Ataxia and Cerebellar Dysfunction: Implications for Pediatric Neurology of Cerebellar Cognition

Harvard Medical School
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CEREBELLAR DISORDERS IN CHILDREN

Eugen Boltshauser and Jeremy Schmahmann
Cerebellar motor syndrome

- Gait ataxia
- Dysmetria of extremities
- Oculomotor abnormalities
- Dysarthria

From Dow and Moruzzi, 1958

Sir Gordon Morgan Holmes
1876 – 1965

From Dow and Moruzzi, 1958
Ataxia Rating Scales

• ICARS  International cooperative Ataxia Rating Scale
• SARA  Scale for the Assessment and Rating of Ataxia
• BARS  Brief Ataxia Rating Scale
• FARS  Friedreich Ataxia Rating Scale
• SCAFI  SCA Functional Index - 9HPBT, 8m walk, PATA rate
• CCFS  Composite Cbllar Functional Score - 9HPBT, click test
• INAS  Inventory of Non-Ataxia Symptoms
• AT Scale  Quantitative Assessment of Ataxia Telangiectasia
• UMSARS  Unified MSA Rating of Scale
BRIEF ATAXIA RATING SCALE (BARS)

Gait
0: Normal
1: Almost normal naturally, but unable to walk with feet in tandem position
2: Walking without support, but clearly abnormal and irregular
3: Walking without support but with considerable staggering; difficulties in half turn
4: Walking without support not possible; uses support of the wall for 10-meter test.
5: Walking possible only with one cane
6: Walking possible only with two canes or with a stroller
7: Walking possible only with one accompanying person
8: Walking impossible with one accompanying person (2-person assist; wheelchair)

Knee-tibia test (decomposition of movement and intention tremor)
(Left and Right scored)
0: Normal
1: Lowering of heel in continuous axis, but movement is decomposed in several phases, without real jerks, or abnormally slow
2: Lowering jerkily in the axis
3: Lowering jerkily with lateral movements
4: Lowering jerkily with extremely long lateral movements, or test impossible

Finger-to-nose test (decomposition and dysmetria of arm and hand)
(Left and Right scored)
0: Normal
1: Oscillating movement of arm and/or hand without decomposition of the movement
2: Segmented movement in 2 phases and/or moderate dysmetria in reaching nose
3: Segmented movement in more than 2 phases and/or considerable dysmetria in reaching nose
4: Dysmetria preventing the patient from reaching nose

Dysarthria
0: Normal
1: Mild impairment of rate / rhythm / clarity
2: Moderate impairment of rate / rhythm / clarity
3: Severely slow and dysarthric speech
4: Speech absent or unintelligible

Oculomotor abnormalities
0: Normal
1: Slightly slowed pursuit, saccadic intrusions, hypo/hypermetric saccade, nystagmus
2: Prominently slowed pursuit, saccadic intrusions, hypo/hypermetric saccade, nystagmus

TOTAL (out of 30)

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BRIEF ATAXIA RATING SCALE (BARS) - revised

Gait:
0: Normal gait and 10-step tandem gait
0.5: Normal gait, but performs 10-step tandem gait only with great difficulty (e.g., flailing arms)
1: Almost normal gait, but unable to walk 10 steps with feet in tandem position
1.5: Cadence, speed, stance is slightly irregular, may take an extra step to turn but not clearly abnormal
2: Walking without support, but clearly abnormal and irregular
2.5: Walking without support, clearly abnormal and irregular, difficulties in half turn, but no staggering
3: Walking without support with considerable staggering, and difficulties in half turn
3.5: Walking mostly without support, touches the wall/furniture once during the 20-meter test (including at the turn)
4: Walking without assistance, uses episodic support of the wall for 20-meter test (including the turn)
4.5: Uses support of the wall for 20-meter test, maintaining contact with the wall throughout
5: Walking 20 meters possible only with one single cane, or holding onto a service dog with one arm
5.5: In the same testing session, scores 5 and 6 on different trials
6: Walking 20 meters possible only with a walker, or two canes
6.5: Walking 20 meters possible only with a walker, or two canes, and needs intermittent 1 person assist
7: Walking 20 meters possible only by holding onto one accompanying person
7.5: Walking 20 meters possible only by holding onto two accompanying individuals
8: Walking 20 meters impossible even with 2-person assist, requires a wheelchair

