CN510: Principles and Methods of Cognitive and Neural Modeling

Synaptic Dynamics and the Biological Bases of Long Term Memory Changes

Lecture 10

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Processing of Memory

**Encoding** – receiving, processing and combining the information

**Storage** – creation of a permanent record

**Retrieval** – calling back the stored information
  - **Strategic** – laborious voluntary retrieval
  - **Associative** – automatic retrieval caused by cue presentation
Classification of Memory by Duration

Sensory memory: very short term, can’t be rehearsed
  – *Sperling (1960)* – partial report paradigm

Short term: seconds to minutes
  – *Miller (1956)* seven plus or minus two; later 4±2
  – Chunking helps to keep more items
  – Believed to be acoustic based – harder to remember phonologically similar words (*Conrad 1964*)

Long term: large capacity, indefinite duration
  – Semantic encoding – harder to remember words with similar meanings (*Baddeley 1964*)
Atkinson-Shiffrin Model

Simple interpretation of relationships between sensory, short-term and long-term memories

Does not take into account multiple modalities; e.g. there are patients that have verbal STM impaired but visual STM intact

Can be extended to have multiple parallel streams of processing to include this
Low Level Physiology of Memory

Sensory memory can be represented simply by a decaying trace of neuronal activity:

- Leakage parameter (membrane time constant) can be adjusted to match experimental durations

Short-term or working memory probably needs some recurrent network architecture to reverberate the activity over longer periods of time

- Sample recurrent architecture was covered last time; different parameter regimes allow flexibility

Long term memory is generally associated with the change in synaptic efficacy

- Today’s topic (and a few upcoming lectures)
Terminology

Excitatory postsynaptic potential (EPSP) – an increase in membrane potential (depolarization) of postsynaptic cell caused by transmitter binding at a chemical synapse.

Inhibitory postsynaptic potential (IPSP) – a decrease in membrane potential (hyperpolarization) of postsynaptic cell caused by transmitter binding at a chemical synapse.

Synaptic efficacy – measure of the degree to which a presynaptic action potential (or high membrane potential) produces a change in the postsynaptic membrane potential. Also known as “synaptic strength” or “weight.”
Time Scales

Time necessary to induce a change

- **Facilitation** – increase in synaptic efficacy occurring within about 1 s of start of stimulation

- **Potentiation/Depression** – change in synaptic efficacy occurring within about 10 s of start of stimulation

Time scale of the persistence of a change

- **Short term** – does not persist for longer than a second

- **Long term** – persists for an hour or more

There is also **homeostatic plasticity** – a self-regulating mechanism to maintain total input to the cell within dynamic range – that acts on a time scale of minutes-hours
Two Types Of Synapses

Electrical

– Transmission is virtually instantaneous
– Can lead to synchronous firing of a group of cells
– Most electrical synapses are bidirectional, but some allow current flow in only one direction (rectifying)
– Connections between pre- and postsynaptic cell are through “gap junctions”

Chemical

Some advantages of chemical transmission:

– Single action potential releases thousands of neurotransmitter molecules, allowing amplification of signal in postsynaptic cell
– Efficacy is more easily modifiable
Structure of Ion Channels

Gap junctions and ion channels are all membrane-spanning protein chains with 4, 5, or 6 subunits:

Voltage-gated

Transmitter-gated

Gap Junction
Electrical Synapses

Utilize direct structural connections called gap junctions:
Chemical Synapse

Do not involve structural connections between the pre- and postsynaptic cells (unlike electrical synapses)

The gap between the pre- and postsynaptic components of a chemical synapse is called the synaptic cleft
Chemical Synapse

Transmitter released from the axonal terminal of the presynaptic cell.

It binds to the receptors linked to ion channels on the postsynaptic cell.

Ions start to flow and affect postsynaptic membrane potential.
Transmission at a Chemical Synapse

Presynaptic action potential

Reaction of transmitter with postsynaptic receptors

Increased presynaptic Ca$^{2+}$ permeability; Ca$^{2+}$ influx

Activation of synaptic channels: synaptic current produces postsynaptic potential

Release of transmitter by exocytosis of vesicles

Postsynaptic action potential
Some Common Transmitters

The polarity (excitatory/inhibitory) of a transmitter’s effect depends on the type of ion channels gated by the transmitter at a particular synapse.

