Psych 1XX3 –Behavioural Neuroscience (NSIII) Notes – Feb 2, 2010

Introduction to Cognitive Behavioural Neuroscience:

Role of Cognitive Neuroscientists:

- Understand abstract mental processes in a neural framework.
- Traditional paradigms used to study cognitive functions such as learning, memory language, and problem solving are complemented by techniques such as neuroimaging to trace the routes of neural processing.

Role of Behavioural Neuroscientists:

- Understand the neural processes underlying behaviours such as reward, sexual motivation, and feeding mechanisms.
- Typically, these complex behaviours are simplified into component behaviours that are modeled in simple animal systems to use the full range of techniques available in neuroscience such as electrophysiology, pharmacology and behavioural genetics.

Learning, Memory and Behaviour:

- Focus of lecture will be on addressing the question of how you learn about the world, remember information, and apply knowledge moving from lower to higher levels of processing.

Neural Plasticity:

- Head injuries: Depending on the severity and the region of the insult, deficits can affect changes in planning, motor control, language production or even induce coma or brain death.
- However in some cases, rehabilitation can lead to miraculous recovery allowing an injured person to regain lost abilities.

Everyday Neural Plasticity:

- The brain is changing in every interaction with the environment. This 'everyday neural plasticity' allows your brain to adapt incoming stimuli and rewire itself to optimize interactions with the outside world.

- Beginning in the 1950s, researchers were well aware that environmental influences can lead to enduring changes in complex behaviour that can be observed.
- Studies (Bingham and colleagues – 1952): demonstrated that exposure to complex environments made animal subjects into better problem solvers.
- However it was not until about a decade later that researchers realized the importance of environmental experience on enduring changes in the physical structure and functional organization of the brain.
- In 1964, Bennett and colleagues compared the brains of rats raised in enriched or impoverished environments. The enriched environment was like a little piece of rat heaven, where the rats lived in social groups in a complex environment filled with toys, ladders, tunnels and running wheels to explore.
- In the impoverished environment, rats lived alone in small cages with access to food and water only.
- Researchers found that brains from the two groups were wired very differently. The brains of rats exposed to the enriched environment had a

much richer network of neurons with more dendrites and synaptic connections compared to the brains of rats raised in the impoverished environment.

- Another dramatic example of the role of environmental input on enduring changes in neural structure comes from studies on maternal care in rat pups.
- Meany and colleagues found that rats raised by mothers that engaged extensively in maternal care behaviours (like licking and grooming) later grow to become less fearful and less responsive to stress than do those raised by mothers that do not engage as frequently in these maternal care behaviours.
- These stress and fear behavioural traits observed in adulthood were matched by measureable stress and fear changes in the brain including increased expression of glucocorticoid receptors in the adult rat's hippocampus [Weaver et al., 2004).

- Many neuroscientists believe that similar effects may also be observed in humans.
- These experimental findings demonstrate that the brain is adaptive and can detect contingencies between particular stimuli. This process of contingency learning allows you to learn, remember and navigate through the world.

Coincidence Detection:

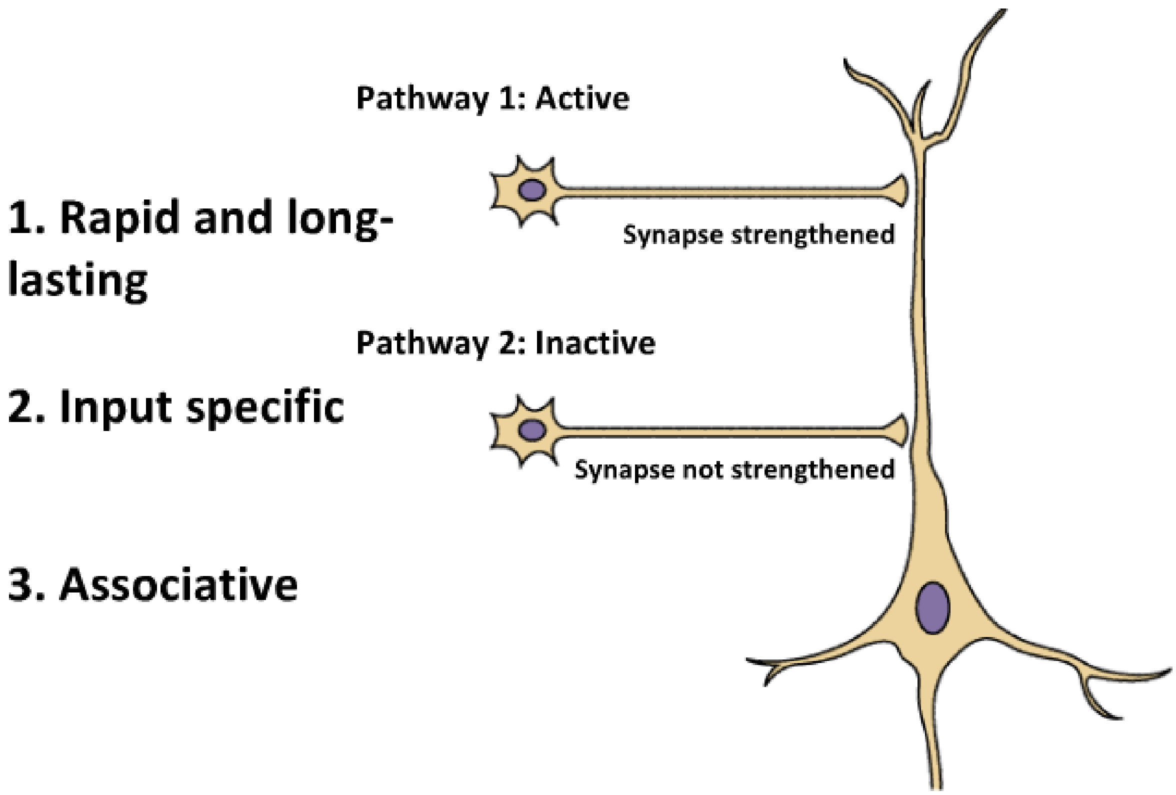
- The first practical theory based on neuroscience principles came in 1949 from a Canadian neuroscientist named Donald Hebb in his seminal work "The Organization of Behaviour".
- Hebb's theory described how connections between individual neurons can be changed, and how combinations of connected neurons can be grouped together as processing units. Hebb called these flexible units "cell-assemblies" which could adapt to the constant adjustments necessary to direct the brain's response to stimuli.
- TF: All your complex thoughts can be built from the sequential activation of neurons.
- Hebb's Law is often paraphrased as "neurons that fire together wire together."

