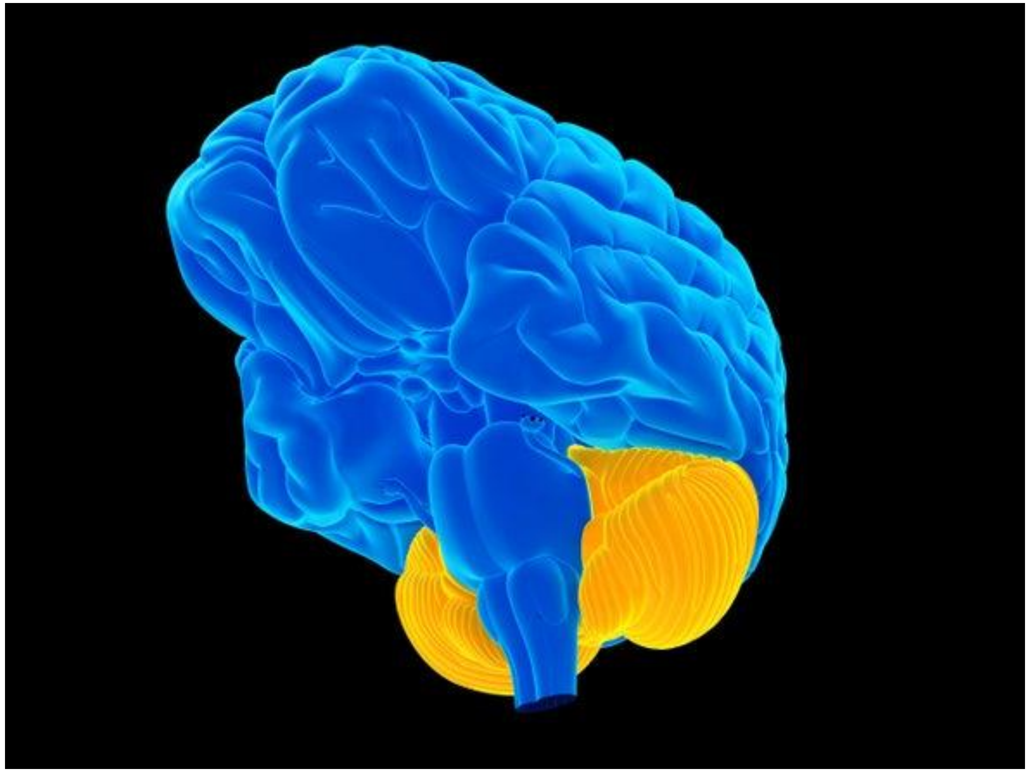
Cerebellum: Motor auxiliary engine? Body memory? or “The great predictor”?



Eyal Cohen, PhD, CEO of CogniFiber LTD

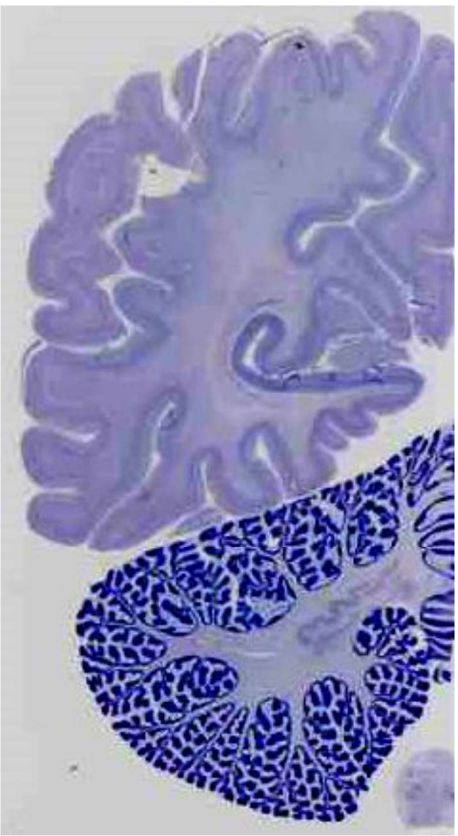
eyalco28@yahoo.com

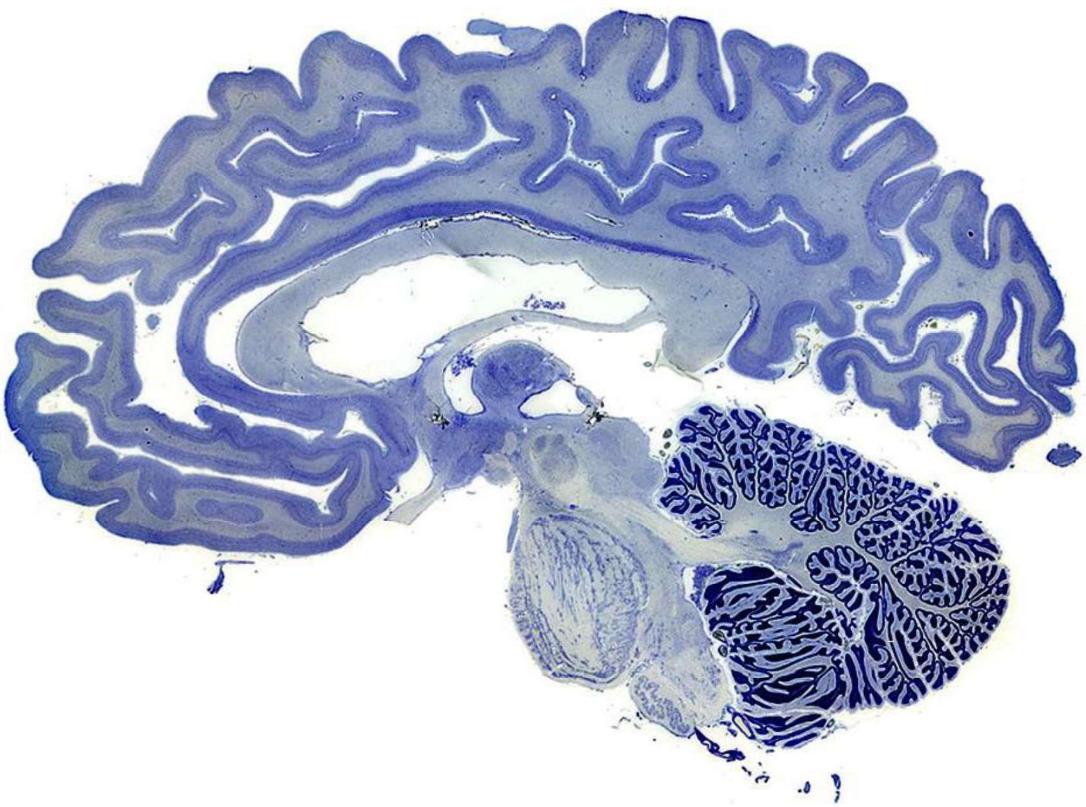
eyalco28@yahoo.com

Cerebellum: the "little brain"

3 The Cerebellum takes ~10% of the Brain in Volume

Small but crafty…

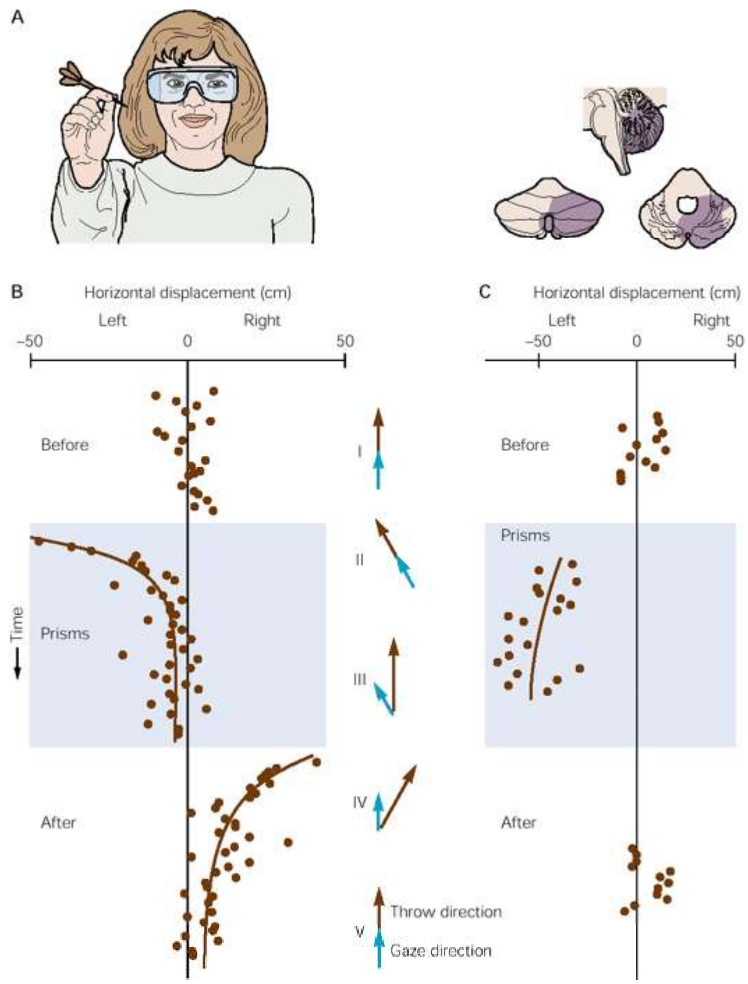




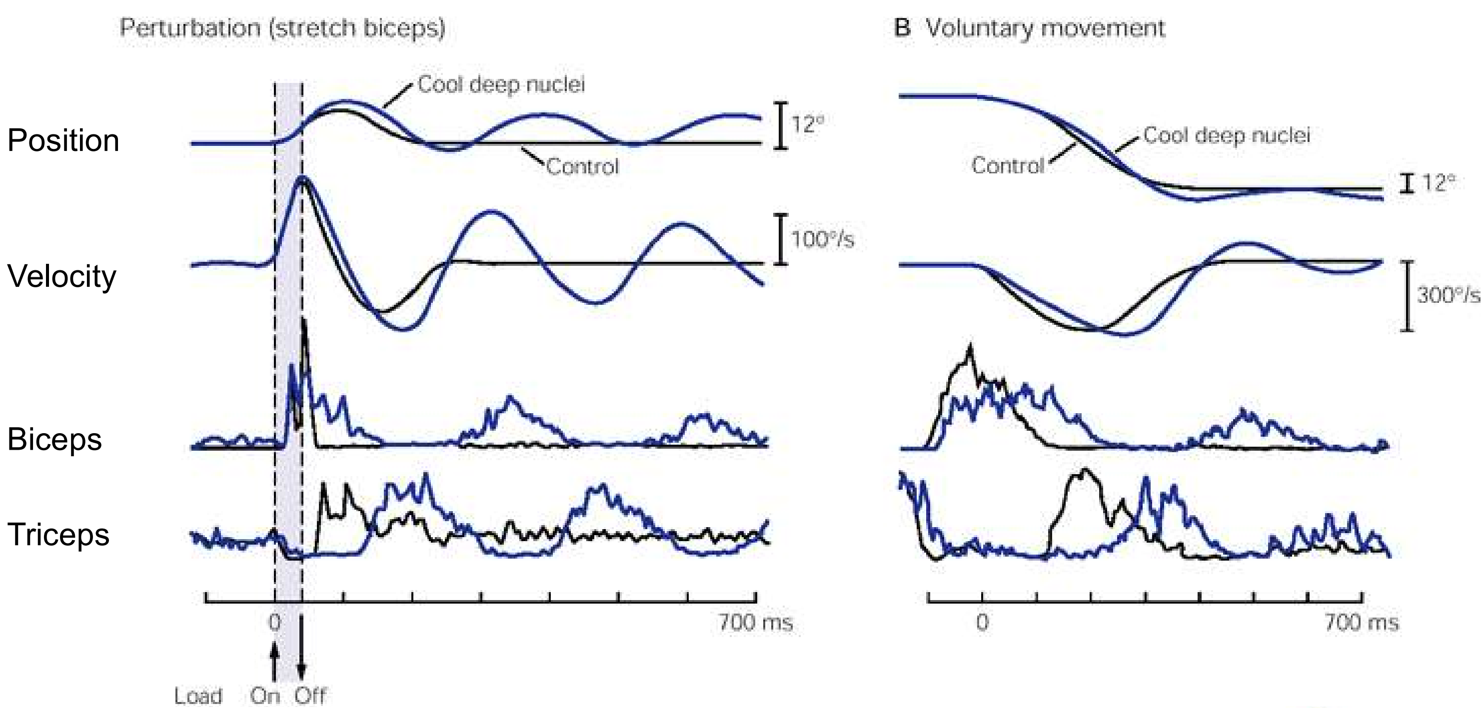
Over 50% of the Brain’s Neurons are in the Cerebellum!

The Convoluted Cerebellar Cortex consists of most Cerebellar Volume

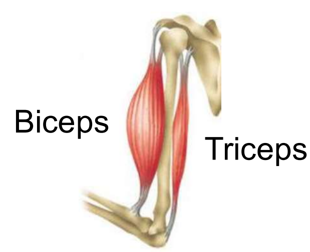
Cerebellar is central in visuo-motor adaptation



Classical role in muscle timing and coordination



Cooling => Reducing Neuronal Firing



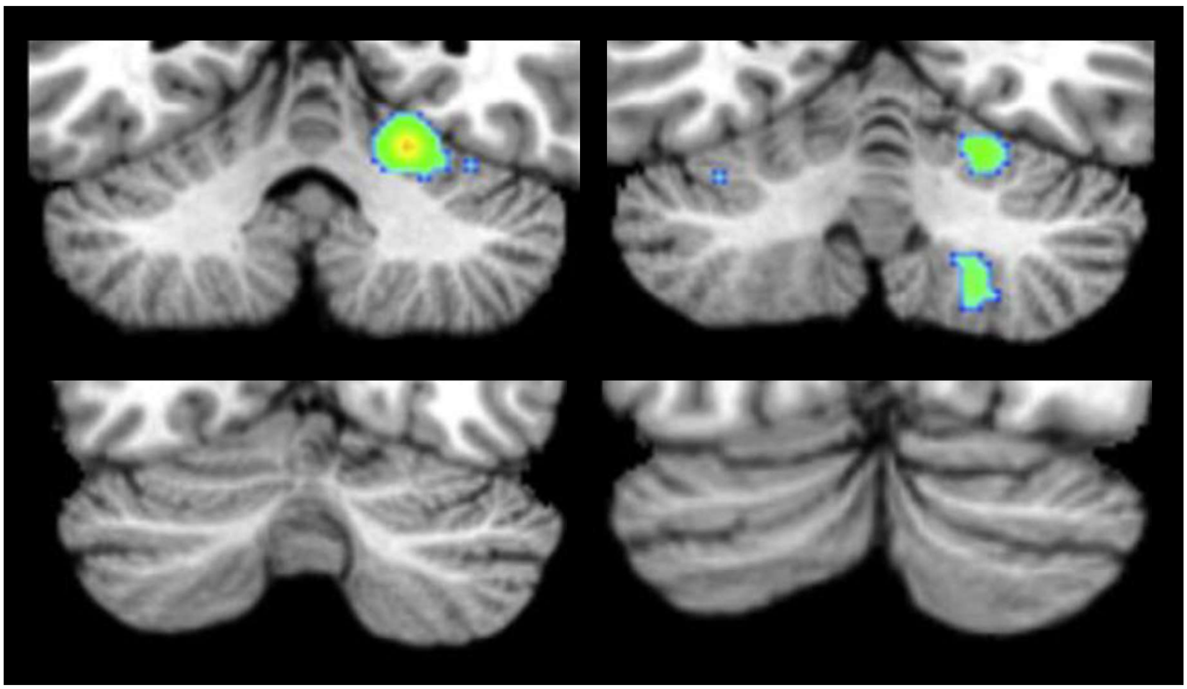
Villis and Hore 1977

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)

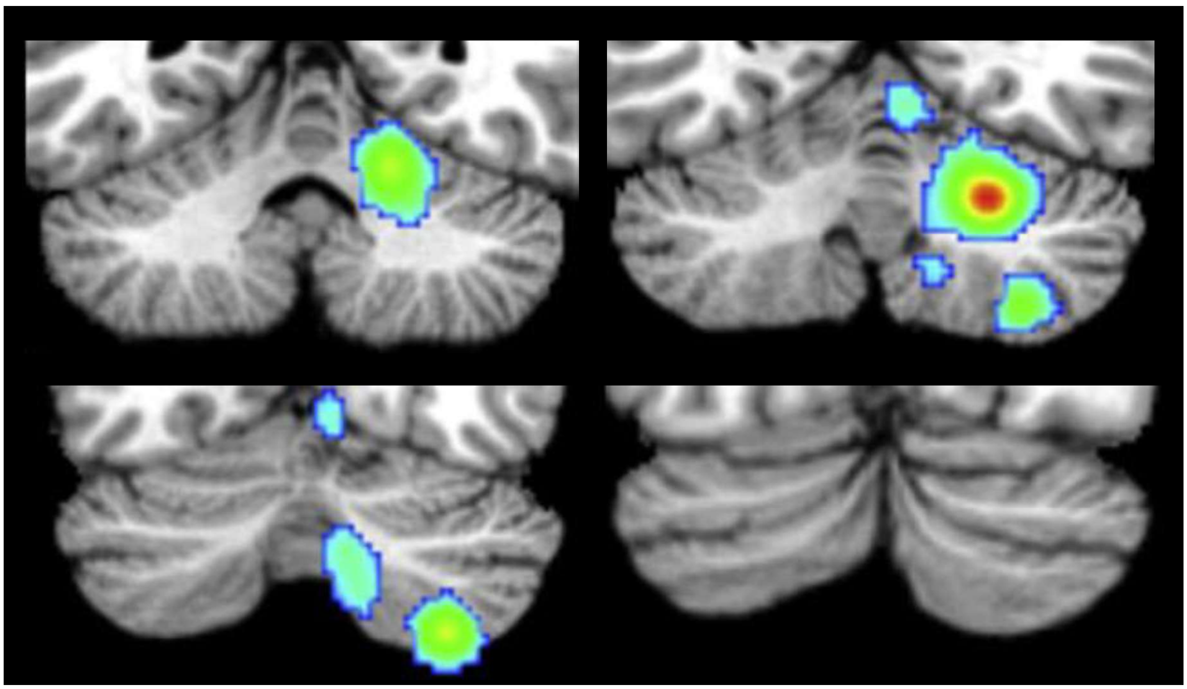
Cerebellar involvement in various processes



Somatosensory Processing

Stoodley and Schmahmann 2009

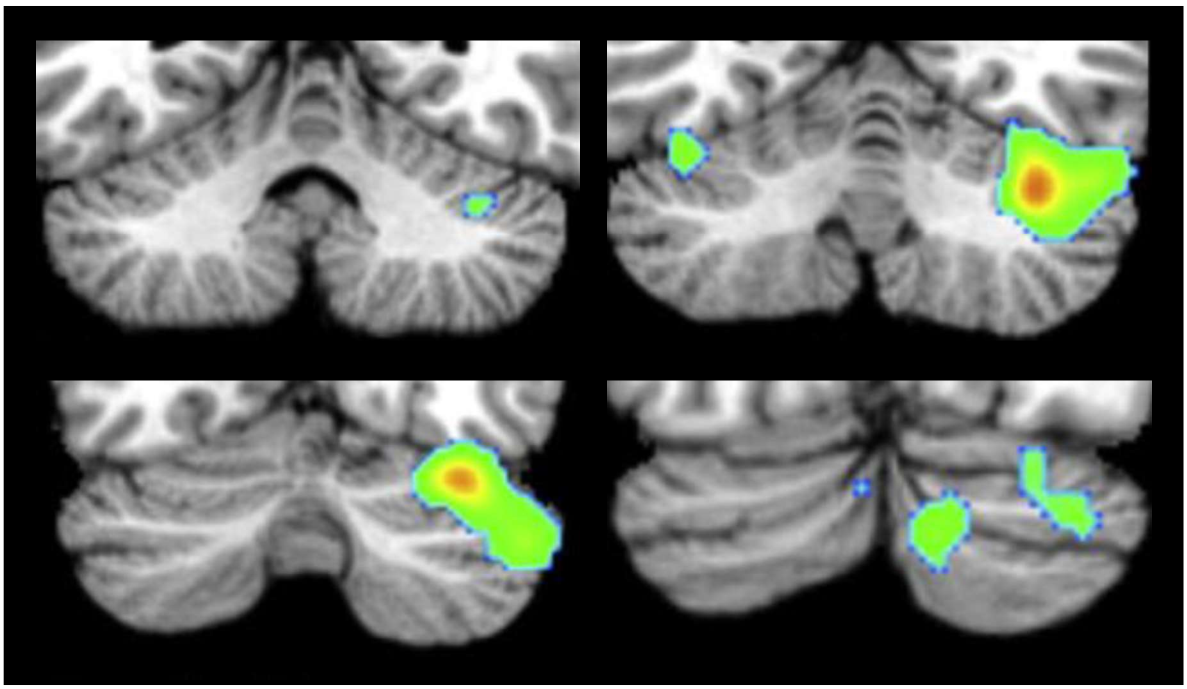
Cerebellar involvement in various processes



Motor Processing

Stoodley and Schmahmann 2009

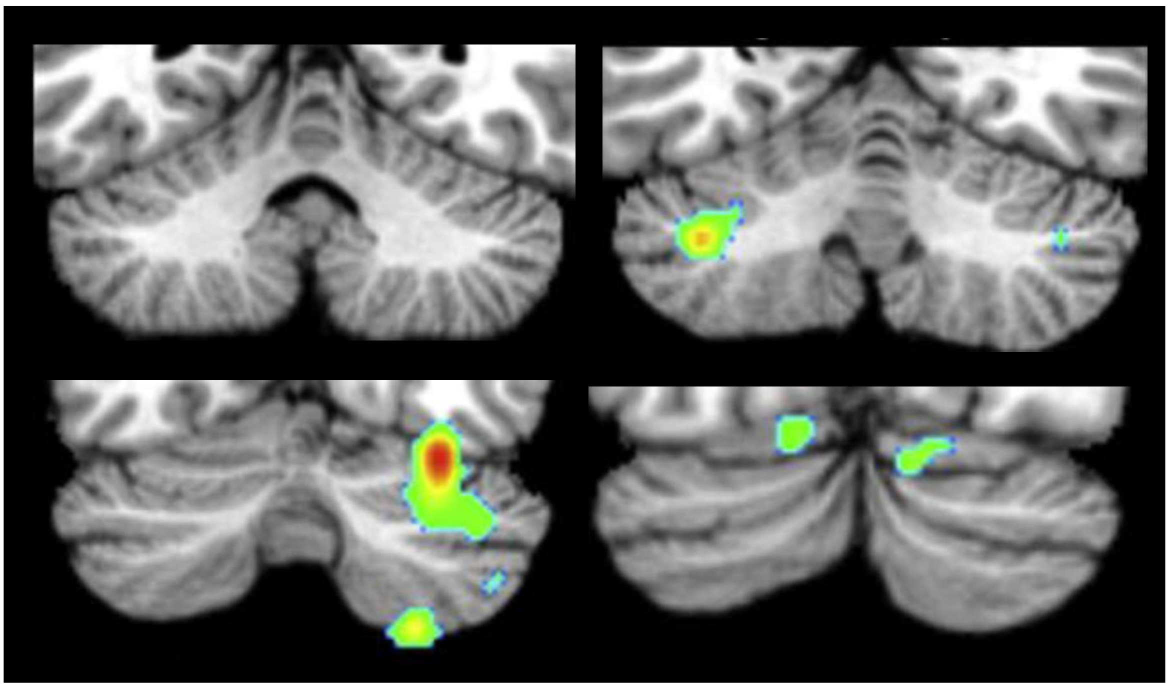
Cerebellar involvement in various processes



Language Processing

Stoodley and Schmahmann 2009

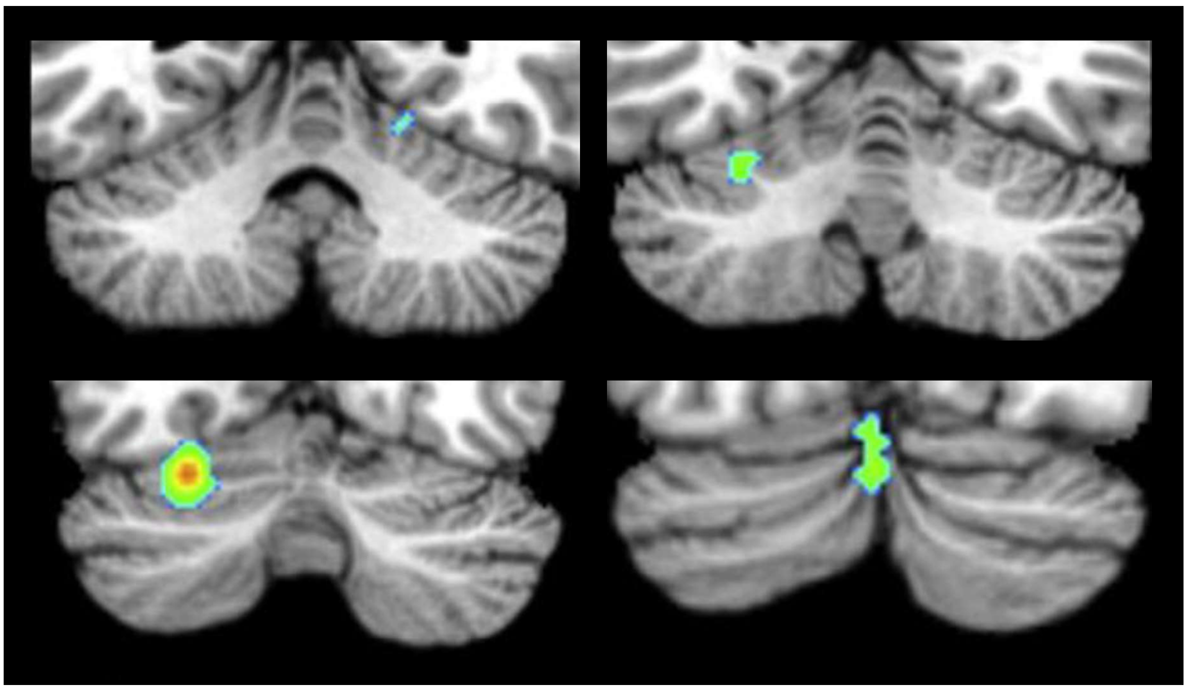
Cerebellar involvement in various processes



Working Memory

Stoodley and Schmahmann 2009

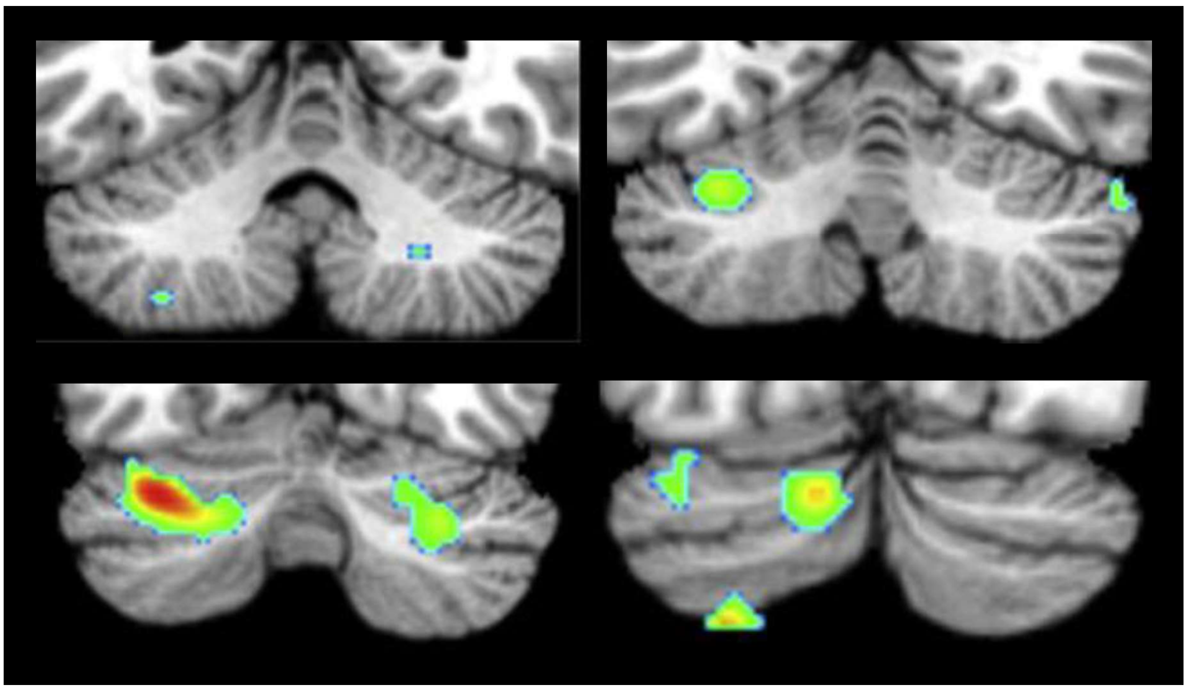
Cerebellar involvement in various processes



