Brain-state and attention dependent membrane potential dynamics in visual cortex.

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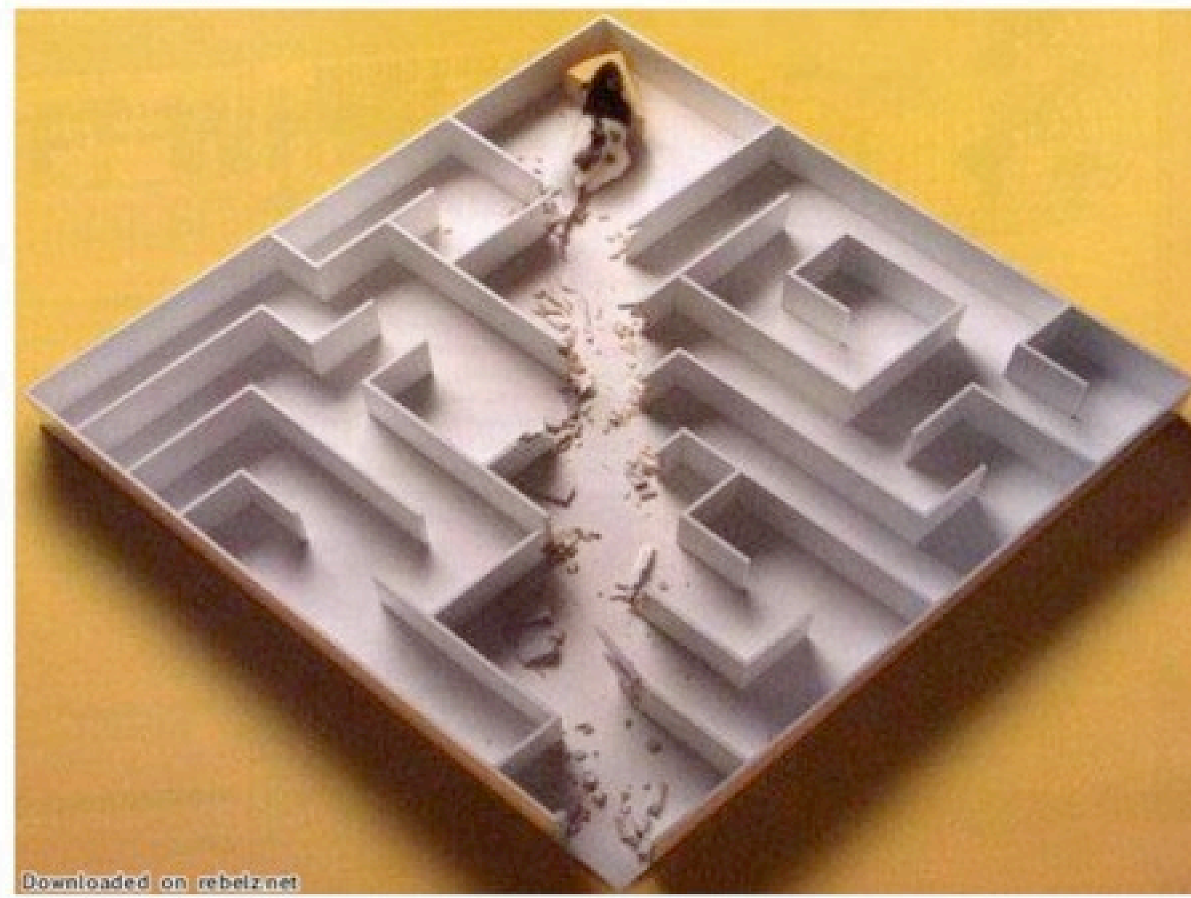
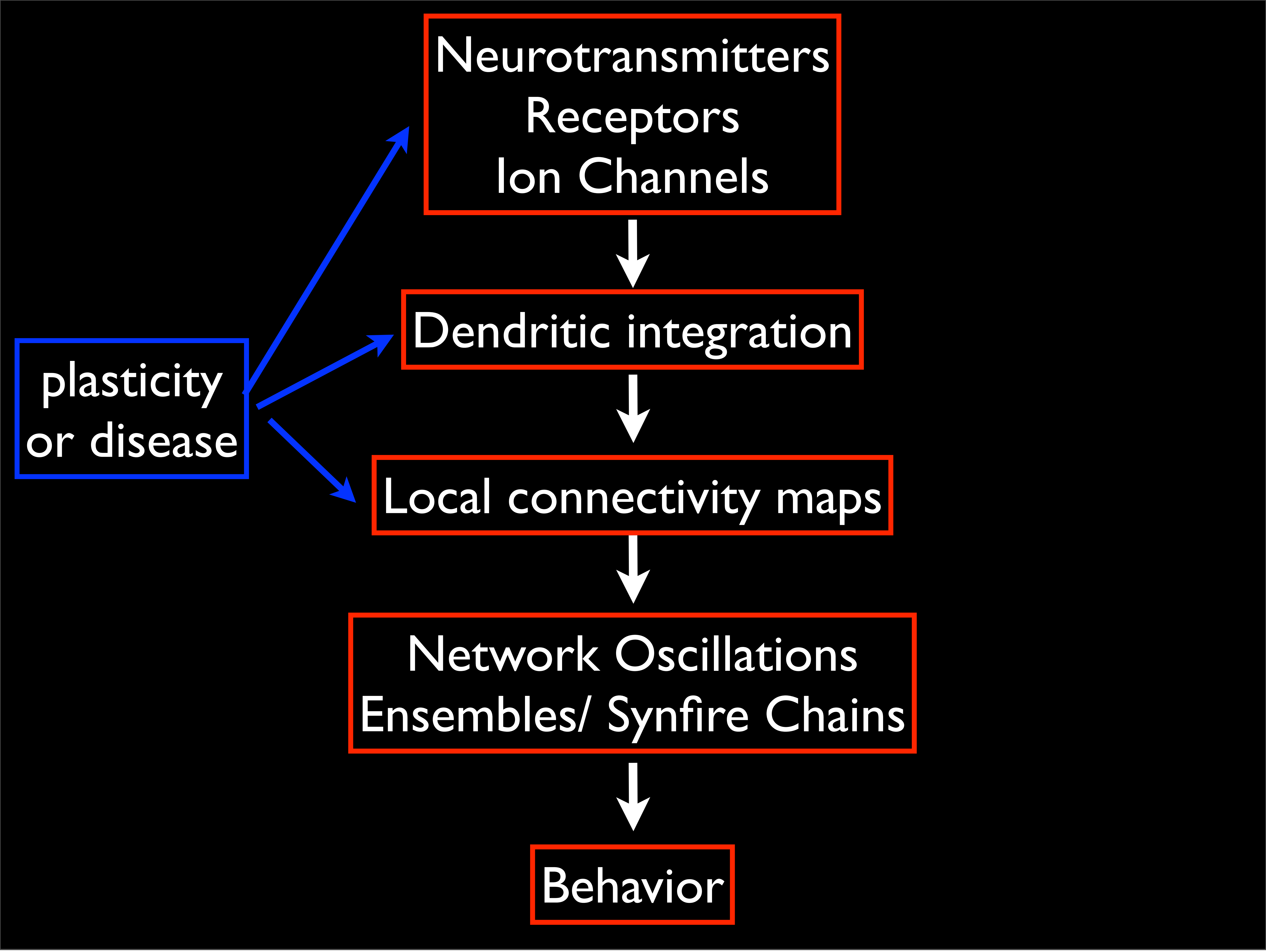
Bridging the gap between synaptic physiology and behavior

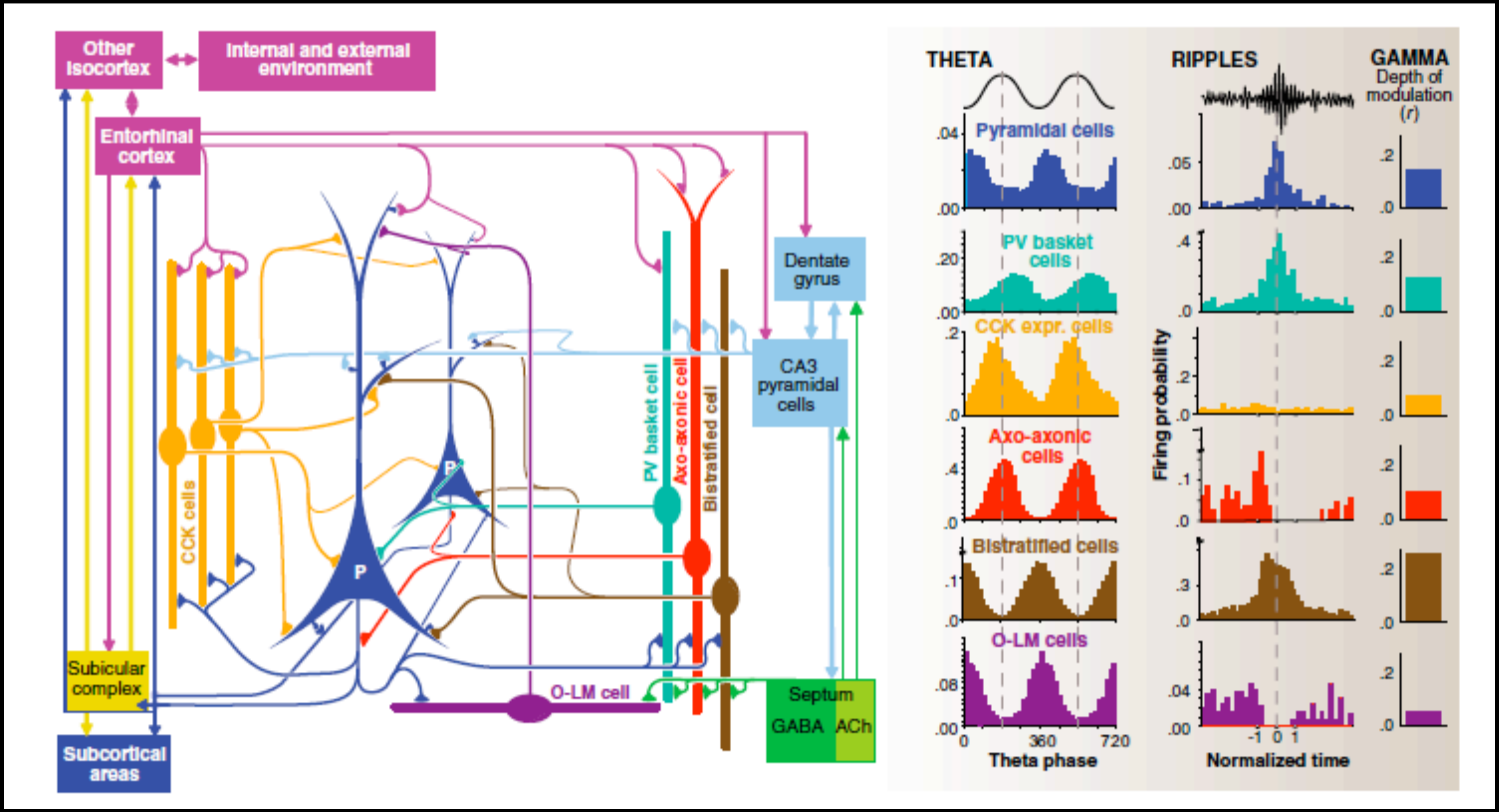



Neurotransmitters
Receptors
Ion Channels
Dendritic integration
Local connectivity maps
Network Oscillations
Ensembles/ Synfire Chains
Behavior
plasticity
or disease

Bridging the gap:
Appreciate the complexity of the circuit

- There are 20 GABAergic interneuron types in cortex and hippocampus.
- Excitatory neurons are NOT a homogenous group. Cells that appear identical even in the same layer can have distinct long-range projections and local connectivity.

- There are more than 20 types of GABAergic neurons in the neocortex and hippocampus.



Bridging the gap: Needs

- Record the activity of large populations of IDENTIFIED neurons in the behaving animal at the speed of the brain over long time periods (days to weeks.)
- Characterize the short and long range connectivity of each cell we record.
- Selectively manipulate the activity (and connectivity) of each cell type.
- Be able to follow how each cell type transforms synaptic input to spike output DURING BEHAVIOR.

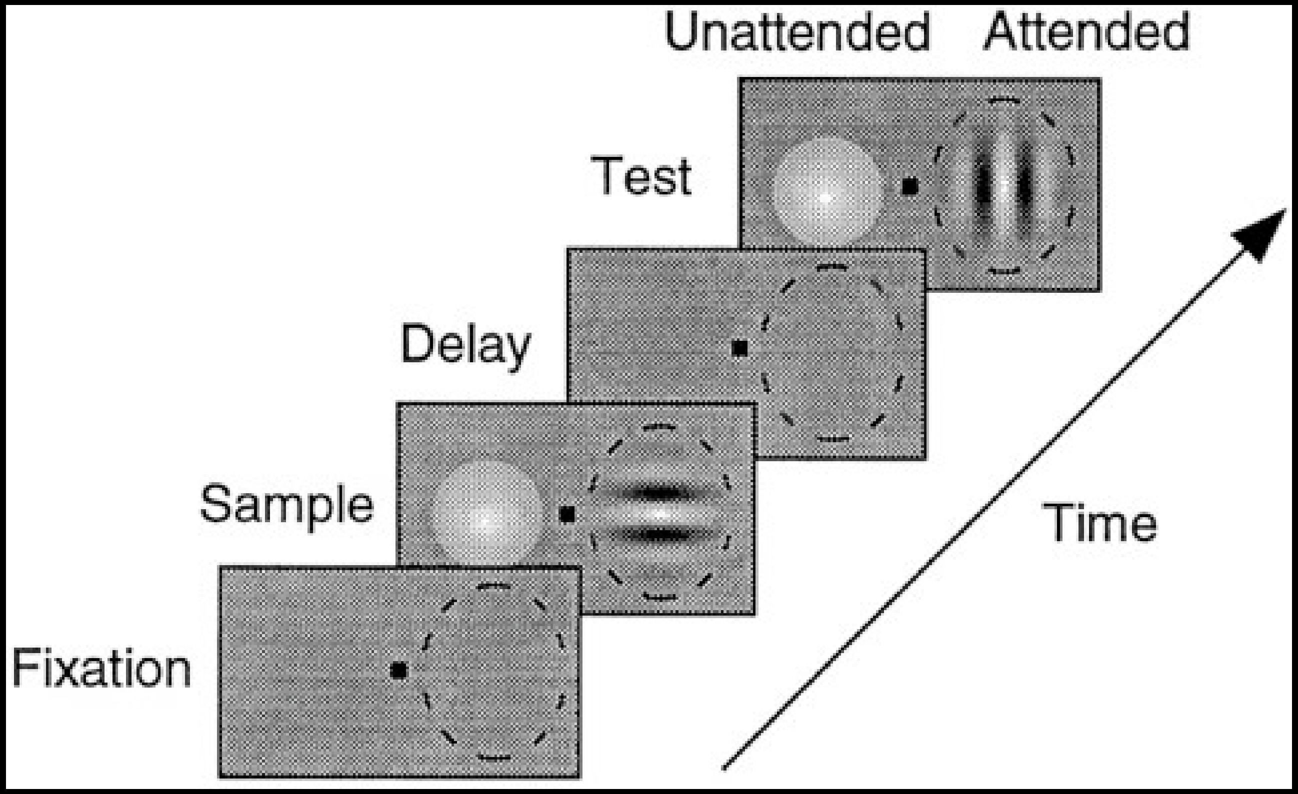
- Part 1: Brain-state dependent changes in membrane potential dynamics in visual cortex.
- Part 2: Membrane potential and network dynamics during decision making.
- Part 3: New tool development

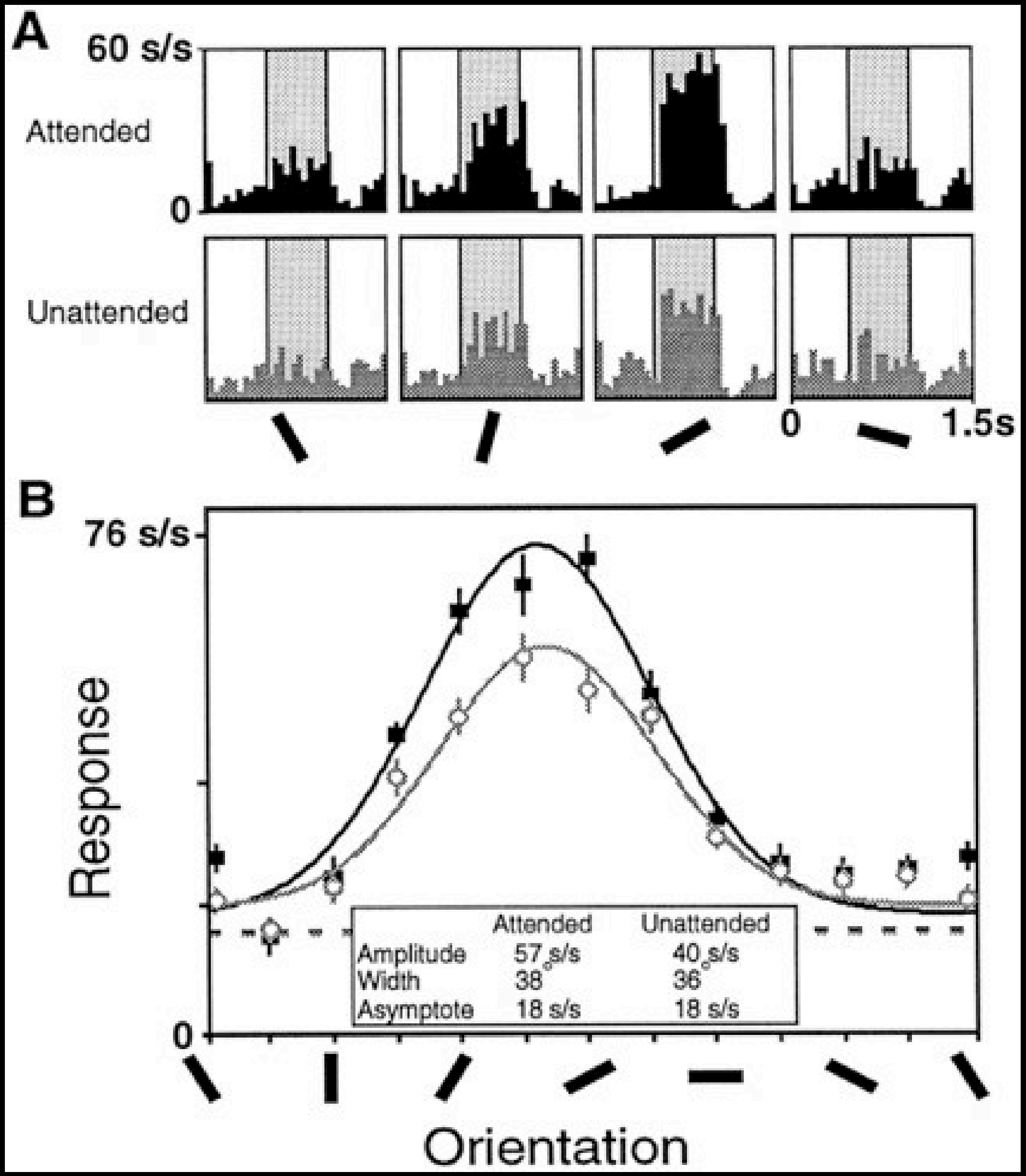
Pierre-Olivier Polack

Neurons in visual cortex are modulated by attributes other than the pattern of light hitting the eye.

The role of attention, level of arousal, and non-visual attributes.

