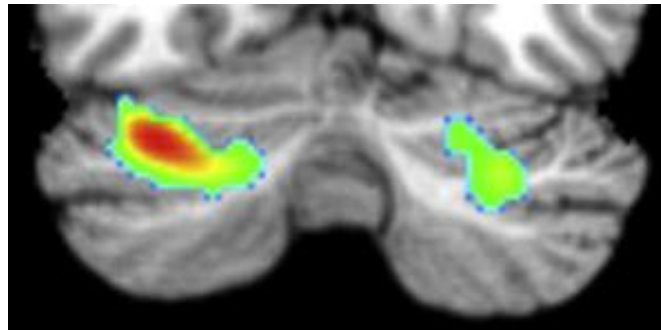
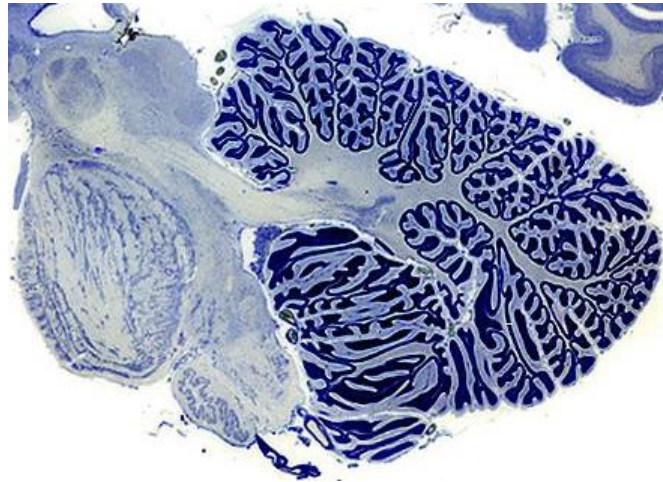
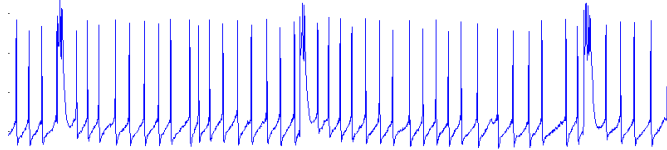


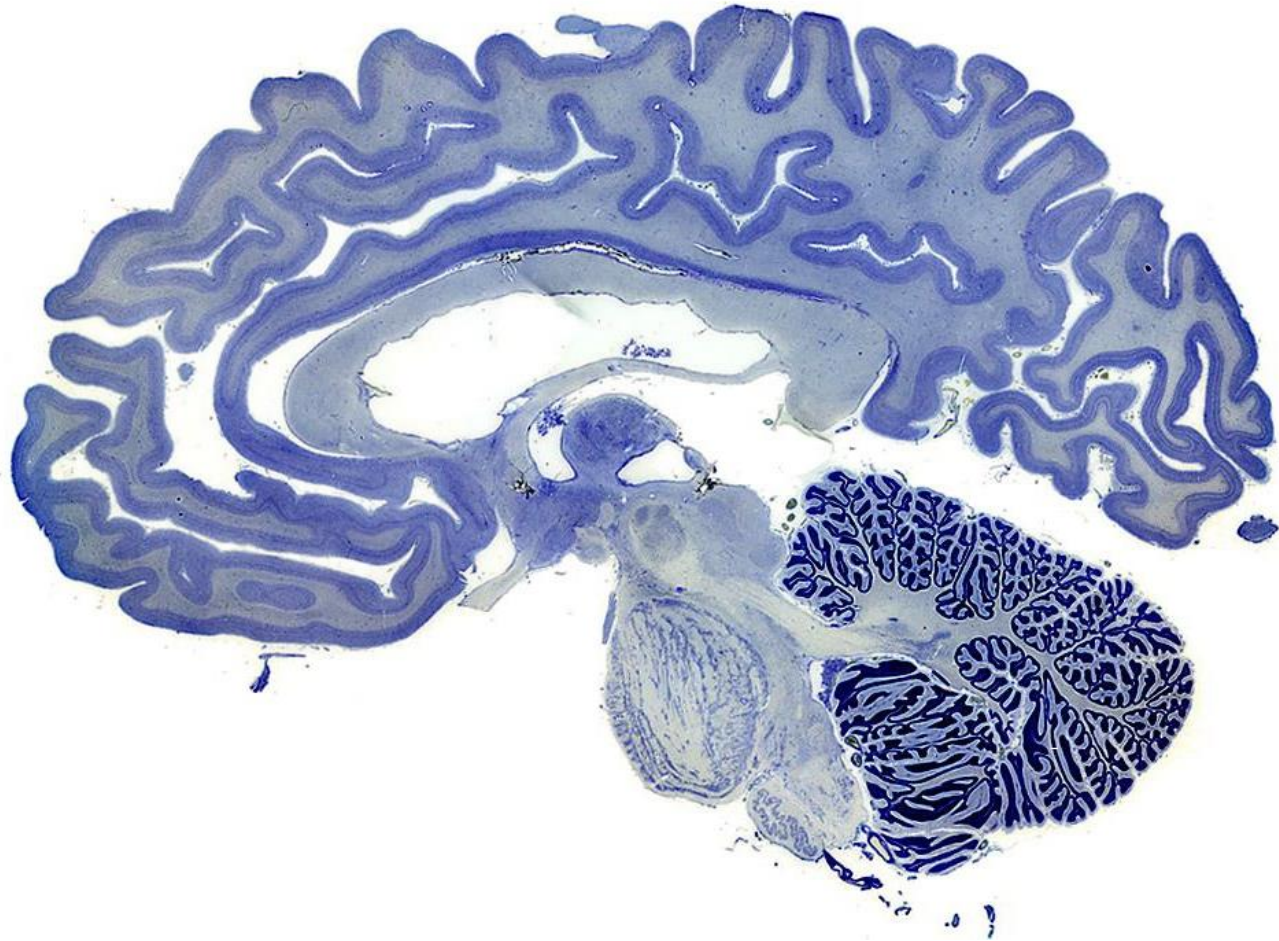
Cerebellum, motor and cognitive functions: What are the common grounds?



Cerebellum – The “Little Brain”



Small but Hefty...



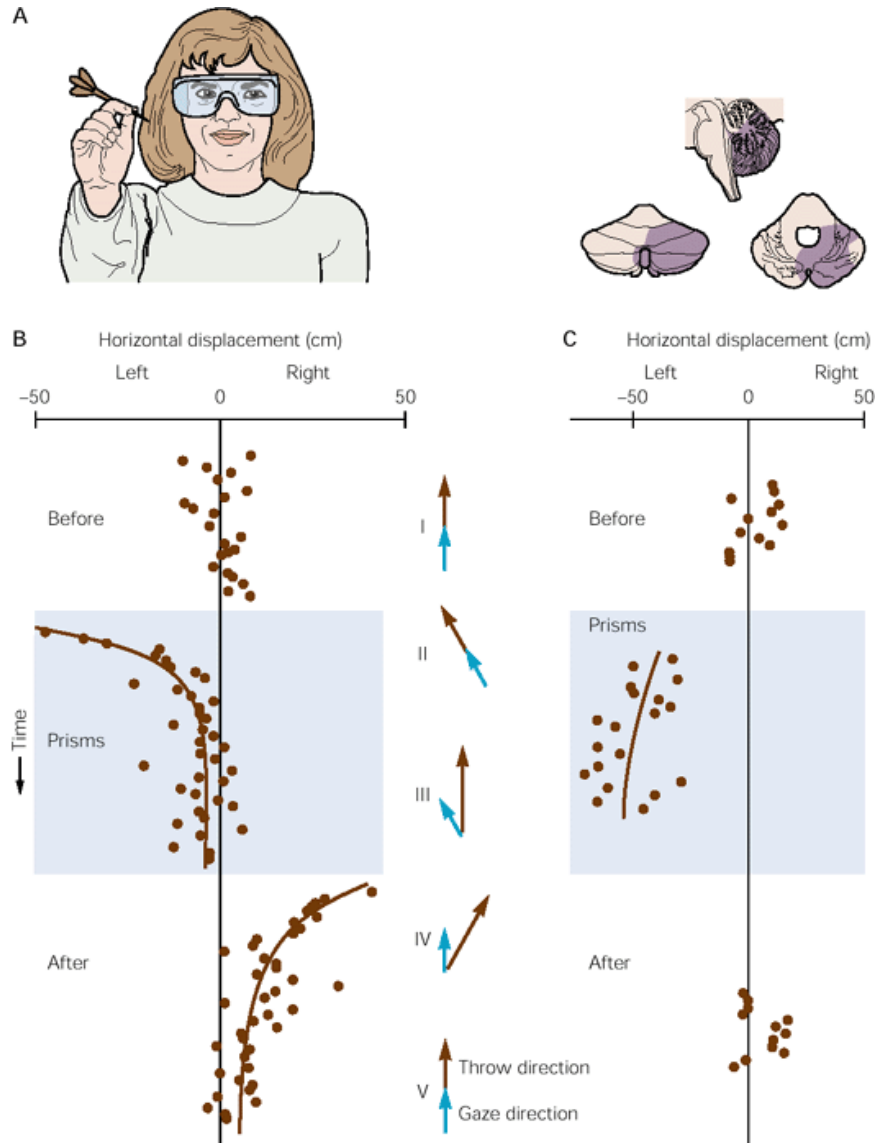
Over 50% of the Brain's Neurons are in the Cerebellum!!

“Classical” symptoms of Cerebellar dysfunction

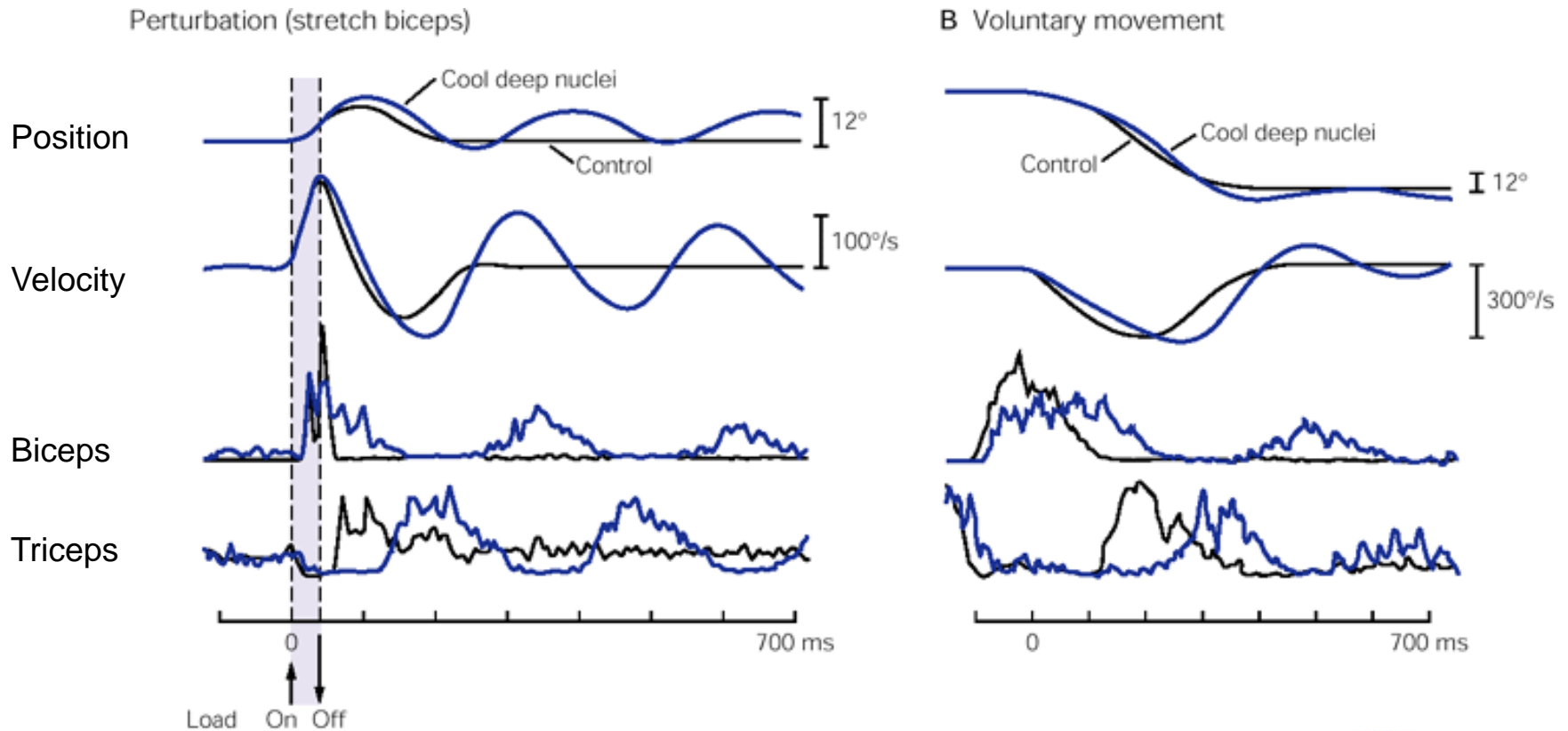


- Hypotonia = loss of muscle tone
- Tremor: limbs, jaw, neck, larynx
- Ataxia = loss of motor coordination:
 1. Postural instability, “drunken sailor” gait , sway, wide standing base
 2. Walking: uncertain, asymmetric, irregular
 3. Failure in execution of planned movements i.e. intentional tremor, dysmetria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

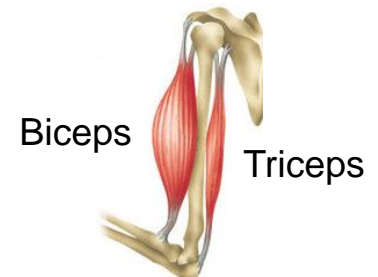
Cerebellar is Central in Adaptation



Classical Role in Muscle Timing and Coordination



Cooling => Reducing Neuronal Firing



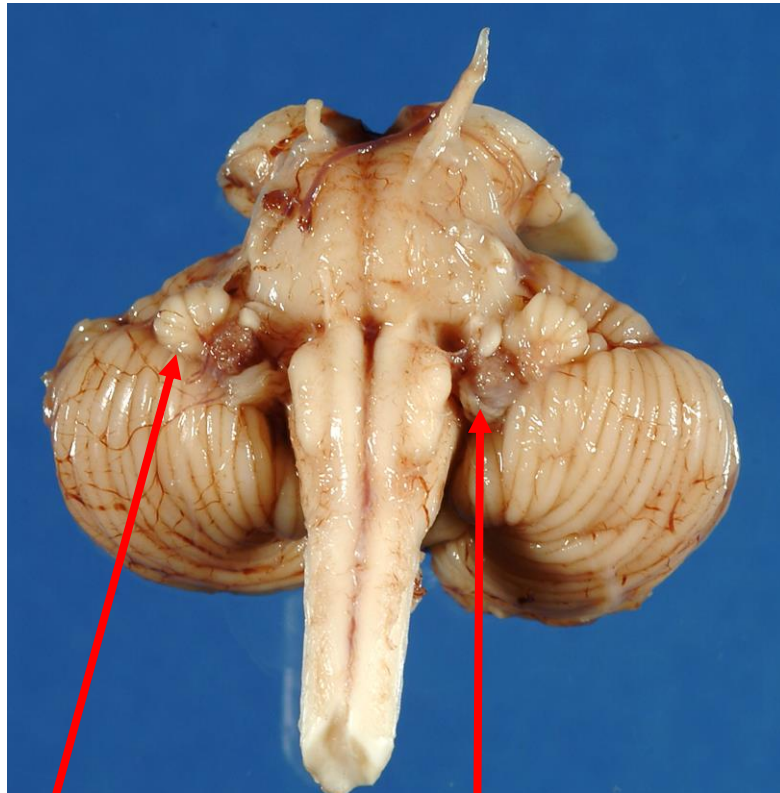
“Non-Classical” symptoms of Cerebellar dysfunction



- ❖ 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

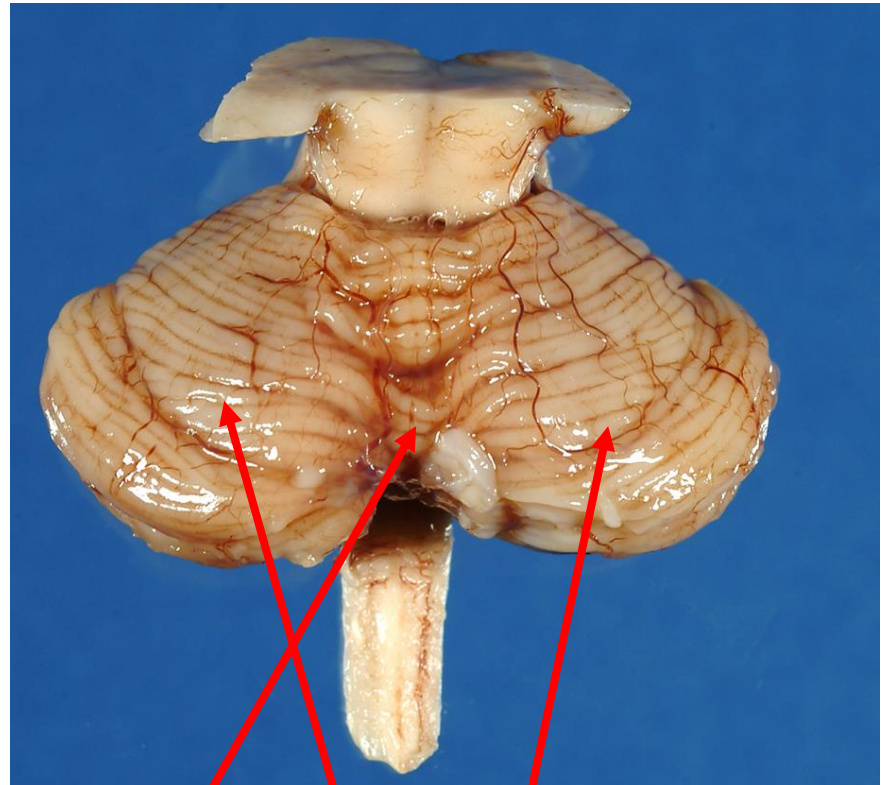
Ventral/Anterior View



Flocculus

Tonsil

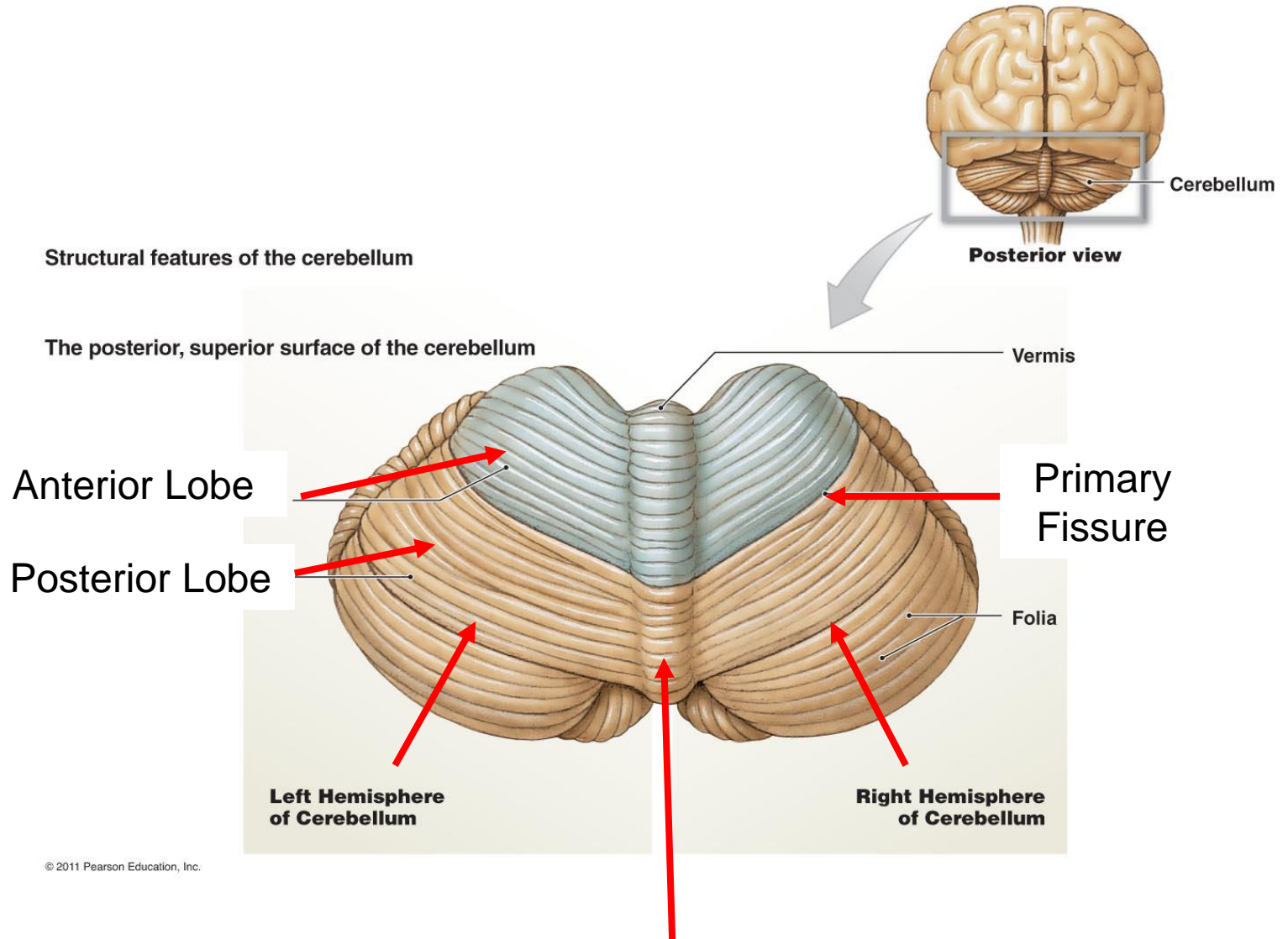
Dorsal/Posterior View



Vermis

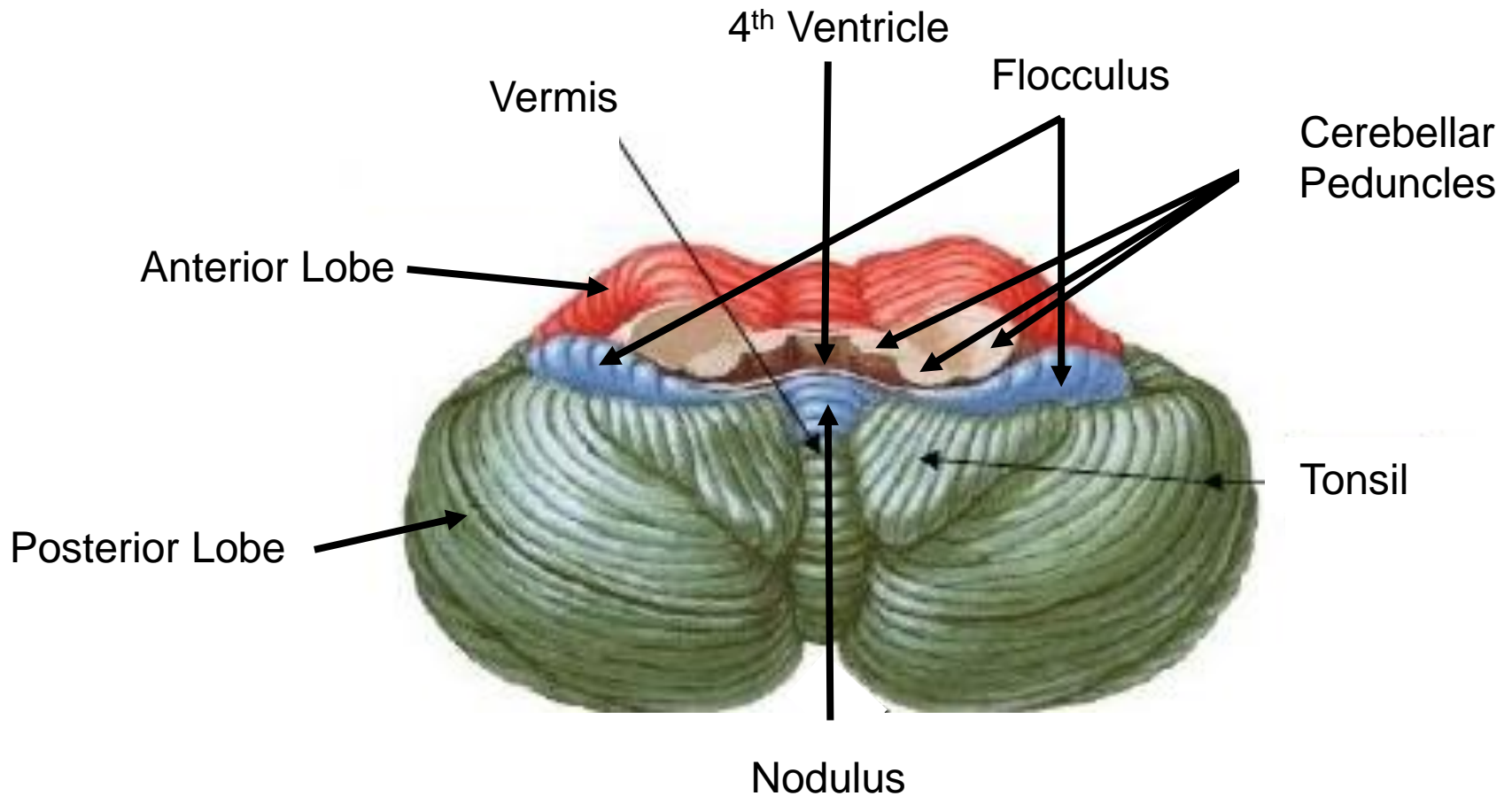
Hemispheres

Posterior/Dorsal view of the Cerebellum



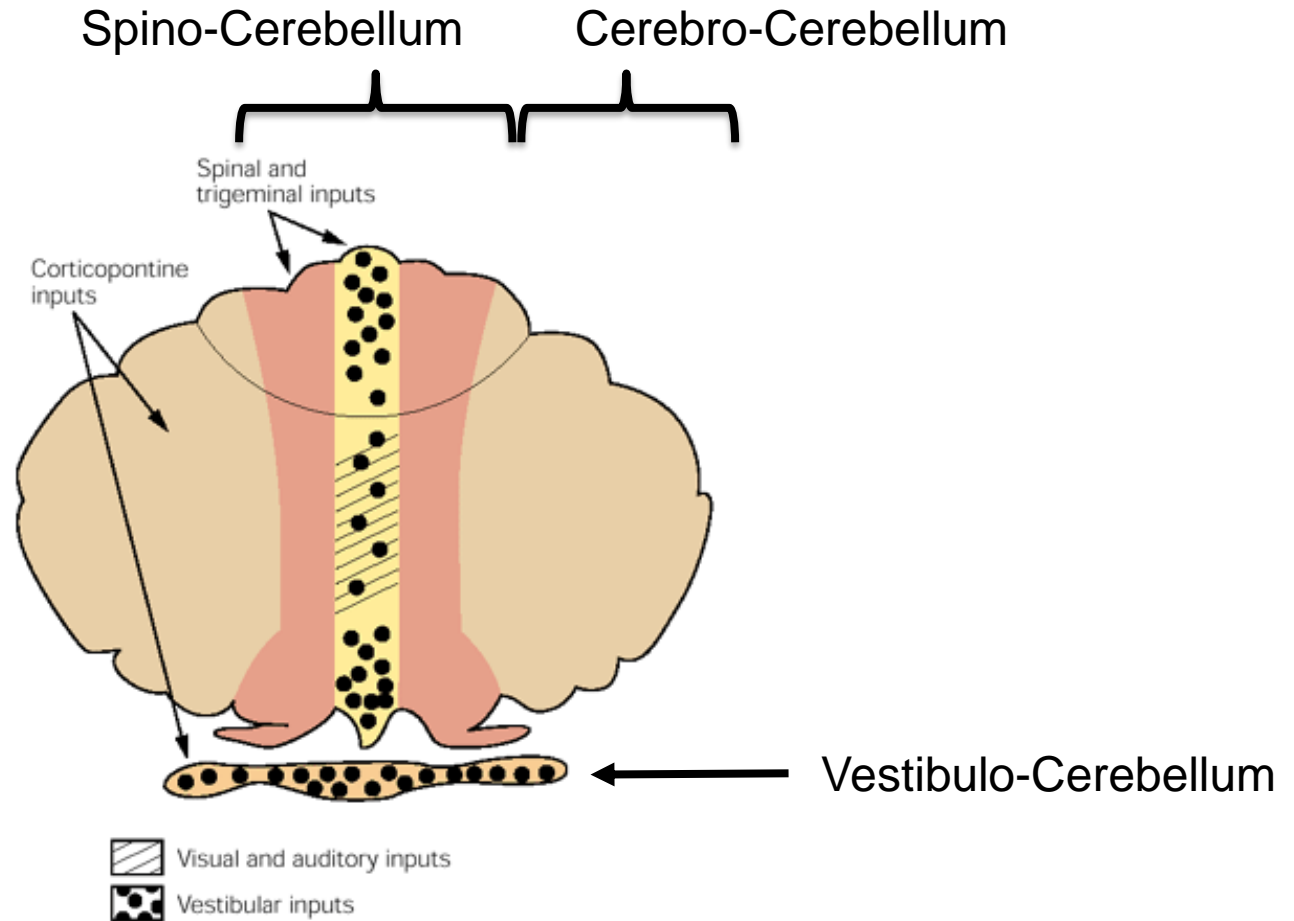
© 2011 Pearson Education, Inc.

