Cognitive and Emotional Aspects of Cerebellar Function and Dysfunction: 2. Clinical Presentations

Annual Meeting, Pacific Northwest Neuropsychological Society
University of Washington Faculty Club
Seattle, WA
March 6th, 2010

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Cerebellar clinical features – the cerebellar “motor” syndrome

- Gait ataxia
- Dysmetria of extremities
- Eye movement abnormalities
- Dysarthria

Clinical Reports - Cerebellum and Behavior: 1800's

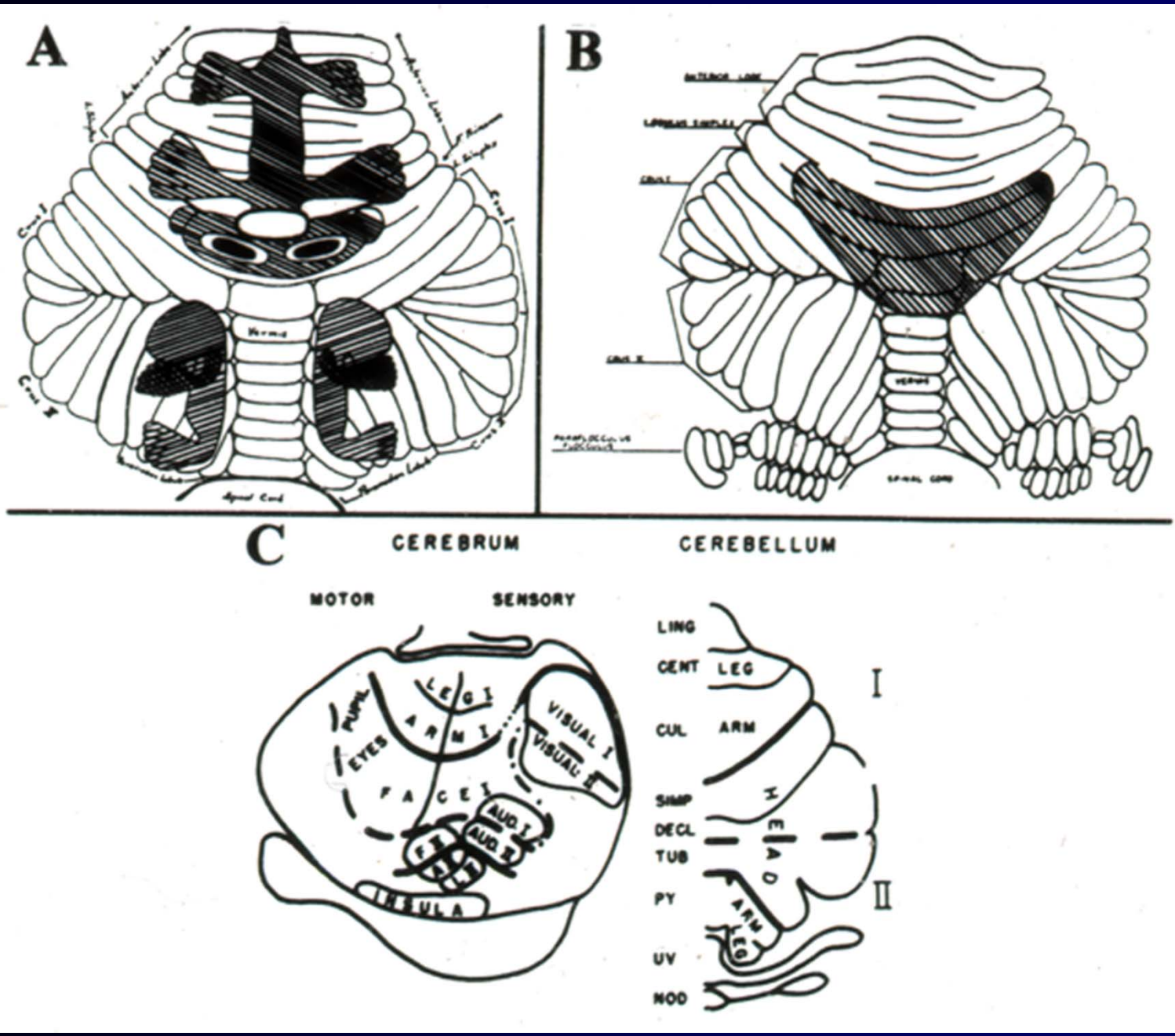
INVESTIGATOR	LESION	BEHAVIOR
Combettes, 1831	Agenesis	Delayed development, aberrant behavior
Andral, 1848	Agenesis, left	"Imbecile, weakness of character"
Vulpian, 1866	Atrophy	Aberrant behavior
Otto, 1873	Agenesis	Low intelligence, aberrant / deviant behavior
Ferrier, 1876	Agenesis	Feeble minded
Doursout, 1891	Atrophy	"Idiocy, irritability, brutality"
Fusari, 1892	Agenesis	Mental retardation ("grave imbecility")
Neff, 1894	Atrophy	Mental deficiency
Bond, 1895	Atrophy	"Foolishness"
Londe, 1895	Spastic ataxia	Mental difficulties
Claasen, 1898	Atrophy	Mental deficiency
Whyte, 1898	Friedreich's ataxia	Mental impairment

Clinical Reports - Cerebellum and Behavior: 1900-1940

INVESTIGATOR	LESION	BEHAVIOR
Anton 1903,	Agenesis	Mental retardation
Batten, 1905	Agenesis	Mental retardation
Vogt, Astwazaturow, 1912	Hypoplasia	Mental retardation
Beyerman, 1917	“Congenital atrophy”	Mental retardation
Schob, 1921	“Congenital atrophy”	Mental retardation
Curschmann, 1922	Hereditary ataxia	Mental impairment
Koster, 1926	Hypoplasia	Mental retardation
Walter and Roese, 1926	Hereditary ataxia	Mental impairment
Santha, 1930	“Congenital atrophy”	Mental retardation
Scherer, 1933	“Congenital atrophy”	Mental retardation
Akelaitis, 1938	Cortical atrophy	Dementia (late stages)
Rubinstein, Freeman, 1940	Agenesis	Mild mental retardation, poor memory, delusions

Clinical Reports - Cerebellum and Behavior: 1950-1975

INVESTIGATOR	LESION	BEHAVIOR
Knoepfel, Macken, 1947	Degeneration	Psychosis
Jervis, 1950	“Congenital atrophy”	Mental retardation
Schut, 1950	OPCA	Intellectual difficulty (late)
Mutrux et al, 1953	“Congenital atrophy”	Mental retardation
Gillespie, 1965	Degeneration, aniridia	“Oligophrenia”
Carpenter, Schumacher 1966	Infantile atrophy	Mental retardation
Aguilar et al, 1968	Ataxia-telangiectasia	Mental deficiency (late)
Joubert et al, 1969	Vermal agenesis	Mental retardation
Keddie, 1969	Cortical atrophy	Paranoid psychosis
Hoffman et al, 1971	Degeneration	Impaired intellect (late)
Landis et al, 1974	OPCA	Mild cognitive impairment



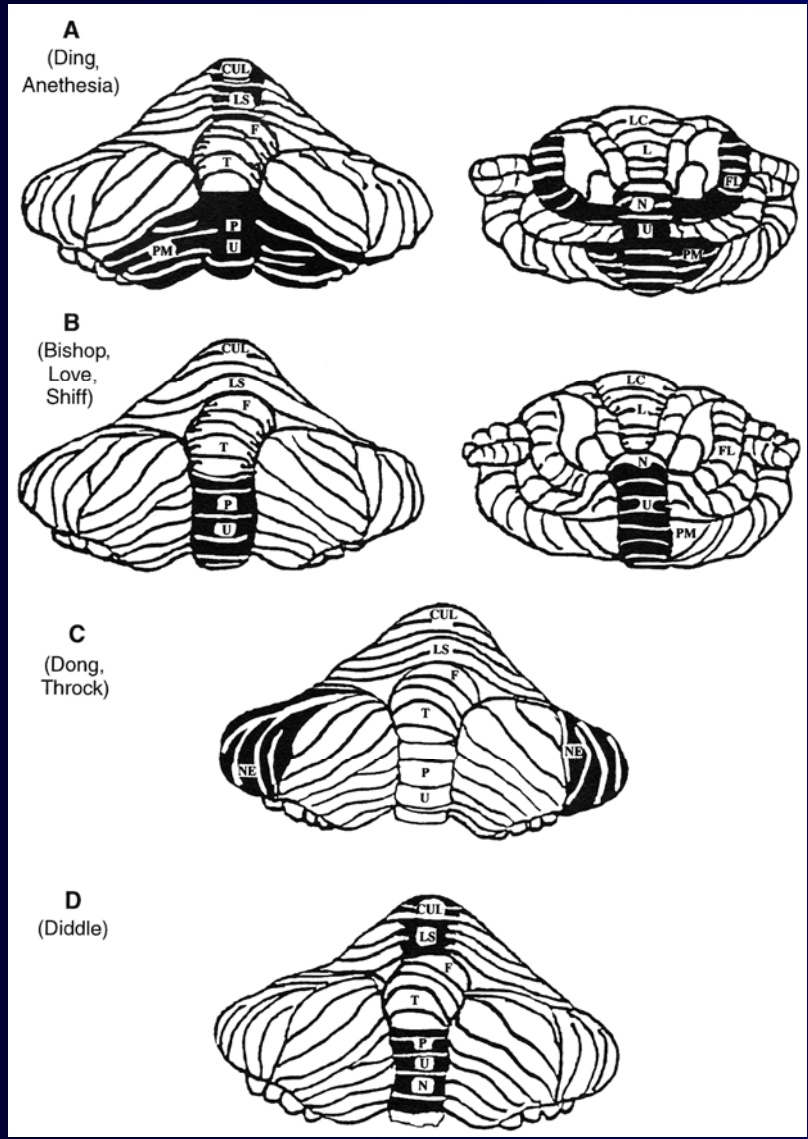
Snider, 1950; Woolsey, 1950

If cerebellar action is exerted on cerebral centers either to potentiate or to dampen activity…then the cerebellum stands out as **'the great modulator of neurologic function'** and new horizons of cerebellar action are introduced into neurology and psychiatry.

Ray S. Snider

Arch Neurol. Psych. **1950**;64:196-219.

Amelioration of aggression in monkeys by cerebellar lesions.



Berman et al., 1978.

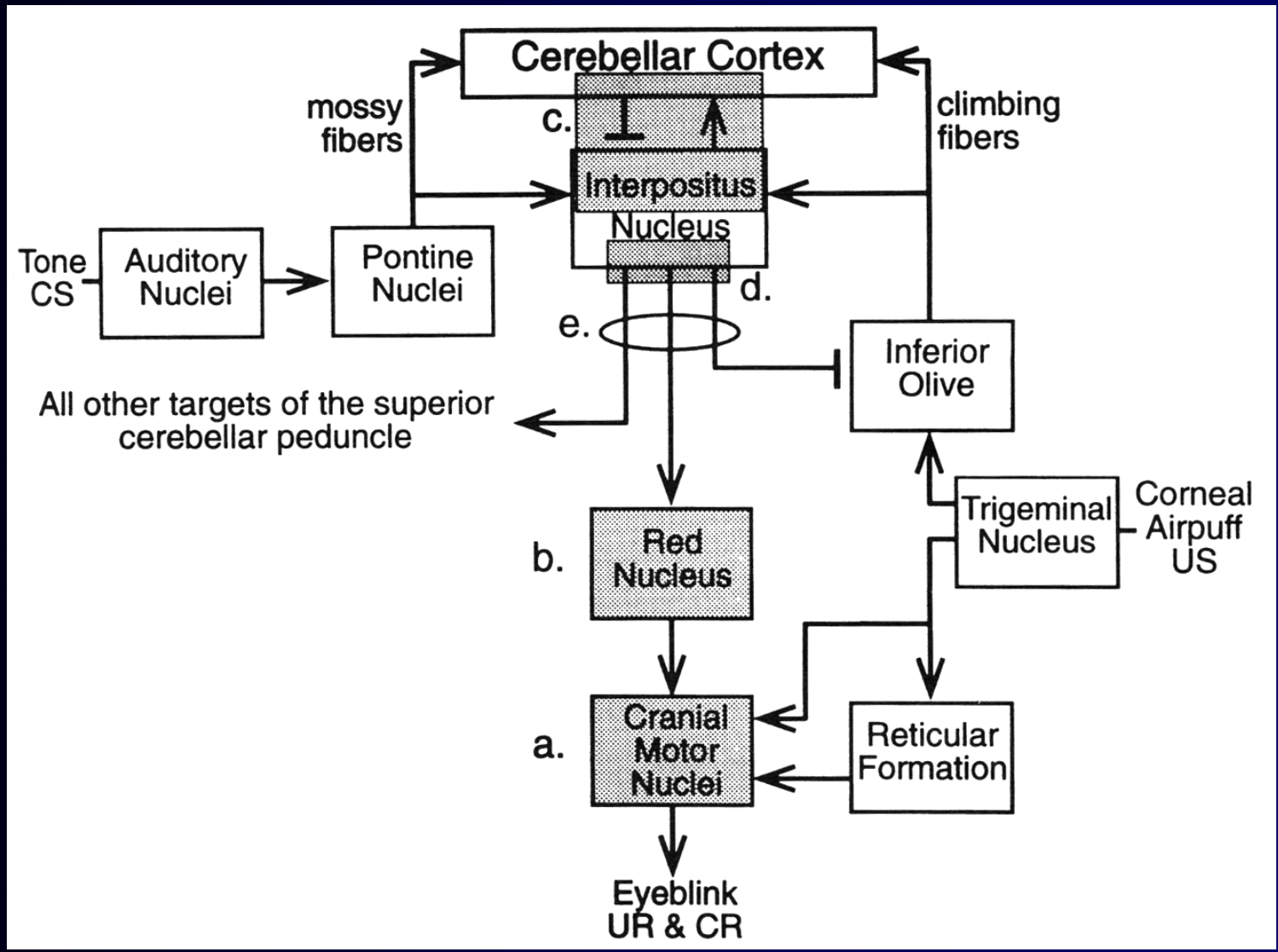
Demonstration of cerebellar – limbic physiological interactions.

The midline cerebellum (vermis and fastigial nucleus) is an integral part of the neural network for emotional expression and asserts a unique modulating effect on brain sites where physiological activity correlates with pathological behavior and epilepsy.

Robert G. Heath et al.

J. Nerv. Ment. Dis. **1979**;167:585-592

Essential brain circuitry involved in eyeblink conditioning.



