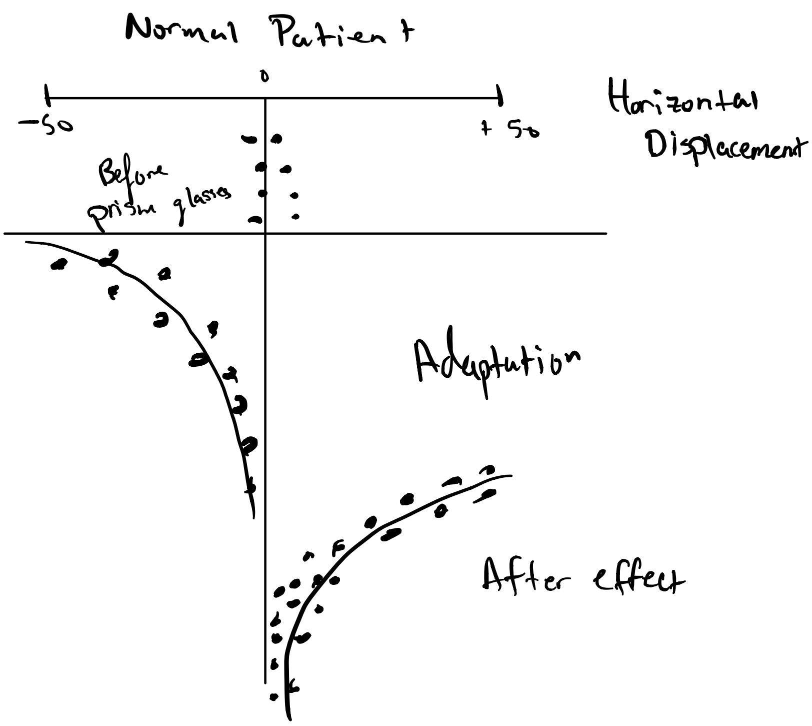
Pre-Lecture Video

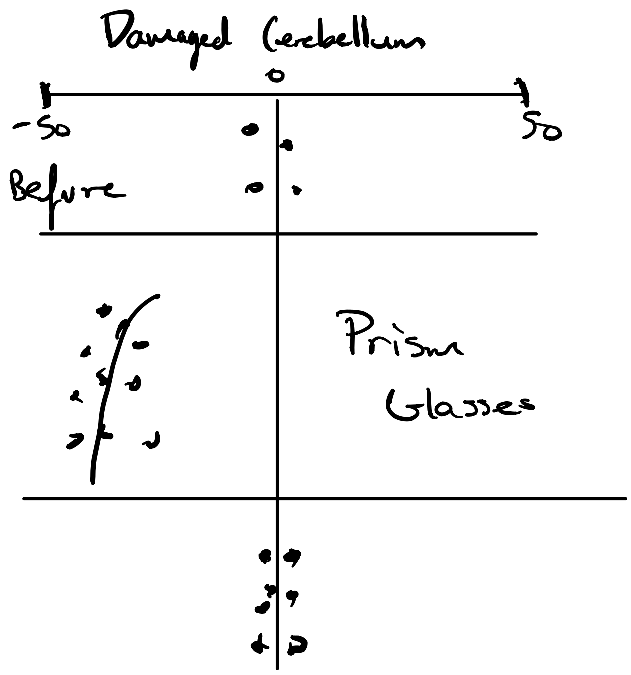
Cerebellar disease causes ATAXIA ← loss of motor control/balance

How we implement Algorithm

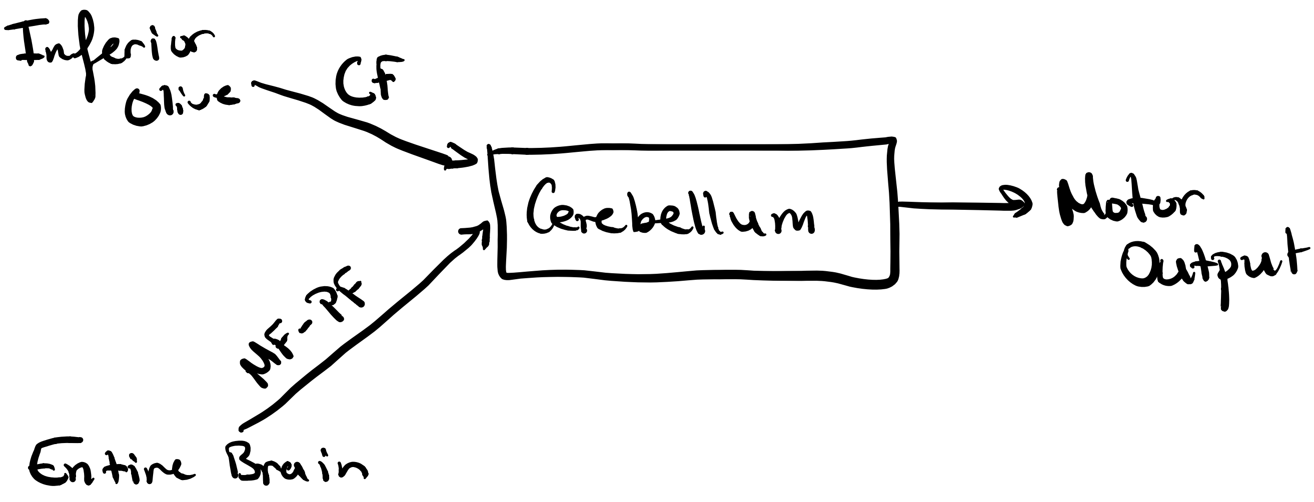
Climbing fiber modulated long-term-depression of Parallel Fiber to Purkinje cell synapse

Feedback error = Target - Outcome





NO AFTER EFFECT



Two Input Pathways

(1) Mossy Fiber - Parallel Fiber Pathway (Sensorimotor Cortex)

(2) Inferior Olive - Climbing Fiber Pathway (Feedback Error)

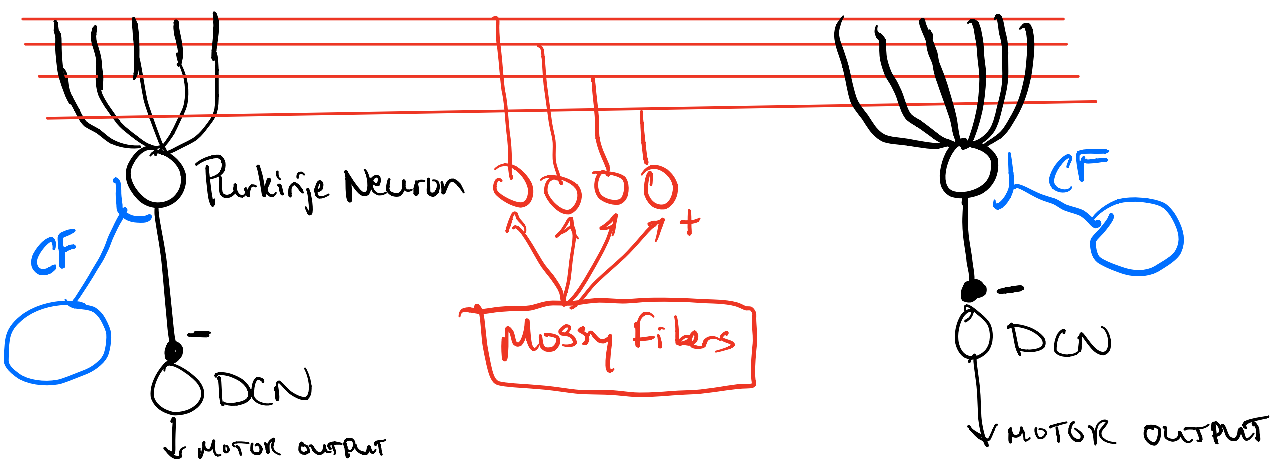
One Output Pathway

(1) Purkinje Neuron → Deep Cerebellar Nucleus (DCN)

Each Purkinje cell is innervated by ~ 200,000 parallel fibers!

Each Purkinje cell is innervated by **ONLY ONE** Climbing fiber

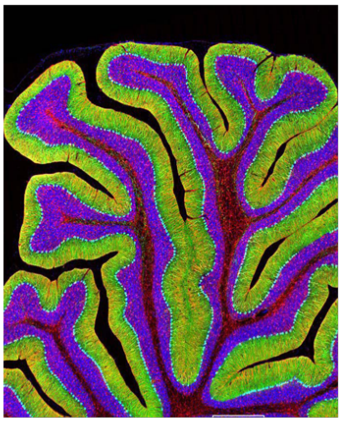
CEREBELLAR MICROCIRCUIT

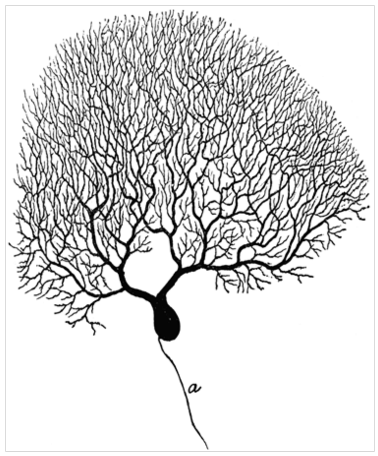


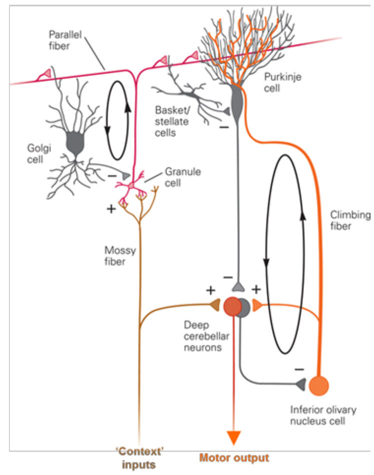
*Climbing Fibers carry direction-specific (feedback error) signals

Lecture 26. Supervised Learning in the Cerebellum

Dr. Jesse Goldberg







Pre lecture materials (you will be tested on this content)

1. L20 – Panopto video: Supervised Learning
2. L20 – Panopto video: The cerebellar microcircuit
3. L20 – Panopto video: Climbing fiber-mediated long term depression of parallel fiber to Purkinje inputs implement supervised learning

Learning Objectives

A PDF of the PowerPoint slides from this lecture will be made available on the class website and will contain all key figures and concepts you need to know for this unit.