Attentional modulation of visual responses in V4



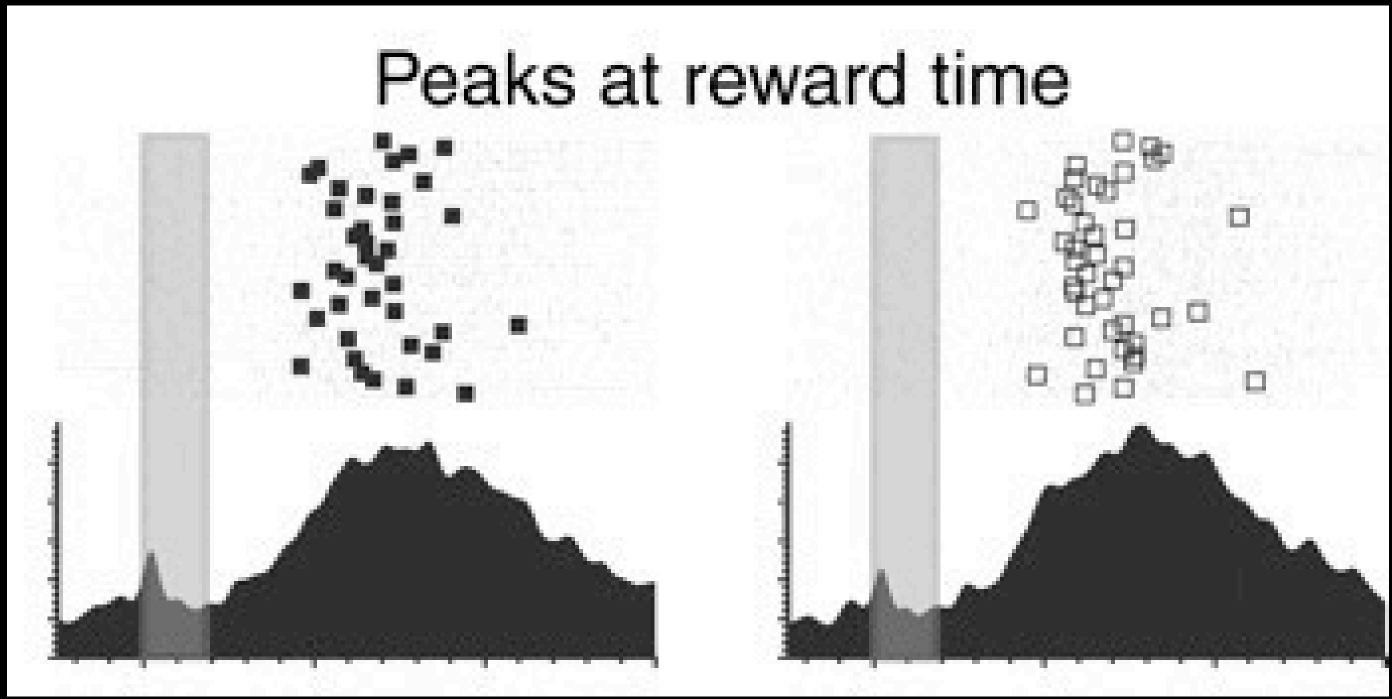


McAdams and Maunsell, 2002

Visual cortical neurons code for behavioral state rather than simple attributes of visual world

Reward Anticipation

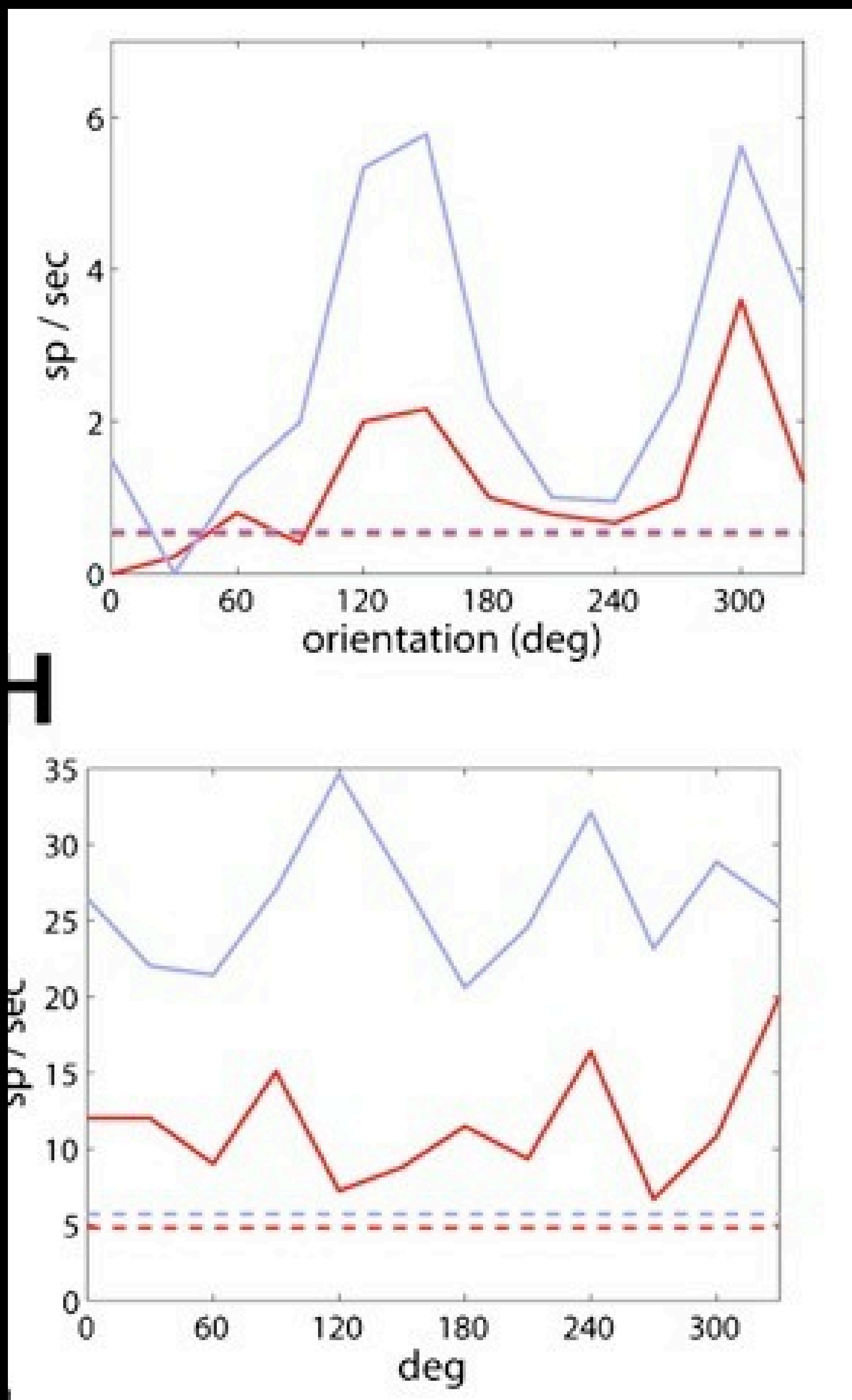
Firing rate



Rewarded Unrewarded

Shuler and Bear, 1996

Changes in brain state modulate responsiveness of cortical neurons

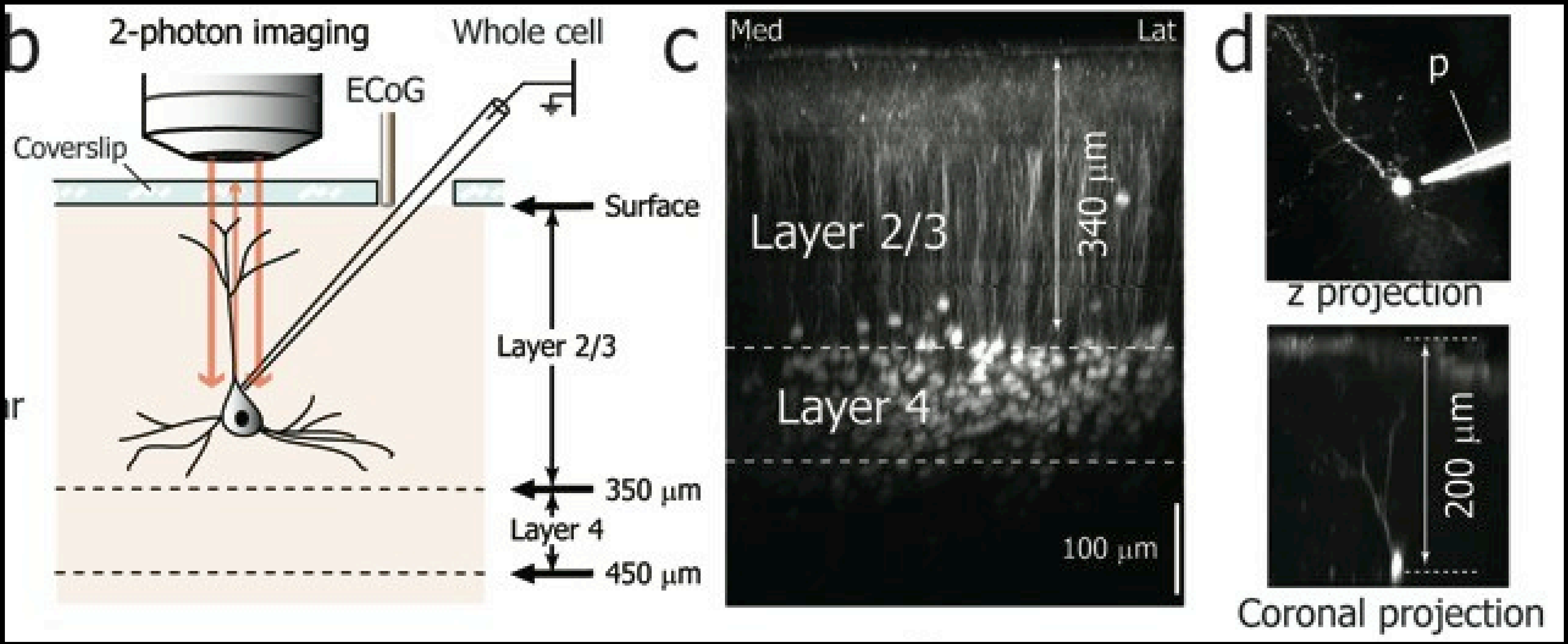


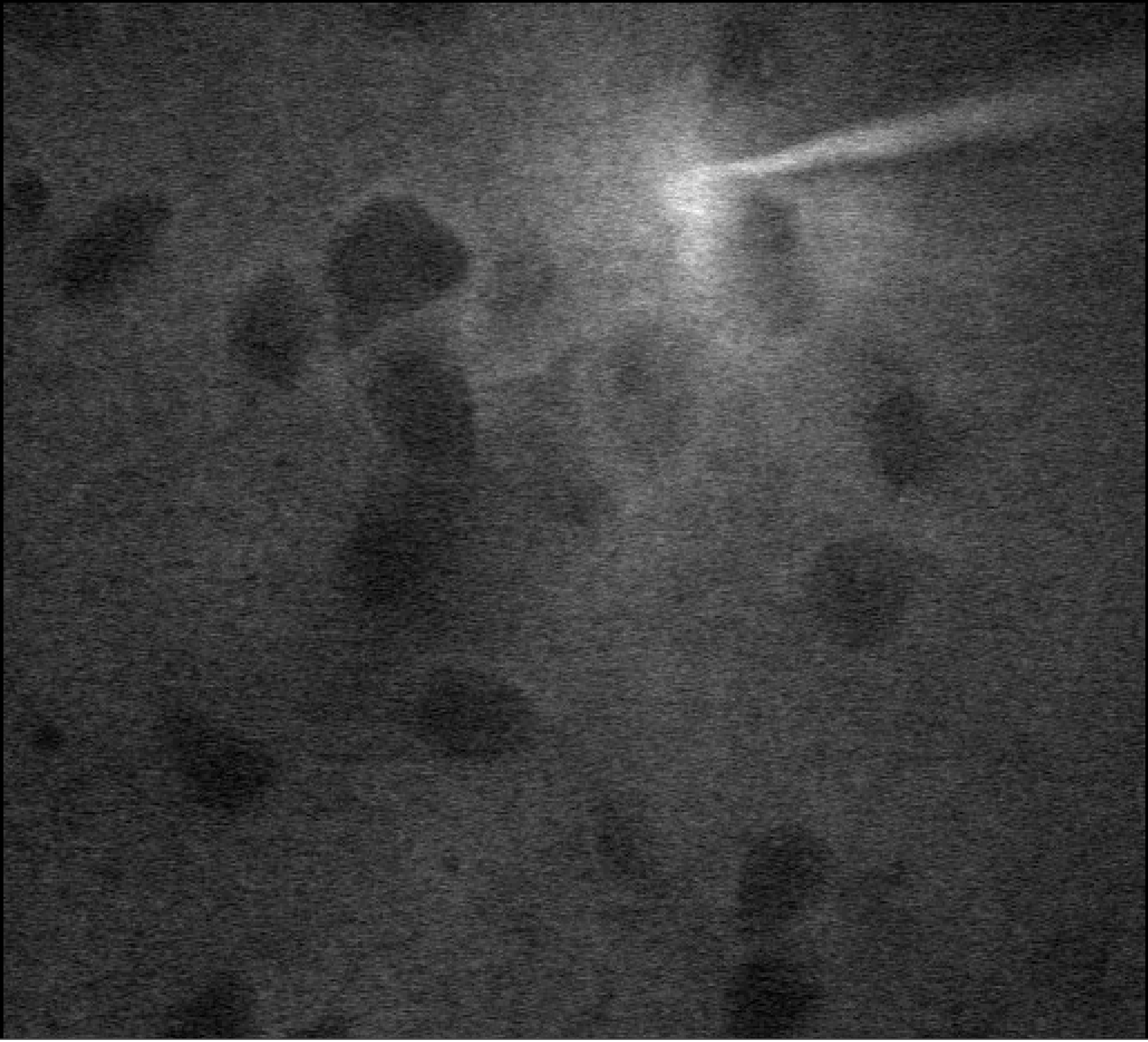
Stillness
Running

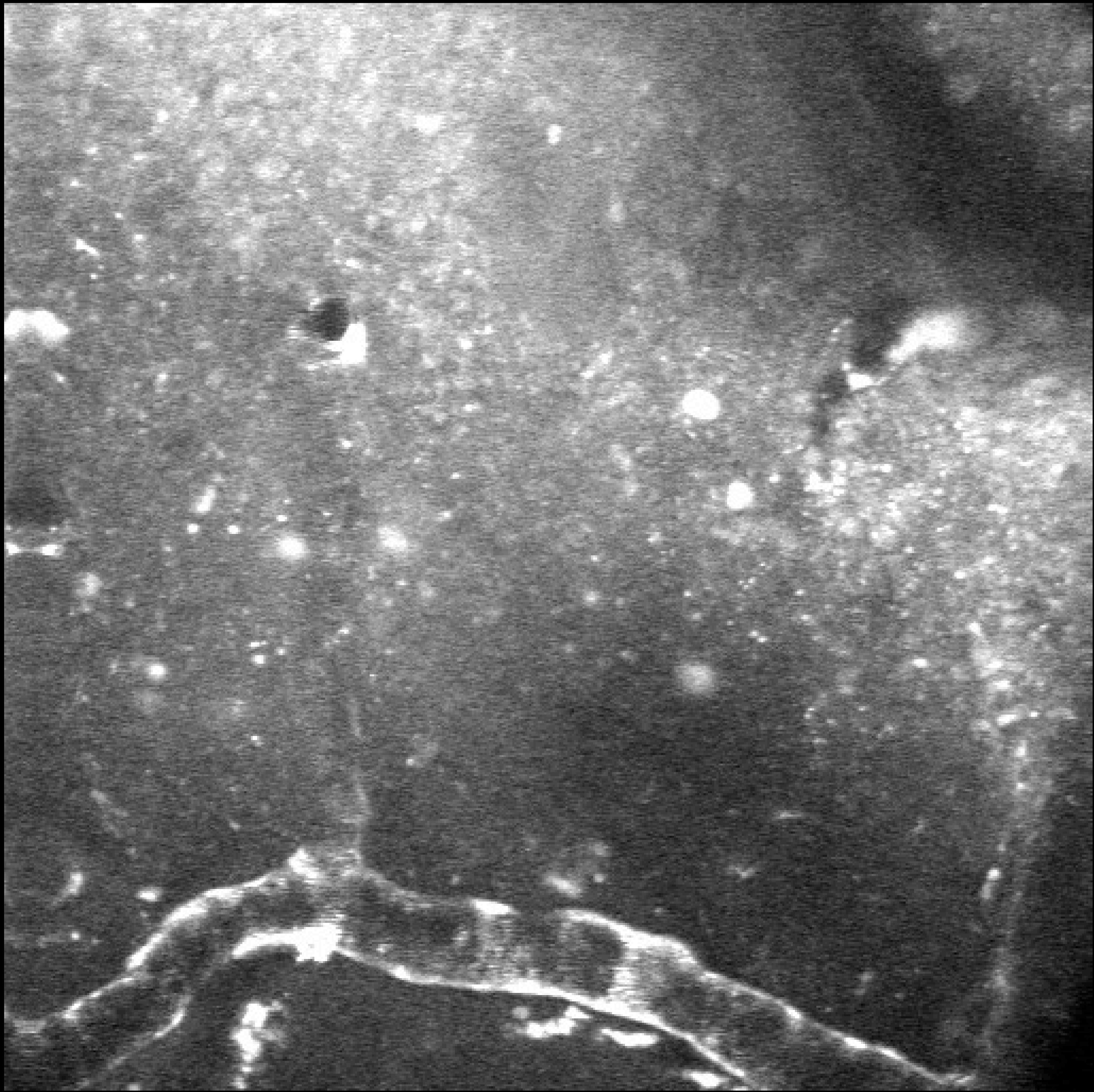
Niell and Stryker , 2010

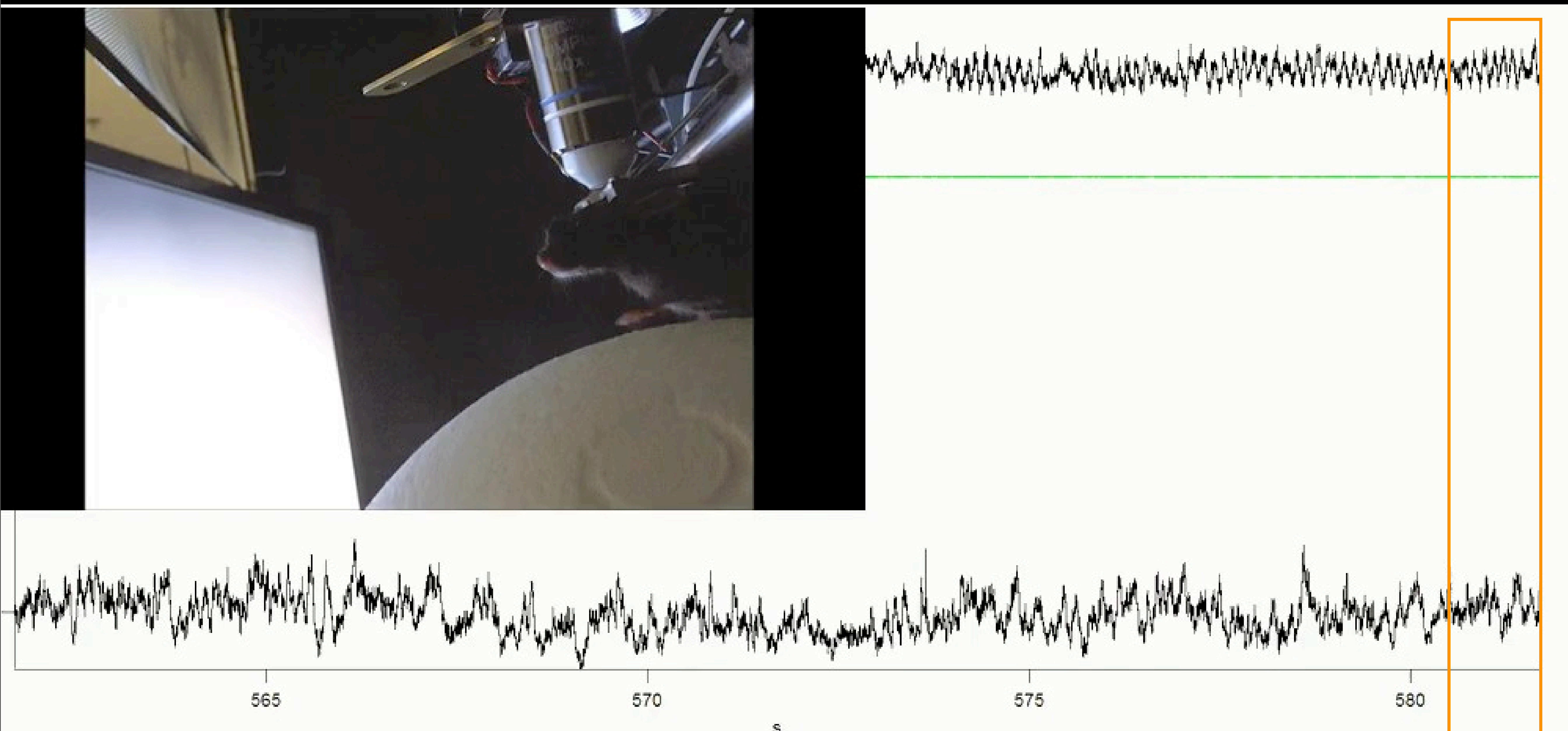
Questions

- What are the mechanisms underlying changes in the responsiveness of cortical neurons during changes in arousal state
- Which neuromodulatory systems mediate these changes?
- What are the contributions of identified interneurons to these alterations?

