The Cerebellum: A Super-Resolution Predictor in the use of the automated Brain?

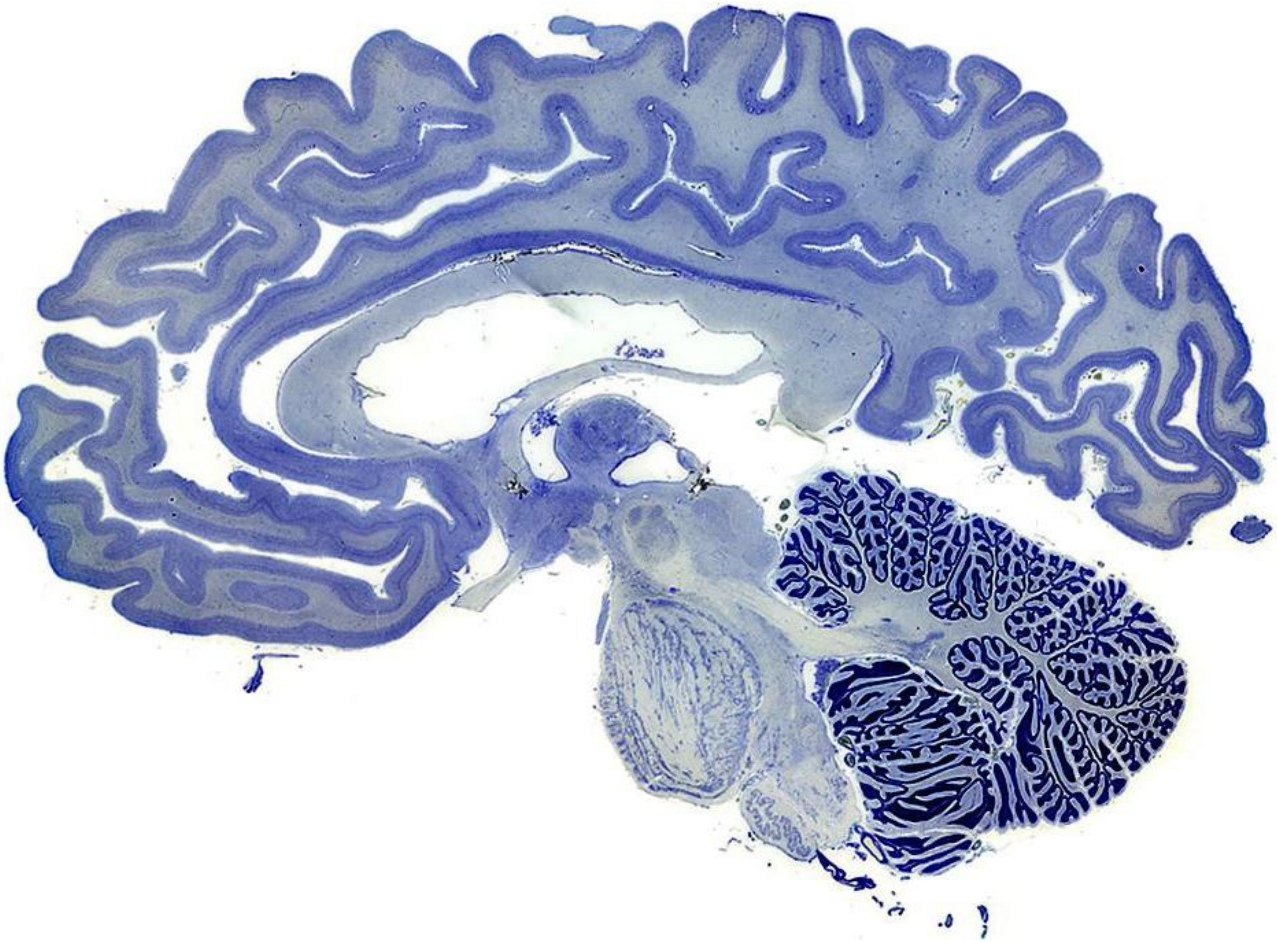
Eyal Cohen, PhD

(HUJI & BIU)

Cerebellum – The "Little Brain"

The Cerebellum takes ~10% of the Brain in Volume

Small but Hefty…



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

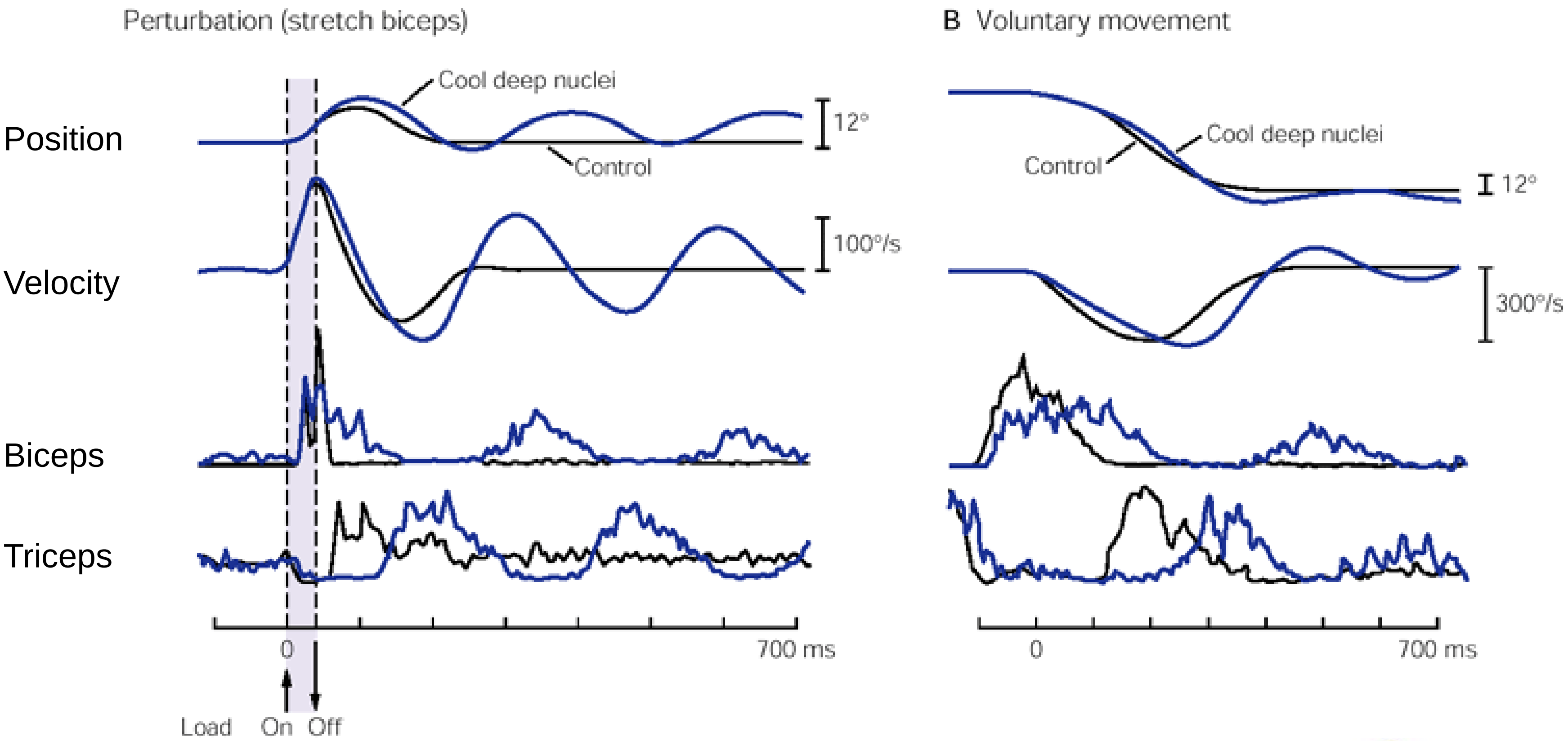
The Convoluted Cerebellar Cortex consists of most Cerebellar Volume

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 coordination) 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)

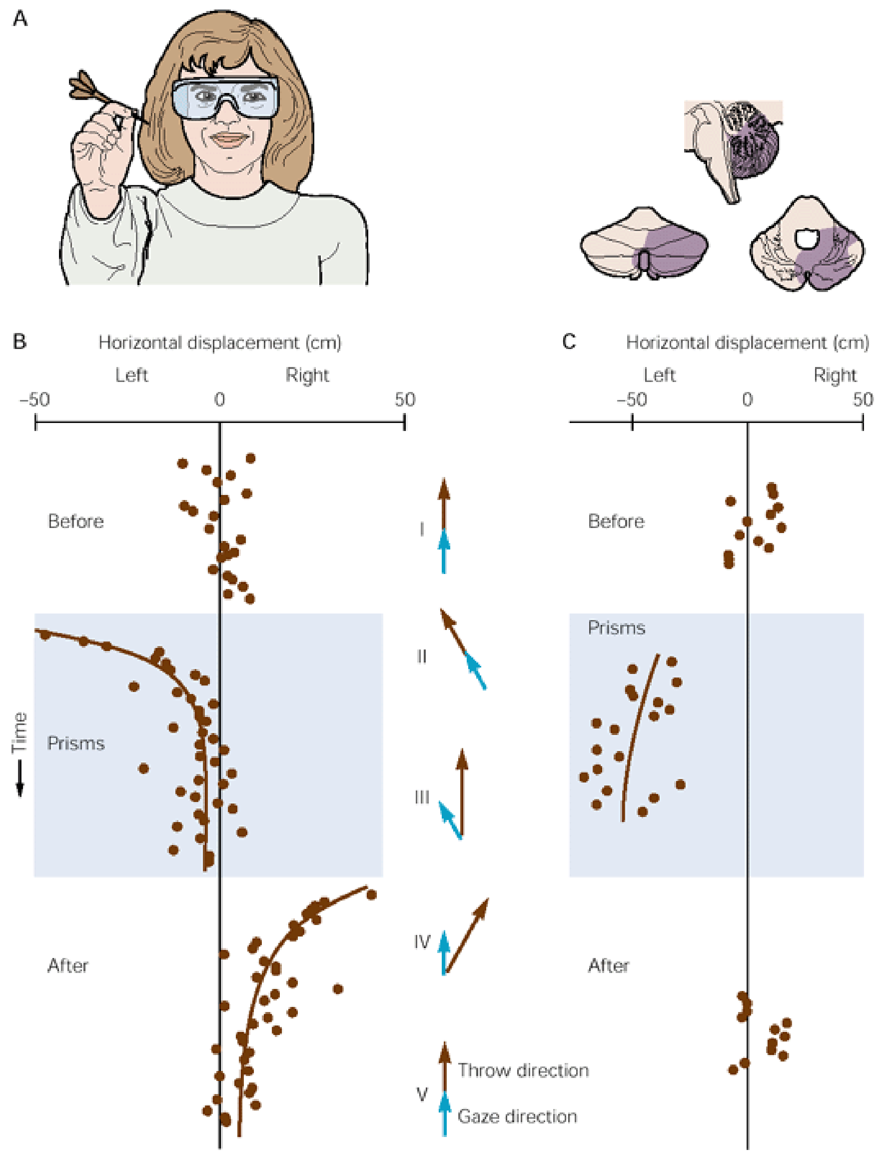
Cerebellar Role in Muscle Timing and Coordination



Cooling = Reducing Neuronal Firing

Villis and Hore 1977

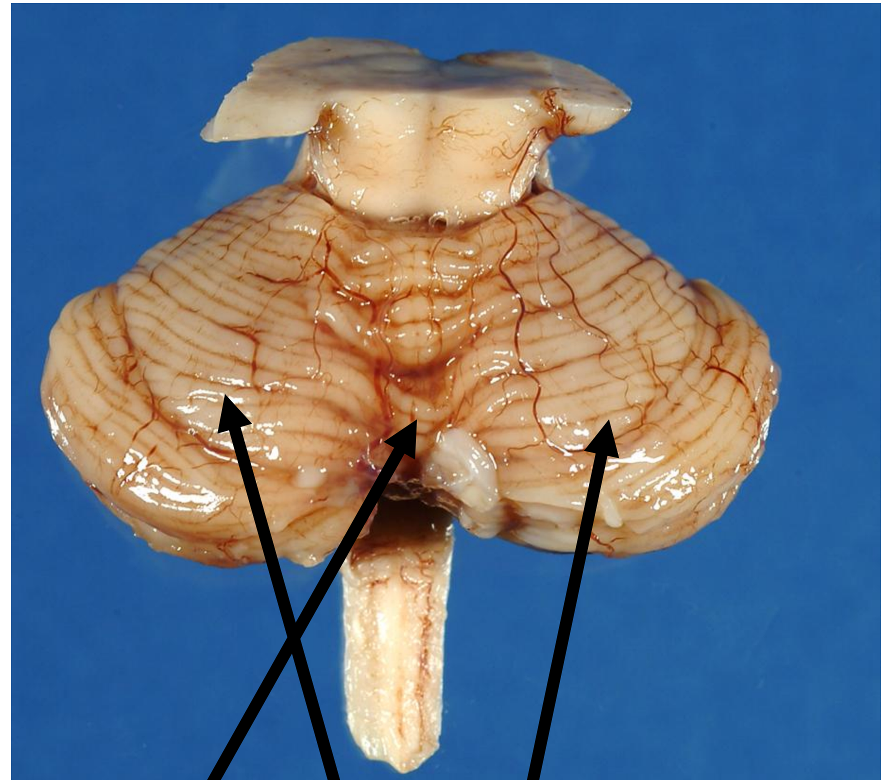
Cerebellar is Central in Adaptation



General Structure of the Cerebellar Cortex

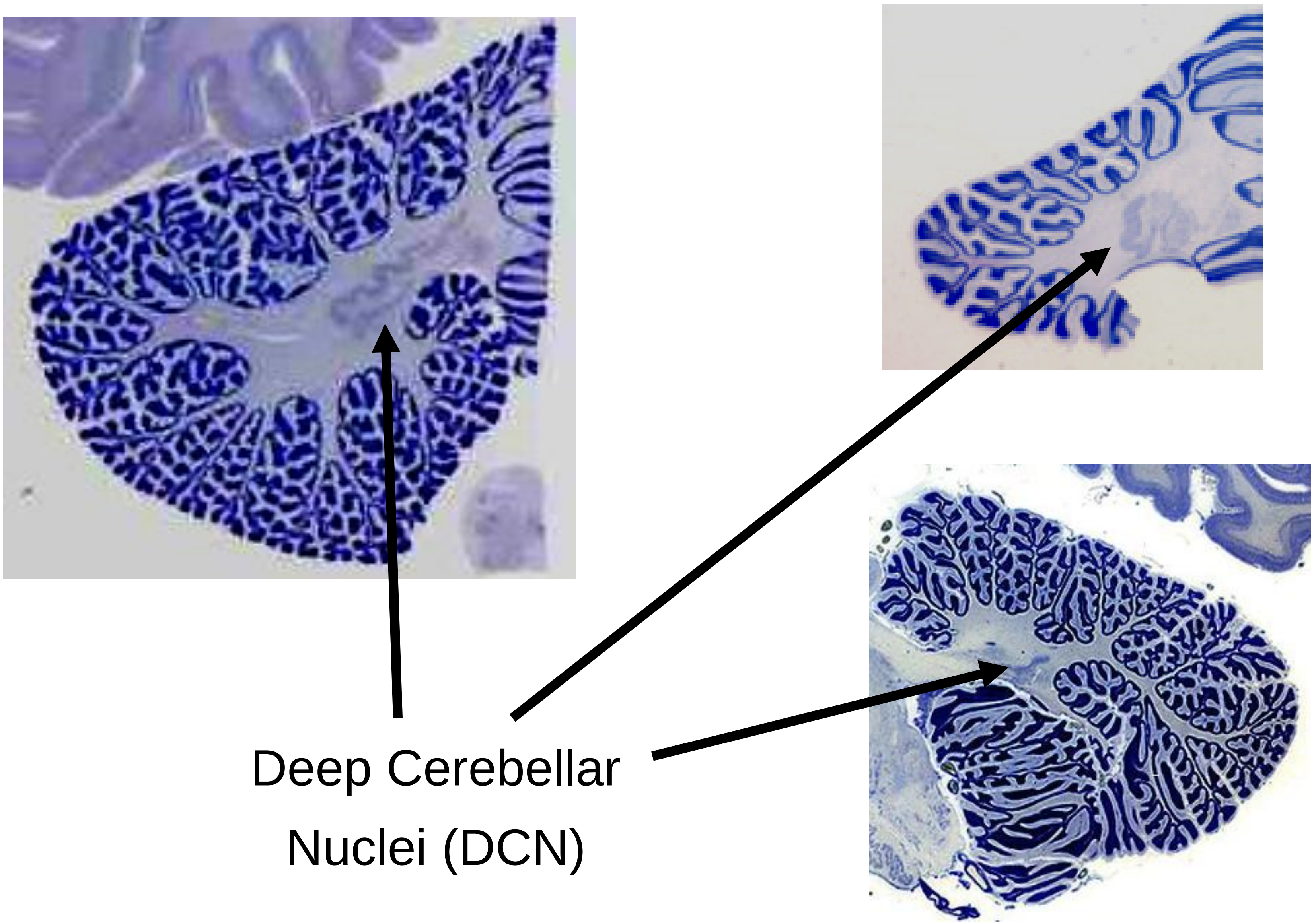
Ventral/Anterior View

Dorsal/Posterior View

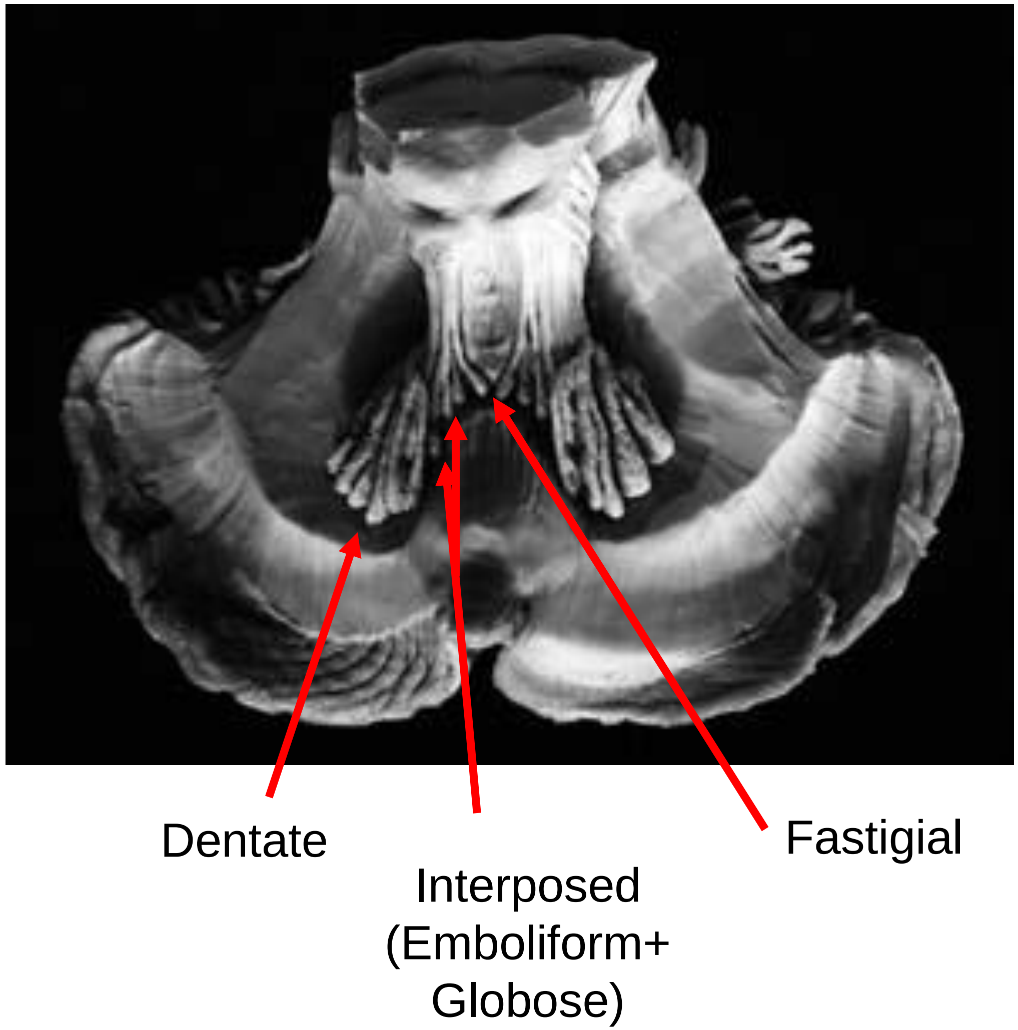


Lobes and Lobules of the Cerebellar Cortex

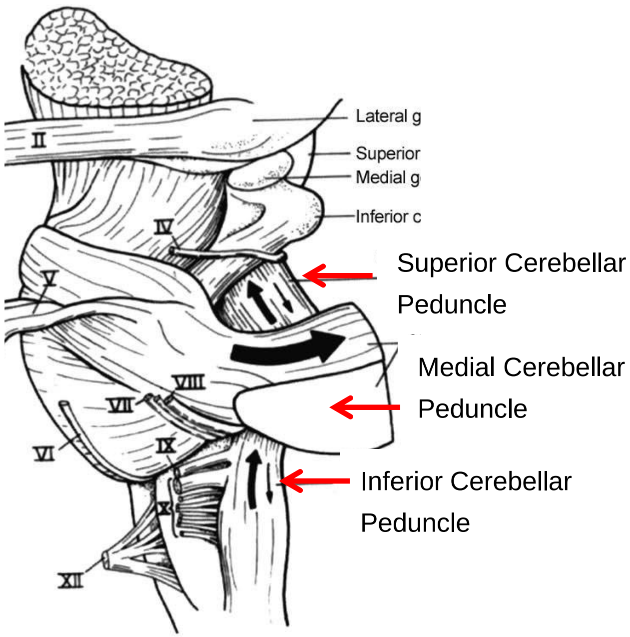
The Cerebellum is not Only Cortex…

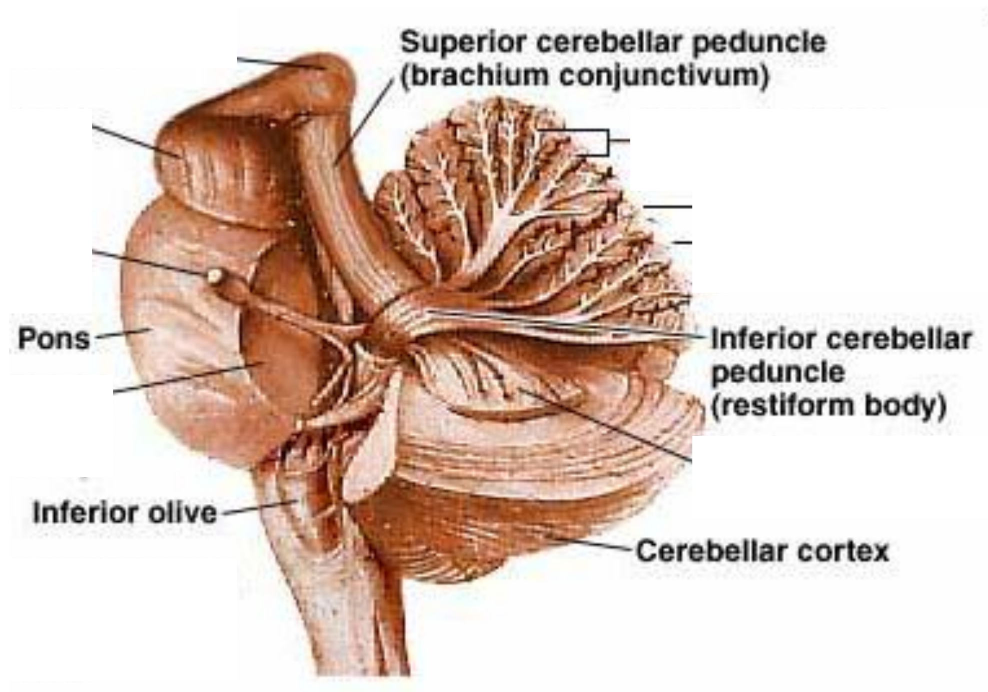


The Deep Cerebellear Nuclei (DCN) are the Output Relays of the Cerebellum



Cerebellar Peduncles: Input / Output Highways



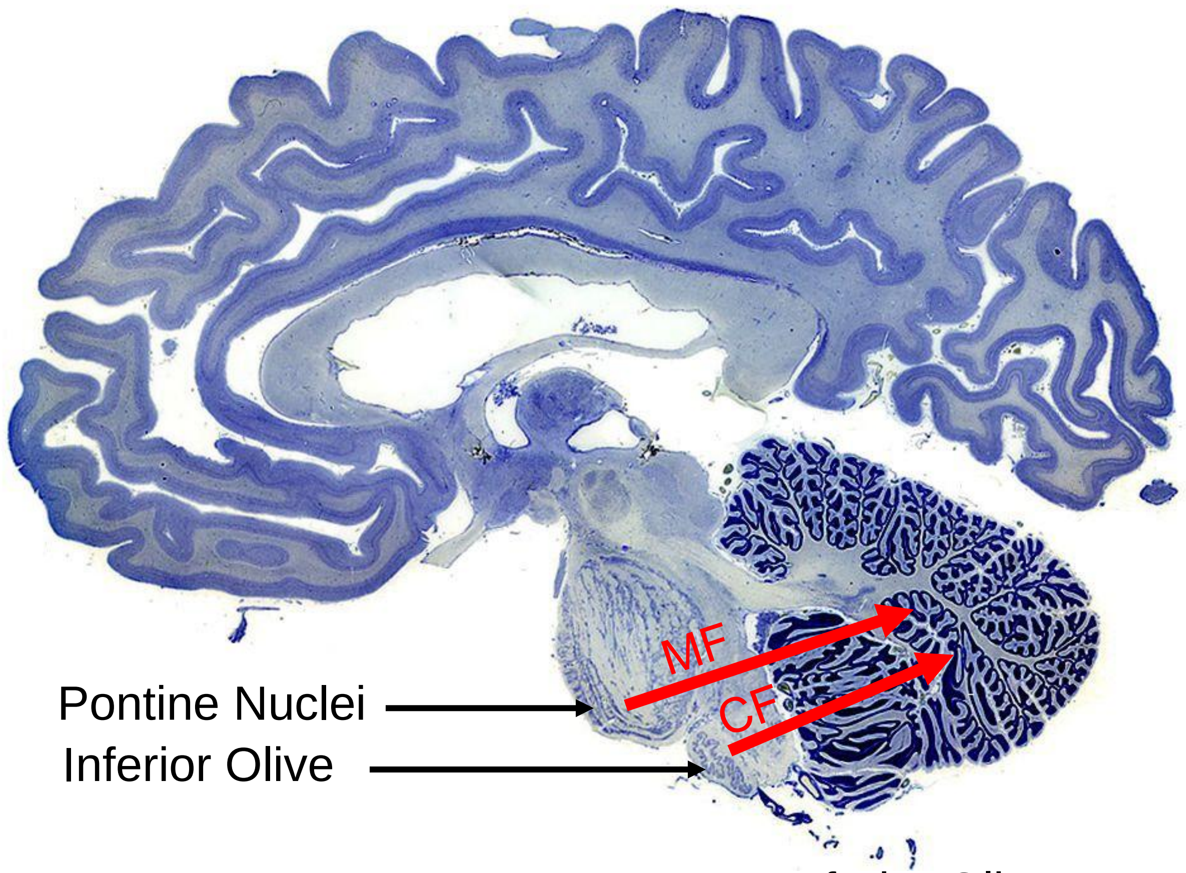


Superior: Cerebrum/Midbrain Inputs/Outputs

Medial: Pontine Inputs and Commissure

Inferior: Spinal/Medullary Inputs/Outputs

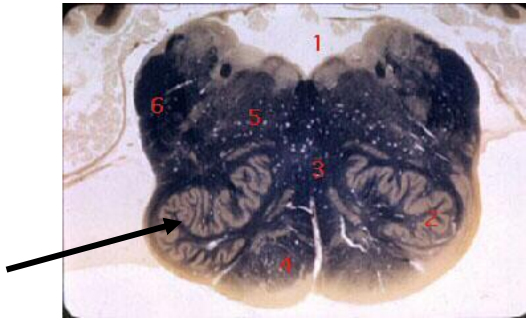
Two Major Input Pathways Serve the Cerebellum



