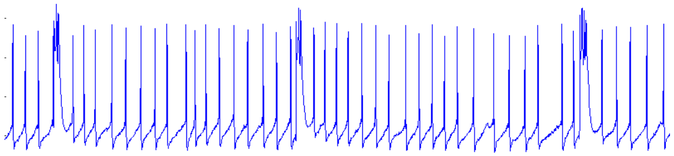
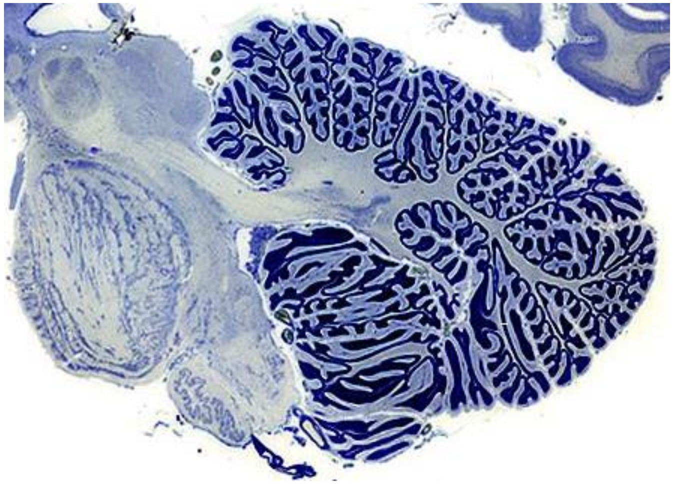
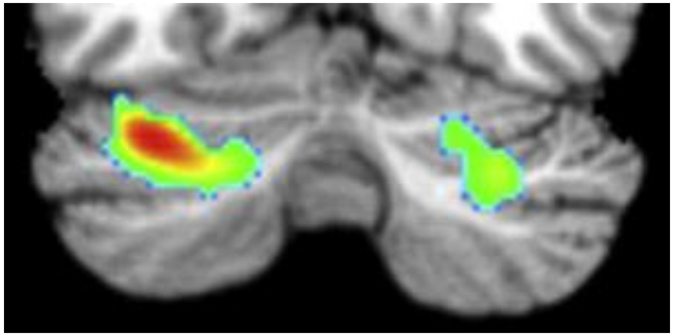
Cerebellum, motor and cognitive functions: What is the common ground?







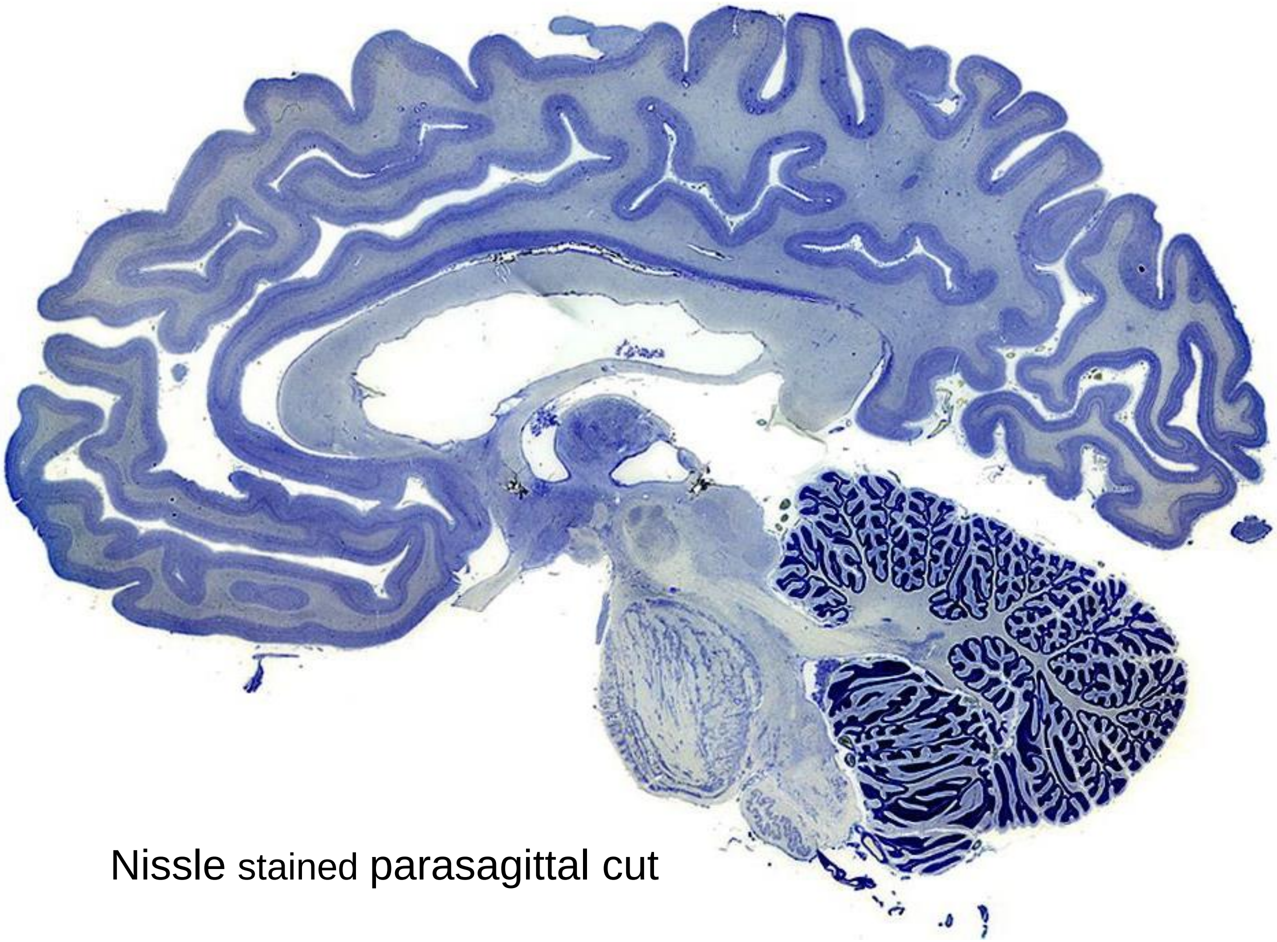
Eyal Cohen, PhD
(Engineering, BIU)

Cerebellum – The "Little Brain"

The Cerebellum takes ~10% of the Brain in Volume

Small but Hefty…

Nissle stained coronal cut

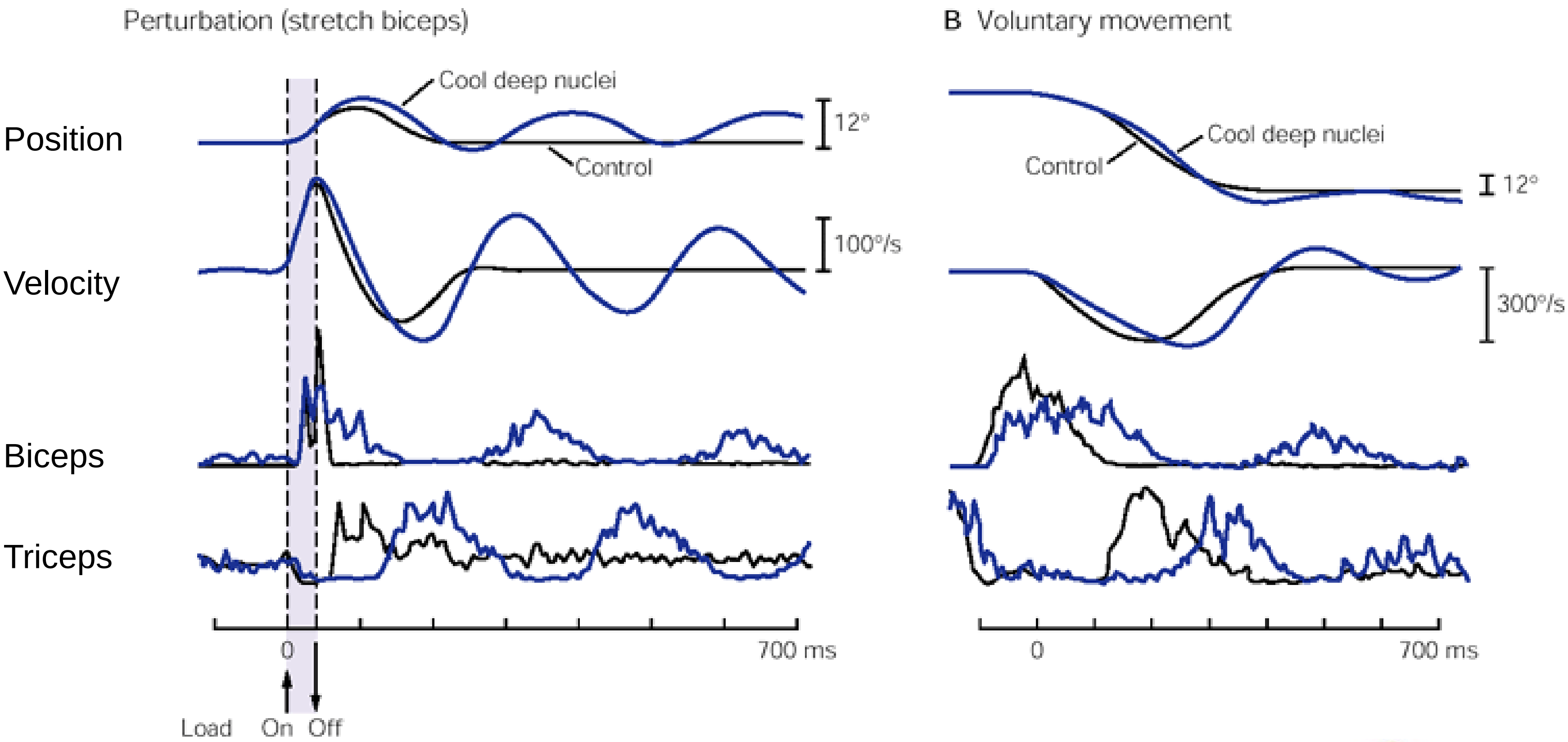


Nissle stained parasagittal cut

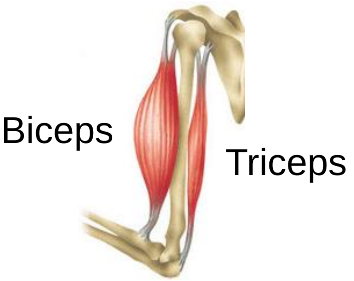
Over 50% of the Brain's Neurons are in the Cerebellum!!

The Convoluted Cerebellar Cortex consists of most Cerebellar Volume

Classical Role in Muscle Timing and Coordination



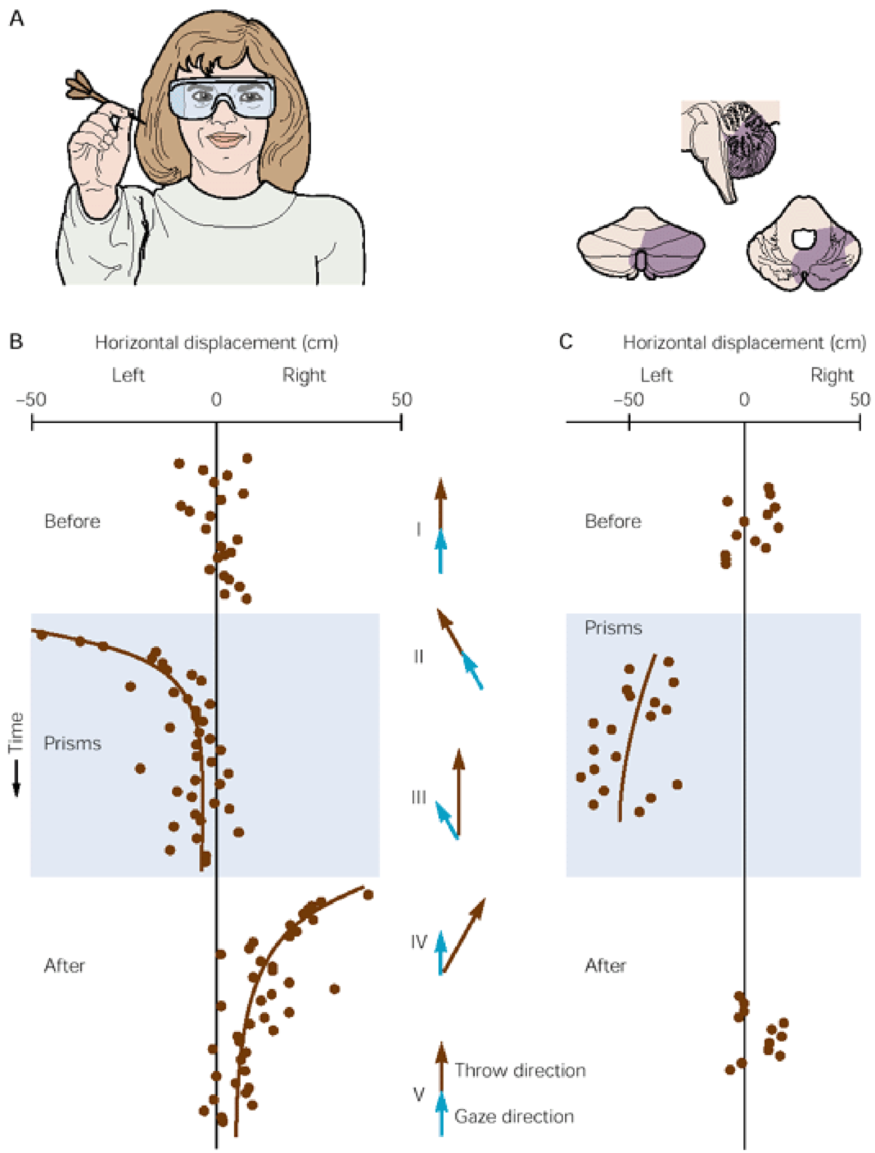
Cooling => Reducing Neuronal Firing
Results: oscillatory movements when cerebellar outputs are shut down



Villis and Hore 1977

Cerebellar is Central in Adaptation

Quick coordinative adaptation depends on an intact cerebellum (middle and right side)



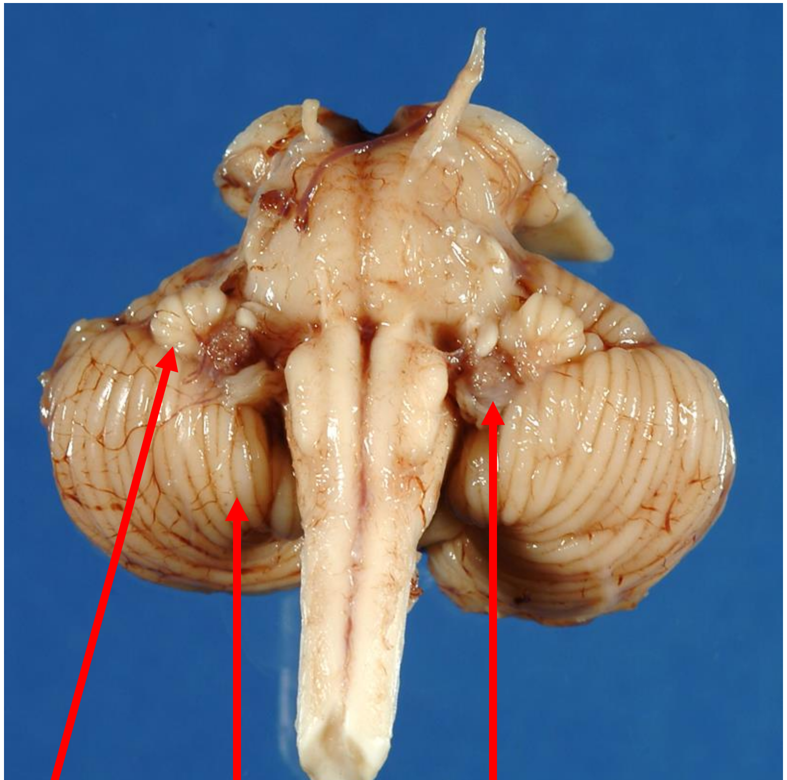
Results of Cerebellar Lesions or Volume reduction

- Hypotonia = loss of muscle tone
- Ataxia = loss of motor coordination:
  1. Postural instability, “drunken sailor” gait , sway, wide standing base
  2. Walking: uncertain, asymmetric, irregular
  3. Failure in execution of planned movements i.e. intentional tremor, dysmetria (lack of precision) and dysarthria (speech slurring)
  4. Deficits in eye movement control

- Correlative Non-Motor Symptoms:
  1. Lower Intelligence (Verbal)
  2. Lower visuospatial abilities
  3. Memory problems (i.e. working, procedural) and Dementia
  4. Emotional control problems, impulsiveness, aggression
  5. Reduced ability of strategy formation
  6. Psychosis, Schizophrenia (associated with reduced volume)

General Structure of the Cerebellar Cortex

Ventral/Anterior View

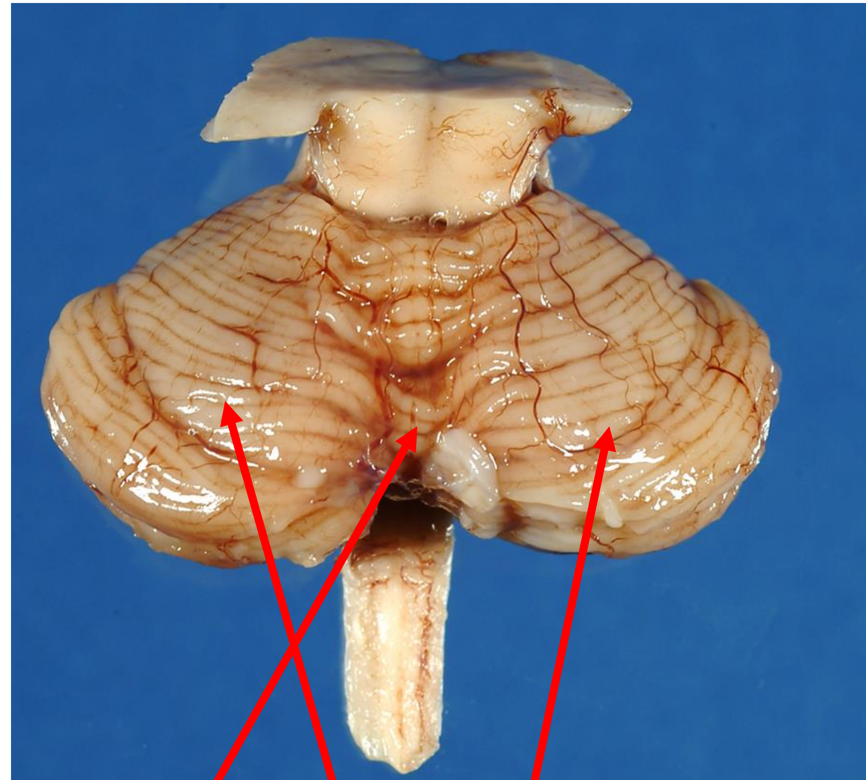


Flocculus

Tonsil

Nodulus

Dorsal/Posterior View

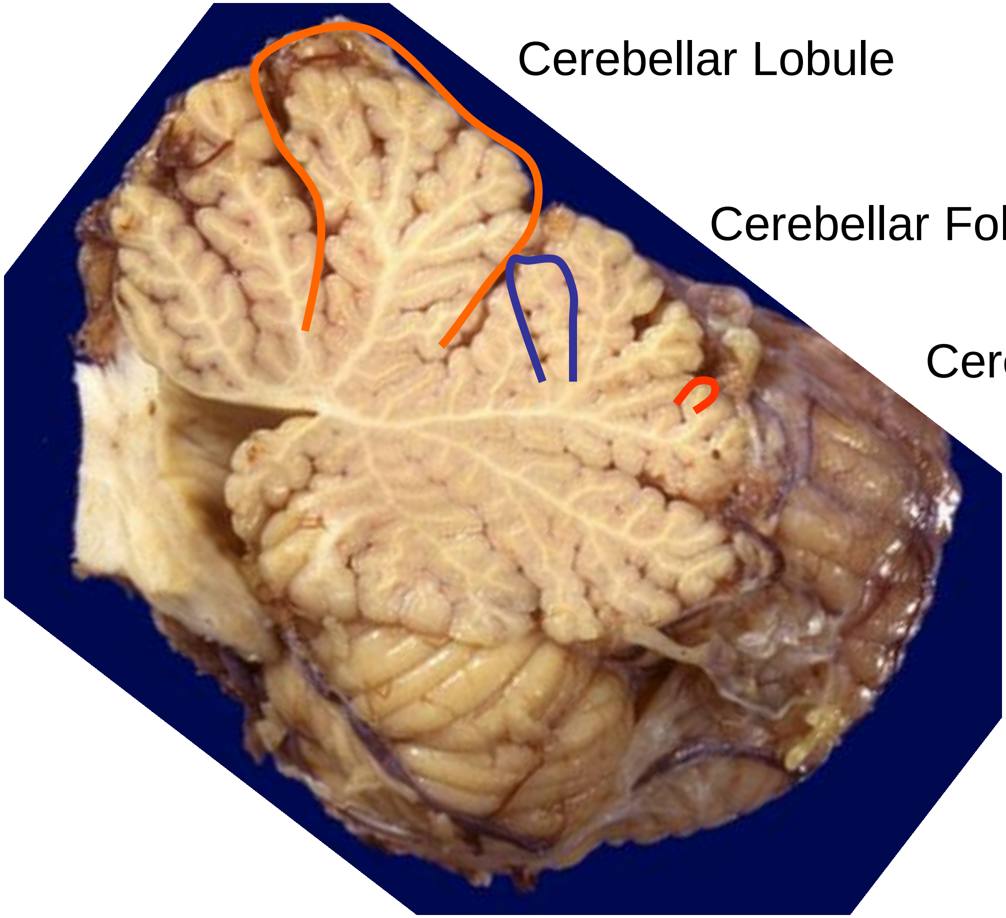


Vermis

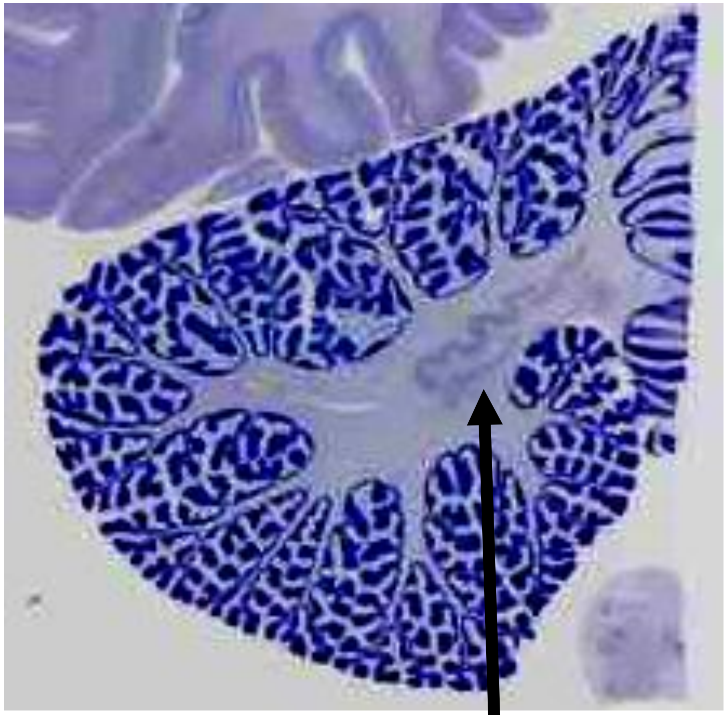
Hemispheres

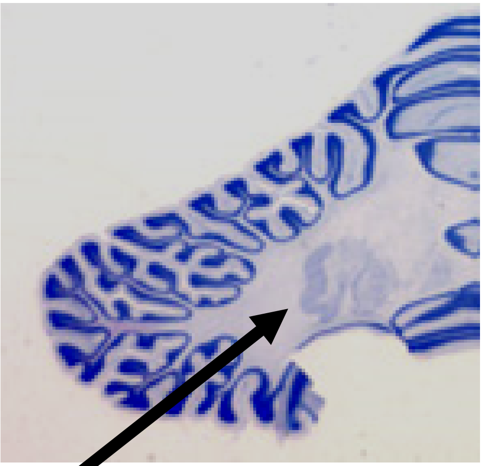
Flocculus+ Nodulus = Flocculunodular lobe, the oldest part of the cerebellum

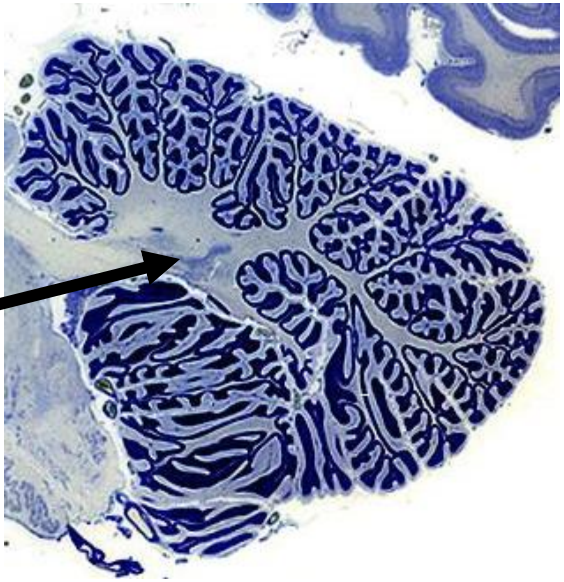
Lobes and Lobules of the Cerebellar Cortex