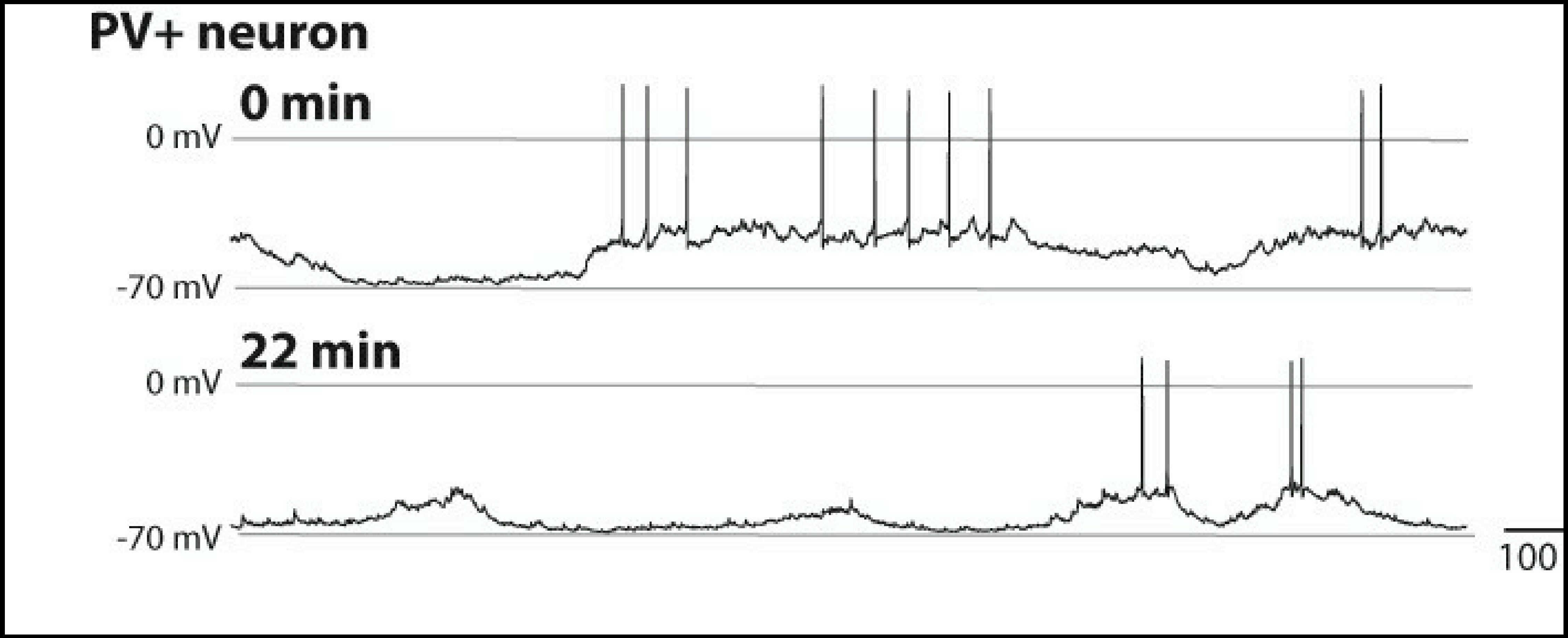

b
2-photon imaging
Whole cell
ECoG
Coverslip
Surface
Layer 2/3
350 μm
Layer 4
450 μm
r
c
Med
Lat
Layer 2/3
340 μm
Layer 4
100 μm
d
p
z projection
200 μm
Coronal projection



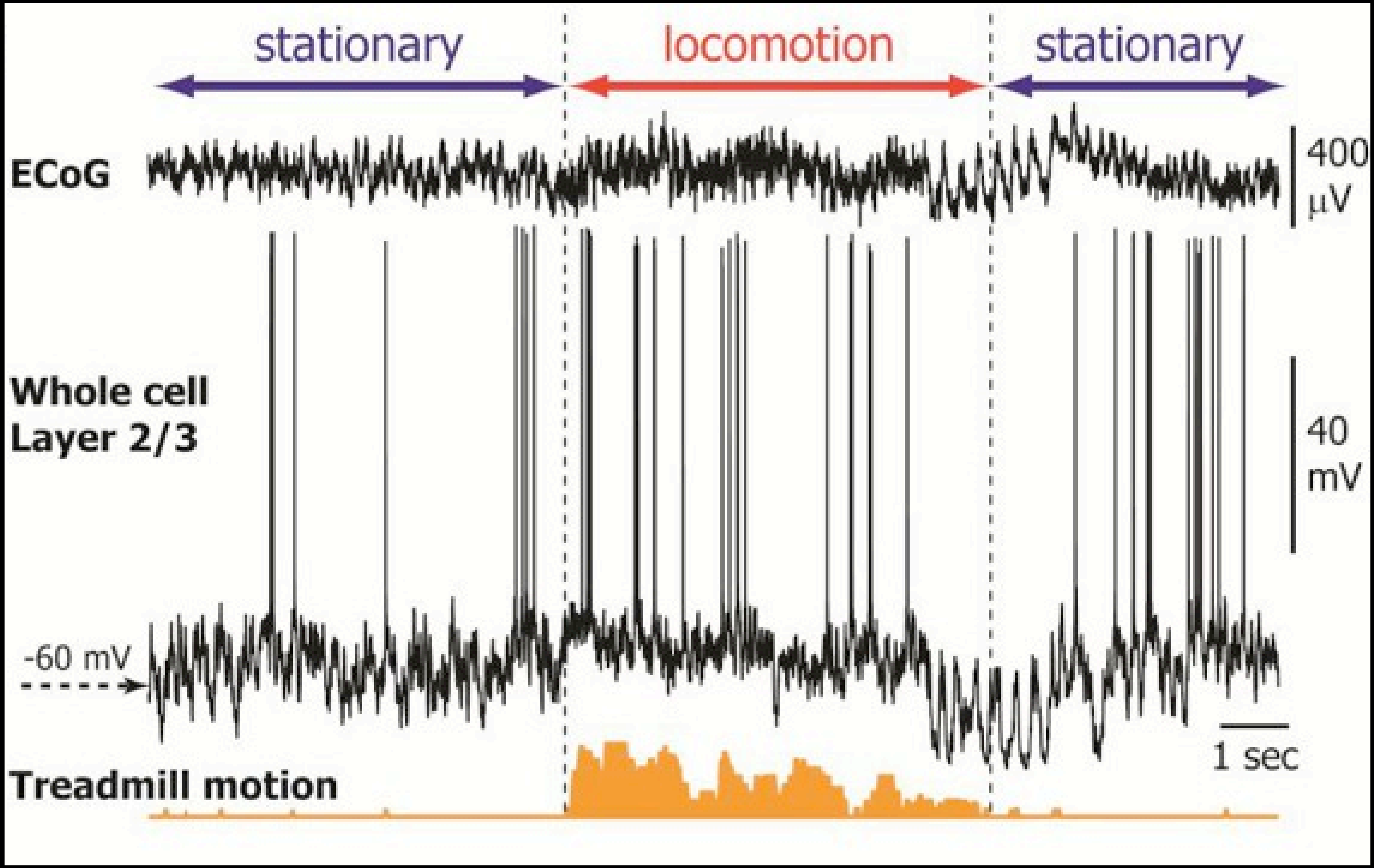



565
570
575
580
s

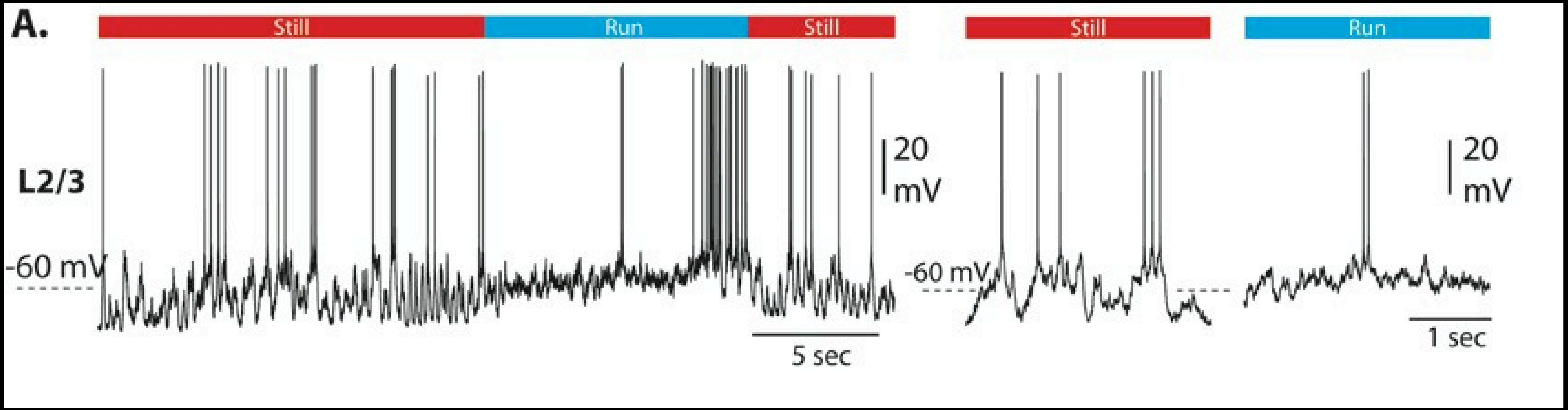
Stable whole cell recordings in running mice.



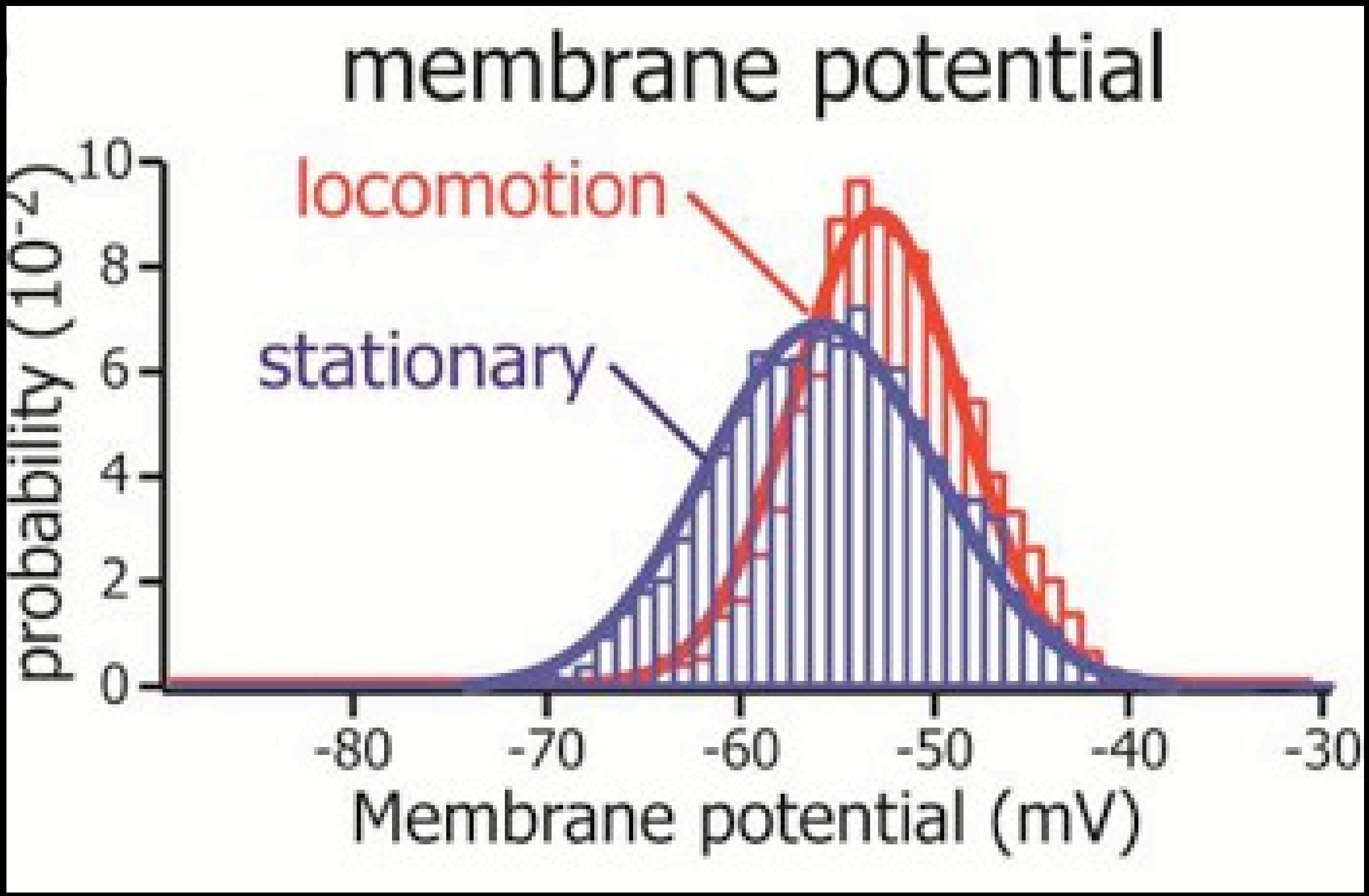
Depolarization and decreased variance of the membrane potential with running: L2/3 excitatory neurons.



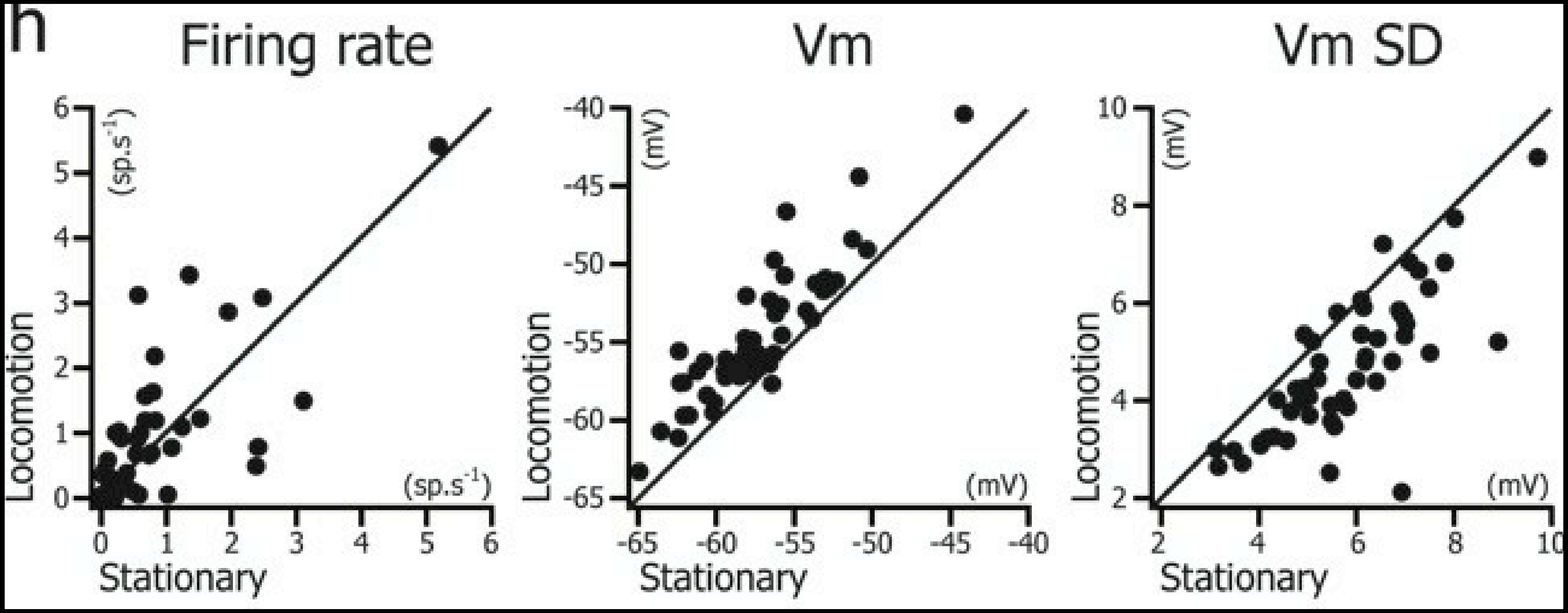
Depolarization and decreased variance of the membrane potential with running: L2/3 excitatory neurons.



