The Cerebellum and Cognition

Elsdon Storey

Van Cleef Roet Centre for Nervous Diseases, Monash University, (Alfred Hospital Campus)
Summary

The *cerebellar cognitive-affective syndrome* describes a pattern of cognitive impairment (particularly executive and language impairment) and/or behavioural dysregulation due to interruption of cerebello-cortical loops.
Outline

1) Evidence for cerebellar involvement in cognition in normals
   A) Neuroanatomical studies
   B) Functional neuroimaging studies

2) Evidence for cerebellar involvement in cognition in disease
   A) Focal lesions
   B) Cerebellar degenerations
1) Evidence for cerebellar involvement in cognition in normals
A) Neuroanatomical studies

- cerebellum - 10% of brain weight, but more neurons than rest of brain together

- dentate - greatly increased in size, in parallel with lateral cerebellum and frontal lobe, in great apes and humans (Matano S. 2001)
  - ventral portion (phylogenetically new) smoother, smaller neurons - different function?
1A) Neuroanatomical studies (continued)

• microcorticonuclear units have same structure; likely perform same computation on different information (uniform cerebellar transform)

• “function” of a cerebellar region depends on source of inputs and destination of outputs

i.e. connectivity is destiny!
1A) Neuroanatomical studies (continued)

– cortical input to cerebellum is via pontine nuclei
– dentate output to cortex is via thalamic nuclei

BUT

• classical pathway tracing techniques cannot trace trans-synaptically
• recent advance: trans-synaptic viral tracers (HSV strains)
1A) Neuroanatomical studies (continued)

• parallel loop structure through cerebellum (analogy - basal ganglia loops)
  - association cortex (mainly prefrontal)
    → defined pontine nuclei (different from motor projections)
    → posterolateral cerebellum and ventromedial + ventrolateral dentate
    → motor and non-motor thalamus (e.g. medial dorsal)
    → association cortex
1) Evidence for cerebellar involvement in cognition in normals

B) Functional neuroimaging

• typically compared with a control (usually motor - “output”) task

• demonstrates cerebellar involvement in a number of non-motor domains
  - sensory discrimination
  - attention
  - working memory
  - episodic memory retrieval (a pure thought experiment)
  - reading (phonemic/semantic judgement)
  - propositional language/verbal fluency
1B) Functional neuroimaging (continued)

i) Attention

- fMRI study
- anatomical double dissociation in cerebellar hemisphere activation region between
  - non-motor visual attention task (mid-lateral)
  and
  - motor task (medial)
1B) Functional neuroimaging (continued)

ii) Working memory - fMRI study

- retaining 6 letters to judge later match
  (working memory task) activated right inferior cerebellar hemisphere
- motor tapping (response mode) activated right paravermal region
1B) Functional neuroimaging (continued)

- baseline task - line orientation judgement
- compared with control tasks
  (- upper vs. lower case judgement)
  (- real word rhyming judgement)
- non-word rhyme judgement and semantic (meaning) comparison tasks activated posterolateral cerebellar hemispheres
1B) Functional neuroimaging (continued)

iii) Reading - semantic judgement - fMRI study


- 3 semantic judgement tasks of increasing cognitive load but identical reading/subvocalisation

- increasing right cerebellar activation with increasing cognitive load
iv) Propositional language - PET study


- verb association task (e.g. respond “barks” if shown word “dog”):
  - activated:
    - right lateral cerebellum as well as Broca’s area, BUT

- control tasks (reading aloud/silent reading) did not activate cerebellum
iv) Verbal fluency - PET study
- silent letter fluency activates left frontoparietal cortex and right cerebellum in right hander;
  right frontoparietal cortex and left cerebellum in left hander
2) Evidence for cerebellar involvement in cognition in disease

A) Focal lesions

i) (Schmahmann JD, Sherman JC. Brain 1998; 121: 561-579)

- 20 adult patients with isolated cerebellar lesions
  - posterior lobe lesions produced impairment of
    - planning, set shifting, abstract reasoning, semantic verbal fluency, working memory
  - posterior vermis lesions produced
    - personality change with blunting/disinhibition
  - anterior lobe lesions produced
    - motor deficit

“cerebellar cognitive-affective syndrome”
2A) Focal lesions (continued)

- 24 prospectively collected patients aged 18-44 years with infratentorial infarcts; 14 age-matched controls
- deficits in working memory, cognitive flexibility, visuospatial skills
- WAIS-R FSIQ and episodic memory unaffected
- most made good motor recovery BUT only half returned to work
2A) Focal lesions (continued)

