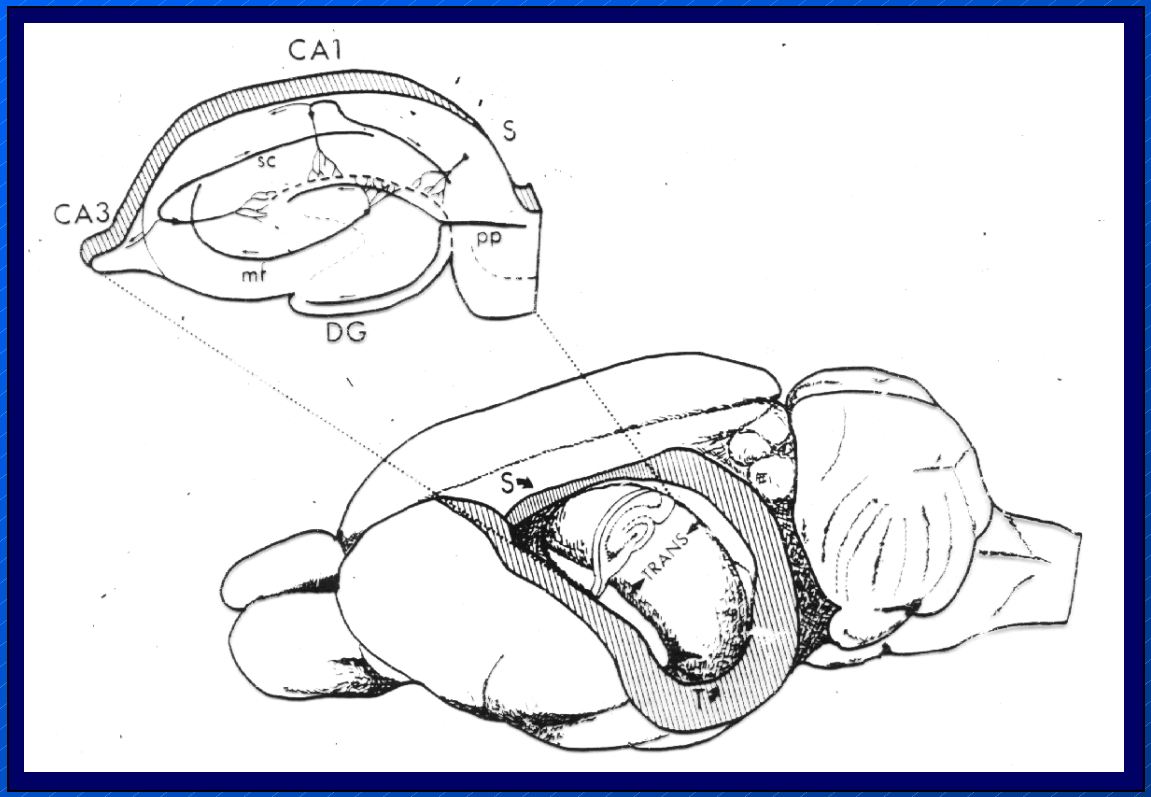
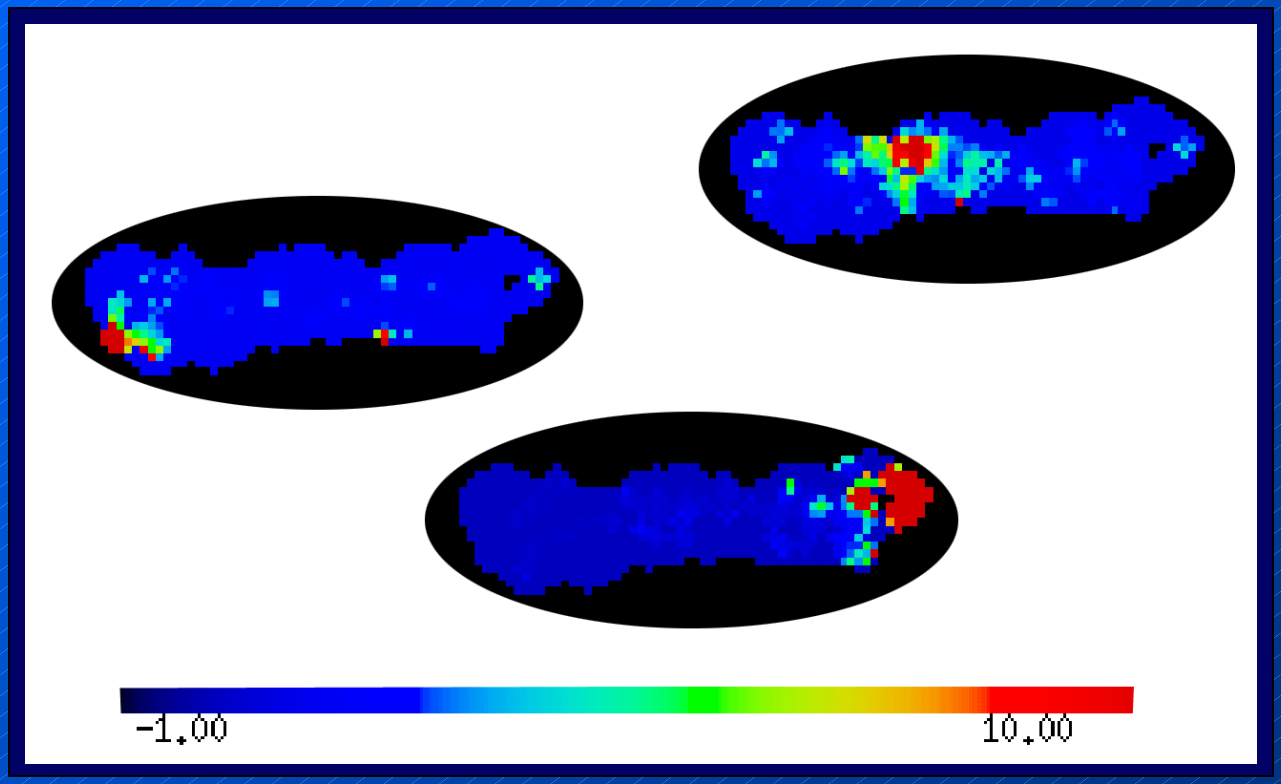
Brain and Cognitive Sciences 9.96
Experimental Methods of Tetrode Array Neurophysiology
IAP 2001

An Investigation into the Mechanisms of Memory
through Hippocampal Microstimulation

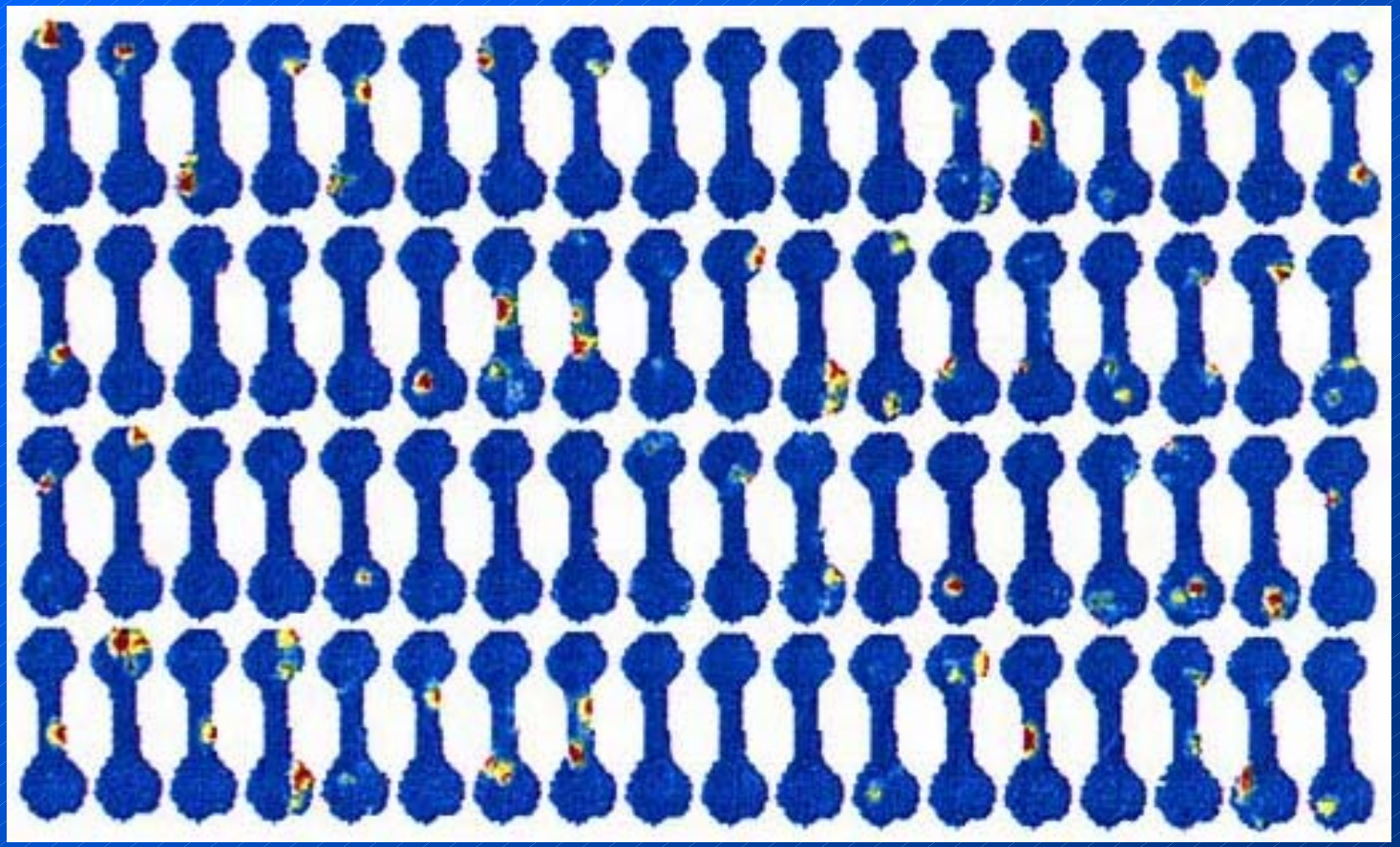
In rodents, the hippocampus is particularly involved in spatial navigation and learning.



