Physiology Undergraduate League of Students

McIntyre Medical Building
3655 Promenade Sir William Osler
Montréal, Québec
Canada H3G 1Y6

Phone: 514-398-8253
Email: puls@sus.mcgill.ca
Website: http://puls.sus.mcgill.ca

puls ntcs

phgy314

set #13

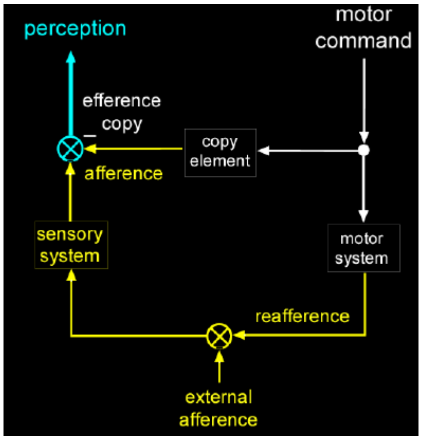
lecture #:	*date:*	*professor:*
37	*Monday, December 4, 2006*	*Dr. Chacron*

announcements:

- *This is the last lecture of the PHGY 314 course*
- *Good luck on the Final Exam!*

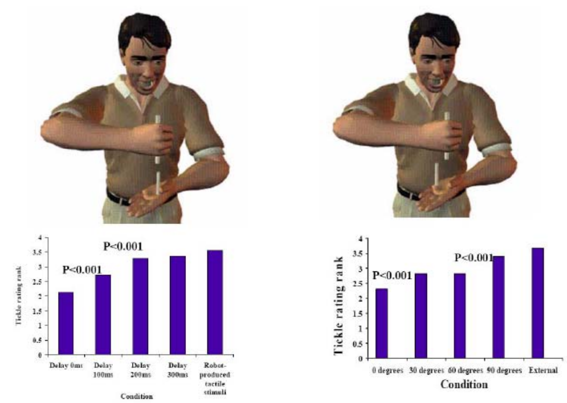
Previous lecture: Song learning in song birds

- Listening phase: As juveniles, songbirds need to store a template of the song they learn from their tutor, sung by their father.
- Learning phase: birds attempt to reproduce the model. They hear what they sing, and compare this with the tutor song. Differences generate an error signal, and they perform vocal motor correction.
- Over time, their song becomes closer to tutor song.



Neural mechanism for generation of error signals

- **reafference** = sensory input to brain caused by animal's own motion
  - o eg. Movement of head leads to shift in visual field.
- **efference copy** = copy of the efferent motor impulses produced by brain to move a muscle, which is left in the CNS
- When the efference copy (prediction of how the muscle should be moving) is compared/combined with the reafference, it gives rise to the **perceived sensory signal.**



The Tickling Experiment

- by Von Holst and Mittelstaedt, 1950
- In the model:
  - **Efference copy = motor command** that gives rise to arm movement (<u>contains both temporal and spatial information</u>)
  - **reafference** = tactile stimulus
  - **perceived stimulus** = tickling sensation

Experimental set up:

- the subject gives a motor command through a device linked to a computer, which may alter the input, and then feeds back a tickling sensation on the subject's hand through an actuator

Varying temporal delay: (blue graph on left side)

- The actuator generates tickling stimulus the hand after a certain time delay following the motor command.
- The greater the time delay, the greater the subject's rating perceived tickling sensation.

Varying angular (spatial) discrepancy: (blue graph on right side)

- The actuator generates a motion stimulus different in direction than the motor command.
- An increased angle of mismatch of motion increases perceived tickling sensation.
- As the discrepancy between predicted (efference copy) and actual sensory feedback (reafference) increases, your system realizes that the perceived stimulus is more likely due to an external stimulus, and a tickling sensation occurs.

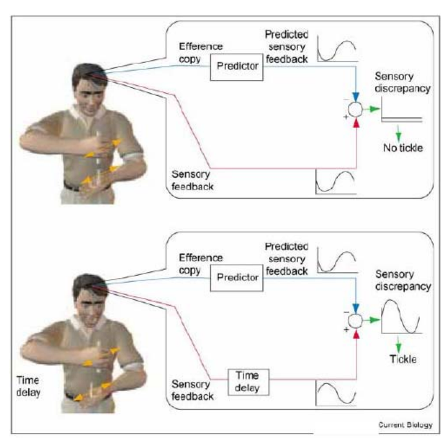
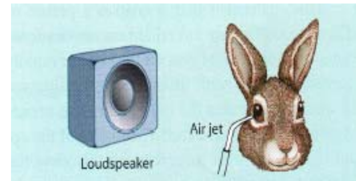


