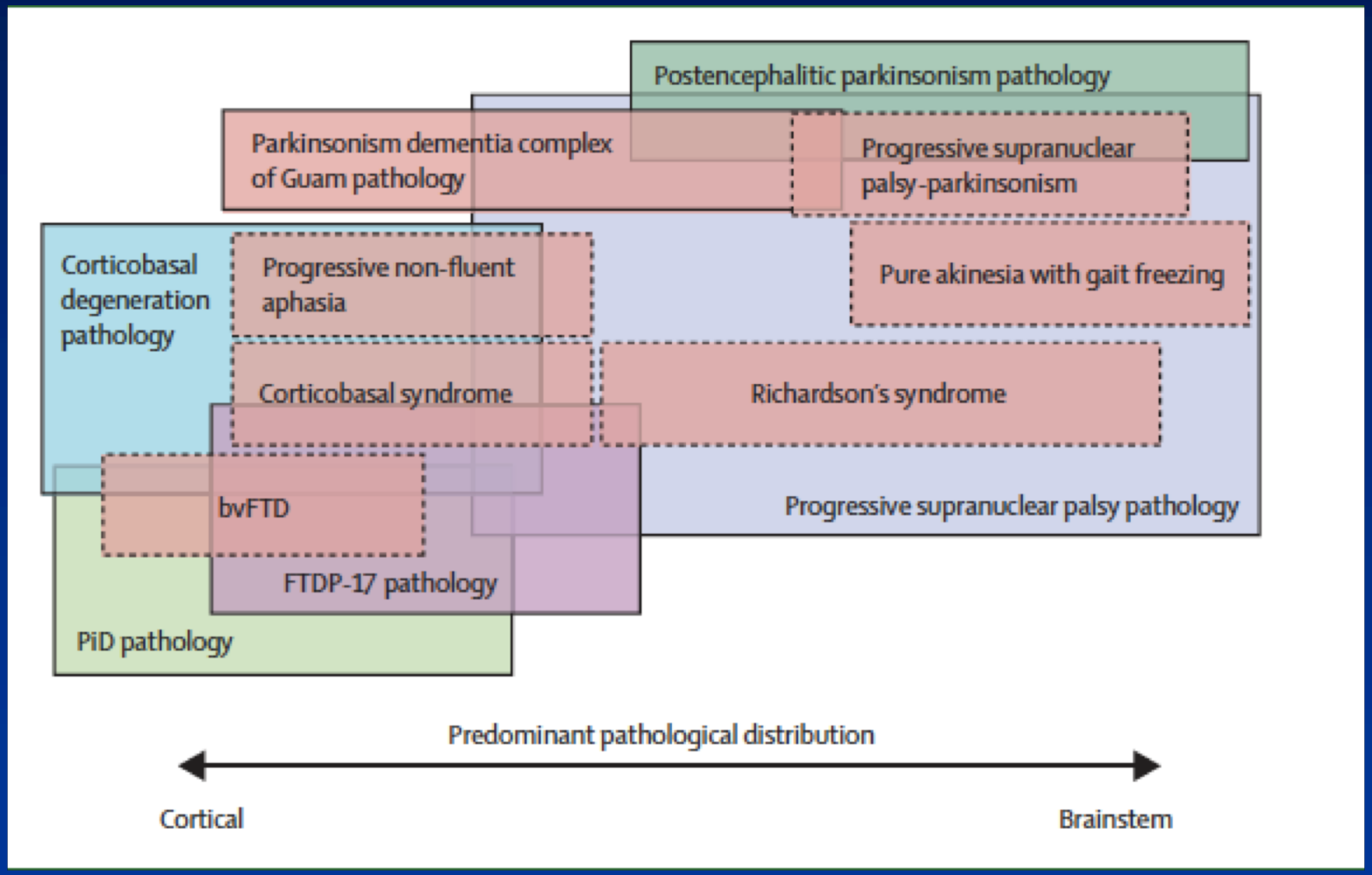
Taupathies including:

- Progressive Supranuclear Palsy
- Corticobasal syndrome
- Frontotemporal dementia

Distribution of tau pathology in clinical and pathological nosological syndromes of progressive supranuclear palsy



Dashed boxes=clinical syndromes. Solid boxes=pathologically defined diseases. PiD=Pick's disease. FTDP-17=frontotemporal dementia with parkinsonism-17. bvFTD=behavioural variant of frontotemporal dementia.[3,6,45,64,65]

