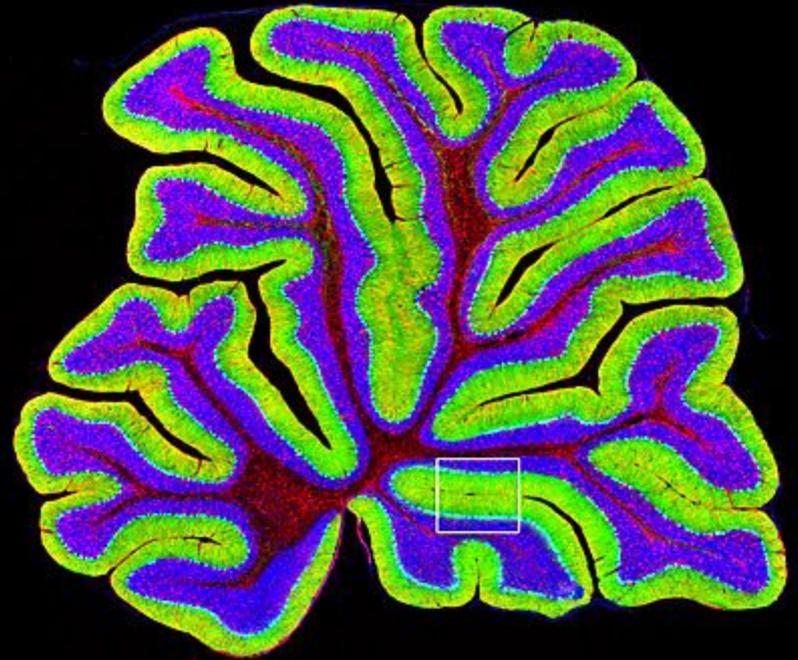
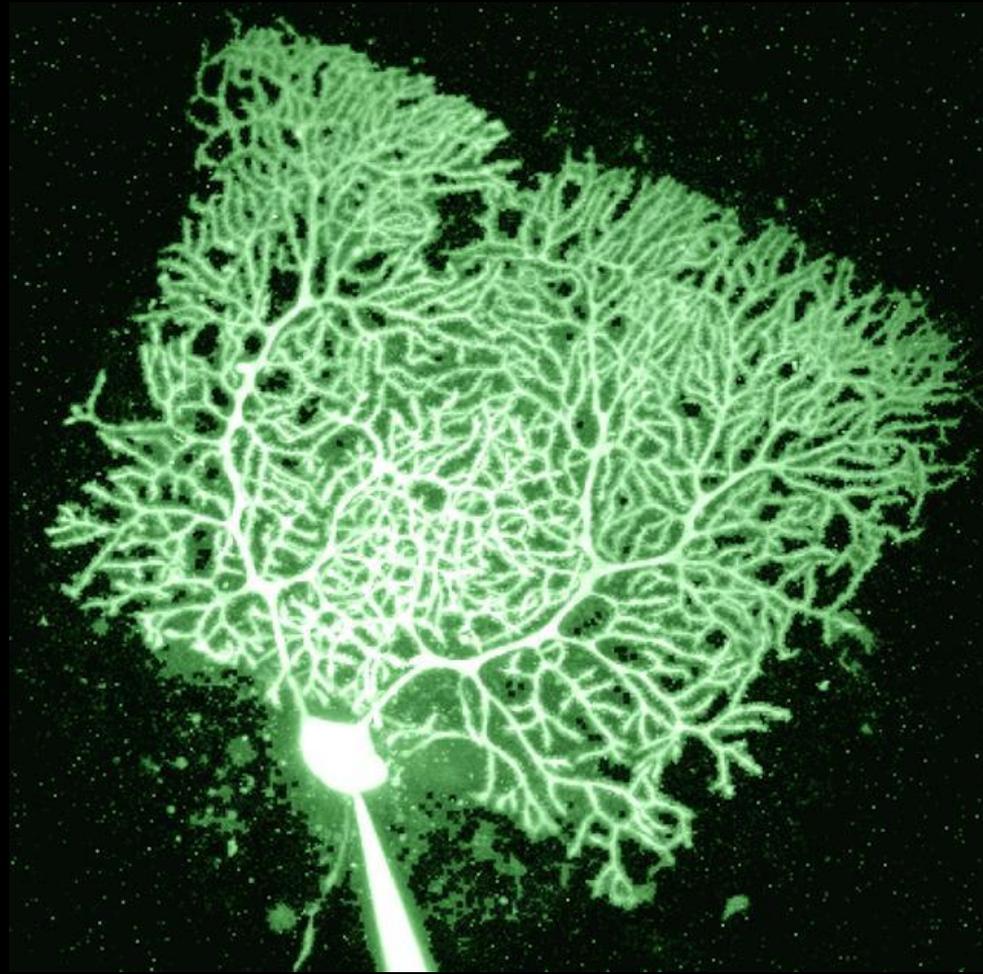


# The cerebellum as a subsecond prediction machine



Sam Wang



Sir Gordon  
Holmes  
(1867-1965)

# The Croonian Lectures

ON THE

## CLINICAL SYMPTOMS OF CEREBELLAR DISEASE

AND THEIR INTERPRETATION.

*Delivered before the Royal College of Physicians of  
London*

BY GORDON HOLMES, C.M.G., C.B.E., M.D.,  
F.R.C.P. LOND.,

PHYSICIAN TO OUT-PATIENTS, NATIONAL HOSPITAL FOR THE  
PARALYSED AND EPILEPTIC; ASSISTANT PHYSICIAN,  
CHARING CROSS HOSPITAL; PHYSICIAN, ROYAL  
LONDON OPHTHALMIC HOSPITAL.

### LECTURE IV.\*

*(Delivered on June 20th.)*

THERE remain two symptoms of destructive lesions of the cerebellum which we must consider before we put together our conclusions on the nature of the defect phenomena dealt with in the preceding three lectures, and the theory of cerebellar function to which these conclusions lead us.

#### BÁRÁNY'S POINTING TEST.

The importance lately attached to Bárány's pointing test in cerebellar diseases makes it necessary to record fully the results obtained in my cases. As is well known, Bárány discovered that the deviations of the limbs in certain directions which are evoked by appropriate labyrinthine stimulation may be absent when the cerebellum is affected, and that deviations in the opposite direction may occur when the limbs are unsupported. In most of my cases spontaneous deviations only were investigated, since it was neither possible nor advisable to excite the labyrinthine reflexes by rotation or irrigation of the ear in the patients with recent gunshot wounds. This was, however, carried out in a certain number of those with more chronic affections.

#### *The Appreciation of Weight.*

There is, however, no doubt that a patient with a unilateral lesion may be unable to compare accurately equal weights, or weights in which the difference is small, placed in his two hands. In 18 of my cases this test was used, and in many of them on several occasions over long periods. In 4 cases equal weights were always adjudged equal, in 3 the results were so irregular that no conclusion can be drawn from them, and in 11 the weight placed on the affected hand was constantly estimated by the patient as the heavier, when they were actually equal or the difference was small. Consequently, the majority of my patients over-estimated the weight on the abnormal side. Some of the more intelligent recognised this subjectively, particularly when heavy weights were employed; one man three months after receiving a gunshot wound in the right lateral lobe of the cerebellum, stated, "every weight I try to lift seems heavier to my right hand." The only patient who, when identical weights were employed, ever judged the weight on the affected hand as lighter, was variable in his replies during the first four weeks after the wound, and during the next two months generally described the weight on this hand as heavier.

Such observations do not, however, necessarily indicate a disturbance in the appreciation of weight since the tendency to over-estimate on the abnormal limb might be due to an affection of mobility rather than to a sensory defect. Every paretic limb exaggerates the load it carries if its sensation be normal, and the asthenic cerebellar arm may similarly over-estimate the resistance that the test object opposes to its movement. The difficulty in raising and lowering the hand regularly, as is normally done in attempting to estimate a weight, may also contribute.

THE LANCET, JULY 15, 1922.



## LETTER TO THE EDITOR

### A new case of complete primary cerebellar agenesis: clinical and imaging findings in a living patient

Feng Yu,<sup>1</sup> Qing-jun Jiang,<sup>2</sup> Xi-yan Sun<sup>1</sup> and Rong-wei Zhang<sup>1</sup>



In the nine living patients, eight patients having complete or near-complete cerebellar agenesis were characterized by motor dysfunction and impaired development. We conclude that the cerebellum is necessary for normal motor, language functional and mental development even in the presence of the functional compensation phenomenon.

**Table 1** Summary of all published living cases with primary cerebellar agenesis

Author	Age	Gender	Motor	Aphasia	Ataxia	Mental and development	Notes
Yoshida and Nakamura, 1982	4 mths	Female	Retardation	–	–	Retardation	Consanguinity, total absence
Sener and Jinkins, 1993	58 years	Female	Normal	N	N	Normal	Subtotal absence
Sener, 1995	6 years	–	Retardation	Y	Y	Normal	Moderate cerebellar symptom
Sener, 1995	–	–	Retardation	Y	Y	Normal	Moderate cerebellar symptom
Van Hoof and Wilmink, 1996	46 years	Male	Spasticity	Dysarthria	Y	Mild Retardation	Total absence, confirmed by surgery
Velioglu <i>et al.</i> , 1998	22 years	Male	Retardation	Dysarthria	Y	Retardation	Subtotal absence
Deniz <i>et al.</i> , 2002	7 years	Female	Retardation	Dysarthria	Y	Retardation	Total absence
Timmann <i>et al.</i> , 2003	59 years	Female	Retardation	Dysarthria	Y	Retardation	Total absence

*The cerebellum processes sensory and internal information to rapidly shape activity via closed loops with brainstem, neocortex, and basal ganglia.*

# Gordon Research Conferences, then and now

## Cerebellum 2013

**Adam Hantman** (Janelia Farm HHMI)

"Convergence of cortical and sensory information in the cerebellum"

**Amy Bastian** (Johns Hopkins University)

"Moving and sensing with cerebellar damage"

**Chris de Zeeuw** (Erasmus Medical Center)

"Cerebellar motor learning and distributed synergistic plasticity"

