Cerebellum & Psychiatry

Dr Malay Dave

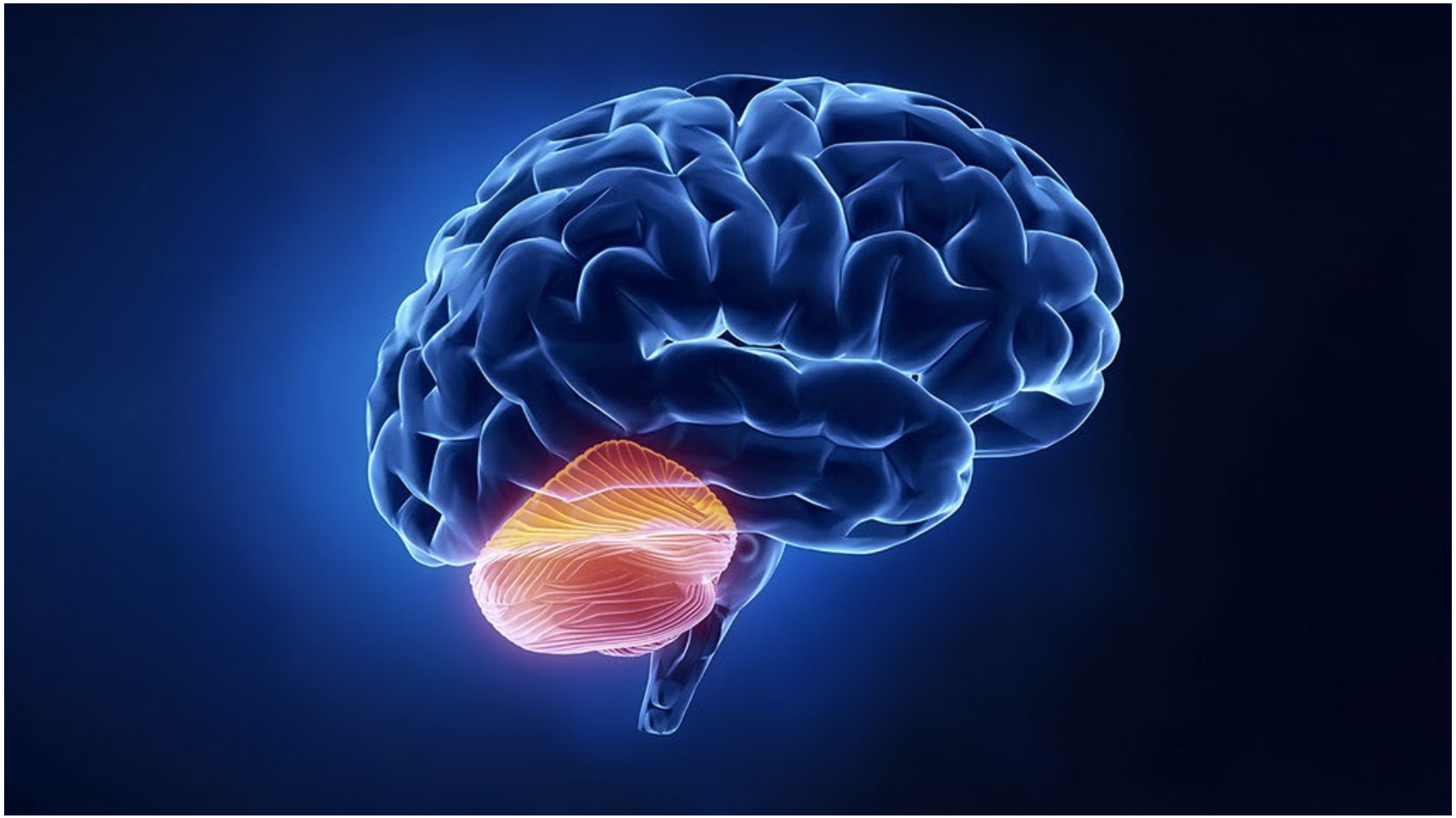
06-07-2023

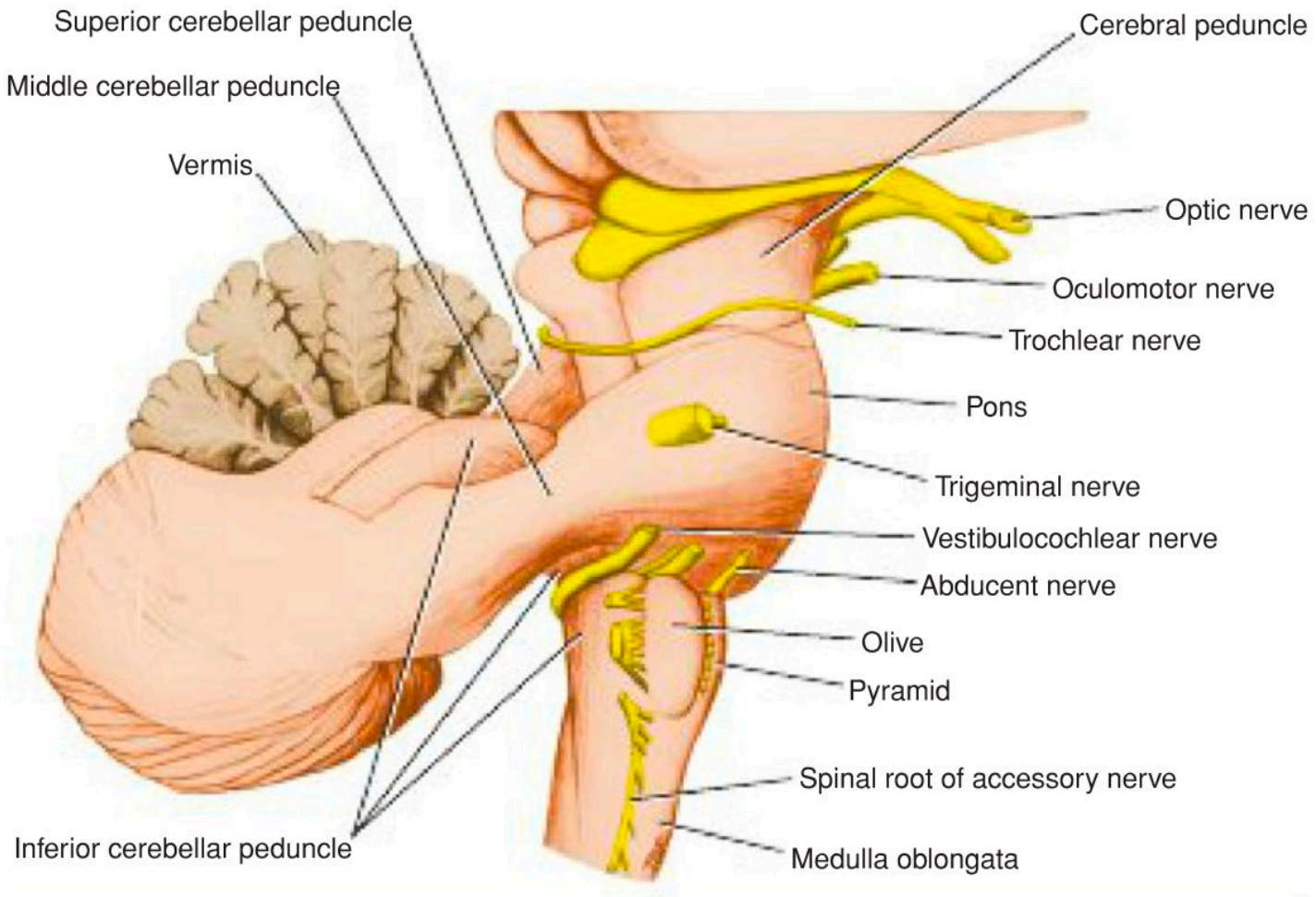
Figure 1. Psychopathology, Executive Control, and the Cerebellum

Right: plate 43 from 'Los Caprichos': The sleep of reason produces monsters by Francisco de Goya y Lucientes.,1799. Source: The Metropolitan Museum of Art. New York, NY. Open Access/Public Domain image. Left: drawing of Purkinje cells (A) and granule cells (B) from pigeon cerebellum by Santiago Ramón y Cajal, 1899. Source: Instituto Cajal, Madrid, Spain. Open Access/Public Domain image.

Ahmad R. Hariri. The Emerging Importance of the Cerebellum in Broad Risk for Psychopathology. Neuron *102*, April 3, 2019. https://doi.org/10.1016/j.neuron.2019.02.031

Grossly…




Superior cerebellar peduncle
Middle cerebellar peduncle
Vermis
Inferior cerebellar peduncle
Cerebral peduncle
Optic nerve
Oculomotor nerve
Trochlear nerve
Pons
Trigeminal nerve
Vestibulocochlear nerve
Abducent nerve
Olive
Pyramid
Spinal root of accessory nerve
Medulla oblongata

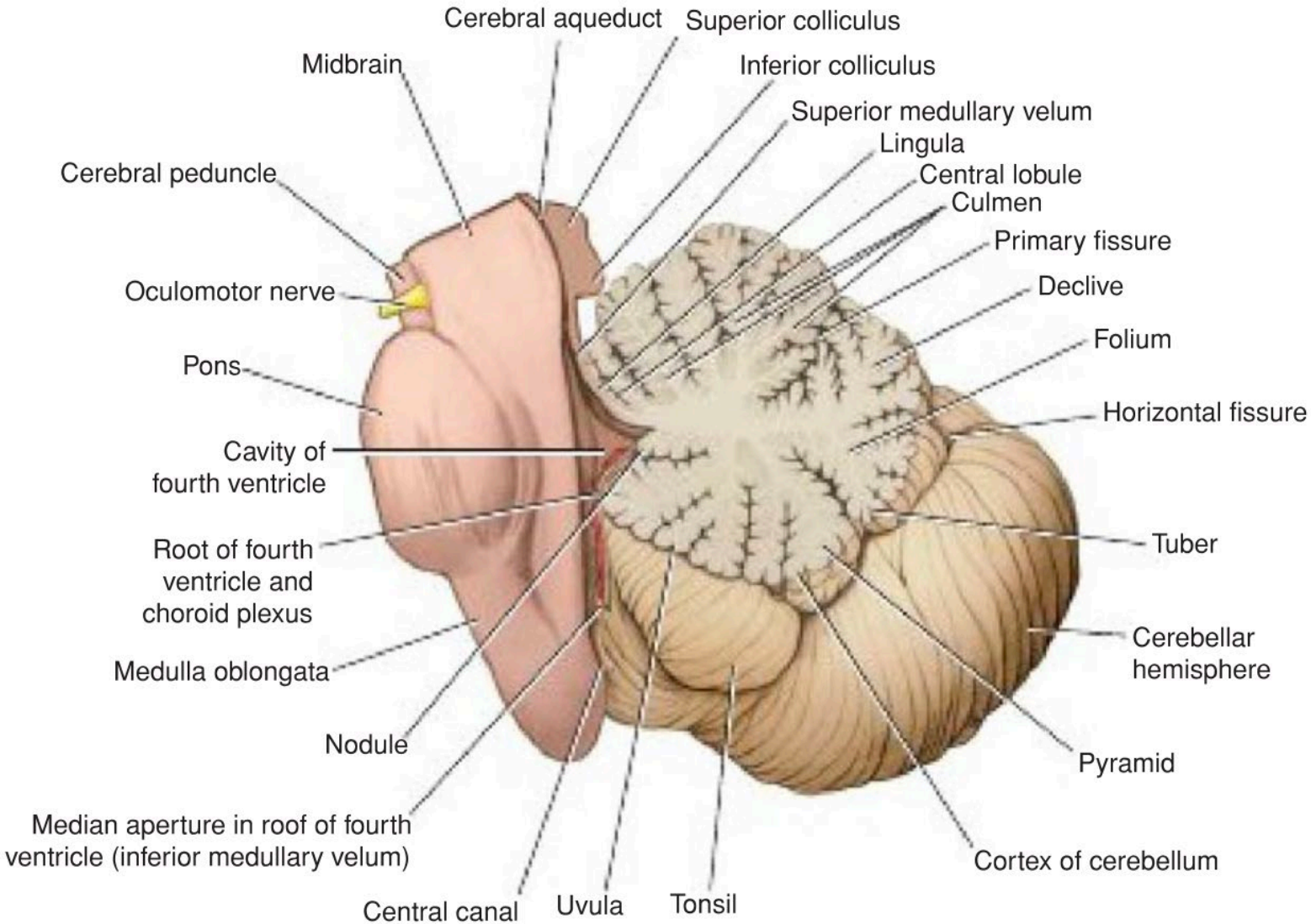


Figure 6-1 Sagittal section through the brainstem and the vermis of the cerebellum.

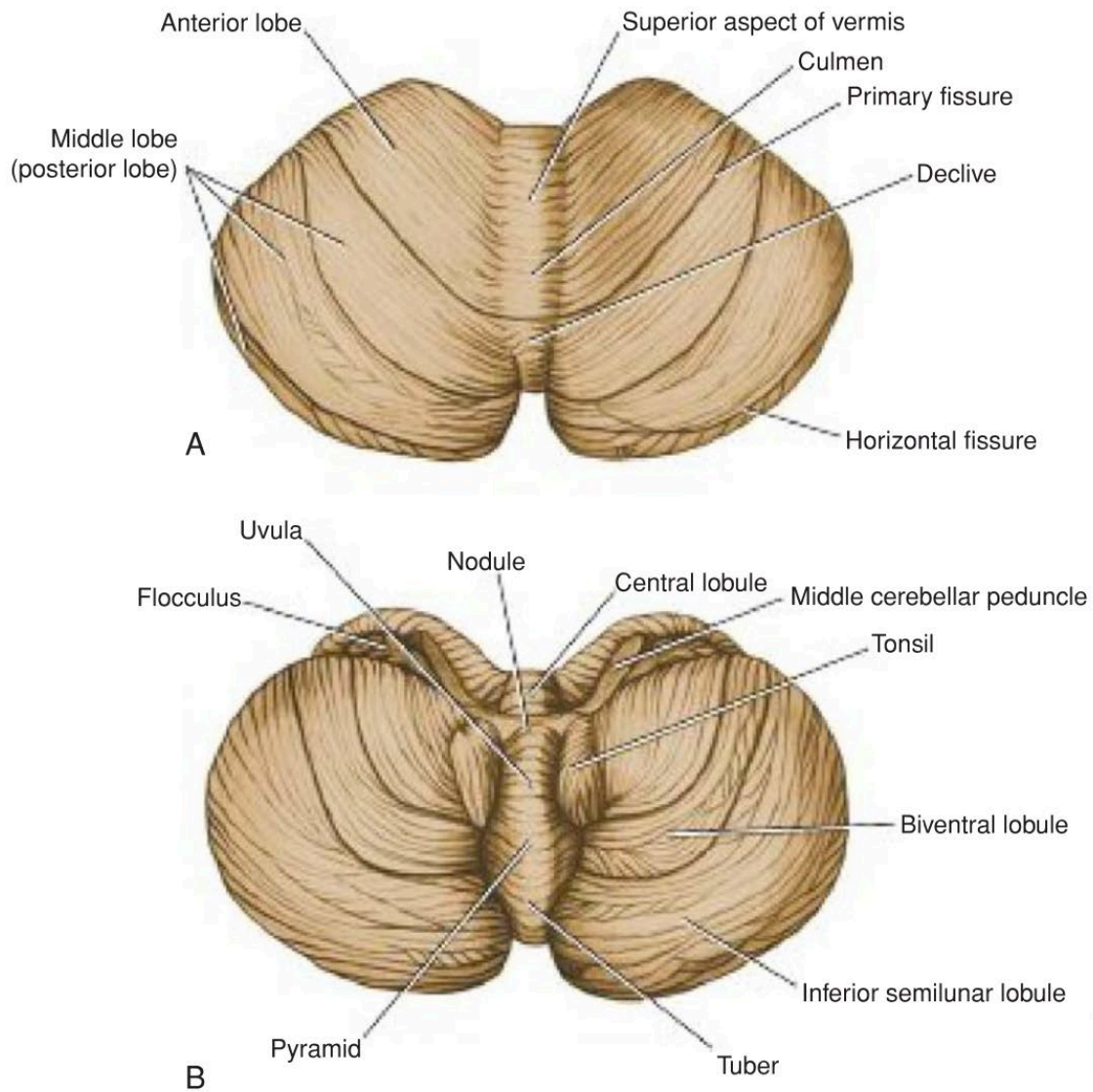


Figure 6-2 The cerebellum. **A:** Superior view. **B:** Inferior view.

