Cerebellum and cognition: New information, new implications

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Mouse cerebellum.
DTI of fiber tracks - location and orientation of parallel fibers

Juelich, Takahashi, Jafari, Zoghbi, Schmahmann. 2013, Unpublished
DTI shows axons in human cerebellar cortex; orientation of parallel and interneuron fibers (basket and stellate cells)
The cerebrocerebellar circuit

Harvard Magazine, 1999

Schmahmann, 1994
Cerebro-cerebellar loops: Feedforward limb

Schmahmann, 1994, 1996
Schmahmann and Pandya, 1987, 1997
Cerebellar projections to frontal lobe

Middleton and Strick, 1997

Kelly and Strick, 2003
Human cerebrocerebellar connections - fcMRI
Functional topography in the human cerebellum, fMRI

Key:
- Tapping = red-orange
- Verb generation = blue
- n-back = purple
- Mental rotation = green
- IAPS = yellow

Blood supply of human cerebellum
Adapted from Tatu et al., 1996
Blood supply of human cerebellum
Adapted from Tatu et al., 1996

The cerebellar cognitive affective syndrome

Jeremy D. Schmahmann and Janet C. Sherman

5-days following cerebellar midline ganglioglioma resection
23-yr woman following removal of a cerebellar tumor

Schmahmann and Sherman. Brain, 1998
The Cerebellar Cognitive-Affective Syndrome

- Executive Function
  Planning, set-shifting, verbal fluency, abstract reasoning, working memory
- Spatial Cognition
  Visual spatial organization and memory
- Language Deficits
  Agrammatism and aprosodia
- Personality Change
  Blunting of affect, disinhibited and inappropriate behavior

Schmahmann and Sherman. Brain, 1998
Cerebellar tumor resection in children

5-yr-old boy. Medulloblastoma

Rey figure.
6-yr-old boy.
Left cerebellar
cystic astrocytoma

Levisohn, Cronin-Golomb, Schmahmann. Brain, 2000
Cerebellar cognitive affective syndrome in children after tumor resection

- **Problem-solving**
  Failure to organize verbal or visual-spatial material

- **Visual-spatial**
  Impaired planning and organization

- **Expressive language**
  Long latencies, poor initiation, brief responses, lack of elaboration, word finding, confrontation naming

- **Memory**
  Impaired for stories; better with multiple-choice

- **Regulation of affect (vermis lesions)**
  Irritable, impulsive, disinhibited, labile affect

Levisohn, Cronin-Golomb, Schmahmann. Brain, 2000
Preterm infants with isolated cerebellar hemorrhagic infarction (n = 51)

- Neurological abnormality 66%
  - Hypotonia, abnormal DTRs, gait, ocular alignment, visual field defects, microcephaly, lethargy/irritability, motor asymmetry
- Motor delay – gross (40%), fine (54%)
- Severe functional limitations 40%
  - Communication deficits (34%); socialization difficulties (26%)
- Visual receptive defects 40%
- Expressive language defects 43%
- Receptive language defects 37%
- Behavioral and social outcomes
  - Withdrawn 40%, decreased attention 37%, affective problems 29%, pervasive difficulties 34%
- Autism scores 43%

Limperopoulos et al, Pediatrics 2007
Cerebellar agenesis

Sensorimotor impairments

Abnormal eye movements - impaired saccades, pursuit, VORC
Oral motor apraxia
Gross and fine motor delay; Mild clumsiness and ataxia

Chheda, Sherman, Schmahmann, 2002
Cerebellar agenesis

Chheda, Sherman, Schmahmann, 2002
Cerebellar Agenesis
Behavioral observations (n=6)

- **Executive impairments**
  Perseveration, disinhibition, impaired abstract reasoning, working memory and verbal fluency

- **Spatial cognition**
  Poor perceptual organization, copying and recall

- **Language**
  Expressive language delay – requiring sign language in two. Impaired prosody. Over-regularization of past tense verbs

- **Psychiatric/affective**
  Autistic-like stereotypical performance, obsessive rituals, difficulty understanding social cues. Tactile defensiveness

Chheda, Sherman, Schmahmann, 2002
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Limperopoulos et al, Pediatrics 2007
Cognition in the Ataxias

• Almost all the spinocerebellar ataxias, as well as Friedreich’s ataxia and multiple system atrophy, have now been studied with neuropsychological measures

• The features identified, to varying degrees and levels of severity, match the CCAS
  – Executive
  – Visual spatial
  – Language
  – Emotion
Neuropsychiatry of the Cerebellum

- Attentional Control
- Emotional Control
- Autism Spectrum Disorders
- Psychosis Spectrum Disorders
- Social Skill Set

Positive (exaggerated) symptoms
Negative (diminished) symptoms
in each category
reflecting cognitive / emotional dysmetria

Schmahmann, Weilburg, Sherman. Cerebellum, 2007
Dysmetria of Thought Theory

In the same way that the cerebellum regulates the rate, rhythm, force, and accuracy of movements, so does it regulate the speed, consistency, capacity, and appropriateness of mental or cognitive processes.

