Pathophysiology of the cerebellum

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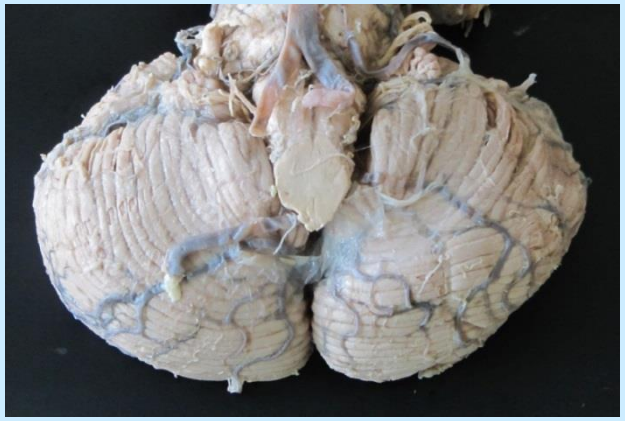
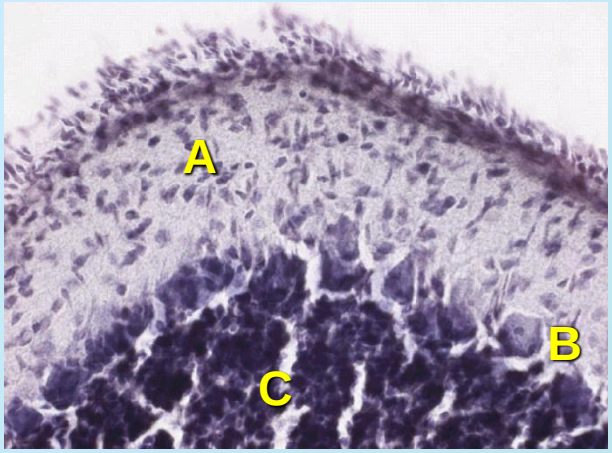
STRUCTURE OF THE CEREBELLUM

3 levels of structure of cerebellar surface: lobi, lobuli, folia (arbor vitae)



- **Cortex**
  - stratum moleculare (A)
  - stratum gangliosum (B)
  - stratum granulosum (C)
- **White matter**
- **Cerebellar nuclei**
  - nc. dentatus
  - nc. emboliformis
  - nc. globosus
  - nc. fastigii

  (nc. globosus + nc. emboliformis = nc. interpositus)



Afferent pathways of the cerebellum:

1. **Climbing fibers** – contralateral inferior olive (reconnection of indirect afferents from the spinal cord, vestibular nuclei, sensory brain stem nuclei, optic structures of the mesencephalon, tegmentum and brain cortex)
   - 1 Purkinje cell – 1 climbing fiber