Unimodal membrane potential distributions in stationary and locomotive periods



Layer 2/3: No visual stimulus

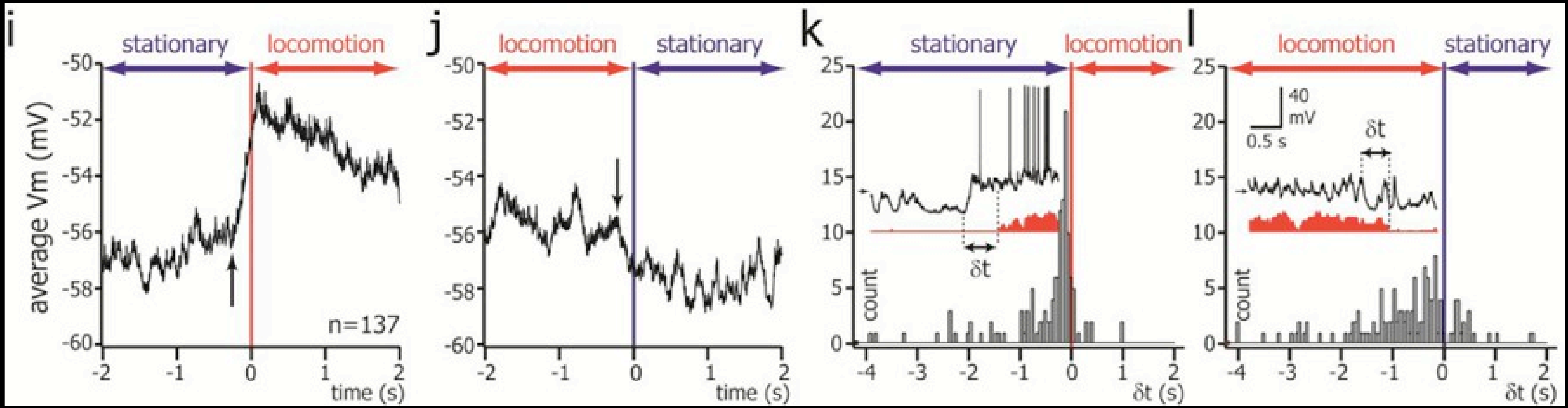


No change in firing rate

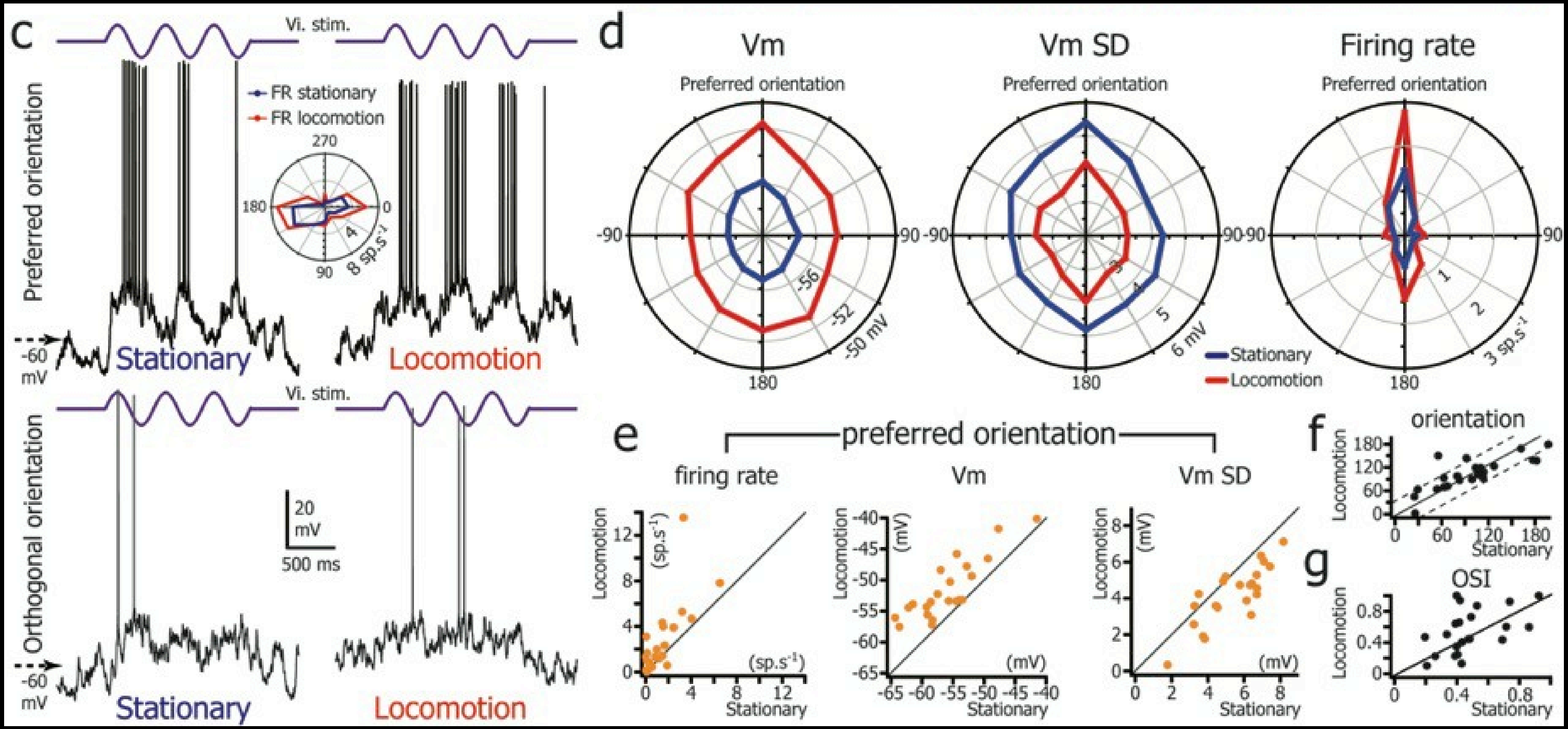
Depolarization of Vm

Decrease in Vm SD

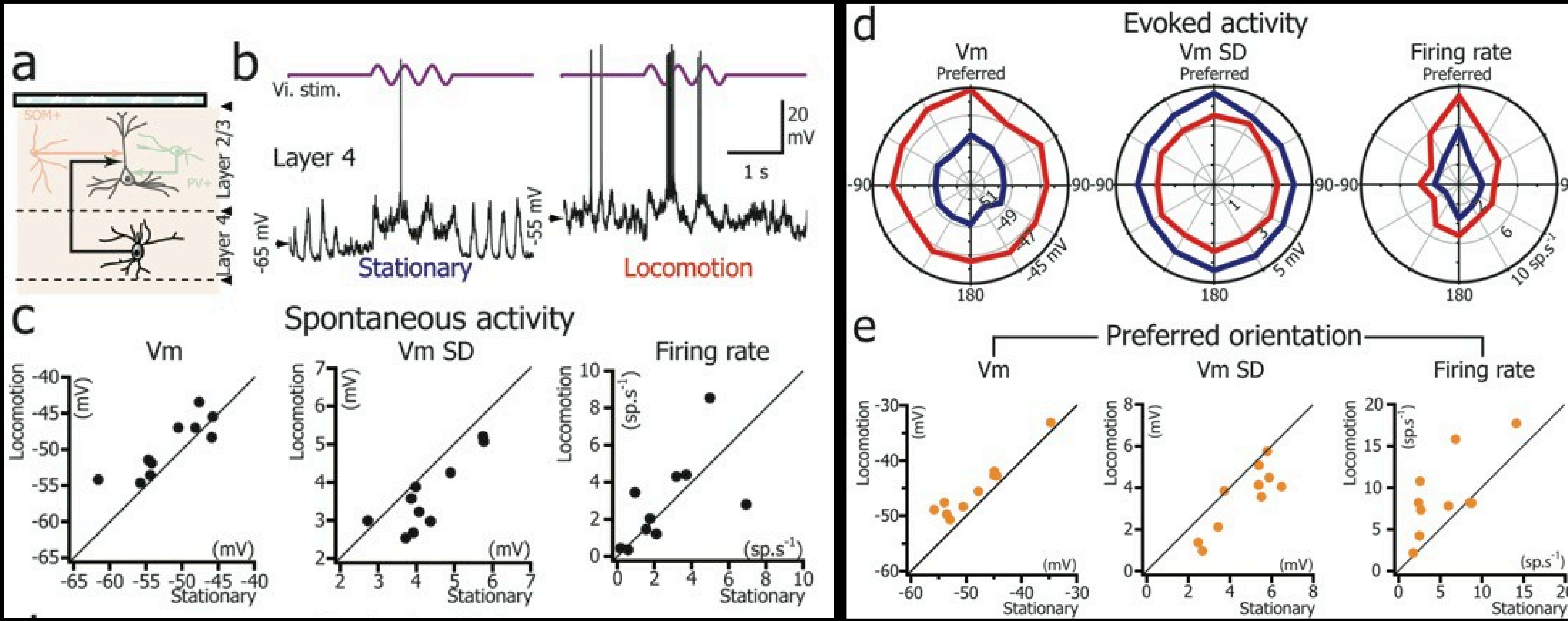
Depolarization starts before the start of locomotion.



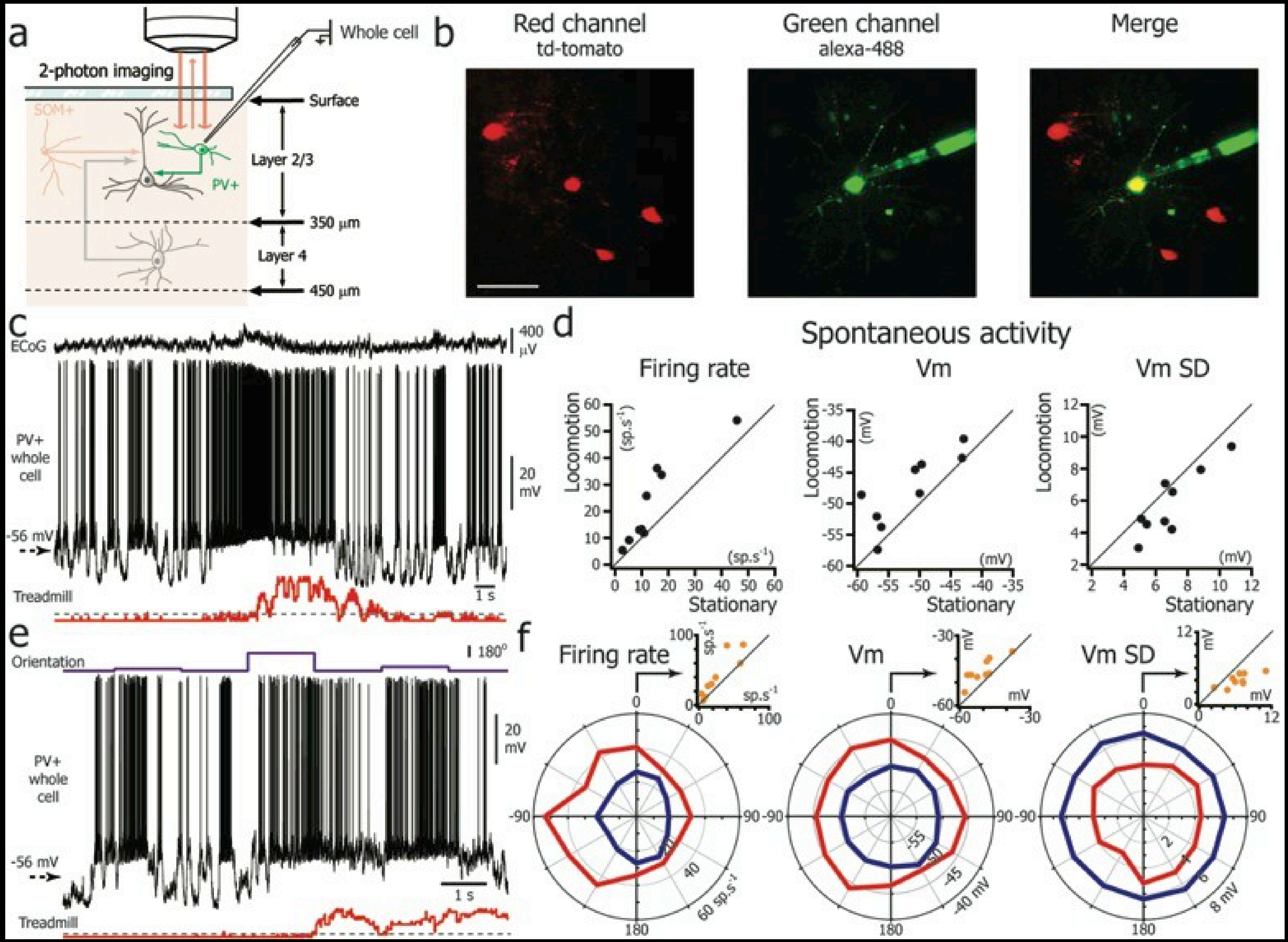
L2/3 Drifting Grating Visual Stimuli



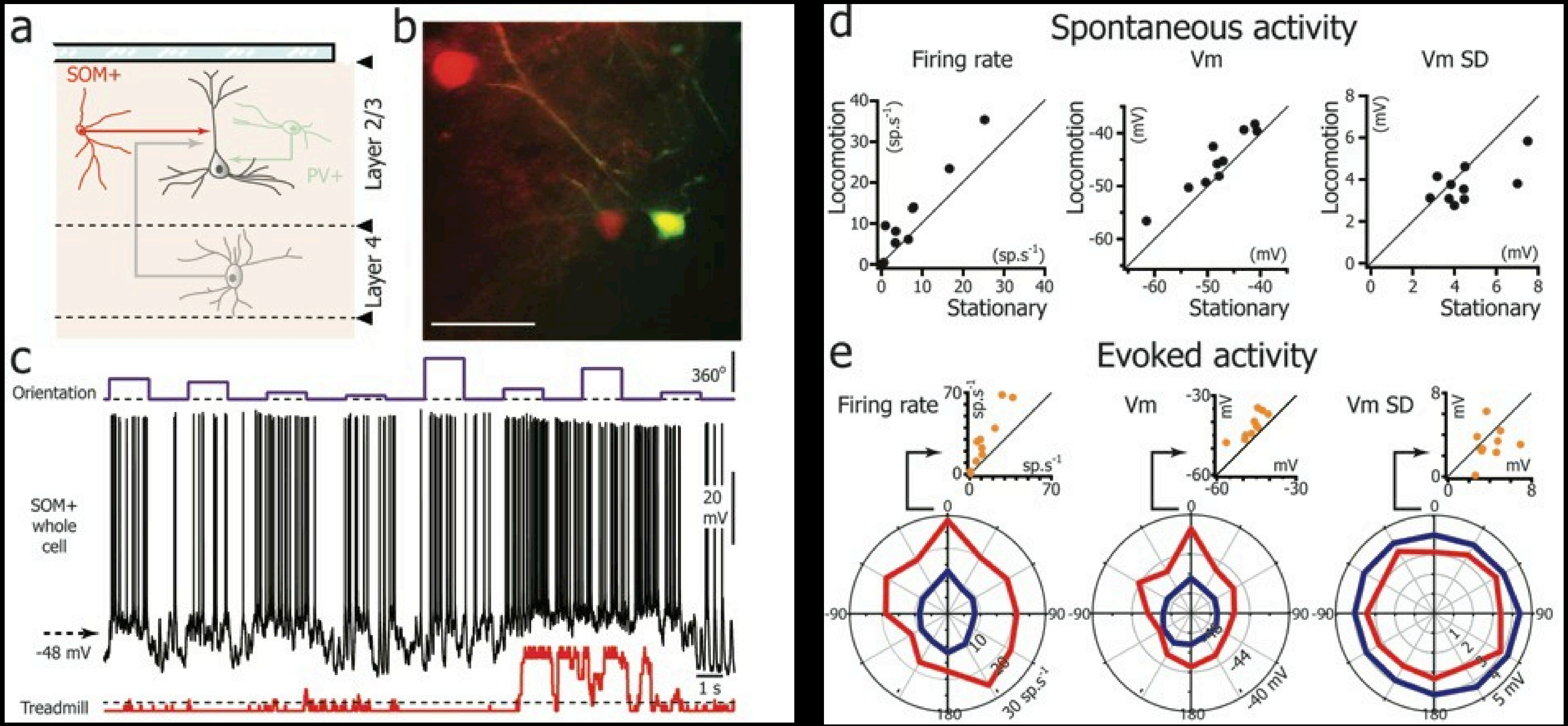
L4 behaves much like L2/3



PV+ interneurons depolarize with locomotion



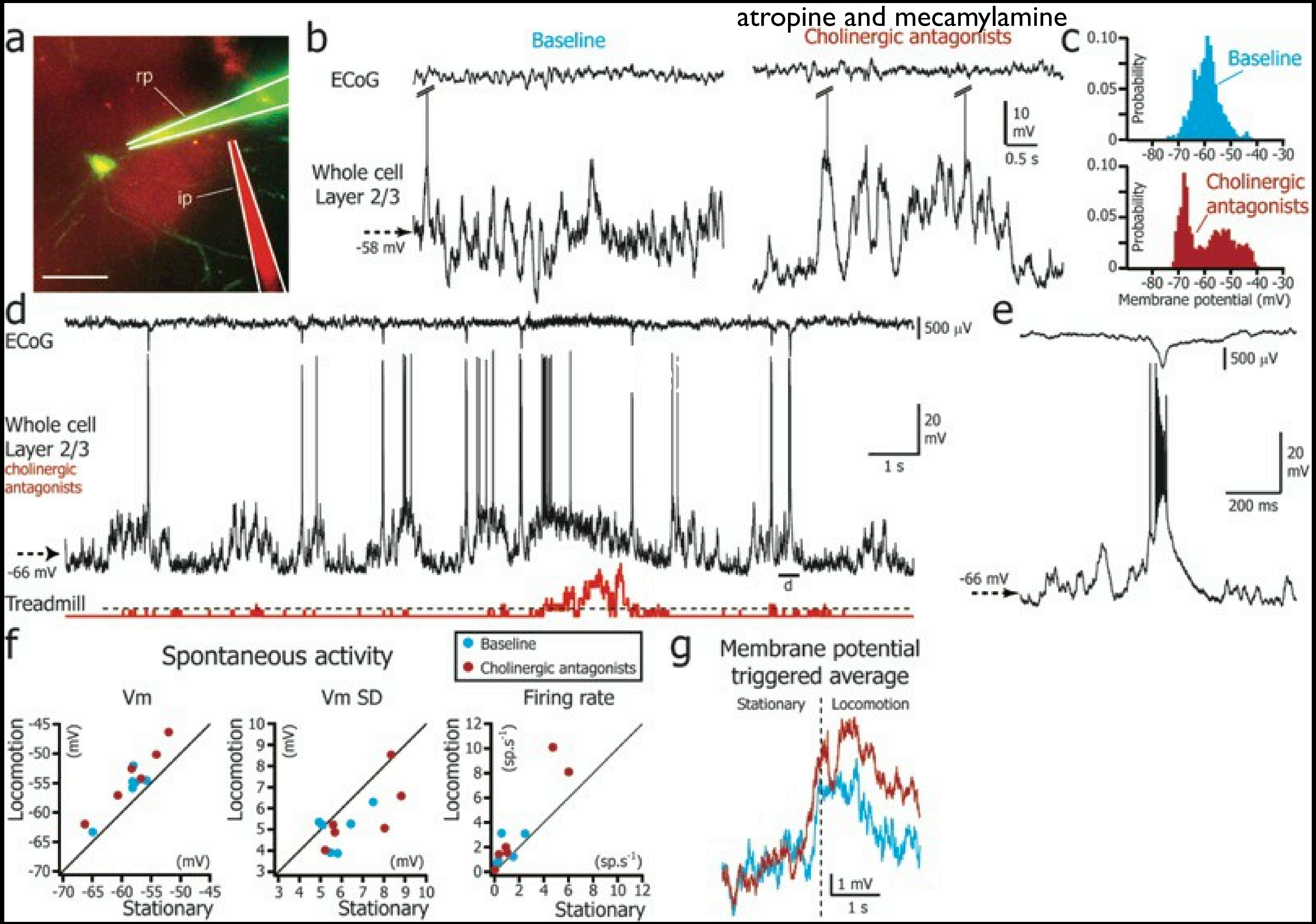
Somatostatin cells depolarize with locomotion



Could neuromodulation play a role ?

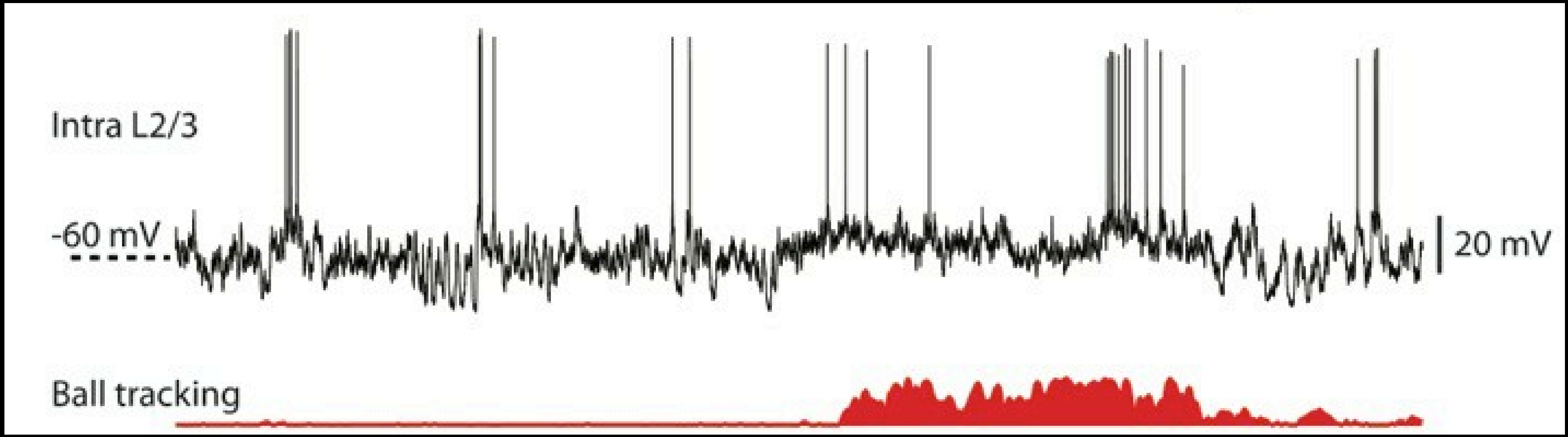
Cholinergic blockade does not prevent Vm changes with locomotion.

atropine and mecamylamine

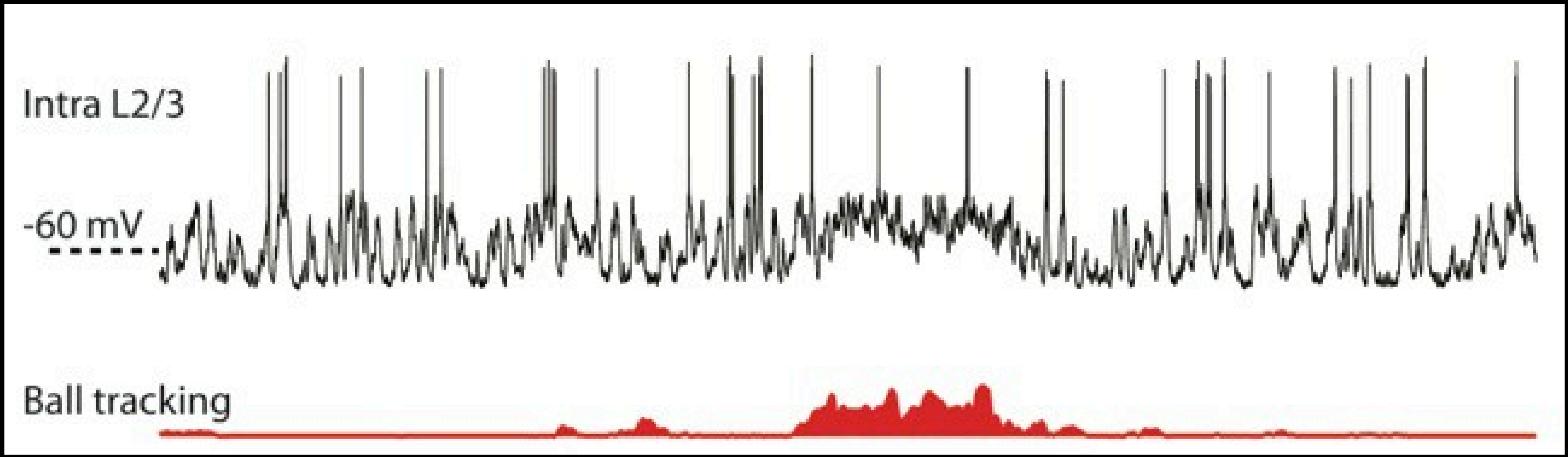


Cholinergic blockade does not prevent membrane potential changes associated with running