**Dagmar Timmann** (University Clinic Essen)

"Cerebellum and motor learning: localization based on human lesion studies"

**Christian Hansel** (University of Chicago)

"Cerebellar dysfunction and motor impairment in autism"

**Yan Yang** (Duke University)

"Single trial plasticity in the cerebellum for motor learning"

**Megan Carey** (Champalimaud Neuroscience Programme)

"Cerebellar contribution to locomotion in mice"

## Cerebellum 2023

**Dagmar Timmann** (Essen University Hospital, University of Duisburg-Essen, Germany)

"Cerebellar Contribution to Fear Learning"

**Cécile Gallea** (Paris Brain Institute, CNRS-INSERM, France, France)

"Cerebellar Networks, Movement Disorders and Neuroimaging: From Motor Execution to Cognitive Aspects of Motor Control"

**Cherie Marvel** (Johns Hopkins University, United States)

"Cerebellar Contributions to Cognition: Evidence from Cerebellar Ataxia"

**Janelle Pakan** (Otto von Guericke University, Germany)

"Cortico - Cerebellar Communication During Task Engagement"

**Richard Wingate** (King's College London, United Kingdom)

"The Evodevo of Cerebellar Nuclei: From Temporal Patterning to Autistic Spectrum Disorder"

**Sikoya Ashburn** (University of North Carolina at Chapel Hill, United States)

"Cerebellar Involvement Within Sub-networks of Working Memory in Children With and Without ADHD"

# Cerebellum: Origins

Found in all vertebrates

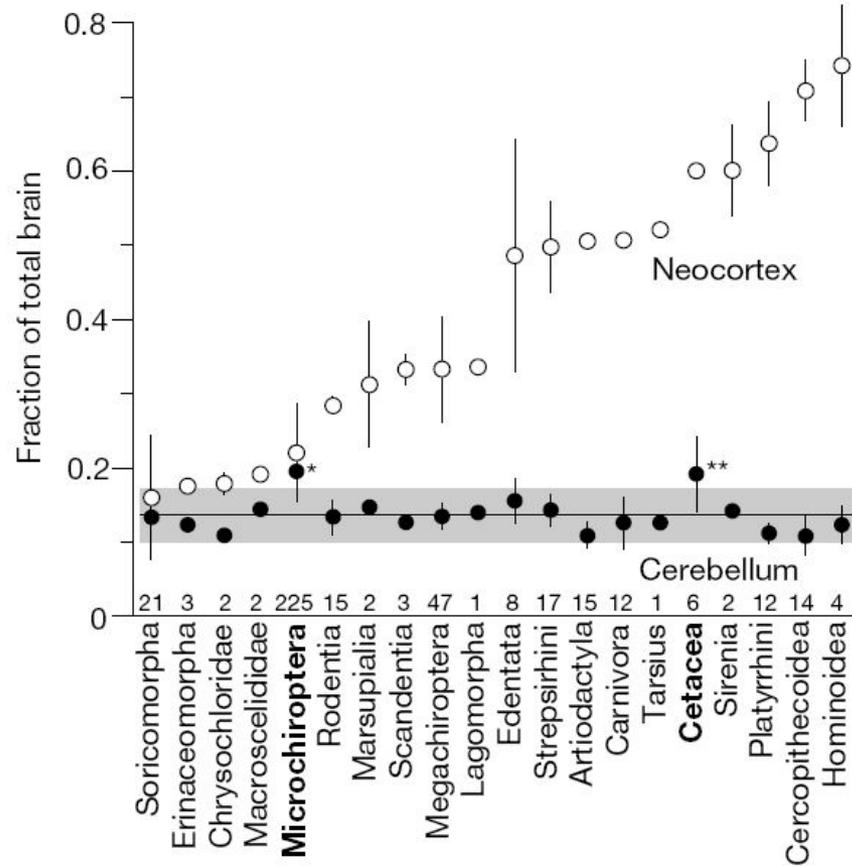
Dorsal lip of developing medulla (rhombencephalon)

Near terminations of vestibular (VIII) and lateral line afferents, which sense fluid displacement

Also inputs from tectum and spinal cord

Ancestral role: “representing an image of the relations of the body in space” (Bullock 1969)

Self vs. non-self?



**Figure 2** Constancy of cerebellar volume fraction across mammalian taxa. Cerebellar volume fractions are plotted at order level with the exception of the primates, which were

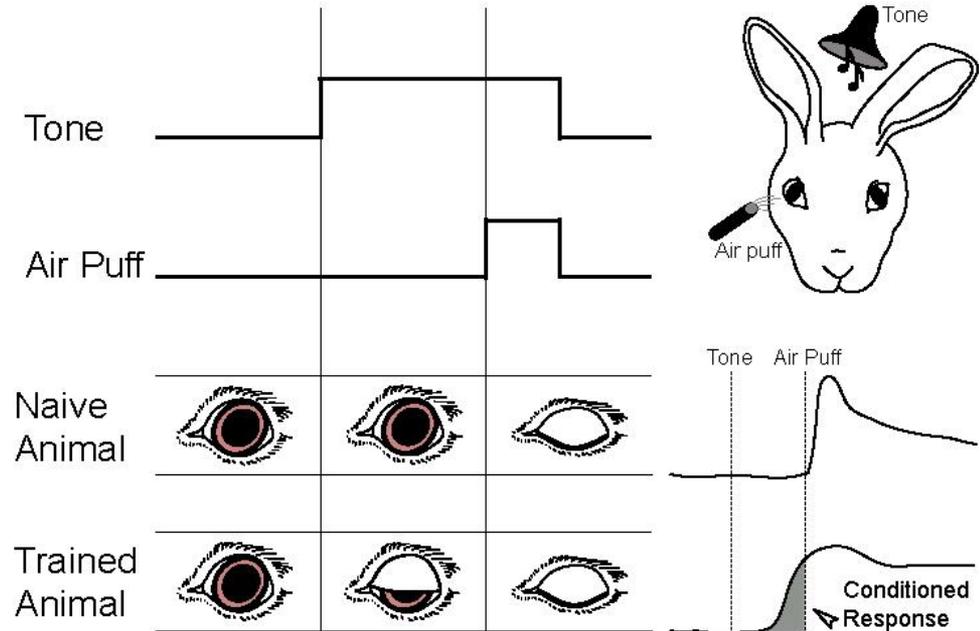
D.A. Clark '01, P.P. Mitra,  
and S.S.-H. Wang (2001)  
*Nature*, 411:189-193

