Sainsbury Wellcome Centre

November 4, 2019

Cerebellar learning

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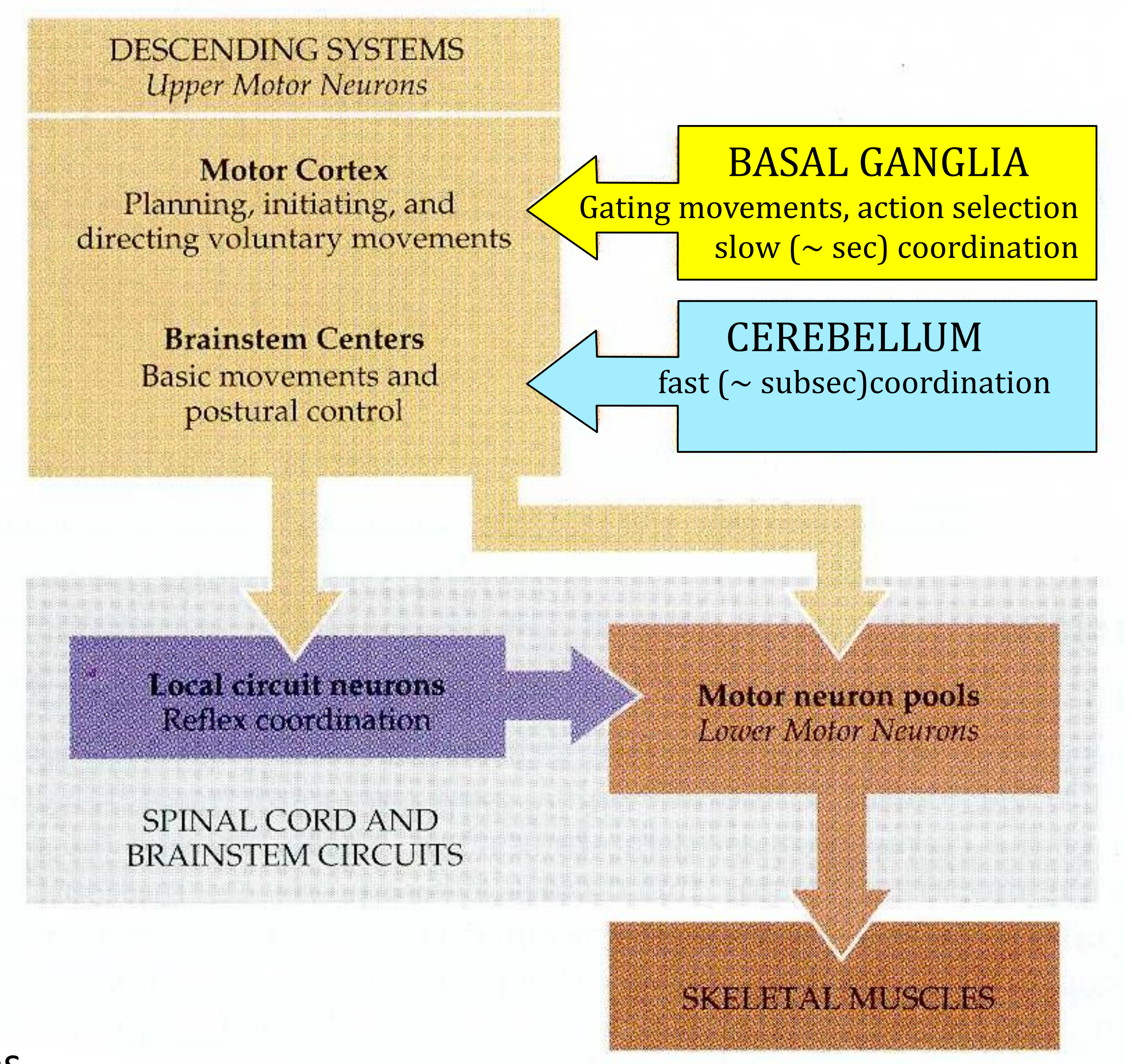
- Brief overview of cerebellum
- Behavioural aspects of cerebellar associative learning
- Some theory and a circuit mechanism
- Cellular mechanisms

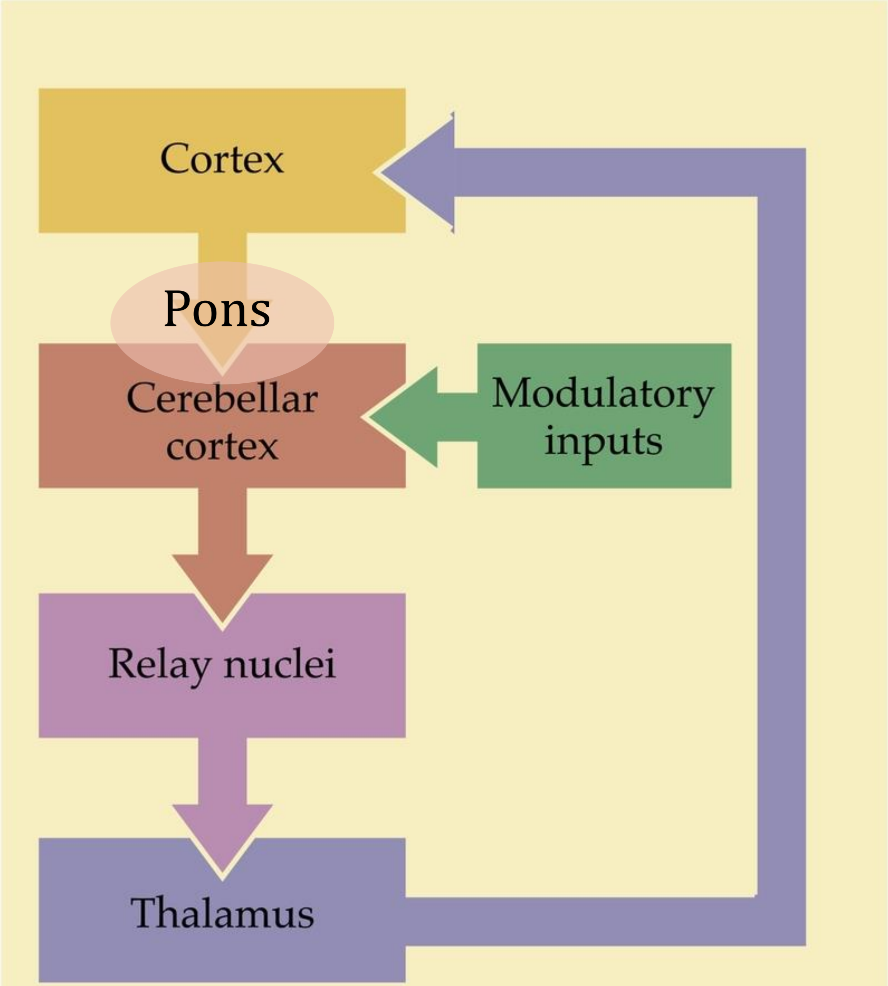
A simplified view of motor system output

The cerebellum functions as a rapid, corrective feedback loop, smoothing and coordinating movements.



from Fig. 15-1, Purves

Fast feedback loops for coordinating movement



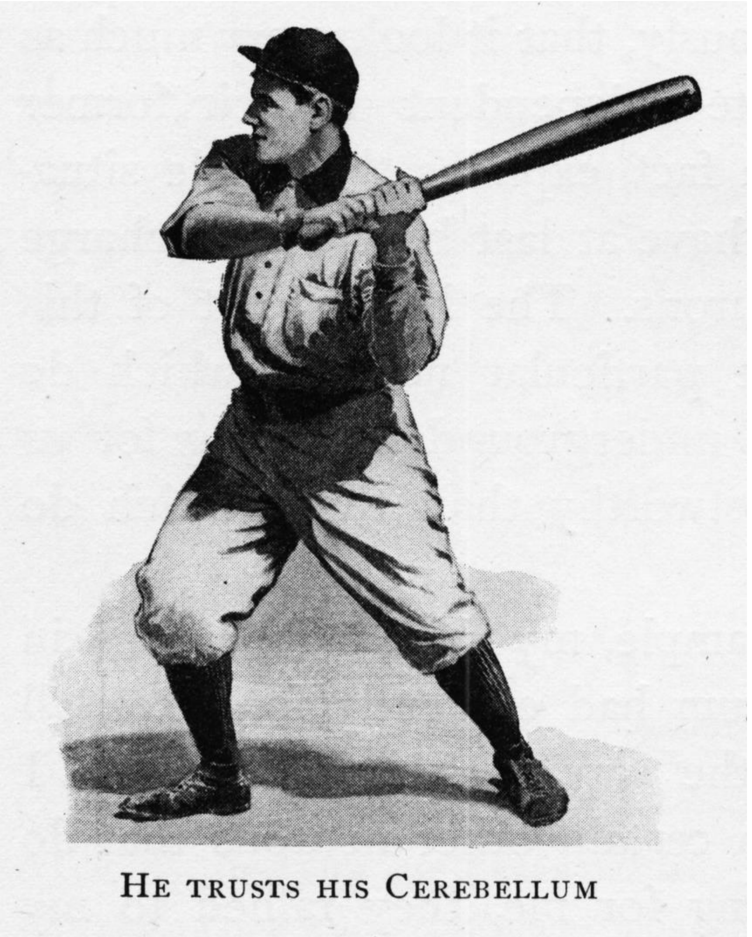
Purves, 18-7

Cerebellar lesions cause:
nystagmus
ataxia
dysdiadochokinesia
dysmetria
intention tremor

also, deficits in
motor learning

What kinds of information does the cerebellum receive?

- somatosensory
- visual
- auditory
- vestibular
- proprioceptive
- *efferent copy*



From *Control of Body and Mind*,
Gulick Hygiene Series, 1908

Nerves are slow relative to movement speed coordination requires *prediction*

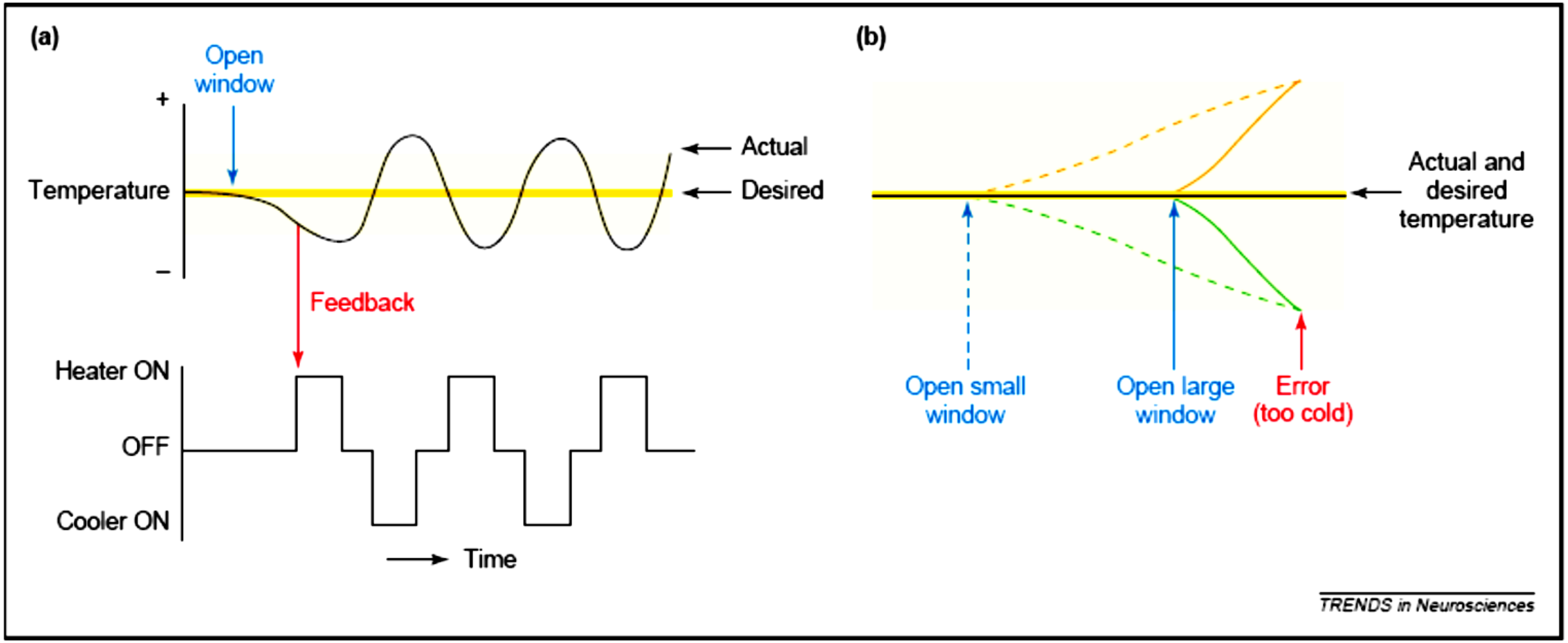
Usain Bolt, 100 m WR: 9.58 s

conduction velocity of many nerve fibers is ~10 m/s

some humans run at ~ 10 m/s

To adapt quickly, control systems must anticipate

i.e. a ‘forward model’



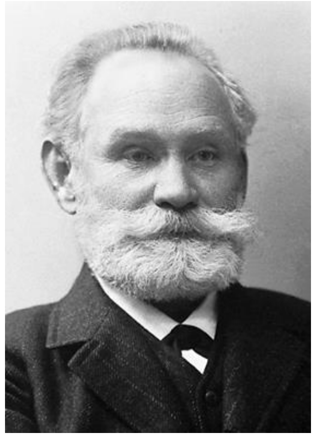
Ohyama et al., 2003

Behavioural aspects of cerebellar associative learning

Classical or Pavlovian conditioning

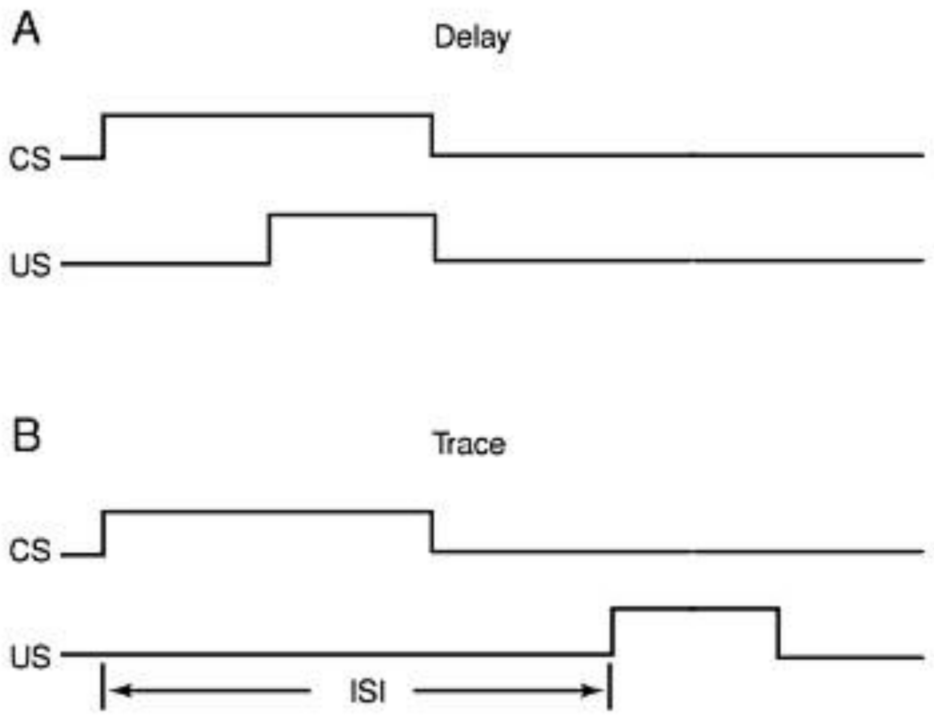
A form of associative learning in which a conditioned stimulus (CS) is linked to an unconditioned stimulus/response (US/UR).

After learning the CS elicits a conditioned response (CR) when delivered by itself.



Ivan Pavlov
Nobel Prize, 1904

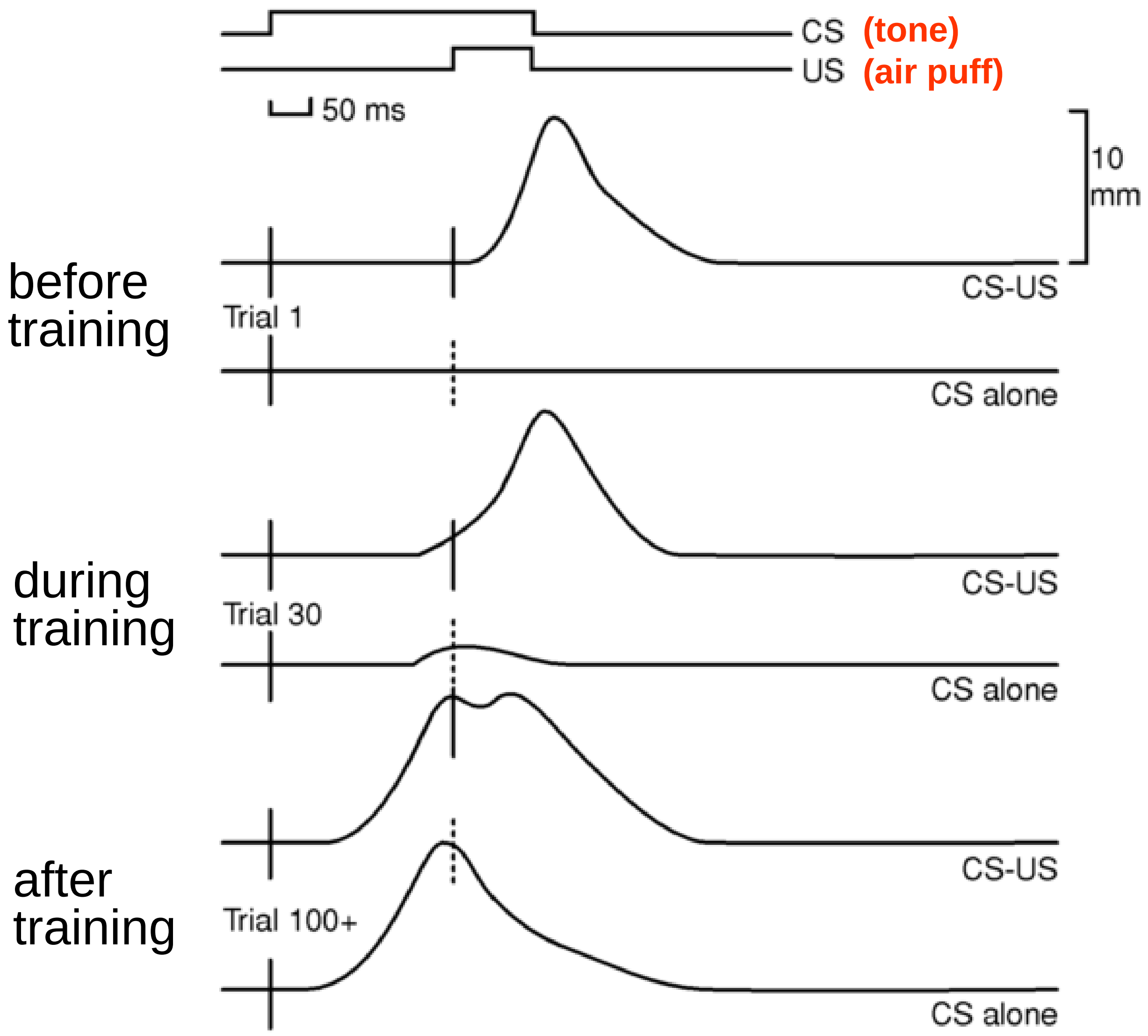
Paradigms for classical conditioning:



Cerebellar lesions disrupt delay conditioning

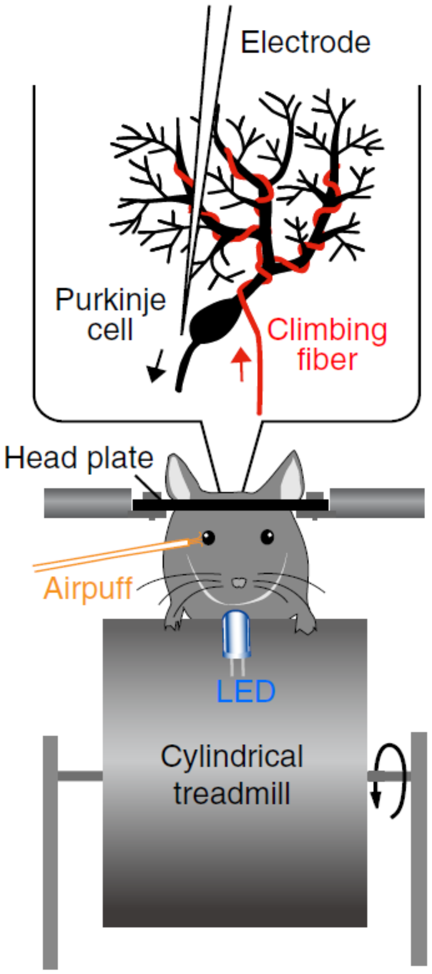
Both cerebellar and hippocampal lesions disrupt trace conditioning