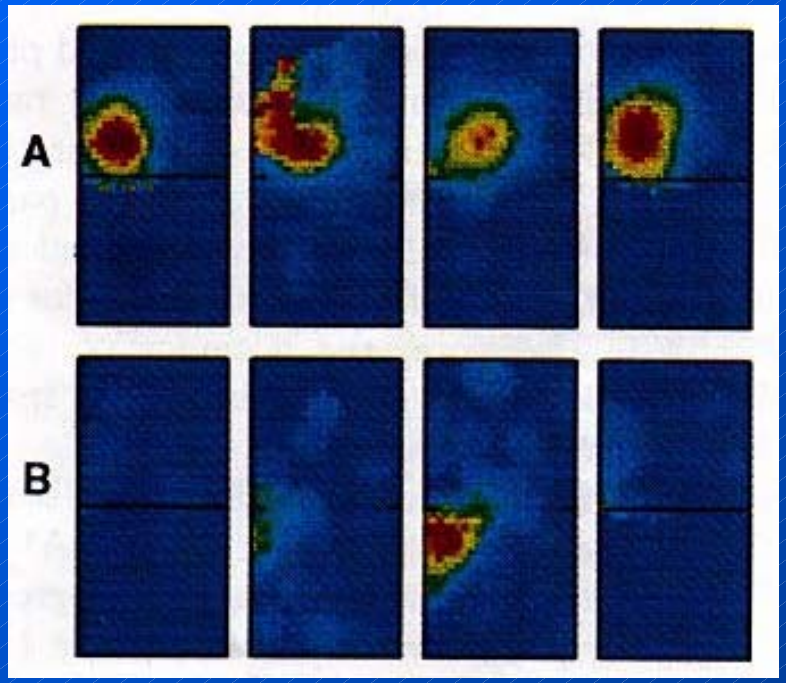
The primary output cells of the hippocampus – the pyramidal neurons – are called "place cells". They are active only in a specific region of physical space within the environment.



We can see from these ensemble recordings that the few 100,000's of place cells in the hippocampus form a "map" of the environment.



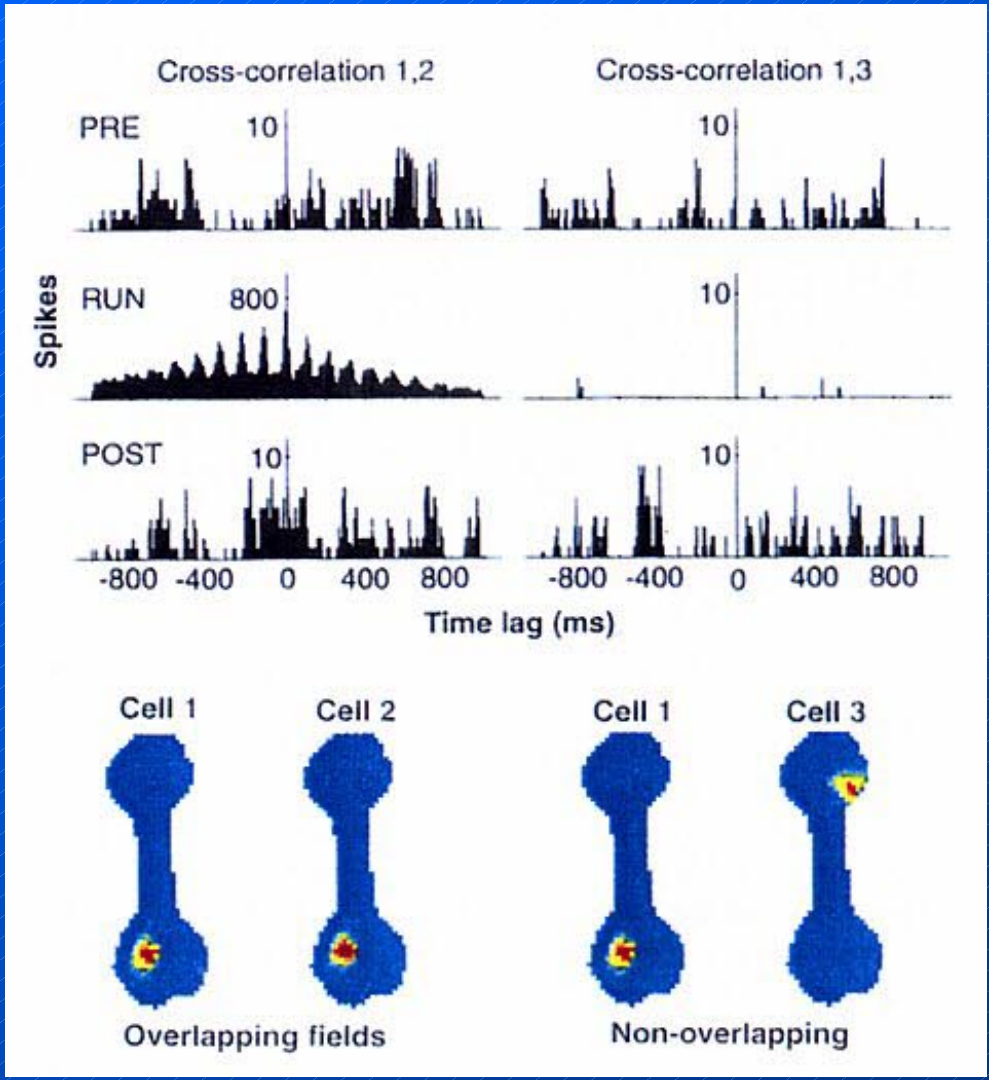
The “place fields” that make up this map develop over 5-15min in a new environment, and can last for many hours.



Time: **5min | 10min | 15min | 20min |**

(animal begins exploring lower half of environment at t=5min, leaves at t=15min)

Cells that are co-active during behavior are more likely to be co-active in the subsequent sleep period……plasticity!



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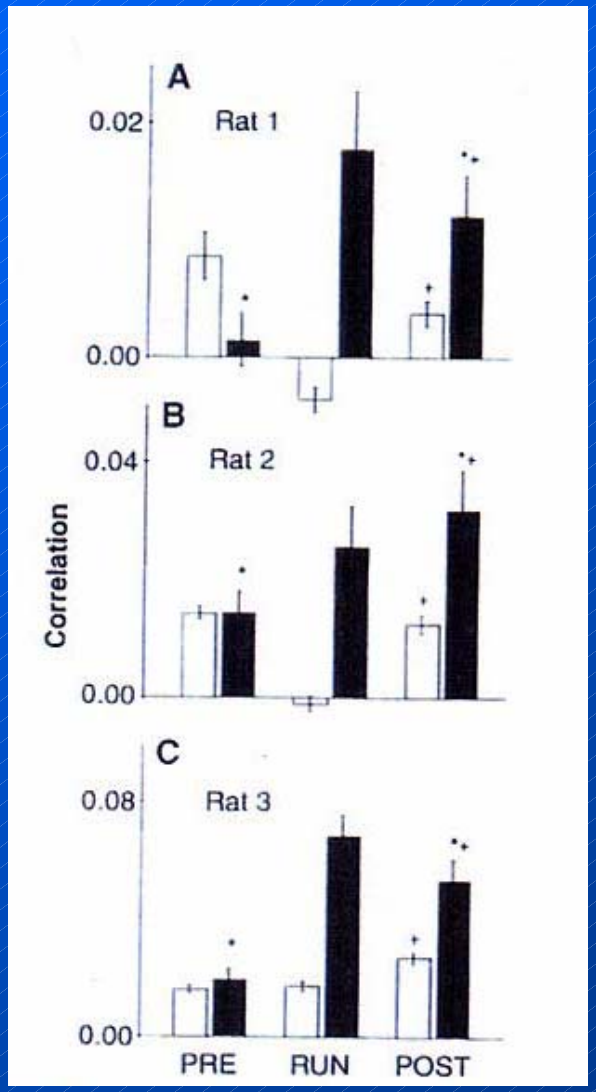
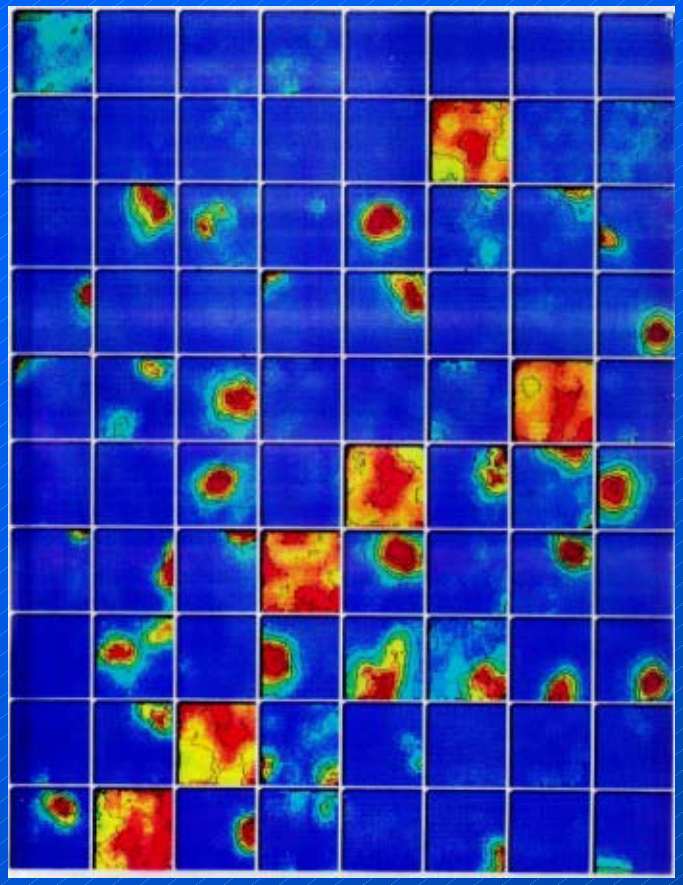
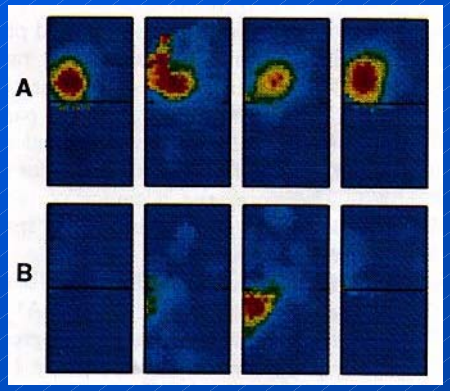