Control

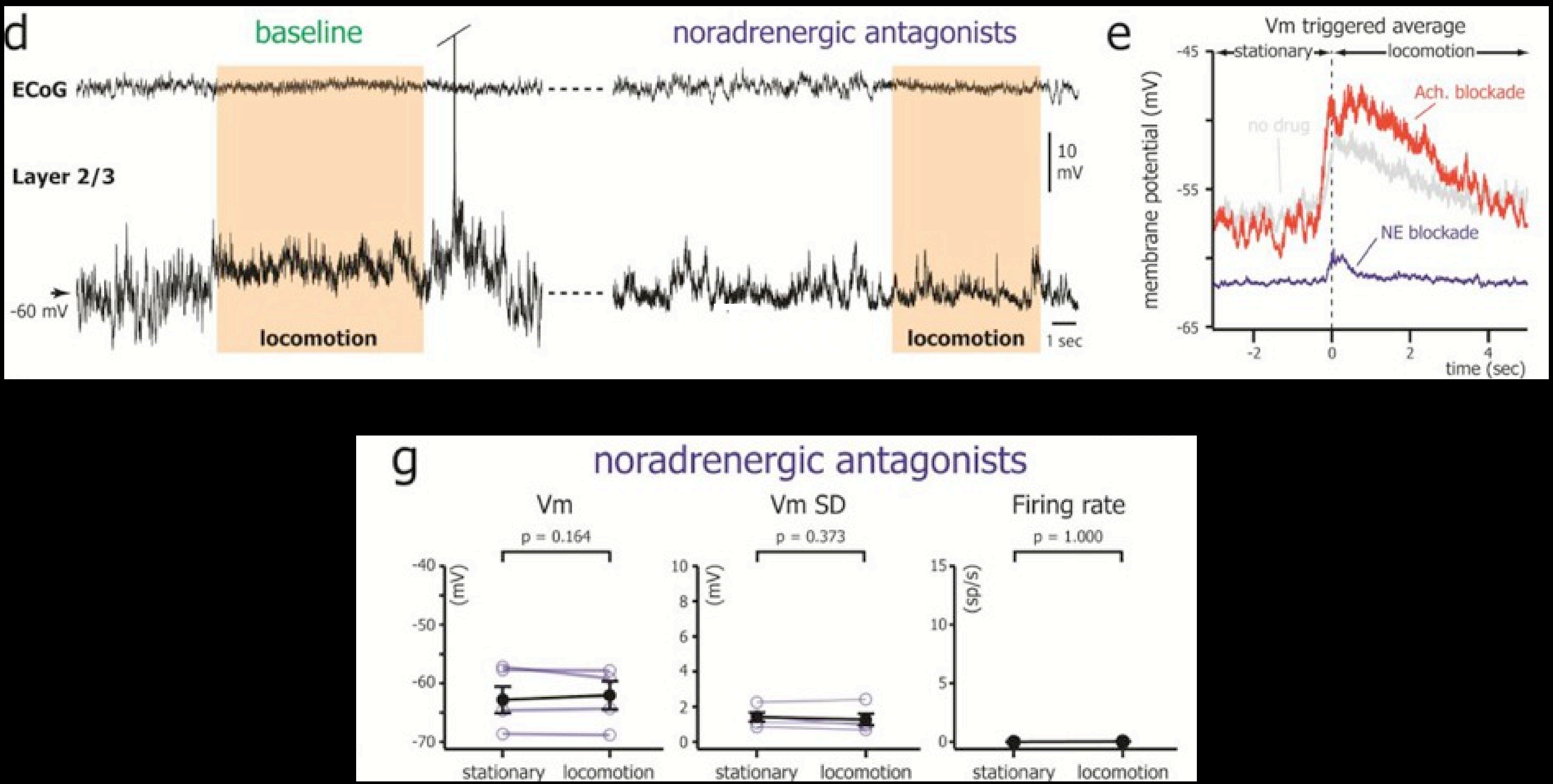


Cholinergic Blockade

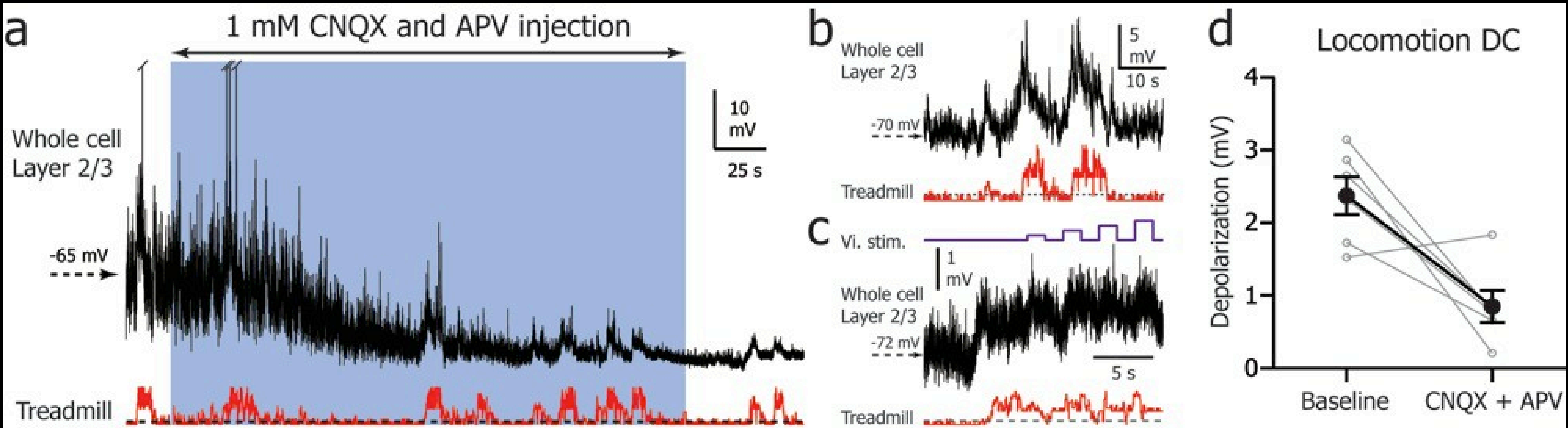


Noradrenergic antagonists block Vm changes associated with locomotion

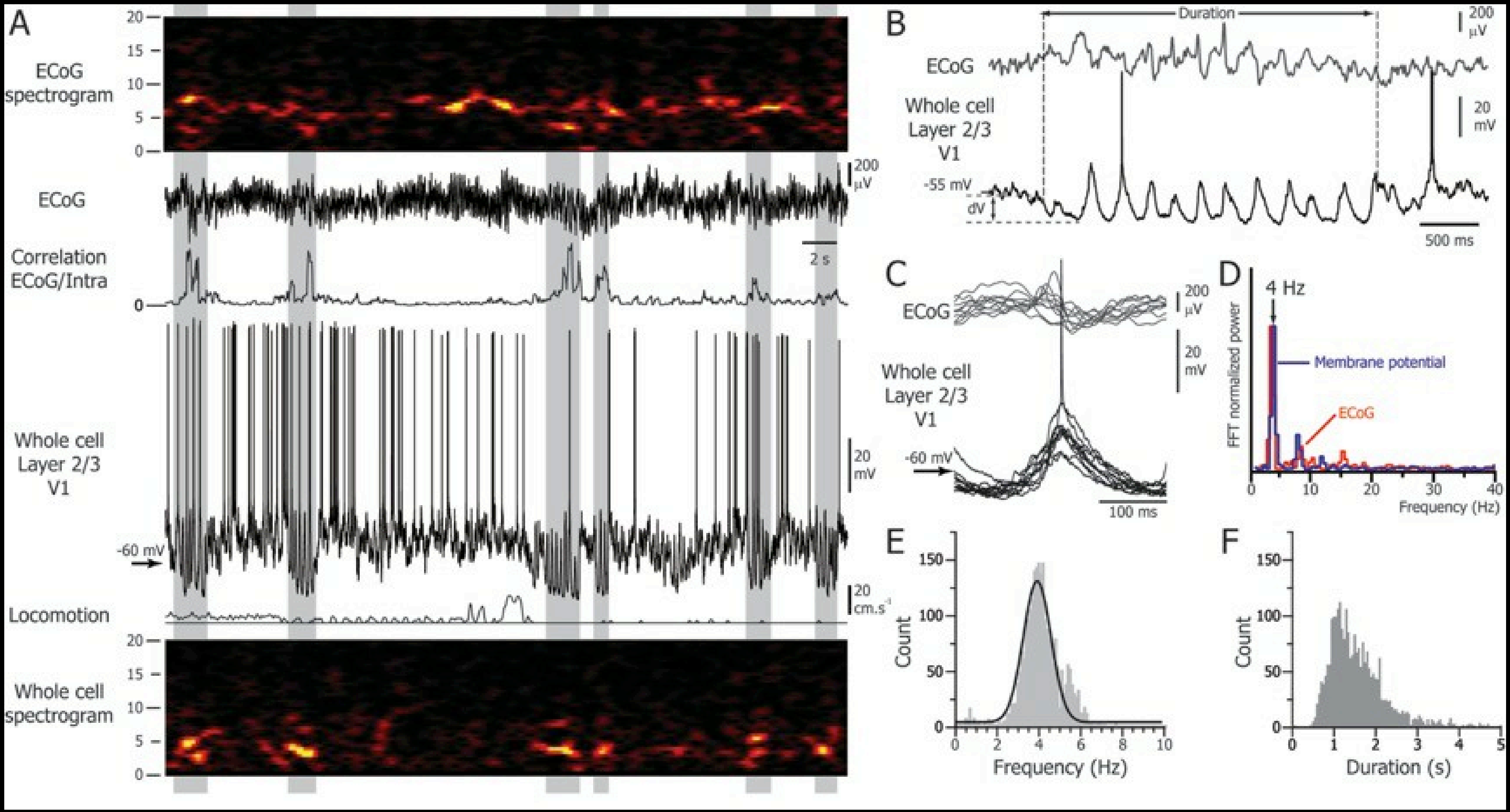
Prazosin, Yohimbine, Propranolol



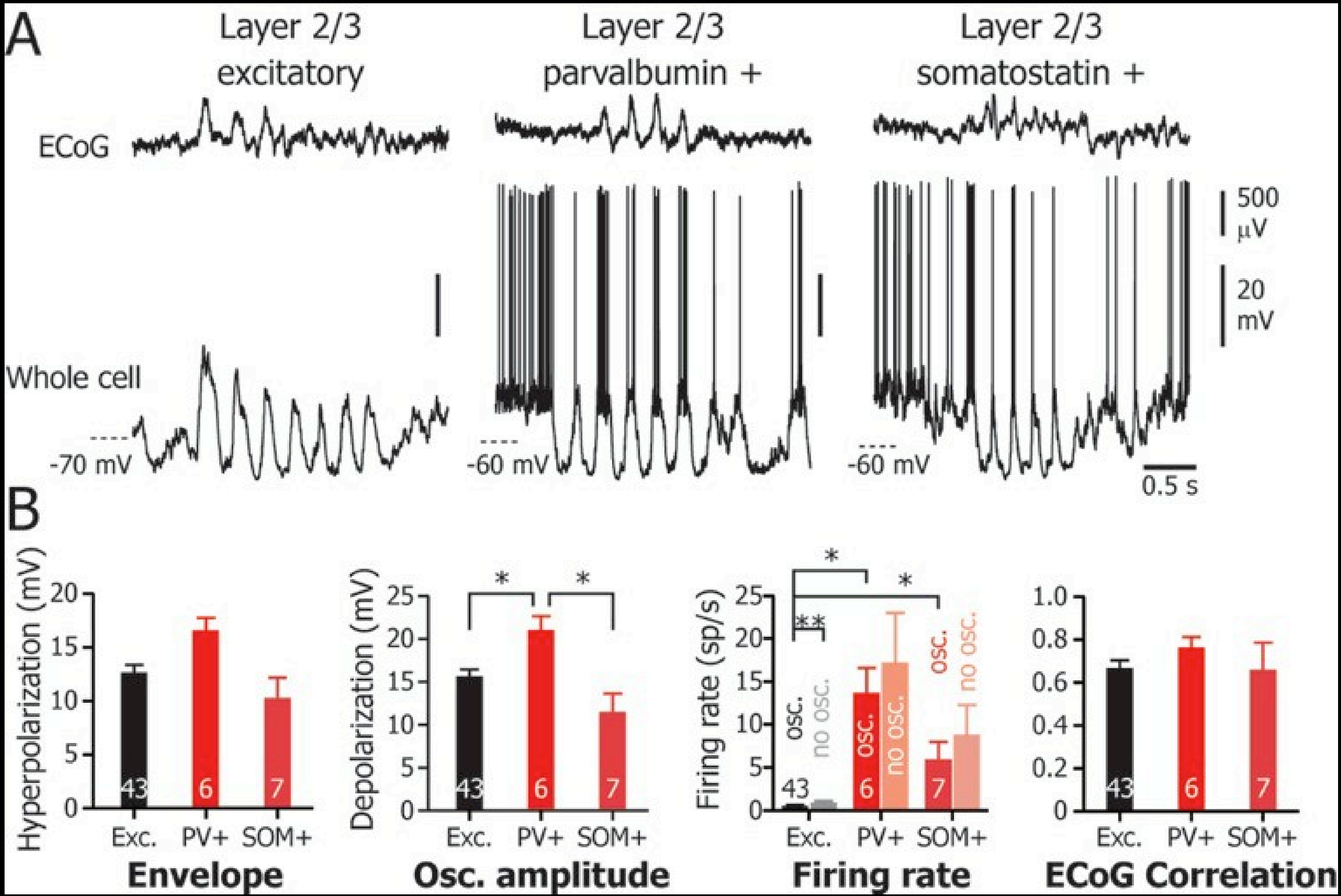
Running induced depolarization persists after blockade of AMPA and NMDA receptors



