Memory: Computation, Genetics, Physiology, and Behavior

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A Playwright's Take on Memory

"What interests me a great deal is the mistiness of the past"

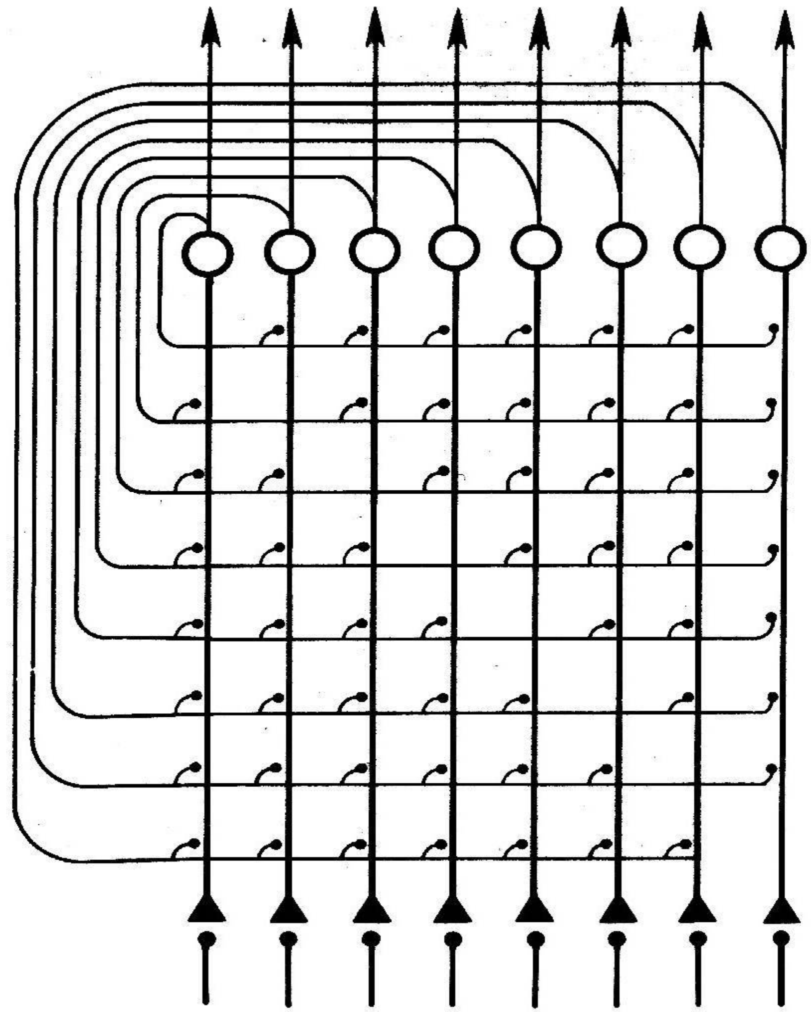
Harold Pinter, Conversation prior to the opening of *Old Times,* 1971

What is a Memory?

- The trace left by an experience?
- A representation of the experience brought "back to mind" later?
- In old-fashioned psychological theories, these things are one and the same
- Not so in today's neuroscientific theories of memory!

Your memories are in your connections

- An experience produces a pattern of activation over many neurons.
- The *memory trace* is adjustments to connections among the neurons.
- The *memory-as-recalled* is a pattern of activation reconstructed with the help of the affected connections.
- Connections are affected by many experiences, so 'recall' is always subject to influence from traces of other experiences.
- Remembering is thus always a process of reconstruction.



Outline

- ✓ What is “a memory”?
  - ✓ The core of contemporary thinking about how memories are formed and retrieved.

- The Complementary Learning Systems framework
  - McClelland, McNaughton, and O’Reilly, 1995

- Some physiological and genetic tests of the theory

Old-fashioned neuroscience of memory

- Seeks dissociations of different forms of learning and memory.
  - Explicit vs. implicit memory
  - Declarative vs. procedural memory
  - Semantic vs. episodic memory
  - Familiarity vs. recollection

- Attempts to assign each to a different area or region of the brain

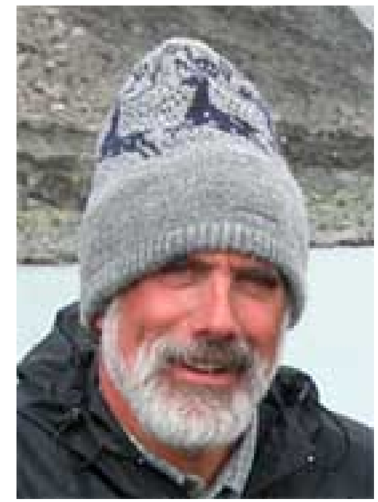
An Alternative Approach

- Complementary and Cooperating Brain Systems
  - Memory task performance depends on multiple interconnected brain systems.
  - The contribution of each system to overall memory performance depends on its neuro-mechanistic properties.
  - Systems work together so that overall performance may be better than the sum of the independent contributions of the parts.

The Complementary Learning Systems Theory

(McClelland, McNaughton & O'Reilly, 1995)

- Neuropsychological motivation
- The basic theory
- Neurophysiology consistent with the account
- Tests relying on genetic manipulations



Bi-lateral destruction of hippocampus and related areas produces:

- Profound deficit in forming new arbitrary associations and new episodic memories.
- Preserved acquisition of skills and item-specific priming.
- Loss of recently learned material w/ preservation of prior knowledge, acquired skills, and remote memory.