Eyelid movements during a classical conditioning experiment

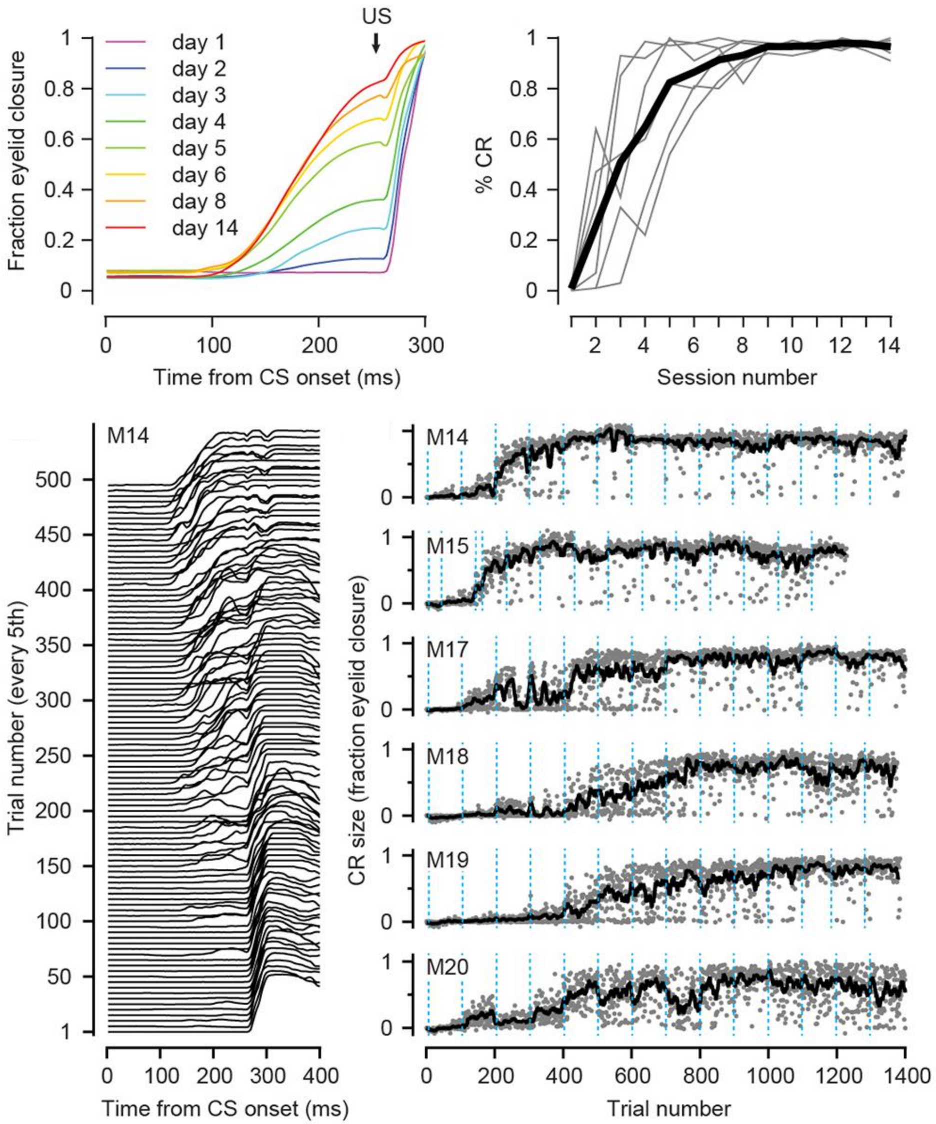


Zigmond et al., 1999

Mouse eyeblink data

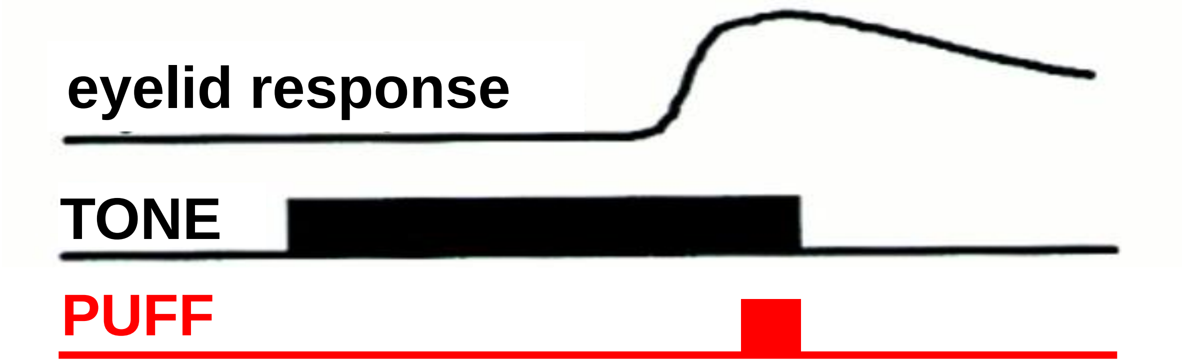


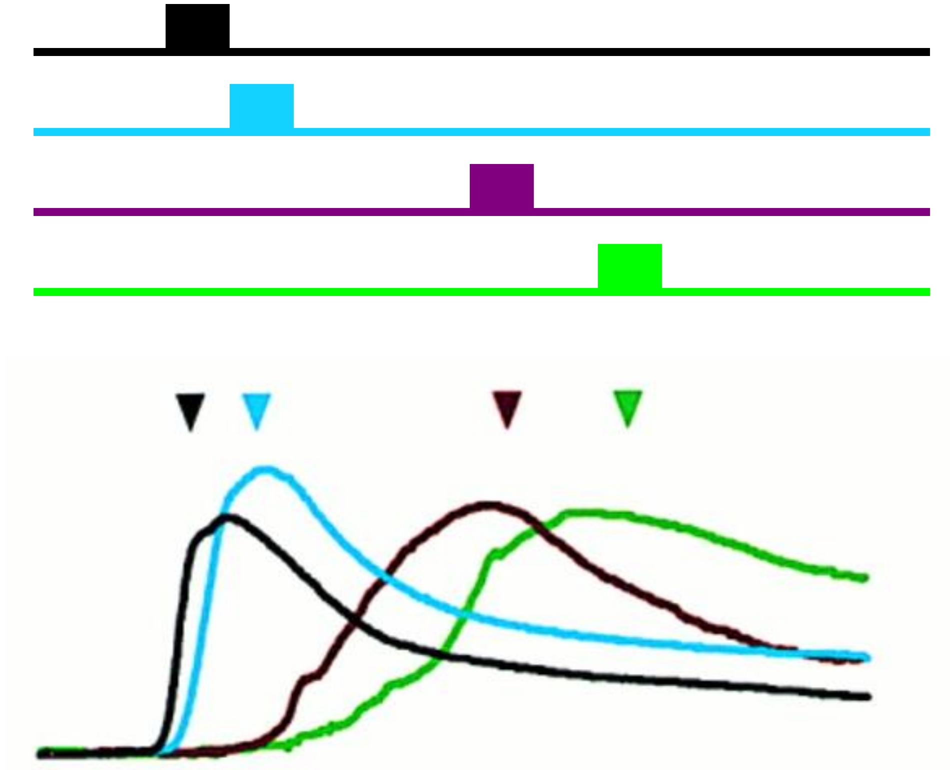
250 ms CS: LED US: Airpuff



Heiney et al, *J. Neurosci.*, 2014

Timing of learned responses dictated by CS-US timing during training



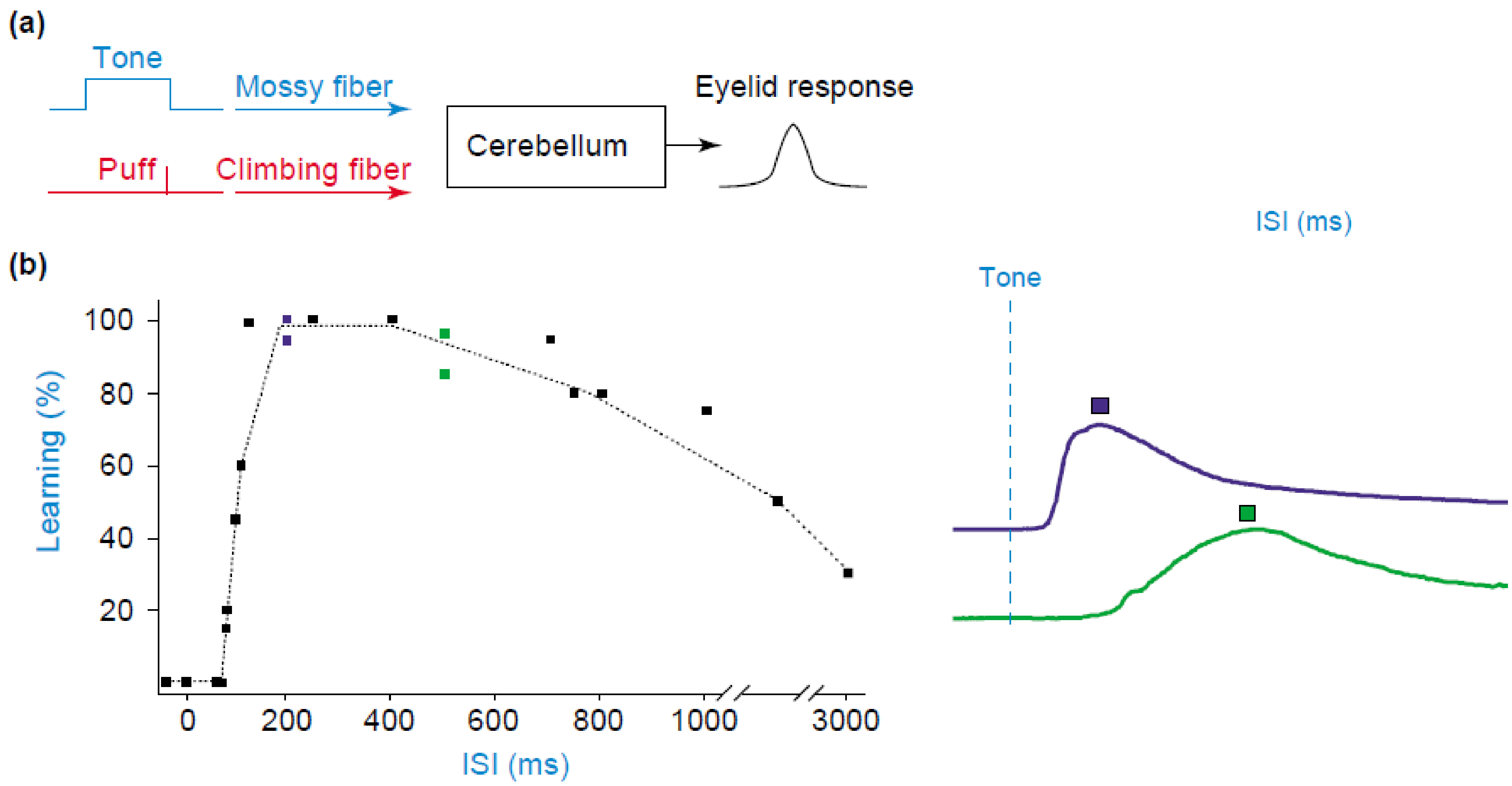


differently timed puffs during training

responses after training

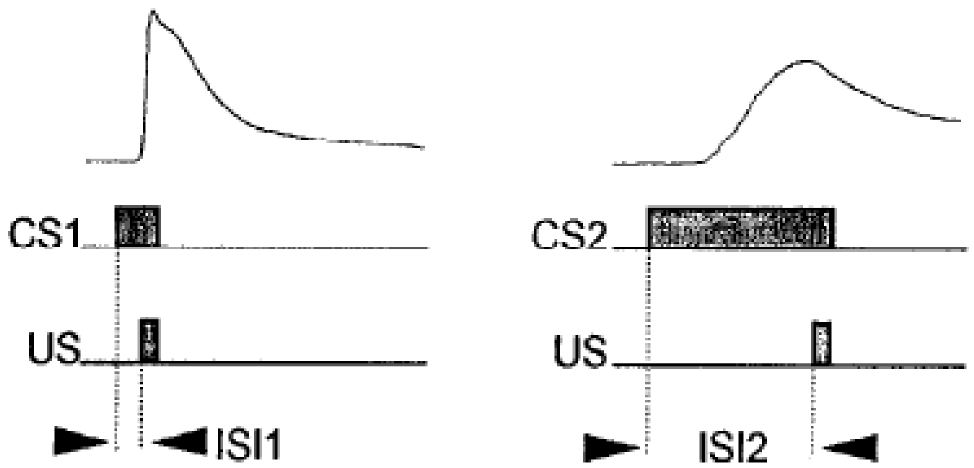
from Mauk et al.,1998

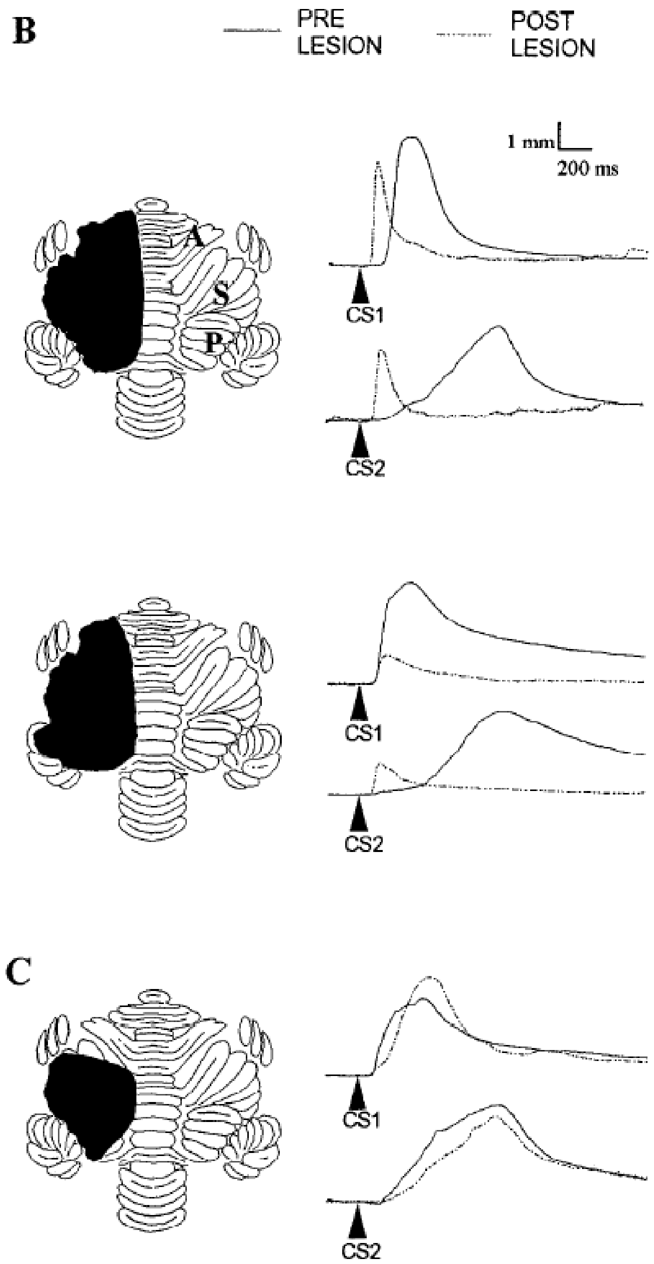
Learning is robust for CS-US intervals of 100 ms to 1 second



Ohyama and Mauk 2003

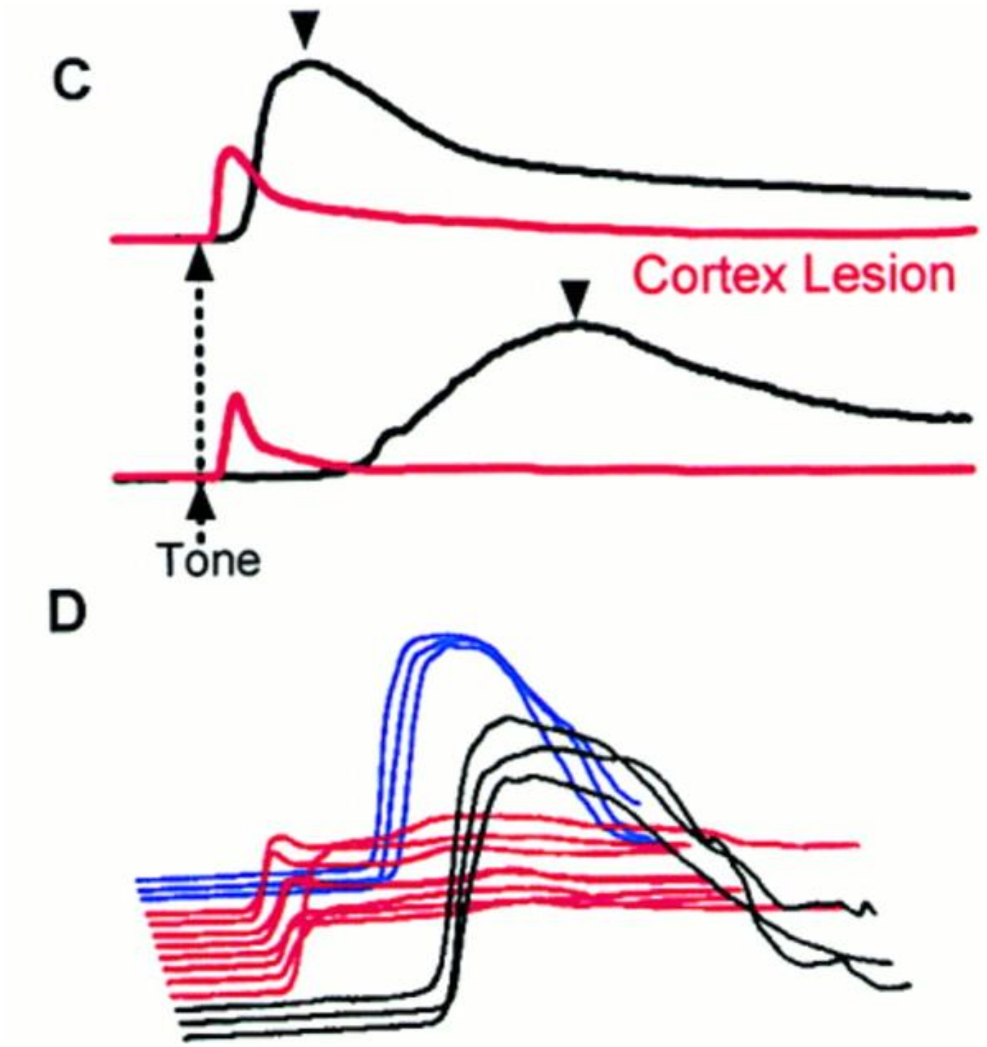
Lesions of cortex alter but do not block memories





Perrett et al., *J. Neurosci.* 13:1708, 1993

Lesions and pharmacological inactivation of cerebellar cortex cause improperly timed learned responses after eyeblink conditioning.