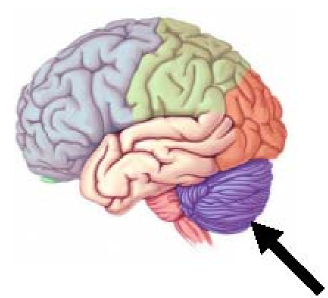
Figure: Summary diagram - Model of the Sensory Circuit. In the second figure, the discrepancy is shown by the phase difference in the sinusoidal waves.

The Cerebellum



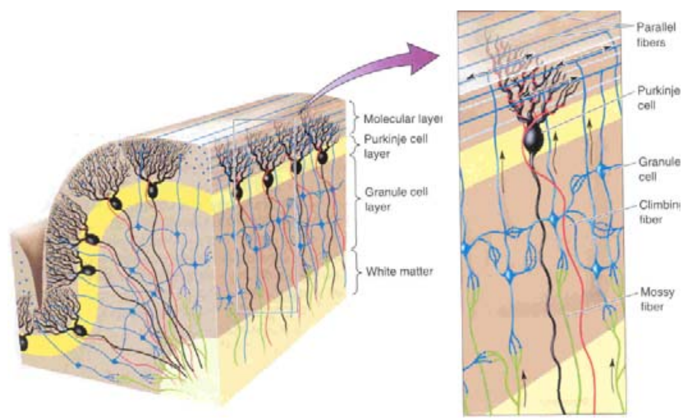
- **Classical conditioning experiment:** a sound is paired to an air jet to cause rabbit to blink
- Early in training, the rabbit is unable to predict the onset of the air jet based on tone – rabbits close eye at the same time of the air puff onset
- Later in training, rabbit learns to predict the onset of the air puff, by measuring the time difference between the tone and air puff
  - o Demonstrated with varying time delay in different trainings sessions
- Cerebellar lesion – late in training, rabbits still unable to measure time delay/unable to associate tone and air jet; however, rabbits still have sensorimotor function intact (ie. can close eyelids)
- Cerebellum is required for motor learning, and is required for timing of movements

The cerebellum is thought to be involved in

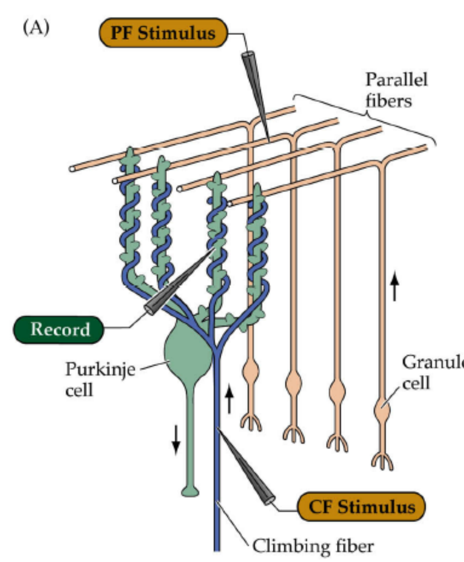


1. Balance
2. Coordinating movement
3. Timing of movements (e.g. in rabbit experiment)
4. Timing of discontinuous movements (e.g. eye movements)
5. Motor learning - acquiring and maintaining already-learned motor movements (e.g. rabbit with cerebellar lesion was unable to learn)

Cerebellum Anatomy



- the cerebellum is present in all vertebrates
- one of the most anatomically conserved structures throughout evolution
  - o ie. the anatomy of the earliest vertebrate animal (lamprey) is similar to ours, while ours is more complex, of course
- **Purkinje cells (PKC)** receive various types of inputs:
  - o **Climbing fiber (CF)** input (sensory), innervate the entirety of Purkinje dendritic trees
  - o **Mossy fiber** input, which contact **granule cells**
- **Granule cell** axons make up **parallel fibers (PF)**, which run the length of cerebellum, and make contact with most Purkinje cells

