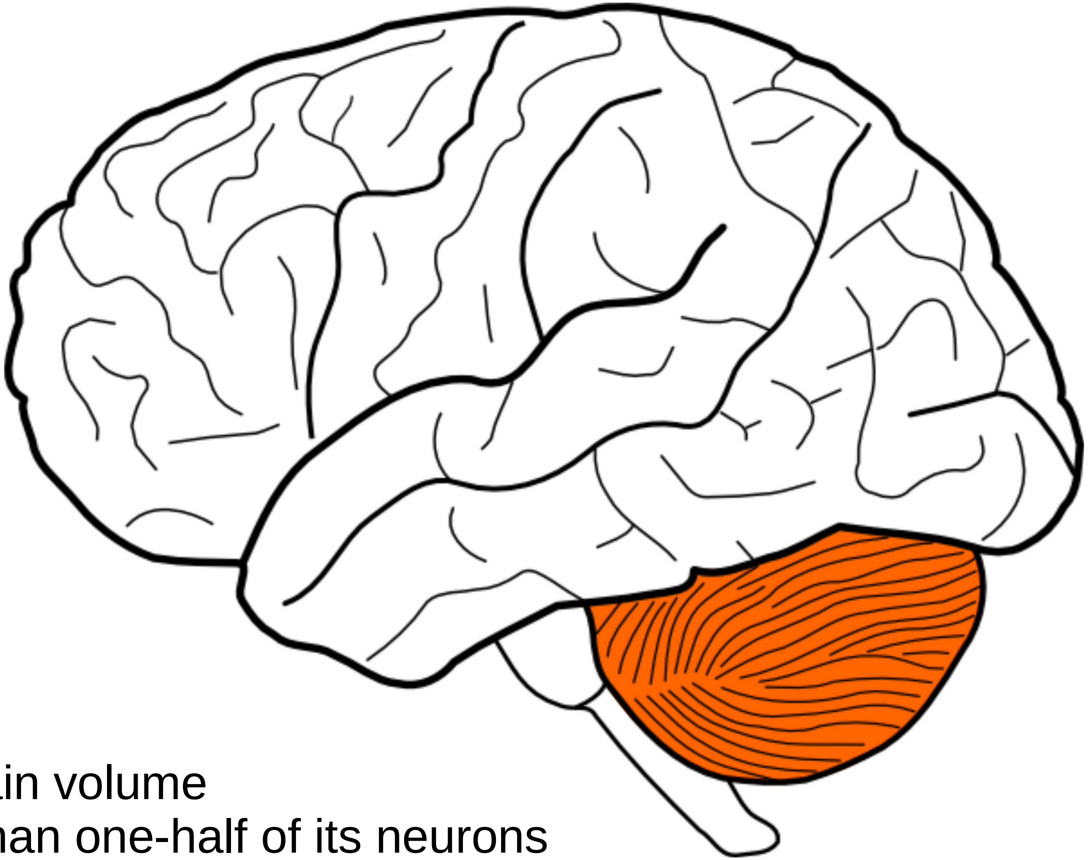
SAINTS-PERES
Paris Institute for
the Neurosciences

Systems Neuroscience :
Motor adaptation and sensory prediction in the Cerebellum

Michael Graupner (PhD)

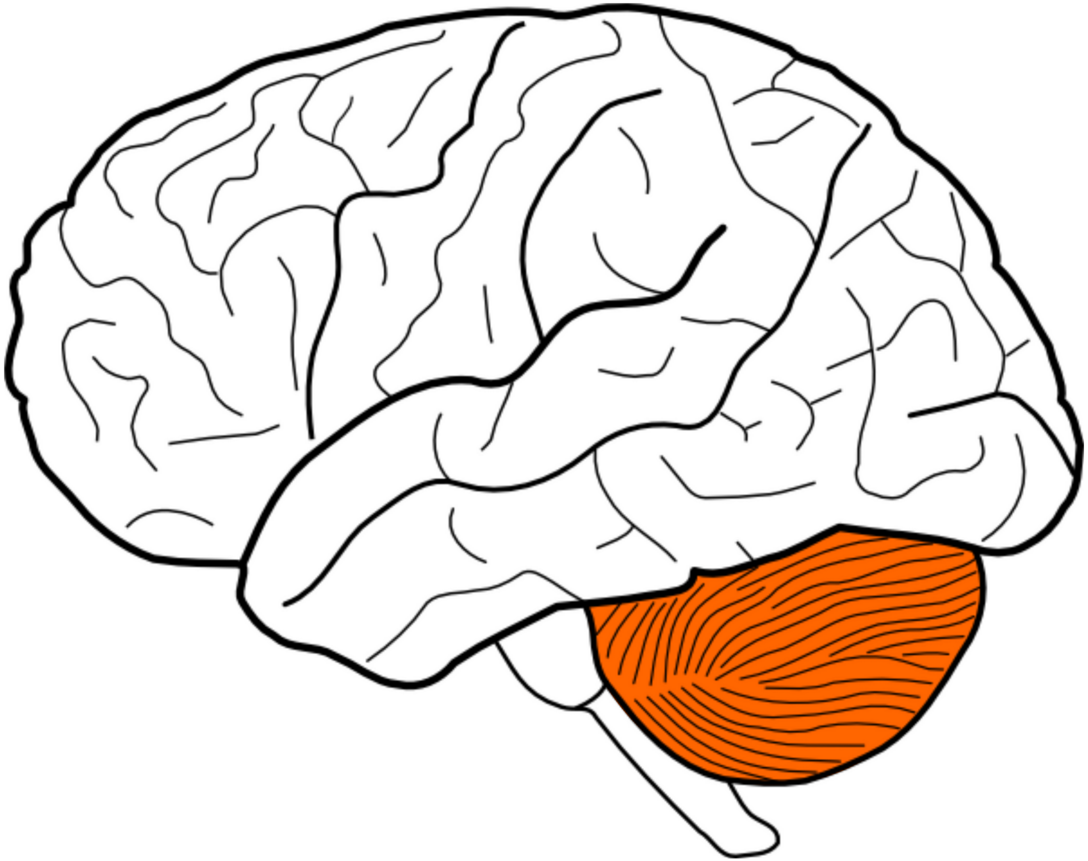
Saints-Pères Paris Institute for the Neurosciences
CNRS UMR 8003, Université Paris Descartes

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

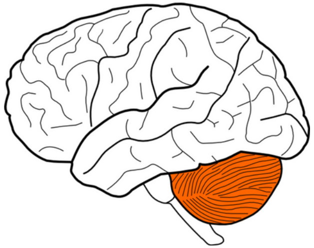
different regions receive inputs from different parts of the brain and project to different motor systems

similarity (architecture, physiology) suggests similar computational operations

Talk outline

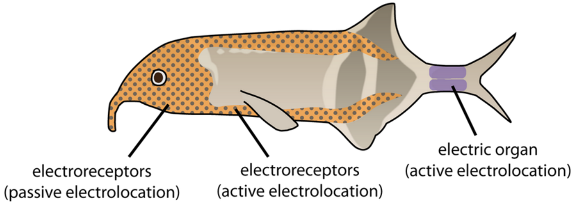
1. Cerebellar disorders

- functions inferred from symptoms
- eye-arm movement coordination with prism glasses



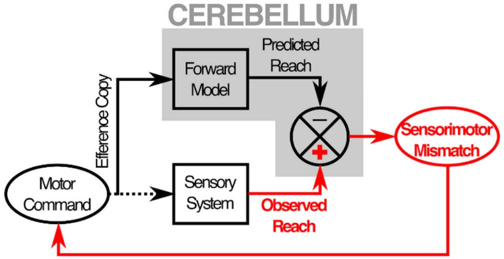
2. Electric fish and prediction of sensory consequences

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



3. Sensory prediction and forward model

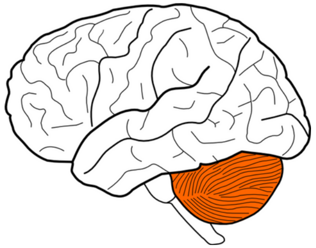
- sensory prediction in the monkeys
- forward model and the cerebellum



Talk outline

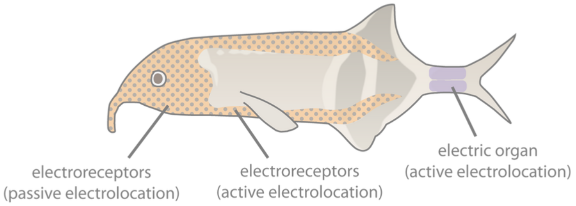
1. Cerebellar disorders

- functions inferred from symptoms
- eye-arm movement coordination with prism glasses



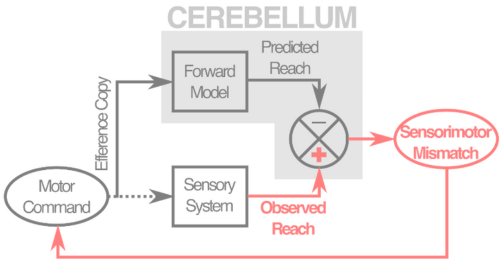
2. Electric fish and prediction of sensory consequences

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

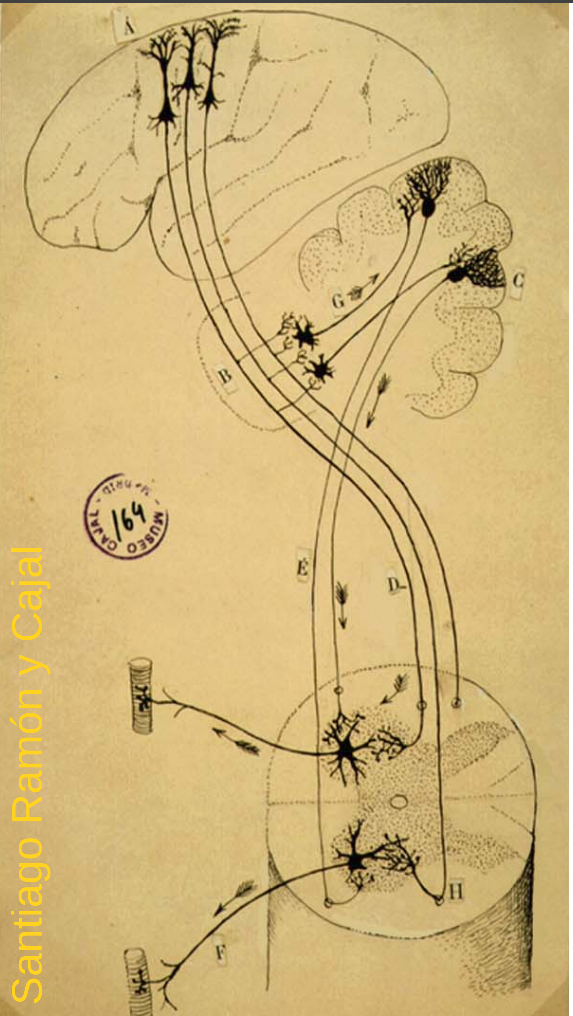


3. Sensory prediction and forward model

- sensory prediction in the monkeys
- forward model and the cerebellum



Cerebellum controls movement



Santiago Ramón y Cajal

Classical view :

Cerebellum *participates* in the control of movement.

The cerebellum ensures that movements are well timed and highly coordinated.

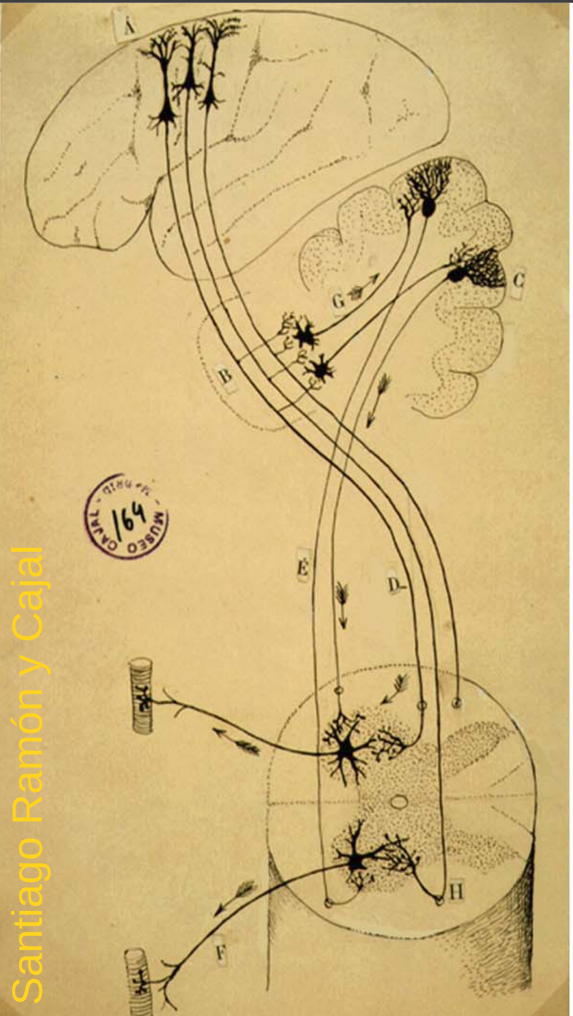
Inferred from cerebellar damage in humans :

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

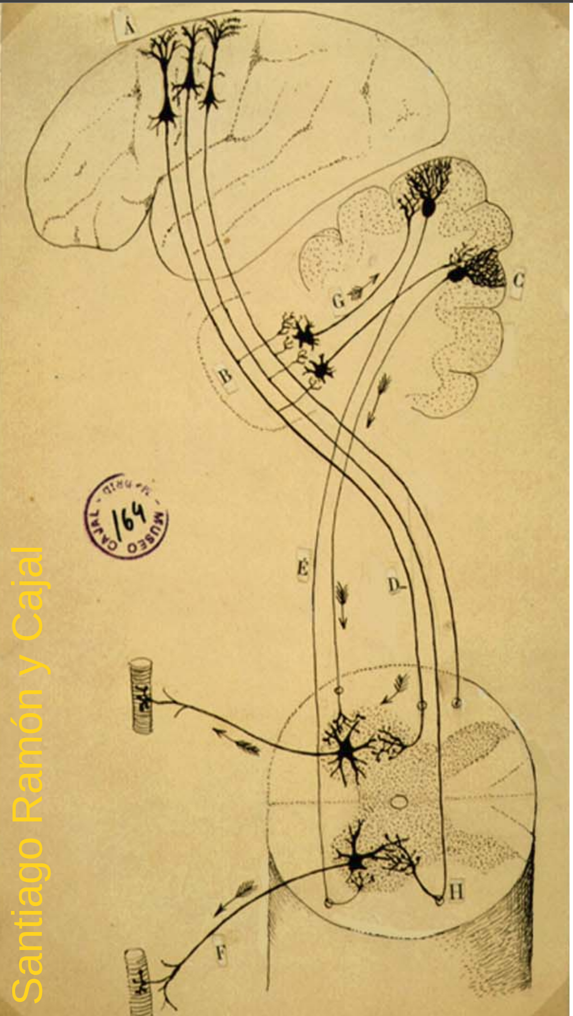
Ataxia :

abnormal execution of multi-joint voluntary movements, lack of coordination

Action tremor :

tremor at the end of movement

Symptoms of cerebellar disorders

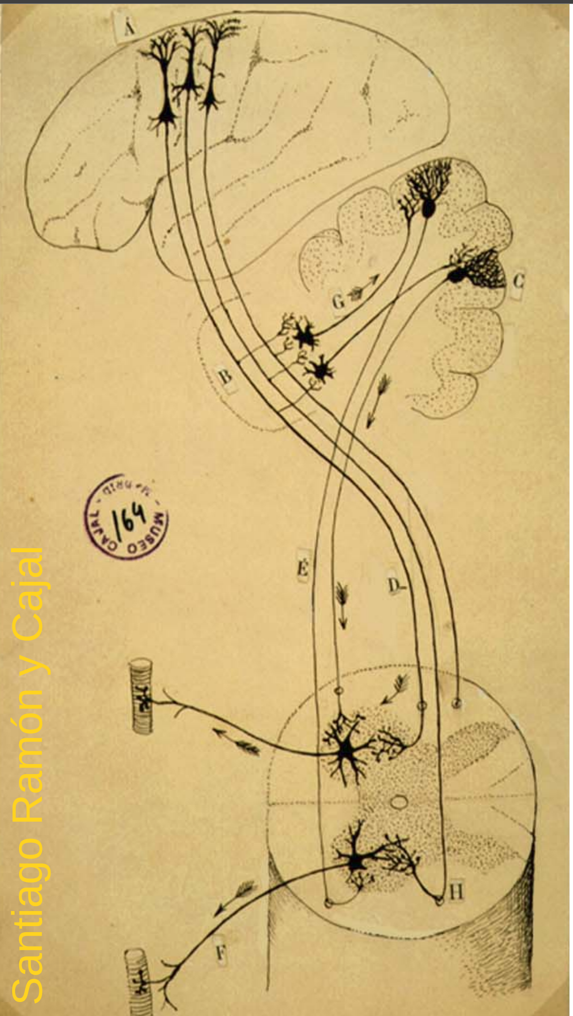


Santiago Ramón y Cajal

Patient with cerebellar ataxia

© 2004 Wright State University

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

Prism glasses

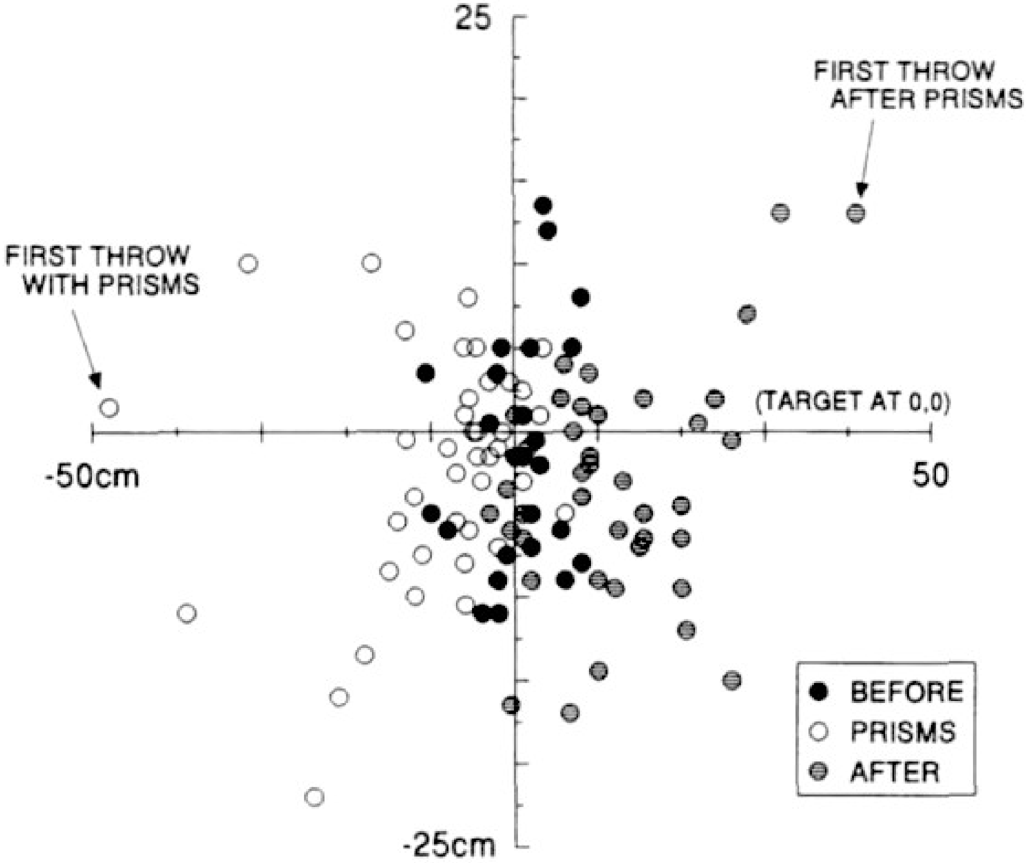
- experimental paradigm to study the learning of a synergy between vision and motor output
- adaptation of the eye-hand coordination when wearing prism goggles

[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

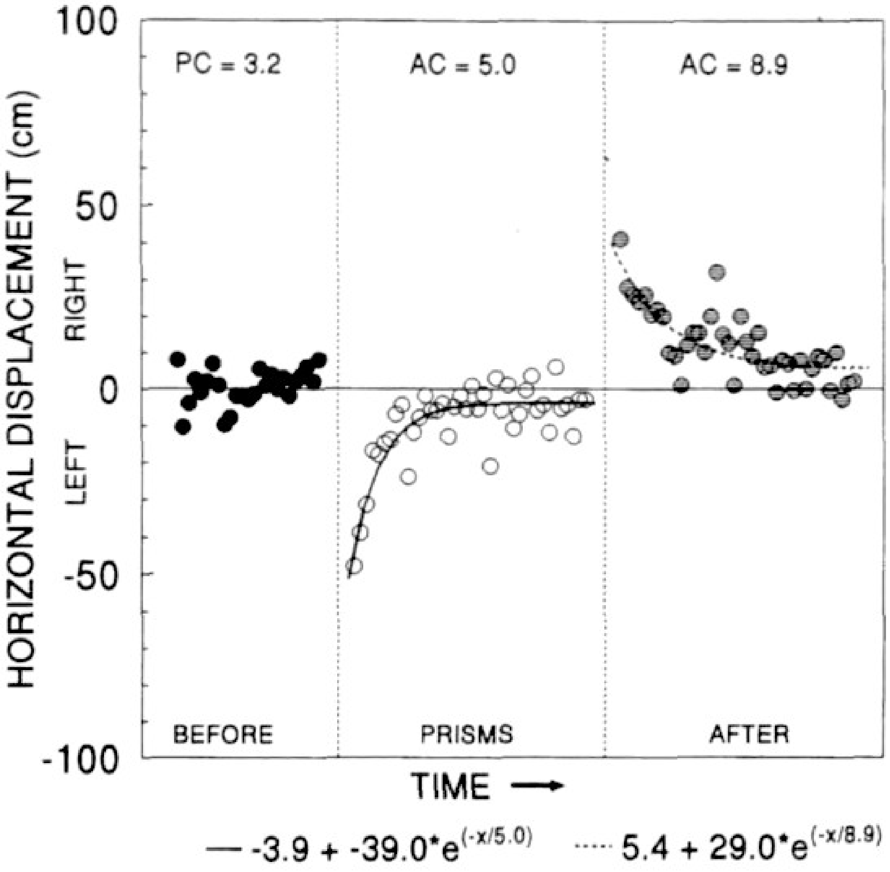
Throwing while looking through prisms



[Martin *et al.* 1996 Brain]

- 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

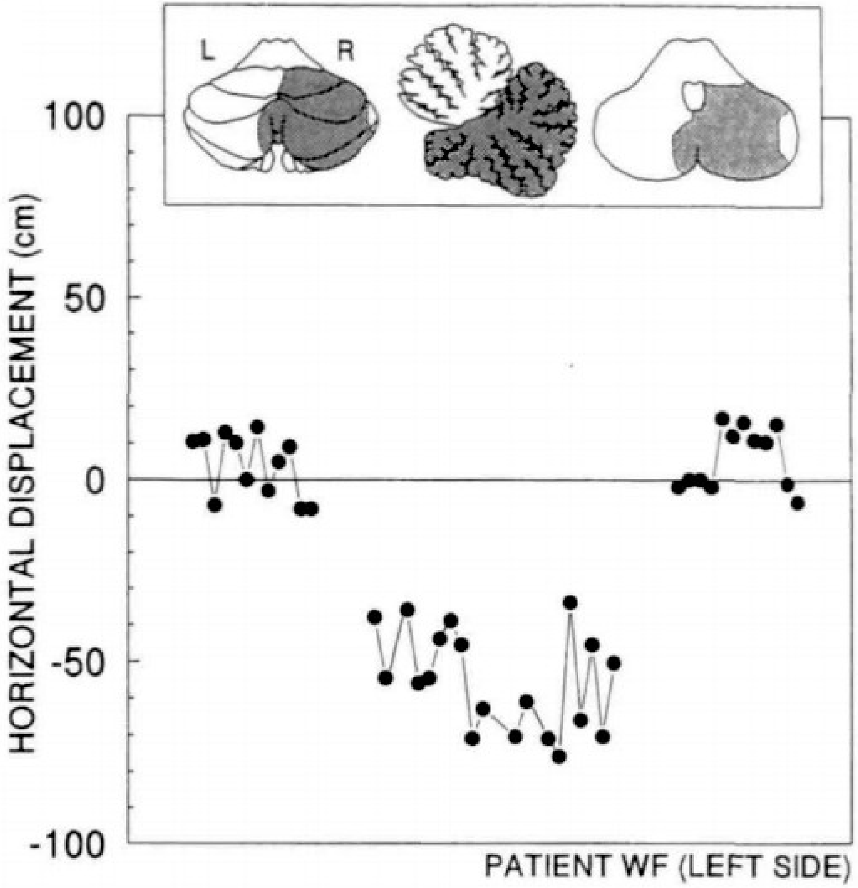
Throwing while looking through prisms



[Martin *et al.* 1996 Brain]