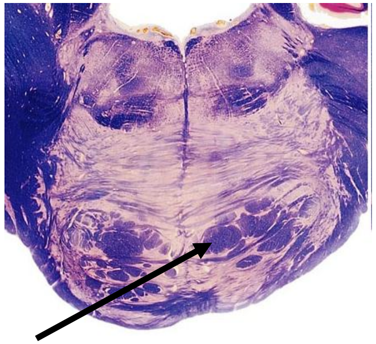
CF = Climbing Fibers

MF = Mossy Fibers

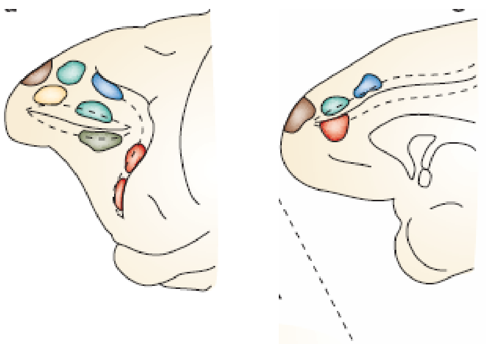
Inferior Olive



Pontine Nuclei

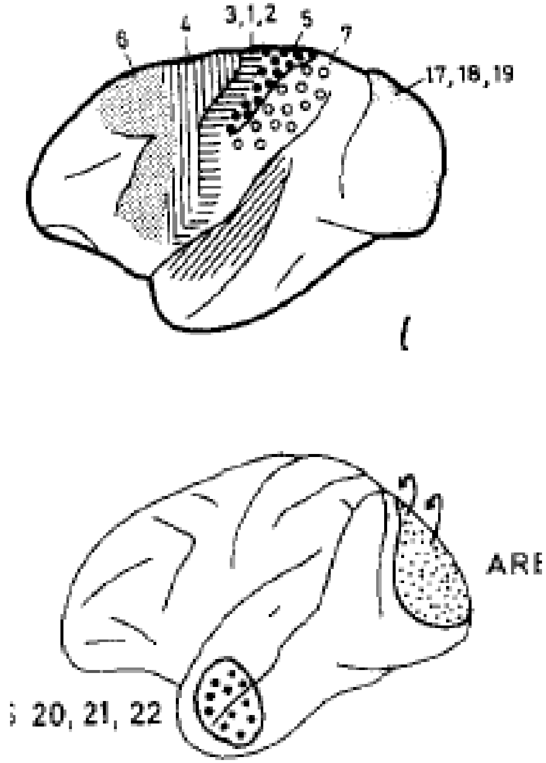


Pontine Nuclei Relay Cerebro-Coritcal Information

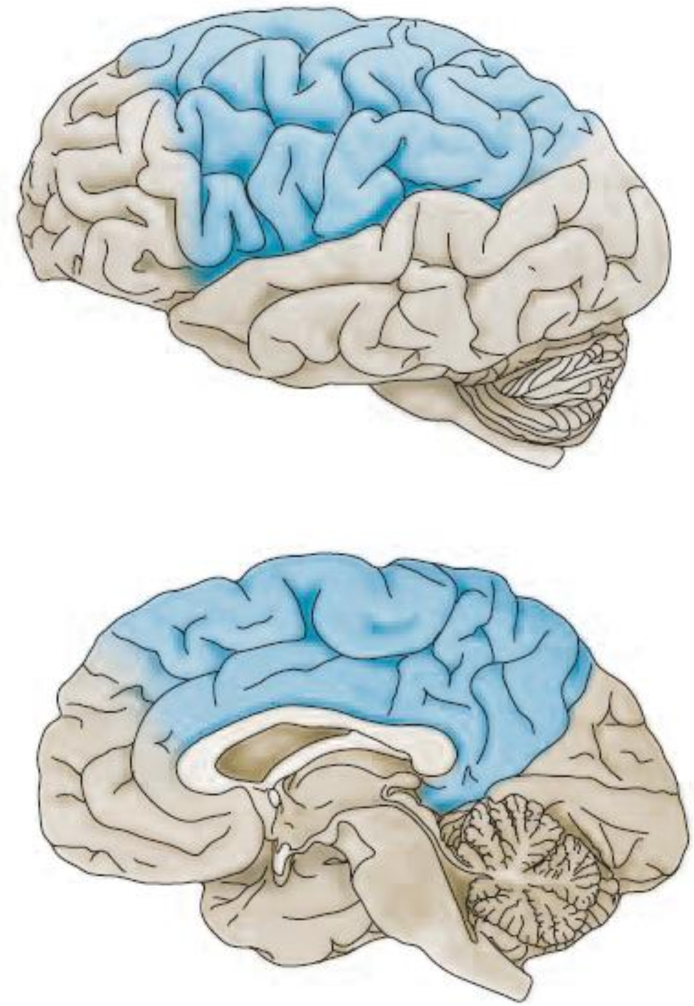


Non-Cortical Inputs:

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



(Brodal 1978)



Cortical Areas That project to the Pontine Nuclei

The IO receive motor and sensory inputs

Visual Inputs:

SC = Superior Coliculus

NOT = Nucleus of Optic Tract

Vestibular Inputs:

VN = Vestibular Nucleus

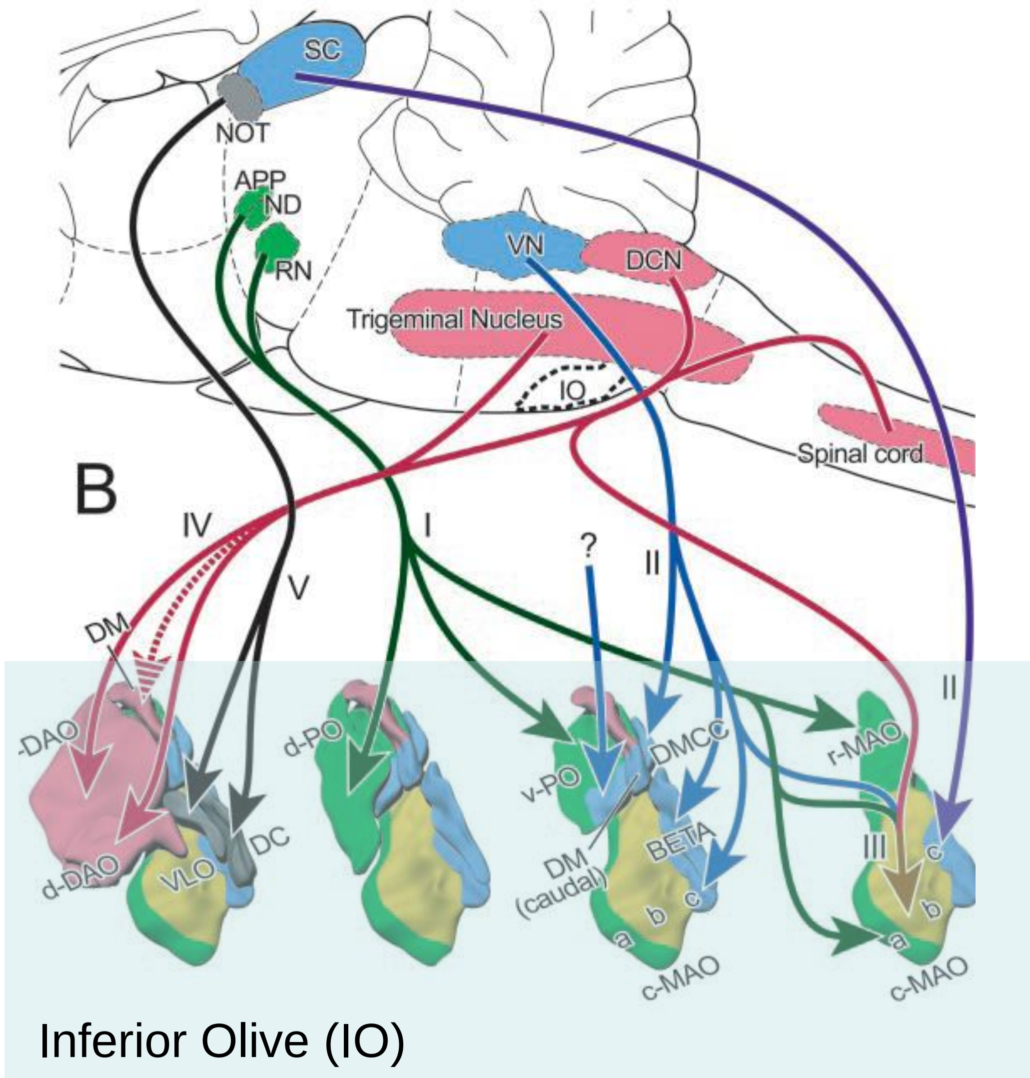
Motor Command:

RN = Red Nucleus

Somatosensory & Proprioceptive:

DCN = Dorsal Column Nucleus

Trigeminal & Spinal Chord

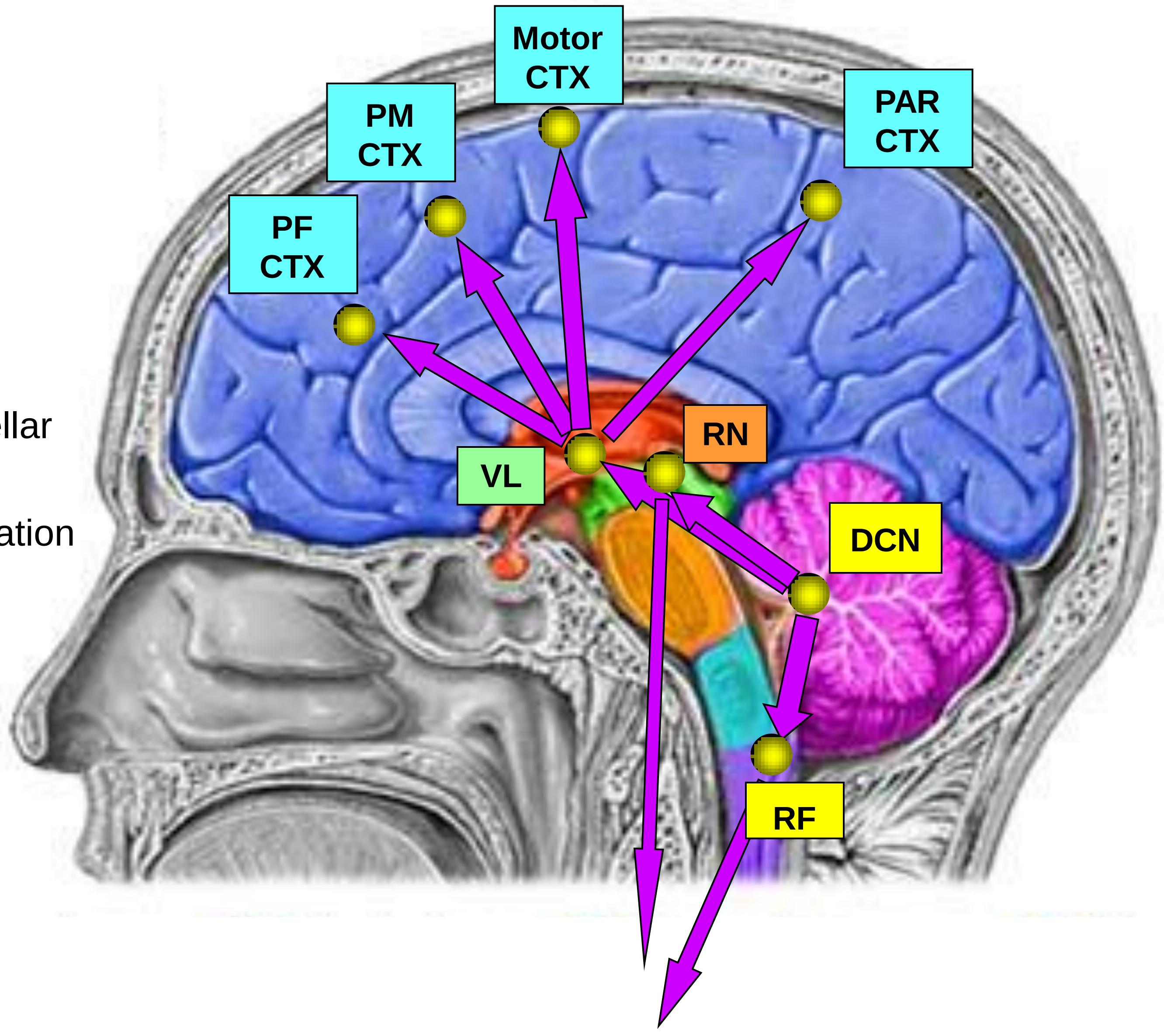


Additionally: Auditory Inputs

Sugihara & Shinoda JNS 2004

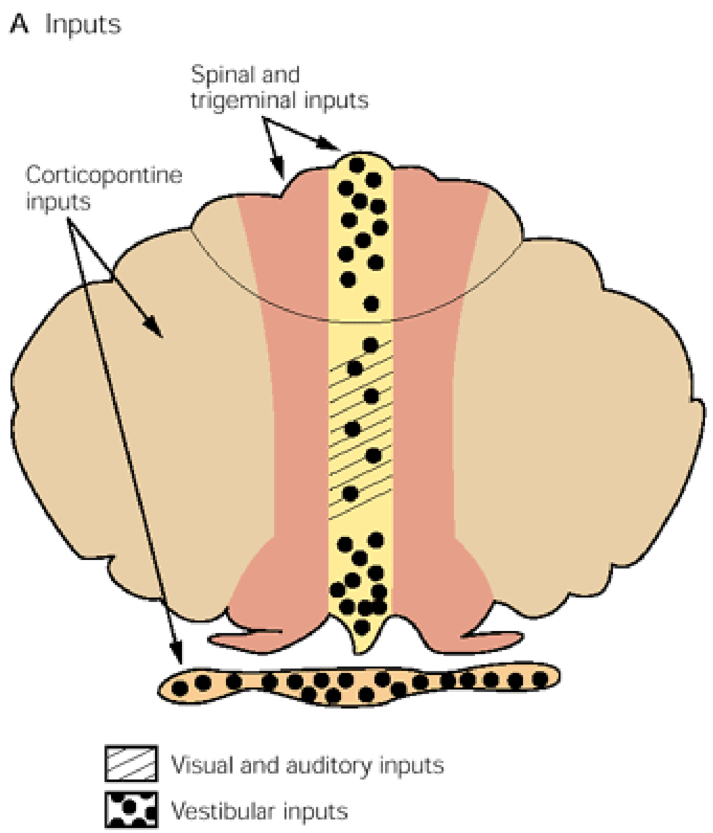
Cerebellar Major Output Pathways

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

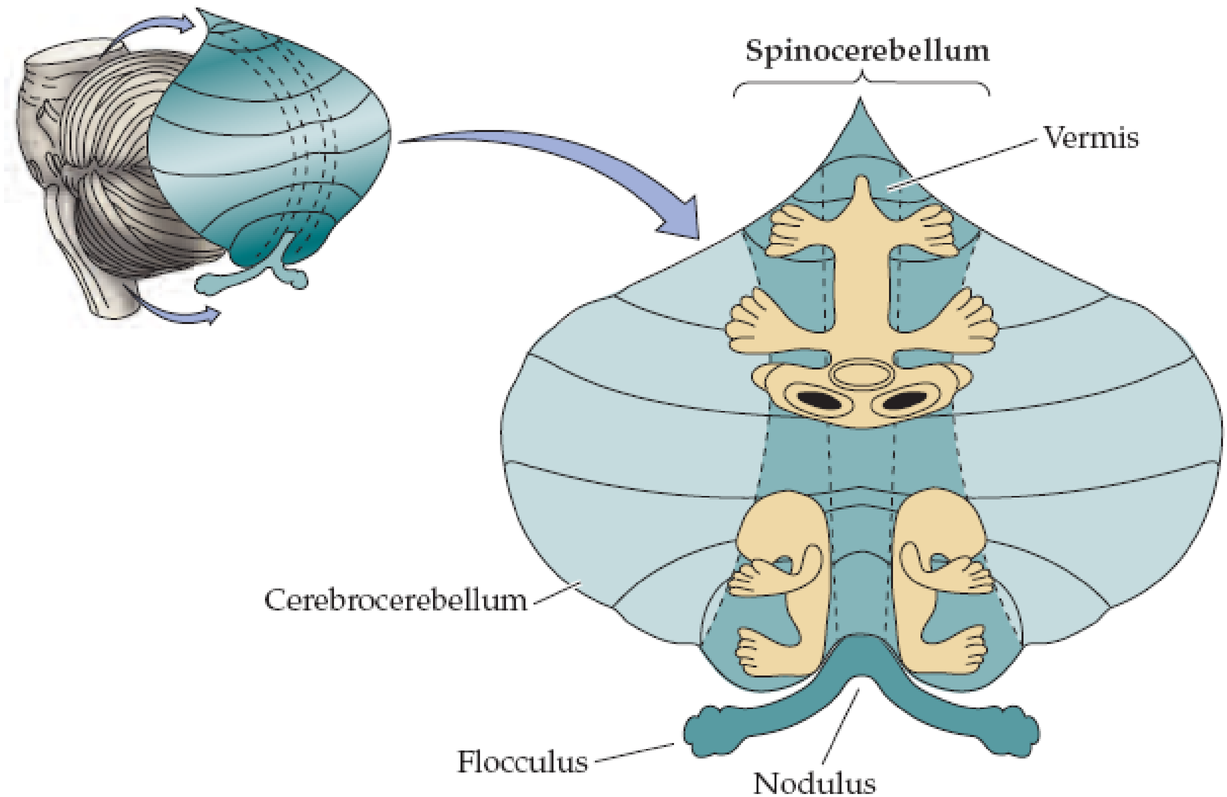


Other Outputs:
Inferior Olive
Hippocampus
Amygdala
Septum

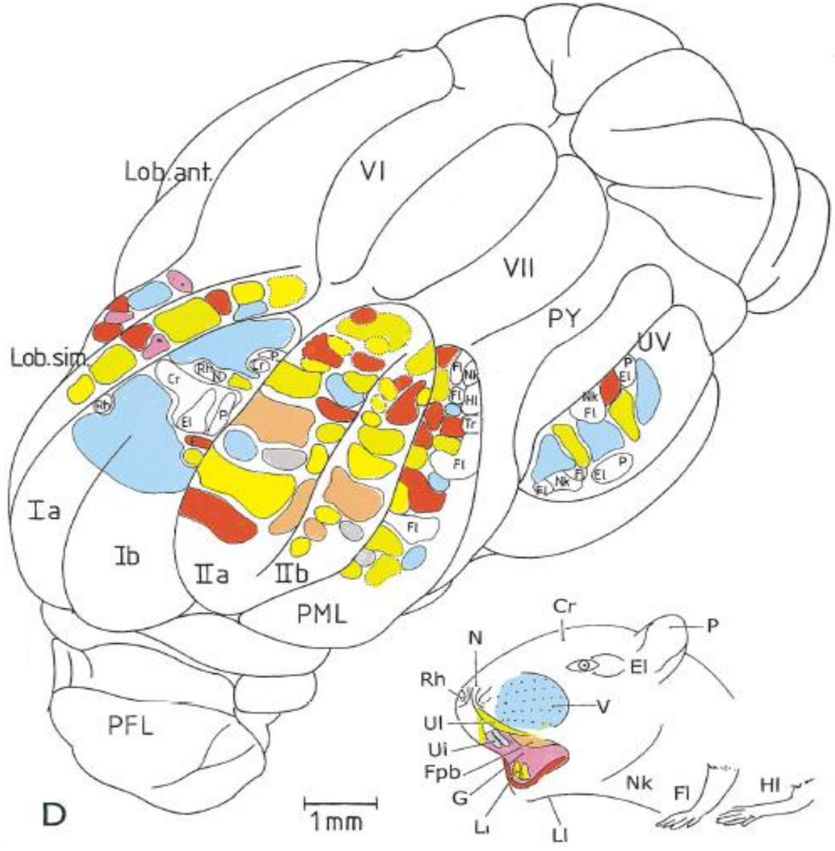
General Mapping of Cerebellar



Mapping of Cerebellar Cortex – Classic View

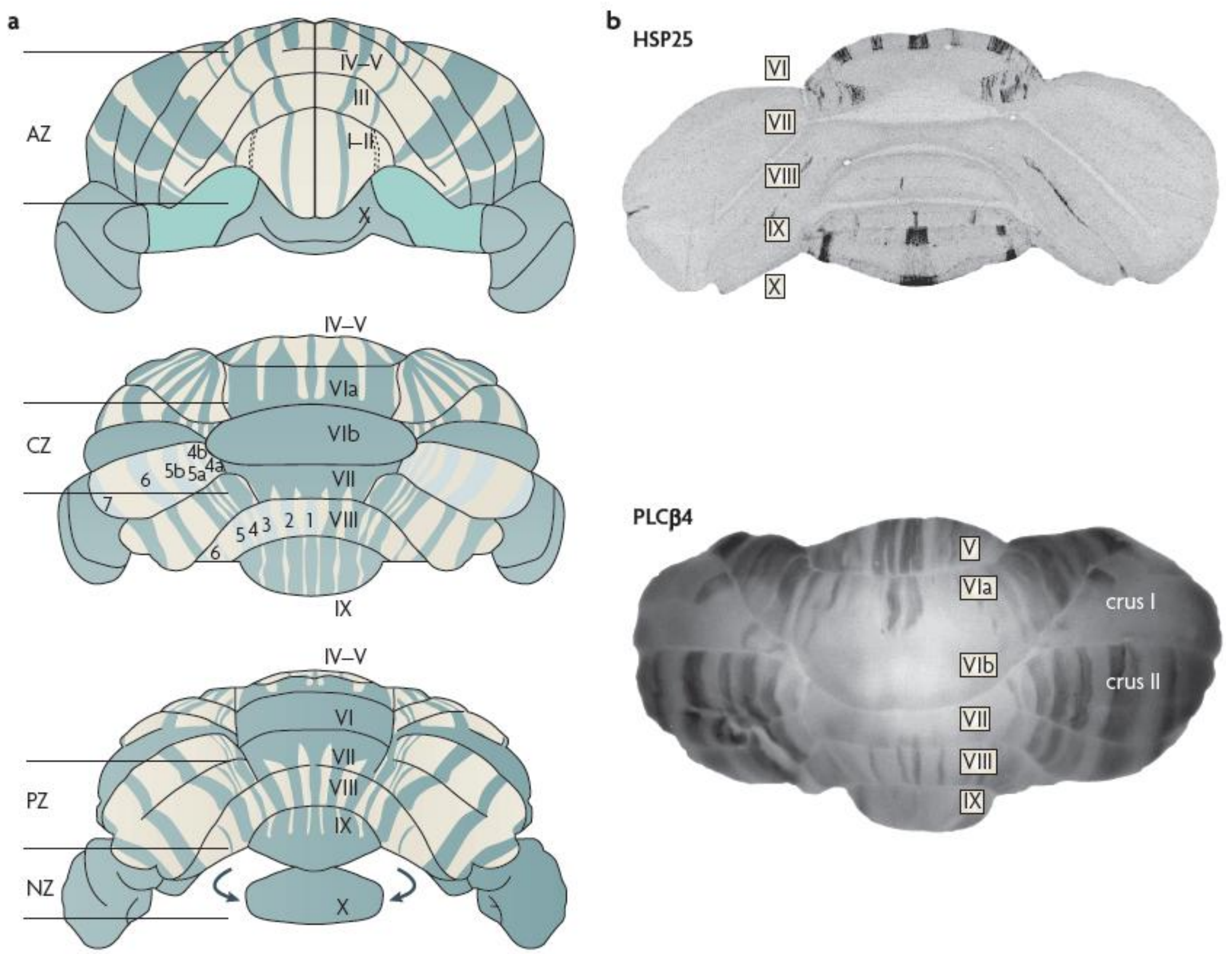


Cerebellar Cortex Mapping is Fragmented



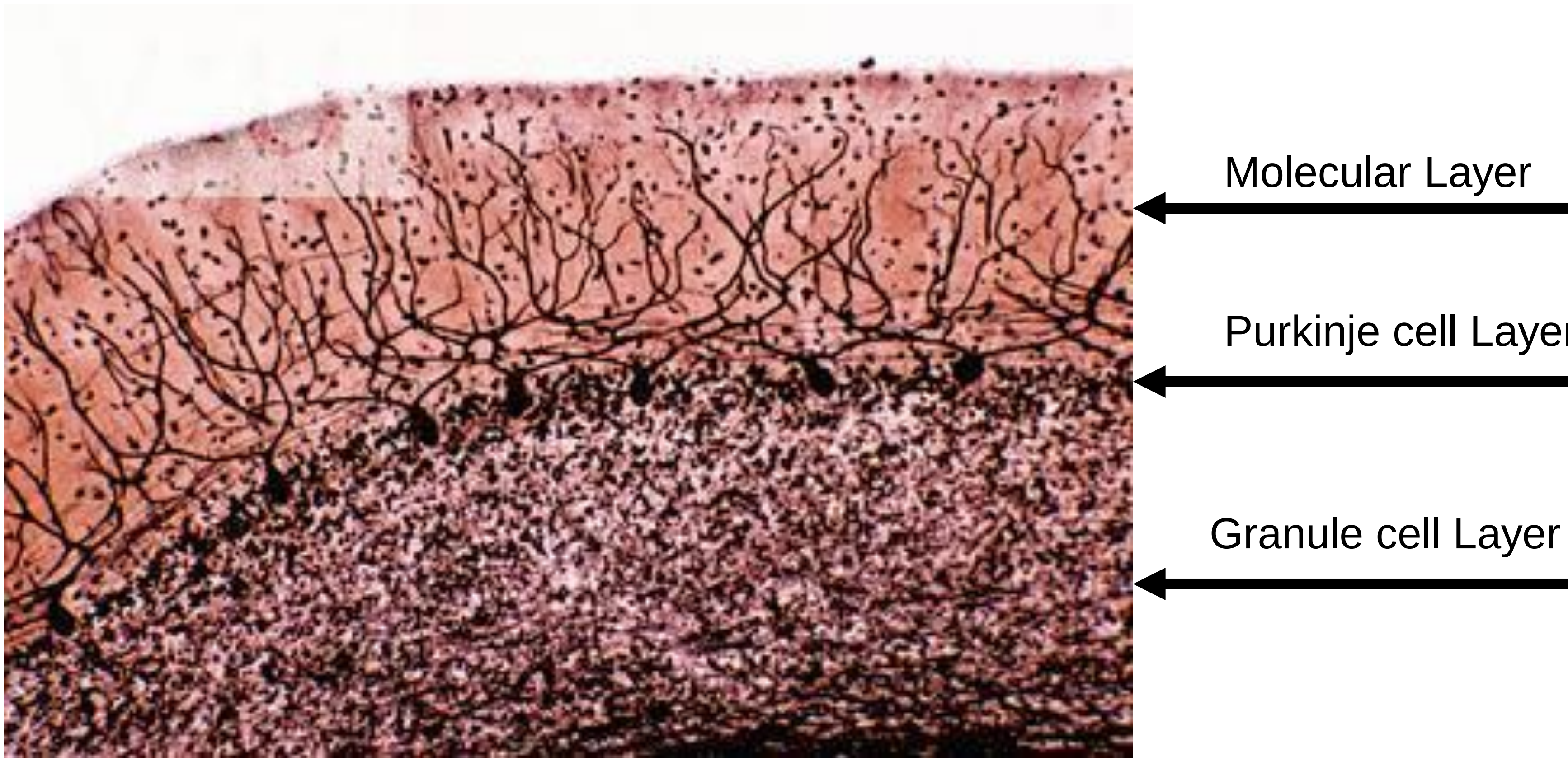
Voogd and Glickstein 1998

Parasaggital Microzones of Cerebellar Cortex

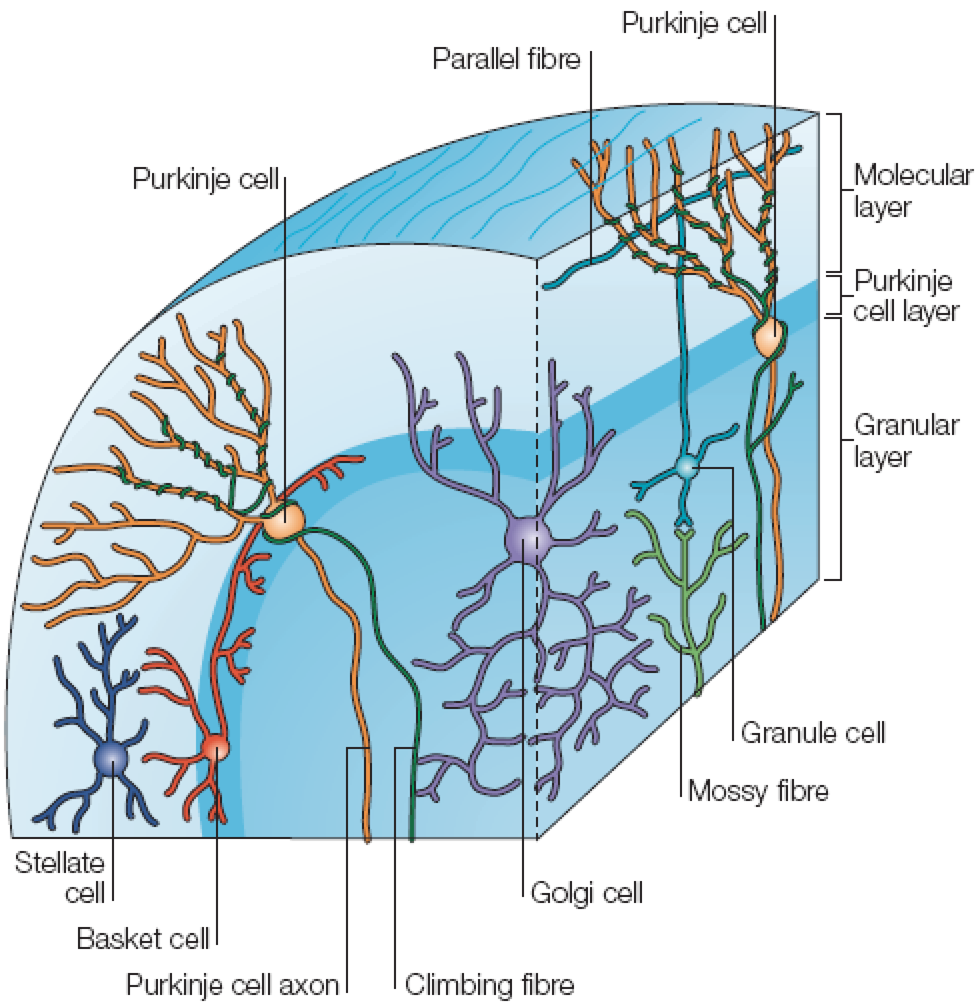


Some Molecular Markers (i.e. Zebrin II) divide Purkinje Cells Populations

The 3 Layers of the Cerebellar Cortex



Cerebellar Cortex Consists of 5 types of Neurons

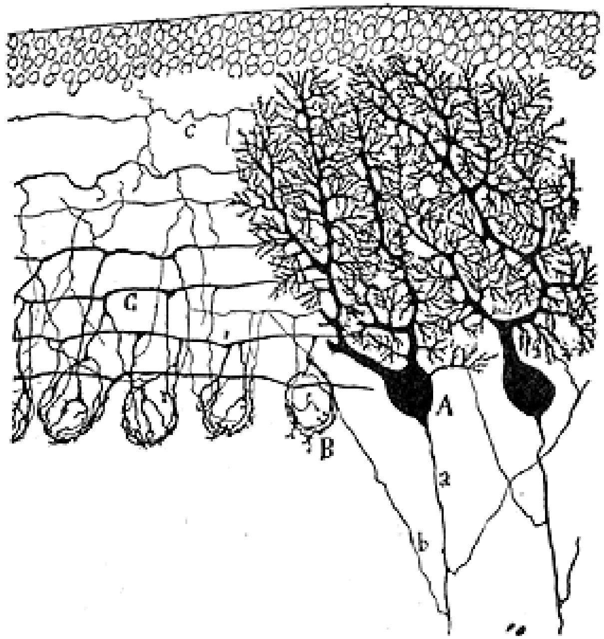


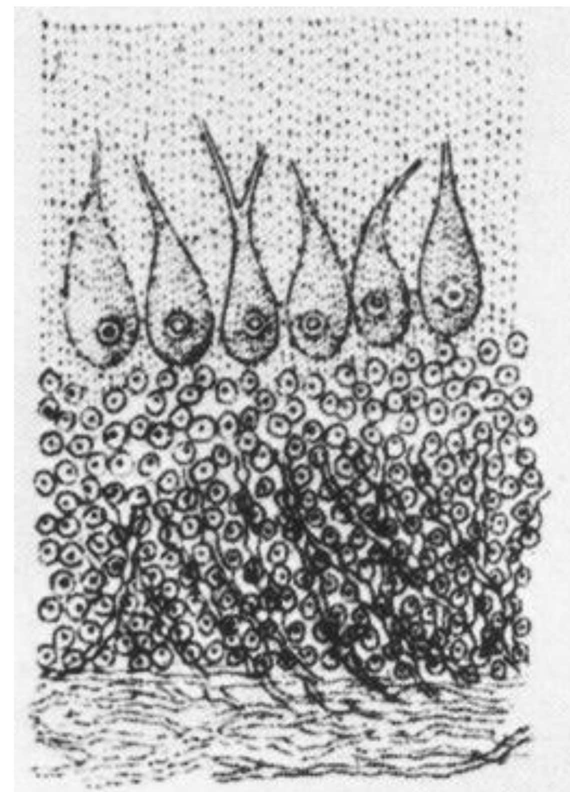
Inhibitory cells:
- Purkinje
- Golgi
- Basket
- Stelate

