Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function
Michael E. Hasselmo* and Bradley P. Wyble

Acetylcholine again!

- thought to be involved in learning and memory
- thought to be involved dementia (Alzheimer's disease)
A few words on neuromodulation!

Can it be defined?

* **Spatial distribution**: neuromodulators often arise from brain nuclei that project widely to large numbers of brain regions

* **Time course of action**: the actions of neuromodulators are often considered to be slower than those of classic neurotransmitters

* **Functionality**: absence of presence of neuromodulators in given behavioral situations; modulation of existing neural function

* Neuromodulators have a large **variety of effects**: they change intrinsic neural properties; modulate synaptic events; modulate learning and many others.

* Some neurotransmitters, like GABA or Acetylcholine can be regarded as **neurotransmitters** or as **neuromodulators** depending on the nature of the receptors they act on.
Acetylcholine: arises from several nuclei each projecting to targeted brain areas
Acts on nicotinic and muscarinic receptors
Thought to be important for learning and attentional processing
Examples:
  * in humans, the muscarinic antagonist scopolamine impairs list learning
  * in rats, certain memory tasks (watermaze, short term memory) are impaired by scopolamine
  * however, lesions of cholinergic nuclei can often not reproduce these data
  * loss of cholinergic innervation thought to be implicated in memory loss in Alzheimer’s disease
Dopamine
* Loss of dopaminergic neurons is associated with Parkinson disease
* Increase of dopaminergic activity can be associated with Schizophrenia
* Activity of dopaminergic neurons in VTA has been shown to increase during behaviorally relevant stimuli, and are thought to be important for reward associations
**Noradrenaline (NA)**
* NA neurons in the locus coeruleus project all over the brain
* NA has been associated with “signal-to-noise” ratio and signal-detection capabilities
Serotonin
Example: Modulation of signal-to-noise ratio (noradrenaline)

NA present

NA absent
Some commonly observed neuromodulatory effects:

* Cholinergic agonists can evoke oscillatory activity in hippocampal slices
* Oscillatory activity in the hippocampus of behaving rats depends on cholinergic inputs
* Pyramidal cells in hippocampus and cortex are often depolarized by ACh and NA
* Synaptic potentials can be modulated (increased or decreased) by ACh or NA
* Long term potentiation is modulated by ACh and NA

and many others ..

* Rats are impaired in long-term and short term memory experiments when certain neuromodulatory effects are blocked
* Rats show attentional deficits when cholinergic modulation is decreased

etc …
Most models of human memory function are interpretive—they help us understand behavioral data and guide behavioral experiments.

The model presented here is mechanistic—directly addressing the physiological and anatomical substrates of performance in human memory tasks such as free recall and recognition.

Adresses these questions by:

1. by simulating specific human memory tasks, such as free recall and recognition

2. by addressing a current issue in human memory modeling—the list strength effect

3. by explicitly modeling the effect of the cholinergic antagonist scopolamine on human memory function, and

4. by generating an experimentally testable prediction about the effect of scopolamine on paired associate learning.
Why model the effects of drugs?

Modeling drug effects on memory function allow us to link effects at a cellular level to effects at a behavioral level.
Why model the effects of drugs?

To test any model, you need to perturb it! One perturbation that can be done in humans is a change in neural and synaptic function due to drugs.

You have to:

1) have some idea of how the brain function you are looking at is implemented by a neural circuit

2) know the effect of your drug in that neural circuit

3) be able to correlate the function of your circuit with experimental observations
Example we have talked about before

1) Observable behavior: gill withdrawal after siphon touch
Example we have talked about before

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2) Neural circuit underlying the behavior has been identified
Example we have talked about before

1) Observable behavior: gill withdrawal after siphon touch

2) Neural circuit underlying the behavior has been identified

3) Manipulation of neural circuit leads to observable change in behavior
Example we have talked about before

1) Observable behavior: gill withdrawal after siphon touch

2) Neural circuit underlying the behavior has been identified

3) Manipulation of neural circuit leads to observable change in behavior

The manipulation can be used to test how well established the relationship between the neural circuit (or a model thereof) and the behavior is.
Acetylcholine acts on two types of receptors in the brain: muscarinic and nicotinic.

