Synchronous activation of distinct cell ensembles in CA3 integrates two memories

海馬CA3領域の二つの異なるセルアンサンブルの同期活性化による記憶の統合

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Abstract

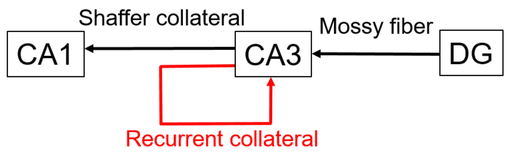
The hippocampal area CA3 forms CA3-CA3 recurrent excitatory circuits. Previous studies showed that this circuit is important for the paired association learning or sequence learning. However, whether the recurrent CA3 network plays an important role in the interaction between previously stored information is still unclear. To address this question, we focus on whether the coincident firing of distinct pre-stored ensembles in CA3 induce integration of these memories by using optogenetics.

We induced the expression of ChR2-mCherry to CA3 cell ensembles responded to “context exploration” and “contextual fear conditioning (CFC) in a different context” using tet-tag system and Cre-loxP system. Then, we induced coactivation of ChR2-mCherry expressing neurons by 20 Hz laser stimulation followed by memory tests. In “the context which mice didn’t received CFC”, laser on group showed significantly higher freezing than that of laser OFF control group, indicating that the two context memories were associated. However, there was no difference between the two groups in freezing in “the context in which mice received CFC” and “another new context”, suggesting that the memory had a context specificity.

Also, we checked whether 20 Hz optical stimulation can induce long-term potentiation (LTP) in CA3-CA3 synapses to elucidate the mechanisms of the observed memory integration. Using in vivo excitatory post synaptic potential (fEPSP) recording, LTP was observed after 20 Hz laser stimulation in the control mice but not in the CA3 pyramidal cell-restricted N-methyl-D-aspartate (NMDA) receptor knock out mice, which lack NMDA receptor function at CA3-CA3 synapses.

Taken together, our results suggest that the strengthening of synaptic efficacy between CA3 ensembles connected by recurrent circuit associate two memories.

Introduction

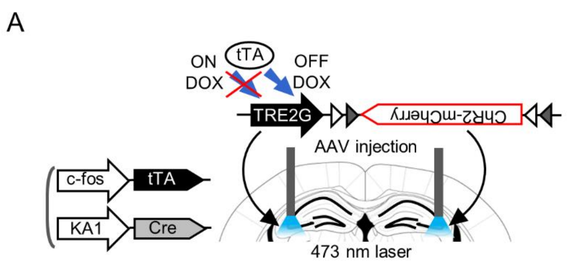


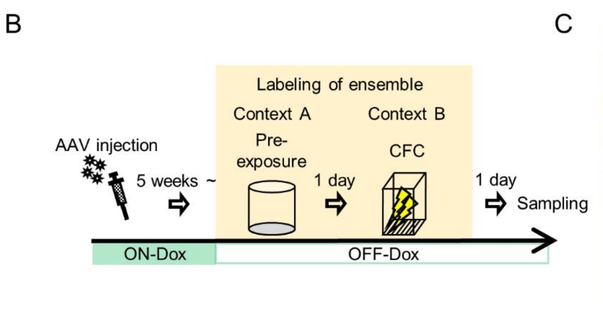
- Recurrent circuits in the CA3 is important for paired association learning or sequence learning.
- However, the role for the interaction between previously stored information is still unclear.

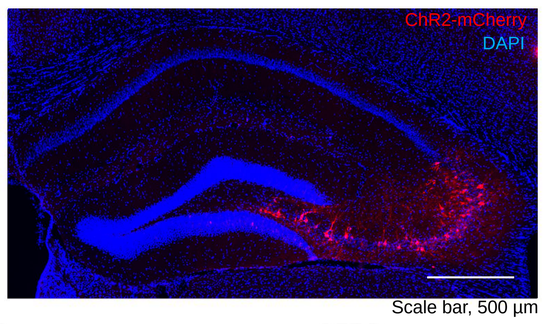
Questions

Does the coincident firing of distinct pre-stored ensembles in the CA3 induce integration of memories?

