# *Systems Neuroscience :*
# Motor adaptation and sensory prediction in the Cerebellum

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slides : https://biomedicale.u-paris.fr/~mgraupe/teaching.php

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The role of bodily feedback in pre-frontal regulation of fear states.

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***Jean-Rémi King*** **Jan 10th, '25**

AI and the Brain: the unexpected similarities and the remaining differ-ences

**ENS / Meta**

***Laura Dugué*** **Feb 7th. '25**

Traveling Waves in Human Brain

**Paris Cité**

***Kathleen Cho*** **Mar 7th, '25**

Prefontal interneu-ron function in cognitive control

**ICM**

***Joao Barbosa*** **April 4th, '25**

Distributed computations for flexible cognition

**INM / Neurospin**

***Sebastien Wolf*** **May 2nd, '25**

Decision-making and attentional processes in the auditory cortex

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***Jean-Baptiste Masson*** **Jun 13th, '25**

Embodied neuroAI with drosophila larva

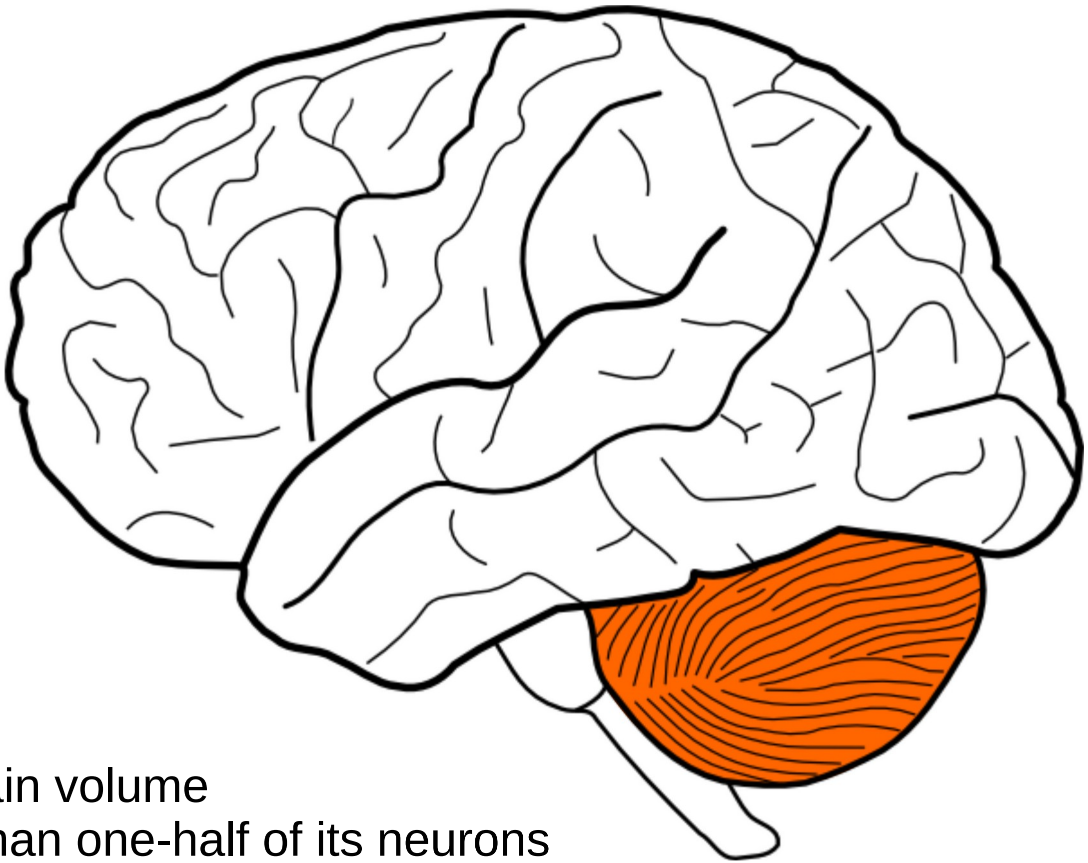
**Pasteur**

***Fani Koukouli*** **Jul 4th, '25**

Cholinergic modu lation of cortical inhibitory circuits and its dysfunc-tion in psychiatric disorders

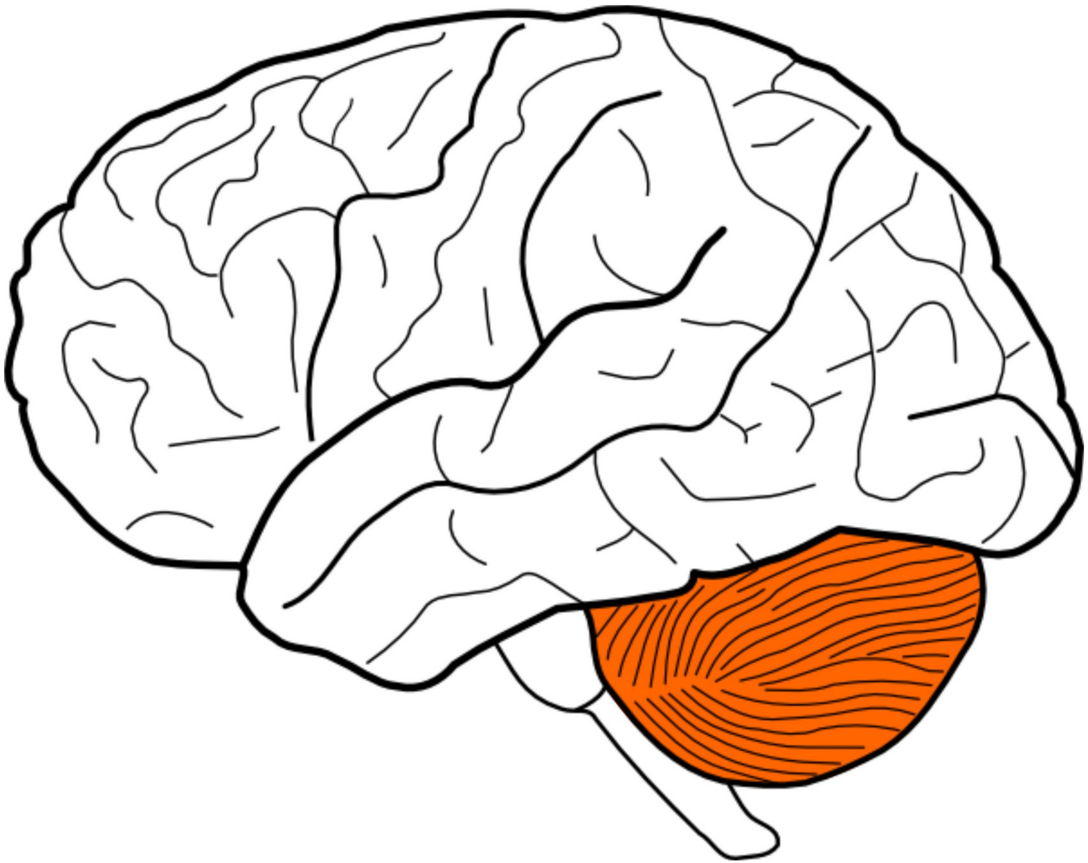
**IPNP**

# Cerebellum



10 % of the total brain volume
but contains more than one-half of its neurons

# Cerebellum



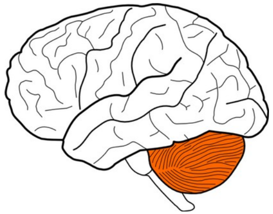
contains highly regular, repeating units with the same basic microcircuit

different regions receive inputs from different parts of the brain and project to different motor systems

similarity (architecture, physiology) suggests similar computational operations

# Talk outline

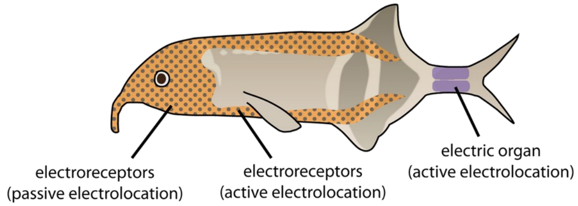
**1. Cerebellar disorders**
- functions inferred from symptoms
- eye-arm movement coordination with prism glasses



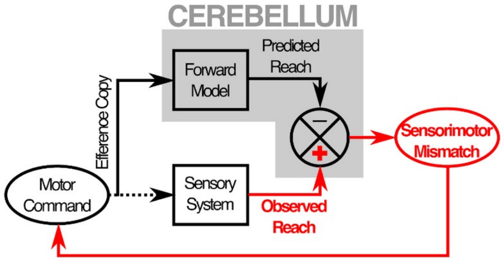
**2. Prediction of sensory consequences**

*Electric fish*
- anatomy and physiology of the weakly electric fish
- cerebellar circuitry
- cerebellum-like structures
- electric fish and prediction of sensory consequences

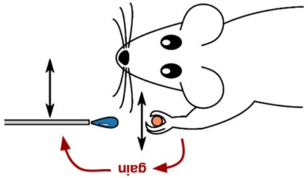
*Sensory prediction in mammals*




**3. Motor control and internal models**
- forward and inverse model
- forward model and the cerebellum




**4. Experiments implemented in the lab to unravel cerebellar function**
- sensorimotor mismatches in mice



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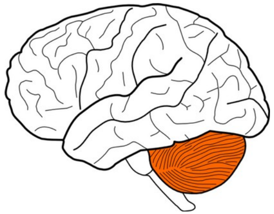

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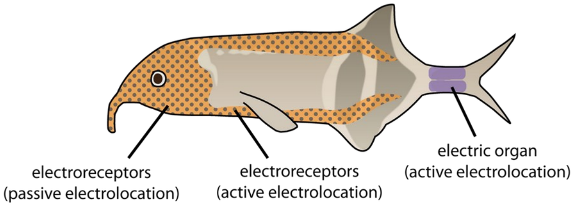


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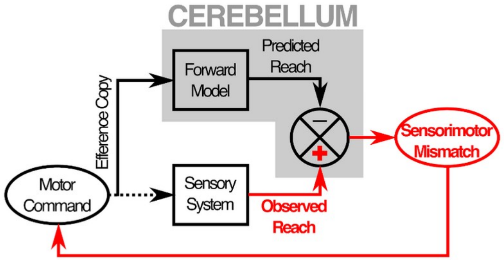


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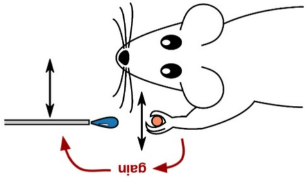
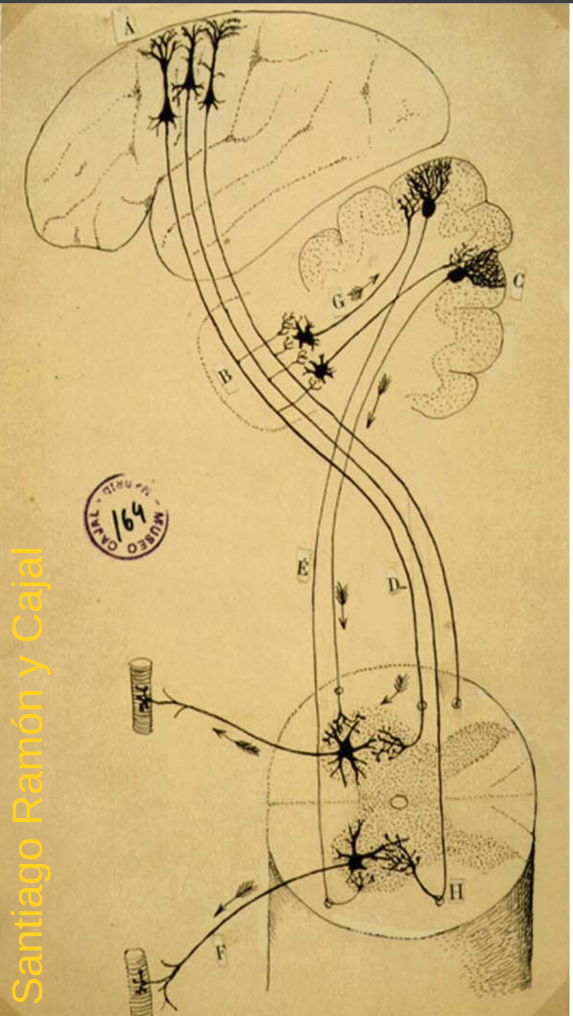


# Cerebellum controls movement




**Classical view :**

Cerebellum *participates* in the control of movement.
The cerebellum ensures that movements are well timed and highly coordinated.

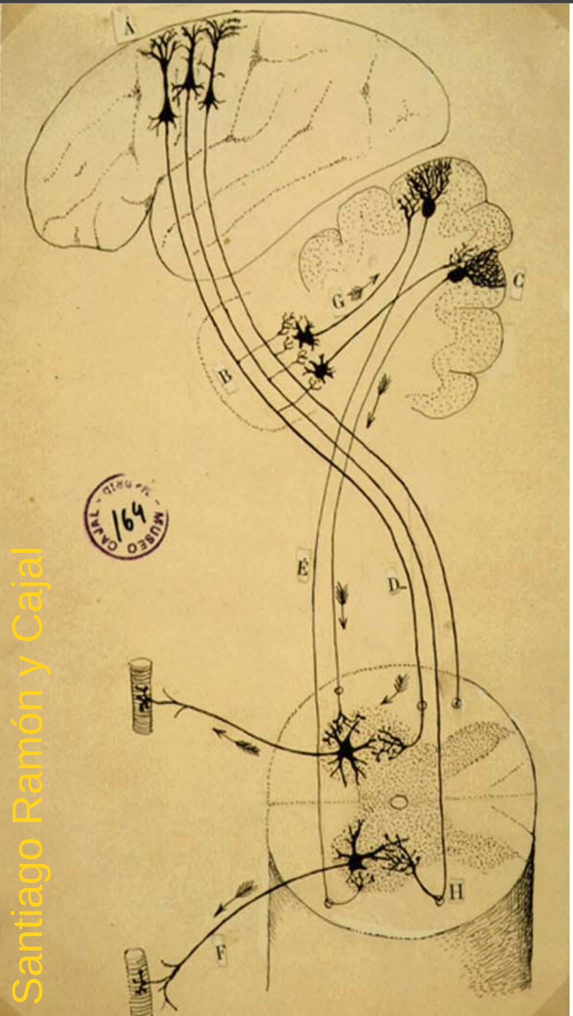
**Inferred from cerebellar damage in humans :**

Disorders result in disruptions of normal movement.

**Goal of cerebellar research :**

How to the connections and physiology of cerebellum define the role in motor control.

# Symptoms of cerebellar disorders




Santiago Ramón y Cajal

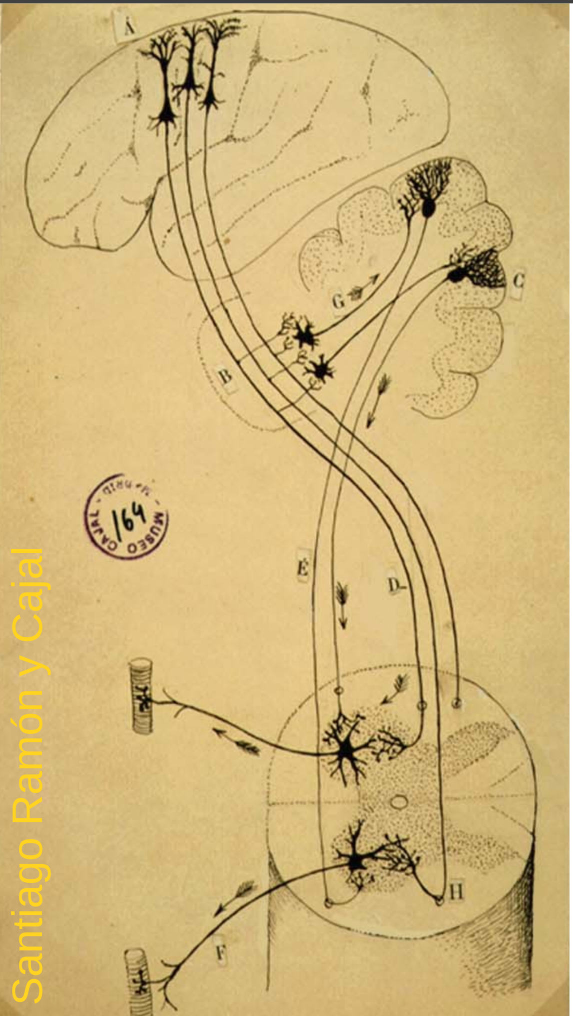
**Hypotonia :**
diminished resistance to passive limb displacement

**Astasia-abasia :**
inability to maintain steady limb or body posture across multiple joints - inability to maintain upright stance against gravity

**Ataxia :**
abnormal execution of multi-joint voluntary movements, lack of coordination

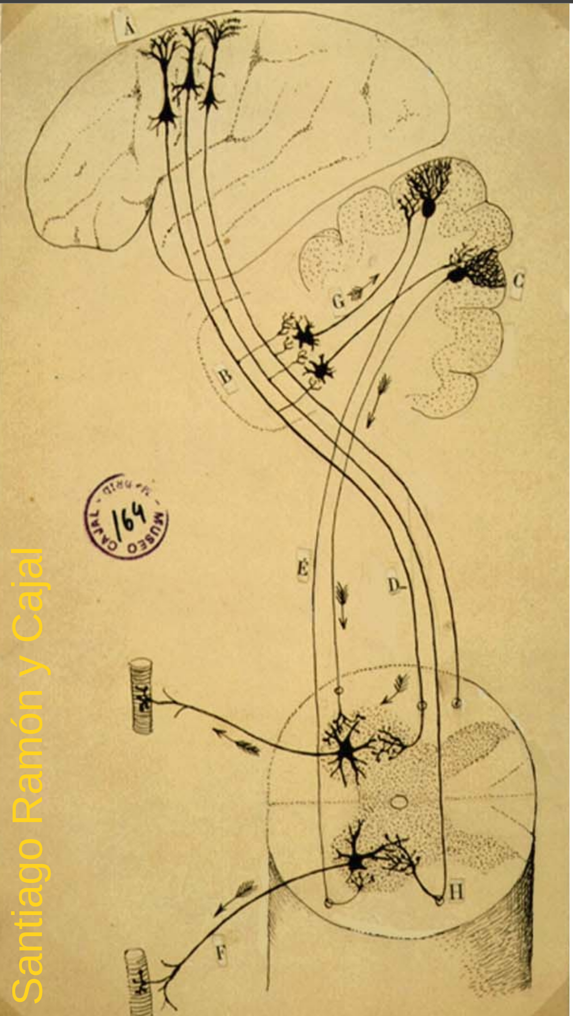
**Action tremor :**
tremor at the end of movement

