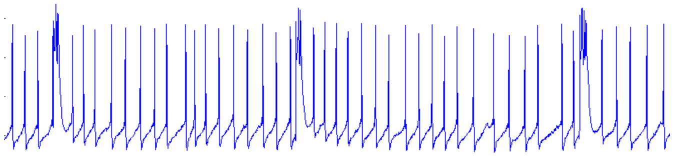
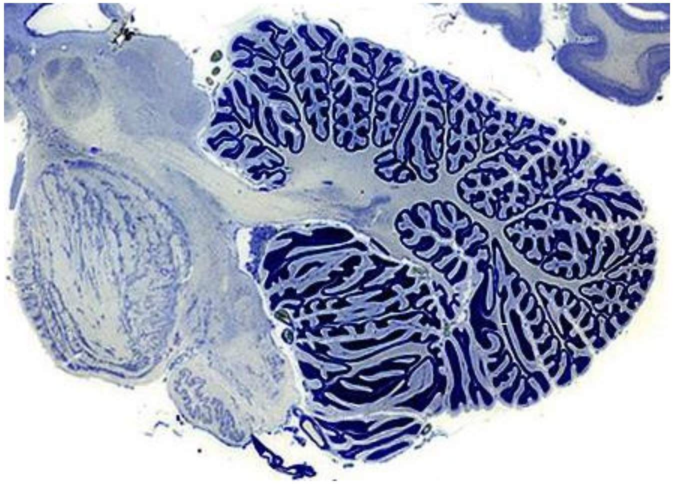
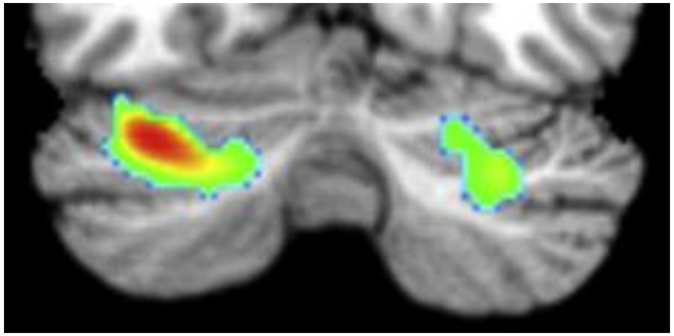
Cerebellum, motor and cognitive functions: What are the common grounds?





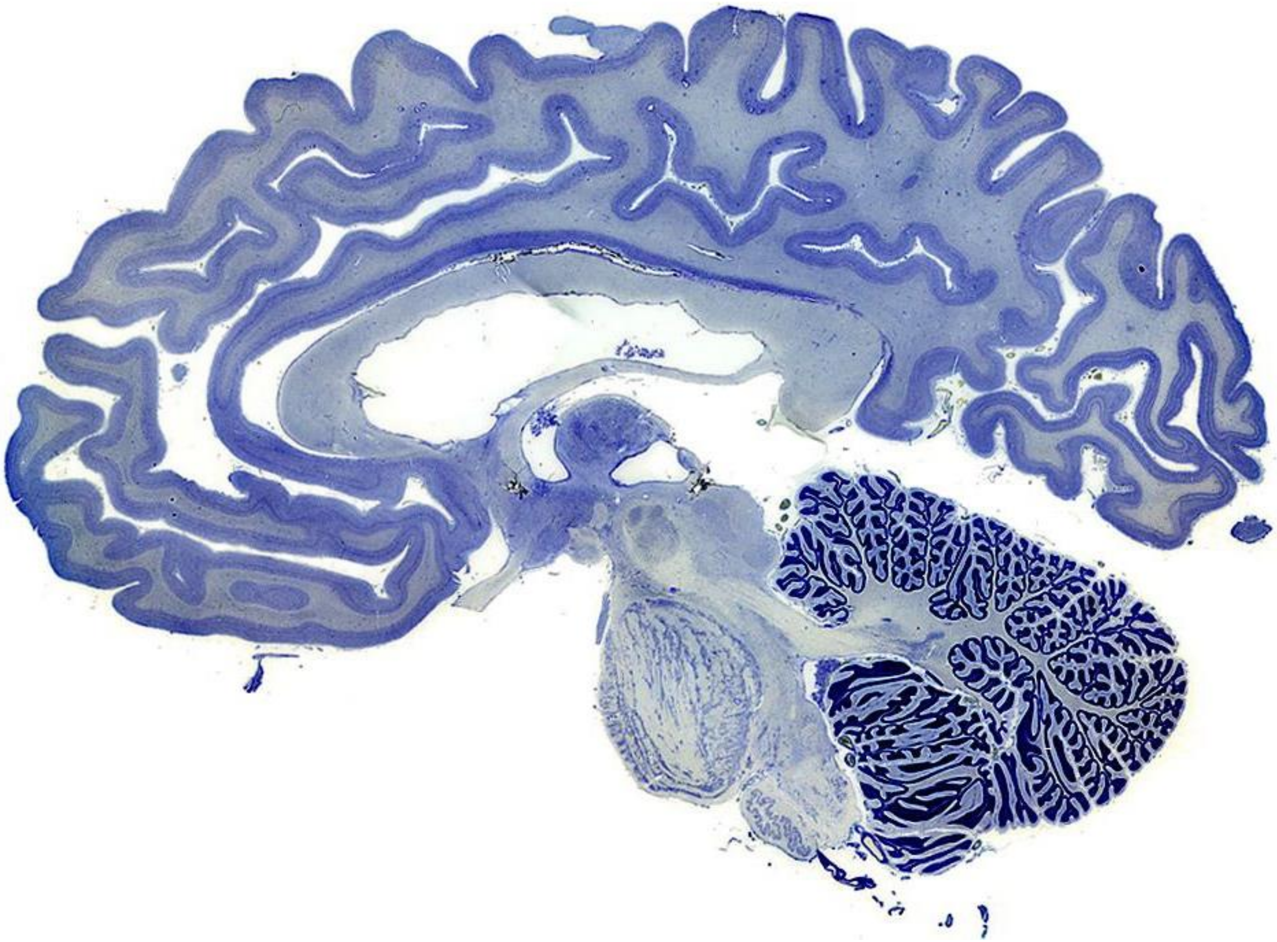


Eyal Cohen, PhD
(Engineering, BIU)

Cerebellum – The "Little Brain"

The Cerebellum takes ~10% of the Brain in Volume

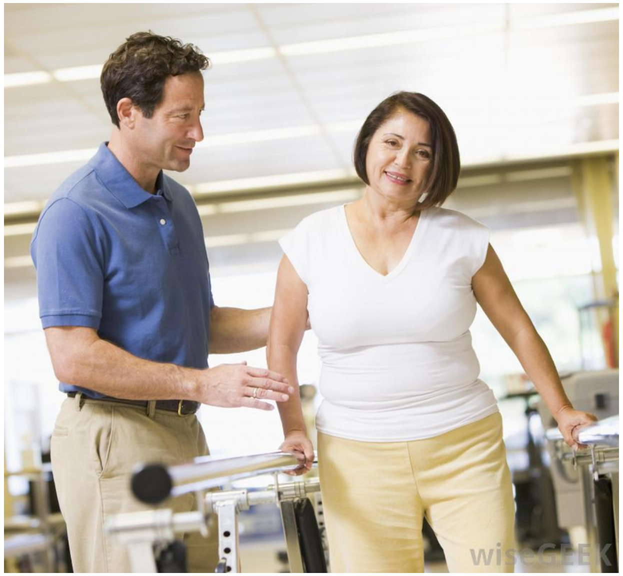
Small but Hefty…



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

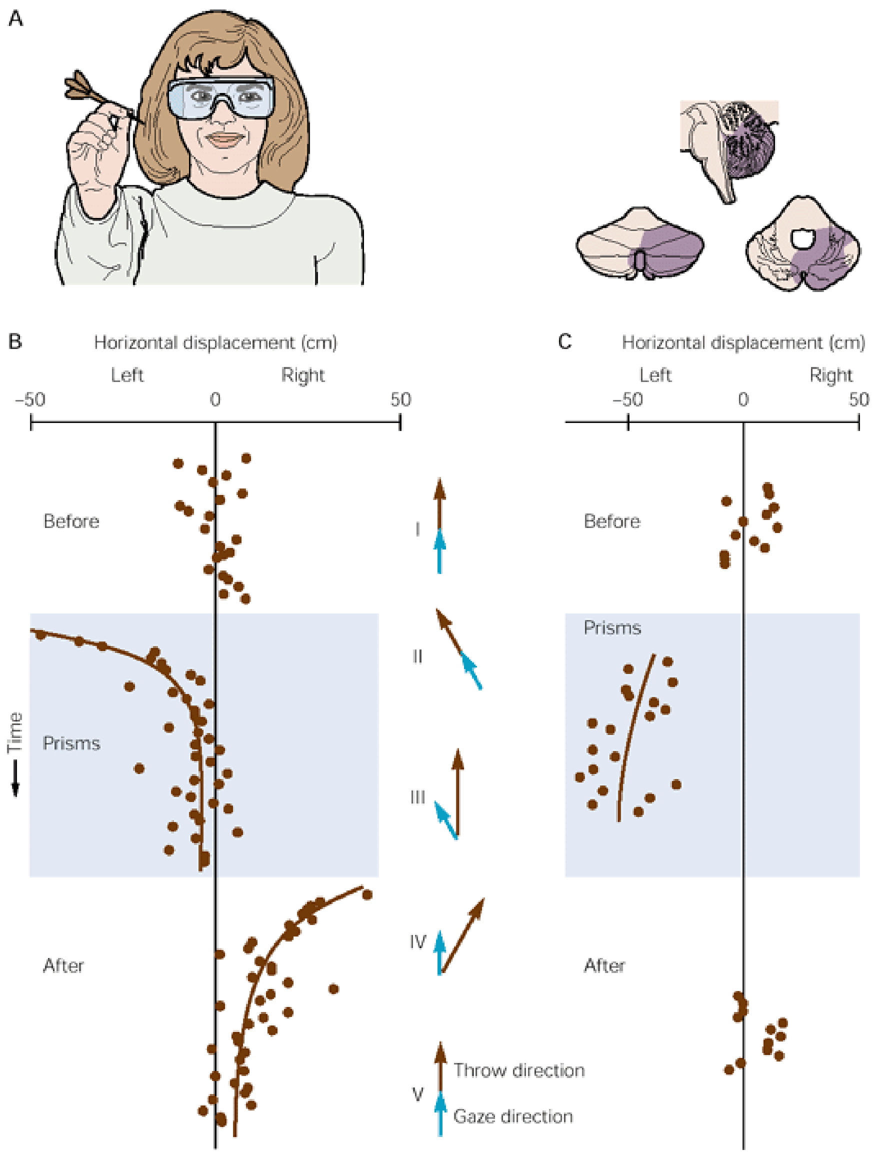
The Convoluted Cerebellar Cortex consists of most Cerebellar Volume

"Classical" symptoms of Cerebellar dysfunction

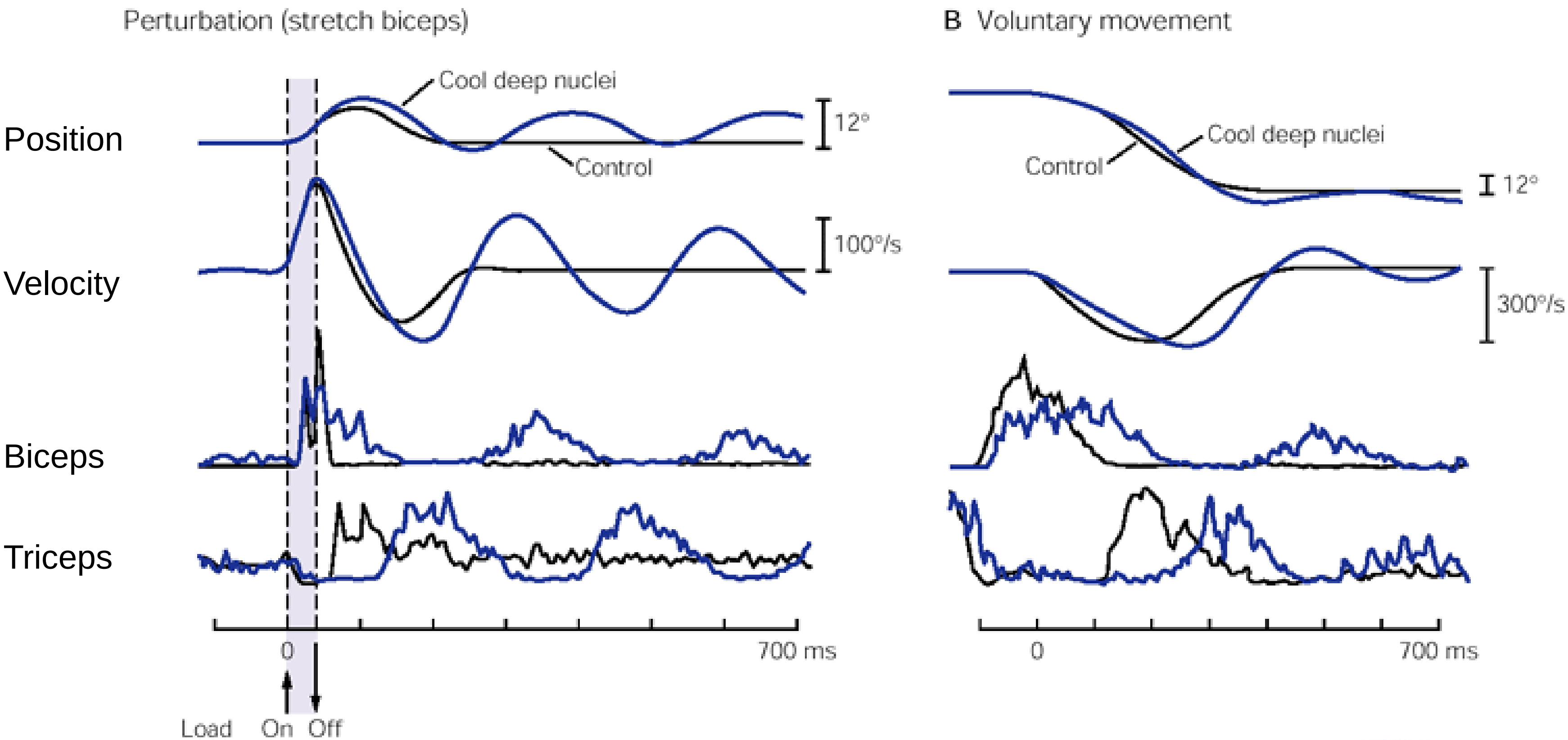


- Hypotonia = loss of muscle tone
- Tremor: limbs, jaw, neck, larynx
- Ataxia = loss of motor coordination:
  1. Postural instability, "drunken sailor" gait , sway, wide standing base
  2. Walking: uncertain, asymmetric, irregular
  3. Failure in execution of planned movements i.e. intentional tremor,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

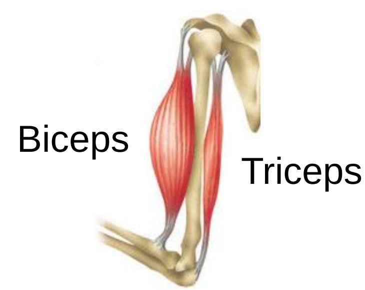
Cerebellar is Central in Adaptation



Classical Role in Muscle Timing and Coordination

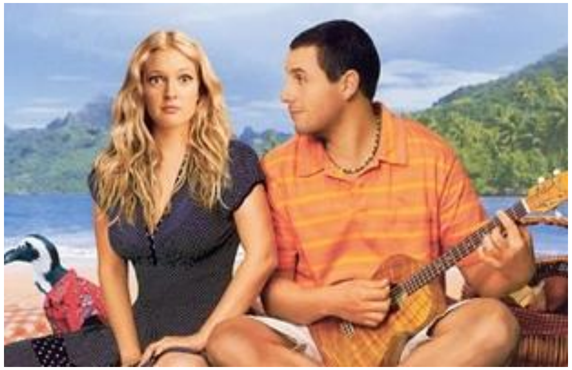


Cooling => Reducing Neuronal Firing



Villis and Hore 1977

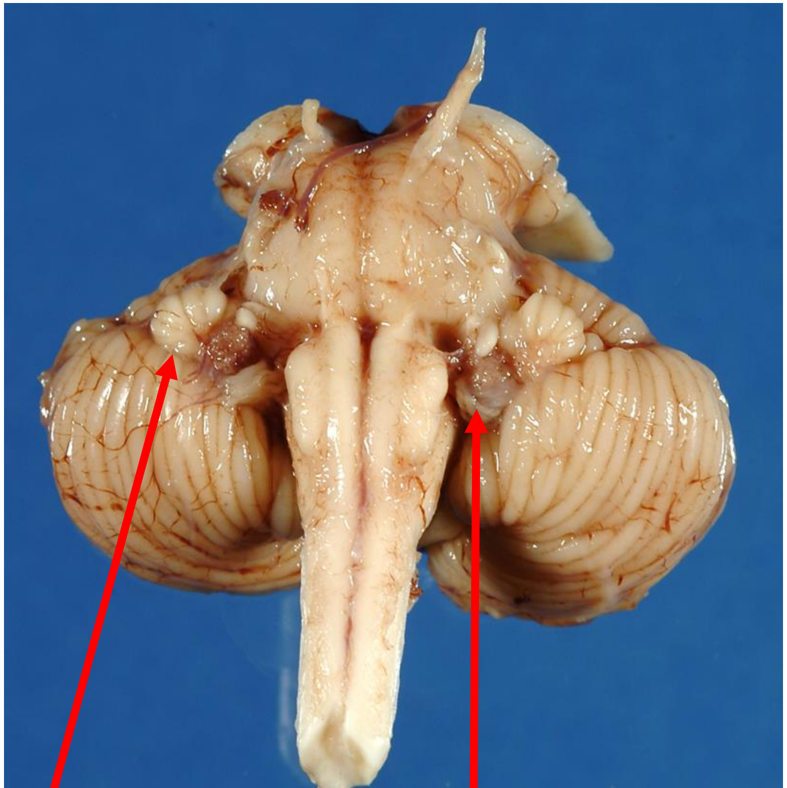
"Non-Classical" symptoms of Cerebellar dysfunction

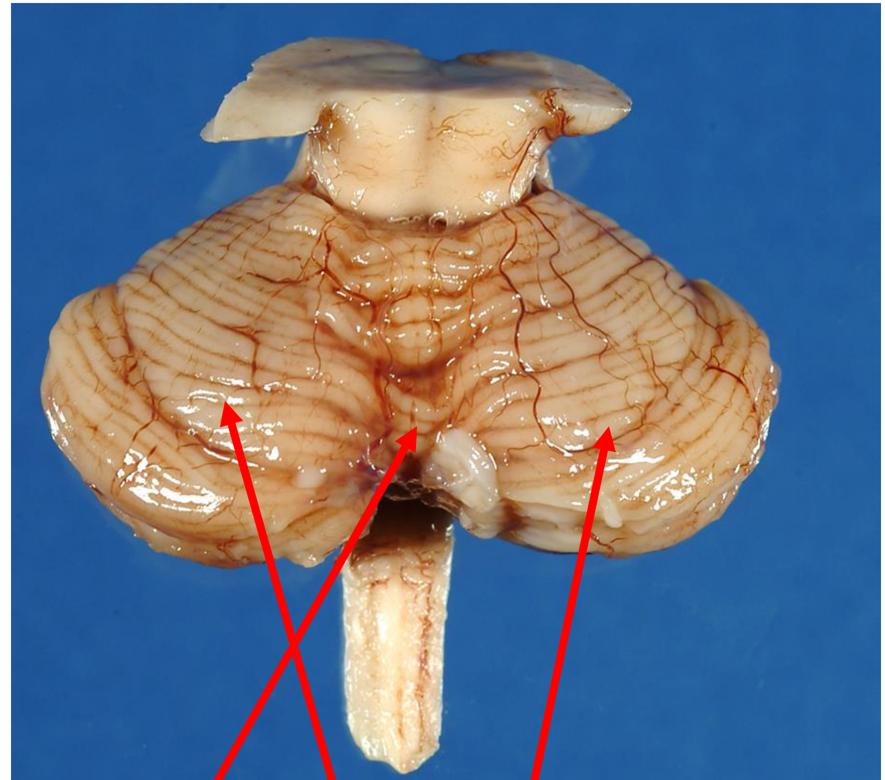

- ❖ Lower Intelligence (Verbal)
- ❖ Lower visuospatial abilities
- ❖ Memory problems (i.e. working, procedural) and Dementia
- ❖ Emotional control problems, impulsiveness, aggression
- ❖ Reduced ability of strategy formation
- ❖ Psychosis, Schizophrenia (co-morbid with reduced volume)

