Cognition in the Little Brain

Pacific Northwest Neuropsychological Society

March 5, 2022

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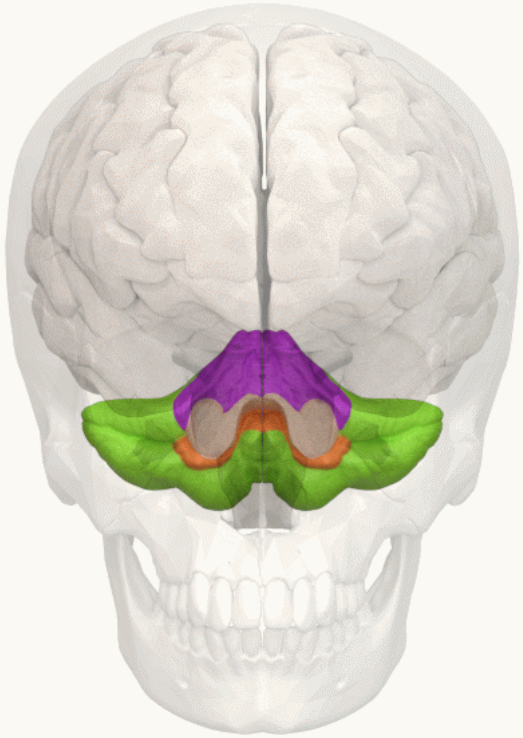
Cleveland Clinic



Cerebellum Trivia Time!

The cerebellum contains what proportion of the brain's total neurons?

5-10%

40-50%

20-30%

60-80%

The cerebellum constitutes what percentage of the brain's total weight?

10%

40%

25%

60%

If unfolded, how much of the cerebrum's surface area would the cerebellum cover?

10%

50%

25%

75%

Cerebellar development is complete at what age?

At birth

10 years

2 years

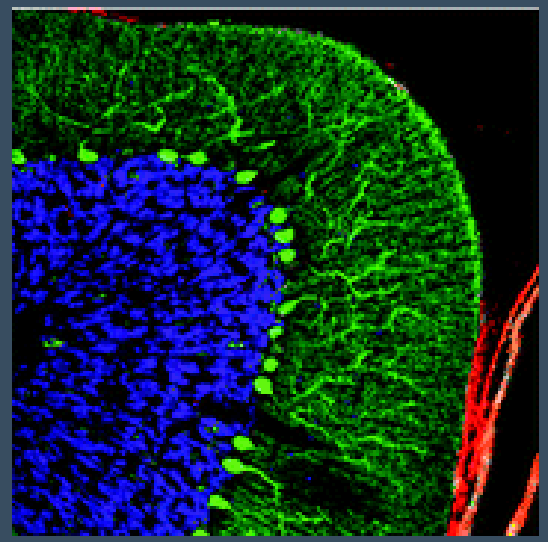
20 years

Learning Goals

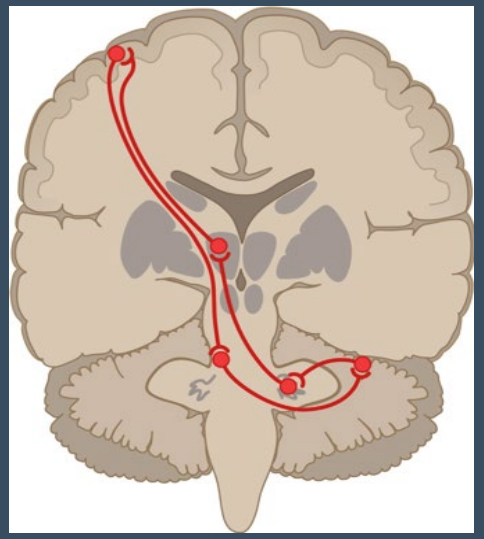
1. Understand the anatomy of the cerebellum as the basis for its role in cognition
2. Explore current evidence for its functional role
3. Clinical assessment of cognitive impairments
4. Emerging data in special populations

Section 1: Cerebellar Structure

Gross Anatomy

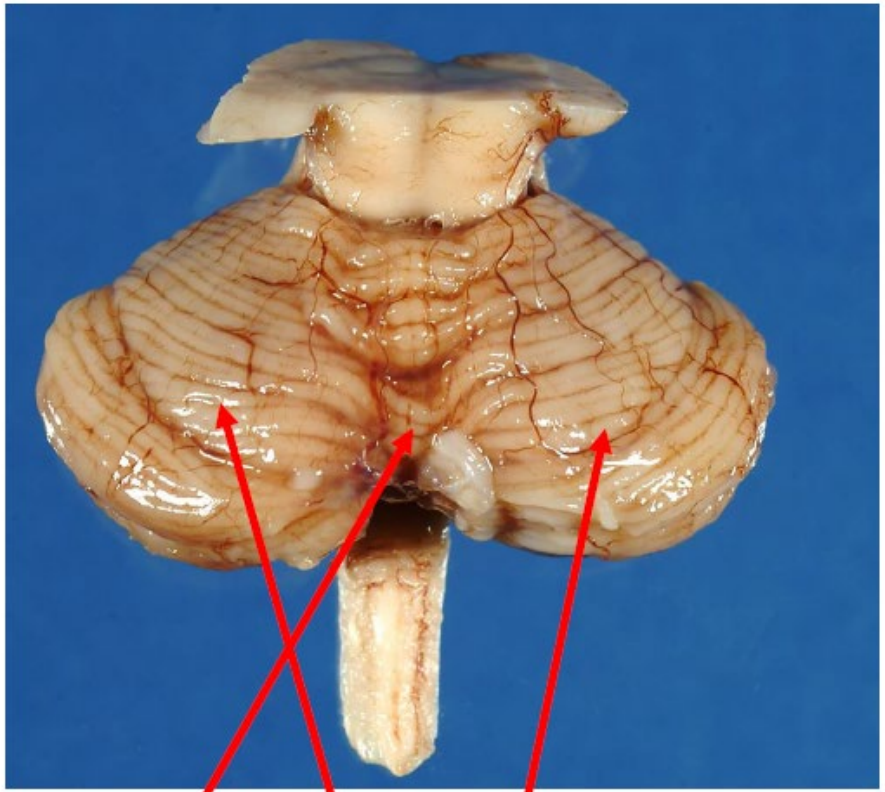


Internal Circuitry



Connectivity

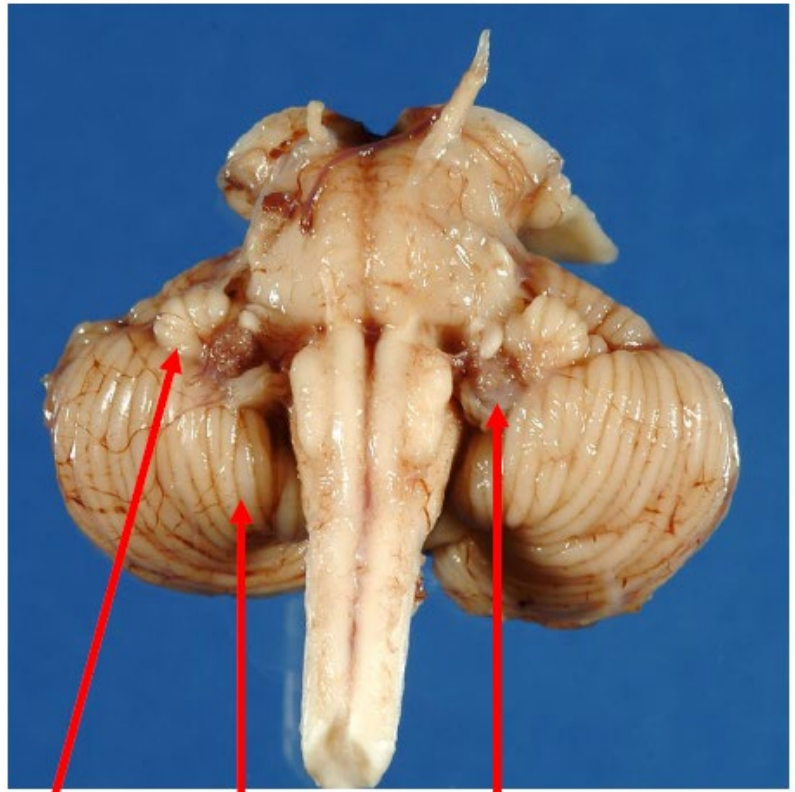
Dorsal/Posterior View



Vermis

Hemispheres

Ventral/Anterior View

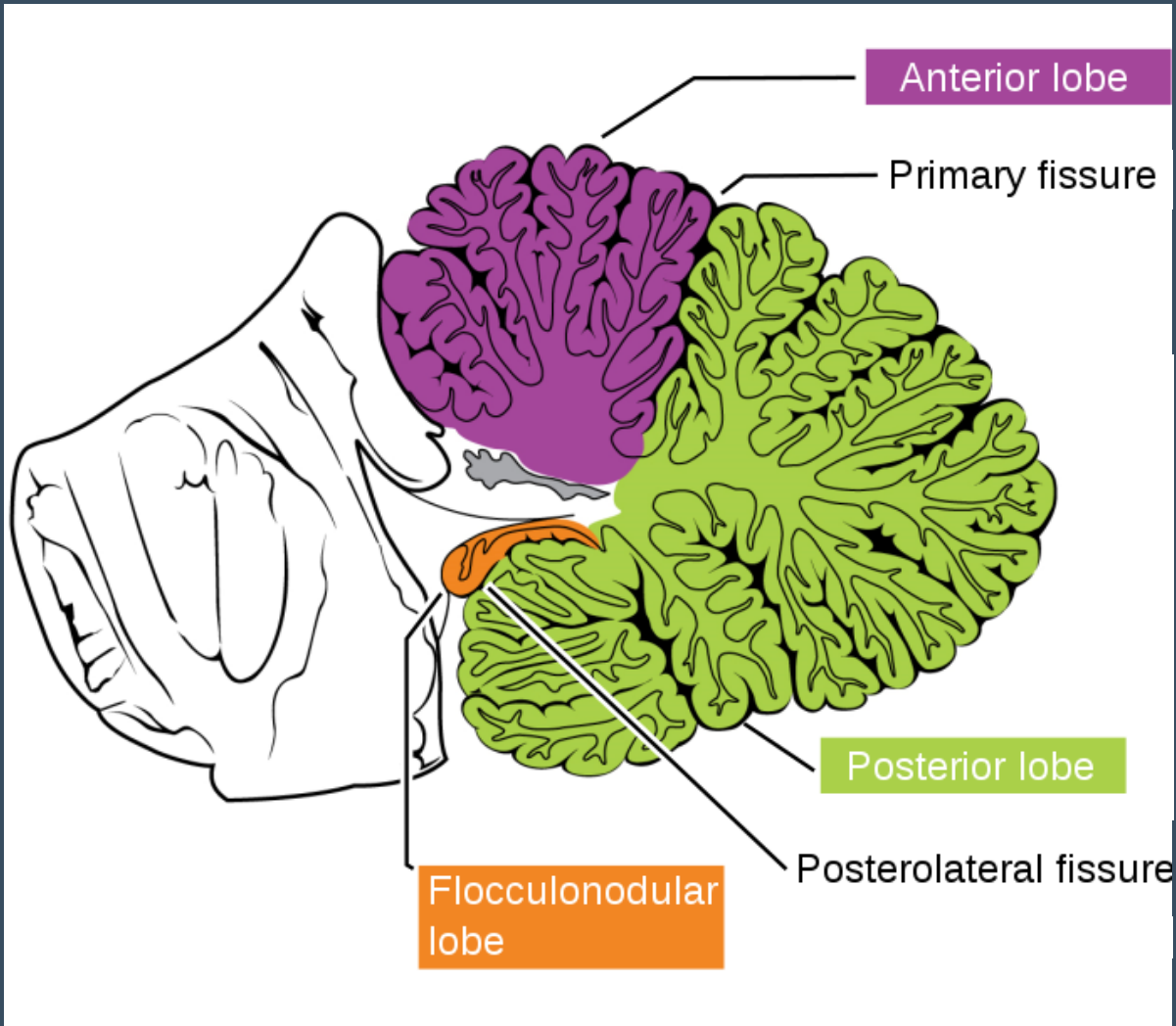


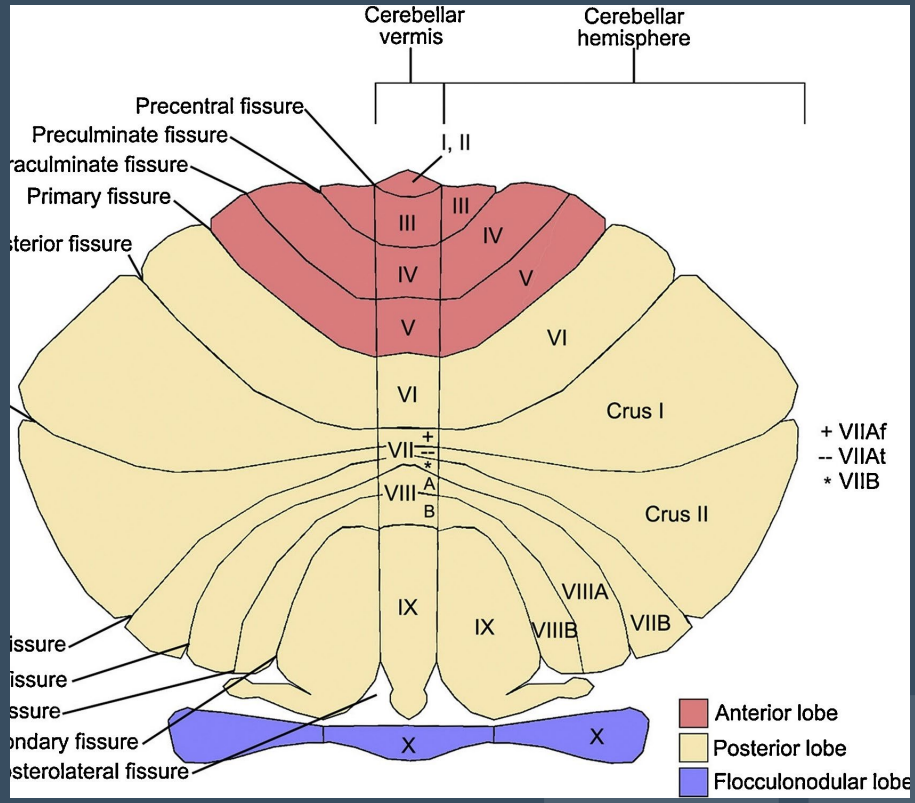
Flocculus

Tonsil

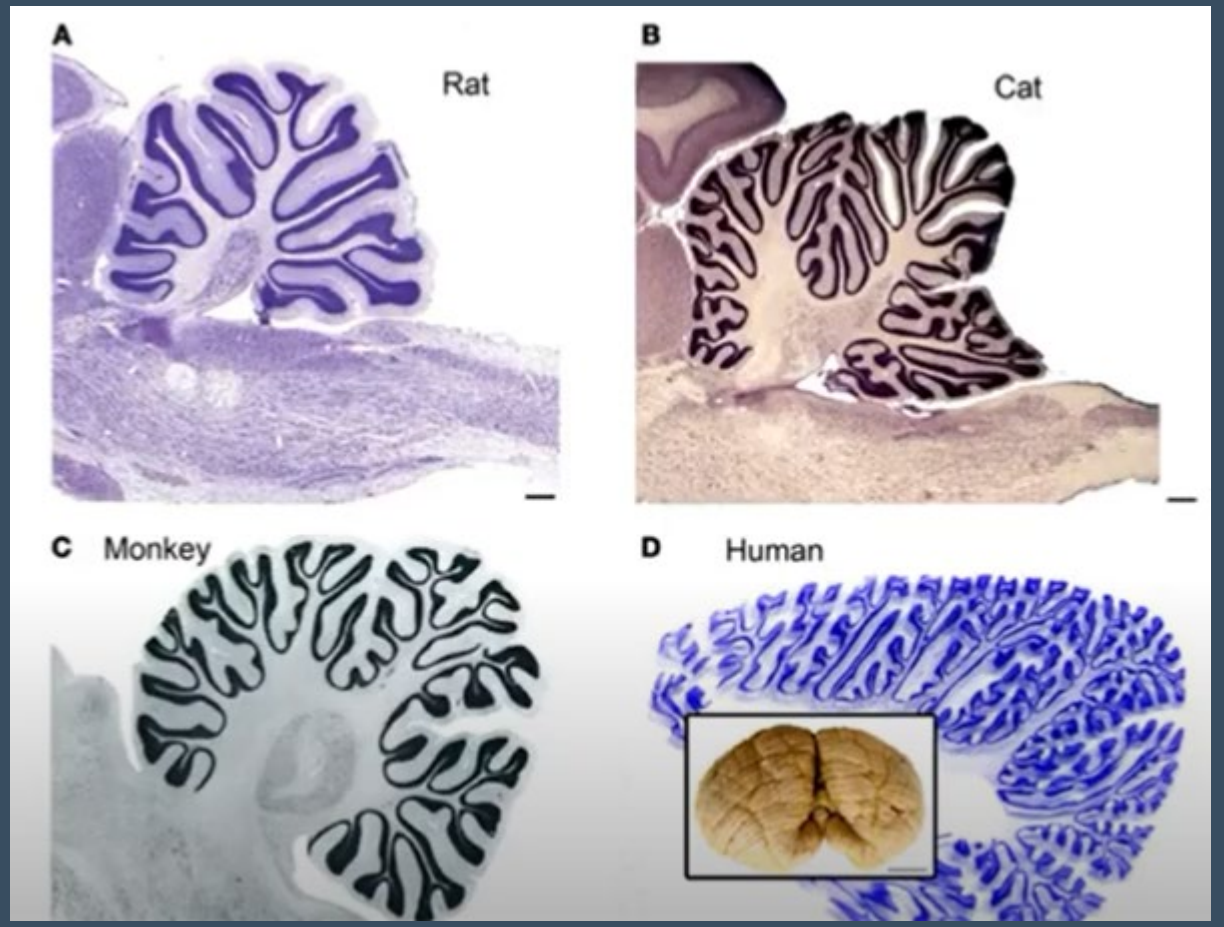
Nodulus

Three Cortical Divisions



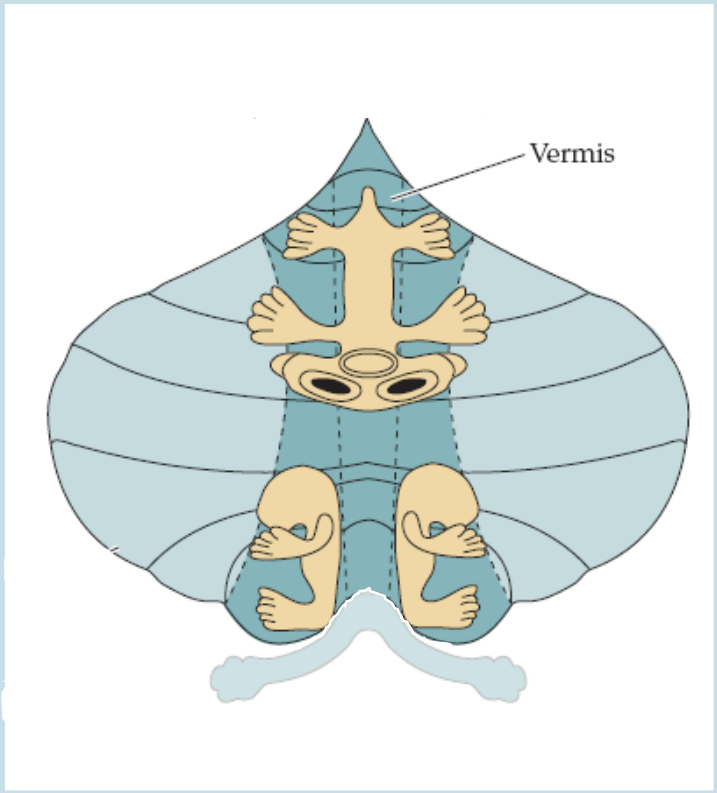


https://commons.wikimedia.org/w/index.php?title=File:1613_Major_Regions_of_the_Cerebellum-02.jpg&oldid=466502798

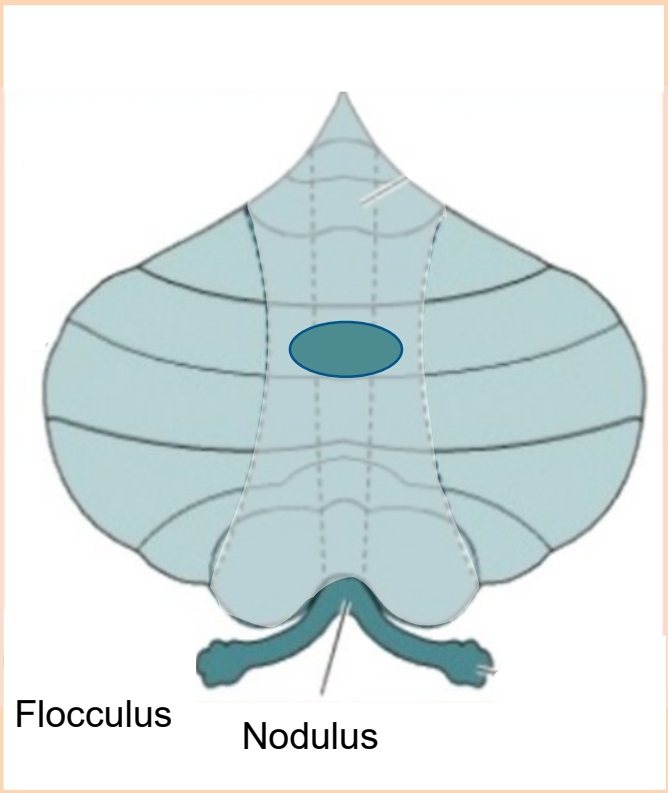

A
Rat
B
Cat
C
Monkey
D
Human

Three Anatomical Circuits

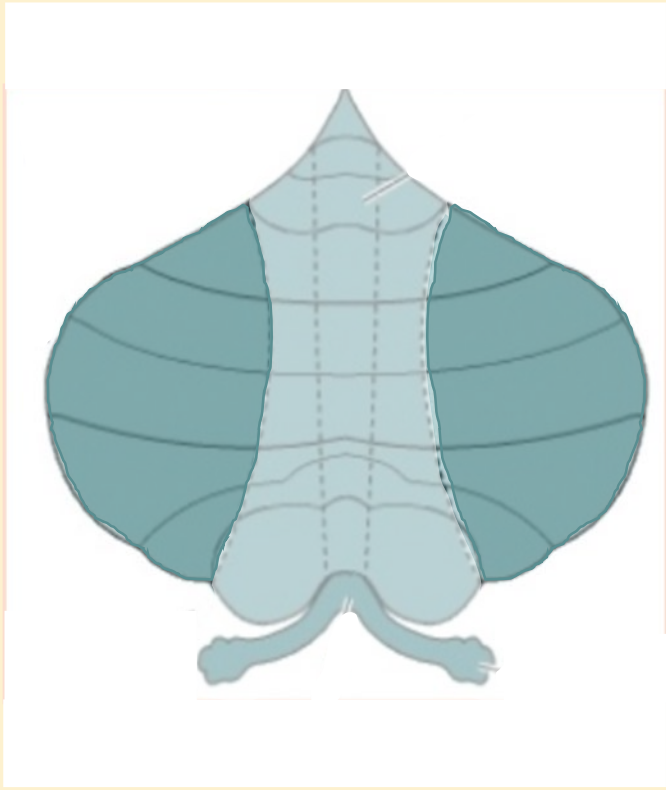
Spinal/Motor



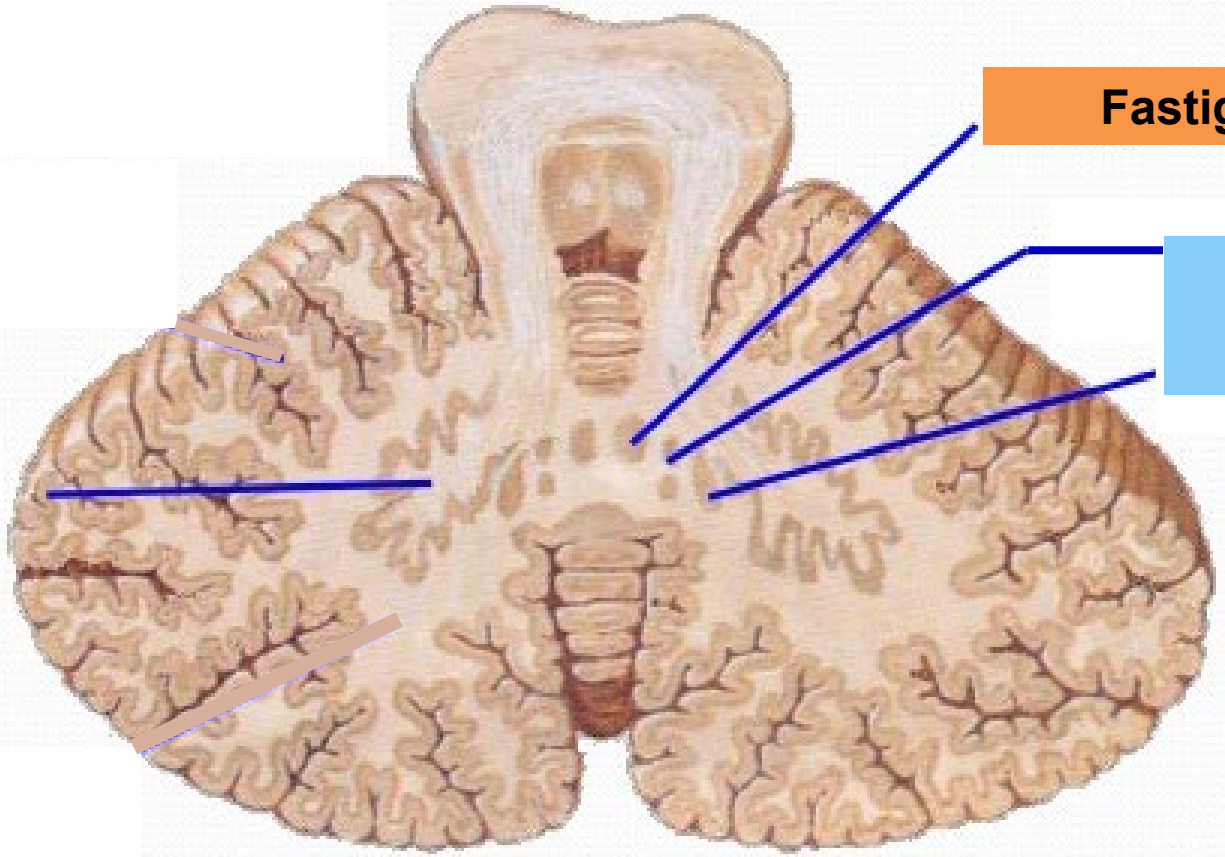
Vestibular/ Occular



Cerebral



Three Deep Nuclei



Vestibular/occular

Fastigial n.

