Physiology Undergraduate League of Students

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lecture #:	date:	professor:
34	Monday, Novemeber 27th	Dr. Chacron
35	Wednesday, November 29th	Dr. Chacron
36	Friday, December 1st	Dr. Chacron

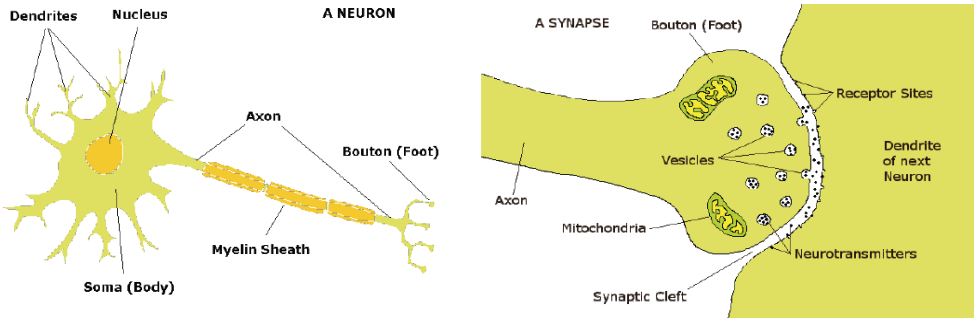
announcements:

- ***Last day of PULS office hours.*** *The PULS office will close for the semester on Tuesday, December 5th, 2006 at 14:00. Come before then to purchase or pickup NTCs, physio-clothing and/or handle any unfinished business with PULS.*
- ***Physiology Ski Trip*** *– Ski all weekend in a condo with 10 of your friends at Mont Ste Anne - Janunary 19-21, 2007 for only $249 – Deadline to sign up is Tuesday December 5th!!!*
- *Good Luck on Finals!*

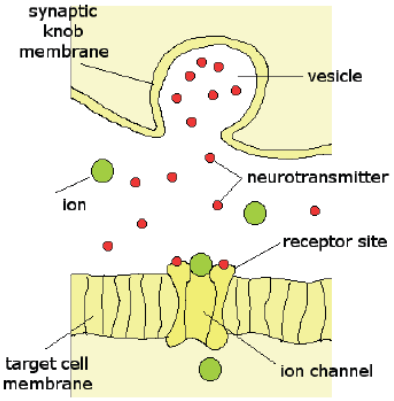
PLEASE NOTE MONDAY'S NTC (December 4th) WILL BE AVAILABLE ONLINE ON ATHENA (unedited)

Lecture 3: Neural Mechanisms Underlying Memory Foundation

Review of Synaptic Transmission: The Basics

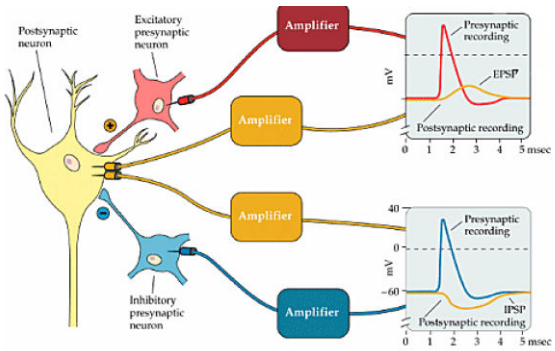


- The figure above (left) shows the anatomy and structure of a neuron. Dendrites receive synaptic input from other neurons and carry this information to the cell body where the signal is processed and propagated down the axon to the synaptic boutons.
- The synaptic cleft (above and to the right) is where communication between neurons takes place.
- In the presynaptic cleft there are various vesicles that contain neurotransmitter.
- An action potential will cause vesicle exocytosis, releasing neurotransmitter into the synaptic cleft.
- The neurotransmitter will now bind onto receptors in the postsynaptic membrane.
- Ionotropic receptors on the postsynaptic membrane allow ion flow.



Excitatory vs. Inhibitory Transmission

- The figure (below) shows examples of action potentials that can be recorded in a postsynaptic neuron.



- An excitatory synapse will cause an EPSP which is a measure of the voltage deflection caused by current flowing through the receptors in the postsynaptic membrane.
- An inhibitory synapse will cause an IPSP which is measured by a negative deflection in voltage.
- EPSPs result in the neuron increase its probability of firing
- IPSPs lower the neuron's probability of firing.

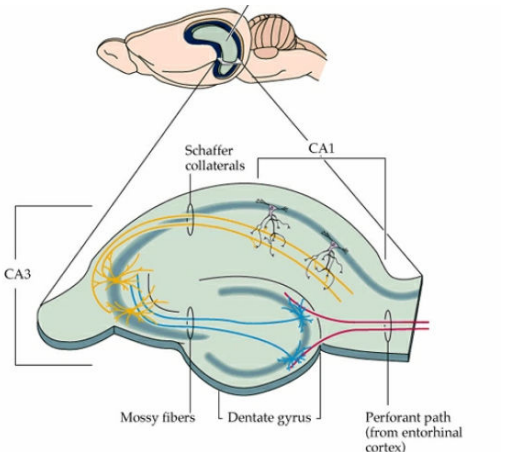
Synapses

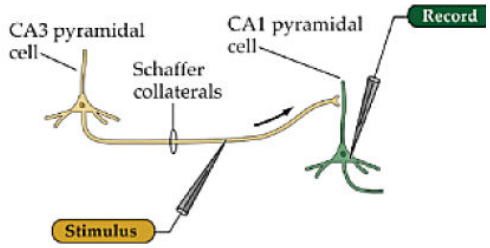
- Pre-synaptic action potentials cause synaptic vesicles to release neurotransmitter in the synaptic cleft.
- Neurotransmitter either has an excitatory (glutamate, aCh) or inhibitory effect (GABA) depending on the neurotransmitter used.
- Neurotransmitters activate receptors on the target cell's membrane. Two major types of receptors: iontropic – lets current flow through (AMPA, NMDA, GABA receptors) and metabatropic (2^{nd} messengers such as cAMP exert downstream effects)
- Activation of these receptors causes post synaptic potentials (PSPs), which can be either excitatory or inhibitory.

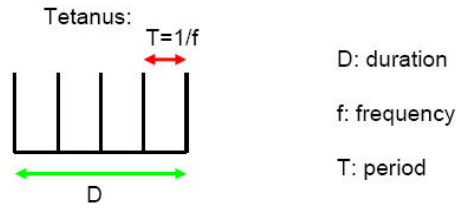
Hebb's postulate:
(Hebb worked here at McGill!)

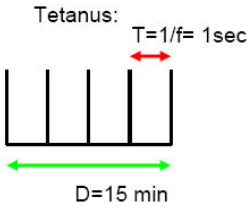
- At the time it was not known what the cellular processes were that were motivating memory formation.
- There was a lot of psychological data from patient HM, but it was not known what the neural mechanisms were.

- When an axon of cell A is near enough to repeatedly excite cell B, some growth process or metabolic change takes place in one or both cells such that A's firing efficiency, is increased (making it easier to excite cell B).
- In other words, if we have cell A that makes a synaptic connection onto cell B, and if whenever cell A fires cell B fires, then the synaptic connection between cell A and B will be strengthen.
- This supports the fact that synaptic connections are plastic.
- It is *correlations between the pre and post-synaptic activities that underlie plasticity*.
- Diagram to the right (review of rodent brain)
  - There is an analogous structure to the hippocampus in rodents which is highlighted.
  - We will concentrate on the connection between CA3 pyramidal cells and CA1 pyramidal cells (which are connected by the Schaffer collaterals)
- It is possible to slice the hippocampus and record and stimulate from various parts of the slice. It is also possible to stimulate the Schaffer collaterals and record from a pyramidal cell in the CA1 region.
- This allows us to see any changes in the synapse between the Schaffer collaterals and CA1 pyramidal cells.