Long-Term Potentiation:

- A promising candidate mechanism for Hebbian learning is Long-term potentiation (LTP)
- LTP is the strengthening of the connection between two neurons and this effect can last for an extended period of time; from minutes to a lifetime. It is also sometimes referred to as an increase in synaptic efficacy, meaning a presynaptic neuron becomes more efficient at generating a larger response in the postsynaptic neuron.
- In the lab, this LTP can be measured by the change in amplitude of the EPSP.

- LTP was first observed in 1973 by a PhD candidate studying the functional circuitry of the hippocampus, which plays an important role in memory.
- Terje Lomo made the startling observation that following activation by brief, repeated bursts of high frequency stimulation, a single test pulse could make it easier for adjacent cells to fire action potentials - an effect which could last for several hours over the duration of an experiment.
- This long term potentiation of signalling provided a cellular mechanism for the synaptic change described in Hebbian Learning.

- There are several properties of LTP that make it such a promising candidate for the neural basis of learning and memory.
- LTP occurs very rapidly and is long-lasting, giving it a dynamic flexibility to form new memories. Like memories, LTP is input specific, facilitating only the synapses activated during the original stimulation.
- The strong activity in Pathway 1 initiates LTP at the synapse, without initiating LTP at the inactive synapse of Pathway 2.
- Finally, LTP is associative, meaning that it can strengthen inputs from multiple pathways if they are active simultaneously, as might naturally occur when two related events are presented.
- In this example, the weak stimulation of Pathway 2 alone does not trigger LTP, However, when the weak input from Pathway 2 occurs together with the strong input from pathway 1, both sets of synapses are strengthened.

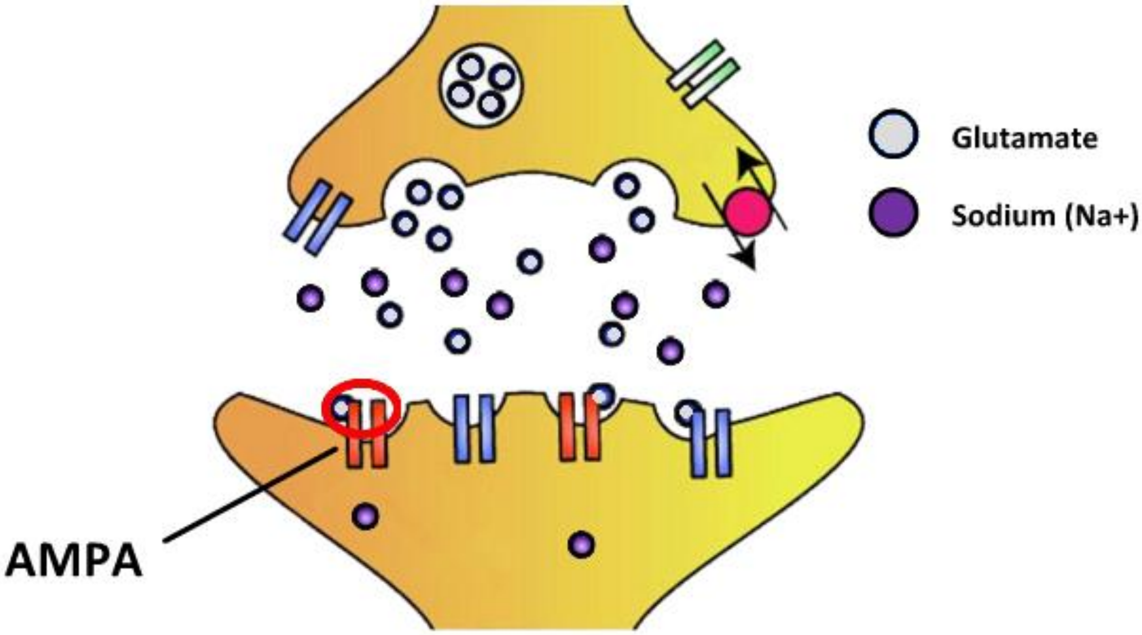


Mechanism of Classical Hippocampal LTP:

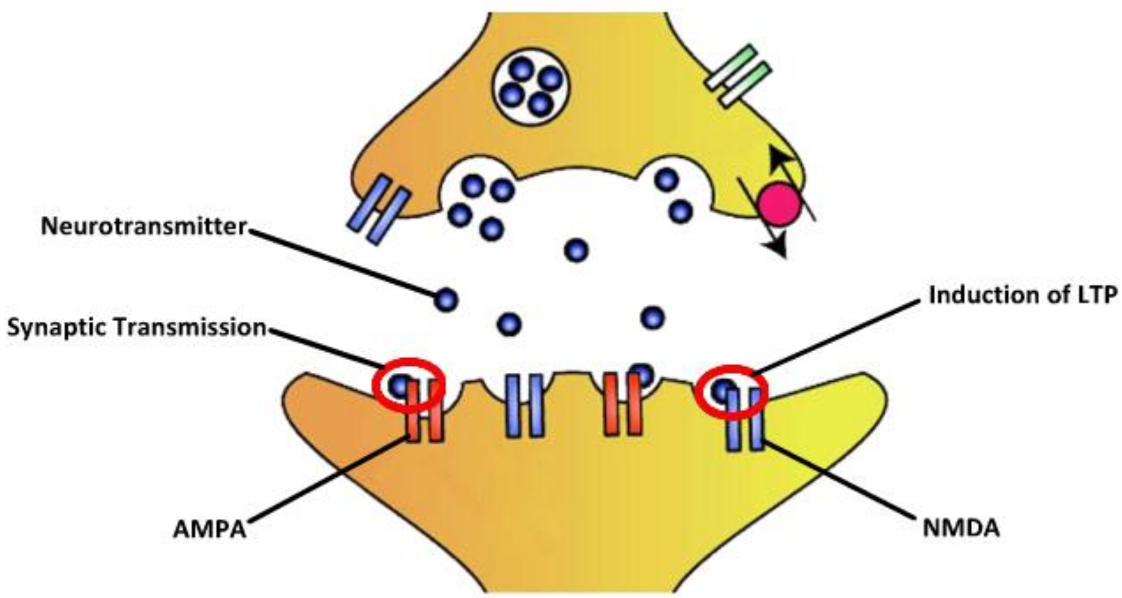
- Lomo's original observations were made using an in vivo hippocampal preparation, which limited the techniques that could be used in an experiment.
- However; with the development of an in vitro tissue preparation, a fresh hippocampal tissue slice could be kept alive in a dish, allowing many new experimental tools to be used.

The Mechanism of LTP:

- When the neurotransmitter glutamate is released from the presynaptic neuron it binds to the AMPA receptor, which is in fact both a receptor and an ion channel.
- This binding causes the channel to open, allowing the flow of positively-charged ions in.
- This depolarizes the post-synaptic cell moving it away from its' -70 mv resting potential, and closer to the -50mv threshold for an action potential to occur.
- TF: binding of glutamate at the AMPA receptor alone can be sufficient to cause a short-lived EPSP. Diagram shown on next page.



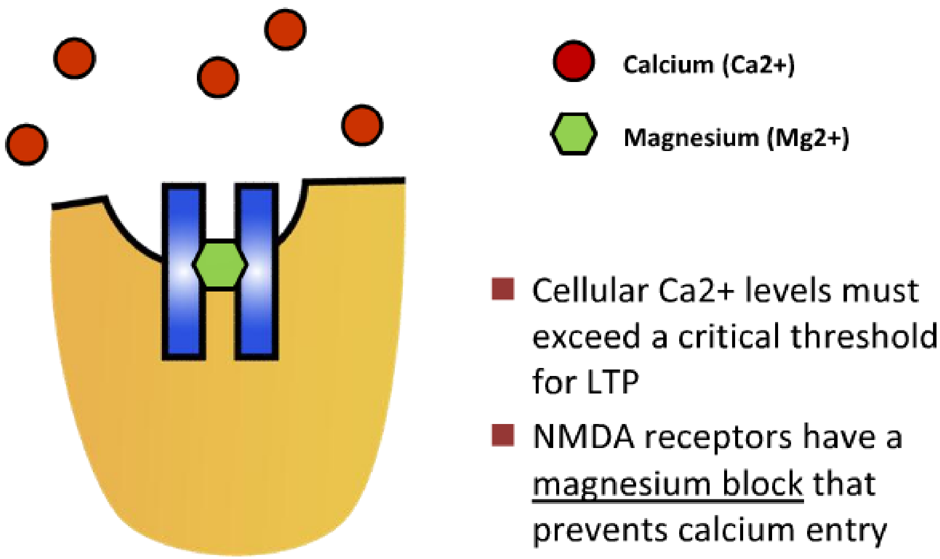
- Classical LTP begins with the presynaptic release of the neurotransmitter glutamate, which can bind to the AMPA receptor and another receptor called the NMDA receptor.
- Glutamate binding to the AMPA receptor is associated with the normal synaptic transmission that you are already familiar with
- Glutamate binding to both its NMDA and AMPA receptor types is associated with the induction or development of LTP (Image below)