Scopolamine is a muscarinic antagonist

This means that when present, scopolamine binds to the muscarinic receptor without activating it. It prevents the binding of acetylcholine to the receptor and thus the activation of the receptor.
Scopolamine impairs encoding but not retrieval, free recall but not recognition.

Learn list #1

Table
Car
Plant
Flower
Buddy
Hammer
Chair
.
Scopolamine impairs encoding but not retrieval, free recall but not recognition.

Learn list #1

Scopolamine injection

Prevents ACh from activating muscarinic receptors

Table
Car
Plant
Flower
Buddy
Hammer
Chair
Scopolamine impairs encoding but not retrieval, free recall but not recognition.

Learn list #1
Scopolamine injection
Recall list #1 (no effect)
Recognition list #1 (no effect)

List words on list
Prevents ACh from activating muscarinic receptors
Recognize if words were on list

Table
Car
Plant
Flower
Buddy
Hammer
Chair
Scopolamine impairs encoding but not retrieval, free recall but not recognition.

Learn list #1

Scopolamine injection

Recall list #1 (no effect)
Recognition list #1 (no effect)

Learn list #2

List words on list

Prevents ACh from activating muscarinic receptors

Recognize if words were on list

Table
Car
Plant
Flower
Buddy
Hammer
Chair

Bed
Apple
Nail
Friend
Scopolamine impairs encoding but not retrieval, free recall but not recognition.

Prevents ACh from activating muscarinic receptors.

List words on list

Recognize if words were on list
Scopolamine impairs encoding but not retrieval, free recall but not recognition.

Effect on recall/recognition:
- Learn list #1
- Scopolamine injection
- Recall list #1 (no effect)
- Recognition list #1 (no effect)

Effect on learning:
- Learn list #2
- Recall list #2 (strong impairment)
- Recognition list #2 (no effect)
Cellular effects of ACh in the hippocampus

1) **Suppresses synaptic transmission**
2) Depolarizes pyramidal cells
3) Suppresses neuronal adaptation
4) Enhances LTP

Less feedback excitation (association fibers blocked)
Cellular effects of ACh in the hippocampus

1) Suppresses synaptic transmission

2) **Depolarizes pyramidal cells**

3) Suppresses neuronal adaptation

4) Enhances LTP

Pyramidal cells more easily excitable because they are closer to threshold

\[ V_m \]

\[ -75 \]

\[ -65 \]

\[ \text{time} \]

\[ \text{ACh} \]
Cellular effects of ACh in the hippocampus

1) Suppresses synaptic transmission

2) Depolarizes pyramidal cells

3) **Suppresses neuronal adaptation**

4) Enhances LTP

Pathway:
- ACh injection
- Pyramidal cells spike more when activated
Cellular effects of ACh in the hippocampus

1) Suppresses synaptic transmission
2) Depolarizes pyramidal cells
3) Suppresses neuronal adaptation
4) **Enhances LTP**

“learning rate” is increased
Cellular effects of ACh in the hippocampus

1) Suppresses synaptic transmission
2) Depolarizes pyramidal cells
3) Suppresses neuronal adaptation
4) Enhances LTP

Overall:

1) Afferent or outside inputs dominate in the presence of ACh
2) Cells are more excitable and respond with more action potential to afferent input
3) Plasticity between pyramidal cells is enhanced
Scopalamine prevents all these effects!

Cellular effects of ACh in the hippocampus

1) Suppresses synaptic transmission
2) Depolarizes pyramidal cells
3) Suppresses neuronal adaptation
4) Enhances LTP

Overall:
1) Afferent or outside inputs dominate in the presence of ACh
2) Cells are more excitable and respond with more action potential to afferent input
3) Plasticity between pyramidal cells is enhanced
Effects of scopolamine administration in this model

Scopolamine blocks effects of acetylcholine in the hippocampus

1. Blocks synaptic suppression = Stronger feedback (retrieval dominates)
2. Blocks depolarization = Less depolarization
3. Blocks suppression of adaptation = Less sustained firing
4. Blocks enhanced modification = Less synaptic change
Hippocampal anatomy
Hippocampal anatomy and model
Hippocampal anatomy and model