# The cerebellum: a short-term prediction machine

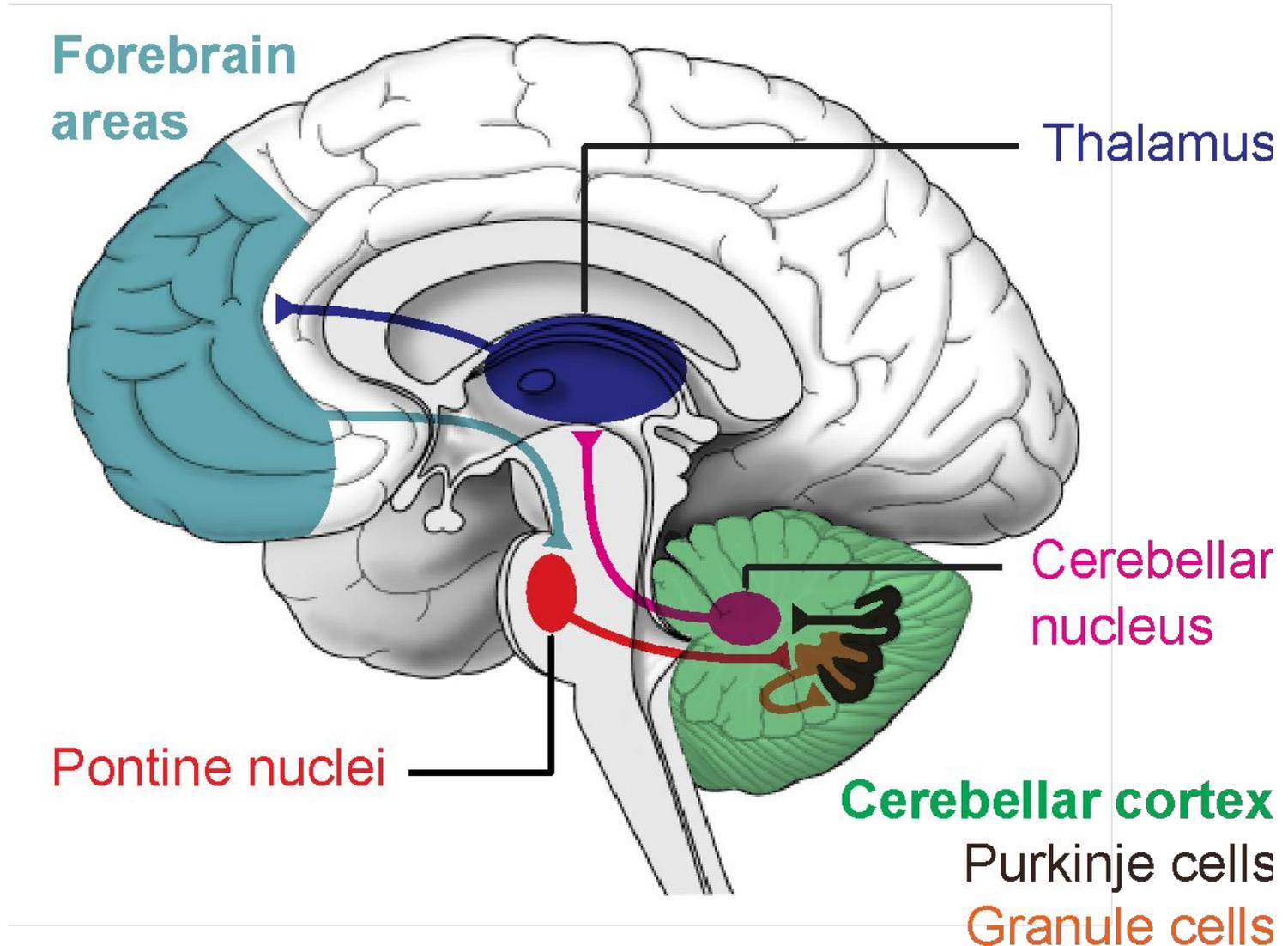
Sensory surprise / error signals



Sensory teaching signal

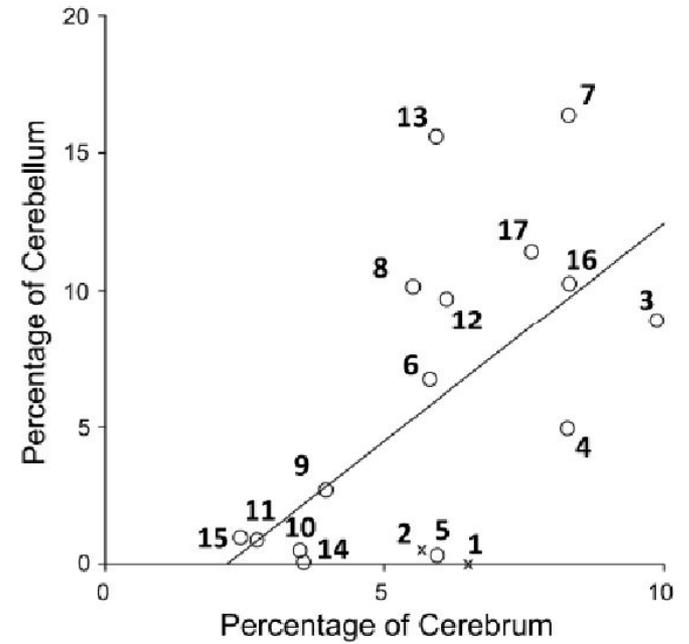
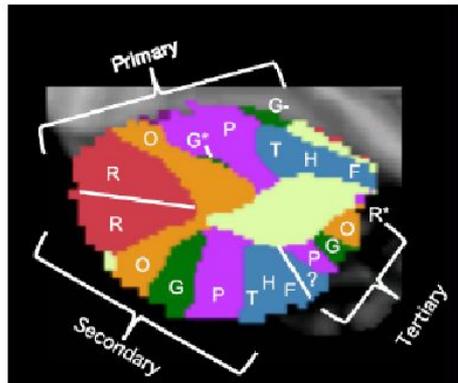
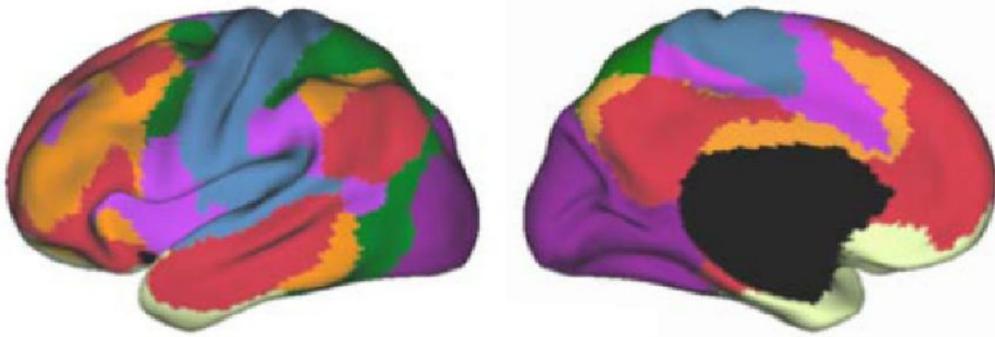


# Bidirectional paths link forebrain and cerebellum



## The organization of the human cerebellum estimated by intrinsic functional connectivity

Randy L. Buckner,<sup>1,2,3,4</sup> Fenna M. Krienen,<sup>2,4</sup> Angela Castellanos,<sup>1,2</sup> Julio C. Diaz,<sup>1,5</sup>  
and B. T. Thomas Yeo<sup>2,4</sup>



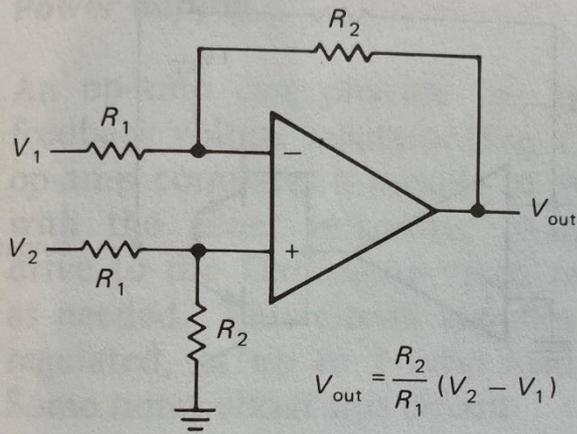


Figure 4.18. Classic differential amplifier.

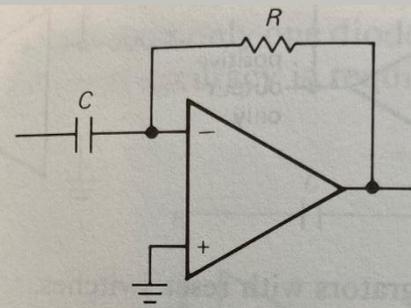


Figure 4.51

### 4.20 Differentiators

Differentiators are similar to integrators, but with  $R$  and  $C$  reversed (Fig. 4.51). Since the inverting input is at ground, the rate of change of input voltage produces a current  $I = C(dV_{in}/dt)$  and hence an output voltage

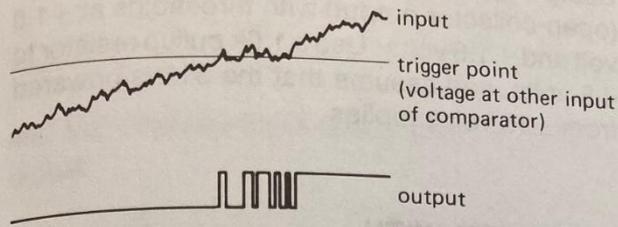


Figure 4.61

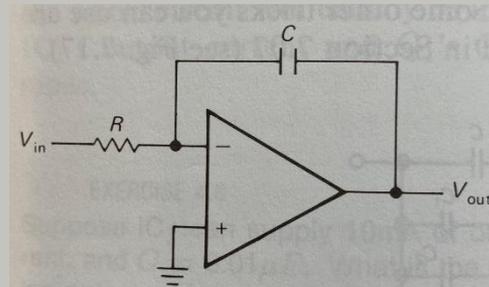
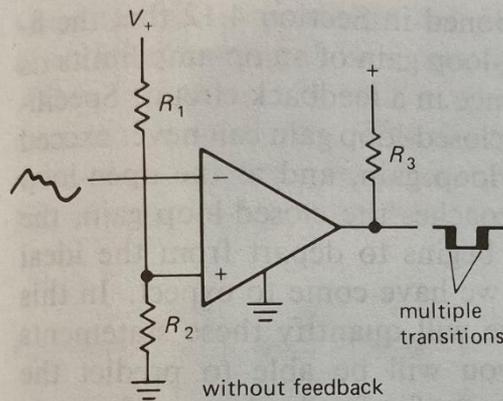


Figure 4.47. Integrator.

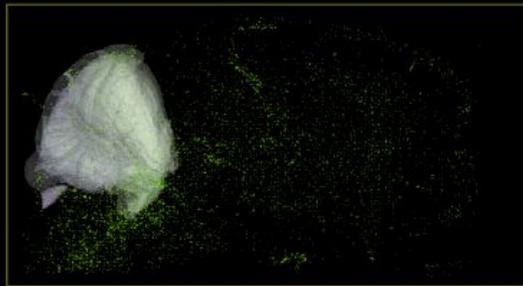
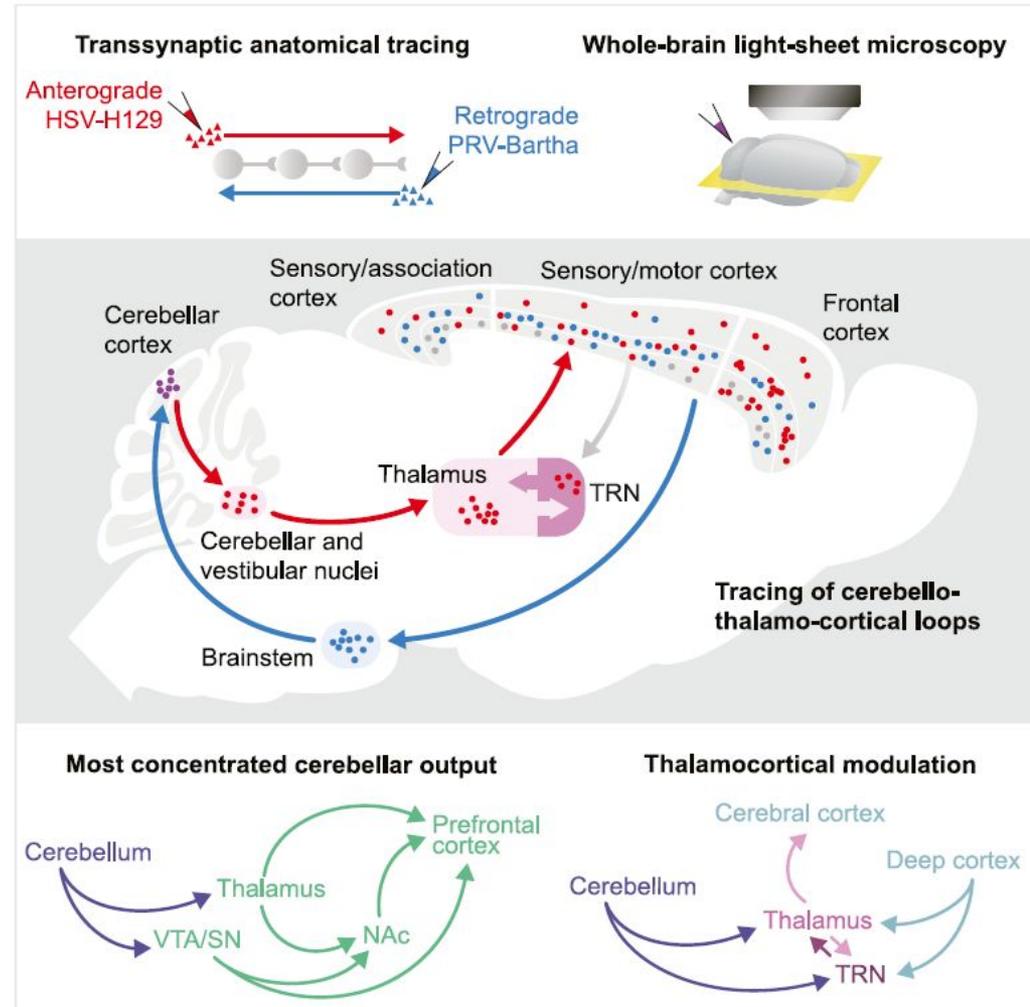
### 4.19 Integrators