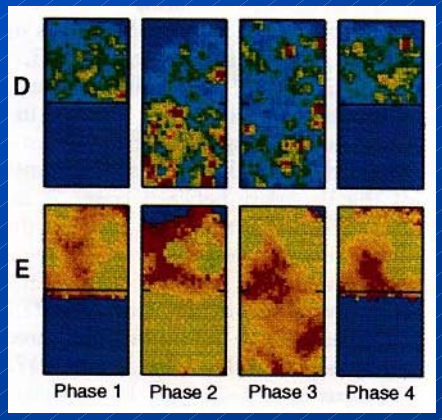
Overlapping fields

Non-overlapping fields

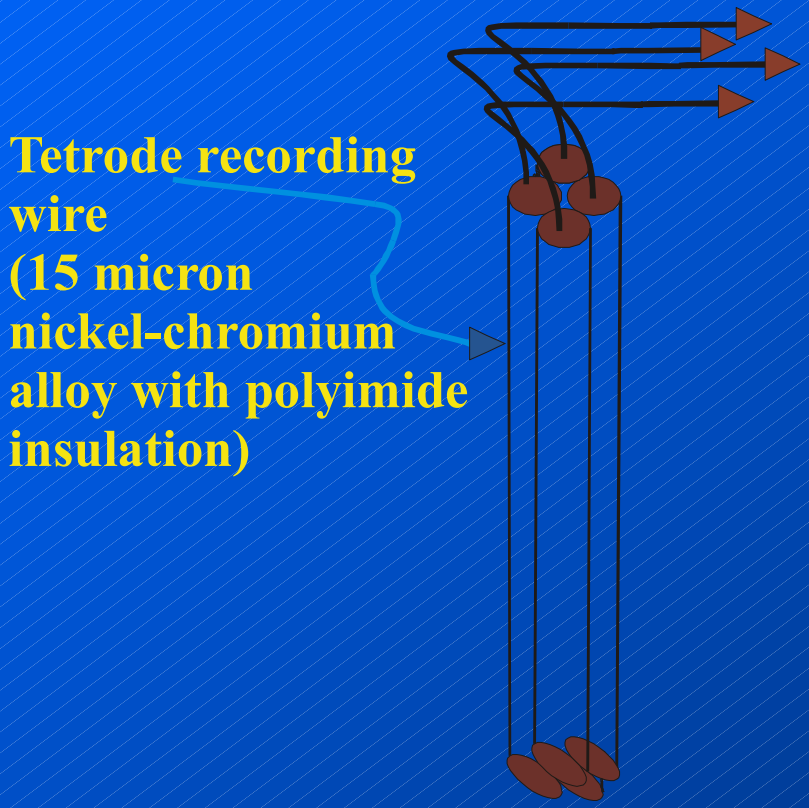
The hippocampal population consists primarily of pyramidal cells and local inhibitory interneurons.







In the Wilson Lab, we use tetrodes to record the activity of multiple hippocampal cells simultaneously.



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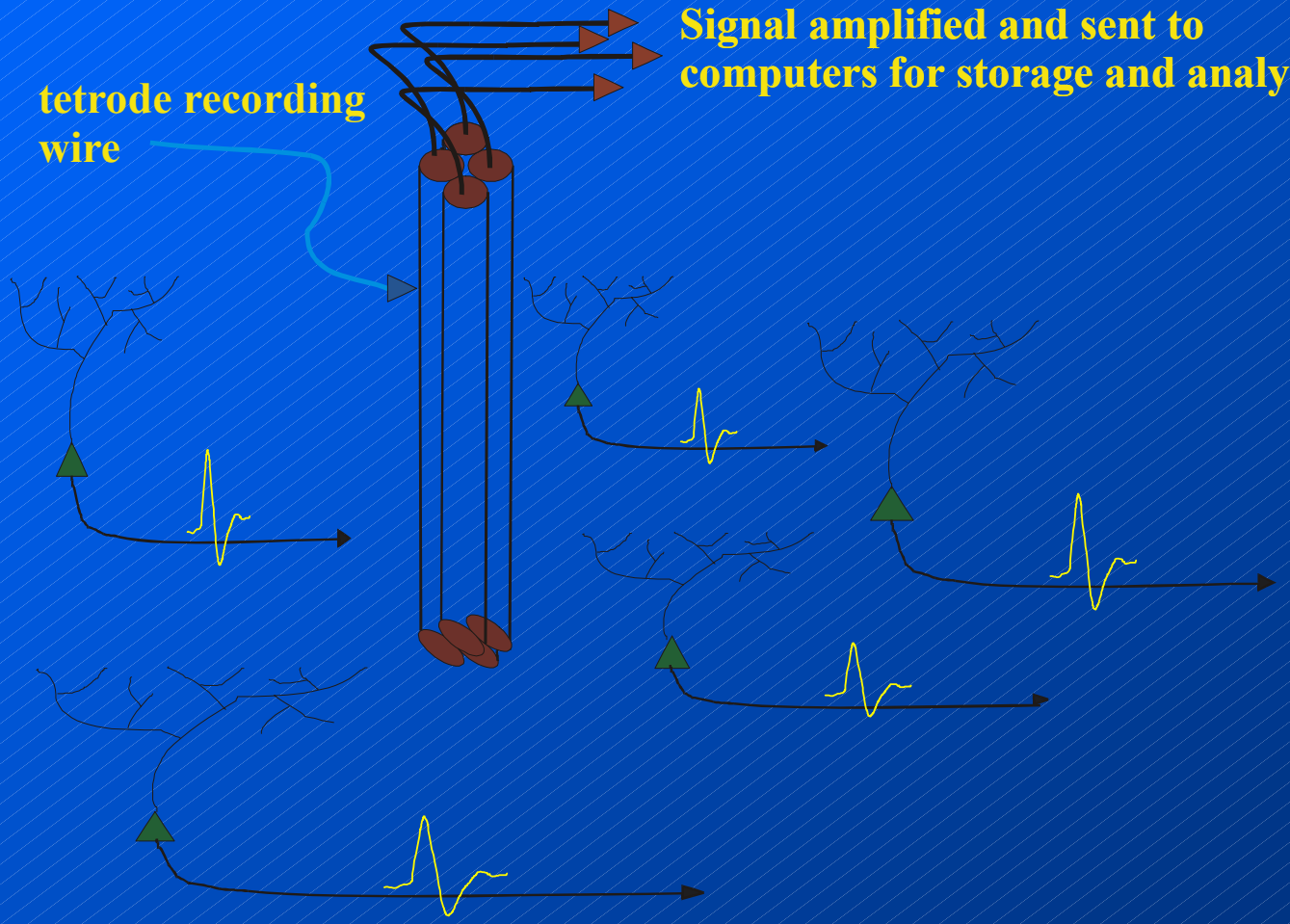
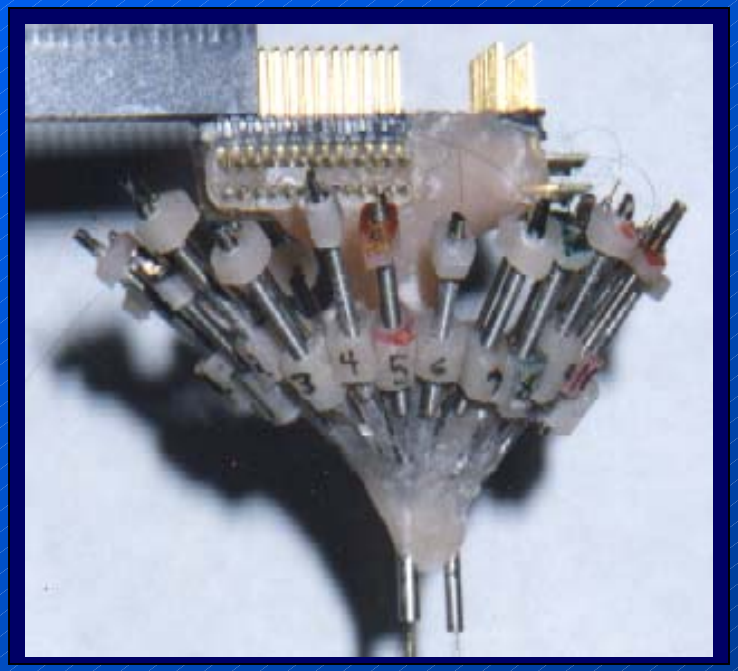
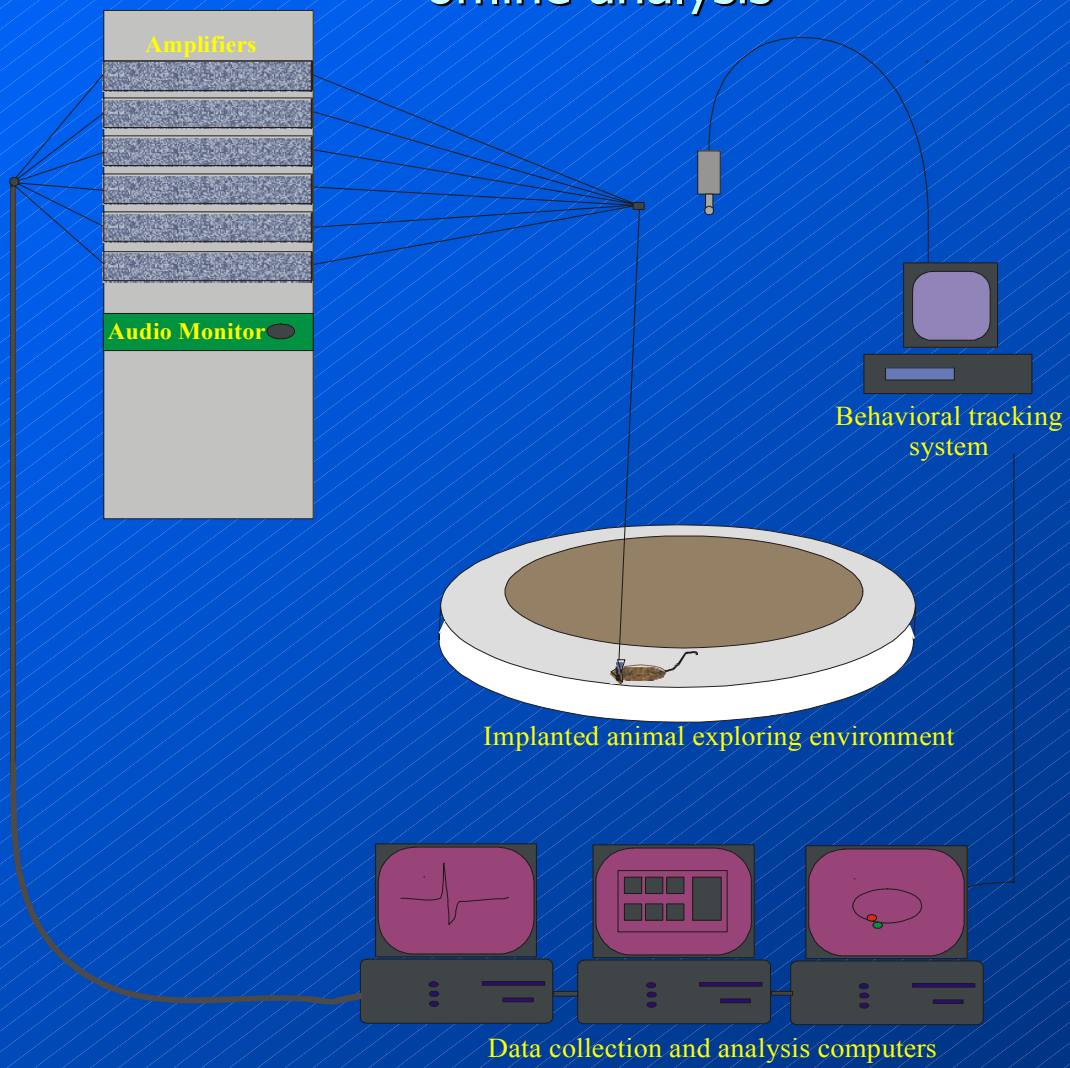