Excitatory Cells:
- Granule cells

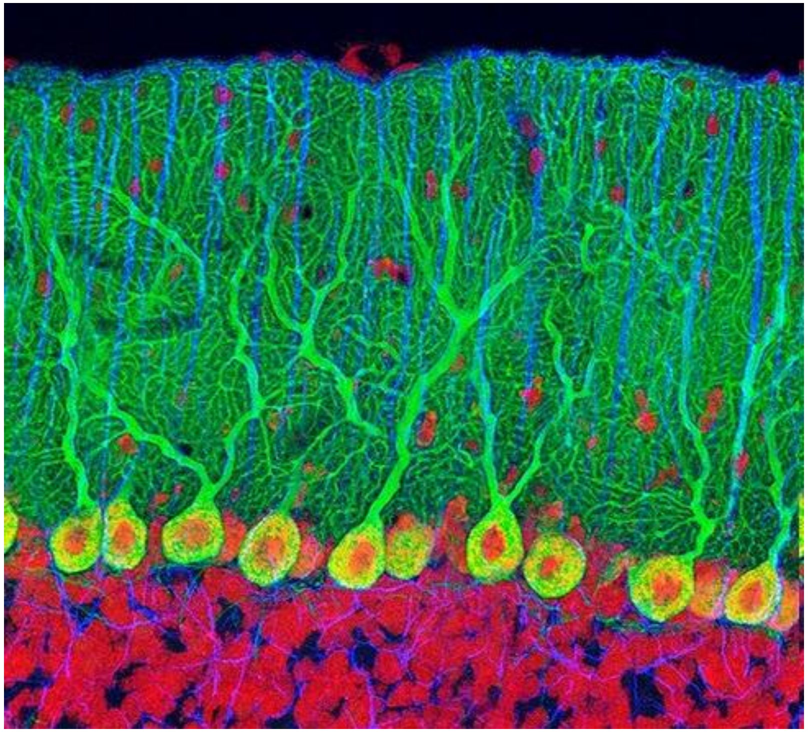
Apps & Garwicz NatRevNeu 2005

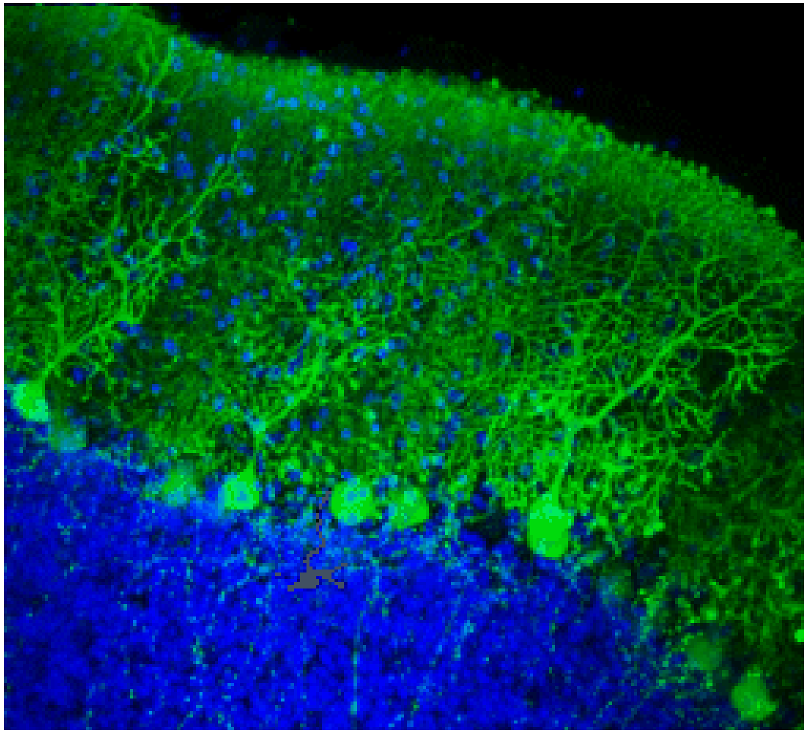
Purkinje Cells: The most Elaborate Neurons of the CNS





Purkinje Cells: The Beauty of Network Structure

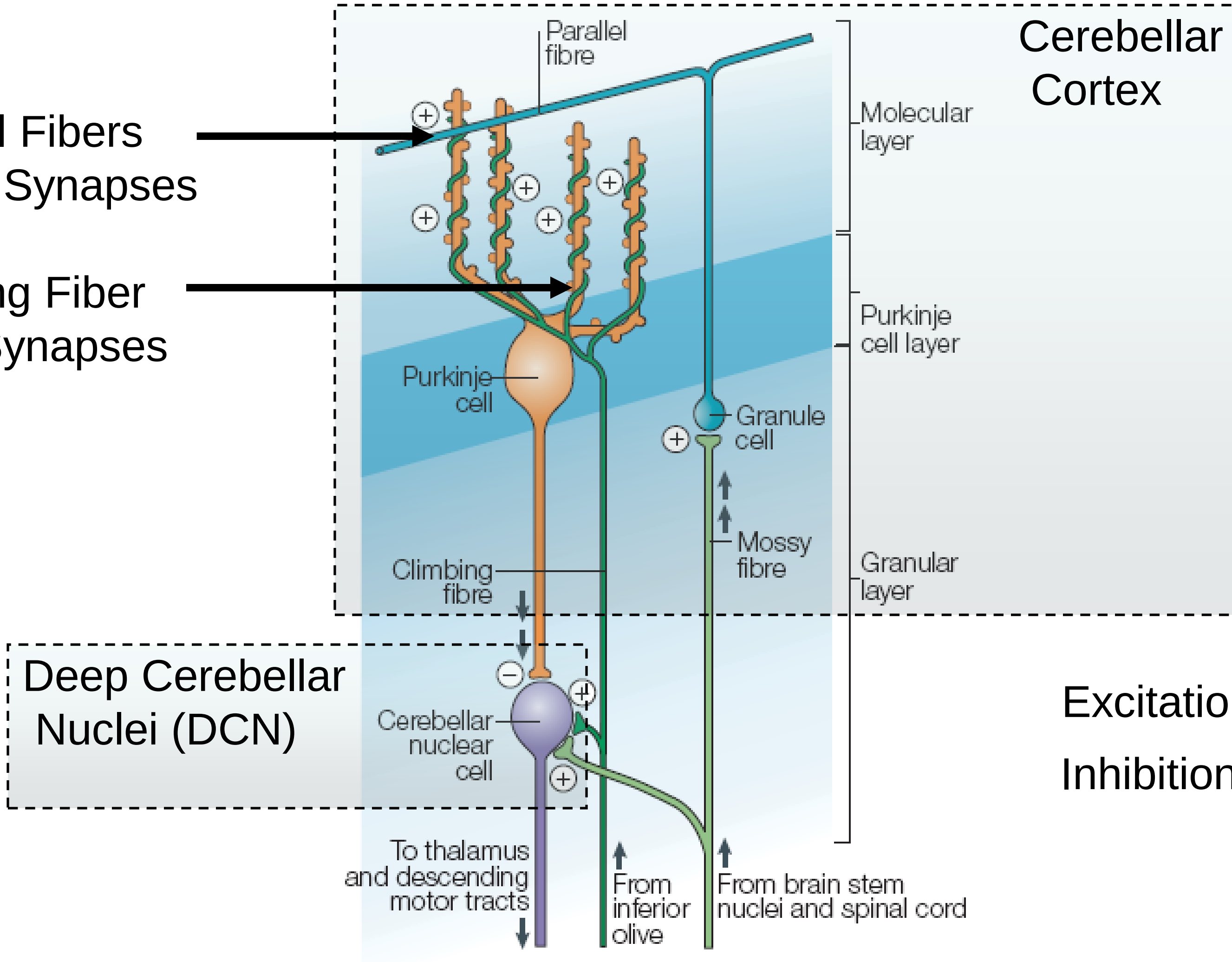




PC: The Principal Cell of Cerebellar Cortex

Parallel Fibers
~200,000 Synapses

Climbing Fiber
~2000 Synapses



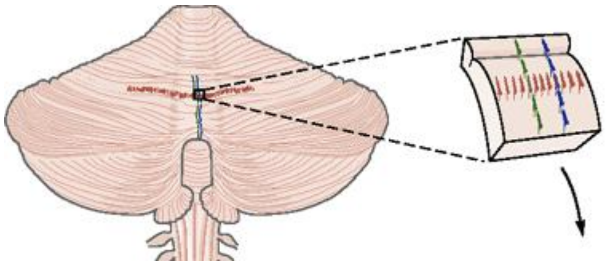
Excitation

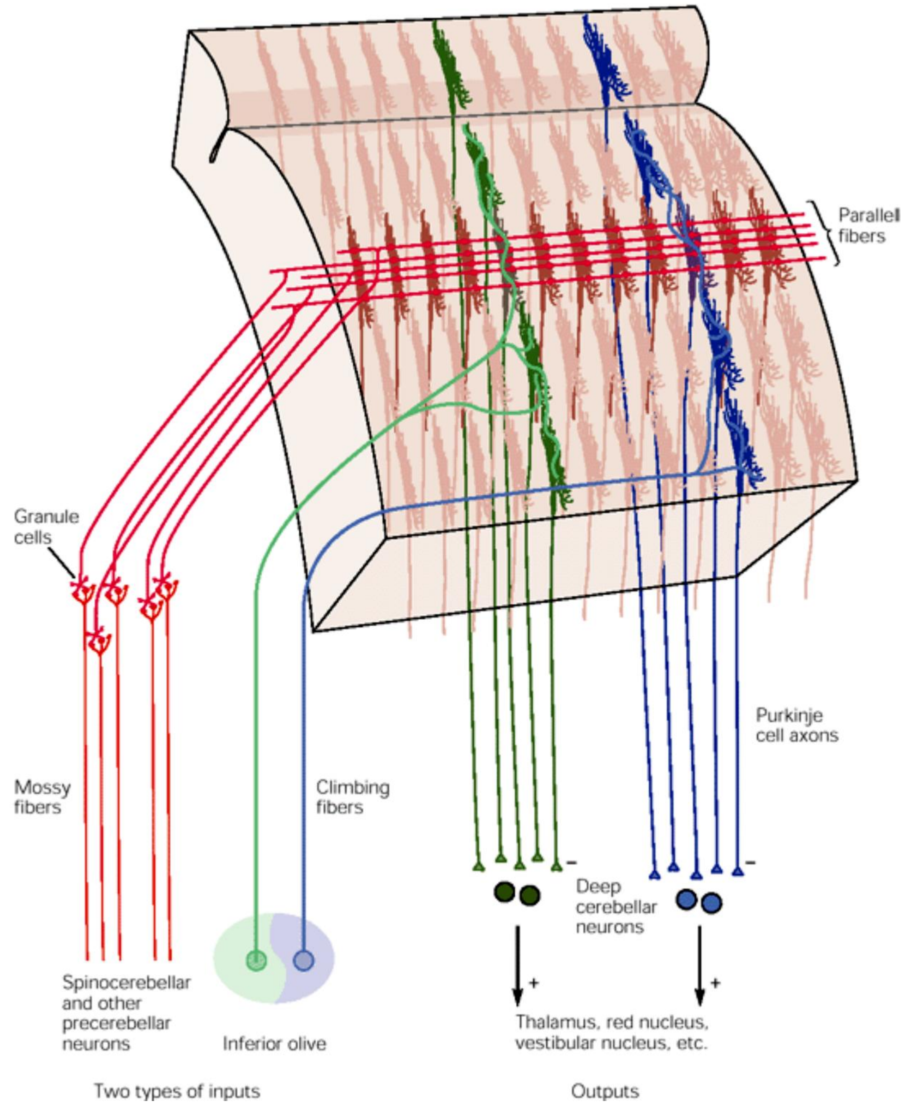
Inhibition

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

Modified from Apps & Garwicz 2005

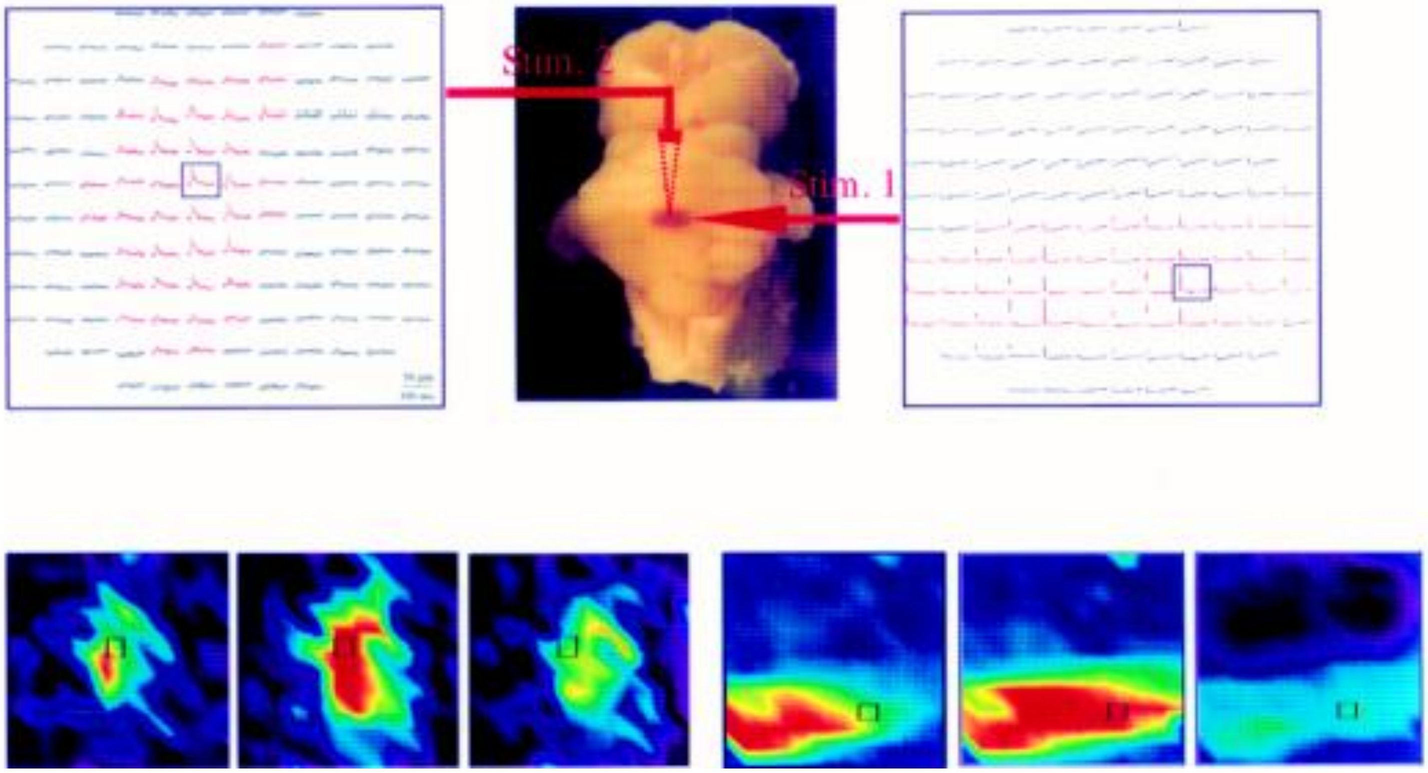
The Spatial Organization of Cerebellar Circuitry





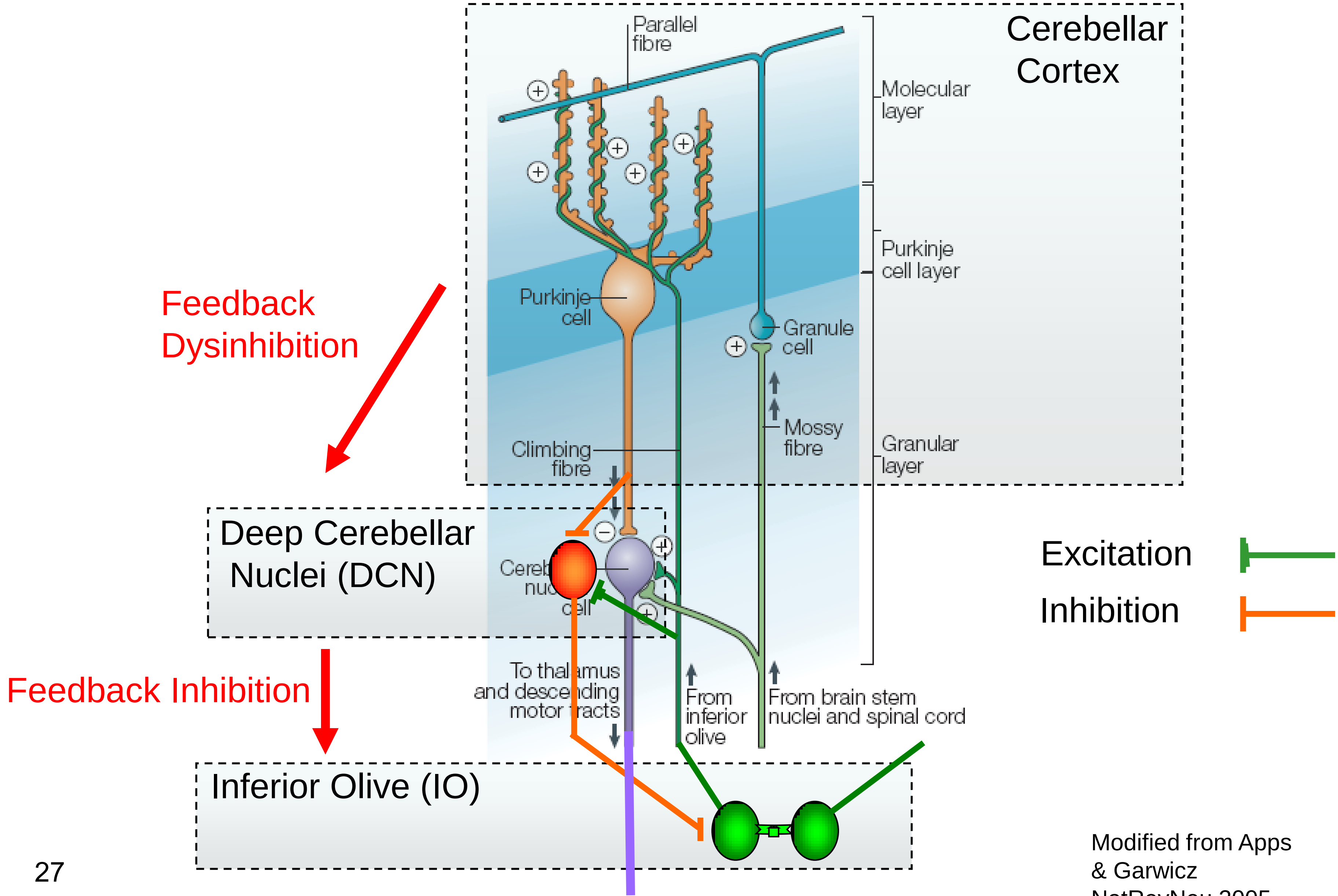
Notice the perpendicular relationship between Mossy Fiber and Climbing Fiber enervations!!

No timed propagation on the parallel fibers



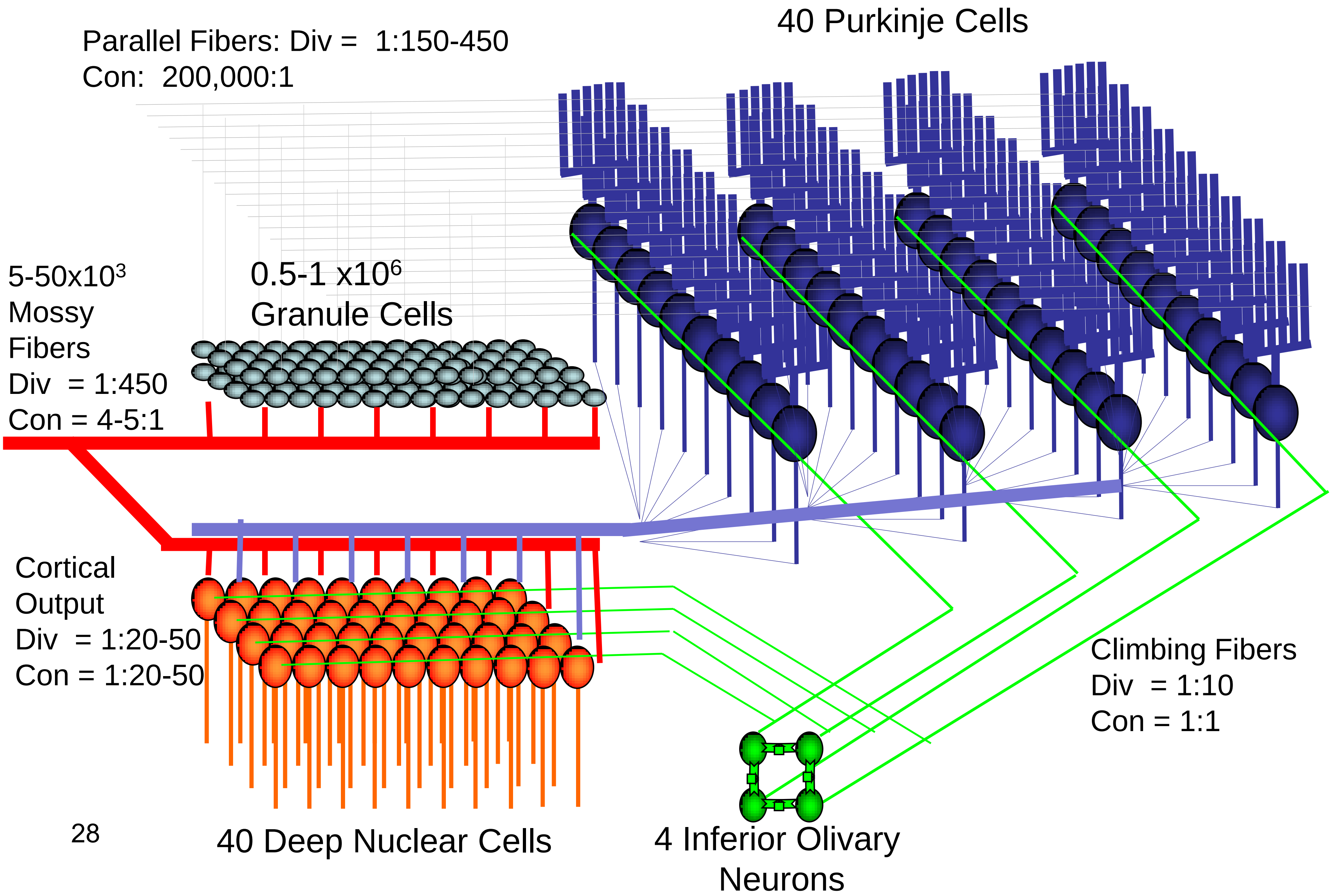
Yarom and Cohen AnnNYAc 2003

Closing the Loop: The Cerebellar Module

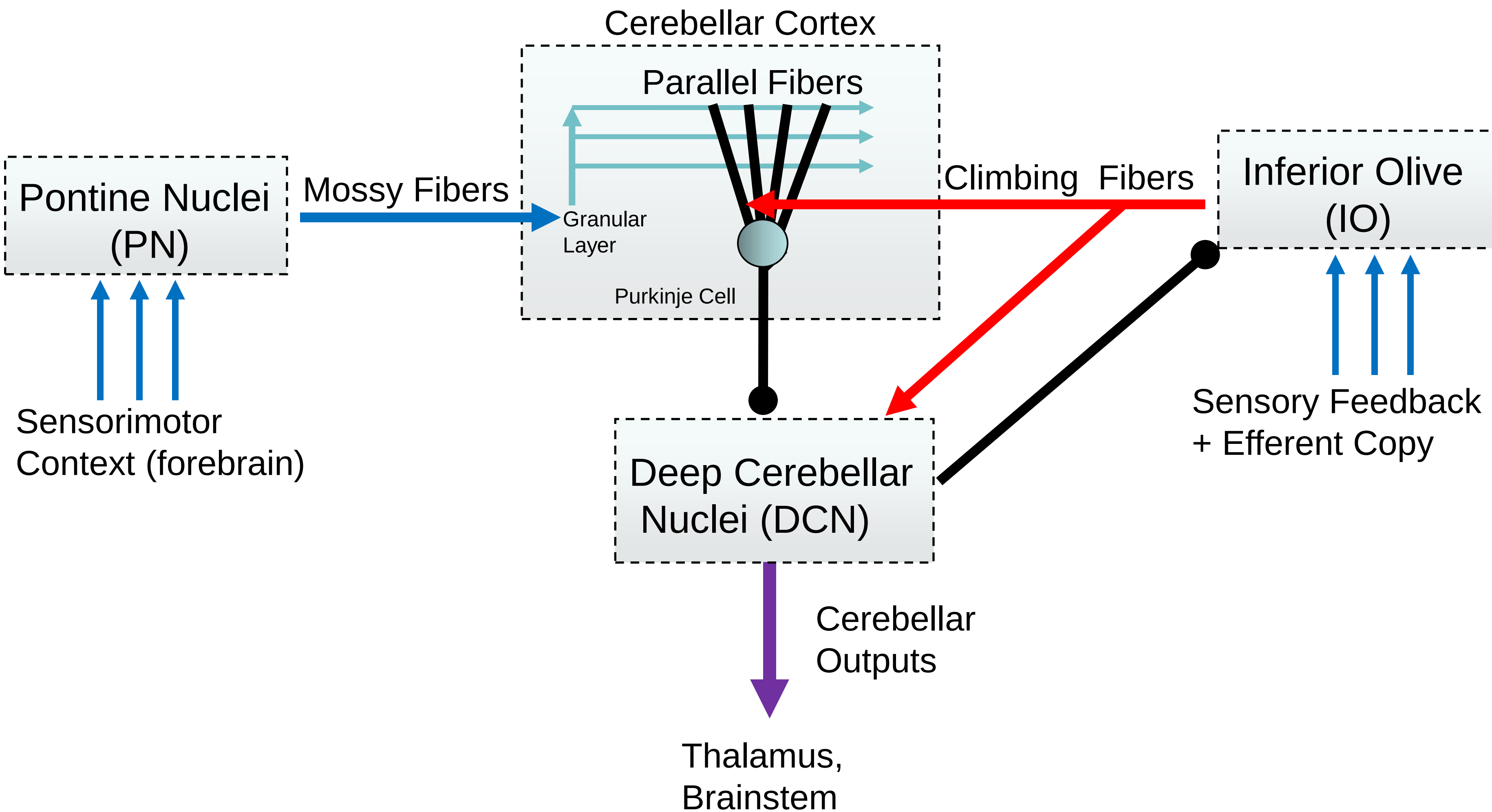


Modified from Apps & Garwicz NatRevNeu 2005

The Numerics of Cerebellar Modules



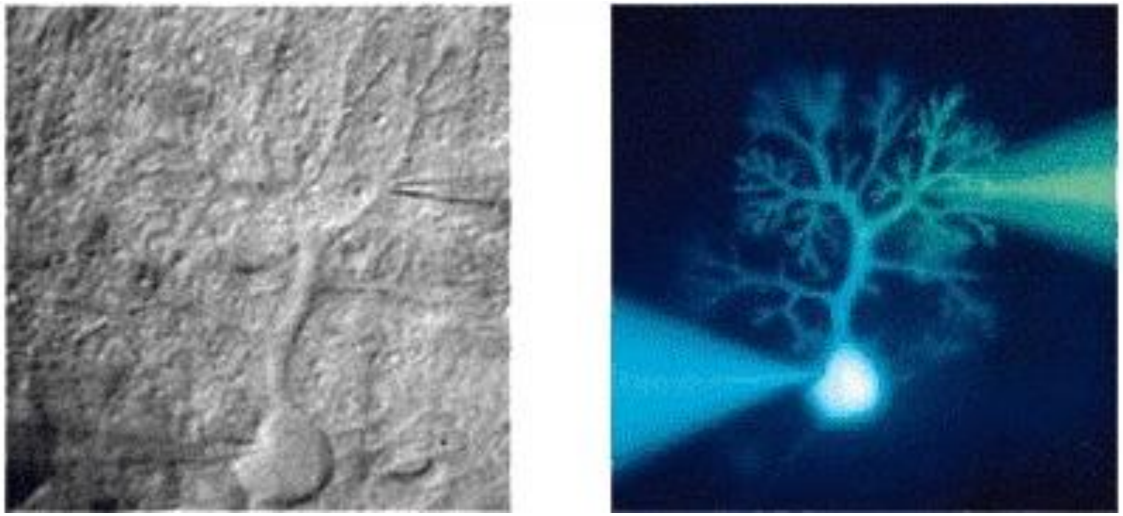
The simplified Olivocerebellar Module



Cerebellar Physiology

Infra Red

Fluorescent Dye

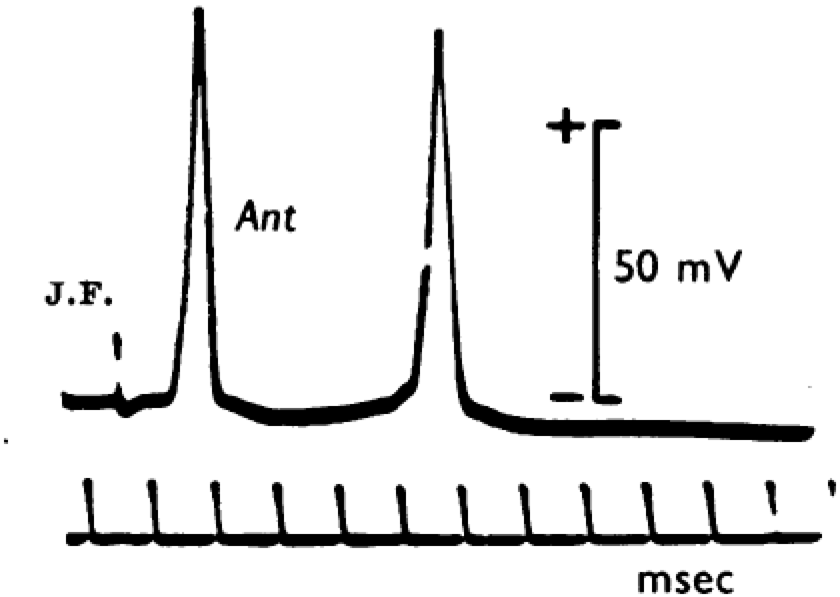


Double Recording of Purkinje Cell in Slice

Hausser M.