Op-amps allow you to make nearly perfect integrators, without the restriction that  $V_{out} \ll V_{in}$ . Figure 4.47 shows how it's done. In

### Homologous organization of cerebellar pathways to sensory, motor, and associative forebrain

#### Authors

Thomas J. Pisano, Zahra M. Dhanerawala, Mikhail Kislin, ..., Ben D. Richardson, Henk-Jan Boele, Samuel S.-H. Wang

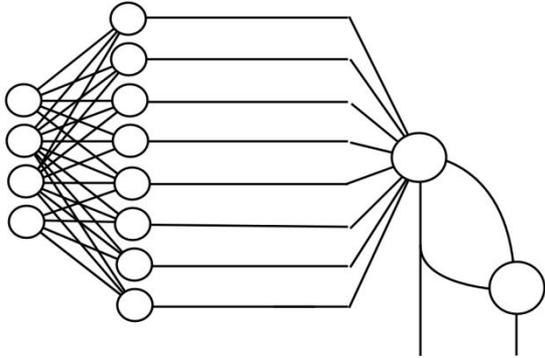


1.5 mm

# The cerebellum as a learning and teaching machine

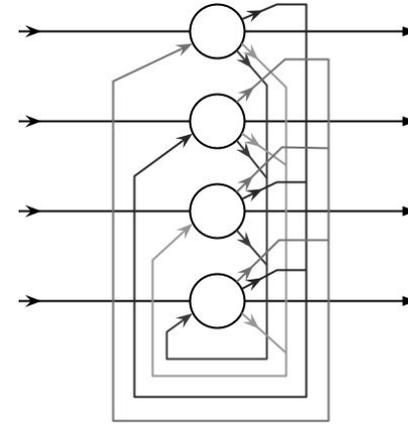
# Cerebellum vs. Neocortex

## Feedforward Architecture



- Learns mapping from many stimuli to one ( $x \rightarrow y$ )
- Less flexible
- Higher asymptotic accuracy
- 'Discriminative model'

## Recurrent Architecture

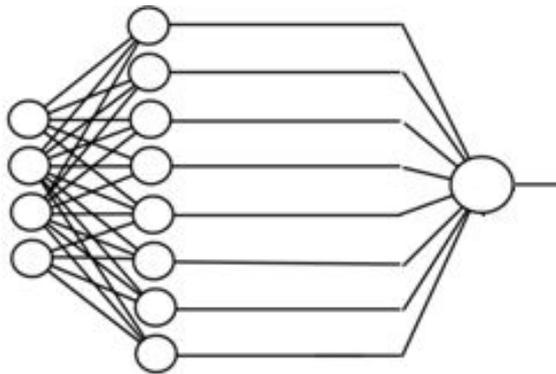


- Learns mappings between many stimuli ( $x_1 \leftrightarrow x_2 \leftrightarrow x_3$ )
- More flexible
- Lower asymptotic accuracy for any one function
- 'Generative model'

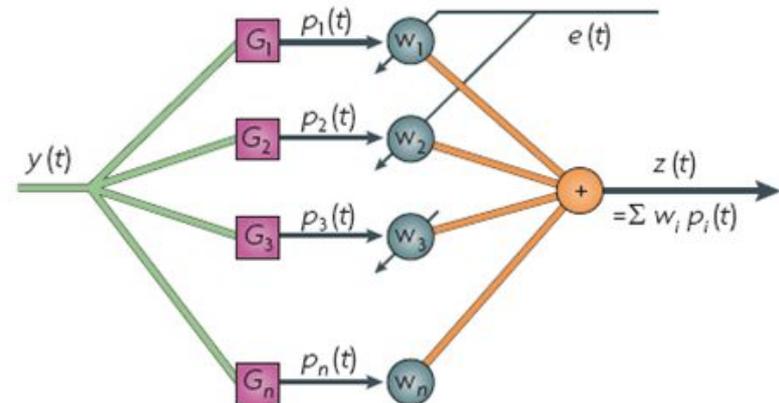
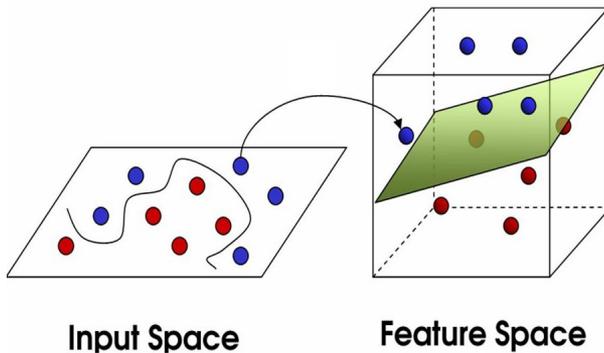
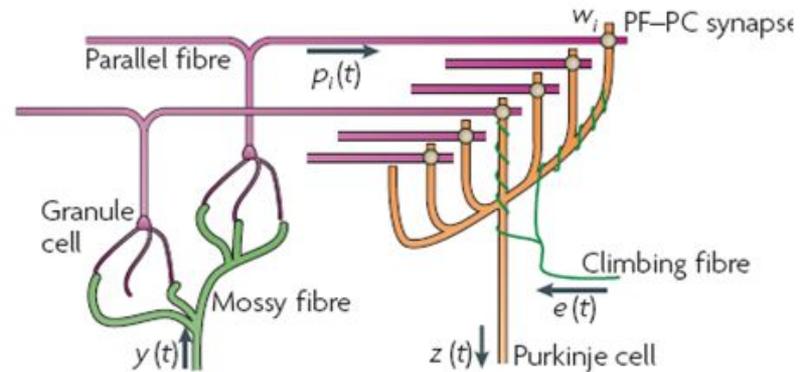


# Cerebellar Supervised Learning

- Multilayer perceptron



- Marr (1969), Albus (1971)



# Circuit elements and organization

# Common features of all cerebella

## 1. Cerebellar cortex

*Purkinje neurons, the sole output: inhibitory*

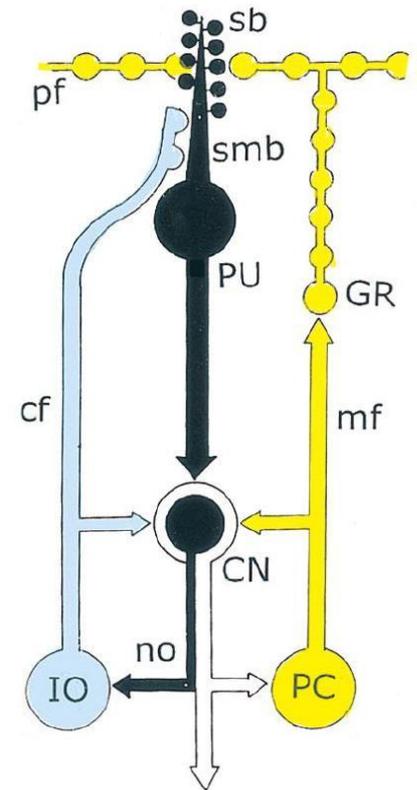
## 2. Inputs:

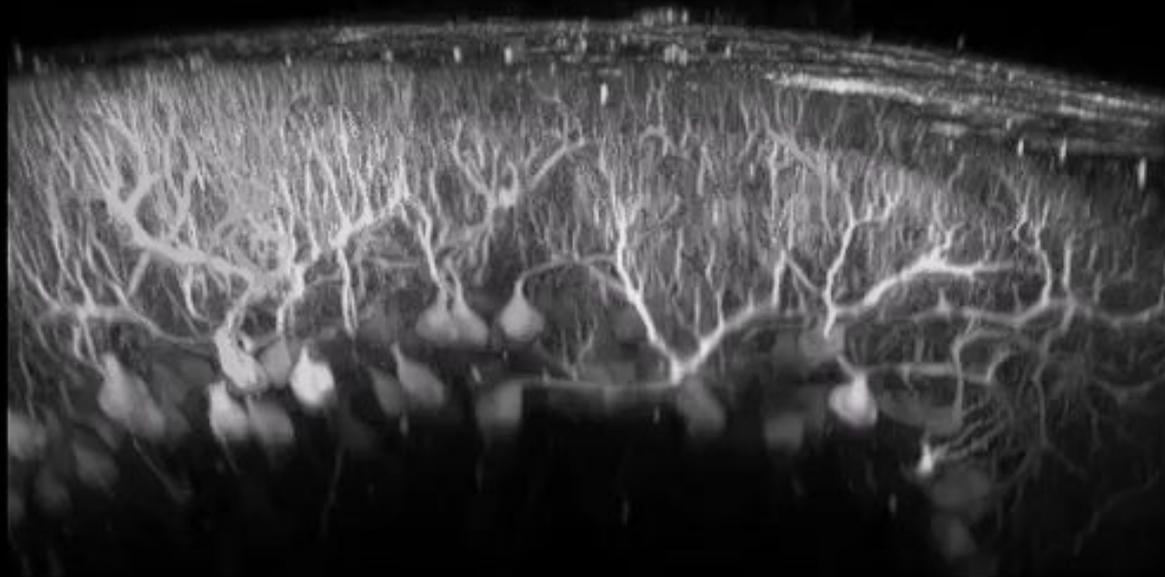
*Mossy fibers >> granule cells > parallel fibers*