Spatial Processing

Stoodley and Schmahmann 2009

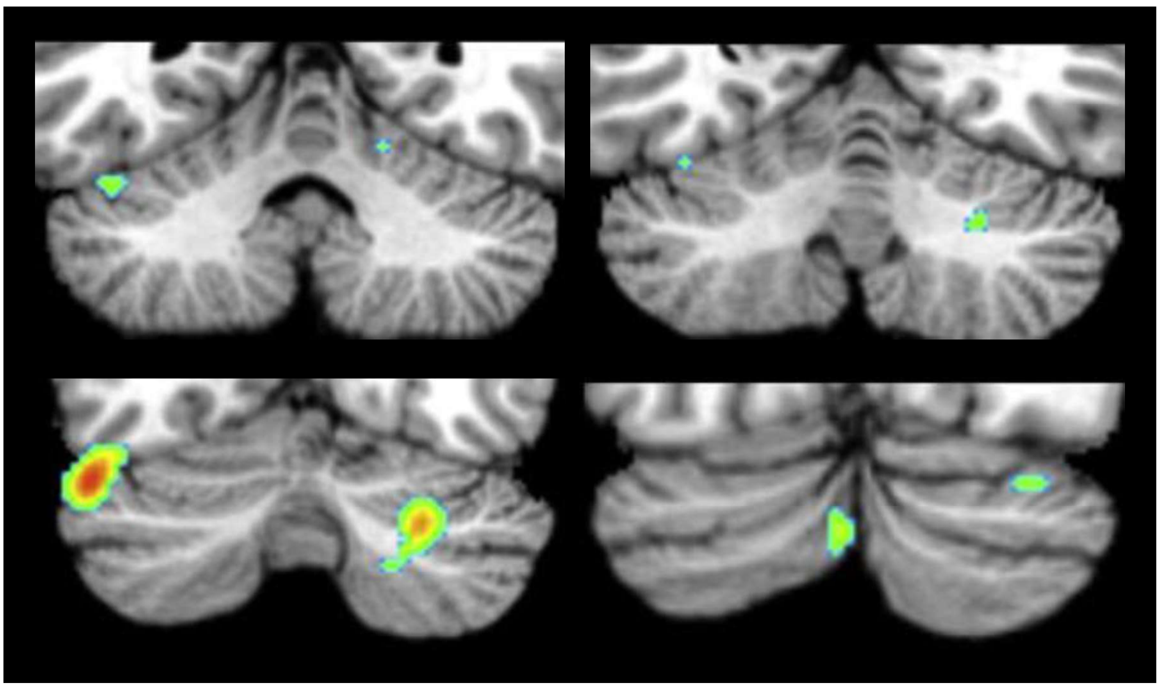
Cerebellar involvement in various processes



Executive Processing

Stoodley and Schmahmann 2009

Cerebellar involvement in various processes



Emotional Processing

Stoodley and Schmahmann 2009

Conclusion 1:

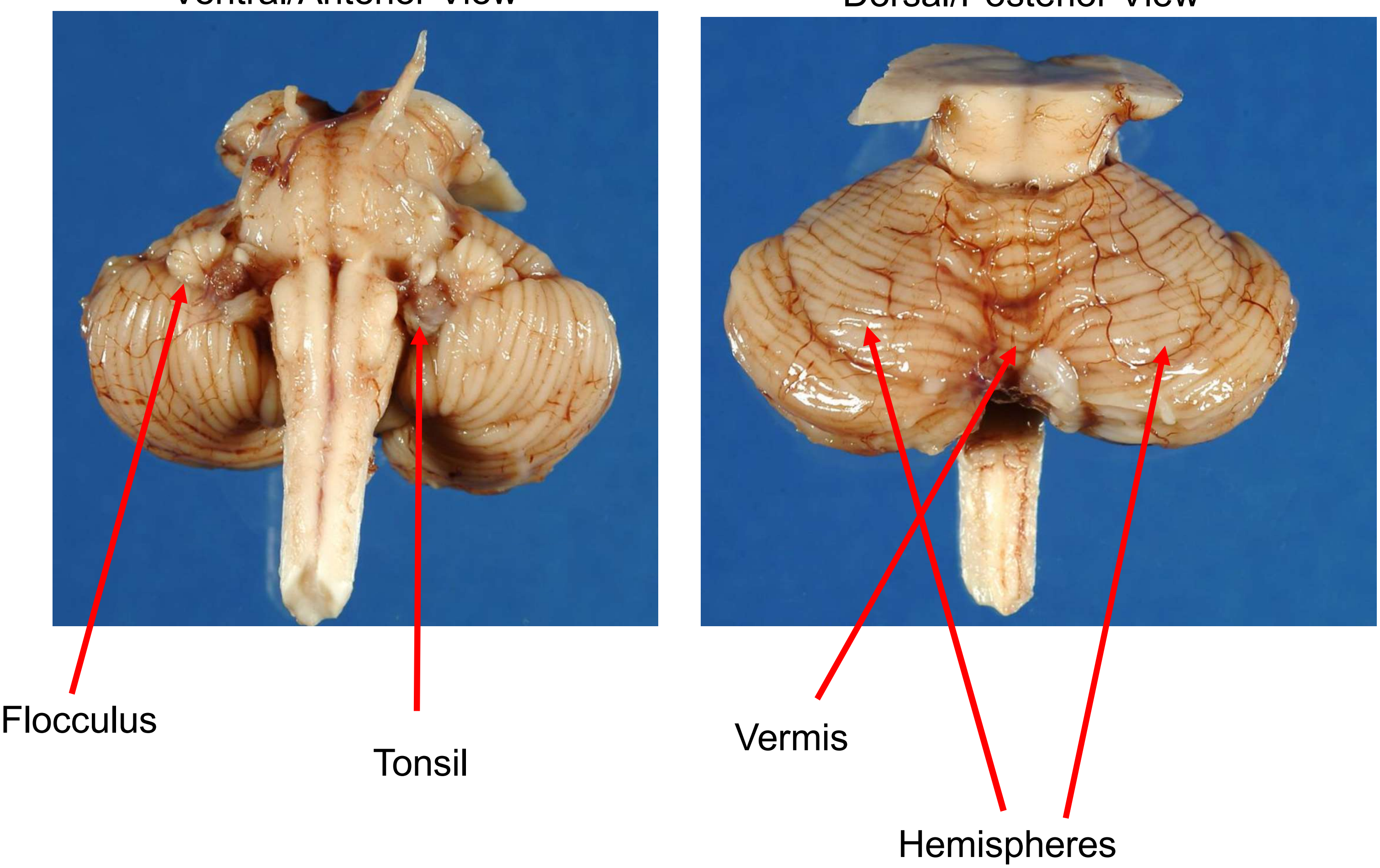
Human cerebellum is not about motor functions only!!

… and now lets get acquainted with it’s anatomy…

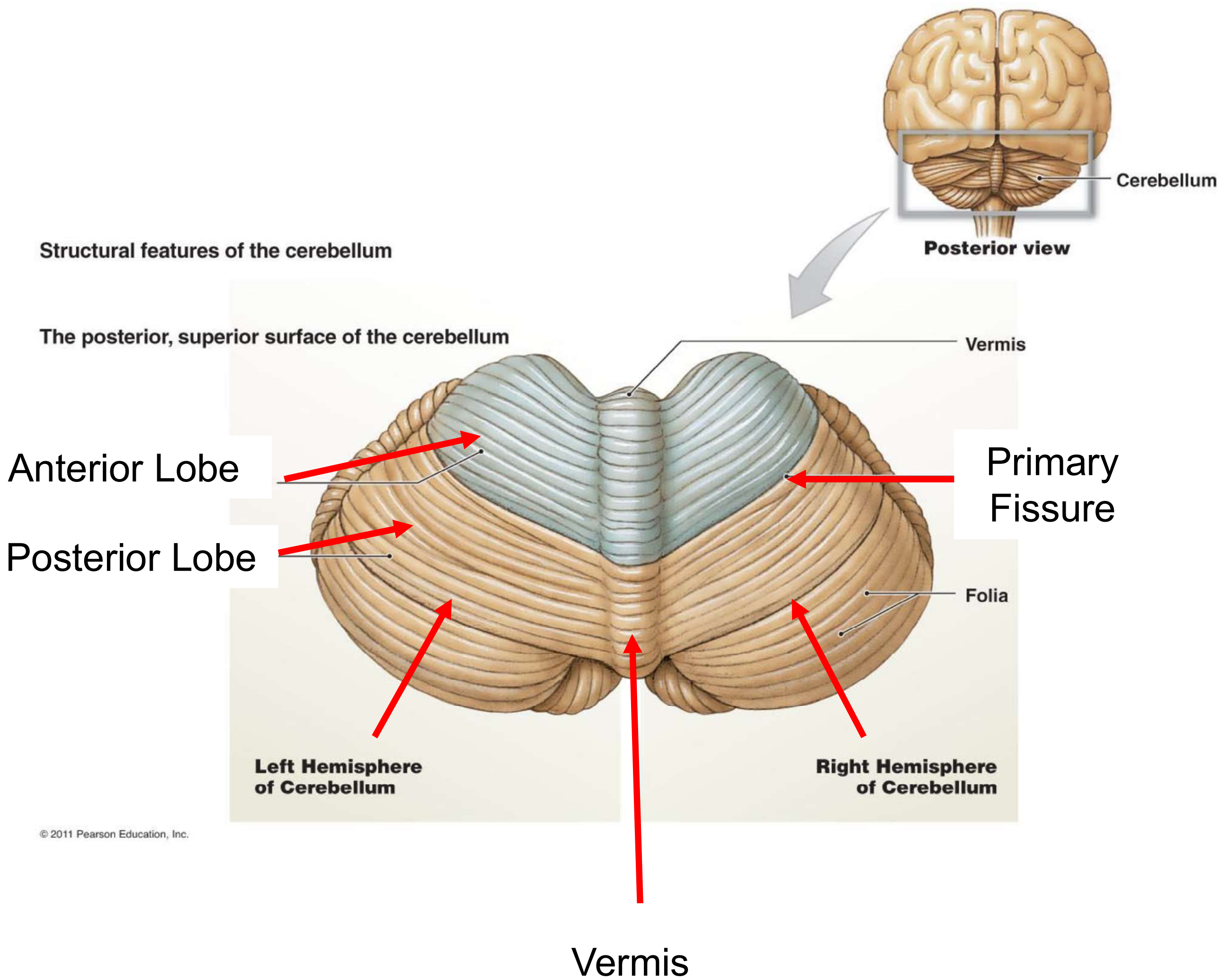
General structure of the Cerebellar Cortex

Ventral/Anterior View

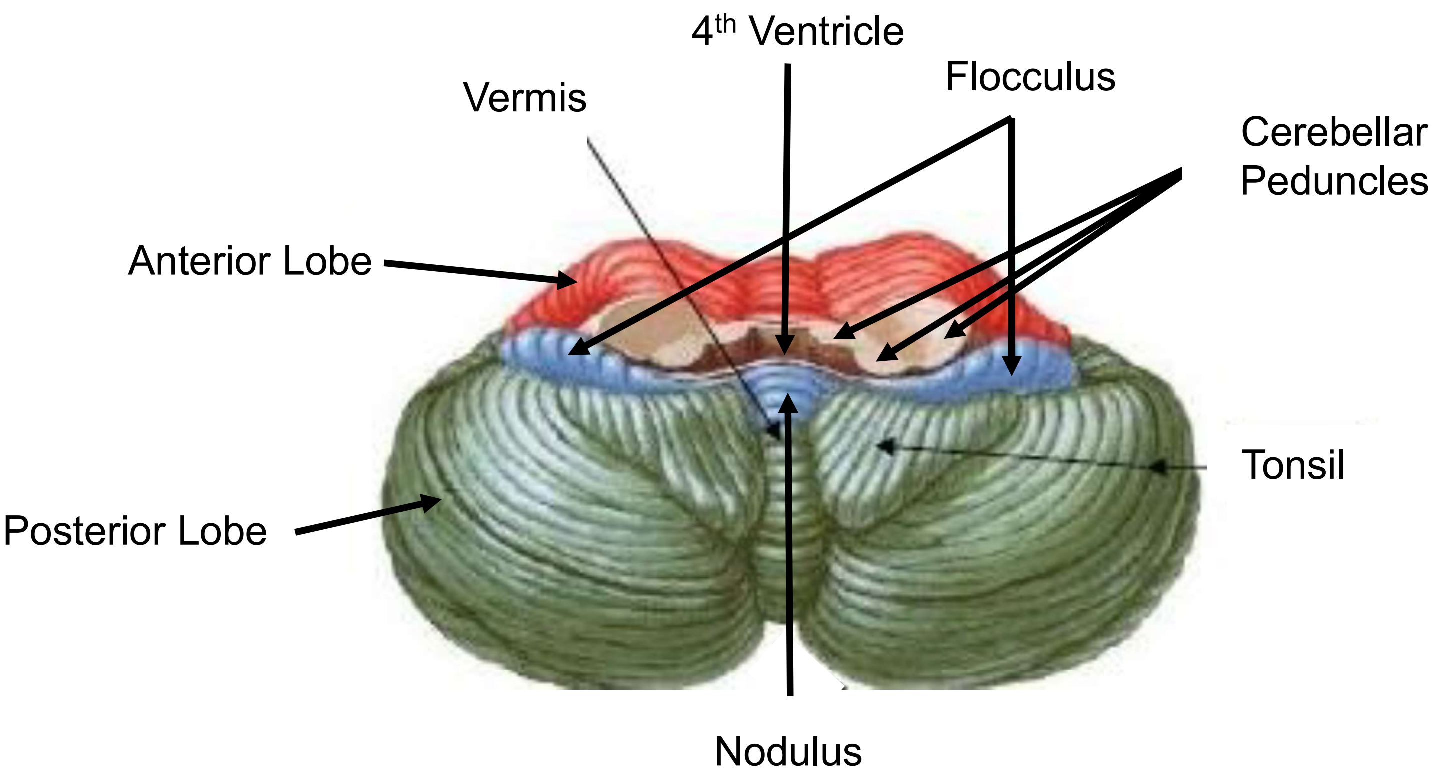
Dorsal/Posterior View



Posterior view of the Cerebellum

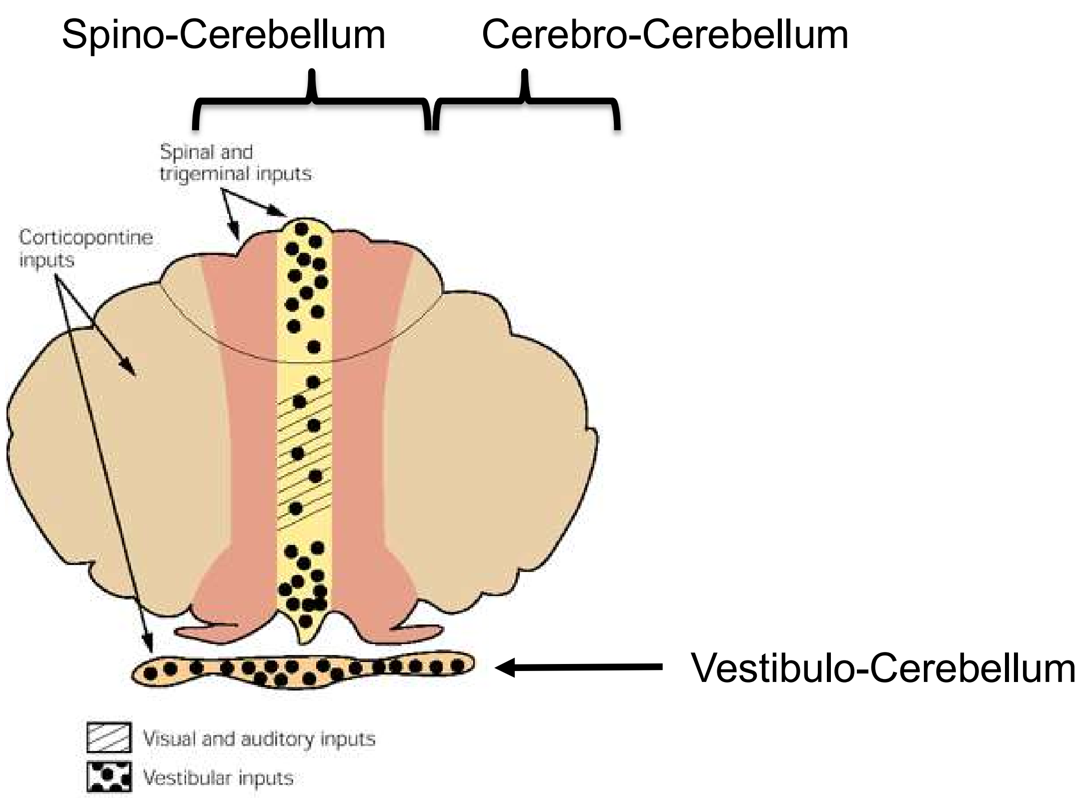


Anterior/Ventral view of the Cerebellum

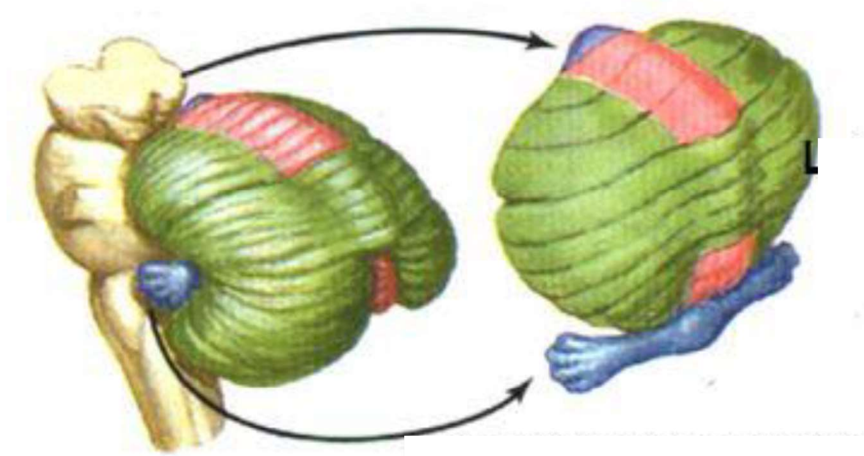


Nodules + Flocculi = Flocculu-Nodular Lobe

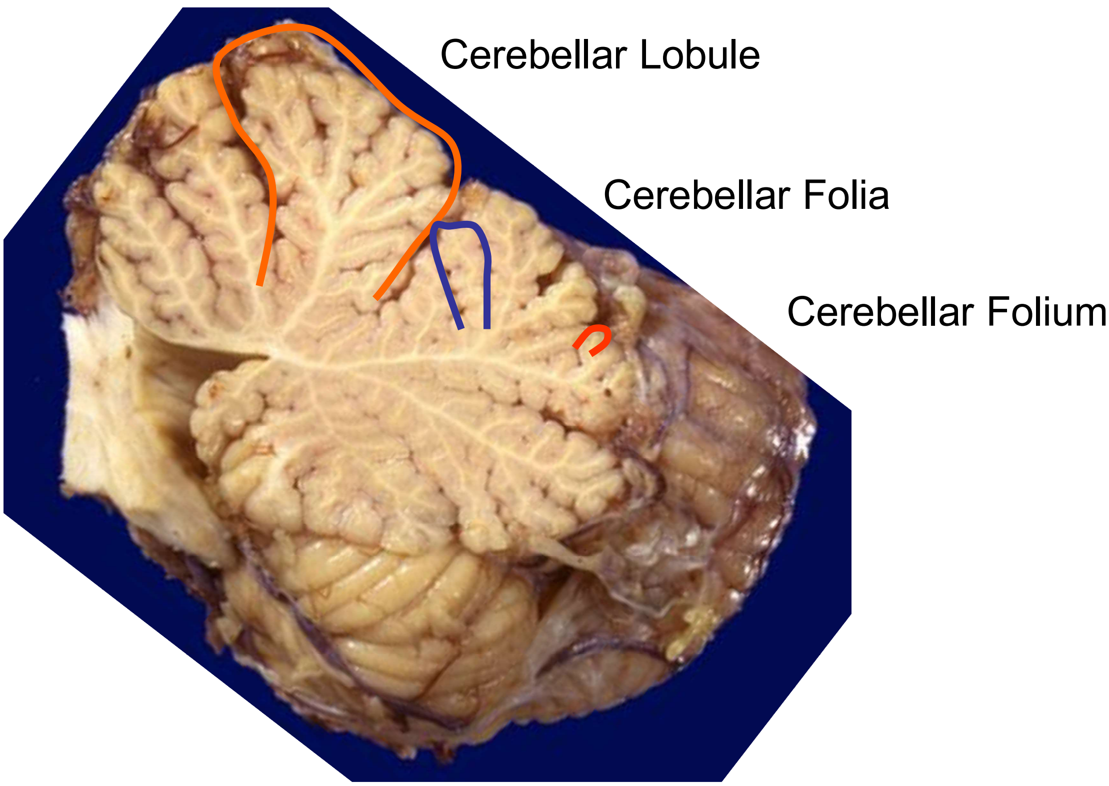
Medio-lateral gross partition of the Cerebellum



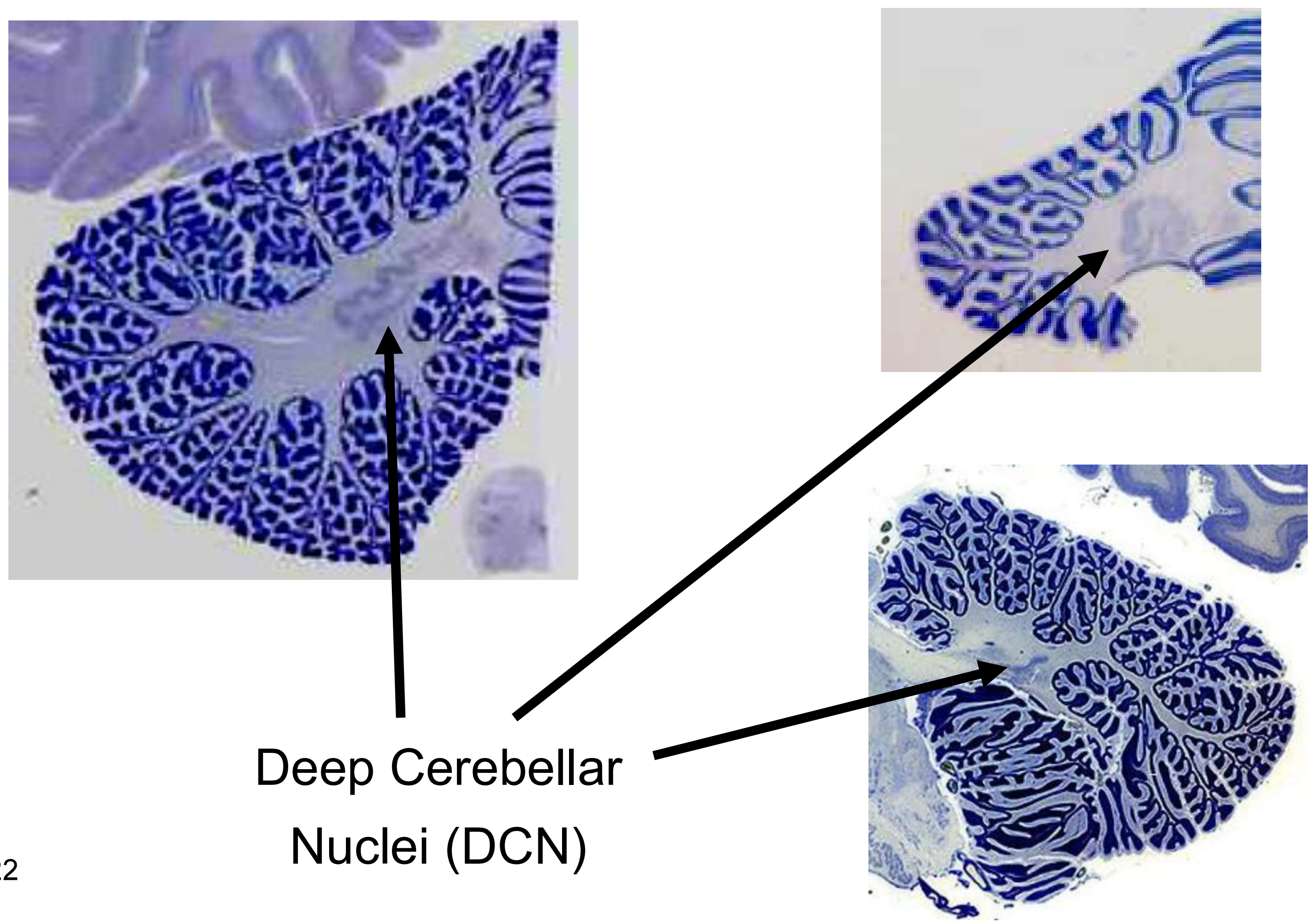
The 3D Folding of the Cerebellar Lobes



Lobules and Folia of the Cerebellar Cortex



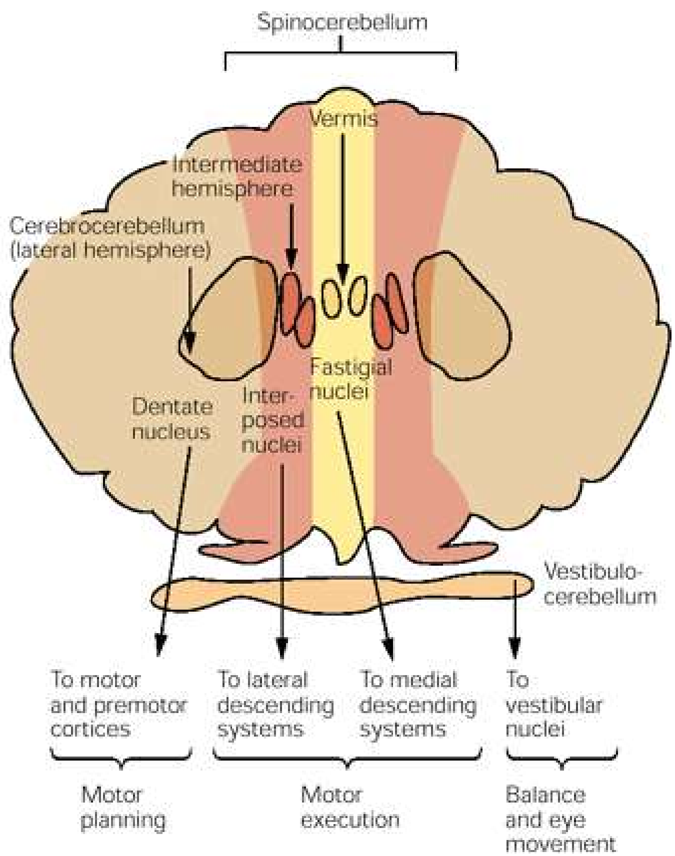
The Cerebellum is not only cortex…



The deep cerebellar nuclei (DCN) - the output stations of the Cerebellum

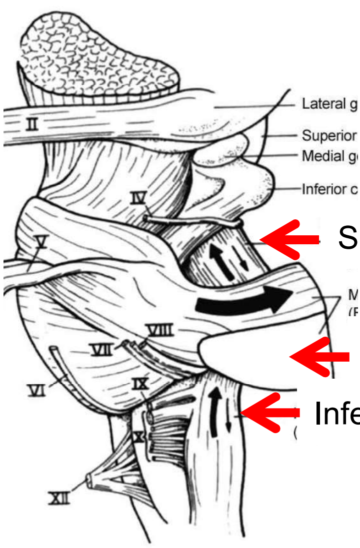
All cerebellar parts evolved during evolution, but the hemispheres and their DCN counterpart, the Dentate nucleus have gained by far the largest volume as they evolved in parallel to the cerebral cortex.