The Cerebellum is not Only Cortex…







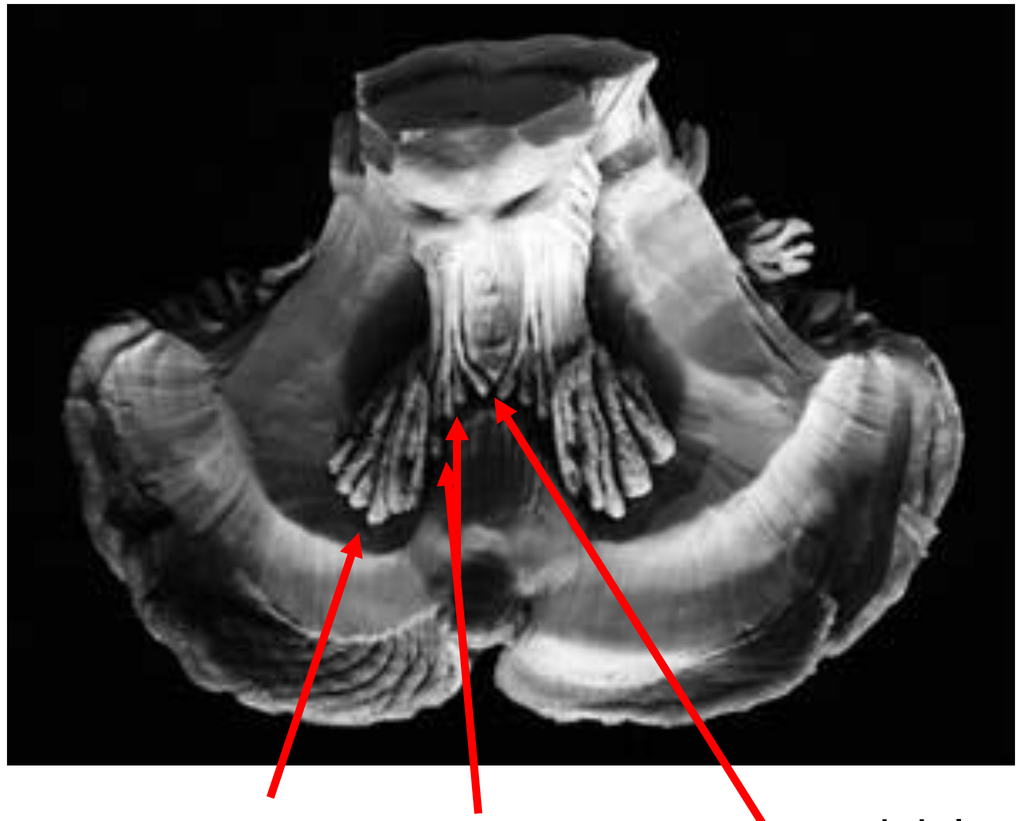
Deep Cerebellar

Nuclei (DCN)

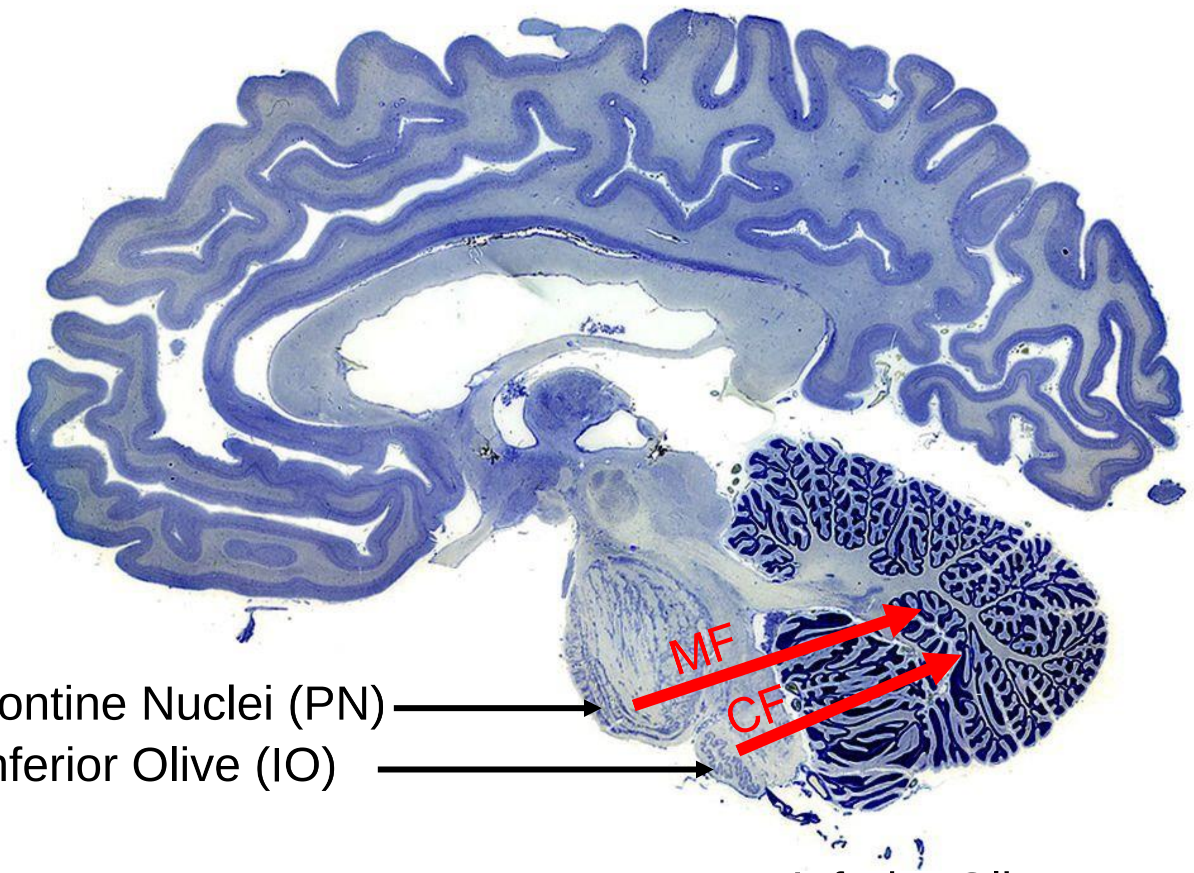
The Deep Cerebellar Nuclei (DCN) are the Output Relays of the Cerebellum

The DCN are the only output relay of the entire system

The vestibular nucleolus, In the medulla, anatomically and functionally is an external DCN which subserves vestibular cerebellar regions (mainly flocculunodular lobe and vermis)



Two Major Input Pathways Serve the Cerebellum



Pontine Nuclei (PN)

Inferior Olive (IO)

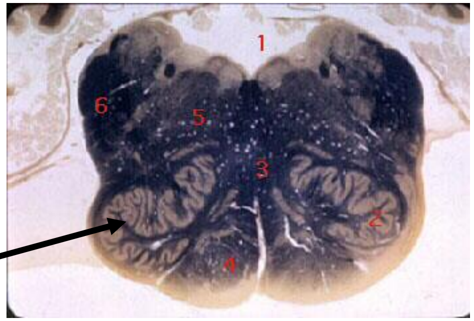
CF = Climbing Fibers

(All via the IO)

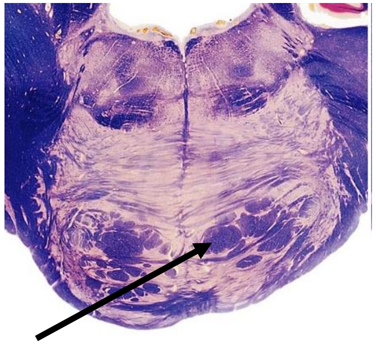
MF = Mossy Fibers

(~90% via the PN)

Inferior Olive



Pontine Nuclei



The IO receive low level motor and sensory inputs

Visual Inputs:

SC = Superior Coliculus

NOT = Nucleus of Optic Tract

Vestibular Inputs:

VN = Vestibular Nucleus

Motor Command:

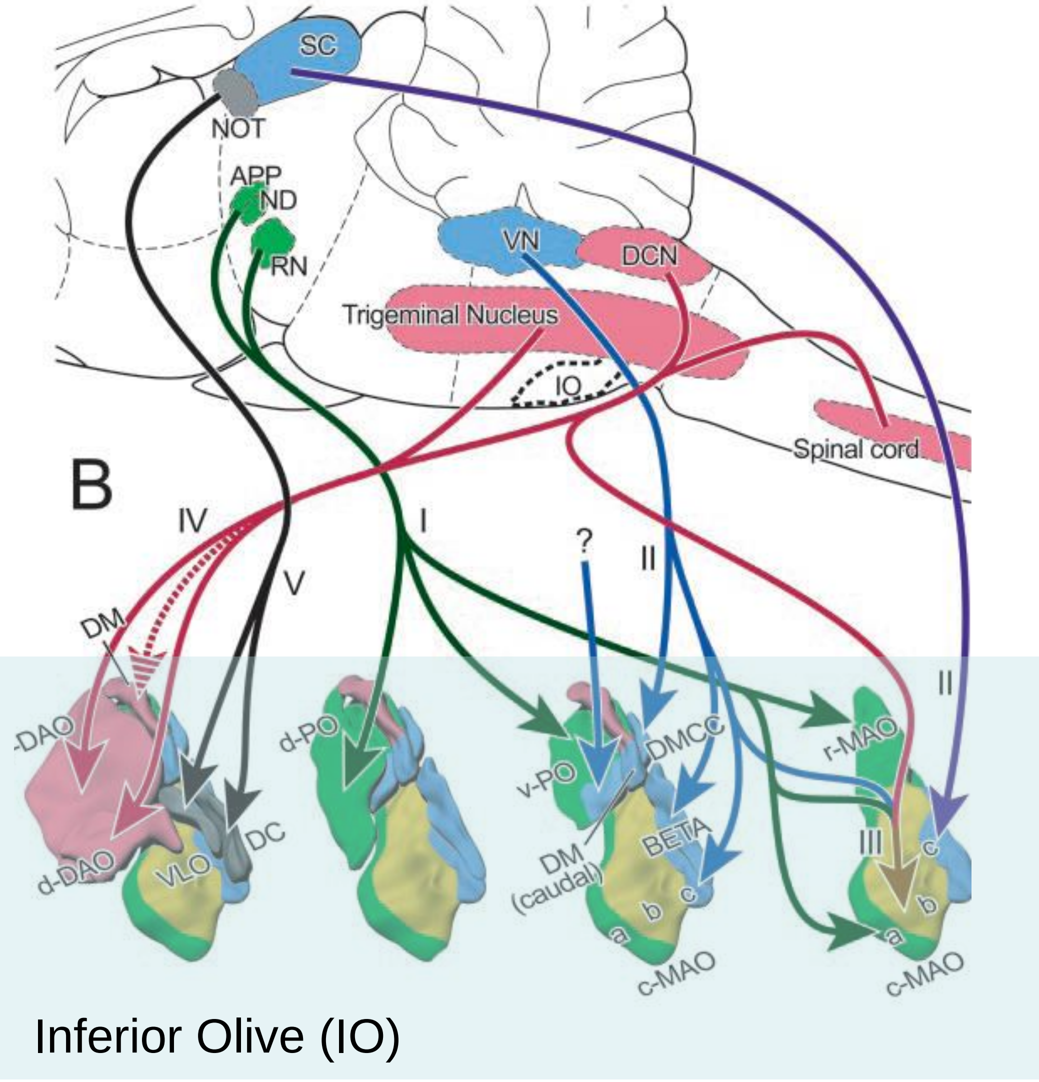
RN = Red Nucleus

Somatosensory & Proprioceptive:

DCN = Dorsal Column Nucleus

Trigeminal & Spinal Chord

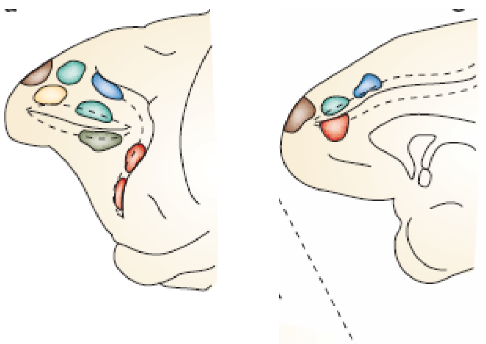
Additionally: Auditory Inputs

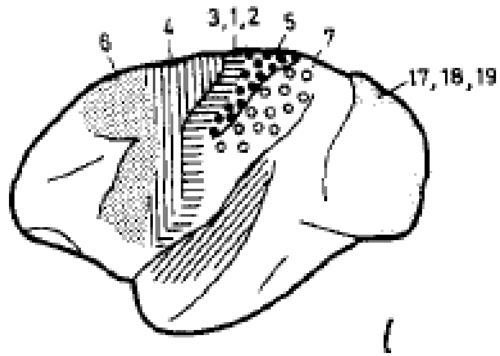


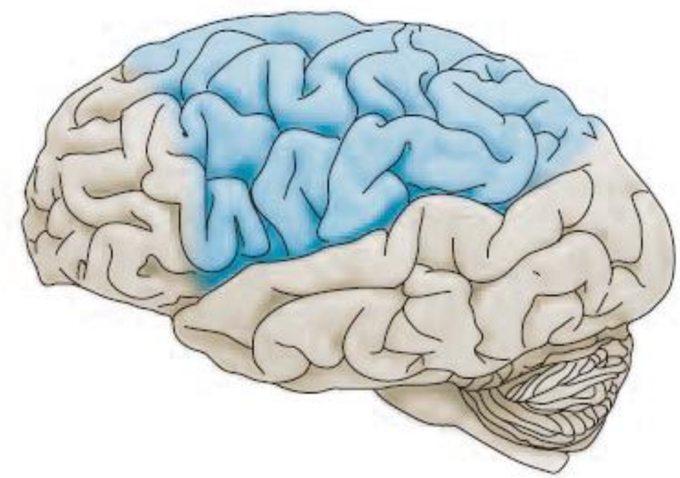
Each olivary sub-nuclei receive specific types of inputs and project to specific cerebellar region

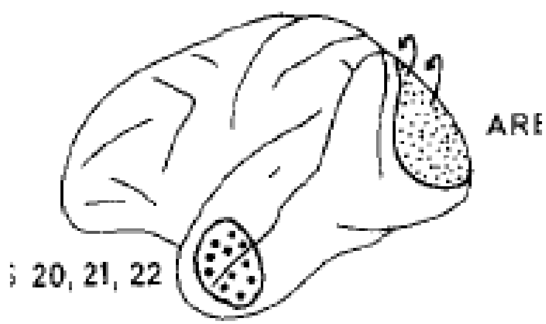
Sugihara & Shinoda JNS 2004

The Pons relay extensive Forebrain Information

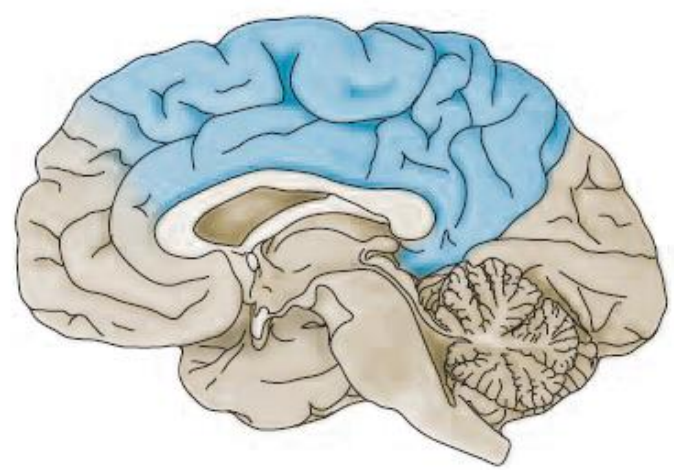








(Brodal 1978)

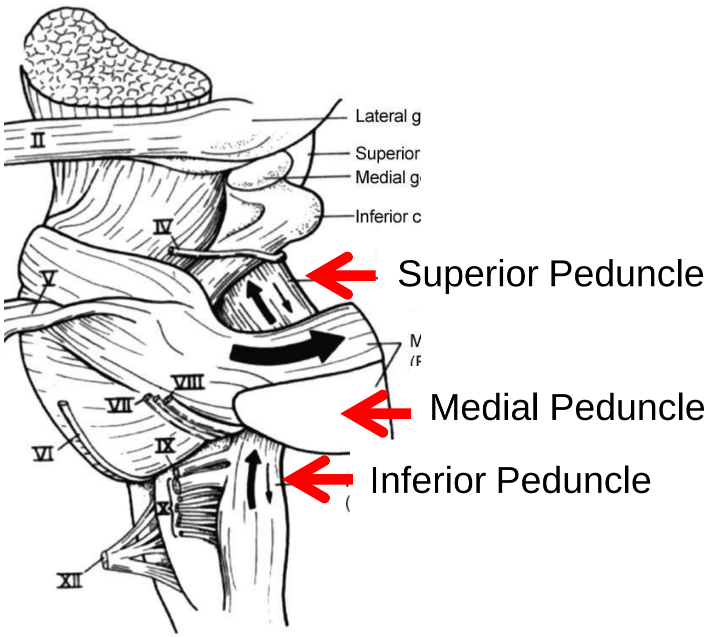


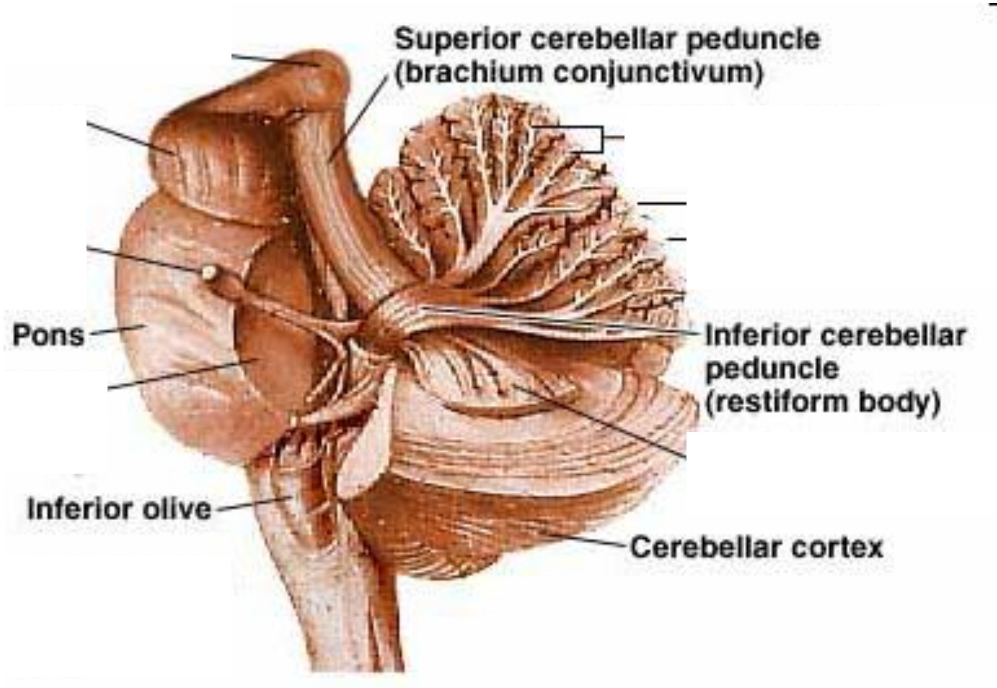
Non-Cortical Inputs:

1. Mamilary Body
2. Amygdala
3. Midbrain Nuclei
4. Spinal Inputs

Cortical Areas That project to the Pontine Nuclei (retrograde tracing)

Cerebellar Peduncles: Input / Output Highways





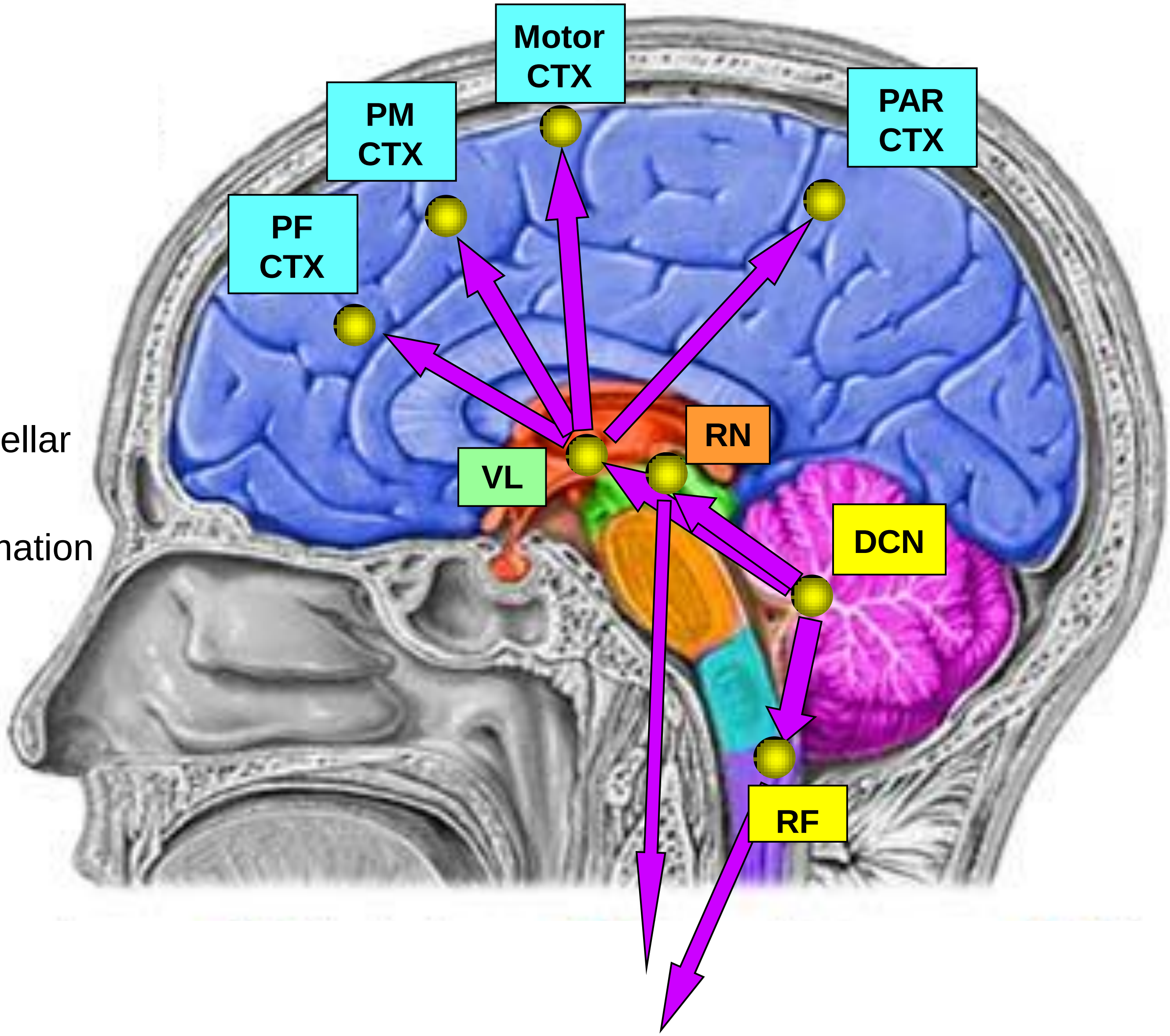
Superior: Thalamus/Midbrain Inputs/Outputs

Medial: Pontine Inputs and Commissure

Inferior: Spinal/Medullary Inputs/Outputs

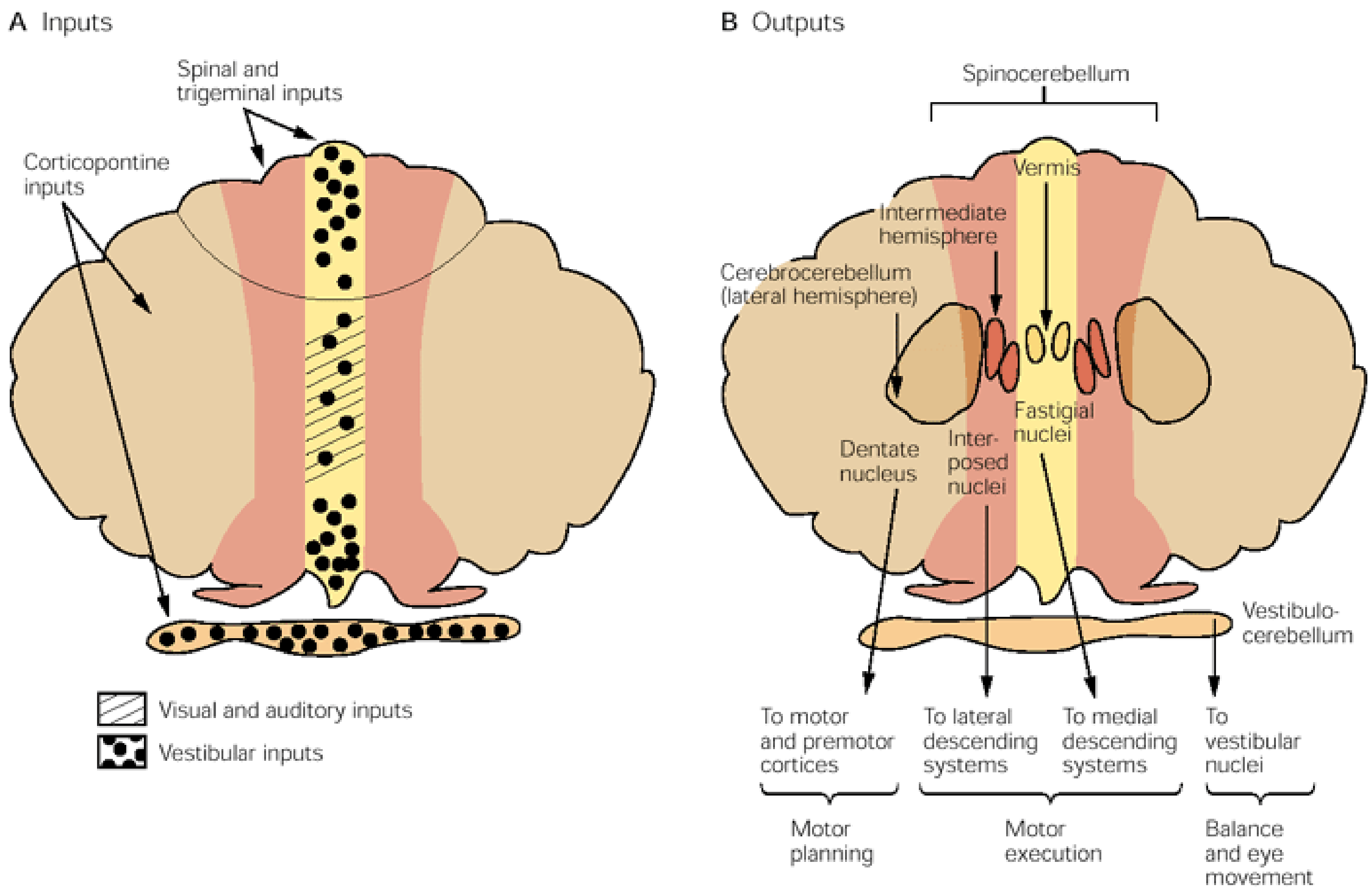
Cerebellar Major Output Pathways

CTX = Cortex
PM = Premotor
PAR = Parietal
PF = Prefrontal
RN = Red Nucleus
VL = Ventrolateral Thalamus
DCN = Deep Cerebellar Nuclei
RF = Reticular Formation