General Structure of the Cerebellar Cortex

Ventral/Anterior View



Dorsal/Posterior View



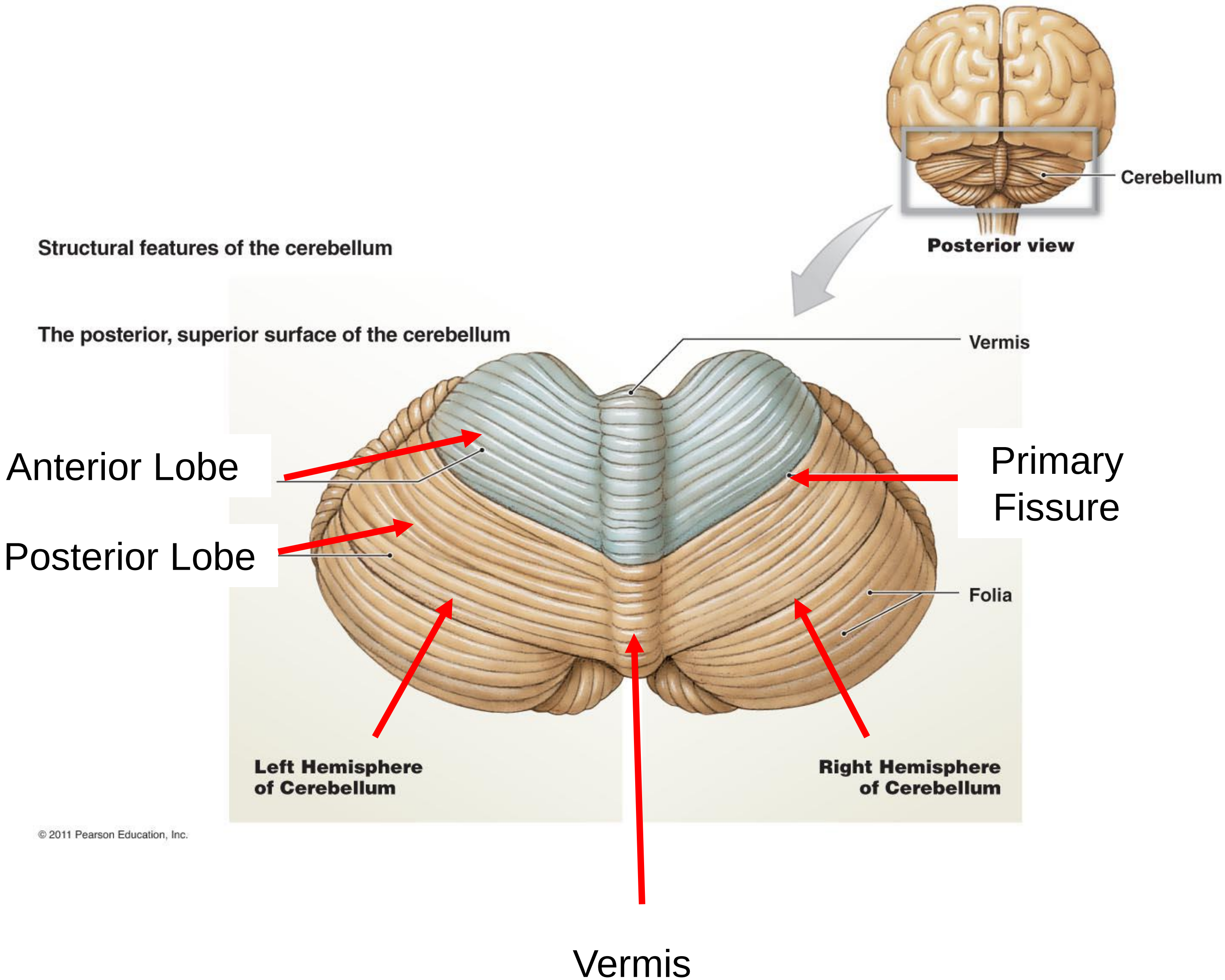
Flocculus

Tonsil

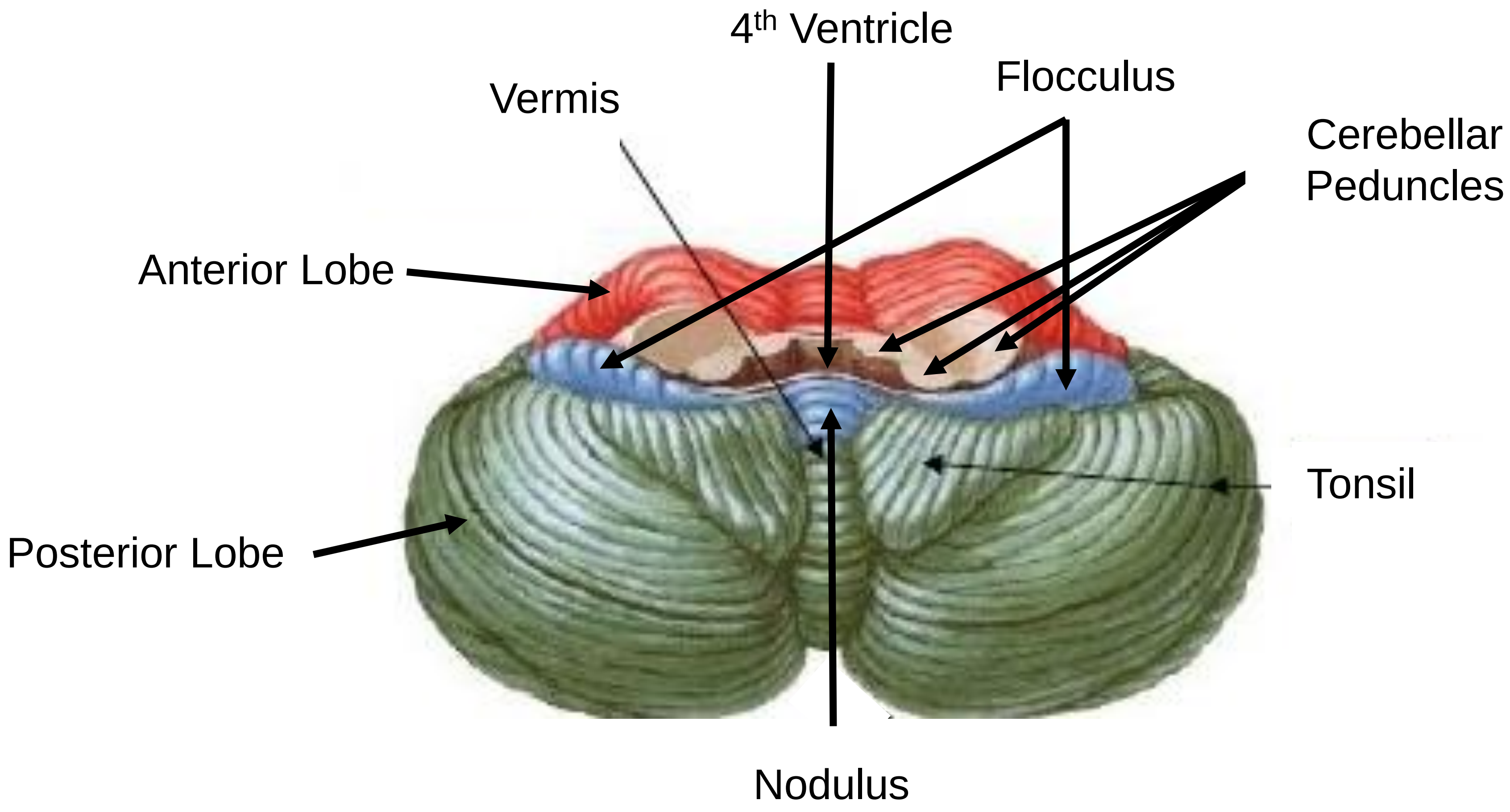
Vermis

Hemispheres

Posterior/Dorsal view of the Cerebellum

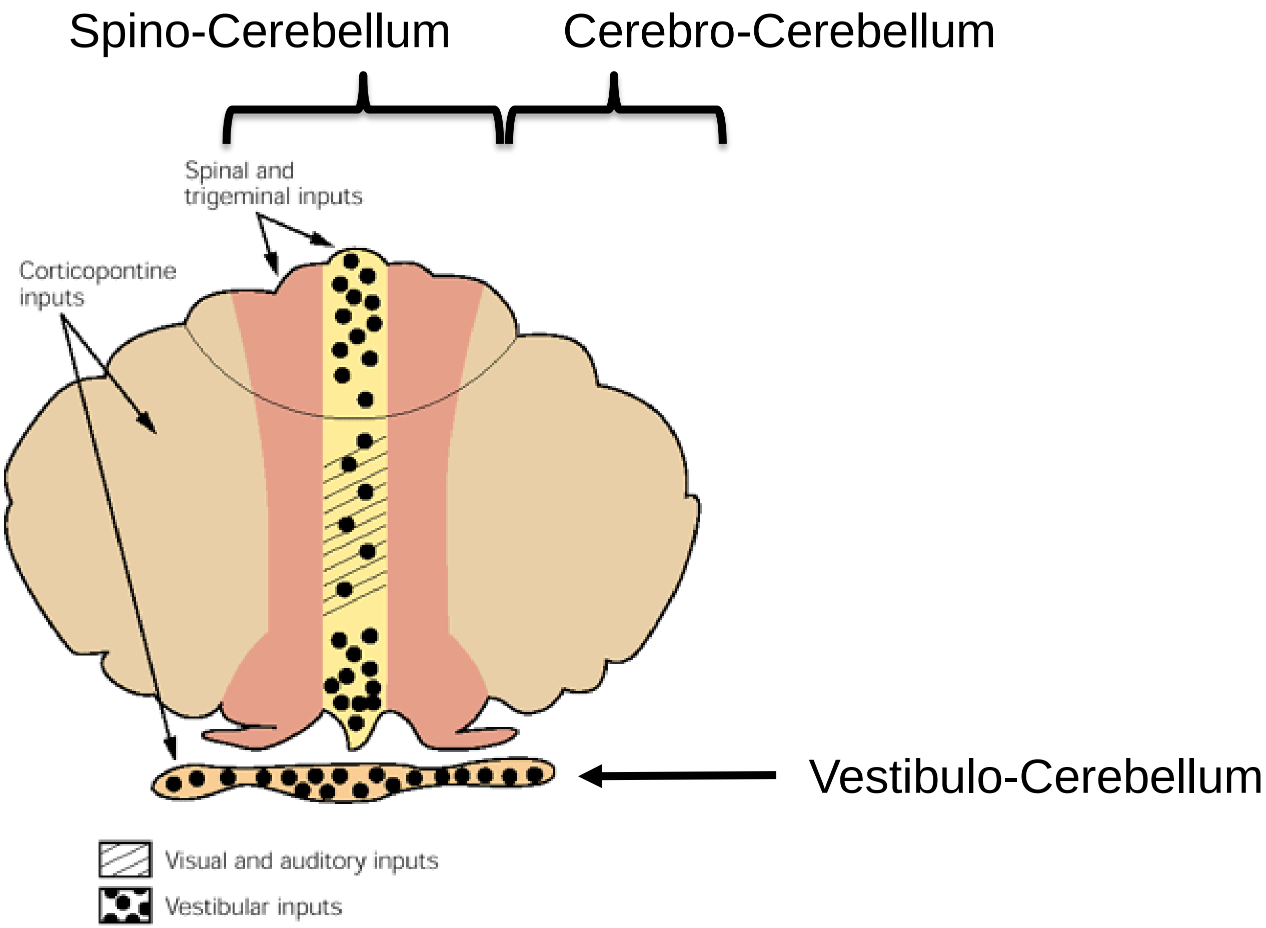


Anterior/Ventral view of the Cerebellum

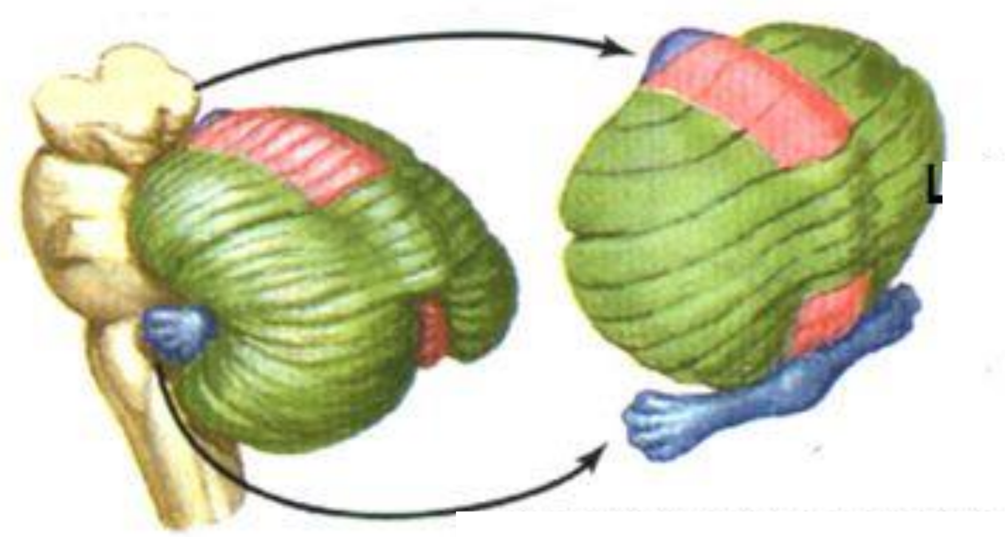


Nodules + Flocculi = Flocculu-Nodular Lobe

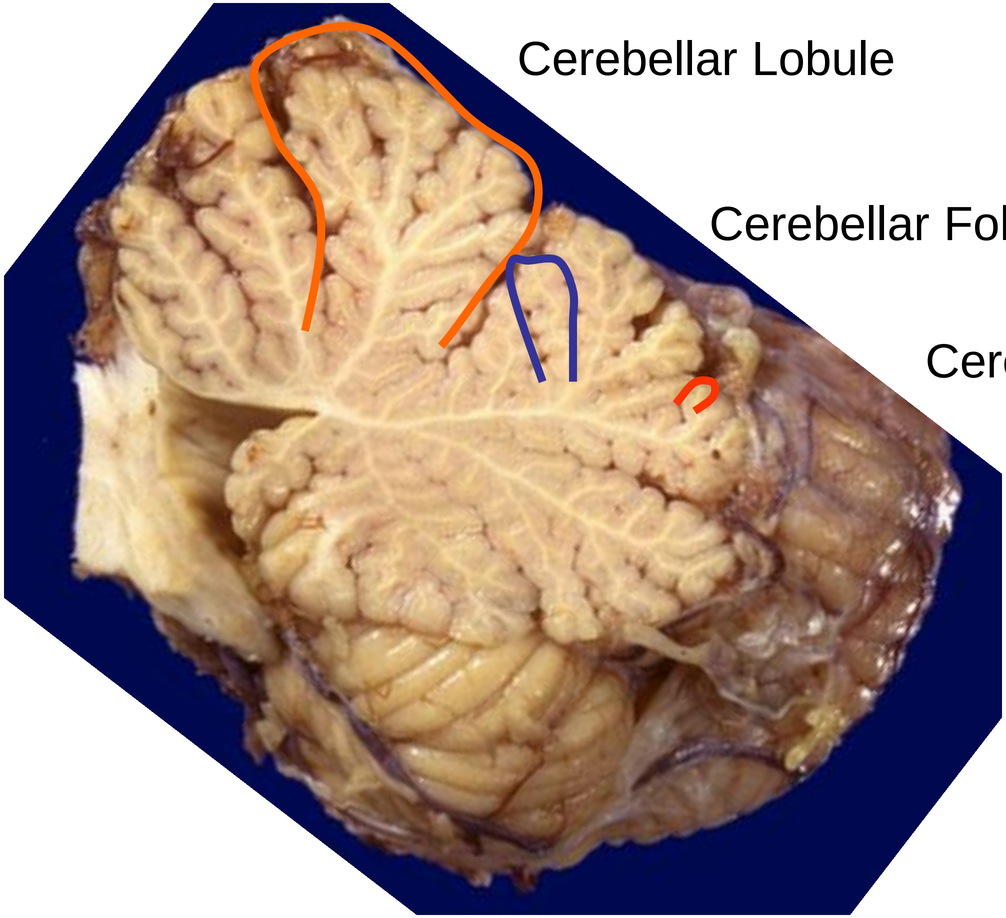
Medio-lateral gross partition of the Cerebellum



The 3D Folding of the Cerebellar Lobes



Lobes and Lobules of the Cerebellar Cortex

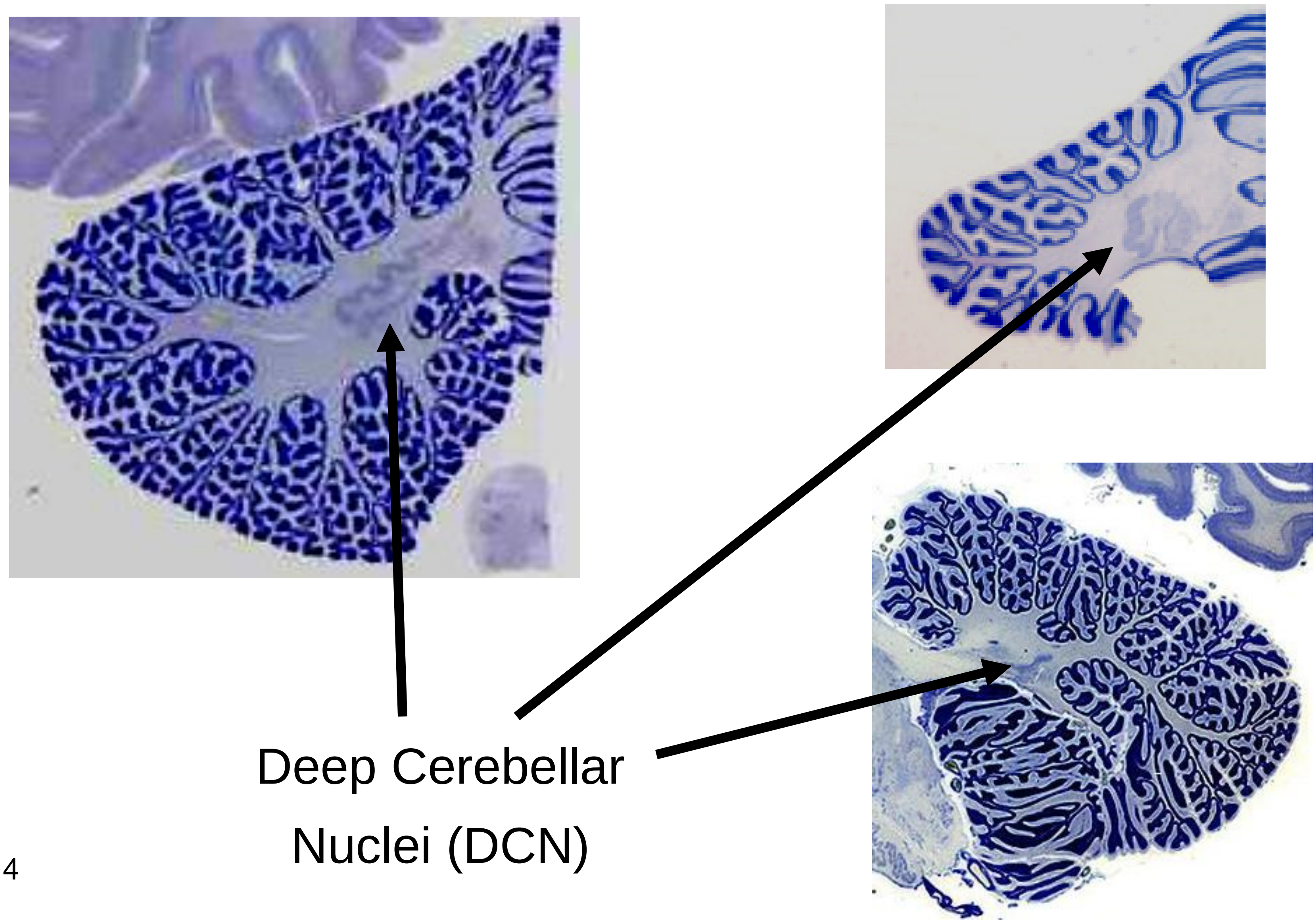


Cerebellar Lobule

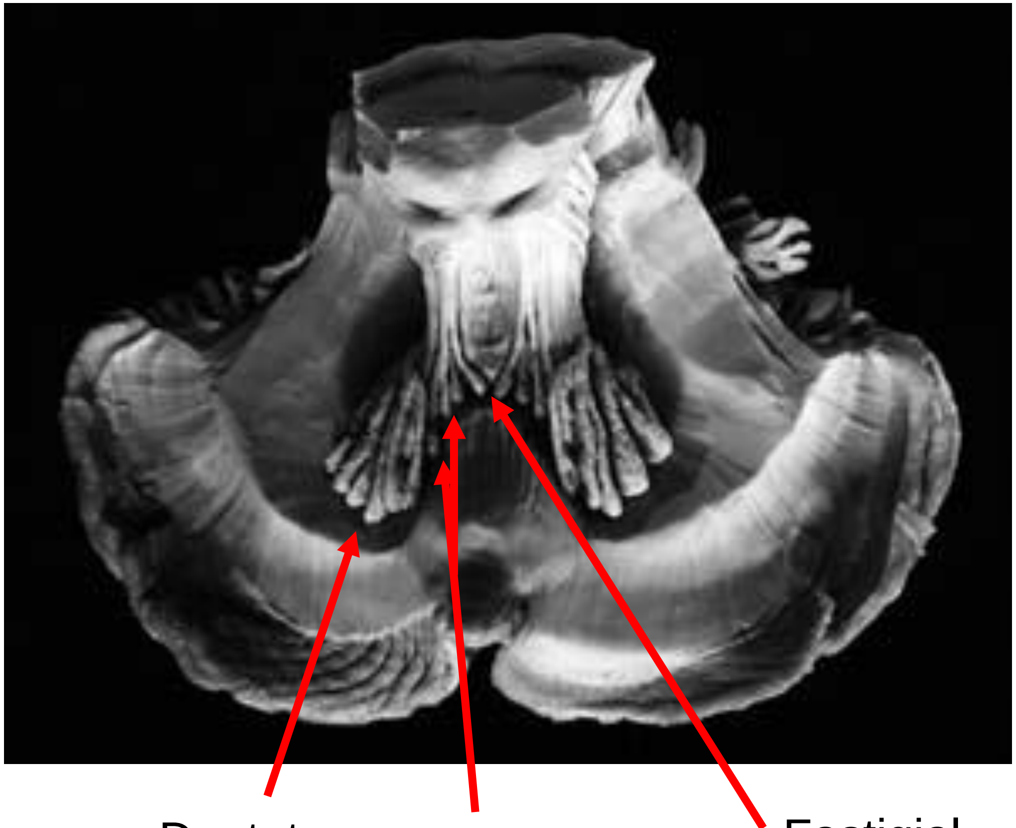
Cerebellar Folia

Cerebellar Folium

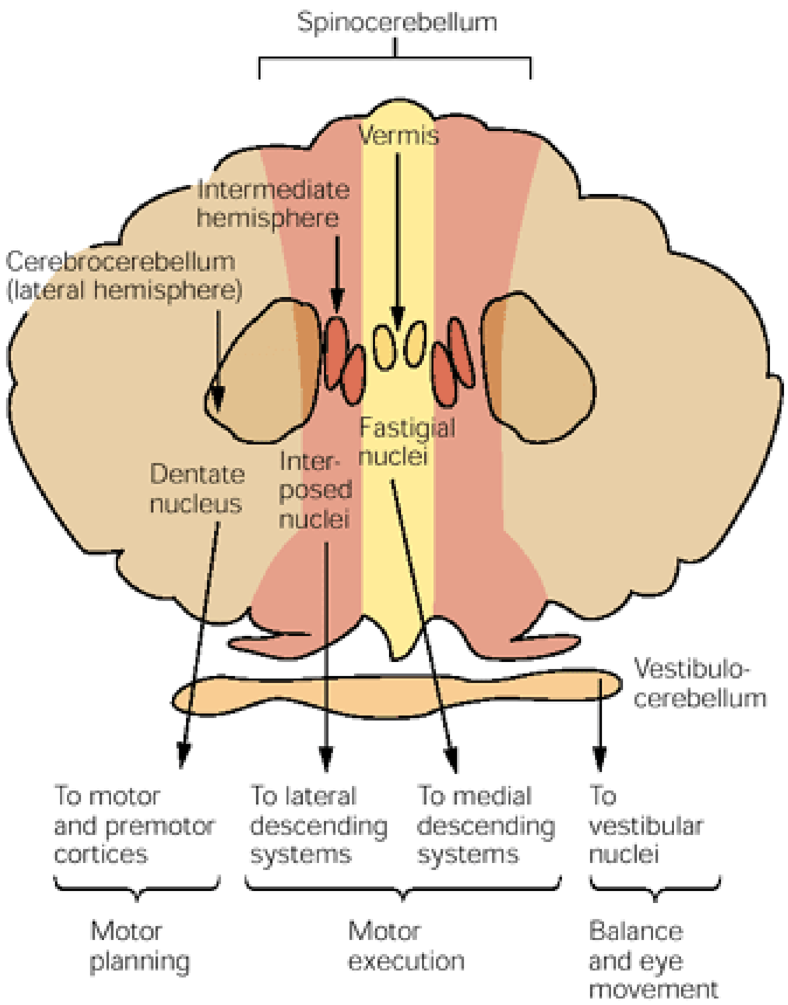
The Cerebellum is not Only Cortex…



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

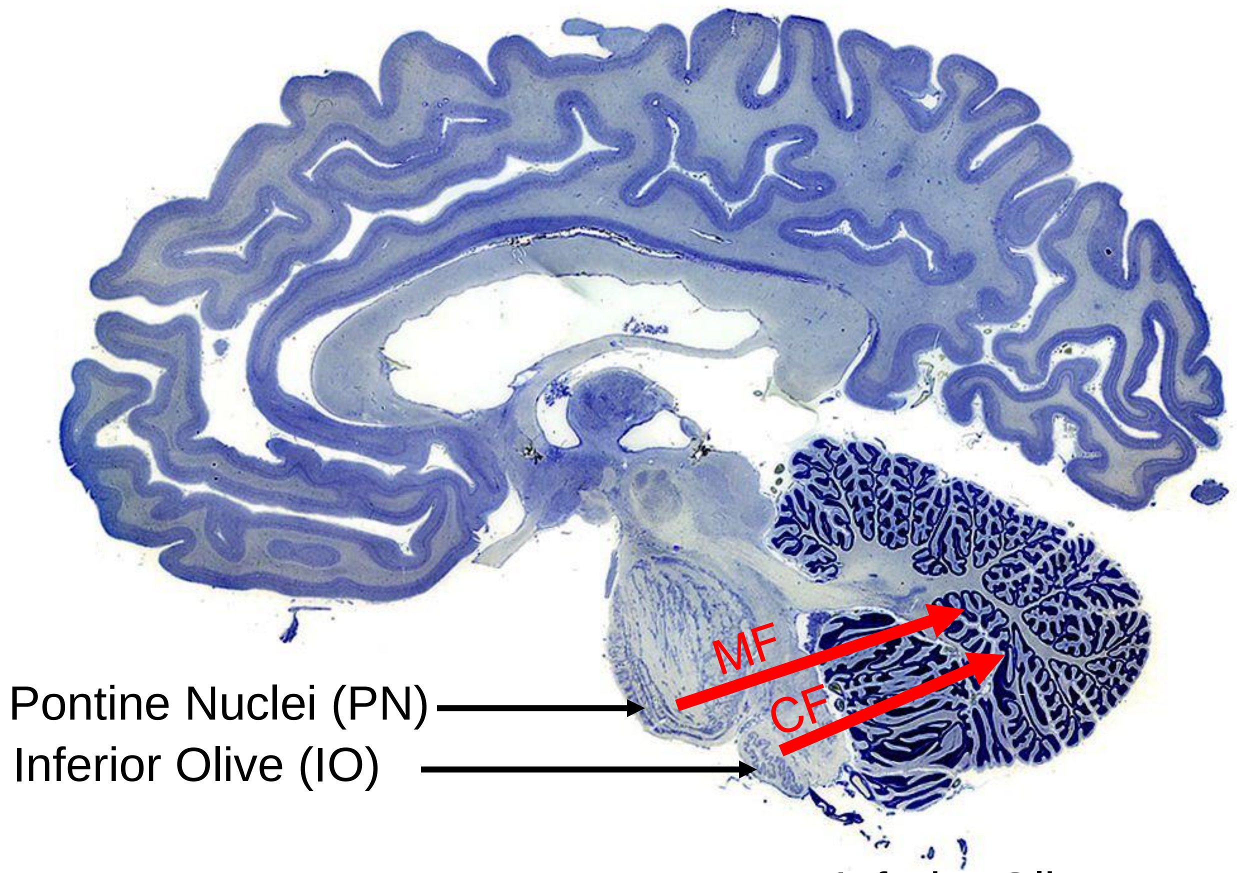


Functional mapping of the Cerebellar nuclei

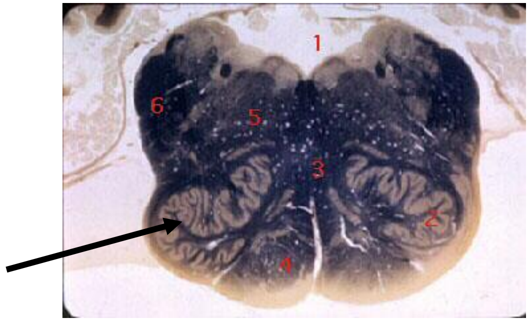


The Vestibular Nucleus in the Brainstem is <u>Functionally Homologous</u> to cerebellar nuclei.

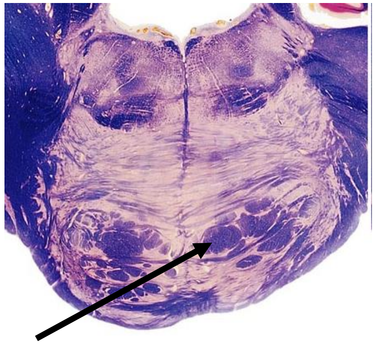
Two Major Input Pathways Serve the Cerebellum



Inferior Olive



Pontine Nuclei



MF = Mossy Fibers
(~90% via the PN)
CF = Climbing Fibers
(All via the IO)

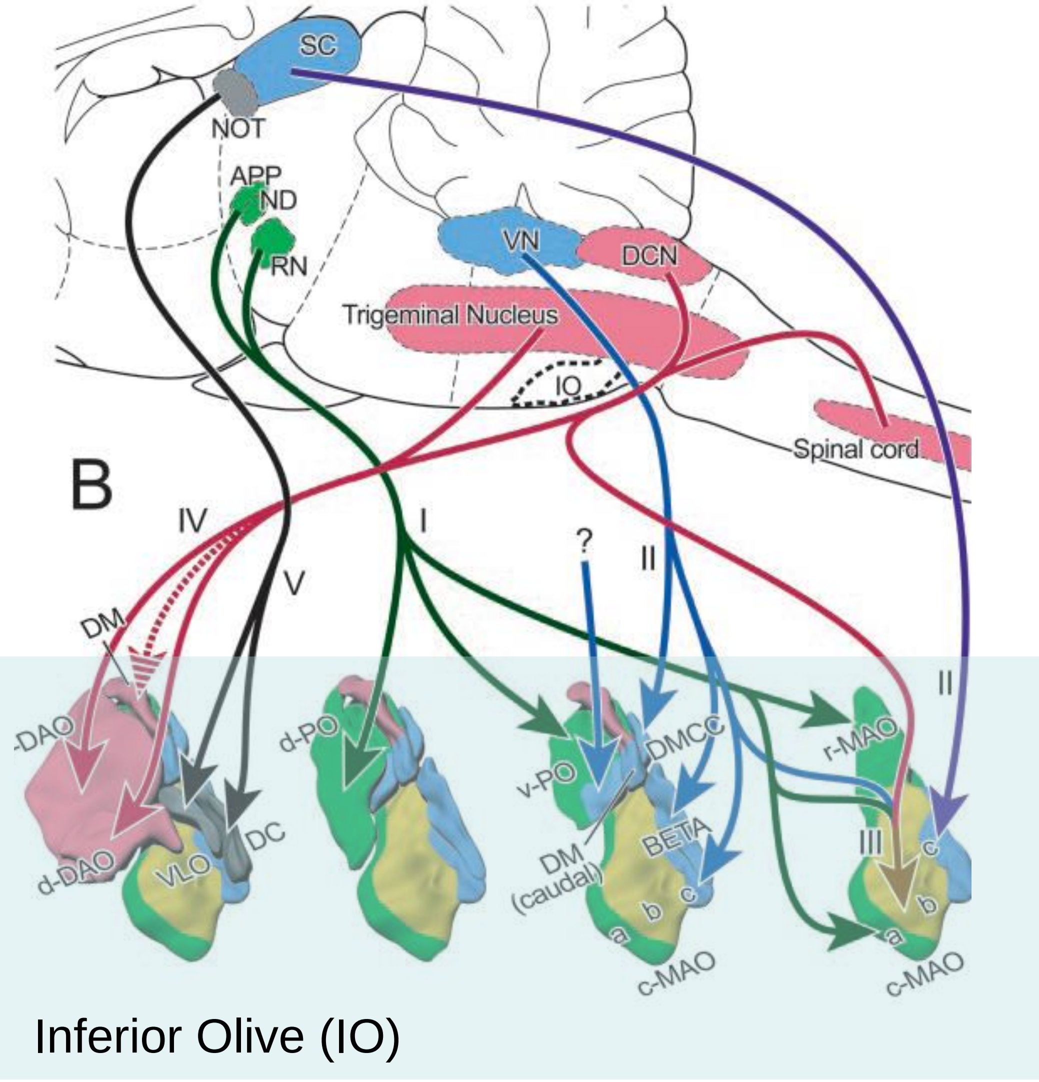
The IO receive low level motor and sensory inputs

Visual Inputs:
SC = Superior Coliculus
NOT = Nucleus of Optic Tract

Vestibular Inputs:
VN = Vestibular Nucleus

Motor Command:
RN = Red Nucleus

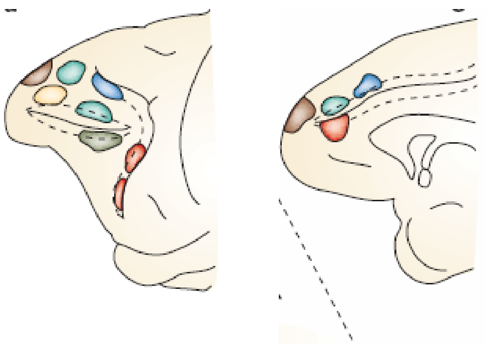
Somatosensory & Proprioceptive:
DCN = Dorsal Column Nucleus
Trigeminal & Spinal Chord

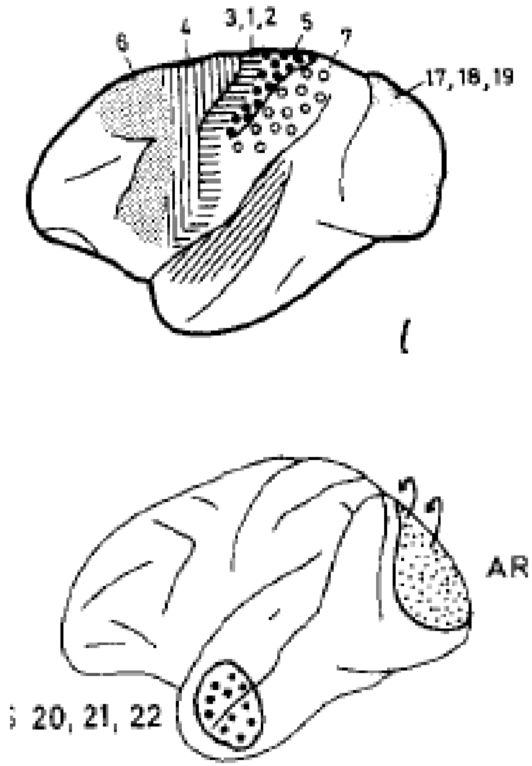


Additionally: Auditory Inputs

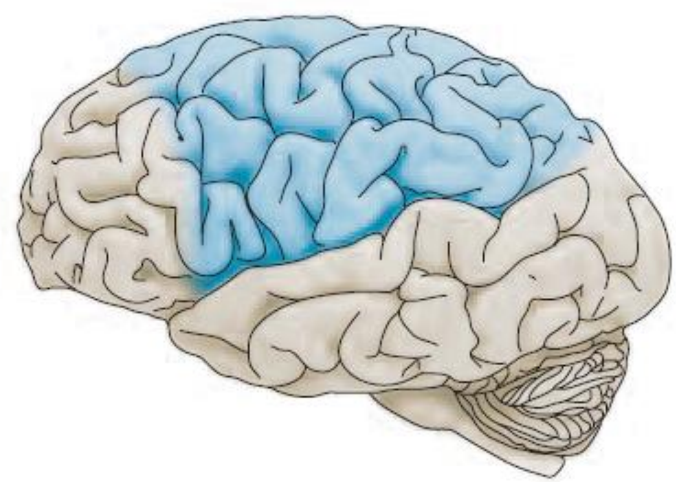
Sugihara & Shinoda JNS 2004

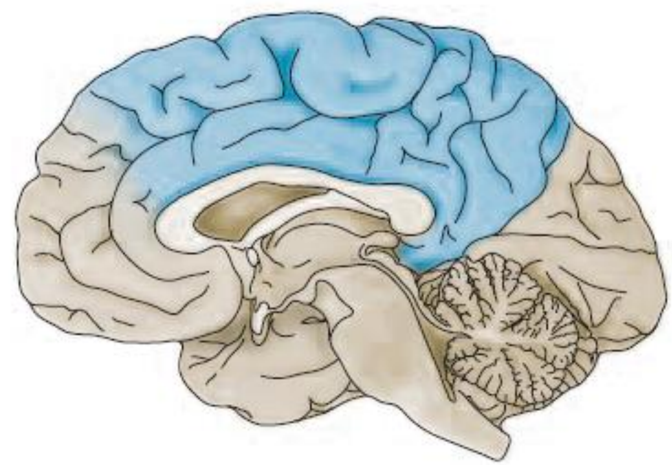
Pontine Nuclei Relay Cerebro-Coritcal Information





(Brodal 1978)



