The role of the cerebellum in cognition and behavior: beyond coordination in the Central Nervous System

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Outline

• Anatomy of the cerebellum
• Role of the cerebellum in normal function of the nervous system
• A role for the cerebellum in cognition and behavior?
Anatomy
Anatomy

• Largest motor structure in the CNS
• More neurons than the cortex (10% of volume of CNS, > 50% of neurons)
• Six main cell types
• Regular, repetitive structure
• Three layered sheet
• Wrapped around three deep nuclei
• Connected to the brain stem by three peduncles
Anatomy -2

• Anterior to posterior: three lobes
  • Anterior, posterior, flocculonodular
    » Lobules > folia

• Medial to lateral: three zones
  • Vermis, intermediate (paravermian), lateral

• Cortical zones project to three nuclei
  • Vermis > fastigial; intermediate > interpositus (globose + emboliform); Lateral > dentate; flocculododular > Lateral vestibular (Deiter’s)
Sagittal cerebellum
Lateral cerebellum

- Cerebral peduncle
- Anterior lobe of cerebellum
- Primary fissure
- Horizontal fissure
- Posterior lobe of cerebellum
- Trigeminal nerve
- Pons
- Middle cerebellar peduncle
- Cerebellopontine angle
- Flocculus
- Olive
- Posterolateral fissure
Anterior cerebellum
Cerebellar cortex
Cerebellar nuclei

- Fastigial nucleus
- Vermis
- Globose nuclei
- Emboliform nucleus
- Dentate nucleus
- Lateral part
- Intermediate part
- Median part
## Classification

<table>
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<tr>
<th>Functional</th>
<th>Phylogenetic</th>
<th>Anatomic</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Vestibulocerebellum</td>
<td>Archicerebellum</td>
<td>Flocculonodular</td>
<td>Truncal, stance, gait ataxia Vertigo, nystagmus, vomiting</td>
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<tr>
<td>Spinocerebellum</td>
<td>Paleocerebellum</td>
<td>Anterior lobe, parts of vermis, posterior lobe (medial)</td>
<td>Ataxia (lower limb) Oculomotor Speech</td>
</tr>
<tr>
<td>Pontocerebellum</td>
<td>Neocerebellum</td>
<td>Posterior lobe, hemispheres</td>
<td>Dysmetria Intention tremor Nystagmus Hypotonia</td>
</tr>
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</table>
Normal physiology of the cerebellum
Functional anatomy

- Spinal inputs (spinocerebellum)
- Pontine inputs (pontocerebellum)
- Vestibular inputs (vestibulocerebellum)

- Dentate nucleus
- Globus pallidus
- Fastigial nucleus

- Lateral vestibular nucleus
- Medial descending systems
- Lateral descending systems
- Emboliform nucleus
- Globus pallidus

- Dentate nucleus
- Premotor cortex

- Vestibular nuclei
- Balance, oculo-motor function

Execution
Planning, programming
Cerebellar circuitry

- **Glu**: Glutamate, excitatory neurotransmitter
- **GABA**: Gamma-Aminobutyric Acid, inhibitory neurotransmitter
- **Asp**: Aspartate, excitatory neurotransmitter

**Afferent connections**
- Mossy fibers: Pontine nuclei, spinal cord, vestibular nuclei and ganglion
- Climbing fibers: Inferior olive

**Axon collaterals**

**Granule cells**

- Excitatory input from mossy fibers

**Inhibitory interneurons**

- GABAergic input from granule cells

**Purkinje cells**

- GABAergic input from inhibitory interneurons
- Excitatory input from climbing fibers

**Neurons of cerebellar nuclei**

- Efferent connections to:
  - Thalamus, red nucleus, vestibular nuclei, reticular formation
Does the cerebellum have a role in cognition and behavior?