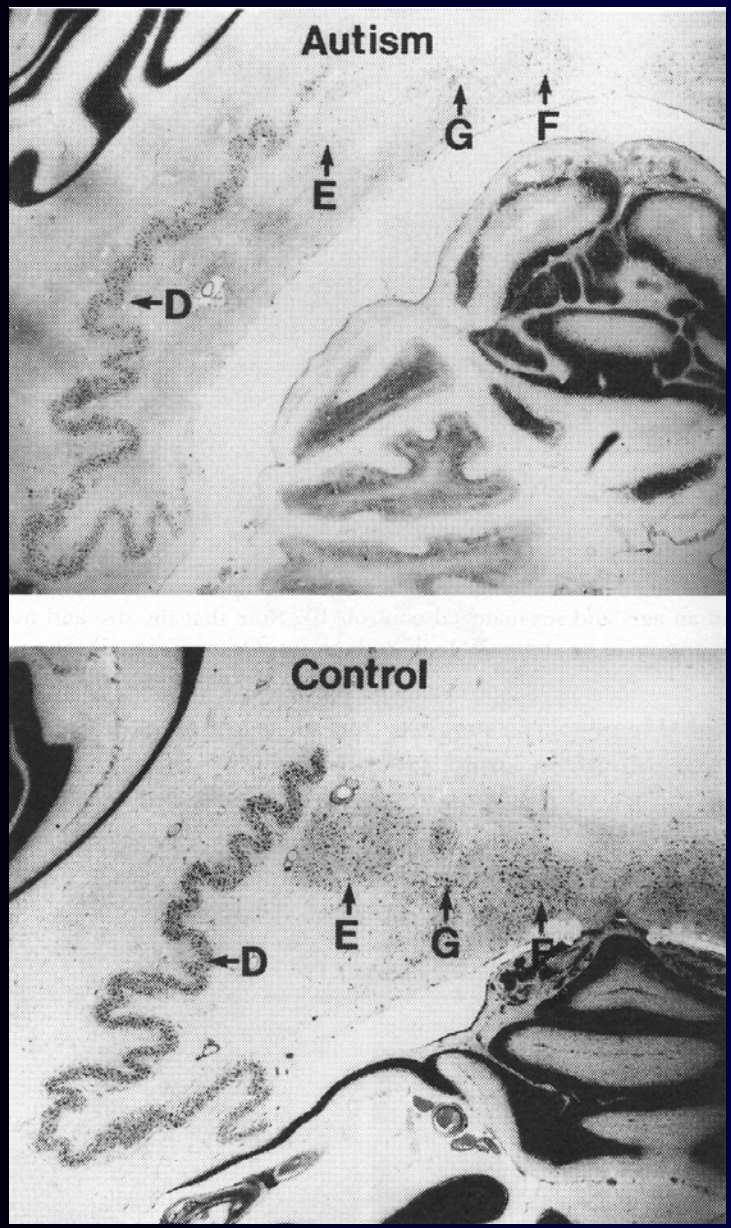
Thompson et al., 1997

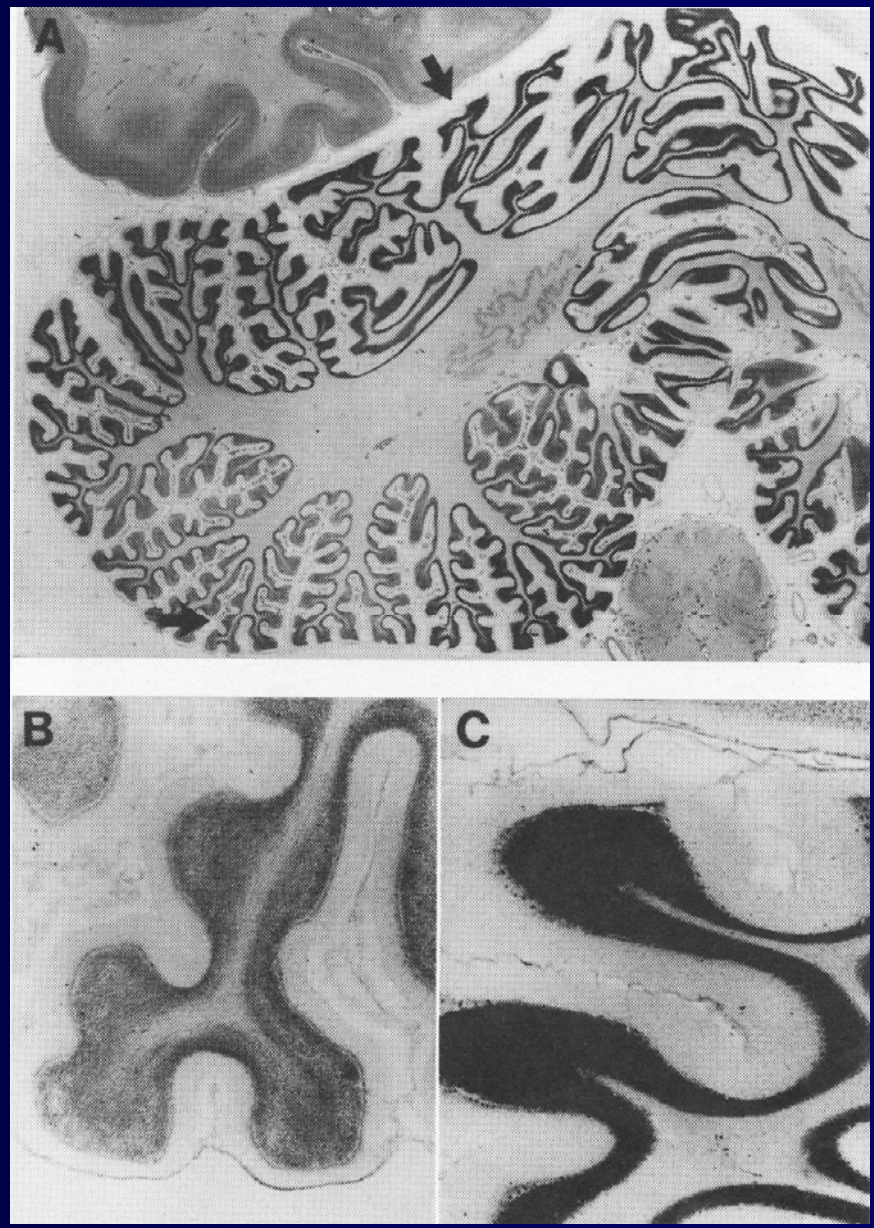
Something important seems to happen to convulsive phenomena, to a variety of vegetative functions, to emotional behavior and perhaps even to the highest level of intellectual function when a cerebellar influence is introduced into the nervous system. Whatever it does to modify the activity of other parts of the brain, it probably does the same thing in all its possible varied roles. Its uniformity of structure throughout vertebrates and within its various subdivisions in higher mammals makes this most likely.

Robert S. Dow

Mt. Sinai J. Med 1974;41:103-119.

Cerebellar histopathology in Autism





Bauman and Kemper, 1997

5-days following cerebellar midline ganglioglioma resection

A Journey Through Emotions

The times used to be so different.
Although I know there were so
Many good times, I can only seem
to remember the bad ones....

Why is that the case?

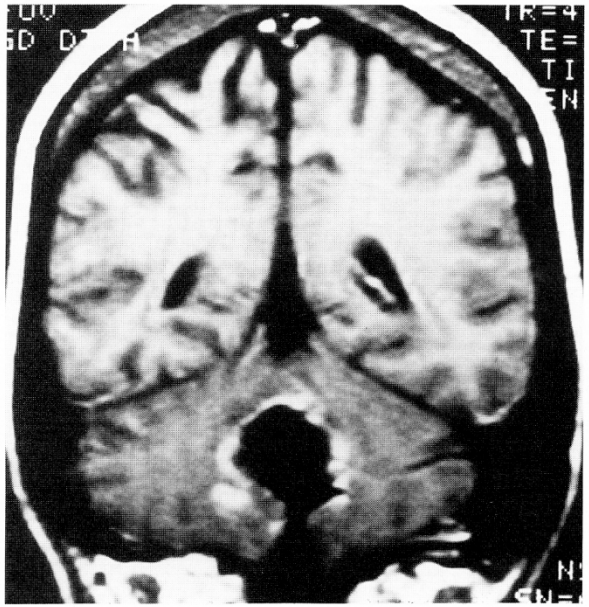
Years ago, the tears rolled down
My cheeks as if if were a once in
A lifetime journey to the edge of
My face. Now, if is as though that
Journey has turned into a routine.
Performed weekly.

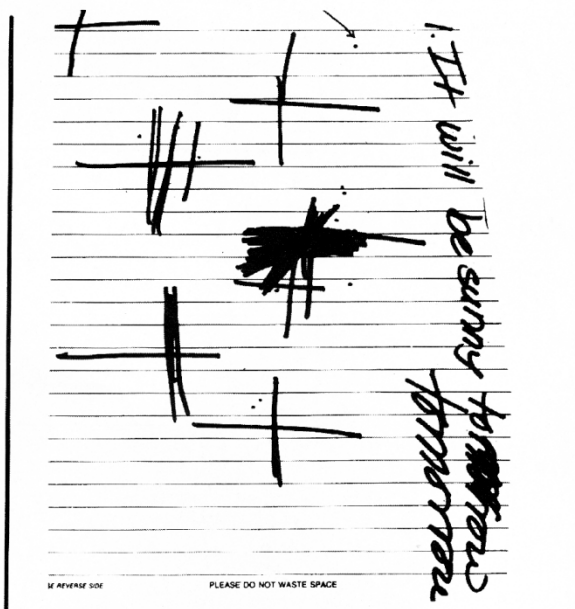
How can ones life be ever changing
At each moment if is looked upon?
And who can say that tomorrow's trauma
Will not be better or worse than yesterday's?

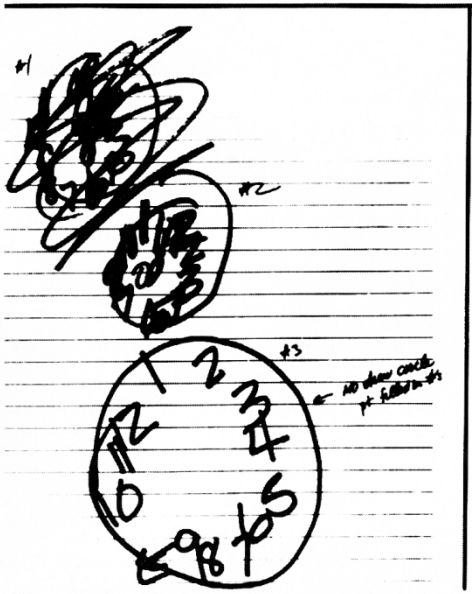
I wonder who controls these emotions
felt day after day, year from year.

Is if God? Me? Or some being unknown
to these eyes I call my own? I wonder....

23-yr. woman post gangioglioma resection







I am a young girl
who is twenty ~~and~~ three.

the the young girl
went into her closet.

Schmahmann and Sherman, 1998

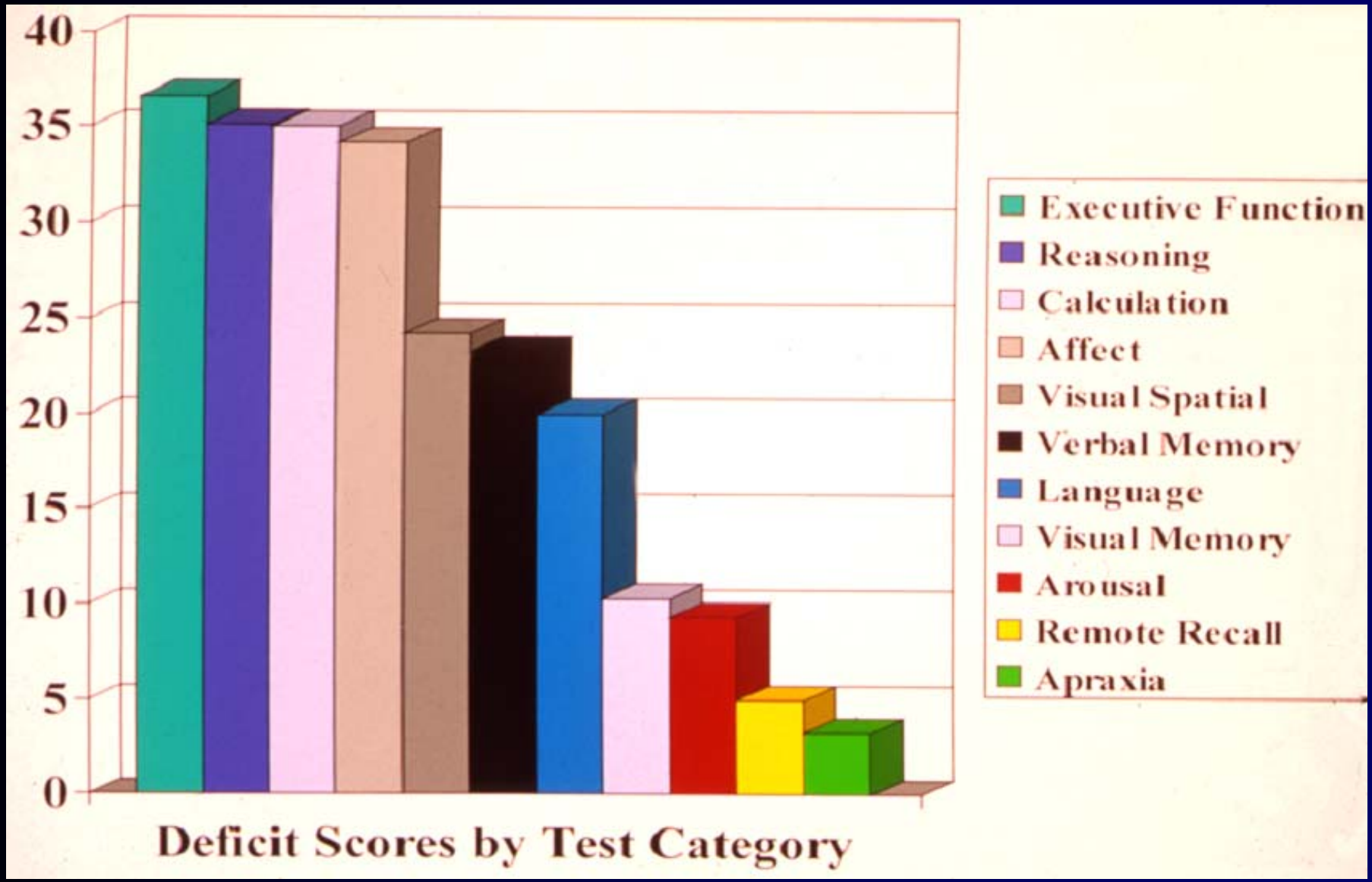
Table 1 *Patient characteristics*

Patient	Age (years)	Education (years)	Diagnosis	Interval: onset–examination
1	23	16	Midline/paravermis resection	1 week
2	44	12	Bilateral PICA stroke	1 month
3	57	20	Bilateral PICA stroke	2 weeks
4	32	16	Right PICA stroke	2 weeks
5	62	18	Right PICA stroke	2 weeks
6	74	12	Right PICA stroke	2 weeks
7	56	12	Right PICA (medial) stroke	1 month
8	58	18	Right PICA (branch) stroke	2 years
9	67	12	Left PICA stroke	1 week
10	66	9	Left PICA stroke	2 weeks
11	58	12	Left PICA stroke	2 weeks
12	50	16	Right AICA stroke	1 week
13	58	12	Left SCA stroke	2 weeks
14	36	12	Right SCA stroke	1 week
15	22	16	Postinfectious cerebellitis	1 month
16	12	Grade 6	Postinfectious cerebellitis	1 month
17	42	12	Postinfectious cerebellitis	3 months
18	24	12	Cerebellar cortical atrophy	6 years
19	31	16	Cerebellar cortical atrophy	4 years
20	56	12	Cerebellar cortical atrophy	5 years

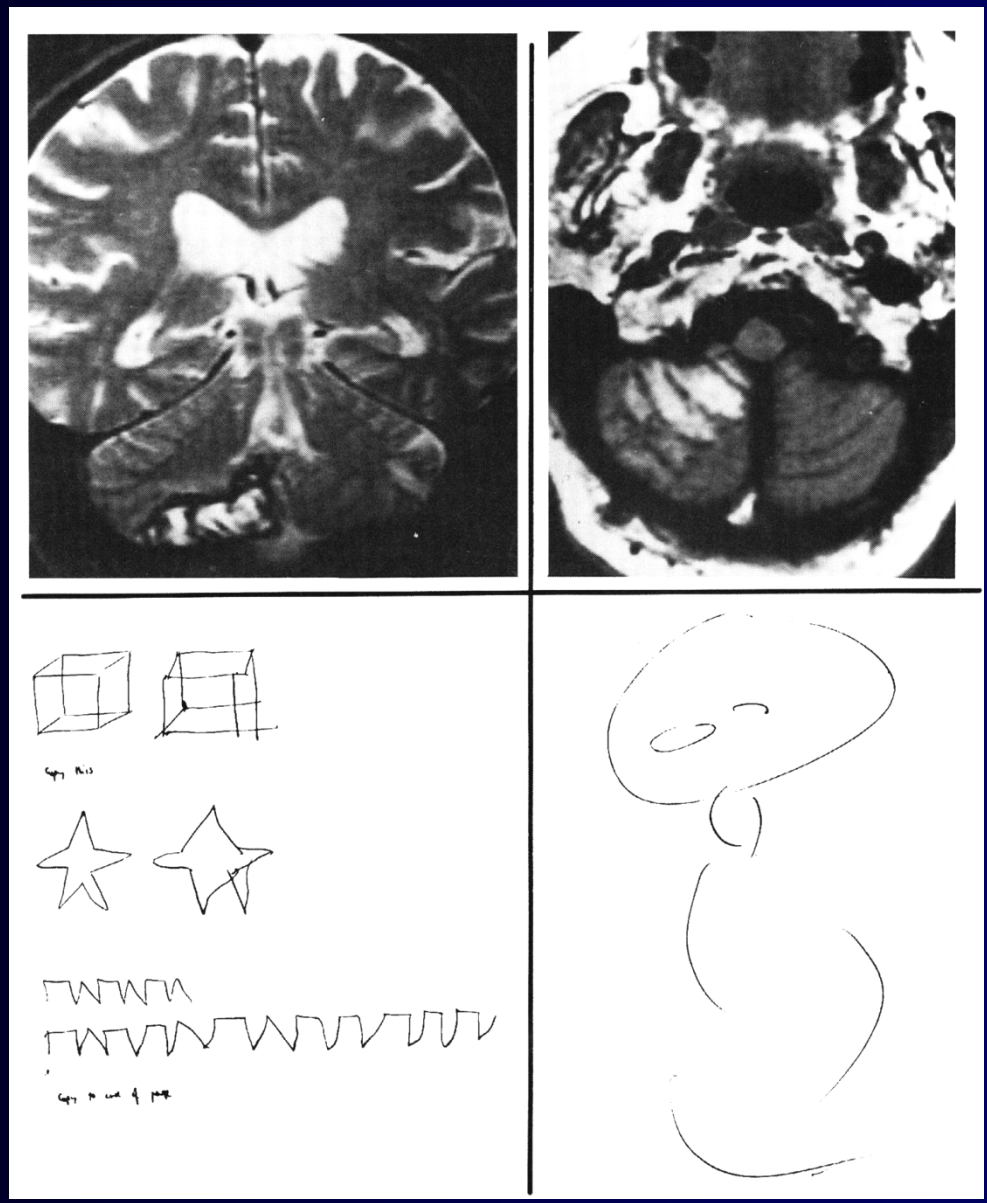
AICA = anterior inferior cerebellar artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery.

Schmahmann and Sherman, 1998

Clinical impairments in patients with cerebellar lesions

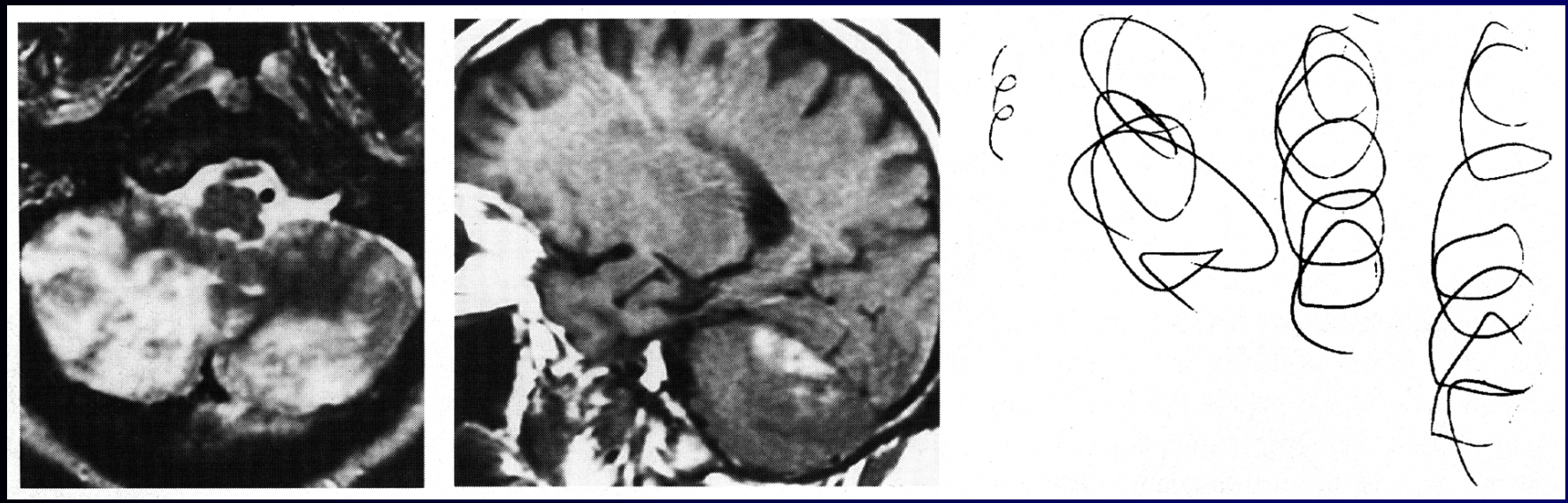


62.-yr man with R-PICA infarction.