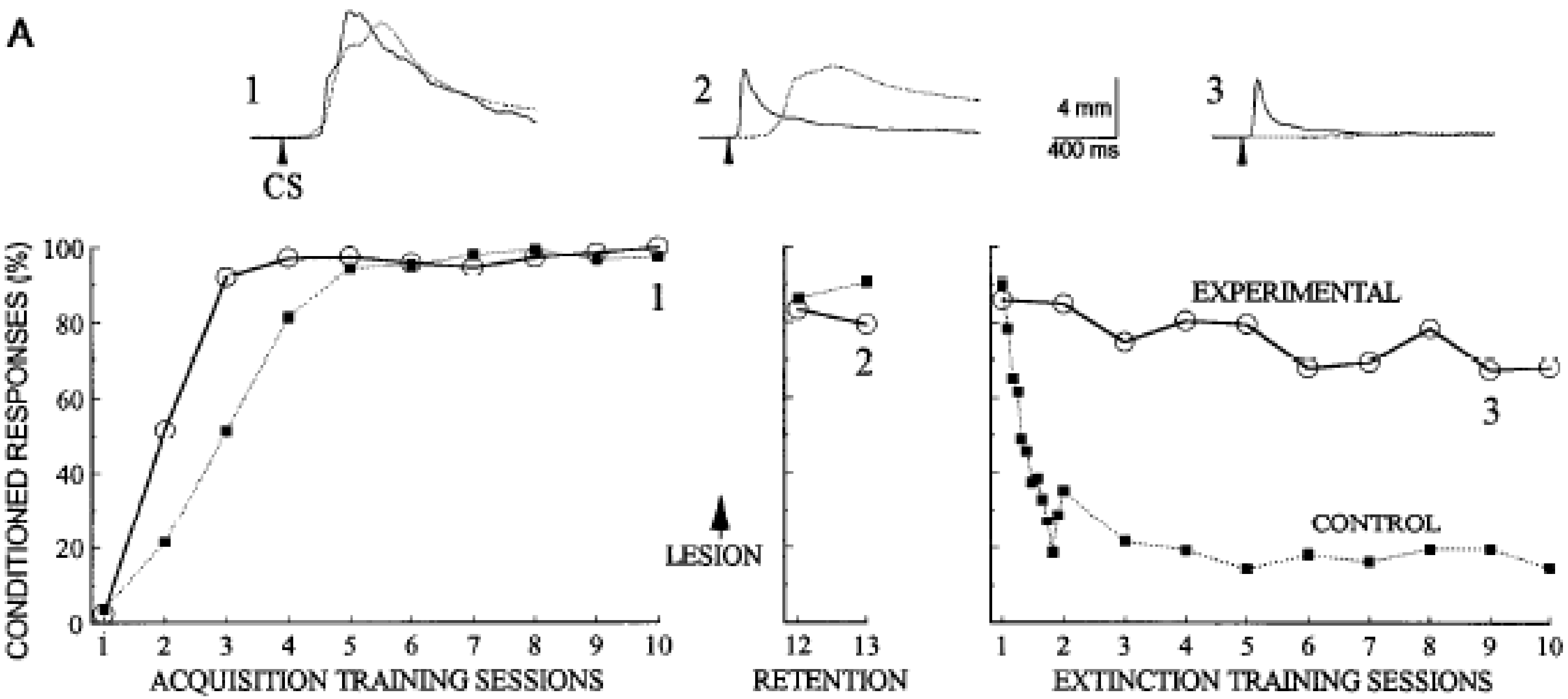


Mauk et al.,1998

Lesions of cerebellar cortex (anterior lobe)

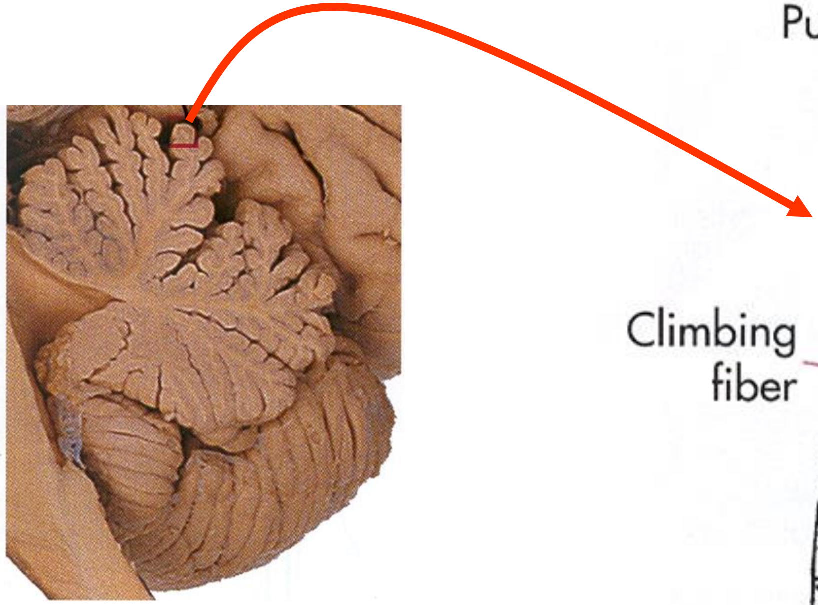
$GABA_A$ receptor antagonist (picrotoxin) injected into interpositus nucleus

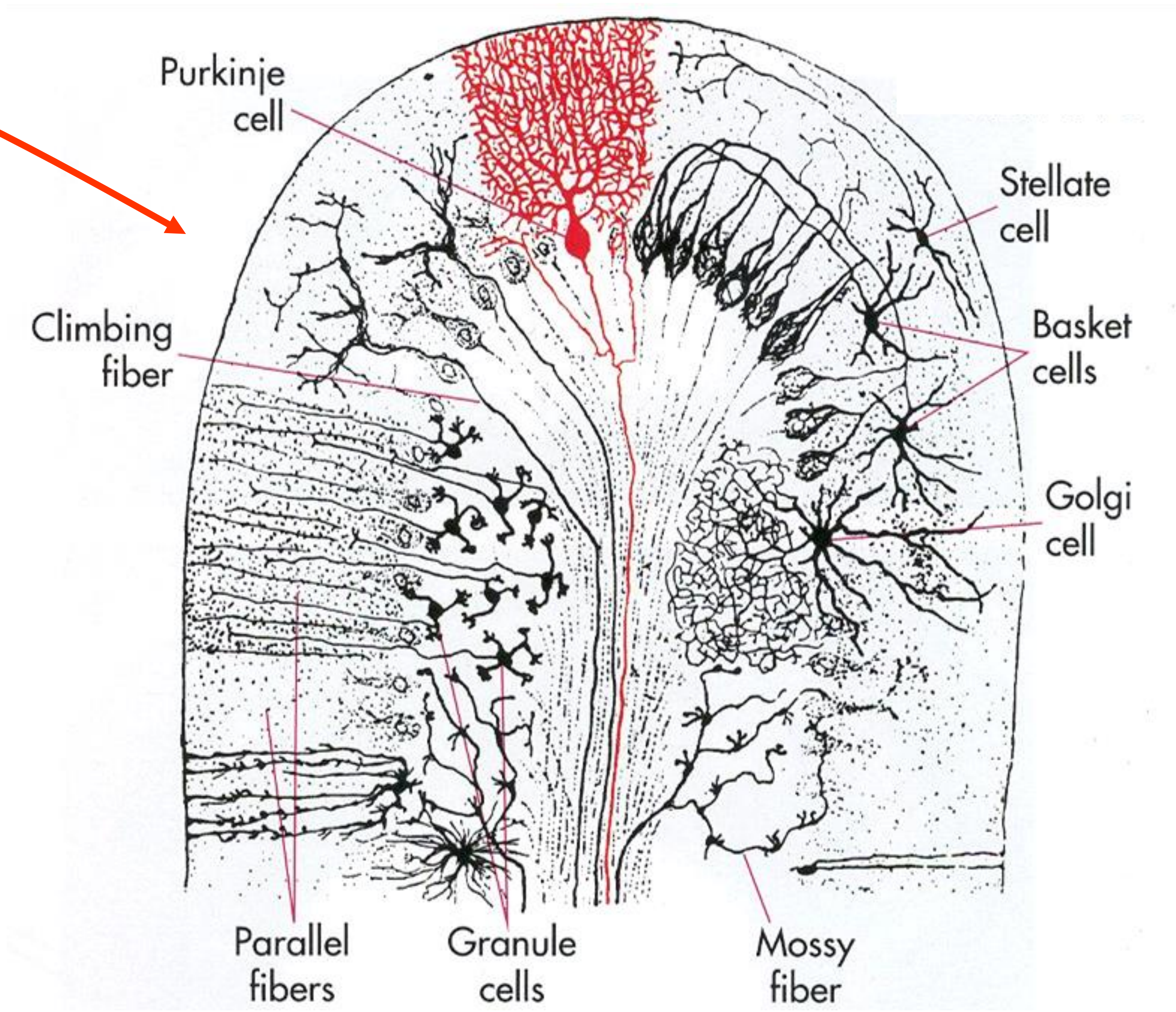
Extinction requires the cortex



Perrett and Mauk, *J Neurosci.* 15:2074, 1995

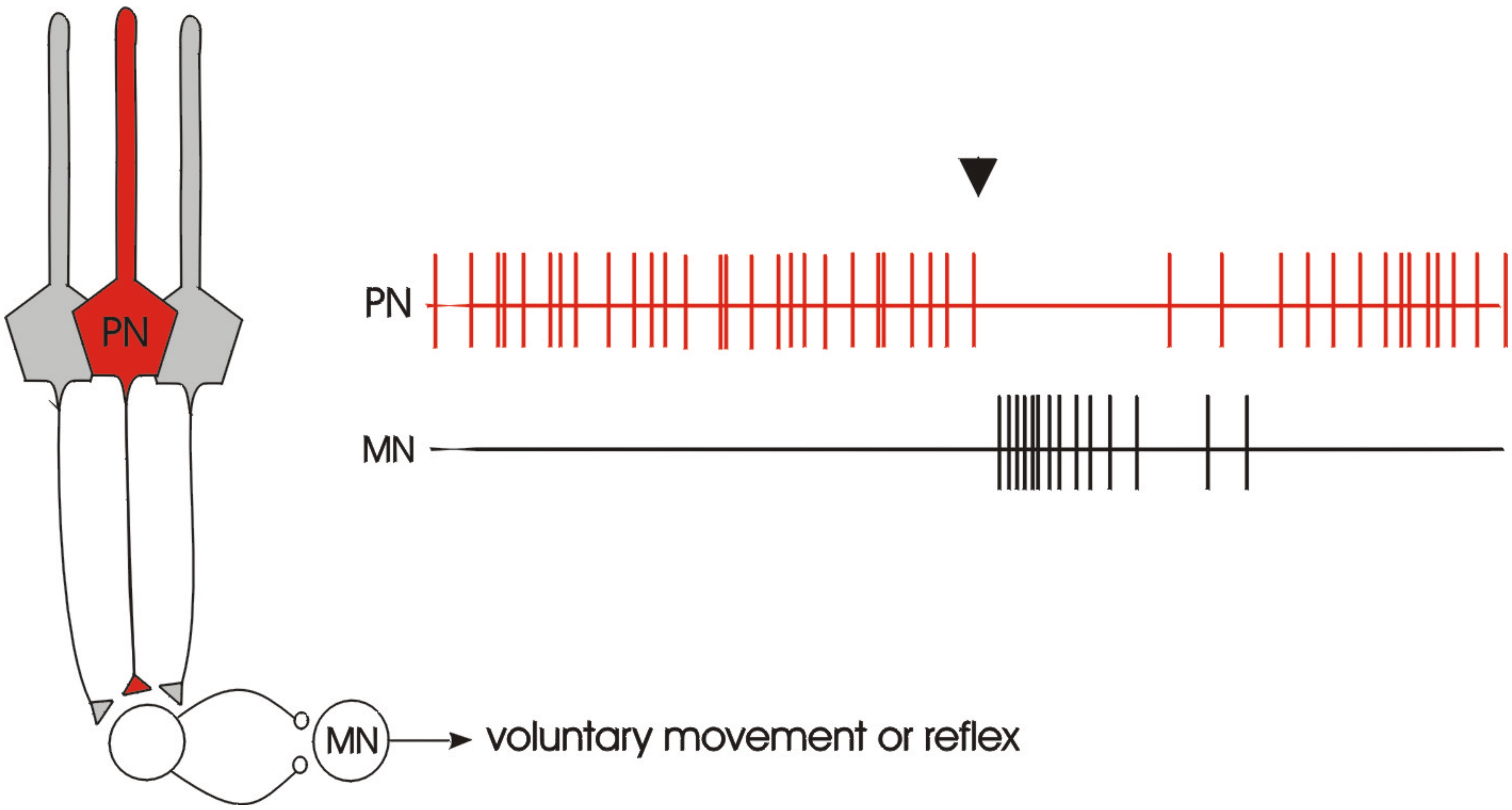
Cellular anatomy of cerebellum





20-10, Nolte

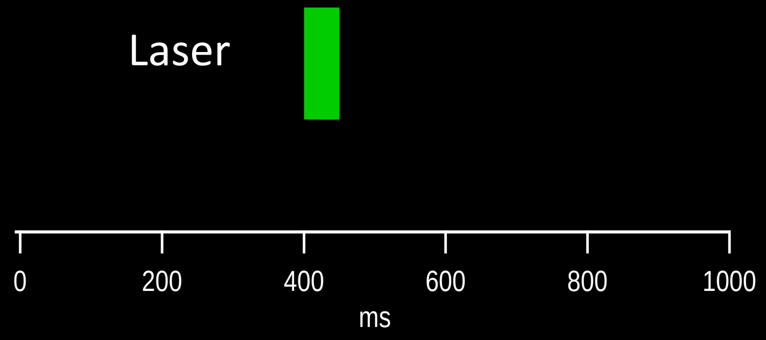
How does Purkinje neuron firing affect movement?

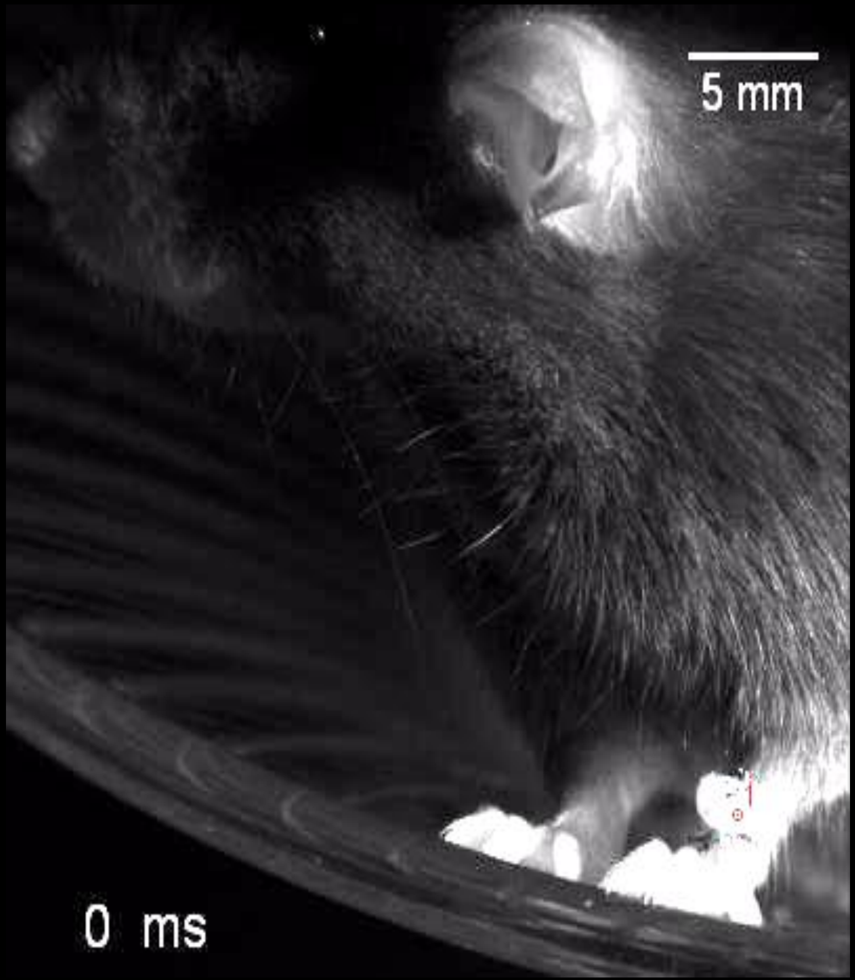


Purkinje neurons are inhibitory, thus when they slow or stop firing their targets are excited

Rapid, short latency arm movements triggered by brief PN inhibition

- Archearhodopsin (inhibitory opsin) expressed in PNs
- Optic fiber delivering 532nm laser light to forelimb region of cerebellar cortex

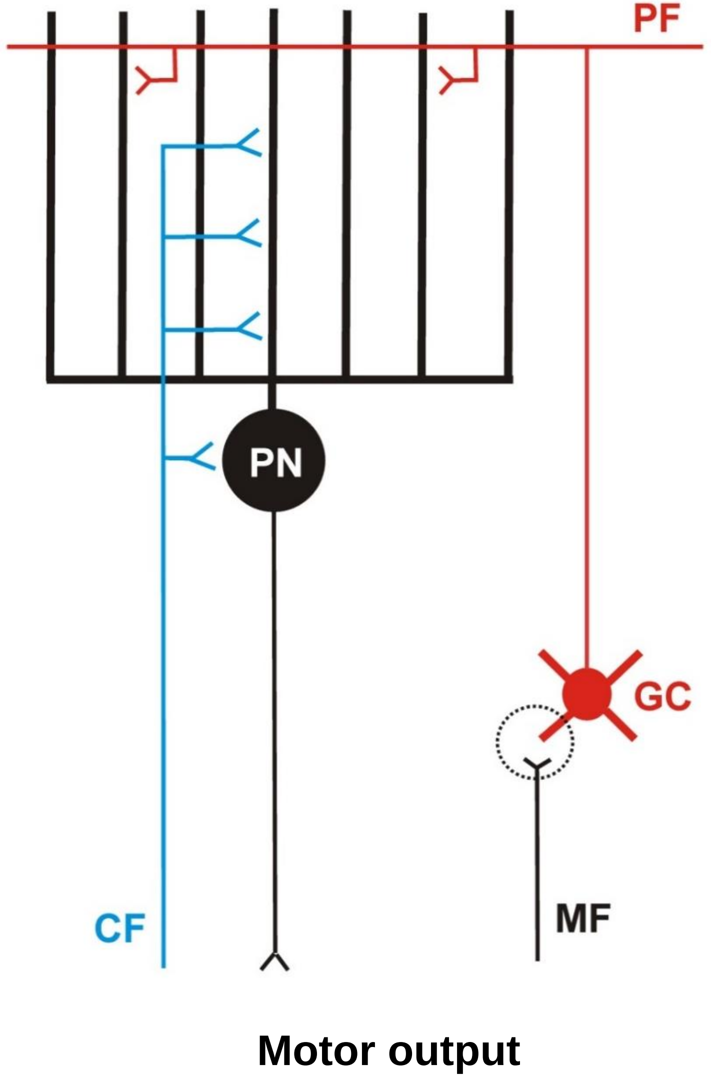




Lee, & Mathews et al, *Neuron*, 2015

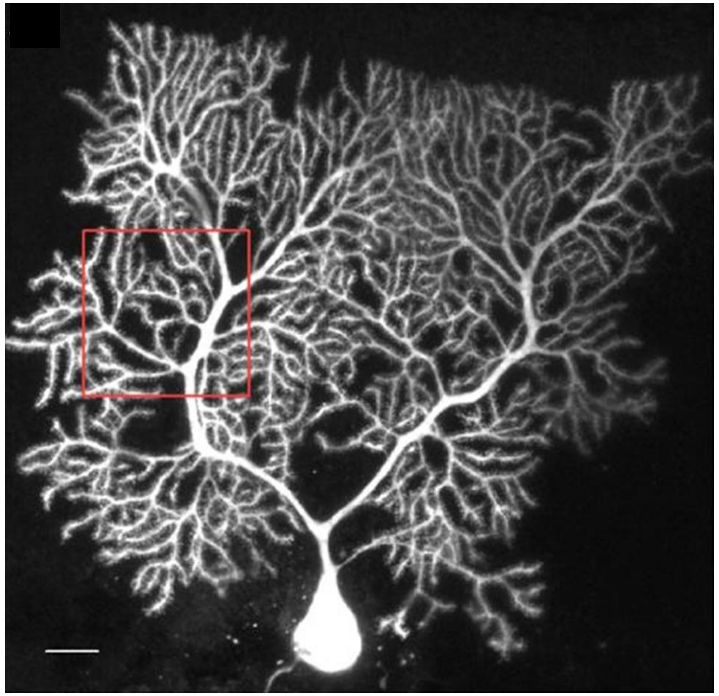
Circuit hypotheses for cerebellar associative learning

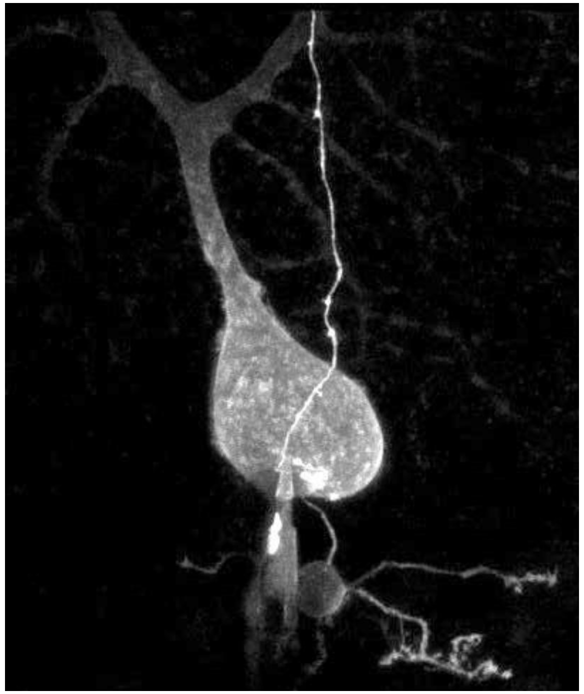
Two inputs to Purkinje cells transmit distinct types of information



Mossy Fiber (MF) to Parallel Fiber (PF) system
weak & highly convergent - the sensorimotor context