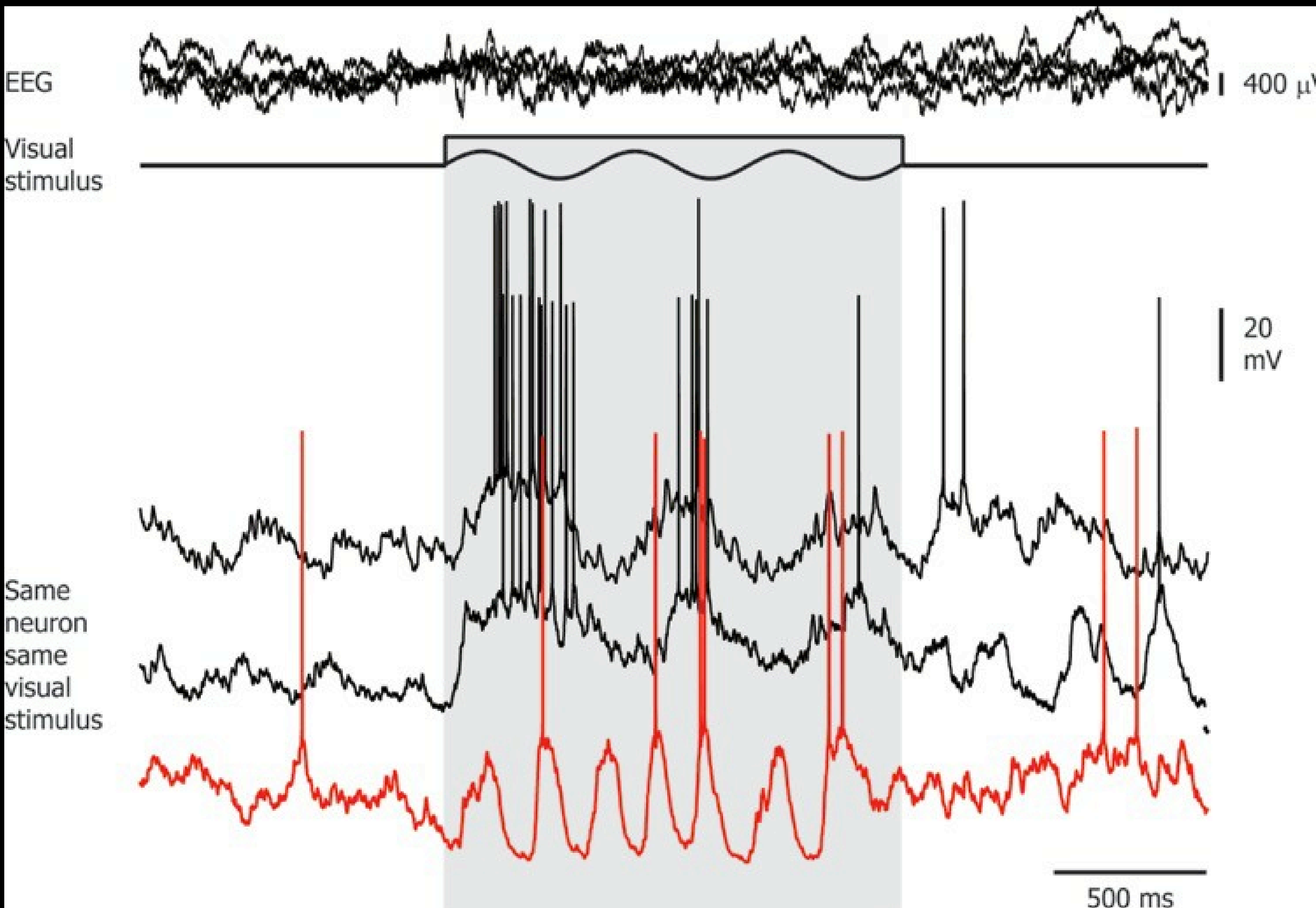
4 Hz Oscillation



4 Hz Oscillation



4 Hz oscillation disrupts visually evoked spiking

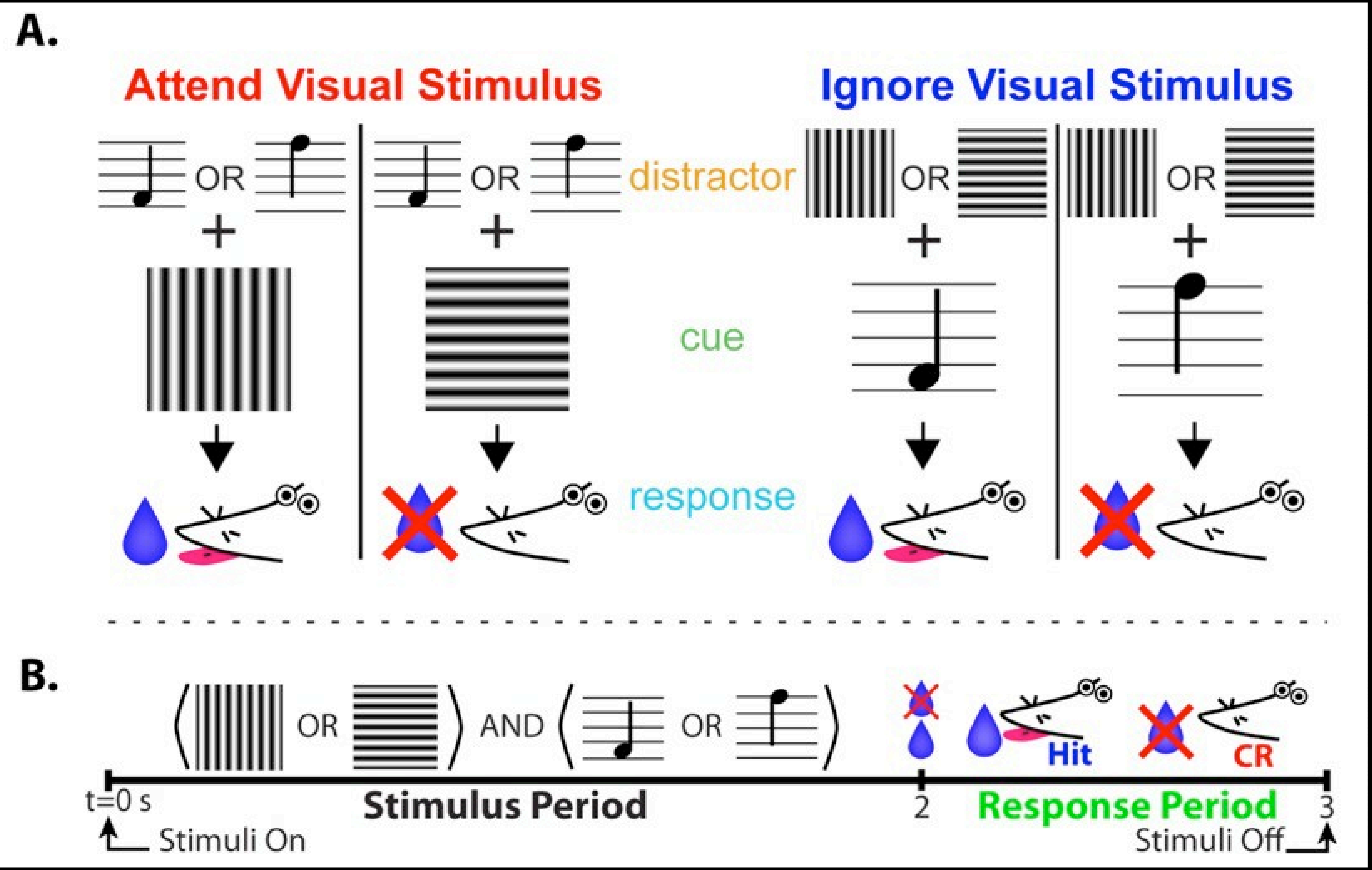


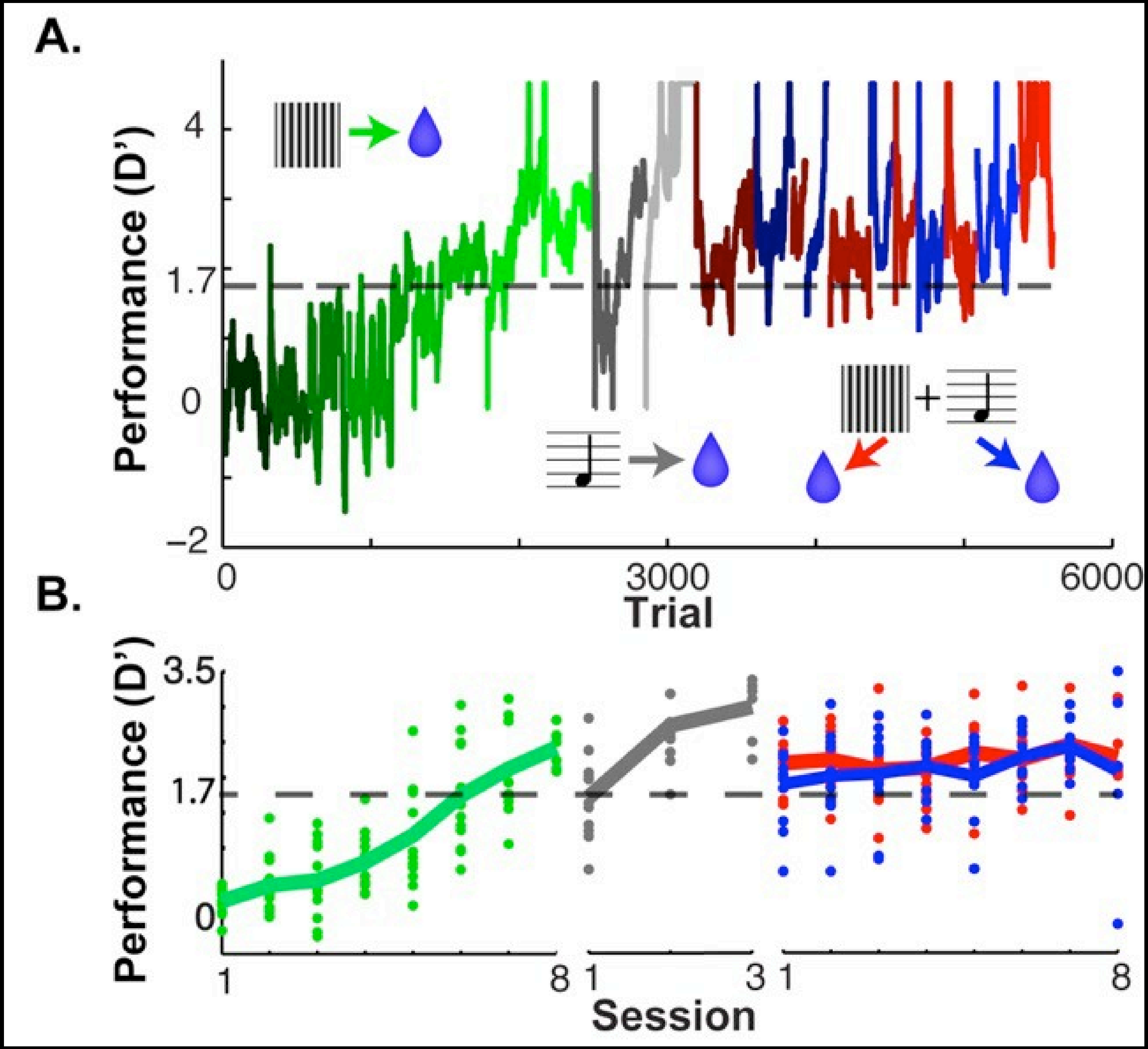
Conclusions

- Long-lasting stable targeted whole-cell recordings in mice free to run on a treadmill are possible
- Cells depolarize and their variance of the membrane potential decreases just prior to running.
- Noradrenergic input is essential for maintenance of the depolarized, low variance state.
- This depolarization increases firing rates to sensory stimuli.

Micheal Einstein

Pierre-Olivier Polack


A.
Attend Visual Stimulus
Ignore Visual Stimulus
OR
distractor
cue
response
B.
OR
AND
Hit
CR
t=0 s
Stimulus Period
2
Response Period
3
Stimuli On
Stimuli Off

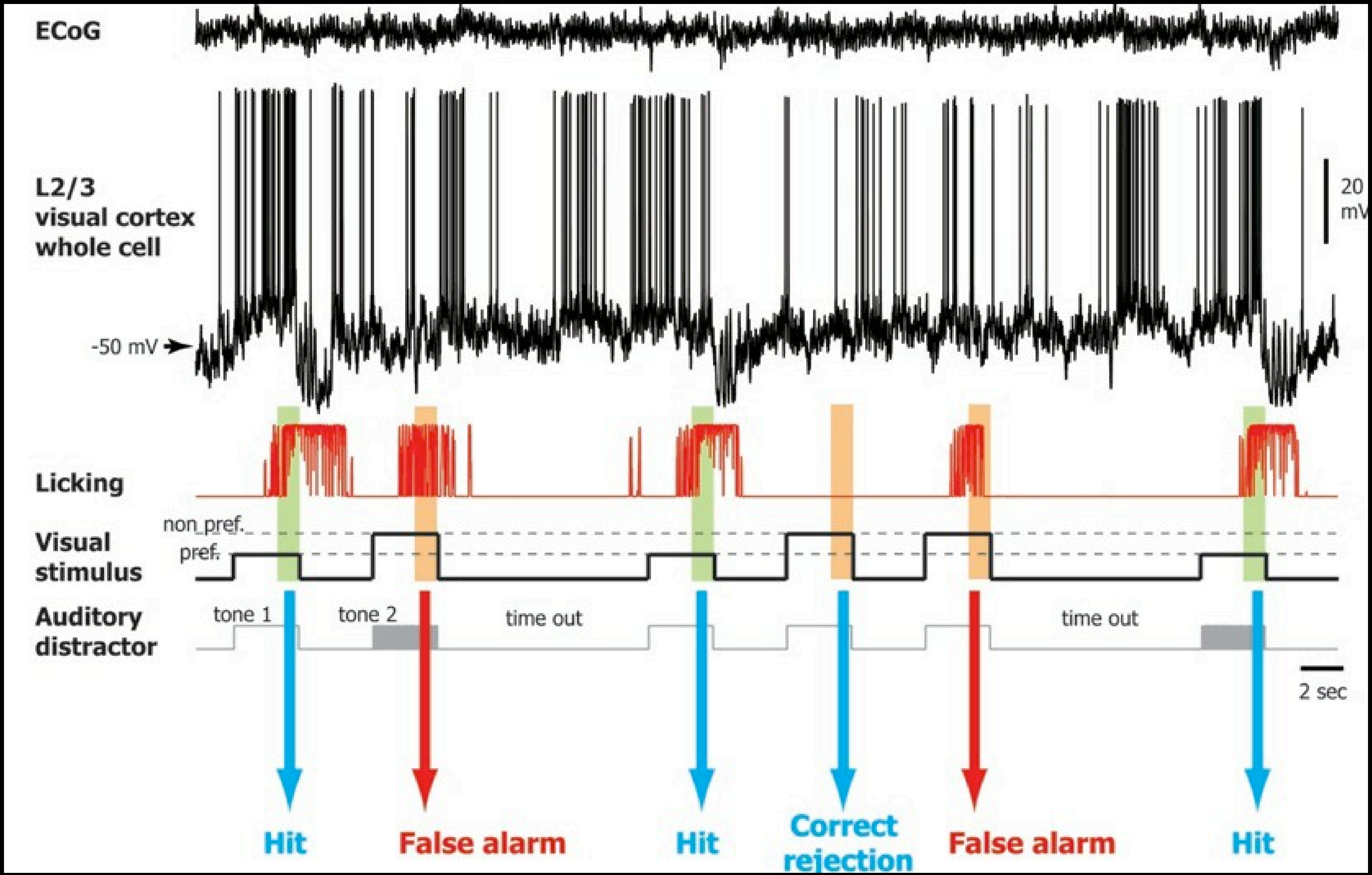


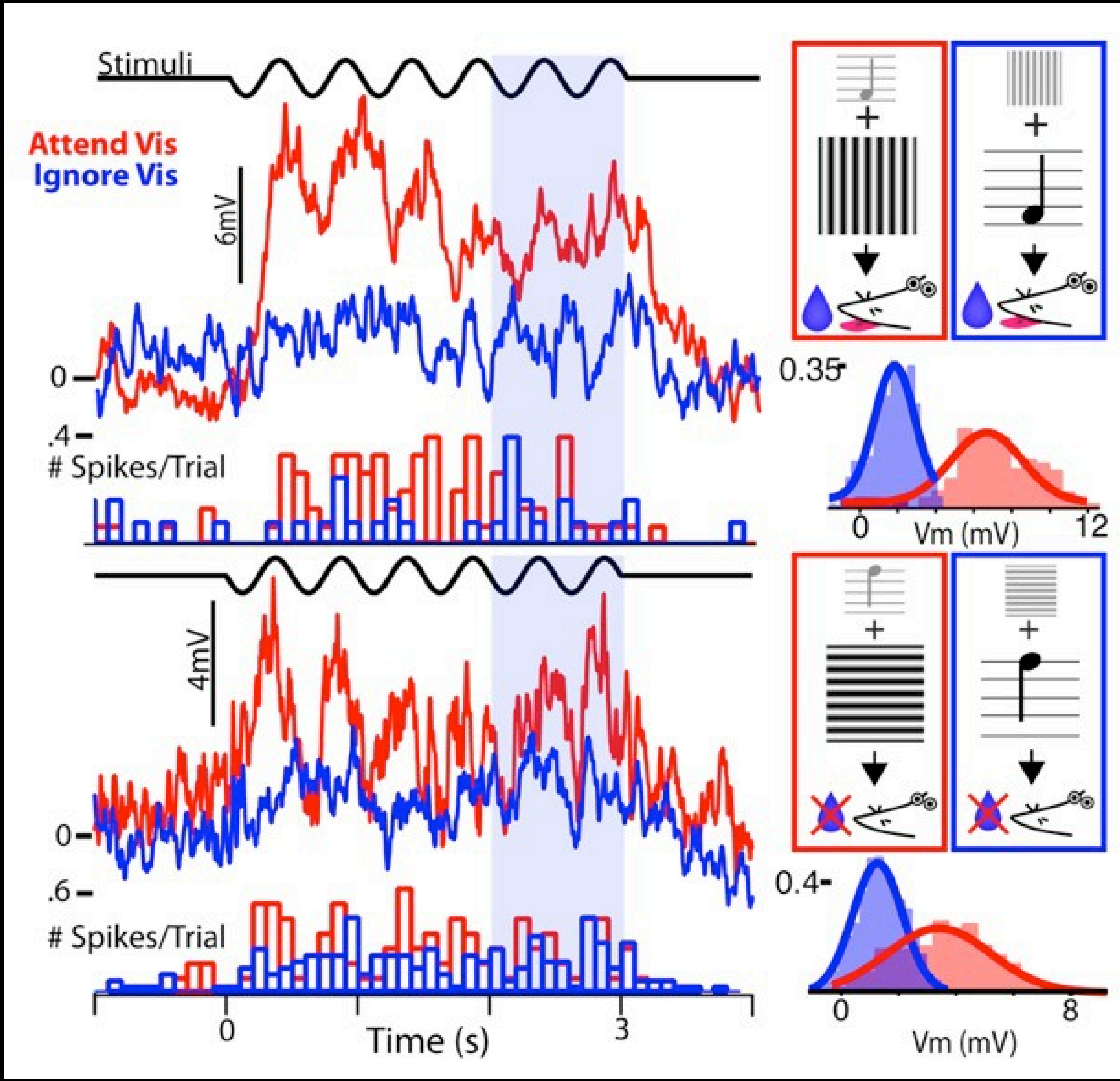
A.
Performance (D')
4
1.7
0
−2
0
3000
6000
Trial
B.
Performance (D')
3.5
1.7
0
1
8
1
3
1
8
Session

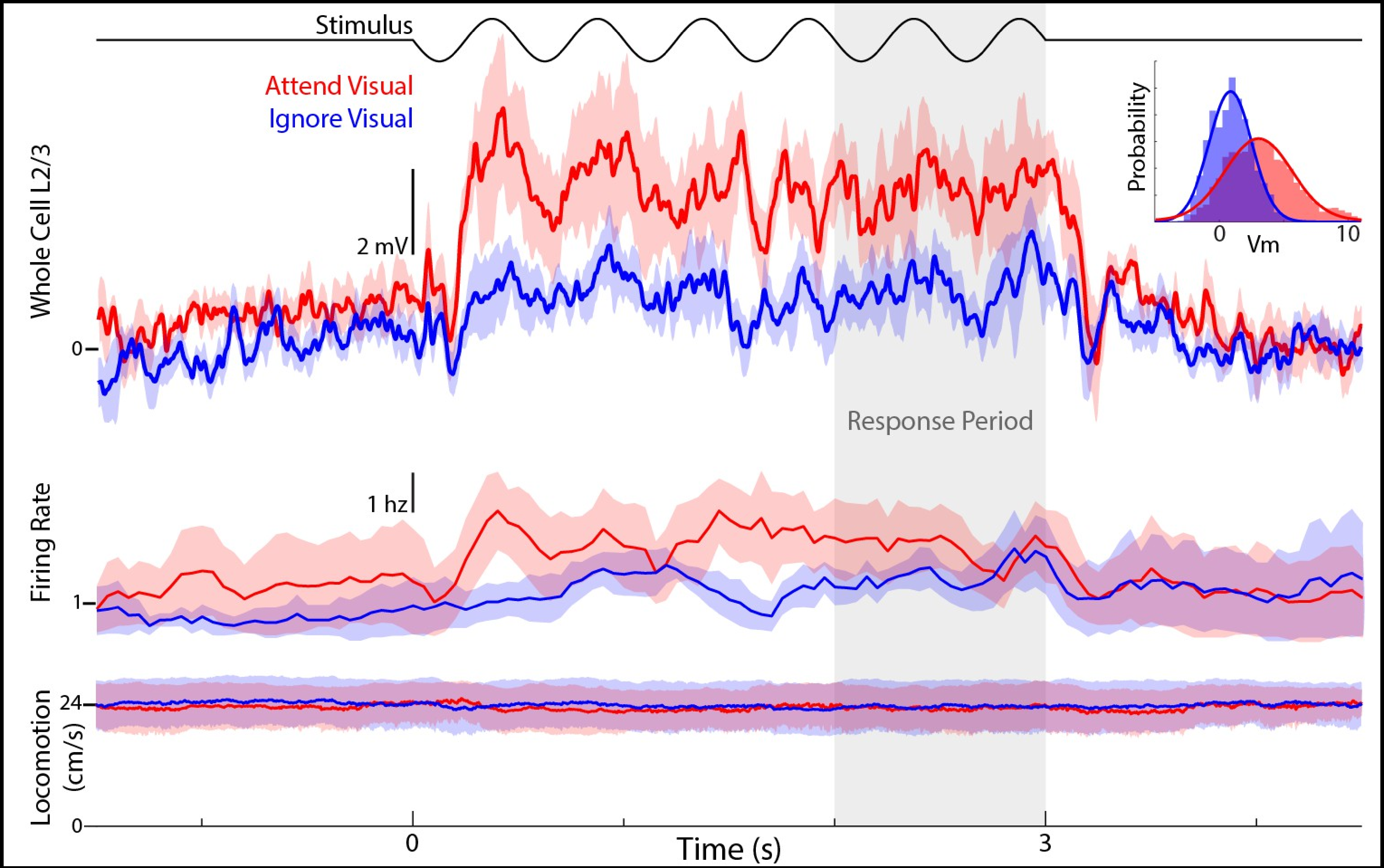
visual attention

auditory attention

Membrane potential dynamics during a GO/NO-GO task

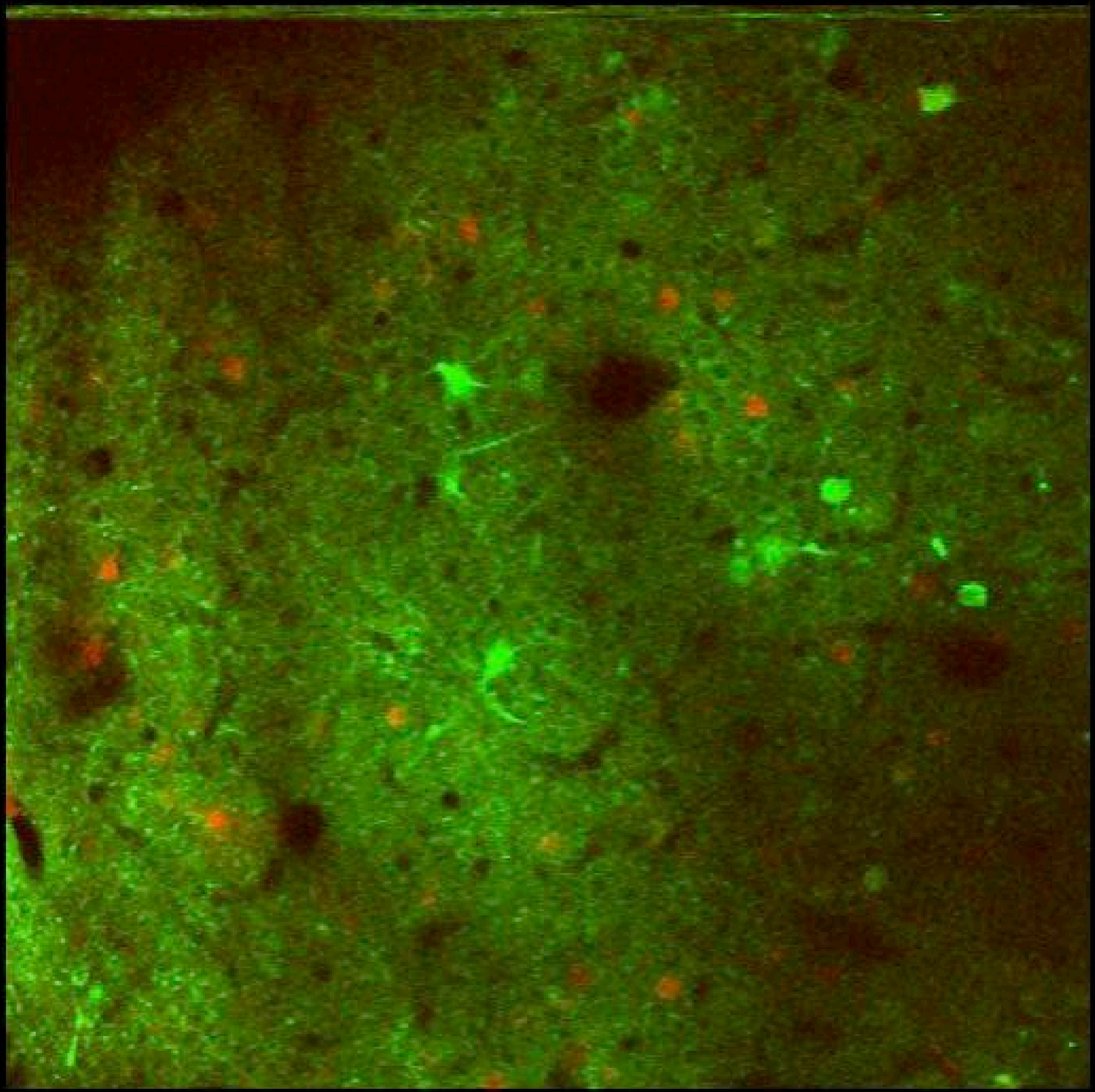



Stimuli
Attend Vis
Ignore Vis
6mV
0
.4
Spikes/Trial
0.35
0
Vm (mV)
12
4mV
0
.6
Spikes/Trial
0.4
0
8
Vm (mV)
0
3
Time (s)