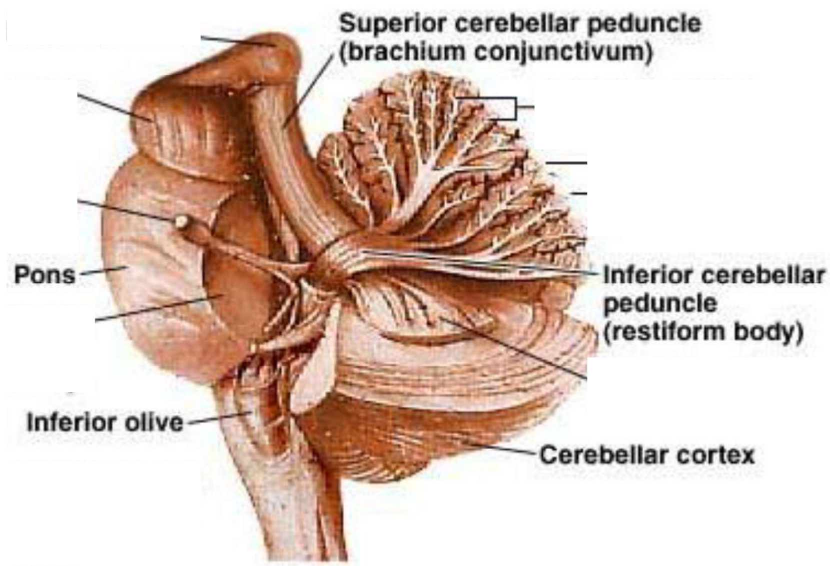
Functional mapping of the Cerebellar nuclei



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

Cerebellar peduncles: input / output highways



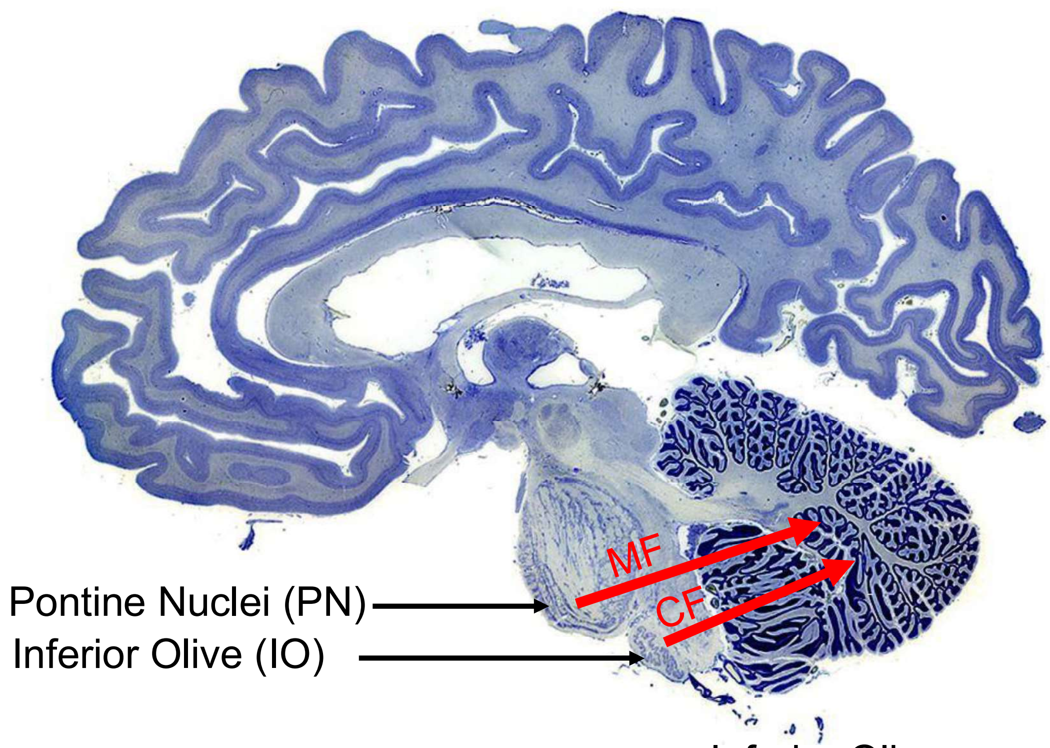


Superior: Thalamus/Midbrain Inputs/Outputs

Medial: Pontine Inputs and Commissure

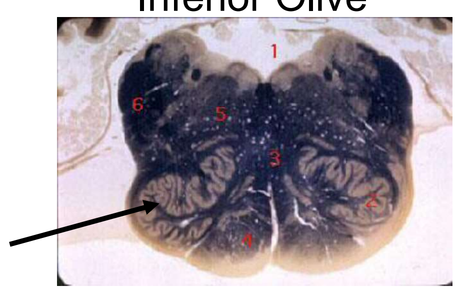
Inferior: Spinal/Medullary Inputs/Outputs

Two major input pathways serve the Cerebellum

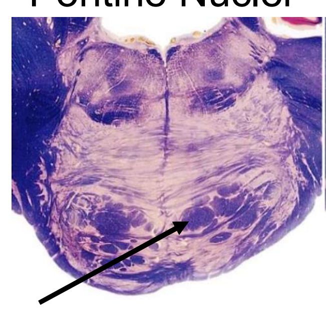


CF = Climbing Fibers
(All via the IO)
MF = Mossy Fibers
(~90% via the PN)

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

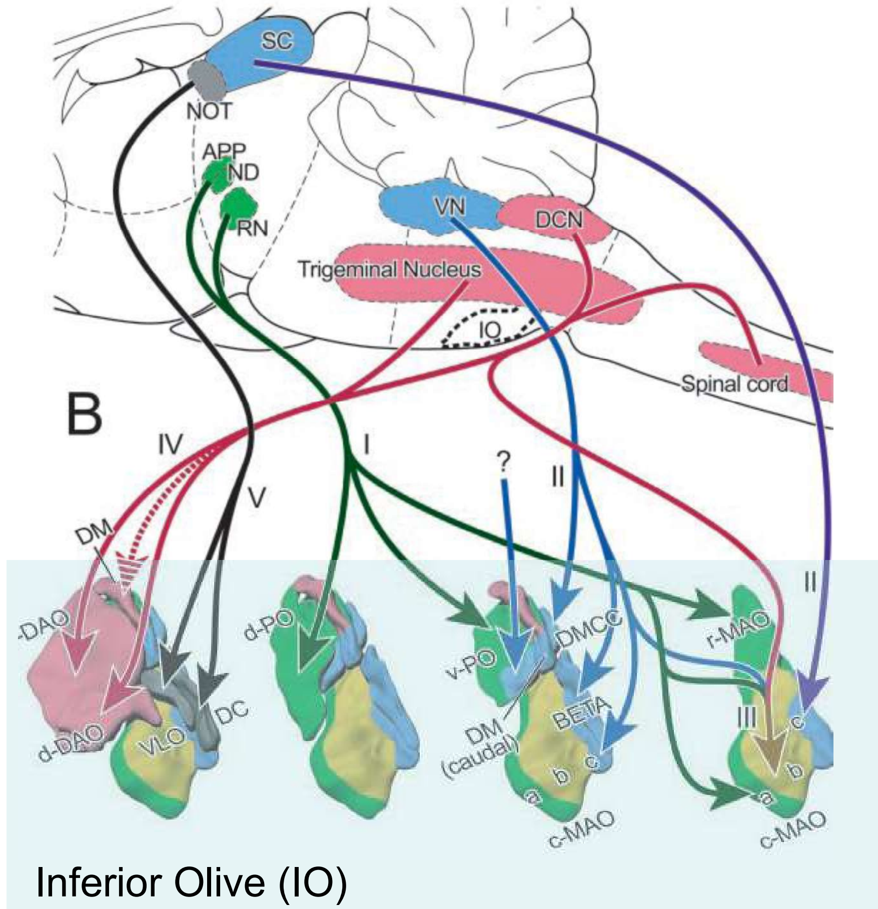
Motor Command:

RN = Red Nucleus

Somatosensory & Proprioceptive:

DCN = Dorsal Column Nucleus

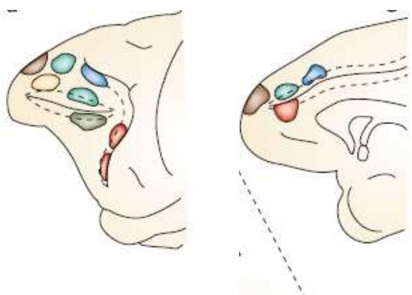
Trigeminal & Spinal Chord

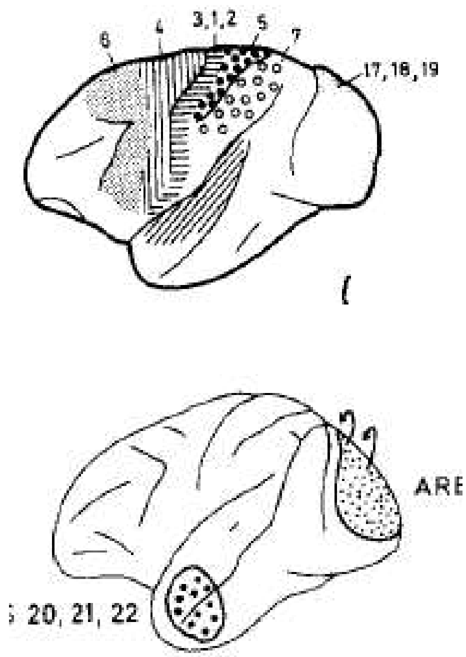


Sugihara & Shinoda JNS 2004

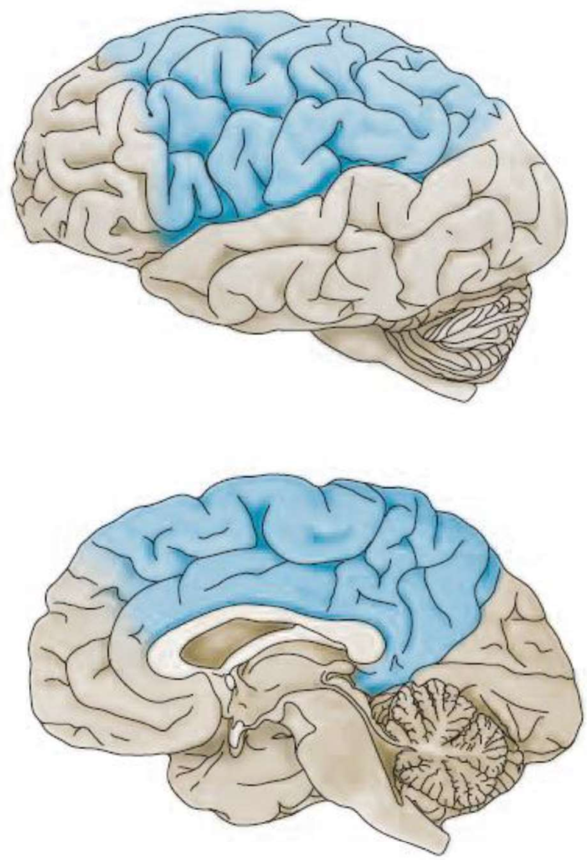
Additionally: Auditory Inputs

Pontine Nuclei relay Cerebro-Coritcal Information





(Brodal 1978)



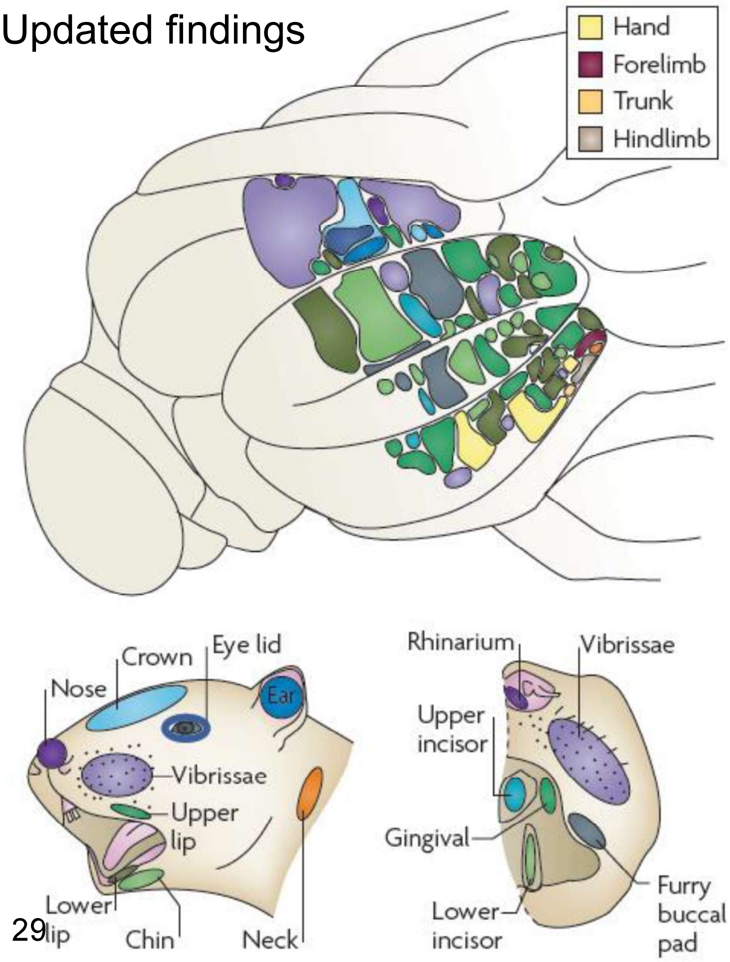
Non-Cortical Inputs:

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

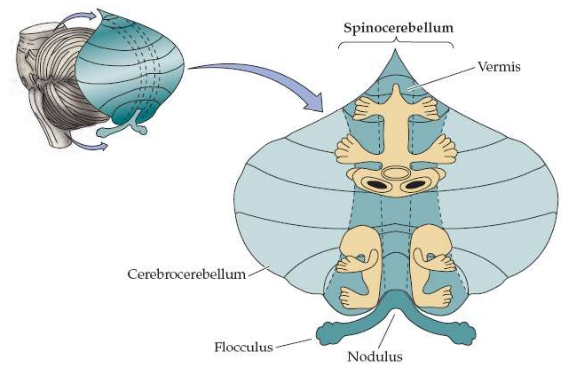
Cortical Areas That project to the Pontine Nuclei

Fragmented cerebellar cortical map

Updated findings

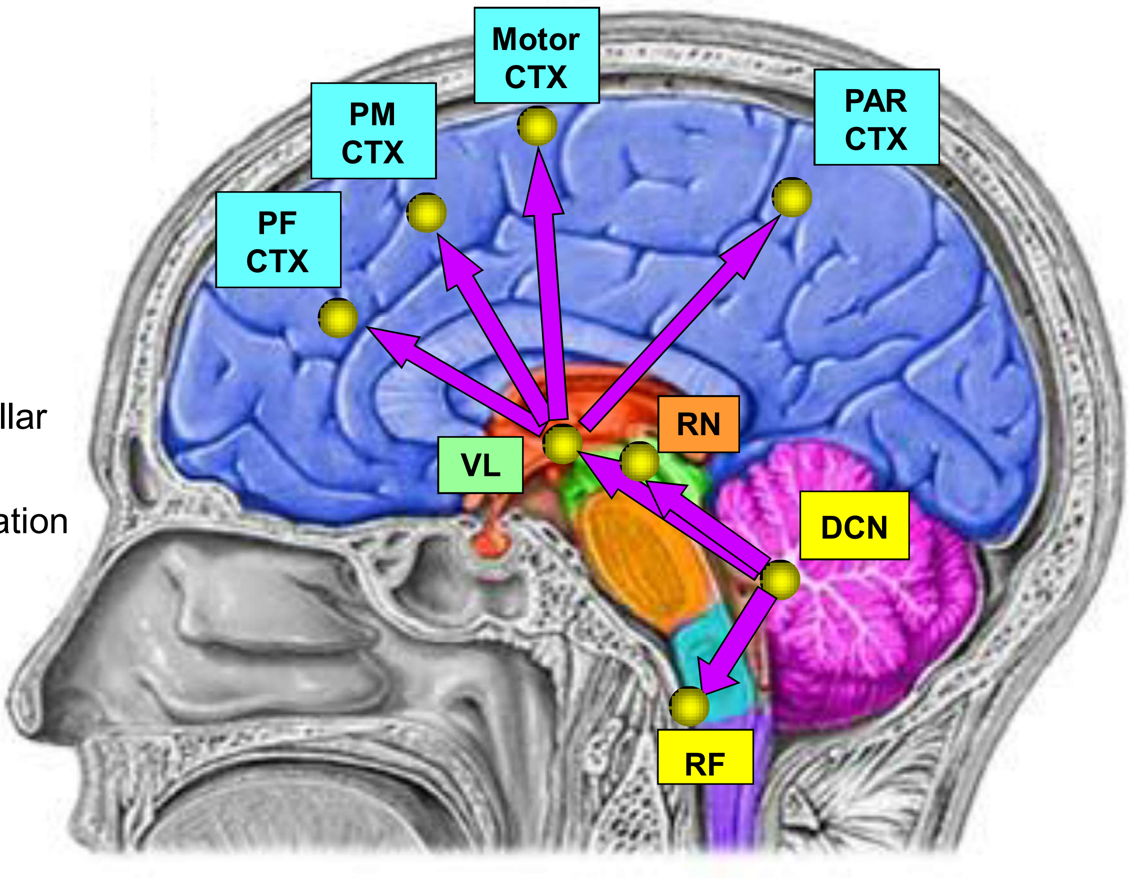


Initial Models



Cerebellar major output targets

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



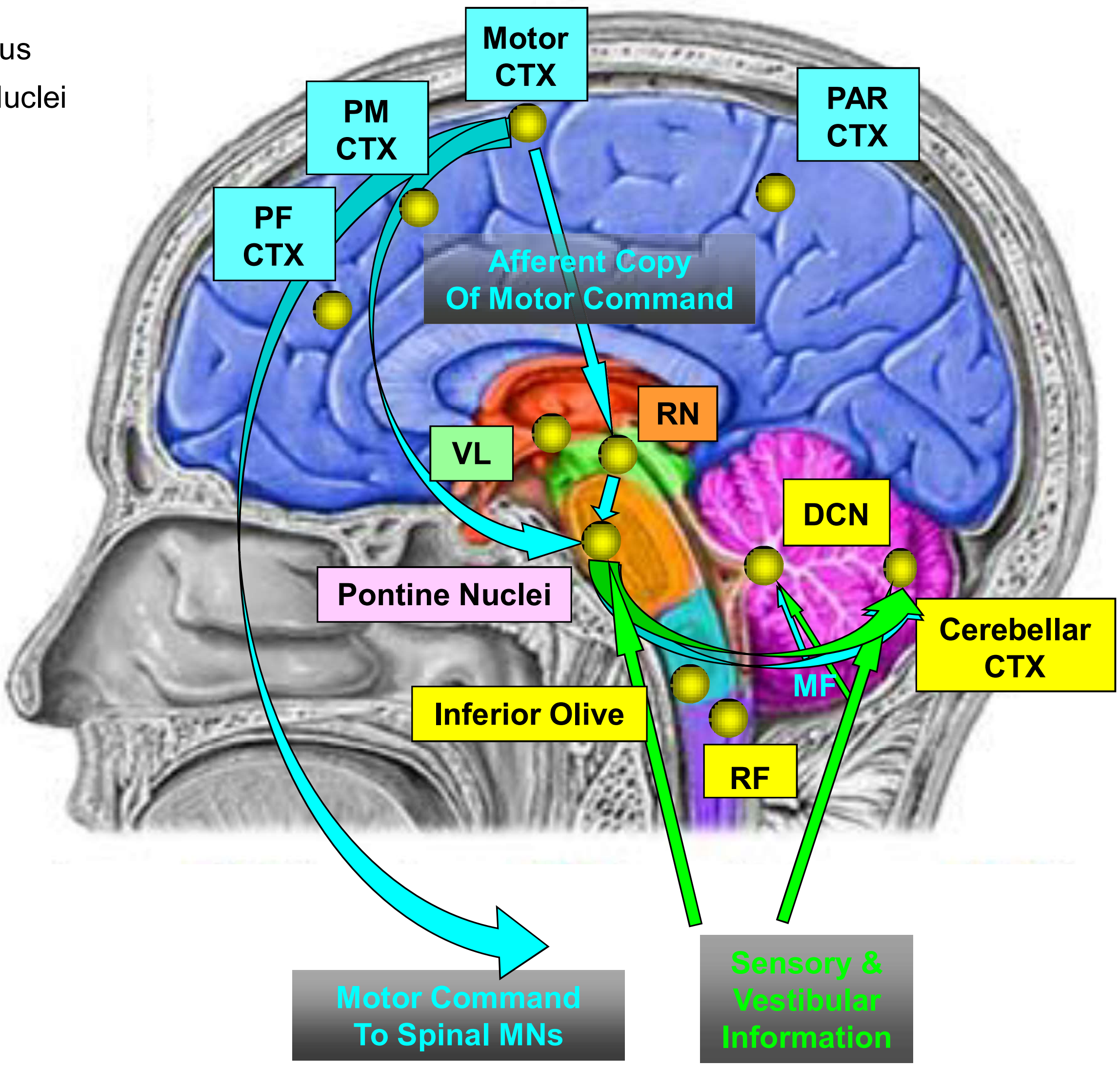
Other Outputs:
Inferior Olive
Hippocampus
Amygdala
Septum
Caudate Nucleus (BG)

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

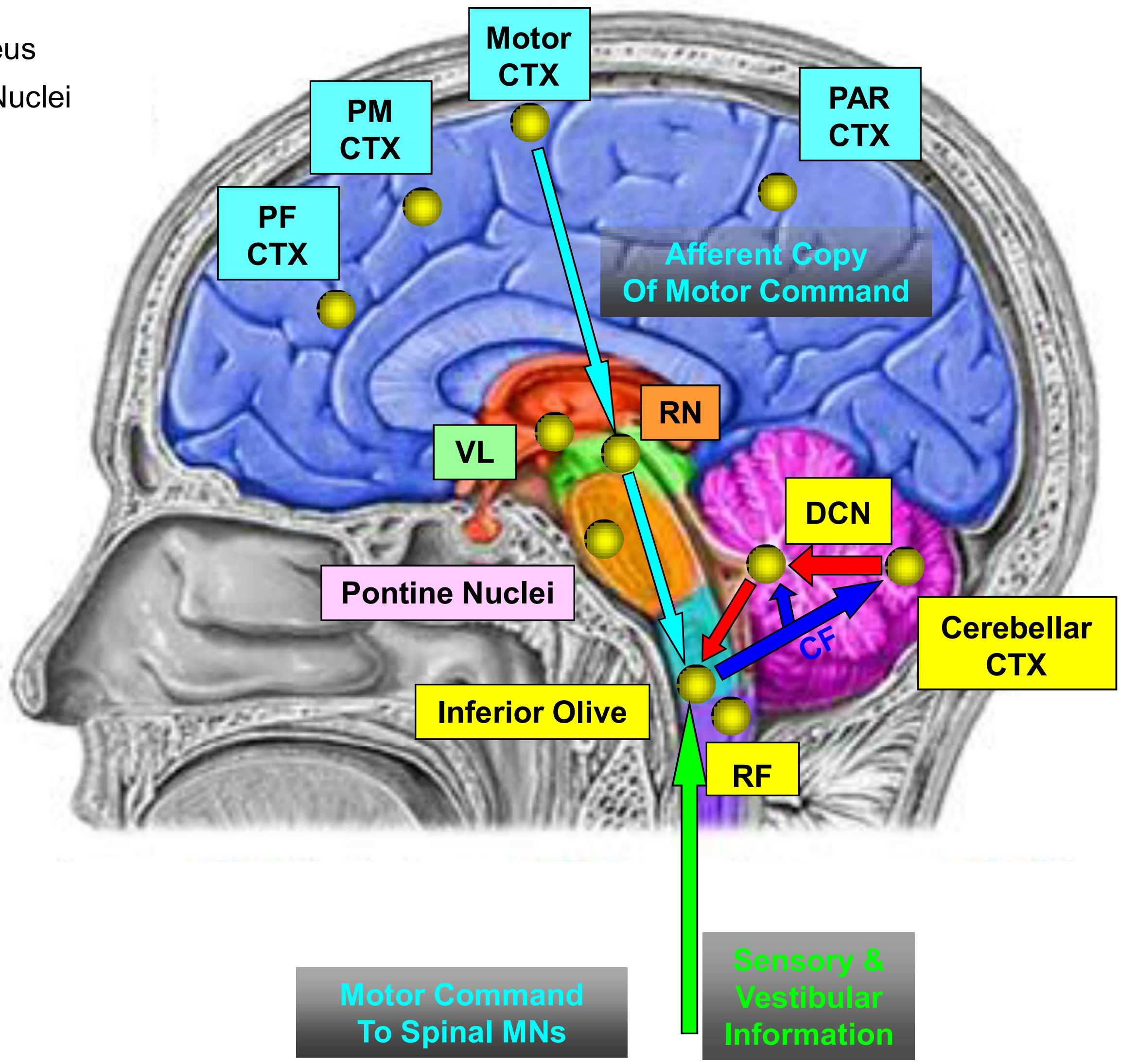


Olivocerebellar Information flow : Climbing Fibers Inputs

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

CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers

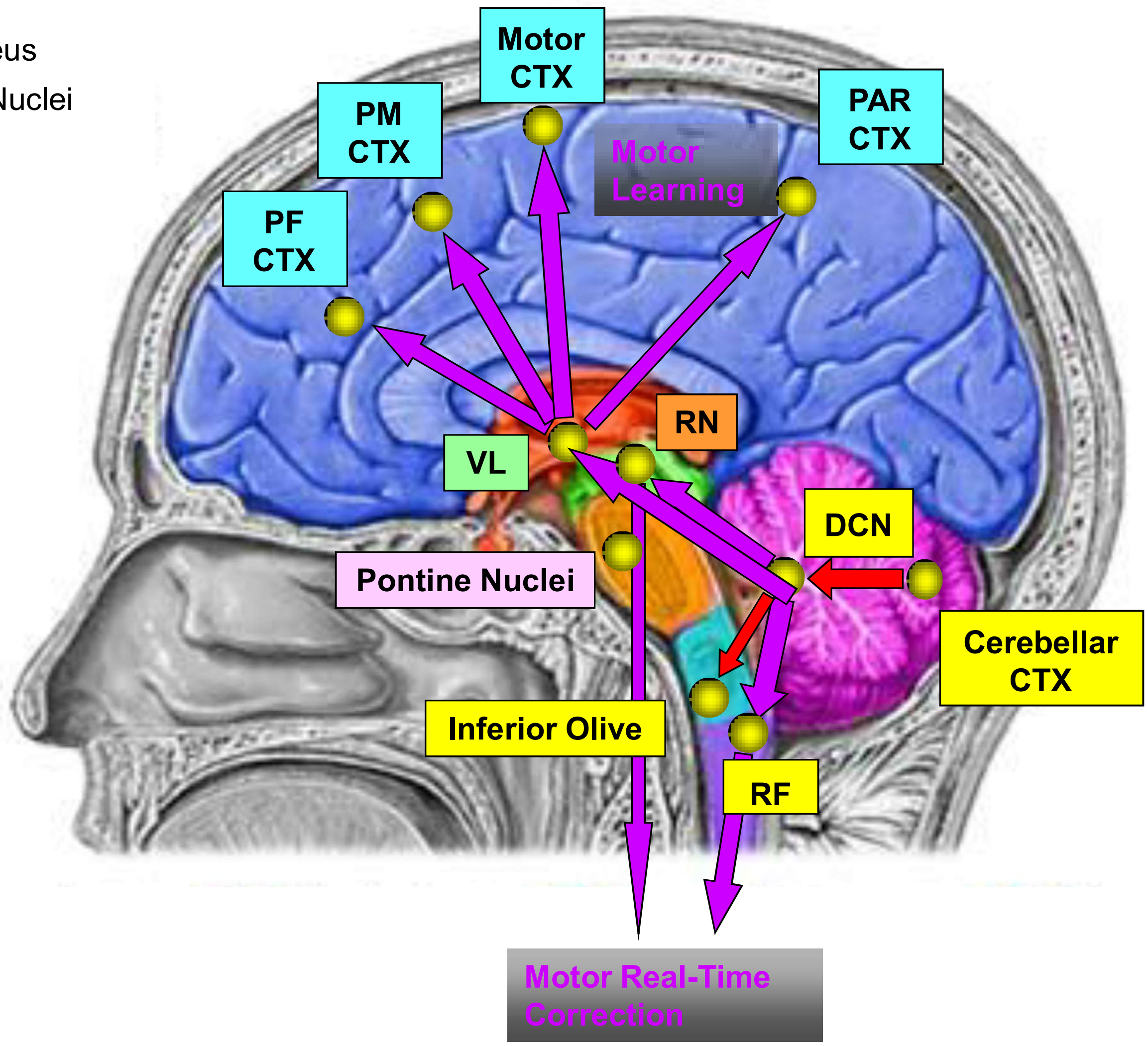


Hypothesized information flow during Cerebellar function

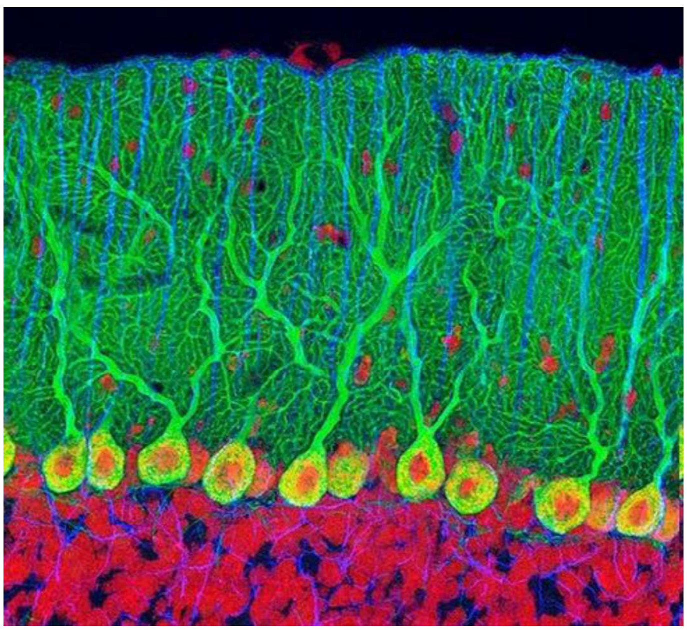
VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

