A glimpse of memory mechanisms at the network level

15 Sept., 2016

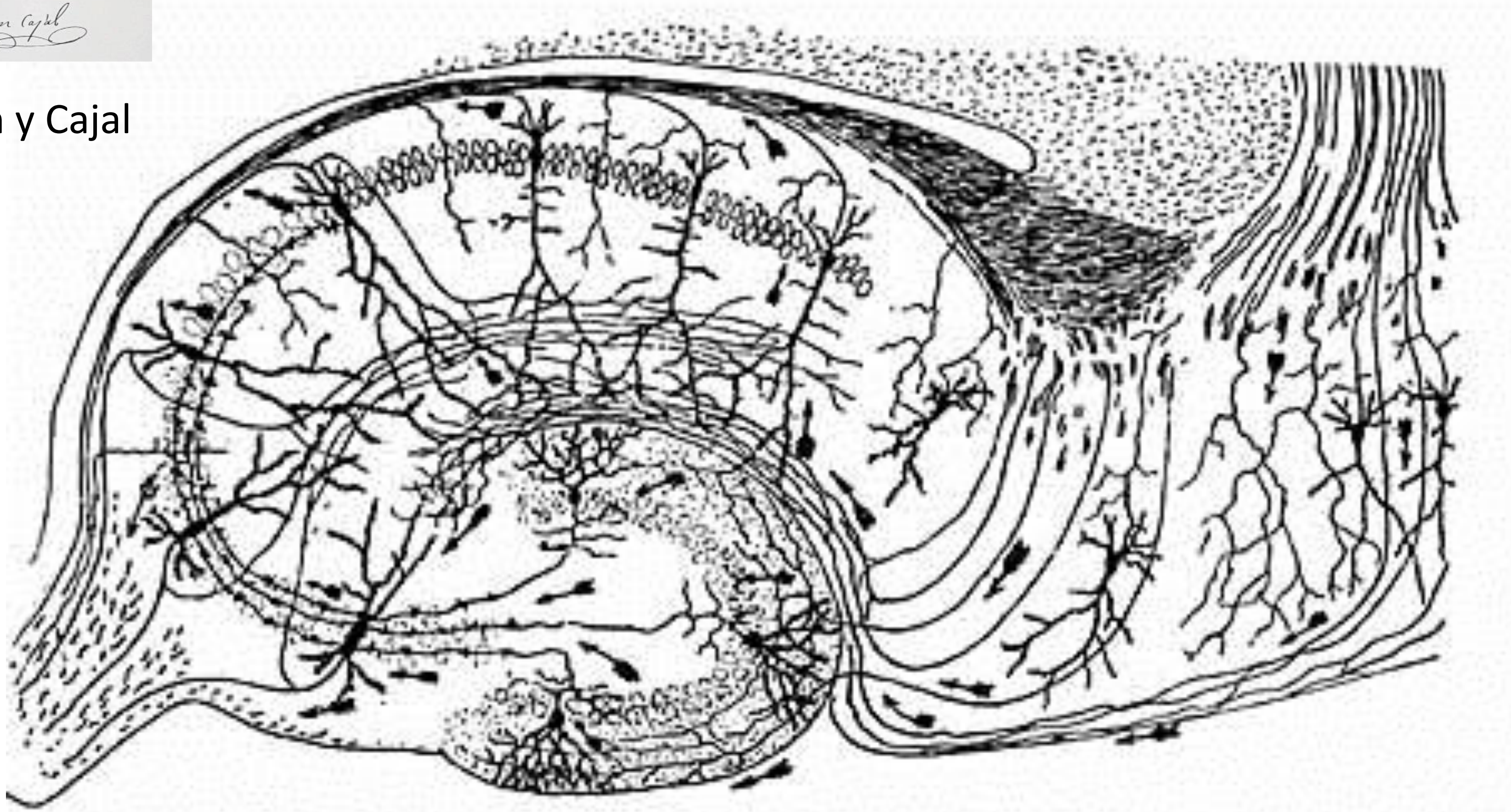
Review

- Synapses can show long-term potentiation (LTP), long-term depression (LTD)
- Synapses show associative properties (weak input paired with strong input becomes strong)
- Hippocampus is thought to be a structure where new memories are first stored (case of H.M., animal lesion studies)

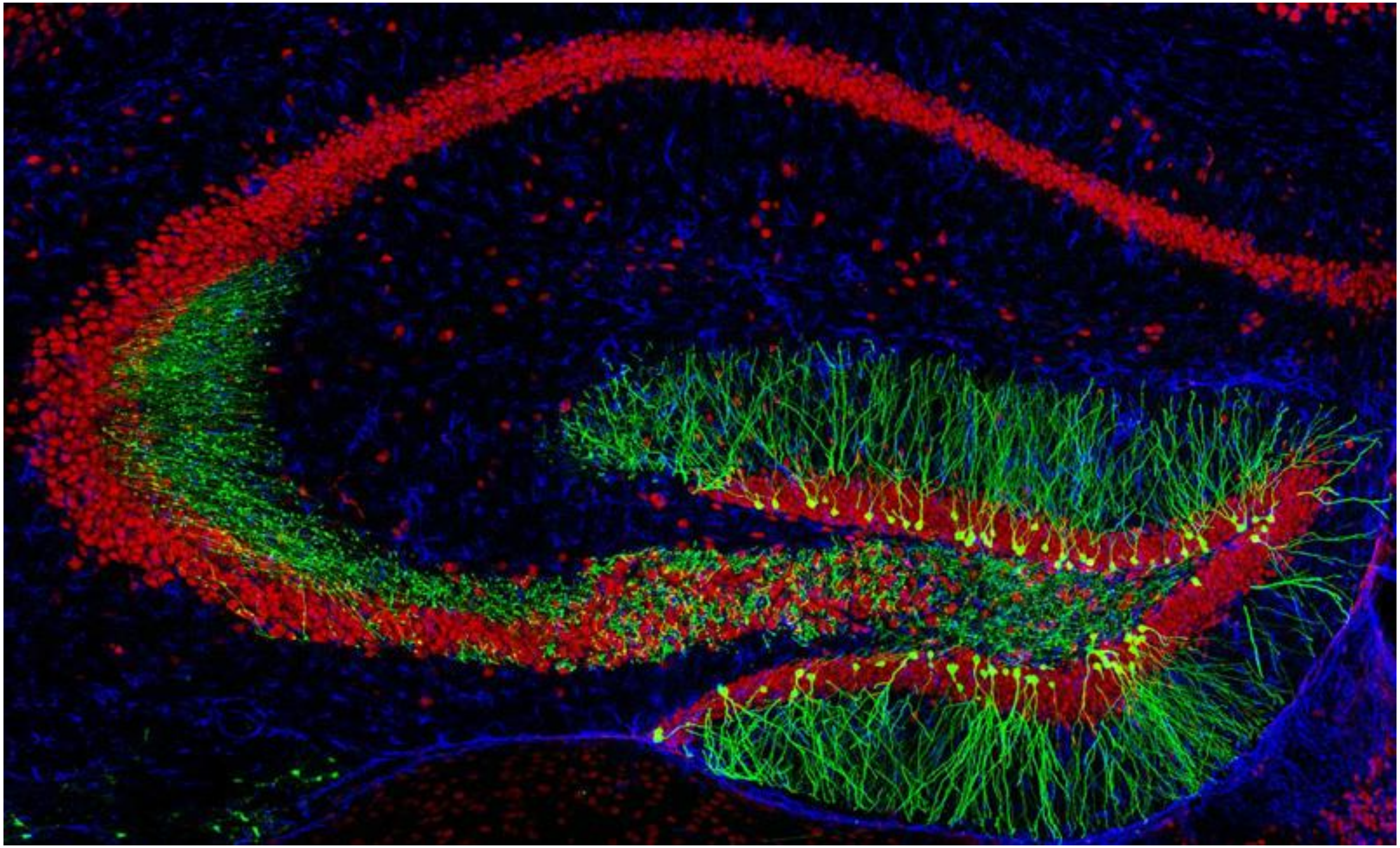
But how can a complex pattern be stored among many synapses?

