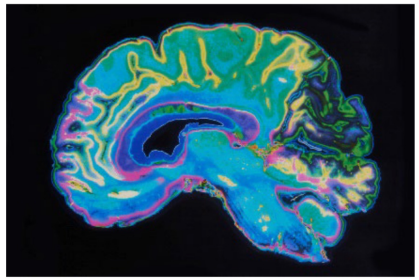
European Reference Network
for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

ERN-RND Winter School 2023 - 'NEUROIMAGING'

Online, 23-25. March 2023, Times in CET



NeuroN Neuroimaging Naples

Ataxia and HSP

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Learning objectives

- Identify common imaging features

- Understand the recommended sequences

- Recognize the MRI patterns in the respective disease(s)

- Interpret and apply the results of neuroimaging accurately in the clinical context

Outline

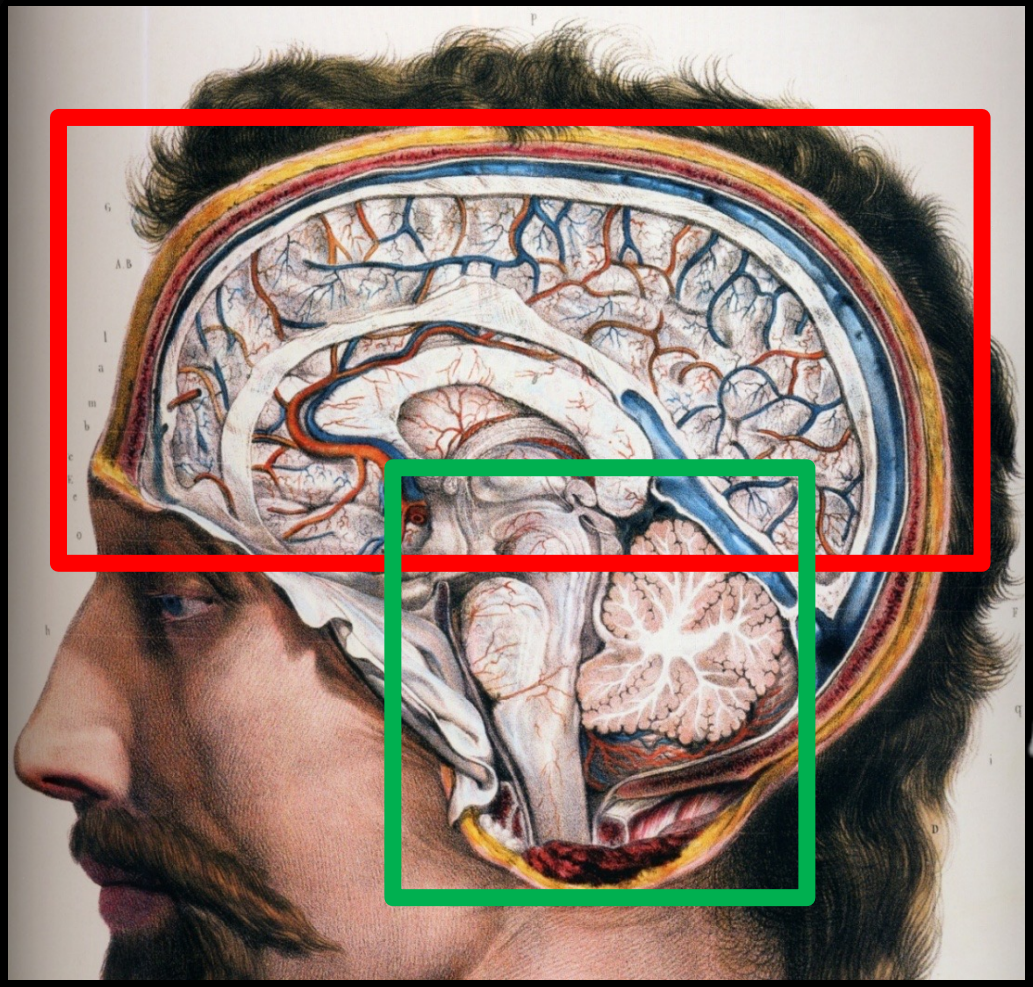
- Anatomy

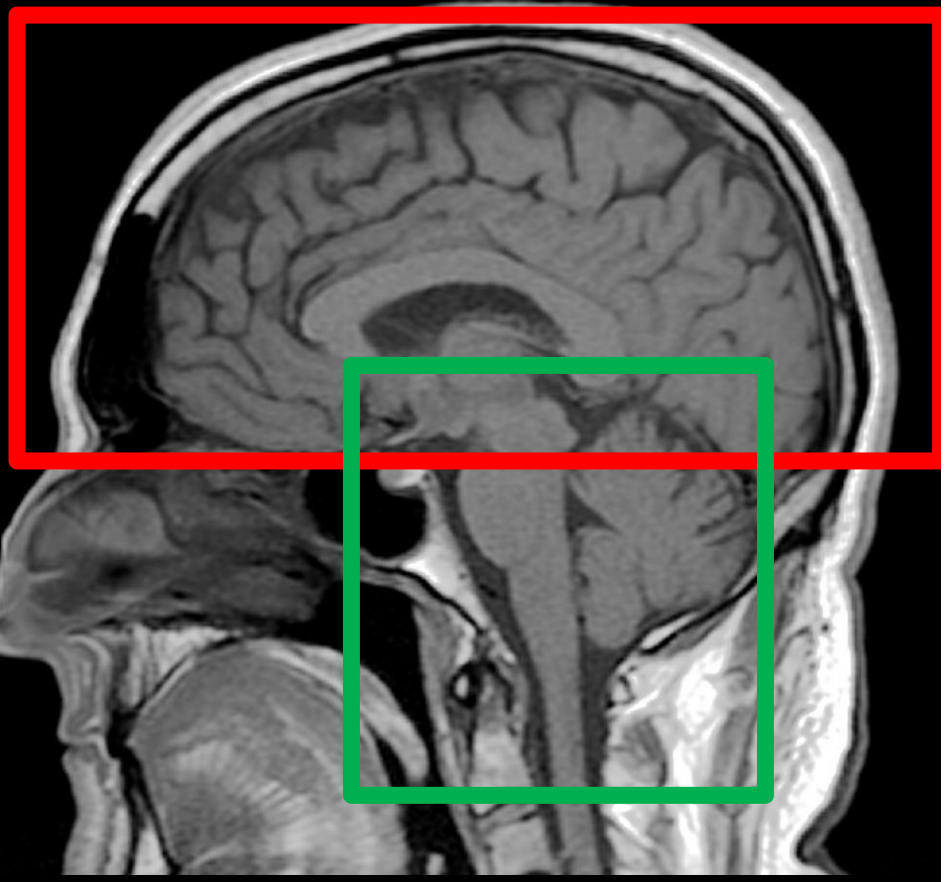
- Conventional MRI – Sequences

- Conventional MRI findings in main hereditary ataxias

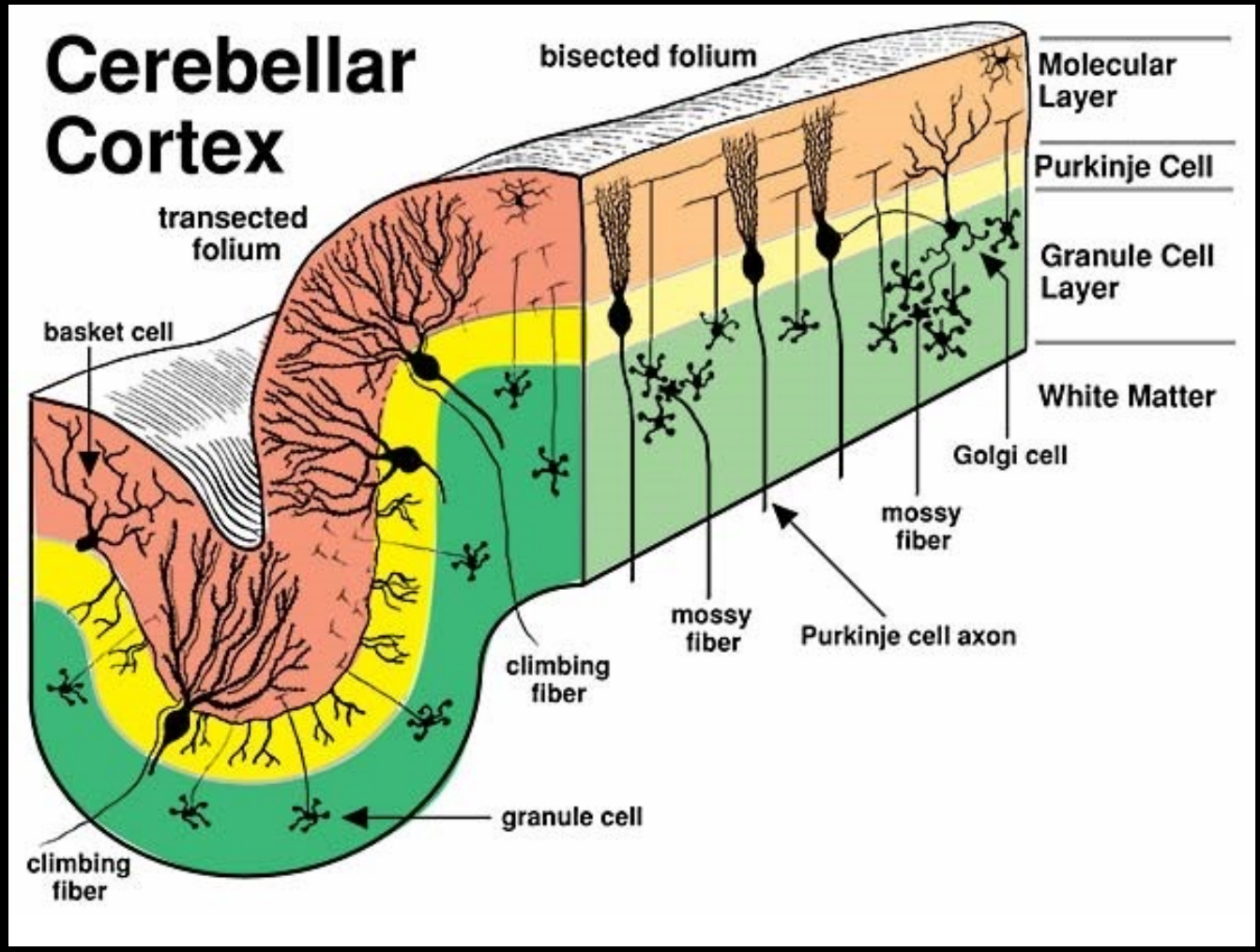
- Neuroradiological diagnostic algorithm

Brain anatomy





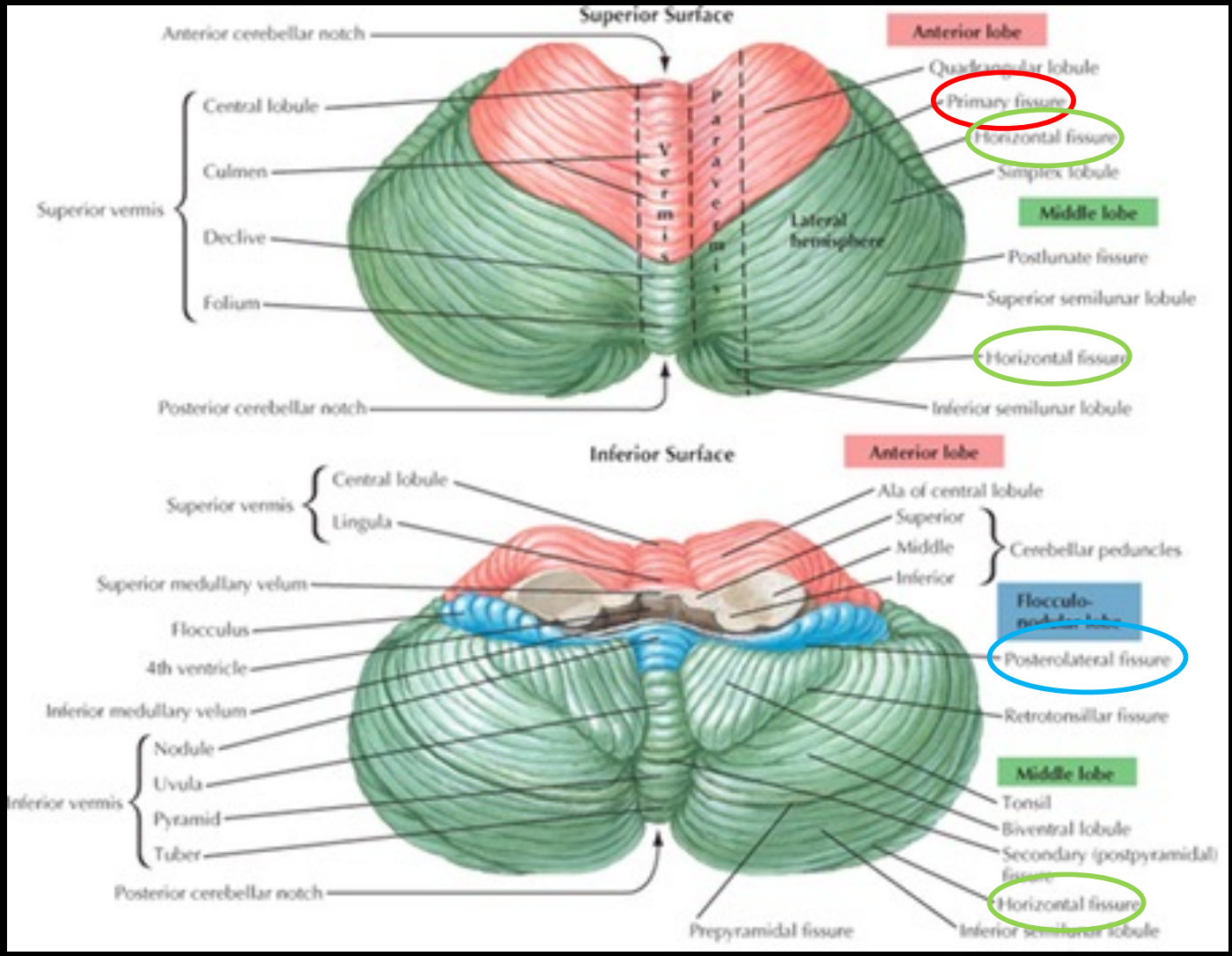
Cerebellar anatomy (1)



- Three layers:

  Molecular layer, Purkinje cell layer, granular layer

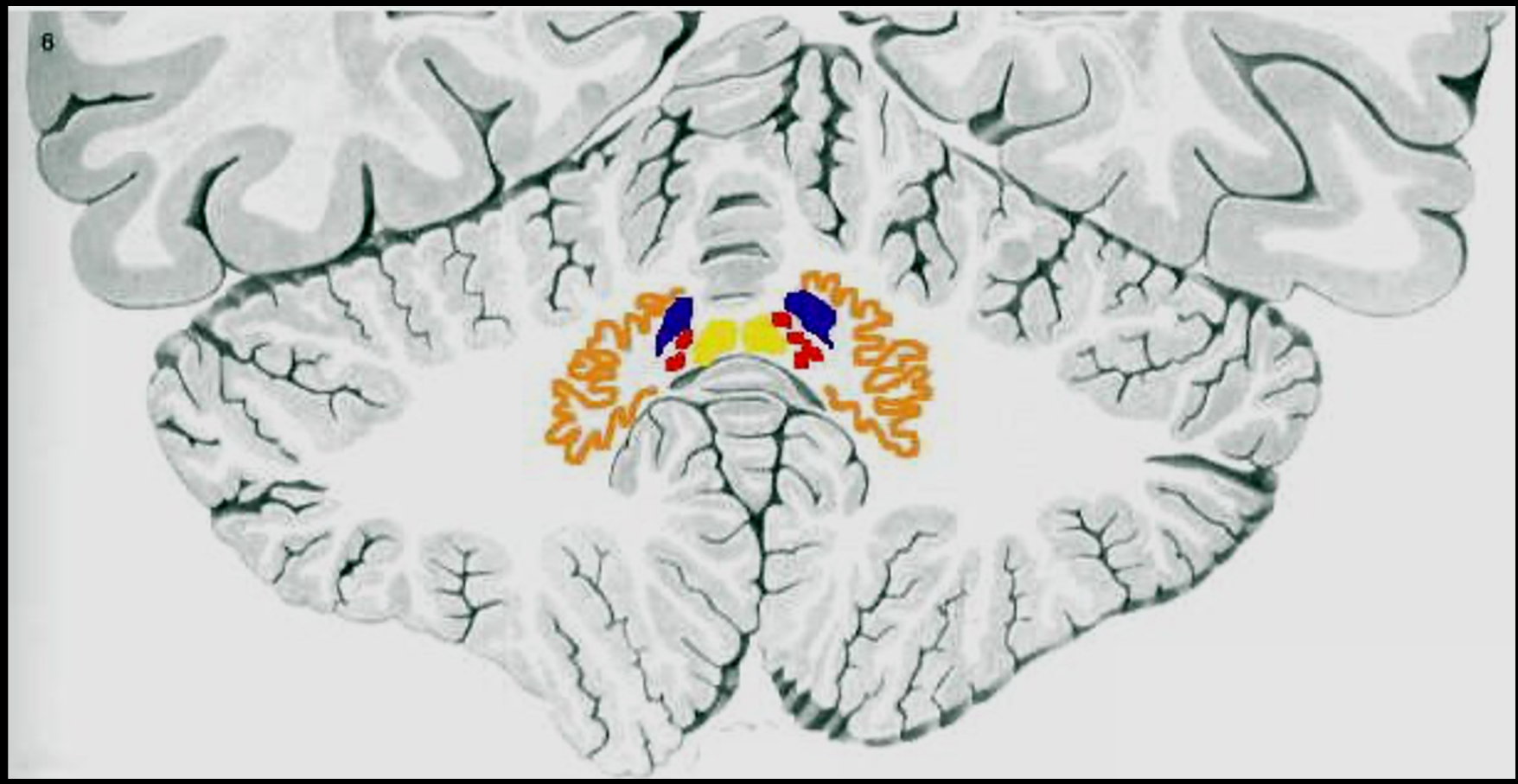
Cerebellar anatomy (2)



- Three lobes:

  Anterior, Posterior and Flocculonodular

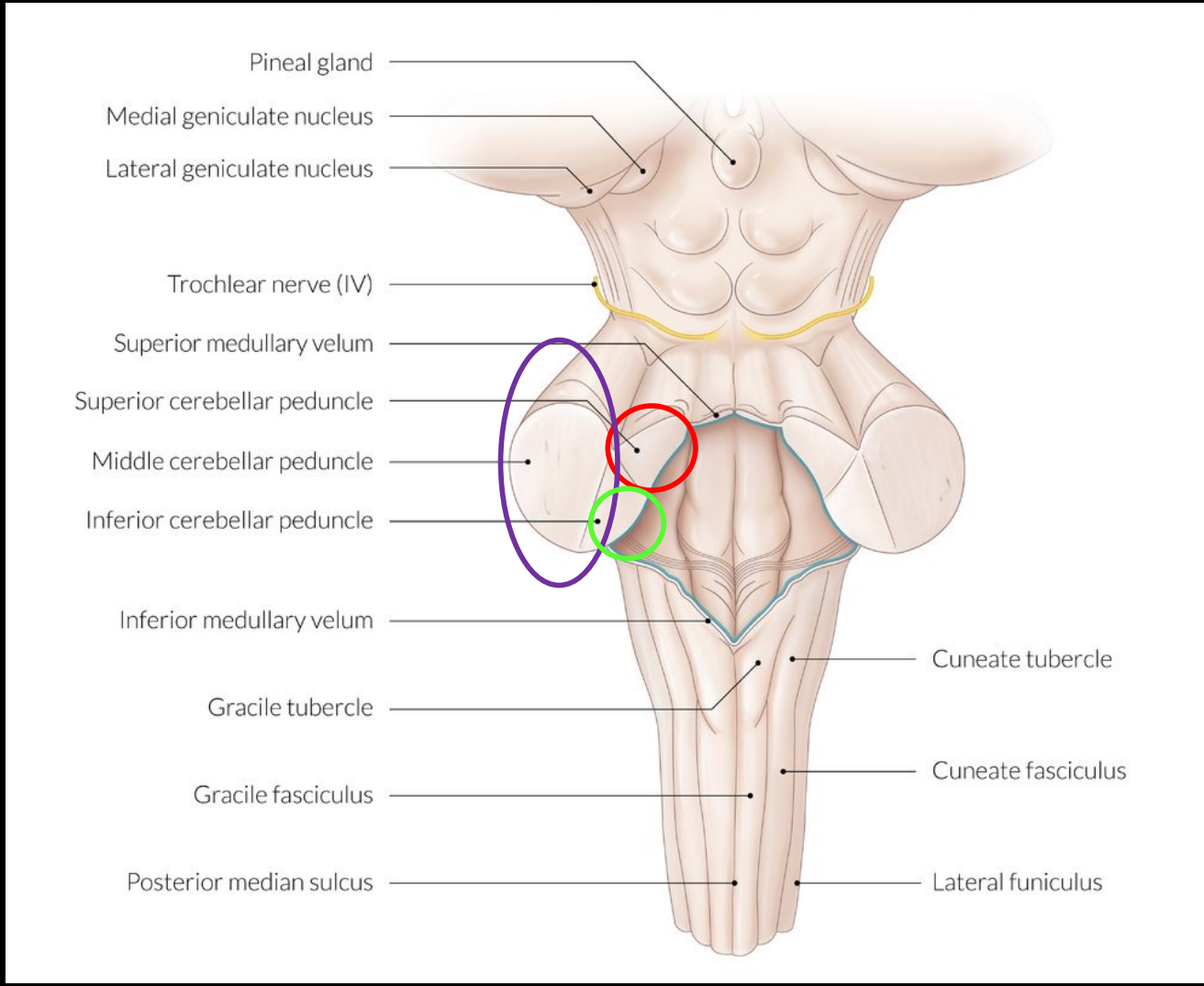
Cerebellar anatomy (3)



- Three nuclei:

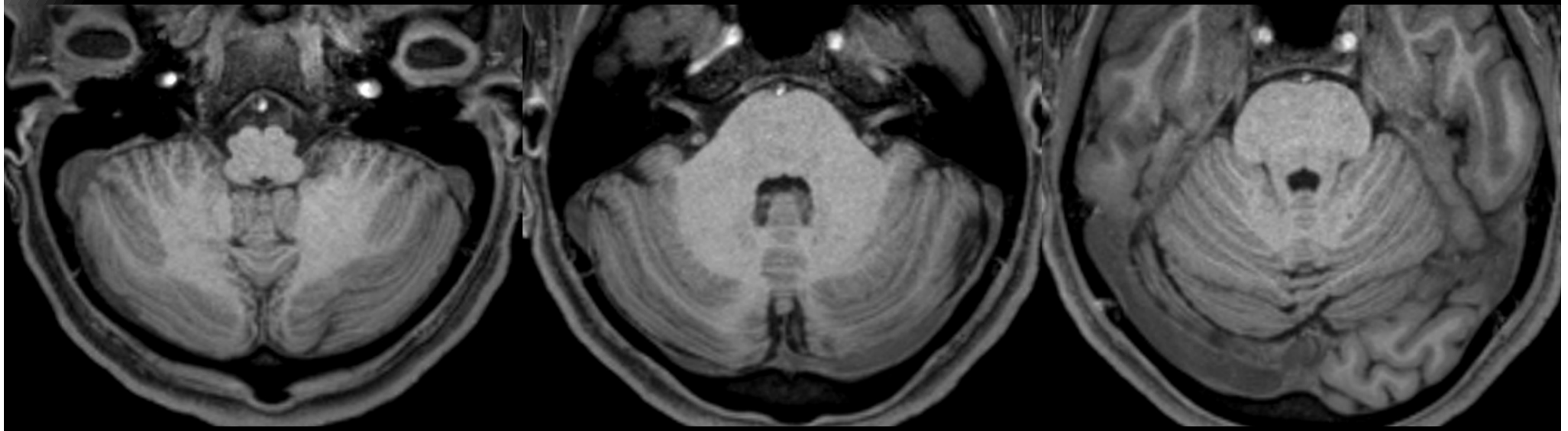
  Fastigial, Interposed (emboliform + globose nuclei) and Dentate nuclei

Cerebellar anatomy (4)

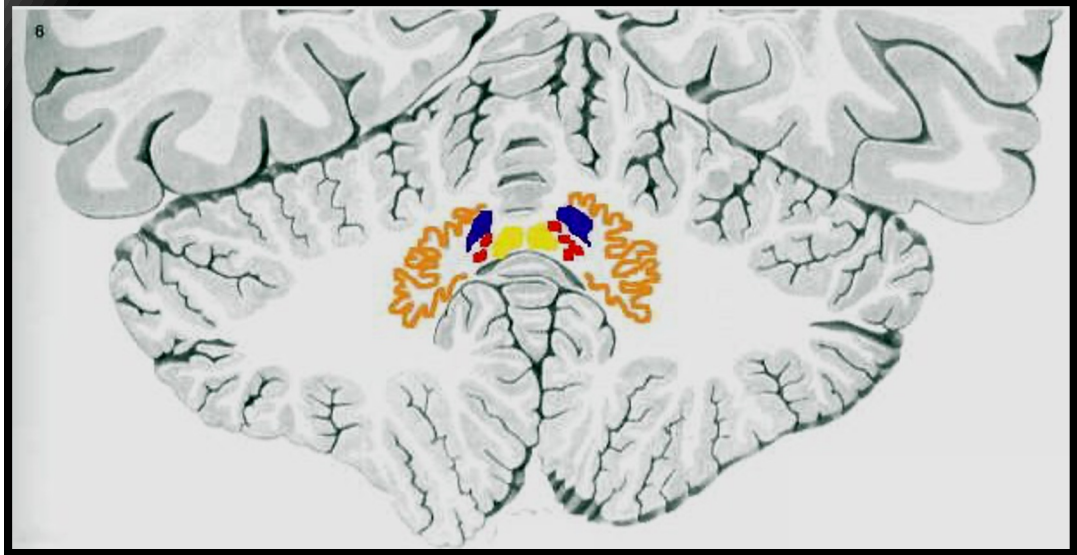


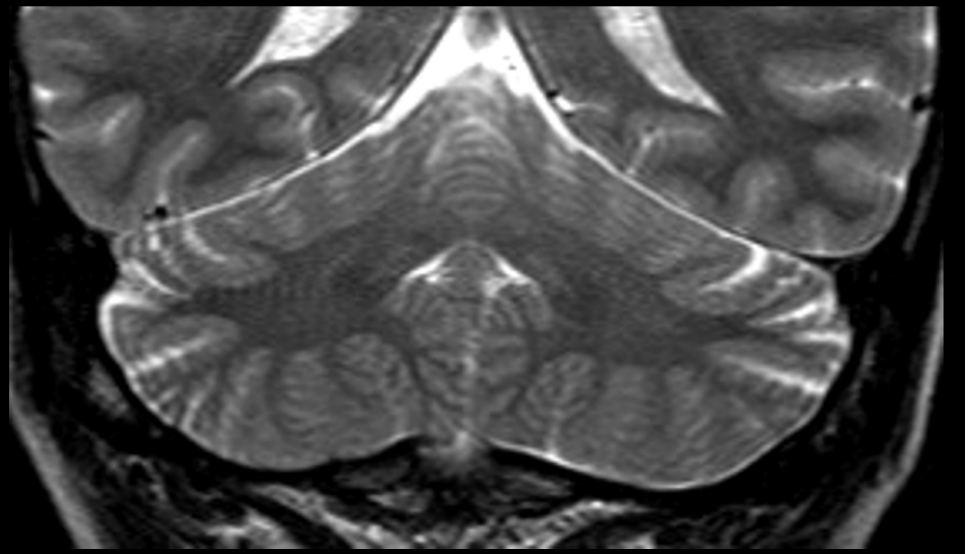
- Three peduncles:
  superior, middle and inferior

