Cerebellum: Motor auxiliary engine? Body memory? or “The great predictor”? 

Eyal Cohen, PhD, CEO of CogniFiber LTD

eyalco28@yahoo.com
The Cerebellum takes ~10% of the Brain in Volume
Over 50% of the Brain’s Neurons are in the Cerebellum!

The Convoluted Cerebellar Cortex consists of most Cerebellar Volume
Cerebellar is central in visuo-motor adaptation
Classical role in muscle timing and coordination

Cooling => Reducing Neuronal Firing

Villis and Hore 1977
Results of Cerebellar lesions or volume reduction

- **Hypotonia = loss of muscle tone**
- **Ataxia = loss of motor coordination:**
  1. Postural instability, “drunken sailor” gait, sway, wide standing base
  2. Walking: uncertain, asymmetric, irregular
  3. Failure in execution of planned movements i.e. intentional tremor, dysmetria (lack of precision) and dysarthria (speech slurring)
  4. Deficits in eye movement control

- **Correlative Non-Motor Symptoms:**
  1. Lower Intelligence (Verbal)
  2. Lower visuospatial abilities
  3. Memory problems (i.e. working, procedural) and Dementia
  4. Emotional control problems, impulsiveness, aggression
  5. Reduced ability of strategy formation
  6. Psychosis, Schizophrenia (associated with reduced volume)
Cerebellar involvement in various processes

Somatosensory Processing
Cerebellar involvement in various processes
Cerebellar involvement in various processes

Language Processing

Stoodley and Schmahmann 2009
Cerebellar involvement in various processes

Working Memory

Stoodley and Schmahmann 2009
Cerebellar involvement in various processes
Cerebellar involvement in various processes
Cerebellar involvement in various processes

Emotional Processing

Stoodley and Schmahmann 2009
Conclusion 1:
Human cerebellum is not about motor functions only!!

... and now lets get acquainted with it’s anatomy...
General structure of the Cerebellar Cortex

Ventral/Anterior View

Dorsal/Posterior View

Flocculus

Tonsil

Vermis

Hemispheres
Posterior view of the Cerebellum
Anterior/Ventral view of the Cerebellum

Nodules + Flocculi = Floccu-Nodular Lobe
Medio-lateral gross partition of the Cerebellum

- Spino-Cerebellum
- Cerebro-Cerebellum
- Vestibulo-Cerebellum

- Spinal and trigeminal inputs
- Corticopontine inputs
- Visual and auditory inputs
- Vestibular inputs
The 3D Folding of the Cerebellar Lobes
Lobules and Folia of the Cerebellar Cortex
The Cerebellum is not only cortex…

Deep Cerebellar Nuclei (DCN)
The deep cerebellar nuclei (DCN) - the output stations of the Cerebellum

All cerebellar parts evolved during evolution, but the hemispheres and their DCN counterpart, the Dentate nucleus have gained by far the largest volume as they evolved in parallel to the cerebral cortex.
Functional mapping of the Cerebellar nuclei

The Vestibular Nucleus in the Brainstem is Functionally Homologous to cerebellar nuclei.
Cerebellar peduncles: input / output highways

Superior: Thalamus/Midbrain Inputs/Outputs
Medial: Pontine Inputs and Commissure
Inferior: Spinal/Medullary Inputs/Outputs
Two major input pathways serve the Cerebellum

- CF = Climbing Fibers
  (All via the IO)
- MF = Mossy Fibers
  (~90% via the PN)
The IO receive low level motor and sensory inputs

**Visual Inputs:**
SC = Superior Colliculus
NOT = Nucleus of Optic Tract

**Vestibular Inputs:**
VN = Vestibular Nucleus

**Motor Command:**
RN = Red Nucleus

**Somatosensory & Proprioceptive:**
DCN = Dorsal Column Nucleus
Trigeminal & Spinal Chord

Additionally: Auditory Inputs

Sugihara & Shinoda JNS 2004
Pontine Nuclei relay Cerebro-Cortical Information

Non-Cortical Inputs:
1. Mammillary Body
2. Amygdala
3. Midbrain Nuclei
4. Spinal Inputs

(Brodal 1978)

Cortical Areas That project to the Pontine Nuclei
Fragmented cerebellar cortical map

Updated findings

Initial Models
Cerebellar major output targets

CTX = Cortex
PM = Premotor
PAR = Parietal
PF = Prefrontal
RN = Red Nucleus
VL = Ventrolateral
Thalamus
DCN = Deep Cerebellar Nuclei
RF = Reticular Formation

Other Outputs:
Inferior Olive
Hippocampus
Amygdala
Septum
Caudate Nucleus (BG)
Olivocerebellar Information flow: Mossy Fibers Inputs

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

CTX = Cortex
MF = Mossy Fibers
CF = Climbing Fibers
Olivocerebellar Information flow: Climbing Fibers Inputs

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers
Hypothesized information flow during Cerebellar function

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
RN = Red Nucleus
(+ mid brain nuclei)