Williams & Lees Lancet Neurology 2009

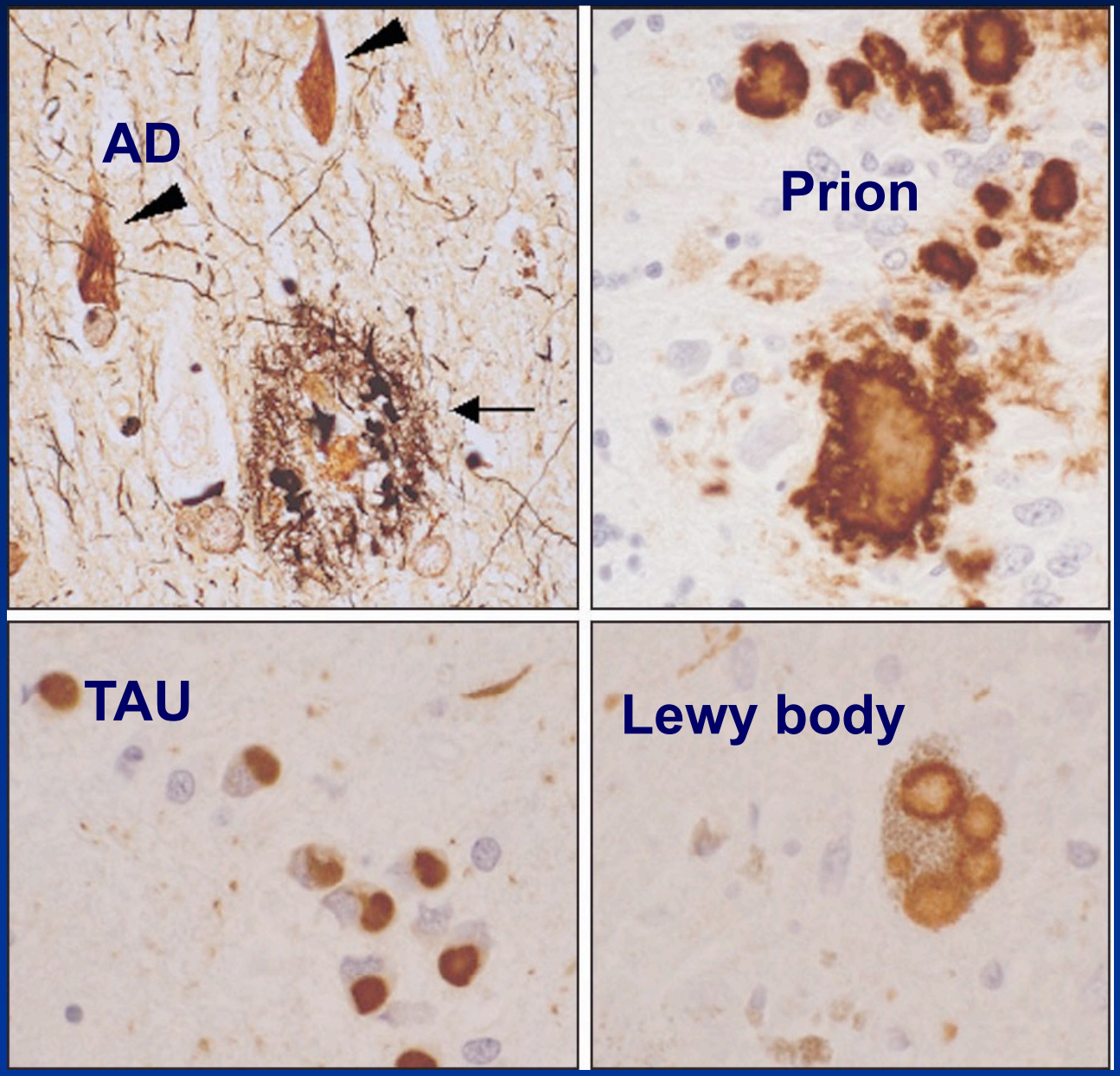
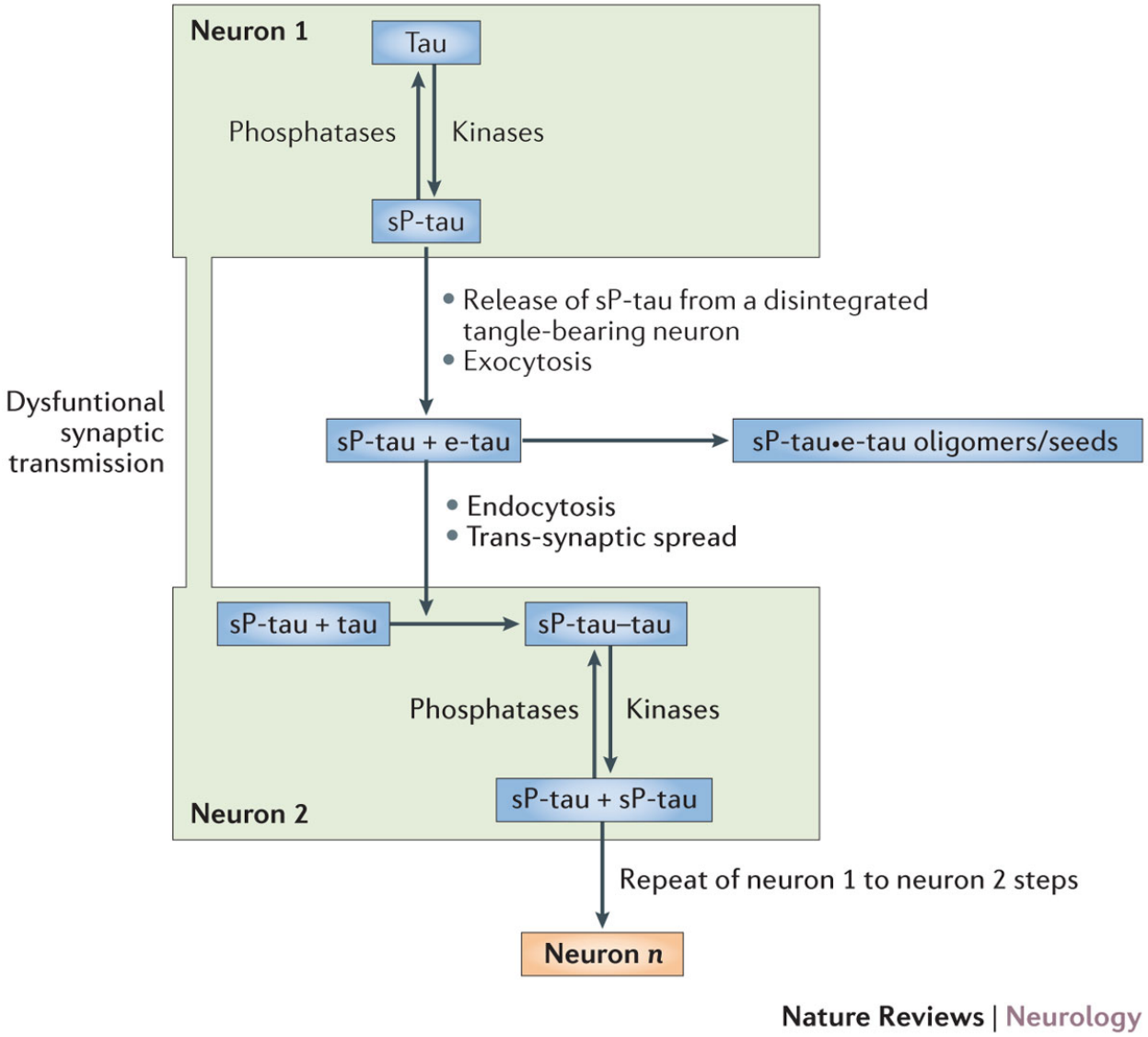