# Symptoms of cerebellar disorders




Patient with cerebellar ataxia

# Derived functions of the cerebellum



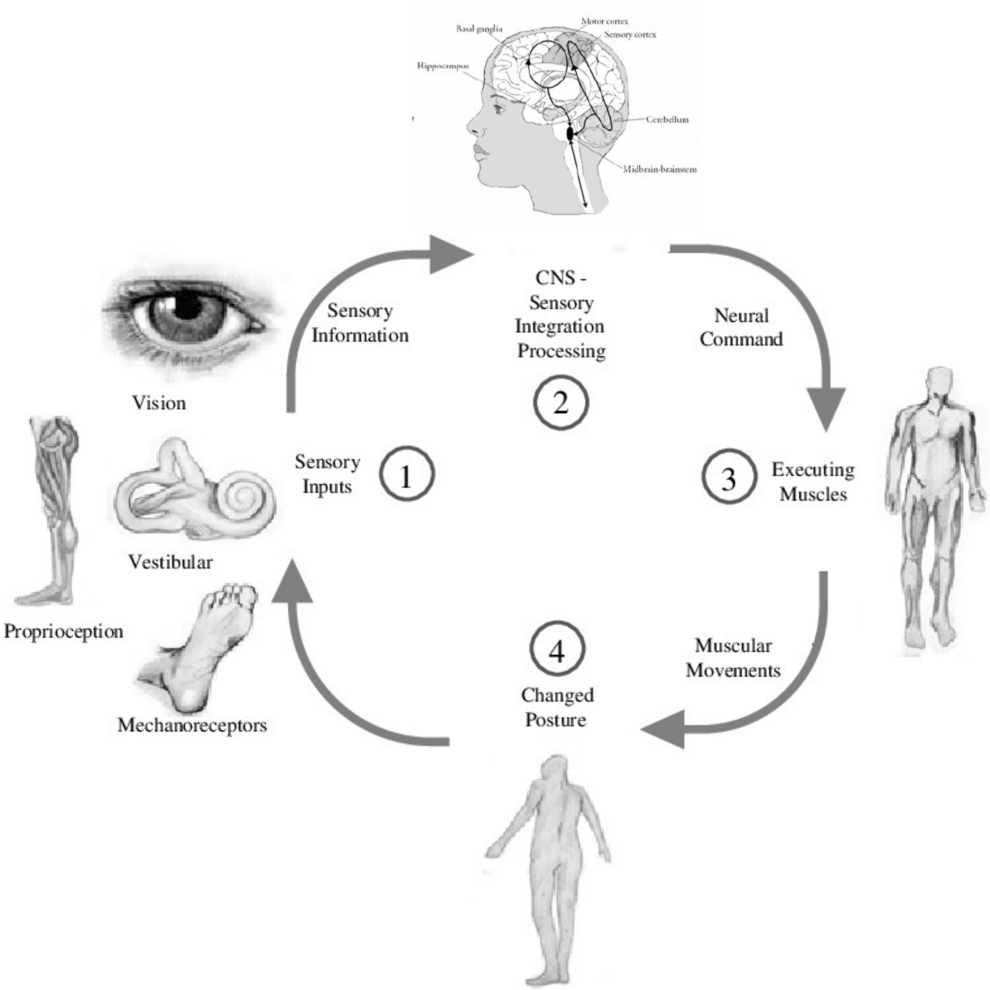

Santiago Ramón y Cajal

- Initiation and control of voluntary movements
- Timing of movement/muscle action
- Moment-to-moment corrections of errors
- Compensating for lesions of the cerebral cortex
- Motor learning and adaptive adjustments

# What is movement ?

sensory and motor inputs are integrated to generate appropriate activation of muscle and joint combinations

# What is movement ?




sensory and motor inputs are integrated to generate appropriate activation of muscle and joint combinations

# Prism glasses

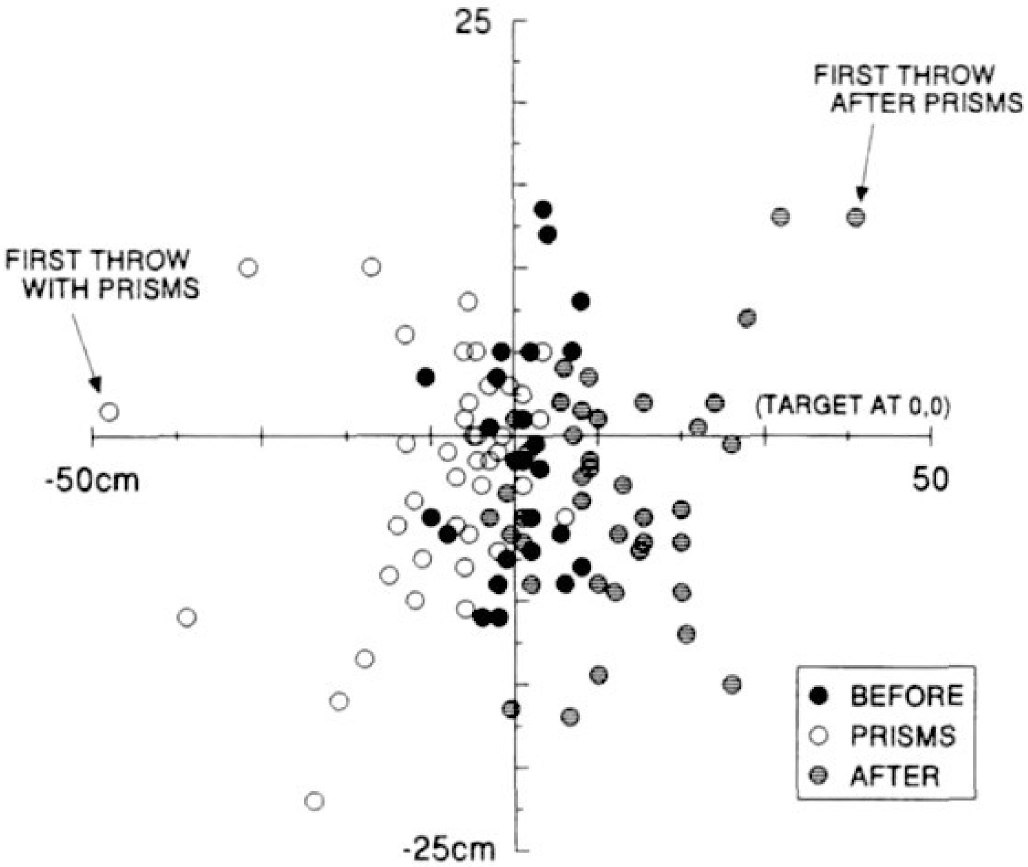
- experimental paradigm to study the learning of a synergy between vision and motor output
- adaptation of the eye-hand coordination when wearing prism goggles

[experiment]

# Prism glasses

- humans usually fixate a target and throw in the direction of the gaze
- relationship between the direction of the gaze and arm movement is adjustable

# Throwing while looking through prisms




- The initial throw in the direction of gaze misses target to the side by an amount proportional to the diopter of the prism (in our case 30 %)
- subject gradually increase angle between gaze and trow to land on target again
- after glasses are removed, gaze is on traget, but the widened angle btw. gaze and throw persists; this 'negative after-effect' diminished with repeated throws

[Martin *et al.* 1996 Brain]

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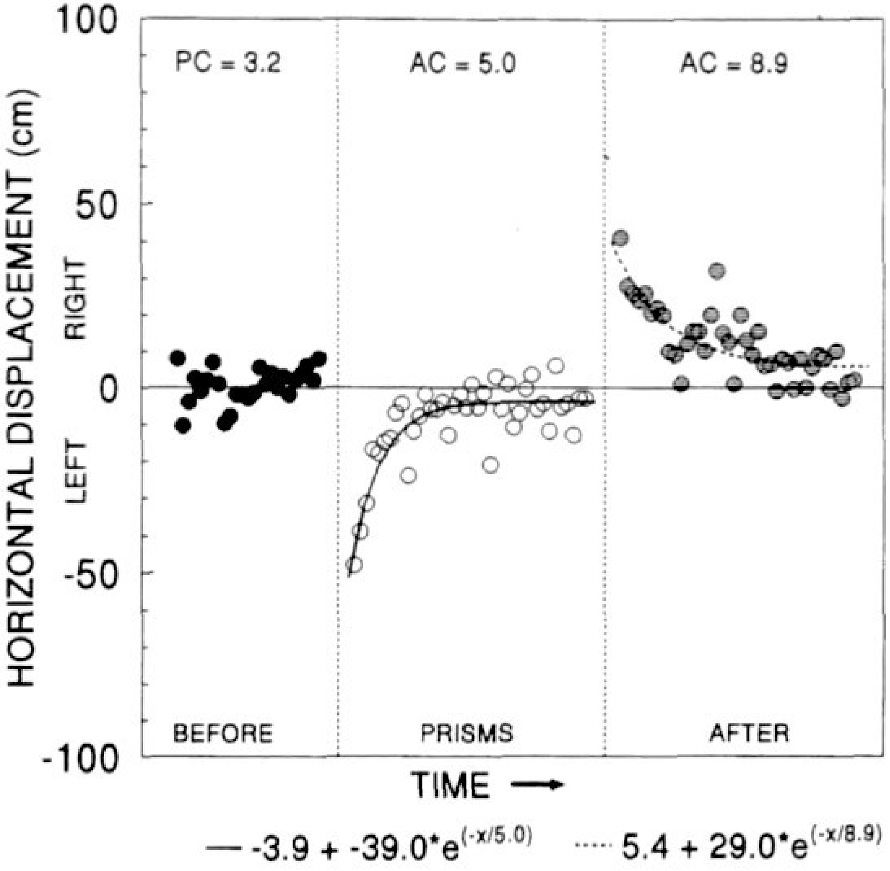


[Martin *et al.* 1996 Brain]

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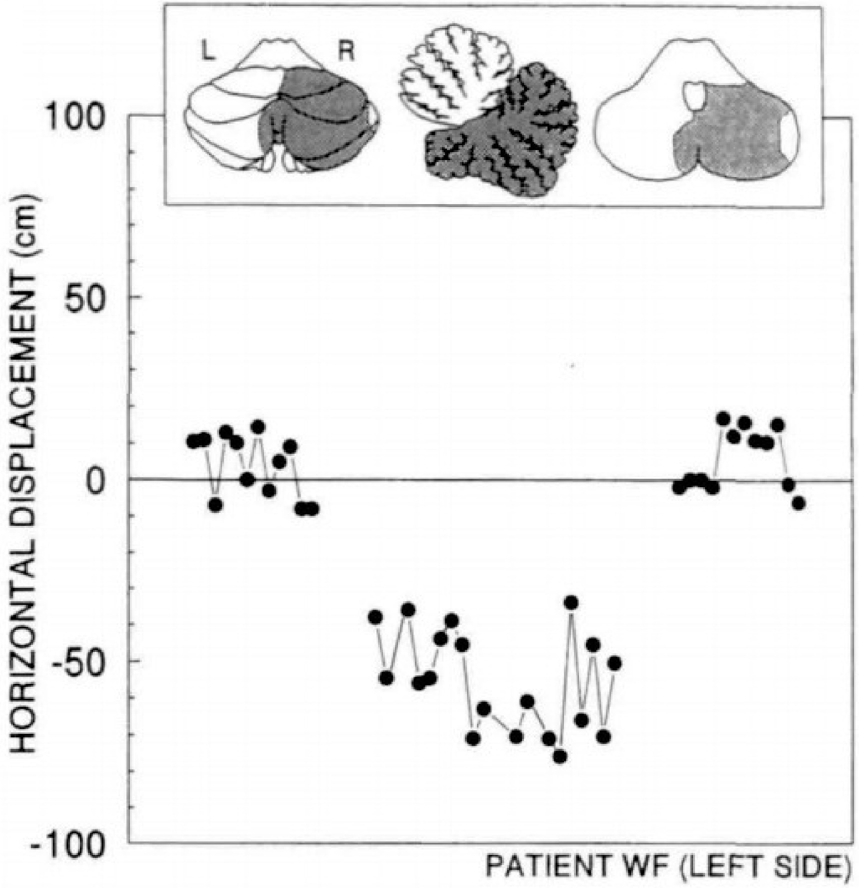
# Cerebellar patients : throwing while looking prisms




[Martin *et al.* 1996 Brain]

- patients with cerebellar disorders show slow or no adaptation of the eye-hand
- example on the left : patient with right sided infarct of the posterior inferior cerebellar artery

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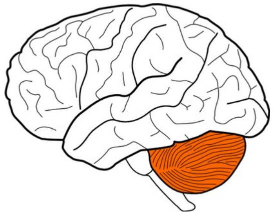
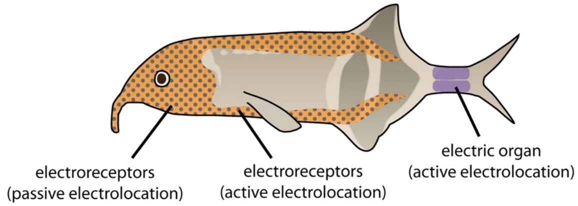
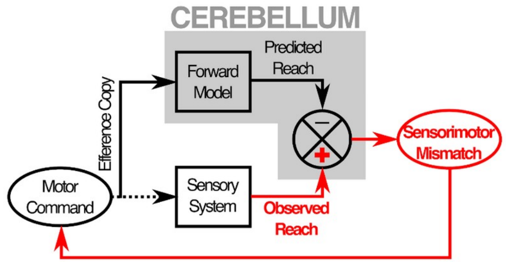
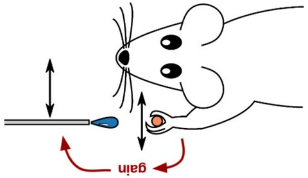


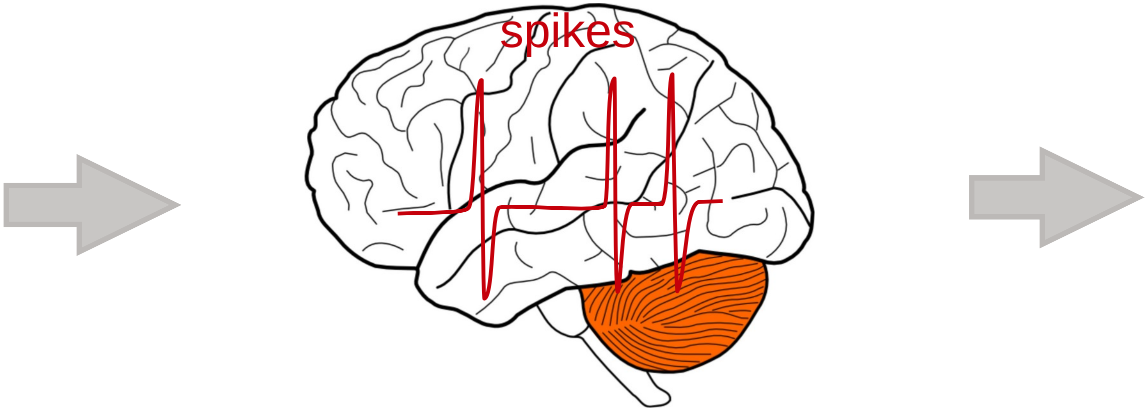


# Neural code and cerebellum

stimulus

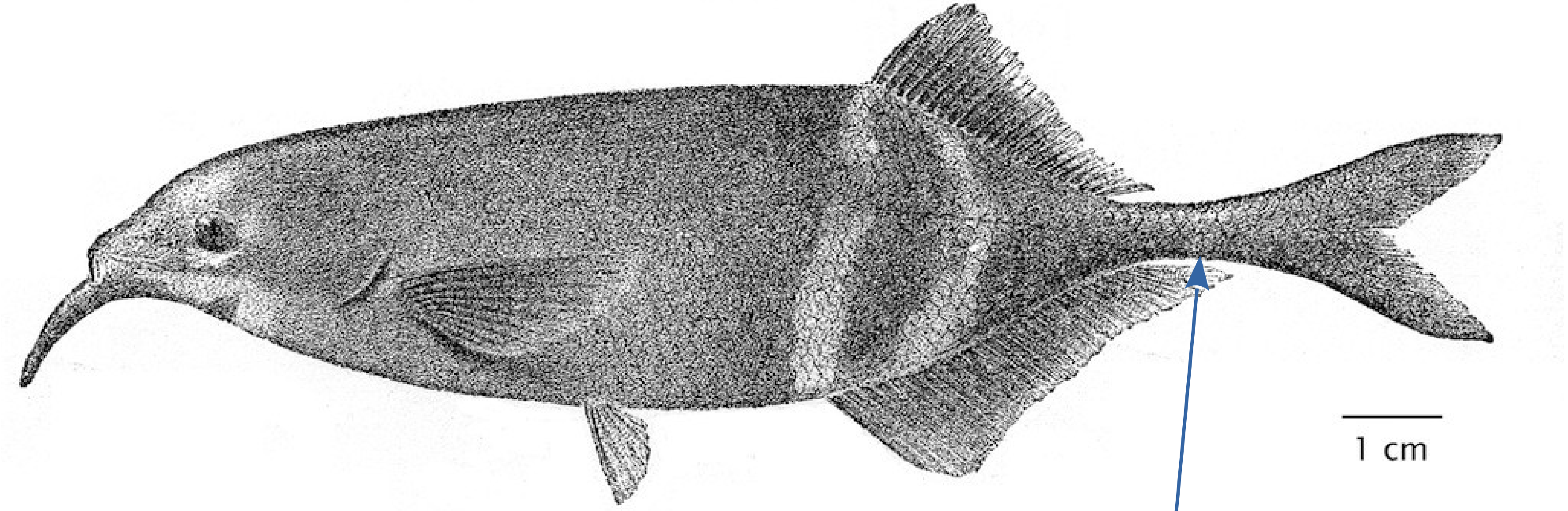



response

- Neural coding : establishing the relationship between stimulus and individual or ensembles of neuronal responses
- Which information is represented ?

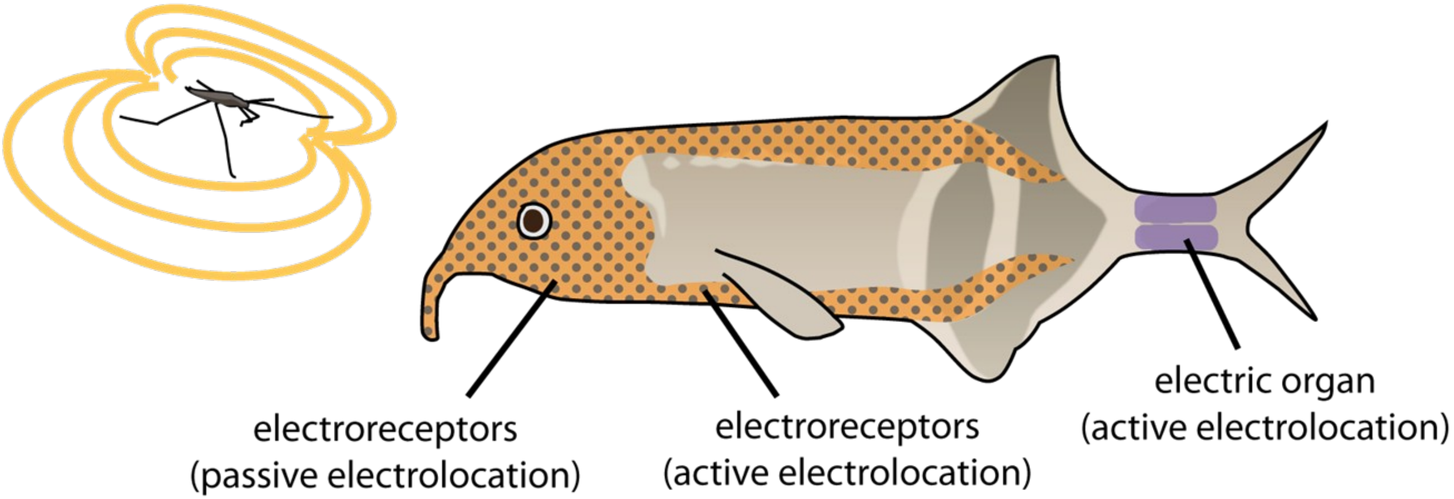
- **Cerebellum** : cerebellar circuits generate and test predictions about movement, but also reward, and other non-motor operations.