CTX = Cortex
MF = Mossy Fibers
CF = Climbing Fibers
Cerebellar Cortex:
The beauty of network architecture
Purkinje Cells: the most elaborate neurons of the CNS
The 3 layers of the Cerebellar Cortex
Cell types of the Cerebellar Cortex

Inhibitory cells:
- Purkinje
- Golgi
- Basket
- Stelate

Excitatory Cells:
- Granule cells
Parasagittal distribution of climbing fibers

Each olivary neuron sends a single axon which gives rise to climbing fibers enervating ~10 PCs. These PCs are normally aligned along a parasagittal plane. One the left, 2 IO neurons with their 2 distinct planes.
PC: The Principal Cell of Cerebellar Cortex

- **Parallel Fibers**: ~200,000 Synapses
- **Climbing Fiber**: ~2000 Synapses

Deep Cerebellar Nuclei (DCN)

**Excitation**
**Inhibition**

Purkinje Cells are the only neurons projecting from the Cerebellar Cortex!!
Closing the Loop: The Cerebellar Module

Notice:
Short Loop: Negative feedback
Long Loop: Positive Feedback
=> Contributes to oscillations
Summary: Simplified Olivocerebellar System

All major pathways are shown here. Minor pathways are mostly neglected. Notice that in vestibular circuits, vestibular nuclei replace the DCN with all appropriate connectivity.
Perpendicular arrangement of mossy and parallel fibers

While PCs that are innervated from the same olivary neuron are arranged along a parasagittal stripe, parallel fibers are arranged in a perpendicular arrangement along the mediolateral axis.
Parallel fibers are not a delay line

Stimulation of granular layer

Stimulation of parallel fibers
Cerebellar cortex anatomy suggest parasagittal segmentation

Anatomical labeling shows that specific areas in the olive and DCN (bottom 2 rows in the table below) are innervating parasagittal zones in the cerebellar cortex.
(in mouse Medial DCN(Med) ~ Fastigial, and lateral (NL, DLH) ~ Dentate)
Zebrin II markers also form parasagittal stripes in the cortex.

Zebrin expression seems to match the parasagittal zones.
Aldolase C compartmentalization

Staining for Aldolase C segregates both cerebellar cortex and the DCN into specific areas.
Inferior olive projections partially preserve the stripes

Dye injection to specific areas in the inferior olive stains parasagittal-like areas in the cerebellar cortex (crus IIa)

MAO = medial accessory olive
DAO = dorsal accessory olive
PO = primary olive
DM/CC = dorsomedial (column)
/ Cup of Kooy
Inferior olive projections partially preserve the stripes

Dye injection to specific areas in the inferior olive stains parasagittal-like areas in the cerebellar cortex
Inferior olive projections partially preserve the stripes

Dye injection to specific areas in the inferior olive stains parasagittal-like areas in the cerebellar cortex.
Stripes formed by muscle labeling

Muscle Num 1
ipsilateral gastrocnemius

Muscle Num 2
ipsilateral tibialis anterior
Cerebellar Modules: DCN Neurons receive matching inputs from olivary neurons and PCs

Olivary group of neurons, their PC targets and corresponding DCN neurons form closed loops that presumably may act as a functional unit called micro-complex, a cerebellar module.
Co-Labeling Climbing and Mossy fibers substantiate the Modules
Cerebellar Physiology

Double Recording of Purkinje Cell in Slice

Hausser M.
Purkinje cells exhibit two distinct spike types

Simple Spike (SS)  Complex Spike (CS)

Mossy Fiber Stimulation  Inferior Olive Stimulation

Eccles, 1966
Simple Spikes are modulated during movement

Simple spikes of 2 Purkinje cells in awake monkey during hand movements show modulation with movements

Roitman 2005
Olivary spikes (hence CS) are fired in unexpected events
The general role of the cerebellum: Internal model

A

B

The prevailing hypothesis of cerebellar function:
Forward model = internally predicting the sensory inputs following motor execution. This shortens response time from 100-200ms cortical decision loops (5-10Hz oscillations) to 10-20ms. The incoming feedback helps to correct errors in real-time and to refine the cerebellar predictions.
Plasticity in the Cerebellar Cortex

The temporal relationship between CS and SS determine the direction of plasticity in parallel fiber synapses

Coesmans et al. Neuron 2004
Vestibulo - Ocular Adaptation (VOR)

Retinal Slip, an error in eye-pursuit during head motion, results in CS, followed by ocular-muscle activation which reduces the slip in real-time.

VG = Vestibular Ganglion
VN = Vestibular Nucleus
PA = Pontine Area
AOS = Accessory Optic System
OM = Oculomotor Neurons
Vestibulo - Ocular Adaptation (VOR)

VG = Vestibular Ganglion
VN = Vestibular Nucleus
PA = Pontine Area
AOS = Accessory Optic System
OM = Oculomotor Neurons

Repeating (consistent) errors will drive plasticity in parallel fiber synapses. This will change motor patterns and lead to reduction in retinal slip over the long run.