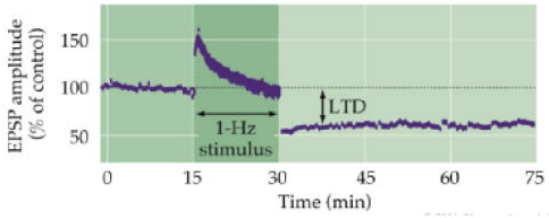




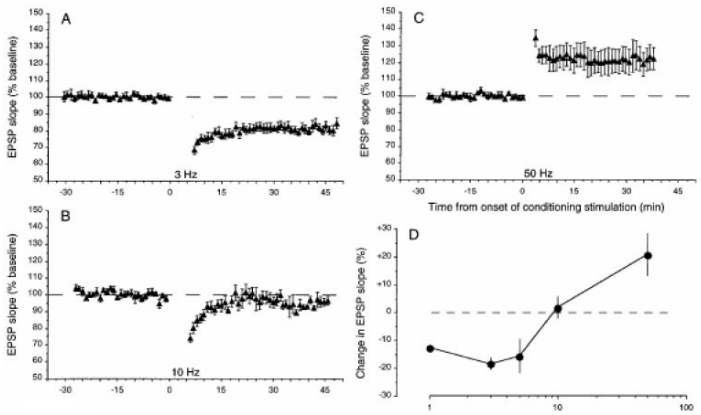


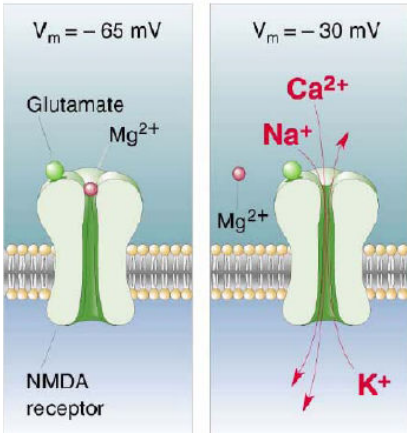


- The first type of stimulus used in this experiment was 1Hz tetanus.
- What is measured in the graph on the right is the EPSP amplitude. When the tetanus was applied an increase in EPSP amplitude was recorded that rapidly decayed.
- When the tetanus stimulation stopped, the EPSP amplitude became about 50% of what it used to be. This modification persisted for over 45 minutes.
- This phenomenon was termed long term depression (LTD) because there was a reduction in the size of the EPSP and because it had an enduring effect.



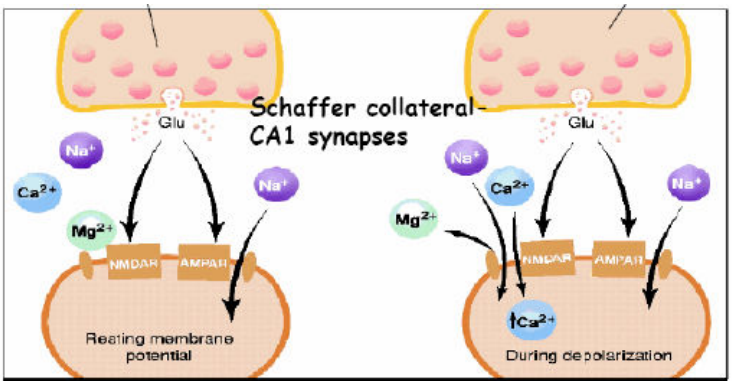
- In the experiment to the right the frequency of the tetanus was varied. A 3 Hz stimulus caused LTD, however the 10 Hz stimulus showed almost no depression. When the frequency was increased to 50 Hz the EPSP amplitude actually increased. This is called LTP or long term potentiation.
- Graph D summarizes the changes in EPSP amplitude with changing frequencies of tetanus stimulation.



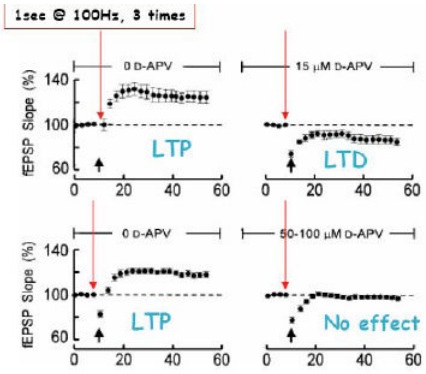


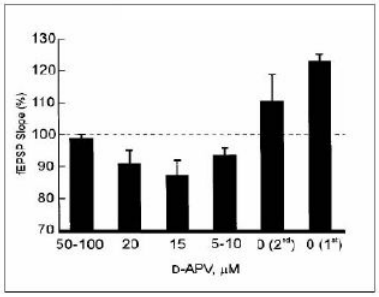
- Depending on the type of stimulation one gives, one can either increase or decrease the strength of the synaptic connection between the Schaffer collaterals and the CA1 neurons.

- What are the receptors that underlie LTD and LTP?
- NMDA Receptors – located at the synapse between the Schaffer collaterals and the CA1 neurons. NMDA receptors are responsive to glutamate. NMDA receptors are voltage dependent.
  - NMDA Receptors are normally blocked by Mg^{2+} at resting membrane potential but the Mg^{2+} block is removed by strong postsynaptic depolarization
  - NMDA receptors let sodium, calcium, and potassium pass through.

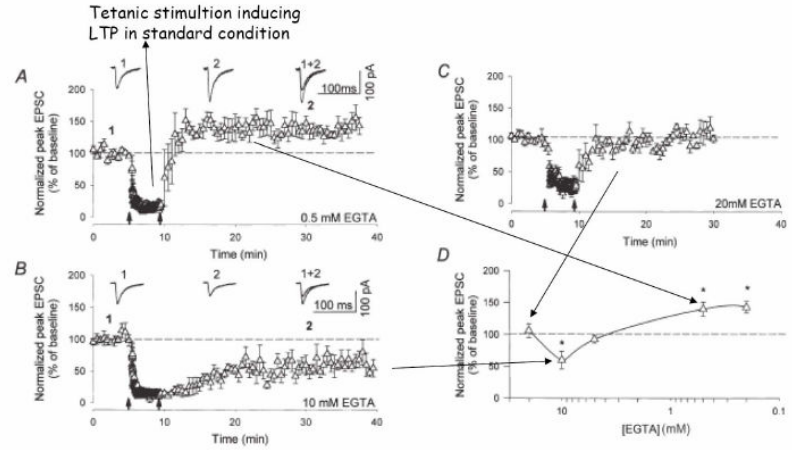


- The diagram on the right shows a typical synapse between the Schaffer collateral cells and the CA1 cells.
- The two major receptors present are NMDA receptors and AMPA receptors.
- APV blocks NMDA receptors (i.e. it prevents current from flowing through).
- EGTA is a calcium chelator, meaning that it will bind to calcium and render it inactive.
- Plasticity requires NMDA receptors
- Experiment: perused a slice of CA1 and CA3 cells they were recording with APV (blocks NMDA receptors)
- A 100 Hz tetanus was given which gives rise to LTP.
- When they gave 15µmol APV the same stimulus gave rise to LTD instead of LTP.
- When a wash-out was done to remove the APV the LTP was restored. This suggests this is a reversible effect.
- When they increased the concentration of APV to 50-100µM they found no effect. This suggests that the plasticity required NMDA receptors.
- The bar graph is a summary diagram which shows what is happening on the EPSP amplitude at various APV concentrations.
- Experiment (on the right) – they used EGTA which doesn't prevent calcium from entering the cell but prevents it from acting.
- At a low concentration of EGTA this drug is not sufficient to prevent LTP.
- However if one increases the concentration of this drug to 10µM a stimulus which would normally cause LTP, initiates a LTD.

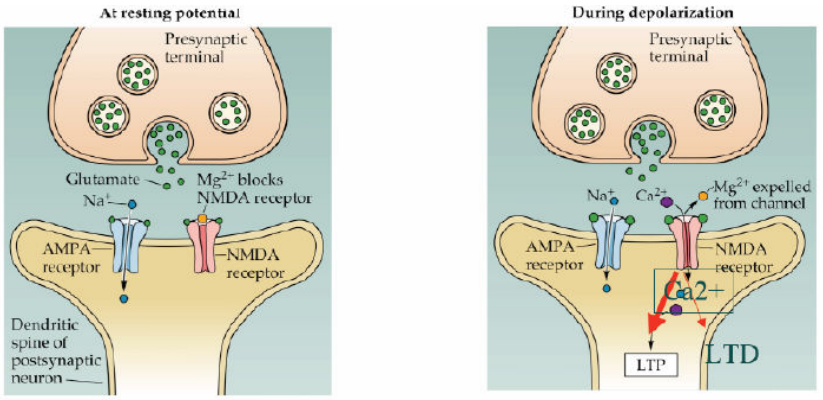




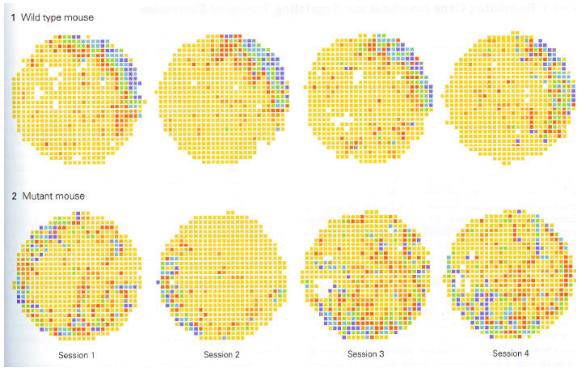
Cummings et. al , 1996



- Similarly to APV, at a high concentration the EGTA acts to simply bring the EPSP to its 100% value.
- Summary (on the right)
  - Again shows that NMDA receptors are blocked when the cell is at resting potential.
  - The cell needs to be depolarized by current flow through AMPA receptors in order for the NMDA receptors to become unblocked.