AD
Prion
TAU
Lewy body

Figure 4 Generation of tau seeds and spread of tau pathology



Iqbal, K. *et al.* (2015) Tau and neurodegenerative disease: the story so far
Nat. Rev. Neurol. doi:10.1038/nrneurol.2015.225

NINDS-SPSP Consensus Conference:

Diagnostic categories for Progressive Supranucler Palsy

I. Possible PSP: gradually progressive disorder; onset after age 40; vertical SNGP OR slowing of vertical saccades AND postural instability with falls in the first year of symptom onset; no evidence of other diseases

II. Probable PSP: gradually progressive disorder; onset after age 40; vertical SNGP; postural instability with falls in the first year of symptom onset; no evidence of other diseases

III. Definite PSP: pathologically confirmed

There is a significant overlap between different taupathies and in particular between PSP and CBD/CBS

- **Progressive supranuclear palsy (PSP)**
  - Supranuclear vertical gaze palsy
  - Upright posture/frequent falls
  - Pseudobulbar emotionality
  - Furrowed brow/stare
  - Fronto-limbic dementia
- **Corticobasal degeneration (CBD)**
  - Unilateral, coarse tremor
  - Limb apraxia/limb dystonia/alien hand

Exclusion criteria

For possible and probable:

- Recent history of encephalitis
- Alien limb
- Focal frontal and temporoparietal atrophy
- Hallucinations or delusions unrelated to dopaminergic therapy
- Cortical dementia of Alzheimer type
- Prominent early cerebellar symptoms or unexplained dysautonomia
- Neuroradiological evidence of relevant structural anomaly
- Whipples disease confirmed by polymerase chain reaction
- Evidence of other diseases that could explain the clinical features

Supportive criteria

- Symmetric akinesia or rigidity
- Proximal more than distal
- Abnormal neck posture, especially retrocollis
- Poor or absent reponse of parkinsonism to levodopa
- Early dysphagia, dyarthria
- Early onset of cognitive impairment including > 2 of: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitiation behavior or frontal release signs

Clinical and anatomical correlations of PSP-tau pathology

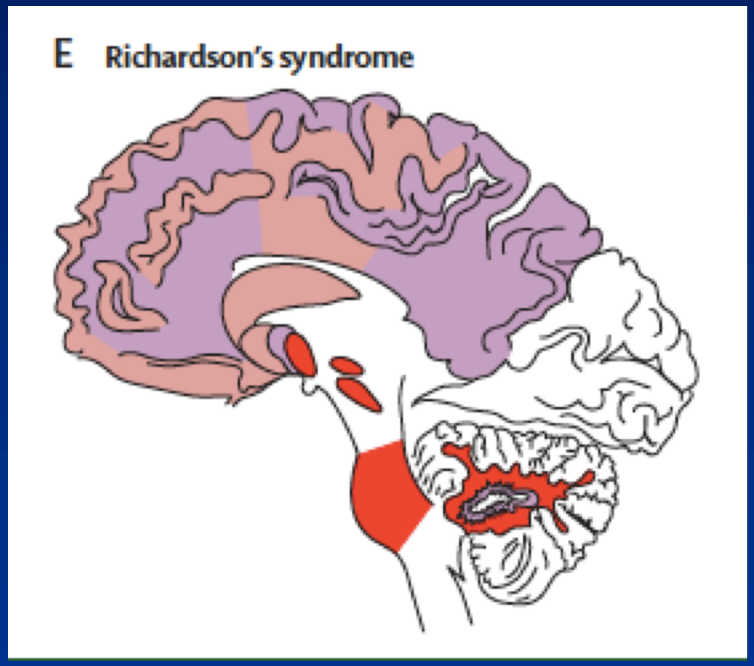
	Clinical features
Frontal cortex	Dysexecutive syndrome; progressive non-fluent aphasia; perseveration; impulsivity
Parietal cortex	Alien limb
Substantia nigra	Rigidity; bradykinesia; postural instability; dystonia
Extranigral midbrain dopamine neurons	No response to levodopa
Periaqueductal grey and raphe nucleus	Sleep disturbances
Dentate nucleus	Gaze fixation (excess of square wave jerks)
Pontine and medullary nuclei	Dysarthria; dysphagia
riMLF (premotor burst neurons)	Slow saccades
Cholinergic neurons of the lower pontine reticular formation	No startle response; oculomotor dysfunction

riMLF=rostral interstitial nuclei of the medial longitudinal fasciculus.