Medial septum: provides ACh to hippocampus

Autoassociative network: stores patterns

Self-organization: external input imposed only on input layer (dentate gyrus) but not on target layer (CA3)

hetero-associative: association between two patterns (CA1 and CA3)
Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

hebbian learning rule
self-organization

Let's look at the details slowly
Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

Hebbian learning rule
self-organization

Hebbian learning rule
autoassociation

Neocortex (input and output)

Medial septum
Regulation of learning dynamics

Hippocampus
Self-organization

Region CA1
Comparison

Region CA3
Autoassociative Recall

Dentate gyrus
Self-organization

Entorhinal cortex
Input and Output

A

B

CA1

IV

III

II

CA3

Dentate gyrus

Entorhinal cortex

Lets look at the details slowly
Let's look at the details slowly

**Entorhinal cortex**
- Input pattern: (1,0,0,0,1,1,1)
- Self-organized pattern: (0,0,1,0,0,1,0)
- Hebbian learning rule
- Self-organization

**Dentate gyrus**
- Self-organized pattern: (0,0,1,0,0,1,0)

**CA3**
- Autoassociation of pattern transmitted by CA3: (0,0,1,0,0,1,0)
- Hebbian learning rule
- Auto-association

**CA1**
- Comparison between input imposed by EC and pattern in CA3: (0,0,1,0,0,0,1)
Lets look at the details slowly

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)
Lets look at the details slowly

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)
1) Neurons in layer 2 are activated by layer neurons and random synaptic weights.

2) Inhibitory neuron is activated by all neurons in layer 2.

3) Inhibitory neuron inhibits all neurons in layer 2.

4) Hebbian learning rule strengthens weights between active layer 1 and layer 2 neurons.

5) Layer 2 neuron responds strongly to layer 1 input.

Layer 1
- Small, random synaptic weights

Layer 2
- Inhibitory neuron

Inhibitory neuron

Layer 2
- Inhibitory neuron

Layer 1
- Strengthened synaptic weights

Layer 2

Mathematical formulas:

- $X_{L2}(i) = \sum w_{ij}X_{L1}(j)$
- $X_{IN} = 1/N \sum X_{L2}(j)$
- $X_{L2}(i) = \sum w_{ij}X_{L1}(j) - X_{IN}$
- $w_{ij} = w_{ij} + X_{L2}(j)X_{L1}(i)$
Let's look at the details slowly.

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
Autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
Comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Hebbian learning rule accompanied by inhibition creates sparse representation in DG.

Hebbian learning rule stores association between elements of the same pattern.
Lets look at the details slowly

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
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comparison between input imposed by EC and pattern in CA3
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Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)
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Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)
Let's look at the details slowly.

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
Autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
Comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Hebbian learning rule accompanied by inhibition creates sparse representation in DG

Self-organization

Hebbian learning rule stores association between elements of the same pattern

Hebbian learning rule stores association between the pattern in CA3 and the pattern in CA1

Hebbian learning rule accompanied by inhibition creates sparse representation in CA1
Incomplete input pattern

Entorhinal cortex
Input pattern \((1,0,0,0,1,1,1)\)

Dentate gyrus
Self-organized pattern \((0,0,1,0,0,1,0)\)

CA3
autoassociation of pattern transmitted by CA3
\((0,0,1,0,0,1,0)\)

CA1
comparison between input imposed by EC and pattern in CA3
\((0,0,1,0,0,0,1)\)

Entorhinal cortex
Input pattern \((1,0,0,0,1,1,1)\)

existing synaptic weights transmit pattern to DG

hebbian learning rule
self-organization

hebbian learning rule
association

EC: Output pattern

CA1 activates completed output pattern in EC

association fibers recall previously stored pattern
How does the model know when to learn???

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

When input pattern from CA3 and pattern in CA1 (from EC) MATCH the previously stored association, activity level in CA1 is high!
How does the model know when to learn???

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

When input pattern from CA3 and pattern in CA1 (from EC) DON'T match the previously stored association, activity level in CA1 is low!
How does the model know when to learn???

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

EC: Output pattern

ACh

hebbian learning rule
self-organization

hebbian learning rule
autoassociation

hebbian learning rule
association

inhibitory
How does the model know when to learn???