Spinal

Interposed n.

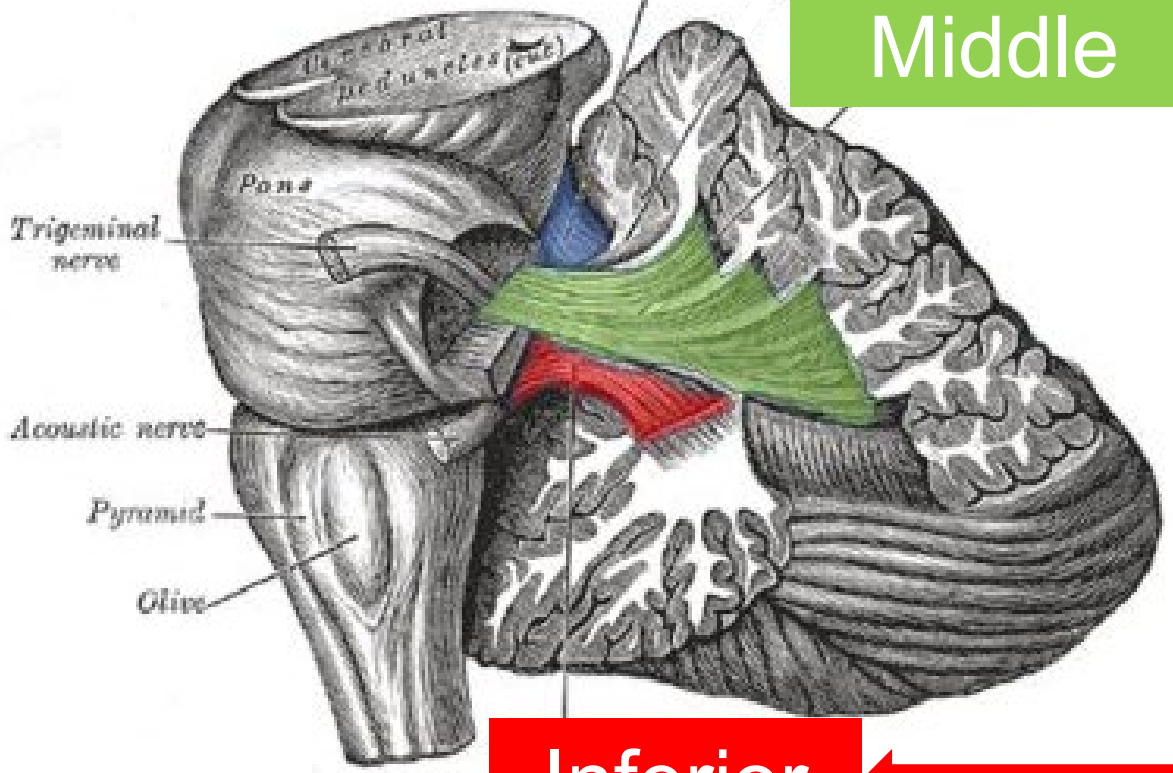
Brain stem n.
Spinal cord

Motor/ Cognitive

Dentate n.

Cerebral cortex

Three Peduncles



Superior

Middle

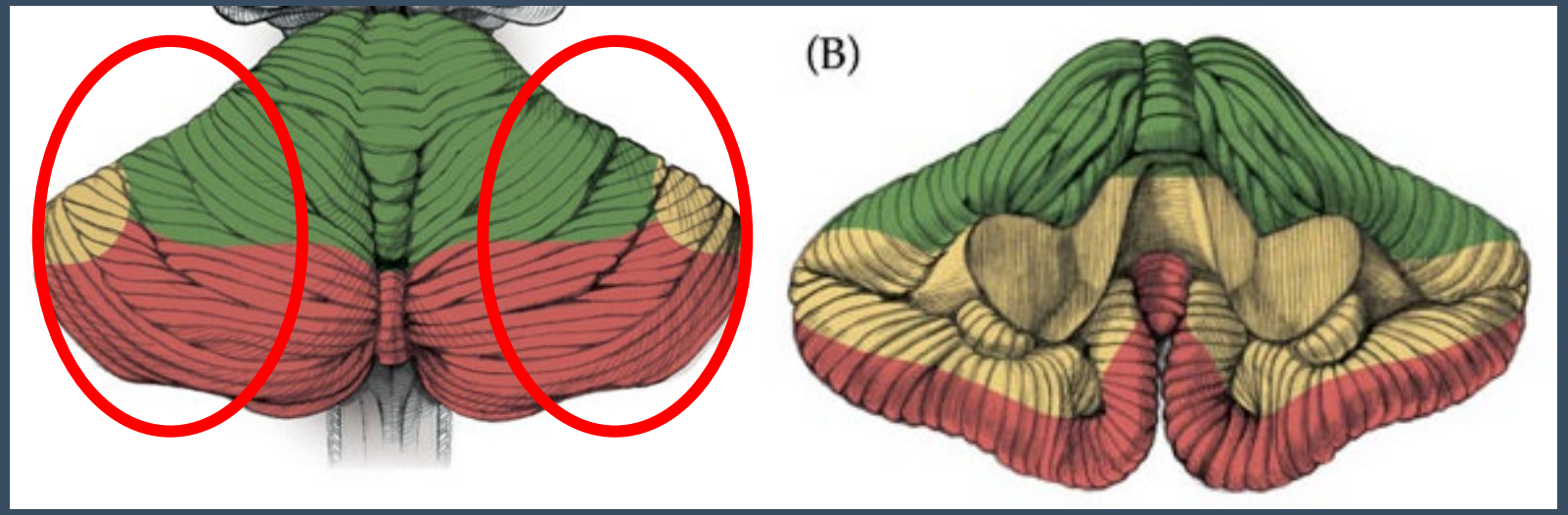
Inferior

Output
Input

Input

Input
Output

Three Vascular Territories



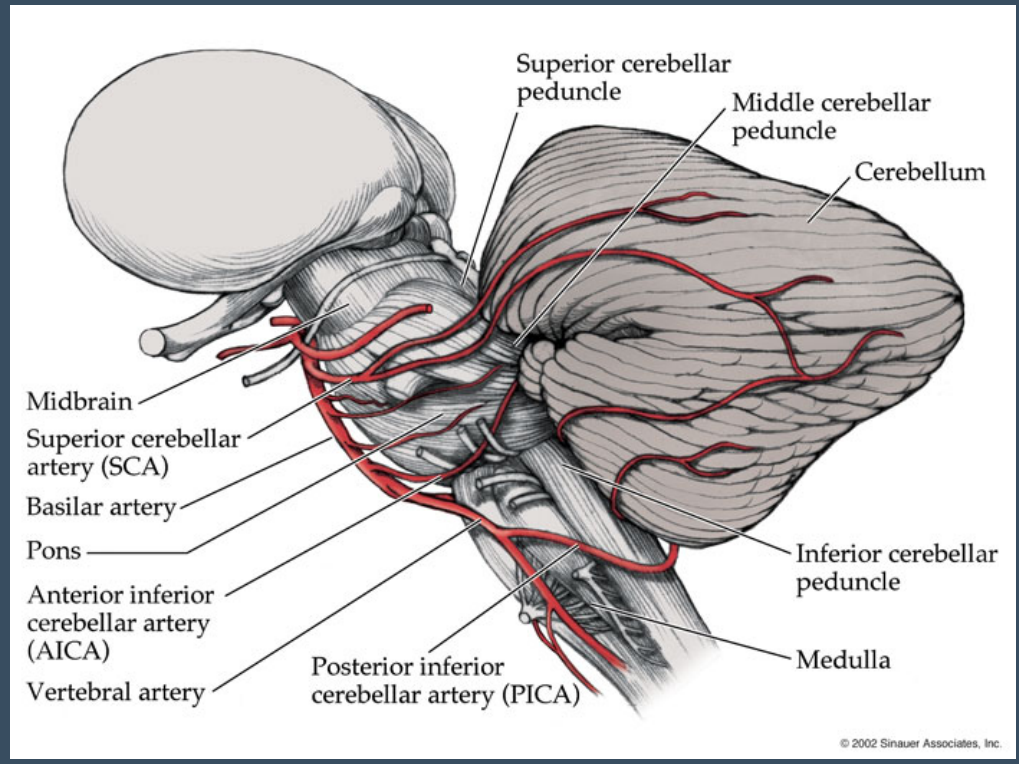
Superior Cerebellar Artery

Anterior Inferior Cerebellar Artery

Posterior Inferior Cerebellar Artery

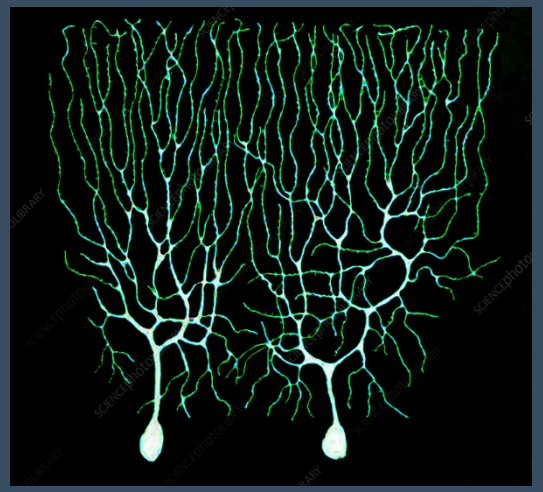
Blumenfeld H. Neuroanatomy through Clinical Cases 2nd Ed, 2010