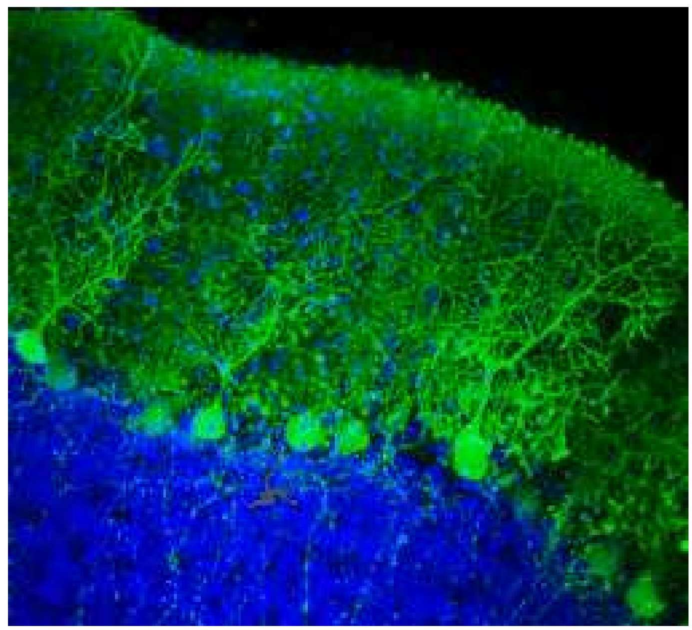
CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers

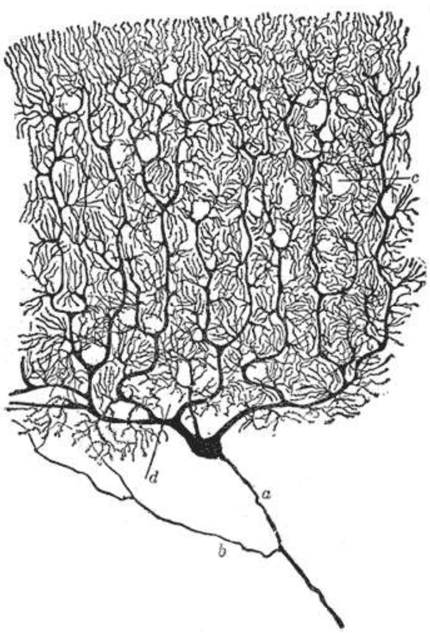


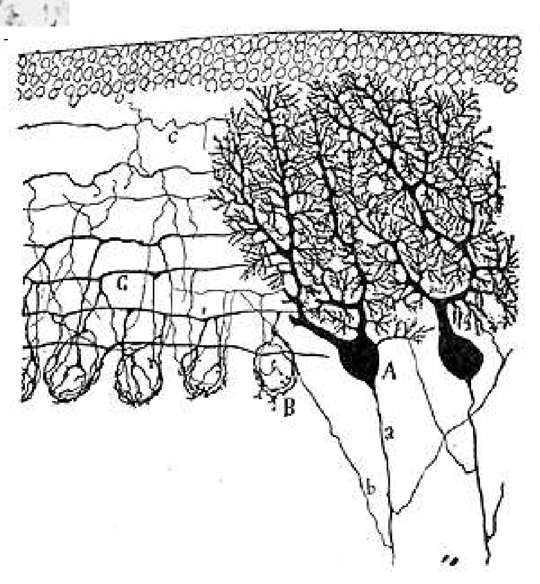
Cerebellar Cortex:
The beauty of network architecture

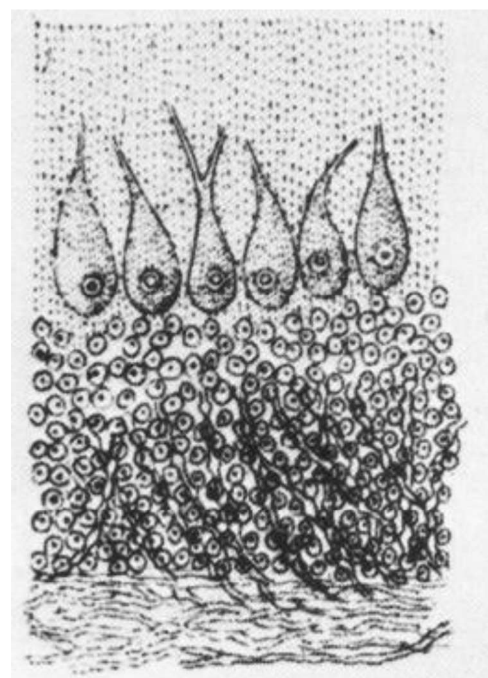




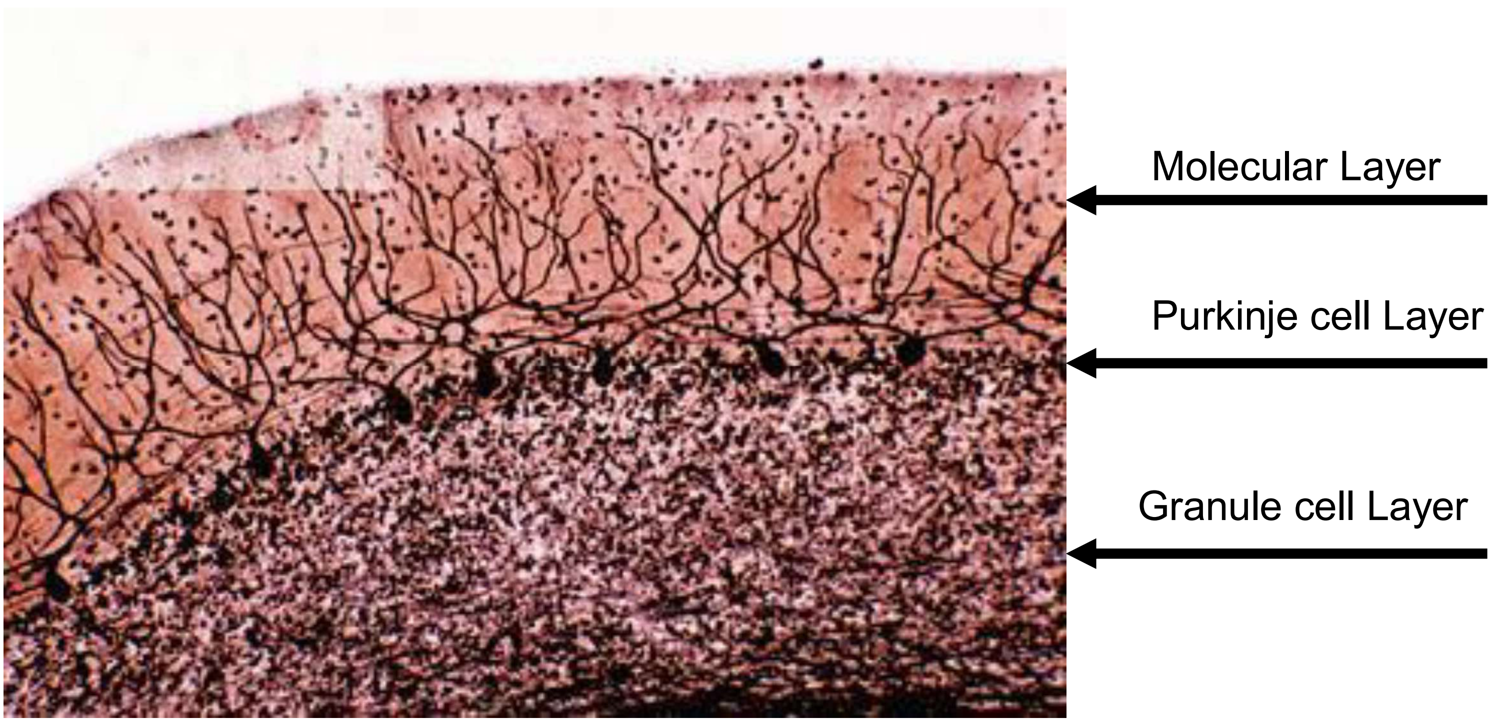
Purkinje Cells: the most elaborate neurons of the CNS



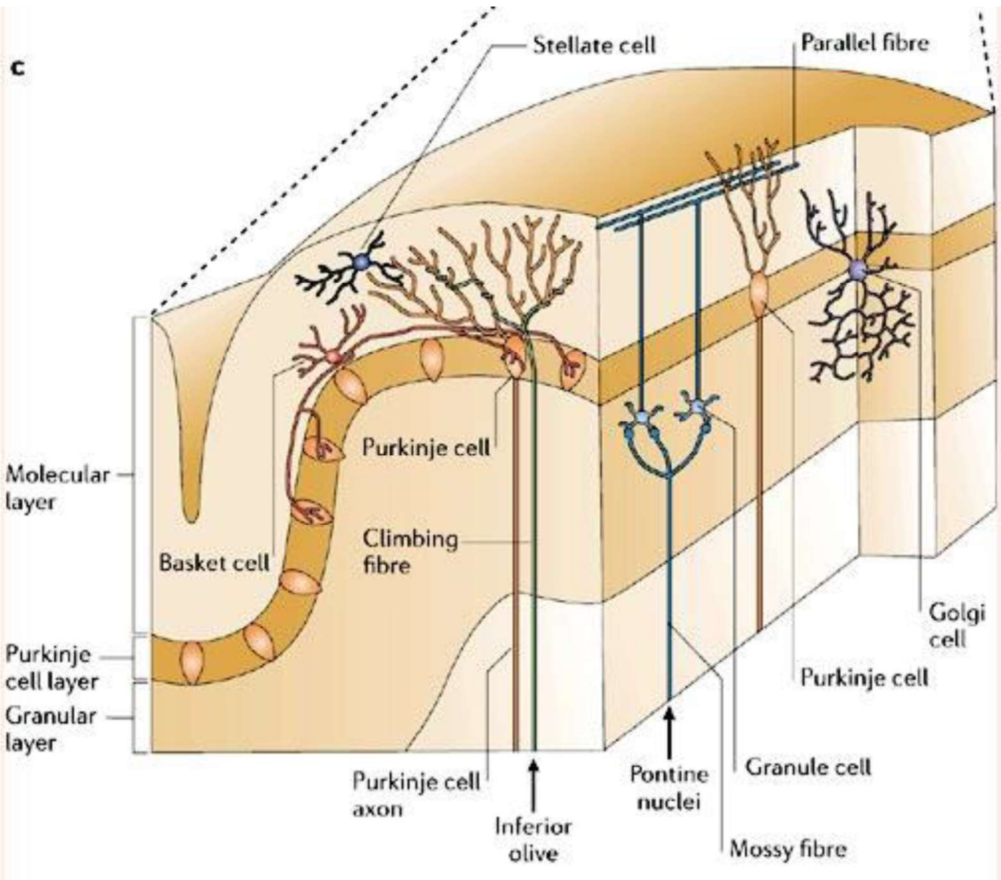




The 3 layers of the Cerebellar Cortex



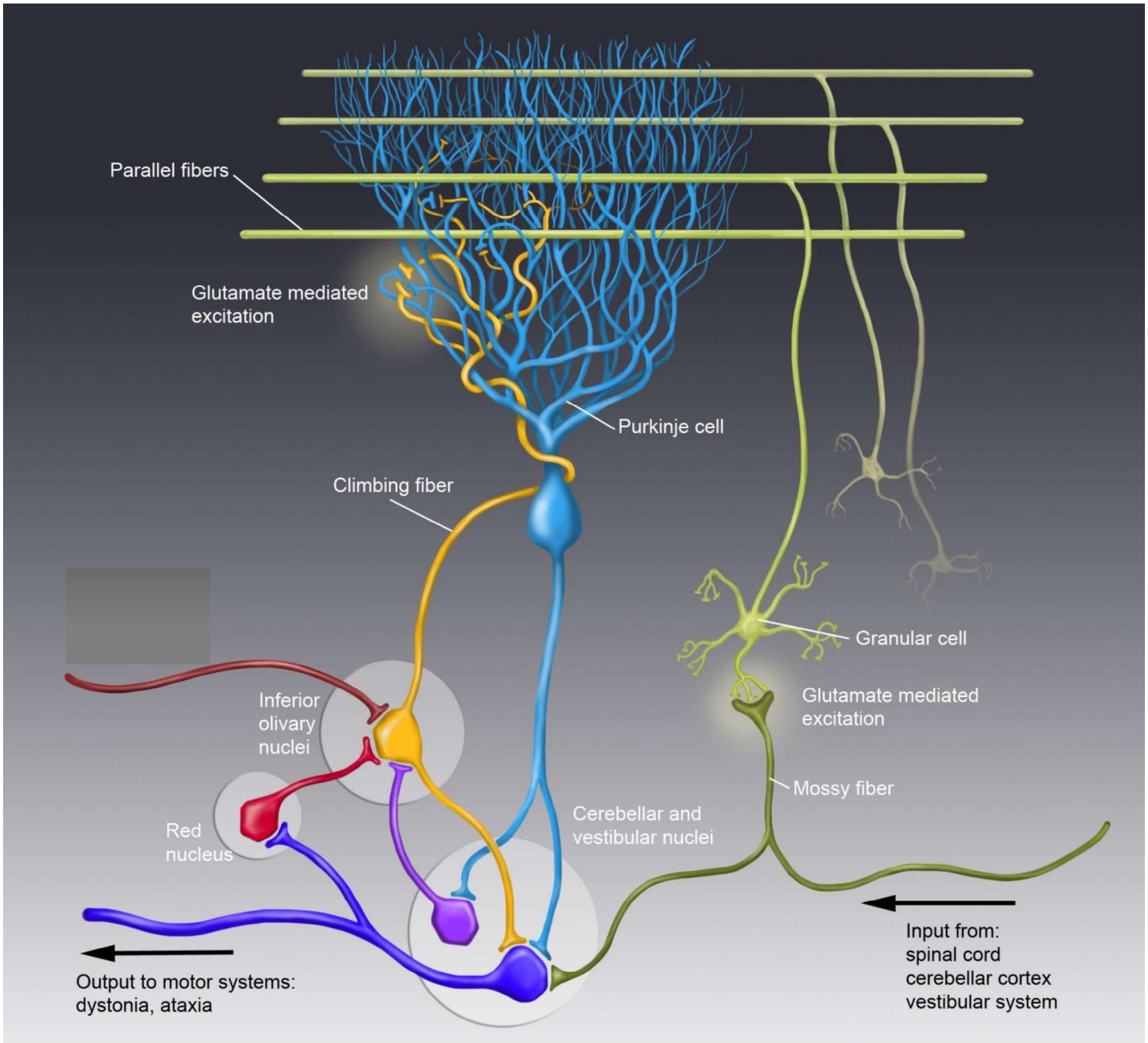
Cell types of the Cerebellar Cortex



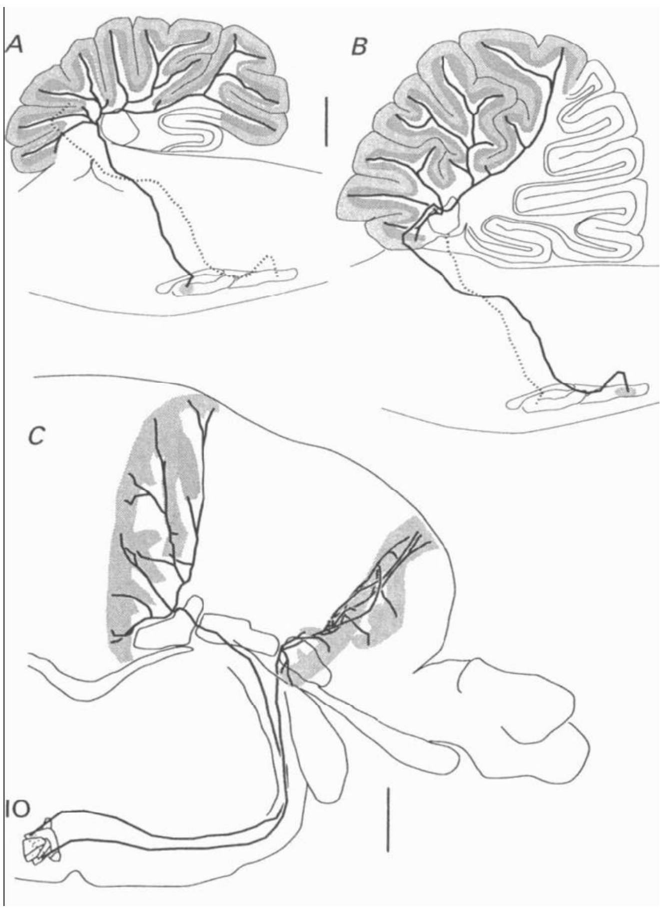
Inhibitory cells:
- Purkinje
- Golgi
- Basket
- Stelate

Excitatory Cells:
- Granule cells

Ramnani 2006


Parallel fibers
Glutamate mediated excitation
Purkinje cell
Climbing fiber
Granular cell
Glutamate mediated excitation
Inferior olivary nuclei
Mossy fiber
Red nucleus
Cerebellar and vestibular nuclei
Input from:
spinal cord
cerebellar cortex
vestibular system
Output to motor systems:
dystonia, ataxia

Parasaggital distribution of climbing fibers



Sugihara et al. JPhysiol 1993

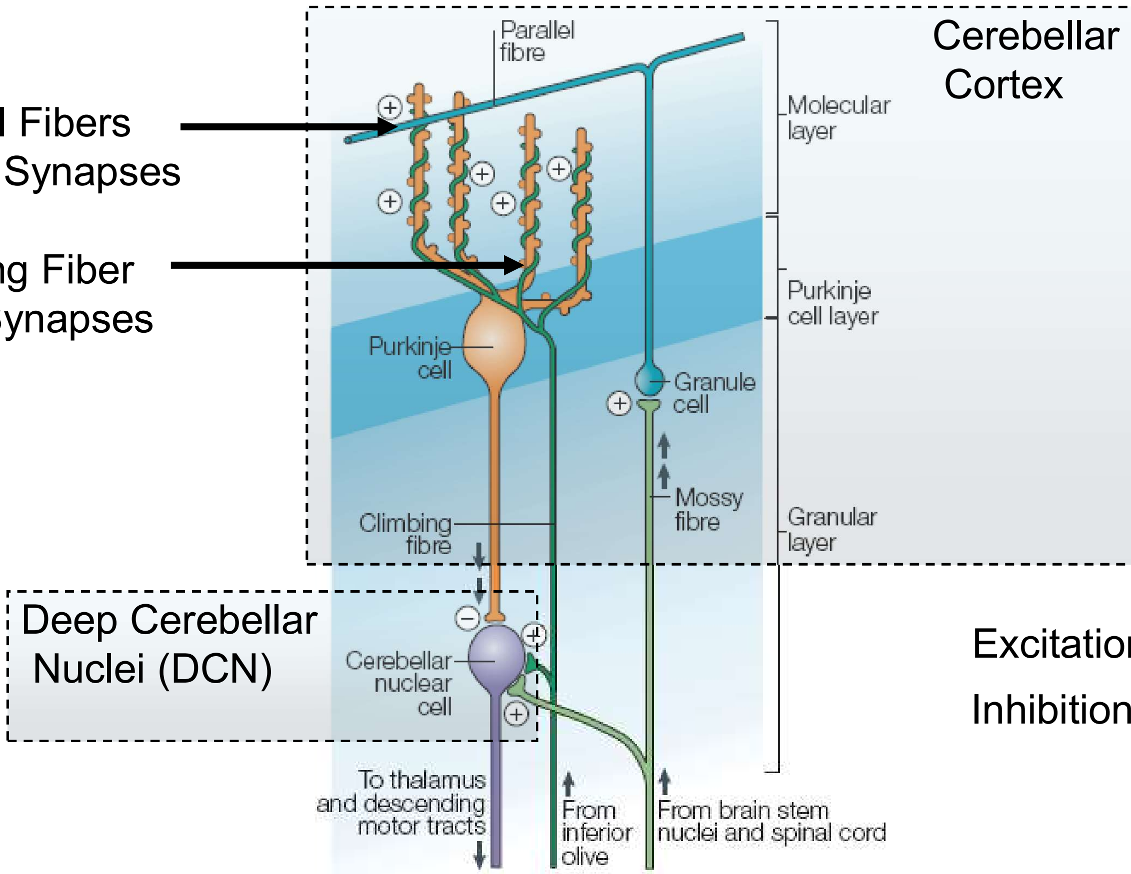
Sugihara JCompNeurol 2005

Each olivary neuron sends a single axon which gives rise to climbing fibers enervating ~10 PCs. These PCs are normally aligned along a parasagittal plane.
One the left, 2 IO neurons with their 2 distinct planes.

PC: The Principal Cell of Cerebellar Cortex

Parallel Fibers
~200,000 Synapses

Climbing Fiber
~2000 Synapses



Excitation

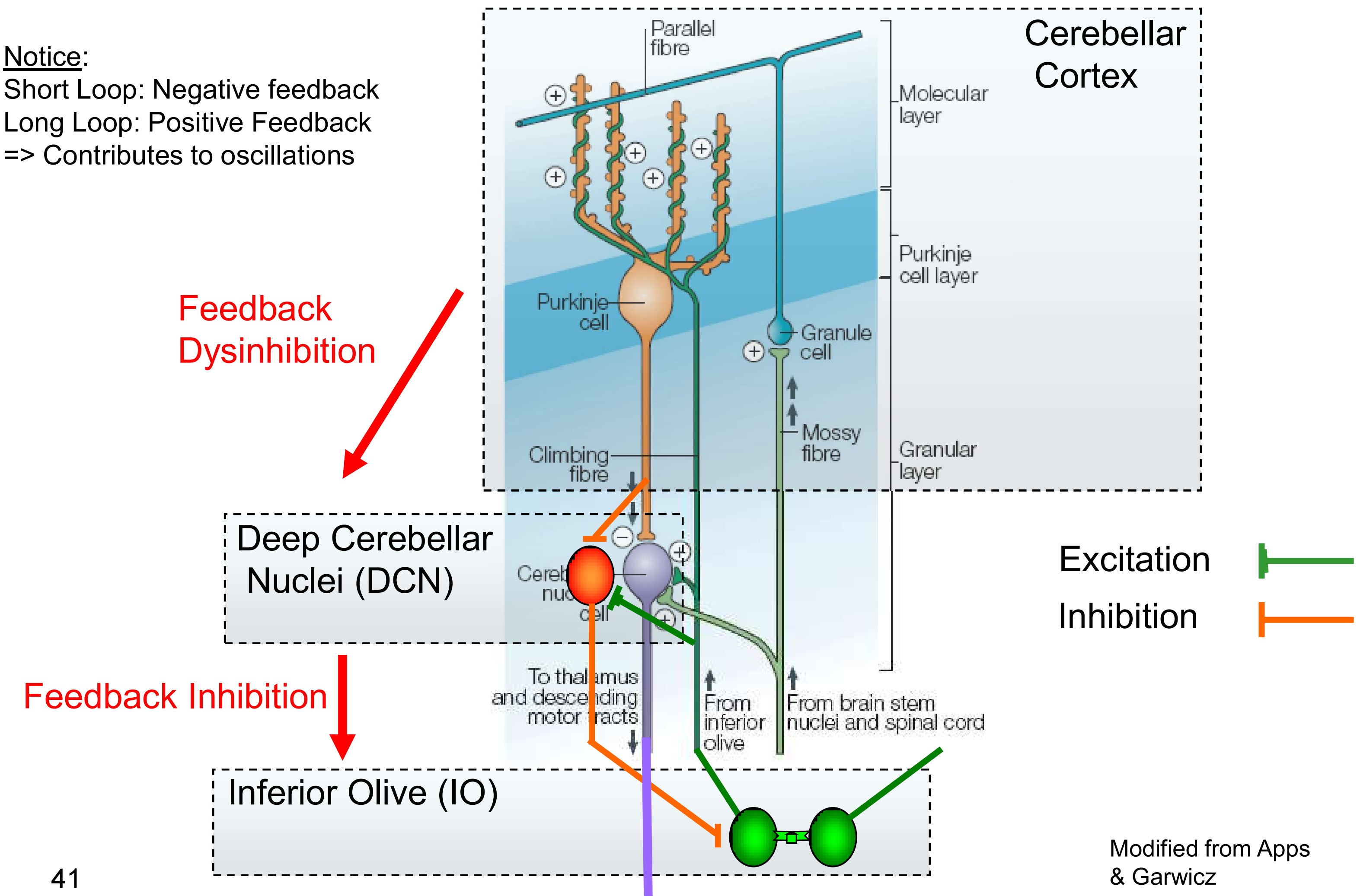
Inhibition

<ins>Purkinje Cells are the only neurons projecting from the Cerebellar Cortex!!</ins>

Modified from Apps & Garwicz 2005

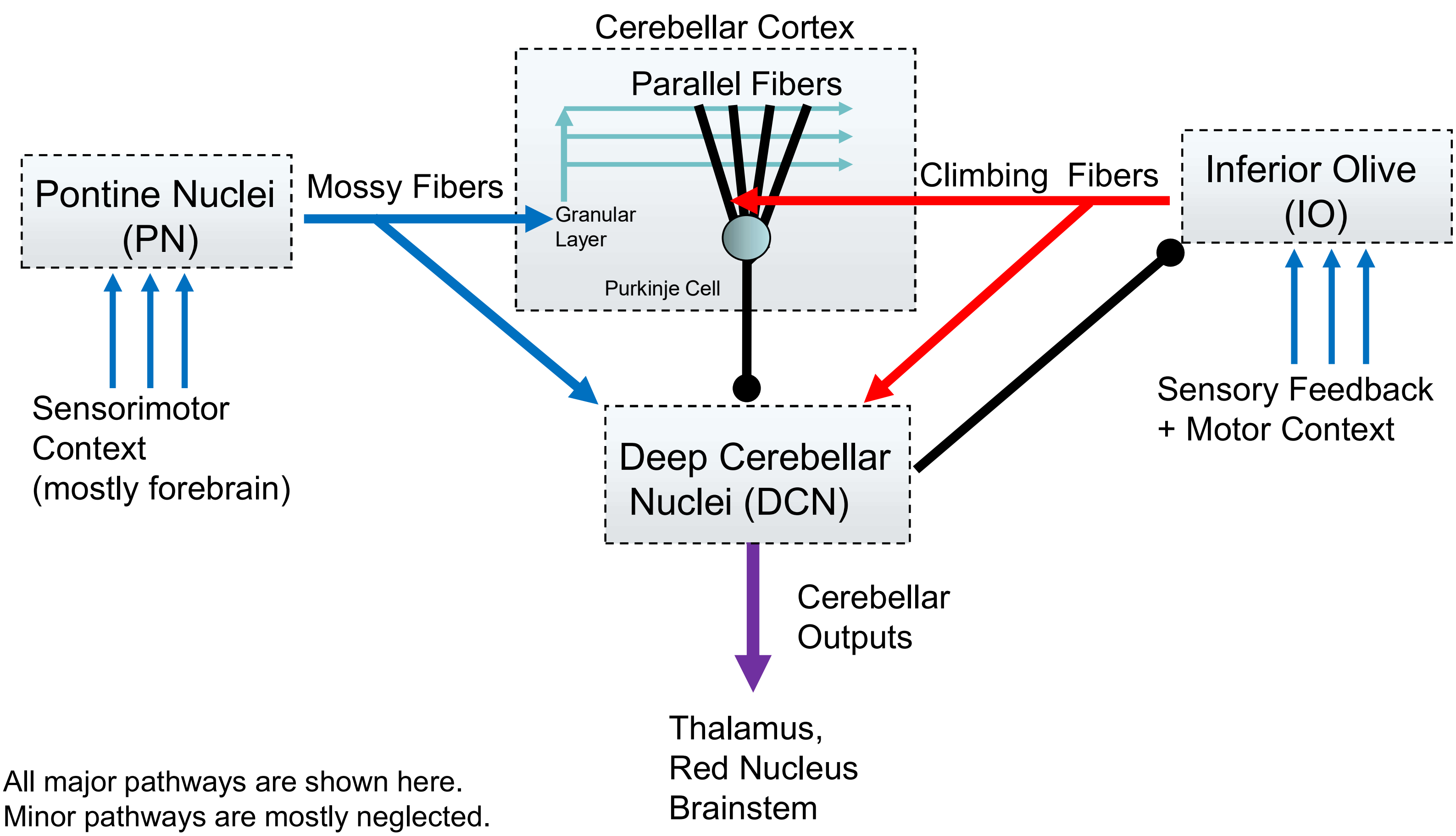
Closing the Loop: The Cerebellar Module

<u>Notice</u>:
Short Loop: Negative feedback
Long Loop: Positive Feedback
=> Contributes to oscillations