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern
transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed
by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

hebbian learning rule
self-organization

hebbian learning rule
autoassociation

hebbian learning rule
association

EC: Output pattern

NO MATCH

ACh

Non-match:
ACh neurons have high output:
- neurons depolarized
- LTP high
- association fiber synaptic transmission supressed
- learning is ON

Inhibitory
How does the model know when to learn???

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

Dentate gyrus
Self-organized pattern (0,0,1,0,0,1,0)

CA3
autoassociation of pattern transmitted by CA3
(0,0,1,0,0,1,0)

CA1
comparison between input imposed by EC and pattern in CA3
(0,0,1,0,0,0,1)

Entorhinal cortex
Input pattern (1,0,0,0,1,1,1)

EC: Output pattern recall

MATCH

ACh

Match:
ACh neurons have low output:
- neurons not depolarized
- LTP low
- association fiber synaptic transmission not suppressed: recall mode

Learning is OFF
What is being modeled? List learning in humans

Experiment

List #1
- fish
- chair
- dish towel
- apple
- lamp
- ...

List #2
- chalk
- watch
- ...

What is being modeled? List learning in humans

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Model</th>
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</thead>
<tbody>
<tr>
<td>List #1</td>
<td>fish</td>
</tr>
<tr>
<td></td>
<td>chair</td>
</tr>
<tr>
<td></td>
<td>dishtowel</td>
</tr>
<tr>
<td></td>
<td>apple</td>
</tr>
<tr>
<td></td>
<td>lamp</td>
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<td></td>
<td>...</td>
</tr>
<tr>
<td>List #2</td>
<td>chalk</td>
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<tr>
<td></td>
<td>watch</td>
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<tr>
<th>Context #1</th>
<th>Item #1 - 10011000</th>
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<tbody>
<tr>
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<td>Item #2 - 01001001</td>
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<td>Item #3 - 01010001</td>
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<td>Item #4 - 11000100</td>
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<td>Item #5 - 00110010</td>
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<th>Item #1 - 01010100</th>
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<td>Item #2 - 10001100</td>
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0100100 .. neural activation pattern
What is being modeled? List learning in humans

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<td>Context #2</td>
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<td>watch</td>
<td>Item #1 - 01010100</td>
</tr>
<tr>
<td>...</td>
<td>Item #2 - 10001100</td>
</tr>
</tbody>
</table>

0100100 .. neural activation pattern
Free **recall**: input to model is context and model recalls items. This corresponds to telling subject to recall items from a given list.

Scopolamine impairs encoding but not retrieval, free recall but not recognition.

0100100 .. neural activation pattern
Recognition: input to model is item and model recalls context. This corresponds to asking subject which list a given item belonged to.

Scopolamine impairs encoding but not retrieval, free recall but not recognition.

0100100 .. neural activation pattern
external input $A_i$

association fibers $w_{ij}$

pyramidal cells with activation $a_i$

single inhibitory neuron which inhibits all pyramidal neurons in proportion to the average activity
external input $A_i$

association fibers $w_{ij}$

pyramidal cells with activation $a_i$

single inhibitory neuron which inhibits all pyramidal neurons in proportion to the average activity

associative memory in region CA3 stores associations between context and items as well as associations between elements of each.

*Associative weights between context units are stronger because context is repeatedly presented!*
Equations!

change in activation (what we call membrane potential)

\[ \Delta a_i = A_i - \eta a_i + (E_{Na} - a_i) \sum_j x_j W_{ij} [a_j - \Theta_a]_+ + (E_{Cl} - \]

\[ a_i) \sum_j x_j H_{ij} [a_i - \Theta_b]_+ + \mu c_i (E_K - a_i) \]

inhibitory synaptic inputs

models adaptation as a function of calcium influx

calcium influx as a function of activation

\[ \Delta c_i = \gamma [a_i - \Theta_c]_+ - \Omega c_i \]
More equations!

\[ \Delta W_{ij} = \kappa (1 - \chi_s (1 - \psi))(s_i - \theta_w) + \omega_{\text{pre}} W_{ij} ([s_j - \theta_w]_+ - \omega_{\text{post}} W_{ij}) \]

\[ \Delta s_i = \phi [a_i - \theta_a]_+ - \beta s_i \]

\[ \Delta s_j = \phi [a_j - \theta_a]_+ - \beta s_j \]
More equations!