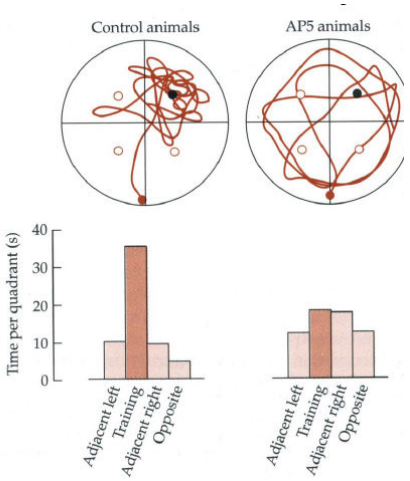


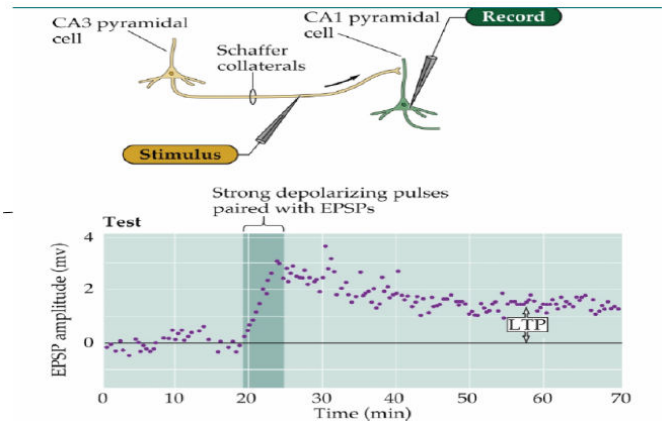
  - Moderate amounts of calcium will cause LTD and high concentrations of calcium will cause LTP.
  - What is thought to happen in LTD is that calcium will trigger intracellular signaling mechanisms which will lead to the removal of AMPA receptors (also sensitive to glutamate). AMPA receptors cause depolarization and therefore if there are less of these receptors the EPSP will be smaller.
  - Another hypothesis is that the amount of neurotransmitter per vesicle might decrease.
- LTD requires moderate NMDA activation and moderate calcium elevation
- LTP requires strong NMDA activation and high calcium elevation



- How does this relate to place fields?
- Place fields from wild-type mice are stable over time
- The mutant mouse has a knockout which antagonizes LTP
- Selective knockout of LTP does not prevent the formation of place fields
- Selective knockout of LTP **does prevent place field retention**
- This is a direct correlation between plasticity and the retention of place fields

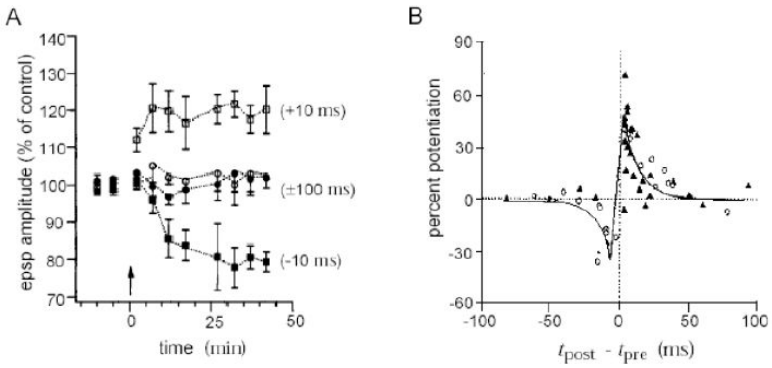
- Diagram on the right: Morris Water Maze
- The rat or mouse is placed in a water maze. There is a platform in the maze which the rat prefers to go to (so it doesn't have to swim). In control animals the rat or mouse will learn where the platform is located and it will learn to swim directly to it.
- In the mutated animal APV was injected into the animal and it blocked plasticity. As can be seen from the graph the animal never learned where the platform was.
- This shows that *plasticity is critical for memory*.





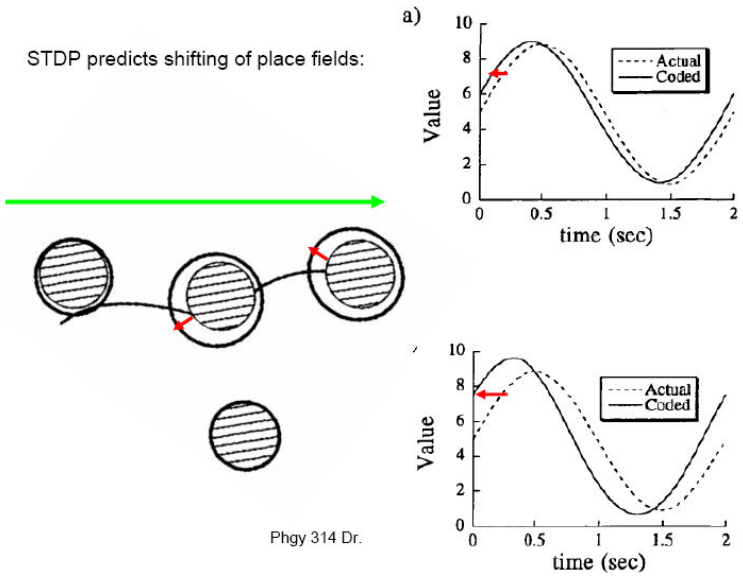
- Left diagram: One will pair stimulation of the Schaffer collaterals with EPSPs in the CA1 pyramidal cells and this will give rise to LTP.
- Therefore plasticity depends on the stimulus used.

- Spike Timing Dependent Plasticity: The type of plasticity is dependent on the actual timing of action potentials.
- In STDP it is important to look at the time difference between the presynaptic neuron and the postsynaptic EPSP
- Experiment (figure below). They stimulated both the pre and post synaptic cell they varied the time difference between the two stimulations and measured the change in EPSP size. If the post synaptic EPSP occurred before the presynaptic stimulation, one found depression of amplitude, whereas if the reverse occurred one found potentiation. If the time difference was too long (see the edges of diagram B) there was no change in amplitude.



Bi and Poo (1998).

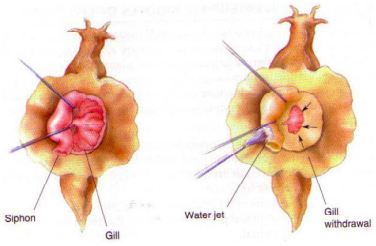
- STDP predicts the shifting of the place fields that we saw in the previous lecture (diagram below).
- STDP is ubiquitous and occurs in many places throughout the brain.