1. A system for the activity-dependent labeling of the hippocampal CA3 neurons







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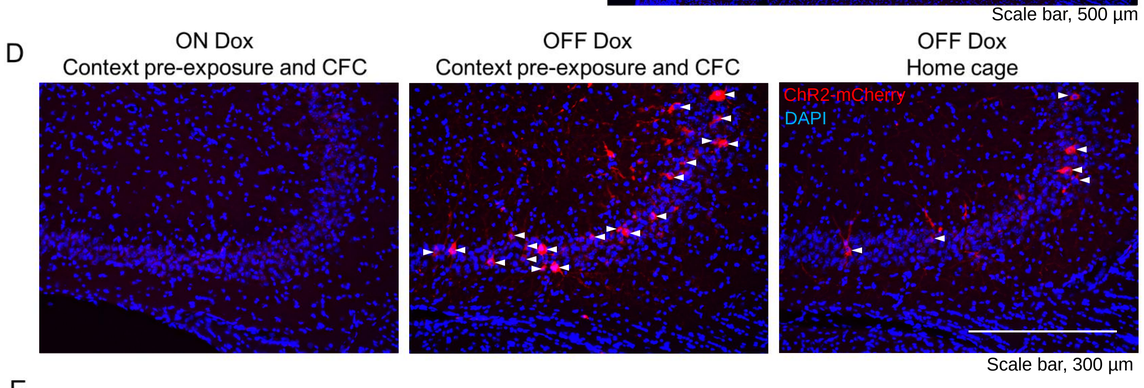

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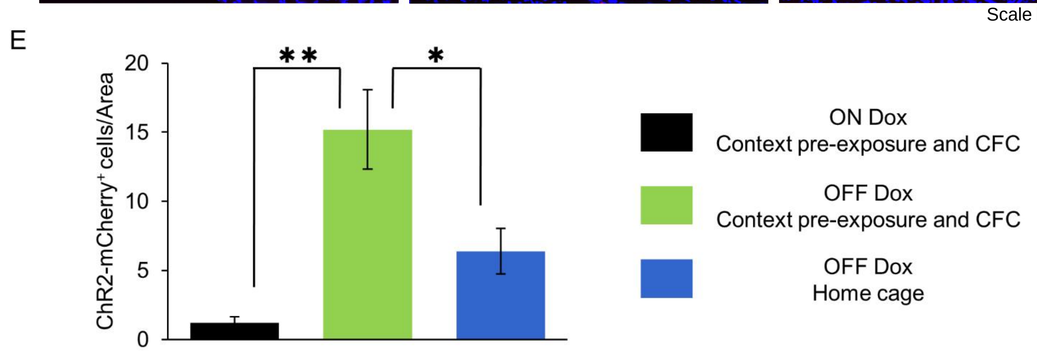


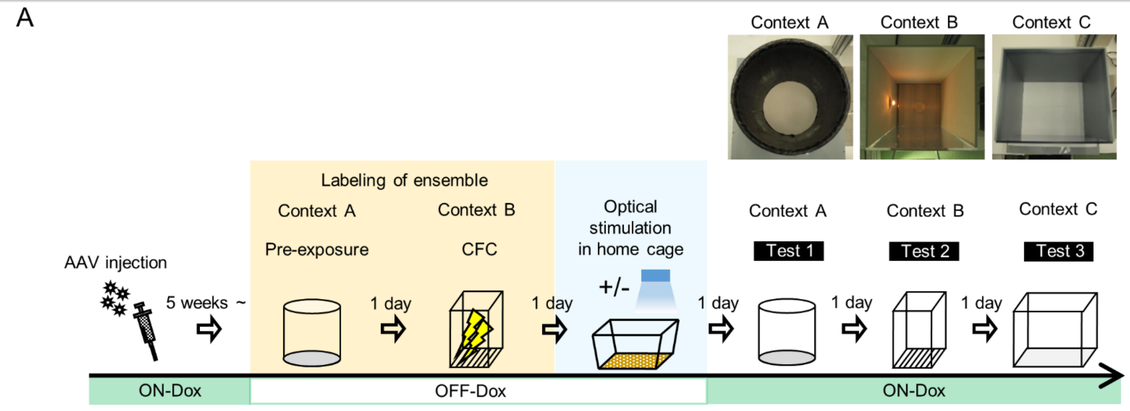
n = 4 mice/group; p < 0.01, one-way ANOVA; * p < 0.05, ** p < 0.01, Tukey's post hoc multiple comparisons test; Error bars, mean ± SEM