2. **Mossy fibres** – all other inputs

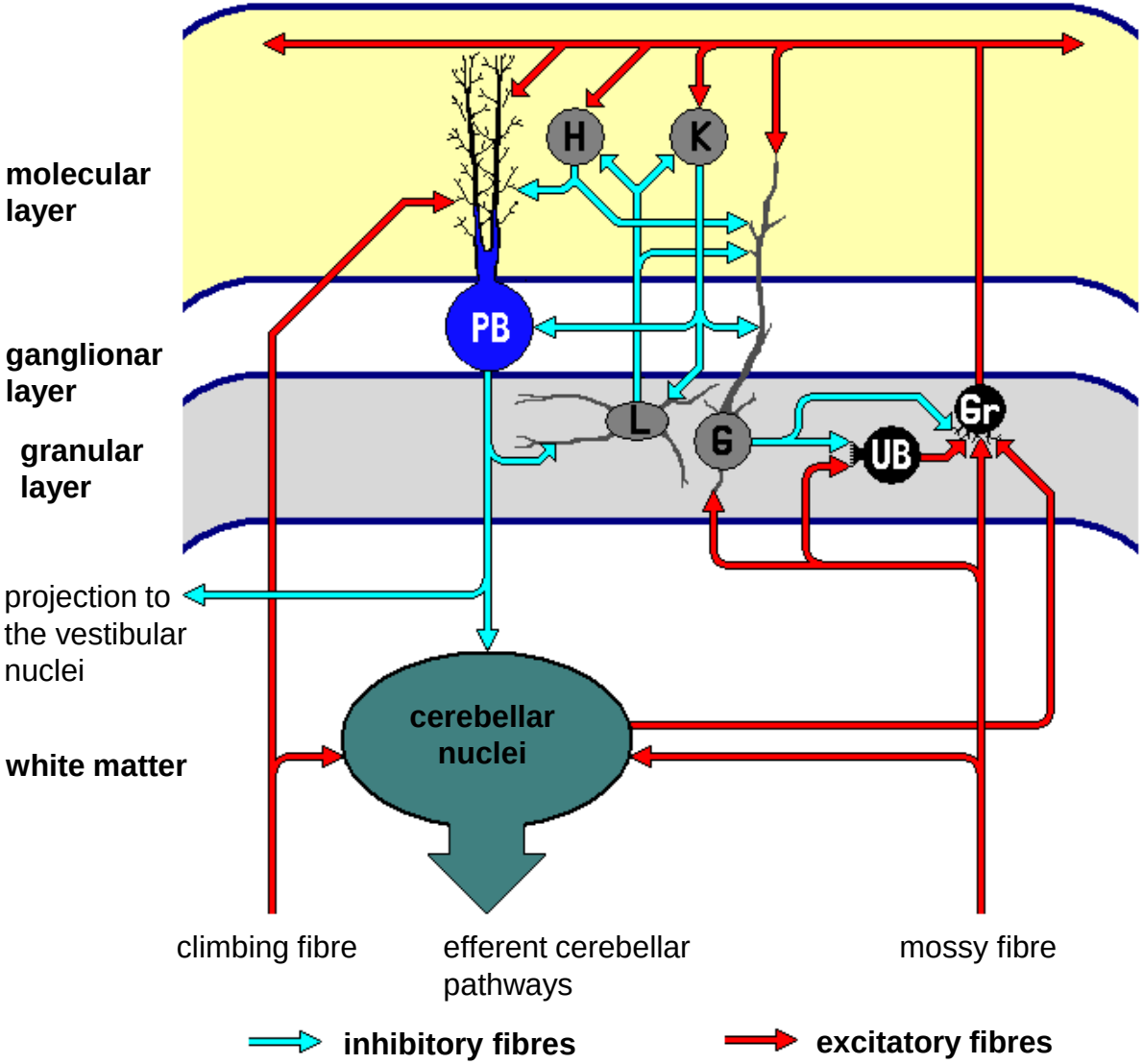
- vestibular nuclei
- proprioception: tr. spinocerebellaris (most of the body), tr. cuneocerebellaris (upper limbs, neck), tr. trigeminocerebellaris (head)
- visual inputs (via pons)
- auditory inputs (via colliculus inferior)

Efferent pathways of the cerebellum

(axons of the cerebellar nuclei, some axons of PC)

- projections to the brain cortex: crossed, reconnection in the thalamus
- cortex: motor, prefrontal, posterior parietal, upper temporal, parahippocampal
- hippocampus, amygdale, septum, ventral tegmental area, hypothalamus
- vestibular nuclei
- inferior olive (reciprocal innervation)
- reticular formation, nc. ruber, tectum

Scheme of intracerebellar connections



PB … Purkinje cell
Gr … granule cell
G … Golgi cell
UB … unipolar brush cell
L … Lugaro cell
K … basket cell
H … stellate cell

Candelabrum cell (inhibitory)
- by now, unknown connection with other cells
- dendrites into the molecular and upper granular layer
- axons horizontal around the Purkinje cells + vertical branches toward the surface of the molecular layer