Heel-to-Shin test
0: Normal movement of the heel down the opposite shin
0.5: Not entirely smooth movement of the heel down the shin
1: Moves the heel down the shin in continuous axis, decomposed in several phases, without jerking, or abnormally slow
1.5: Slowing of movement of the heel down the shin, with occasional superimposed jerking component
2: Moves the heel down the shin jerkily, but in the axis
2.5: Moves the heel down the shin jerkily in the axis, with occasional lateral movements superimposed
3: Side to side (lateral) movements predominate when attempting to move the heel down the shin
3.5: Difficulty maintaining contact of the heel on the shin because of the lateral movements
4: Lowering jerkily with extremely long lateral movements, or the test is impossible

Finger-to-Nose test
0: Normal pointing of examiner's finger and to tip of the subject's nose
0.5: Slowed, or with minimal instability at endpoint (e.g., mild finger wobble)
1: Oscillating movement of hand and/or arm without decomposition of the movement
1.5: Mild to moderate dysmetria (captures variation of performance within the same examination)
2: Segmented movement in 2 phases at the elbow and/or moderate dysmetria in reaching the finger or nose
2.5: Moderate to severe dysmetria (captures variation of performance within the same examination)
3: Segmented movement in > 2 phases at the elbow and/or considerable dysmetria in reaching the finger or nose
3.5: Dysmetria so severe as to almost prevent patient from reaching the finger or nose
4: Dysmetria so severe that it prevents the patient from reaching the finger or nose

Speech
0: Speech is normal including rapid production of consonants (buccal-lingual-palatal)
0.5: Speech is normal, but attempted rapid production of consonants is dysrhythmic (impaired rate/rhythm/clarity)
1: Mild dysarthria with impaired rate/rhythm/clarity, but all words are intelligible
1.5: Mild to moderate dysarthria (captures variation of speech clarity within the same interview)
2: Moderate dysarthria with impairment of rate/rhythm/clarity, some words difficult to understand
2.5: Moderate to severe dysarthria (captures variation of speech clarity within the same interview)
3: Speech is severely slow and/or dysarthric, and many words are difficult to understand
3.5: Speech is severely slow and/or dysarthric, and only occasional words are produced or intelligible
4: Speech is absent or unintelligible

Oculomotor
0: Normal oculomotor exam (eyes are quiet in primary position; pursuit is normal; saccades are normal; no nystagmus)
0.5: One of four cardinal oculomotor findings is abnormal (movements at rest, saccadic pursuit; hypo/hypermetric saccades; nystagmus)
1: Two of the four cardinal oculomotor findings are present
1.5: Three of the four cardinal oculomotor findings are present
2: All four of the cardinal oculomotor findings are present

TOTAL BARS SCORE (out of 30)

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CHILDREN WITH ATAXIA - VIDEOS
Problems encountered using adult rating scales in children

• Age-dependence – young healthy children score in the abnormal range [Sival 2009]

• Some motor test items are not appropriate for young children
Plots of total scores related to age.

- age-dependency until 12.5, 10, and 11 years of age (for ICARS, SARA, and BARS, respectively)

- 9-hole PEG-board test shows age-dependency until 11.5 years of age.

- Ataxia rating scale ranges from zero reflecting no ataxia, to 100, 40, and 30 representing maximum ataxia in ICARS, SARA, and BARS respectively.

(Brandsma et al., 2014)

Problem I: potential misinterpretation of therapeutic trial outcomes when using adult-based scales in children
Subscales indicated for (a) ICARS and (b) SARA. Figures reveal that mature **speech** tends to develop earlier than gait, and gait earlier than kinetic function.

Problem 2: Population of children < 4 years not tested
Selected causes of ataxia in children

- **Congenital / Genetic**
  - CNS Malformations
    - Cerebellar hypoplasia
    - Vermian aplasia / Joubert syndrome
    - Dandy-Walker
    - Chiari malformation
    - Rhombencephalosynapsis
  - Hereditary / Genetic
    - Autosomal recessive
      - Friedreich’s ataxia
      - Ataxia-telangiectasia
      - Ataxia oculomotor apraxia types 1, 2
      - Abetalipoproteinemia
      - Vitamin E deficiency (AVED)
      - Pontocerebellar hypoplasia, types 1-10
      - Refsum disease
    - X-linked recessive
      - Sideroblastic anemia and ataxia
      - SCA-X linked, type 1
    - Autosomal dominant
      - Spinocerebellar ataxias types 1 – 43
      - Episodic Ataxias
    - Mitochondrial
      - Kearns Sayre Syndrome
  - Sensory Ataxia
    - Guillain-Barre
    - Multiple sclerosis