LEARNING AND MEMRY IN APLYSIA

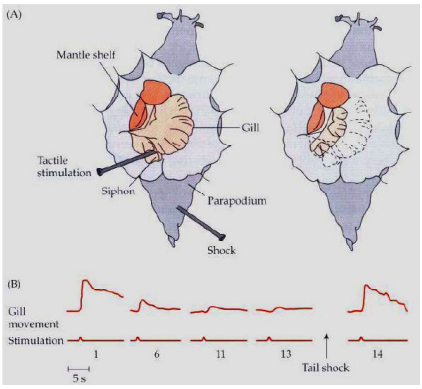
HISTORICAL PERSPECTIVE

- Dr. Kandel won the Nobel Prize in 2000 for his work
  - At the time, multi-recording units were not available, so it was difficult for work in the hippocampus because you couldn't related neural activity and what the animal was experiencing
  - Therefore, he worked on **implicit memory**, which **requires simple behavior, repeatable** behavior and has a well understood anatomy
  - Experimental works is most easily achieved in **invertebrates**, because of the simplicity of the nervous system compared to our own

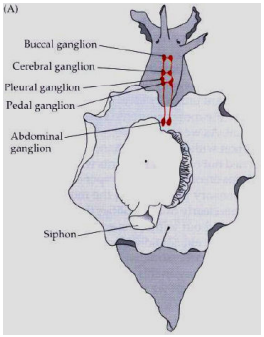


- Consider the **Aplysia Californica**
  - It has a **siphon** for excretion and ink ejection (protection) and a **gill** for respiration
  - If one gives a **tactile stimulation** to the **siphon**, the animal **withdraws its gill**
    - This is a classic, reflexive defensive mechanism
  - It is a slow moving gastropod mollusk, which has the advantages of having only a **few number of neurons (~20,000),** compared o 10^{11} neurons in the human brain
  - The gill-withdraw reflex, among other behaviour, is a very **reproducible**, especially in response to **unitary** stimuli
    - Advantage for experimental understanding

BEHAVIOUR AND ANATOMY OF APLYSIA

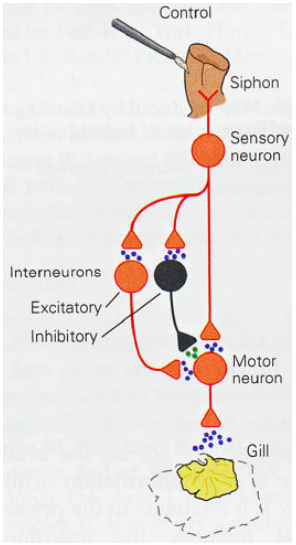


- **Habituation**
  - The aplysia will respond well to a given tactile stimulation
  - Over a given number of trials, response to the same stimuli will **decrease**
    - The animal becomes more accustomed to it, does not need to respond as much, as it sees the stimuli as **harmless**
  - At a certain point the animal will become **completely unresponsive** behaviourally (does not mean there are no sensory signals being sent)
  - Once different stimuli are applied (harmful), the habituation is removed **[dishabituation]**
    - Therefore, habituation of one stimuli does not necessarily mean it will have a decreased response to an alternate stimulus (tactile stimulation vs tail shock)
      - Especially when concerning **harmful stimuli**
  - In the diagram, the aplysia receives a harmful stimuli (tail shock) and the habituation of the response to tactile stimuli is removed and returns to control values
    - The response is continuously being modified and changed
    - (if the animal forgets about the harmful stimuli, it will continue to habituate)



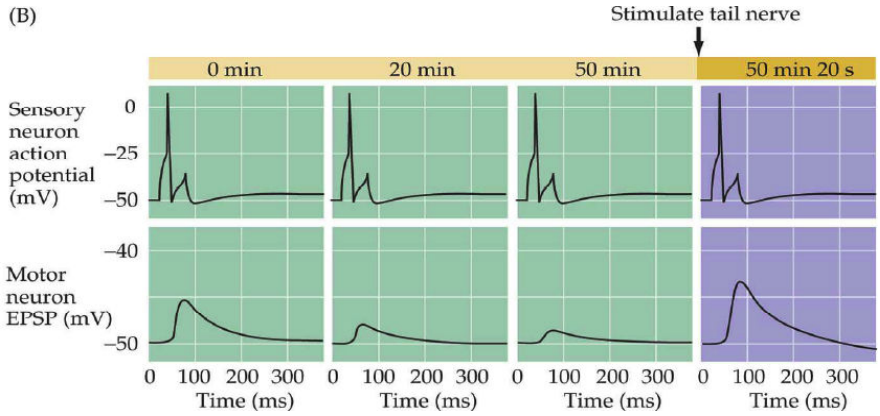
- **Neural Anatomy**
  - Although it has many ganglia [groups of neurons which are connected to represent different sensory areas], **the cerebral ganglion** is the central coordination center of the animal

- The animal is innervated by **touch receptors** in the siphon, which connect sensory neurons, which connect to **motor neurons** to modulate the gill withdrawal; there are also **interneurons present**
- There are **modulating effects:** the same sensory neurons in the siphon will contact both inhibitory and excitatory interneurons, which contact motor neurons

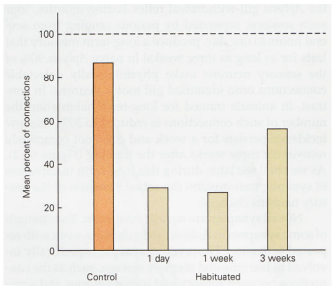


- **Simplified Anatomy:**
  - If one touches the siphon, one actives sensory neurons, which contact motor neurons and interneurons [excitatory and inhibitory] and activity from the motor neuron will drive the gill reflex
    - Simple feedforward mechanism
  - With this, one can determine how neuron activity correlates with gill withdrawal

- **Habituation Revisited:**
  - Rather than touching siphon, the experimenter is stimulating **sensory nerves** in the siphon
  - The motor neurons are simultaneously recorded, and the correlation between the two can be seen
  - We can see a decreased response of the motor neuron, although the amplitude of the EPSP in the pre-synaptic neuron is constant
  - Conclusion: ***the same action potential in the sensory nerve will elicit a smaller response in the post-synaptic cell (motor neuron)***
  - However, Upon activation of an alternate stimulus, the habituation is removed
  - *Can see neural mechanisms and behaviour correlate well*



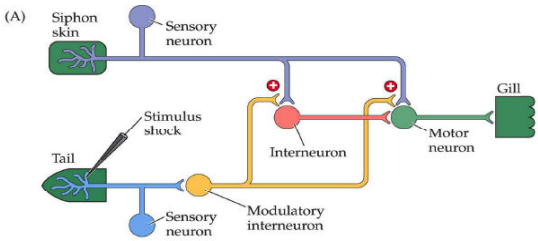
- **Why does this correlation take place?**
  - **Vesicles:**
    - Further experiments look at the number of vesicles released from the pre-synapse
    - Since the amount of neurotransmitter released is directly related to the number of vesicles, the average number of vesicles released will tell us approximately how much neurotransmitter is being released
      - Compare this amount between a habituated aplysia and a control
    - **Conclusion:** ***fewer vesicles released in habituated*** organisms, which means less neurotransmitter is being released, and a weaker impulse is received in the postsynaptic neuron
      - ***This must be at least one of the mechanisms to decreased the amplitude of the EPSP and is implicated in short-term habituation***
  - **Number of synaptic connections:**
    - Here, experimenters examine the number of connections between pre- and post- synapses.
    - After the animal is habituated for one day, the number of synaptic connections decreases



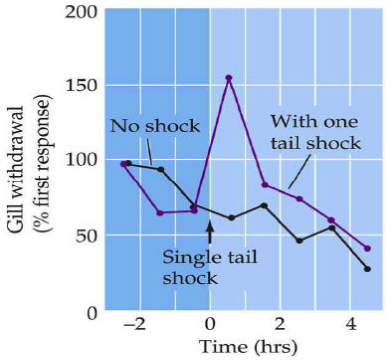
dramatically. The decrease is retained for an extended period of time and then begins to rise, if the stimuli is no longer present

- ***The number of synaptic connections decreasing leads to a weaker post-synaptic response and is implicated in long-term habituation***
  - Even if it begins to rise, the number of connections are well below the control values

- **Sensitization:**
  - Used to determine the neural mechanisms the animal uses to dehabituate
  - The siphon skin and the tail are connected to the same motor neurons of the gill
    - Therefore, when tail is shocked, the signal contacts modulatory interneurons, which will lead to motor neuron activation, which determines the amount by which the gill will withdraw



- **Short-term vs. long-term Habituation**
  - **First experiment shows:**
  - Graphs represent the amount of gill withdrawal as a percentage of total withdrawal
  - The aplysia were then habituated in different forms
    - i.e. with one tail shock
  - The representation shows that the animal becomes briefly sensitized, but the sensitization decreases over a period of time (i.e. the response returns to the control level)

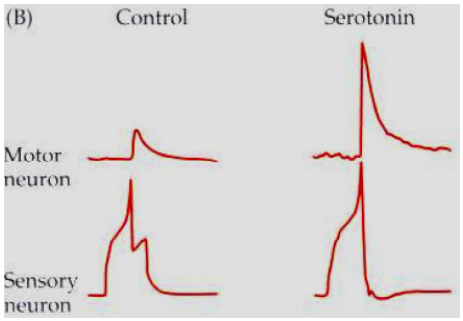


  - **Second experiment shows:**
  - Graphs show three different trials:
    - **1.** 4 single tails shocks: sensitization lasts for a longer time than previous experiment
    - **2.** 4 trains of tail shocks: is even longer (1 week)
    - **3.** 4 trains of tail shocks over four days: longest time of sensitization (up to 2 weeks)