# African weakly electric mormyrid fish




- possess electroreceptors on their skin that are sensitive to weak, low-frequency electrical fields in the environment
- additionally has specialized organ (typically located in the tail) that generates a weak electrical field known as an electric organ discharge (**EOD**)

# African weakly electric mormyrid fish



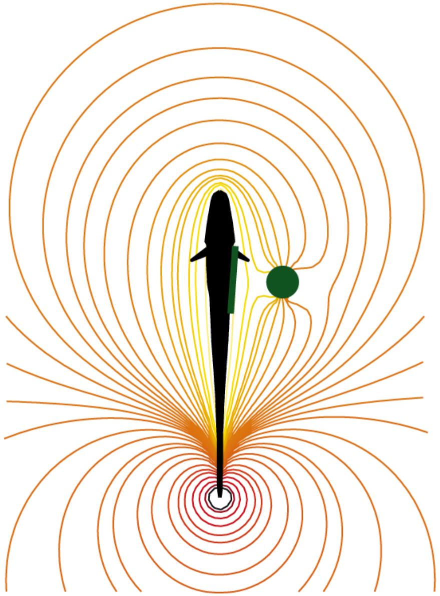

- Active and passive electrolocation are mediated by separate classes of electroreceptors

- electric organ discharge (**EOD**) used to sense environment and communicate (like whisking in rodents)
- 2-4 /s in resting-, 10-30 /s in moving fish

# Electric organ discharge : usage

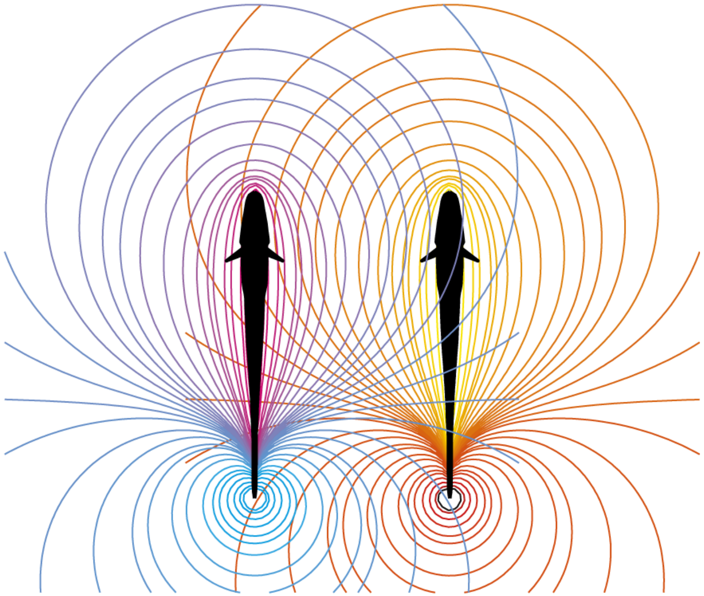
- Active and passive electrolocation are mediated by separate classes of electroreceptors; 3 receptor classes in total

**electrolocation**



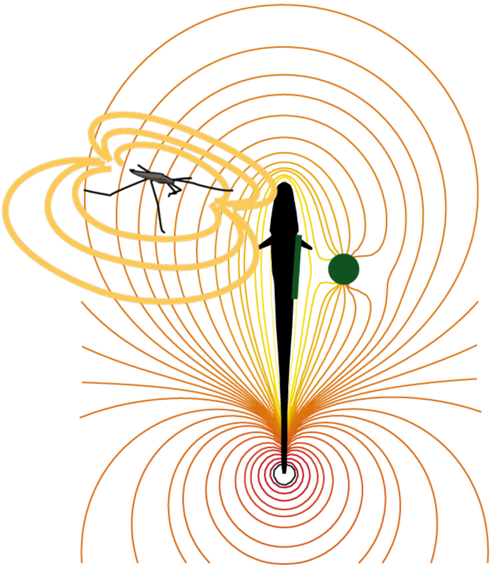
1) mormyromast : active electrolocation

**electrocommunication**



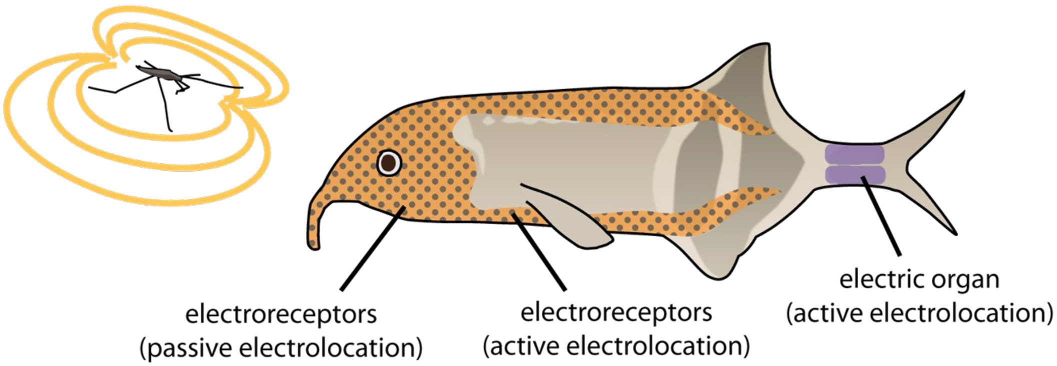
2) Knollenorgan : detecting EOD of other fish

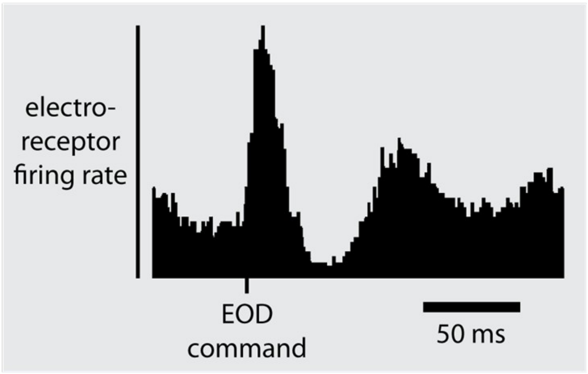
**electrolocation**

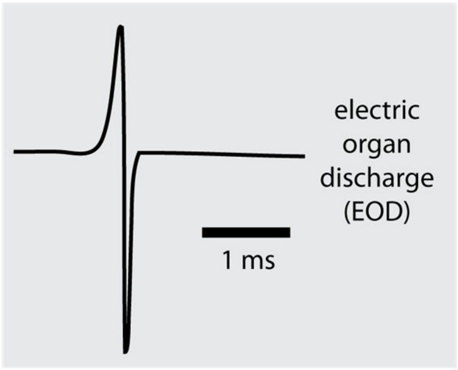


3) ampullary : can measure weak electric fields that all animals generate in water

# Challenge for the fish

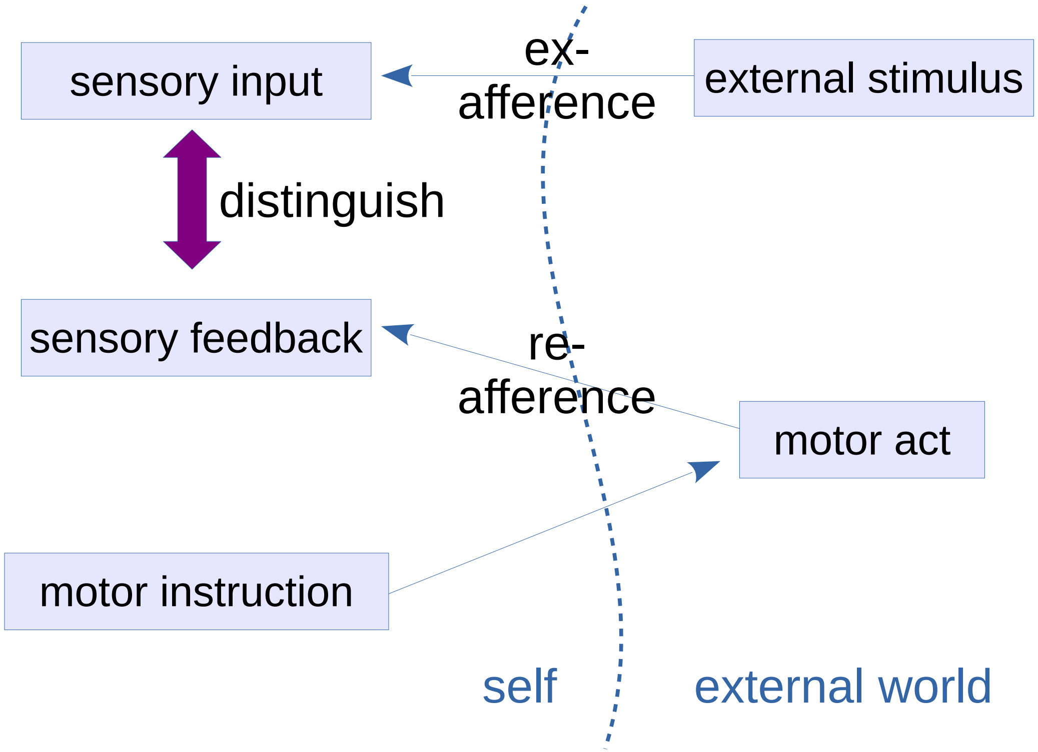


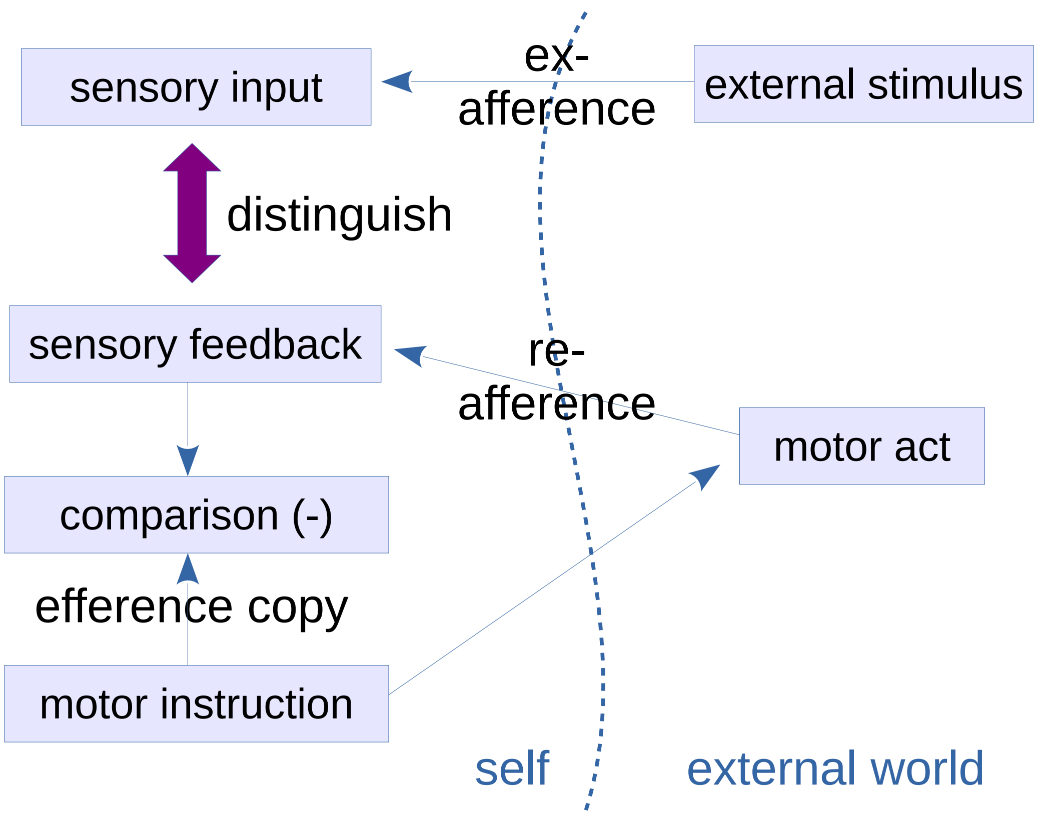

- **problem :** passive (ampullary) electroreceptors are strongly affected by the fish's own EOD pulse
- **possible solution :** external and self-generated input can be distinguished based on additional information about own movement and behavior
- **implementation :** convergence of two distinct input streams – peripheral electrosensory input *and* information about own movement and behavior

# Challenge for the fish and others species



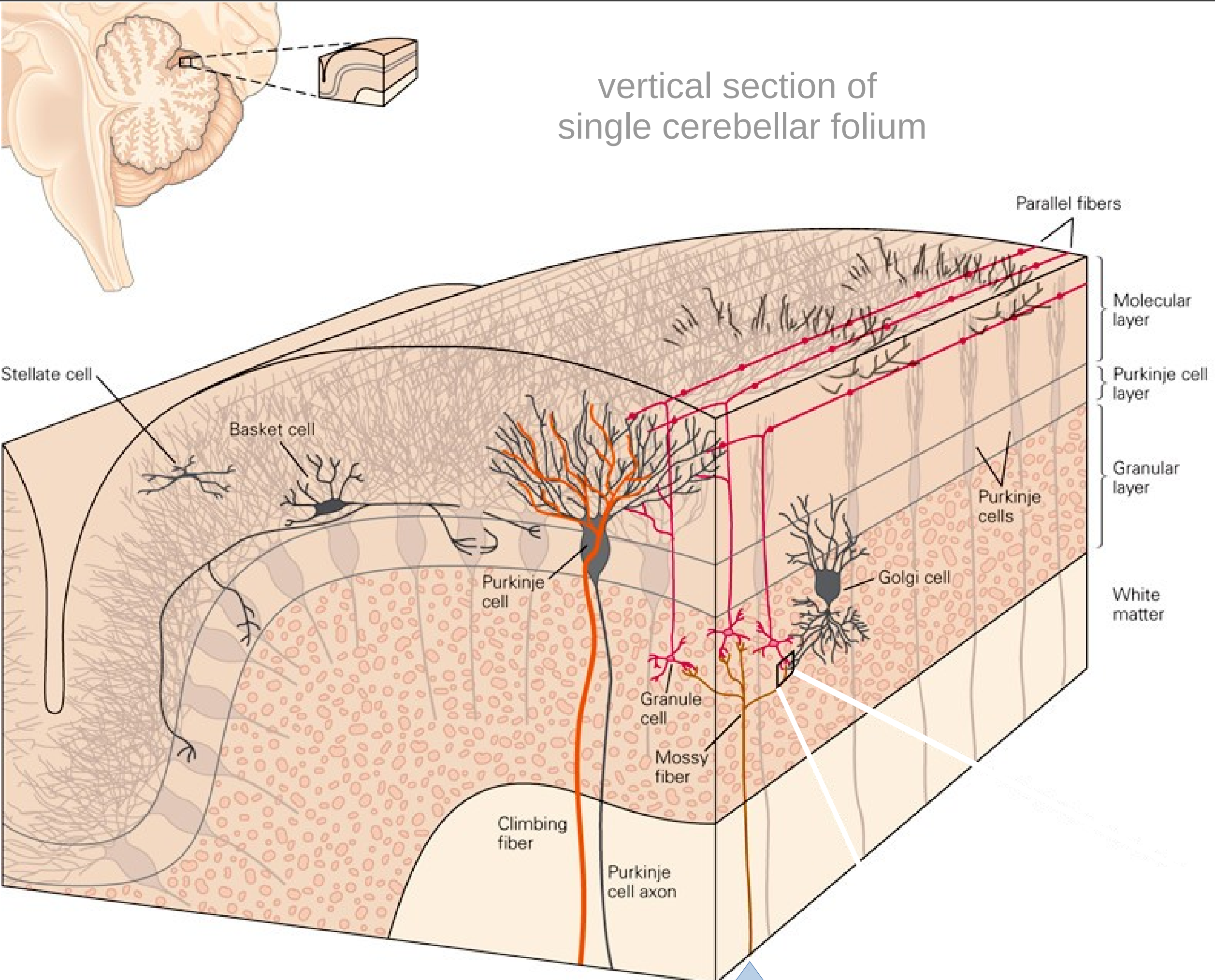

- sensory inputs are evoked by external stimuli (ex-afference)
- every motor act will also elicit sensory inputs (re-afference)
- this can be disruptive because it can interfere with sensing of external stimulus sources
- **challenge** : distinguish between externally and self-generated inputs

# Challenge for the fish and others species




- every motor act will elicit sensory inputs (called reafference)
- reafference can be disruptive because it can interfere with sensing of external stimulus sources
- problem can be solved with signals from the motor command center to appropriate sensory receiving areas that nullify the effect of the unwanted reafference
- these signals are called efference copies/corollary discharges
- appropriate summation (negative image) of efference copy  and reafference could reduce reafference effect
- requires implementation of an adaptive filter which removes predictable features of the sensory input

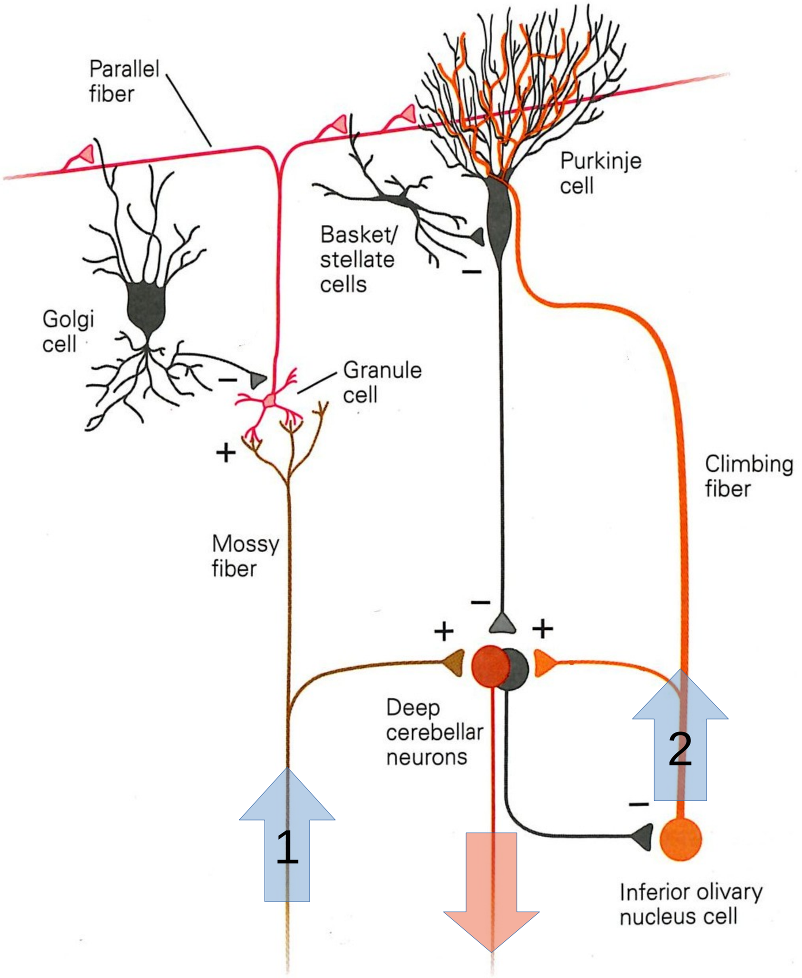
# Microcircuit organization of the cerebellar cortex




**cerebellar cortex :** five types of neurons organized in three layers

- *granular layer :* input layer, vast number of granule cells and Golgi interneurons; mossy fibers terminate in this layer
- *Purkinje cell layer :* output layer of the cerebellar cortex; input from parallel fibers, Stellate and Basket cells and climbing fibers
- *molecular layer :* inhibitiory neurons; axons of granule cells - parallel fibers