However, transmitters usually bind to a family of channels permeable to certain ions and thus can be called excitatory or inhibitory based on this:

- Acetylcholine (ACh) – used in all nerve-skeletal muscle junctions in vertebrates (excitatory), as well as elsewhere in the nervous system (modulatory).
- Glutamate – major excitatory transmitter in the vertebrate brain.
- GABA (gamma-aminobutyric acid) – major inhibitory transmitter in brain and spinal cord; inhibits by opening Cl\(^-\) (GABA\(_A\)) or K\(^+\) (GABA\(_B\)) channels.
Some Common Transmitters

- Glycine – inhibitory transmitter in spinal cord; opens Cl⁻ channels
- Dopamine
- Norepinephrine
- Serotonin
- … about 100 or more total
Conditions for Transmitters

A chemical can be classified as a neurotransmitter if it meets the following conditions:

– There are precursors and/or synthesis enzymes located in the presynaptic side of the synapse
– The chemical is present in the presynaptic neuron
– It is available in sufficient quantity in the presynaptic neuron to affect the postsynaptic neuron
– There are postsynaptic receptors and the chemical is able to bind to them
– A biochemical mechanism for inactivation is present
Two Main Types of Transmitters

**Small molecule transmitters** – often produce fast postsynaptic effects (ms time scale)
- The transmitters on the previous slides are most common of the generally accepted small-molecule transmitters
- Consist of amino acids (GABA, Glycine, Glutamate), monoamines (DA, NE, 5HT) and some others (ACh)

**Neuroactive peptides** – often produce much slower postsynaptic effects (time scale of seconds to hours)
- Peptides are chains of amino acids (proteins)
- Many are also hormones that can act on targets outside of the brain
- More than 50 neuroactive peptides are known
Two Main Types of Transmitters

Small-molecule and peptide transmitters can coexist and be coreleased.

Because the actions of different transmitters can occur on very different time scales, coreleased transmitters provide a tremendously rich substrate for information transfer between cells.

Compare with very simple form of synaptic transmission in most neural network models.
Transmitter Release by Action Potential

Recall that action potential is a combination of a fast transient Na inward current followed by a slow K outward current.

But neither Na nor K and not even membrane potential have a direct effect on transmitter release.
Transmitter Release by Action Potential

Katz and Miledi (1967):
- Na influx is neither necessary nor sufficient to cause transmitter release
- K efflux is neither necessary nor sufficient to cause transmitter release
- Ca influx is essential

Ca concentration outside is much higher than inside the cell
Transmitter Release by Action Potential

During an action potential, voltage-gated Ca channels open up, allowing Ca to flow down its concentration gradient into the cell.

Unlike voltage-gated Na channels which open only transiently, the voltage-gated Ca channels stay open as long as the presynaptic membrane potential remains depolarized.

Ca influx is a graded function of presynaptic membrane potential, and transmitter release is in turn a graded function of the amount of Ca in the presynaptic cell.
Quantal Nature of Transmitter Release

Fatt and Katz (1952) noted that the smallest postsynaptic potentials at nerve-muscle synapses had a fixed size of about 0.5-1.0 mV.

It has also been shown that postsynaptic potentials tend to be integral multiples of such a “unit synaptic potential.”

Later studies showed that a single transmitter molecule opening a single ion channel produced postsynaptic potentials much smaller than this 0.5 mV potentials required on the order of 2,000 ion channels or about 5,000-10,000 transmitter molecules.

Why then is the postsynaptic potential quantized?
Quantal Nature of Transmitter Release

Transmitter is released in individual “bundles” of about 5,000-10,000 molecules.

These “transmitter bundles” are stored in organelles called synaptic vesicles.

The unit synaptic potential results from release of the contents of a single synaptic vesicle.

Transmitter is “sucked into” vesicles by an active process powered by hydrolysis of ATP (also used to power Na/K ion pumps in neurons).