Williams & Lees Lancet Neurology 2009


20 20
F r i d a y
abc

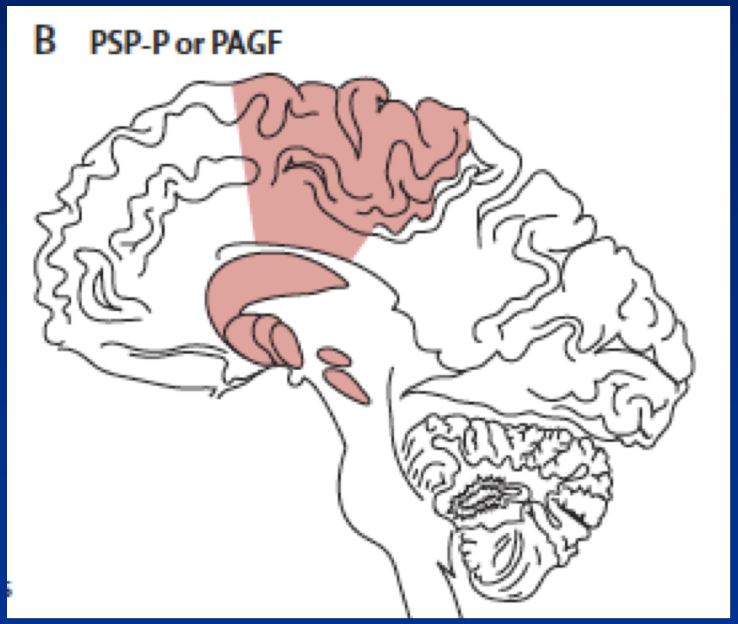
Richardson's syndrome



- Lurching gait
- Unexplained falls backwards without loss of consciousness
- Personality change or cognitive slowing within the first 2 years
- Slowing of saccadic eye movements (with later vertical gaze palsy)
- Absence of limb rigidity and bradykinesia but presence of axial rigidity

Williams & Lees 2009

PSP-Parkinson type



- Limb bradykinesia, rigidity although with significant axial involvement
- Presence of jerky postural tremor and even 4–6 Hz rest tremor
- Falls and cognitive dysfunction occur later in PSP-P than in the Richardson type
- Moderate effect of levodopa especially in the first years

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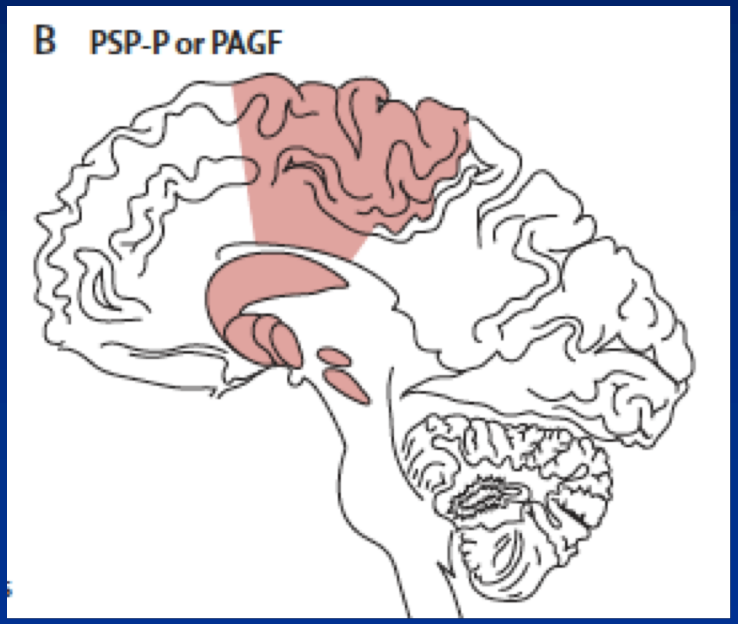
PSP-PAFG

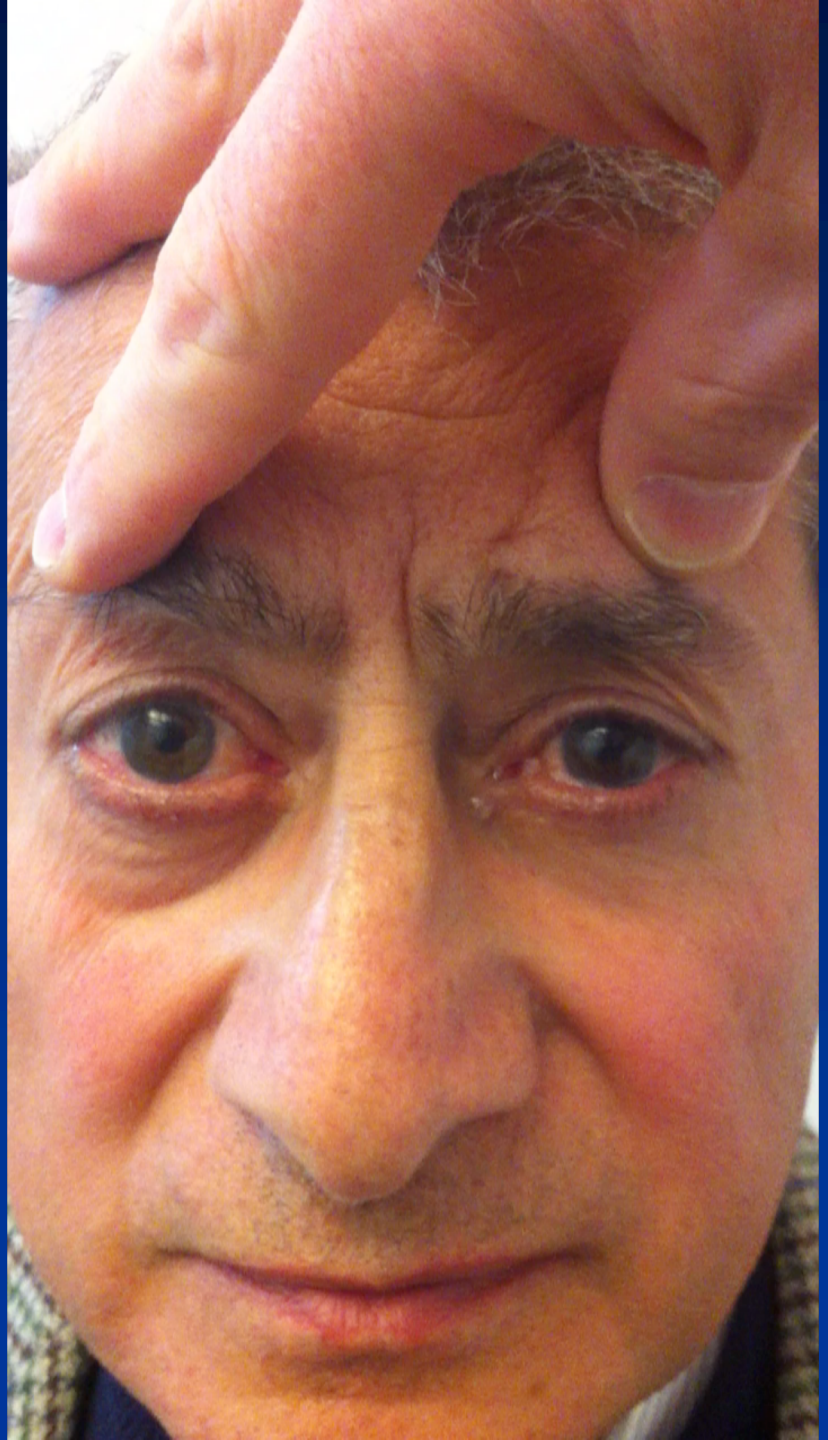
(pure akinesia and freezing of gate)