Three Vascular Territories

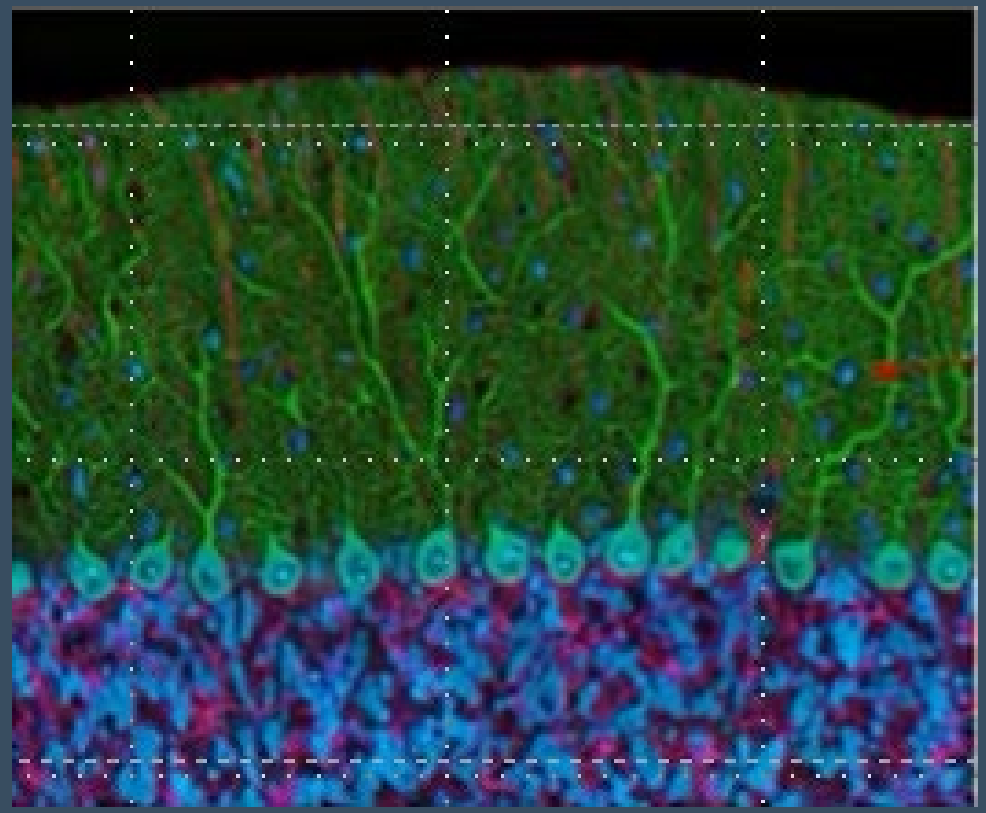


Blumenfeld H. Neuroanatomy through Clinical Cases 2nd Ed, 2010

Three Cortical Layers



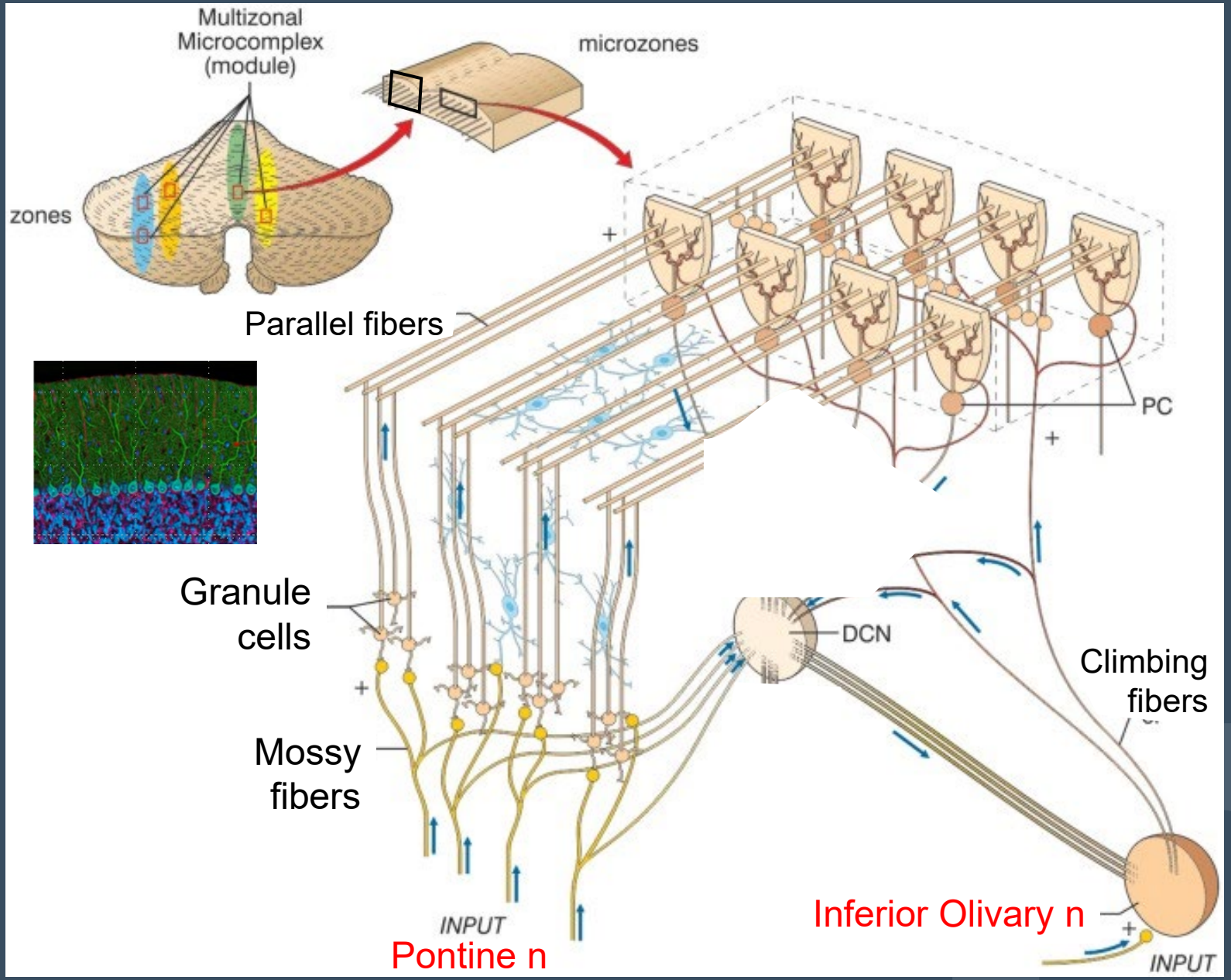
Purkinje



Molecular

Granule

Modular Architecture



Modified from D'Angelo E, Casali S. Front Neural Circuits. 2013 Jan 10;6:116

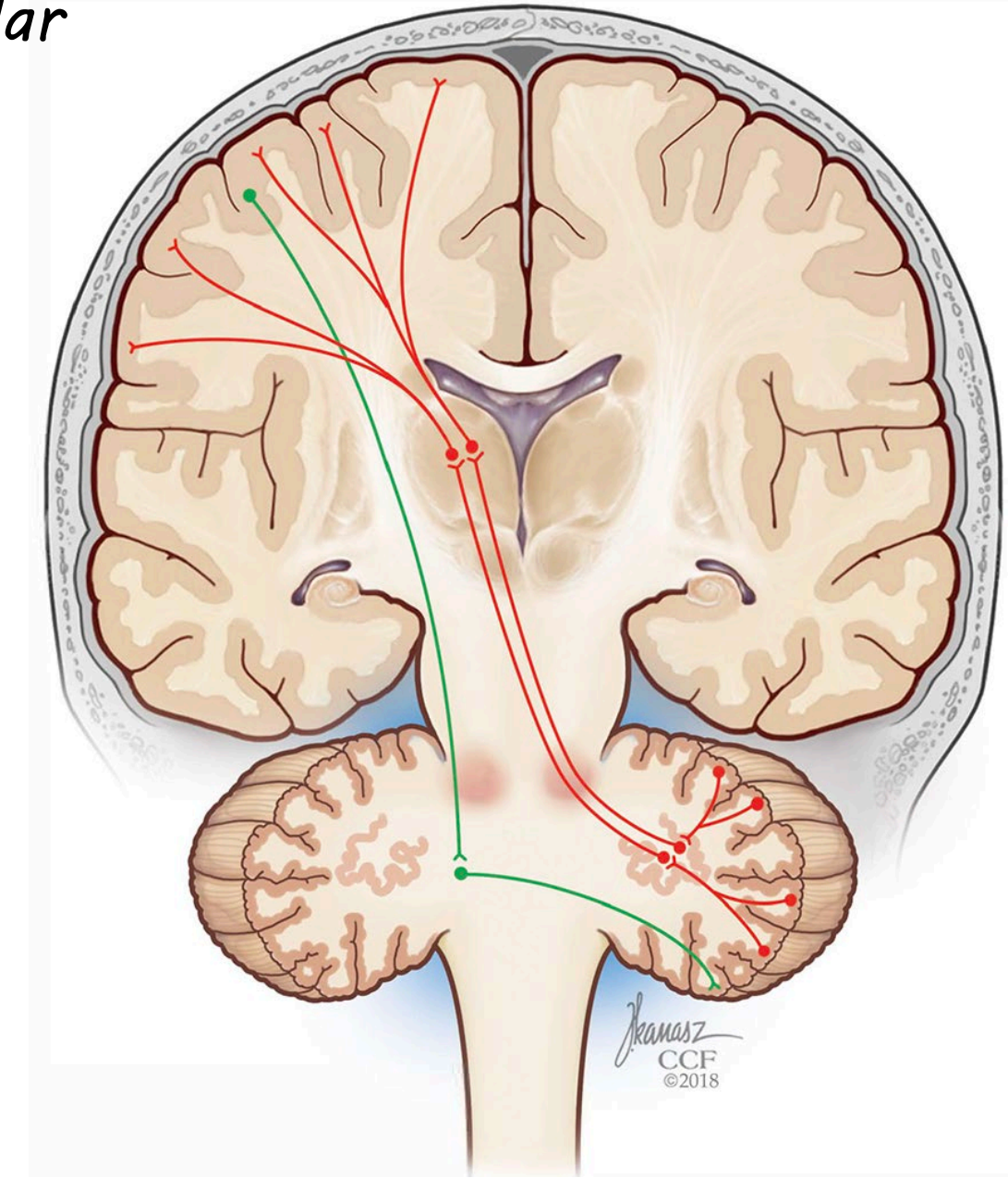
Cerebral-Cerebellar Circuit

Cortex

Pons

middle c. peduncle

Hemisphere



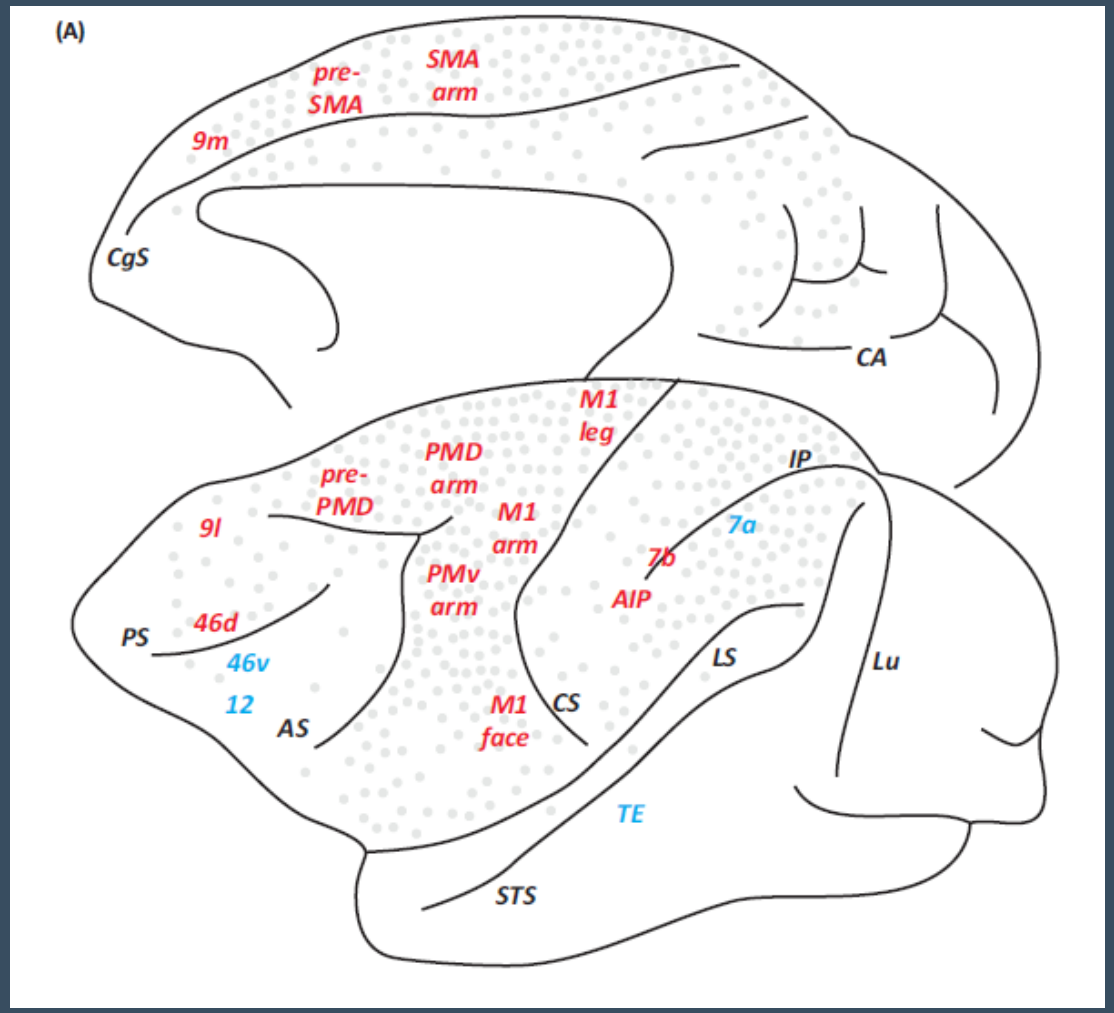
Cortex

Thalamus

superior c. peduncle

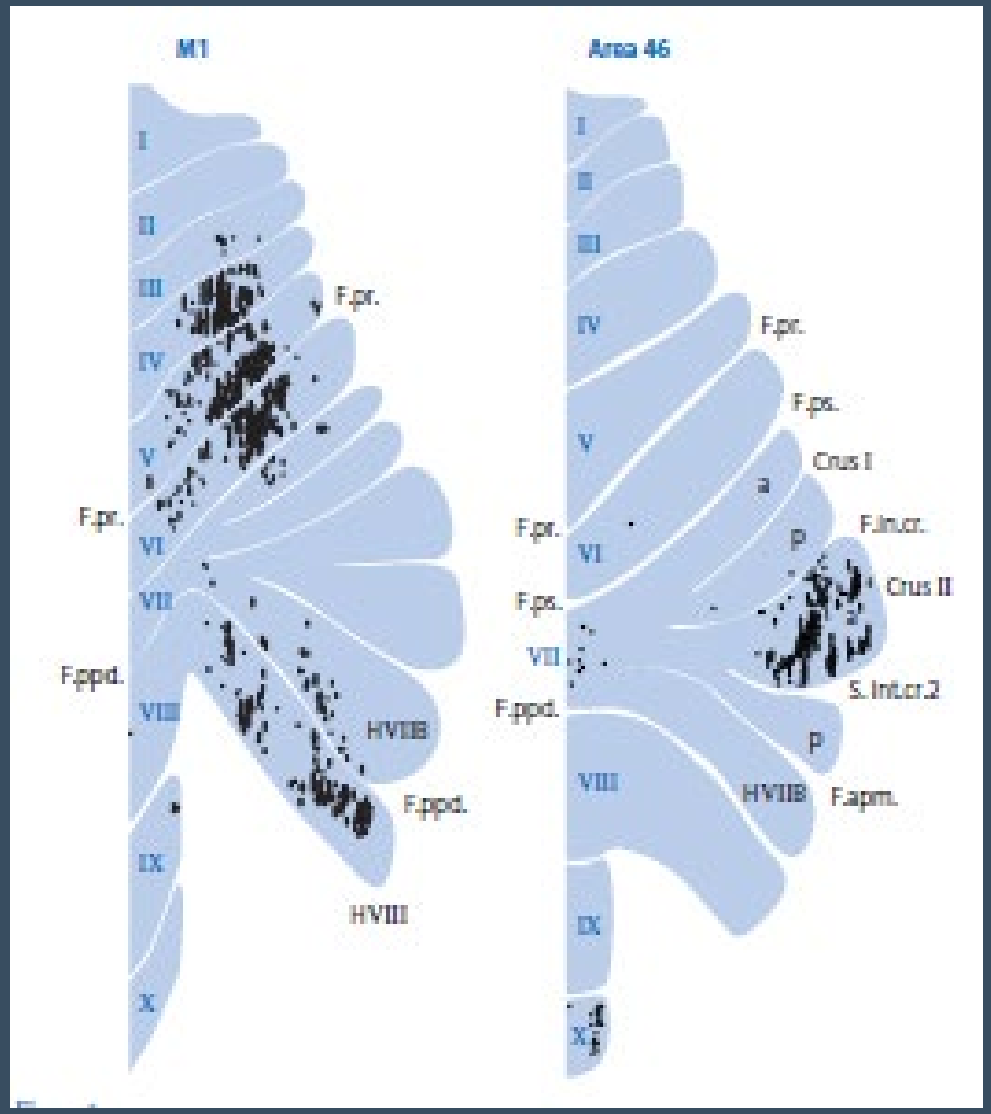
Dentate n.

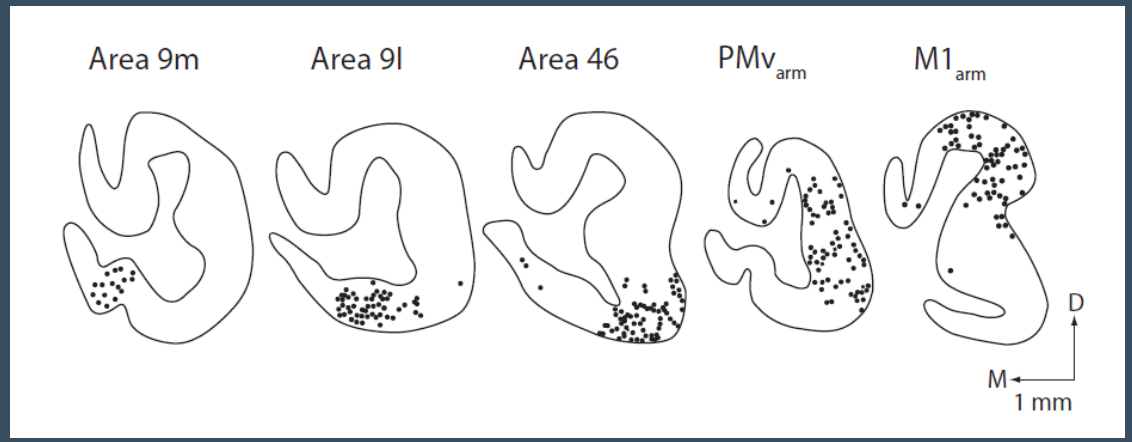
Anatomical Connectivity



Bostan, Dum, Strick, Trends Cog Sci, 2013; 17(5):241-54

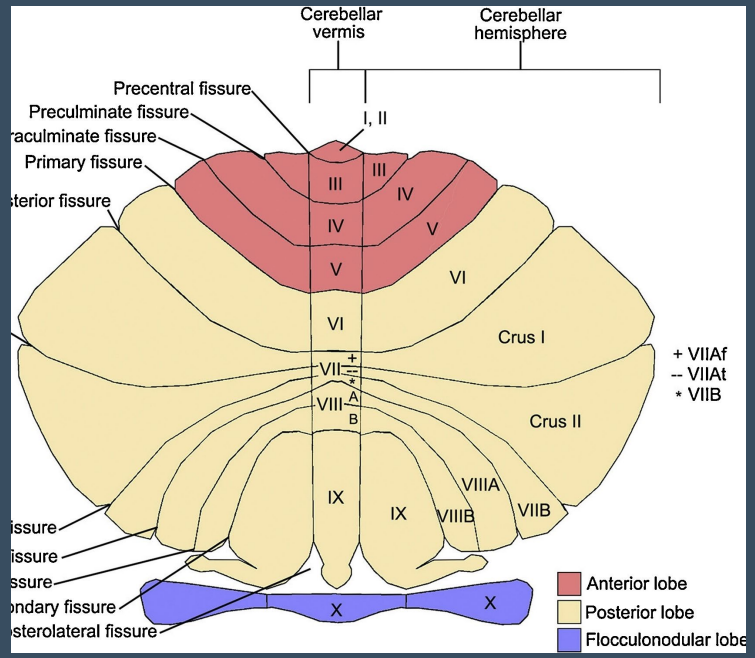
Anatomical Connectivity

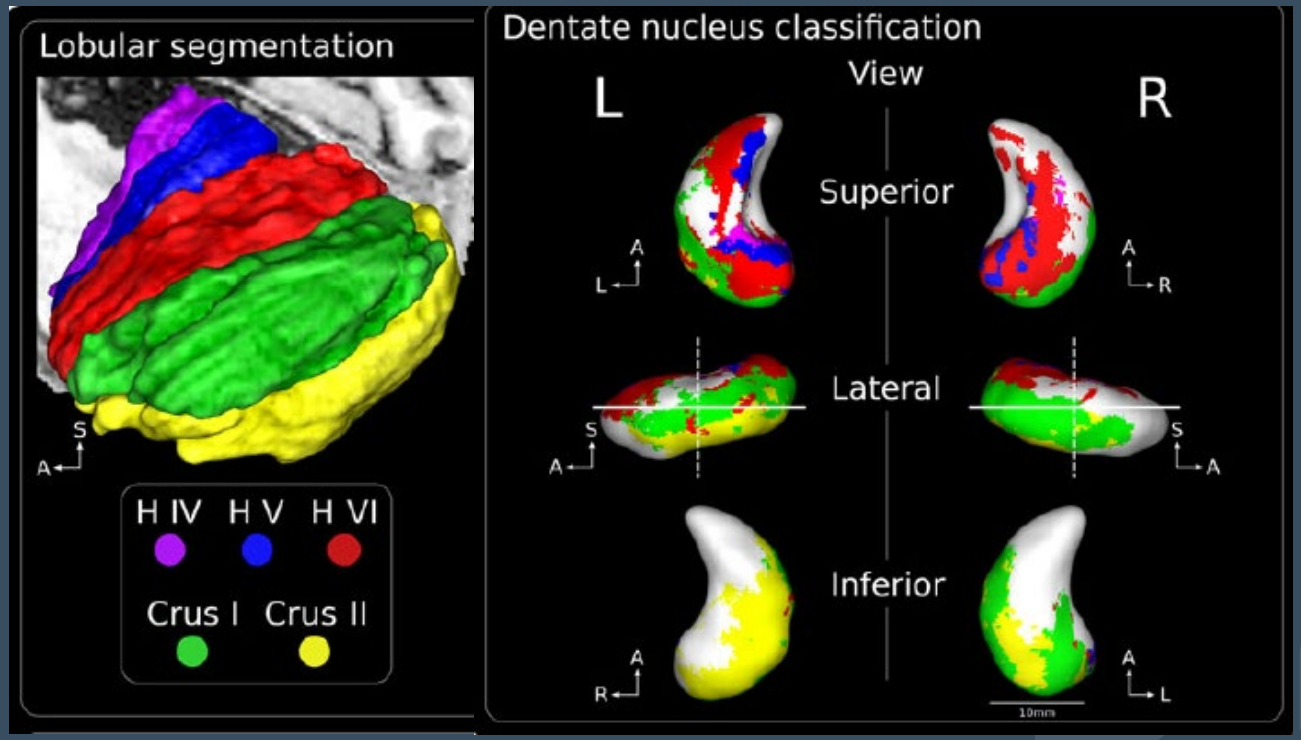




Strick, Dum, Fiez. Annu. Rev. Neurosci. 2009; 32:413–34

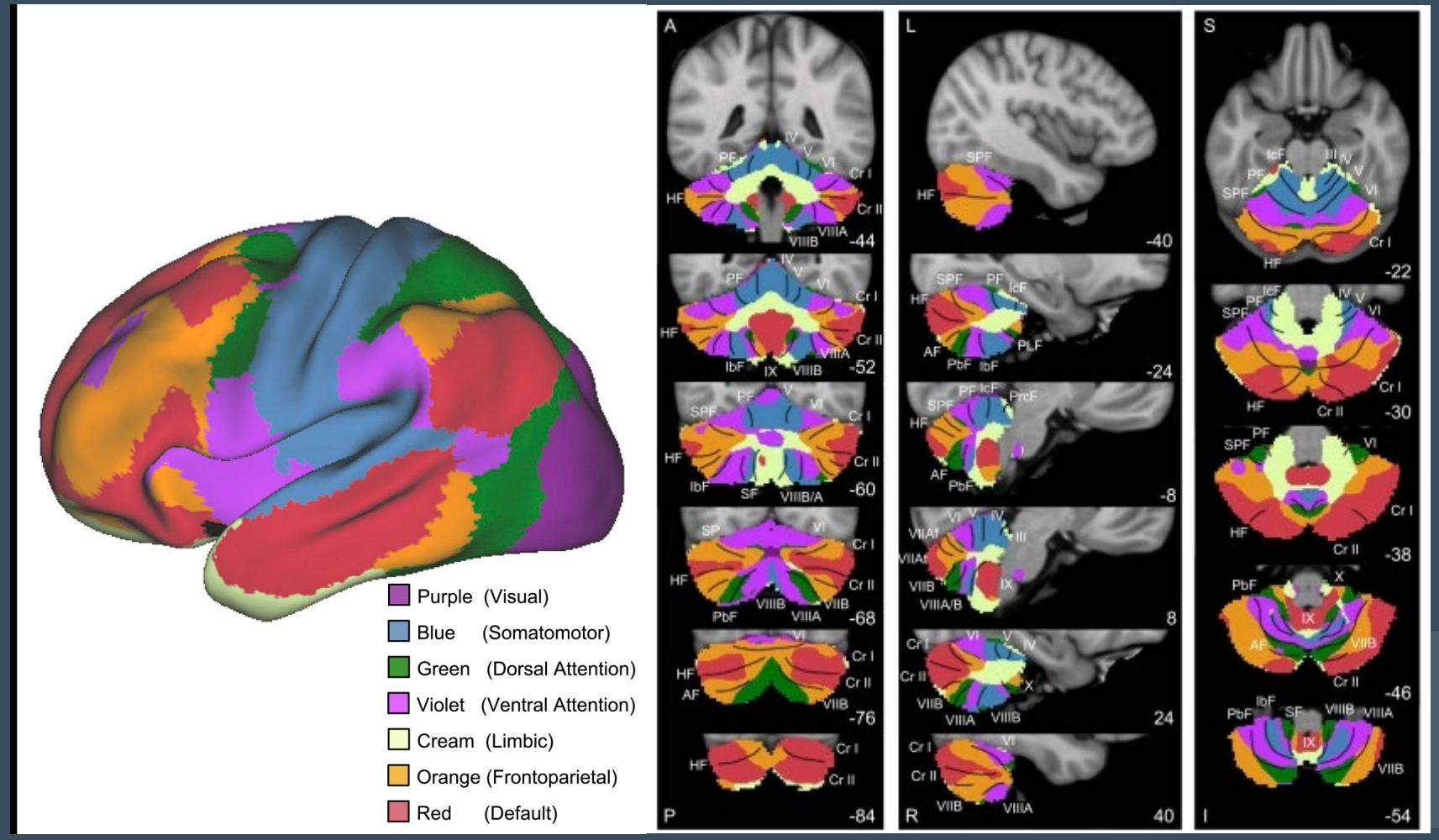
Anatomical Connectivity





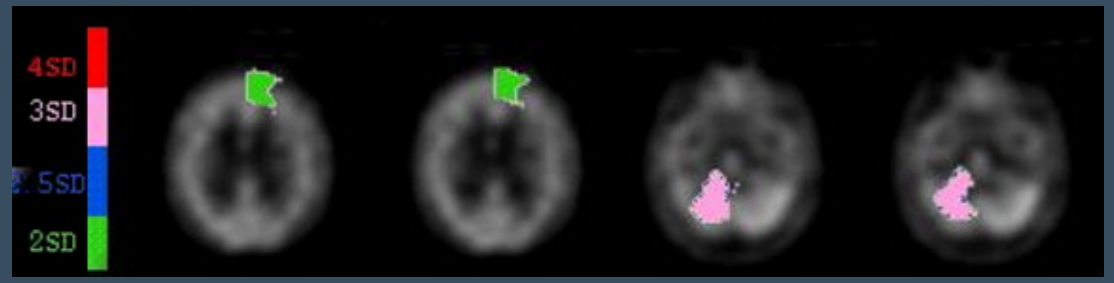
Steele et al, *Cerebral Cortex*,, 2017; 27(9),:4537–4548

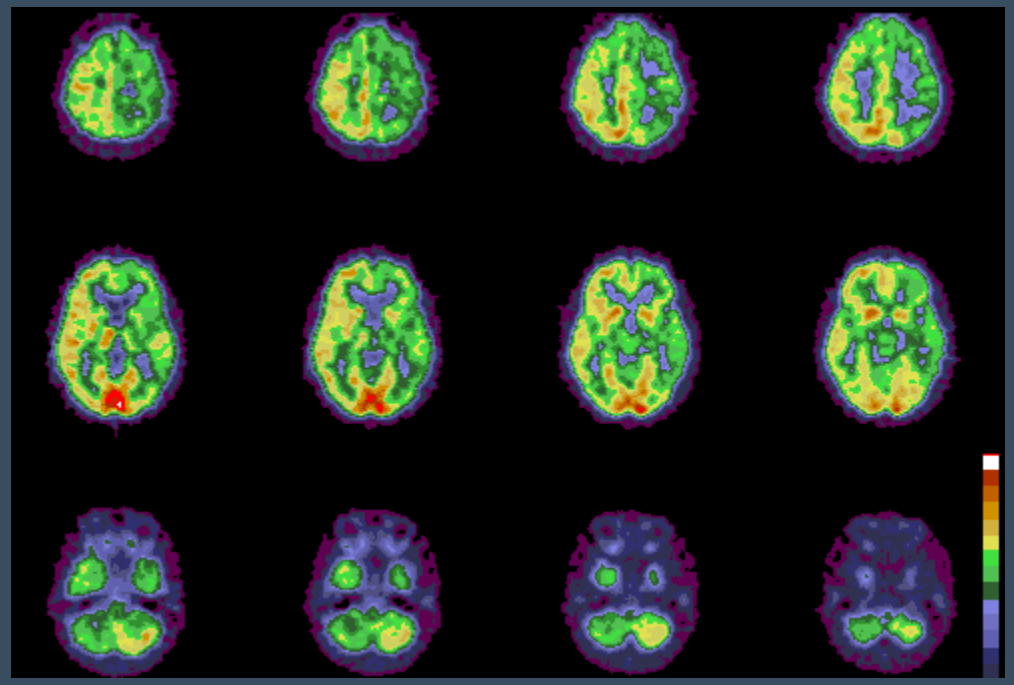
Functional Connectivity

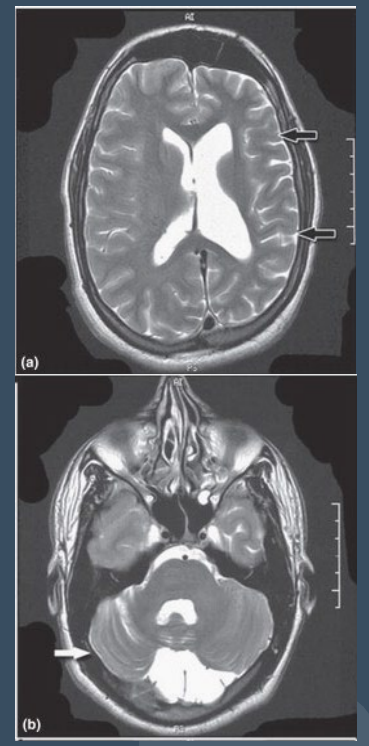


Buckner, RL. Neuron, 2013; 80:807-815

Crossed Cerebellar Diaschisis

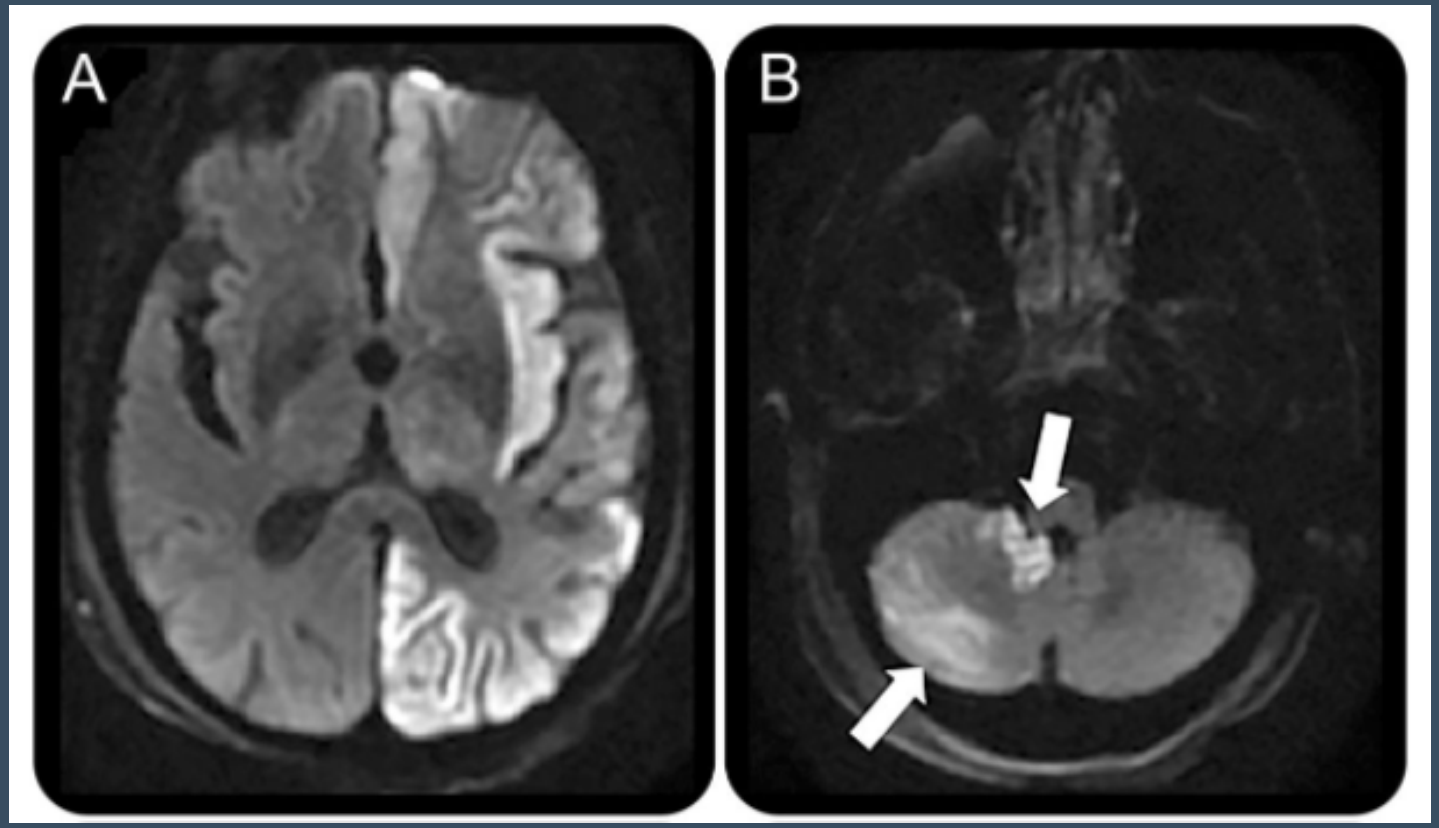






Marien et al., 1996, Marien et al., 2009; Baradaran et al, 2016; Roarke & Dedashti, http://gamma.wustl.edu/pt006te117.html

Crossed Cerebellar Diaschisis



Baradaran, Omran, and Chazen, Neurology, 2016, 86 (14) e154-e155

The cerebellum contains what proportion of the brain's total neurons?

