Monitoring plasticity-associated dendritic calcium dynamics during learning

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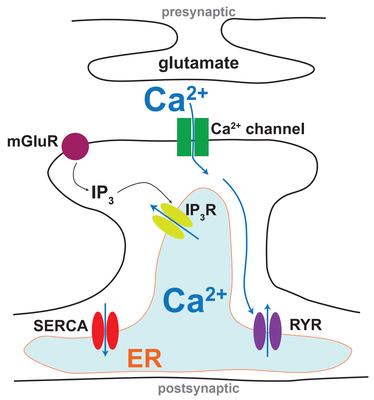
Background

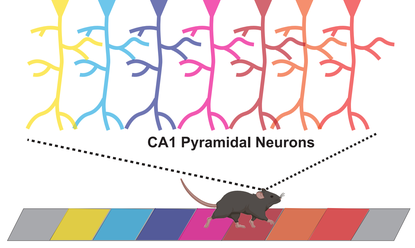
Ca^{2+} is a central signaling molecule in synaptic plasticity
Activity-dependent Ca^{2+} release from the endoplasmic reticulum can promote Ca^{2+} spread in dendrites



The ER sequesters Ca^{2+} through the Ca^{2+}-ATPase SERCA. Glutamatergic input and Ca^{2+} influx through the plasma membrane can trigger intracellular Ca^{2+} release from the ER in an activity-dependent manner.

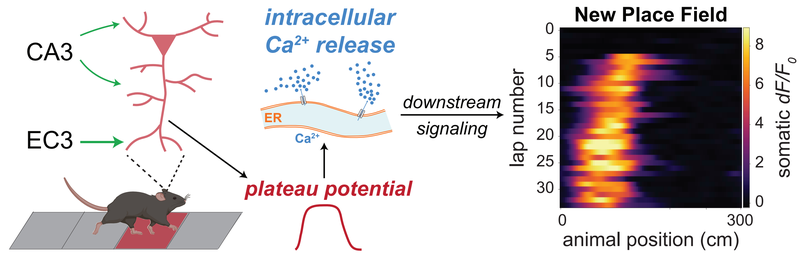
ICR can dramatically increase local Ca^{2+} concentrations in dendritic segments, which may be a mechanism for controlling synaptic plasticity.
Adapted from [1].

Hippocampal place fields are a cellular substrate of learning



Place fields are spatial receptive fields of hippocampal CA1 pyramidal neurons that manifest as a cell's tendency to fire when the animal occupies a specific location. They emerge in an experience-dependent manner and collectively form cognitive maps of the environment.

Hypothesis: Intracellular Ca^{2+} release is preferentially engaged during place field formation



Presynaptic inputs onto CA1PNs initiate a dendritic plateau potential, which triggers ICR at the moment a new place field forms.

References

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2. Blockus, H. et al. *Synaptogenic activity of the axon guidance molecule Robo2 underlies hippocampal circuit function.* Cell Reports, 2021
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The authors report no conflicts of interest. This work was supported by MSTP T32 (T32GM149361), PharmMM PhD Program T32 (T32GM158468), R00 (R00NS127815), Klingenstein Philanthropies and the Whitehall Foundation. This work was supported by CU NeuroTechnology Center Machine Shop Core.