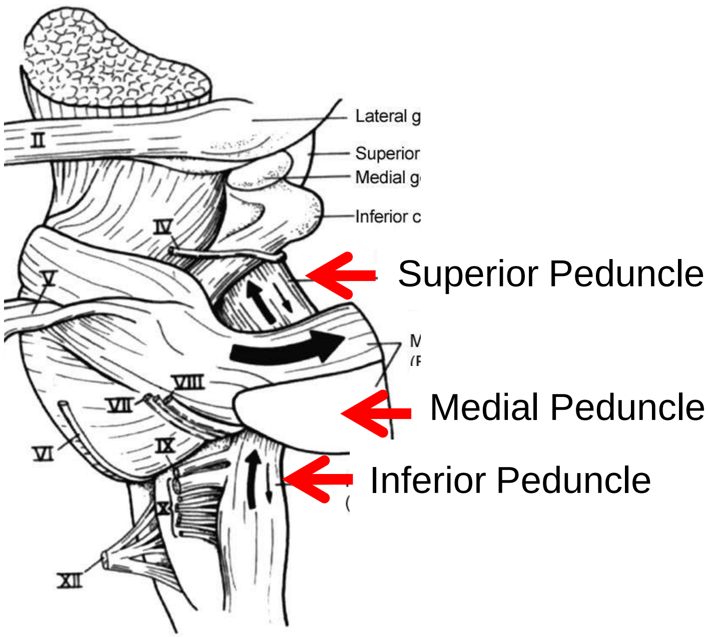


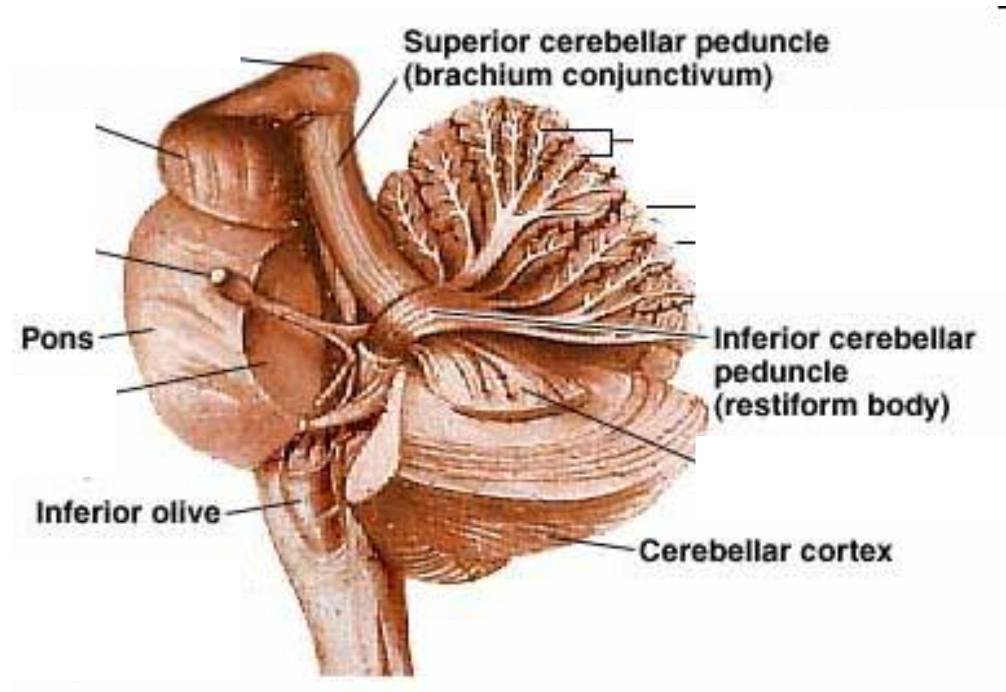
Non-Cortical Inputs:

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

Forebrain Areas That project to the Pontine Nuclei

Cerebellar Peduncles: Input / Output Highways





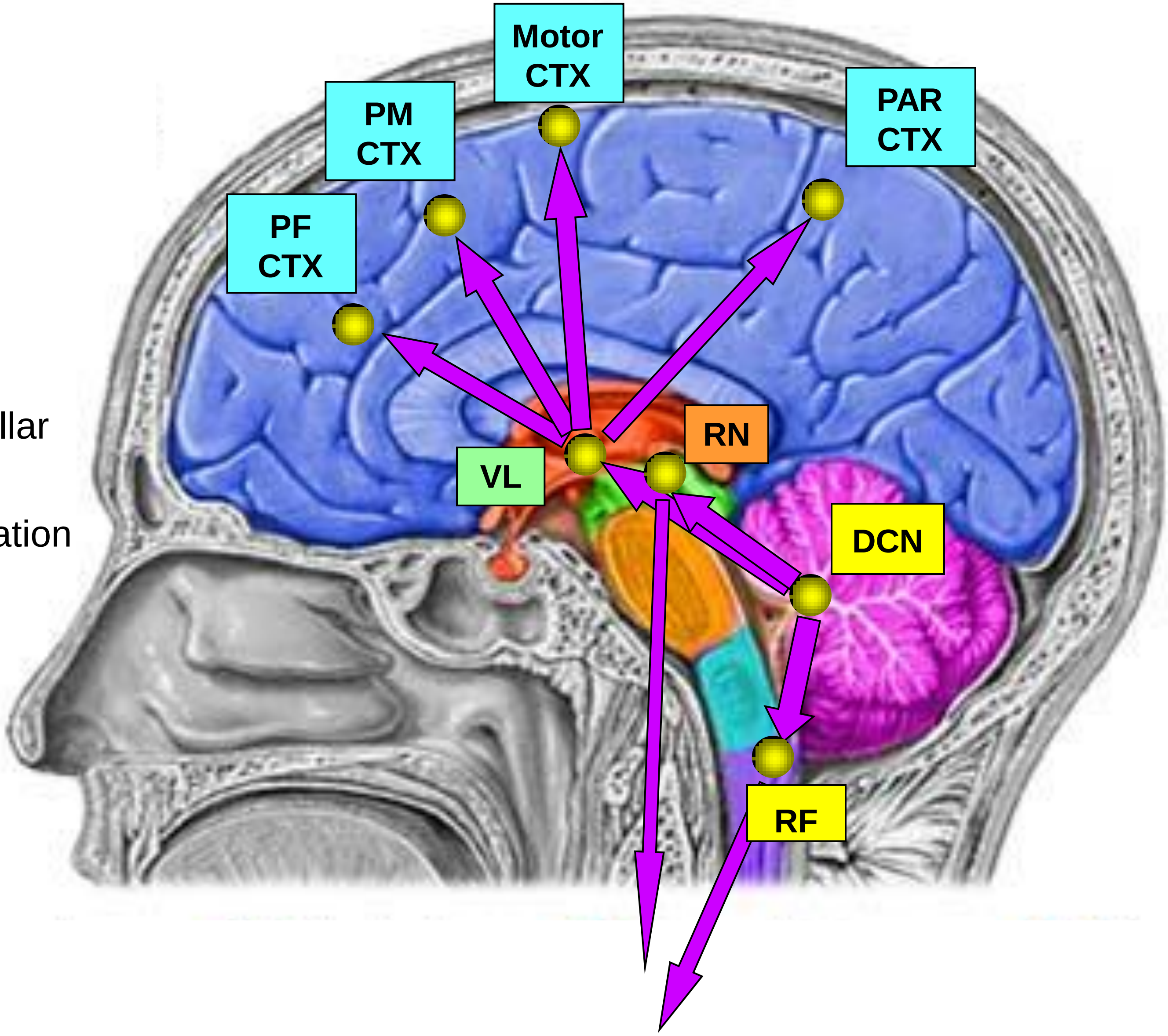
Superior: Thalamus/Midbrain Inputs/Outputs

Medial: Pontine Inputs and Commissure

Inferior: Spinal/Medullary Inputs/Outputs

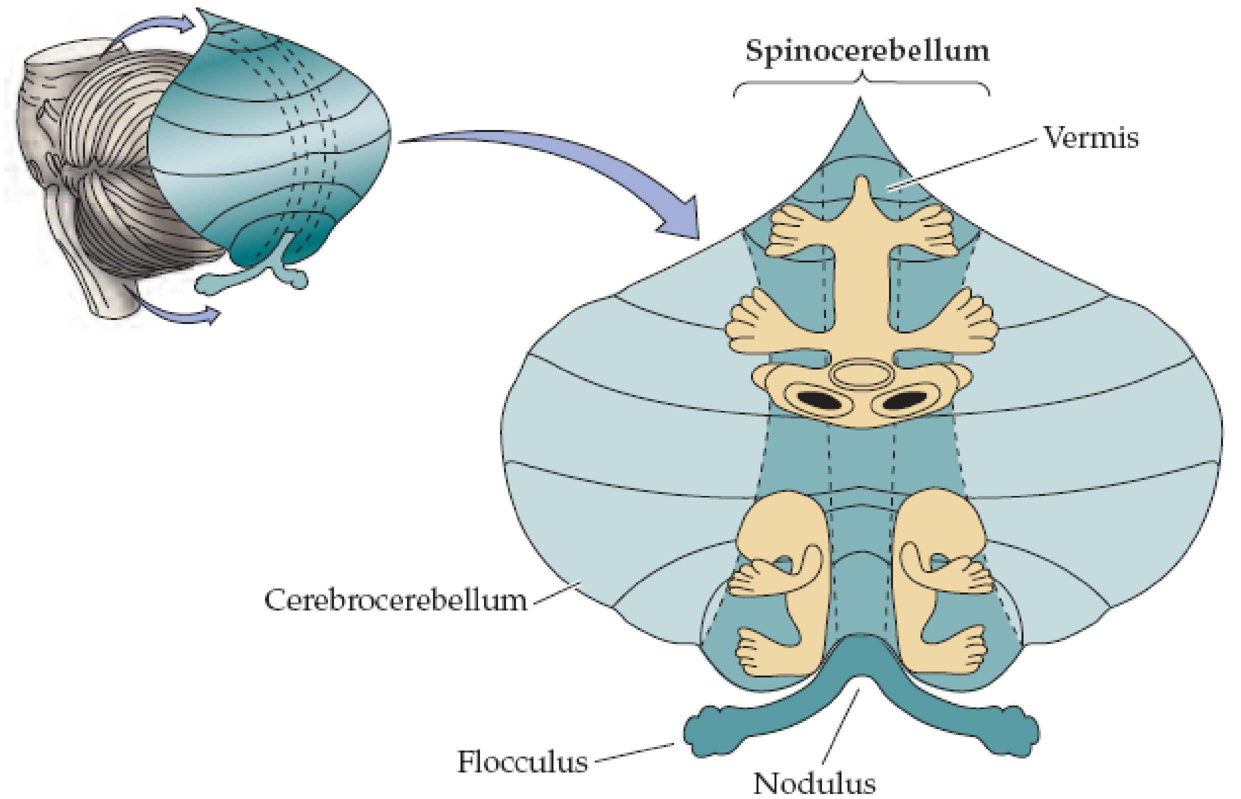
Cerebellar Major Output Pathways

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

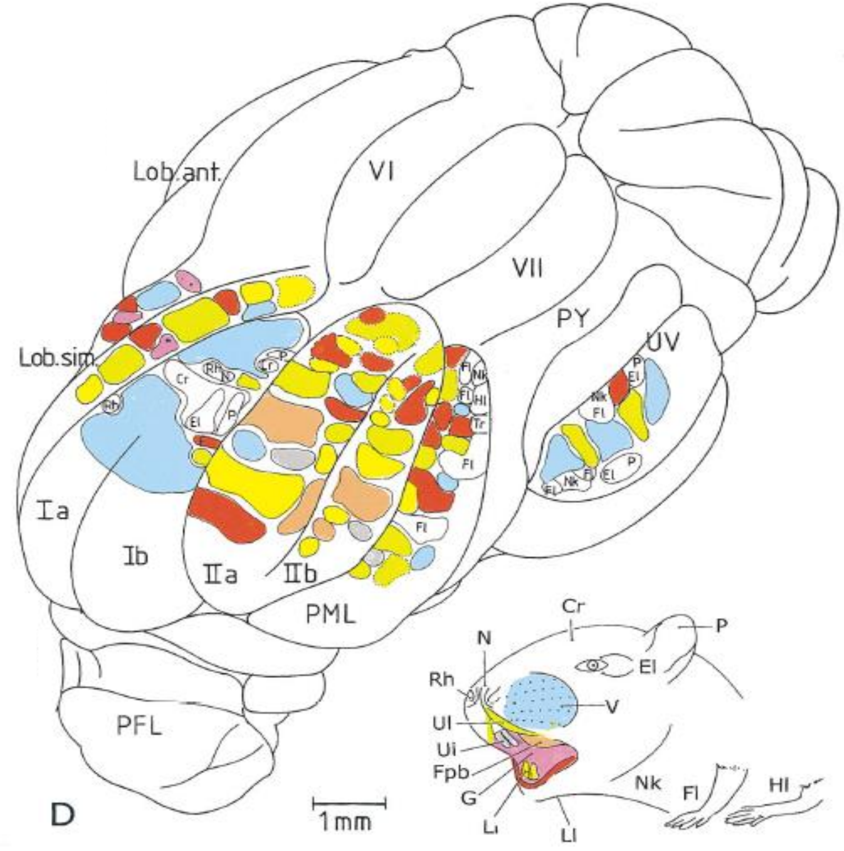


Other Outputs:
Inferior Olive
Hippocampus
Amygdala
Septum

Mapping of Cerebellar Cortex – Classic View

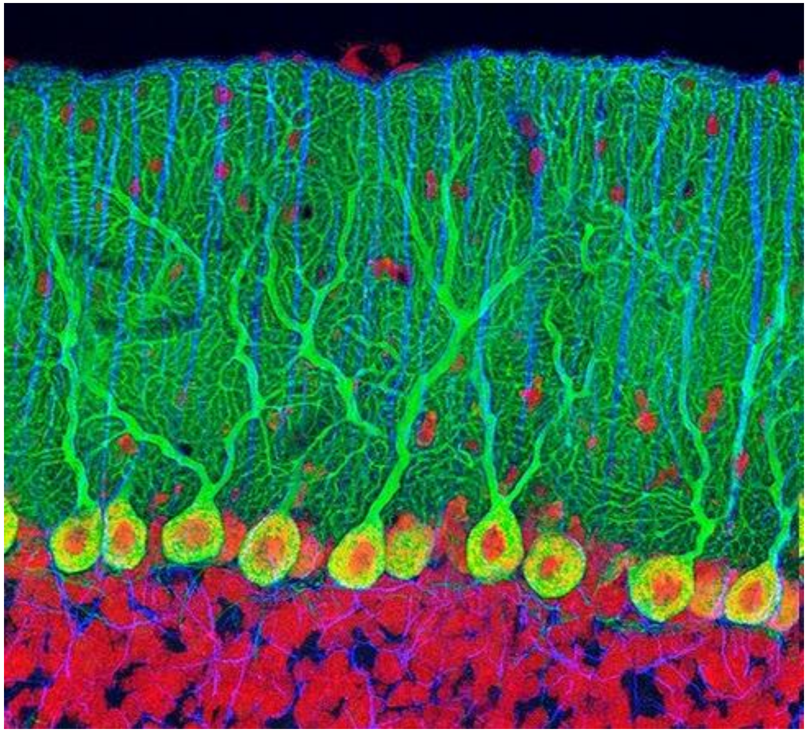


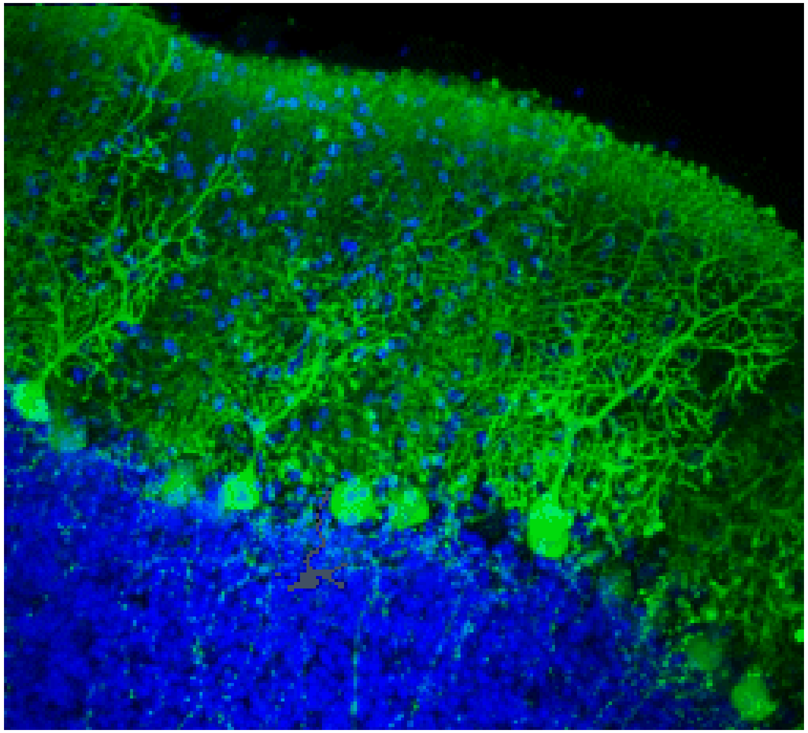
Cerebellar Cortex Mapping is Fragmented



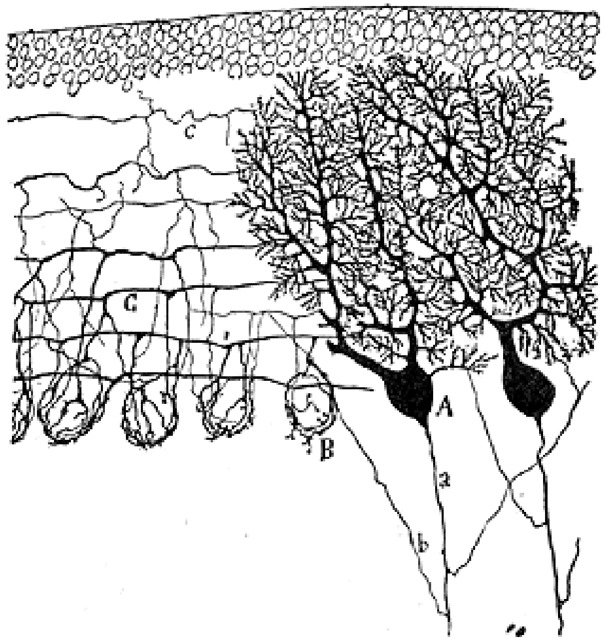
Voogd and Glickstein 1998

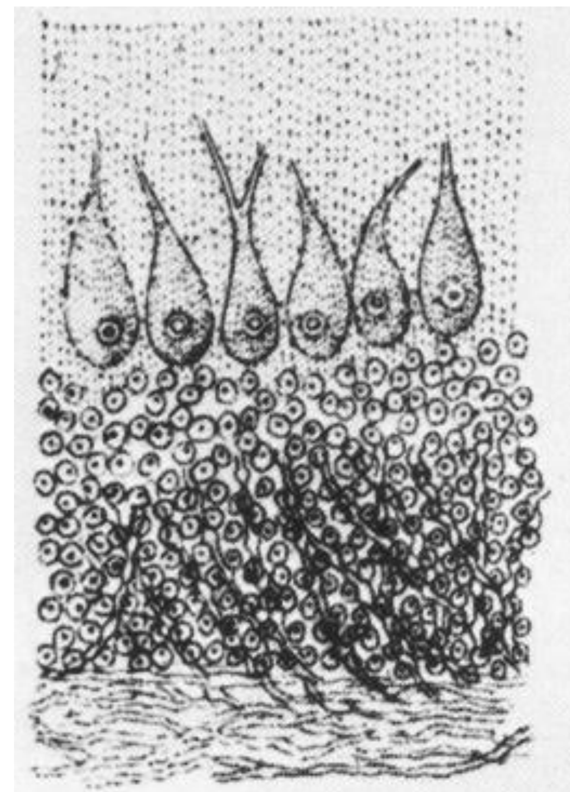
Cerebellar Cortex:
The Beauty of Network Architecture



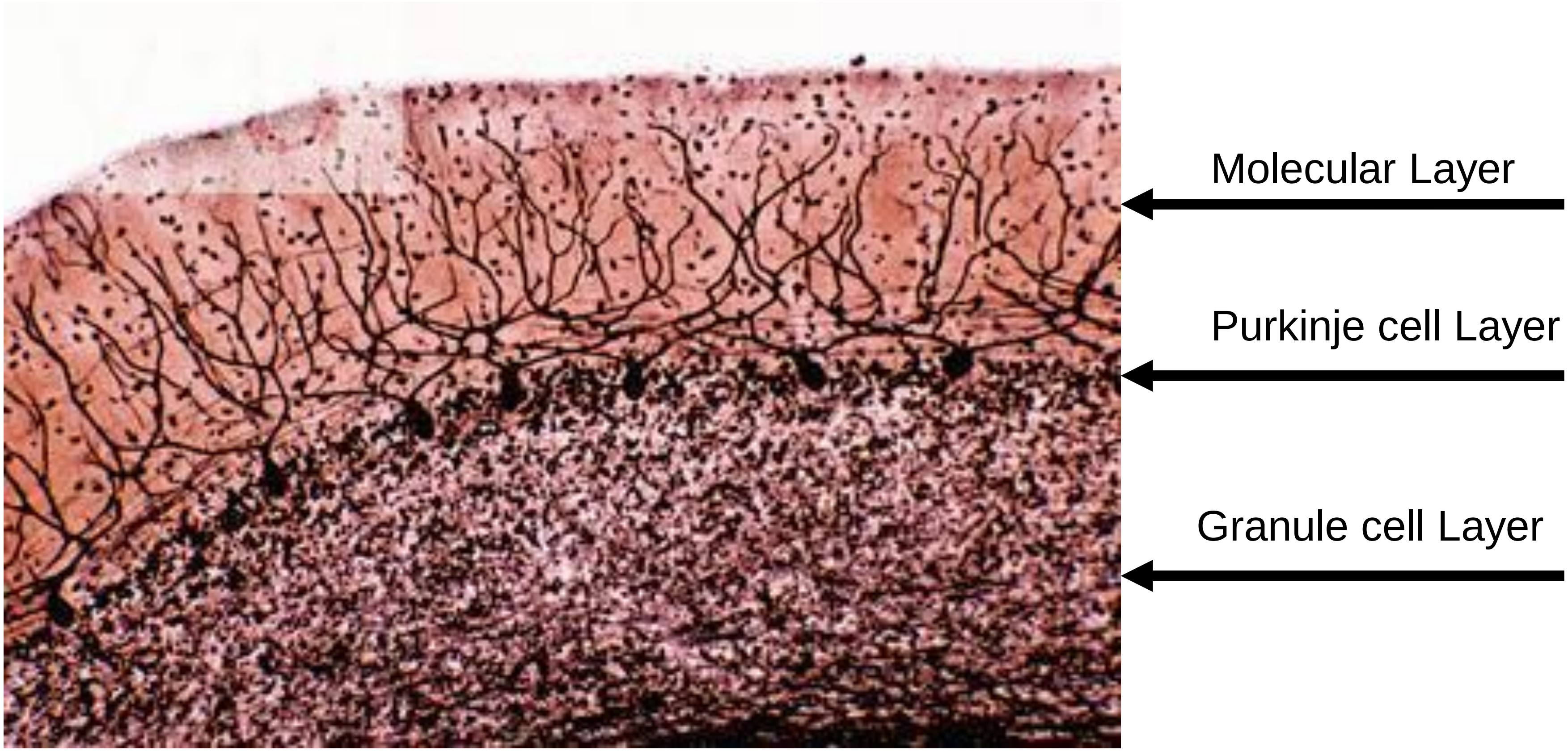


Purkinje Cells: The most Elaborate Neurons of the CNS

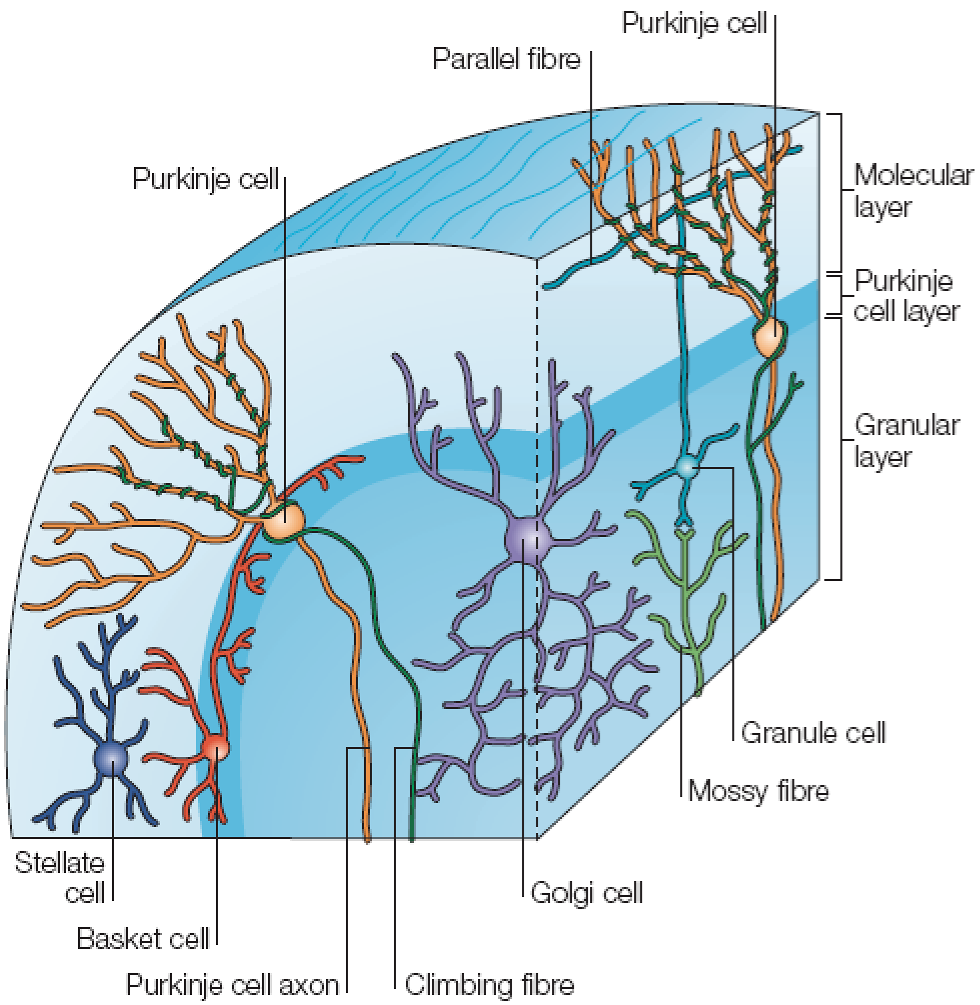




The 3 Layers of the Cerebellar Cortex



Cerebellar Cortex Consists of 5 types of Neurons

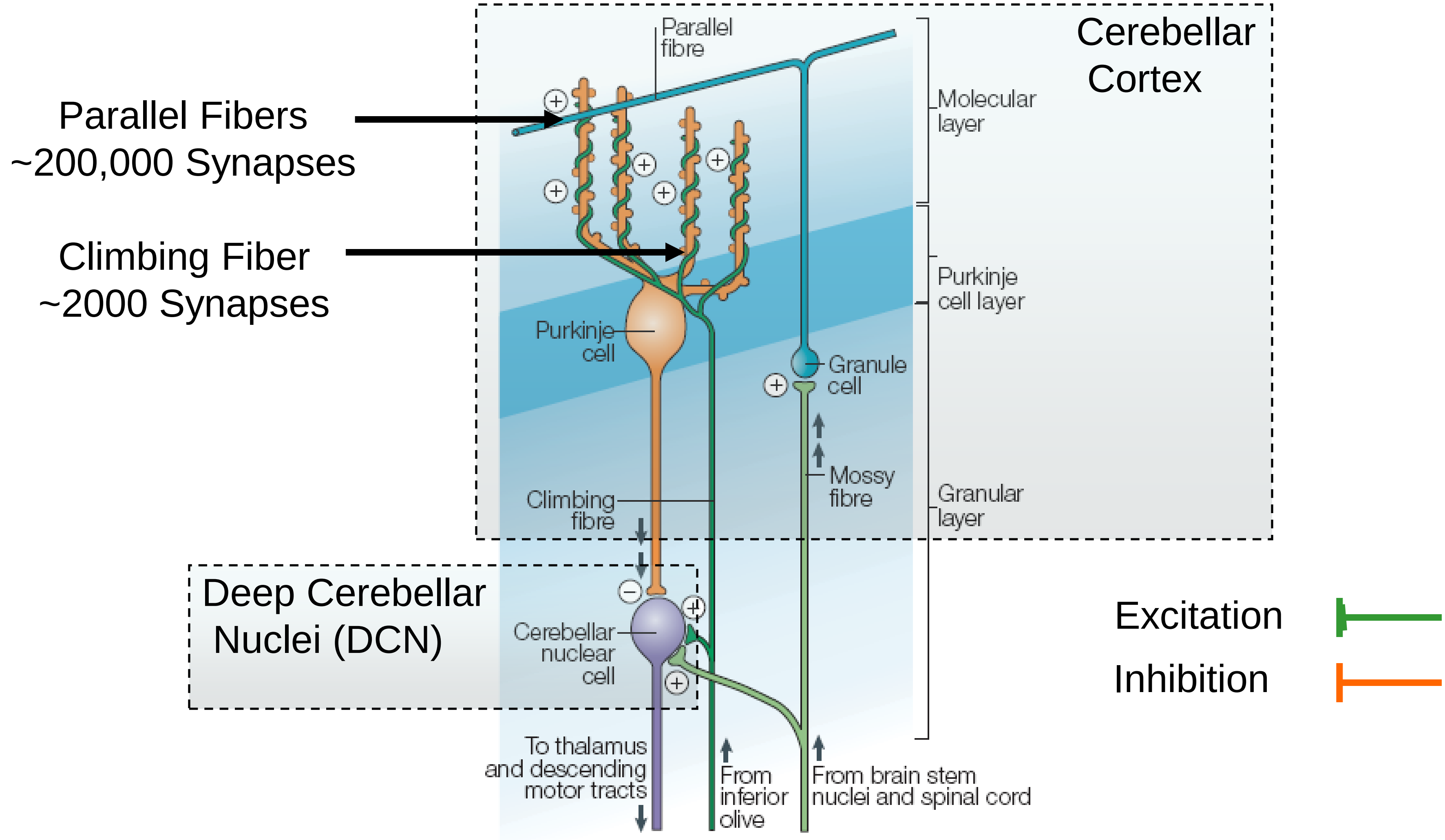


Inhibitory cells:
- Purkinje
- Golgi
- Basket
- Stelate

Excitatory Cells:
- Granule cells

Apps & Garwicz NatRevNeu 2005

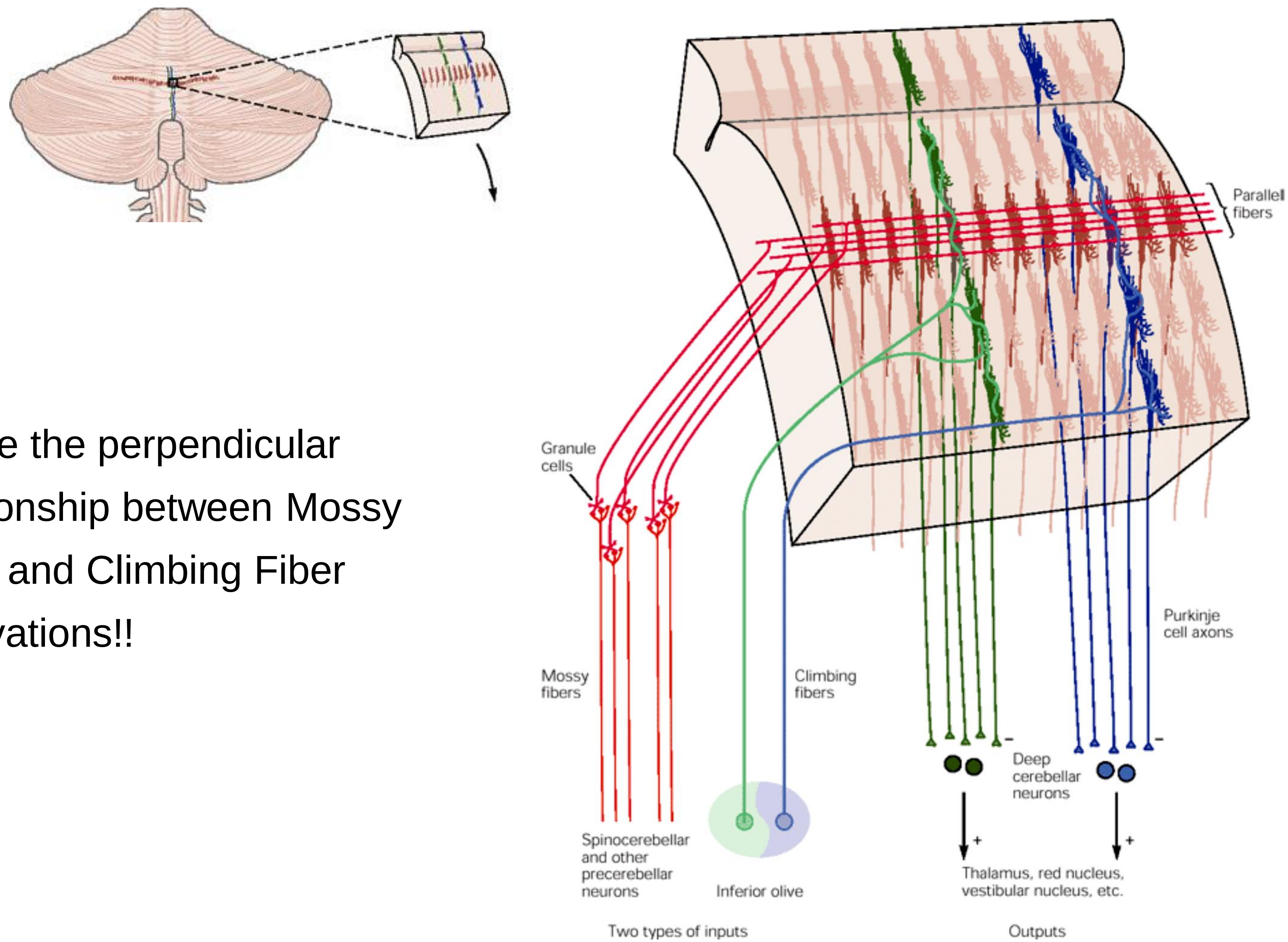
PC: The Principal Cell of Cerebellar Cortex