- 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

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

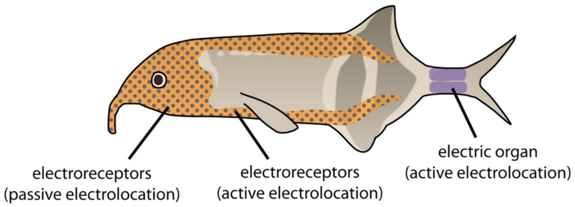
Talk outline

1. Cerebellar disorders

- functions inferred from symptoms
- eye-arm movement coordination with prism glasses

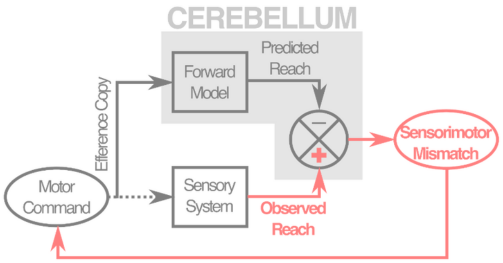
2. Electric fish and prediction of sensory consequences

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

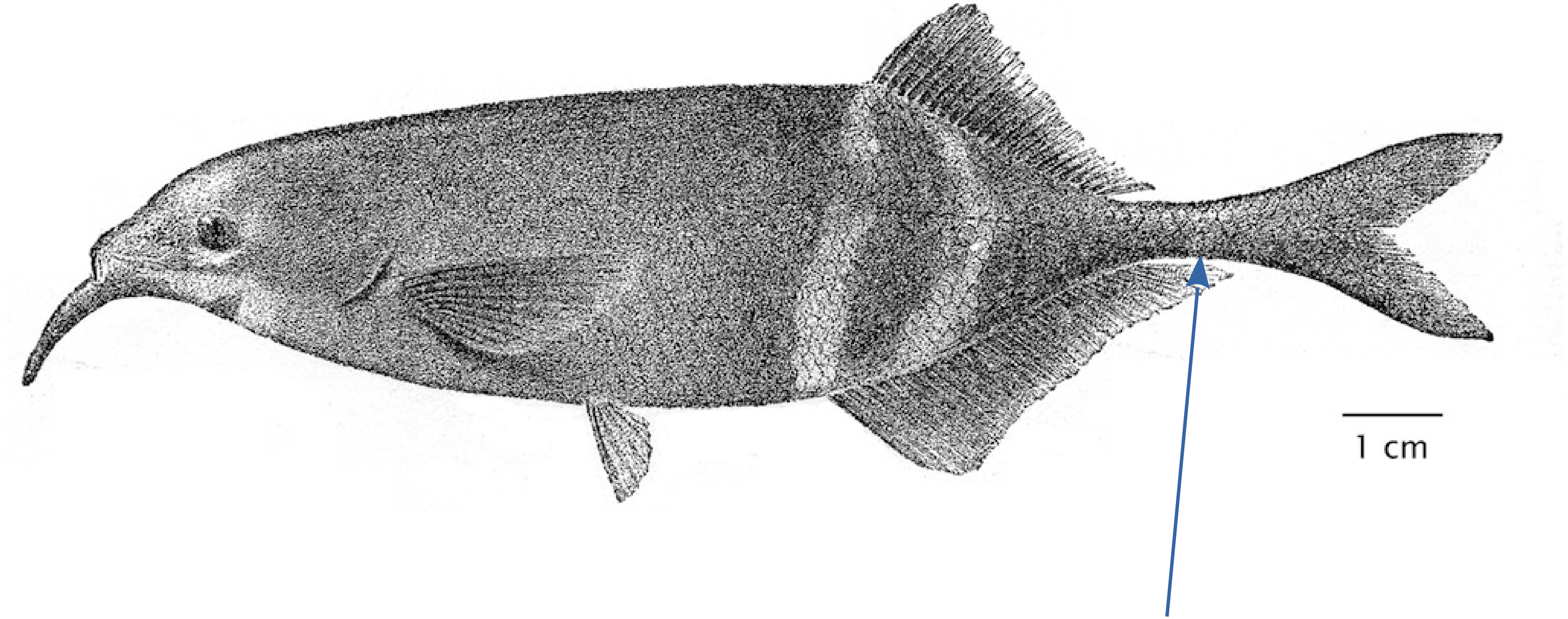


3. Sensory prediction and forward model

- sensory prediction in the monkeys
- forward model and the cerebellum

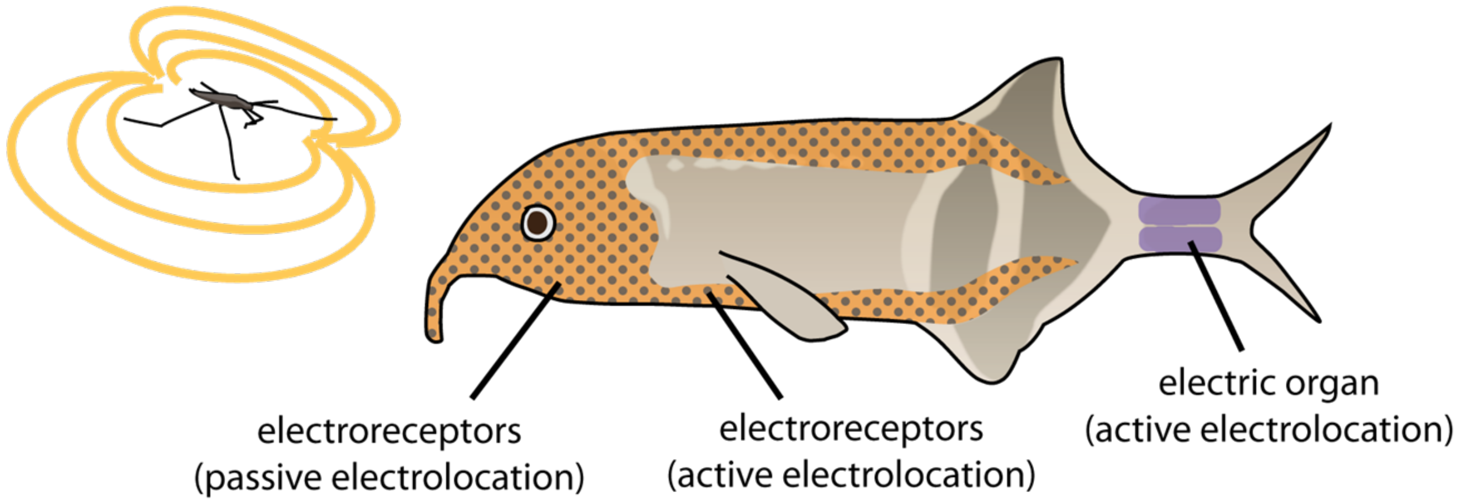


African weakly electric mormyrid fish



- 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



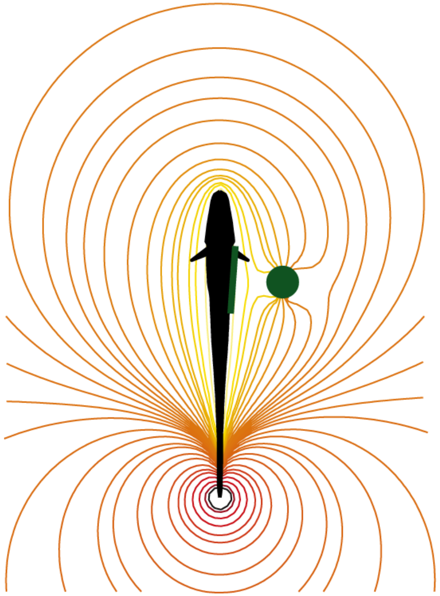
- Active and passive electrolocation are mediated by separate classes of electroreceptors

- 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

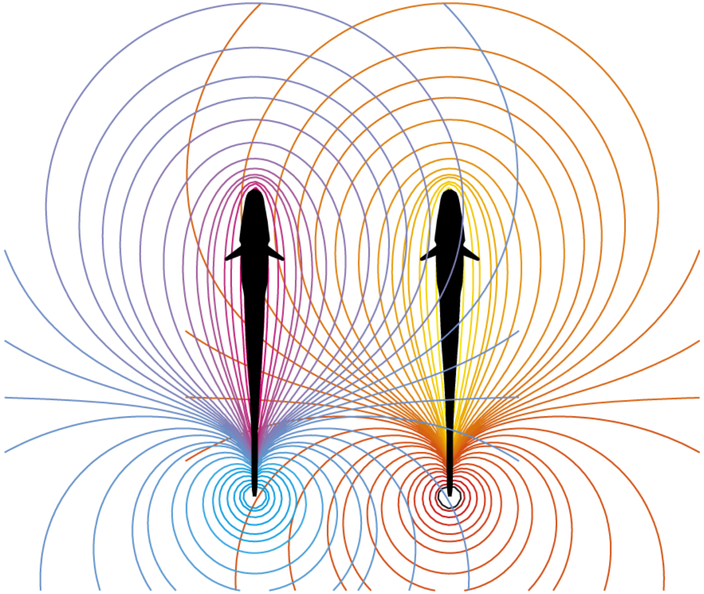
- Active and passive electrolocation are mediated by separate classes of electroreceptors; 3 receptor classes in total

electrolocation



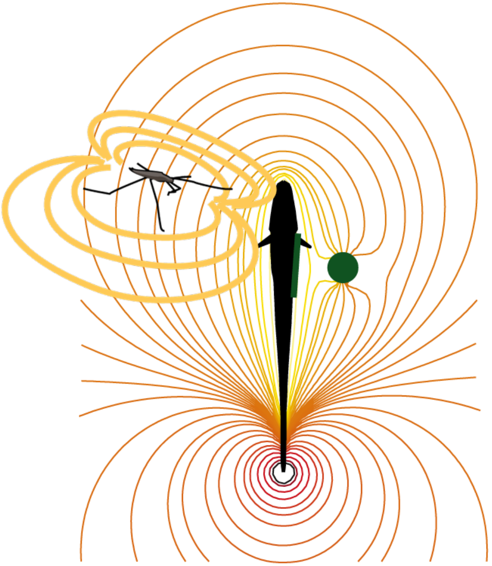
1) mormyromast : active electrolocation

electrocommunication



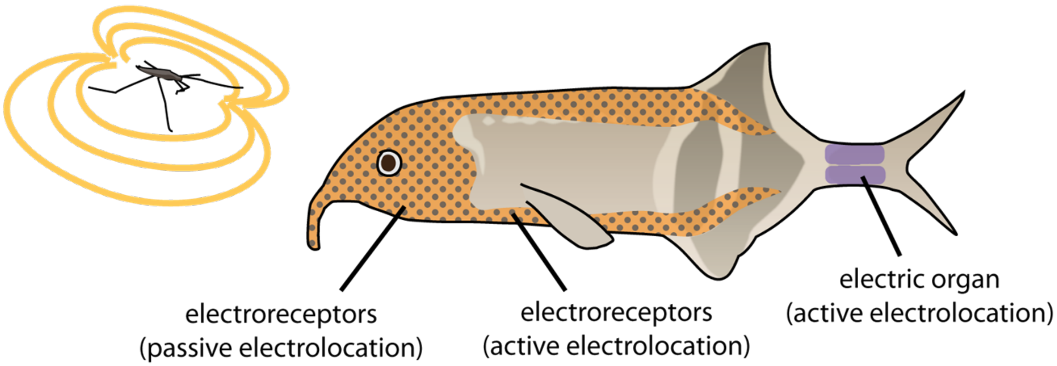
2) Knollenorgan : detecting EOD of other fish

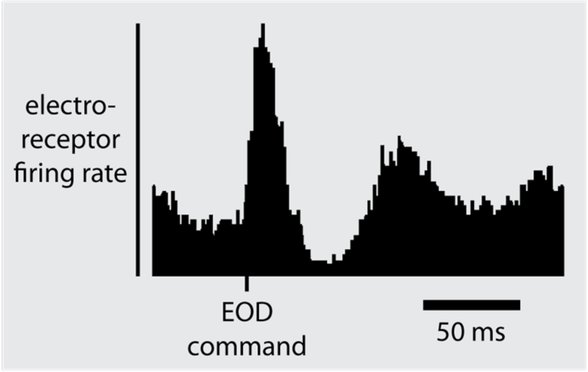
electorsensing

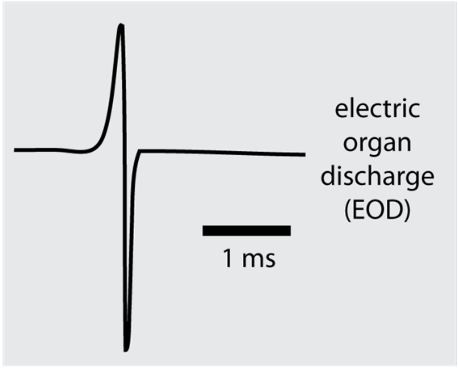


3) ampullary : can measure weak electric fields that all animals generate in water

Challenge for the fish

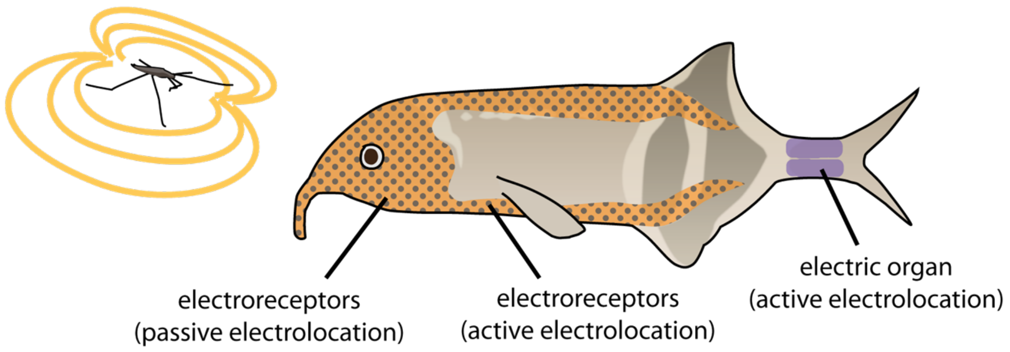


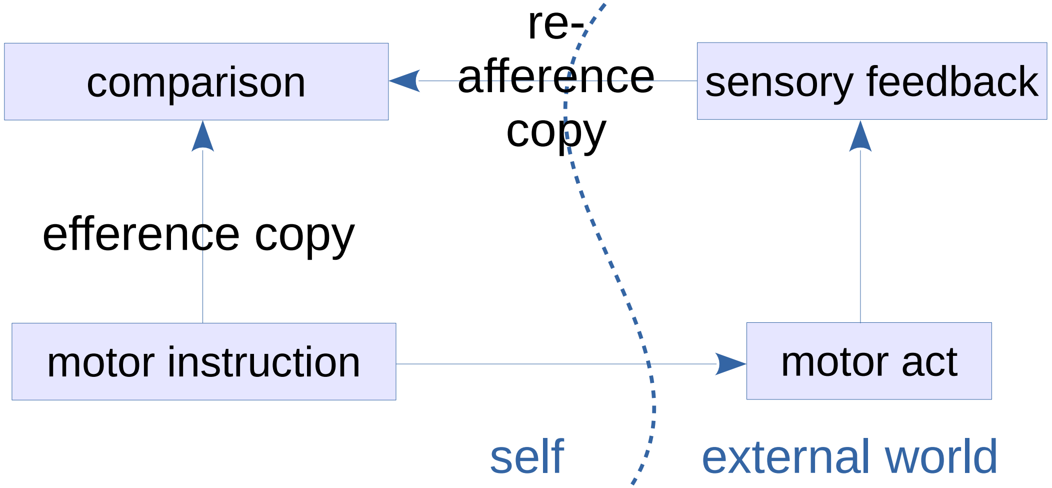




- **problem :** passive (ampullary) electroreceptors are strongly affected by the fish's own EOD pulse
- **possible solution :** external and self-generated input can be distinguished based on additional information about own movement and behavior
- **implementation :** convergence of two distinct input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

Challenge for the fish and others species




comparison

re-afference copy

sensory feedback

efference copy

motor instruction

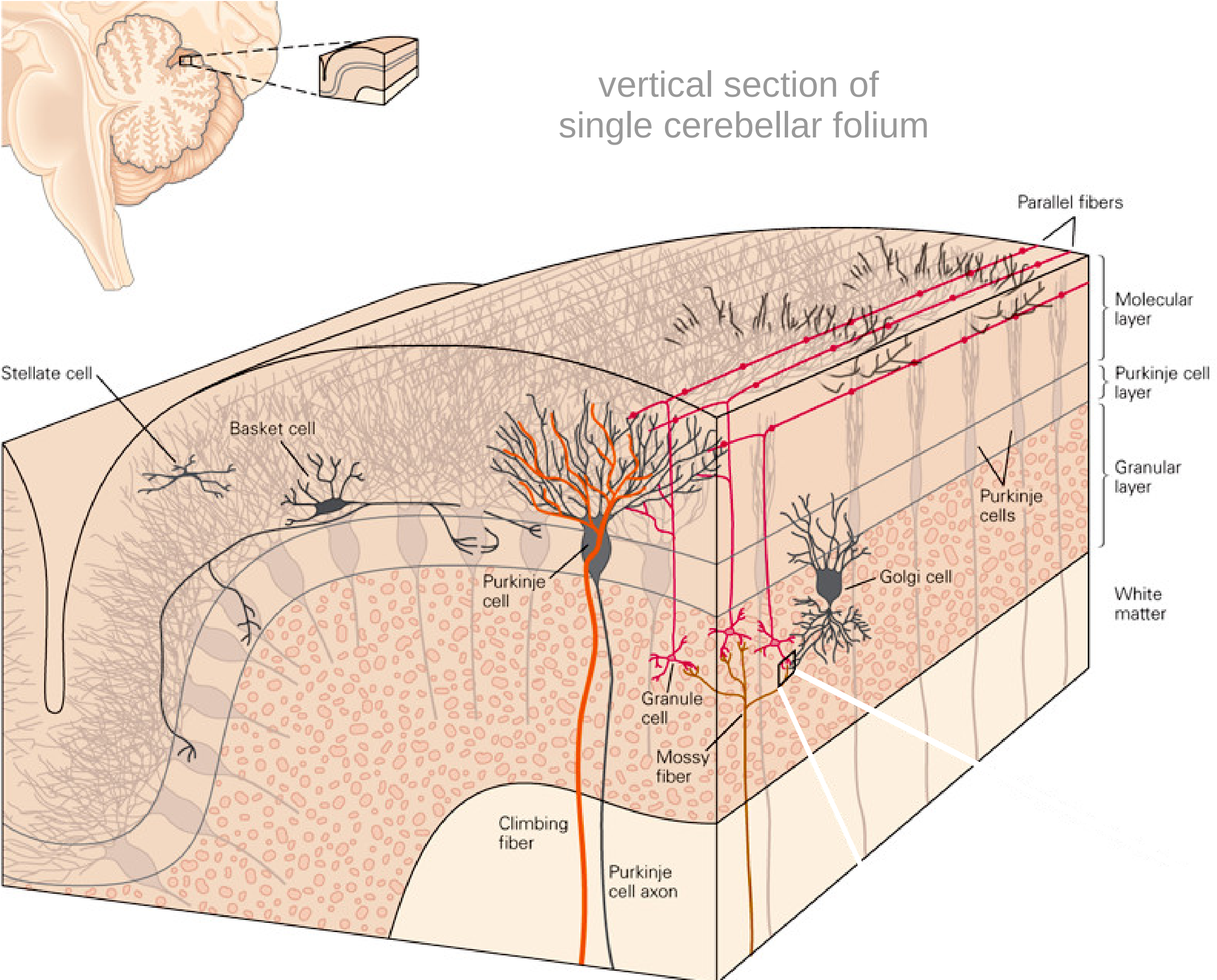
motor act

self

external world

- 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

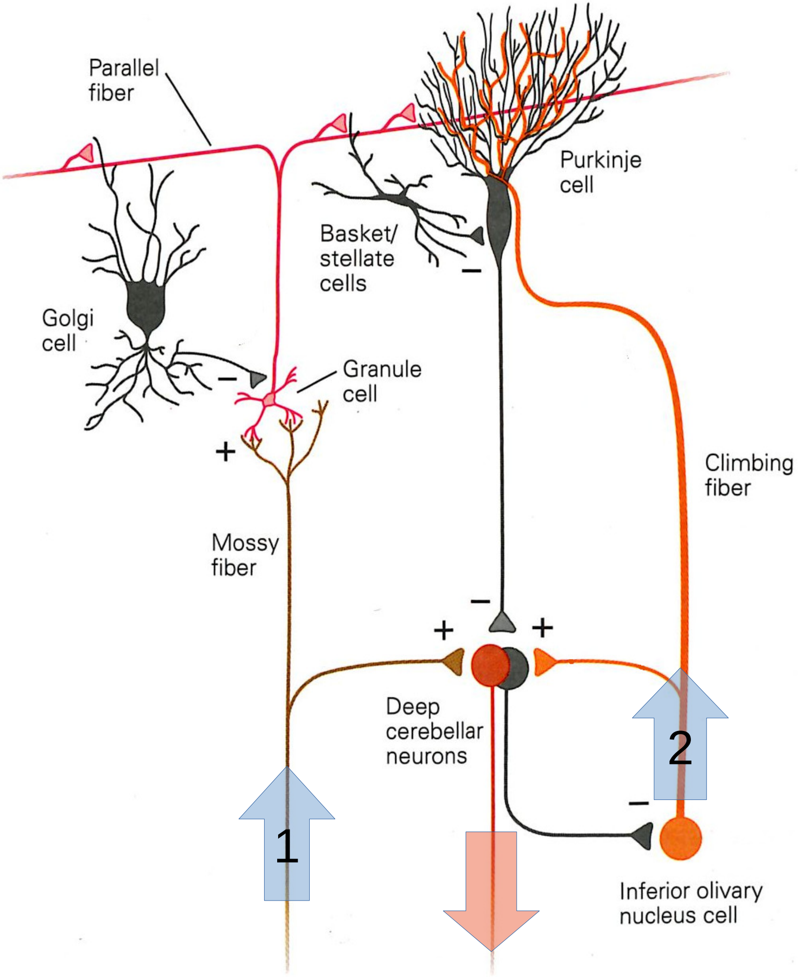
Microcircuit organization of the cerebellar cortex


