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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;
- Hence 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

Current Methods & Limitations
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)
  - Distinguishes individual cells.
- 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

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

Figure 1. Mouse Hippocampus and Dentate Gyrus

Figure 2. Tetrode Recording

Figure 3. Cluster Cutting and Analysis

Figure 4. A neuron with light response selected from recording sessions.
4.a & 4.b: Light stimulation sessions. Histogram of IF of spikes without (4a) or with (4b) light stimulation. X-axis = time, yellow region = laser stimulation time window.
4.c & 4.d: Spatial exploration sessions. Rate map, firing location map, and interspike interval histogram suggest no significant place cell activity.

Project Title: Optogenetics-mediated targeted recording from adult-born granule cells in the dentate gyrus of behaving mice
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Category: PHYSICAL AND BIOLOGICAL SCIENCES
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FYP-URECA Project ID: SBS16052
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