Cerebellar anatomy (5)



Cerebellar anatomy (6)

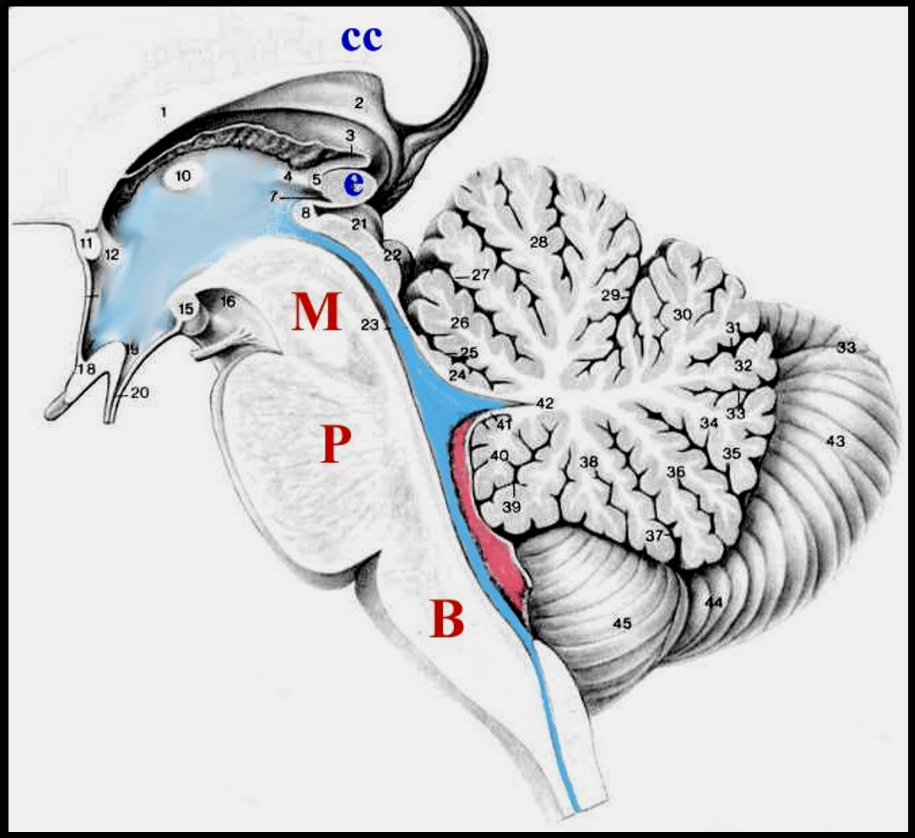


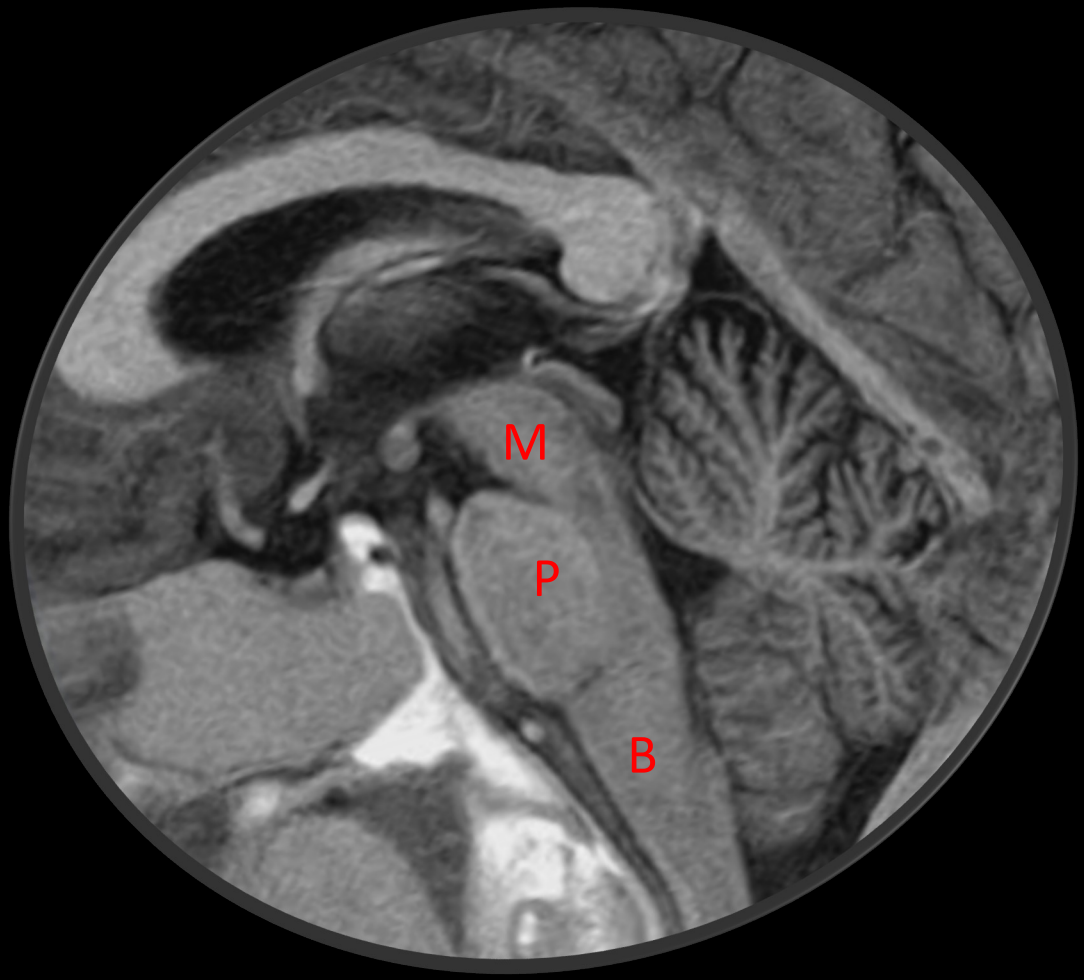


- Fastigial nucleus
- Interposed nucleus (emboliform + globose nuclei)
- Dentate nucleus

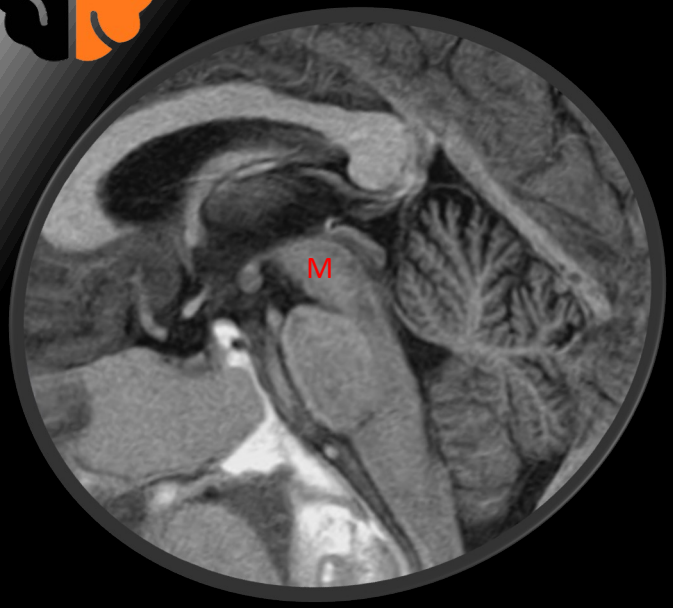
Brainstem

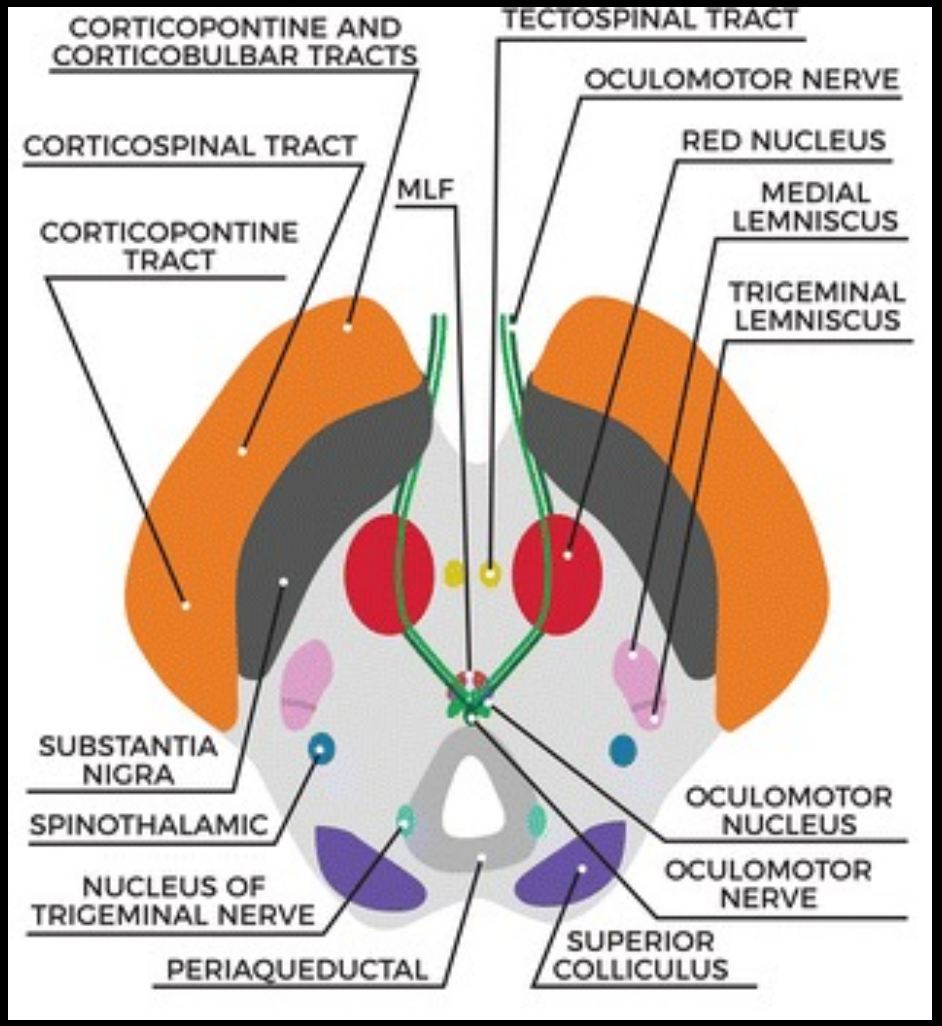
Midbrain Pons medulla oBlungata



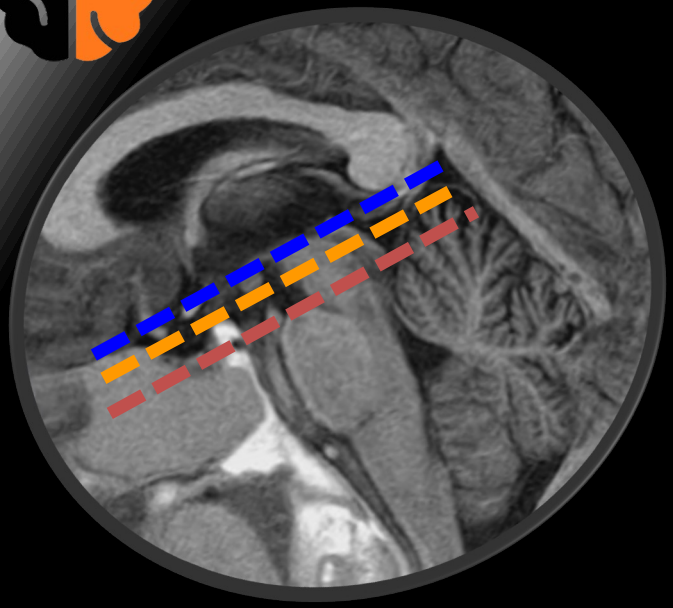


Midbrain

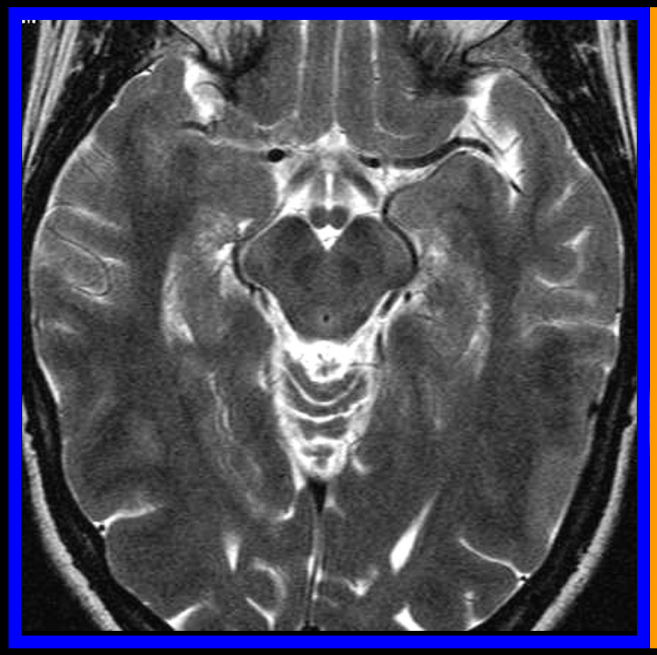

M

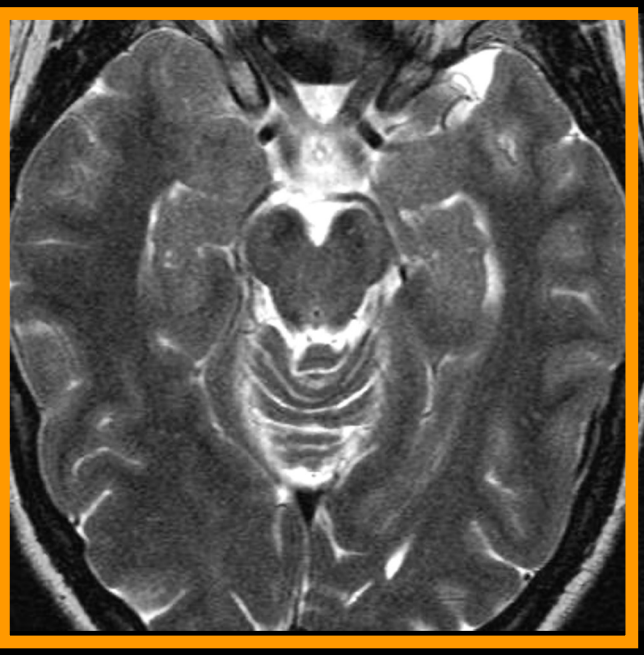

CORTICOPONTINE AND CORTICOBULBAR TRACTS
TECTOSPINAL TRACT
OCULOMOTOR NERVE
CORTICOSPINAL TRACT
RED NUCLEUS
MLF
MEDIAL LEMNISCUS
CORTICOPONTINE TRACT
TRIGEMINAL LEMNISCUS
SUBSTANTIA NIGRA
SPINOTHALAMIC
OCULOMOTOR NUCLEUS
OCULOMOTOR NERVE
NUCLEUS OF TRIGEMINAL NERVE
PERIAQUEDUCTAL
SUPERIOR COLLICULUS

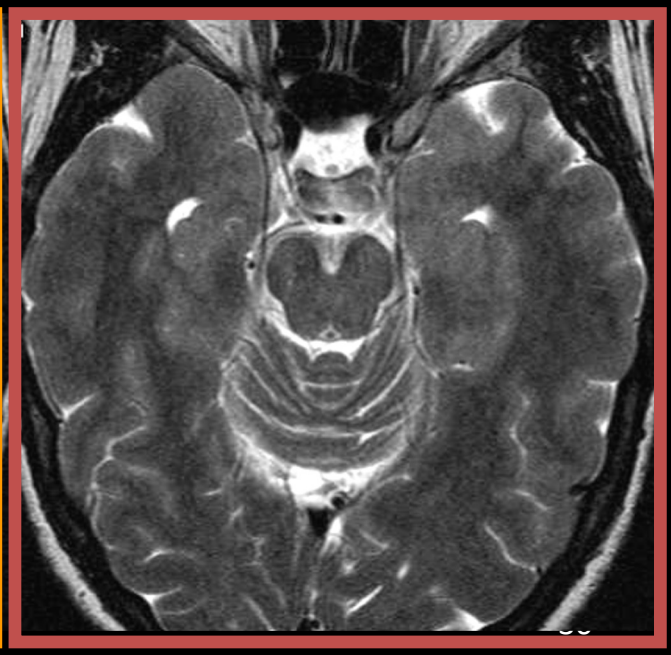
Midbrain



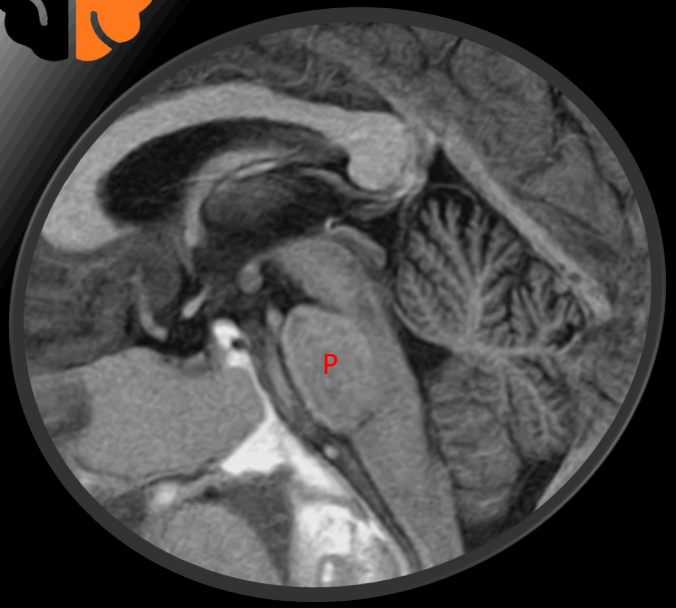
- Cerebral peduncles
- Substantia Nigra
- Red Nucelus
- Quadrigeminal plate







Pons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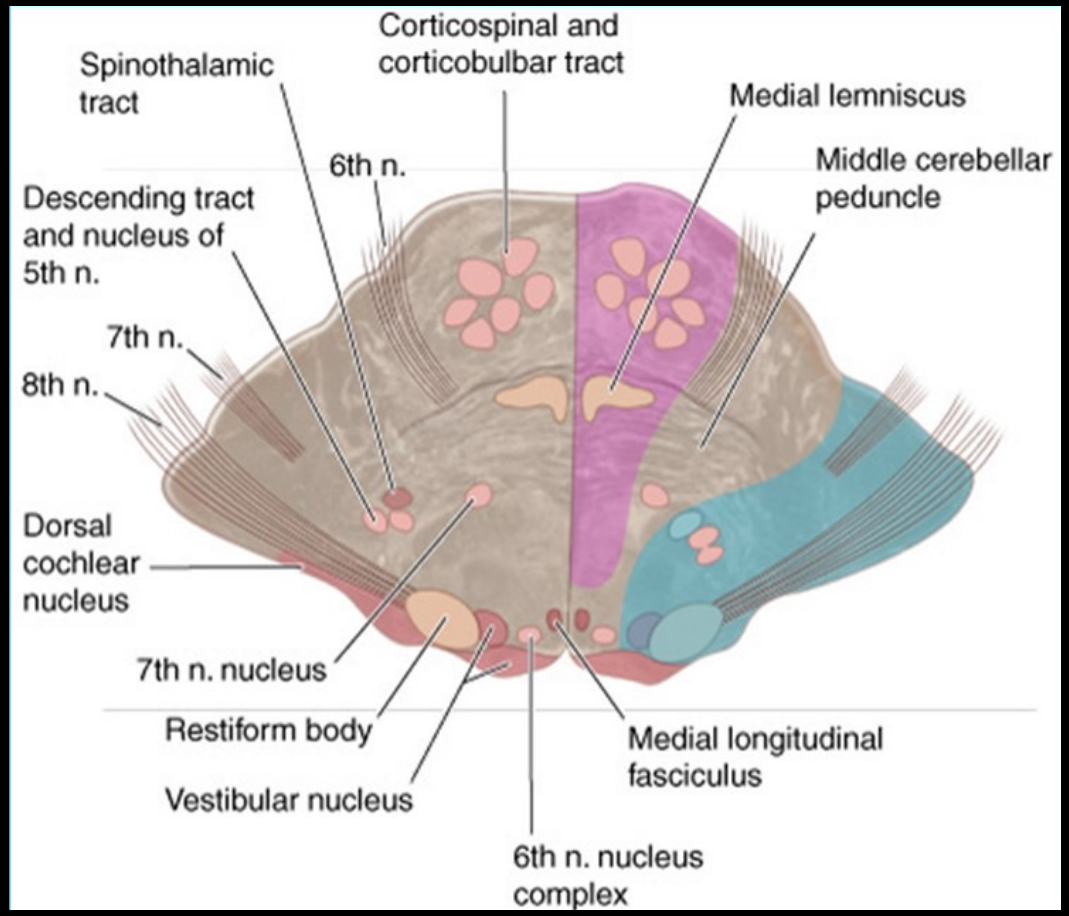
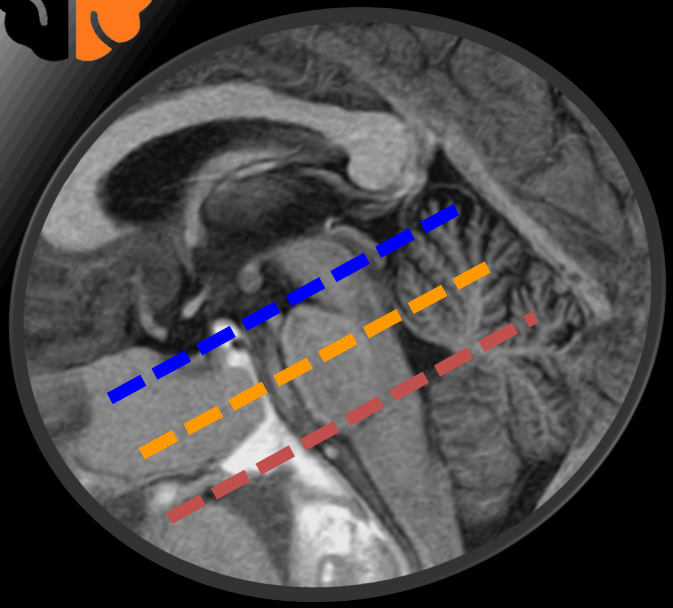
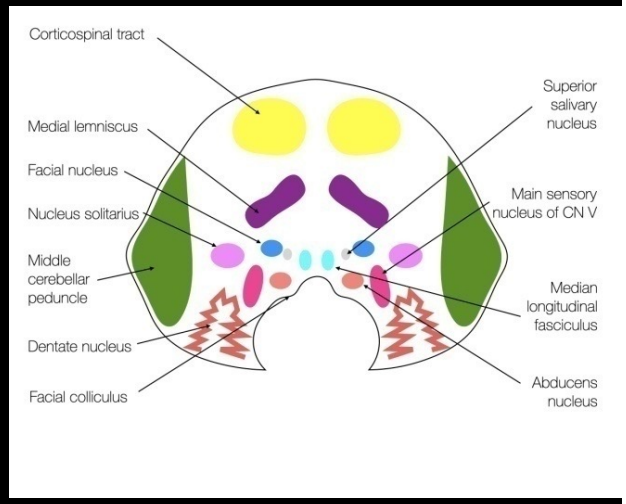
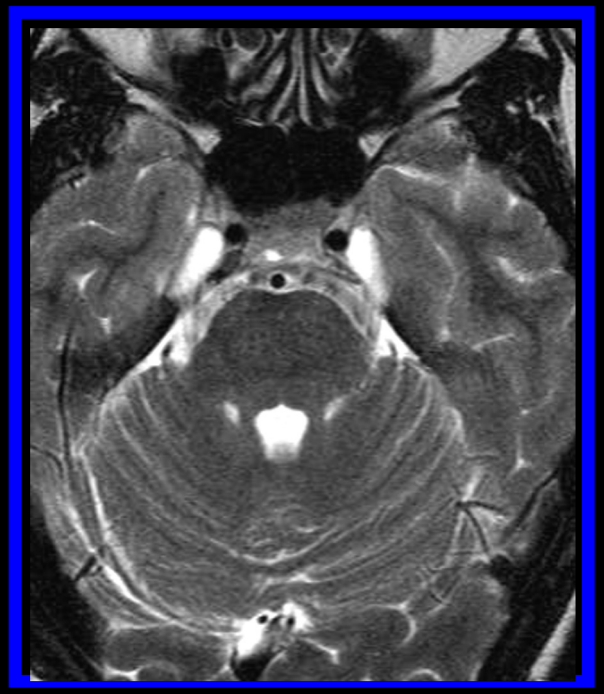

Spinothalamic tract
Corticospinal and corticobulbar tract
Medial lemniscus
6th n.
Middle cerebellar peduncle
Descending tract and nucleus of 5th n.
7th n.
8th n.
Dorsal cochlear nucleus
7th n. nucleus
Restiform body
Vestibular nucleus
Medial longitudinal fasciculus
6th n. nucleus complex