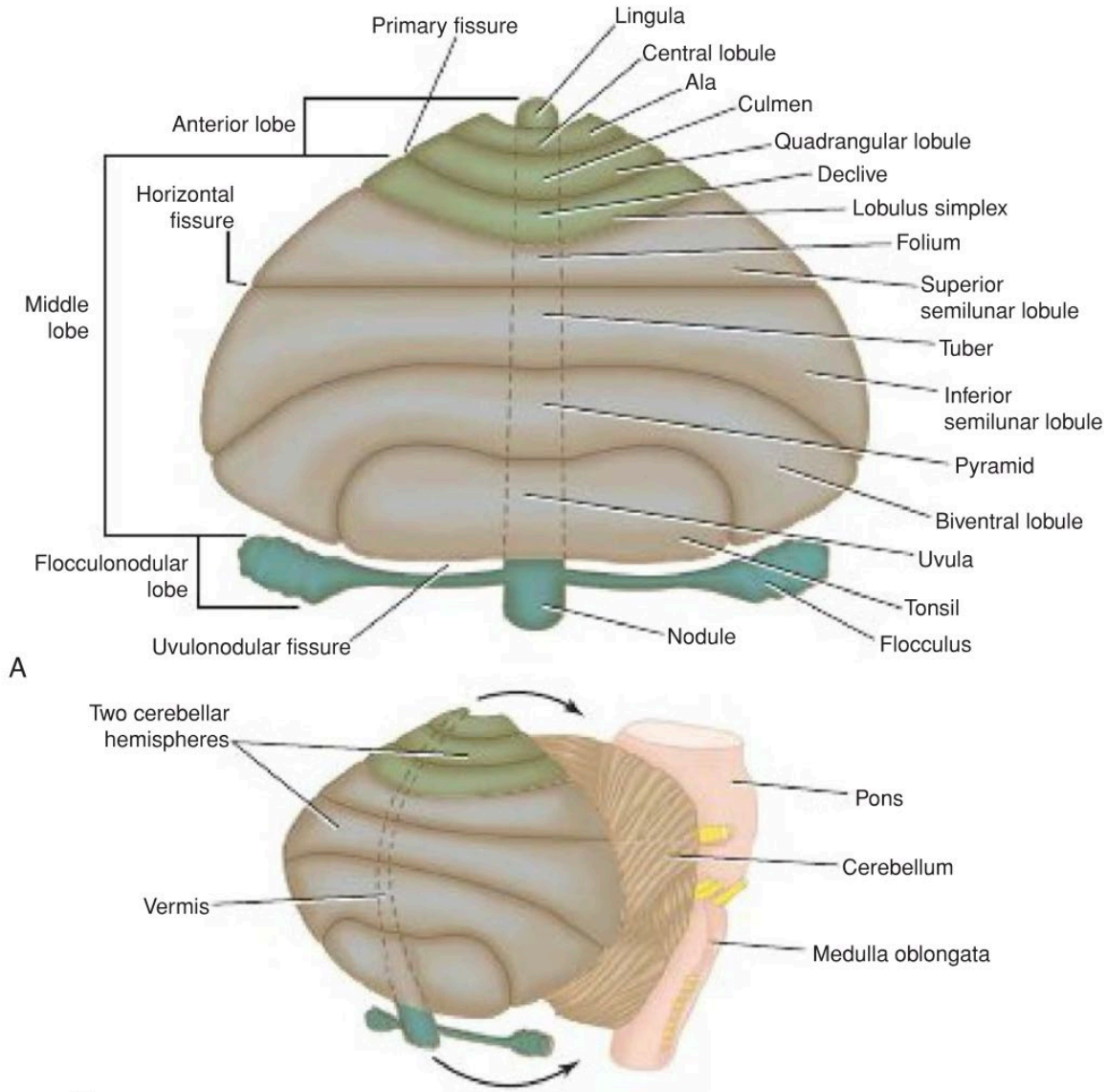
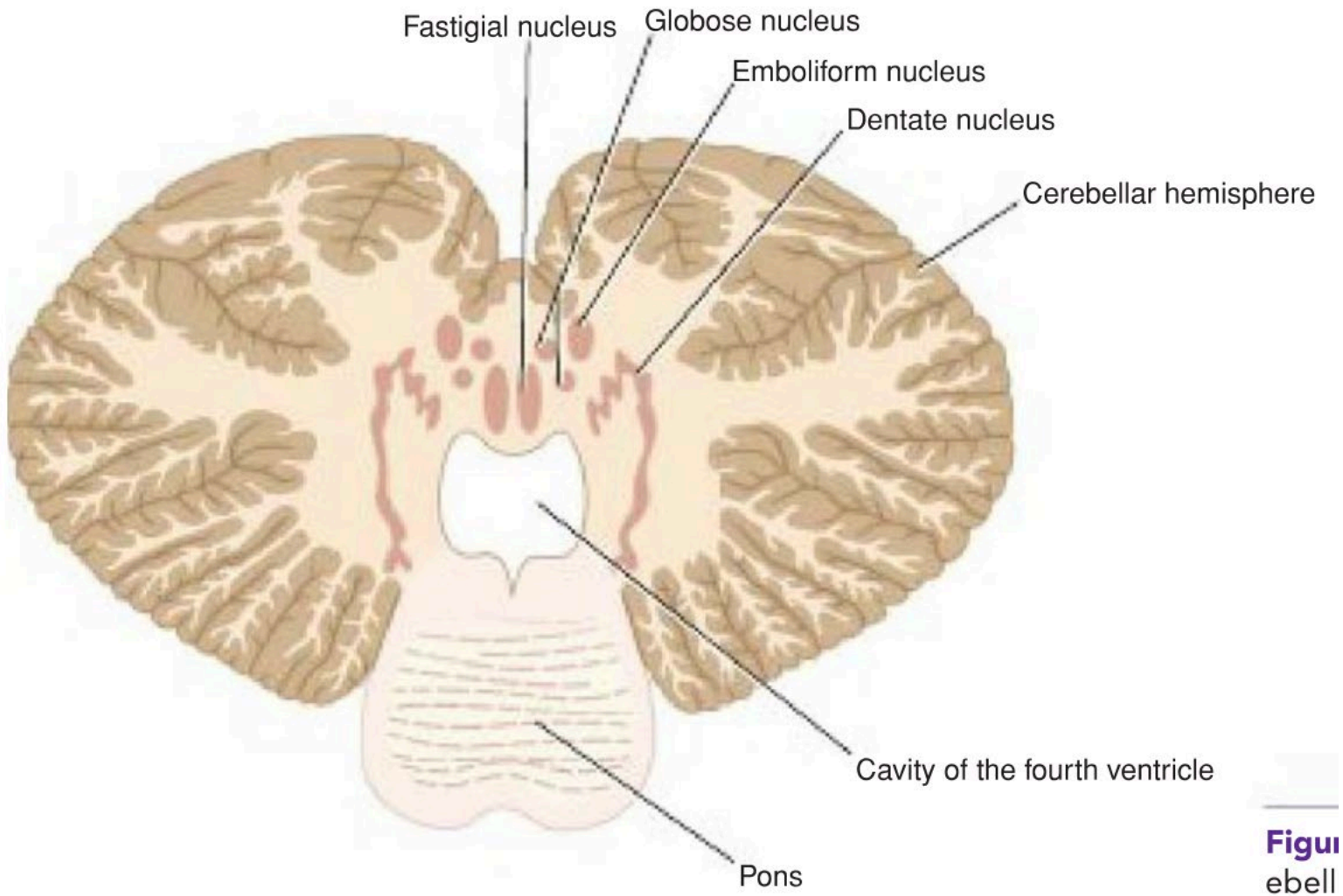


Figure 6-3 **A:** Flattened view of the cerebellar cortex showing the main cerebellar lobes, lobules, and fissures. **B:** Relationship between the diagram in (**A**) and the cerebellum.


Fastigial nucleus
Globose nucleus
Emboliform nucleus
Dentate nucleus
Cerebellar hemisphere
Cavity of the fourth ventricle
Pons

Figu
ebell

Lobe	*Components*
Anterior lobe	Lingula
	Central lobule
	Culmen
	Ala of central lobule
	Quadrangular lobule
Middle lobe	Declive
	Folium
	Tuber
	Pyramid
	Uvula
	Lobulus simplex
	Biventral lobule
	Semilunar lobule
	Tonsil
Flocculonodular lobe	Nodule
	Flocculus

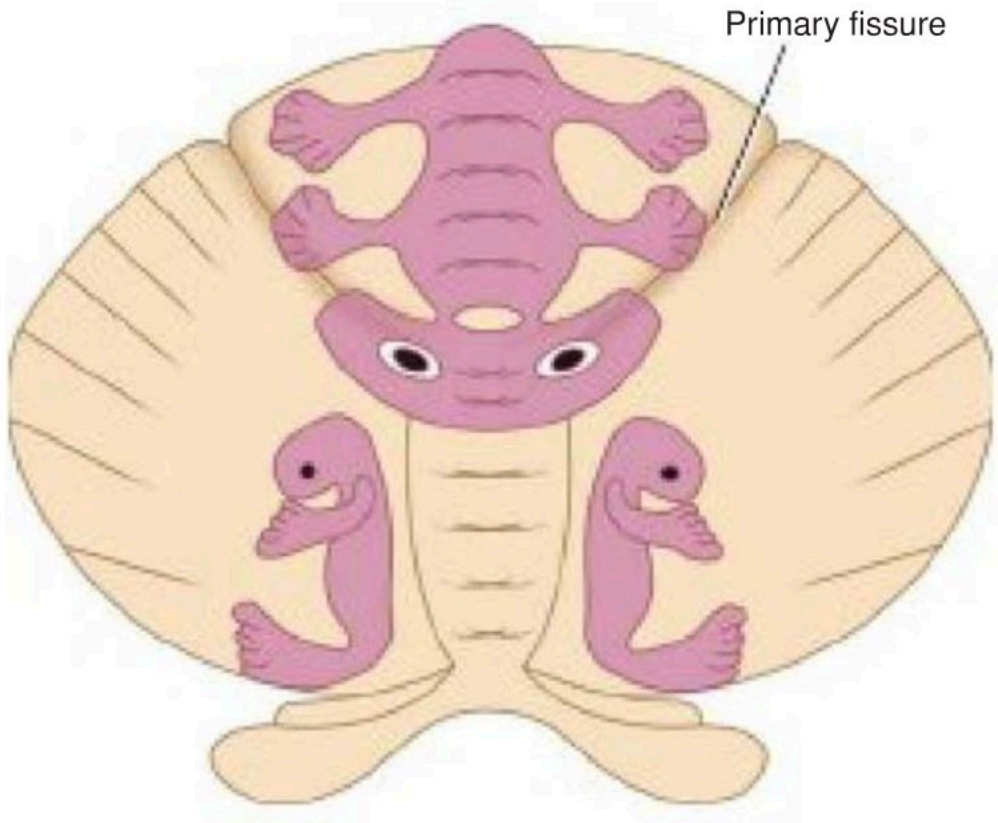


Figure 6-6 Somatosensory projection areas in the cerebellar cortex.

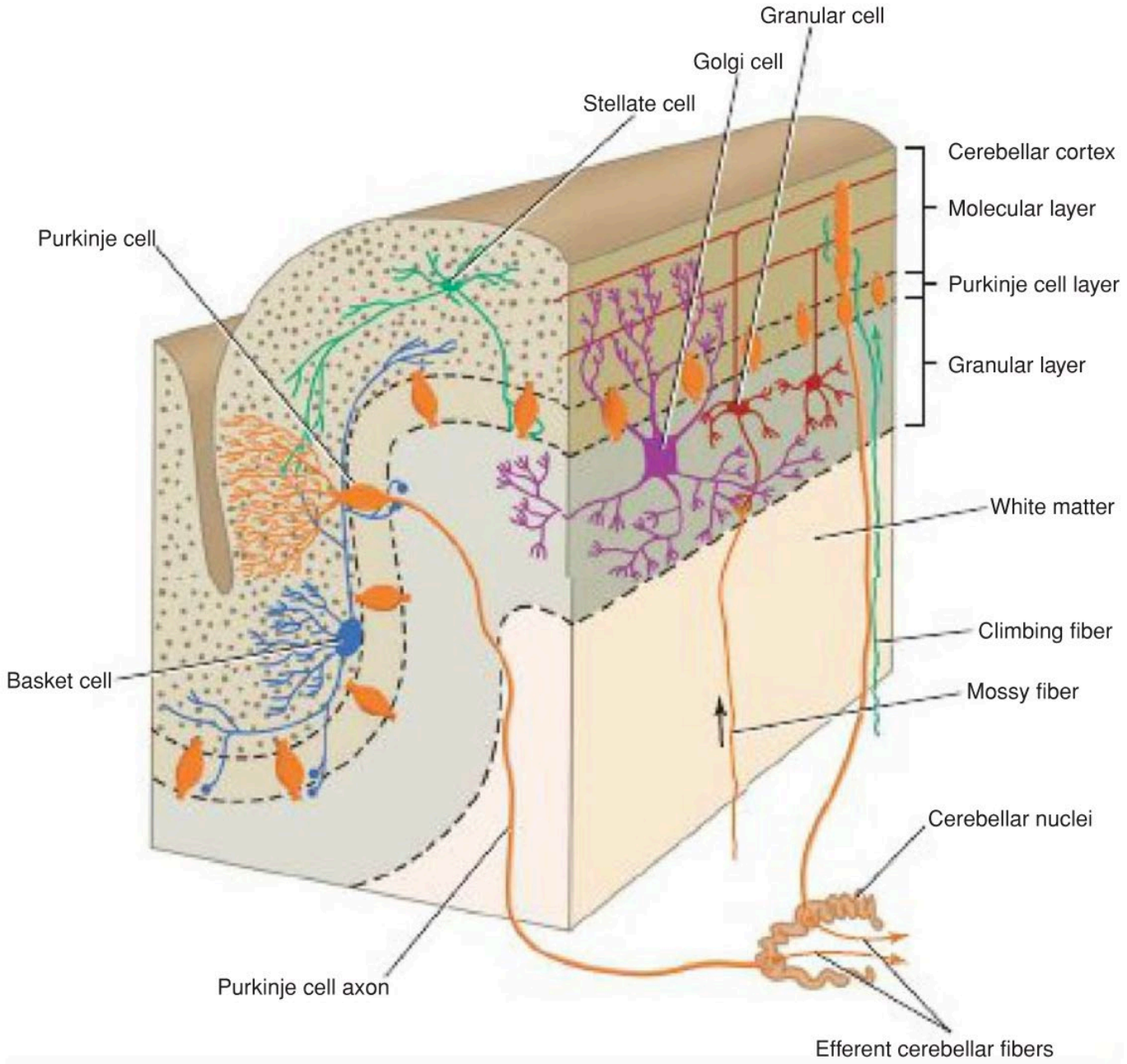
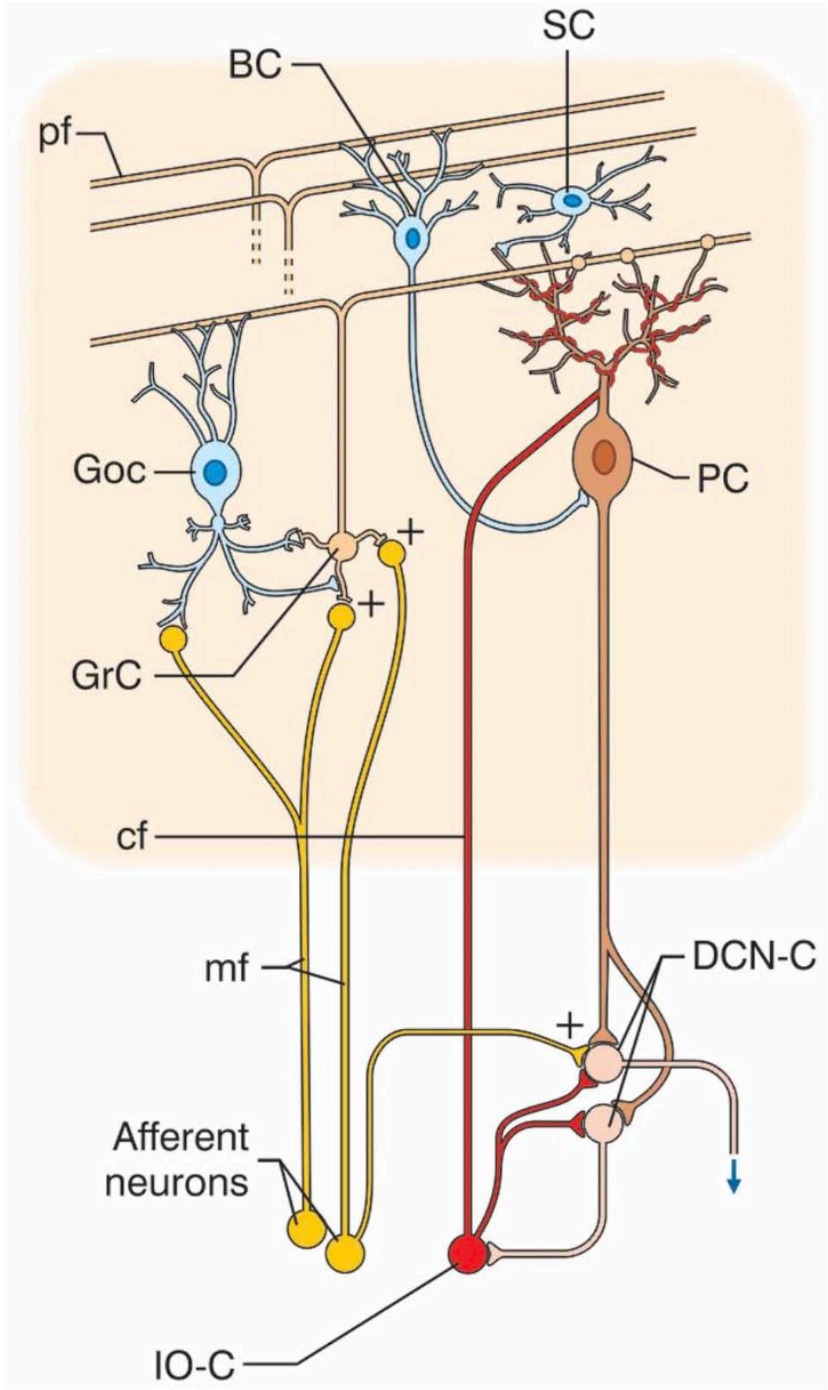


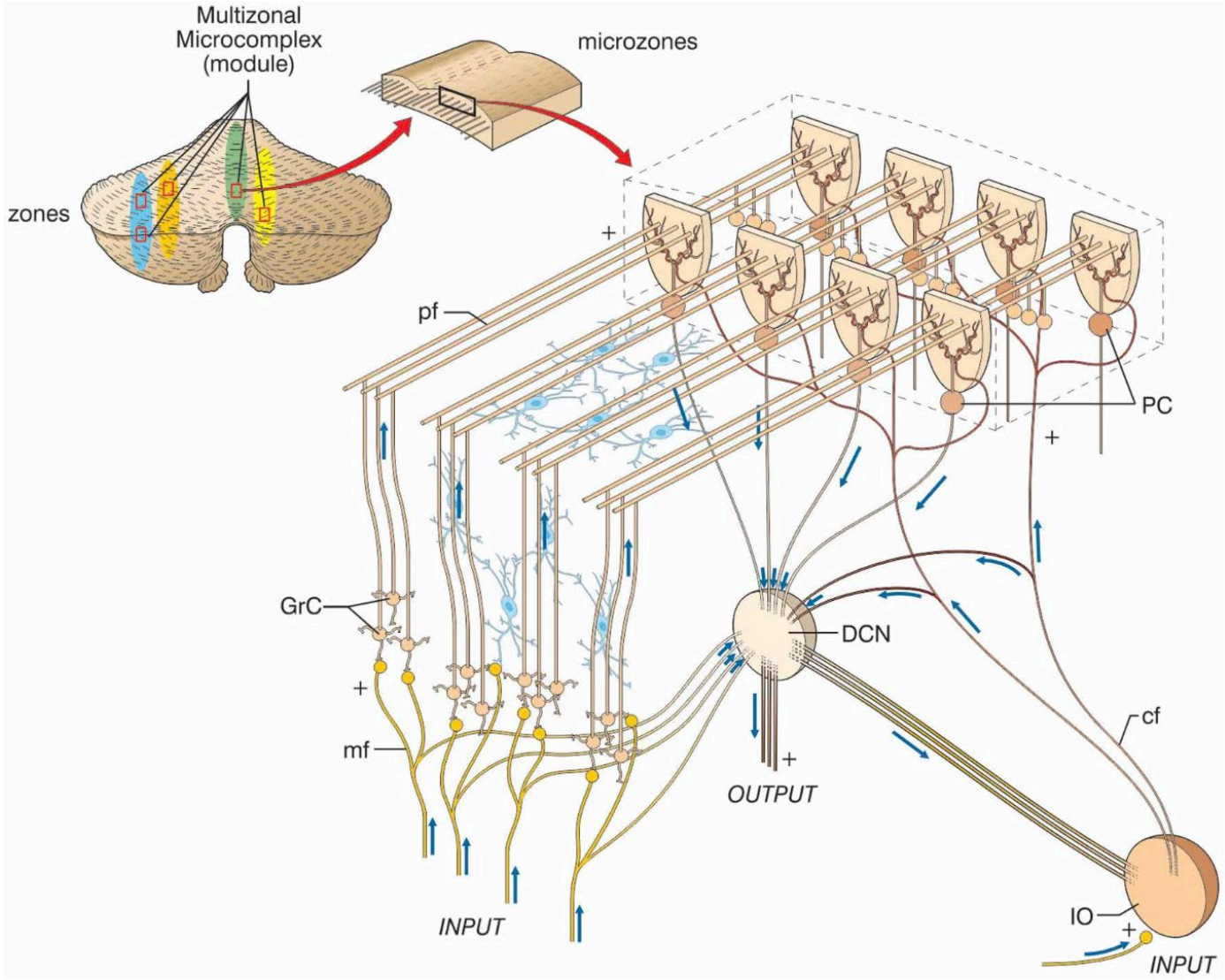
Figure 6-4 Cellular organization of the cerebellar cortex. Note the afferent and efferent fibers.