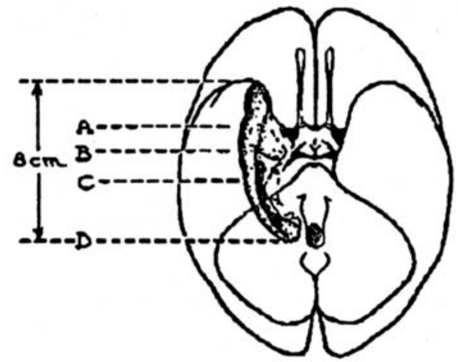
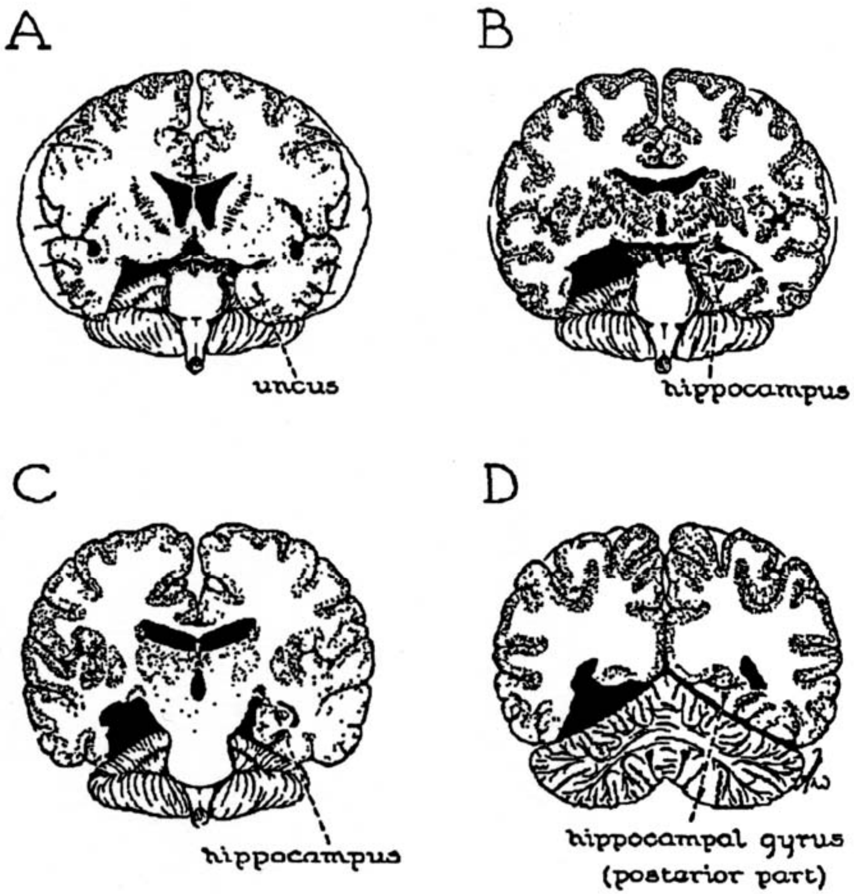
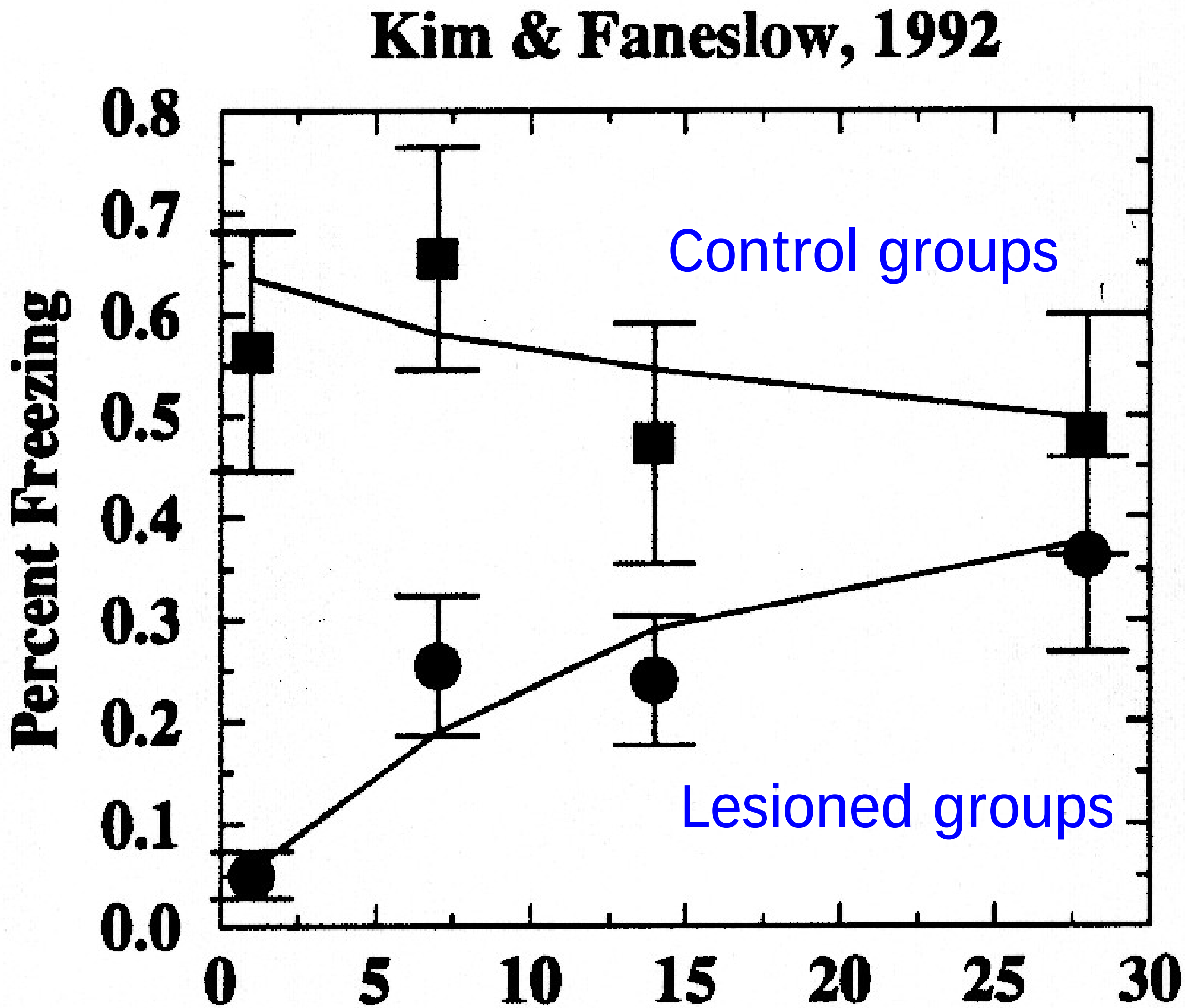


Fig. 2—Diagrammatic cross-sections of human brain illustrating extent of attempted bilateral medial temporal lobe resection in the radical operation. (For diagrammatic purposes the resection has been shown on one side only.)

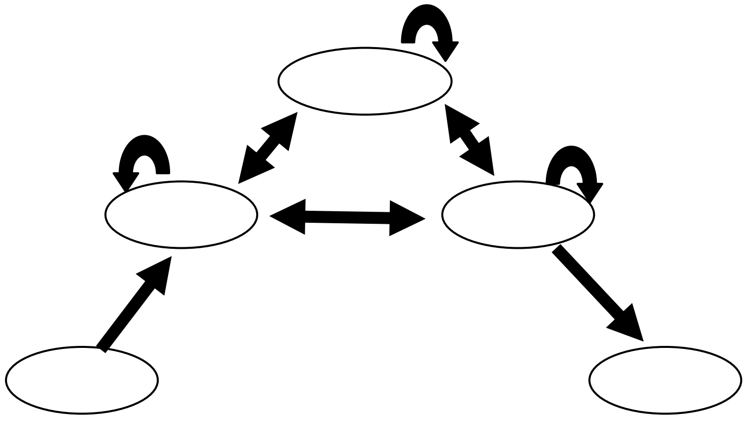




Time from experience to lesion in days

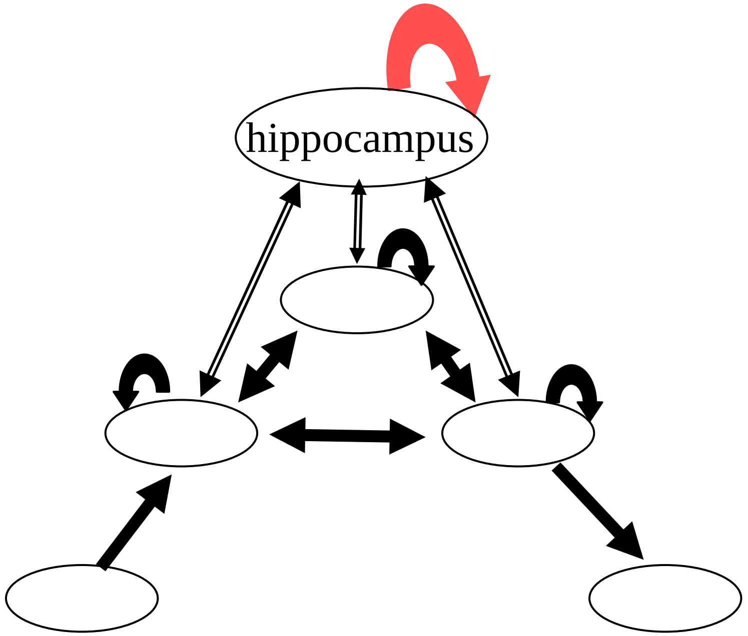
The Neuro-Mechanistic Theory: Processing and Learning in Neocortex

- An input and a response to it result in activation distributed across many areas in the neocortex.
- Small connection weight changes occur as a result, producing
  - Item-specific effects
  - Gradual skill acquisition
- These small changes are not sufficient to support rapid acquisition of arbitrary new associations.