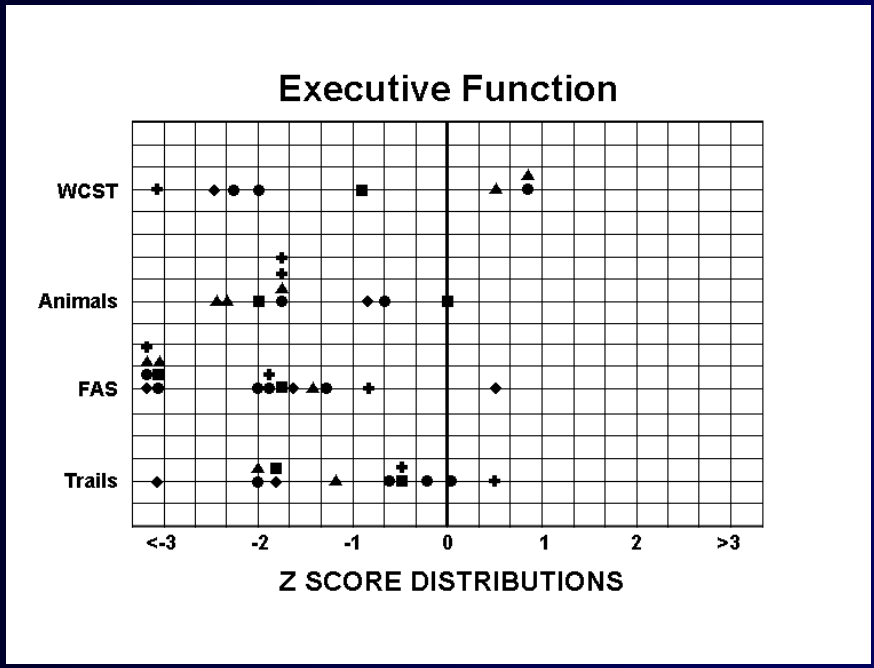


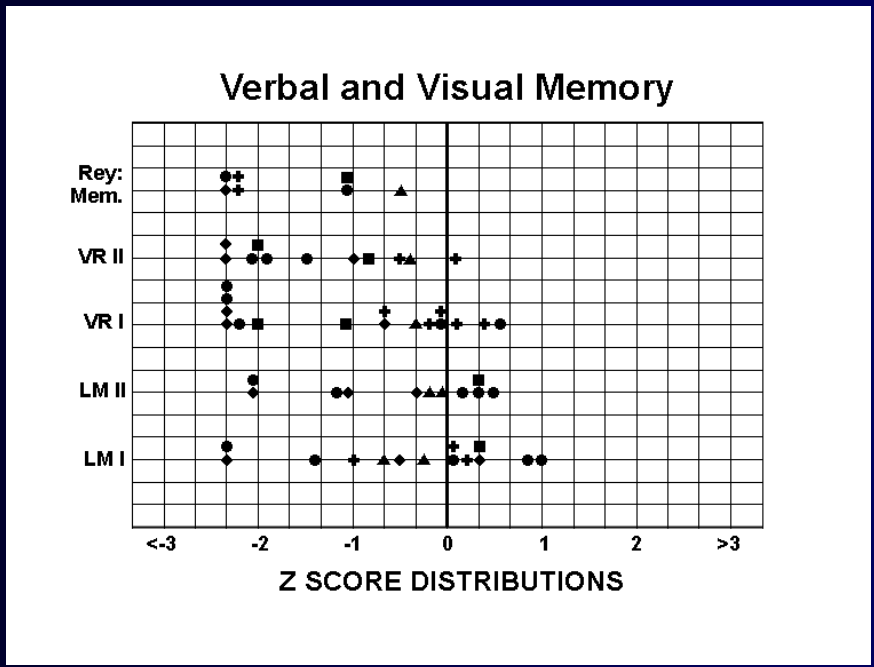
Schmahmann and Sherman, 1998

57-yr man with bilateral PICA and right SCA infarction.
Perseverative copying of a 2-loop diagram

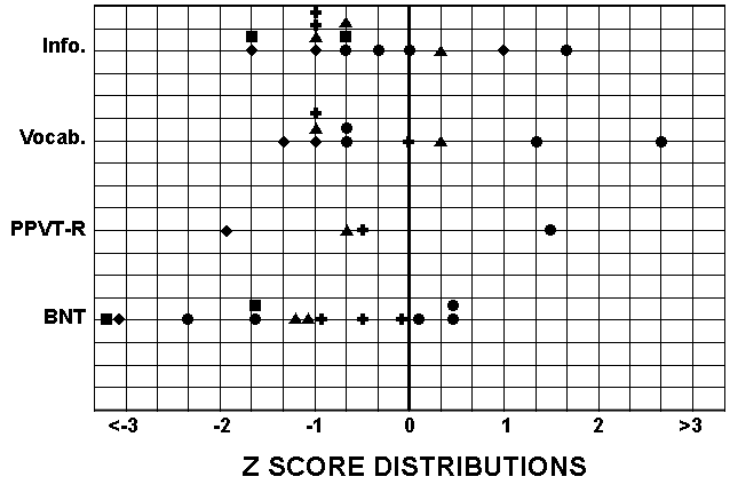


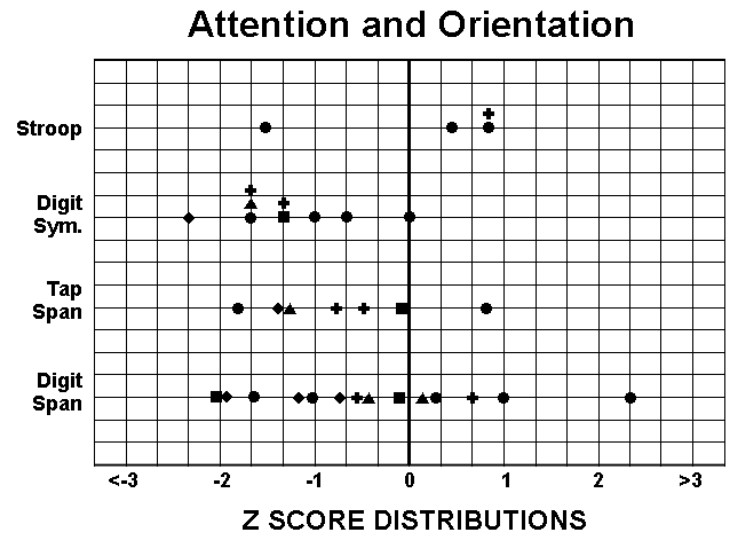
Schmahmann and Sherman, 1998



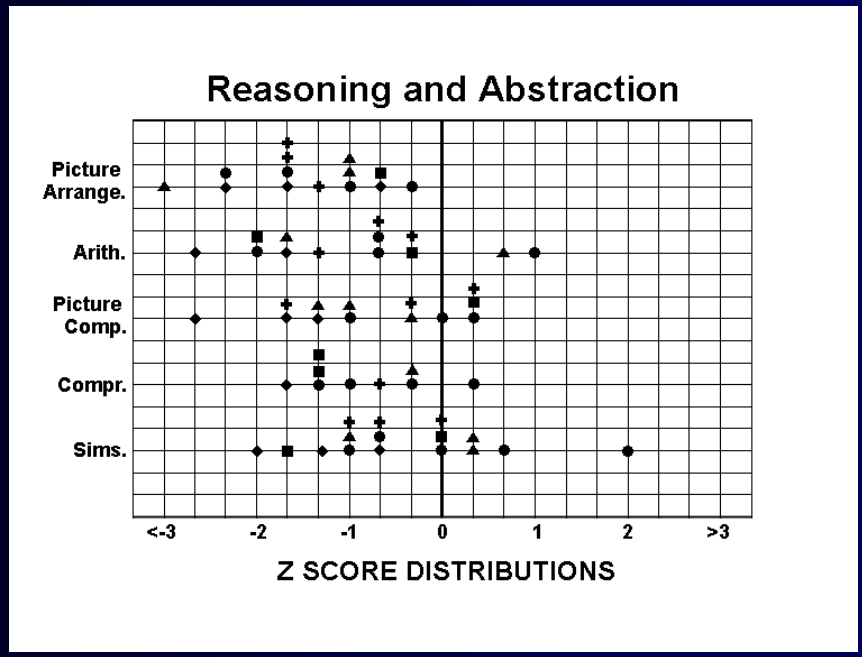


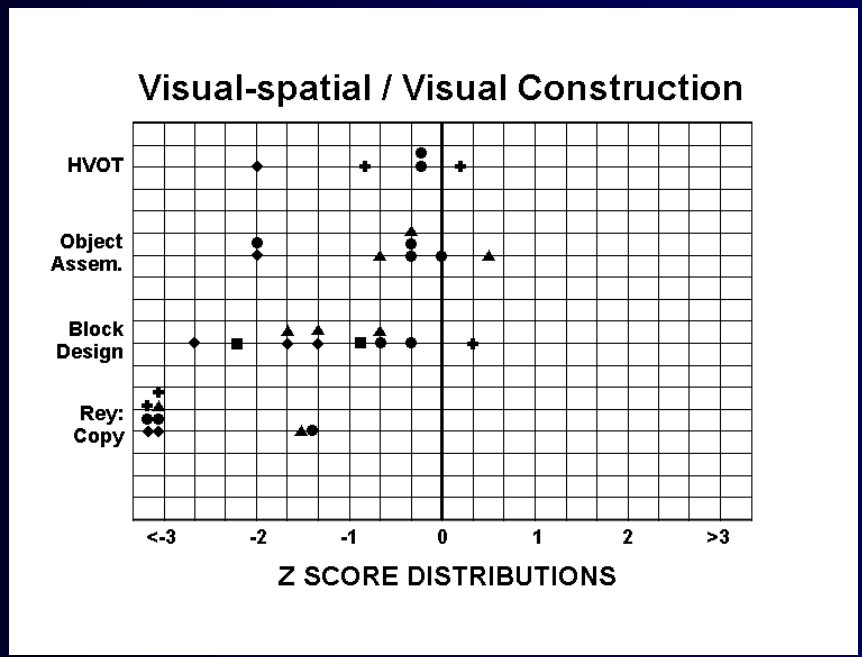
Schmahmann and Sherman. Brain, 1998.





Schmahmann and Sherman. Brain, 1998.



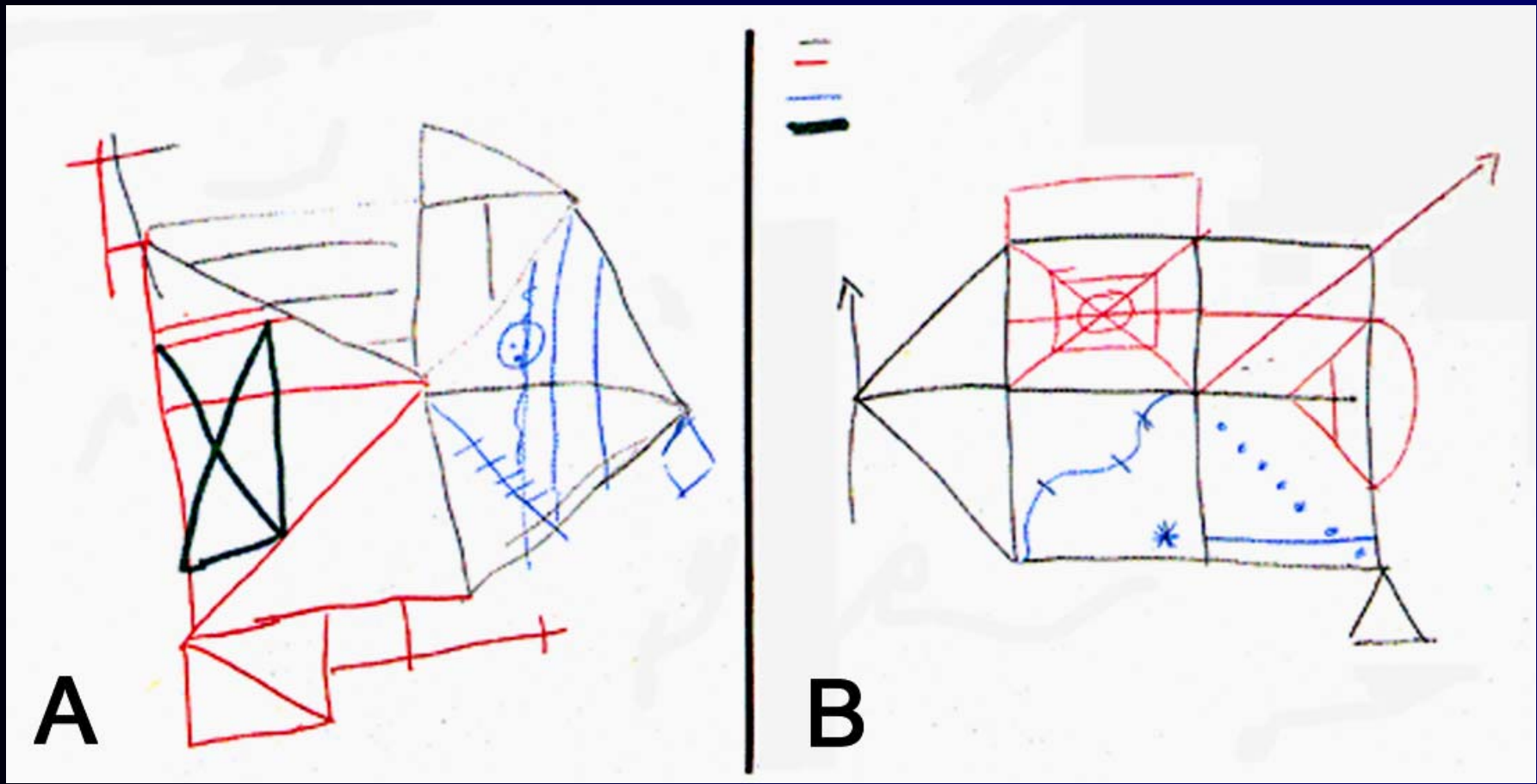


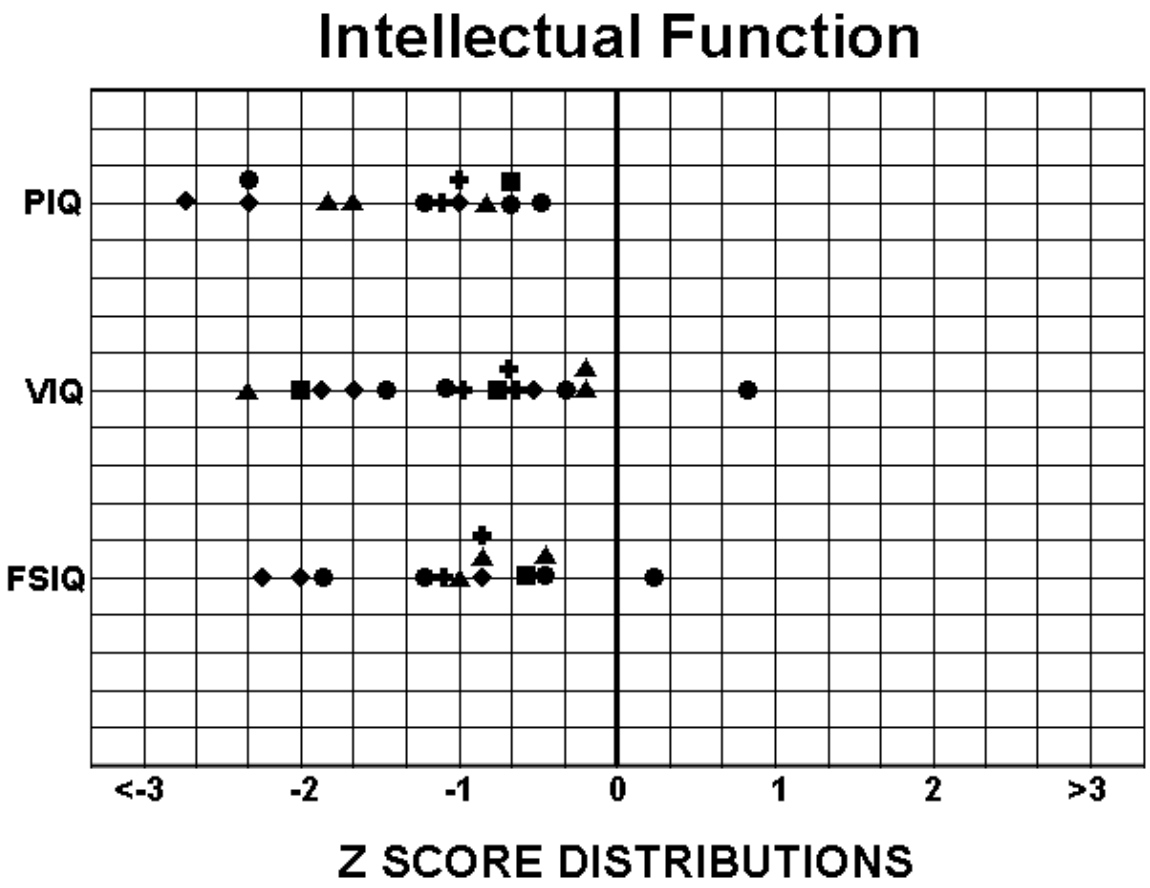
Schmahmann and Sherman.
Brain, 1998.