- Progressive onset of gait disturbance with start hesitation and subsequent freezing of gait, speech, or writing
- Long disease duration without development of other parkinsonian features for many years

Williams & Lees Lancet Neurology 2009

- His age is now 76
- 12 years disease duration
- Started in 2002 with gait problems
-He would not tolerate any dopaminergic agent because worsened his walking



Clinical Characteristics of the various PSP phenotypes

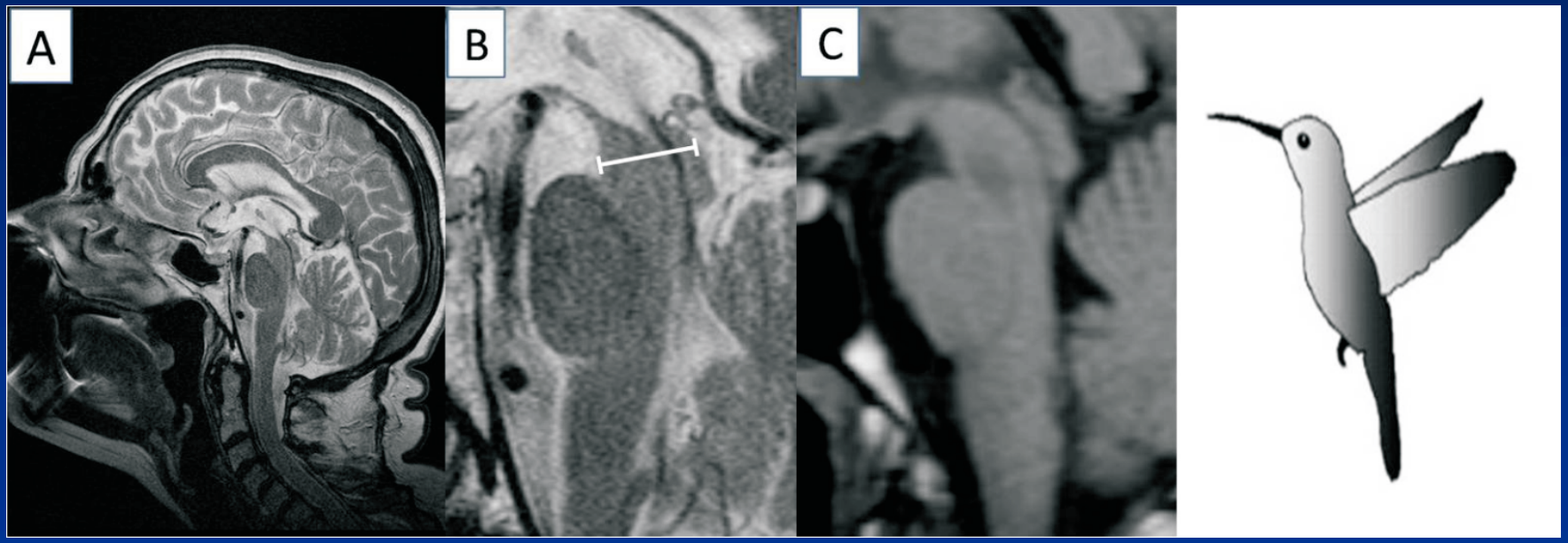
	Richardson's syndrome	PSP-P	PSP-PAGF	PSP-CBS	PSP-PNFA	Parkinson's disease
Rigidity	Axial much more than limb	Axial less than or the same as limb	Axial	Yes	Sometimes	Limb much more than axial
Bradykinesia	Mild	Moderate	Moderate	Yes	Mild	Moderate
Tremor	No	Yes/no (rest or jerky postural)	No	No	No	Yes (at rest)
Early falls	Yes	No	No	Sometimes	Sometimes	No
Early postural instability	Yes	No	Yes	..	..	No
Early cognitive decline	Often	No	No	No	Yes	No
Early abnormalities of eye movement	Yes	No	No	No	Sometimes	No
Response to levodopa	No	Often	No	No	No	Usually
Hyposmia	No	No	..	..	..	Yes
Cardiac MIBG	Normal	Normal*	Normal*	..	..	Abnormal

PSP=progressive supranuclear palsy. CBS=corticobasal syndrome. PAGF=pure akinesia with gait freezing. PNFA=progressive non-fluent aphasia. MIGB=^{131}I-labelled meta-iodobenzylguanidine. ..=unknown. *Author's unpublished data.