- Damage to anterior lobe results in dysmetria of movement = ATAXIA
- Damage to posterior lobe results in dysmetria of thought and emotion = THE CEREBELLAR COGNITIVE AFFECTIVE SYNDROME (CCAS)

Schmahmann 1991, 2000, 2004
Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia

Asli Demirtas-Tatlidede a,b, Catarina Freitas a,b, Jennifer R. Cromer a,c, Laura Safar a,c, Dost Ongur a,d, William S. Stone a,e, Larry J. Seidman a,e, Jeremy D. Schmahmann a,f, Alvaro Pascual-Leone a,b,*
Cerebellar transcranial magnetic stimulation in schizophrenia

Enhancing cerebellar function using transcranial magnetic stimulation improves schizophrenia (pilot study)

Inhibition of Gamma Oscillations Post iTBS Therapy*

*Gamma Inhibition Is Induced by TMS Paired Pulse Paradigm (LICI) Applied to the DLPFC

Note: Hot colors represent inhibition of gamma oscillations; Cold colors represent lack of inhibition

Why is this important? Impairment in modulation of cortical gamma oscillations have been associated with pathophysiology of schizophrenia, specifically, cognitive deficits.

Farzan F et al., Brain, 2010. Evidence for gamma inhibition deficits in patients with schizophrenia

Farzan, Halko, Schmahmann, Pascual-Leone, 2013
What does this mean for you?
Non-motor problems that a person with ataxia may experience (CCAS)

- Problems with multitasking
- Less mental agility with planning, forming strategies, and organizing oneself
- Mental flexibility may be affected
- Working memory is not as sharp
- Short term recall can be troublesome
- Mental arithmetic, and complex concepts are challenging
- Big picture thinking, creativity, spatial skills may be impaired
- Depression, apathy, irritability, aggression sometimes noted
- Emotional expression may be excessive or inappropriate
What you can do about it

• Cognitive Behavioral Therapy (Motor / Cognitive / Emotional)
• Bring actions to conscious awareness
• Avoid multitasking
• Simplify actions into manageable steps
• Use aids for recall if necessary
• Take notes, keep a diary, maintain consistency
• Stay mentally and physically active
• Engage in cognitively challenging and new tasks
• Get help – counseling, medications, new approaches
• Be kind to yourself
• Know that it is not “in your head”, it is in your brain
What your doctor can do about it

Recognize and treat neuropsychiatric symptoms in patients with cerebellar diseases

- Depression, anxiety, and panic disorder
- Executive dysfunction, memory impairment
- REM sleep behavior disorders
- Pathological laughing and crying
- Developmental and language delay in children, psychological and emotional distress
- Psychosis following cerebellar tumor resection
- Autism spectrum disorders in cerebellar malformations, hypoplasia, post-tumor resection, agenesis
- Medications appropriate to relieve each symptom
- Physical rehabilitation for motor control, mood, and cognition
Recap…

- Cerebellum is not a “black box” – it has different parts
- These parts are linked to different brain / spinal cord areas
- The different cerebellar regions engage in different functions (sensorimotor, cognition, limbic / autonomic)
- Cerebellar damage impairs motor control, intellect, and emotion in a similar manner (dysmetria of thought theory)
- The architecture of the cerebellum is consistent throughout
- The cerebellum performs the same computation on all information it modulates (the universal cerebellar transform)
- These findings have implications for treatment of people with ataxia, and for the wider field of neuropsychiatry
### Collaborators

<table>
<thead>
<tr>
<th>Neuroanatomy</th>
<th>Clinical investigations</th>
<th>Cerebellar parcellation, MRI, fMRI, PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deepak Pandya</td>
<td>Lou Caplan</td>
<td>Nathaniel Alpert</td>
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<tr>
<td></td>
<td>Milan Chheda</td>
<td>David Borsook</td>
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<td>Alice Cronin-Golomb</td>
<td>Verne Caviness</td>
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<td>Stefanie Freeman</td>
<td>Anders Dale</td>
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<td>Matthew Frosch</td>
<td>Bruce Fischl</td>
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<td>Amy Hurwitz</td>
<td>Bruce Rosen</td>
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<td>Catherine Stoodley</td>
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<td>Janet Sherman</td>
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<td>Primate behavior</td>
<td>Kathie Sims</td>
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<td>Julian Doyon</td>
<td>Mark Vangel</td>
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<td>Alan Evans</td>
<td>Jeffrey Weilburg</td>
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<td>SCA 1 mouse</td>
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<td>Huda Zoghbi</td>
<td>Katherine Hermann</td>
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<td>Paymaan Jafari</td>
<td>Franziska Hoche</td>
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**Photo by Jinny Sagorin**

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