Modified from Apps & Garwicz NatRevNeu 2005

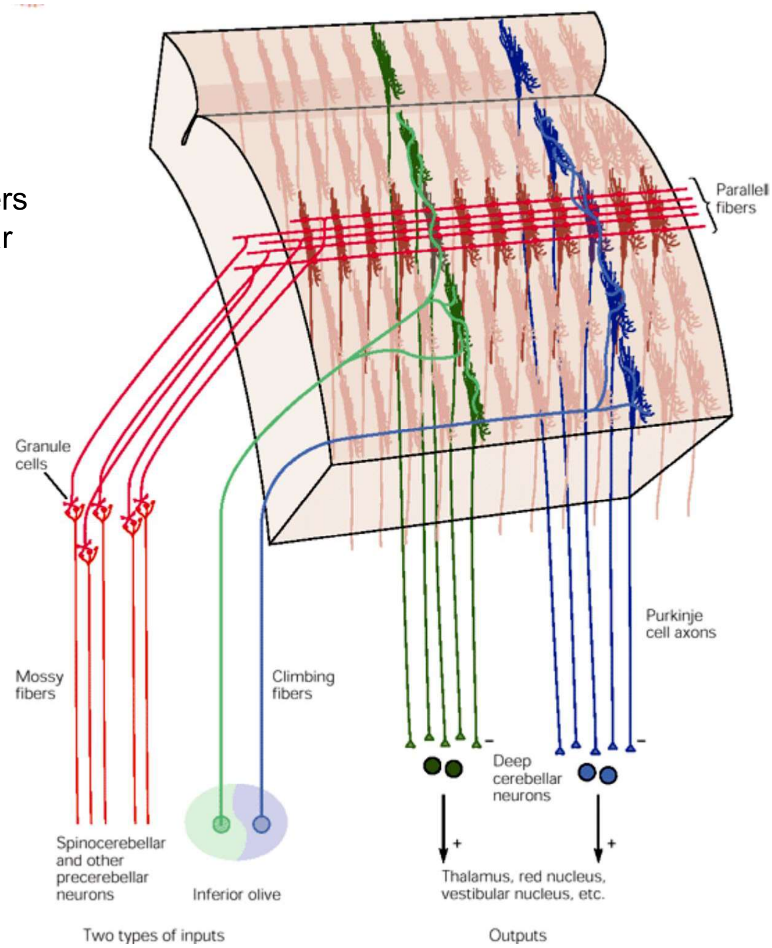
Summary: Simplified Olivocerebellar System



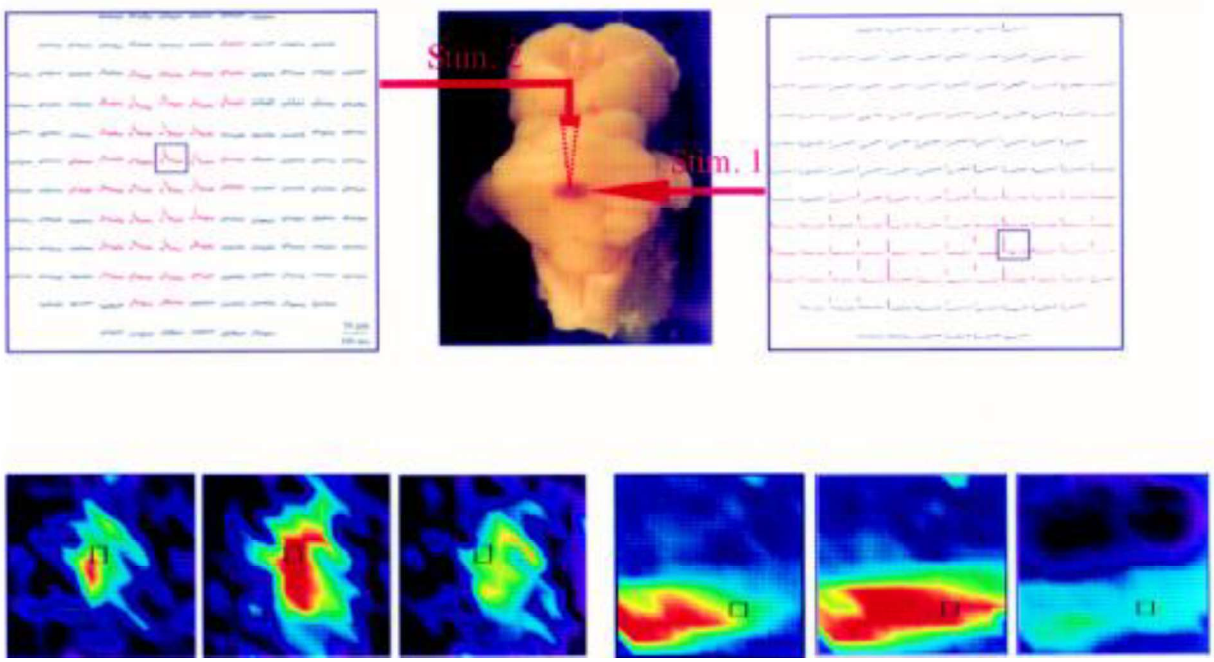
All major pathways are shown here.
Minor pathways are mostly neglected.
Notice that in vestibular circuits, vestibular nuclei replace the DCN with all appropriate connectivity

Perpendicular arrangement of mossy and parallel fibers

While PCs that are innervated from the same olivary neuron are arranged along a parasagittal stripe, parallel fibers are arranges in a perpendicular arrangement along the mediolateral axis.



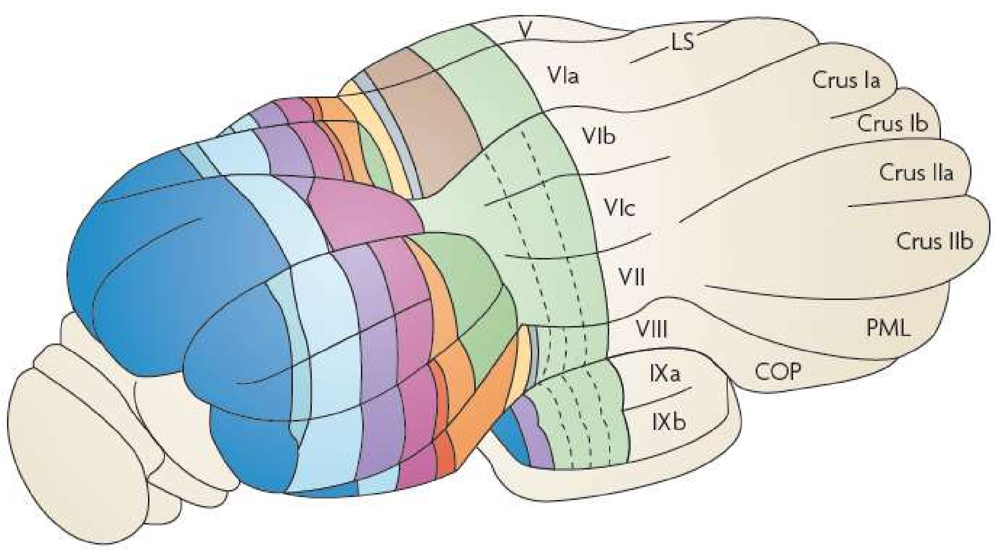
Parallel fibers are not a delay line



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

Yarom and Cohen AnnNYAc 2003

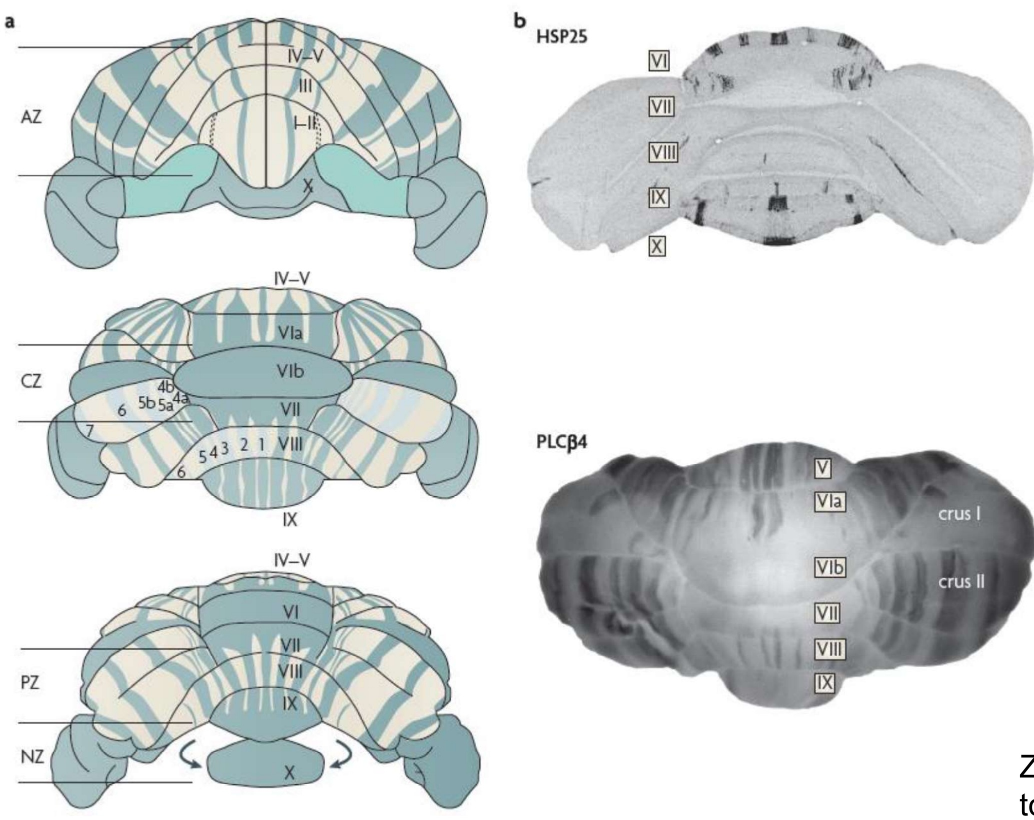
Cerebellar cortex anatomy suggest parasagittal segmentation



Anatomical labeling shows that specific areas in the olive and DCN (bottom 2 rows in the table below) are innervating parasagittal zones in the cerebellar cortex.
(in mouse Medial DCN(Med) ~ Fastigial, and lateral (NL, DLH) ~ Dentate)

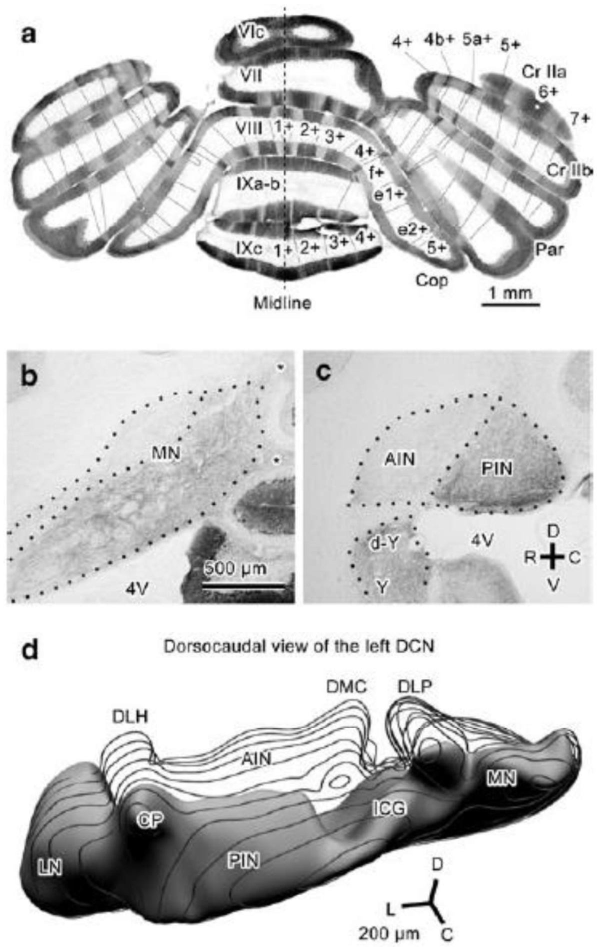
Hemisphere			Paravermis				Vermis					
D2	D0	D1	C3	C2	CX	C1	A2	B	X	AX	A	
dIPO	dmPO	vIPO	vfDAO	rMAO	iMAO (med)	vfDAO	cMAO (subnuc b[1]/c)	dfDAO	iMAO (lat)	cMAO (subnuc a)	cMAO (subnuc b)	Inferior olive (input)
NL (parvo)	DLH	NL (magno)	NIA	NIP	ICG; NIP	NIA	DLP	LVN	ICG; NIP	MedN (lat); ICG	MedN (lat); ICG	Cerebellar nuclei (output)

Zebrin II markers also form parasagittal stripes In the cortex



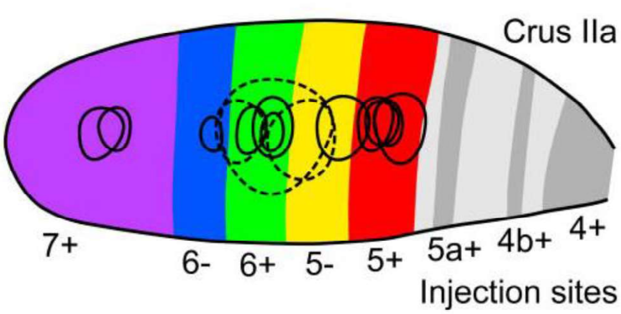
Zebrin expression seems to match the parasagittal zones

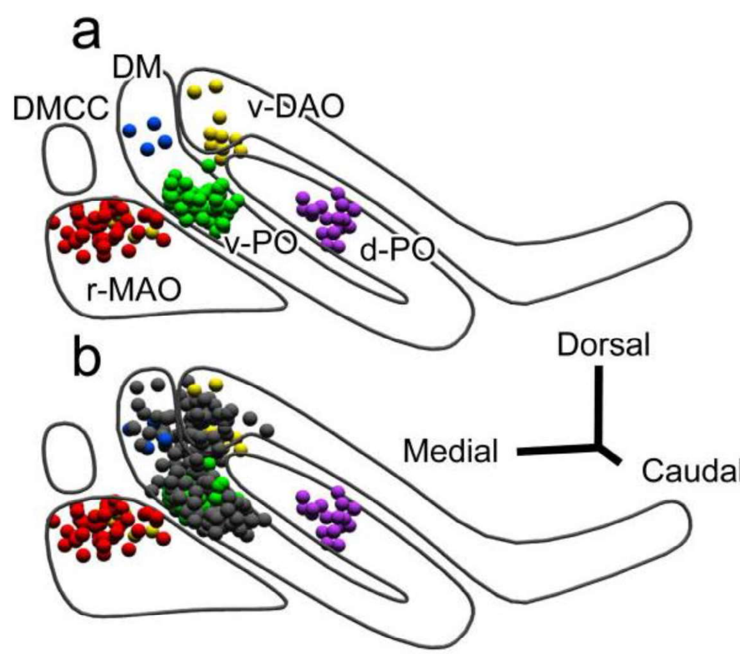
Aldolase C compartmentalization



Staining for Aldolase C segregates both cerebellar cortex and the DCN into specific areas

Inferior olive projections partially preserve the stripes

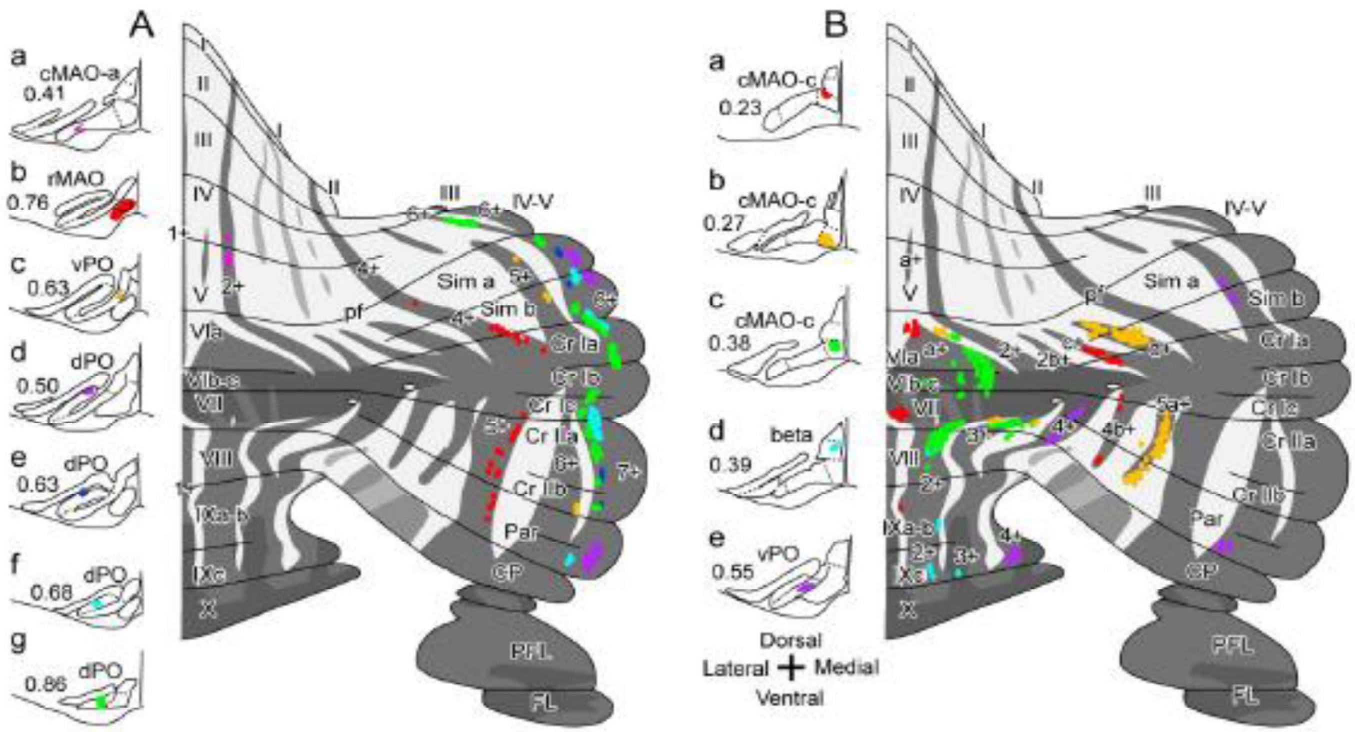




Dye injection to specific areas in the inferior olive stains parasagittal-like areas in the cerebellar cortex (crus IIa)

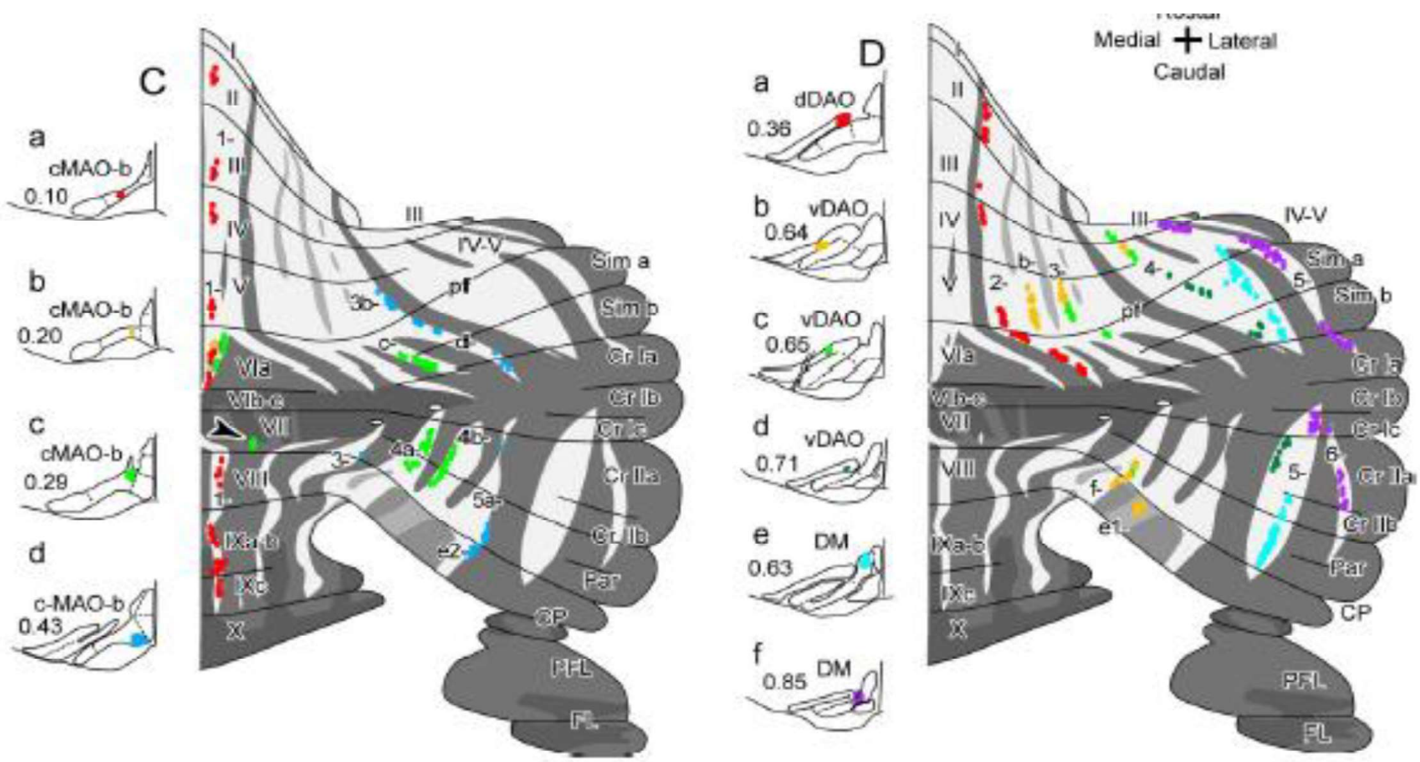
MAO = medial accessory olive
DAO = dorsal accessory olive
PO = primary olive
DM/CC = dorsomedial (column) / Cup of Kooy

Inferior olive projections partially preserve the stripes



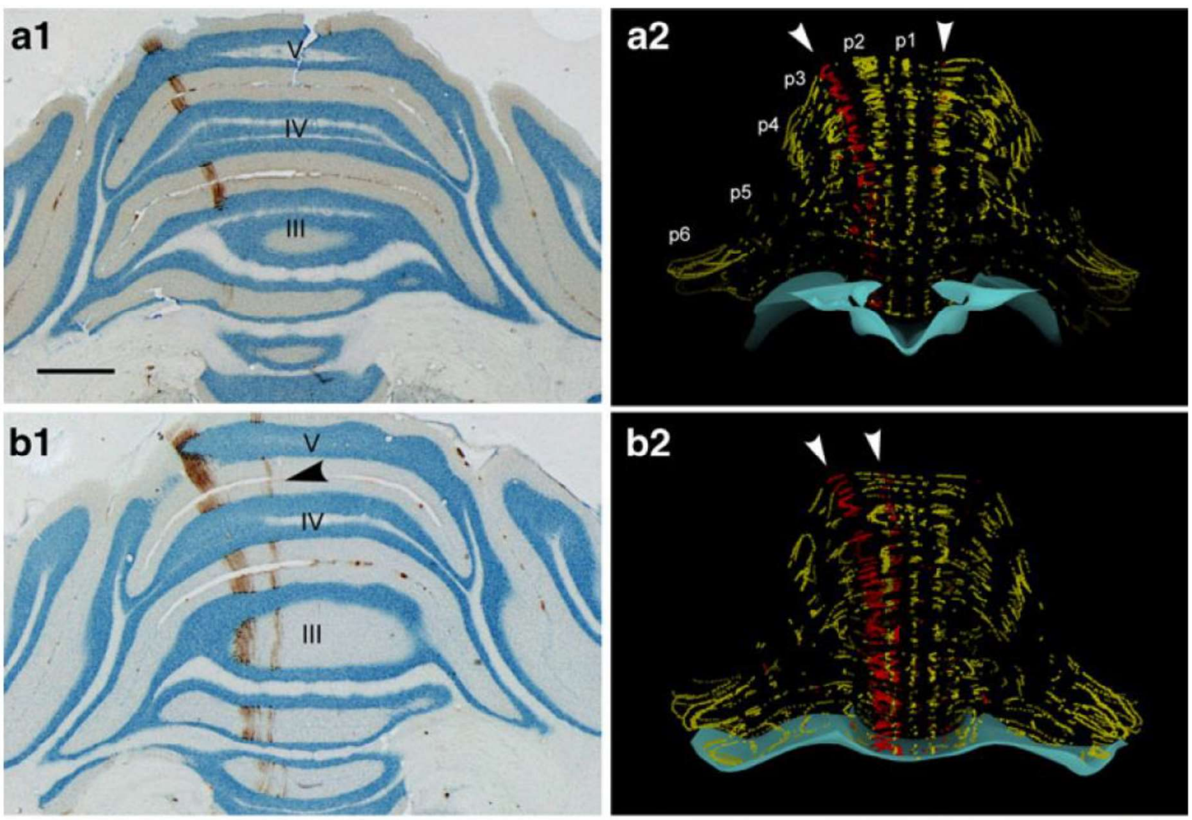
Dye injection to specific areas in the inferior olive stains parasagittal-like areas in the cerebellar cortex

Inferior olive projections partially preserve the stripes



Dye injection to specific areas in the inferior olive stains parasagittal-like areas in the cerebellar cortex

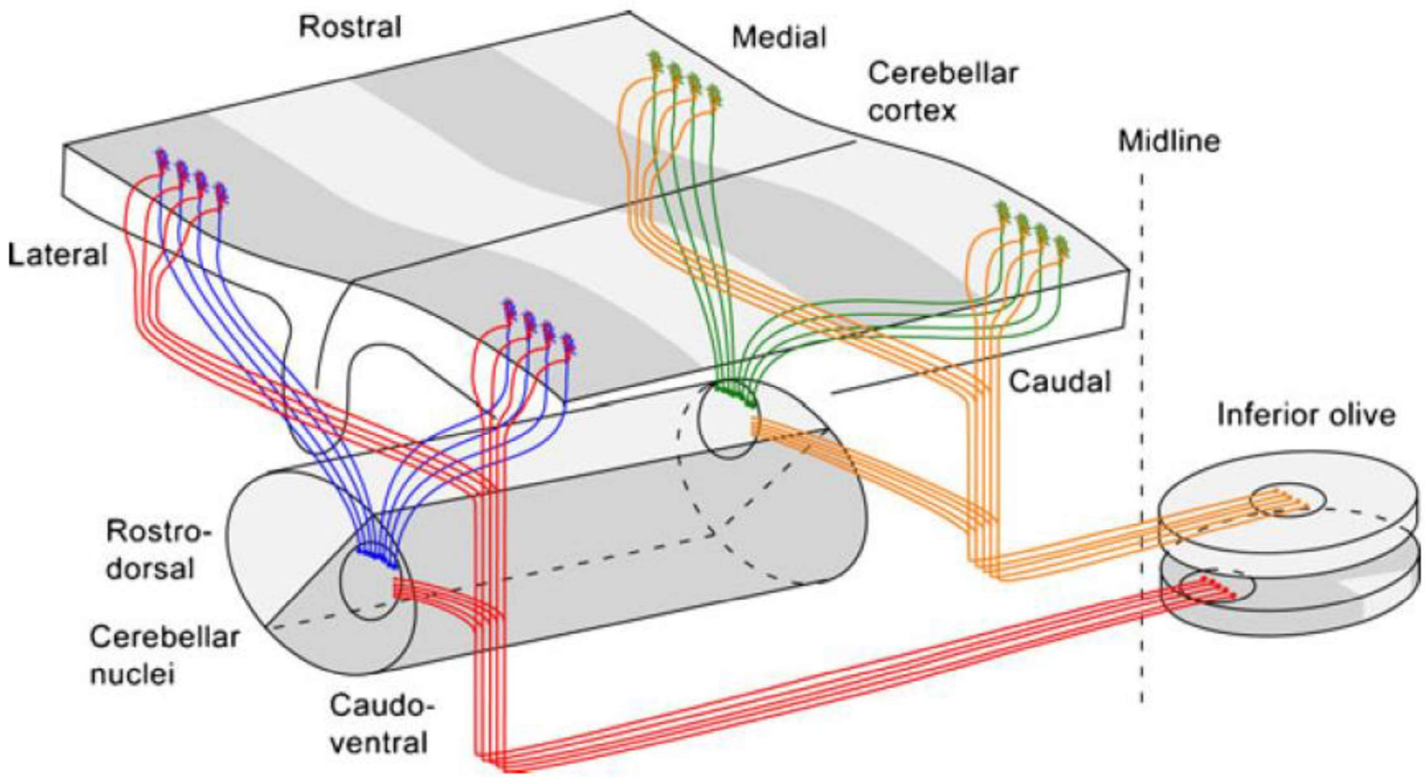
Stripes formed by muscle labeling



Muscle Num 1
ipsilateral
gastrocnemius

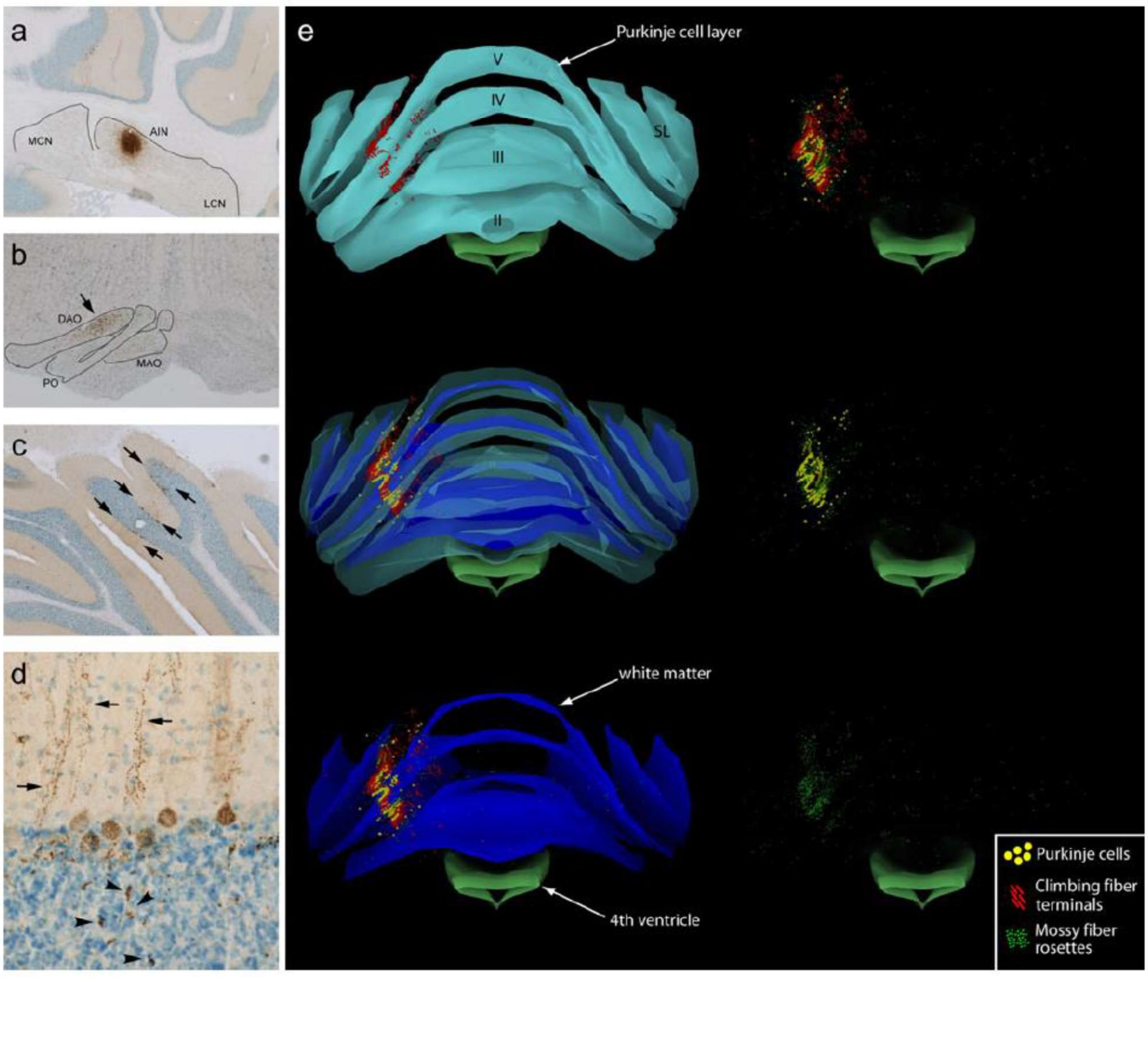
Muscle Num 2
ipsilateral tibialis
anterior

Cerebellar Modules: DCN Neurons receive matching inputs from olivary neurons and PCs



Olivary group of neurons, their PC targets and corresponding DCN neurons form closed loops that presumably may act as a functional unit called micro-complex, a cerebellar module.