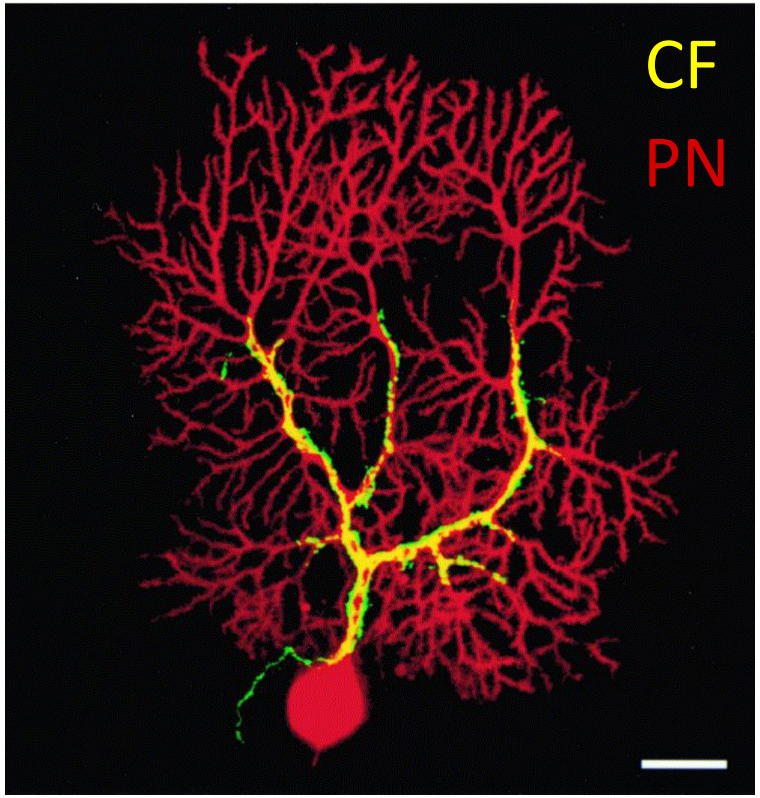
Climbing Fiber (CF) from the inferior olive
strong, one CF per PC - the instructive signal



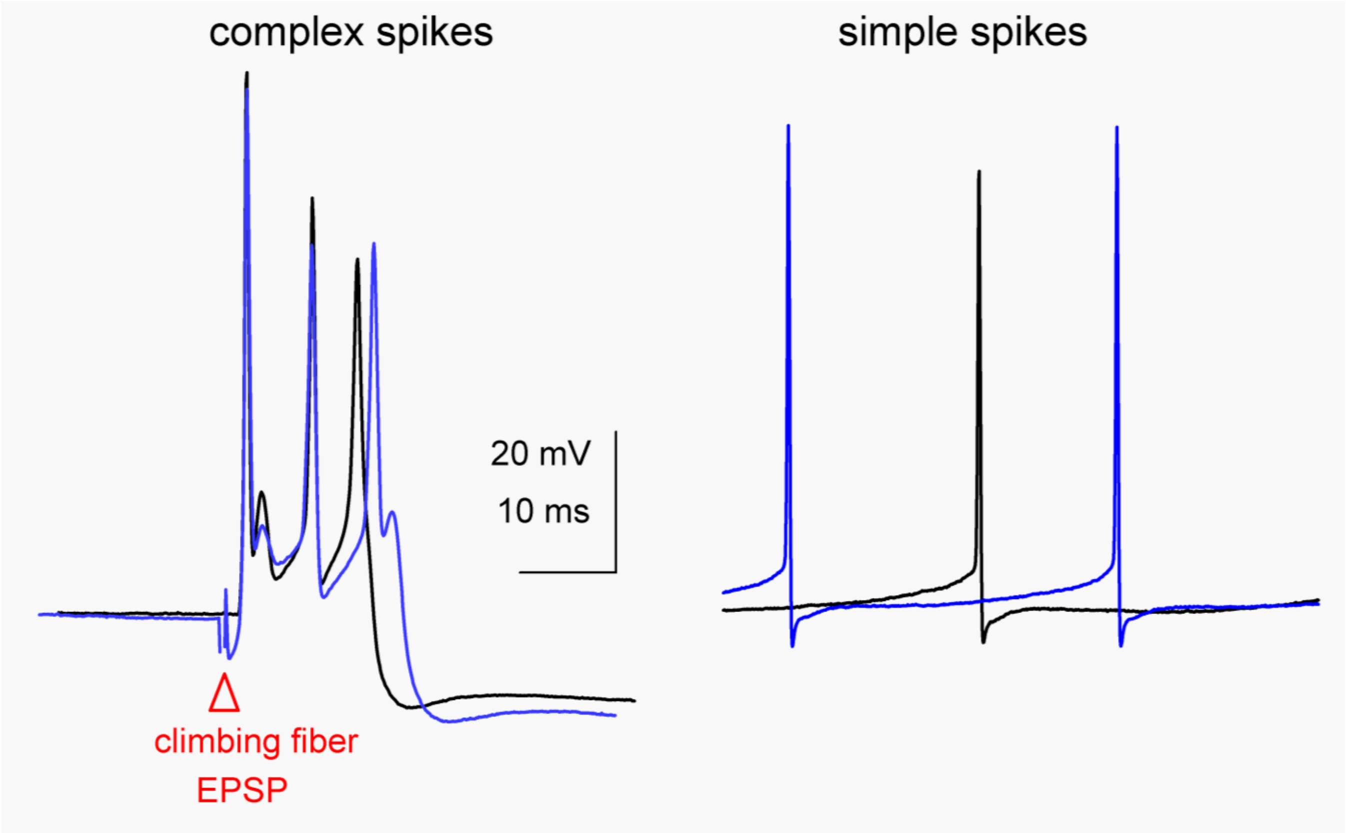


D. DiGregorio, Inst. Pasteur

CFs generate a unique, cell-wide signal



Kreitzer et al, 2000

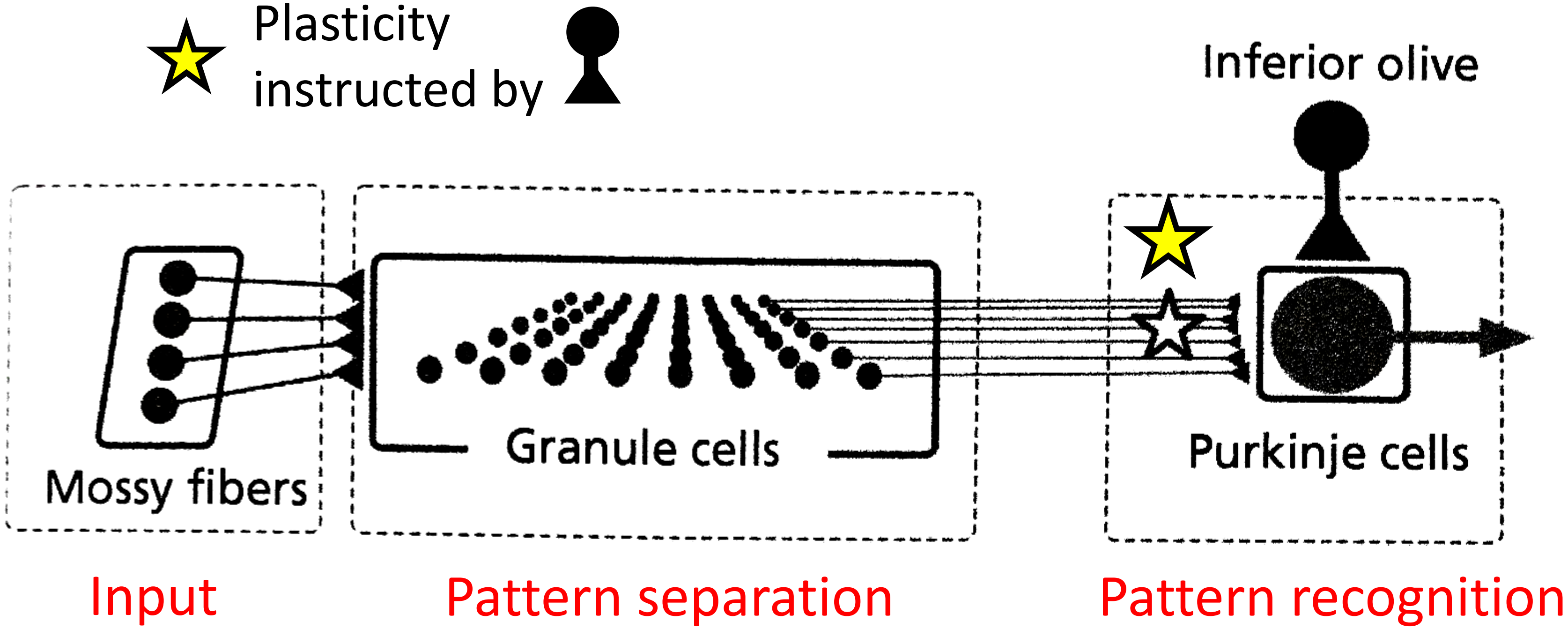


- Simple spikes are typical action potentials.
- Complex spikes occur in response to climbing fiber excitation.

Marr's theory for how the cerebellar cortex contributes to learning actions

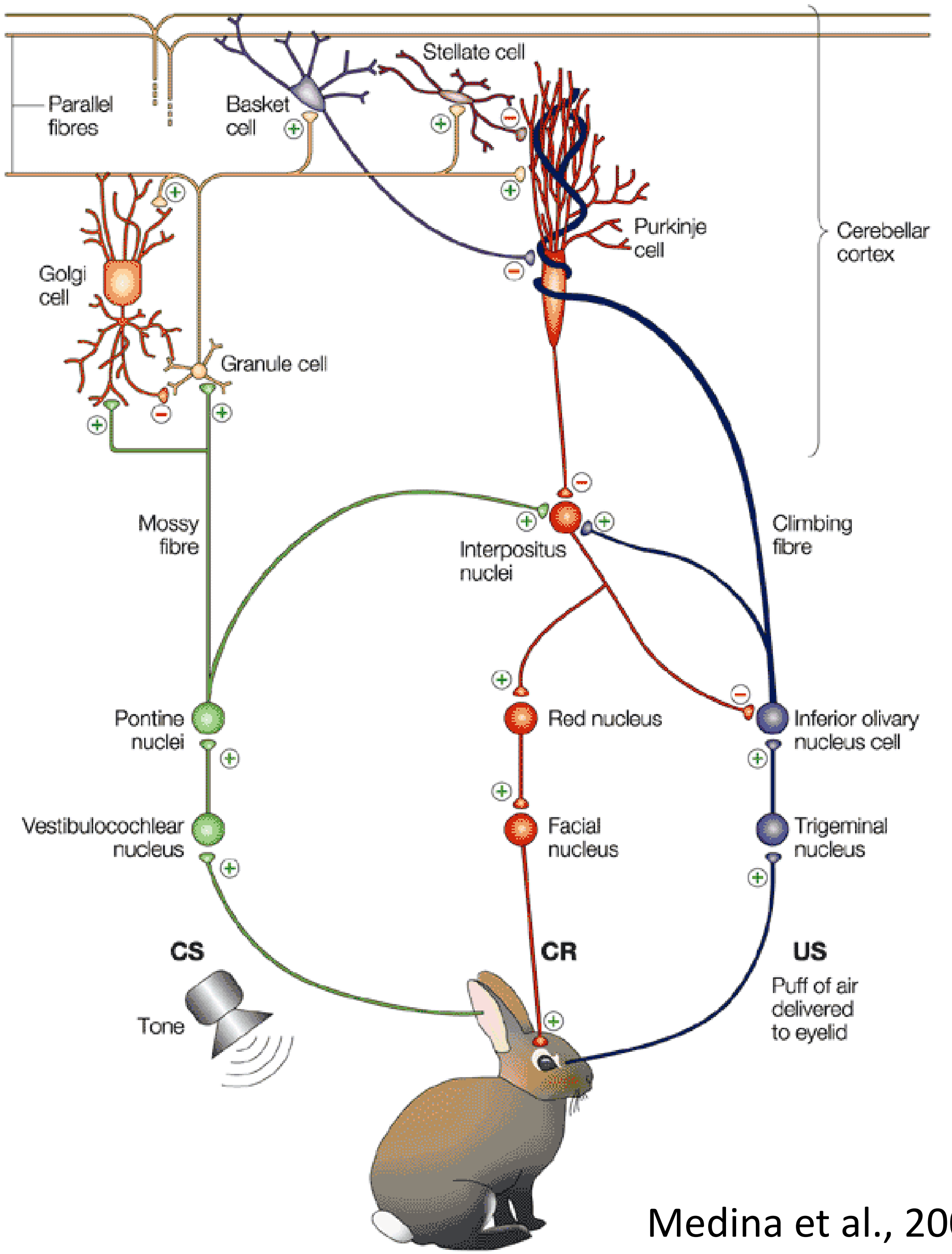
- Each PC can learn to recognise a number of contexts provided by the MF- GC pathway
- Olivary cells correspond to *elemental movements;* every action is composed of such elemental movements and actions are defined by patterns of olivary firing
- Parallel fiber synapses are strengthened upon coactivation of olivary inputs to PCs (Hebbian plasticity)

David Marr, 1970



Adapted from Ito in *Computational Theories and Their Implementation in the Brain*, Vaina & Passingham (Eds.)

Eyeblink conditioning circuitry

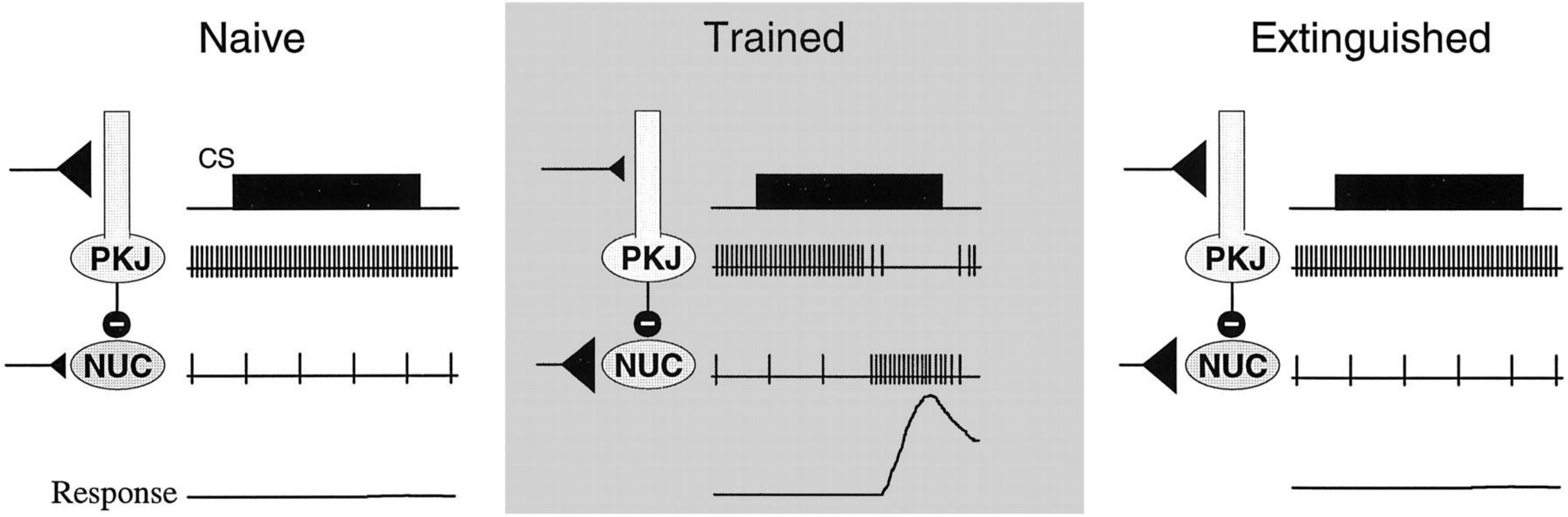


Medina et al., 2002

Evidence for the anatomical substrates of CS and US

- Lesions of the mossy fibers prevent learning (McCormick & Thompson, ‘84)
- Stimulation of the mossy fibers (pons) can substitute for the CS (Steinmetz et al, ‘89)
- Lesions of the olive (climbing fibers) prevent learning
- Stimulation of olive can substitute for the US (Mauk et al, ‘86)
- Inactivation of the climbing fibers extinguishes learning

What does the CF ‘teach’ the Purkinje neuron?

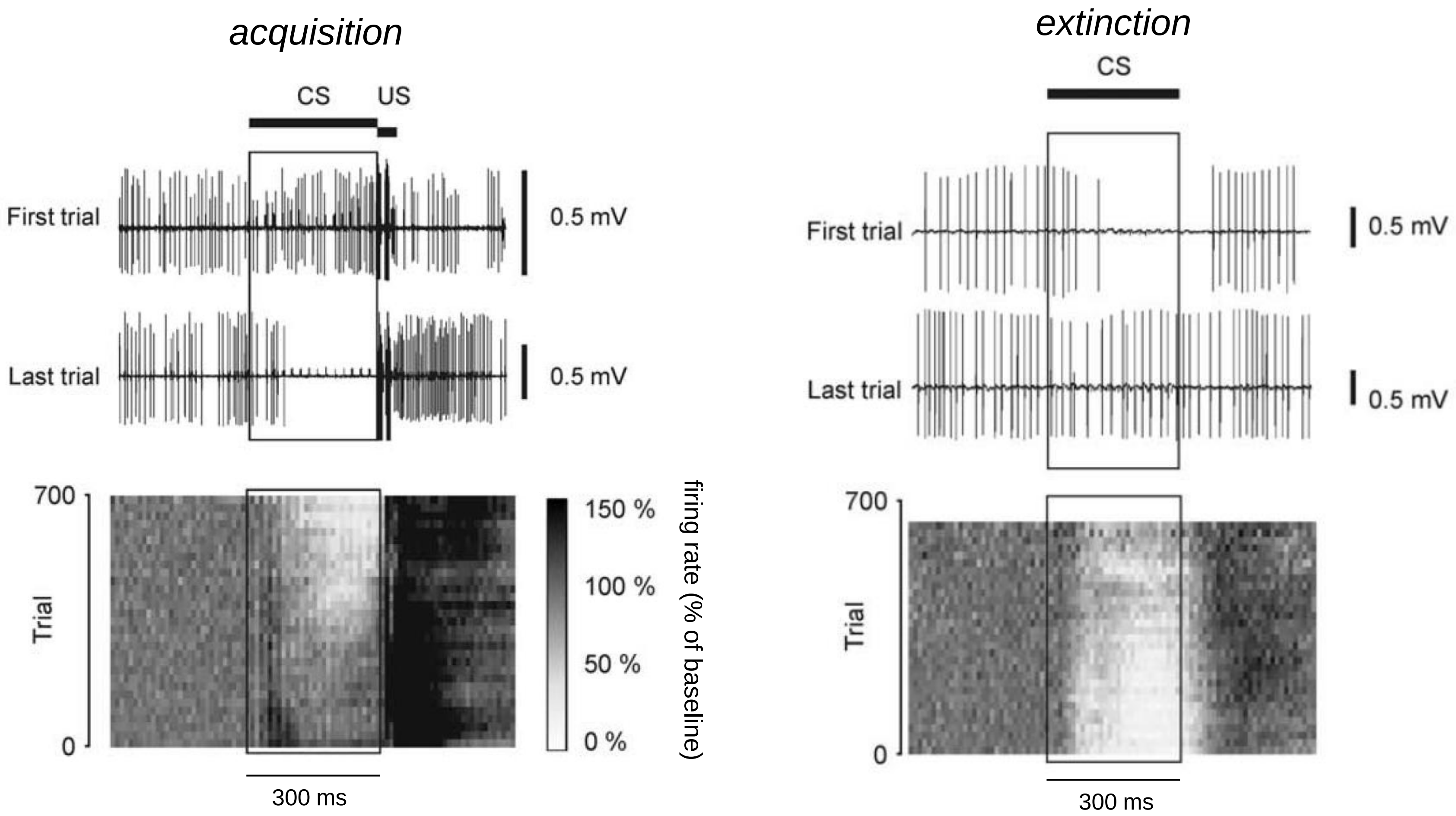


Garcia, Steele, and Mauk, *J. Neurosci.* 19:10940, 1999

The Journal of Neuroscience, March 7, 2007 • 27(10):2493–2502 • 2493

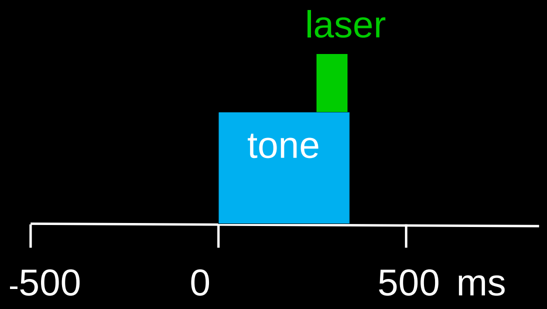
Acquisition, Extinction, and Reacquisition of a Cerebellar Cortical Memory Trace

Dan-Anders Jirenhed, Fredrik Bengtsson, and Germund Hesslow
Department of Experimental Medical Science, Lund University, 22184 Lund, Sweden