This leads to a transmitter concentration that is 10 to 1000 times higher inside the vesicle than outside of it.
Transmitter Synthesis

Transmitter is either “recycled” (described later) or synthesized in the nerve cell.

Small-molecule transmitters can be synthesized anywhere in a neuron, but mostly at synaptic terminals.

- Synthesis and uptake by synaptic vesicles can occur very quickly at the terminal during spiking, thus allowing rapid and sustained transmitter release.

Peptide transmitters are synthesized only in the cell body, where uptake into vesicles also occurs.

- Thus, once release occurs a new supply of the peptide vesicles must arrive from the cell body before release can occur again.
Transmitter Release

Calcium influx acts in two ways to cause the release of transmitter:

– By breaking down actin filaments which hold vesicles together and away from the membrane (actin is a protein)
– By aiding in the fusion of vesicles to the membrane — “exocytosis”
Exocytosis of Synaptic Vesicles

After exocytosis, vesicles are “recycled”
Removal Of Transmitter From The Synaptic Cleft

After release into the synaptic cleft, transmitter is quickly “washed away”

If transmitter were not removed, constant exposure to transmitter would lead to receptor desensitization and would prevent new signals from being transmitted
In fact, many nerve gases act by preventing removal of transmitter at nerve-muscle junctions, resulting in paralysis and death due to respiratory failure
Removal Of Transmitter From The Synaptic Cleft

Three means for removing transmitter:

– **Diffusion** – high concentration in synaptic cleft diffuses away

– **Enzymatic degradation** – certain enzymes break down transmitter molecules
  
  • Usually these enzymes are transmitter-specific

– **Reuptake** – transmitter or “broken down” transmitter components can be “sucked back in” to presynaptic cell to be taken in by vesicles and reused
  
  • Up to 50% of released transmitter can be reused in this manner
Plasticity Opportunities

Short term:
- Change the amount of transmitter released
- Change the time transmitter spends in the cleft

Long term:
- Change the number of receptors (channels)
- Change the number of synapses
Two Kinds of Chemical Synapse Receptors

Transmitter binding at the postsynaptic membrane can either directly gate ion channels (left) or act through a second messenger (right):
Directly Gated Synapses

In a directly gated synapse, transmitter binds to a receptor protein that is also an ion channel:

The effect of the channel depends on its permeability
Transmission in directly gated synapses is much faster than in second messenger synapses
Excitatory directly gated synapses act by opening channels permeable to both Na\(^+\) and K\(^+\) leading to reverse potential around 0mV, which is higher than a spiking threshold. Some directly gated channels are also permeable to Ca\(^{2+}\).
In directly gated synapses the timing of

- Presynaptic action potential
- Ca\(^{2+}\) influx
- Transmitter release
- Postsynaptic potential

can be as fast as 1ms after the presynaptic action potential
Second Messenger Synapses

In contrast to directly gated synapses where the receptor and channel are the same protein, second messenger receptors can only affect ion channels indirectly:

The time scale of 2nd messenger actions is usually seconds to minutes (cf. ms time scale for directly gated synaptic actions)
Second Messenger Synapses

Four second messenger molecules have been well-characterized:

- cAMP (Cyclic adenosine monophosphate)
- DAG (Diacylglycerol)
- IP (Inositol polyphosphate)
- Arachidonic acid
Second Messenger Synapses

Typical synaptic transmission process for a second messenger synapse:

– Transmitter binding at the postsynaptic site causes activation of a G-protein
– G-protein activation leads to the synthesis of a second messenger (transmitter being the first messenger)
– The G-protein or the second messenger act directly to open/close ion channels

or

– The second messenger sets off a chain of biochemical events (involving a protein kinases) that leads to mobilization of $\text{Ca}^{2+}$ or to opening/closing of ion channels

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Second Messenger Synapses

FIGURE 12-12
Synaptic excitation mediated by second messengers need not involve protein phosphorylation (B) but channel opening can be mediated by the direct action of a G-protein (A) or a second-messenger molecule such as cAMP or cGMP.
Effects of Second Messengers

Inhibition can be caused by opening K$^+$ channels and driving the cell towards $E_K$

Excitation can be caused by two mechanisms (at least):

- By opening channels permeable to both Na$^+$ and K$^+$ (similar to directly gated synapses except on a slower time scale)
- By closing normally open or voltage-gated K$^+$ channels

The latter reduces the negative contribution of $E_K=-75 \text{ mV}$ to the membrane potential, thus depolarizing the cell

Directly gated receptors do not close ion channels
Effects of Second Messengers

Recall that a $K^+$ outward current causes the downswing of the action potential.