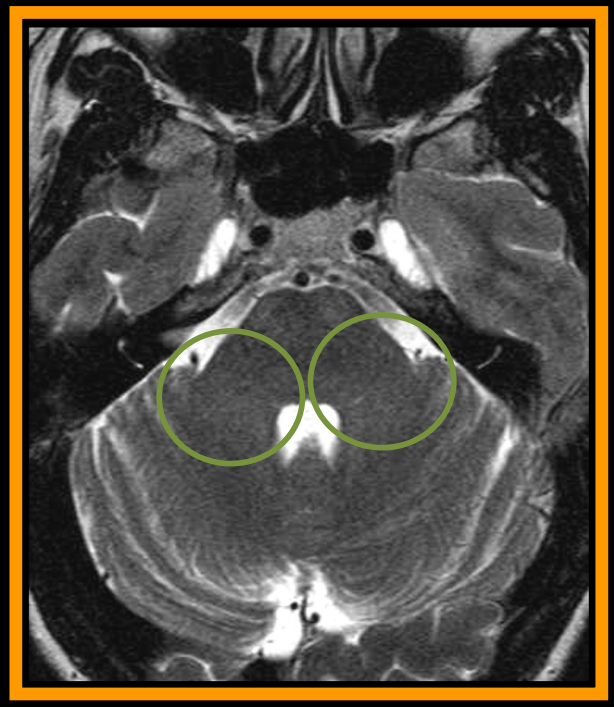
Pons

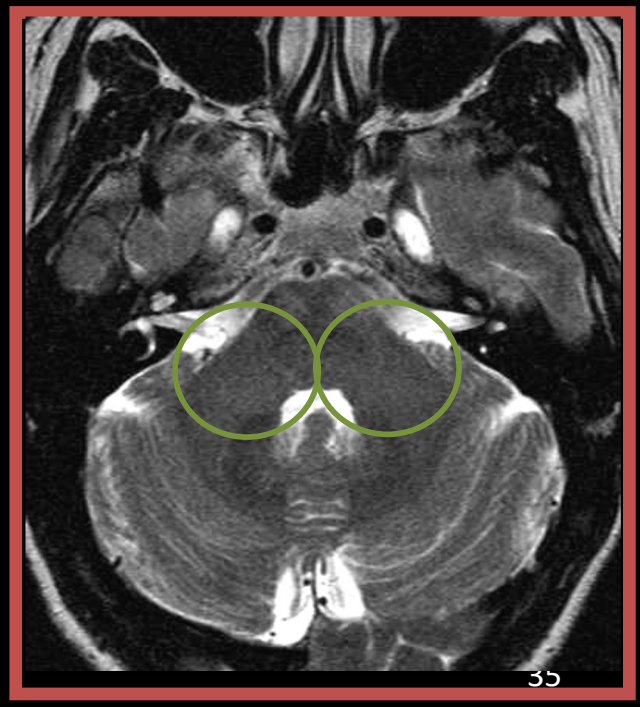


- Superior cerebellar peduncles
- Middle cerebellar peduncles

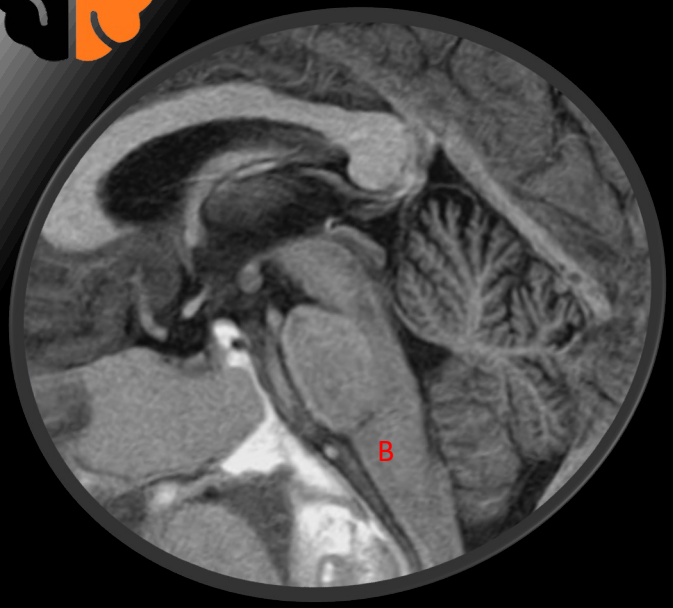


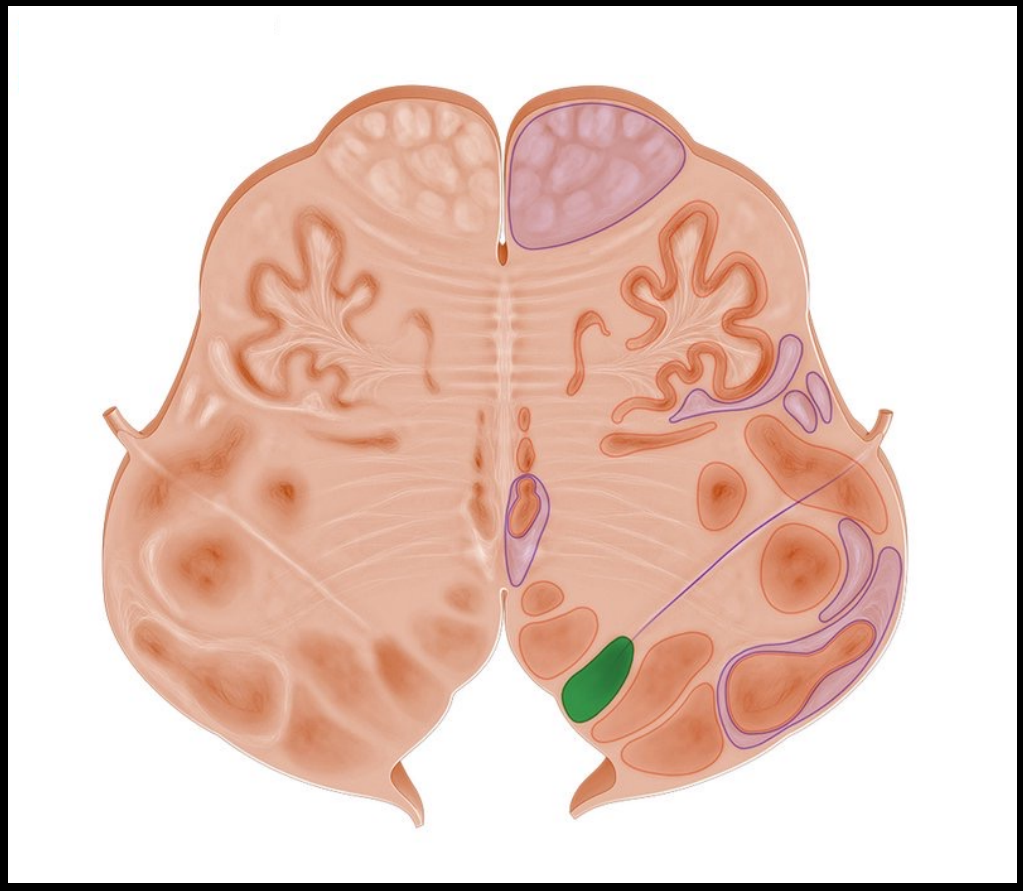




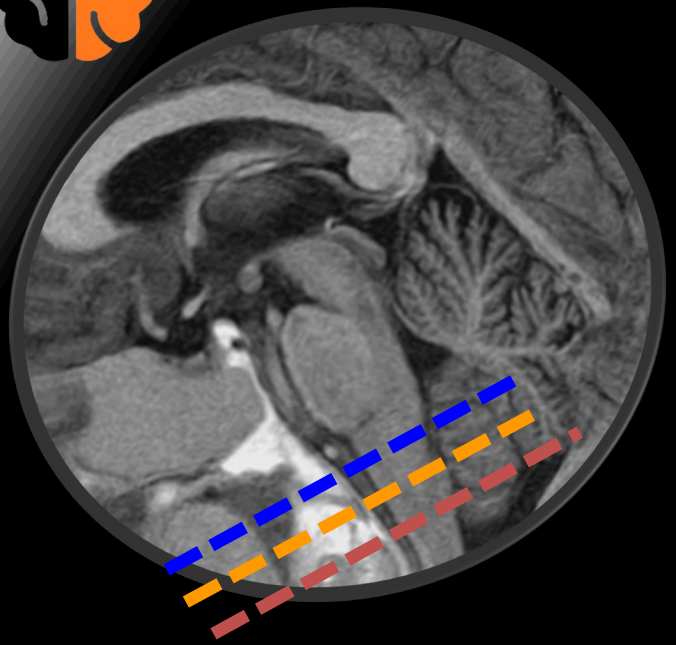


Medulla

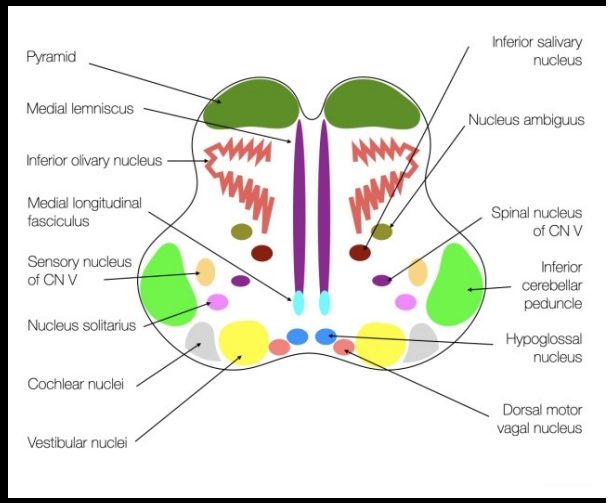


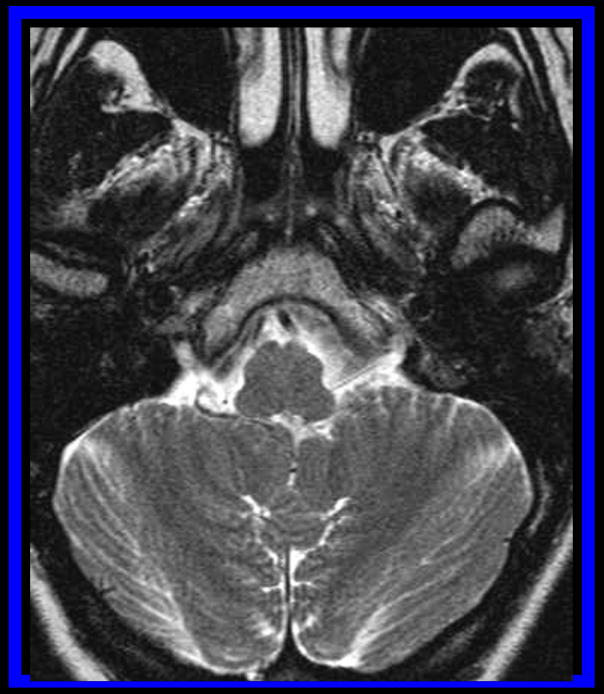


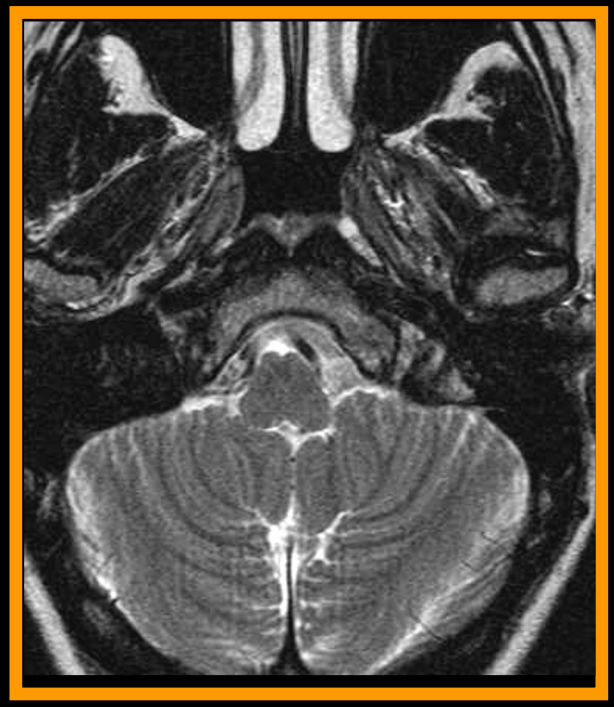
Medulla

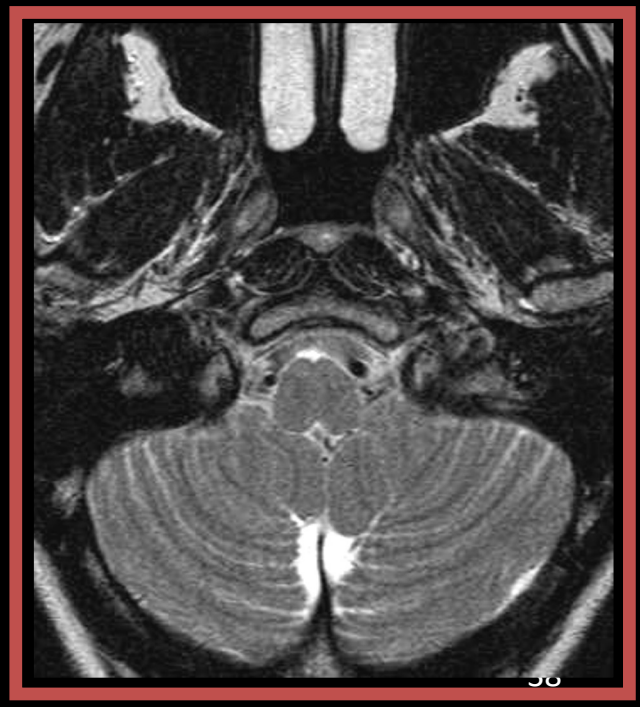


- Pyramids
- Olives
- Inferior cerebellar peduncles









Outline

- Anatomy

- Conventional MRI – Sequences

- Conventional MRI findings in main hereditary ataxias

- Neuroradiological diagnostic algorithm

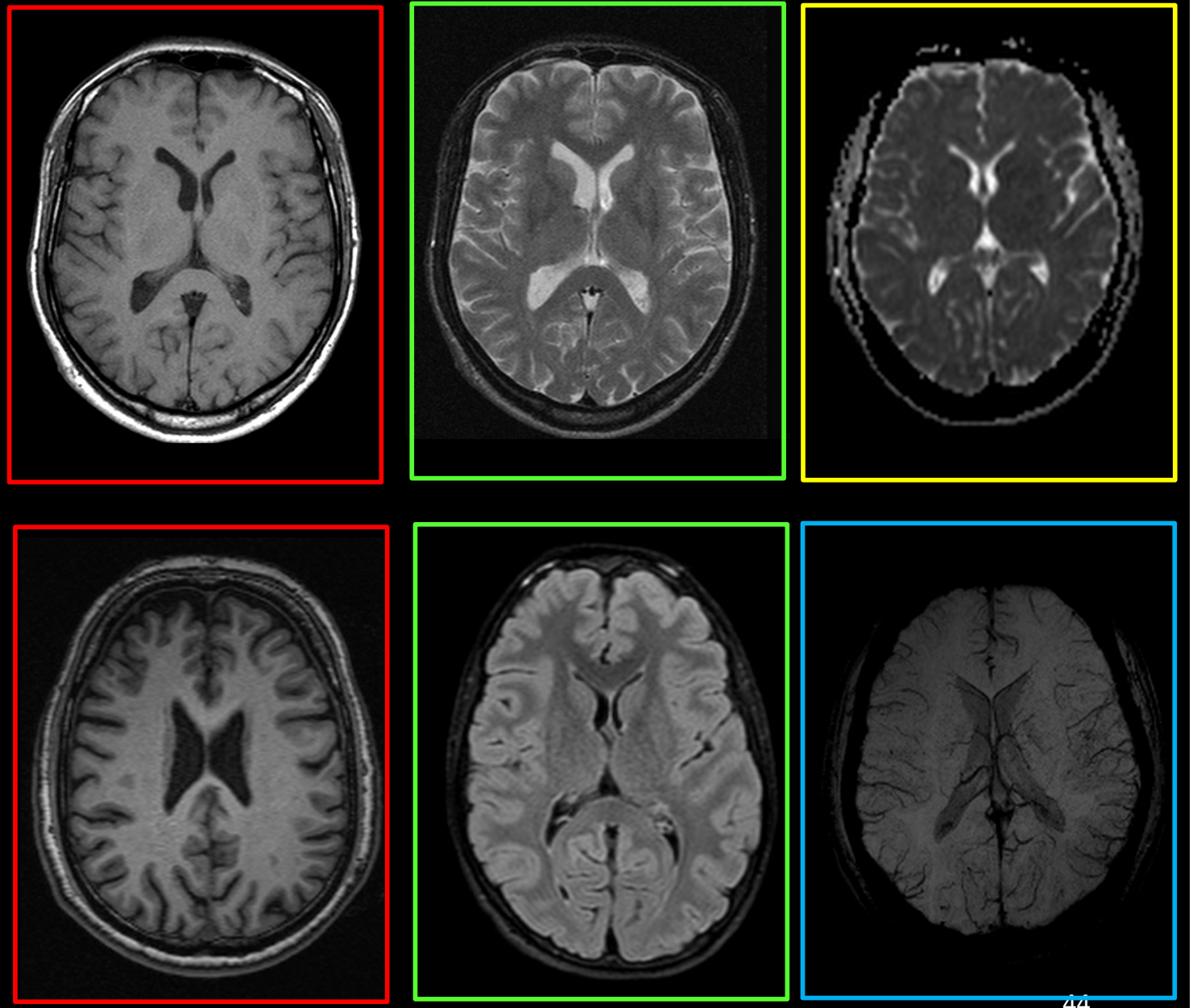
Conventional MRI sequences

- T1-weighted

- T2-weighted

- DWI

- SWI



Conventional MRI sequences

- T1-weighted

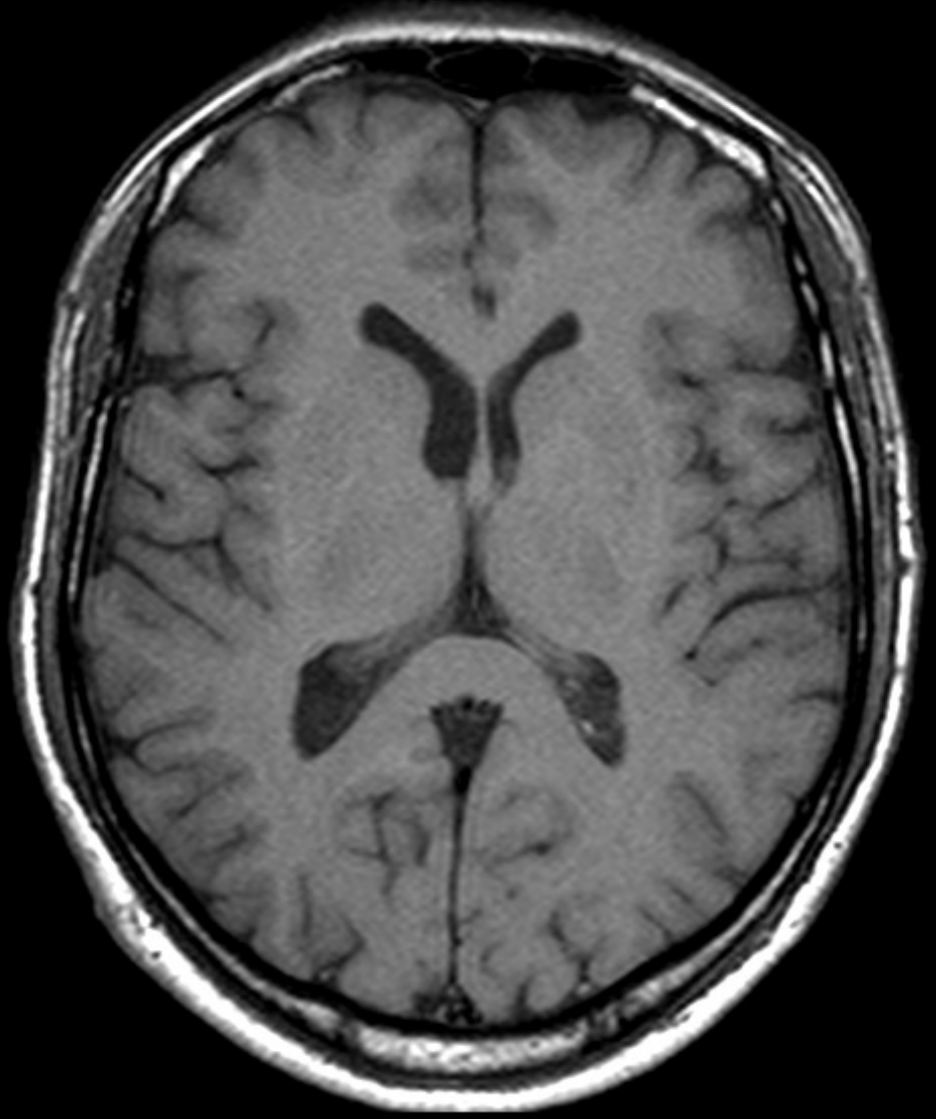
- T2-weighted

Ideally: all sequences, all planes!

Conventional MRI sequences

- T1-weighted

- T2-weighted

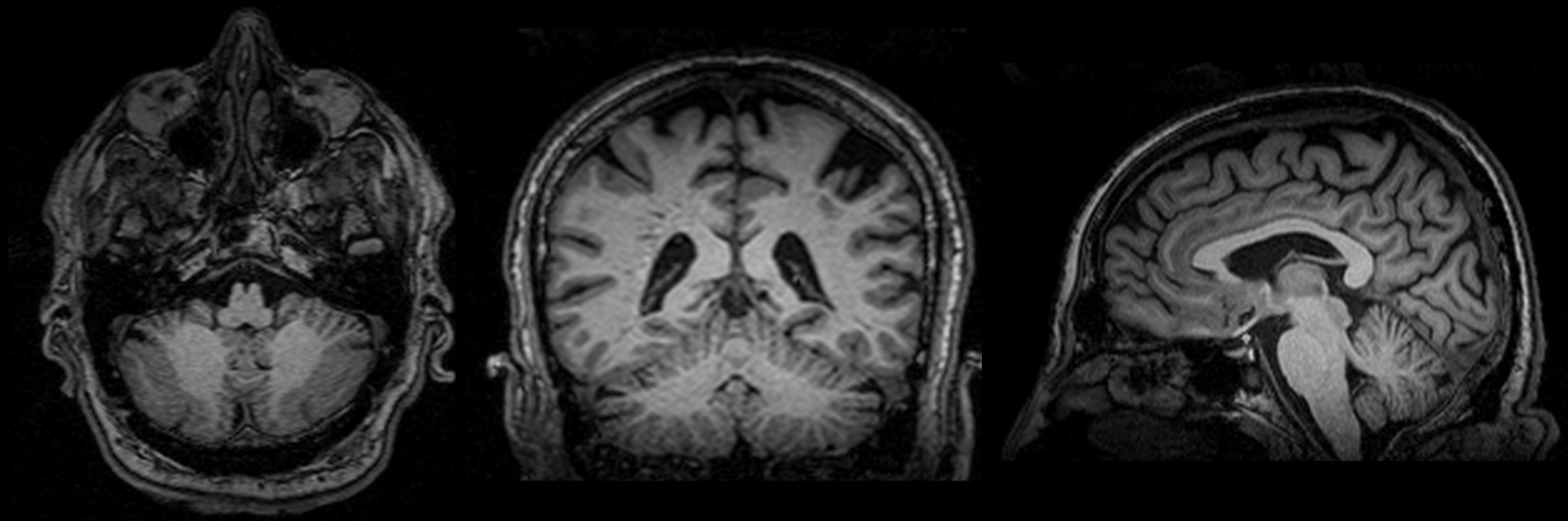


"Gray is gray, white is white"