Egidio D'Angelo and Stefano Casali,
doi: 10.3389/fncir.2012.00116

- The cerebellar circuit consists of cortical and subcortical sections
- At subcortical level, the afferent fibers activate DCN cells (DCN-C) and IO cells (IO-C)
- The DCN emits the output and at the same time inhibits the IO
- In the cerebellar cortex, there are different types of neurons including granule cells (GrC), Golgi cells (GoC), Purkinje cells (PC), stellate and basket cells (SC, BC), Lugaro cells, and unipolar brush cells.
- The two main inputs are represented by mossy fibers (mf) originating in various brain stem and spinal cord nuclei, and by climbing fibers (cf) originating from the IO
- Signals conveyed through the mossy fibers diverge to DCN and activate the granular layer (containing GrC and GoC)
- The ascending axon of the GrC bifurcates in the molecular layer (containing PC, SC, and BC) forming the parallel fibers (pf)
- The cerebellar cortical circuit is organized as a feedforward excitatory chain assisted by inhibitory loops: mfs excite GrCs, which activate all the other cortical elements
- In the granular layer, inhibition is provided by GoC, in the molecular layer by SC and BC
- PC inhibit DCN
- The IO, which is also activated by brain stem and spinal cord nuclei, controls PC activity though a single powerful synapse
- Thus, the whole system can be seen as a complex mechanism controlling the DCN output

Egidio D'Angelo and Stefano Casali, doi: 10.3389/fncir.2012.00116



Egidio D'Angelo and Stefano Casali, doi: 10.3389/fncir.2012.00116

- Four ideal zones are shown in color, each one containing microzones forming a multizonal microcomplex
- The microzones have the basic structure reported in the expansion on the right
- A microzone is defined as a group of the order of 1000 Purkinje cells all having the same somatotopic receptive field
- These Purkinje cells are arranged in a long, narrow strip, oriented perpendicular to the cortical folds, so that Purkinje cell dendrites are flattened in the same direction as the microzones extend and are crossed by parallel fibers at right angles
- The climbing fibers branches (about 10) usually innervate Purkinje cells belonging to the same microzone and the olivary neurons generating such climbing fibers tend to be coupled by gap junctions
- This helps synchronizing Purkinje cells within a microzone on a millisecond time scale
- The Purkinje cells belonging to a microzone all send their axons to the same small cluster of output cells within the deep cerebellar nuclei
- Finally, the axons of basket cells are much longer in the longitudinal direction than in the mediolateral direction (not shown), causing them to be confined largely to a single microzone
- Thus, cellular interactions within a microzone are much stronger than those between different microzones

Egidio D'Angelo and Stefano Casali, doi: 10.3389/fncir.2012.00116

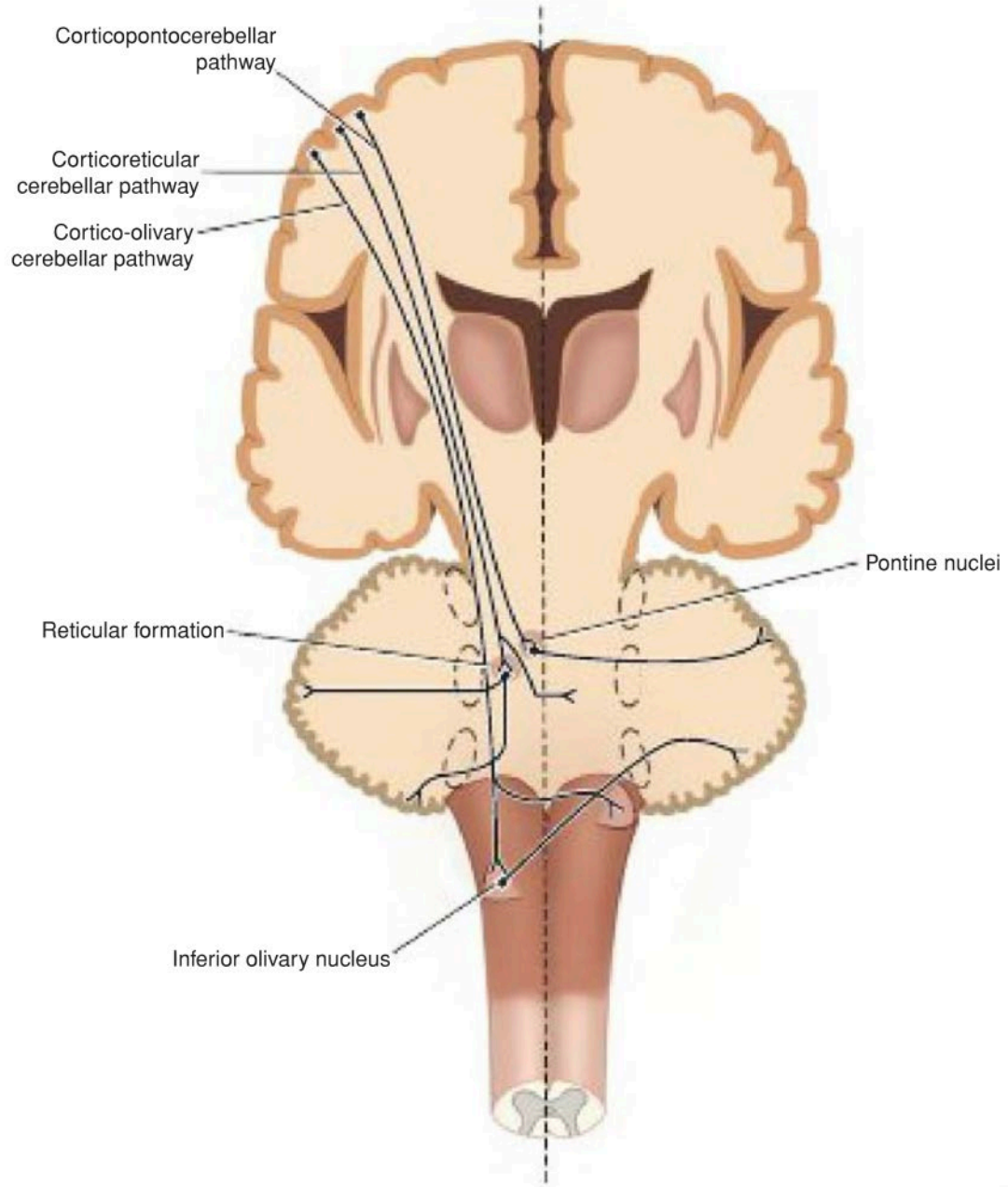


Figure 6-10 Cerebellar afferent fibers from the cerebral cortex. The cerebellar peduncles are shown as *ovoid dotted lines*.

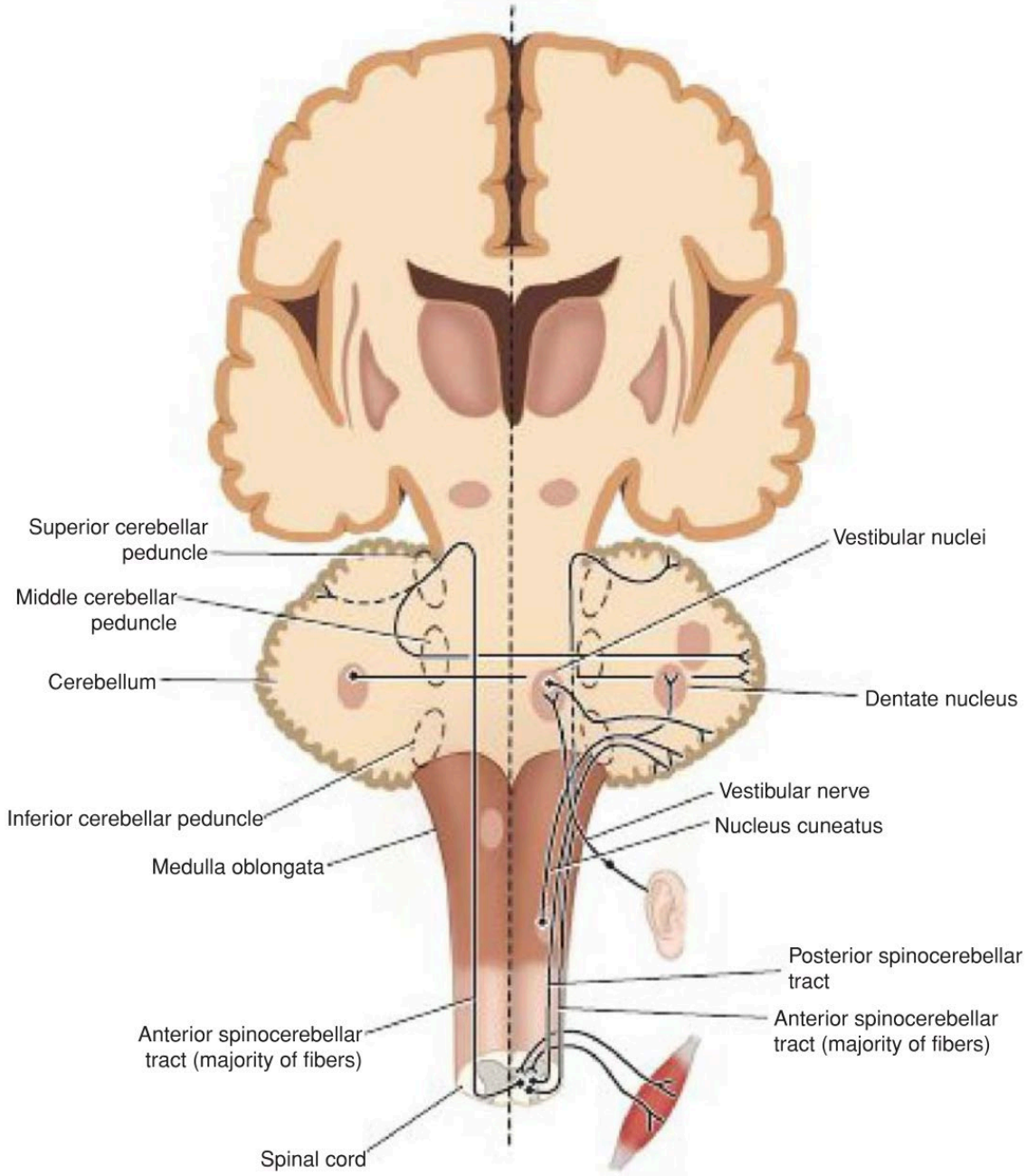


Figure 6-11 Cerebellar afferent fibers from the spinal cord and internal ear. The cerebellar peduncles are shown as *ovoid dotted lines*.

Snell's Clinical Neuroanatomy, 8e

Table 6-1 Afferent Cerebellar Pathways

Pathway	Function	Origin	Destination
Corticopontocerebellar	Conveys control from cerebral cortex	Frontal, parietal, temporal, and occipital lobes	Via pontine nuclei and mossy fibers to cerebellar cortex
Cerebro-olivocerebellar	Conveys control from cerebral cortex	Frontal, parietal, temporal, and occipital lobes	Via inferior olivary nuclei and climbing fibers to cerebellar cortex
Cerebroreticulocerebellar	Conveys control from cerebral cortex	Sensorimotor areas	Via reticular formation
Anterior spinocerebellar	Conveys information from muscles and joints	Muscle spindles, tendon organs, and joint receptors	Via mossy fibers to cerebellar cortex
Posterior spinocerebellar	Conveys information from muscles and joints	Muscle spindles, tendon organs, and joint receptors	Via mossy fibers to cerebellar cortex
Cuneocerebellar	Conveys information from muscles and joints of upper limb	Muscle spindles, tendon organs, and joint receptors	Via mossy fibers to cerebellar cortex
Vestibular nerve	Conveys information of head position and movement	Utricle, saccule, and semicircular canals	Via mossy fibers to cortex of flocculonodular lobe
Other afferents	Conveys information from midbrain	Red nucleus, tectum	Cerebellar cortex

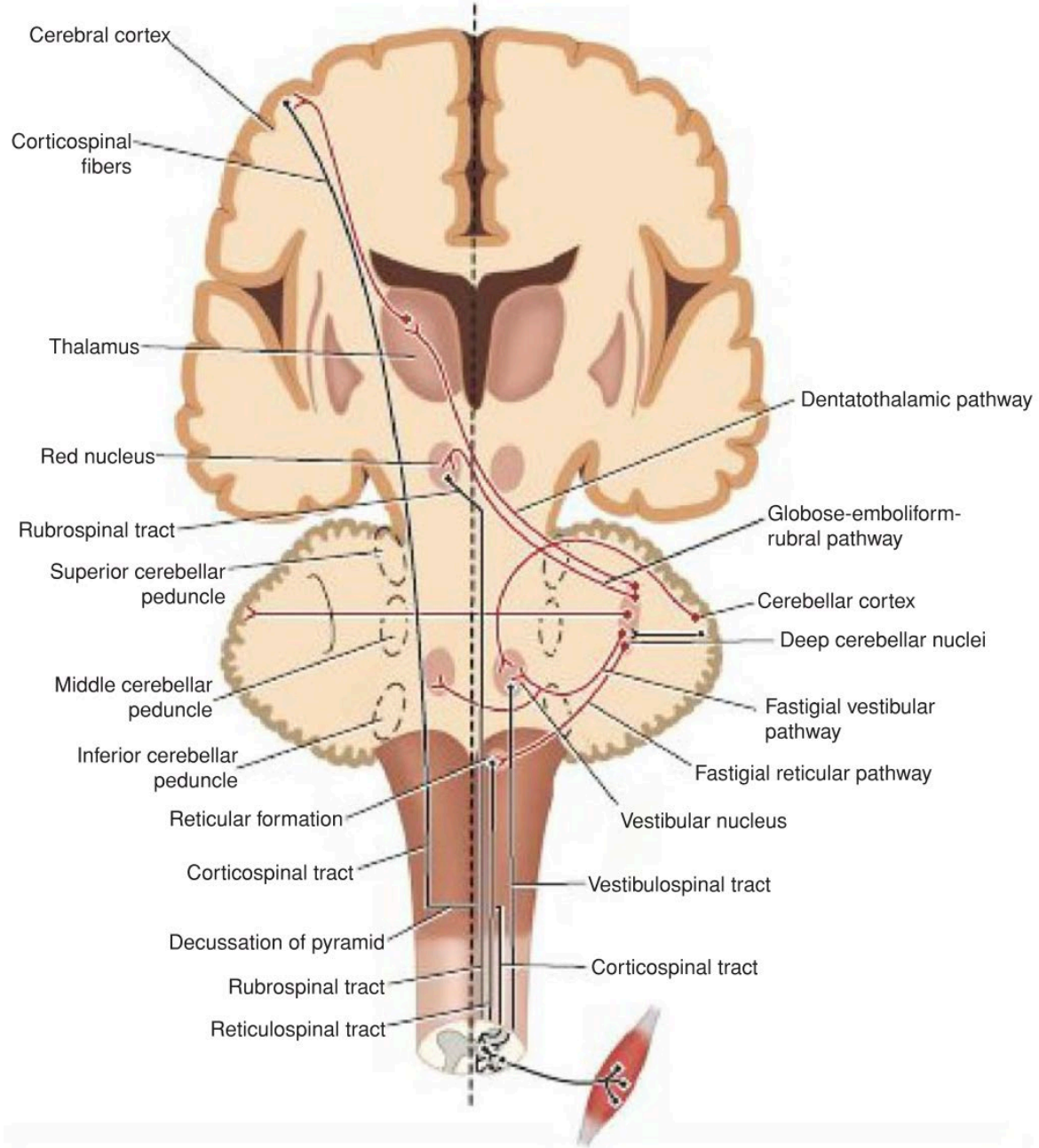
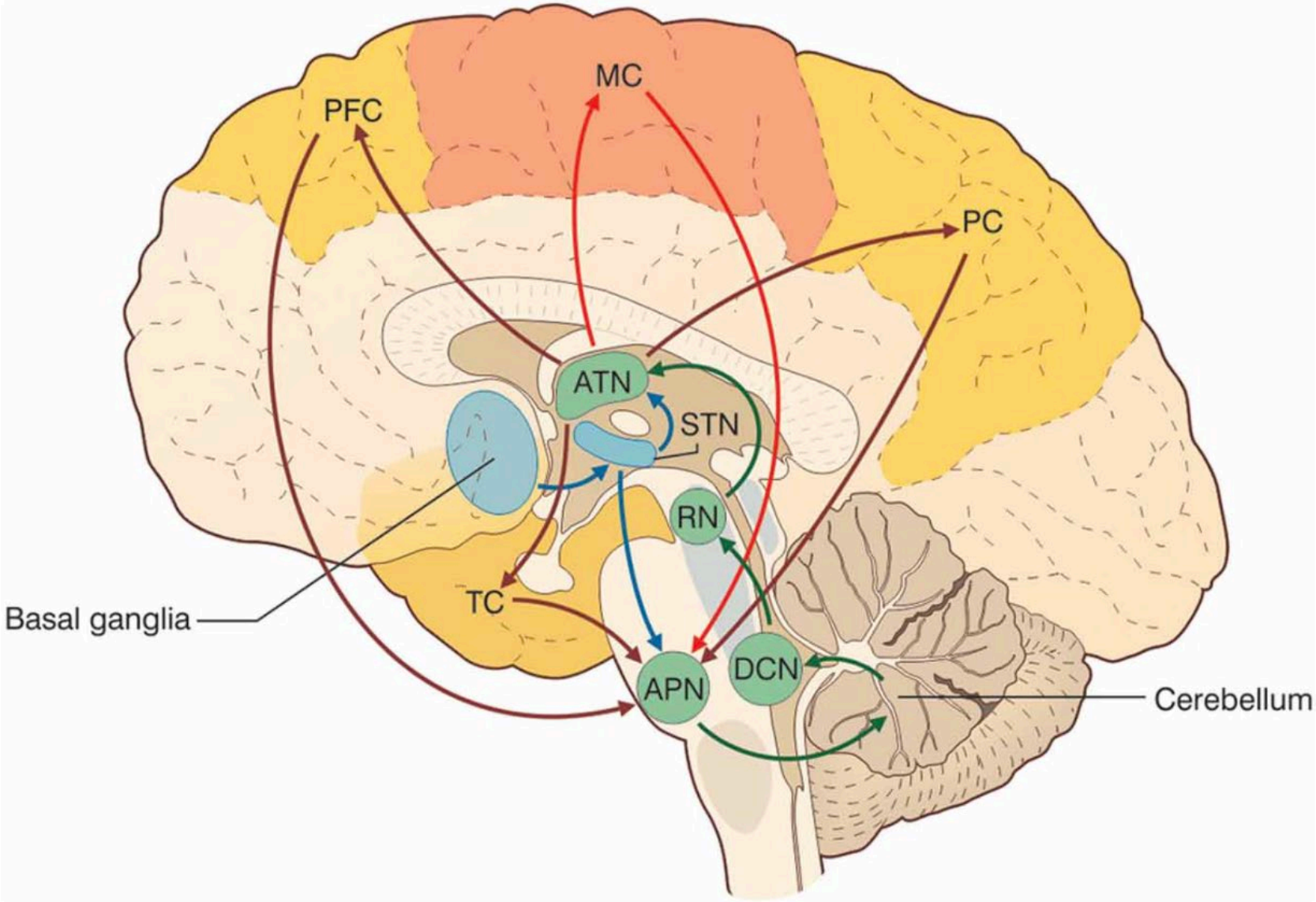