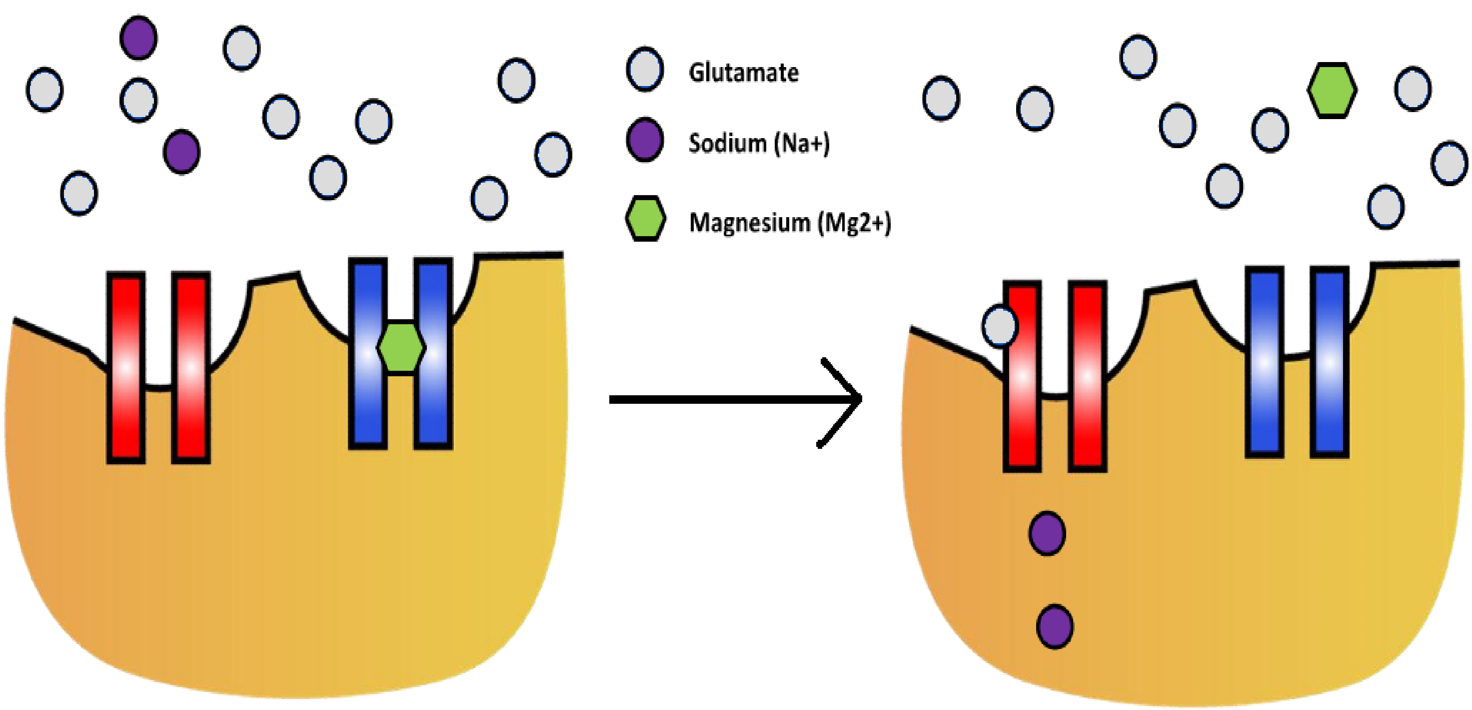
- Glutamate binding to NMDA and AMPA → LTP
- Glutamate binding to AMPA → Synaptic transmission

- Glutamate binding to both AMPA and NMDA receptors turns out to be important for another key player necessary for LTP induction.
- The concentration of positively charged calcium ions <u>inside</u> the postsynaptic cell must exceed a critical threshold.