- **Acute/Sub-acute**
  - Infectious / Immune-mediated
    - Infectious Cerebellar Ataxia
    - Post-infectious Cerebellar Ataxia
    - Acute disseminated encephalomyelitis
    - Acute labyrinthitis
  - Drug/Toxin-related
    - Alcohol, BZDs, anticonvulsants, heavy metals, carbon monoxide
  - Mass lesions
    - Tumor
    - Vascular lesions (AVM)
    - Abscess
  - Trauma
    - Hemorrhage
    - Vertebral artery dissection
  - Paraneoplastic
    - Opsoclonus-myoclonus (neuroblastoma)
  - Other
    - Basilar migraine, benign paroxysmal vertigo, non-convulsive seizures

GeneReviews®
Case Study

Age 14: Ruptured cerebellar AVM

Age 17: Persistent mutism - occasional high pitched sounds
Follows instructions intermittently
Aggression, striking out, inability / refusal to eat
Bed-ridden, mild dysmetria
Langerhans cell histiocytosis
Cerebellar involvement, age 6

MRI scans ages 10 though 27

At age 22:

Brief Ataxia Rating Scale 13/30

Neuropsychiatric features
Impetuous, impulsive, inappropriate
Poor judgment, perseverative
Aggression, agitation, depression
Distributed neural systems comprise anatomic regions, or nodes
- Unique architectural properties
- Geographically arranged throughout cortical and subcortical areas
- Linked anatomically in a precise and unique manner
from The Sorcerer's Apprentice.
Reticular influence - EEG Arousal, sleep wake cycle
Autonomic phenomena
Grooming, sham rage, predatory attack
Conditional associative learning (eyeblink)

Snider and Stowell, 1946
Snider, 1950
Snider and Eldred, 1951
Schmahmann, Doyon, Toga, Petrides, Evans, 2000
Cerebellar histology consistent throughout

Santiago Ramon y Cajal, 1911
www.vocesdelaciencia.com.ar

Eccles, Ito, Szentágothai, 1967
Corticonuclear microcomplexes; cerebello-olivary modules

Voogd, 1965
Voogd and Glickstein, 1998
Leclerc et al, 1990
Cerebellar growth (by MRI) in the 3rd trimester

**Graph:**
- X-axis: Postconceptional Age (weeks)
- Y-axis: Cerebellar Volume (cc)
- Data points show an increase in cerebellar volume with increasing postconceptional age.
- N=187
- p<0.001

**Bar Chart:**
- Cerebellar Volume
- ICC Volume
- Brain Volume
- % increase between 28-40 weeks PCA
- p<0.001

*Limperopoulos et al, Pediatrics 2005*
Cerebro-cerebellar circuits: Feedforward limb

Schmahmann, 1994, 1996
Schmahmann and Pandya, 1987, 1997
Cerebro-cerebellar circuits: Feedback limb

Middleton and Strick. Science, 1994
Cerebellar functional topography. Case series task-fMRI

Red = Sensorimotor > Cognitive
Blue = Cognitive > Sensorimotor

Cerebellar functional topography. Comparison task fMRI studies

- Meta-analysis
- Case Study
- Group Results

Motor
- y = -55

Language
- y = -68

Spatial
- y = -64

Spatial
- y = -78

Working Memory
- y = -60
Functional topography of human cerebrocerebellar connections as determined by resting state fCMRI
CEREBELLAR STROKE WITHOUT MOTOR DEFICIT: CLINICAL EVIDENCE FOR MOTOR AND NON-MOTOR DOMAINS WITHIN THE HUMAN CEREBELLUM

**SCA infarction**  
MICARS = 20

**PICA infarction**  
MICARS = 1

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

23-yr woman s/p resection, cerebellar gangioglioma
Clinical impairments in patients with cerebellar lesions

Schmahmann and Sherman. Brain, 1998
Cerebellar Cognitive Affective Syndrome (CCAS)

- **Executive Function**
  Planning, set-shifting, verbal fluency, abstract reasoning, working memory

- **Spatial Cognition**
  Visual spatial organization and memory

- **Language Deficits**
  Agrammatism, aprosodia, anomia

- **Personality Change**
  Blunting of affect, disinhibited and inappropriate behavior

Schmahmann and Sherman. Brain, 1998

Schmahmann’s syndrome - identification of the third cornerstone of clinical ataxiology

Mario Manto and Peter Mariën. Cerebellum and Ataxias 2015;2:2
Post-infectious (EBV) cerebellitis

Rey copy during illness  Taylor copy after recovery

A  B
Metalinguistic functions in cerebellar patients

Test of Language Competence – Expanded (TLC-E)

25 cerebellar patients, 25 healthy controls.