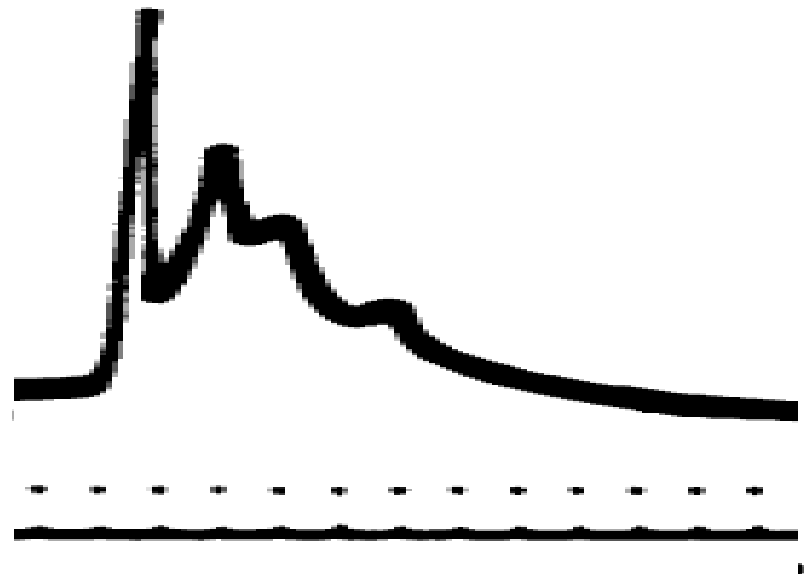
Purkinje Cells exhibit Two distinct Spike Types

Simple Spike



Mossy Fiber Stimulation

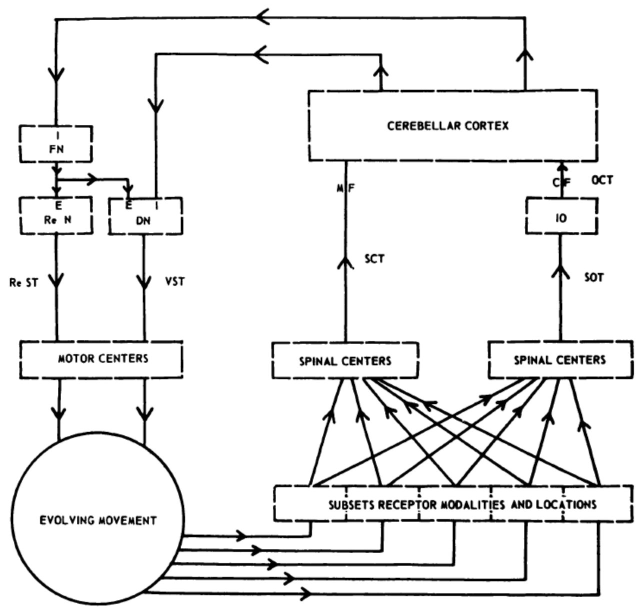
Complex Spike



Inferior Olive Stimulation

Eccles, 1966

Cerebellar Learning Theories



Eccles, 1967

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)

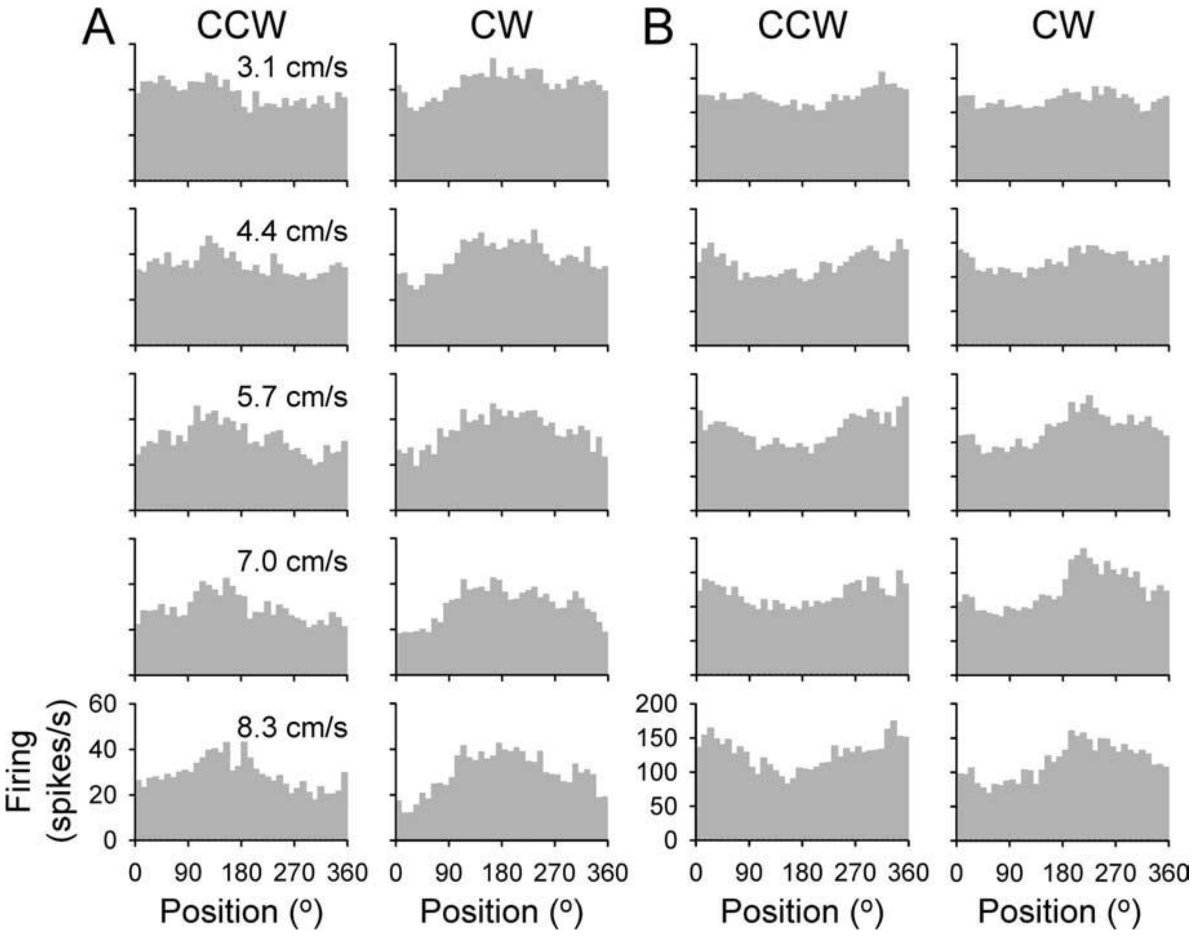
MATHEMATICAL BIOSCIENCES

A Theory of Cerebellar Function

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

1971

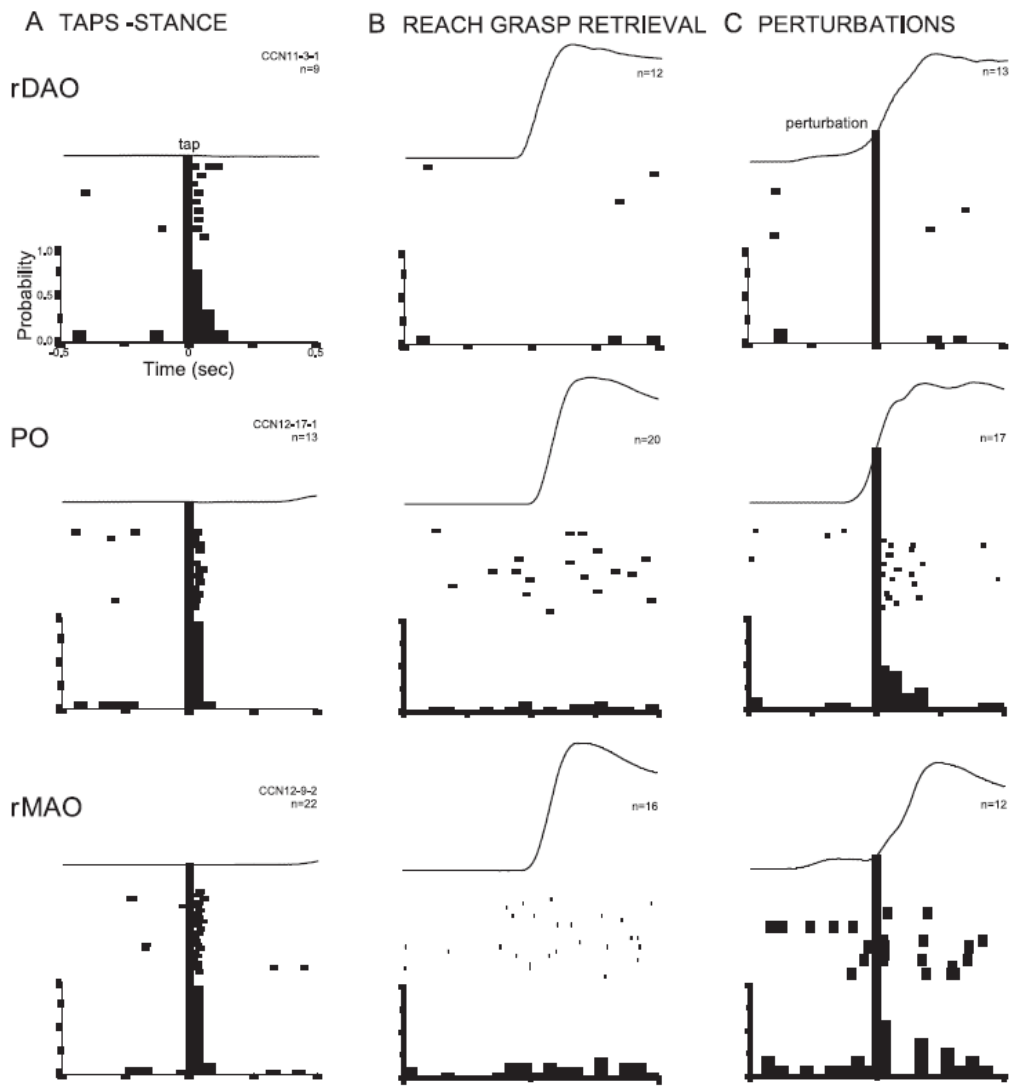
Simple Spikes are Modulated by Inputs



Simple spikes of 2 Purkinje cells in awake monkey during hand movements

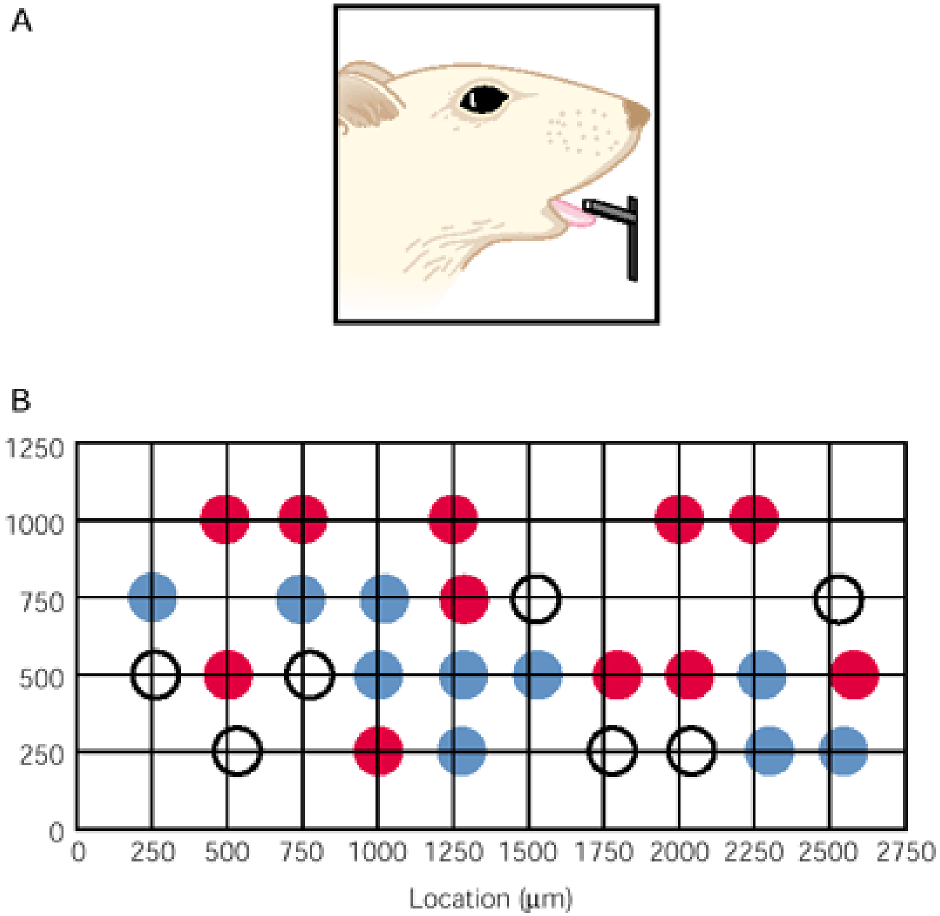
Roitman 2005

Complex Spikes are fired in Unexpected Events



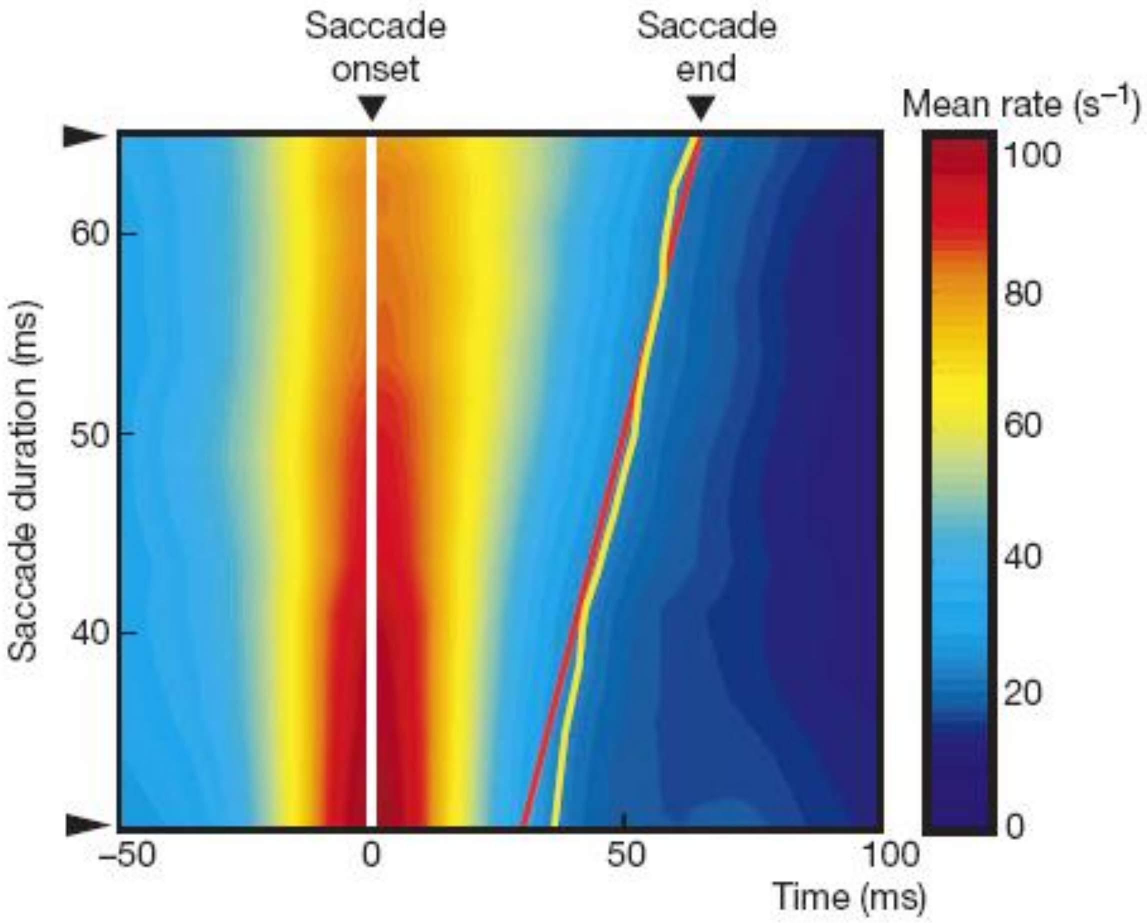
Horn, Pong & Gibson 2002

Synchronous Population Coding by Purkinje Cells



Welsh 1995

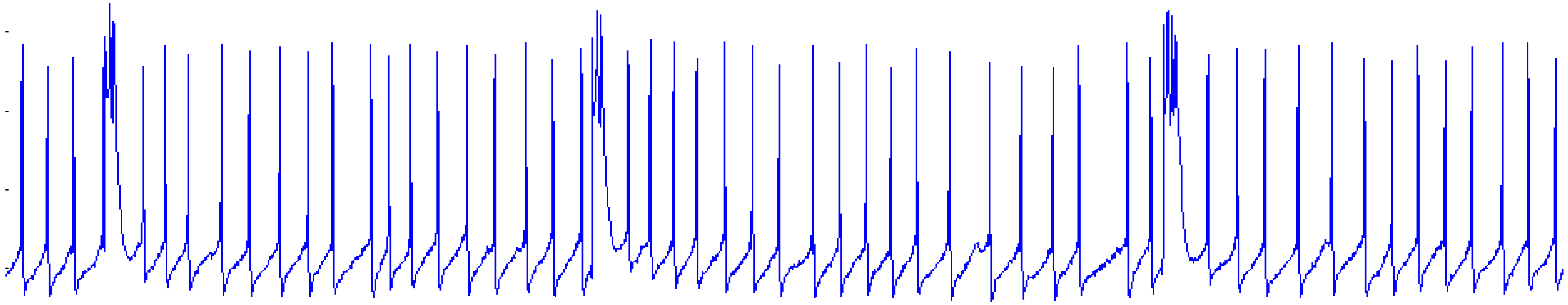
Saccade attributes are encoded by a population of ~100 Purkinje cells



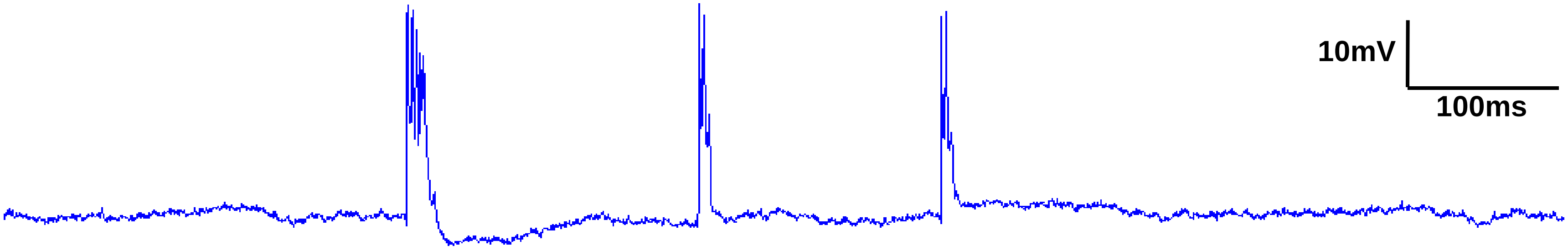
Tier-Barash 2000

Distinct Firing Regimes of Purkinje Cells

Complex Spikes & Simple Spikes (Up-State)



Complex Spikes Only (Down-State)

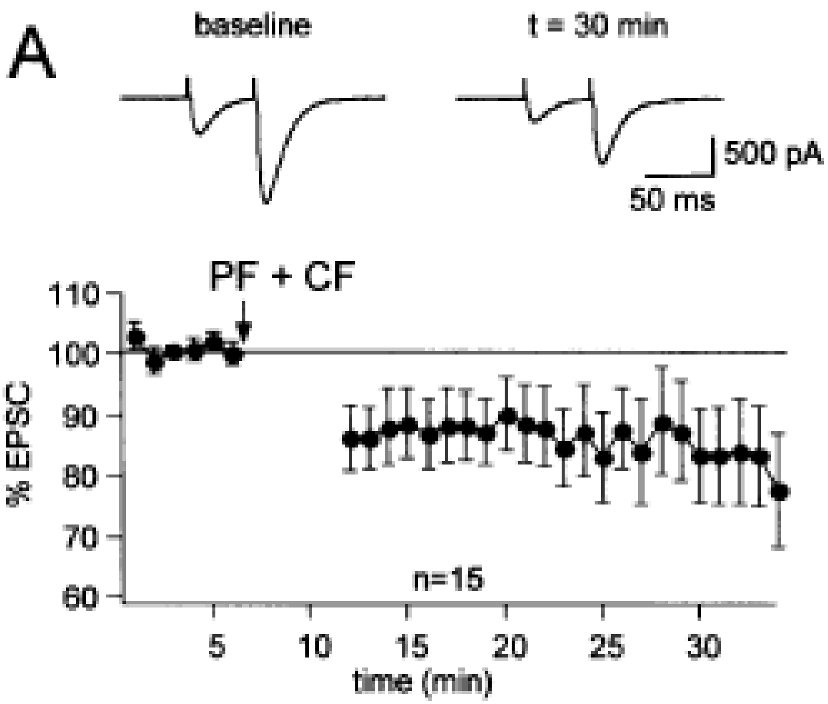


Simple Spikes: 0 - ~80Hz
(Mostly 0Hz or 4-8Hz or 20-80Hz, with possible phasic >100Hz)