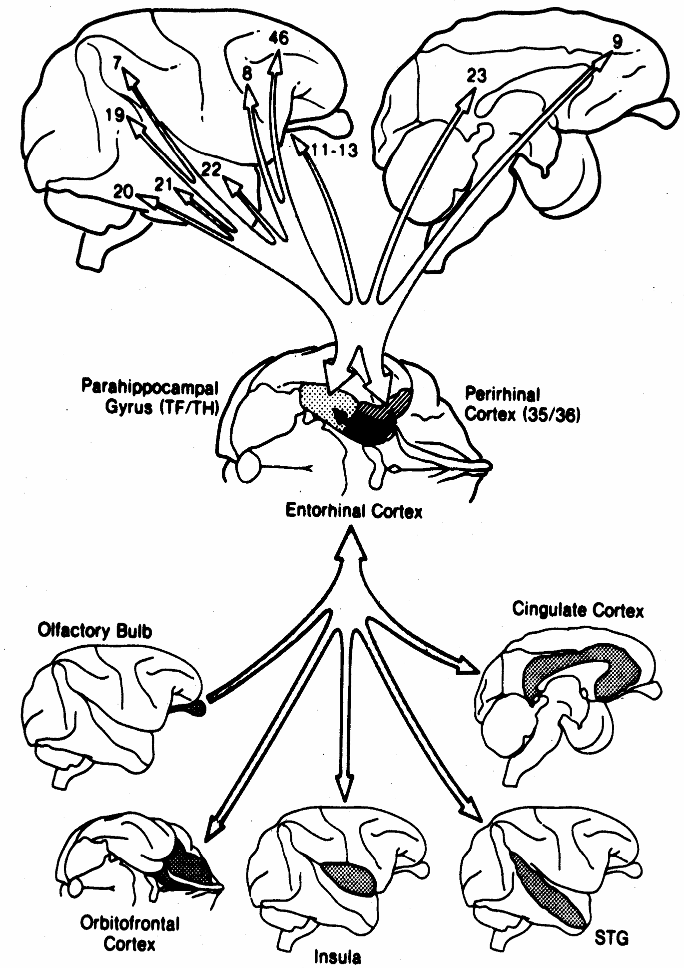
Complementary Learning System in the Hippocampus

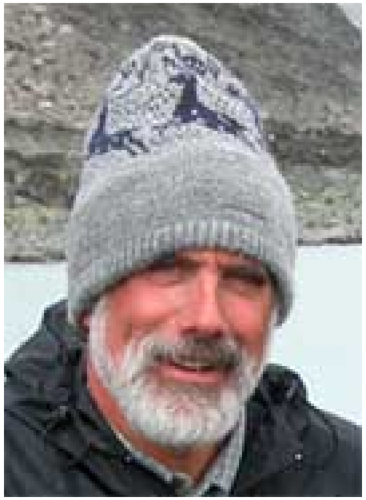
- Bi-directional connections produce a reduced description of the cortical pattern in the hippocampus.
- Large connection weight changes bind bits of reduced description together
- Cued recall depends on pattern completion within the hippocampal network
- Consolidation occurs through repeated reactivation, leading to cumulation of small changes in cortex.

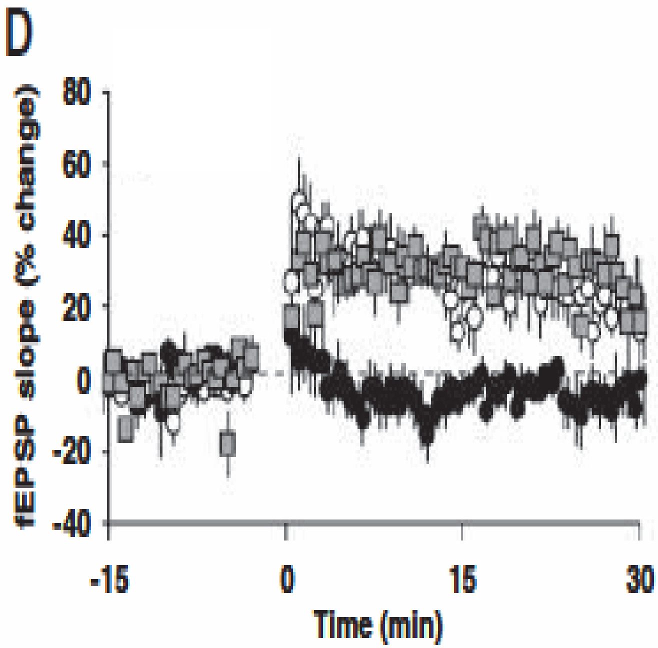


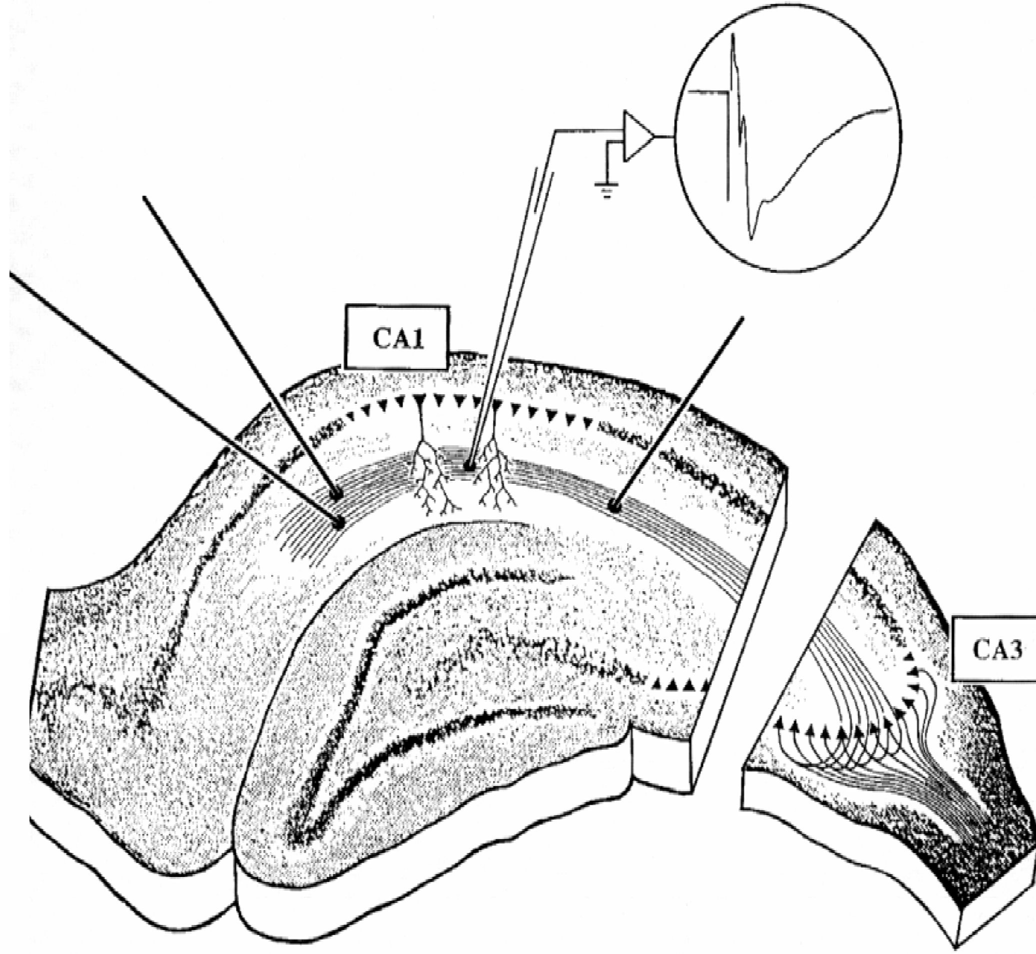
Supporting Neurophysiological Evidence

- The necessary pathways exist.
- Anatomy and physiology of the hippocampus support its role in fast learning.
- Reactivation of hippocampal representations during sleep.