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

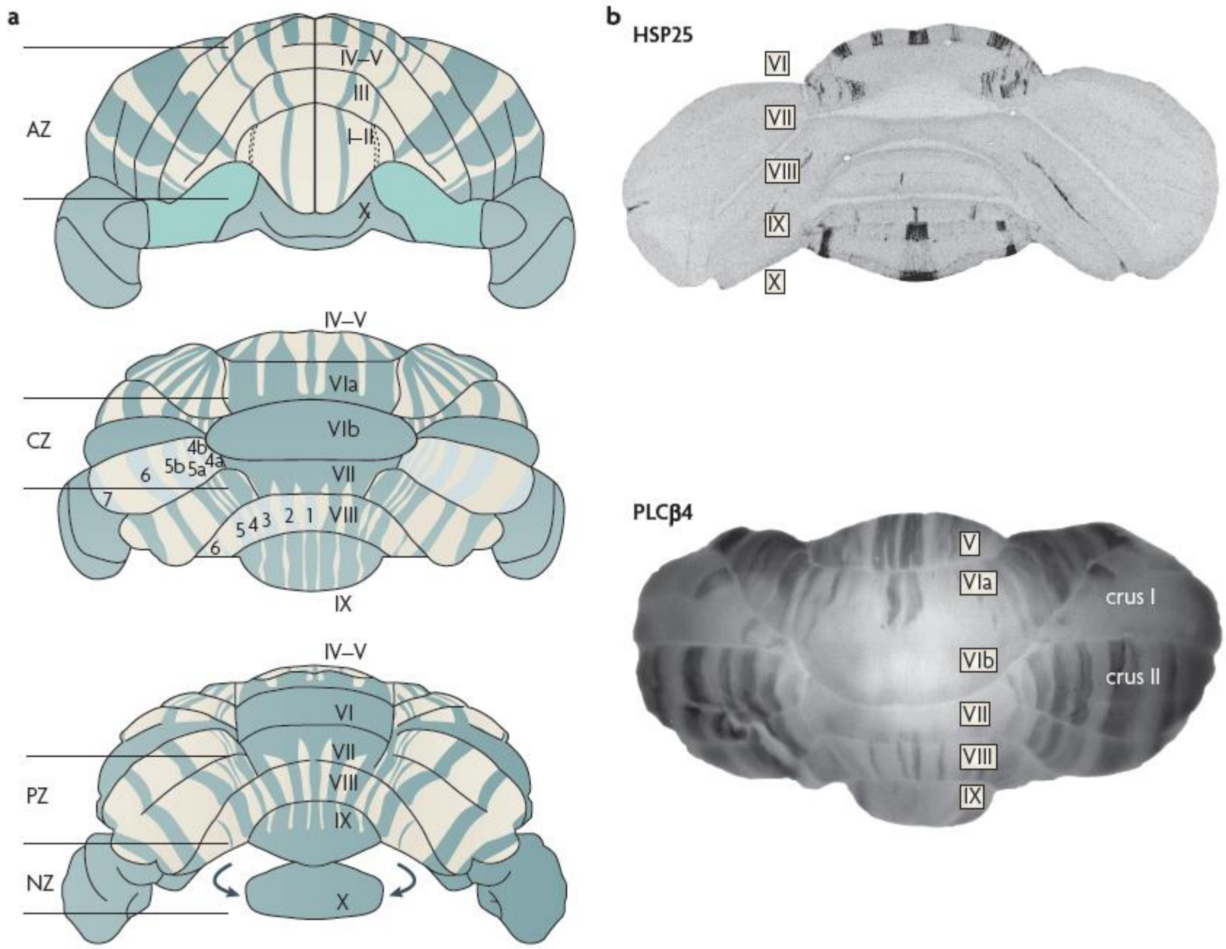
Modified from Apps & Garwicz 2005

The Spatial Organization of Cerebellar Circuitry



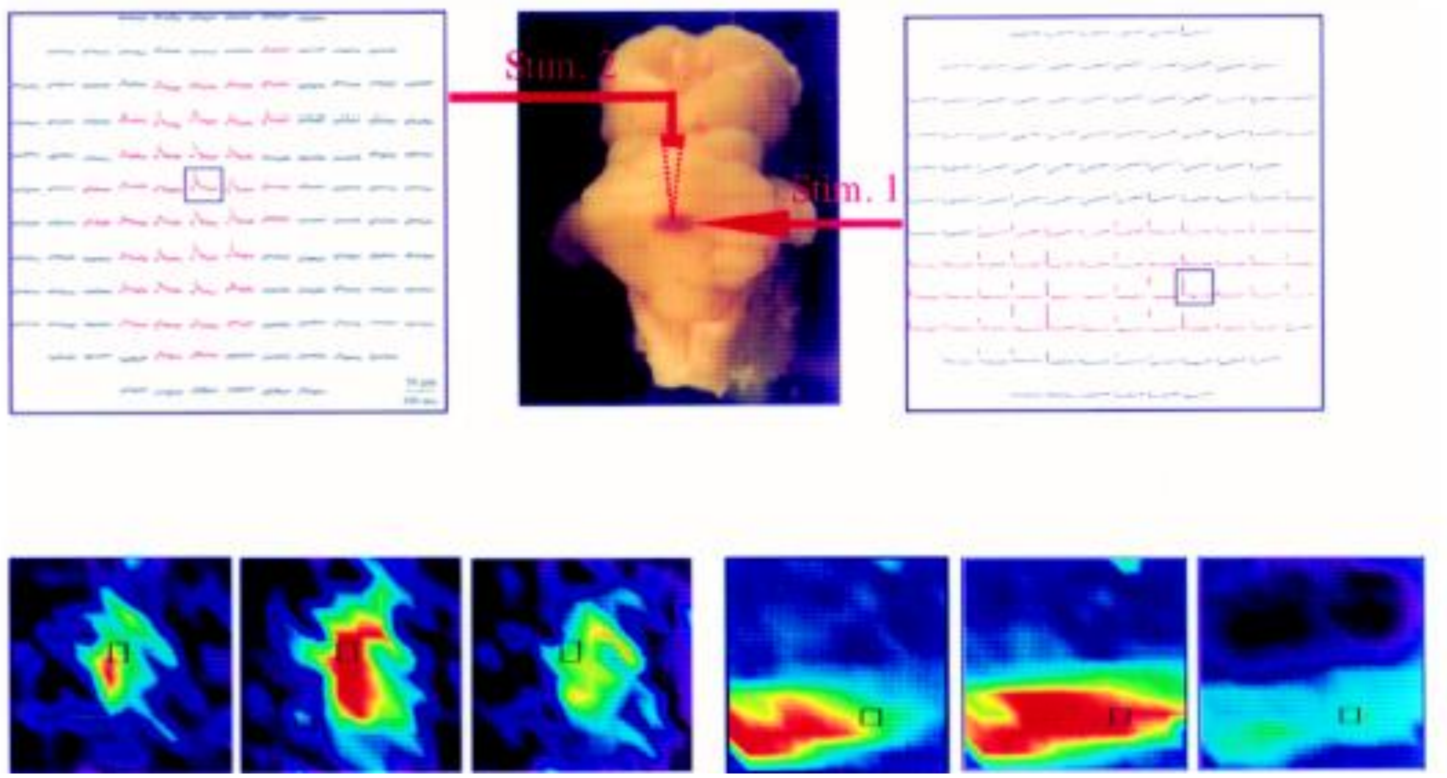
Notice the perpendicular relationship between Mossy Fiber and Climbing Fiber enervations!!

Parasaggital Microzones of Cerebellar Cortex



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

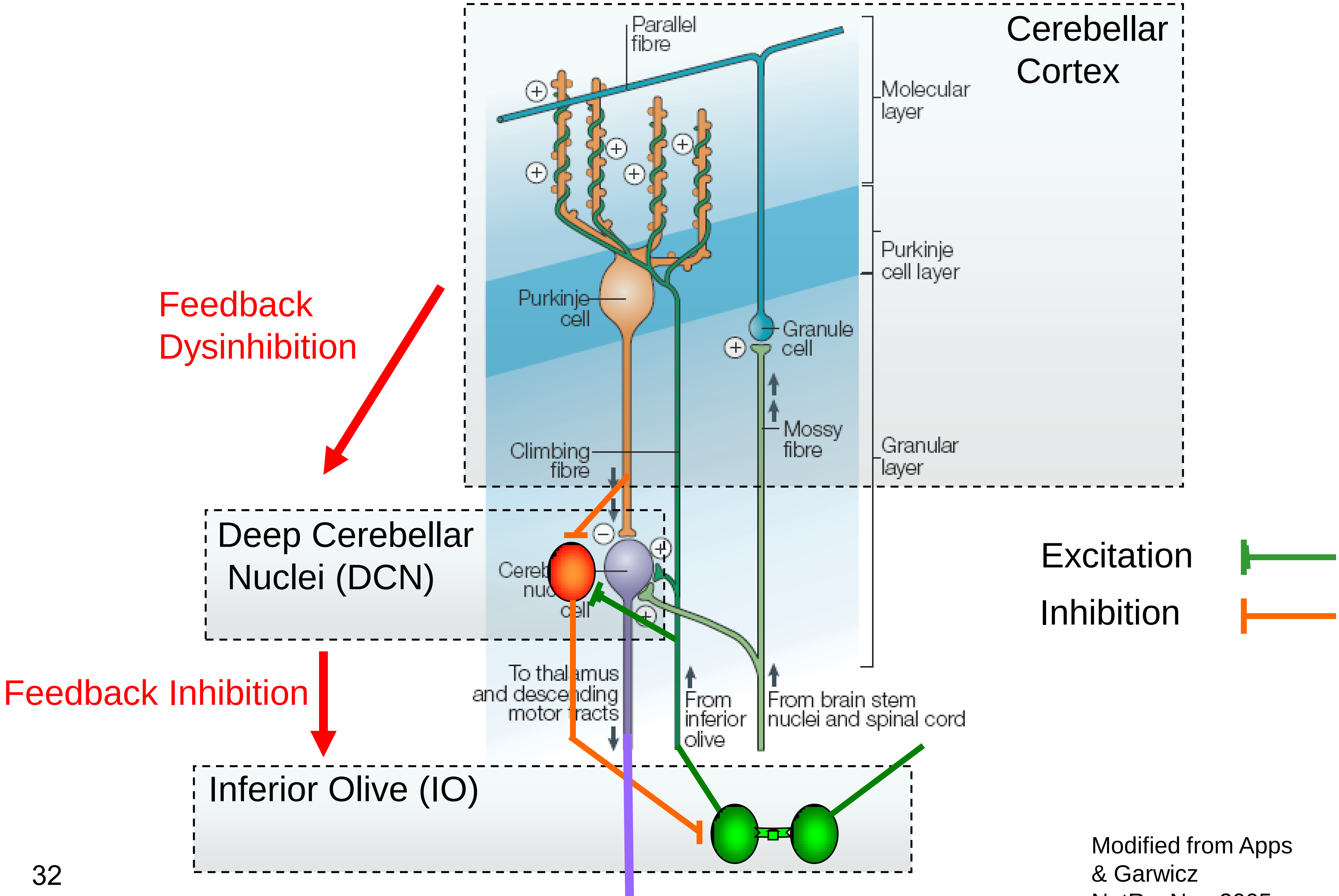
Parallel fibers are not a delay line: local inhibition prevents signal propagation



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

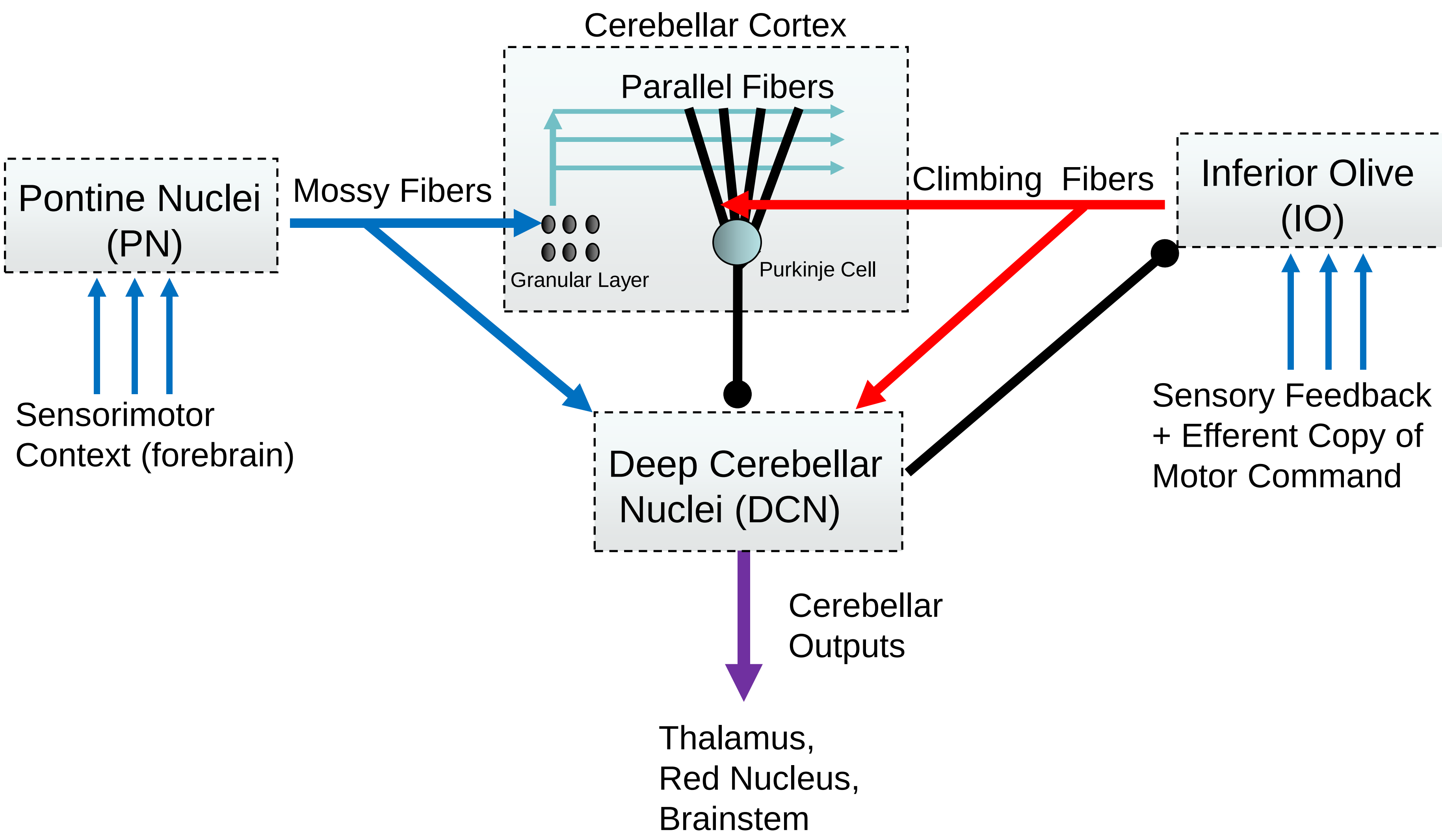
Yarom and Cohen AnnNYAc 2003

Closing the Loop: The Cerebellar Module



Modified from Apps & Garwicz NatRevNeu 2005

The simplified Olivocerebellar Module



Cerebellar Physiology

Infra Red

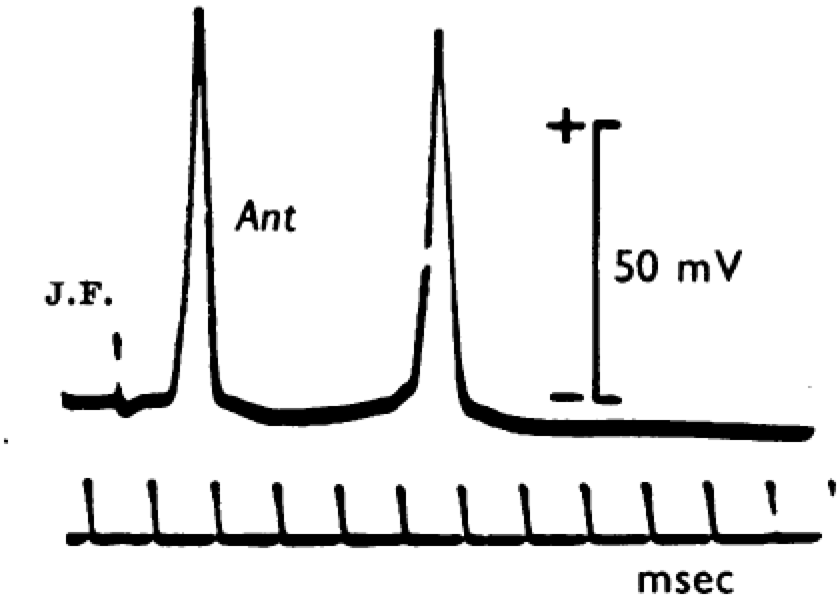
Fluorescent Dye

Double Recording of Purkinje Cell in Slice

Hausser M.

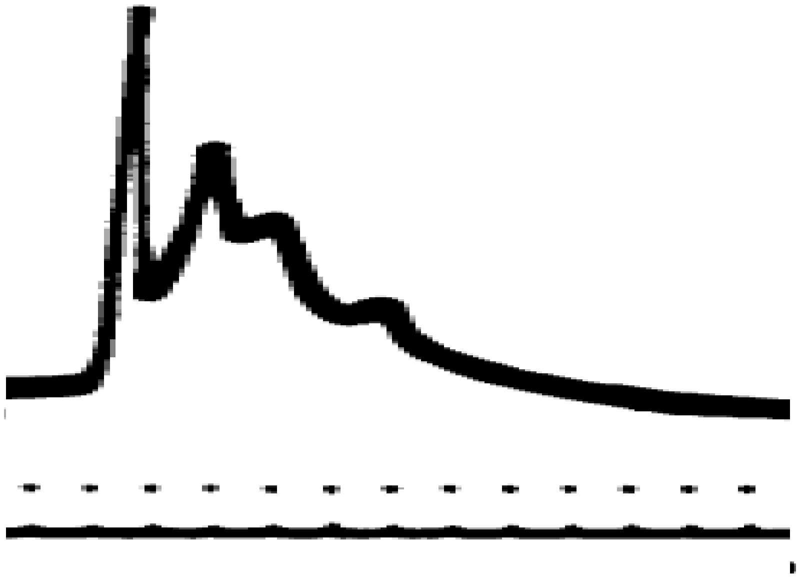
Purkinje Cells exhibit Two distinct Spike Types

Simple Spike



Mossy Fiber Stimulation

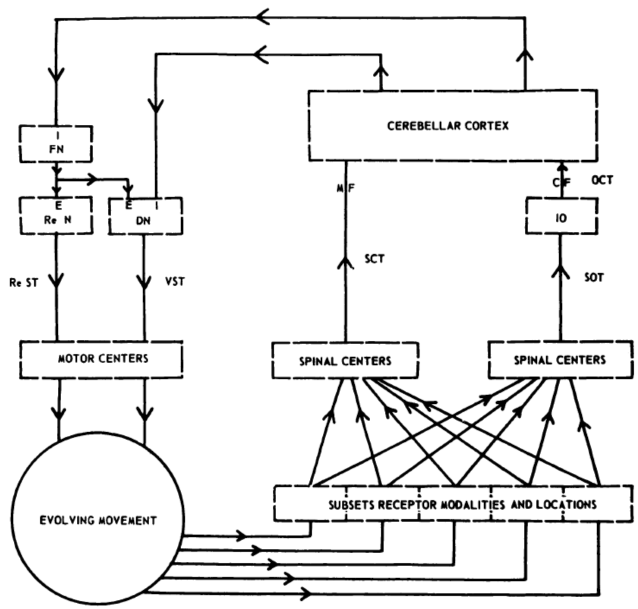
Complex Spike



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)

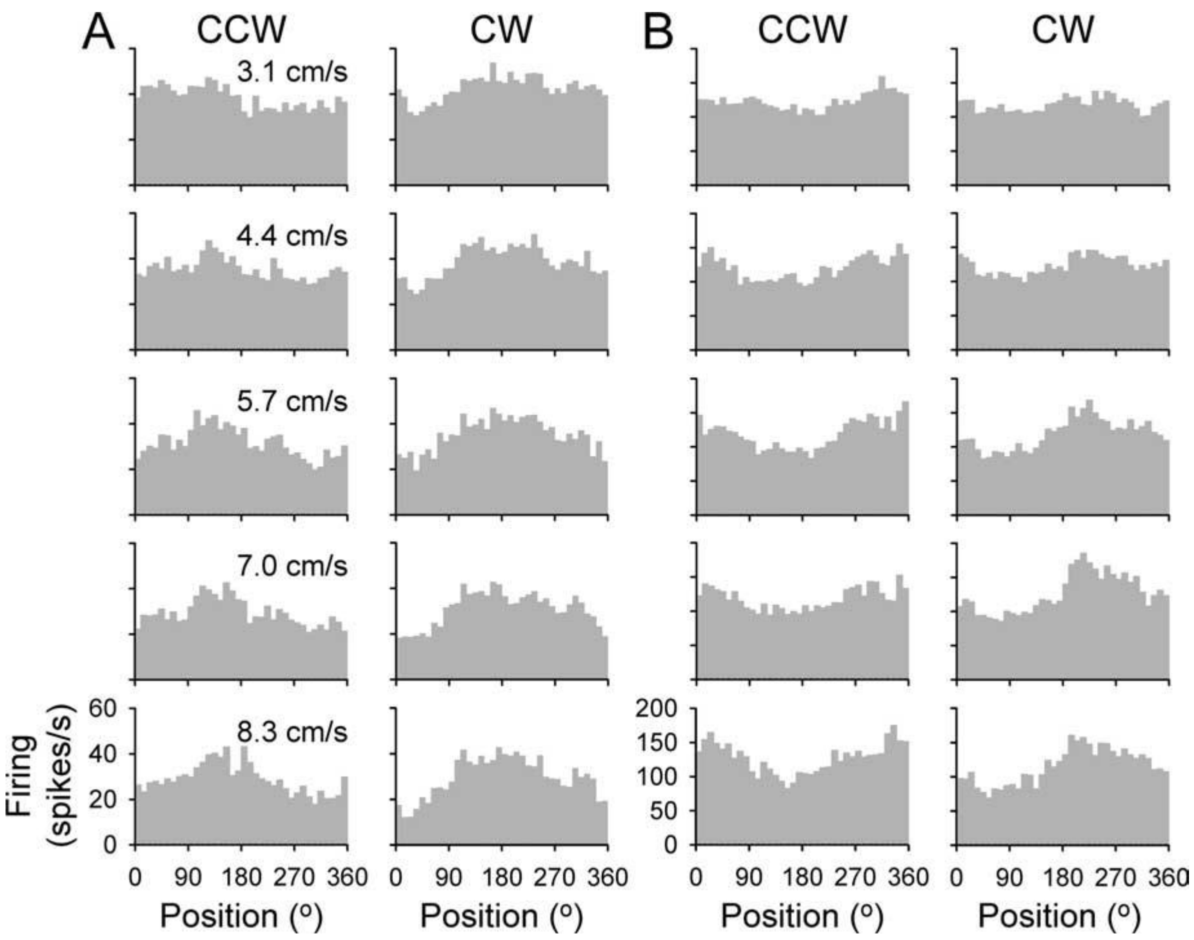
MATHEMATICAL BIOSCIENCES

A Theory of Cerebellar Function

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

1971

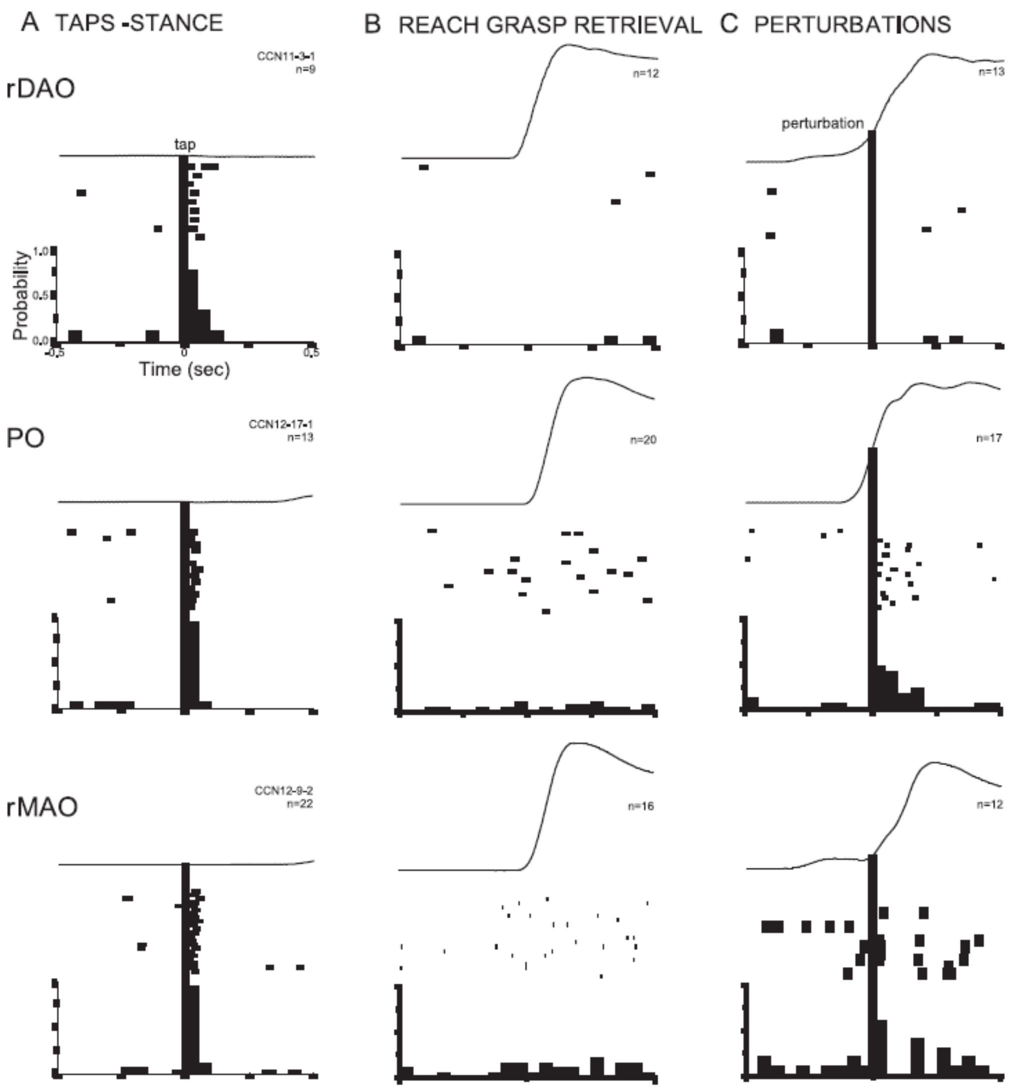
Simple Spikes are Modulated by Inputs



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

Roitman 2005

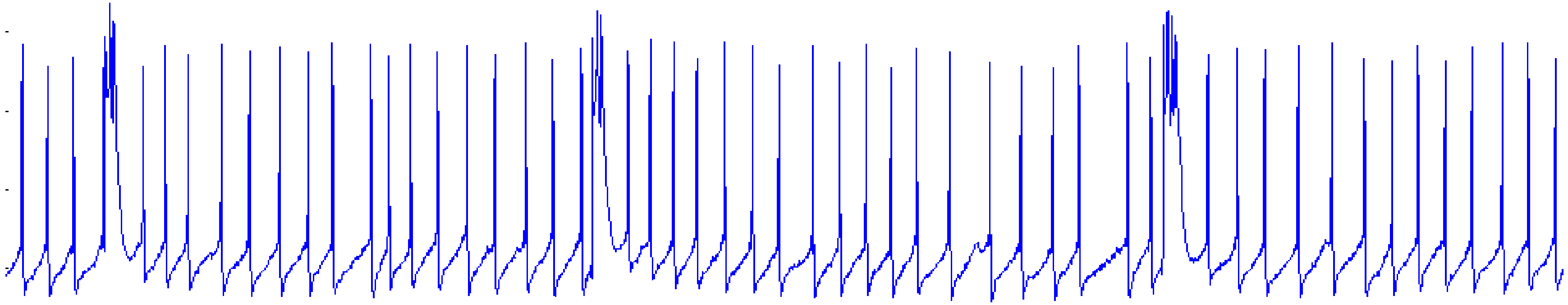
Olivary Spikes are fired in Unexpected Events