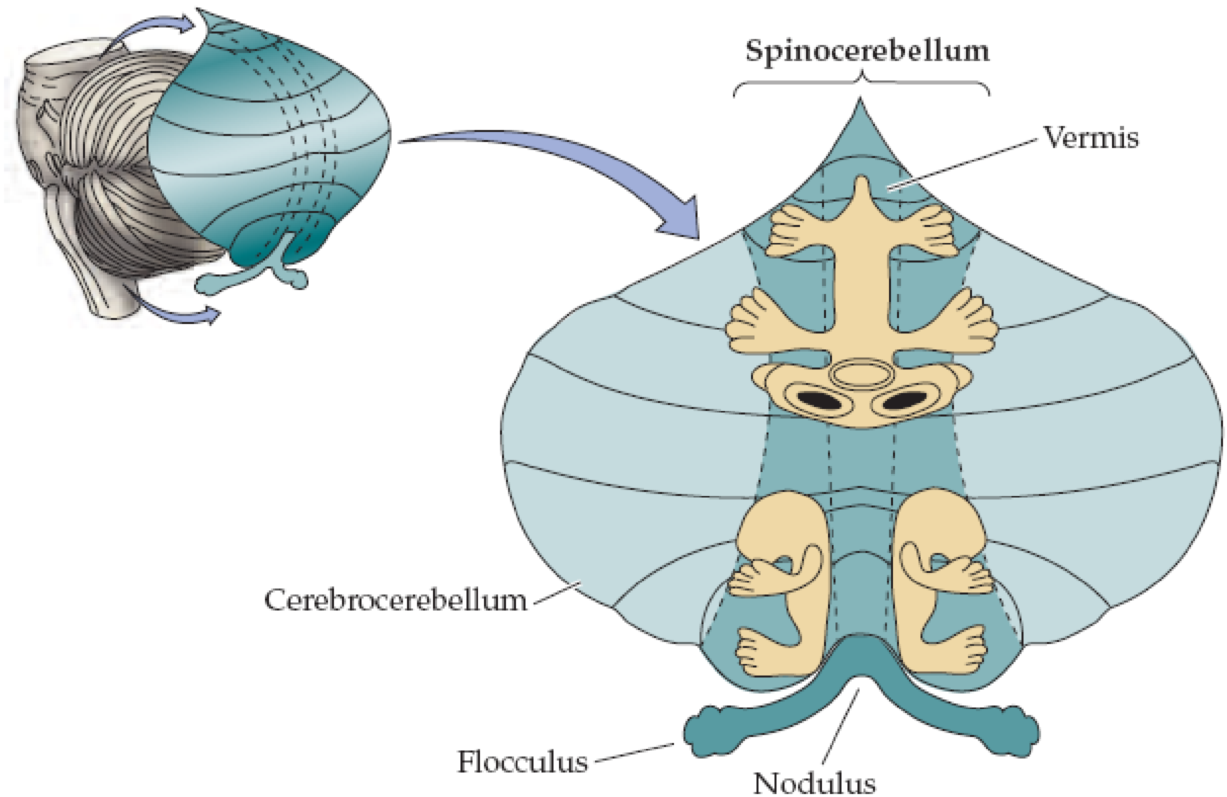
Other Outputs:
Inferior Olive
Hippocampus
Amygdala
Septum

General Mapping of Cerebellar Areas

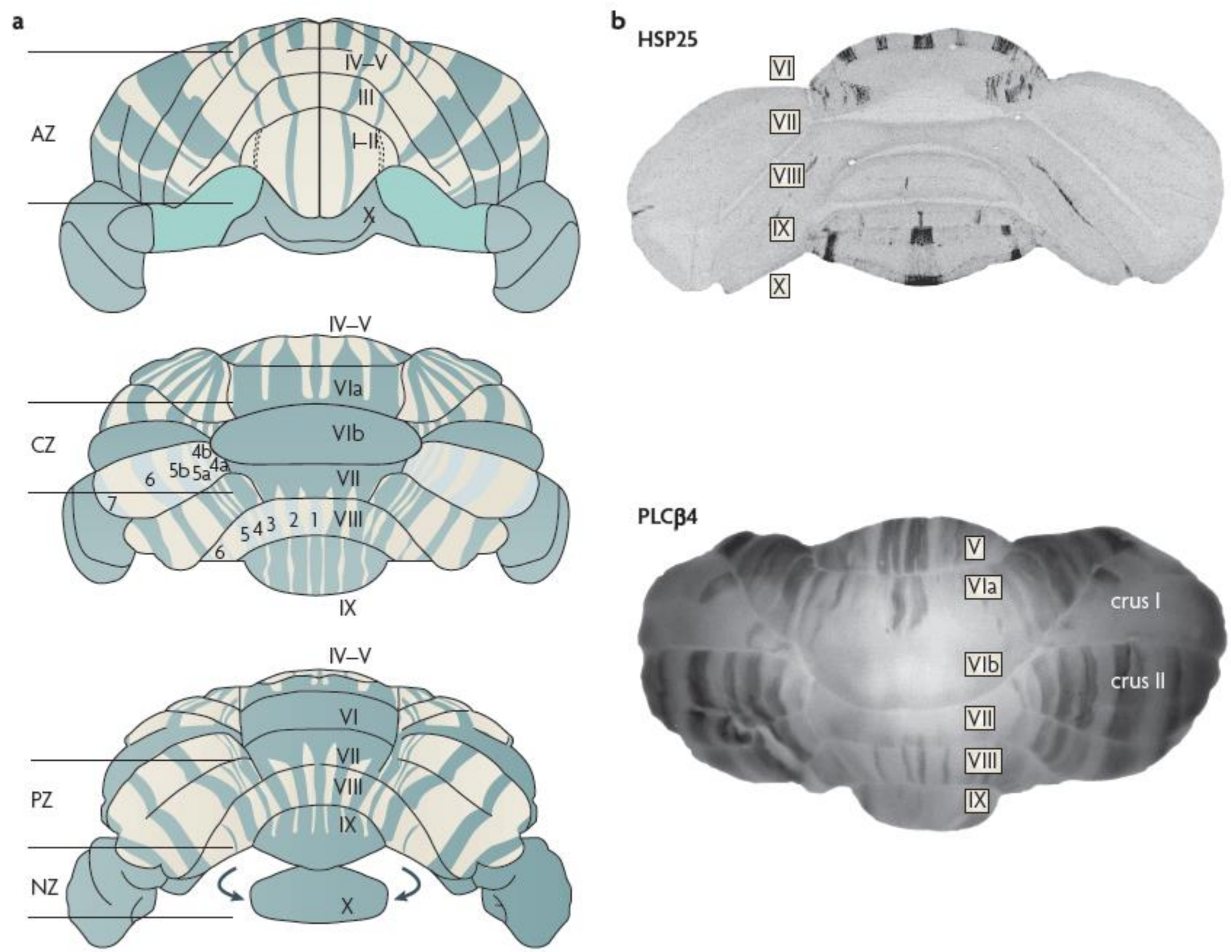


Dentate nucleus outputs also target parietal and prefrontal cortices. All projections to the cerebral cortex are relayed via the thalamus (mostly ventrolateral portion).

Mapping of Cerebellar Cortex – Classic View

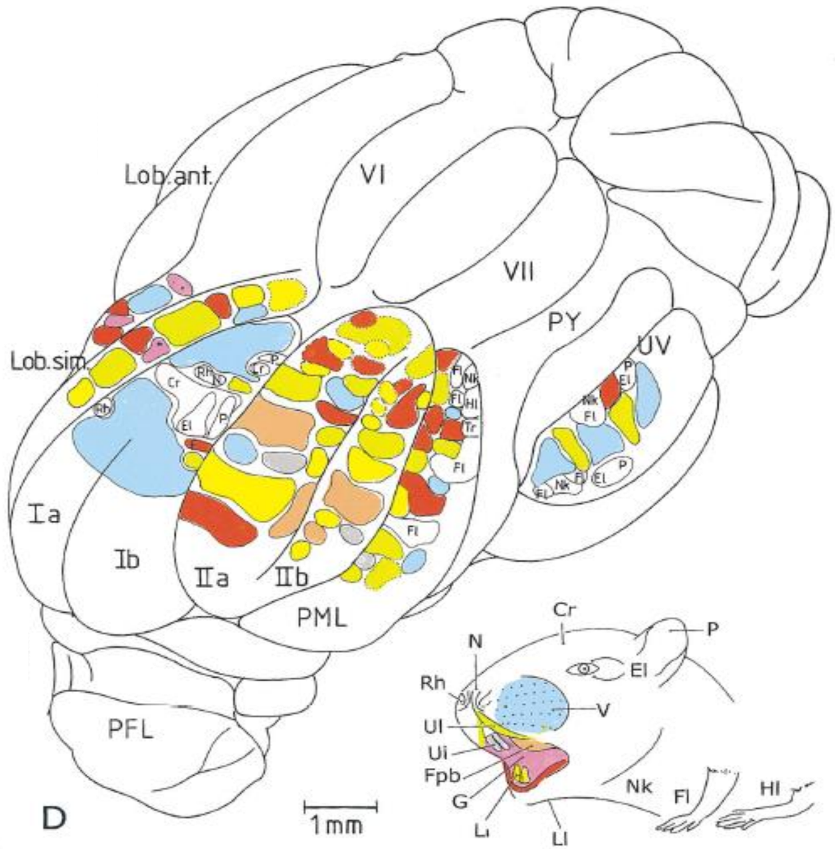


Parasaggital Microzones of Cerebellar Cortex



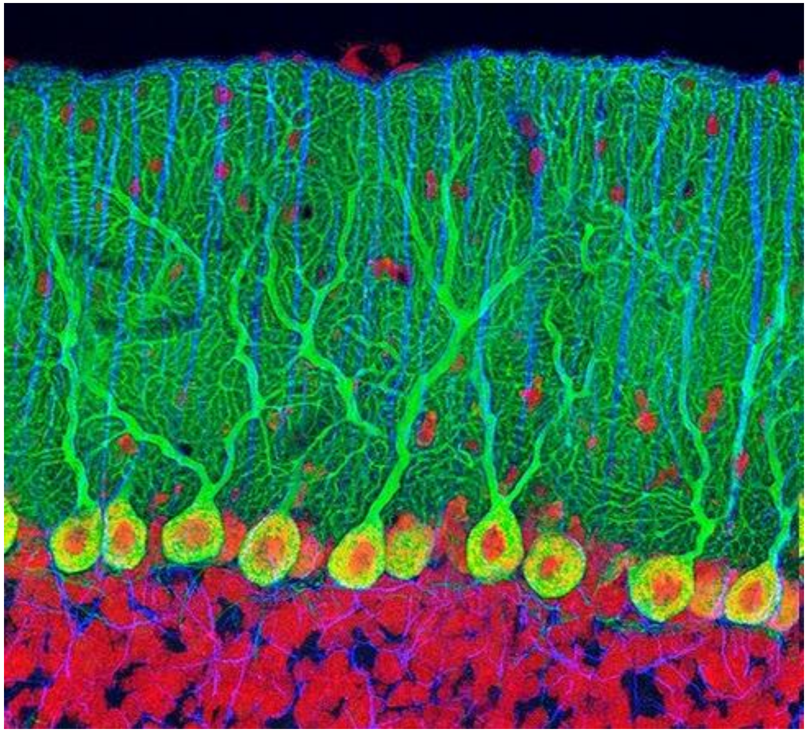
Some Molecular Markers (i.e. Zebrin II) divide Purkinje Cells Populations into parasaggital stripes.

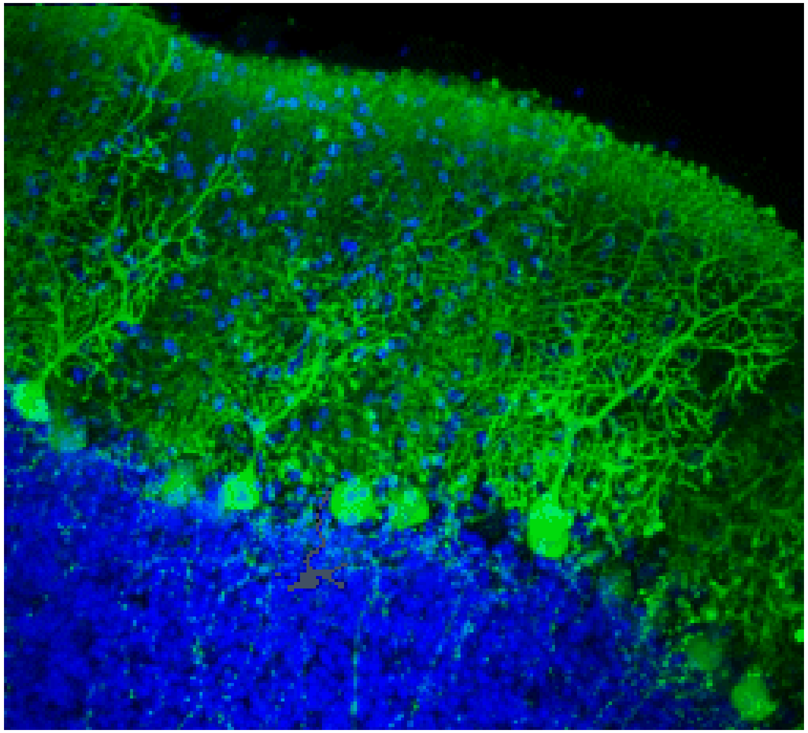
Functional Cerebellar Mapping is Fragmented



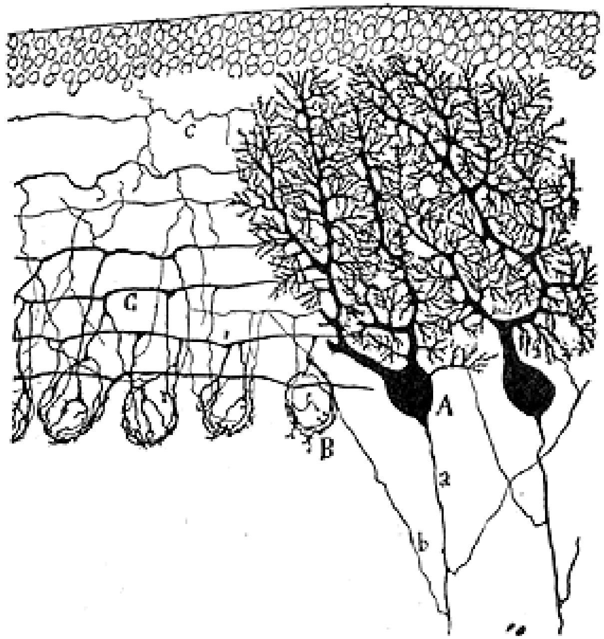
Voogd and Glickstein 1998

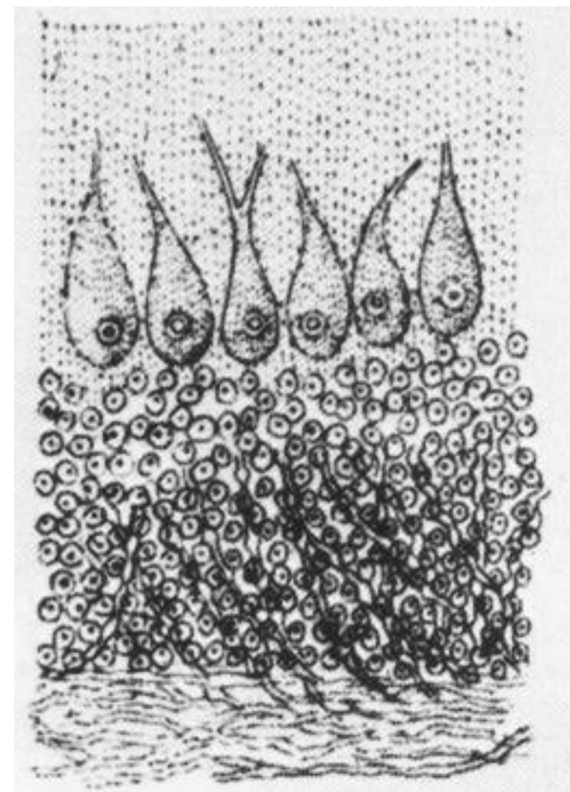
Cerebellar Cortex:
The Beauty of Network Architecture



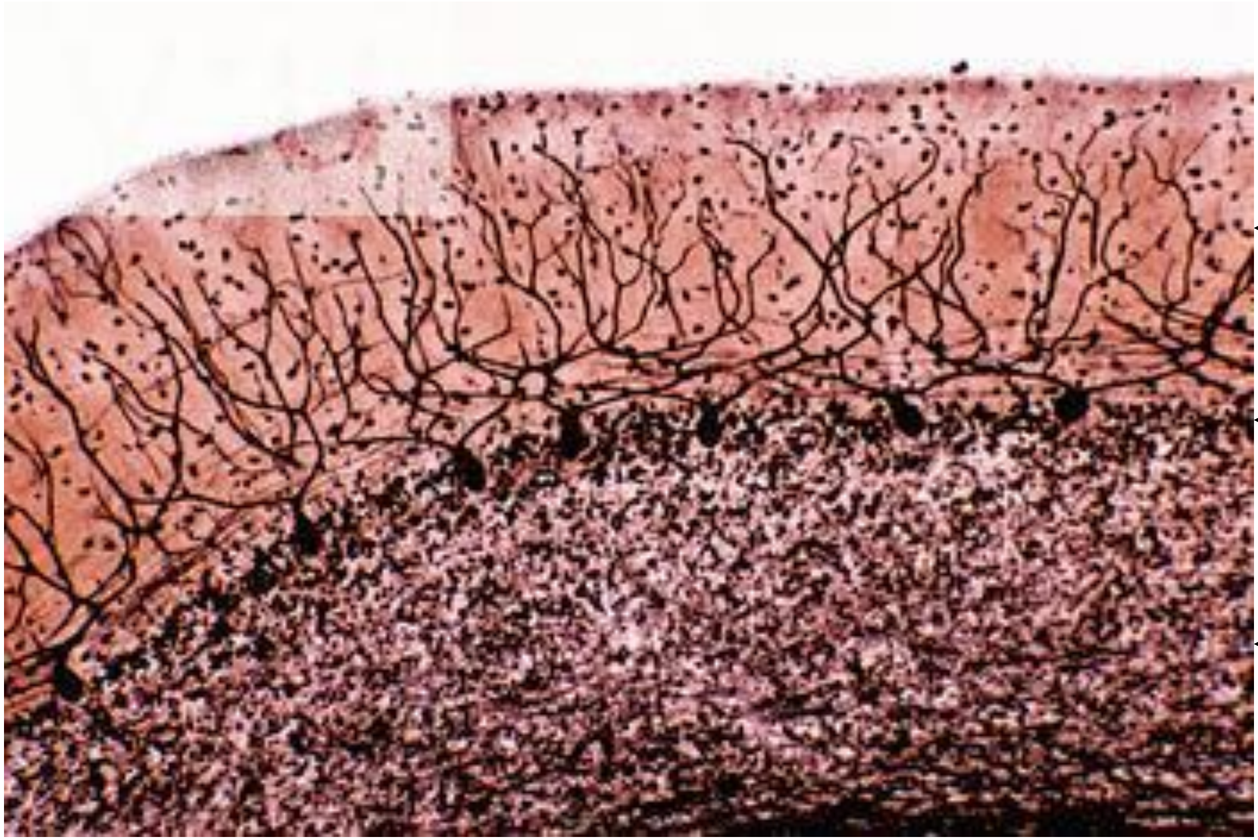


Purkinje Cells: The most Elaborate Neurons of the CNS





The 3 Layers of the Cerebellar Cortex

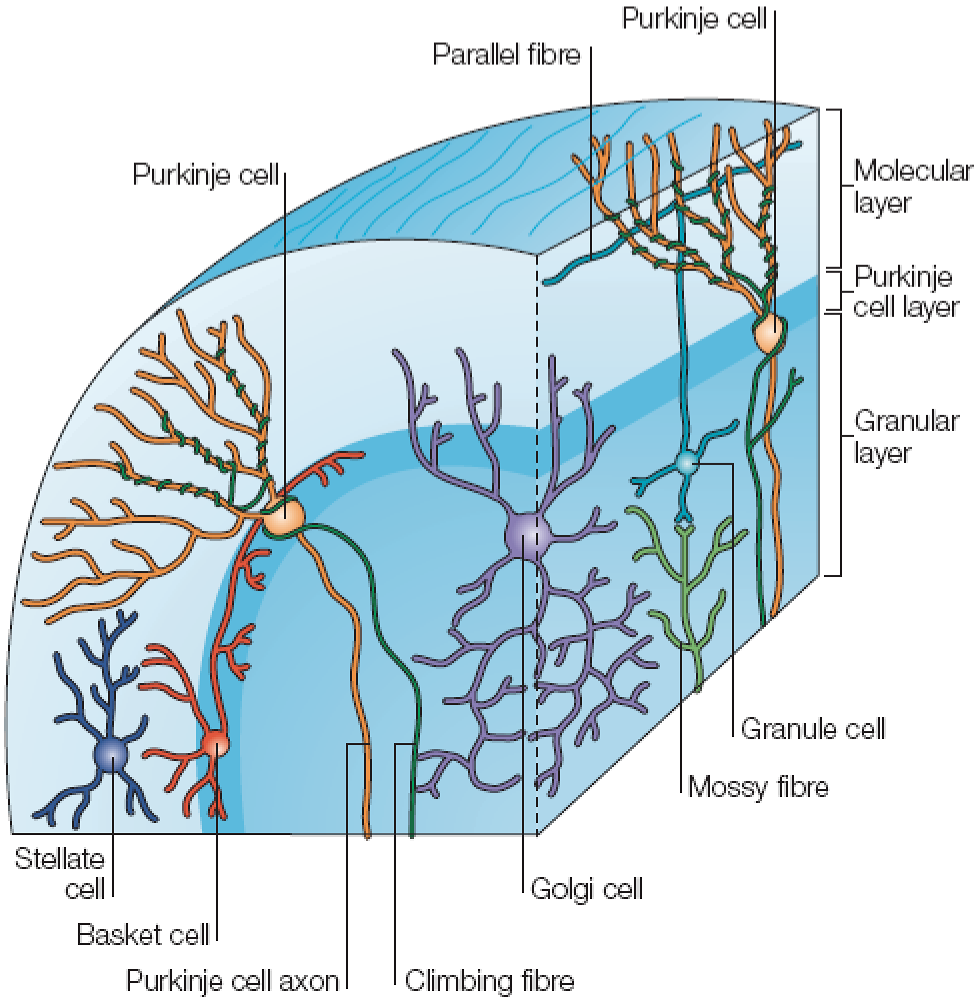


Molecular Layer

Purkinje cell Layer

Granule cell Layer

Cerebellar Cortex Consists of 5 types of Neurons

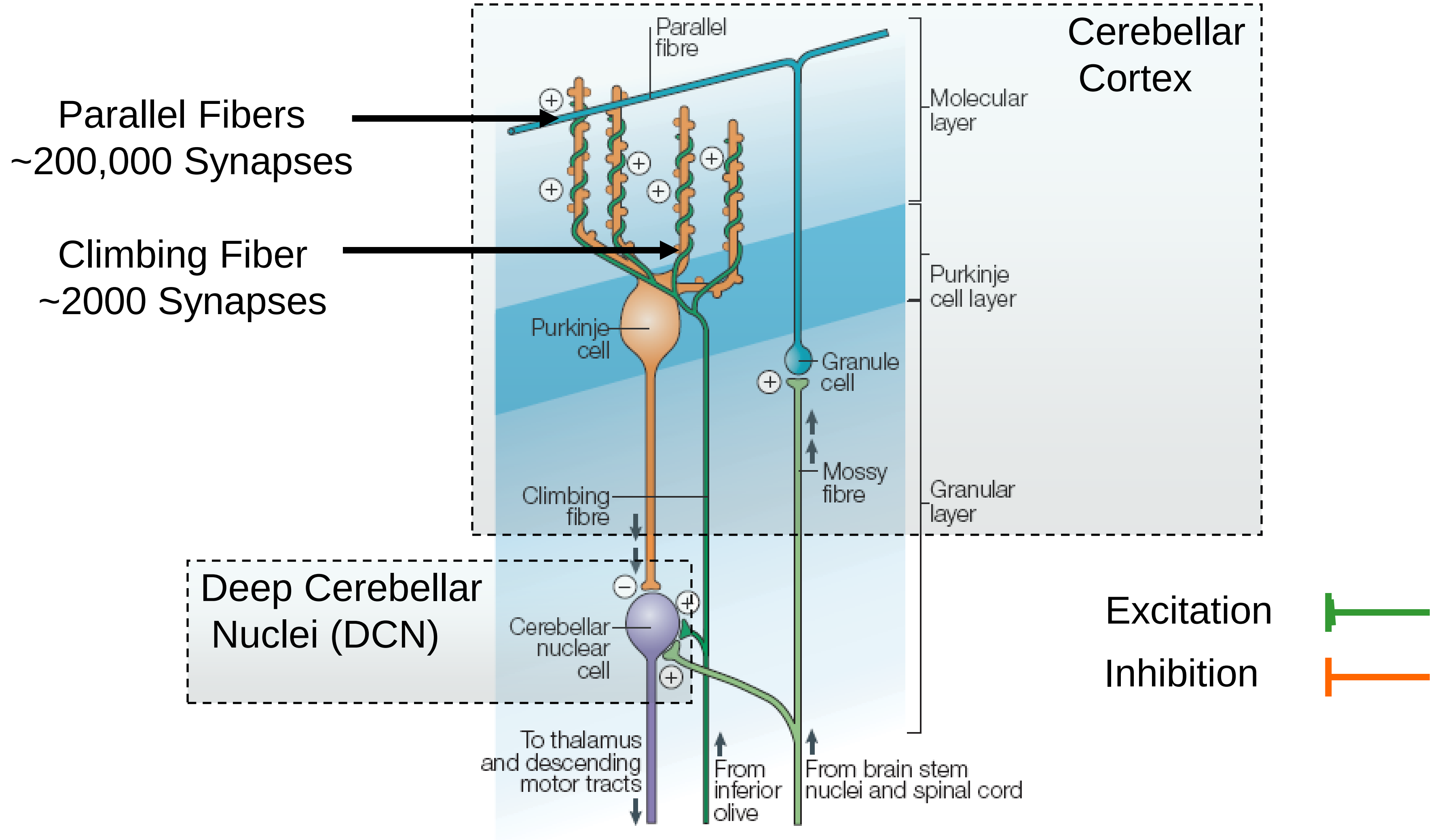


Inhibitory cells:
- Purkinje
- Golgi
- Basket
- Stelate

Excitatory Cells:
- Granule cells

Apps & Garwicz NatRevNeu 2005

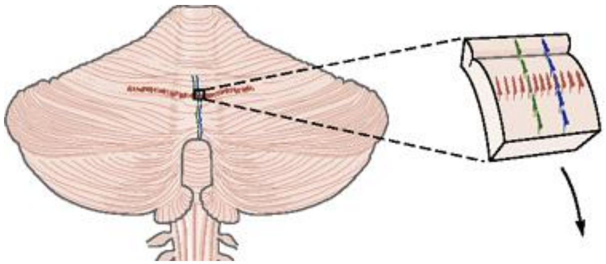
PC: The Principal Cell of Cerebellar Cortex



Purkinje Cells are the only neurons projecting from the Cerebellar Cortex!!