Multiple tetrode recording bundles can be combined into an adjustable array, allowing for up to 150 cells to be monitored simultaneously.



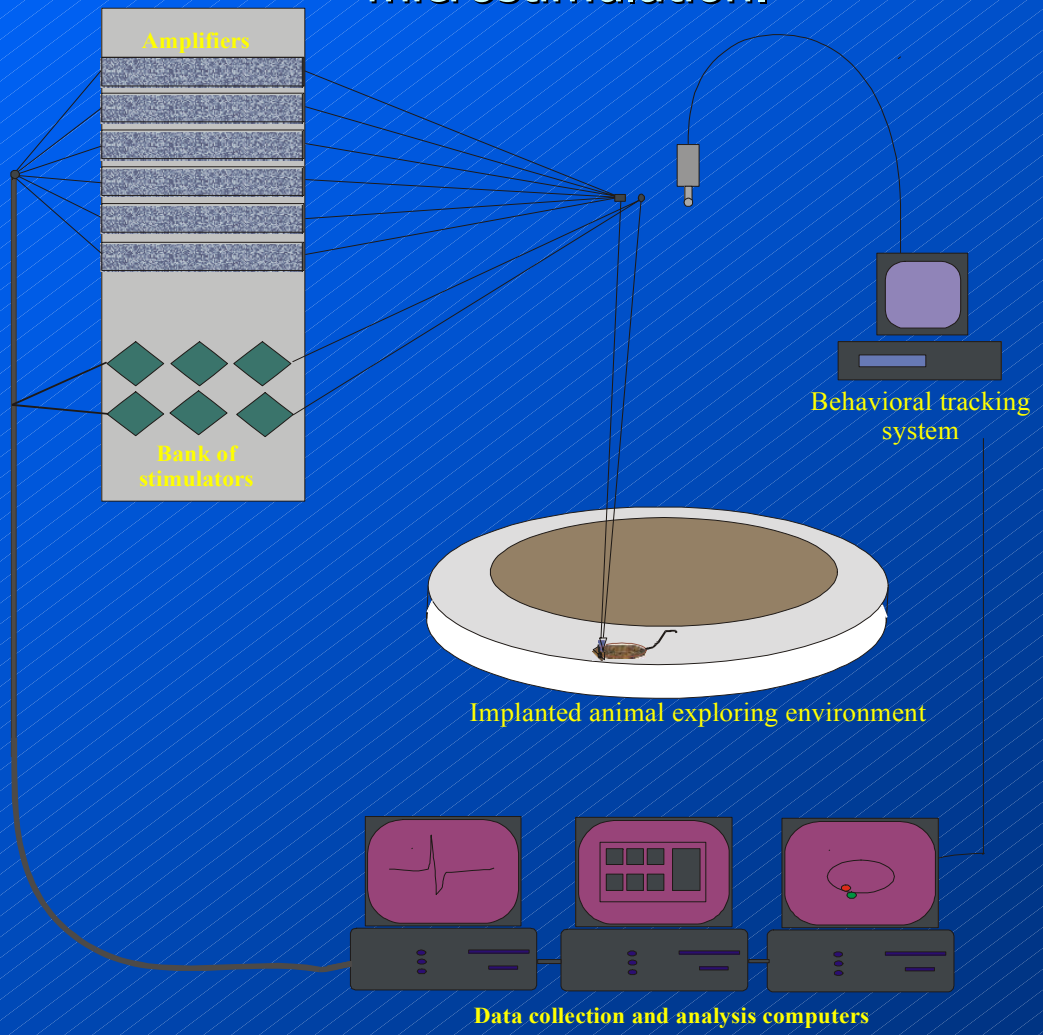
The microdrive arrays are permanently implanted into animals, who’s neural signals can then be monitored during sleep and active behaviors.

The neural data are amplified and recorded along with position and other information, then transferred to networked computers for offline analysis

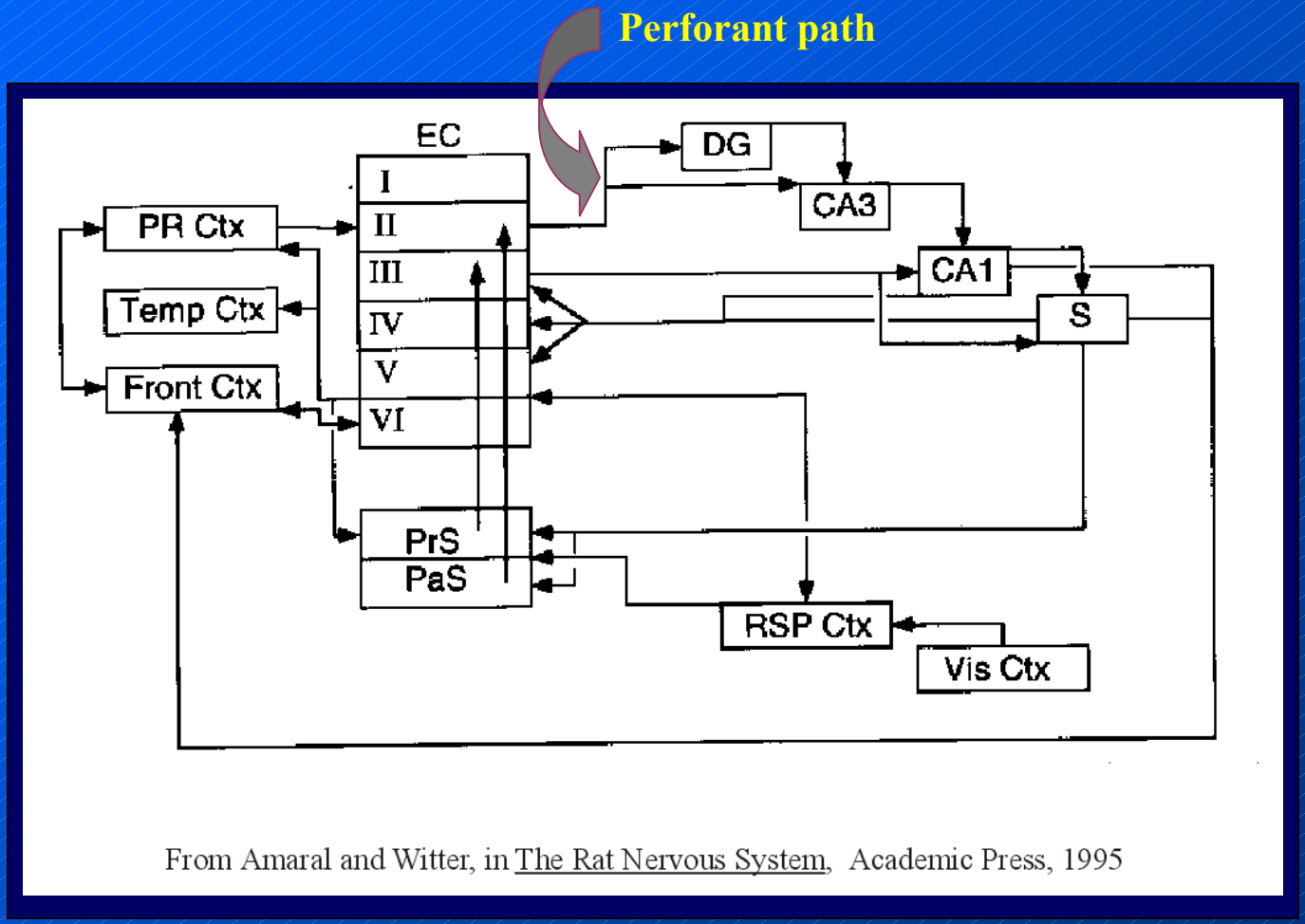


So….it takes a lot of computers……..

To further investigate the roles and mechanisms of hippocampal place cell plasticity in spatial navigation and learning, we are pairing this ensemble recording technique with targeted, patterned microstimulation.