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

Cohen and Lampl, unpublished

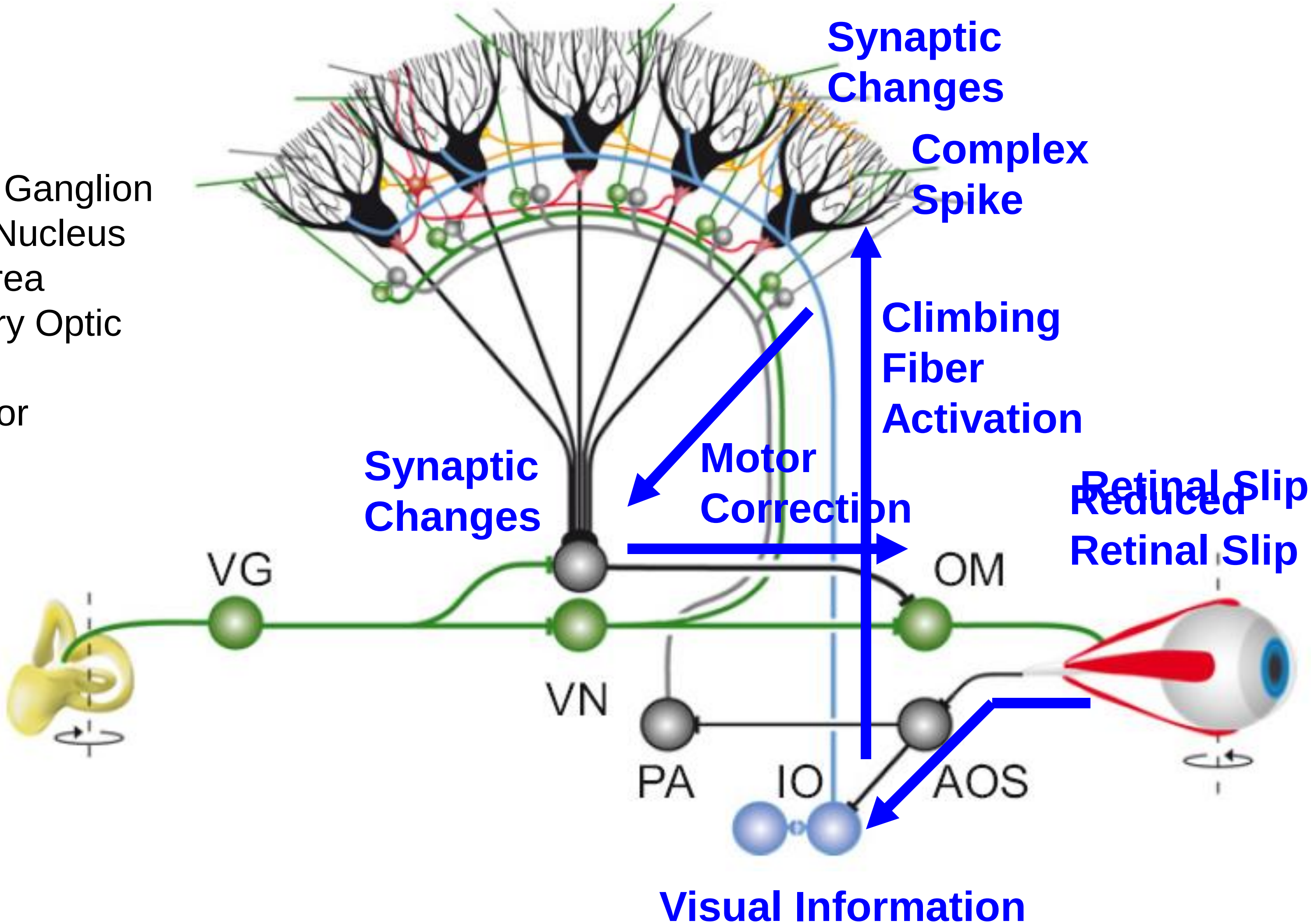
Plasticity in the Cerebellar Cortex



Coesmans et al. Neuron 2004

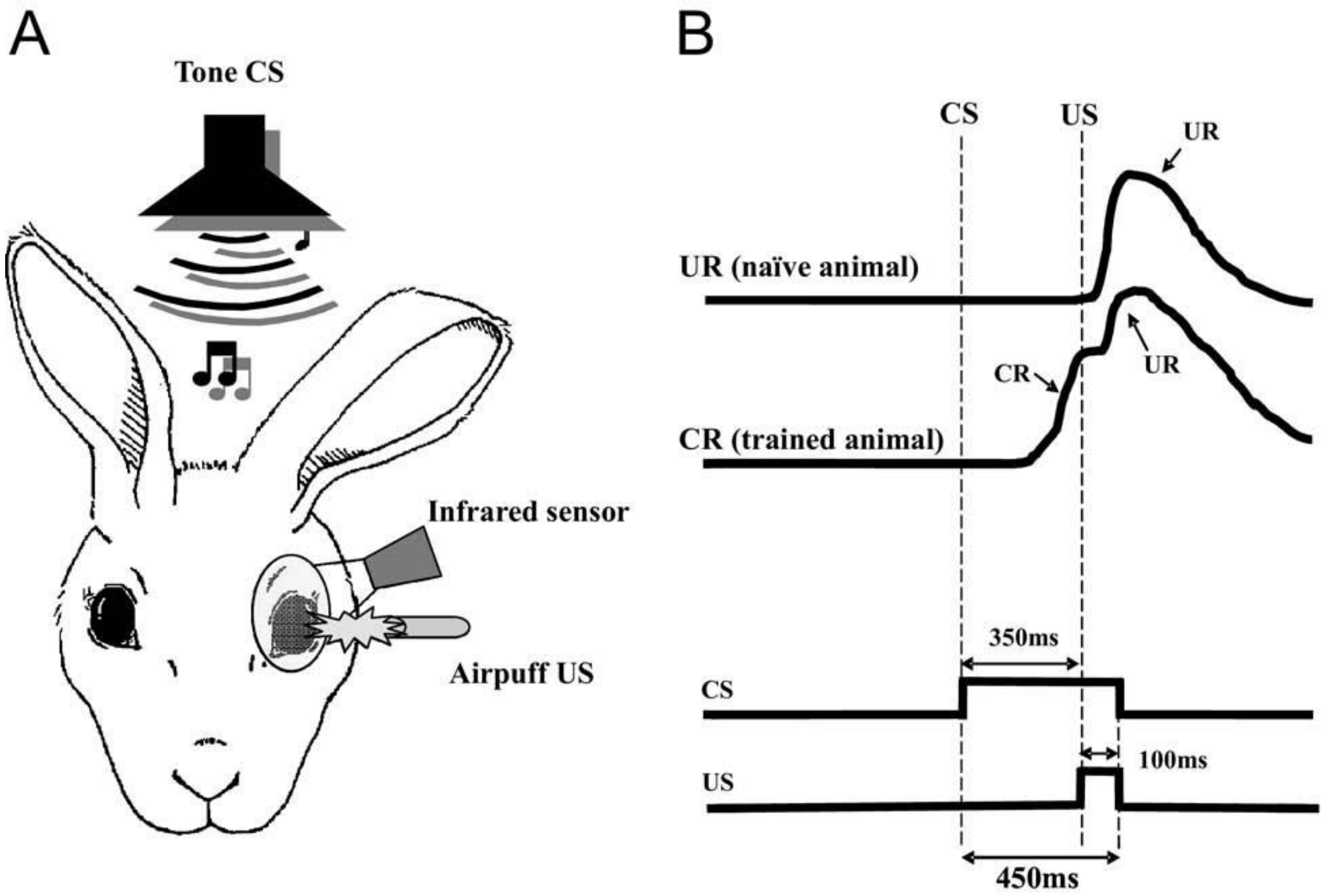
Vestibulo - Ocular Adaptation

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



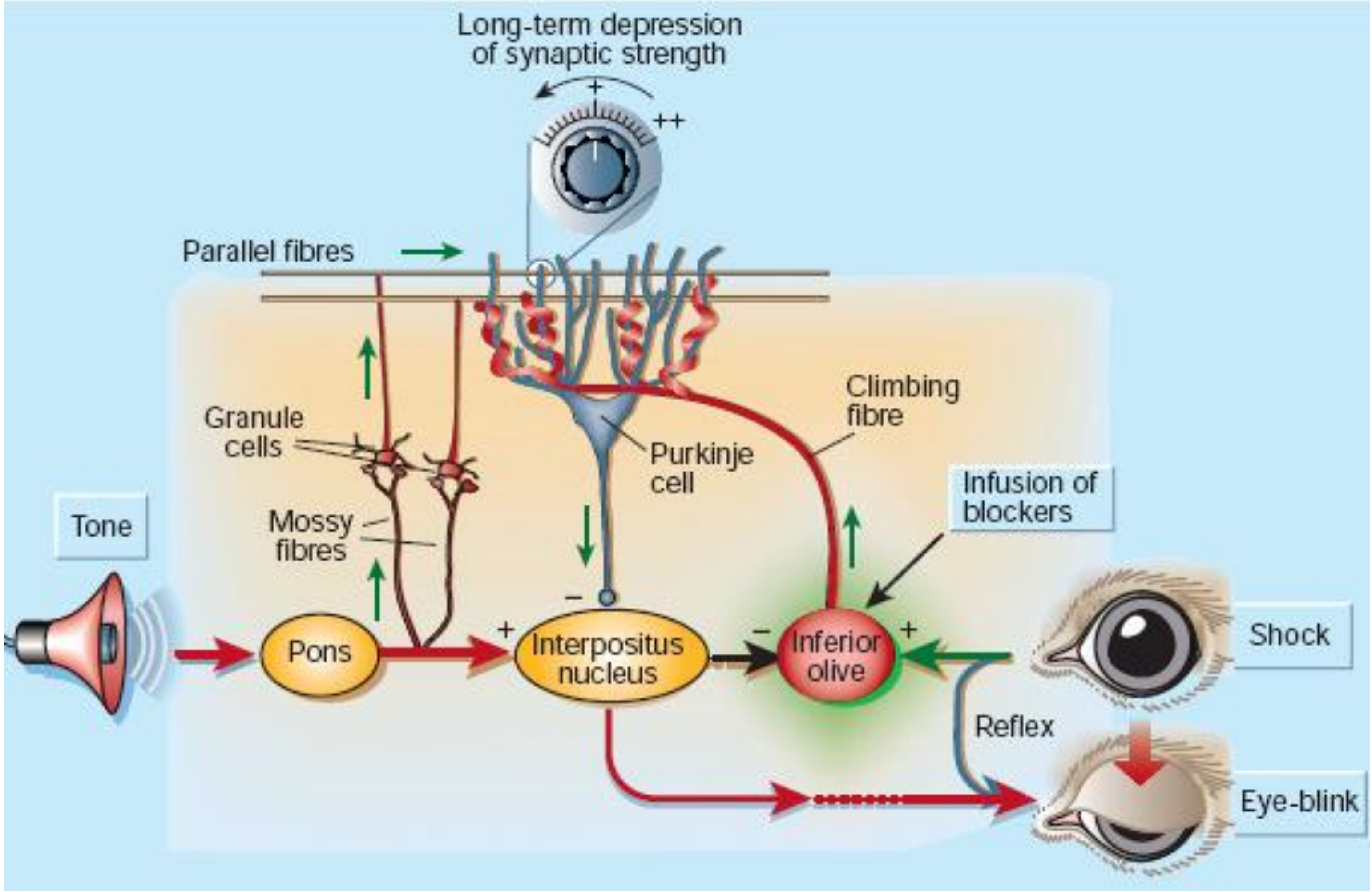
Ito 1984, Schonville et al. 2010

Eyelid Reflex Conditioning



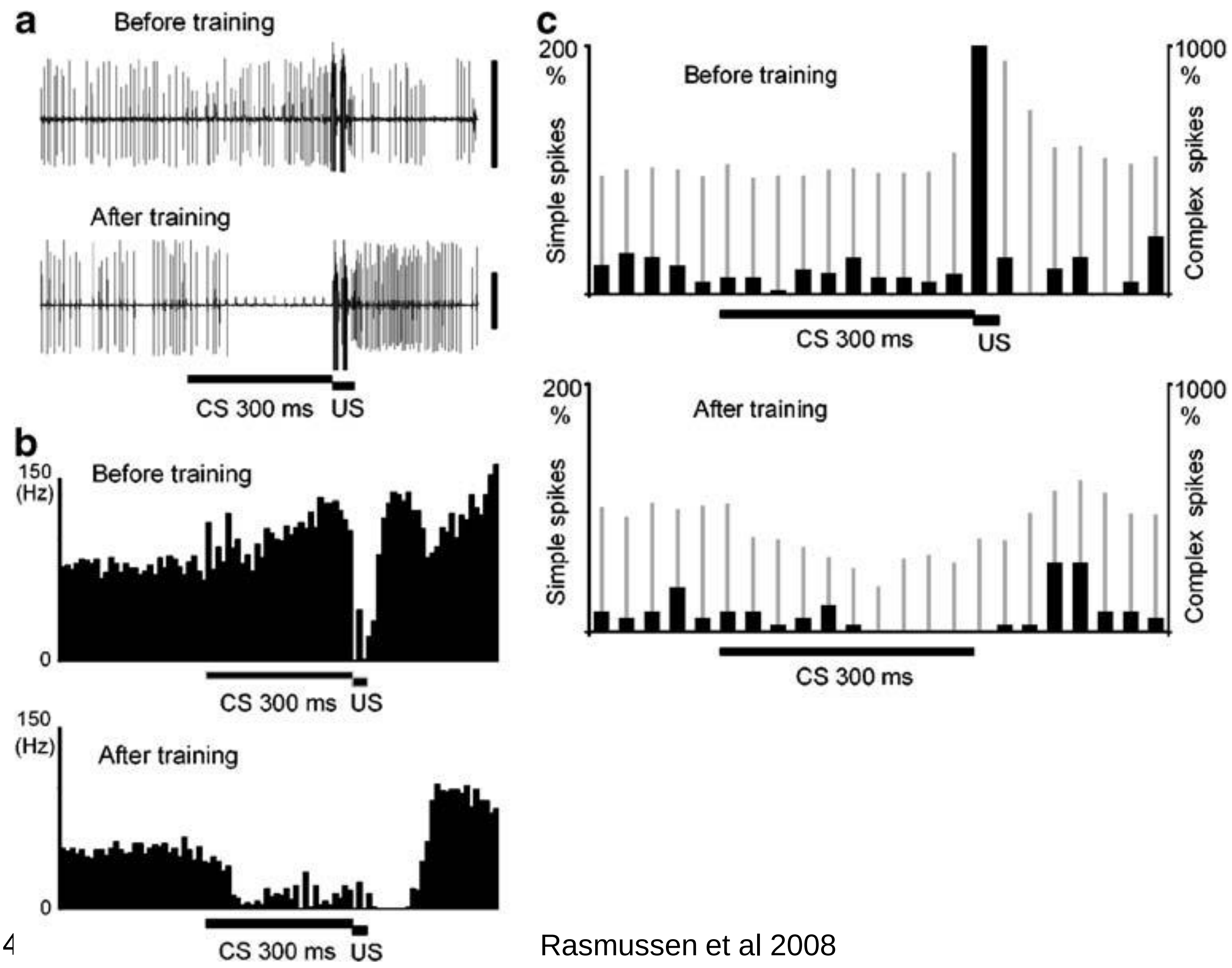
Bracha and Bloedel 2009

Eyelid Reflex Conditioning



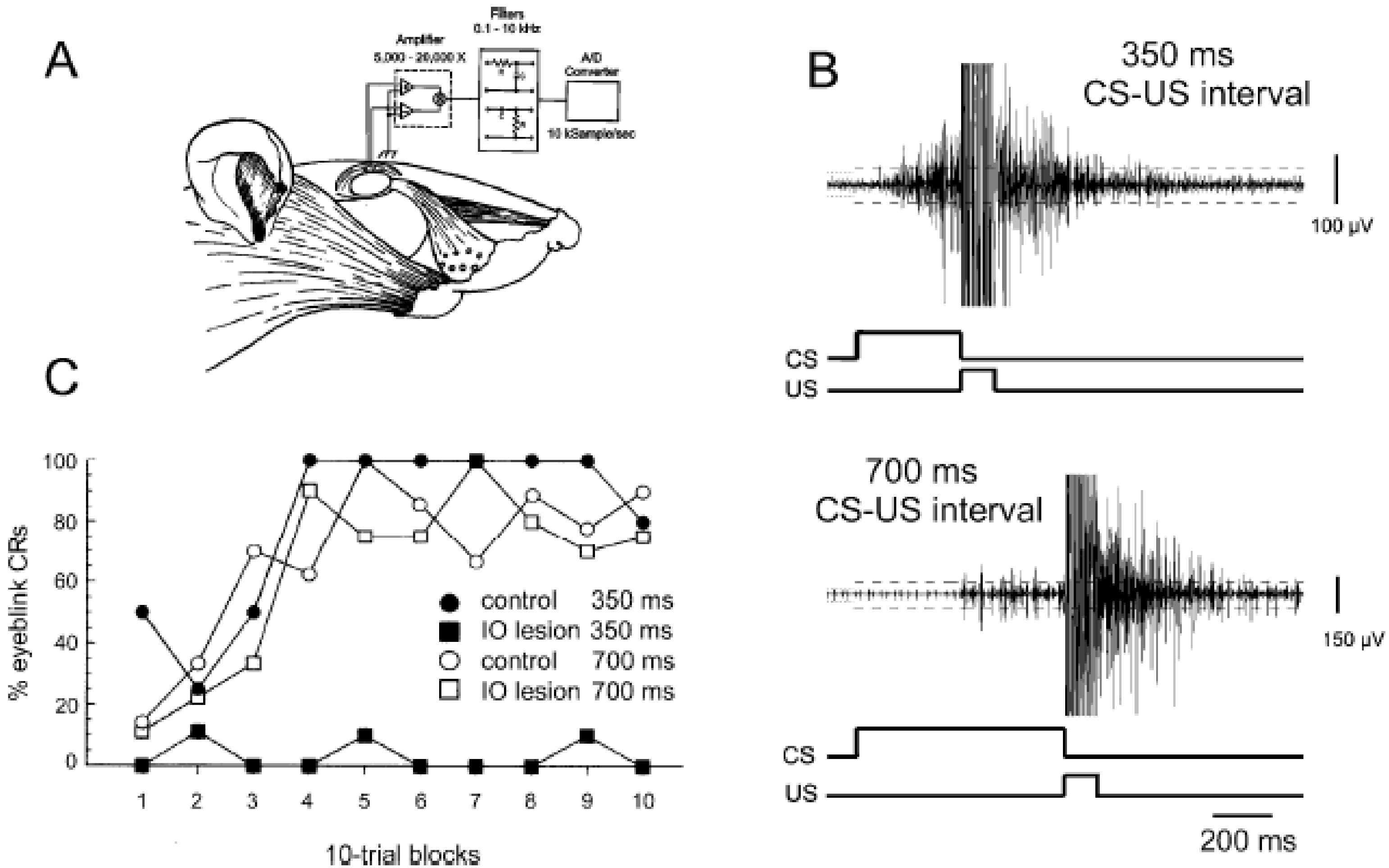
Medina et al. Nature 2002

Eyelid Reflex Conditioning



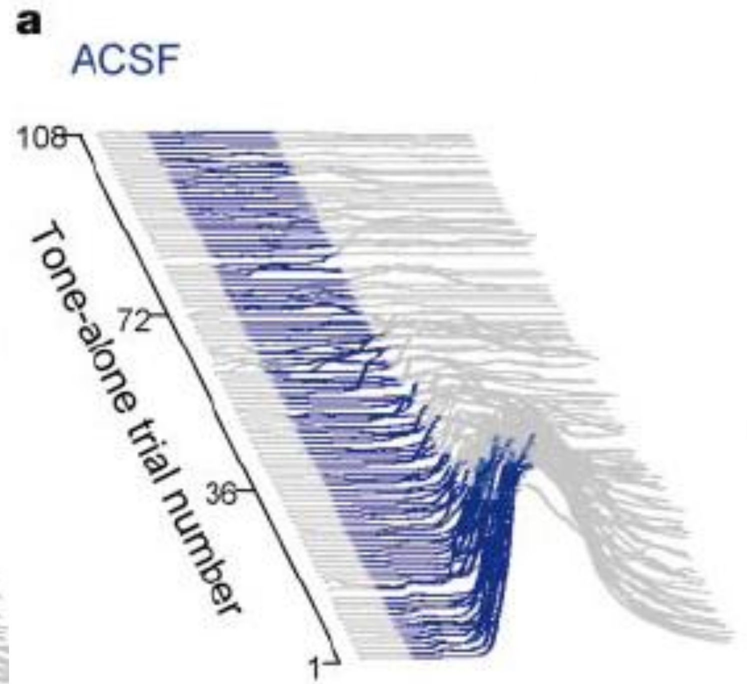
Rasmussen et al 2008

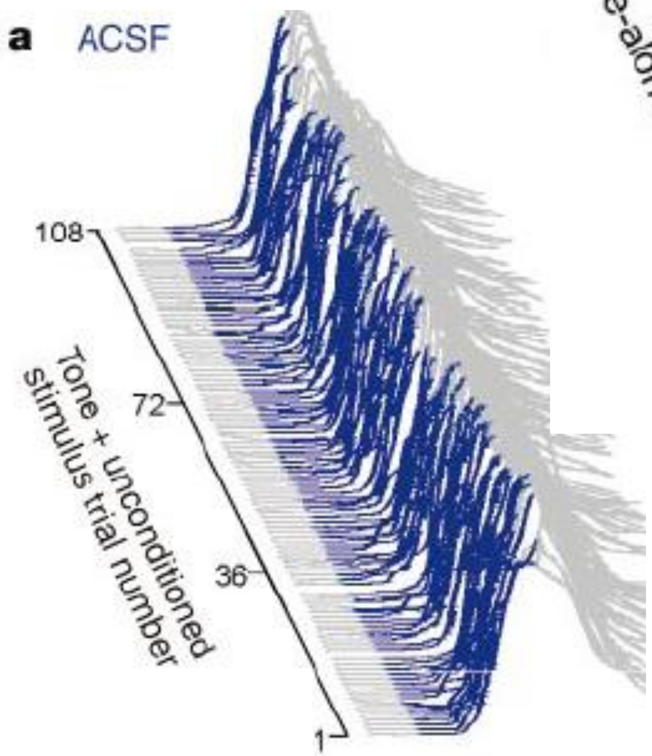
IO is crucial for Learning @350ms but not 700ms



Welsh 2002

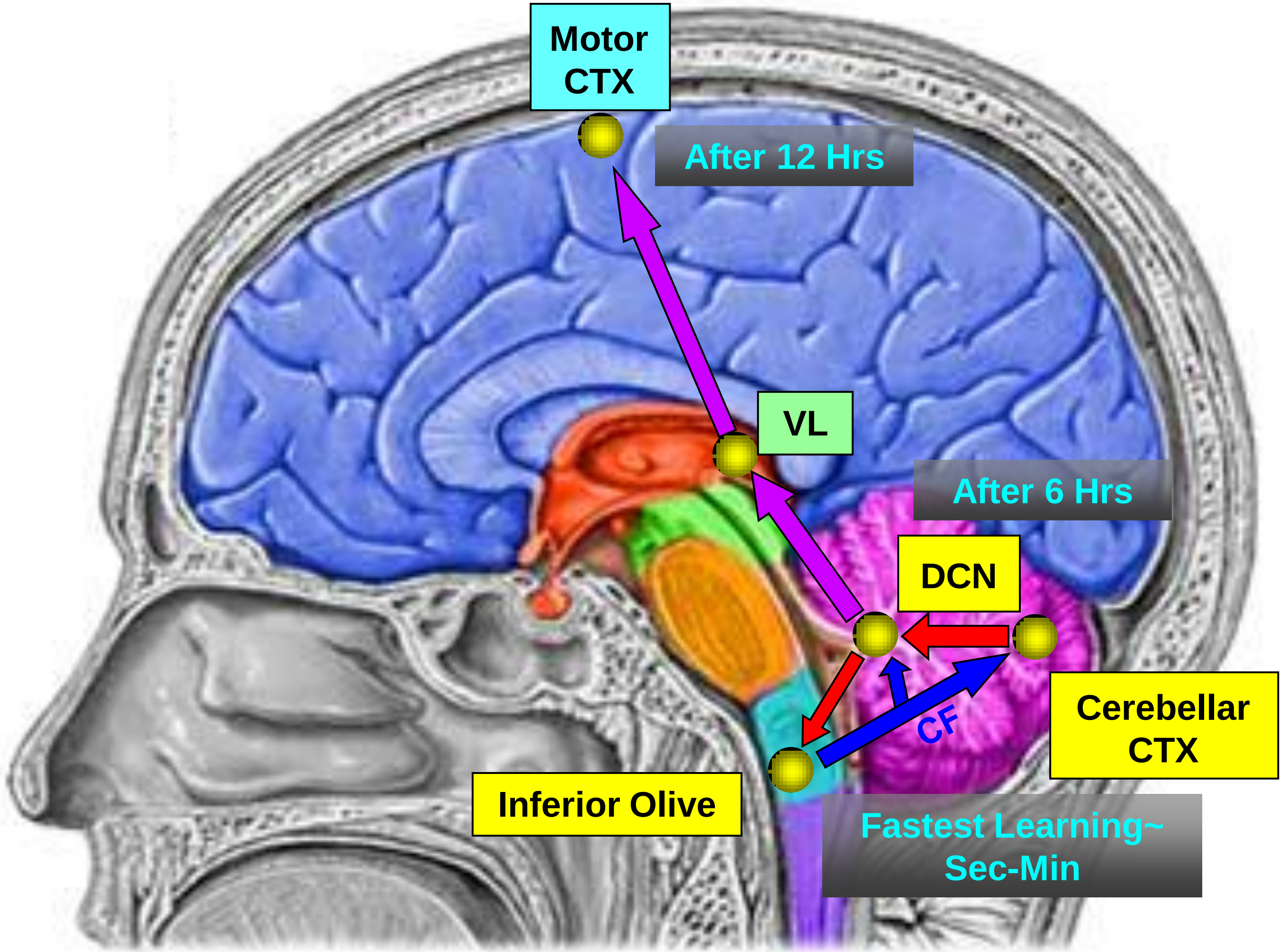
Conditioning Memory Retention depends on Nucleo-Olivary Inhibition





Medina et al. Nature 2002

The Learning Transfer Hypothesis



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

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:

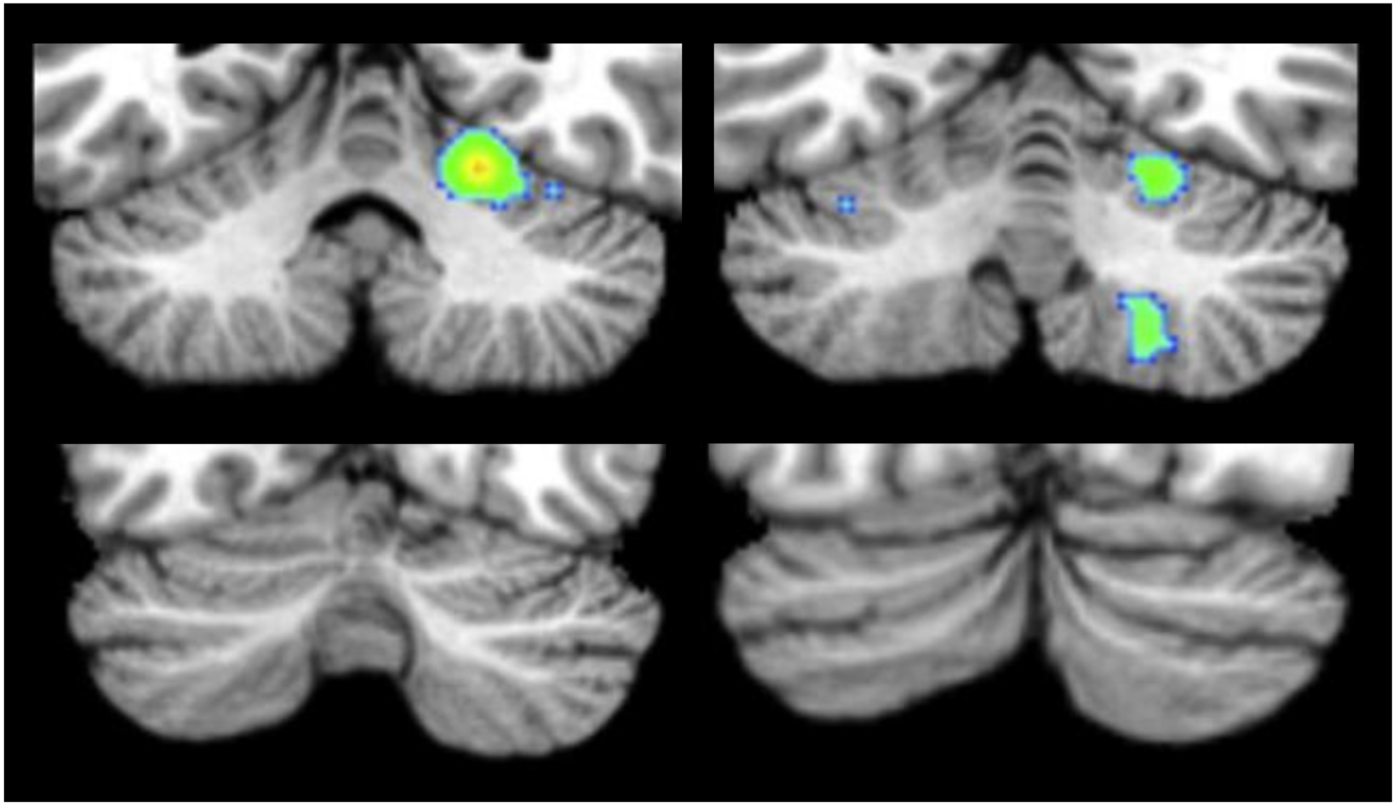
1. Irritability
2. impulsivity
3. Disinhibition
4. Emotional lability

Complex verbal dysfunction associated with right cerebellar damage

Dysprosodia – associated with left cerebellar damage

Schmahmann J.