Deficits in the ability to:

• **Resolve ambiguity:** “I don’t know about you, but visiting relatives can be a nuisance.”

• **Make inferences:** “The sun was shining, when the Robertsons started out for the picnic. Unfortunately, they had the picnic in the living room.”

• **Use and interpret metaphor:** “He is as transparent as we thought.”

• **Formulate propositions in grammatically complete sentences:**

P20: I never thought I would meet you here, nor did I, because everything seems so fresh here to buy

Guell, Hoche, Schmahmann. Cerebellum 2015;14:50-8
Theory of Mind
Mental processes required to understand, generate, and regulate social behavior

57 cerebellar patients tested on the RMET (Baron-Cohen et al., 2001):
- 31 complex (cerebrocerebellar)
- 26 isolated (cerebellar)
CCAS following tumor resection in children

5-yr-old boy. Medulloblastoma

Rey figure.
6-yr-old boy.
Left cerebellar
cystic astrocytoma
Neuropsychological consequences of cerebellar tumour resection in children
Cerebellar cognitive affective syndrome in a paediatric population

Lisi Levisohn, Alice Cronin-Golomb and Jeremy D. Schmahmann

- Problem-solving
  Failure to organize verbal or visual-spatial material
- Visual-spatial
  Impaired planning and organization
- Expressive language
  Latency, initiation, elaboration, word finding, anomia
- Memory
  Impaired for stories; better with multiple-choice
- Regulation of affect (vermis lesions)
  Irritable, impulsive, disinhibited, labile affect

Levisohn, Cronin-Golomb, Schmahmann, 2000
Post-operative Pediatric Cerebellar Mutism Syndrome

"Post-operative Pediatric CMS is characterized by delayed onset mutism/reduced speech and emotional lability after cerebellar or 4th ventricle tumor surgery in children. Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia. It may frequently be accompanied by the cerebellar motor syndrome, cerebellar cognitive affective syndrome and brain stem dysfunction including long tract signs and cranial neuropathies. The mutism is always transient, but recovery from CMS may be prolonged. Speech and language may not return to normal, and other deficits of cognitive, affective and motor function often persist."

Gudrunardottir et al., Consensus Statement on Pediatric Post-operative Cerebellar Mutism Syndrome: Iceland Delphi Results. In review
Cerebellar agenesis: Developmental CCAS

FSIQ  VIQ  PIQ  BNT  PPVT-III  Rey  VMI  WRAML Visual  Learning  FAS  Semantic Trails  A-B

Rey Figure

Chheda, Schmahmann, et al., 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
Cerebral lesions with secondary cerebellar growth impairment

Mean Cerebellar volume (cc)

- VM
- PVL
- PVHI
- Term

p<0.001

Limperopoulos et al, Pediatrics 2005
Transtentorial diaschisis

Ipsilateral: 10.4 cc
Contralateral: 7.1 cc

Limperopoulos et al, Pediatrics 2005
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
Behaviorally Defined Disorders with Cerebellar Anomalies

• Attention Deficit Hyperactivity Disorder
  Berquin et al. Neurology, 1998; 50: 1087-93
  Castellanos et al. Arch Gen Psychiatry, 2001; 58: 289-95

• Dyslexia
  Nicolson et al. Lancet, 1999; 353: 1662-7

• Cognitive deficits in infants born very pre-term
  Allin et al. Brain, 2001; 124: 60-66

• Autism
  Bauman and Kemper, 1984, 1997
  Tsai et al. Nature 2012;488:647-51
  Loss of Tsc1 in mouse PCs, autistic-like, abnormal social interaction, repetitive behaviors