I. Explain the difference between supervised learning and reinforcement learning, invoking Marr's three levels

In reinforcement learning, the learning signal specifies if an action had a good or bad outcome. If good, then it should be reinforced. If bad, then it should be suppressed. But if a mistake was made, the reinforcement signal does not specify exactly what needs to be done on the next trial to correct for it. In supervised learning, the learning signal specifies if a mistake was made and as well as exactly how to correct for it on the next trial. For example, if you throw a dart and it misses to the right, you know that the next through should be more to the left. The dopamine input to the basal ganglia is the reinforcement signal. The climbing fiber input to the cerebellum is the 'error' signal in supervised learning. II. Be able to visualize the cerebellar microcircuit, well enough so that you could draw it on a blank sheet of paper.

III. Be able to explain what type of synaptic plasticity occurs in the cerebellum and how this implements supervised learning

IV. Understand what happens to patients with cerebellar damage, and why.

Lecture Outline

A PDF of the PowerPoint slides from this lecture will be made available on the class website and will contain all key figures and concepts you need to know for this unit.

In this lecture we will systematically march through an example of how the cerebellum participates in learning from mistakes. We will use the example of reaching for a pen on a desk (any example would suffice, from throwing a dart, to swinging a tennis racquet or even moving your eyes to a target!):

Let's do the following exercise together:

1. Reach for a pen in front of you.
    a. (Reach for the pen) Your motor system has to translate that goal of bringing your hand from its current position to the target pen position. i.e. into signals that drive muscles. (Think about the kinematic to kinetic transformation from last lecture).
    b. You may not be aware of it, but you have a predicted outcome of your own actions.
        i. Your motor system has outgoing signals, but they can also feed into other parts of the brain that monitor these outgoing signals to build a prediction. This is called *efference copy:* an internal copy of an outgoing (efferent), movement-producing signal generated by the nervous system. Most outgoing motor projections have axon collaterals (branches of the axon) that re-innervate other structures. In this way, the organism receives information about the action that it is about to take! You can't tickle yourself because there are no surprises.
        ii. Efference copy can be integrated with sensory input that results from the action, and this enables a comparison of the actual movement with desired movement.
    c. So as you are reaching for the pen, you are integrating efferent copy signals (what you think your motor system told your arm to do) with sensory feedback (e.g. what you see or feel your arm doing). When all is in proper alignment, you grasp the pen and all is working great!

2. But what if you miss the pen!? This could occur if you were wearing prism glasses or if your motor system was not skilled at the task (babies miss things all the time! They have not yet calibrated their motor systems). How do they learn? Well, when you miss, you get an error signal.
    a. An *error signal* constitutes the neural signals that encode the mistake.
    b. In the cerebellum, the error signal is thought to convey not just *that you missed the pen*, but also *how you missed it* (e.g. <u>I missed to the right</u>).
    c. Know how this type of error can be used by the cerebellum to learn so that on your <u>next trial is biased a tad to the left</u> so that you accurately grab the pen.
    d. You just engaged the process of adaptive feedforward motor control. *This is what the cerebellum does!*
3. **Know the cerebellar microcircuit**
    a. The cerebellum has two inputs: climbing fibers (CFs) and mossy fibers (MFs).

i. CFs make a 1:1 connection with Purkinje cells. CFs encode the error signal.
ii. There are billions of MF inputs to the cerebellum! They innervate the granule cells, which in turn give rise to parallel fibers that synapse on Purkinje cells. <u>So a given Purkinje cell is innervated by >20,000 parallel fibers and only a single CF.</u>

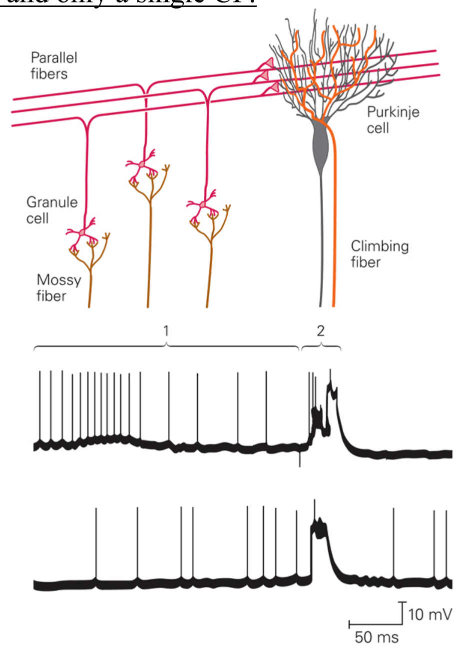


Figure 42–5 Simple and complex spikes recorded intracellularly from a cerebellar Purkinje cell. Simple spikes are produced by mossy fiber input (**1**), whereas complex spikes are evoked by climbing fiber synapses (**2**). (Reproduced, with permission, from Martinez, Crill, and Kennedy 1971.)

iii. The MFs encode both sensory inputs and efference copy from motor inputs. Together they can encode basically any sensori-motor context that the animal will find itself in, including the motor and sensory signals associating with reaching for a pen.

b. The cerebellum has one main output: The Purkinje cells project to Deep cerebellar nuclei, which in turn project to downstream motor neurons.
   i. Purkinje cell discharge can directly influence motor output through its <u>inhibitory</u> input to the DCN.
   ii. Purkinje neurons and their target DCN neurons have *direction preferences*. That is, a given Purkinje cell – DCN channel might contribute to biasing your reach leftwards, and another channel might contribute biasing it rightwards.

c. Learning in the cerebellum
   i. So if you just missed to the right, you need your reach biased leftwards on the next movement to accurately grab the pen. You need the activity of the DCN neuron that biases your reach leftwards to *increase* its activity. This can be accomplished by suppressing the activity of the Purkinje cell that projects to the Left-biasing DCN neuron <u>(because the Purkinje neuron is inhibitory).</u>
   ii. Luckily, the CF input that encoded the error "Too much to the right!" sends a signal to the Purkinje cell in the rightward biasing channel neuron that induces long-term-depression of the PF inputs.

iii. So next time you reach, the MF pathway will encode the context: "I am currently reaching." And the Purkinje cell that projects to the rightward biasing DCN neuron will fire less because these inputs have been weakened (LTD) by the previous mistake. This will disinhibit the rightward biasing DCN neuron, correcting for the mistake.

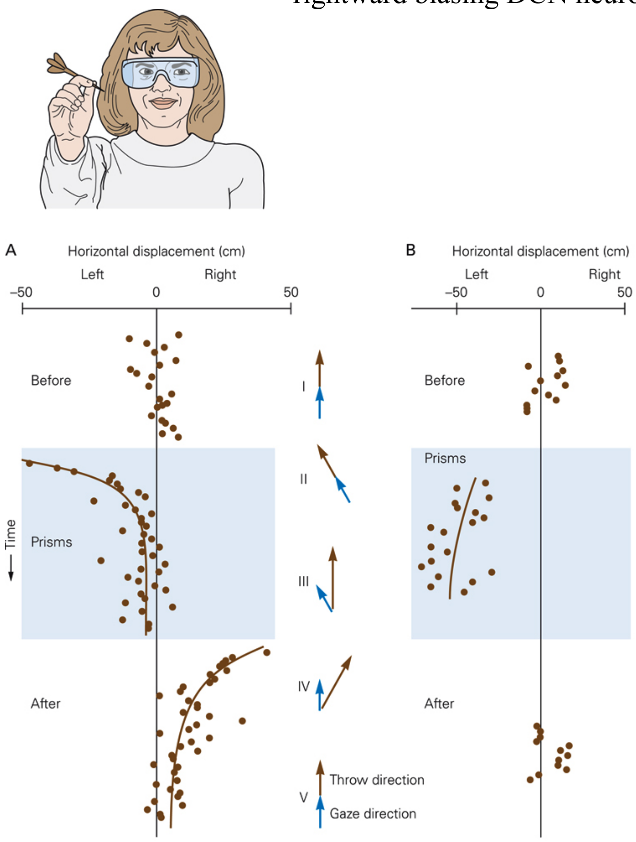


Figure 42–13 Adjustment of eye-hand coordination to a change in optical conditions. The subject wears prisms that bend the optic path to her right. She must look to her left along the bent light path to see the target directly ahead. (Adapted, with permission, from Martin et al. 1996a, 1996b.)

A. Without prisms the subject throws with good accuracy. The first hit after the prisms have been put in place is displaced left of center because the hand throws where the eyes are directed. Thereafter hits trend rightward toward the target, away from where the eyes are looking. After removal of the prisms the subject fixes her gaze in the center of the target; the first throw hits to the right of center, away from where the eyes are directed. Thereafter hits trend toward the target. Data during and after prism use have been fit with exponential curves. Gaze and throw directions are indicated by the **blue** and **brown arrows**, respectively, on the right. The inferred gaze direction assumes that the subject is fixating the target. Before donning the prisms the subject looks at and throws toward the target (**I**). Just after donning prisms, when her gaze is directed along the bent light path away from the target, she throws in the direction of gaze, away from the target (**II**). After adapting to the prisms she directs her gaze along the bent light path away from the target but directs her throw toward the target (**III**). Immediately after removing the prisms she directs her gaze toward the target; her adapted throw is to the right of the direction of gaze and to the right of the target (**IV**). After recovery from adaptation she again looks at and throws toward the target (**V**).

B. Adaptation fails in a patient with unilateral infarctions in the territory of the posterior inferior cerebellar artery that involve the inferior cerebellar peduncle and inferior lateral posterior cerebellar cortex.

Study Questions

1. Why can't you rely entirely on real-time sensory feedback to correct your hand trajectory during a reach? Relatedly, what is intention tremor and why might it result from cerebellar damage?
2. What are the two main inputs to the cerebellum? What information do they carry?
3. Imagine you are a Purkinje cell. What are the differences between the strength of the inputs from the one climbing fiber input compared to the thousands of parallel fiber inputs? What kind of plasticity occurs when you get activated by both at the same time?

GET YOUR CLICKERS OUT RIGHT NOW

Clicker Question: What are the two inputs to Purkinje Neurons of the cerebellum?