Figure 6-12 Cerebellar efferent fibers. The cerebellar peduncles are shown as *ovoid dotted lines.*

Table 6-2 Efferent Cerebellar Pathways[a]

Pathway	Function	Origin	Destination
Globose-emboliform-rubral	Influences ipsilateral motor activity	Globose and emboliform nuclei	To contralateral red nucleus, then via crossed rubrospinal tract to ipsilateral motor neurons in the spinal cord
Dentatothalamic	Influences ipsilateral motor activity	Dentate nucleus	To contralateral ventrolateral nucleus of the thalamus, then to contralateral motor cerebral cortex; corticospinal tract crosses midline and controls ipsilateral motor neurons in the spinal cord
Fastigial vestibular	Influences ipsilateral extensor muscle tone	Fastigial nucleus	Mainly to ipsilateral and to contralateral lateral vestibular nuclei; vestibulospinal tract to ipsilateral motor neurons in the spinal cord
Fastigial reticular	Influences ipsilateral muscle tone	Fastigial nucleus	To neurons of reticular formation; reticulospinal tract to ipsilateral motor neurons to the spinal cord



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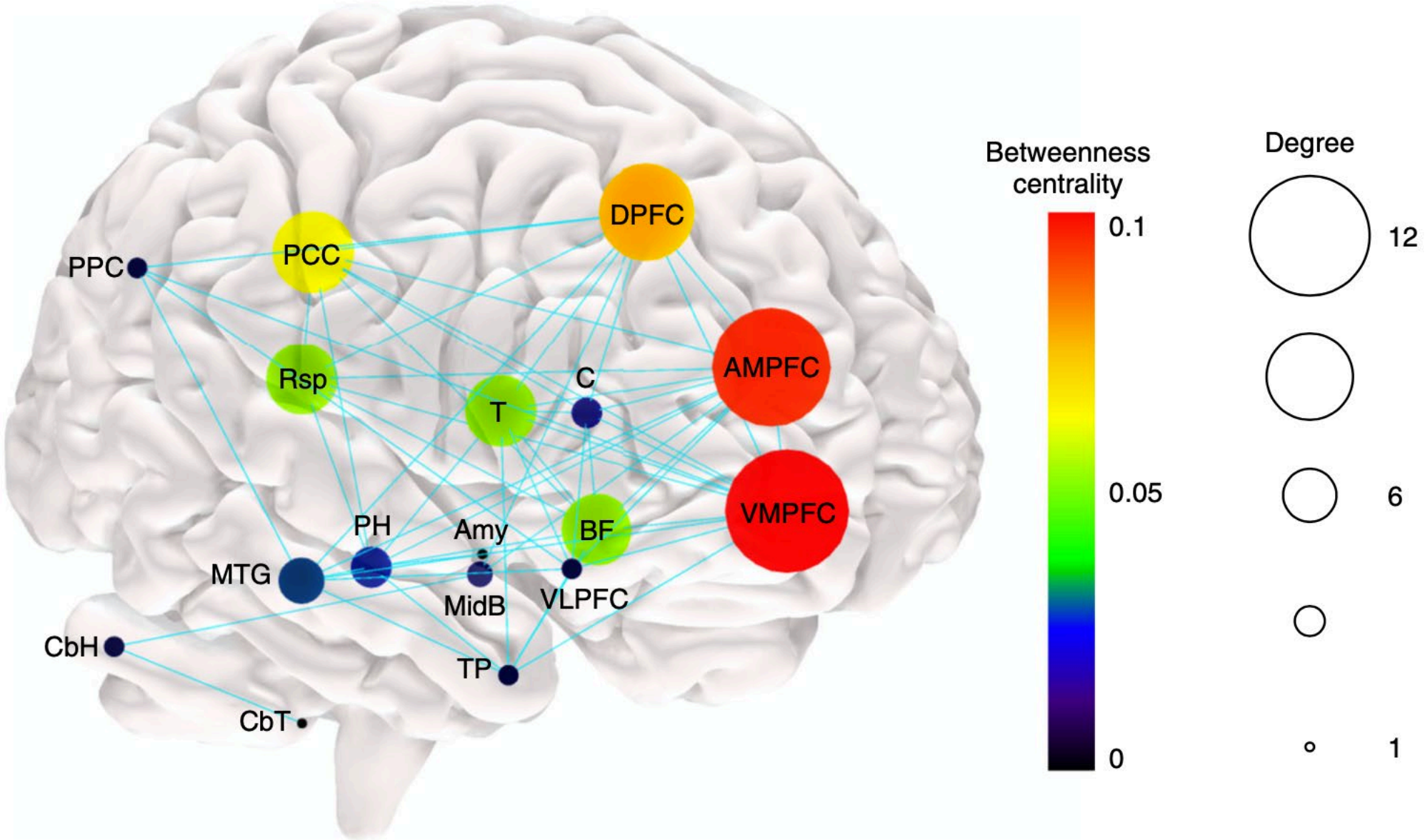

Alves, P.N., Foulon, C., Karolis, V. et al. An improved neuroanatomical model of the default-mode network reconciles previous neuroimaging and neuropathological findings. Commun Biol 2, 370 (2019). https://doi.org/10.1038/s42003-019-0611-3

1. Graph theory analysis of structural connectivity
2. The node size represents node degree and the node colour illustrates node betweenness centrality
3. The edges denote presence of structural connection

- DPFC - dorsal prefrontal cortex
- PPC - posterior parietal cortex
- VLPFC - ventrolateral prefrontal cortex
- Rsp - retrosplenial cortex
- MTG - middle temporal gyrus
- PCC - posterior cingulate cortex
- C – caudate
- DPFC - dorsal prefrontal cortex
- AMPFC - antero-median prefrontal cortex
- VMPFC - ventro-median prefrontal cortex
- TP - temporal pole
- BF - basal forebrain
- T - thalamus
- PH - parahippocampal region
- CbH - cerebellar hemisphere
- CbT - cerebellar tonsil
- Amy – amygdala
- MidB - midbrain

Alves, P.N., Foulon, C., Karolis, V. et al. An improved neuroanatomical model of the default-mode network reconciles previous neuroimaging and neuropathological findings. Commun Biol 2, 370 (2019). https://doi.org/10.1038/s42003-019-0611-3

Developmentally.....

Phylogenetic part of cerebellum	*Example*	*Components*	*Function*
Archicerebellum	Aquatic vertebrates	Flocculonodular lobe, lingula	Maintenance of equilibrium
Paleocerebellum	Terrestrial vertebrates	Anterior lobe except lingula, pyramid and uvula	Controls tone, posture and crude movements of limbs
Neocerebellum	Higher animals	Middle lobe except pyramid and uvula	Regulation of fine movements of body

External of differentiation of cerebellum

Metencephalon

↓

Proliferation of cells *rhombic lip*

↓

Fusion of rhombic lips in midline

↓

Formation of cerebellar plate

↓ *Proliferation*

Primitive cerebellum

↓ *Differentiation*

Central vermis and
bilateral cerebellar hemispheres

↓ *Development of fissures*

Separation of lobes and lobules

Cellular differentiation of cerebellum

3 layers of rhombic lips
(ependymal, mantle, marginal)

↓

Outward migration

Cerebellar nuclei
(dentate, emboliformis,
globusus and fastigius)

Formation of external
granular layer

↓ Differentiation

Cerebellar cortex

BOX 4.1 Timetable of Major Developmental Events in the Posterior Fossa

Before 20 Weeks

- 4 weeks: neural tube closure
- 5 weeks: anterior neural tube flexures form
- 7–8 weeks: neuronal proliferation accelerates in dorsomedial ventricular zone—origin of all inhibitory GABAergic neurons (express *Ptf1*)
- 10 weeks: transverse crease (plica choroidea) forms in fourth ventricular roof
- 10 weeks: foramen of Magendie begins to form
- 10 weeks Blake pouch begins to perforate; by 24–26 weeks ~⅔ have resolved
- 12 weeks: neuronal proliferation accelerates in dorsolateral subventricular zone of the rhombic lips—origin of all excitatory glutamatergic neurons (express *Atoh*)
- 12–13 weeks: cerebellar hemispheres and vermis (see Box 4.2) begin to emerge
- 14–17 weeks (as late as 26 weeks): foramina of Luschka form

Volpe's Neurology of the Newborn, 6e.pdf

By 20 Weeks

- Radial migration of GABAergic interneurons from ventricular zone to form deep cerebellar nuclei and Purkinje cell layer
- Tangential migration of glutamatergic cells (1) from rostral rhombic lip to form external granular layer; (2) from caudal rhombic lip to form pontine and inferior olivary nuclei

From 20 to 30 Weeks

- Rapid expansion of external granular layer (EGL) and early foliation
- At peak thickness EGL 6–9 cells deep, divided into inner and outer layers
- 29 weeks: external granular cell precursors cover entire cerebellar surface
- EGL neurons begin inward radial migration along Bergmann glial cells to form internal granular layer (IGL)
- Purkinje cells differentiate and secrete *Shh* that stimulates proliferation of precursor cells in the EGL

Volpe's Neurology of the Newborn, 6e.pdf

From 30 to 40 Weeks

- Massive EGL proliferation and inward migration leads to fivefold volumetric growth of the cerebellum.

After 40 Weeks

- EGL gradually dissipates throughout first postnatal year and IGL cells become greatly compacted
- Purkinje cells enlarge and differentiate as major outflow to dentate nuclei
- Purkinje cell differentiation enlarges the molecular layer several fold

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BOX 4.2 Normal Development of the Vermis (Figs. 4.7, 4.8, and 4.9)

By 18–20 Weeks' Gestation

- Normal gestational age-appropriate rostrocaudal length as late as 24 weeks
- Caudal edge covers the fourth ventricle and reaches the obex
- Primary fissure is present between the anterior and posterior lobes of the vermis
- Fastigium-declive line divides the vermis into anterior and posterior lobes with a 1:2 ratio.

By 27–28 Weeks' Gestation

- Mature pattern of vermian lobules and fissures.

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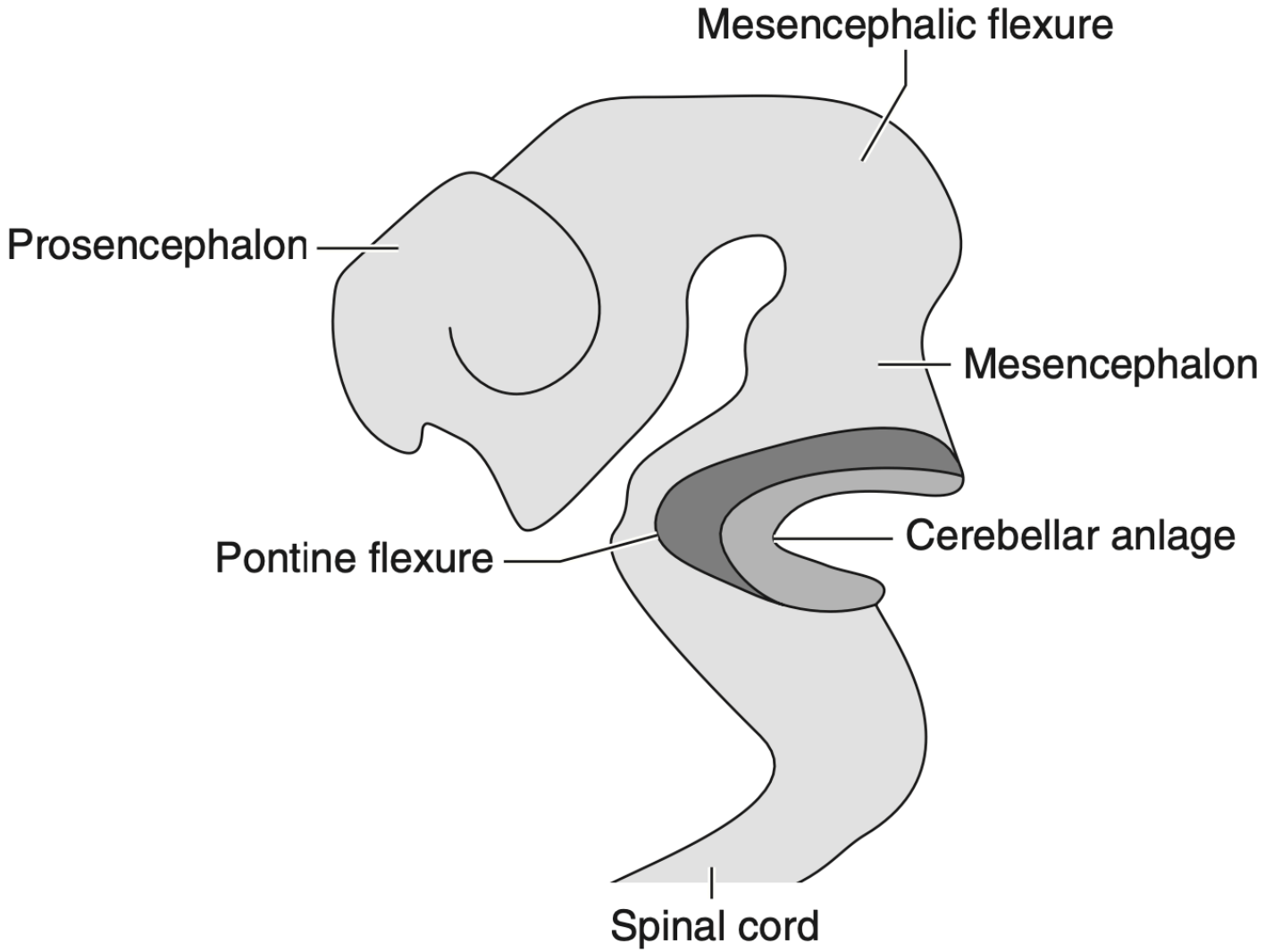

Figure 4.1 Human fetal brain stem at 7 weeks gestational age. Note the kink formed by the mesencephalic, pontine, and cervical flexures. (Image based on Stroustrup Smith et al. *J Ultrasound Med*. 2006; and image courtesy Veronika Doljenkova [Rhode Island School of Design, Providence, RI] with reference to Sarnat[1] and Sadler[2].)