Post-infectious (EBV) cerebellitis

Rey copy during illness

Taylor copy after recovery

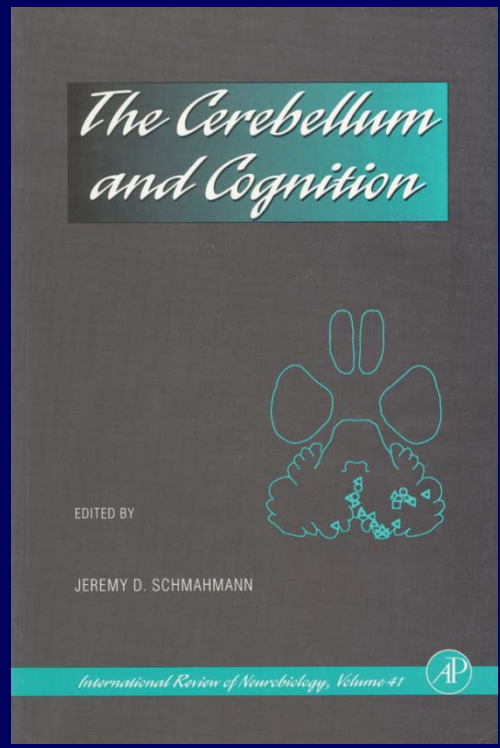




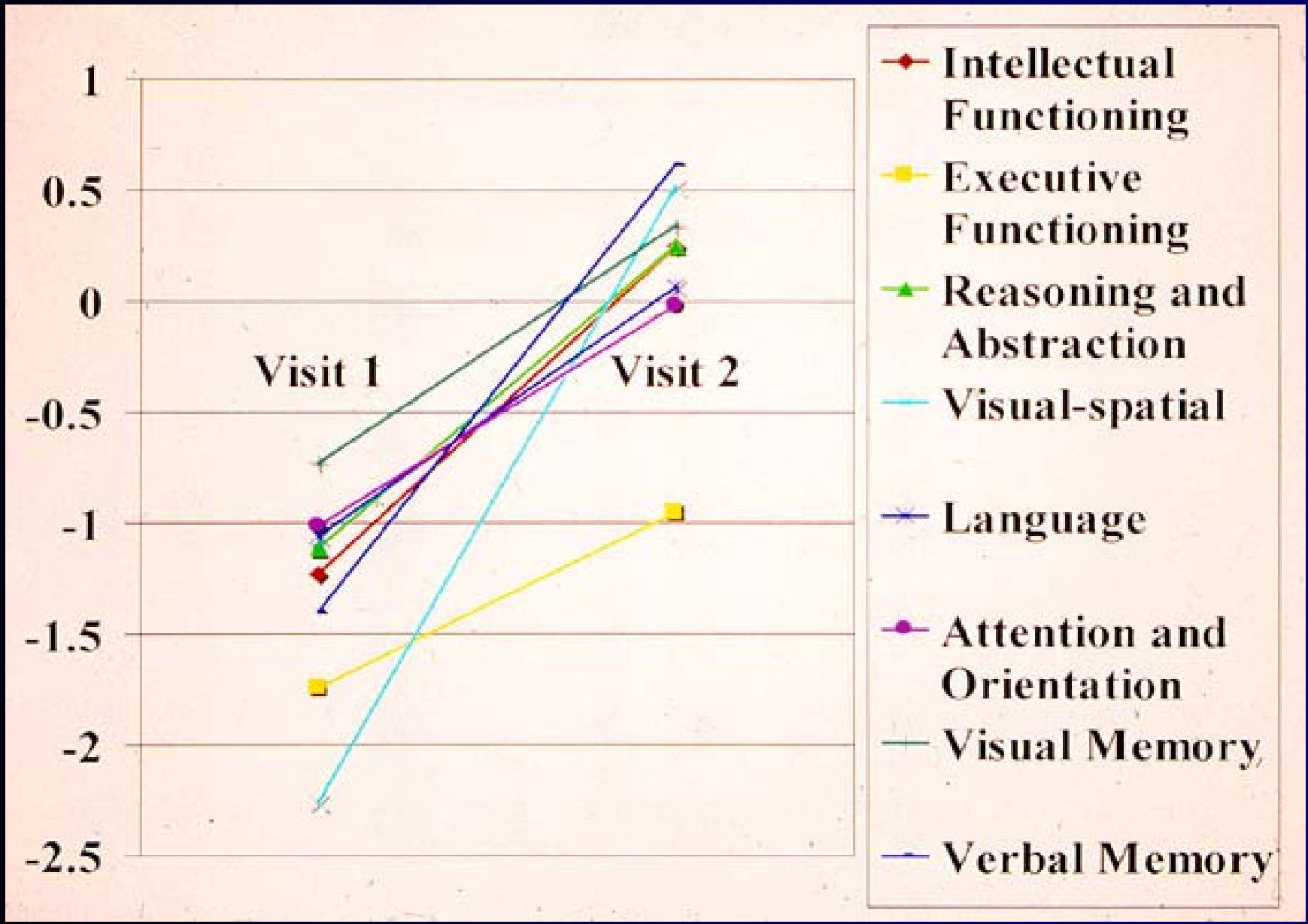
Schmahmann and Sherman.
Brain, 1998.

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

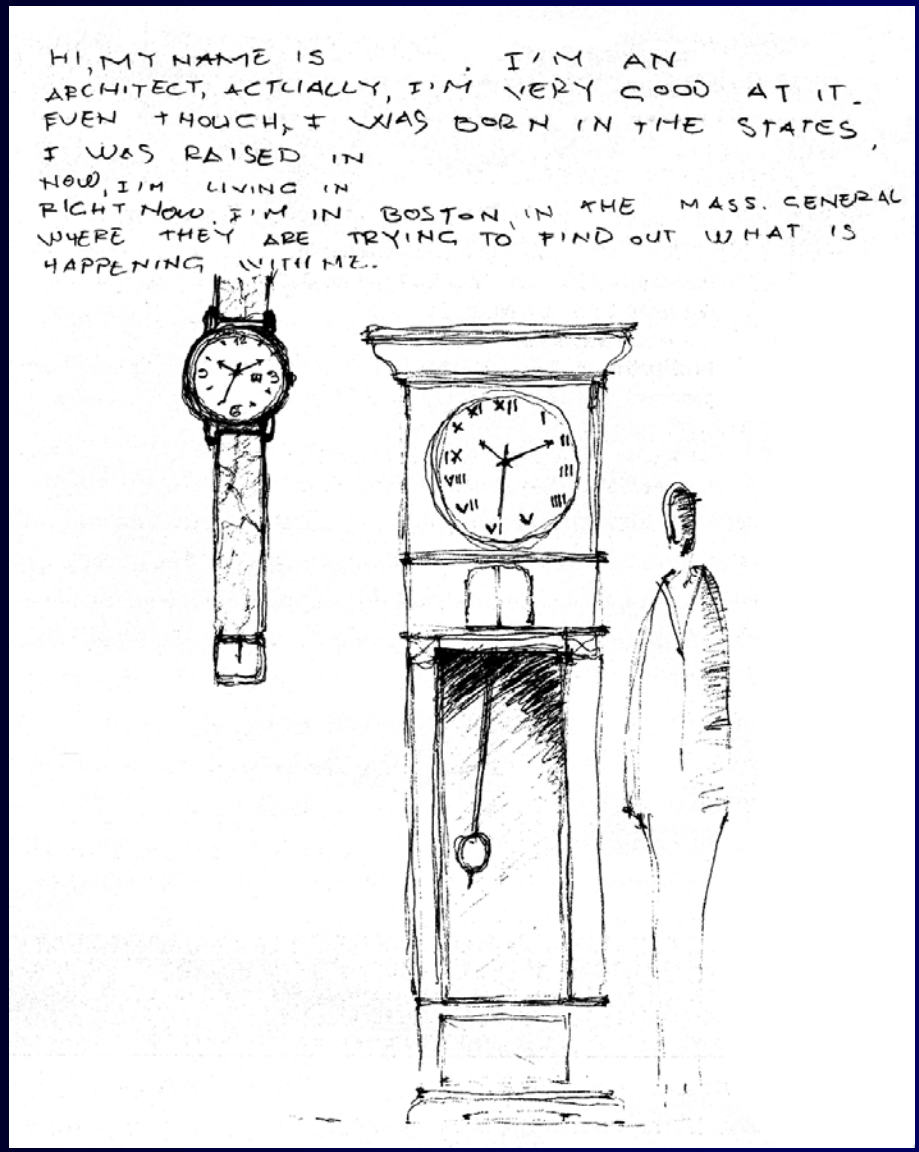


Schmahmann and Sherman, 1998



Schmahmann and Sherman. Brain, 1998.

Cognitive overshoot?



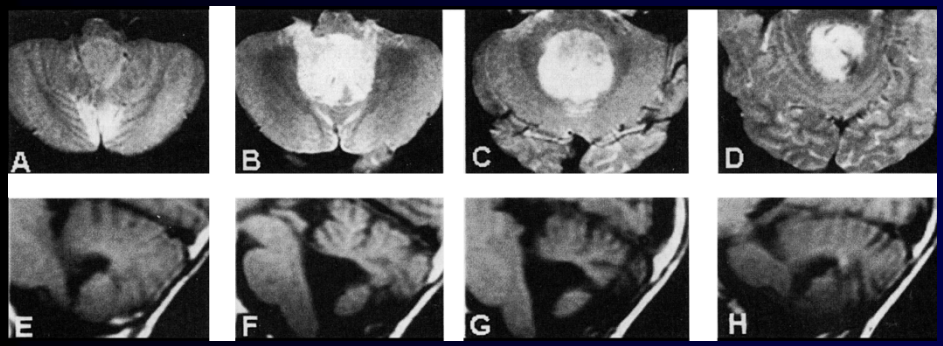
Schmahmann, 1998

CCAS in children

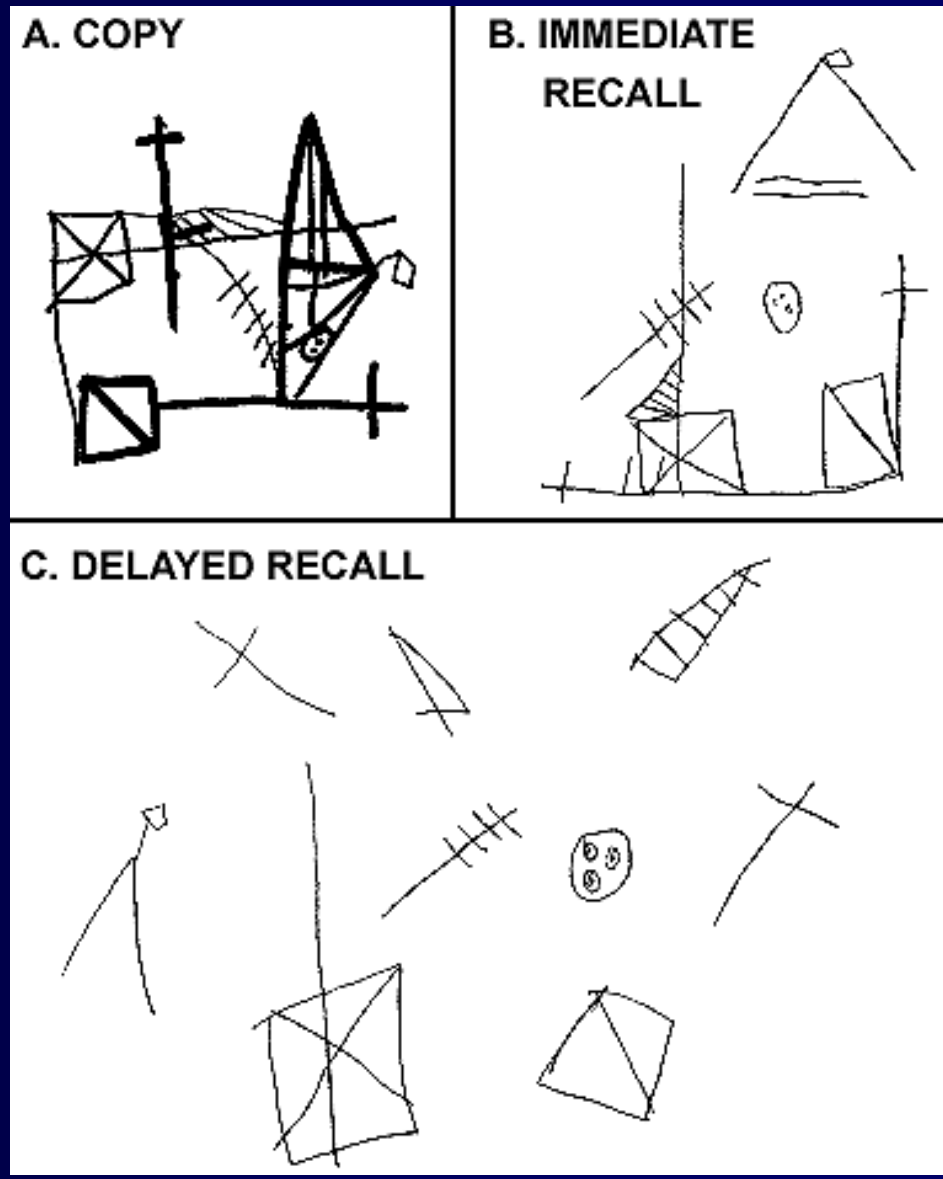
- 19 children (3-3 to 14-10)
- Surgical excision of tumors
- 11 medulloblastoma, 7 astrocytoma, 1 ependymoma
- Evaluated 1 to 22 months post-operatively
- Behavioral deficits more apparent in older children

Levisohn, Cronin-Golomb, Schmahmann, Brain, 2000

CCAS following tumor resection in children



5-yr-old boy. Medulloblastoma



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

CCAS 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**

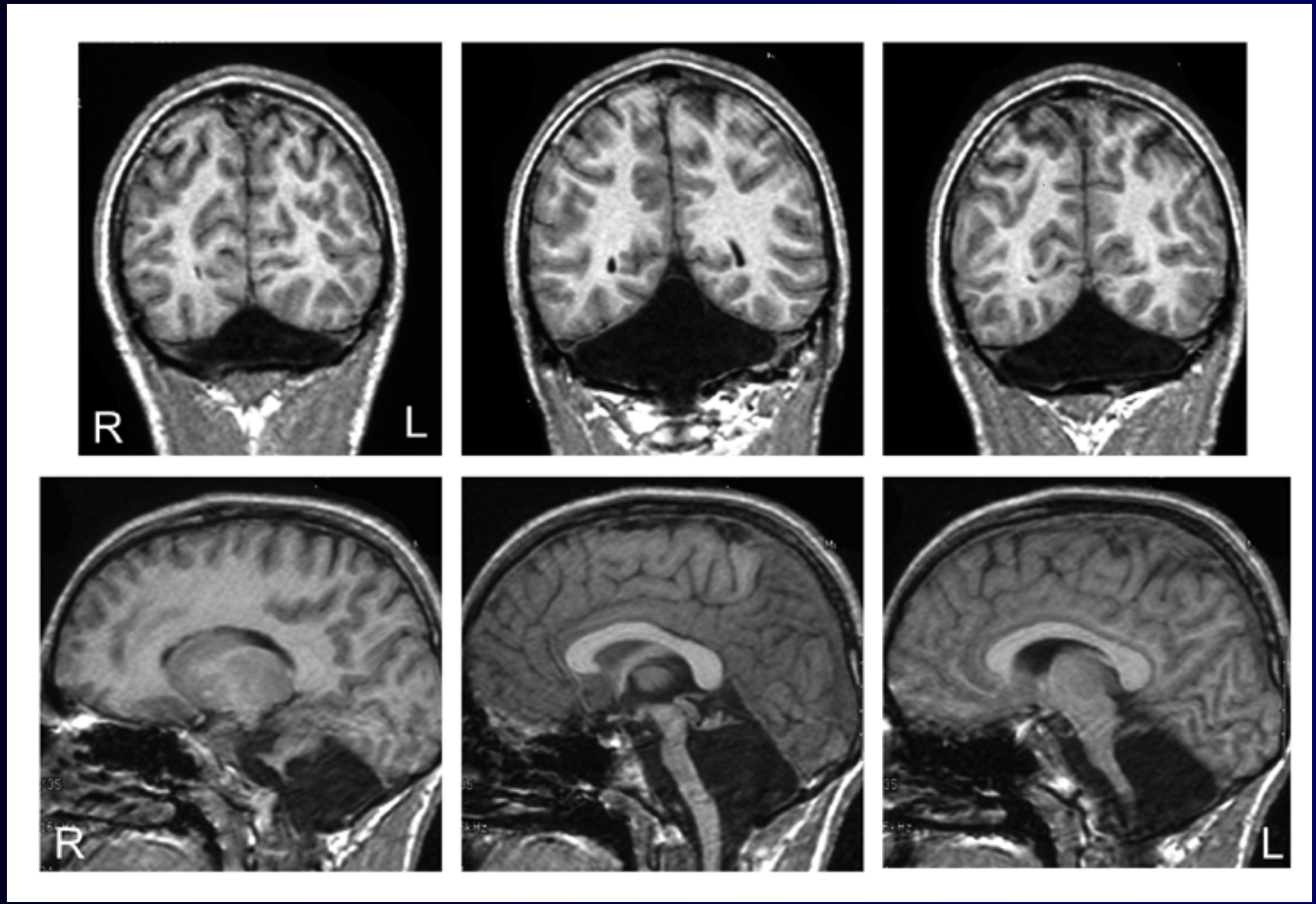
  Impaired for stories; better with multiple-choice