\[ \Delta W_{ij} = \kappa(1 - \chi_s(1 - \psi))(s_i - \theta_w) + \omega_{\text{pre}} W_{ij}(s_j - \theta_w) + \omega_{\text{post}} W_{ij} \]

- change in synaptic weight
- slow change in postsynaptic activity
- slow change in presynaptic activity
- ACh modulation
- learning threshold for postsynaptic activity
- learning threshold for presynaptic activity
- learning rate
More equations!

\[ \Delta W_{ij} = \kappa (1 - \chi_s (1 - \psi)) ([s_i - \theta_w] + \omega_{pre} W_{ij}) ([s_j - \theta_w]_+ - \omega_{post} W_{ij}) \]

- Learning rate
- Learning threshold for postsynaptic activity
- Learning threshold for presynaptic activity
- Decay of synaptic strength necessary for self-organization
- High in CA3 for auto-associative learning
- Low in DG to allow self-organization
learning ruled allowed both associative learning and self-organization.

for self-organization, plasticity of inhibitory connections was also necessary

for self-organization, learning thresholds were lower (because NO external input activates second layer of neurons, thus, activations will be lower)
Time Course Display of Free Recall in Region CA3

Neuron receives DG input
Time Course Display of Recognition of Items by Recalling Context

Region CA3

- Context
- Item #1
- Item #2
- Item #3

Encode Item #1 w/context | Encode Item #2 w/context | Item #1 Recognized | Item #2 Recognized | Item #3 Not Recognized

400 steps

Neuron receives DG input

EC
DG
CA3
CA1
Impaired Encoding, Spared Retrieval

<table>
<thead>
<tr>
<th>Input Patterns List 1</th>
<th>Successful Recall: List 1</th>
<th>Input Patterns List 2</th>
<th>Failed Recall: List 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entorhinal cortex layer II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Region CA3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region CA1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entorhinal cortex layer IV</td>
<td></td>
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Time Steps 0 1600 3200 4800 6400

Scopolamine

EC II
DG
CA3
EC IV
CA1
EC II
Impaired Recall, Spared Recognition

<table>
<thead>
<tr>
<th>Input Patterns</th>
<th>Free Recall Failure</th>
<th>Recognition Successful</th>
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<tr>
<td>Entorhinal cortex layer II</td>
<td>![Pattern]</td>
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<td>![Pattern]</td>
<td>![Pattern]</td>
</tr>
<tr>
<td>Entorhinal cortex layer IV</td>
<td>![Pattern]</td>
<td>![Pattern]</td>
</tr>
</tbody>
</table>

Time Steps 0 1200 2400 3600

Time — Scopolamine —

Diagram:

- EC II
- DG
- CA3
- EC IV
- CA1
- EC II
Free Recall

Number of Words Recalled

- Control
- Scopolamine

Ghoneim & Mewaldt (1975)

Model
A word on recalling multiple patterns sequentially!

context presented - recall pattern 1 - recall pattern 3 - recall pattern 2 - recall pattern 5 --

each pattern has formed an attractor! We learned that once a network has reached an attractor, it cannot move out of it. So how does this work then?
1) Context presented

2) Context neurons activate many item neurons

3) because of differences in synaptic weights (due to random initial conditions), one pattern is more activated than others. Global inhibition deactivates neurons belonging to other patterns.

4) spike-adaptation gradually reduces activity of the recalled item, and a different item can be recalled because it is freed from inhibition
Stress, memory and neurogenesis