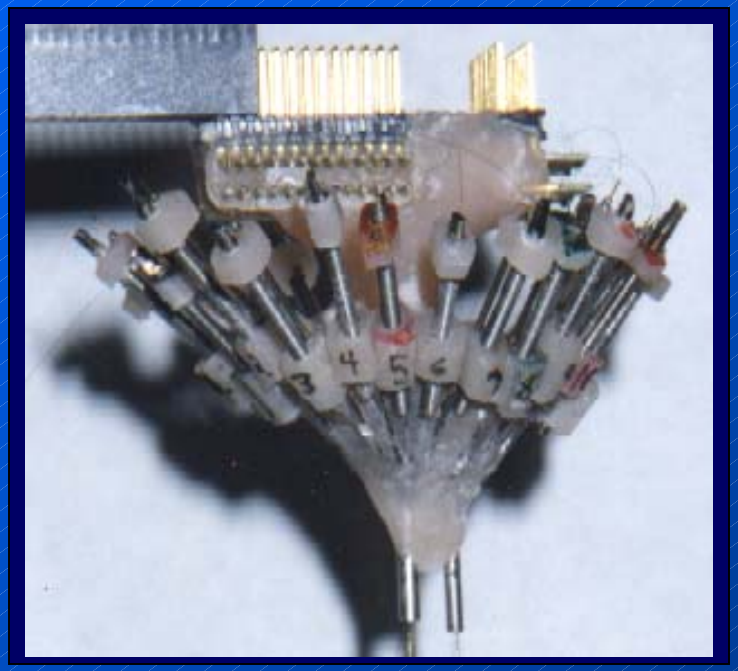
Patterns of activation will be induced in the hippocampus by computer controlled microstimulating pulses injected into the perforant path, its primary input pathway.



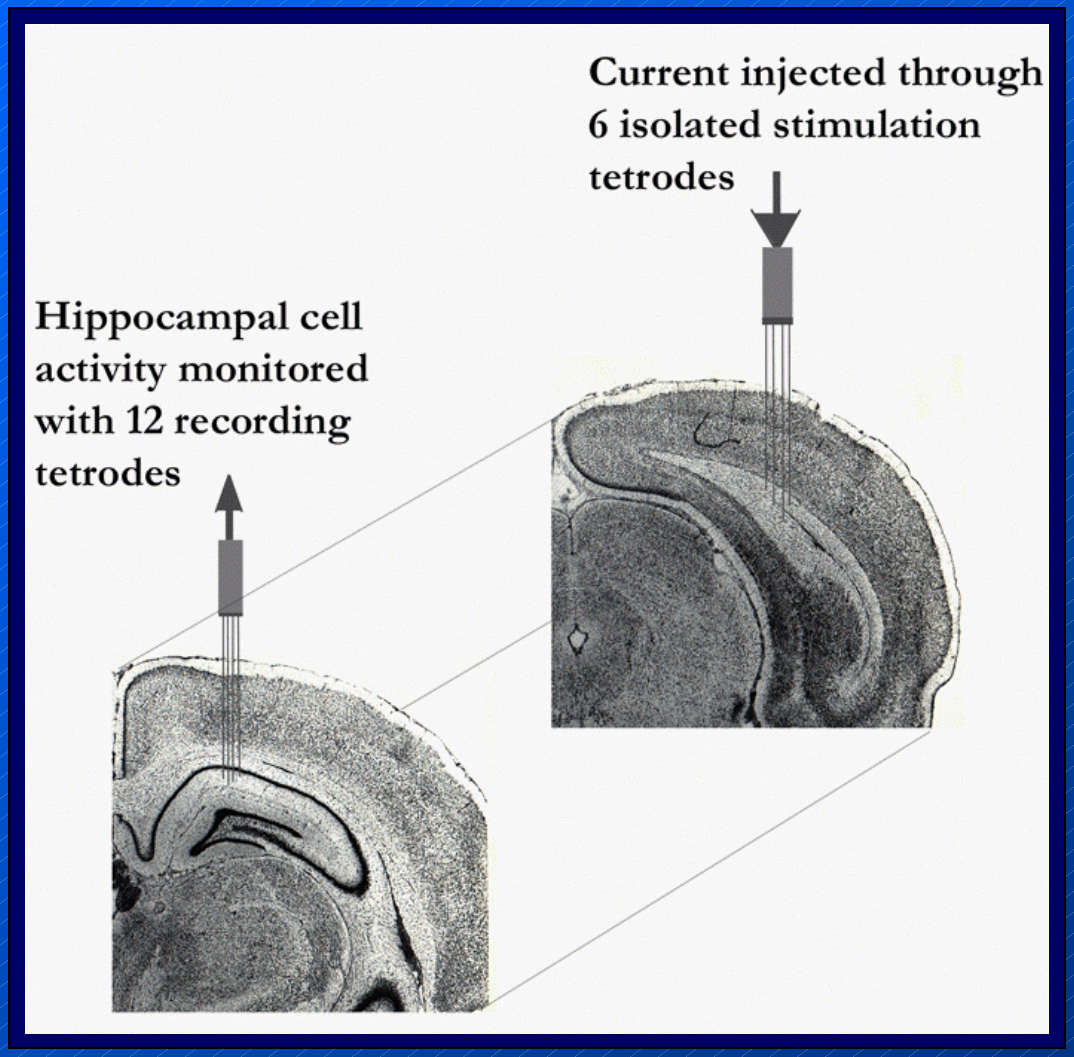
From Amaral and Witter, in The Rat Nervous System, Academic Press, 1995

Functional connectivity of the hippocampal formation

A new microdrive array was designed to enable simultaneous stimulation and recording .



Anatomy of hippocampal microstimulation



Implanted animal with recording preamps and stimulation cable

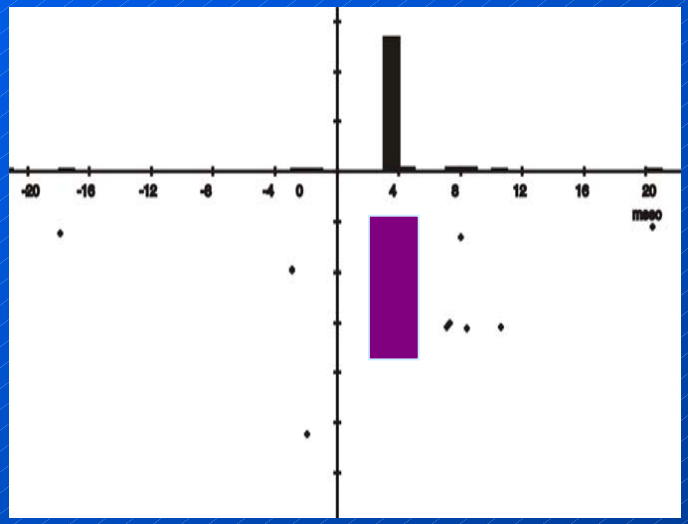
Differential activation of hippocampal neurons has been achieved.

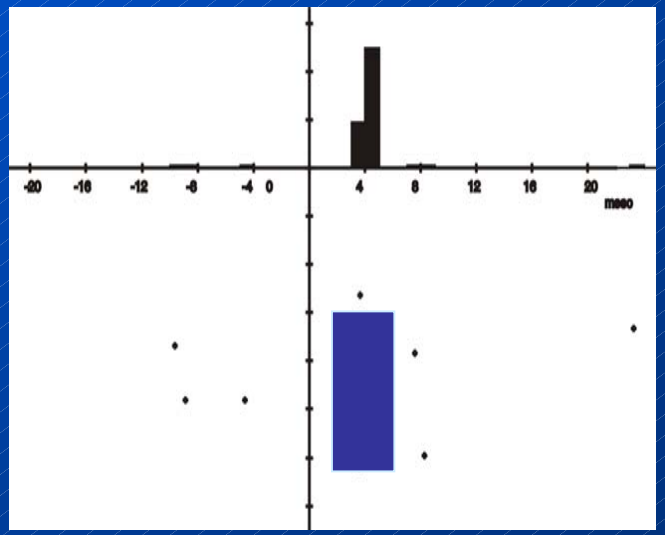
Evoked, differential unit responses to different spatial and temporal stimulation patterns have been observed in Dentate, CA1 and CA3 neurons.