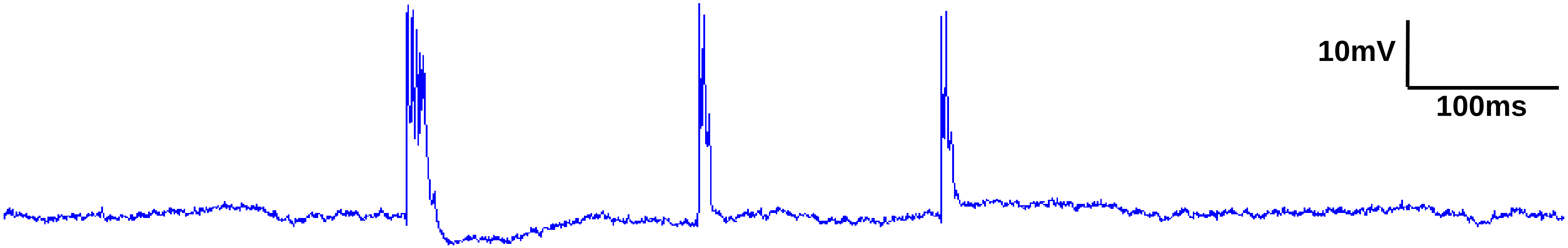
Horn, Pong & Gibson 2002

Distinct Firing Regimes of Purkinje Cells

Complex Spikes & Simple Spikes (Up-State)



Complex Spikes Only (Down-State)

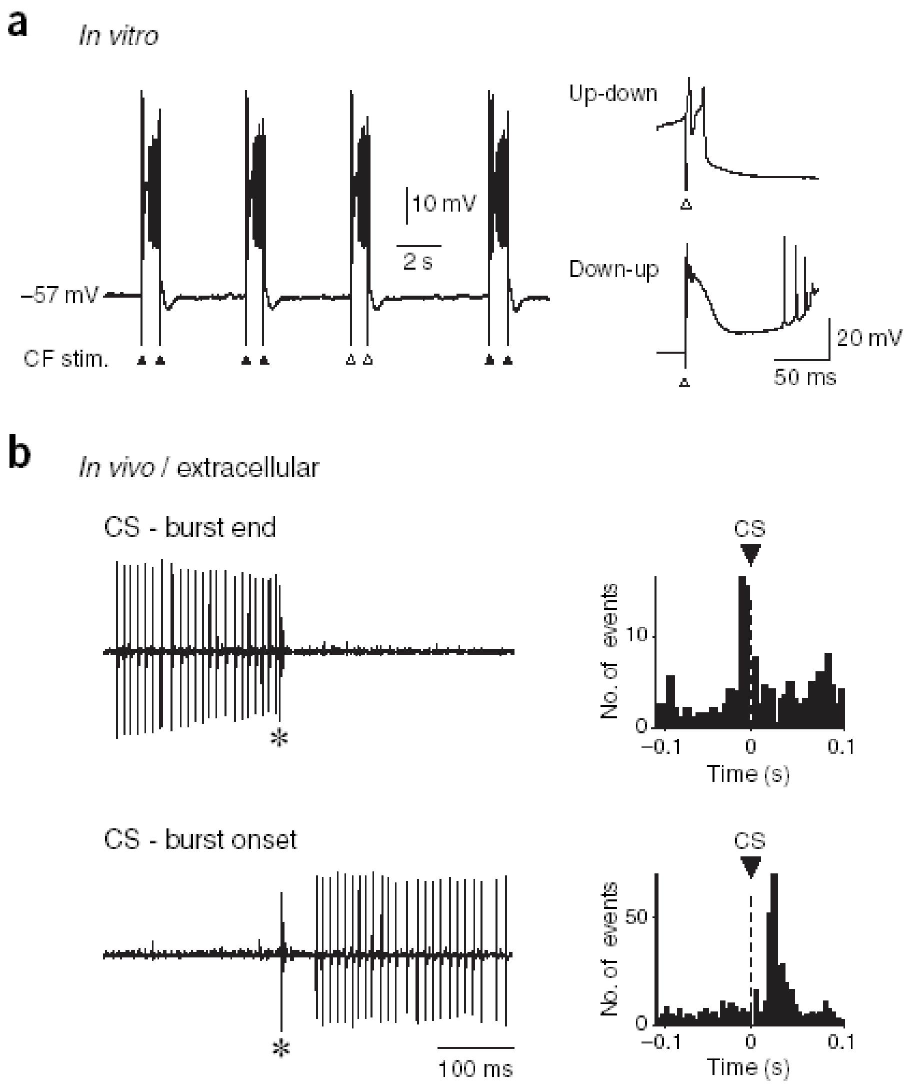


Simple Spikes: 0 - ~80Hz
(Mostly 0Hz or 4-8Hz or 20-80Hz, with possible phasic >100Hz)

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

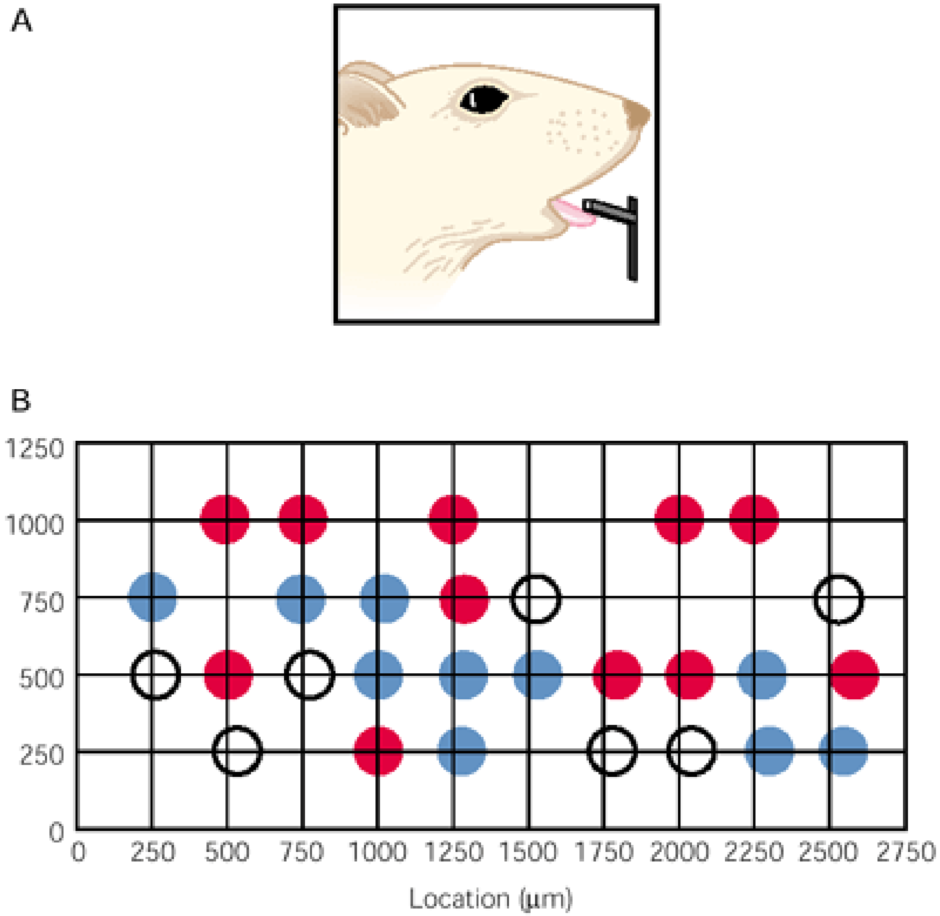
Cohen and Lamp (unpublished)

Complex Spikes as Purkinje Cell Switches



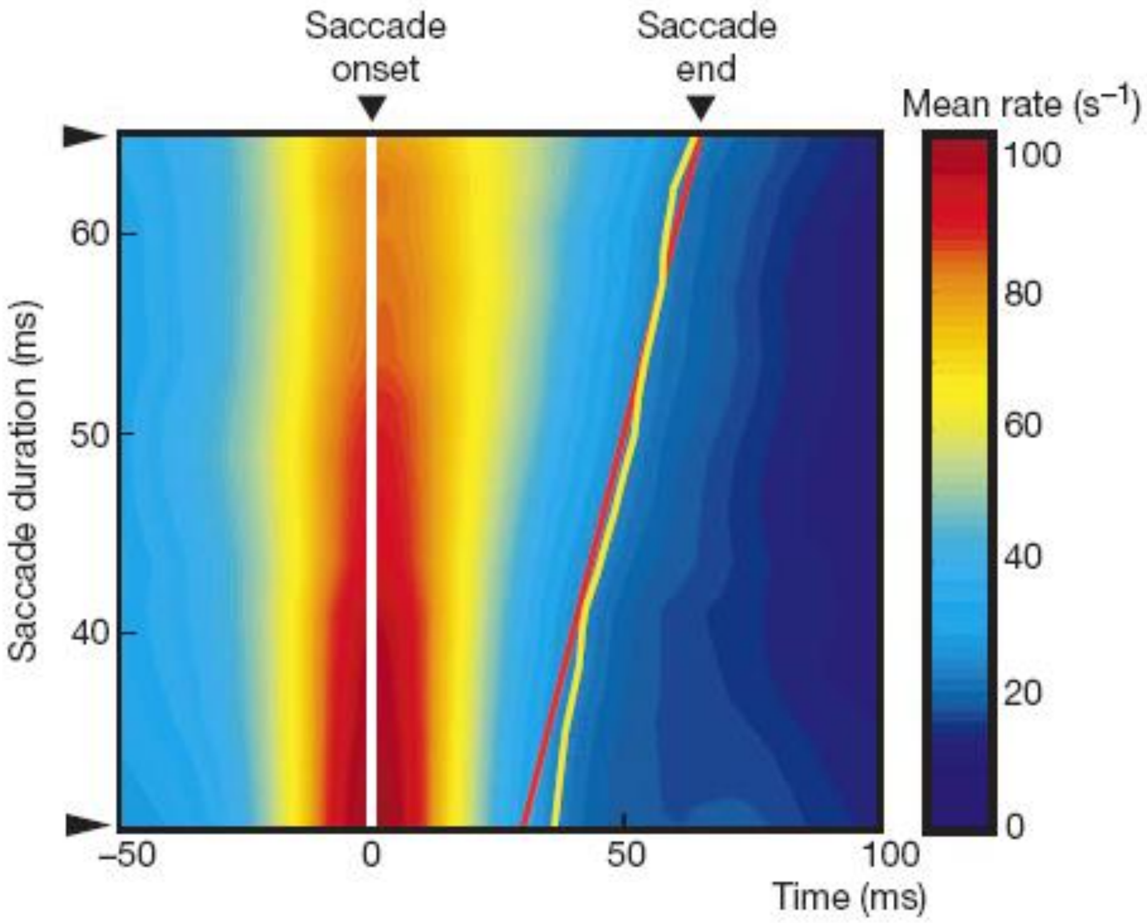
Loewenstein et al. NatNS 2005

Synchronous Population Coding by Purkinje Cells



Welsh 1995

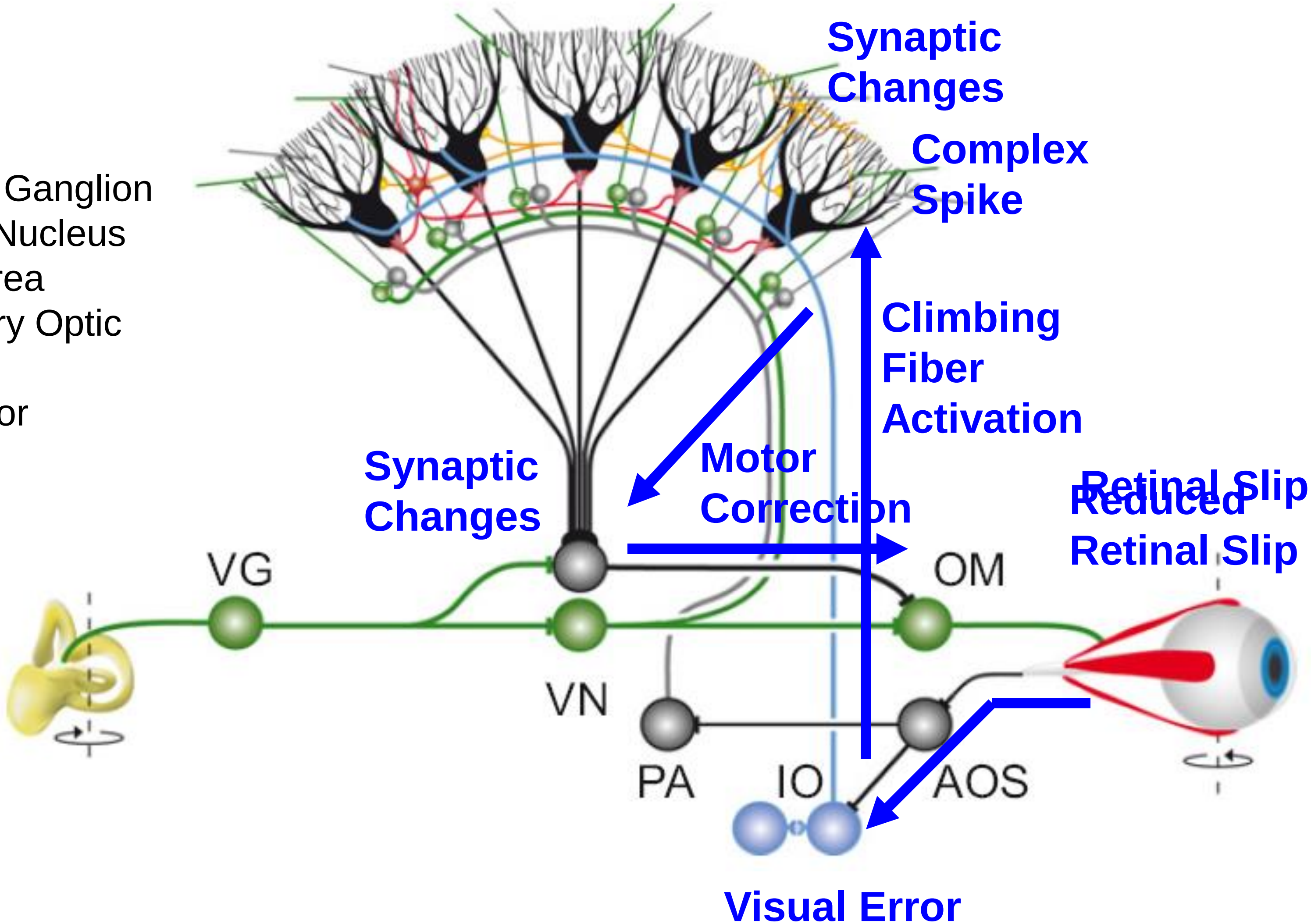
Saccade attributes are encoded by a population of ~100 Purkinje cells



Tier-Barash 2000

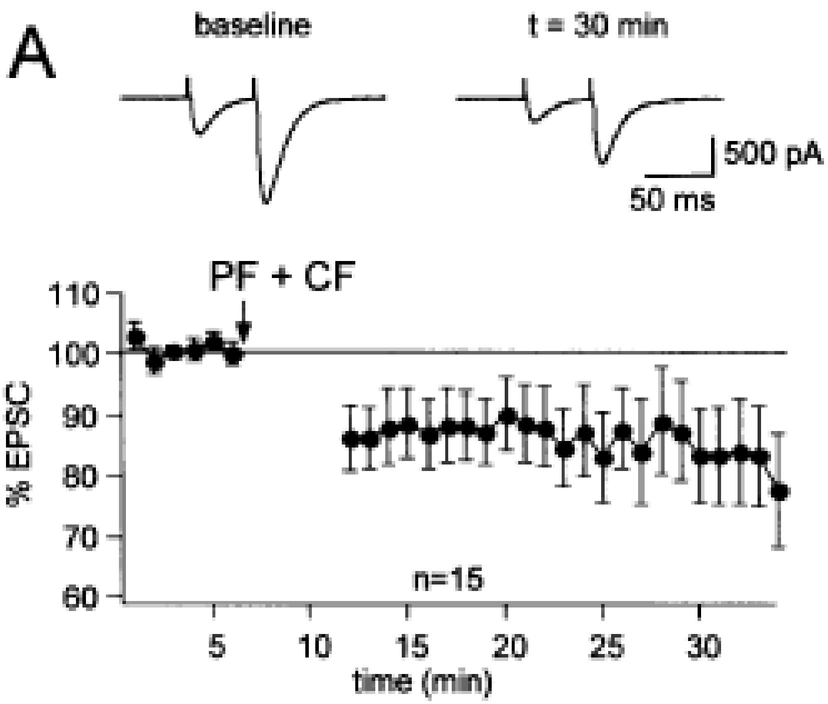
Vestibulo - Ocular Adaptation (VOR)

