Cerebellum and Inferior Olivary Nucleus

Spinocerebellum

- Somatotopically organised (vermis controls axial musculature; intermediate hemisphere controls limb musculature)
- Control of body musculature
- **Inputs…** Vermis receives somatosensory information (mainly from the trunk) via the spinocerebellar tracts and from the spinal nucleus of V. It receives a direct projection from the primary sensory neurons of the vestibular labyrinth, and also visual and auditory input from brain stem nuclei.
- Intermediate hemisphere receives somatosensory information (mainly from the limbs) via the spinocerebellar tracts (the dorsal spinocerebellar tract, from Clarke's nucleus of the lower limb, and the cuneocerebellar tract, from the accessory cuneate nucleus of the upper limb, carry information from muscle spindle afferents; both enter via the ipsilateral inferior cerebellar peduncle).
- An internal feedback signal arrives via the ventral spinocerebellar tract (lower limb) and rostral spinocerebellar tract (upper limb). (Ventral s.t. decussates in the spinal cord and enters via the superior cerebellar peduncle, but some fibres re-cross in the cerebellum; rostral s.t. is an ipsilateral pathway and enters via sup. & inf. cerebellar peduncles.)
- **Outputs** to fastigial nucleus, which projects to the medial descending systems: (1) reticulospinal tract [? n. reticularis tegmenti pontis and prepositus hypoglossi?]; (2) vestibulospinal tract [lateral and descending vestibular nn.]; and (3) an ascending projection to VL thalamus [→ cells of origin of the ventral corticospinal tract]; (4) reticular grey of the midbrain [=periaqueductal?]; (5) inferior olive [medial accessory, MAO].
- … and interposed nuclei, which project to the lateral descending systems: (1) magnocellular portion of red nucleus [→ rubrospinal tract]; (2) VL thalamus [→ motor cx which gives rise to lateral corticospinal tract]; (3) reticular nucleus of the pontine tegmentum; (4) inferior olive [dorsal accessory, DAO]; (5) spinal cord intermediate grey.
- **Hypotheses.** Does the interpositus compare the movement command with feedback to correct errors rapidly? Very unclear (Thach, Goodkin & Keating, 1992). Fastigius probably specialized for control of stance and gait.

Cerebrocerebellum

- Involved in the planning of movement
- Major **input** is from contralateral cerebral cortex (via pontine nuclei and middle cerebellar peduncle). Most of the input to the pontine nuclei comes from (1) premotor cortex and SMA; (2) primary motor cortex; (3) primary somatosensory cortex; (4) higher-order somatosensory cortex.
- **Output** to dentate nucleus, which projects (1) to VL thalamus [→ motor/premotor cortex]; (2) to parvocellular portion of the red nucleus [→ inf. olivary n.]; (3) inferior olive [principal, PO]
- **Hypotheses.** Does the dentate translate mental percepts and concepts into action plans for movement? Dentate discharge leads movement, and leads motor cortex activity slightly. Inactivation delays both, but only slightly (50–150ms). Discharge may be related to movement but is not causal (sudden inactivation doesn't cock up direction). Dentate ablation causes tremor (>5°, 3-6Hz). The cerebellum might control the gain of the stretch reflex: physiological and cerebellar tremor might result from instability of the stretch reflex.

Vestibulocerebellum

- Balance and control of eye muscles
- **Input** from primary vestibular afferents and secondary vestibular neurons in the vestibular nuclei.
- **Output** to the fastigial nucleus, and to medial/superior/inferior vestibular nuclei [→ medial vestibulospinal tract and fibres of the MLF].

Inferior olivary nucleus

- Only source of climbing fibres
- Projects to cerebellar cortex and deep cerebellar nuclei
- There is input from somatosensory cortex that is homotopic to the IO's projection to spinocerebellum. [Comparison of M1 commands with their effects on spinal centres?]