vertical section of
single cerebellar folium

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

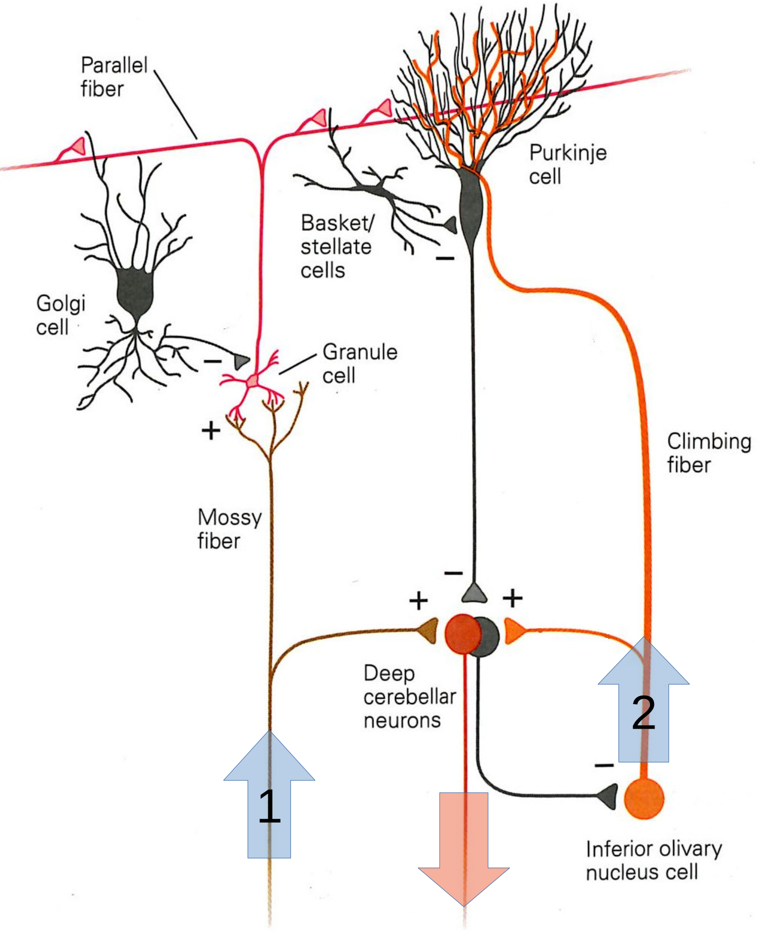


Two afferent fiber systems encode information differently

- *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



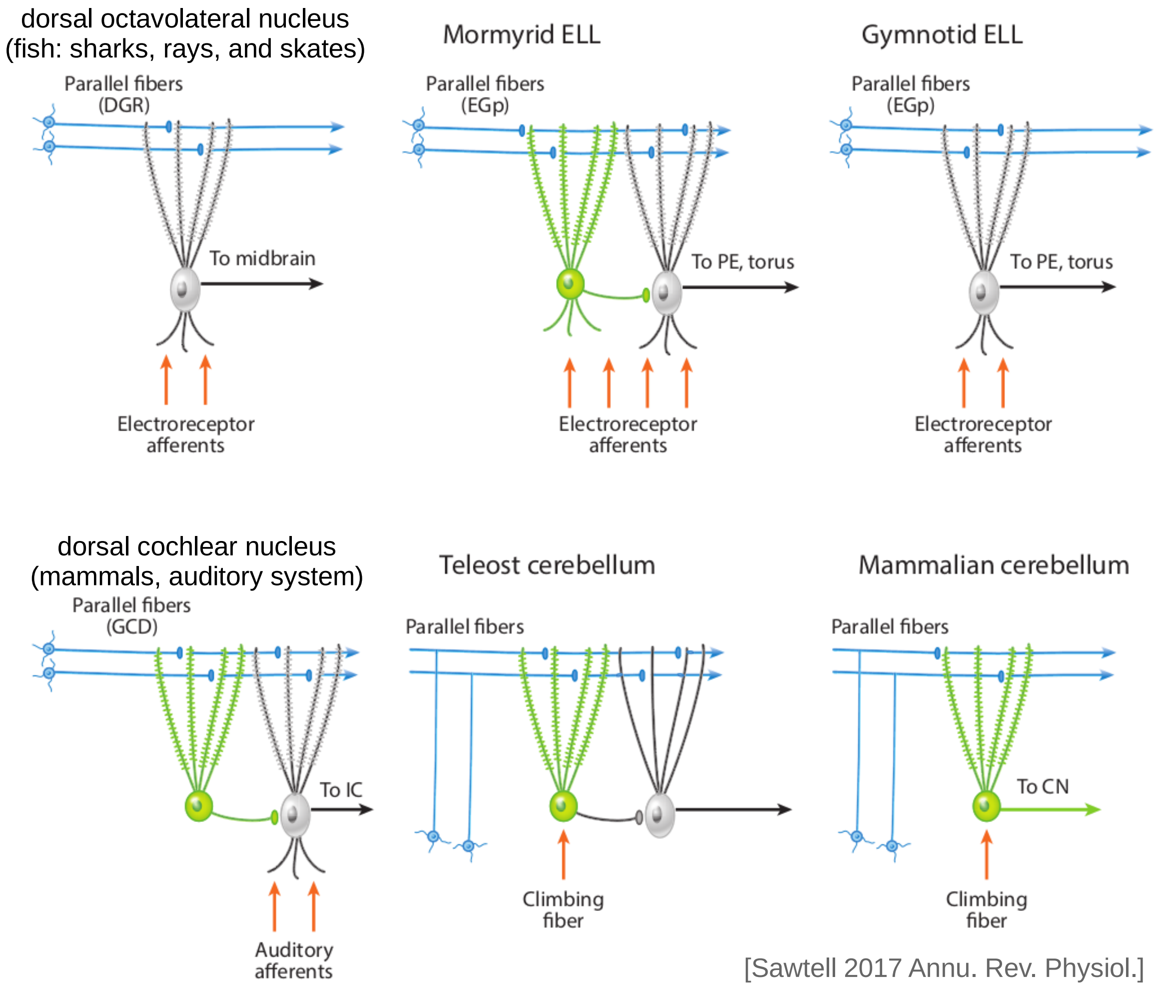
1. mossy fibers

- 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

Cerebellum-like structures


dorsal octavolateral nucleus (fish: sharks, rays, and skates)

dorsal cochlear nucleus (mammals, auditory system)

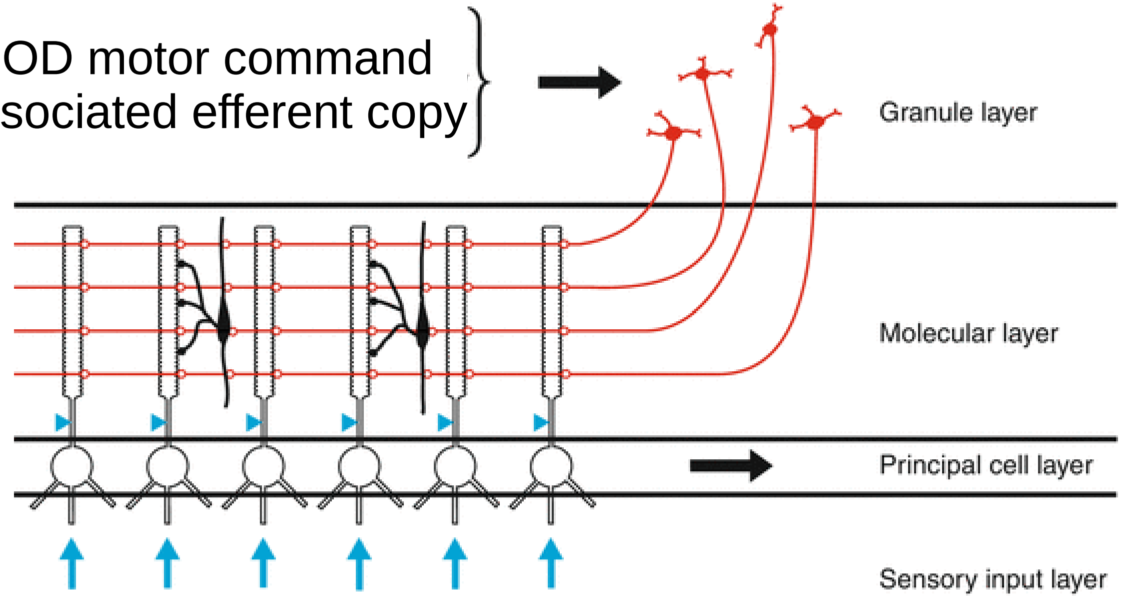
[Sawtell 2017 Annu. Rev. Physiol.]

- presence of two input streams is the defining feature of the cerebellum(-like) structures from fish to mammals
- 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

EOD motor command
associated efferent copy



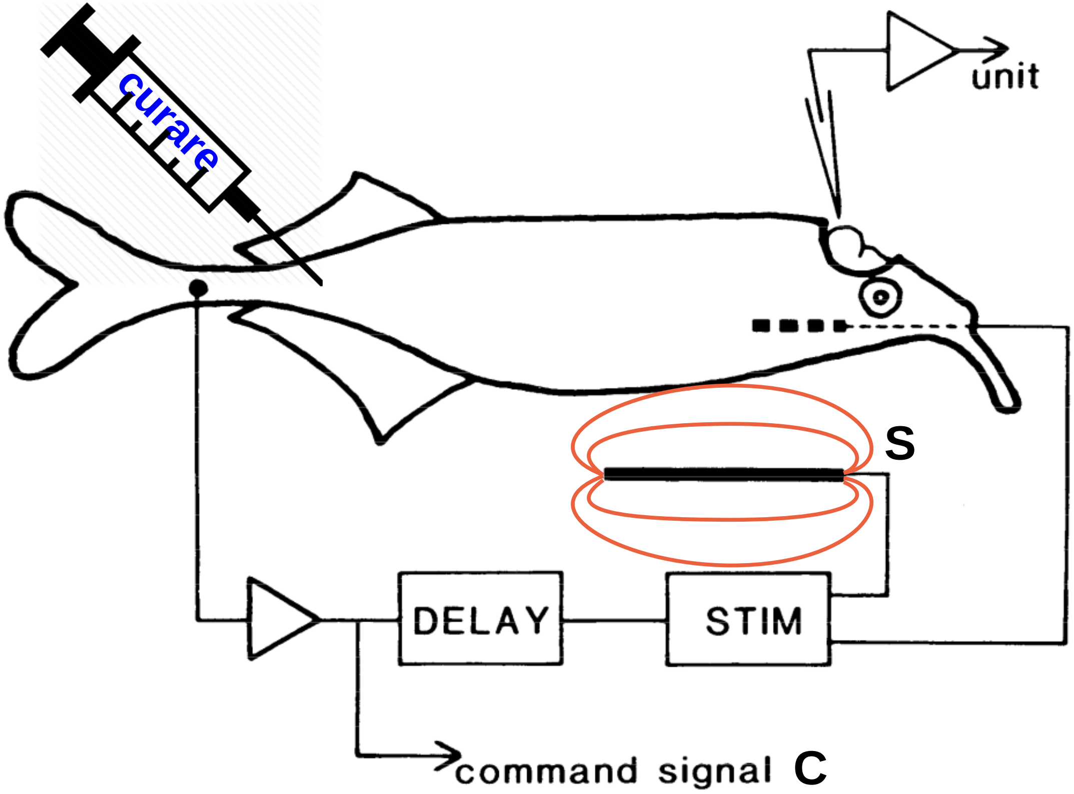
afferent activity
(input from sensory surface:
electroreceptors)

[Sawtell and Bell 2013, Cerebellum-like structures]

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

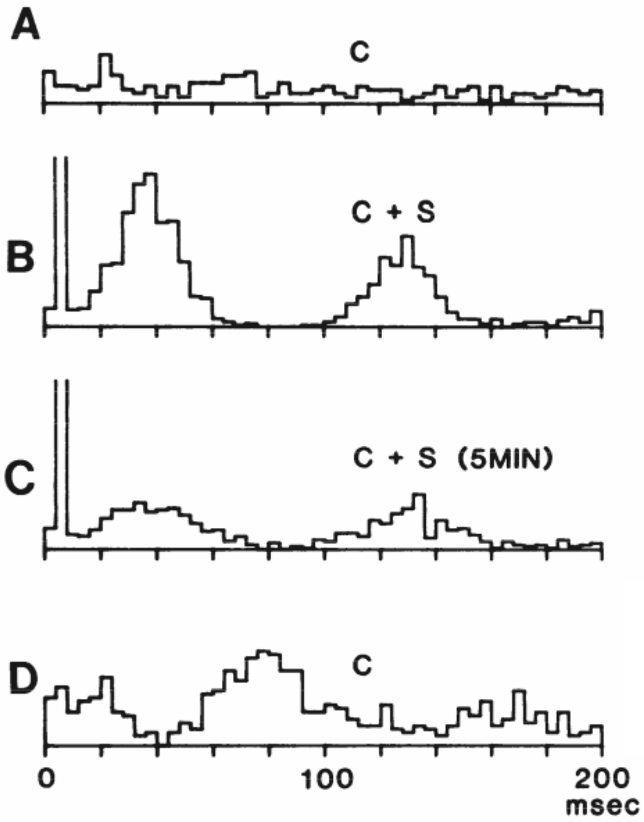
Electric fish experiment: Bell 1982 J Neurophysiol



[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



[Bell 1982 J Neurophysiol]

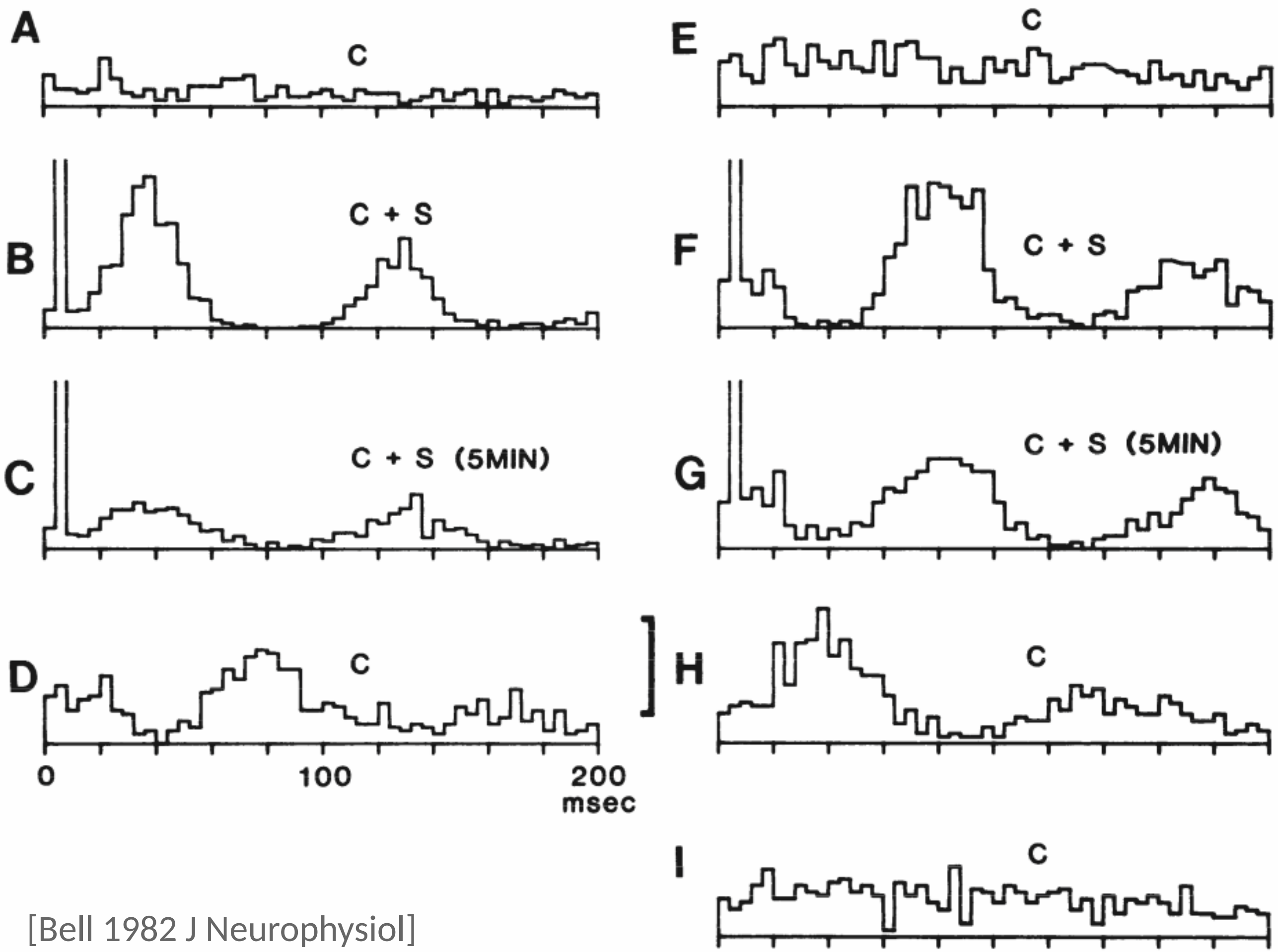
A) Command alone evokes no response

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

Electric fish: effect of Command-Stimulus pairings



E) Command alone : 7 min after stimulus off

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

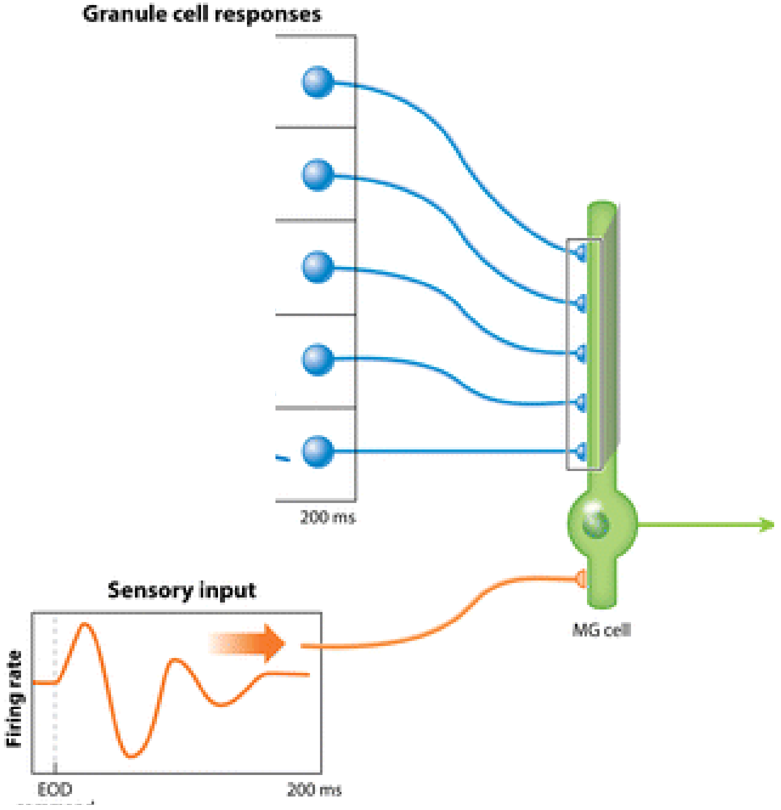
G) Command-stimulus paring: reduced response after 5 min of pairing response

H) Effect of command alone

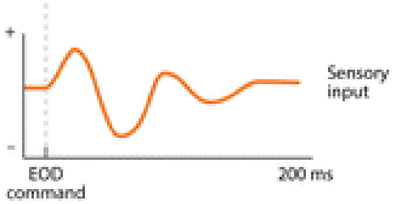
I) Command after 15 min of stimulus off

[Bell 1982 J Neurophysiol]

Electric fish experiment: circuit implementation

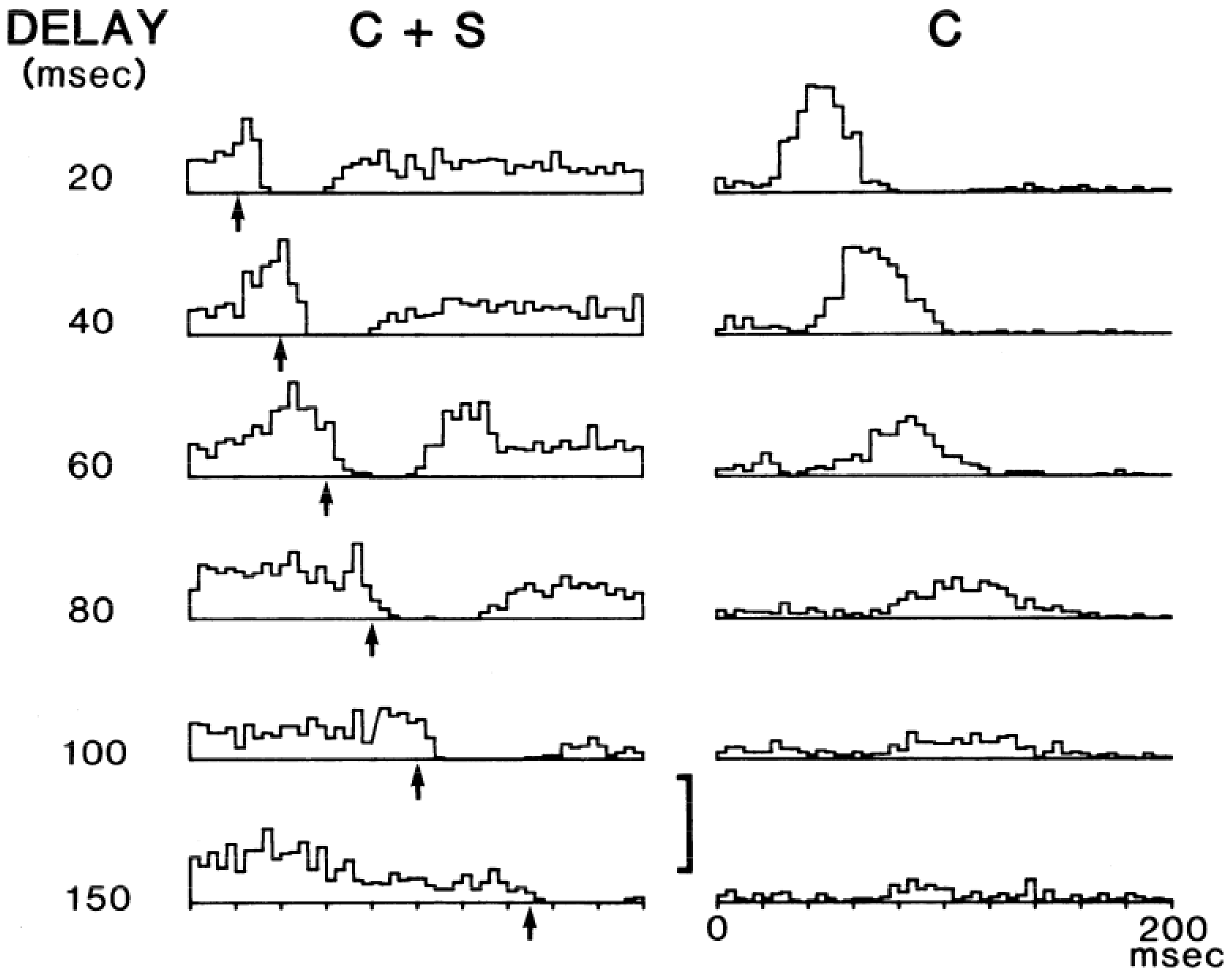


[Sawtell 2017 Annu. Rev. Physiol.]