Co-Labeling Climbing and Mossy fibers substanciate the Modules



Cerebellar Physiology

Infra Red

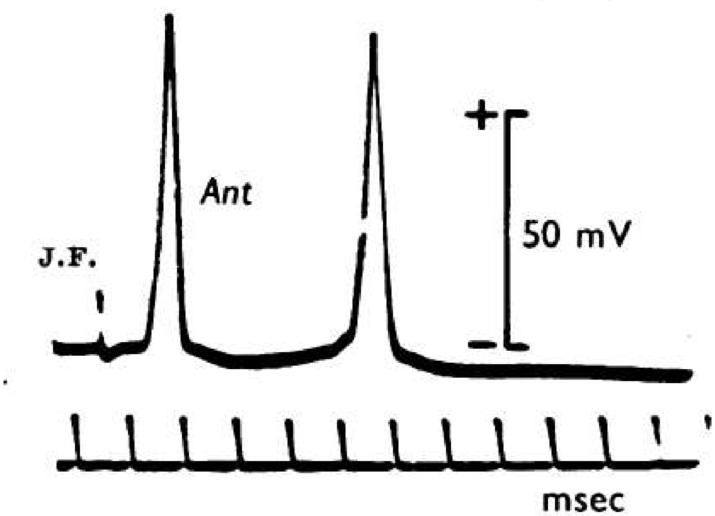
Fluorescent Dye

Double Recording of Purkinje Cell in Slice

Hausser M.

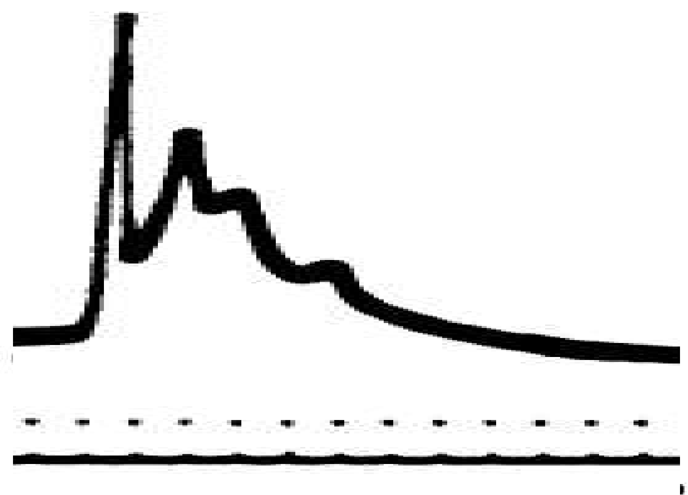
Purkinje cells exhibit two distinct spike types

Simple Spike (SS)



Mossy Fiber Stimulation

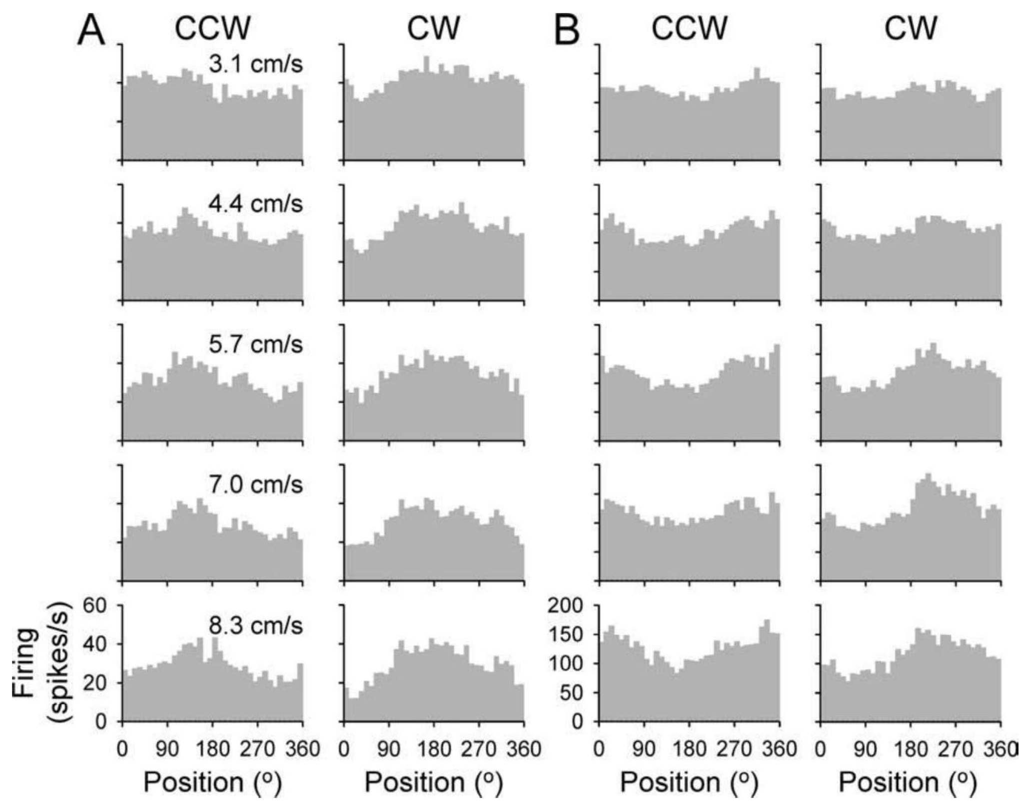
Complex Spike (CS)



Inferior Olive Stimulation

Eccles, 1966

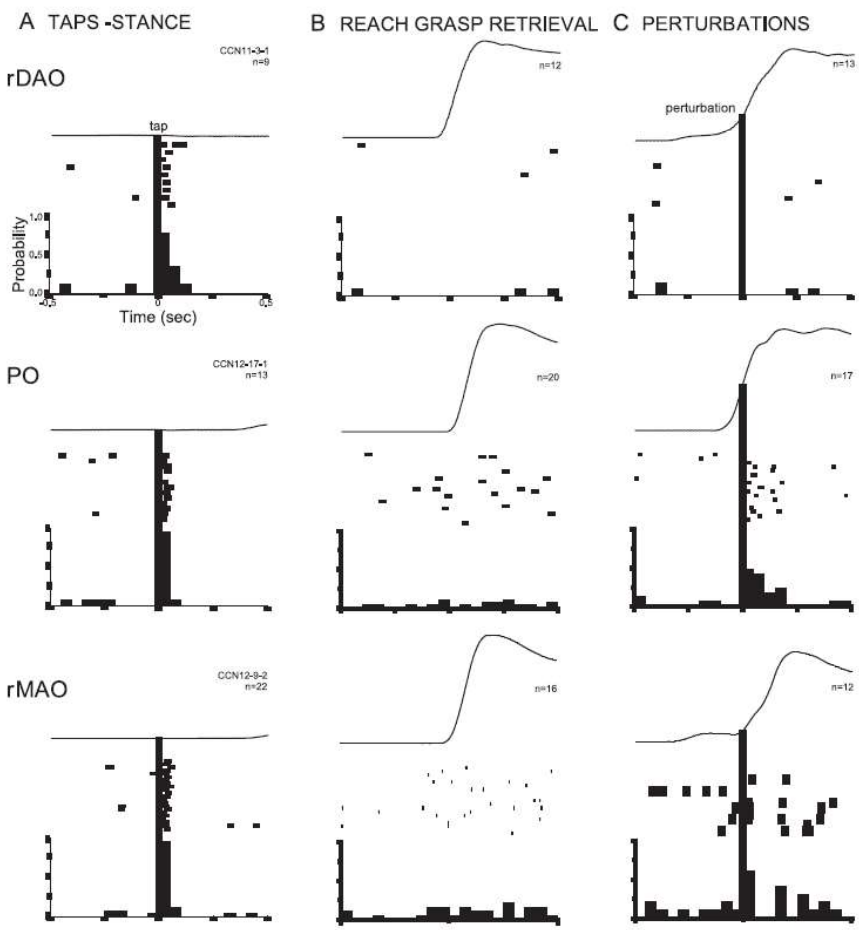
Simple Spikes are modulated during movement



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

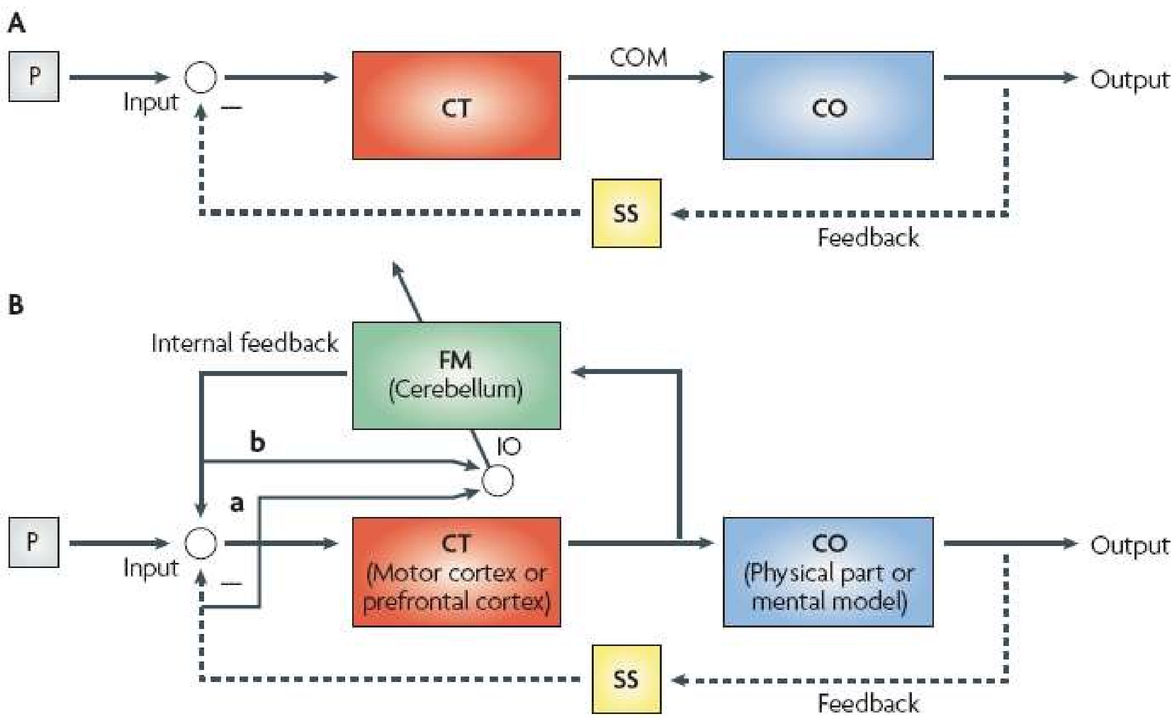
Roitman 2005

Olivary spikes (hence CS) are fired in unexpected events



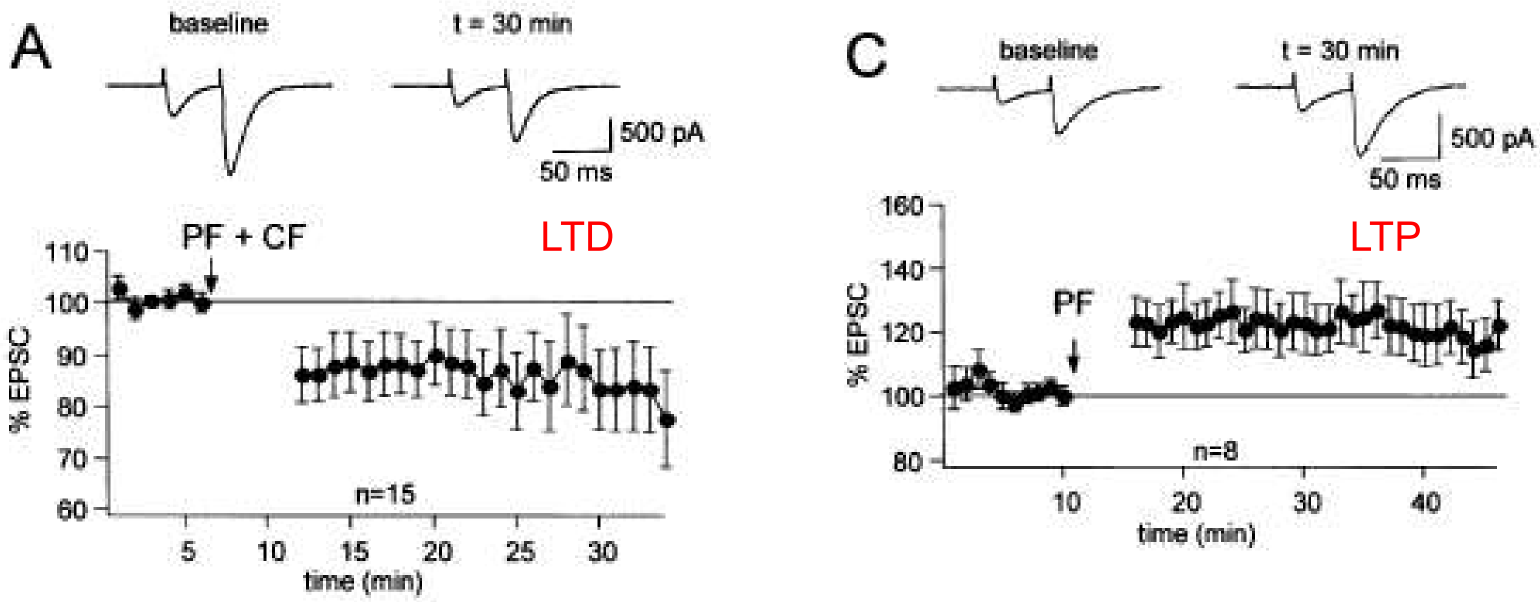
Horn, Pong & Gibson 2002

The general role of the cerebellum: Internal model



The prevailing hypothesis of cerebellar function:
Forward model = internally predicting the sensory inputs following motor execution. This shortens response time from 100-200ms cortical decision loops (5-10Hz oscillations) to 10-20ms. The incoming feedback helps to correct errors in real-time and to refine the cerebellar predictions.

Plasticity in the Cerebellar Cortex

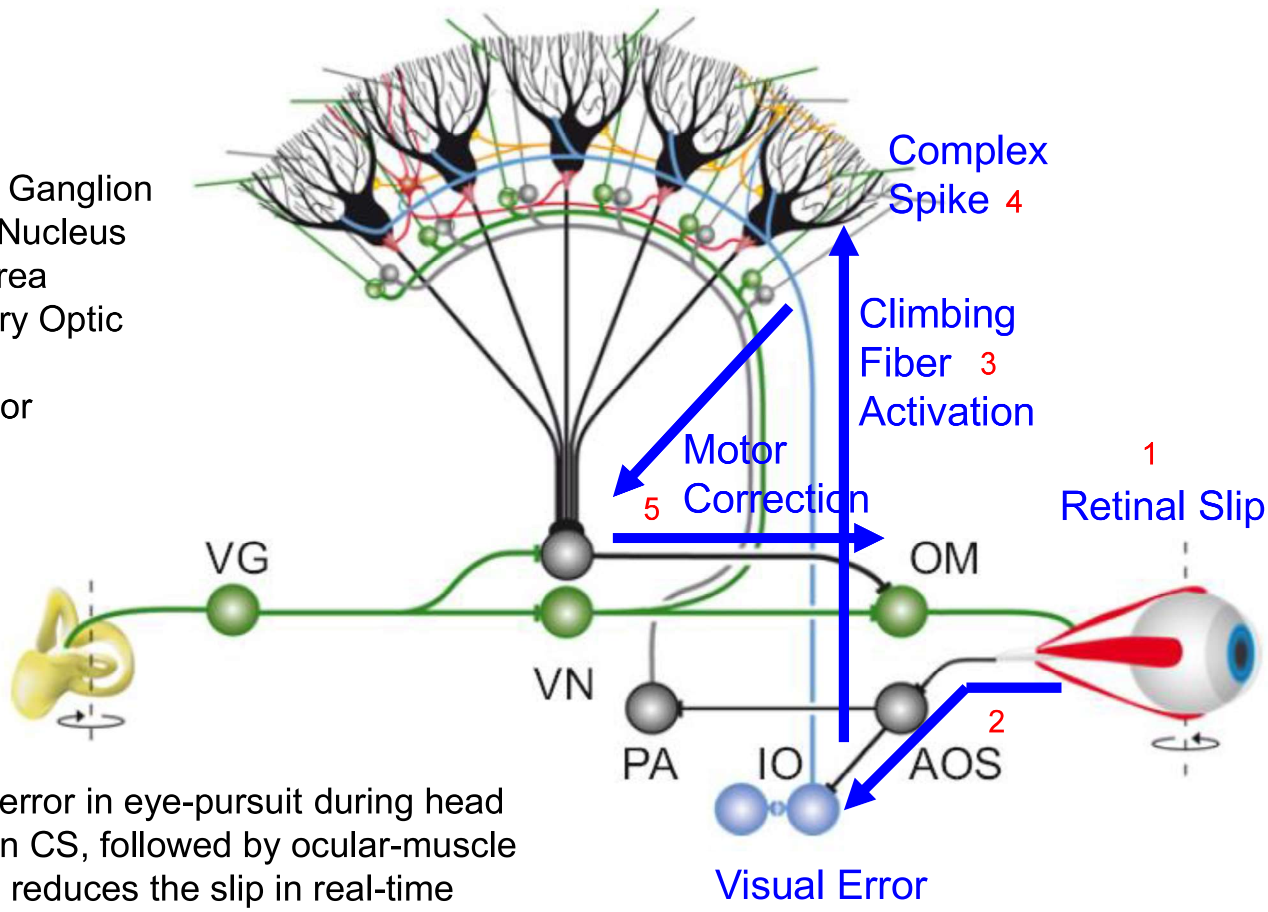


The temporal relationship between CS and SS determine the direction of plasticity in parallel fiber synapses

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, an error in eye-pursuit during head motion, results in CS, followed by ocular-muscle activation which reduces the slip in real-time

Ito 1984, Schonville et al. 2010

Vestibulo - Ocular Adaptation (VOR)

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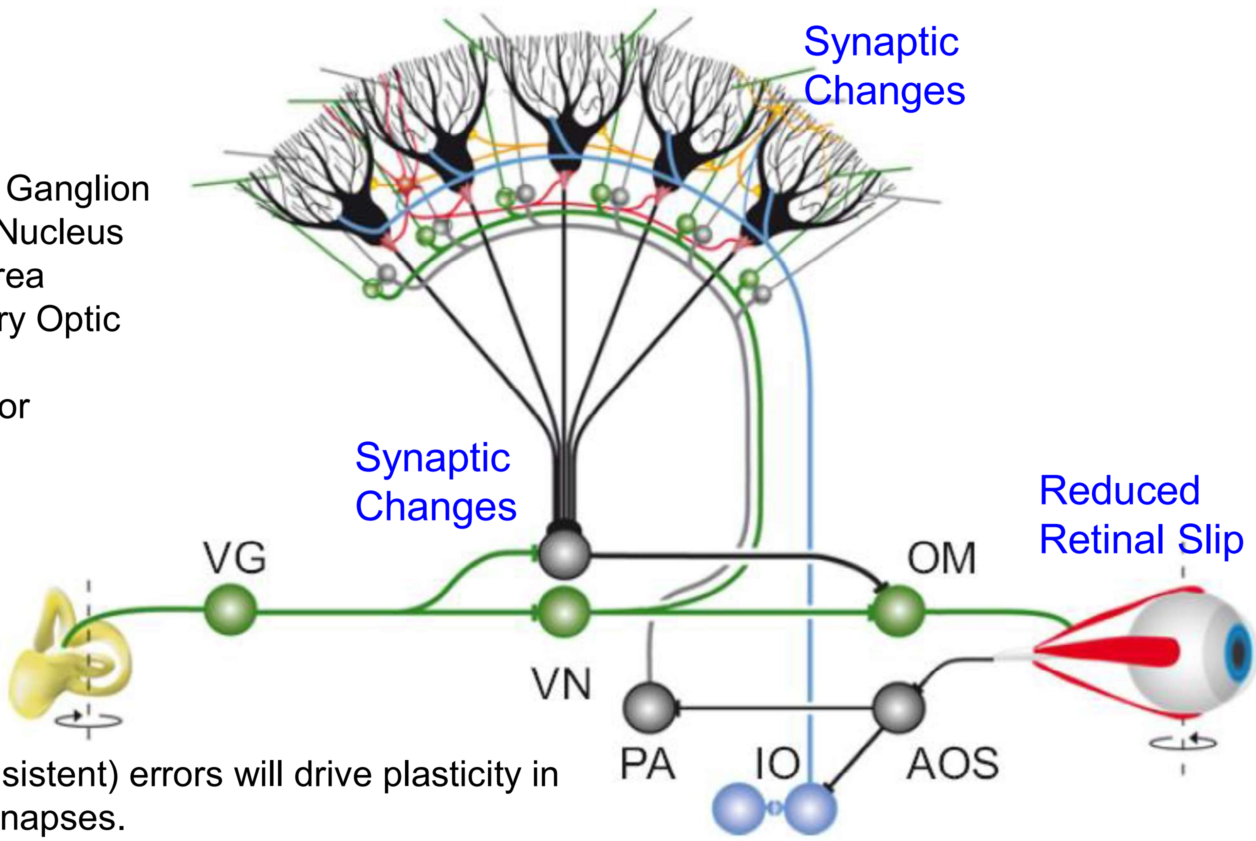
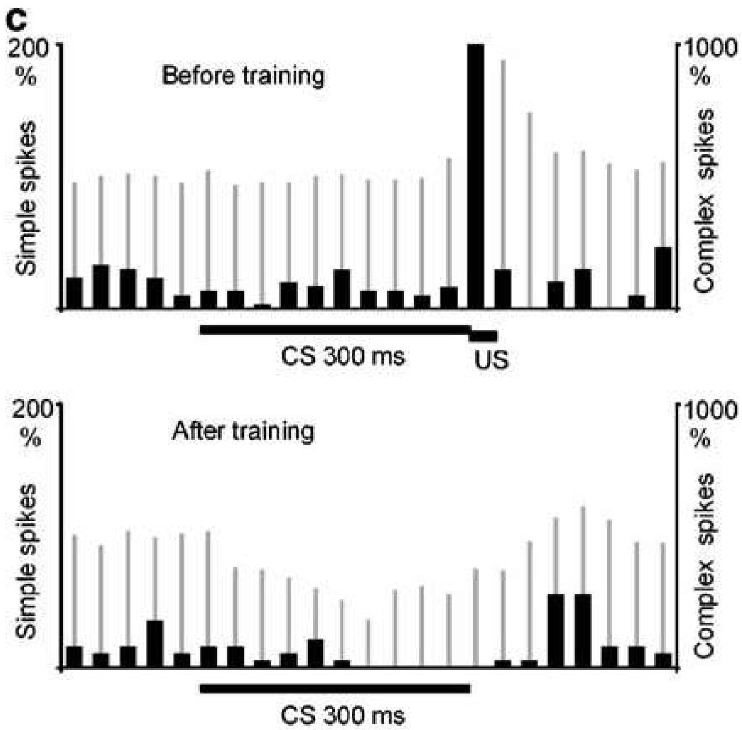


Repeating (consistent) errors will drive plasticity in parallel fiber synapses.
This will change motor patterns and lead to reduction in retinal slip over the long run