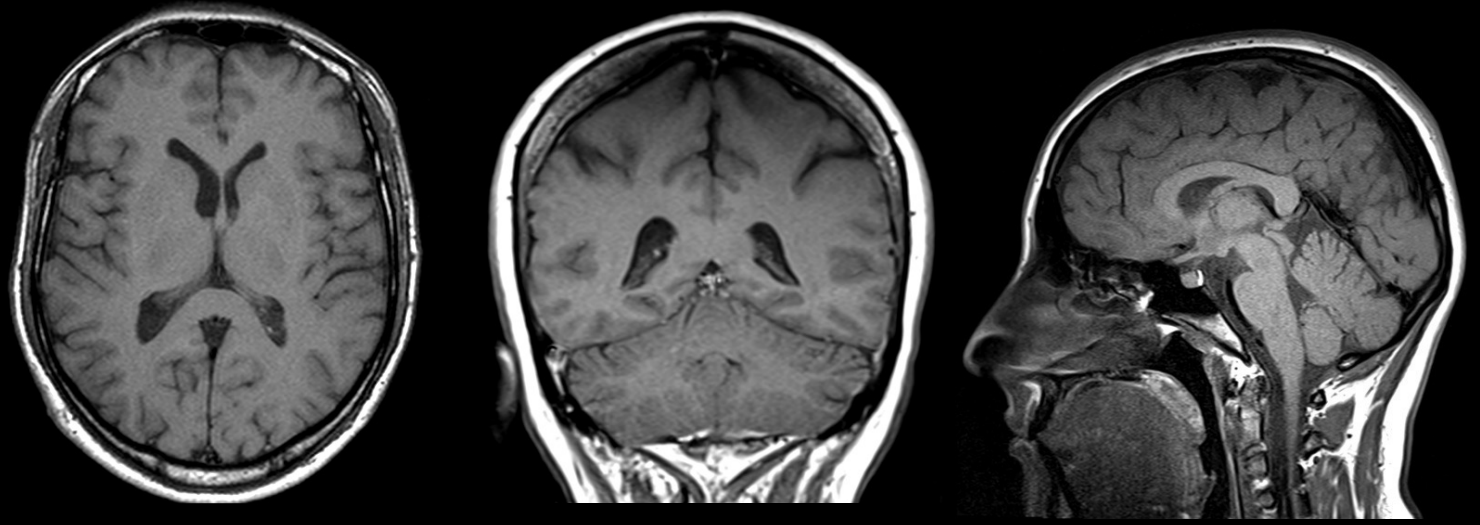
Conventional MRI sequences

- T1-weighted

- T2-weighted

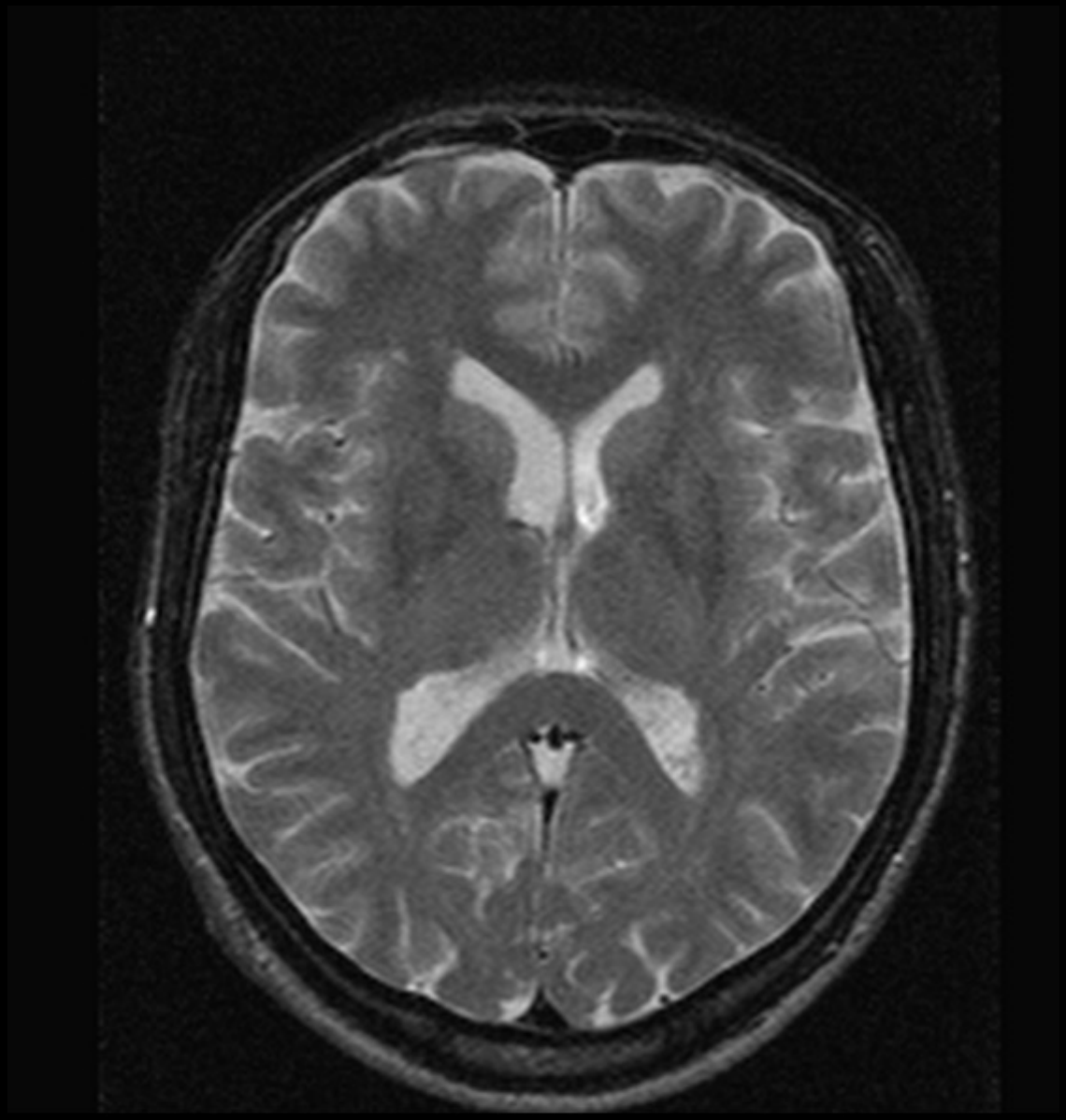


GrE-T1w



Conventional MRI sequences

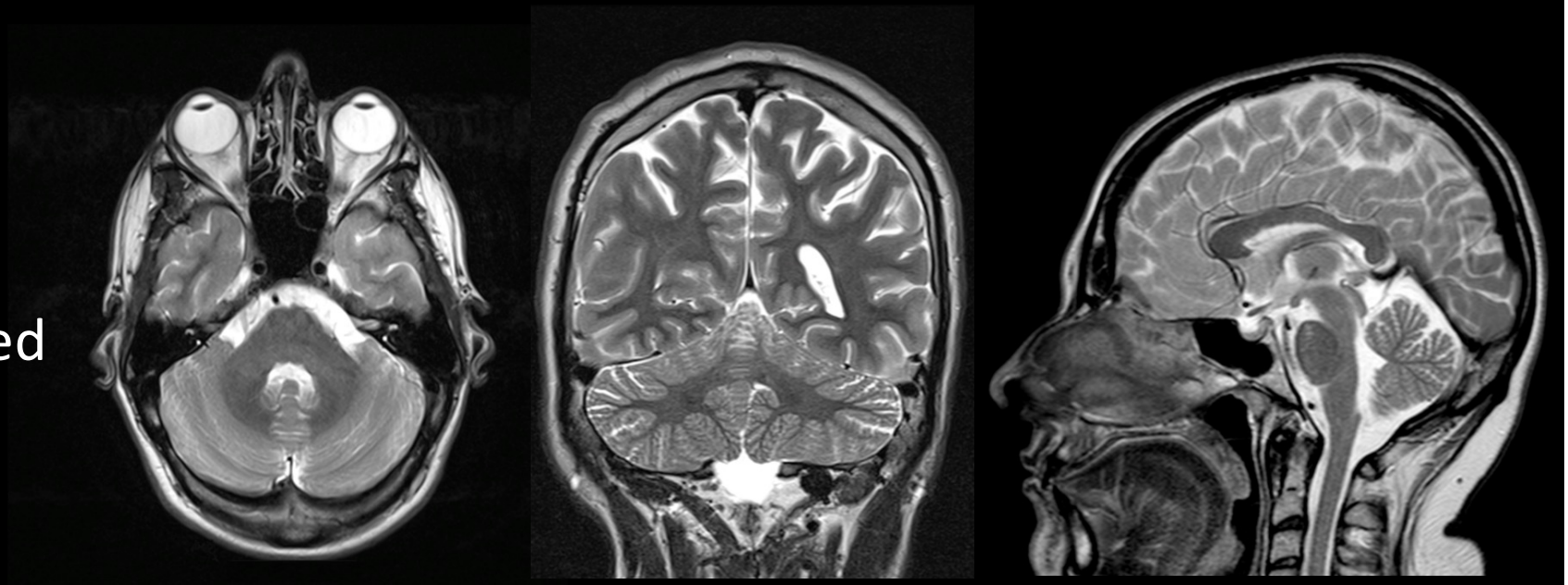
- T2-weighted

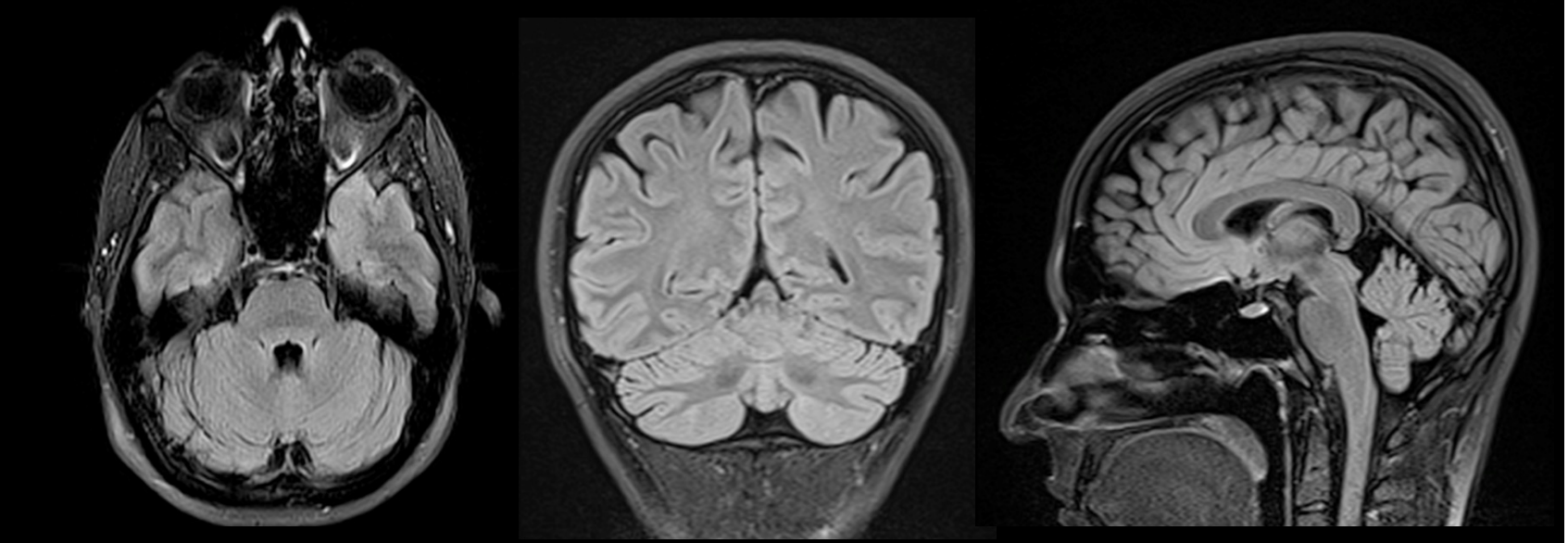


"Gray is white, white is gray"

Conventional MRI sequences

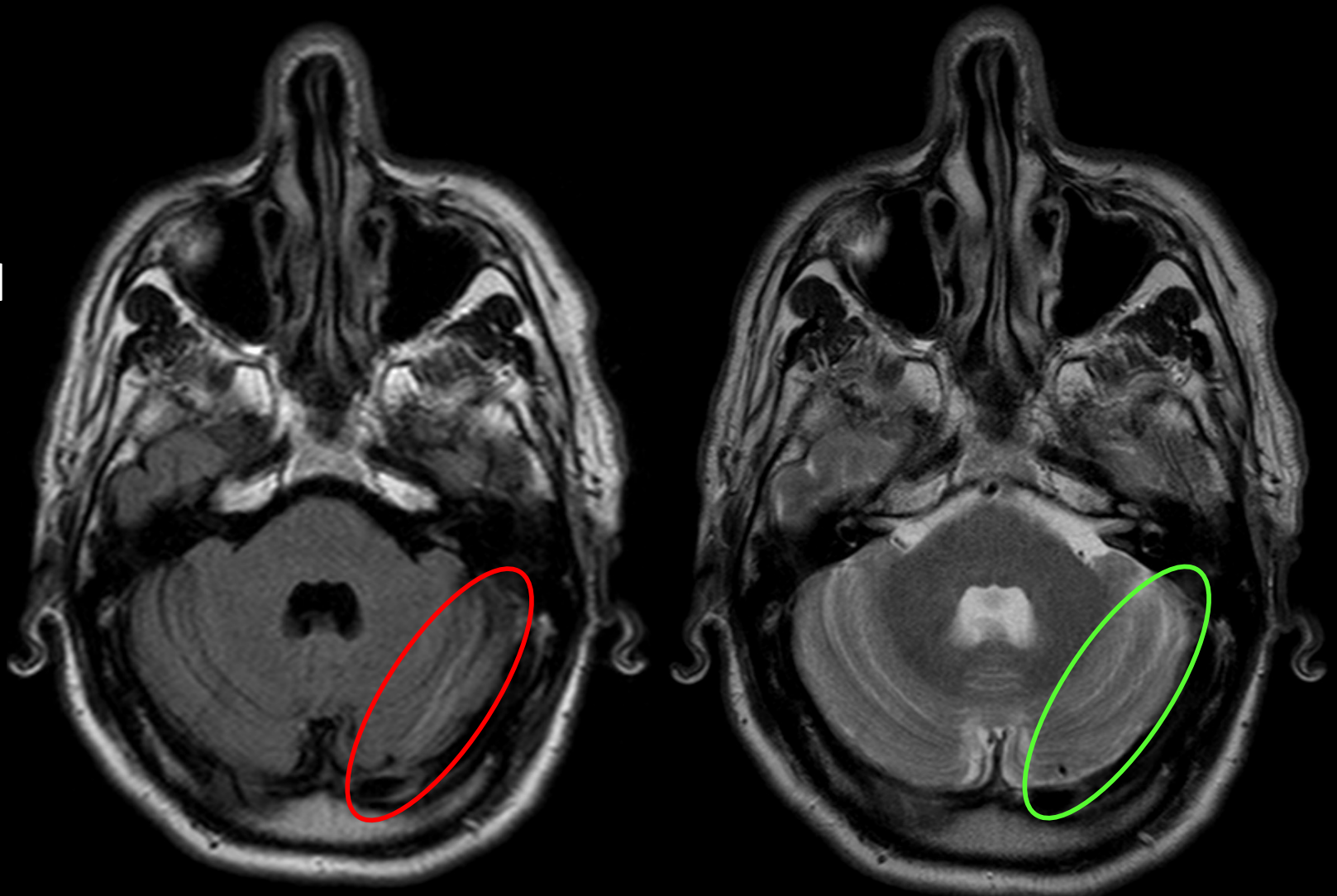
- T2-weighted



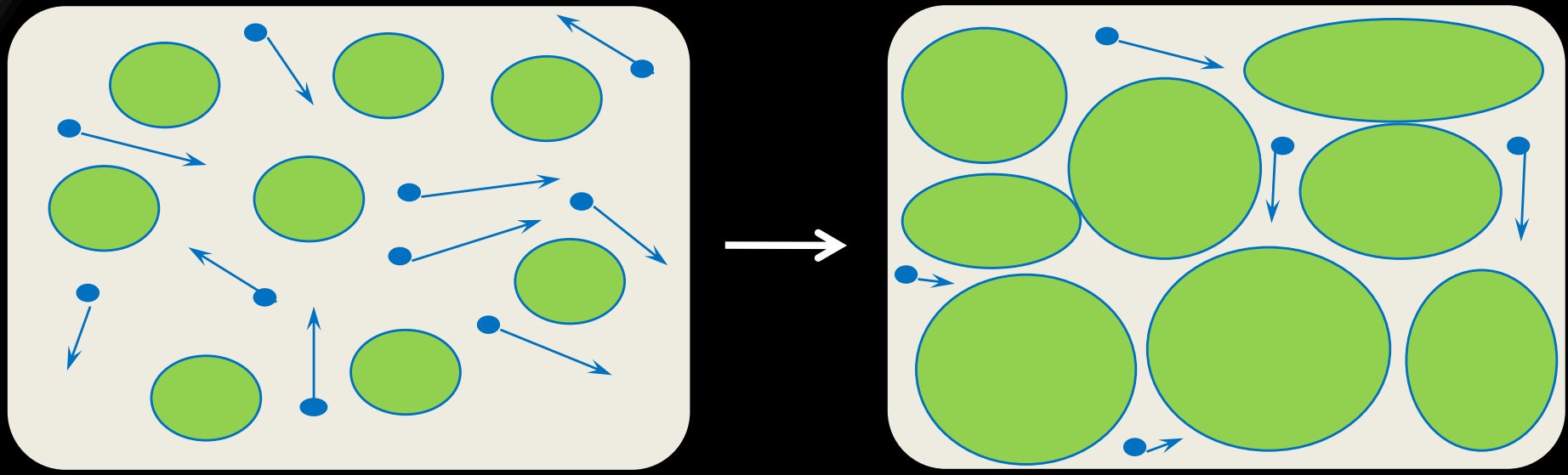


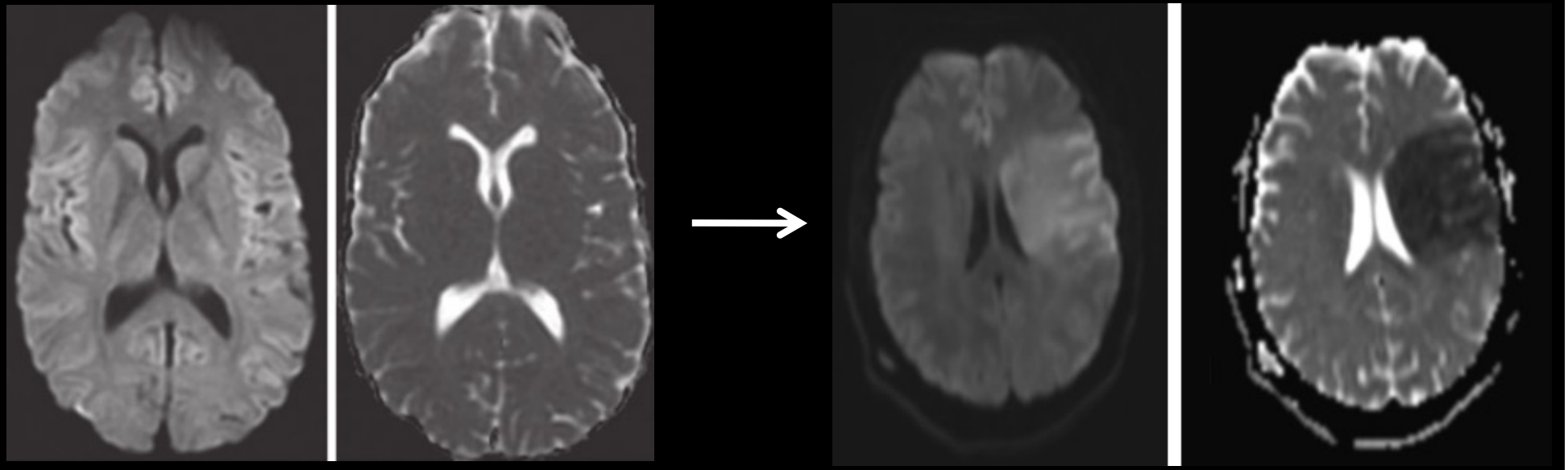
Conventional MRI sequences

- T2-weighted

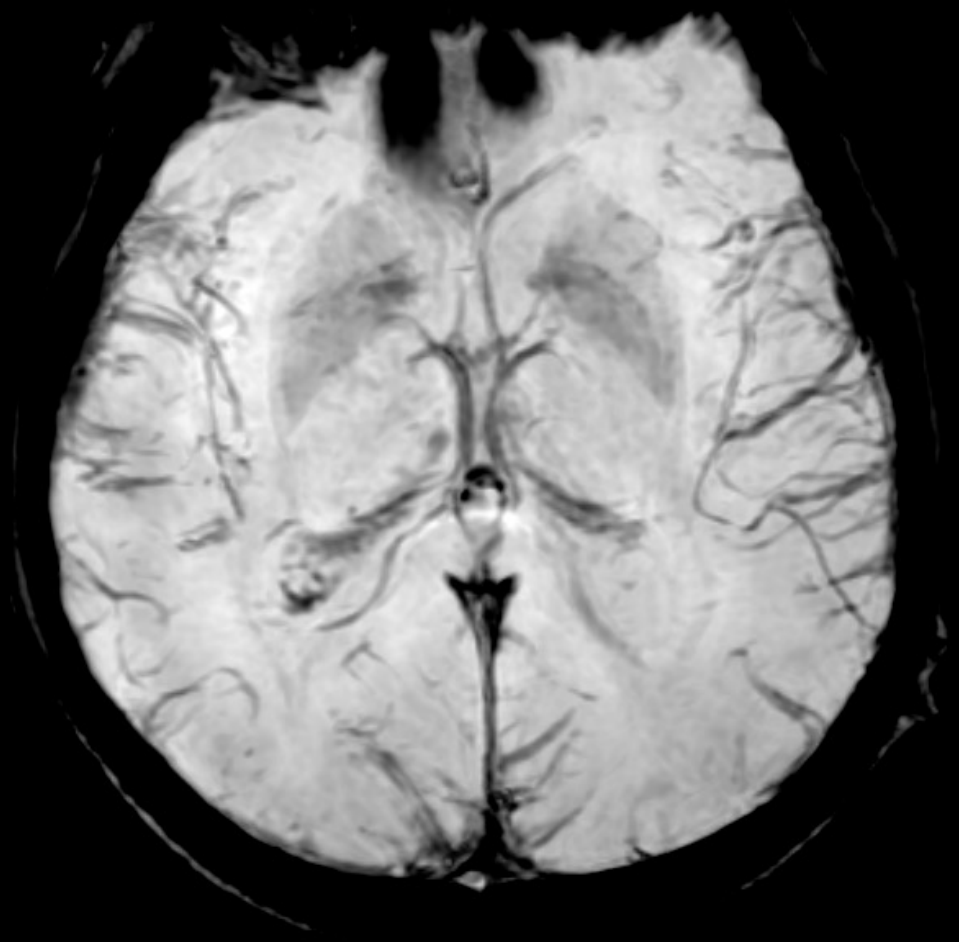


Conventional MRI sequences

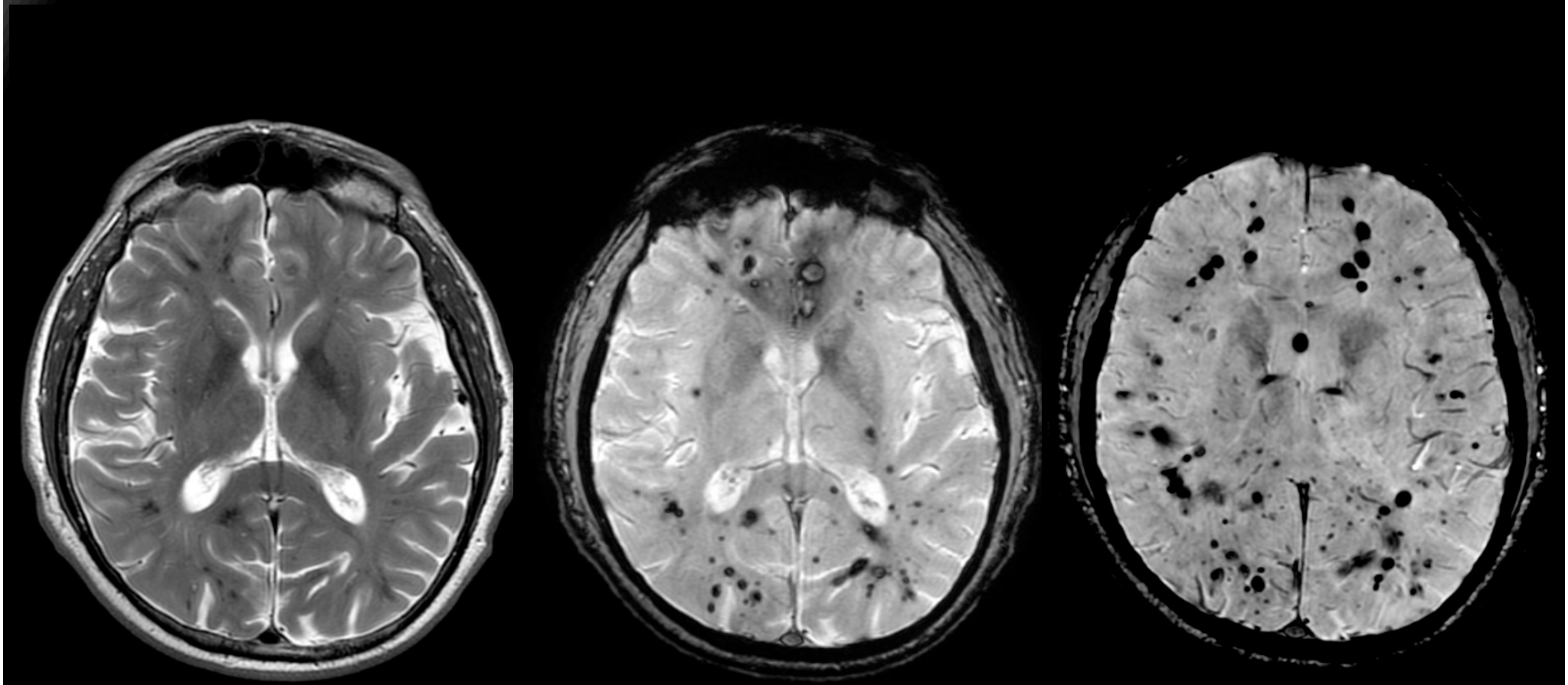




Conventional MRI sequences



Conventional MRI sequences



HA: classification

-Three major groups: acquired, sporadic and hereditary ataxias [1]

Table 1 Autosomal recessive ataxias: molecular genetics

Disorder	Gene product	Function
Mitochondrial/oxidative stress		
FRDA	Frataxin	Synthesis of iron sulphur clusters
MIRAS	POLG	Mitochondrial DNA proofreading
IOSCA	Twinkle	Mitochondrial DNA proofreading
Autosomal recessive cerebellar ataxia type 2 (ARCA2, SCAR9)	ADCK3	Coenzyme Q10 synthesis
AVED	α-Tocopherol transport protein	Vitamin E
Abetalipoproteinemia	Microsomal triglyceride transfer protein	Vitamin E
DNA repair		
AT	ATM protein	Phosphoinositol-3 kinase activity: cell cycle checkpoint control and DNA repair
ATLD	MRE11	Double-strand DNA repair
AOA1	Aprataxin	Single-strand DNA repair
Ataxia with oculomotor apraxia type 2 (AOA2, SCAR2)	Senataxin	Single-strand DNA repair
SCAN1	TDP1	DNA replication
Other mechanisms		
Refsum disease	Phytanoyl-CoA hydroxylase	Oxidation of phytanic acid
CTX	Sterol-27 hydroxylase	Sterol hydroxylation
ARSACS	Sacsin	Proteasomal system
Ataxia and motor neuropathy 2	ANO10	Channel dysfunction
Ataxia with epilepsy and mental retardation	Rundataxin	Unknown
MSS	SIL1	ER glycoprotein
Autosomal recessive cerebellar ataxia type 1 (ARCA1, SCAR8)	SYNE1	Member of spectrin family
PHARC	ABHD12	Endocannabinoid metabolism: hydrolysis 2-arachidonoyl glycerol (2-AG)

ANO10, anoctamin 10; AOA1, ataxia with oculomotor apraxia type 1; ARSACS, autosomal recessive spastic ataxia of Charlevoix–Saguenay; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia-like disorder; AVED, ataxia with isolated vitamin E deficiency; CTX, cerebrotendinous xanthomatosis; ER, endoplasmic reticulum; FRDA, Friedreich ataxia; IOSCA, infantile onset spinocerebellar ataxia; MIRAS, mitochondrial recessive ataxia syndrome; MSS, Marinesco–Sjögren syndrome; PHARC, polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract. POLG, polymerase gamma; SCAN1, spinocerebellar ataxia with axonal neuropathy 1; TDP1, tyrosyl-DNA phosphodiesterase-1.