Hippocampal network

Ramon y Cajal



Hippocampal network



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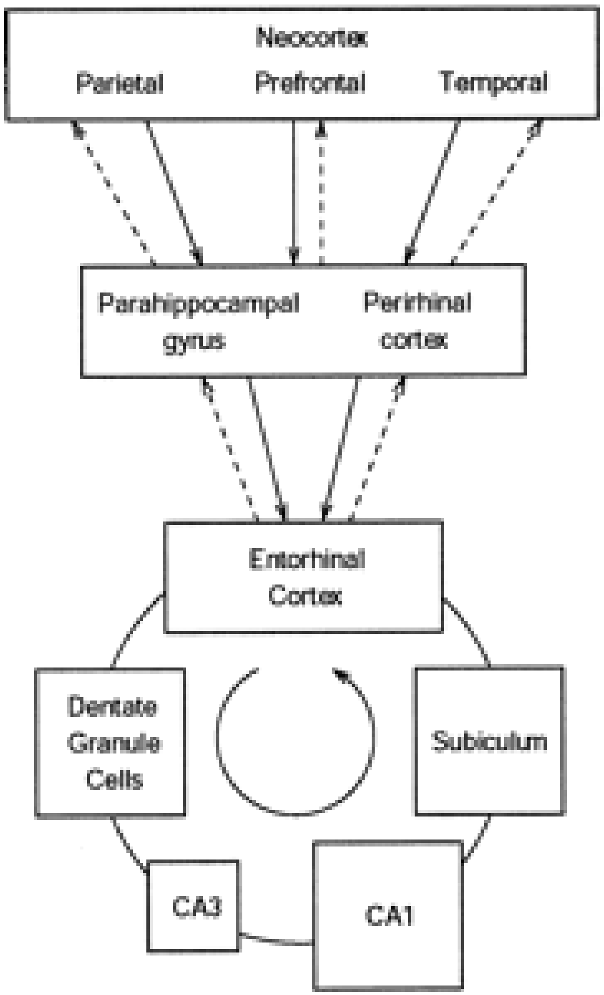
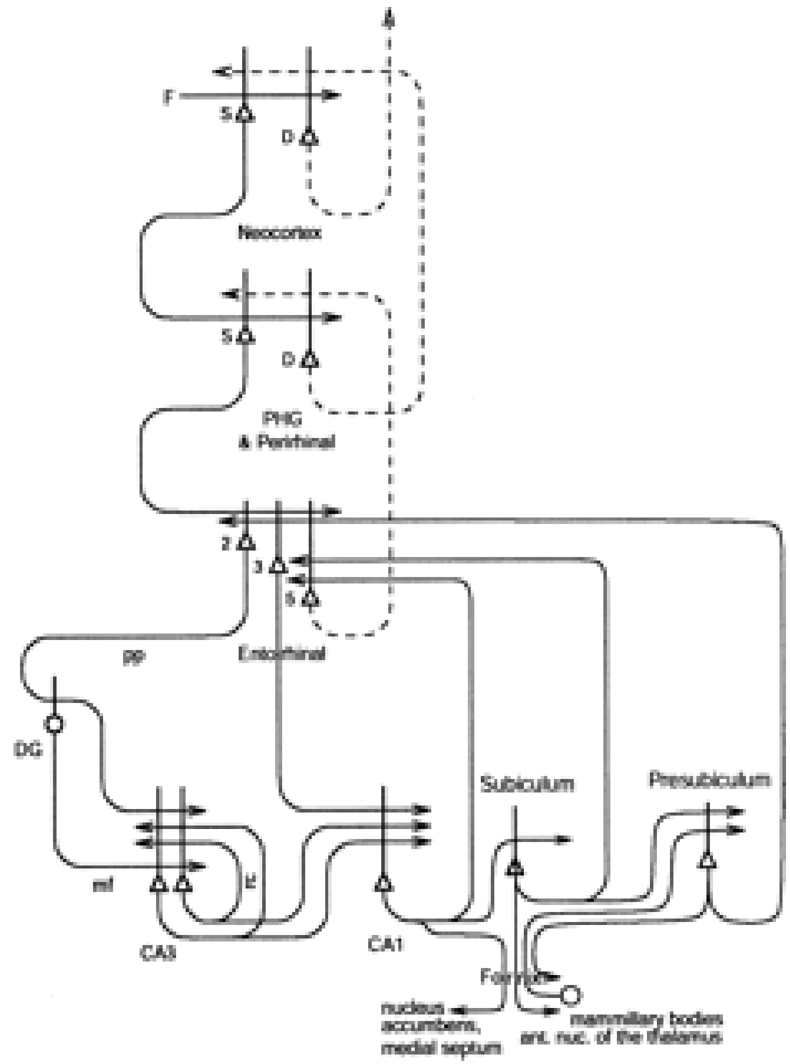
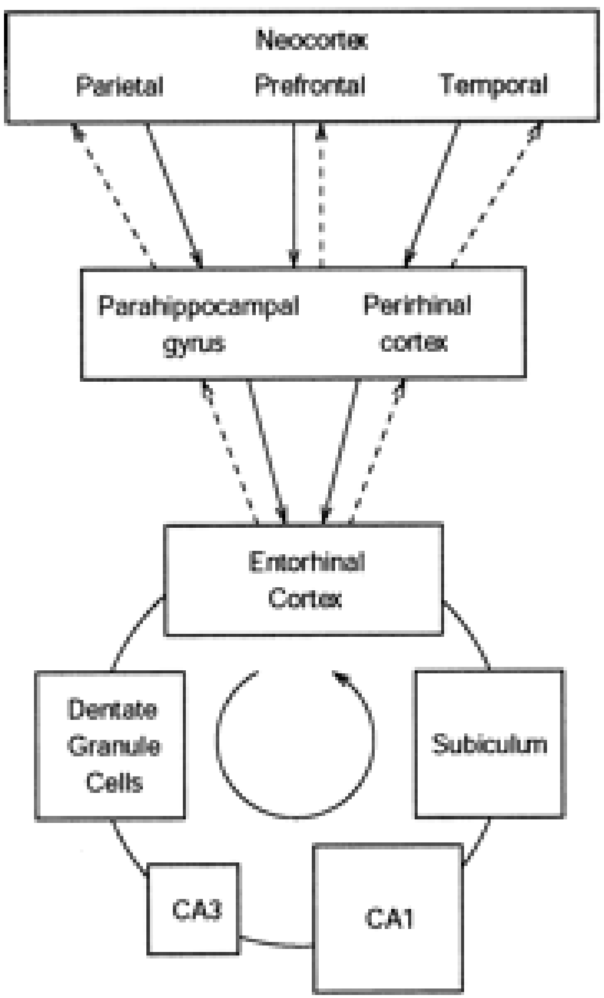
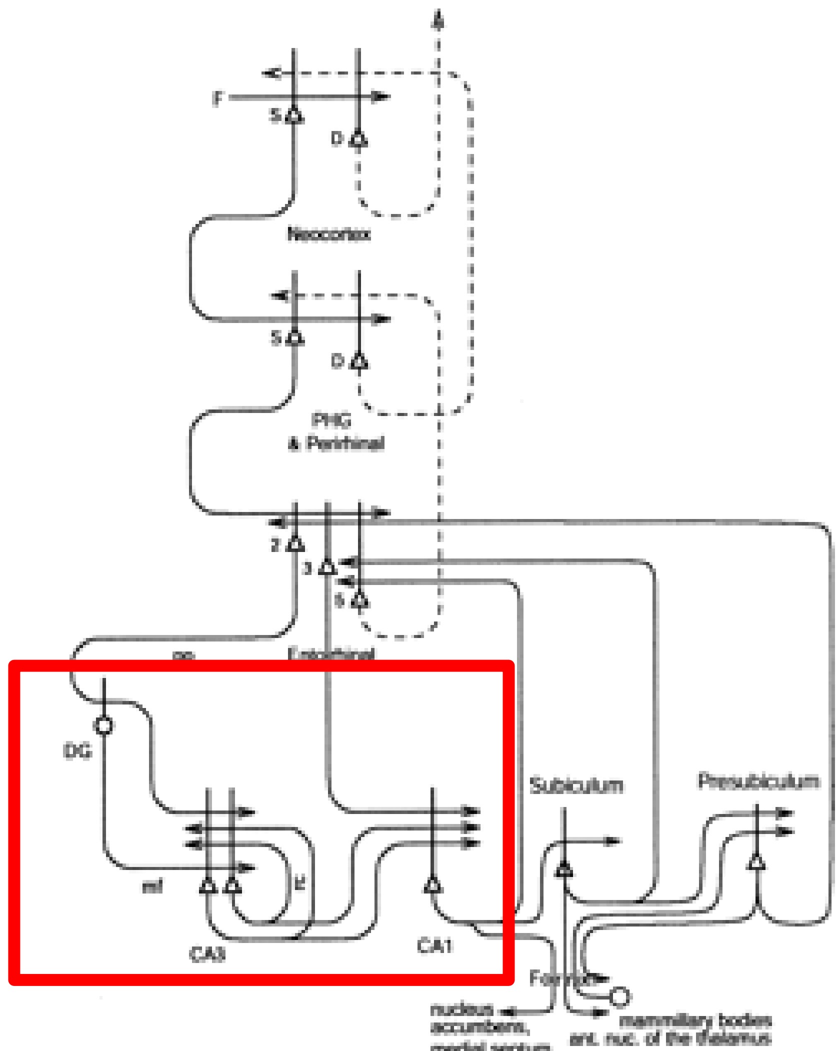