- 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

Electric fish experiment: varying stimulus delay

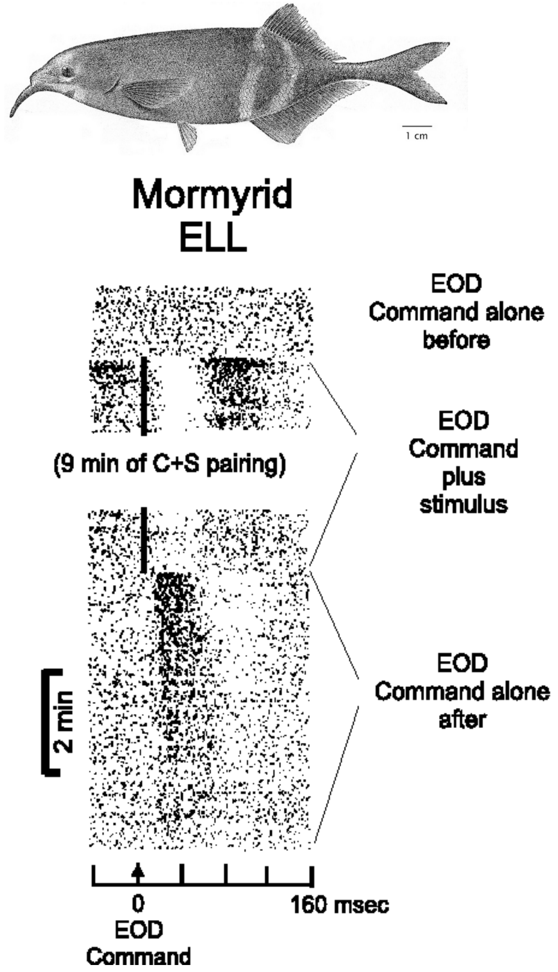


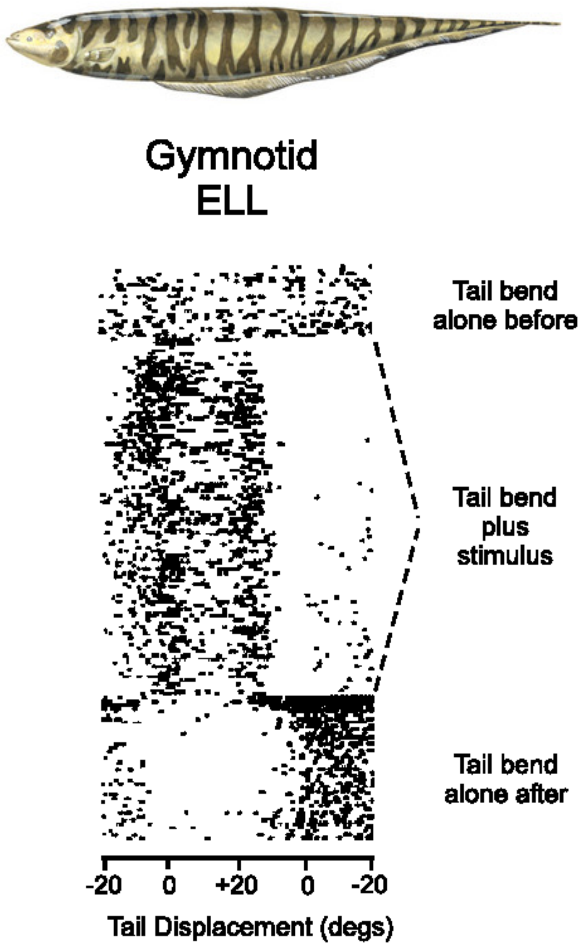
- effect of varying stimulus delay
- **left column :**
  command and stimulus were paired for 3-4 min

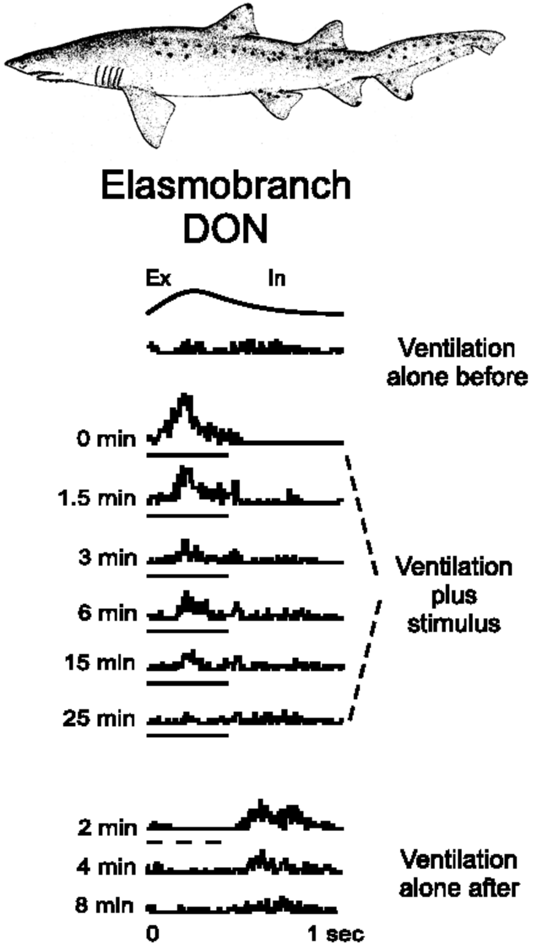
- **right column :**
  effect of the command alone

- in effect, tests the learning curve which implements the formation of the negative image

Formation of negative images in 3 cerebellum-like structures







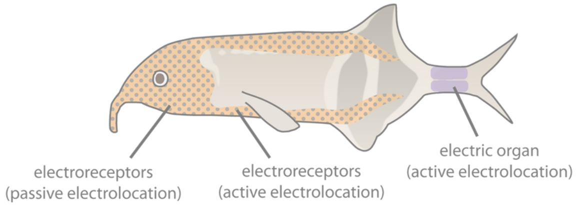
Talk outline

1. Cerebellar disorders

- functions inferred from symptoms
- eye-arm movement coordination with prism glasses

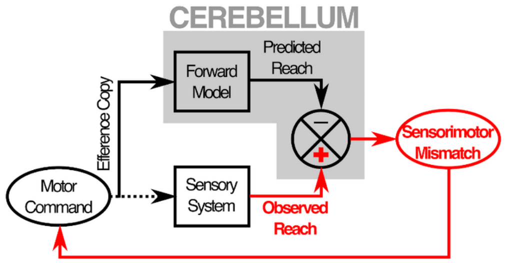
2. Electric fish and prediction of sensory consequences

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

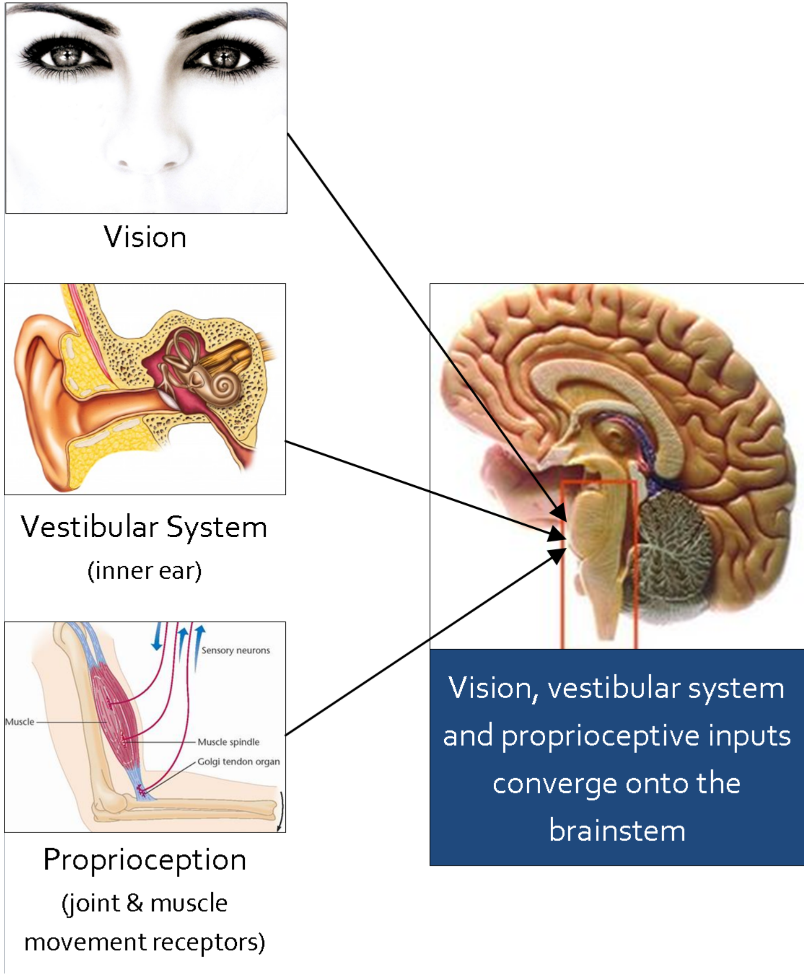


3. Sensory prediction and forward model

- sensory prediction in the monkeys
- forward model and the cerebellum



Sensory system activated during movement



Vision

Vestibular System
(inner ear)

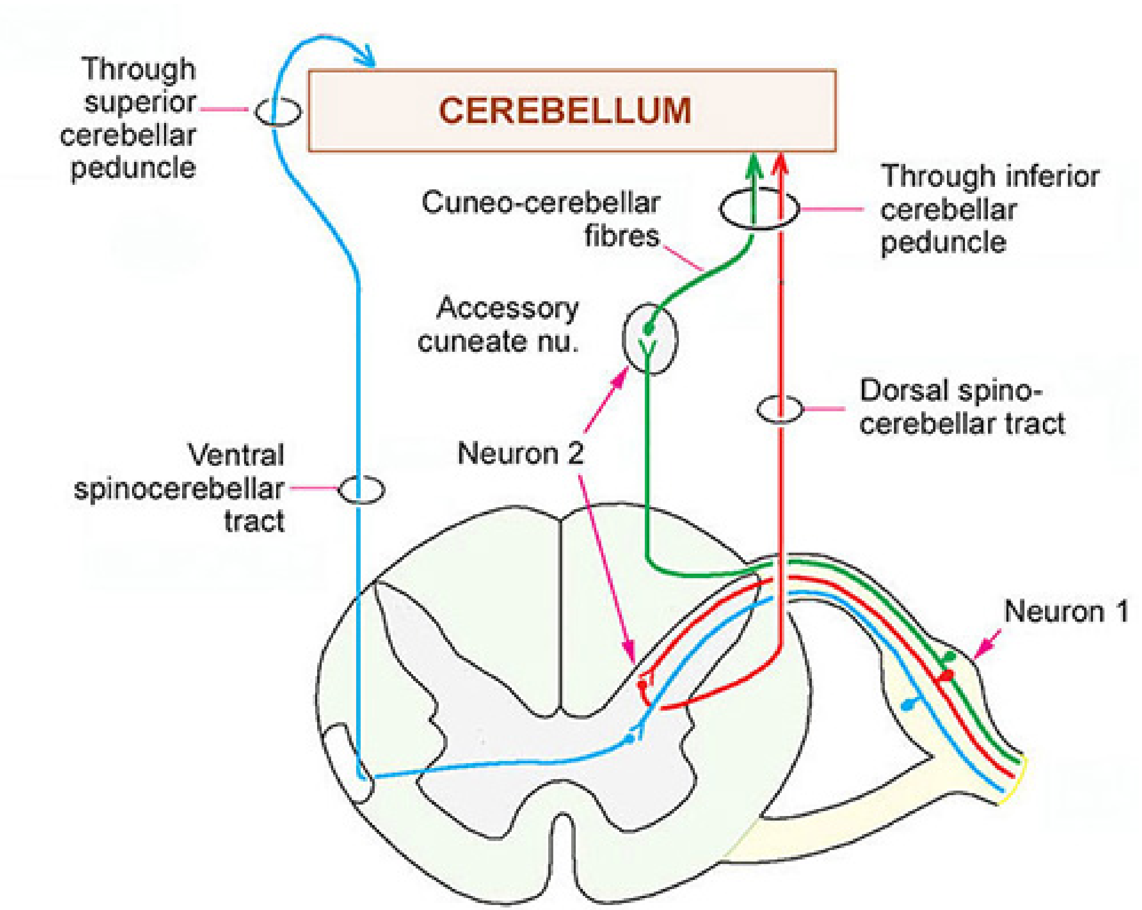
Proprioception
(joint & muscle
movement receptors)

Vision, vestibular system and proprioceptive inputs converge onto the brainstem

- 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) ?

[experiment]

Prediction of sensory consequences : two input streams



dorsal spinocerebellar tract

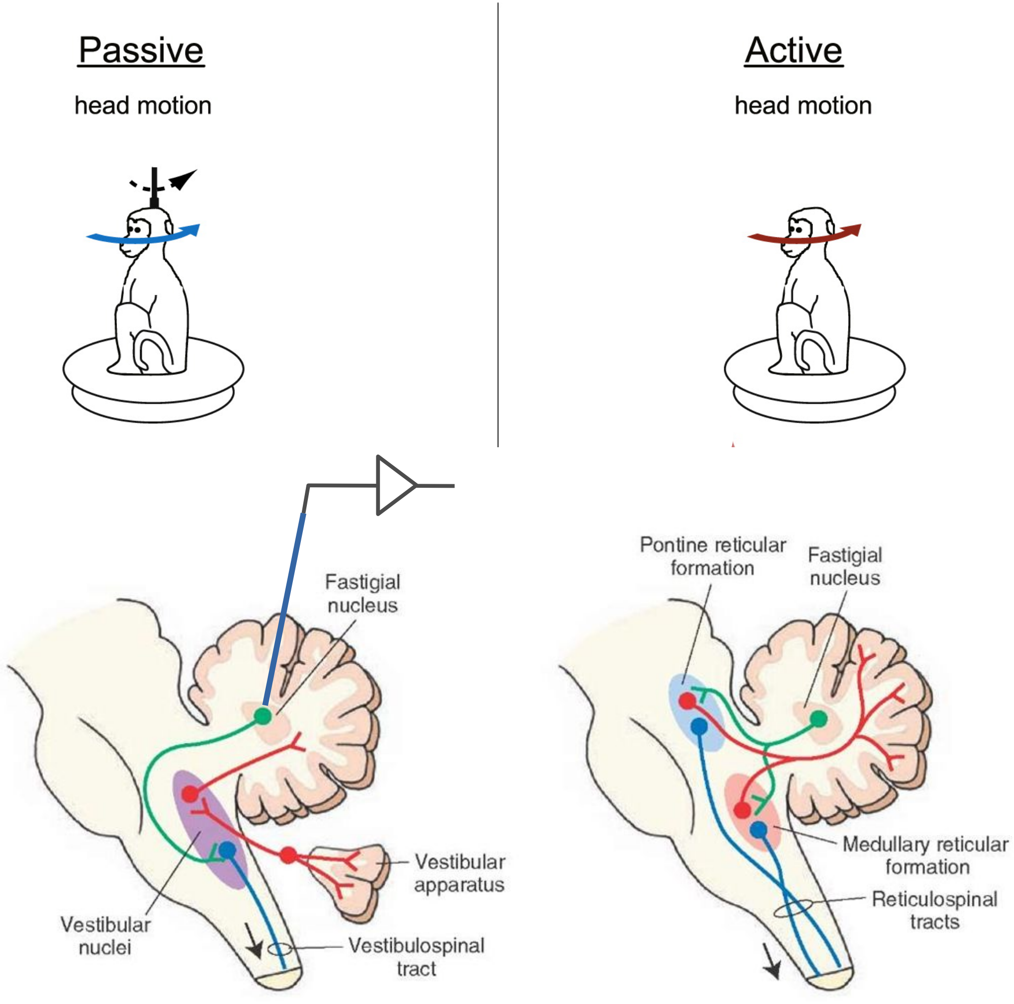
- conveys somatosensory information from muscle and joint receptors
- sensory feedback about consequences of movement (active of passiv)
  → reafference signal

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

Monkey experiment: sensory processing in cerebellum



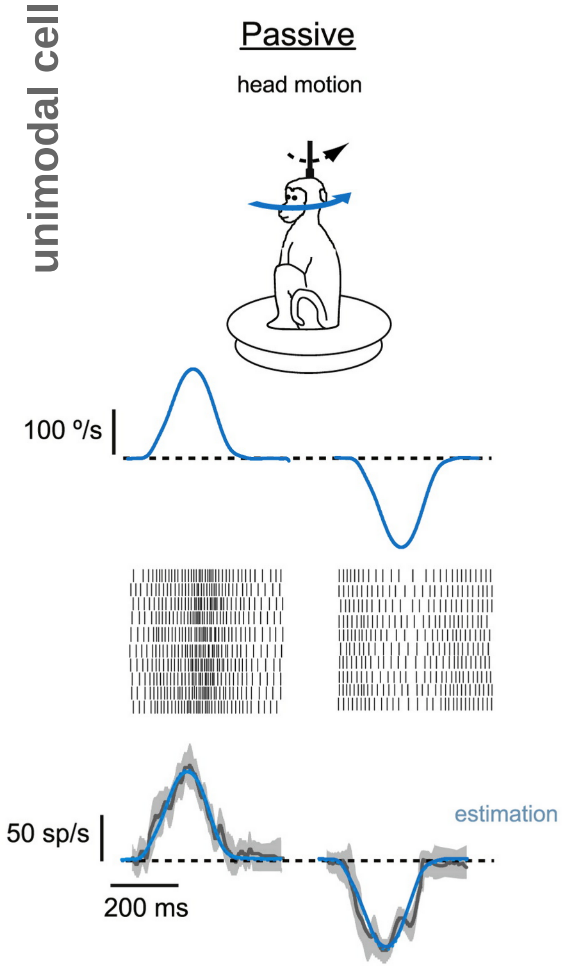
behavioral paradigm

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

recording

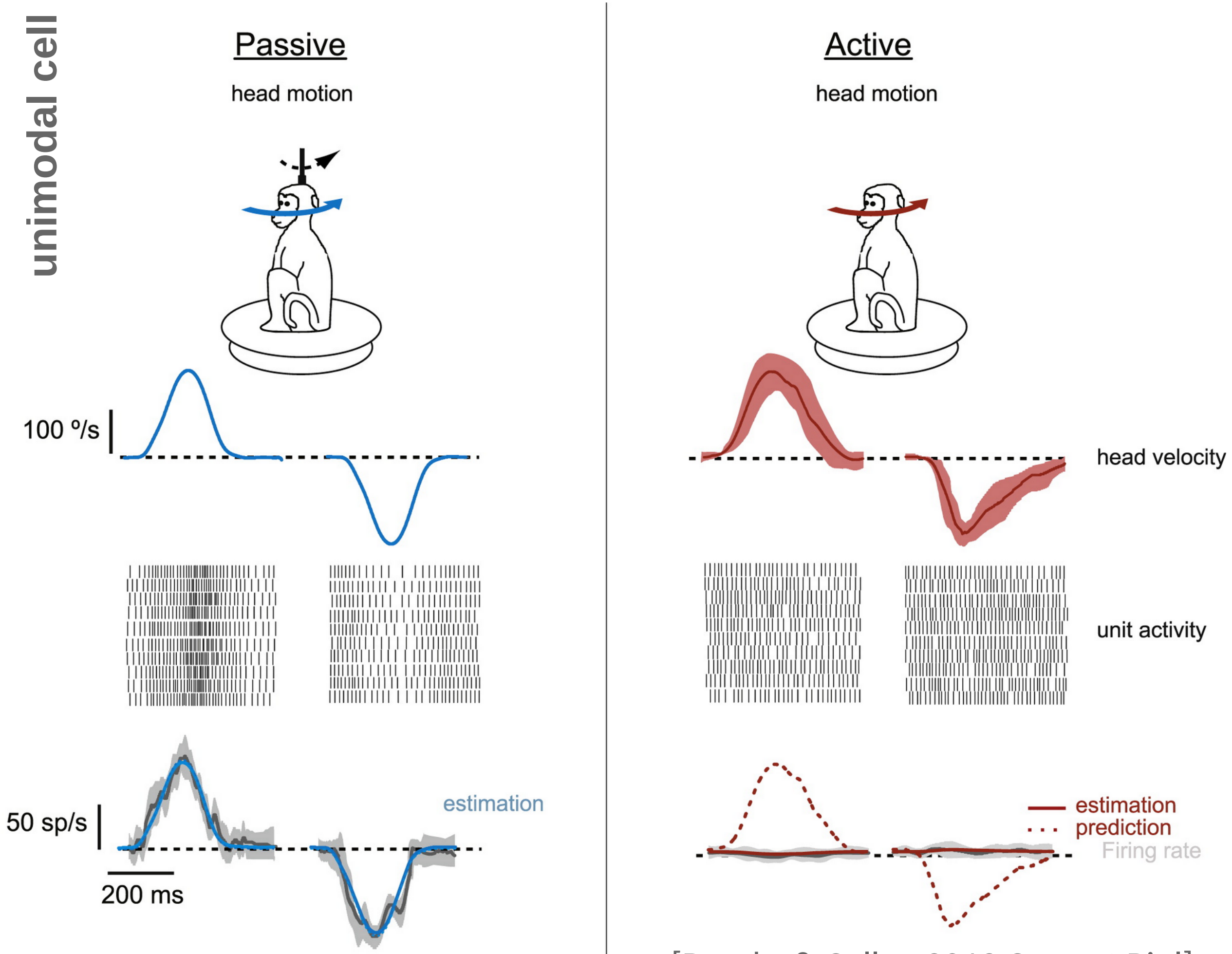
- tungsten electrode in fastigial nucleus (postural control)
- unimodel neurons : only responsive to vestibular stimulation
- bimodal neurons : responsive to passive vestibular and proprioceptive stimulation

Cells responsive to passive but not active movement



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

Experimental evidence in mammals for negative image

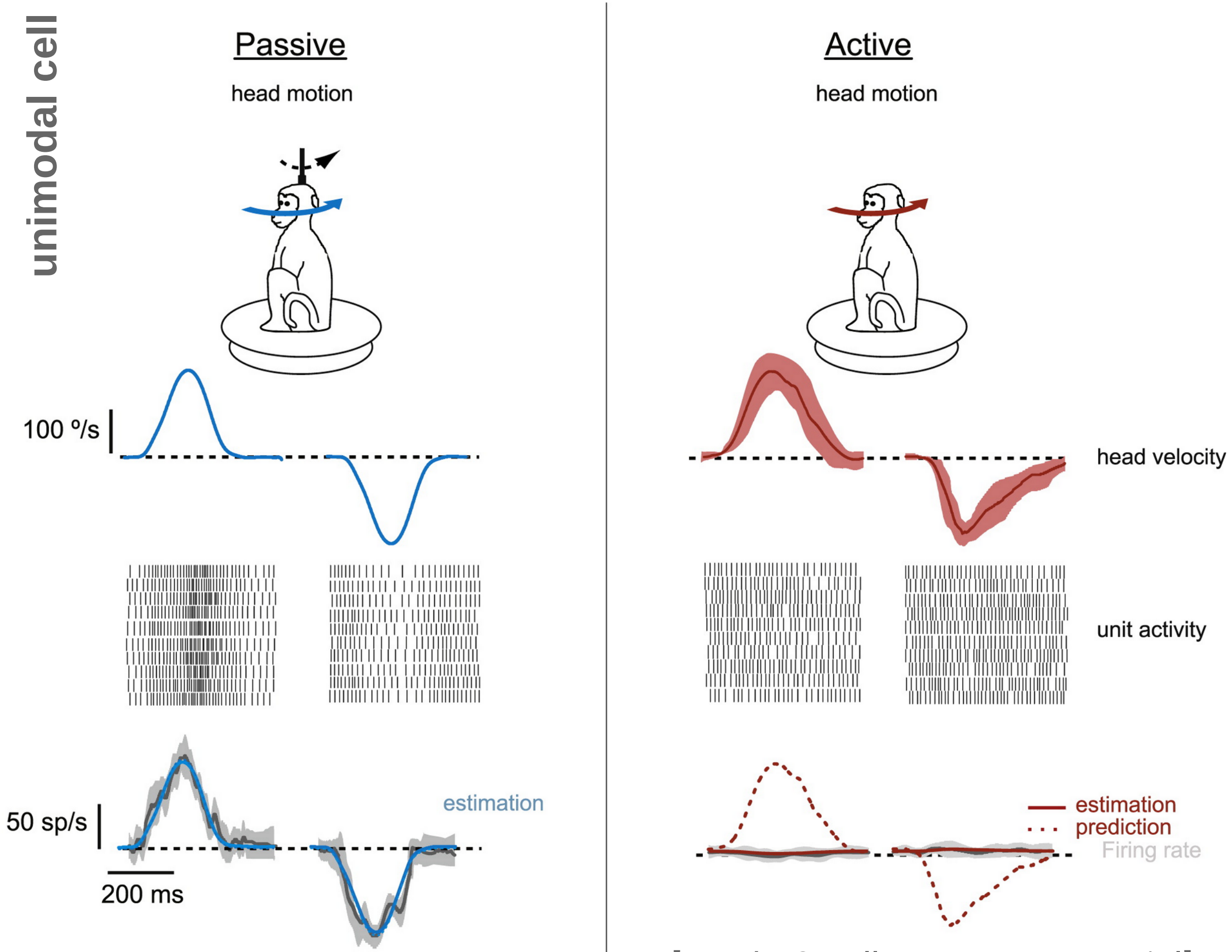


- cells (unimodal and bimodal) were strongly modulated during *passive* head and body motion