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



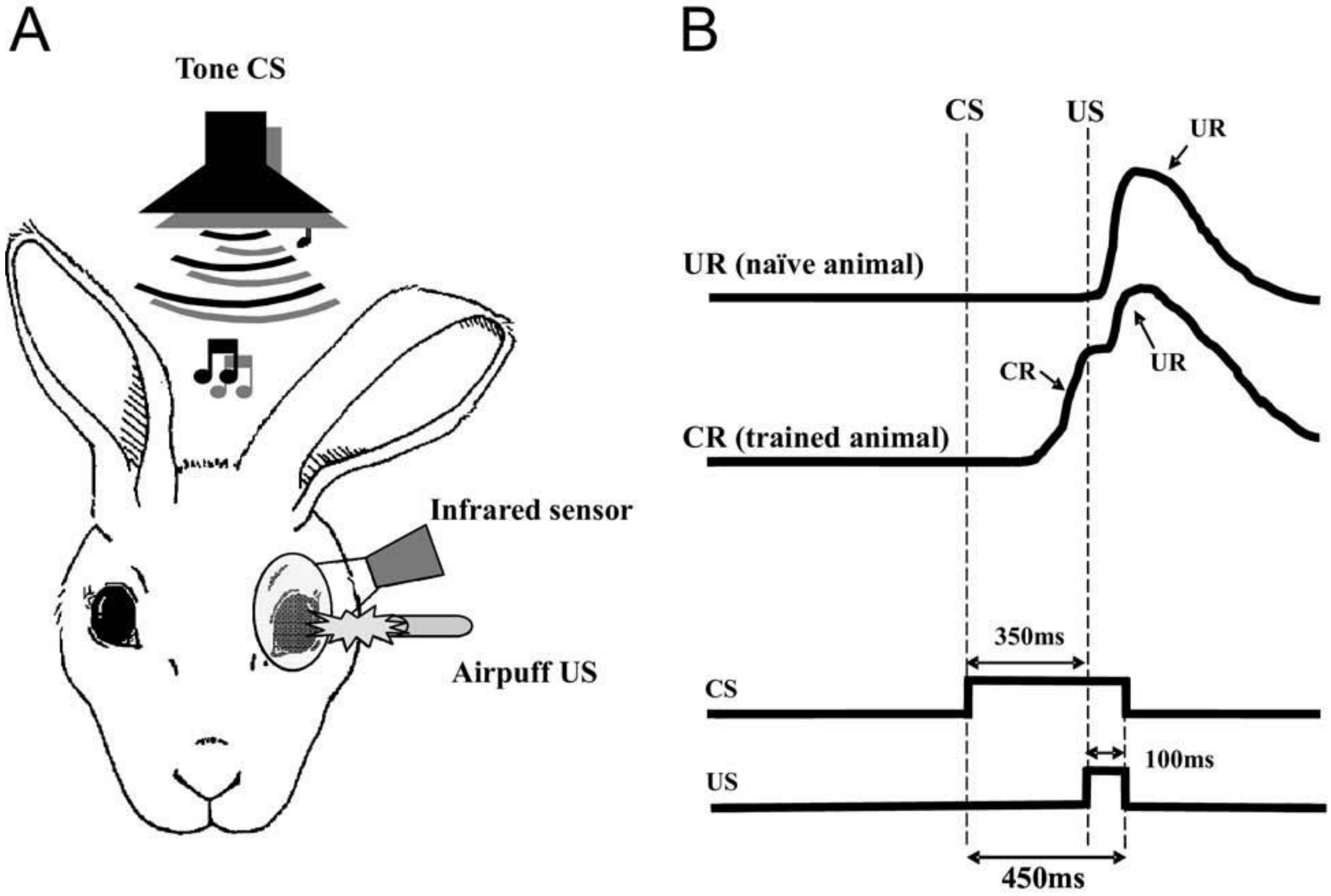
Ito 1984, Schonville et al. 2010

Plasticity in the Cerebellar Cortex



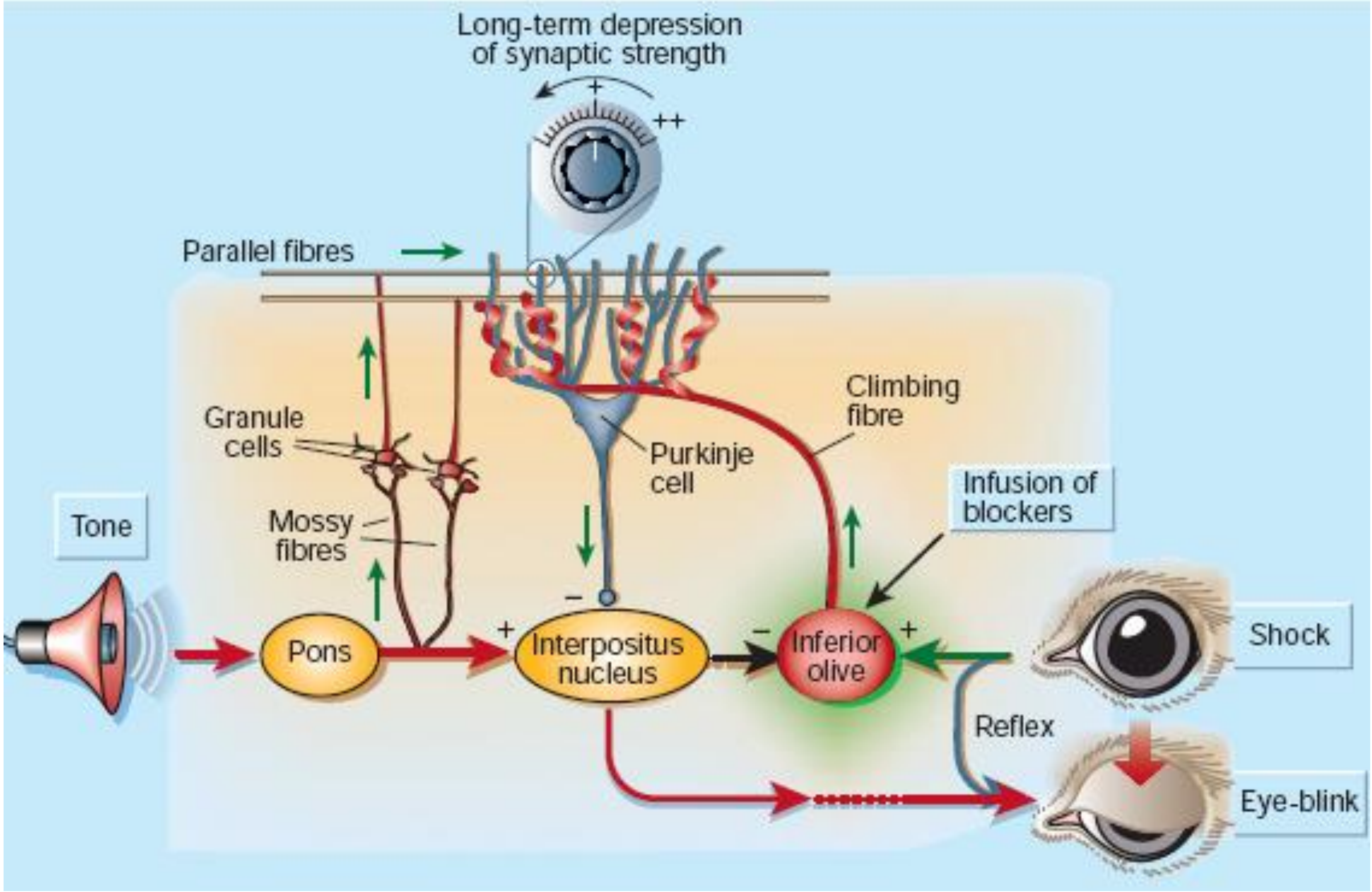
Coesmans et al. Neuron 2004

Eyelid Reflex Conditioning



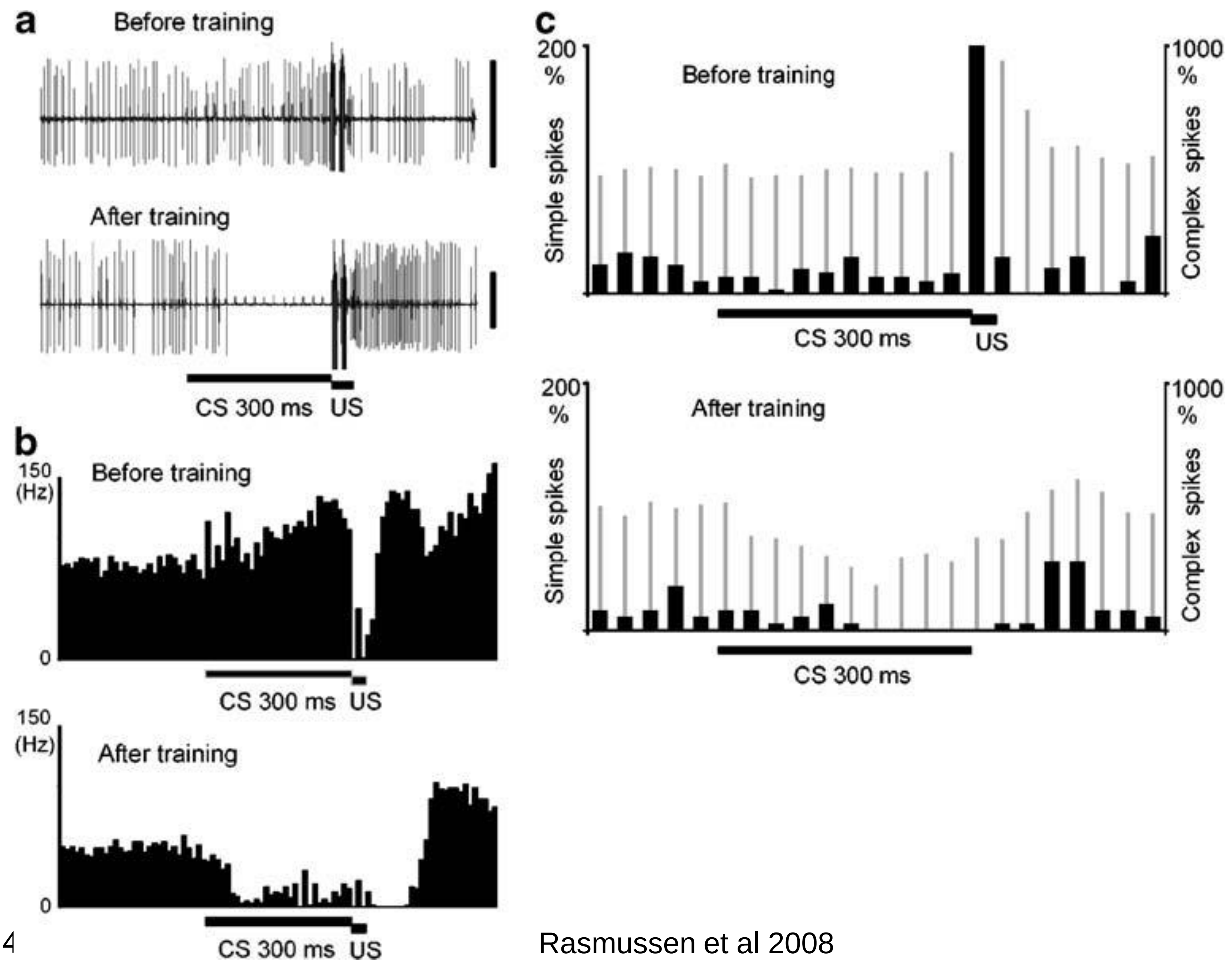
Bracha and Bloedel 2009

Eyelid Reflex Conditioning



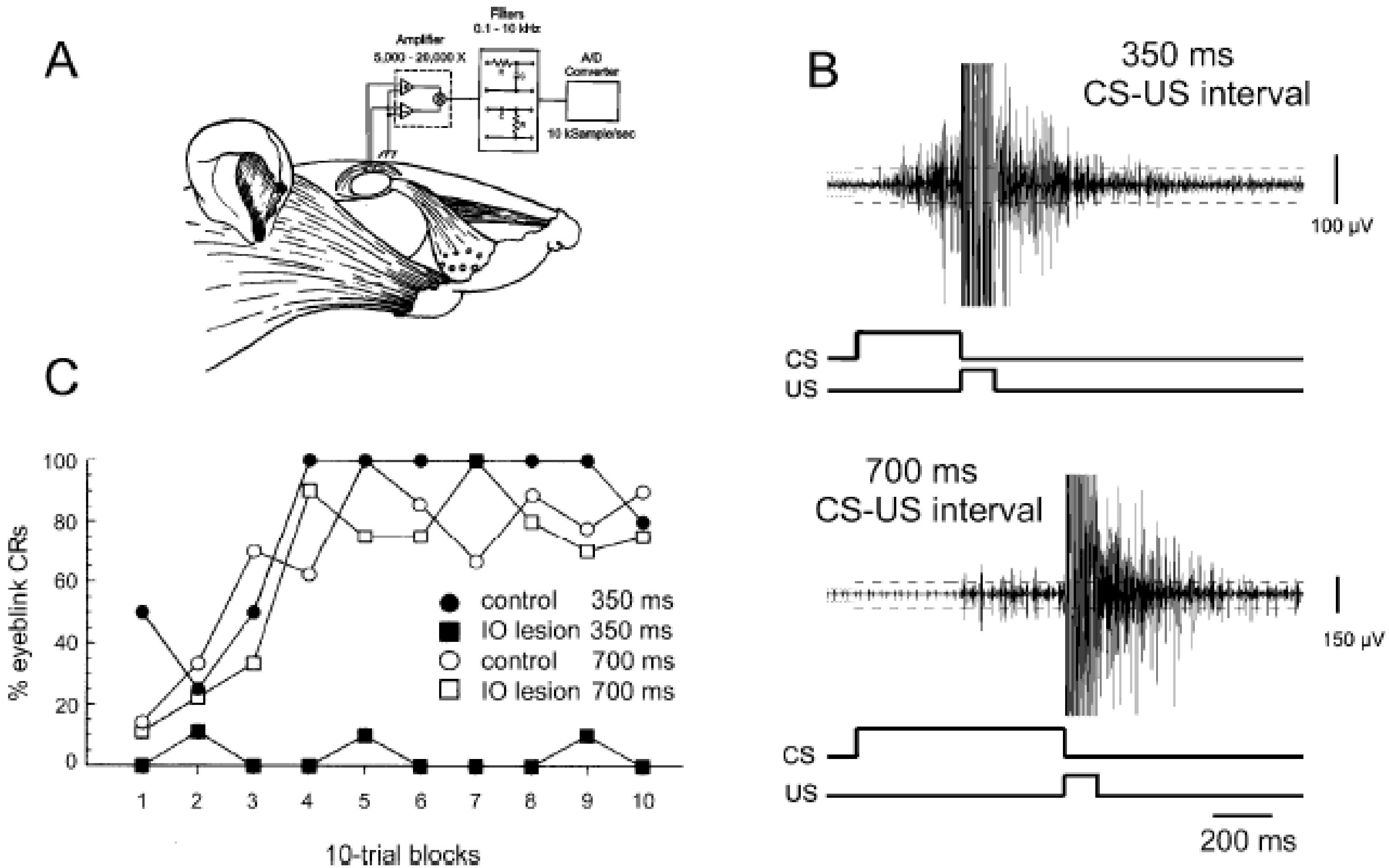
Medina et al. Nature 2002

Eyelid Reflex Conditioning



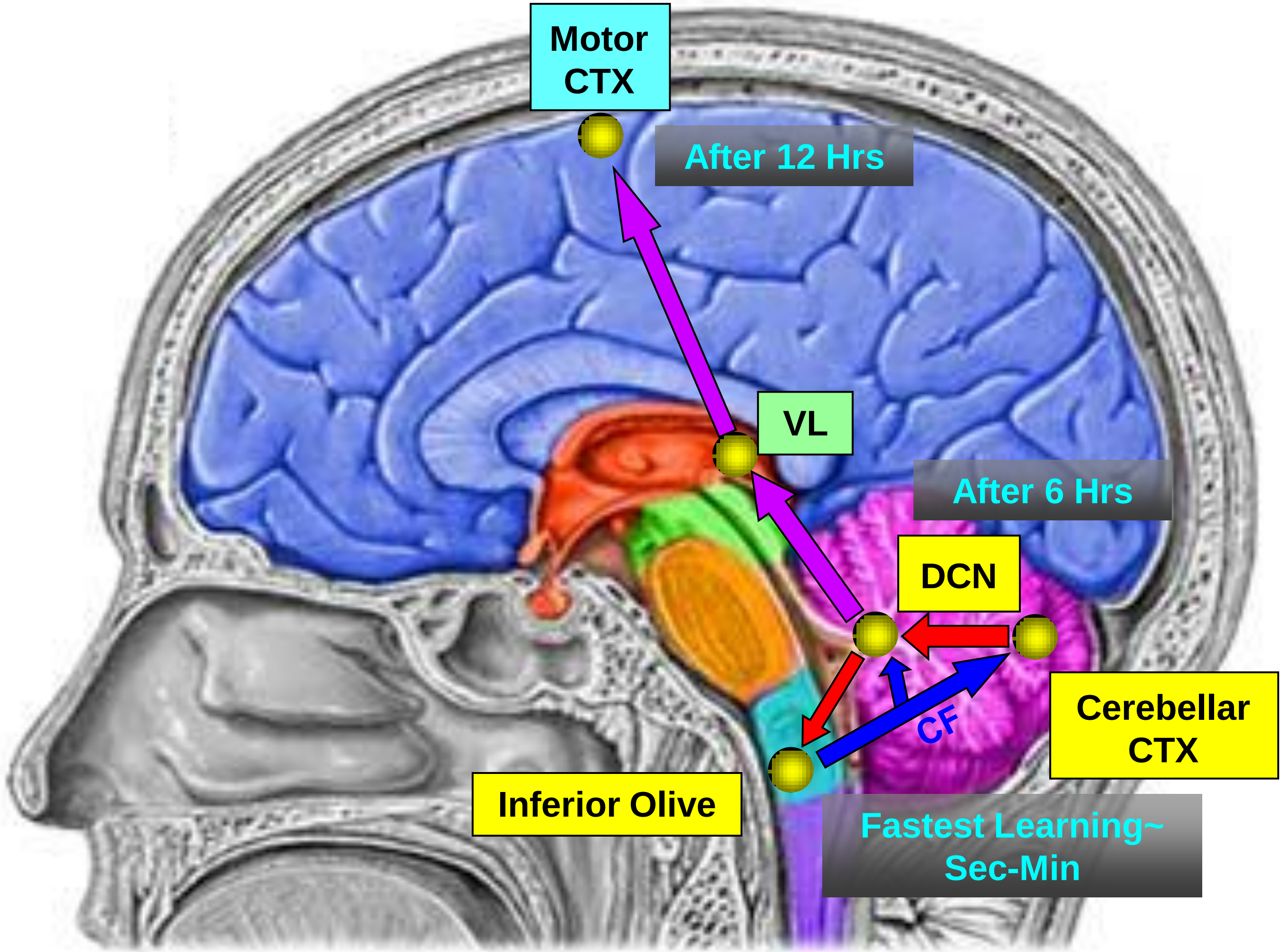
Rasmussen et al 2008

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



Welsh 2002

The Learning Transfer Hypothesis



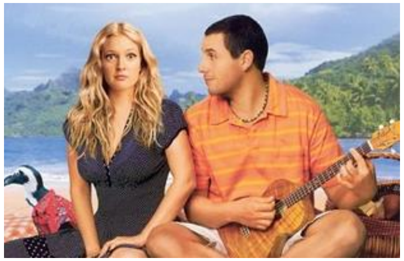
VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
CTX = Cortex
CF = Climbing Fibers

What about the “Non-Classical” symptoms?



- All physiological results so far:
  - in animals
  - related to motor function
  - or coordination
  - or timing
- Can timing be also related to higher cognitive functions?
- Is there evidence from human real-time physiology?
- Are there specific areas in the cerebellum which relate to cognitive functions?

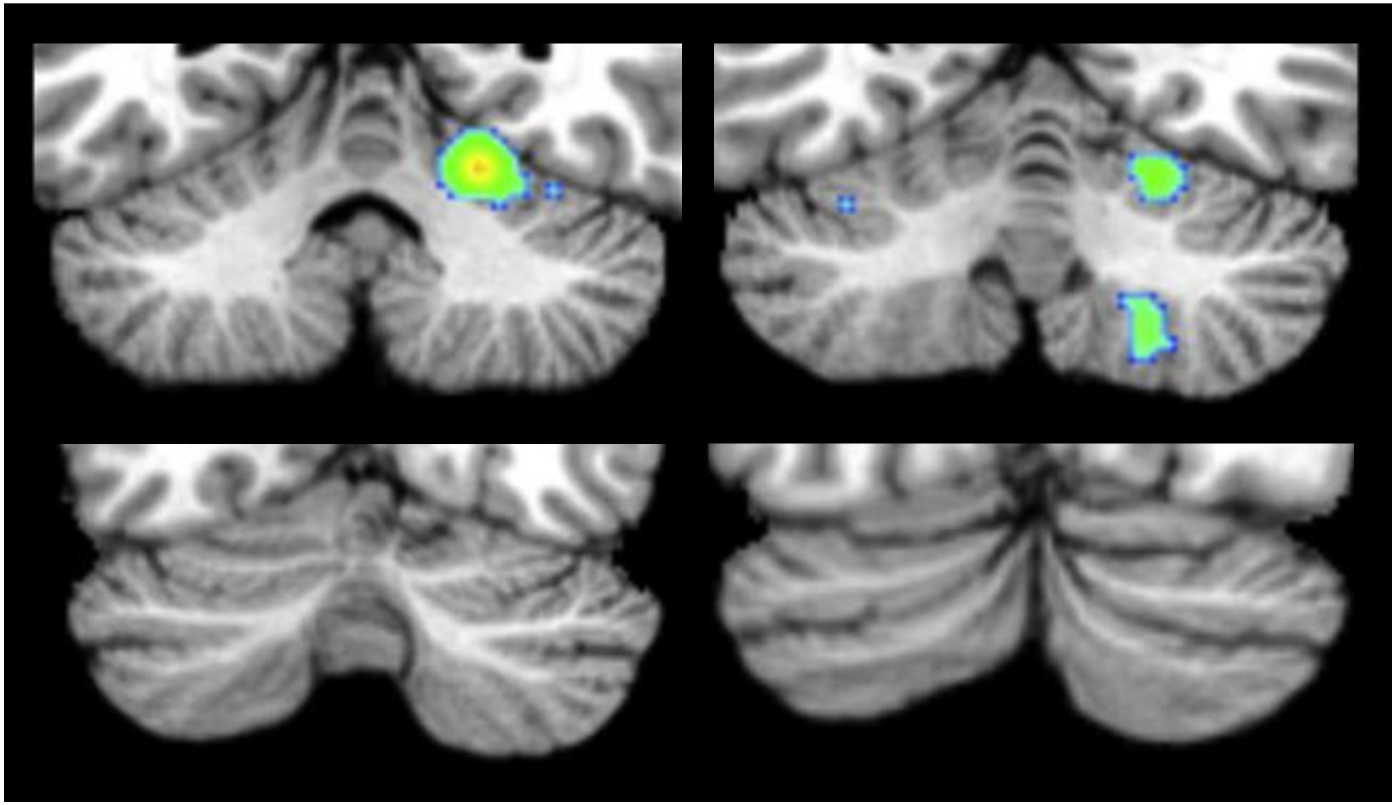
Specific cerebellar regions with cognitive dysfunction following focal damage


Cognitive effects of focal damage were found when:

1. The damage involved the vermis
2. The damage was in an areas which get blood supply from the posterior inferior cerebellar artery
3. Children with Vermal damage show autistic-like features:
    - Irritability
    - impulsivity
    - Disinhibition
    - Emotional lability
4. Complex verbal dysfunction associated with right cerebellar damage
5. Dysprosodia (pronunciation fault): associated with left cerebellar damage

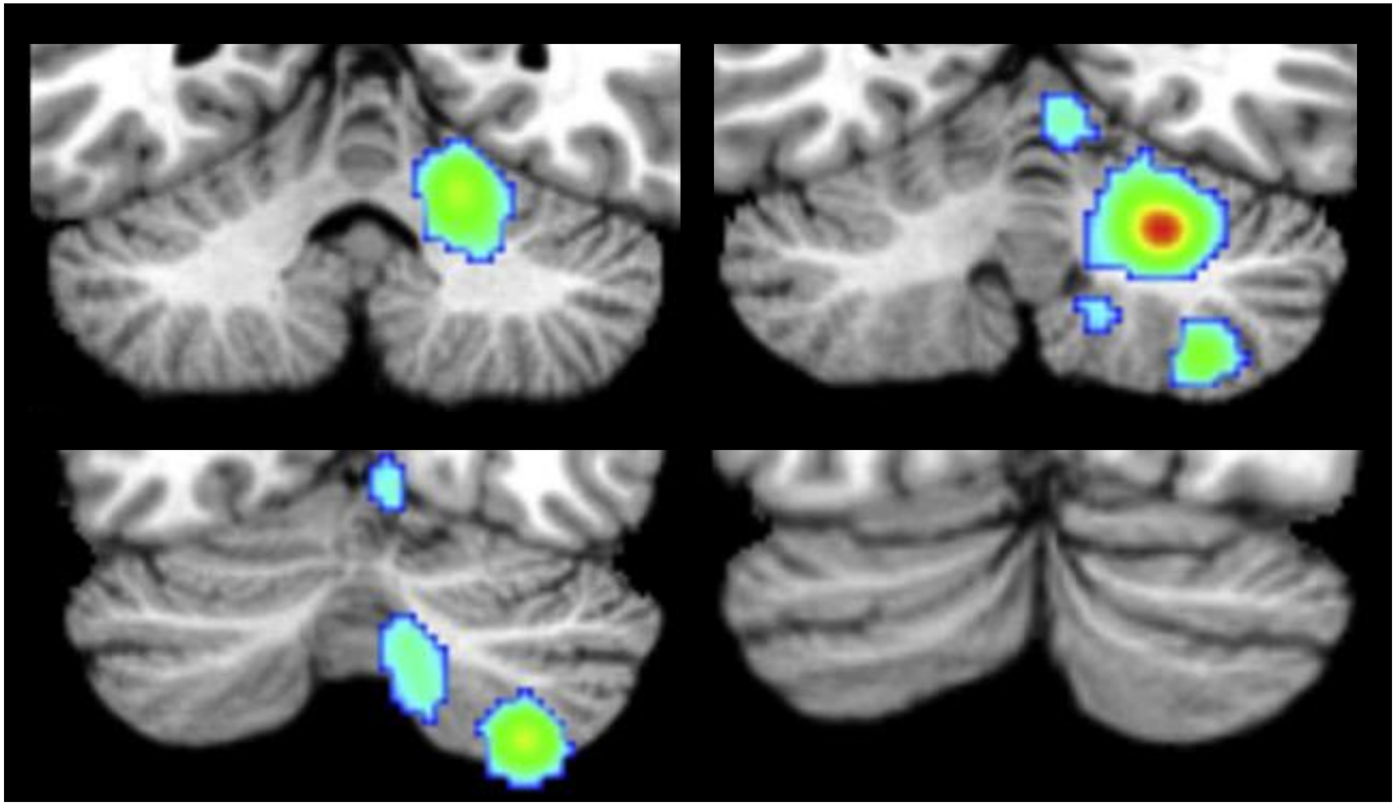
FMRI Mapping pf Cerebellar Involvement in Various Processes



Somatosensory Processing

Stoodley and Schmahmann 2009

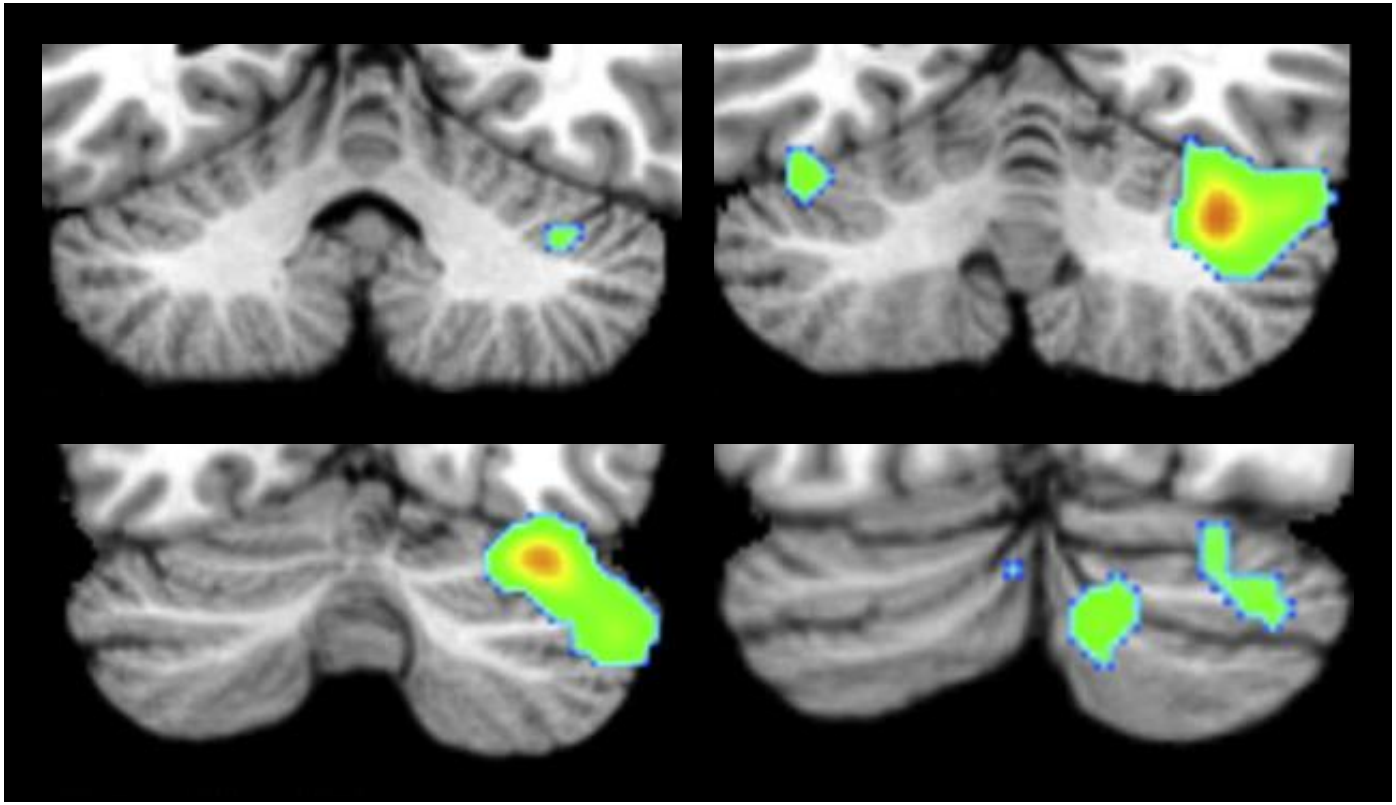
FMRI Mapping pf Cerebellar Involvement in Various Processes



Motor Processing

Stoodley and Schmahmann 2009

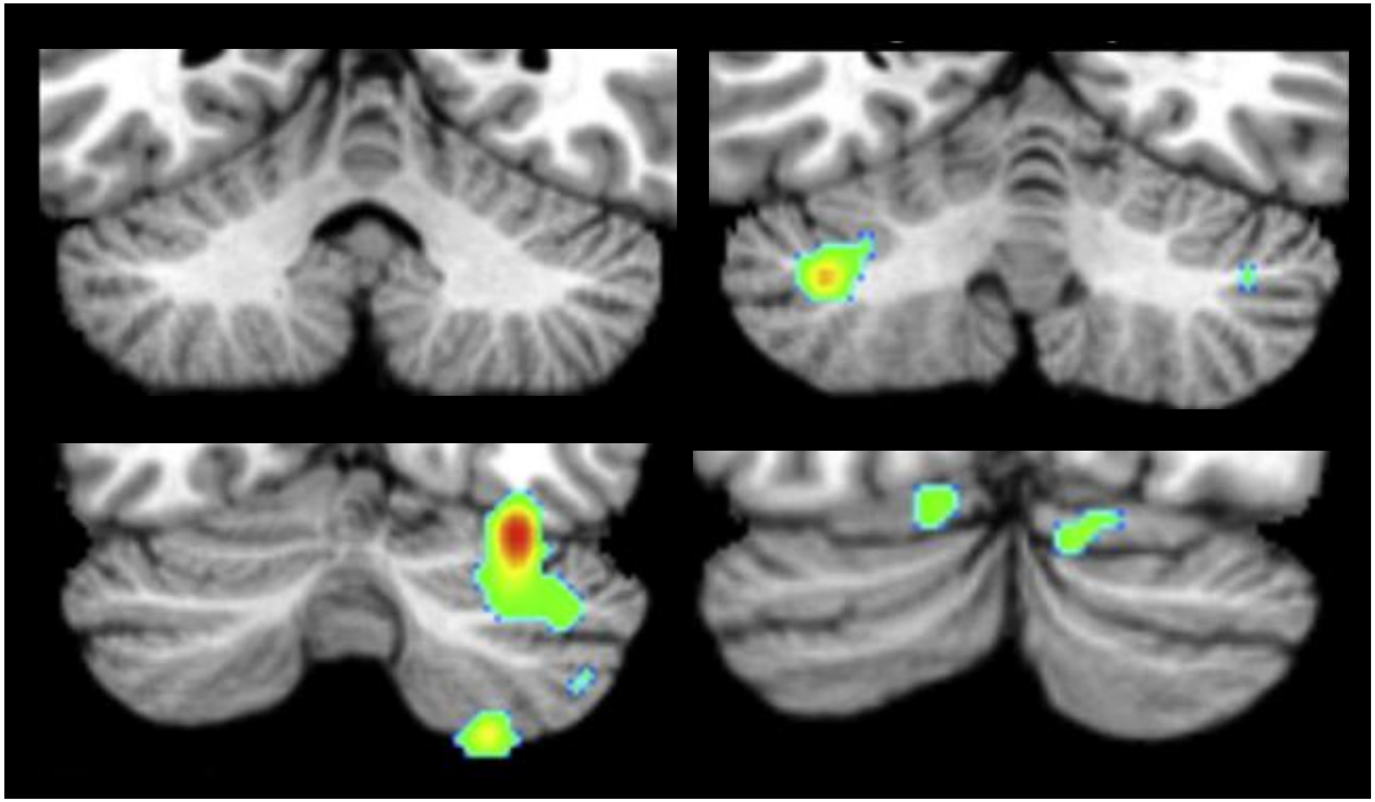
FMRI Mapping pf Cerebellar Involvement in Various Processes



Language Processing

Stoodley and Schmahmann 2009

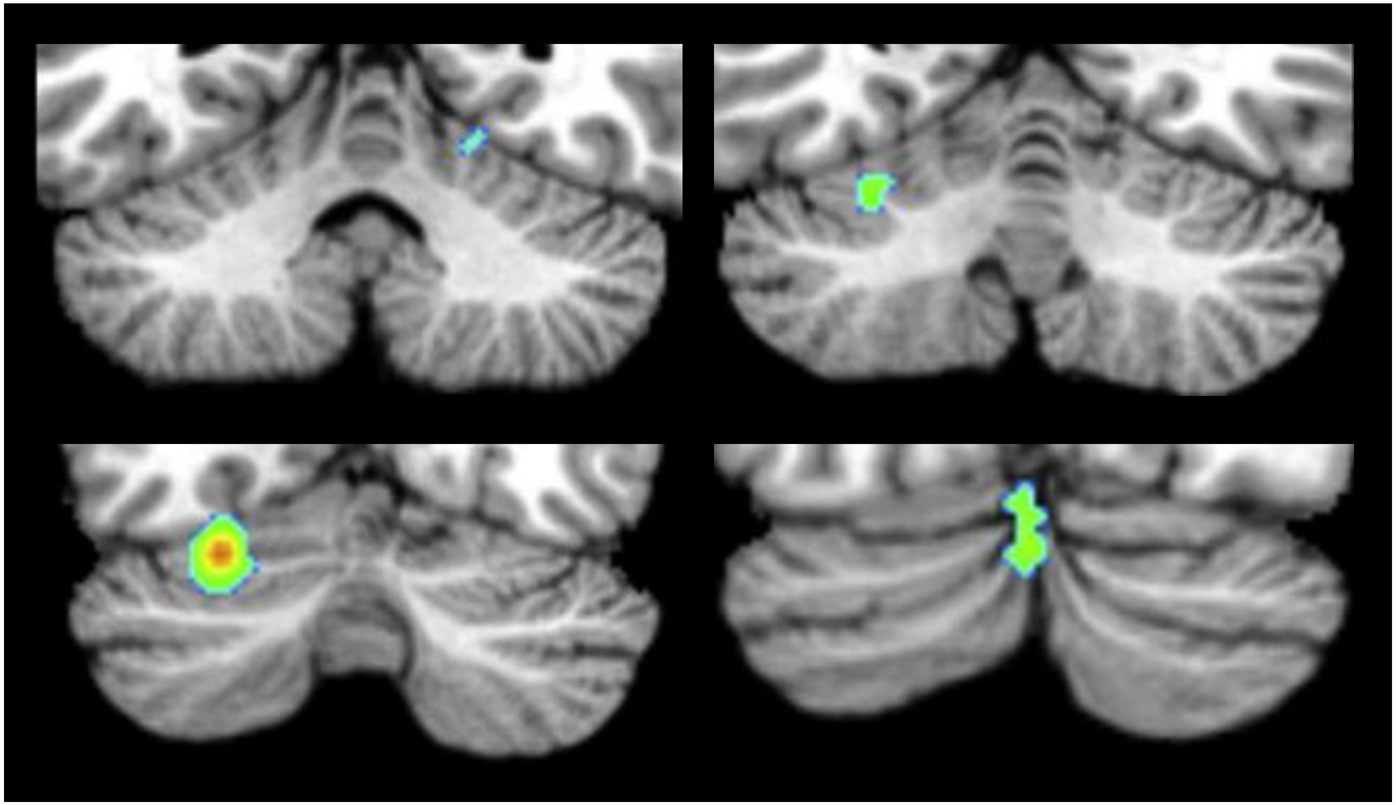
FMRI Mapping pf Cerebellar Involvement in Various Processes



Working Memory

Stoodley and Schmahmann 2009

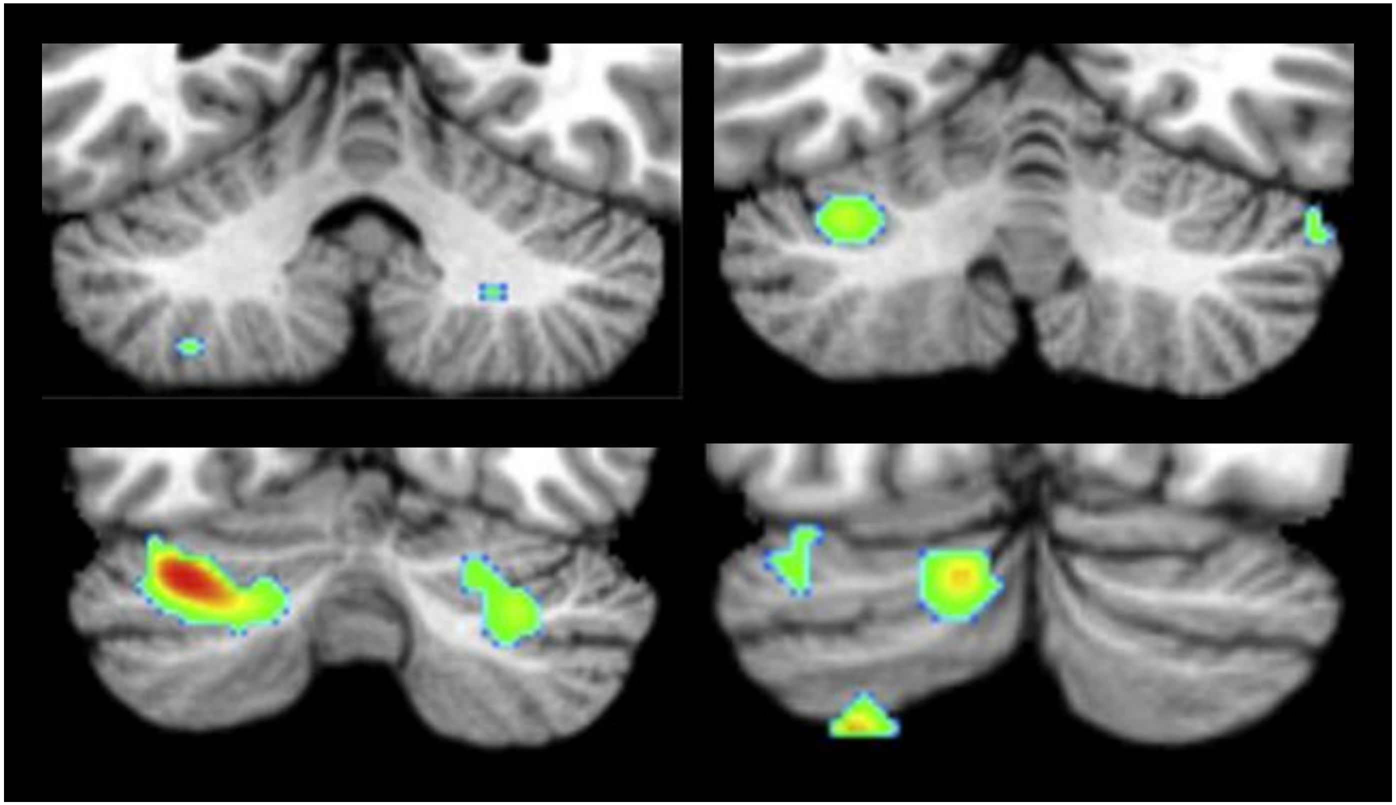
FMRI Mapping pf Cerebellar Involvement in Various Processes