Hippocampal network





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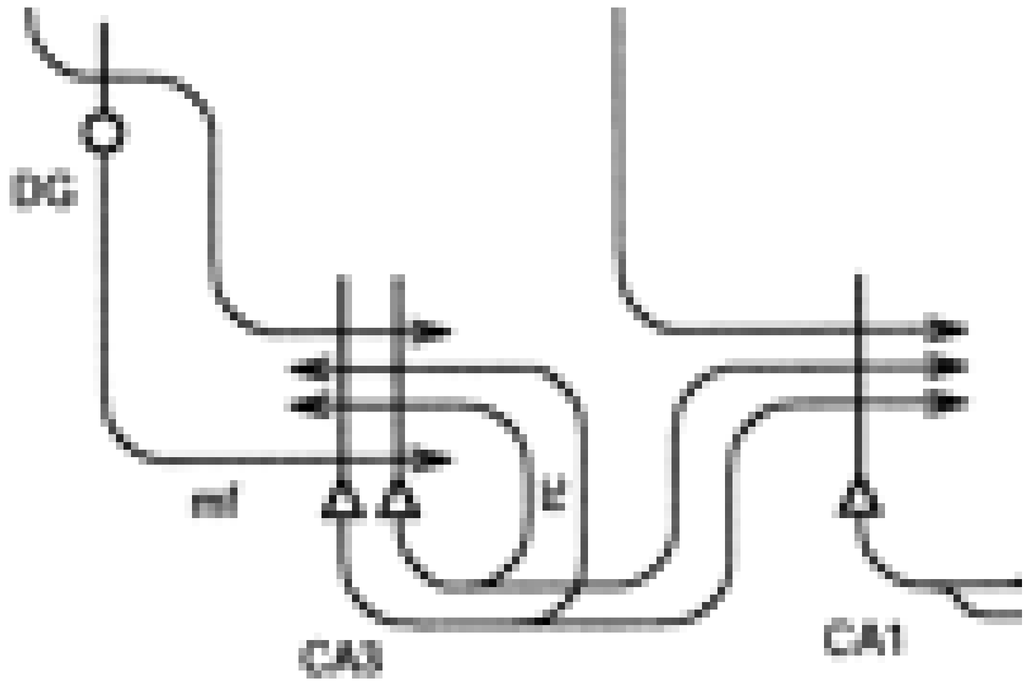
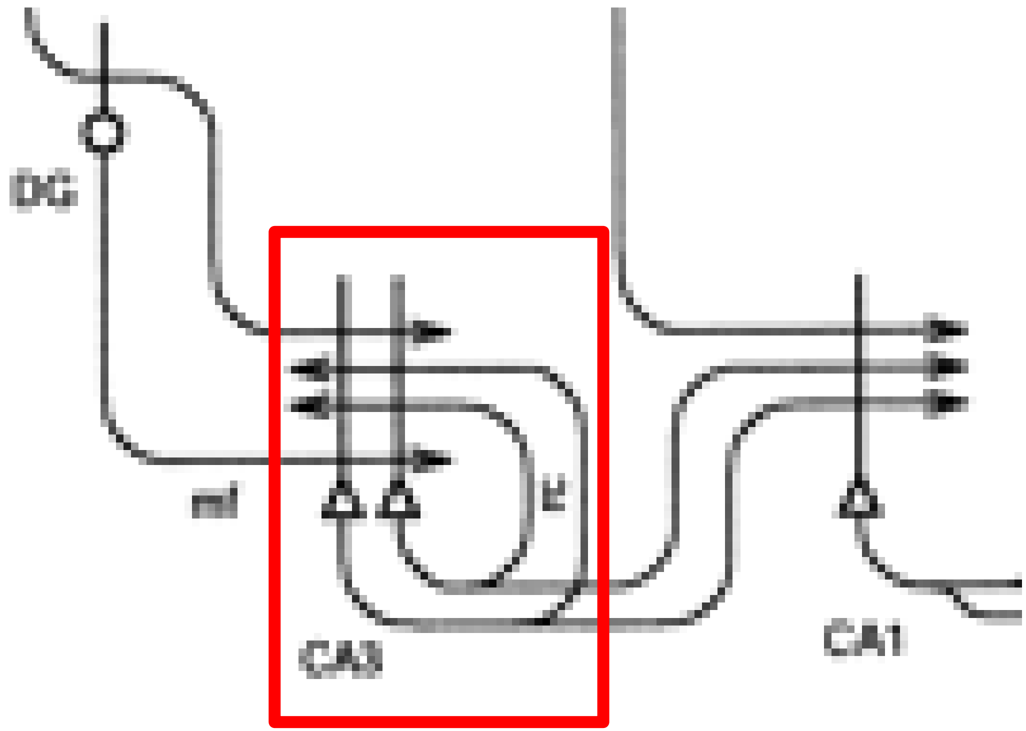
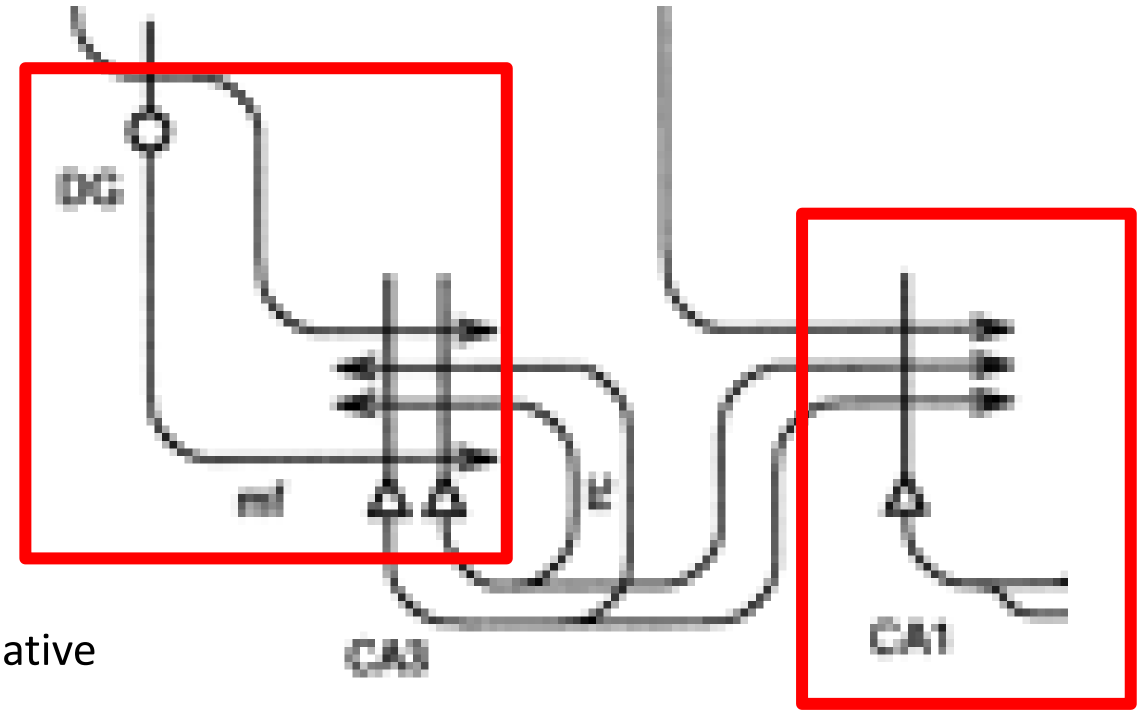