- same cells were unresponsive to same motion when voluntarily produced

[Brooks & Cullen 2012 Current Biol]

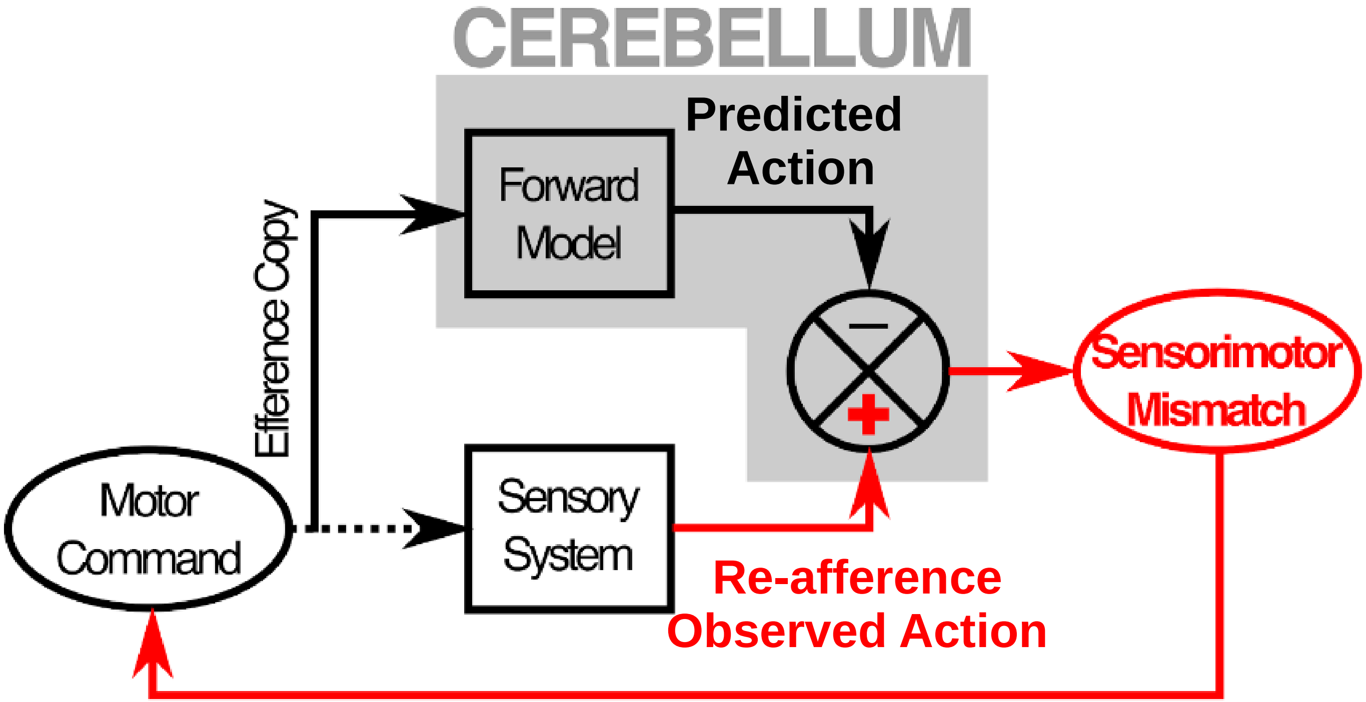
Experimental evidence in mammals for negative image



[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

Cerebellum possibly implements a forward model

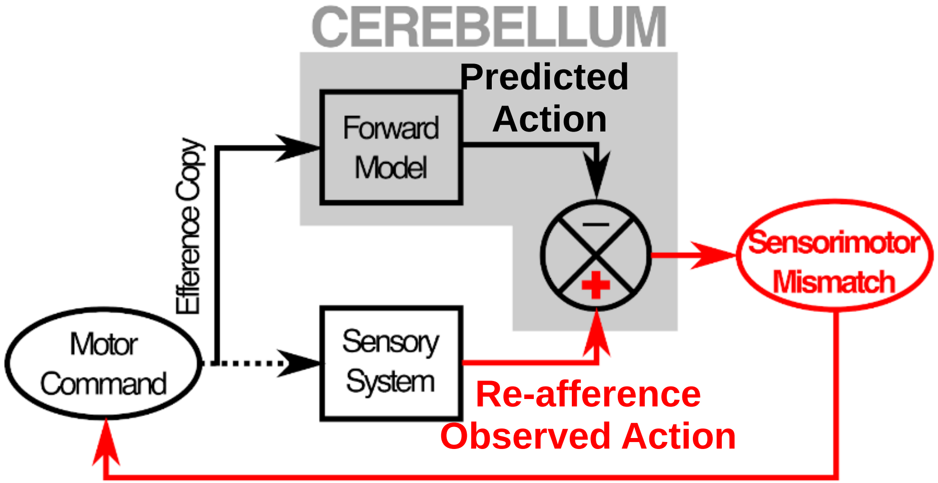


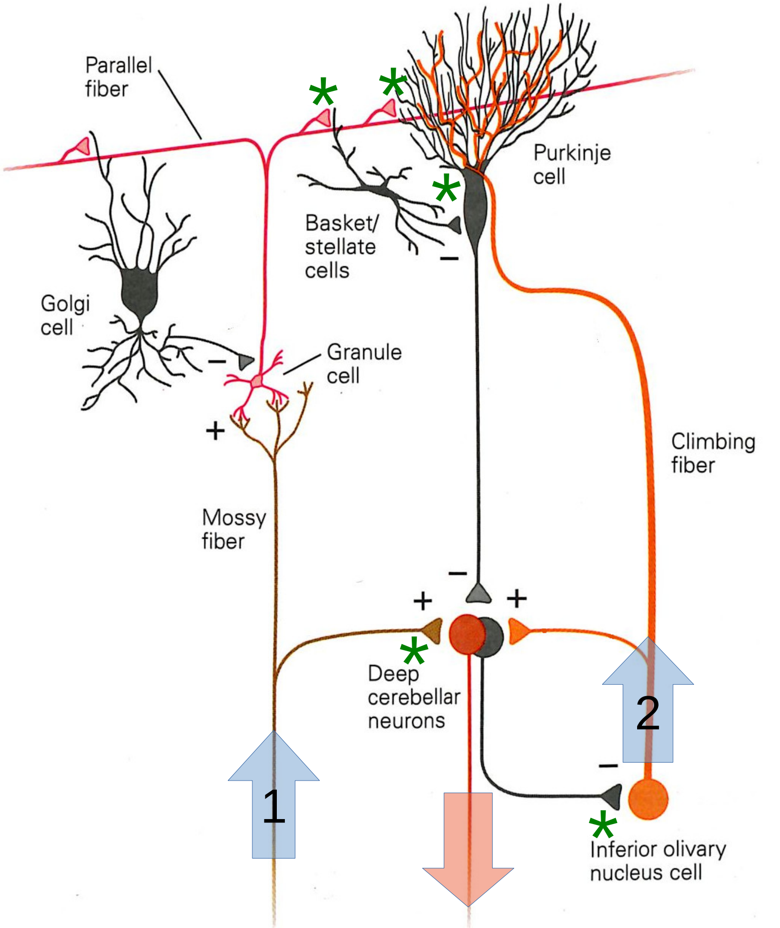
- cerebellum computes a prediction of sensory consequences which is compared to the sensory consequences of the actual movement

usefulness

- comparison can be used to compute error that in turn guides updating of the motor program
- computation of sensory prediction errors enables brain to distinguish between self-generated and externally produced actions

Forward model requirements





* ... plastic synapses

- 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

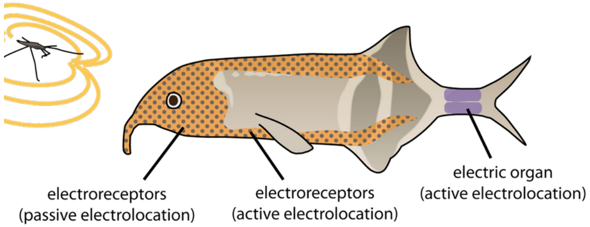
Talk outline

1. Cerebellar disorders

- functions inferred from symptoms
- eye-arm movement coordination with prism glasses

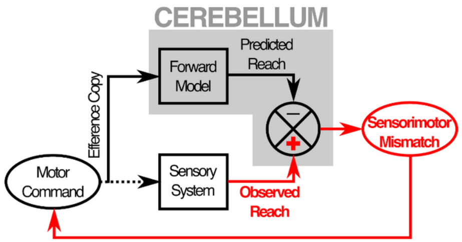
2. Electric fish and prediction of sensory consequences

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



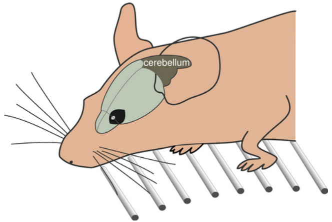
3. Movement prediction and forward model

- sensory prediction in the monkeys
- forward model and the cerebellum

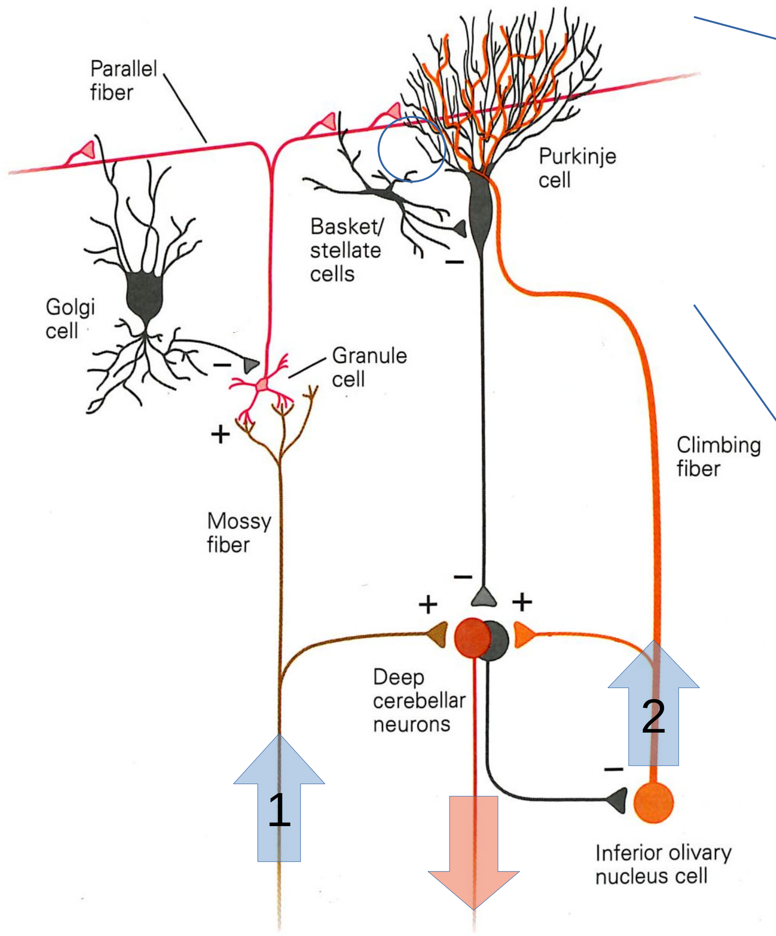


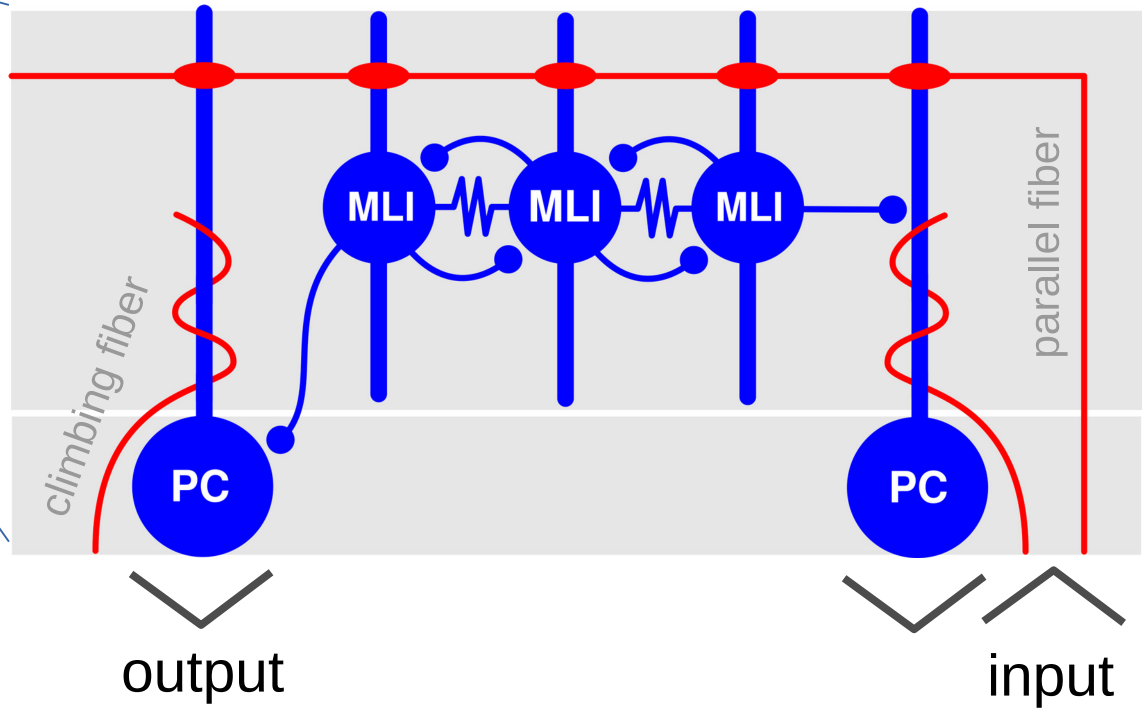
4. Experiments implemented in the lab to unravel cerebellar function

- whisker virtual reality
- learning and adaptation in complex locomotion task



Cerebellar cortex molecular and Purkinje layer network *in vivo*



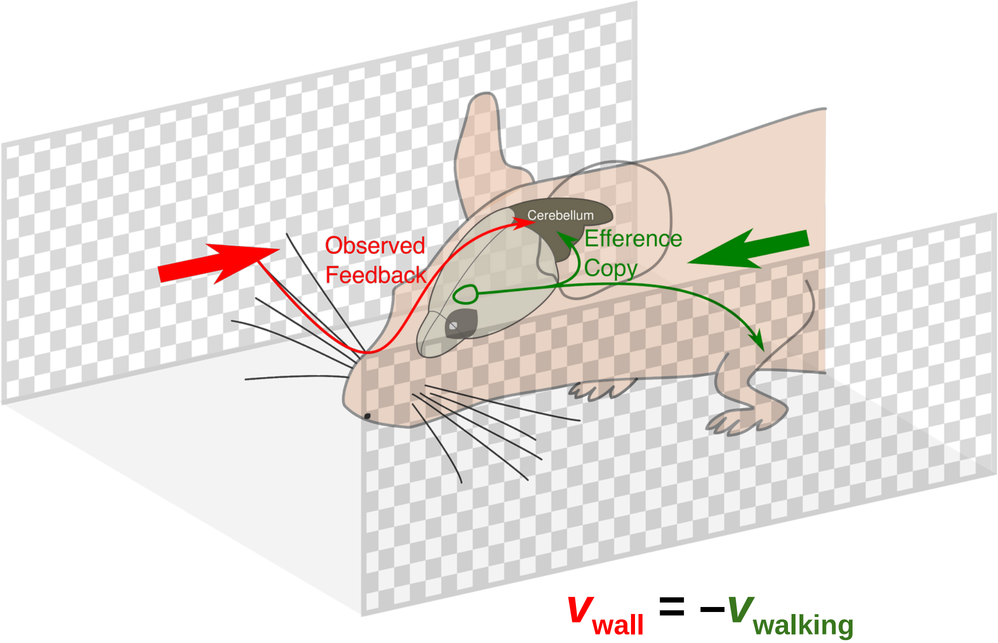


MLI ... molecular layer interneuron

PC ... Purkinje cell

Rodent navigating through tunnel

Aim: study effect of sensorimotor mismatch during locomotion in rodent cerebellum.

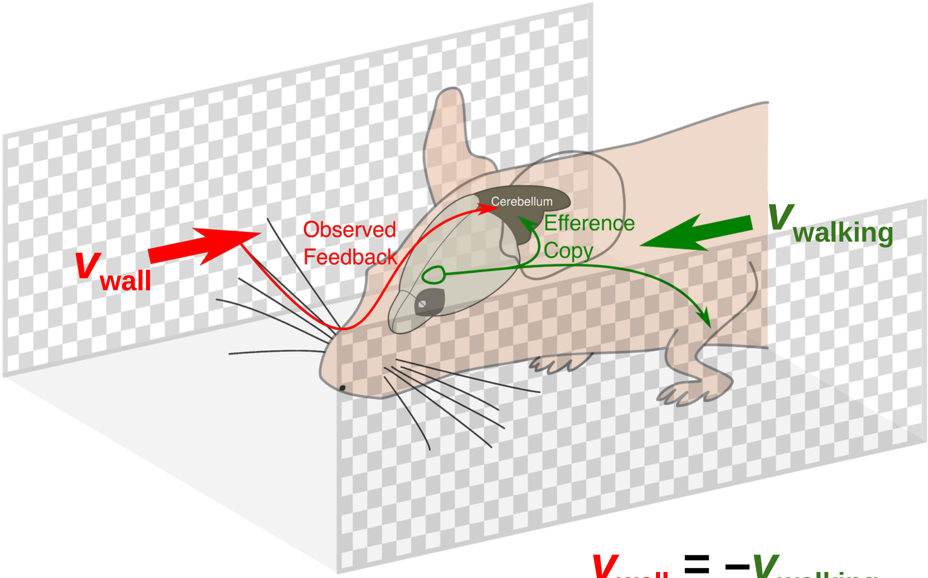


$v_{\text{wall}} = -v_{\text{walking}}$

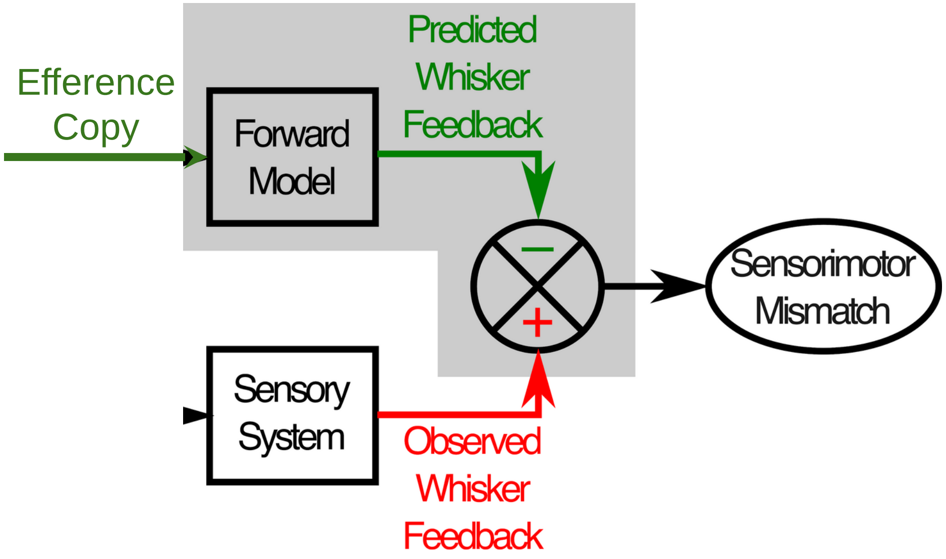
Locomotion with side-walls generates sensory feedback

Sensorimotor mismatch can be introduced by altering observed whisker feedback.

Are the different signals present in the cerebellum and where is the possible comparison between expected and received sensory feedback computed ?