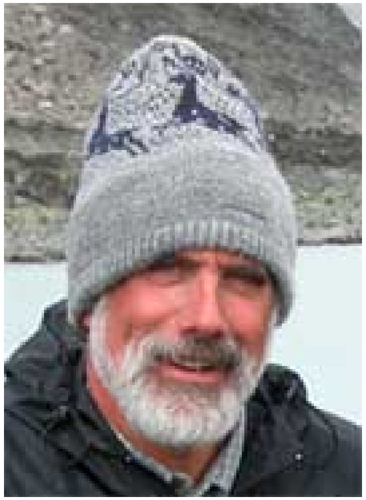


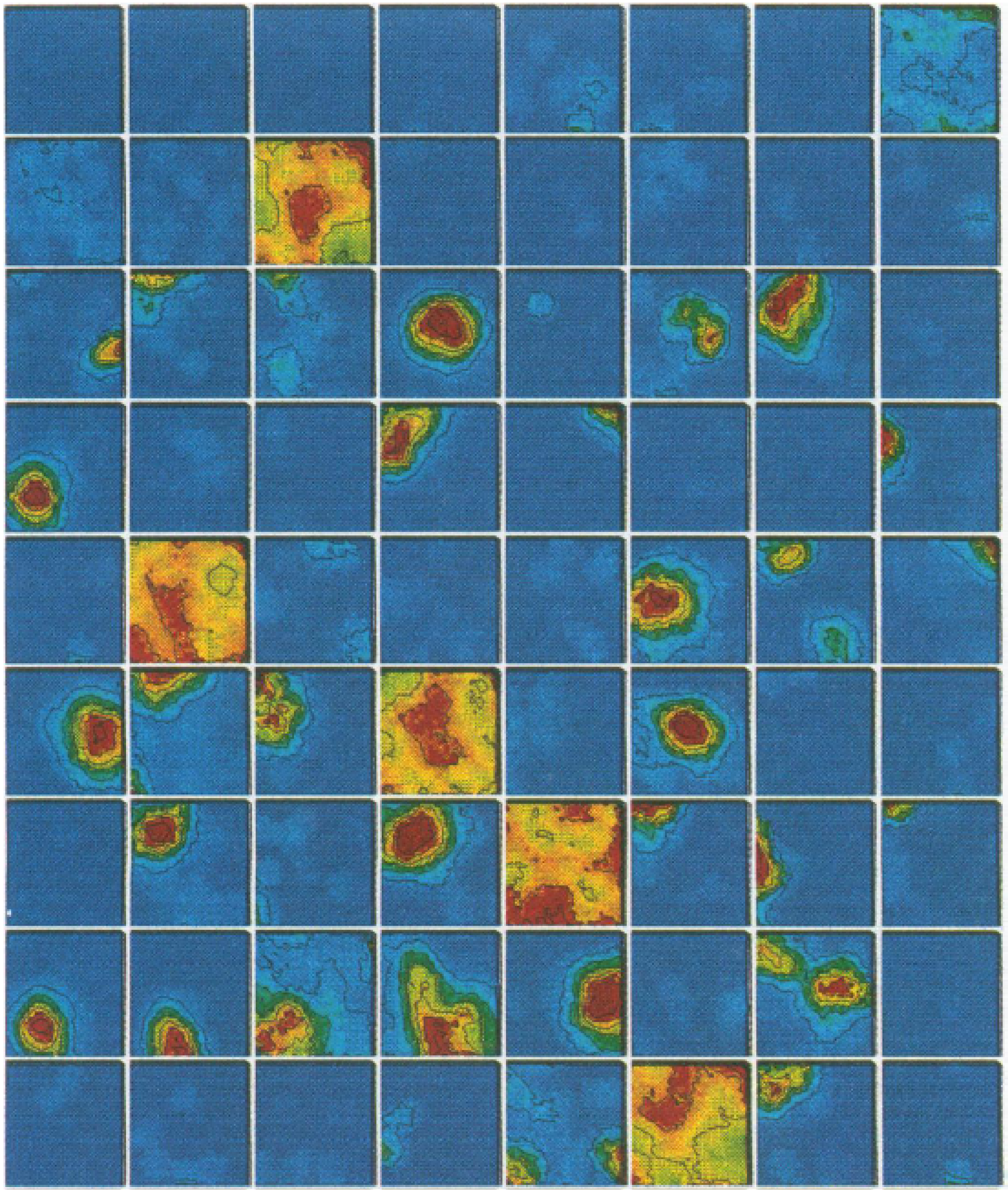

D
fEPSP slope (% change)
80
60
40
20
0
-20
-40
-15
0
15
30
Time (min)