• Schizophrenia
The neuropsychiatry of the cerebellum – insights from the clinic

JEREMY D. SCHMAHMANN¹, JEFFREY B. WEILBURG² & JANET C. SHERMAN¹

<table>
<thead>
<tr>
<th>Positive (exaggerated) symptoms</th>
<th>Negative (diminished) symptoms</th>
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</thead>
<tbody>
<tr>
<td><strong>Attentional Control</strong></td>
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<tr>
<td>Inattentiveness</td>
<td>Ruminativeness</td>
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<td>Distractibility</td>
<td>Perseveration</td>
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<td>Hyperactivity</td>
<td>Difficulty shifting focus of attention</td>
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<tr>
<td>Compulsive and ritualistic behaviors</td>
<td>Obsessional thoughts</td>
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<tr>
<td><strong>Emotional control</strong></td>
<td></td>
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<tr>
<td>Impulsiveness, disinhibition</td>
<td>Anergy, anhedonia</td>
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<tr>
<td>Lability, unpredictability</td>
<td>Sadness, hopelessness</td>
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<tr>
<td>Incongruous feelings, pathological laughing / crying</td>
<td>Dysphoria</td>
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<tr>
<td>Anxiety, agitation, panic</td>
<td>Depression</td>
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<tr>
<td><strong>Autism spectrum</strong></td>
<td></td>
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<tr>
<td>Stereotypical behaviors</td>
<td>Avoidant behaviors, tactile defensiveness</td>
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<tr>
<td>Self stimulation behaviors</td>
<td>Easy sensory overload</td>
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<tr>
<td><strong>Psychosis spectrum</strong></td>
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<tr>
<td>Illogical thought</td>
<td>Lack of empathy</td>
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<tr>
<td>Paranoia</td>
<td>Muted affect, emotional blunting</td>
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<tr>
<td>Hallucinations</td>
<td>Apathy</td>
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<tr>
<td><strong>Social skill set</strong></td>
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<tr>
<td>Anger, aggression</td>
<td>Passivity, immaturity, childishness</td>
</tr>
<tr>
<td>Irritability</td>
<td>Difficulty with social cues and interactions</td>
</tr>
<tr>
<td>Overly territorial</td>
<td>Unawareness of social cues and interactions</td>
</tr>
<tr>
<td>Oppositional behavior</td>
<td>Overly gullible and trusting</td>
</tr>
</tbody>
</table>
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 domain
reflecting cognitive / emotional dysmetria

We have ataxia rating scales
   ICARS, SARA, BARS, others

BUT:

How do we assess cognition and neuropsychiatric features in patients with cerebellar disorders?

- The cerebellar cognitive affective / Schmahmann syndrome scale (CCAS-scale)
- Cerebellar neuropsychiatric rating scale (CNRS)
**CCAS / Schmahmann Scale**

Hoche, Guell, Sherman, Vangel, Schmahmann. Under review

## CEREBELLAR COGNITIVE AFFECTIVE / SCHMAHMANN SYNDROME SCALE (CCAS-Scale)

**DATE:**

**ID #:**

### SEMANTIC FLUENCY

Score = total correct words typed to a maximum of 26 words. Fail if Score 15 or less.

<table>
<thead>
<tr>
<th>RAW SCORE</th>
<th>PASS 0</th>
<th>FAIL -1</th>
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Please name as many animals or living creatures as you can in one minute

/26

### PHONEMIC FLUENCY

Score = total correct words typed to a maximum of 19 words. Fail if Score 9 or less.

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<tr>
<th>RAW SCORE</th>
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<th>FAIL -1</th>
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Please name as many words as you can in one minute that start with the letter F. Do not use names of people or places or repeat the same word in different forms.

/19

### CATEGORY SWITCHING

Score = total number of correct alternating words typed to a maximum of 15 alternations. Repetitions or set loss errors are not scored. Fail if Score 9 or less.

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<th>RAW SCORE</th>
<th>PASS 0</th>
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Please name a type of vegetable and then a type of profession or job, and then another vegetable and another profession, and so on, switching between the two lists. Name as many as you can in one minute.

/15

### VERBAL REGISTRATION

This test is not scored. (This test for 4 attempts to learn 5 words raises concerns for cerebral predominance.)

I am going to read you a list of words which I would like you to learn. Please repeat these words. I am going to ask you to give them back in a few minutes. (Read 5 words at a rate of 1 / second. Subject repeats them once, then repeats them again. Repeat trials until subject recalls all 5 words. Stop after 4 attempts.)