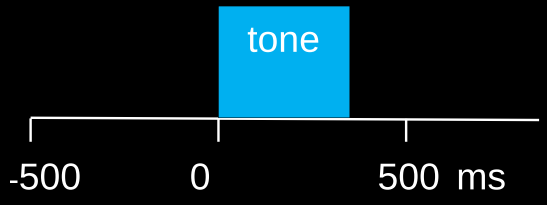


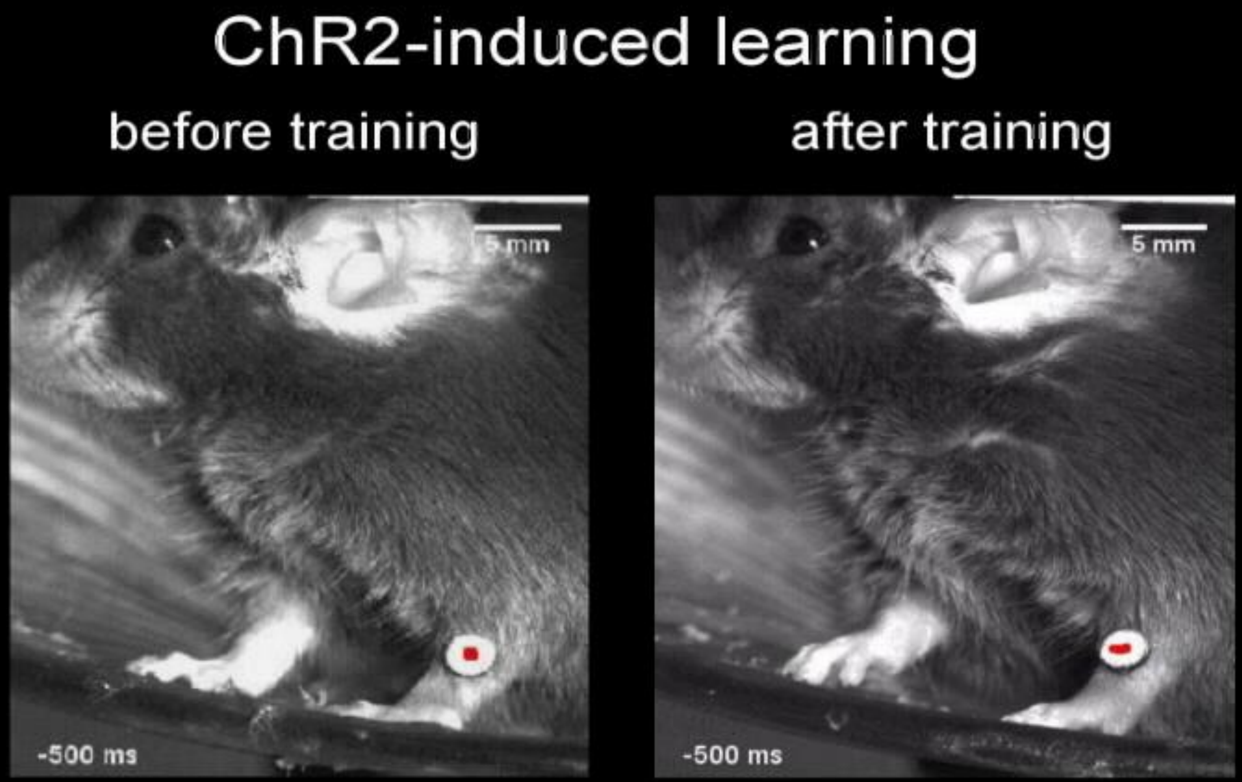
Pairing PC excitation with a tone leads to robust learned movements

Training: 90 trials/day



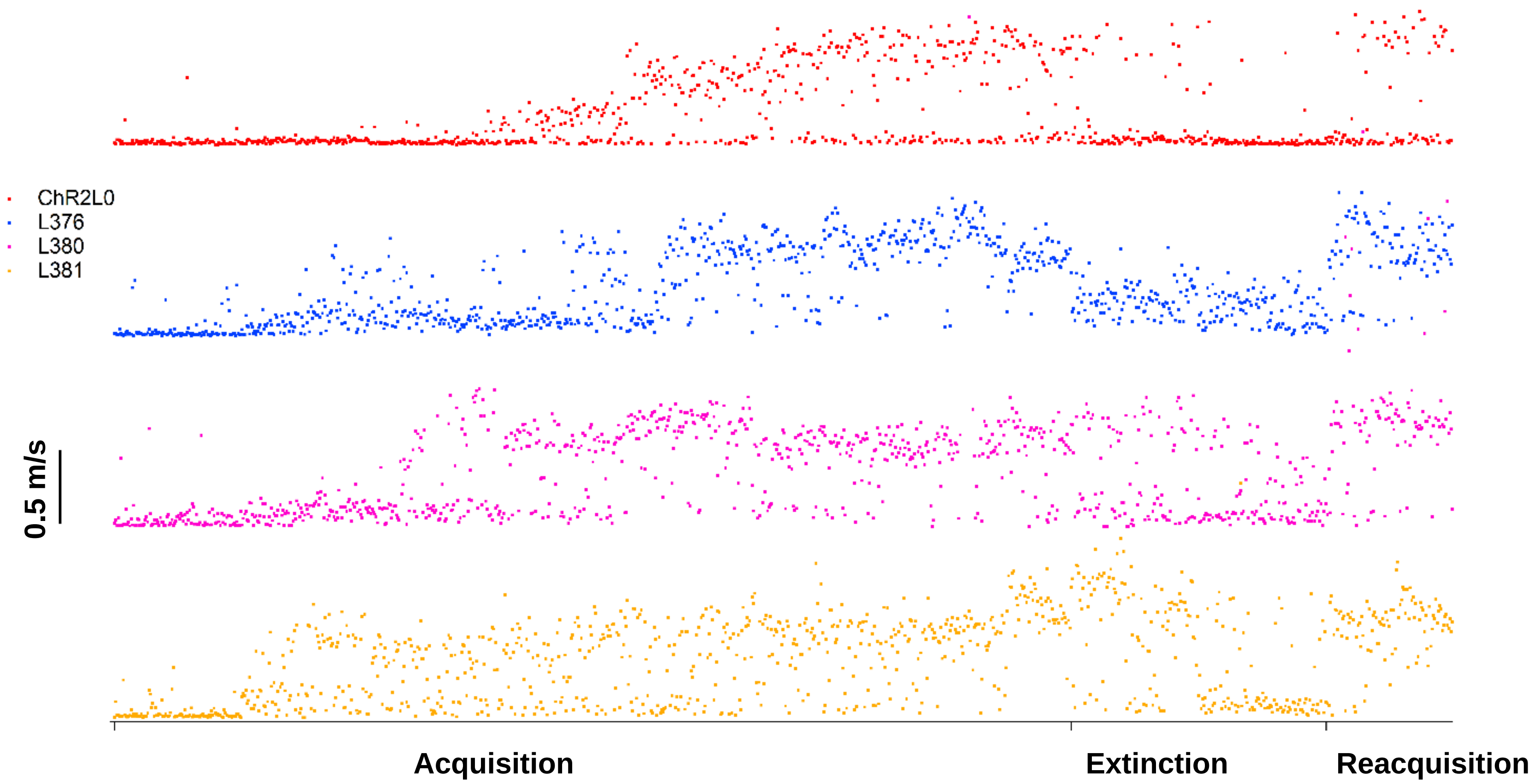
Testing:





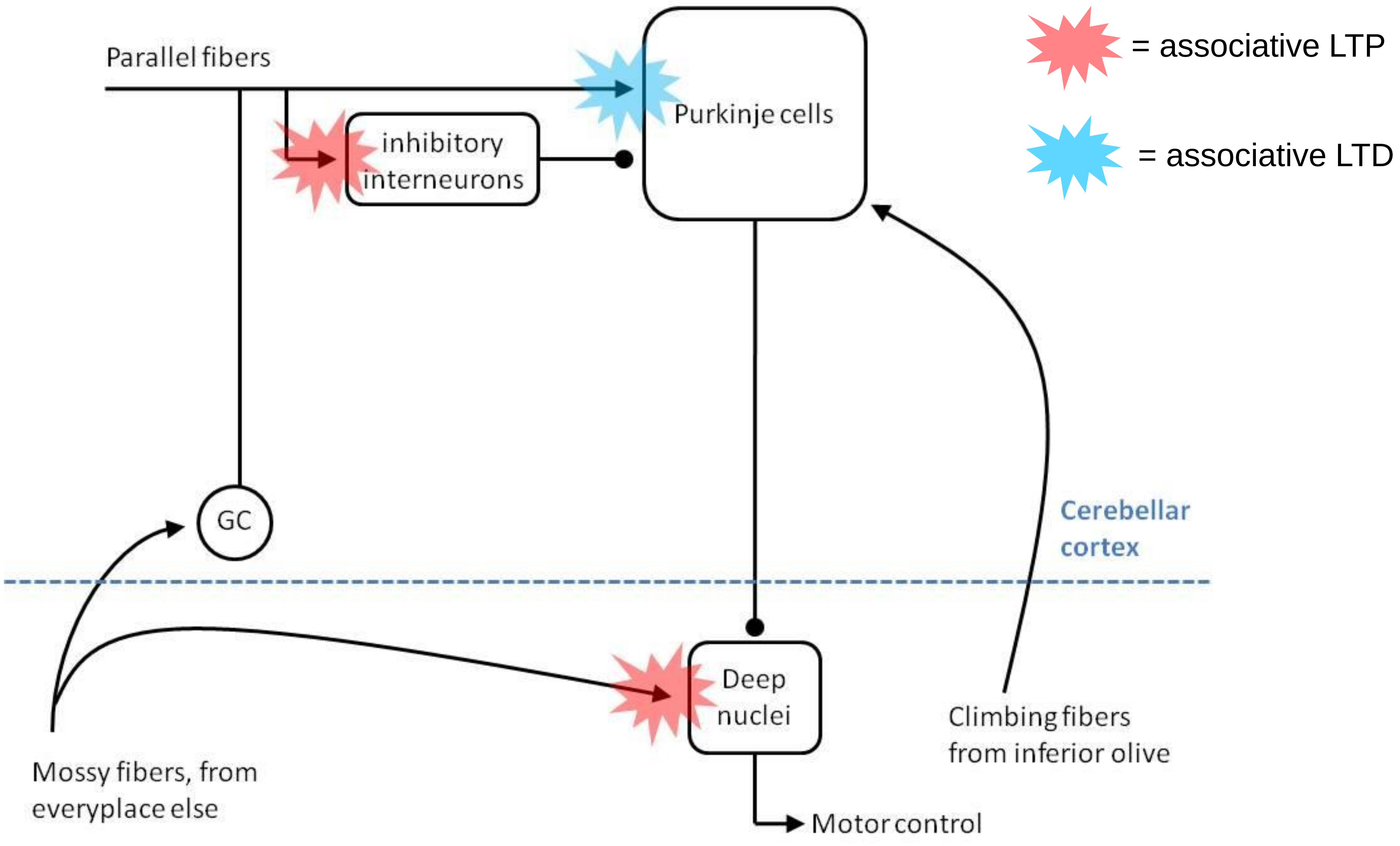
Lee, & Mathews et al, *Neuron*, 2015

Chr2 training, individual mice

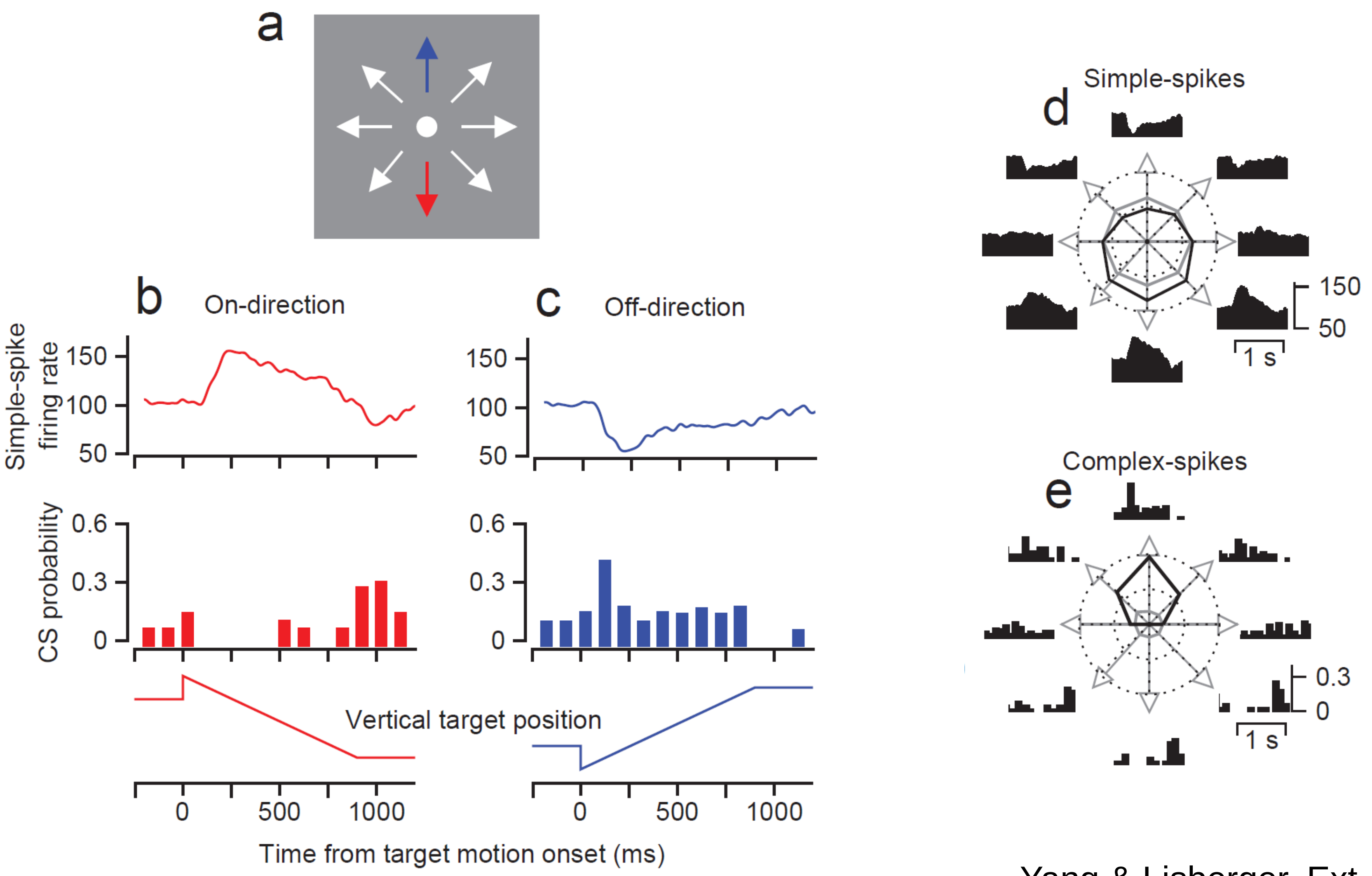


A. Reeves, unpublished

Summary: sites of plasticity



PNs in flocculus are directionally tuned to smooth pursuit eye movements



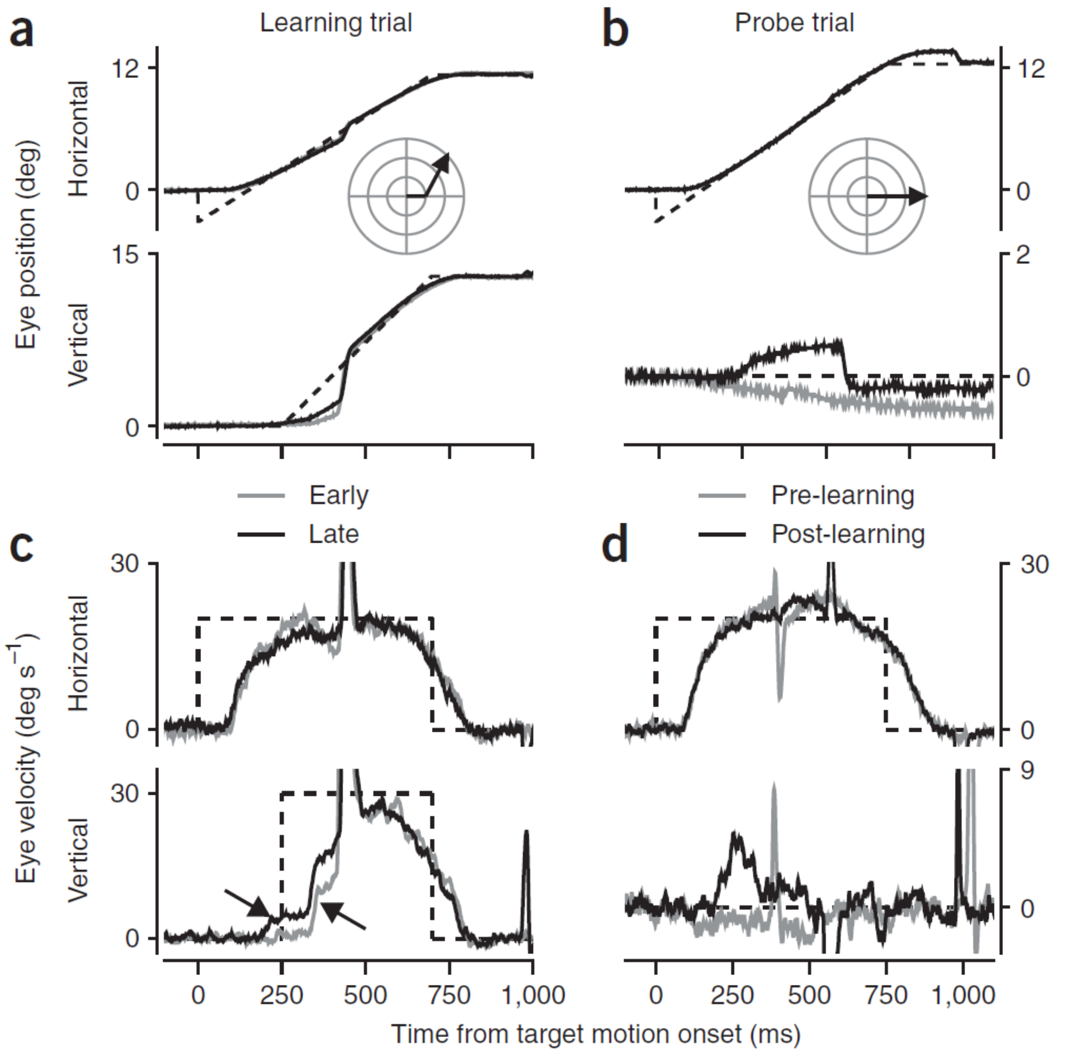
Yang & Lisberger, Ext. Fig. 1, *Nature* 2014

Smooth pursuit learning task

Medina & Lisberger, *Nat. Neurosci.* 2008

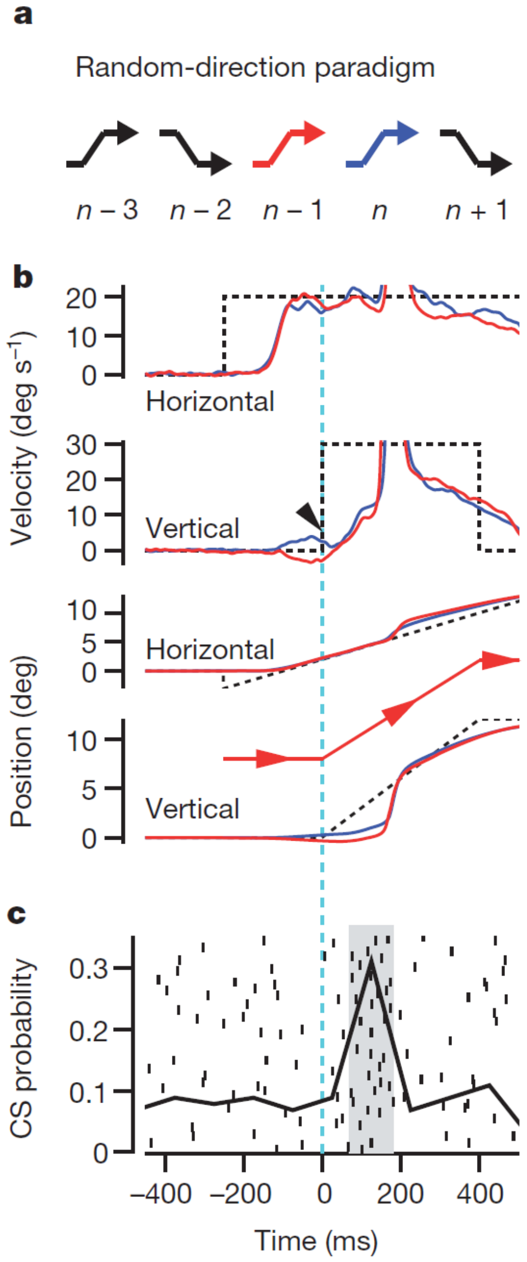
Smooth pursuit learning task

- **task shows single trial learning**
- **complex spikes predict learning on a trial by trial basis**



