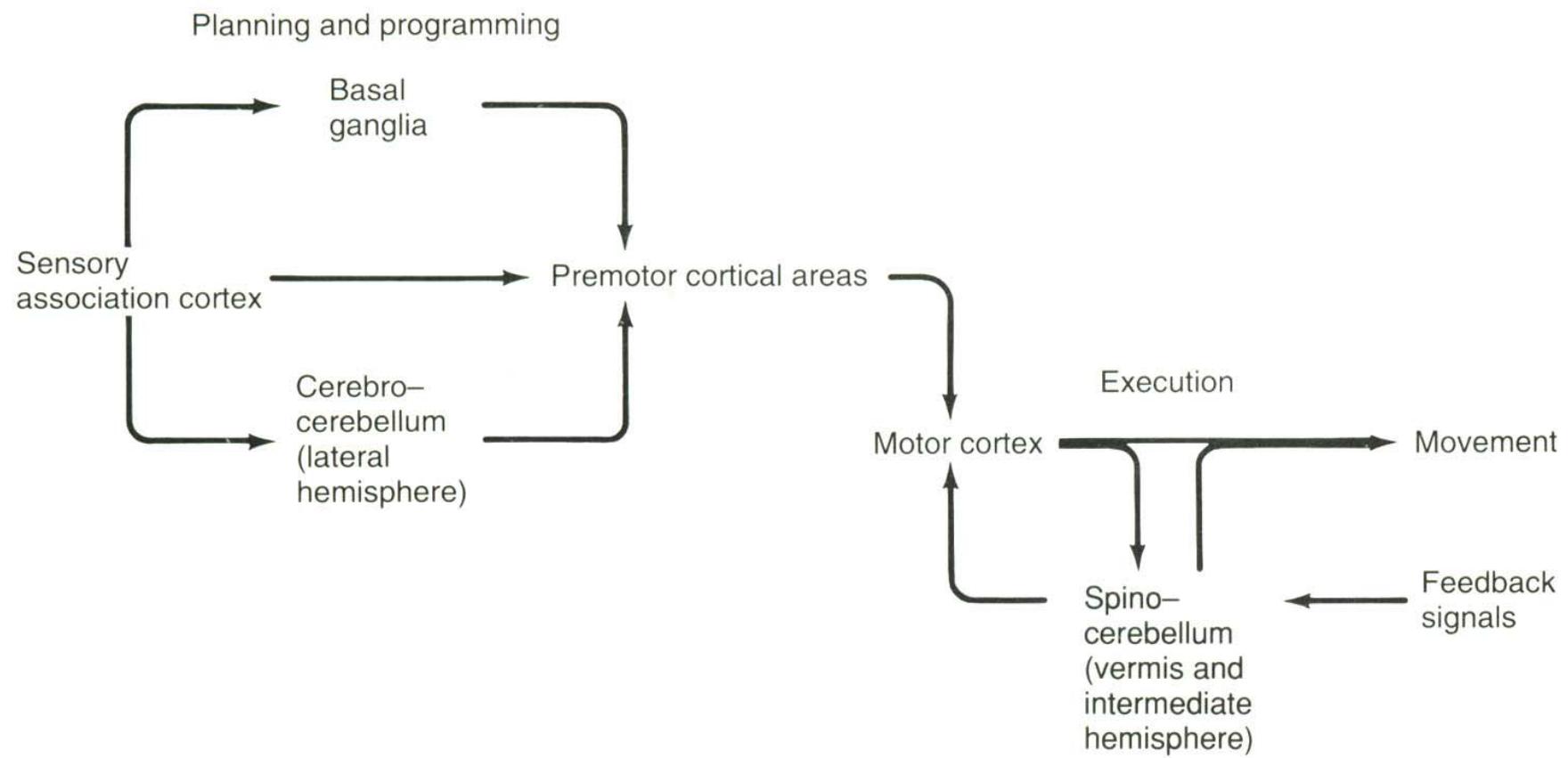
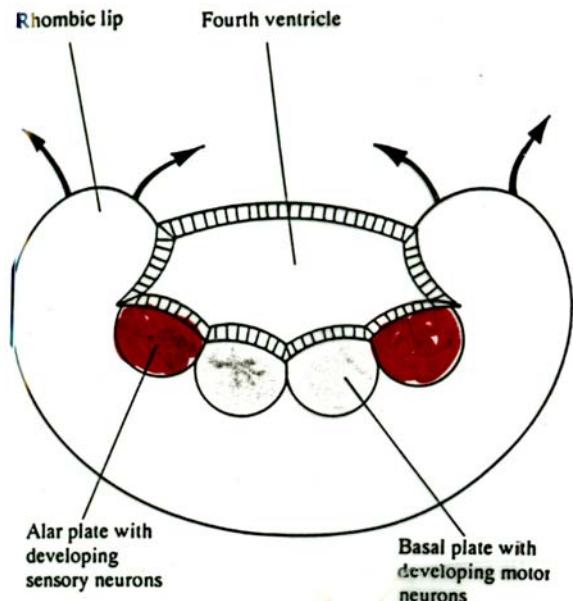
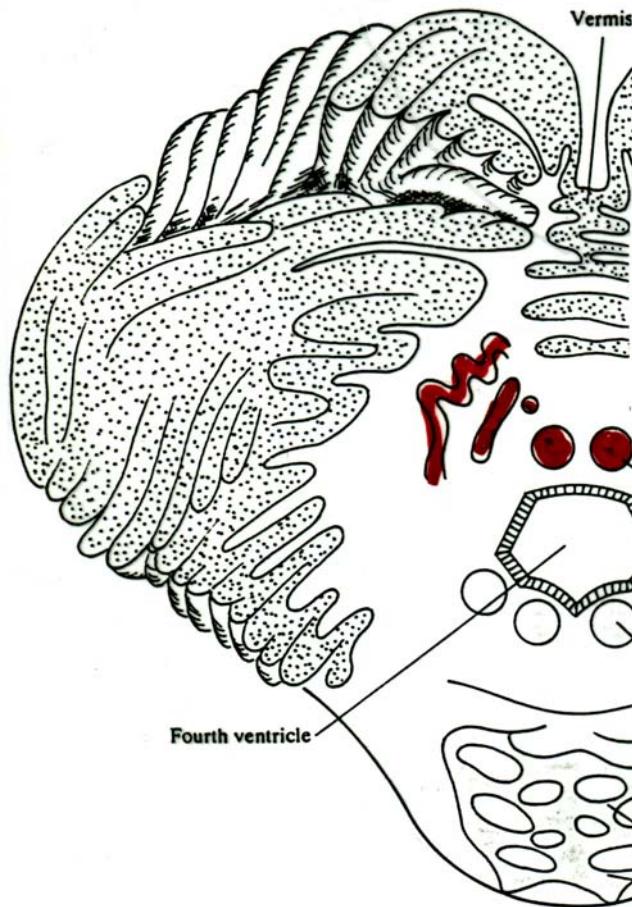
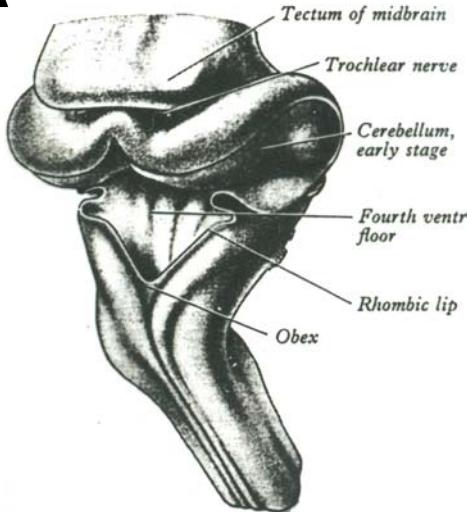
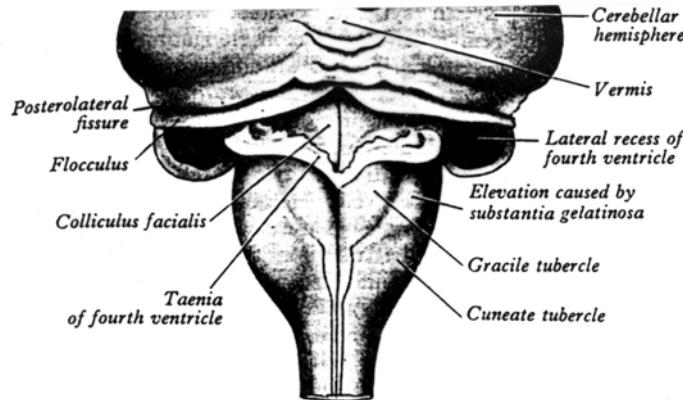
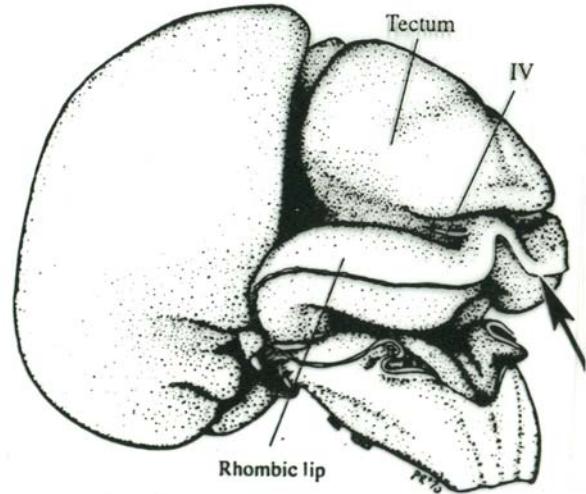
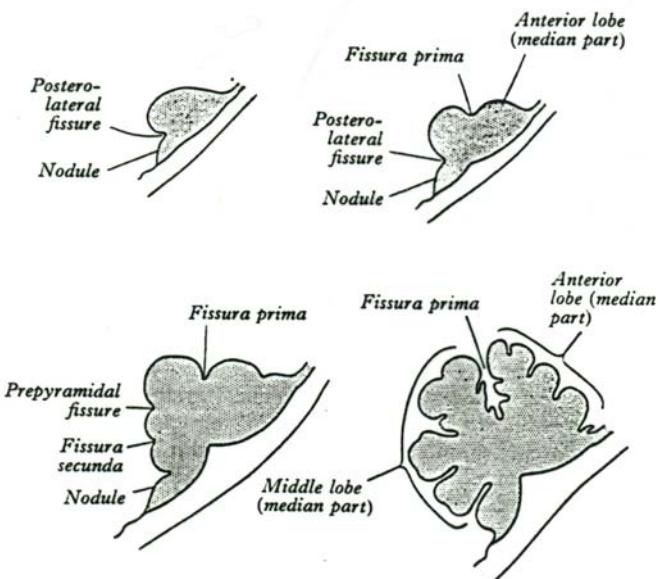


CEREBELLUM

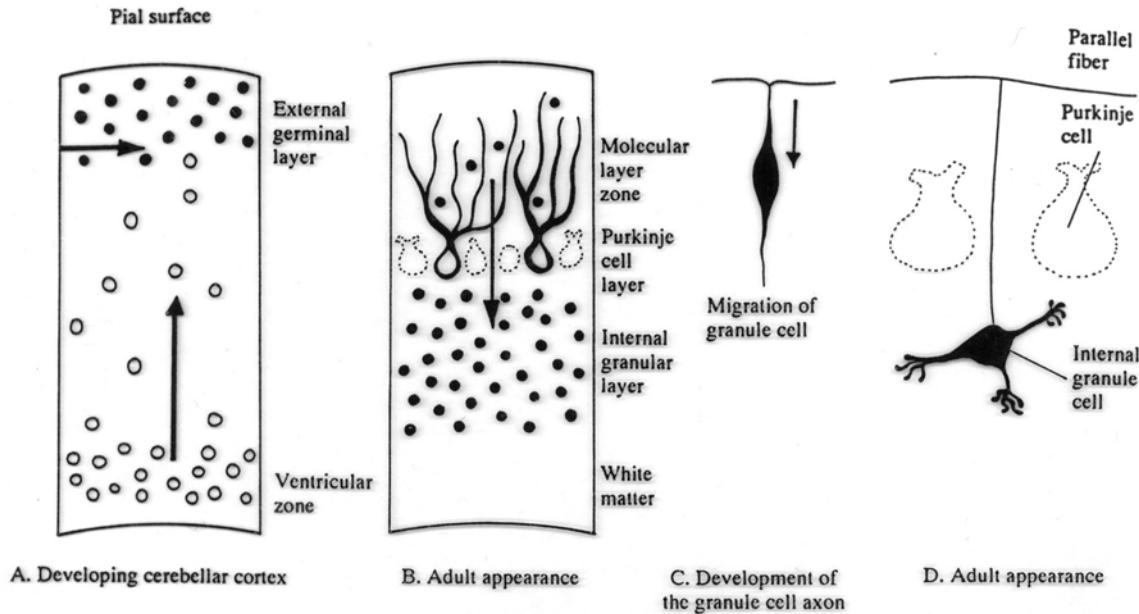


A**B**

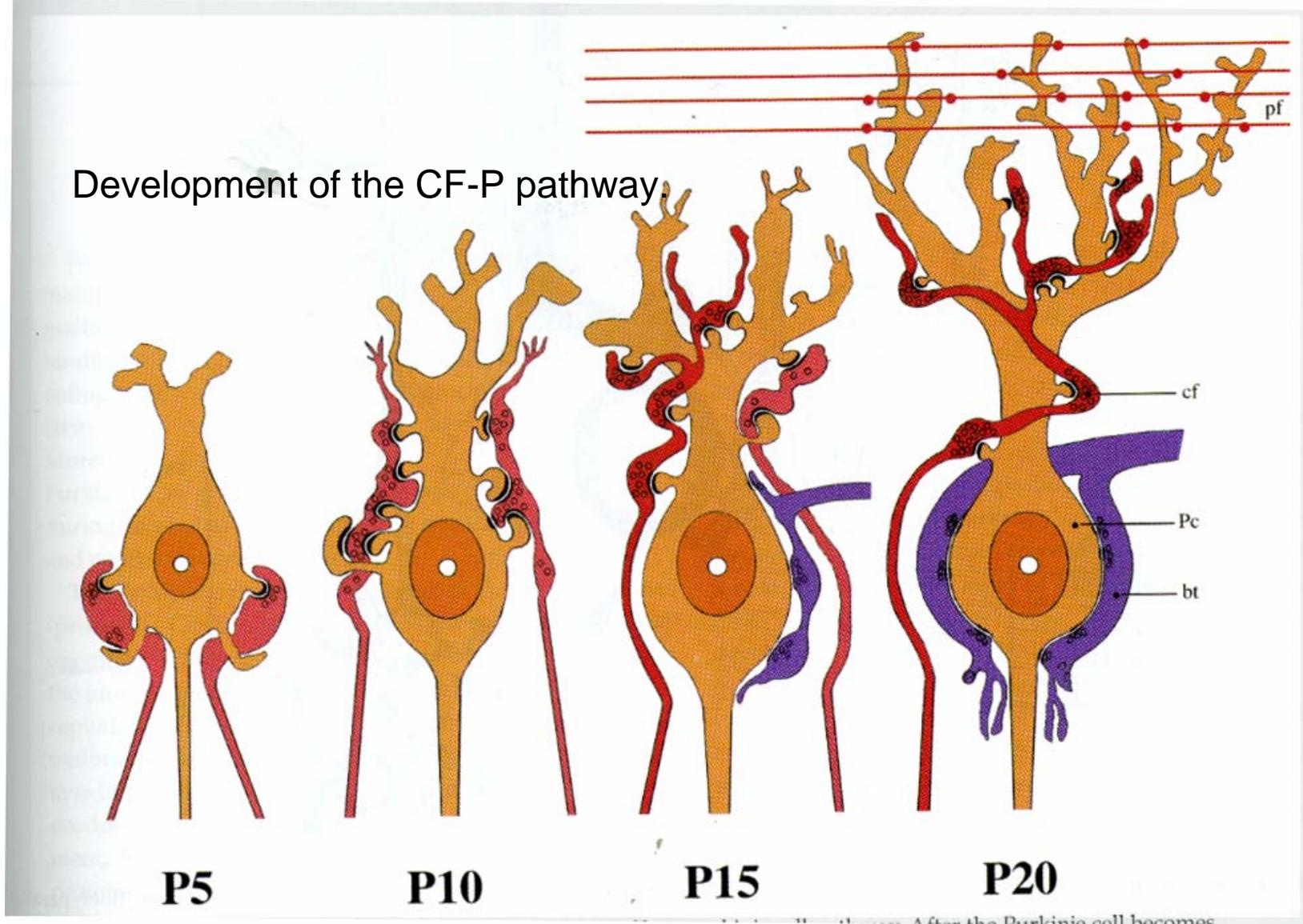
A: The rhombic lip expands in dorsal direction and give rise to the cerebellum. B: The ventral part of the metencephalon, the pons develops mainly from the alar plate. The cerebellar nuclei develops from the alar plates.

A**B****C****D**

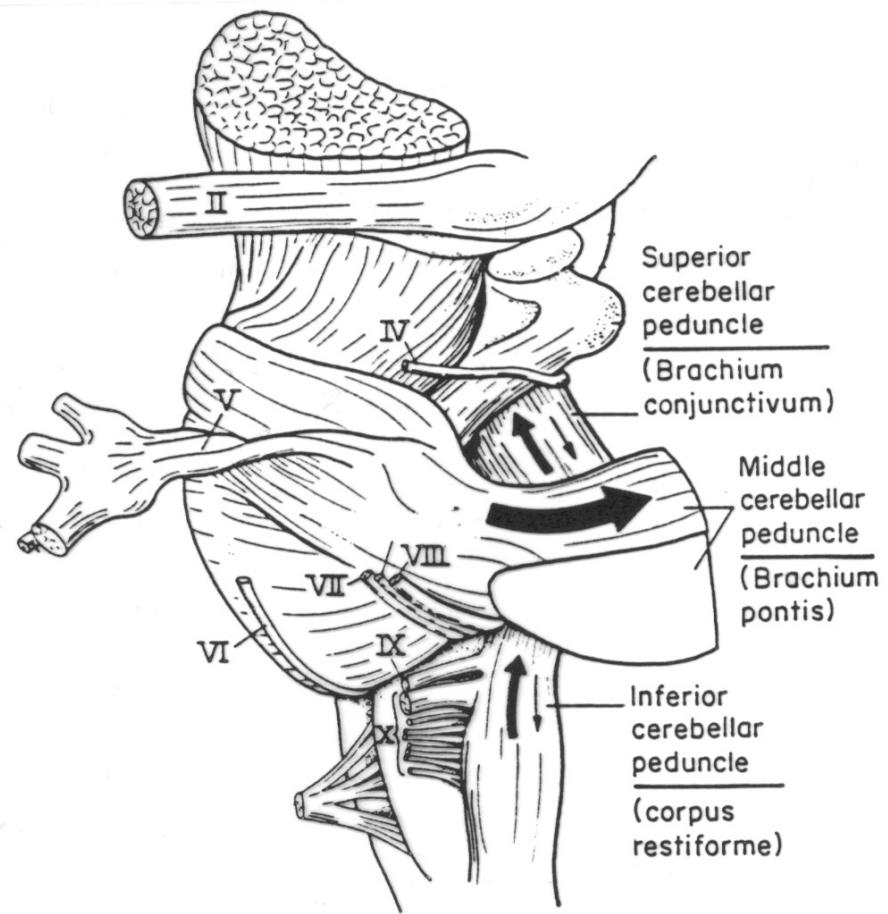
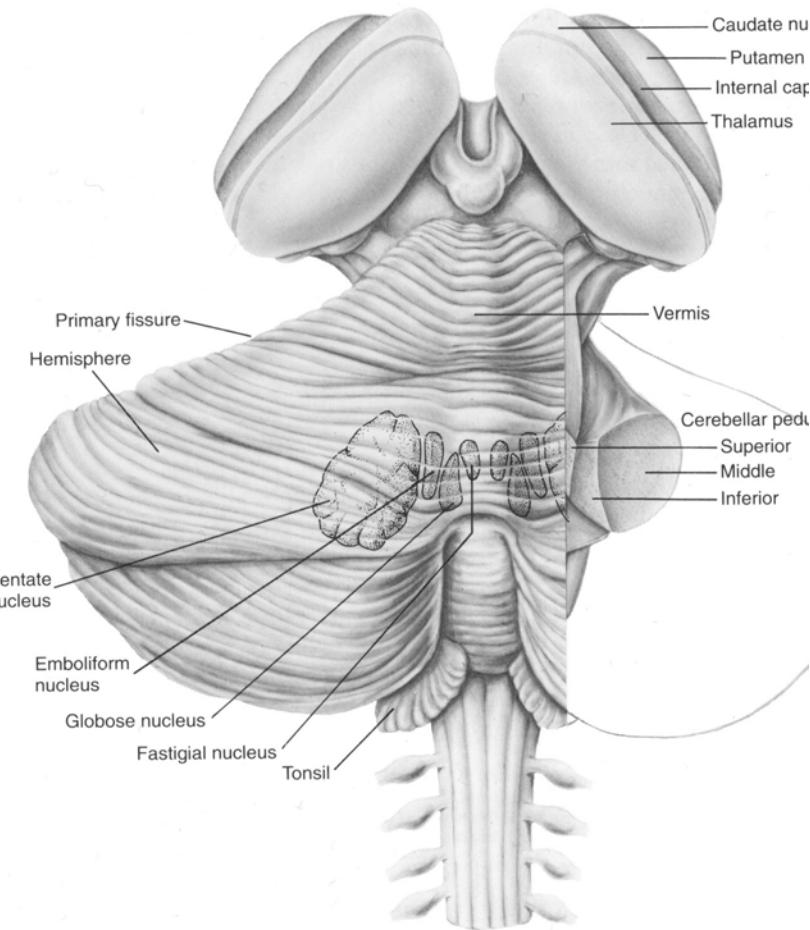
A: B: The cerebellum of a fetus in the fifth month. C: The human brain at approx. 10 weeks of gestation. VI=trochlear nerve. The arrow points to the attachment of the cut rhombencephalic membrane. D: Median sagittal sections through the developing cerebellum, showing four different stages.