In the dentate gyrus of the young adult rat hippocampus, for example, there are about 1,000,000 granule cells, and about 10,000 new neurons are generated per day, of which about 40% survive to maturation (McDonald and Wojtowicz, 2005). The dentate gyrus is critically situated within the so-called trisynaptic circuit in the hippocampus (see Fig. 1), so that information flows from the rest of the brain, via the entorhinal cortex (EC), through the dentate gyrus and CA3/CA1 subregions. On the other hand, there are also short-circuit connections from the EC to the CA3/CA1 by-passing the dentate gyrus. Thus not all forms of learning and memory may be dependent upon the dentate gyrus, and hence dependent upon neurogenesis. Indeed, empirical evidence from studies using selective ablation and/or genetic manipulation of the dentate gyrus supports a role for this structure, and hence for the entire trisynaptic circuit, in rapid learning of novel contexts (Nakashiba et al., 2008) and in maintaining distinct representations of similar events such as nearby spatial representations (Gilbert, Kesner and Lee, 2001), while the short-circuit pathways by-passing the dentate gyrus are sufficient to support paired associates learning and incremental spatial learning ([Nakashiba et al., 2008] and [Gilbert and Kesner, 2003]). Thus, the role of neurogenesis is most likely tied to the dentate-gyrus specific learning and memory functions.
A. High inhibition in DG limits firing to only most excited GCs. Mossy fiber output only targets sparse set of downstream CA3 neurons. Sparse set of CA3 neurons now selected to encode cortical inputs.

B. Context 1: Sparse set of GCs represent one context. Context 2: Orthogonal set of GCs represent different context.

C. Animal exposed to object in one location. Animal must be able to discriminate old location from nearby foil.

D. Subset of GCs show multiple place fields in one context. Same subset of GCs show different place fields in new context.
Environment | Neurogenesis | Pattern separation | Pattern completion | Adaptive response | Maladaptive response
---|---|---|---|---|---
Enrichment, Exercise, Learning, Antidepressants | Increased neurogenesis | DG/OB | CA3/PC | Discrimination, Cognitive flexibility | Excessive attention to details (Autism, OCPD ?)
Normal | | | | |
Stress, Aging, Sensory deprivation | Decreased neurogenesis | | | Generalization | Excessive generalization (Anxiety, PTSD, MCI ?)
Nottebohm (2002) suggested that the newly born neurons may be recruited preferentially for storing new memories, thereby protecting old memories from interference.

Consistent with this hypothesis, Wiskott, Rasch and Kempermann (2006) demonstrated in a simple neural network model that the addition of highly plastic new neurons does effectively prevent new learning from interfering catastrophically with older memories.

Conversely, Feng et al. (2001) proposed that neurogenesis is important for clearing out older memories once they are consolidated, and several modelers have demonstrated in abstract neural network models that neuronal turnover improves acquisition by helping to discard older memories.
Fig. 1 – The major subregions and connections within the hippocampus. Most of the communication with the rest of the brain occurs via reciprocal connections with the entorhinal cortex (EC). Input pathways are shown with blue arrows; feedback pathways are shown with purple arrows. The hippocampus, via its extensive connections with many brain regions, is optimally positioned for both encoding and recall of complex associations. The EC in turn projects via the trisynaptic circuit through the dentate gyrus, CA3 and CA1 subregions and then back to the EC. There are also more direct pathways within the hippocampus from the EC to the CA3/CA1, bypassing the dentate gyrus. The dentate gyrus is neurogenic through the lifespan, and is therefore well positioned to influence coding throughout the hippocampus, by contributing a distinct neural encoding of context that constantly evolves over time, as new neurons constantly mature and become active.
Spatial learning in the Morris water maze is disrupted by hippocampal lesions (Morris et al., 1990) but not by irradiation (Snyder et al. 2005; Wojtowicz et al., 2008).

While irradiated animals learn the water maze at a normal rate, their long-term memory retention of the hidden platform location is greatly impaired relative to controls when they are re-tested four or more weeks later (Snyder et al., 2005).

Animals lacking new hippocampal neurons show deficits on trace conditioning (Shors et al., 2001), contextual fear conditioning and delayed non-match to sample (DNMS) at long delays (Winocur et al., 2006; Wojtowicz et al., 2008), while performing normally on corresponding non-hippocampal control tasks, delay conditioning (Shors et al., 2001), cued fear conditioning and DNMS at short delays (Winocur et al., 2006), respectively.

Moreover, voluntary running enhances neurogenesis in rodents (van Praag et al., 1999) and correlates weakly with improved performance on contextual fear conditioning (Wojtowicz et al., 2008).
These include stress-related reduction in neurogenesis (e.g. Gould et al., 1998; McEwen and Magarinos, 2001), and exercise and environmental enrichment-related increases in neurogenesis (van Praag et al., 1999; Nilsson et al., 1999; Olson et al., 2006; Pereira et al., 2007).

