Dopamine in long-term memory formation

Trevor Bekolay, Xuan Choo, Olivia Lin

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Outline

1. Experimental procedure
2. Experimental results
3. Reward systems
4. Long-term memory
5. Questions
Experimental procedure

Two categories of visual cues. Initially we know:

- One category indicates rewarded trials.
- One category non-rewarded (neutral) trials.
Experimental procedure

Memory task - Study phase

<table>
<thead>
<tr>
<th>Cue Present’n (1500ms)</th>
<th>Response (500 – 4500ms)</th>
<th>Number Flash (100ms)</th>
<th>Response (1000ms)</th>
<th>Feedback (1500ms)</th>
<th>Wait Interval (400 – 4400 ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory Task (Unknown to subject)</td>
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</tr>
<tr>
<td>Reward expected</td>
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<tr>
<td>Reward not expected</td>
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<td>Number less than 5</td>
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<tr>
<td>Number more than 5</td>
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</tr>
</tbody>
</table>

Button Legend
Reward system results

- Rewarded trials had faster reaction times than neutral trials.

**Reward anticipation**
- Striatum, left globus pallidus, right substantia nigra
- Insula, anterior cingulate, thalamus

**Reward outcomes**
- Right middle frontal gyrus (BA 10), secondary visual areas, fusiform gyrus, cerebellum, cingulate, thalamus
Reward system results
Immediate recall test phase

- **Cue Present’n (1500ms)**
- **Response (500 ms)**
- **Wait Interval (400 – 4400 ms)**

**Button Legend**
- Green: Picture from reward session
- Blue: Picture not from reward session
Immediate recall test results

Hippocampus, Parahippocampal Gyrus
Experimental procedure

Delayed recall (after 3 weeks) test phase

Diagram:
- **Cue Present’n (1500ms)**
- **Response (500 ms)**
- **Source Question (1500ms)**
- **Response (500 ms)**
- **Wait Interval (400 – 4400 ms)**

**Button Legend**
- **Green**: Remembered picture
- **Red**: Known picture
- **Blue**: New picture
- **Yellow**: Picture from study session
- **Purple**: Picture from test session
Comparison between recognized items vs forgotten items indicated increased activity in the hippocampus for recognized items.
Comparison between rewarded items vs neutral items indicated increased activity in the substantia nigra for rewarded items.
Comparison of the rewarded / neutral pictures vs recognized and forgotten items revealed the following activity changes.
Conclusions

- Reward cues increase activity in dopaminergic system
- Increased dopamine levels enhance episodic memory performance.
Reward system

- Behavioural level
  - rewards reinforce behaviour

- Neural level
  - activates dopaminergic neurons in “reward pathway”
Different types of rewards

Reward outcomes
- Medial frontal cortex

Reward anticipation
- Dorsal and ventral striatum
- Globus pallidus
- Substantia nigra
Dopaminergic projections

Caudate
Putamen

Prefrontal Cortex

Mesostriatal

Mesolimbic

Substantia Nigra

Ventral Tegmental Area

Cingulate Cortex
Medial Orbital Frontal Cortex
Hippocampus
Parahippocampal Gyrus
Amygdala

Mesocortical
Dopaminergic pathways

Mesocortical Pathway

Mesostriatal Pathway

Mesolimbic Pathway
Dopamine! What is it?

- It’s a neurotransmitter (duh!)
  - Modulatory (mainly) instead of excitatory / inhibitory
- It looks like this:
Synthesis of Dopamine

- Starts of as an amino acid L-tyrosine
- Processed to L-DOPA (L-Dihydroxyphenylalanine)
  - This is used to treat Parkinson's patients
  - But has side effects...
- Then becomes Dopamine
- Which in some neurons is further processed to Norepinephrine and then Epinephrine
Primarily function is in the reward system

Activates five types (and their variants) of receptors: D1, D2, D3, D4, D5

- (D1, D5): Memory
- (D2, D3, D4): Motor control

Fun fact! Invertebrates have a reward system too

- Uses Octopamine
Dopamine release sites are places outside the synaptic cleft.

When released, it diffuses in the surrounding fluid, where it is slowly cleared.

Does not directly affect activity of post-synaptic neuron, but changes the behavior of it (more later!) \(^1\)

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Dopamine and Synapses

- What the synapses look like:\(^2\)

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Dopamine & Illnesses

- Parkinsons Disease
- Schizophrenia
- ADHD (Attention deficit hyperactivity disorder)
- Cocaine abuse (increases dopamine production)
- Bipolar disorder
So what does DA do? It’s modulatory! (Huh?)

- It changes the behavior of the post-synaptic neuron without directly affecting the activity

Let’s go to an example:

- The spiny neuron (Gruber et al)\(^3\)

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Dopamine & Modulation

- The spiny neuron:
  - Changes its behavior with dopamine input

![Graph A](image1)  ![Graph B](image2)
So how does this help? Let's check it out!
Example continued:

![Diagram showing modulatory example with Unrewarded target and Rewarded target]

- **Unrewarded target**: Time progression from 0 to 1.5 seconds with target, cortex, and context indicated.
- **Rewarded target**: Time progression from 5.0 to 6.5 seconds with target and context indicated.