Ito 1984, Schonville et al. 2010

Eyelid Reflex Conditioning: Purkinje cell plasticity

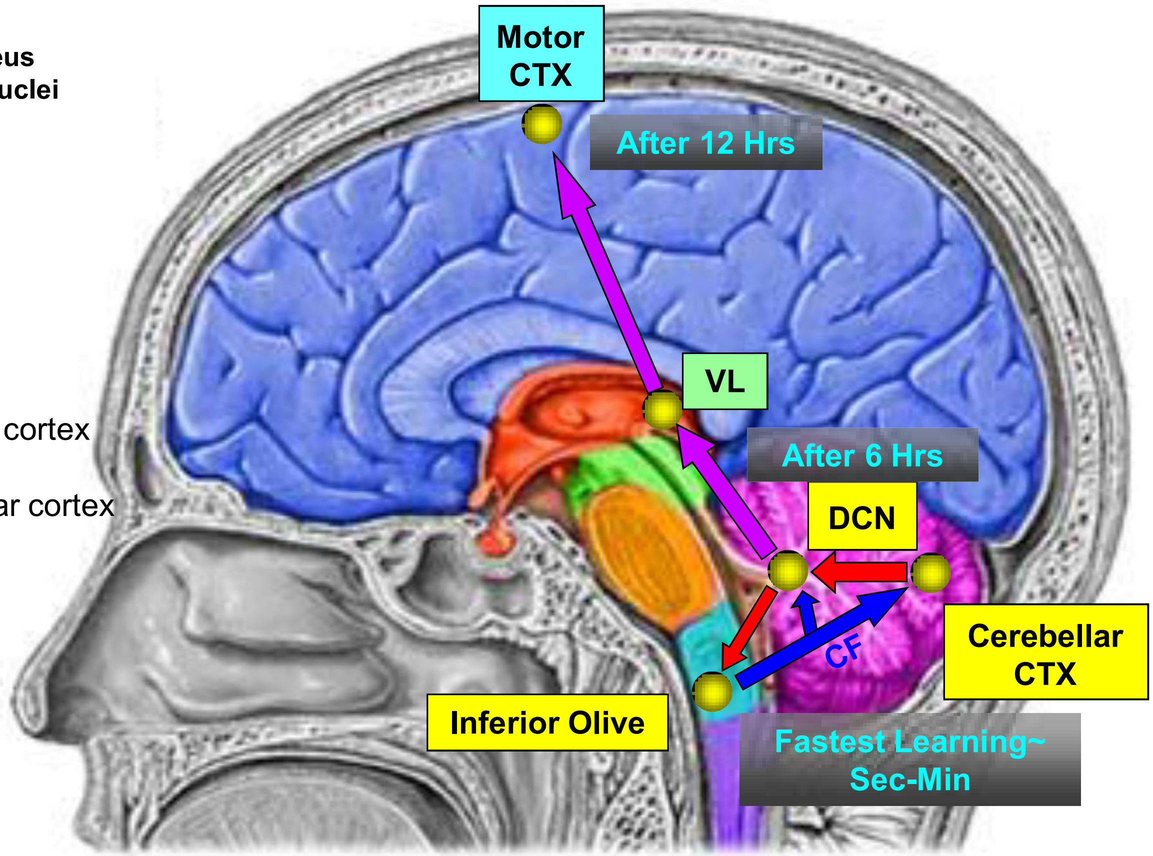


As learning progresses, Firing complex spikes decreases

The learning transfer hypothesis

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

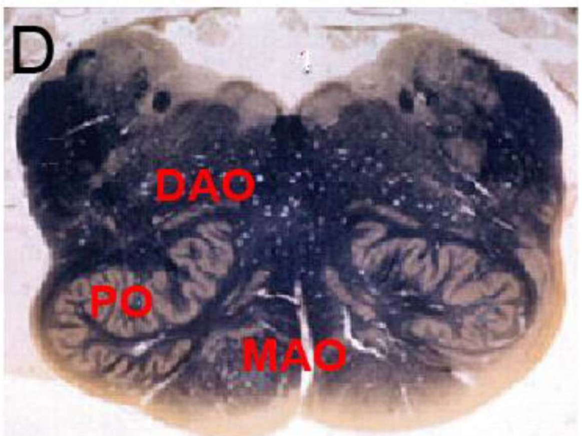
Up to 6hrs:
dependent on cerebellar cortex
After 6hrs:
independent on cerebellar cortex
After 12hrs:
independent on DCN



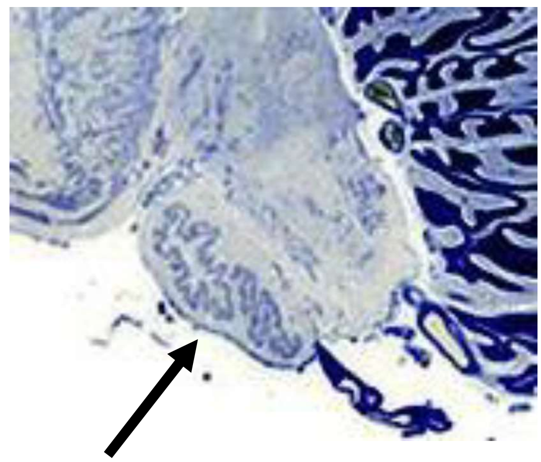
Location of plasticity in the olivocerebellar system and its targets is progressing and every 6hrs is independent of previous location

The Human Inferior Olive

Coronal Section of the IO (axonal staining)



Sagittal Section of the IO (Nissle staining)

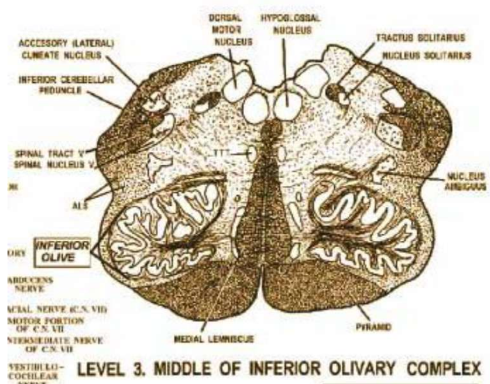


PO = Primary Olive

MAO = Medial Accessory Olive

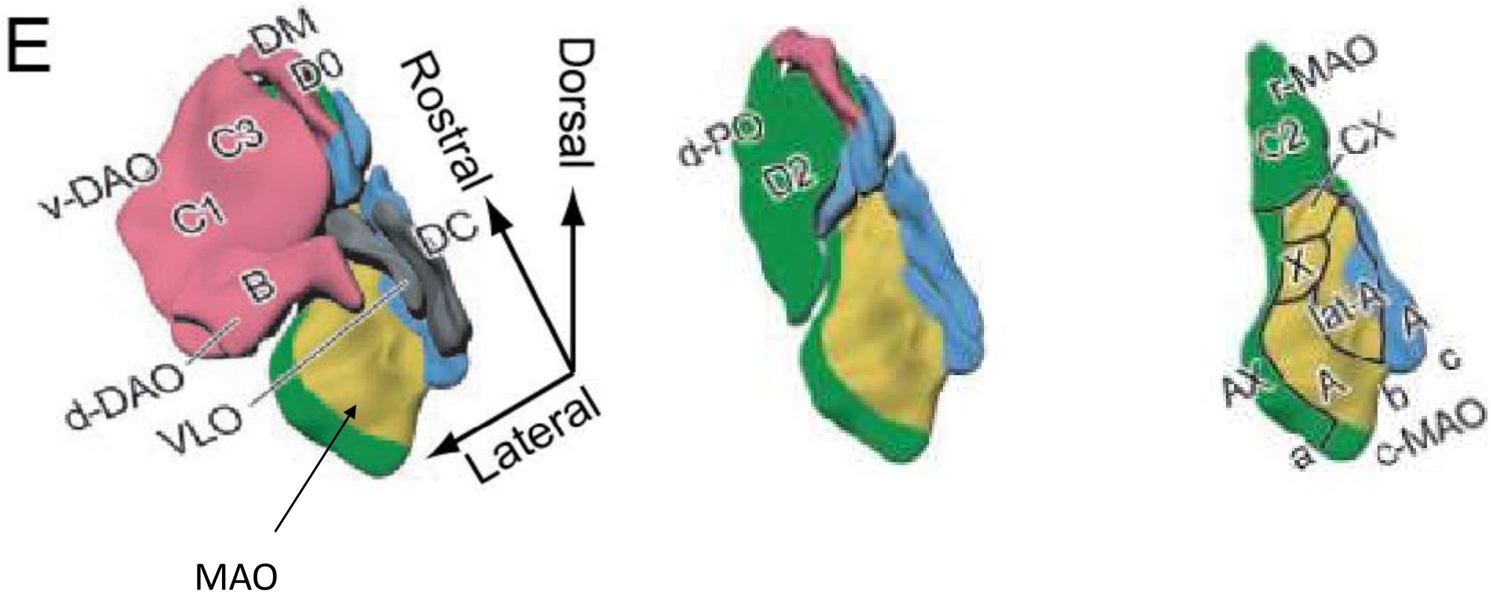
DAO = Dorsal Accessory Olive

~500,000 Neurons in humans



- PO: evolved in parallel to human cerebral cortex
- PO holds more than 80% of IO neurons
- DAO: also in fish
- Rats: 30,000 olivary neurons only

Sub Nuclei of Rat IO



MAO = Medial Accessory Olive
DAO = Dorsal Accessory Olive
DM = Dorsomedial Portion of PO
DC = Dorsal Cap of Kooy
“v-” = Ventral “d-” = Dorsal
“c-” = Caudal

- Shown: only the lest hemisphere of the IO
- DAO in pink is removed in the medial image
- MAO alone is shown in right image

Modified from Sugihara and Shinoda 2004

The IO receive motor and sensory inputs

Visual Inputs:

SC = Superior Colliculus

NOT = Nucleus of Optic Tract

Vestibular Inputs:

VN = Vestibular Nucleus

Motor Command:

RN = Red Nucleus

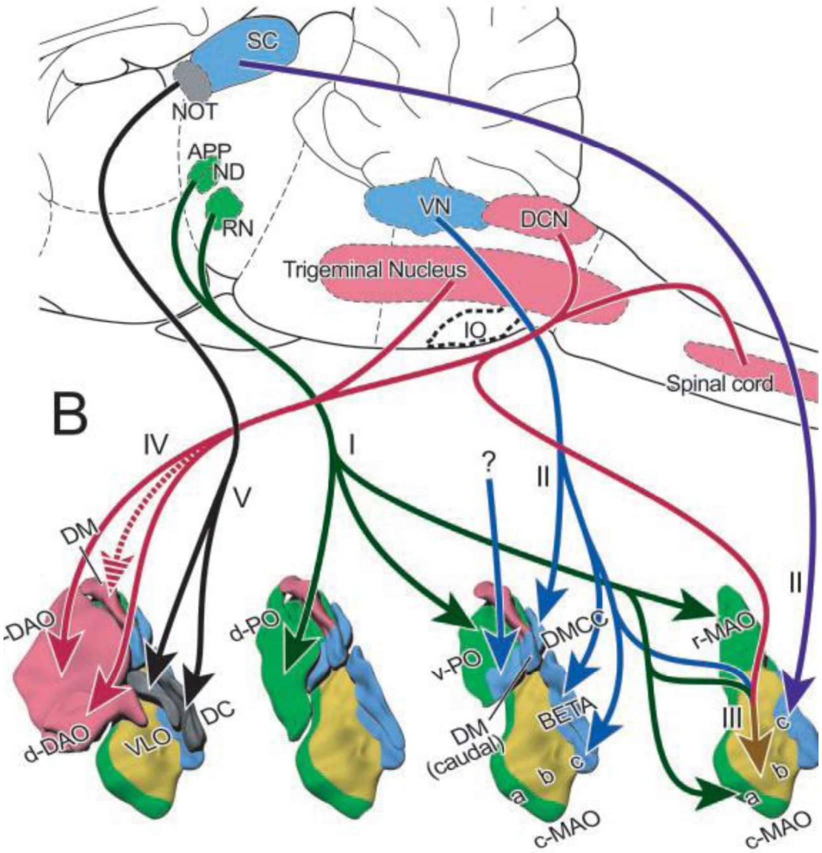
Somatosensory & Proprioceptive:

DCN = Dorsal Column Nucleus

Trigeminal & Spinal Chord

Not shown but exist: Auditory Inputs

- Gray: Pure Visual
- Blue: Visual + Vestibular
- Pink: Somatosensory
- Green: Motor
- Yellow: Combined

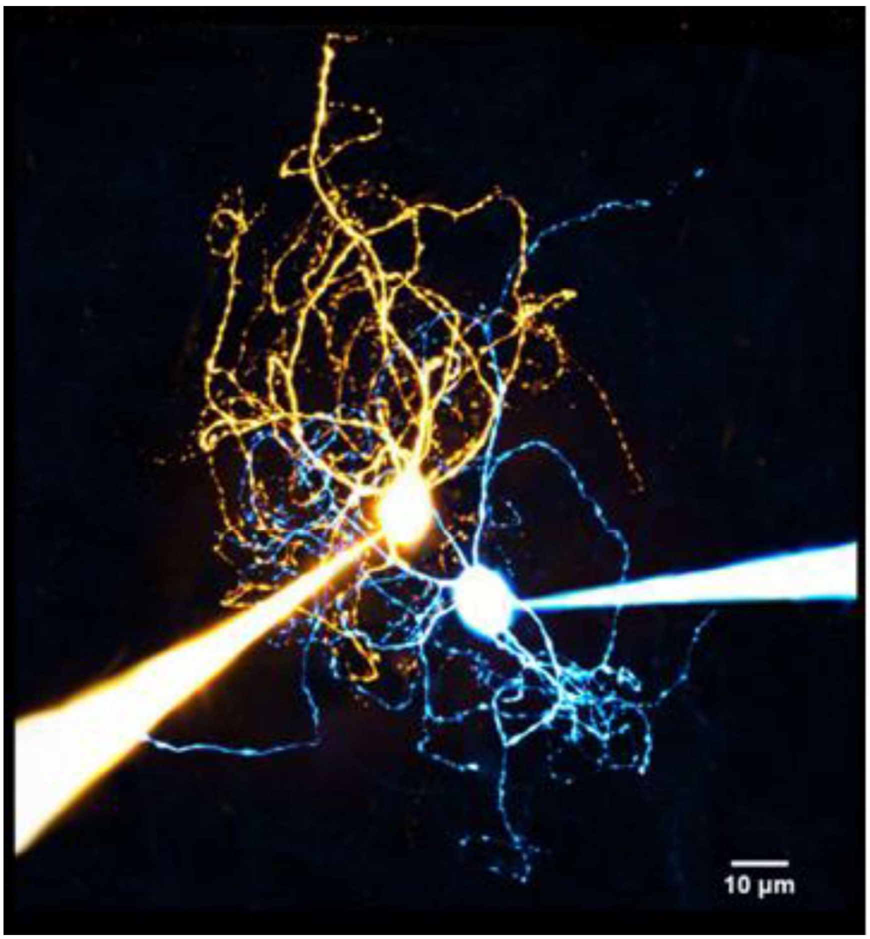


Inferior Olive (IO)

- PO: mostly motor
- DAO: mostly somatosensory
- MAO: mixed

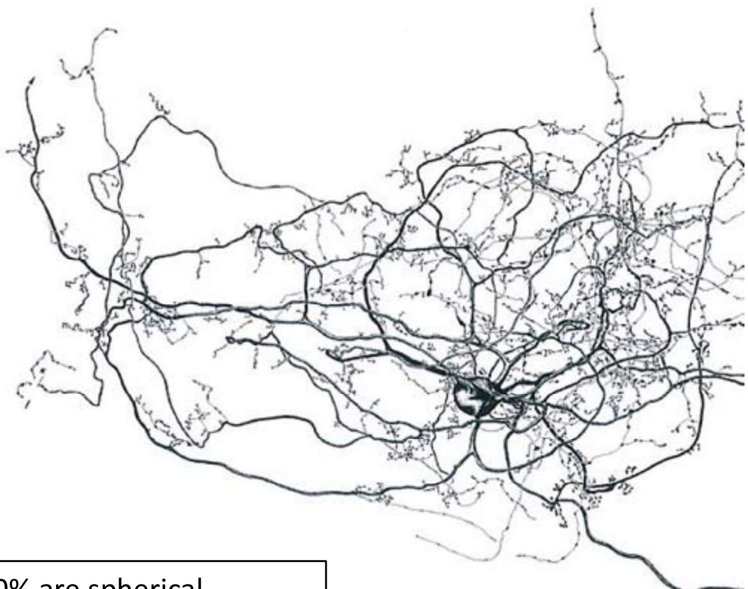
Sugihara & Shinoda JNS 2004

The Unique Neurons of the Inferior Olive



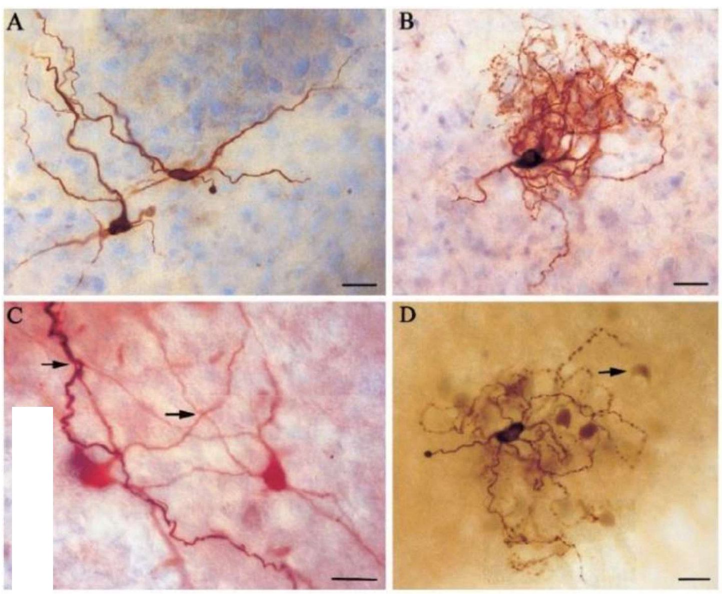
- Olivary neurons may have spherical dendritic tree
- The dendrites of close IO neurons may overlap

At least 50% of IO neurons have globular shaped dendrites

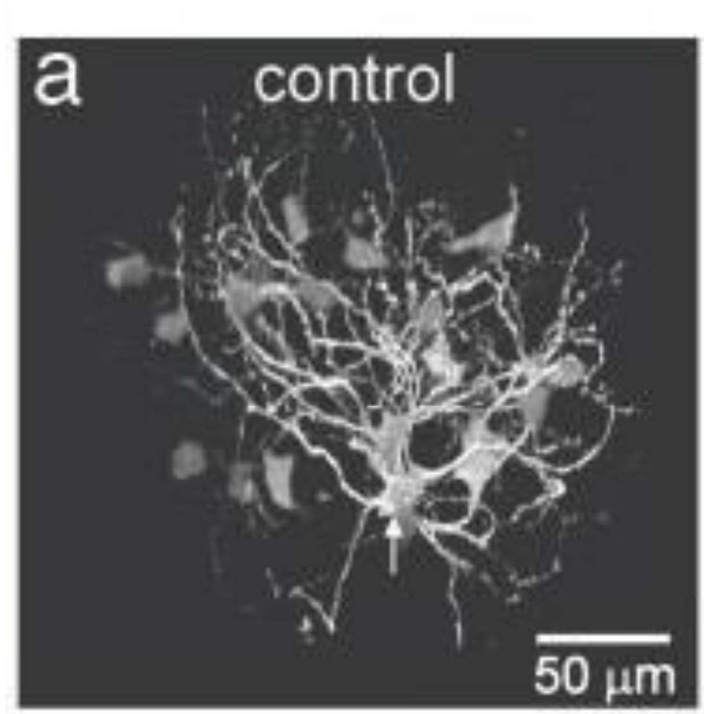


- In human PO more than 90% are spherical
- With evolution PO neuron spheres became smaller (radius-wise) and with stronger overlap (more than 100 are overlapping in humans)
- In DAO and MAO there are non-spherical neurons (up to 50% in humans)

IO Neurons are Connected by Gap Junctions



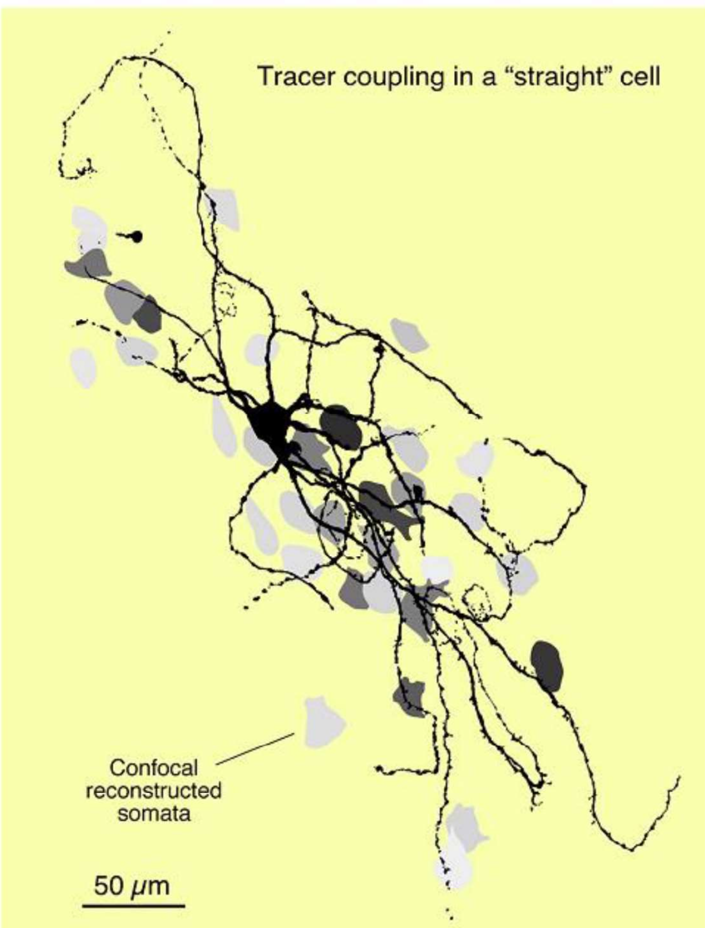
Devor and Yarom JNPhysiol 2002

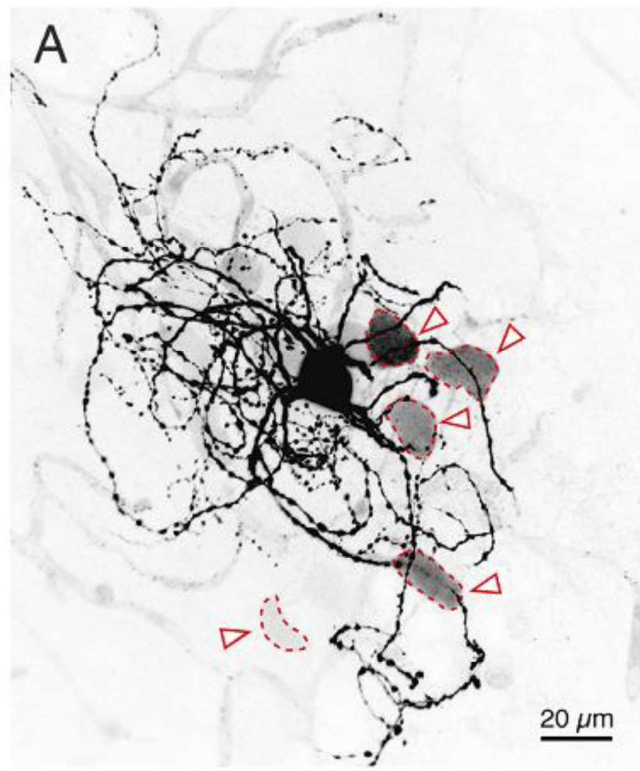


Placantonakis et al. PNAS 2004

- IO neurons are couples by gap-junctions (chemical synapses)
- 3-20 neurons (7-10 in average) are coupled to a single neuron

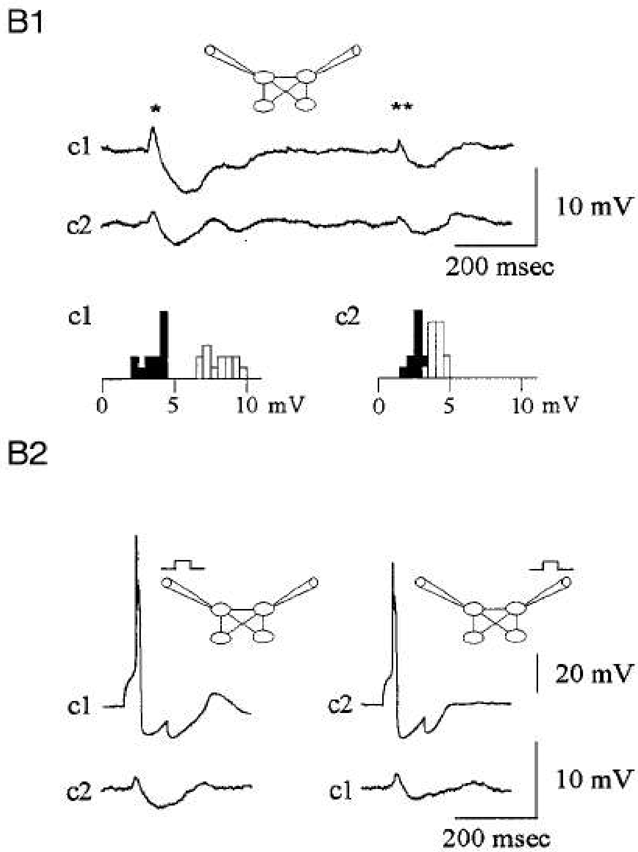
IO Neurons are Connected by Gap Junctions





- Coupling in both spherical and "straight" neurons

IO Neurons are Electrotonically Coupled

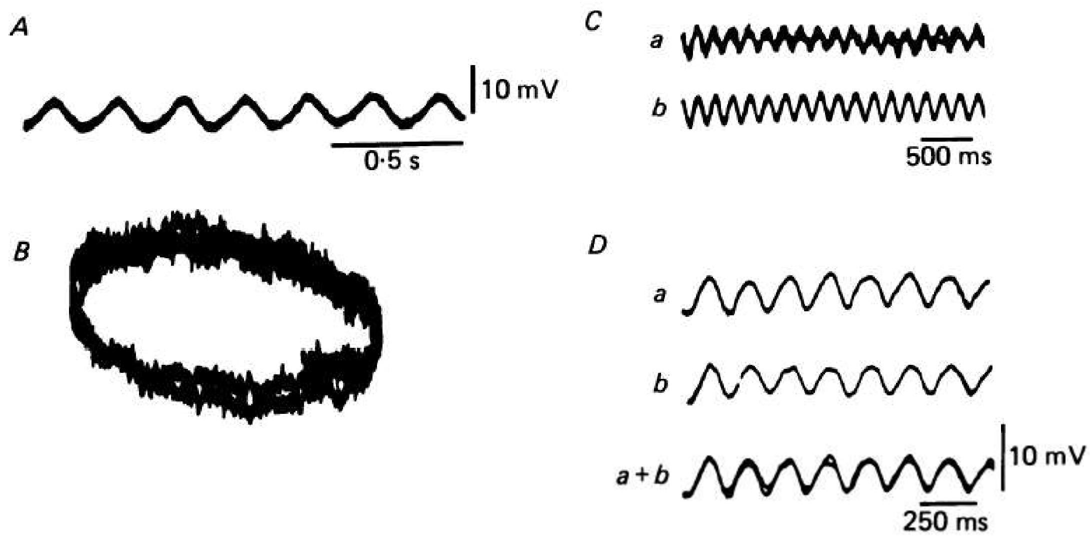


Gap-junctions act like temporal Low-pass filter, strongly decreasing fast events (like action potential) but reliably transmitting slower events (changes in membrane potential)

Measurement of electrotonic coupling is done by recording two cells, stimulation of one cell and measuring the changes in the other. Notice that the voltage changes in the second are quite small (few mV)

Devor and Yarom JNPhysiol 2002

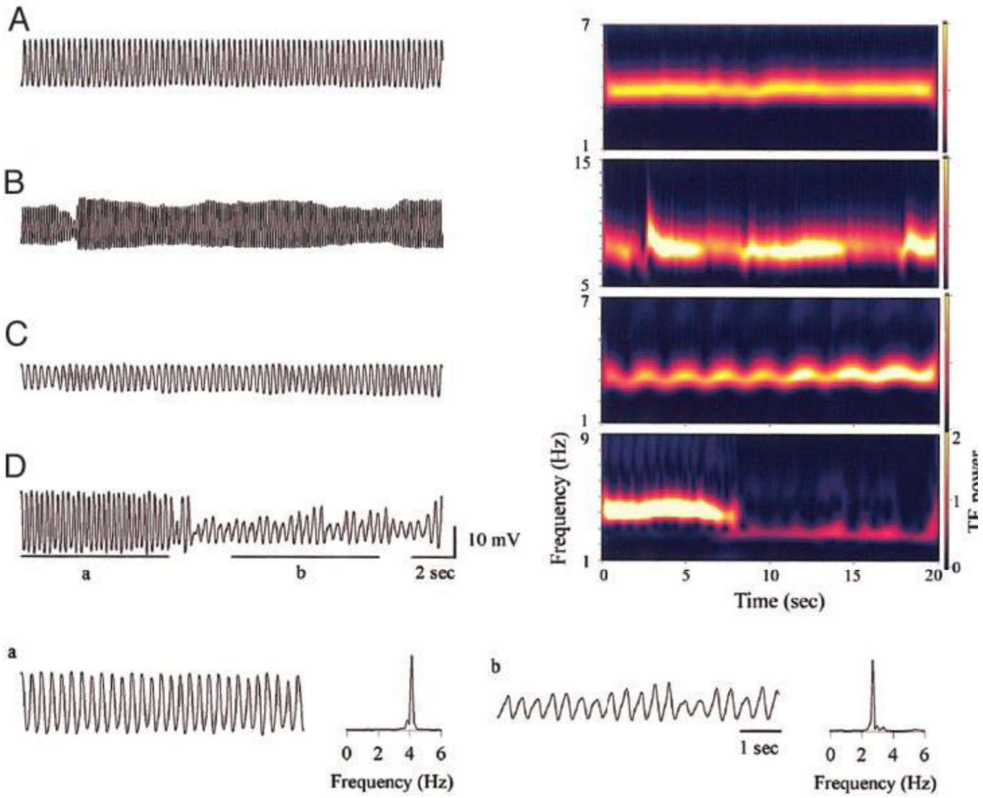
IO Neurons are Natural Oscillators



Many IO neuron oscillate, some constantly and
some conditionally (i.e. after stimulus).
Thought of as a timing machine (i.e. clock)