Anterior/Ventral view of the Cerebellum

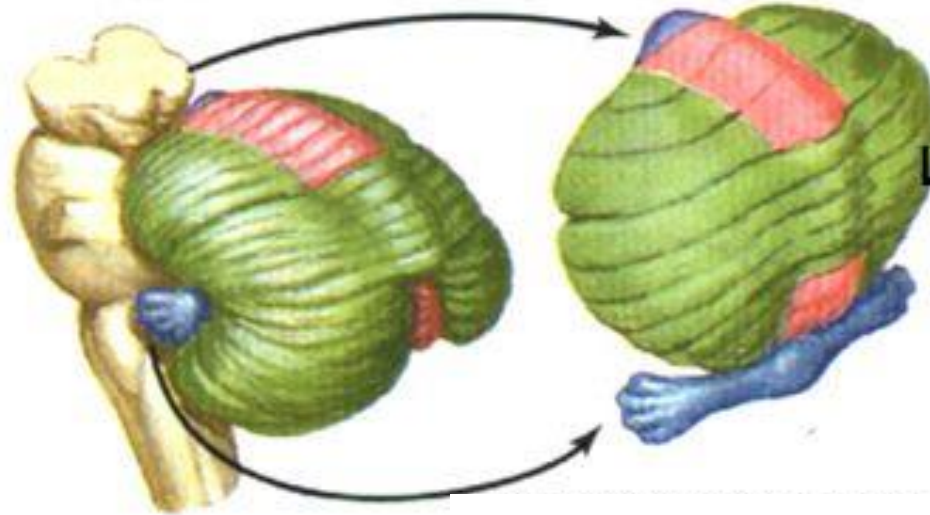


Nodules + Flocculi = Flocculo-Nodular Lobe

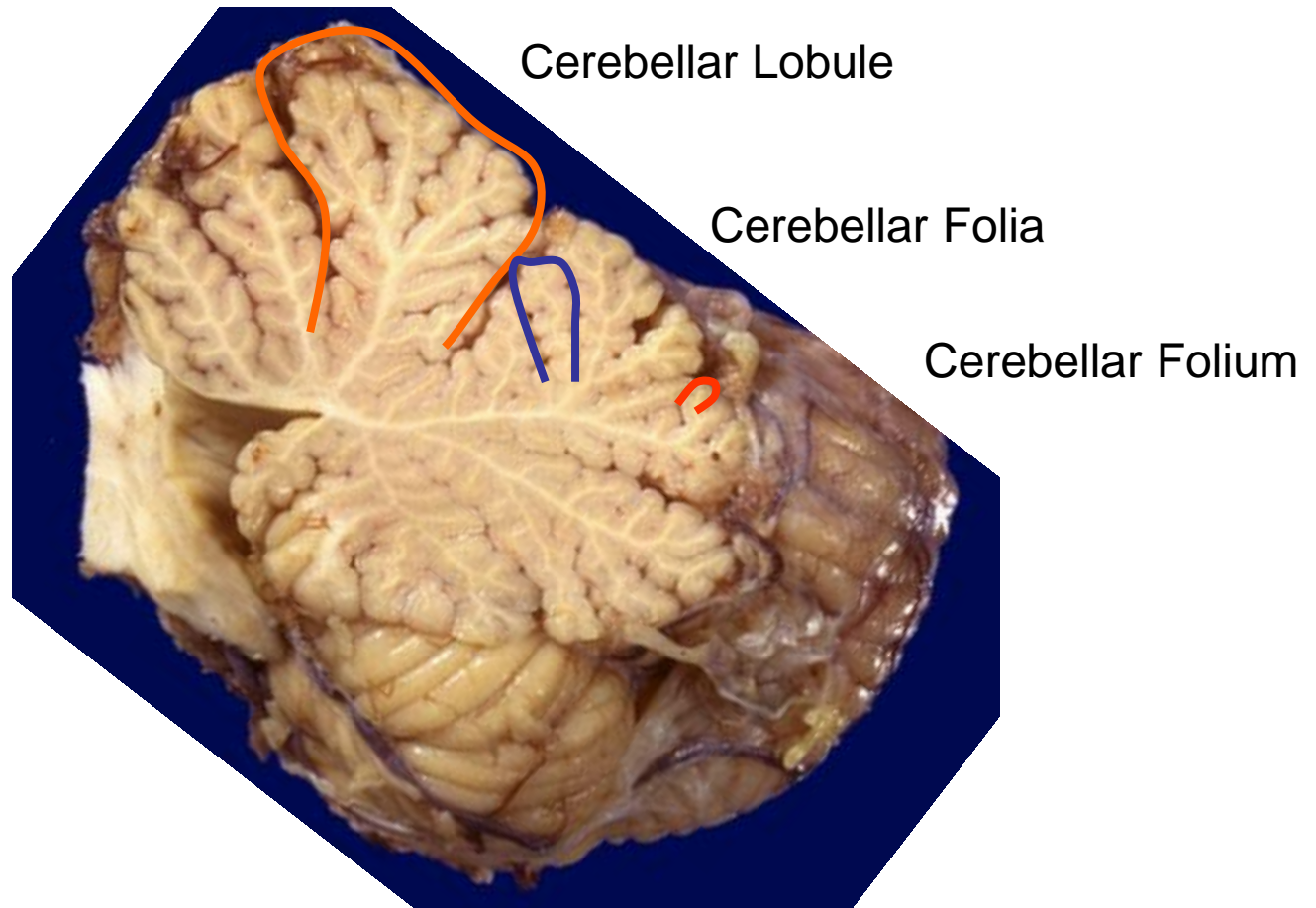
Medio-lateral gross partition of the Cerebellum



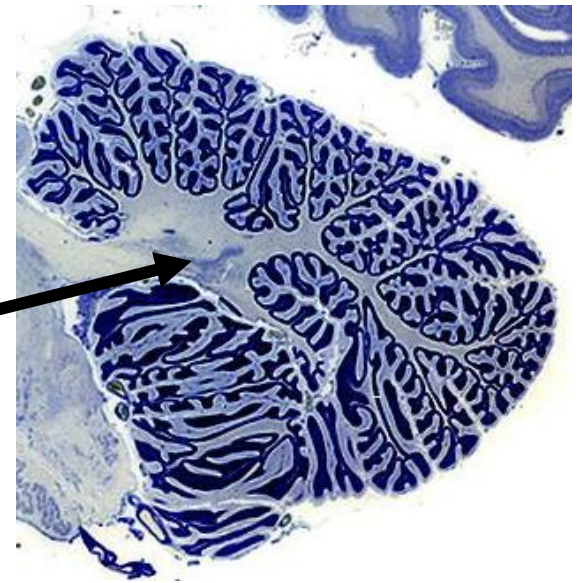
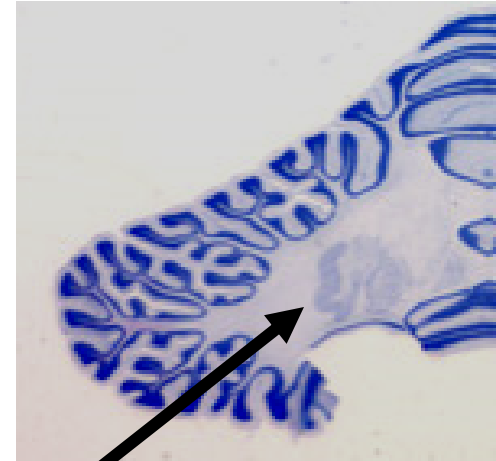
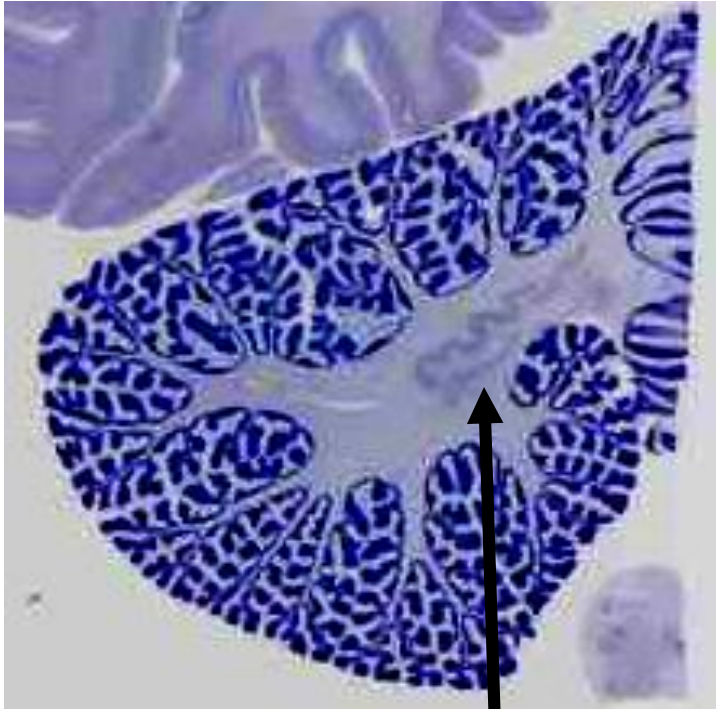
The 3D Folding of the Cerebellar Lobes



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

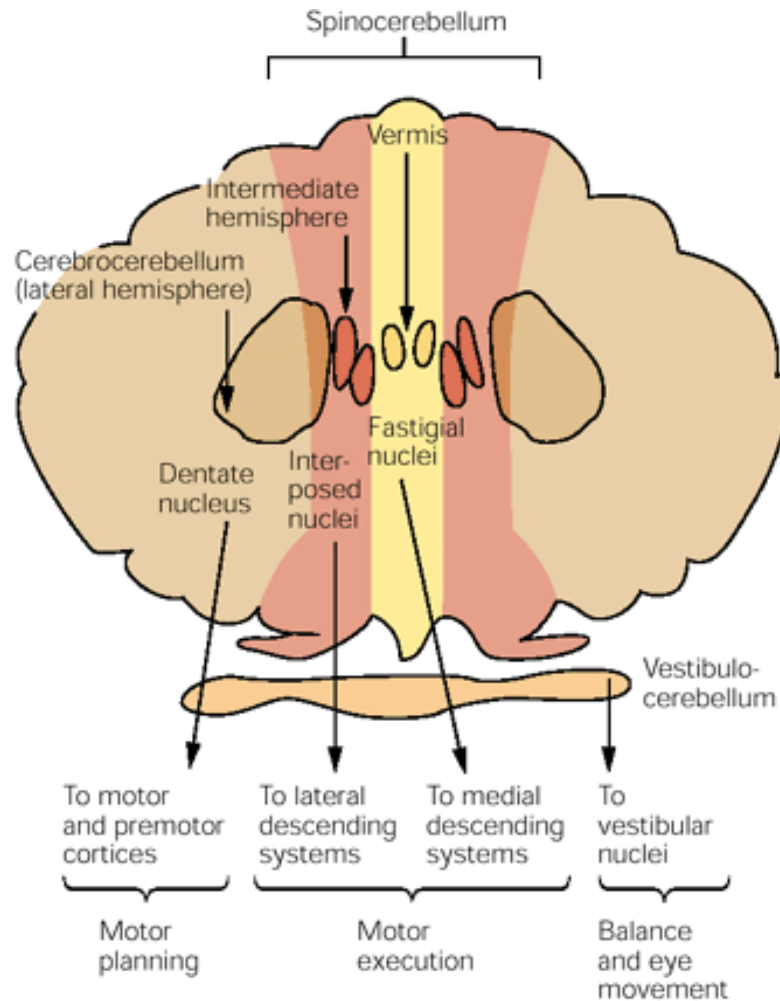


Dentate

Interposed
(Emboliform+
Globose)

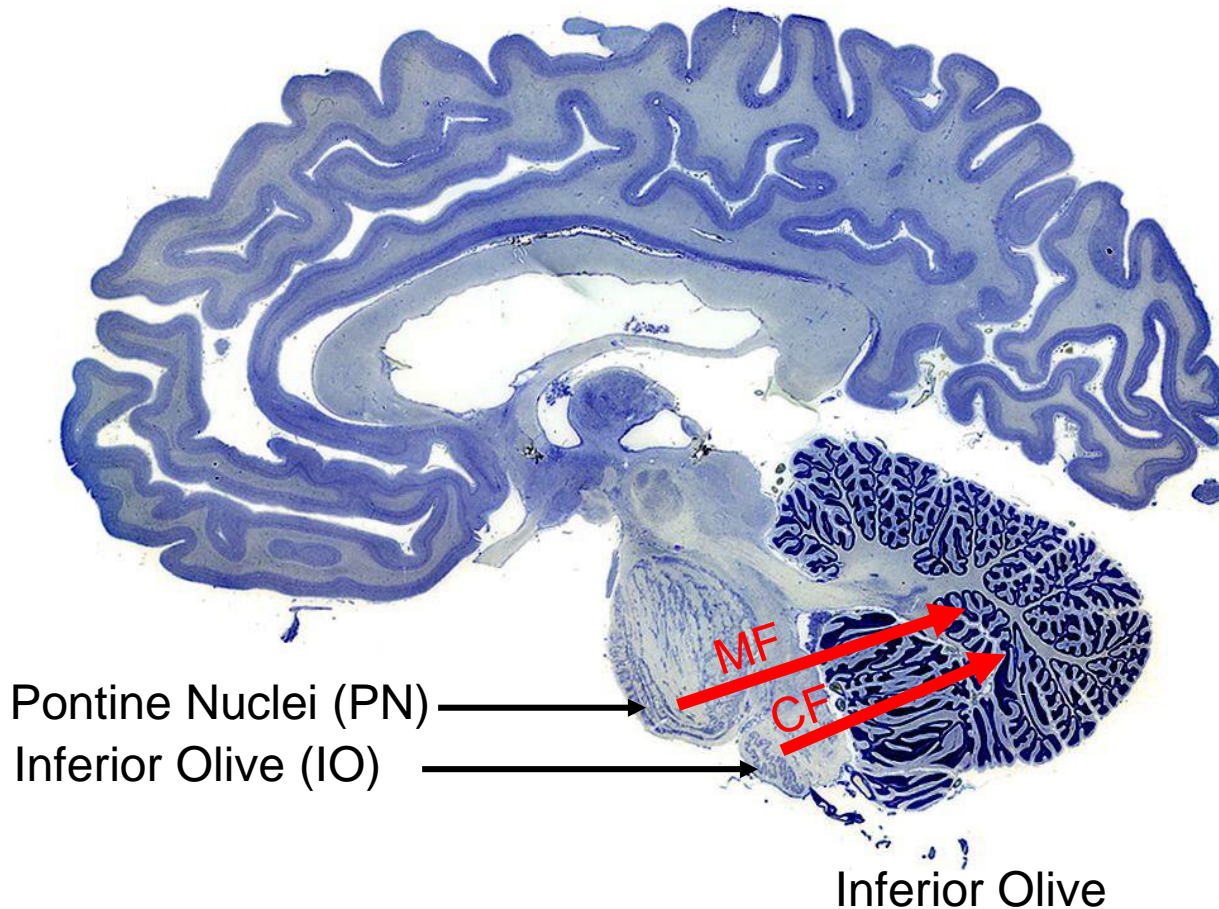
Fastigial

Functional mapping of the Cerebellar nuclei

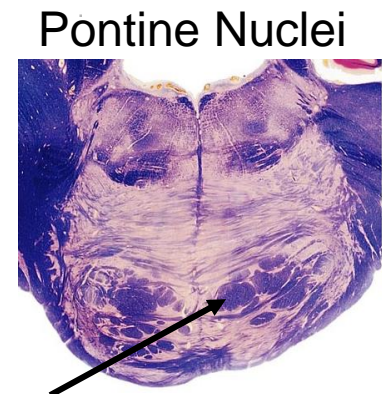
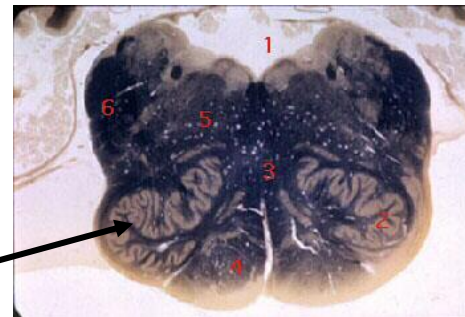


The Vestibular Nucleus in the Brainstem is Functionally Homologous to cerebellar nuclei.

Two Major Input Pathways Serve the Cerebellum



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

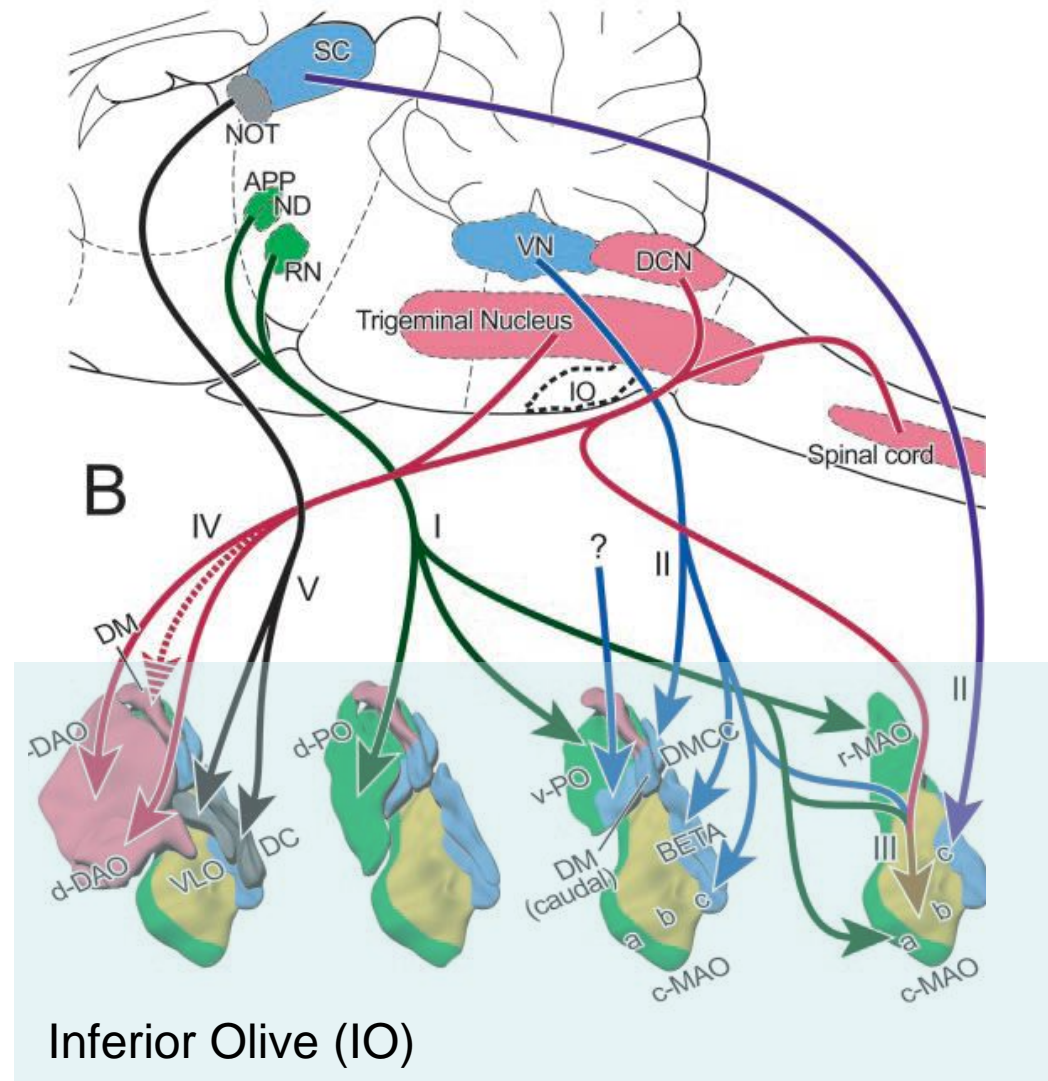
Motor Command:

RN = Red Nucleus

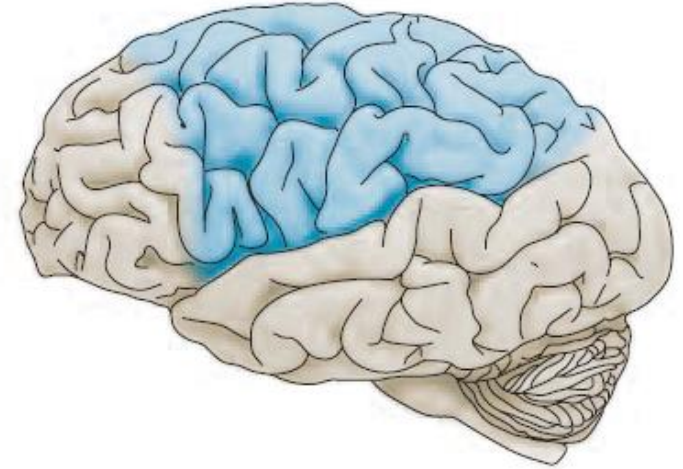
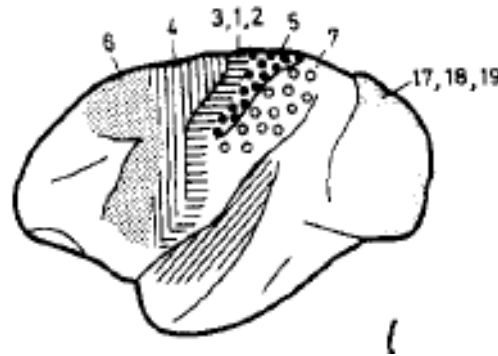
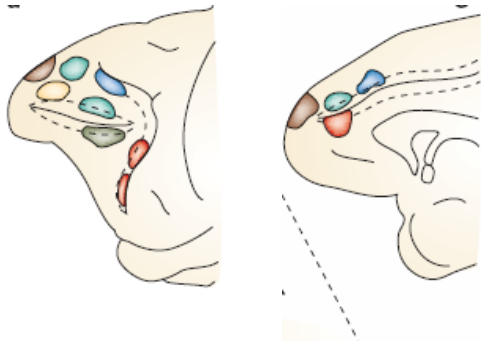
Somatosensory & Proprioceptive:

DCN = Dorsal Column Nucleus

Trigeminal & Spinal Chord

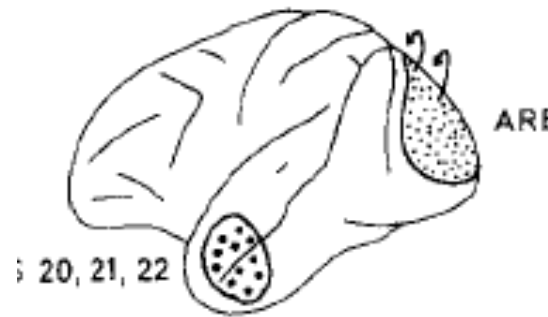


Pontine Nuclei Relay Cerebro-Cortical Information

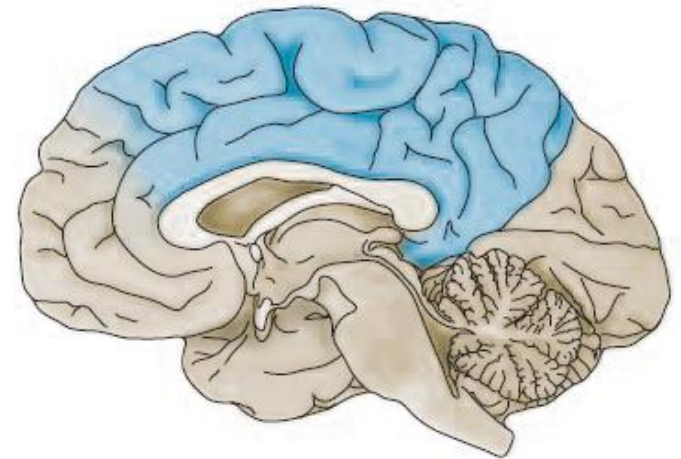


Non-Cortical Inputs:

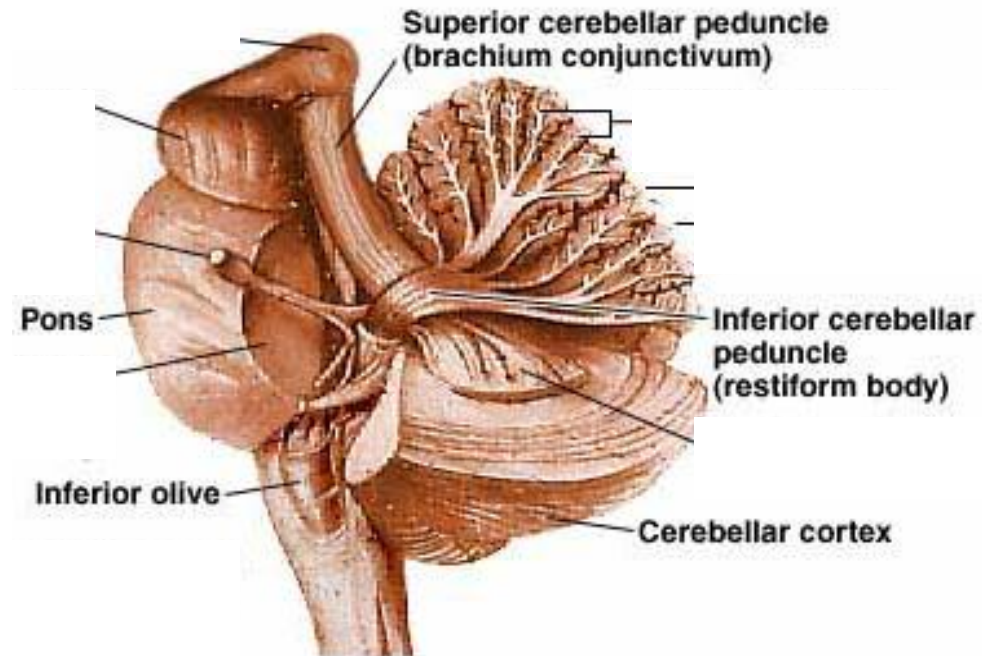
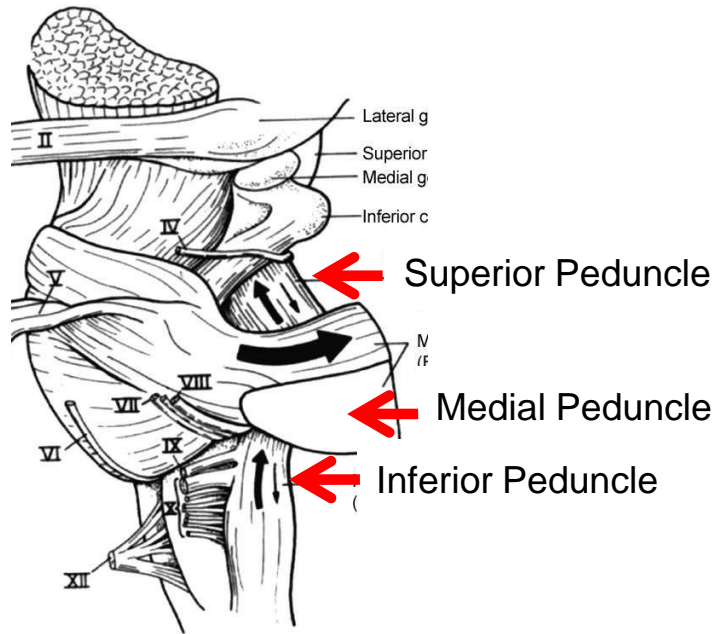
1. Mamilary Body
2. Amygdala
3. Midbrain Nuclei
4. Spinal Inputs