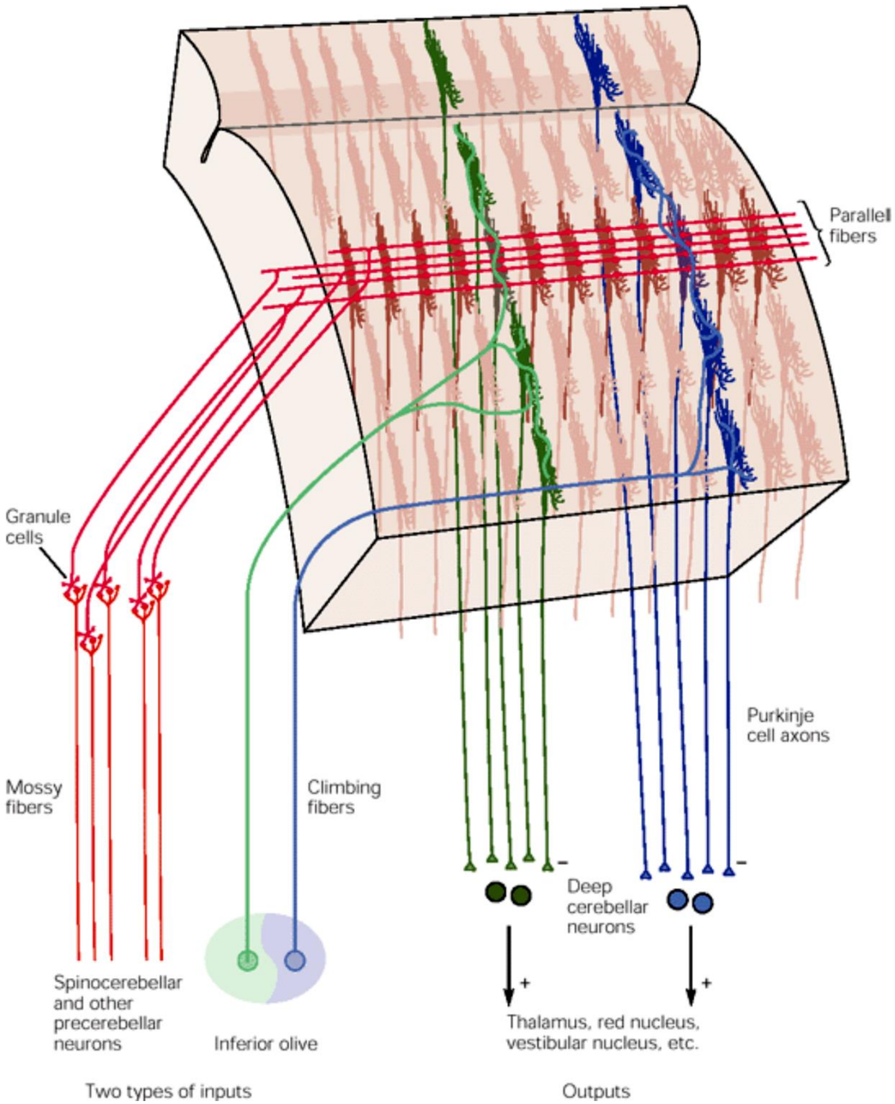
Modified from Apps & Garwicz 2005

The Spatial Organization of Cerebellar Circuitry

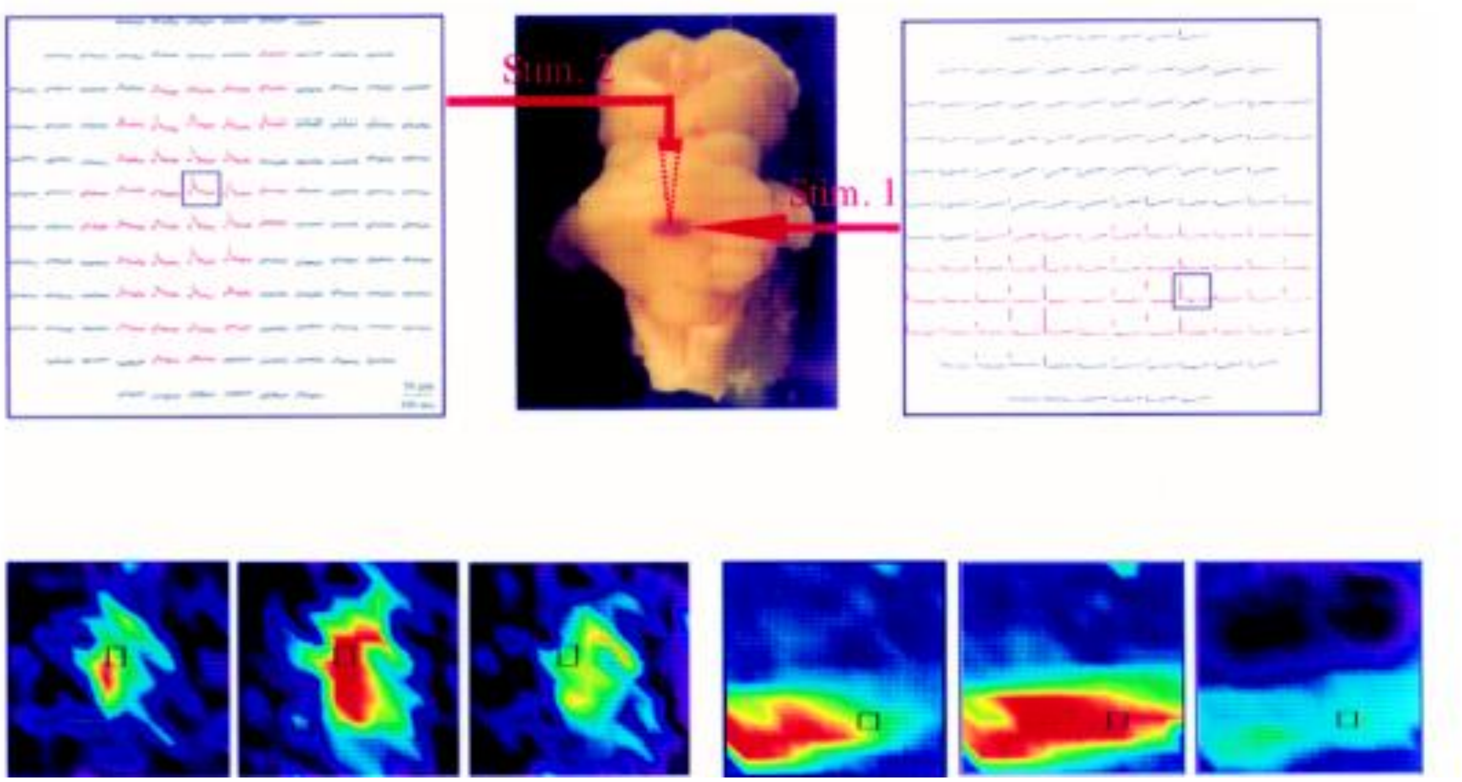


Notice the perpendicular relationship between Mossy Fiber and Climbing Fiber enervations!!

The arrangement of PCs that are innervated by a single olivary neuron (or an ensemble) match the parasagittal microzones



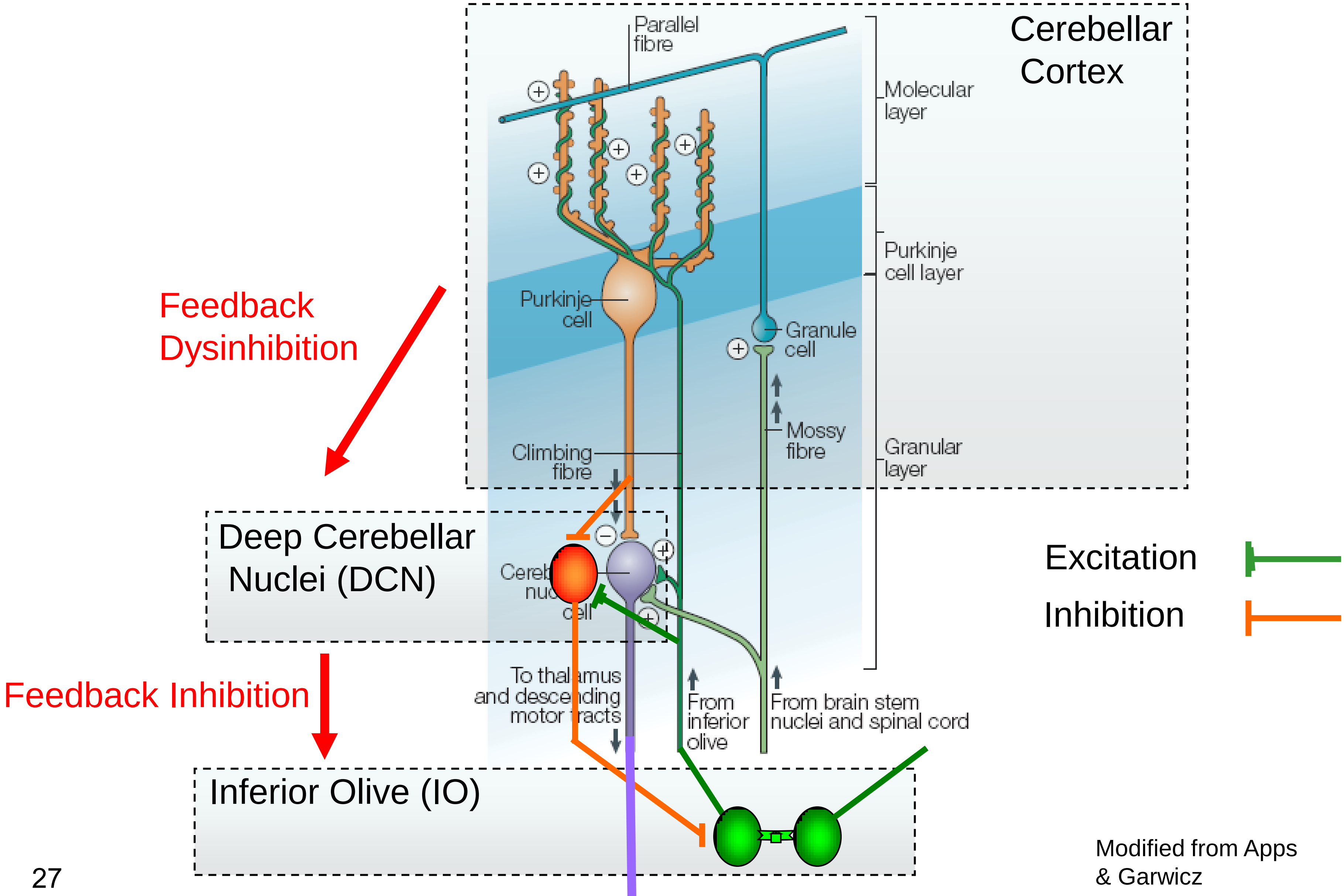
Parallel fibers are not a delay line: local inhibition prevents signal propagation



Stimulation of granular layer **Stimulation of parallel fibers**

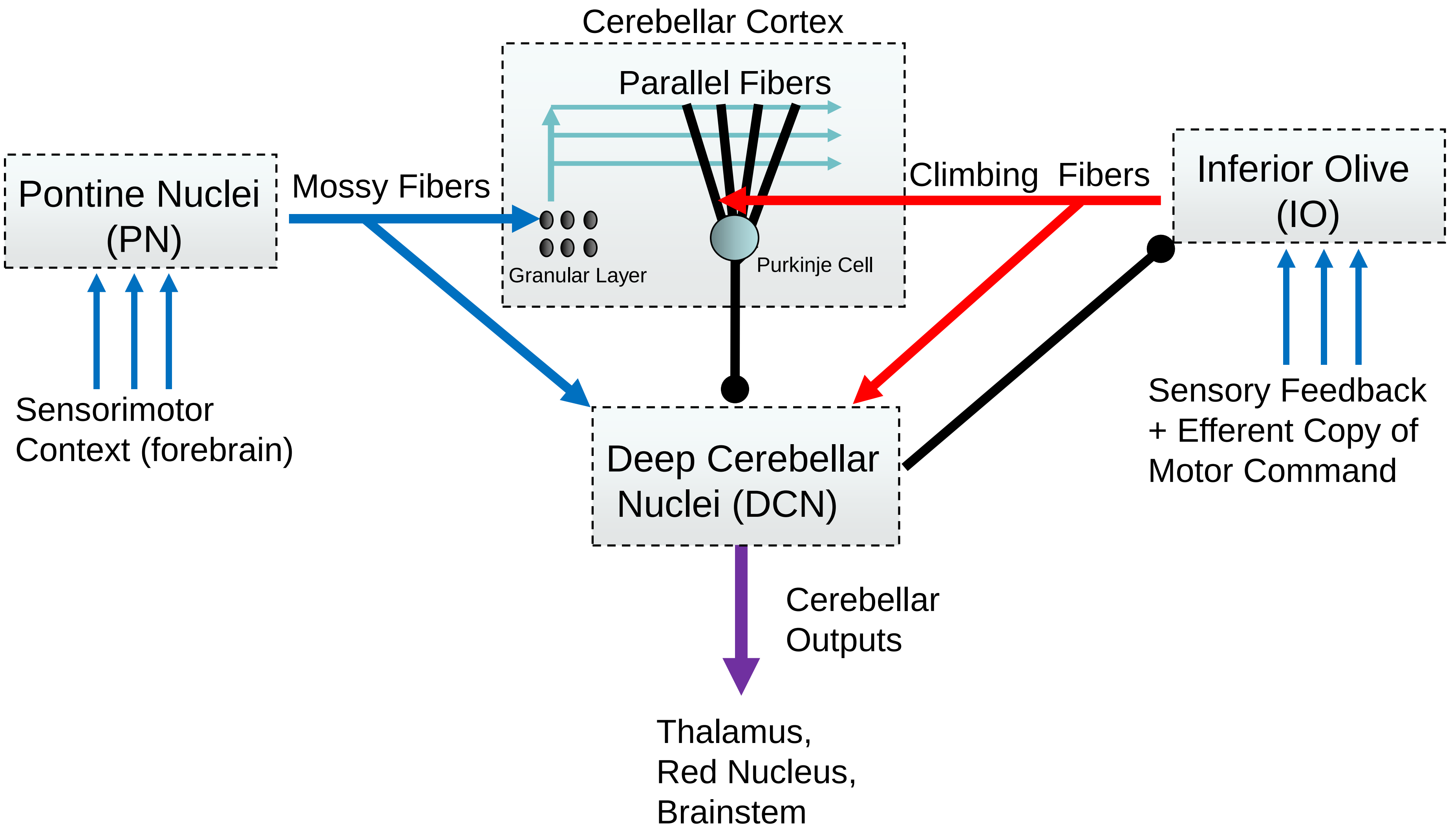
Yarom and Cohen AnnNYAc 2003

Closing the Loop: The Cerebellar Module

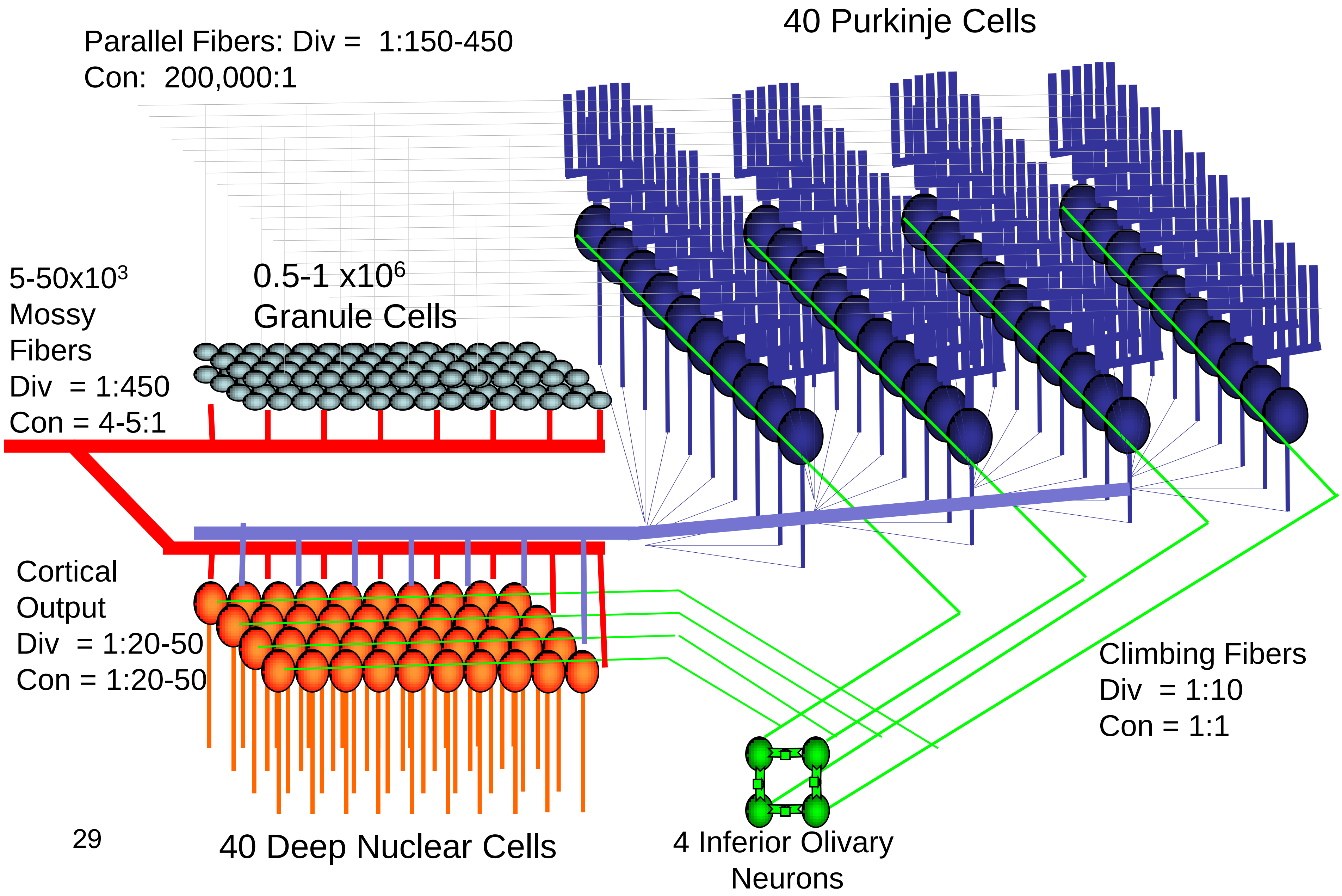


Modified from Apps & Garwicz NatRevNeu 2005

The simplified Olivocerebellar Module



The Numerics of Cerebellar Modules



Cerebellar Physiology

Infra Red

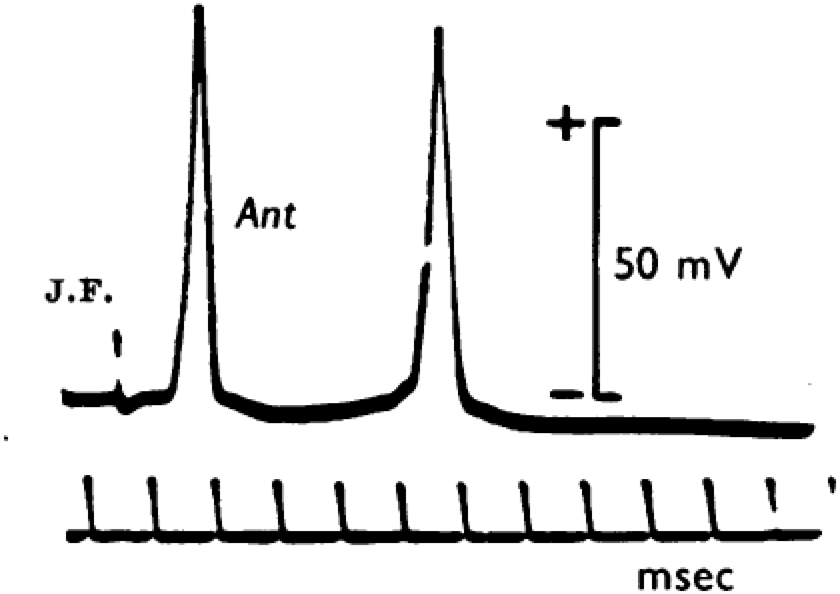
Fluorescent Dye

Double Recording of Purkinje Cell in Slice

Hausser M.