Approach

In vivo visually guided single-cell DNA electroporation

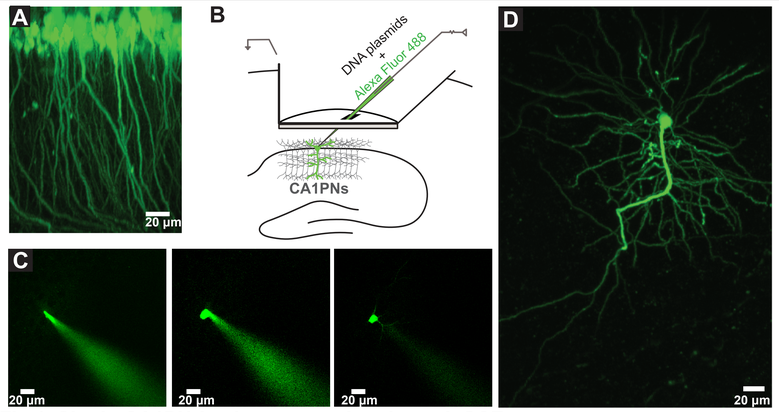

Fig 1. Single-CA1PN *in vivo* preparation through SCE.
(A) Cross-section of CA1PNs showing the challenge of matching dendrites to their soma. Adapted from [2]
(B) Schematic of SCE of CA1PNs
(C) Images before, during, and after SCE of a single CA1PN
(D) Maximum intensity Z projection of CA1PN expressing a construct following SCE

In vivo volumetric dual-color 2-photon imaging across the dendritic arbor of cytosolic and ER Ca^{2+} signals

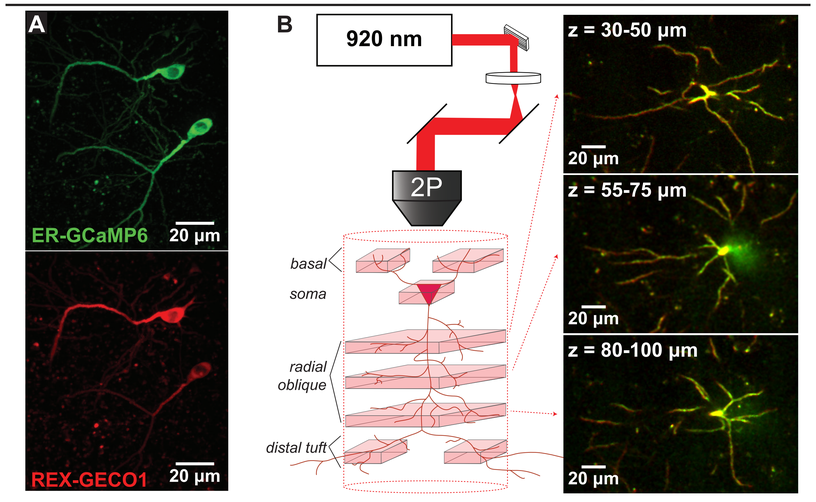

Fig 2. Volumetric imaging approach for the dendritic arbor
(A) Maximum intensity projections of two CA1PNs expressing ER and cytosolic Ca^{2+} indicators ER-GCaMP6-150 and REX-GECO1, respectively
(B) Left: High-speed volumetric imaging approach which generates a focal volume and leverages a digital micromirror device to subsample the volume at rapid speeds.
Right: Sample volumetric images of radial oblique dendrites from a single CA1PN

Virtual reality-based teleportation paradigm to promote spontaneous place field formation

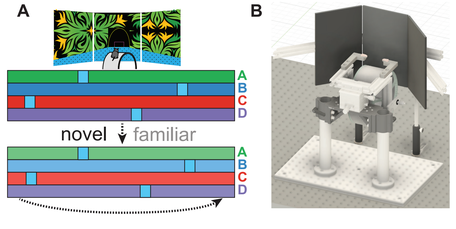

Fig 3. Behavioral approach
(A) Schematic of VR paradigm: mice learn to navigate 4 new environments with rewards located at fixed locations. Adapted from [3].
(B) Rendering of mouse running wheel and VR displays