# Synaptic organization of the cerebellar microcircuit

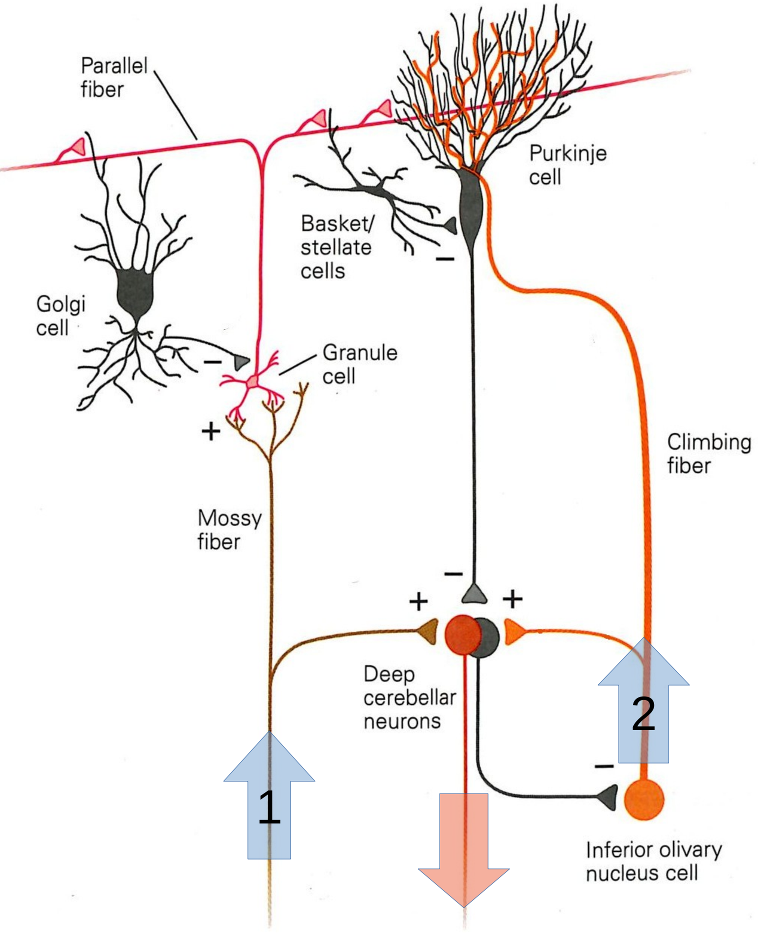



Two afferent fiber systems encode information differently

- *1. mossy fibers :* from cells in spinal cord and brain stem, carry sensory information about periphery and cerebral cortex

- *2. climbing fibers :* originate in inferior olivary nucleus and convey sensory information from periphery and cerebral cortex

# Differences in the two input streams



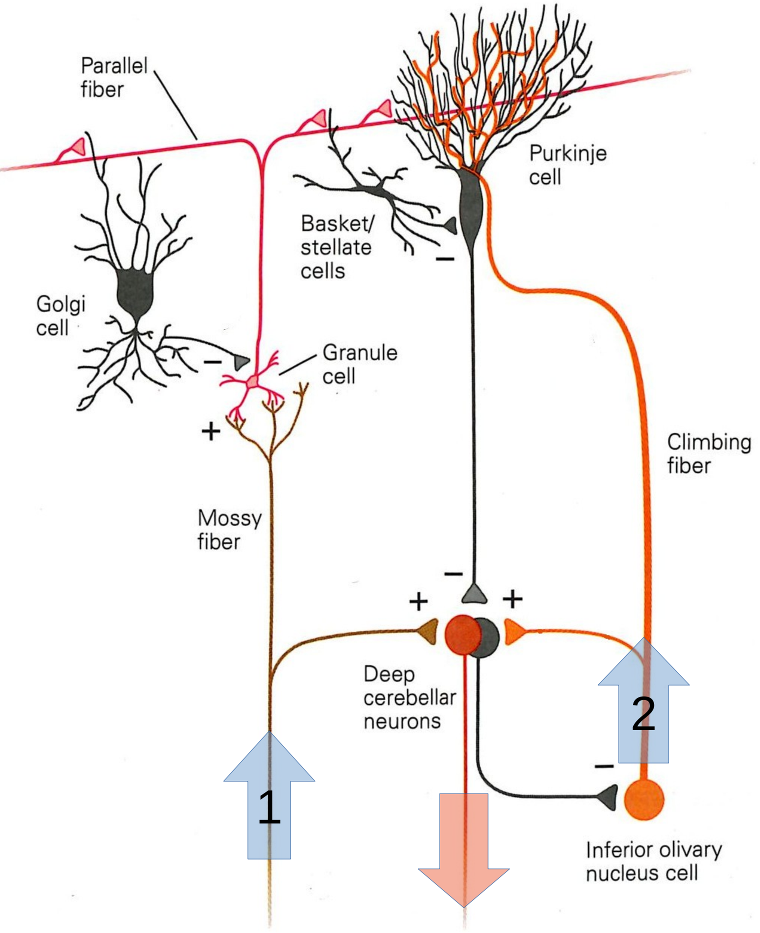

**1. mossy-parallel fibers**

- convergence (mossy fiber to granule cell) and divergence (parallel fiber run across long distances) of signal flow
- produce brief, small excitatory events → simple spikes; inputs from many needed to have substantial effect on PC firing rate
- encodes magnitude and duration of peripheral stimuli or behaviors

**2. climbing fibers**

- specific connectivity : arranged topographically btw. inferior olive, PCs in parasagittal strips, deep nuclear neurons
- powerful influence on PC activity → complex spike
- seems specialized for event detection; synchronous activation signal important event

# Differences in the two input streams

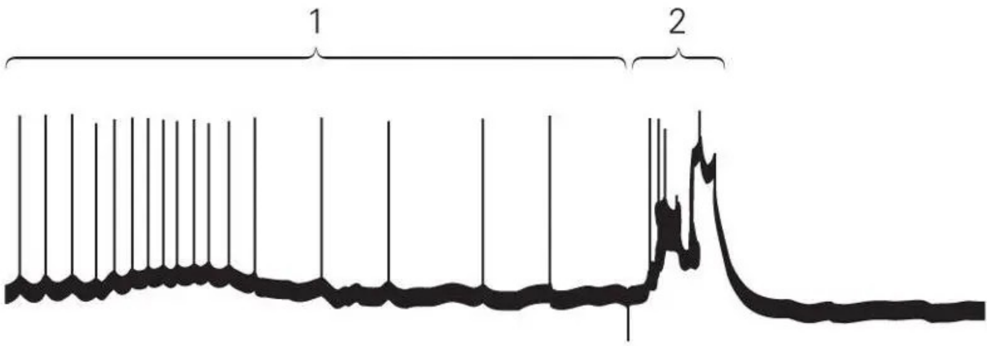



**1. mossy-parallel fibers**

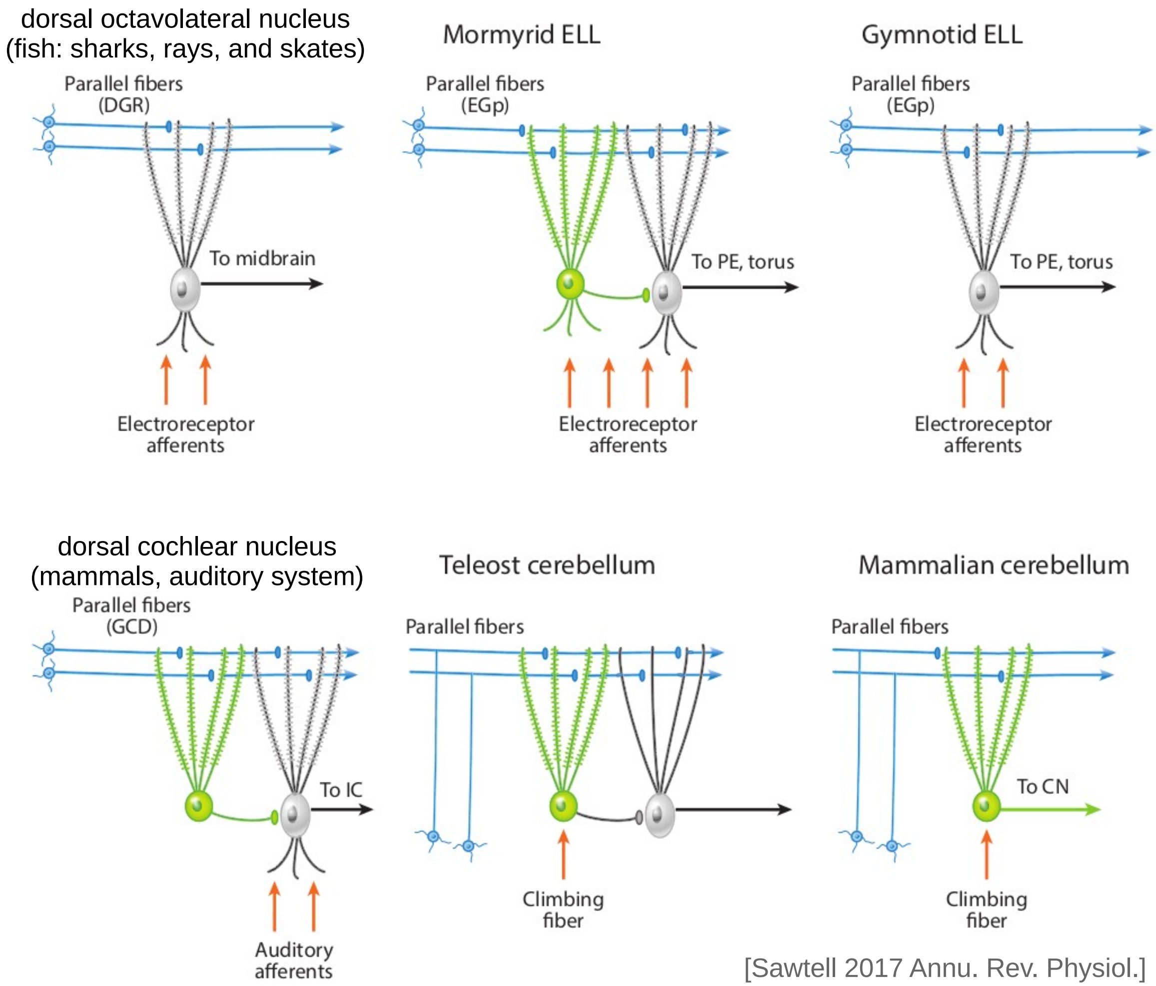
**2. climbing fibers**

simple spikes

complex spike



# Cerebellum-like structures



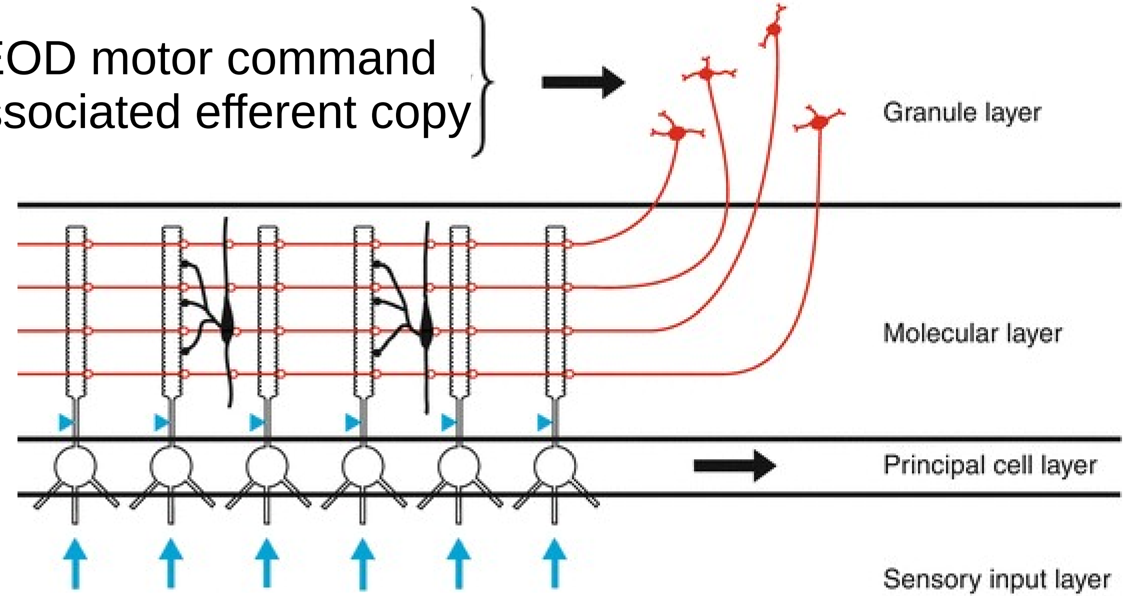

[Sawtell 2017 Annu. Rev. Physiol.]

- presence of two input streams is the defining feature of the cerebellum(-like) structures from fish to mammals
- all have principal cells, stellate cells and granule cells
- For all of the circuits shown, signals conveyed by parallel fibers can be used to predict signals from the sensory periphery or from climbing fibers

electrosensory lobe (ELL)

# Cerebellum-like structures : electrosensory lob (ELL)

EOD motor command
associated efferent copy



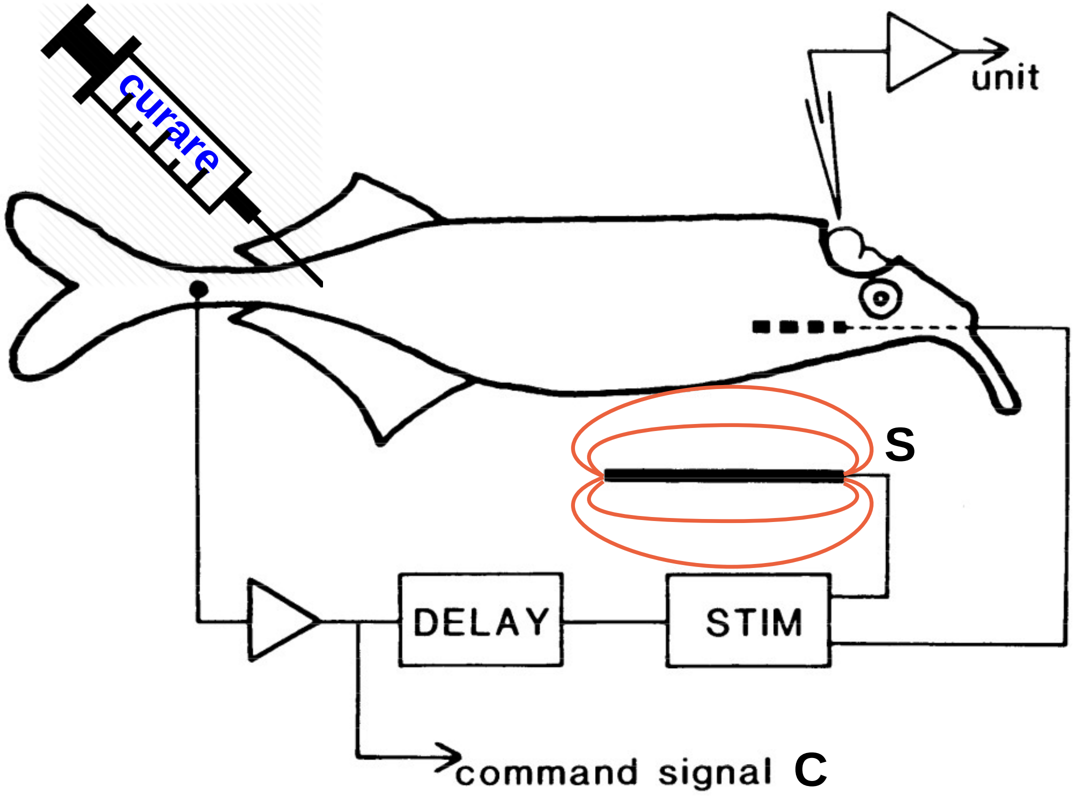

afferent activity
(input from sensory surface:
electroreceptors)

**Granule cells:**
convery efference copy that is associated with the motor command that causes the EOD

**Principal cells:**
also receive afferent activity : sensory input from electroreceptors

[Sawtell and Bell 2013, Cerebellum-like structures]

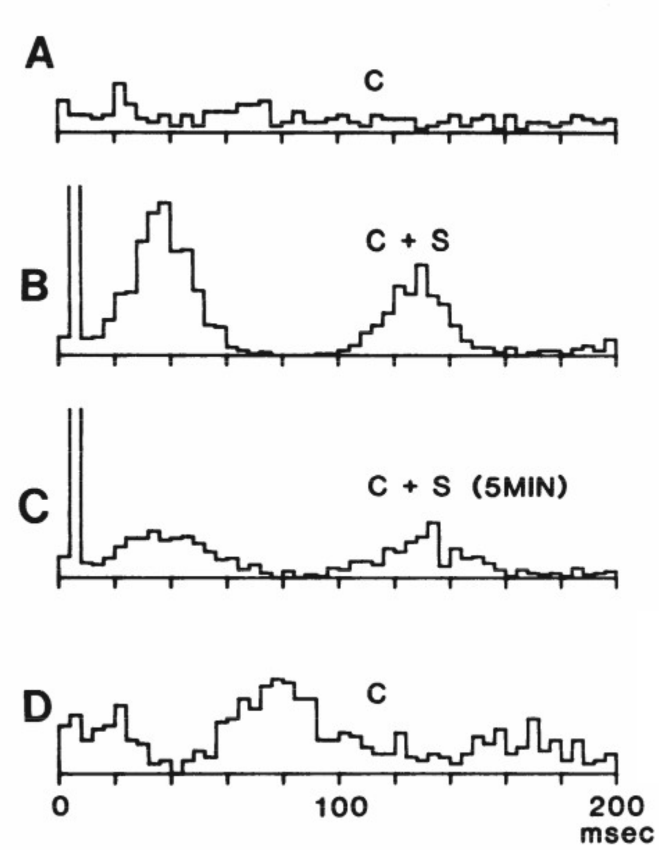
# Electric fish experiment: Bell 1982 J Neurophysiol




[Bell 1982 J Neurophysiol]

- Fish is curarized : curare blocks effect of motorneurons on electric organ (inhibitor of nAChRs)
  → no discharge
- command signal (**C**) of electromotorneurons recorded (occurrence rate 2-4 /s)
- this signal is used to trigger artificial electric pulses (**S**) in the water (delay ~1.5 ms) mimicking aspects of the EOD
- extracellular recordings from ELL
- fish in wax block perfused by water

# Electric fish: effect of Command-Stimulus pairings




A) Command alone evokes no response

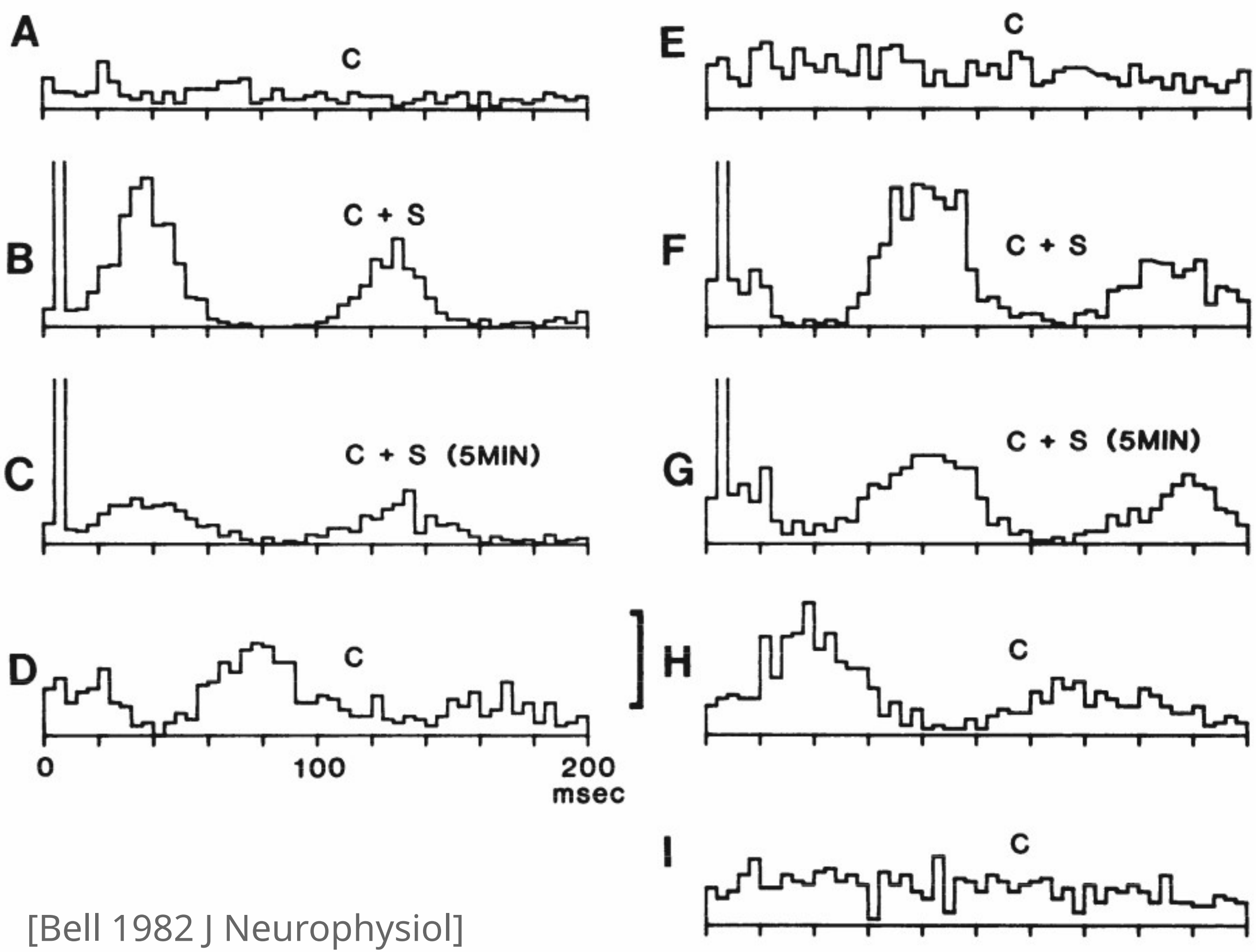
B) Command-stimulus pairing: initial response