Hippocampal network



Autoassociative
sub-network

Hippocampal network

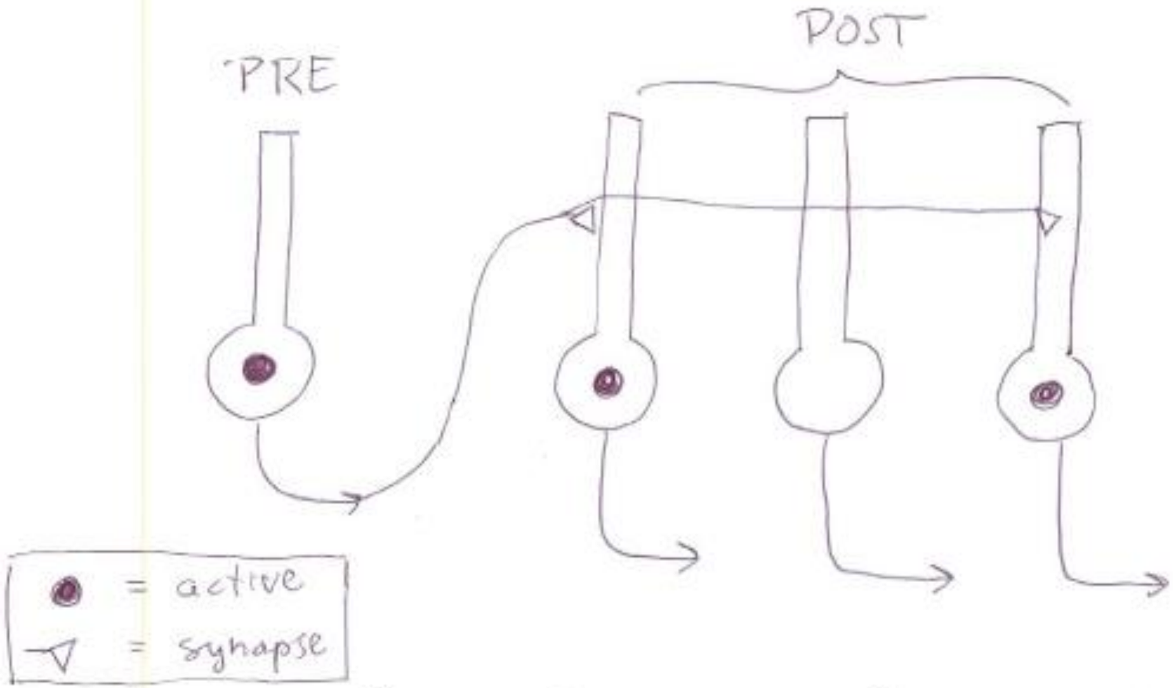


Heteroassociative
sub-network

Heteroassociative
sub-network

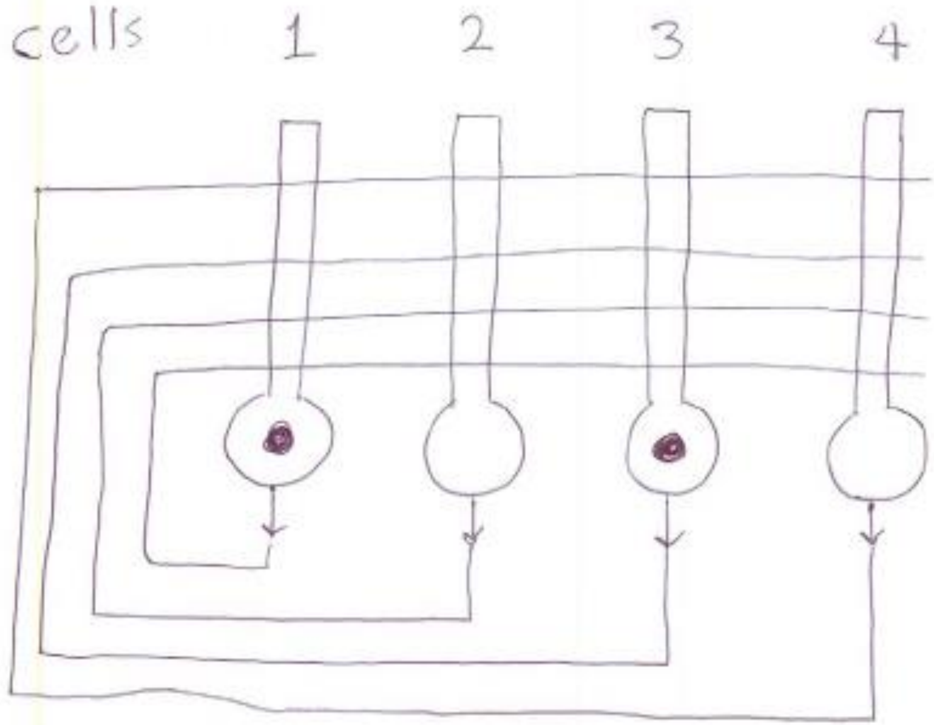
And now for a model of this…

Hebbian rule



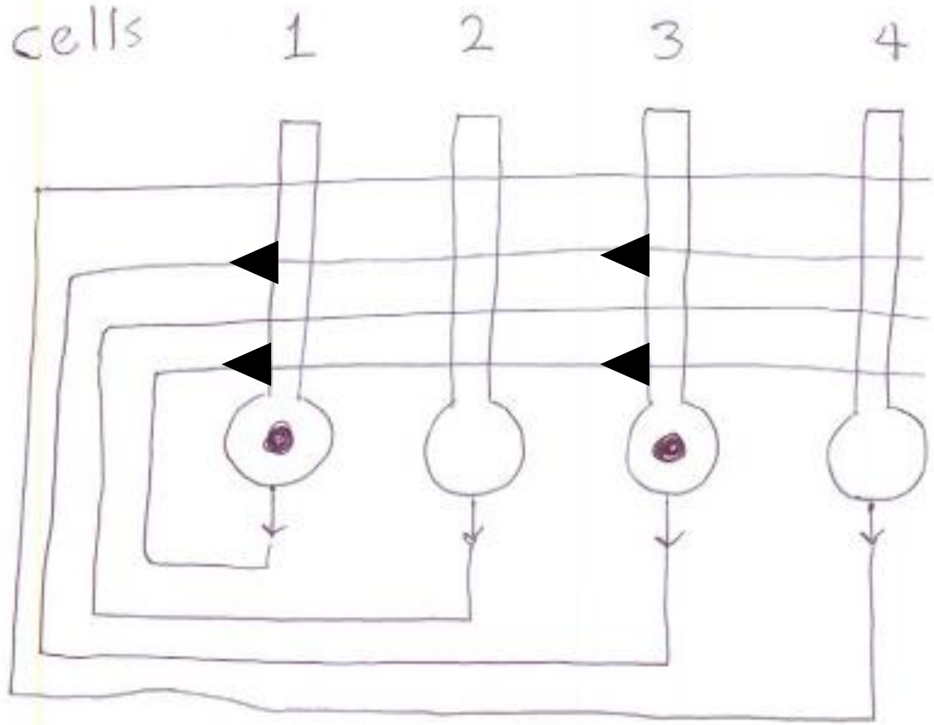
Consider: Synapses form only if there is coactivity between the pre- and post-synaptic cells.

An autoassociative network



Draw the synapses that form with this rule if neurons 1 and 3 are active.

An autoassociative network



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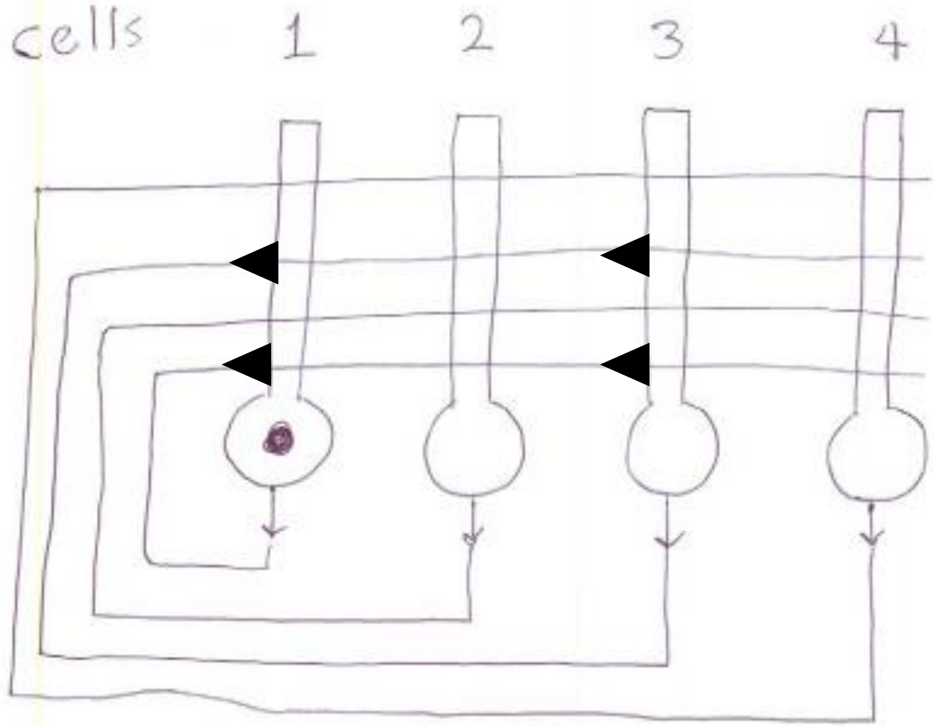
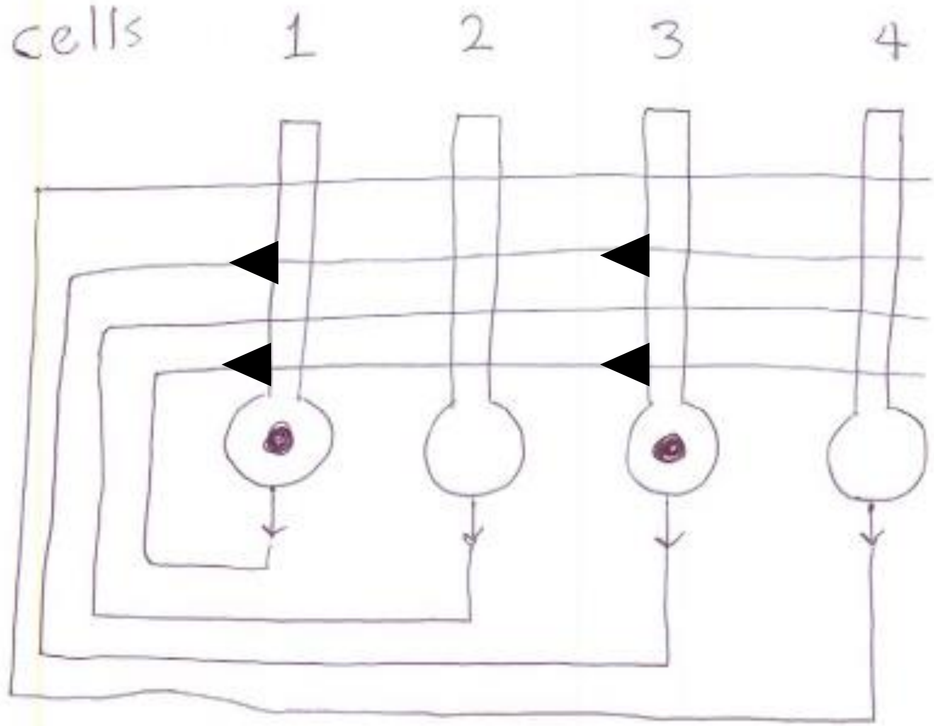


Now what happens if only neuron 1 is activated?

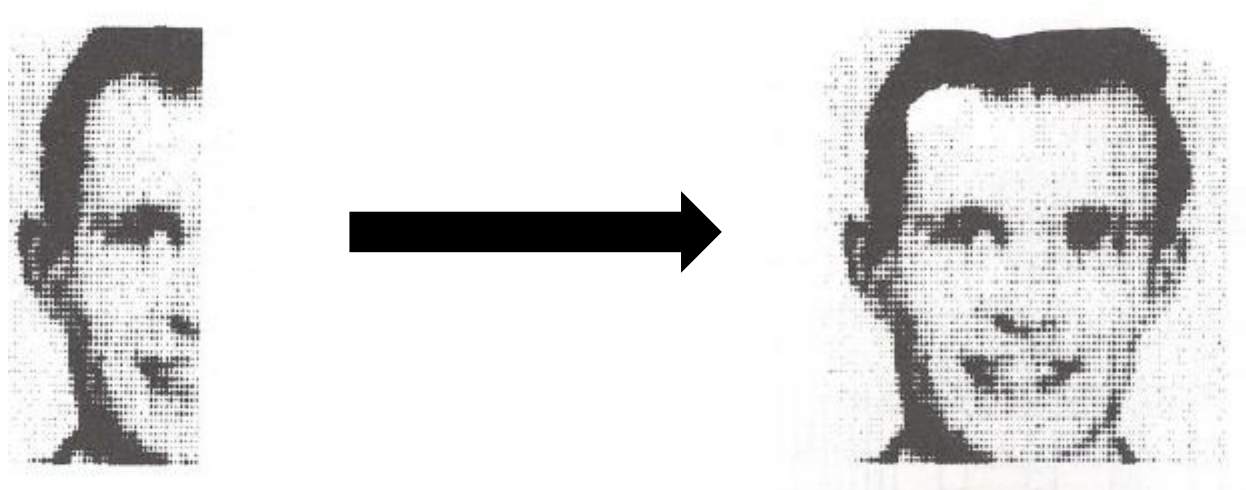
An autoassociative network



It reactivates neuron 3
Because of the
previously enhanced
synapses

Now what happens if only neuron 1 is activated?