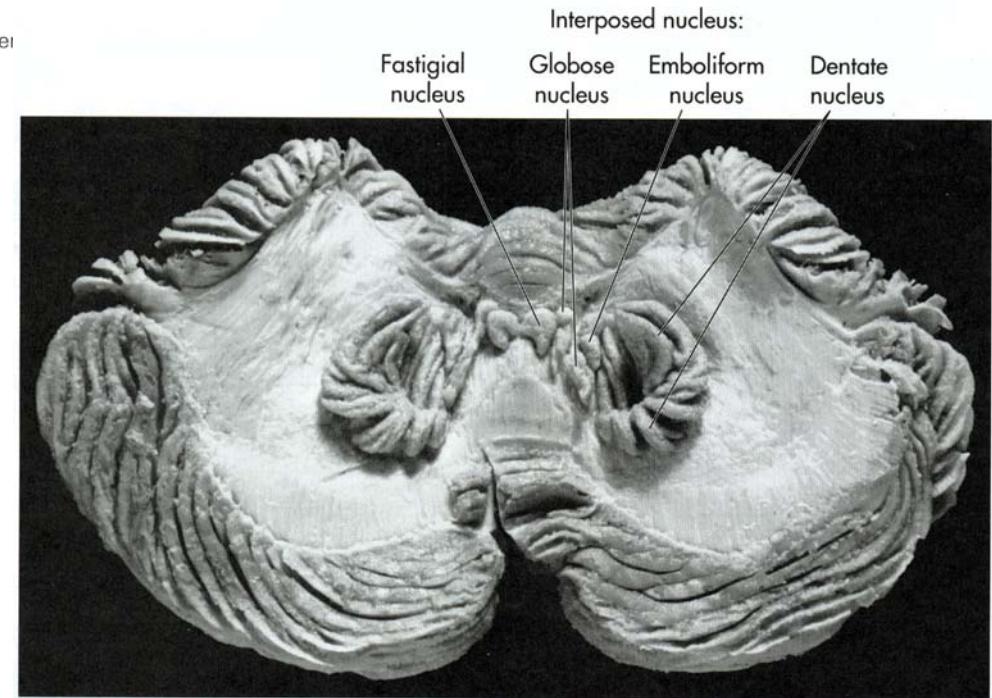
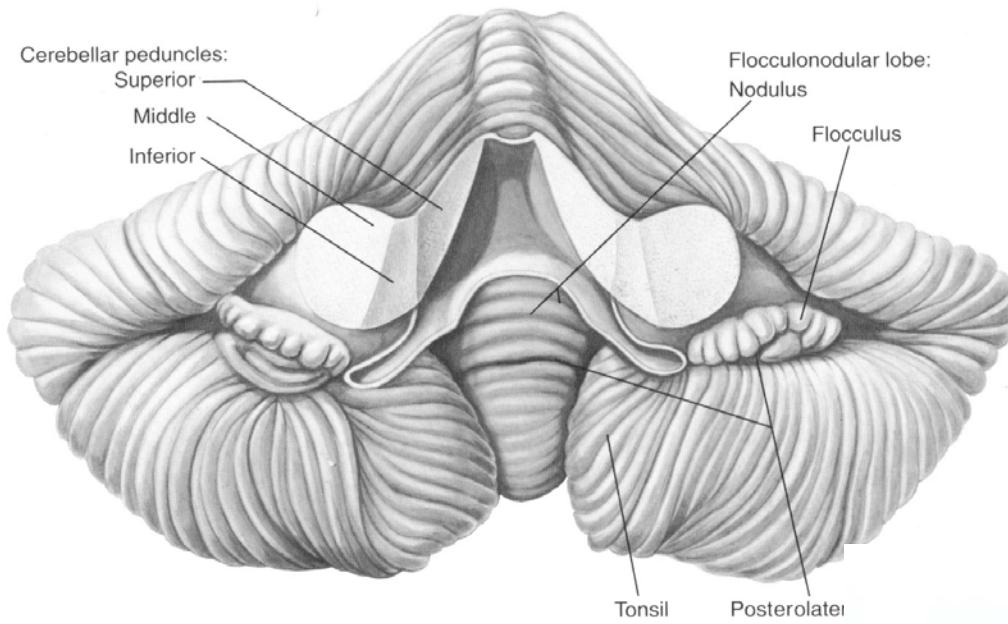


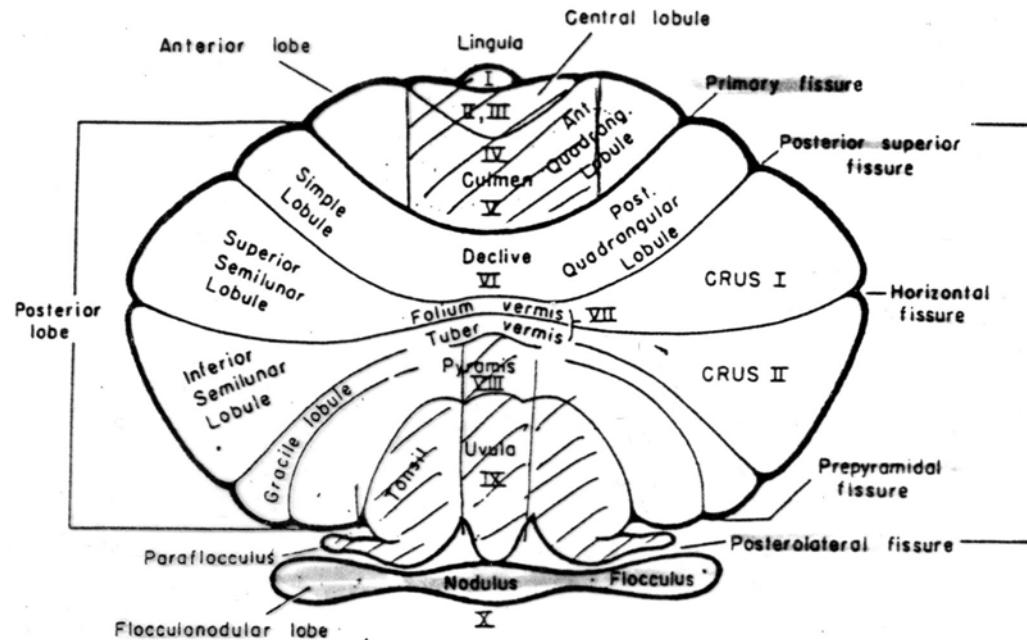
Development of the cerebellar cortex. Young neurons from the ventricular zone migrate in a radial direction to form the layer of the Purkinje cells. Another set of neuroepithelial cells migrate along the pial surface to form a secondary germinal matrix, the external germinal (granular) layer. The cells in this layer retain the capacity to divide and many of the daughter cells are destined to form the internal granular layer. The external granular cells develop tangentially oriented axonal processes before they develop radial processes along which the cell bodies migrate inward to form the internal granular layer. During the migration, the cells leave behind a perpendicular process, giving the axon a typical T-shaped appearance (from Heimer, 1995).



After the P cell becomes synaptically competent at P5, branches from two or more climbing fiber establish contact with short processes arising from the soma and successively grow to occupy the entire dendritic tree (P15). During formation of the spiny branchlets and parallel fiber synapses, supernumerary climbing fiber branches retract, leaving only one CF per P cell (P20). (Mugnaini and Sekerkova)



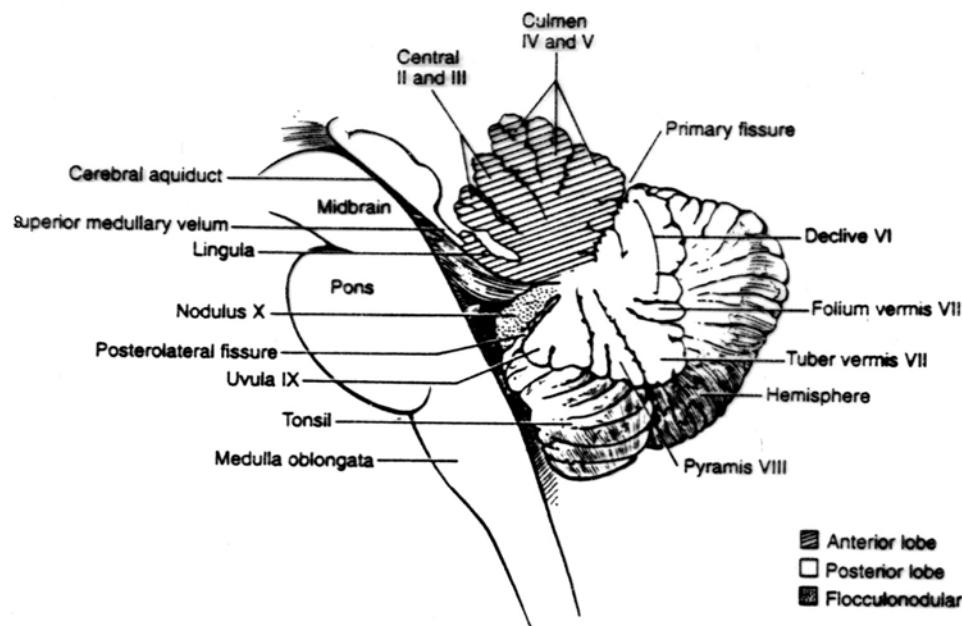




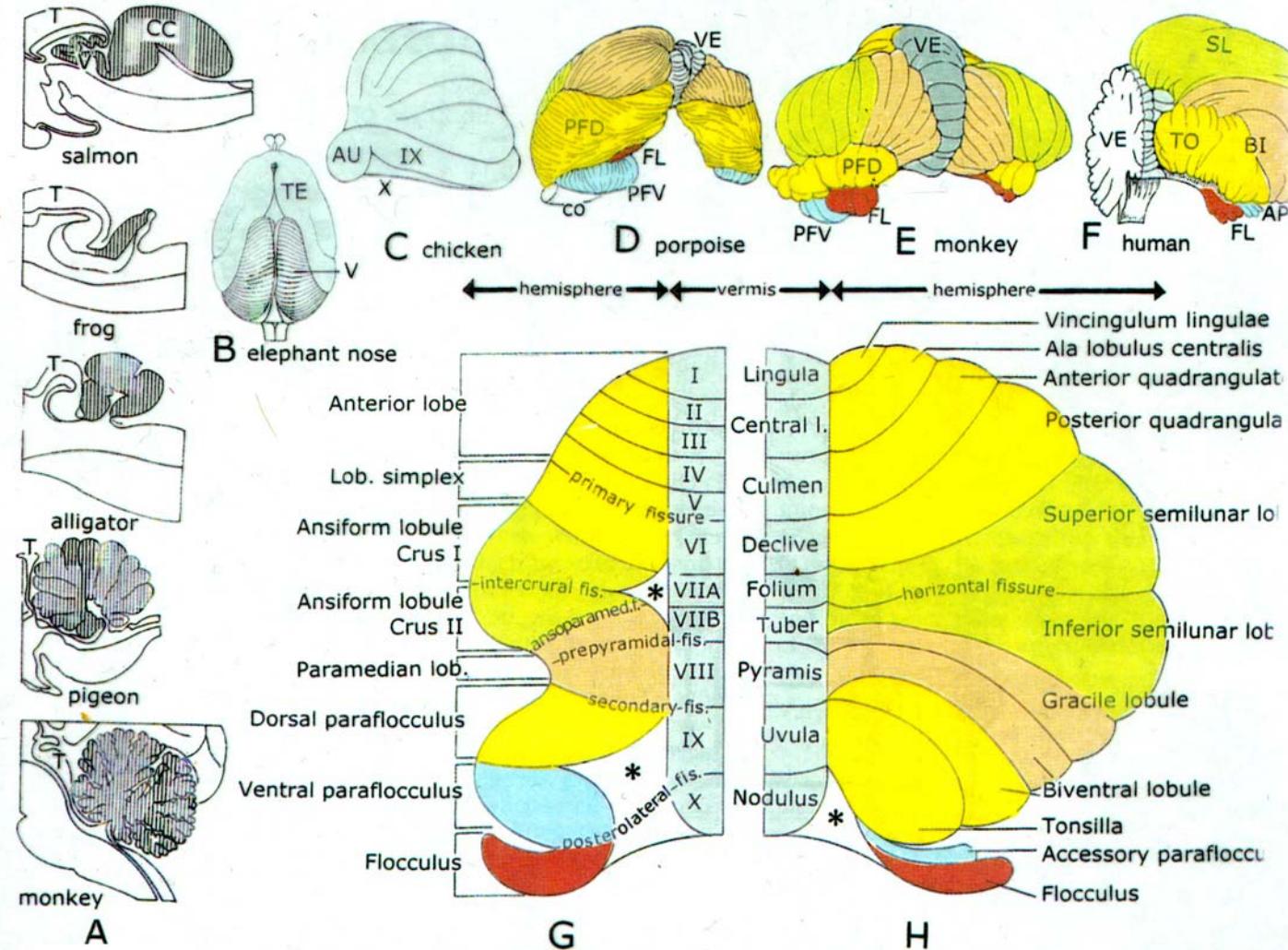
paleo cerebellum
spino cereb.

neo-cerebellum

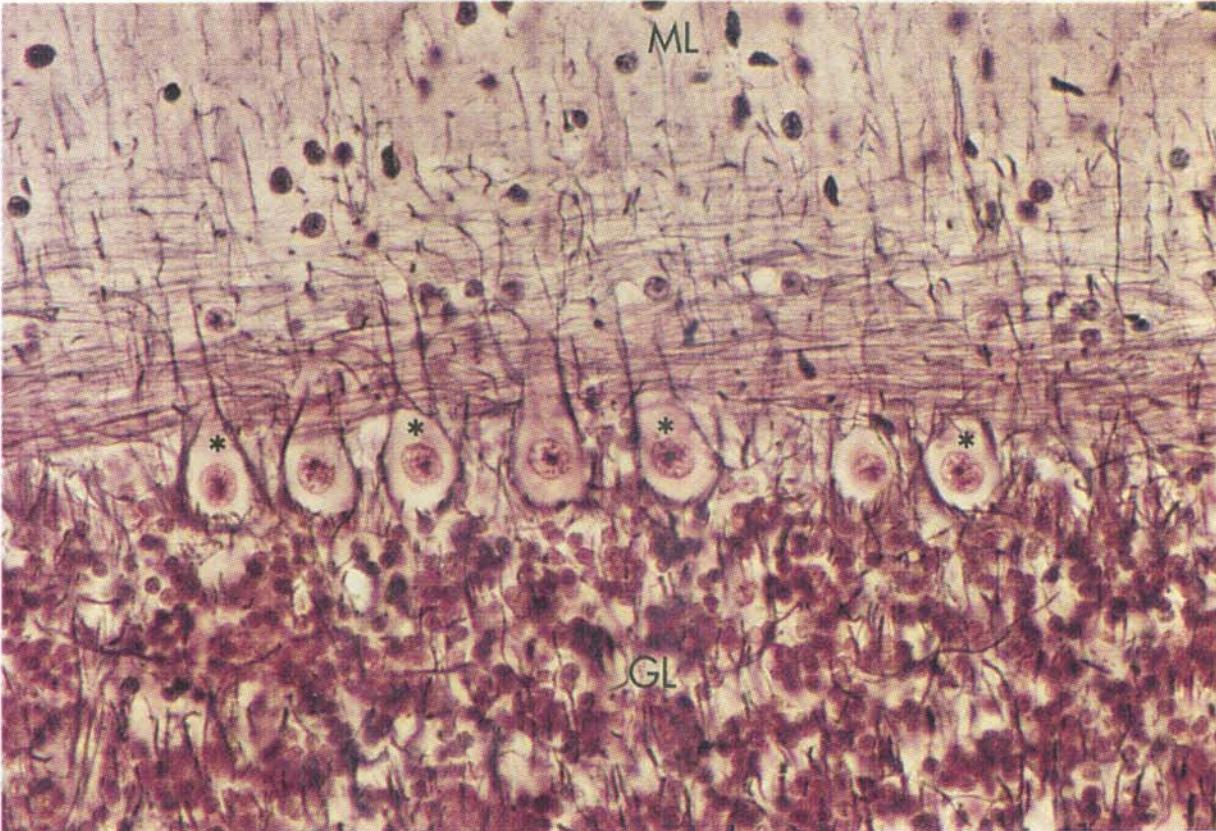
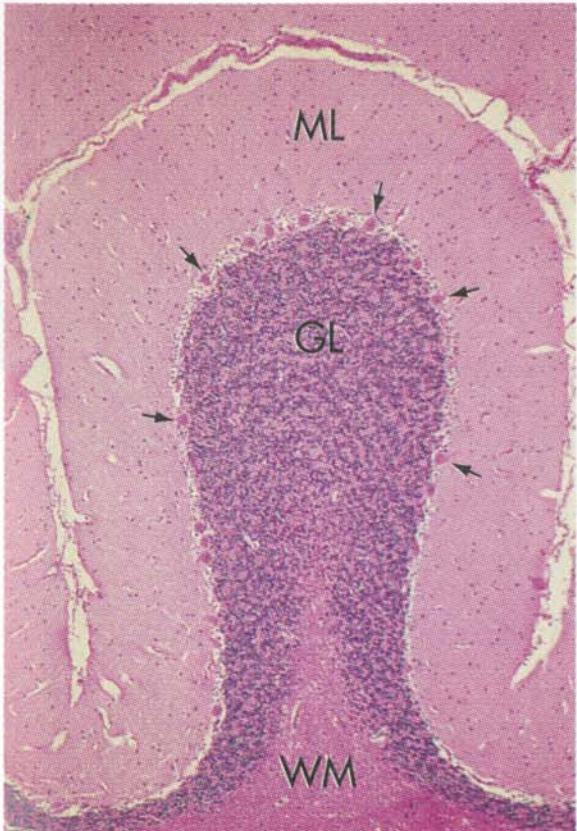
Archicerebellum



- Anterior lobe
- Posterior lobe
- Flocculonodular lobe



Variations in the external form of the cerebellum in sagittal (A), ventral (B) and dorsal views (C-F) through representative species of the different vertebrate classes. The comparative anatomical nomenclature for the mammalian cerebellum is shown in (G), the nomenclature for human in (H). VE=vermis; TO=tonsilla; FL=flocculus; V=valvula cerebelli; TE=telencephalon.

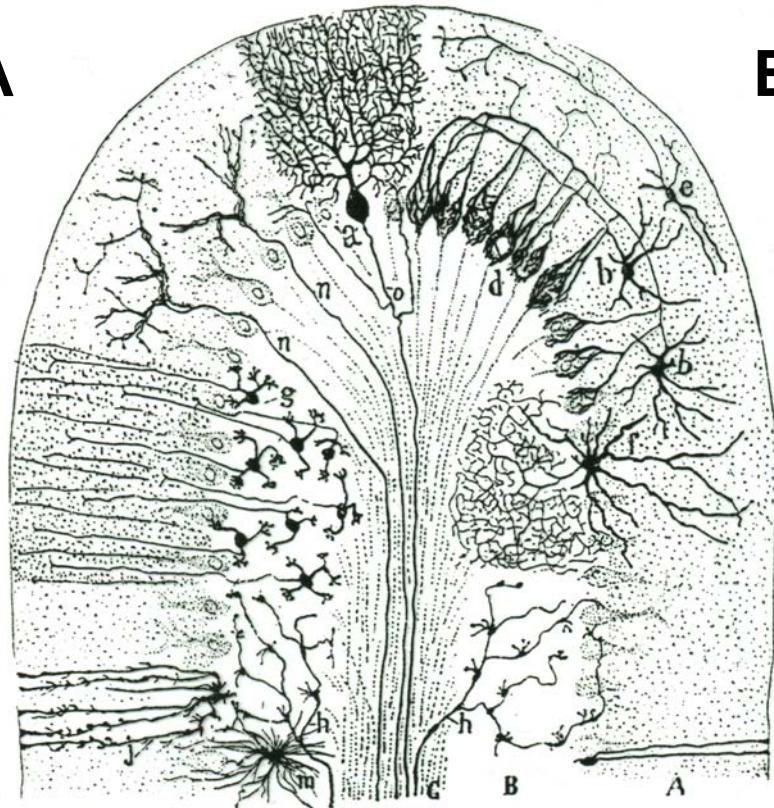


Light micrograph of cerebellar cortex. Left: cross section of a single folium from a human cerebellum (Hematoxylin-eosin). ML= molecular layers; GL: granular layer; WM= central white matter. Arrows point to Purkinje cells. Right: Higher-magnification view of the Purkinje cell layer of monkey cerebellar cortex (Bodian silver stain). (From Nolte)

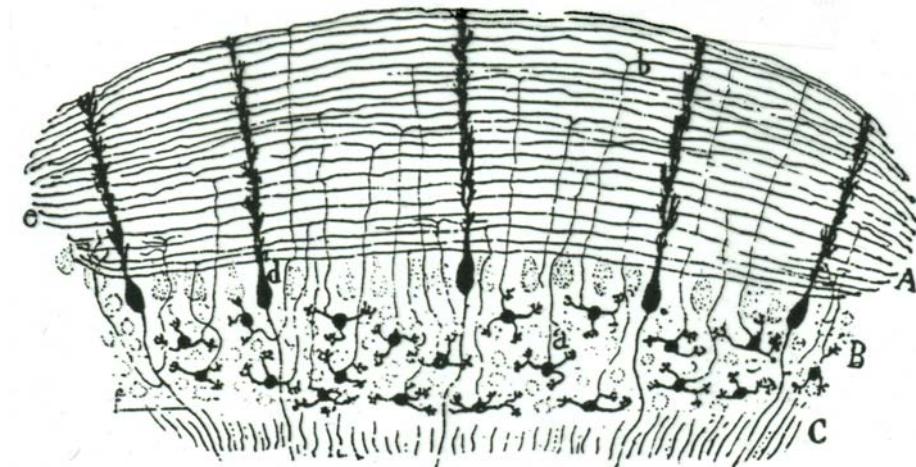
CEREBELLAR MICROCURCUITRY 1.:

R.Y. CAJAL

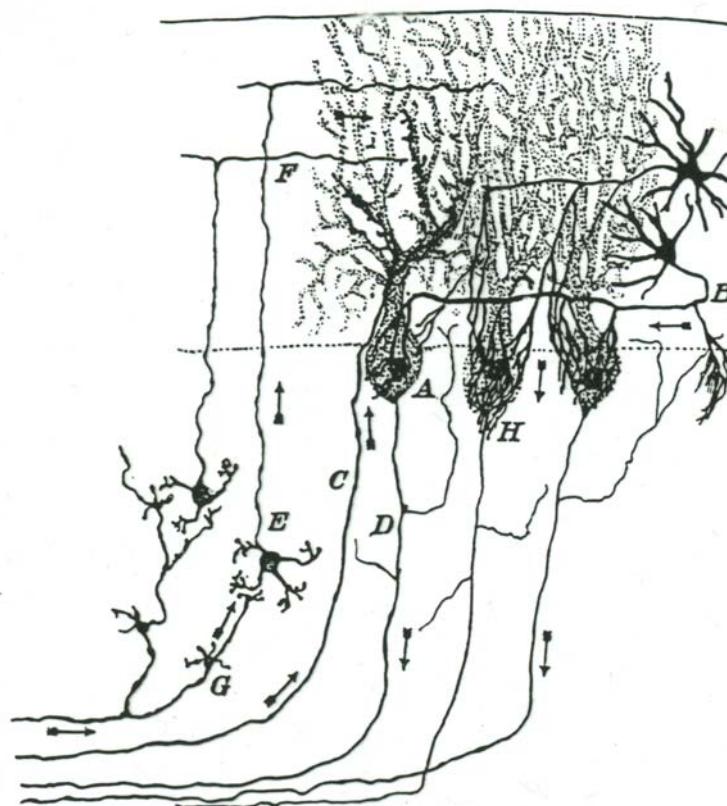
A



B



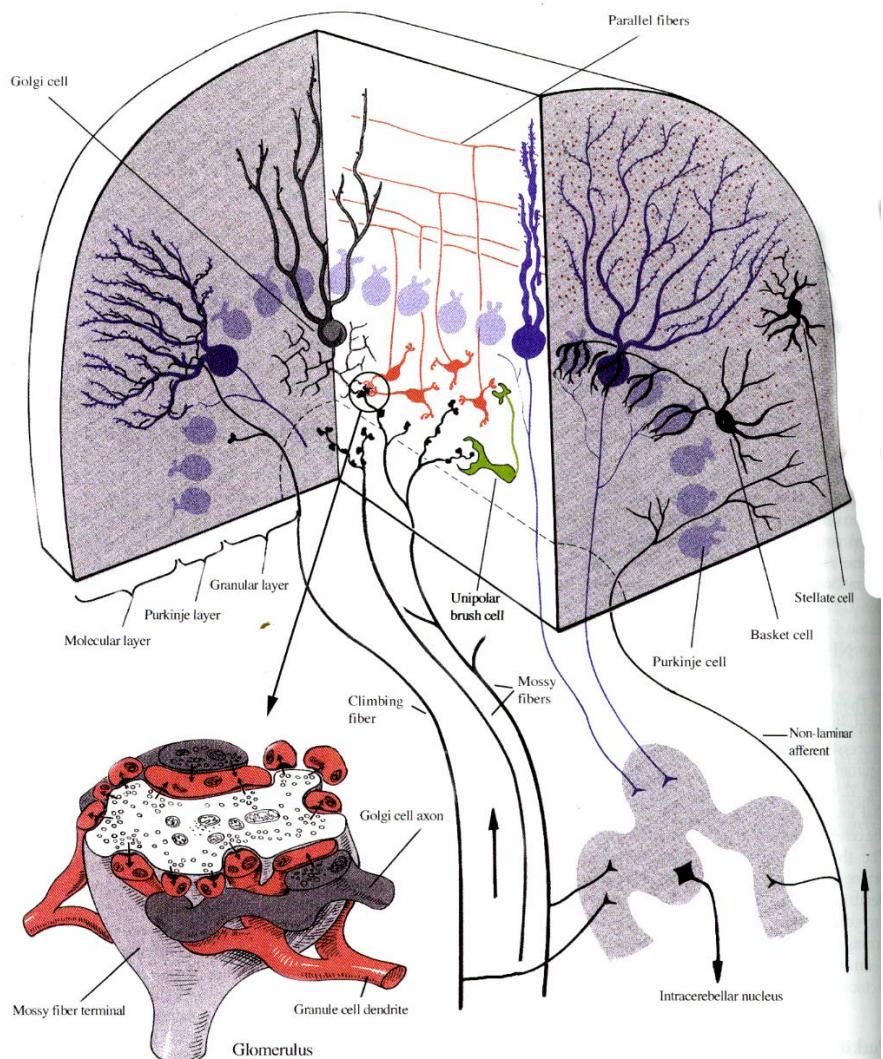
C



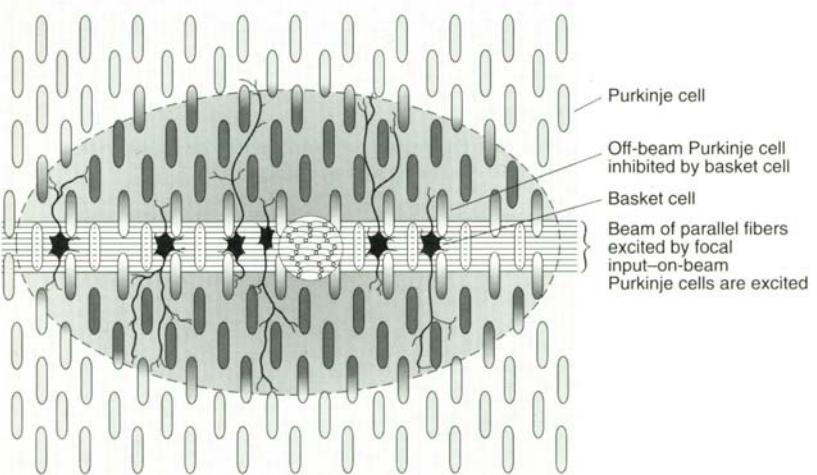
A: Semidiagrammatic transverse section through a mammalian cerebellar folium. A: molecular, B: granular zone; C: white matter. a=Purkinje cell; b=small stellate neuron; e=superficial stellate cell; f=large stellate cell; g= granule cell; h=mossy fiber; n=climbing fiber. **B:** Semidiagrammatic longitudinal section through a cerebellar folium **C:** Schema of the connections of Purkinje cells of the cerebellum (Cajal).

CEREBELLAR MICROCURCUITRY 2.

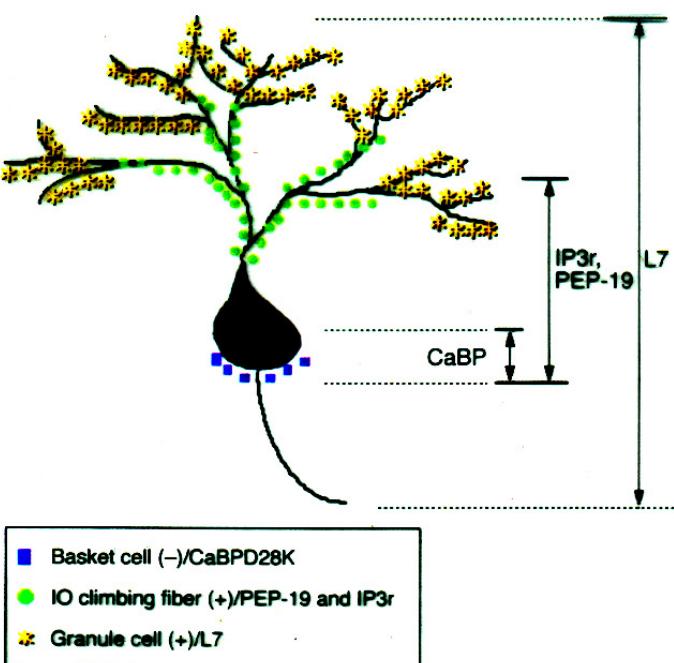
A



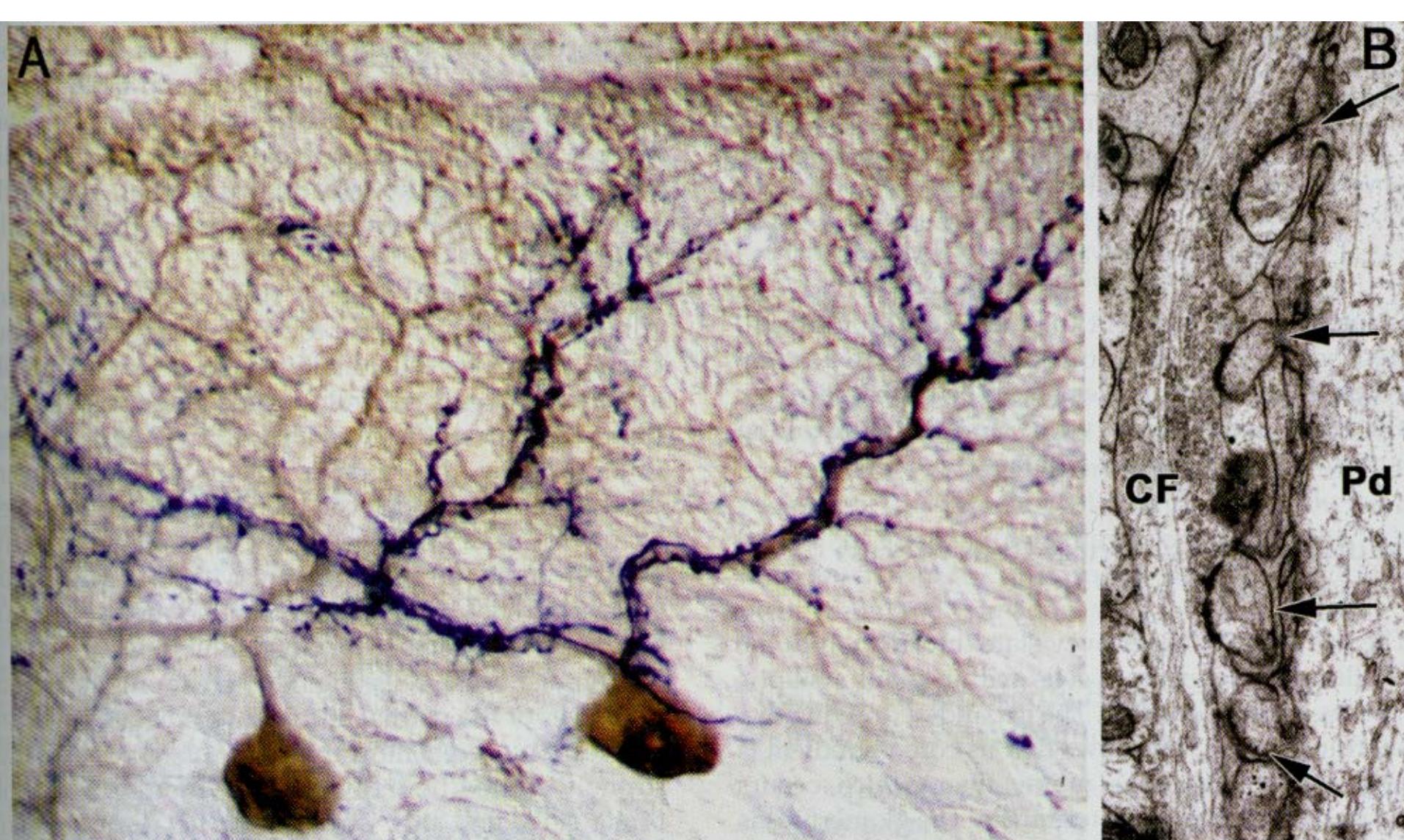
B



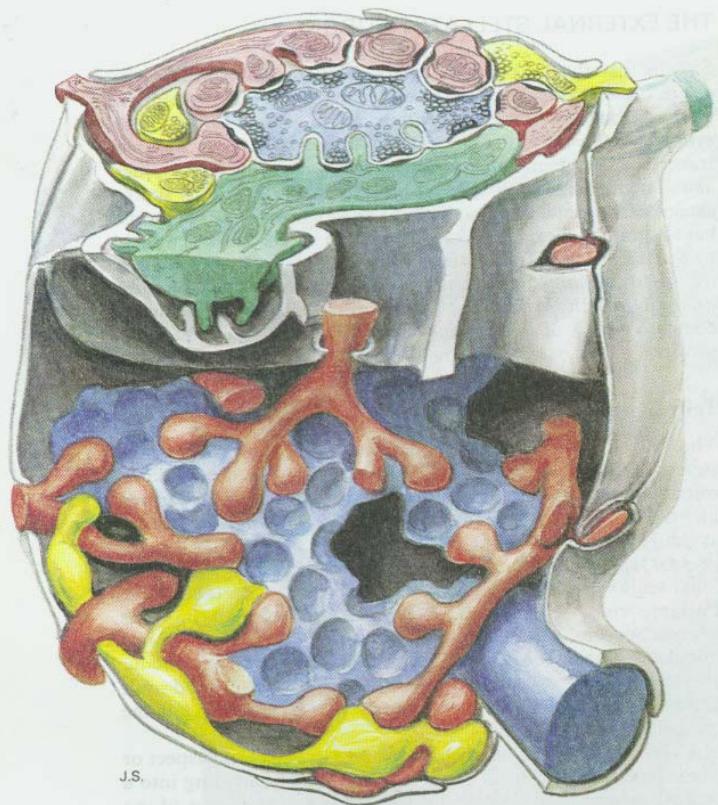
C



A: from Heimer. **B:** Excitation of a beam of parallel fibers by focal mossy fiber input leads to excitation of a central (on-beam) region of Purkinje cells and inhibition of surrounding (off-beam) Purkinje cells (via excitation of inhibitory basket cells, from Szentagothai). **C:** Diagram showing segregation of afferents on P-cell surface and correlation with subcellular domains defined by mRNA distributions. (Oberdick et al).

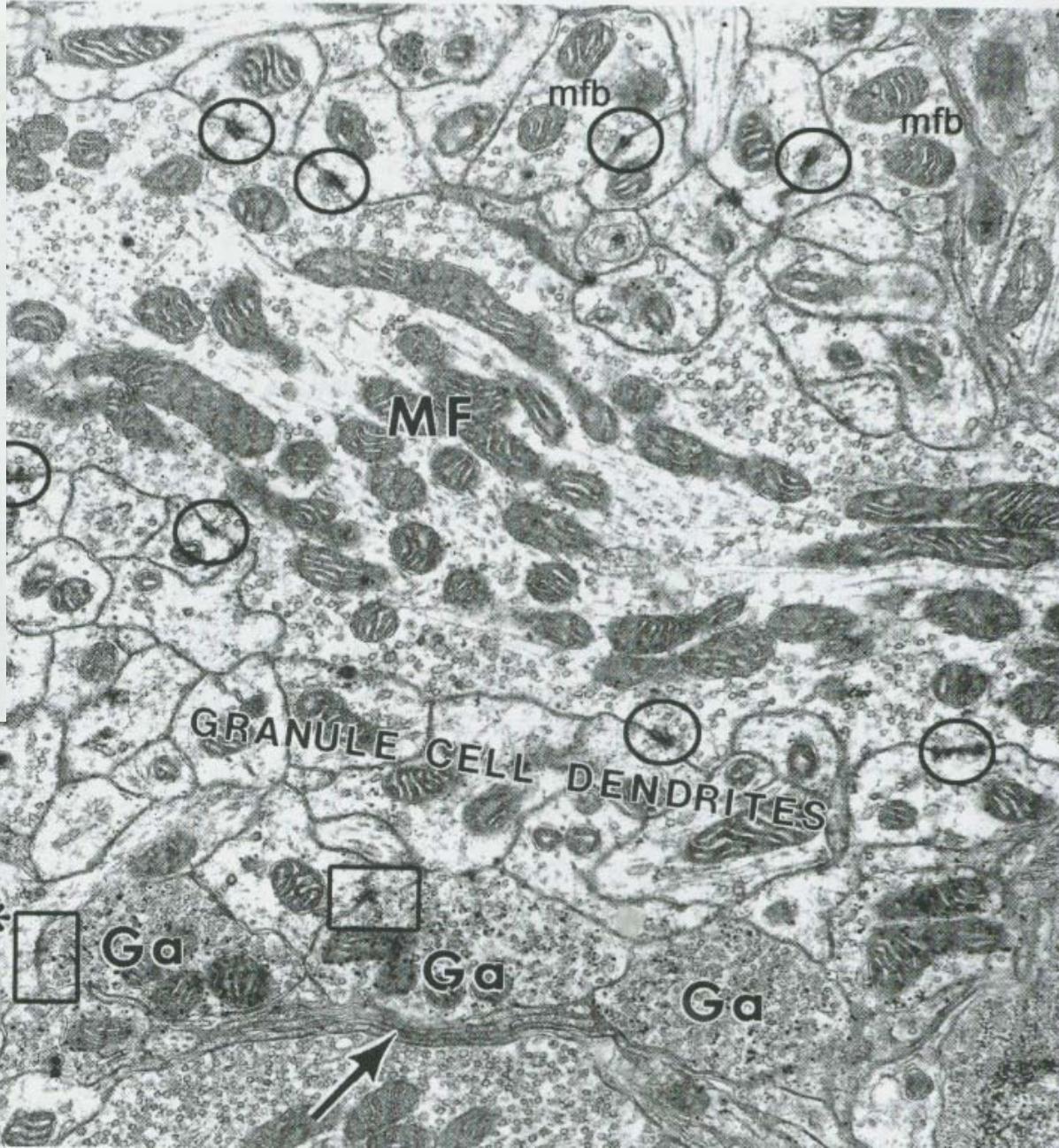


Climbing fibers (labeled with lectin, Rossi et al, 1993). CF-P synapse. A CF varicosity (CF) in synaptic contact with spines of a proximal dendritic domain (Mugnaini)



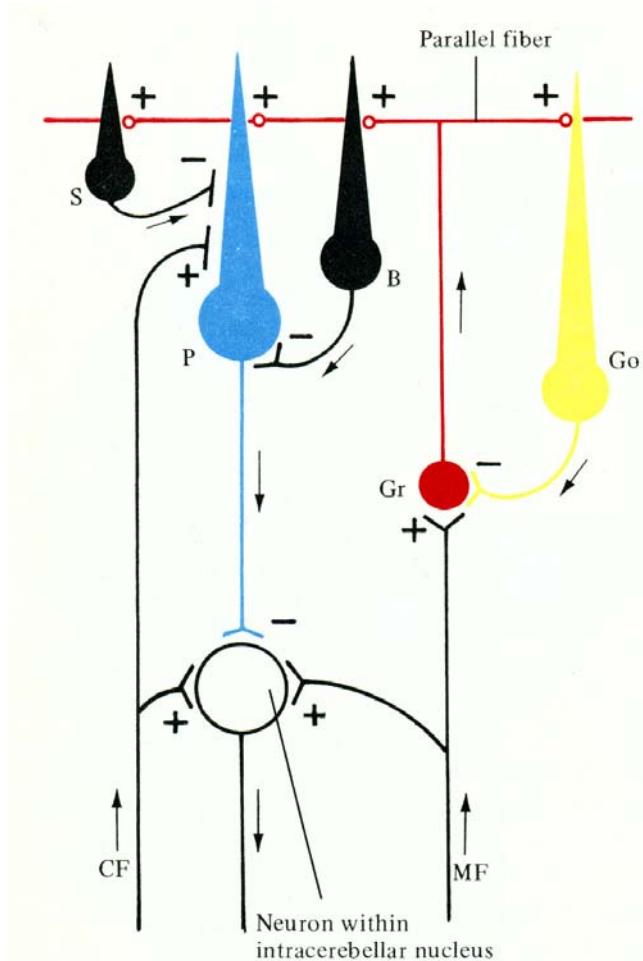
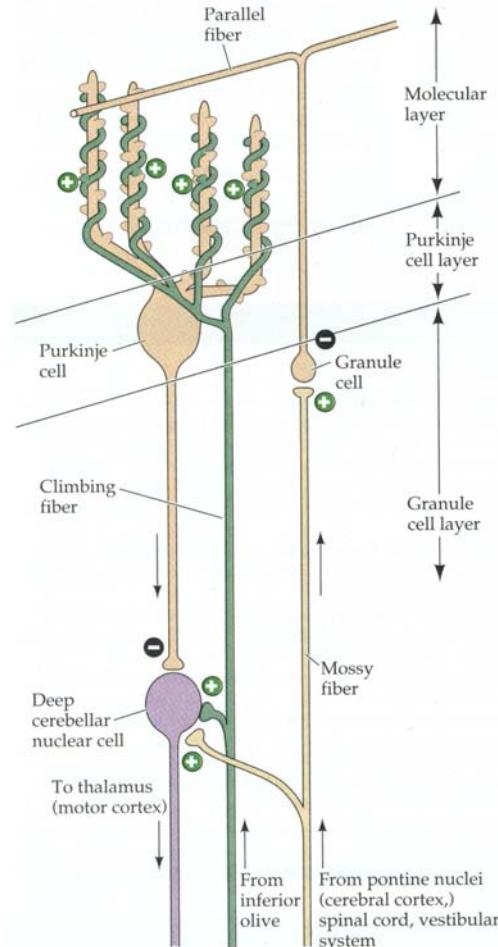
Blue:mossy fiber;
yellow: Golgi axon;
yellow Go dendrite

(Eccles, Ito,
Szentagothai, 1967)



MF-mossy; Ga-golgi axon (labeled with immunogold method for GABA)
Mugnaini, from Heimer 1995

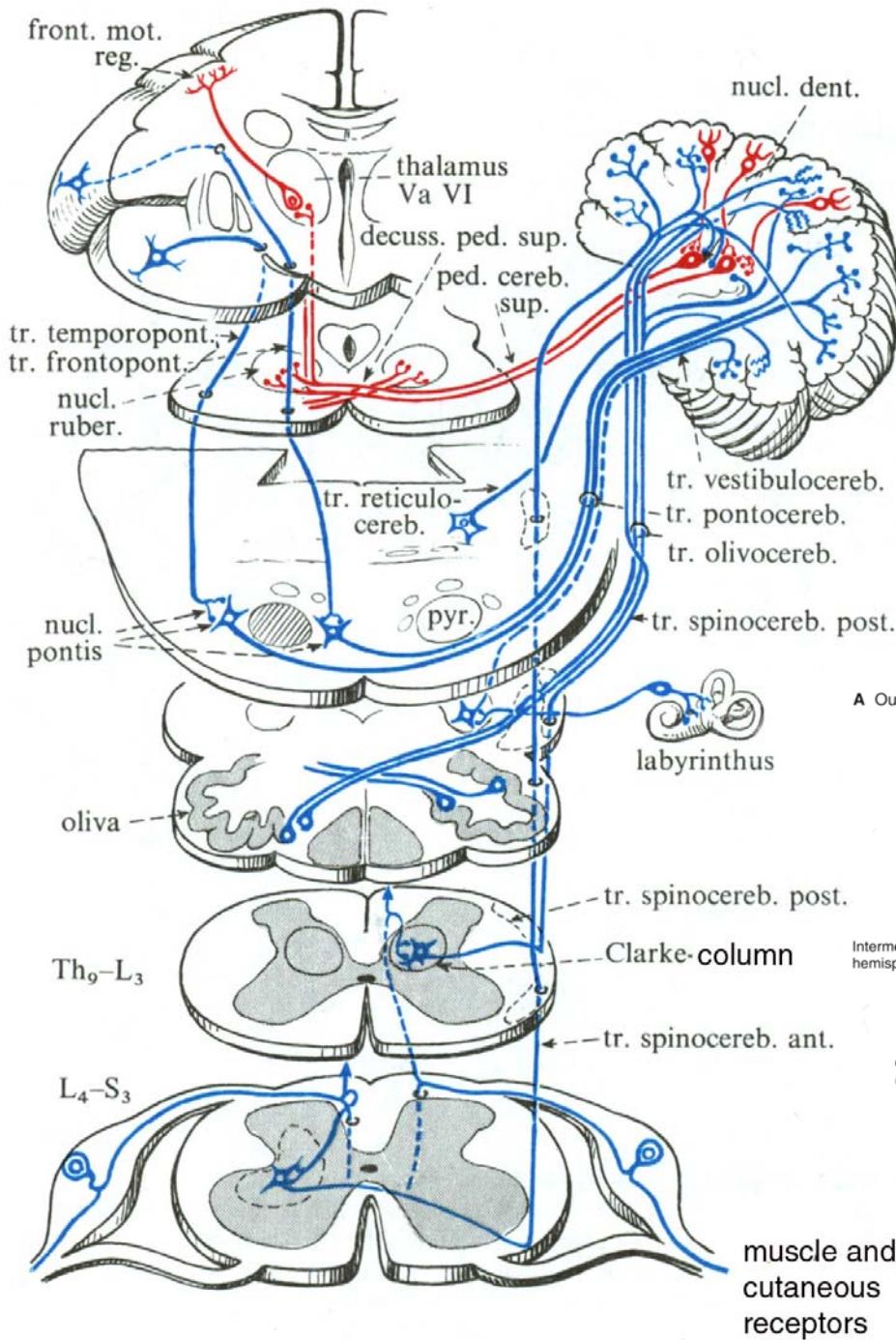
CEREBELLAR MICROCURCUITRY 3.