(Brodal 1978)



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

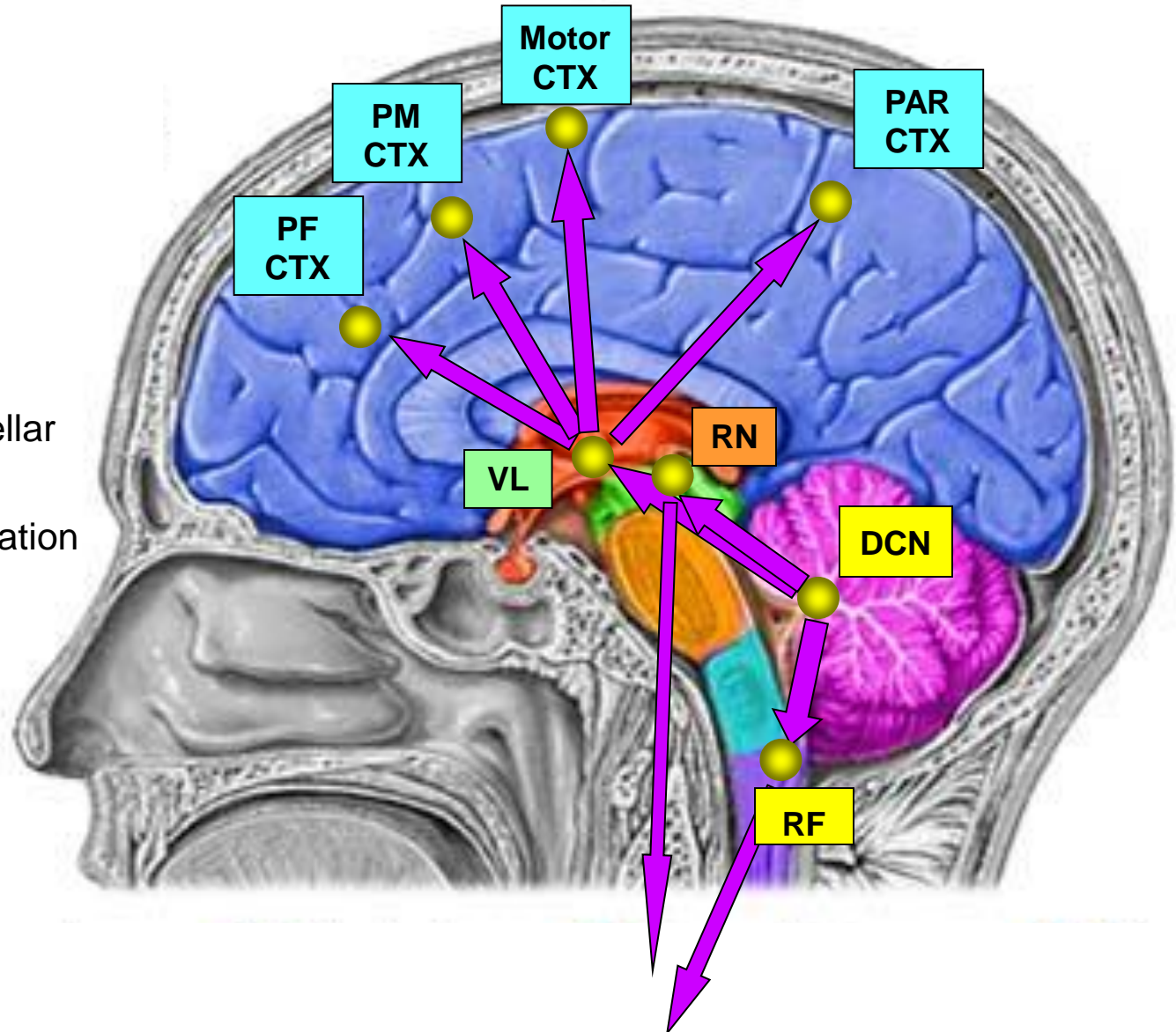
Other Outputs:

Inferior Olive

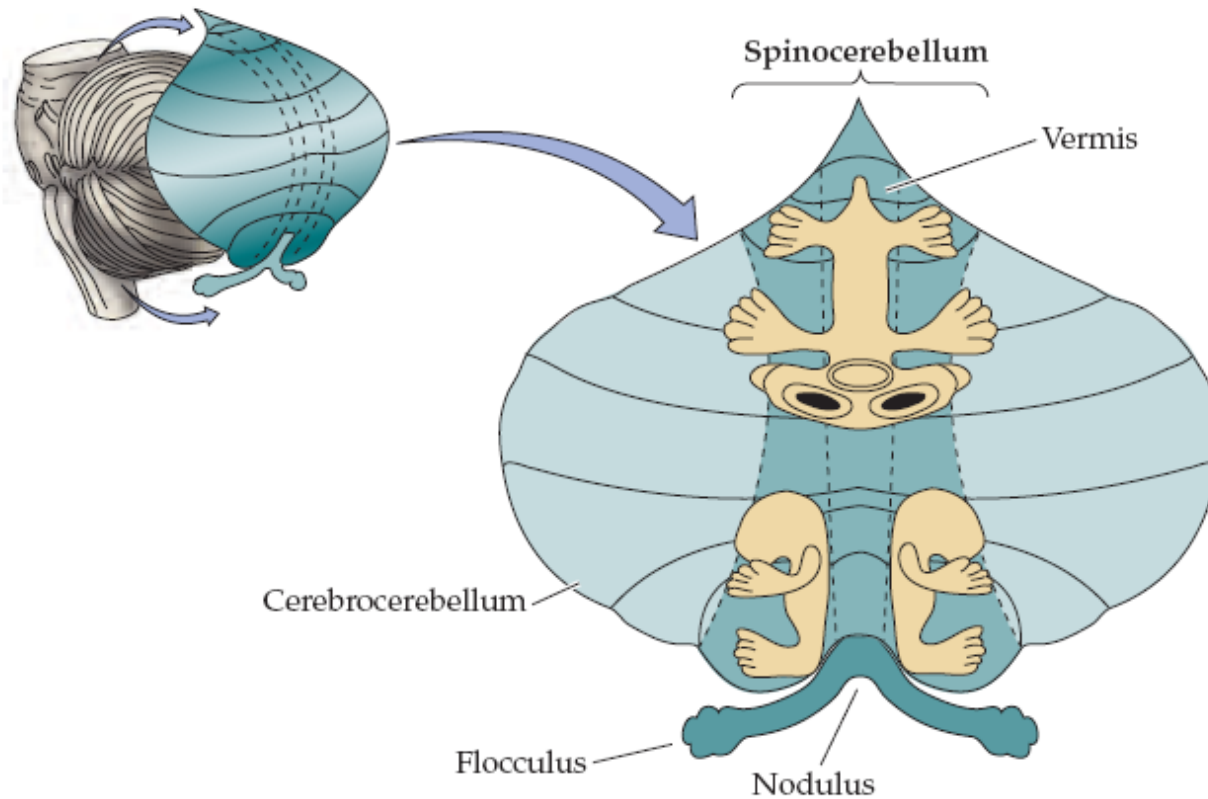
Hippocampus

Amygdala

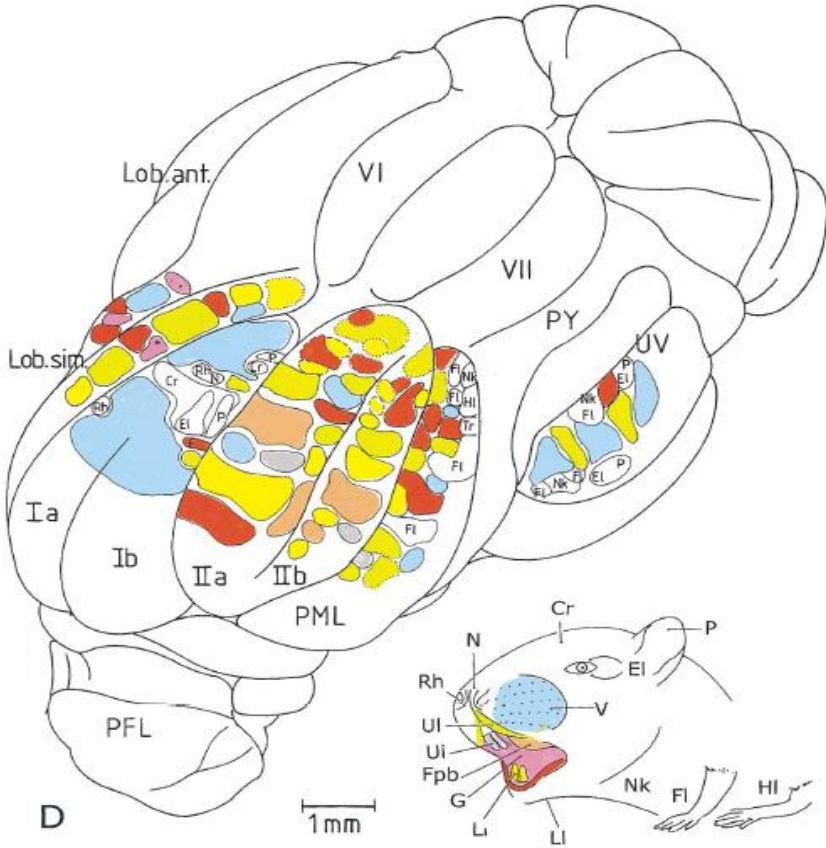
Septum



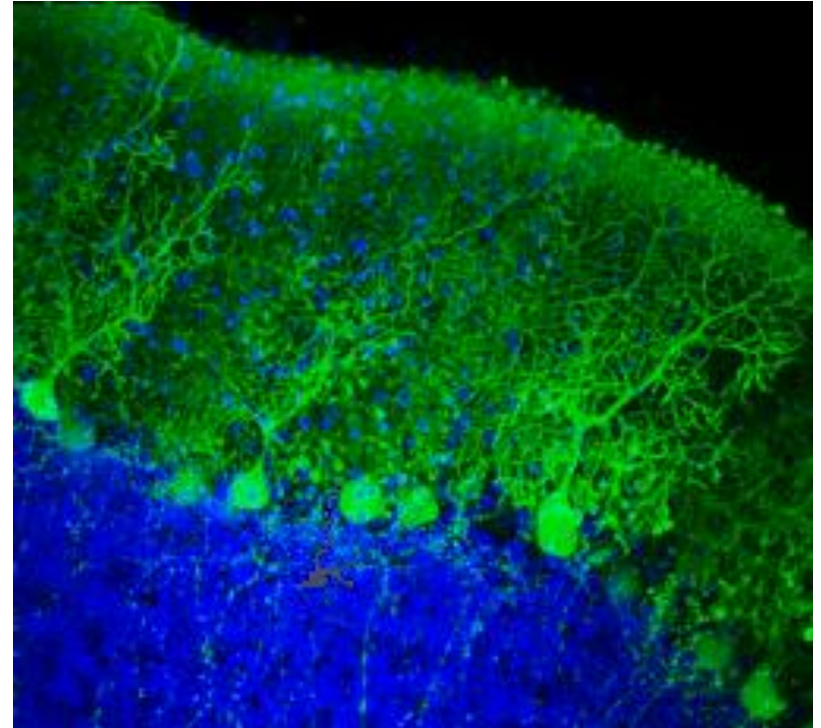
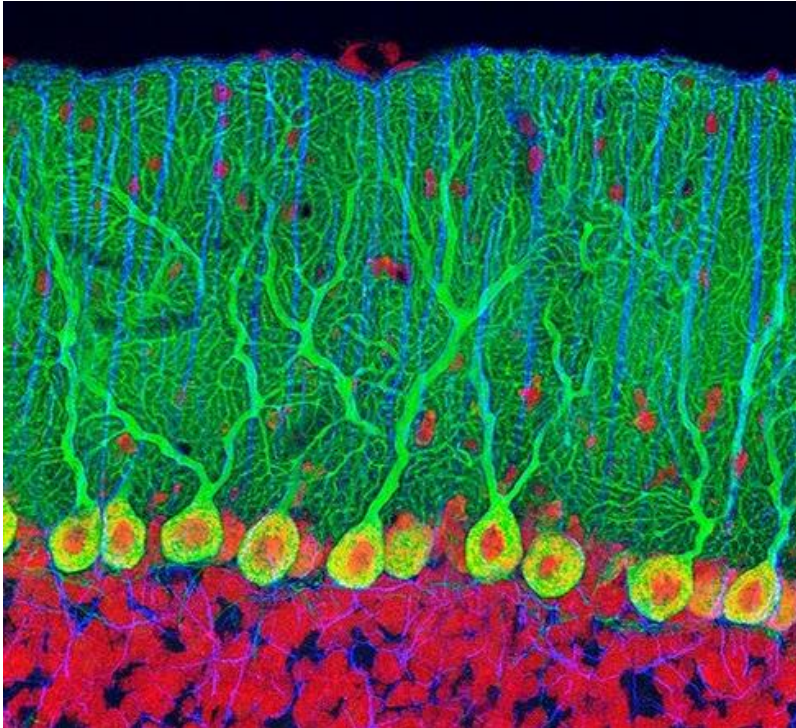
Mapping of Cerebellar Cortex – Classic View



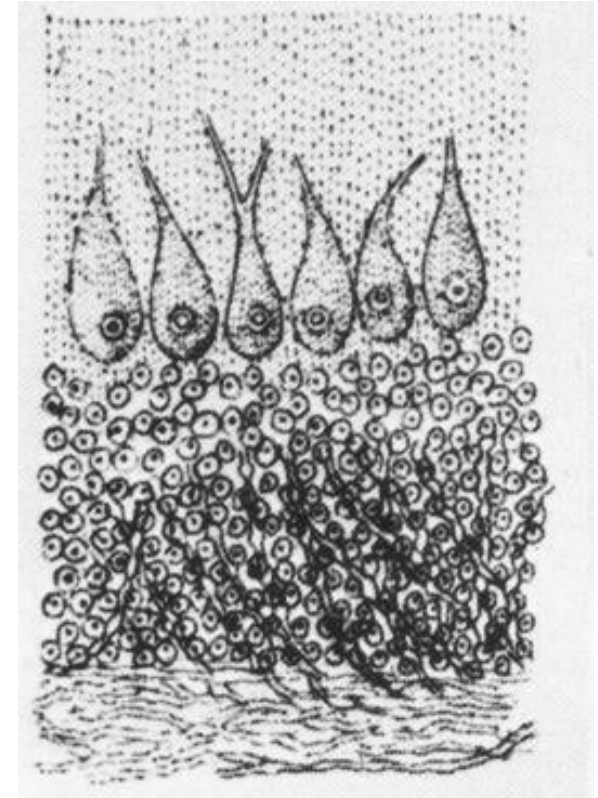
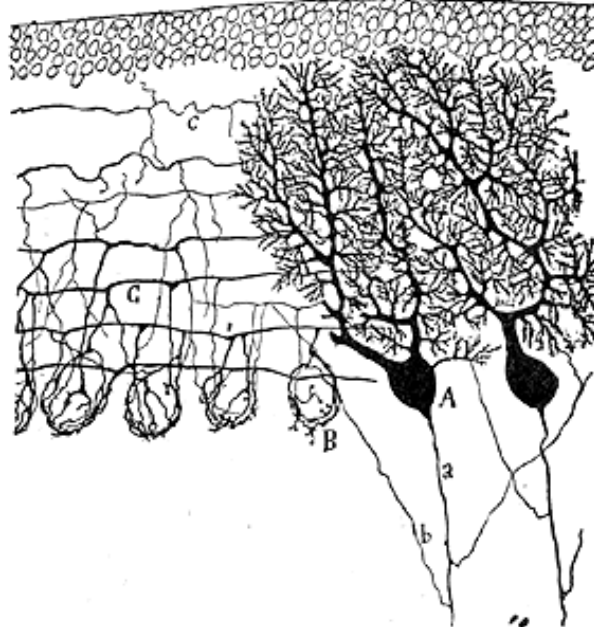
Cerebellar Cortex Mapping is Fragmented



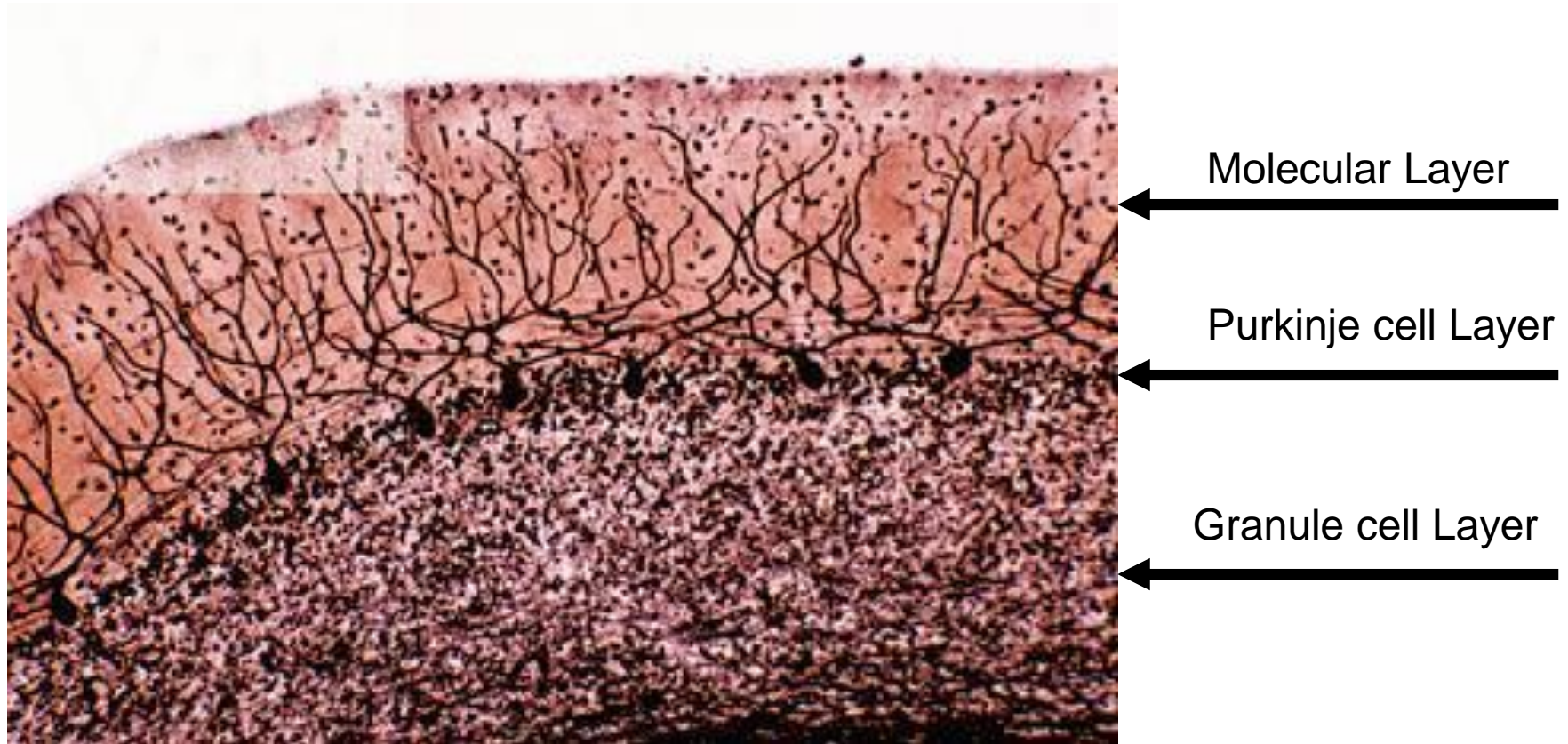
Cerebellar Cortex: The Beauty of Network Architecture



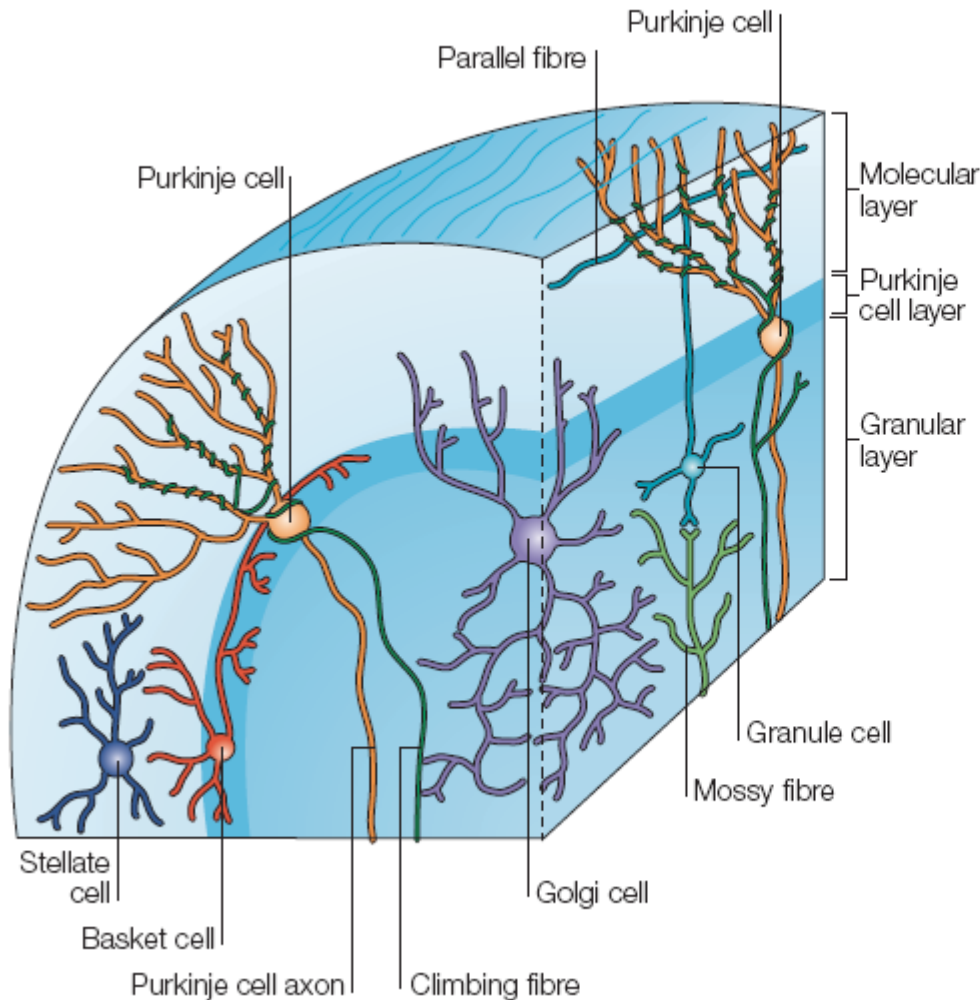
Purkinje Cells: The most Elaborate Neurons of the CNS



The 3 Layers of the Cerebellar Cortex



Cerebellar Cortex Consists of 5 types of Neurons



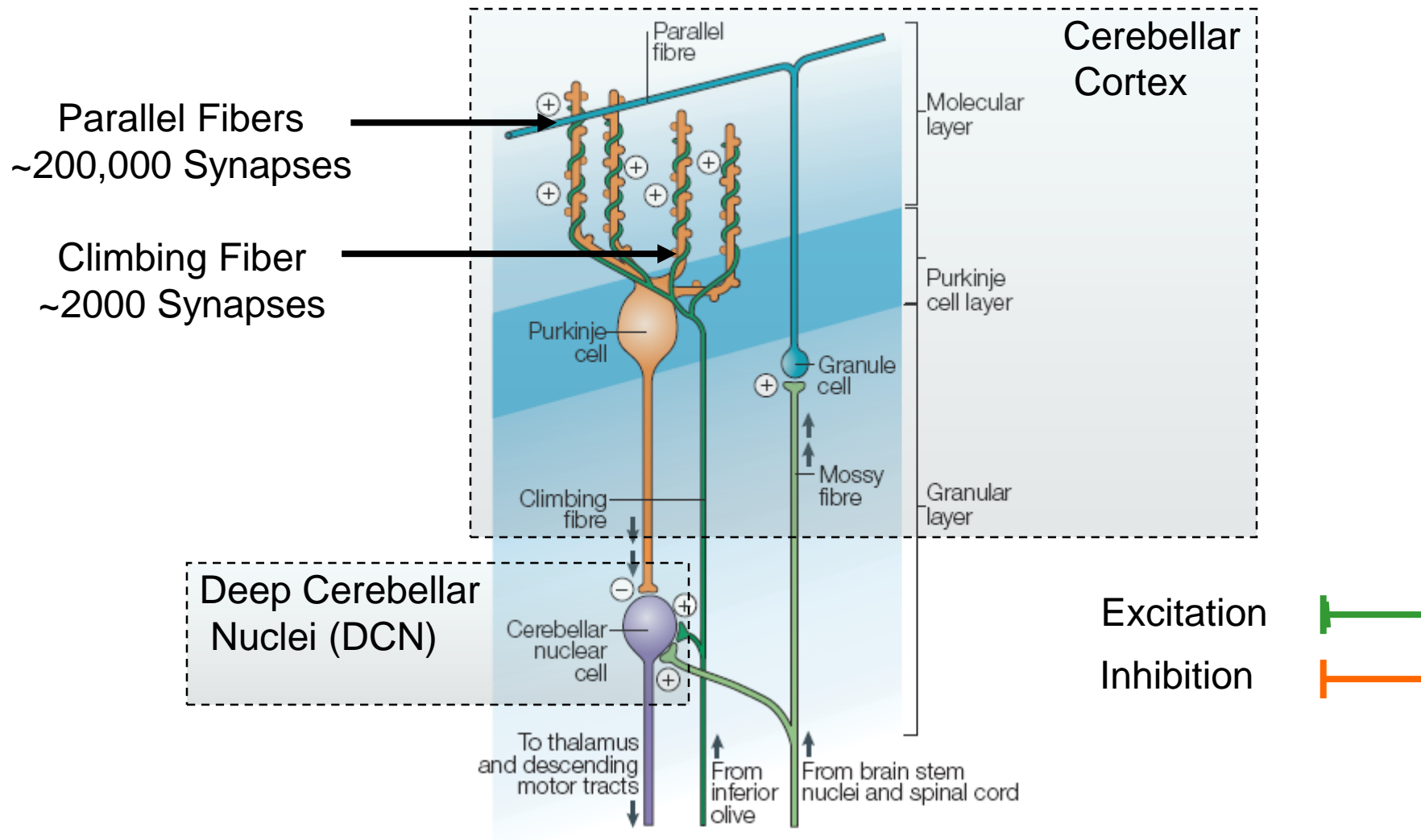
Inhibitory cells:

- Purkinje
- Golgi
- Basket
- Stellate

Excitatory Cells:

- Granule cells

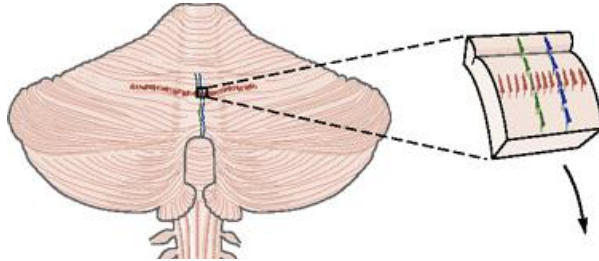
PC: The Principal Cell of Cerebellar Cortex



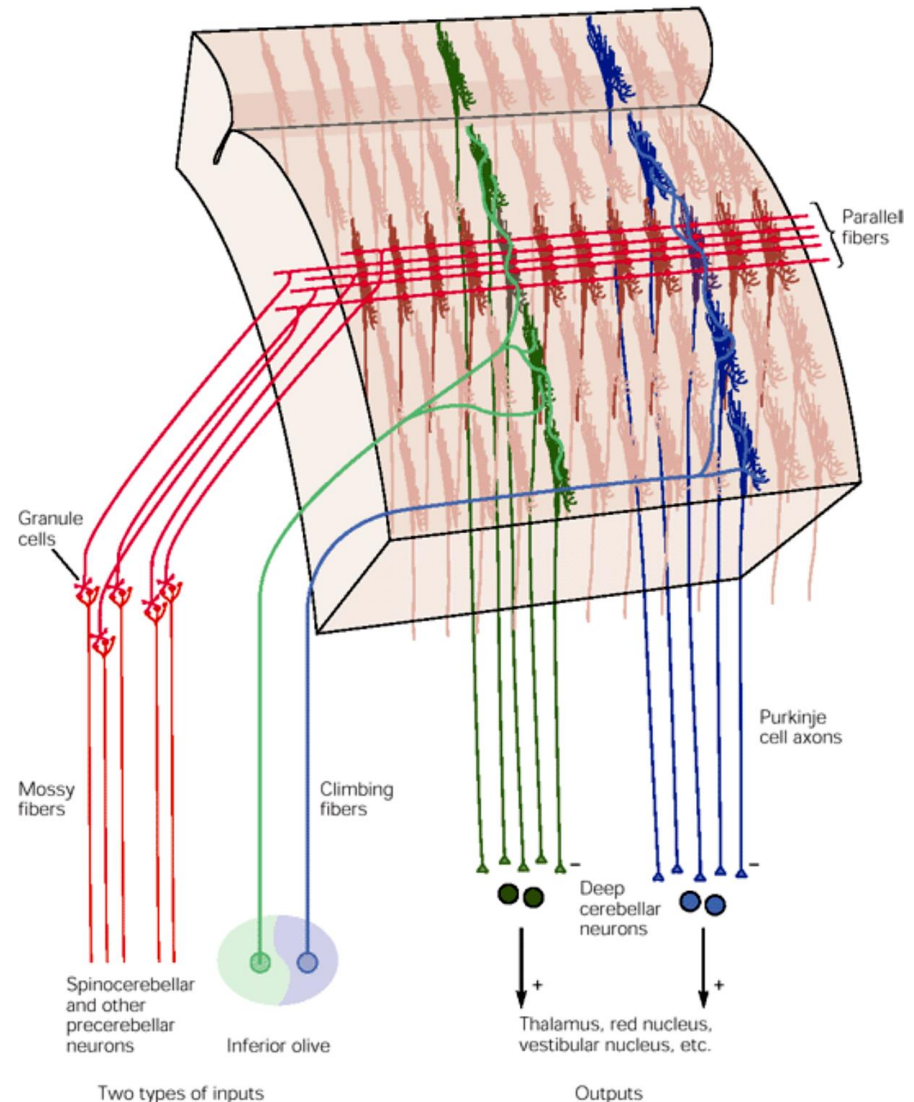
Purkinje Cells are the only neurons projecting from the Cerebellar Cortex!!