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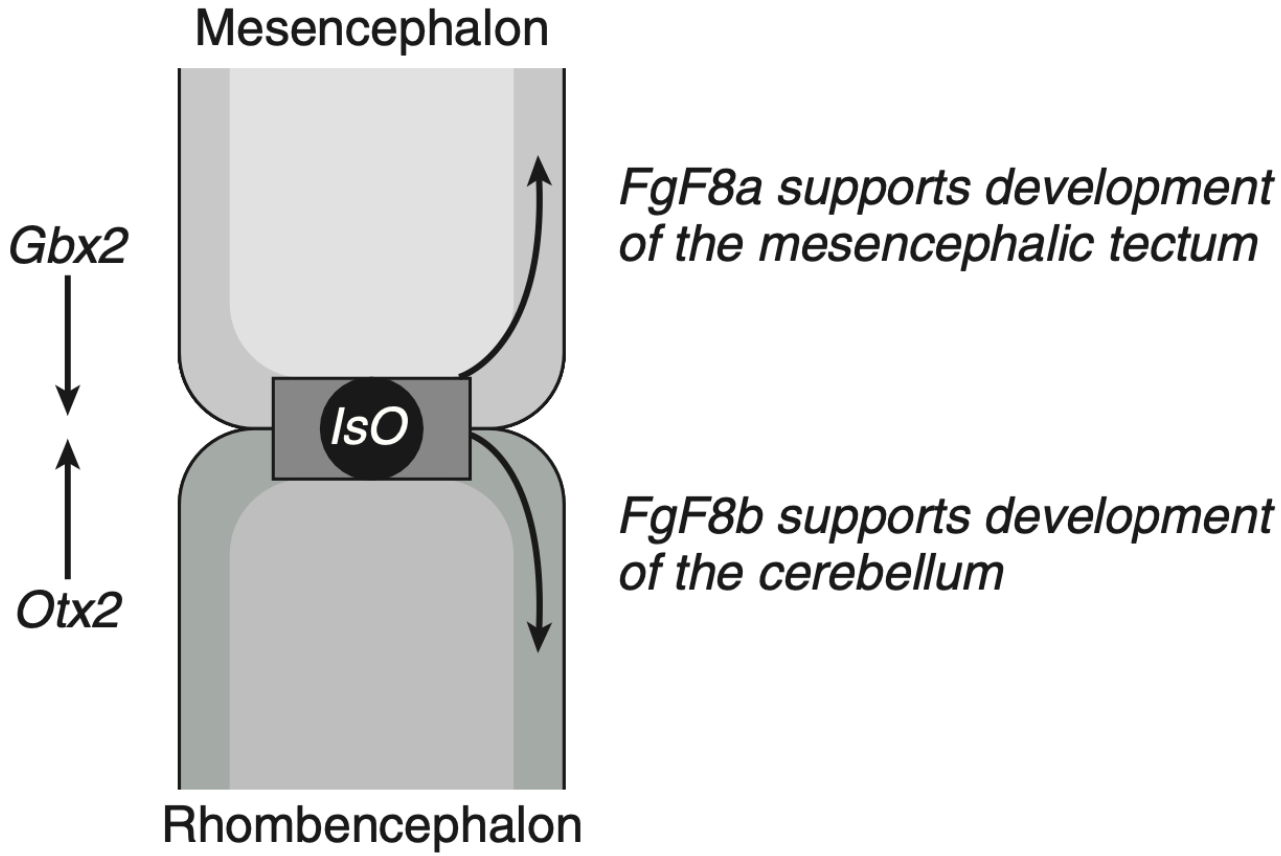

Figure 4.2 Patterning events at the developing midbrain-hindbrain junction. *IsO*, isthmic organizer; *Otx2*, homeobox protein encoded by the orthodenticle homeobox 2 (OTX2) gene; *Gbx2*, homeobox protein encoded by the gastrulation brain homeobox 2 (GBX2) gene; *FgF8a* and *b*, fibroblast 8 growth factors a and b encoded by the FgF8 gene.

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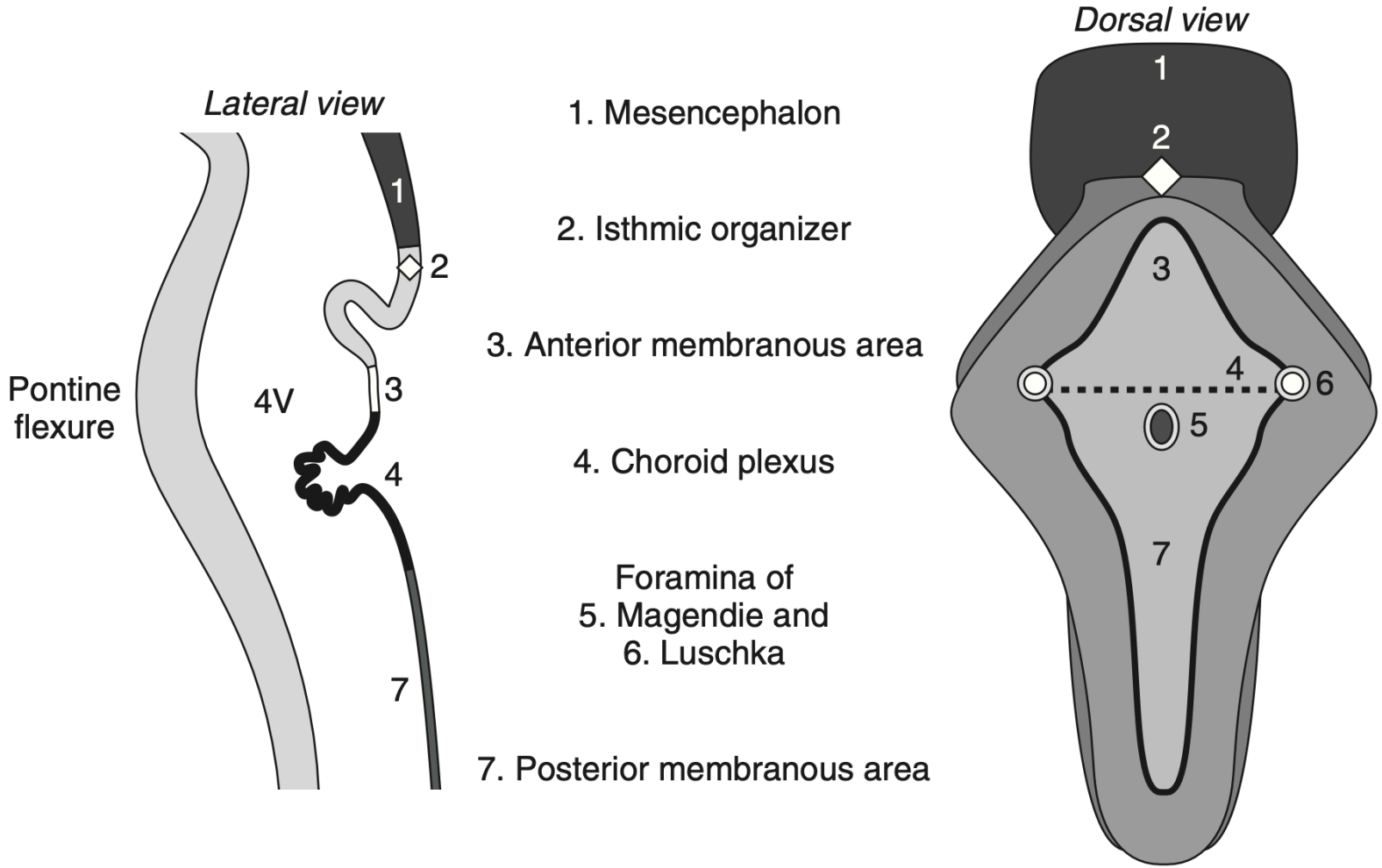

Figure 4.3 Normal landmarks of the developing fourth ventricular roof.

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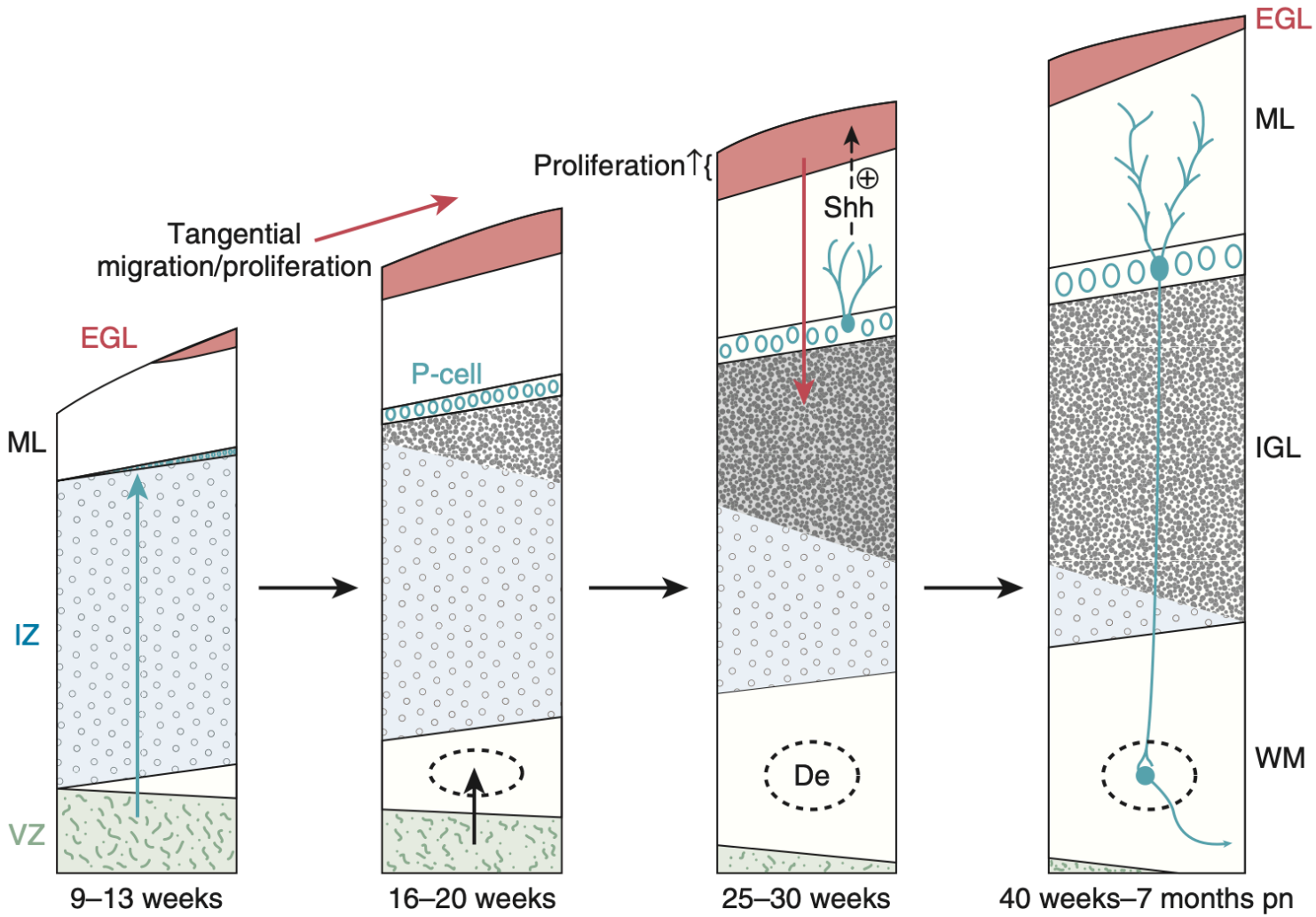

Figure 4.4 Major events in the histogenesis of the cerebellum in four major time periods from 9 weeks of gestation to 7 months postnatal (pn). The two zones of proliferation are the ventricular zone (VZ) and the external granule cell layer (EGL). Three directions of migration are indicated by arrows; that is, radial from the VZ, tangential over the surface of the cerebellum to form the EGL, and later, inward to form the internal granular layer (IGL). Proliferation in the outer half of the EGL is under positive control by Sonic hedgehog (Shh) secreted by Purkinje cells (P-cells). Note the markedly active proliferation and migration of the granule precursor cells of the EGL during the premature period. Not shown is the marked increase in size of the molecular layer (ML) during the postnatal period. *De*, dentate; *IZ*, intermediate zone; *WM*, white matter. (From Limperopoulos C, Soul JS, Gauvreau K, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. *Pediatrics*. 2005;115:688-695, with permission.)

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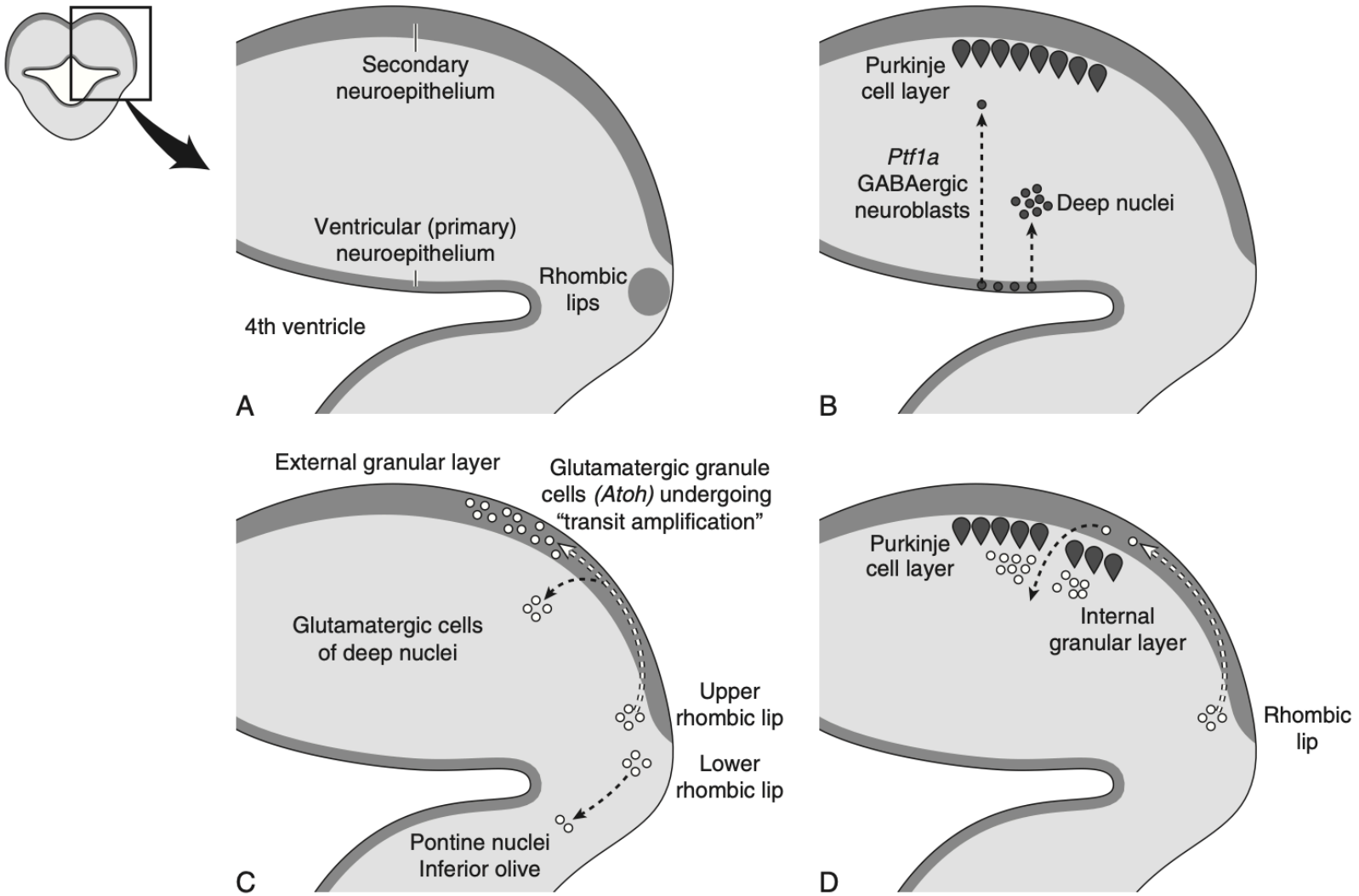

Figure 4.5 (A) Cerebellar primary and secondary neuroproliferative sites. (B) Neuronal migration of GABAergic cells from the primary ventricular neuroepithelium. (C) Neuronal proliferation and migration of glutamatergic neuronal precursors from the rhombic lips into the secondary neuroproliferative zone of the external granular layer. (D) Internal migration of the granule cells from the external granular layer through the Purkinje cell layer to form the internal granular layer.

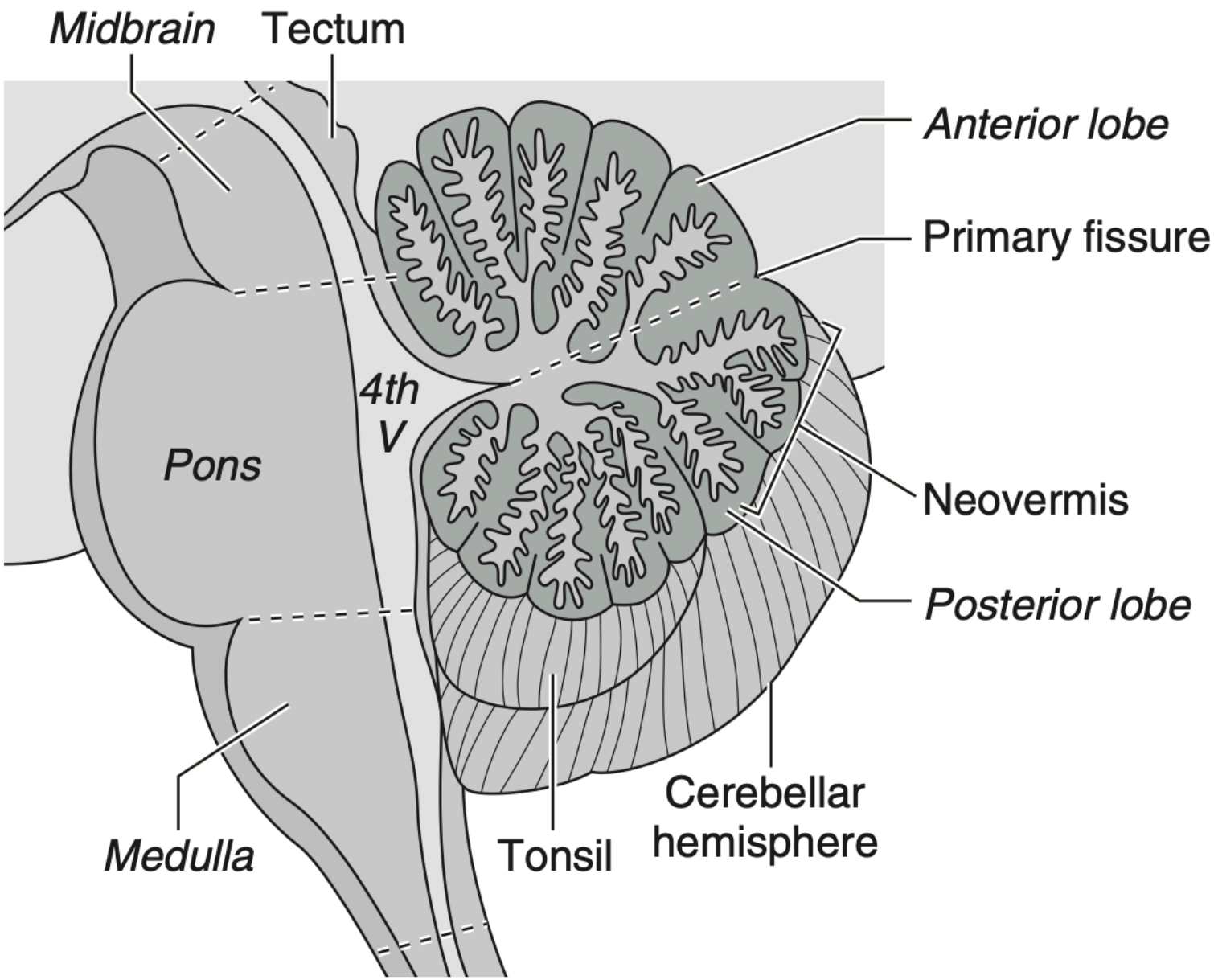

Figure 4.7 Normal mature vermis and its landmarks.