CA1
CA3

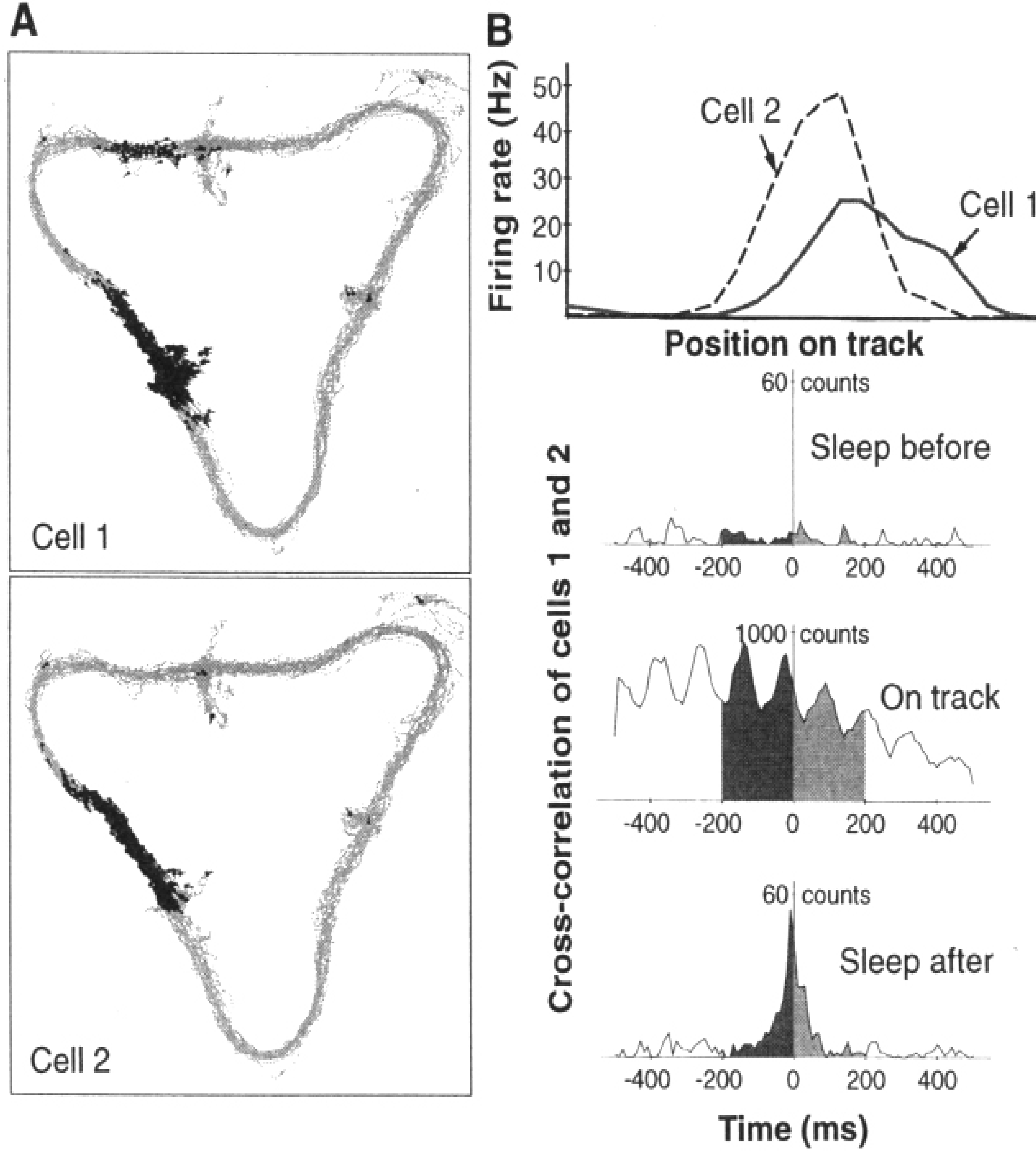
Reactivation of memories during sleep

How To Study This Problem?

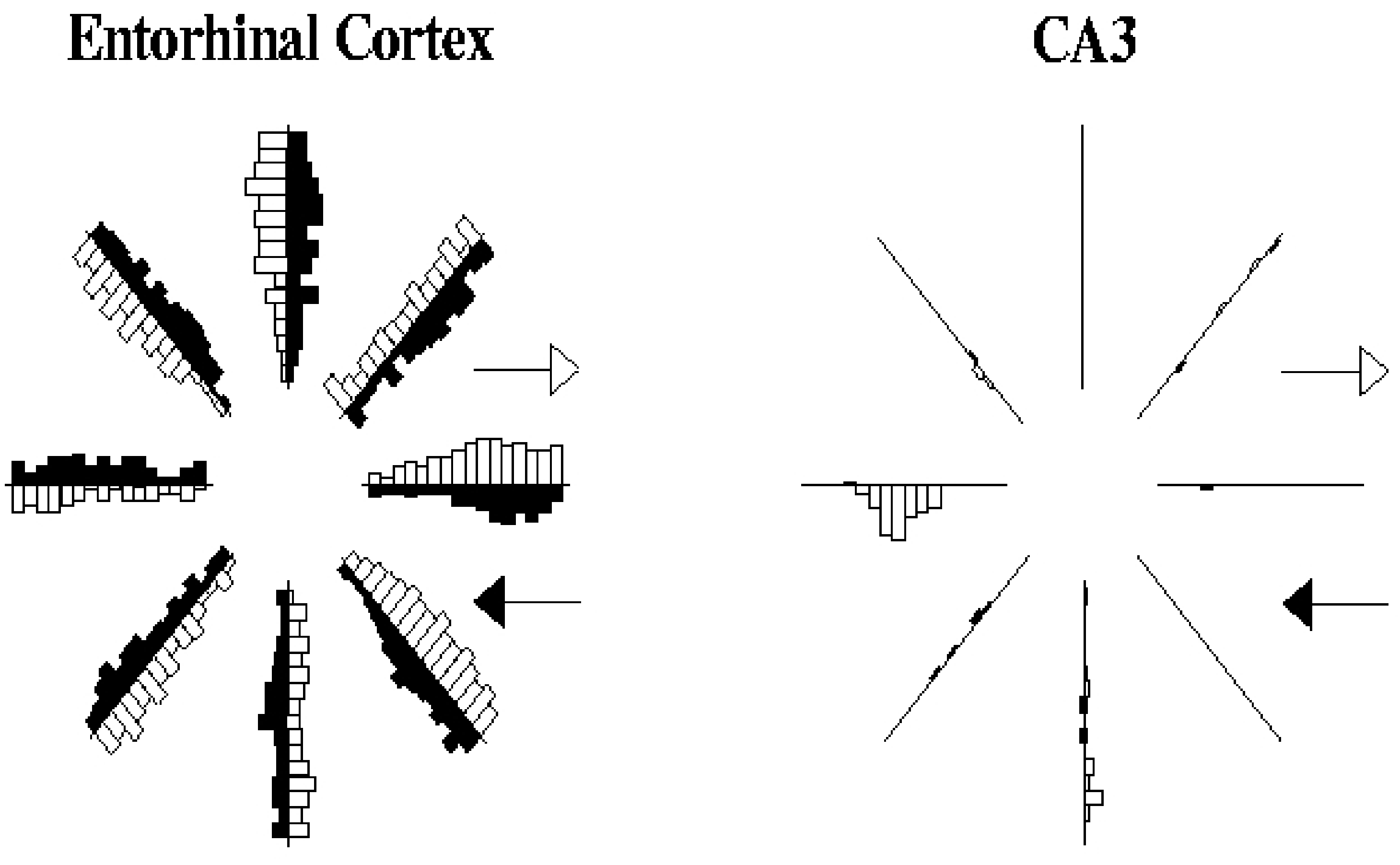




Place Cells on a Triangular Track


A
Cell 1
Cell 2
B
Firing rate (Hz)
50
40
30
20
10
Cell 2
Cell 1
Position on track
Cross-correlation of cells 1 and 2
60 counts
Sleep before
-400 -200 0 200 400
1000 counts
On track
-400 -200 0 200 400
60 counts
Sleep after
-400 -200 0 200 400
Time (ms)