Therefore, closing of voltage-gated $K^+$ channels by second messengers can lengthen a postsynaptic action potential by decreasing the rate of $K^+$ outflow.
Effects of Second Messengers

In addition to opening/closing ion channels that are not directly transmitter gated, second messengers can also modulate the effects of transmitter on directly gated ion channels

– e.g., presence of a second messenger can sometimes desensitize directly gated receptors, effectively reducing the ability of the appropriate transmitter to open the corresponding ion channels

Second messengers can diffuse within the cell and affect distant parts of the neuron (e.g. closing voltage-gated K+ channels to prolong action potential). Directly gated effects are limited to the immediate area of the synapse

Finally, as we will see later, second messengers can mediate long term changes in synaptic efficacy
Chemical Synapses

The majority of chemical synapses are either axosomatic, axodendritic (spine or shaft), or axo-axonic.

In addition, there are a few somatosomatic and dendrodendritic synapses.
Chemical Synapses

Axosomatic synapses tend to be inhibitory
  – This is apparently because inhibition due to “shunting away” of depolarizing current is much more effective near the trigger zone
Axodendritic synapses terminating at spines tend to be excitatory
Axo-axonic synapses tend to be modulatory
  – These synapses have a limited direct effect on trigger zone, but they can affect (“modulate”) the amount of transmitter release of the postsynaptic neuron by affecting the amount of Ca²⁺ influx
  – presynaptic inhibition or presynaptic facilitation
Presynaptic Inhibition

Axo-axonic connections allow one neuron to selectively inhibit transmission from an axon at a single synapse without affecting the same axon’s effects at other synapses.

From Hall (1992), *Introduction to Molecular Neurobiology*, p. 171:

Note that most neural network models do not make use of this form of selective inhibition.
Long Term Potentiation and Depression

Well studied case is NMDA-dependent LTP in the hippocampus.

To activate NMDA receptor two transmitters (glutamate and glycine) are necessary.

Also the membrane potential has to be high enough to push Mg$_2^+$ block out.

NMDA allows through Ca$_2^+$ which can trigger a second messenger cascade, so it is in a way a mixed (direct action/second messenger) channel.
Early Long Term Potentiation

Possible sequence of events:
- AMPA activation by glutamate
- Membrane depolarization
- Removing Mg block
- NMDA activation
- Ca$^{2+}$ inflow
- Second messenger cascades (calpain, CaMKII)
- New AMPA receptors
Late Long Term Potentiation

- NMDAR
- AMPAR
- mGluR

  - PI-3K
  - PKA
  - PKC
  - CaMKII

  - ERK

  - Signaling proteins
  - Cytoskeletal proteins
  - Nuclear proteins

  - Gene transcription
  - Protein synthesis
  - Morphological changes

  - LTP expression
Possibilities For Long-term Changes In Synaptic Efficacy

Could permanently increase/decrease the amount of Ca$^{2+}$ influx per action potential at the presynaptic terminal. This will increase/decrease the amount of transmitter release for a given presynaptic potential.

Could permanently increase/decrease K$^+$ or Na$^+$ permeability at either the presynaptic or postsynaptic sites.

Could increase/decrease the number of synapses between two cells.

In second messenger synapses, could permanently increase/decrease amount of second messenger produced per unit of transmitter.

Which of these are realized in vivo? Probably all of them.
Next Time

We will discuss current-based and conductance-based models of synaptic responses in spiking networks and possible applications of Rotter-Diesmann approach to these models.

Readings:
- D&A Chapter 5 (sections 8-9)

Homework due: additive and shunting network