Cerebellum, motor and cognitive functions: What is the common ground?
Cerebellum – The “Little Brain”

The Cerebellum takes ~10% of the Brain in Volume
Small but Hefty…

Over 50% of the Brain’s Neurons are in the Cerebellum!!
The Convoluted Cerebellar Cortex consists of most Cerebellar Volume
Classical Role in Muscle Timing and Coordination

Cooling => Reducing Neuronal Firing
Results: oscillatory movements when cerebellar outputs are shut down

Villis and Hore 1977
Cerebellar is Central in Adaptation

Quick coordinative adaptation depends on an intact cerebellum (middle and right side)
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)
General Structure of the Cerebellar Cortex

Ventral/Anterior View

Dorsal/Posterior View

Flocculus + Nodulus = Flocculonodular lobe, the oldest part of the cerebellum
Lobes and Lobules of the Cerebellar Cortex
The Cerebellum is not Only Cortex…

Deep Cerebellar Nuclei (DCN)
The Deep Cerebellar Nuclei (DCN) are the Output Relays of the Cerebellum

The DCN are the only output relay of the entire system.

The vestibular nucleolus, in the medulla, anatomically and functionally is an external DCN which subserves vestibular cerebellar regions (mainly flocculonodular lobe and vermis).

- Dentate
- Fastigial
- Interposed (Emboliform + Globose)
Two Major Input Pathways Serve the Cerebellum

- CF = Climbing Fibers (All via the IO)
- MF = Mossy Fibers (~90% via the PN)

Inferior Olive (IO)
Pontine Nuclei (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

Each olivary sub-nuclei receive specific types of inputs and project to specific cerebellar region

Sugihara & Shinoda JNS 2004
The Pons relay extensive Forebrain Information

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

Cortical Areas That project to the Pontine Nuclei (retrograde tracing)
Cerebellar Peduncles: Input / Output Highways

Superior: Thalamus/Midbrain Inputs/Outputs
Medial: Pontine Inputs and Commissure
Inferior: Spinal/Medullary Inputs/Outputs
Cerebellar Major Output Pathways

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
Dentate nucleus outputs also target parietal and prefrontal cortices. All projections to the cerebral cortex are relayed via the thalamus (mostly ventrolateral portion).
Mapping of Cerebellar Cortex – Classic View
Parasaggital Microzones of Cerebellar Cortex

Some Molecular Markers (i.e. Zebrin II) divide Purkinje Cells Populations into parasaggital stripes.
Functional Cerebellar Mapping is Fragmented

Voogd and Glickstein 1998
Cerebellar Cortex: 
The Beauty of Network Architecture
Purkinje Cells: The most Elaborate Neurons of the CNS
The 3 Layers of the Cerebellar Cortex

Molecular Layer

Purkinje cell Layer

Granule cell Layer
Cerebellar Cortex Consists of 5 types of Neurons

Inhibitory cells:
- Purkinje
- Golgi
- Basket
- Stelate

Excitatory Cells:
- Granule cells
Deep Cerebellar Nuclei (DCN)

Parallel Fibers
~200,000 Synapses

Climbing Fiber
~2000 Synapses

PC: The Principal Cell of Cerebellar Cortex

Purkinje Cells are the only neurons projecting from the Cerebellar Cortex!!
The Spatial Organization of Cerebellar Circuitry

Notice the perpendicular relationship between Mossy Fiber and Climbing Fiber enervations!!

The arrangement of PCs that are innervated by a single olivary neuron (or an ensemble) match the parasagittal microzones.
Parallel fibers are not a delay line: local inhibition prevents signal propagation
Closing the Loop: The Cerebellar Module

Deep Cerebellar Nuclei (DCN)

Inferior Olive (IO)

Cerebellar Cortex

Feedback Inhibition

Feedback Dysinhibition

Excitation

Inhibition

Modified from Apps & Garwicz, NatRevNeu 2005
The simplified Olivocerebellar Module

- Pontine Nuclei (PN)
- Mossy Fibers
- Granular Layer
- Purkinje Cell
- Deep Cerebellar Nuclei (DCN)
- Parallel Fibers
- Climbing Fibers
- Inferior Olive (IO)
- Sensorimotor Context (forebrain)
- Sensory Feedback + Efferent Copy of Motor Command
- Cerebellar Outputs
- Thalamus, Red Nucleus, Brainstem

Cerebellar Cortex

Mossy Fibers and Climbing Fibers connect to Deep Cerebellar Nuclei (DCN), which in turn send outputs to Thalamus, Red Nucleus, Brainstem.
The Numerics of Cerebellar Modules

Parallel Fibers: Div = 1:150-450
Con: 200,000:1

5-50x10³ Mossy Fibers
Div = 1:450
Con = 4-5:1

0.5-1 x10⁶ Granule Cells

Climbing Fibers
Div = 1:10
Con = 1:1

4 Inferior Olivary Neurons

Cortical Output
Div = 1:20-50
Con = 1:20-50

40 Deep Nuclear Cells

40 Purkinje Cells
Cerebellar Physiology

Infra Red

Fluorescent Dye

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 by Inputs

Simple spikes of 2 Purkinje cells in awake monkey during hand movements: Rate encodes position and depth of modulation encodes the speed.
Due to the immense differences between simple spikes and complex spike dynamics, investigators like Eccles and theoreticians like Albus and Marr, developed models where olivary signal was a teaching signal (positive or negative) which generated refined parallel fiber input-output associational mapping.

\[ \text{MATHEMATICAL BIOSCIENCES} \]

A Theory of Cerebellar Function

JAMES S. ALBUS
Cybernetics and Subsystem Development Section
Data Techniques Branch
Goddard Space Flight Center
Greenbelt, Maryland

1971
Indeed, olivary neurons fire mostly to unexpected stimulus or an omission of an expected stimulus (reach perturbation).