Globular cells
- class of Lugaro cells with different shape of the soma

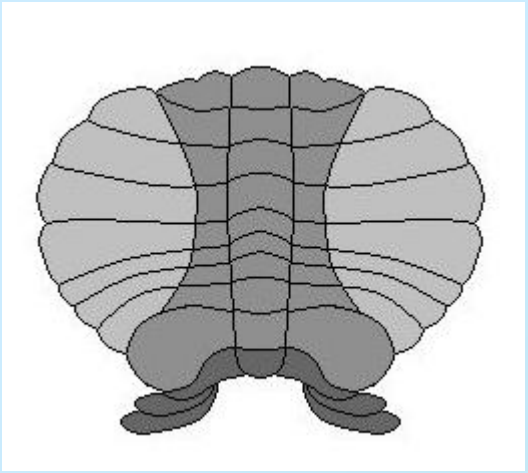
Neurons of the cerebellar nuclei

- **Projection neurons**
  - glutamatergic neurons – the most frequent
  - small GABAergic neurons → contralateral inferior olive
  - large glycinergic neurons (nc. fastigii) → ipsilateral vestibular and reticular ncl.

- **Interneurons**
  - GABAegic/glycinergic interneurons
  - non-GABAergic interneurons (probably glutamatergic)

Cerebellum-like structures:
- in mammals dorsal cochlear nucleus

CEREBELLAR FUNCTION



1. **Archicerebellum** (vestibular cerebellum):
   - lobus flocculonodularis, nc. fastigii
   - vertical posture maintenance
   - coordination of head and eye movements

2. **Paleocerebellum** (spinal cerebellum):
   - most of the vermis, medial parts of the hemispheres, nc. interpositus (globosus + emboliformis)
   - muscle tone regulation, coordination of posture motorics
   - somatotopic organisation

Archicerebellum + paleocerebellum:
- adequate muscle tone, cooperation of agonists and antagonists participating in posture and gait

3. **Neocerebellum** (cortical cerebellum):
   - medial part of the vermis, lateral parts of the hemispheres + nc. dentatus
   - coordination of goal directed movements
   - information about planned voluntary movements
   - modification (inhibition) of pyramidal and extrapyramidal motor stimuli

Other cerebellar functions

- motor learning
- classical conditioning
- probably also cognitive functions in general
- emotional processes
- coordination of sensory inputs
- compensatory oculomotor reflexes
- timing (circadian rhythm? - peripheral oscillator)
- verbal functions(not only motor aspect)
- prediction – information about present state, its development and plan
  → prediction of future state (state estimate)
    – not only movements, but also mental state and expected sensory perceptions

→ The cerebellum plays a role in behavior control.

Functional topography

Archicerebellum: vestibular cerebellum

Ventral: sensorimotor cerebellum

Dorsal: cognitive and emotional cerebellum

Internal model theory

Fast coordinated movements cannot be performed adequately only under control of the feedback, since nerve circuitries providing it are too slow (Wolpert et al., 1998; Kawato, 1999). **Internal model** theory suggests a principle of faster and more effective motor control.

Analogous principle also in other cerebellar functions

- **Mental model** = psychologic substrate of real or imaginary situation that enables explaining recent phenomena and prediction of future events (Ito, 2008).

Existence of similar models is expected in all brain structures that show synaptic plasticity and receive and process information and generate responses (Kawato, 1999).

CAUSES OF CEREBELLAR DISORDERS

- Developmental disorders – often accompanied with brainstem affection
  - Arnold-Chiari malformation – dislocation of the cerebellum and oblongata into the foramen occipitale magnum
  - Aplasia, hypoplasia
- Traumatic injuries – accident, surgery (tumors) – posterior fossa sy.
- Poisoning - acute or chronic ethanol intoxication
- Vascular disorders – ischemia, hemorrhage
- Cerebellar tumors
- Multiple sclerosis
- Inflammation = cerebellitis – infection, autoimmune
- Sporadic degenerative diseased
  - idiopathic late onset cerebellar ataxia (ILOCA)
  - multiple system atrophy (MSA)
- Hereditary cerebellar degenerations

Hereditary cerebellar degenerations

1. Autosomal recessive
- Friedreich‘s ataxia (the most frequent hereditary ataxia, prevalence 1.8 – 4.7/100 000)
- ataxia teleangiectasia
- abetalipoproteinemia
- ataxia with isolated vit. E deficiency
- autosomal recessive spastic ataxia (ARCAS)
- autosomal recessive cerebellar ataxia (ARCA-1, ARCA-2)
- ataxia with oculomotor apraxia (AOA-1, AOA-2)