Circuitry

Purkinje cells: monolayer; planar dendritic trees (sagittal plane); only cells that project out of the cortex; GABAergic; >200,000 inputs to each. **Granule cells:** only excitatory cells in cortex; most numerous cell type in NS; synapse on P cells; about 4 inputs each; excited by mossy fibres; axons are parallel fibres, which run perpendicular to P cell dendritic tree are thin/unmyelinated (slow: 2–3ms^{-1}) and release glutamate. **Golgi cells:** occupy non-overlapping hexagonal prisms of cortex; receive parallel fibre input; inhibit granule cells (feedback inhibition of itself and the Purkinje cells). **Stellate/basket cells:** receive excitatory input from granule cells and inhibit P cells on either side, not underneath themselves [lateral inhibition? WTA?].

Mossy fibre input: each input has 4 excitatory branches onto 4 granule cells; this divergence means it reaches a 5mm region of cortex. A Purkinje cell has a very small input from any one mossy fibre. The mossy fibre also excites the deep nucleus (which is inhibited by the P cell). The fibre to the nucleus is thin and slow while that to the cortex is faster: might the signals

arrive at the nucleus simultaneously? **Climbing fibre input:** from IO nucleus to about 1 Purkinje cell; many synapses on/near cell body. Cause complex spikes (burst of APs). CFs fire in sagittal strips (Thach, Goodkin & Keating, 1992, p426).

Modular organization: zones (strips of cortex 1mm wide, 100mm long, running A–P, with specific inputs and output nuclei) and microzones (width ≤ 200μm; equivalent to cortical columns?) with respect to climbing fibre input; mossy fibre inputs are more distributed. [Note cortex isn't completely uniform…] *Input mapping shows fractured somatotopy.*

Electrophysiology

Purkinje cells fire simple spikes at 50Hz, in periodic fashion (phase-locked to movement); complex spikes at 1Hz. Nuclear cells also active at about 50Hz. In anaesthetised animals, PCs are 180° out of phase with nuclei; in awake animals, they're in phase. Activity does not appear to encode simple parameters like force in monkeys making simple movements.

Lesions or stimulation of the climbing fibre pathway resemble cerebellectomy. Complex spikes seem to suppress simple spike activity (continuous modulation?). Climbing fibres have a physical upper limit of 10Hz. They receive a lot of sensory input, and project somatotopically to the cortex.

Timing? [In cats, nose and feet well represented in CFs. But the CFs that respond to foot input aren't responsive to phases of the step cycle.]

Concerned with errors? [CF responses occur during unexpected somatosensory input, e.g. rung giving way under a cat climbing a ladder. Timing relationship unclear.]

Hypotheses

(1) **Computing device; CFs = timing signal for external events.** *Llinás.*

Braitenberg (1961) suggested the use of the circuitry as delay lines… alarm clock, stopwatch, coincidence / timeshift detector.

The alkaloid harmaline produces 8Hz whole-body tremor by binding to IO and influencing cerebellar output. Natural human tremor is also 8Hz. IO neurons show powerful electrical coupling: the subthreshold oscillations lead to network synchronization of APs. Complex spikes in cerebellar cortex also show synchrony. Harmaline and picrotoxin increase synchrony; GABA activity in the IO "separates" gap junctions by shunting to the Cl^- equilibrium potential at the electrical junction. The gap junctions are in tightly intermingled sets of dendrites. The GABAergic input to the IO, which modulates which cells are coupled (fractionating the coupled nucleus?), is from the cerebellum. Conduction time to the cerebellar cortex is constant (despite differences in length of CFs, 8–18mm, and the fact that the part of the IO close to the cerebellum projects to nearby bits and vice versa): longer fibres have a higher conduction velocity. Synchrony also occurs in volitional movement. Llinas suggests that motor control has a digital timebase of 8Hz (my phrasing).