C) Command-stimulus paring: reduced response after 5 min of pairing response

D) Effect of command alone immediately after 7 min of pairing

[Bell 1982 J Neurophysiol]

# Electric fish: effect of Command-Stimulus pairings




E) Command alone : 7 min after stimulus off

F) Command-stimulus paring: inverted electrical stimulation, initial response

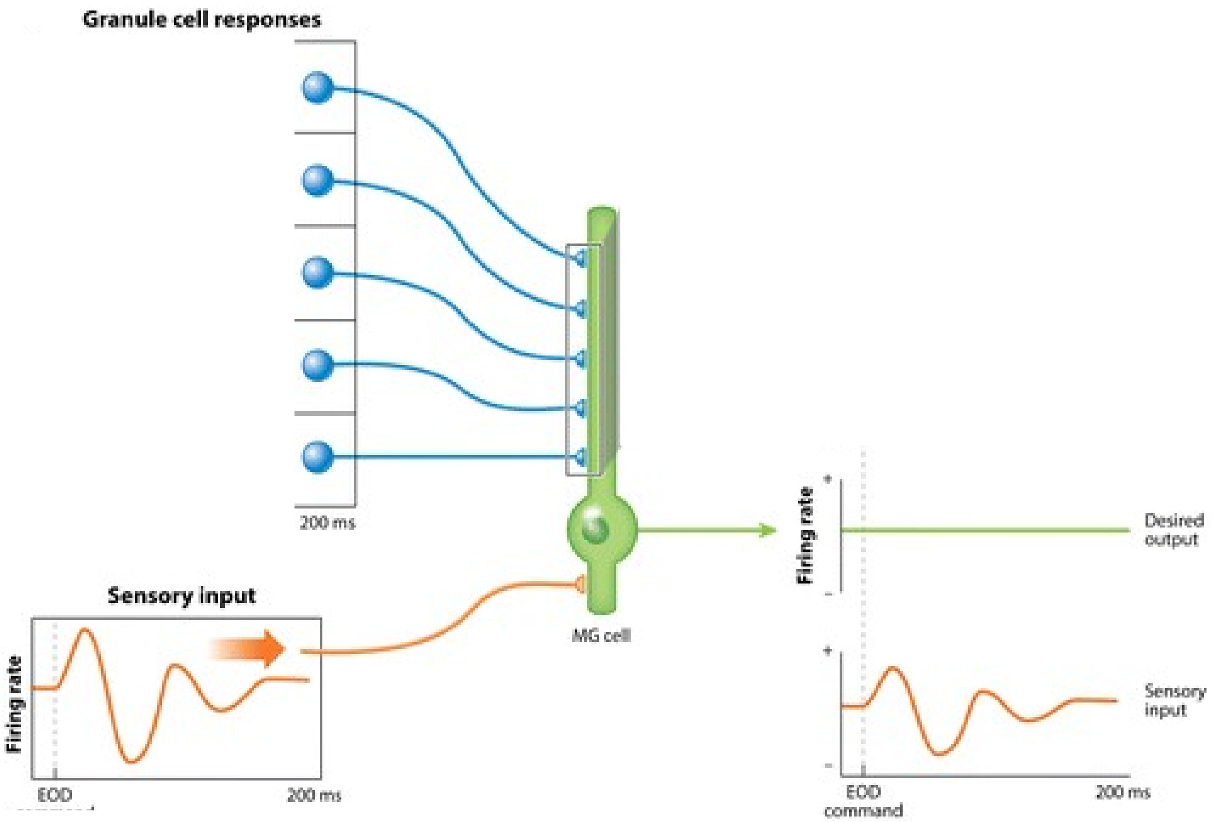
G) Command-stimulus paring: reduced response after 5 min of pairing response

H) Effect of command alone

I) Command after 15 min of stimulus off

[Bell 1982 J Neurophysiol]

# Electric fish experiment: circuit implementation




[Sawtell 2017 Annu. Rev. Physiol.]

- Sensory input (reafferance) should be suppressed
- Desired output : no response to reafferance
- Animal can use efference copies to create *negative image* of sensory input
- granule cell responses must be varied and prolonged
  [Kennedy et al. 2014 Nat Neursci]
- Requires plastic synapses : anti-hebbian plasticity rule
  - correlations between pre- and postsynaptic activity should decrease synaptic strength

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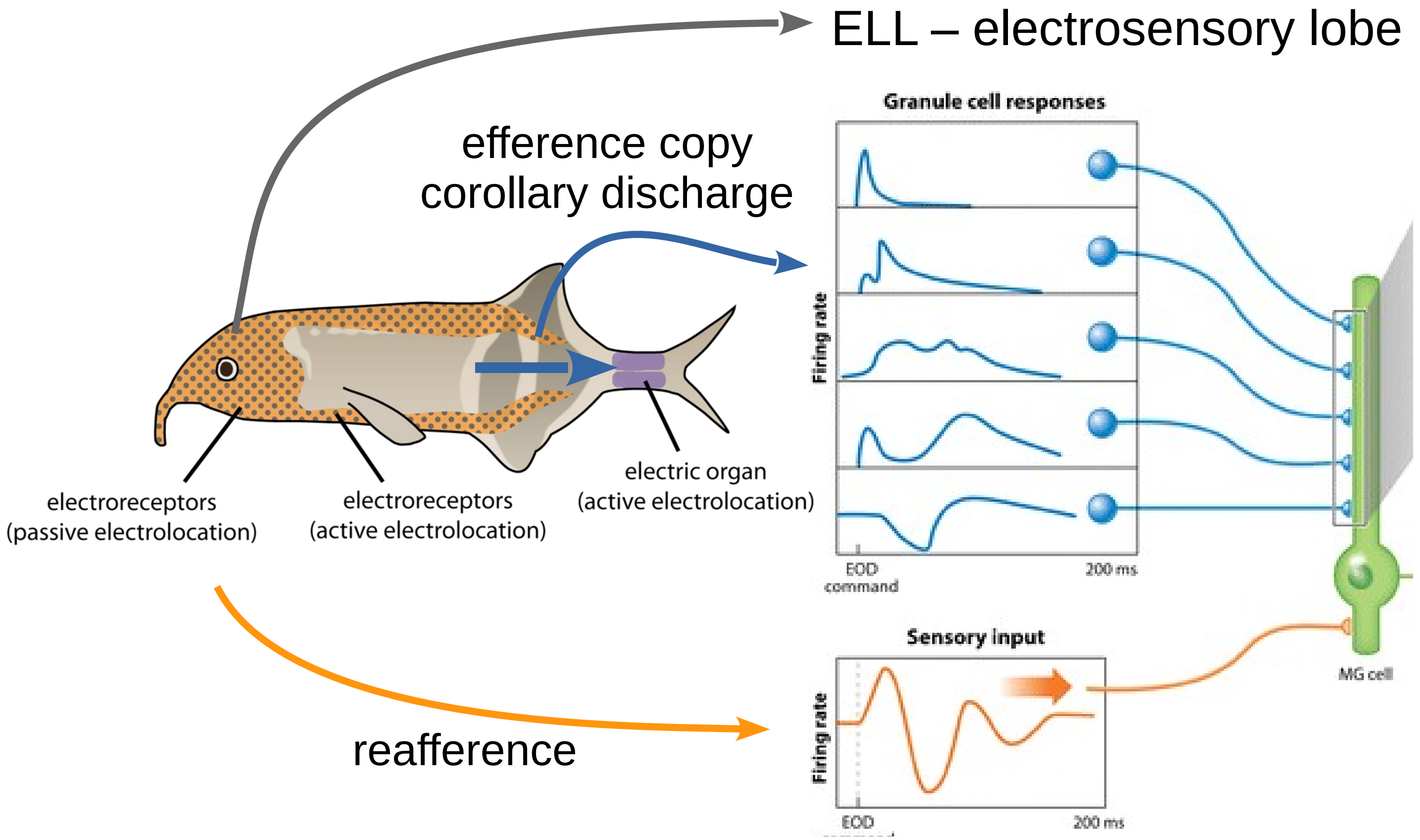
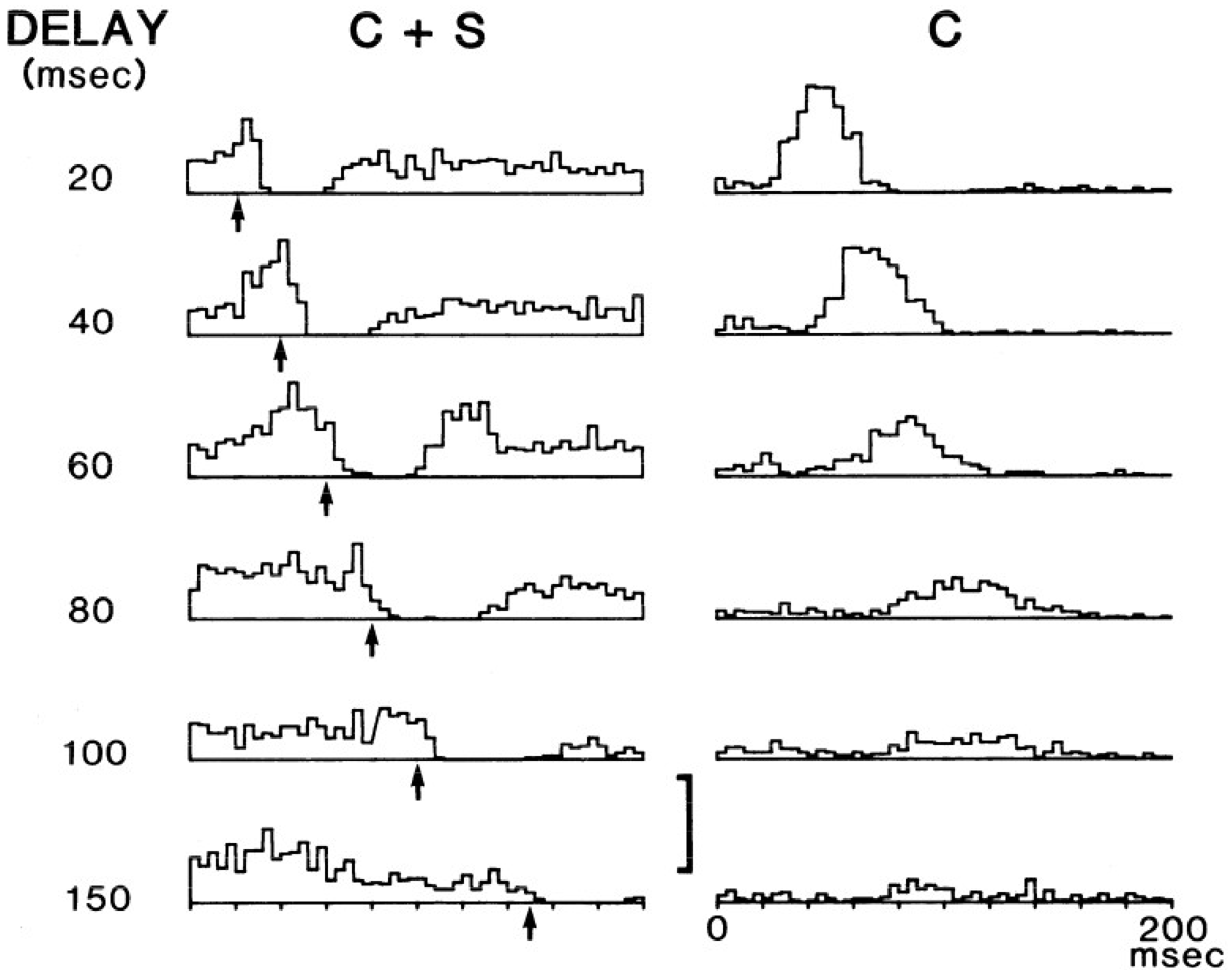


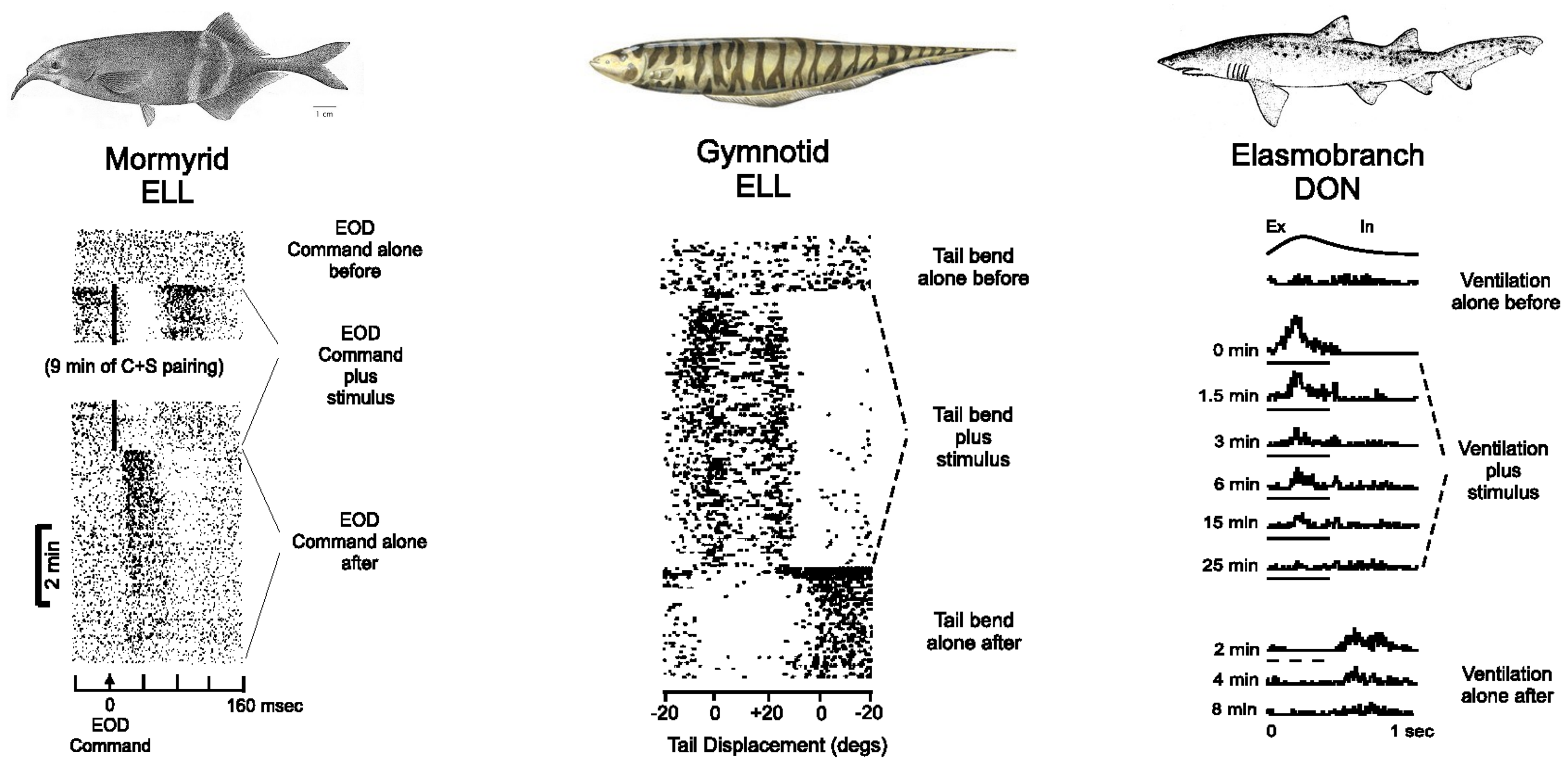

[Sawtell 2017 Annu. Rev. Physiol.]

# Electric fish experiment: varying stimulus delay

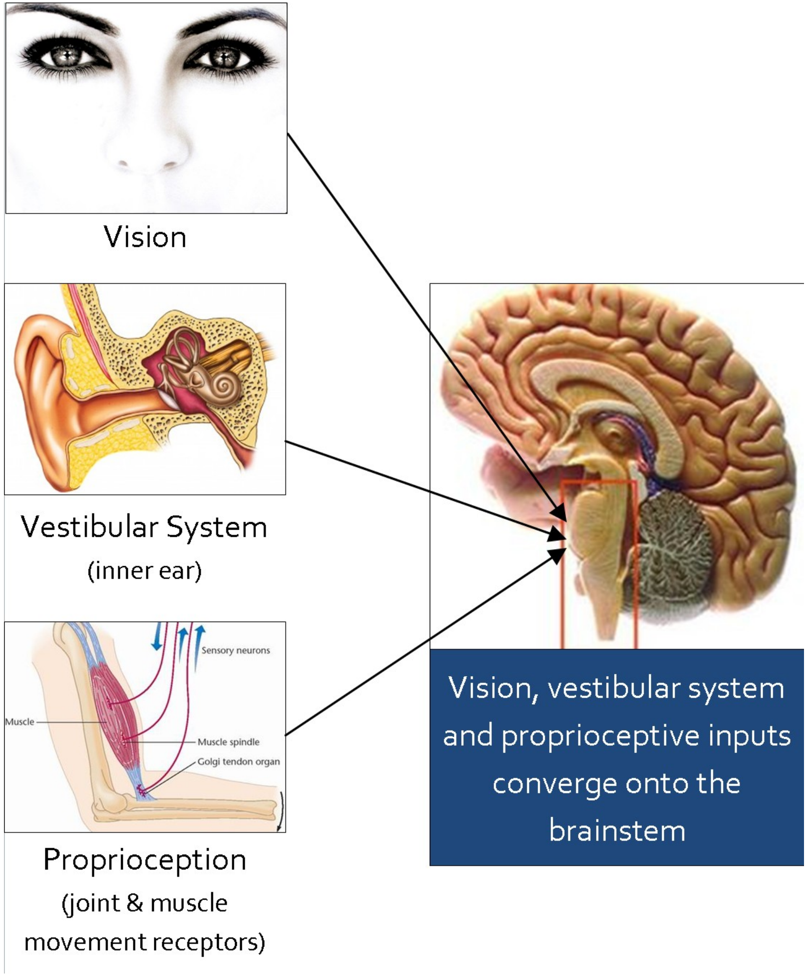



- effect of varying stimulus delay
- **left column :**
  command and stimulus were paired for 3-4 min
- **right column :**
  effect of the command alone
- in effect, tests the learning curve which implements the formation of the negative image

# Formation of negative images in 3 cerebellum-like structures



# Mammals: Sensory system activated during movement



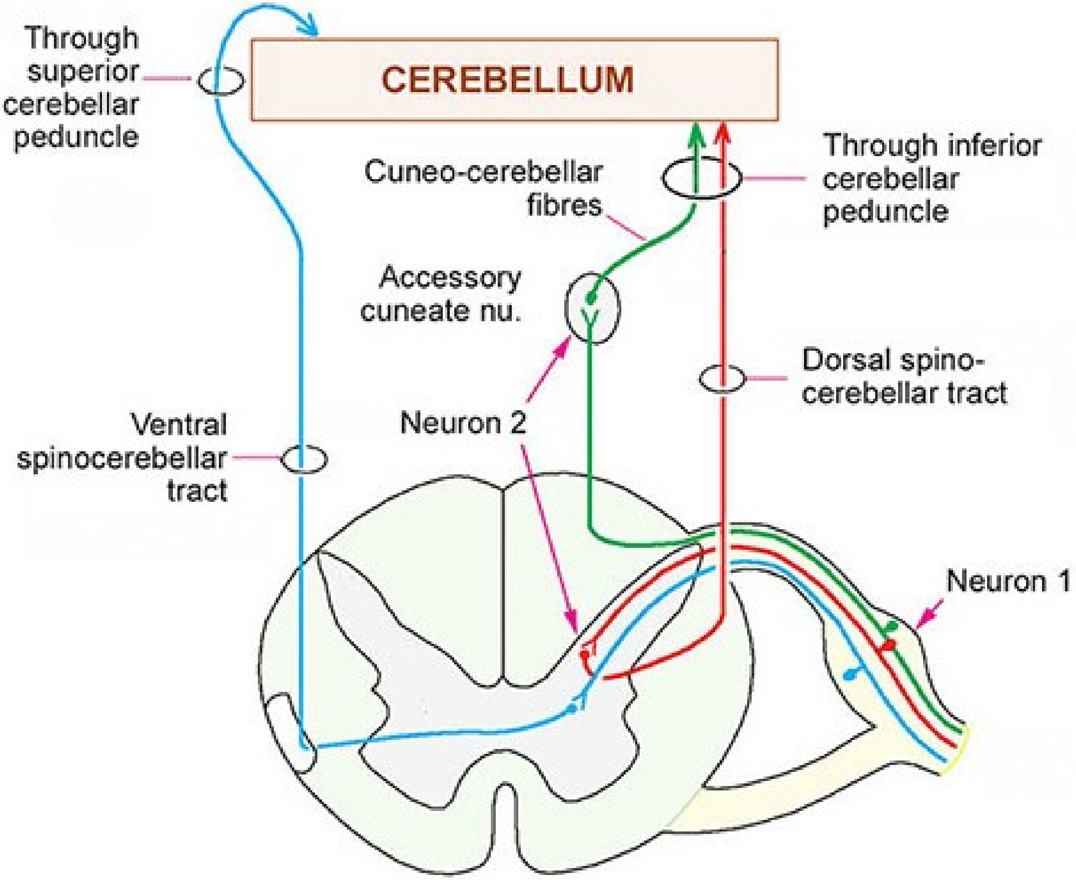

- Movement involves visual, vestibular and proprioceptive inputs

- How can the brain distinguish between consequences of our own self-generated actions (sensory re-afference) and stimulation that is externally produced (sensory ex-afference) ?