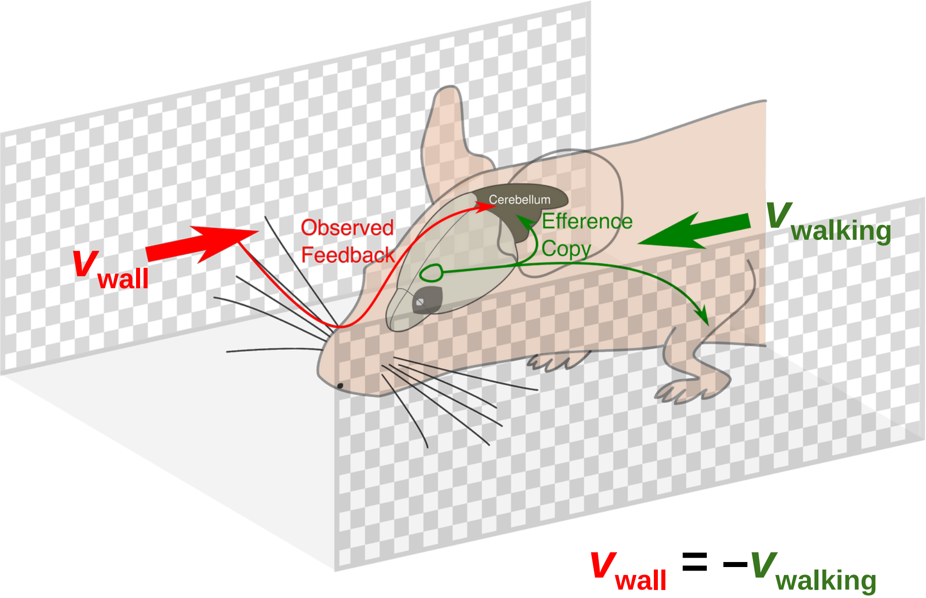


$$v_{\text{wall}} = -v_{\text{walking}}$$

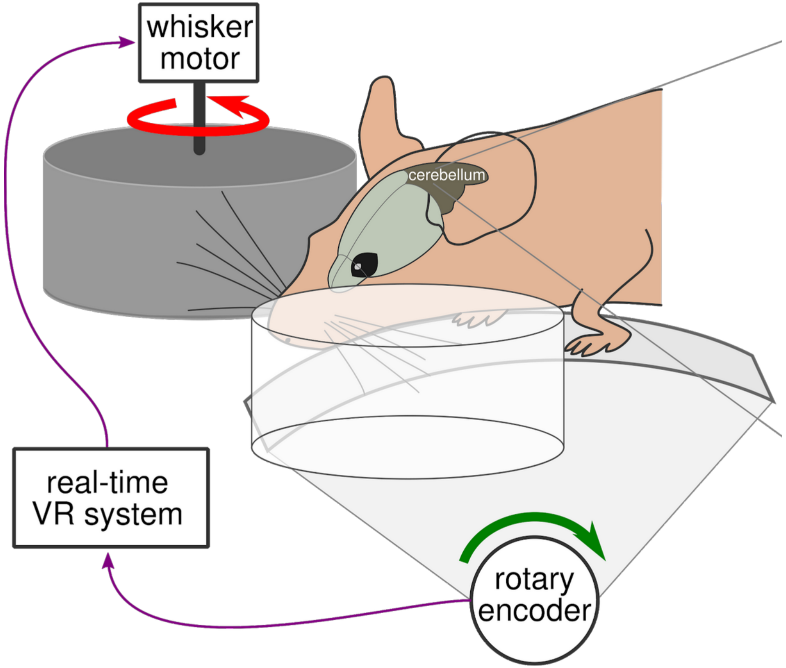


Whisker virtual reality

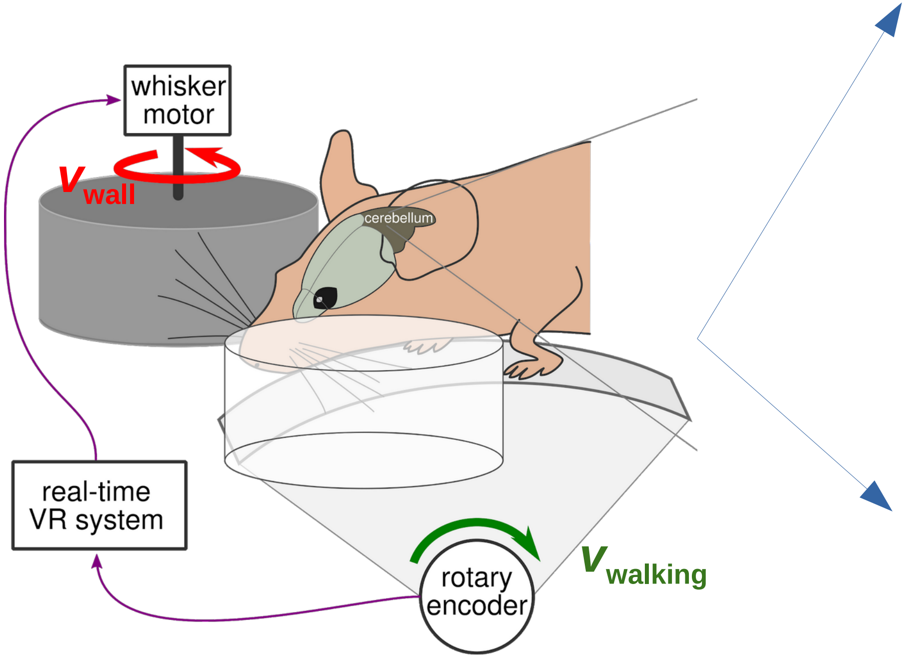
The virtual reality setting allows to externally control the perceived whisker feedback



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



Whisker virtual reality



closed loop configuration :

- walls move at the walking speed

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

- provided tactile feedback matches expected feedback from locomotion

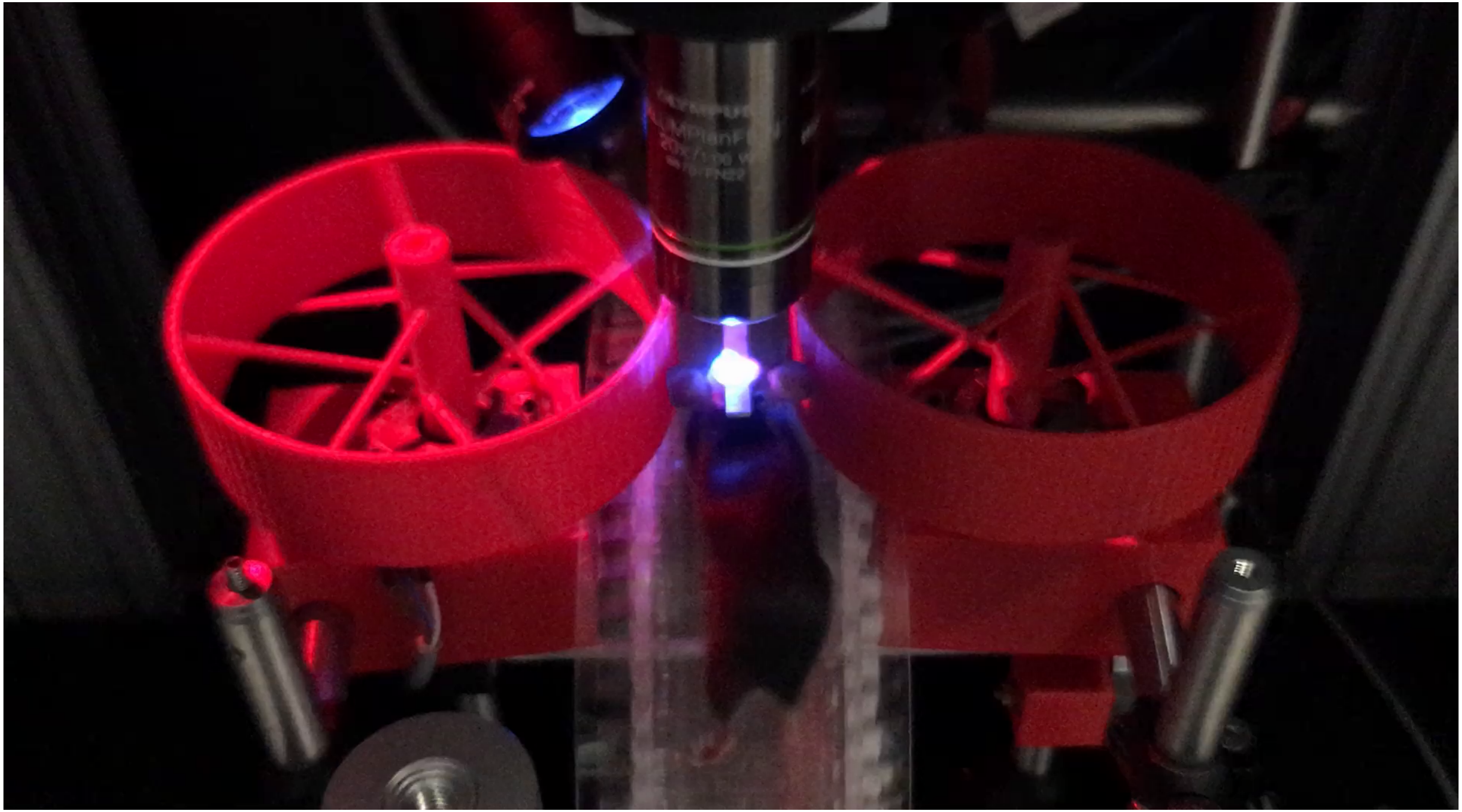
open loop configuration :

- walls move at a different speed than the walking speed

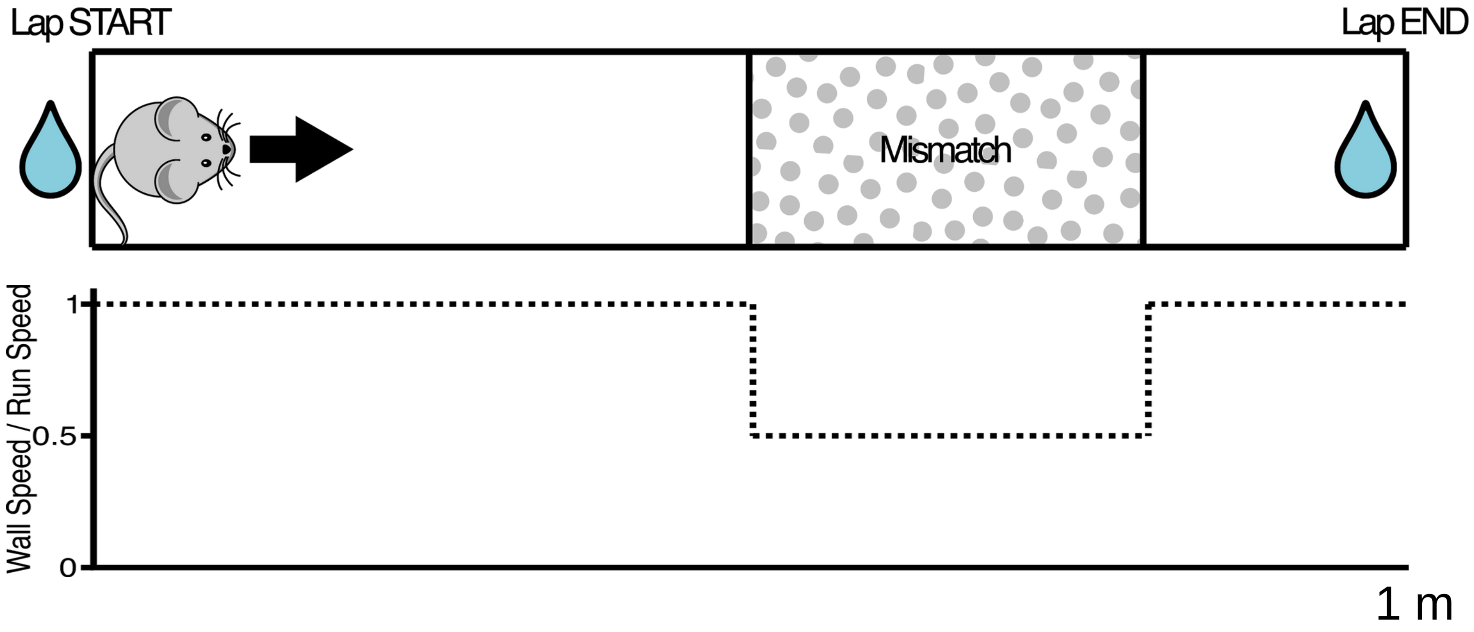
$$v_{\text{wall}} \neq -v_{\text{walking}}$$

- sensorimotor mismatch : tactile feedback speed does not correspond to locomotion speed

Whisker virtual reality

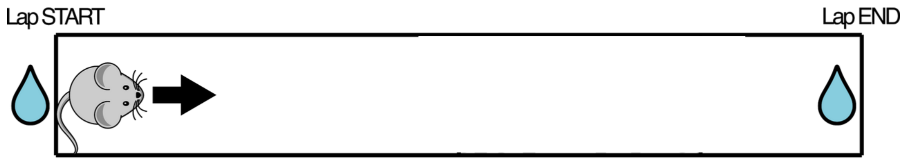


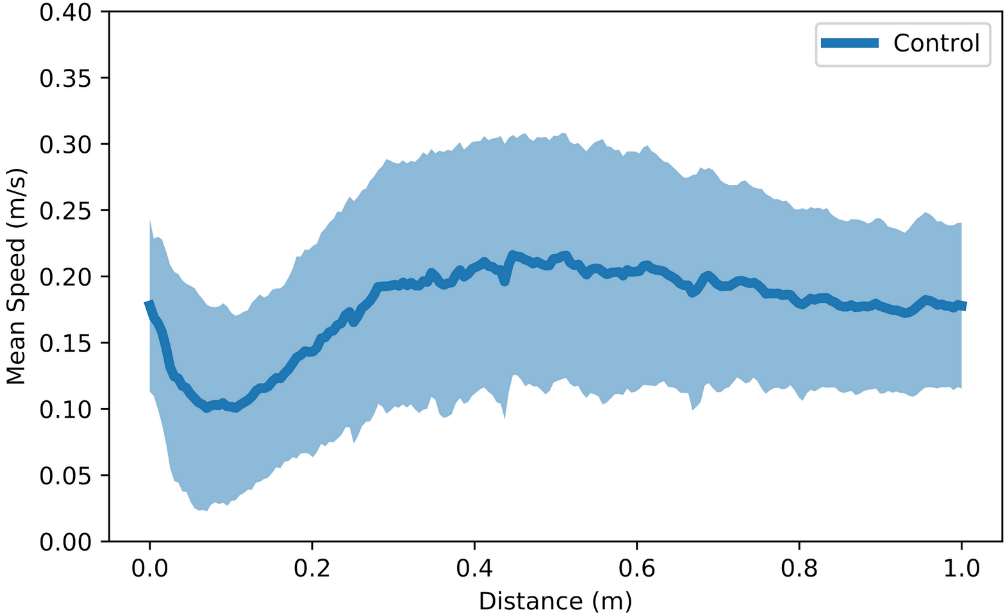
Introducing transient sensorimotor mismatch



- mice are motivated to run 1 m long laps through water rewards
- **Our hypothesis :** animals will accelerate in response to wall speed decrease

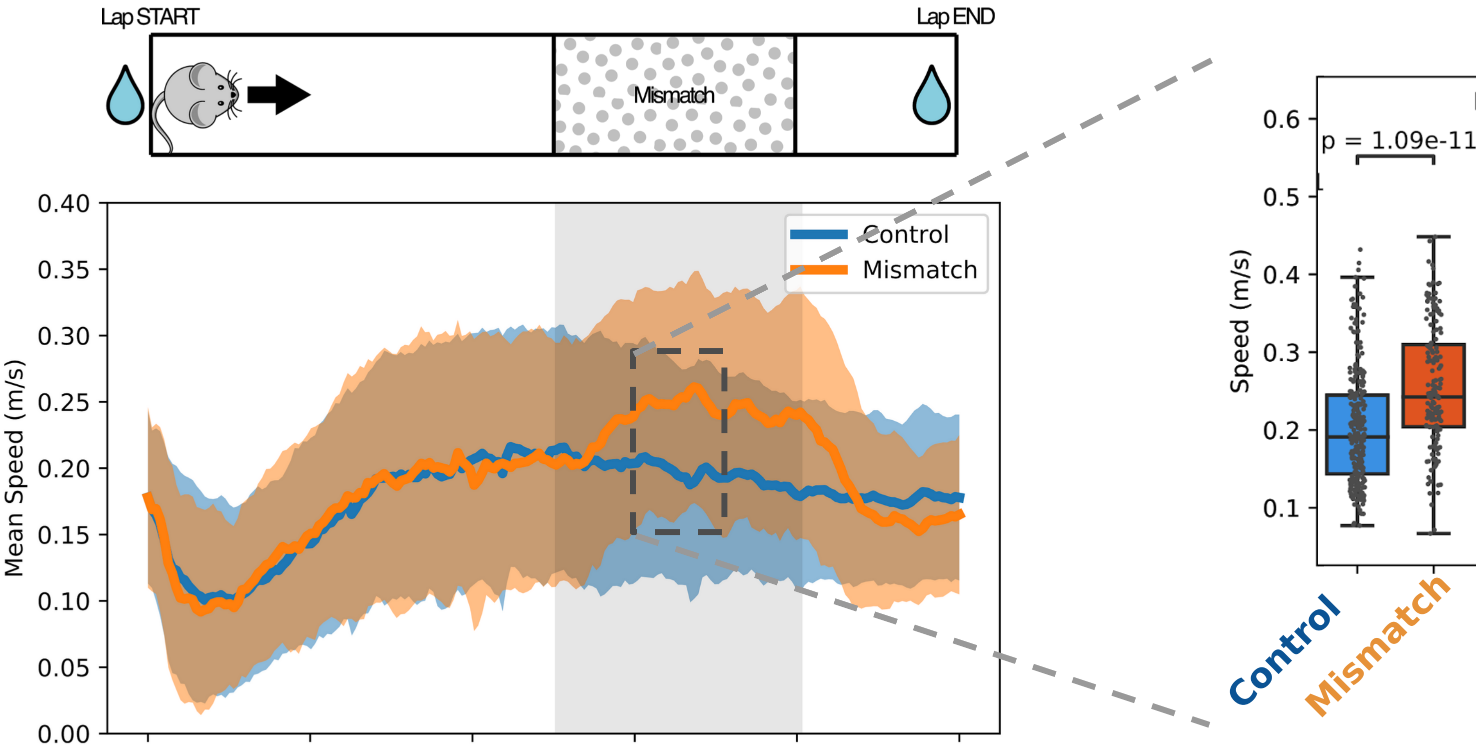
Mice run readily 1m laps for water reward





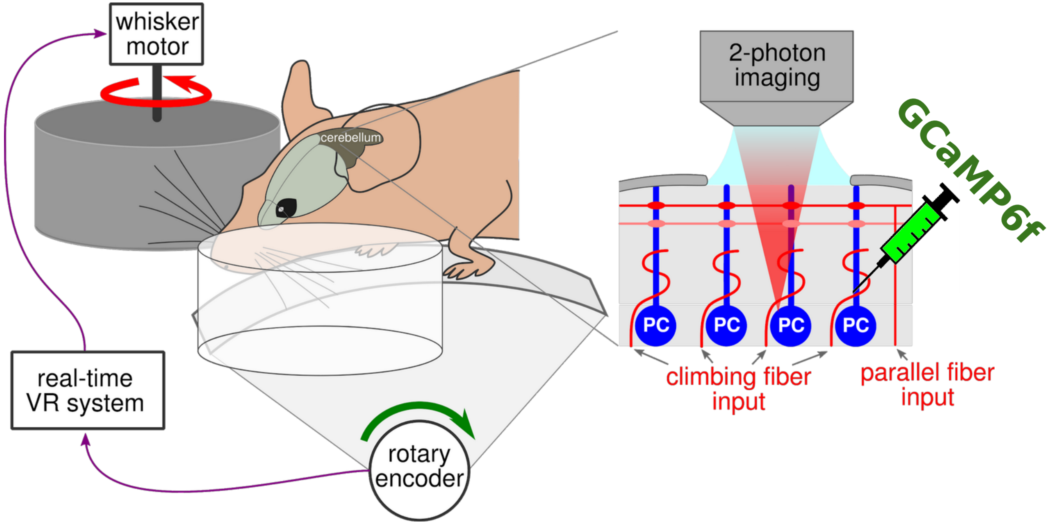
Mean speed over 280 **control** laps

Locomotion is modulated by whisker feedback



Mean speed over 280 **control** laps, 165 **mismatch** laps

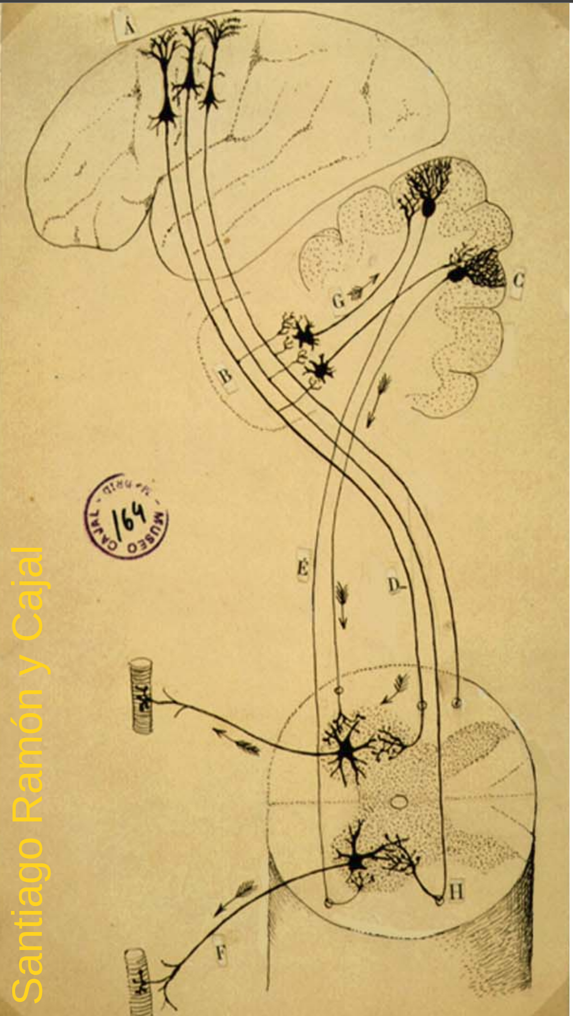
Two-photon calcium imaging from Purkinje cells



Questions :

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

Cerebellum and locomotion



Santiago Ramón y Cajal

Cerebellum ensures that movements are well timed and highly coordinated.

During walking :

→ Cerebellum is essential for on-the-fly corrections of posture and gait

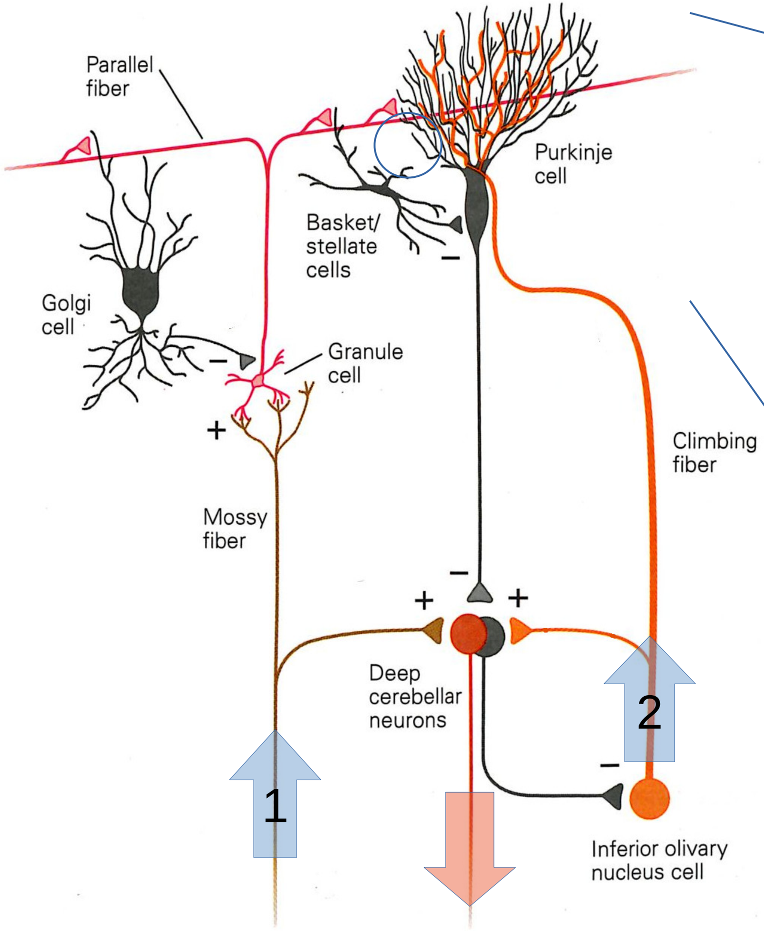
→ cerebellar dysfunction leads to balance problems and walking abnormalities

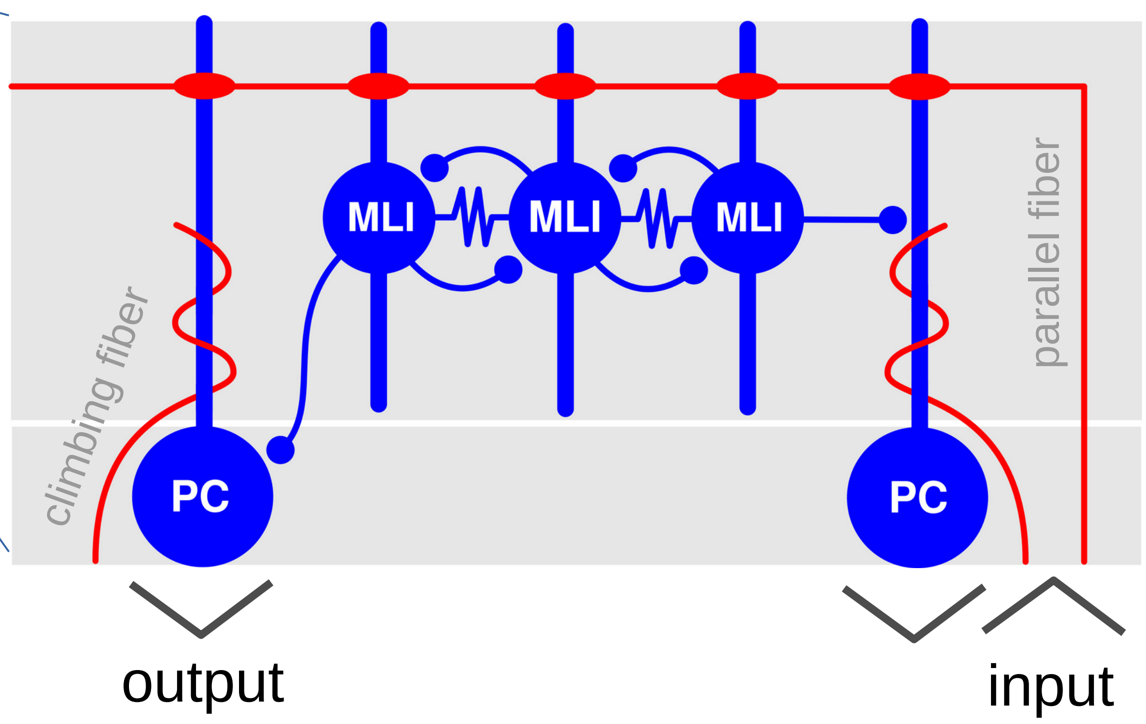
Questions :

→ What are the cellular underpinnings of motor coordination ?