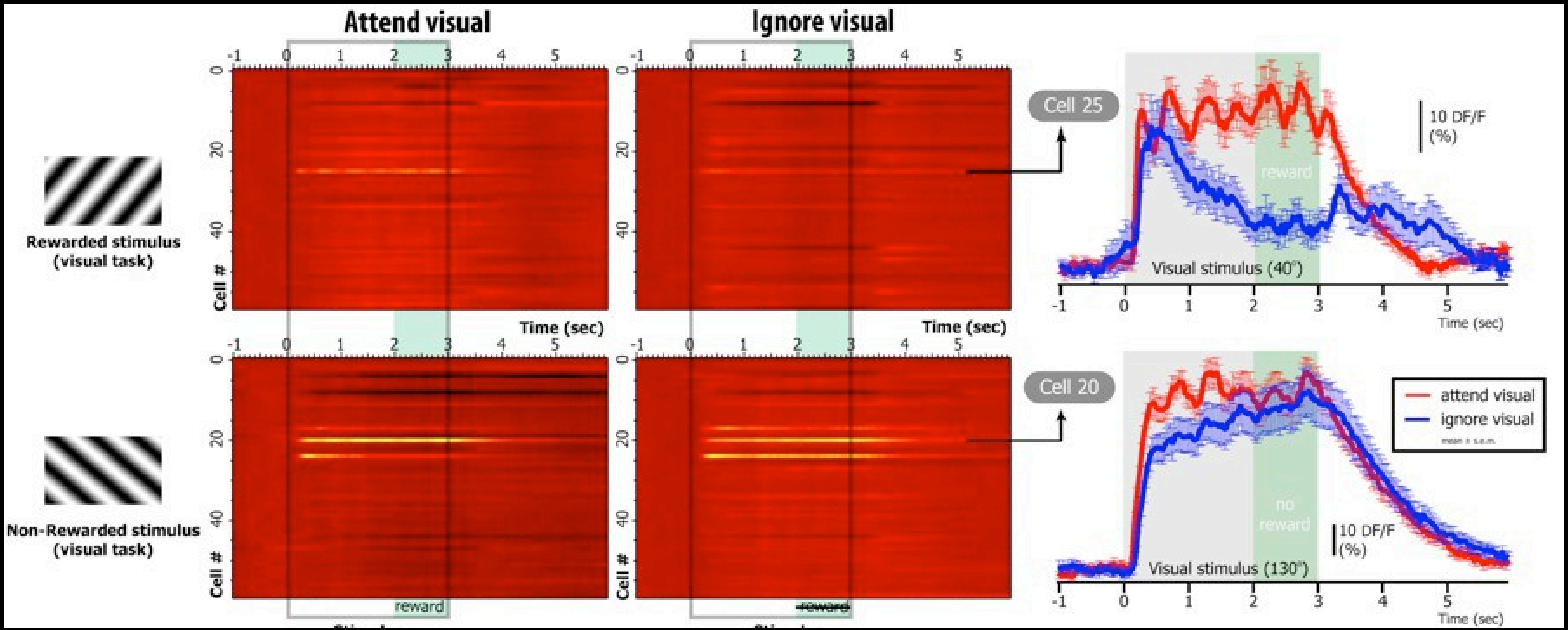


Stimulus
Attend Visual
Ignore Visual
Whole Cell L2/3
2 mV
0
Probability
0
Vm
10
Response Period
Firing Rate
1 hz
1
Locomotion (cm/s)
24
0
0
3
Time (s)

GCAMP6 Calcium Imaging: Visual Cortex Attention Task



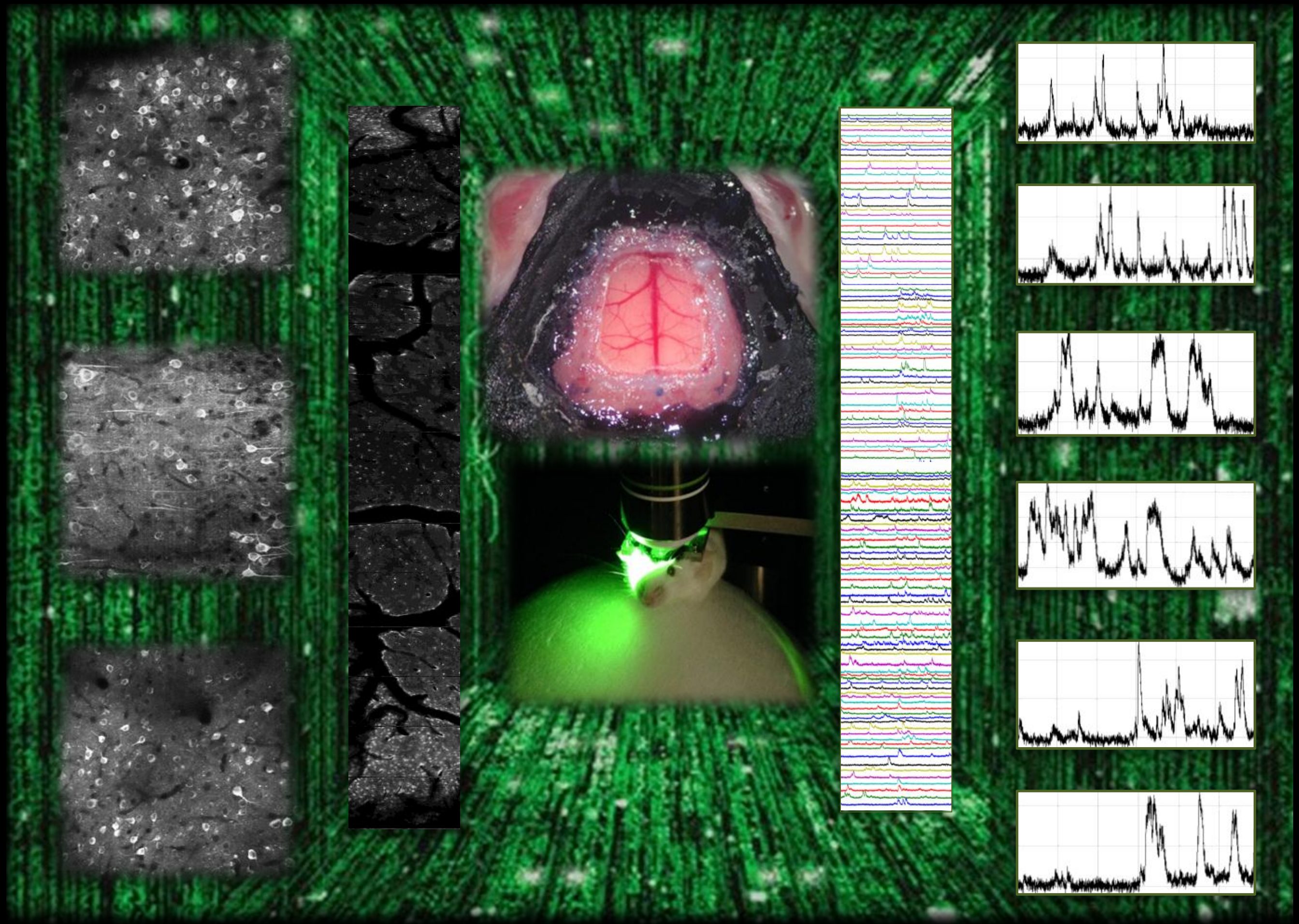
Attention dependent effects on V1 activity



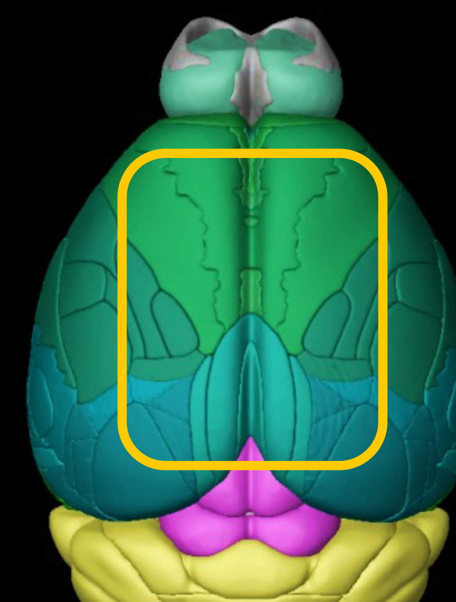
New Tools/ Future Directions

- Giant Cranial Window and Prism
- Development of New Miniaturized Microscopes.

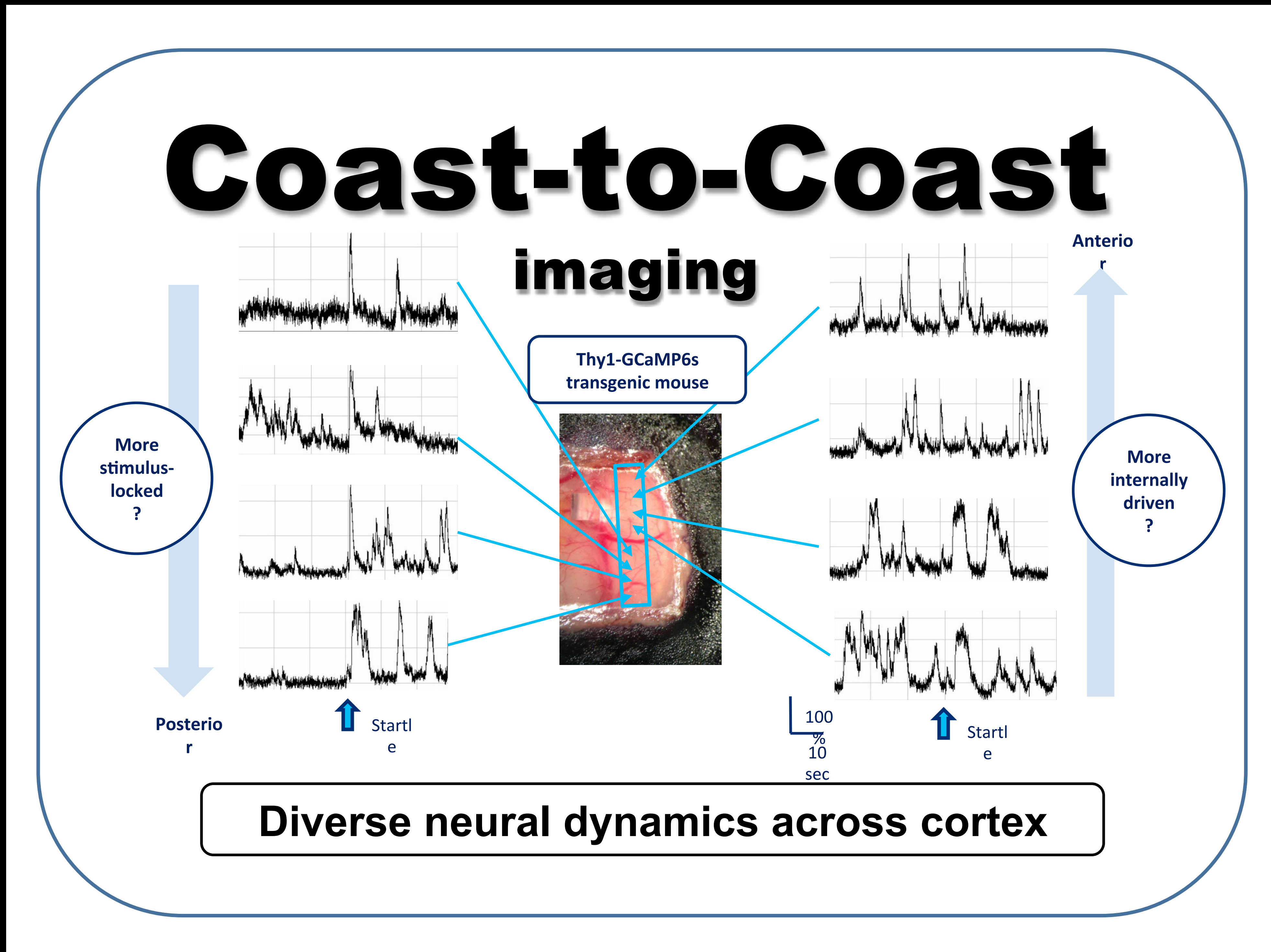
Big Cranial Window and Prism



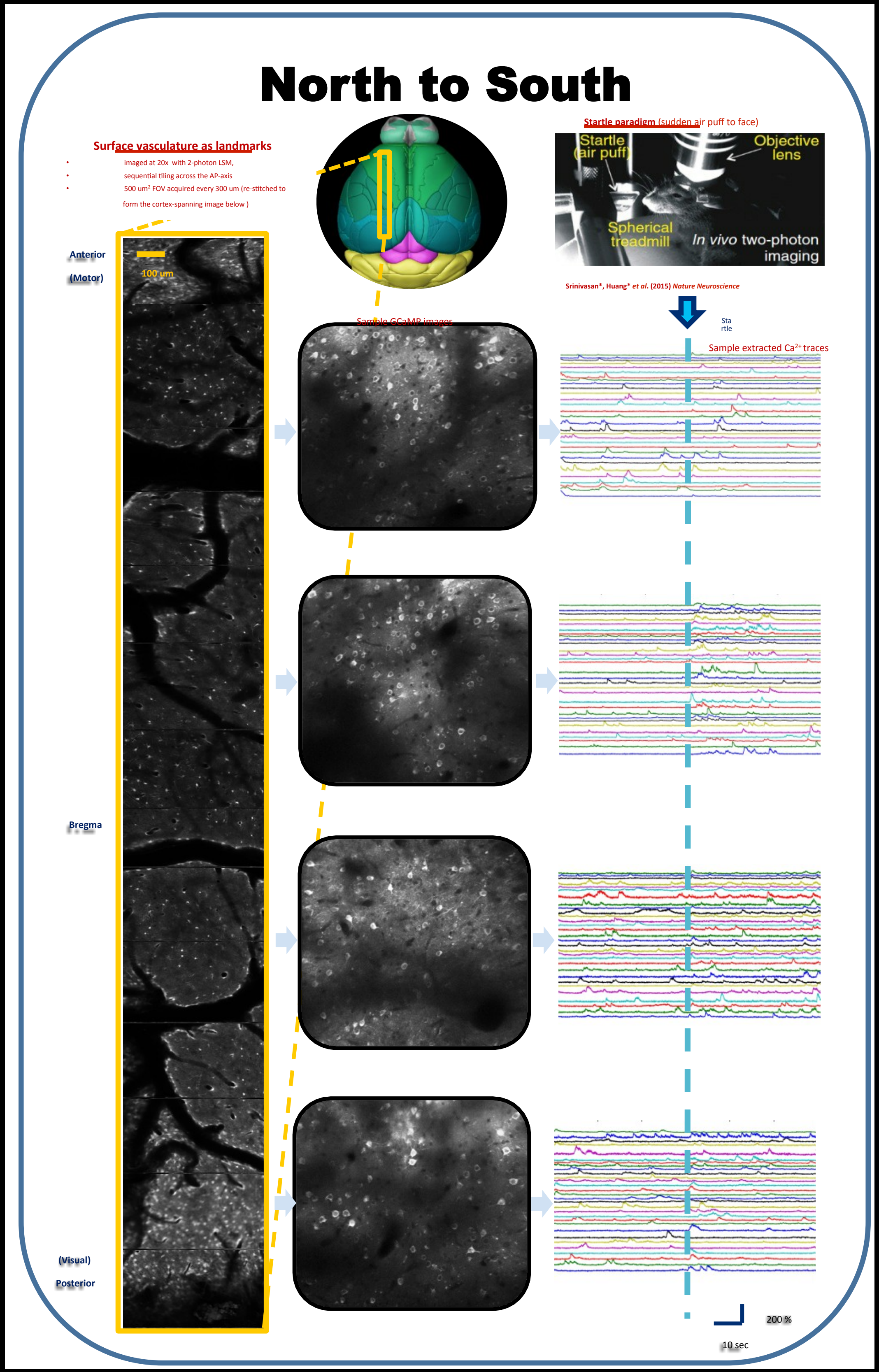
Bilateral, 6X8 mm



Chronic Optical Access



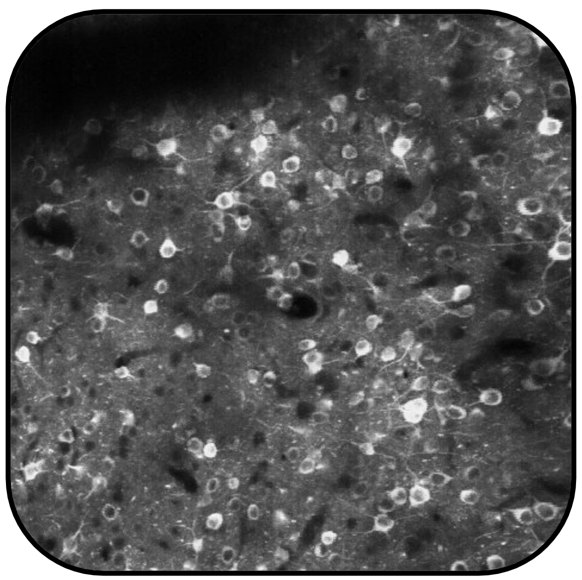
Mice described in Dana et al., PLOS ONE, 2014



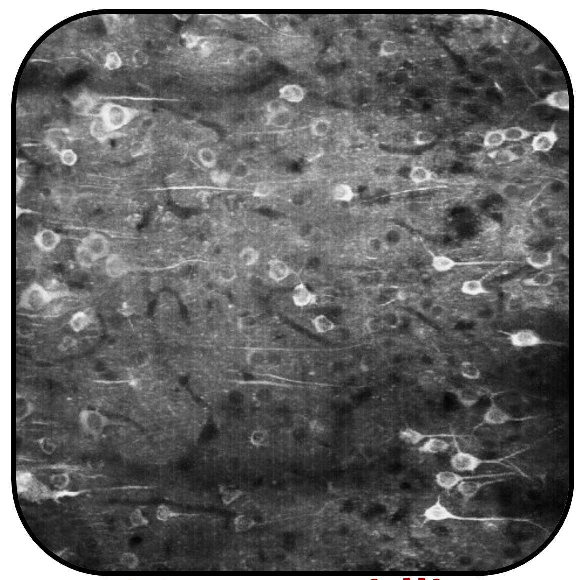
Segmentation and Data Extraction using software from Pnevmatikakis et al.