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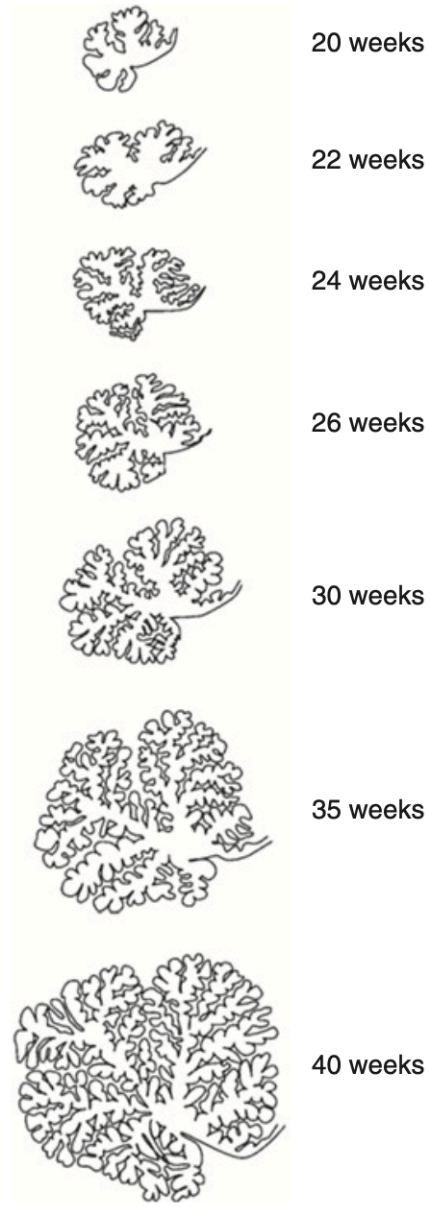

Figure 4.8 Growth of the cerebellar surface from 24 to 40 weeks. Drawings were made in the mid-sagittal plane. Note the extraordinary increase from 24 weeks to 40 weeks in cerebellar surface area, related primarily to increased foliation but also to increased overall cerebellar growth. (Adapted from Rakic P, Sidman RL. Histogenesis of cortical layers in human cerebellum, particularly the lamina dissecans. *J Comp Neurol*. 1970;139:473–500.)

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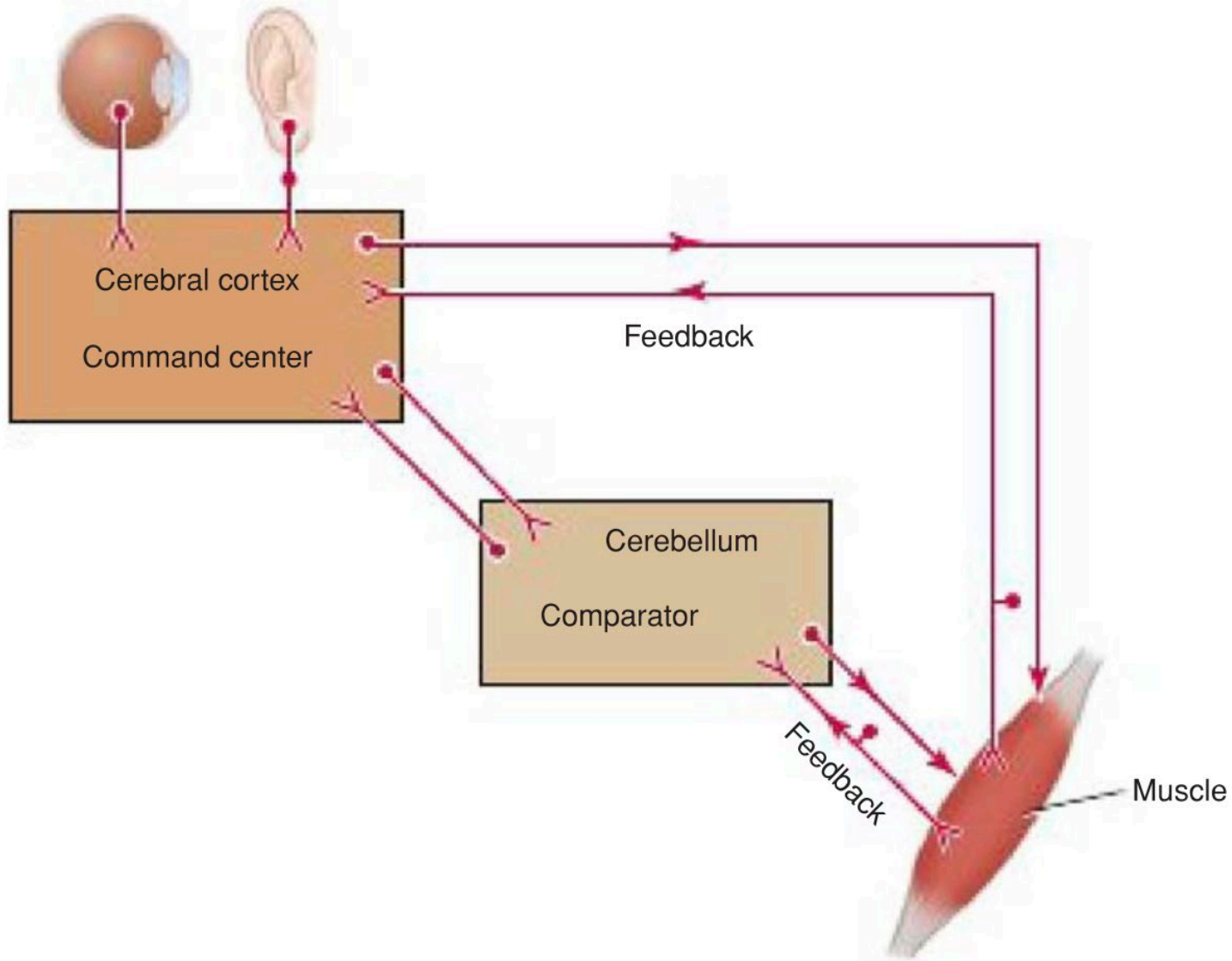
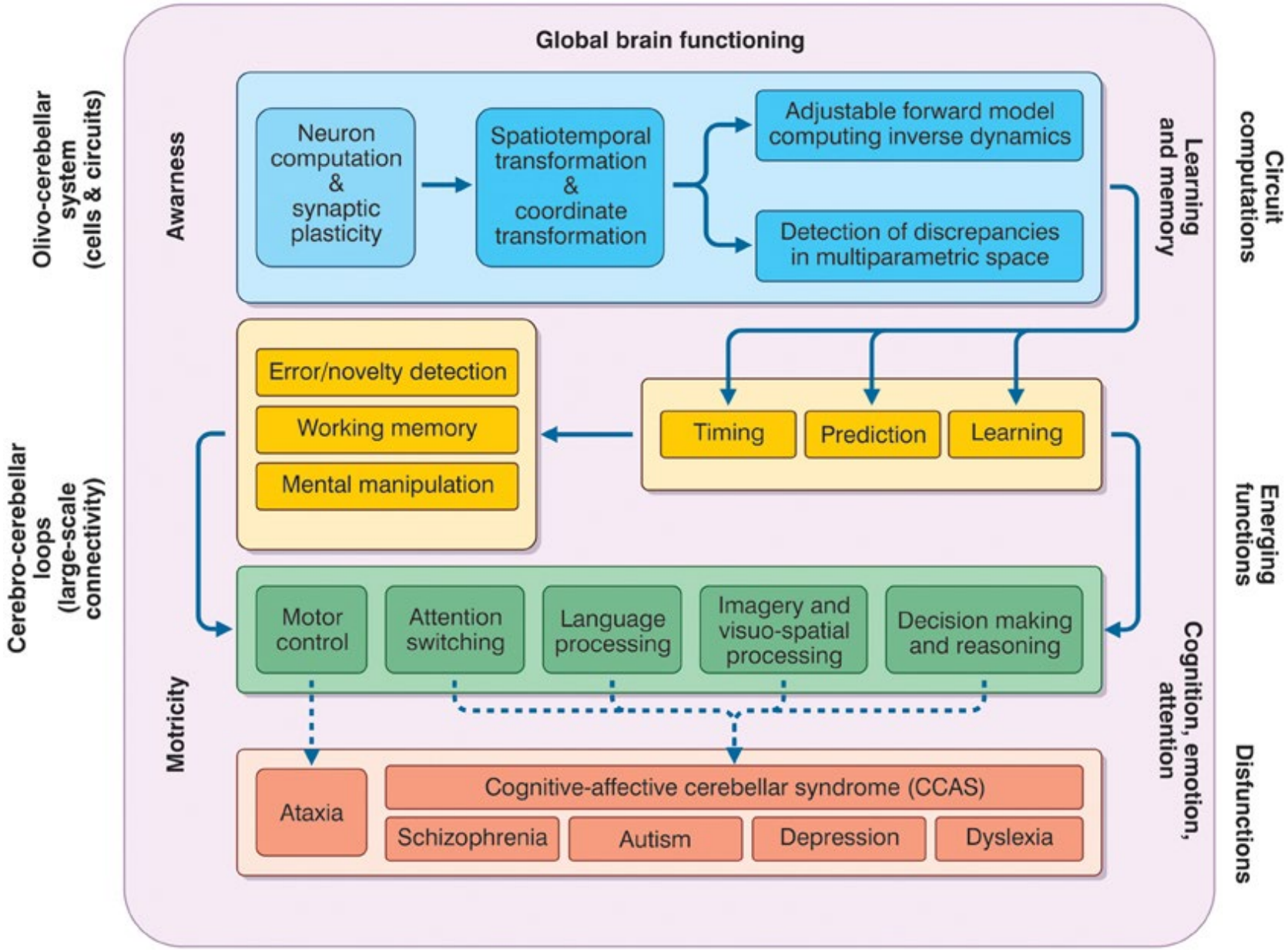


Figure 6-13 Cerebellum serving as a comparator.



Egidio D'Angelo and Stefano Casali, doi: 10.3389/fncir.2012.00116

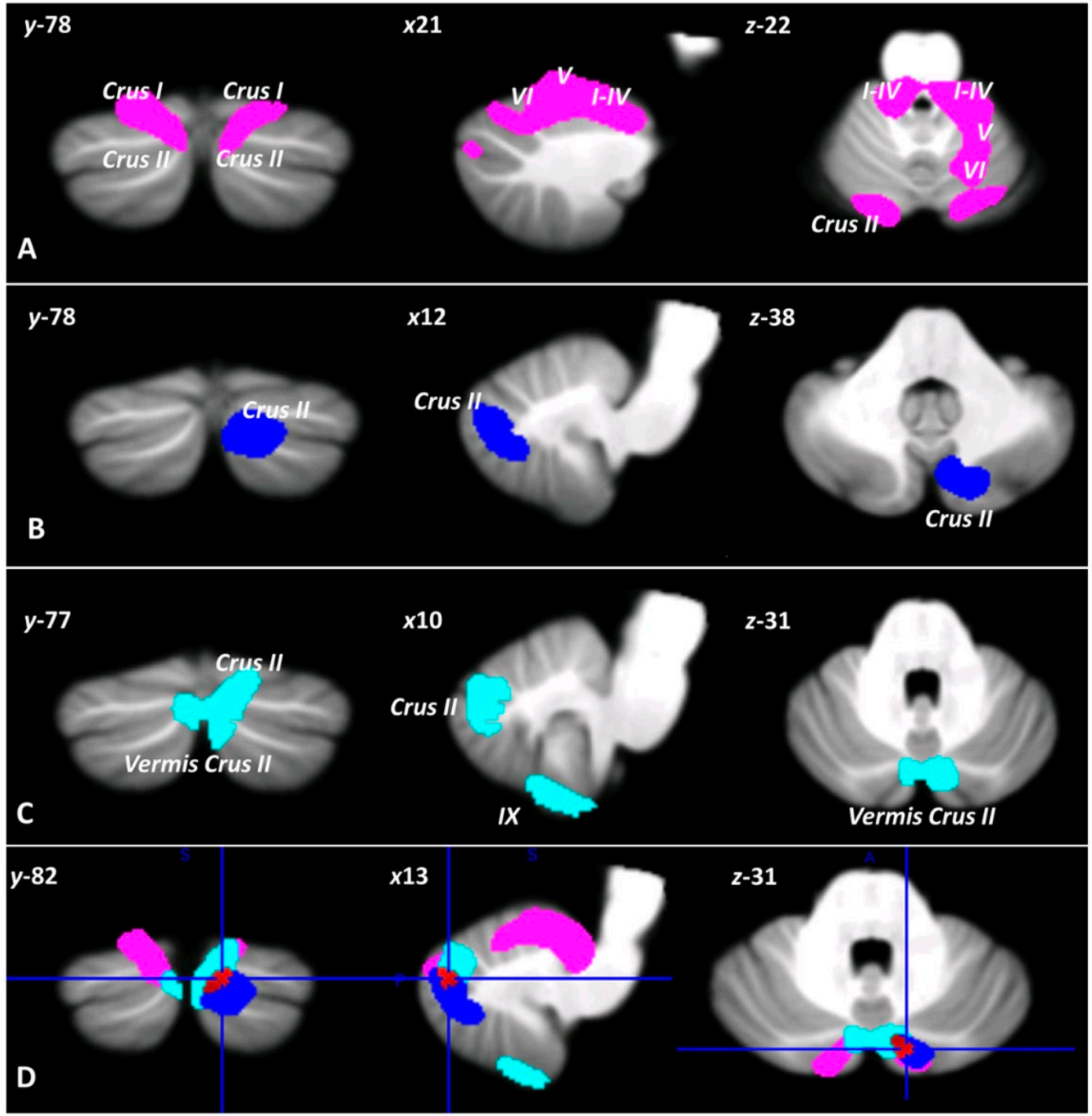
Clinically……

- Inputs from the spinal cord and brainstem enter the cerebellum through the inferior cerebellar peduncle
- Afferents from the cerebral cortex (relayed in the pontine nuclei) enter through the middle cerebellar peduncle - balance and movement
- The cerebellum projects to the brainstem and cerebral motor cortex via the red nucleus and ventrolateral nucleus of the thalamus
- There are three output pathways from the cerebellum
  - the cerebellar vermis indirectly to the pons, medulla, and reticular formation
  - the intermediate zone of the cerebellum indirectly to the red nucleus and thalamus
  - the lateral zone of cerebellar hemisphere indirectly to the thalamus
- Thalamus - cerebral cortex, including frontal cortex, motor cortex, and parietal cortex
- The cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways allow the cerebellum to affect information processing in cortical areas responsible for cognitive and emotional processes

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

- Social prediction is a key feature of social cognition (SC)
- SC profiles of individuals with cerebellar neurodegenerative disorders (CB), autism (ASD), bipolar disorder type 2 (BD2), or healthy subjects (HS) using a battery of social tests requiring different degrees of prediction processing.
- The patterns of cerebellar gray matter (GM) alterations were compared among the groups using voxel-based morphometry
- Compared to HS, the clinical groups showed common SC deficits in tasks involving a moderate to high level of prediction
- The behavioral results of the clinical groups are consistent with the presence of overlapping GM reduction in cerebellar right Crus II, an area notably involved in complex social processing and prediction

Olivito, G et al. The Cerebellum Gets Social: Evidence from an Exploratory Study of Cerebellar, Neurodevelopmental, and Psychiatric Disorders. Biomedicines 2023,11,309. https://doi.org/ 10.3390/biomedicines11020309



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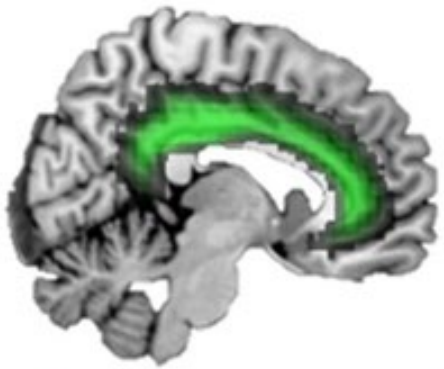
Autism Spectrum Disorders

- Cerebellar damage in infants can predict the occurrence of autism in older age
- Influence the motor cortex and prefrontal cortex area - motor control and social cognition
- PM investigations have also shown a decrease in Purkinje cell density in patients with ASD
  - Being GABAergic, a reduction of these cells may increase activity in the cerebellum-cortex pathway, which may explain the occurrence of repeated movements in ASD
- Altered connectivity in the superior peduncles and the short intra-cerebellar fibers in patients with Asperger's syndrome
- Activity in the peduncle regions have also been related to poorer motor abilities in ASD
- Additional possible defect in the formation of cerebello-frontal circuits in Asperger's syndrome

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

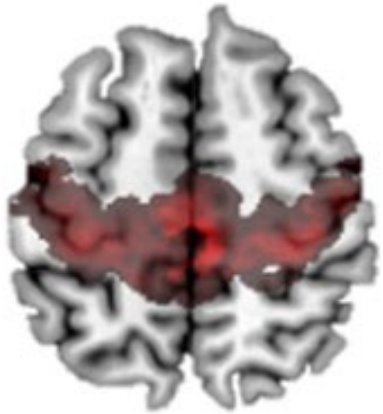
- Impairment of adaptation of social behavior in patients with ASD may be caused by malfunctioning feedback pathways from the cerebellum to the cerebral cortex
- The fibers of the middle and inferior cerebellar peduncles connecting the cerebellum with the frontal lobe are abnormally organized
- Direct cause or a consequence of changes in the cerebral cortex and cerebellar nuclei in patients with autism
- Specifically, pathological changes are evident in the superior peduncles of the cerebellum in children with ASD
- 3 main cerebellar abnormalities observed in patients with ASD
  - diminished Purkinje cells
  - reduced cerebellar volume
  - interrupted feedback pathways between the cerebellar and cerebral areas
  - the latter two may also be bi-products of diminished Purkinje cells