Modified from Apps & Garwicz 2005

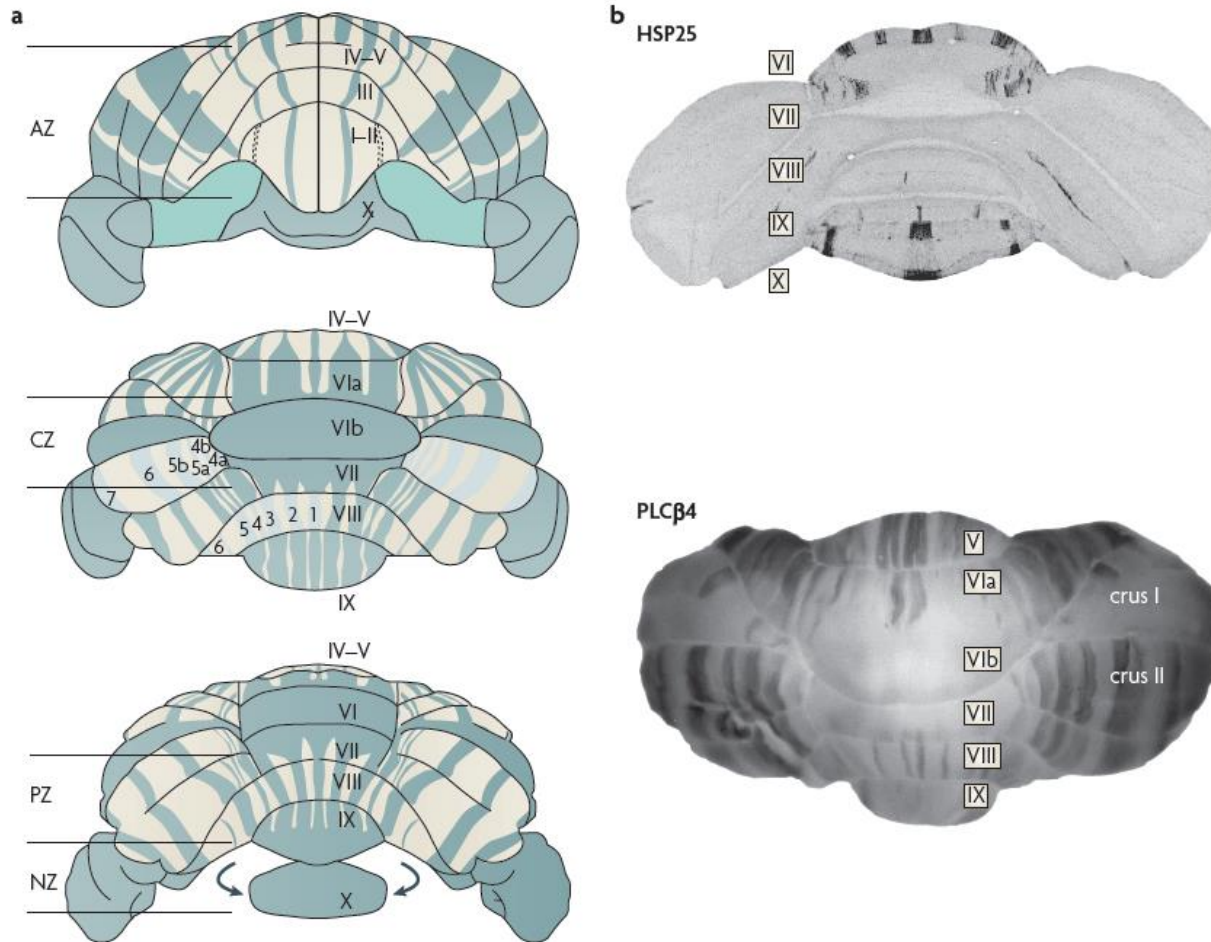
The Spatial Organization of Cerebellar Circuitry



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

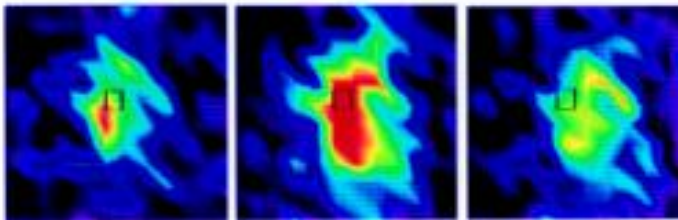
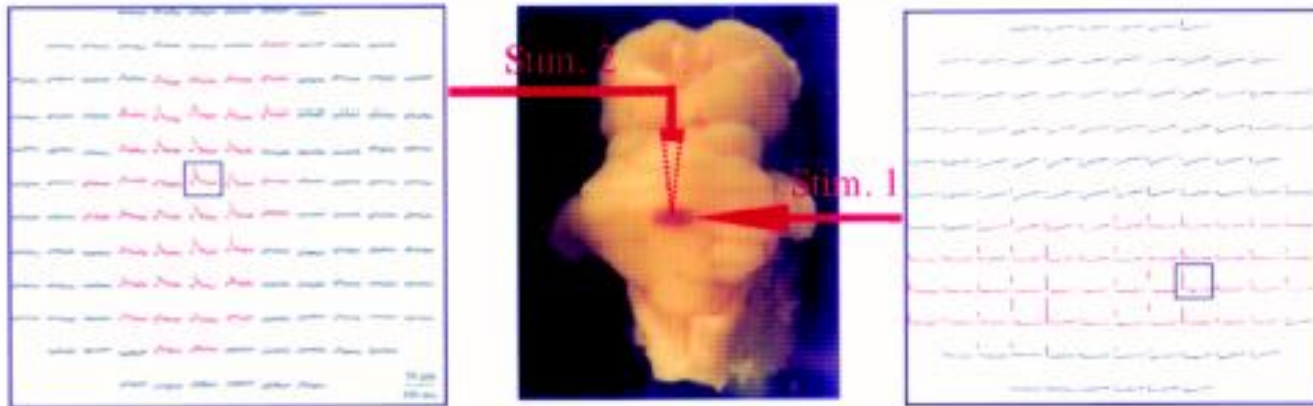


Parasagittal Microzones of Cerebellar Cortex

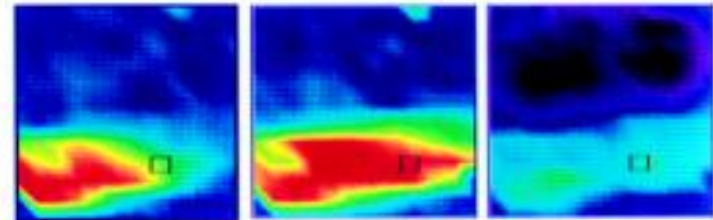


Some Molecular Markers (i.e. Zebrin II) divide Purkinje Cells Populations into parasagittal stripes.

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

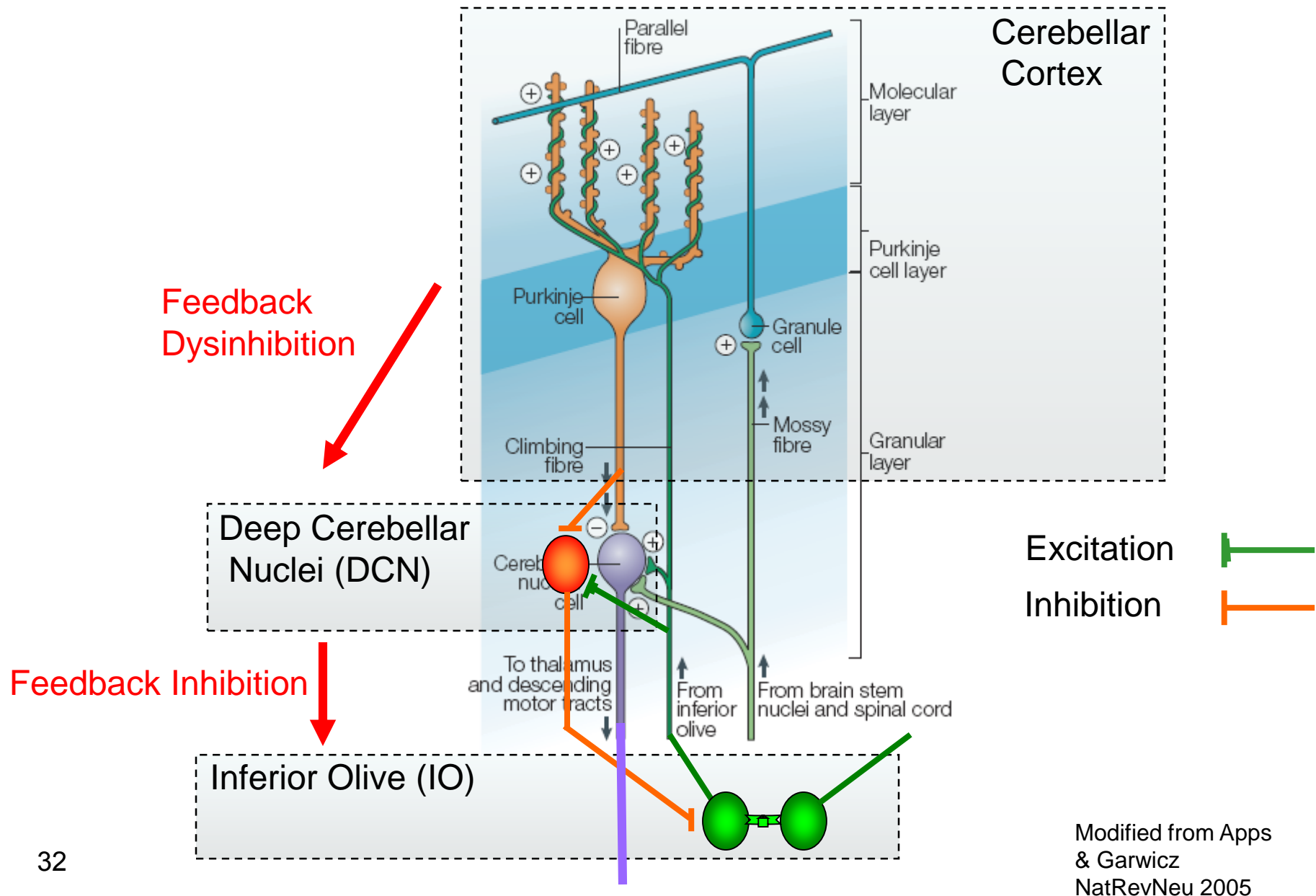


Stimulation of granular layer



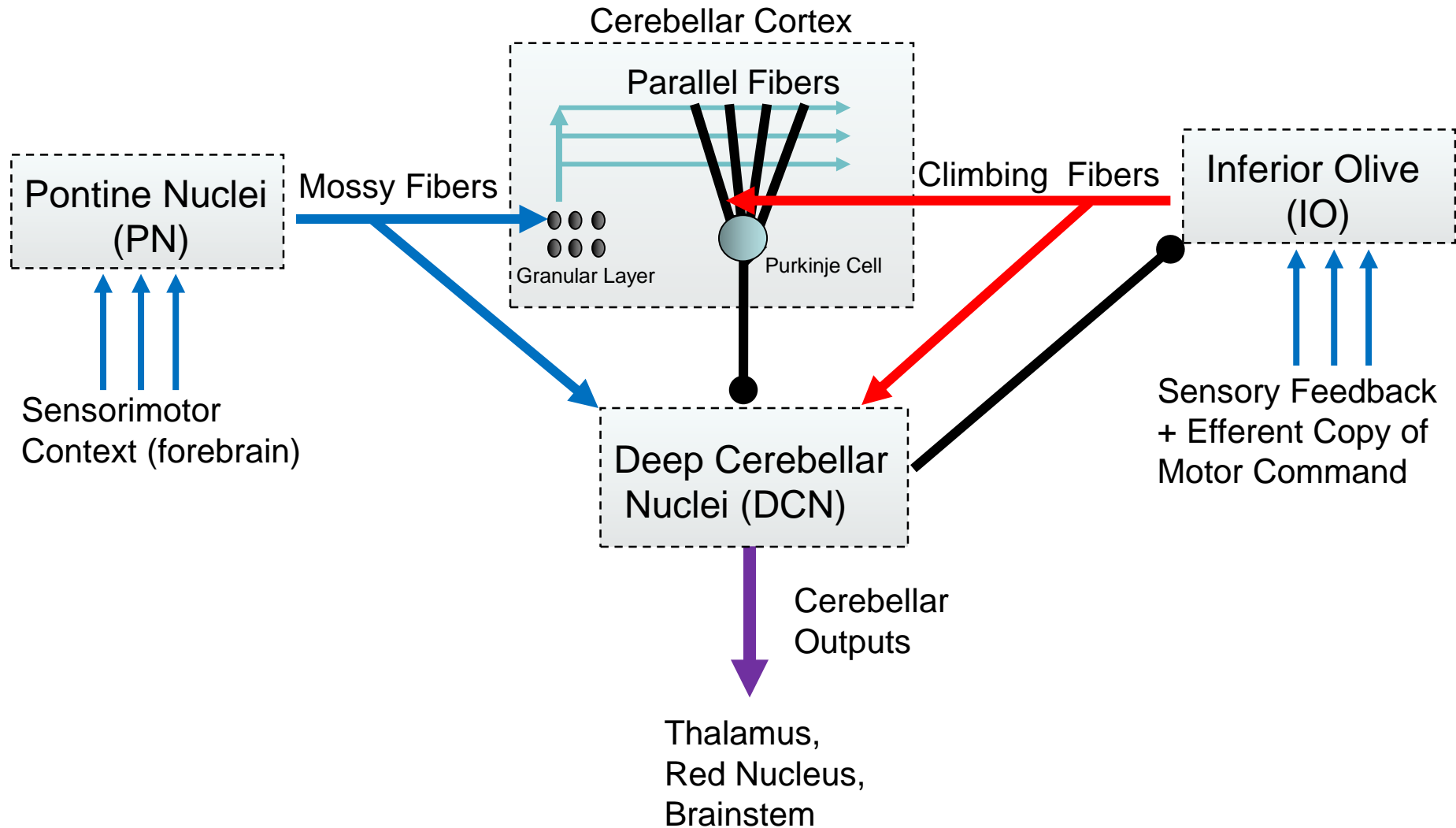
Stimulation of parallel fibers

Closing the Loop: The Cerebellar Module



Modified from Apps
& Garwicz
NatRevNeu 2005

The simplified Olivocerebellar Module

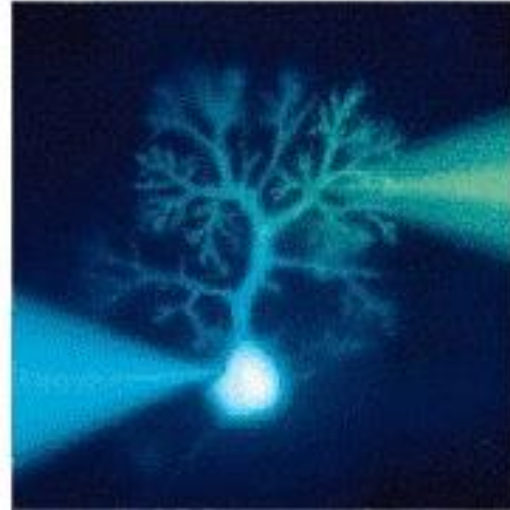


Cerebellar Physiology

Infra Red



Fluorescent Dye

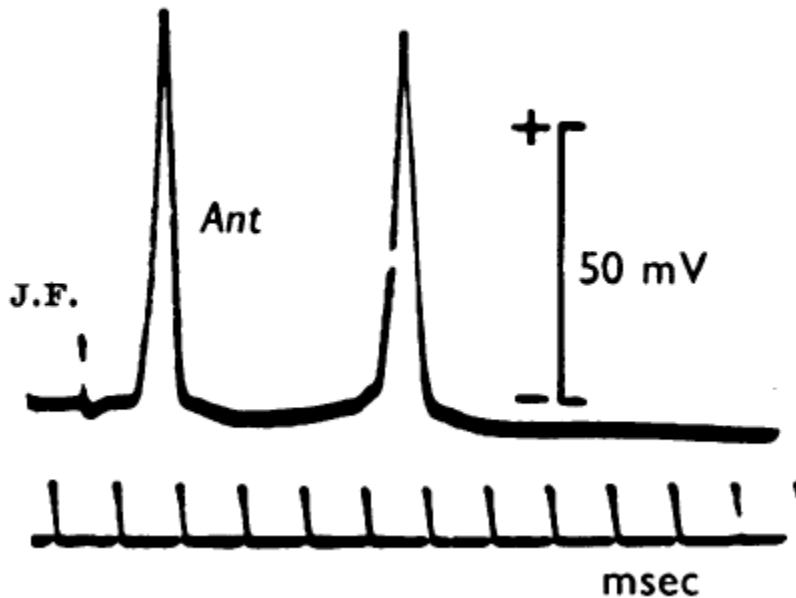


Double Recording of Purkinje Cell in Slice

Hausser M.

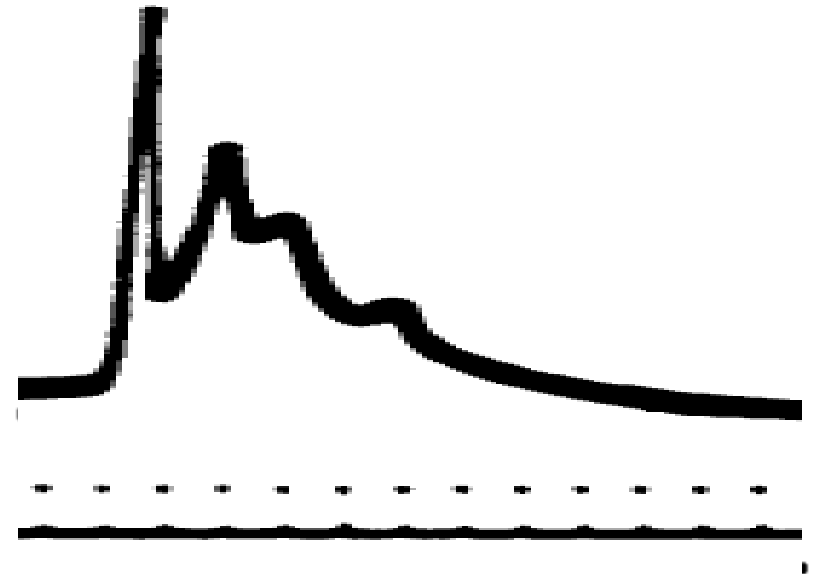
Purkinje Cells exhibit Two distinct Spike Types

Simple Spike



Mossy Fiber Stimulation

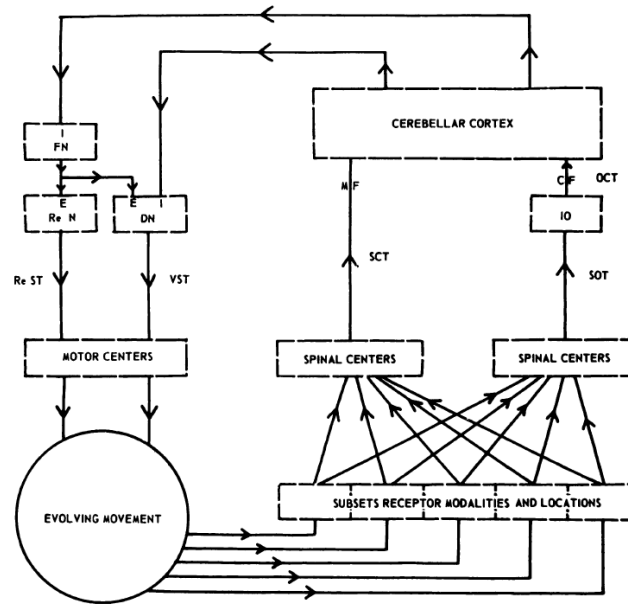
Complex Spike



Inferior Olive Stimulation

Eccles, 1966

Cerebellar Learning Theories



Eccles, 1967

MATHEMATICAL BIOSCIENCES

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)

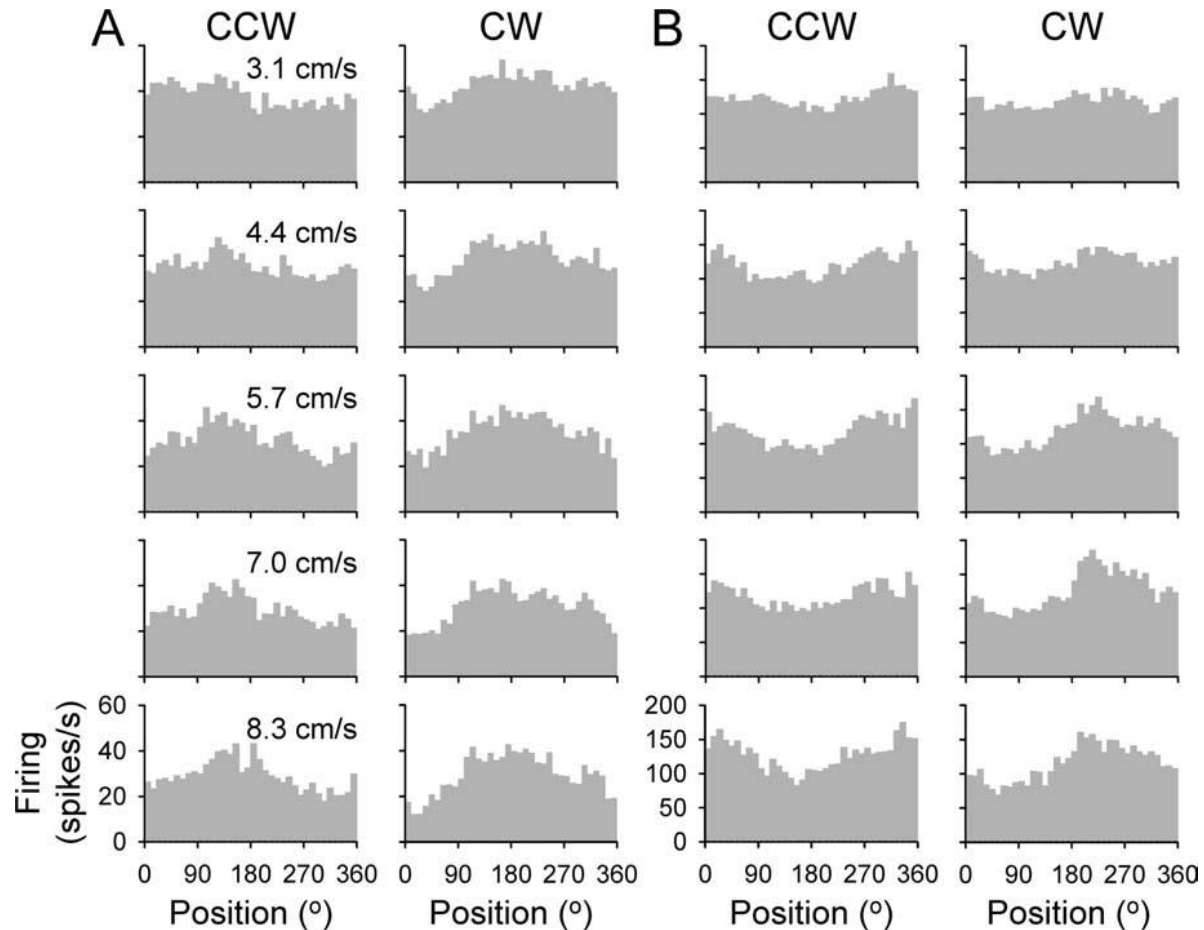
A Theory of Cerebellar Function

JAMES S. ALBUS

*Cybernetics and Subsystem Development Section
 Data Techniques Branch
 Goddard Space Flight Center
 Greenbelt, Maryland*