Table 2 Spinocerebellar ataxias: molecular genetics and clinical phenotype

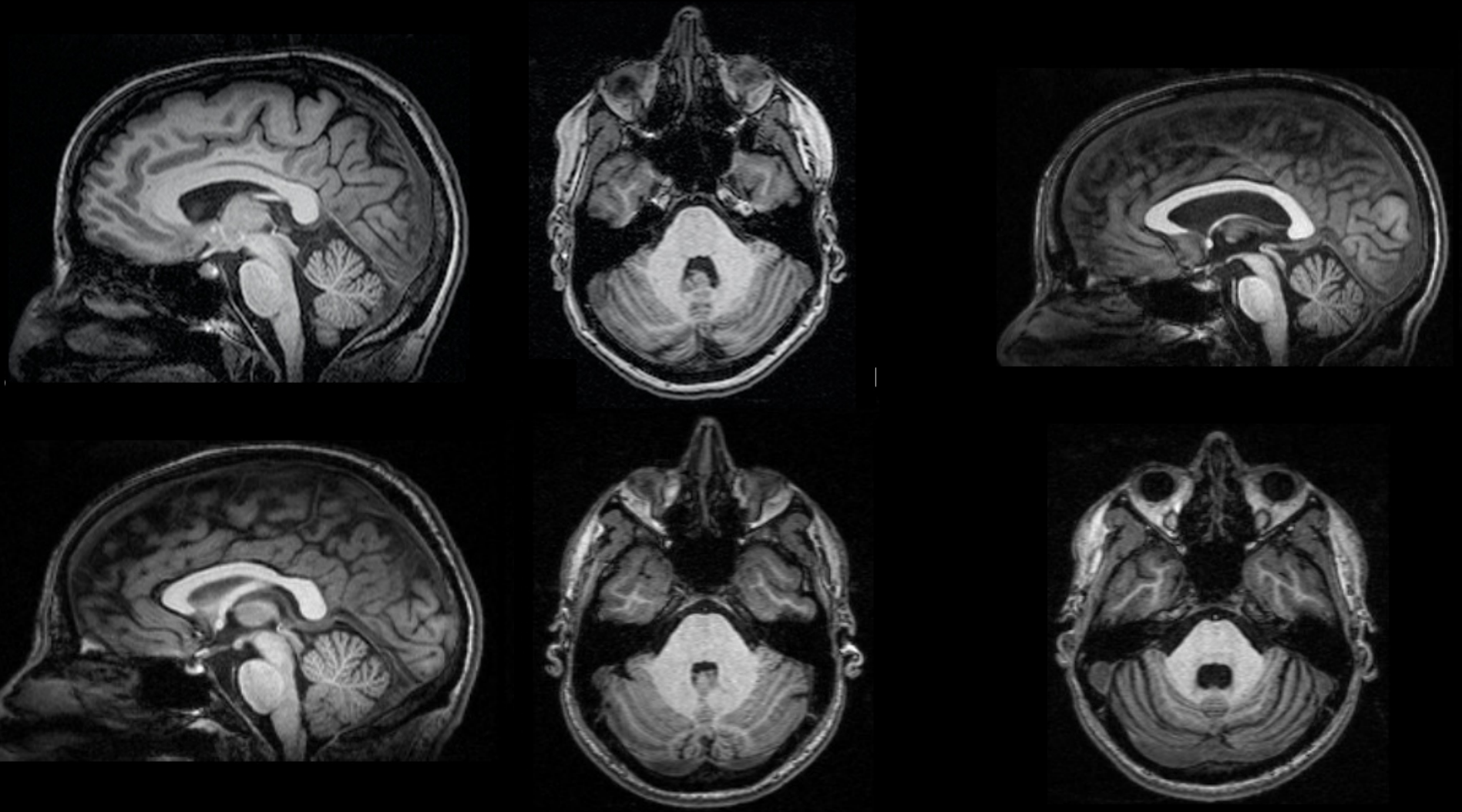
Disorder	Mutation	Gene product	Clinical phenotype
SCA1	Translated CAG repeat expansion	Ataxin-1	Ataxia, pyramidal signs, neuropathy, dysphagia, restless legs syndrome
SCA2	Translated CAG repeat expansion	Ataxin-2	Ataxia, slow saccades, neuropathy, restless legs syndrome
SCA3/MJD	Translated CAG repeat expansion	Ataxin-3	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia, restless legs syndrome
SCA4	Unknown	Unknown	Ataxia, sensory neuropathy
SCA5	Point mutation	Beta-III spectrin (SPTBN2)	Almost purely cerebellar ataxia
SCA6	Translated CAG repeat expansion	Calcium channel subunit (CACNA1A)	Almost purely cerebellar ataxia
SCA7	Translated CAG repeat expansion	Ataxin-7	Ataxia, ophthalmoplegia, visual loss
SCA8	3' Untranslated CTG repeat expansion	Ataxin-8	Ataxia, sensory neuropathy, spasticity
SCA10	Intronic ATTCT repeat expansion	Ataxin-10	Ataxia, epilepsy
SCA11	Insertion, deletion	TTBK2	Almost purely cerebellar ataxia
SCA12	5' Untranslated CAG repeat expansion	Phosphatase subunit (PP2A-PR55β)	Ataxia, tremor
SCA13	Point mutation	Potassium channel (KCNC3)	Ataxia, mental retardation
SCA14	Point mutation	PKCγ	Ataxia, myoclonus, dystonia, sensory loss
SCA15/16	Deletion	ITPR1	Almost purely cerebellar ataxia
SCA17	Translated CAG repeat expansion	TBP	Ataxia, dystonia, chorea, dementia, psychiatric abnormalities
SCA18	Unknown	Unknown	Ataxia, sensory neuropathy, neurogenic muscle atrophy
SCA19/22	Unknown	Unknown	Ataxia, myoclonus, cognitive impairment
SCA20	Unknown	Unknown	Ataxia, dysphonia
SCA21	Unknown	Unknown	Ataxia, parkinsonism
SCA23	Missense	PDYN	Ataxia, sensory neuropathy, pyramidal signs
SCA25	Unknown	Unknown	Ataxia, sensory neuropathy
SCA26	Unknown	Unknown	Almost purely cerebellar ataxia
SCA27	Point mutation	FGF14	Ataxia, tremor, mental retardation
SCA28	Missense	AFG3L2	Ataxia, opthalmoparesis, pyramidal signs
SCA30	Unknown	Unknown	Almost purely cerebellar ataxia
SCA31	Intronic pentanucleotide (TGGAA) repeat insertion	BEAN	Almost purely cerebellar ataxia
SCA-TGM6	Missense	TGM6	Ataxia, pyramidal signs

AFG3L2, ATPase family gene 3-like 2; BEAN, brain expressed associated with NEDD-4; FGF14, fibroblast growth factor 14; ITPR1, inositol 1,4,5-triphosphate receptor, type 1; MJD, Machado–Joseph disease; PDYN, prodynorphin; PKCγ, protein kinase C γ; SCAs, spinocerebellar ataxias; TBP, TATA binding protein; TGM6, transglutaminase 6; TTBK2, tau tubulin kinase 2.

[1] Klockgether T. Curr Opin Neurol 2011

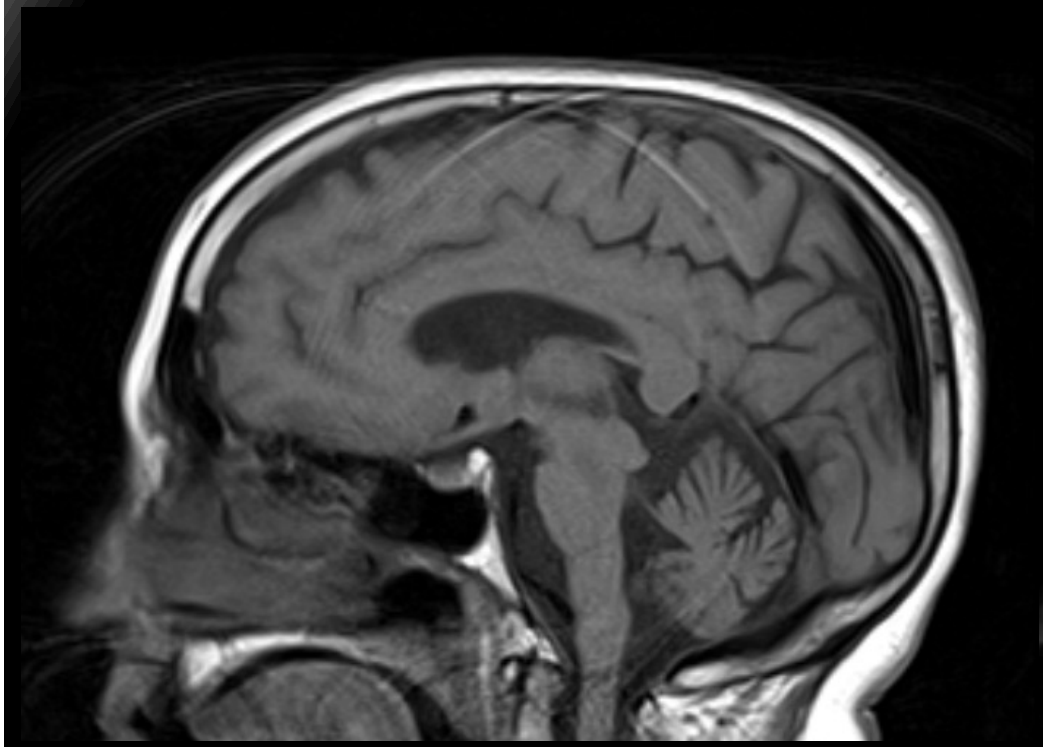
Conventional MRI: FRDA

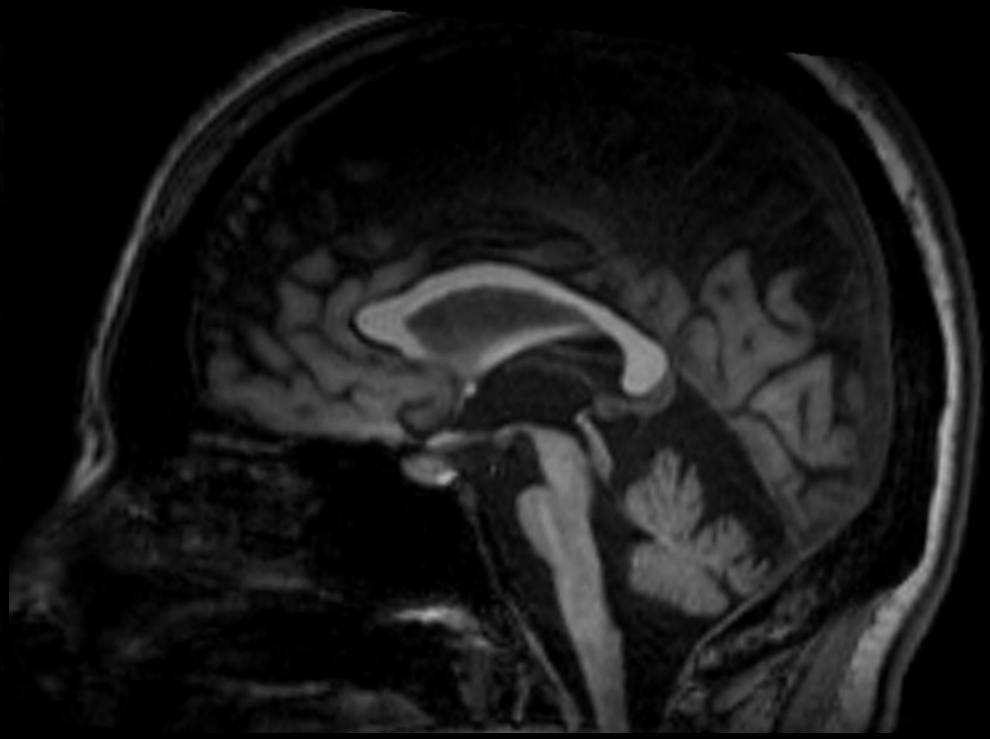
- Mild atrophy only in advanced stages of the disease [1]

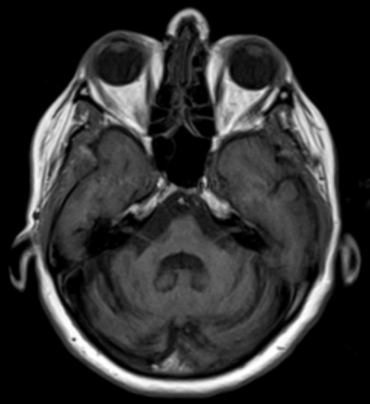


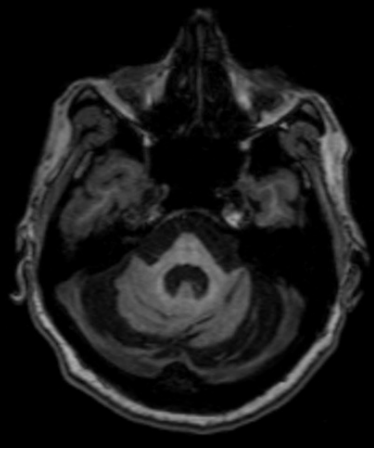
[1] Mascalchi M. AJNR Am J Neuroradiol 2013

SCA1 vs SCA2



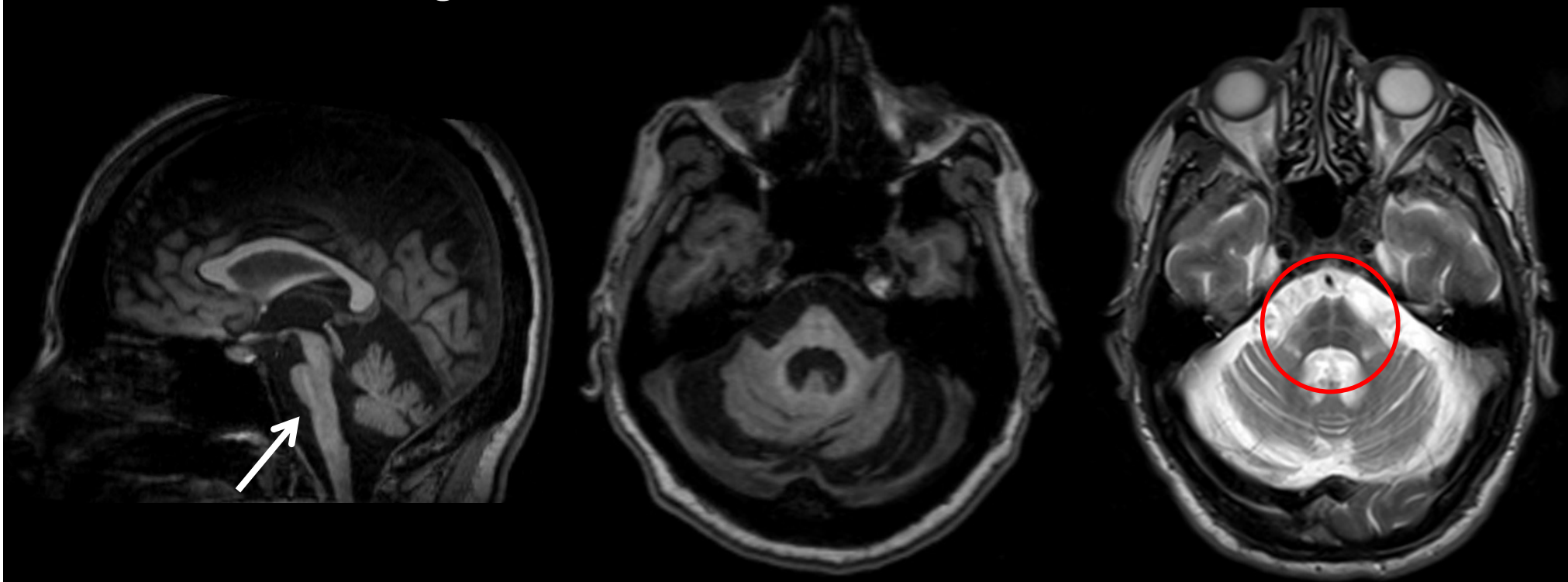






Conventional MRI: SCA2

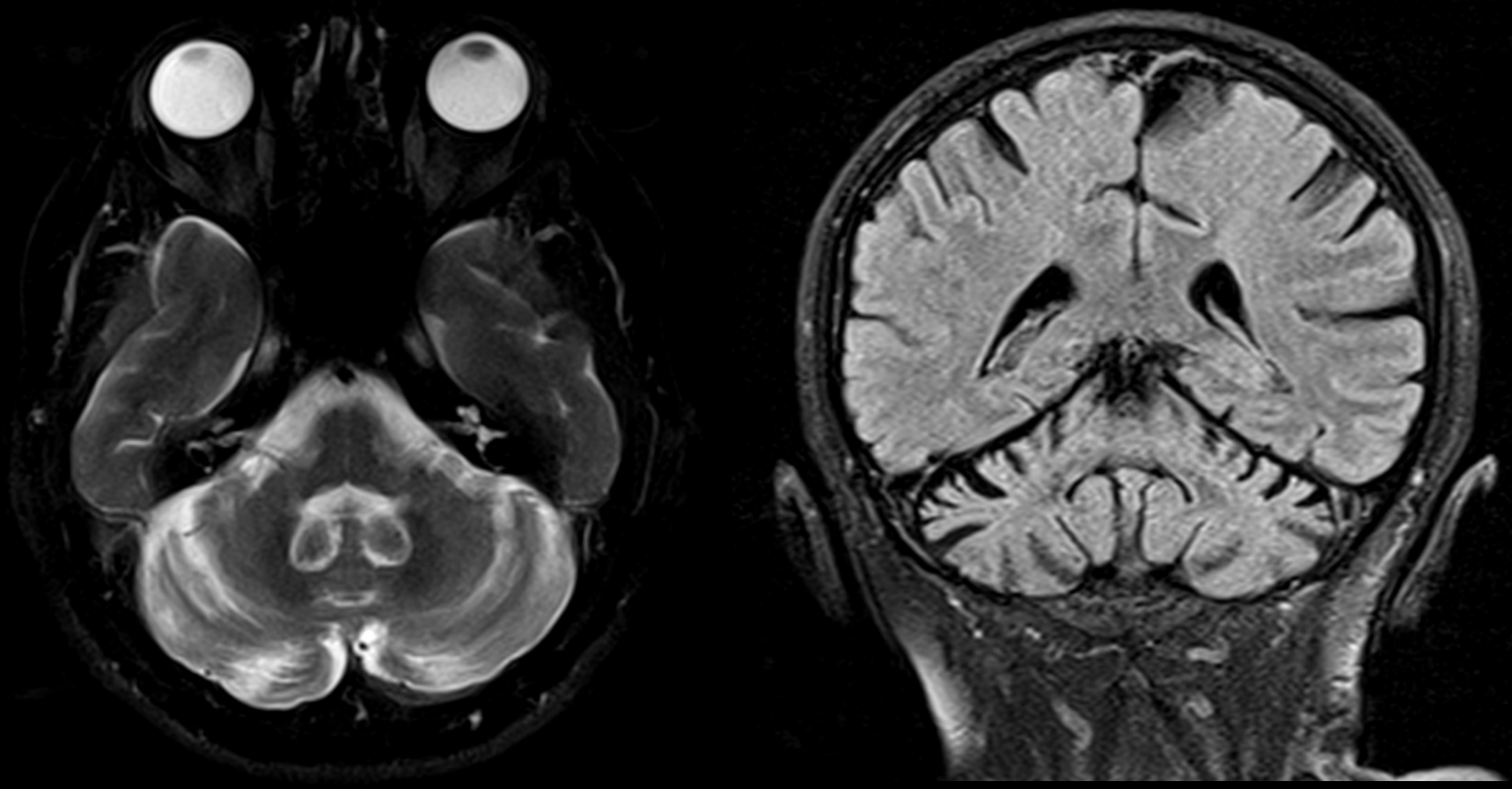
- Significant diffuse cerebellar + pontine atrophy + cruciform pontine T2-hyperintensity (“hot cross bun” sign) reported, due to ponto-cerebellar fibers degeneration [1]



[1] Velázquez-Pérez LC, et al. Front Neurol. 2017

Conventional MRI: SCA1

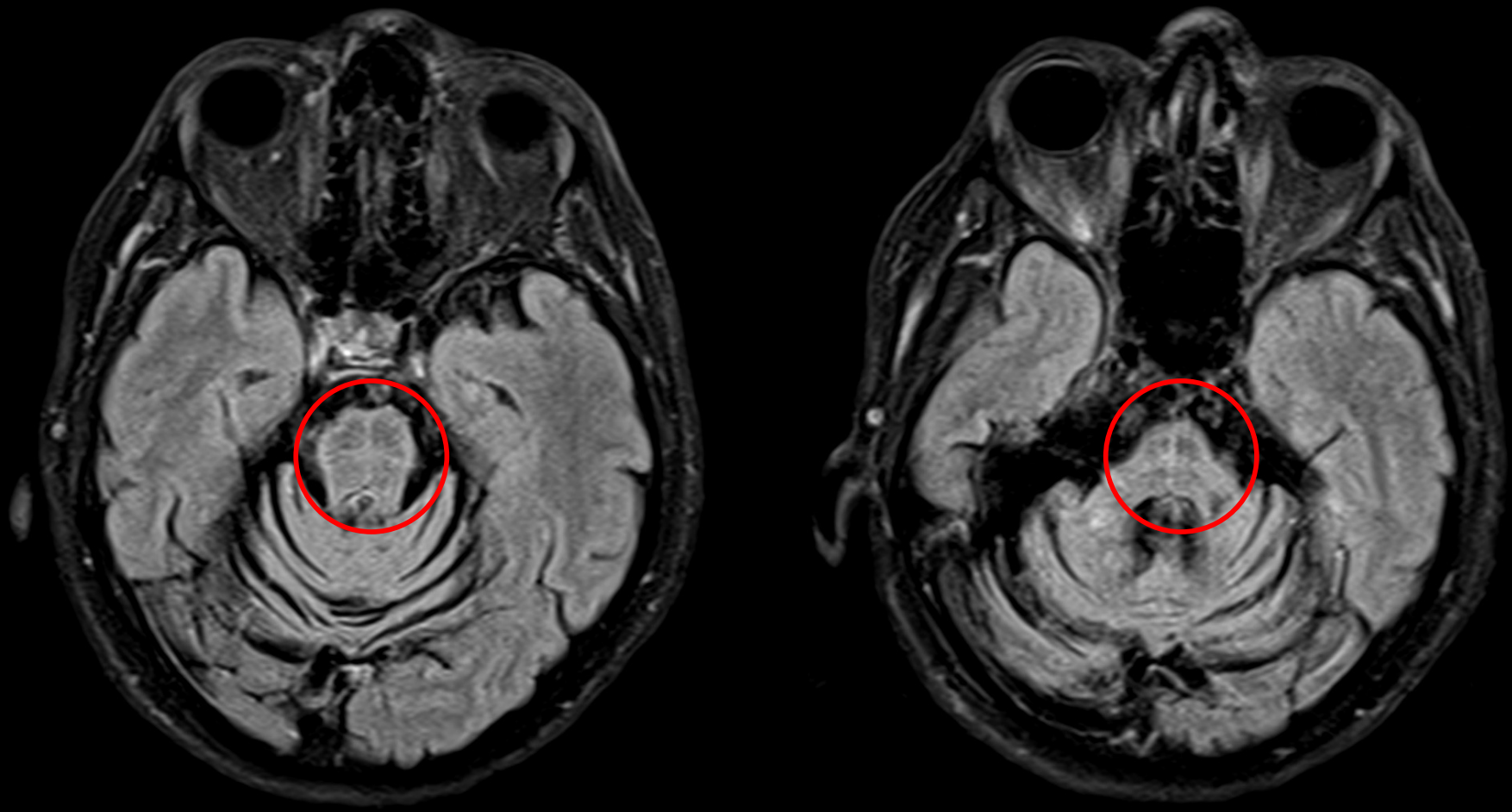
- Olivo-ponto-cerebellar atrophy with a similar distribution but less severe than SCA2 [1]



[1] Guerrini L, et al. Brain 2004

Conventional MRI: SCA1

- “Hot cross bun” sign also reported [1]

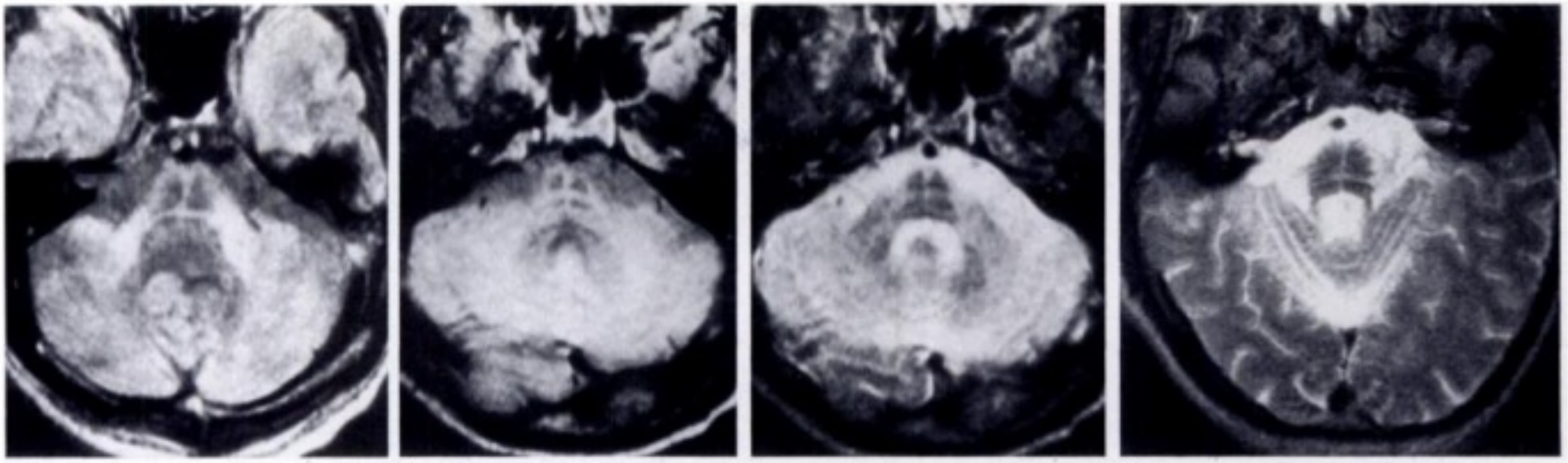


[1] Namekawa M, et al. Intern Med. 2015

HCB sign

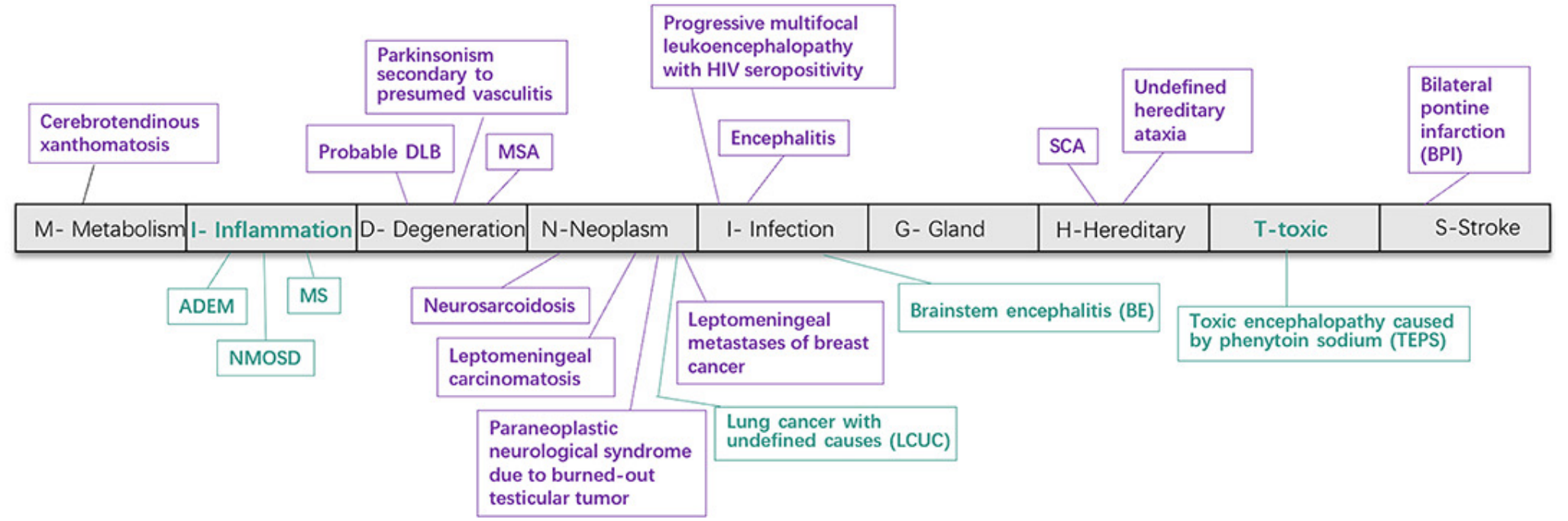
Mario Savoiardo, MD • Liliana Strada, MD • Floriano Girotti, MD • Robert A. Zimmerman, MD • Marina Grisoli, MD • Daniela Testa, MD • Raffaele Petrillo, MD

Olivopontocerebellar Atrophy: MR Diagnosis and Relationship to Multisystem Atrophy[1]



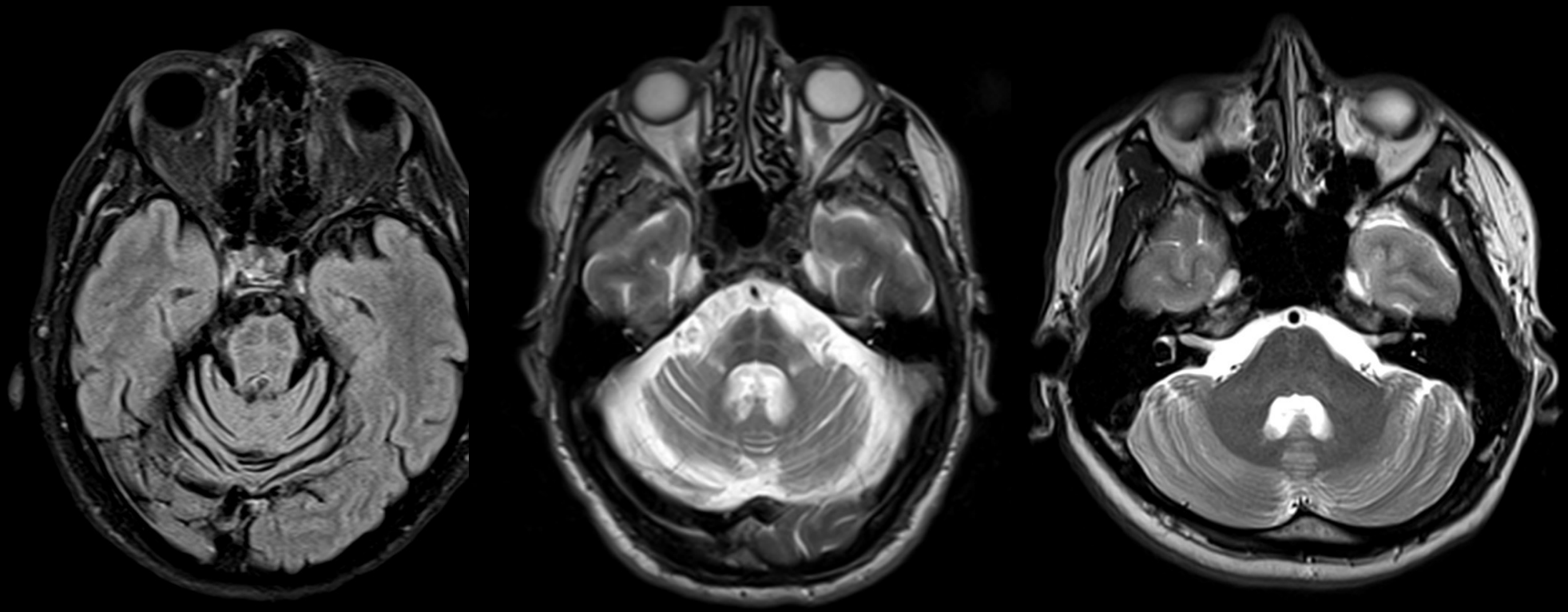
a. b. c. d.