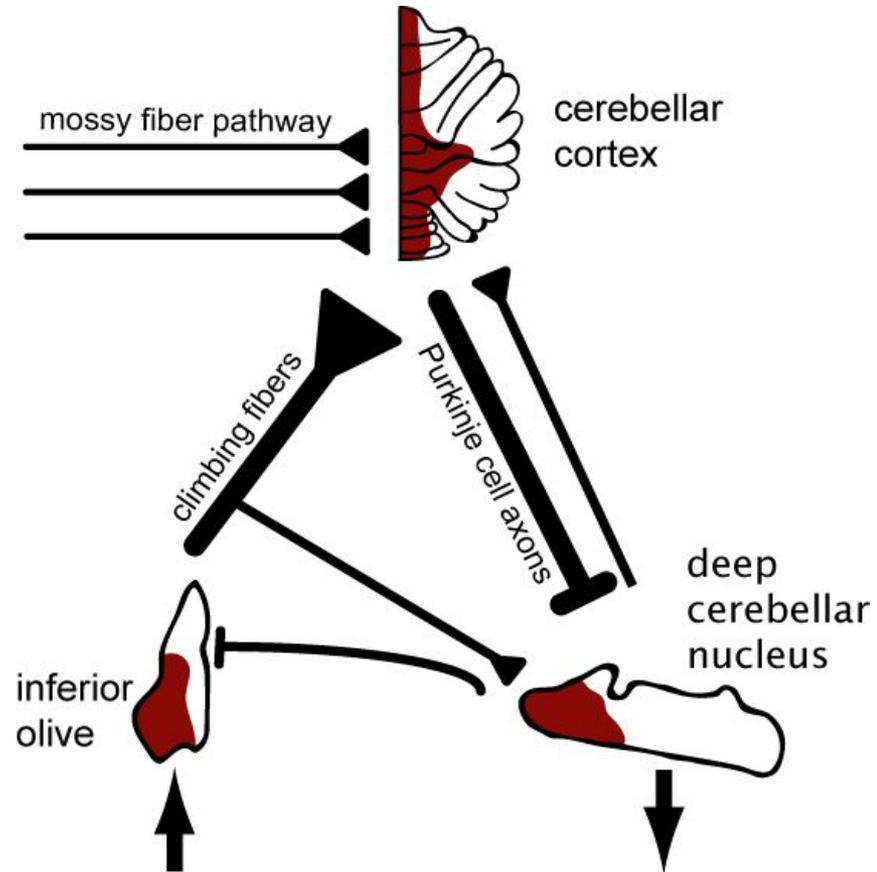
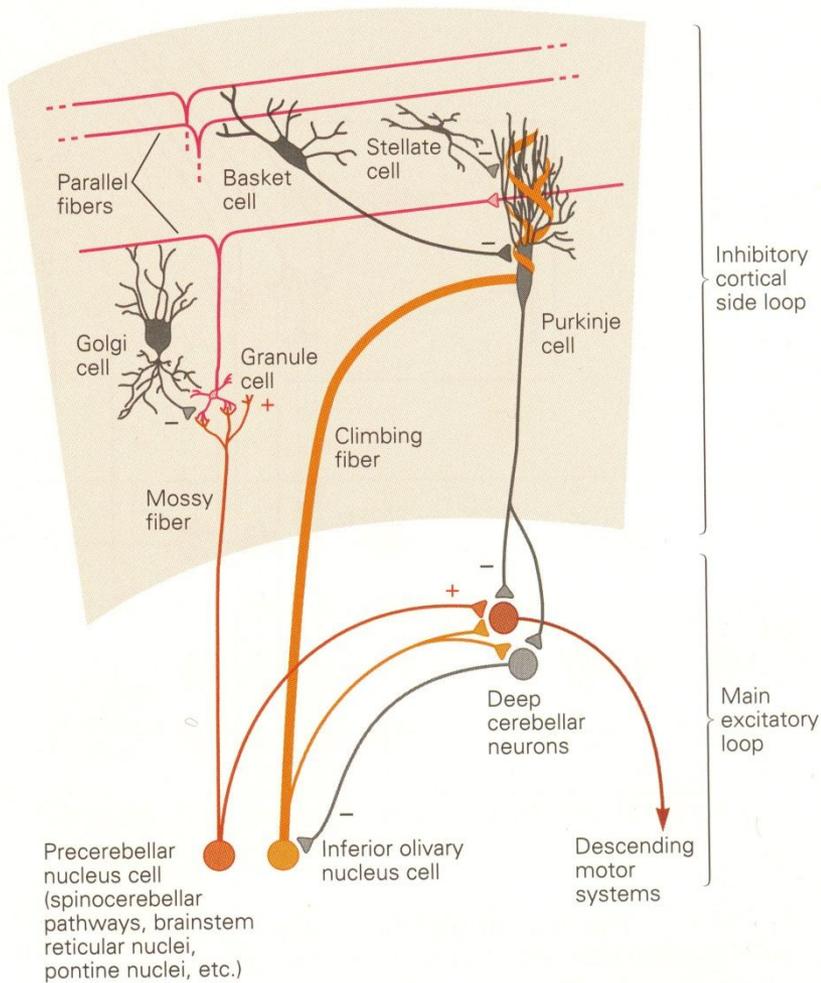
*The inferior olive > climbing fibers*

## 3. Output: The vestibular nuclei and deep nuclei

## 4. A few local inhibitory neurons: stellate and Golgi neurons







**Figure 42-6** Synaptic organization of the basic cerebellar circuit module. Mossy and climbing fibers convey output from

# Massive divergence of neural information in the cerebellum

	Purkinje cells (10 <sup>3</sup> )	Granule cells (10 <sup>6</sup> )	Inferior olive (10 <sup>3</sup> )	Deep nuclei (10 <sup>3</sup> )	Purkinje:deep n. cell ratio	Olive:deep n. cell ratio
human	16,500	54,000	1,030	620*	26	1.7
monkey	3,600	3,500	-	260*	14	-
cat	1,500	2,200	140	46 <sup>†</sup>	33	3.0
rat	400	120	50*	78*	5	0.6
mouse	200	41	30	19	11	1.6
dogfish	35	11	-	1.1*	33	-
					<b>20 ± 12</b>	<b>1.7 ± 1.0</b>

\*n=1.

<sup>†</sup>Deiters' nucleus excluded.

From data summarized in KWT Caddy and TJ Biscoe (1978) *Phil Trans Roy Soc Lond Ser B* 287:167-201. Additional measurements from BB Gould and P Rakic (1981) *Exp Brain Res* 44:195-206, R Alvarez and R Anadón (1987) *J Hirnforsch* 28:133-137, RJ Harvey and RMA Napper (1991) *Prog Neurobiol* 36:437-463, JA Heckroth (1994) *J Comp Neurol* 343:173-182, and R Alvarez-Otero et al (1996) *J Comp Neurol* 368:487-502.

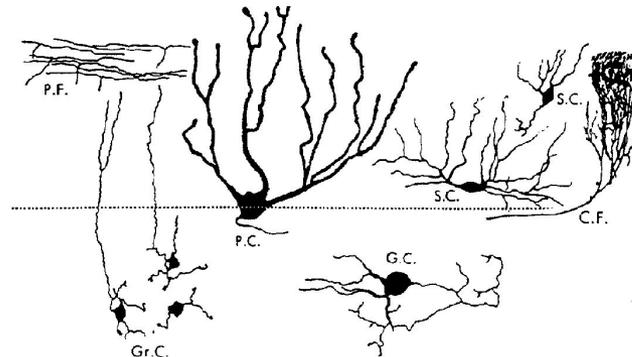


Fig. 5. Neural elements of the dogfish cerebellum. These drawings of Golgi preparations are reproduced from figures prepared by SCHAPER (1898 [25]), by HOUSER (1901 [12]) and by ARIENS KAPPERS, HUBER, and CROSBY (1936 [1]). The broken line represents the plane of the Purkinje cell bodies and separates the molecular layer from the granular layer. Full description in text

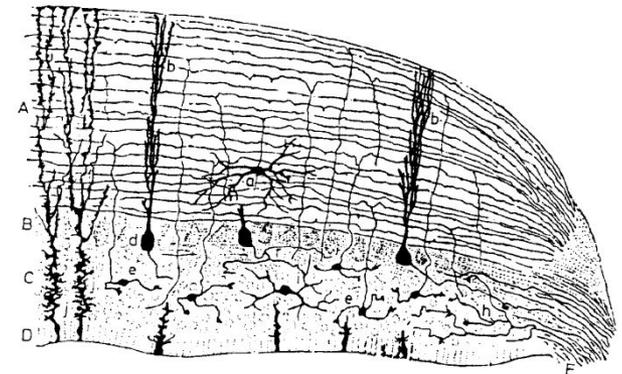
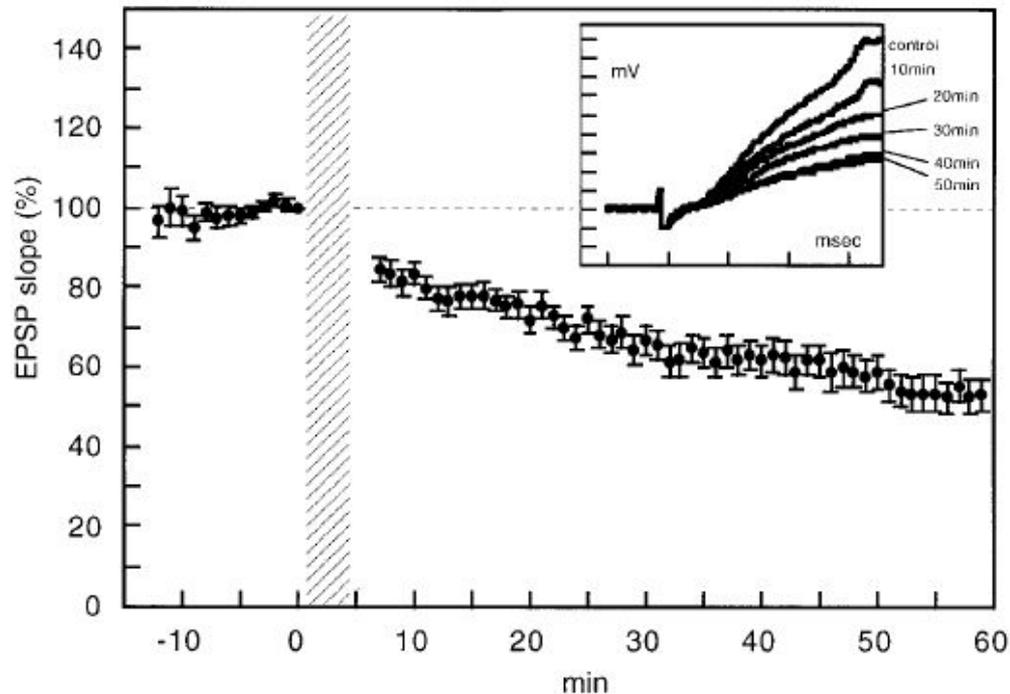