1st attempt: [ ] [ ] [ ] [ ] [ ]
2nd attempt: [ ] [ ] [ ] [ ] [ ]
3rd attempt: [ ] [ ] [ ] [ ] [ ]
4th attempt: [ ] [ ] [ ] [ ] [ ]

/15

### DIGIT SPAN FORWARD

Score = maximum string of numbers correctly repeated. Fail if Score 5 or less.

<table>
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<th>RAW SCORE</th>
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I am going to read you some numbers. Please repeat them in exactly the same order (Read aloud at a rate of 1 / per second. Subject repeats the numbers if subject fails to repeat).

5-9: [ ] [ ] [ ] [ ] [ ]
2-1-3: [ ] [ ] [ ] [ ] [ ]
7-3-1-9-8-4-6: [ ] [ ] [ ] [ ] [ ]

/15

### DIGIT SPAN BACKWARD

Score = maximum string of numbers correctly repeated. Fail if Score 5 or less. Inability to reverse 2 digits scores 0.

Now please say these numbers backwards, in reverse order. (Give example, then start with *,).

(e.g., 5-8 = 8-5) *6-1 [ ] [ ] [ ] [ ] [ ]
3-8-2 [ ] [ ] [ ] [ ] [ ]
4-7-0-9 [ ] [ ] [ ] [ ] [ ]
6-5-2-8-1 [ ] [ ] [ ] [ ] [ ]
5-9-0-3-7-4 [ ] [ ] [ ] [ ] [ ]

/6

### CUBE (DRAW)

Score = 15 points if 12 lines present and diagram is 3-dimensional. If 12 lines not present or the diagram is not 3-dimensional, administer "CUBE (COPY)."

Please draw a cube – a six-sided box, make it transparent or see-through. (Use space below left).

/6

### CUBE (COPY)

Score = 12 points. 5 for each line. Deduct 1 point if not 3-D. 1 point for each line not drawn. 1 point for each additional line = 12. Fail if Score = less.

/15

<table>
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Please copy the cube shown on PAGE 2. (Features not scored).

---

### VERBAL RECALL

Spontaneous recall = 3 points per word. Category = 2 points, multiple choice = 1 point. Score = total points. Fail if Score 10 or less. Result: ability to recall more than 1 word from multiple choice raises concern for cerebral involvement.


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Recognize category cue: [ ] [ ] [ ] [ ] [ ]
Recognize recall with multiple choice:

/15

### SIMILARITIES

Correct answer (conceptual) = 2 points, partial correct (concrete) = 1 point. Incorrect answer = 0 points. Score = total points. Fail if Score 6 or less. Key: bottom right.

How are the following words alike: what is the same about them? (Provide example, than test items).

- (e.g., Ball/Moon = Round)
- 1. Nose/Ear
- 2. Sheep/Elephant
- 3. Lake/River
- 4. Airplane/Motorcycle

/6

### GO NO-GO

2 points for 5 correct, 1 point for 10 errors, 0 points for two or more errors.

Score = total correct.

I am going to tap the table. When I tap once, please raise your finger then put it back down again. When I tap twice, don't do anything. (Give example of each condition to make sure subject understands)

1-1 1-2 1-2 1-2 1-2 1-2 1-2 1-2 1-2 1-2

/2

### AFFECT

Score 6 points if none are present. Subtract 1 for each item present. Fail if Score 4 or less. (Rater assesses if the following are present, incorporating input from patient and/or caregiver)

- Difficulty with focusing attention or mental flexibility
- Emotionally labile, incongruous emotions, appears hopeless or depressed
- Shows easy sensory overload or avoidant behaviors
- Expresses illogical thoughts or paranoia
- Lacks empathy, is apathetic, or has blunted affect
- Angry or aggressive, irritable, oppositional, difficulty with social cues and social boundaries

/6

### TOTAL SCORE

Calculate total raw score (1st column) and total number of failed tests (2nd column).