5-10%

40-50%

20-30%

60-80%

Section 2: What does the cerebellum do?

- Anatomical Connectivity ✓
- Functional Connectivity ✓
- Function?

Classic Motor Symptoms

- Ataxia
- Dysmetria
- Dysdiadochokinesia
- Nystagmus
- Dysarthria

Cerebellum's Role in Motor Function

Coordination of Movement

- regulates the rate, rhythm, force, and accuracy of movements
- Automatically, and without awareness

Requires an internal model of the environment that integrates:

1. current state information (sensory input from arm)
2. Information about motor commands (reaching movement)

Allows for fine tuning ongoing activity

Temporal Control Theory

Cerebellum coordinates movement timing:

Dysmetria and dysdiadochkinesia attributed to impaired ability to time activation of antagonist muscles

Dysarthria – impaired temporal coordination of muscular events involved in articulation

- Cerebellar output precedes activity in motor cortex
- Cerebellocortical signal contains explicit timing information
- Electrophysiological rhythms/oscillatory activity predicts movement accuracy

Keele & Ivry, 1991; Sasaki, 1984; Dichgans, 1984)

Motor Learning Theory

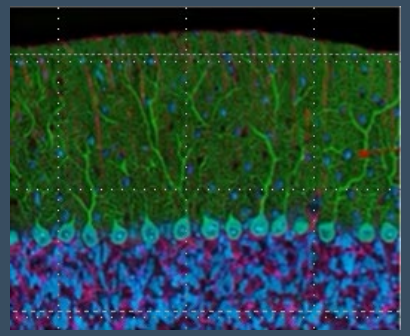
Cerebellum is an error-monitoring system to promote learning:

Ataxia/dysmetria due to absence of sensorimotor error correction

- Motor adaptation & skill learning - (e.g., prism studies, gait development)
- Classical conditioning – stimulus-response learning through association (eye blink conditioning)
- Sensorimotor error signals produce long-term depression (reduced firing) in cerebellar cortex (similar to the hippocampus)
- Precise patterns of spiking activity in cortex associated with rate of motor learning

Translation to Cognitive Function

Dysmetria of thought – regulates the speed, consistency, capacity, and appropriateness of mental or cognitive processes.



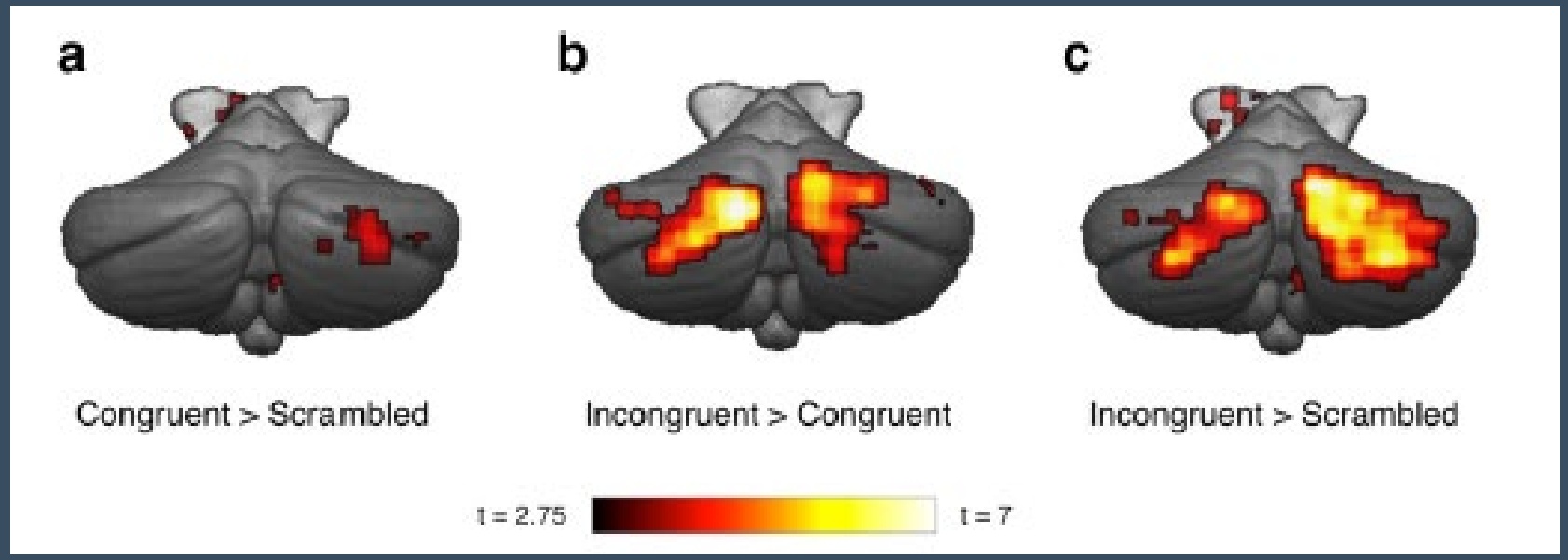
Homogeneous architecture = every area of the cerebellum does the same thing
Universal Cerebellar Transform (UTC)

The connections of each region determine functional domain to which the UCT is applied – spinal, motor, association, language, etc

Schmahmann JD. *Neurosci Lett.* 2019; 688:62-75.

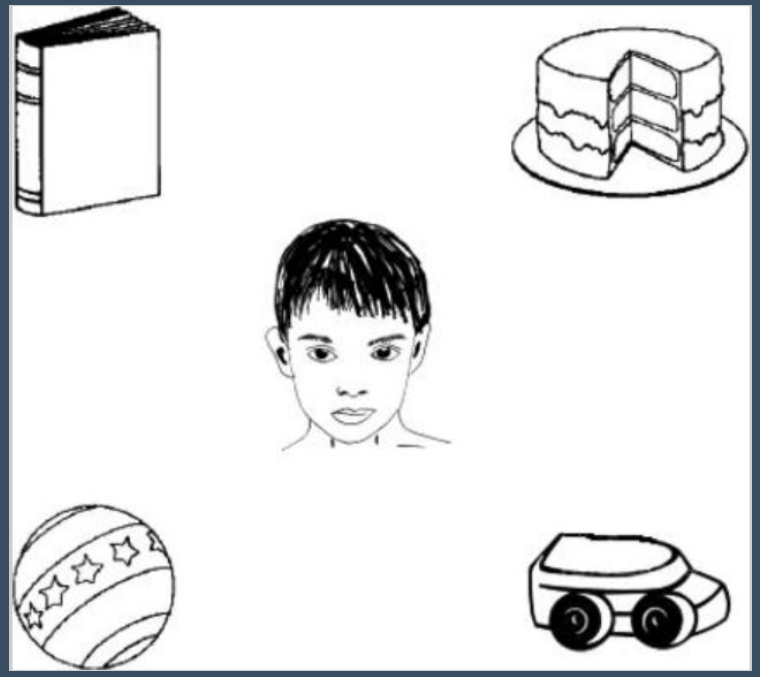
Non-motor Internal Models

Congruent: Two plus two is … *four.*
Incongruent: The water had frozen to … cars.
Scrambled: Fast in clock … plane.



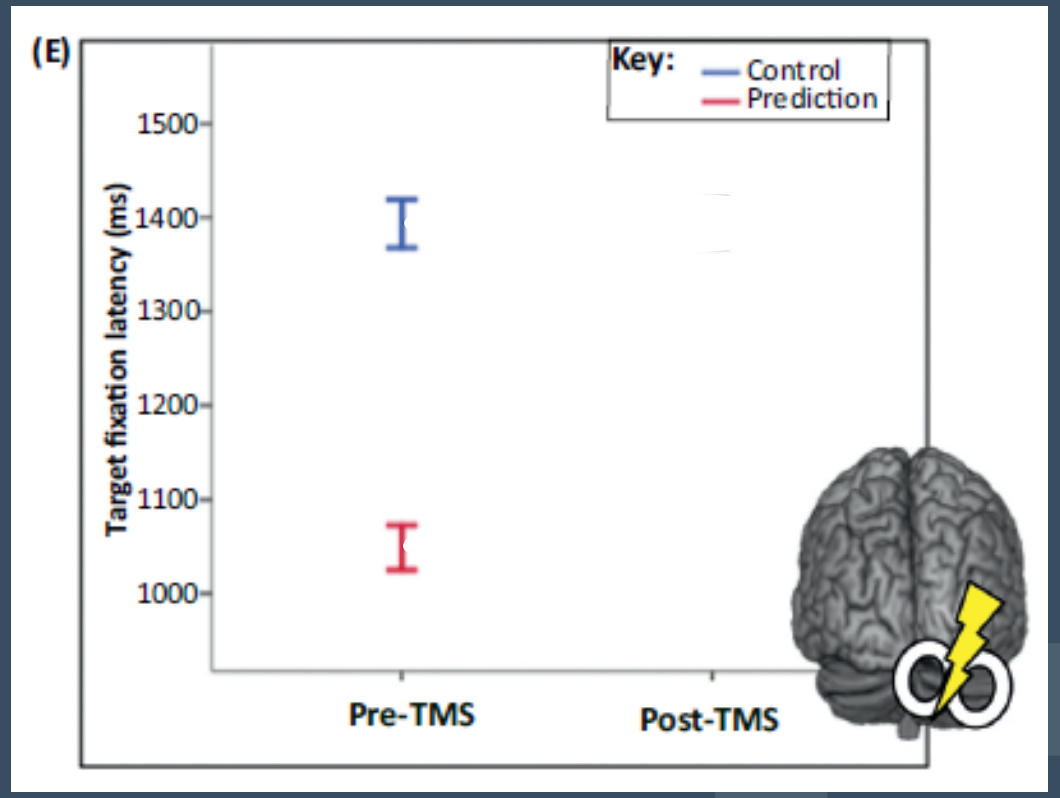
Moberget et al., 2014 *J Neurosci*, 34, 2871-78

Non-motor Internal Models



Predictive: “The boy will <u>eat</u> the cake”

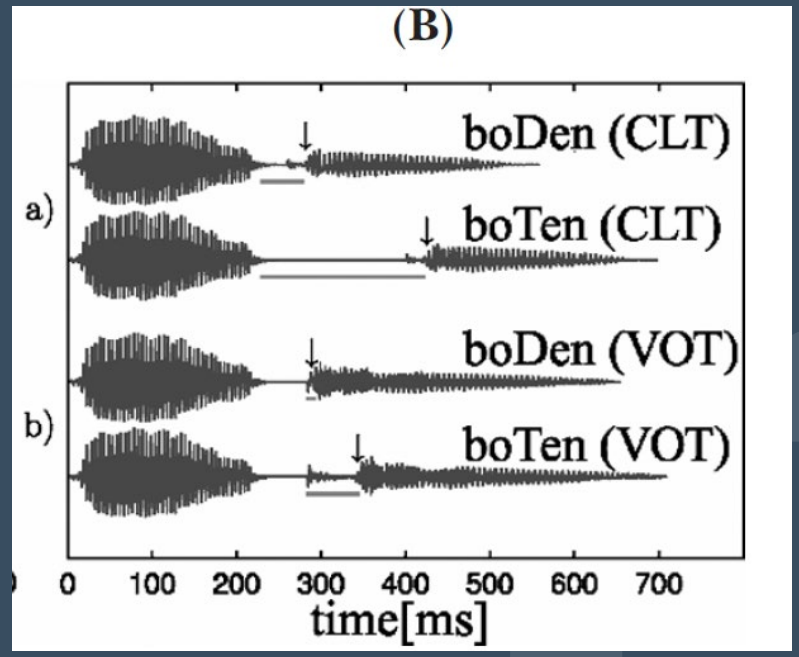
Control: “The boy will <u>move</u> the cake”



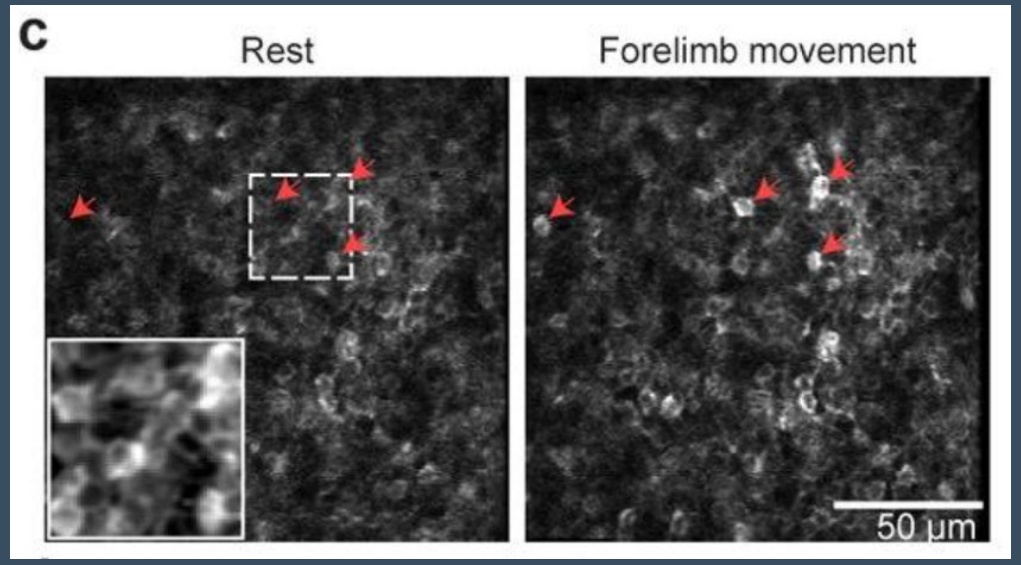
rTMS (Lesage et al., 2012)
tDCS (Miall et al., 2016)

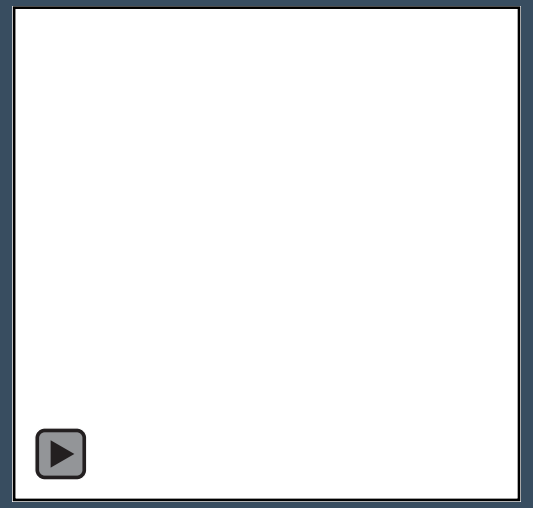
Cognitive Timing

- Pts are impaired in judging relative duration of time intervals (Casini, 1999; Ivry, 1989; Mangels, 1998)
- Impaired at judging the velocity of moving visual stimuli (Grill, 1994; Ivry, 1991; Nawrot, 1995)
- Speech perception
  - Intact discrimination of voice onset times or vowel durations (Ackermann, 1997; Ivry, 1992).
  - When other acoustical cues during phonological encoding are controlled, discrimination of two spoken words differing in durational parameters is severely impaired in pts w/ diffuse atrophy (Ackermann, 1997)



Non-motor Learning

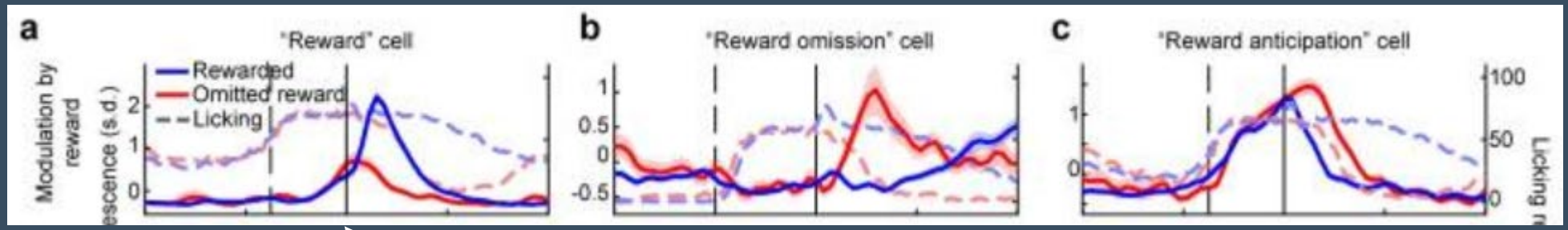




in vivo two-photon microscopy images of cerebellar granule cells at rest and during a forelimb movement

Wagner MJ et al, Nature. 2017; 544(7648):96-100

Non-motor Learning



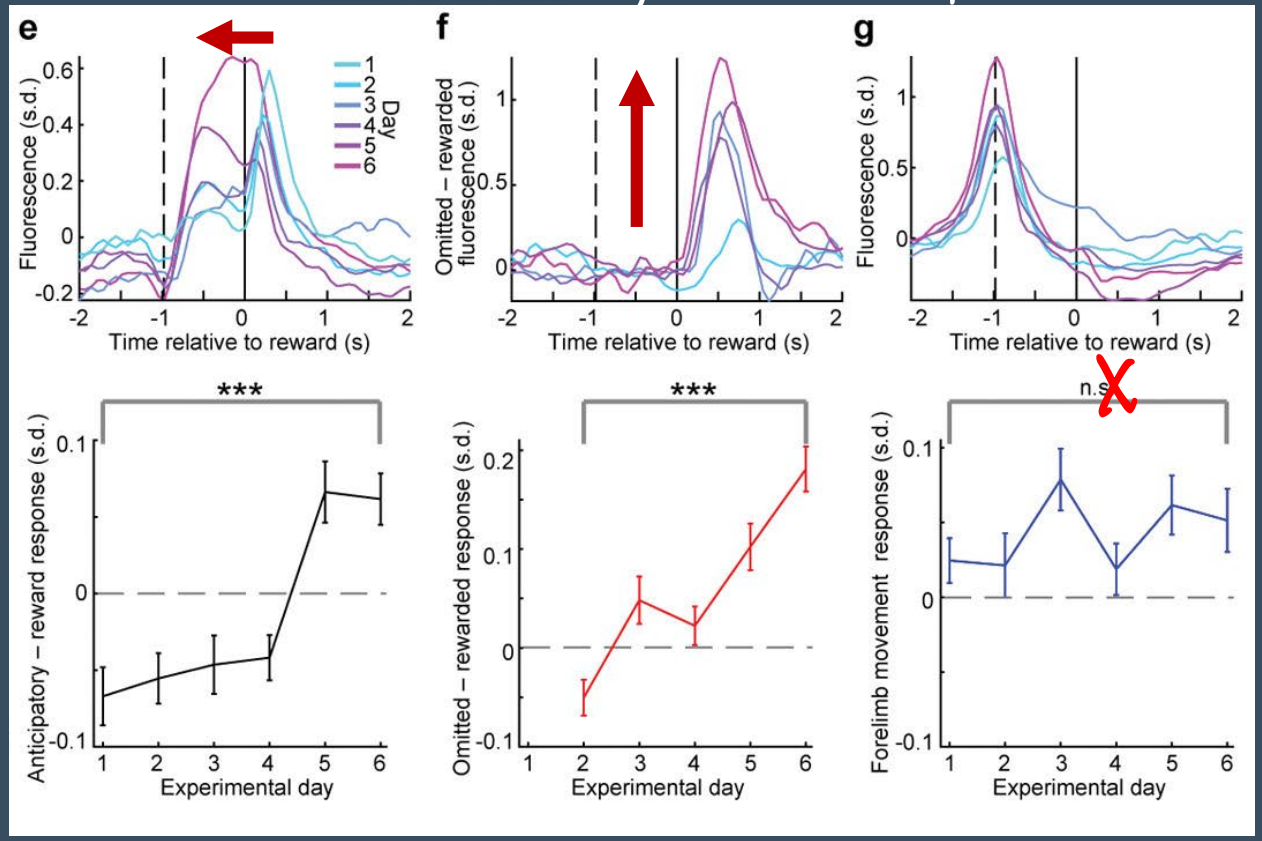
Lever press

Sugar water

Wagner MJ et al, Nature. 2017; 544(7648):96-100

Non-motor Learning

Prediction Error signal Lever press



Wagner MJ et al, Nature. 2017; 544(7648):96-100

The cerebellum constitutes what percentage of the brain's total weight?