This is only for a very, very simple pattern. But the process of "pattern completion" from a fragment can be extended to much larger patterns in models of recurrent networks.



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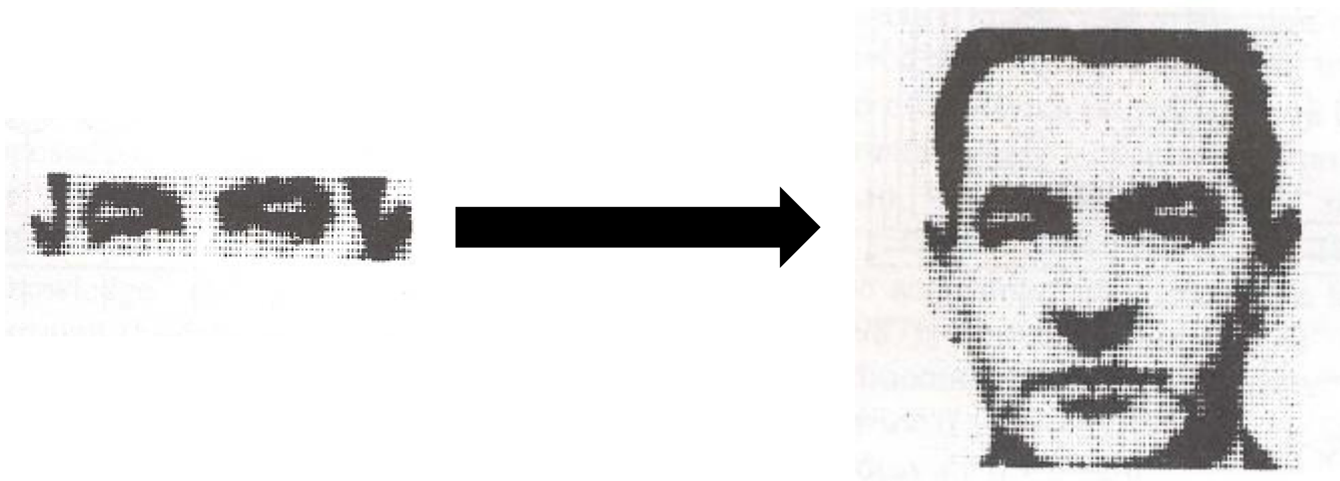
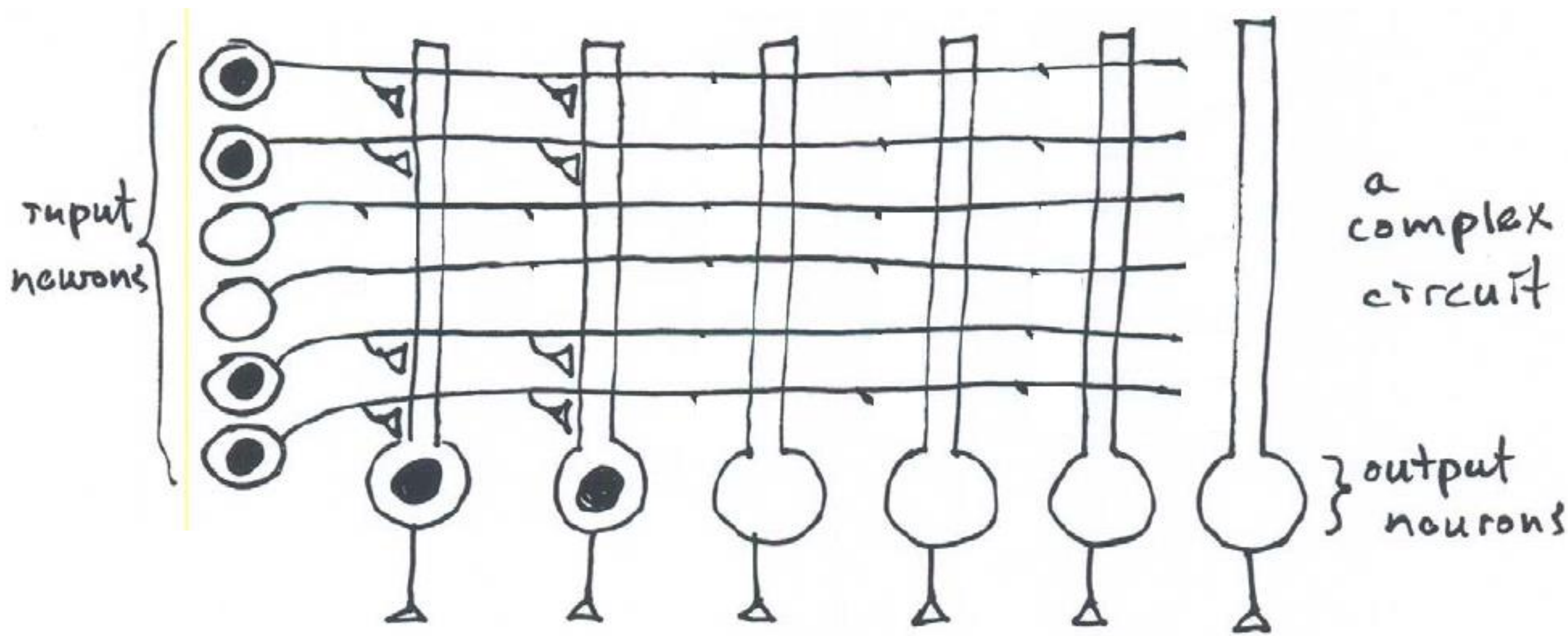


So autoassociative networks can perform pattern completion.

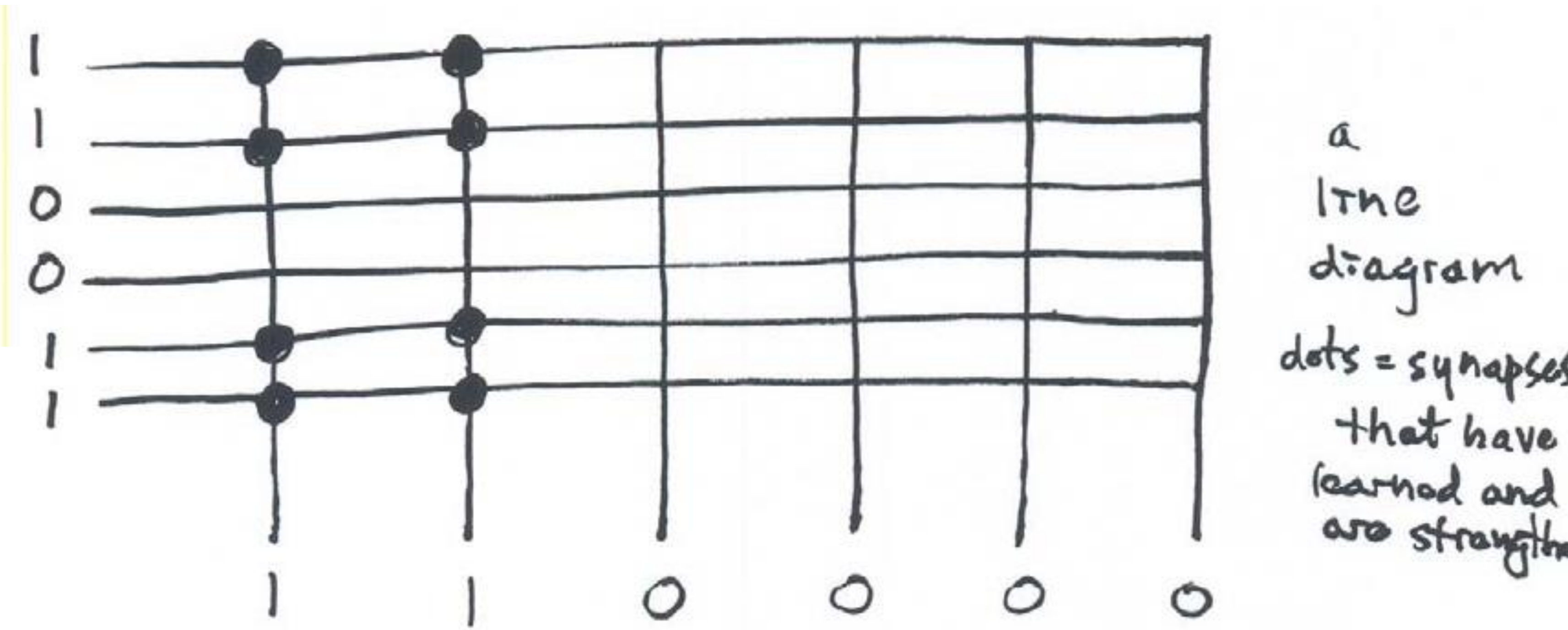
So autoassociative networks can perform pattern completion.