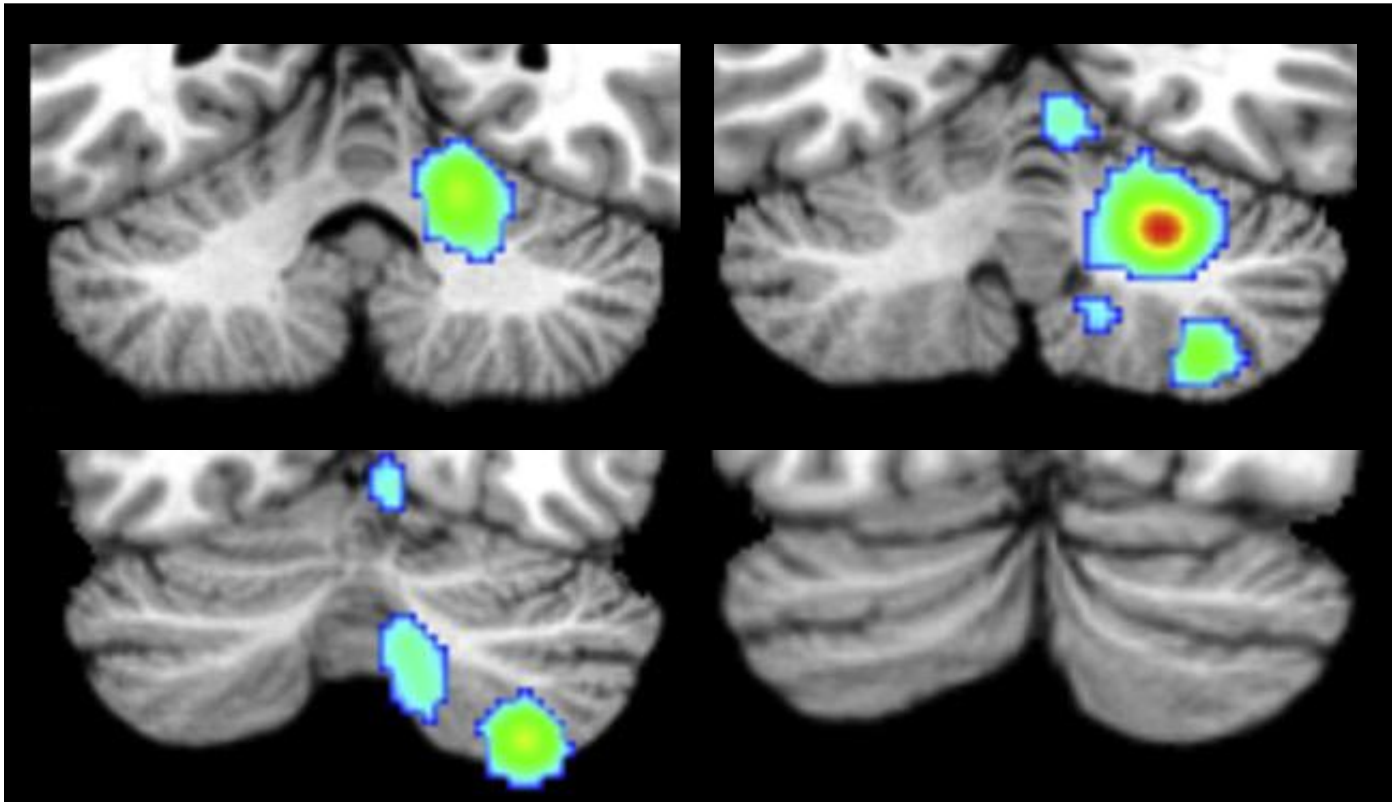
FMRI Mapping pf Cerebellar Involvement in Various Processes



Somatosensory Processing

Stoodley and Schmahmann 2009

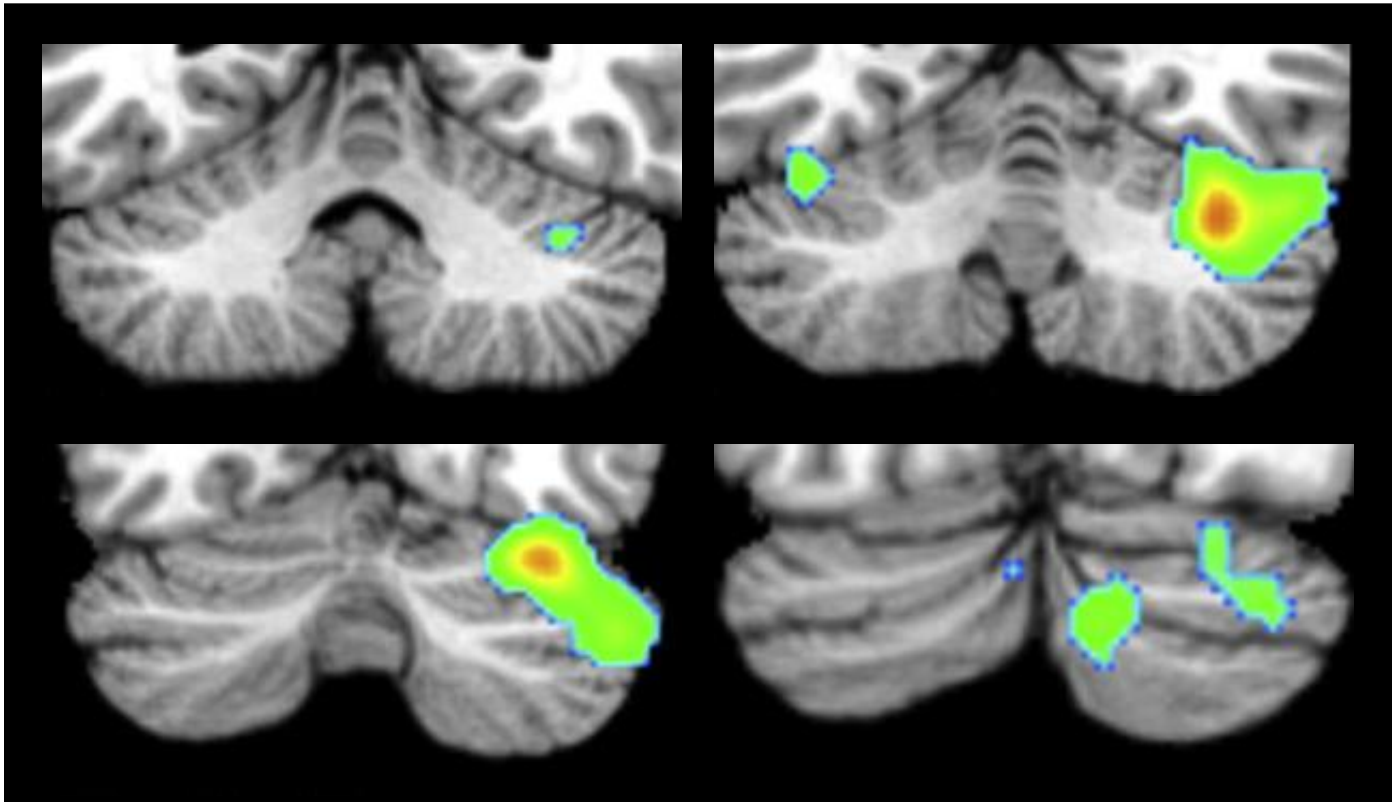
FMRI Mapping pf Cerebellar Involvement in Various Processes



Motor Processing

Stoodley and Schmahmann 2009

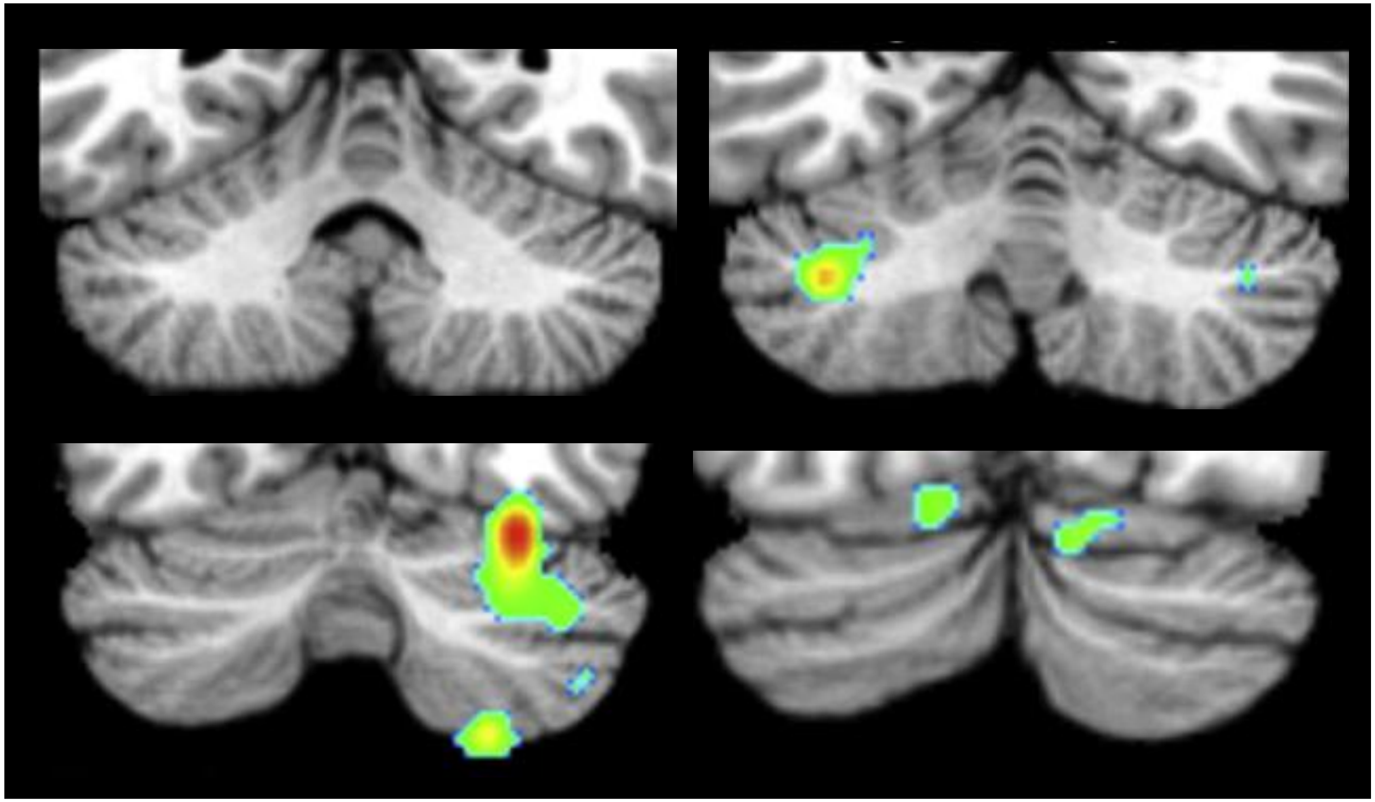
FMRI Mapping pf Cerebellar Involvement in Various Processes



Language Processing

Stoodley and Schmahmann 2009

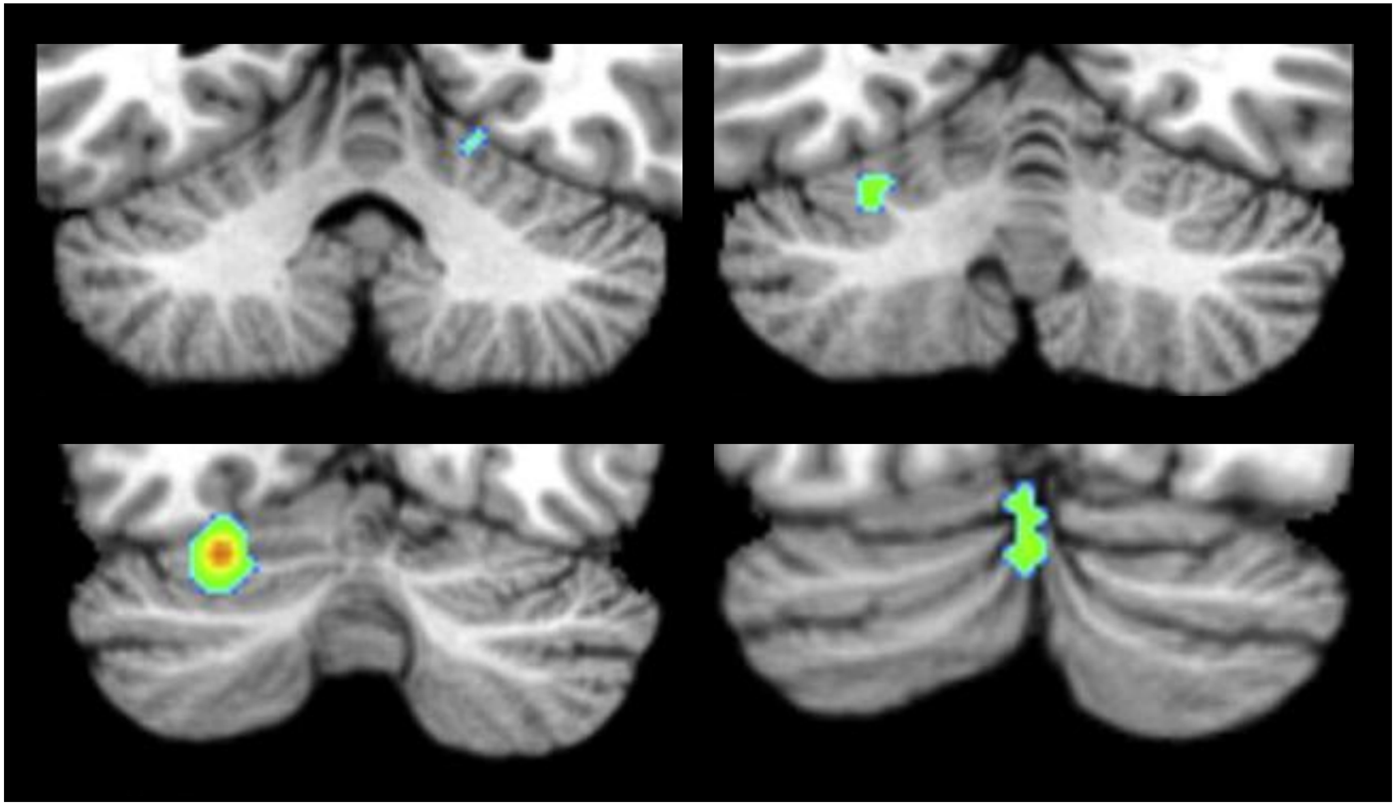
FMRI Mapping pf Cerebellar Involvement in Various Processes



Working Memory

Stoodley and Schmahmann 2009

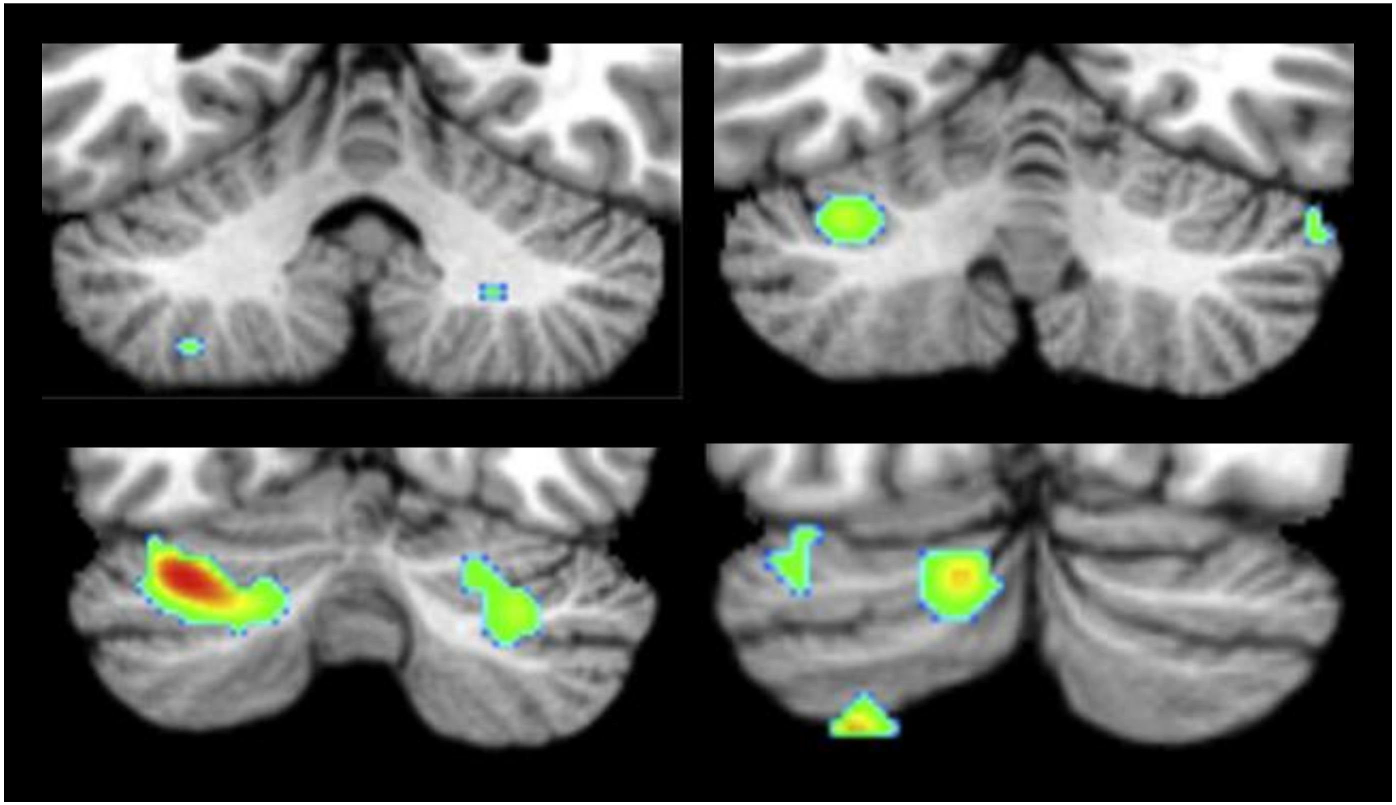
FMRI Mapping pf Cerebellar Involvement in Various Processes



Spatial Processing

Stoodley and Schmahmann 2009

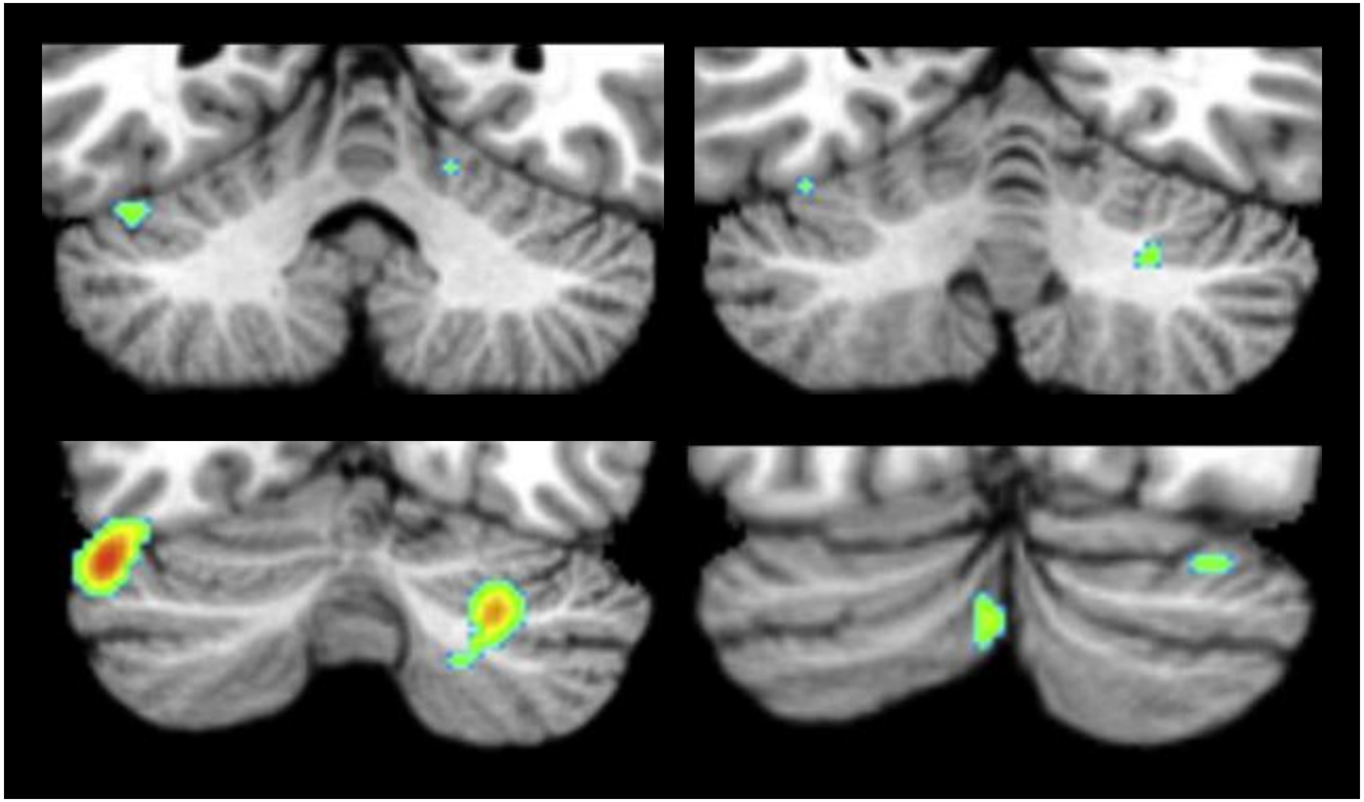
FMRI Mapping pf Cerebellar Involvement in Various Processes



Executive Processing

Stoodley and Schmahmann 2009

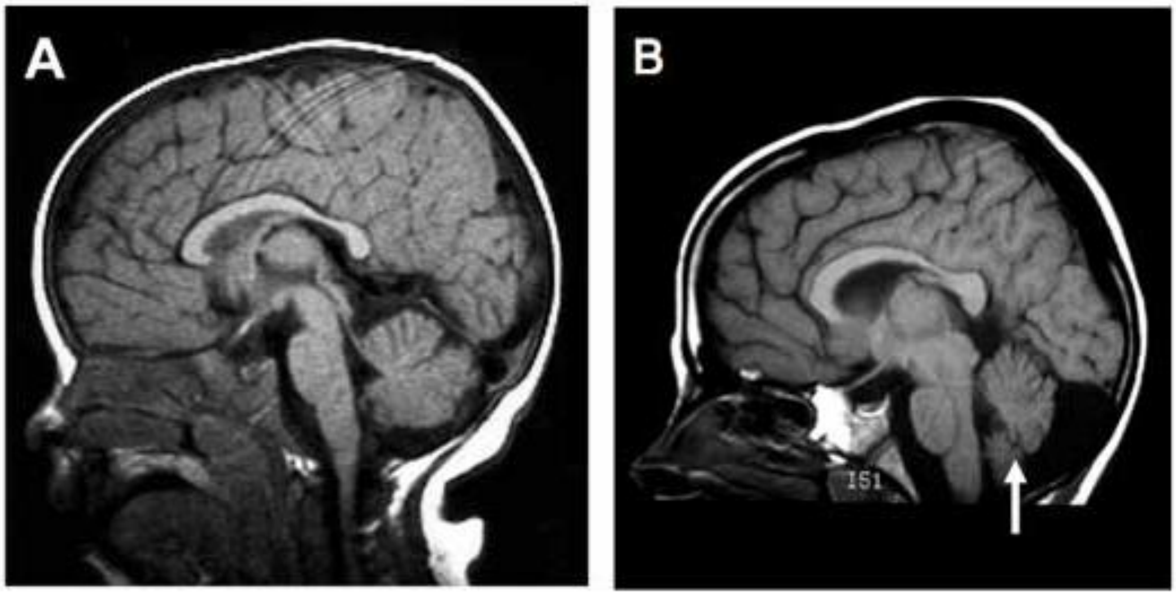
FMRI Mapping pf Cerebellar Involvement in Various Processes