Fig. 6. Drawing of a longitudinal section along the transverse folium of a lizard cerebellum. A, B, C and D show respectively the molecular, Purkinje, granular and ependymal layers and E is the peduncle. Glia cells are shown in j. Full description in text [24]

# Parallel Fiber LTD

- PF stimulation followed by CF stimulation results in LTD
  - optimally induced by ~300 pairings @ 1 Hz, 125-250 ms delay



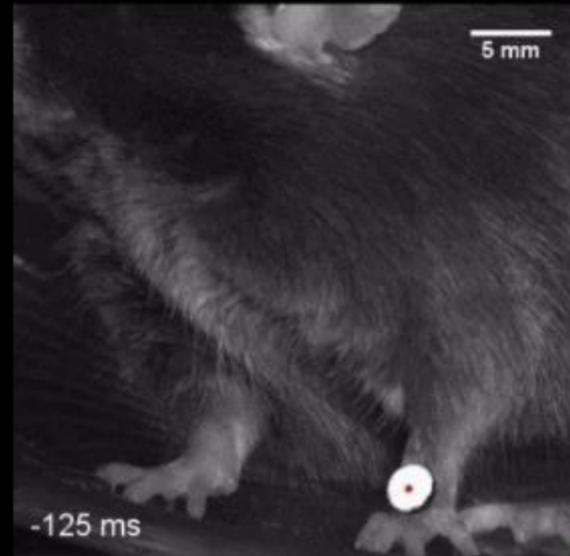
- depends on inositol-1,4,5-trisphosphate ( $IP_3$ ) receptors, an ER Ca release channel
- requires coincident  $IP_3$  and  $Ca^{2+}$  coagonists temporally ordered
- AMPA endocytosis

laser-evoked movements

100 ms laser pulse

ChR2

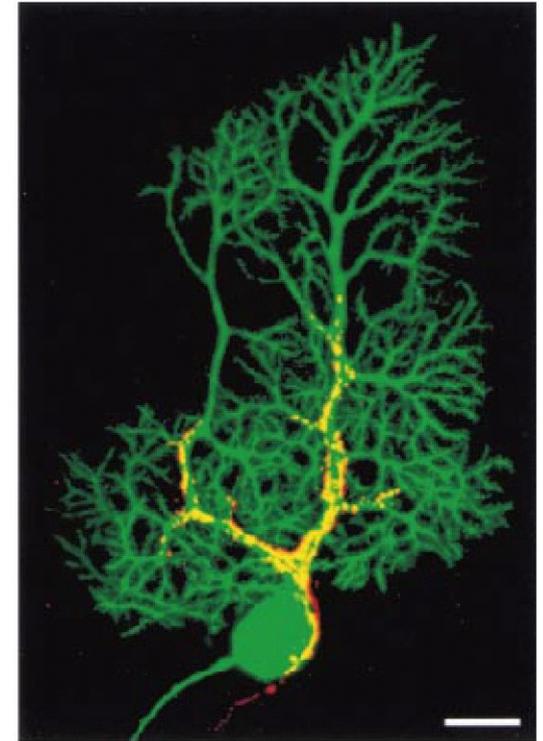
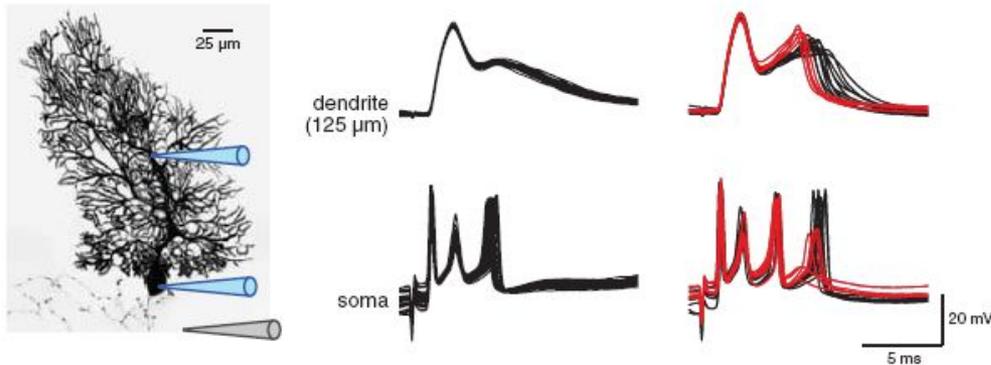
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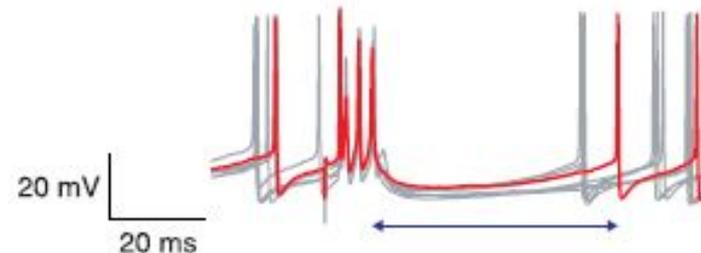
Lee, Mathews et al. 2015 *Neuron* 86:529-540

# Climbing fibers and complex spikes

- Strong multisynaptic connection
  - ~25,000 synapses
  - strongest afferent in CNS
  - glutamatergic
- Purkinje cell complex spikes
  - very large EPSP with Calcium spikes



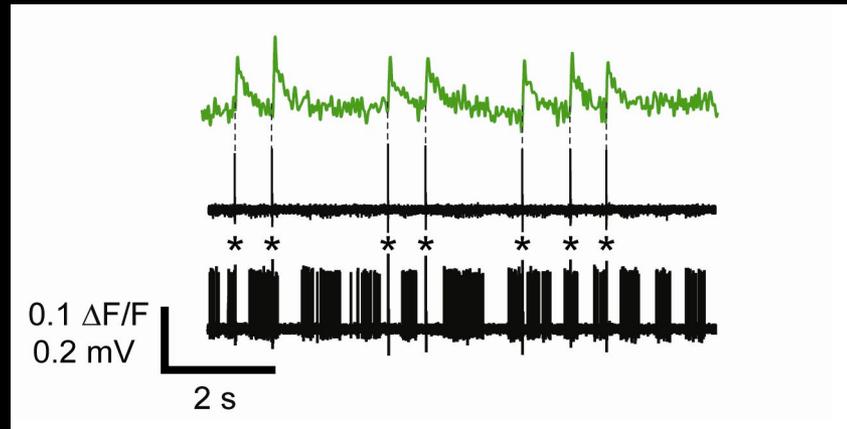
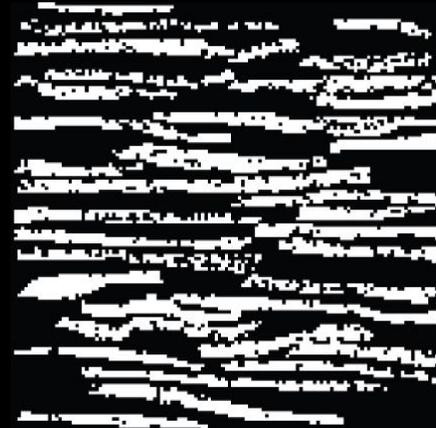
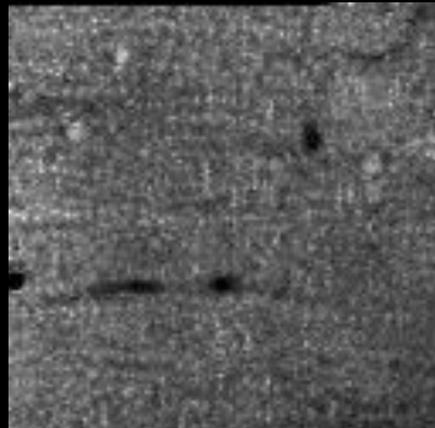
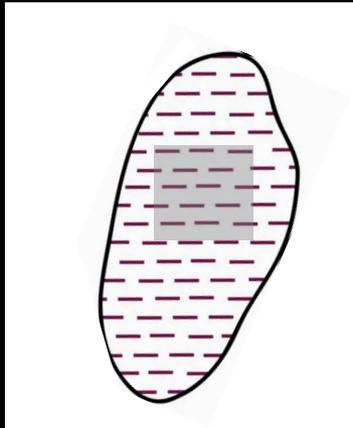
- Complex results in a pause of simple spike pacemacing