- This process of calcium ion flow can only occur when glutamate binds to the NMDA receptor. However, at the resting state, the NMDA receptor-channels are blocked by magnesium, preventing calcium from entering the cell. (Image below)

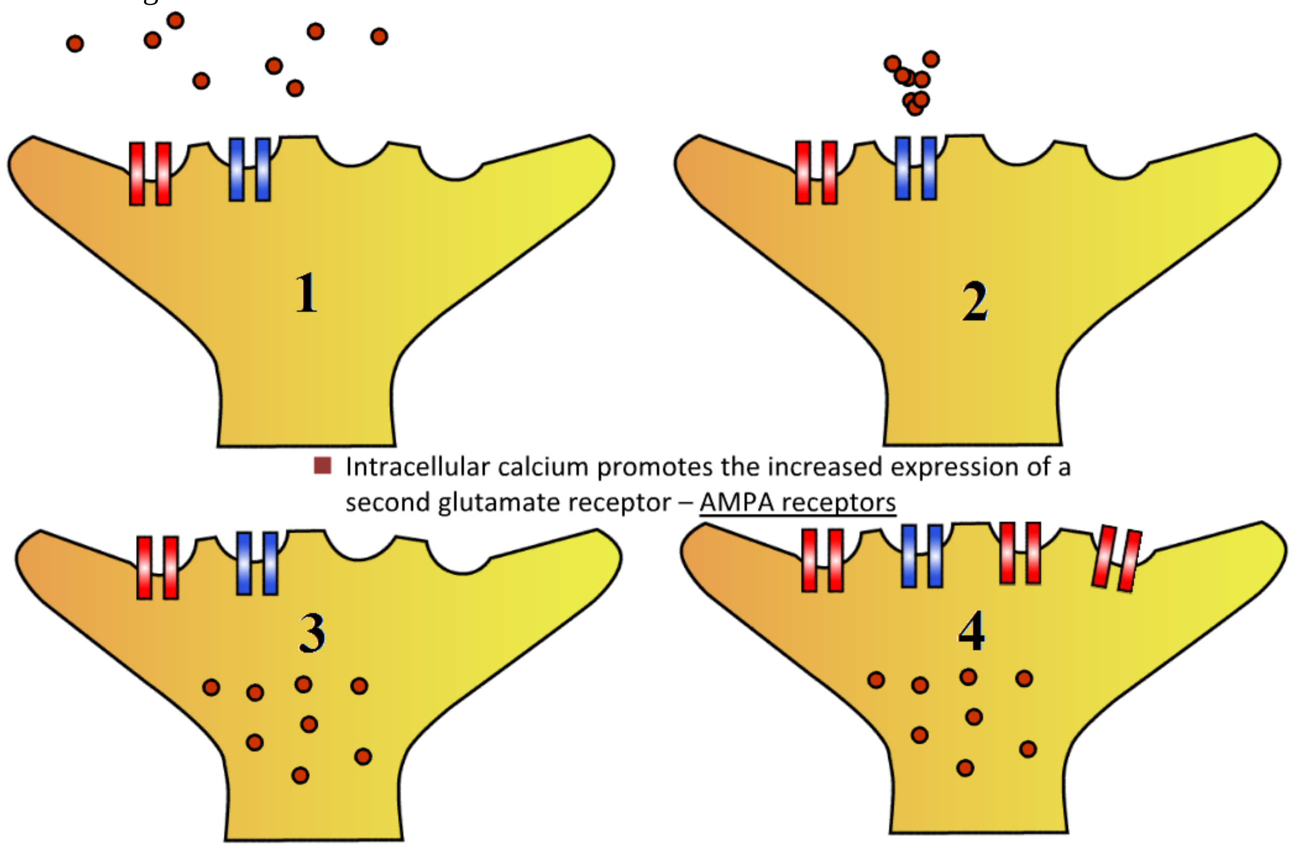


- So what's a postsynaptic cell to do? Fortunately, successive EPSPs via the binding of glutamate to the AMPA receptors, leads to sufficient depolarization that unblocks the Mg. This allows calcium to enter the post-synaptic cell and induce LTP.
- This takes a lot of coordination. Calcium entry requires both presynaptic and postsynaptic activity to occur.



- The depolarisation of the postsynaptic neuron must be perfectly timed with the firing of the presynaptic neuron to allow the calcium channel to fully open. The requirement of this coincident activity is what makes LTP so compellingly related to learning. (Diagram shown below)

- Why does calcium entry lead to a strengthening of the synaptic connection?
- Calcium entry into the postsynaptic neuron has a number of complex effects, but one important result of this activity is to promote the expression of more AMPA receptors in a specific region of the post-synaptic neuron.
- A specific synapse on the postsynaptic neuron becomes more sensitive to glutamate release from a specific presynaptic cell, strengthening the connection.
- Diagram shown below.



LTP and LTD:

- The increased expression of AMPA receptors in the post-synaptic cell can last for hours, weeks and even months in lab preparations.
- Just as there are IPSPs to counter EPSPs, another mechanism, called long-term depression (LTD), exists to decrease the sensitivity of synaptic connections,
- Together, research on LTP and LTD help to explain why neurons that fire together wire together

A Functional Role for LTP:

- How is LTP directly involved in behaviours associated with learning and memory?