10%

40%

25%

60%

Section 3: Neuropsychological Deficits

- Connectivity ✓
- Functional Role ✓
- Clinical Manifestations

Case #1

35 year-old, right-handed, single Caucasian male

ED: Graduated from high school and joined Army as flight engineer – helicopter repair; some college coursework during military

PMHx: No history of chronic diseases or psychiatric illnesses

Substances: Denied history of drug or alcohol abuse – smokes pack of cigarettes per day since the age of 12

Presenting Problem

GSW on active duty - entrance approximately 2 cm anterior to right tragus, which traversed right temporal, mastoid, and posterior fossa, and had a right suboccipital exit

Right suboccipital/craniectomy/debridement/ resection of the lateral third of the cerebellum performed the day after the injury

NP testing 9 weeks post-injury
Mild ataxia R>L

NP Results

WAIS-III			SS
	Similarities		10
	Arithmetic		9
	Information		12
	LNS		9
	Block Design		11
	Picture arrangement		9
	Matrix Reasoning		15
	Symbol Search		5
WMS-R			Percentile
	Digit Span		32
	Forward	longest = 7	81
	Backward	longest = 3	3
	Spatial Span Forward		46
	Spatial Span Backward		75
	LM I		52
	LM II		67
	Verbal Paired Assoc I		71
	Verbal Paired Assoc II		73
	Visual Paired Assoc I		66
	Visual Paired Assoc II		67

CVLT-II			Z-score
	Trial 1	5	-1
	Trial 5	10	-1
	Trial B	4	-1
	Long Delay Free Recall	8	-1
	Recognition Hits	11	-3
	False Positives	1	-0.5
Language			Percentile
	COWAT	7,3,5 10 err	3
	Animals	10, 1 err	3
	Supermarket	15, 2 err	7
	BNT	30/30	>75
	WRAT Reading		73
	WRAT Spelling		32
SDMT oral			3

Stroop			
	Word Reading		1
	Color Naming	1 err	1
	Color Word	2 err	2
	Interference		70
Trails			
	Part A	0 err	1
	Part B	0 err	2
WCST			
	Categories	6	16
	Perseverative Responses	4	99

Speech: Dysarthric, slow, and monotone
Behavior and affect: unremarkable

Case #2

77 year-old, right-handed, married Caucasian male

ED: 13 yrs

Occupation: Retired heavy equipment operator

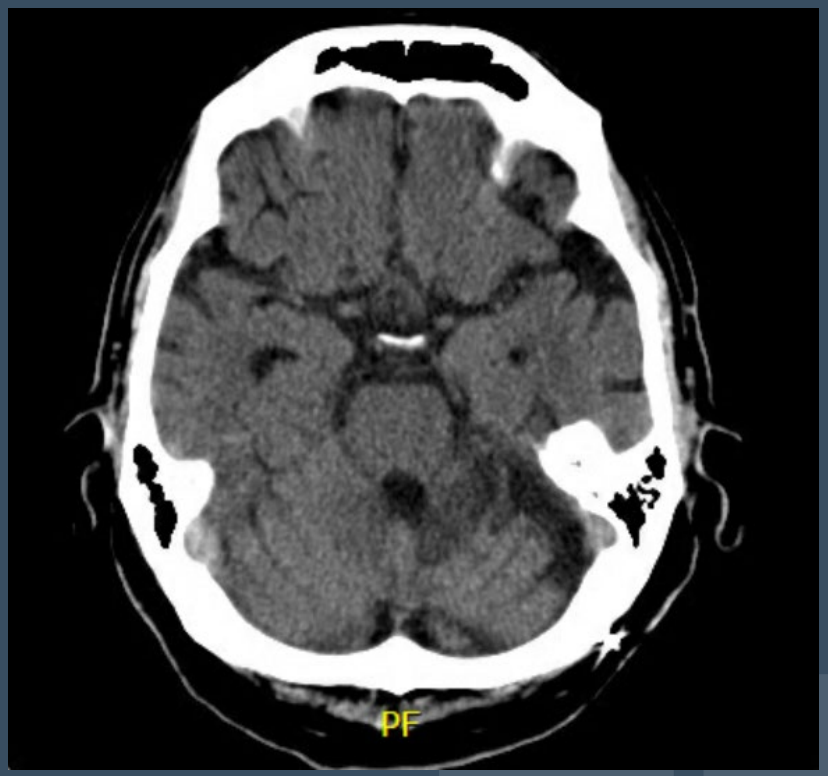
PMHx: HTN, Hyperlipidemia, DM, CAD, diverticulosis, ET

Substances: 8 mini cigars/day, occasional scotch

Presenting Problem

2006 – Right VIM DBS surgery for ET

- 2-weeks postop complaints of dizziness
- Mild L>R ataxia, RAM
- Right gaze horizontal nystagmus
- CT showed left SCA territory infarct
- Tremor resolved, DBS never turned on



2012 – referred for NP d/t subj cognitive decline – trouble remembering names, delays to retrieve known information

NP Results

				2006			2012
WASI			Raw			Raw	
	Vocabulary	T		51			
	Similarities	T		64			50
	Block Design	T		59			57
	Matrix Reasoning	T		62			67
WRAT Reading		Std		105			102
BNT							
	Total	SS	54	10		52	10
	Phonemic correct					3	
COWA		SS	35	9		17	5
Semantic (Anim, Fruits, Veg)			33	7		17	3
JOLO		SS		16			11
SDMT Oral		Std		101			85
WMS-III							
	LM1	SS		10			12
	LM2	SS		10			12
	Digit Span	SS		11			11
	LNS	SS		12			12

				2006			2012
			Raw			Raw	
RAVLT							
	T1	SS	6	12		4	9
	Total	SS	47			37	
	List B	SS	3	9		3	9
	T6	SS	11	13		9	12
	Delay	SS	13	15		7	11
	Recognition	SS	15	13		14	12
DKEFS Color-Word						Err	
	Color	SS				2	11
	Word	SS				2	9
	Color-word	SS				10	9
	Switching	SS					
WCST							
	Categories	%	6	>16		1	>16
	Persev Errors	Std				10	141
BDI-II				7			10
BAI				17			10

Behavior and affect: unremarkable

Case #3

45 year old, right-handed, married female

ED: 18 yrs

Occupation: Teacher, terminated 1 year prior

PMHx: Hyperlipidemia, hypothyroidism, OSA, migraine, depression

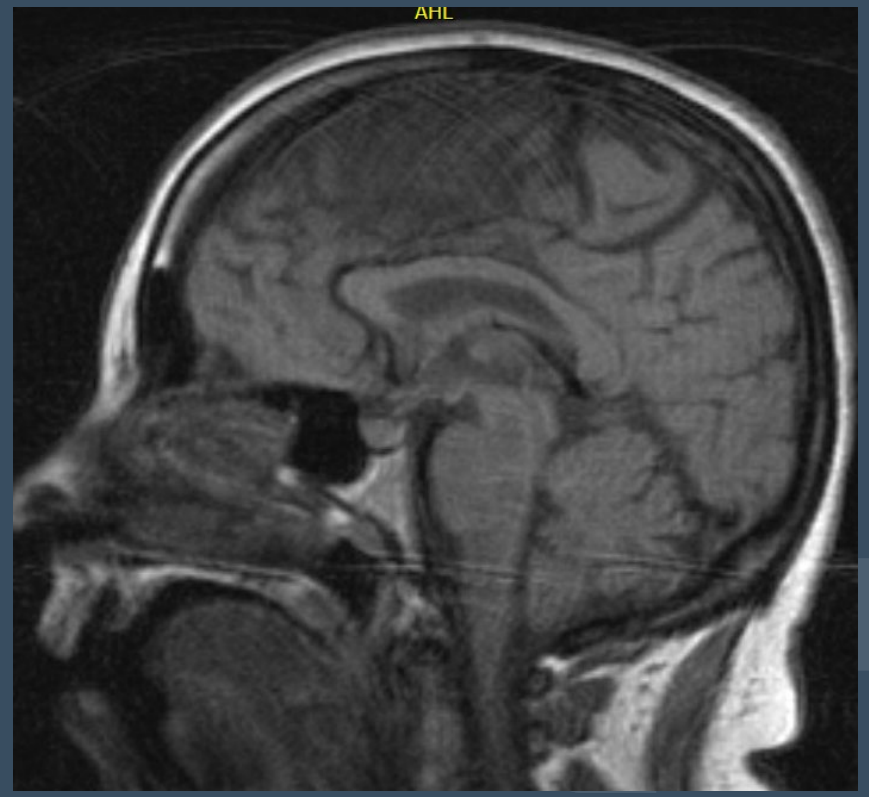
Substances: denied

Presenting Problem

Initial sx: slowed speech 10 years ago

Current: severe dysarthria, psuedobulbar affect (improved on Neudexta), nystagmus, moderate to severe dysmetria, dysdiadochokinesia, ataxic gait, urinary incontinence

Cognitive complaints: slow SOP, poor organization, distractible, wfd



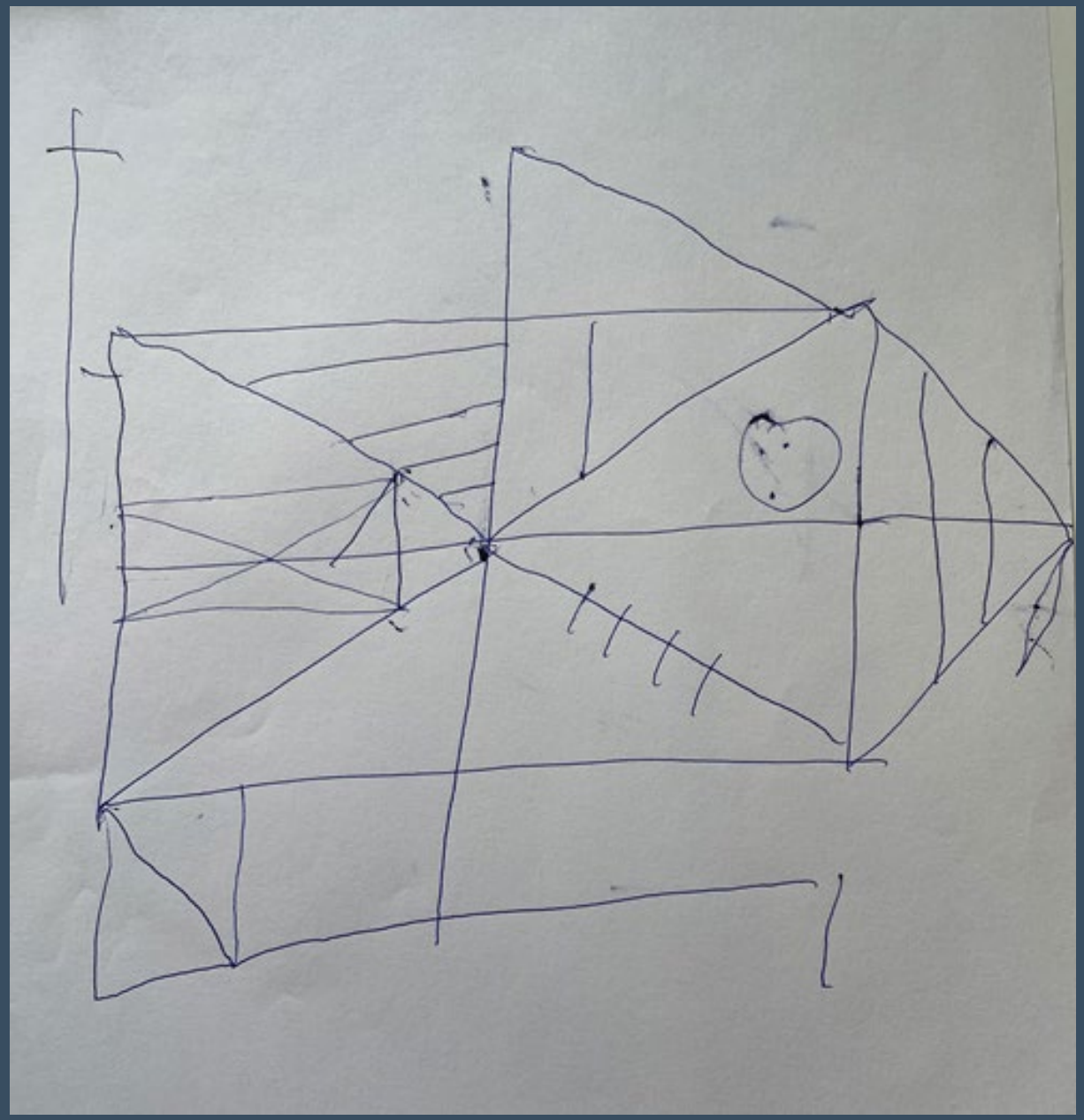
NP results

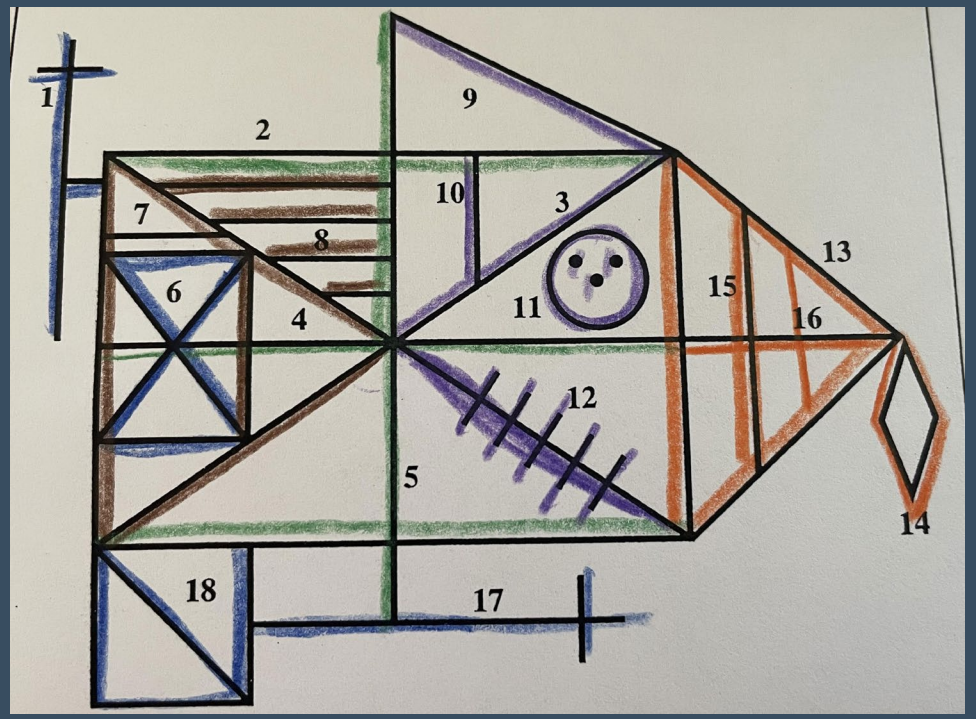
WAIS-IV		Raw	SS
	Vocabulary		9
	Similarities		8
	Matrix Reasoning		8
	Digit Span		8
	Forward		9
	Backward		7
	Sequencing		11
	Symbol Search		4
	Coding		5
			Std
WRAT Reading			105
BNT			
	Total	43	57
	Phonemic correct	5	
			%ile
Rey-O copy		29.5	<1

Grooved Pegs			Std
	Dom	143	45
	Nondom	189	42
			SS
WMS-IV	LM1		5
	LM2		6
	VR1		11
	VR2		9
	VR Copy		>75 (%)
			Z
CVLT-III	T1	5	-1
	Total	41	40 (T)
	List B	6	0
	SDFR	7	-1.5
	LDFR	7	-2
	Recognition d'		-2

			Std
Trails	Part A	48	73
	Part B	96	76
			%ile
WCST	Categories	3	6-10
	Persev Errors	41	<1
	LOS	2	6-10
BDI-II		12	
BAI		16	

- “Surprised” affect
- Appropriate interpersonal interaction





1 2 3 4 5

NP results

WAIS-IV		Raw	SS
	Vocabulary		9
	Similarities		8
	Matrix Reasoning		8
	Digit Span		8
	Forward		9
	Backward		7
	Sequencing		11
	Symbol Search		4
	Coding		5
			Std
WRAT Reading			105
BNT			
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Grooved Pegs			Std
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	VR2		9
	VR Copy		>75 (%)
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CVLT-III	T1	5	-1
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	Persev Errors	41	<1
	LOS	2	6-10
BDI-II		12	
BAI		16	

- “Surprised” affect
- Appropriate interpersonal interaction

In the beginning…

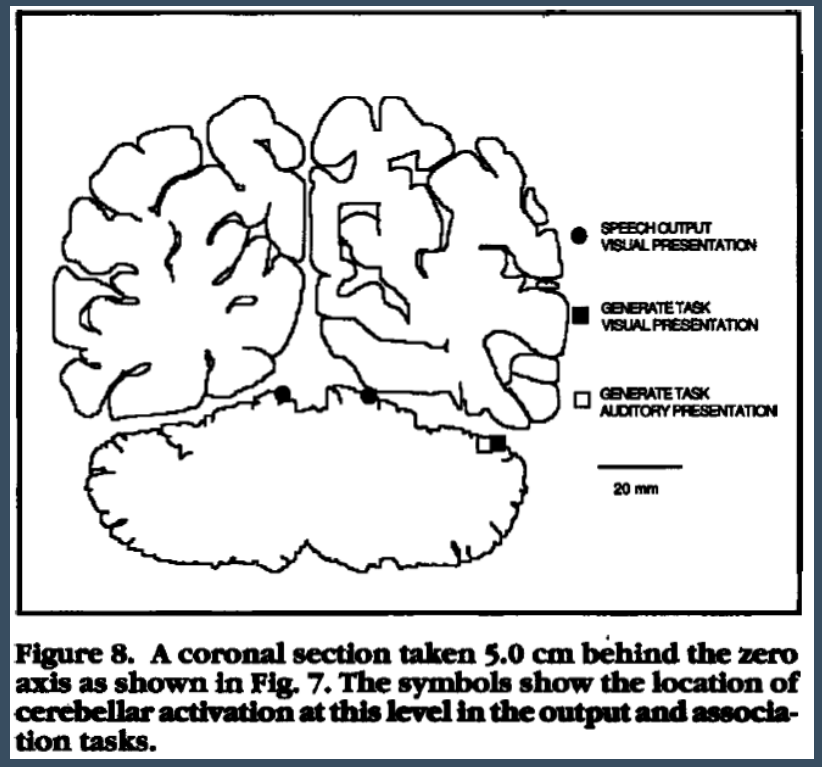


Figure 8. A coronal section taken 5.0 cm behind the zero axis as shown in Fig. 7. The symbols show the location of cerebellar activation at this level in the output and association tasks.

Petersen et al., JoCN, 1989; 1: 153–170.

Case reports and case series began to emerge

- Language deficits unrelated to speech
- Variable data for executive function, working memory, visuospatial abilities

Confounding factors

- Motor contributions?
- Cerebellar+ damage?
- Acute vs chronic recovery stage
  - Deficits resolved on retest

Cerebellar Cognitive Affective Syndrome

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

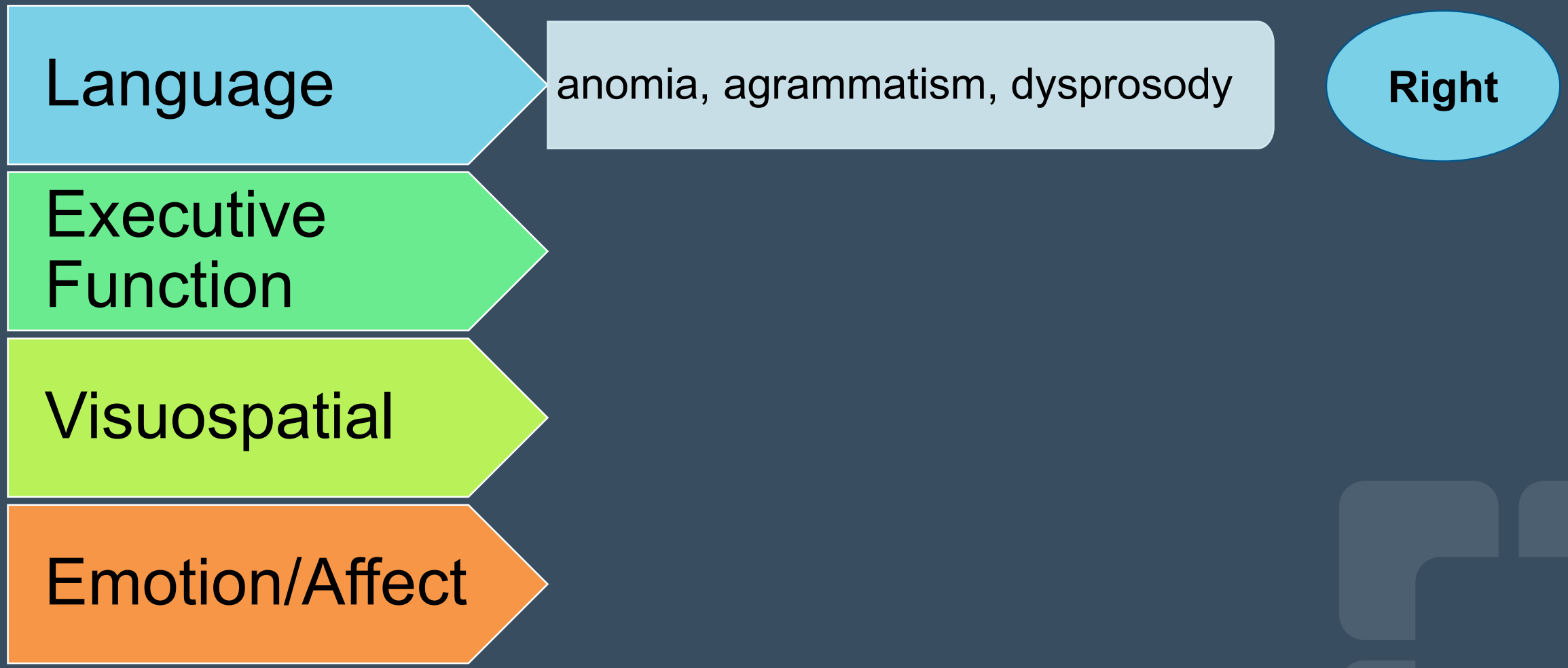
AICA = anterior inferior cerebellar artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery.

Ataxic patients between 1989-97

Excluded age > 75; other MRI abnormality; pre-existing neurological or psychiatric diagnoses; systemic disease; psychoactive/sedating meds; non-cerebellar findings on neuroexam

Schmahmann & Sherman, Brain, 1998; 121:561-79

Cerebellar Cognitive Affective Syndrome



Schmahmann JD. *Neurosci Lett.* 2019; 688:62-75.

Subacute Right Hemisphere

BNT ✓
Reading ✓
Spelling ✓

Verb Generation ✗

Mild dysarthria

Chronic Left SCA

BNT ✓
Reading ✓

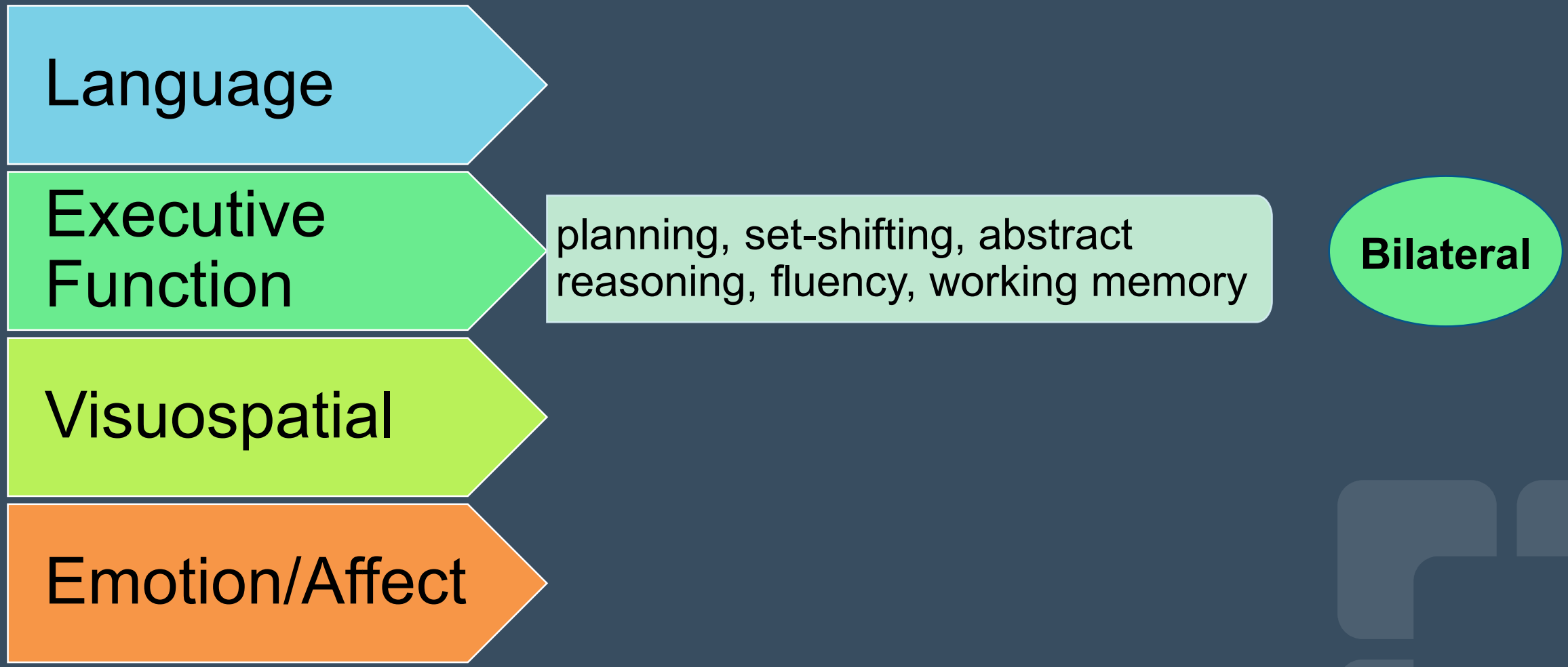
Minimal dysarthria

Progressive Diffuse

BNT ✗
Reading ✓
Vocabulary ✓

Severe dysarthria

Cerebellar Cognitive Affective Syndrome



Schmahmann JD. *Neurosci Lett.* 2019; 688:62-75.