When the cats did a non-perturbed reaching movement there was no elevated firing, suggesting encoding of error (expectation mismatch) which suits a teaching signal.
Distinct Firing Regimes of Purkinje Cells

Complex Spikes & Simple Spikes (Up-State)

Simple Spikes: 0 - ~80Hz
(Mostly 0Hz or 4-8Hz or 20-80Hz, with possible phasic >100Hz)

Complex Spikes : 1-3Hz (Phasic 10-15Hz)

Cohen and Lamp (unpublished)
Complex Spikes as Purkinje Cell Switches

Loewenstein et al. NatNS 2005

Transitions of up-down states in PCs are accompanied by elevation in CS firing, but not every CS drives a change...
Motor function like licking is correlated with synchronous CS firing across large groups of PCs.
Saccade attributes are encoded by a population of ~100 Purkinje cells

Reading out the SS firing rate of about 100 PCs can tell you the exact position within a saccade (behaving monkeys).
Plasticity in the Cerebellar Cortex

Bidirectional plasticity in parallel fiber synapses of PCs can subserve an exact temporal tuning to optimal execution time point.
Retinal slip (error in object following) during head movement is corrected by acute PC spiking and activation of ocular motor neurons.
Repeated retinal slip will generate plasticity in PC (and later VN) spiking and will result in better association between head movement and eye counter movement such that the slip is reduced.
Cerebellar dependent conditioning:
The rabbit learns to close its eyelid and expect the air puff before it comes by “counting” the duration of the preceding sound.
It was established that the tone is carried by parallel fibers while the air puff strongly activates olivary neurons and generates CS activity in the relevant PCs.
Along the training of conditioning, firing of simple spikes is diminished in parallel to preparatory action (eyelid closing).

Rasmussen et al 2008
IO is crucial for Learning @350ms but not 700ms

Welsh 2002
Conditioning Memory Retention depends on Nucleo-Olivary Inhibition

Blocking Gabaergic inputs into the inferior olive caused in re-emergence of the learned and “forgotten” association, suggesting that the learned trace exists and the choice between the two behaviors depends on inhibitory input to the IO (possibly from DCN)

Medina et al. Nature 2002
The Learning Transfer Hypothesis

The formation of cerebellar associative memory is shifting from cerebellar cortex to target areas such that dependency on each area exists only until the association is already formed in the next station.
Cerebellar Involvement in Cognitive Processes

Cognitive effects of focal damage were found when:
1. The damage involved the vermis
2. The damage was in an area which blood supply is from the posterior inferior cerebellar artery

Further research showed problems in attention and working memory

Children with Verma damage show autistic-like features:
1. Irritability
2. impulsivity
3. Disinhibition
4. Emotional lability

Complex verbal dysfunction associated with right cerebellar damage
Dysprosodia (pronunciation fault)– associated with left cerebellar damage
FMRI Mapping of Cerebellar Involvement in Various Processes

Somatosensory Processing

Stoodley and Schmahmann 2009
FMRI Mapping of Cerebellar Involvement in Various Processes

Motor Processing
FMRI Mapping pf Cerebellar Involvement in Various Processes

Language Processing

Stoodley and Schmahmann 2009
FMRI Mapping of Cerebellar Involvement in Various Processes

Working Memory

Stoodley and Schmahmann 2009
FMRI Mapping of Cerebellar Involvement in Various Processes

Spatial Processing
FMRI Mapping of Cerebellar Involvement in Various Processes

Executive Processing

Stoodley and Schmahmann 2009
FMRI Mapping of Cerebellar Involvement in Various Processes

Emotional Processing

Stoodley and Schmahmann 2009
Cerebellar Involvement in Autism

Control Subject

Autistic Subject

Levitt J. 1999
Autism candidate genes affects the Cerebellum

Lose of Purkinje Cells in Autistic
Saskia 2004

Developmental Problems in KO mice
Sadakata 2007
Cerebellar Involvement in Dyslexia

Control Subject

Dyslexic Subject
Information Flow during On-Line Corrections

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

- CTX = Cortex

- MF = Mossy Fibers
- CF = Climbing Fibers

Information flow into the system

Motor Command To Spinal MNs
Information Flow during On-Line Corrections

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

CTX = Cortex

MF = Mossy Fibers
CF = Climbing Fibers

Information flow out from the system to targets
The General Role of the Cerebellum

The olivocerebellar systems supposedly generates an updated prediction of sensory feedback, expected motor command or expected cognitive patterns, and by that shortens the delay (and oscillations) that would have occurred with simple loop of sensory feedback.