What can heteroassociative networks do?

A heteroassociative network



A heteroassociative network



A heteroassociative network

input pattern

$$\begin{bmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 1 \end{bmatrix} \quad \begin{bmatrix} 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \end{bmatrix}$$

synaptic strengths

compact matrix representation

$$\begin{bmatrix} 1 & 1 & 0 & 0 & 0 & 0 \end{bmatrix}$$

output pattern

A heteroassociative network

Calculate the memory associated with stimulus vector A.

Multiply A by a column.
Sum.
Divide by the number of active lines.

$$\begin{array}{cc} & \text{Ma} \\ A \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} & \begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \\ & \begin{bmatrix} \quad & \quad & \quad & \quad & \quad & \quad \end{bmatrix} a \end{array}$$

A heteroassociative network

$$
\begin{array}{cc}
 & M_a \\
A \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} &
\begin{bmatrix}
1 & 1 & 0 & 0 & 1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}
\end{array}
$$

$$
\begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \end{bmatrix} a
$$

Calculate the memory associated with stimulus vector A.

Multiply A by a column.
Sum.
Divide by the number of active lines.

A heteroassociative network

$$
B \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}
\qquad
\begin{array}{c} M_b \\ \begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \end{array}
$$

In another matrix, calculate the memory associated with stimulus vector B.

A heteroassociative network

$$B \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \begin{array}{c} M_b \\ \begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \end{array}$$

A heteroassociative network

$$B \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \overset{M_b}{\begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}}$$

$$\begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \end{bmatrix}$$

Superposition: Can the same network store more than one pattern?

$$\begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^{M_a} + \begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^{M_b} = \begin{bmatrix} \quad & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \end{bmatrix}^{M_{a+b}}$$

Superposition: Can the same network store more than one pattern?

$$\begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^{M_a} + \begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^{M_b} = \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^{M_{a+b}}$$

Test recall of combined matrix:

$$A \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} M_{a+b}$$

Test recall of combined matrix:

$$A \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} M_{a+b}$$

$$\begin{bmatrix} 3/3, & 3/3, & 2/3, & 0, & 3/3, & 3/3 \end{bmatrix}$$

Test recall of combined matrix:

$$A \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} M_{a+b}$$

$$\begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \end{bmatrix}$$

Test recall of combined matrix:

$$B \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\begin{bmatrix} \qquad\qquad \end{bmatrix}$$

Test recall of combined matrix:

$$B \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

[2/3, 2/3, 3/3, 0 , 3/3 , 2/3]

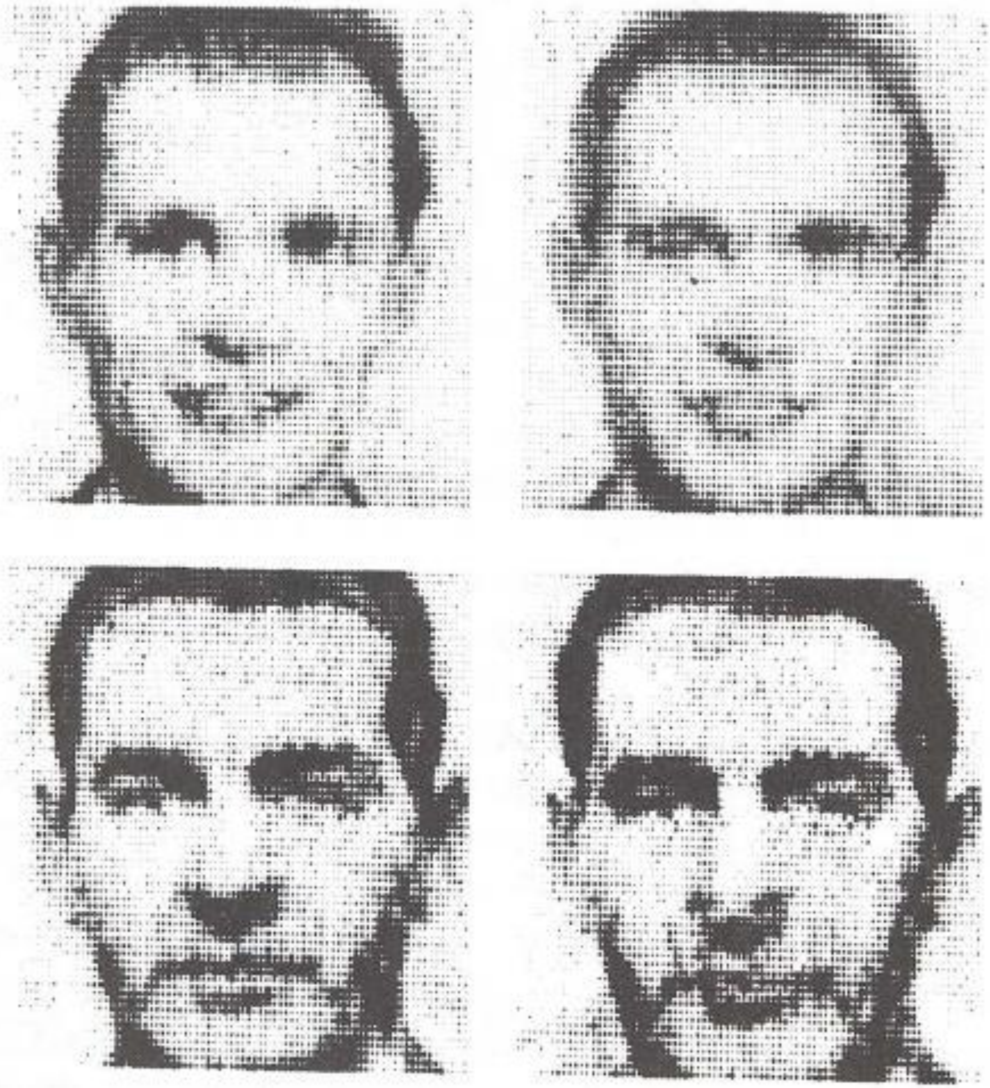
Test recall of combined matrix:

$$B \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 & 1 & 0 & 1 & 0 \end{bmatrix}$$

Heteroassociative networks can link different complex patterns together. The same network can link many pairs of patterns.

But if too many patterns are stored:



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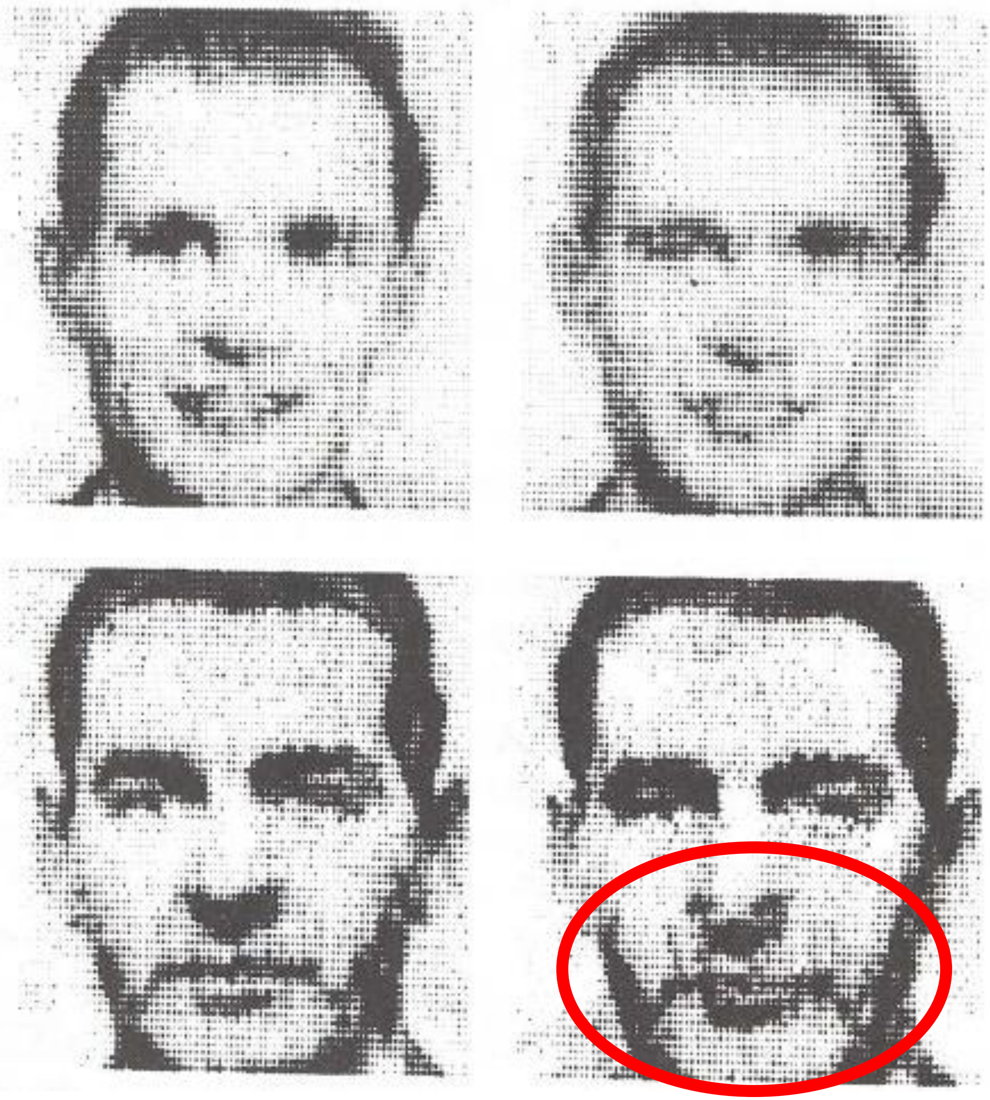