Results

Multi-plane imaging across the dendritic arbor in a single neuron

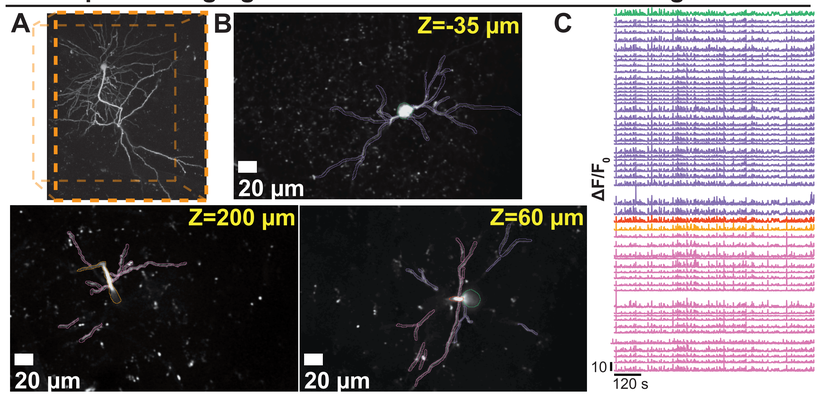

Fig 4. Simultaneous somatic and dendritc imaging
(A) Volumetric projection of CA1PN expressing jGCaMP7s-p2a-mRuby3 following SCE
(B) Planes imaged during VR teleportation task. Z-axis depth is relative to somatic plane Averaged motion-corrected frames were contrast-adjusted to show detail. Individual segments are outlined and color-coded by compartment as in Fig 5 (below)
(C) Somatic fluorescent Ca^{2+} signals extracted from each segment, color-coded by compartment over a single 30-minute recording session

Differential activity of dendritic compartments & changes in spatial tuning with novel context exposure

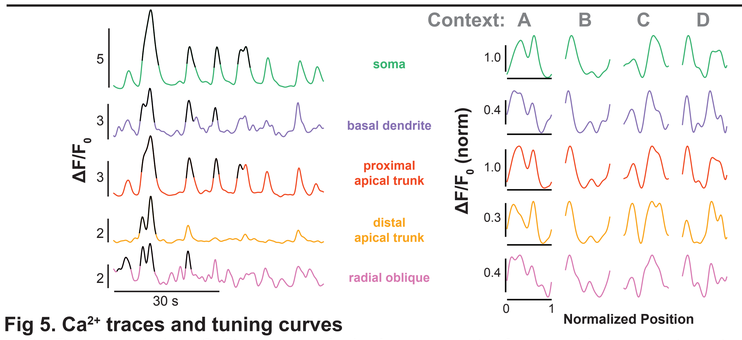

Fig 5. Ca^{2+} traces and tuning curves
Left: Representative Ca^{2+} traces of single segments from each compartment over 60 seconds. Ca^{2+} transients, identified with template-based detection, are overlaid in black.
Right: Average tuning curves derived from normalized $\Delta F/F_0$ for each context of the VR teleportation navigation task. Data used running-only frames and normalized by occupancy

Future Directions

What is occuring in dendrites during place field formation?

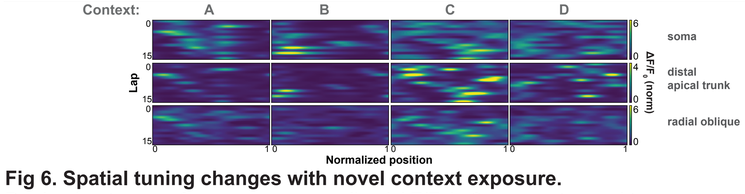

Fig 6. Spatial tuning changes with novel context exposure.
Per-lap heatmaps of occupancy-normalized $\Delta F/F_0$ in 3 segments used to assess spatial tuning. Future analyses will use an algorithmic approach to identify place field formation

When do ICR events occur *in vivo*?

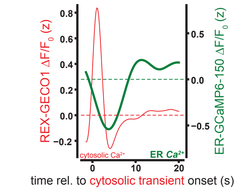

Fig 7. Peri-event time histogram-based analysis of dendritic ER Ca^{2+} dynamics.
Example analysis of ER Ca^{2+} dynamics as they correspond to dendritic Ca^{2+} transients in a single dendritic compartment. These analyses can be performed with respect to other neural or behavioral events such as PF formation, rewarded licking, animal velocity, etc.