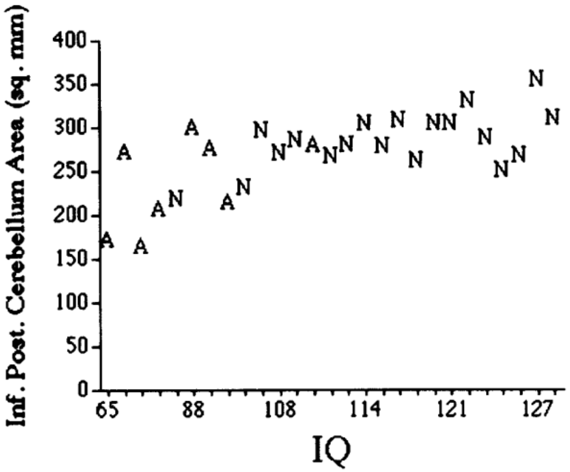
Emotional Processing

Stoodley and Schmahmann 2009

Cerebellar Involvement in Autism

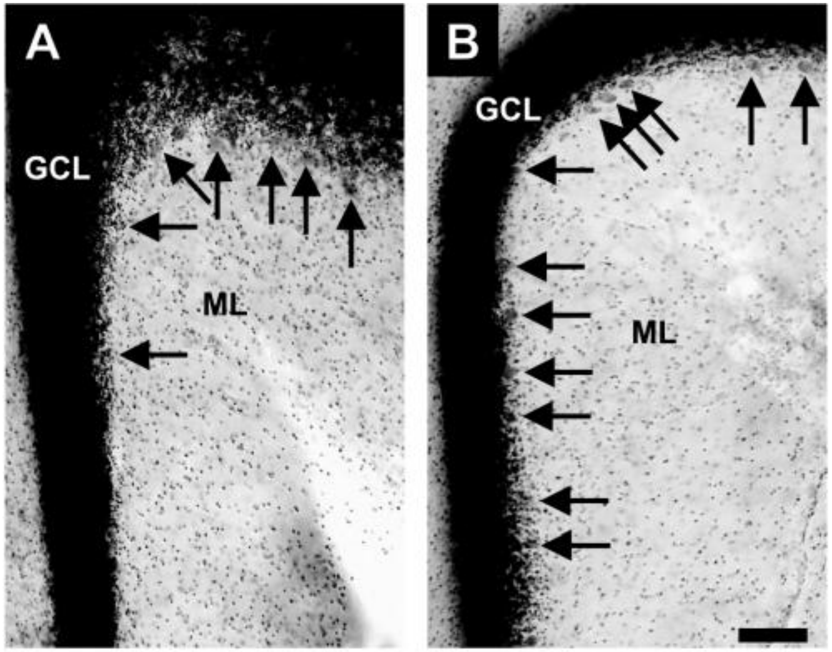


Control Subject Autistic Subject

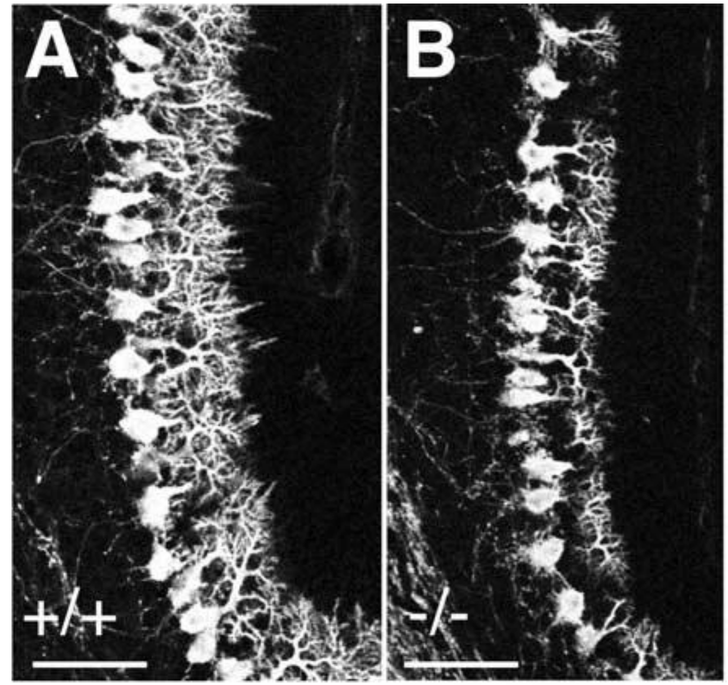


Levitt J. 1999

Autism candidate genes affects the Cerebellum



Autistic Control



Control CASP2 -/-

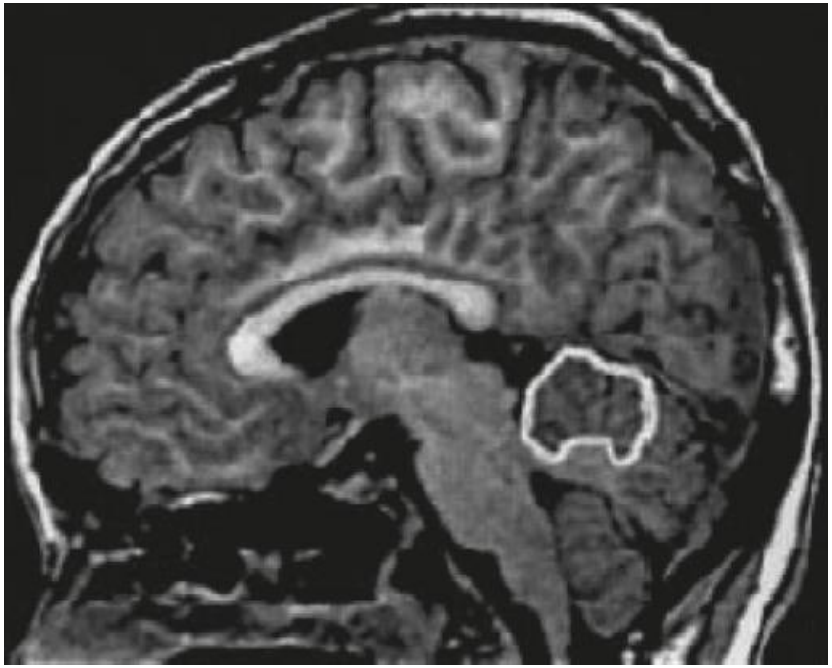
Lose of Purkinje Cells in Autistic

Saskia 2004

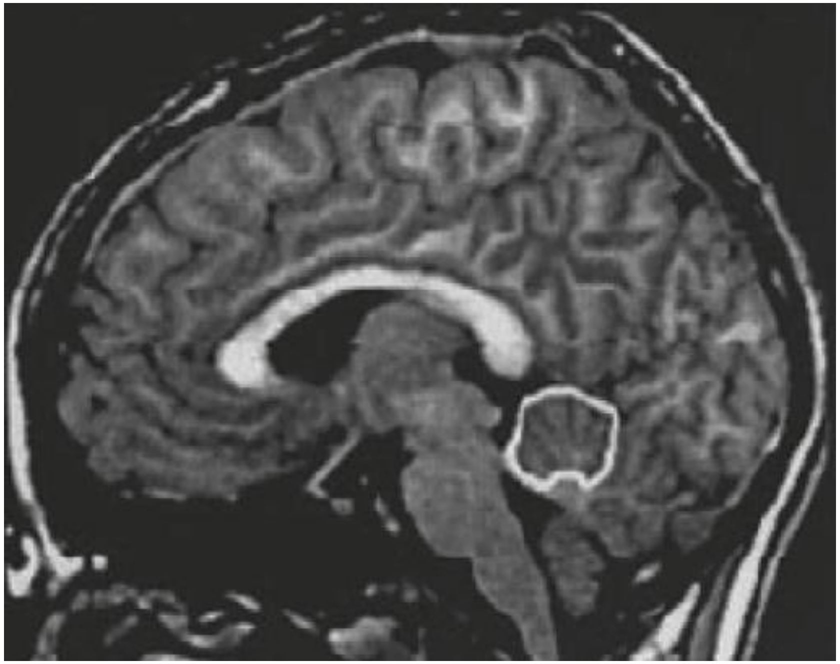
Developmental Problems in KO mice

Sadakata 2007

Cerebellar Involvement in Dyslexia



Control Subject



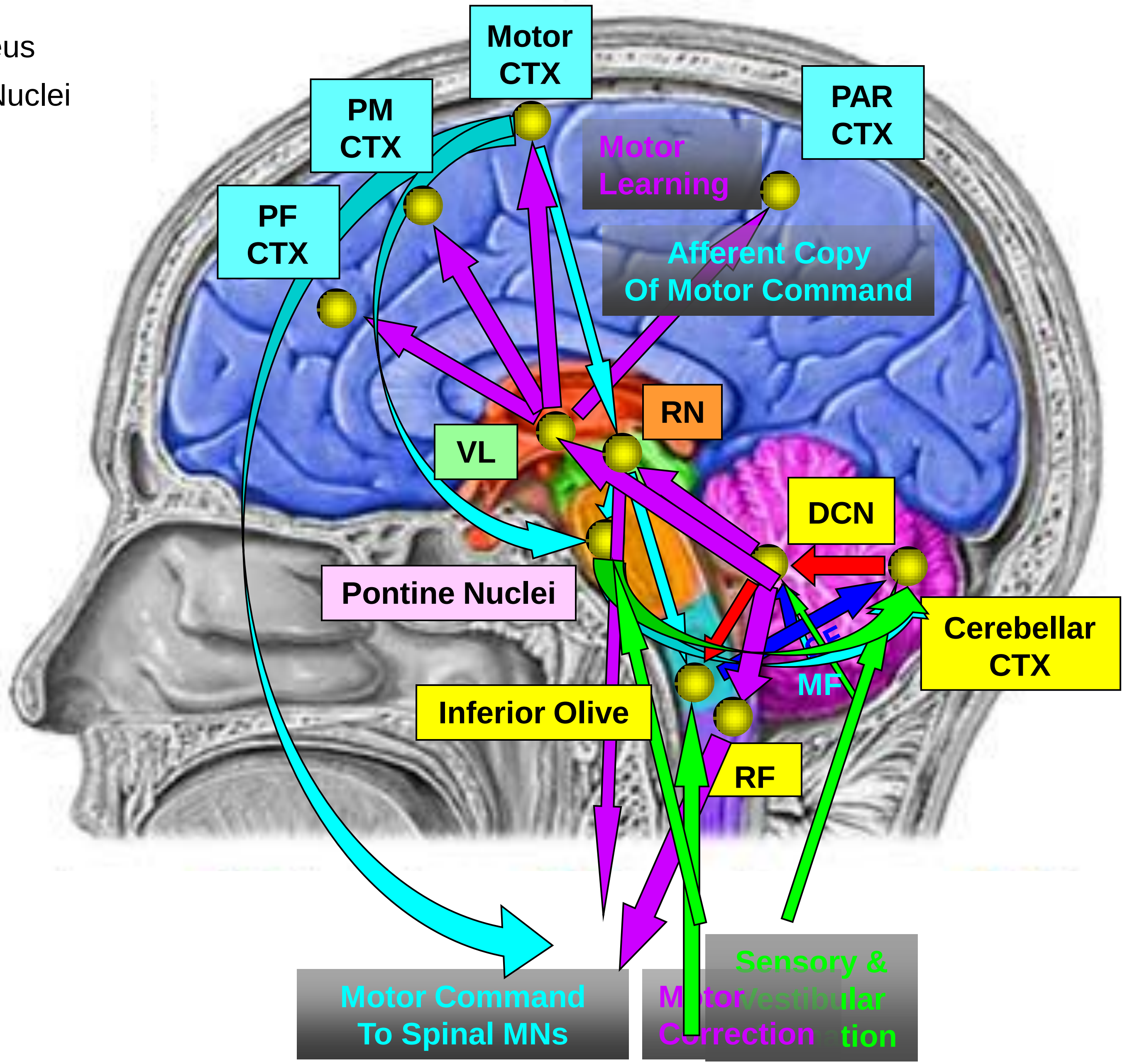
Dyslexic Subject

Information Flow during On-Line Corrections

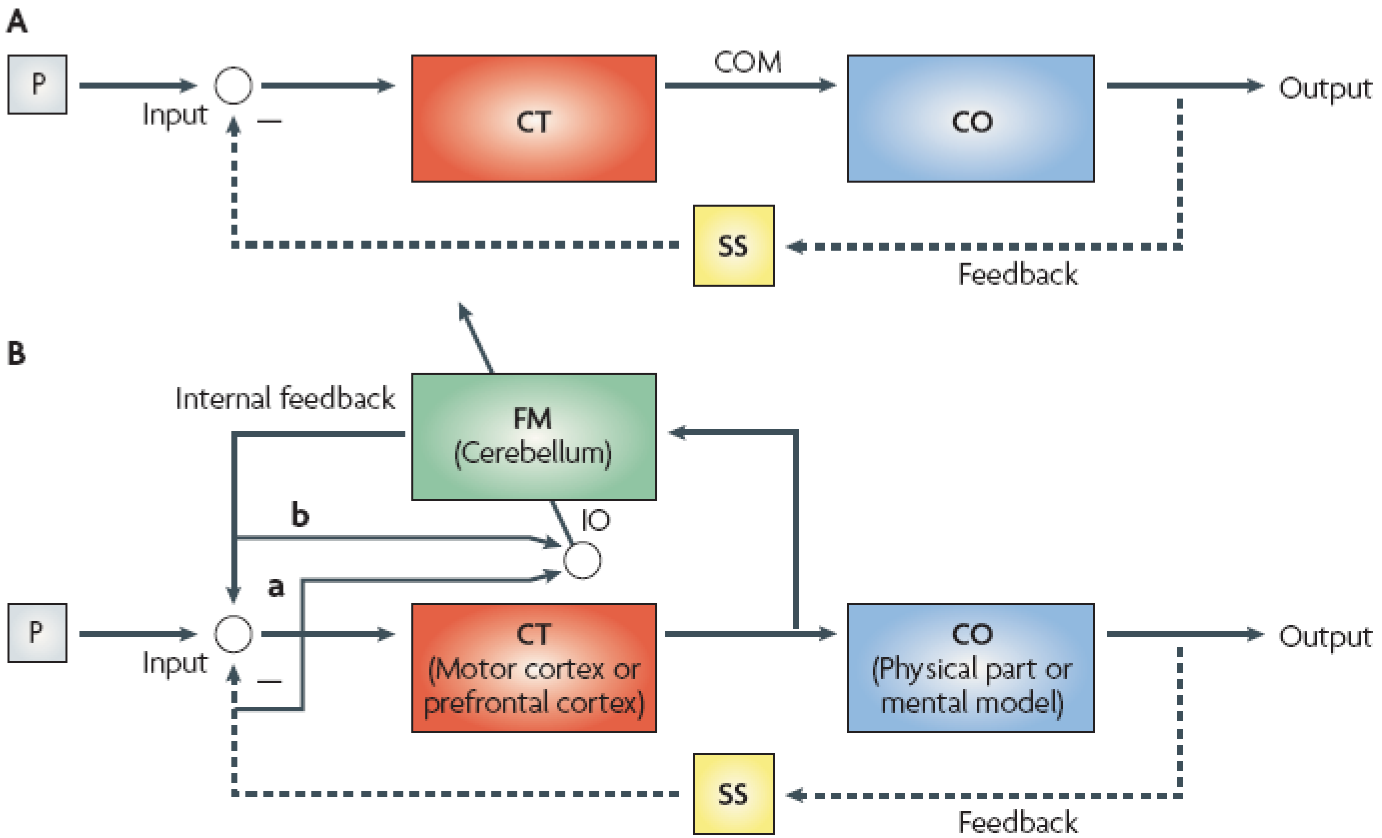
VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

CTX = Cortex

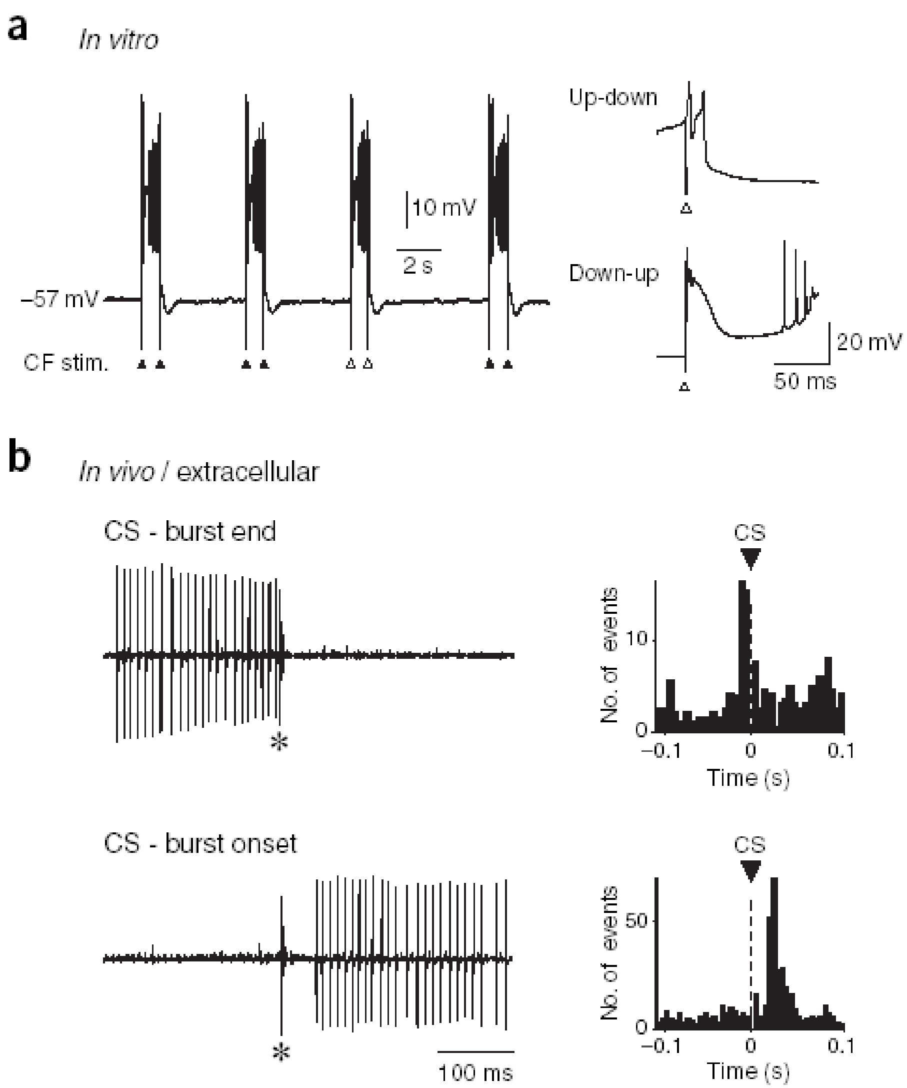
MF = Mossy Fibers
CF = Climbing Fibers



The General Role of the Cerebellum

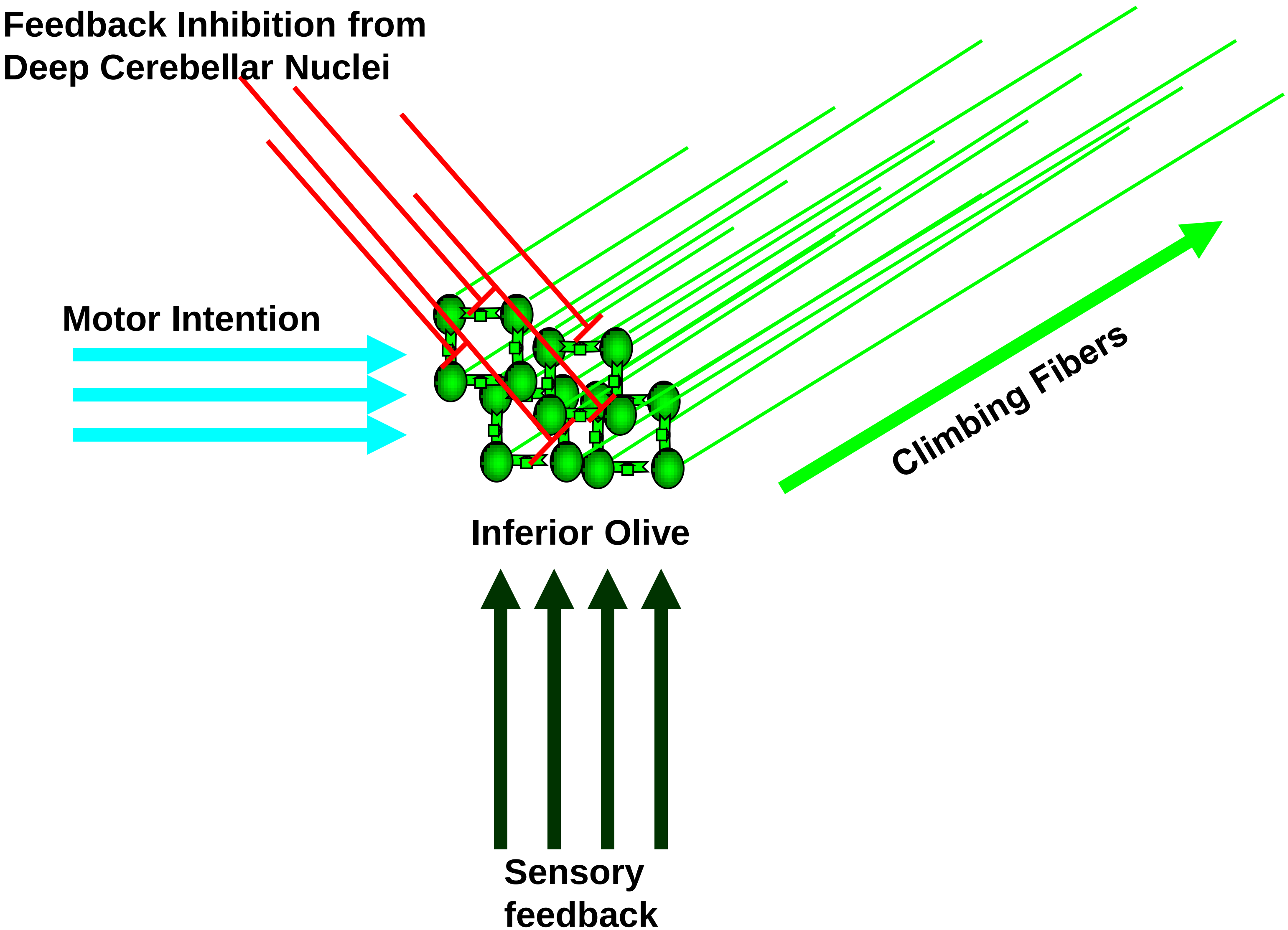


Complex Spikes as Purkinje Cell Switches

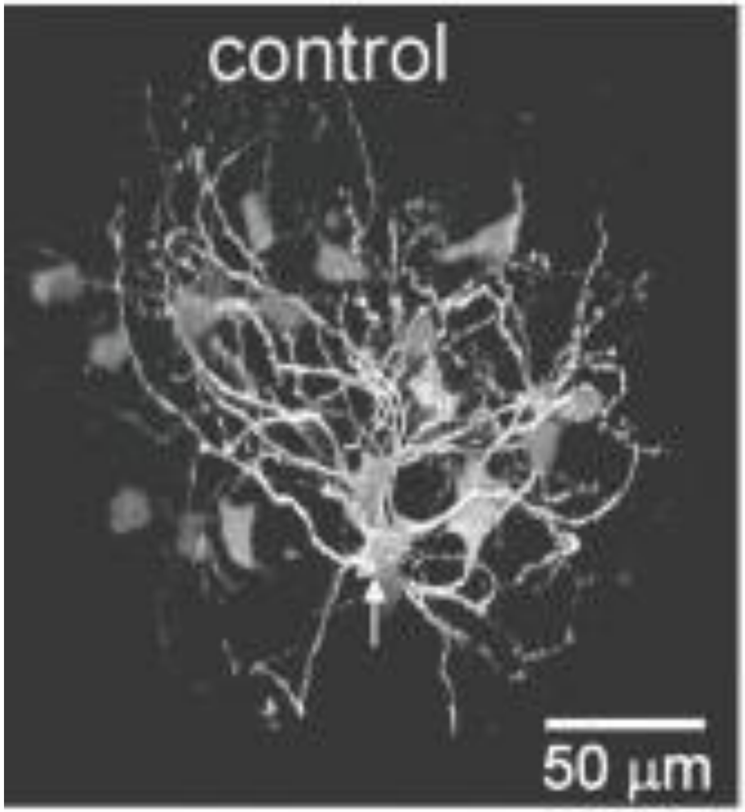


Loewenstein et al. NatNS 2005

The Inferior Olive as the Great Comparator

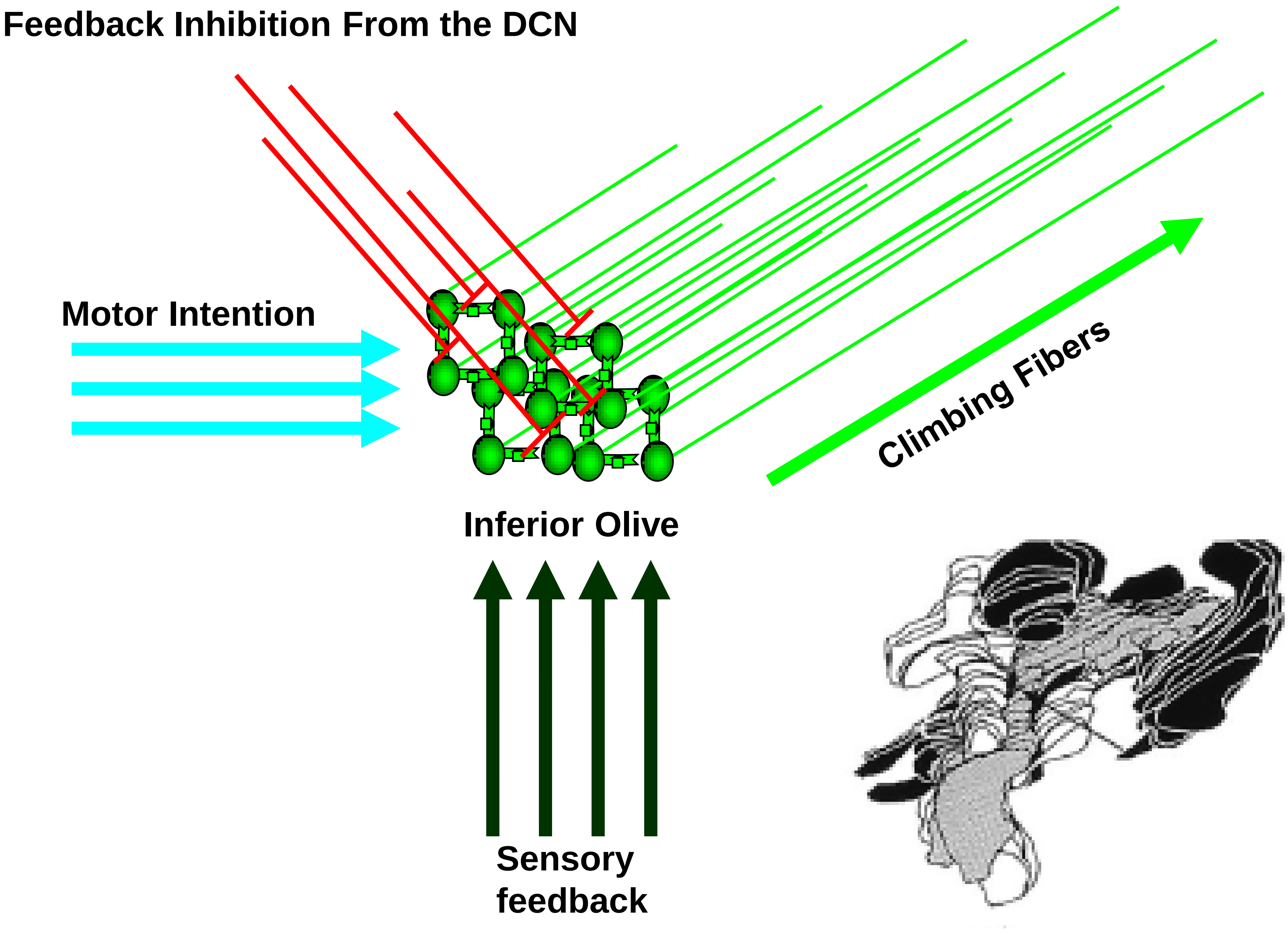


IO Neurons are Coupled by Gap Junction

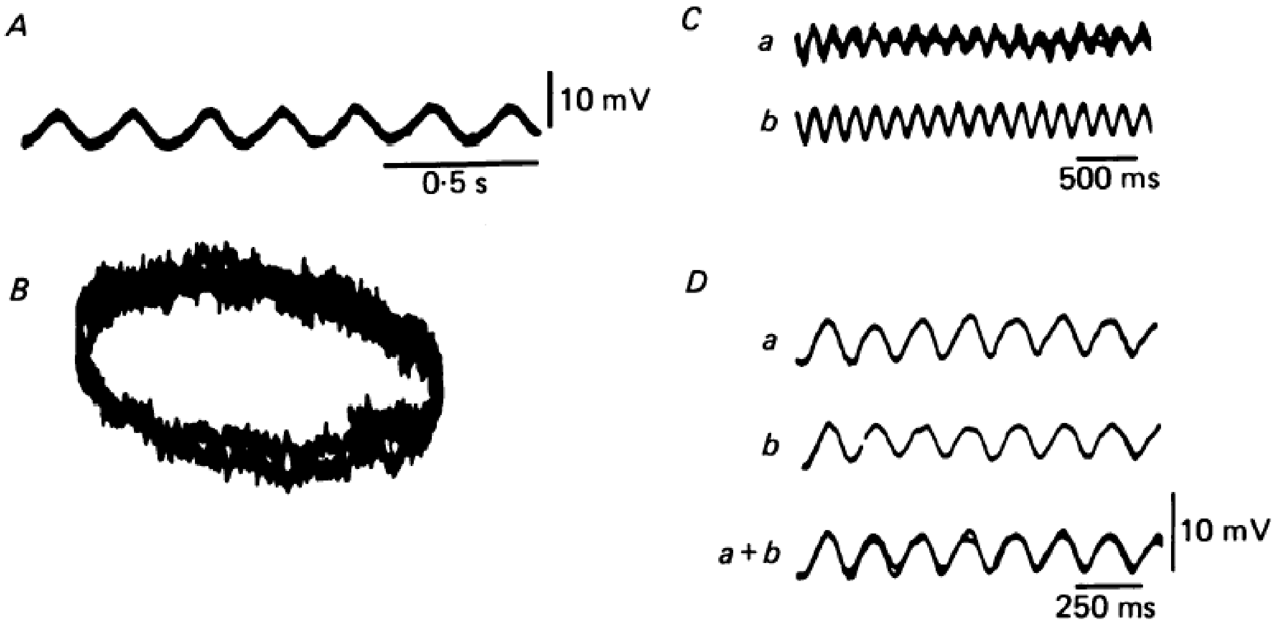


Placantonakis et al. PNAS 2004

The Inferior Olive as the Great Comparator

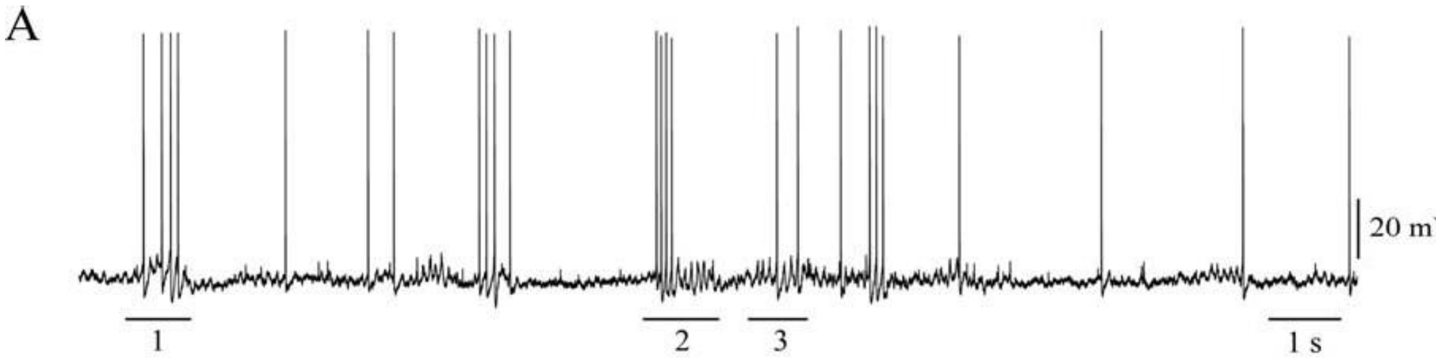


IO Neurons are Natural Oscillators

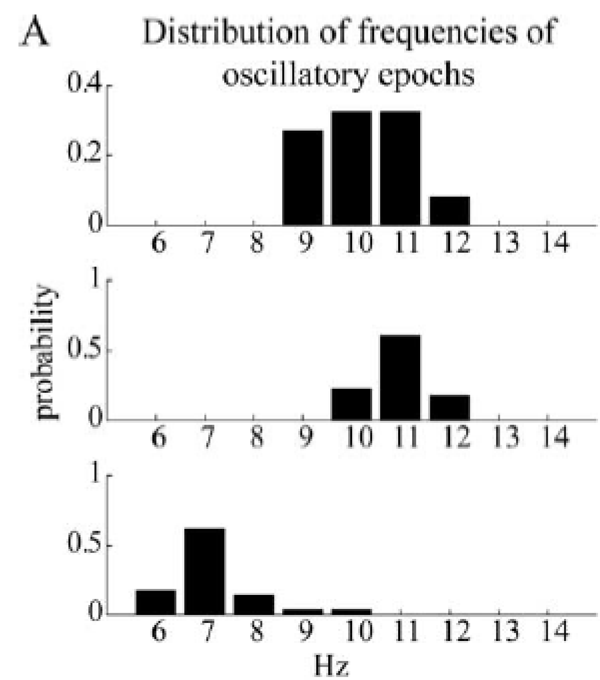


Llinas and Yarom JPhysiol 1986

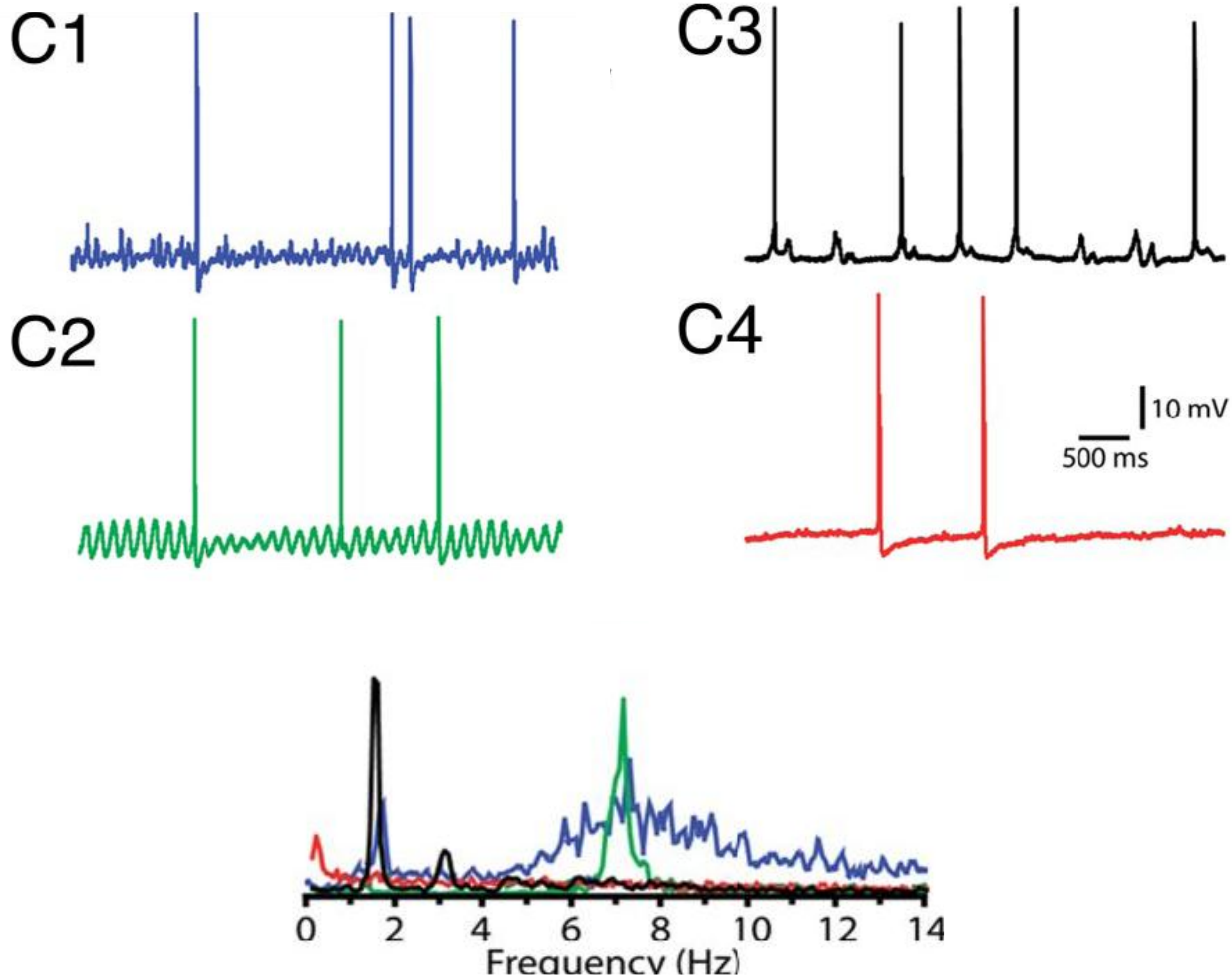
IO neurons are not Harmonious Oscillators *in-vivo*