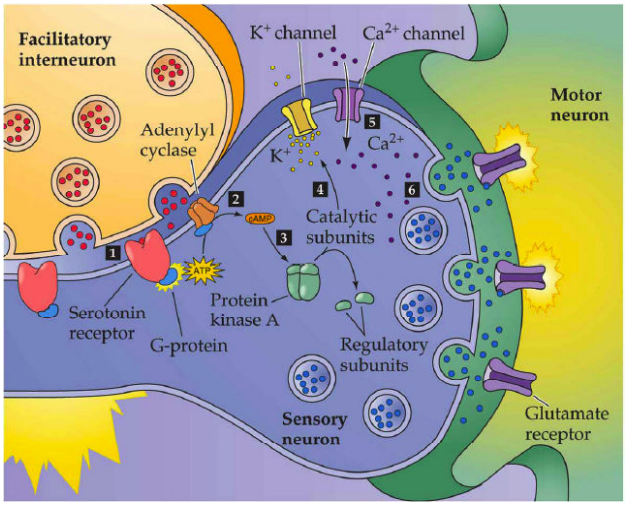
  - **Conclusion:** ***the more the animal is exposed to this stimuli, the longer the sensitization will last***
    - Few tail shocks lead to short-term memory/sensitization
    - Many tail shocks lead to long-term memory/sensitization

NEURAL MECHANISMS UNDERLYING LEARNING AND MEMORY

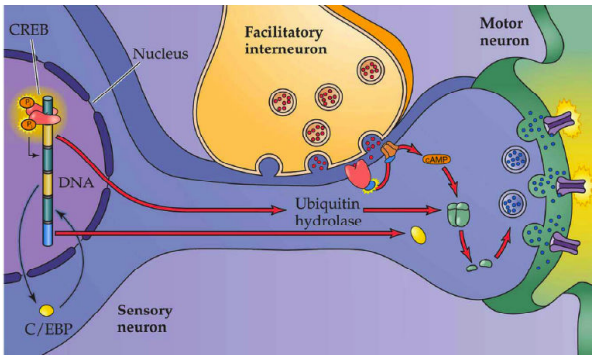
- **Experiment 1:**
  - **1.** Controlled stimulation of sensory neuron and motor response is seen to the left
  - **2.** Stimulation when the cell is bathed in **serotonin** is seen to the right → shows a much larger response
  - **Conclusion:** the serotonin response shows a larger motor neuron response than the control, so sensitization must be governed by synaptic facilitation mediated by serotonin (5HT)



- **Short-term Facilitation by Serotonin**
  - Note: Interneuron is synapsing on axon terminal
  - Stimulation of the interneuron causes serotonin to be released, which activates a G-protein cascade [cAMP and PKA]. PKA then downregulates a K^+ channel [in the pre-synaptic terminal], which hyperpolarizes the cell and one needs to further depolarize the cell. This depolarization opens voltage-dependent Ca^{2+} channels, which further depolarizes the cell and overall, the increased amount of depolarization will lead to the increased probability of vesicle release, which causes a greater amount of glutamate to be released and therefore an **increased response of the motor neuron**

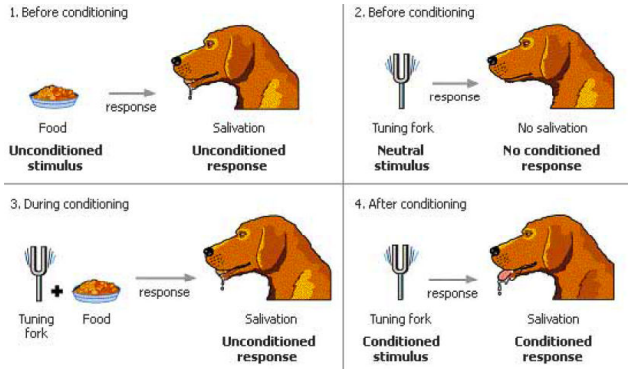


- **Long-term Facilitation by Serotonin**
  - The interneuron causes a greater release of serotonin, which goes through the same G-protein steps as stated above. However, the production of PKA causes the sensory neuron to release **ubiquitin hydrolase** and **mRNA** via the CREB pathway. The ubiquitin will give rise to **new synaptic connections**. *The details are in the text,* but the important point to note is that there is **creation of new synapses,** which allows for long-term sensitization to the signal

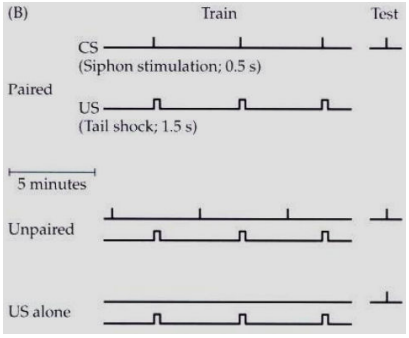


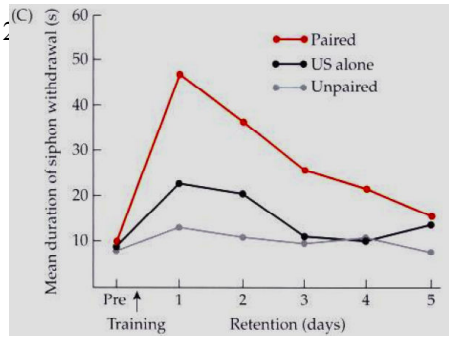
CLASSICAL CONDITIONING IN APLYSIA

- Classical Conditioning may be better known as **Associative Learning**
- **Experiment One:**
  - A dog is given food, which causes him to mount a hunger response (unconditioned). The food is then paired with a noise (from tuning fork), that alone, the dog will not respond to. After conditioning the dog to realize that the noise means food, he will then mount the same response (as the unconditioned response to food), when he hears the noise, even if no food is present. *See diagram to the right*



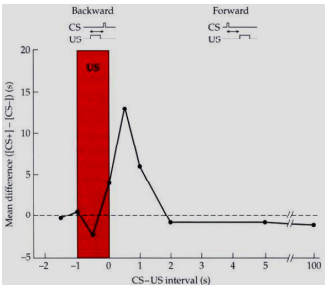
- **Experiment Two:**
  - In this case, the stimulation of the siphon is paired with a tail shock. There is then a separate trial conducted that unpairs the stimuli and one which stimulates the tail alone.
  - The resulting graph shows that:
    - **Pairing both stimuli causes a longer duration of retraction over time** [habituation]



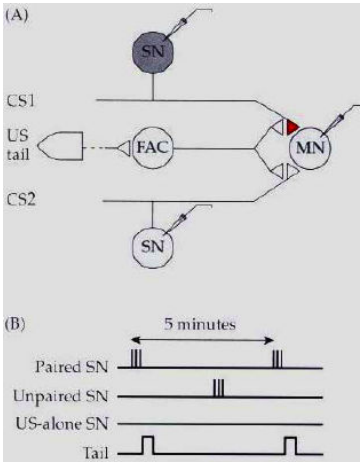


    - Can be implicated in long-term memory
  - If the stimuli are unpaired, there is no change in sensitization over time
  - If the tail is stimulated alone, there will be a slight retention of sensitization, but no where near the sensitization due to the paired stimuli

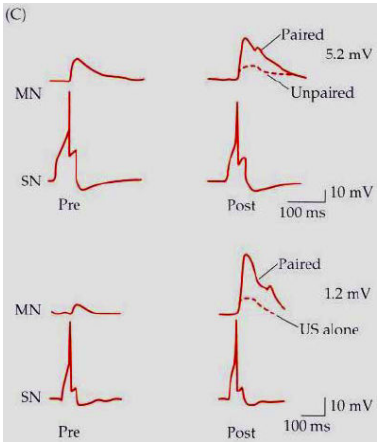
- **Experiment Three:**
  - Relates to spike-timing dependent plasticity [*see last class*]
  - In this case, the **time difference** between each stimuli was varied
  - Depending on **temporal order** between the two, there are drastic differences in behavioural response to the animal:
    - If the tail is stimulated before touching the siphon, there is an **increase in facilitation**
    - If the siphon is touched before the tail, there is **no facilitation** [dotted graph]
  - **Conclusion:** the animal is able to predict occurrence of order, in certain cases, but the **timing is important in habituation of aplysia**