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066



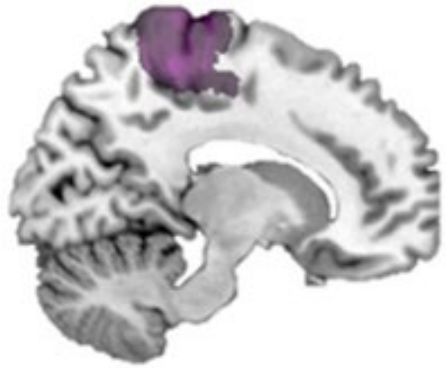
Posterior Vermis

- Affective dysregulation
- Social processing deficits
- Irritability



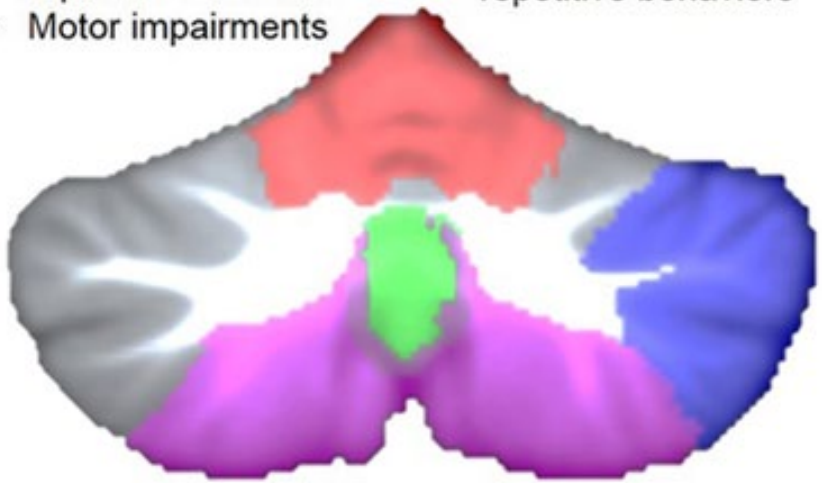
Anterior lobe

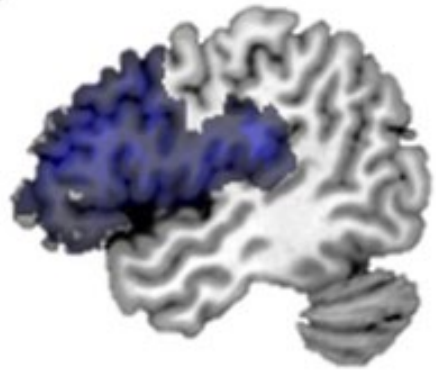
- Stereotyped and repetitive behaviors
- Motor impairments



VIIIA & VIIIB

- Stereotyped and repetitive behaviors



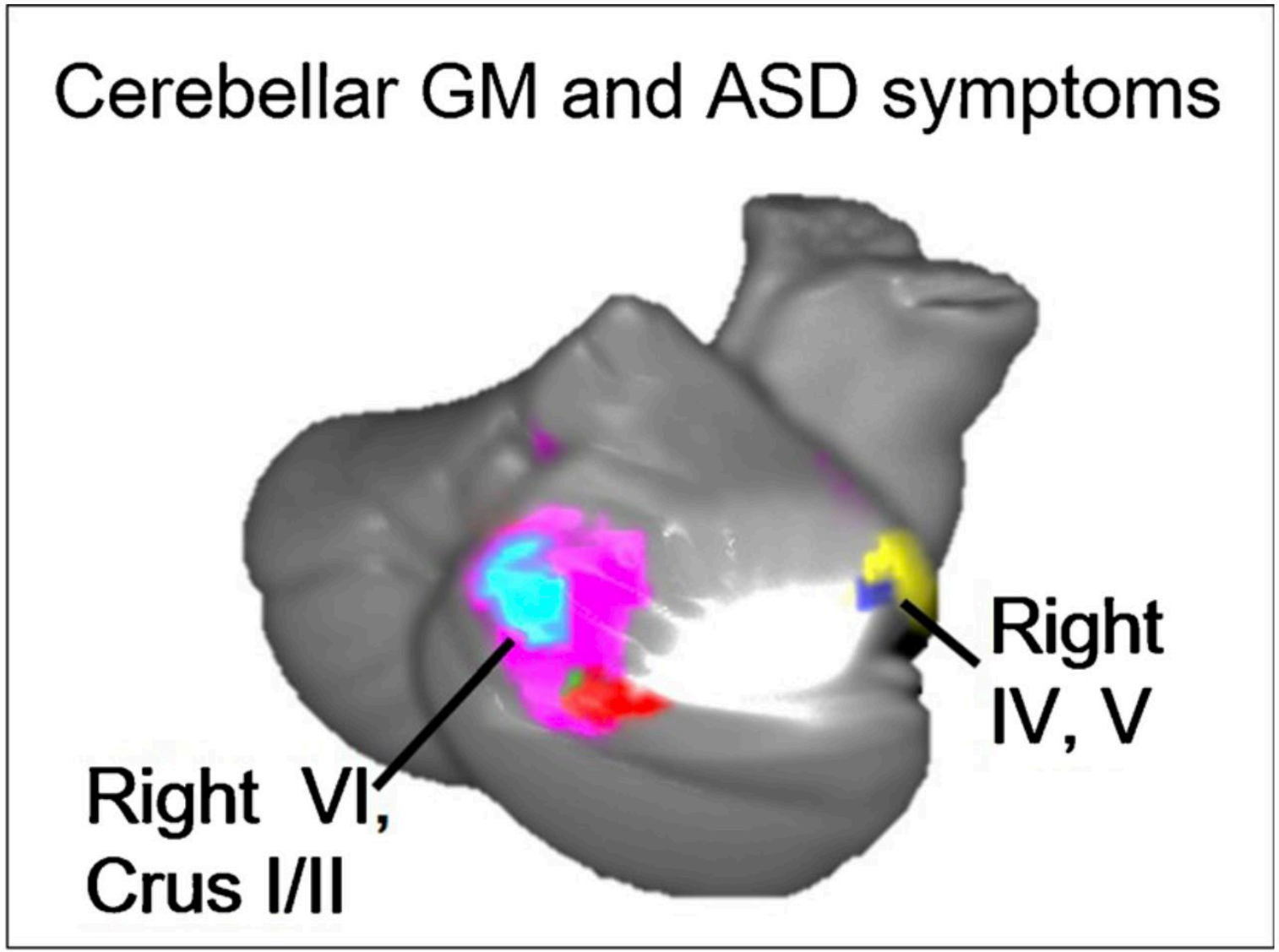


Right Crus I & II

- Language deficits
- Social cognition deficits
- Theory of mind deficits
- Face processing impairments
- Imitation impairments
- Stereotyped and repetitive behaviors

https://www.stoodleylab.org/research

Cerebellar GM and ASD symptoms



Catherine J. Stoodley. The Cerebellum and Neurodevelopmental Disorders. Cerebellum. DOI 10.1007/s12311-015-0715-3

- Red - region in right Crus I where ASD children showed significantly reduced grey matter compared with a group of age-matched typically developing children

- Correlations between cerebellar grey matter and scores converged on right lobules VI and VII for ADOS Social Interaction (violet), ADOS Social Interaction + Communication (cyan), and ADOS Stereotyped Behaviors & Restricted Interests (green)

- ADI Social Interaction (blue) and ADI Restricted, Repetitive, & Stereotyped Behaviors (yellow) scores were associated with grey matter volume in the anterior cerebellum

Catherine J. Stoodley. The Cerebellum and Neurodevelopmental Disorders. Cerebellum. DOI 10.1007/s12311-015-0715-3

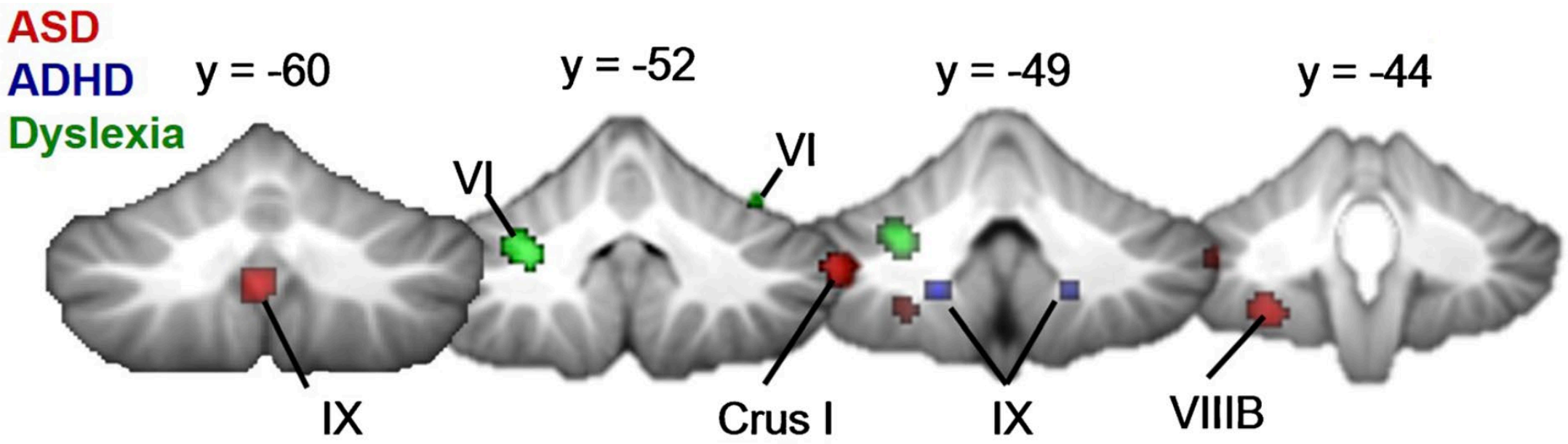
- No striking difference in cerebellar anatomy of individuals with autism.

Charles Laidi et al. Cerebellar Atypicalities in Autism. Biological Psychiatry October 15, 2022; 92:674–682. https://doi.org/10.1016/j.biopsych.2022.05.020

ADHD

- Structural and functional neuroimaging studies show changes in prefrontal cortex, cingulum, basal ganglia, corpus callosum, and cerebral total volume
- Volumetric abnormalities with reduced cerebrum and cerebellum size that increased with age, while changes in the caudate nucleus volume disappeared as the subjects got older
  - Results were found to be unrelated to psychostimulant treatments
- Stimulant treatment - larger overall cerebellar volume than untreated ADHD patients
- Cerebellar differences between children with ADHD and healthy controls over the period of 2–14 years
- ADHD patients - smaller vermis than controls, which did not change with development
  - Smaller superior vermis volumes predicted poorer outcomes
- Patients with smaller vermis lobules due to stroke or other developmental abnormalities also demonstrate a diminished attention-orienting ability

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066



Catherine J. Stoodley. The Cerebellum and Neurodevelopmental Disorders. Cerebellum. DOI 10.1007/s12311-015-0715-3

- Different cerebellar regions show grey matter reductions in ASD (red), ADHD (blue), and developmental dyslexia (green)

Catherine J. Stoodley. The Cerebellum and Neurodevelopmental Disorders. Cerebellum. DOI 10.1007/s12311-015-0715-3

Schizophrenia

- Disturbances in the cortico-thalamic-cerebellar-cortical circuits – impaired cognitive functioning
- Lower level of cortico-thalamic-cerebellar activity compared to healthy controls during task performance
- Reduced cerebellar volumes in schizophrenia patients - including diminished cerebellar vermis volume
- Changes in cerebellar volume in patients with schizophrenia have been linked to:
  - neural and behavioral abnormalities occurring in the perinatal period
  - male patients
  - onset at extremes of age
  - chronic nature of the disease
  - predominantly positive symptoms

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

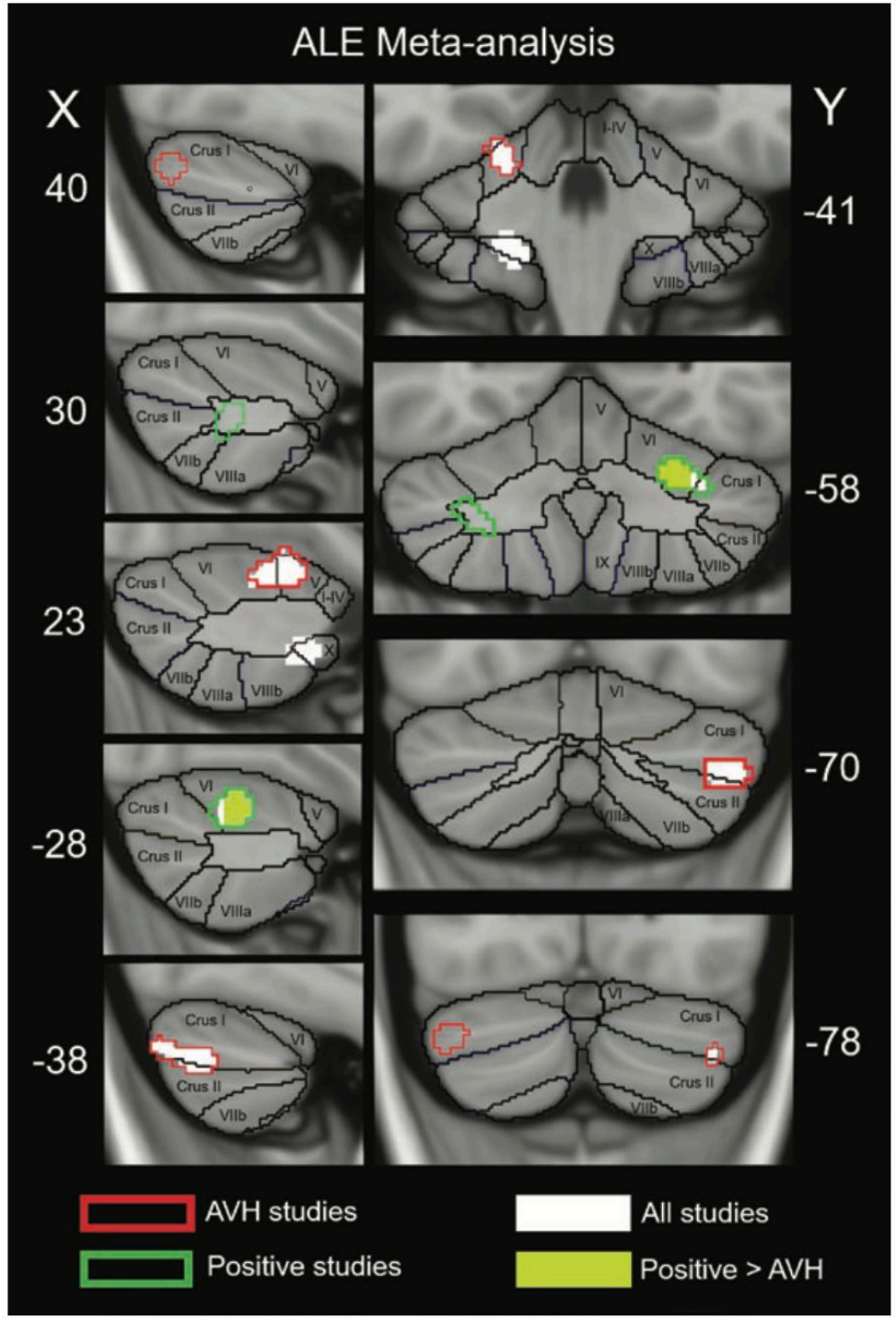
- Diminished blood flow to the cerebellar cortex and vermis during the performance of many cognitive tasks, such as attention, memory, including both short-term and working memory tasks, and social inference

- Reduction in cerebellar activity in patients with schizophrenia developing akathisia during treatment with olanzapine

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

- Cerebellar differences were more consistently associated with AVH than with aggregated positive symptom measures, particularly when considering resting-state functional connectivity data
- These differences were not moderated by age, sex, medication, or symptom severity
- The ALE meta-analysis revealed a spatial convergence of these differences in lobules V–VI and crus I
- Cerebellar dysconnectivity might indicate a specific liability for AVH, particularly in sensorimotor (lobules V–VI) and cognitive (crus I) cerebellar zones
- These abnormalities may contribute to altered sensory feedback processing and, consequently, affect higher level cognitive functions (eg, cognitive control) in AVH

Ana P. Pinheiro et al. The Cerebellum Links to Positive Symptoms of Psychosis: A Systematic Review and Meta-analysis. Schizophrenia Bulletin Open. https://doi.org/10.1093/schizbullopen/sgab039



Ana P. Pinheiro et al. The Cerebellum Links to Positive Symptoms of Psychosis: A Systematic Review and Meta-analysis. Schizophrenia Bulletin Open. https://doi.org/10.1093/schizbullopen/sgab039

Bipolar Disorder

- Smaller cerebellar regions present in both patient populations
- Volume of the V3 vermal subregion of the cerebellum is significantly reduced in multiple-episode bipolar disorder patients compared to healthy controls
- Volume of V2 vermal subregion is smaller in multiple-episode patients than first-episode patients
- Severity of bipolar symptoms is associated with increased vermal damage
- Cerebellar volume reduction is much higher in medication naïve patients compared to patients undergoing anti-manic drug regime
- Increased glucose metabolism was found in the cerebellum of BD patients that were resistant to treatment
- ?? primary or secondary to BD