- **Regulation of affect (vermis lesions)**

  Irritable, impulsive, disinhibited, labile affect

Levisohn, Cronin-Golomb, Schmahmann
Brain 2000;123 :1041-50

Cerebellar agenesis



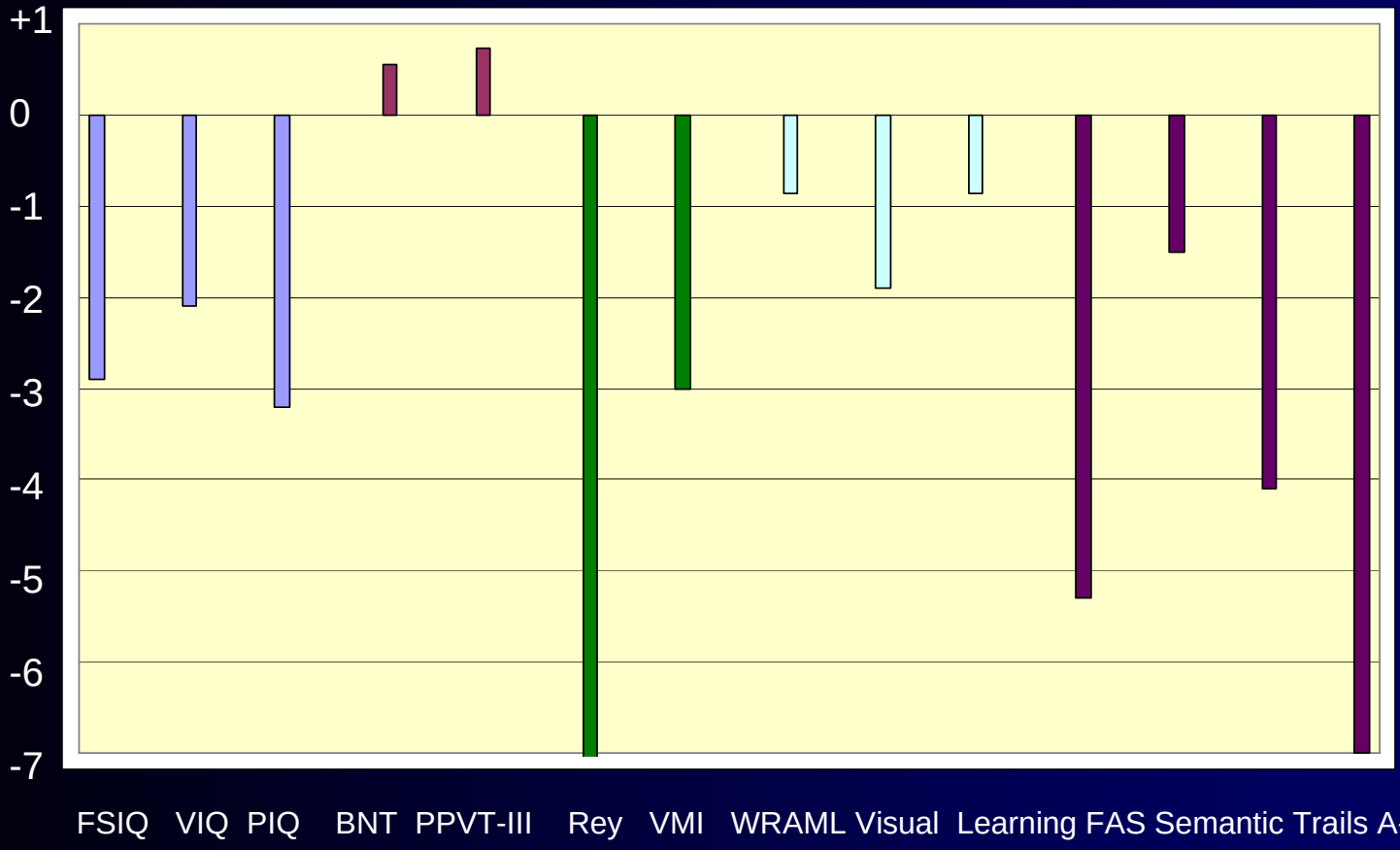
Sensorimotor impairments

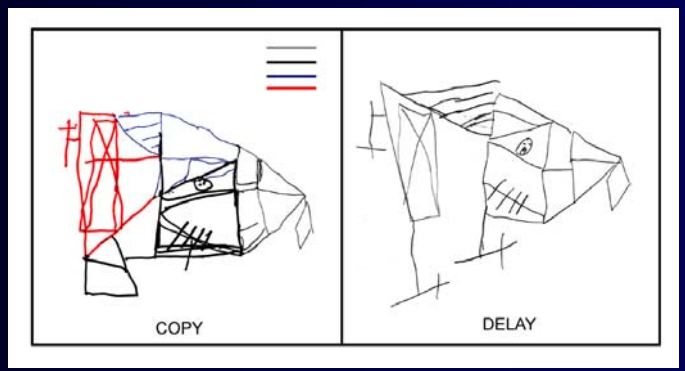
Abnormal eye movements - impaired saccades, pursuit, VORC

Oral motor apraxia

Gross and fine motor delay; Mild clumsiness and ataxia

Cerebellar agenesis





Rey Figure

Cerebellar Agenesis
Behavioral observations (n=6)

- Executive impairments

  Perseveration, disinhibition, impaired abstract reasoning, working memory and verbal fluency
- Spatial cognition

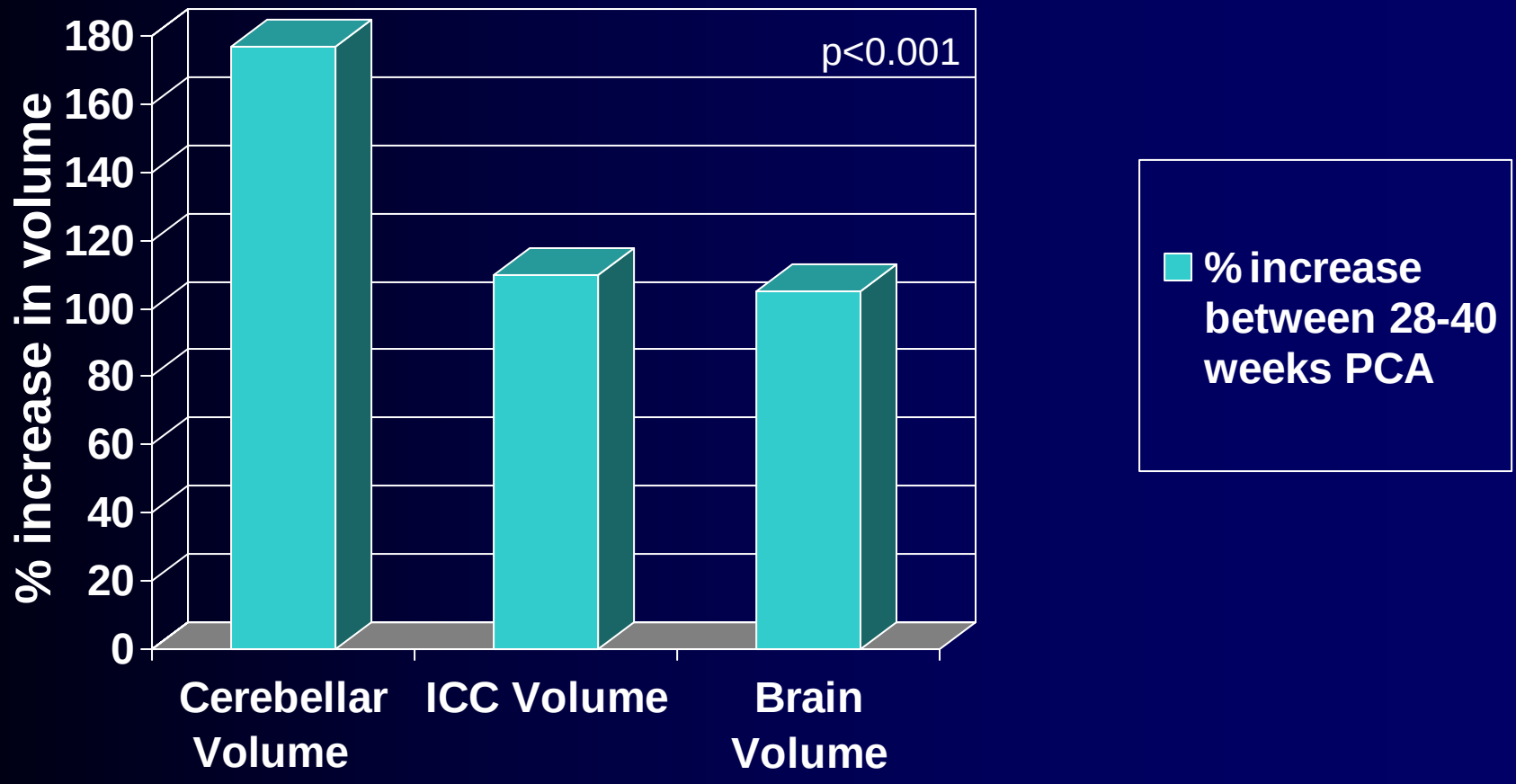
  Poor perceptual organization, copying and recall
- Language

  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

Cerebellar growth in 3rd Trimester



Limperopoulos et al, Pediatrics 2005

Premature Birth
(Before 33 weeks gestation)

- Reduced cerebellar volume compared to controls
- Associated with deficits in:

  Executive and visual-spatial function

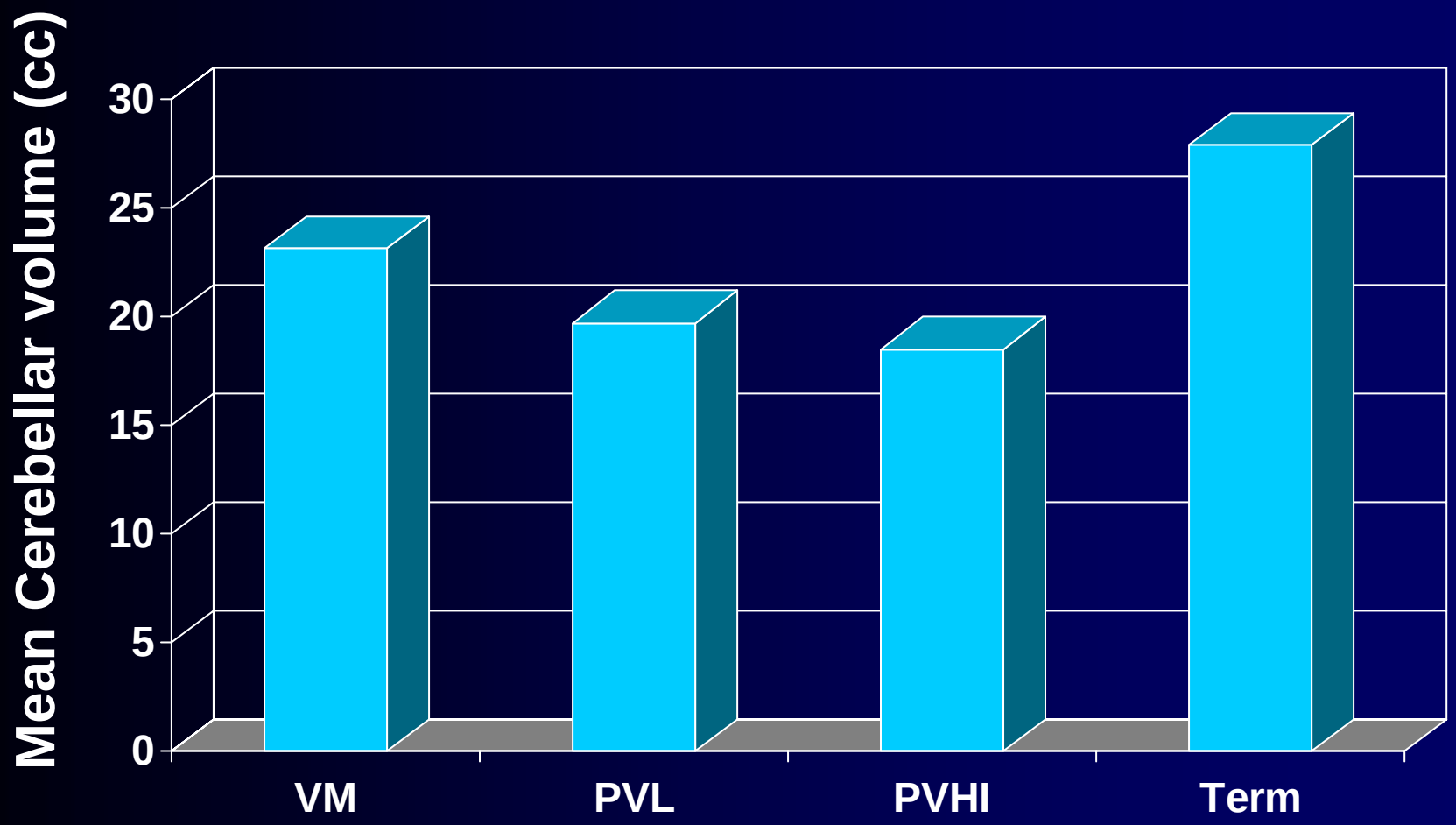
  Block design, object assembly subtests of WISC-R

  Language skills

  Schonnel reading age, Similarities subtest of WISC-R, Riddle interpretation, Reading – decoding and understanding subtests of K-ABC

Allin et al., Brain 2001; 124: 60-66.

Cerebral lesions with secondary cerebellar growth impairment



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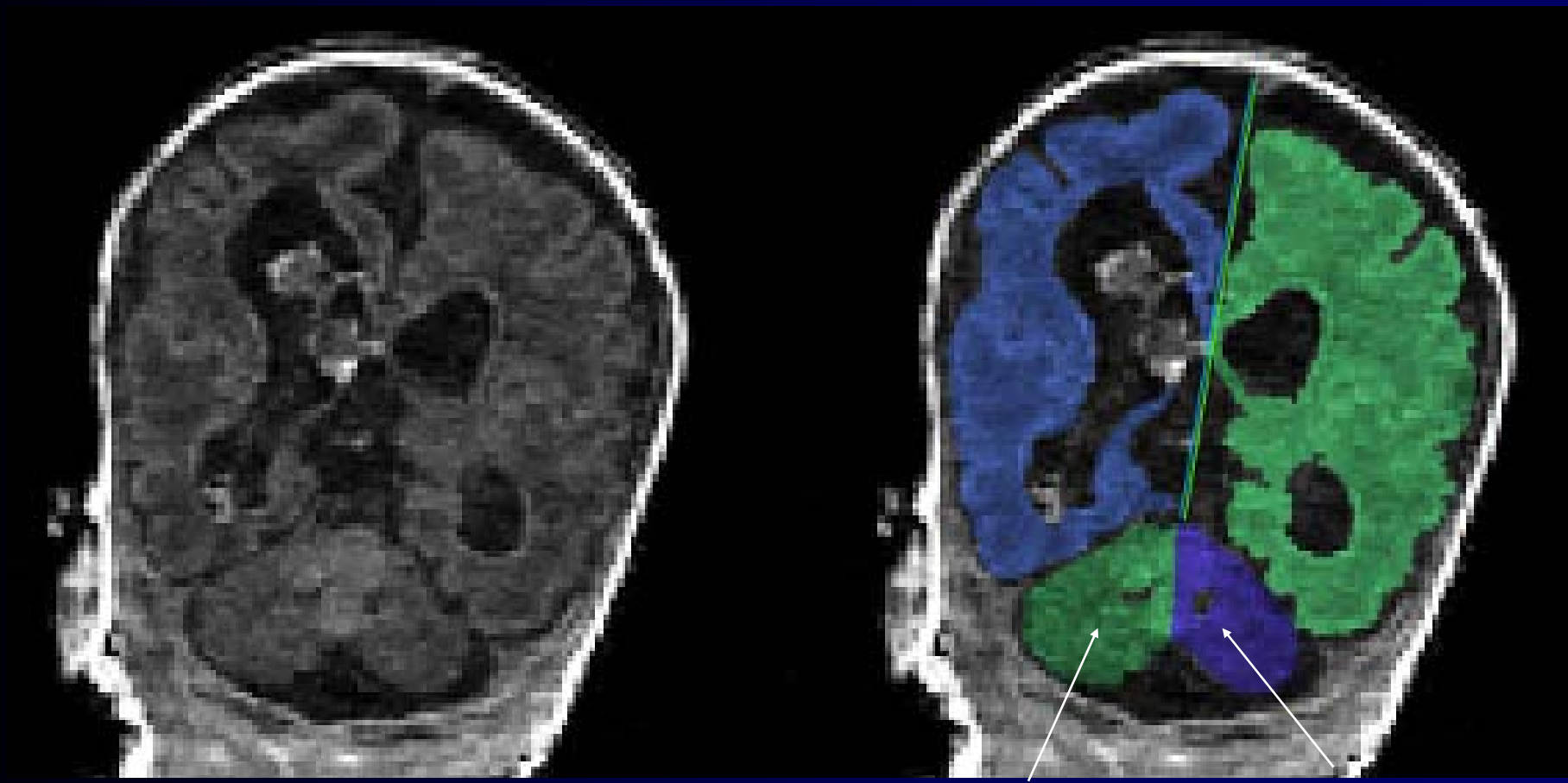
Limperopoulos et al, Pediatrics 2005