Subacute Right Hemisphere

- Fluency ✗
- Similarities ✓
- Matrix Rs ✓
- Arithmetic ✓
- Digits Back ✗
- Spatial Back ✓
- LNS ✓
- Stroop ✓
- Trails ✓
- WCST ✓

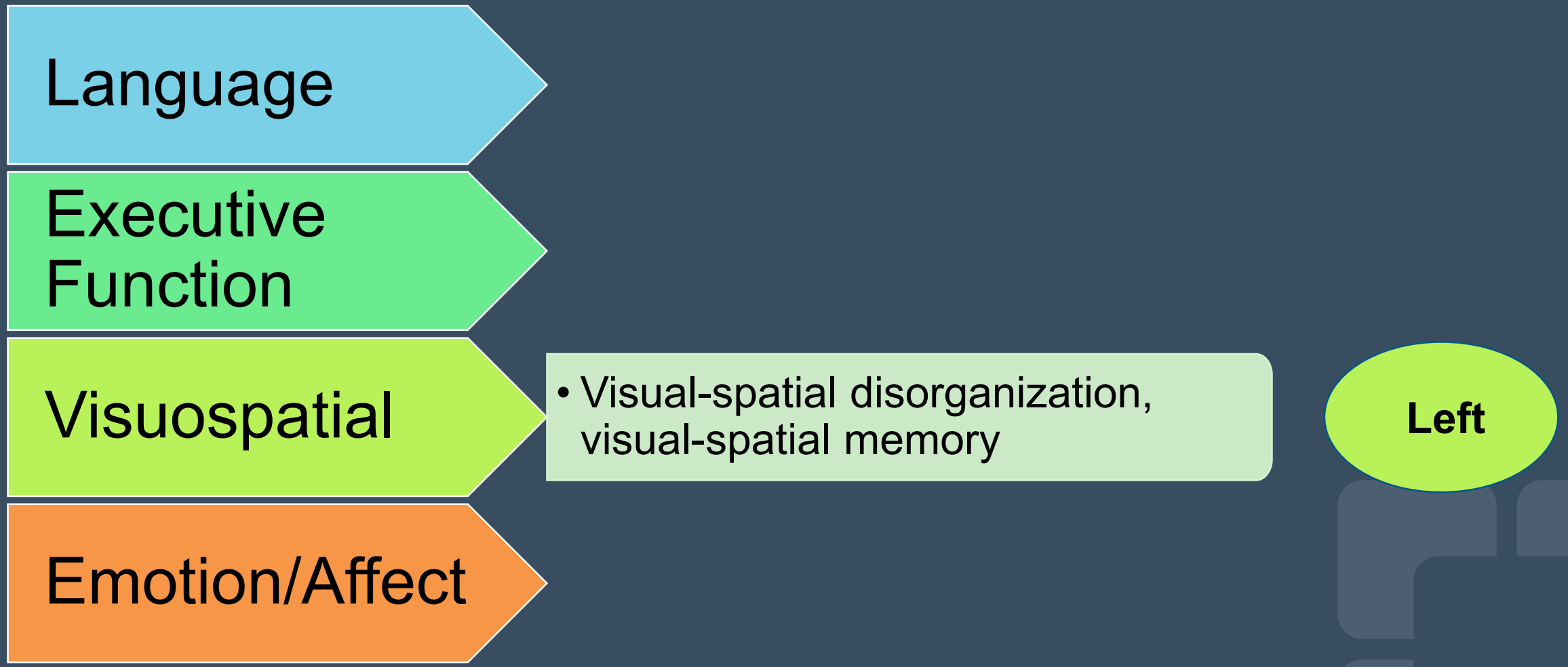
Chronic Left SCA

- Fluency ✗
- Similarities ↓
- Matrix Rs ✓
- Digits Back ✓
- LNS ✓
- Stroop ✗
- WCST ↓

Progressive Diffuse

- Similarities ✓
- Matrix Rs ✓
- Digits Back ✓
- Sequencing ✓
- Trails ✓
- WCST ✗

Cerebellar Cognitive Affective Syndrome



Schmahmann JD. *Neurosci Lett.* 2019; 688:62-75.

Subacute Right Hemisphere

- Block Design ✓
- Picture Arr ✓
- Vis PA I ✓
- Vis PA II ✓

Chronic Left SCA

- Block Design ✓
- JOLO ↓

Progressive Diffuse

- Rey-O copy ✗
- VisReprod I ✓
- VisReprod II ✓
- VR Copy ✓

Cerebellar Cognitive Affective Syndrome

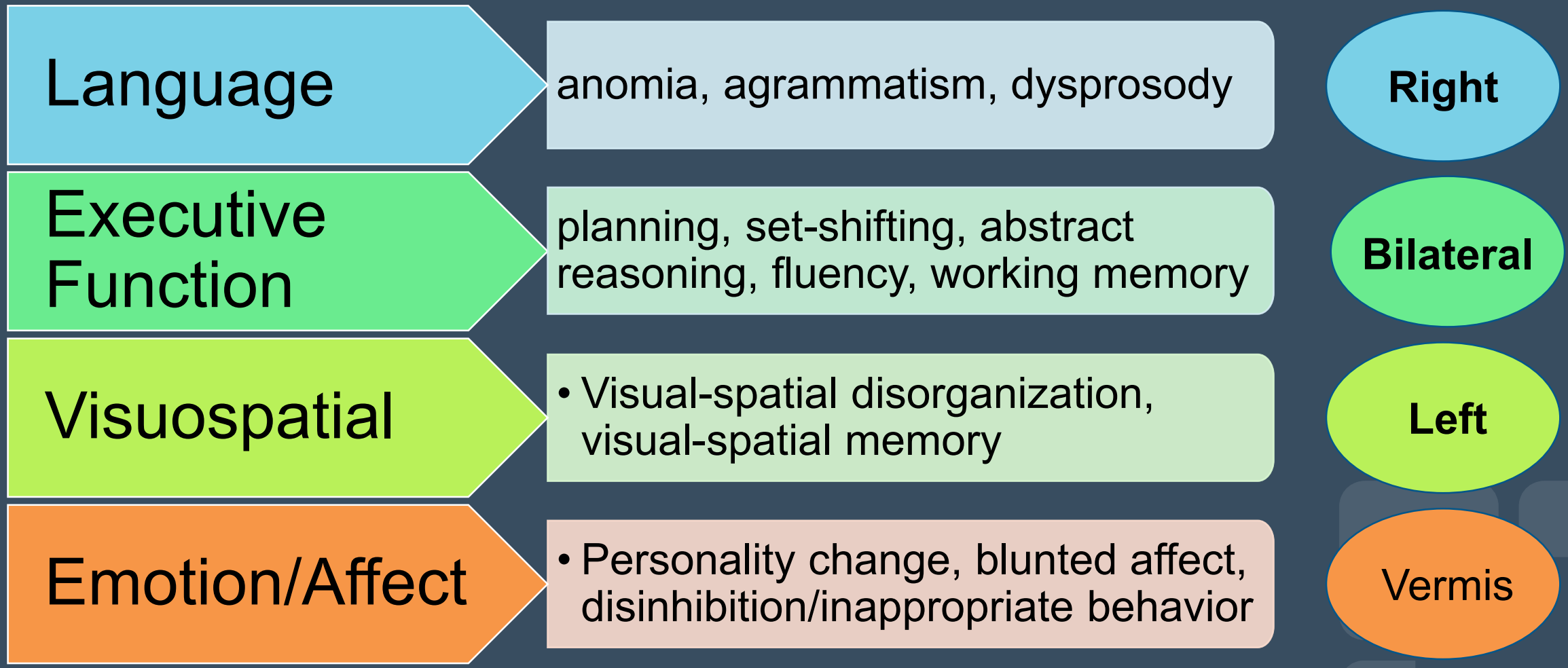
- Language
- Executive Function
- Visuospatial
- Emotion/Affect
  - Personality change, blunted affect, disinhibition/inappropriate behavior

Vermis

Schmahmann JD. *Neurosci Lett.* 2019; 688:62-75.

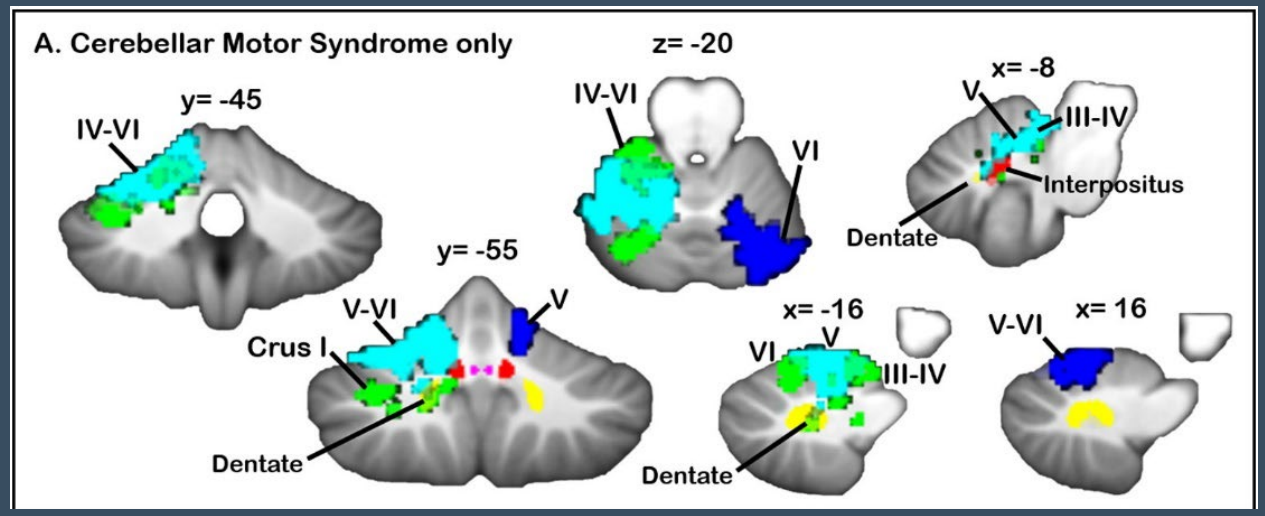
Subacute Right Hemisphere	Chronic Left SCA	Progressive Diffuse
Unremarkable	Unremarkable	Wide-eyed affect Pseudobulbar

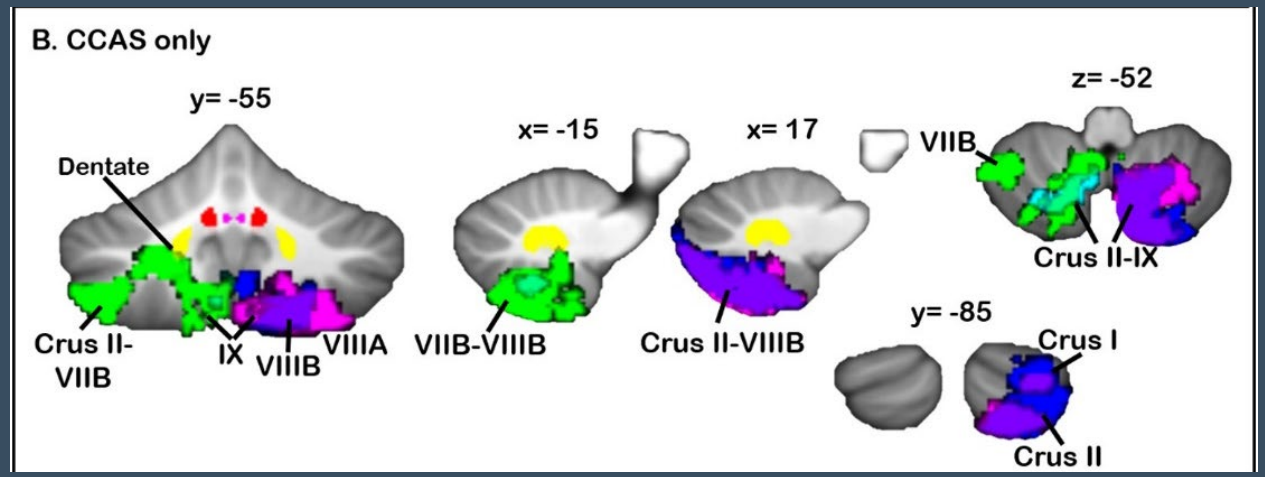
Cerebellar Cognitive Affective Syndrome

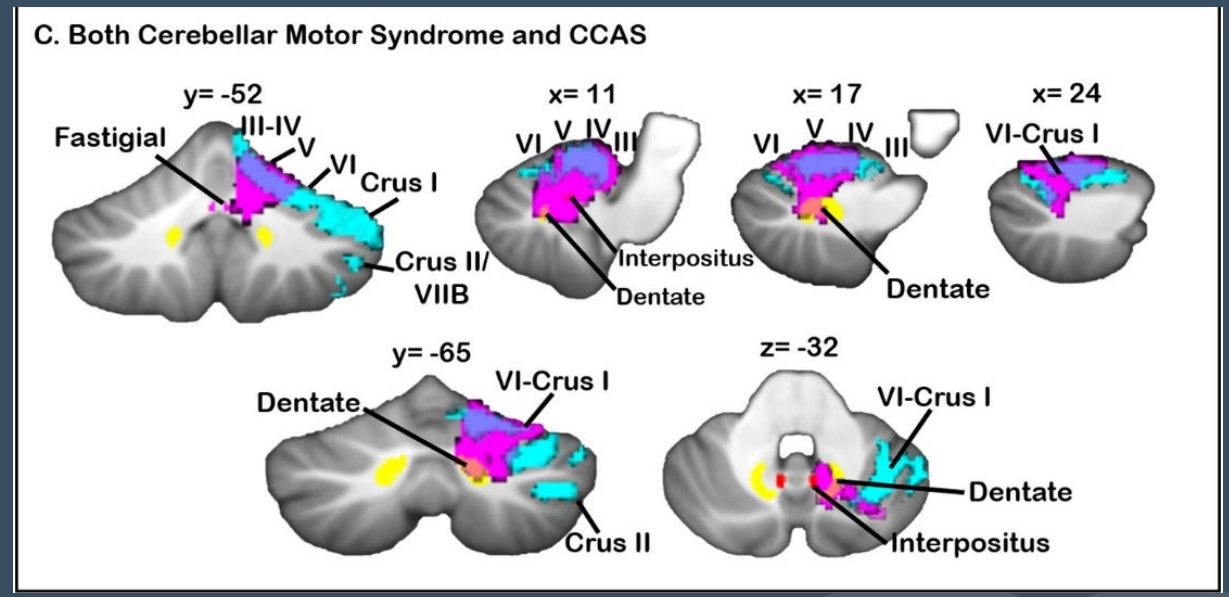


Schmahmann JD. *Neurosci Lett.* 2019; 688:62-75.

Voxel-based Lesion Symptom Maps







Stoodley CJ, et al. Neuroimage Clin. 2016;12:765-775

Language

Visuospatial

Executive

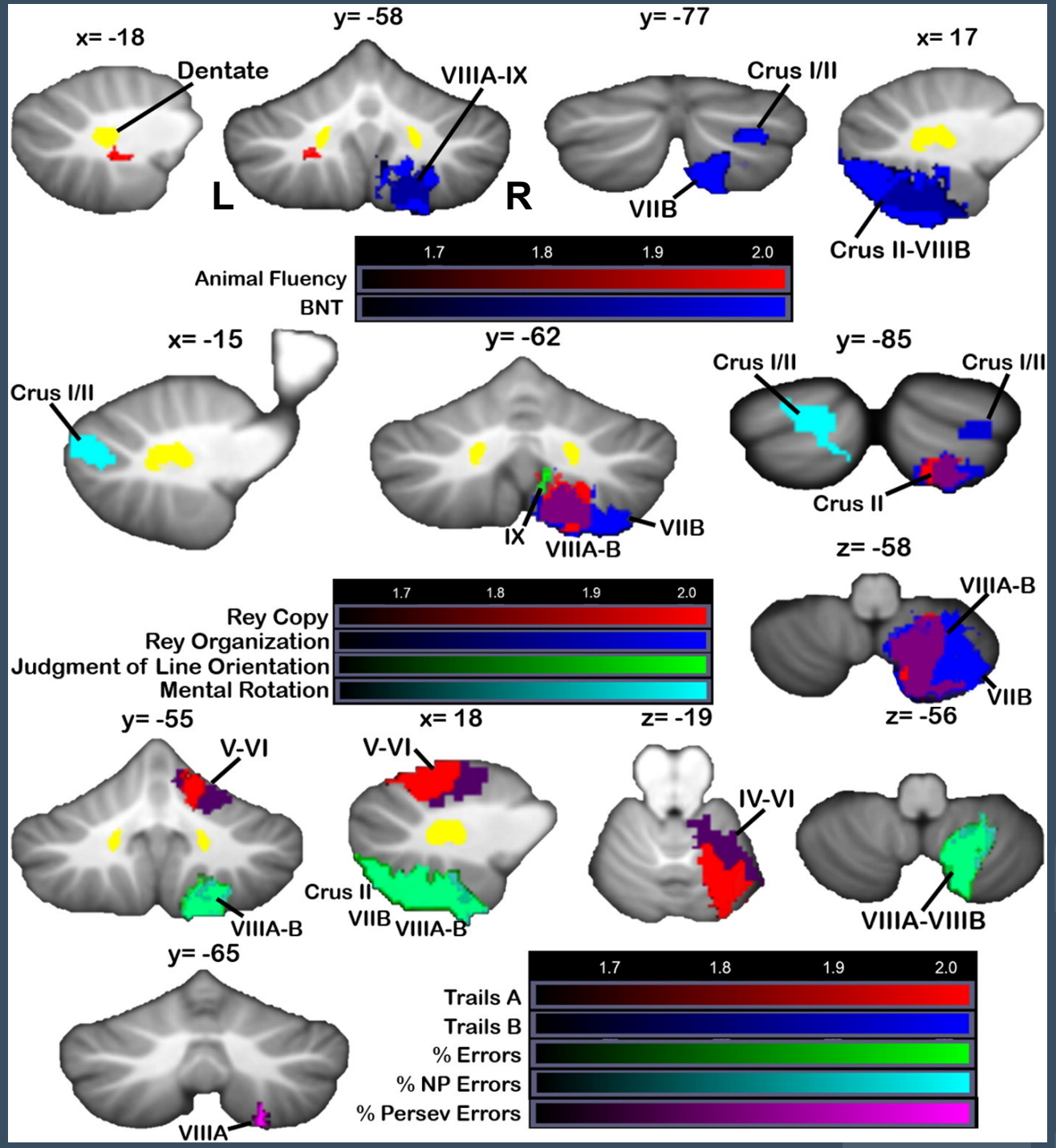


Table 2
Motor and neuropsychological test z-scores. The percent of the sample that showed impaired performance on each measure is noted, with the exception of the Mental Rotation task, for which raw scores are given. This was based on published norms for MICARS, and a z-score of >−1 for other measures.

Category	Task	Mean ± SD	Range	% Impaired
Premorbid IQ	Barona premorbid estimated IQ	0.9 ± 0.4	0.1–1.3	0%
Motor	MICARS ataxia scale	9.1 ± 8.8	0–35	28% minimal impairment; 28% impaired
	Grooved peg board R hand	−1.3 ± 3.6	−15.1–1.4	33%
	Grooved peg board L hand	−1.0 ± 1.4	−4.9–0.7	33%
	Finger tapping R hand	−0.1 ± 1.2	−3.3–1.5	11%
	Finger tapping L hand	0.2 ± 1.4	−2.0–2.9	22%
Wechsler Adult Intelligence Test – 3	Vocabulary	0.5 ± 0.8	−0.7–2	0%
	Similarities	0.2 ± 0.8	−1–2	17%
	Matrix reasoning	0.7 ± 0.7	−0.7–2	0%
	Mean WAIS subtest	0.5 ± 0.6	−1.3–0.6	6%
	Mathematics raw score (spatial quantitative battery)*	61.2 ± 19.2	35–100	N/A
Executive function	Trails A	−0.2 ± 1.4	−4.0–1.7	33%
	Trails B	−0.5 ± 1.0	−2.9–1.2	33%
	Wisconsin Card Sorting Task % errors*	−0.1 ± 0.8	−1.7–1.3	17%
	Wisconsin Card Sorting Task % non-perseverative errors*	−0.3 ± 0.91	−1.9–1.2	22%
	Wisconsin Card Sorting Task % perseverative errors*	0.14 ± 1.0	−1.5–1.8	11%
	Wechsler Memory Scale – 3 digit span	0.2 ± 0.8	−1.3–2	6%
	Wechsler Memory Scale – 3 spatial span	0.1 ± 0.9	−1.7–1.7	17%
	Cognitive Estimation Task	0.6 ± 0.6	−0.9–1.7	0%
Language	FAS letter fluency	−0.6 ± 0.9	−1.8–1.7	33%
	Animal semantic fluency	−0.04 ± 1.0	−2.0–2.1	11%
	Boston Naming Test	−0.04 ± 0.9	−1.9–1.3	28%
Spatial	Benton Judgment of Line Orientation (raw)	26.7 ± 3.7	17–31	5%
	Mental rotation A (raw)	8.5 ± 2.6	5–15	N/A
	Mental rotation B (raw)	7.7 ± 3.1	3–13	N/A
	Mental rotation total (raw)	16.2 ± 4.8	8–25	N/A
	Rey figure copy	−2.9 ± 2.8	−11.8–0.1	78%
	Rey figure organization	0.3 ± 1.2	−2.8–1.5	17%

* $n = 17$.

Stoodley CJ, et al. Neuroimage Clin. 2016;12:765-775

Cognitive Recovery

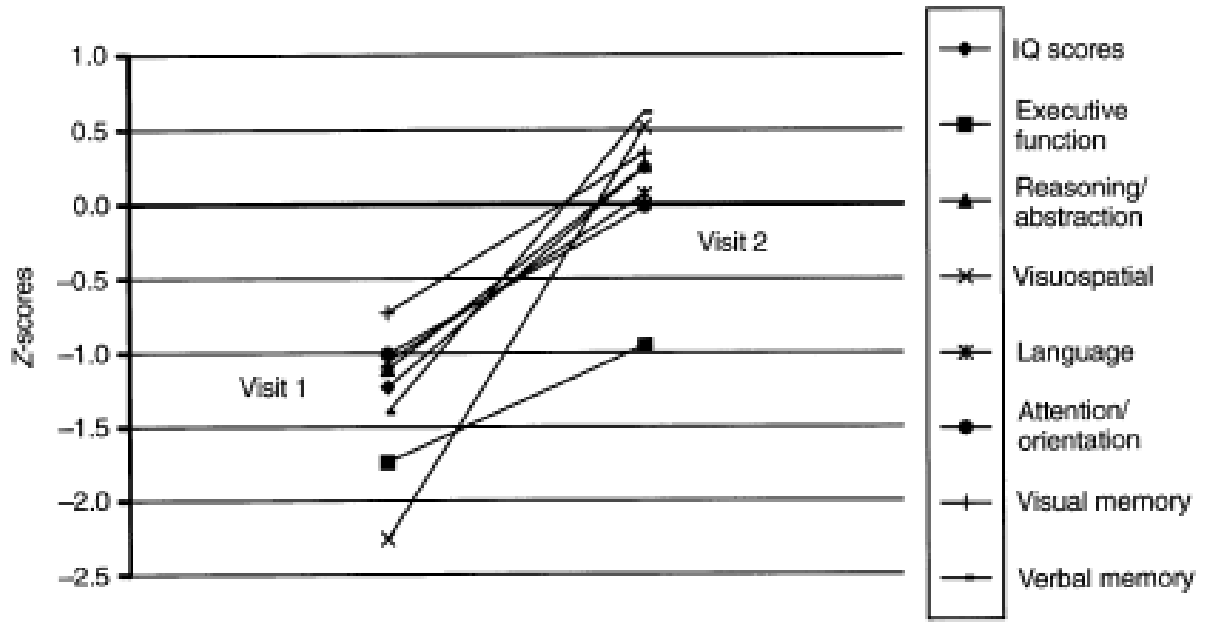


Fig. 3 Mean performances on neuropsychological tests in four patients (Cases 1, 3, 14, 15) tested within weeks of the acute insult (stroke or cerebellitis) are shown on the left, and the results of the same tests 1–9 months later are shown on the right.