• Lines of evidence
  • Argument by analogy
  • Clinical-pathological – acquired injury, autism
  • Functional imaging
  • Tracer studies
Argument by analogy
Argument by analogy

- Humans and apes are clever
- Humans and apes have a large cerebellum
- Therefore, the cerebellum has a role in cognition

- Glickstein M. Current Biology 2007: 17 (19) R824-7
Alternative hypothesis

• Humans and apes are good at moving their fingers and eyes
• Humans and apes have a large cerebellum
• Therefore, the cerebellum has a role in finger movement and eye movement.
Supporting data

• Cerebellar lesion in humans and monkeys are associated with impaired responses to
  • Unilateral eye deviation, fatigue and vestibular injury

• Cerebellar lesion in humans lead to impaired finger movement

• Glickstein M. Current Biology 2007: 17 (19) R824-7
Clinical pathological correlations
Clinical pathological correlations

• 49-yr-old male (RC1) with right cerebellar damage
• Performance on standard tests of memory, intelligence, 'frontal function' and language skills was excellent,
• Profound deficits in two areas: (1) practice-related learning; (2) detection of errors.

• Not replicated in other patients with cerebellar disease
Clinico-pathological correlation - 2

• 18-year-old patient - surgical removal of the right cerebellar hemisphere for tumor
• After surgery, neuropsychological examination was normal except for a transient selective verbal short-term memory (STM) impairment characterized by reduced verbal digit span and rapid forgetting of verbal material
Clinico-pathological correlation - 3

• Impairments in shifting attention between rare auditory and visual stimuli
  • 5 children with surgical lesions, one adult with degenerative disease (J Cogn Neurosci 6: 388–399, 1994)
  • Not reproduced in ten children with cerebellar lesions and ten controls (J Neurophysiol. 2004 Sep;92(3):1856-66.)
Clinico-pathological correlation - 4

- Cerebellar mutism
  - Lack of speech without long tract signs, impaired consciousness, or cranial nerve palsies
  - ¼ of children operated for medulloblastoma
  - More likely with brainstem/midline involvement
  - Transient, often followed by dysarthria
  - May be accompanied by irritability, emotional lability, apathy
  - Involvement of the hemispheres alone likely does not produce mutism
Clinico-pathological correlation - 4

• Cerebellum and autism:
  • Decreased or increased size of lobules VI and VII on MRI (but not at autopsy)
  • TSC1 mutation expressed in Purkinje cells in mice causes ASD-like phenotype [socialization repetitive behavior and vocalizations] (Nature 488(7413) 647–51, 2012)
Functional imaging
Cerebellar activation during a cognitive task (generating action verbs related to words)

Summary of functional imaging studies

• The cerebellum is part of "cognitive" networks with prefrontal and parietal association cortices.
• The cerebellum can be broadly divided into functional regions based on the patterns of anatomical connectivity between different regions of the cerebellum and sensorimotor and association areas of the cerebral cortex.
• The distinct contribution of the cerebellum to cognitive tasks is not clear.

Somatomotor topography

A. Cortical representation of foot, hand and face in monkey (Adrian. Brain, 1943; 66: 289-315)

B. Functional MRI – human cerebellar representation of face, hand and foot

Most of the cerebellum maps to association cortex (intrinsic functional connectivity)


Executive control – orange; default – red.
2 Mirrored maps + 1

Executive control – orange; default – red.
Tracer studies
Cerebrocerebellar circuits – polysynaptic pathways – degeneration studies not possible
Anterograde tracing

- Virus-associated label injected into cortex
- Able to cross synapses
Tracing studies – Cerebellar cortex – BA 46 (DLPFC) – attention and working memory

Rabies virus injected into BA 46 – labeling Purkinje cells

HSV-1 injected into BA 46 – labeling granule cells
Summary

• The role of the cerebellum in motor function is well established
• Clinical, imaging and anatomic data support a role for the cerebellum in language, behavior and cognition
• Separating motor anticipation and visual processing from cognitive function per se may confound these data
Acknowledgements

• Patients and families

• NIH/NINDS

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Questions?