Spatial Processing

Stoodley and Schmahmann 2009

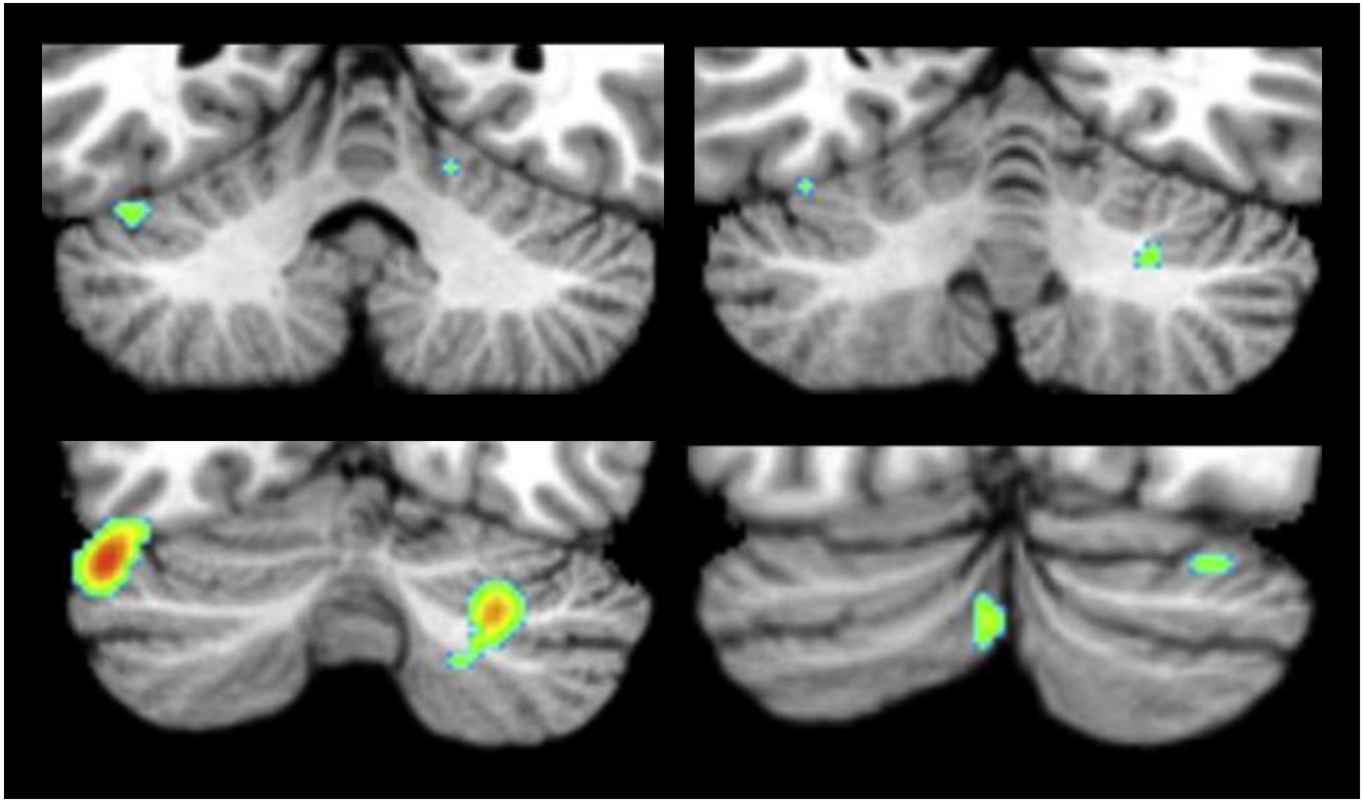
FMRI Mapping pf Cerebellar Involvement in Various Processes



Executive Processing

Stoodley and Schmahmann 2009

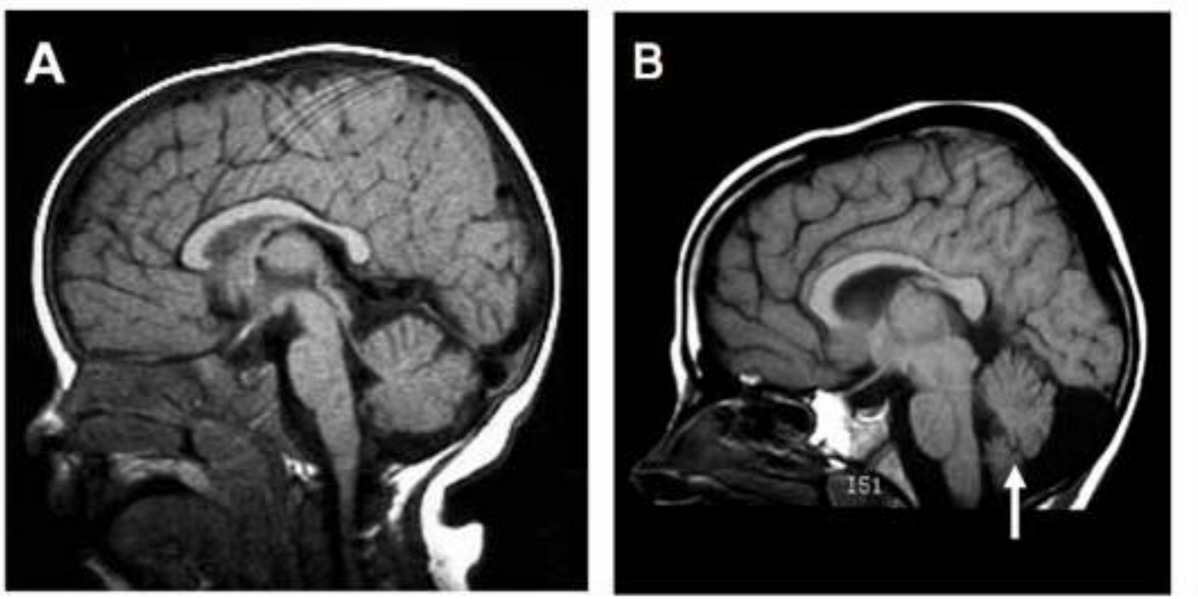
FMRI Mapping pf Cerebellar Involvement in Various Processes



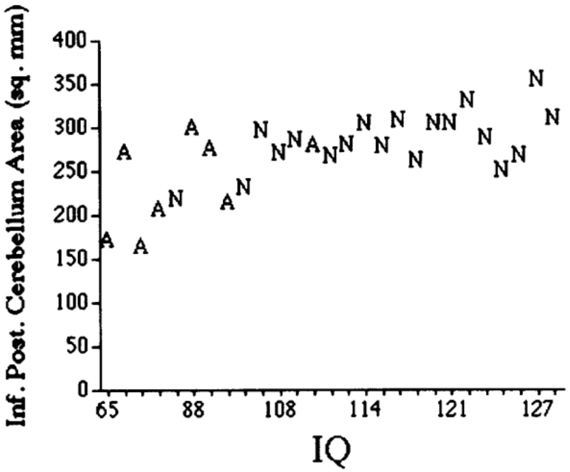
Emotional Processing

Stoodley and Schmahmann 2009

Cerebellar Involvement in Autism

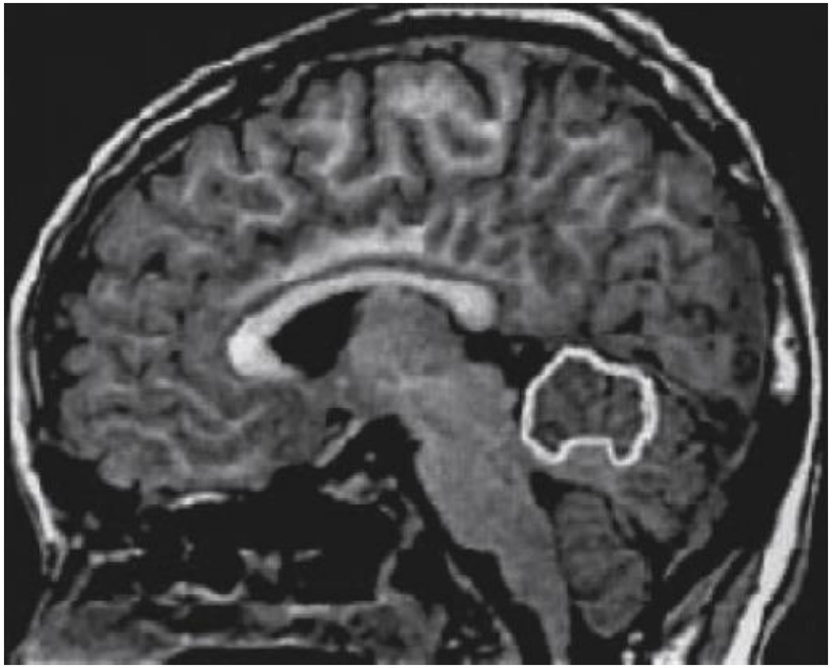


Control Subject Autistic Subject

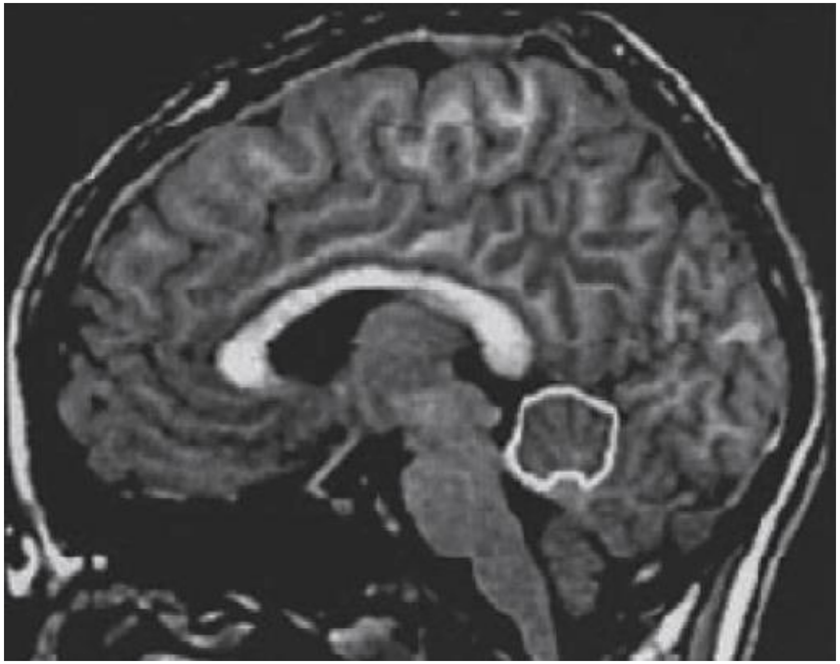


Levitt J. 1999

Cerebellar Involvement in Dyslexia

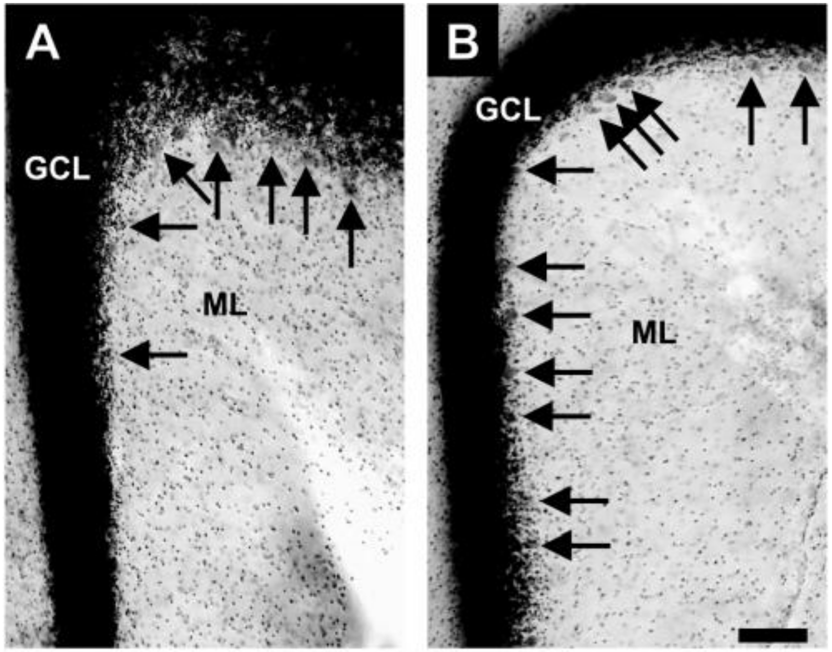


Control Subject



Dyslexic Subject

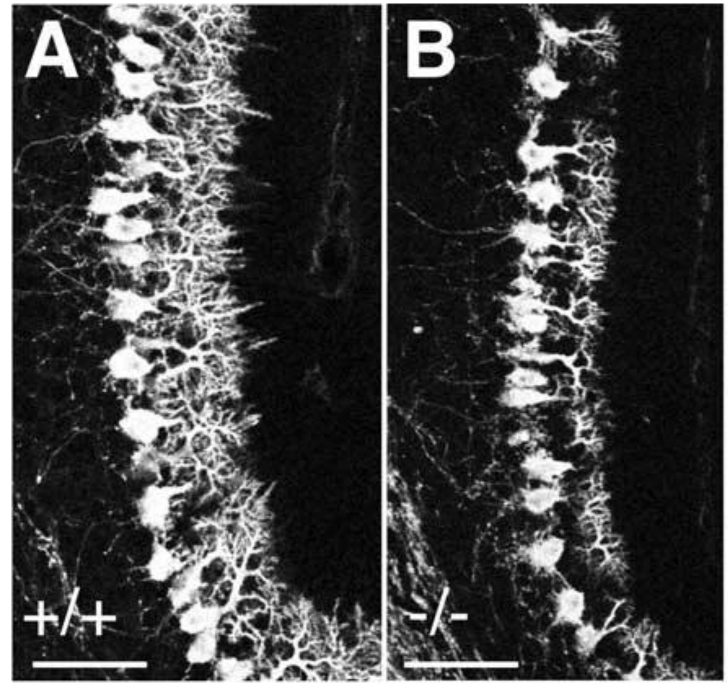
Autism candidate genes affects the Cerebellum



Autistic Control

Lose of Purkinje Cells in Autistic

Saskia 2004



Control CASP2 -/-

Developmental Problems in KO mice

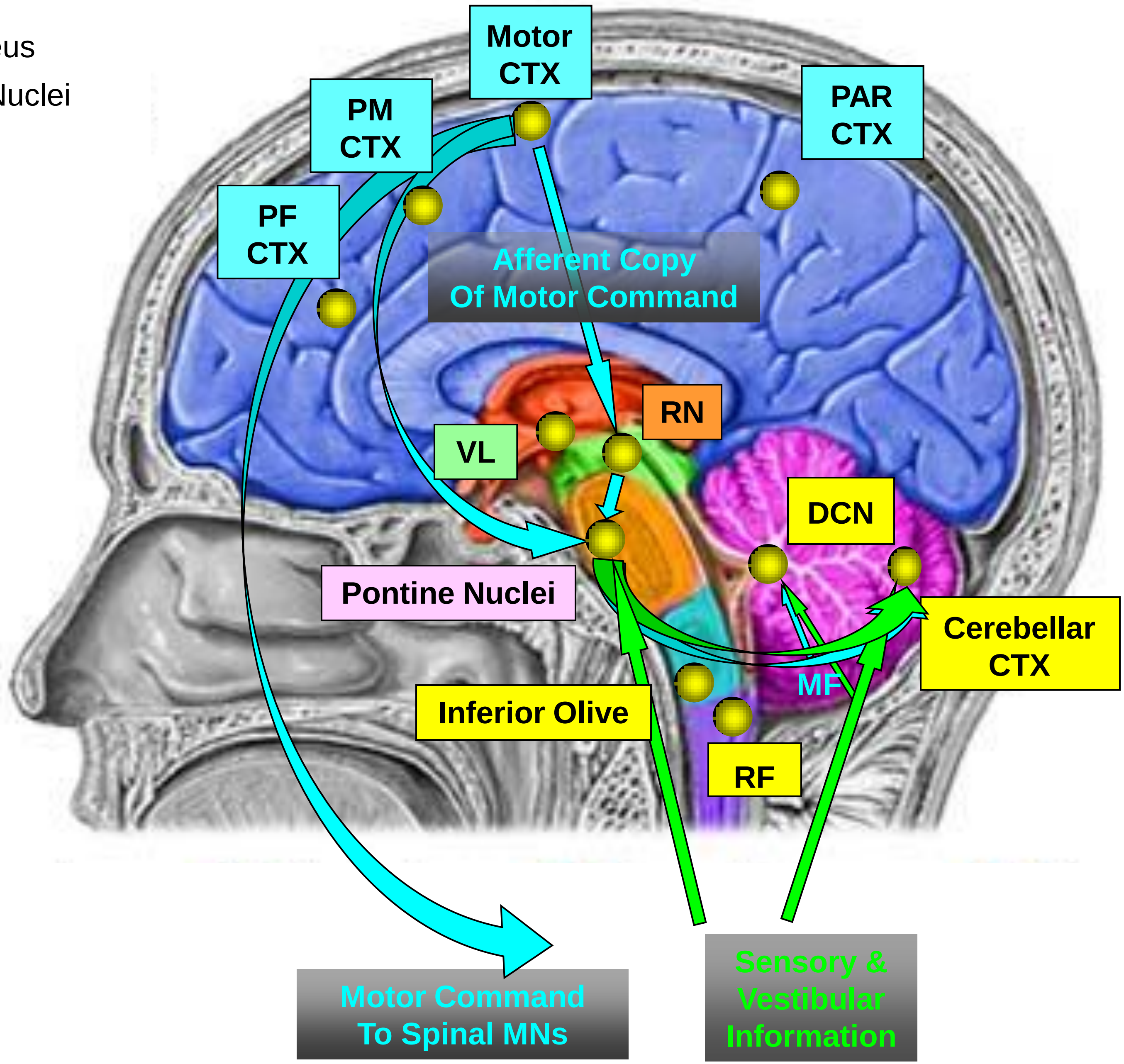
Sadakata 2007

Olivocerebellar Information flow : Mossy Fibers Inputs

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

CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers



Olivocerebellar Information flow : Climbing Fibers Inputs

VL = Ventro-Lateral Nucleus
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RN = Red Nucleus
 (+ mid brain nuclei)

CTX = Cortex

MF = Mossy Fibers
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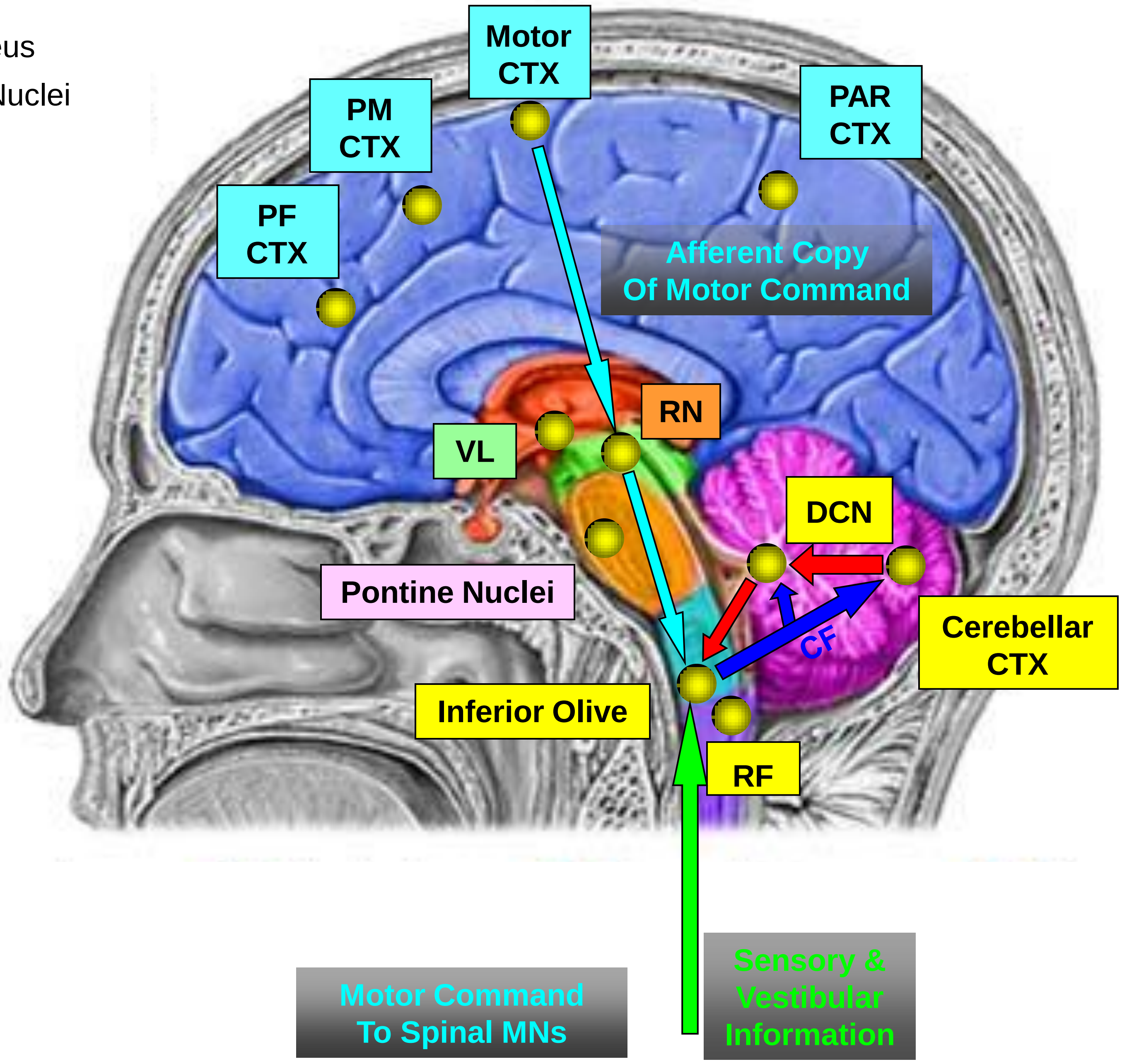

Hypothesized information flow during Cerebellar function

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

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MF = Mossy Fibers
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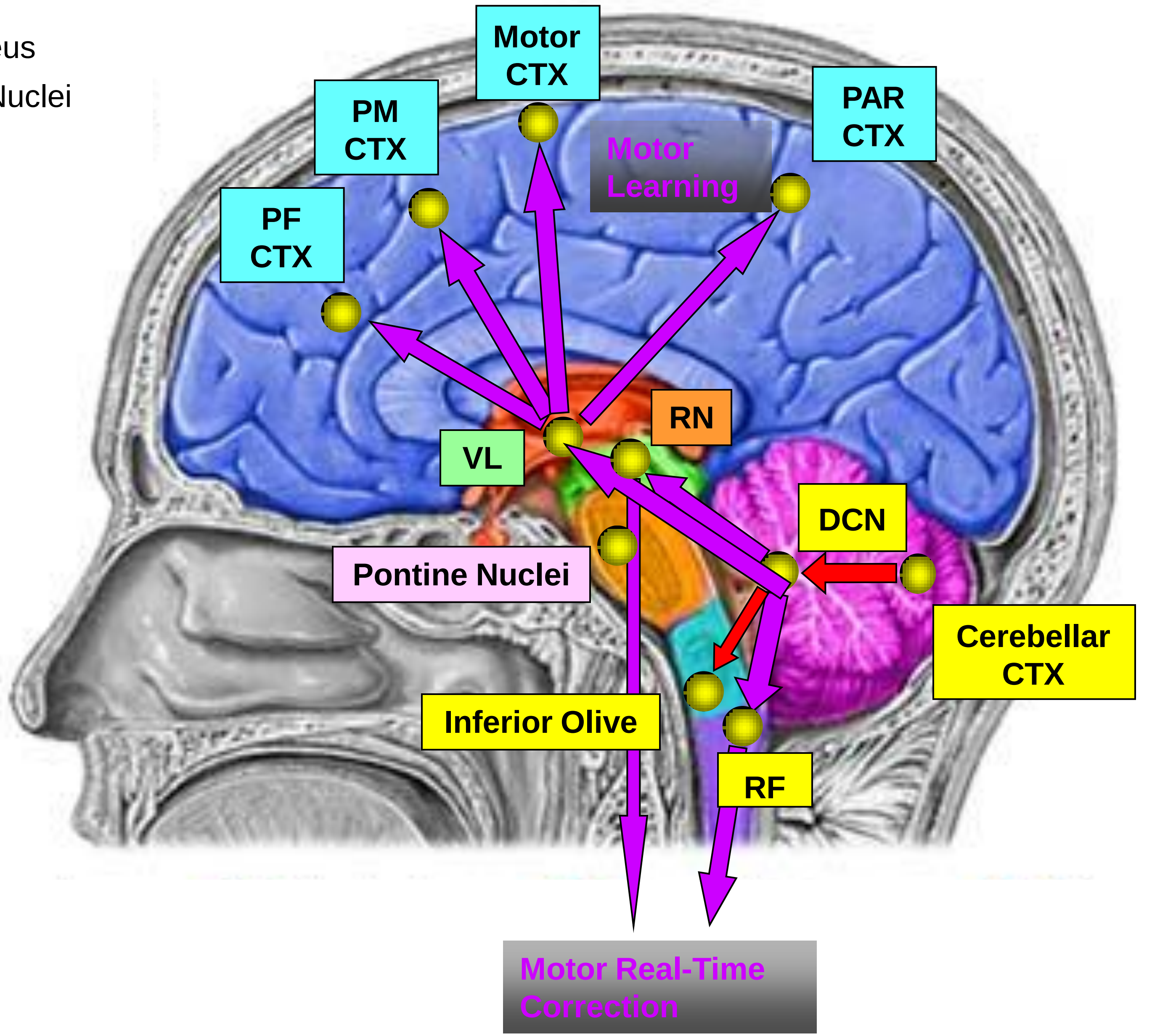
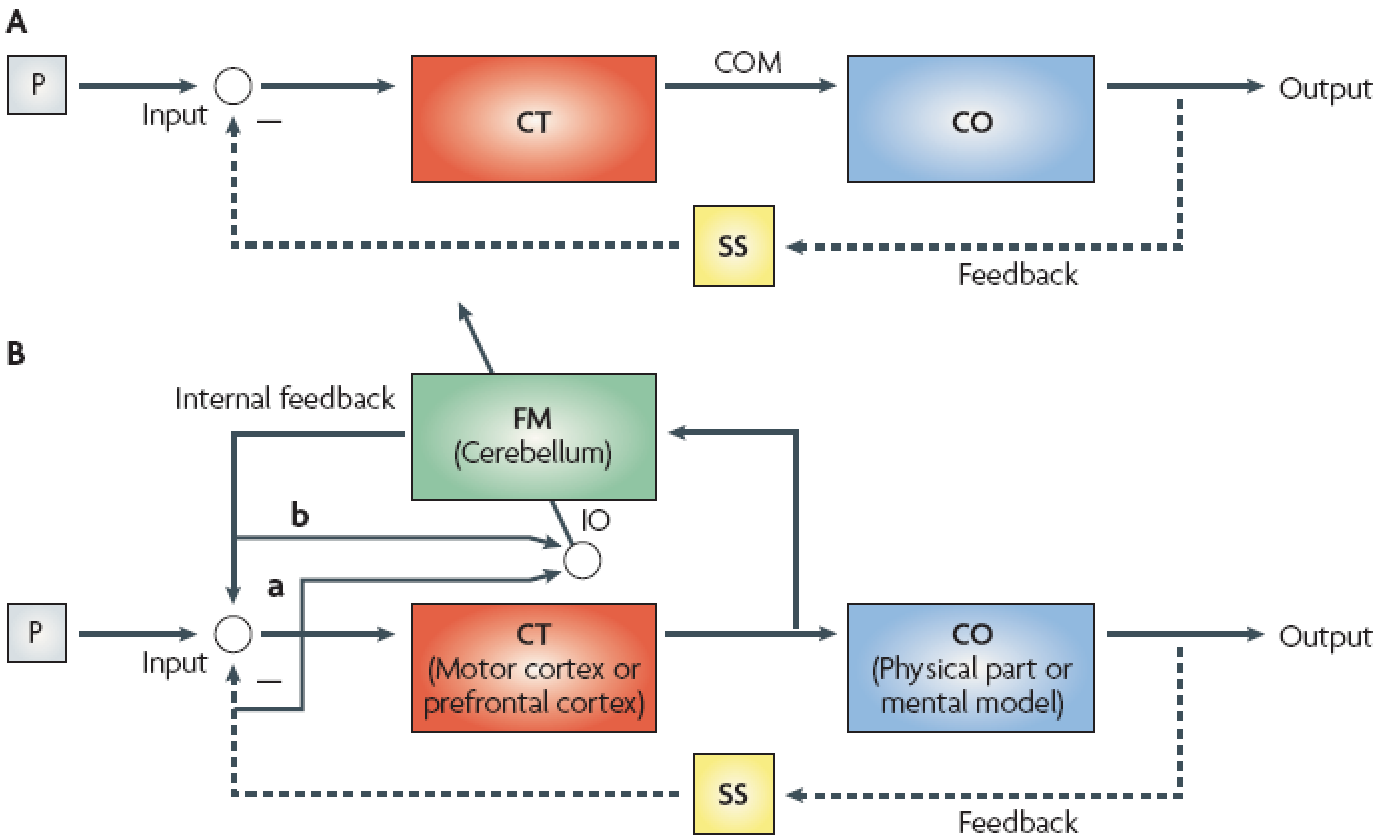
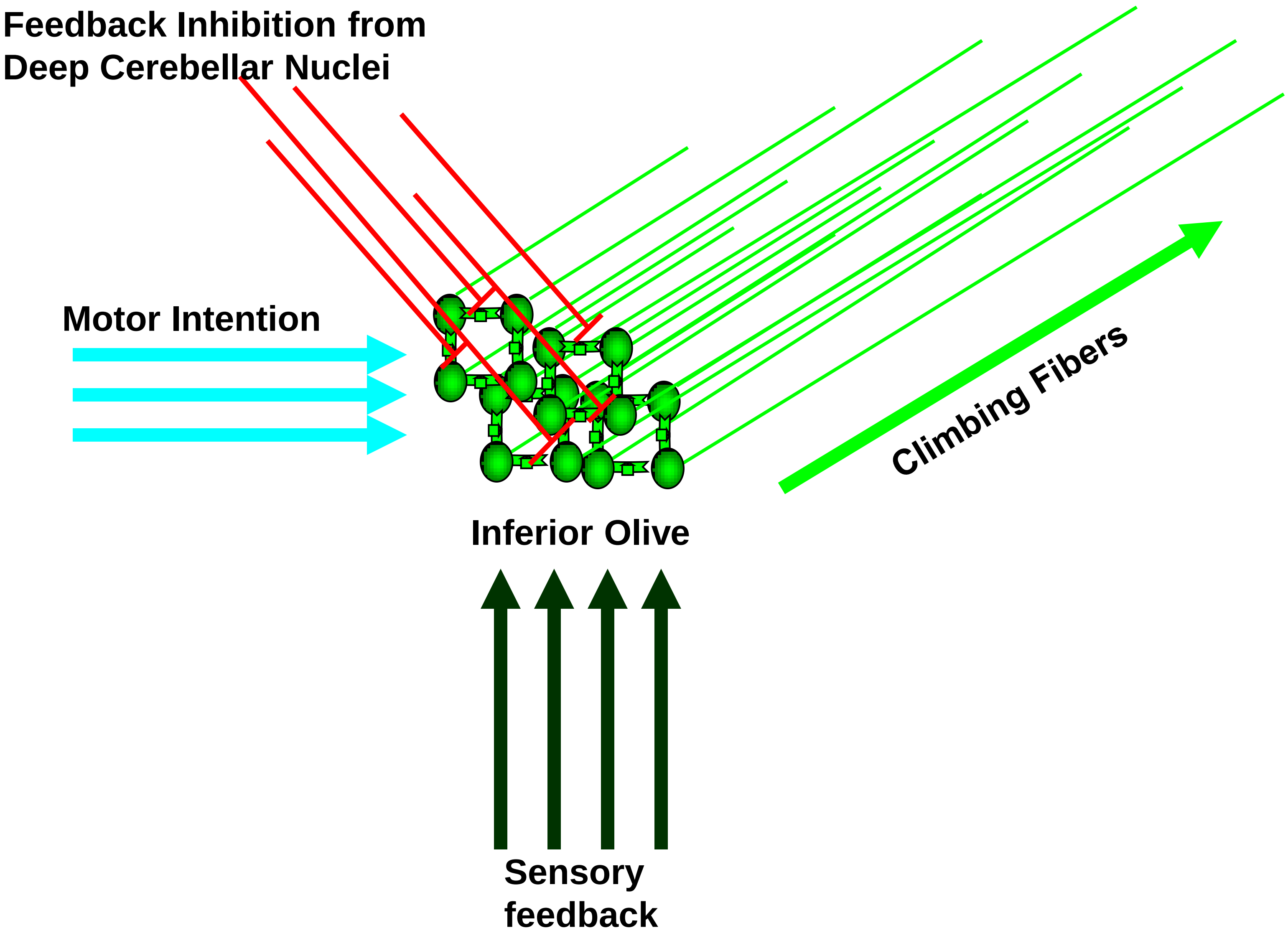