HCB sign



Shuzhen Z, et al. Frontiers in Aging Neuroscience 2020

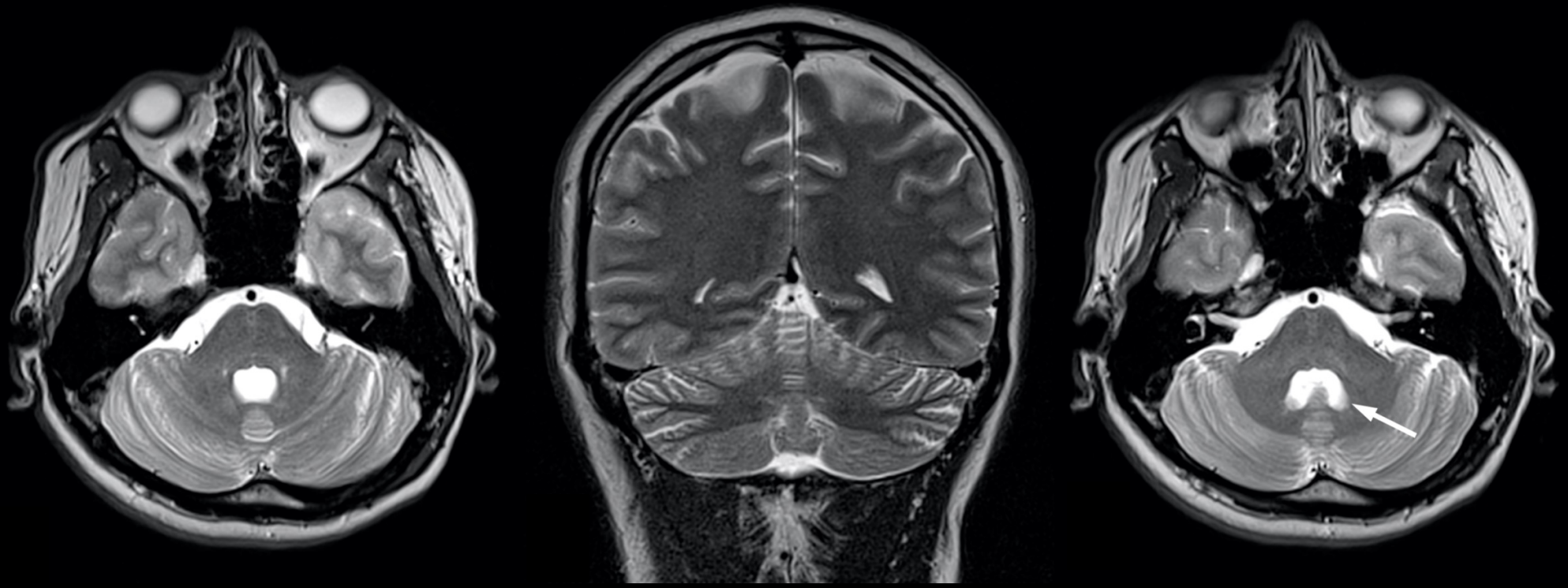
HCB sign in SCAs



SCA1 SCA2 SCA3

Conventional MRI: SCA3

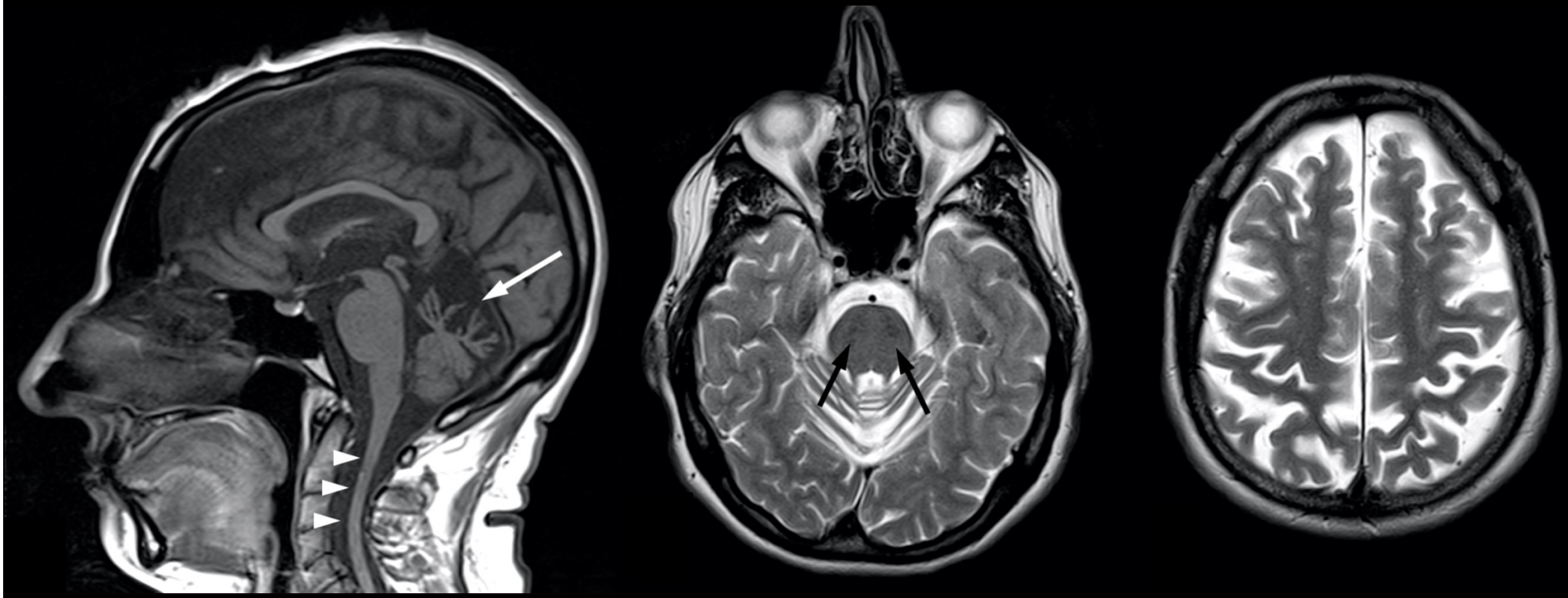
- Variable degree of ponto-cerebellar atrophy, less severe compared to the one found in SCA1 and SCA2 [1]



[1] Eichler L, et al. AJNR Am J Neuroradiol. 2011

Conventional MRI: ARSACS

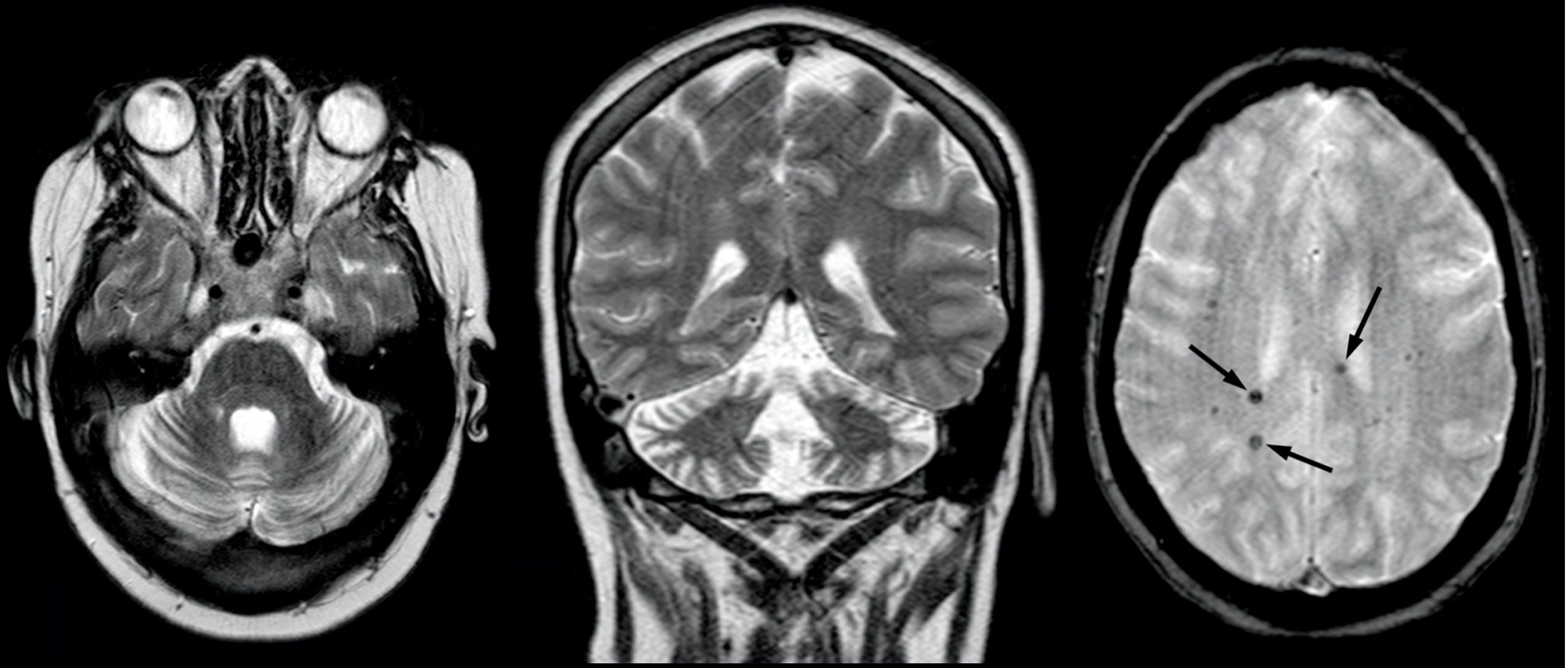
- Superior vermis atrophy + linear pontine T2w hypointensities + thickened MCP + bilateral parietal atrophy [1]



[1] Cocozza S, et al. Neuroradiology 2021

Conventional MRI: AT

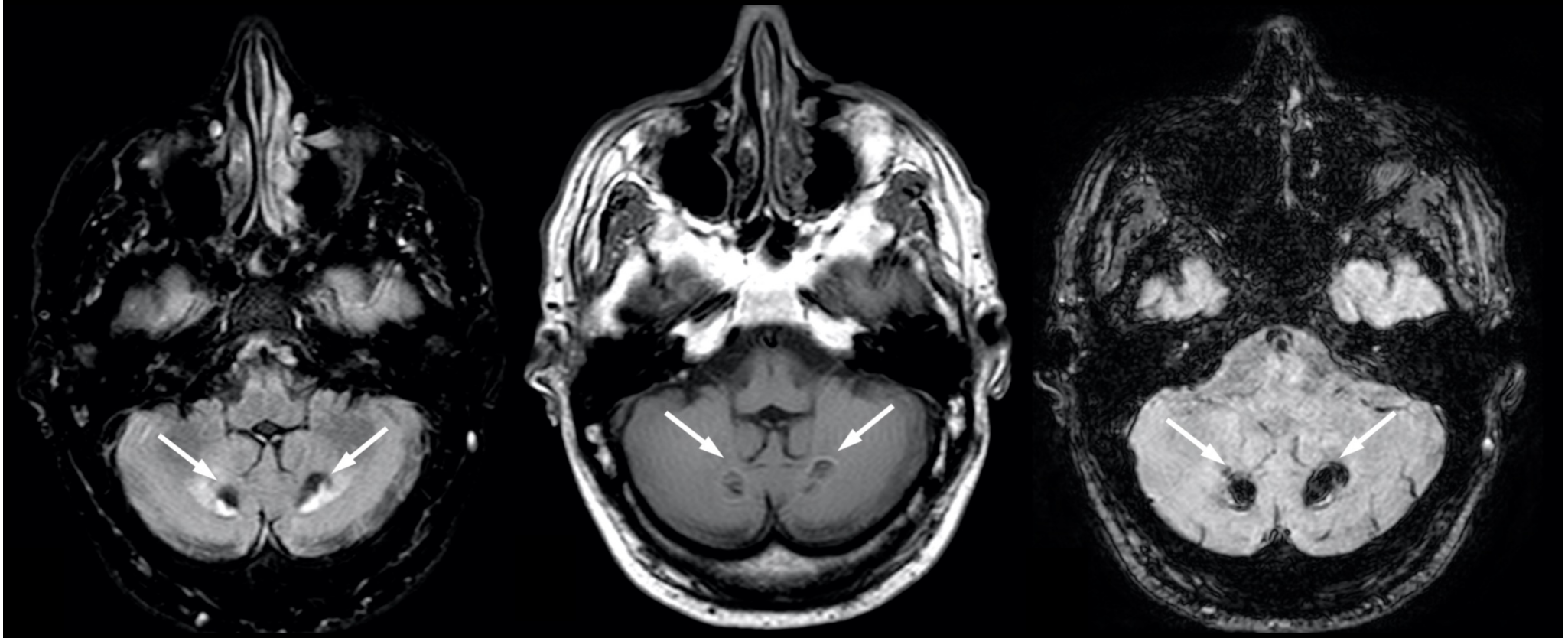
- Mainly vermian atrophy + supratentorial SWI hypointensities [1]



[1] Cocozza S, et al. Neuroradiology 2021

Conventional MRI: CTX

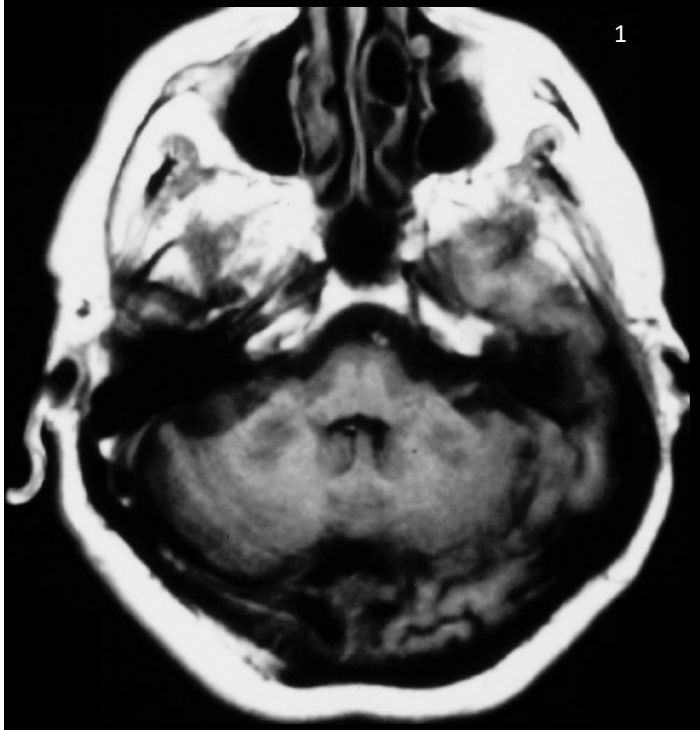
- Variable degree of cerebral and cerebellar atrophy + SWI hypointensity & non-homogeneous T2w hyperintensity signal in dentate nuclei and surrounding cerebellar white matter (vacuolization + calcification) [1]

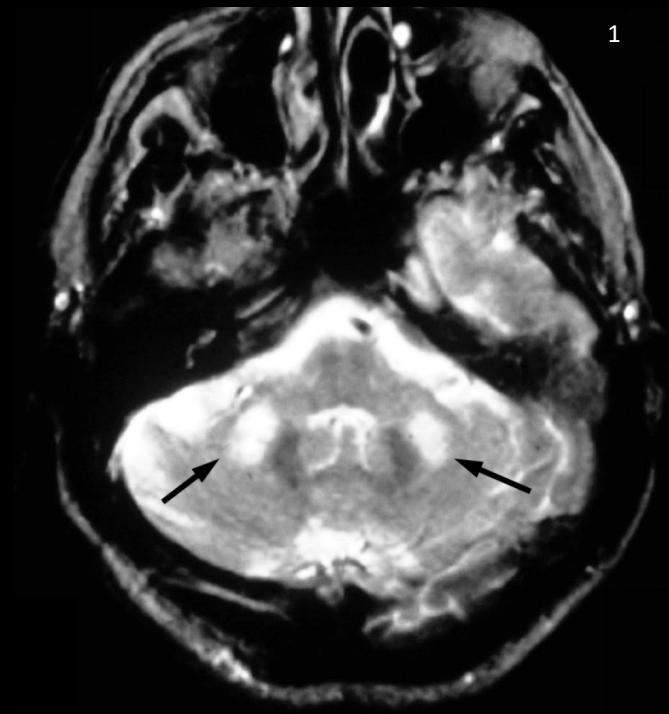


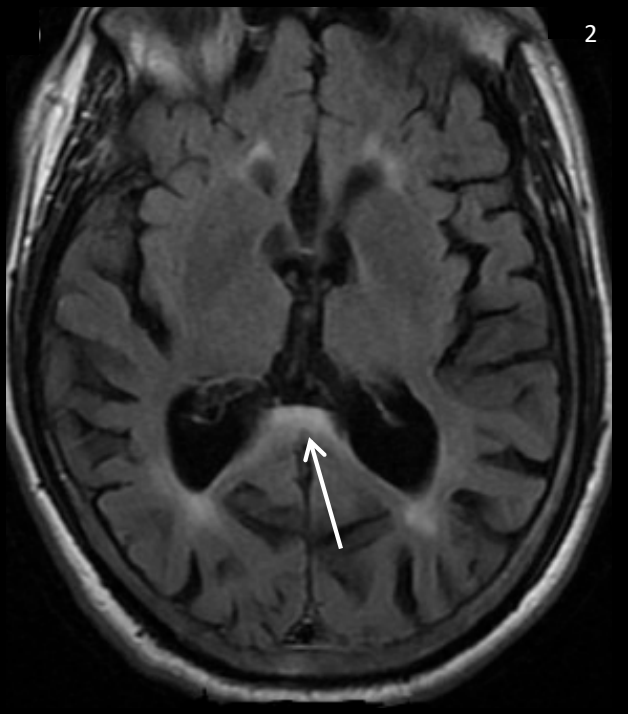
[1] Cocozza S, et al. Neuroradiology 2021

Conventional MRI: FXTAS

- Two major radiological features (white matter lesions in middle cerebellar peduncles and in corpus callosum splenium) [1] are part of the revised FXTAS diagnostic criteria [1]







[1] Cocozza S, et al. Neuroradiology 2021 ; [2] Hall DA, et al. Neurodev Disord. 2014

Conventional MRI “checklist”

- Pattern of atrophy

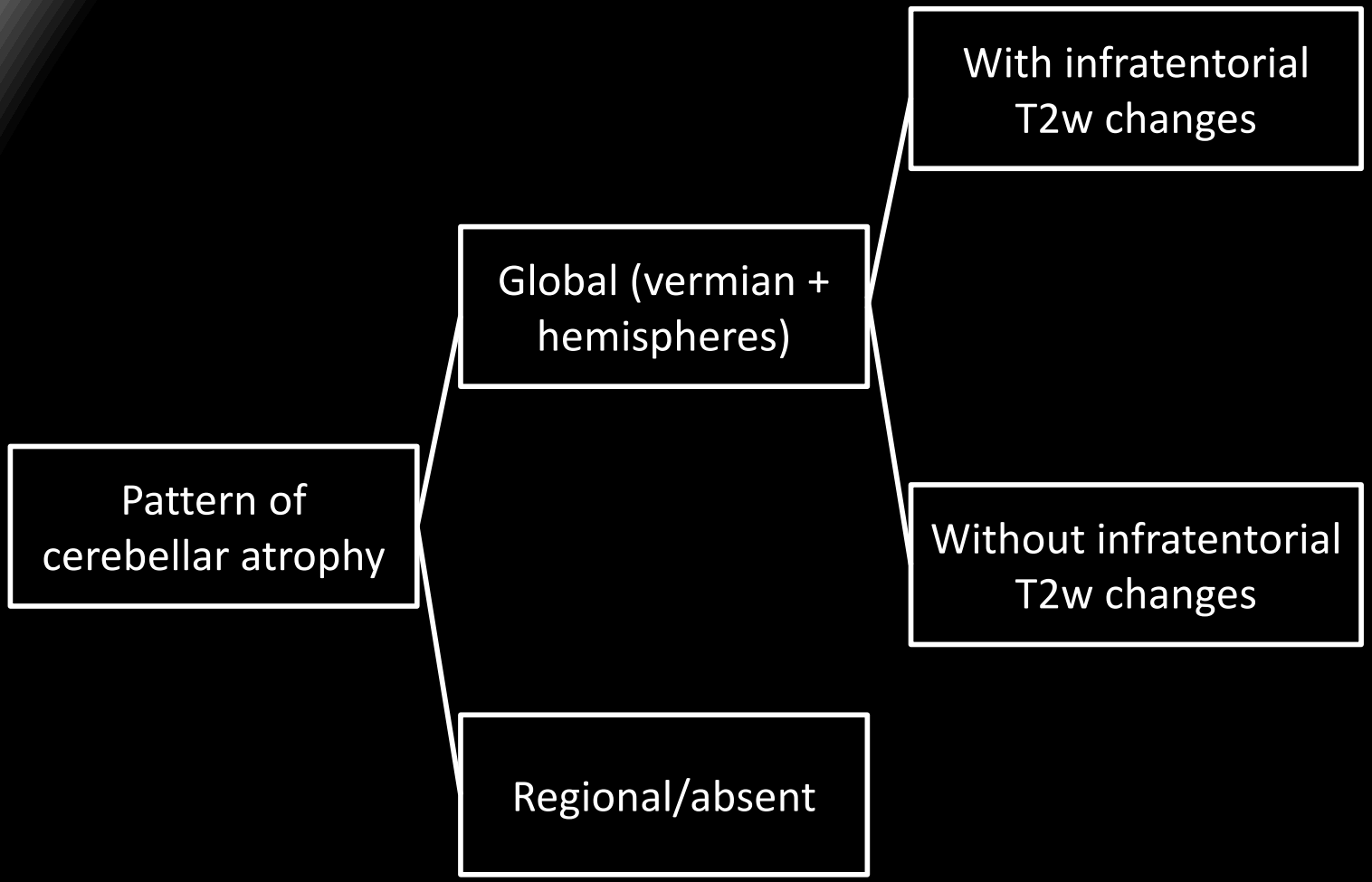
Conventional MRI “checklist”

- Pattern of atrophy
  - “Pure” cerebellar
    - Mainly vermian
    - Mainly hemispheric
    - Diffuse
  - Cerebellar + brainstem
    - Mainly pontine
    - Pontine + Midbrain
    - Diffuse

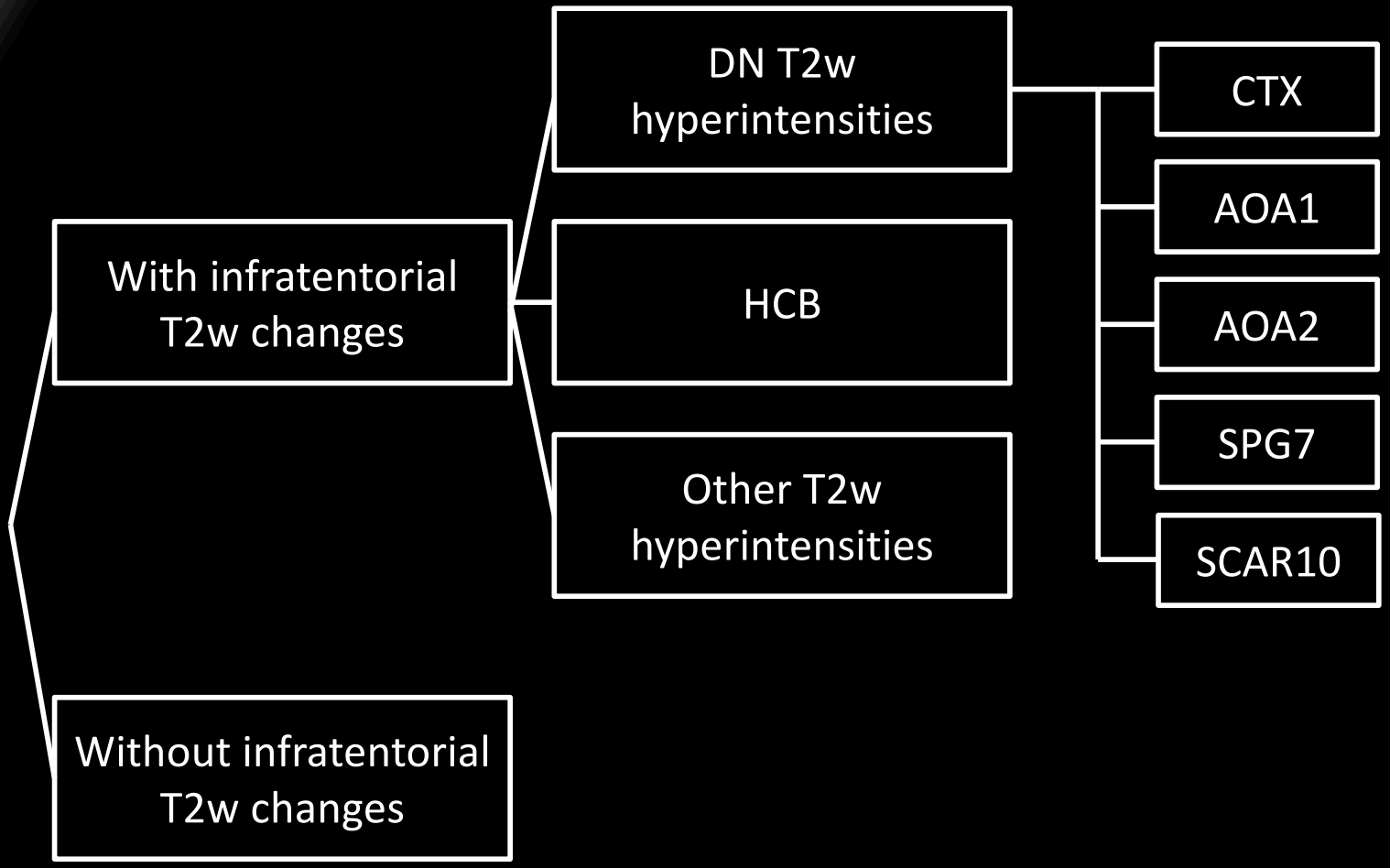
- Infratentorial signal changes

- Supratentorial involvement (atrophy and/or signal changes)