Schmahmann & Sherman, Brain, 1998; 121:561-79

Cerebellar Cognitive Reserve

Transient deficits in humans, recovery of motor function in rodent models, effectiveness of rehabilitation in some degenerative disorders, immunotherapy effectiveness in immune-mediated cerebellar ataxias

Acute focal etiologies (e.g., stroke, trauma) - other cerebellar areas or extracerebellar structures compensate for damage

= Structural cerebellar reserve

Progressive degeneration (e.g., metabolic and immune-mediated cerebellar ataxias, neurodegenerative ataxias) - the affected area itself compensates for the slowly evolving cerebellar lesion

= Functional cerebellar reserve

Mitoma et al., Cerebellum, 2020; 19:131-53

Development sample

- 77 diverse cerebellar patients (36 'isolated' cerebellar damage)
- 17-80 years old
- Recruited from Ataxia Unit
- 54 matched controls

36 NP tests (71 Z scores)

1. One-tailed t-tests comparing patients and controls
2. Rank-ordered significant tests by Z difference
3. Selected tests that index EF, linguistic, VS, affective
4. Narrowed to short/shortened tests
5. Selected raw score cutoffs on each test to maximize selectivity (true negatives) over sensitivity (true positives)

CEREBELLAR COGNITIVE AFFECTIVE / SCHMAHMANN SYNDROME SCALE (CCAS-Scale) VERSION 1A.

NAME: ID# DATE

DOB: Education (Yrs)

		RAW SCORE	PASS=0 FAIL=1
SEMANTIC FLUENCY	Score = total correct words (up to a maximum of 26 words). Fail if Score 15 or less. *(Use space bottom right for notation).*		
Please name as many animals or living creatures as you can in one minute		/26	
PHONEMIC FLUENCY	Score = total correct words (up to a maximum of 19 words). Fail if Score 9 or less. *(Use space bottom right for notation).*		
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 (up to a maximum of 15 alternations). Repetitions or set loss errors are not scored. Fail if Score 9 or less. *(Use space bottom right for notation).*		
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. (The need for 4 attempts to learn 5 words raises concern for cerebral involvement).		
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 rate of 1 / second. Subject repeats them once, then repeats them again. Repeat trials until subject recalls all 5 words. Stop after 4 attempts.)*			
[Flower] [Robert] [Courage] [Speak] [Yellow]			
1st attempt [ ] - [ ] - [ ] - [ ] - [ ]			
2nd attempt [ ] - [ ] - [ ] - [ ] - [ ]			
3rd attempt [ ] - [ ] - [ ] - [ ] - [ ]			
4th attempt [ ] - [ ] - [ ] - [ ] - [ ]			
DIGIT SPAN FORWARD	Score = maximum string of numbers correctly repeated. Fail if Score 5 or less.		
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. Start with * and administer previous items if subject fails to repeat *).*			
5-9 [ ] 4-8-7-0 * [ ] 3-0-1-2-6-4 [ ] 2-0-5-6-9-7-3-8 [ ]			
2-1-3 [ ] 1-6-9-2-5 [ ] 7-3-1-9-8-4-6 [ ]		/8	
DIGIT SPAN BACKWARD	Score = maximum string of numbers correctly repeated. Fail if Score 3 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 bottom left).*			
CUBE (COPY)	Score = 12 points, 1 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 11 or less.		
Please copy the cube shown on PAGE 2. *(Neatness not scored).*		/15	

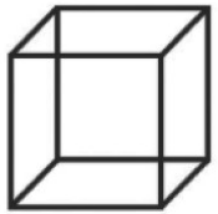
Draw cube here.

Notation:

Semantic Fluency	Phonemic Fluency	Category switching

		RAW SCORE	PASS=0 FAIL=1
VERBAL RECALL	Spontaneous = 3 points per word, category = 2 points , multiple choice = 1 point. Score = total points. Fail if Score 10 or less. Inability to recall more than 1 word from multiple choice raises concern for cerebral involvement.		
What were the words I asked you to learn earlier? *(Subject recalls the words learned previously. Use cues and multiple choice alternatives bottom left if needed).*			
	[Flower] [Robert] [Courage] [Speak] [Yellow]		
Spontaneous recall:	[ ] - [ ] - [ ] - [ ] - [ ]		
Recall with category cue:	[ ] - [ ] - [ ] - [ ] - [ ]		
Recall with multiple choice:	[ ] - [ ] - [ ] - [ ] - [ ]	/15	
SIMILARITIES	Correct answer (conceptual) = 2 points, partial answer (concrete) = 1 point, incorrect answer / no 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, then test items).*			
(e.g., Ball/Moon = Round)	1.Nose/Ear [__/2] 2. Sheep/Elephant [__/2] 3. Lake/River [__/2] 4. Airplane/Motorcycle [__/2]	/8	
GO NO-GO	2 points for no errors, 1 point for one error, 0 points for two or more errors. Score = total points. Fail if Score 0.		
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 an example of each condition to make sure subject understands).*			
1 – 1 – 1 – 2 – 2 – 1 – 2 – 2 – 2 – 1 – 2 – 1 – 2 - 1		/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		/120	/10

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



Copy the cube here.

CUES AND MULTIPLE CHOICE ITEMS FOR VERBAL RECALL TEST

Test word	Flower	Robert	Courage	Speak	Yellow
Cue	Grows in the garden	Boy's name	Trait or virtue	Way of communicating	Color
Multiple choice items	Tree	Stephen	Bravery	Speak	Red
	Bush	Michael	Courage	Talk	Green
	Flower	Joseph	Honesty	Sing	Blue
	Grass	Robert	Patience	Shout	Yellow

SIMILARITIES	Correct conceptual answers (examples)	Partial correct / concrete answers (examples)
Nose/Ear	Sense organs	Face, body part
Sheep/Elephant	Mammals, animals	Legs, tails
Lake/River	Bodies of water	Wet, cold, swim
Airplane/Motorcycle	Vehicles, transportation	Use fuel, ride them

Hoche, Guell, Vangel, Sherman, Schmahmann
Ataxia Unit, Cognitive Behavioral Neurology Unit, Schmahmann Laboratory for Neuroanatomy and Cerebellar Neurobiology, Department of Neurology, Massachusetts General Hospital.

doi:10.1093/brain/awaa417 BRAIN 2021: 144; 1–5 | e20

BRAIN
A JOURNAL OF NEUROLOGY

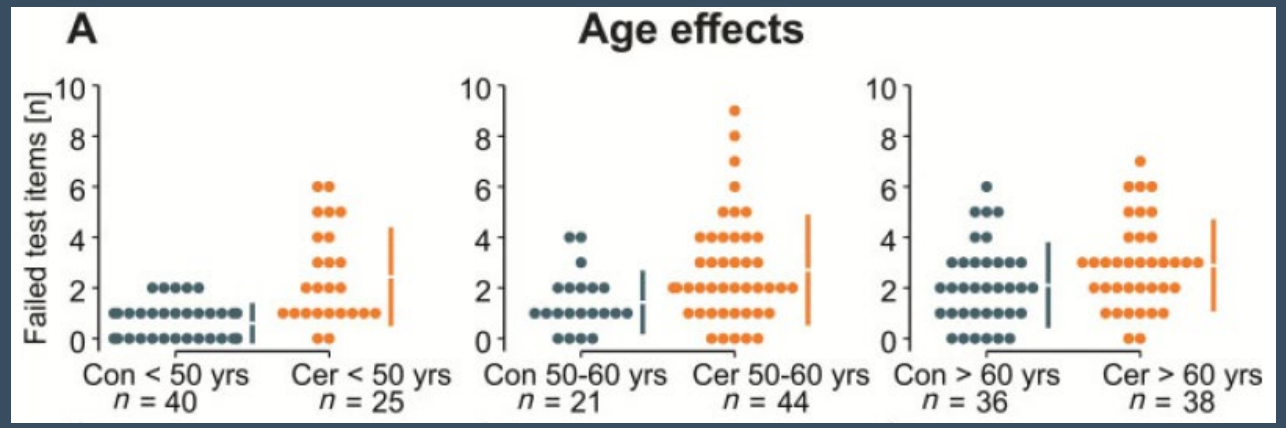
LETTER TO THE EDITOR

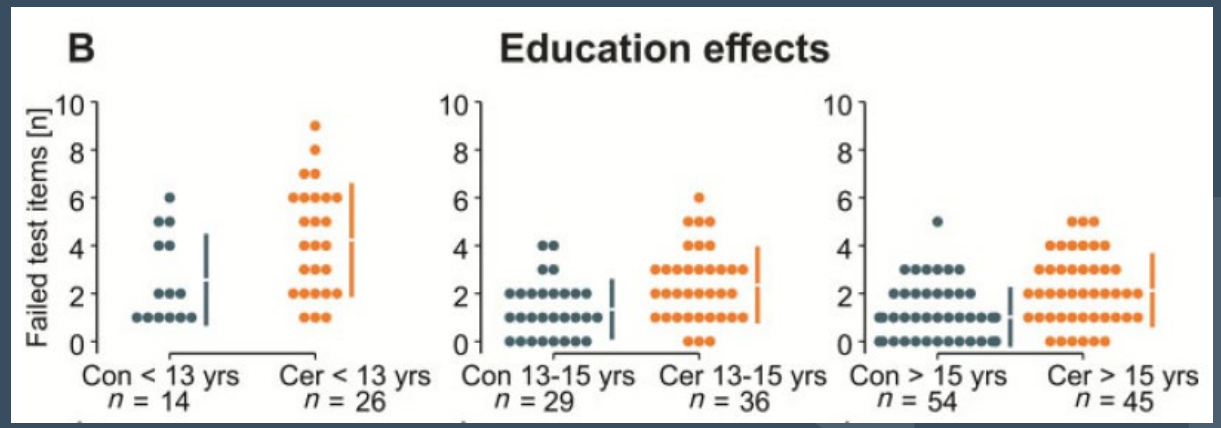
Reference values for the Cerebellar Cognitive Affective Syndrome Scale: age and education matter

Andreas Thieme,[1] Sandra Röske,[2] Jennifer Faber,[2,3] Patricia Sulzer,[4,5] Martina Minnerop,[6,7,8] Saskia Elben,[7,8] Kathrin Reetz,[9,10] Imis Dogan,[9,10] Miriam Barkhoff,[2] Jürgen Konczak,[11] Elke Wondzinski,[12] Mario Siebler,[12] Susann Hetze,[13] Oliver Müller,[13,†] Ulrich Sure,[13] Thomas Klockgether,[2,3] Matthis Synofzik[4,5] and Dagmar Timmann[1]

- German study in 107 patients
- Translated CCASS

"Useful if age < 50 and education > 12"





NP Assessment Tools

- Study inclusion: consecutive patients; N > 20; tested >75% of patients (minimize missing data); control group, <1 year of diagnosis = 10 studies

- ‘Aphasia Tests’
- Rey Complex Figure Test, Block Design Test
- Phonological and Semantic Verbal Fluency
- Five Point Test (~Ruff Figural Fluency)
- Trail Making Test, Stroop Test, Go/No-Go Test
- Digit Span Forward and Digit Span Backward
- Wechsler Memory Scale-R Visual Memory (VR; Spatial span)

Ahmadian et al., Cerebellum, 2019; 18:941-50

Motor considerations for test selection

Patients with Dysarthria/Ataxic speech

- Speeded verbal tests require a true ‘control’ condition.
  - Differential phonemic vs semantic word generation vs switching
  - Derived interference scores for Stroop (e.g., Stroop/Color Naming)

Patients with Ataxia/Incoordination

- Manual responses may be slowed or imprecise
  - Focus on error rates, rule breaks rather than timed metrics (e.g., Trails, WCST, Tower)
  - Motor control conditions for derived scores (e.g., TrailsB/A)

Patients with Nystagmus/Imbalance

- Verbal or Foveal presentation to avoid visual scanning errors
  - Oral vs Written Trails, Hooper Visual Organization Test vs JOLO

NP Assessment

1. No pathognomonic neuropsych deficit for Cerebellar damage
2. Expectations for abnormal performance will depend on location and extent of damage within the cerebellum, involvement of non-cerebellar structures, etiology and chronicity of dysfunction
3. Thorough understanding of the patient's motor deficits help guide test selection or, at least, inform test interpretation
   - Recognize that movement and speech may take extra effort to normalize and thereby require greater attentional resources
4. Test development specific to cerebellum role (mental timing, semantic priming/models) may produce greater yields

If unfolded, how much of the cerebrum's surface area would the cerebellum cover?

10%

50%

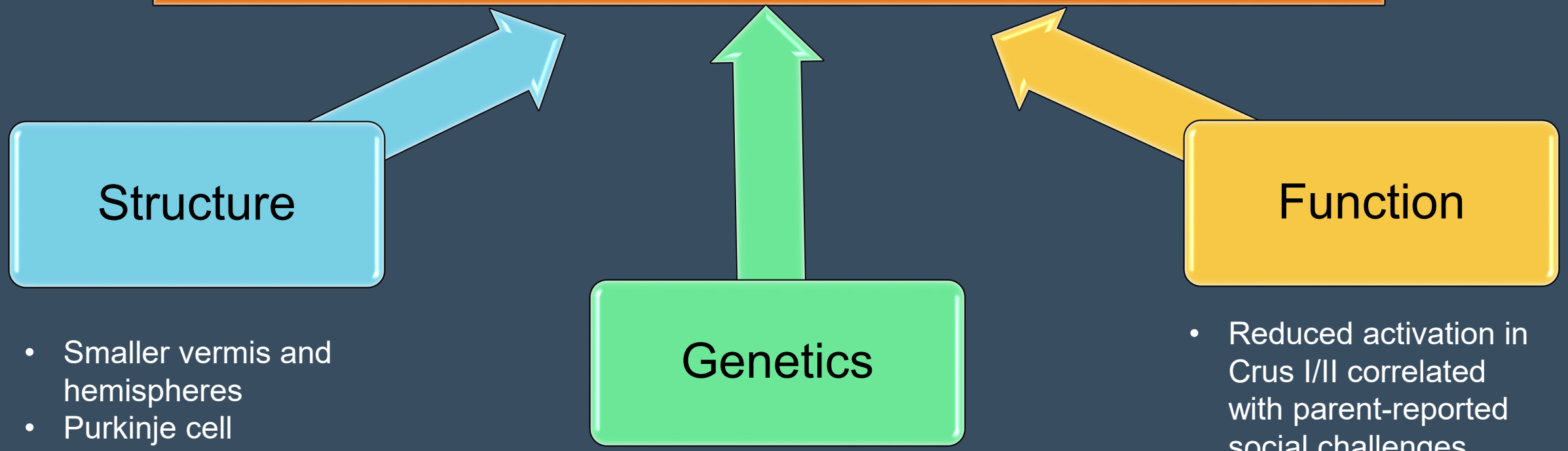
25%

75%

Section 4: Special Populations

- Connectivity ✓
- Functional Role ✓
- Clinical Manifestations ✓
- Clinical Syndromes

Autism Spectrum Disorder



- Smaller vermis and hemispheres
- Purkinje cell reductions in Crus I/II

38 genes with cerebellar-enriched expression identified as ASD-linked susceptibility genes

- Reduced activation in Crus I/II correlated with parent-reported social challenges
- Abnormal connectivity between right Crus I/II and contralateral cerebral cortex associated behavior symptoms.

Murakami et al. 1989; Fatemi et al., 2002; Sarnat & Netsky, 2002; Jack et al., 2017; Mosconi et al., 2015; Jack and Morris, 2014

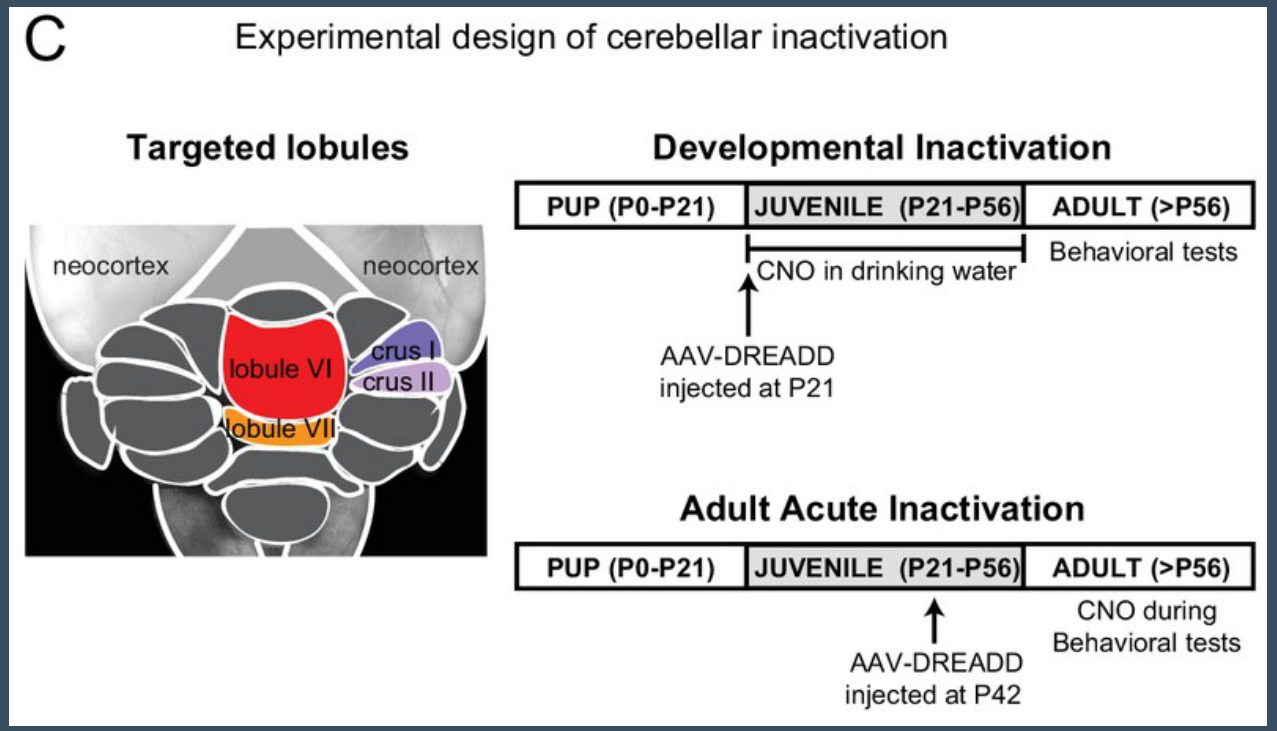
Cerebellum & Social Cognition

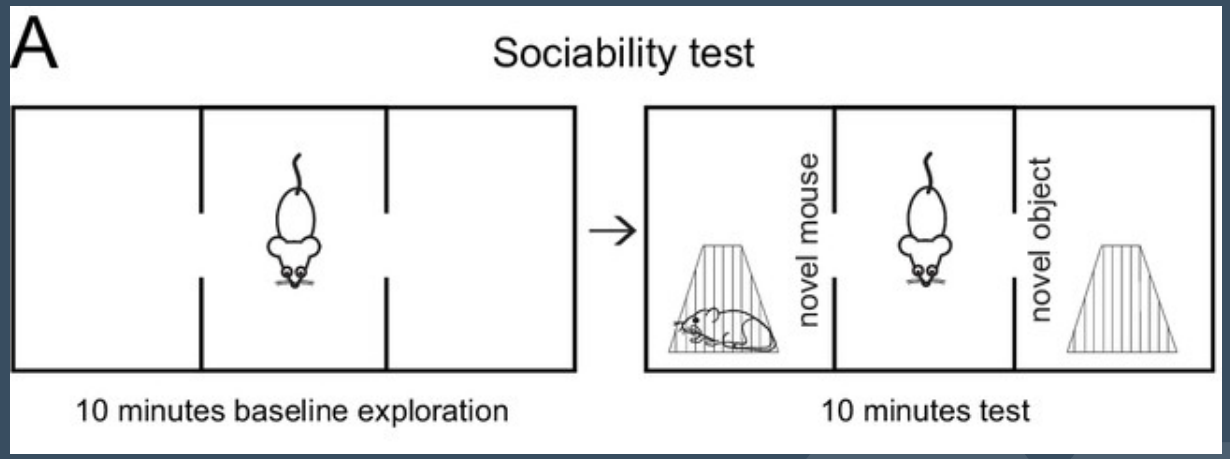
Adaptive Prediction:

Reflexively use past experiences to:

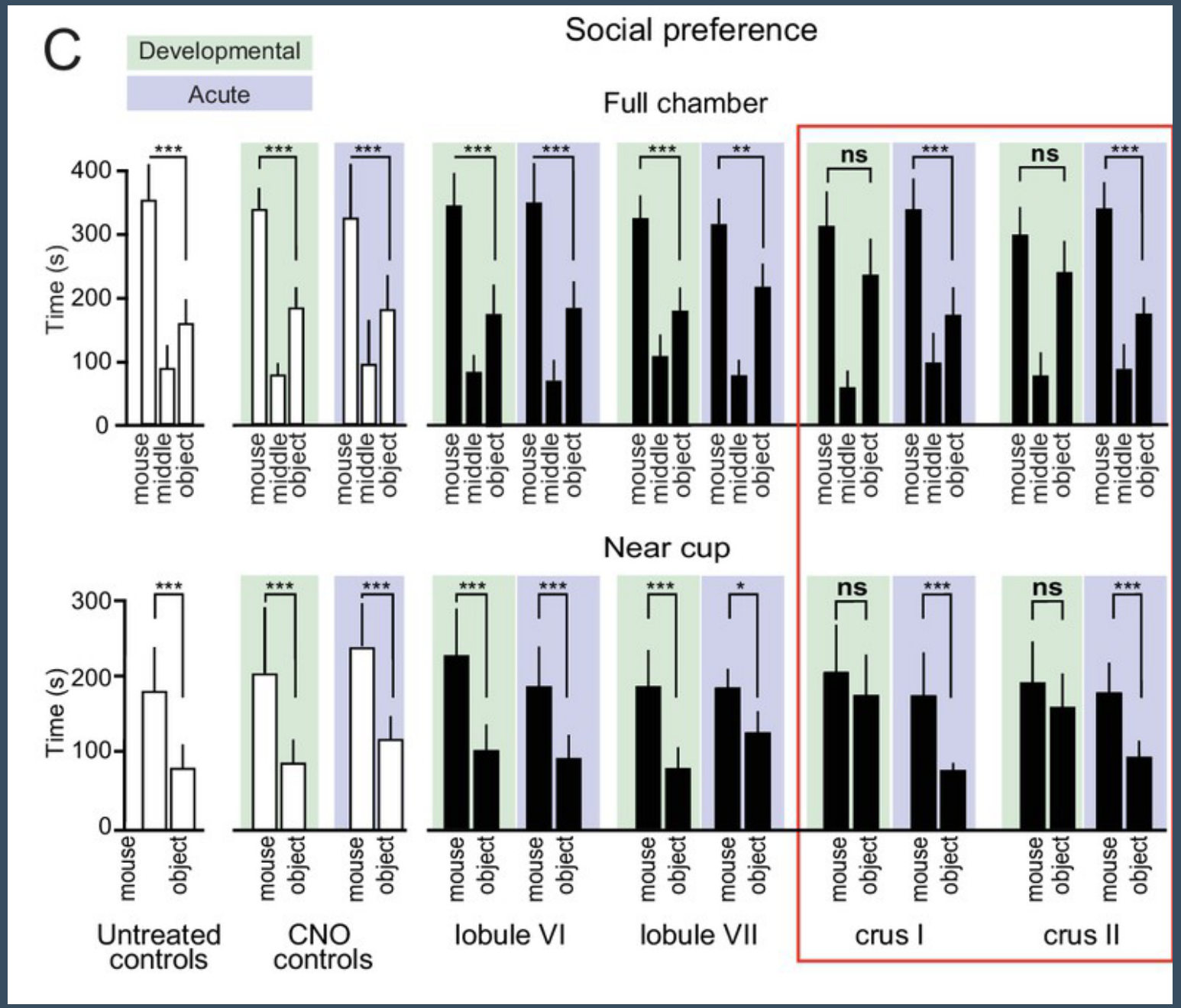
1. derive intent from the actions of others;
2. anticipate what they may say;
3. infer their mental states to rapidly correct own behaviors in response

