

The Cerebellum and Cognition

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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

(Allen G, *et al.* Science 1997; 275: 1940-1943)

- 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
(Desmond JE, *et al.* J Neurosci 1997; 17: 9675-9685)
 - 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)

- iii) Reading - phonemic/semantic judgement- fMRI study
(Fullbright RK, *et al.* Am J Neurocardiol 1999; 20: 1925-1930)
 - 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
(Xiang H, *et al.* Hum Brain Mapping 2003; 18: 208-214)
 - 3 semantic judgement tasks of increasing cognitive load but identical reading/subvocalisation
 - increasing right cerebellar activation with increasing cognitive load

1B) Functional neuroimaging (continued)

iv) Propositional language - PET study

(Petersen SE, *et al.* J Cog Neurosci 1989; 1: 153-170)

- 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

1B) Functional neuroimaging (continued)

iv) Verbal fluency - PET study

(Hubrich-Ungureanu P, *et al.* Neurosci Lett 2002; 319: 91-94)

- 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)

- ii) (Malm J, *et al.* Neurology 1998; 51: 433-440)
- 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)

- iii) (Neau J-Ph, *et al.* Acta Neurol Scand 2000; 102: 363-370)
 - 15 consecutive patients with cerebellar infarcts compared with 15 matched controls; assessed subacutely ($< 3/_{12}$) 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)

2A) Focal lesions (continued)

- iv) (Exner C, *et al.* Neurology 2004; 63: 2132-2135)
- 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)

- v) (Gottwald B, *et al.* J Neurol Neurosurg Psychiatry 2004; 75: 1524-1531)
- 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)

- vi) (Hokkanen LSK, *et al.* Eur J Neurol 2006; 13: 161-170)
- 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)

2A) Focal lesions (continued)

- vii) (Richter S, *et al.* J Neurol 2007; 254: 1193-1203)
- 21 patients with *chronic* cerebellar infarcts ($\geq 17/12$) examined:
 - right posterolateral (PICA; crus II) infarcts associated with impairment on verbal fluency
 - otherwise, cognitively intact

2A) Focal lesions (continued)

viii) (Leggio MG, *et al.* Brain 2008; 131: 1332-1343)

- 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

(Grafman J, *et al.* Neurology 1992; 42: 1493-1496)

- 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

2B) Cerebellar degenerations (continued)

Since then, cognitive (primarily executive) deficits have been reported with:

– SCA 1

- Burk K, *et al.* Eur Neurol 2001
- Burk K, *et al.* J Neurol 2003

– SCA 2

- Gambardella A, *et al.* J Neurol 1998
- Storey E, *et al.* Arch Neurol 1999
- Burk K, *et al.* Brain 1999
- Le Pira F, *et al.* J Neurol Sci 2002
- Burk K, *et al.* J Neurol 2003

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

- Maruff P, *et al.* Ann Neurol 1996
- Zawacki TM, *et al.* Mov Dis 2002
- Burk K, *et al.* J Neurol 2003
- Kauai Y, *et al.* Arch Neurol 2004

– SCA 6

- Globes C, *et al.* J Neurol 2003 (mild deficits in single executive tasks)
- Suenaga, *et al.* JNNP 2008

– SCA 8

- Lilja *et al.* J Neurol Sci 2005
- Torrens *et al.* Acta Neurol Scand 2008

2B) *Cerebellar degenerations – summary*

- 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