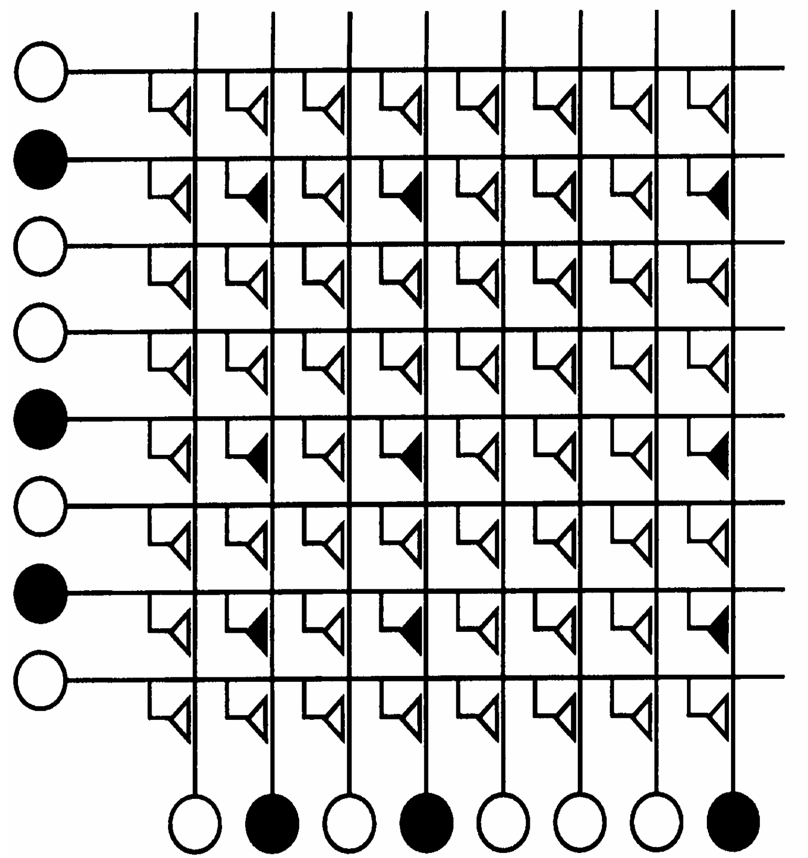
Examples of neurons found in entorhinal cortex and hippocampal area CA3, consistent with the idea that the hippocampus but not cortex uses sparse conjunctive coding



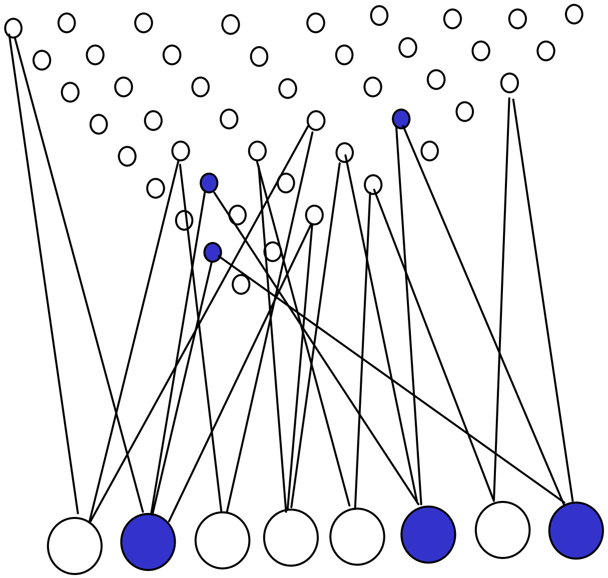
Recording was made while animal traversed an eight-arm radial maze.

A simple pattern associator network illustrating the problem of overlap

- Willshaw (1969) studied simple associative nets, in which connections could be either on or off.
- Connections are switched on to store associations between designated input and output patterns.
- When patterns overlap, the synapses they use also overlap, producing interference in memory.
- The probability that the patterns will overlap goes down if they are sparser (smaller fraction of units active).



Conjunctive coding sparsifies and reduces overlap



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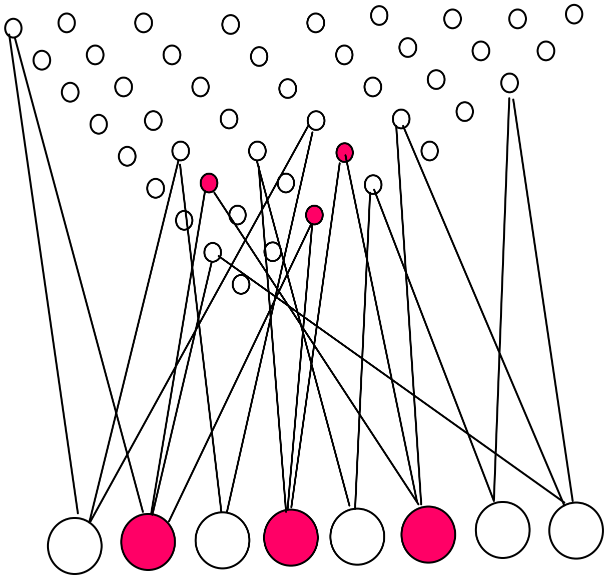
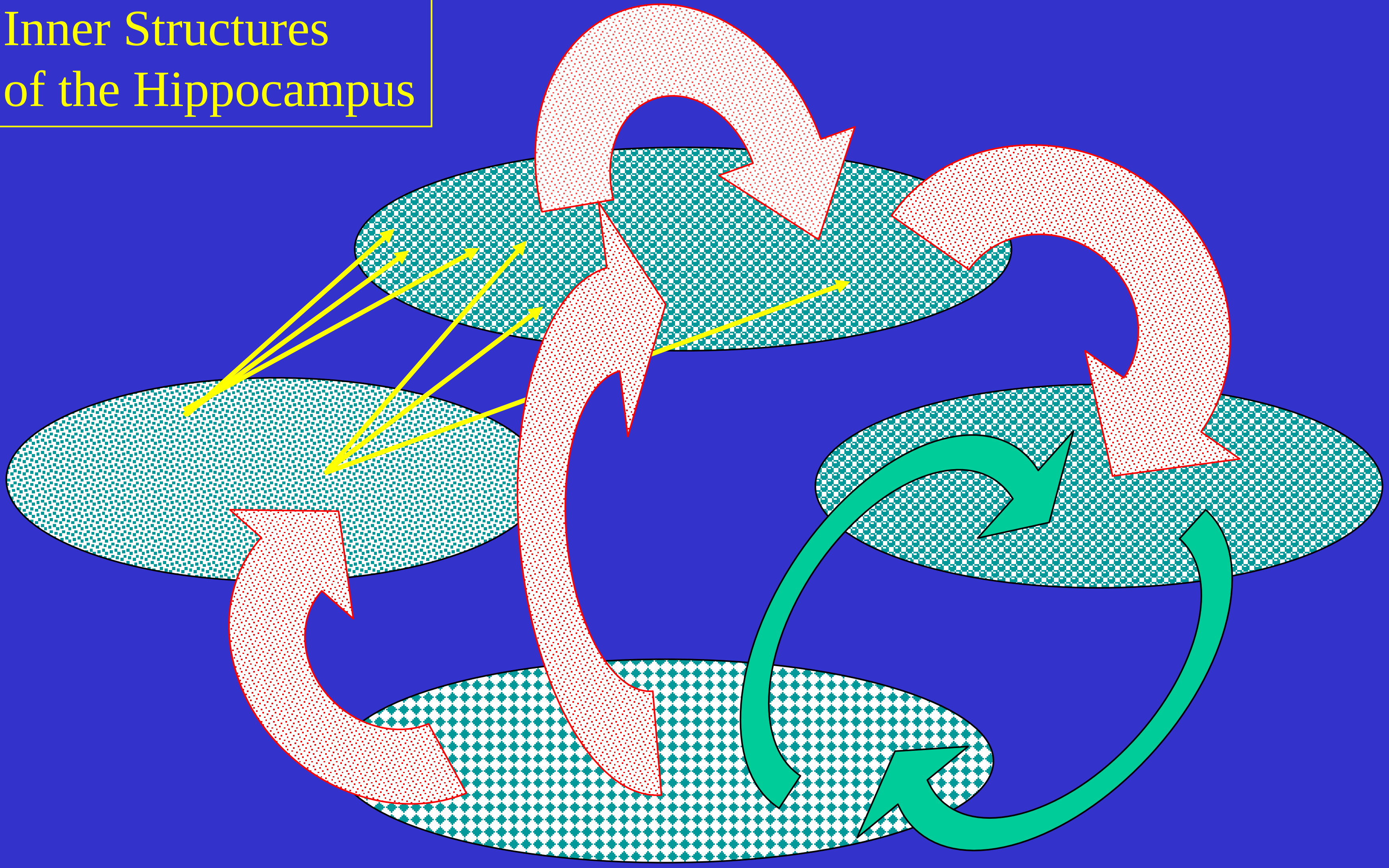