1 Failed test = Possible CCAS; 2 failed tests = Probable CCAS; 3 or more failed tests = Definite CCAS.

<table>
<thead>
<tr>
<th>RAW SCORE</th>
<th>PASS 0</th>
<th>FAIL -1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

CUES AND MULTIPLE CHOICE ITEMS FOR VERBAL RECALL TEST

<table>
<thead>
<tr>
<th>Test word</th>
<th>Flower</th>
<th>Robert</th>
<th>Courage</th>
<th>Speak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Grows in</td>
<td>His name</td>
<td>Trait or value</td>
<td>Way of communicating</td>
</tr>
<tr>
<td>Free</td>
<td>Stephen</td>
<td>Buzzy</td>
<td>Speck</td>
<td>Real</td>
</tr>
<tr>
<td>Nose / Ear</td>
<td>Nose</td>
<td>Nose</td>
<td>Nose</td>
<td>Nose</td>
</tr>
<tr>
<td>Sheep / Elephant</td>
<td>Sheep</td>
<td>Elephant</td>
<td>Courage</td>
<td>Think</td>
</tr>
<tr>
<td>Lake / River</td>
<td>Lake</td>
<td>River</td>
<td>Brice</td>
<td>Sing</td>
</tr>
<tr>
<td>Airplane / Motorcycle</td>
<td>Airplane</td>
<td>Motorcycle</td>
<td>Patience</td>
<td>Short</td>
</tr>
<tr>
<td>Bear</td>
<td>Joseph</td>
<td>Brice</td>
<td>Sing</td>
<td>Blue</td>
</tr>
<tr>
<td>Guss</td>
<td>Robert</td>
<td>Patience</td>
<td>Short</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAW SCORE</th>
<th>PASS 0</th>
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</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Hoch, Guell, Vangel, Sherman, Schmahmann

Atalanta Unit, Cognitive Behavioral Neurology Unit, Schmahmann Laboratory for Neuroanatomy and Cerebellar Neurobiology, Department of Neuropathology, Massachusetts General Hospital. © 2016 The Geisinger Hospital Corporation. All Rights Reserved.
Cerebellar Neuropsychiatric Rating Scale

<table>
<thead>
<tr>
<th>ATTENTIONAL CONTROL</th>
<th>POSITIVE</th>
<th>NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty maintaining focus or sustained attention, makes careless mistakes, or does not attend to details</td>
<td>0 1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>2. Easily distracted by non-essential or irrelevant stimuli</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>3. Is often “on the go,” acting as if “driven by a motor,” (e.g., unable to be or uncomfortable being still or extended time), may appear to be restless, or to difficult to keep up with</td>
<td>0 1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>4. Feels compelled to perform habits that are excessive and repetitive and becomes distressed when prevented from doing so</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>5. Feels driven to complete tasks or behave in a rigid, inflexible way according to specific, personal rules</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>POSITIVE SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>TOTAL ATTENTIONAL CONTROL SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMOTIONAL CONTROL</th>
<th>POSITIVE</th>
<th>NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Acts hastily or carelessly in the moment without thinking (e.g., interrupting others, trouble waiting his/her turn)</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>11. Rapid changes in emotion that are more intense than usual or unrelated to the situation</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>12. Crying and/or laughing without an apparent trigger or inappropriately</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>13. Worries excessively, is overly anxious, and/or experiences sudden episodes of intense fear or discomfort (e.g., heart racing, shortness of breath, dizziness)</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>POSITIVE SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>TOTAL EMOTIONAL CONTROL SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUTISM SPECTRUM</th>
<th>POSITIVE</th>
<th>NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. Repetitive movements, postures, or utterances that follow a particular pattern (e.g., hand flapping, finger fumbling, body rocking, repeating noises or phrases)</td>
<td>0 1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>19. Is drawn to sensory experiences, such as excessive smelling or touching of objects, or fascination with lights or spinning objects</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>POSITIVE SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>TOTAL AUTISM SPECTRUM SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSYCHOSIS SPECTRUM</th>
<th>POSITIVE</th>
<th>NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. Communicates in a way that is difficult to follow, illogical, rambling, or nonsensical</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>23. Expresses irrational concerns or false beliefs that he/she is threatened in some way (e.g., others are out to hurt him/her)</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>24. Sees or hears things that they believe are real but are not present</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>POSITIVE SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>TOTAL PSYCHOSIS SPECTRUM SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL SKILL SET</th>
<th>POSITIVE</th>
<th>NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. Acts or appears to be unreasonably angry or aggressive</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>29. Is easily upset or irritable</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>30. Is intolerant of people entering their personal space or overly assertive or protective about communal space and objects</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>31. Deliberately disobedient, defiant and argumentative</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>POSITIVE SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>TOTAL SOCIAL SKILLS SET SCORE</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNRS TOTAL POSITIVE SCORE (54)</th>
<th>CNRS TOTAL NEGATIVE SCORE (51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

Daly, Sherman, Schmahmann. In progress
CNRS in Chiari malformation – (association vs cause)
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,*
Case Study

Age 18: One week of cerebellar vermal iTBS
Age 20: Aspects of CCAS, walking with a walker, Dean’s list at school
Improvement sustained for 2 years so far
Dysmetria of Thought

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

Dysmetria of movement is matched by unpredictability and illogic to social and societal interaction.