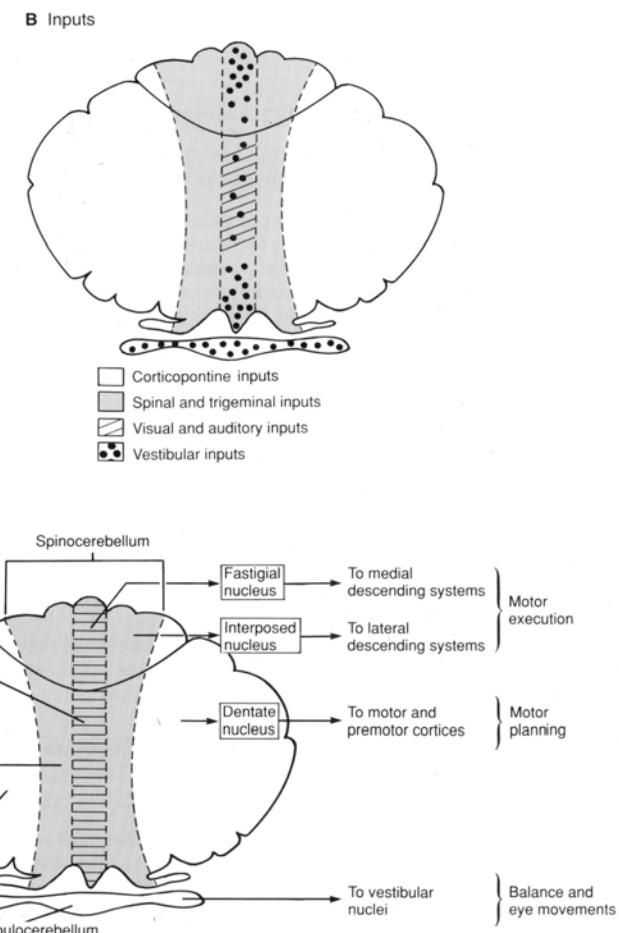
Excitatory and inhibitory connections in the cerebellar cortex and deep cerebellar nuclei (Left: from Purves, right scheme from Heimer). Purkinje cells and neurons in deep cerebellar nuclei receive excitatory input from climbing and mossy fibers. Additional convergent input onto P cells from local interneurons (basket, Golgi, stellate neurons) establishes a basis for the comparison of ongoing movement and sensory feedback derived from it. The P cell output to deep cerebellar nuclei thus generates an error correction signal that can modify movements already begun.

TABLE 41–1. Principal Input and Output Pathways of the Cerebellum

Functional region	Anatomical region	Principal input	Deep nucleus	Principal destination	Function
Vestibulocerebellum	Flocculonodular lobe	Vestibular labyrinth	Lateral vestibular	Medial systems: axial motor neurons	Axial control and vestibular reflexes
Spinocerebellum	Vermis	Vestibular labyrinth, proximal body parts; facial, visual, and auditory inputs to posterior lobe only	Fastigial	Medial systems: vestibular nucleus, reticular formation, and motor cortex	Axial and proximal motor control; ongoing execution of movement
Spinocerebellum	Intermediate part of hemisphere	Spinal afferents (distal body parts)	Interposed	Lateral systems: red nucleus (magnocellular part) and distal regions of motor cortex	Distal motor control; ongoing execution
Cerebrocerebellum	Lateral part of hemisphere	Cortical afferents	Dentate	Integration areas: red nucleus (parvocellular part) and premotor cortex (area 6)	Initiation, planning, and timing

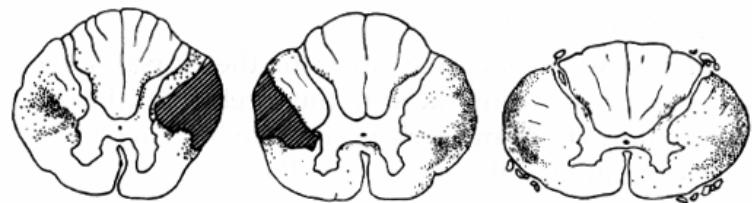
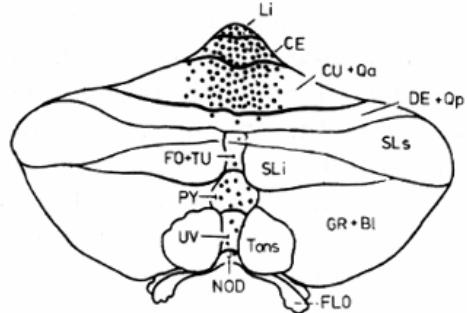
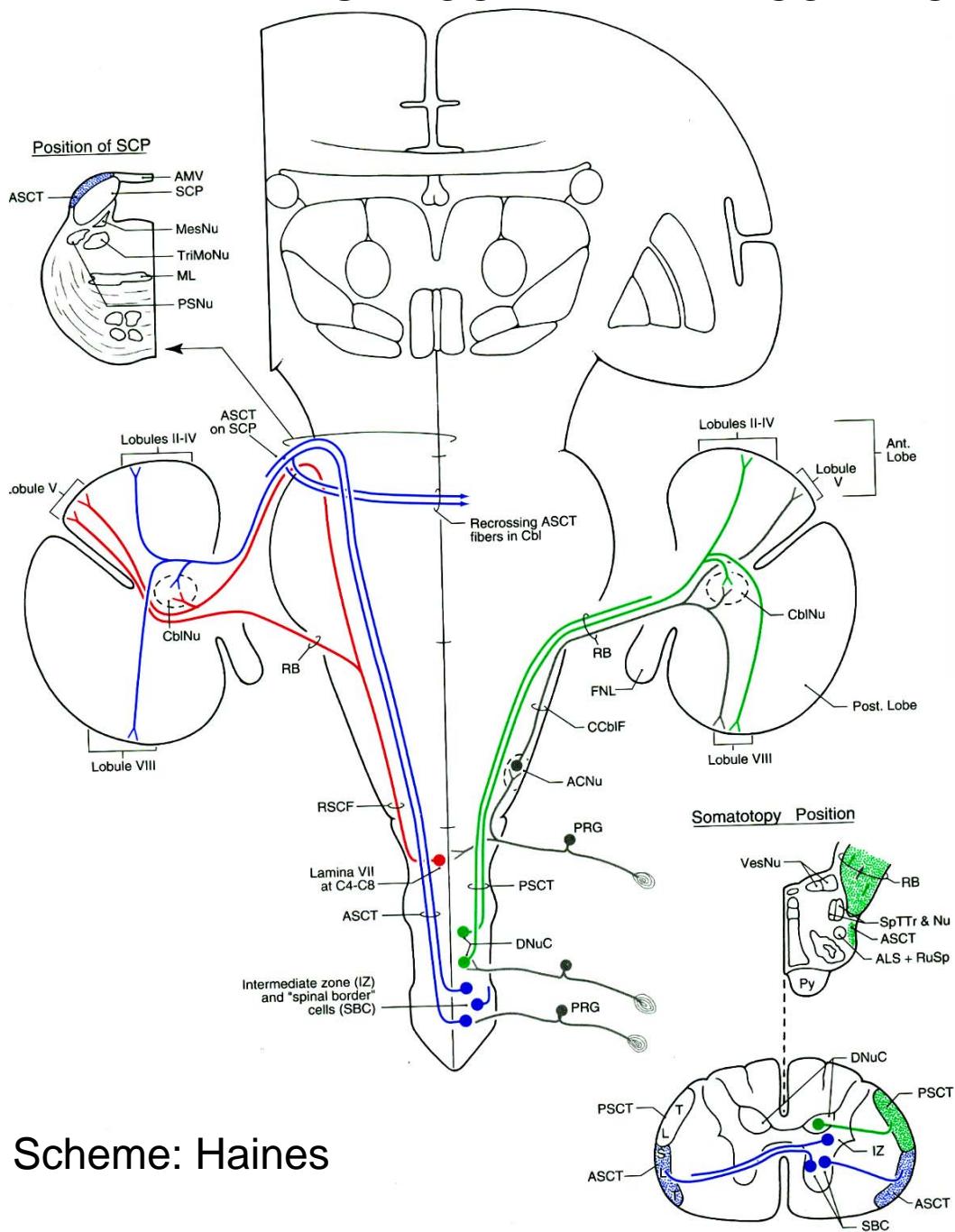


Left: Cerebellar afferents (blue) and efferents from the dentate nucleus (red). (Szentagothai).



Summary diagram of afferent (B) and efferent (A) connections of the cerebellar cortex (Kendel and Schwartz)

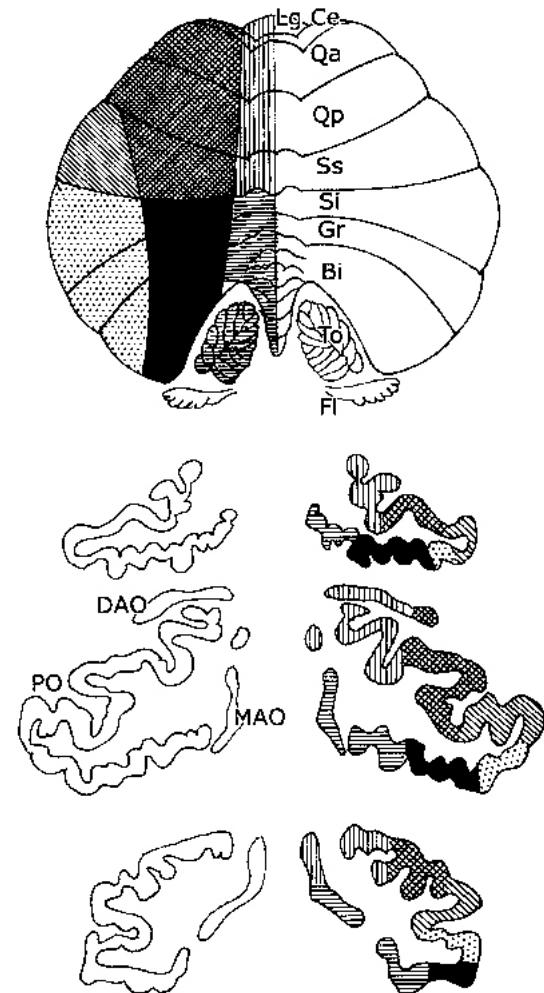
SPINOCEREBELLAR CONNECTIONS



Termination of spinocerebellar fibers in the human cerebellum using the Marchi method after cordotomy at T4-5. From Brodal and Jansen, 1941.

Scheme: Haines

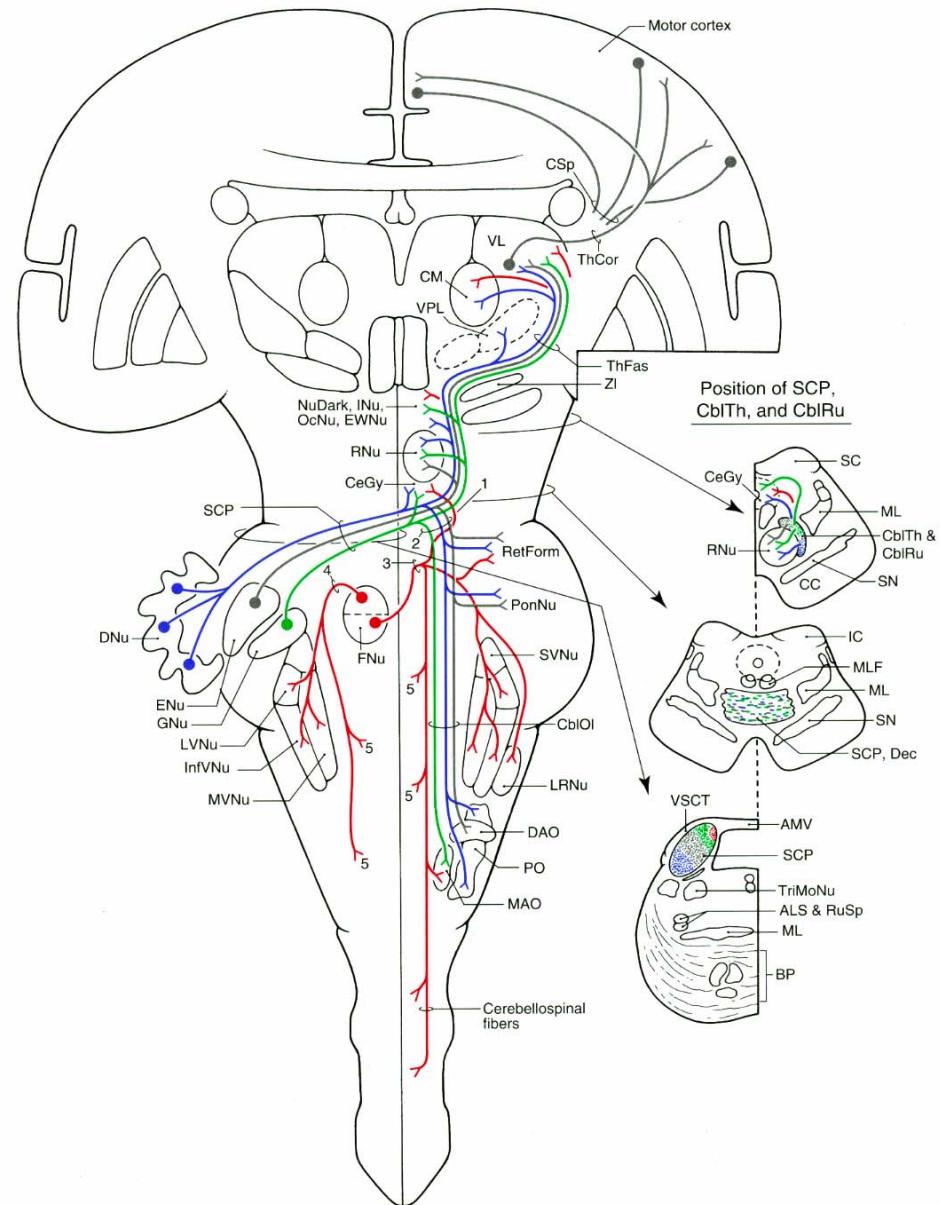
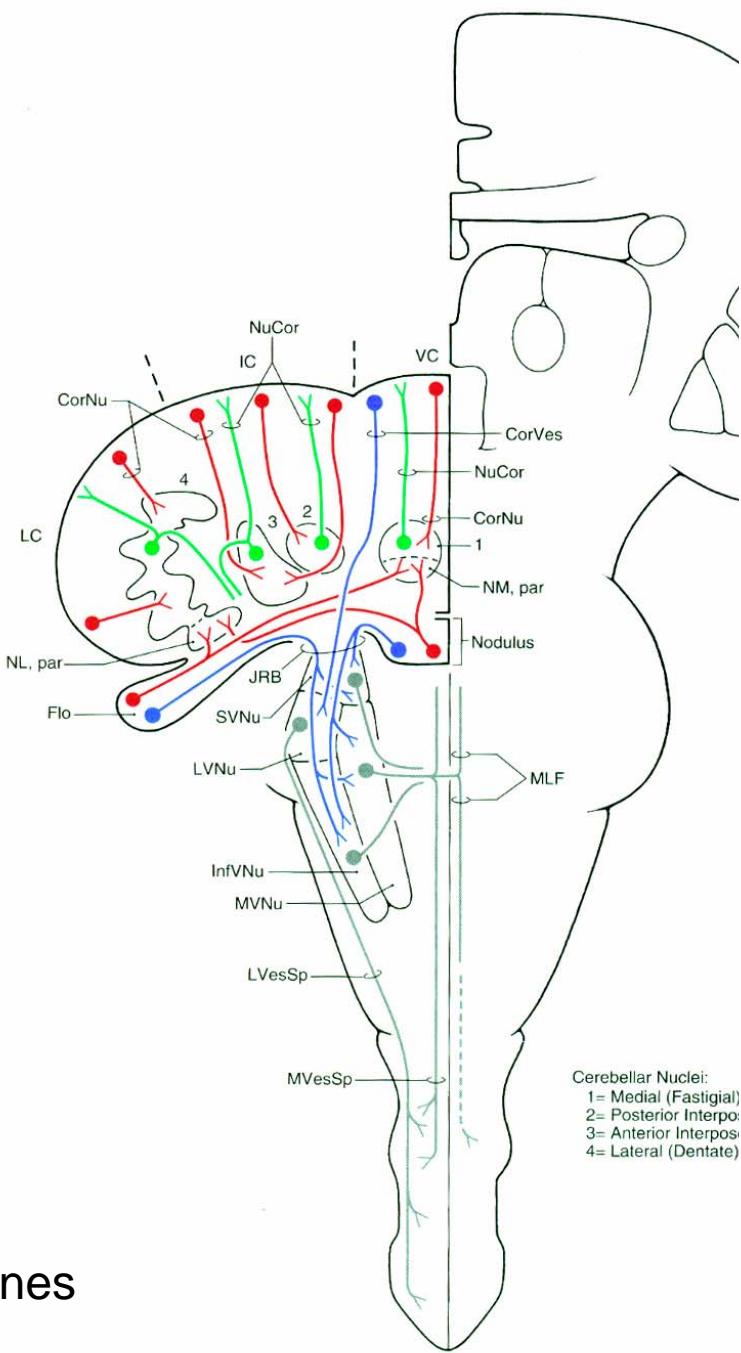
CLIMBING FIBERS ARE ORGANIZED IN PARASAGITTAL ZONES OLIVOCEREBELLAR CONNECTIONS



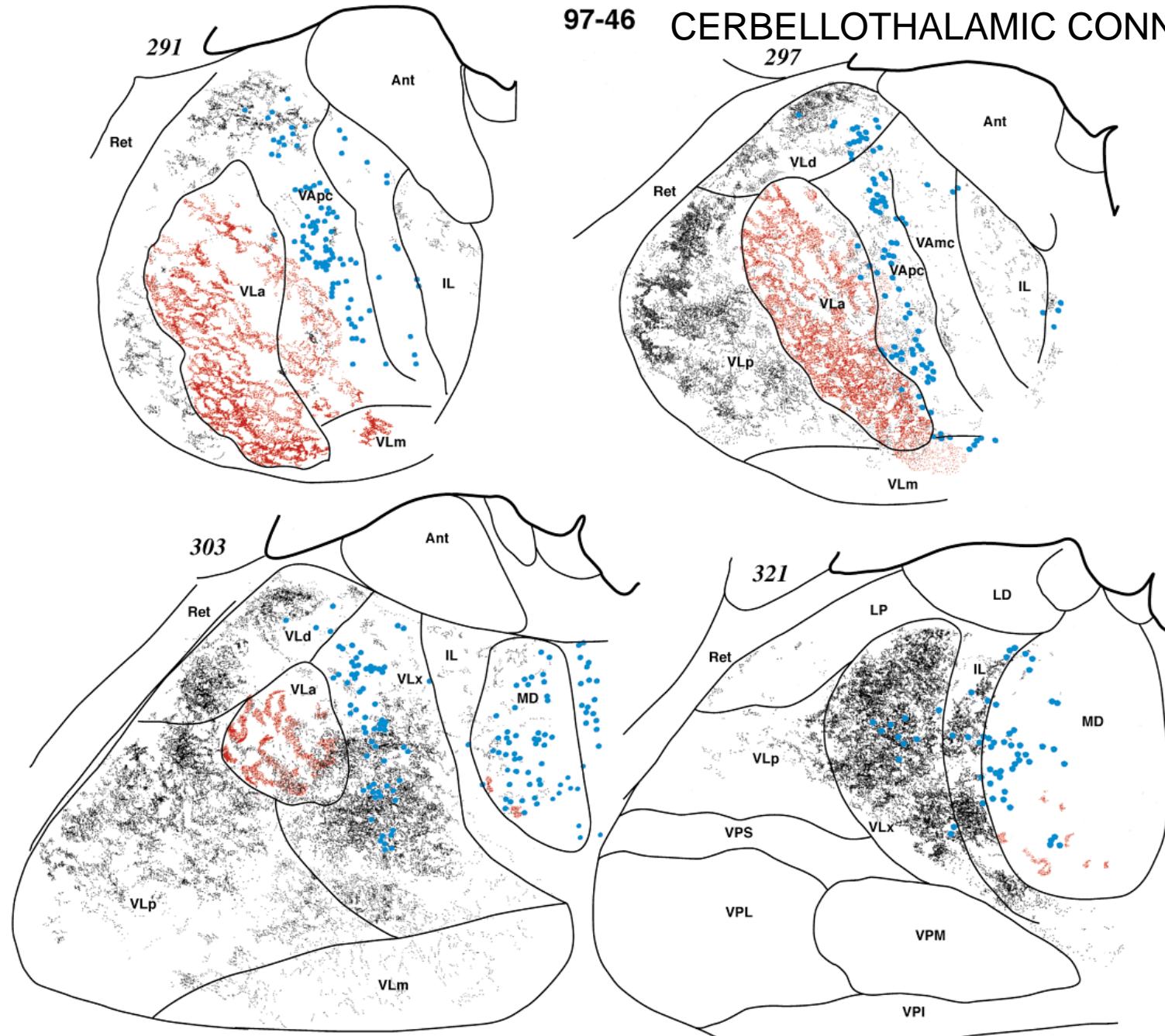
DA= dorsal accessory olive, PO-principal olive;
MA)-medial accessory olive

From Holmes and Stewart, 1908

CEREBELLAR EFFERENTS .



97-46 CERBELLOTHALAMIC CONNECTIONS 1.



Line drawing of coronal sections through the thalamus showing the distribution of pallidothalamic and cerebellothalamic anterograde label and the location of the pre-SMA projection neurons in case 97-46. Note the overlap of pallidal input with pre-SMA projecting neurons at the VApC/VLa border (section 297) and cerebellar input with such neurons in VLx, VLd, and IL (sections 297-321)

From Sakai et al., 2000.