# Functions of climbing fiber firing and complex spikes

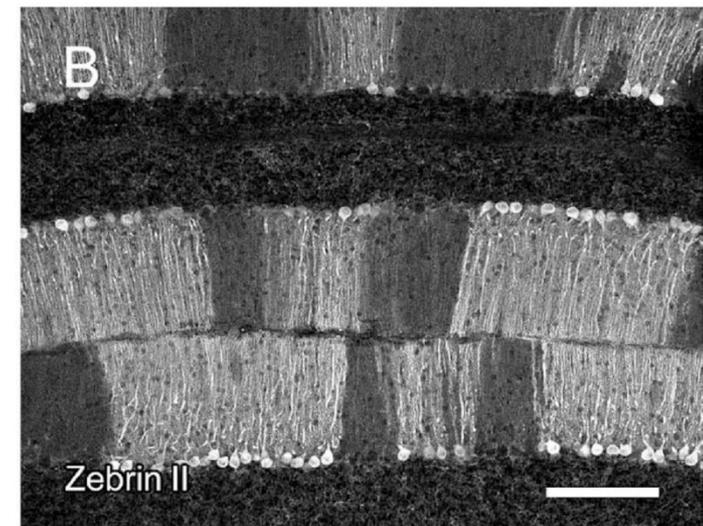
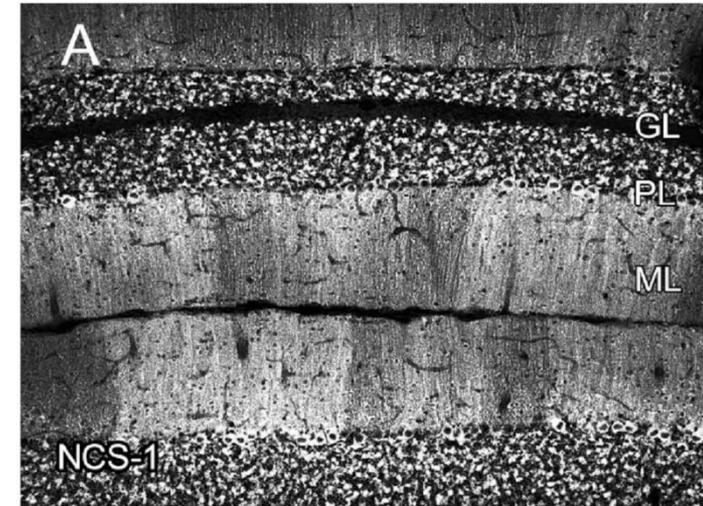
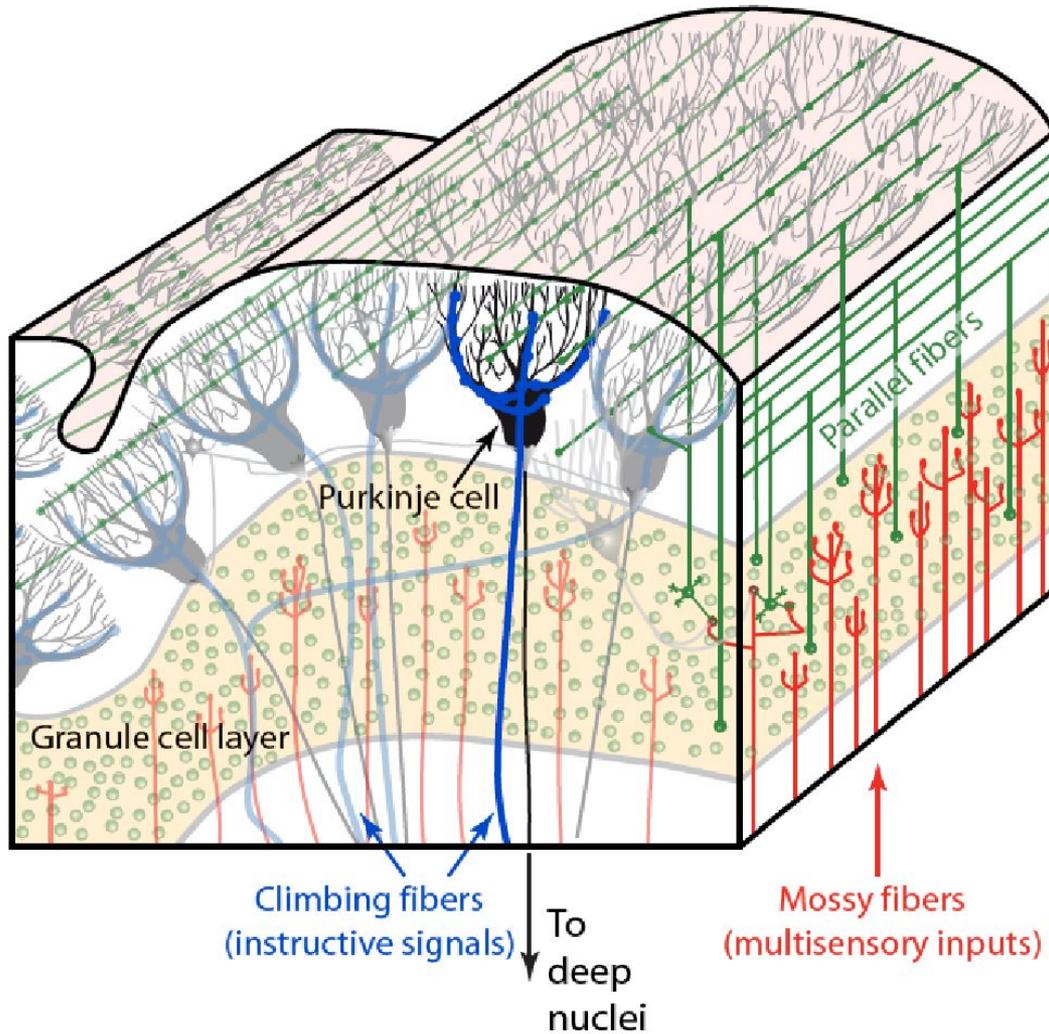
- Sensory events such as error signals (Simpson *et al* 1996 *Behav Brain Sci*)
- Instructive signal for learning (Raymond *et al* 1996 *Science*)
- Synchronization guides timing and activity (Welsh 2002 *NYAS*)

# Purkinje cell dendritic responses using OGB-1/AM



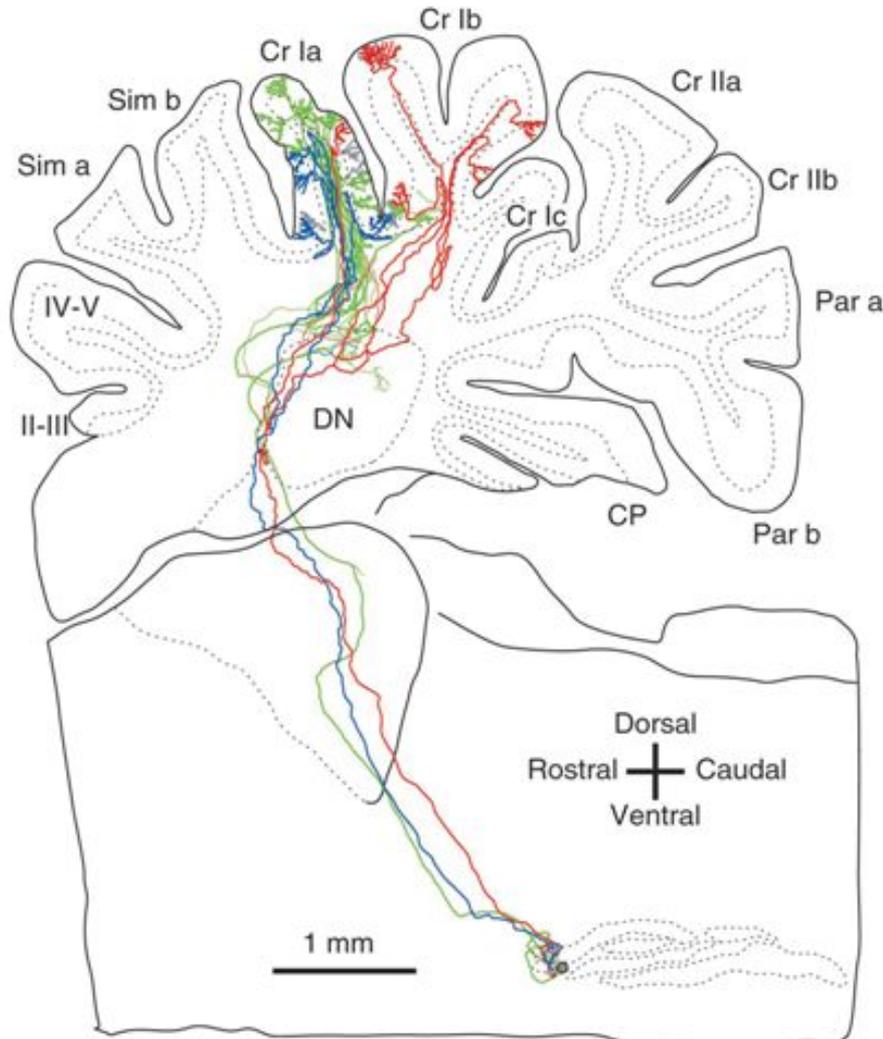
Sullivan et al. (2005) *J. Neurophysiol.* 94:1635  
Ozden et al. (2009) *J. Neurophysiol.* 100:495

# Cerebellar circuitry: modular, convergent, and instructed



Jinno et al. (2004) *Cerebellum* 3:83-88

# Climbing fibers and inferior olive



- Spontaneously active at 1-2 Hz in vivo
- Inferior olive receives feedback inhibition from cerebellar nuclei