Transtentorial diaschisis



Limperopoulos et al, Pediatrics 2005

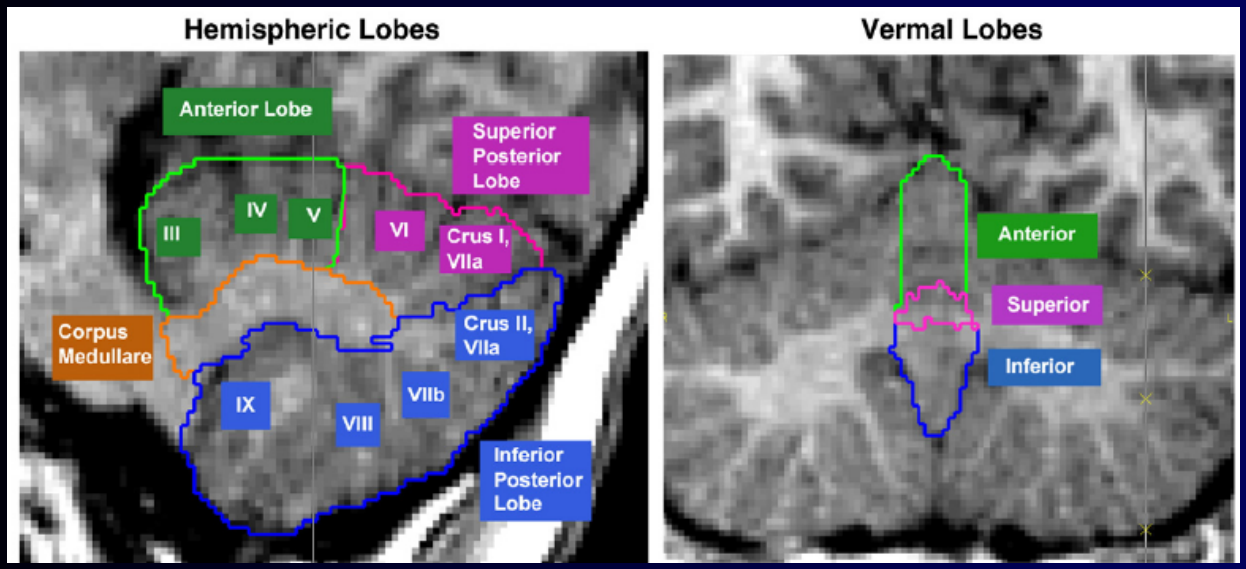
Cerebellar hemorrhage in preterm infants n = 35

NICU - Hemorrhage on ultrasound
Evaluation at 32.1 +/- 11.1 months

- Severe motor disability 48%
- Cognitive deficits 40%
- Language delay
  - expressive 42%
  - receptive 37%
- Autistic features 37%
- Behavioral problems 34%
- Vermis involvement – more severe global developmental, functional, social-behavioral deficits

Limperopoulos et al., Pediatrcis 2007; 120, 584-593

Cerebellar development during childhood and adolescence (n = 50)



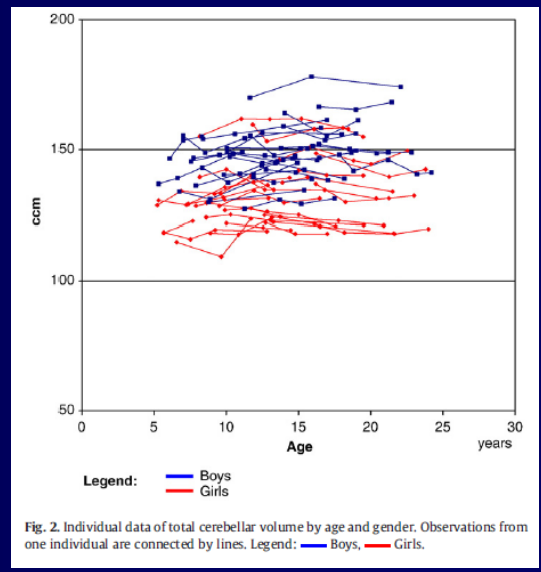
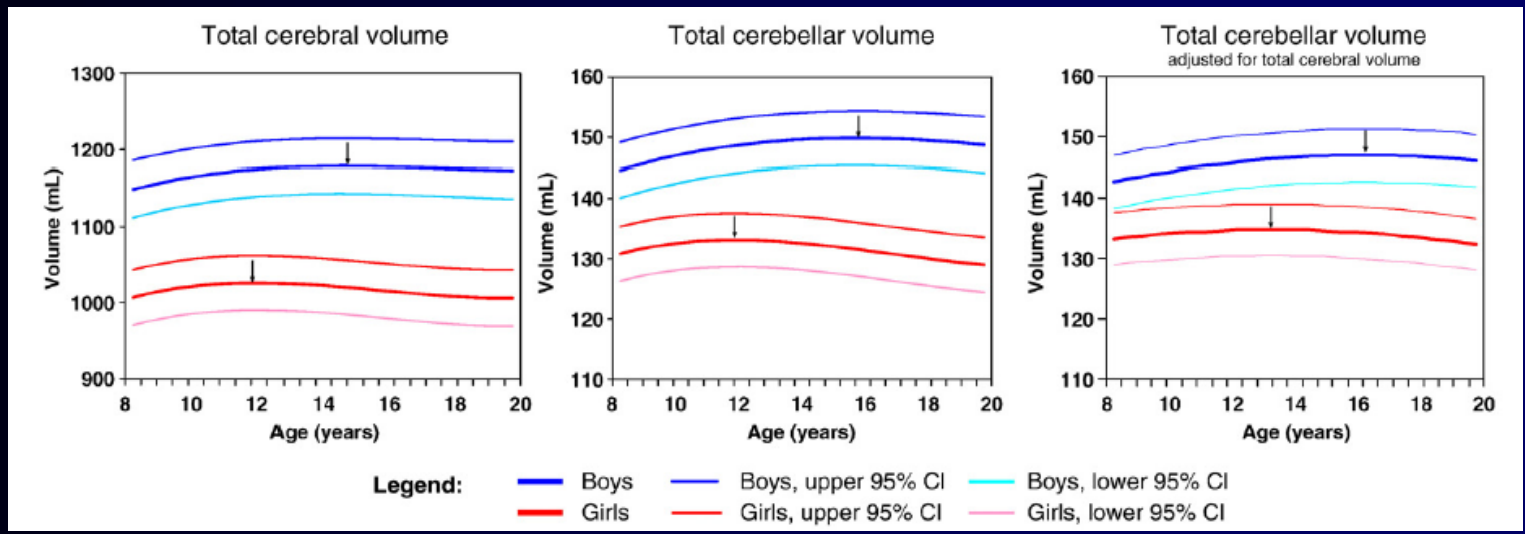


Fig. 2. Individual data of total cerebellar volume by age and gender. Observations from one individual are connected by lines. Legend: Boys, Girls.



Tiemeir, Lenroot, Greenstein, Tran, Pierson, Giedd. NeuroImage 2010; 49: 63-70

Supporting studies - adults

Stroke

- Malm et al. Cognitive impairment in young adults with infratentorial infarcts. Neurology. 1998;51:433-40.
- Neau J et al. Neuropsychological disturbances in cerebellar infarcts. Acta Neurol Scand. 2000;102:363-70.
- Paulus KS et al. Pure post-stroke cerebellar cognitive affective syndrome: a case report. Neurol Sci. 2004;25:220-4.
- Exner C et al. Cerebellar lesions in the PICA but not SCA territory impair cognition. Neurology. 2004;63(11):2132-5.

Cerebellar degenerative disease

- Leroi et al. Psychopathology in patients with degenerative cerebellar diseases: a comparison to Huntington's disease. Am J Psychiatry. 2002;159:1306-14.
- Abel CG et al. Neuropsychological study of 12 patients with pure degenerative cerebellar disease. Rev Neurol. 2005;40:465-72.

Superficial siderosis

- van Harskamp NJ et al. Cognitive and social impairments in patients with superficial siderosis. Brain. 2005;128(Pt 5):1082-92.

Cerebellar Psychopathology

Degenerative Cerebellar disease (31 patients)

Non-cognitive psychiatric disorders	77%
Mood disorders	68%
Personality change	26%
DSM-IV criteria for dementia	19%

Leroi et al., Am. J. Psychiatry 2002; 159:1306-14

Supporting studies - children

Tumors

- Riva D, Giorgi C. The cerebellum contributes to higher functions during development. Evidence from a series of children surgically treated for posterior fossa tumours. Brain 2000; 123: 1051- 1061.
- Steinlin M, et al: Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. Brain 2003;126:1998-2008
- Grill J et al. Critical risk factors for intellectual impairment in children with posterior fossa tumors: the role of cerebellar damage. J Neurosurg. 2004;101(2 Suppl):152-8.
- Maryniak A, Roszkowski M. Cognitive and affective disturbances in children after surgical treatment of cerebellar tumors. Neurol Neurochir Pol. 2005;39:202-6.
- Ronning C et al. Persistent cognitive dysfunction secondary to cerebellar injury in patients treated for posterior fossa tumors in childhood. Pediatr Neurosurg. 2005;41:15-21.

Development

- Steinlin M, Styger M, Boltshauser E.Cognitive impairments in patients with congenital nonprogressive cerebellar ataxia. Neurology. 1999;53:966-73.
- Limperopoulos C. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics. 2005 ;116:844-50.
- Tavano A, et al. Disorders of cognitive and affective development in cerebellar malformations. Brain. 2007;130:2646-60.

Behaviorally Defined Disorders with Cerebellar Anomalies

- Attention Deficit Hyperactivity Disorder

  Berquin et al., Neurology, 1998; 50: 1087-93
  Mostofsky et al., J. Child Neurol. 1998; 13: 434-9
  Castellanos et al., Arch. Gen. Psychaitry 2001; 58: 289-95

- Dyslexia

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

- Cognitive deficits in infants born very pre-term

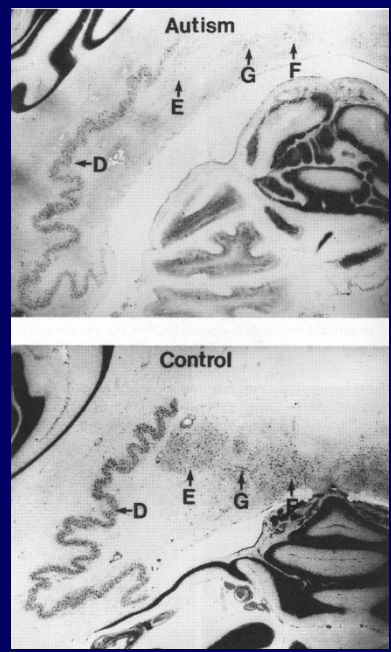
  Allin et al., Brain 2001; 124: 60-66

- Autism

  Bauman and Kemper, 1997

- Schizophrenia

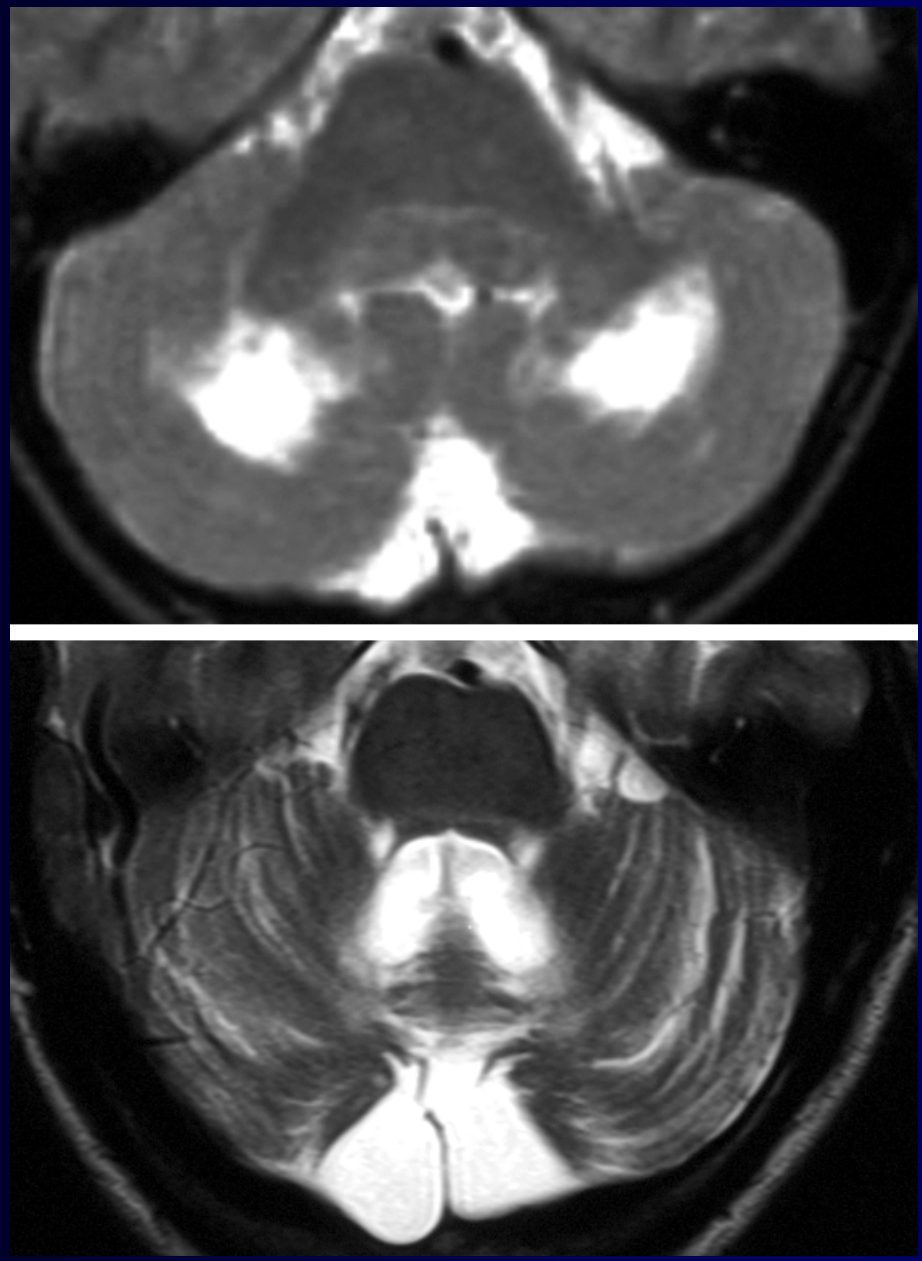
  Levitt et al., Am J Psychiatry. 1999; 156:1105-7
  Nopoulos et al., Biol Psychiatry 1991; 46: 703-11
  Loeber et al., Am J Psychiatry 2001; 158: 952-4



Neuropsychiatry of the Cerebellum

- 23 patient case reports
  - Tumor
  - Non-progressive cerebellar ataxia
  - Focal hypoplasia (vermis)
  - Agenesis (partial or complete)
  - Post-infectious cerebellitis

Langerhans cell histiocytosis of the cerebellum



1991

2000

Neuropsychiatry of the Cerebellum

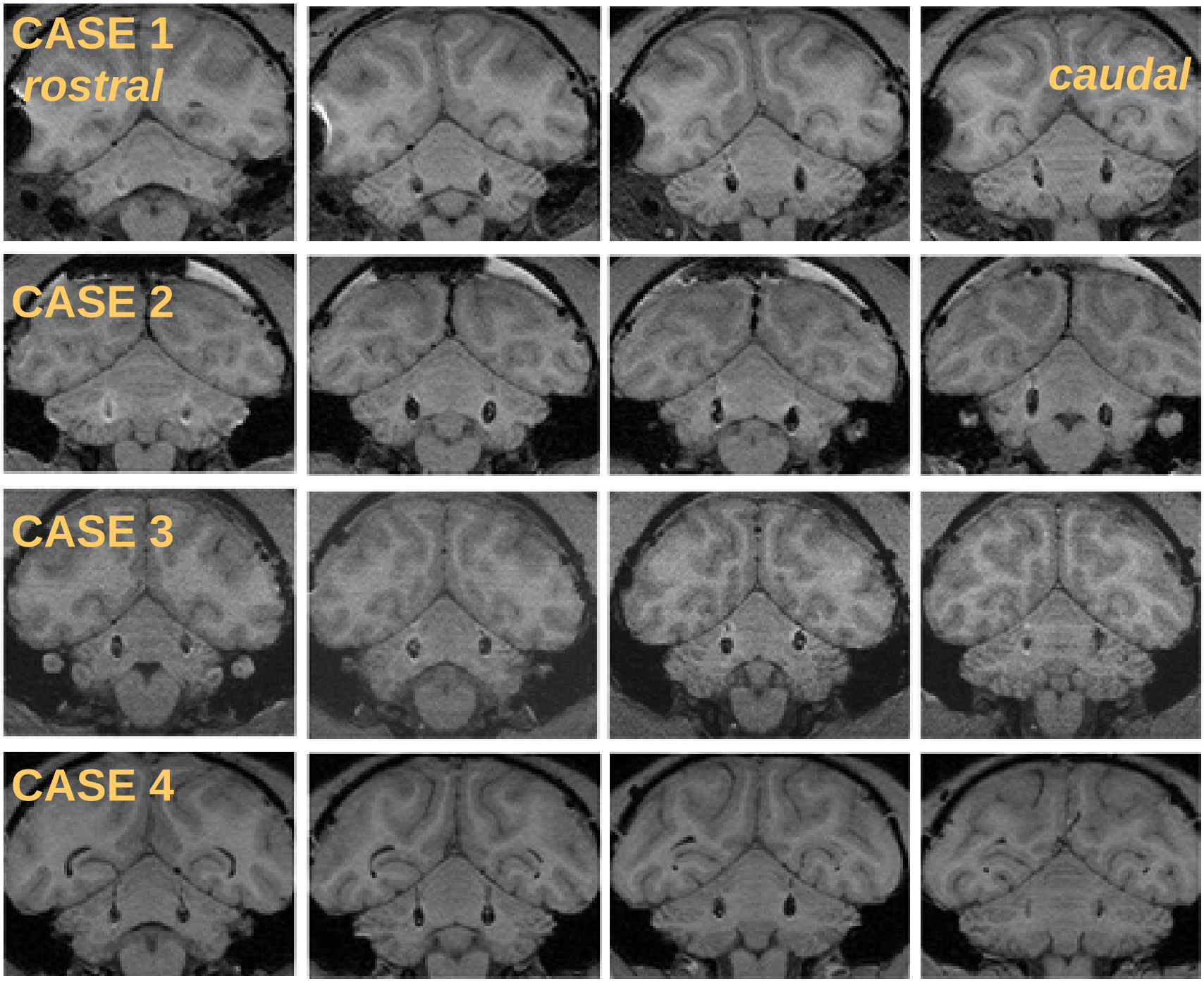
- Attentional Control
- Emotional Control
- Autism Spectrum Disorders
- Psychosis Spectrum Disorders
- Social Skill Set

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

Schmahmann, Weilburg, Sherman
The Cerebellum 2007; 6: 254-67.