Simple Circuits for Memory:

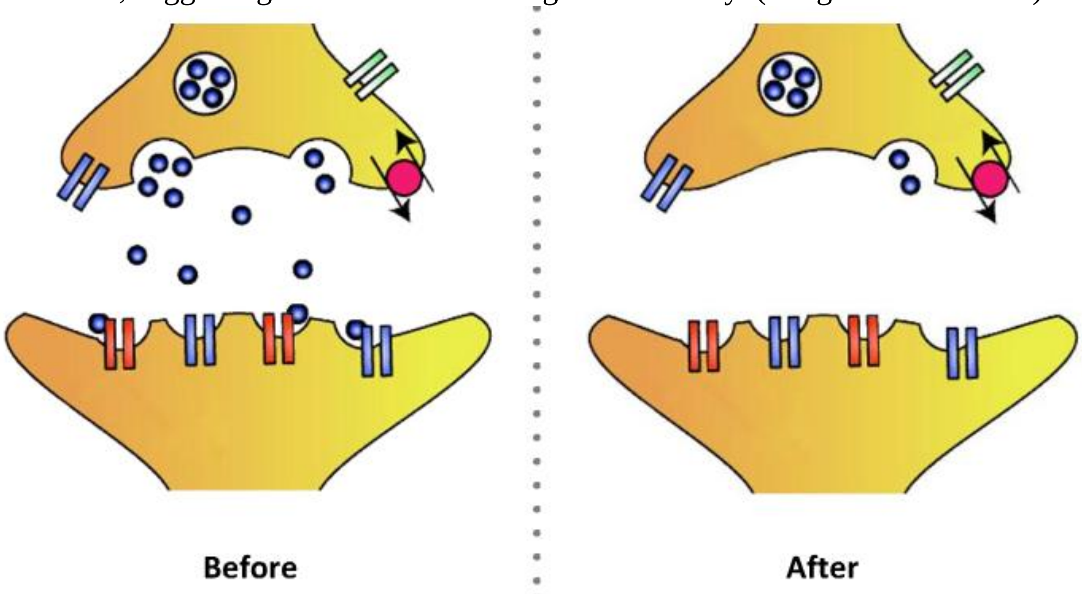
- Eric Kandel has been responsible for much of the pioneering work in linking behaviours associated with learning and memory with synaptic changes in the nervous system.
- In particular, his research addressed the question “what happens in a neural circuit when learning occurs?"
- Much of this work was conducted in a sea slug called the Aplysia.

Aplysia:

- The nervous system of the Aplysia has only about 20 000 neurons (compare that to the 100 billion neurons In your brain). This limited nervous system and it's repertoire of simple behaviours makes the sea slug an ideal model to study the neural basis of learning and memory.
- Kandel focused on a particular behaviour: the gill withdrawal reflex.
- At rest, the Aplysia extends its gill outwards to assist in the collection of oxygen. However, in response to danger, it rapidly retracts these organs for safety. This simple reflex is mediated by a relatively small circuit of neurons that can be used to study fundamental learning processes that you are familiar with such as habituation and classical conditioning.

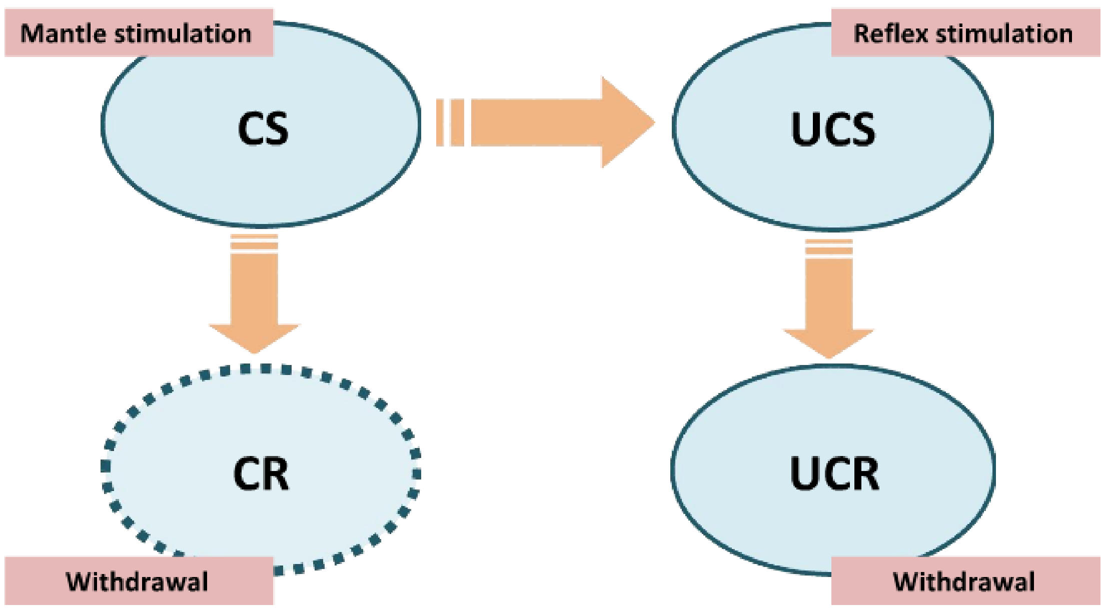
Habituation:

- Def'n of Habituation: a very simple form of learning which involves decreased response to a repeated or constant stimulus.
- For example, you likely don't feel the constant sensory stimulation from the clothes you're wearing right now because your touch receptors habituate to their input.
- In observing the Aplysia, Kandel found that the strength of the gill withdrawal reflex became progressively smaller after repeated stimulation.
- What is happening at the cellular level during habituation? It turns out that this behaviour is mediated by a relatively simple neural circuit.
- At the surface of the skin, a set of sensory neurons receive signals from the outside world. The sensory neurons synapse with motor neurons that return to the gill and control its withdrawal behaviour.
- After mapping the neural circuit responsible for the gill withdrawal reflex, the next step was to understand which part of the circuit was modified during habituation.
- Kandel observed that across trials, the presynaptic sensory neuron continued to fire just as many action potentials and the receptors in the postsynaptic motor neuron remained just as sensitive.
- However, the presynaptic neuron seemed to be releasing less neurotransmitter. ln fact, Kandel found that fewer vesicles were fusing with the membrane, thus releasing less neurotransmitters.
- With repeated training, this change in the efficacy of the synapse would last for weeks, suggesting a mechanism for long term memory. (Image shown below.)



Classical Conditioning:

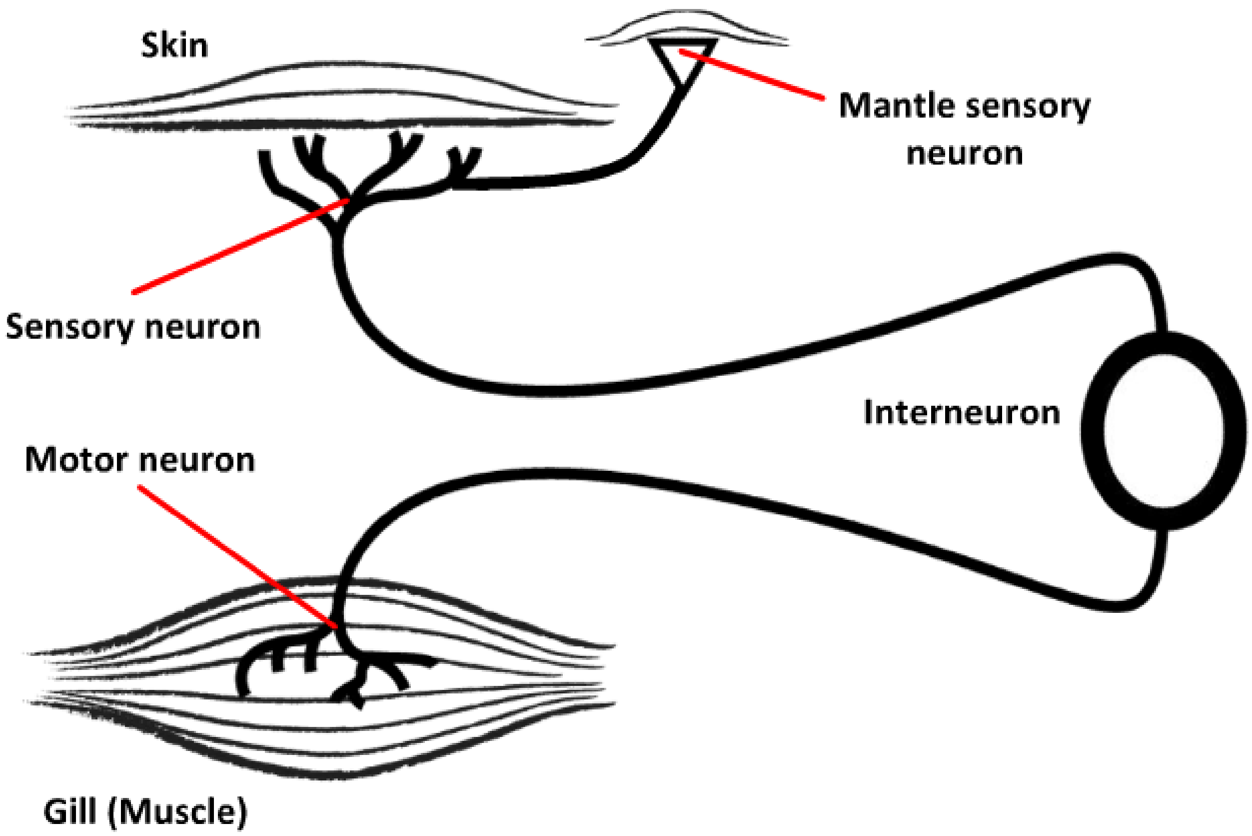
- Involves the learning of a contingency between a Conditional Stimulus (or CS) and an Unconditional Stimulus (or UCS).
- Prior to conditioning, the UCS elicits an unconditional response. After conditioning trials in which the CS and UCS are paired, the CS alone can now elicit a response, called the conditional response.
- Kandel demonstrated that classical conditioning could readily be demonstrated in the lowly Aplysia.
- In these experiments, a separate area of the body called the mantle was stimulated before stimulating the gill withdrawal circuit itself. The mantle stimulation served as a kind of CS which reliably predicted stimulation of the gill withdrawal reflex, which served as the US.
- Eventually the mantle stimulation alone was sufficient to elicit the gill withdrawal reflex. (Image shown below.)