In summary, we predict two important functions of hippocampal neurogenesis, namely, (1) to create distinct representations of similar events, thereby minimizing interference between highly similar memories and between memories acquired at different periods of time, and (2) to create a gradually evolving representation of spatial, temporal and other contextual cues that serves to bind together elements of a memory into coherent episodic memory traces.
Fig. 2. - The hippocampus modulates motivational, emotional and stress-related responses via inhibitory feedback control over the hypothalamic-pituitary-adrenal (HPA) axis, and via gating the flow of information in motivational pathways from the prefrontal cortex to nucleus accumbens (for a review, see Becker and Wojtowicz, 2007).
The learning equations implement a form of simple Hebbian learning in the perforant path (EC-to-dentate gyrus, EC-to-CA3 and EC-to-CA1 connections), heteroassociative Hebbian learning in the CA3-to-CA1 connections and temporal associative learning in the CA3 recurrent collaterals.

The model is built upon several key assumptions regarding hippocampal coding: (1) there is sparse coding (low activity levels) in all regions; (2) the projection pathway from the DG to CA3 (mossy fiber pathway) is strong (very high synaptic strengths) and sparse (very low probability of connectivity); (3) the CA3 pyramidal are highly interconnected via recurrent collaterals; (4) the trisynaptic pathway involving the dentate gyrus participates in encoding, not recall; and (5) the CA3 collaterals are active during recall but not encoding.
1. During encoding, dentate granule cells are active whereas during retrieval they are relatively silent.

2. During encoding, activation of CA3 pyramidals is dominated by the very strong mossy fiber inputs from dentate granule cells.

3. During retrieval, activation of CA3 pyramidals is driven by direct perforant path inputs from the EC combined with time-delayed input from CA3 via recurrent collaterals.

4. During encoding, activation of CA1 pyramidals is dominated by direct perforant path inputs from the EC.

5. During retrieval, CA1 activations are driven by a combination of perforant path inputs from the EC and Shaffer collateral inputs from CA3.
New neurons are added only to the DG, and the DG drives activation in the hippocampal circuit only during encoding, not during retrieval. Thus, the new neurons contribute to the formation of distinctive codes for novel events, but not to the associative retrieval of older memories.
**Paired Associate learning:** the learning of syllables, digits, or words in pairs (as in the study of a foreign language) so that one member of the pair evokes recall of the other.

Each model was trained on a set of 10 paired associates consisting of randomly generated patterns on Day 1, followed by a simulated retention interval of 4 weeks, and then a final cued recall test of the original paired associates. During the retention interval, new unrelated items are learned, a potential source of interference with the original paired associates.
Each of the models simulated had the following architecture: 200 input (EC) neurons, 1000 dentate gyrus neurons, 300 CA3 neurons and 400 CA1 neurons.

Twenty repetitions of each model were run, to generate results of 20 simulated “subjects”. Three different versions of the model were compared: (1) no neuronal turnover; (2) neural turnover and no preferential bias toward new neurons during encoding; i.e. every neuron in the dentate layer has an equal chance of becoming active when a novel pattern is to be encoded; (3) a model with neural turnover and preferential recruitment of new neurons for new memory formation; that is, new neurons were more likely to be selected for activation when a new memory was to be stored.

Each model was first trained on a set of paired associates, and then on subsequent weeks, the passage of time and consequent decay of old memories was simulated by exposing the model to a set of random, unrelated items. On each week, the model was then tested for retention of the original set of paired associates. For each of the three models, the rate of neuronal turnover was
Neuronal turnover was simulated by randomly selecting a fixed percentage of the dentate layer neurons, and rerandomizing their incoming weights from the EC, and reconnecting them randomly to a different subset of CA3 cells. The percentage of “new neurons” created in this manner was either 0, 25, 50, 75, or 100.
Fig. 3 – Effects of neurogenesis on the percentage correctly recalled paired associates across a simulated retention interval of 4 weeks. Top curve: model performance with no neuronal neurogenesis. Middle and bottom curves: performance of models in which 2% of neurons per simulated week are randomly replaced during the retention interval. Bottom curve: in addition to neurogenesis, the new neurons are given a bias so that they are more likely to be activated relative to older neurons.