Social Development





Badura et al., eLife 2018;7:e36401



Badura et al., eLife 2018;7:e36401

Schizophrenia

Structure

- Decreased Purkinje density and size
- Structural vermal abnormalities

Genetics

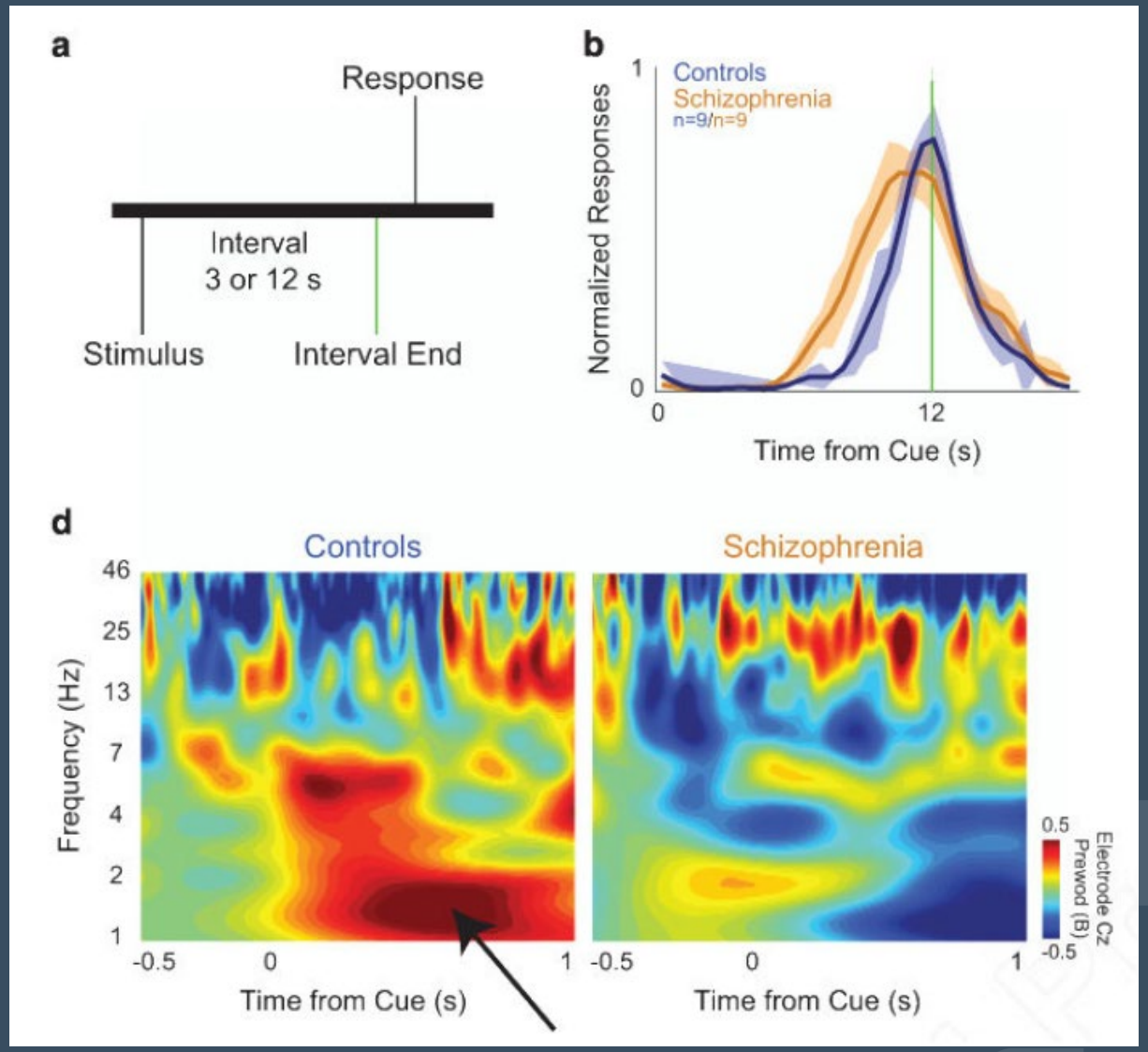
reduced expression of synaptic proteins in cerebellum leading to reduced purkinje output

Function

- Reduced BOLD and metabolic activity during cognitive and emotional tasks
- Abnormal cerebellar functional topography
- Abnormal connectivity in functional networks rTMS to vermis may improve mood and negative symptoms

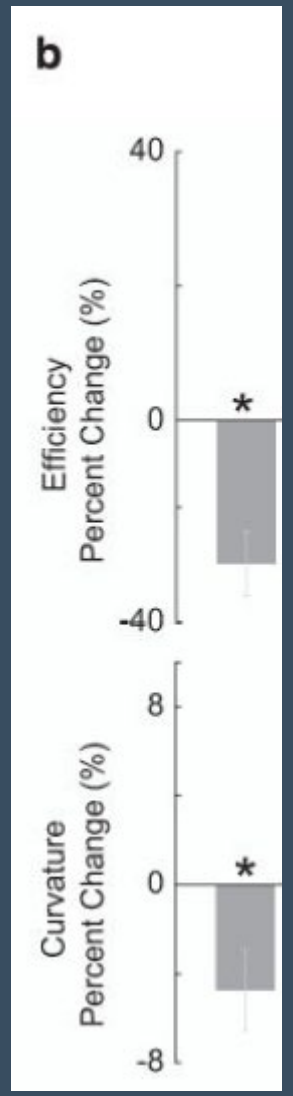
Ichimiyaetal.,2001; Okugawaetal.,2007; Eastwood et al., 2001; Andreasen et al, 1997; Paradiso et al., 2003; Bernard and Mittal, 2015; Chen etal.,2013; Garg et al., 2016; Demirtas-Tatlidede et al., 2010

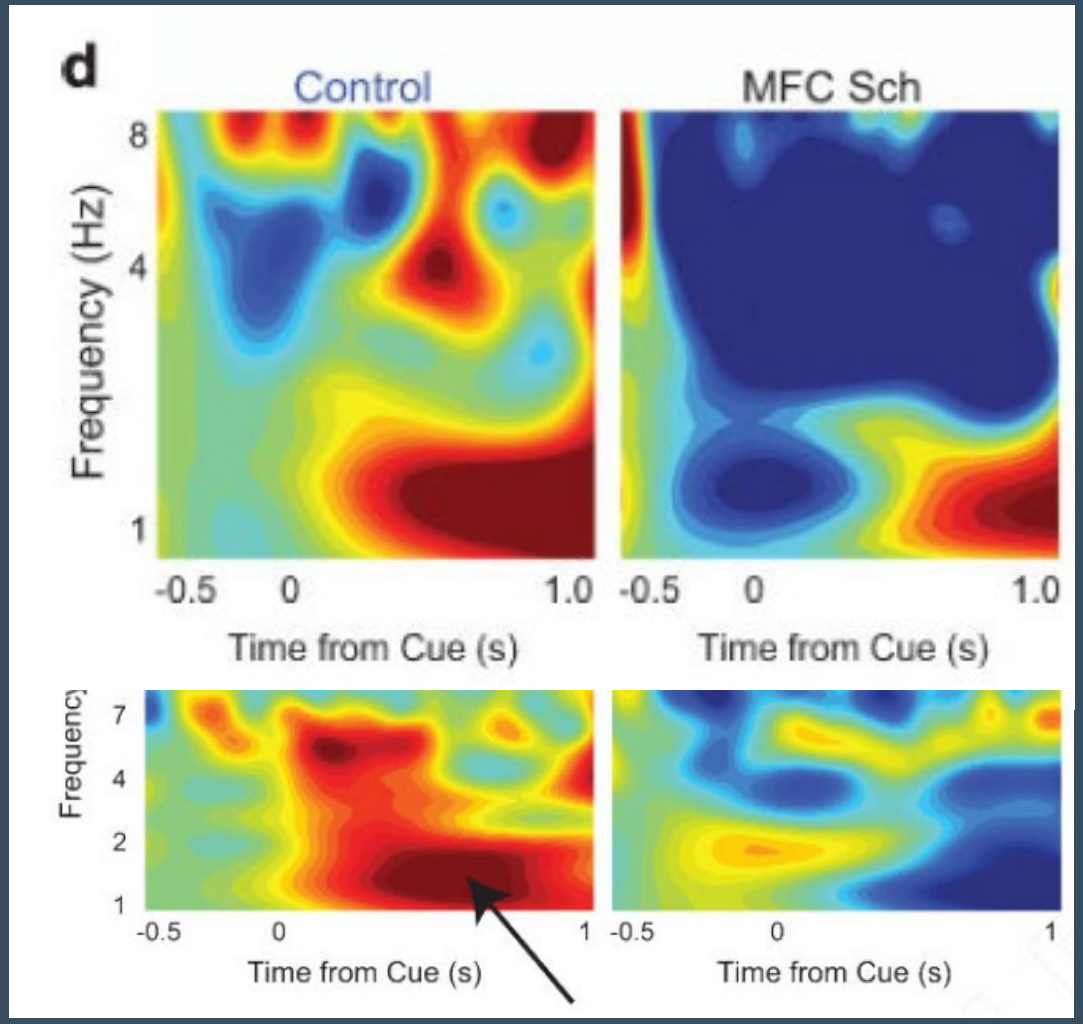
Cognitive Dysmetria



Parker et al., Mol Psychiatry. 2017 May; 22(5): 647–655.

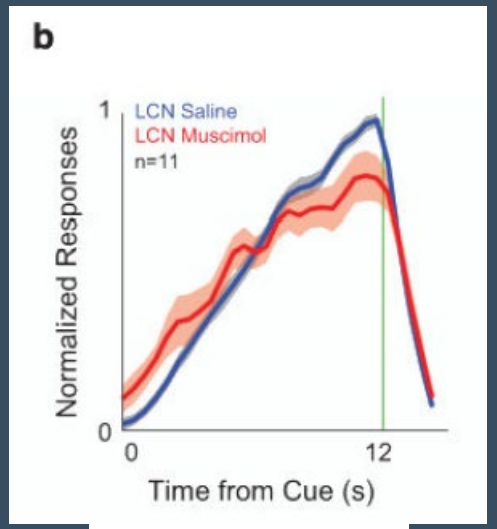
Mouse Schizophrenia and Timing

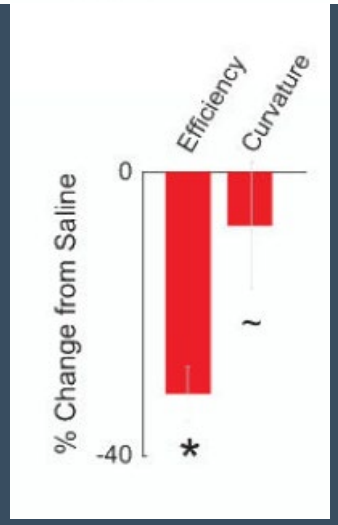


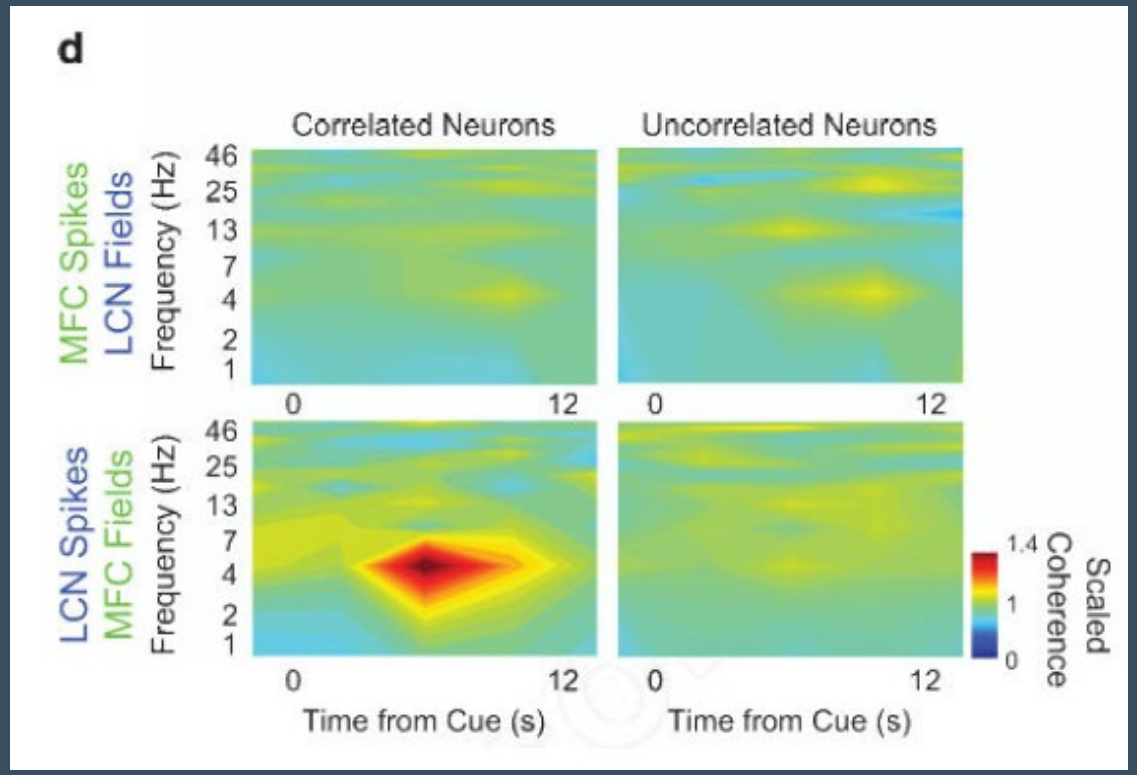


Parker et al., Mol Psychiatry. 2017 May; 22(5): 647–655.

Mouse Cerebellum and Timing

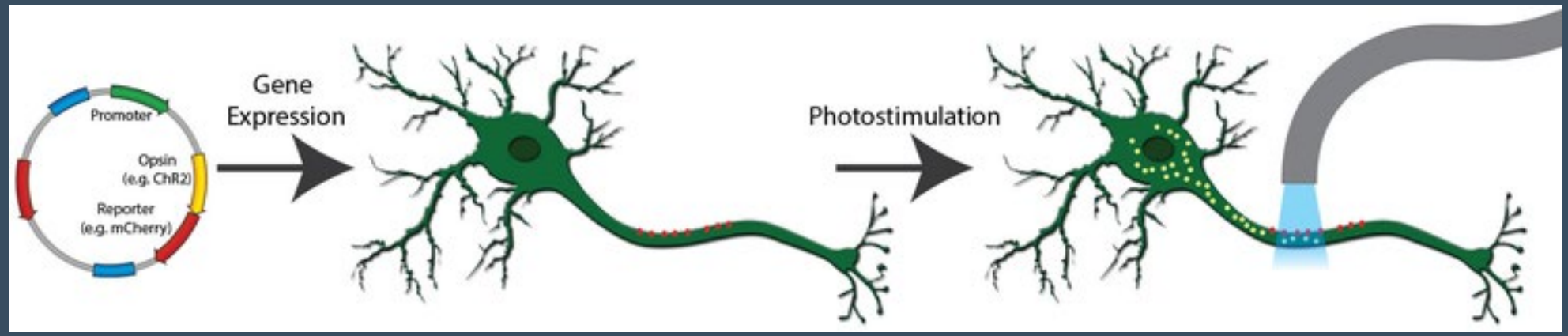




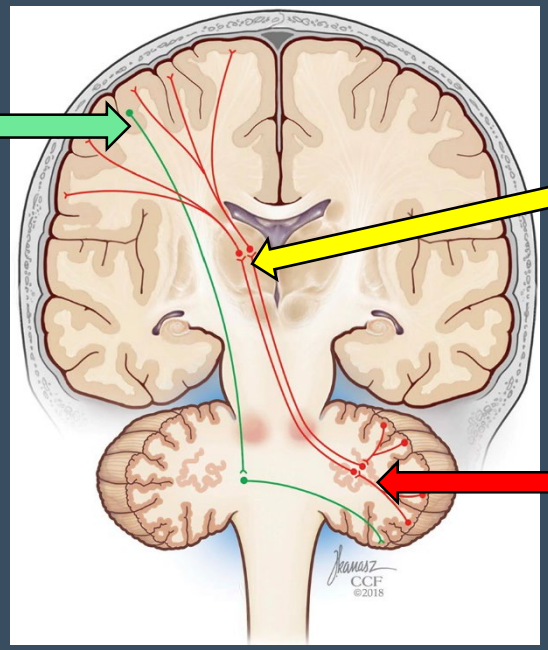


Parker et al., Mol Psychiatry. 2017 May; 22(5): 647–655.

Cerebellar Stimulation



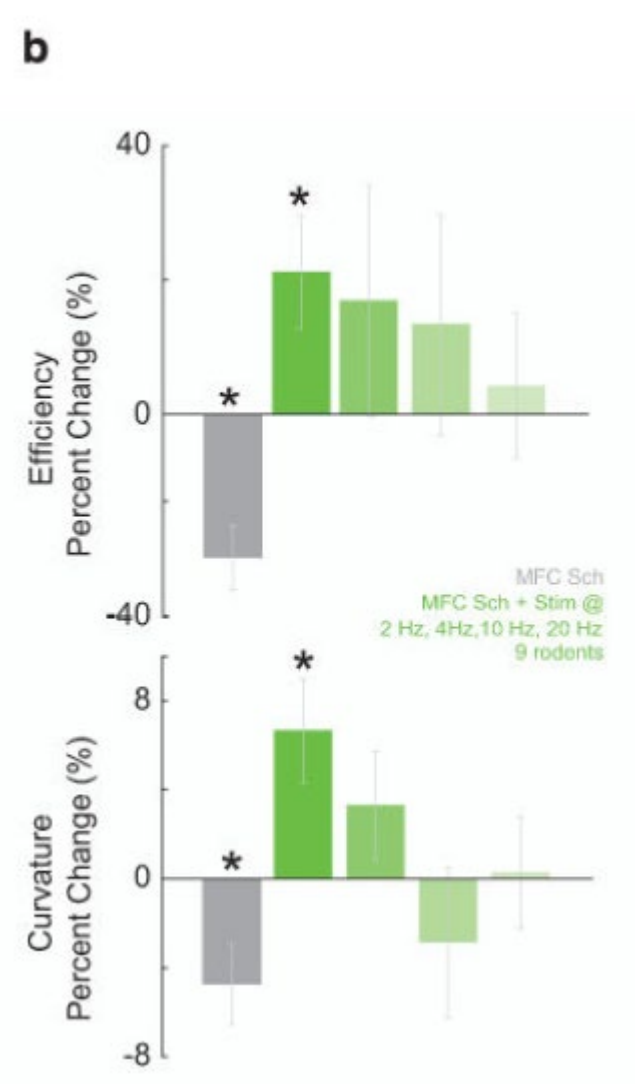
Record activity here

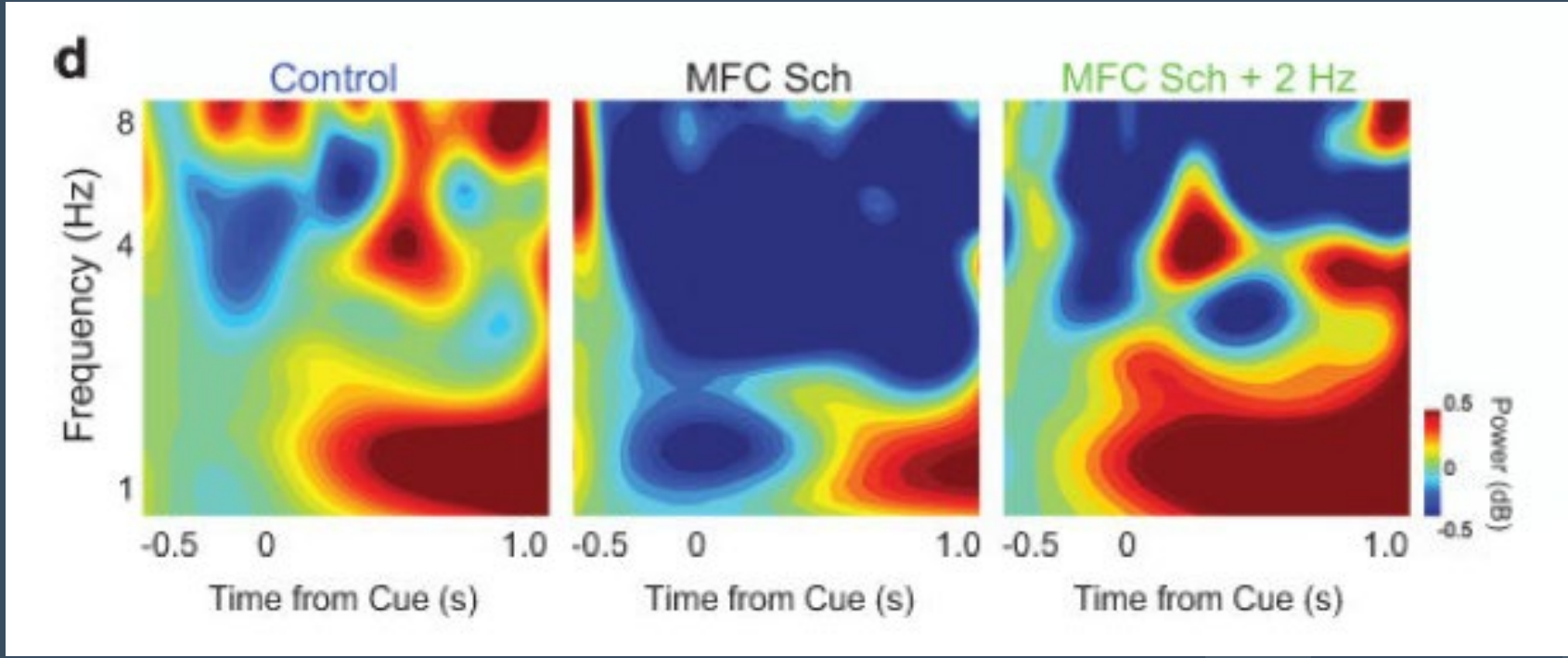


Light stimulation here

Infect cells here

Cerebellar Stimulation





Parker et al., Mol Psychiatry. 2017 May; 22(5): 647–655.

Cerebellar development is complete at what age?

At birth

10 years

2 years

20 years