- **From these Experiments;**
  - Aplysia displays **classical conditioning**
  - Aplysia can learn to **predict** a tactile stimulus from a tail shock, but not the reverse [providing the time difference between the two is not too large]



- **Neural Correlate of Classical Conditioning**
  - ***See set-up of neurons*** *(see left)**:***
    - The sensory neurons synapse on the same motor neuron, so one can stimulate two different sensory neurons that will illicit a response in the same motor neuron
  - **4 paradigms experimented:**
    - Sensory nerves were paired in stimulation; sensory nerves were unpaired in stimulation; tail shock alone; sensory nerve of tail stimulated alone
  - **Results:**
    - Action potentials in the sensory nerve results in an EPSP in the motor nerve
    - After **training (paired or unpaired),** the post-synaptic response is measured again
    - Finds that **correlating behaviour** exists, the ***unpaired training gave rise to a decrease in post-synaptic response (gill withdrawal), but paired shows increased post-synaptic response in the motor neuron***
      - i.e. since the tail shock and tactile stimulus were paired together, after training, when one of the stimulus is felt, the response will be the same
    - **Sensory tail alone:** almost no post-synaptic response in the



motor neuron compared to the paired stimulus

- **Classical conditioning is associated with plasticity**
    - By modulating sensory and motor neuron connections, one can explain the facilitation of the reflexes as well as habituation

TAKE HOME POINT

- The animal can habituate to stimuli is sees as harmless, such as tactile stimuli. However, harmful stimuli, such as a tail shock, will lead to dehabituation of the original stimuli
- Habituation occurs as a result of the sensory neuron releasing less vesicles to the post-synaptic motor neuron as well as decreasing the number of connections between the two
- Neural mechanisms underlying long-term and short-term sensitization involve serotonin
    - Both are mediated by signaling cascades in the axon terminals (*see diagrams*)
- Classical conditioning associates two or more ideas together, so that after training, if one stimulus is presented on its own, the same result is seen for both.
    - Also called associative learning
    - Can be implicated in long-term sensitization [plasticity]
- In aplysia, the timing of the stimuli plays an important role in conditioning and therefore sensitization

SONG LEARNING IN BIRDS

- We are the only primates who **learn** their language

REVIEW OF PREVIOUS LECTURES

- **Lecture One:** Place Fields Within the Hippocampus
  - Hippocampal growth in London taxi drivers:
    - Posterior **hippocampus** was larger in taxi drivers compared to control
  - CA1 cells in rodents were spatially dependent
    - They fired at a specific spot in place: **place fields**
- **Lecture Two:** Sensory Control Over Place Fields
  - How the coding **of place fields can be altered**
    - External versus internal stimuli
      - i.e. rotations, novel stimuli, translations, etc
- **Lecture Three:** Synaptic Plasticity
  - Neural mechanisms that underlie learning
  - Schaffer collaterals were stimulated and CA1 cells were recorded
    - When certain stimuli (tetani) was applied, there were different effects depending on frequency of the trains:
      - Low frequency [3Hz]: **long-term depression [LTD]**
      - High frequency [50Hz]: **long-term potentiation [LTP]**
      - Depending on the frequency, there was a crossing point [10Hz]: which gave no change in the post-synaptic response
  - Molecular mechanisms that give rise to plasticity:
    - In CA1 requires **NMDA receptors** [LTD and LTP are completely blocked without] and **Ca^{2+}** [experiment using Ca^{2+} chelator (EDTA) prevents LTP and LDP]
    - Memory retention requires NMDA receptors [experiment of swimming rat]
      - When NMDA receptors were blocked with APV, rat will not remember training
- **Lecture Four:** Learning in Aplysia
  - Simple neuroanatomy and behavior were easily correlated
  - Habituation occurs based on tactile stimuli to the siphon
    - Will decrease the gill withdrawal over time [decreased behavioral response]
  - If a noxious stimulus is applied, there is immediate sensitization
  - Habituation is due to a decrease in the post-synaptic response

  - **LTP:** glutamate is released and binds to either AMPA receptors (allows Na^+ passage as long as glutamate is bound), as well as NMDA receptors (first require a depolarization to become active (repel Mg^{2+} plug), therefore only adds to the depolarization after AMPA receptor has depolarized the cell to a specific point) (***NMDA receptors allow passage of Na^+ and Ca^{2+}, which is involved in plasticity***)
    - **Ca^{2+}** activate PKC and Ca^{2+}/calmodulin kinase II, which lead to substrate phosphorylation and will allow more receptors to be inserted into the post-synaptic cell, allowing a longer response upon stimulation
  - **LTD:** action potentials release glutamate into the synaptic cleft, AMPA receptors are activated, which activate NMDA receptors, allowing Ca^{2+} in
    - **Ca^{2+}** activates **protein phosphatases**, which modulates the removal of AMPA receptors from the post-synaptic cell through dephosphorylation
  - ***All these activities occur at the same time***
    - Ca^{2+} has different affinities for each enzyme

- **More attracted to the phosphatases**, so if there is a lower Ca^{2+} entrance into the cell, there will be a LTD response based on affinity to Ca^{2+}
- When lots of Ca^{2+} enters, some will bind to PKC and Calmodulin, allowing LTP responses [PKC response dominates over phosphatase response]

- **Aplysia** sensory contacts the motor neurons; the facilitation of the gill withdrawal reflex is mediated by **serotonin**, which leads to cAMP to activate PKA, which will down-regulate K^+ channel, will let Ca^{2+} in and increase the number of vesicles released (short-term) or cAMP will travel to nucleus to give rise to synaptic growth (long-term)
- In **humans**, Ca^{2+} moves into the cell and will activate the Ca^{2+}/calmodulin kinase to lead to insertion or deletion of AMPA receptors (short-term) or **dopamine** activation will lead to longer retention of LTP (long-term) by cAMP traveling to the nucleus to synthesize proteins to facilitate an increase in synaptic connections
  - **Parallel between invertebrates and mammalian hippocampal neuron**

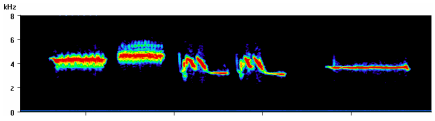
- *Cellular and molecular mechanisms underlying plasticity are similar cross species*
- *Pre- and post-synaptic mechanisms of plasticity*
  - *Pre: increase/decrease in vesicle pool*
  - *Post: insertion/deletion of AMPA receptors, number of synaptic boutons*

CHARACTERISTICS OF HUMAN COMMUNICATION

- Language develops **spontaneously**
  - i.e. sign language *evolved*: deaf people developed this on their own
- Exposure to vocalizations **early in development** is critical for vocal learning
  - i.e. Geenie, who was found at the age of 12, had no interaction with other people in her life, had a lot of difficulty learning how to speak
    - Doesn't have to be direct interaction, could be a tape, etc
- Period of **practice** gradually leading to a match between the model and imitation
  - Infants will mimic people around them and learn over time what the correct pronunciation is
- After learning, **loss of feedback causes a gradual deterioration**
  - i.e. if you become deaf, your vocalizations will decrease
    - Auditory feedback is critical for proper speaking
- **Social interactions** influence development of vocal learning
  - Learn the language we are exposed to as children
- **Highly structured**

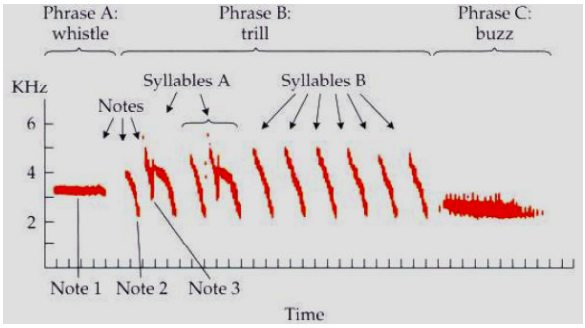
- **Spectrograph:**
  - Represents frequency breakdown over time
  - Can hear 20-20,000Hz
  - This graph is representing the amplitude of different frequency components in speech over time
    - Represents one sentence: "Did you hit it to Tom?"
  - Useful because it provides information about the different frequencies

