has been used to record images of cells in the CA1 area of transgenic (Scnn1a-Cre+Ai93 GCaMP6f) mice (Figure 4).

A)



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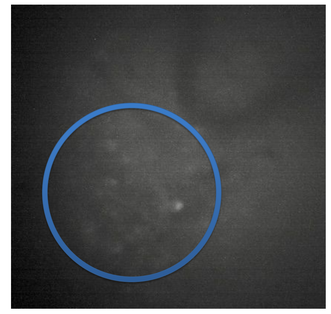

Figure 4. Unprocessed images from the Miniscope camera. A) This image shows blood vessels in the CA1 region of a Scnn1a-Cre + Ai93 GCaMP6f mouse. B) In the region indicated by the blue circle, weakly fluorescent neurons are seen. The animal was under anesthesia at the time the image was taken, so this could account for the weak activity of cells.

Future Directions

- In the future, we will use the Miniscope for imaging neurons as mice perform a novel behavioral task in which they interact with objects based on different task demands (visual, tactile, or visuotactile exploration).
- Images from the Miniscope and behavioral data will be synchronized to generate Ca^{2+} signals corresponding to different behavioral phases of the task that animals will perform.
- In doing so, we will investigate the neuronal properties representing cross modal object representation in the perirhinal cortex of mice.

References

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3. Figure 2. Aharoni, D. (n.d.). Main Page. Retrieved May 10, 2017, from http://miniscope.org/index.php?title=Main_Page

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