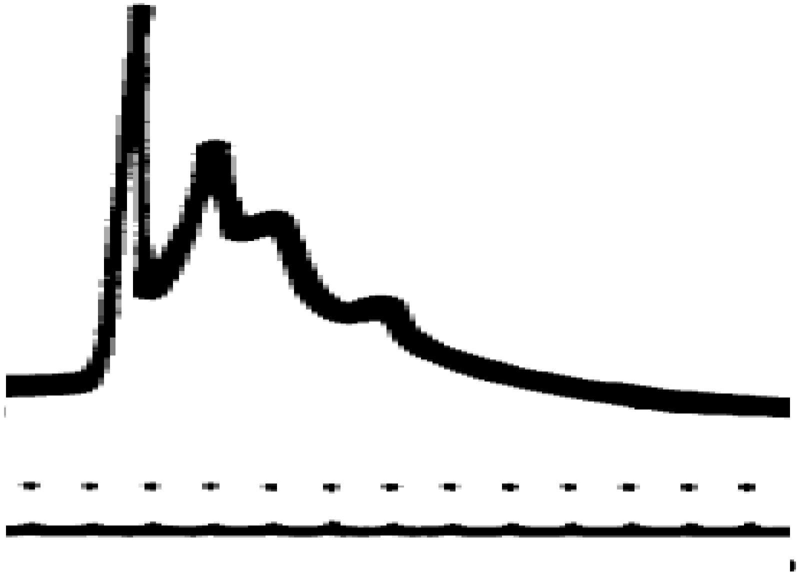
Purkinje Cells exhibit Two distinct Spike Types

Simple Spike (SS)



Mossy Fiber Stimulation

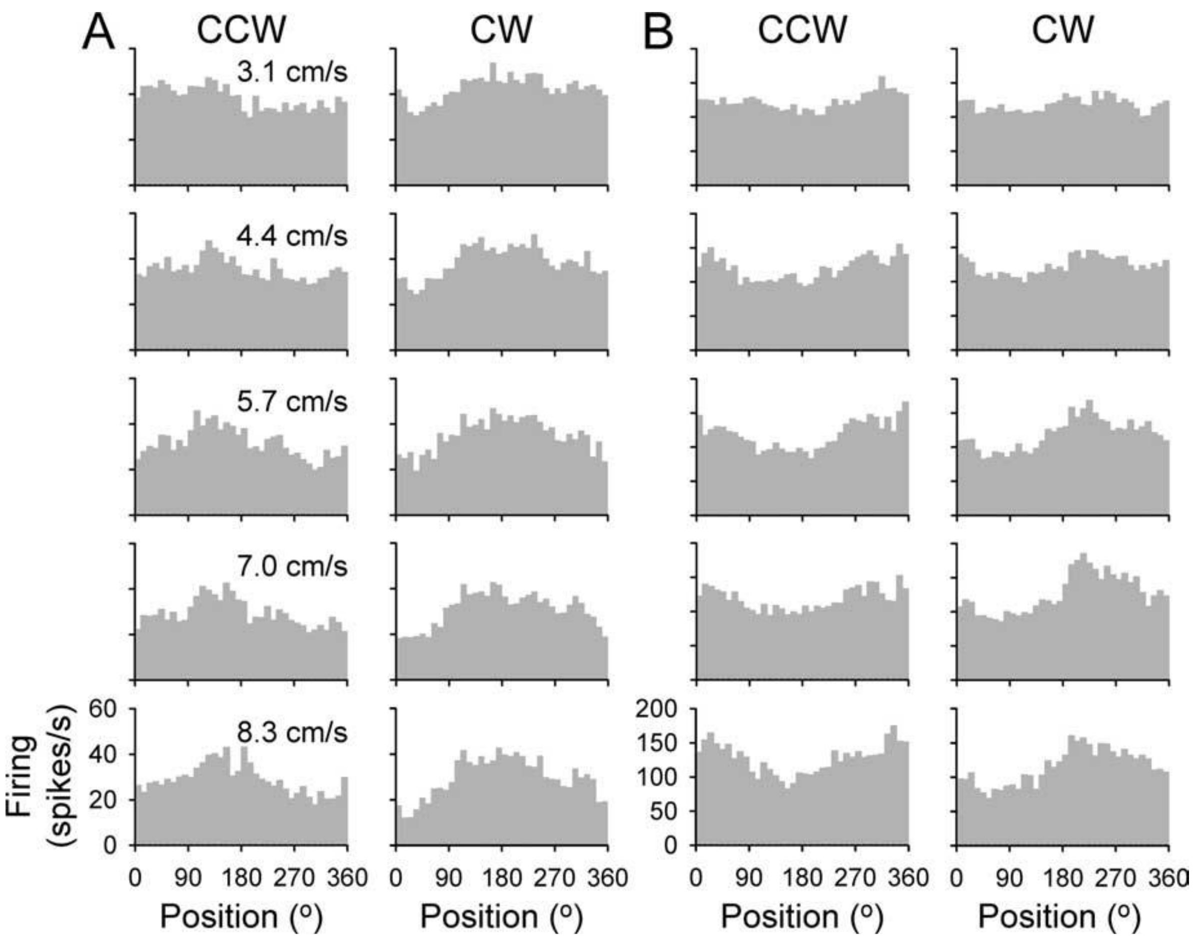
Complex Spike (CS)



Inferior Olive Stimulation

Eccles, 1966

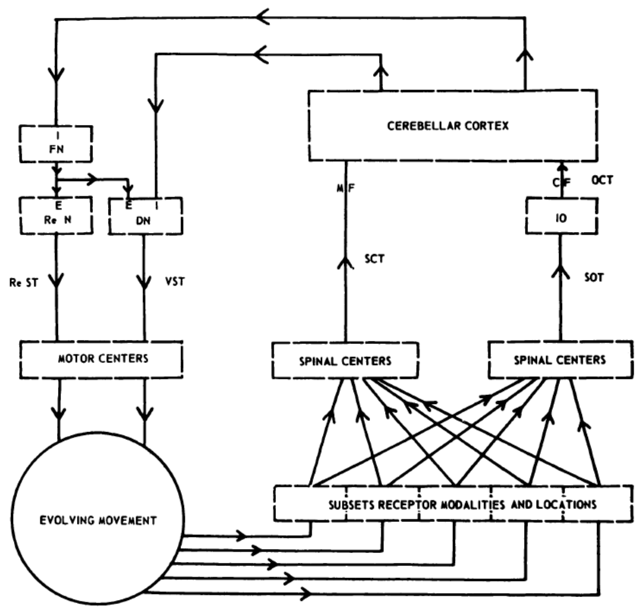
Simple Spikes are Modulated by Inputs



Simple spikes of 2 Purkinje cells in awake monkey during hand movements: Rate encodes position and depth of modulation encodes the speed.

Roitman 2005

Cerebellar Learning Theories



Eccles, 1967

Due to the immense differences between simple spikes and complex spike dynamics, investigators like Eccles and theoreticians like Albus and Marr, developed models where olivary signal was a teaching signal (positive or negative) which generated refined parallel fiber input-output associational mapping.

J. Physiol. (1969), **202**, *pp.* 437–470
With 1 *plate and* 2 *text-figures*
Printed in Great Britain

A THEORY OF CEREBELLAR CORTEX

By DAVID MARR*
From Trinity College, Cambridge

(*Received* 2 *December* 1968)

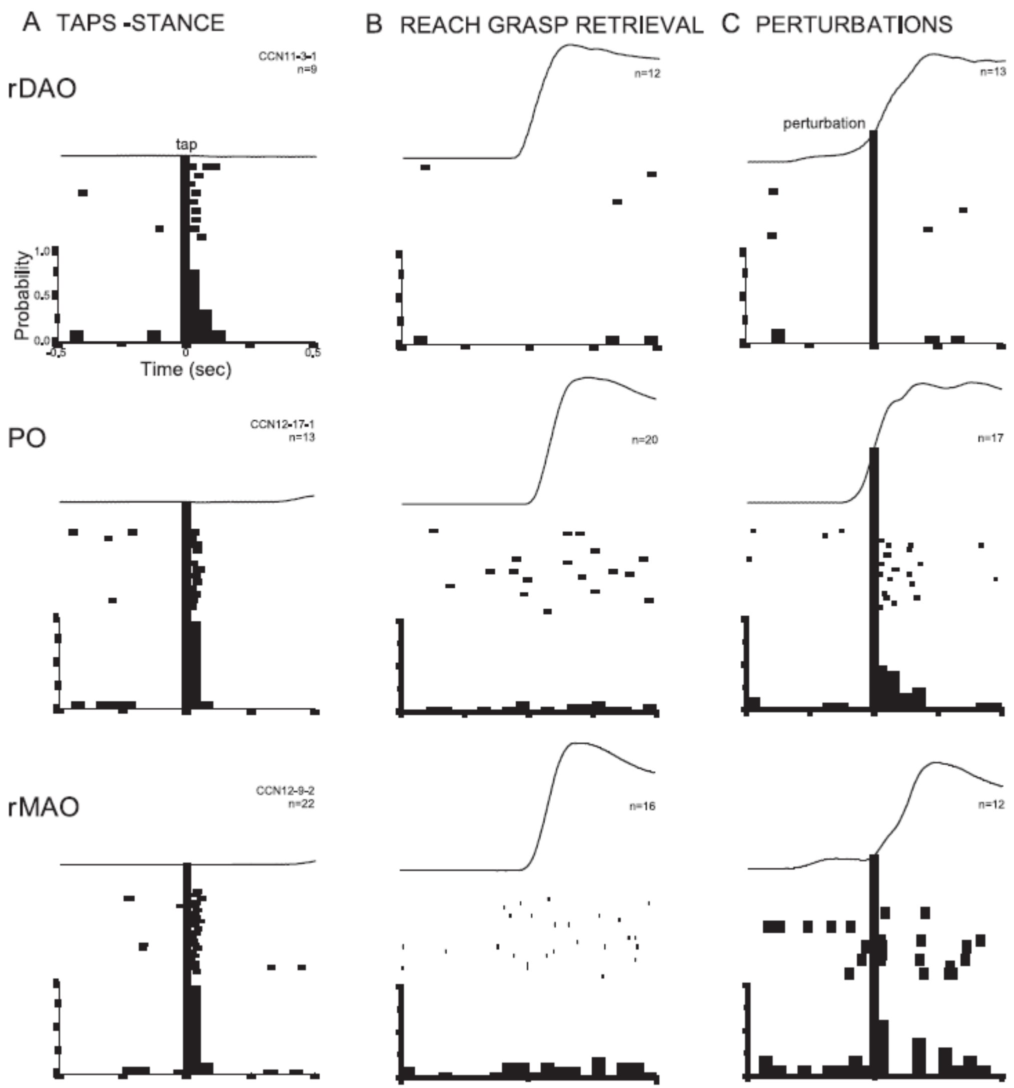
MATHEMATICAL BIOSCIENCES

A Theory of Cerebellar Function

JAMES S. ALBUS
Cybernetics and Subsystem Development Section
Data Techniques Branch
Goddard Space Flight Center
Greenbelt, Maryland

1971

Olivary Spikes are fired in Unexpected Events



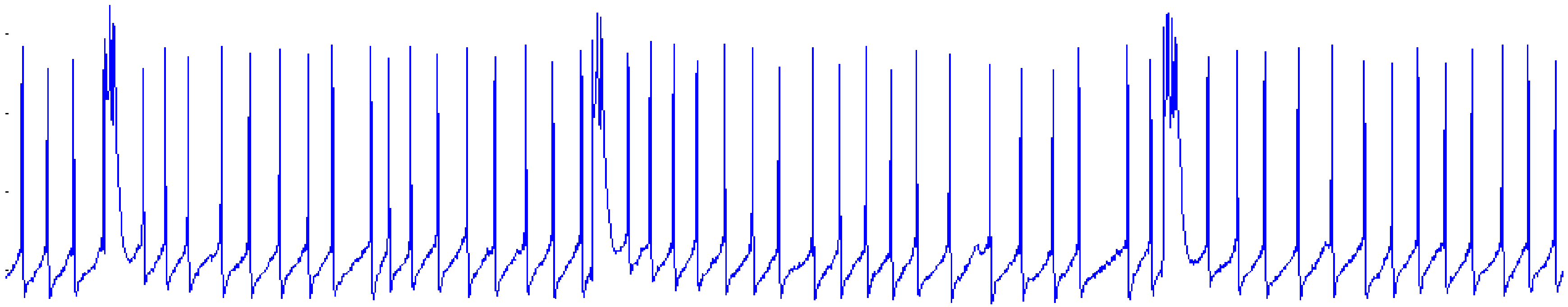
Indeed, olivary neurons fire mostly to unexpected stimulus or an omission of an expected stimulus (reach perturbation)

When the cats did a non - perturbed reaching movement there was no elevated firing, suggesting encoding of error (expectation mismatch) which suits a teaching signal.

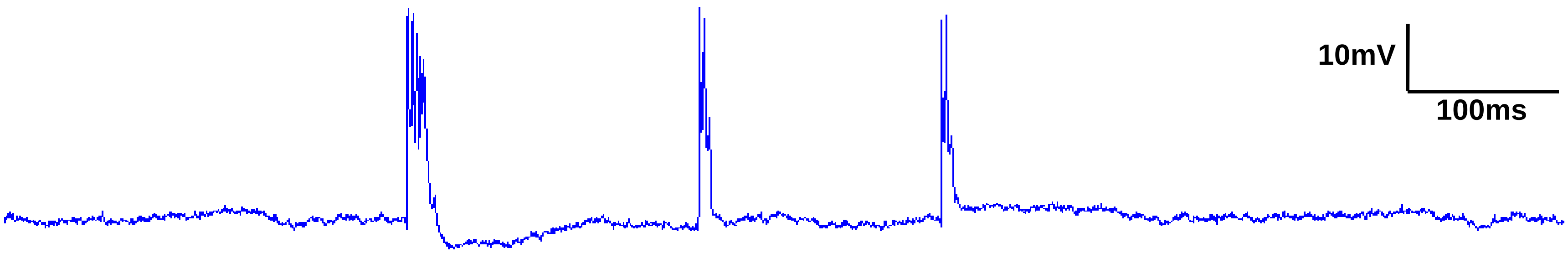
Horn, Pong & Gibson 2002

Distinct Firing Regimes of Purkinje Cells

Complex Spikes & Simple Spikes (Up-State)



Complex Spikes Only (Down-State)

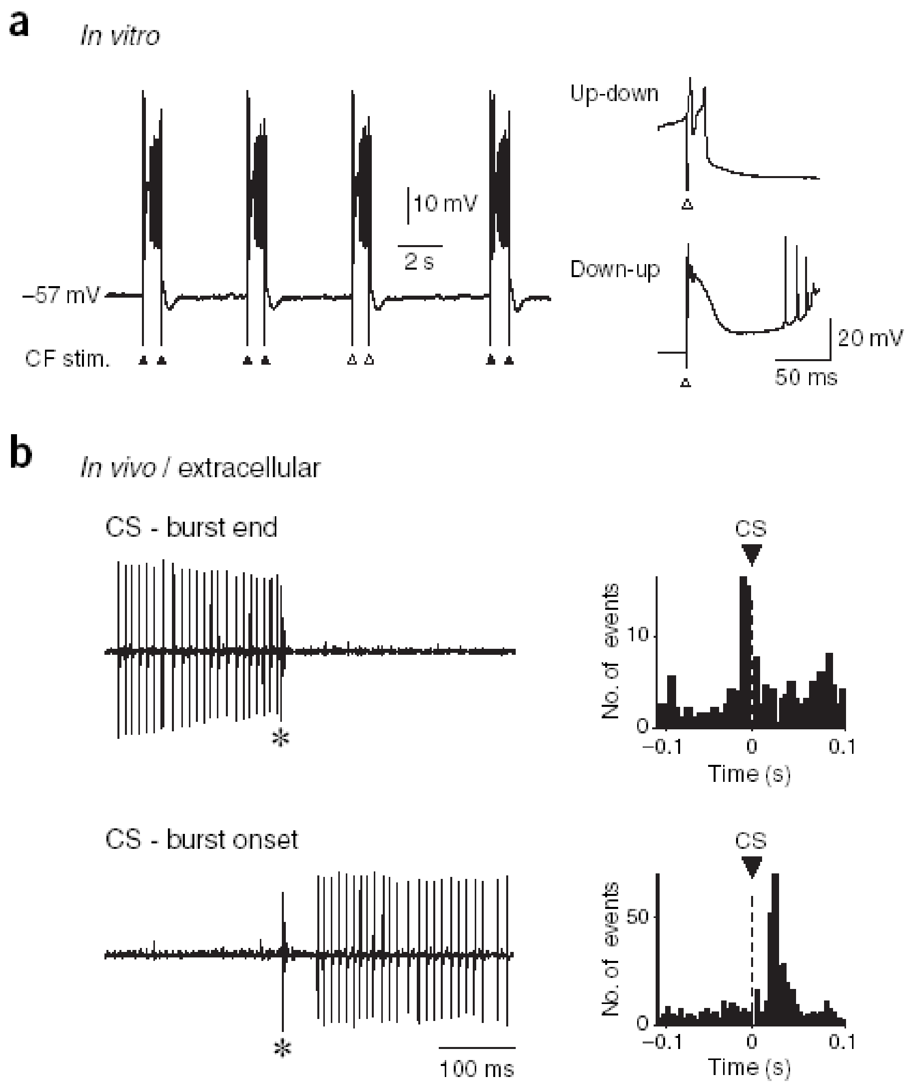


Simple Spikes: 0 - ~80Hz
(Mostly 0Hz or 4-8Hz or 20-80Hz, with possible phasic >100Hz)

Complex Spikes : 1-3Hz (Phasic 10-15Hz)

Cohen and Lamp (unpublished)

Complex Spikes as Purkinje Cell Switches

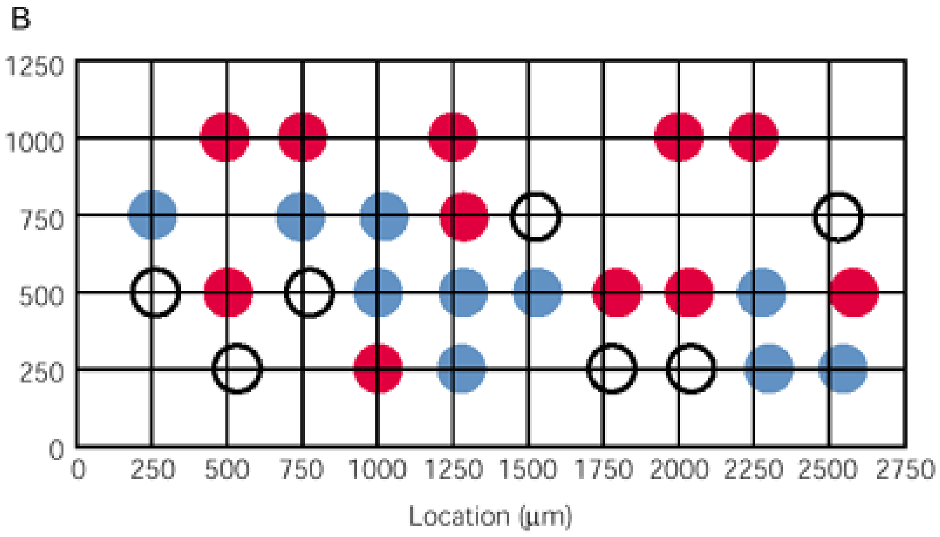


Transitions of up-down states in PCs are accompanied by elevation in CS firing, but not every CS drives a change…

Loewenstein et al. NatNS 2005

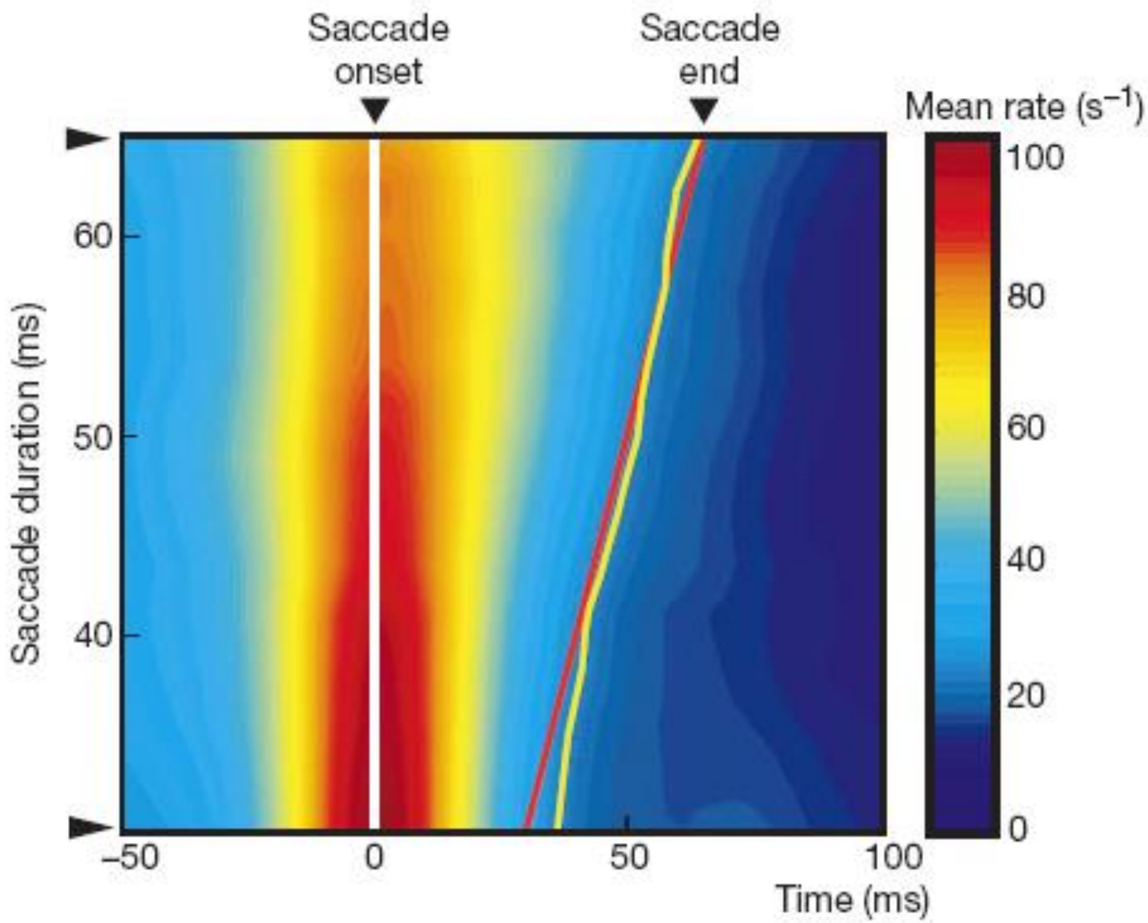
Synchronous Population Coding by Purkinje Cells

Motor function like licking is correlated with synchronous CS firing across large groups of PCs.



Welsh 1995

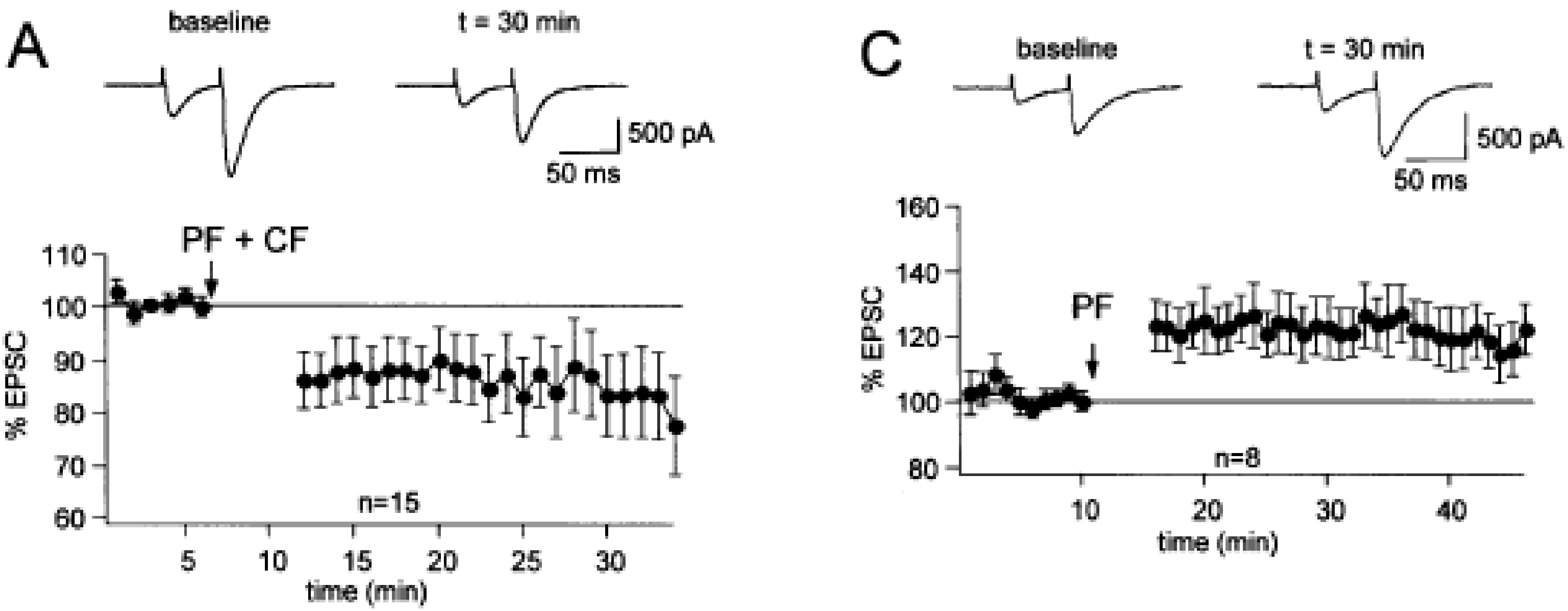
Saccade attributes are encoded by a population of ~100 Purkinje cells



Reading out the SS firing rate of about 100 PCs can tell you the exact position within a saccade (behaving monkeys).

Tier-Barash 2000

Plasticity in the Cerebellar Cortex

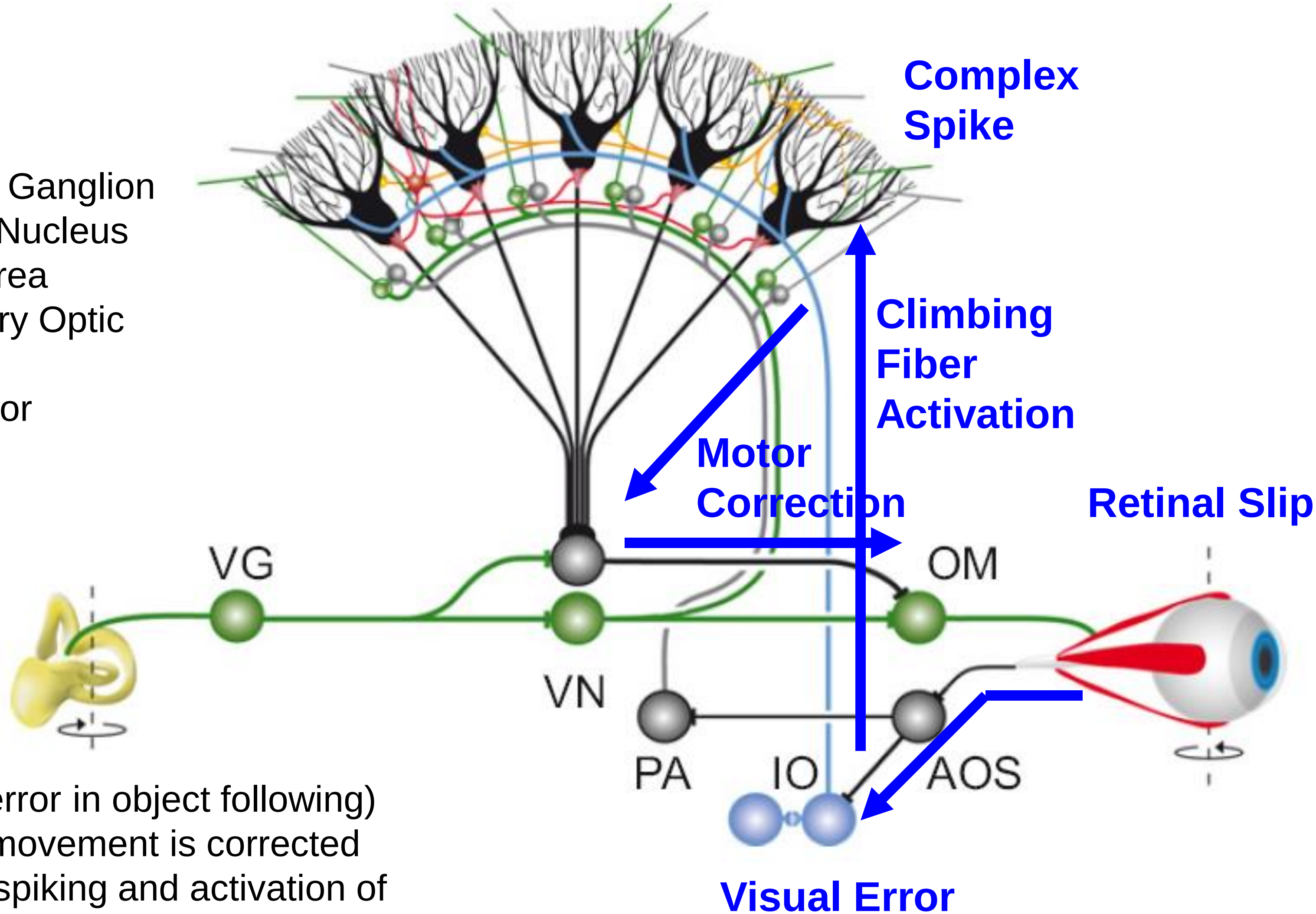


Bidirectional plasticity in parallel fiber synapses of PCs can subserve an exact temporal tuning to optimal execution time point.