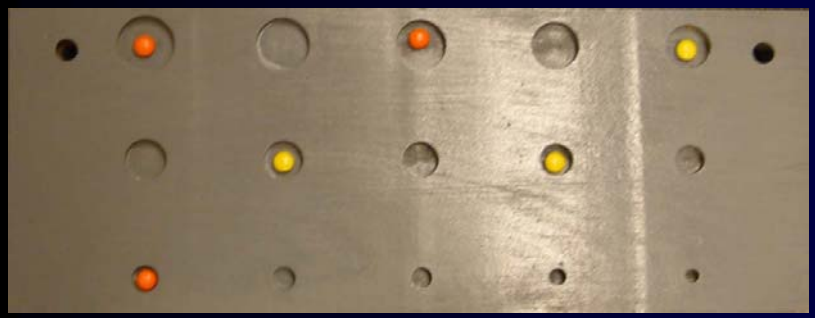
	Positive (exaggerated) symptoms	Negative (diminished) symptoms
Attentional Control	Inattentiveness	Ruminativeness
	Distractibility	Perseveration
	Hyperactivity	Difficulty shifting focus of attention
	Compulsive and ritualistic behaviors	Obsessional thoughts
Emotional control	Impulsiveness, disinhibition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


D
IA
IP
F
F
IP
IA
D
1 mm

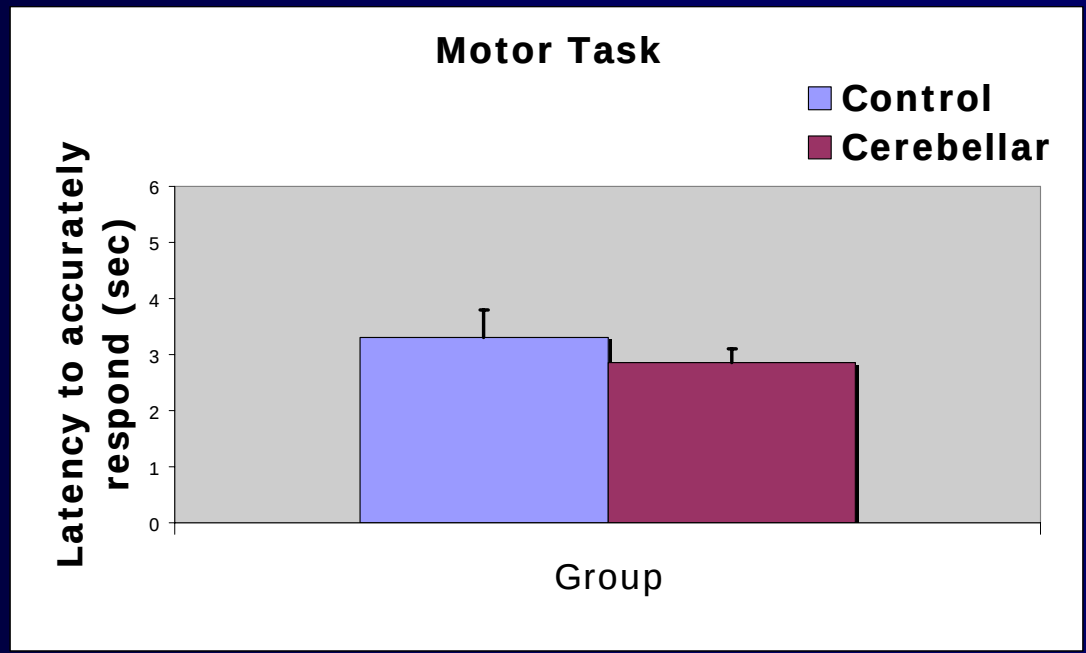

CASE 1
rostral
caudal
CASE 2
CASE 3
CASE 4

Motor Assessment

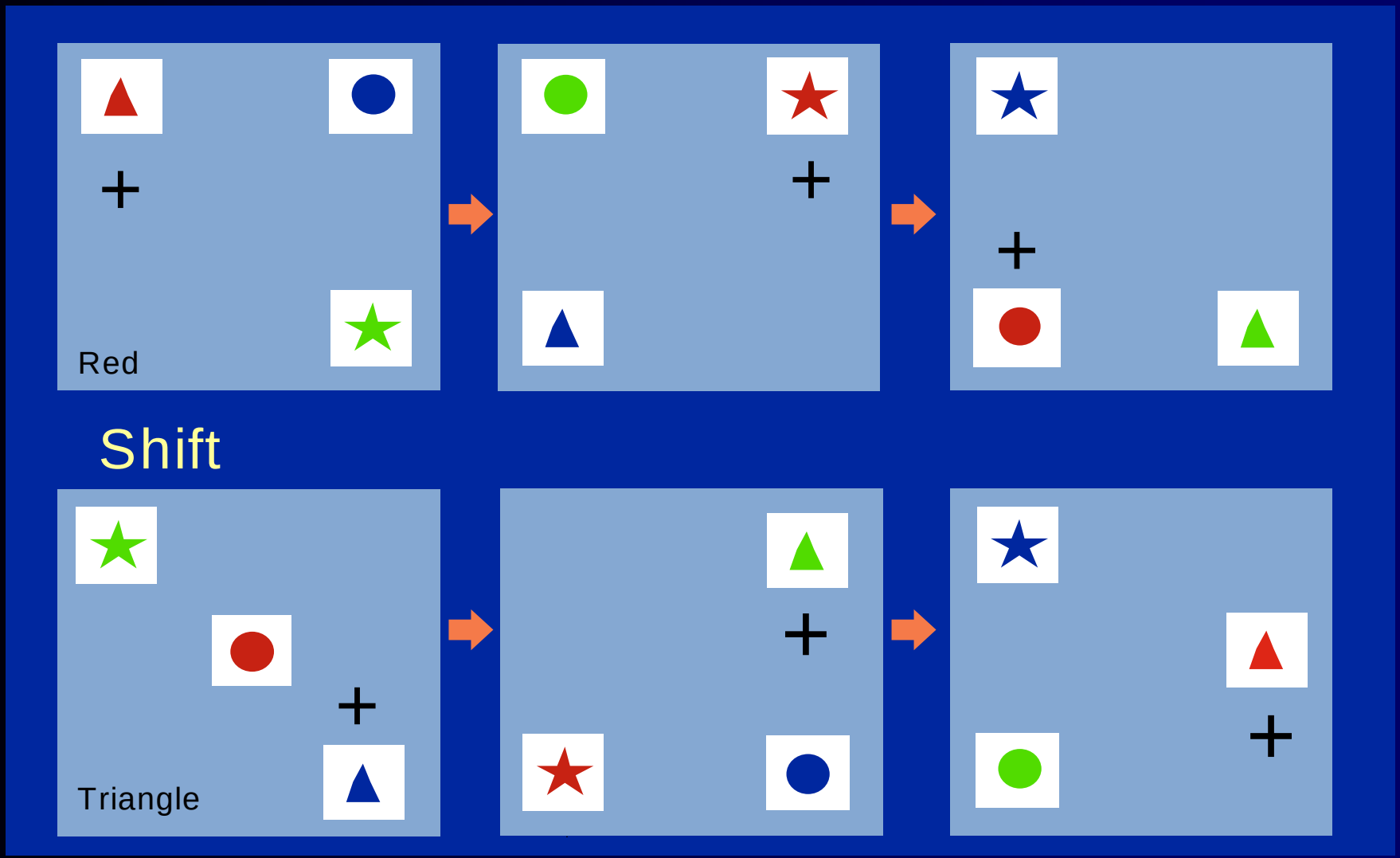
Kuypers' motor task before and after DN lesions (Lawrence and Kuypers, 1968)



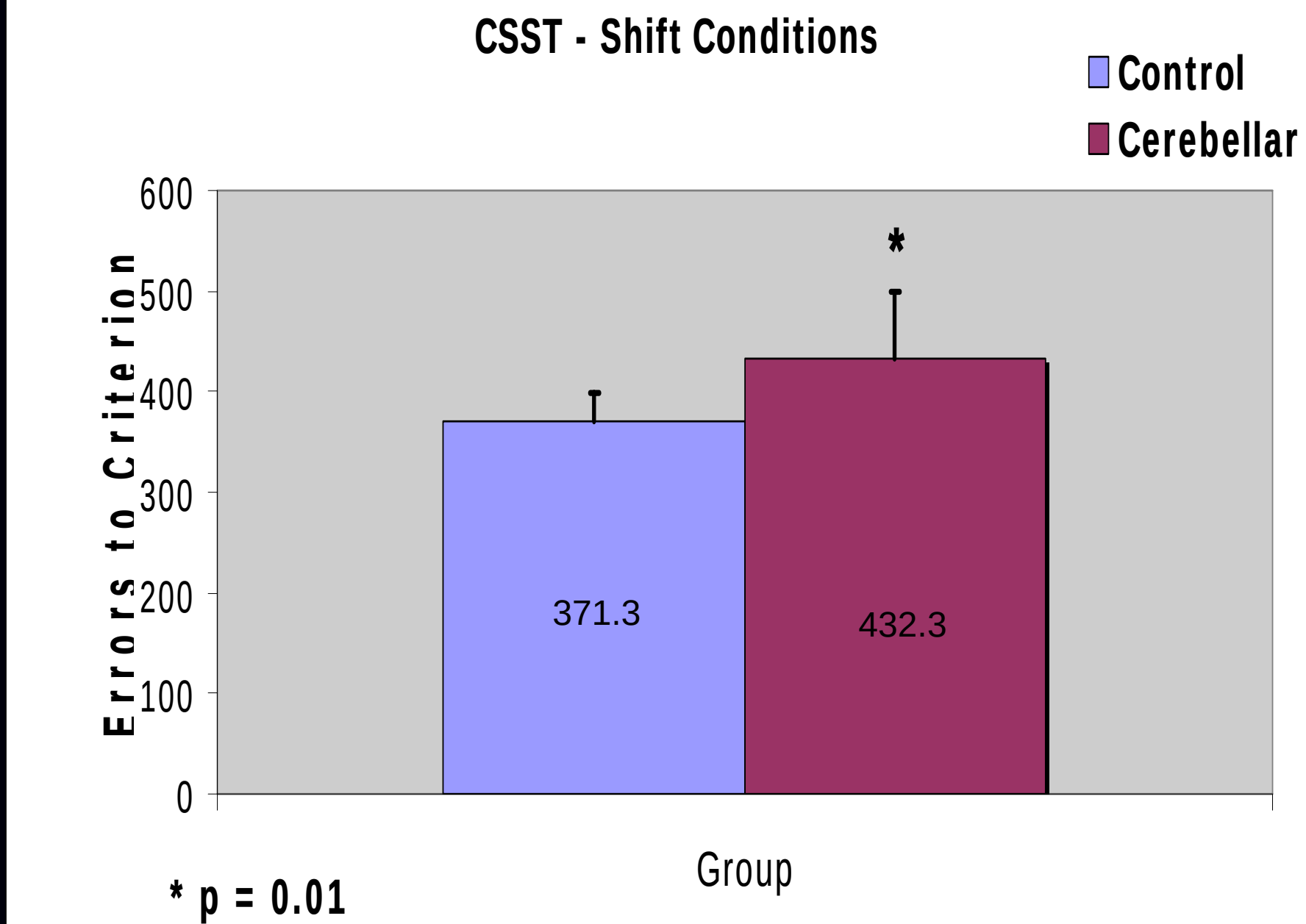
Kuypers' testing board



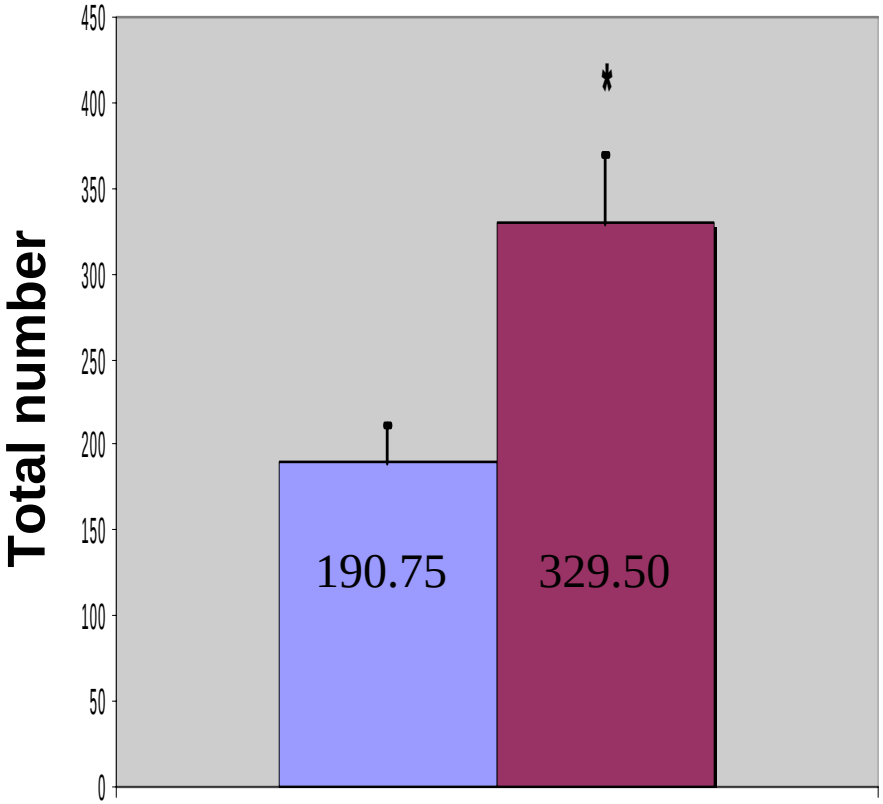
Conceptual Set Shifting Task (CSST)



Moore TL, Killiany RJ, Rosene DL, Prusty S, Hollander W, Moss MB. 2002.

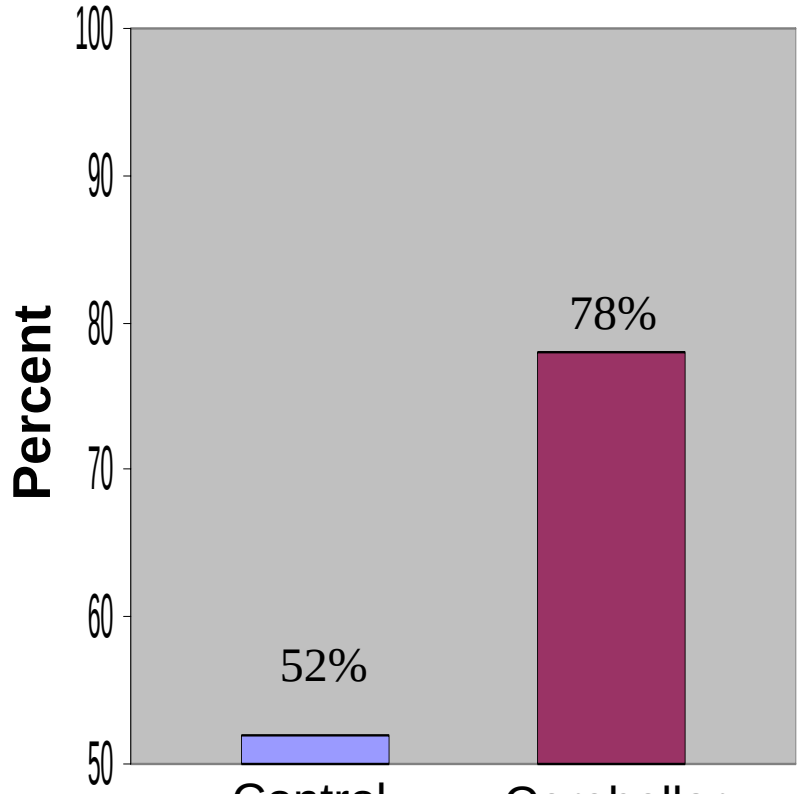

CSST - Shift Conditions
Control
Cerebellar
600
500
400
300
200
100
0
Errors to Criterion
371.3
432.3
*
Group
* p = 0.01

CSST – Perseverative Errors



*** P = 0.006**

Perseverative errors compared to chance



*** P < 0.007**

There are regions of the cerebellum devoted to cognitive processing rather than to motor coordination

The cerebellum appears to be a critical modulator of prefrontal systems mediating executive function

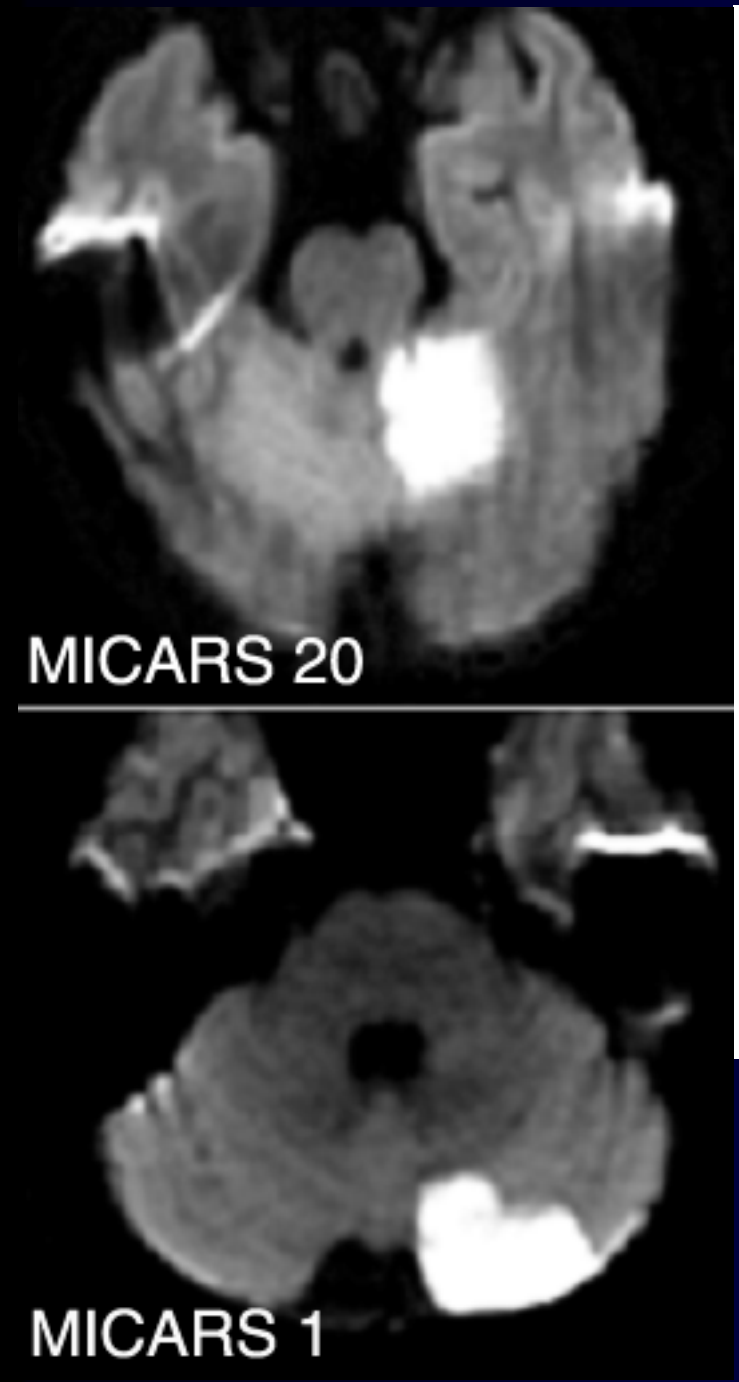
Schmahmann JD, Killiany RJ, Moore TL, DeMong C, MacMore JP, Rosene DL, Moss MB, 2004