Cell 1 **Cell 2**

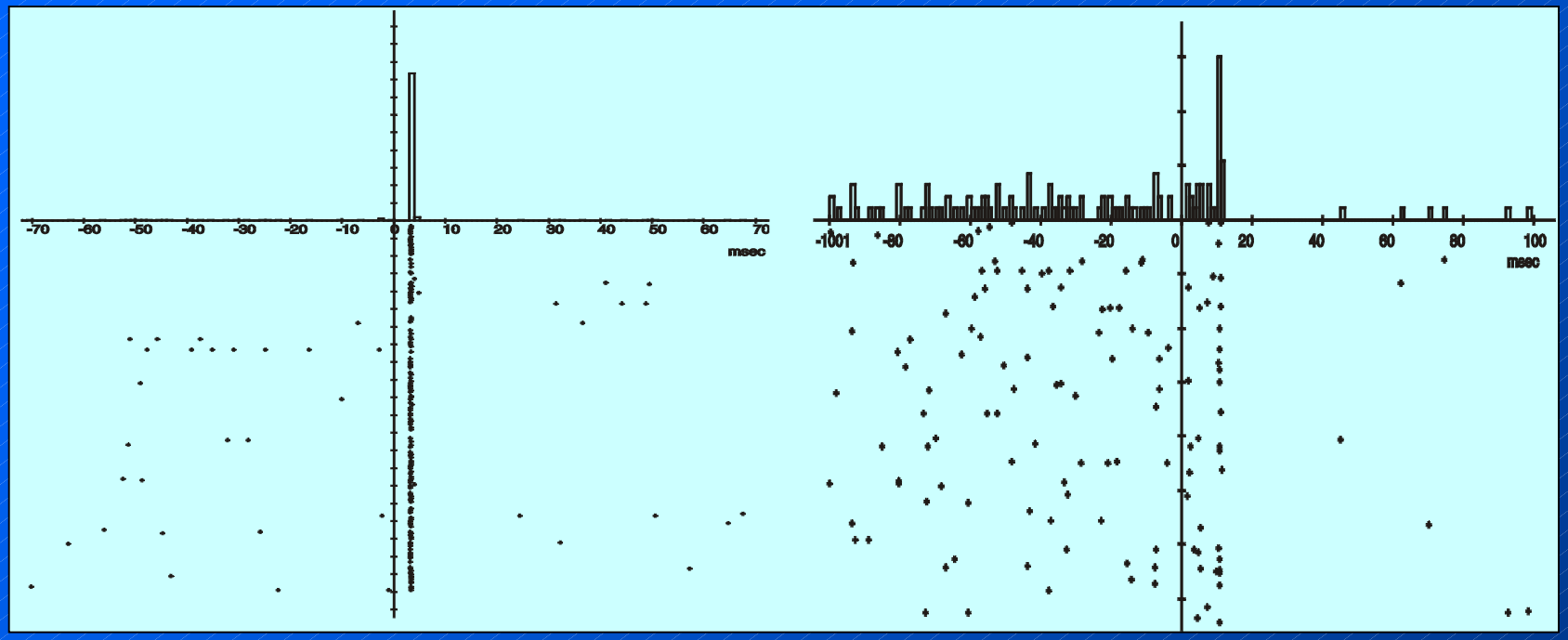
Stimulation on tetrode 2

Stimulation on tetrode 4

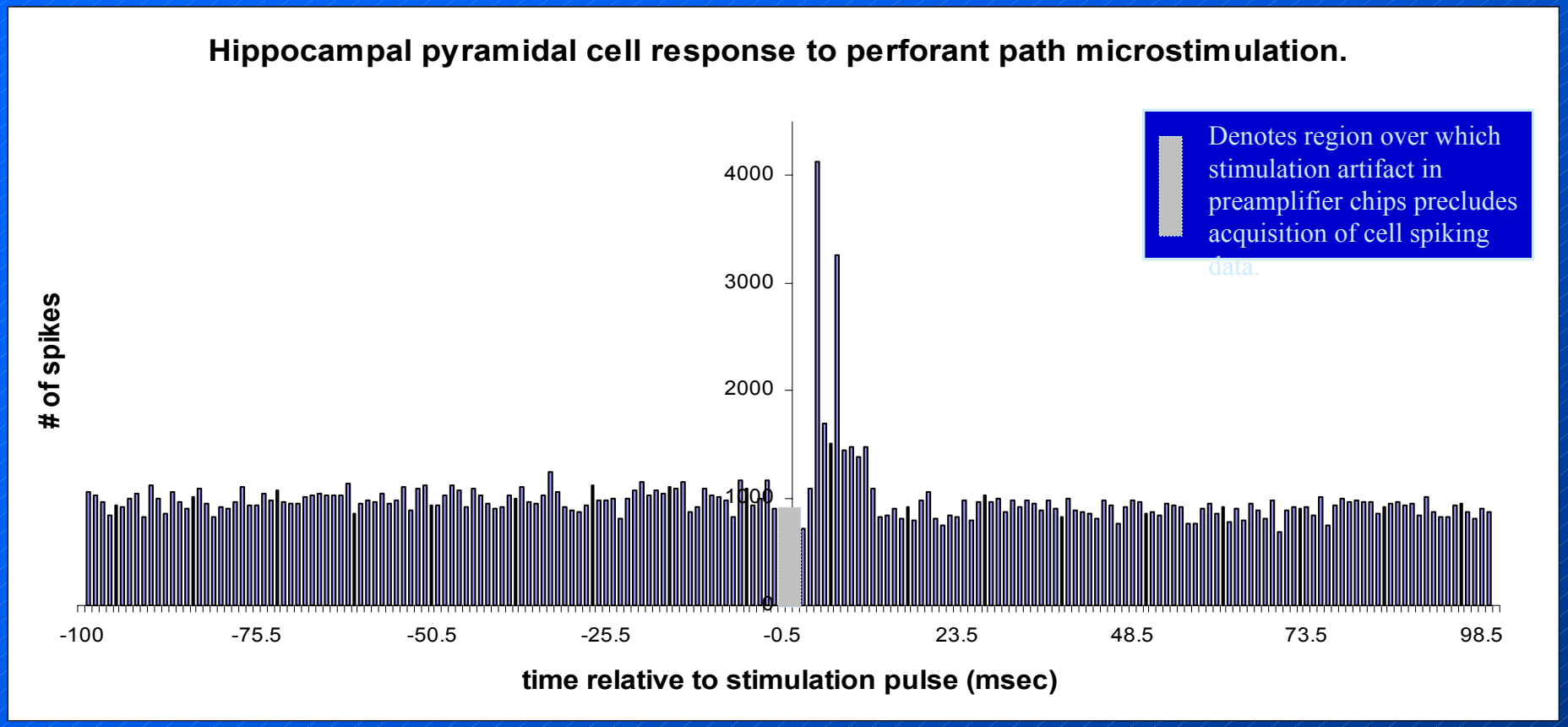




Pyramidal (Complex-Spiking) Cells -

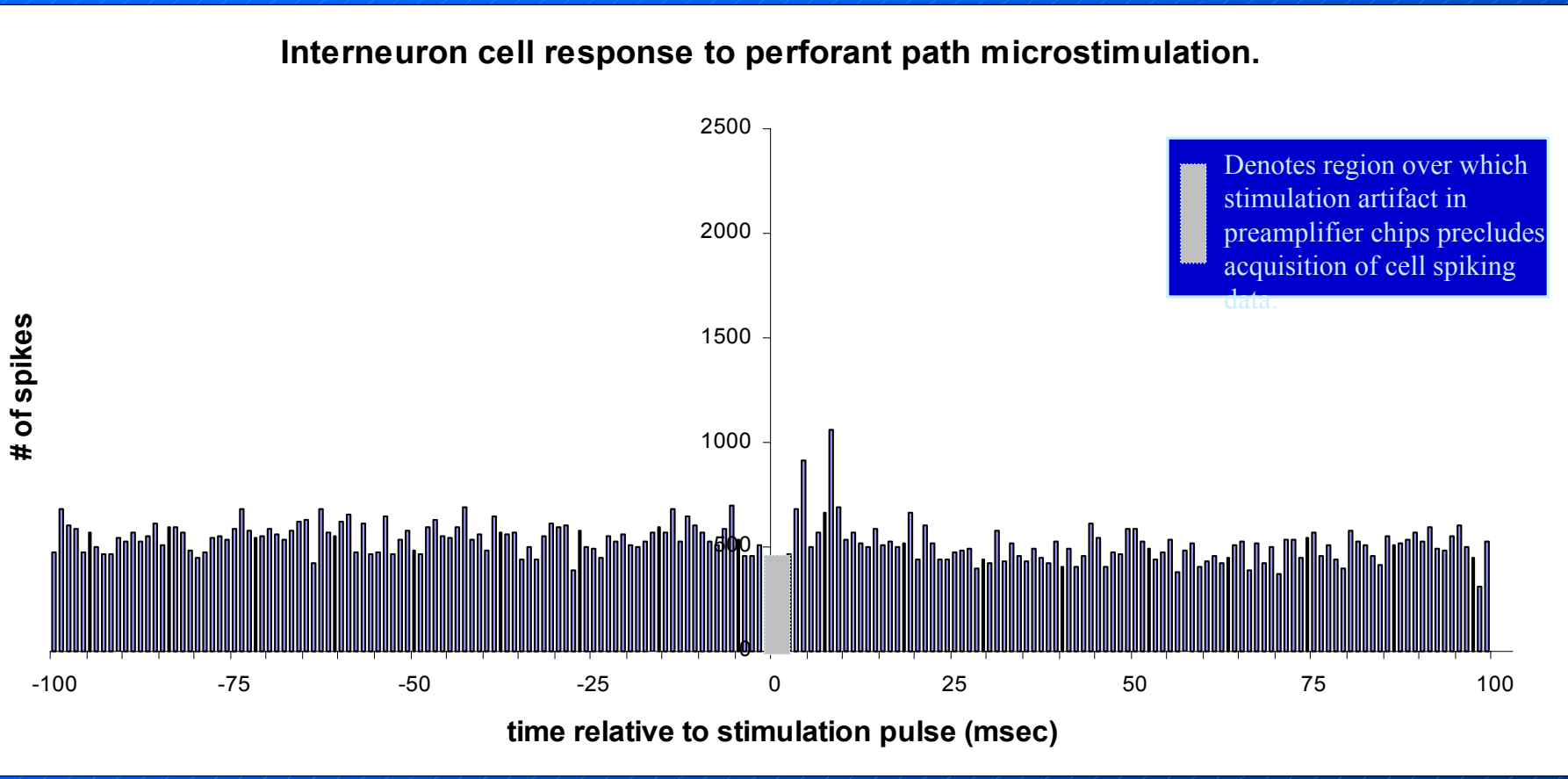


124 complex-spiking cells.
219 cell stimulation epochs.
Two experimental animals.
68 of 219 (31%) showed a reliable stimulation evoked response.
19 of 219 (9%) had significantly suppressed.
132 of 219 (61%) showed no appreciable change in firing.



Stimulation triggered histogram: 219 pyramidal cell epochs

Highly significant evoked responses at 3.5 and 7 msec, (with a 3rd peak at 10.5msec buried in the variance) implying monosynaptic and disynaptic pathways of activation, respectively.



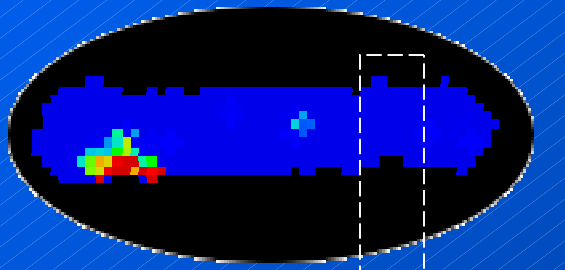
Stimulation triggered histogram: 105 interneuron cell epochs

Marginally significant peaks at 4.5 and 6.5 msec.

