Progressive Supranuclear Palsy Variants

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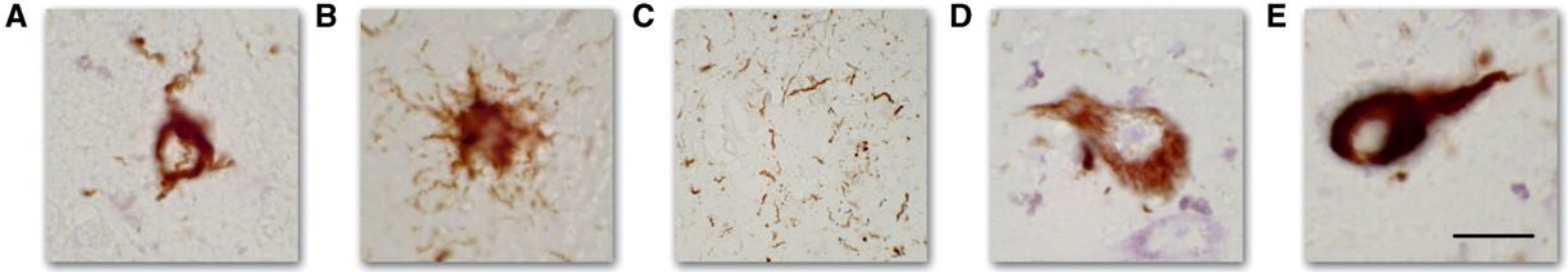
Progressive Supranuclear Palsy

§ primary tauopathy (neuronal and glial accumulation of abnormal, mostly 4R-tau)

ü robust genetic association between PSP and *MAPT* H1 (H1c)



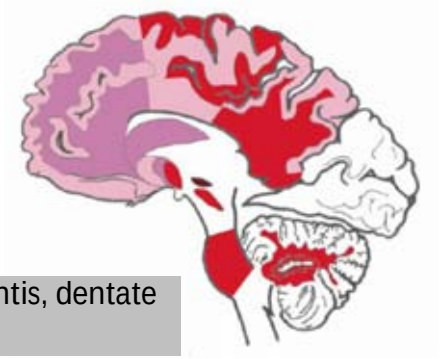
A) cytosolic aggregates in oligodendrocytes *(coiled bodies*), and B) astrocytes (*astrocytic tufts*), and C) neuronal processes *(neuropil threads),* and in neurons as D) pre-tangles or E) neurofibrill tangles

§ 2-6% of all parkinsonian patients (prevalence of 4-6/100,000)

§ age at onset ?”60.-65. yrs (median 64; range 40–77)

§ duration ?á8 yrs (median 5.8)

ü pneumonia, aspiration, craniotrauma



striatum, pallidum, STN, SN, oculomotor complex, periaqueductal gray, superior colliculi, basis pontis, dentate nucleus, prefrontal cortex, spinal cord (intermediolateral cell column)


Richardson JC


J. Steele


J. Olszewski

Progressive supranuclear palsy

NINDS-SPSP clinical criteria. Neurology 1996; 47:1-9

PSP	Mandatory inclusion criteria	Mandatory exclusion criteria	Supportive criteria
Possible	Gradually progressive disorder Onset at age 40 or later	Recent history of encephalitis Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy	Symmetric akinesia or rigidity, proximal more than distal Abnormal neck posture, especially retrocollis
	Either vertical (upward or downward gaze) supranuclear palsy* or both slowing of vertical saccades* and prominent postural instability with falls in the first year of disease onset	Hallucinations or delusions unrelated to dopaminergic therapy Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADRA criteria)	Poor or absent response of parkinsonism to levodopa therapy* Early dysphagia and dysarthria
	No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances)*	Early onset of cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs*
[redacted]		Severe, asymmetric parkinsonian signs (i.e., bradykinesia) Neuroradiologic evidence of relevant structural abnormality (i.e. basal ganglia or brainstem infarcts, lobar atrophy) Whipple's disease, confirmed by polymerase chain reaction, if indicated	
	No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria		
Definite†	Clinically probable or possible PSP *and* histopathologic evidence of typical PSP[10]		

* See Appendix for testing guidelines. Upward gaze is considered abnormal when pursuit or voluntary gaze, or both, have a restriction of at least 50% of the normal range.
† Definite PSP is a clinicopathologic diagnosis.