INTRODUCTION TO SONG BIRDS

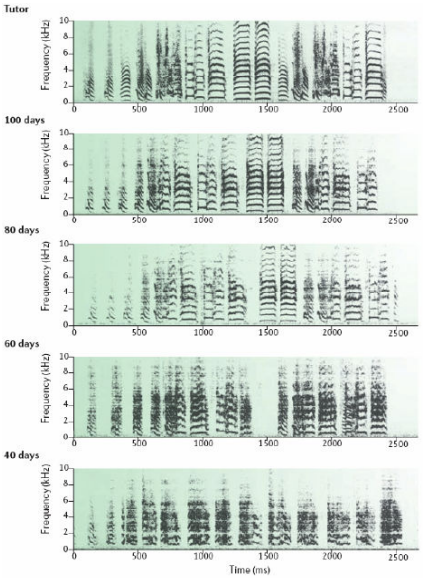


- **White Crown Sparrow (WCS) or Zebra Finch (ZF)**
- Spectrograph of a ZF
  - Sounds nothing like human speech
  - Although you can't tell what the bird is saying, there is **structure** within the frequencies

- Allows the song to be decomposed for analysis
- Spectrograph of WCS
  - This song is broken down into **three phrases**
    - A: whistle
    - B: trill
    - C: buzz
    - Phrases are further decomposed to **syllables**: periods of vocal activity followed by silence
- ***Songs are highly structured and stereotyped***

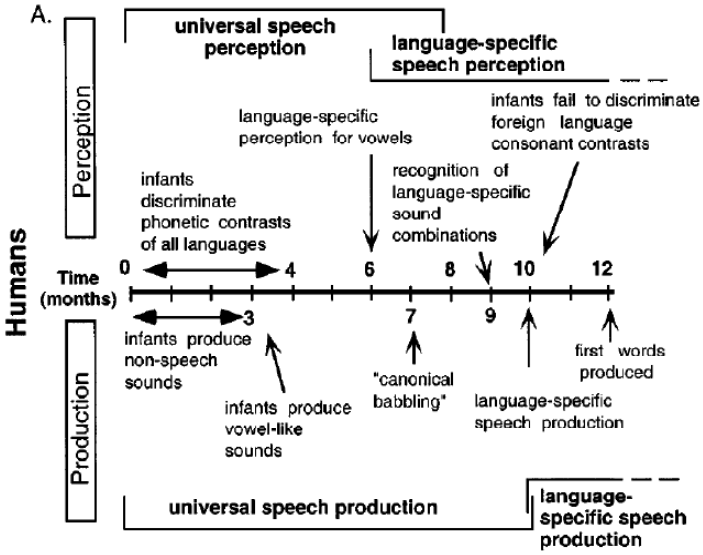


- **Learning:**
  - **Listening Phase:** baby listens to the adults (in this case, only ZF males sing) for a period of approximately 30 days to form a memory template for the song
  - **Practice Phase:** eventually will start practicing and over time becomes better at imitation
  - **Crystallization:** after approximately 90 days, the song will not change anymore: fixed
    - Each bird has its own song: like a calling card
    - Leads to **stereotyped song**



- **Experiment One:** Bolhuis and Gahr, 2006
  - Bird was isolated after hatching, but could listen to a speaker of a tutor, which periodically played a tune
  - The bird sill developed a song
    - Does not need interaction with another bird (the tutor may be an audiotape)
  - Over time, the younger bird's song will mimic the tutor's song more and more, although it will never completely resemble it
  - ***Birds will attempt to imitate what they hear and practice until they have developed their own "way of talking"***

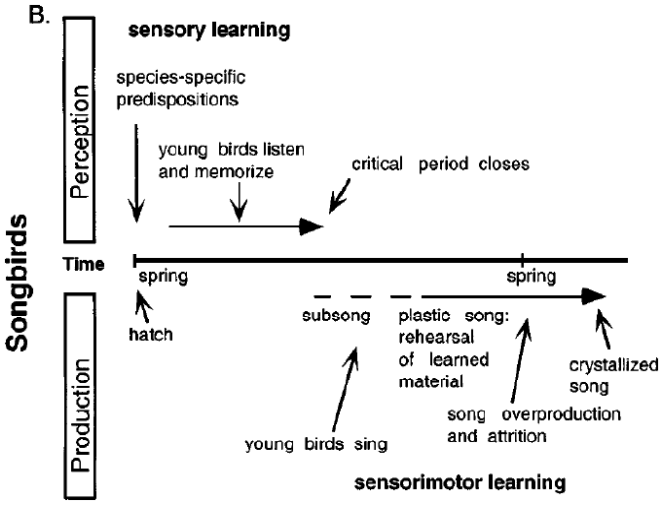
- **Comparison to Human Production:**
  - Babies will initially produce non-speech sounds
  - Around **3 months:** They begin to produce vowel like sounds ("Aaaah")
  - Around **7 months:** canonical babbling: constants and vowels
    - i.e. Ba-Ba-Ba → imitation of words
  - Around **9 months:** can recognize sound combinations of the language they hear
  - Around **10 months:** language-specific speech-production
  - Around **one year:** first words
  - Infants are able reproduce any and all languages on earth
  - As they mature, they become more capable for speech production of one language



- **Comparison to Human Perception:**
  - Infants are able to sense **phonetic contrasts** in different languages

- i.e. will suckle more actively in response to a novel sound [phonetic contrasts]
- Has **universal speech perceptions**
  - Perception is lost over time and is replaced by **language-specific speech perception**
    - There is a critical period to learning languages [first 12 years of life]
      - i.e. it will be harder to learn a new language after this point

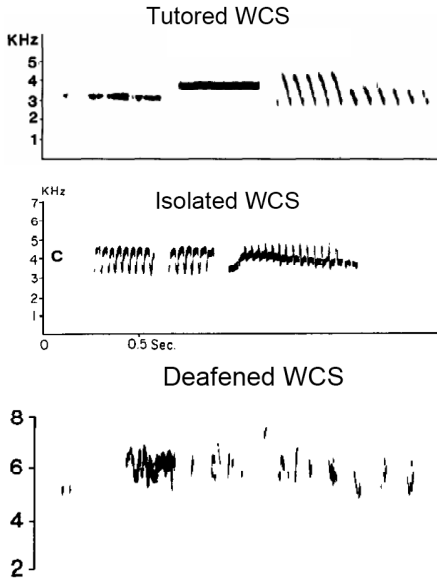
- **Comparison to Songbird Perception:**
  - Born with **species-specific predispositions**
    - i.e. ZF will have a predisposition to learn a ZF song, rather than WSF
  - Young birds **listen to tutor and memorize** their song
    - During this period, they are very **sensitive to changes**, as well as other tutor songs [*see below*]
    - Critical period closes approximately **30 days after birth**



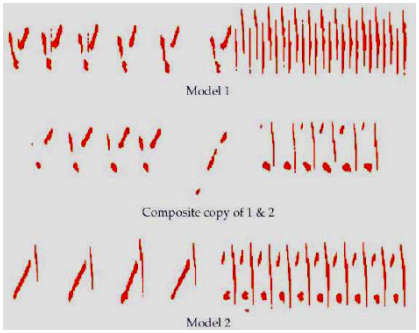
- **Comparison to Songbird Production:**
  - At 30 days: will begin to practice memorized song
    - Will not be very good, but with development and practice, improves
  - After approximately **one year:** song is crystallized in the adult and they will sing their song for the rest of their livelihood

COMMALITIES WITH HUMANS

- **Experiment of WCS:** Konishi, 1985
  - Birds require a tutor
  - If isolated at birth and does not hear any tutor will develop abnormal vocalizations
    - Analogous to Geenie
    - ***Compare two graphs to the right***
  - If the bird is **deafened:** song is not the same, regardless of exposure to other birds
  - ***Auditory feedback must be important in modulation of the song***

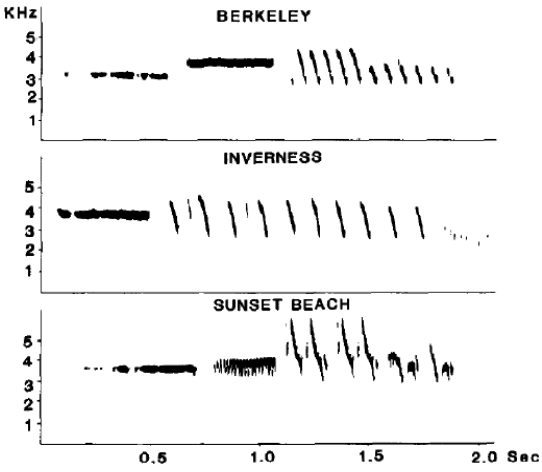


- **Songs and Creativity:**
  - Language is highly creative and evolutionary
  - **Experiment** shows that this is also present in birds
    - Song bird was exposed to two tutor songs
    - The resulting song, after crystallization, the bird had created a **composite model of both songs** [combined songs]