→ What is the influence of activity in the cerebellar cortex on motor behavior ?

Cerebellar cortex molecular and Purkinje layer network *in vivo*



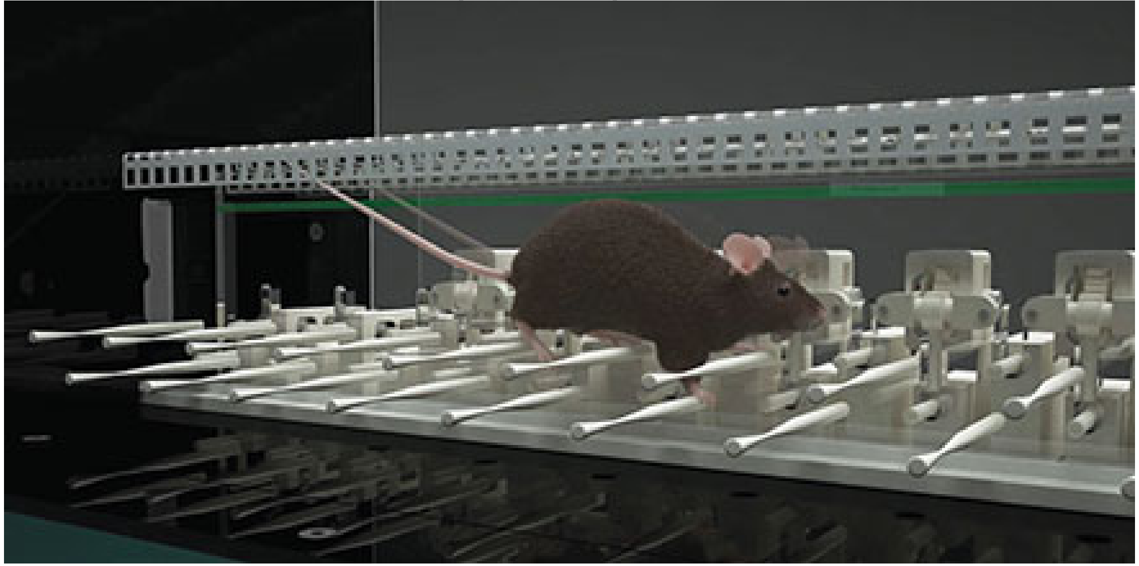


MLI ... molecular layer interneuron

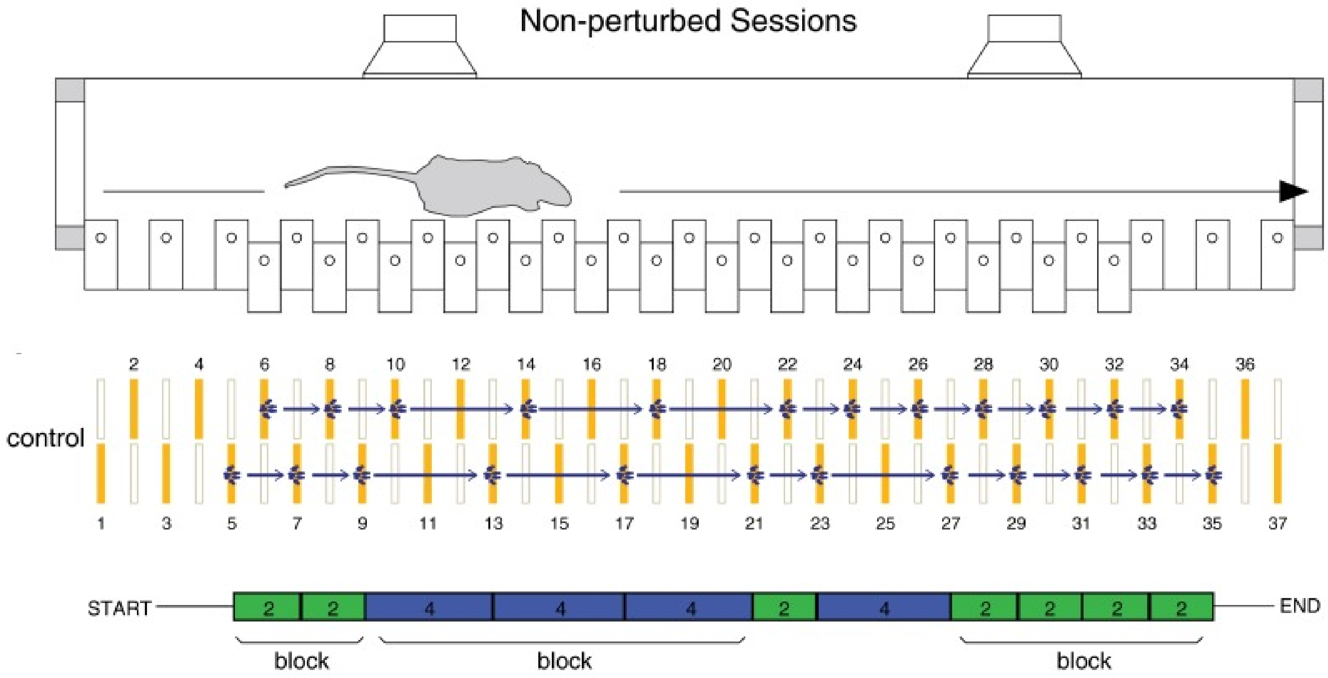
PC ... Purkinje cell

Erasmus lader

Erasmus Ladder™ (Noldus)



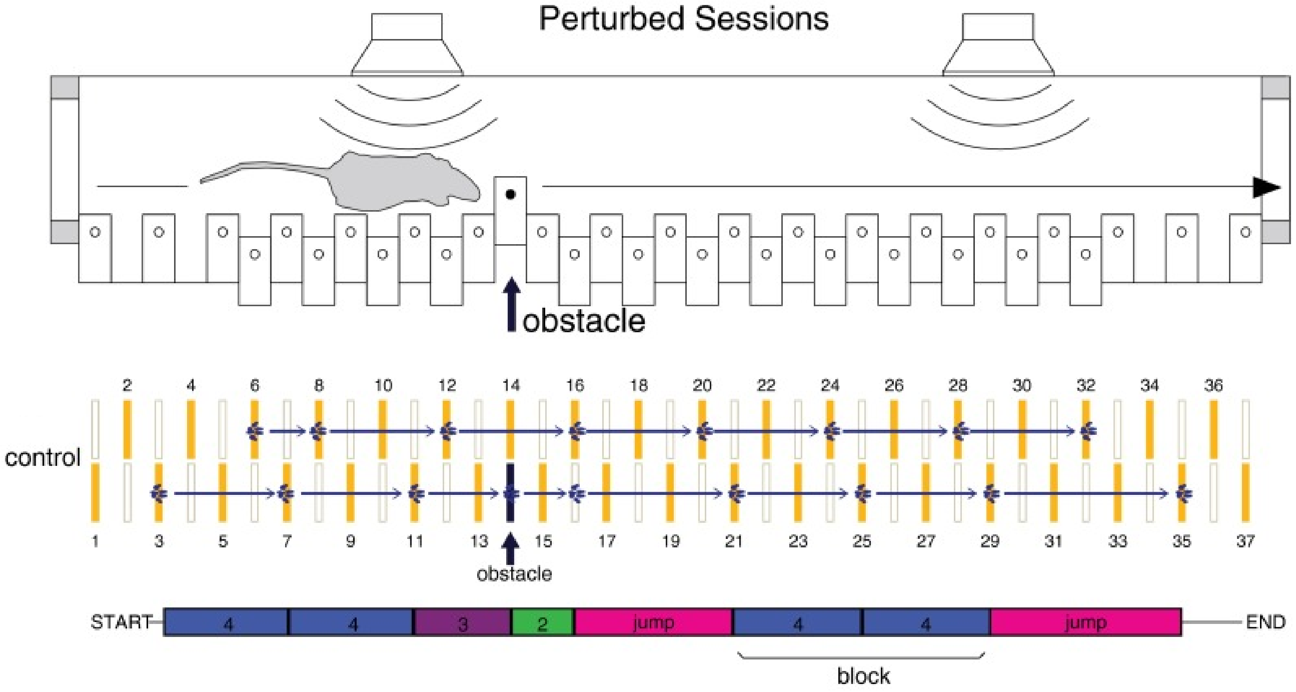
Erasmus ladder: behavioral paradigm



baseline locomotion

- animal is made to cross horizontal ladder
- pressure sensors on rungs/bars allows to extract stepping pattern

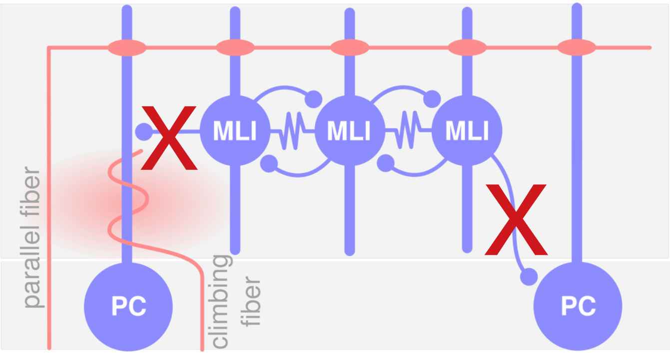
Erasmus lader: behavioral paradigm

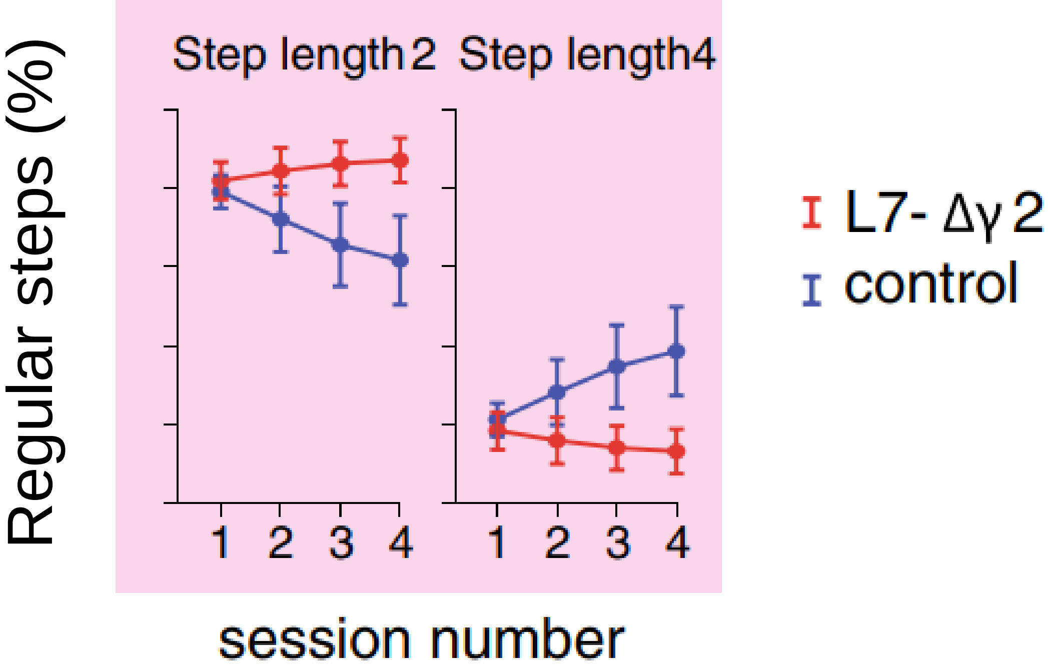


locomotion adaptation

- mice are challenged with the introduction of an obstacle
- obstacle was introduced by elevating one of the rungs, was preceded by a tone 200 ms prior to occurrence

Erasmus ladder: cerebellar inhibition knock-mice

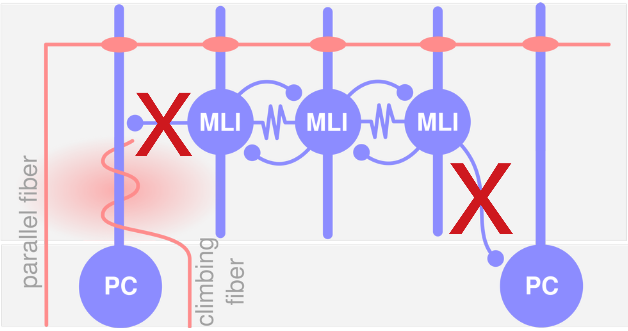


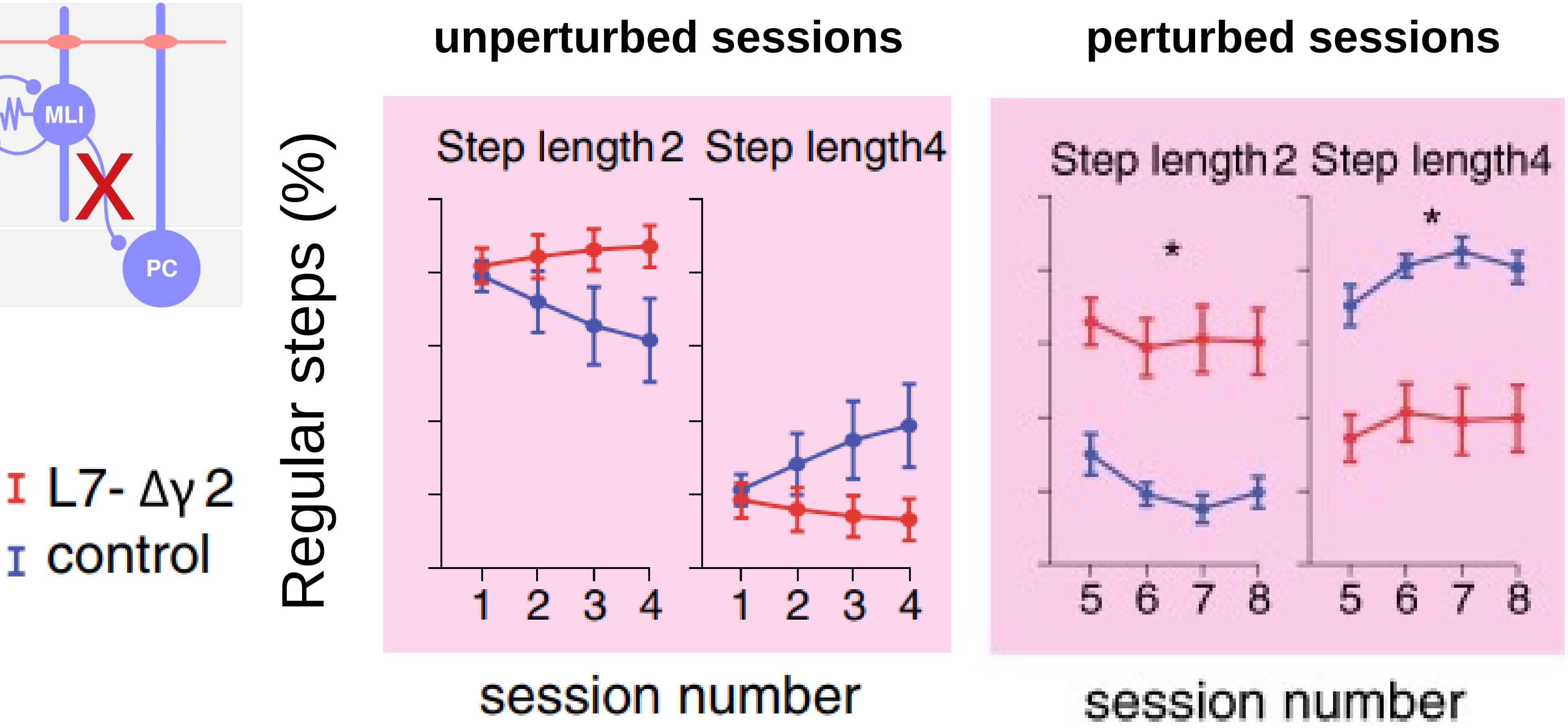


- locomotion learning is impaired in Purkinje cell inhibition knock-out mice (L7-Δγ2)

[Veloz *et al.* Brain Struct Funct 2015]

Erasmus ladder: cerebellar inhibition knock-mice



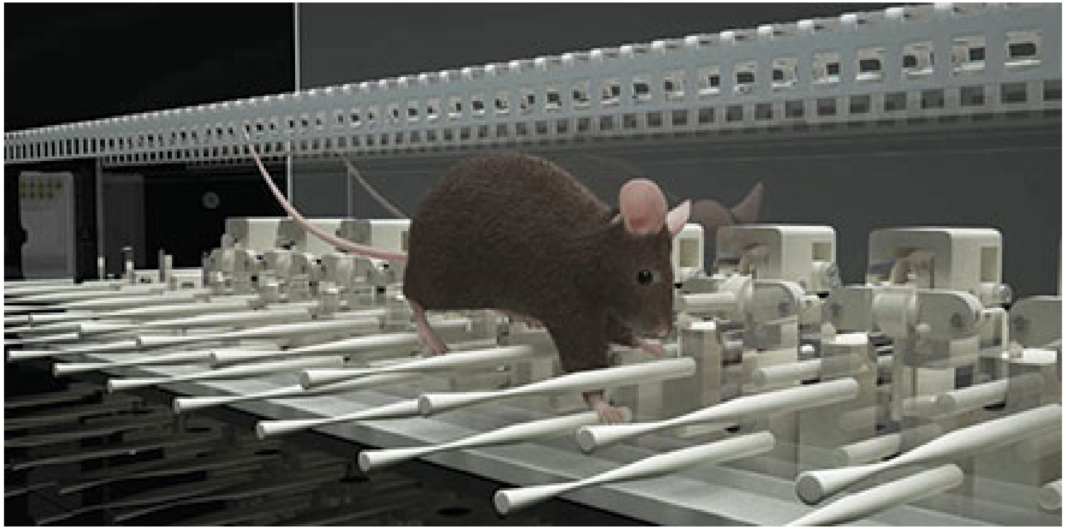


- locomotion learning and adaptation is impaired in Purkinje cell inhibition knock-out mice (L7-Δγ2)

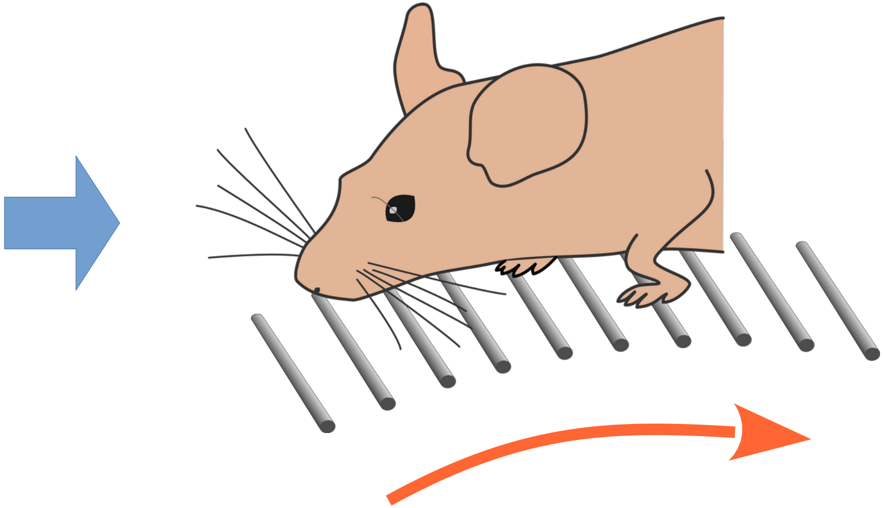
[Veloz *et al.* Brain Struct Funct 2015]

Task to study coordination on cellular level

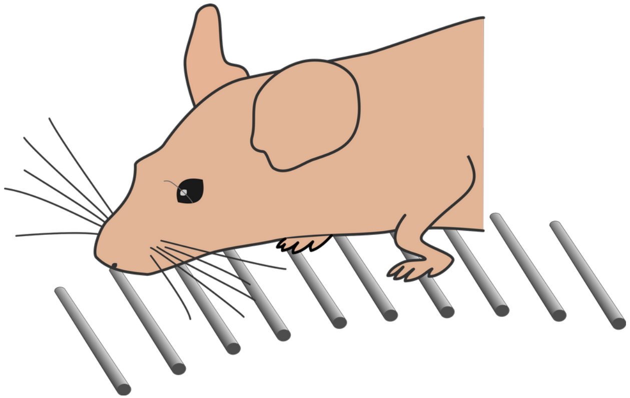
Erasmus Ladder



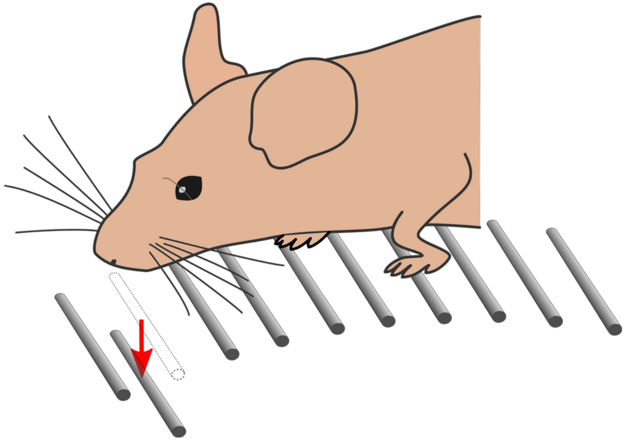
[Veloz *et al. Brain Struct Funct* 2015]



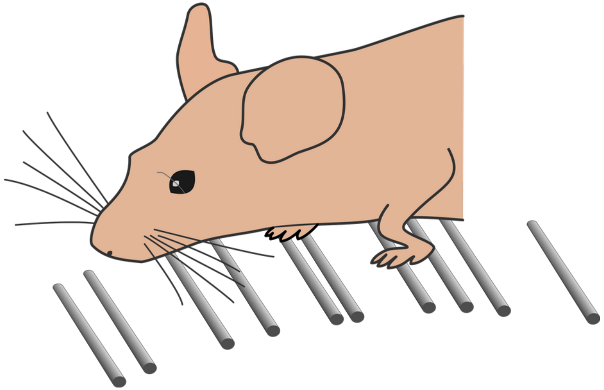
Task to study coordination on cellular level



1) Acquisition of a complex motor task

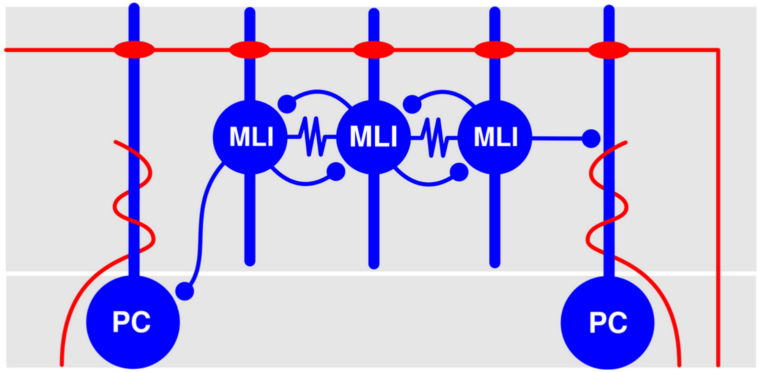


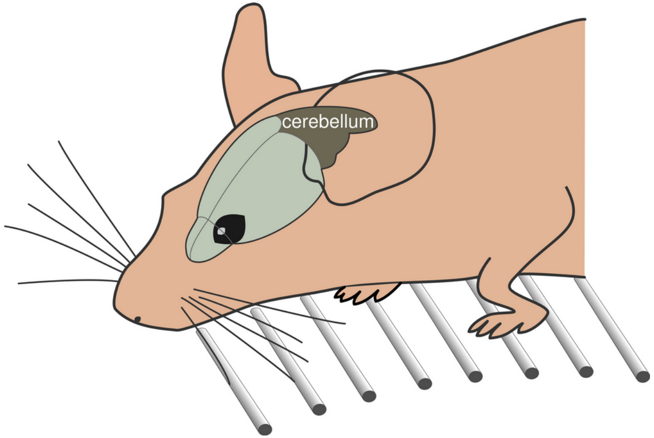
2) Adaptation to sudden environmental change