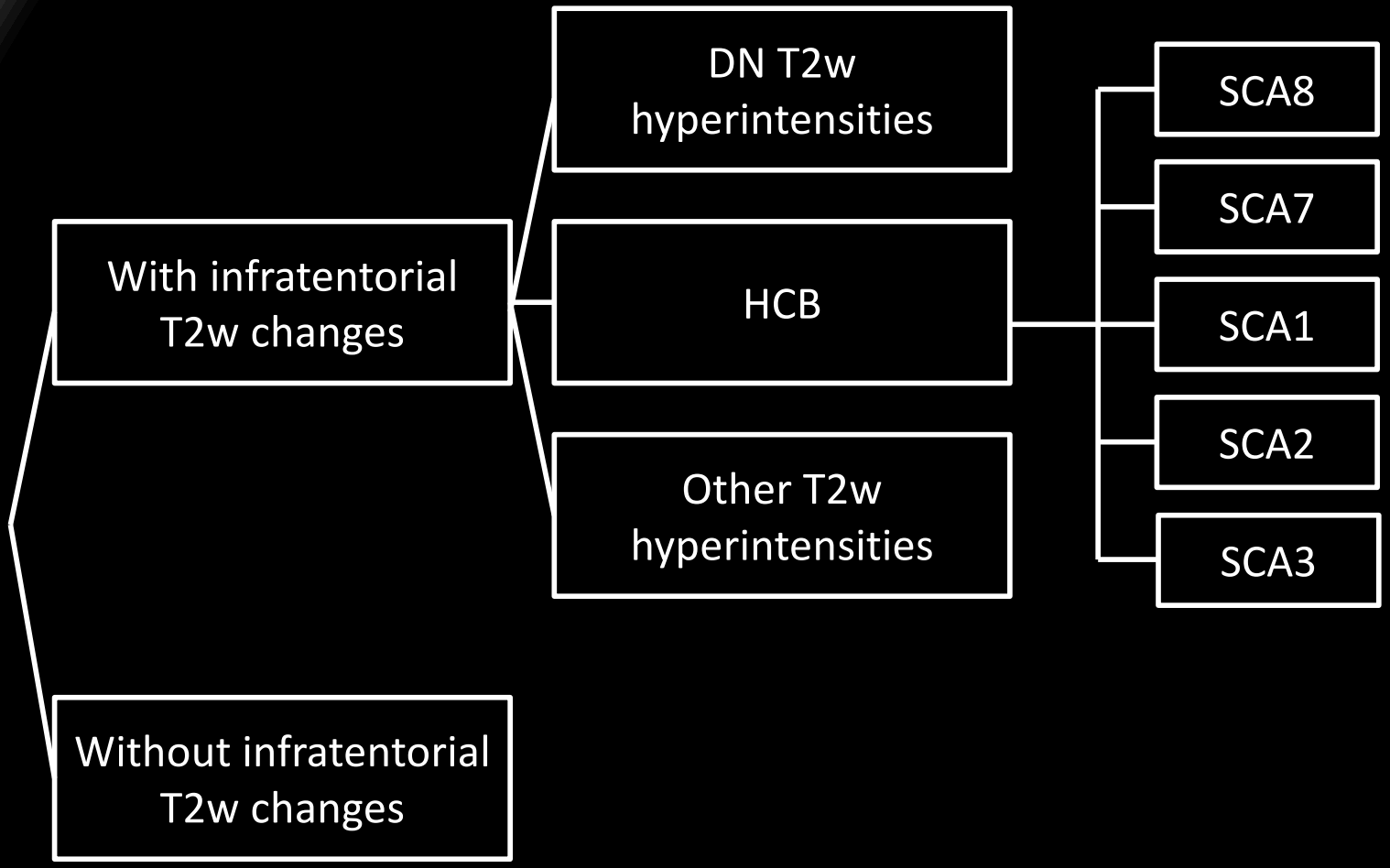
Neuroradiological algorithm



Neuroradiological algorithm



Neuroradiological algorithm



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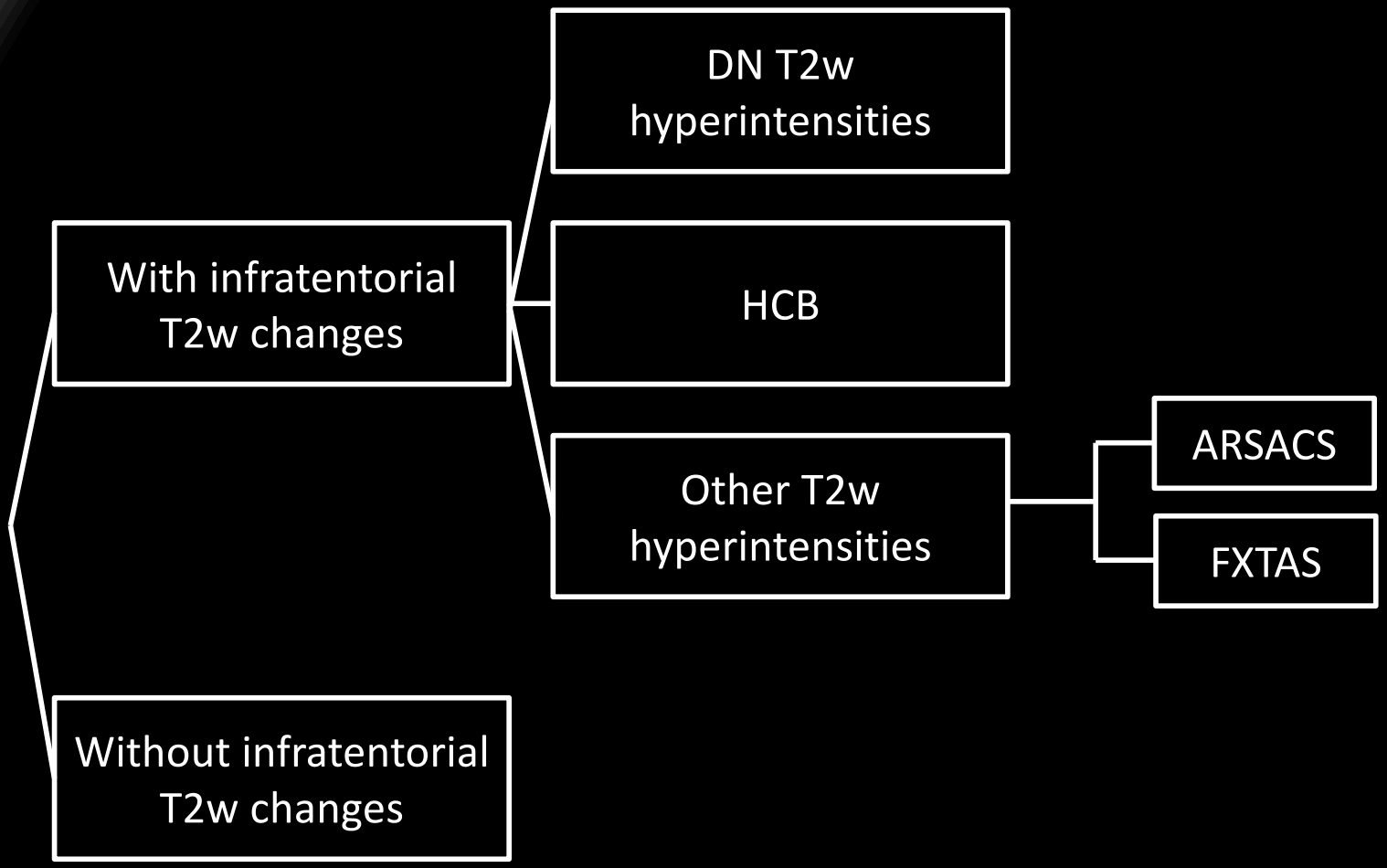

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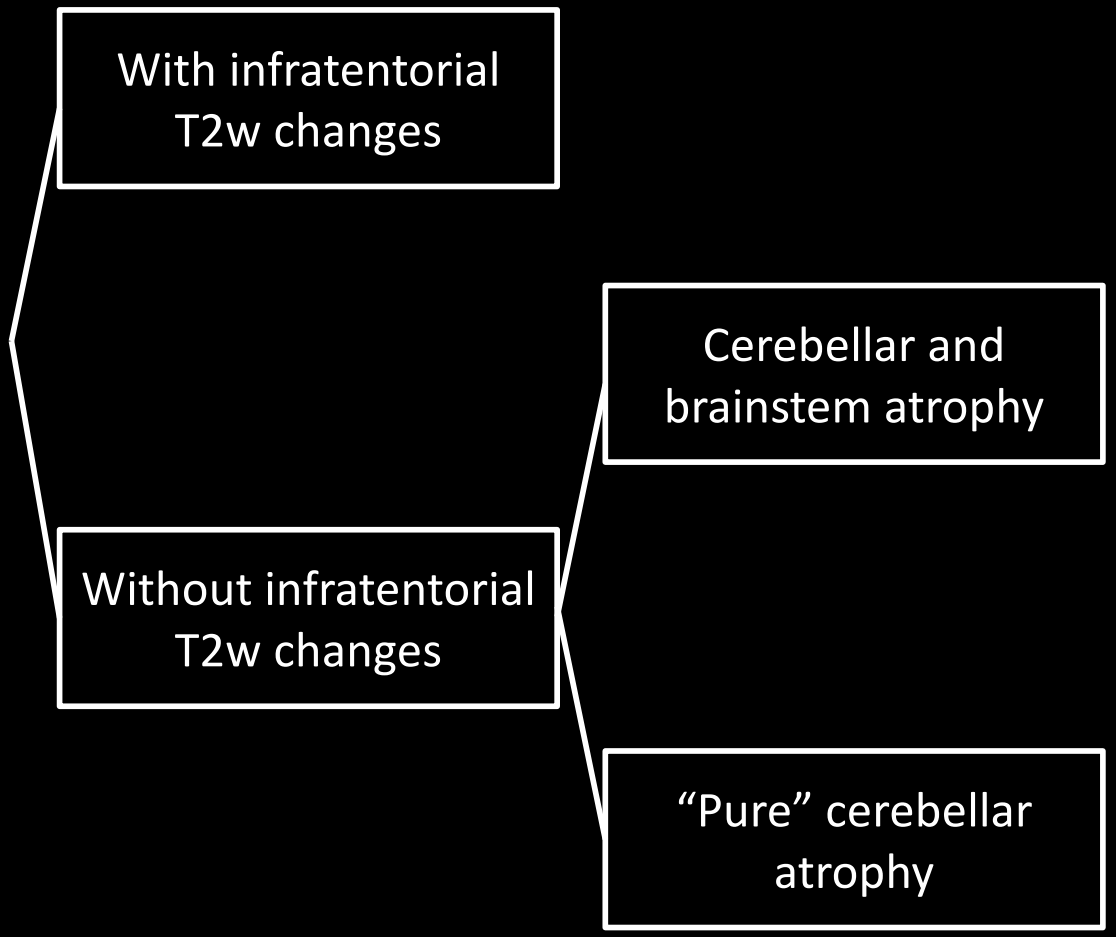

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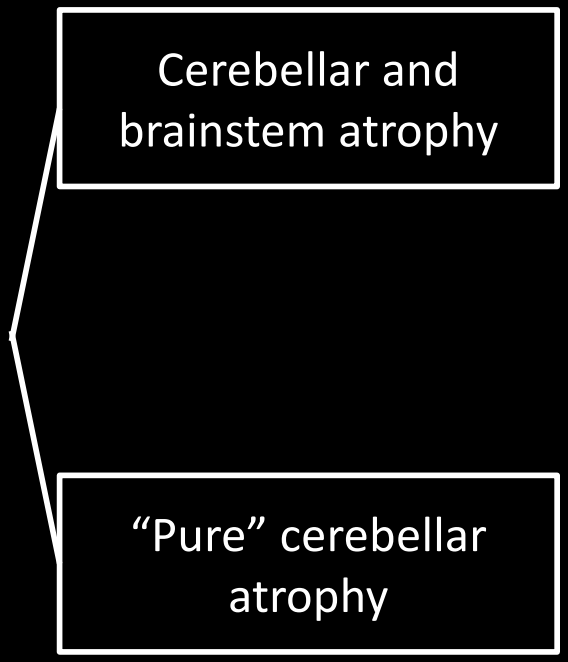
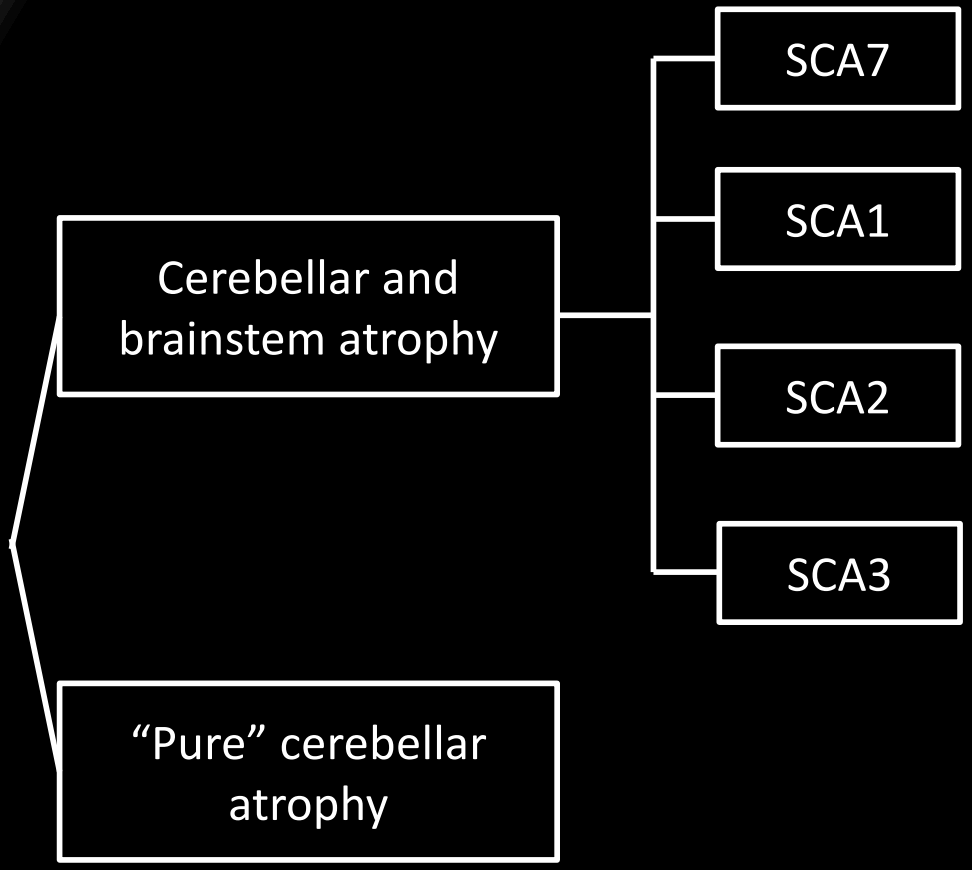


Neuroradiological algorithm



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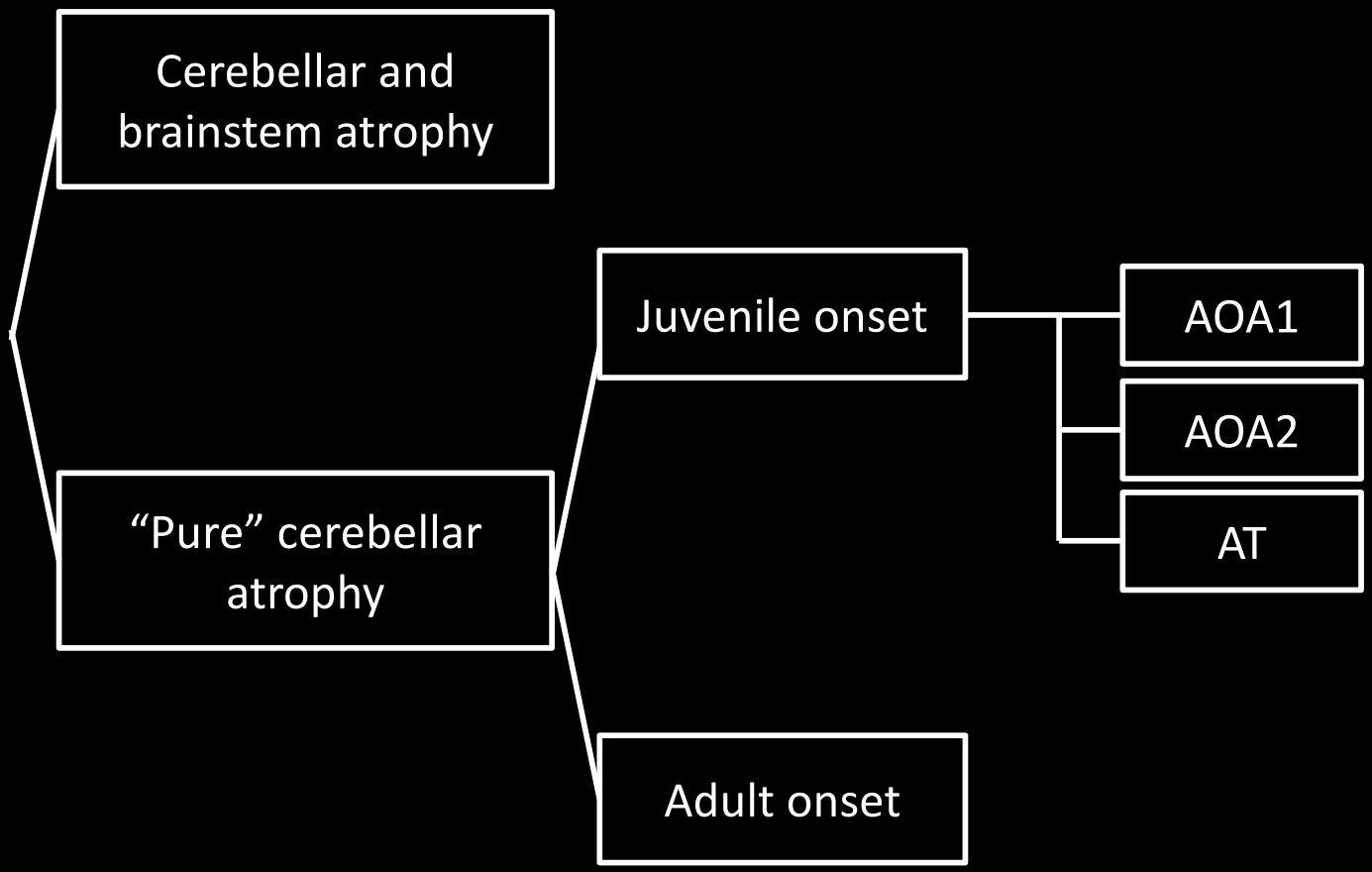

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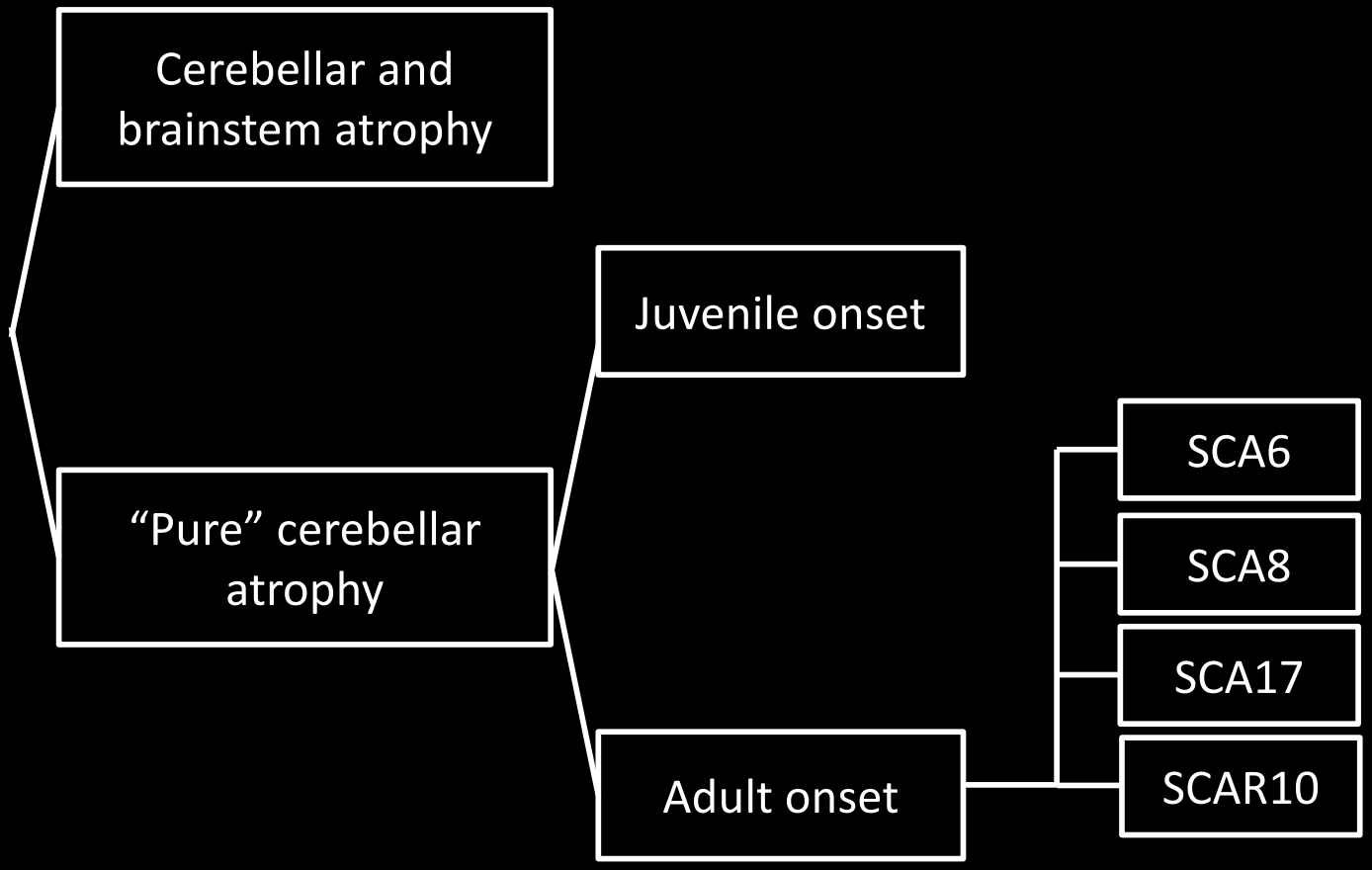

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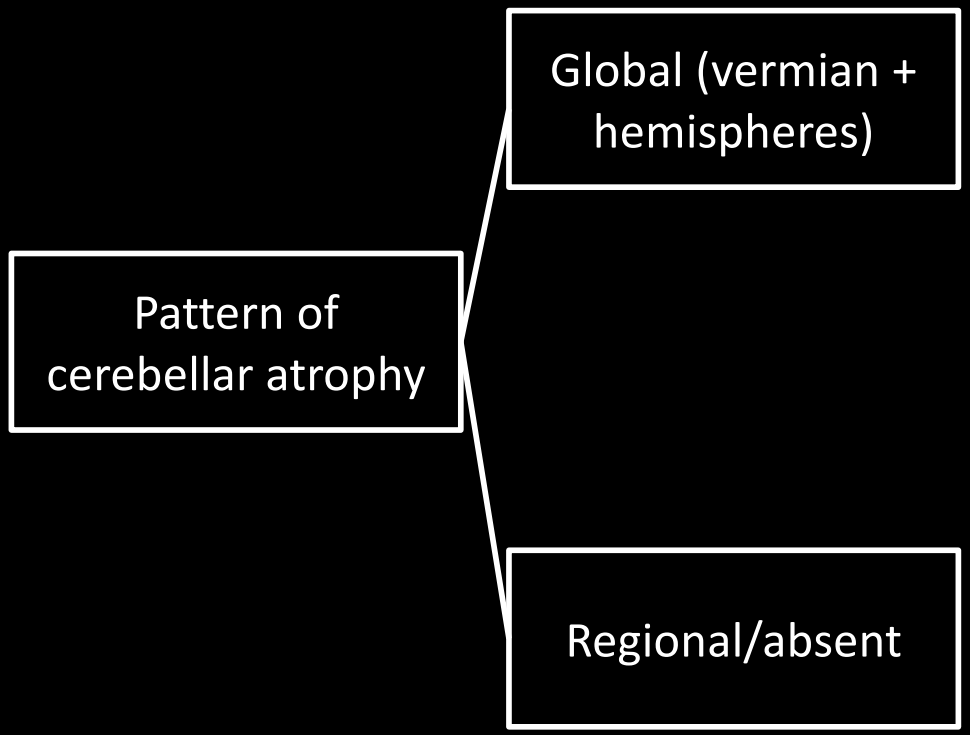

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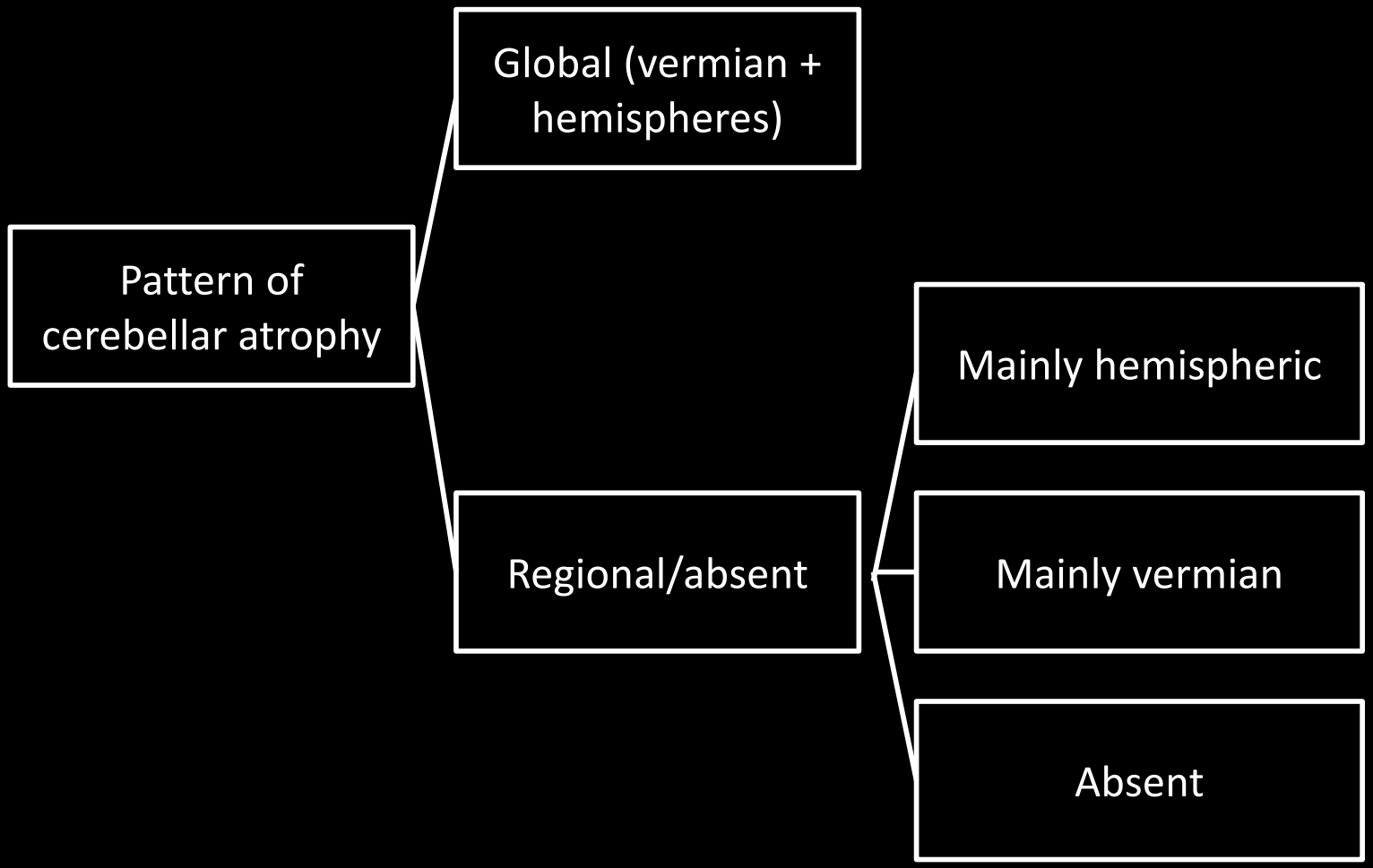

