The Cerebellum
The Cerebellum

- Involved in motor coordination and timing
- Is simple and well documented
- Only has one type of output cell (Purkinje)
- The cerebellum influences motor activity through inhibition
Functions

• Traditional view: Motor system
  – Co-ordination of movements
  – Motor learning
  – Eye movements

• Modern view: Cognition
  – Language
  – Reading
  – Sensory processing
  – Non-motor learning
Motor Learning

- Procedural learning
- Trial-and-error learning
- Activated during the learning of a new task
- Activated (to a lesser extent) during automatic performance
- Motor skill adaptation
Cognitive roles

- **Non-motor attention tasks**
- **Executive functions**
  - Planning
  - Shifting attention
- **Language (non-motor)**
  - Word fluency
  - Verbal working memory
  - Verb generation
  - Reading (tasks that taxed the cognitive systems)
Anatomical & Clinical Review

Cerebellum integrates sensory and other inputs to coordinate ongoing movements and participate in motor planning.

Cerebellum has no direct connections to lower motor neurons but modulates motor function through upper motor neurons.

Vermis and flocculonodular lobes regulate balance and eye movements via connections with vestibular nuclei & oculomotor system. These regions control medial motor systems.

More lateral areas of cerebellum control muscles of extremities. Most lateral areas of cerebellum function in motor planning.

Cerebellar lesions typically produce ataxia (irregular uncoordinated movement).

Ataxia occurs ipsilateral to the side of cerebellar injury.

Midline cerebellar lesions cause unsteady gait (truncal ataxia) and eye movement abnormalities (nystagmus), which are often accompanied by vertigo, nausea & vomiting.

Lateral cerebellar lesions cause limb ataxia.

Cerebellum also appears to function in speech, respiratory movements, motor learning, and higher order cognitive functions.
Cerebellum: Animal Divisions

- Vermis
- Intermediate zone
- Lateral Hemisphere
- Primary fissure
<table>
<thead>
<tr>
<th>REGION</th>
<th>FUNCTIONS</th>
<th>MOTOR PATHWAYS INFLUENCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral hemispheres</td>
<td>Motor planning for extremities</td>
<td>Lateral corticospinal tract</td>
</tr>
<tr>
<td>Intermediate hemispheres</td>
<td>Distal limb coordination</td>
<td>Lateral corticospinal tract, rubrospinal tract</td>
</tr>
<tr>
<td>Vermis and flocculonodular lobe</td>
<td>Proximal limb and trunk coordination</td>
<td>Anterior corticospinal tract, reticulospinal tract, vestibulospinal tract, tectospinal tract</td>
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<td></td>
<td>Balance and vestibulooocular reflexes</td>
<td>Medial longitudinal fasciculus</td>
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Cerebellar Input Pathways

Cerebellar afferents originate from many areas:
1) Many areas of cerebral cortex
2) Vestibular, auditory, visual and somatosensory systems
3) Brainstem nuclei
4) Spinal cord

<table>
<thead>
<tr>
<th>INPUT PATHWAY</th>
<th>MAIN ORIGIN(S) OF INPUT</th>
<th>CELLS PROJECTING TO CEREBELLUM</th>
<th>CEREBELLAR PEDUNCLE OR EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontocerebellar fibers</td>
<td>Cortex</td>
<td>Pontine nuclei</td>
<td>Middle cerebellar peduncle</td>
</tr>
<tr>
<td>Spinocerebellar pathways</td>
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<tr>
<td>Dorsal spinocerebellar tract</td>
<td>Leg proprioceptors</td>
<td>Nucleus dorsalis of Clark</td>
<td>Inferior cerebellar peduncle</td>
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<tr>
<td>Cuneocerebellar tract</td>
<td>Arm proprioceptors</td>
<td>External cuneate nucleus</td>
<td>Inferior cerebellar peduncle</td>
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<tr>
<td>Ventral spinocerebellar tract</td>
<td>Leg interneurons</td>
<td>Spinal cord neurons</td>
<td>Superior cerebellar peduncle</td>
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<tr>
<td>Rostral spinocerebellar tract</td>
<td>Arm interneurons</td>
<td>Spinal cord neurons</td>
<td>Superior and inferior cerebellar peduncles</td>
</tr>
<tr>
<td>Climbing fibers</td>
<td>Red nucleus, cortex, brainstem, spinal cord</td>
<td>Inferior olivary nucleus</td>
<td>Inferior cerebellar peduncle</td>
</tr>
<tr>
<td>Vestibular inputs</td>
<td>Vestibular system</td>
<td>Vestibular ganglia, vestibular nuclei</td>
<td>Juxtarestiform body</td>
</tr>
</tbody>
</table>

Deep cerebellar nuclei and vestibular nuclei

Cerebellar cortex

Mossy fibers
Climbing fibers

Cerebellar outputs
Cerebellar inputs
Granule cell axons ascend to the molecular layer, bifurcate and form parallel fibers that run parallel to folia forming excitatory synapses on Purkinje cell dendrites.