→ **Hypothesis** : prediction of sensory consequences

[experiment]

# Prediction of sensory consequences : two input streams




**dorsal spinocerebellar tract**

- conveys somatosensory information from muscle and joint receptors
- sensory feedback about consequences of movement (active or passiv)

  → reafference signal

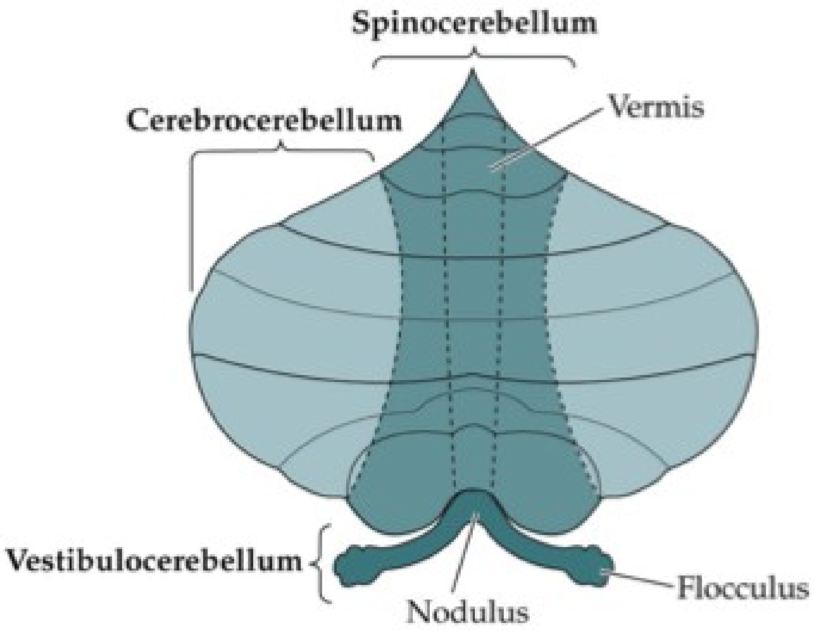
**ventral spinocerebellar tract**

- active only during active movement
- cells receive same inputs as spinal motor neurons

  → efference copy/corollary discharge

both provide information from hind limbs

# Three subdivisions of the cerebellum : related movements




**Vestibulocerebellum**

- Input: Vestibular, visual path
- Output: Feedback to the vestibular nuclei
- Vestibulo-cerebellar system modulating vestibular influences on posture & eye movement

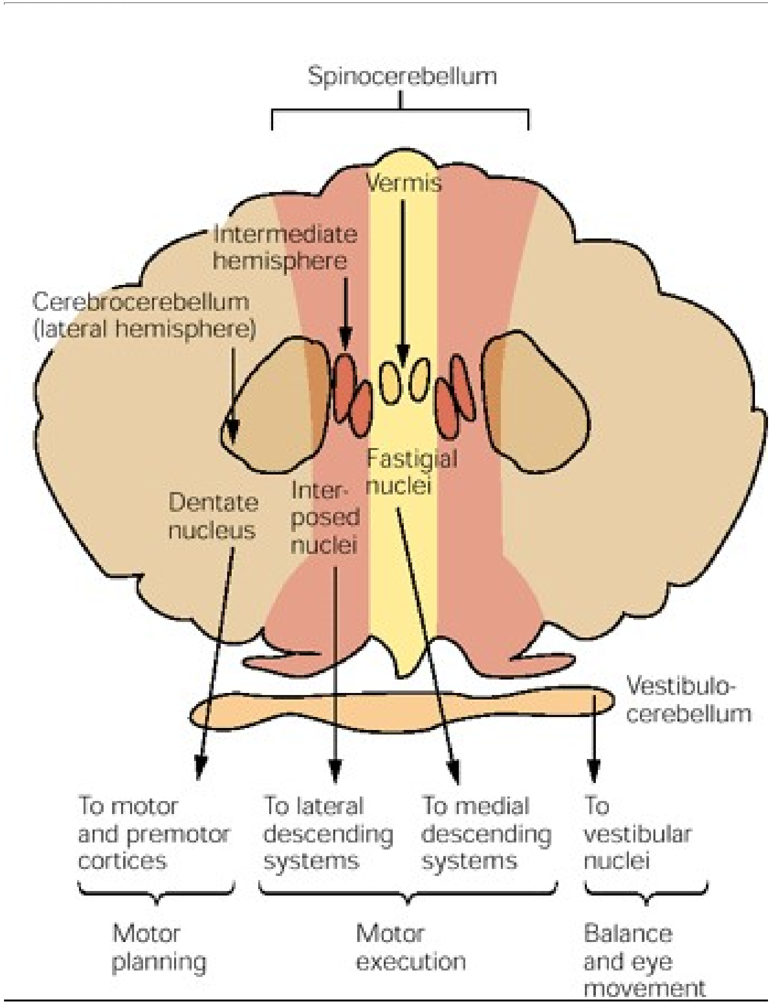
**Spinocerebellum**

- Input: Somatosensory, proprioceptive via the spinal cord
- Output: Brain stem reticular, lateral vestibular nuclei
- Spino-cerebellar system regulating muscle tone, posture & locomotion

**Cerebrocerebellum**

- Input: Cortico-pontine
- Output: Feedback dentate, thalamus, motor and premotor cortex
- Cerebro-cerebellar system regulating skilled movement.

# Three subdivisions and their output pathways

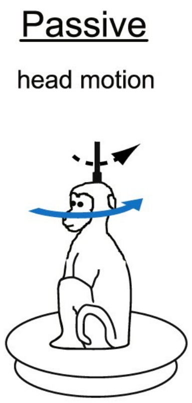


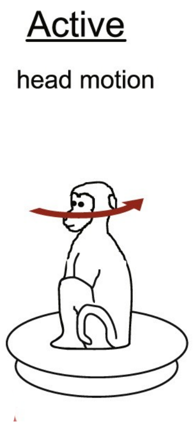

**Vestibulocerebellum**

**Spinocerebellum**

**Cerebrocerebellum**

# Monkey experiment: sensory processing in cerebellum



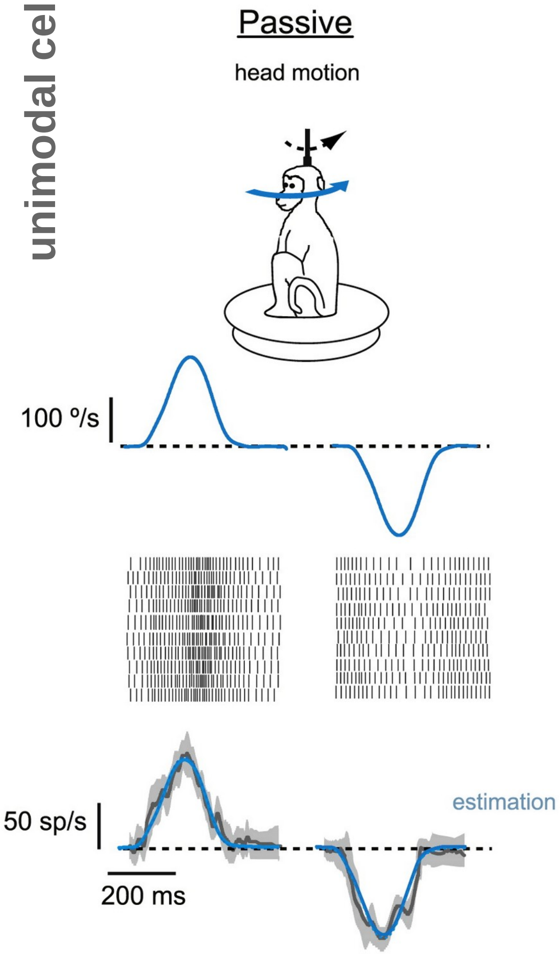




**behavioral paradigm**

- passive versus active movement in monkeys
- passive movement : unexpected vestibular stimulation (exafference)
- active movement : voluntary action evoked vestibular input (vestibular reafference)

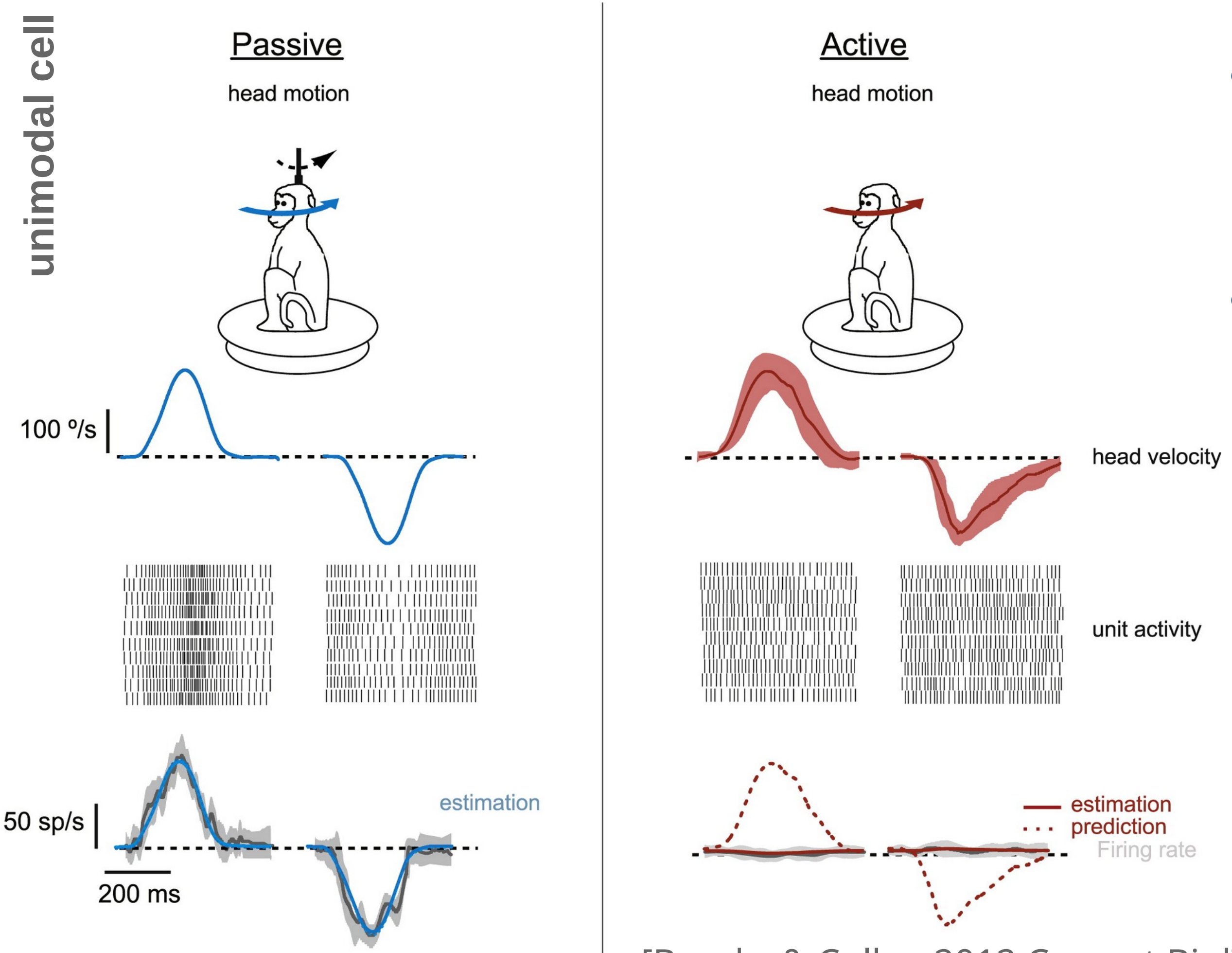
# Cells responsive to passive but not active movement

unimodal cell




- cells (unimodal and bimodal) were strongly modulated during passive head and body motion

# Cells responsive to passive but not active movement

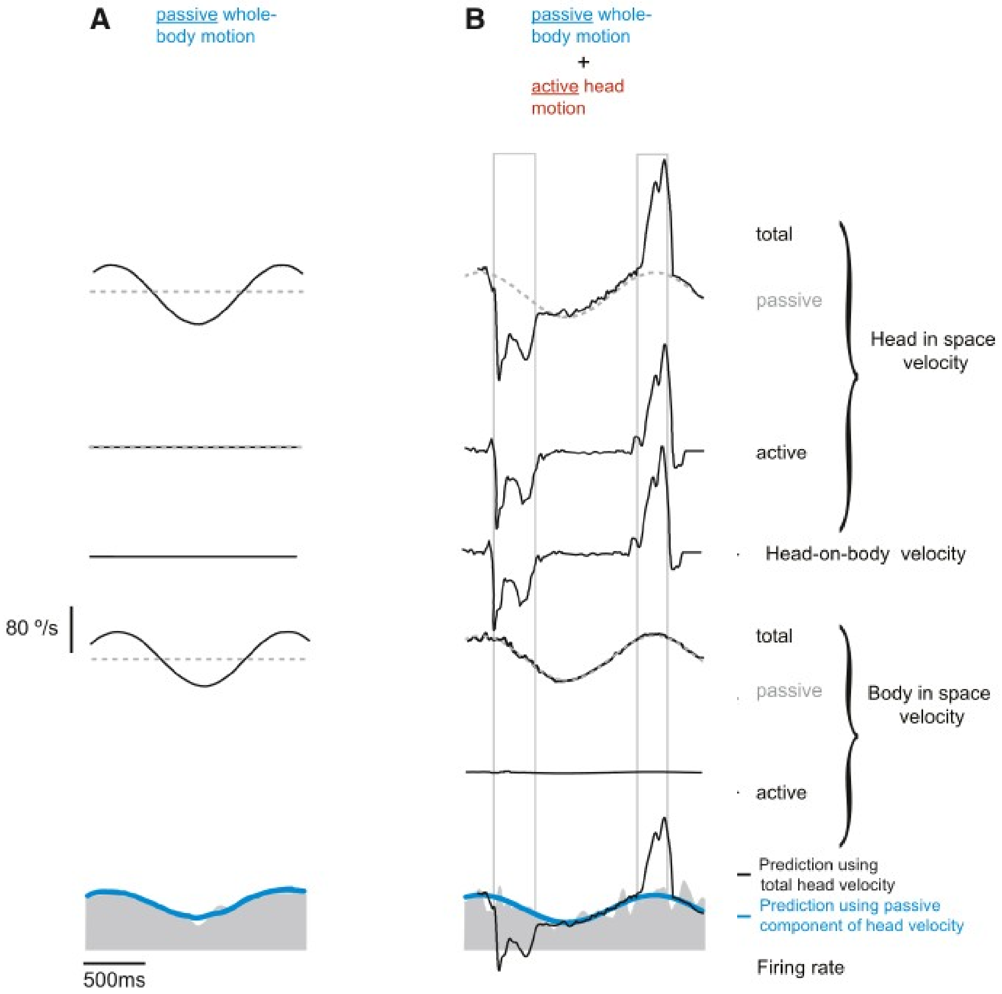



- cells (unimodal and bimodal) were strongly modulated during *passive* head and body motion
- same cells were unresponsive to same motion when voluntarily produced

[Brooks & Cullen 2012 Current Biol]

# Neurons selectively respond to passive movement

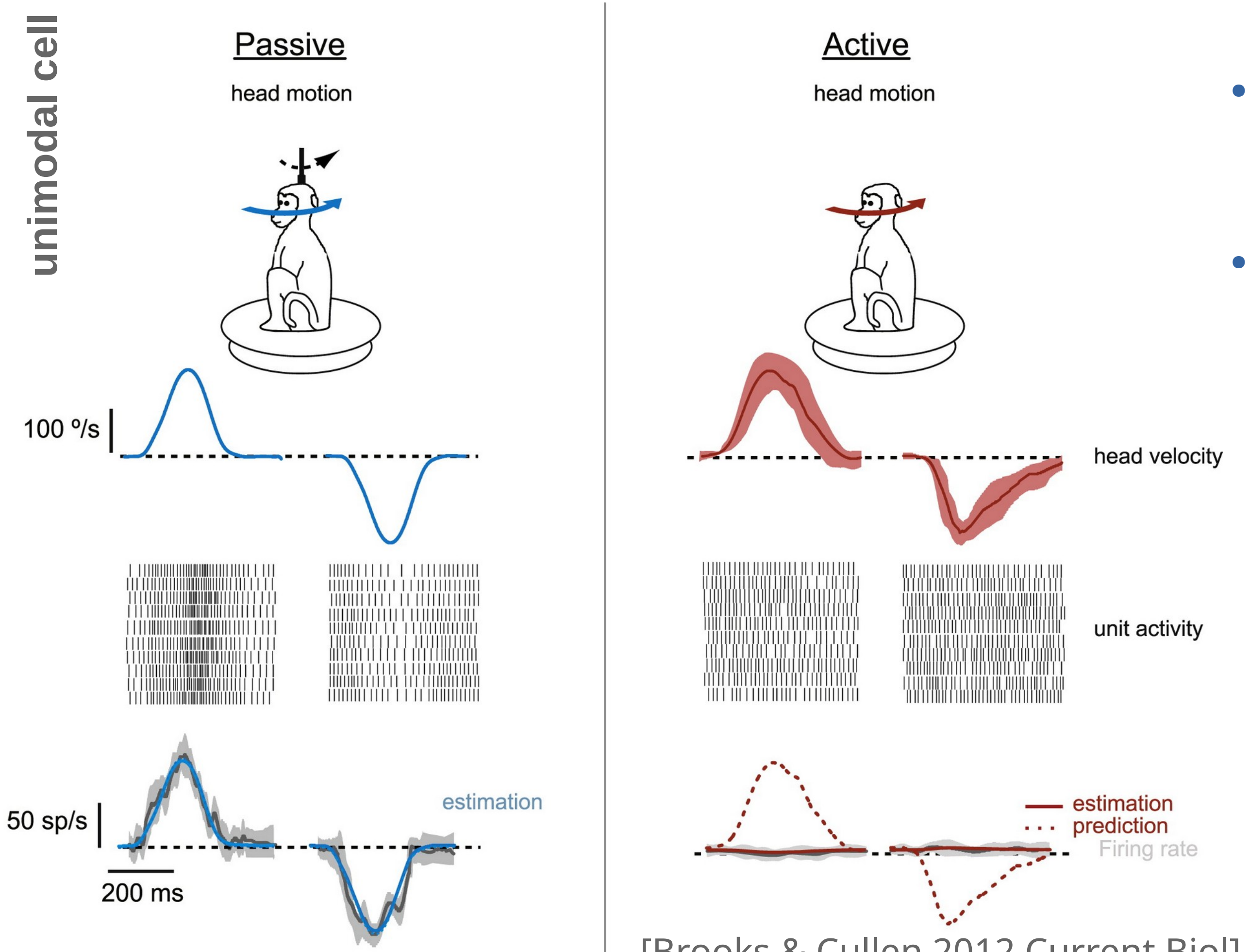
unimodal cell




- unimodal neurons respond selectively to passively applied stimulation
- in combined movements – passive and active – the neuron robustly encode head motion due to passively applied rotation