Medina & Lisberger, *Nat. Neurosci.* 2008

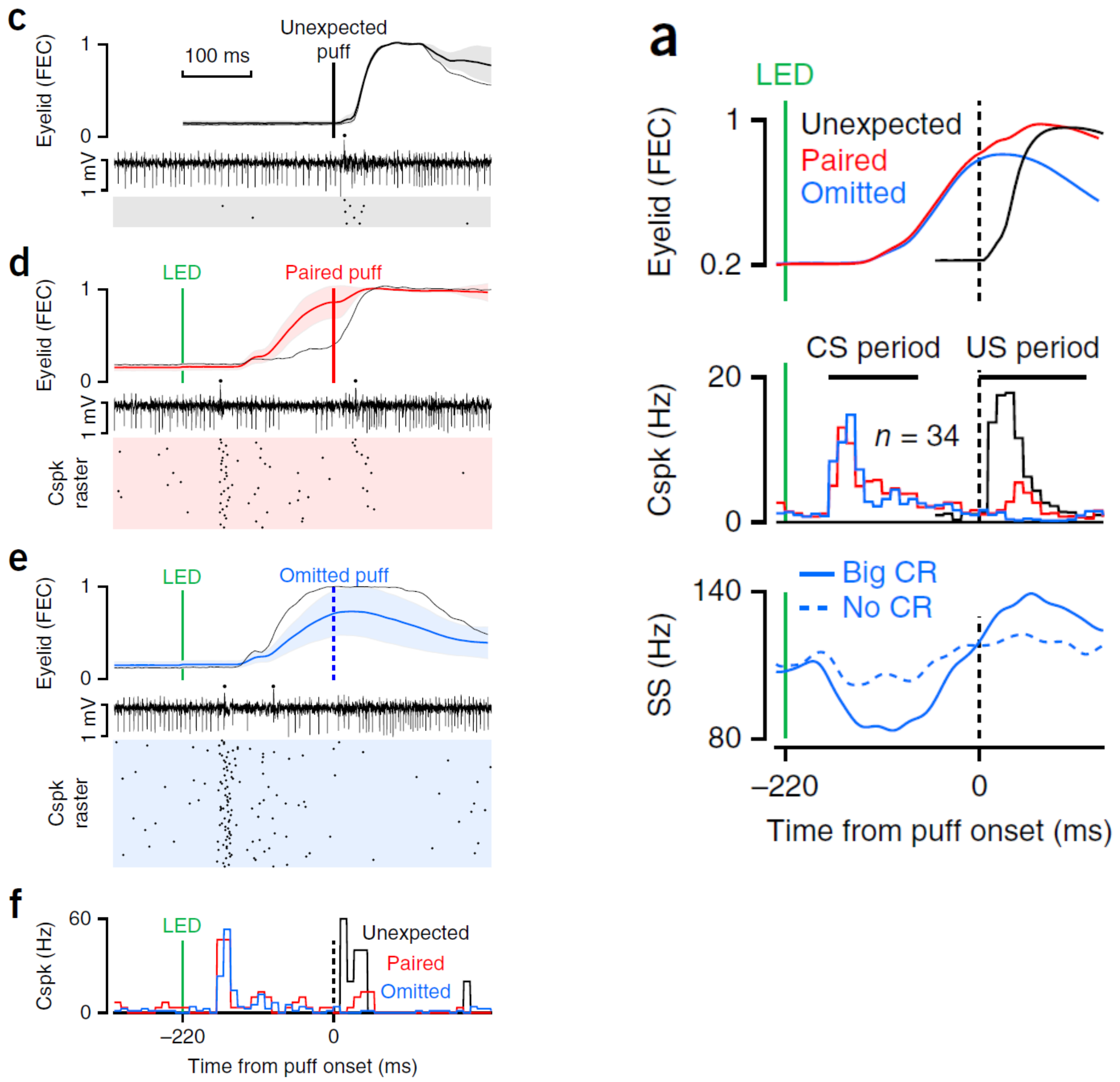
Complex spike signals predict single trial learning



Yang & Lisberger, *Nature* 2014

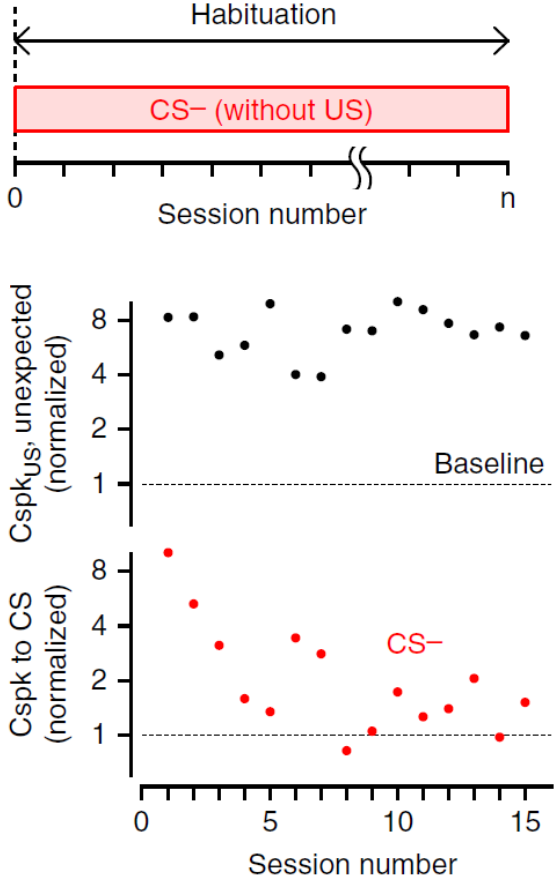
Complex spikes indicate errors or unexpected events

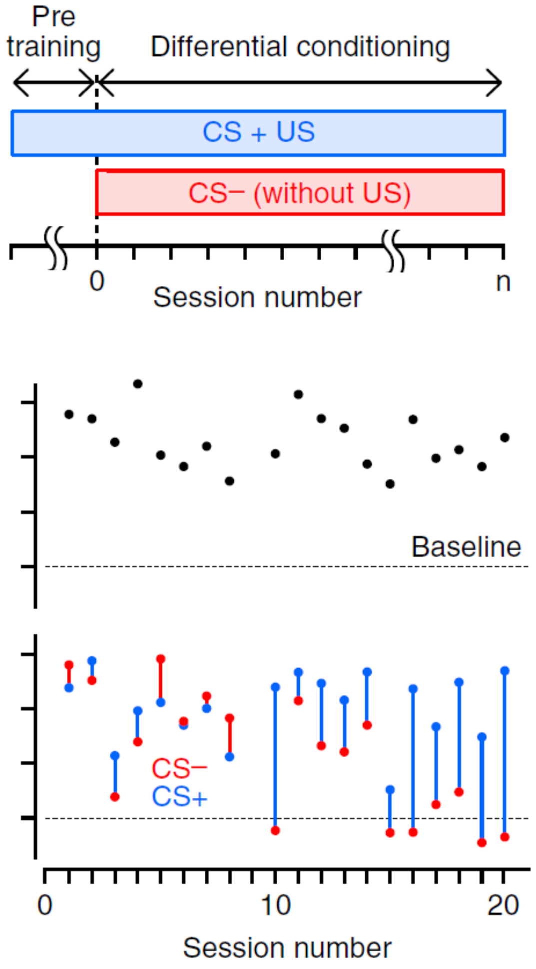
- Baseline rate of complex spikes ~ 1 / s
- Rate of complex spikes increases with errors in a novel task
- Complex spikes to unexpected events
- Rate of complex spikes decreases after learning corrects errors in performance



Ohmae & Medina, *Nat. Neurosci.*, 2015

Complex spikes to unexpected events habituate *unless they are predictive*

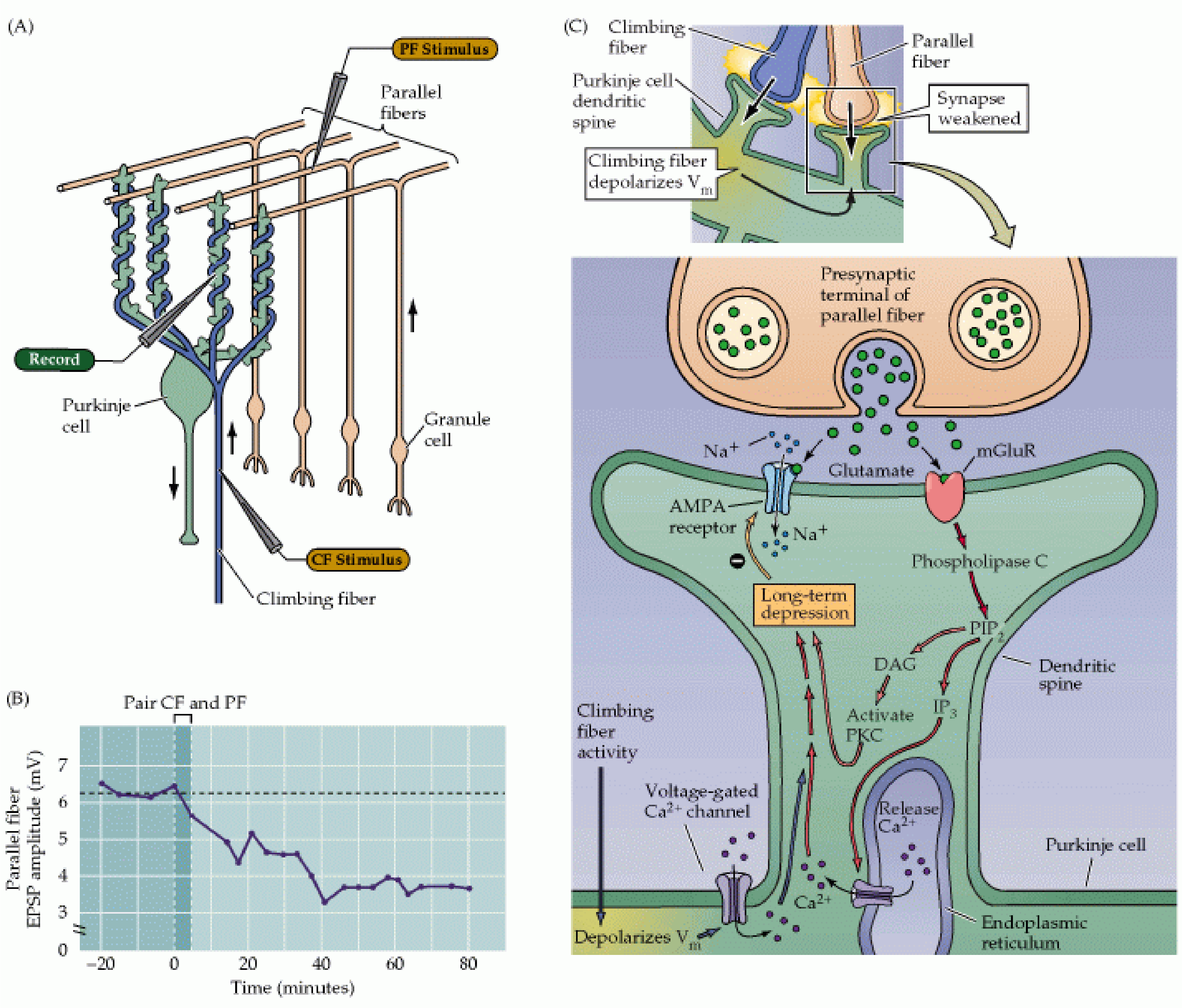




Ohmae & Medina, *Nat. Neurosci.*, 2015

Cellular mechanisms of cerebellar LTD

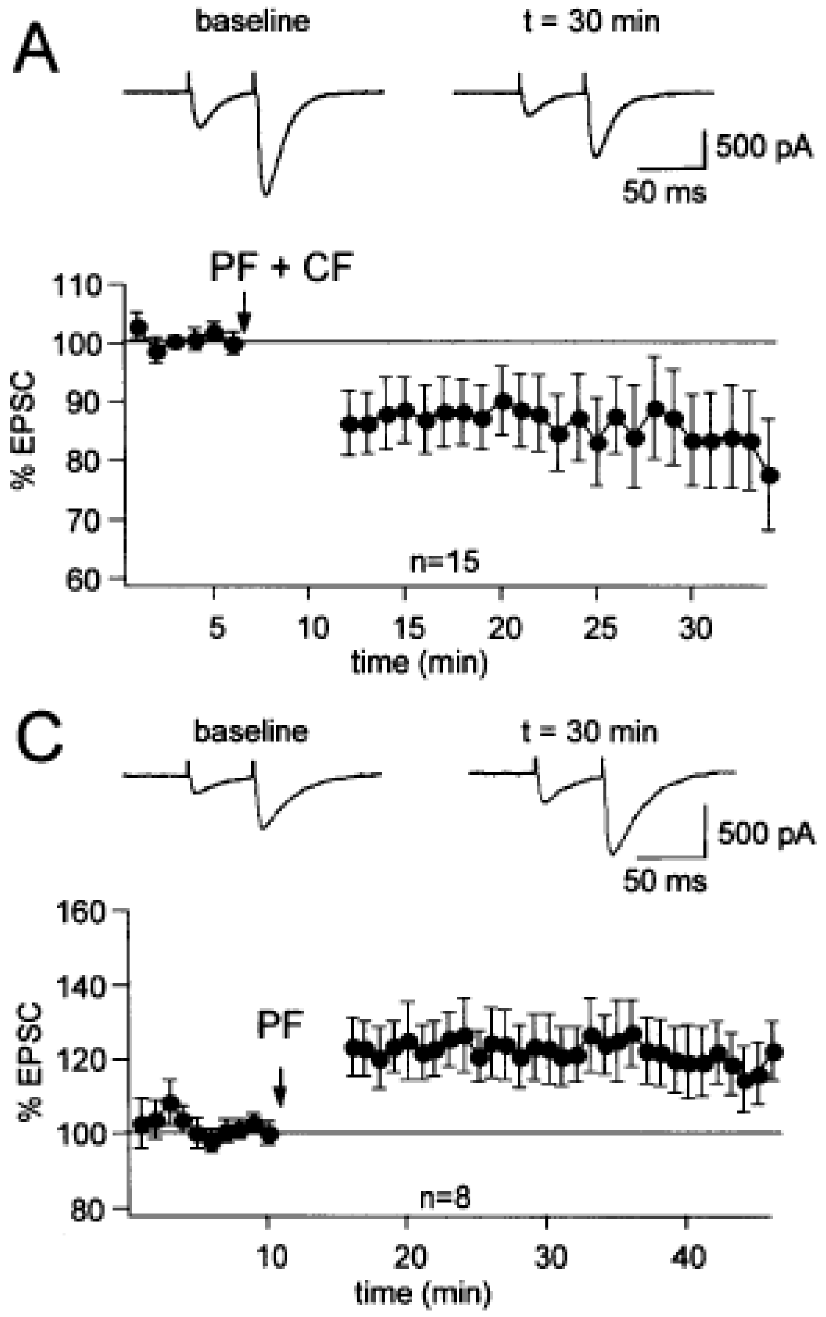
Long term depression (LTD) of PF synapses



AMPA receptors are removed at PF synapses

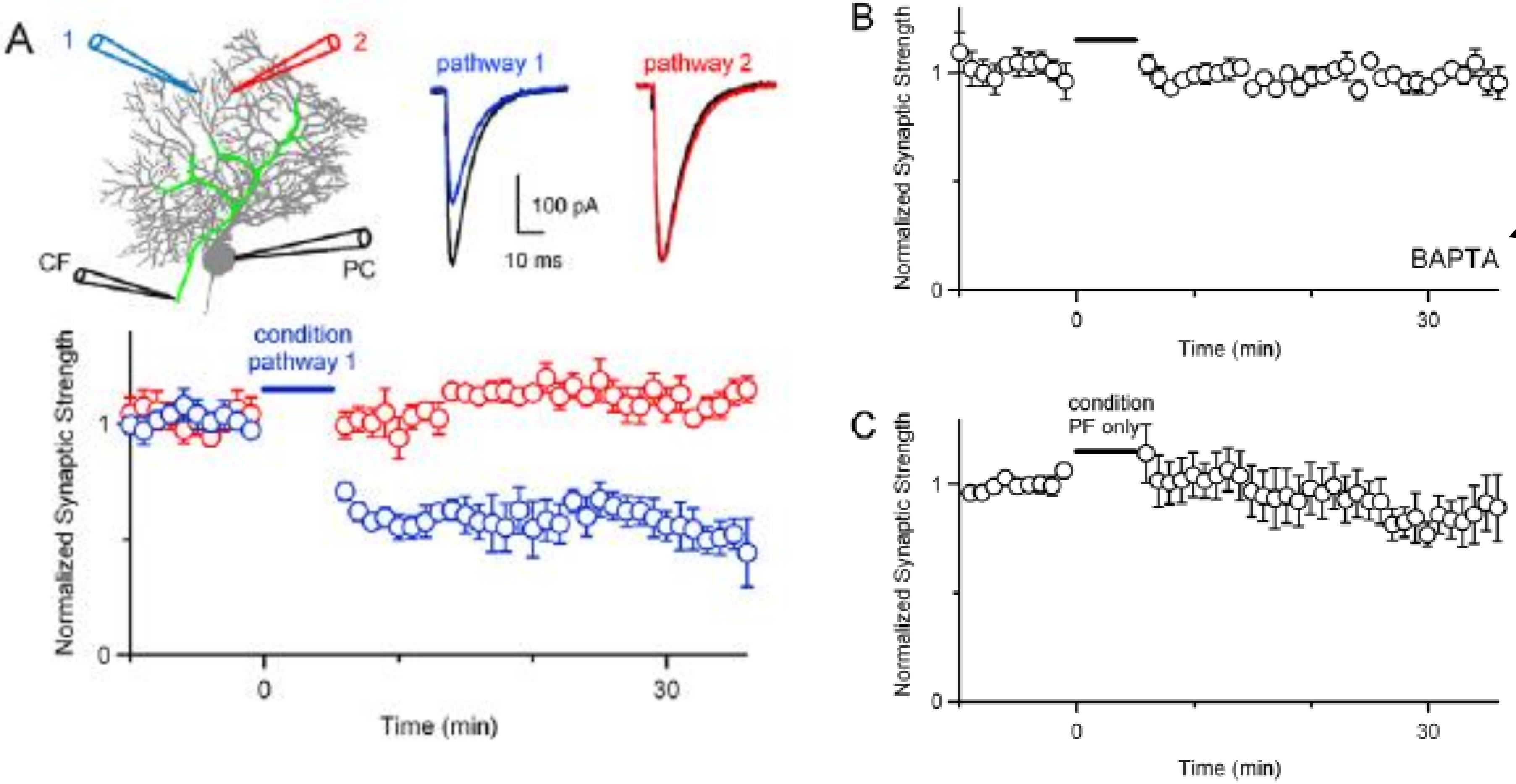
Fig.24-13, Purves

The direction of plasticity is determined by the whether CF is stimulated



Coesmans et al., *Neuron* 44:691, 2004

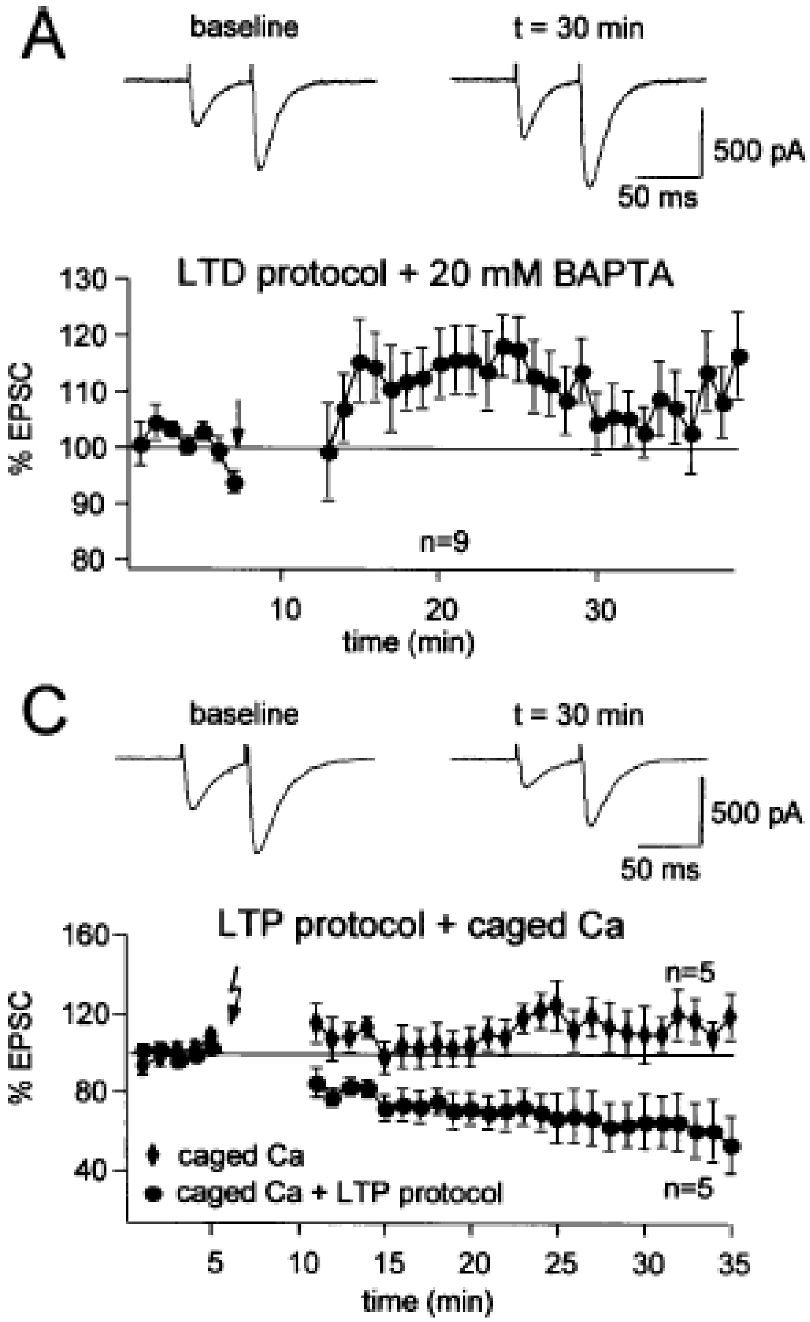
LTD is synapse specific & requires an rise in $[Ca^{2+}]_i$



intracellular
[Ca] buffer

Safo and Regehr, *Neuron* 48:647, 2005

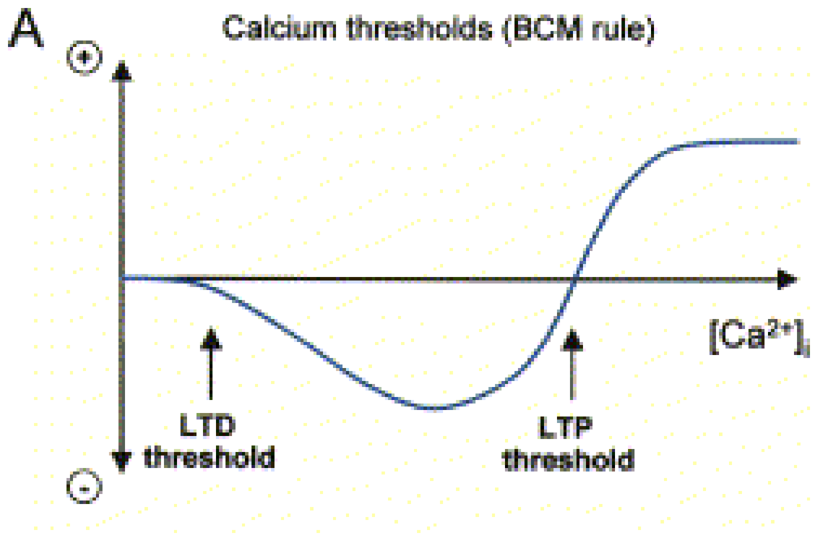
The direction of plasticity is determined by the amount of calcium