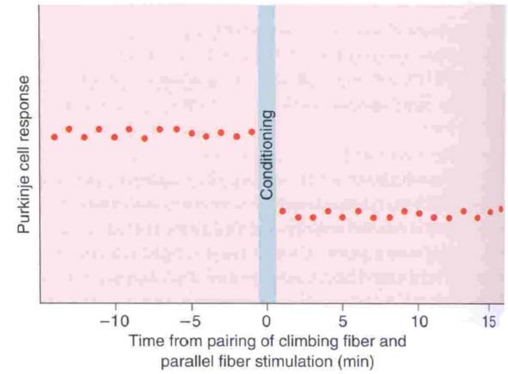


Cerebellum Plasticity

- experiment: slice of rat cerebellum, maintained in artificial cerebral spinal fluid
- electrode recording from Purkinje cell while stimulating CF and PF
  - o PF comes from granule cells and carry efference copy of motor command
- PKC dendrites able to compare the discrepancy between input from PF and CF; PKC axons signal whether there is an error signal or not

Long Term Depression in Cerebellum

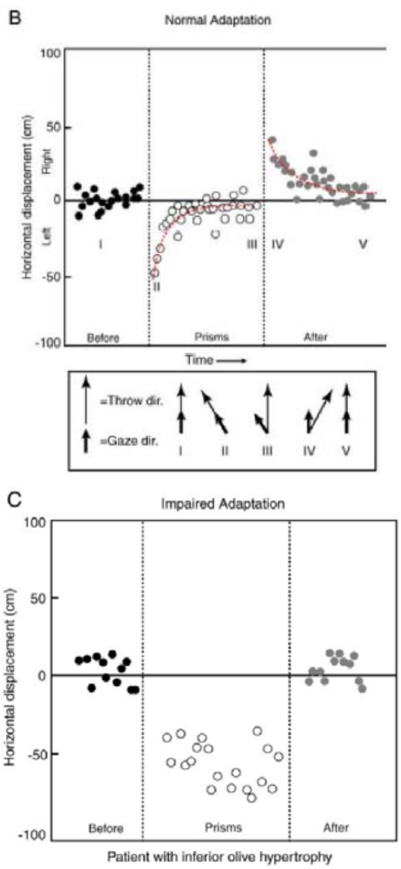
- measure Purkinje response by measuring amplitude of postsynaptic potential
- control: stimulation of PF or CF by itself
- co-activation: pairing CF and PF stimuli at same time <u>decreases</u> PKC response over time (i.e. LTD)



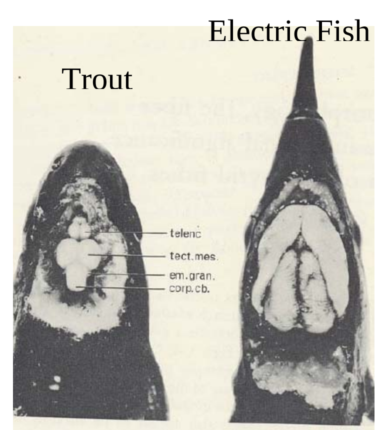
How does cerebellar LTD help achieve cancellation of expected stimuli?

- Plasticity changes the strength of synaptic connections
- cerebellum involved in motor learning

<u>Ball Throwing Experiment</u> (by Martin et al.)



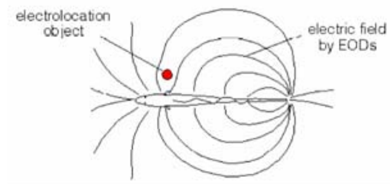
- **Control Experiment:** subject throws clay ball to 2 m target on wall
  - **Before**: normal subjects 24-80 yrs old can perform fairly well
  - **Prisms:** subjects were then asked to wear prism glasses, which bend light in particular direction
    - initially, they threw where they gazed
    - later: they learned the discrepancy between gaze and throwing direction and corrected for it
  - **After:** glasses were removed
    - Discrepancy occurred in the other direction
    - subjects **overcompensated**
- shows that we can learn to correct when there are discrepancies
- **Cerebellar Lesion Experiment**: patients had sufficient sensorimotor accuracy, they were able to throw ball accurately under control conditions
  - **Prisms:** however, patients were <u>incapable of learning</u> to compensate when glasses were donned
  - **After:** glasses removed, throws remain on target
- The experiment shows that cerebellum is **not** required for sensorimotor function, but is required for learning motor skills in new conditions.
  - Similar to what we saw in the rabbit classical conditioning experiment
  - plasticity of the cerebellum is involved in some way