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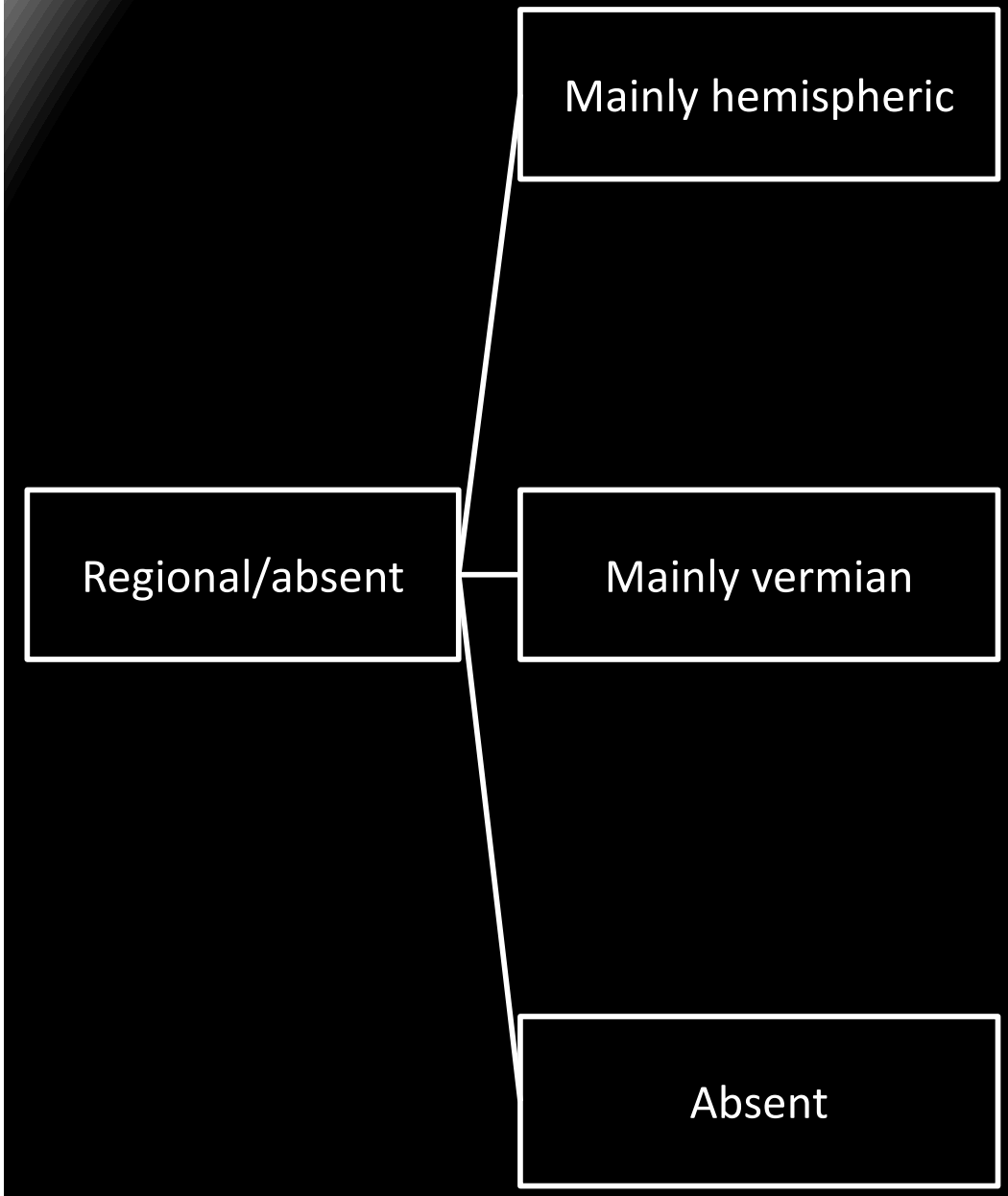

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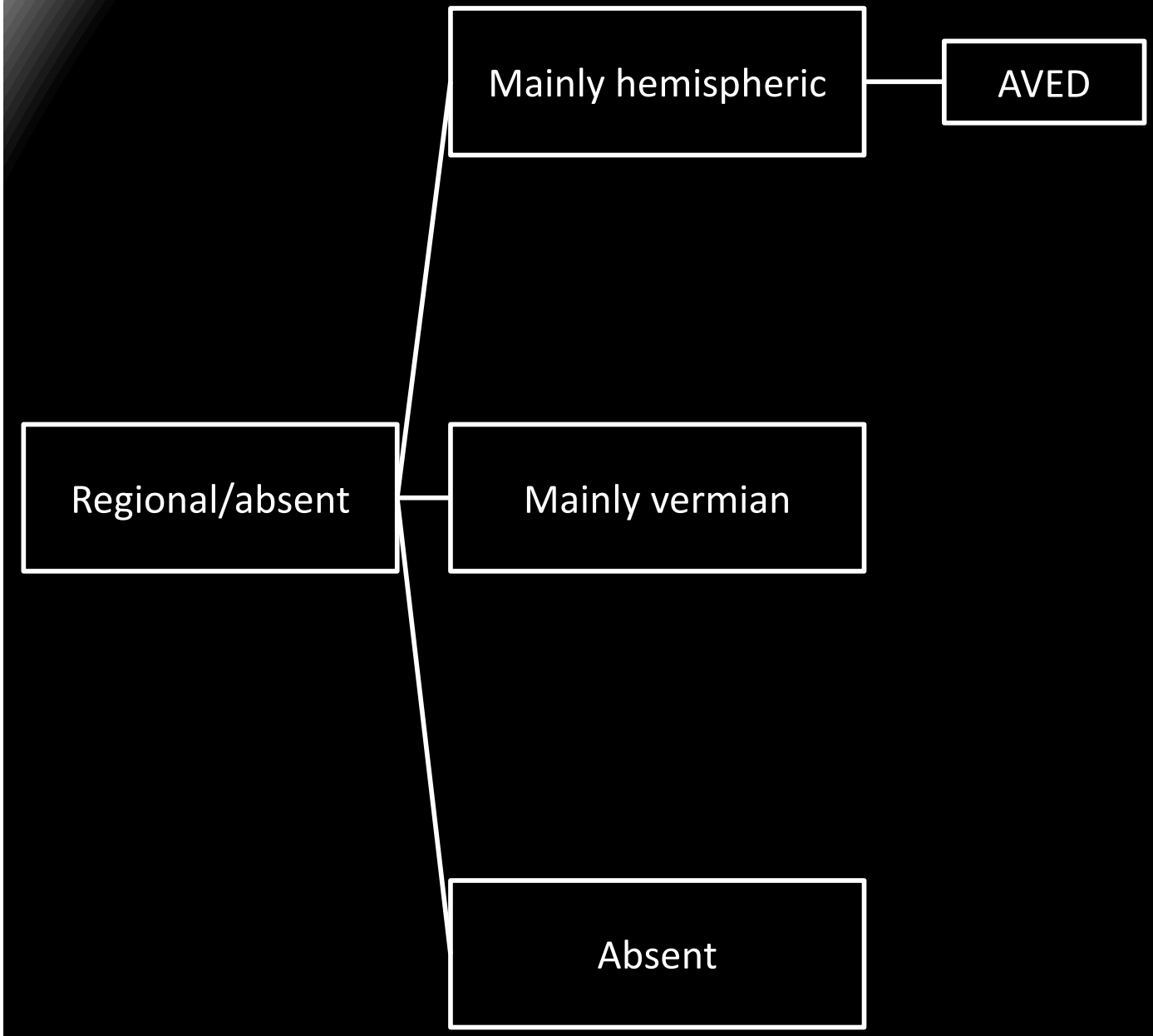

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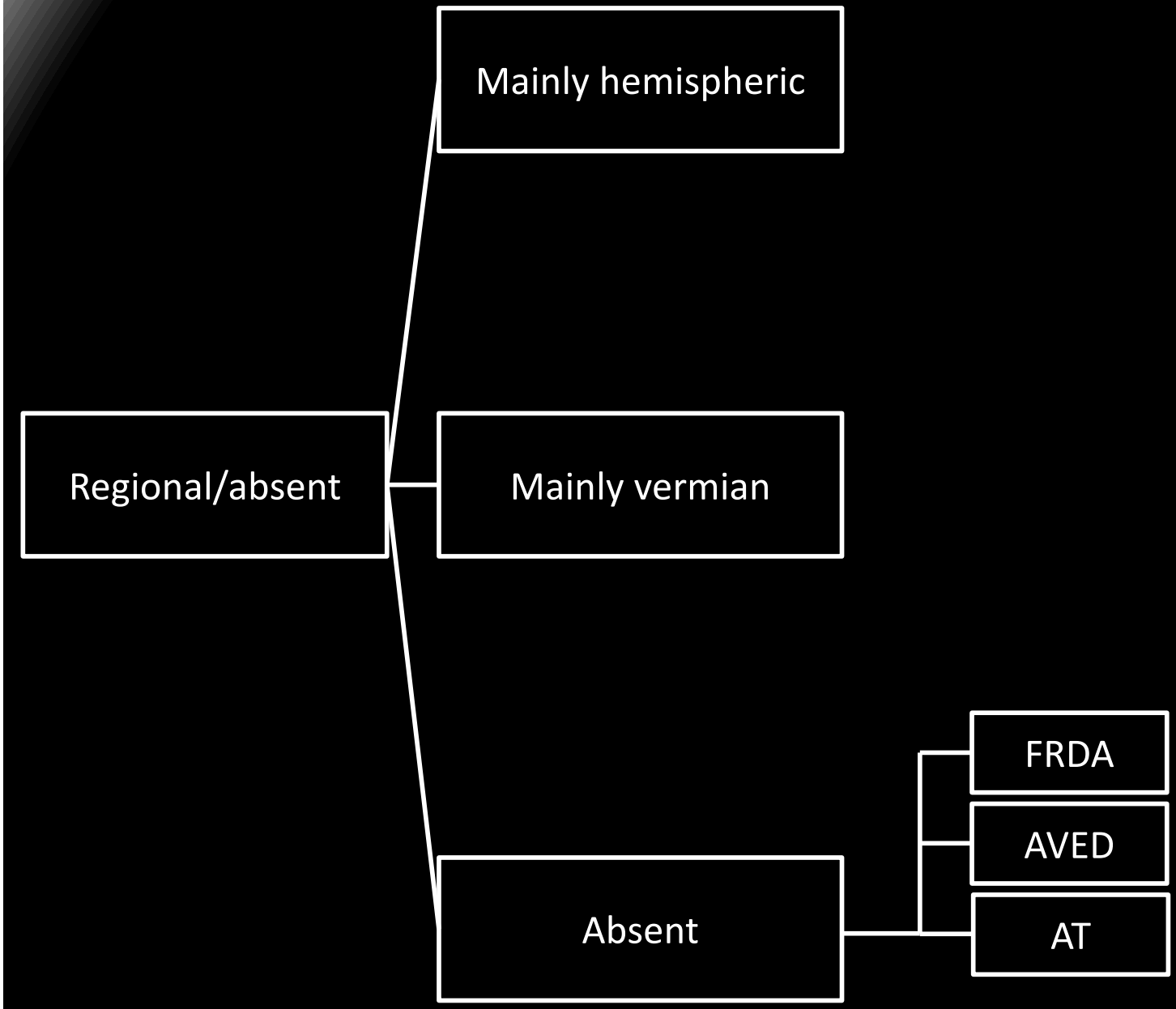

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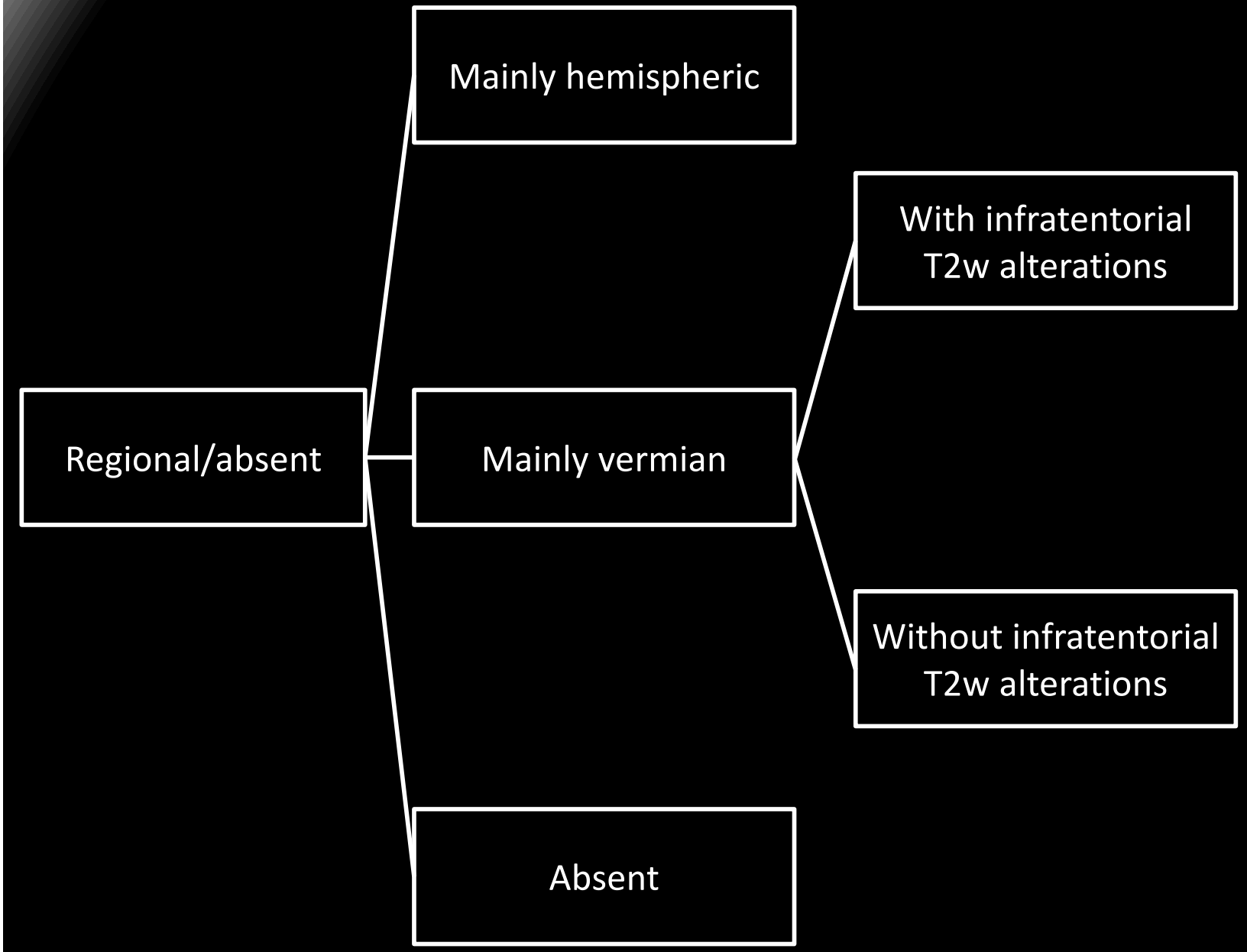

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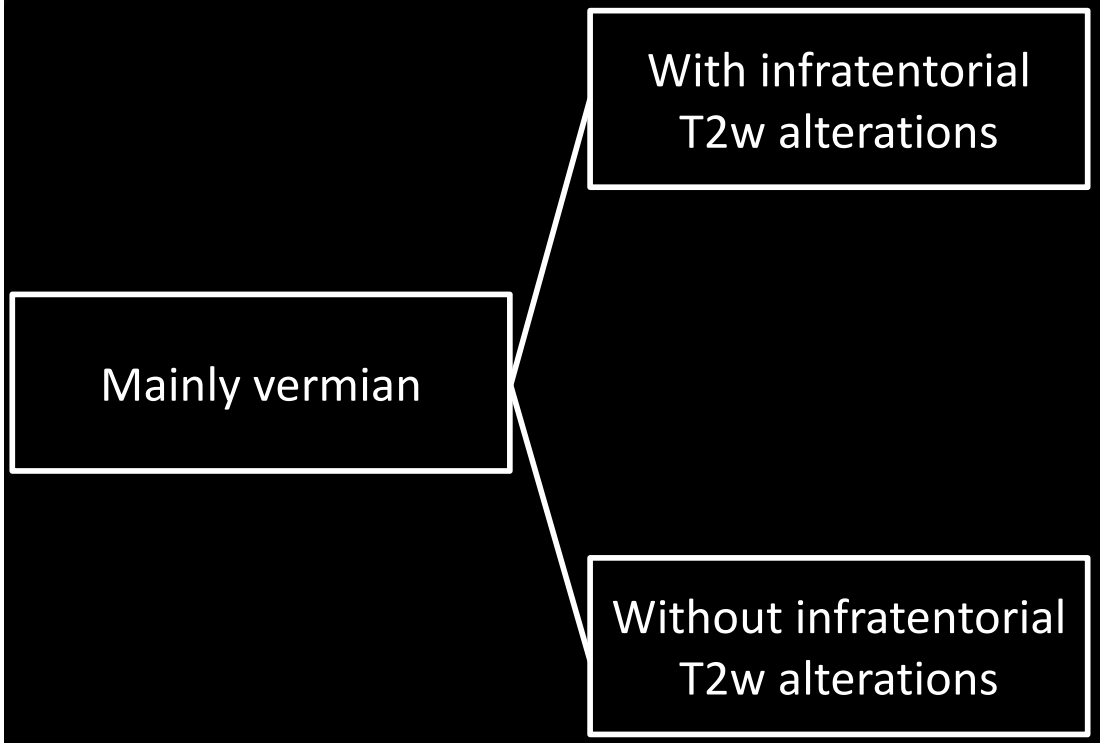

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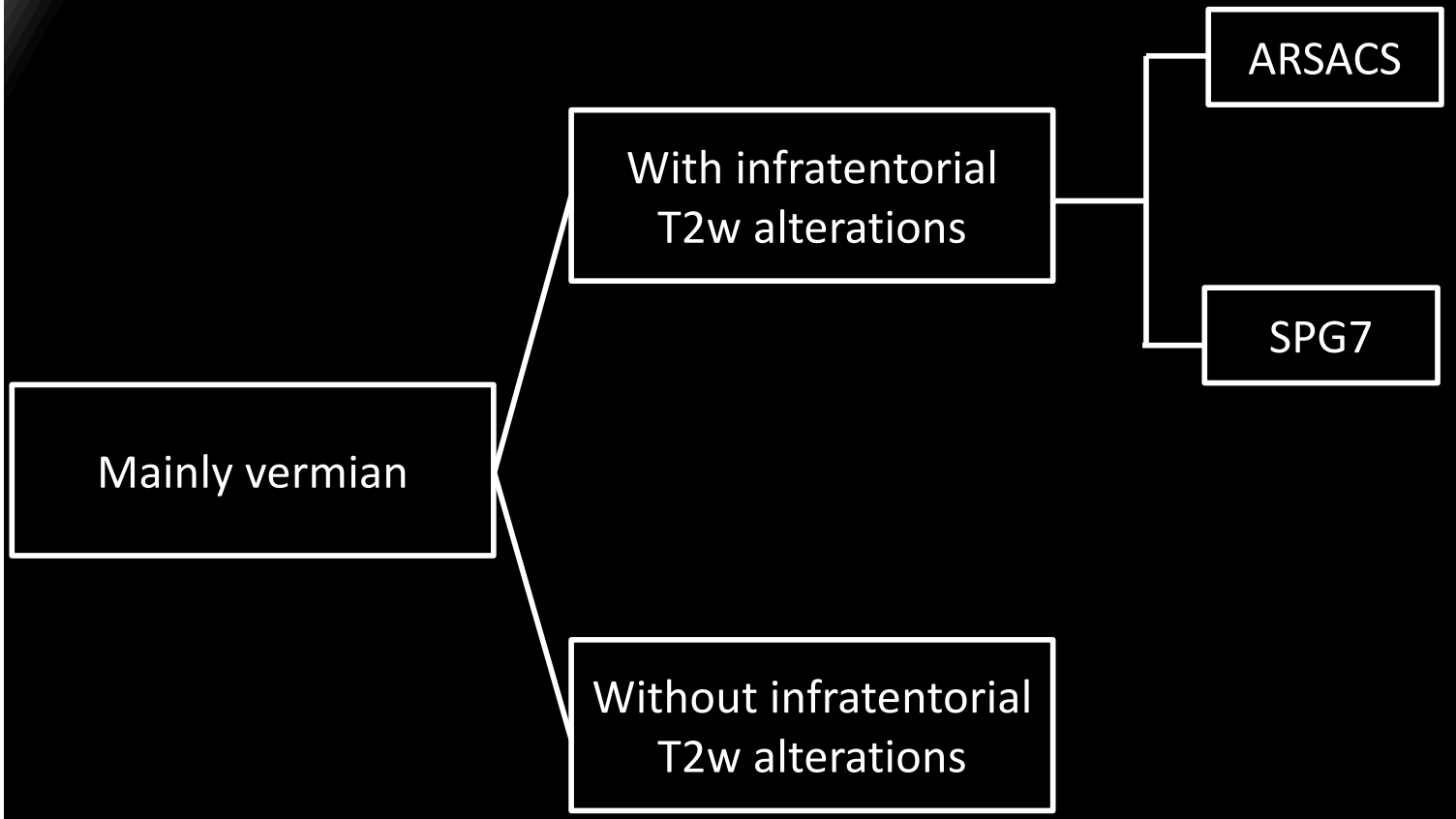

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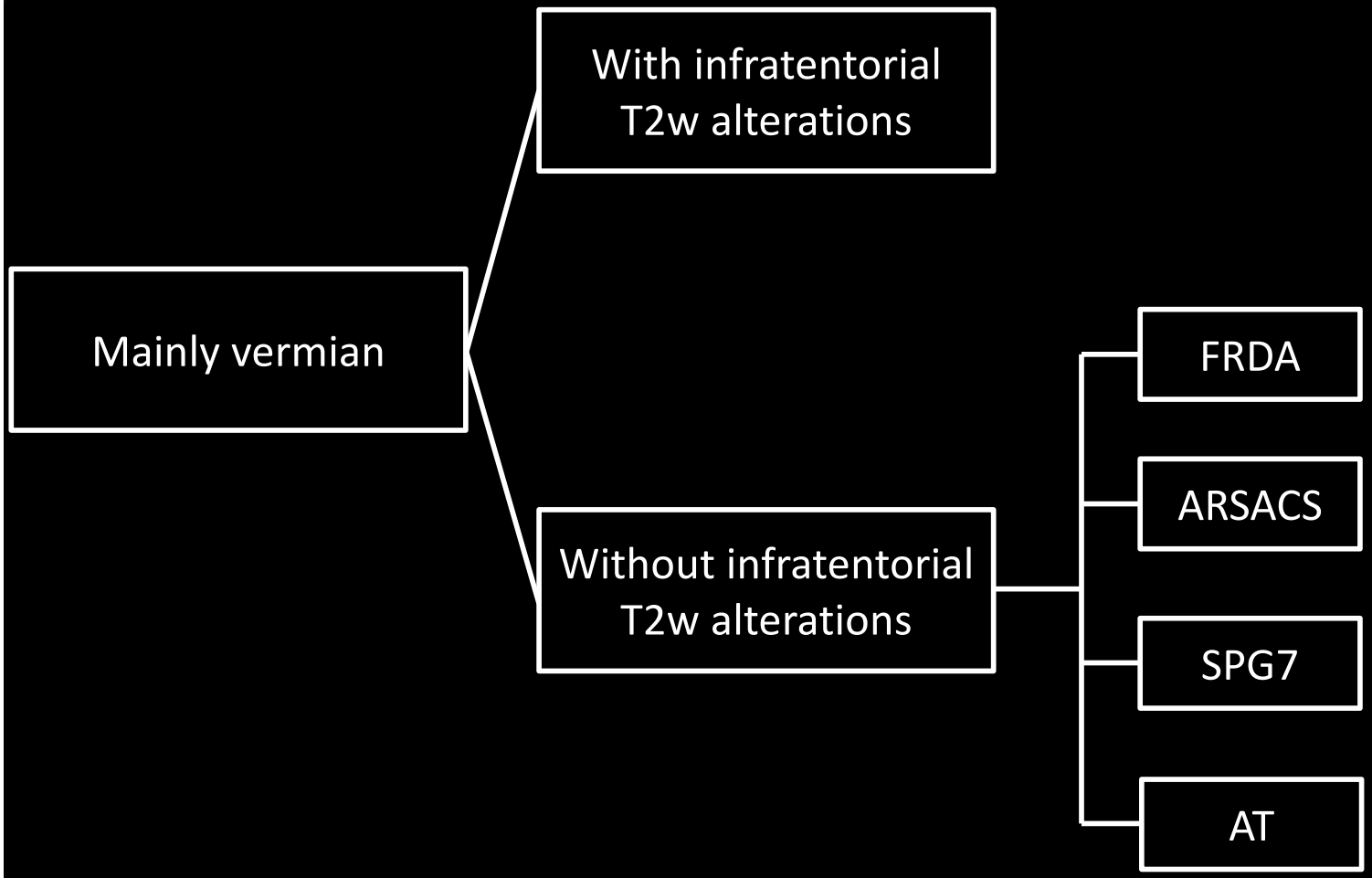

Take home messages

- With conventional MRI it is possible to study almost all the structures of the infratentorial compartment

- 3D-GrE-T1w >>> SE-T1w

- TSE-T2w > FLAIR-T2w

- Lack of “pathognomonic” MRI signs (unfortunately)

- Accurate evaluation and combination of different conventional MRI signs might provide crucial diagnostic information

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