2. Autosomal dominant (prevalence 0.8 – 3.5/100 000)
- spinocerebellar ataxia (SCA1 – SCA...)
- episodic ataxia (EA1 - EA7)

3. X-linked
- fragile X syndrome
- X-linked sideroblastic anaemia with ataxia

4. Mitochondrial

MANIFESTATIONS OF CEREBELLAR DISORDERS – IRRITATION SYNDROME

Opposite to extinction syndrome, similar to parkinsonian syndrome

- increased plastic tone of flexors
- flection position of the trunk and extremities
- resting tremor
- hypokinesia or akinesia

MANIFESTATIONS OF CEREBELLAR DISORDERS – EXTINCTION SYNDROME

1. **Ataxia** (= disorder of movement coordination)
2. **Tremor**
3. **Passivity**
4. **Cognitive-affective syndrome**

Ataxia + tremor + passivity → complex motor disorder

- Gait ataxia, posture ataxia, oculomotor disorders (namely in affection of the archicerebellum, verbal disorders

Cerebellar ataxia:

1. **Asynergy**
   - loss of coordination of cooperation of muscles
2. **Dysmetria = hypermetria and hypometria**
   - incorrectly timed, mostly delayed and insufficient contraction of antagonistic muscles → delayed termination of the movements
   - inaccurate targeting of movements, overshooting,
3. **Adiadochokinesia**
   - inability to perform fast alternating movements

Consequences of cerebellar ataxia: posture and gait ataxia, ataxia of limbs, macrographia, saccadic speech, rebound phenomenon, oculomotor disorders

Cerebellar ataxia does not worsen with closed eyes.

Tremor = intention tremor

- In goal-directed movements

Passivity = cerebellar hypotonia

- Increased range of joint movements
- Decrease of resistance to passive movement of the extremity
- Increased synkinesis

Paleocerebellar syndrome

- usually combination of archicerebellar and paleocerebellar affection (medial lesions)
  (isolated affection of the flocculonodular lobe similar to affection of the vestibulum)
- gait and posture ataxia
- falls and deviations in various directions, but most often backwards

Neocerebellar syndrome

- lateral lesions
- neocerebellar ataxia – asynergy, hypermetria, adiadochokinesis, tremor of the extremities

Combined (global) cerebellar syndrome

- the most frequent
- combination of the symptoms

Cognitive-affective syndrome = Schmahmann‘s syndrome

Schmahmann JD, Sherman JC: Cerebellar cognitive affective syndrome. Int Rev Neurobiol 41:433-440, 1997.

Manifestations:

- disorders of executive functions
- visuo-spatial disintegration
- deterioration of mental arithmetic
- speech disorders (in non-motor point of view)
- affective disorders: flattened emotions, behavioural disinhibition, impulsive actions, infantile behaviour, obsedant-compulsive features)
- attention disorders
- changes of social skills

J. Schmahmann (2013): „The affective component of the CCAS, conceptualized as the neuropsychiatry of the cerebellum, has been grouped according to five major domains: attentional control, emotional control, autism spectrum disorders, psychosis spectrum disorders, and social skill set. Within each of these domains, behaviors may reflect cognitive overshoot or undershoot, akin to the disorder of motor control seen in the cerebellar motor syndrome.“

Causes: - large bilateral cerebellar lesions
- namely affection of the dorsal lobe
- changes of emotions are related namely to injury of the vermis

Psychic changes can be present even without marked motor disorder.

The cerebellum and autism spectrum disorders (ASD)

- Behavioural features, morphological changes
- Hypoplasia of the vermis, less Purkinje cells, inflammation in the cerebellum
- However, these changes are not constantly present

The cerebellum and other psychiatric disorders

- Schizophrenia – smaller ventral part of the vermis in some patients
- Bipolar disorder of affectivity – lower cerebellar volume
- Posttraumatic stress disorder – reduced cerebellar blood flow

The cerebellum and speech disorder

- Cerebellar mutism – typically in posterior fossa syndrome
- Perceptual procession of speech
- Speech fluency
- Grammar
- Cognitive processes important for verbal production and speech analysis

The end