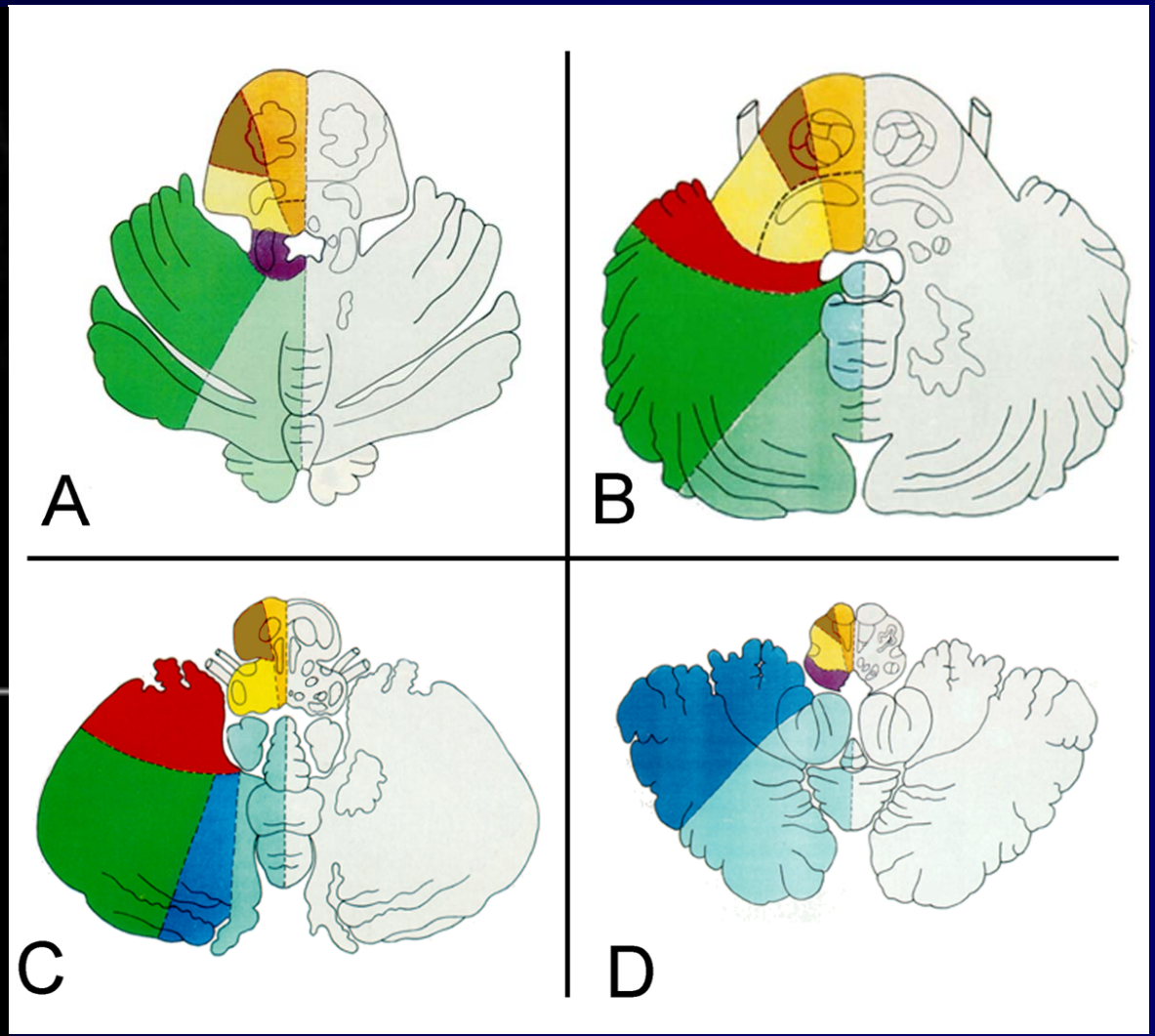
MICARS

(Modified* International Cooperative Ataxia Rating Scale)

Trouillas et al. 1997;
* Schmahmann et al., 2007

I. POSTURE AND GAIT	**34 points**
Walking capacity	
Gait speed	
Standing, eyes open	
Spread of feet in natural position, eyes open	
Body sway with feet together, eyes open	
Body sway with feet together, eyes closed	
Quality of sitting position	
II. KINETIC FUNCTIONS	**68 points**
Knee-tibia test	
Action tremor in heel-to-knee test	
Decomposition of leg movement	
Decomposition of leg tapping	
Finger-to-nose test: decomposition and dysmetria	
Finger-to-nose test: intention tremor of the finger	
Finger-finger test (action, tremor and/or instability)	
Pronation-supination alternating movements	
Rebound of the arms	
Overshoot of the arms	
Drawing of Archimedes' spiral on a predrawn pattern	
III. SPEECH DISORDERS	**10 points**
Dysarthria: fluency of speech	
Dysarthria: Clarity of speech	
Dysarthria: Alternating syllables	
IV. OCULOMOTOR DISORDERS	**8 points**
Abnormal eye movements at rest	
Gaze-evoked nystagmus	
Abnormalities of the ocular pursuit	
Dysmetria of the saccade	
Saccadic intrusions into vestibulo-occular reflex cancellation	
TOTAL	**120 points**

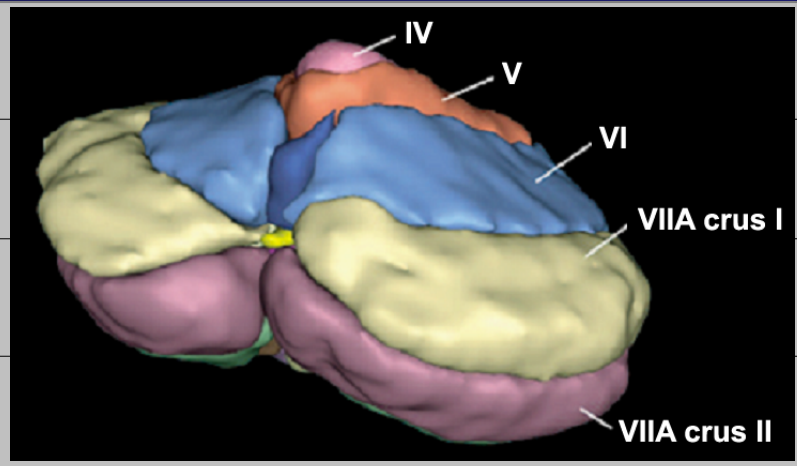




Blood supply of human cerebellum.
Adapted from Tatu et al., 1996

Schmahmann, MacMore, Vangel
Neuroscience 2009; 162: 852 – 861.

Motor deficit (MICARS score) following Cerebellar Stroke



Groups 1+2+5: **20.5 +/- 11.8**
versus
Group 4: **3 +/- 2.0**
* p < 0.0001

All lobules	I-V	I-V, +VI	VII-X, +VI	VII-X only
Group 5	1	2	3	4
n=11	n=1	n=4	n=4	n=13

Schmahmann, MacMore, Vangel, 2009

Neuroscience 162 (2009) 852–861

CEREBELLAR STROKE WITHOUT MOTOR DEFICIT: CLINICAL EVIDENCE FOR MOTOR AND NON-MOTOR DOMAINS WITHIN THE HUMAN CEREBELLUM

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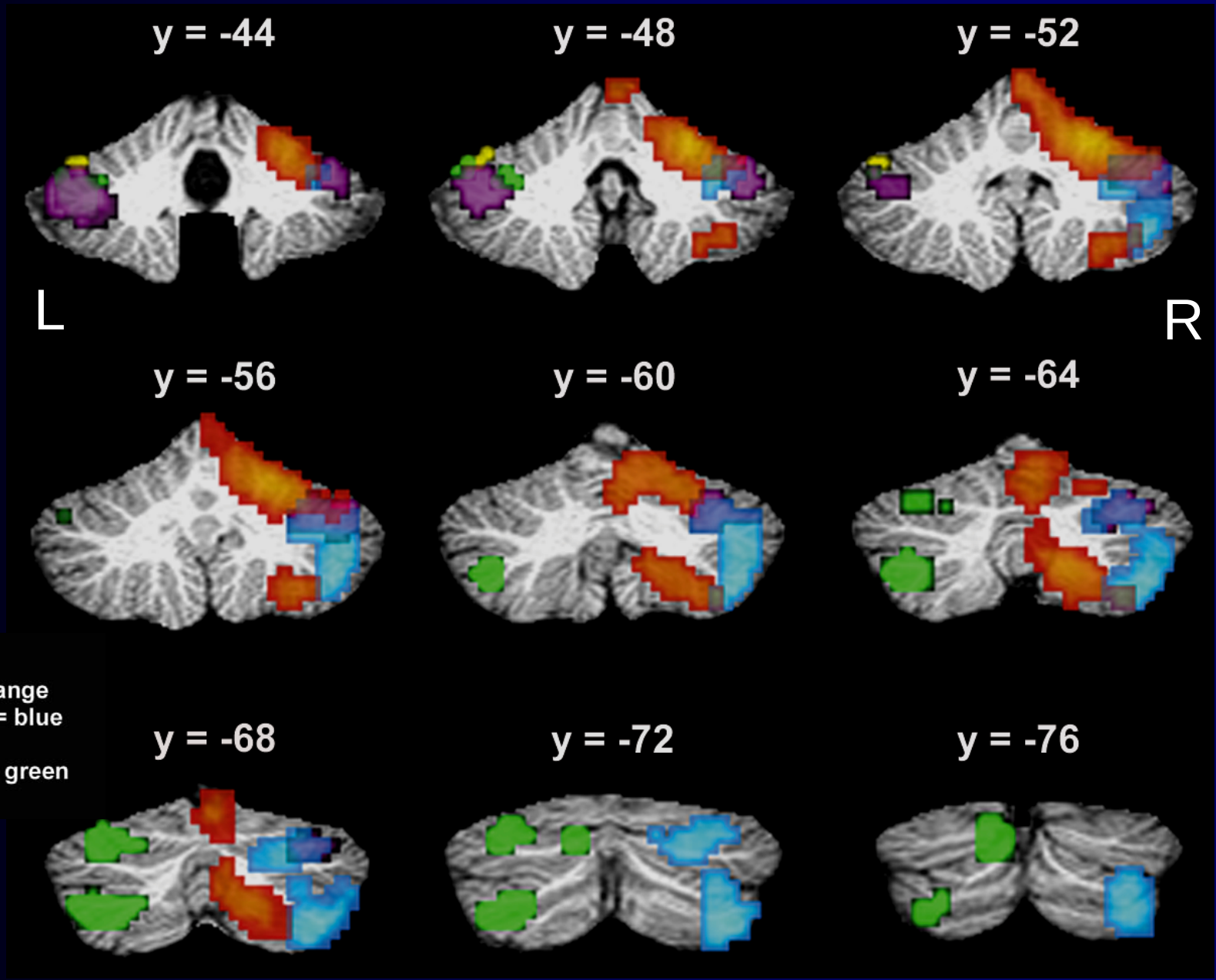
Key words: cerebellum, ataxia, motor control, functional topography.

The notion that the cerebellum is devoted purely to the coordination of gait, extremity and oculomotor movement, and articulation has been deeply entrenched in medical and neurological texts. Evidence pointing to

Cerebellar functional topography. Single case fMRI



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

Stoodley, Valera, Schmahmann, 2010

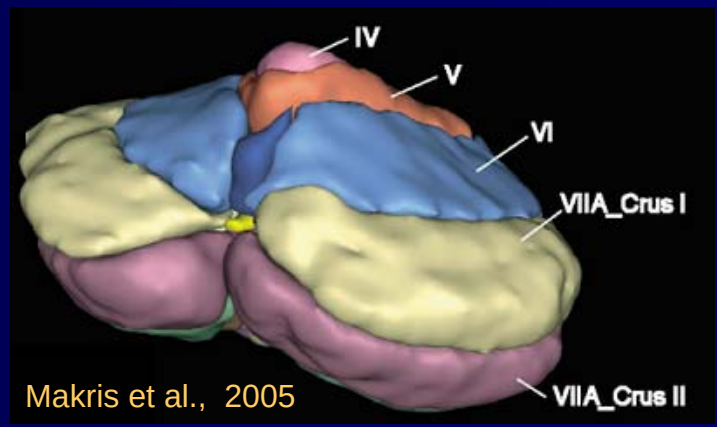
Dysmetria of Thought Theory

Schmahmann, 1991, 1996, 2004

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 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

Schmahmann 1991, 1996, 2004

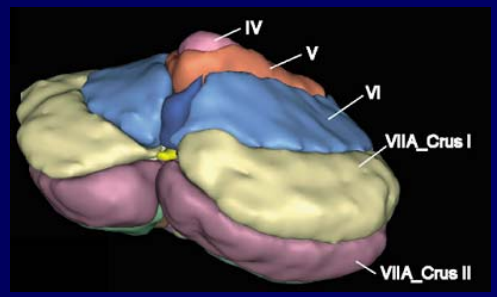
Dysmetria of Thought Theory

The cerebellum detects, prevents, and corrects mismatches between intended outcome and perceived outcome of interaction with the environment. It facilitates actions harmonious with the goal, appropriate to context, and judged accurately and reliably according to the strategies mapped prior to and during the behavior.

Schmahmann 1991, 1996, 2004

Dysmetria of Thought Hypothesis

Topography anterior – posterior



Makris et al., 2005

Sensorimotor –

predominantly anterior lobe (I - V), VI

"secondary" representation in lobule VIII

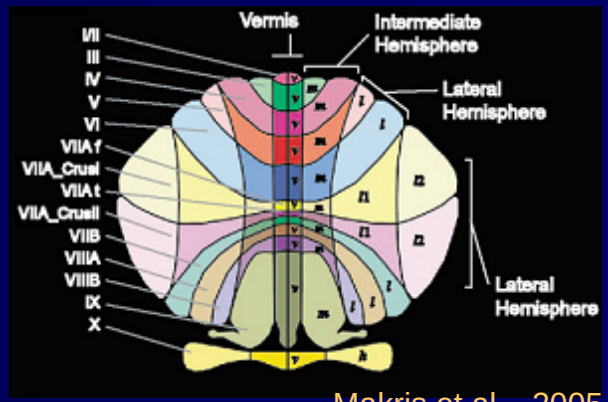
vestibulocerebellum in lobules IX and X

Cognitive, affective –

predominantly neocerebellum (vermal and hemispheric components of lobules VI and VII)

Dysmetria of Thought Hypothesis

Topography medial - lateral



Makris et al., 2005

<u>Vermis and fastigial nucleus -</u>

autonomic regulation, affect, emotionally important memory

<u>Cerebellar hemispheres and dentate nucleus -</u>

executive, visual-spatial, linguistic, learning and memory

Dysmetria of Thought

Postulated fundamental function
distributed throughout the cerebellum -
the **Universal Cerebellar Transform** (UCT)
that cerebellum utilizes to

optimize performance by modulating behavior around a homeostatic baseline automatically and according to context

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

Dysmetria of Thought

By corollary, there is a

Universal Cerebellar Impairment (UCI)

that is hypothesized to be

dysmetria

This includes dysmetria of movement

(*ataxia*);

and dysmetria of thought and emotion

(the *cerebellar cognitive affective syndrome*)

Conclusions

- topographic organization in human cerebellum of sensorimotor function, cognition and emotion
- cerebellar lesions disrupt cerebellar modulation of anatomical-functional subunits within the cerebrocerebellar system
- clinical deficits reflect the domain of function in the cerebral hemisphere that has been deprived of its cerebellar influence
- therapeutic implications of the modulating influence of cerebellum in behavioral neurology and psychiatry

Implications for therapy

- The need-to-know imperative
- Window for cognitive rehabilitation and cross modal therapies
- Implications for behavioral neurology and neuropsychiatry in children
- Potential for novel treatment strategies in psychiatric illness

Collaborators

Neuroanatomy
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Cerebellar Atlas
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Alan Evans
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Michael Petrides
Arthur Toga

Primate behavior
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Lisi Levisohn
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Janet Sherman
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David Kennedy
Nikos Makris
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Catherine Stoodley
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Diffusion Spectrum Imaging
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Helen D'Arceuil
Alex de Crespigny
Ruopeng Wang
Van Wedeen

Cerebellar TMS
Asli Demirtas-Tatlidede
Alvaro Pascual Leone

National Institutes of Mental Health
McDonnell-Pew Program; National Library of Medicine;
Birmingham Foundation, MINDLink Foundation

Photo by Jinny Sagorin