Background

- The hippocampus and medial entorhinal cortex (MEC) are brain regions important for the formation and retrieval of memories.
- Problems with the hippocampus, MEC, and other brain regions underlie neurodegenerative disorders like Alzheimer’s and Dementia. Therefore it is important to understand how these brain regions work and interact.
- Place cells in the hippocampus (CA1 & CA3) fire whenever an animal is in a certain location, this activity-dependent location is known as the place field (O’Keefe 1976).
- Grid cells in the MEC Layer II (MEC-LII) fire in a repeating triangular pattern that covers an environment as an animal moves through the entire area (Hafting et al. 2005).
- The MEC receives inputs from many regions of the cerebral cortex and projects into the hippocampus directly from Layer II.

Methods

1. Transgene Expression
   We used an inducible gene expression technique to constitutively express HM4 or HM3 receptors in MEC-LII. These receptors are activated by an otherwise inert ligand clozapine-N-oxide (CNO), which triggers membrane hyperpolarization (HM4) or depolarization (HM3). This animal model allows us to decrease (HM4) or increase (HM3) MEC-LII activity.

2. Electrophysiology
   We implanted four-channel adjustable-depth tetrodes into the hippocampus or MEC to record neuronal activity while mice move freely through a familiar environment.

3. Experimental Procedure
   - Baseline 1 (BL1): CNO for 2 hr after start of CNO session.
   - CNO for 30 min.
   - BL2: baseline 2 (BL2) 30 min.

Baseline 1 (BL1) 30 min.
Baseline 2 (BL2) 30 min.
CNO 2 hr after start of CNO session.
CNO 30 min.
BL1 BL2 BL3 BL4 CNO1 CNO2 CNO3 CNO4

Figure 1: A) Rate maps from a CA1 place cell in HM3 mice for experimental sessions (10 min per session). B) Spatial correlation scores comparing the CNO sessions to the Baseline 1 session. C) Mean firing rate (Hz) and D) Field size for the baseline and CNO sessions. Green = 0.015 mg/kg CNO injected, blue = 0.1 mg/kg CNO, red = 0.03 mg/kg CNO given to non-double-positive mice as control.

Figure 2: A) Rate maps from a CA2 place cell in HM4 mouse across experimental sessions (10 min per session). B) Spatial correlation scores comparing the BL2 session to CNO and BL2 sessions. C) Mean firing rate (Hz) and D) Peak firing rate (Hz). Green = HM4 +/+ place cells (n = 16).

Figure 3: A) Rate maps from a CA1 place cell in HM3 mouse for experimental sessions (10 min per session). B) Spatial correlation scores comparing the BL2 session to CNO and BL2 sessions. C) Mean firing rate (Hz) and D) Peak firing rate (Hz). Green = HM4 +/+ place cells (n = 14).

Figure 4: A) Rate map for MEC-LII grid cells in HM4 mouse across experimental sessions (10 min per session). B) Grid scores, C) Mean firing rate (Hz) and D) peak firing rate (Hz) across experimental sessions. Green = HM4 +/+ grid cells (n = 5 unless otherwise indicated in parentheses on graph). * p < 0.0004, ANOVA.

Summary

- CA1 and CA3 place cells respond to changes in grid cell activity within MEC-LII as follows:

<table>
<thead>
<tr>
<th>Place Cell Remap</th>
<th>Activity (HM4)</th>
<th>Activity (HM3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Decrease</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
</tbody>
</table>

These findings suggest that there is a threshold between rate and global remapping of place fields relative to grid cell input.

References


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