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

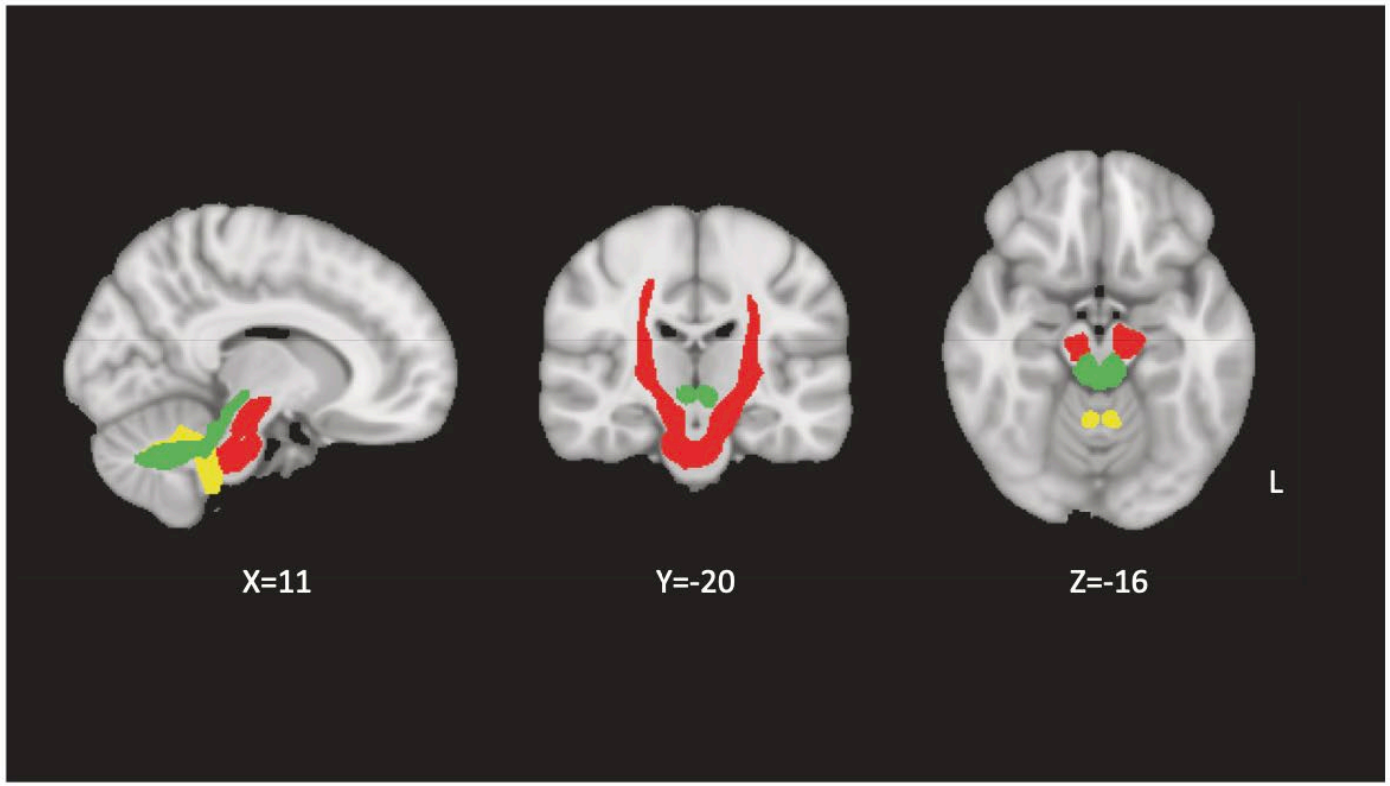


Fig. 1 Tracts of interest. The bilateral cortico-ponto-cerebellar tracts, the superior cerebellar tracts, and the inferior cerebellar tracts, defined by tractography-based atlas, are presented in red, green, and yellow respectively. L = left.

Le Hou et al. Integrity of cerebellar tracts associated with the risk of bipolar disorder. Translational Psychiatry (2022)12:335 ; https://doi.org/10.1038/s41398-022-02097-4

- HR group had significantly reduced mean diffusivity (MD) ($p = 0.043$) and radial diffusivity (RD) ($p = 0.039$) of the left portico-ponto-cerebellar tracts when compared with the BD group

- Logistic regression results showed that the specific diffusivity measures of cerebellar tracts (e.g., cortico-ponto-cerebellar tract), particularly the RD and MD revealed differences between groups at different BD stages after controlling for the covariates

- Structural brain differences across healthy individuals and individuals of different BD stages (high risk, ultra-high risk, and BD) and the risks for developing BD associated with these brain differences

- Specific diffusivity of cerebellar tracts (e.g., cortico-ponto-cerebellar tract) revealed differences between groups at different BD stages which is helpful in detecting the trajectory changes in BD syndromes in the early stages of BD, particularly when the BD syndromes start from HR stage

Le Hou et al. Integrity of cerebellar tracts associated with the risk of bipolar disorder. Translational Psychiatry (2022)12:335 ; https://doi.org/10.1038/s41398-022-02097-4

MDD

- Smaller cerebellum, significantly smaller vermis
- Blood flow in the vermal areas of the cerebellum
  - Acutely depressed patients on various antidepressant medications showed increased cerebellar activity and blood flow in the vermis when compared to remitting or healthy subjects
- Positive correlation with
  - severity of the depressive episodes
  - severity of cognitive deficits
  - resistance to antidepressant medications
- Medication naive patients – abnormal cerebellar connectivity with the ACC
- Abnormal connections between the cerebellum and frontal lobe have also been found in patients with severe depression, treatment resistant & geriatric depression

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

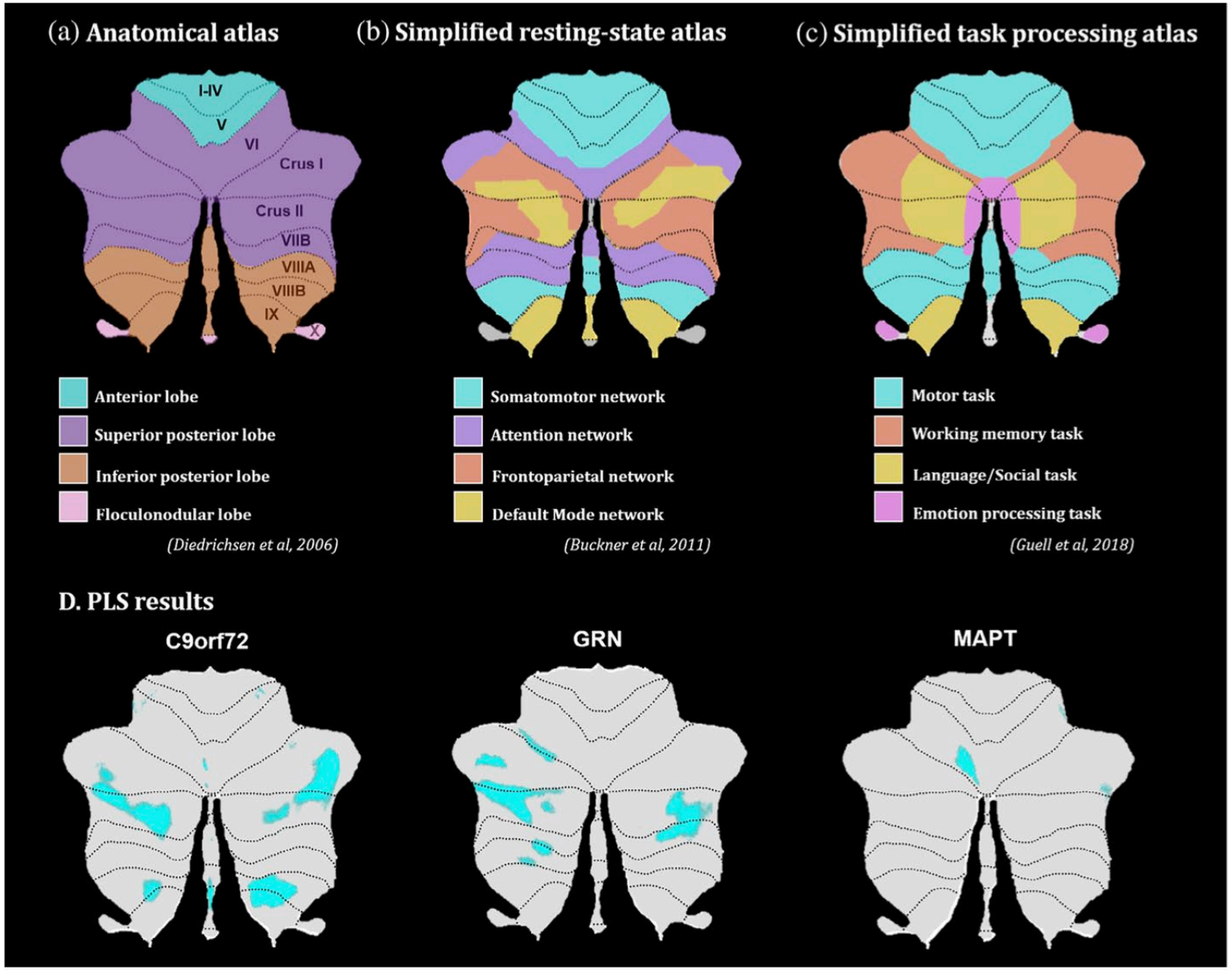
Anxiety disorders

- Impaired cerebellar function - linked to increased arousal present in PTSD, GAD, SAD
- Increased cerebellar activity when re-experiencing the traumatic event in PTSD
- Cerebellar hyperactivity correlated positively with increased blood pressure and heart rate - regulation of sympathetic activity
- Panic Disorder - high-glucose metabolism levels in the pons, midbrain, medulla, thalamus, hippocampus, amygdala, and cerebellum

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

- Early cerebellar and subcortical impact in the disease progression of FTD
- Microtubule-associated protein tau (MAPT), progranulin (GRN) and chromosome 9 open reading frame 72 (C9orf72)
- 983 participants from the Genetic Frontotemporal Dementia Initiative including mutation carriers and noncarrier first-degree relatives of known symptomatic carriers
- Voxel-wise analysis of the thalamus, striatum, globus pallidus, amygdala, and the cerebellum was performed, and partial least squares analyses (PLS) were used to link morphometry and behavior
- Presymptomatic C9orf72 expansion carriers - thalamic atrophy was found compared to noncarriers
- The largest differences were in the cerebellar atrophy (larger extent in C9orf72 expansion group) and more prominent amygdalar volume reduction in the MAPT group
- Atrophy patterns detectable up to 20 years before expected symptom onset

Aurélie Bussy et al. Cerebellar and subcortical atrophy contribute to psychiatric symptoms in frontotemporal dementia. Hum Brain Mapp. 2023;44:2684–2700. DOI: 10.1002/hbm.26220



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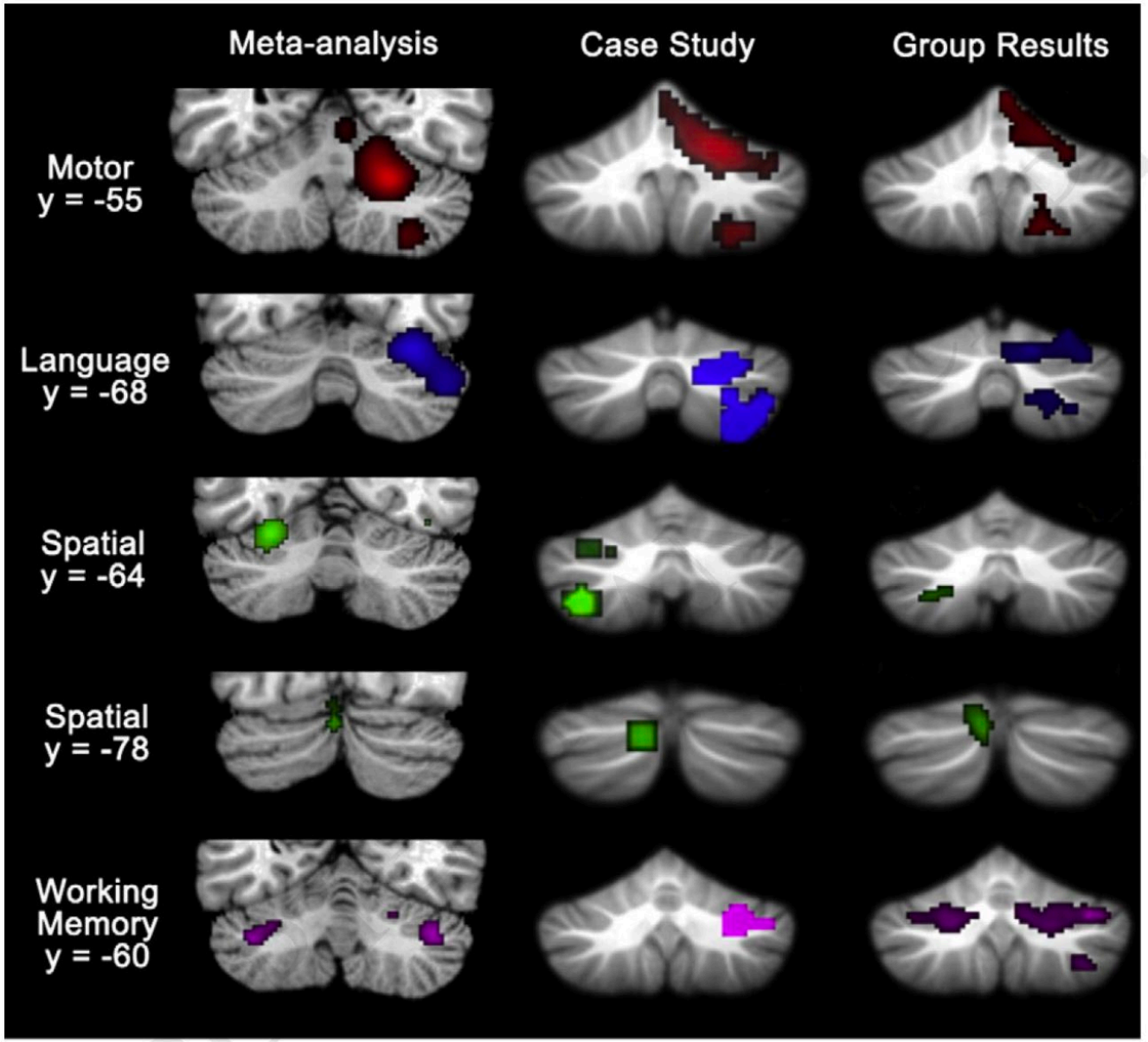
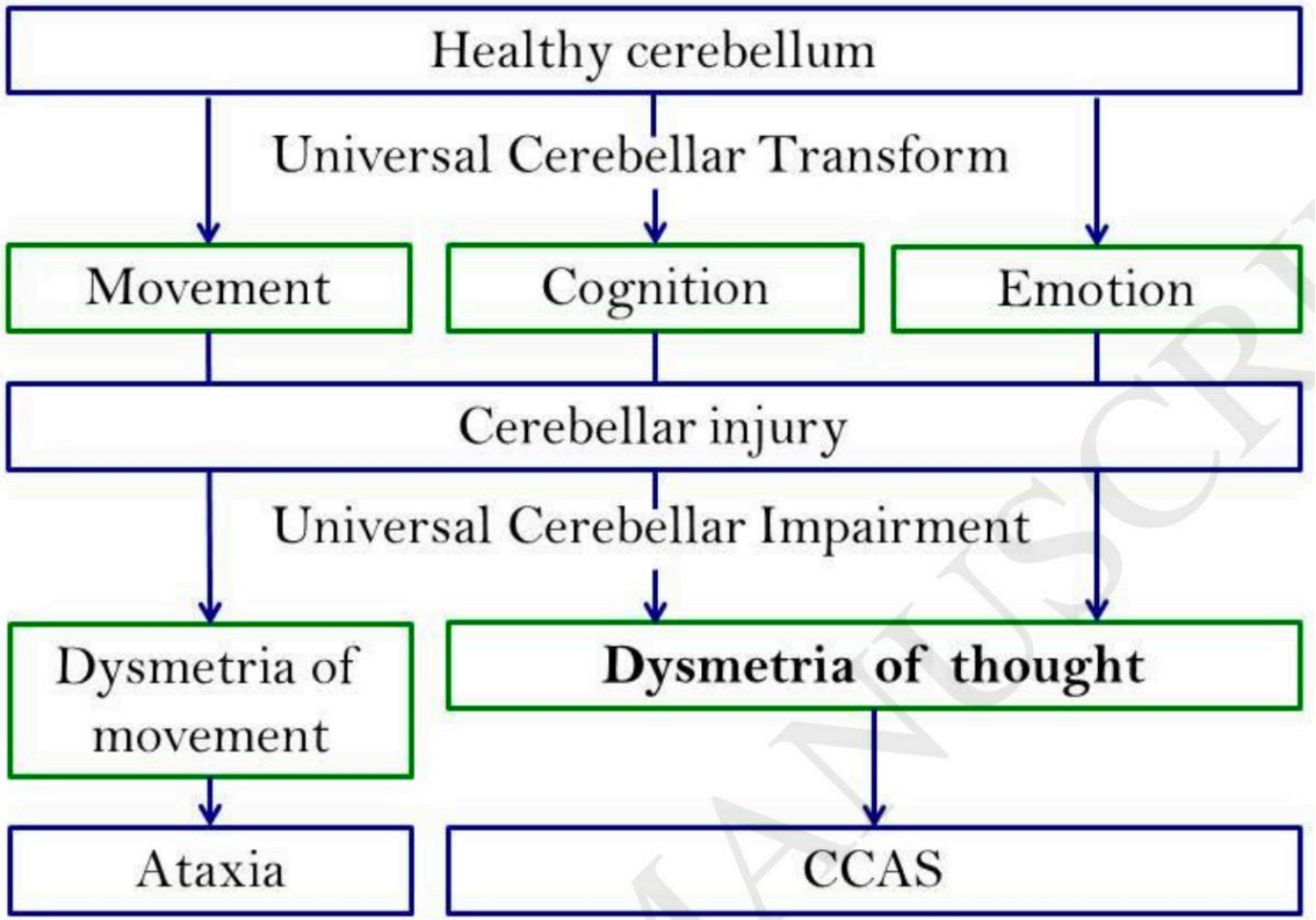


Schmahmann JD, The Cerebellum and Cognition, Neuroscience Letters (2018), https://doi.org/10.1016/j.neulet.2018.07.005



Schmahmann JD, The Cerebellum and Cognition, Neuroscience Letters (2018), https://doi.org/10.1016/j.neulet.2018.07.005

Confusingly….

- Inconclusive studies
- Lack of specificity
- Overlaps
- Heterogeneity
- Poor replication

Phillips JR, Hewedi DH, Eissa AM and Moustafa AA (2015) The cerebellum and psychiatric disorders. Front. Public Health 3:66. doi: 10.3389/fpubh.2015.00066

Thank You