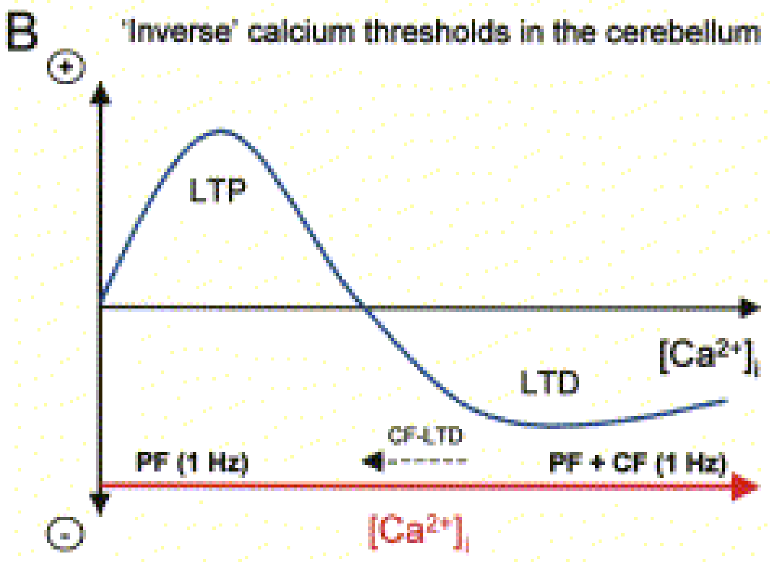
Coesmans et al., *Neuron* 44:691, 2004

An inverse $[Ca^{2+}]_i$ dependence in cerebellum?

Schaffer-collateral synapse

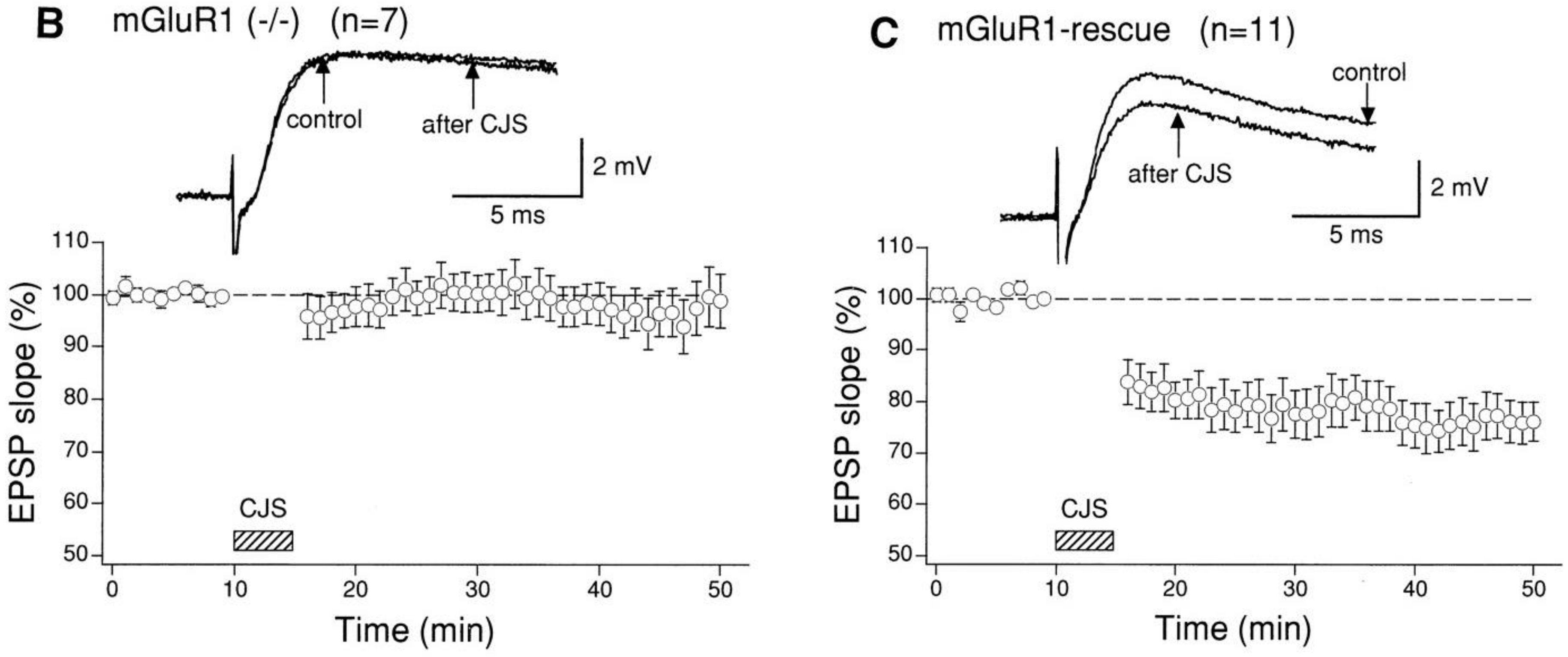


parallel fiber synapse



Coesmans et al., *Neuron* 44:691, 2004

mGluR1 function is required for LTD



Ichise et al., *Science* 288:1832, 2000

Coincidence detection mechanisms

1) PF → mGluR1α → PLCβ → DAG ↘ PKCα
CF → VGCC ⟶ $[Ca^{2+}]$↑ ↗

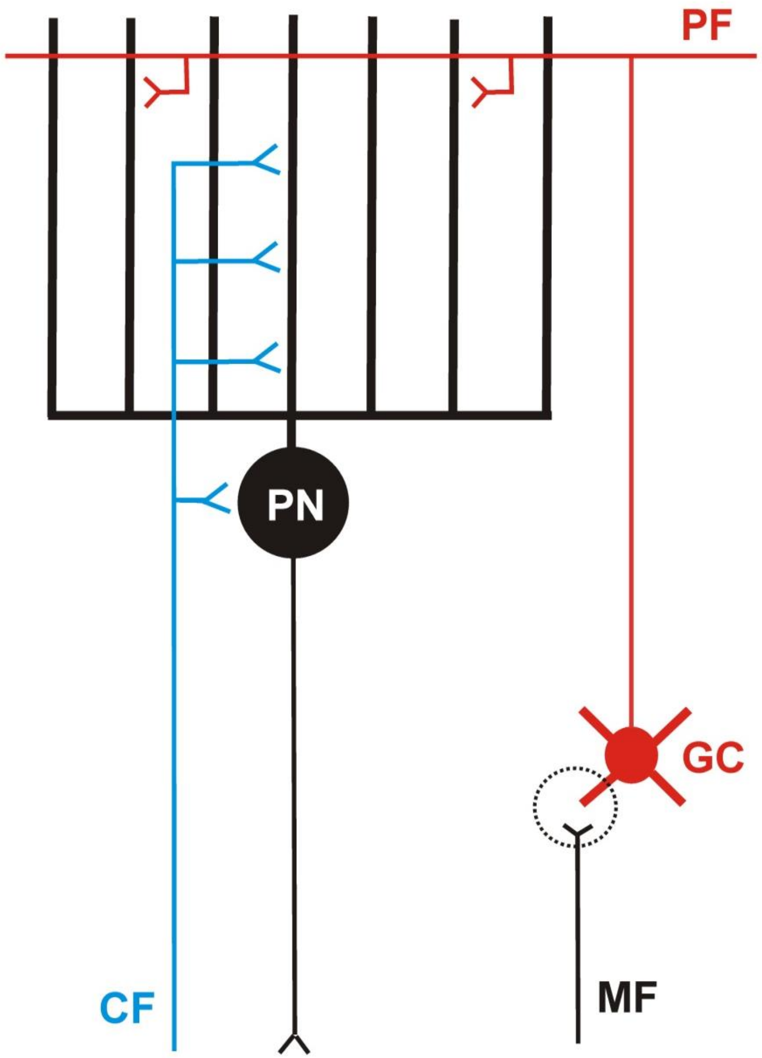
Linden & colleagues

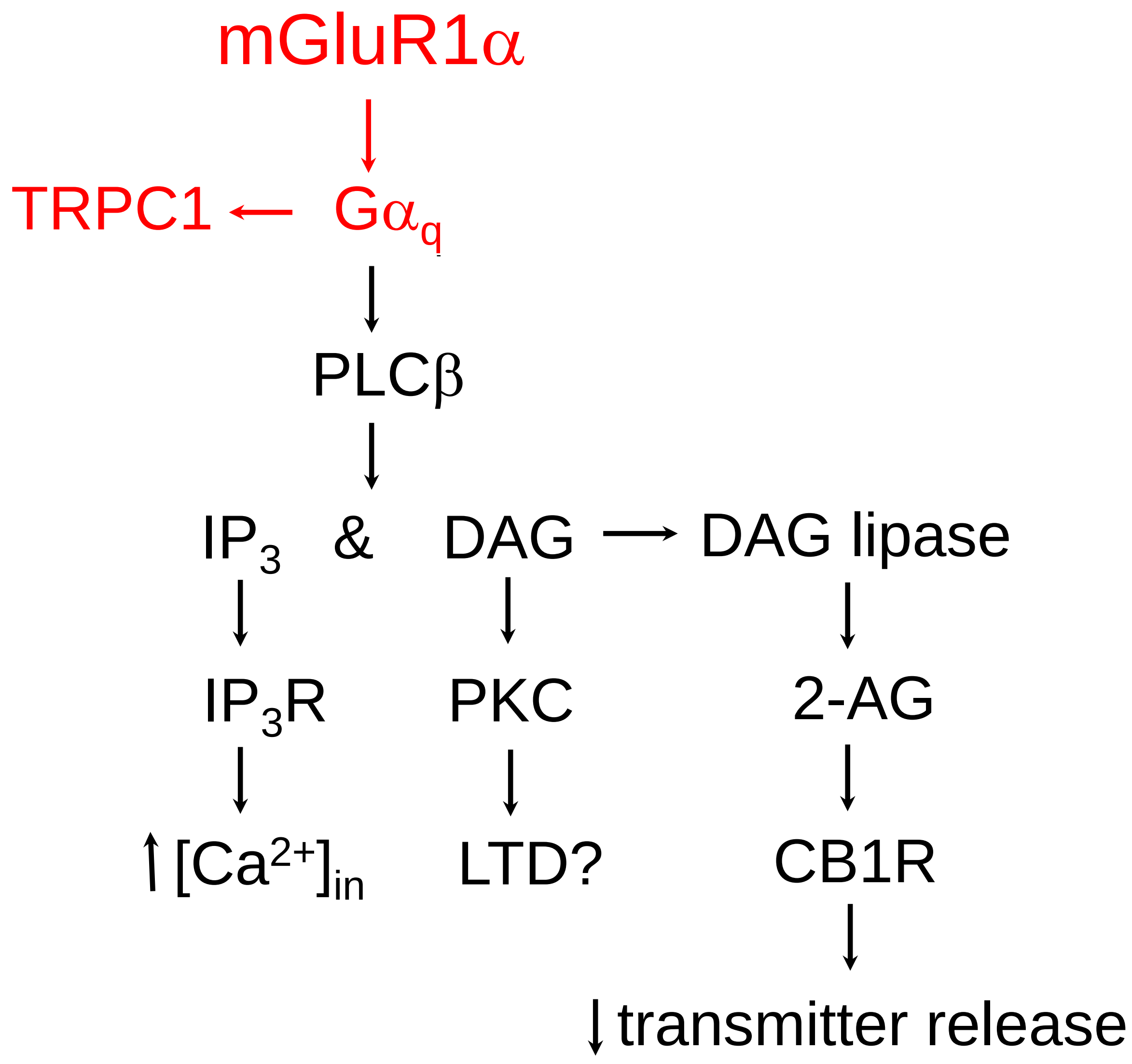
2) PF → mGluR1α → PLCβ → IP_3 ↘ IP_3R
CF → VGCC ⟶ $[Ca^{2+}]$↑ ↗

Augustine, Finch, Wang

3) PF → NO → sGC → cGMP ↘ PKG?
CF → VGCC ⟶ $[Ca^{2+}]$↑ ↗

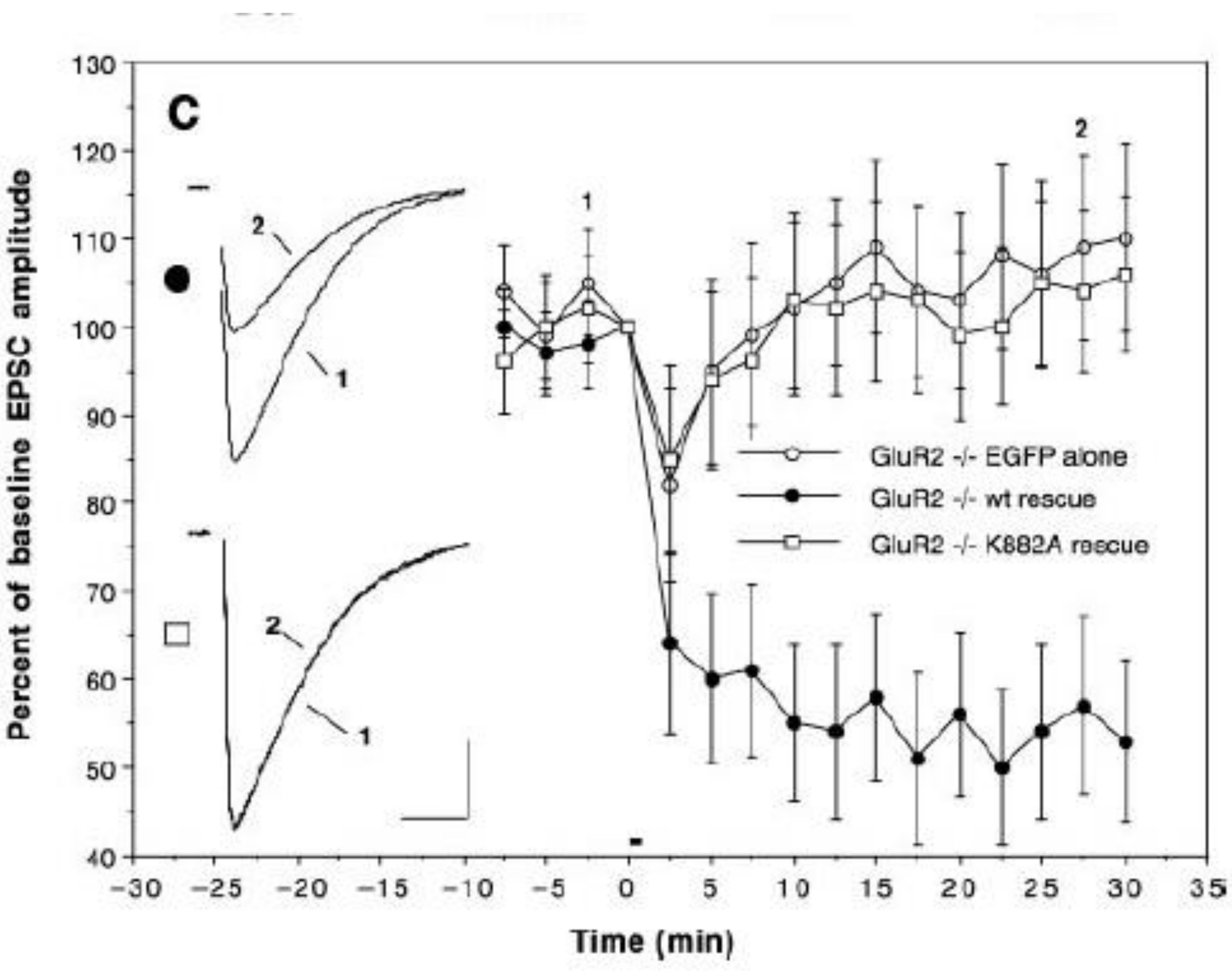
Lev Ram, Hartell, Crepel





mGluR1α
TRPC1
Gα$_q$
PLCβ
IP$_3$ & DAG
DAG lipase
IP$_3$R
PKC
2-AG
↑[Ca^{2+}]$_{in}$
LTD?
CB1R
↓transmitter release

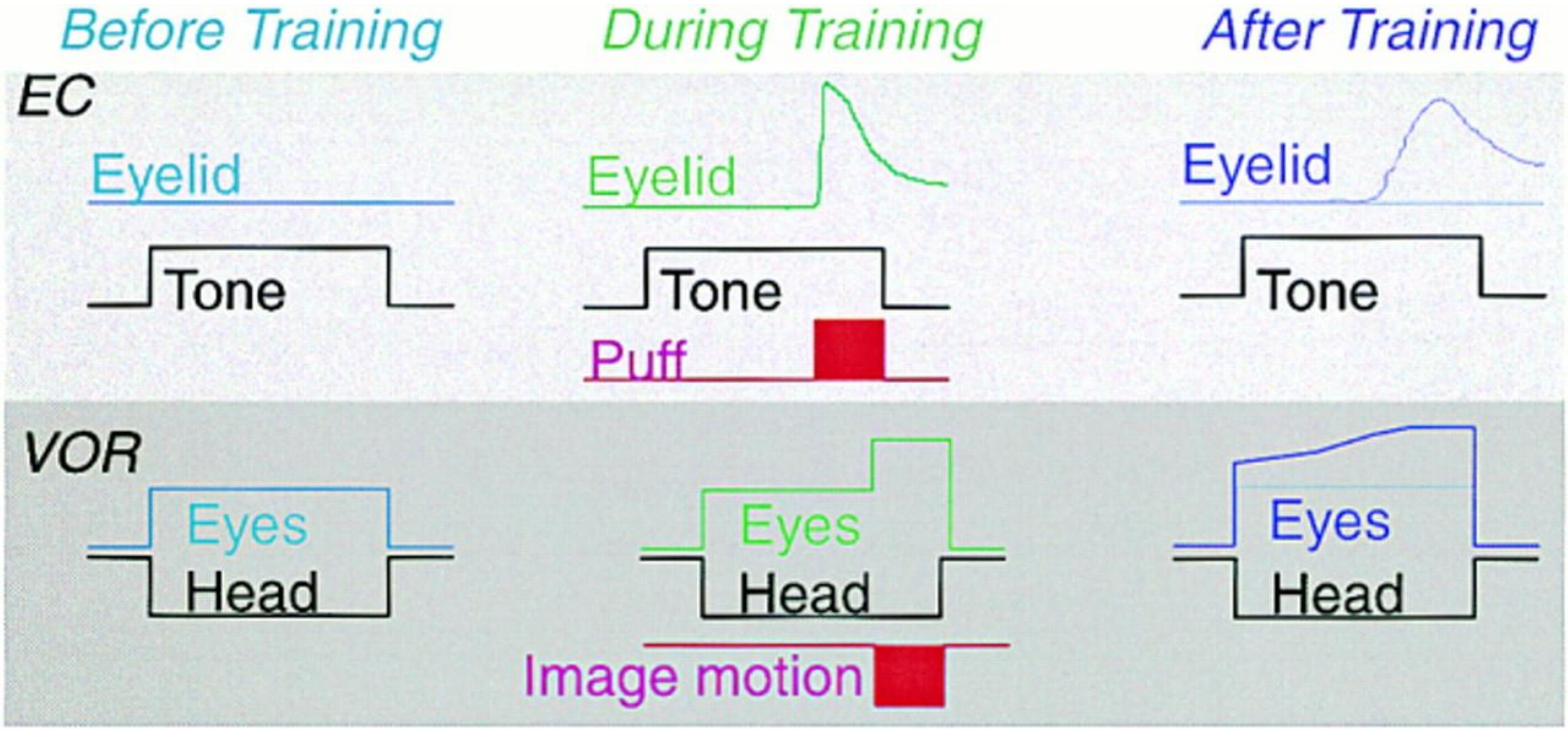
Endocytosis of GluR2-containing AMPARs is the basis for LTD



Chung et al., *Science* 300:1751, 2003

Backup, extra slides

Similarities between classical eyeblink conditioning (*EC*) and plasticity of the vestibulo-ocular reflex (*VOR)*



Mauk, 1997

Some numbers: mossy fibers and climbing fibers

A mossy fiber excites
~30 granule cells.