Coesmans et al. Neuron 2004

Vestibulo - Ocular Adaptation (VOR)

VG = Vestibular Ganglion
VN =Vestibular Nucleus
PA = Pontine Area
AOS = Accessory Optic System
OM = Oculomotor Neurons



Retinal slip (error in object following) during head movement is corrected by acute PC spiking and activation of ocular motor neurons

Ito 1984, Schonville et al. 2010

Vestibulo - Ocular Adaptation (VOR)

VG = Vestibular Ganglion
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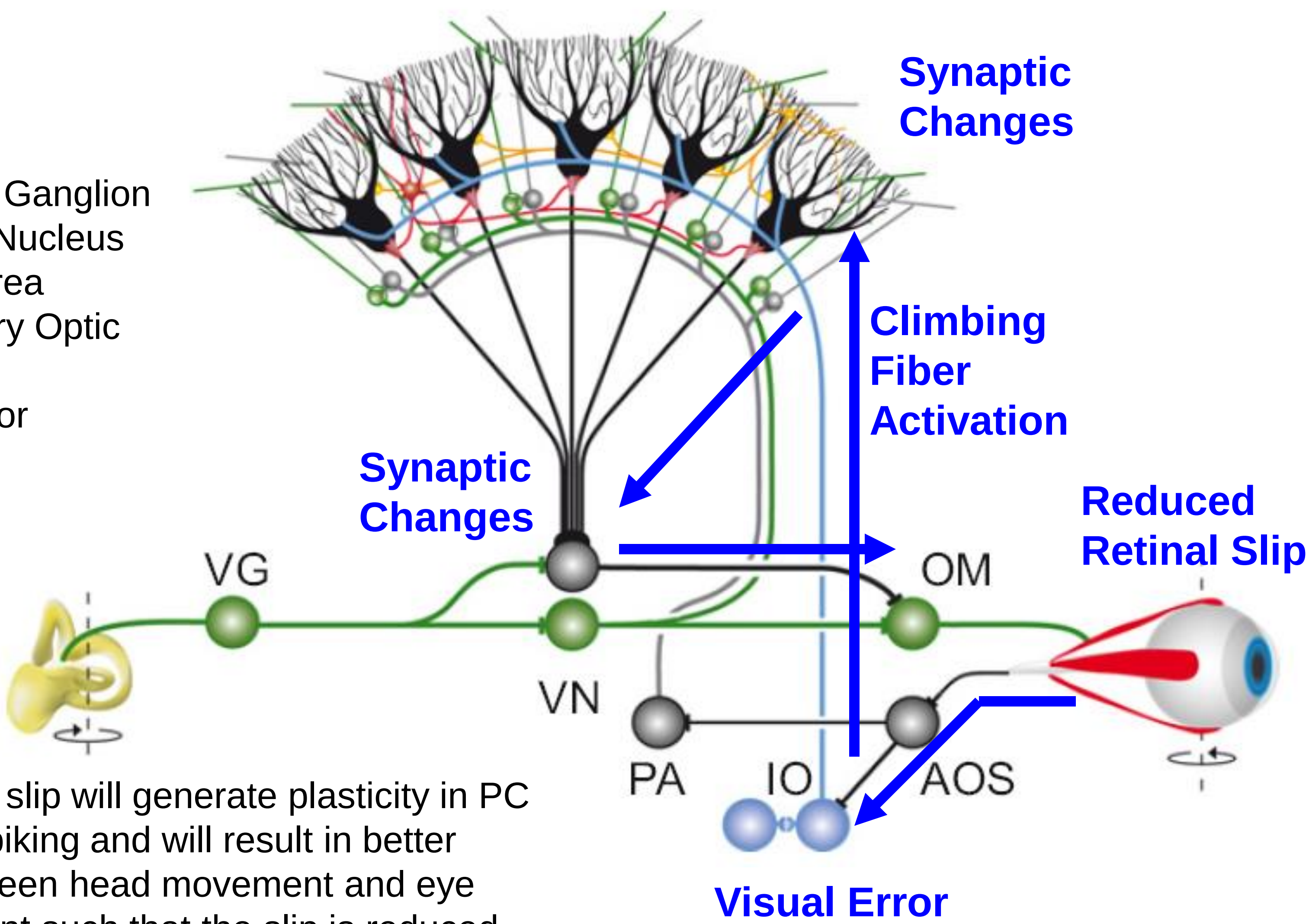
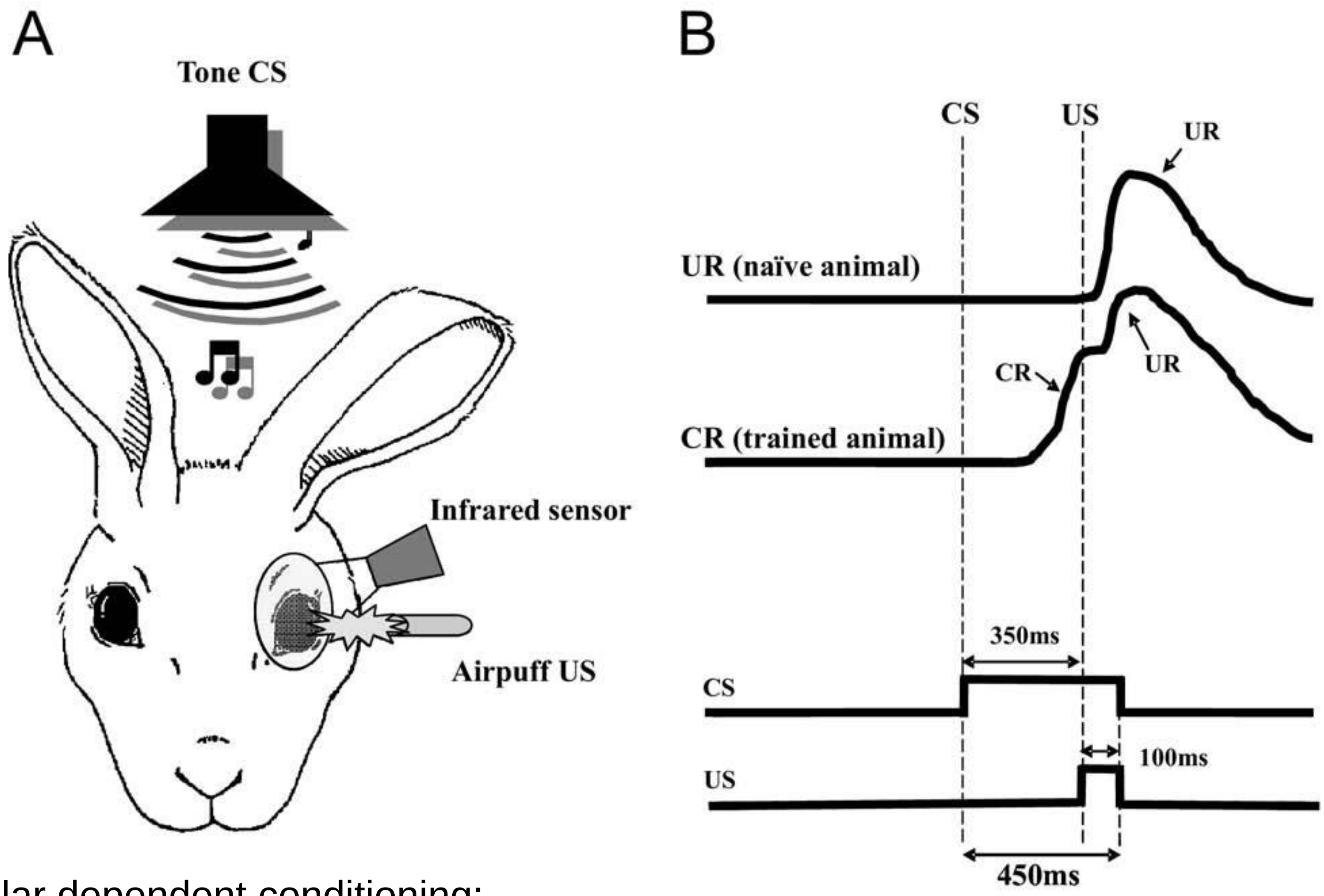
PA = Pontine Area
AOS = Accessory Optic System
OM = Oculomotor Neurons



Repeated retinal slip will generate plasticity in PC (and later VN) spiking and will result in better association between head movement and eye counter movement such that the slip is reduced

Ito 1984, Schonville et al. 2010

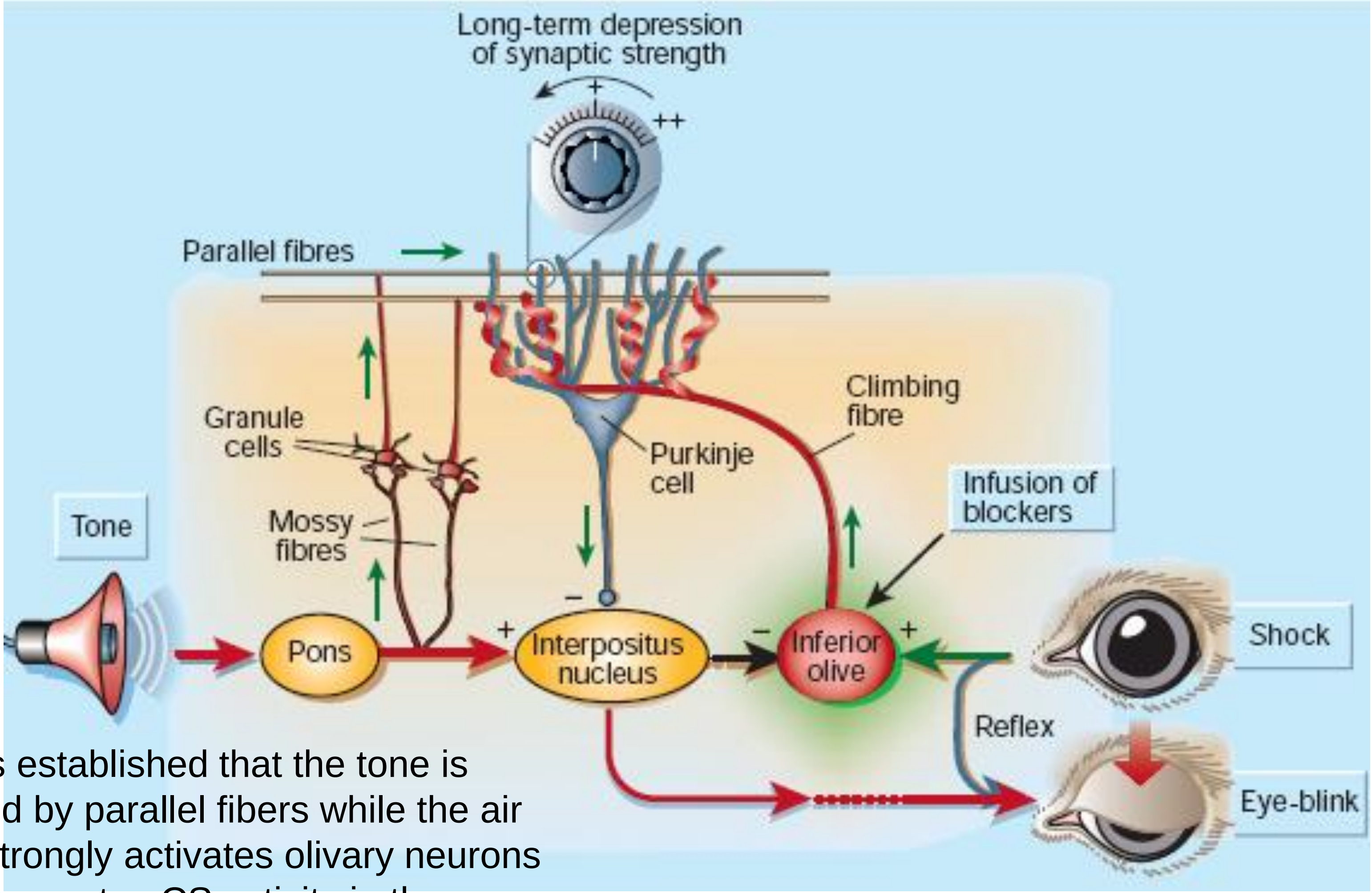
Eyelid Reflex Conditioning



Cerebellar dependent conditioning:
The rabbit learns to close its eyelid and expect the air puff before it comes by "counting" the duration of the preceding sound

Bracha and Bloedel 2009

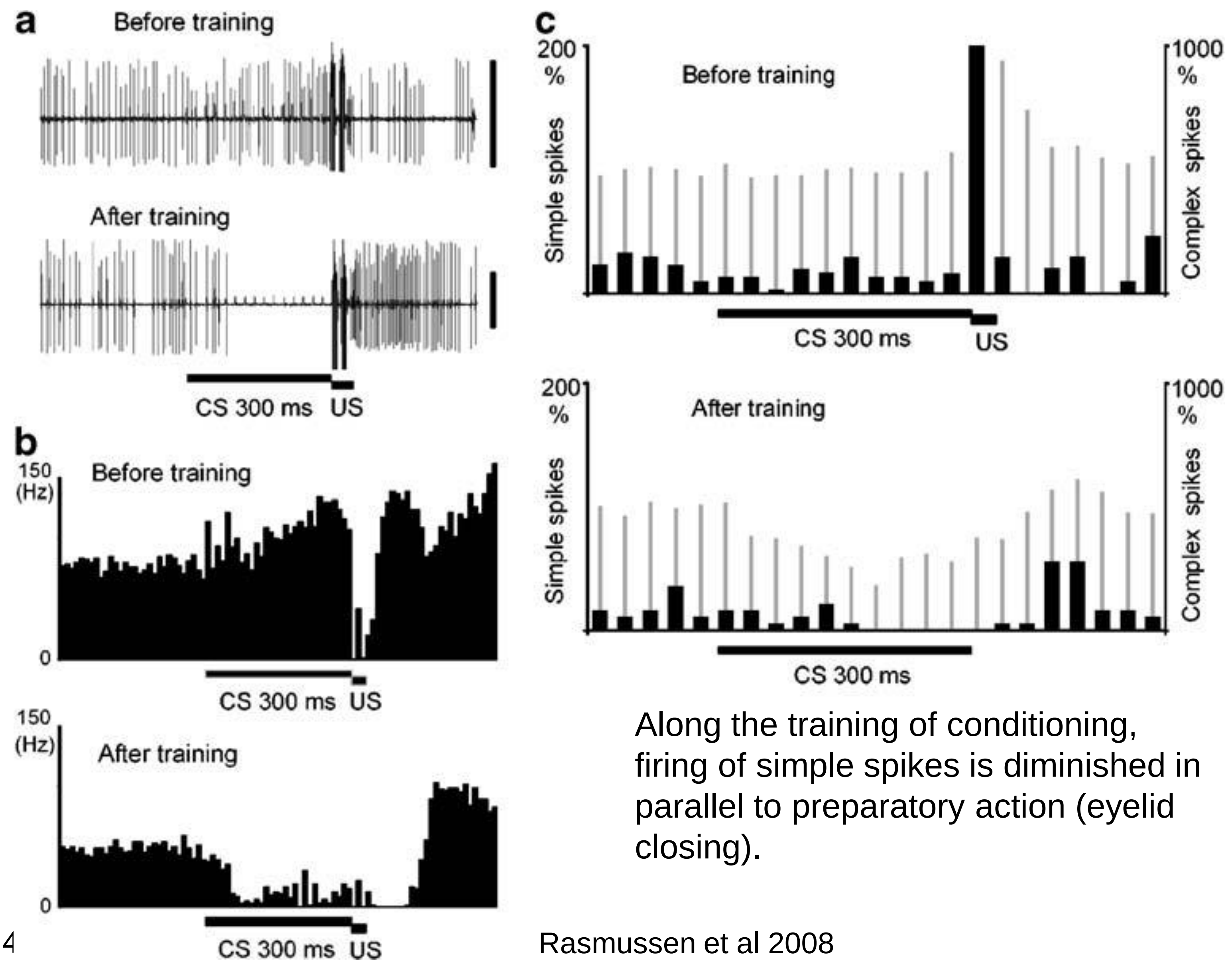
Eyelid Reflex Conditioning



It was established that the tone is carried by parallel fibers while the air puff strongly activates olivary neurons and generates CS activity in the relevant PCs

Medina et al. Nature 2002

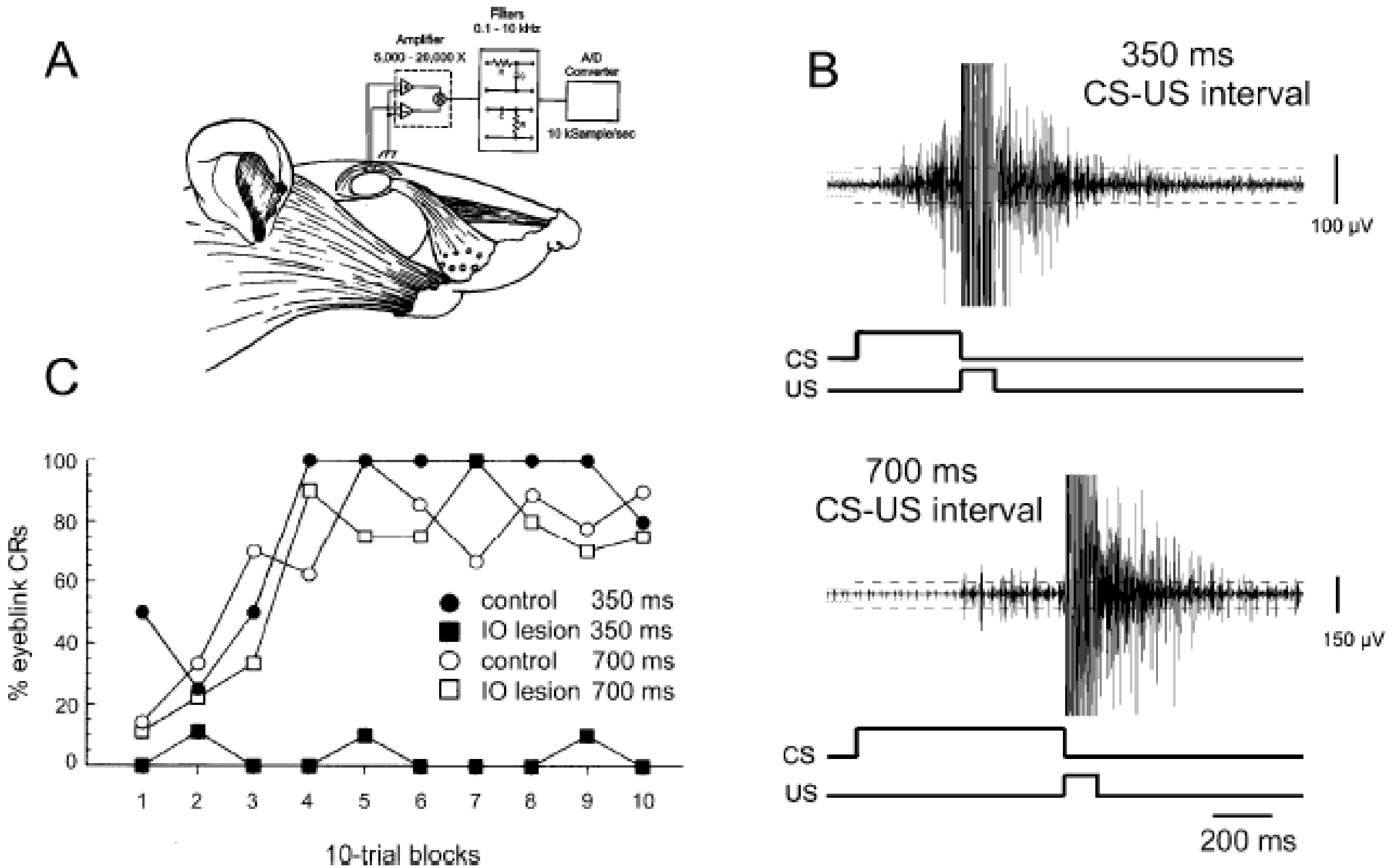
Eyelid Reflex Conditioning



Along the training of conditioning, firing of simple spikes is diminished in parallel to preparatory action (eyelid closing).

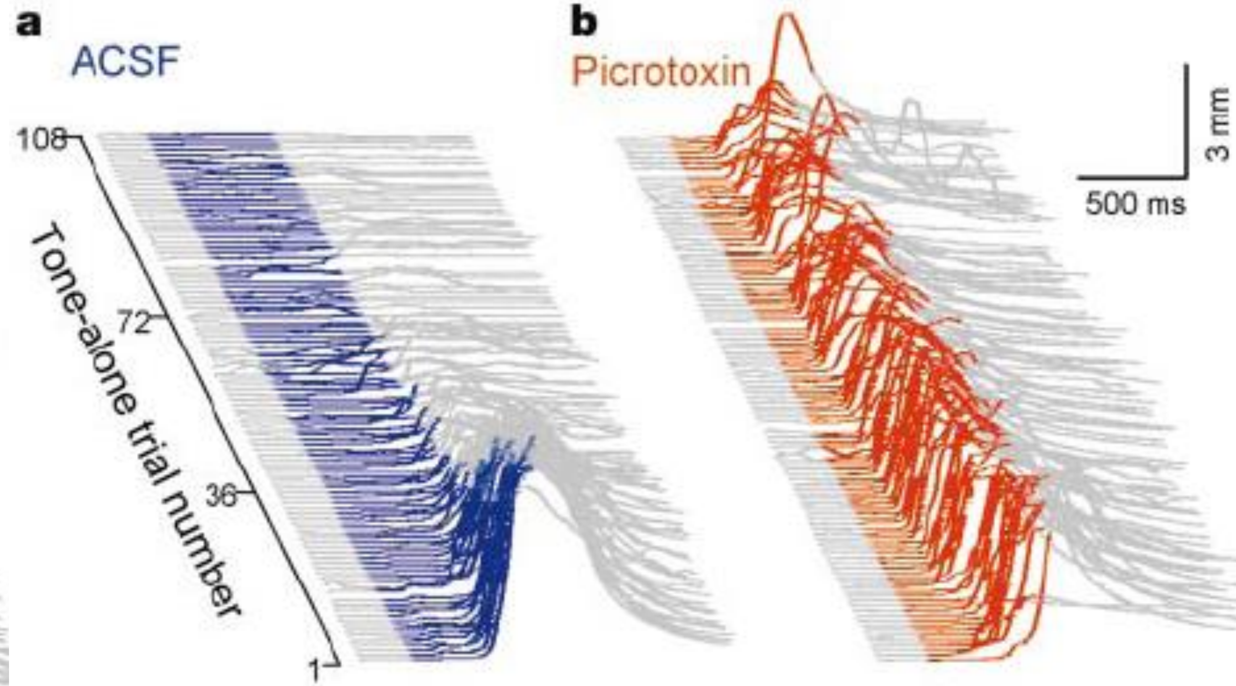
Rasmussen et al 2008

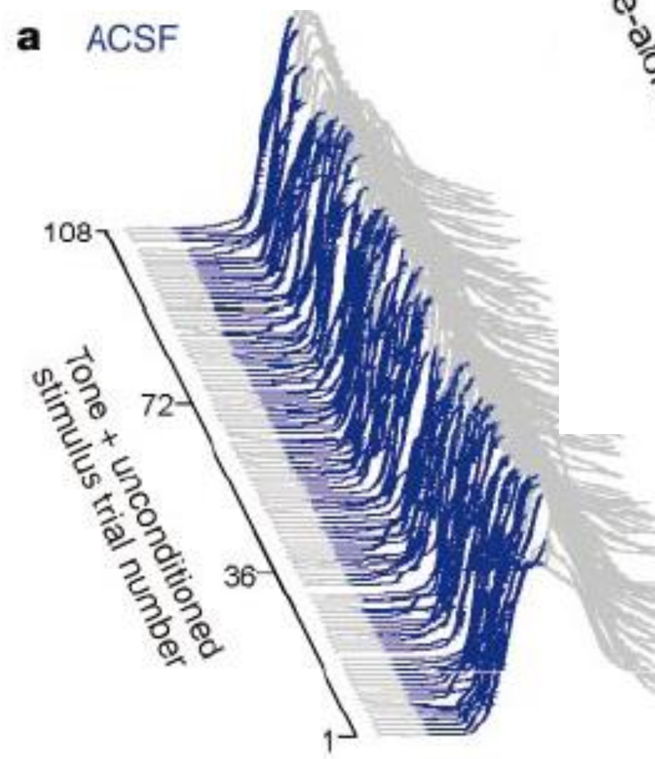
IO is crucial for Learning @350ms but not 700ms