Chorev, Yarom and Lampl JNS 2007

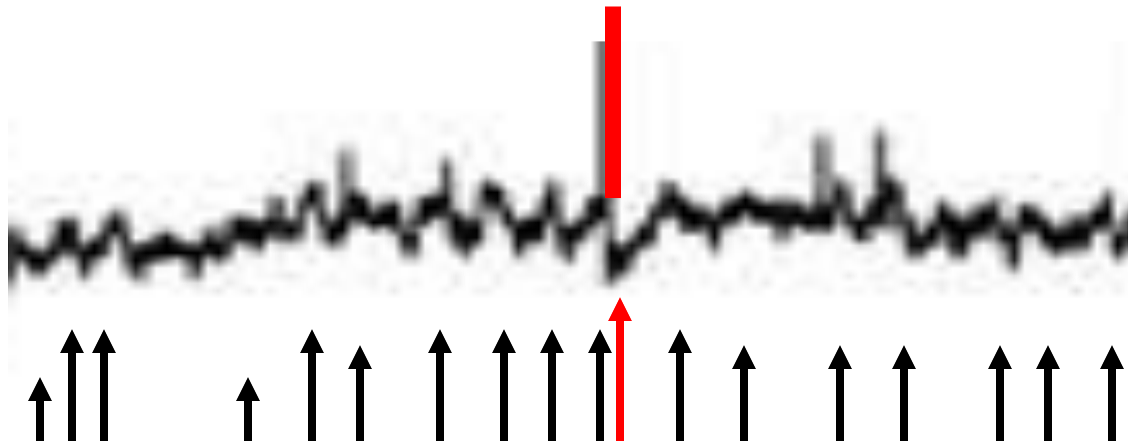


There are Various Oscillation Patterns



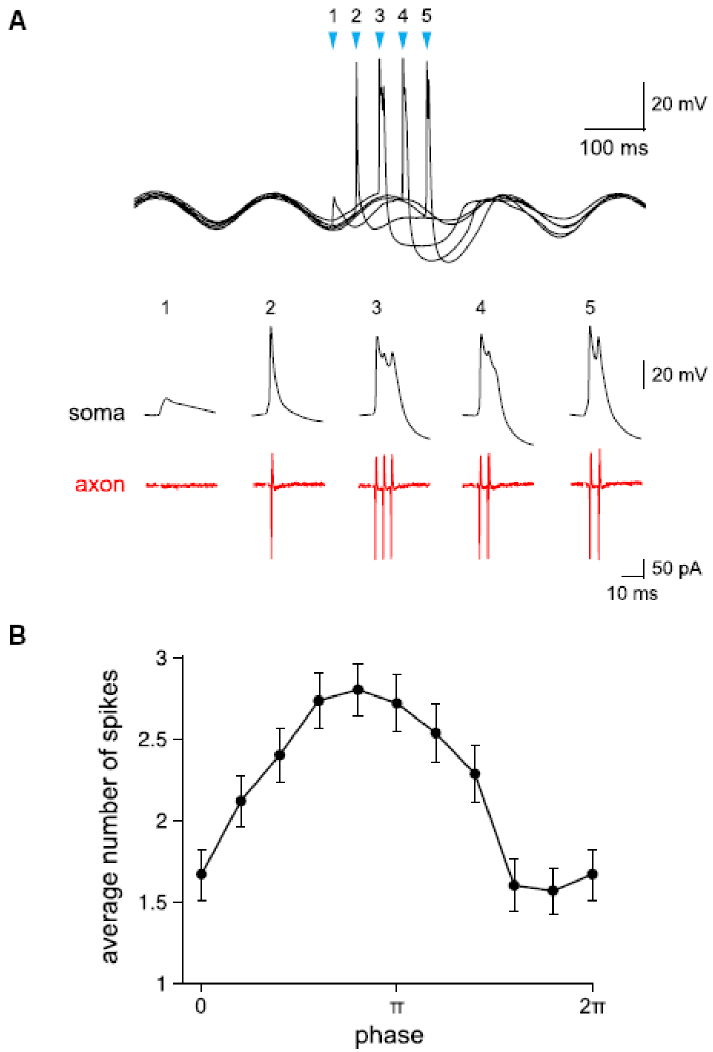
Oscillation as a Blocking Device for expected Inputs

Expected Inputs



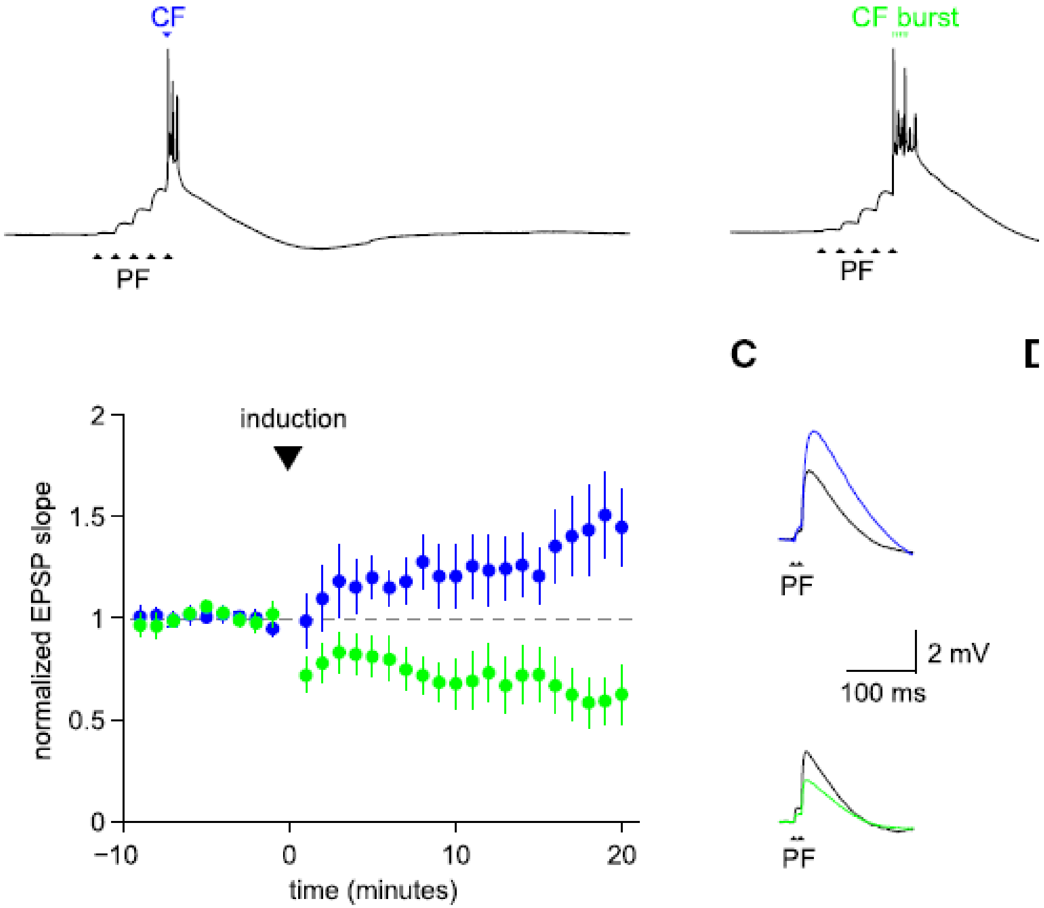
How will The IO Differentiate Early vs. Late Inputs?

ISI vs. Oscillation phase “encoding”



Mathy, et al. 2009

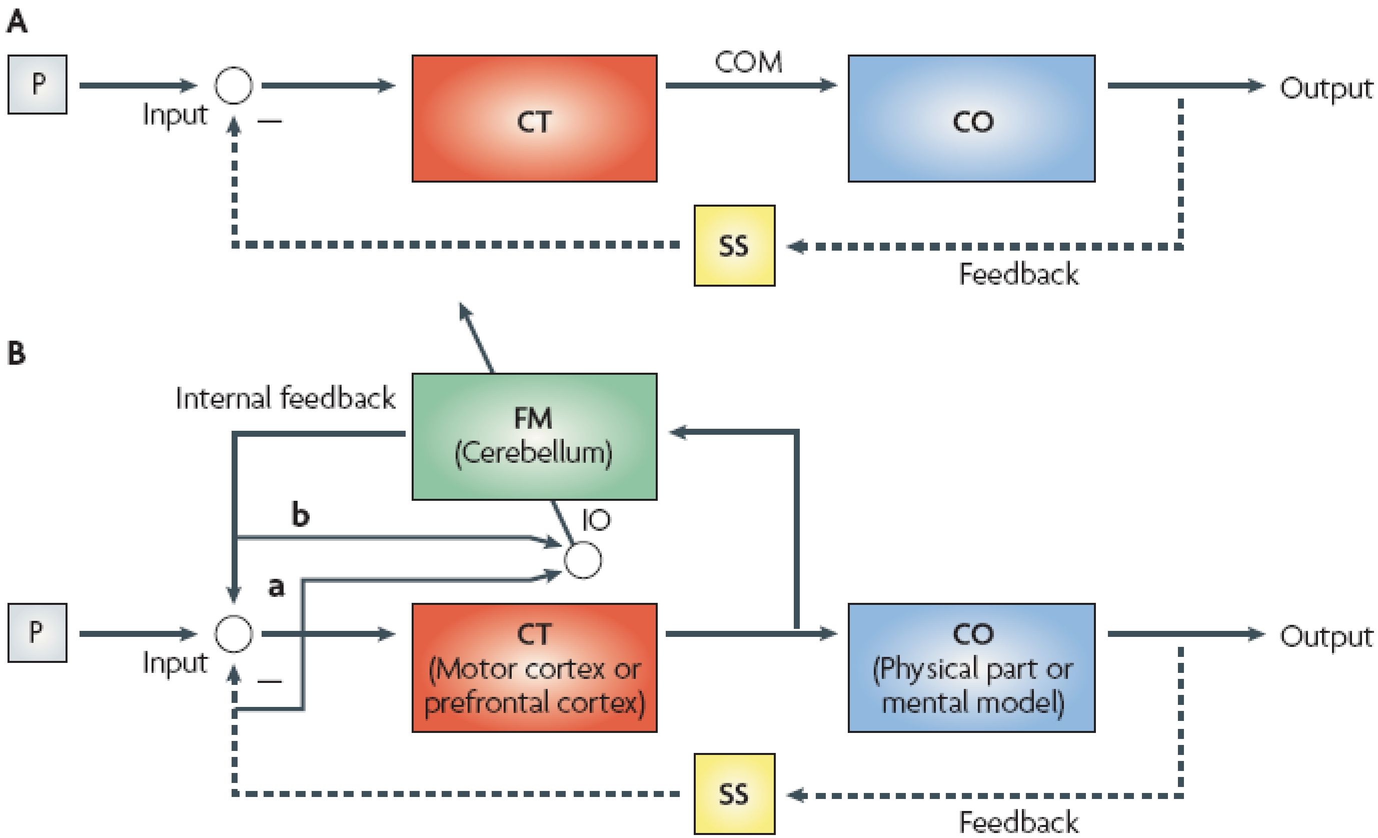
CF activation Pattern sets the direction of plasticity



Mathy, et al. 2009

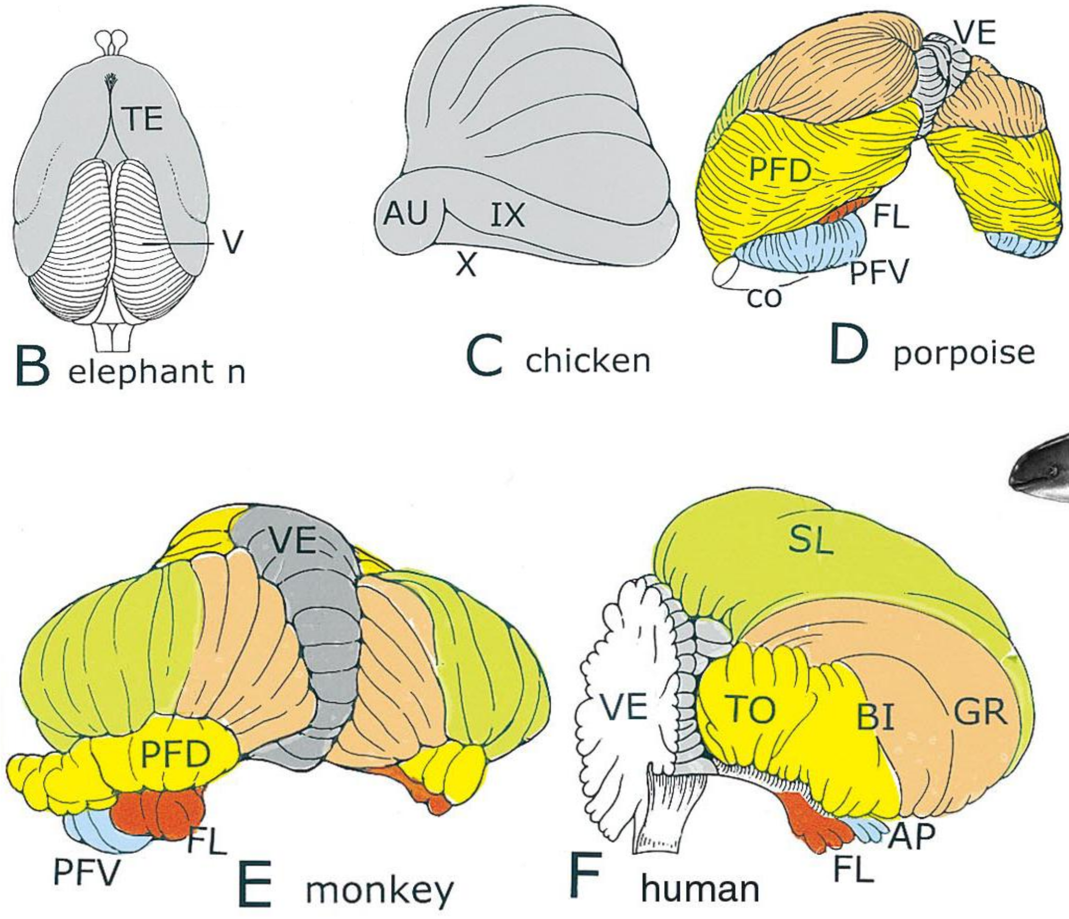
How does the Cerebellum compute?

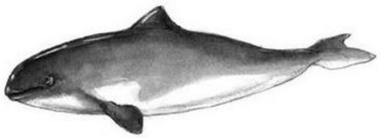
Thank you for Thinking!!



Cerebellar Hemispheres have evolved Later in Evolution

Elephantnose Fish

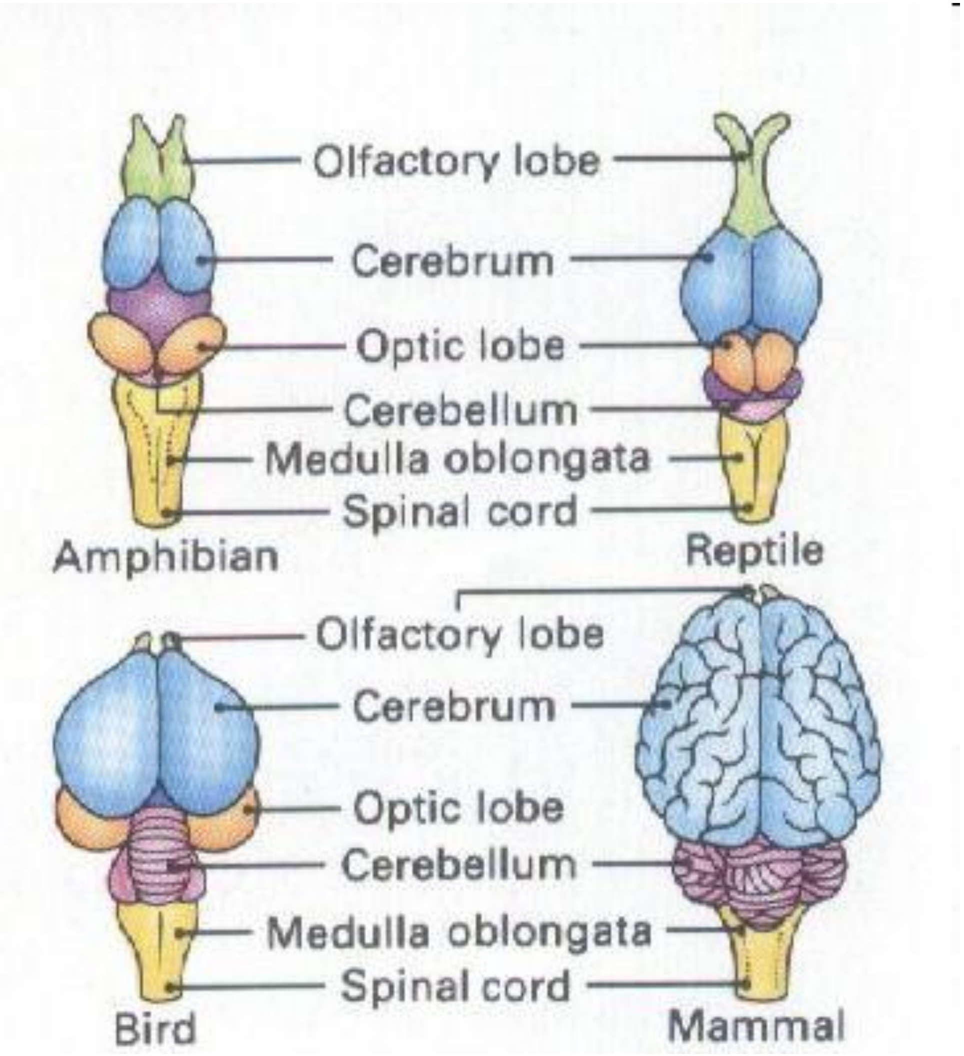




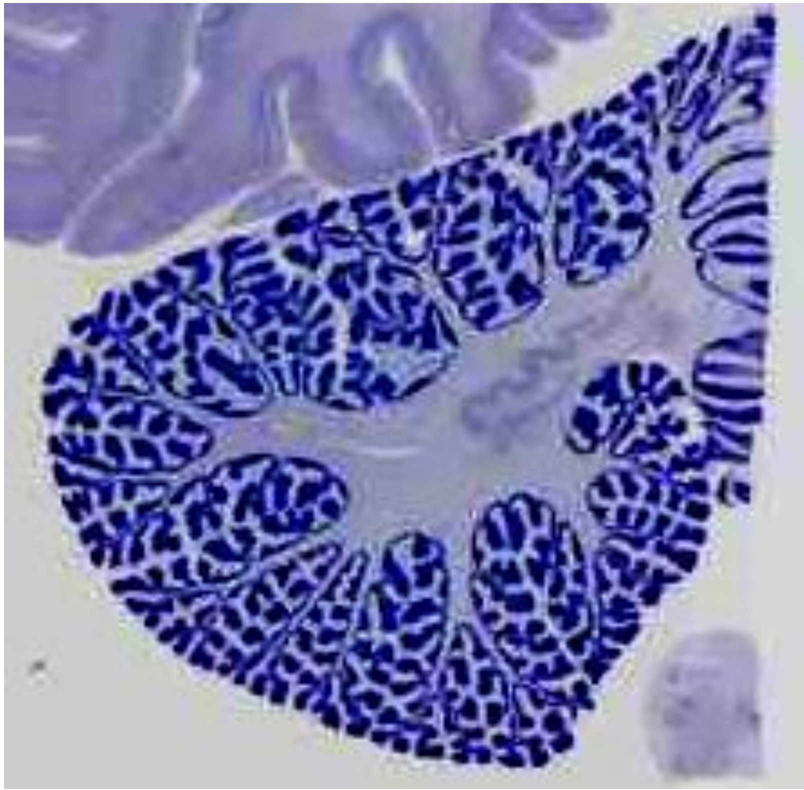
Porpoise

Voogd and Glickstein 1998

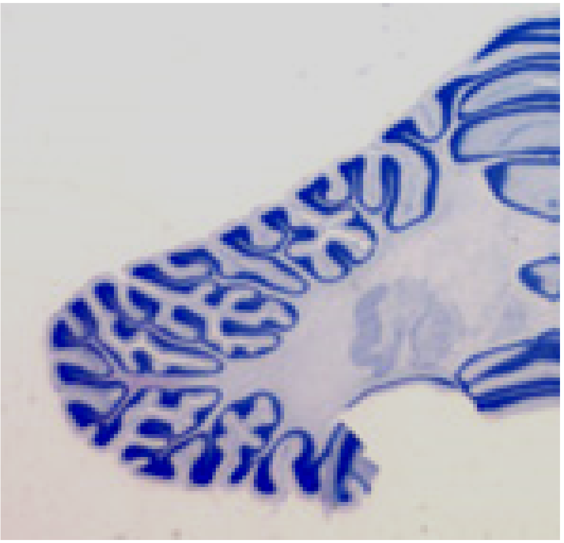
The Cerebellum has Evolved in Evolution



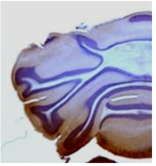
Cerebellum Complexity has also Evolved



Human

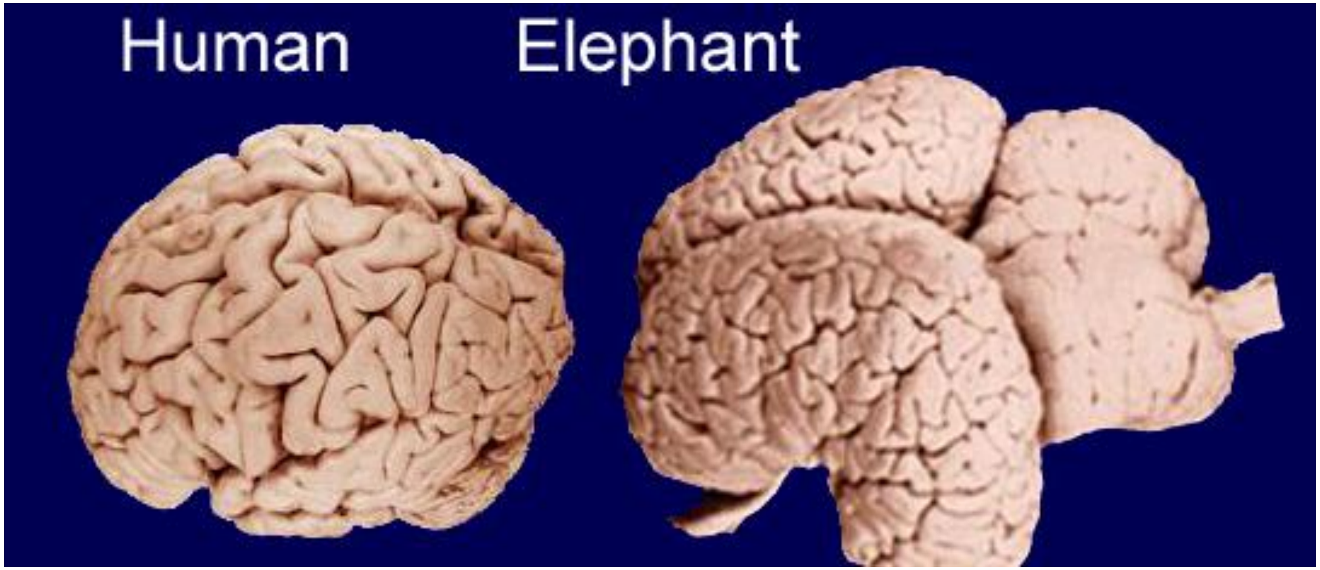


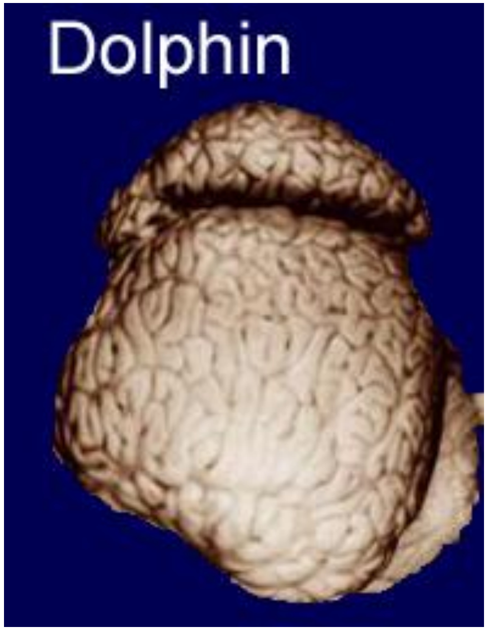
Monkey



Rat

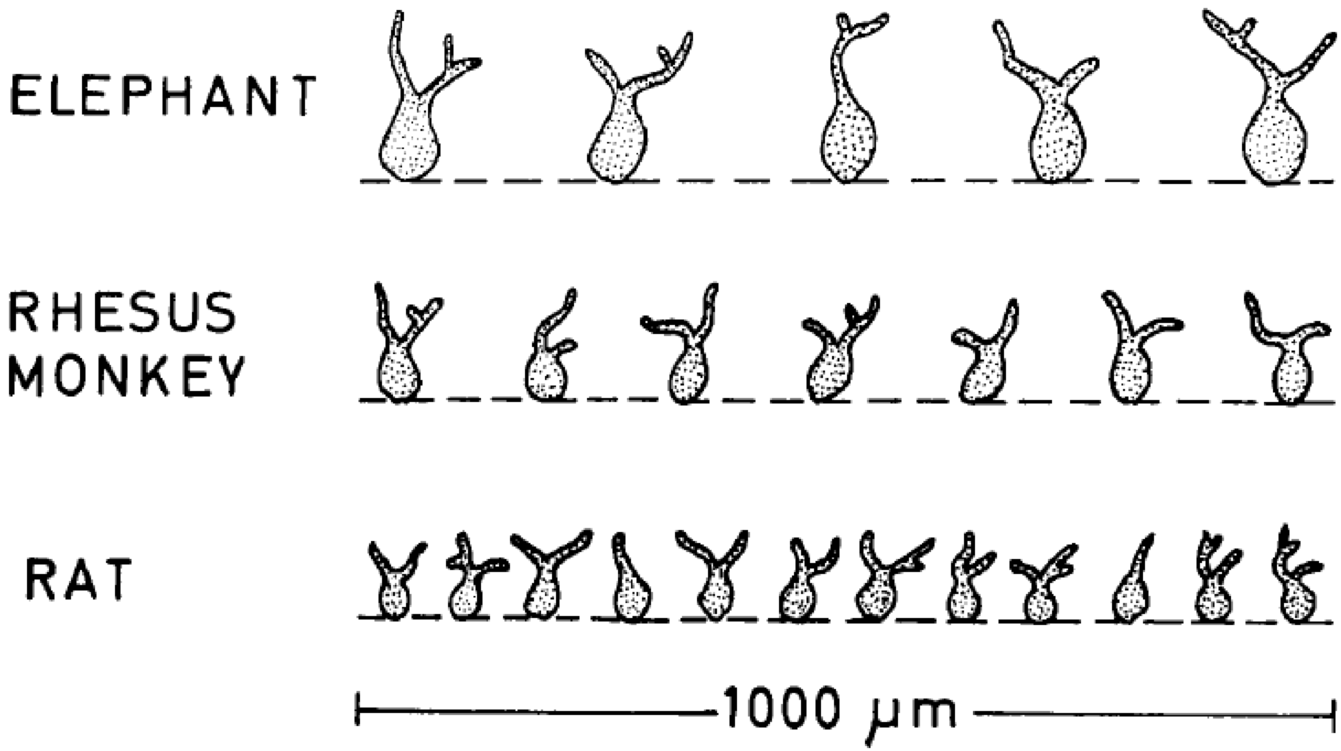
Cerebellar evolution did not stop in humans…





Of course size is not the only thing that counts…

Remember the Elephant's Cerebellum?



Big Cerebellum does not necessarily mean more cells…

Intelligence may lay in the power of Integration…

Table 2. Ratio of Purkinje cells to granule cell in man and some other mammals

Man (*Homo sapiens*)	1:2991	Cat (*Felis domestica*)	1:1580
Vervet monkey (*Cercopithecus aethiops*)	1:2128	Sheep (*Ovis aries*)	1:1568
Rhesus monkey (*Macaca mulatta*)	1:1898	Bull (*Bos taurus*)	1:1508
Elephant (*Loxodonta africana*)	1:1866	Guinea pig (*Cavia cobaya*)	1: 959
Squirrel monkey (*Saimiri sciureus*)	1:1864	Opossum (*Didelphys virginiana*)	1: 952
Bottle-nose dolphin (*Tursiops truncatus*)	1:1812	Rabbit (*Oryctolagus cuniculus*)	1: 931
Pilot whale (*Globicephala macrorhyncha*)	1:1790	Rat (*Rattus norvegicus*)	1: 897
Common porpoise (*Phocaena phocaena*)	1:1762	Mouse (*Mus musculus domesticus*)	1: 778
Fox (*Vulpes vulpes*)	1:1739	Mole (*Talpa europaea*)	1: 706
Horse (*Equus caballus*)	1:1612	Hedgehog (*Erinaceus europaeus*)	1: 609