In decerebrate animals, removal of the cerebellum (which does not abolish stepping) converts the rhythmic pattern of reticulospinal firing into a non-rhythmic (tonic) one (Orlovsky, 1972b, reviewed in Armstrong, 1988). The nucleus interpositus probably generates this rhythm. However, PCs fire *in* phase with the nucleus interpositus… does the cortex damp the effects of other rhythmic inputs?

Ivry & Keele (1988). Cerebellar patients are impaired on motor and perceptual timing tasks. Perhaps one role of the cerebellum is to operate as a "task-independent timing module": when a task requires explicit timing computation, the cerebellum is used. Cerebellar dysfunction can be viewed as an inability to time the onset and offset of antagonist pairs of muscles; the finding of a purely perceptual defect supports this interpretation. Furthermore, the lateral regions of the cerebellum are required for accurate timing whereas the medial regions are primarily involved in the implementation and execution of motor responses. [Medial and intermediate zones are reciprocally connected with motor cortex, areas 4M and 4I respectively; lateral cerebellum has much more extensive reciprocal connections with cerebral cortex, spanning prefrontal and premotor areas as well as motor cortex, area 4L.] Fits with general interpretation that lateral cerebellum is more concerned with movement planning and more medial zones are concerned with movement execution, regulation and correction. They also speculate that classical conditioning may involve the lateral cerebellum because of the need for precise timing (in NMR conditioning, CRs are not made a fixed time after the CS, but at a fixed interval before the US; if the CS–US interval is altered, the CS–CR interval changes). Other forms of classical conditioning (e.g. emotional conditioning) which do not demonstrate such precise temporal linkages do not require the cerebellum.

(2) **Learning device; CFs teach by correcting errors.** *Marr (wrong), Albus (right), Gilbert & Thach, Ebner.*

Albus' theory: CFs = error signal, to suppress synapses that were recently active. Stimulation of CFs with parallel fibres leads to depression of the parallel fibre synapse, specific to that synapse, with a fairly large time window. It stays suppressed for several hours. The LTD is postsynaptic, AMPA-dependent, and requires two Ca^{2+}-activated processes: PKC and NO→cGMP→PKG. *Problem:* this is *in vitro*, where harsh conditions are needed (5Hz CF stimulation, 100–150ms before parallel fibre input). *In vivo*, error signal would have to follow parallel fibre activity. Note also the problem that CFs fire during normal movement, and might be expected to disrupt a previously-learned movement; a 'gate' might be postulated as a simple solution to this. Note in this context that β-adrenergic agonists facilitate adaptation of the VOR when injected into the flocculus, and β-antagonists depress adaptation. To maintain a balanced system, LTD should be counteracted: stimulation of parallel fibres along induces potentiation of parallel fibre–Purkinje cell synapses, at least on the presynaptic side. For cellular details see Ito, 1991.

[Barto's (1981) idea of A_{R-P} elements caught my attention; the CF signal could be a "right/wrong" signal, generally delivered, teaching the cortical network.]

Is the cerebellum involved in motor learning?