CEREBELLOTHALAMIC CONENCTIONS 2.

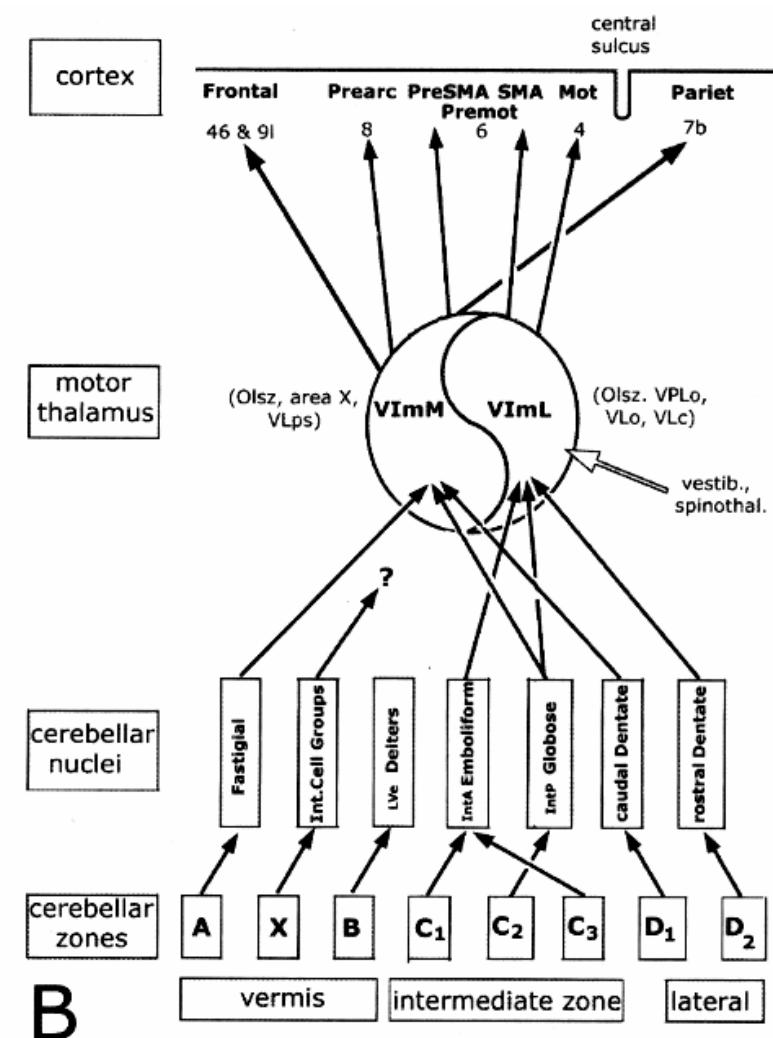
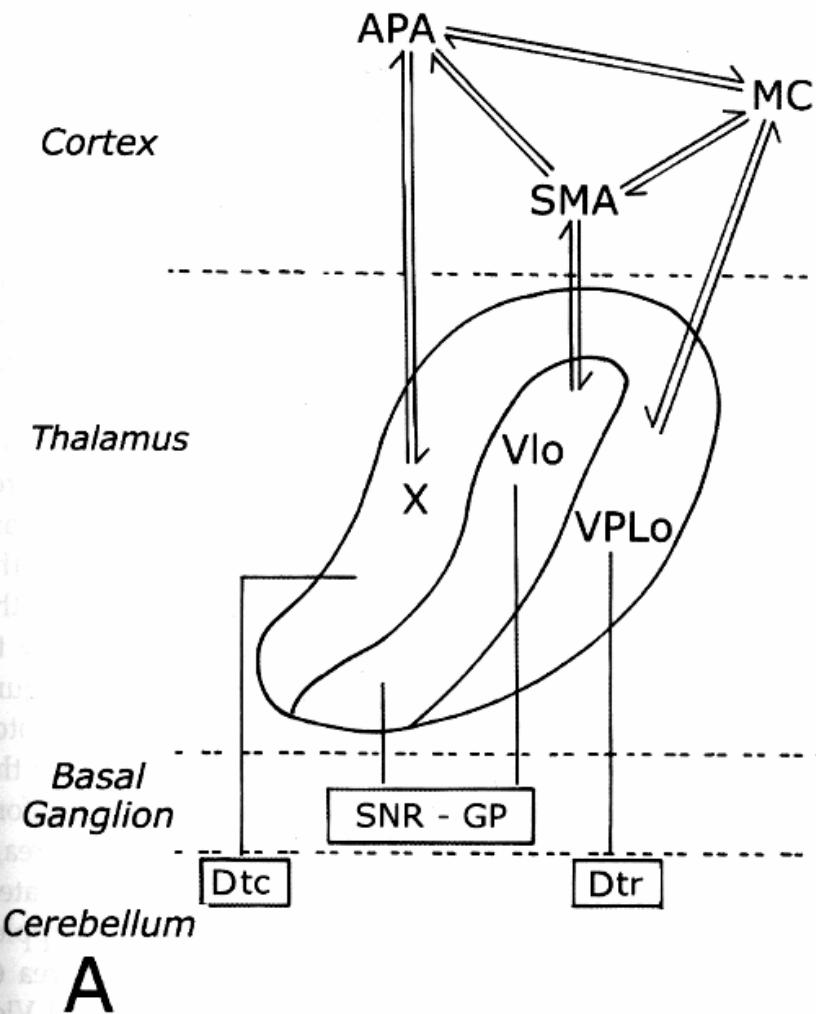


Diagram showing the connections of the basal ganglia and the crebellar nuclei with the motor cortex (MC), the supplementary motor cortex (SMA) and the anterior premotor area and their relay nuclei in the thalamus.
 A: Schell and Strick, 1984; B: Voogd, 2004

CEREBELLOTHALAMIC CONNECTIONS 3

For comparison see the lemniscal
and basal ganglia connections via the
thalamus

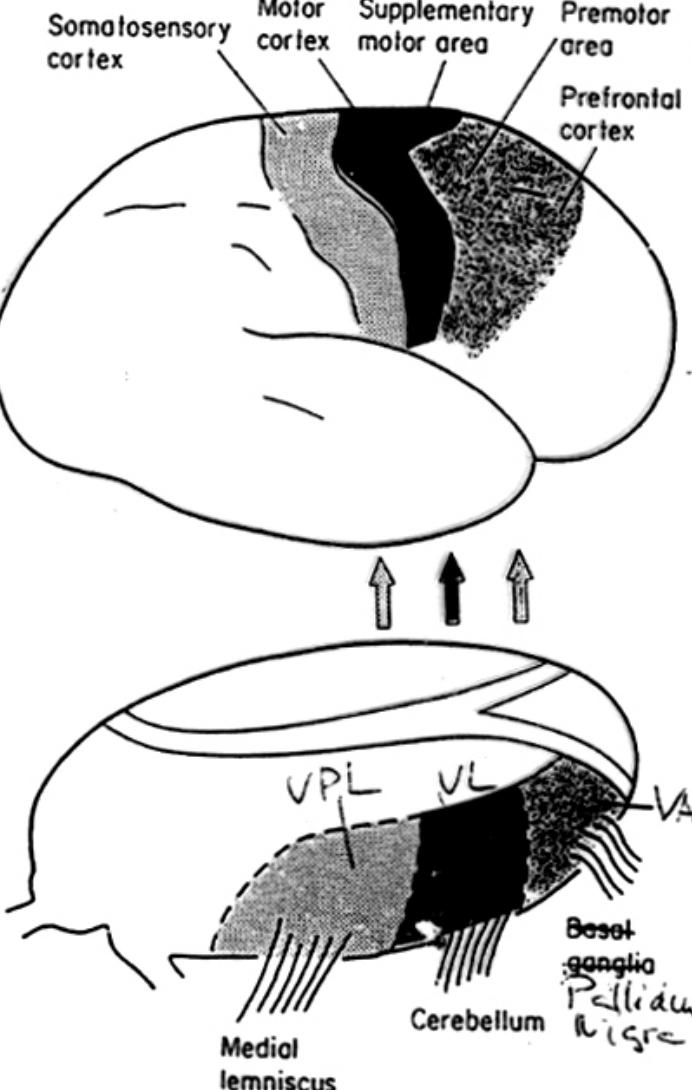


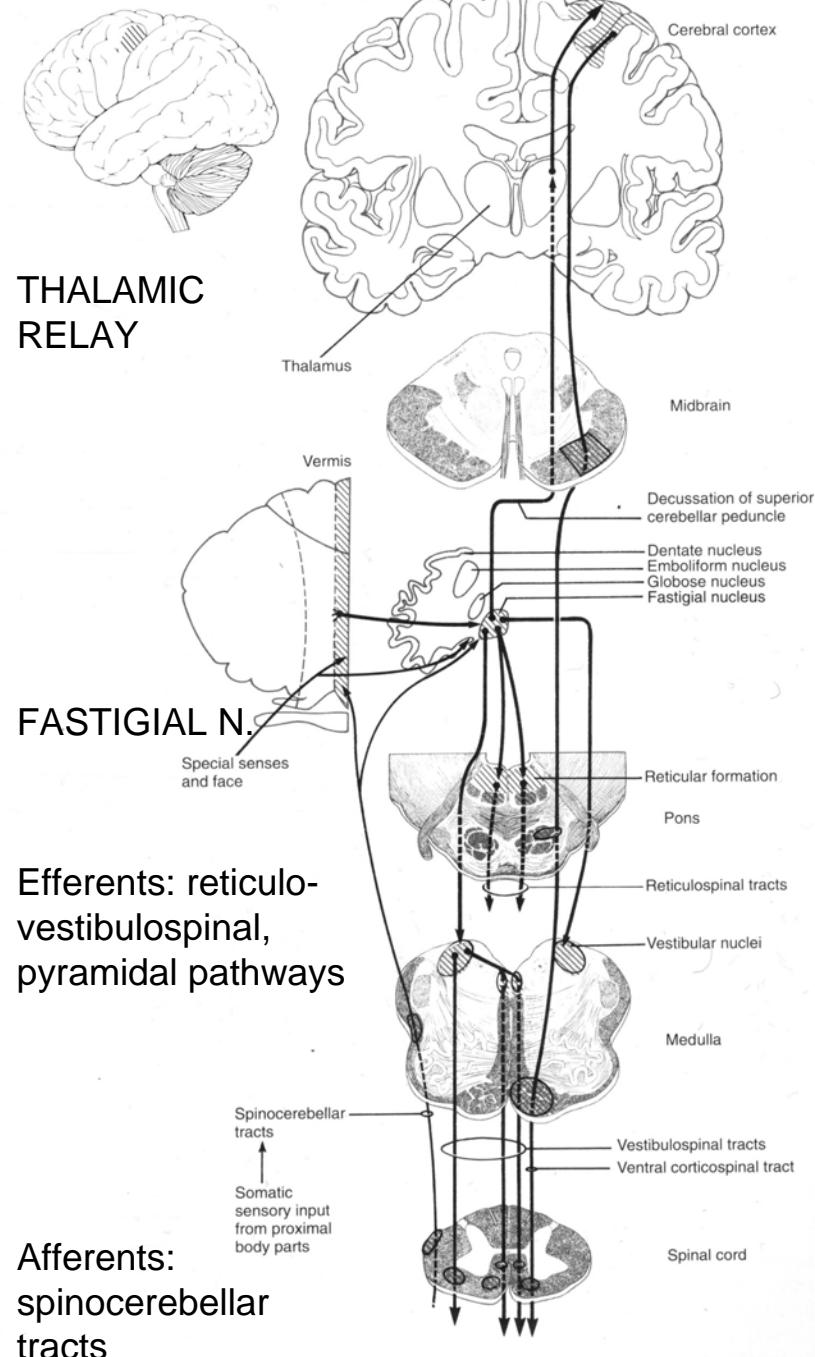
Fig. 11.14. Thalamocortical connections. Schematic presentation of the arrangement within the ventral thalamic nucleus of afferents from the somatosensory pathways, the cerebellum, and the basal ganglia and their further projections to the SI, MI, and the premotor cortex.

From Brodal

A Afferent and efferent connections of the vermis

SPINOCEREBELLUM

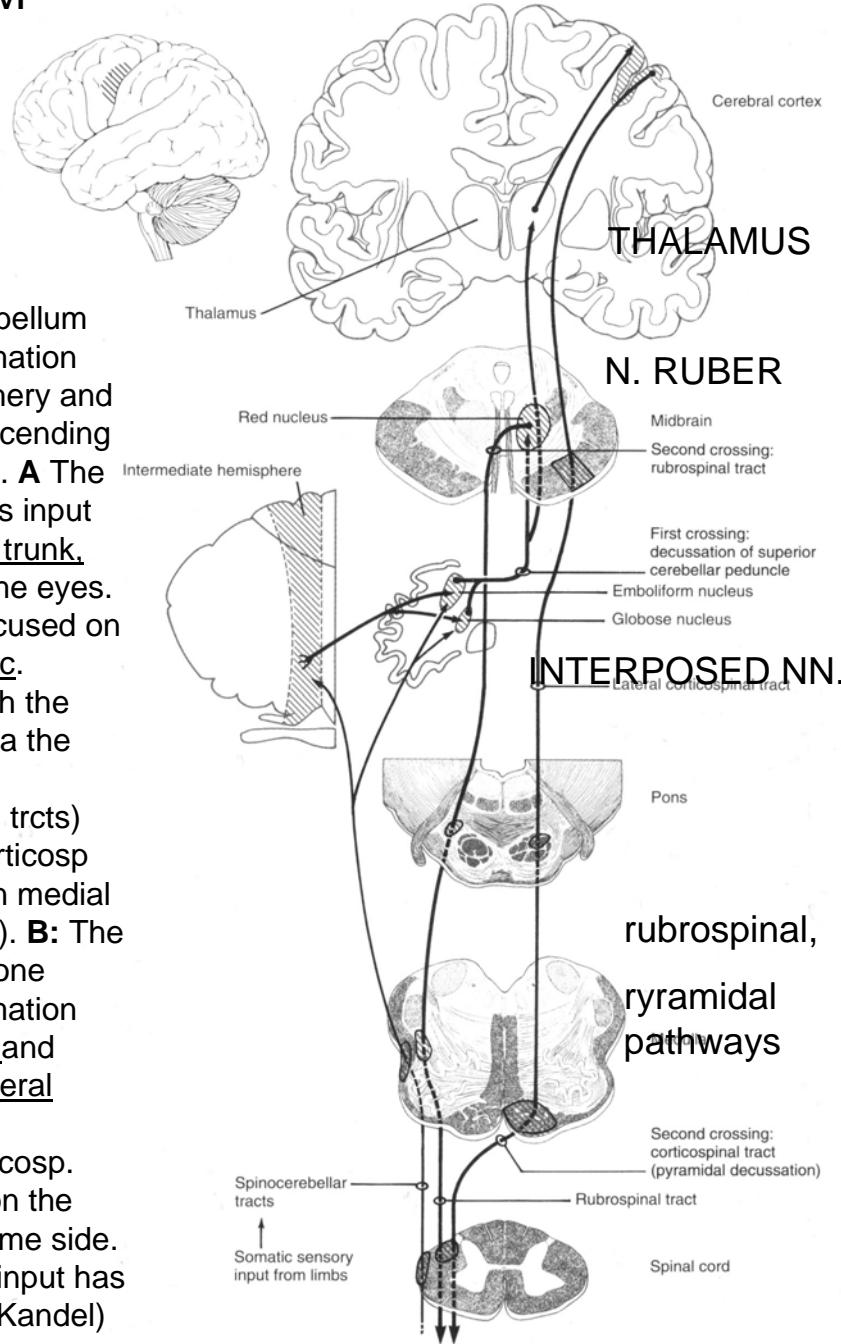
B Afferent and efferent connections of the intermediate hemisphere



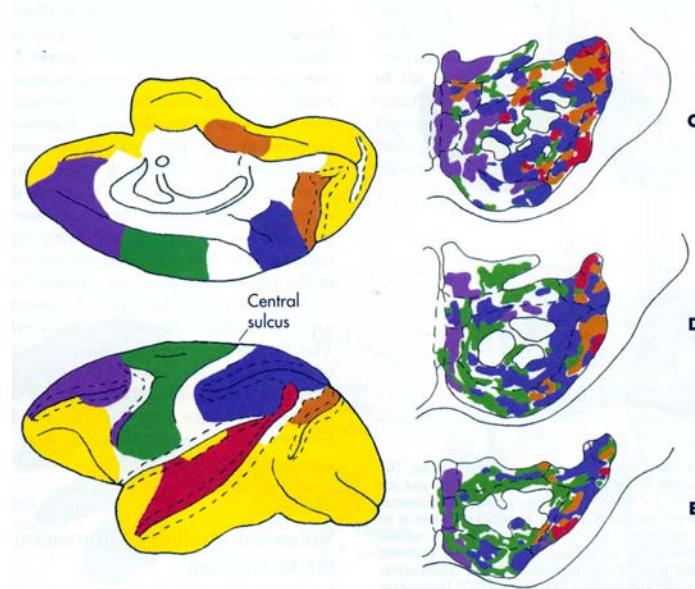
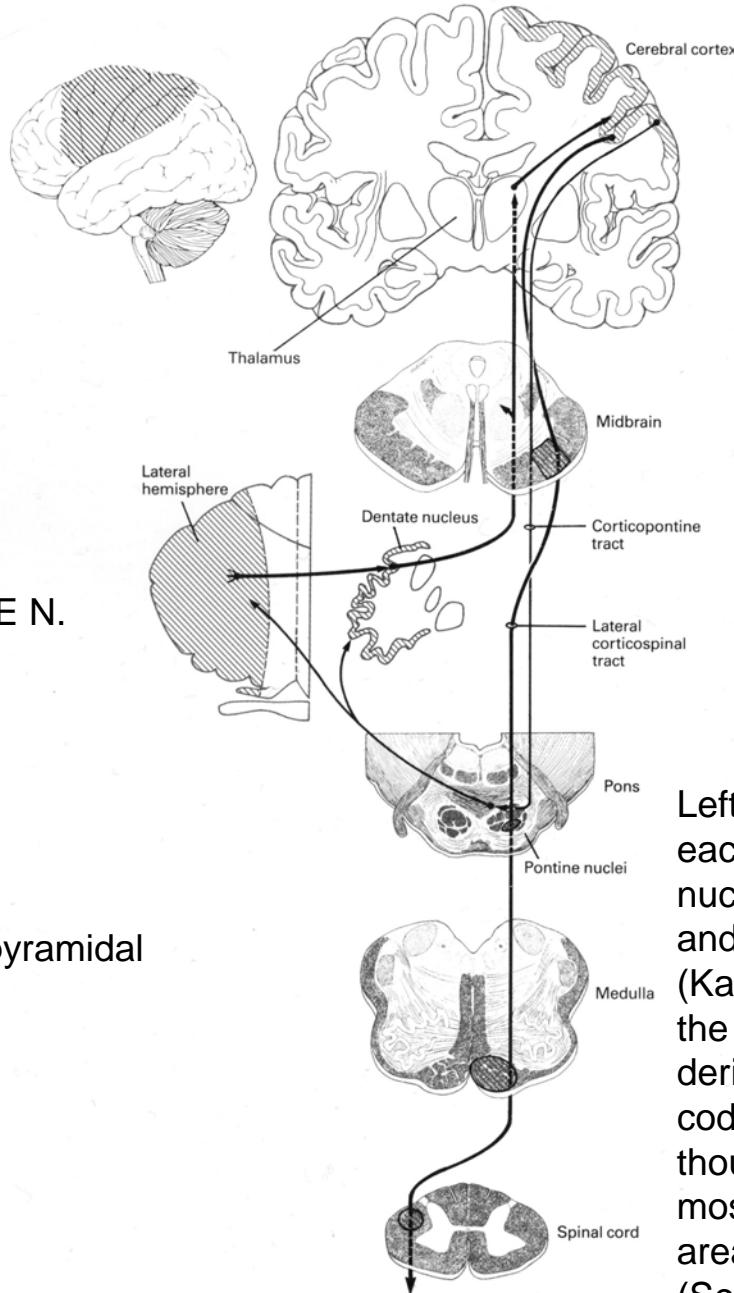
The spinocerebellum receives information from the periphery and projects to descending motor systems. **A** The vermis receives input from the neck, trunk, labyrinth and the eyes. Its output is focused on the medial desc. systems of both the brains stem (via the reticulo- and vestibulospinal trcts) and cortex (corticosp fibers acting on medial motor neurons). **B:** The intermediate zone receives information from the limbs and controls the lateral desc. systems (rubrosp., corticosp. tracts) acting on the limbs of the same side. Climbing fiber input has been omitted (Kandel)