**Graphs**

- **Graph B**: Weak cortical input with voltage (V_m) over time from -40 to -80.
- **Spikes/s**: Activity over time from 0 to 1.5 seconds and 5.0 to 6.5 seconds.
Dopamine and the NEF / Nengo

- Models that have already been created with Dopamine modulation
  - Bryan’s Parkinson’s model
  - Simulation of the Gruber spiny neuron
  - Chris’ learning model (although it doesn’t explicitly use dopamine)
Dopamine in the hippocampus

- The hippocampus is modulated by serotonin, norepinephrine and dopamine.

- Dopamine plays a role in long-term potentiation.
Functional description of long-term memory

- Long-term memory
  - Implicit memory
  - Explicit (declarative) memory
    - Semantic memory
    - Episodic memory
Implicit memory is subtle knowledge gained through previous experience without conscious awareness of those experiences.
- e.g. riding a bike, tying your shoe

Explicit (declarative) memory stores facts or "knowledge" – things that can be declared.
Lesion studies show that damage to the basal ganglia and cerebellum most affect implicit memory.
Types of explicit memory

- **Semantic memory** is information about the world, independent of context.
  - Sometimes called memory of “facts.”
  - e.g. an apple is a type of fruit, “big” and “grand” are synonyms

- **Episodic memory** is information that you’ve personally experienced, dependent on context (the time, place, associated emotions etc. of an event).
  - Sometimes called memory of “events.”
  - e.g. what you did last summer, what running feels like
Explicit memory is generally thought to be centralized in the *medial temporal lobes* and *hippocampal formation*.
Biological basis of LTM (Maybe. Probably.)

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Hebbian theory

In 1949, Donald Hebb postulated:

When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased.
Synaptic plasticity

A change in the strength of a synapse is called **synaptic plasticity**.

- **Short term:**
  - Facilitation
    - Arises from a few APs per second
    - Lasts for 10-100 ms
  - Augmentation
    - Arises from a few hundred APs per second
    - Lasts for 10 s
  - Potentiation
    - Arises from a few thousand APs per minute
    - Lasts for 5 min
  - Depression
    - Arises from excessive use of the synapse.

- **Long term:**
  - Long-term potentiation
  - Long-term depression
  - Metaplasticity
Long-term potentiation

Refers to a permanent increase in synaptic strength. Thought to be the biological mechanism for creating memories.
Long-term potentiation phases

- Short-term potentiation
- Early LTP (LTP1)
- Late LTP (LTP2 and LTP3)
Early LTP

- **Induction**
  - Early LTP is induced by a high concentration of calcium ions
  - Important receptors: AMPA and NMDA (Glutamate)
  - Triggers the activation of several enzymes

- **Maintenance**
  - Early LTP is maintained by persistent activation of enzymes
  - Protein kinase C \( \zeta \) allows phosphorylation

- **Expression**
  - Phosphorylation increases AMPA receptor activity
  - Existing nonsynaptic AMPA receptors move in (**no synthesis**)
Retrograde transmission

- Early LTP, as described, happens in the postsynaptic neuron
- Some believe that, after induction, the presynaptic neuron is signalled
- Much is still unknown, but this would fit in nicely with the backpropogation neural network model
Late LTP

- **Induction**
  - Persistent activation of protein kinases induces protein synthesis

- **Maintenance**
  - Protein kinase Mζ production increases
  - Inhibition of PKMζ in rat hippocampus results in retrograde amnesia

- **Expression**
  - Additional dendritic spines may be created
  - Synaptic vesicles increase, so presynaptic protein synthesis may also occur
  - It is unclear if protein synthesis occurs in the dendritic spines or in the cell body (synaptic tagging)
Long-term depression

- Refers to a permanent decrease in synaptic strength.
- Thought to be the biological mechanism for clearing old memory traces.
- Works like LTP in reverse:
  - Low frequency stimulation causes low calcium concentration
  - Proteins dephosphorylate
  - Receptors decrease in number and strength
  - Dendritic spines may be pruned
Both LTP and LTD depend on calcium concentration.

Shouval et al. created a theoretical model to take advantage of this:

\[ W_i(t) = \frac{1}{\tau([Ca]_i)} (\Omega([Ca]_i) - W_i) \]

- \( W_i \) is the synaptic strength.
- \([Ca]_i\) is the concentration of calcium at synapse \( i \).
Metaplasticity

Refers to plasticity of the plasticity mechanisms themselves.

Heavily concerned with the arrangement of AMPA and NMDA receptors, as they determine LTP and LTD thresholds.

Synaptic homeostasis:

- Without control, LTP and LTD would drive synaptics strengths too high or low, inhibiting new memory development
- Long periods of inactivity increase receptor sensitivity
- Long periods of activity cause receptor desensitization
- Affects both presynaptic and postsynaptic cells
Metaplasticity: synaptic states

Synaptic strength does not lie on a continuum: there are five different synaptic states. (Though the states can have varying degrees of intensity) ⁴

Are there any questions?