- Data from Gilbert & Thach that unfamiliar movements lead to more CSs; adaptation occurs with familiarity. In other words, behavioural adaptation is related to a transient, covarying change in complex and simple spike rates, and a persistent behavioural change to a persistent change (decrease) in the simple spike rate. Data is controversial.
- **VOR** calibration requires flocculus. However, the latency of the altered reflex is too short for the changed reflex to be travelling through the cerebellum (does the flocculus teach the 'direct' reflex pathway?). Also, PC activity varies with nuclear activity; one would expect the opposite. "Floccular shutdown" [high frequency CF stimulation prevents PCs from responding to mossy fibres] blocks learning but doesn't reverse previous learning. Now generally accepted that the site of plasticity is in the vestibular nuclei, and the flocculus is required for that plasticity.
  The VOR has an unmodified component (latency 14ms, gain 0.3); the modified component has a latency of 19ms for both increases and decreases. Visual slip causes CF activity. The mossy fibres have at least three inputs: head motion, visual motion and the eye muscle command. Floccular target neurons (FTNs) are in the vestibular nuclei. Only FTNs and PCs show changes associated with motor learning. Lisberger (1988) reviews evidence that the changes in PC firing are secondary to changes in FTN firing (via feedback, due to the changed eye velocity). A "truth table" suggests that the gain of the vestibular inputs to the FTNs decreases when vestibular and floccular inputs both increase or both decrease; when one increases and the other decreases, the FTNs increase the gain of the vestibular input.
  Vestibular sensitivity in the flocculus does change, but in the wrong direction to cause motor learning. Lisberger hypothesizes as follows. Normally, the flocculus combines several inputs so that the simple-spike firing rate of PCs reflects eye motion with respect to the world. As the VOR keeps the eyes stable, PC firing rate is normally unaffected during the VOR. When the VOR is altered, the activity in the eye movement feedback input to the flocculus changes, as mentioned above; the strength of the vestibular inputs to the flocculus counteract this to some degree. It seems that the flocculus adjusts its vestibular inputs to minimize the changes in PC firing rate during the VOR, and therefore prevent inappropriate changes in the VOR.
  The flocculus is necessary for immediate visual correction of an inaccurate VOR; this makes its output immediately suitable for guiding motor learning.
  Lisberger and Sejnowski (1992) develop a model of the VOR using a positive feedback loop (the corollary discharge of the motor command forms a positive feedback loop through the Purkinje cells and the vestibular nucleus, which is true). The "time constants" of the two inputs to the brainstem nuclei (direct and via PCs, which are of opposite sign) are initially equal; the gain of the system can be altered simply by allowing the vestibular input to the cerebellum to arrive at the PCs earlier or later. There is a transient input into the feedback loop, which is integrated and expressed as a steady-state change in the output.
- Miall *et al.* (1994): Smith Predictors. The cerebellum might form two types of model. (1) Forward, predicting sensory consequences of each movement. (2) Model of the time delays in the control loop. This model delays a copy of the rapid prediction so that it can be compared in temporal register with actual sensory feedback. The result of this comparison is used to correct for errors in performance and to train the first model. They suggest the cerebellum contains at least two Smith Predictors: in the lateral cerebellum, one to predict movement outcome in visual/egocentric/peripersonal coordinates; in the intermediate cerebellum, to predict the consequences in motor coordinates. The concept is generalized: the cerebellum predicts the sensory consequences of actions. Its dynamic prediction and temporal prediction units should be separable: for example, the cerebellum may time the CS–US interval in NMR conditioning.
- **NMR** conditioning. Original idea was that PCs receive information about US via CFs and about CS via mossy fibres. One group found that lesions of dentate and interpositus abolished response and prevented its reacquisition, but cerebellar cortical lesions did not; Yeo *et al.* found that small cortical lesions were sufficient to abolish the response; another group found that anaesthesia of the interpositus doesn't affect NMR conditioning.

Thach, Goodkin & Keating (1992)… Many studies show a good correlation with behaviour, but little effect of ablation. Gain control seems to be the logical answer. But the cerebellum just seems too complex for that! Is its function to actively damp the oscillation that is inherent in the mechanical-reflex design of the motor system, via gamma MN modulation and via the cortex? Cerebellar lesions cause atonia, astasia, asthenia. Ablation studies suggest discrete control of different task modes for each of the nuclei (fastigial – sitting/standing/walking; interpositus – reaching; dentate – compound finger movements), and favours the idea of multijoint over single-joint control.