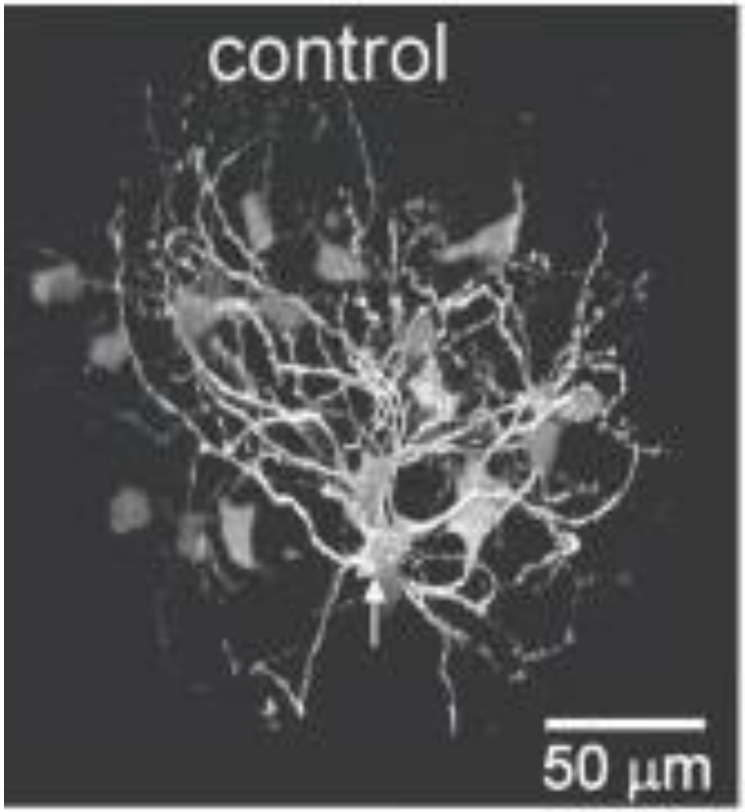
The General Role of the Cerebellum



The Inferior Olive as the Great Comparator

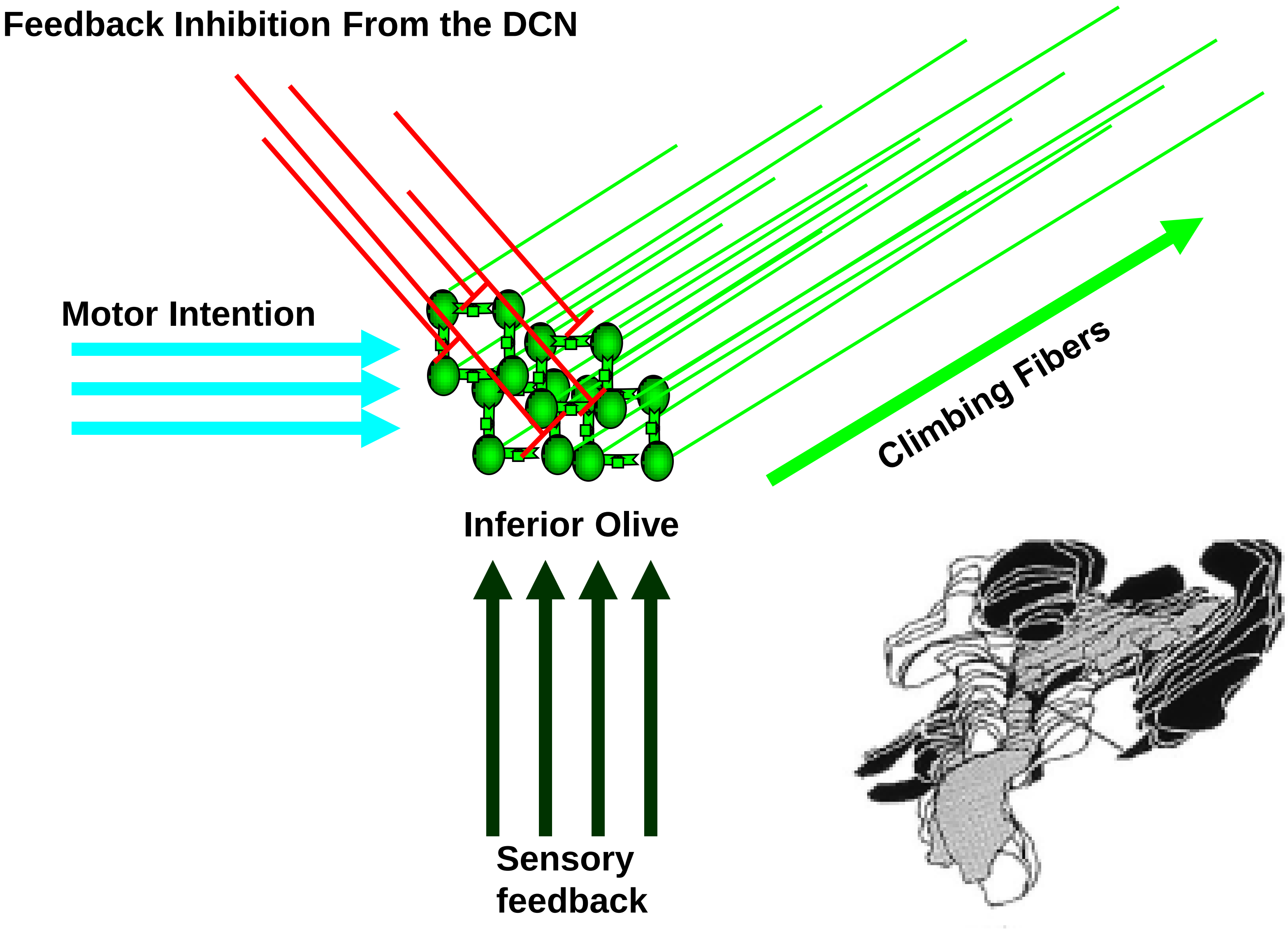


IO Neurons are Coupled by Gap Junction

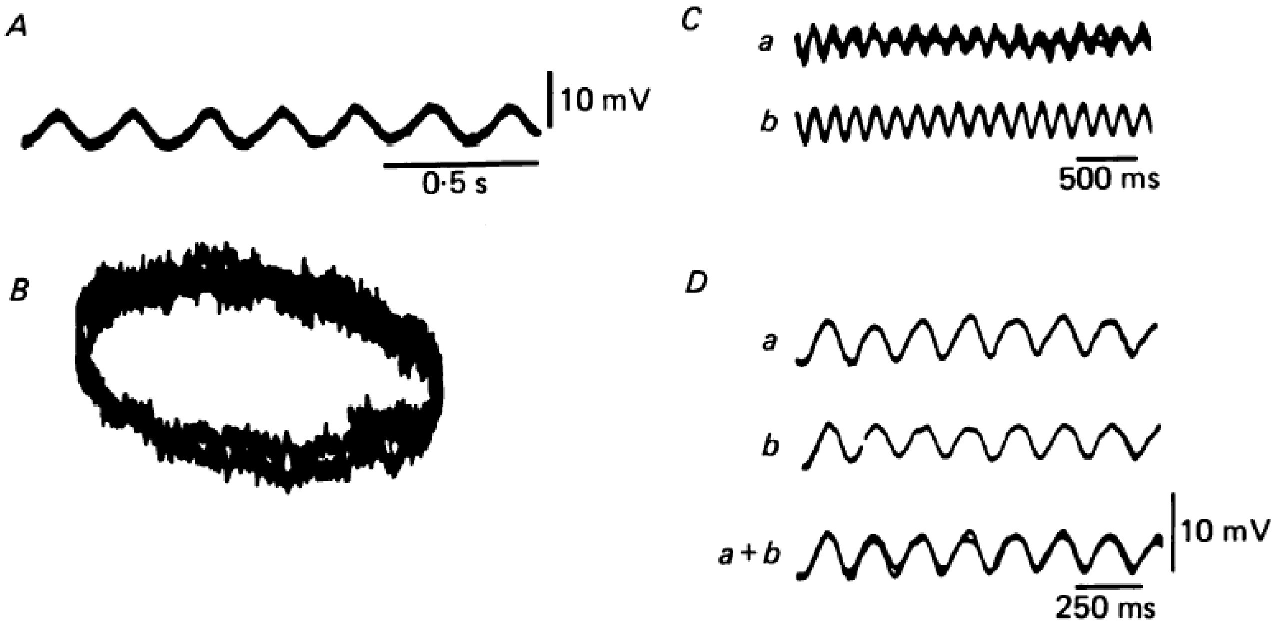


Placantonakis et al. PNAS 2004

The Inferior Olive as the Great Comparator

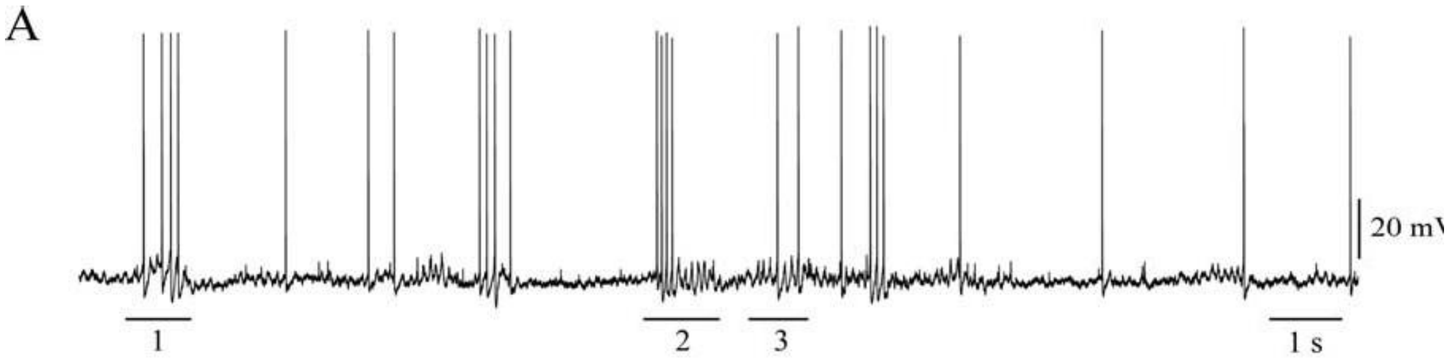


IO Neurons are Natural Oscillators

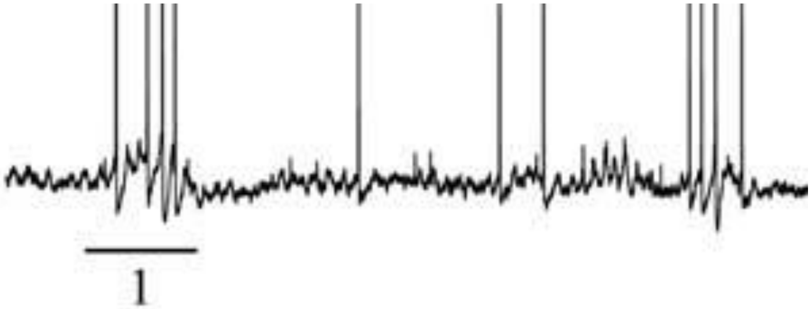


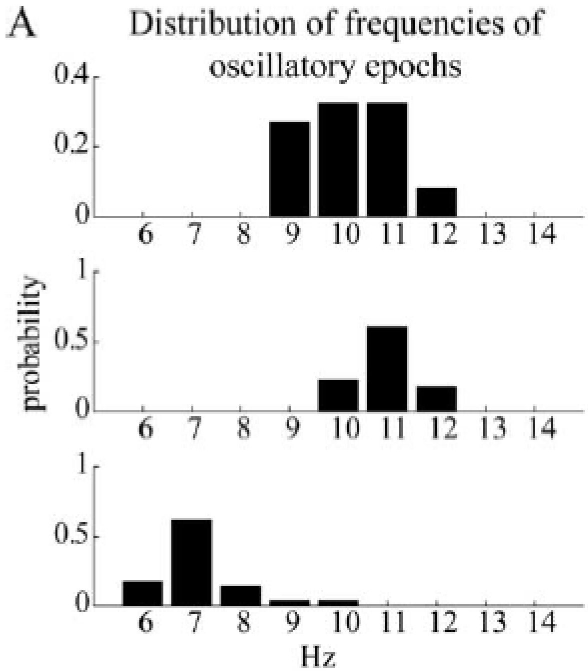
Llinas and Yarom JPhysiol 1986

IO neurons are not Harmonious Oscillators *in-vivo*

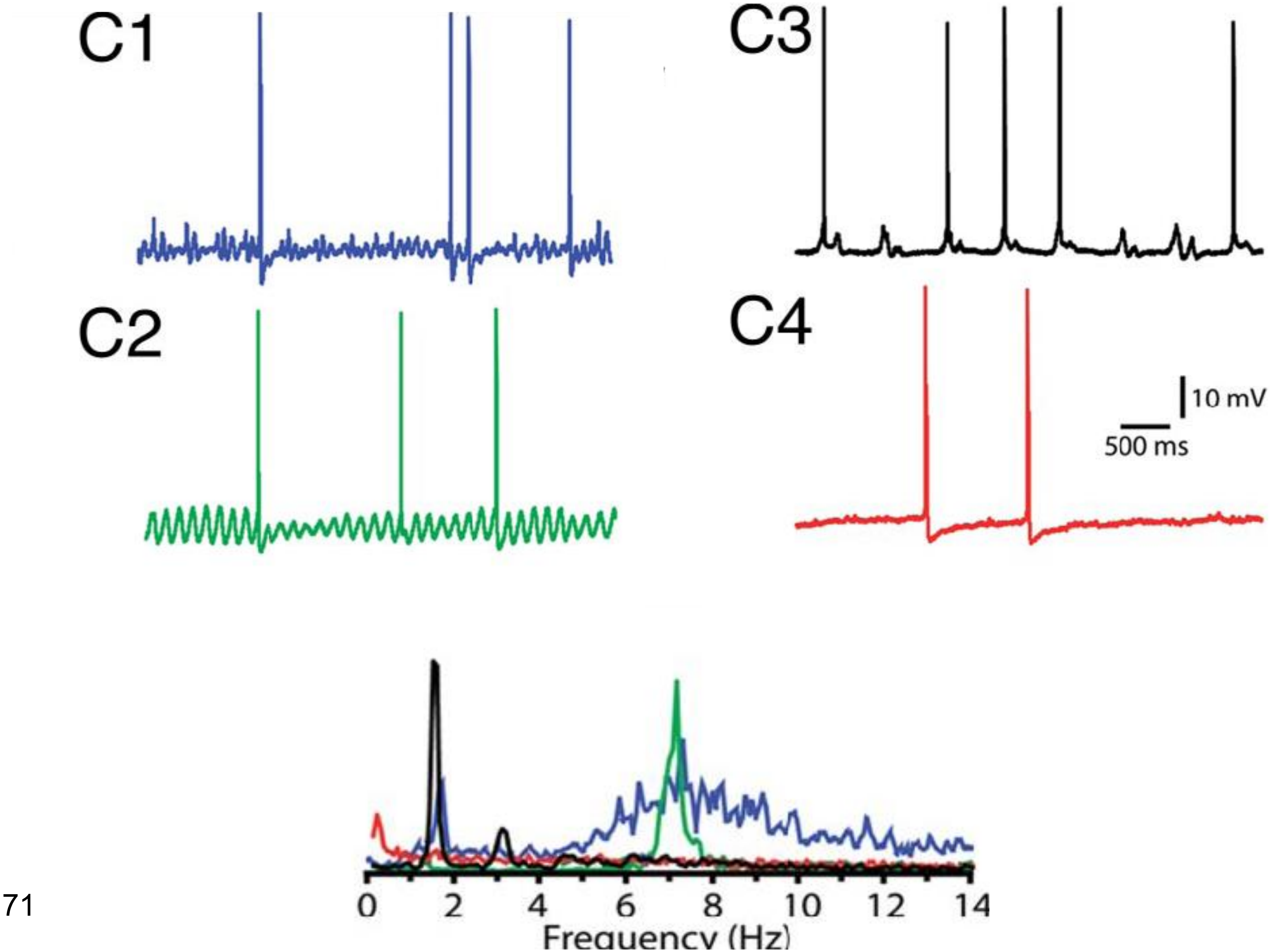


Chorev, Yarom and Lampl JNS 2007



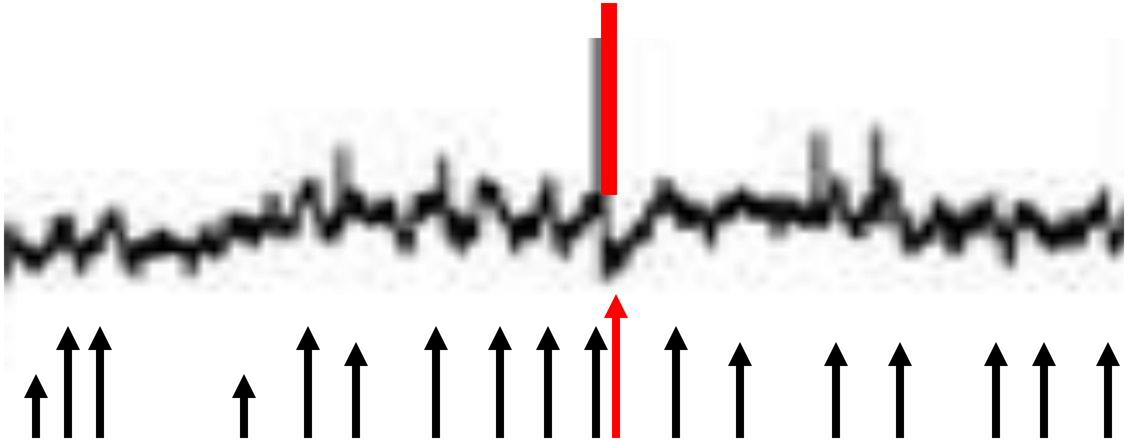


There are Various Oscillation Patterns



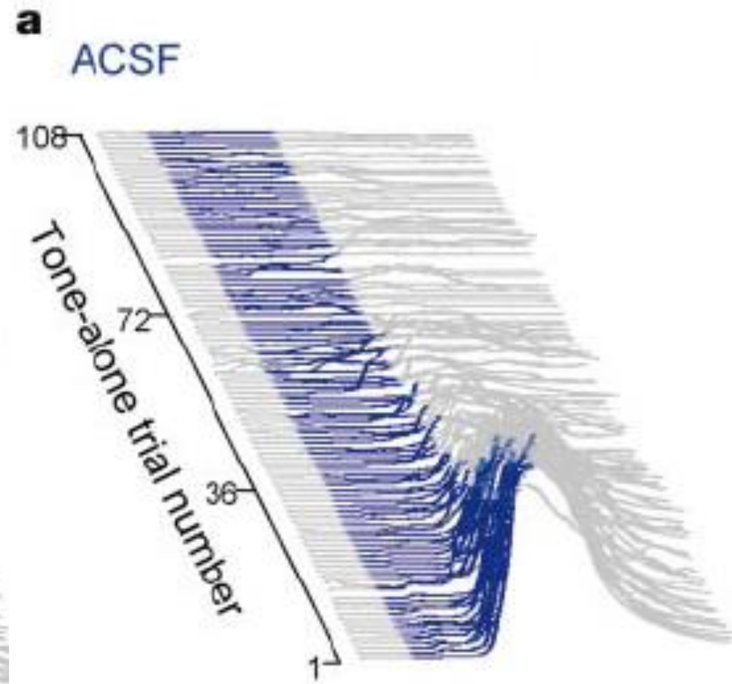
Oscillation as a Blocking Device for expected Inputs

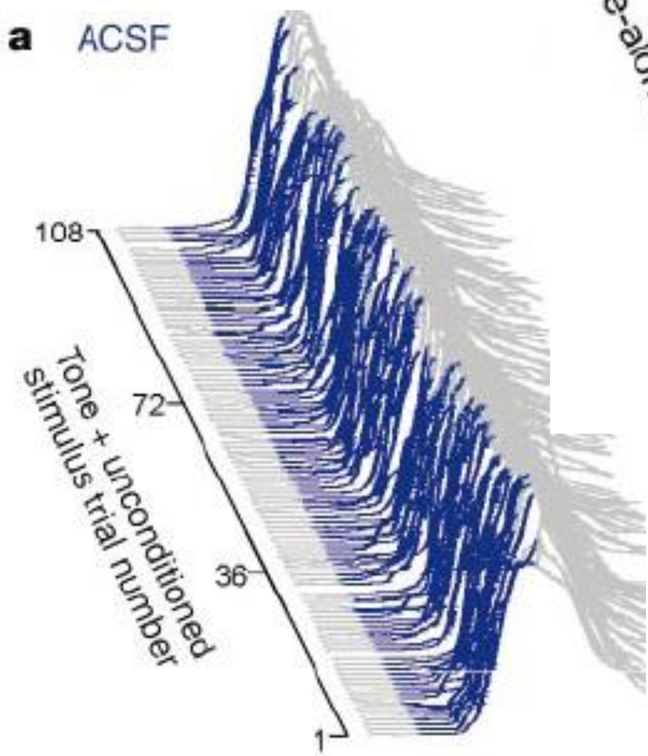
Expected Inputs



How will The IO Differentiate Early vs. Late Inputs?

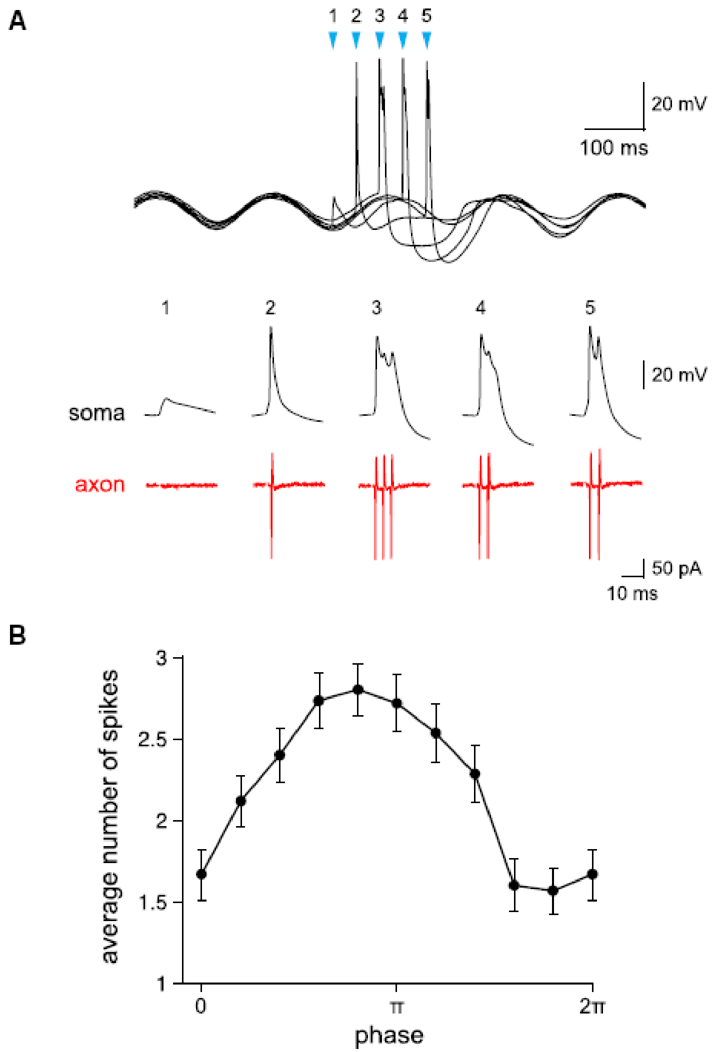
Conditioning Memory Retention depends on Nucleo-Olivary Inhibition





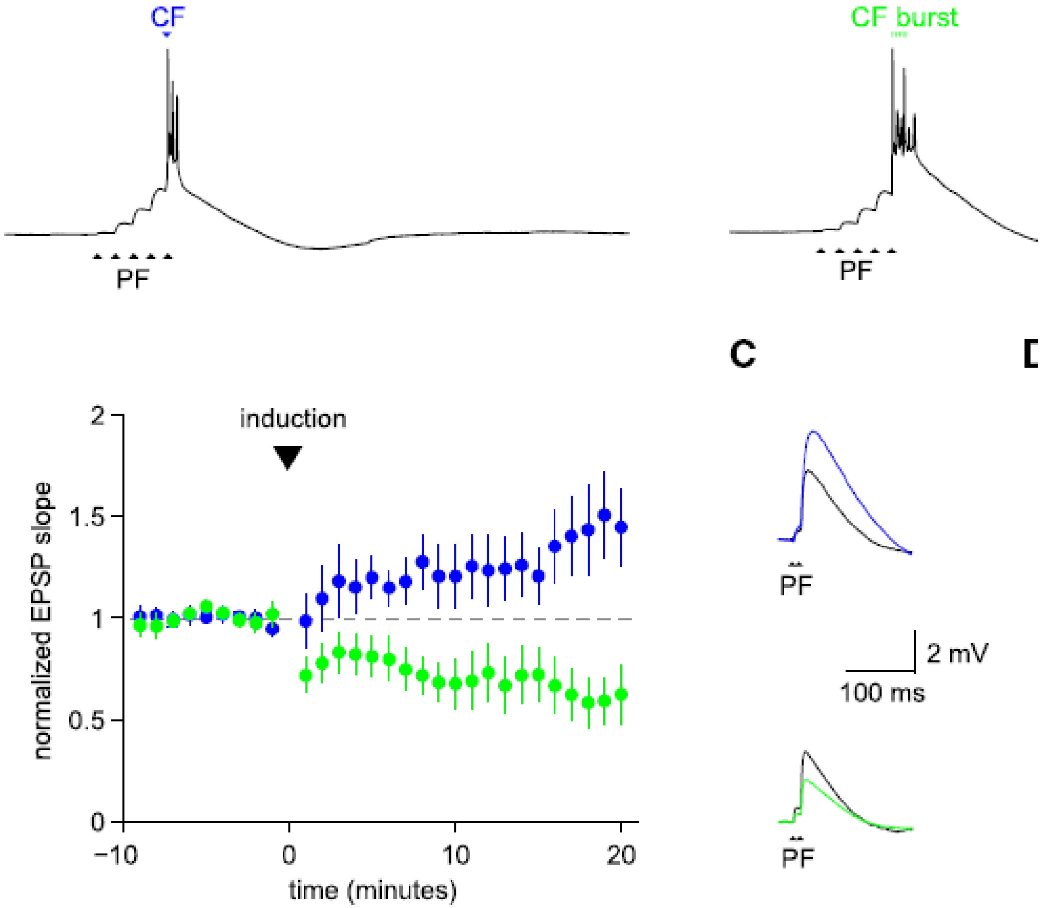
Medina et al. Nature 2002

ISI vs. Oscillation phase "encoding"



Mathy, et al. 2009

CF activation Pattern sets the direction of plasticity



Mathy, et al. 2009