(A) I don’t know, I didn’t prepare for today’s class

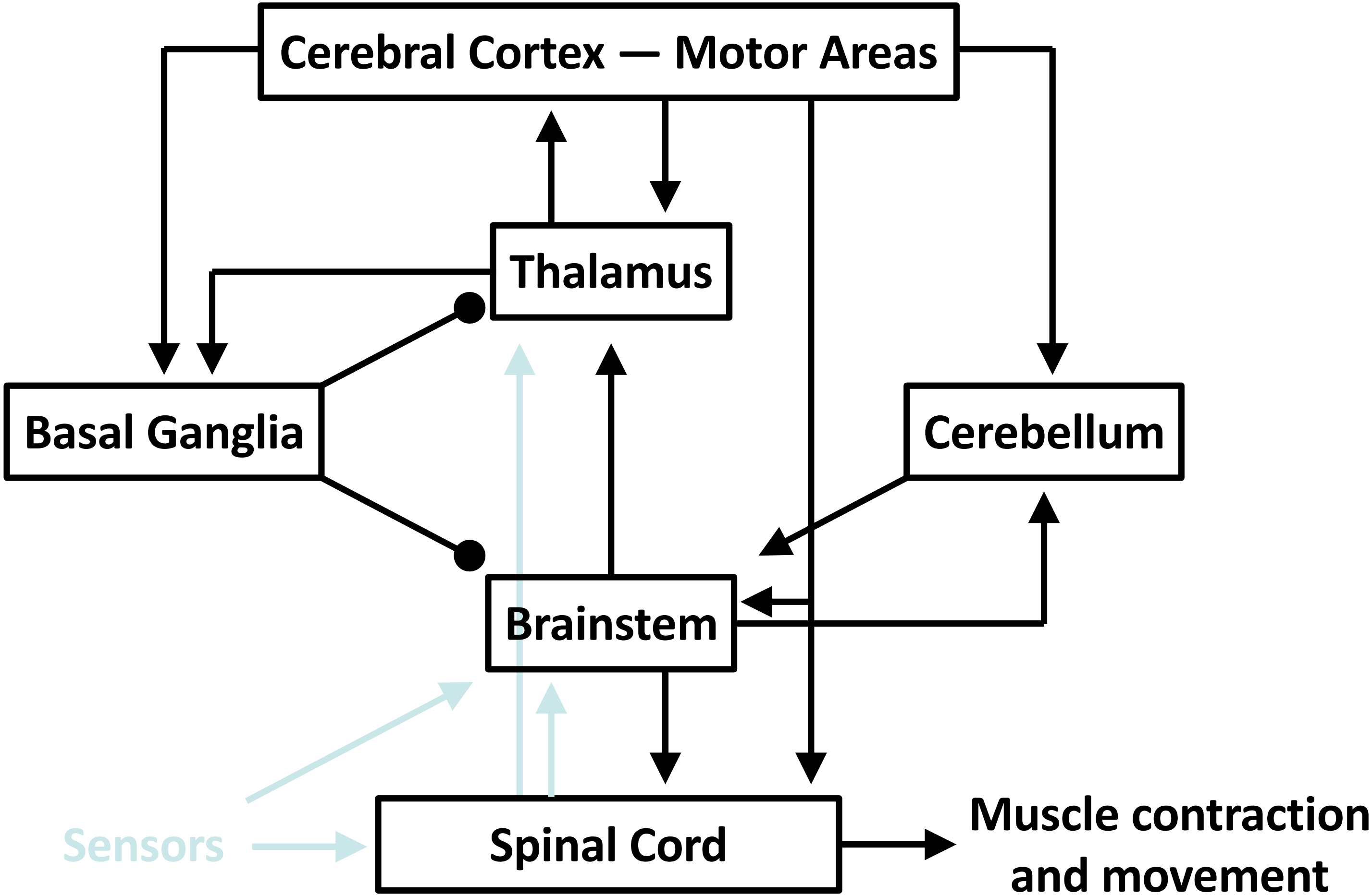
(B) Parallel fibers and climbing fibers

(C) Thalamus and deep cerebellar nuclei

(D) Deep cerebellar nuclei and climbing fibers

(E) Thalamus and mossy fibers

The Cerebellum and Supervised Learning



Today's main points

(1) Cerebellar disease causes ATAXIA, which results from a loss of *feedforward predictive control*

(2) Feedback ERROR-based supervised learning – calibrating your motor system

(3) How the cerebellar microcircuit implements supervised learning
CF modulated long term depression of parallel fiber – Purkinje cell synapse

(4) A test case – a toddler toddling

Why does cerebellar disease cause these specific motor ataxias?

Marr’s Three levels of analysis

1. Behavioral level: Learn to execute goal-directed action *correctly*

Harmony between goals and outcome: balance, ‘calibrated motor system’

2. Algorithmic level: What is the strategy? What representations are used?

Supervised learning

If you miss, compute the FEEDBACK ERROR (difference between target and outcome) → Correct for mistake on next trial(s)

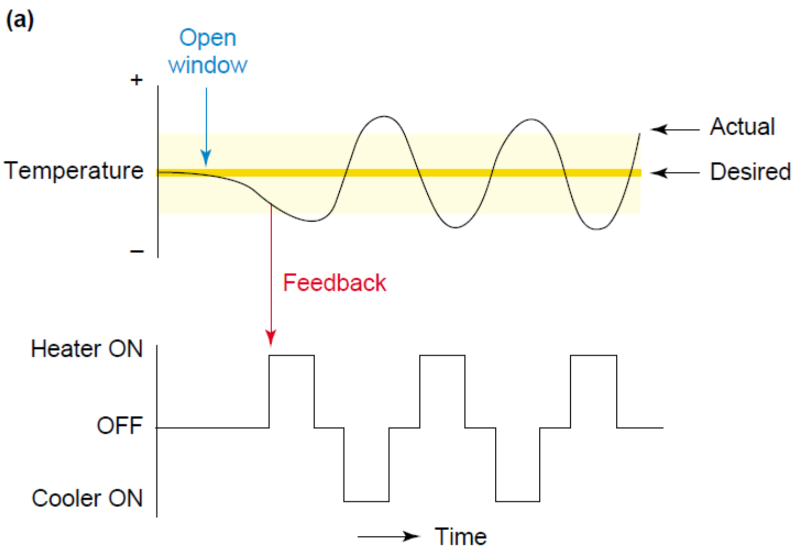
3. Implementation level: How is the algorithm implemented in the brain

Supervised learning implemented in the cerebellum

Climbing Fiber – modulated plasticity in the Parallel Fiber – Purkinje synapse

Feedback versus feed-forward control

Feedback is slow, produces errors

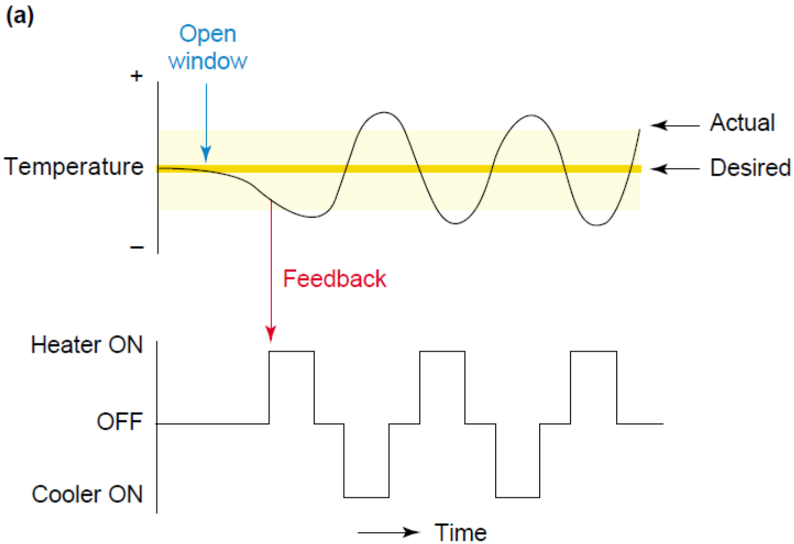


Manual ataxia

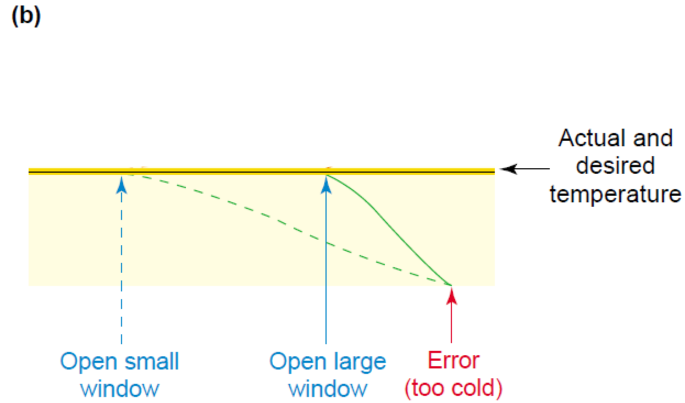
http://www.youtube.com/watch?v=ji-nPrbigxA

Feedback versus feed-forward control

Feedback is slow, produces errors



Feed-forward control requires prediction



Manual ataxia

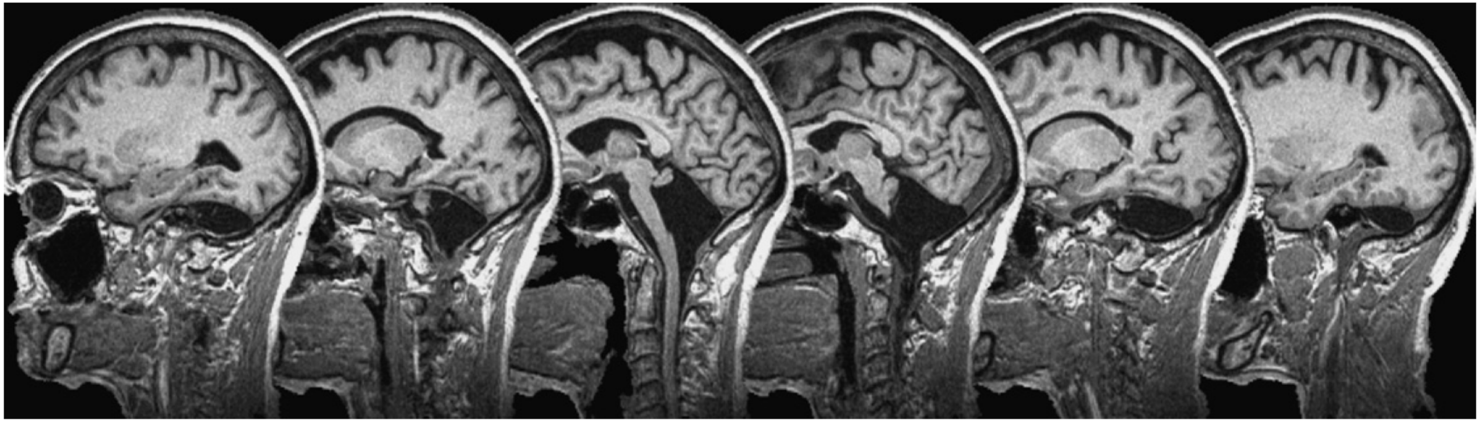
http://www.youtube.com/watch?v=ji-nPrbigxA

Feedback error is the difference between GOAL and OUTCOME
Feedback error can be fixed by 'Feed-forward predictive control'
FEEDFORWARD PREDICTIVE CONTROL IS WHAT YOUR CEREBELLUM DOES

Ataxia: Loss of balance and motor control in cerebellar disease

A case of cerebellar hypoplasia

The patient shows a number of abnormalities in his occulomotor, speech and gait control. Speech developed late and was slurred. Poor dexterity and object grasp. Note *wobbly balance and oscillations on reach to target.*



Boy with Cerebellar Hypoplasia Video Link

http://www.youtube.com/watch?v=Dox3_ox8C2U

1:40 to 2:00

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(2) Feedback ERROR-based supervised learning – calibrating your motor system

(3) How the cerebellar microcircuit implements supervised learning
CF modulated long term depression of parallel fiber – Purkinje cell synapse

(4) A test case – a toddler toddling

Graded question: What is feedback error?