Inner Structures of the Hippocampus

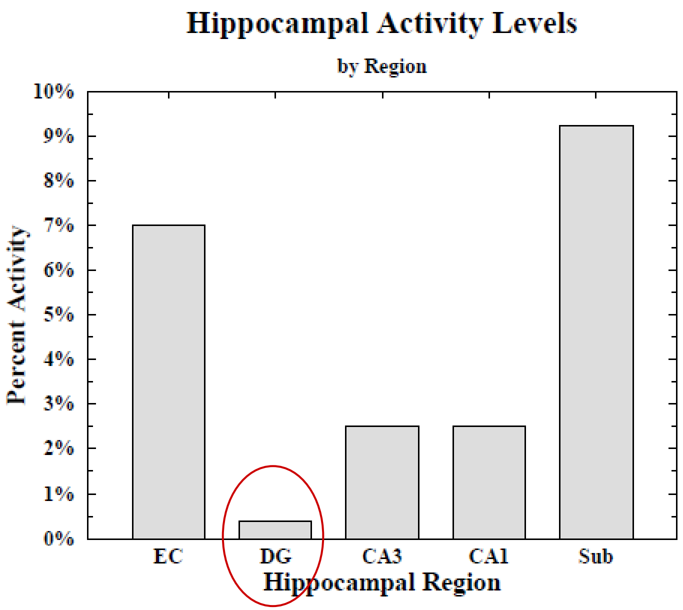


Role of Dentate in Pattern Separation
O'Reilly and McClelland, 1994

- Higher-order conjuncts lead to patterns that are:
  - Sparser
  - Less overlapping

- Dentate gyrus has the sparsest activity in the hippocampus, suggesting it plays a critical role in keeping patterns separate.

- In our theory, dentate neurons activated when a memory is formed help select an arbitrary subset of CA3 neurons to participate in the new memory.



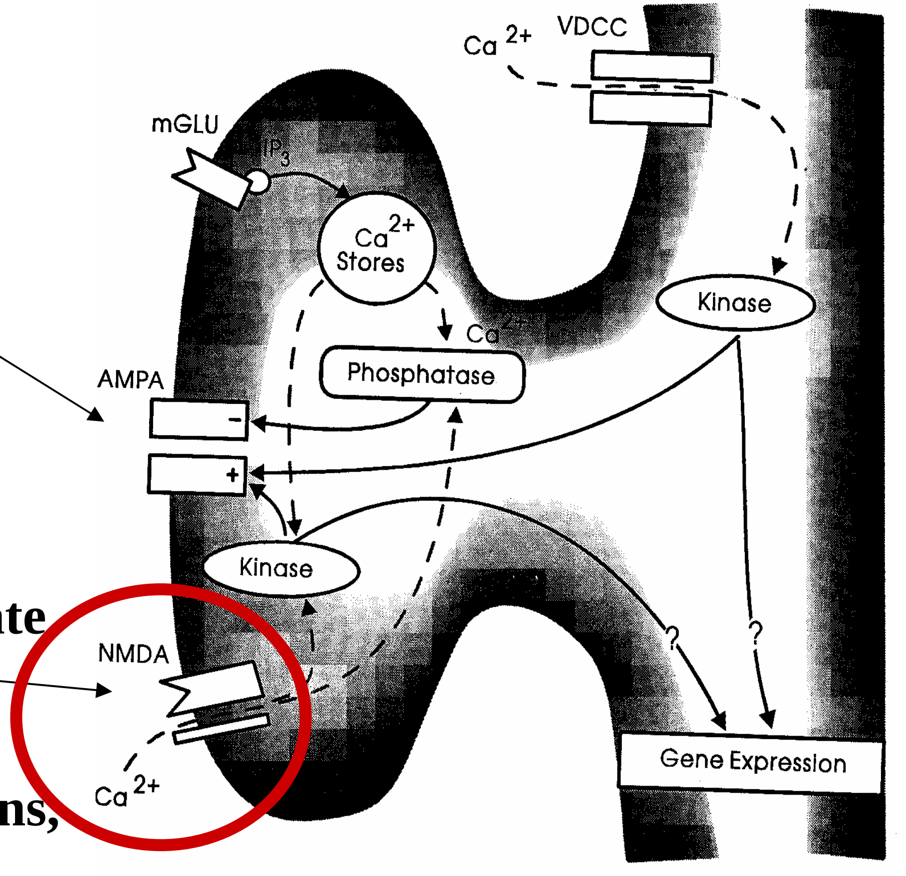
A Test of the Role of Dentate in Pattern Separation

The Molecular Biology of Synaptic Plasticity (Short Course!)

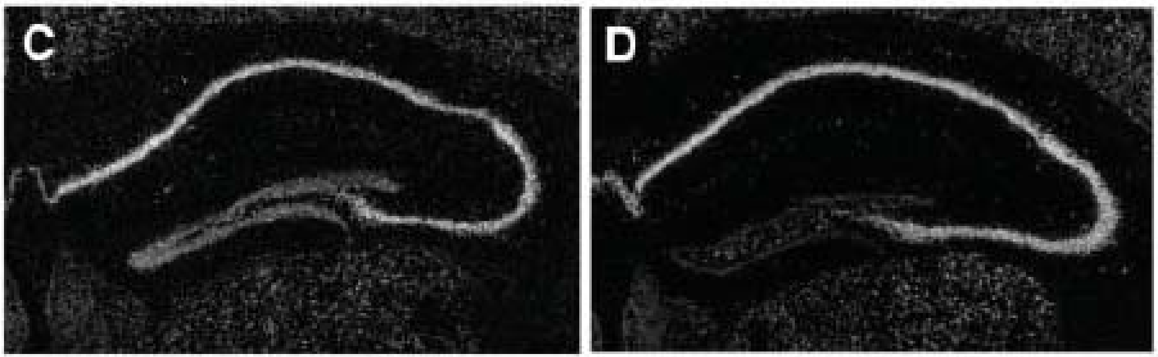
Glutamate ejected from the pre-synaptic terminal activates AMPA receptors, exciting the post-synaptic neuron.