FUTURE DIRECTIONS –

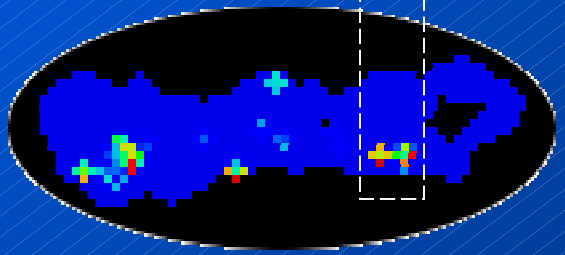
The ability to specifically activate subpopulation of hippocampal neurons, as described here, has been employed in a number of experiments investigating hippocampal function and plasticity to be described in forthcoming publications.

Place field properties can be affected by artificial activation

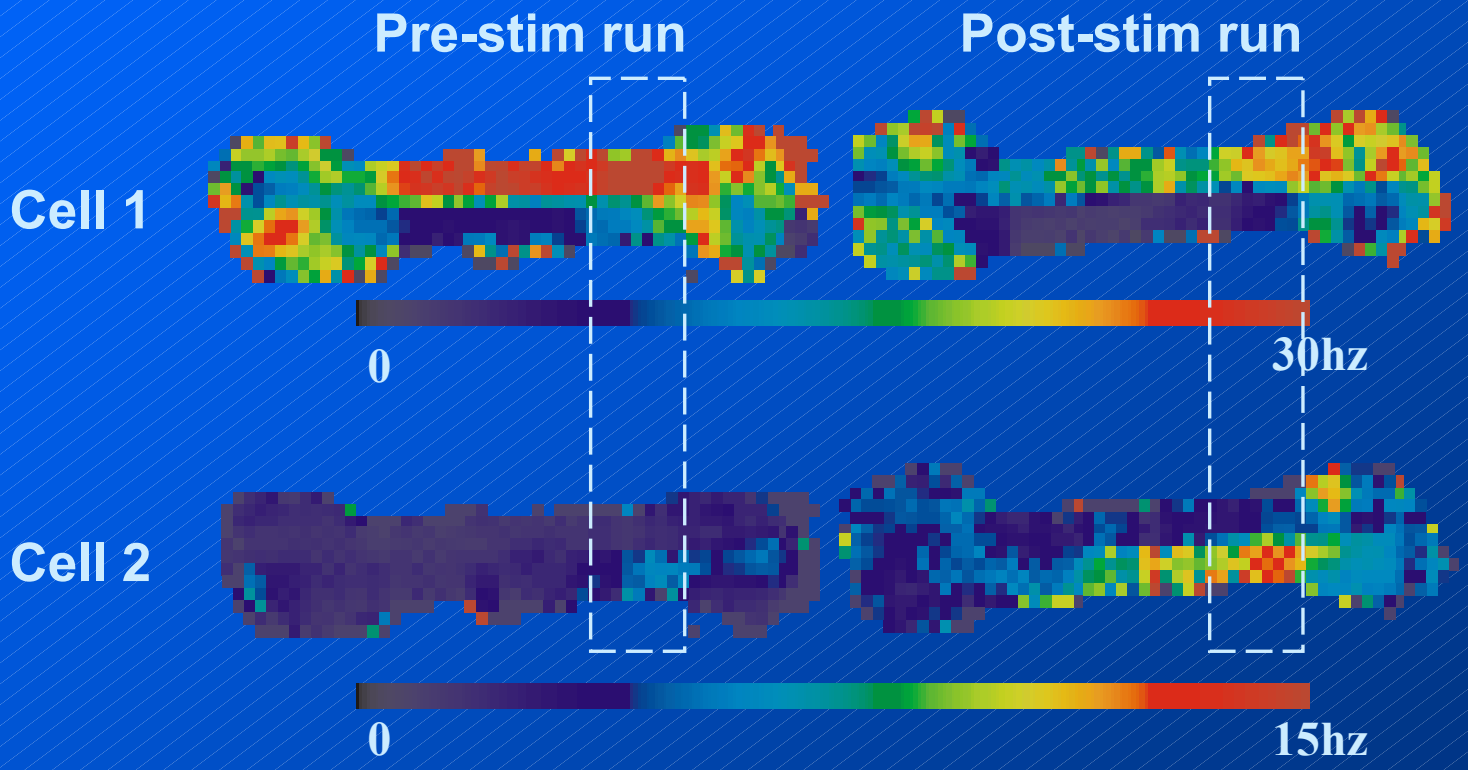


Place field before stimulation

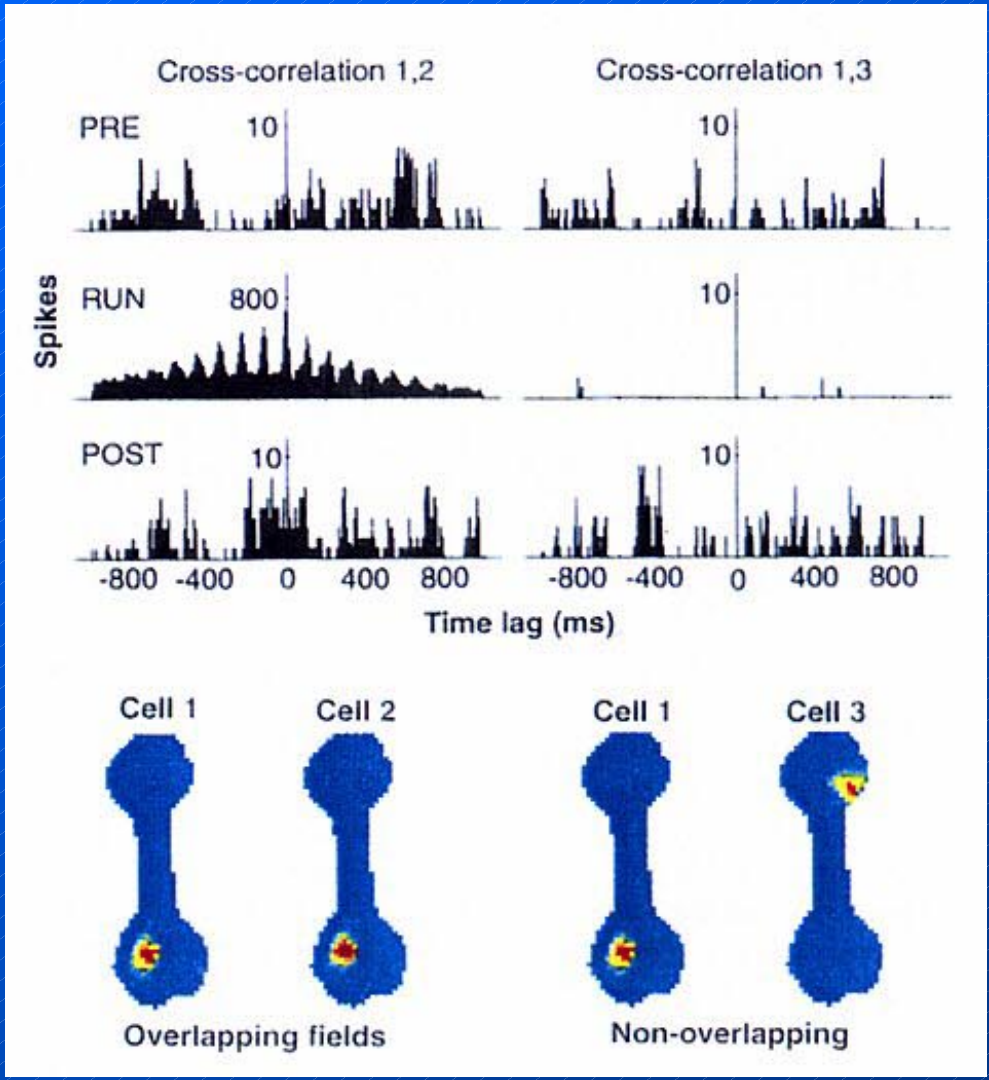
Stimulation pulse applied when animal enters dashed area (unbeknownst to him, of course!)

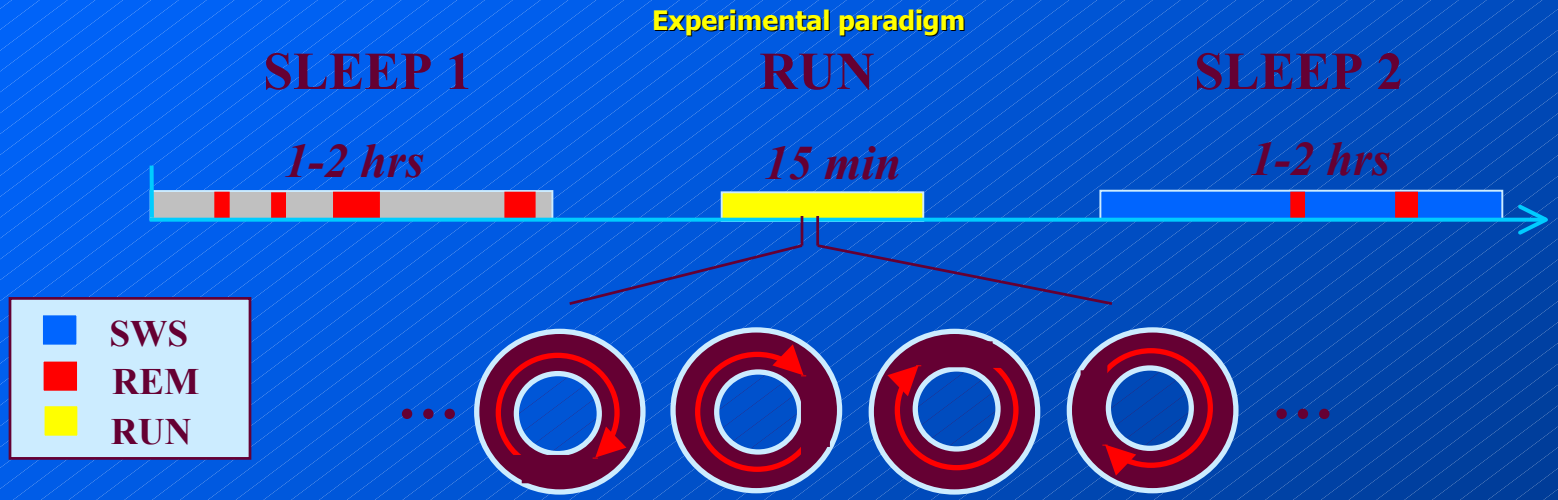


Place field during stimulation


Pre-stim run
Post-stim run
Cell 1
0
30hz
Cell 2
0
15hz

Recapitulation of place-specific correlation increase result using stimulation specific coactivation: Assembly of a network.