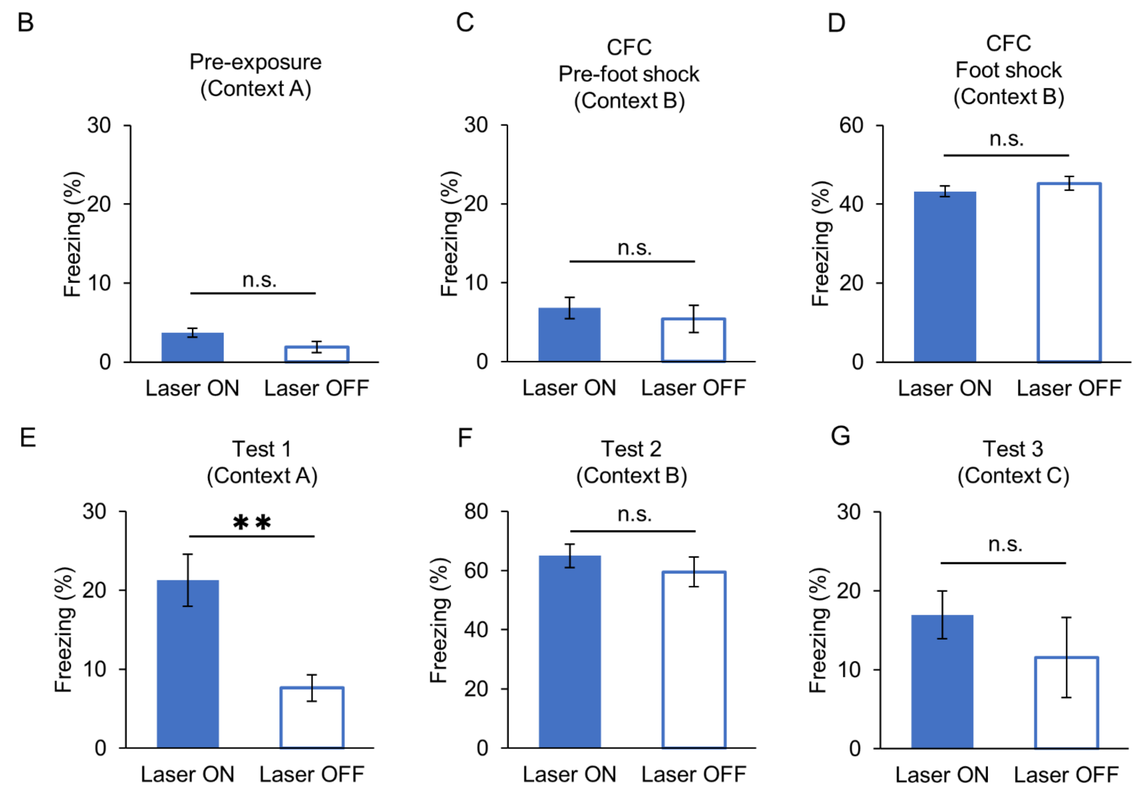
Conclusion

- ❖ A system for the activity-dependent labeling of the hippocampal CA3 neurons is established.
- ❖ Synchronous activation of distinct cell ensembles in CA3 induce memory integration.
- ❖ 20 Hz laser stimulation induce LTP in CA3-CA3 synapses.

Taken together, the strengthening of synaptic efficacy between CA3 ensembles connected by recurrent circuit associate two memories.