Cerebellar cortex also has several types of inhibitory interneurons: basket cells, Golgi cells, and stellate cells.

Purkinje cell axon is only output of cerebellar cortex, is inhibitory and projects to the deep nuclei and vestibular nuclei.

Deep nuclei axons are the most common outputs of the cerebellum.
Internal circuitry

- Mossy fibres ➔ Granule cell ➔ parallel fibres ➔ Purkinje cells ➔ deep cerebellar nuclei ➔ output fibres
Intrinsic circuitry of the cerebellum

- **P**: Purkinje cells
- **St**: Stellate cells
- **Gr**: Granule cells
- **G**: Golgi cells
- **B**: Basket cells
- **GABA**: Gamma-aminobutyric acid

**Parallel fibers**
- From inferior olivary nucleus
- **Climbing fibers**
- **Mossy fibers**

- Spinal cord and brain stem

Adapted from http://137.222.110.150/calnet/cereb/page2.htm
<table>
<thead>
<tr>
<th>Purkinje cells</th>
<th>Granule cells are excitatory and use glutamate as transmitter. Receive input from mossy fibers. All other cells of the cerebellum are inhibitory.</th>
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<tbody>
<tr>
<td>• Each Purkinje cell receives about 175,000 synapses from parallel fibers on dendritic spines (in the rat).</td>
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<tr>
<td>• Parallel fibers make contact with many Purkinje neurons.</td>
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<tr>
<td>• Each Purkinje cell receives one climbing fiber. A single climbing fiber can form up to 26,000 synaptic contacts on a Purkinje cell dendritic spines.</td>
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<td>• They are the main output neurons of the cerebellum via the deep cerebellar nuclei.</td>
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<tr>
<th>Stellate Basket</th>
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<td>localized to the molecular layer</td>
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<th>Golgi</th>
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<tr>
<td>cell bodies are found in the granule cell layer. The axons of Golgi cells, mossy fibers and granule cell dendrites form the Glomeruli.</td>
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Cerebellar Structure
Distal Learning Problem

• Learning Algorithms
  – Supervised: A “teacher” provides information as to the desired state of affairs
  – Reinforcement: A general idea of “goodness” is used to adjust how the system learns
  – Unsupervised: A clustering or feature extraction based on the statistical properties of the input

Where does the teacher come from in supervised learning?
• The “teacher” can be the environment itself
• Target values are available for the distal variables (the “outcomes”) but not for the proximal variables (the “actions”)
• The learner must learn how to modify the proximal (action) vector to minimize the distal error
Questions?

- But how can we take sensory error (i.e., visual image) and use this error to teach motor response?
Cerebellar Model of Pavlovian Eyelid Conditioning

• Traditional conditional paradigm
  – US (Air puff into the eye, invokes a reflexive closing of the eyelid)
  – CS (Tone preceding US)
    • After repeated pairings with US, CS is able to elicit the reflexive response
    • After repeated presentations of CS without the US, the CS undergoes extinction

• The way in which eyelid conditioning engages the cerebellum permits a close correspondence between experiments and simulations
The Model – First Try

- Mossy and climbing fiber inputs used to represent CS and US respectively
- LTD for acquisition (and NOT LTP).
- Spontaneous climbing fiber activity (about 1 Hz)
- Spontaneous granule activity as well
- LTD in Purkinje is shown to occur \( \text{Gr – Pkj} \) synapses when presynaptic activity happens in close proximity to a climbing fiber spike
- Purkinje cells tonically inhibit cerebellar nucleus cells
How can the cerebellum transform mossy and climbing fiber inputs into output that generates conditioned responses?
Results

- Could not account for even the most basic elements of conditioned responses
- LTD saturated the Purkinje cells which uninhibited the deep nuclei
- Additional information added to the model
  - LTP added to gr-Pkj synapses adding the ability to reverse LTD
  - Deep nuclei were added including a inhibitory connection to the inferior olive (climbing fiber input)
Results

- LTD cannot account for acquisition alone, a dynamic system involving LTD, LTP and many other factors are necessary!
- This model shows how the cerebellum can take climbing and mossy fiber inputs and transform them into a conditioned motor response
- Predictions about extinction were made, were able to be tested and were validated
Discussion

• Can we explain the Pavlovian conditioning model in terms of the cerebellum using internal model?
• What “exactly” is the cerebellum computing anyway?
Disorders
Cerebellar Artery Infarcts

Infarcts are more common in PICA and SCA than AICA.

Common symptoms in cerebellar infarcts:

Vertigo, nausea, vomiting, horizontal nystagmus, limb ataxia, unsteady gait, headache

Lateral medullary infarct can cause cerebellar symptoms due to damage of cerebellar peduncles, however, in these cases, medullary symptoms will also occur including Horner’s syndrome.