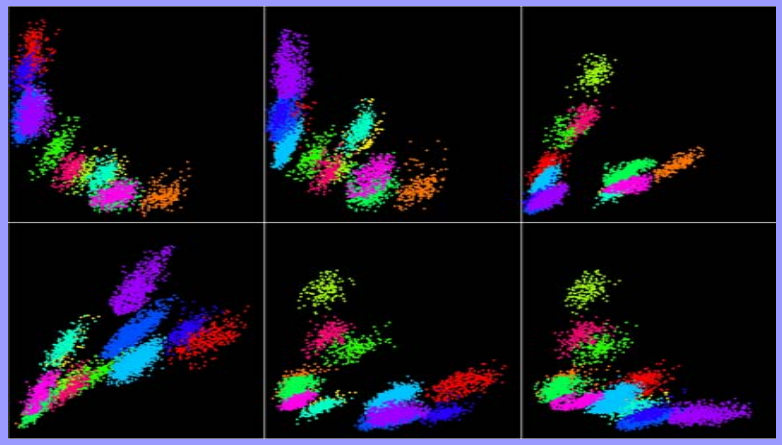




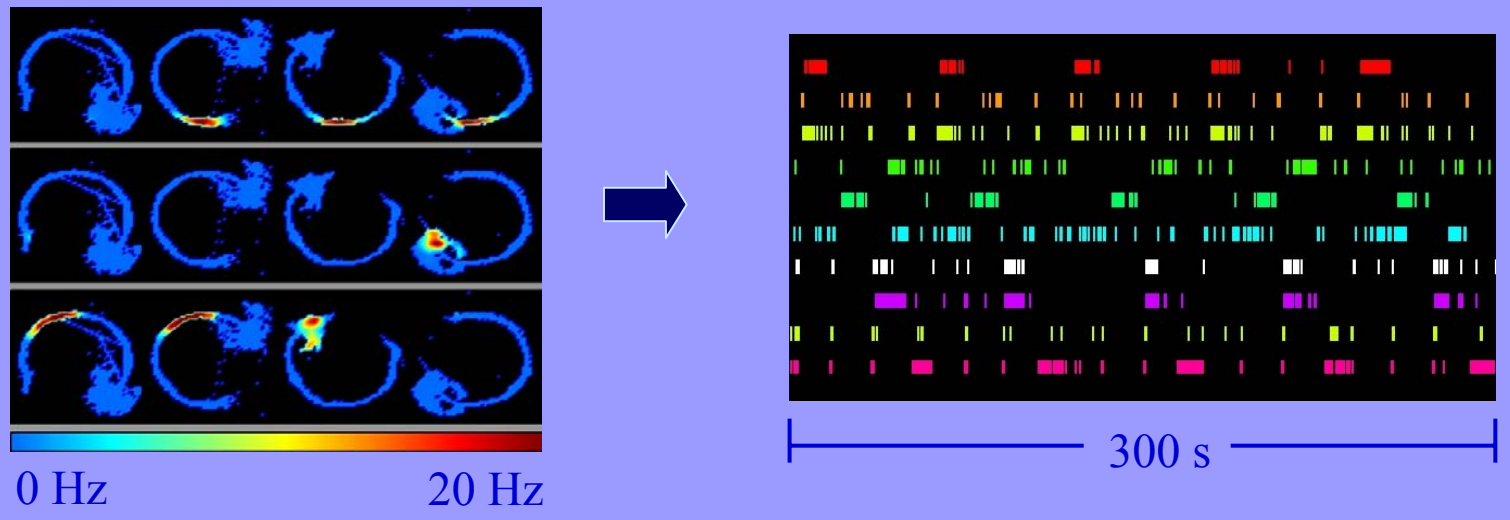
- repetitive spatial locomotion task
- animal trained on familiar task prior to recording
- single recording day: SLEEP-RUN-SLEEP
- individual recording sessions conducted on consecutive days

Electrophysiology

- Male Long-Evans rats (4)
- Target: pyramidal cell layer of CA1 region of hippocampus
- Simultaneous spike-triggered recording from 12 independently adjustable tetrode microdrives
- Continuous local field potential from subset of recording channels
- Complex spiking cells and interneurons isolated offline

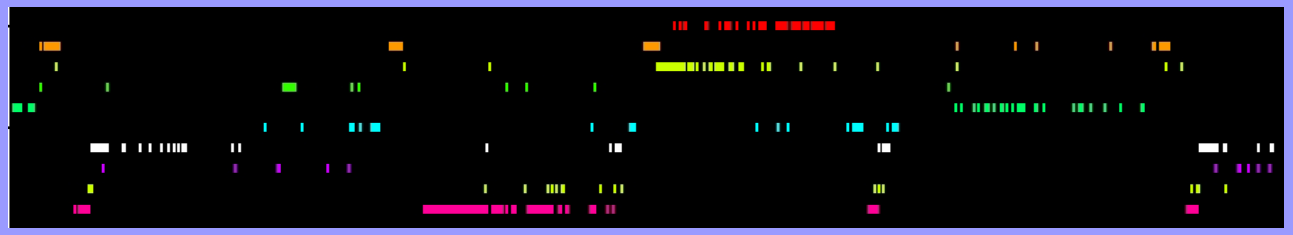


Structured spatial task leads to structured hippocampal activity



- robust spatial receptive fields (place fields)
- structured spatial behavior + spatial selectivity → structured neural activity
- ensemble patterns of activity uniquely characteristic of behavioral experience

REM reactivation of RUN ensemble activity



RUN

20 s

REM

20 s

Characteristics of REM-RUN correspondence:

- correspondence in both temporal and across-cell dimensions
- emerges in the activity of multiple cells
- across long temporal durations

Acknowledgements

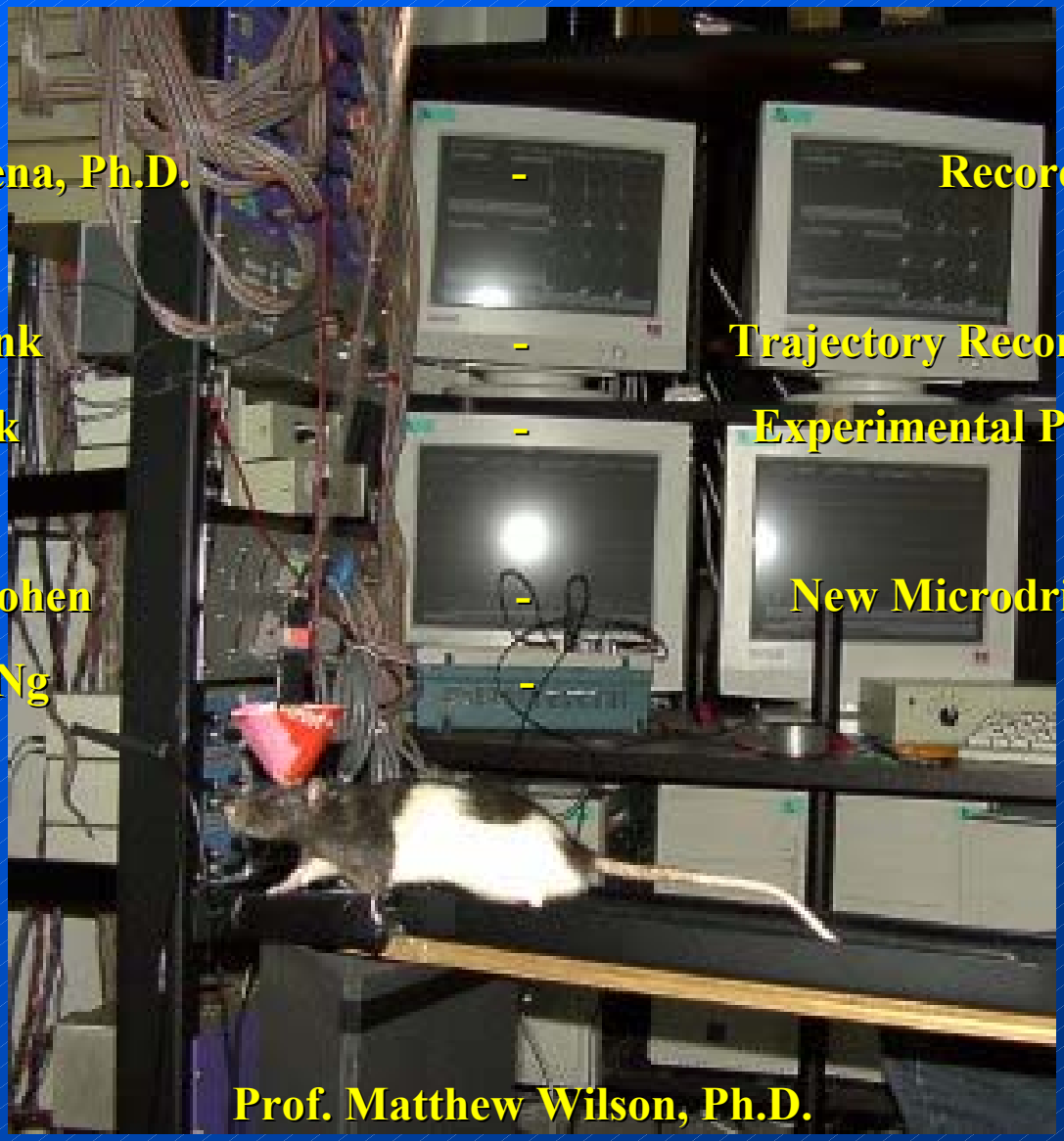
Clement Lena, Ph.D. - **Recording Setup**

Loren Frank - **Trajectory Reconstruction**

Mike Quirk - **Experimental Procedures**

Marlene Cohen - **New Microdrive Design**

Catherine Ng - **Histology**



Prof. Matthew Wilson, Ph.D.

Construction of the microdrive array assembly begins from the bottom up:

5 mil wire

6 mil wire

30 gauge tubing

23 gauge tubing

19 gauge tubing

Polyimide insulation

Tetrode wire

0-80 screw

Delrin top and bottom pieces