Afferents:
spinocerebellar
tracts

Efferents: reticulo-
vestibulospinal,
pyramidal pathways

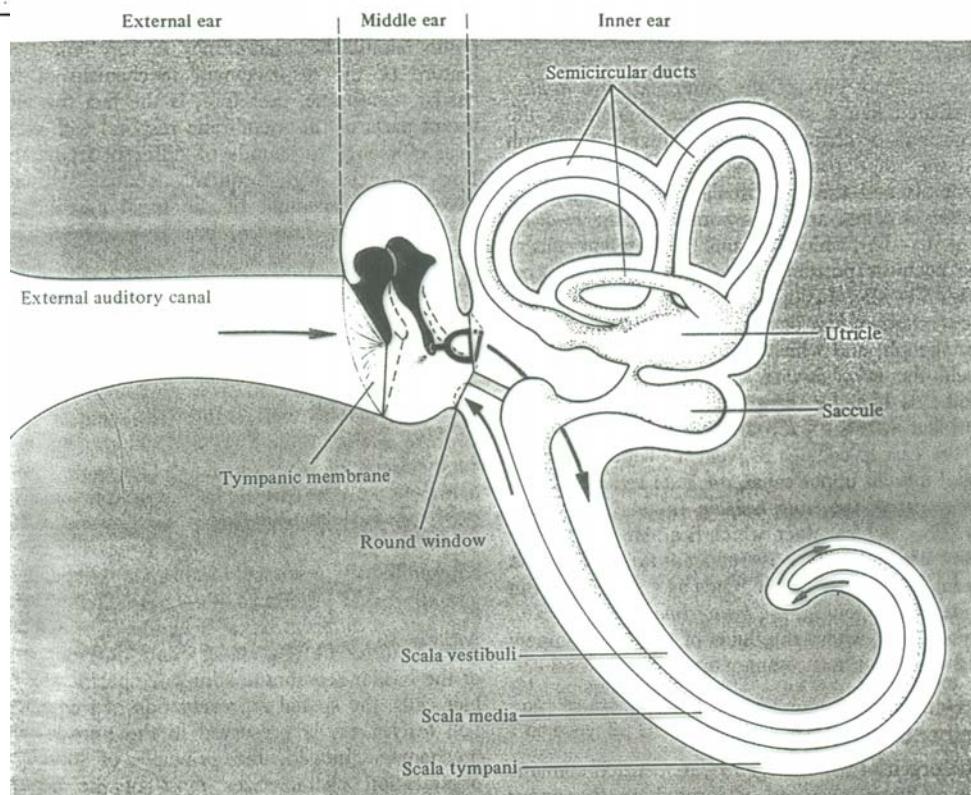
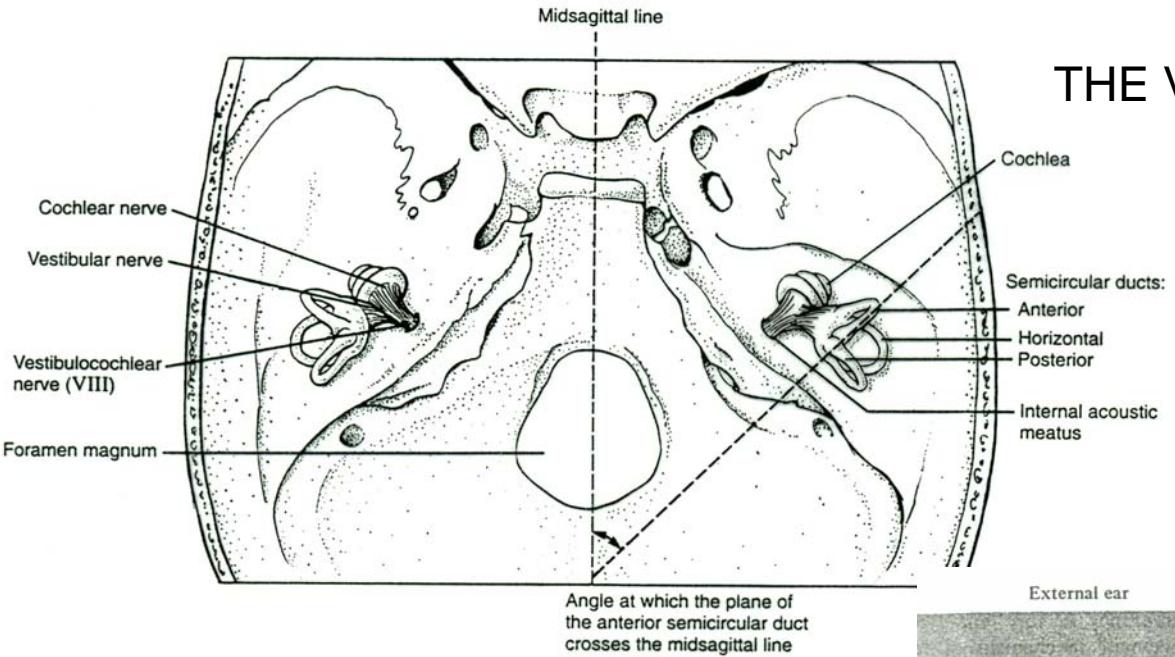


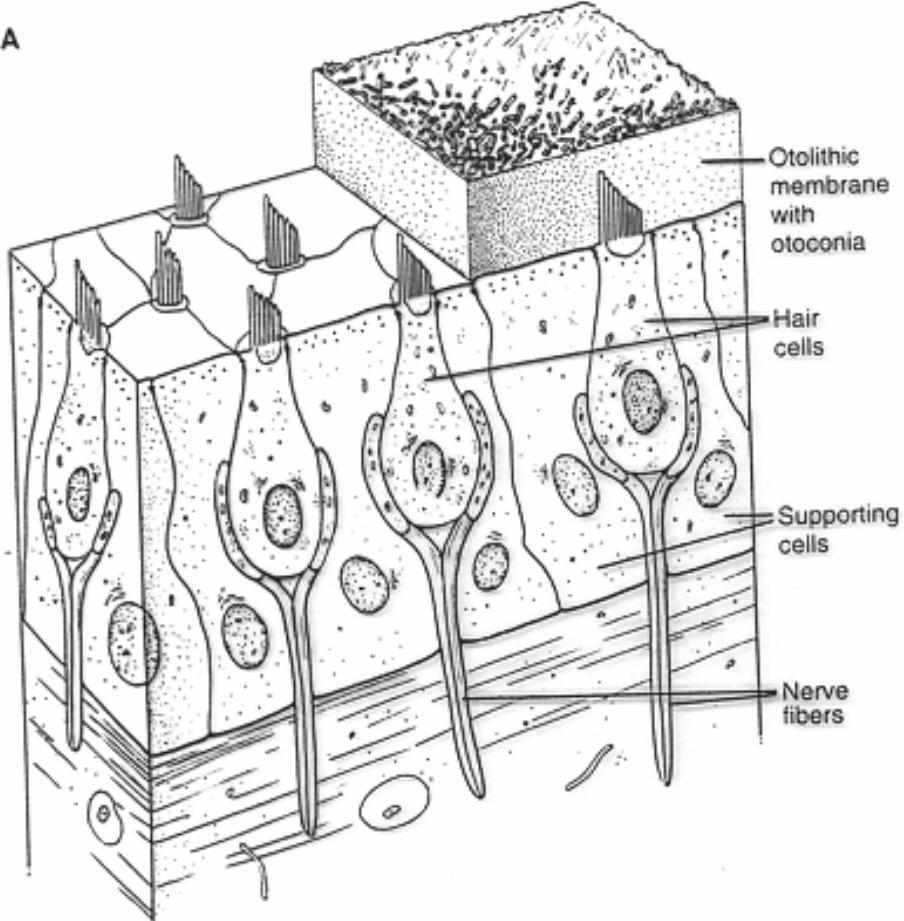
CEREBROCEREBELLUM



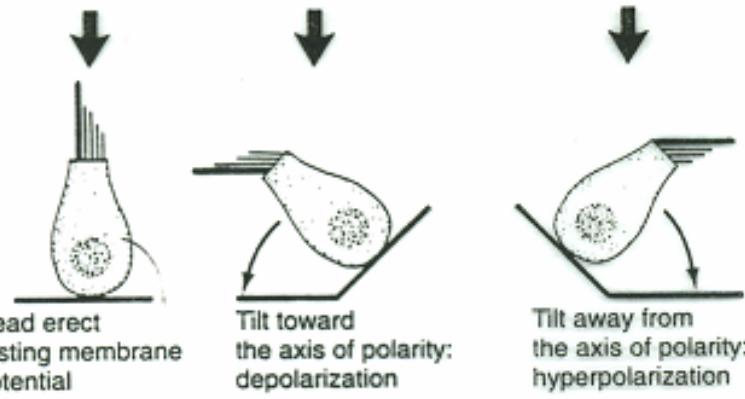
Left figure: The cerebrocerebellum (the lateral zone of each hemisphere) receives cortical input via the pontine nuclei (color inset from Nolte) and influences the motor and premotor cortices via the VA nucleus of the thalamus (Kandel). Right: Diagram illustrating the distribution within the basal pons of the rhesus monkey of projections derived from various cortical areas using the same color code. Cortical areas shown in yellow are not currently thought to have pontine projections. There is a complex mosaic of terminations in the pons, with each cerebral areas having preferential sites of pontine terminations (Schmahmann, Nolte).

THE VESTIBULAR APPARATUS

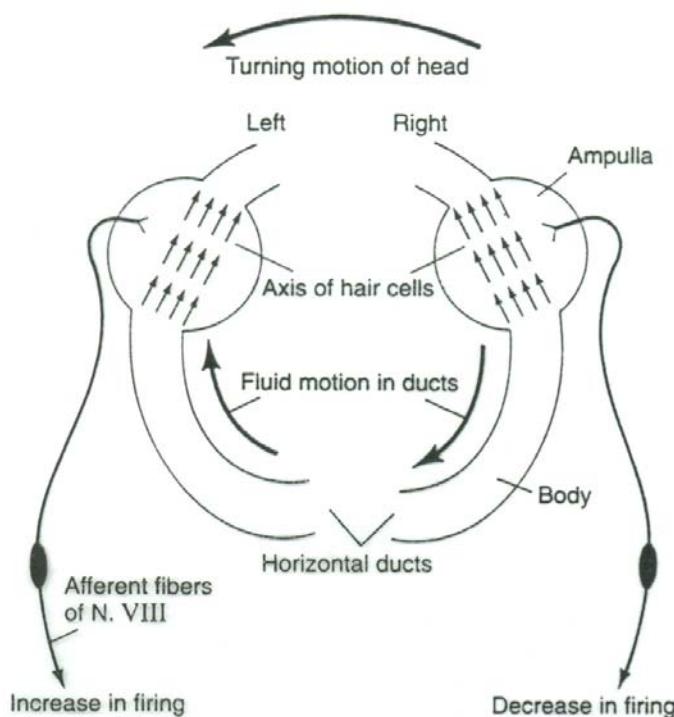


A**B**

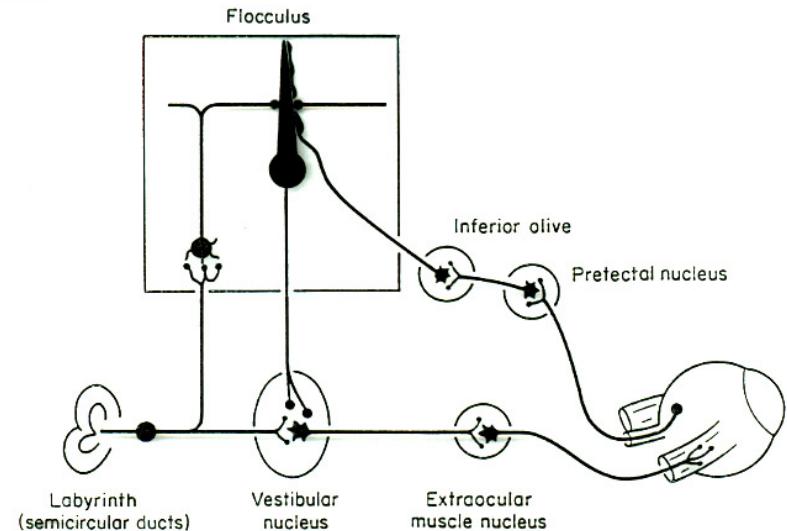
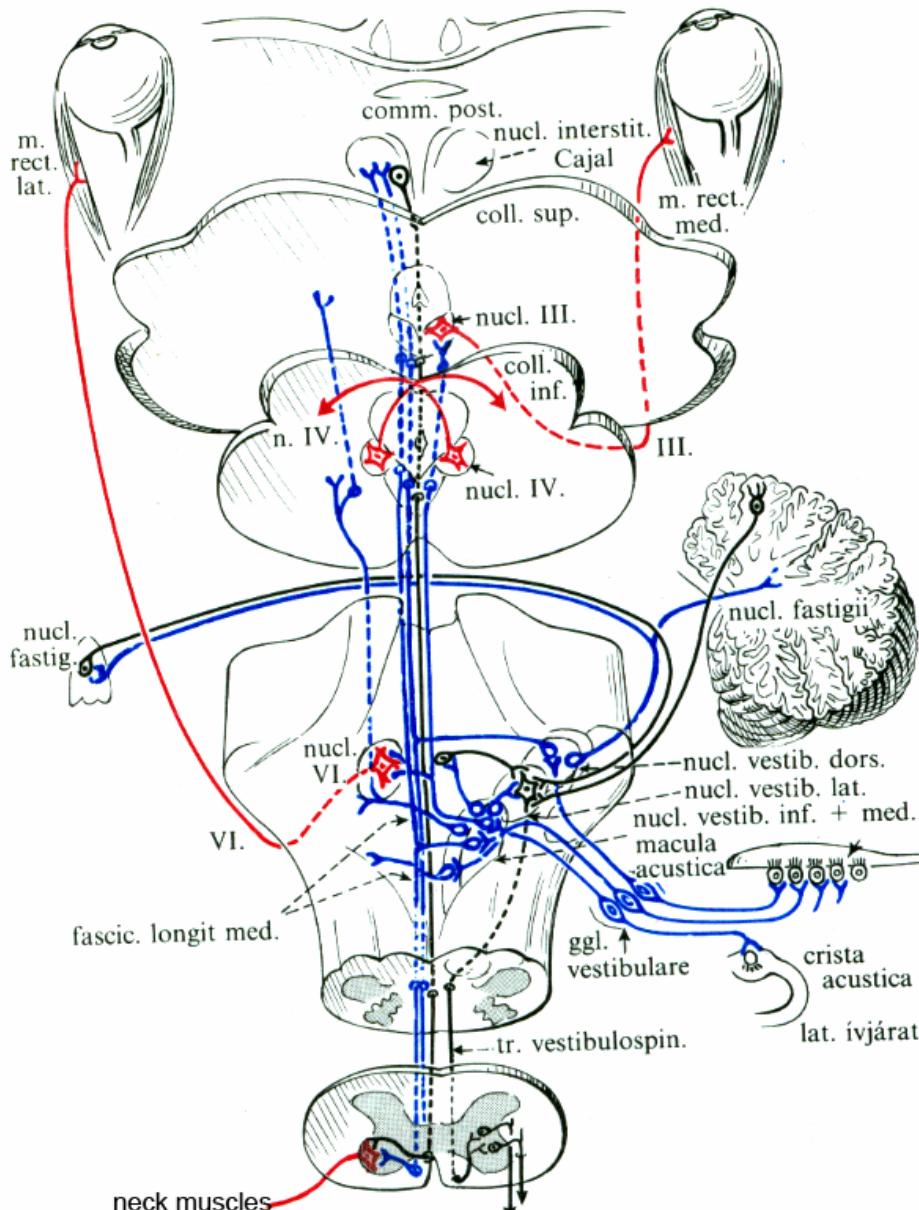
Gravitational force exerted by otoliths



Turning motion of head



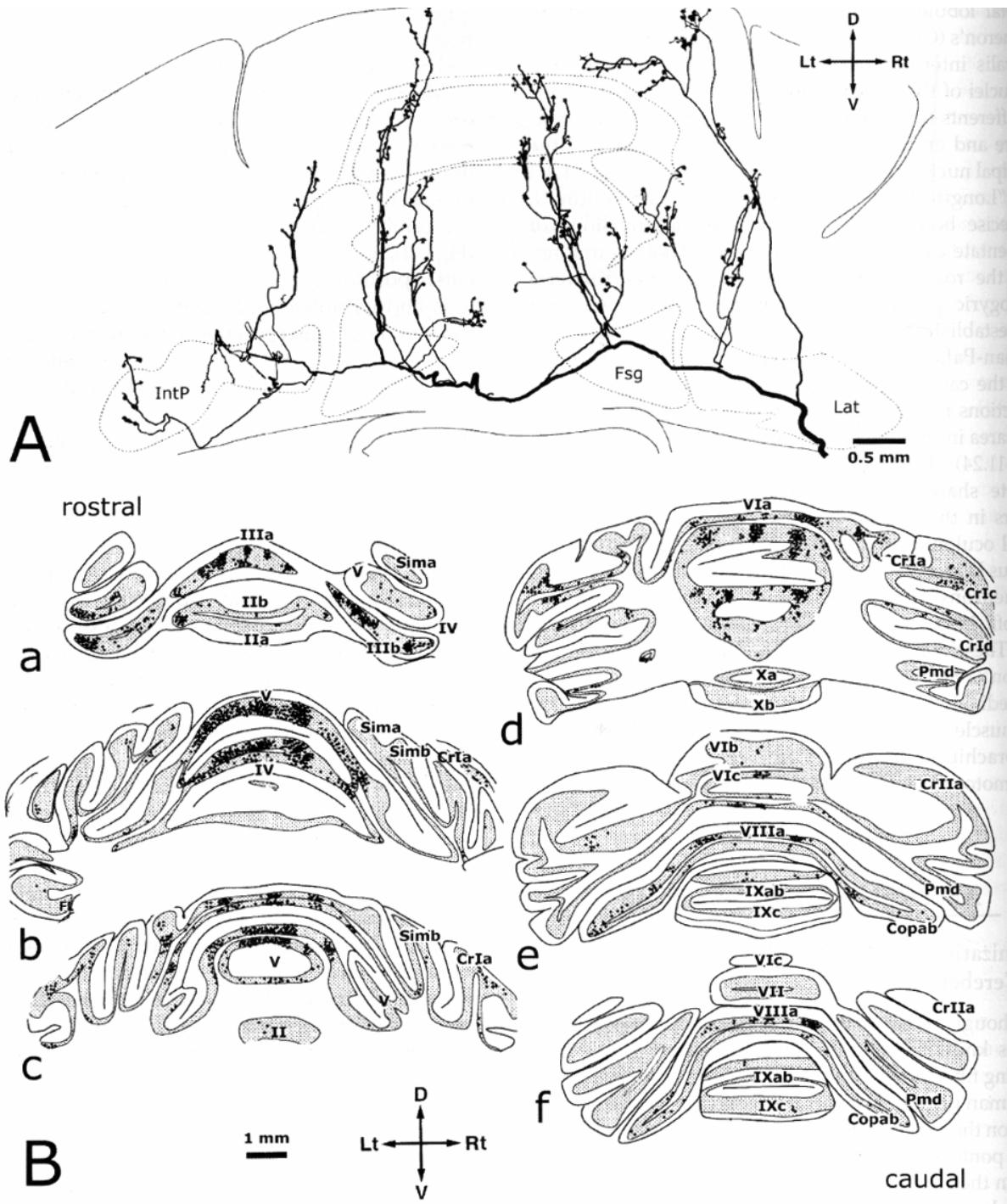
VESTIBULO-OCULAR /VESTIBULOSPINAL REFLEXES



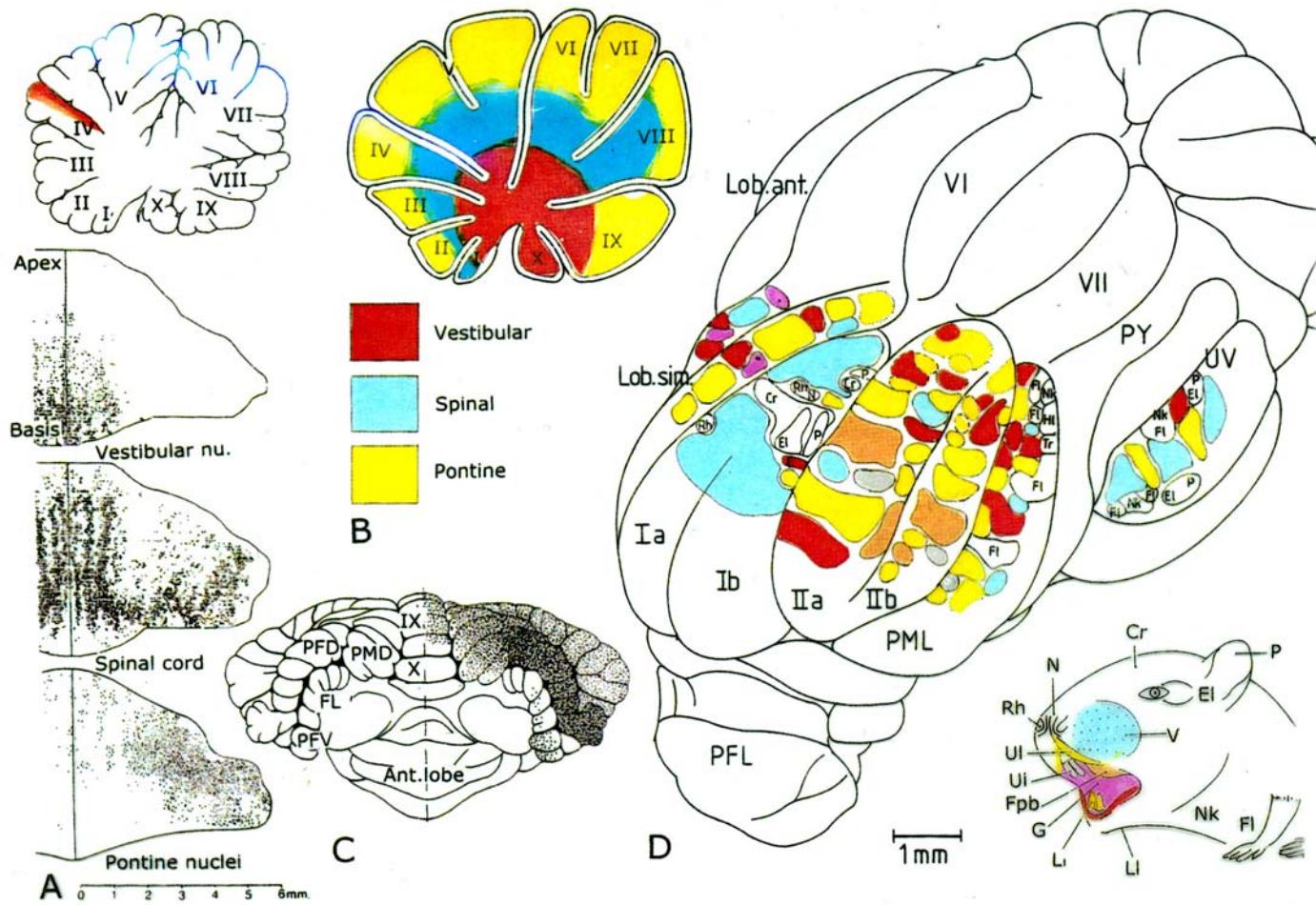
Simplified scheme of the vestibulo-ocular reflex Only excitatory connections are shown. The reflex arc consists of 3 neurons from the semicircular duct to the extraocular muscles. The cerebellar flocculus receives signals from the labyrinth via direct projections through the vestibular nerve and indirect input from the retina (via the pretectal nucleus and the inferior olive). The output of the Purkinje cells can adjust the sensitivity of the vestibular neurons, if necessary, to avoid retinal slip. (Ito, 1984; Brodal).

The pathways for compensatory eye and head movement initiated by stimuli from the semicircular duct and the macula (Szentagothai)

MOSSY FIBERS- FRACTURED TOPOGRAPHY



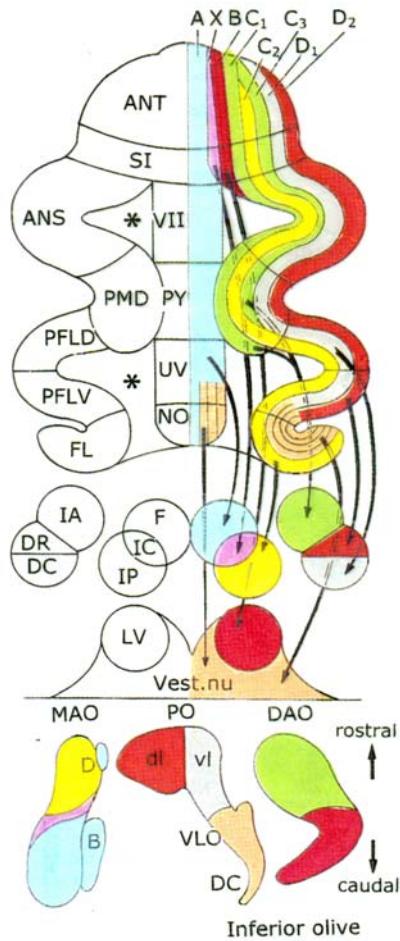
Course and termination of single mossy fibers in the cerebellum of the rat. A: frontal view of a completely reconstructed, biotinylated dextran amine-labeled, single mossy fiber from the lateral reticular nucleus. B: mapping of mossy rosettes in the cerebellar cortex after BDA injection in the lateral reticular nucleus (Wu et al., 1999; Voogd, 2004).