Degradation

Interim summary

- Hippocampus CA3 has autoassociative structure
- Hippocampus CA1, DG have heteroassociative structures
- Pattern completion in autoassociative
- Links between different patterns in heteroassociative
- Superposition allows multiple memories – up to a limit (high overlap: more degradation)

A biological example

Creating a False Memory in the Hippocampus

Steve Ramirez,[1*] Xu Liu,[1,2*] Pei-Ann Lin,[1] Junghyup Suh,[1] Michele Pignatelli,[1] Roger L. Redondo,[1,2] Tomás J. Ryan,[1,2] Susumu Tonegawa[1,2]†

Memories can be unreliable. We created a false memory in mice by optogenetically manipulating memory engram–bearing cells in the hippocampus. Dentate gyrus (DG) or CA1 neurons activated by exposure to a particular context were labeled with channelrhodopsin-2. These neurons were later optically reactivated during fear conditioning in a different context. The DG experimental group showed increased freezing in the original context, in which a foot shock was never delivered. The recall of this false memory was context-specific, activated similar downstream regions engaged during natural fear memory recall, and was also capable of driving an active fear response. Our data demonstrate that it is possible to generate an internally represented and behaviorally expressed fear memory via artificial means.

Science AAAS

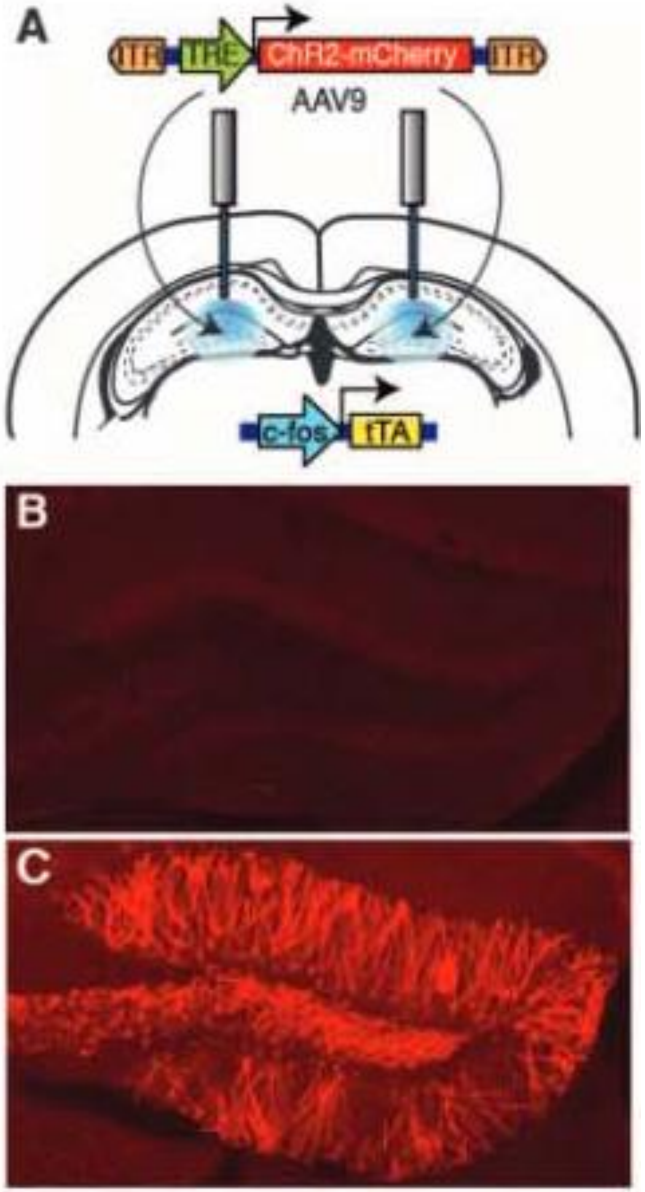
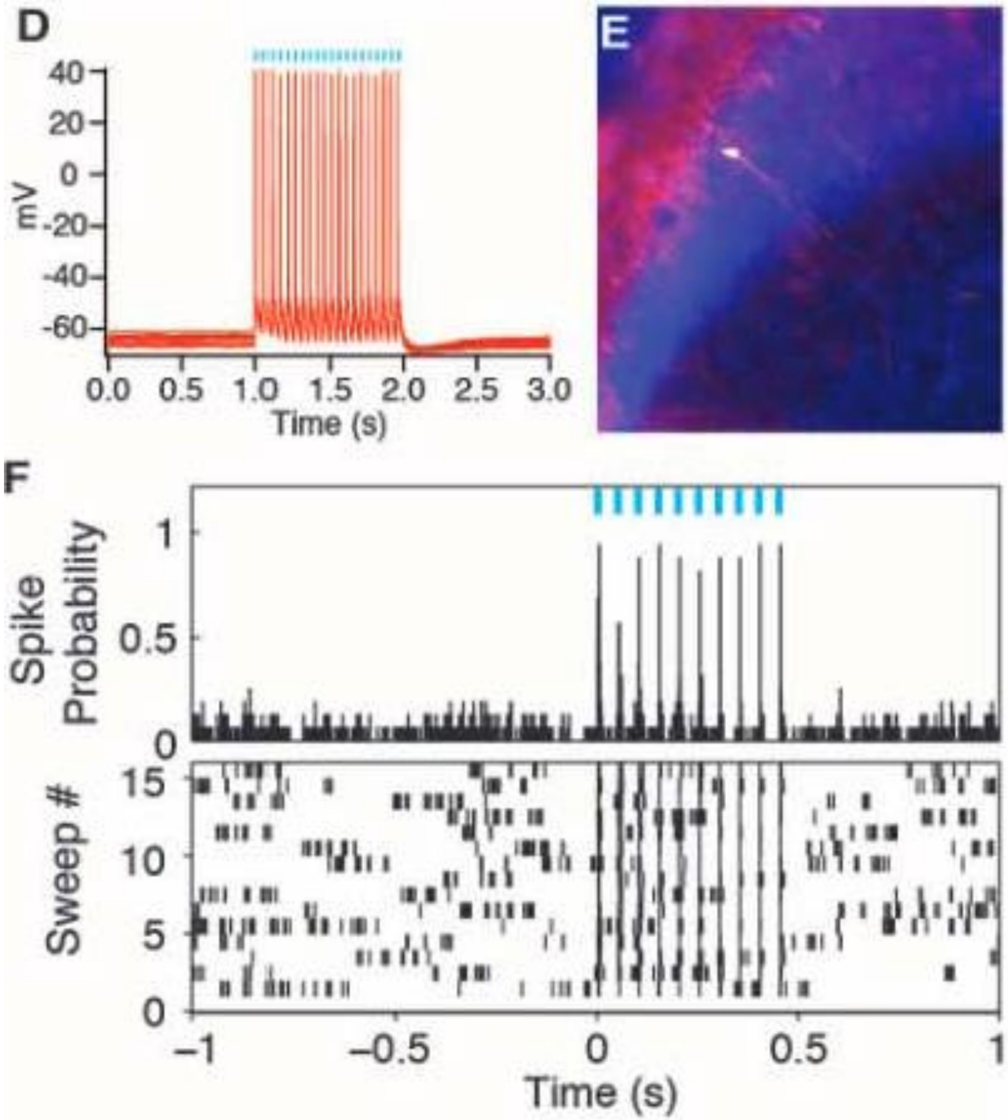
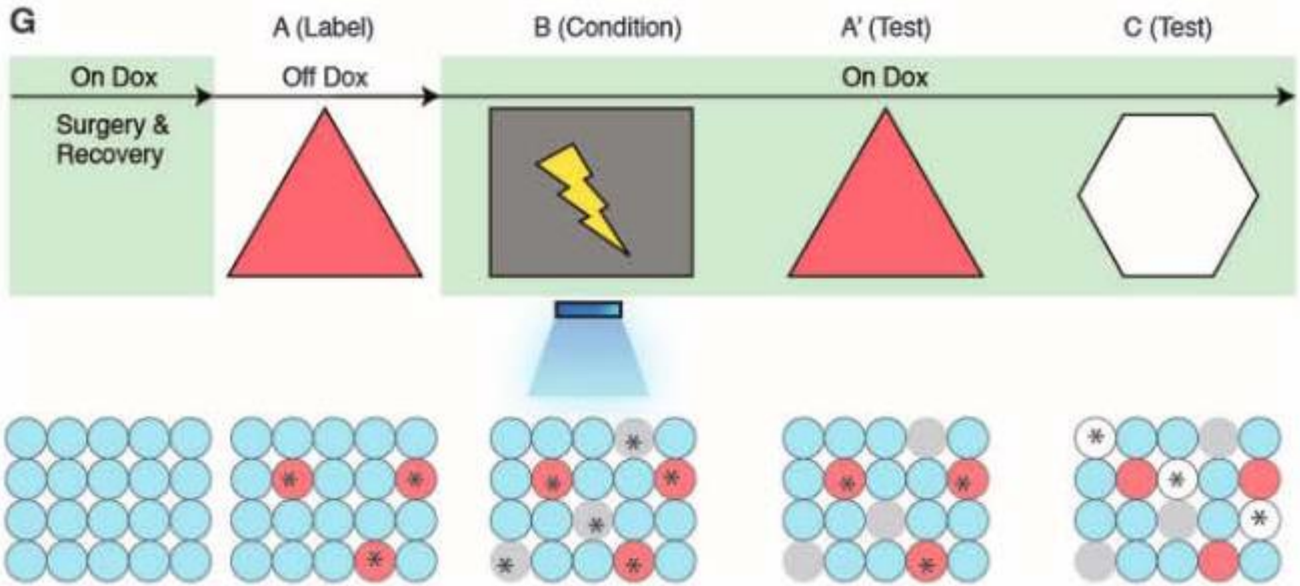