- **Region-Specific:**
  - WCS are found all around CA
    - Each area of CA is different
  - *Similar to dialects of the human language*

- Transmitted from generation to generation



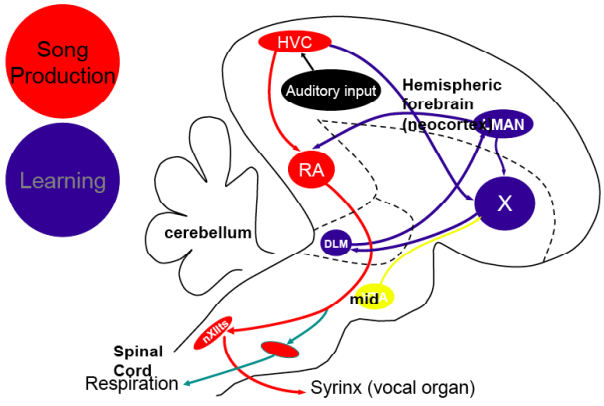
- **Overview:**
  - Commonalities with humans
  - Song has a detailed structure
  - Song develops spontaneously
  - Normal song requires social interaction
  - Normal song requires auditory feedback
  - *It is important to note that there is no grammar, words, etc. subsets and blocks to not have the same meaning, but still shares many commonalities with humans*

NEURAL CIRCUITRY MEDIATING SONG LEARNING

- **Experiment:** Constructing Song Syntax: Rose et al., 2004
  - Breakdown into syllables
    - Easier to remember the order of syllables than the entire line
  - WCS was trained with **only pairs** of syllables, not a complete song
    - i.e. A-B, B-C , C-D, D-E
  - Training with these syllables for a year
  - Developed a **completely normal song**
    - i.e. ABCDE
  - Animal just stores temporal order of syllables
  - Can be sung forward or backwards, depending on how syllables are placed together

  - **If the order is presented differently, or without syllables** [i.e. AB, BC]
    - The final song will be random

- **Error-Driven Model for Leaning and Maintaining the Song:**
  - **1.** Birdbrain stores a model of the song, or template
  - **2.** Bird attempts to reproduce the model
  - **3.** Acoustic and motor feedback allows comparison of the system
    - Attempt to correct the mismatch during the plastic phase

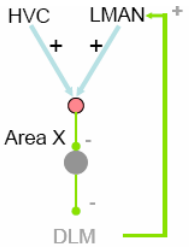


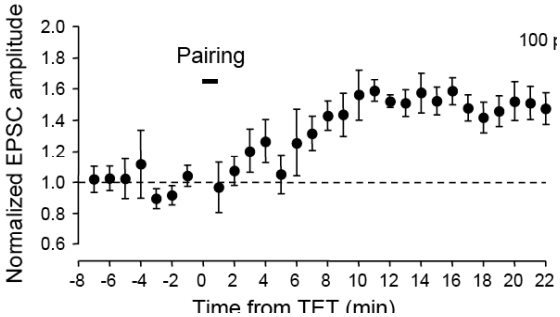
- **The Song System:**
  - **Neocortex** is the most important place
  - Auditory input moves through the **HVC**
    - Two pathways from here:
      - **1.** Song Production

- **HVC** is tuned to the animals own song
- Move to the **RA:** control of motor functions, such as the trachiosyringeal portion of the nucleus hypoglossus, **[nXIIts]** which projects to the **syrinx** [vocal organ]

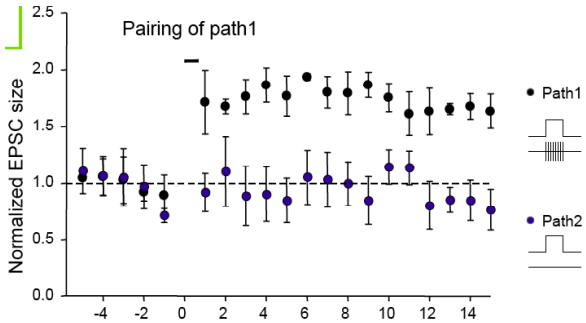
- **2.** Learning
  - Consists of three areas:
    - **LMAN:** respond to the tutor's song
      - Assume template storage here
    - **X:** respond to the own song [from HVC] and template [from LMAN]
      - Assume comparison here and generate signal for learning
    - **DLM:**
  - There is a **feedback loop** between all three areas and LMAN projects to the song production pathway [RA]
  - If there is a **bilateral lesion** in between X and LMAN in juveniles, there is decrease in song learning**;** if in adults, no effect

- **LTP in Adult Birds:**
  - All graphs will now show recordings from Area X, which receives inputs from both LMAN and HVC
  - **1. LTP:** 100 pulse at 100Hz for several trials
    - Observes increase in post-synaptic response in adult birds [LTP]

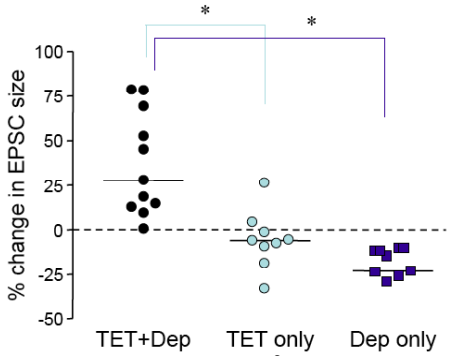




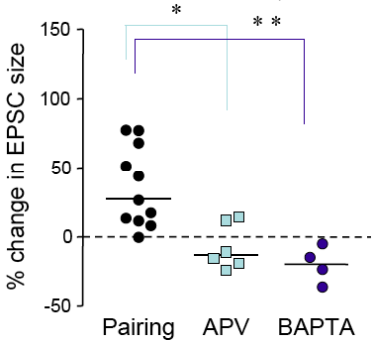
  - **2. Synapse specific**
    - i.e. if you stimulate Path One and record, there is LTP
    - i.e. if you stimulate Path One and record, but then stimulate Path Two [HVC], there is no LTP



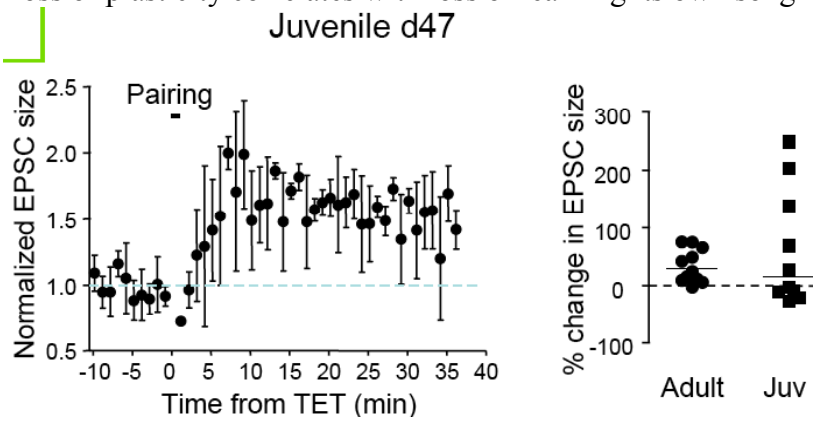
  - **3. Pre- and Post-synaptic activity**
    - Depolarization of post-synaptic membrane and a tetanus shows a greater LTP than if just a tetanus by itself or just a depolarization by itself



- **4.** NMDA Receptors and Ca^{2+}
  - **APV: blocks NMDA, BAPTA: another Ca^{2+} chelator**



- **5.** LTP and Juvenile birds
  - Plasticity is more prevalent in juvenile birds than in adults
  - Loss of plasticity correlates with loss of learning its own song



TAKE HOME POINTS

- Human speech, like the songbirds, is highly structured into specific components
- Can be represented as a spectrograph [time varying frequency spectrum]
- Song birds move through three stages to crystallize their song
  - Do not have to be exposed to a living being to do this, any noise is fine
- Song develops spontaneously
- Song development requires social interaction [includes listening to a microphone] and auditory feedback
- Can be modulated depending on exposure [i.e. creativity] or region
- Learning of the song depends on temporal order of the syllables presented
- Acoustic and motor feedback allows the comparison of the new song with the template for modulation
- Auditory input move through the HVC, which gives rise to the Song Production Pathway and the Learning Pathway [which consists of Area X, LMAN, and DLM, which create a feedback loop]
- LTP occurs in song birds to modulate synaptic plasticity