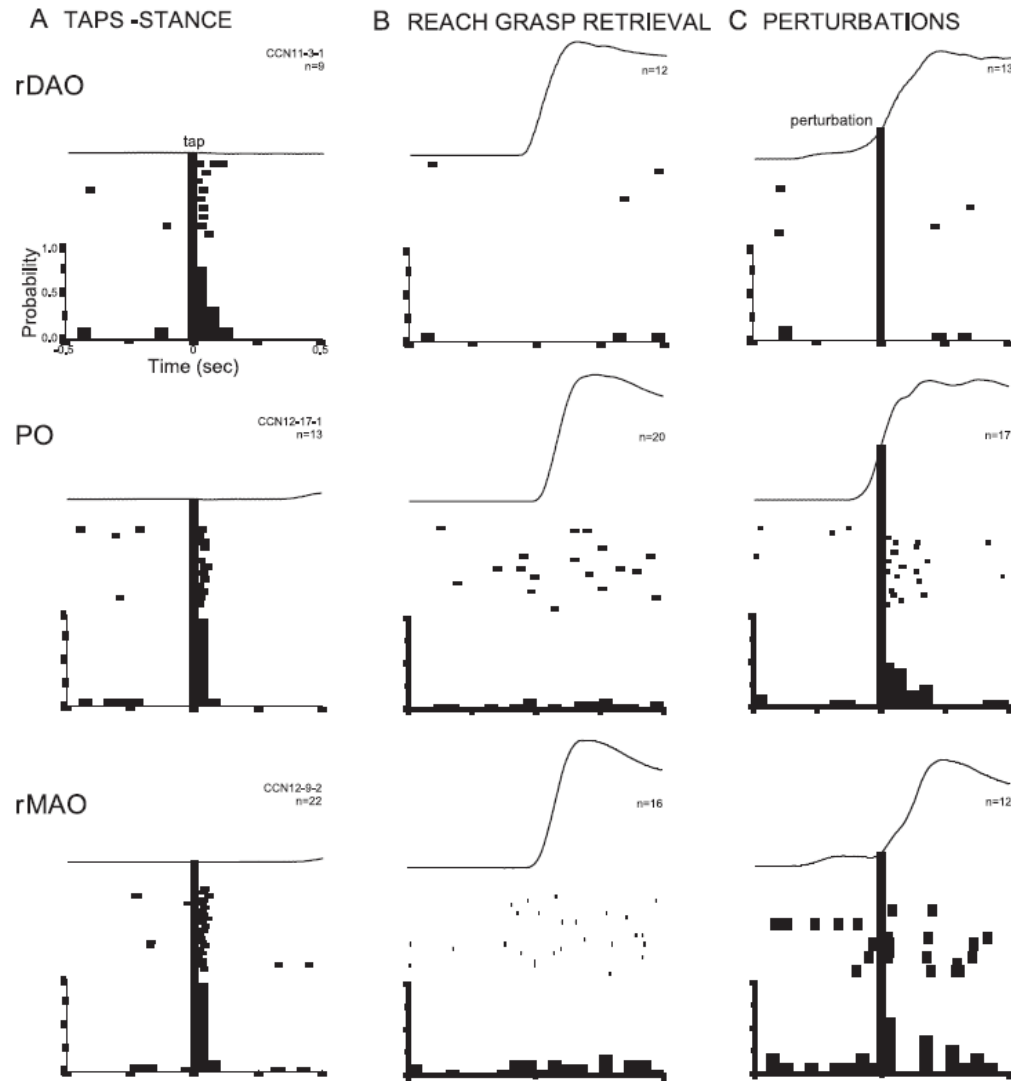
1971

Simple Spikes are Modulated by Inputs



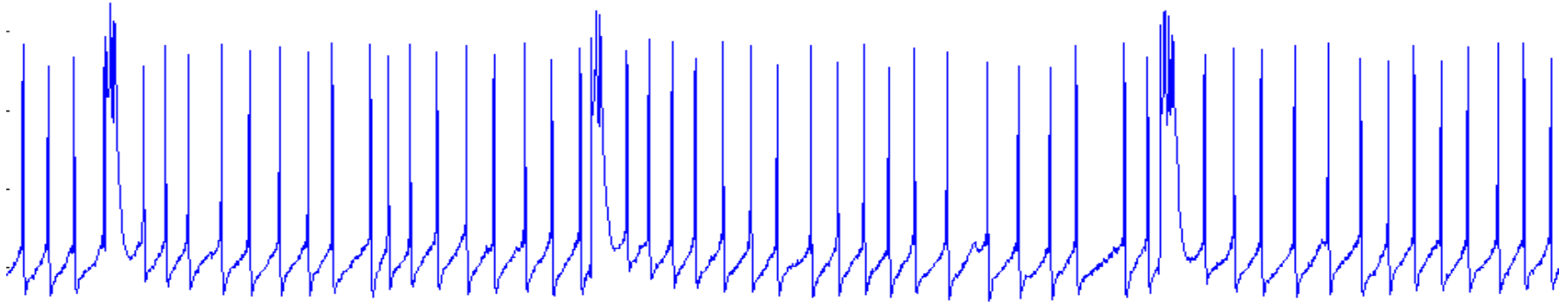
Simple spikes of 2 Purkinje cells in awake monkey during hand movements

Olivary Spikes are fired in Unexpected Events

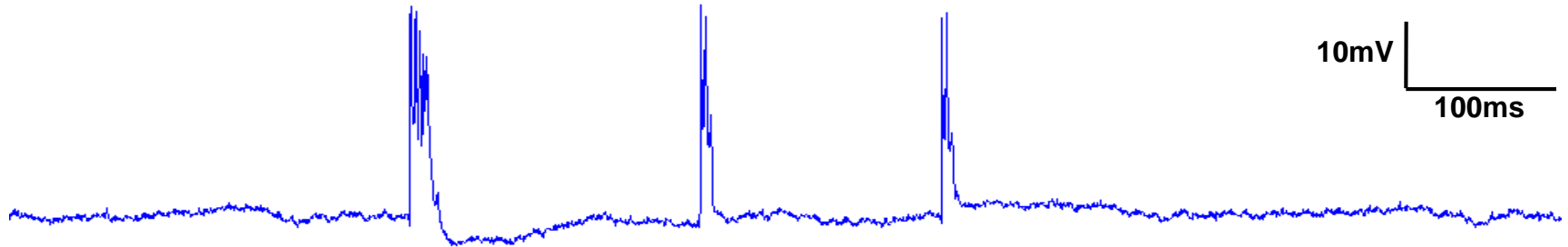


Distinct Firing Regimes of Purkinje Cells

Complex Spikes & Simple Spikes (Up-State)



Complex Spikes Only (Down-State)

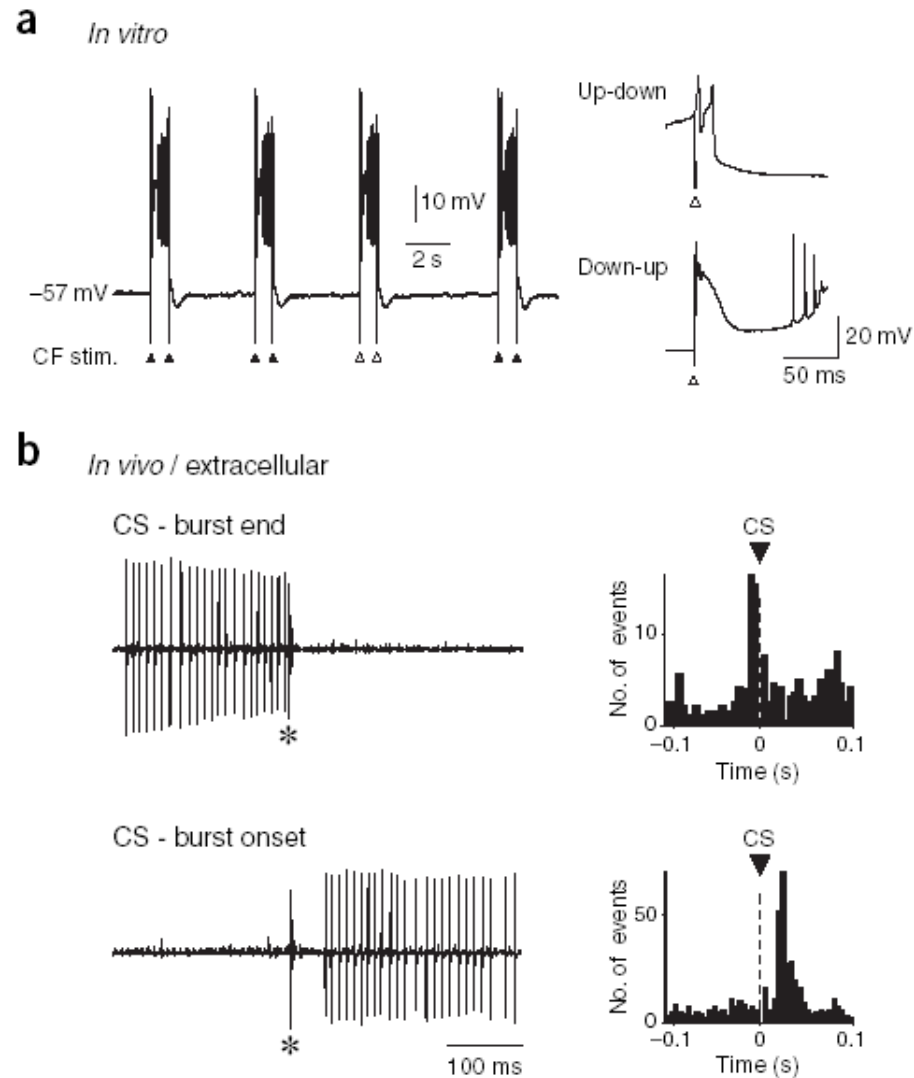


Simple Spikes: 0 - ~80Hz

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

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

Complex Spikes as Purkinje Cell Switches

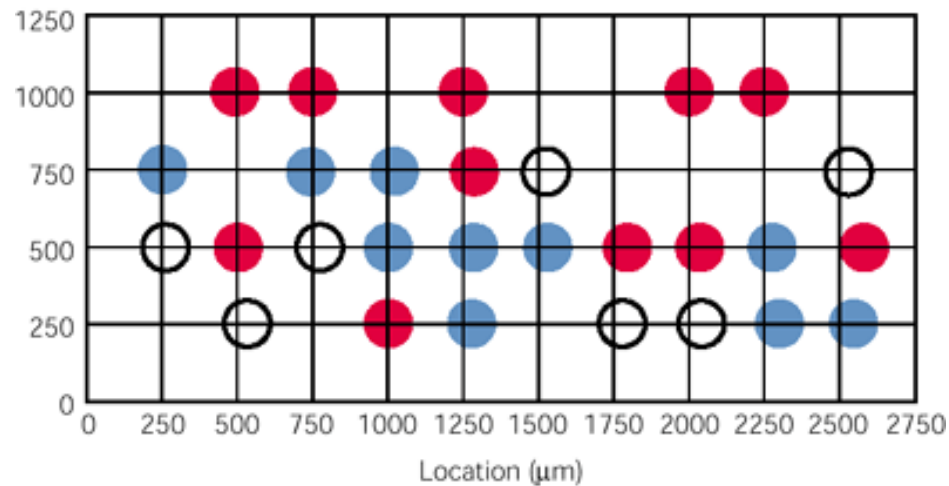


Synchronous Population Coding by Purkinje Cells

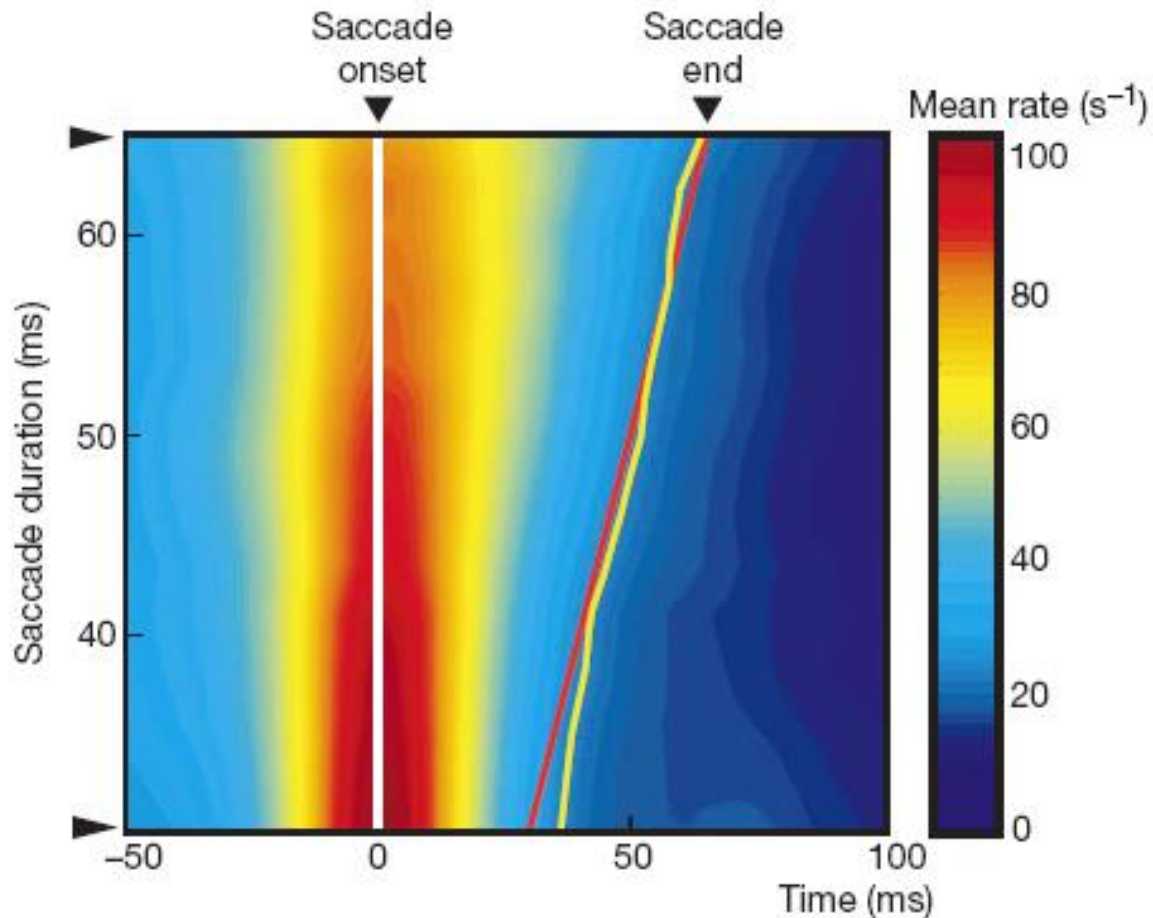
A



B

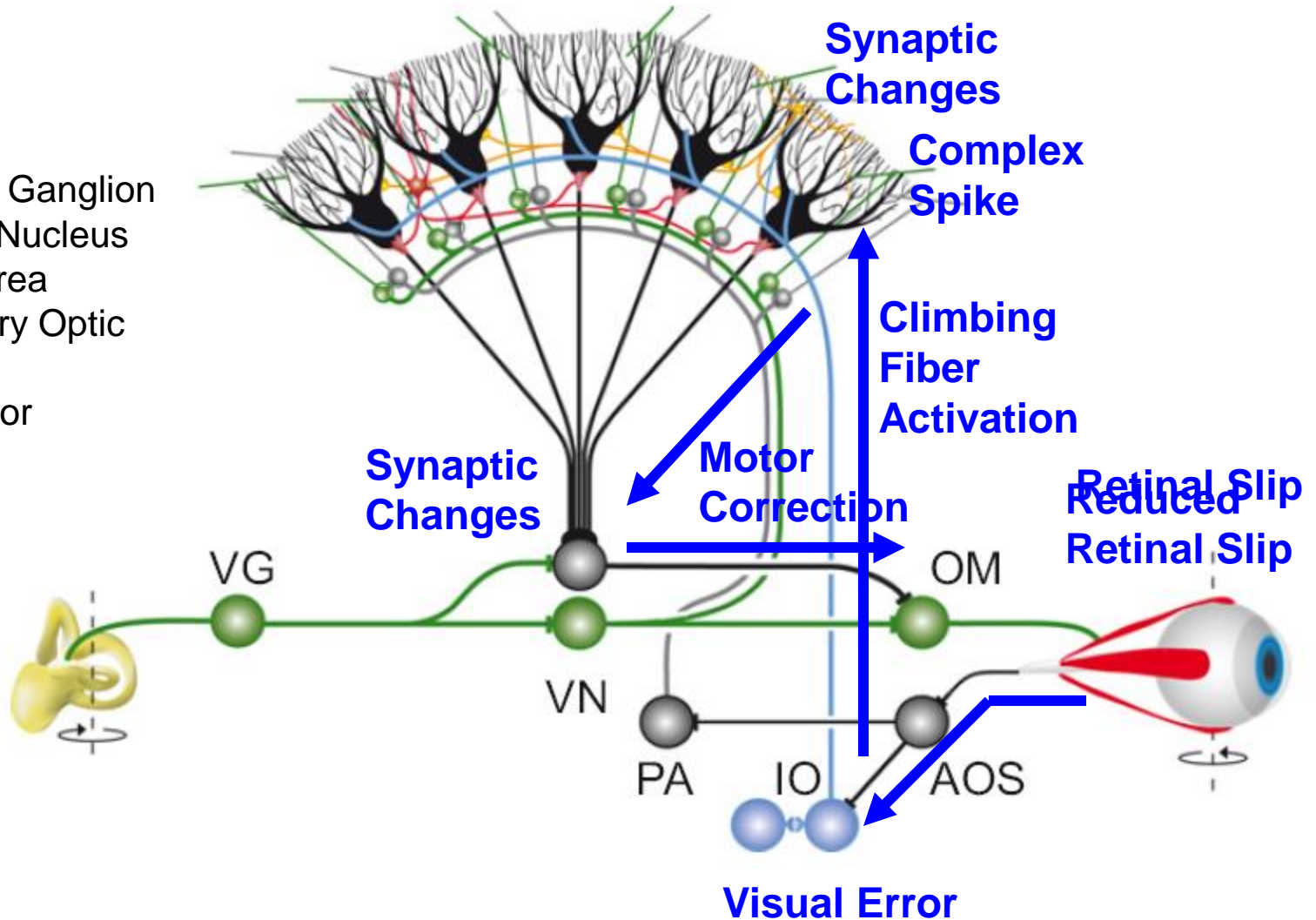


Saccade attributes are encoded by a population of ~100 Purkinje cells

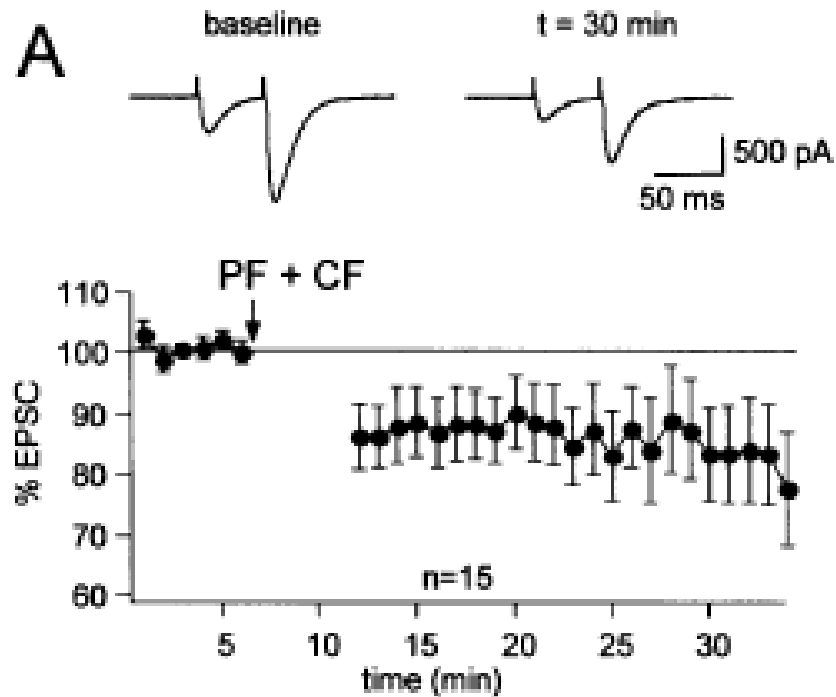


Vestibulo - Ocular Adaptation (VOR)

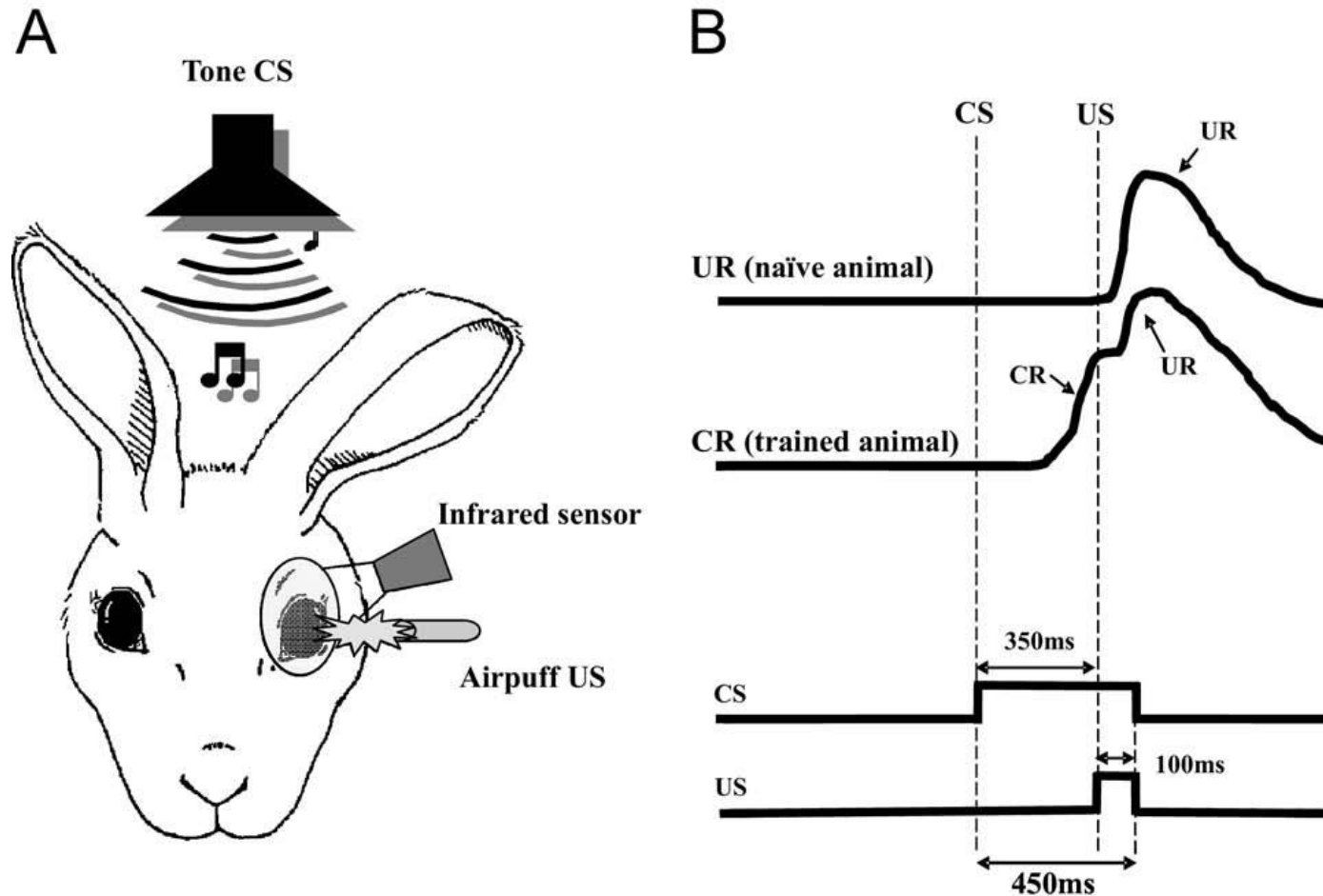
VG = Vestibular Ganglion
VN = Vestibular Nucleus
PA = Pontine Area
AOS = Accessory Optic System
OM = Oculomotor Neurons