A. Feedback error is positive when you hit your target after having missed it on the previous trial

B. Feedback error is zero when you miss your target the exact same way twice in a row.

C. Feedback error is the difference between your target and the outcome

D. Feedback error is zero when you hit your target

E. C and D

What is feedback error?

Feedback error = Target - Outcome

A. Feedback error is positive when you hit your target after having missed it on the previous trial

B. Feedback error is zero when you miss your target the exact same way twice in a row.

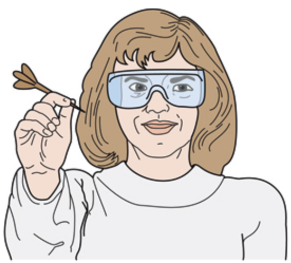
C. Feedback error is the difference between your target and the outcome

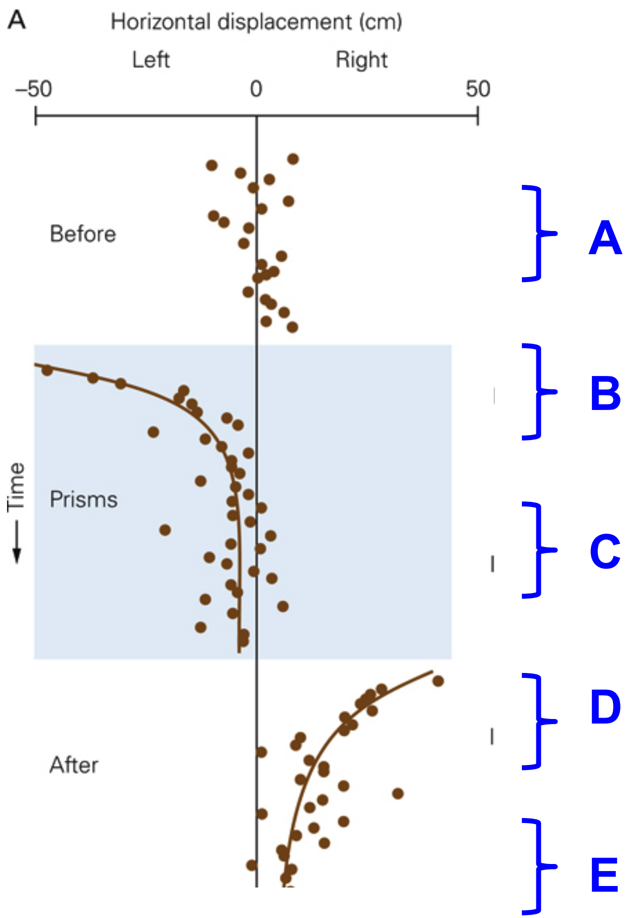
D. Feedback error is zero when you hit your target

E. C and D

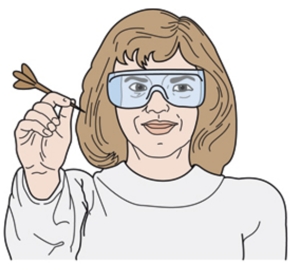
Close your eyes, make a quick movement with one finger to the finger on the opposite hand
The feedback error signal has information about how to fix the error.

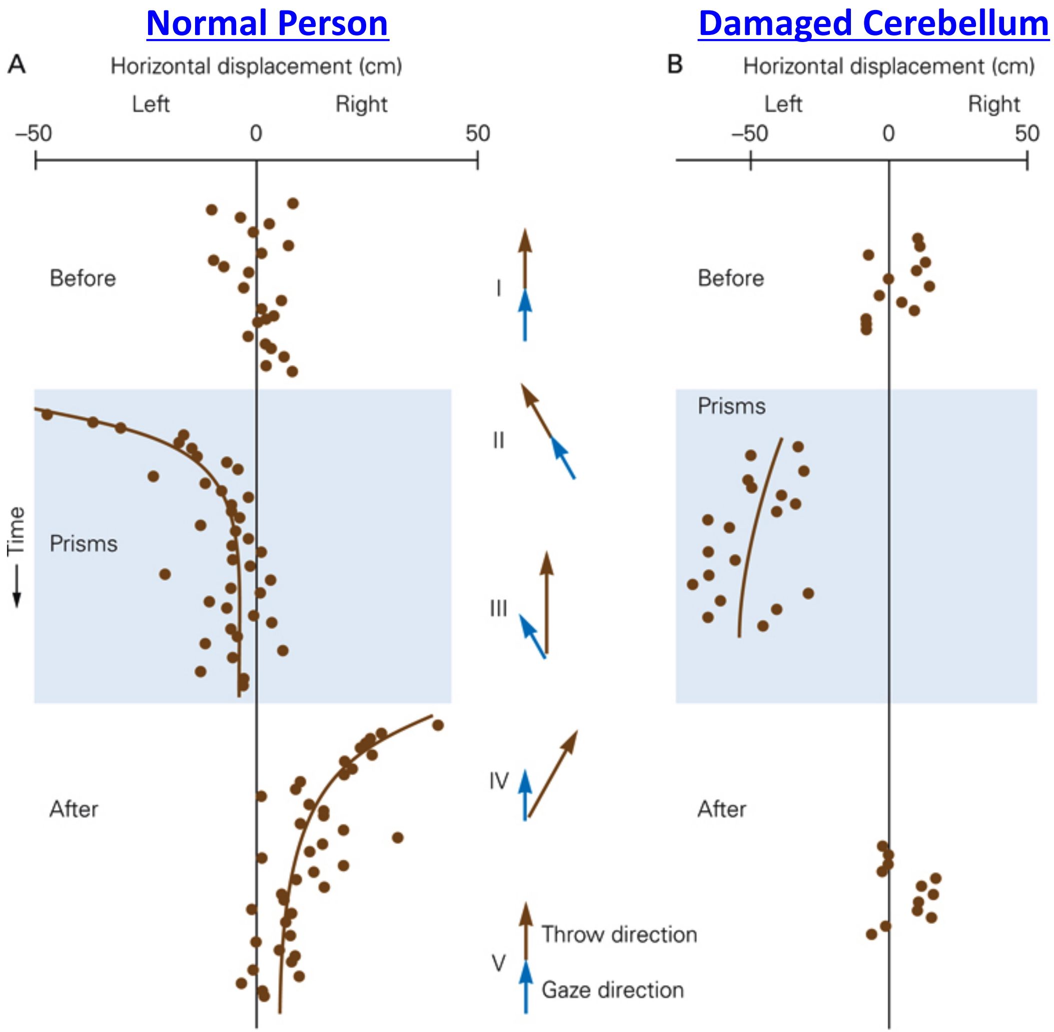
Graded question: Where is the after effect?





Cerebellar damage prevents learning (adaptation)





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Graded question: What are the two inputs to Purkinje Neurons of the cerebellum?