Welsh 2002

Conditioning Memory Retention depends on Nucleo-Olivary Inhibition

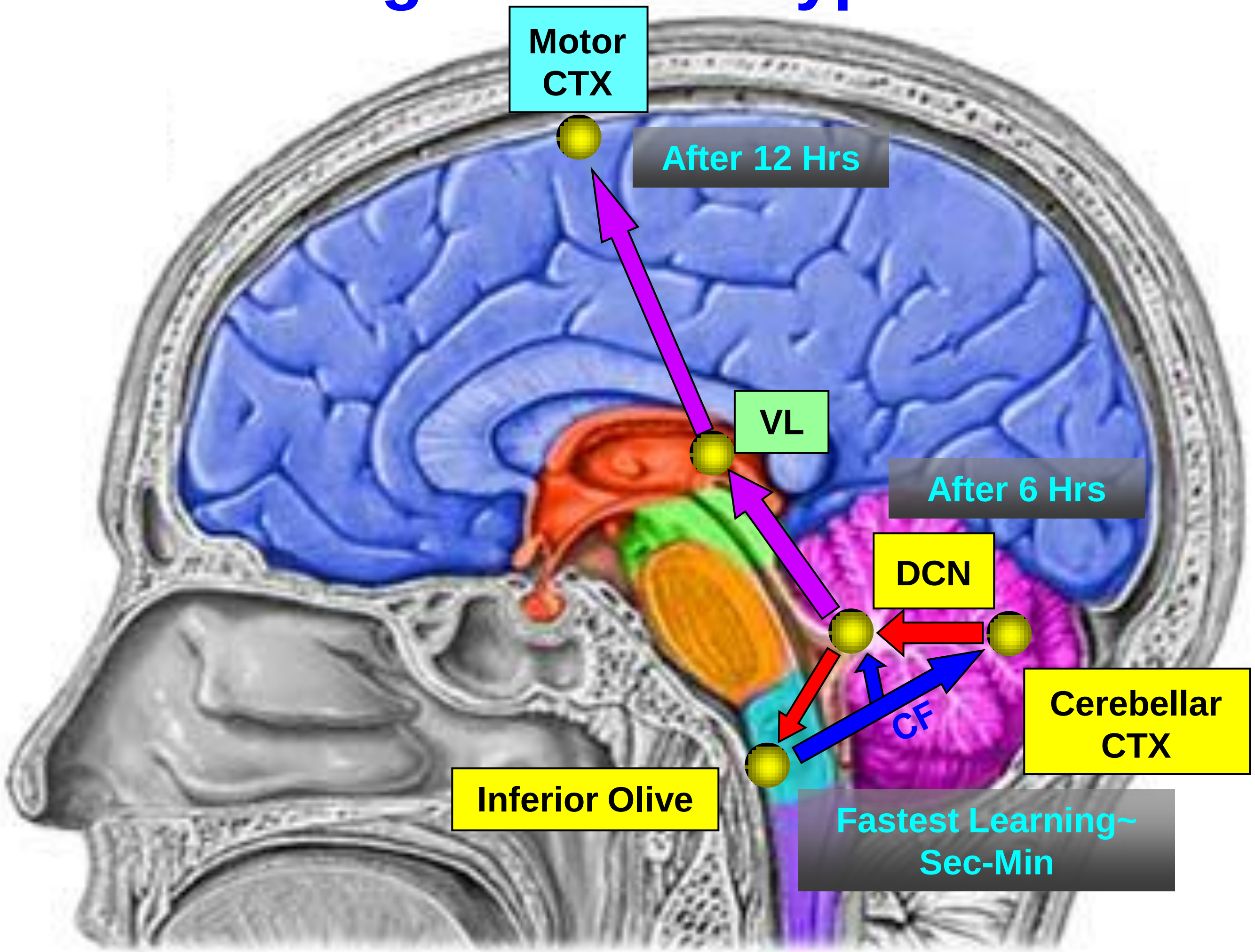




Blocking Gabaergic inputs into the inferior olive caused in re-emergence of the learned and “forgotten” association, suggesting that the learned trace exists and the choice between the two behaviors depends on inhibitory input to the IO (possibly from DCN)

Medina et al. Nature 2002

The Learning Transfer Hypothesis



VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
CTX = Cortex
CF = Climbing Fibers

The formation of cerebellar associative memory is shifting from cerebellar cortex to target areas such that dependency on each area exists only until the association is already formed in the next station

Cerebellar Involvement in Cognitive Processes

Cognitive effects of focal damage were found when:

1. The damage involved the vermis
2. The damage was in an area which blood supply is from the posterior inferior cerebellar artery

Further research showed problems in attention and working memory

Children with Vermal damage show autistic-like features:

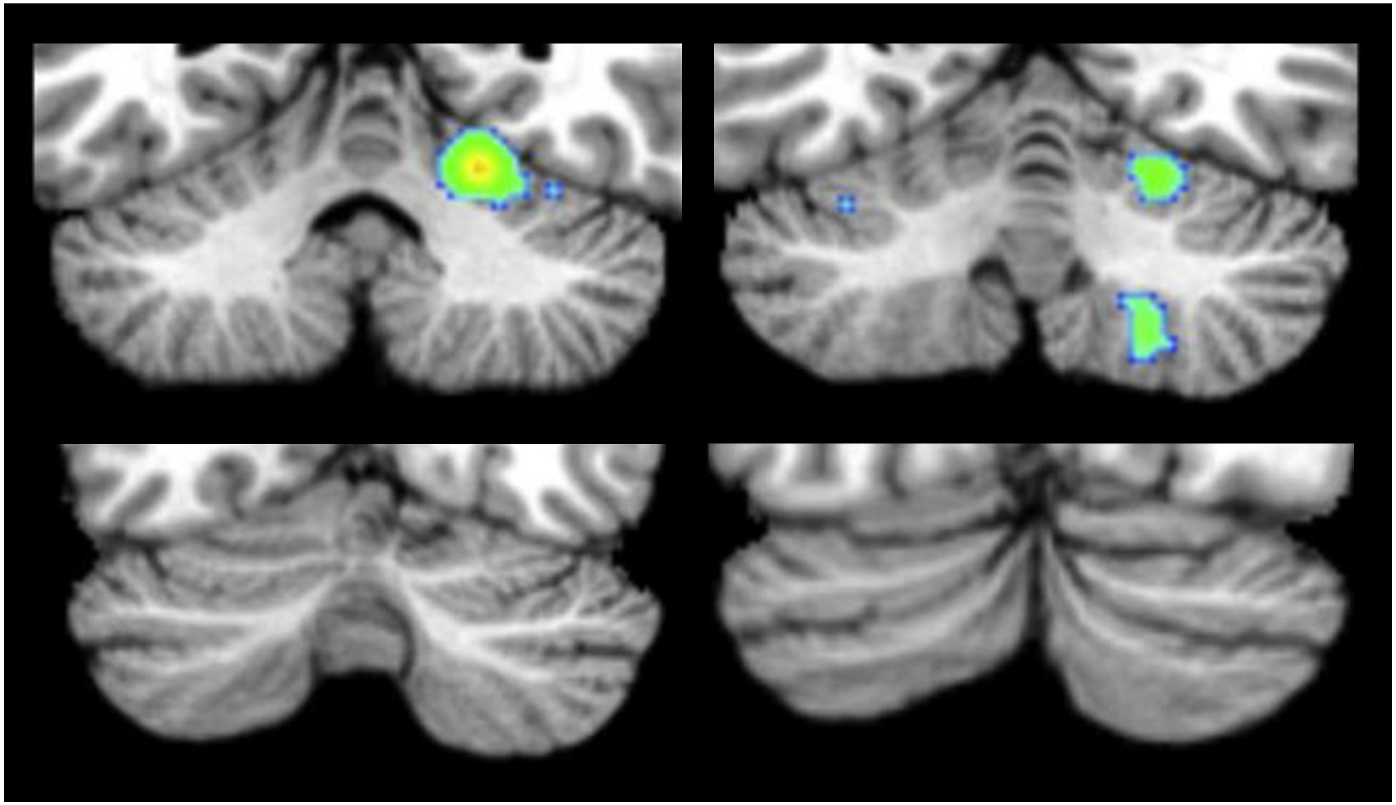
1. Irritability
2. impulsivity
3. Disinhibition
4. Emotional lability

Complex verbal dysfunction associated with right cerebellar damage

Dysprosodia (pronunciation fault)– associated with left cerebellar damage

Schmahmann J.

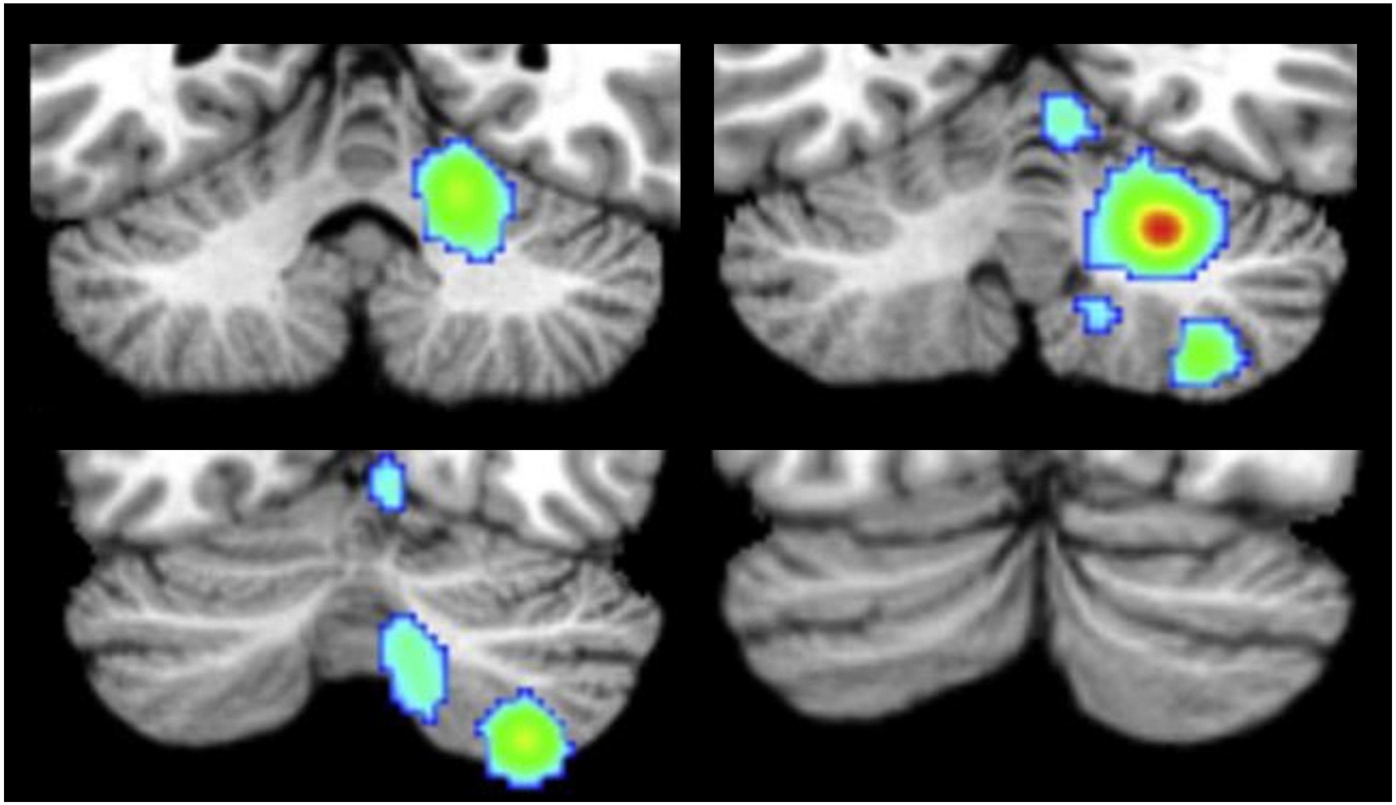
FMRI Mapping pf Cerebellar Involvement in Various Processes



Somatosensory Processing

Stoodley and Schmahmann 2009

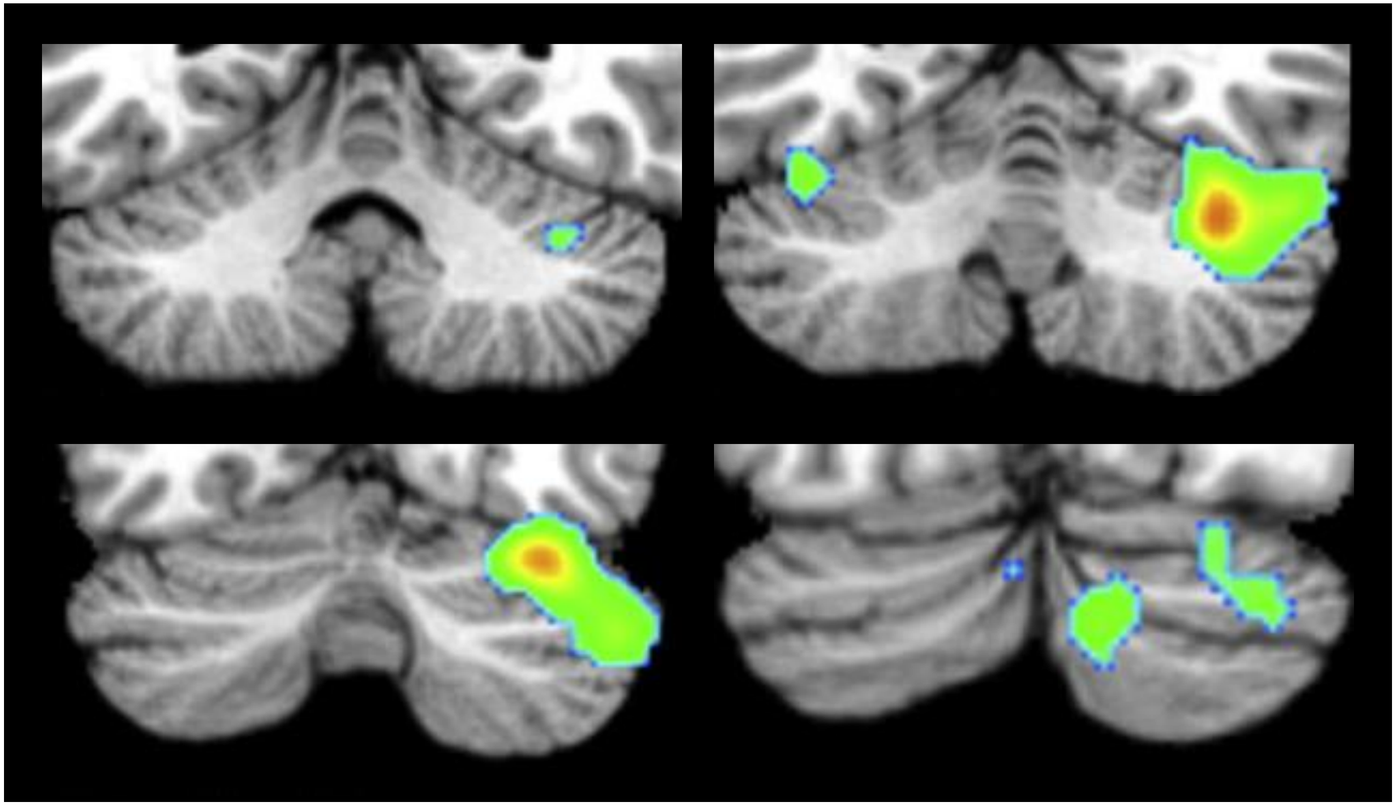
FMRI Mapping pf Cerebellar Involvement in Various Processes



Motor Processing

Stoodley and Schmahmann 2009

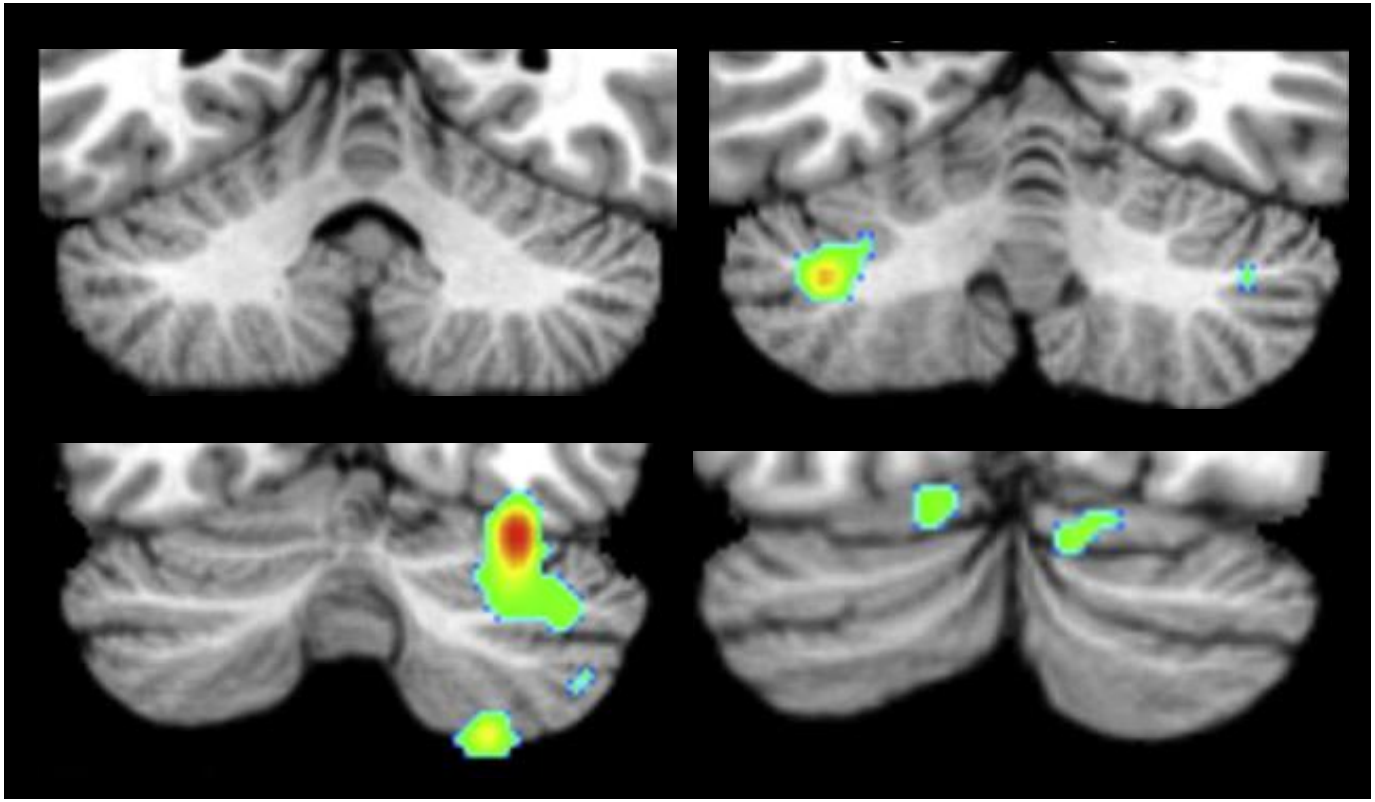
FMRI Mapping pf Cerebellar Involvement in Various Processes



Language Processing

Stoodley and Schmahmann 2009

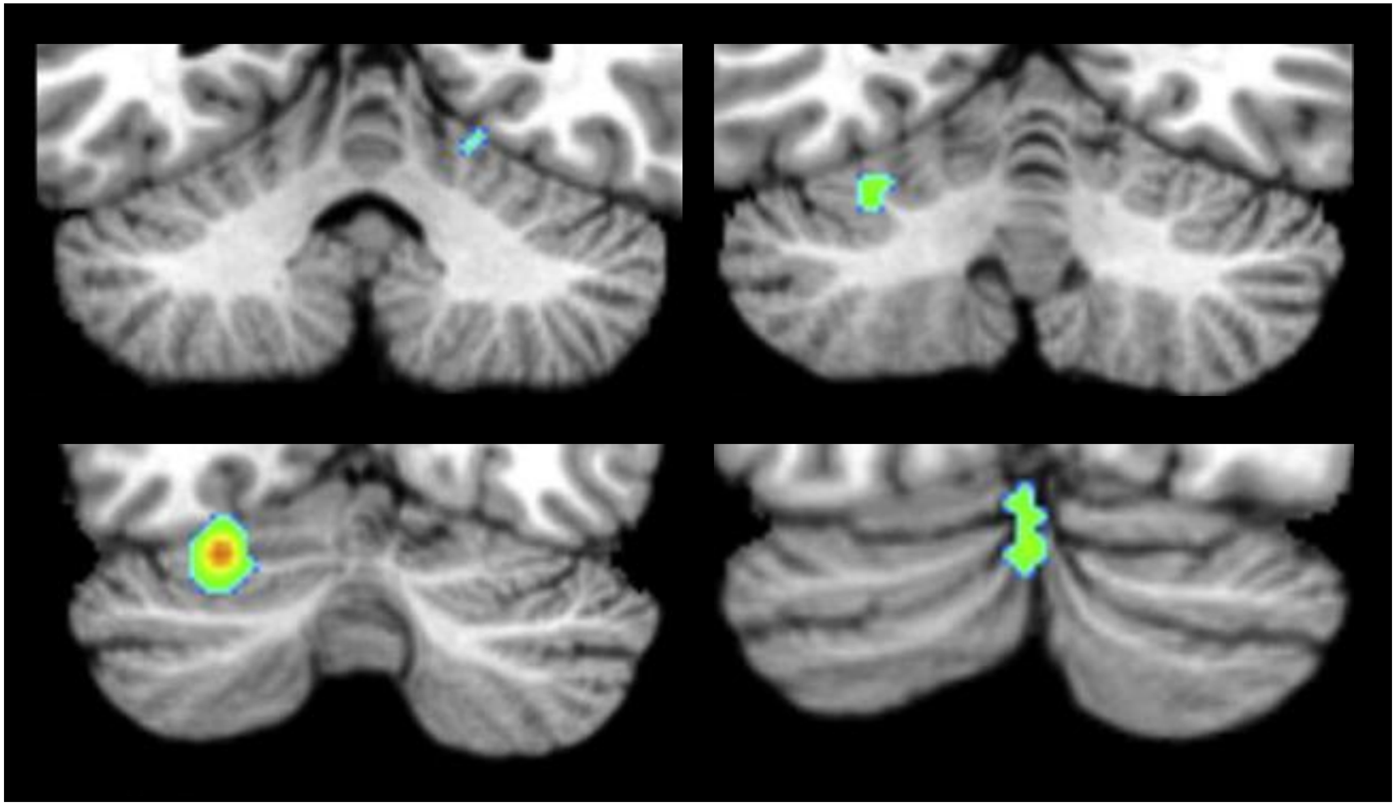
FMRI Mapping pf Cerebellar Involvement in Various Processes



Working Memory

Stoodley and Schmahmann 2009

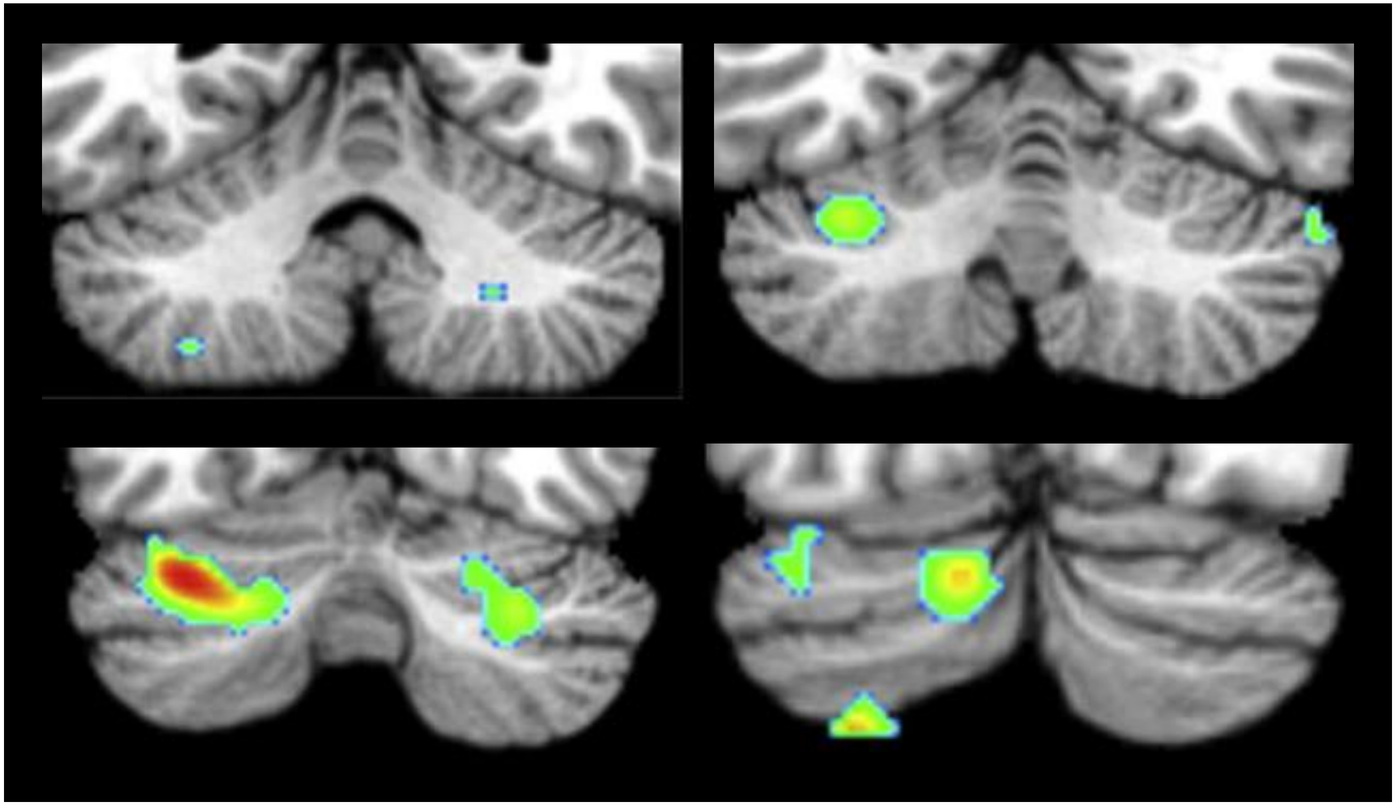
FMRI Mapping pf Cerebellar Involvement in Various Processes