2. Laser stimulation of distinct cell ensembles in the hippocampal CA3 induces memory integration

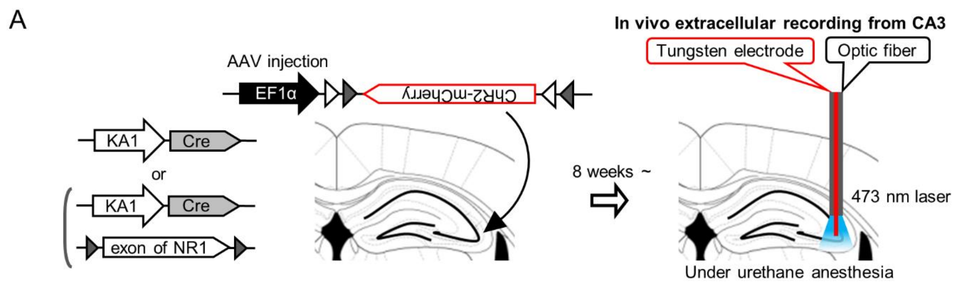


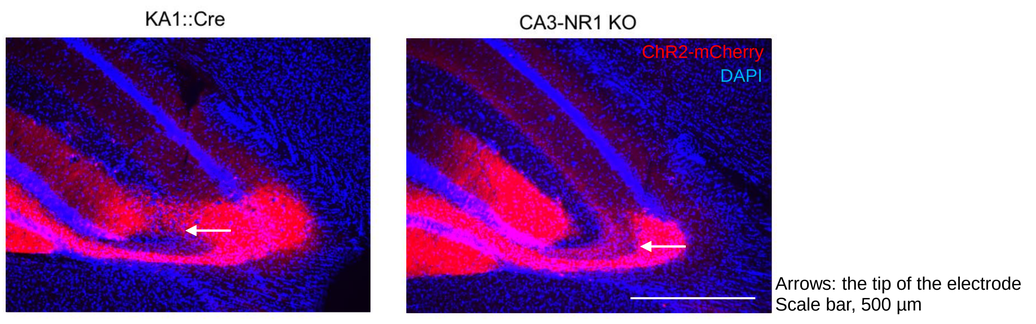


Laser ON, n = 12; Laser OFF, n=10; ** p < 0.01, unpaired t-test; n.s., no significant difference; Error bars, mean ± SEM

Laser stimulation: 10 trains of light (20 Hz, 100 pulses of light, 500 μsec each, 473 nm, 10 mW) at 45 sec inter-train intervals

3. In vivo field excitatory post synaptic potential (fEPSP) recording in the hippocampal CA3





Arrows: the tip of the electrode

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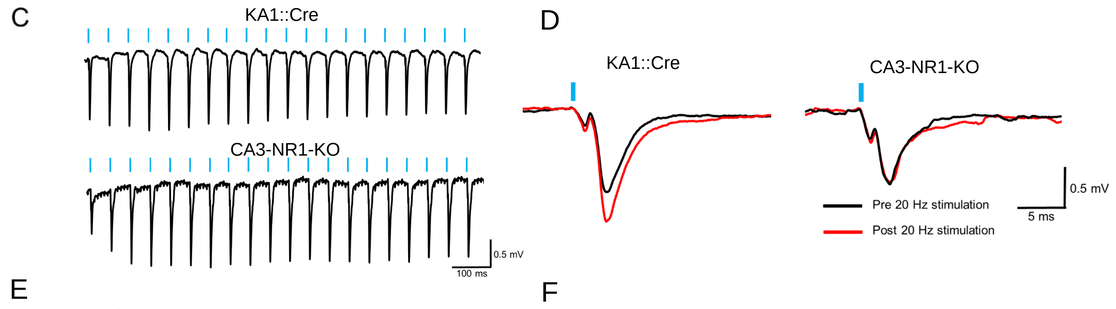

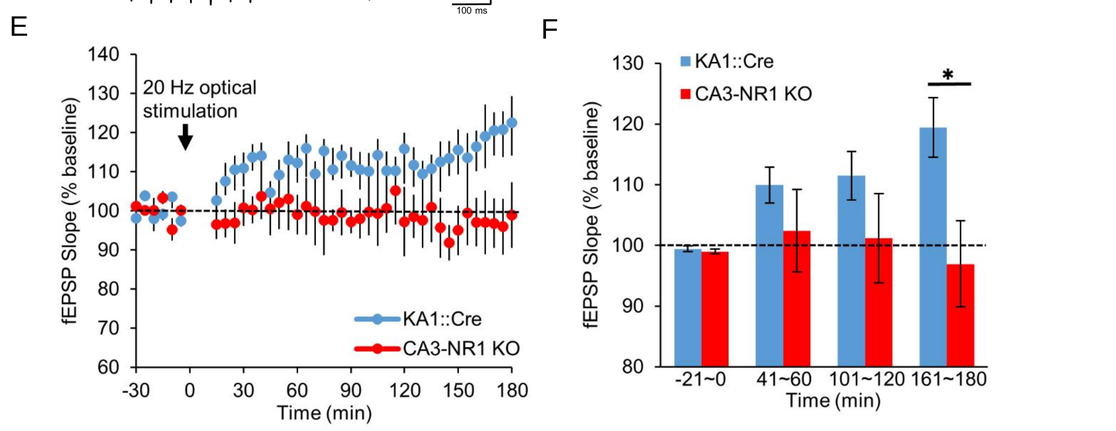

n = 4 mice/group; * p < 0.05, unpaired t-test; Error bars, mean ± SEM

● We declare no Conflict of Interest (COI).