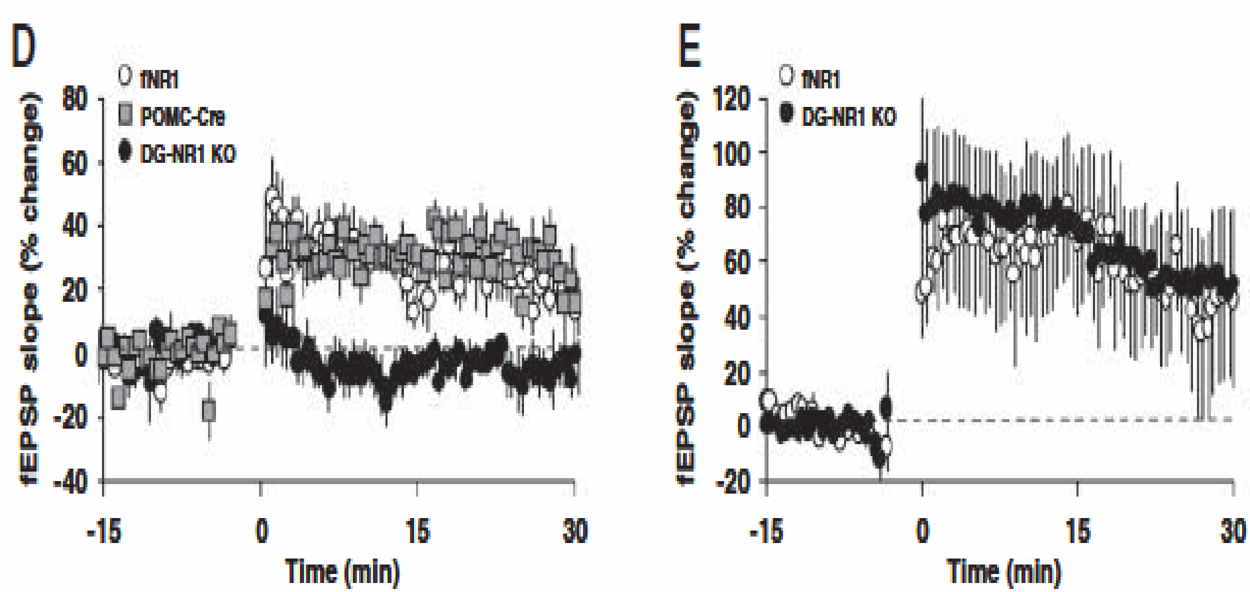
Glutamate also binds to the NMDA receptor, but it only opens when the neuron is sufficiently excited and glutamate is bound to the receptor.

When the NMDA Receptor opens, Ca++ flows in, triggering a biochemical cascade that results in an increase in AMPA receptors.



Genetic Manipulations of the Hippocampus

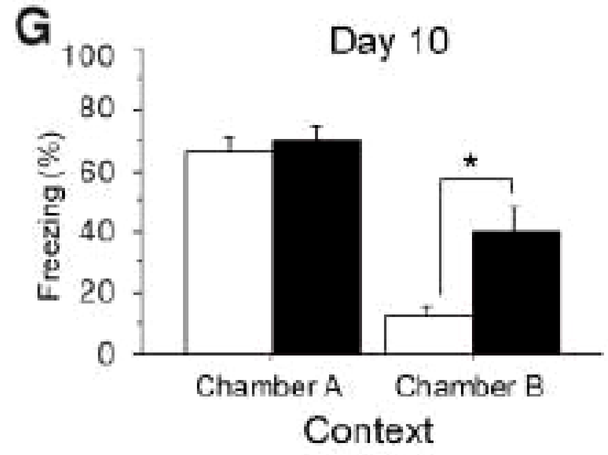




McHugh et al, *Science*, 2007

Prediction: Dentate Knockout Should Impair Discrimination Learning

- Dentate knockout should reduce separation of similar memories.
- So knockout animals should have trouble keeping similar memories distinct.
- McHugh et al test this by comparing knockout and control mice's ability to discriminate two similar environments.



McHugh et al, *Science*, 2007

Recap: The Neural Basis of Memory

- Computational models, genetics, and neurophysiology all complement the study of human and animal behavior in the contemporary investigation of memory.

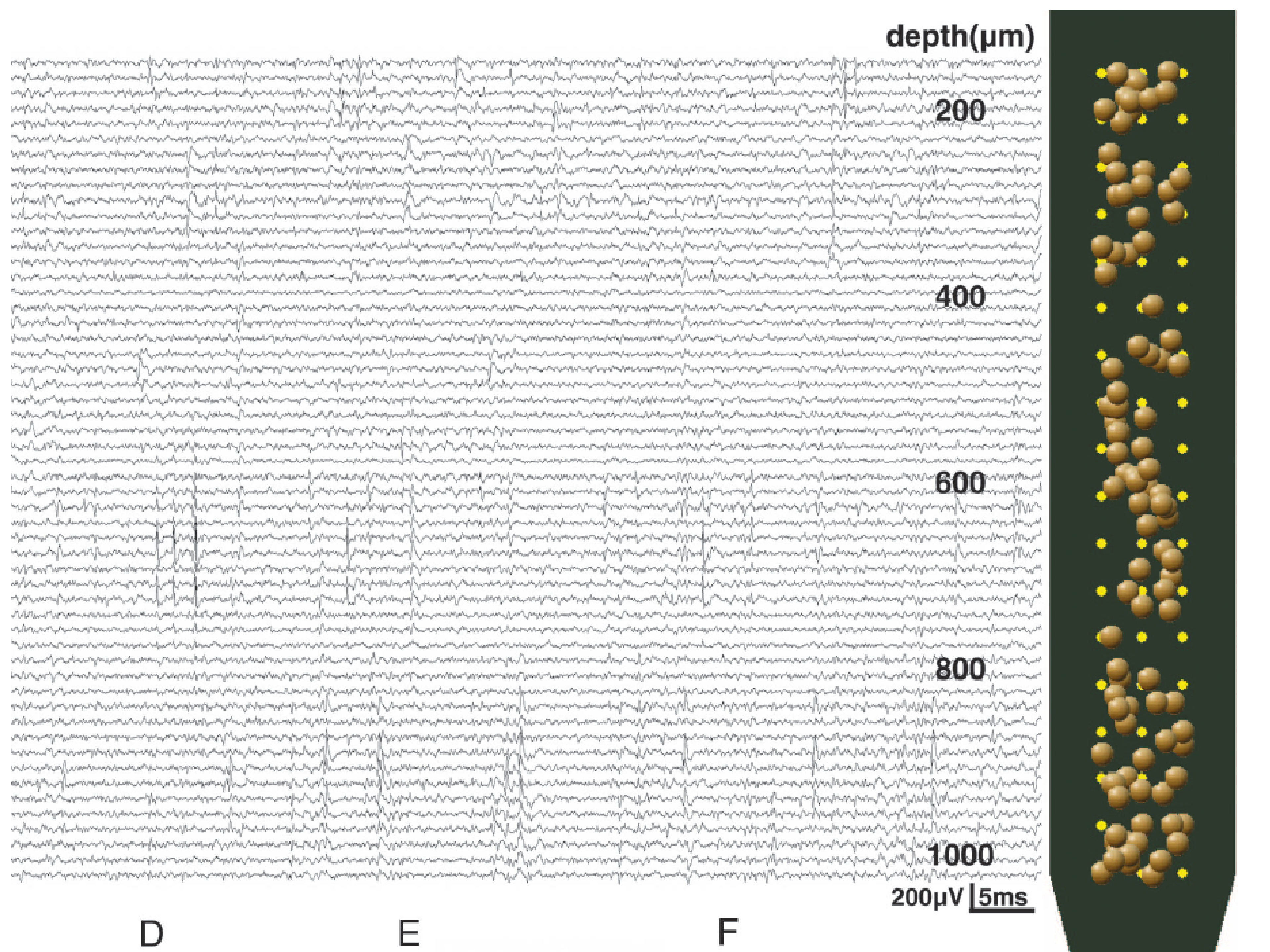
- Together these methods have lead to highly specific and detailed hypotheses about the roles of specific brain areas in memory, and these predictions are being confirmed.

- Unraveling all of the mysteries of memory will take time.

  - Tools for manipulating learning in cortex are less well developed, and the mechanisms of neocortical learning remain to be more fully understood.

- In the meantime just remember:

  What you know is in your connections



depth(μm)
200
400
600
800
1000
200μV
5ms
D
E
F