Inability in the motor system to check parameters of movement is equated with a mismatch between reality and perceived reality, and erratic attempts to correct errors of thought or behavior.

Dysmetria of Thought

Cerebellum is an integral node in the distributed neural circuits subserving sensorimotor, cognitive, autonomic and affective processing.

The cerebellar cortex is anatomically homogeneous, but different cerebellar regions modulate different functional domains i.e., functional topography.

- Sensorimotor
- Cognitive
- Limbic

Makris et al., 2005

Dysmetria of Thought

Topography anterior lobe – posterior lobe

Sensorimotor –
- anterior lobe (I - V), encroaches on VI
- “secondary” representation in VIII
- vestibulocerebellum in lobules X

Cognitive, affective –
- predominantly posterior lobe (vermal and hemispheric components of lobules VI and VII, likely including IX and X)

Makris et al., 2005

Dysmetria of Thought
Topography medial - lateral

Vermis and fastigial nucleus -
autonomic regulation, affect, emotionally important memory

Cerebellar hemispheres and dentate nucleus -
Executive (including working memory), visual-spatial, linguistic, learning

Dysmetria of Thought

Universal Cerebellar Transform

Cerebellum optimizes performance by modulating behavior around a homeostatic baseline automatically, implicitly, and according to context

Anatomic specificity in cerebrocerebellar loops permits cerebellum to contribute to multiple domains

Dysmetria of Thought

Universal Cerebellar Impairment

= Dysmetria

Lesions of sensorimotor cerebellum
Dysmetria of movement
The cerebellar motor syndrome

Lesions of cognitive – limbic cerebellum
Dysmetria of thought and emotion
The cerebellar cognitive affective syndrome

Cerebellum modulates cognition and emotion: Implications for patient care

In patients with overt cerebellar lesions:
- The need to know imperative (CCAS is not “in their head, it is in their brain”)
- Recognition leads to intervention
- Window for cognitive rehabilitation and cross modal therapies

In patients with primary neuropsychiatric or behavioral neurology disorders:
- Evolving role of cerebellum in pathophysiology of these disorders
- Potential for novel treatment strategies in psychiatric illness
Collaborators

Neuroanatomy
Deepak Pandya

Cerebellar Atlas
Julien Doyon
Alan Evans
David McDonald
Michael Petrides
Arthur Toga

Diffusion Imaging
George Dai
Ellen Grant
Cristina Granziera
Emi Takahashi
Ruopeng Wang
Van Wedeen

Clinical studies
Louis Caplan
Milan Chheda
Alice Cronin-Golomb
Maureen Daly
Xavier Guëll
Franziska Hoche
Stefanie Freeman
Matthew Frosch
Winthrop Harvey
Tessa Hedley-Whyte
Katherine Hermann
Raquel Gardner
Laura Horton
Richard Lewis
Lisi Levisohn
David Lin
Jason MacMore
Marygrace Neal
Janet Sherman
Christopher Stephen
Mark Vangel
Jeffrey Weilburg

fMRI, morphometry
Lino Becerra
David Borsook
Nikos Makris
Eric Moulton
Catherine Stoodley
Eve Valera

Cerebellar TMS
Jennifer Cromer
Asli Demirtas-Tatlidede
Faranak Farzan
Catarina Freitas
Irene Gonsalves
Mark Halko
Dost Ongur
Alvaro Pascual Leone
Laura Safar
Larry Seidman
William Stone

Clinical Consortia
Cerebellar Research Consortium for the Study of Spinocerebellar Ataxias (CRC-SCA)

Posterior Fossa Society
Primate behavior
Ronald Killiany
Tara Moore
Mark Moss
Douglas Rosene

Funding:

Photo by Jinny Sagorin