- The sensory neuron of the Mantle synapses with the postsynaptic motor neuron of the reflex circuit.
- The stimulation from the mantle causes a slight depolarization of the postsynaptic neuron, releasing the Mg blockage at the NMDA receptor. Then, when the US stimulation arrives shortly after, the release of glutamate allows calcium to enter the cell and LTP to take place.
- In this wary, NMDA receptors can serve as perfect contingency detectors in the learning circuit.

- Kandel was able to demonstrate a direct link between cellular mechanisms and behavioural output, strengthening the understanding of how learning and memory proceeds in the brain.

- Diagram shown on next page.



Human Memory
The Curious Case of H.M.

- The first major breakthrough in understanding the neuroscience of memory in humans came in 1957, with what would become a very famous case study by Scoville and Milner on a patient called H.M.
- When H.M. was 7 years old, he fell and hit his head, leaving him with seizures that continued to worsen throughout his life.
- By the time he was 21, the seizures worsened to the point where he could no longer function normally. After anticonvulsant drugs failed to relieve his symptoms, Dr, William Scoville proposed an experimental surgery to remove the medial temporal lobes from H.M.'s brain.
- The operation was successful in relieving the seizures, but it also had some distressing side effects.
- During the surgery, most of HM's hippocampus were removed, leading him to experience some very interesting memory deficits.

- After his operation, HM returned home and lived a relatively normal life.
- Although his memory for the past was completely intact HM was completely unable to form new memories. To HM. it was always 1953 and he was always 27 years old.
- Because he had a fully intact short-term memory HM was able to carry on a normal conversation without difficulty but once the conversation ended, his attention would break, and he would forget everything that just happened. In a sense, HM was trapped living in a perpetual present.

Different Forms of Memory:

- The case study of HM revealed to researchers that distinct memory systems and functions exist in humans.
- One important distinction is between procedural memory and declarative memory.
    - Procedural or implicit memory is your memory for actions, sequences and skills; it often occurs outside of your awareness and can be difficult to explain to another. An example of procedural memory is your ability to ride a bike, play a musical instrument, or learning to swim. This "know-how" memory can be very durable.
    - Declarative memory is your memory for facts and knowledge and your personal experiences. Declarative memory is often prone to forgetting, but it can be markedly improved by using elaborative rehearsal and active recall.

Procedural Memory:

- Because procedural memory encompasses such varied tasks as motor commands and spatial representations, its neural correlates are quite diverse.
- However the processing mechanisms for procedural memory must be independent of those for declarative memory. This would explain why HM could have no difficulty learning new tasks, yet never remember practicing them.
- A key region involved in motor learning is the cerebellum. The cerebellum is involved in conditioned motor responses ranging from simple eyeblink responses, balance and more complex motor tasks.
- Another important region is called the striatum, a collection of nuclei in the forebrain. The striatum is implicated in motor disorders such as Parkinson's and Huntington's Diseases and patients with damage to the striatum show marked defecits in learning new motor skills.

Declarative Memory:

- HM's case demonstrates that at least part of the declarative memory system must involve the hippocampus.
- The declarative memory system extends to include the cerebral cortex and the parahippocampal region, the area of cortex immediately surrounding the hippocampus.
- The process of forming declarative memories begins in the cortex, where information you are currently working with is processed. From there, information travels to an “intermediate-term memory storage" in the parahippocampal region
- Here, information is stored on the scale of minutes. Finally the hippocampus begins the process of forming new long-term memories, which are later stored throughout the brain.

- Once information reaches the hippocampus, it is represented in at least three levels.
    1. At the lowest level, the hippocampus carries a representation of your current experience in the context of the entire event.
    2. Next, the hippocampus links these episodes together based on common episodes and places you have experienced in the past.
    3. Finally the hippocampus creates a flexible declarative memory, which is organized according to the most salient or important information, and stored permanently in the brain.

Place Cells in the Hippocampus:

- In an early study of the cellular processes in the hippocampus, James Ranck Jr. attempted to understand how the hippocampus can accomplish the task of creating a new declarative memory.
- Ranck found that the firing of hippocampal cells correlated with specific behaviours, such as approach, withdrawal, eating, and drinking.
- Later studies found that cells in the hippocampus can fire to even more specific events.
- Example: O'Keefe observed a very different sort of firing pattern in the hippocampus. He found that specific hippocampal cells fired in relation to the specific location of the animal, independent of the behaviour being performed.
- O'Keefe and colleagues would later call these hippocampal 'place' cells. He proposed that the hippocampus receives information about the outside world to create a cognitive map. Each hippocampal cell fires when the animal is in a particular region of this cognitive map.
- In later studies, researchers have identified a variety of hippocampal place cells that fire not only in response to location, but also to behaviours being performed in a particular location, and perhaps even to the rewards and implications associated with each.
- Of course, the hippocampus responds to non-spatial events as well, but this new understanding of spatial processing provides insight into the workings of memory.
- TF → Memories seem to be better recalled in the location where they were first learned.

Working with our Memories:

- Once information is learned and remembered, it can guide your future thoughts and behaviour as you navigate through the environment to perform goal-driven behaviour.