Ito 1984, Schonville et al. 2010
Eyelid Reflex Conditioning: Purkinje cell plasticity

As learning progresses, Firing complex spikes decreases
The learning transfer hypothesis

VL = Ventro-Lateral Nucleus
DCN = Deep Cerebellar Nuclei
CTX = Cortex
CF = Climbing Fibers

Location of plasticity in the olivocerebellar system and its targets is progressing and every 6hrs is independent of previous location
The Human Inferior Olive

Coronal Section of the IO (axonal staining)

Sagittal Section of the IO (Nissle staining)

PO = Primary Olive
MAO = Medial Accessory Olive
DAO = Dorsal Accessory Olive

- PO: evolved in parallel to human cerebral cortex
- PO holds more than 80% of IO neurons
- DAO: also in fish
- Rats: 30,000 olivary neurons only

~500,000 Neurons in humans
Sub Nuclei of Rat IO

MAO = Medial Accessory Olive
DAO = Dorsal Accessory Olive
DM = Dorsomedial Portion of PO
DC = Dorsal Cap of Kooy
“v.-” = Ventral “d.-” = Dorsal
“c.-” = Caudal

- Shown: only the left hemisphere of the IO
- DAO in pink is removed in the medial image
- MAO alone is shown in right image

Modified from Sugihara and Shinoda 2004
The IO receive motor and sensory inputs

**Visual Inputs:**
- SC = Superior Colliculus
- NOT = Nucleus of Optic Tract

**Vestibular Inputs:**
- VN = Vestibular Nucleus

**Motor Command:**
- RN = Red Nucleus

**Somatosensory & Proprioceptive:**
- DCN = Dorsal Column Nucleus
- Trigeminal & Spinal Chord

Not shown but exist: Auditory Inputs

- Gray: Pure Visual
- Blue: Visual + Vestibular
- Pink: Somatosensory
- Green: Motor
- Yellow: Combined

---

Inferior Olive (IO)

- PO: mostly motor
- DAO: mostly somatosensory
- MAO: mixed

Sugihara & Shinoda JNS 2004
The Unique Neurons of the Inferior Olive

- Olivary neurons may have spherical dendritic tree
- The dendrites of close IO neurons may overlap
At least 50% of IO neurons have globular shaped dendrites

- In human PO more than 90% are spherical
- With evolution PO neuron spheres became smaller (radius-wise) and with stronger overlap (more than 100 are overlapping in humans)
- In DAO and MAO there are non-spherical neurons (up to 50% in humans)
IO Neurons are Connected by Gap Junctions

- IO neurons are coupled by gap-junctions (chemical synapses)
- 3-20 neurons (7-10 in average) are coupled to a single neuron
IO Neurons are Connected by Gap Junctions

- Coupling in both spherical and “straight” neurons
IO Neurons are Electrotonically Coupled

Gap-junctions act like temporal Low-pass filter, strongly decreasing fast events (like action potential) but reliably transmitting slower events (changes in membrane potential).

Measurement of electrotonic coupling is done by recording two cells, stimulation of one cell and measuring the changes in the other. Notice that the voltage changes in the second are quite small (few mV).

Devor and Yarom JNPhysiol 2002
IO Neurons are Natural Oscillators

Many IO neuron oscillate, some constantly and some conditionally (i.e. after stimulus). Thought of as a timing machine (i.e. clock)

Llinas and Yarom JPhysiol 1986
Oscillations (In Vitro) Change in Time

Oscillation amplitude and frequency can change
GABA Application Affects Oscillations

Inhibition close to gap junction can potentially provide a mechanism to un-couple neurons
In the population of IO neurons:
Close-by neurons may have similar frequency and phase. Far neurons may be with similar frequency but phase-shifted or frequency shifted.
In-Vitro Oscillations: Synchrony and Propagation

Oscillatory activity may propagate over the population in time like waves in the sea (or football stadium)
IO neurons are not Harmonious Oscillators in-vivo

Chorev, Yarom and Lampl JNS 2007

Oscillatory activity was shown also in-vivo
Various In-Vivo Oscillation Patterns

Khosrovani et al. 2007

Different types of oscillators
The Olivary Spike

Olivary spikes are also different: very wide (4-12 ms instead of just 1-2) and carry spikelets.
The IO Spike – In-Vivo

Non-binary coding of IO firing
Somatic ADP bumps reflect axonal spikes generation

Mathy et al. proved that olivary ADP wavelets are indeed the result of additional axonal spikes. They recorded in an olivary slice the soma and the axon (in its cut edge) of olivary neurons simultaneously.

Non-binary coding of IO firing: carried also to the axon (in red)
Encoding of Oscillation phase by Olivary

Non-binary coding may encode oscillation phase while emitting a spike

Oscillatory phase may set the direction of plasticity


Non-binary coding may affect the direction of plastic changes at target synapses (green = triplet, blue = singlet)
The general role of the cerebellum: Internal model

The prevailing hypothesis of cerebellar function:
Forward model = internally predicting the sensory inputs following motor execution. This shortens response time from 100-200ms cortical decision loops (5-10Hz oscillations) to 10-20ms. The incoming feedback helps to correct errors in real-time and to refine the cerebellar predictions.