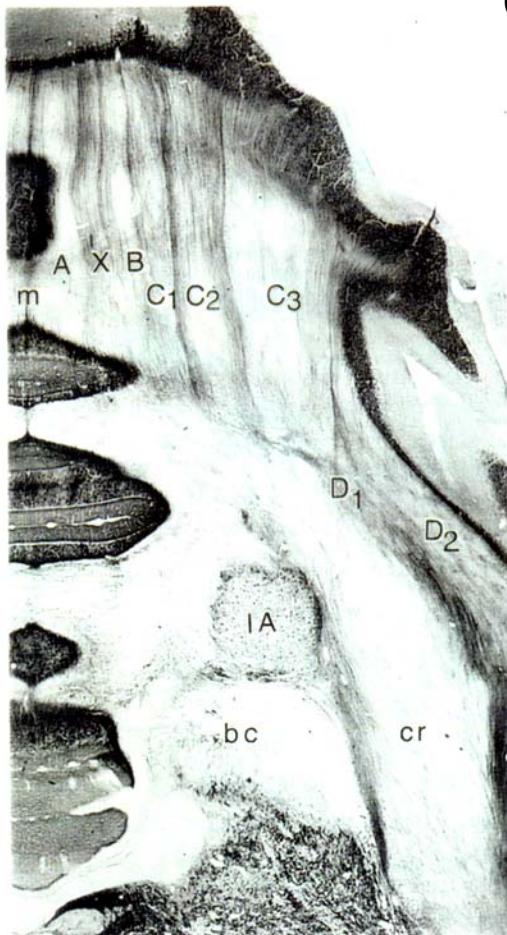
The lobule-specific, patchy and zonal distribution of different mossy-fibre systems. **A:** lobule IV of the cat. **B:** The distribution of vestibulo cerebellar and pontocerebellar mossy fibers in medial cerebellum as seen in sagittal section. **C:** Pontocerebellar fibers terminate heavily in the hemisphere, but spare the flocculus (FL) and ventral paraflocculus (PFV). **D:** Mossy fibers in the posterior lobe terminate in a fractured somatotopical pattern in multiple patches V-vibrissae, Li-lower incisor, Ui- upper incisor; Fi- furry buccal pad, Cr-crown; El- eye lid. (From Voogd and Glickstein, 1998)

SAGITTAL ZONAL ARRANGEMENT

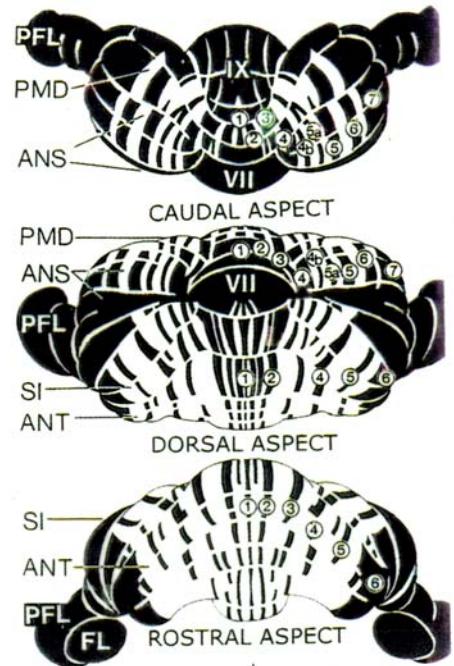
A



B

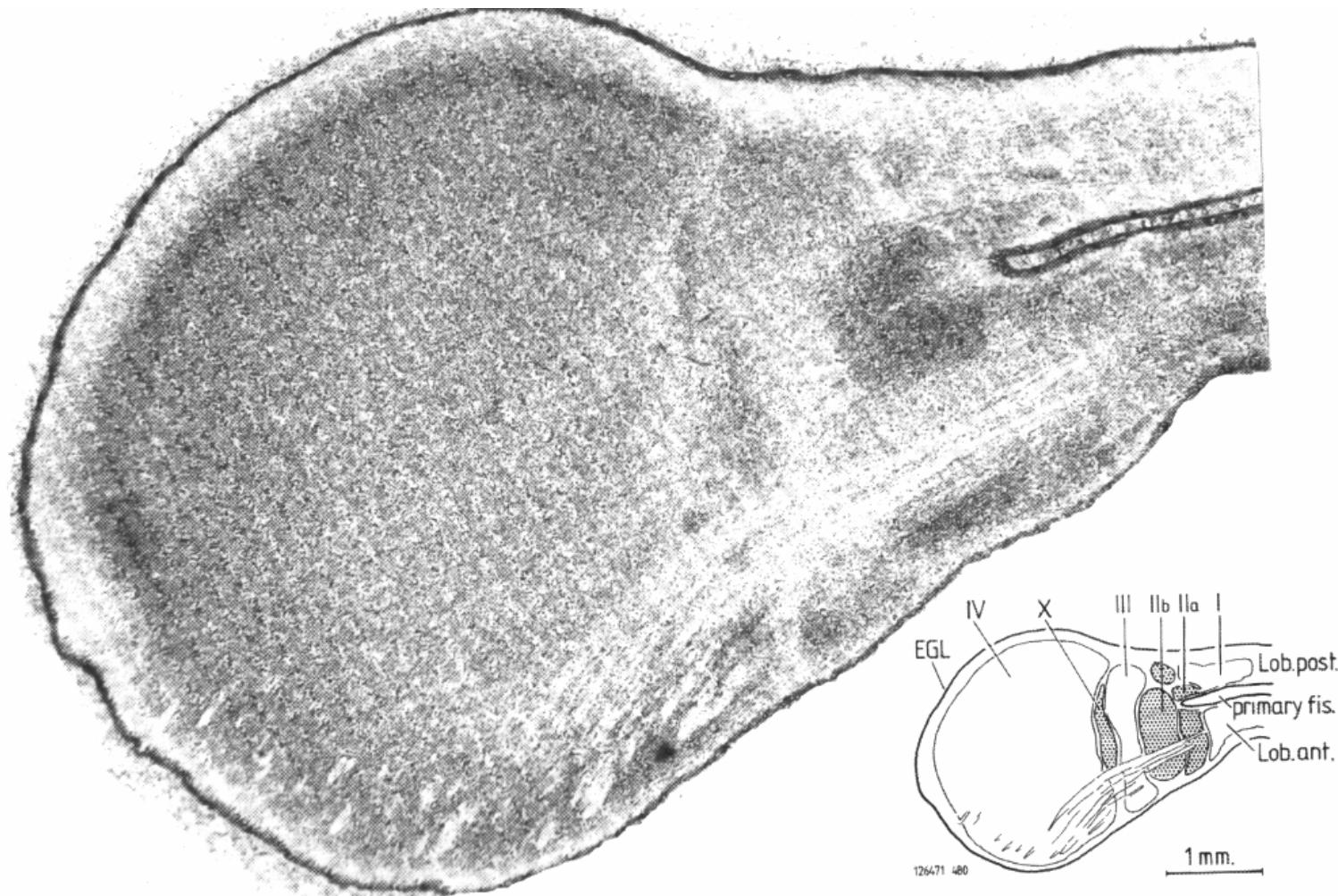


C

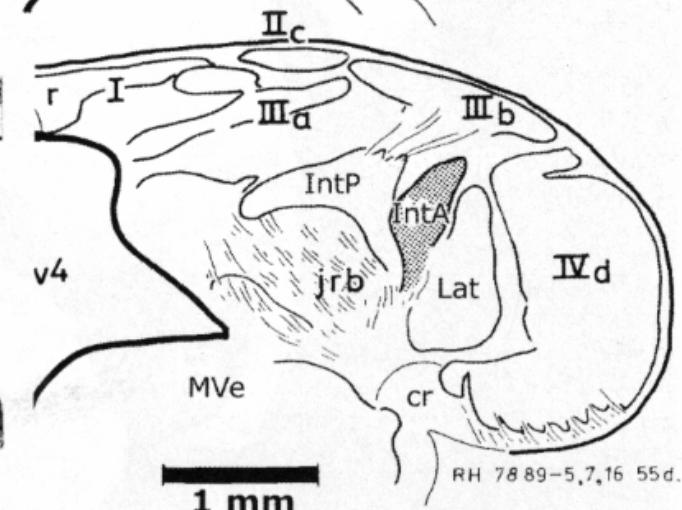
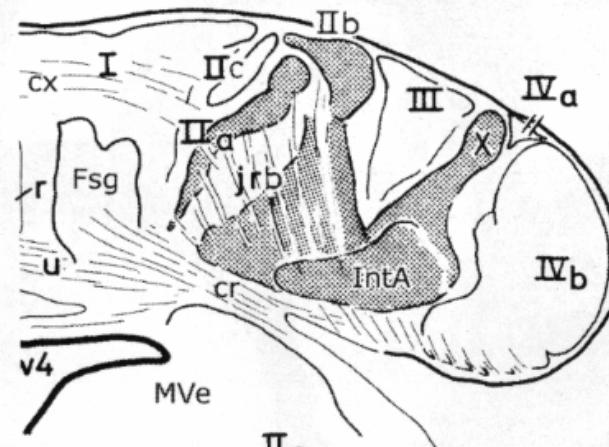
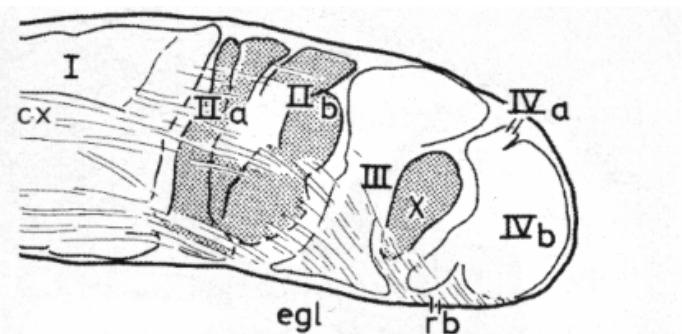
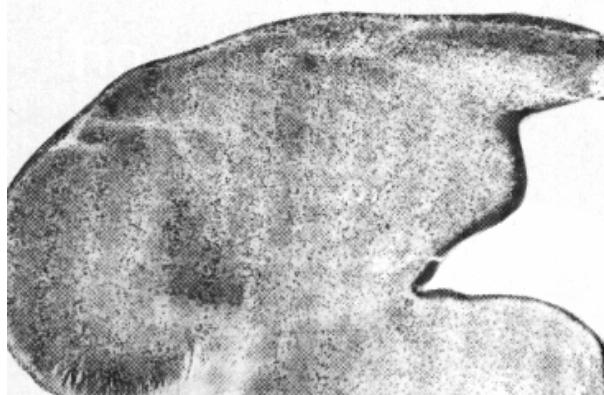
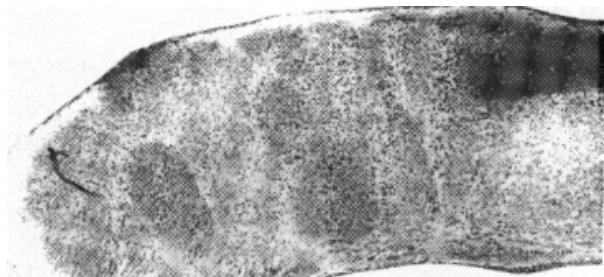


Zonal arrangements in the cerebellum. **A:** The zonal arrangement in the corticonuclear and olivocerebellar projections illustrated in a flattened cerebellar cortex of the cat. F=fastigial; IC=intermediate; IP=globbose; IA=emboliform; DR and DC=dentate; LV=lateral vestibular nuclei. MAO, PO,DAO= medial, principal, dorsal accessory olive. **B:** Transverse section through the anterior lobe of the monkey stained for acetylcholinesterase, showing the modular architecture of the cerebellum. **C:** The longitudinal zonal distribution of the zebrin-positive and 'negative' Purkinje cells in different views of the cerebellum of the rat. From Voogd and Glickstein, 1998.

PURKINJE CELL CLUSTERS



PURKINJE CELL CLUSTERS



1 mm

55day old rhesus monkey fetus. Voogd, 2004

CEREBELLAR MICROCURCUITRY 4: FUNCTIONAL ZONATIONS

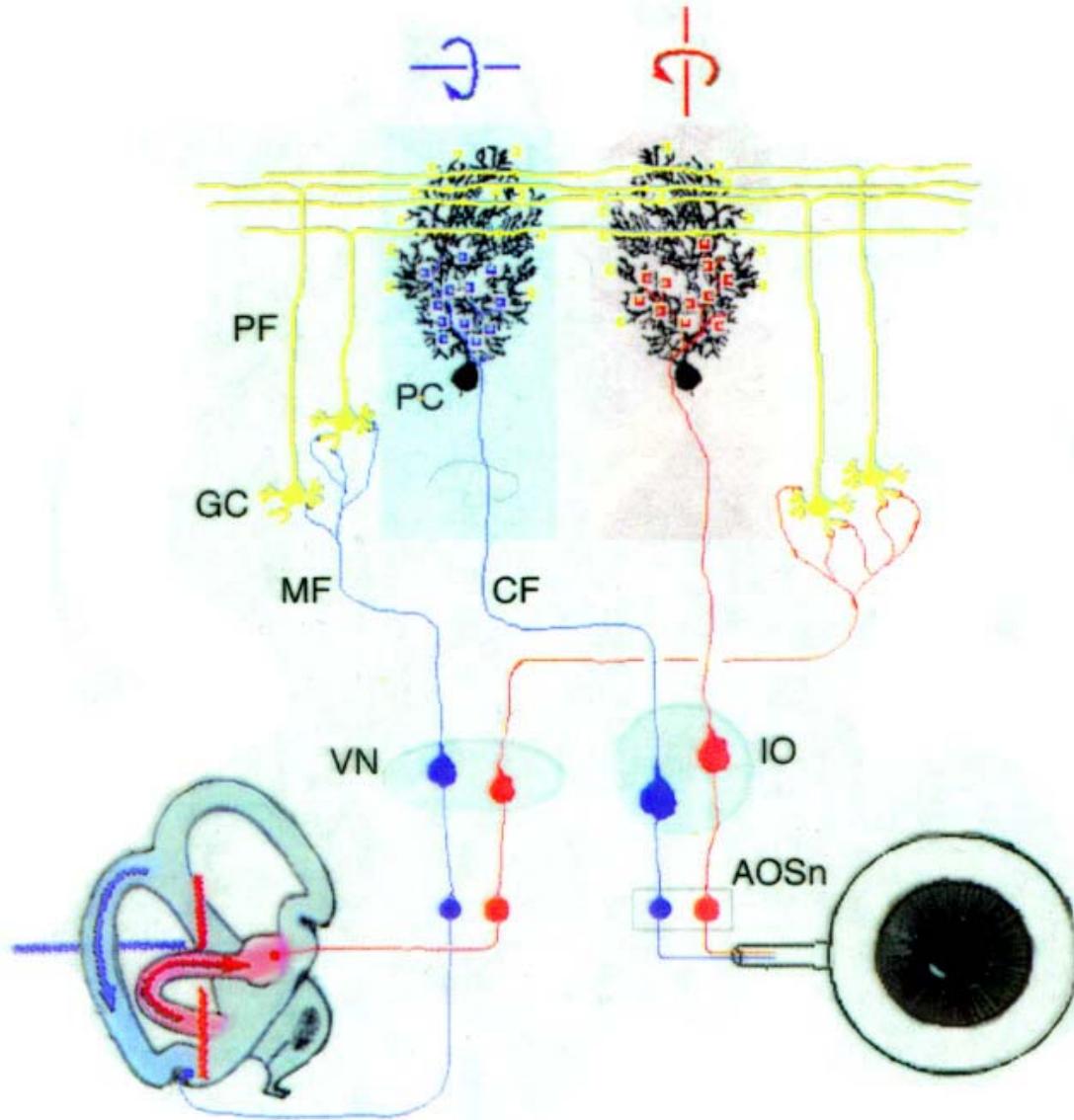
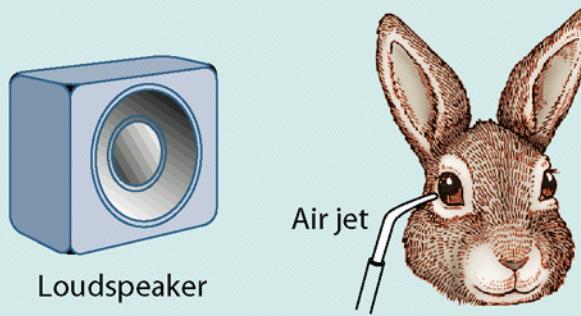


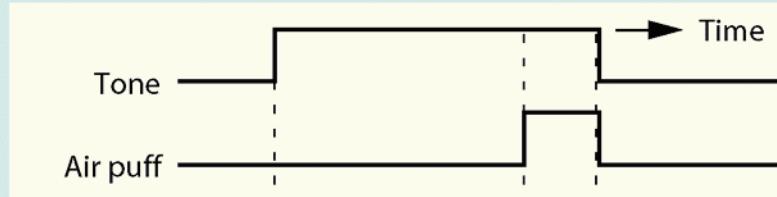
Diagram showing putative functional zonation of the cerebellum using the vestibulo-ocular reflex as a model. The main intention is to show that directional components of the VOR are segregated in sagittal zones. Here, 'blue' mossy fibers relay vertical vestibular signals to blue sagittal zone (via the vestibular [VN] nuclei), while 'red' mossy fibers (MF) relay horizontal signals to red zone. Retinal signals are transmitted via the accessory optic system (AOSn) and the inferior olive (IO). For simplicity cortical outputs are not shown. The second point to note is that climbing and mossy (via granule cells) fiber inputs are segregated on the surface of the Purkinje (PC) cells. PF:=paralell fibers; GC=granule cells. From Oberdick et al. 1998

THE CEREBELLUM IN MOTOR LEARNING

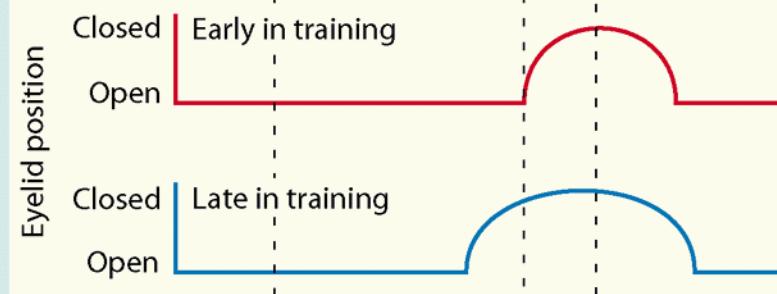
Lesions of the cerebellum disrupt the learned response in eye blink conditioning. (a) A neutral tone precedes and coterminates with an aversive air puff to the eye. (b) Early in training, the air puff causes the animal to blink. Late in training, the animal blinks in response to the tone, thus reducing the impact of the air puff. (c) Lesions of the deep cerebellar nuclei abolish the learned response. The fact that the animal continues to blink reflexively in response to the air puff indicates that the lesion has produced learning deficit and not a motor deficit. Hemispheric lesions results in anticipatory, learned responses that are timed inappropriately. (Gazzaniga, 2002)



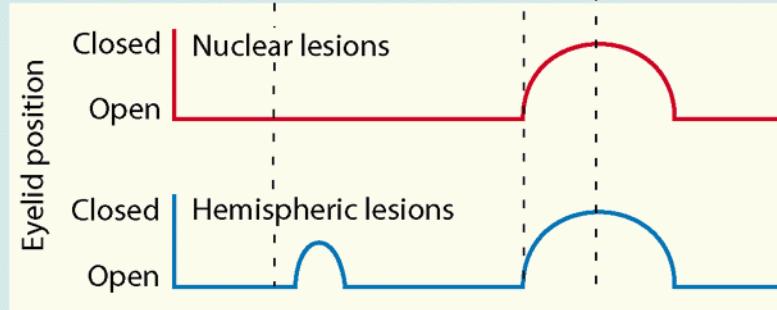
(a) Stimulus



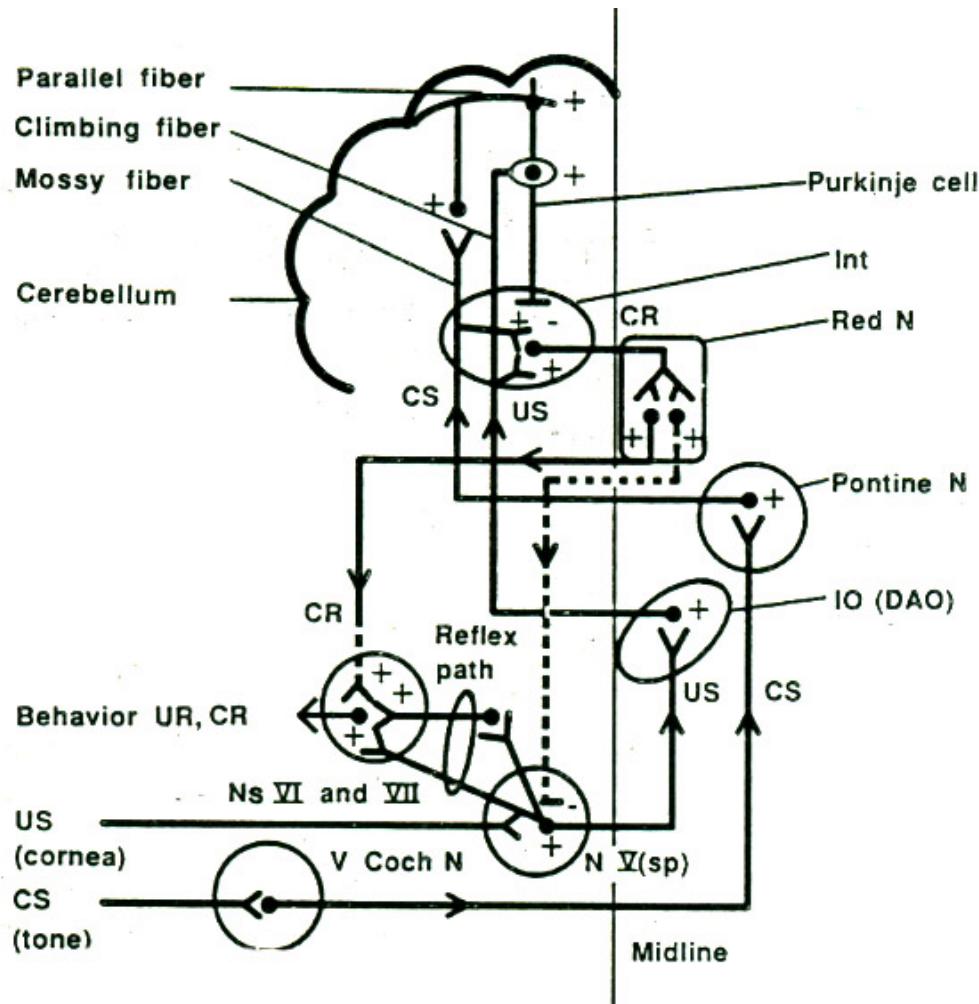
(b) Acquisition of eye blink conditioning