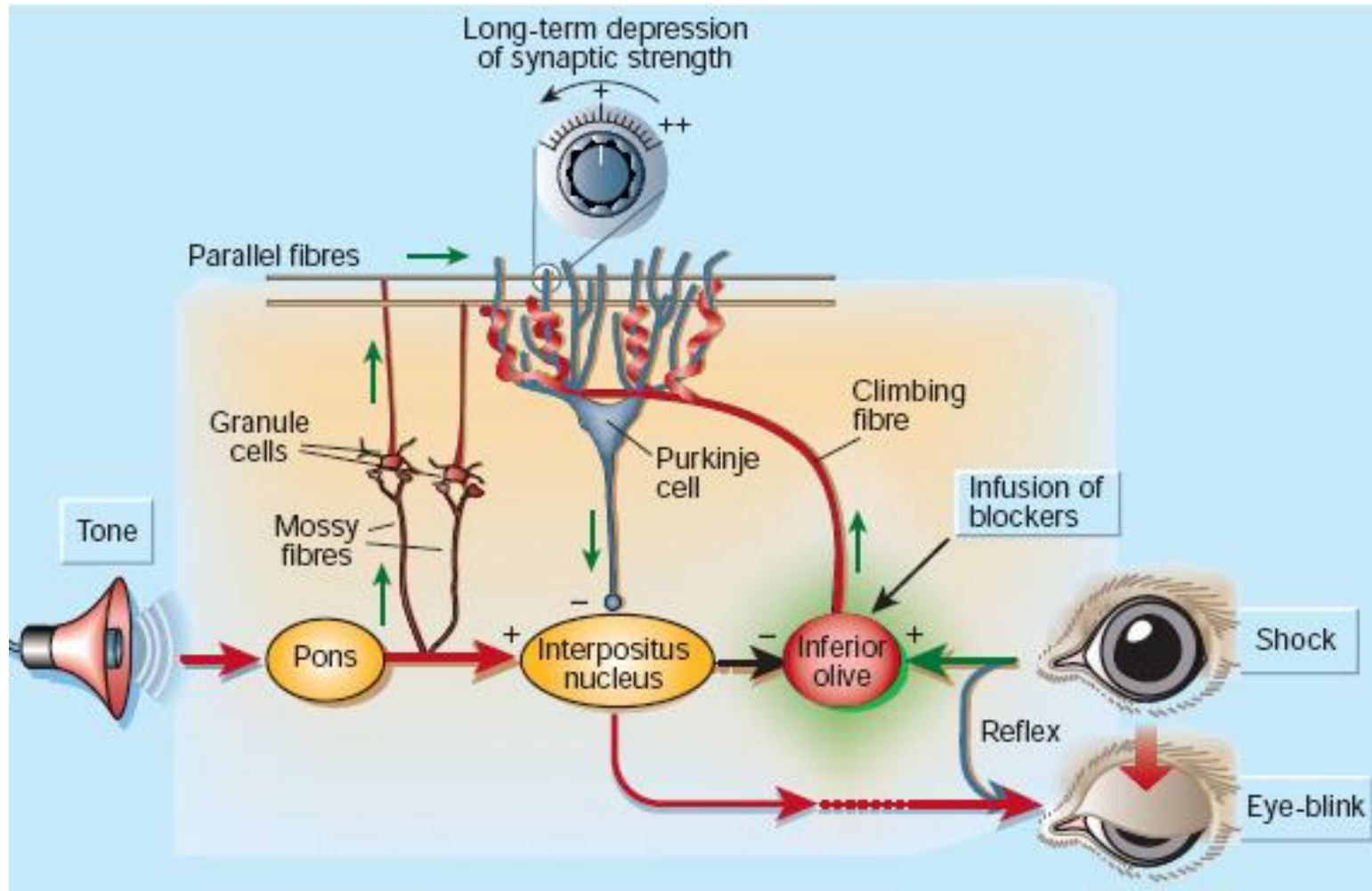
Plasticity in the Cerebellar Cortex



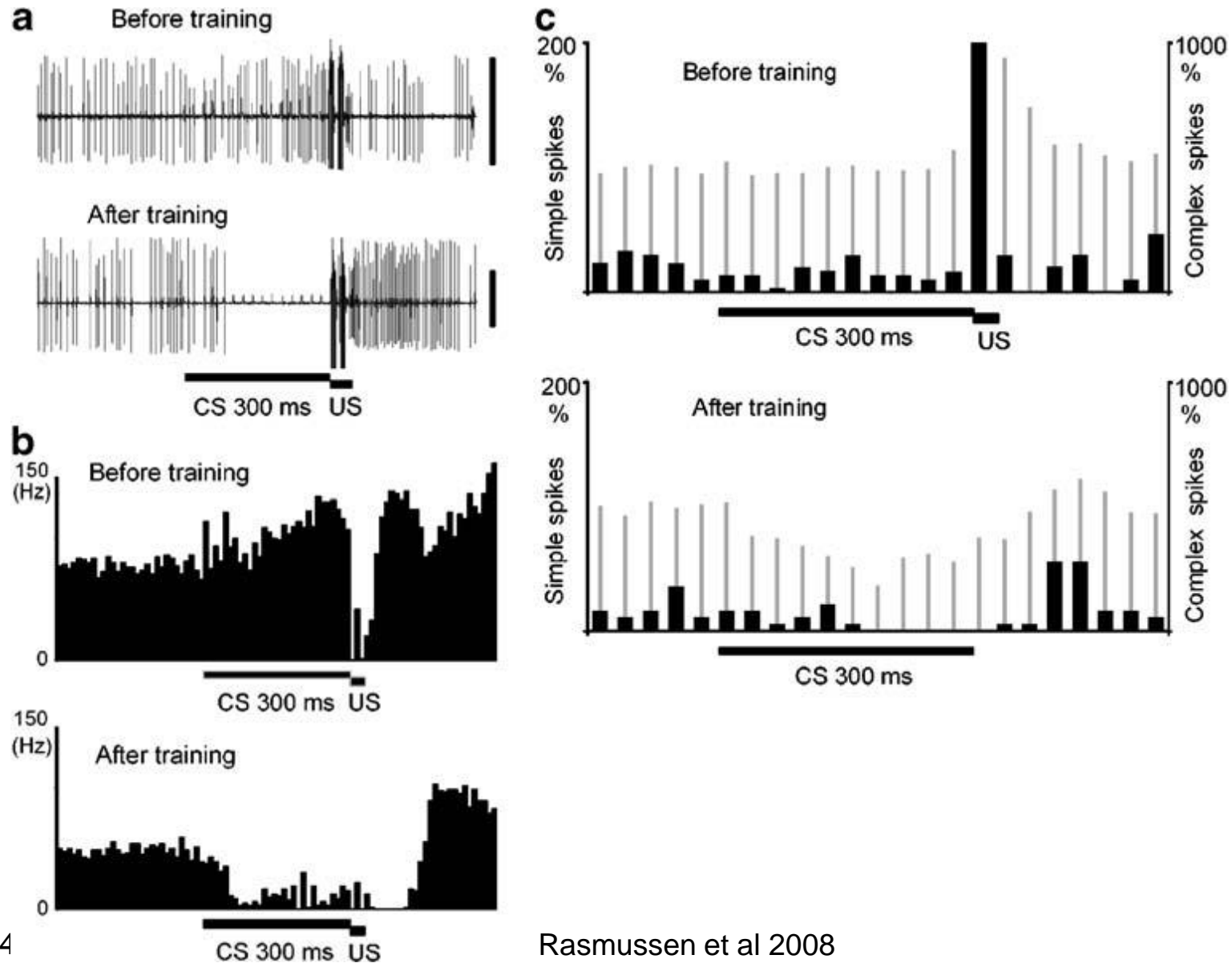
Eyelid Reflex Conditioning



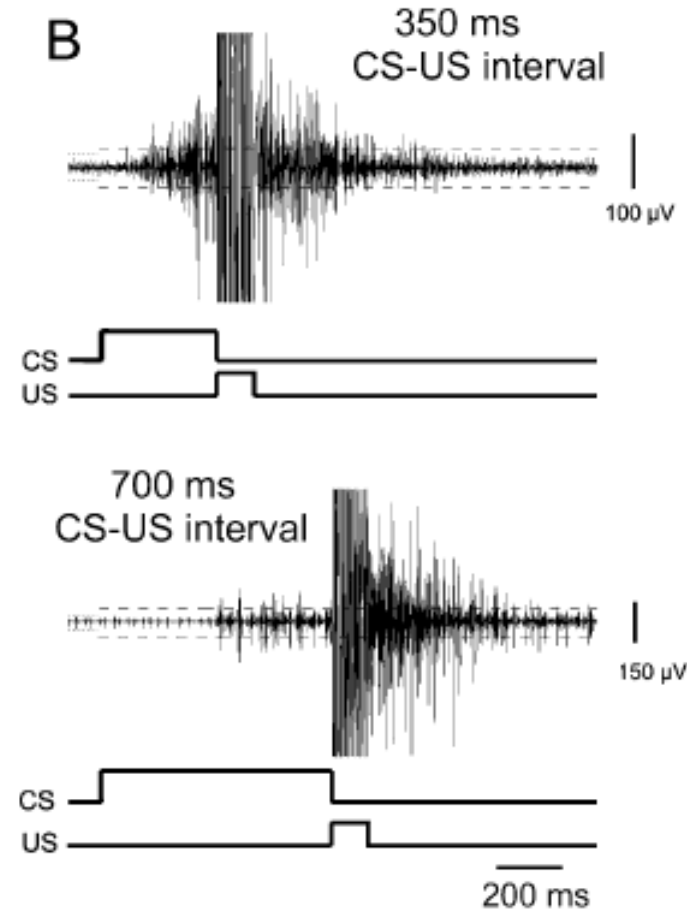
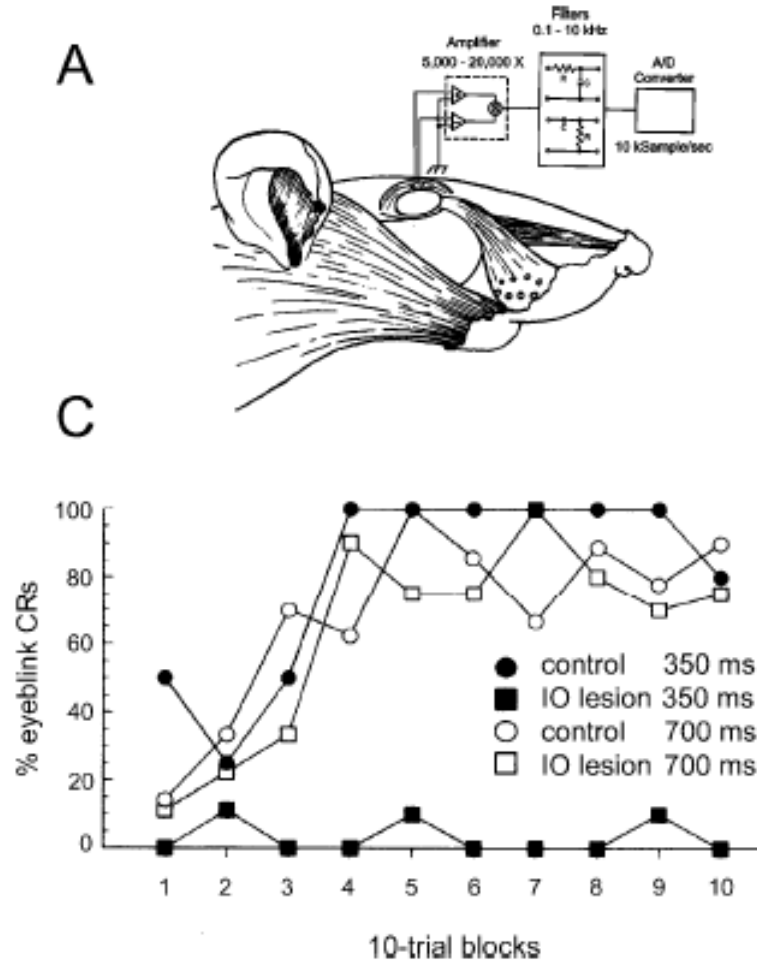
Eyelid Reflex Conditioning



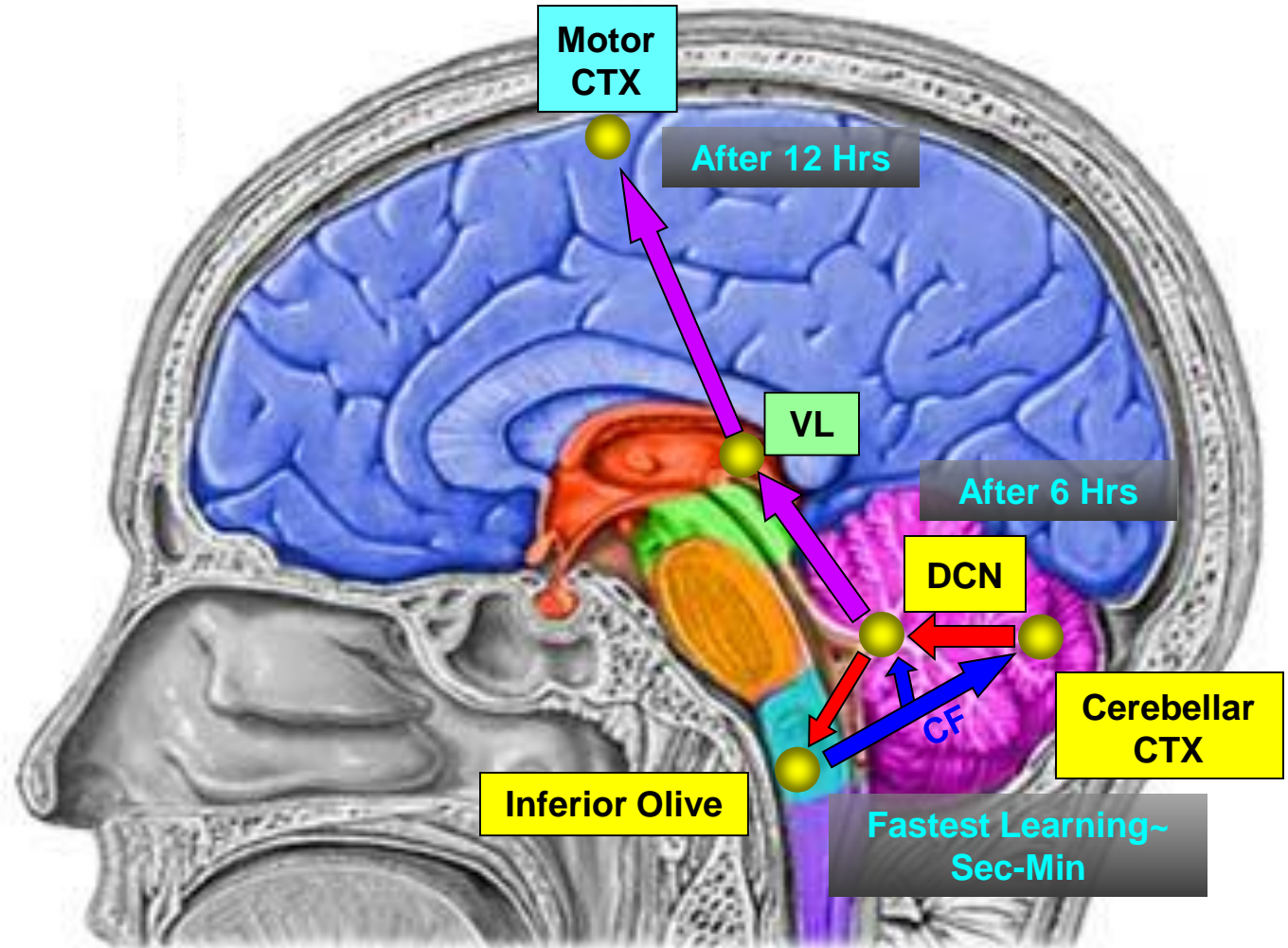
Eyelid Reflex Conditioning



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

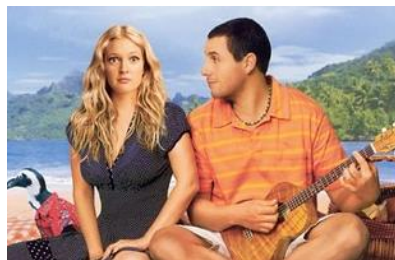


The Learning Transfer Hypothesis



VL = Vento-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?

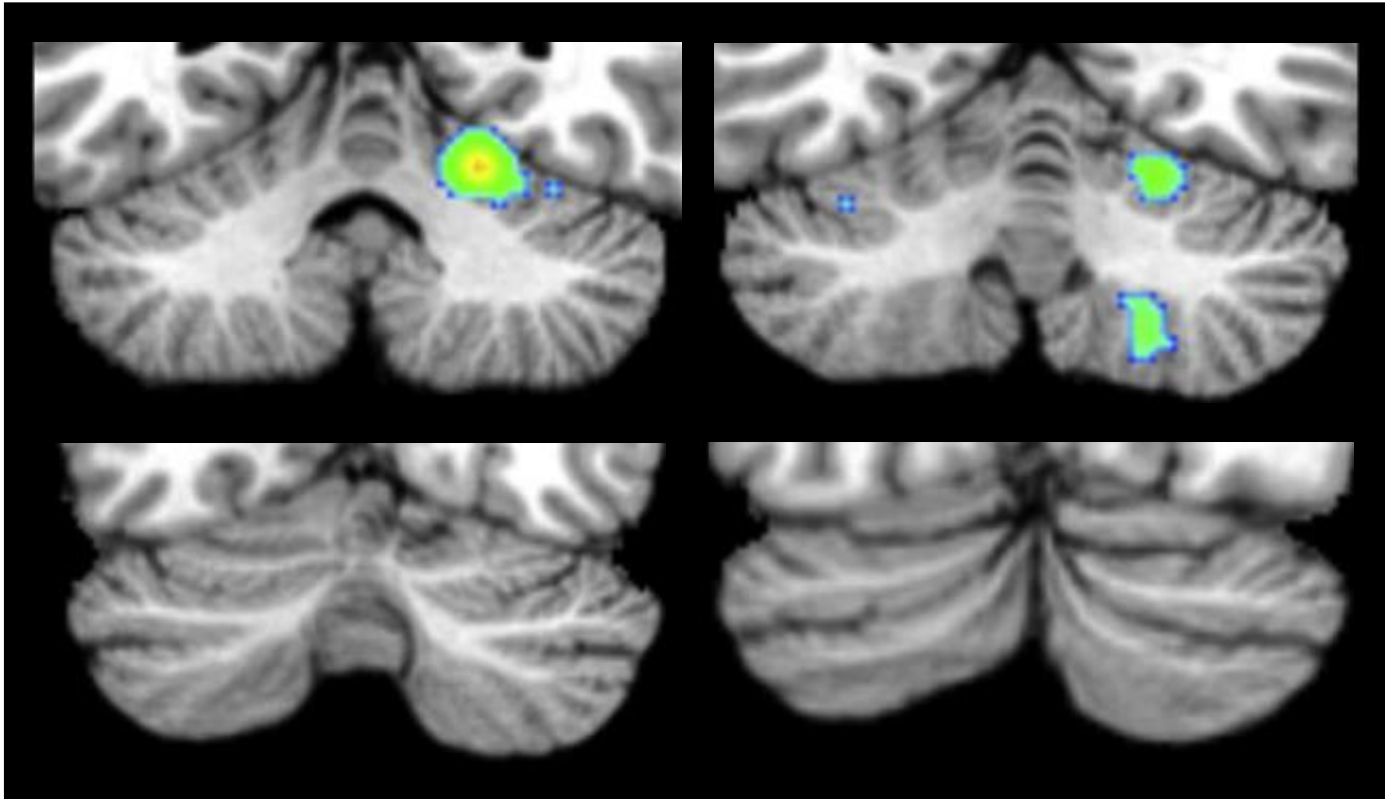
Specific cerebellar regions with cognitive dysfunction following focal damage



Cognitive effects of focal damage were found when:

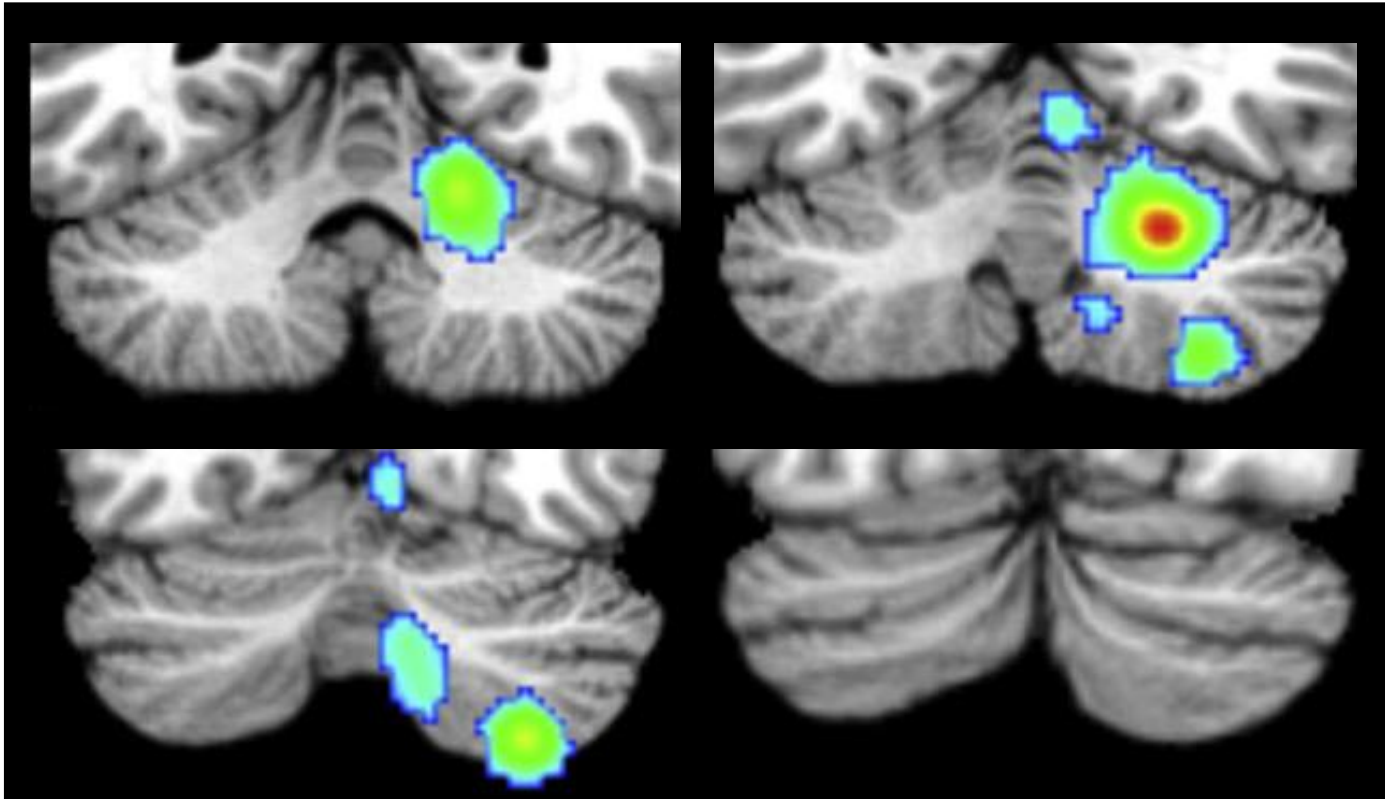
1. The damage involved the vermis
2. The damage was in an areas which get blood supply from the posterior inferior cerebellar artery
3. Children with Vermal damage show autistic-like features:
 - Irritability
 - impulsivity
 - Disinhibition
 - Emotional lability
4. Complex verbal dysfunction associated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