"A Model for Controlling and Adapting Movement Synergies"

1. The body is multiply represented within the deep cerebellar nuclei, with at least one body may within each nucleus.
2. Each body map controls a different mode of bodily movement, and each map and mode operate in parallel with the others.
3. Each mode has its own triggering input and its own output target (with its own inherent motor synergies), and these input-output connections determine the difference between modes.
4. The parallel fibres of the cerebellar cortex link Purkinje cells into long beams that project down onto the nuclei, which in turn link the somatotopically arranged nuclear cells into functional subgroupings.
5. These subgroupings are unique and task specific, and are the basis for the cerebellar coordination of movement.

6. The parallel fibre–Purkinje cell linkages are adjustable and are the basis of specific ad hoc learned motor synergies.
7. The learning is determined by the climbing fibre effect on the parallel fibre–Purkinje cell linkage: an error in movement activates the climbing fibre, which works to reduce the strength of connections of the parallel fibre (see below).
8. Learning occurs at synapses outside the cerebellar cortex as well, but for a different purpose: Adaptations at those closer to the motor output (or sensory input) will be generalized across all performances via those outputs (and inputs). These adaptations are useful in balancing the properties of the motor apparatus (e.g. muscles) or input (e.g. sensory organ) structures, but they are not and cannot be the mechanism for memory and control of unique task-specific synergies
9. Memory for task-specific synergies can occur in the cerebellar cortex, where it is remote from input and output processing, and where there are adequate type and number of structures to code the many and various synergies that make up higher vertebrate movement repertoires. The best candidate is the granule cell–parallel fibre–Purkinke cell synapse.
10. The model has predictive value.

Verification of this model will require showing…

1. Purkinje cells are differentially controlled in single vs. multijointed movement.
2. The parallel fibre is the agent of this control on the Purkinje cell.
3. After cerebellar cortical injury, multijointed movements are sufficiently more impaired than single-jointed movements, such that the sum of the abnormalities at the single joints cannot account for the magnitude of teh abnormalities in the compound movement for all three zones and modes.
4. The climbing fibres fire along the beam when learning a synergy that involves many muscles and joints in a limb.
5. Ablation of the beam removes the learned synergy from the behavioural repertoire.

Explains… why focal lesions are not severe (few synergies wiped out: examples are the pianist who couldn't play sequences in left hand after removal of a left lateral tumour, a gunshot victim who couldn't play the flute, and a card sharp who was normal on clinical testing but who had lost specialized sleight-of-hand abilities) but even partial damage diffusely is devastating. And finally, "executive vs. modulator" models – both!

Update, Feb 99.

This was taken straight from my Part II notes (~April 1996). If you want the references, tell me.
Things you may also want to know:

- ***Cellular basis of cerebellar plasticity*** *(Ito, 1991). Cerebellar LTD of parallel fibre synapses requires coactivation of parallel fibres and climbing fibres. Parallel fibres release glutamate onto Purkinje cells, using AMPA receptors. LTD is caused by a reduction in the sensitivity of the Purkinje cell to glutamate (AMPA receptor desensitization). The neurotransmitter released by the climbing fibres is unknown (1991), thought possibly to be homocysteate. Climbing fibres cause* Ca^{2+} *influx into Purkinje cells. This acts to desensitive the appropriate synapses – second messenger process unknown (NO is a candidate!). Since LTD must be counteracted by potentiation in a balanced system (just as LTP elsewhere requires a corresponding process of depression), one has been sought: repetitive stimulation of parallel fibres alone induces potentiation of parallel fibre–Purkinje cell synapses; this certainly involves presynaptic changes, postsynaptic change unknown.*
- ***Cortex versus deep nuclear learning*** *(Raymond, Lisberger & Mauk, 1996,* Science ***272:*** *1126, strongly recommended). Their theory is that (i) cerebellar cortex and deep nuclei learn; (ii) cortex learns movement timing information; (iii) deep nuclei learn amplitudes; (iv) cortex 'teaches' the deep nuclei somehow, which serve as a long-term memory store.*
- ***Other functions.*** *More data is implicating the cerebellum in non-motor tasks (discrimination, even language functions) but this is vague at present.*