- 15 consecutive patients with cerebellar infarcts compared with 15 matched controls; assessed subacutely (< \(\frac{3}{12}\)) and chronically (> 1 year)
- multiple domains impaired; many resolved at > 1 year (Stroop, block design deficit did not)
- no effect of lesion site/side (but small n’s)

- 6 patients with PICA infarcts, 5 with SCA infarcts, 11 controls
- SCA patients significantly impaired only on visual memory span forwards
- PICA patients impaired on verbal/visual anterograde episodic memory, visual memory span forwards, trail-making
2A) Focal lesions (continued)


- 21 subjects with isolated cerebellar tumours or haemorrhages + 21 well-matched controls
- most cognitive functions impaired; many did not correlate with Purdue pegboard performance
  
  *e.g.*  
  - verbal/visual anterograde episodic memory
  - block design
  - TMT (parts A and B)
- right-sided lesions most impaired, but left-sided worse at RCFT planning
2A) Focal lesions (continued)


- 26 subjects with cerebellar infarcts + 14 controls
- right-sided lesions → verbal anterograde memory impairment
- left-sided lesions → slower at RCFT copy
- problems had usually resolved by three months post-infarct
  (77% had returned to work; one had continuing deficit)

- 21 patients with *chronic* cerebellar infarcts (≥ 17/12) examined:
  - right posterolateral (PICA; crus II) infarcts associated with impairment on verbal fluency
  - otherwise, cognitively intact
2A) Focal lesions (continued)


- 42 patients with *chronic* cerebellar infarcts compared with 69 controls
- unimpaired on standard neuropsychological testing, but
- left-sided lesions → impaired on picture sequencing
- right-sided lesions → impaired on verbal story sequencing
2A) **Focal lesions - summary**

- Cognitive impairment can occur across multiple domains in acute/subacute cerebellar infarcts, *not* just related to motoric or visual scanning deficits
- Cognitive impairment is probably more likely with PICA than SCA infarcts
- Right cerebellar lesions produce similar effects to left cerebral hemisphere lesions—“linguistic cerebellum” (and left cerebellar to right cerebral?)
- Cognitive deficits tend to improve after cerebellar stroke, but do not always do so completely
2) Evidence for cerebellar involvement in cognition in disease

B) Cerebellar degenerations


- 9 patients with “pure CCA”; 12 controls
- Tower of Hanoi task (planning)
  - CCA patients - solved fewer problems (p < 0.001)
    - made more illegal moves (p < 0.05)
    - spent longer planning 1st move (p < 0.04)
  - no differences in PALT, verbal fluency, procedural learning
Since then, cognitive (primarily executive) deficits have been reported with:

- **SCA 1**

- **SCA 2**
  - Storey E, *et al.*  *Arch Neurol* 1999
  - Burk K, *et al.*  *Brain* 1999
2B) Cerebellar degenerations (continued)

(Storey E, et al. Arch Neurol 1999; 56: 43-50)

- 5 of 6 affected members of SCA 2 pedigree showed executive impairment despite normal MMSE
  (e.g. average Stroop error z-score = -8!)
2B) Cerebellar degenerations (continued)

- SCA 3

- SCA 6
  - Suenaga, et al. JNNP 2008

- SCA 8
  - Lilja et al. J Neurol Sci 2005
pure cerebellar degenerations (e.g. SCA 6, and presumably ILOCA) may cause cognitive impairment

although

most cerebellar degenerations also cause extracerebellar degeneration (especially SCA’s 2 and 17)
Avoiding potential confounding effects when testing ataxic patients

1) use tests with internal visuomotor controls, e.g.
   – Stroop test
   – Trail Making test

2) use untimed tasks
   – Wisconsin Card Sorting Test (not Tower of London!)
   – Raven’s progressive matrices
   – Rey Auditory/California/Hopkins Verbal Learning Tests
3) use visuoperceptual (not visuoconstructional) tests
   – Benton Judgement of Line Orientation
   – Benton form discrimination

4) use tasks where planning/intent can be assessed separately from accuracy of execution
   – Rey Complex Figure Test
   – Lurian motor sequences
   – antisaccade task

5) use timed tasks only if experience shows slowness of execution is not the limiting factor
   – verbal fluency tasks
Conclusion

• the cerebellum, and particularly the posterior lobes, contributes to cognition, although in exactly what way is yet to be clarified (attentional switching? sequencing? refining new/effortful cognition?)

• there is lateralisation of cerebellar cognitive function, at least as regards language

• cognitive deficits from cerebellar infarcts improve, but probably do not entirely resolve

• executive deficits are common in cerebellar degenerative disease, and do not just reflect motor deficits