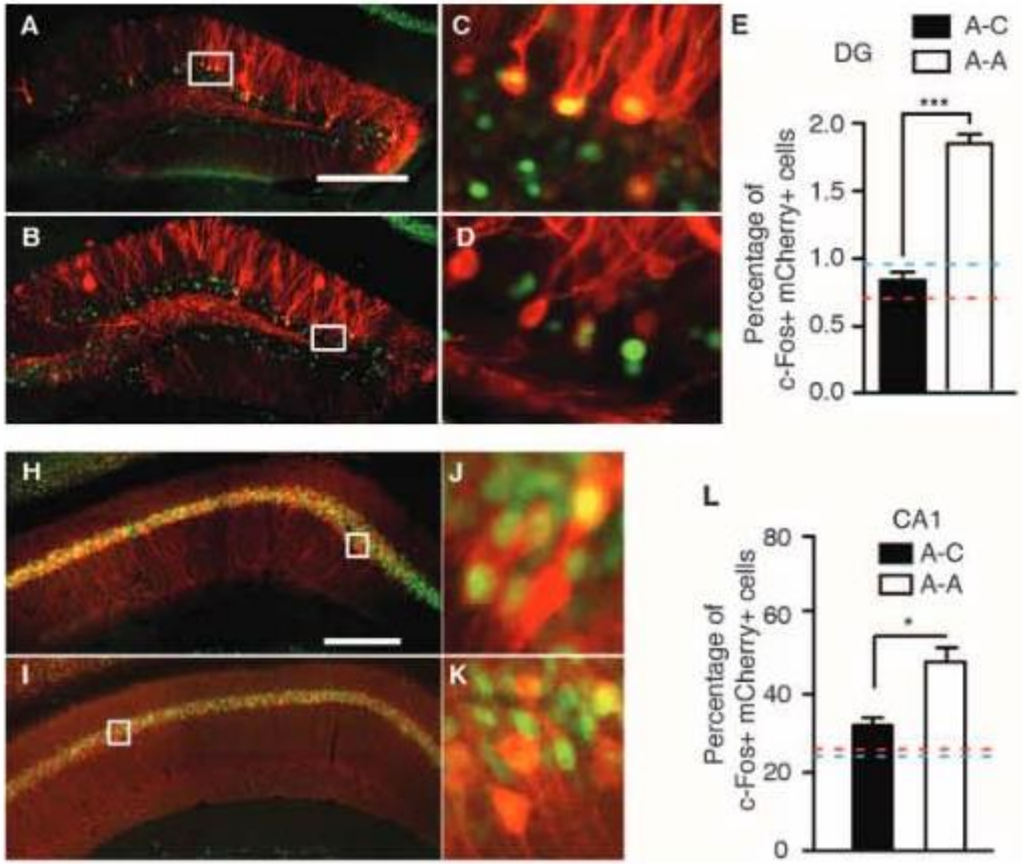
Fig. 1. Activity-dependent labeling and light-activation of hippocampal neurons, and the basic experimental scheme. (**A**) The c-fos-tTA mice were bilaterally injected with AAV_9-TRE-ChR2-mCherry and implanted with optical fibers targeting DG. (**B**) While on Dox, exploration of a novel context did not induce expression of ChR2-mCherry. (**C**) While off Dox, exploration of a novel context induced expression of ChR2-mCherry in DG. (**D**) Light pulses induced spikes in a CA1 neuron



in DG. (**D**) Light pulses induced spikes in a CA1 neuron expressing ChR2-mCherry. The recorded neuron is shown labeled with biocytin in (**E**). (**F**) Light pulses induced spikes in DG neurons recorded from a head-fixed anesthetized c-fos-tTA animal expressing ChR2-mCherry. (**G**) Basic exc-fos-tTA animal expressing ChR2-mCherry. (**G**) Basic experimental scheme. Post-surgery mice were taken off Dox and allowed to explore context A in order to let DG or CA1 cells become labeled with ChR2-mCherry. Mice were put back on Dox and fear conditioned in context B with simultaneous delivery of light pulses. Freezing levels were then measured in both the original context A and a novel context C. The light green shading indicates the presence of Dox in the diet during corresponding stages of the scheme. Prime indicates the second exposure to a given context. The yellow lightning symbol and blue shower symbol indicate foot shocks and blue light delivery, respectively. Red circles represent neurons encoding context A that are thus labeled with ChR2-mCherry. Gray and white circles represent neurons encoding context B and C, respectively. Asterisks indicate neurons activated either by exposure to context or light stimulation.

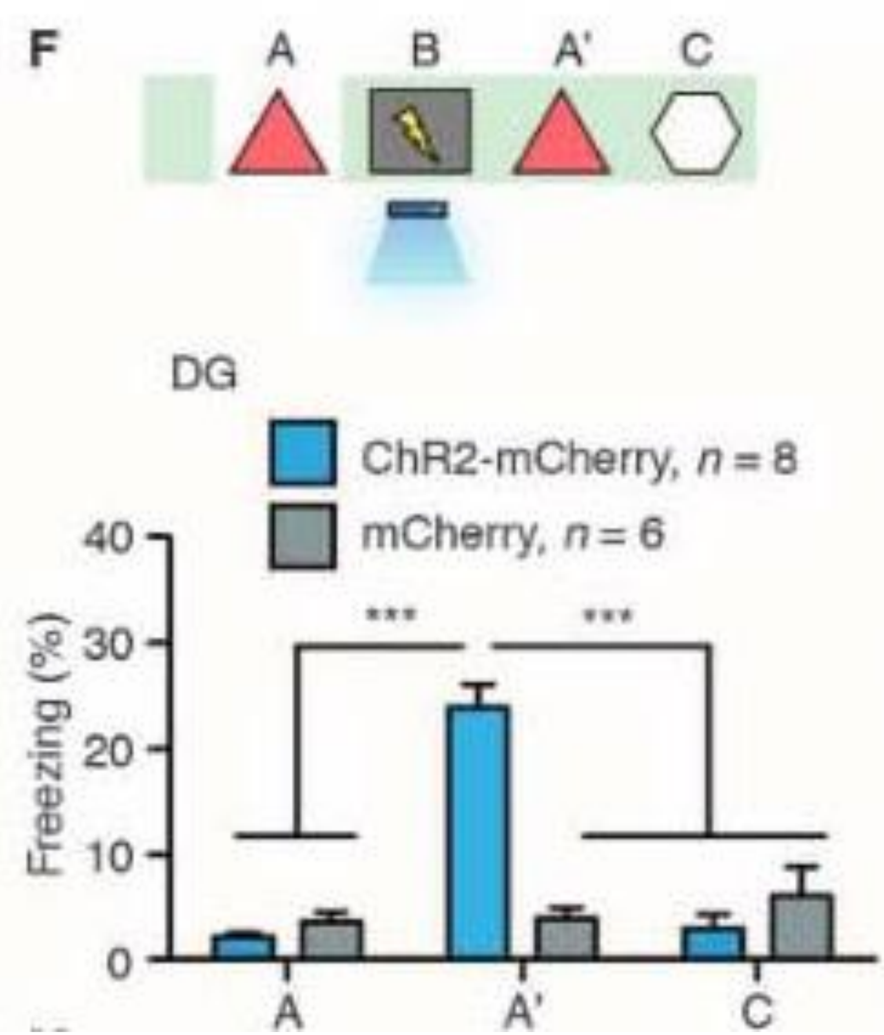
G





(**A** to **E**) c-fos-tTA mice injected with AAV_9-TRE-ChR2-mCherry in the DG were taken off Dox and exposed to context A in order to label the activated cells with mCherry (red), then put back on Dox and exposed to the same context A [(A) and (C)] or a novel context C [(B) and (D)] 24 hours later so as to let activated cells express c-Fos (green). Images of the DG from these animals are shown in (A) to (D), and the quantifications are shown in (E) ($n = 4$ subjects each; $^{***}P < 0.001$, unpaired Student's t test). Blue and red dashed lines indicate the chance level of overlap for A-A and A-C groups, respectively. (**F**) (Top) Training and testing

Pattern overlap is less in DG and more in CA1



(F) (Top) Training and testing scheme of animals injected with AAV$_9$-TRE-ChR2-mCherry or AAV$_9$-TRE-mCherry. Various symbols are as explained in Fig. 1. (Bottom) Animals' freezing levels in context A before fear conditioning and in context A and C after fear conditioning [n = 8 subjects for ChR2-mCherry group, and n = 6 subjects for mCherry group; ***P < 0.001, two-way analysis of variance (ANOVA) with repeated measures followed by Bonferroni post-hoc test]. **(G)**

Interim summary

- DG neurons activated by a neutral context could be made to have aversive valence if they were optogenetically stimulated during fear conditioning.
- This was not the case for CA1 neurons
- Proper controls done
- Heteroassociation in DG may be stronger because of less pattern overlap
- Consistent with network models of memory

Conclusions

- Hebbian synapses have properties of a memory substrate
- Models offer an explanation for how complex patterns could be stored and recalled
- Biological experiments so far are consistent with these models