(A) Parallel fibers and mossy fibers

(B) Parallel fibers and climbing fibers

(C) Thalamus and deep cerebellar nuclei

(D) Deep cerebellar nuclei and climbing fibers

(E) Thalamus and mossy fibers

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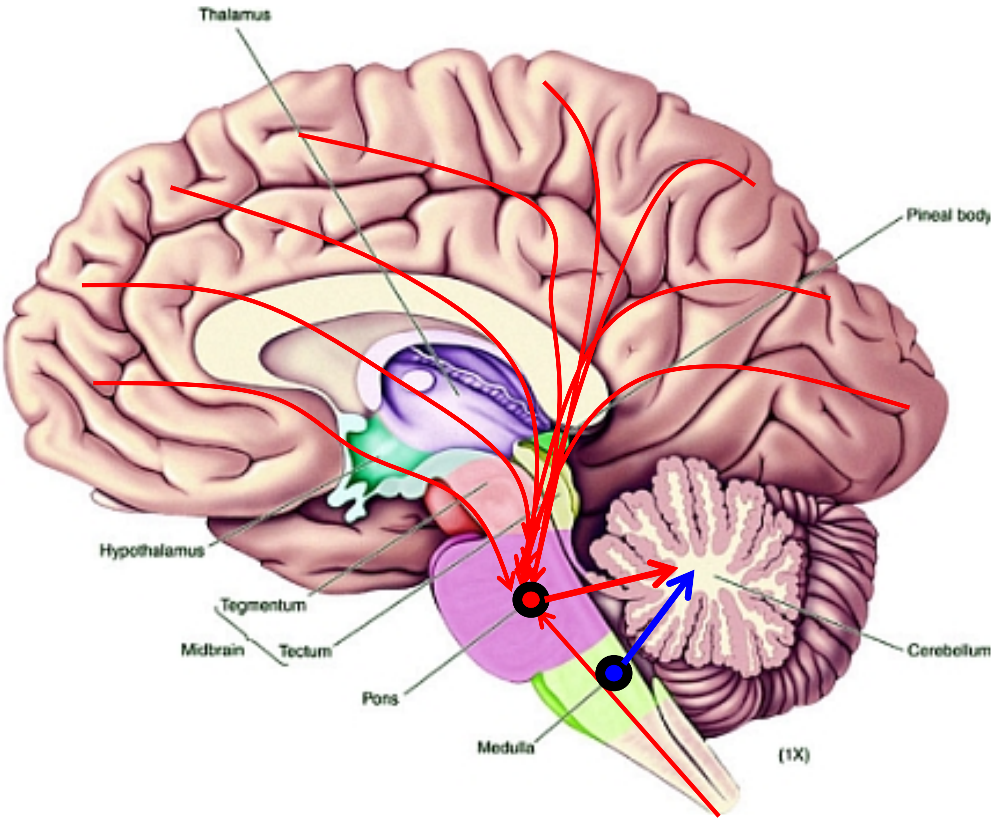
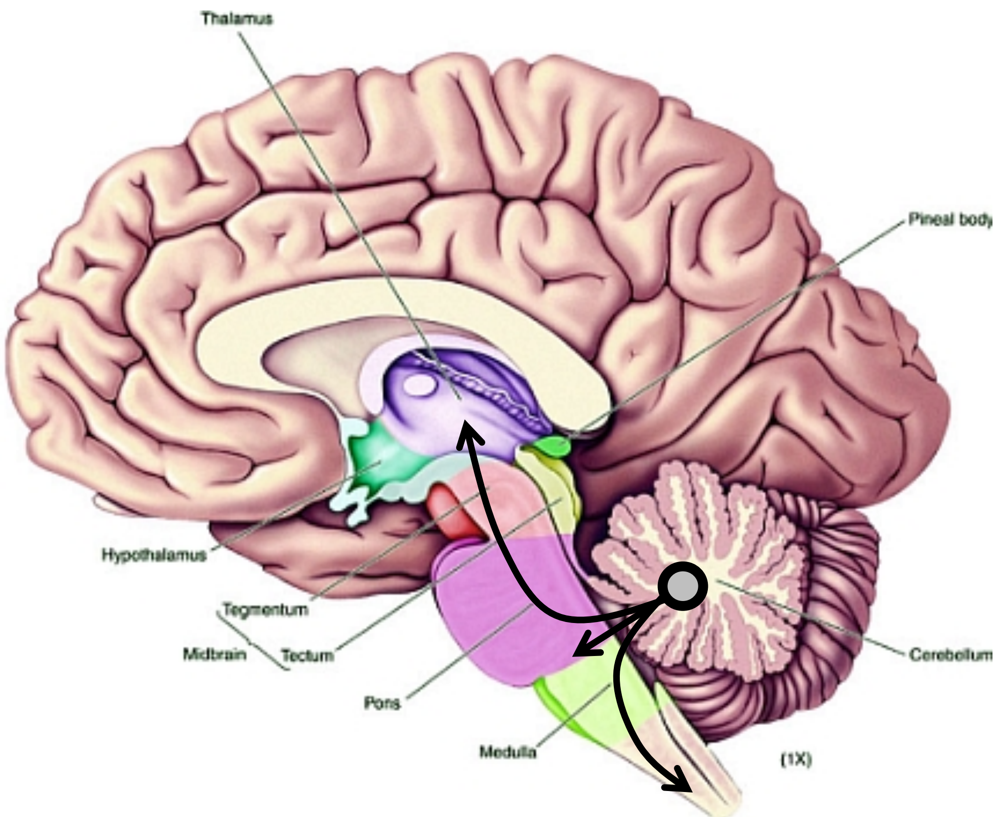
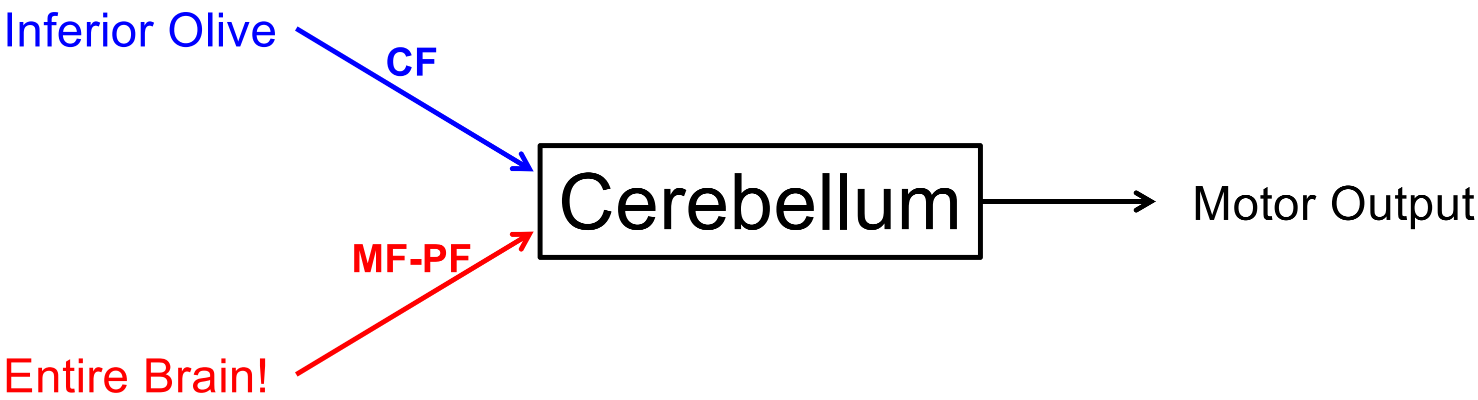
Neuroanatomy review: Cerebellum ("the little brain")



Neuroanatomy review: Cerebellum ("the little brain")



Cerebellum: Two inputs, one output



Two Input Pathways

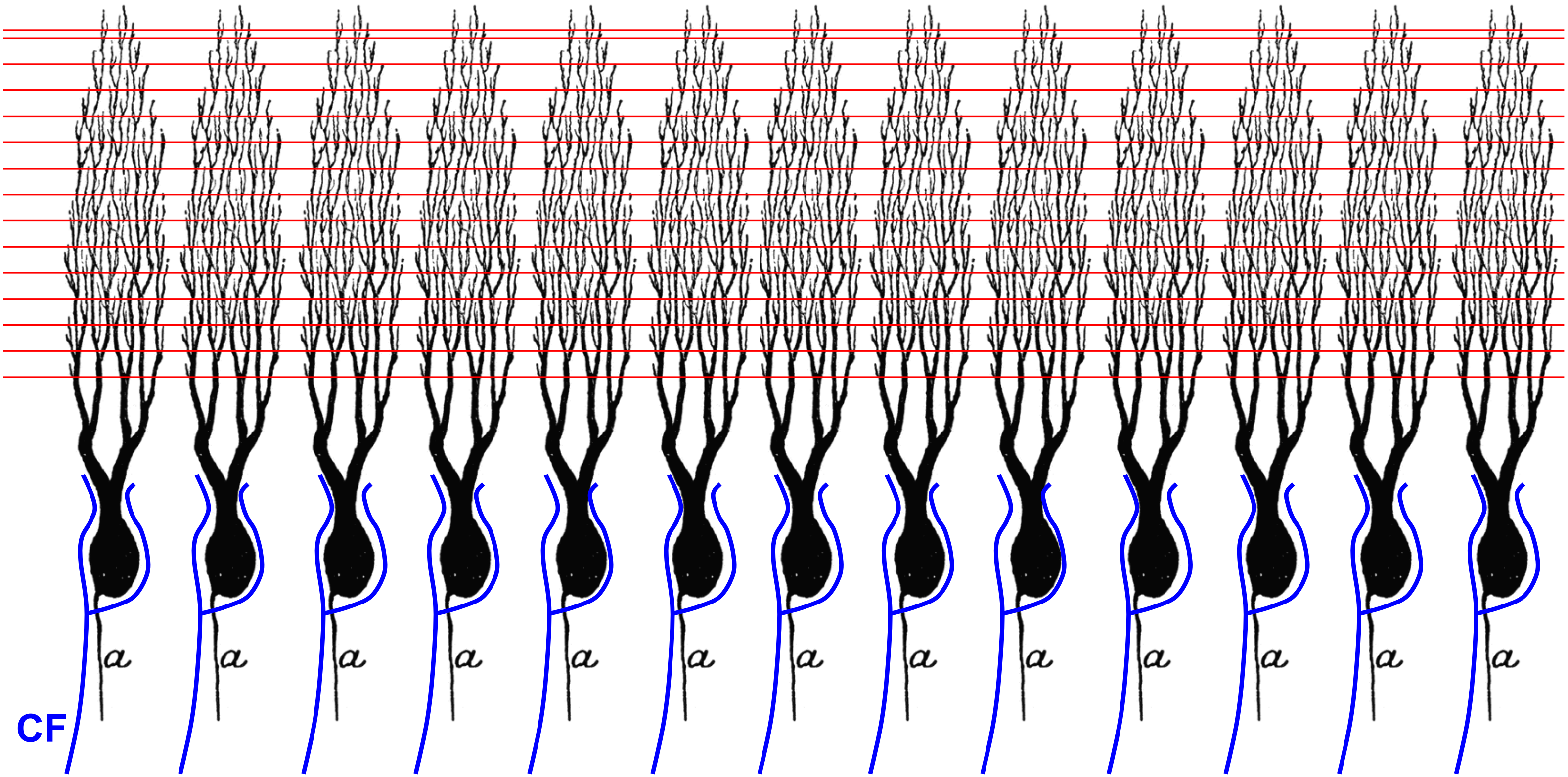
(1) Mossy Fiber - Parallel Fiber pathway *(Sensorimotor Context)*