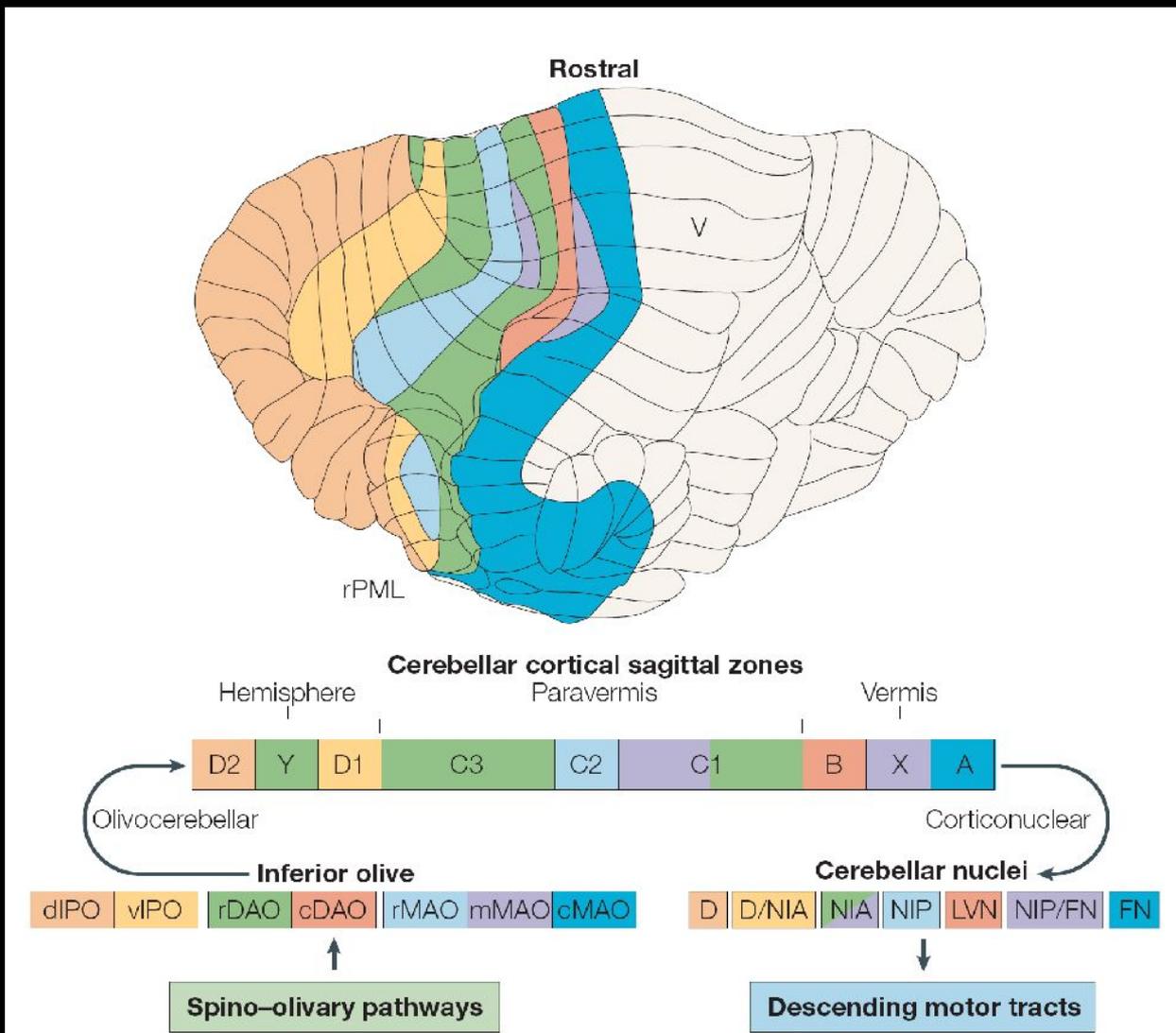
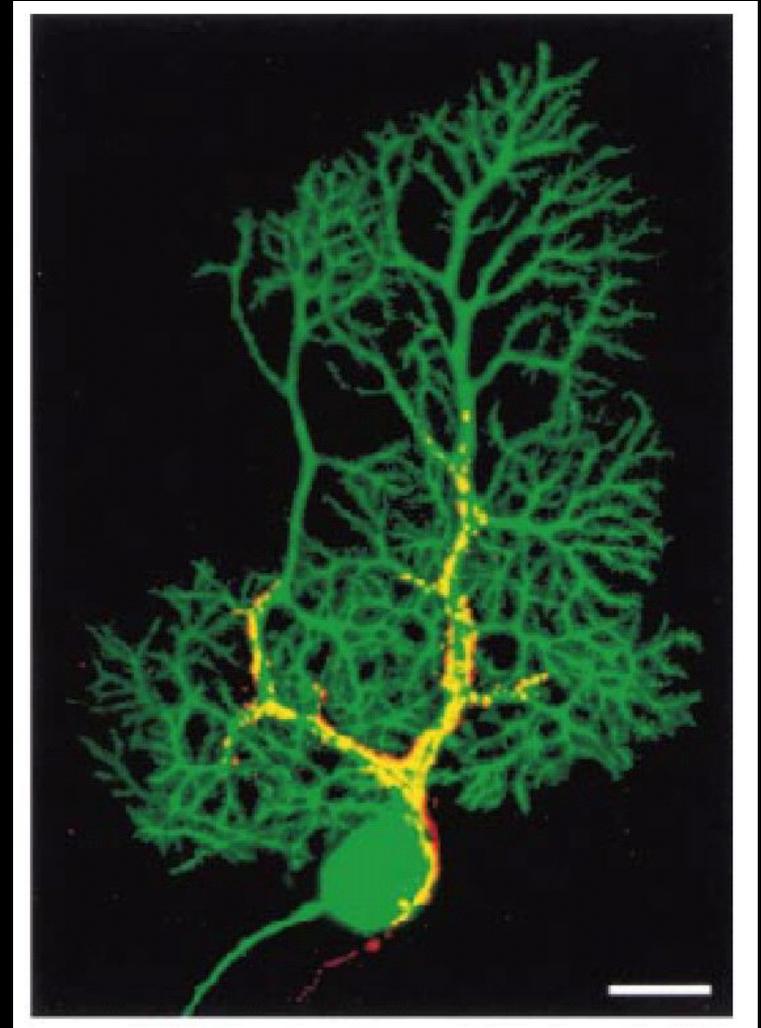


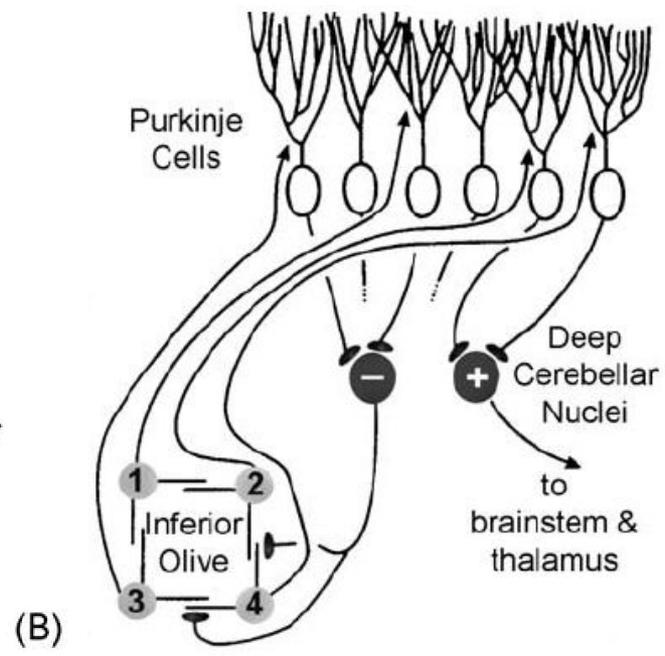
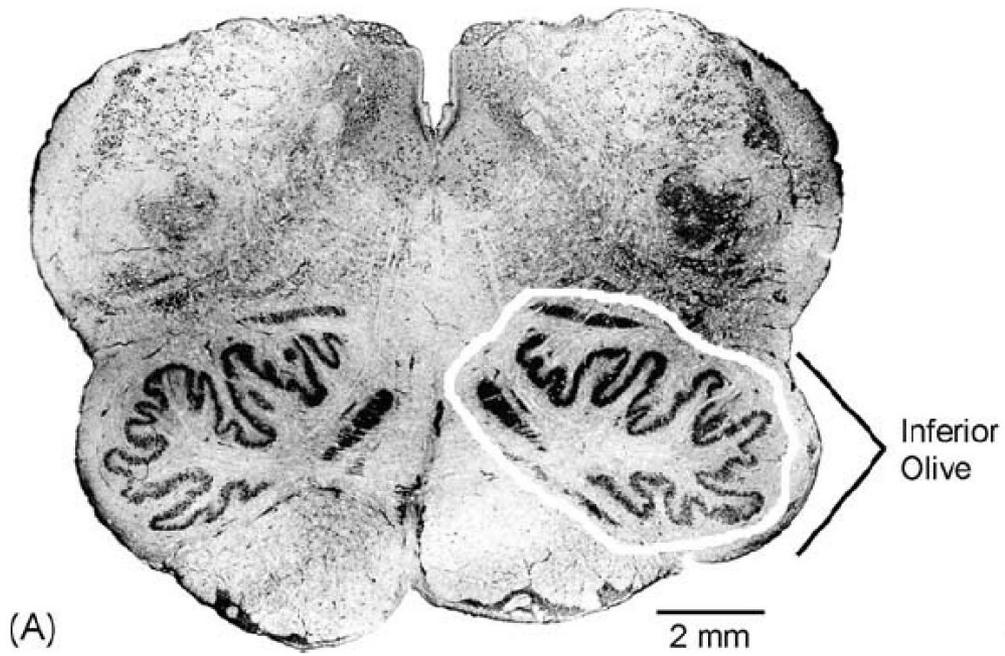
Figure 2 | **Connectivity of the cerebellum.** The top panel shows a dorsal view of the cat cerebellum, indicating the approximate location of different sagittal zones on the cerebellar surface. In the simplified block diagrams below, matching colours show, for individual cerebellar cortical zones, the sites of origin of climbing fibres in the contralateral inferior olive, and the corresponding corticonuclear output targets in the ipsilateral cerebellar nuclei. Different regions of the inferior olive

# Climbing fibers

- Powerful input causing massive dendritic spike
- More focused in their branching than mossy fibers
- Instructive signal conveying errors or other sensory events (Marr, Albus, Ito)
- Regulation of Purkinje cell excitability:  
Synchronize sodium spike activity of Purkinje cells (Llinás, Welsh)  
Fire together to accelerate movement (Bloedel)



Kreitzer *et al.* 2000





50  $\mu\text{m}$