Williams & Lees 2009

MRI in Progressive Supranuclear Palsy

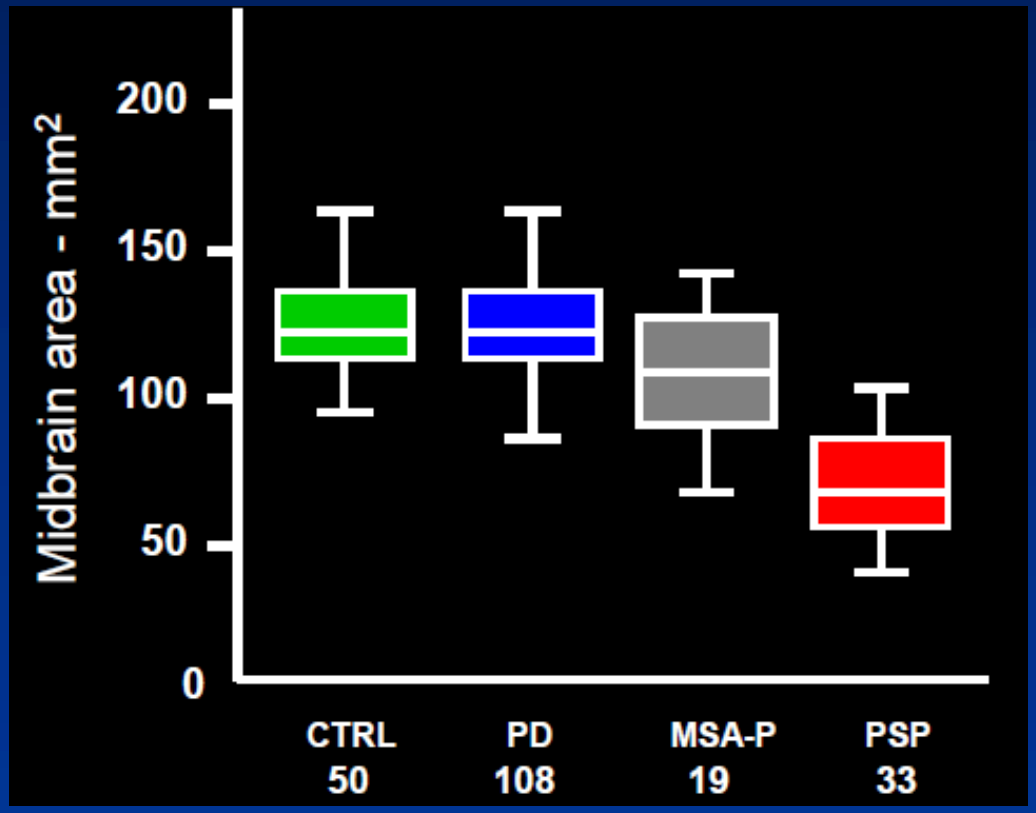
Midbrain atrophy and 'humming bird sign' in PSP

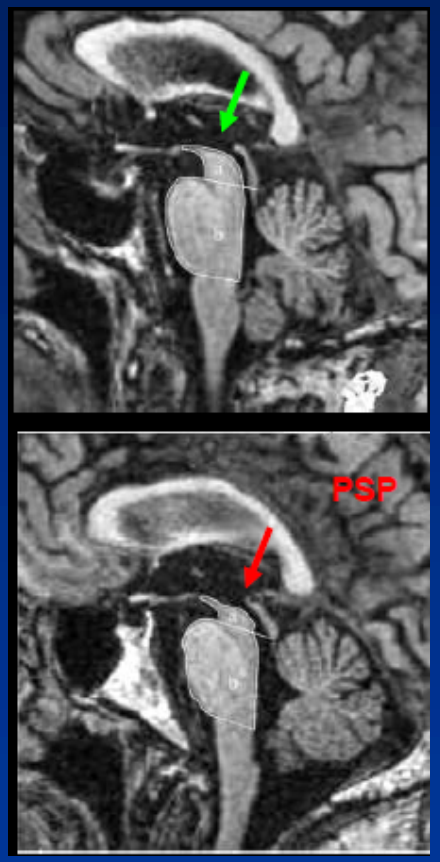


A: T2 MRI in a patient with PSP
B: Detailed picture of the brainstem in the same patient showing midbrain atrophy (diameter of 13.3 mm = white line) resulting in the so-called 'humming bird sign'
C: detailed picture of a normal brainstem