(2) Inferior Olive - Climbing Fiber pathway *(Feedback error!)*

One Output Pathway

(1) Purkinje Neuron —• Deep Cerebellar Nucleus (DCN) → *Modify* Motor output

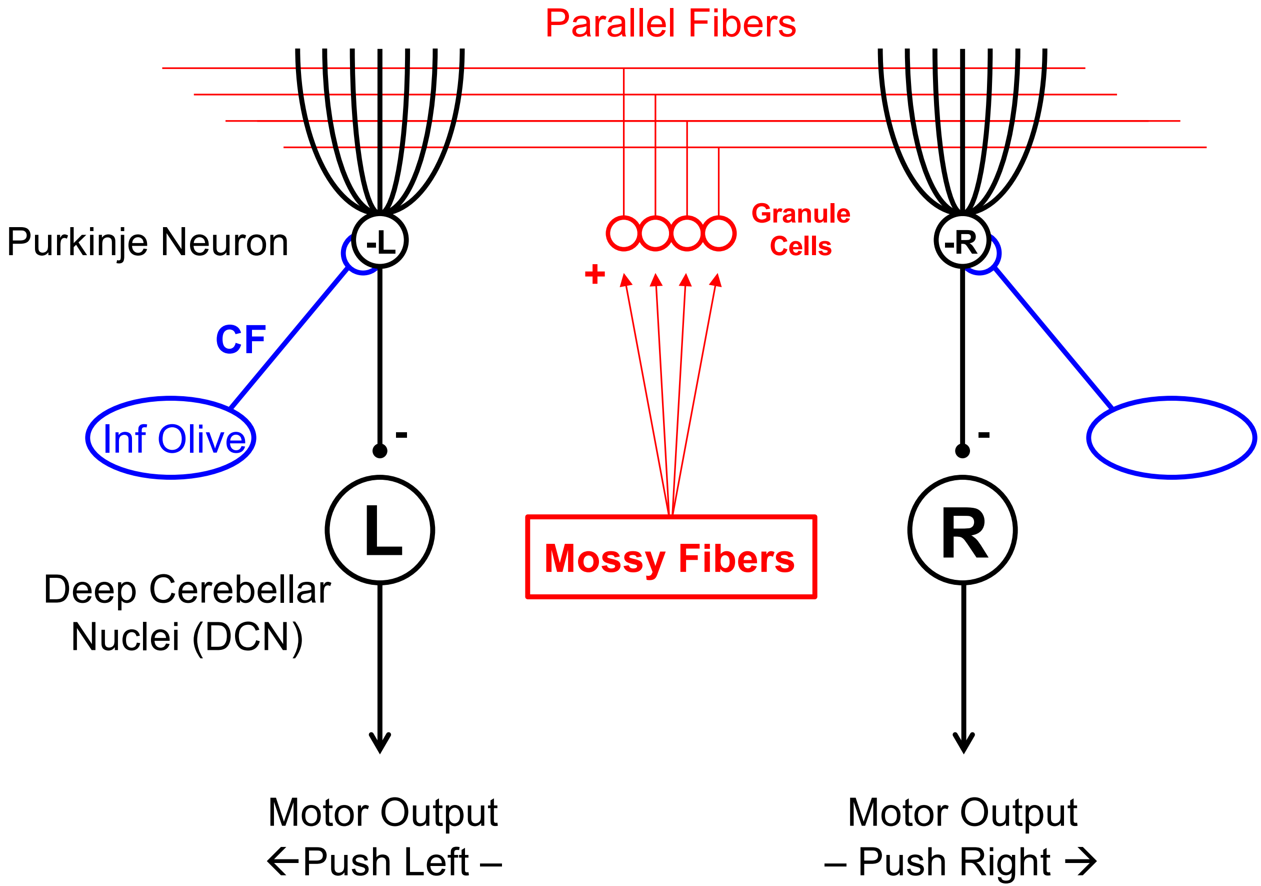
Purkinje cell dendrites are elaborate structures in 2-D



(1) Each Purkinje cell is innervated by > 200,000 parallel fibers

(2) Each Purkinje cell is innervated by ONLY ONE CLIMBING FIBER

The cerebellar microcircuit (You need to know this)



Cerebellar Output (Purkinje → DCN pathway) is functionally segregated
Distinct motor output channels (Just like the BG)

Question: What is a main learning rule in the cerebellum?

(A) If the parallel fiber and the Purkinje cell are co-active, then weaken the connection from the PF→Prk.

(B) If the Purkinje cell and the climbing fiber are co-active, then weaken the connection from the CF→Prk

(C) If Parallel fiber and Climbing Fiber are co-active, then weaken connection from PF → Prk.

(D) If the PF and the CF and co-active, then strengthen the connection from the PF to the CF.

(E) None of the above.

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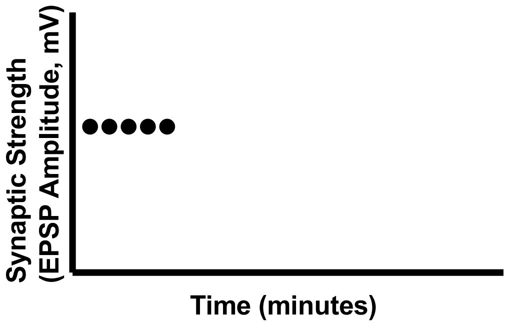
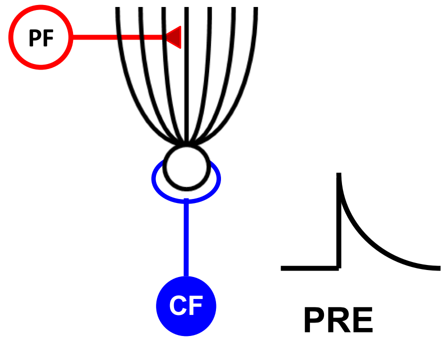
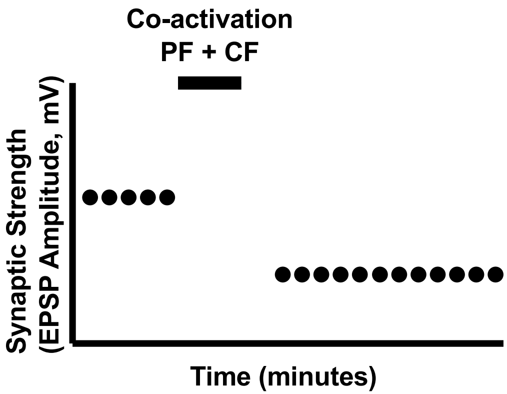
(E) None of the above.

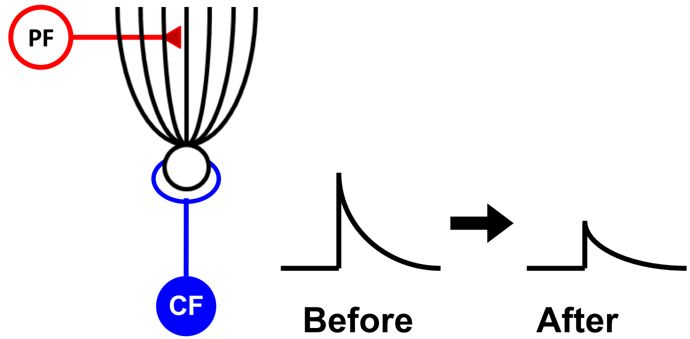
Learning rule at the Purkinje cell implements SL





Two factor learning rule at the Purkinje cell implements SL





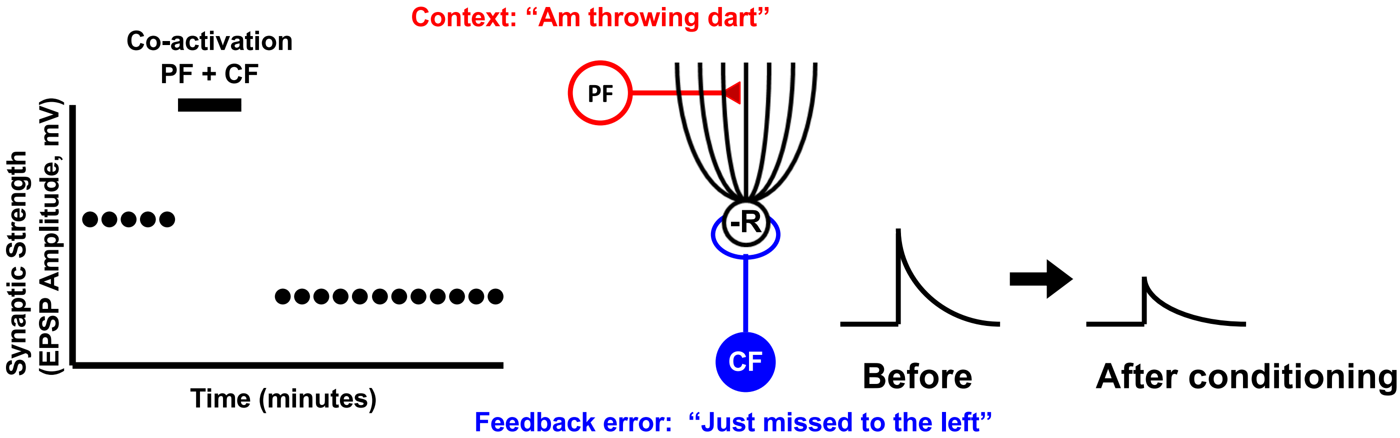
Learning Rule

If (1) PF and (2) CF are co-active, then weaken connection from PF → Prk

Co-activation of CF and PF causes *long term depression (LTD)* of PF-Prk syanpse

Synchronous activation of PF, CF → LTD; so smaller EPSP afterwards!