[Brooks & Cullen 2012 Current Biol]

# Experimental evidence in mammals for predictive signal

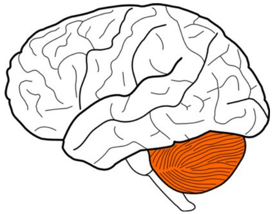



[Brooks & Cullen 2012 Current Biol]

- cells in fastigial nucleus encode unexpected movements of head and body
- supports the notion that the cerebellum computes a prediction of sensory consequences which is compared to the sensory consequences of the actual movement

# Talk outline

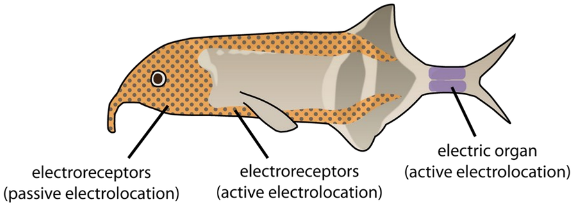
**1. Cerebellar disorders**
- functions inferred from symptoms
- eye-arm movement coordination with prism glasses



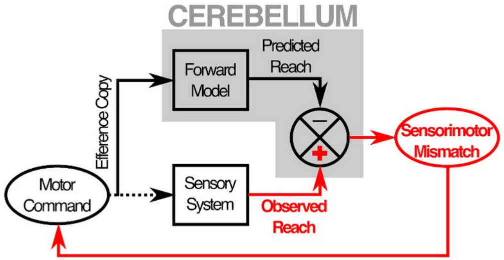
**2. Prediction of sensory consequences**

*Electric fish*
- anatomy and physiology of the weakly electric fish
- cerebellar circuitry
- cerebellum-like structures
- electric fish and prediction of sensory consequences

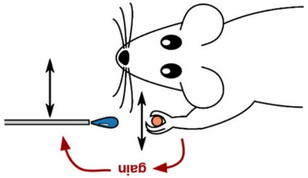
*Sensory prediction in mammals*




**3. Motor control and internal models**
- forward and inverse model
- forward model and the cerebellum

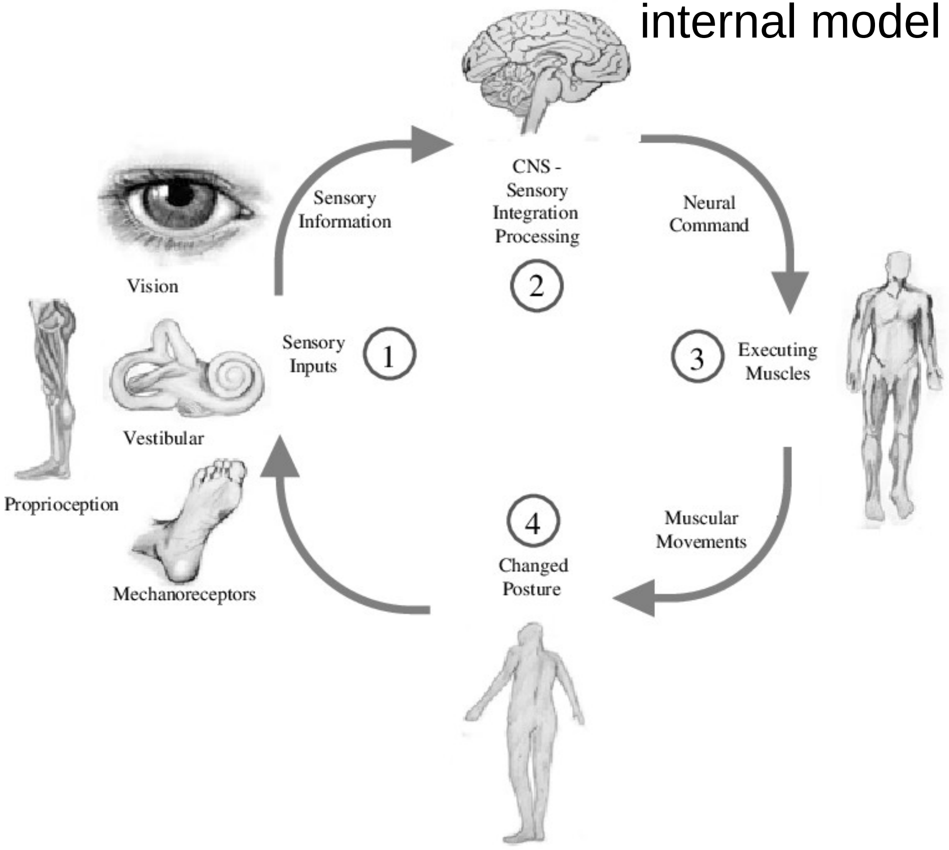



**4. Experiments implemented in the lab to unravel cerebellar function**
- sensorimotor mismatches in mice



# Theory : motor execution based on internal model

brain implements internal model

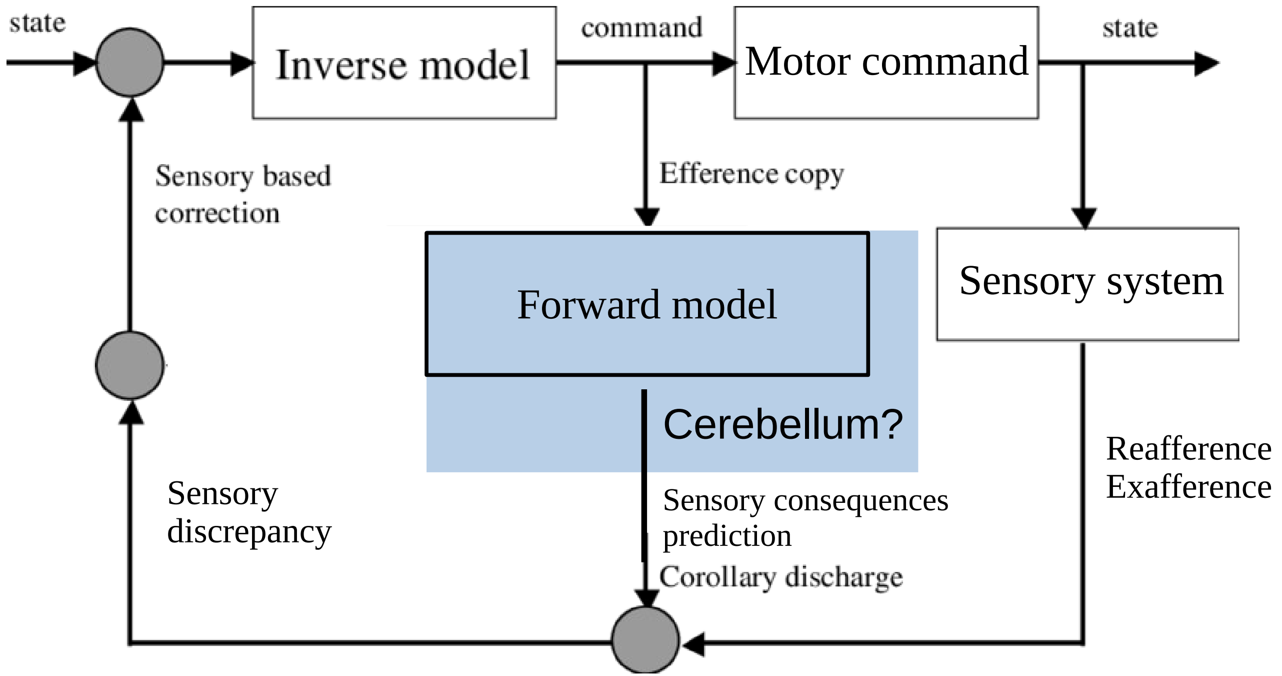



- internal model simulates the behavior of the sensorimotor system
- internal model allows the CNS to predict the consequences of motor commands and to determine the motor commands required to perform specific tasks

# Models of motor control

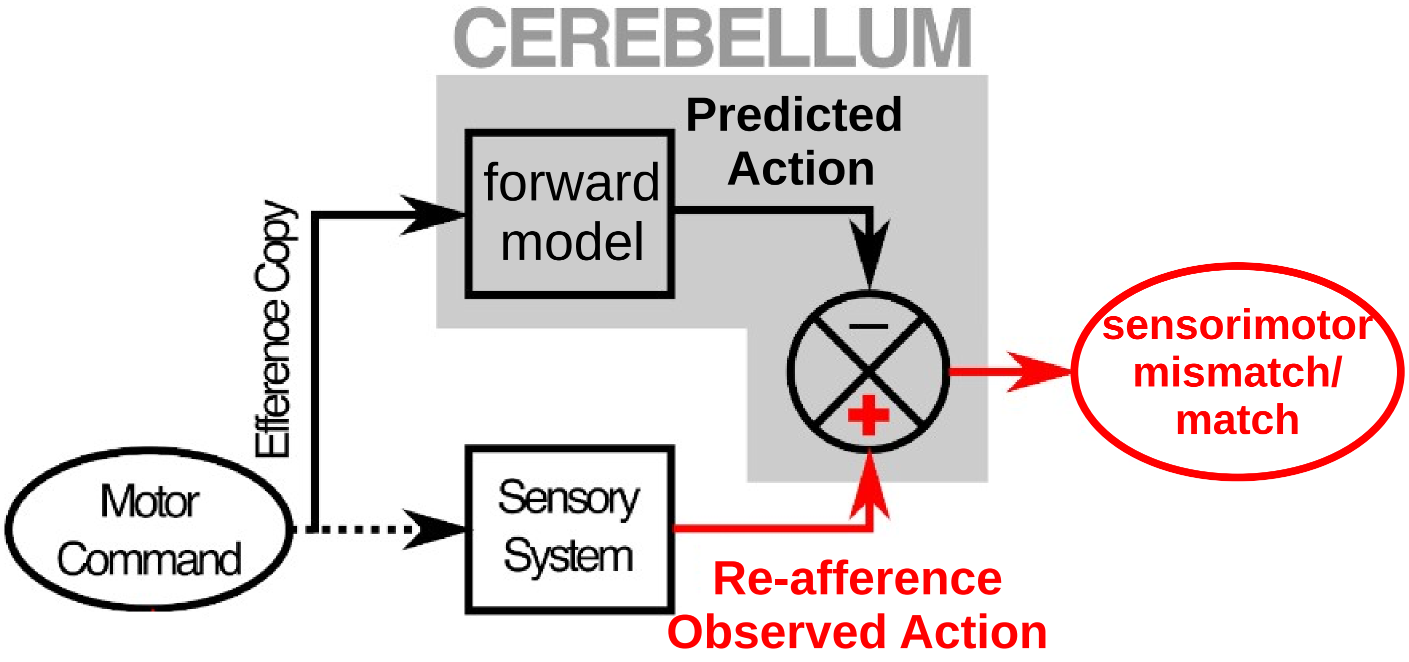
**forward model :** predict the sensorimotor consequences (feedback) of the motor command, predict future state

**inverse model :** convert desired action into appropriate motor commands



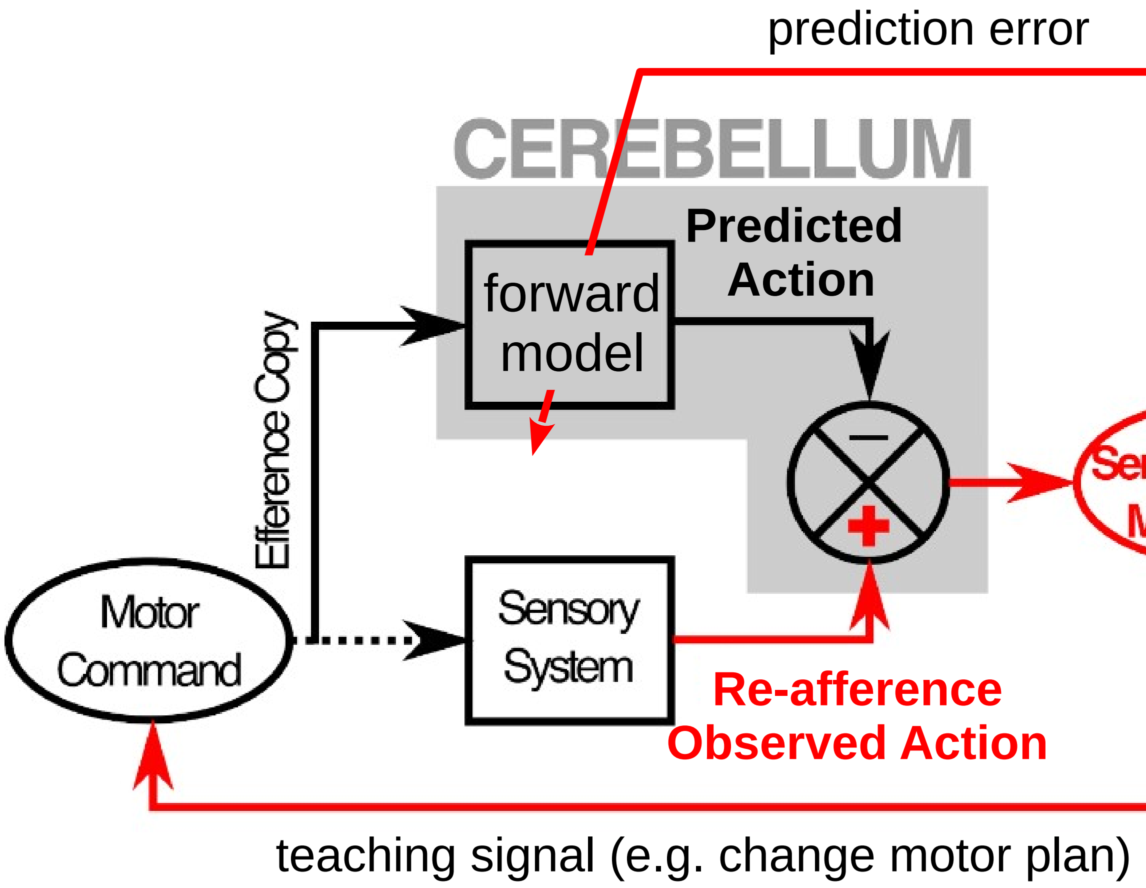

Schematic representation of inverse and forward models for the control of movement

# Suggestion : Cerebellum implements a forward model




- cerebellum computes a prediction of sensory consequences which is compared to the sensory consequences of the actual movement
  - **sensorimotor match**: the sensory afference should be interpreted as internally caused
  - **sensorimotor mismatch**: the difference between the actual and the predicted input should be interpreted as externally caused