Righini, et al., AJNR 2004

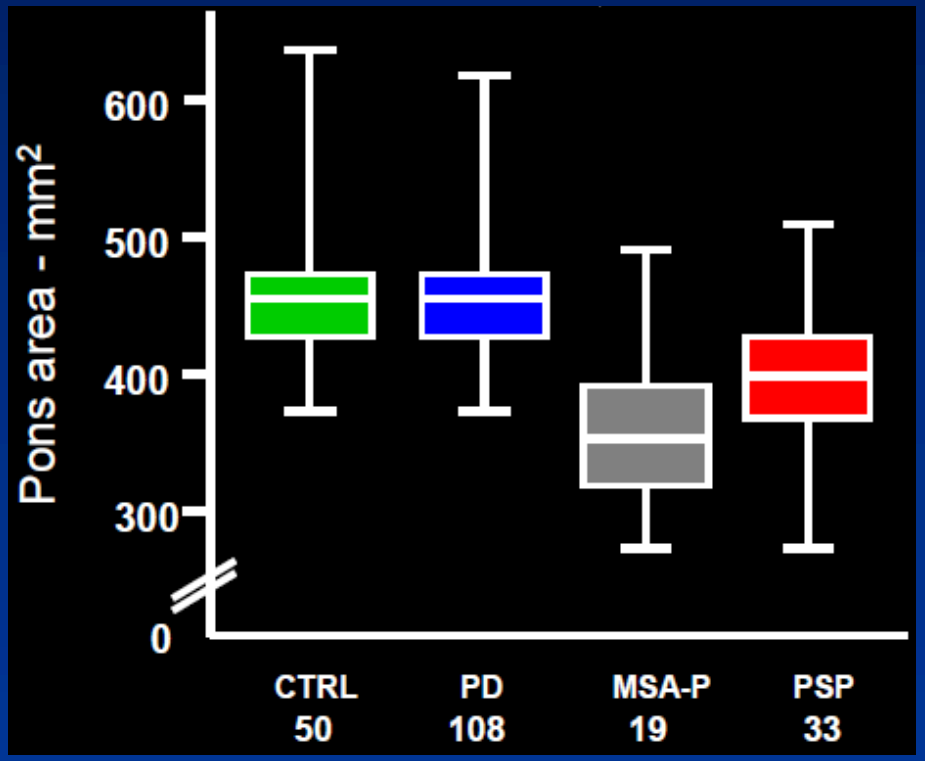
Midbrain area in PSP, MSA-P, PD and Controls

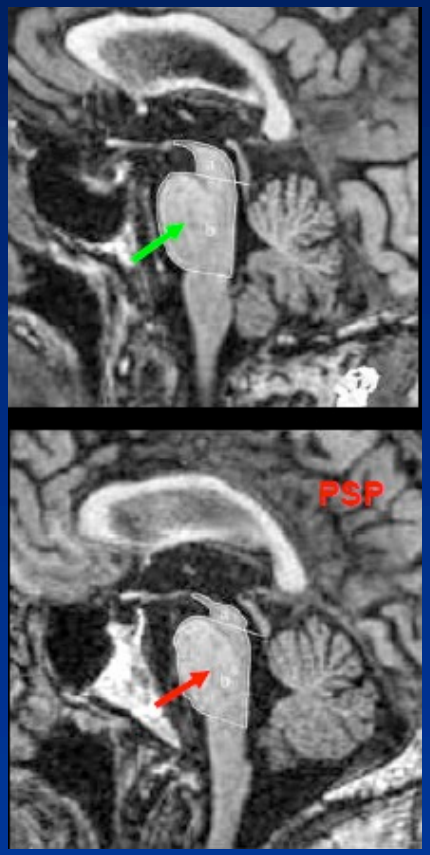




Quattrone et al., 2008

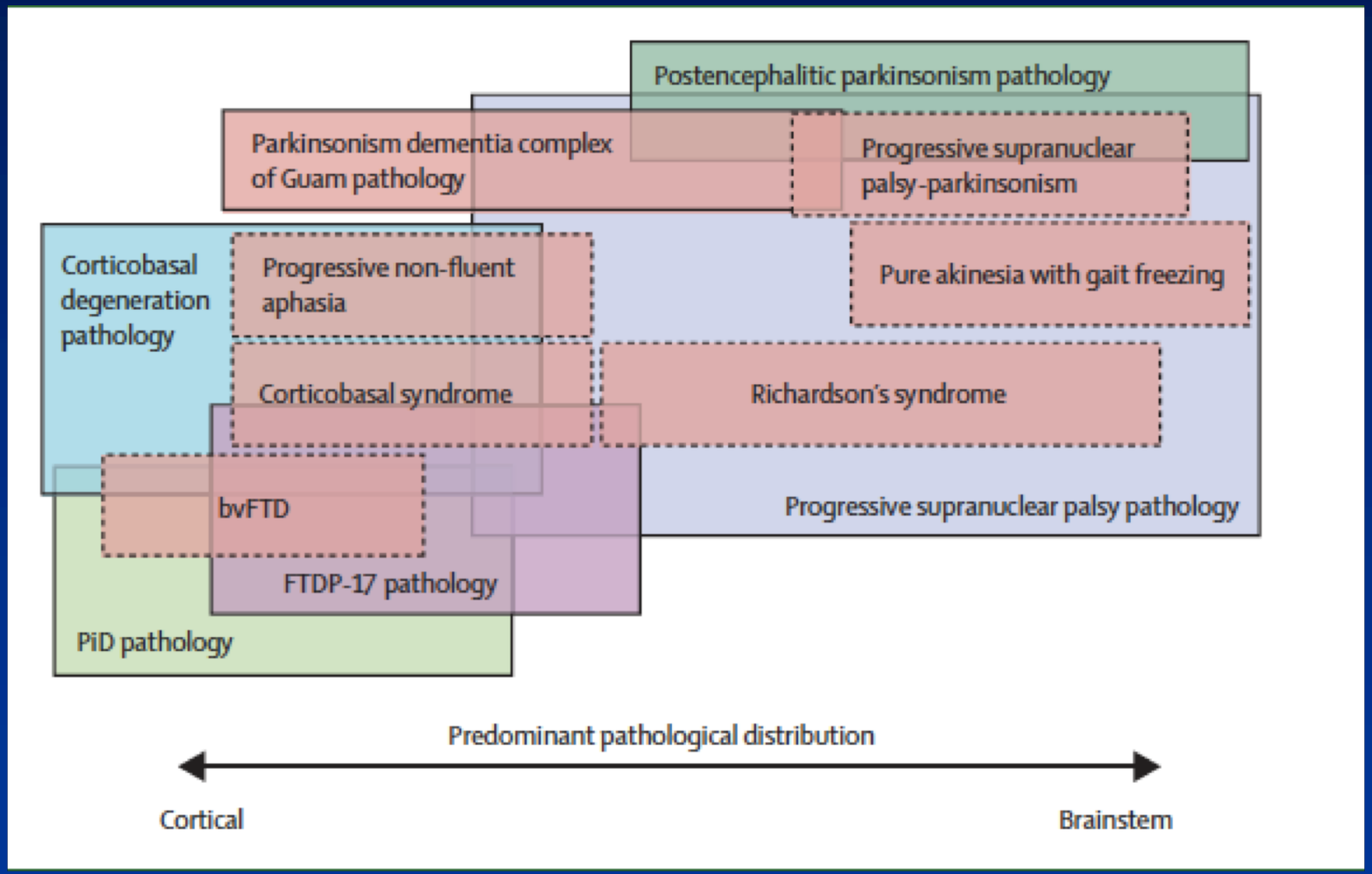
Pons area in PSP, MSA-P, PD and Controls





