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<tr>
<td>Author(s)</td>
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<td>Citation</td>
<td>Yang, M. (2017, March). Optogenetics-Mediated Targeted Recording from Adult-Born Granule Cells in the Dentate Gyrus of Behaving Mice Presented at Discover URECA @ NTU poster exhibition and competition, Nanyang. Technological University, Singapore.</td>
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<tr>
<td>Date</td>
<td>2017</td>
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<td>URL</td>
<td><a href="http://hdl.handle.net/10220/42840">http://hdl.handle.net/10220/42840</a></td>
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Optogenetics-Mediated Targeted Recording from Adult-Born Granule Cells in the Dentate Gyrus of Behaving Mice

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I. Hippocampus & Dentate Gyrus

Anatomy & Function

Hippocampus: brain structure in the limbic system, known for its crucial role in spatial navigation, long-term memory formation, and learning.

Dentate Gyrus: subregion of hippocampus; one of few regions with adult neurogenesis in the brain, possible role in memory formation.

Studying Hippocampus

What to study:
- The activity (neuron firing) of different cells in different locations under different circumstances
- The need to establish the relationship between electrophysiological properties and specific cell type
- i.e., to record from a cell

Challenges:
- Multiple existing cell types
- Ambiguous cell-type classifying criteria
  > Morphology, biomarker, firing pattern
> 1 cell - More than 1 categories

II. Extracellular Recording & Analysis

Tetrode Recording

- Component: 4 small electrodes
- Dimension: ~50 μm in diameter
- Advantages:
  > Real-time in vivo recording
  > Distinguish action potentials from individual neurons based on different channel inputs

Spike Sorting

- Theoretical principle:
  > 4 micro-electrodes = 4 inputs
  > Slight relative distance differences of each electrode from the firing neuron creates differences in recorded values from a single spike firing

Grouping of spikes (dots) into clusters based on similarity in their input properties (e.g.: peak)
  - Single-cell resolution

Limitations

- Identities of the recorded cells remain unclear
  > Unable to match the isolated cluster to the specific cell that generated the firing based on spike sorting analysis alone

III. Overcoming Limitations

Aim of the Study

The aim of the study is to develop a new recording method to overcome the difficulty in determining cellular identity of neurons generating recorded activity in traditional electrophysiological extracellular recording which will help to investigate the properties of adult-born granule cell which is thought to be related to memory formation and learning.

IV. Electrophysiology + Optogenetics

Experimental Design

1. Animal Model: Channelrhodopsin-2 (ChR2)-YFP mouse
   - CHR2: Light gated non-selective cation channel
   > Selectively expressed in adult-born granule cells
   - YFP: yellow fluorescent protein tag

2. Pretraining, Surgical implantation of the electrode drive

3. Recording Sessions

   - Spatial exploration: box sessions
     > Spatial task: box exploration task
     > Possible place cell activity

   - Light stimulation: light sessions
     Light-ON sessions:
     > Laser >> DG through optic fiber
     > ChR2+ cell activity
     Light-OFF sessions:
     > No laser applied
     > Negative control

   - Data Analysis

4. Perfusion, Brain Sectioning, Histology Analysis

5. EpiFluorescence Imaging

   > Identification of ChR2+ cells in brain sections by YFP tag
   > Localization of the cell that generated the recorded activity during recording sessions.

V. Preliminary Results

Project Title: Optogenetics-mediated targeted recording from adult-born granule cells in the dentate gyrus of behaving mice
Supervisor: Asst Prof Ayumu Tashiro
Co-Supervisor/Collaborator: Mr Luis Cobar