3) permanent changes of the motor plan in an irregular environment

Questions





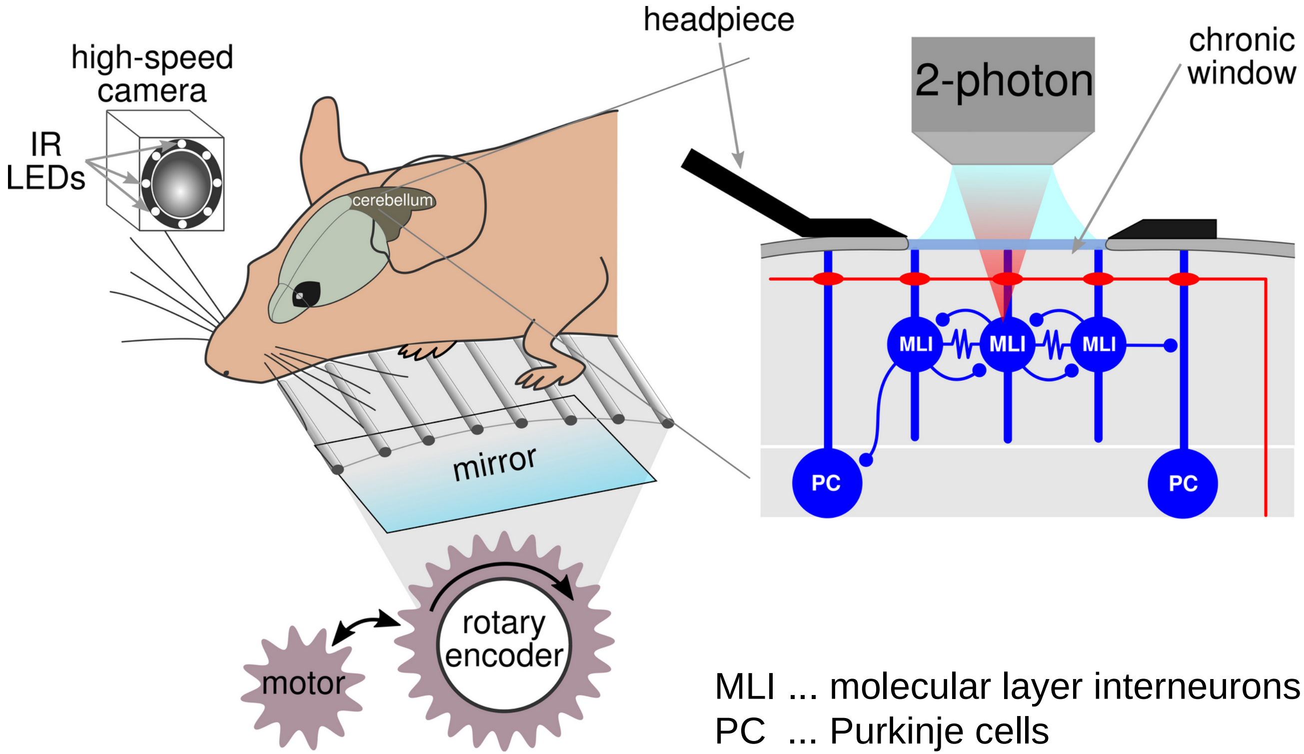
(1.) Which activity patterns occur in the interneuron network *in vivo* ?

(2.) What is the spatial spread of inhibition ?

(3.) How is the activity in the interneuron network linked to motor behavior?

→ What is the link between microcircuit connectivity, activity regimes and the role in motor behavior ?

Experimental methods and setup



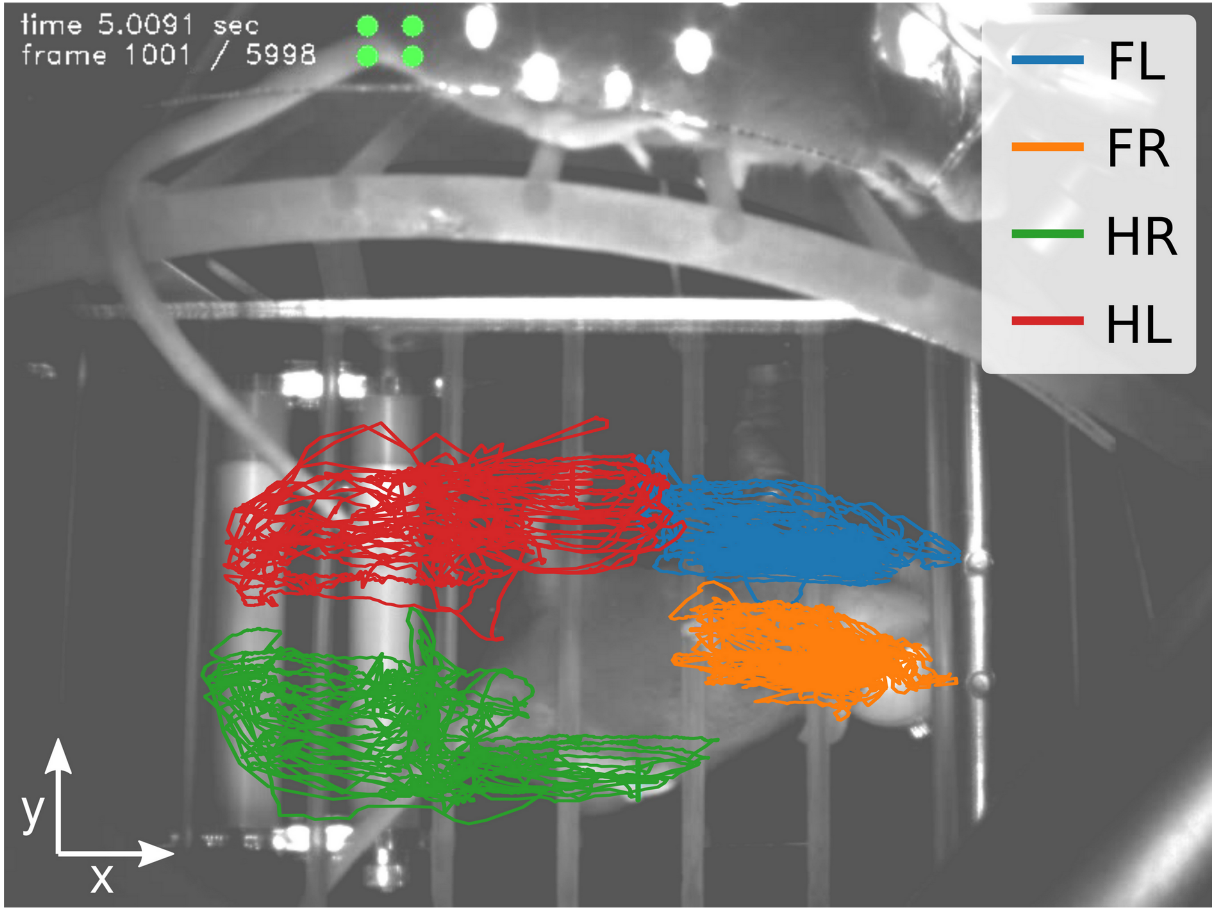
MLI ... molecular layer interneurons
PC ... Purkinje cells

- calcium imaging from MLIs
- electrophysiological recordings from MLIs
- lobule IV/V in Vermis
- mice : reporter GCaMP6f-Tigre x promoter PV-Cre

Mouse walking on treadmill with bars (rungs)

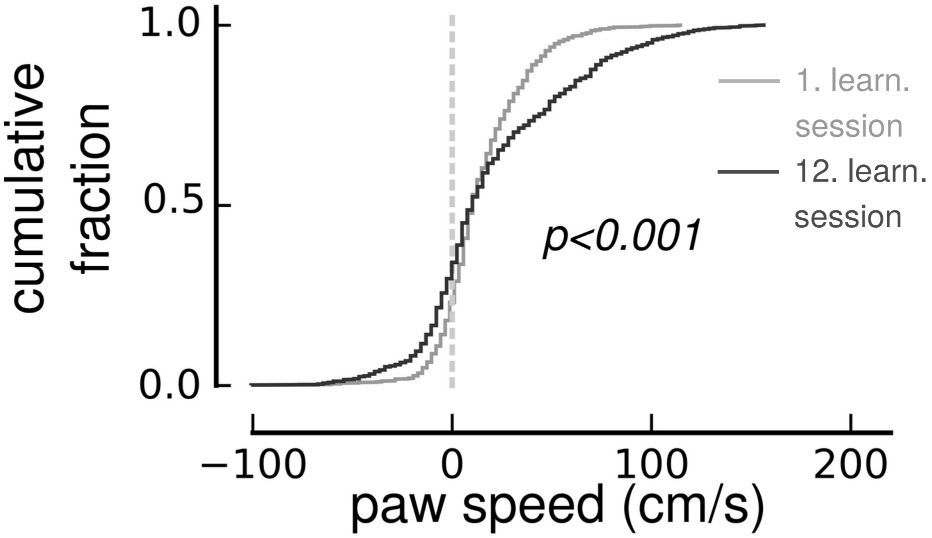
[video]

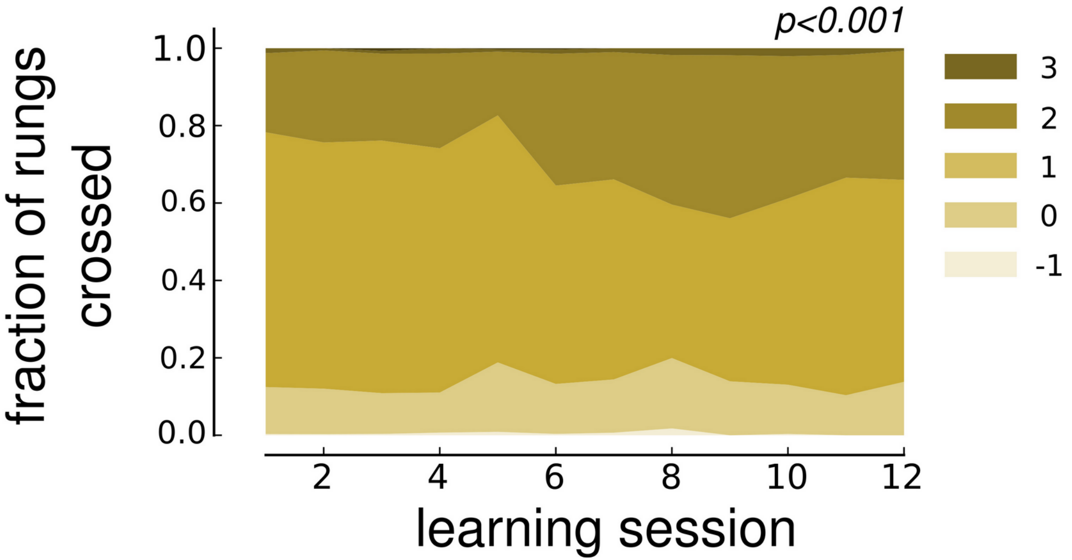
Extraction of paw trajectories with DeepLabCut



[Mathis *et al. Nat Neurosci* 2018]

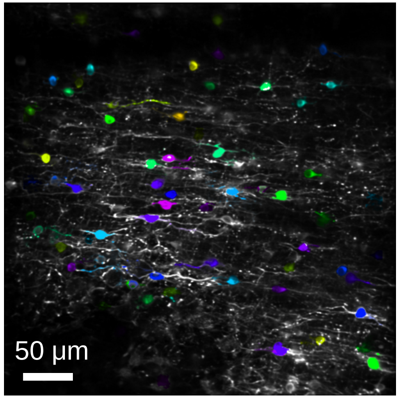
Evolution of paw trajectoris over learning sessions


stride speed histogram

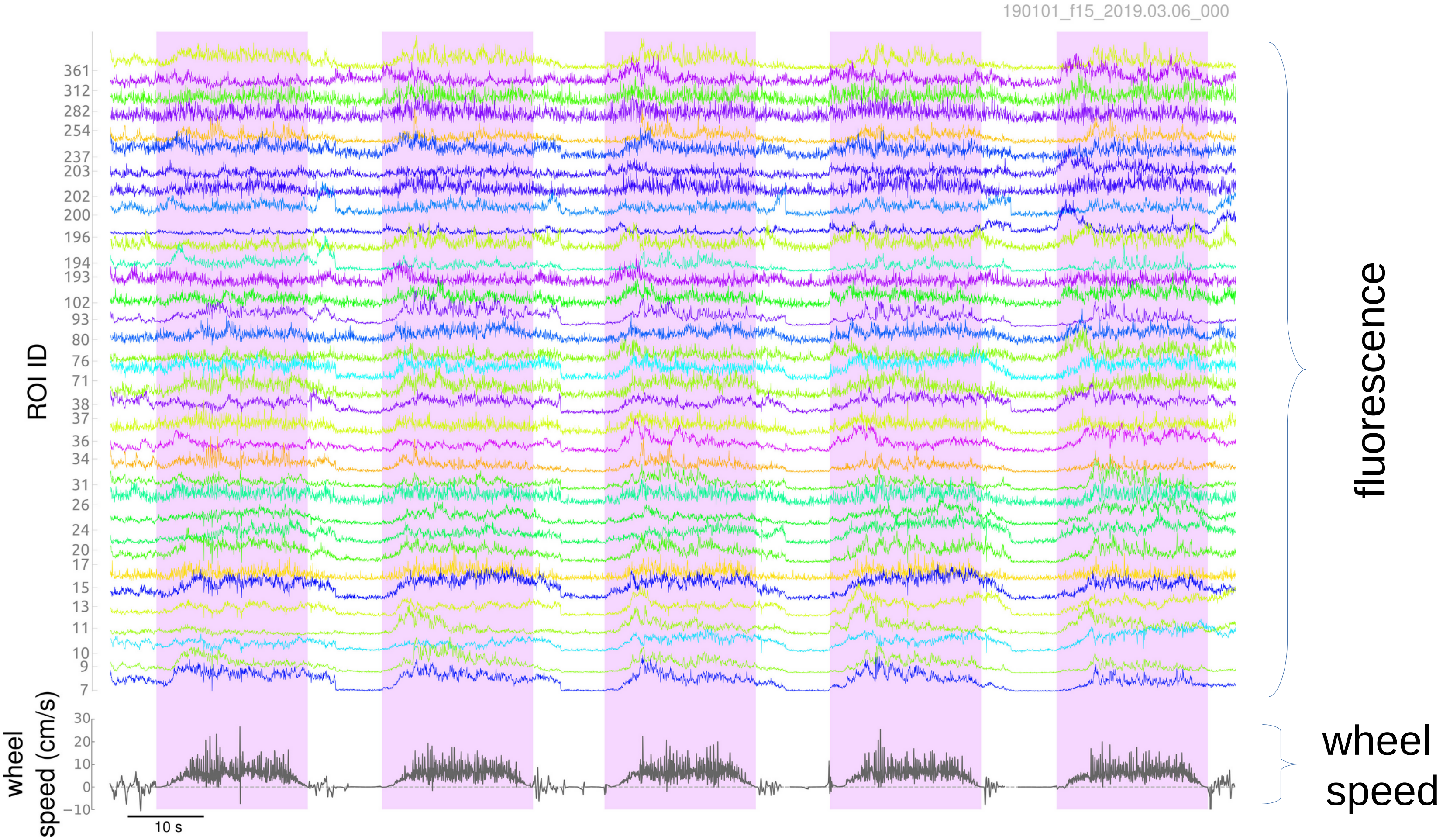

number of rungs crossed with single stride

example : FrontLeft paw

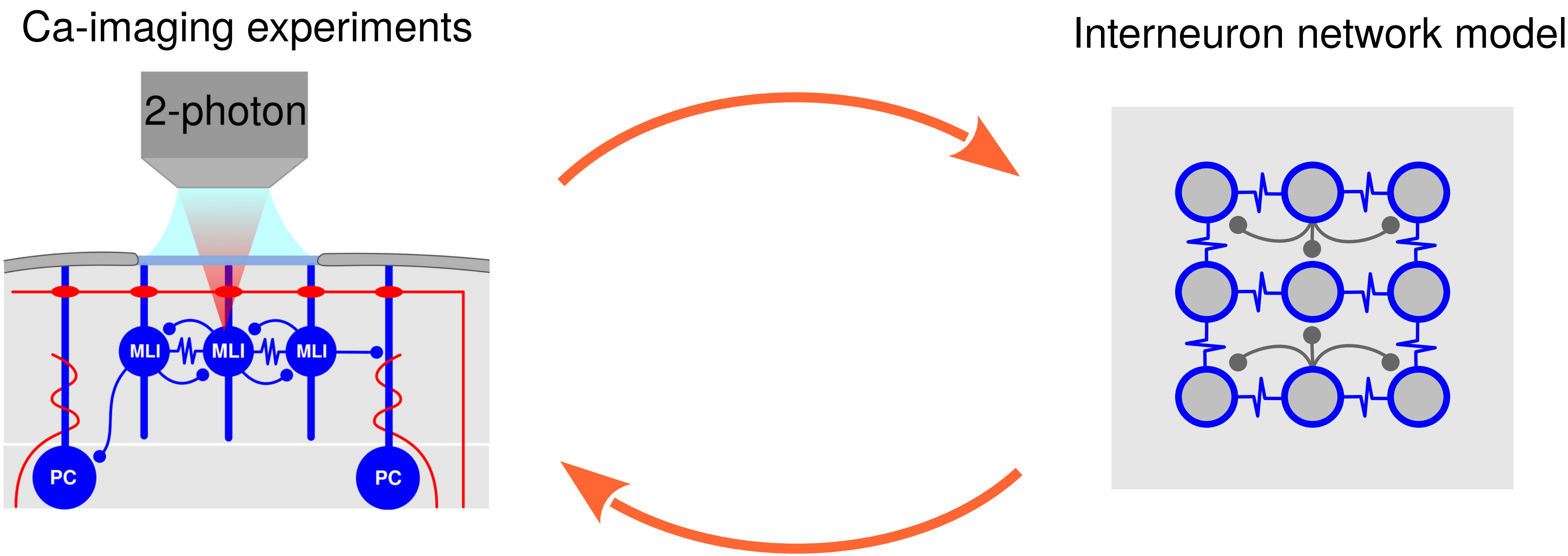
Interneurons exhibit locomotion related activity



67 ROIs

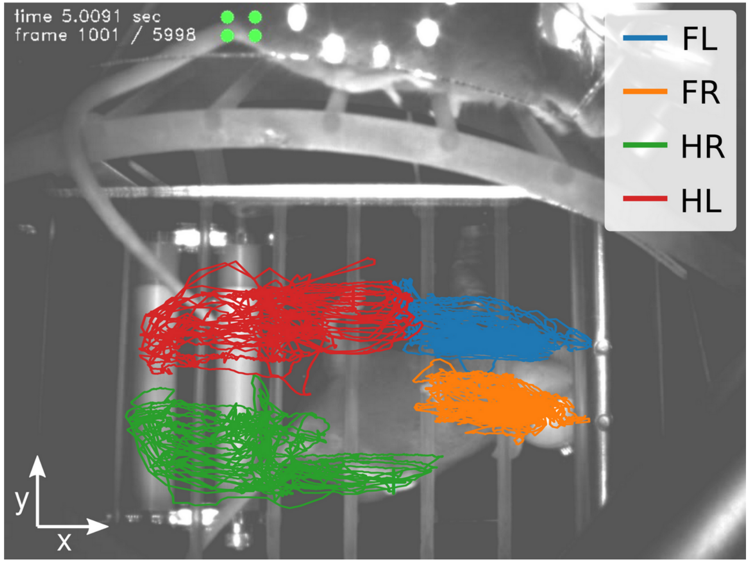


Experiments accompanied by neural network modelling



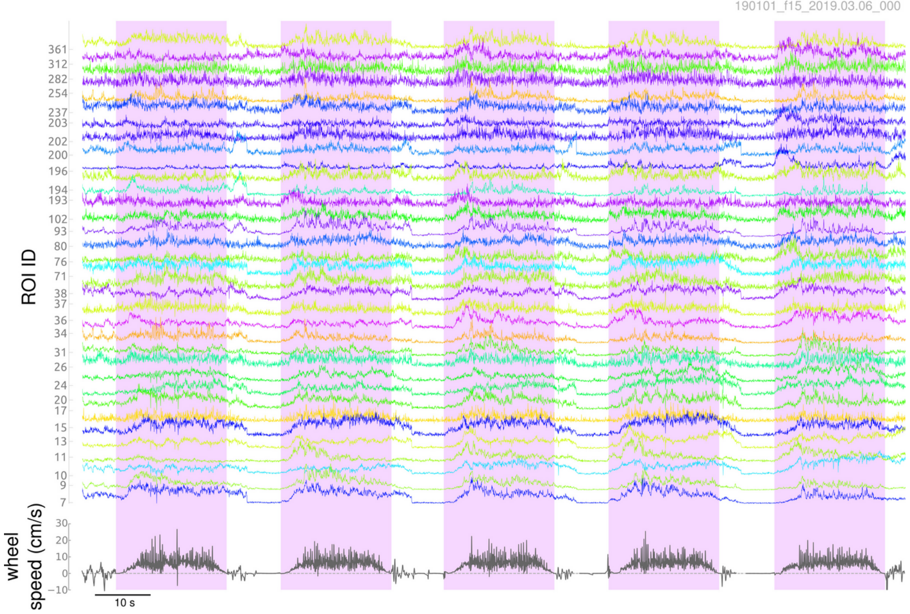
Linking individual paw movement with neural activity

paw trajectories/speed
stride length/precision



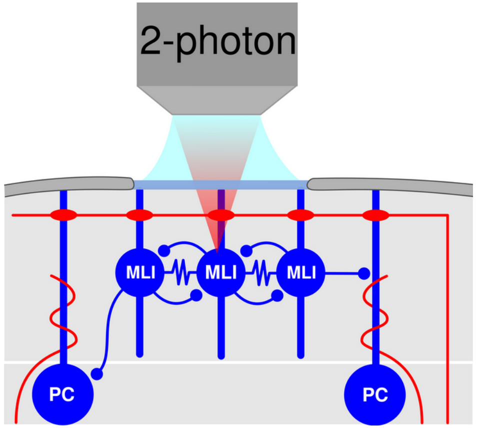
?

activity of interneuron
population

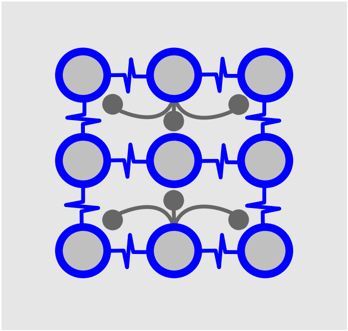


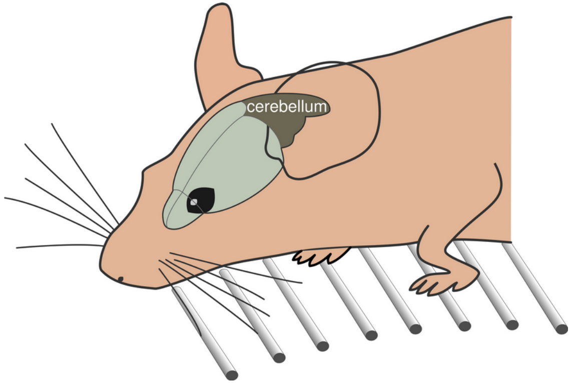
Linking activity to motor behavior and learning

Interneuron activity



Interneuron network model





motor behavior