Learning rule at the Purkinje cell implements SL



If (1) PF and (2) CF are co-active, then weaken connection from PF → Prk
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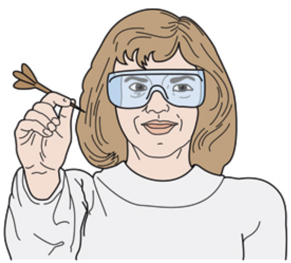
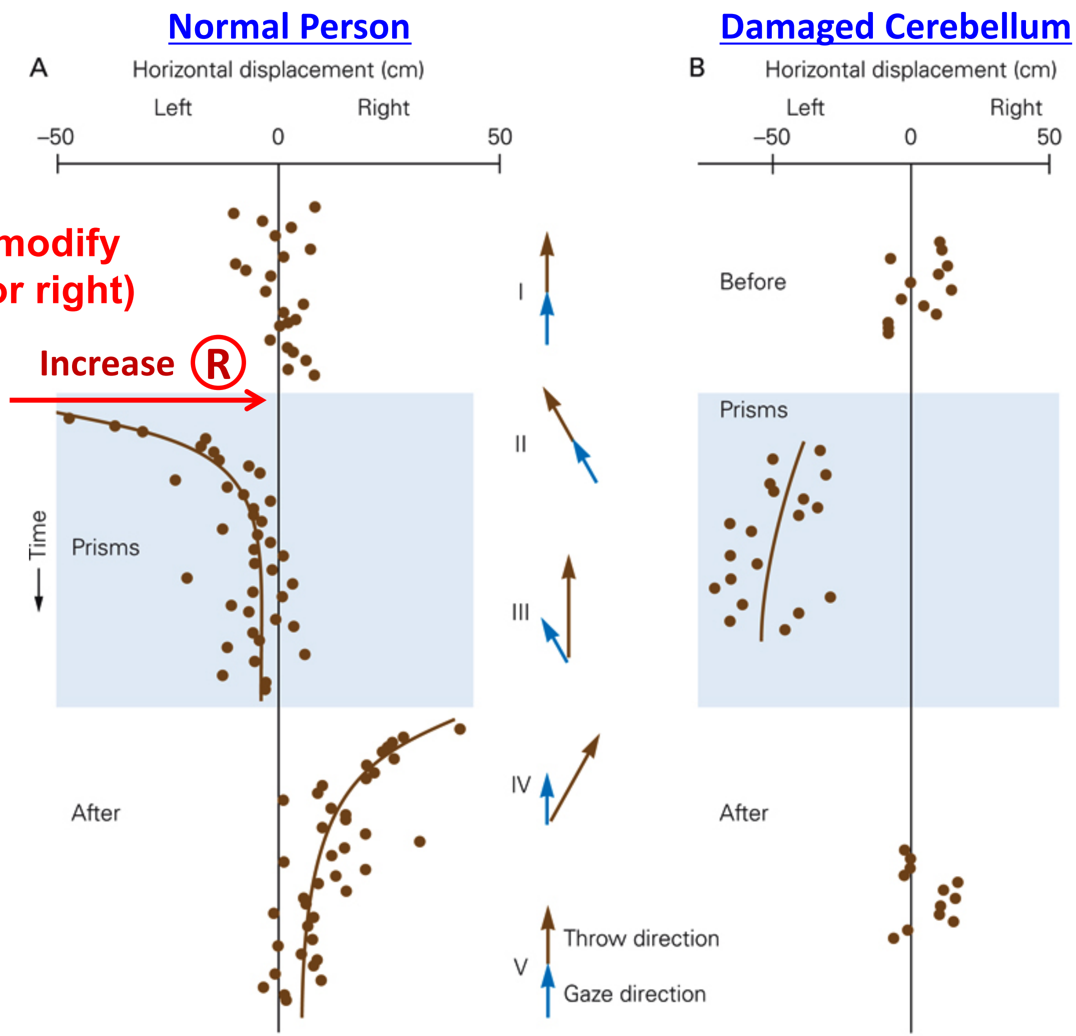
Climbing Fibers regulate plasticity in PF – Purkinje cell synapses

Cerebellar damage prevents learning (adaptation)

Cerebellar output can modify ongoing behavior (left or right)





You throw a free-throw and it falls short…but you swish it on the next throw. Which statement is true?

(A) Because PF inputs to Purkinje cells are excitatory,

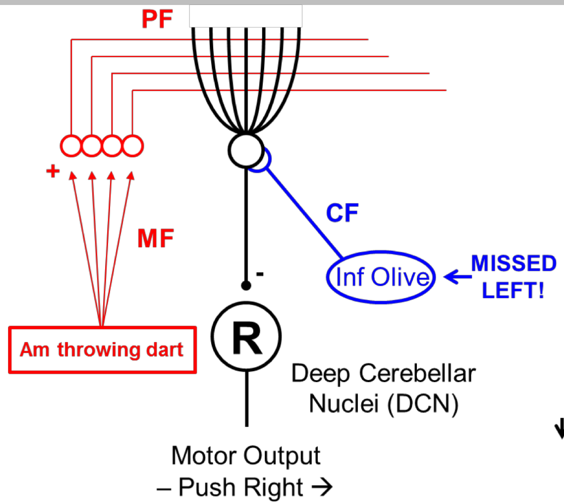
(B) CF-modulated PF LTD will suppress Prk firing during the free throw,

(C) which in turn will disinhibit a DCN neuron

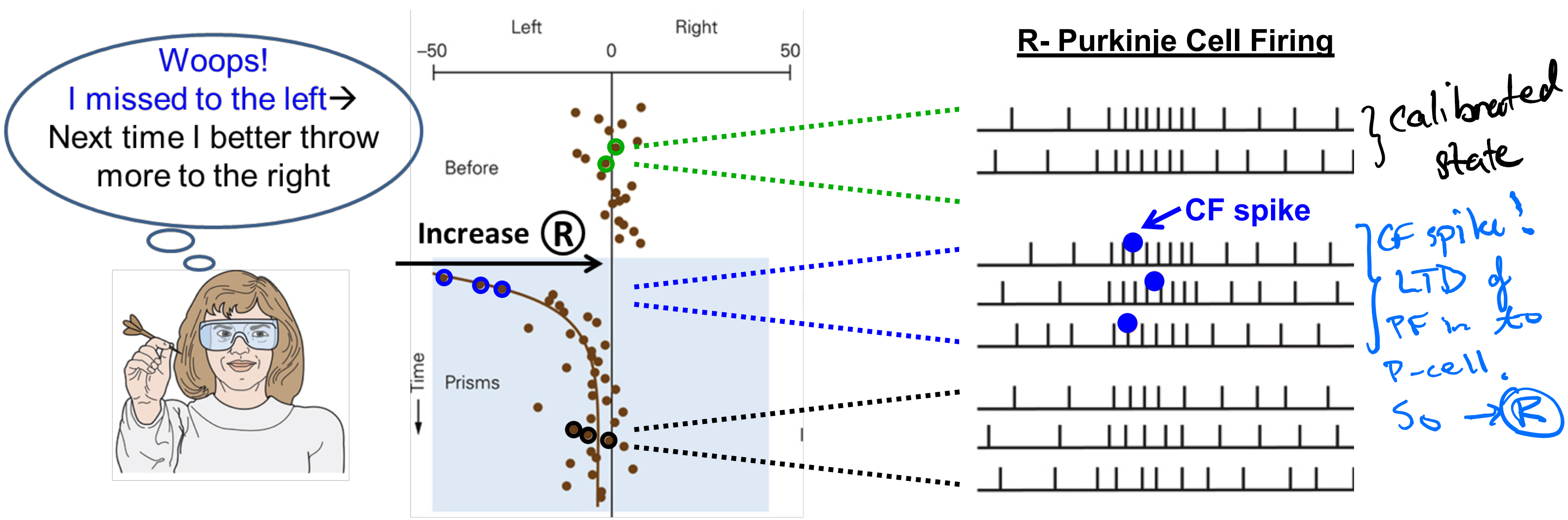
(D) This DCN neuron is likely in the ‘throw farther’ channel.

(E) All of the above

Cerebellar output can modify ongoing behavior (left or right)



An exercise: Let's track Purkinje cell firing during learning (Kandel 42-12)



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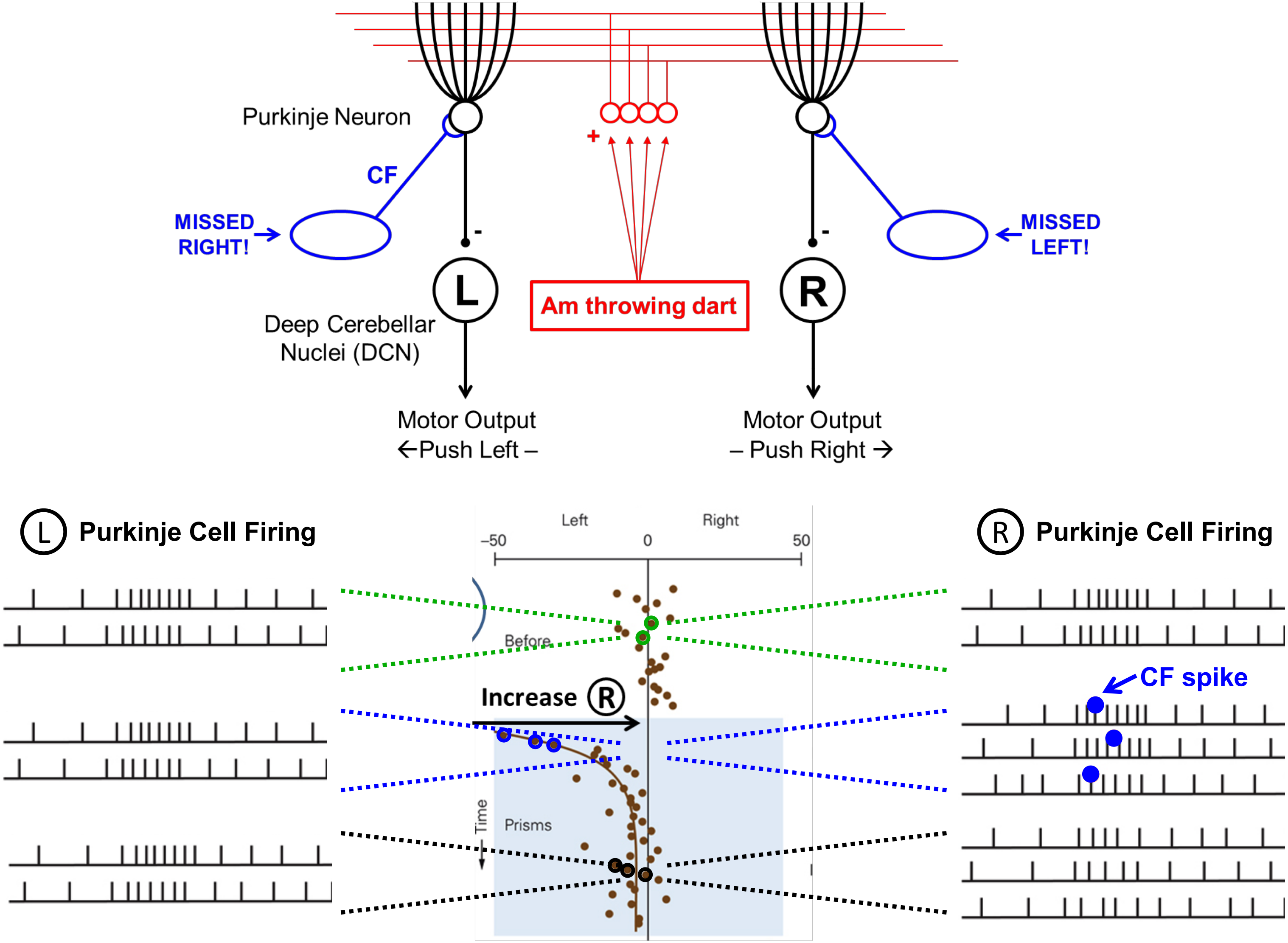
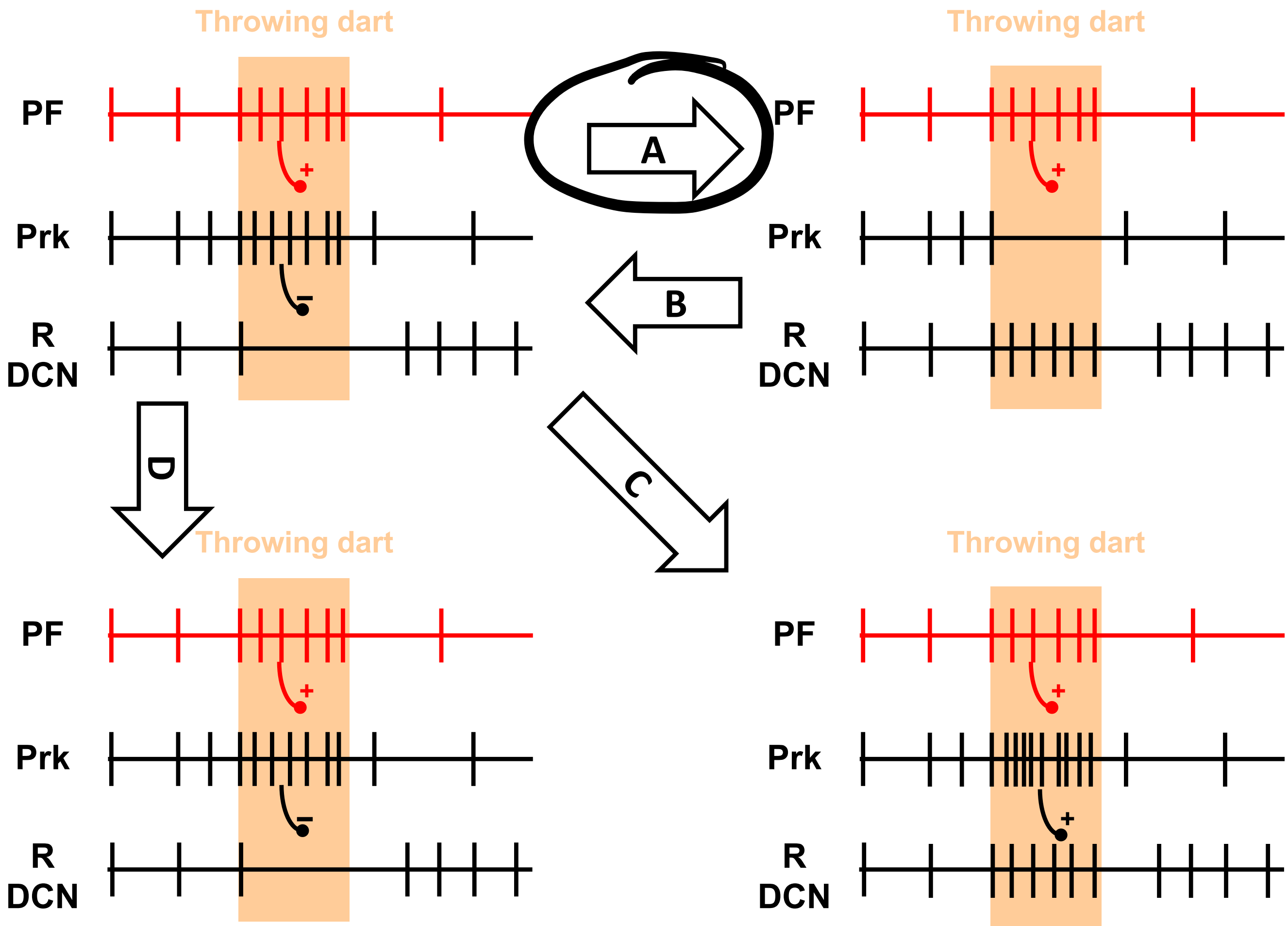