Quattrone et al., 2008

Corticobasal syndrome



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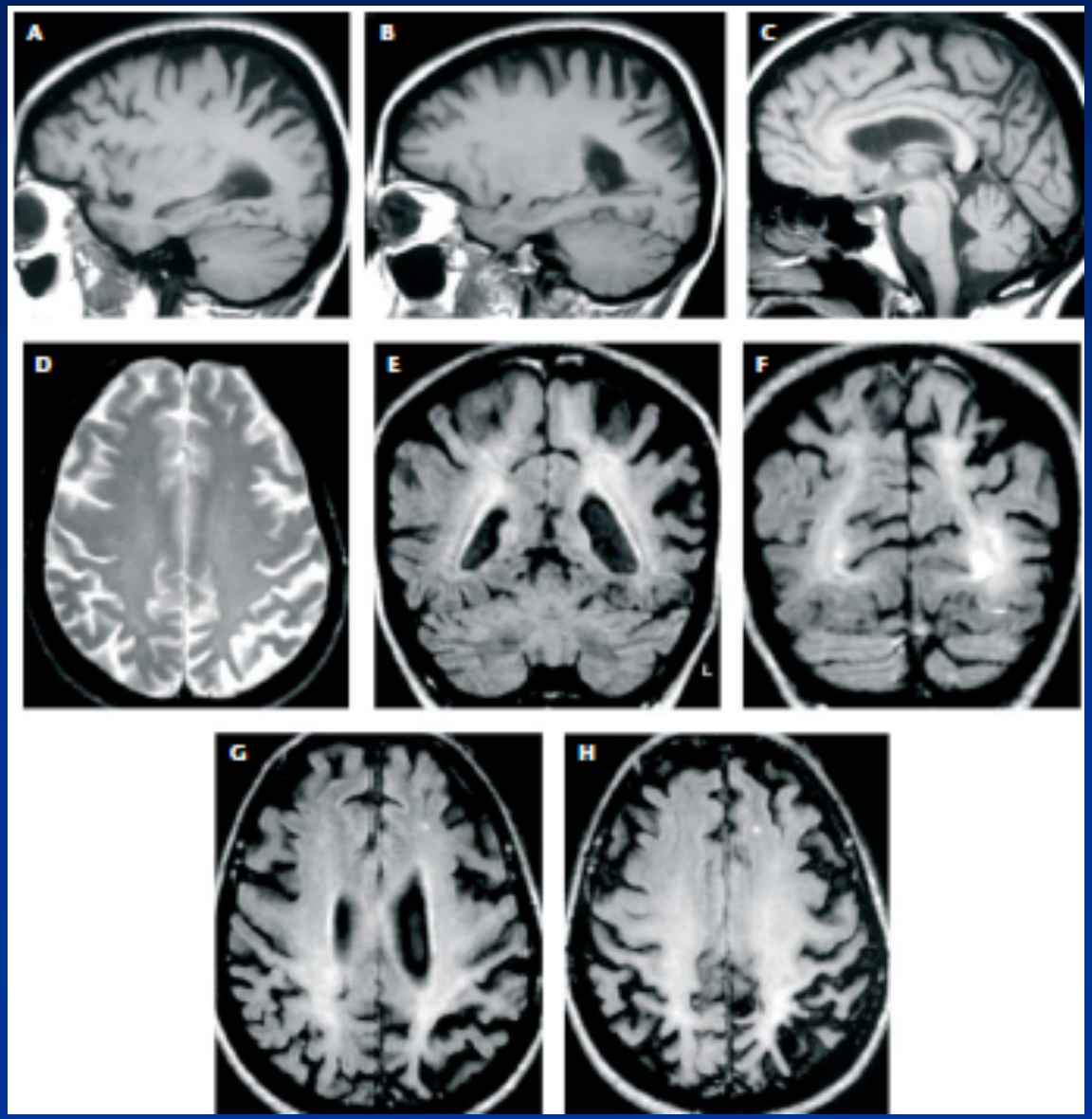
Williams & Lees Lancet Neurology 2009

Cortical Basal Degeneration/Syndrome

Asymmetric atrophy in the parietal-occipital region




PAZIENTE N° 2

Frontal atrophy – Fronto-Temporal Dementia