FMRI Mapping of Cerebellar Involvement in Various Processes



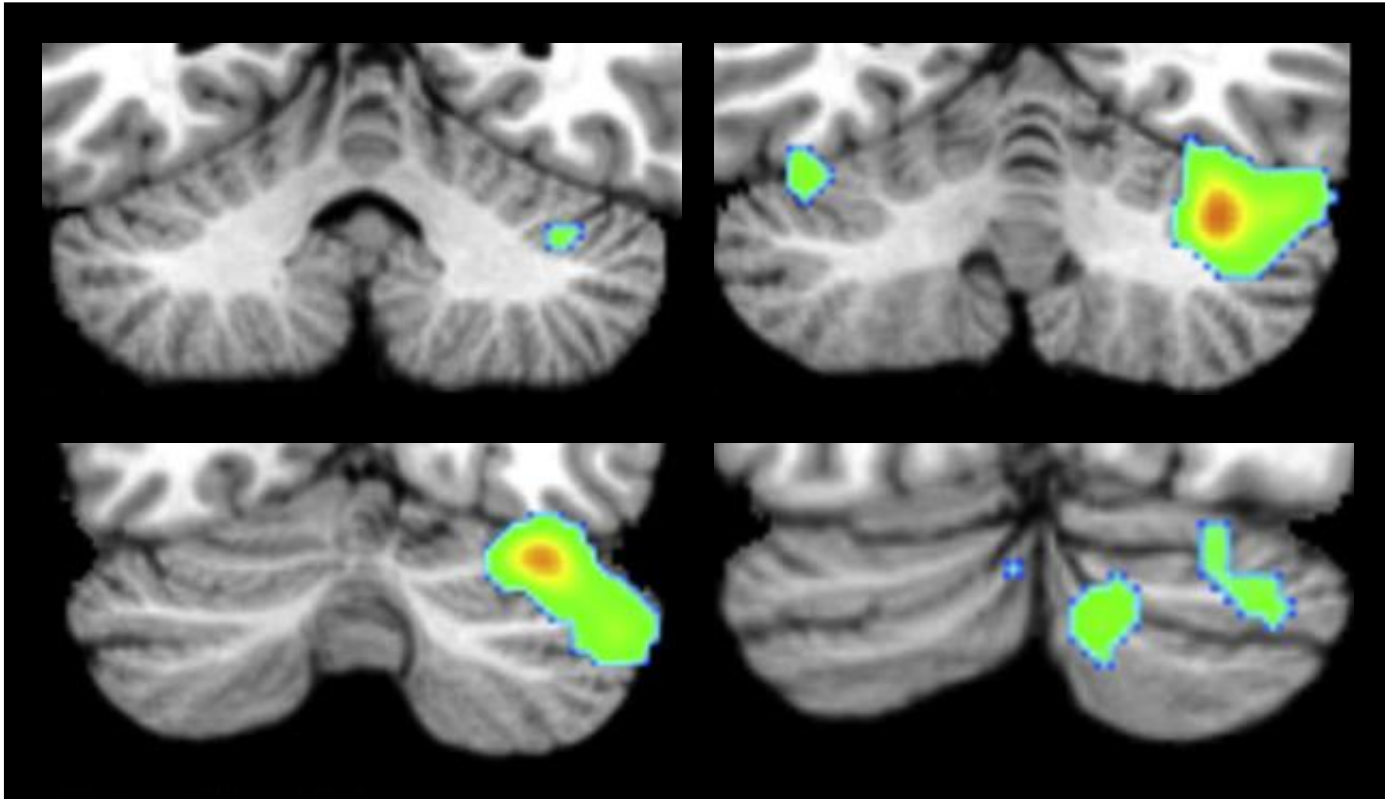
Somatosensory Processing

FMRI Mapping of Cerebellar Involvement in Various Processes



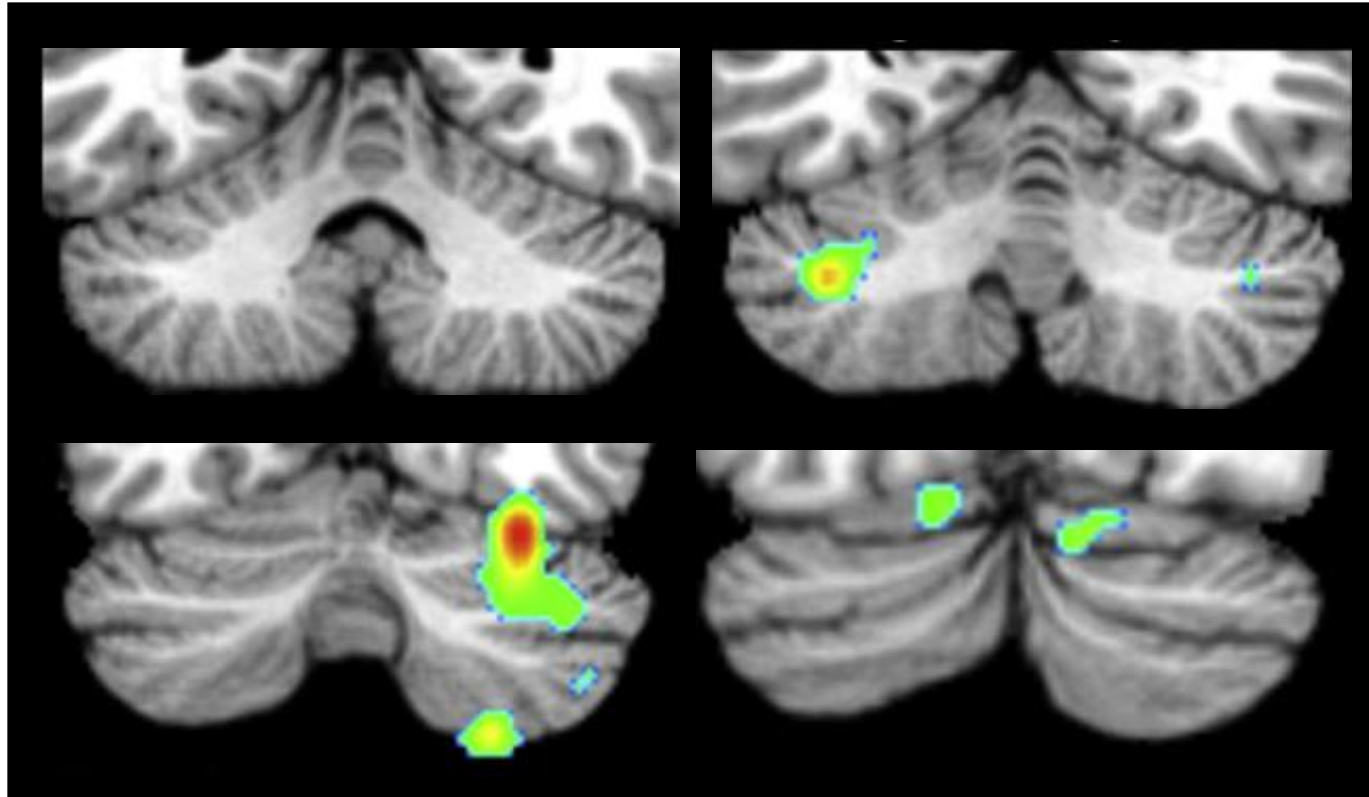
Motor Processing

FMRI Mapping of Cerebellar Involvement in Various Processes



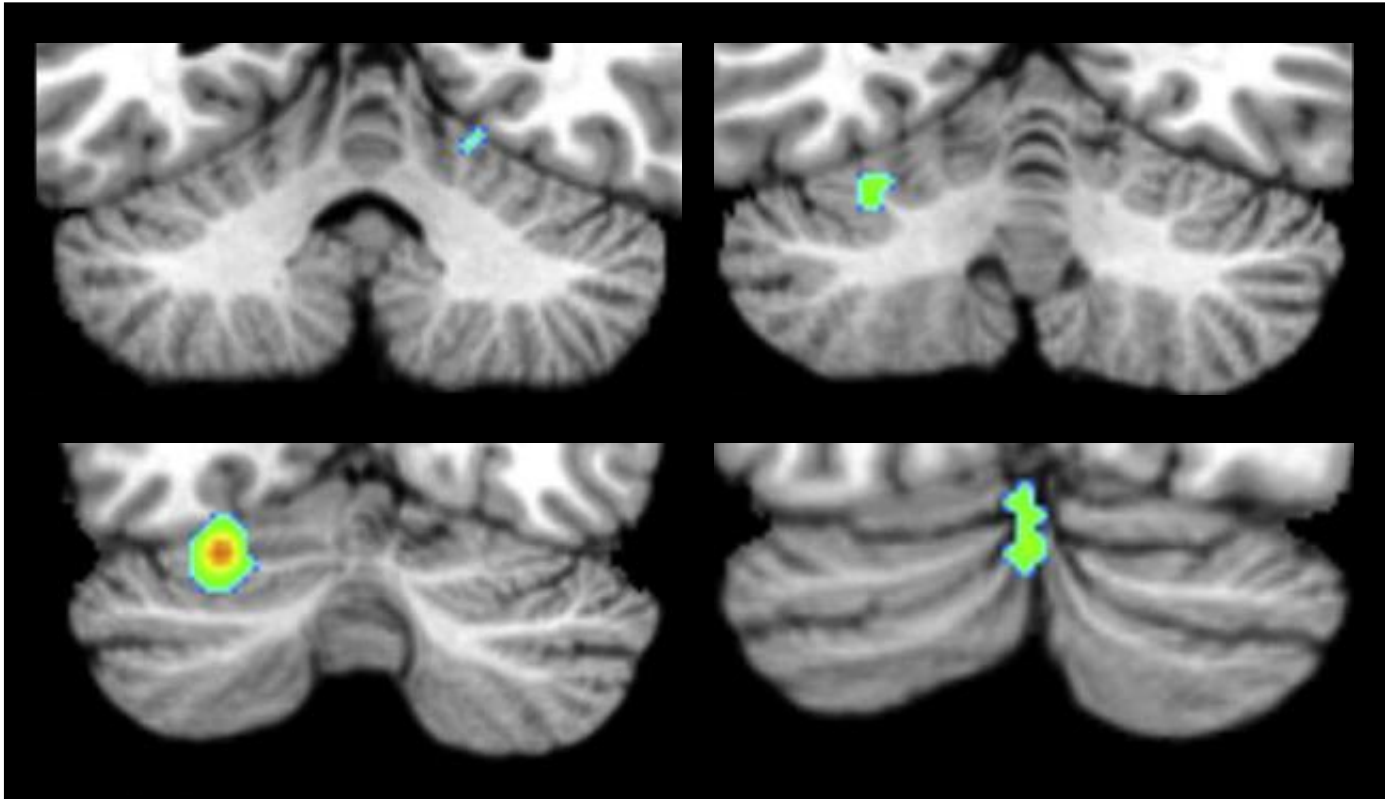
Language Processing

FMRI Mapping of Cerebellar Involvement in Various Processes



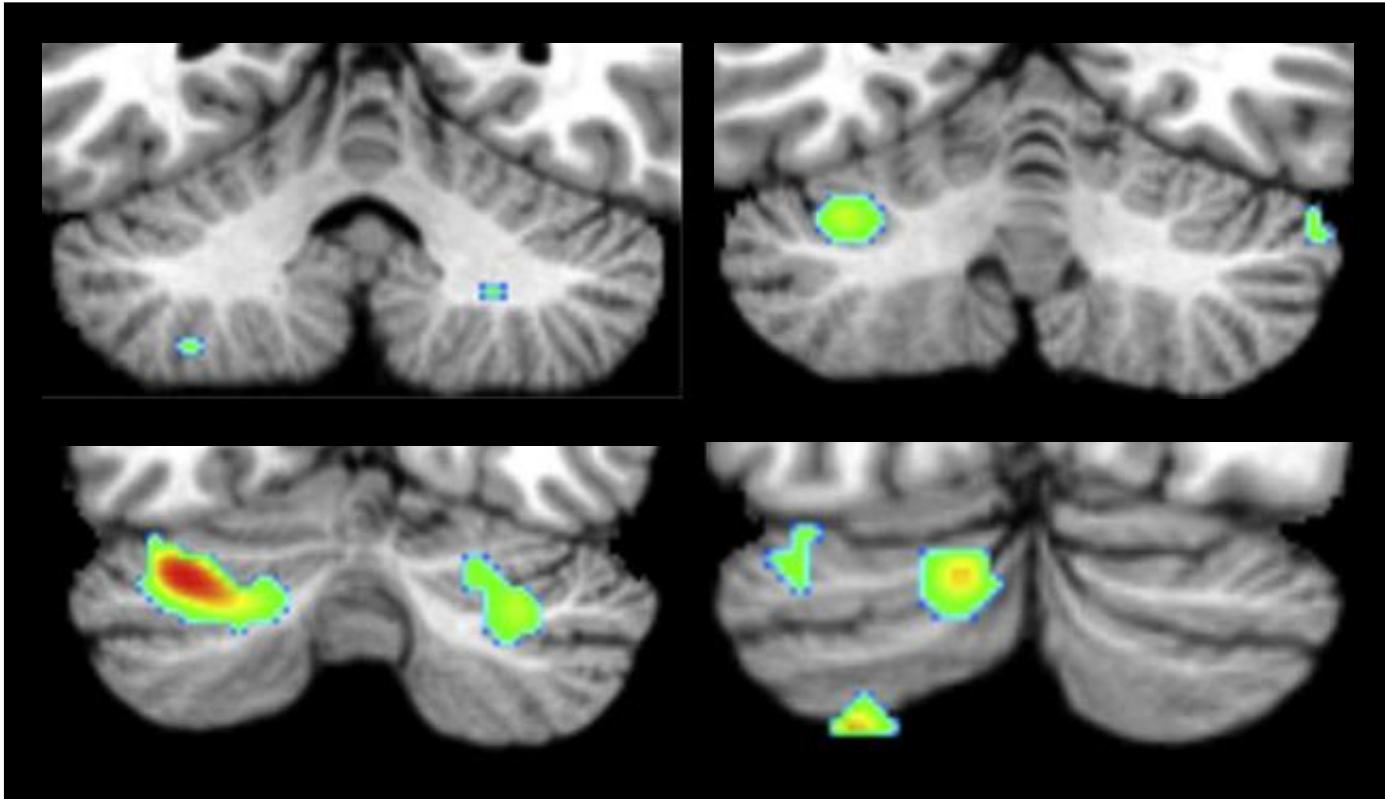
Working Memory

FMRI Mapping of Cerebellar Involvement in Various Processes



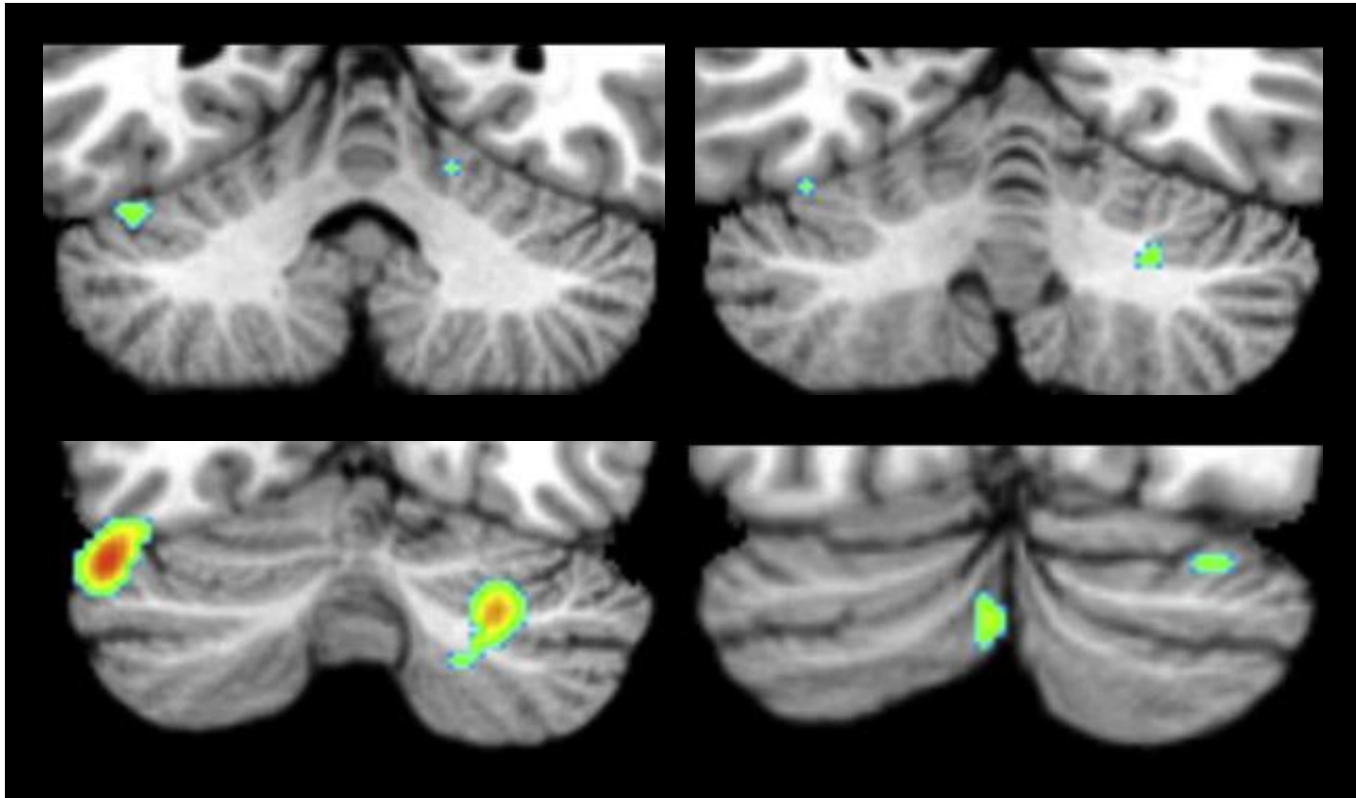
Spatial Processing

FMRI Mapping of Cerebellar Involvement in Various Processes



Executive Processing

FMRI Mapping of Cerebellar Involvement in Various Processes



Emotional Processing

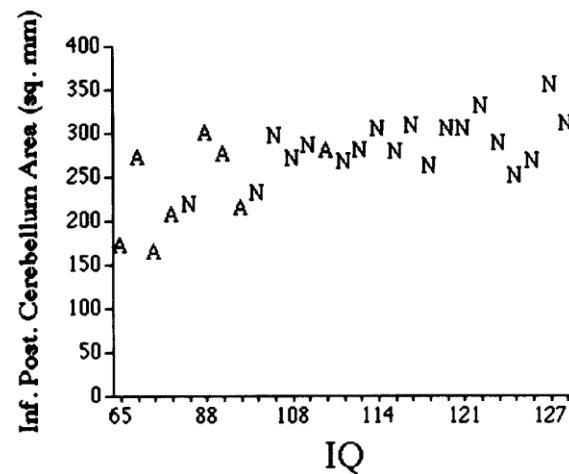
Cerebellar Involvement in Autism



Control Subject

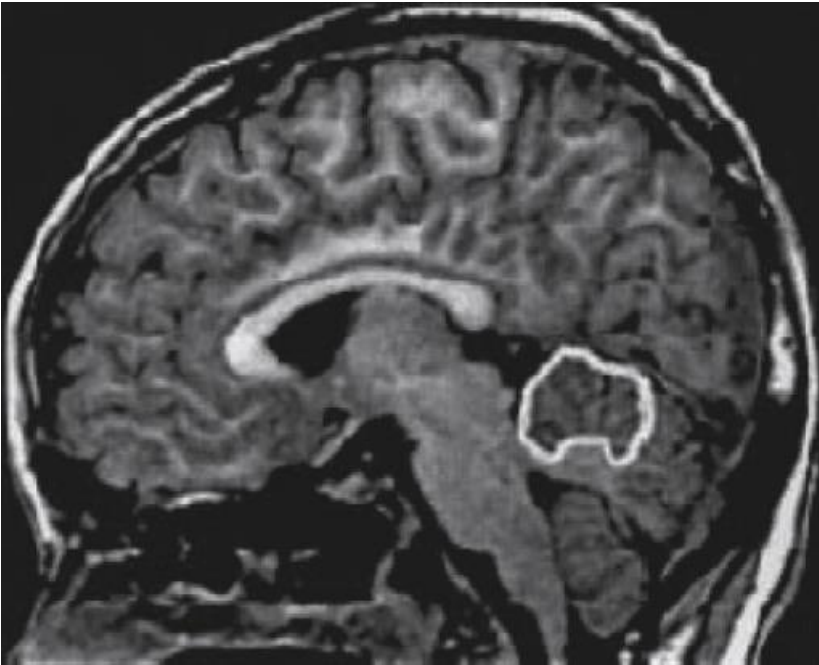


Autistic Subject

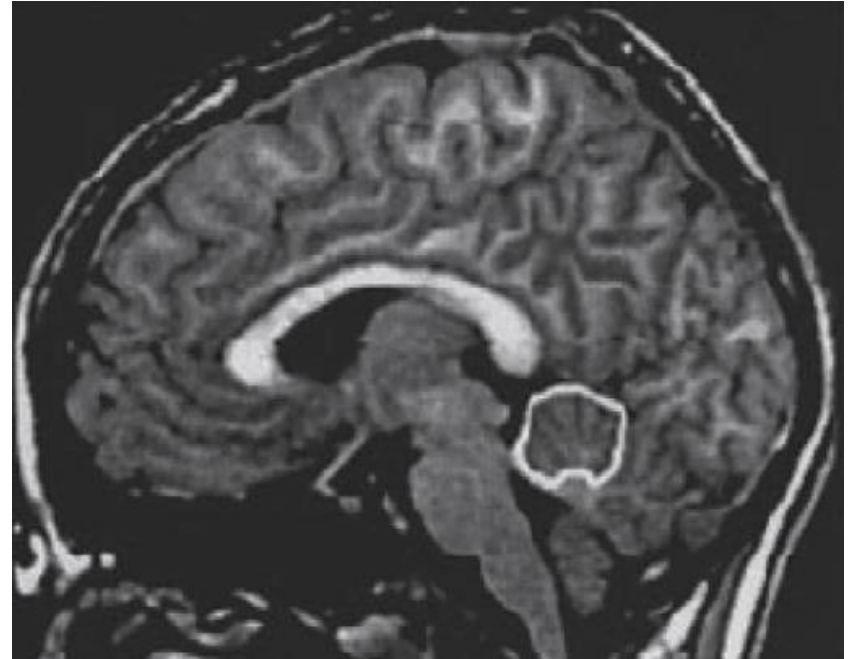


Levitt J. 1999

Cerebellar Involvement in Dyslexia

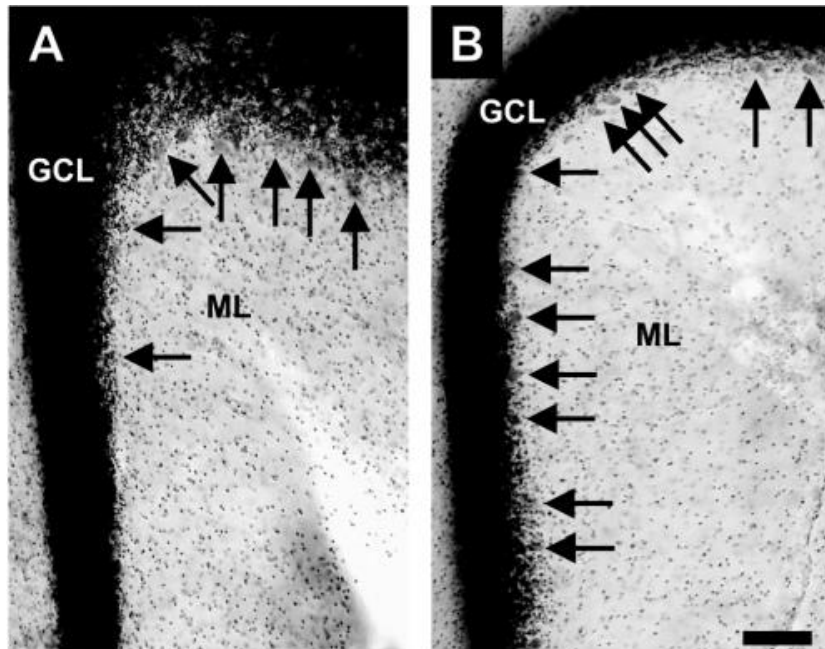


Control Subject



Dyslexic Subject

Autism candidate genes affects the Cerebellum

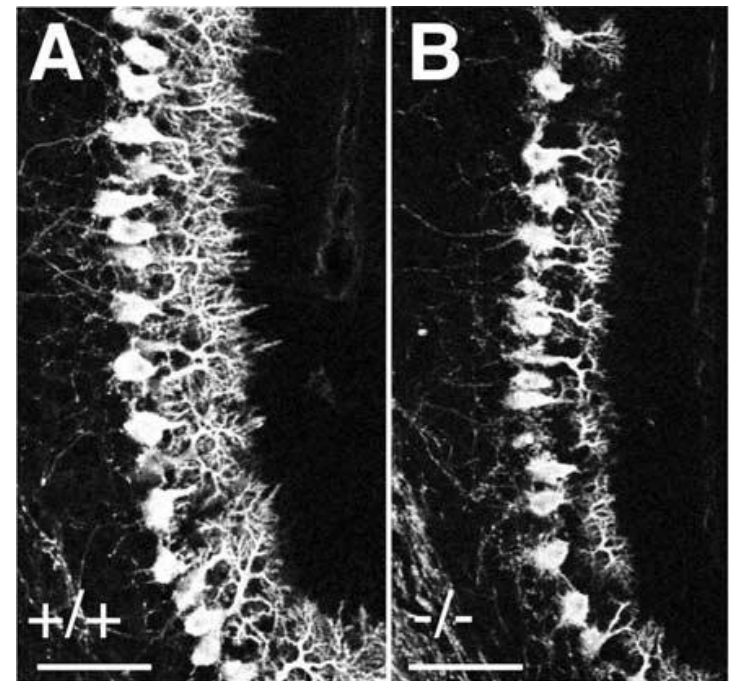


Autistic

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

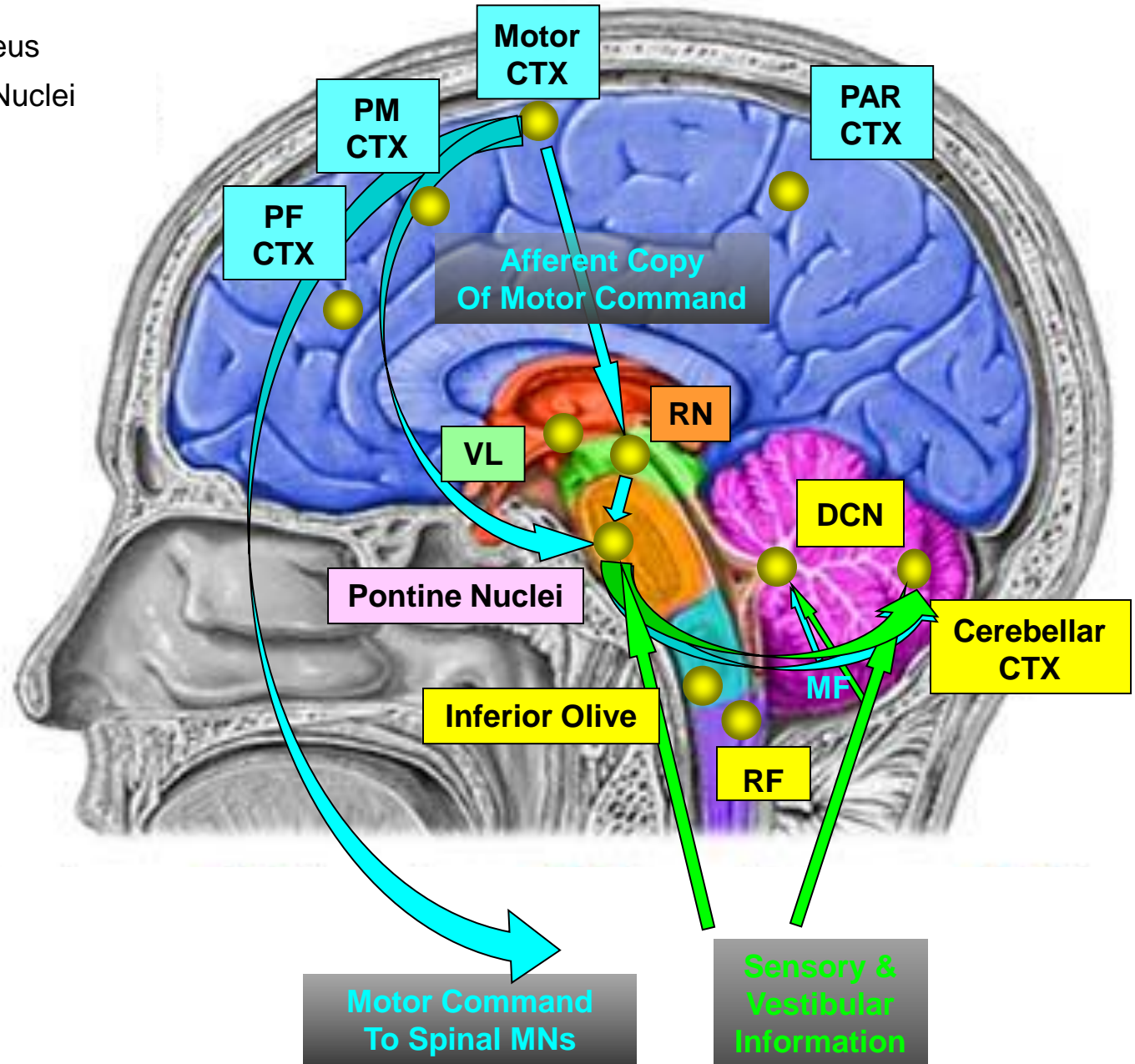
RN = Red Nucleus

(+ mid brain nuclei)

CTX = Cortex

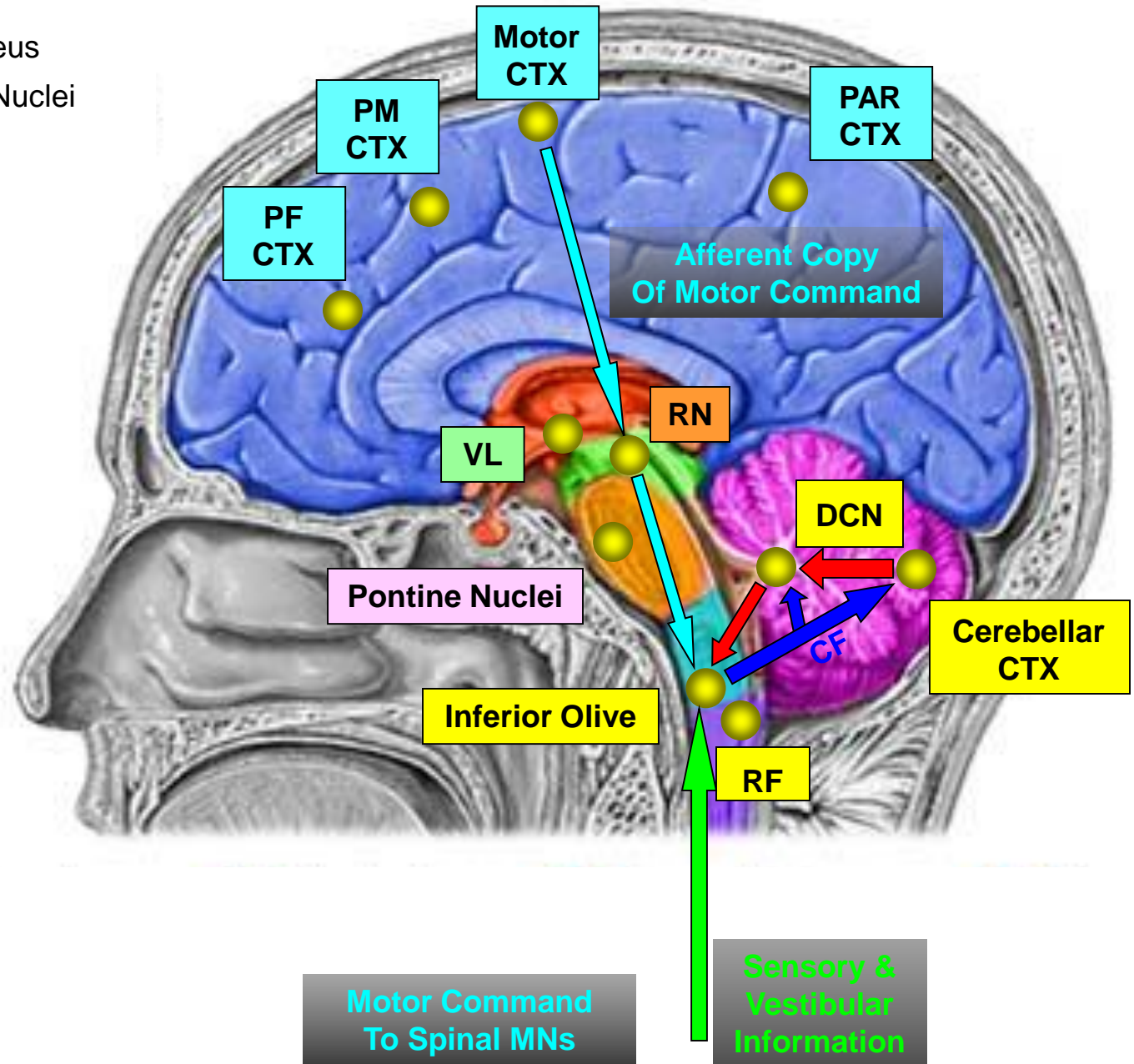
MF = Mossy Fibers

CF = Climbing Fibers



Olivocerebellar Information flow : Climbing Fibers Inputs

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)
CTX = Cortex
MF = Mossy Fibers
CF = Climbing Fibers



Hypothesized information flow during Cerebellar function

VL = Ventro-Lateral Nucleus

DCN = Deep Cerebellar Nuclei

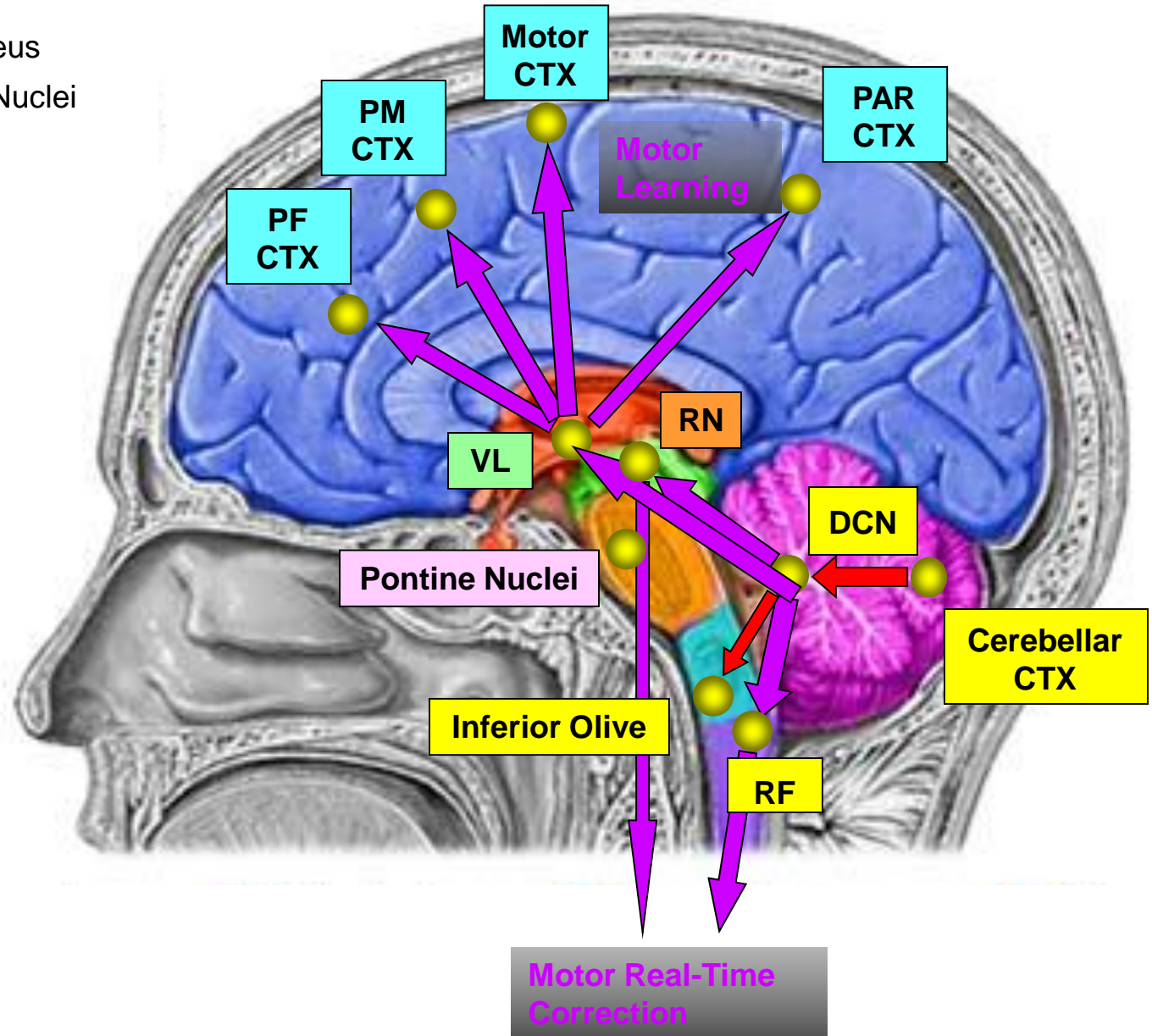
RN = Red Nucleus

(+ mid brain nuclei)