Clicker: Which arrow links before missing left to after correct adaptation?



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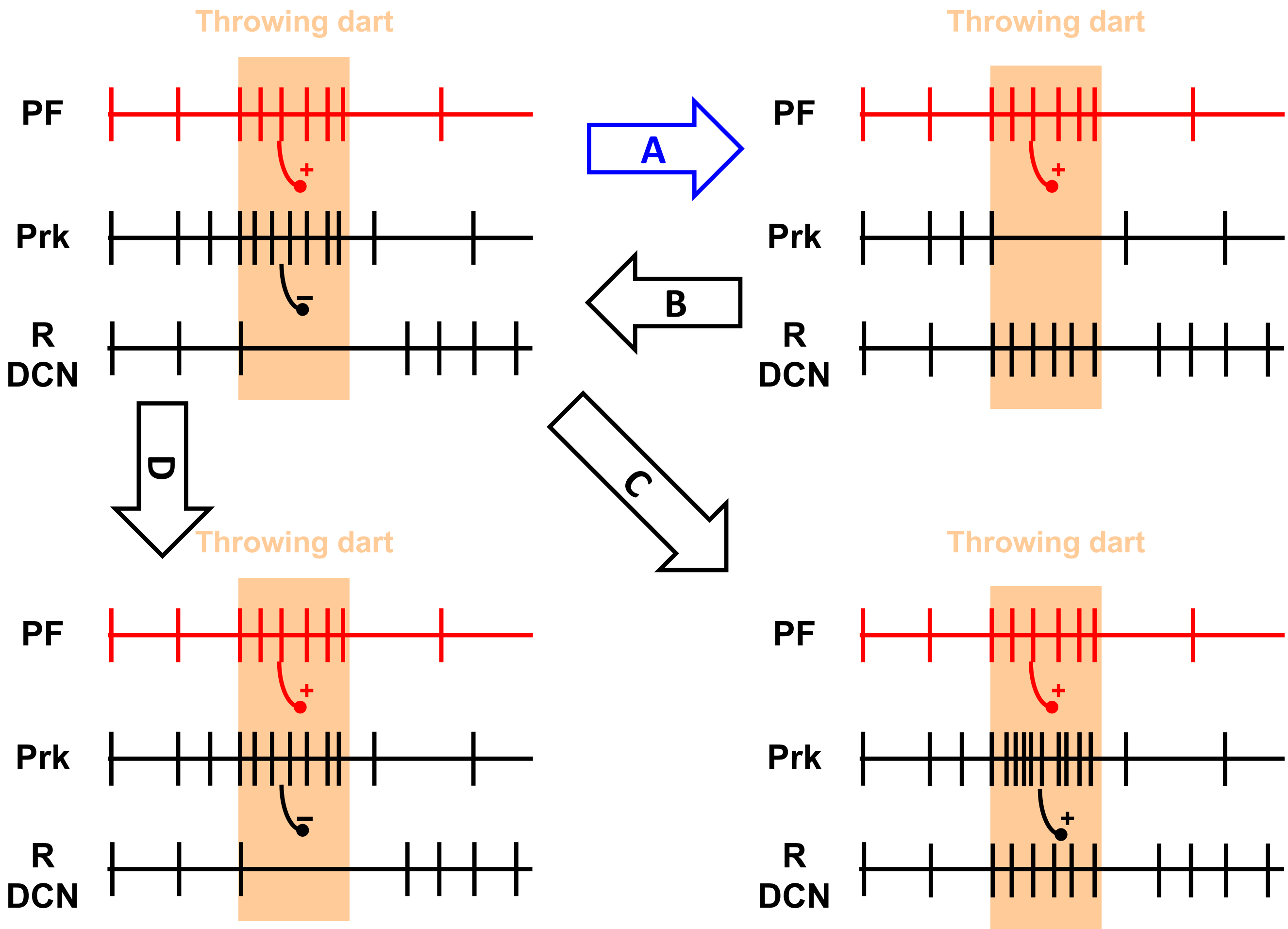

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(D) This DCN neuron is likely in the ‘throw farther’ channel.

(E) All of the above

You throw a free-throw and it falls short…but you swish it on the next throw. Which statement is true?

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Today's main points

(1) Cerebellar disease causes ATAXIA, which results from a loss of *feedforward predictive control*

(2) Feedback ERROR-based supervised learning – calibrating your motor system

(3) How the cerebellar microcircuit implements supervised learning
    CF modulated long term depression of parallel fiber – Purkinje cell synapse

(4) A test case – a toddler toddling

CLICKER QUESTIONS

-C

(1) You are dropping your right hand from a raised position while spinning left

(2) ERROR! You just fell to the right! -D

(3) Motor command signal to adjust center-of-gravity to the left -A

(4) Integrate #1 and #2 so that next time # 1 happens you can make #3 happen

-B

(A) Deep cerebellar nuclear neuron

(B) Purkinje Neuron

(C) MF-PF pathway

(D) Climbing Fiber pathway

(E) C and D

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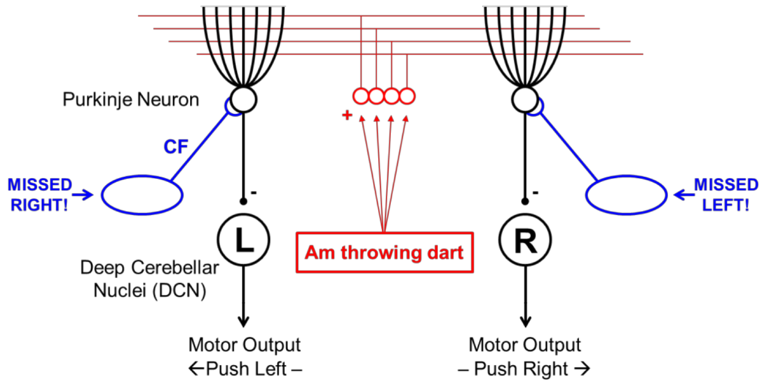
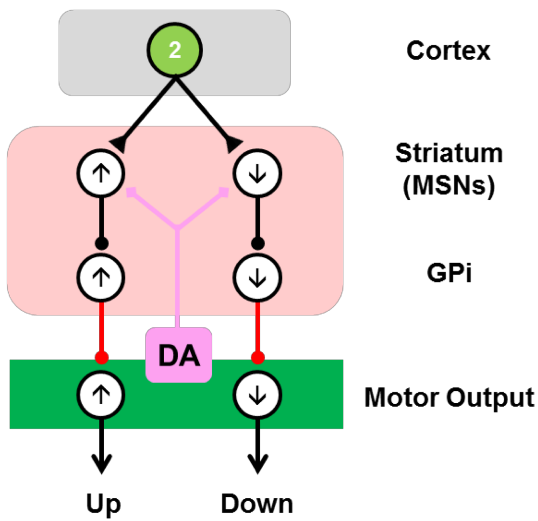
The cerebellum implements supervised learning



The basal ganglia implement reinforcement learning



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