(c) Lesion effects on eye blink conditioning

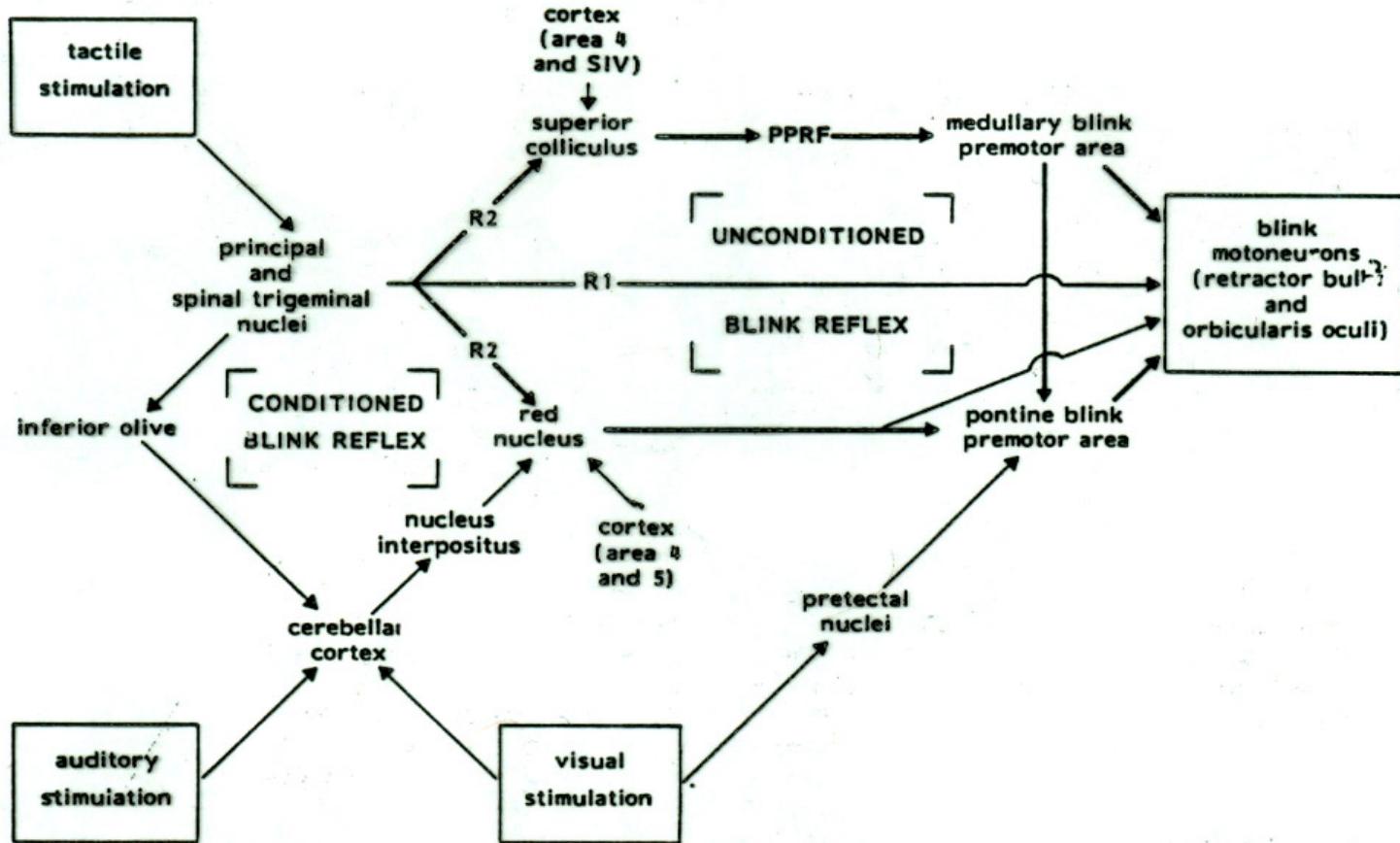


Schematic of eye blink reflex circuitry 1.



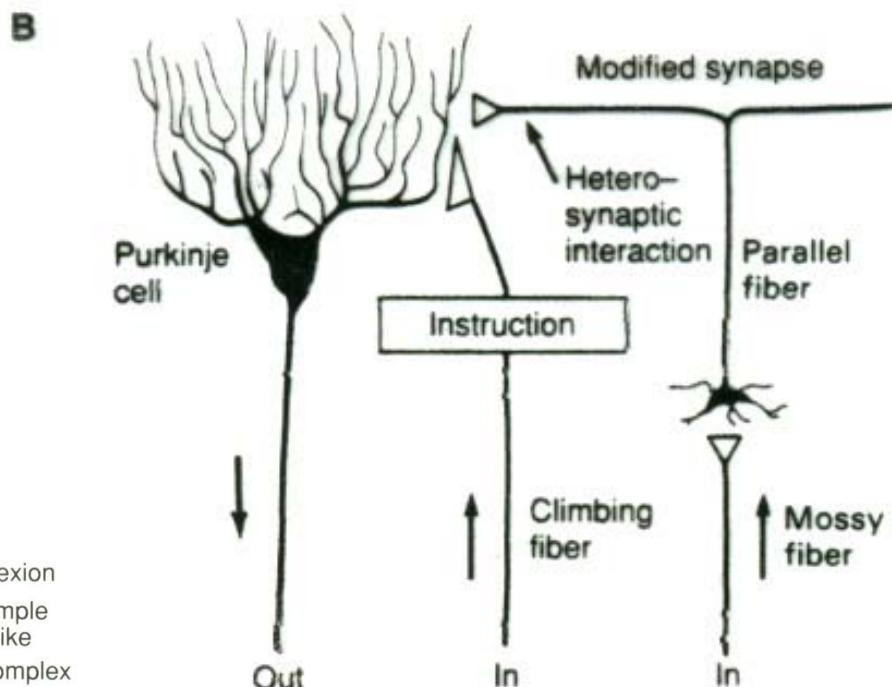
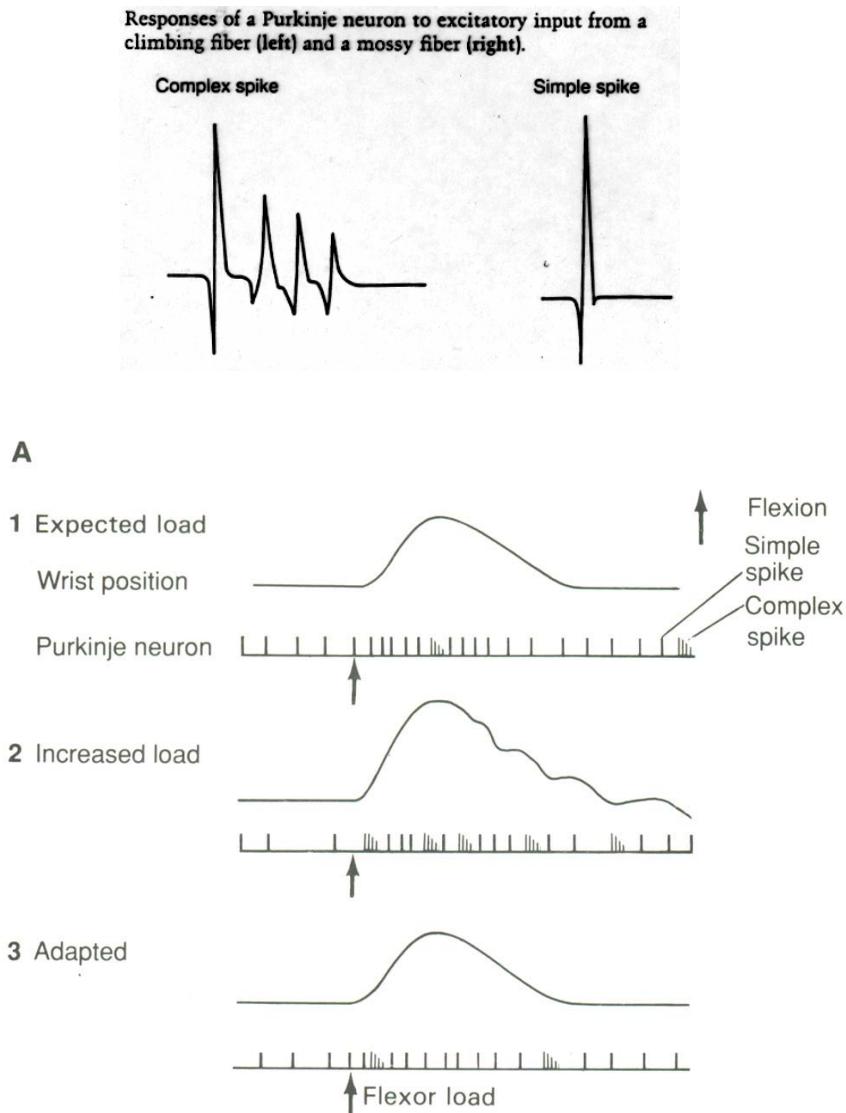
“Simplified” schematic of hypothetical memory trace circuit for discrete behavioral responses learned as adaptations to aversive events. The US (corneal airpuff) pathway consist of somatosensory projections to the dorsal accessory portion of the olive (IO, DAO) and its climbing fiber projections to the cerebellum. The tone CS pathway consist of auditory projections to pontine nuclei and their mossy fiber projections to the cerebellum. The efferent (eyelid closure) CR pathway projects from the interpositus (Int) nucleus of the cerebellum to the red nucleus (red N) and via the descending rubral pathway to act on motor neurons. The red nucleus may also exert inhibitory control over the transmission of somatic sensory information about the US to the inferior olive , so that when a CR occurs (eyelid closure), the Red N dampens US activation of climbing fibers. (From Thompson)

SCHEMATIC OF THE EYE BLINK REFLEX 2.



Pathways mediating the unconditioned and conditioned blink reflex (after Holstege).

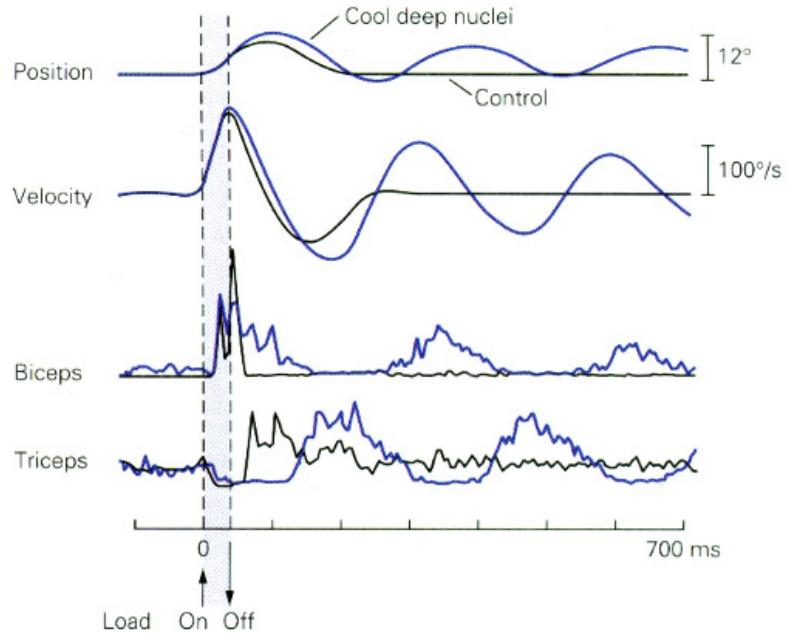
CEREBELLAR CIRCUITS ARE MODIFIED DURING LEARNING



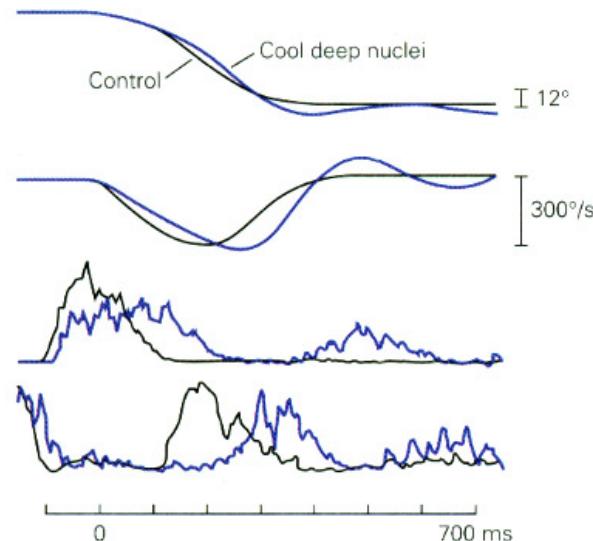
A: Changes in the simple and complex spike activity in the P neuron take place as the monkey learns to adapt to a novel motor task. 1. A control response is produced with only occasional complex spikes. 2. In the trial immediately following application of an increased load, the neuron fires numerous complex spikes. 3. After practice with the new load, activity in the neuron returns to the control frequency of complex spikes while the frequency of simple spikes decreased. **B:** Simplified neural circuit showing the convergence of the mossy (MF) and climbing fibers (CF). The changes that occur in the cerebellum following the learning of a novel motor task result from the ability of the climbing fibers to depress the actions of the parallel fibers on the P cells. According to this view, the CF instruct or modulate the action of mossy fibers. (Ito, 1984; Kandel)

CEREBELLAR SYMPTOMS 1: ASYNERGIA AND OVERTSHOOTING

A Perturbation (stretch biceps)

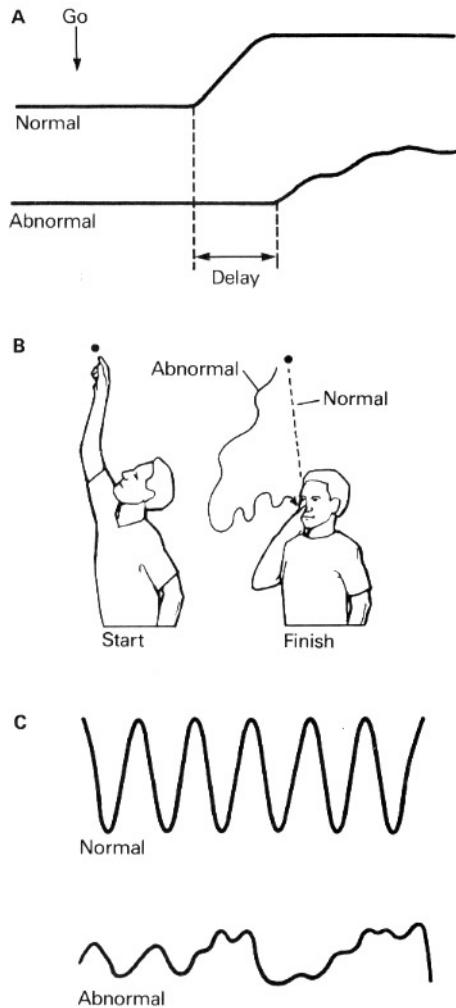


B Voluntary movement



Inactivation of the interposed and dentate nuclei disrupt the precisely timed sequence of agonist and antagonist activation that follows external perturbation or voluntary movement. **A:** The records show position, velocity, and EMG responses in biceps and triceps of a trained monkey after the forearm was suddenly displaced from a held stationary position. Prior to inactivation of the cerebellar nuclei, through local cooling, the limb returns to its original position after the external torque is stopped; only minimal overshooting is evident on the position trace. While the nuclei are cooled the limb returns with marked overshoot and sequential corrections produce oscillations. **B:** With inactivation of the nuclei, agonist (biceps) activation becomes slower and more prolonged; activation of the antagonist (triceps), which is needed to stop the movement at the correct location, is delayed and prolonged so that the initial movement overshoots. (From Kandel)

CEREBELLAR SYMPTOMS 2: DELAY IN INITIATION, DYSMETRIA, TERMINAL TREMOR, DYSDIADOCHOKINESIS

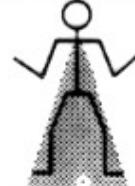
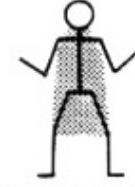
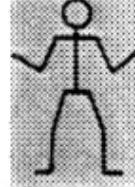


Typical defects in cerebellar diseases.

A: A lesion in the right cerebellar hemisphere causes a delay in the initiation of movement. The patient is told to flex both arms at the same time on a 'go' signal. The left arm is flexed later than the right, as evident in the recordings of elbow position.

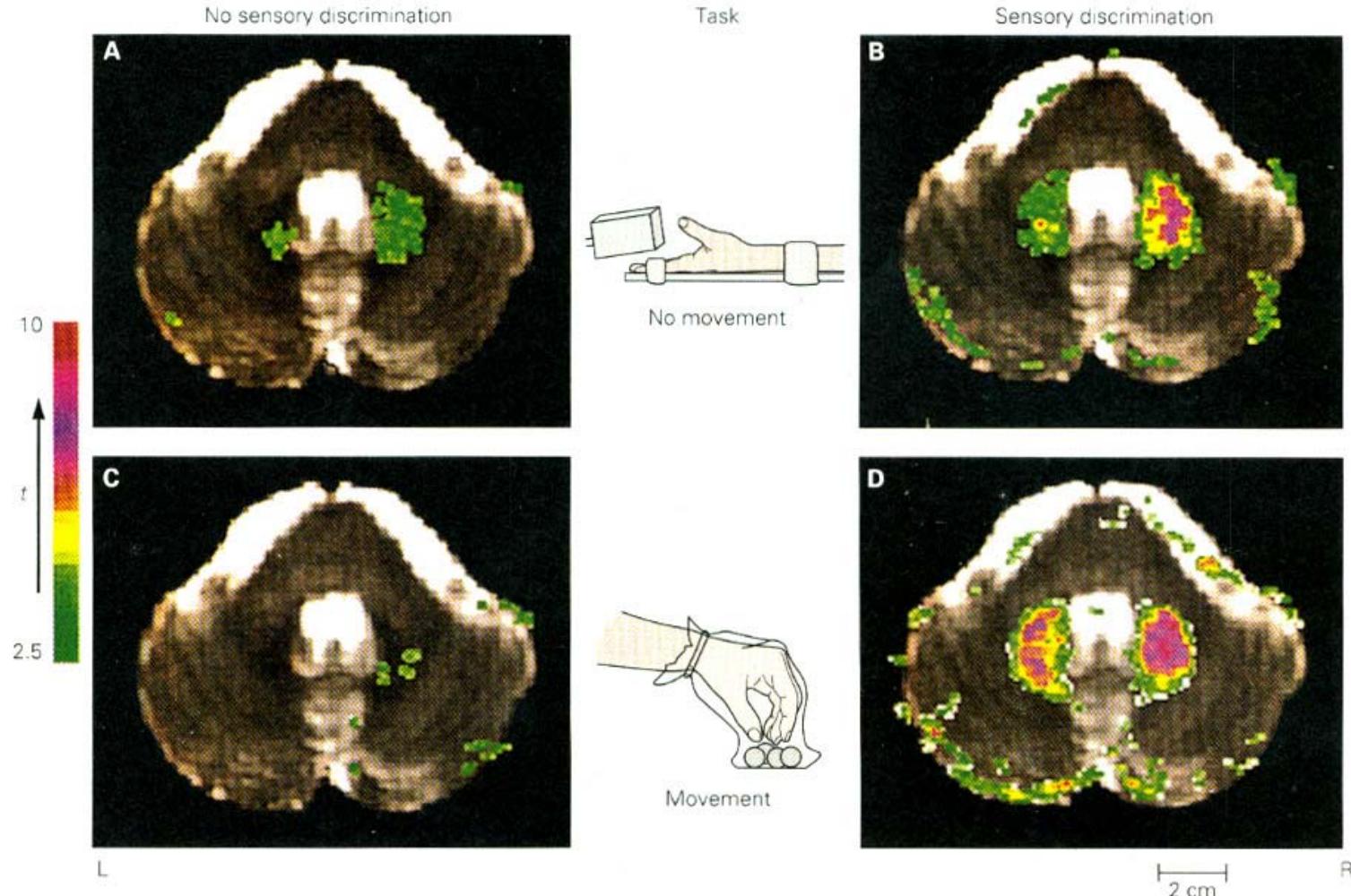
B: A patient moving his arm from a raised position to touch the tip of his nose exhibits dysmetria (inaccuracy in range and direction) and unsMOOTH movement with increased (terminal) tremor on approaching the nose.

C: Dysdiadochokinesia, an irregular pattern of alternating movements, can be seen in the abnormal position trace (From Kandel).

Distribution of deficits	Dysarthria	Arm overshoot	Hypotonia	Dystaxia of			Nystagmus	Clinical syndrome	Lobe or lobes affected
				Arms	Gait and trunk	Legs			
	+	+	+	+	+	+	Bidirectional, coarser to side of lesion Fast component to sides of gaze	Cerebellar hemisphere syndrome	Mainly posterior lobe, variably anterior lobe neoplasmas infarction
	0	±	+	±	+	+	0	Rostral vermis syndrome	Anterior lobe chronic alc.
	0	0	±	0	+	±	Variable	Caudal vermis syndrome	Flocculonodular and posterior lobes tumors of the vermis
	+	+	+	+	+	+	Variable	Pancerebellar syndrome	All lobes acute alc.

Summary of four cerebellar syndromes with their likely causes. (Modified after Duus).

DENTATE N. ACTIVATION IN A PURELY COGNITIVE TASK



Activity in the dentate nucleus is significantly greater when the subject is mentally active during movement. An fMRI image overlaid on an anatomical image shows activation of the dentate n. during two pairs of tests. In one pair, subjects first passively experienced sandpaper rubbed across the fingers (**A**) and then were asked to discriminate the degree of roughness of the sandpaper (**B**). In the other pair, subjects were asked to lift and drop a series of objects (**C**) and then had to identify the felt object from a similar group near the other hand (**D**). From Gao et al., 1996).