Large cerebellar infarcts can cause cerebellar swelling leading to block of 4th ventricle apertures and hydrocephalus. Swelling in posterior fossa is life-threatening due to potential for brainstem compression.
Cerebellar Hemorrhage

Causes include chronic hypertension, arteriovenous malformation, hemorrhage in a previous infarct, and tumor necrosis. Symptoms usually include headache, nausea, vomiting, ataxia and nystagmus. If hemorrhage large it can cause hydrocephalus, abducent palsy, impaired consciousness, brainstem compression and death.
Clinical Findings and Localization of Cerebellar Lesions

Ataxia refers to disordered contractions of agonist and antagonist muscles and lack of coordination between movements at different joints typically seen in patients with cerebellar lesions. Normal movements require coordination of agonist and antagonist muscles at different joints in order for movement to have smooth trajectory. In ataxia movements have irregular, wavering course consisting of continuous overshooting, overcorrecting and then overshooting again around the intended trajectory.
Truncal Ataxia vs. Appendicular Ataxia

Vermis functions to control medial muscle groups (posture/equilibrium). Lesions here produce wide-based, unsteady, staggering gait known as truncal ataxia. Patients often fall toward the side of the lesion. In severe cases patients cannot even sit up without assistance.

Lesions of intermediate and lateral regions of cerebellum typically cause appendicular ataxia (see finger to nose test).

More severe deficits occur with lesions of intermediate hemisphere, vermis, deep nuclei, or peduncles.

Due to double cross-over in cerebellar/motor pathways, deficits are ipsilateral to lesion in cerebellum.
Ataxia Due to Other Lesions

Ataxia can also be cause by damage to cerebellar input or output paths. Hydrocephalus can damage frontopontine pathways and lesions of prefrontal cortex can produce gait abnormality. Ataxia-hemiparesis is caused by lacunar infarcts; symptoms include unilateral upper motor neuron sings and ataxia on the same side. Both are usually contralateral to the lesion. Most often caused by lesion in corona radiata, internal capsule or pons & involves corticospinal & corticopontine fibers. Sensory ataxia occurs when dorsal column – medial lemniscus pathway is damaged. In this situation impaired proprioception occurs. Function improves with visual input and worsens with eyes closed or in the dark.
Symptoms and Signs of Cerebellar Disorder

Dysmetria = abnormal undershoot or overshoot during movements toward a target (finger-nose-finger test).
Dysdiadochokinesia = inability to do rapid alternating movements (alternately tapping one hand with palm and back of other hand).
Action or intention tremor = tremor with onset while moving limb to target.
Wide-based unsteady gait (drunken stagger).
Ocular dysmetria = saccades overshoot or undershoot target.
Jerky saccadic movement during visual tracking.
Nystagmus = abnormal jerky eye movements when eyes look toward target in periphery.
Differential Diagnosis of Ataxia

Ataxia can be caused by a wide variety of disorders.
Most common causes of acute ataxia:
- toxin ingestion
- ischemic or hemorrhagic stroke
Most common causes of chronic ataxia:
- brain metastases
- alcoholism
- multiple sclerosis
- degenerative disorders of cerebellum

Chronic ataxia in children is often caused by cerebellar astrocytoma, medulloblastoma, or Friedreich’s ataxia (idiopathic degeneration of dorsal columns & spinocerebellar tracts).
Developmental Dyslexia
(Suzanna with Prof. Rod Nicolson and colleagues, Psychology)

- Abnormal functioning leading to difficulties in:
  - balance,
  - reading,
  - writing,
  - learning new skills
  - automatisation

- Anterior lobe?
- Right hemisphere?
- Abnormal function?
- Connectivity?
Ataxia Telangiectasia

(Dr Lauren Wallis with Dr Ritchie, Nottingham City Hospital)

- Genetic defect

- Symptoms:
  - Ataxia
  - predisposition to cancer
  - sensitive to ionising radiation
  - immune system deficiencies

- Symptoms expressed from ~18 months
- Atrophy of the vermis and hemispheres
- Abnormal capillaries in the brain
Gluten Ataxia

(Dr Lauren Wallis with Dr Hadjivassiliou, Department of Neurology)

– Gluten sensitivity
– Own antibodies attack their Purkinje cells
– Degeneration of Purkinje cells
– Can be controlled with diet

– Symptoms
  – Ataxia
  – GI problems
  – Itchy skin
Take-home messages…. 

• Cerebellum – linked to almost all other brain regions
• Involved in a circuit
• Involved in a diverse range of tasks
  – Motor
  – Cognitive
• How? What role?
• Involved in a diverse range of illnesses
  – Ataxias
  – Dyslexia?
  – Schizophrenia?
How does the cerebellum work?

- No-one really knows!!
- Monitors sensory information (Bower)
- Anticipates the needs of the brain (Courchesne)
- Context-response linkage (Thach)
- Temporal specific learning (Mauk)
- Decorrelation (Dean, Sheffield Uni.)