<u>Electric Fish: Model System for Studying Sensory Reafference</u>

- Gives us an understanding of how LTD gives rise to reafferent stimuli
- These fish are found in the basin of the Amazon river where the water is murky water, therefore eyesight not effective. They developed electrolocation, where the fish emit electric fields through an electric organ in their tail
- Even though humans do not sense electric fields, we study them because for understanding cancellation of reafferent input because they are a good model system for us:
  - They have an **enormous** cerebellum (large cerebellum to body

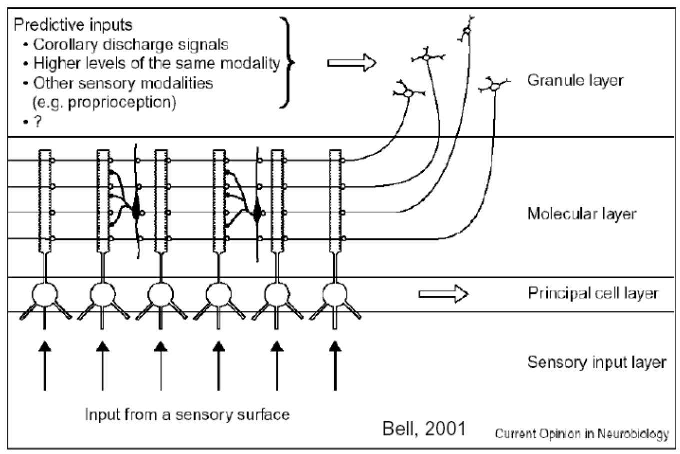
weight ratio
- o Cerebellar anatomy is conserved across vertebrates
- o Electric fish have "simple" anatomy and behaviors.



Electrolocation
- electric fields are produced in pulses, typically 20-30 pulses/min
- frequency of pulses increase/decrease depending on the novelty of the environment
- fish needs to sense perturbations of emitted electric fields in the environment generated by prey/objects etc. and distinguish these from the perturbations generated by their own tail movement
- **Movie shown in class:** shows effects of tail bending on electric field, since the electric organ is located in the tail. The electric field increases on same side as the tail movement, decreases on the opposite side.

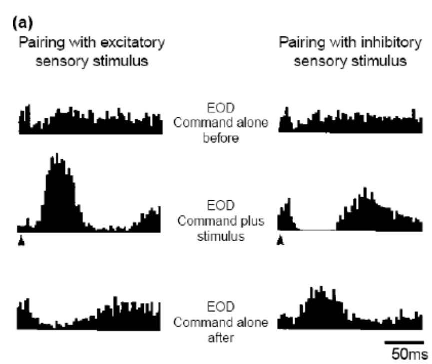
Cerebullar-like Anatomy of the Electric Fish

- the **principal cell layer neurons** of the electrosensory line lobe of the fish:
  - o are equivalent to PKC in our cerebellum
  - o are one synapse away from the periphery, receiving sensory from sensory surface (in this case, electro receptors on sensory surface)
  - o also receive input from granule layer sent via parallel fibers (as in our cerebellum), such as
    - corollary discharge signals
    - higher levels of the same modality (electrosensation)
    - other sensory modalities (e.g. proprioception)
  - o are the major outputs of sensory information to the cerebellum
- Corollary discharge signals are sent to granule cells when the fish generate a pulse in electric organ



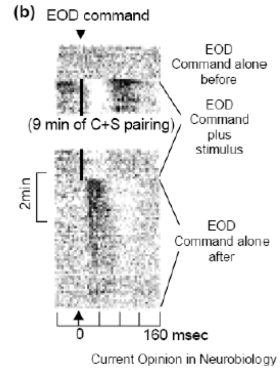
Recording from a <u>Principal Cell Layer Neuron</u> of the Lateral Electrosensory Line Lobe

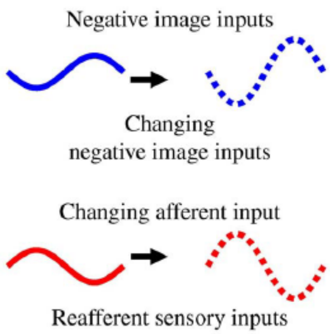
A) These are post-stimulus time histograms (PSTH)
- **Before:** Neuron did not respond to EOD (electric organ discharge) command by itself – relatively flat distribution
  - EOD is equivalent to PF stimulation
- **Repeated paired stimulation:** pairing EOD command with excitatory sensory stimulus (equivalent to co-activation of CF input) elicits an excitatory response
- **After:** after paired stimulation, we now remove the excitatory sensory stimulus, and the neuron now responds to EOD command alone, with <u>inhibition</u>
- Therefore, by pairing, we gave rise to a negative image of the stimulus of the electric field copy = **efference copy**
- Repeating experiment with an inhibitory sensory stimulus (reverse polarity of stimulus) gives the reverse effect – after pairing, the cell responds to EOD command with increased <u>excitatory</u> response
-



