The effects of inhibiting neurons in Layer-II of the Medial Entorhinal Cortex on Hippocampal Place Cells in CA1 and CA3

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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 underlay neurodegenerative disorders like **Alzheimer's** and **Dementia**. Therefore it is important to understand how these brain regions work and interact. (Braak & Braak 1991)
- **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. (Andersen et. al. 2007)
- Our goal is to test how increasing or decreasing the activation of MEC-LII neurons will effect CA1 and CA3 place cells.
- Previous data from our lab has shown that increasing the excitability of MEC-LII neurons causes some CA1 place cells to **globally remap (see panel 3)** and/or increase in place field firing rate

How will decreasing the excitability of MEC-LII grid cells effect CA1 and CA3 place cells?

Methods

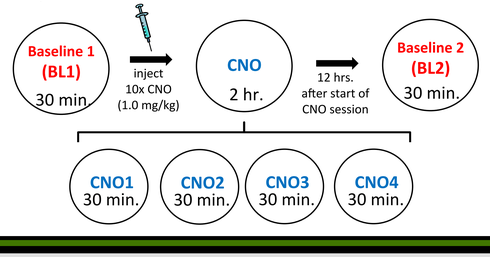
1. Transgene Expression

   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. (Armbruster et al 2007)

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



HM3: Experiments with CA1 place cells display global remapping and rate increase

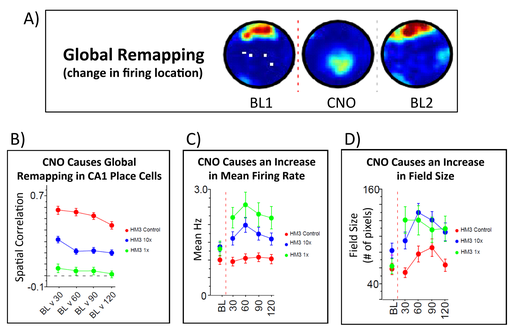


Figure 1: A) Rate maps from a **CA1 place cell in HM3 mouse** for experimental sessions (30 min per session). B) Spatial correlation scores comparing the CNO sessions to the Baseline 1 session. C) Mean firing rate (Hz) and D) field size for the baseline and CNO sessions. Green = 0.01mg/kg CNO injection, blue = 0.1 mg/kg CNO, red = 0.01 mg/kg CNO given to non-double-positive mice as control.

HM4: Experiments with CA1 place cells display rate remapping (increase or decrease)

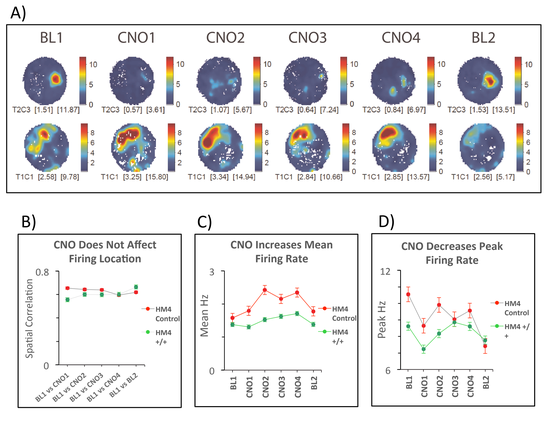


Figure 2: A) Rate maps from **CA1 place cells in HM4 mice** across experimental sessions (30 min per session). B) Spatial correlation scores comparing the BL1 session to CNO and BL2 sessions. C) Mean firing rate (Hz) and D) Peak firing rate (Hz). Green = HM4 +/+ place cells (n = 43), red = place cells of control (n = 16).

HM4: Experiments with CA3 place cells display rate remapping (decrease)

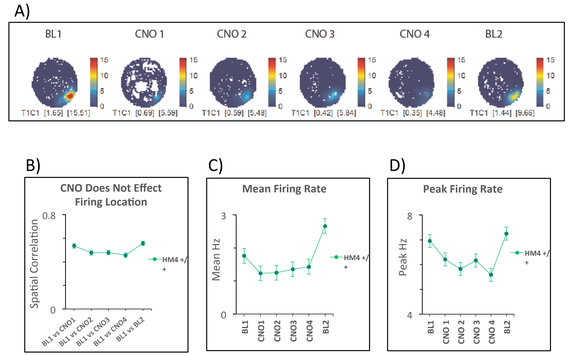


Figure 3: A) Rate map from a **CA3 place cell in HM4 mouse** across experimental sessions (30 min per session). B) Spatial correlation scores comparing the BL1 session to CNO and BL2 sessions. C) Mean firing rate (Hz) and D) Peak firing rate (Hz). Green = HM4 +/+ place cells (n = 34).

HM4: Experiments with MEC-LII grid cells display reversible decrease in grid properties

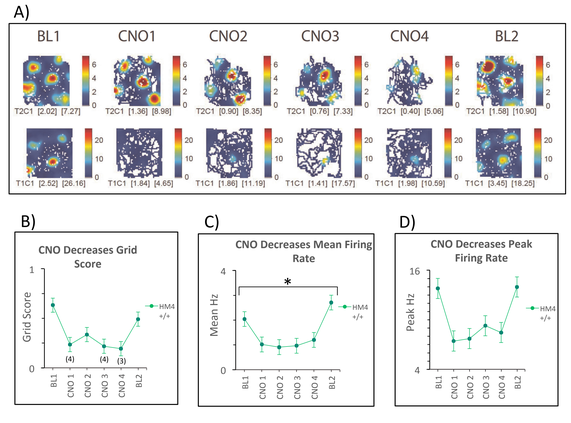


Figure 4: A) Rate map for **MEC-LII grid cells in HM4 mouse** across experimental sessions (30 min per session). B) Grid scores, C) Mean firing rate (Hz) and D) peak firing rate (Hz) across experimental sessions. Green = HM4 +/+ grid cells (n = 5 unless otherwise indicated in parentheses on graph.); * p = 0.0004, ANOVA.

Summary

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

Table 1. Summary of Place Cell Response to Change in MEC-LII Activity

Hippocampal Subregion	Place Cell Response	
	Increase in MEC-LII Activity (HM3)	Decrease in MEC-LII Activity (HM4)
CA1	Global Remapping and Rate Increase	Rate Remapping (Increase and Decrease)
CA3	Global Remapping and Rate Increase[1]	Rate Remapping (Decrease)

[1]Data collected but not shown

- 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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