Bilateral Access

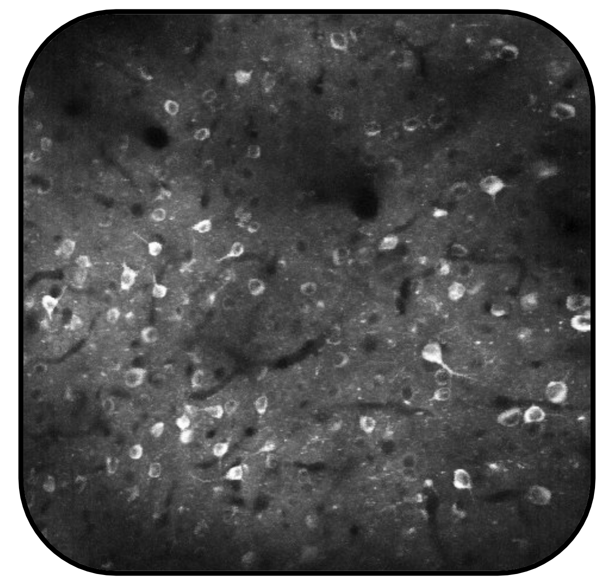
East to West



Left PPC

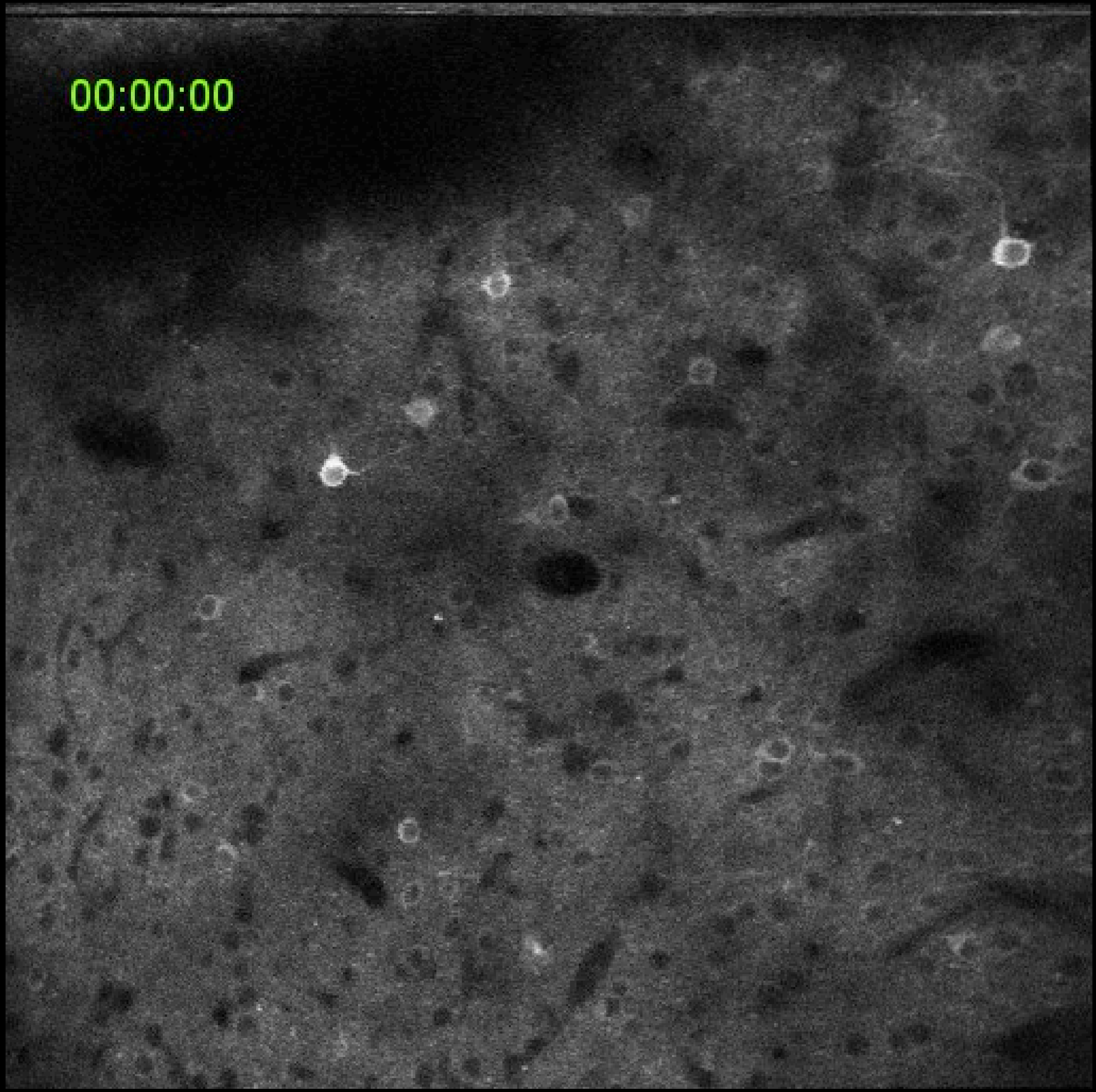


RSC near midline

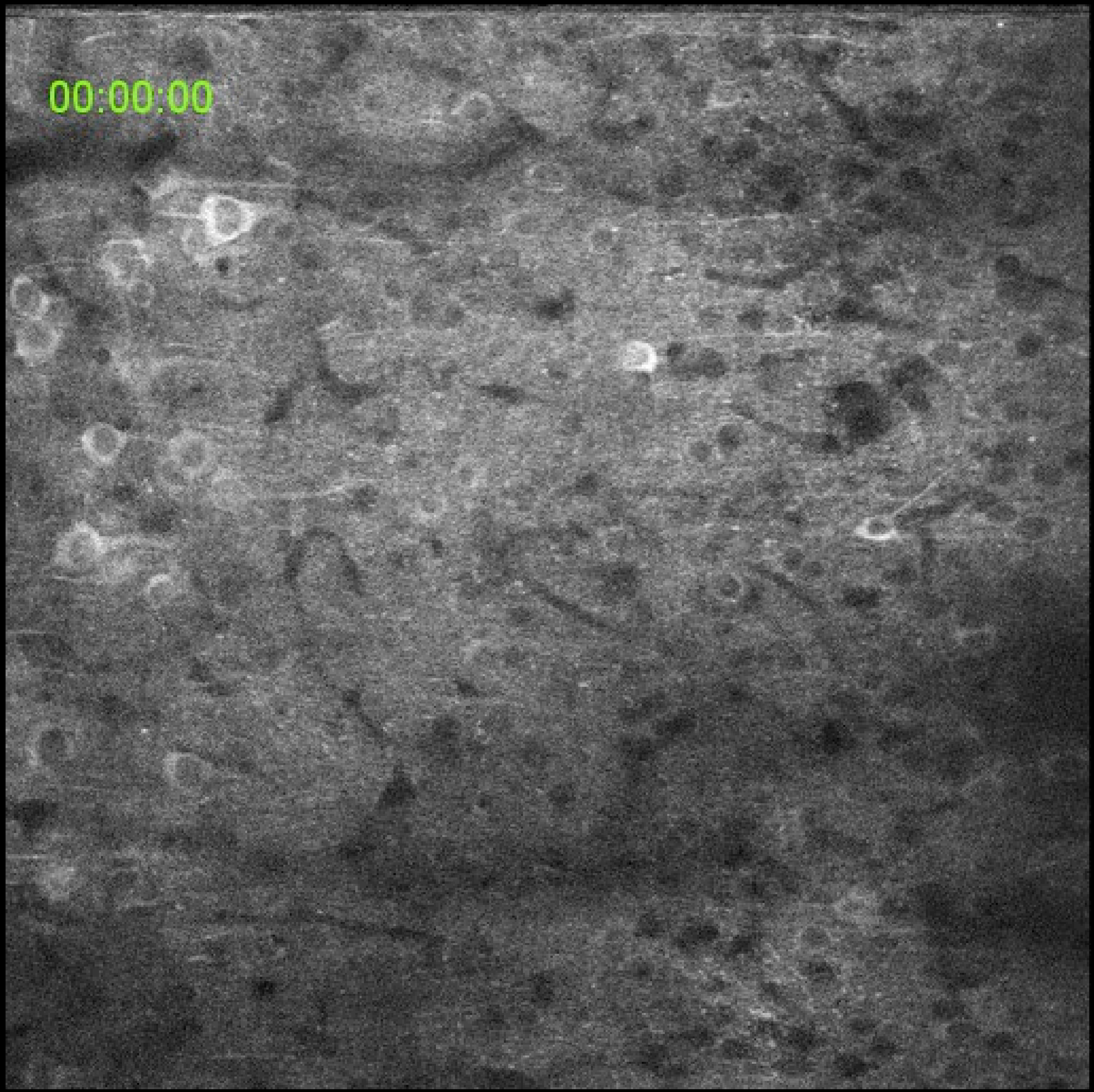


Right PPC

Left PPC



Left RSC



Open Source Miniaturized Microscope

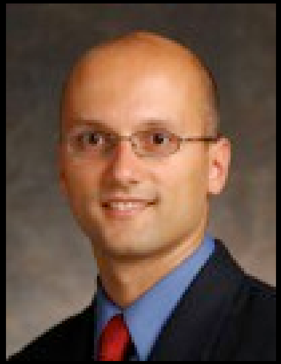
miniscope.org

Daniel Aharoni

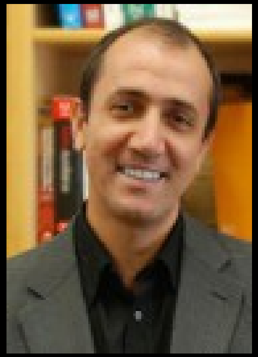
Tristan Shuman

Denise Cai

Baljit Khakh



Dejan Markovic



Alcino Silva

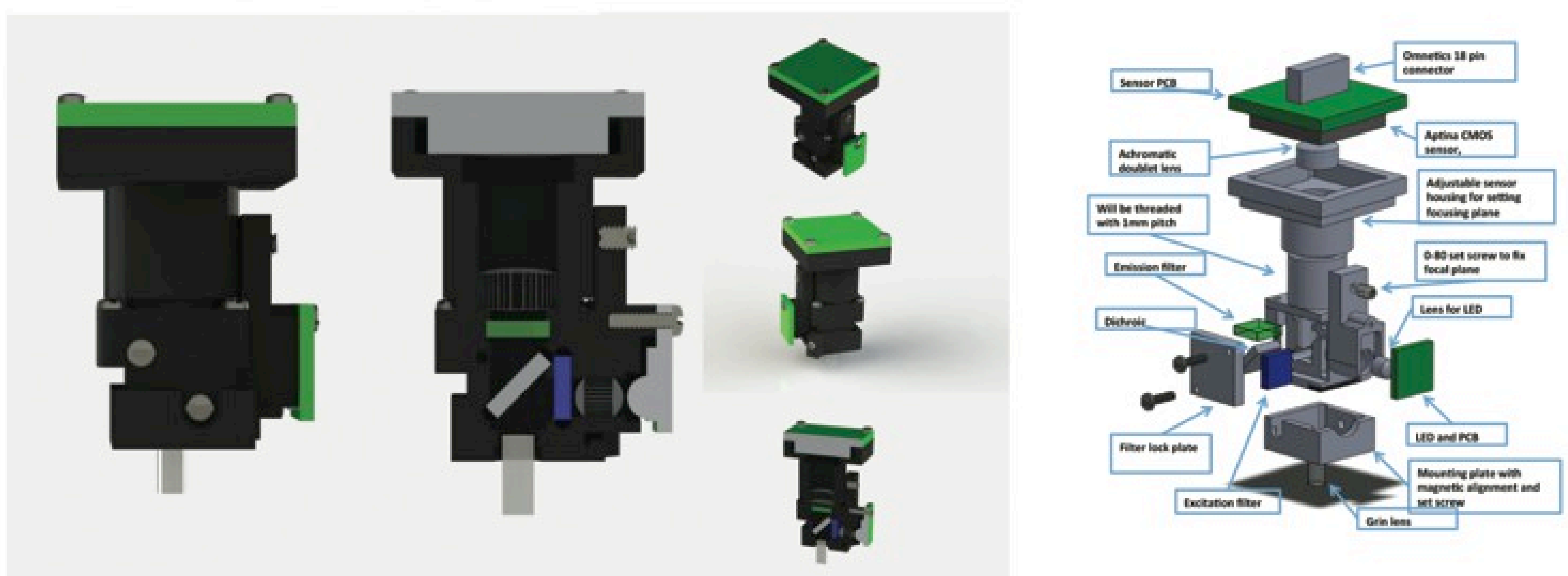
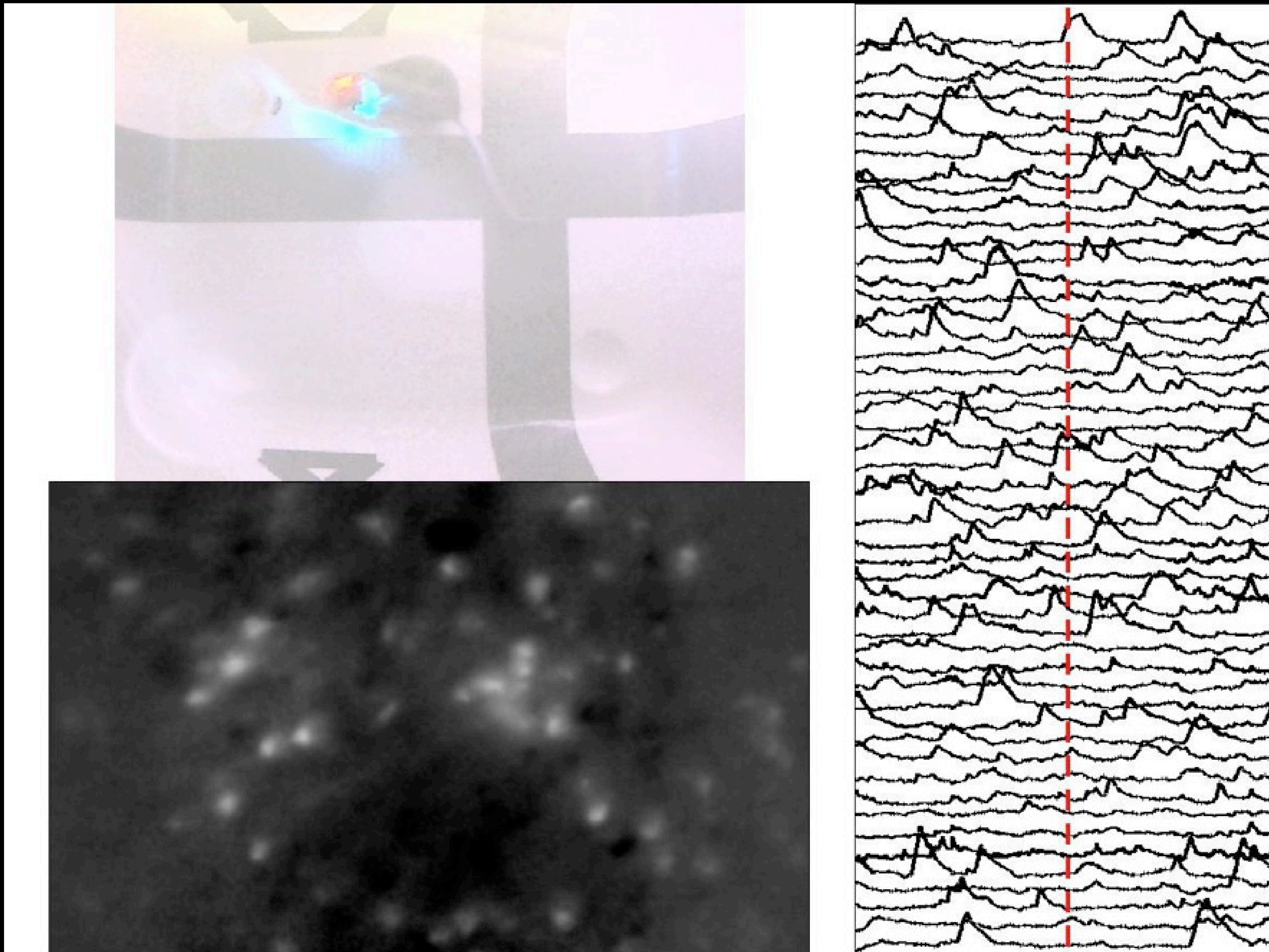
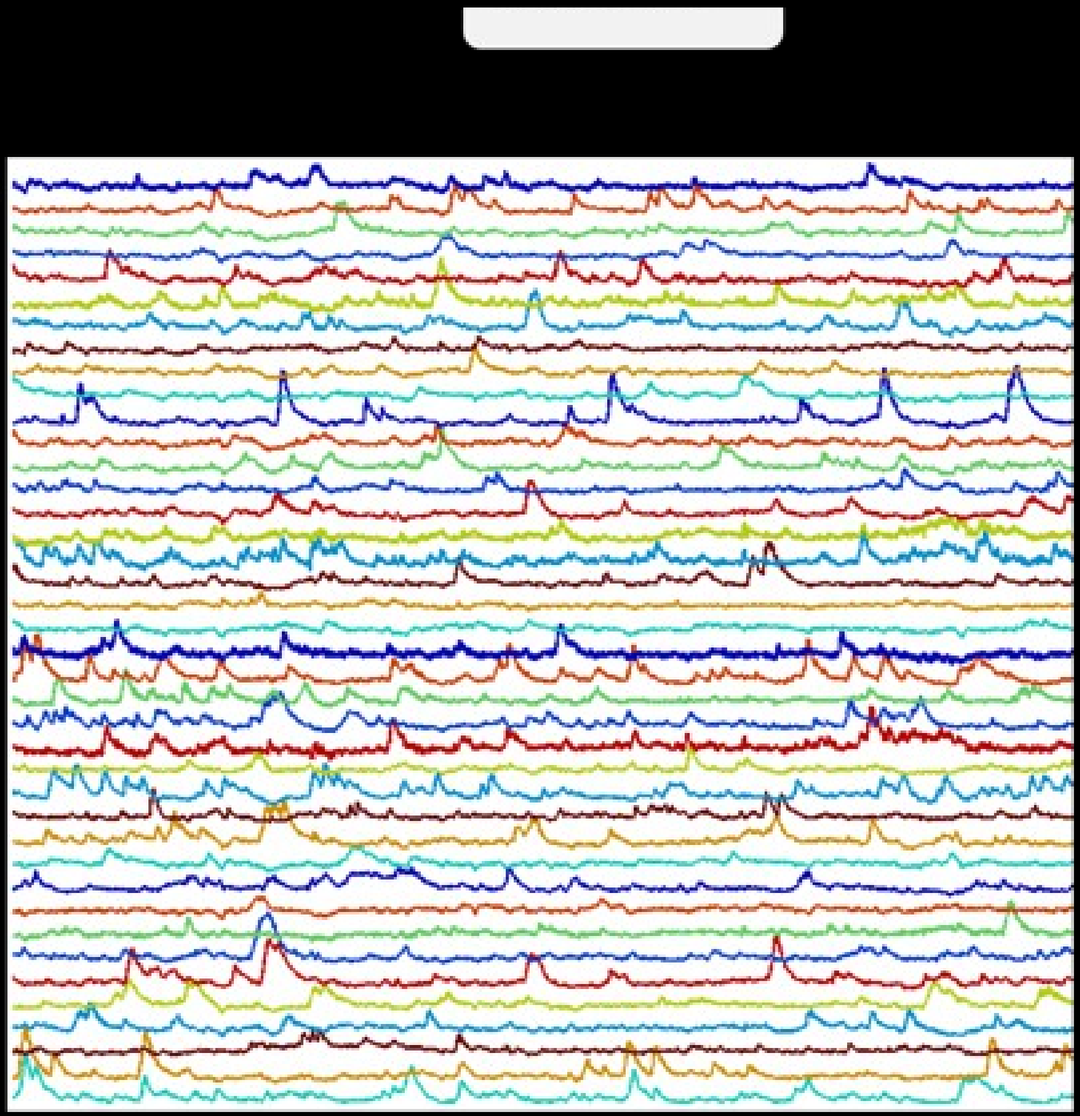


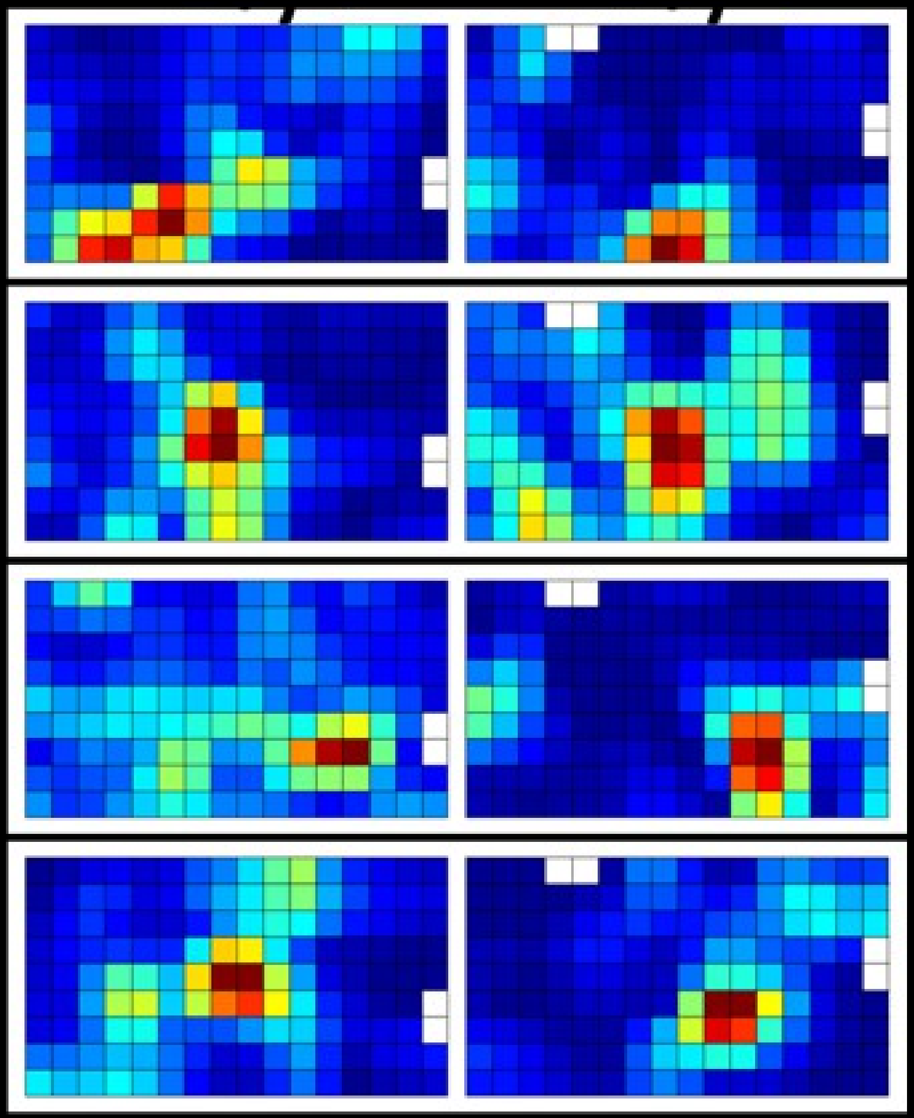
Figure 1: Drawings of our custom-designed miniaturzed microscopes for calcium imaging in freely moving mice. The illumination is provided by an LED, focused through a GRIN lens, and imaged onto a miniaturized Aptiva sensor. Based on miniaturized microscopes developed by the Schnizter Lab.

CA1 hippocampal neurons during running



CA1 recordings by miniscope





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NINDS
NIA
Whitehall Foundation
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