B) These are raster plots, each line represents one trial

- At first cell does not respond to EOD command alone.
- After pairing, the cell shows increased excitatory response = overcompensation, similar to what we see in the ball throwing/prism experiment
- overcompensation drops out after 4-5 minutes
- Therefore, changing the reafference stimulus cause change the efference copy
    - o similar to plasticity experiment





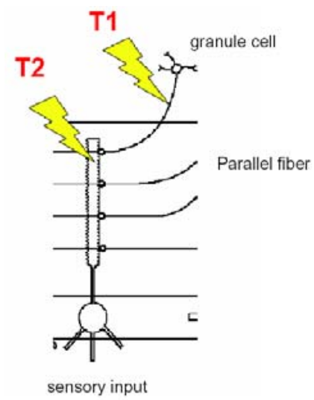
<u>Neural Mechanisms Underlying These Changes</u>

- Blue = Predicted afferent stimulus (efference copy)
- Red = Reafference sensory
- If Blue + red = 0, no perceived stimulus
- Efference can increase/decrease in amplitude in order to match the reafferent stimulus

<u>Slice Experiment done in Ideal Electric Fish</u>

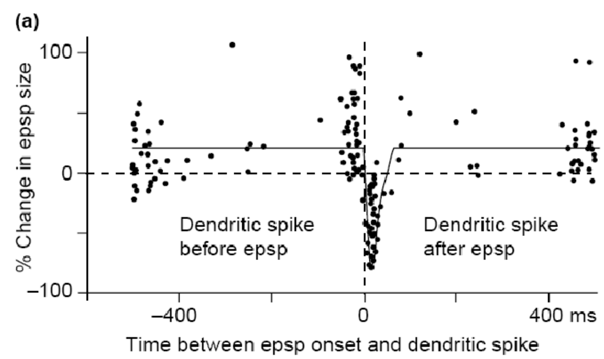
What they did:

- Electrode stimulus in PF of granule cell
- Electrode stimulus in dendrite of pyramidal cell to mimic sensory input
- Recording electrode measures magnitude of postsynaptic response
- Vary time difference between PF and dendritic stimulation



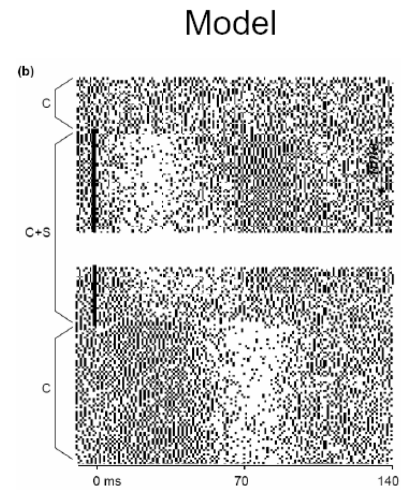
Anti-Hebbian STDP (Spiking timing dependent plasticity)

- depends on timing difference between presynaptic/postsynaptic cell
- For 10-15ms time difference
    a. if dendritic spike from sensory input **before** epsp from PF: increase in EPSP size
    b. if dendritic spike **after** epsp: decrease in EPSP size
- if time difference is large, then no change in EPSP magnitude observed
- Anti-Hebbian: it's different from what we saw previously, it's opposite of Hebb's postulate



Mathematical Model of the experiment done by Bell

- What they did:
  - Endowed the rule for STPD
  - C: replicate an EOD command by stimulating PF directly
  - C+S: then paired the command with sensory stimulus
  - C: then returned to original EOD command stimulation alone
- this model reproduced experimental data quite well:
  - initially, the cell was not very responsive to PF stimulus
  - after pairing, a response was elicited
  - over time, the overcompensation decayed again



Lecture In Summary:

- Cancellation of unwanted stimuli requires precise timing
  - as shown in electric fish)
- Anti-Hebbian STDP plasticity underlies the adaptive cancellation of reafferent input.
  - This was first shown in electric fish, and later shown in the cerebellum of mammals

Reminder:
Course evaluation for the entire class is available on WebCT. Evaluations are completely anonymous