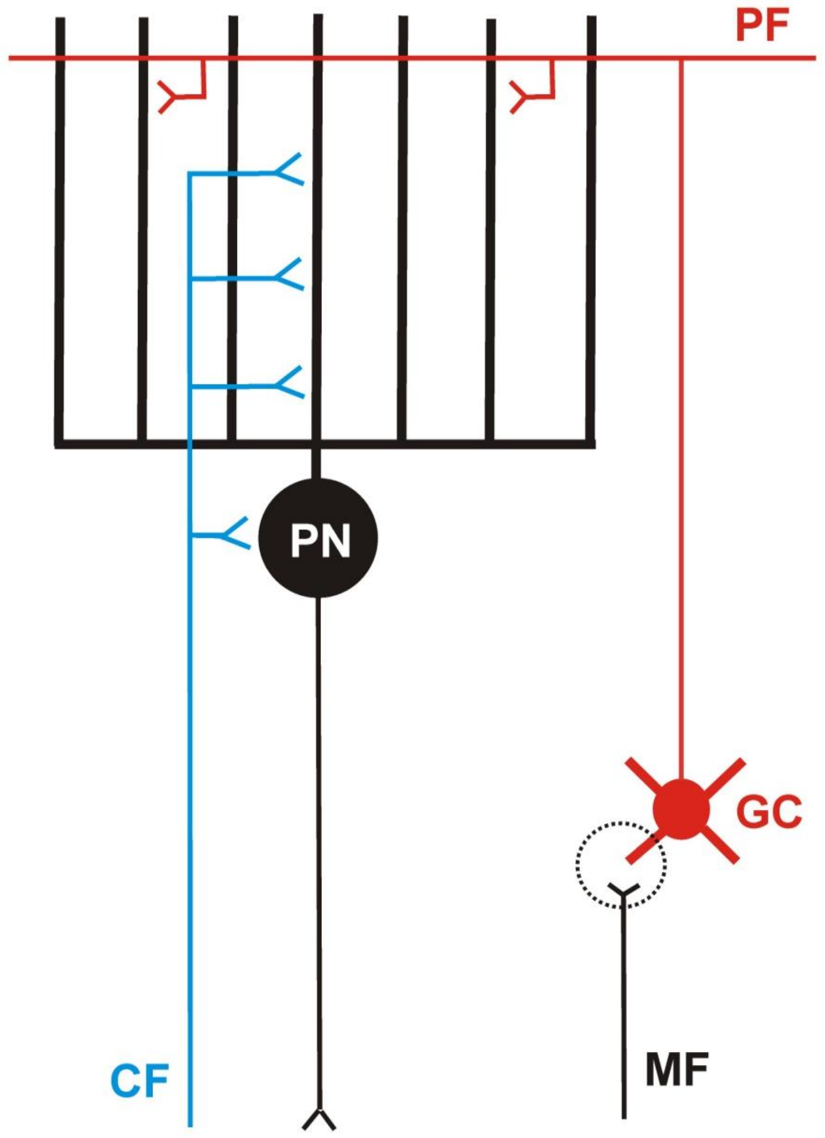
A granule cell is excited by
4-6 mossy fibers.

A parallel fiber excites ~300 PNs.

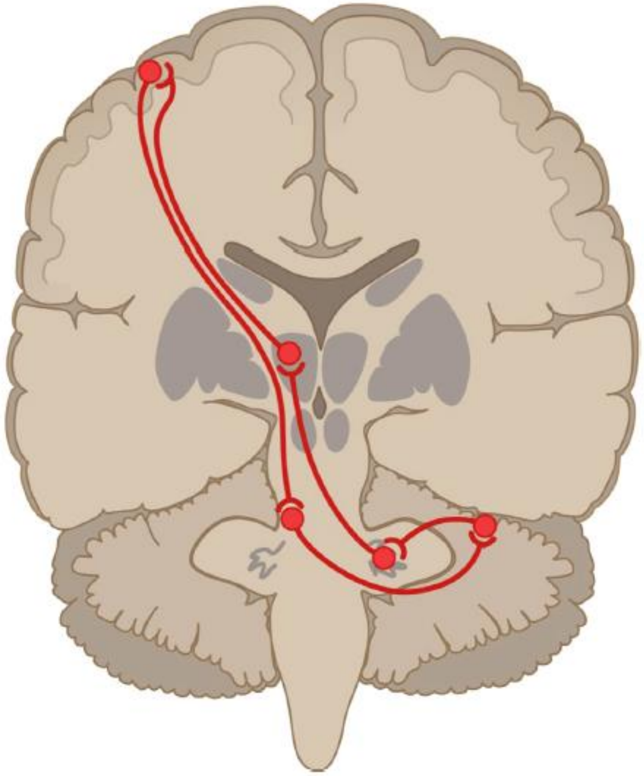
A PN is excited by ~100,000
parallel fibers.

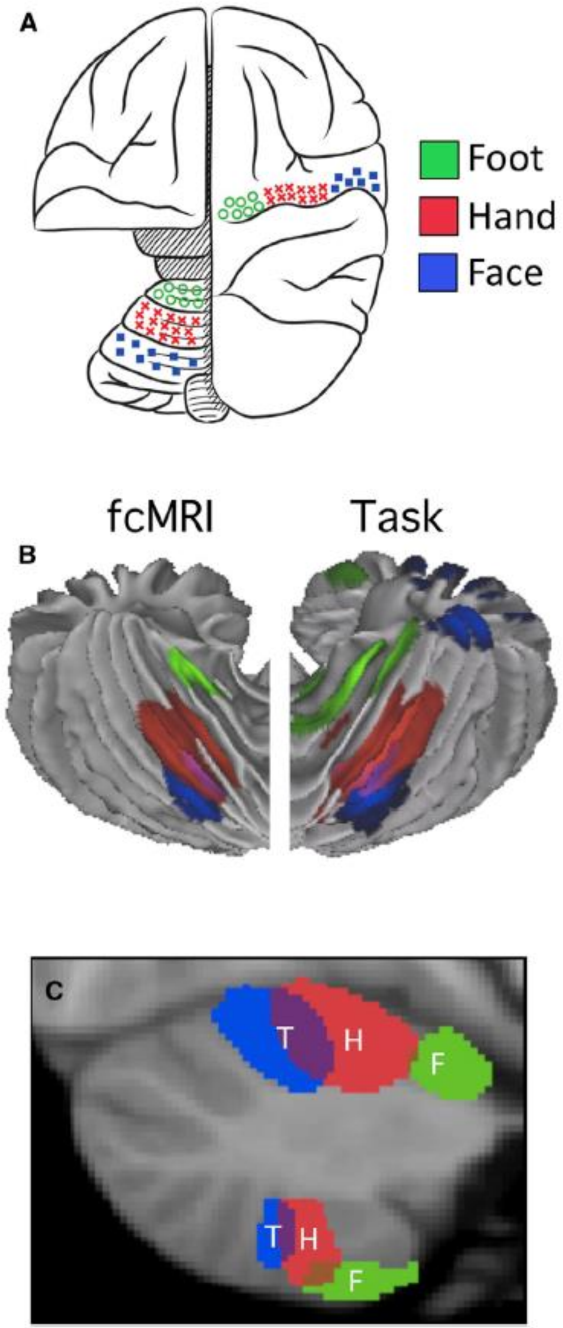
A climbing fiber excites ~10 PNs.

A PN is excited by 1 climbing fiber.



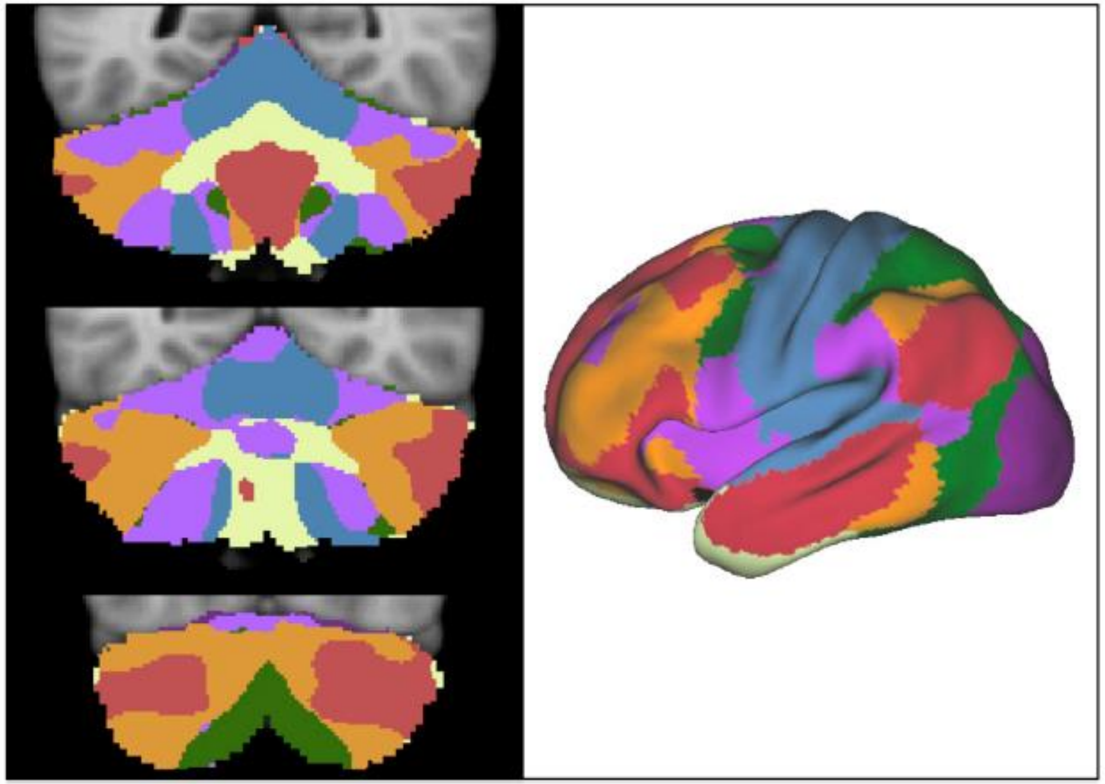
Reciprocal disynaptic connections between motor areas of cerebellum and neocortex

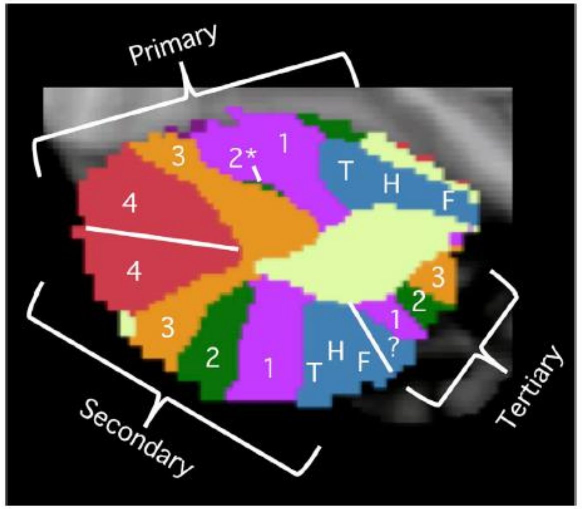




Buckner, *Neuron* 80:807-815, 2013

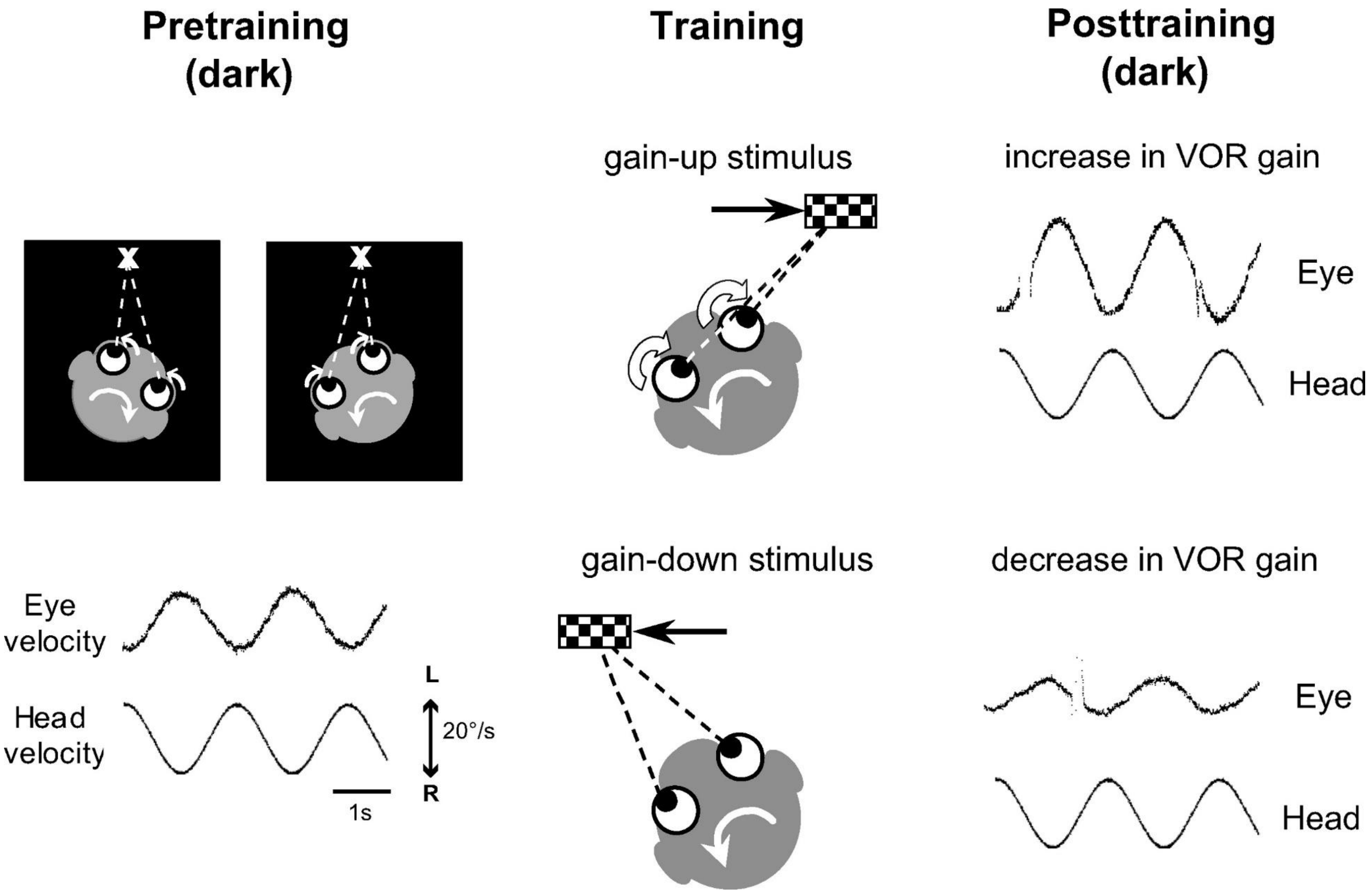
Reciprocal connections between cerebellum and <u>all</u> of neocortex





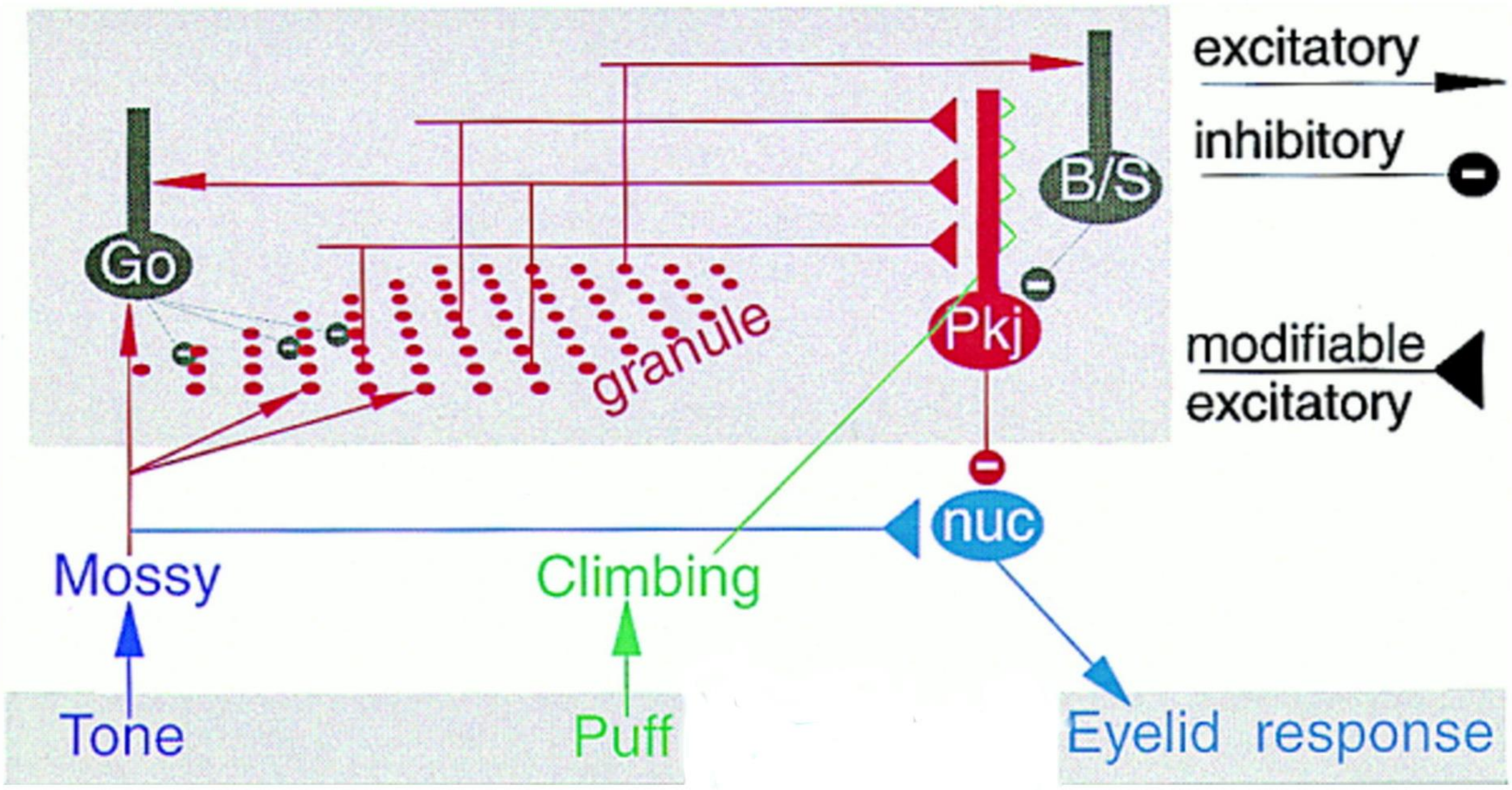
Buckner, *Neuron* 80:807-815, 2013; see also work by Strick and colleagues, and Schmahmann on cerebellar cognitive syndrome & "*dysmetria of thought*"

VOR learning



Boyden et al., 2004

Which pathways carry the information critical for learning?



Mauk, 1997