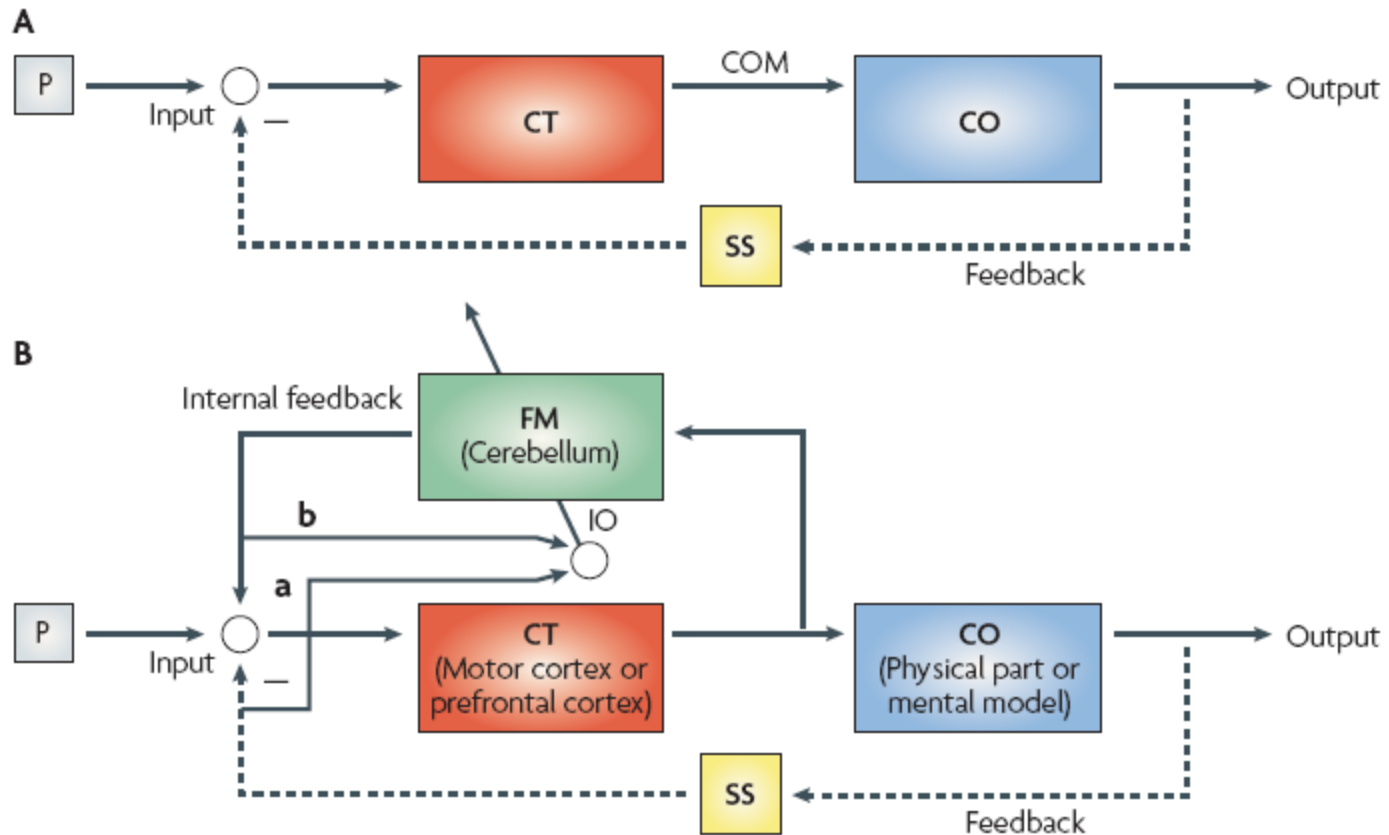
CTX = Cortex

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CF = Climbing Fibers



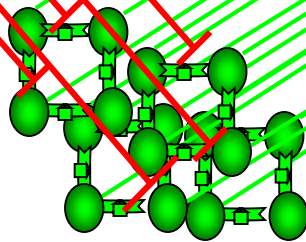
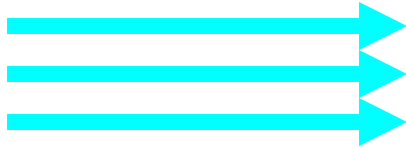
The General Role of the Cerebellum



The Inferior Olive as the Great Comparator

Feedback Inhibition from
Deep Cerebellar Nuclei

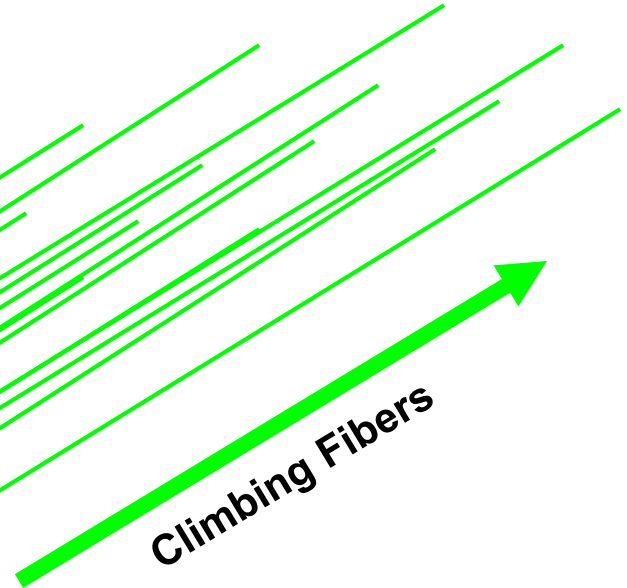
Motor Intention



Inferior Olive

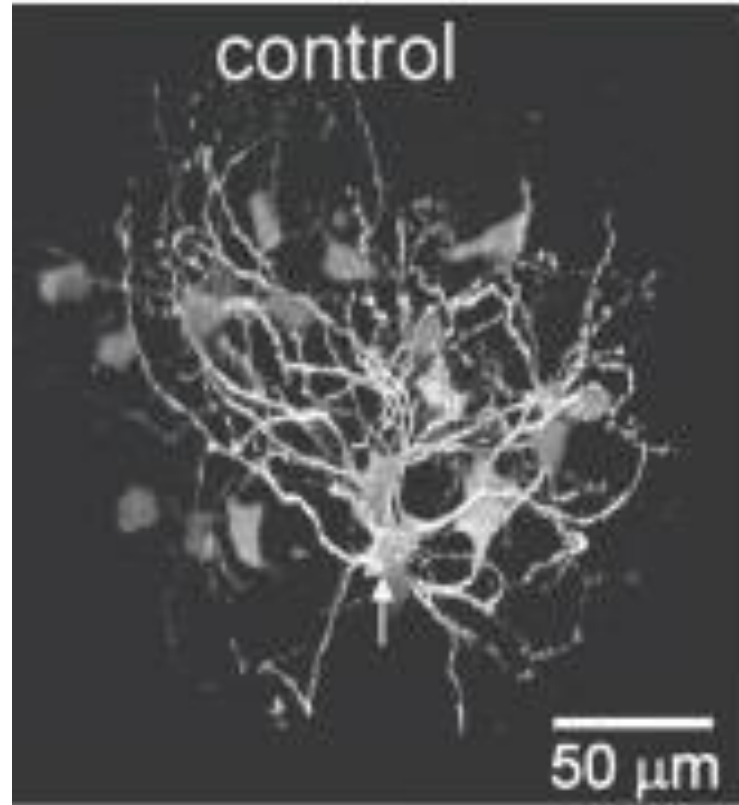


Sensory
feedback



Climbing Fibers

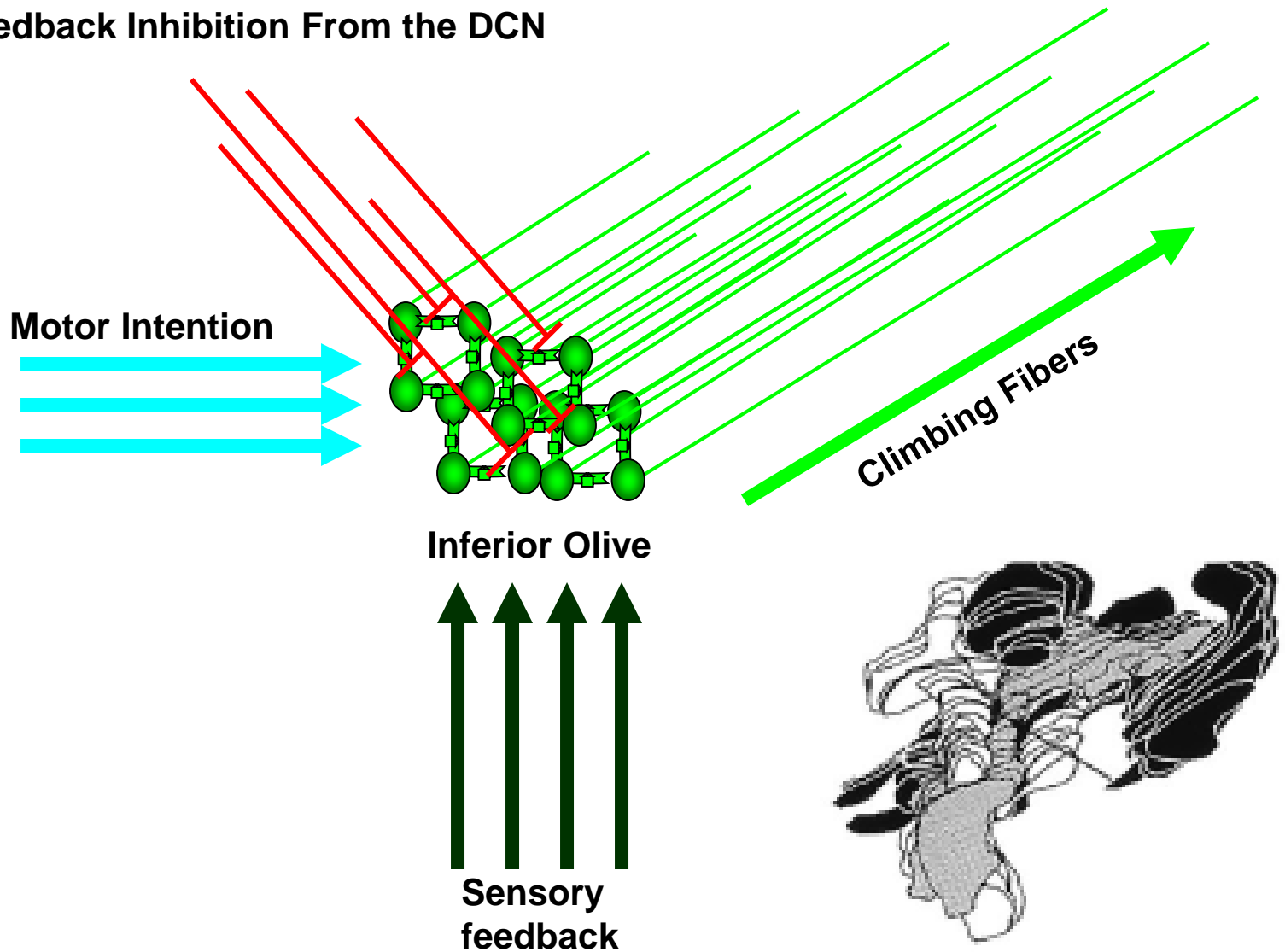
IO Neurons are Coupled by Gap Junction



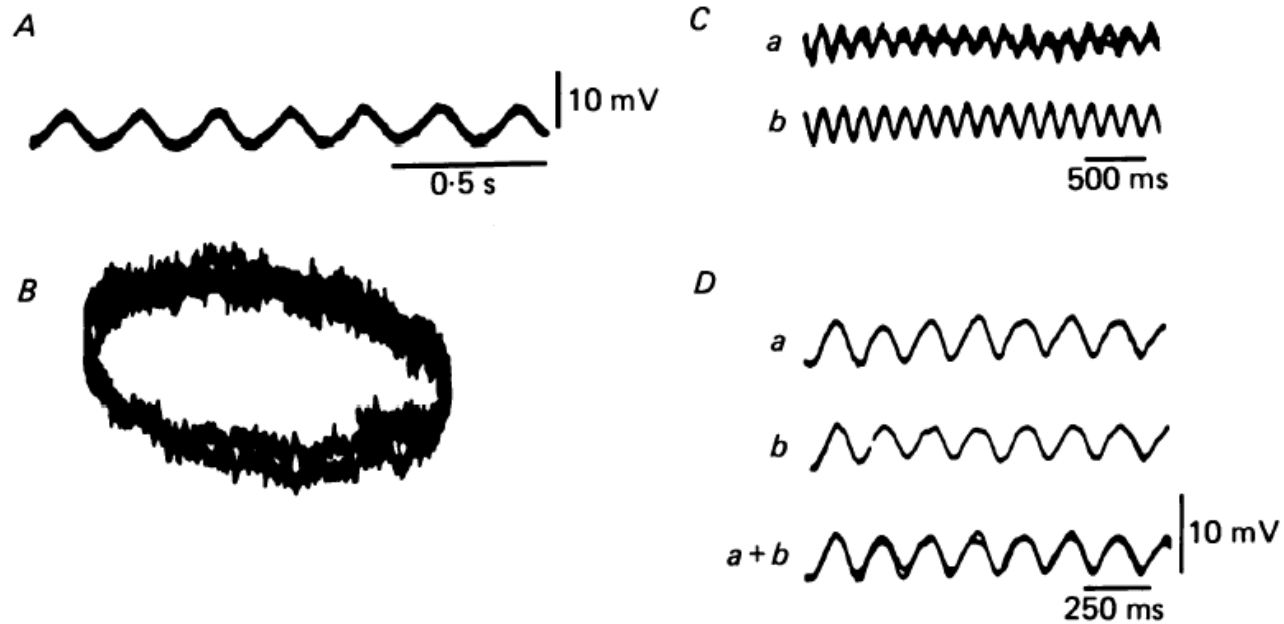
Placantonakis et al. PNAS 2004

The Inferior Olive as the Great Comparator

Feedback Inhibition From the DCN

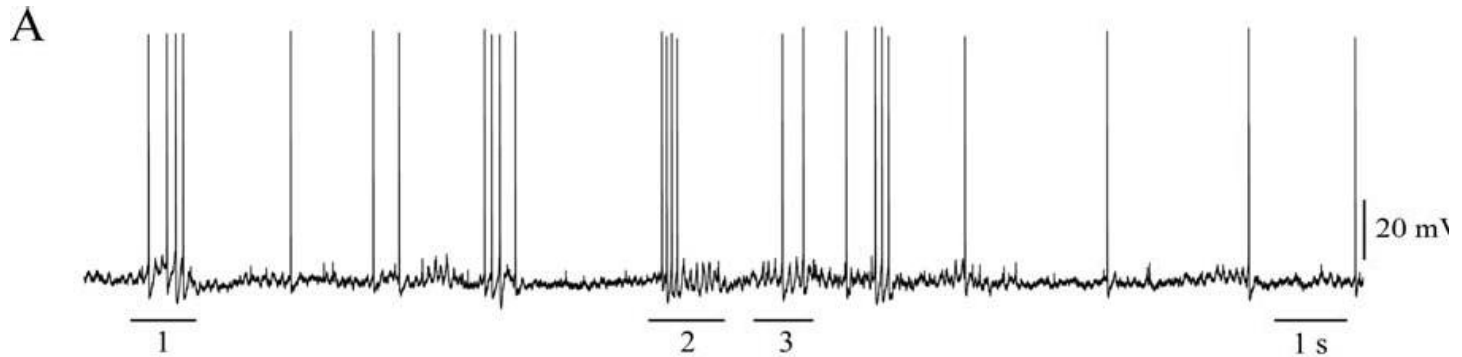


IO Neurons are Natural Oscillators

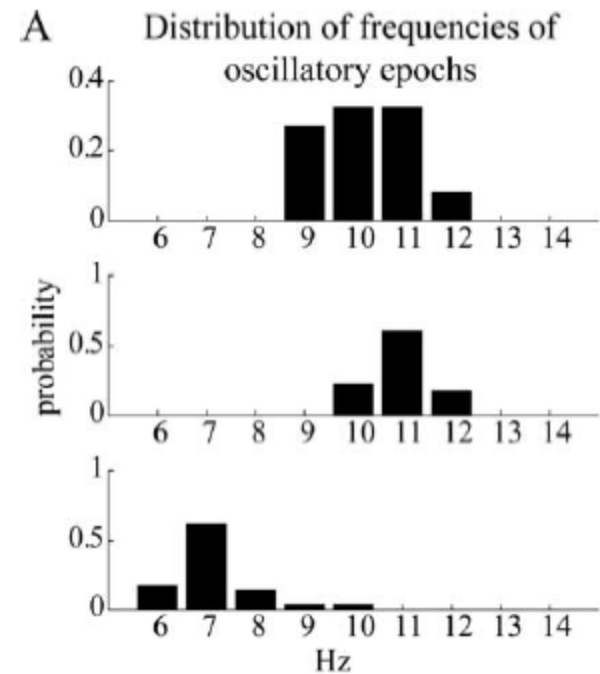


Llinas and Yarom JPhysiol 1986

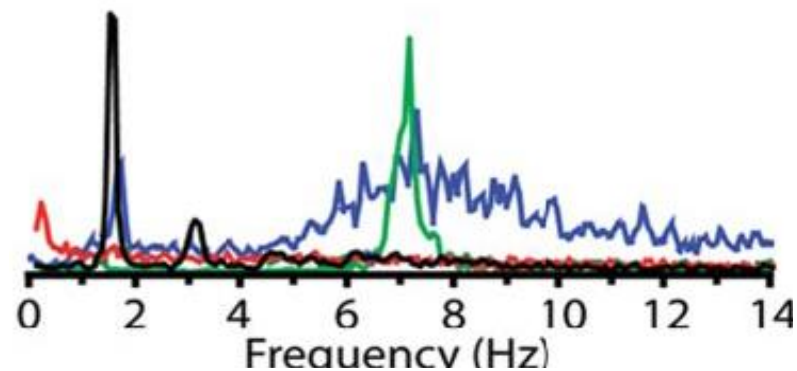
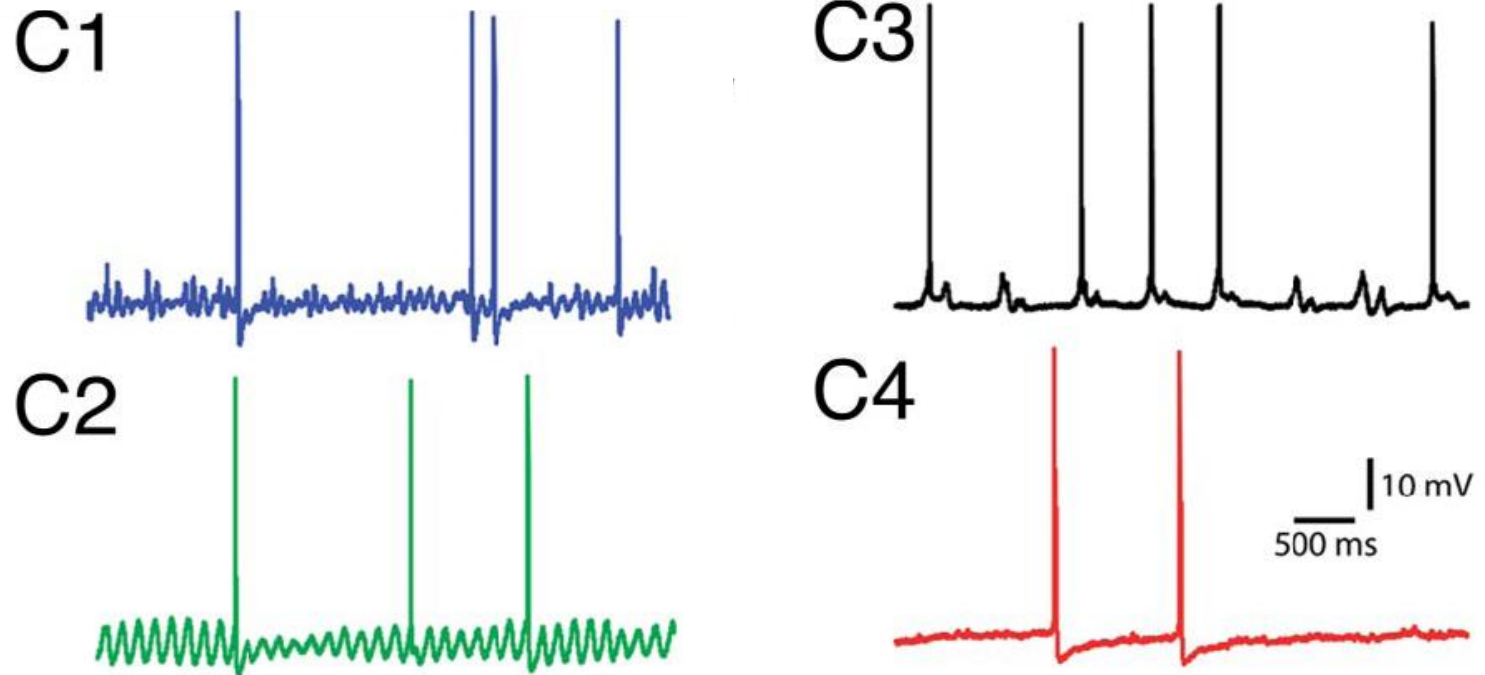
IO neurons are not Harmonious Oscillators *in-vivo*



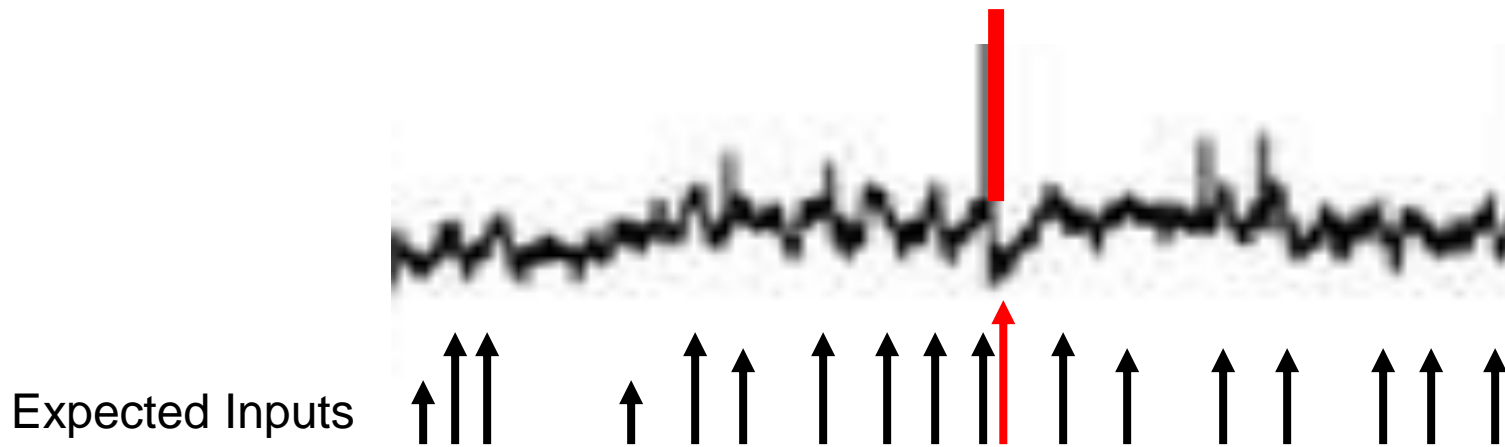
Chorev, Yarom and Lampl JNS 2007



There are Various Oscillation Patterns

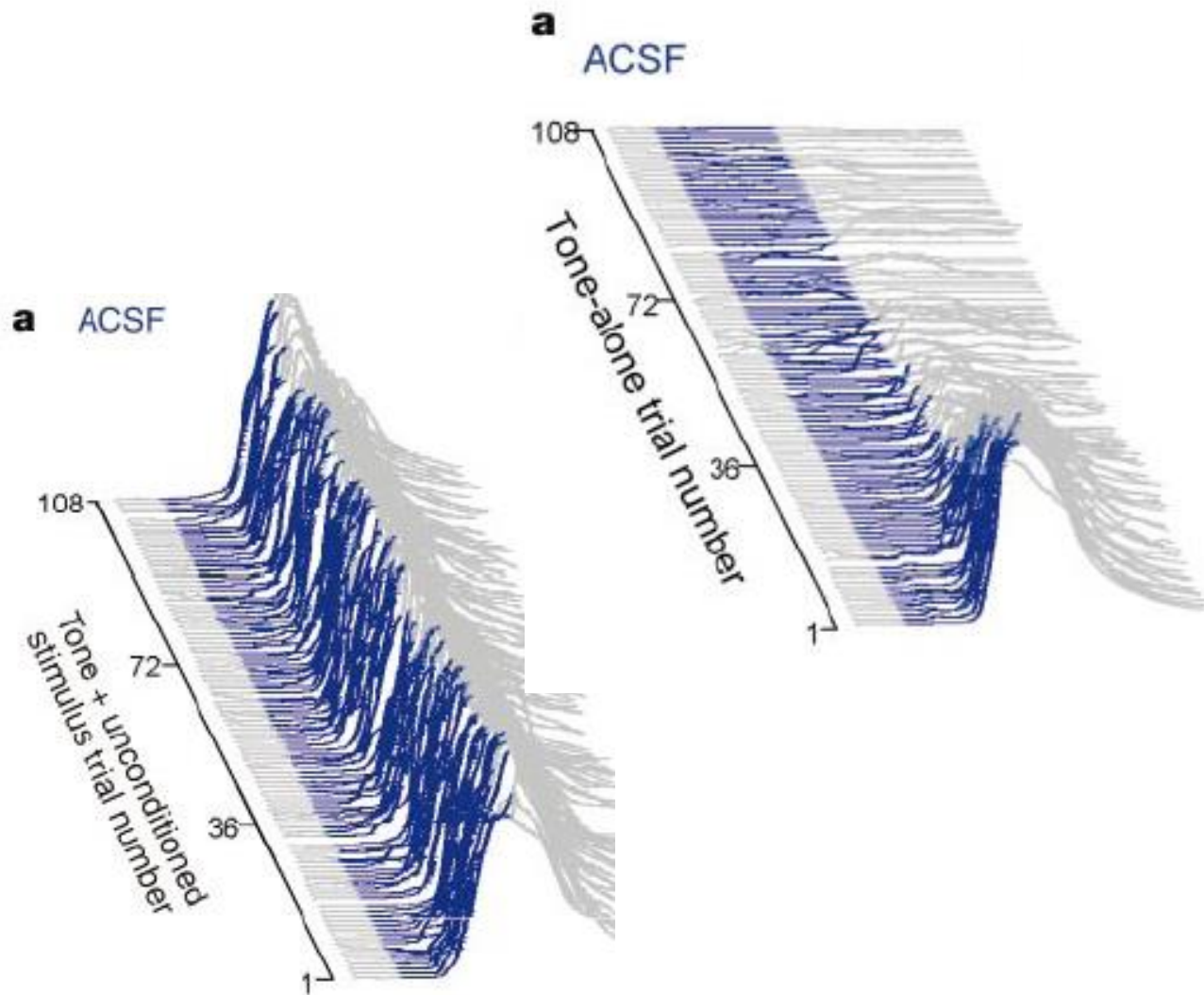


Oscillation as a Blocking Device for expected Inputs

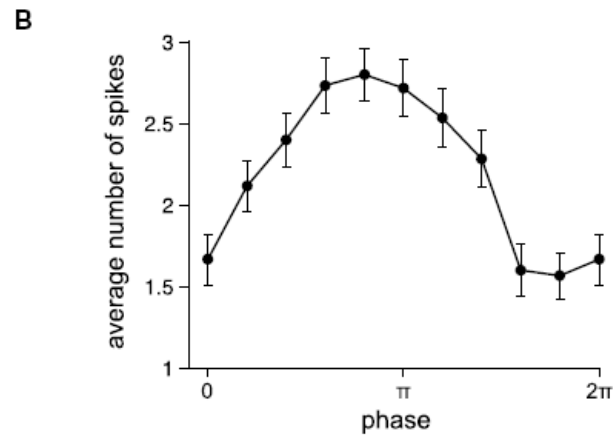
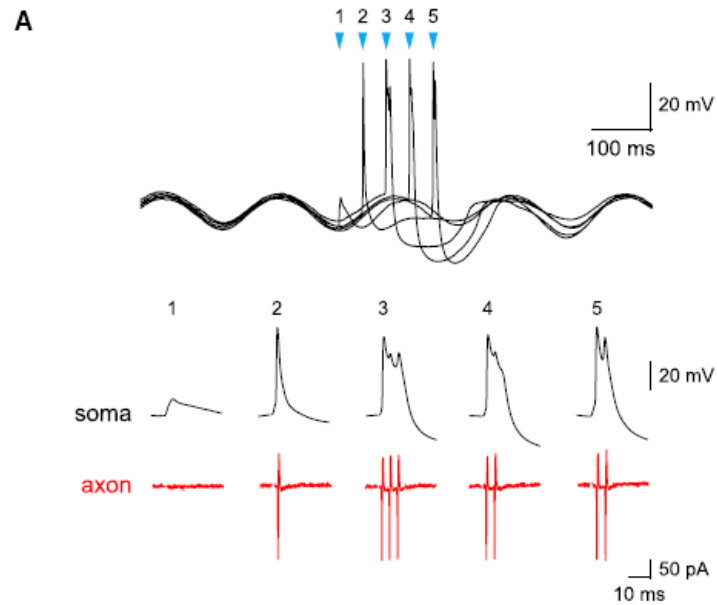


How will The IO Differentiate Early vs. Late Inputs?

Conditioning Memory Retention depends on Nucleo-Olivary Inhibition



ISI vs. Oscillation phase “encoding”



CF activation Pattern sets the direction of plasticity