Spatial Processing

Stoodley and Schmahmann 2009

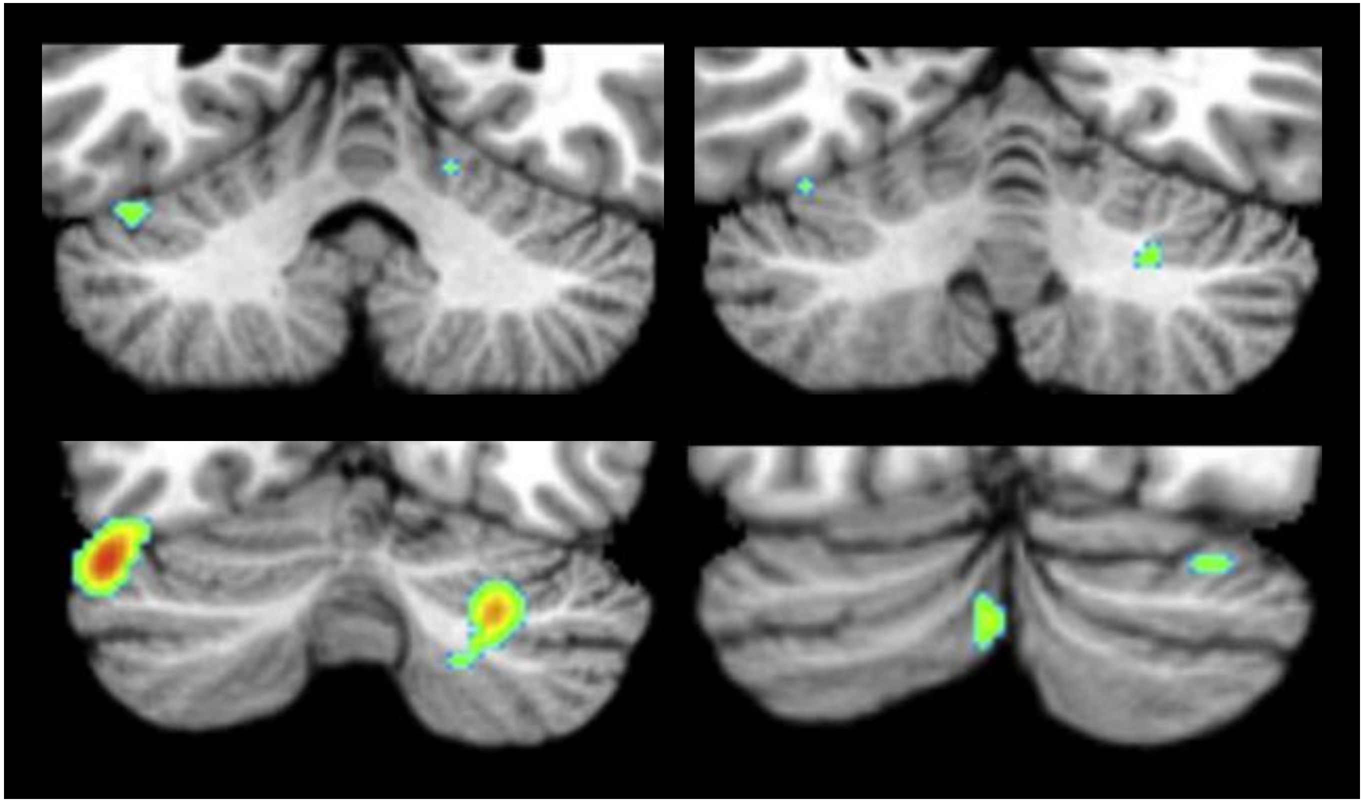
FMRI Mapping pf Cerebellar Involvement in Various Processes



Executive Processing

Stoodley and Schmahmann 2009

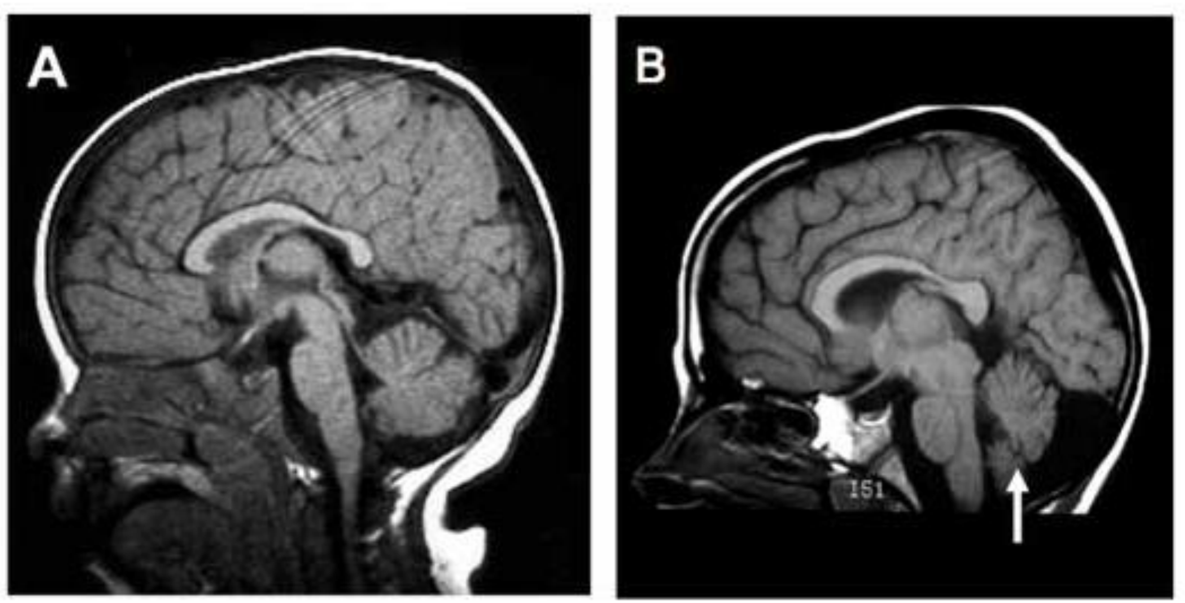
FMRI Mapping pf Cerebellar Involvement in Various Processes



Emotional Processing

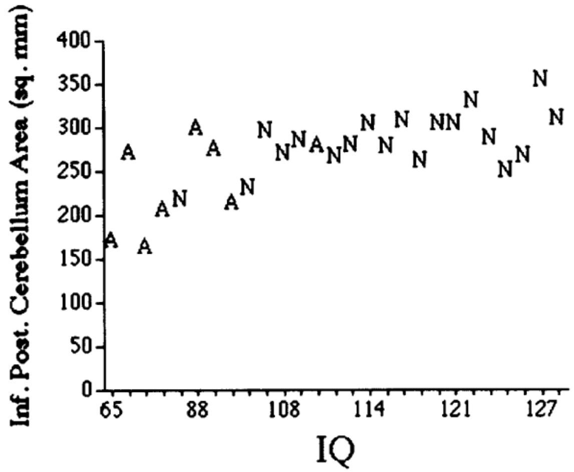
Stoodley and Schmahmann 2009

Cerebellar Involvement in Autism



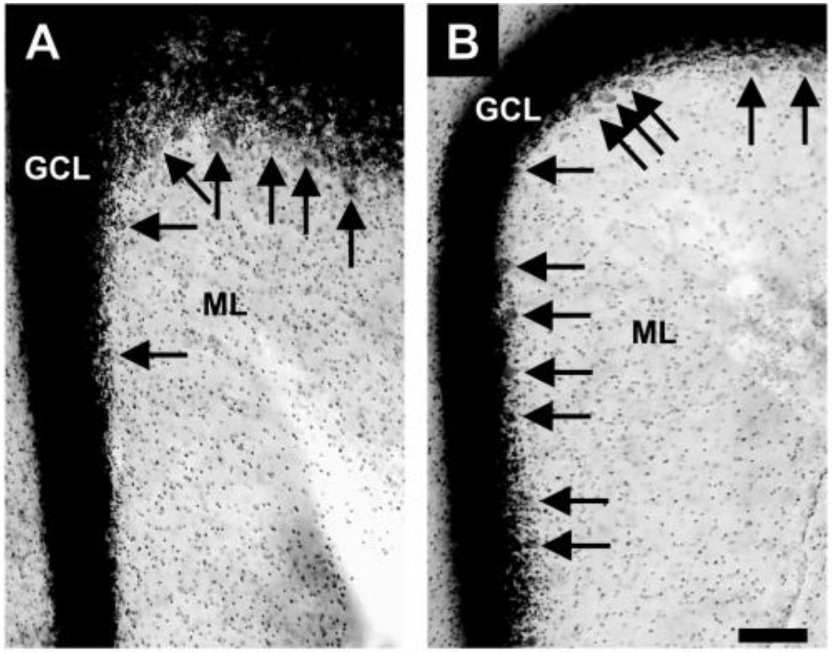
Control Subject

Autistic Subject

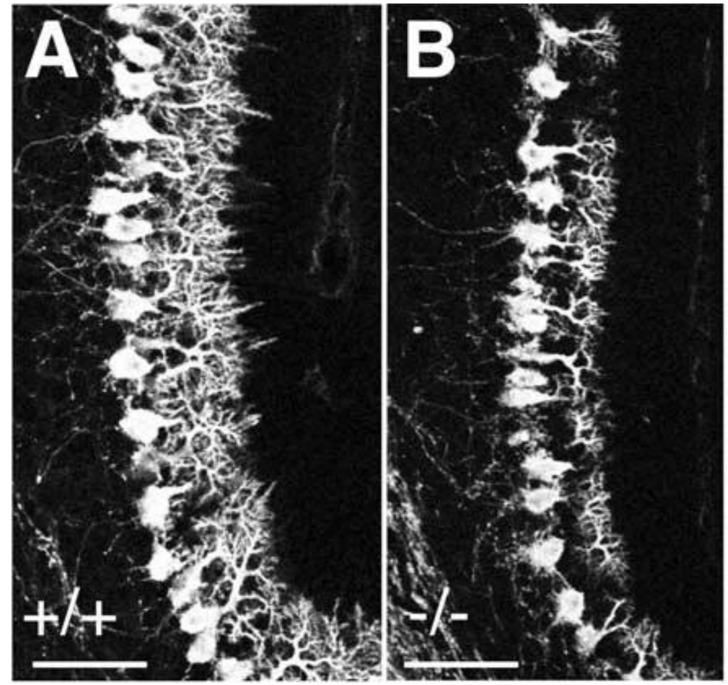


Levitt J. 1999

Autism candidate genes affects the Cerebellum



Autistic　　　　Control



Control　　　　CASP2 -/-

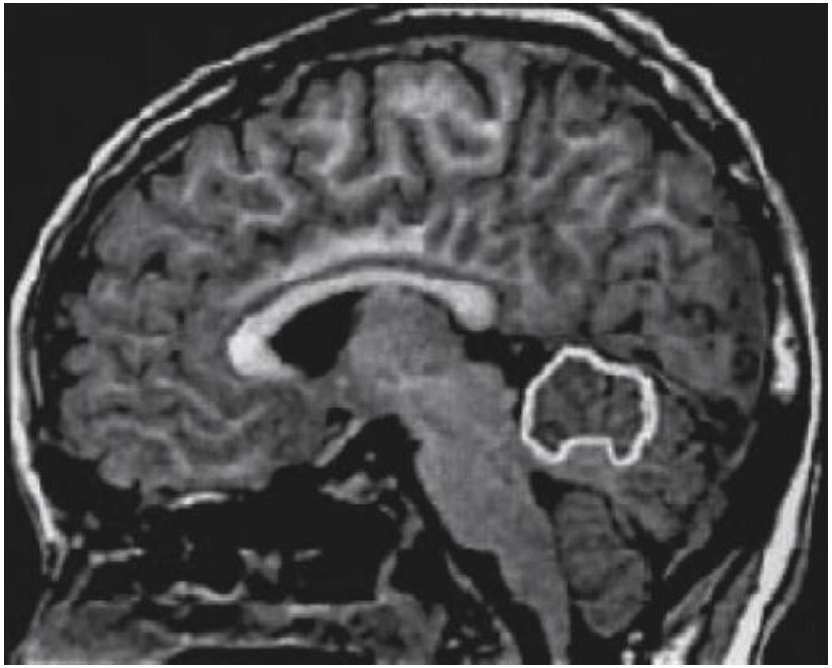
Lose of Purkinje Cells in Autistic

Saskia 2004

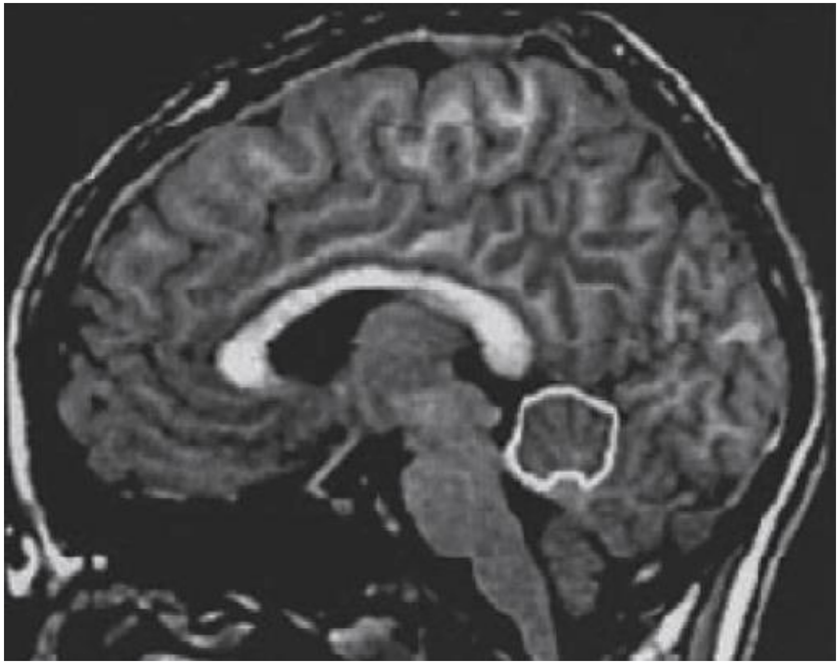
Developmental Problems in KO mice

Sadakata 2007

Cerebellar Involvement in Dyslexia



Control Subject



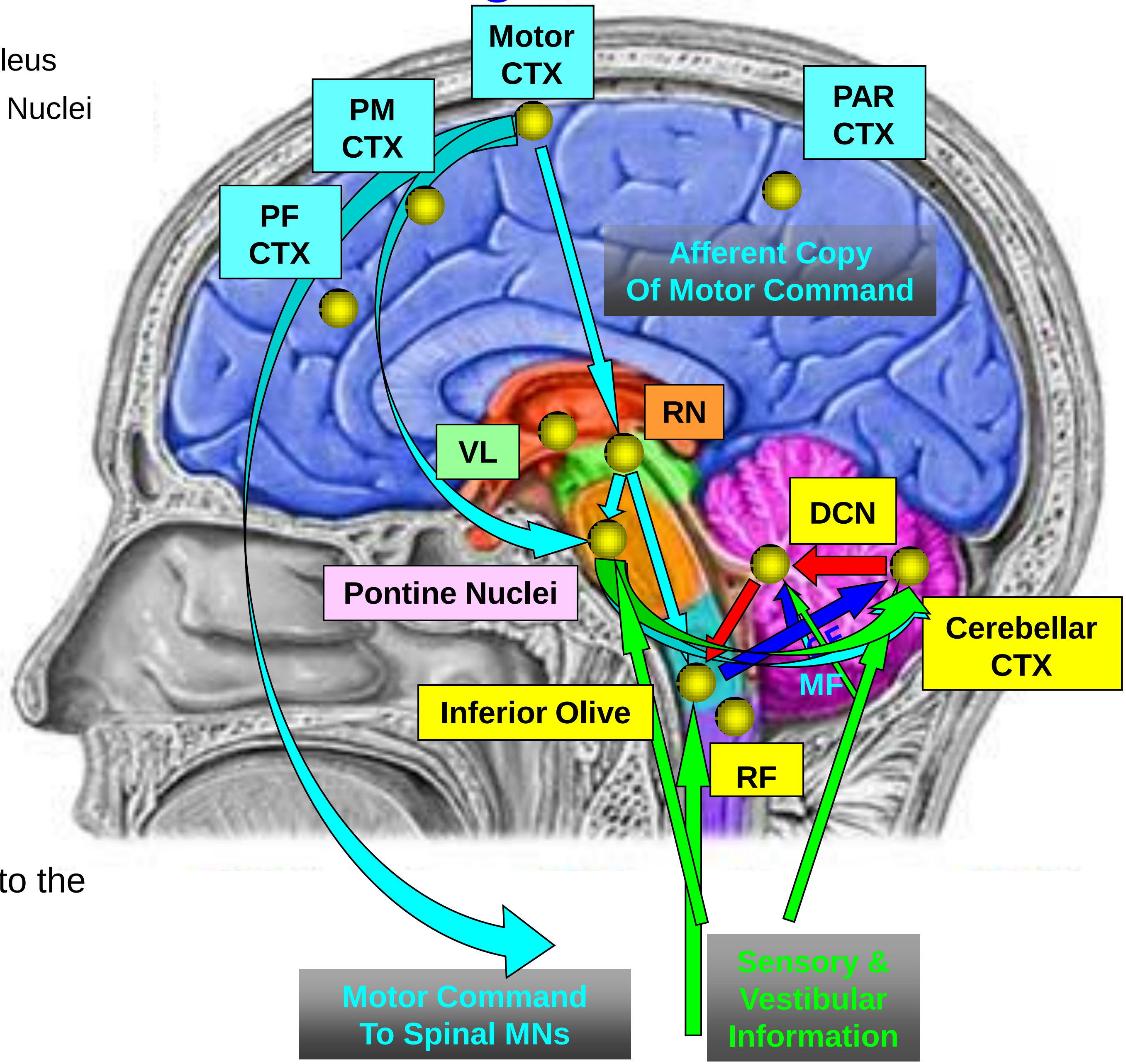
Dyslexic Subject

Information Flow during On-Line Corrections

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers



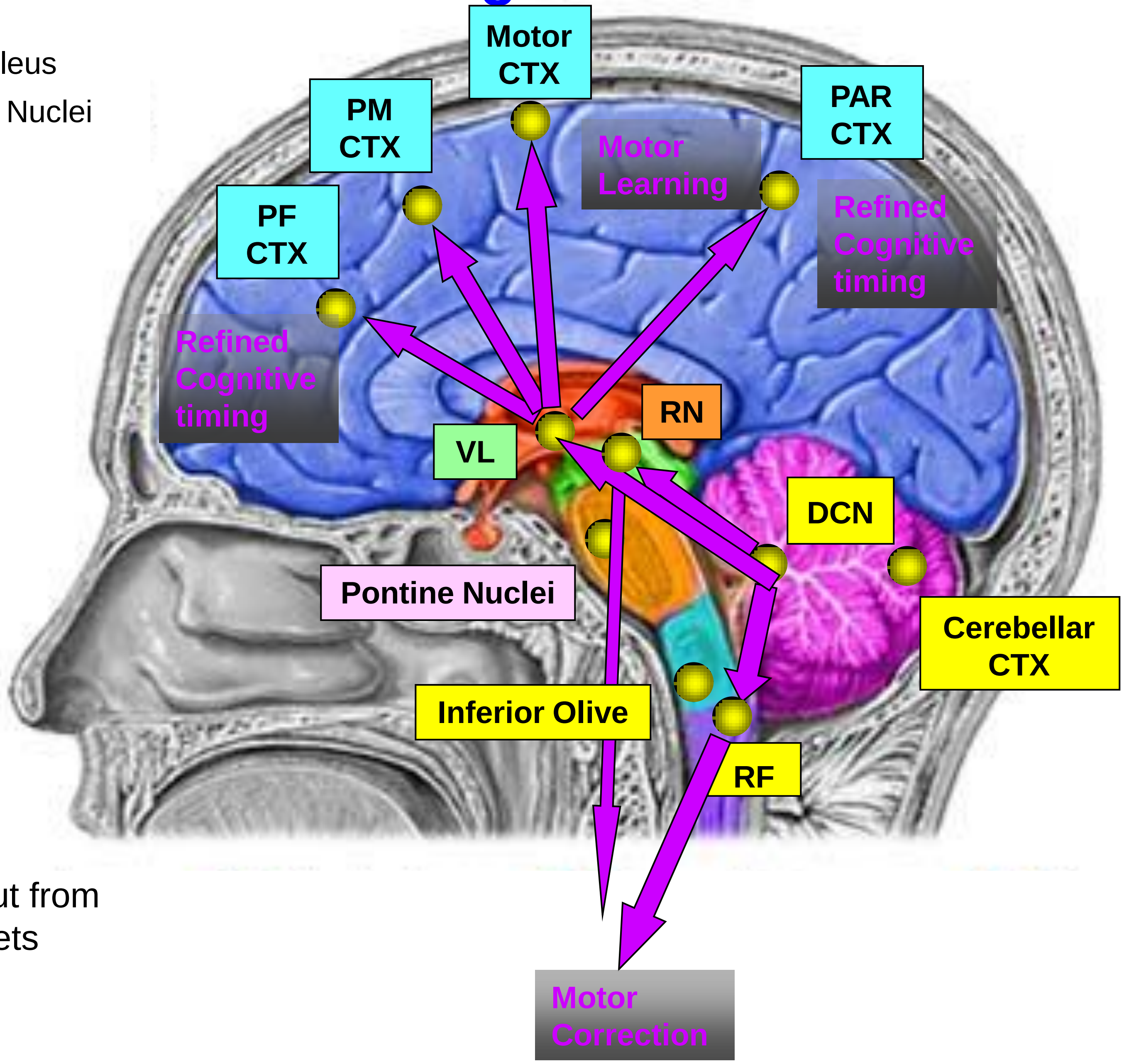
Information flow into the system

Information Flow during On-Line Corrections

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

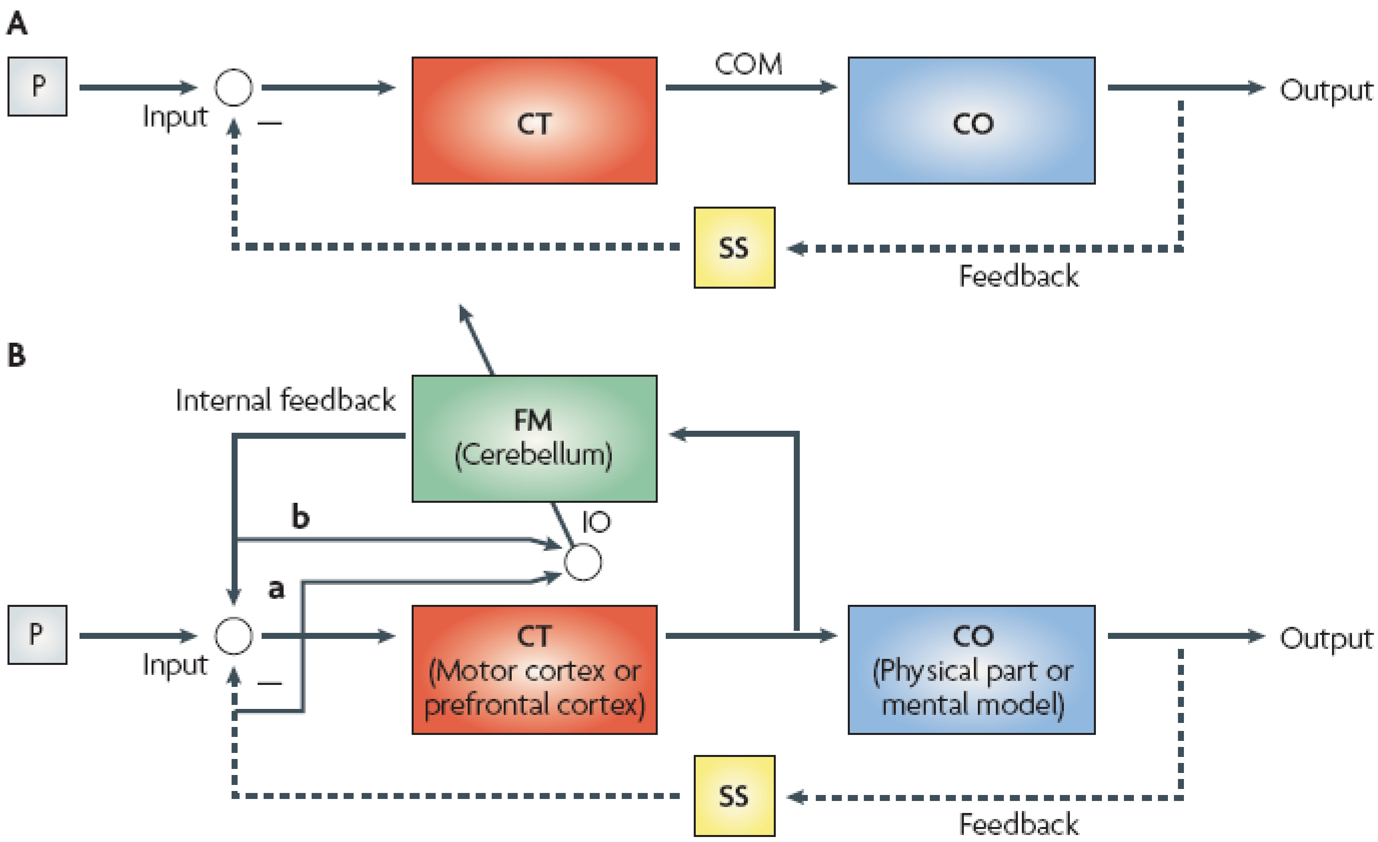
CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers



Information flow out from the system to targets

The General Role of the Cerebellum



The olivocerebellar systems supposedly generates an updated prediction of sensory feedback, expected motor command or expected cognitive patterns, and by that shortens the delay (and oscillations) that would have occurred with simple loop of sensory feedback.