Llinas and Yarom JPhysiol 1986

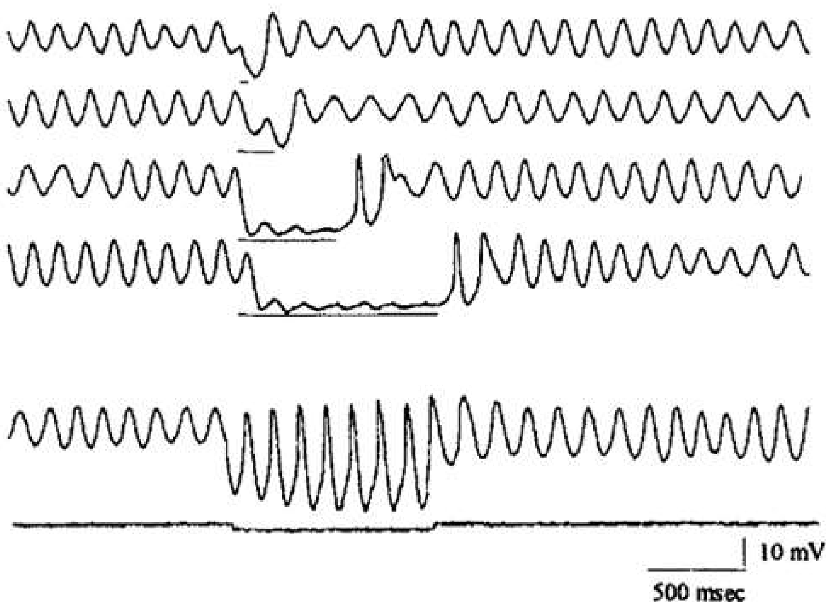
Oscillations (In Vitro) Change in Time

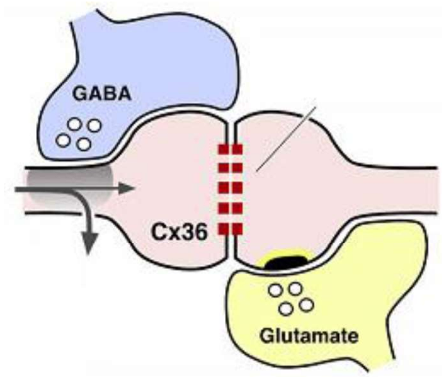


Devor and Yarom JNPhysiol 2002

Oscillation amplitude and frequency can change

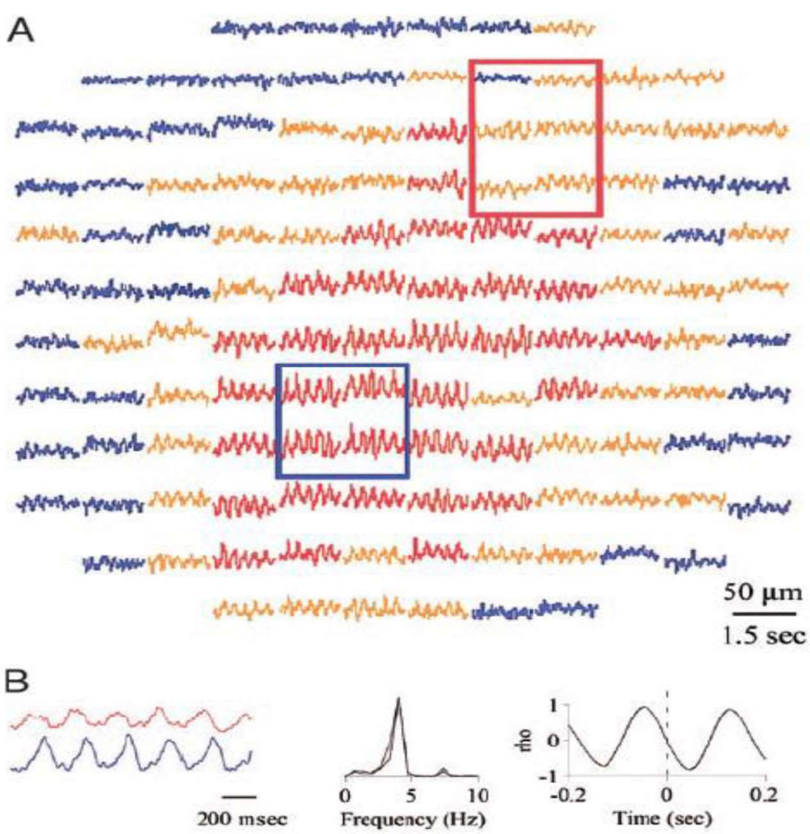
GABA Application Affects Oscillations





Inhibition close to gap junction can potentially provide a mechanism to un-couple neurons

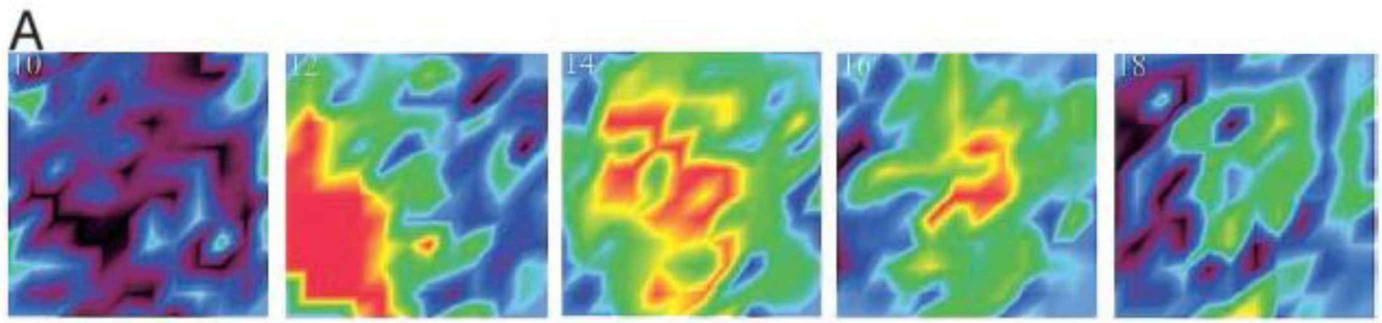
In-Vitro Oscillations: Synchrony and Propagation



Devor and Yarom JNPhysiol 2002

In the population of IO neurons:
Close-by neurons may have similar frequency and phase. Far neurons may be with similar frequency but phase-shifted or frequency shifted.

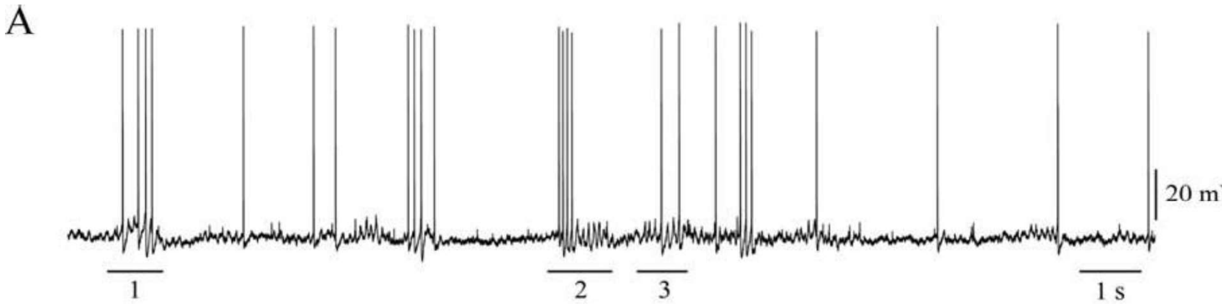
In-Vitro Oscillations: Synchrony and Propagation



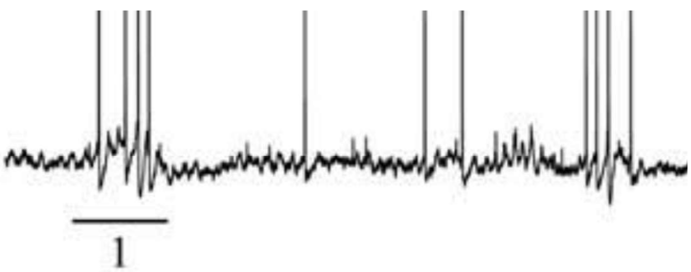
Devor and Yarom JNPhysiol 2002

Oscillatory activity may propagate over the population in time like waves in the sea (or football stadium)

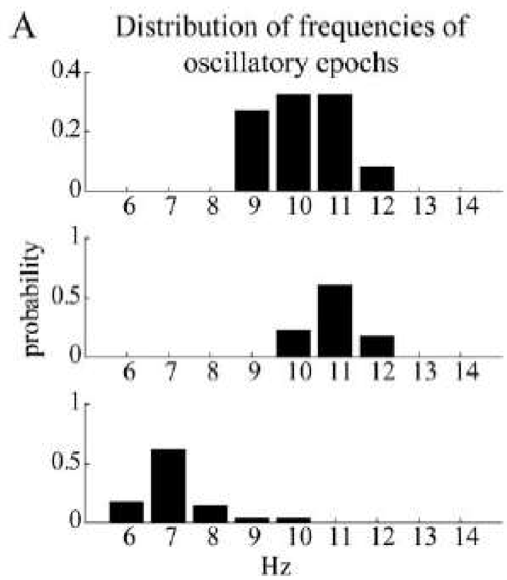
IO neurons are not Harmonious Oscillators *in-vivo*



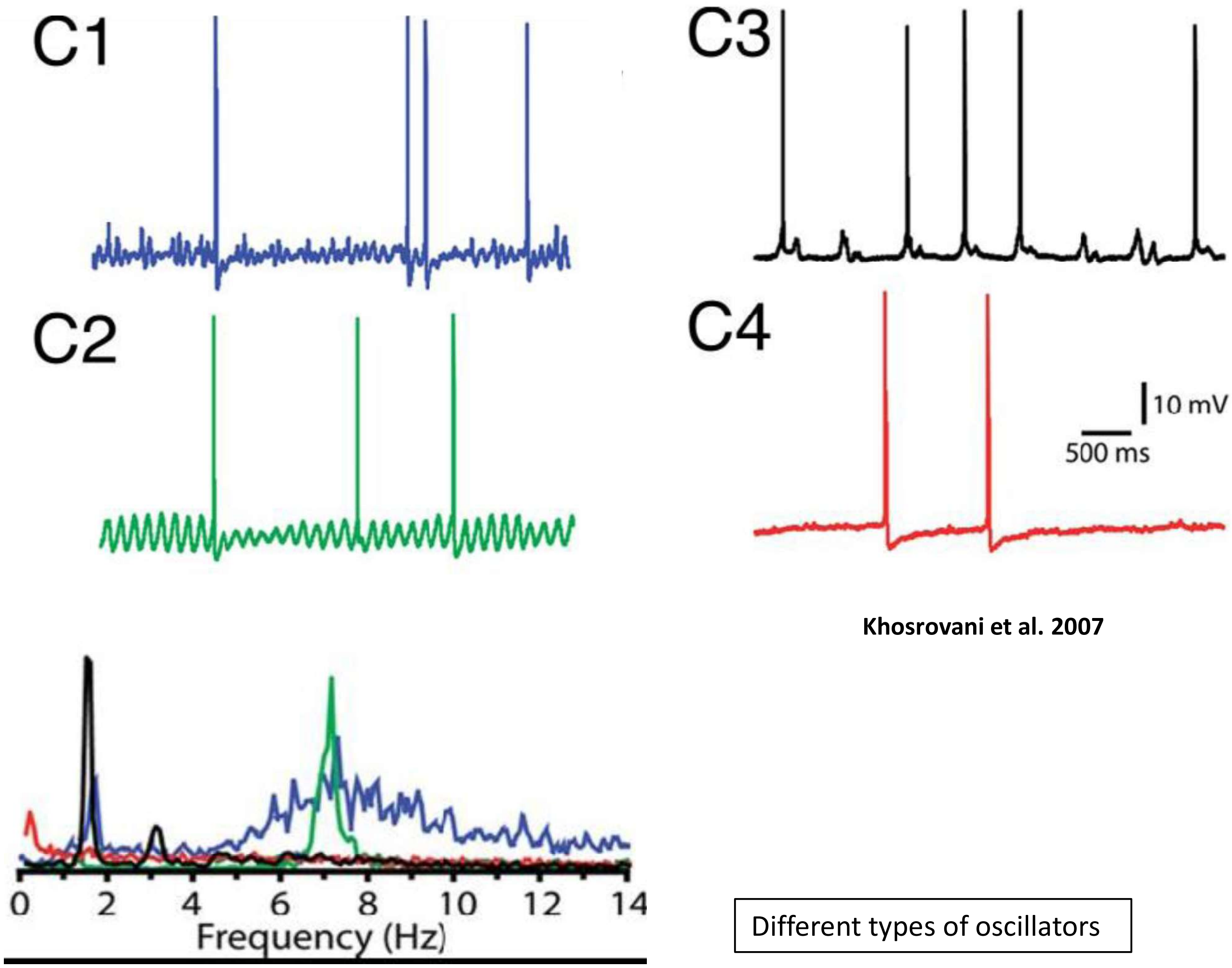
Chorev, Yarom and Lampl JNS 2007



Oscillatory activity was shown also in-vivo



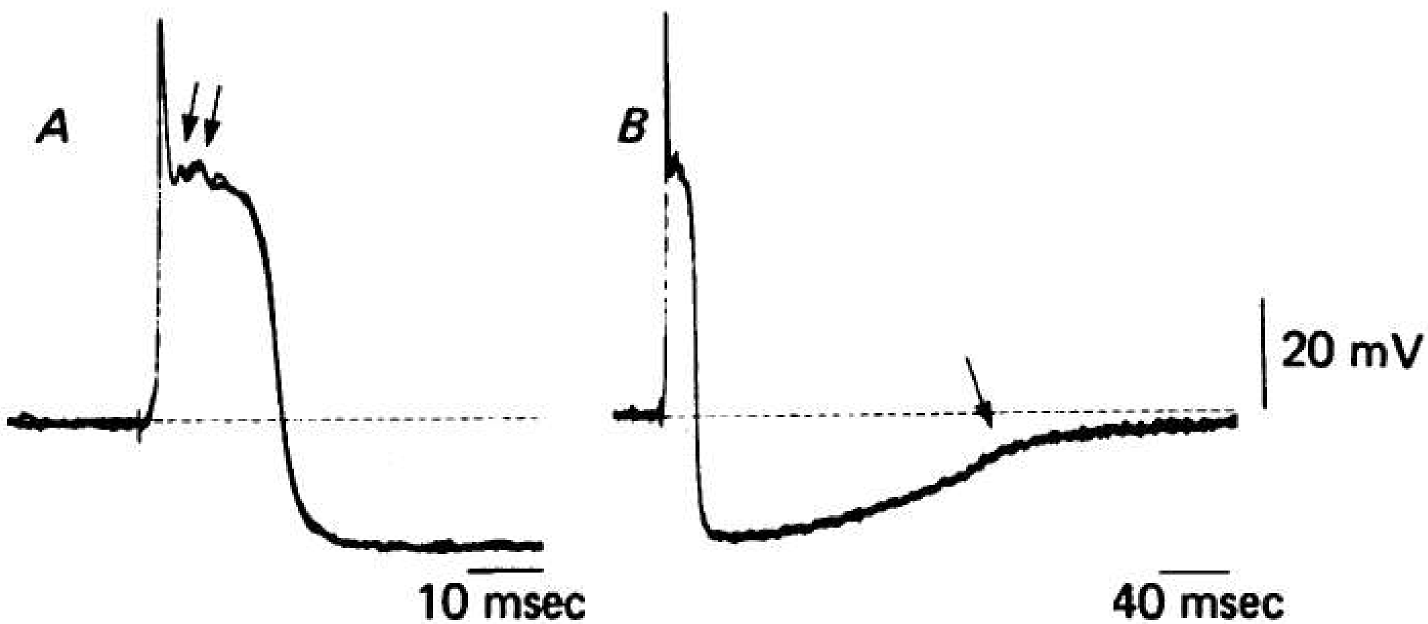
Various In-Vivo Oscillation Patterns



Khosrovani et al. 2007

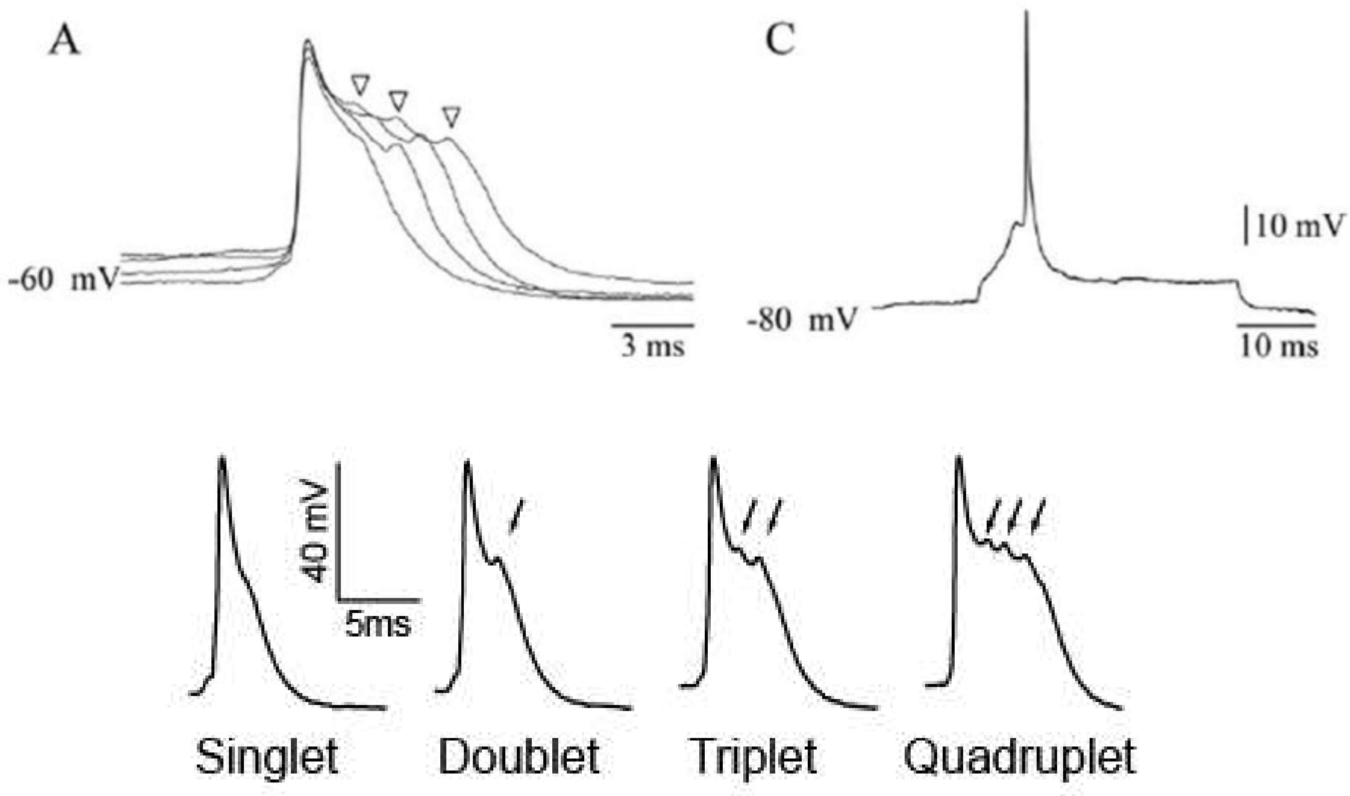
Different types of oscillators

The Olivary Spike



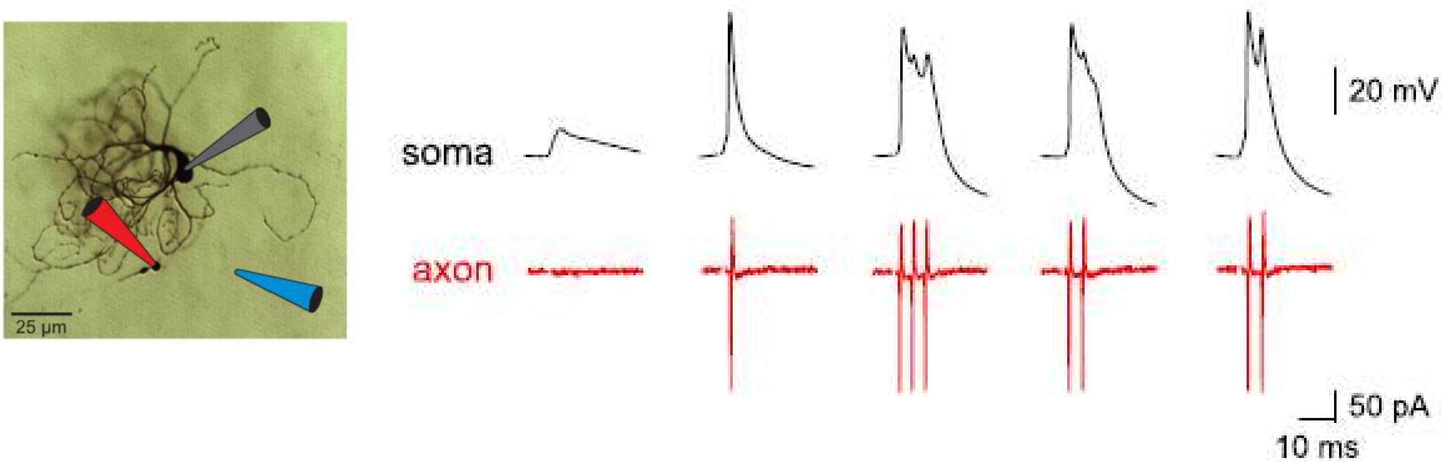
Olivary spikes are also different: very wide (4-12 ms instead of just 1-2) and carry spikelets

The IO Spike – In-Vivo



Non-binary coding of IO firing

Somatic ADP bumps reflect axonal spikes generation

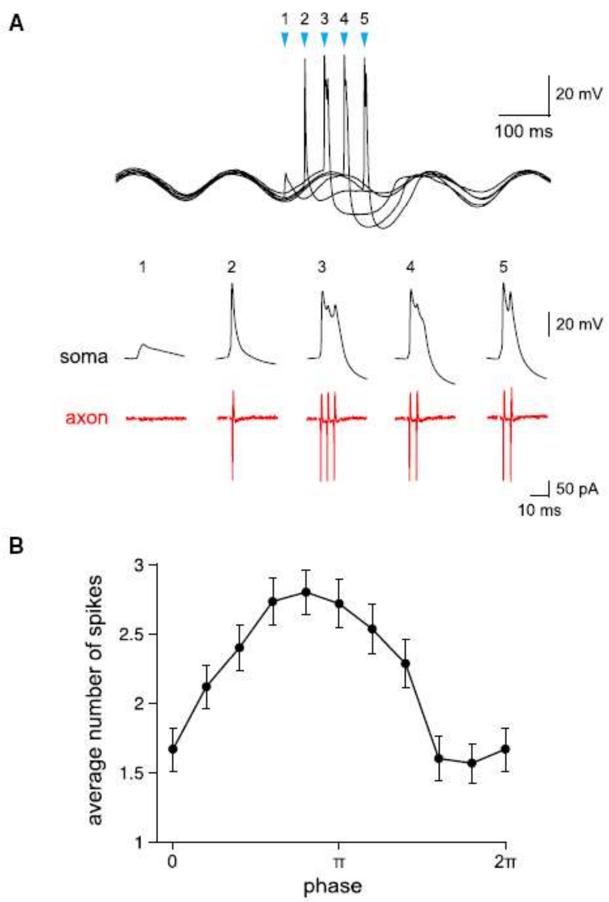


Mathy et al. Neuron 2009

Mathy et al. proved that olivary ADP wavelets are indeed the result of additional axonal spikes. They recorded in an olivary slice the soma and the axon (in its cut edge) of olivary neurons simultaneously.

Non-binary coding of IO firing: carried also to the axon (in red)

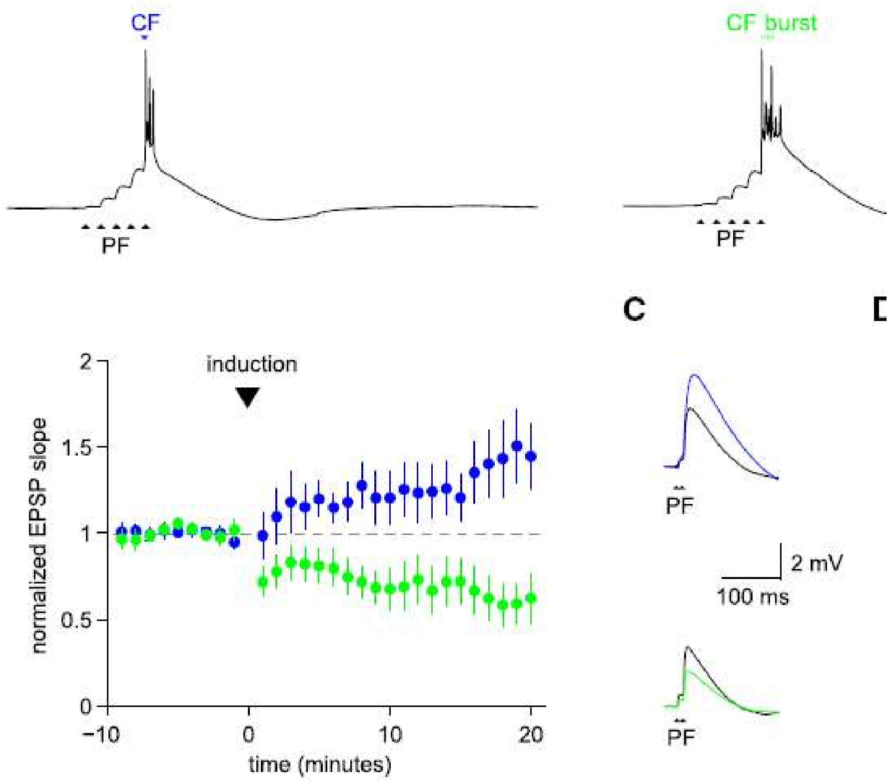
Encoding of Oscillation phase by Olivary



Mathy, et al. 2009

Non-binary coding may encode oscillation phase while emitting a spike

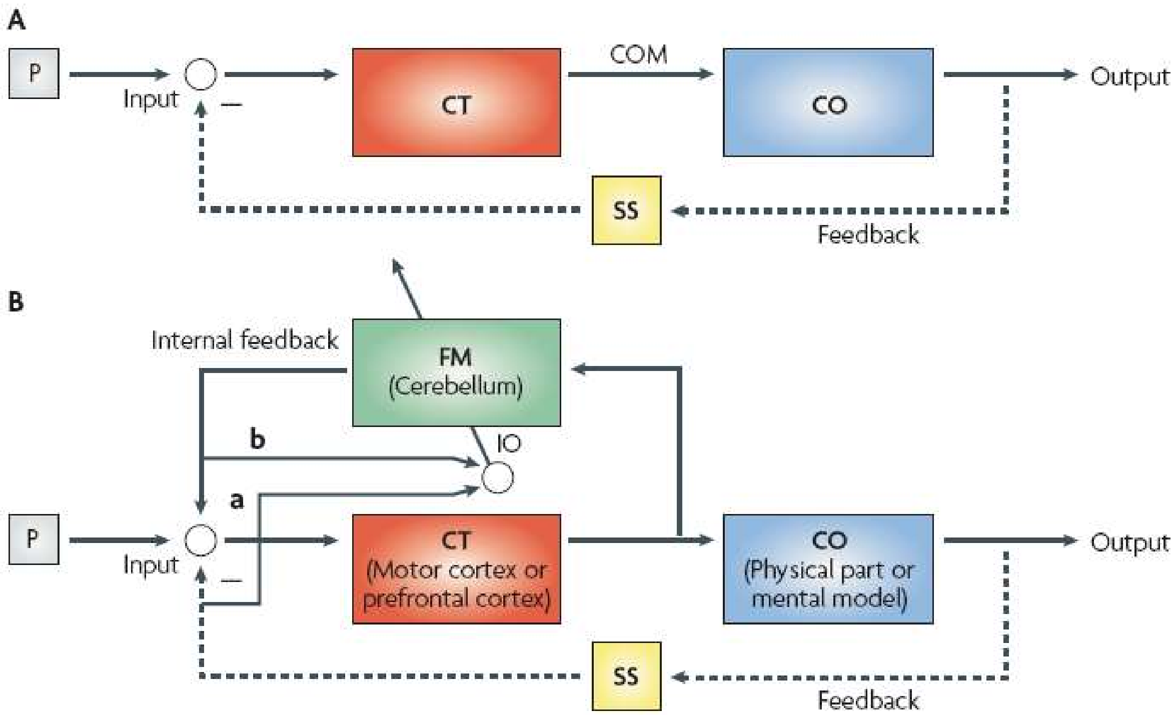
Oscillatory phase may set the direction of plasticity



Mathy, et al. 2009

Non-binary coding may affect the direction of plastic changes at target synapses (green = triplet, blue = singlet)

The general role of the cerebellum: Internal model



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