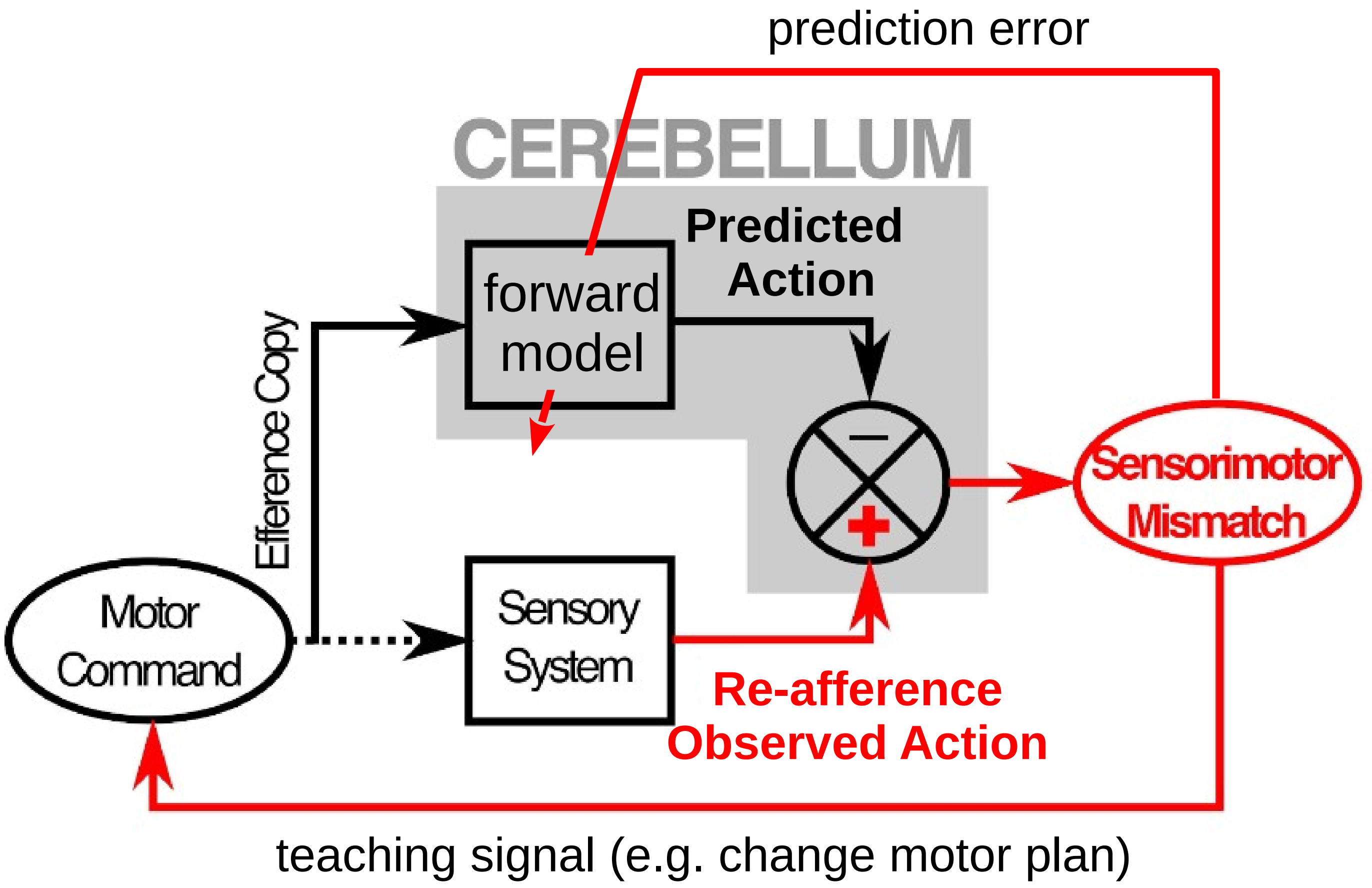
# Sensorimotor mismatch




**correct outcome but repeated mismatch :** prediction needs to be updated

**undesired outcome (fail):** sensorimotor mismatch can be used as teaching signal to adapt motor plan

# Suggestion : Cerebellum implements a forward model

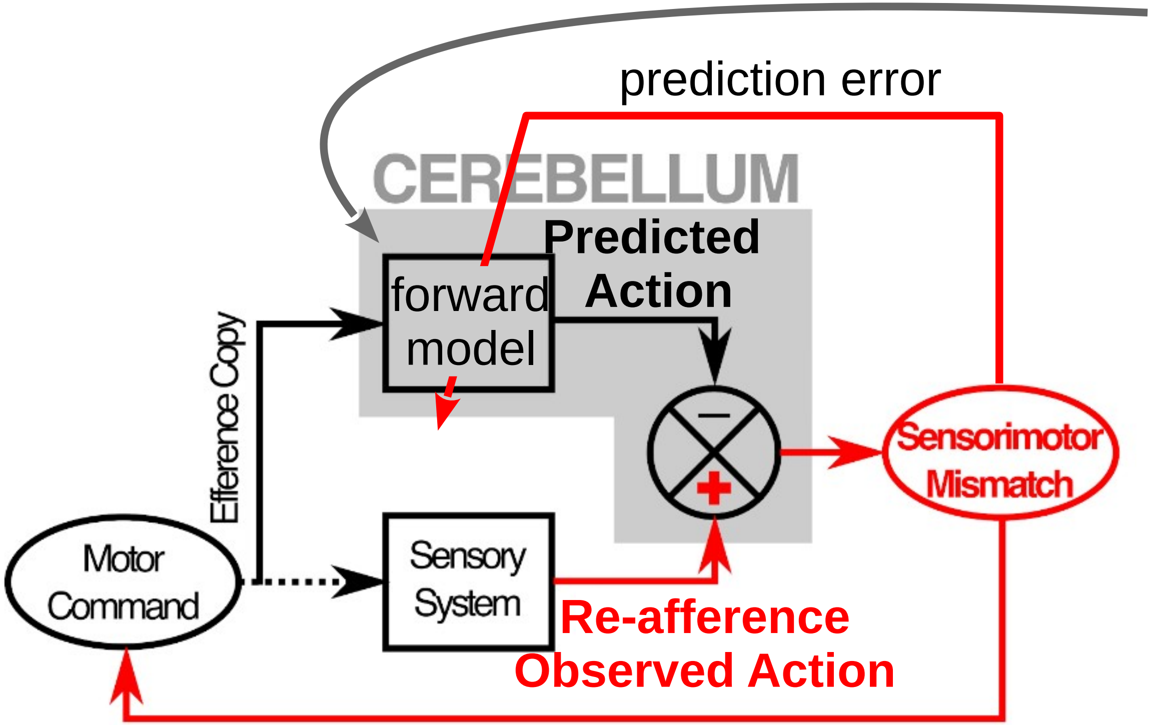



- cerebellum computes a prediction of sensory consequences which is compared to the sensory consequences of the actual movement

**usefulness**

- comparison can be used to compute error used as teaching signal to update the motor program
- computation of sensory prediction errors enables brain to distinguish between self-generated and externally produced actions

# Forward model requires an adaptive filter

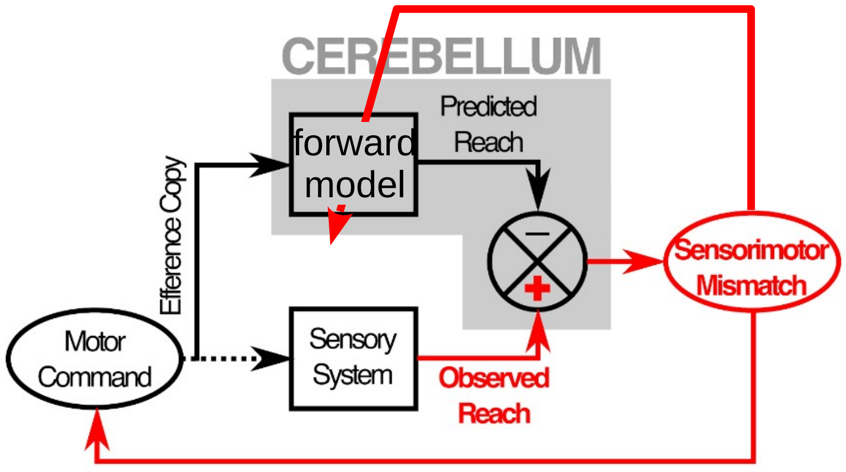


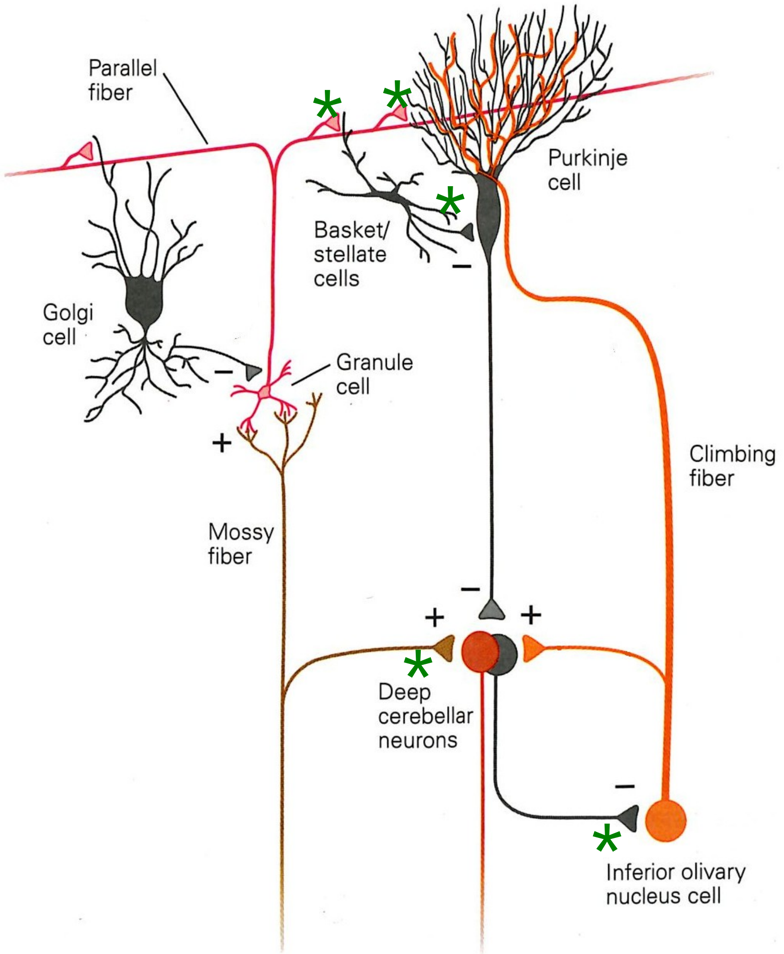

teaching signal (e.g. change motor plan)

**calculation of prediction based on adaptive filter:**

- input signals consists of a large number of components
- combining these components by weighting them individually and then summing to produce the filter output
- adjustment of the weights by a teaching signal

# Forward model requirements




- two distinct input streams :
  - mossy and climbing fibers
- adaptive filter requires to adjust prediction during learning, or due to changes in environment :
  - parallel fiber → Purkinje cell synapse
  - mossy fiber → deep cerebellar nuclei synapse

* ... plastic synapses

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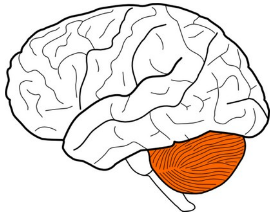

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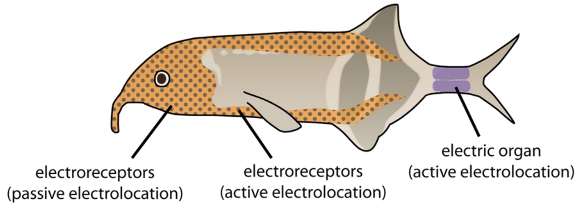


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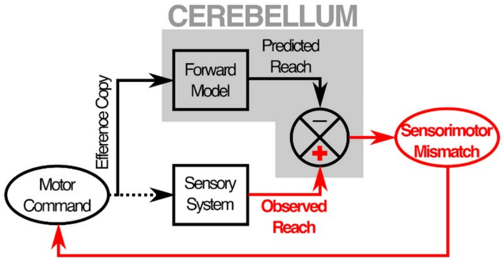


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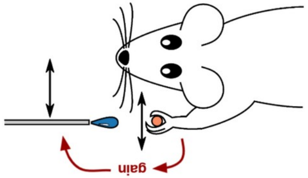
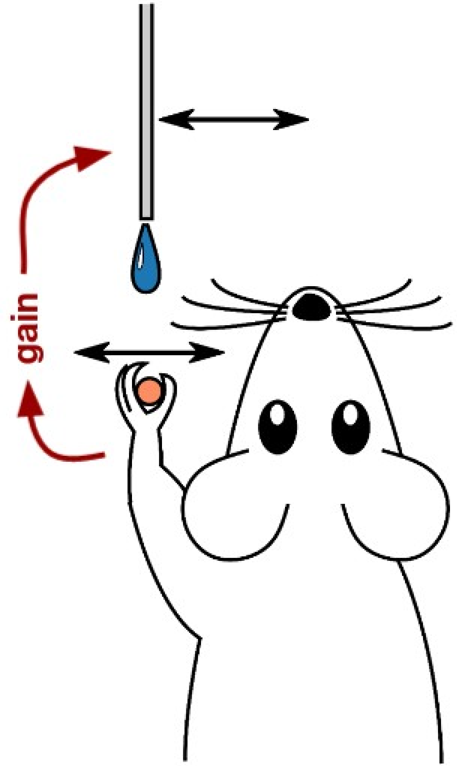


# Project : Adaptation to sensorimotor mismatches in the Cerebellum

**Aim :** Study cellular underpinnings of sensorimotor mismatch of whisker-paw coordination in rodent cerebellum.

**Method :**




- Mice move feeding tube towards mouth to receive reward, by manipulating joystick with forelimb
- Feeding tube coupled to joystick in closed-loop by variable gain ratio
- Mice adapt their behaviour to varying gain ratios
- Control: **gain = 1.0**
- Test: **gain = 2.0**

$v_{wall} = -v_{walking}$

[PI: Brandon Stell @ SPPIN]

# Project : Adaptation to sensorimotor mismatches in the Cerebellum

**Aim :** Study cellular underpinnings of sensorimotor mismatch of whisker-paw coordination in rodent cerebellum.

**Paradigm :**

[video]

# Aim: mismatch between expected and observed whisker feedback

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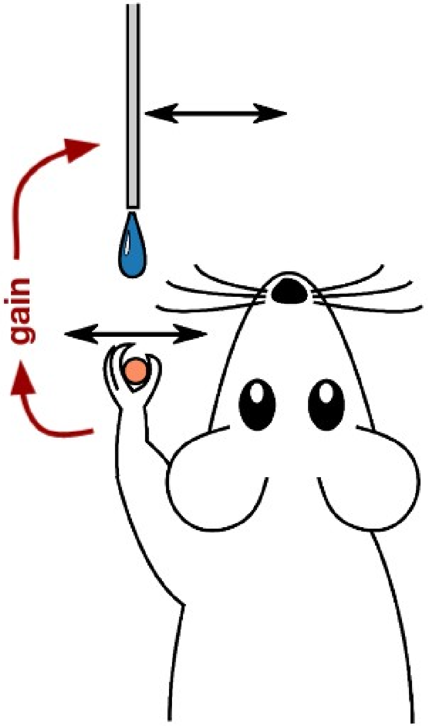
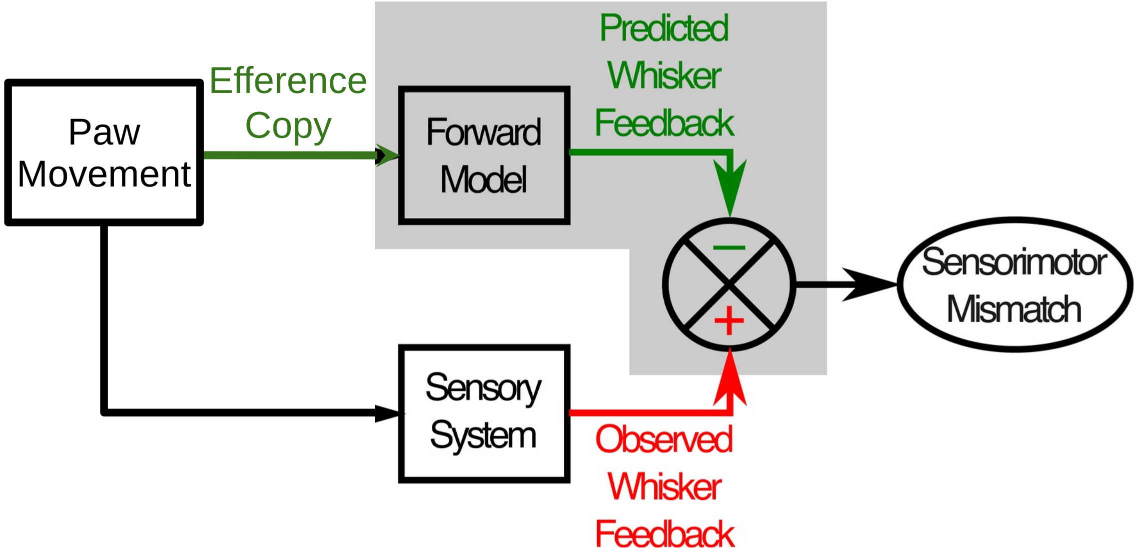
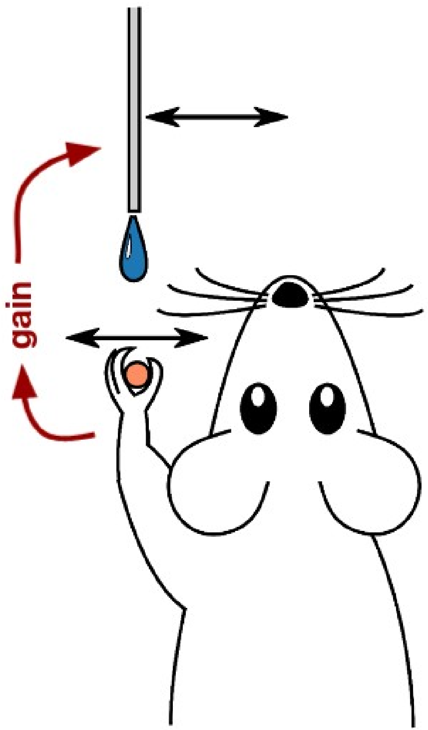
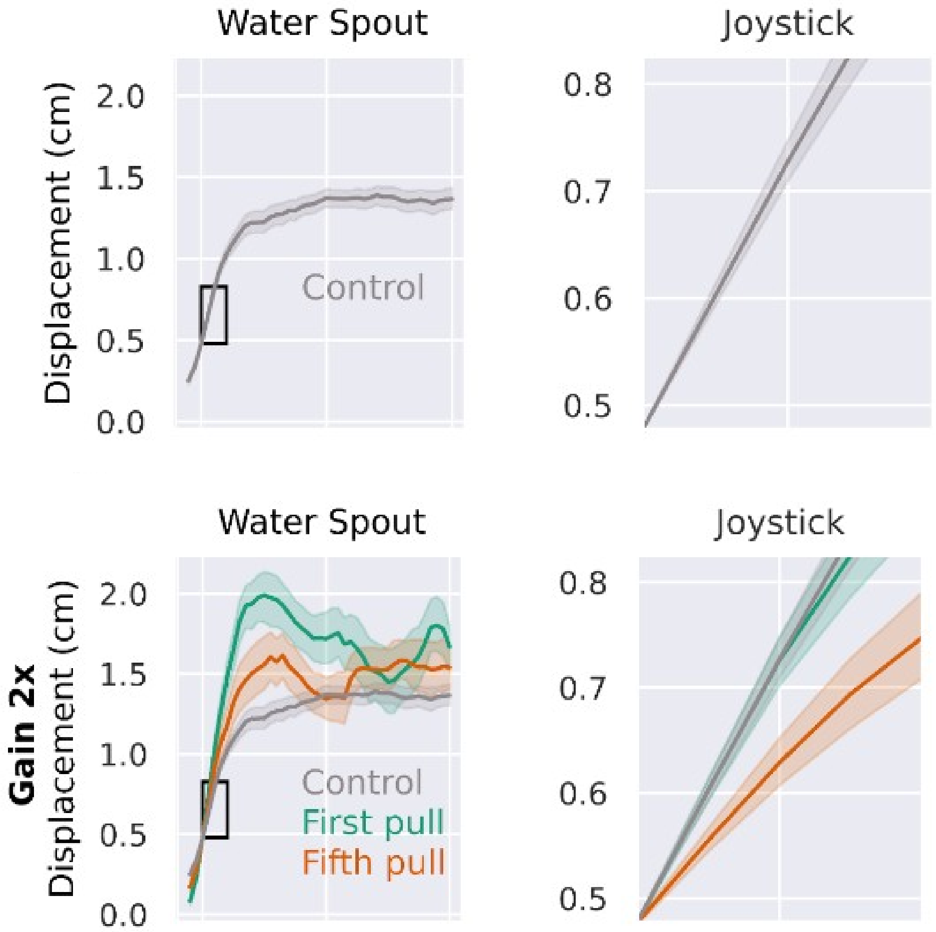


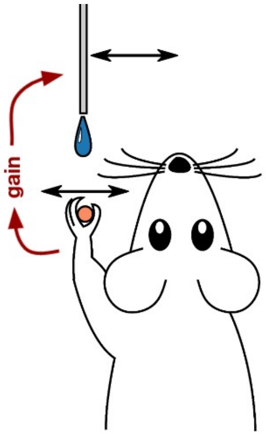

[PI: Brandon Stell @ SPPIN]

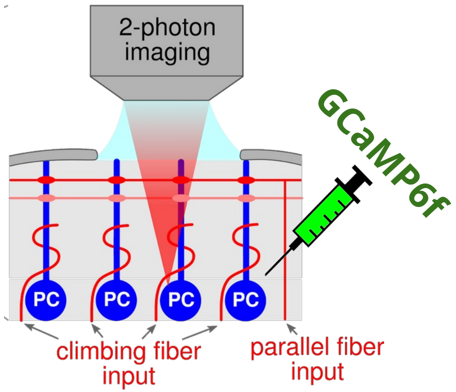
# Behavior: Mice overshoot after gain increase and adapt rapidly

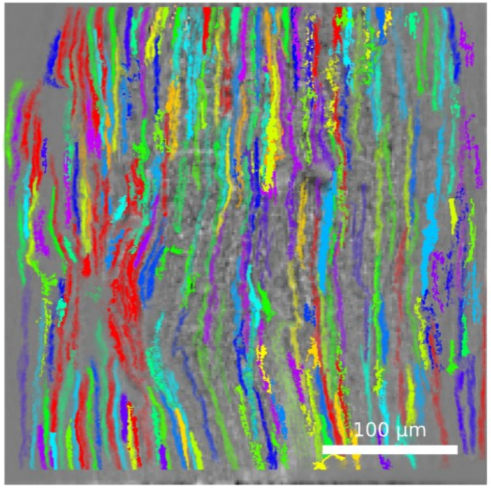


# Two-photon calcium imaging from Purkinje cells




Purkinje cells complex spikes

**Questions :**

1. Do we find neural correlates for efferent copy and re-afference ?
2. At which stage could a comparison between the two take place ?
3. What is the cellular signature of the sensorimotor mismatch in the cerebellar cortex ?

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