1.5T MRI Recommendations: **PSP** signs

- Midbrain atrophy
- Indirect signs of midbrain atrophy
  - reduced AP midbrain diameter (< 14 mm)
  - abnormal superior MB profile (flat or concave)
  - "(king) penguin silhouette" or "hummingbird sign"
  - ↓ ratio between midbrain and pontine areas
  - ↓ MRPI
- Dilatation of the third ventricle
- Atrophy of the SCP
- Signal increase in SCP (on FLAIR images)
- Signal increase in GP
- Signal increase in nucleus ruber
- Putaminal atrophy
- Frontal and parietal atrophy

Penguin silhouette sign: atrophy of the midbrain tegmentum and the normal pons looking like a lateral view of a standing penguin with a small head and a big body

"morning glory flower" sign

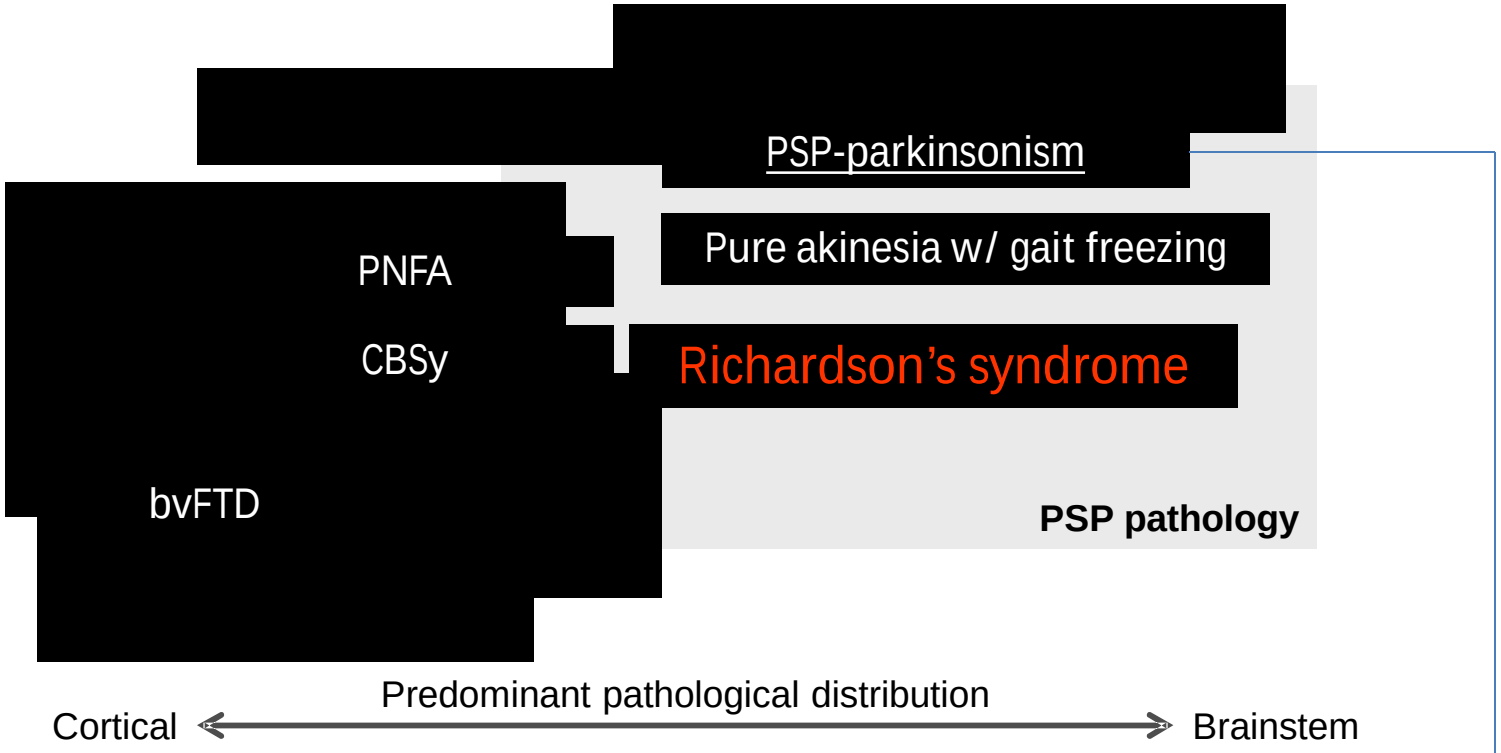
Sethi, 2011; Berardelli et al. (EFNS/MDS-ES Guidelines), 2013

Distinctive features of PSP
Early falls and loss of postural reflexes
Extended neck
Vertical (downgaze) supranuclear palsy
Axial rigidity
Pseudobulbar signs
Bradyphrenia
MRI midbrain atrophy

Donaldson et al., 2012

Tauopathies with parkinsonism

"lumping versus splitting" *(Scaravilli et al., 2003)*



asymmetric onset, tremor, mild/moderate levodopa response, better prognosis (disease duration 9-12 years), lower overall tau load, relatively restricted tau pathology

Williams and Lees. Lancet Neurology 2009

- Litvan et al. Neurology 1996;47:1-9.
  - with the exception of “in the first year of the disease” in PSP-P

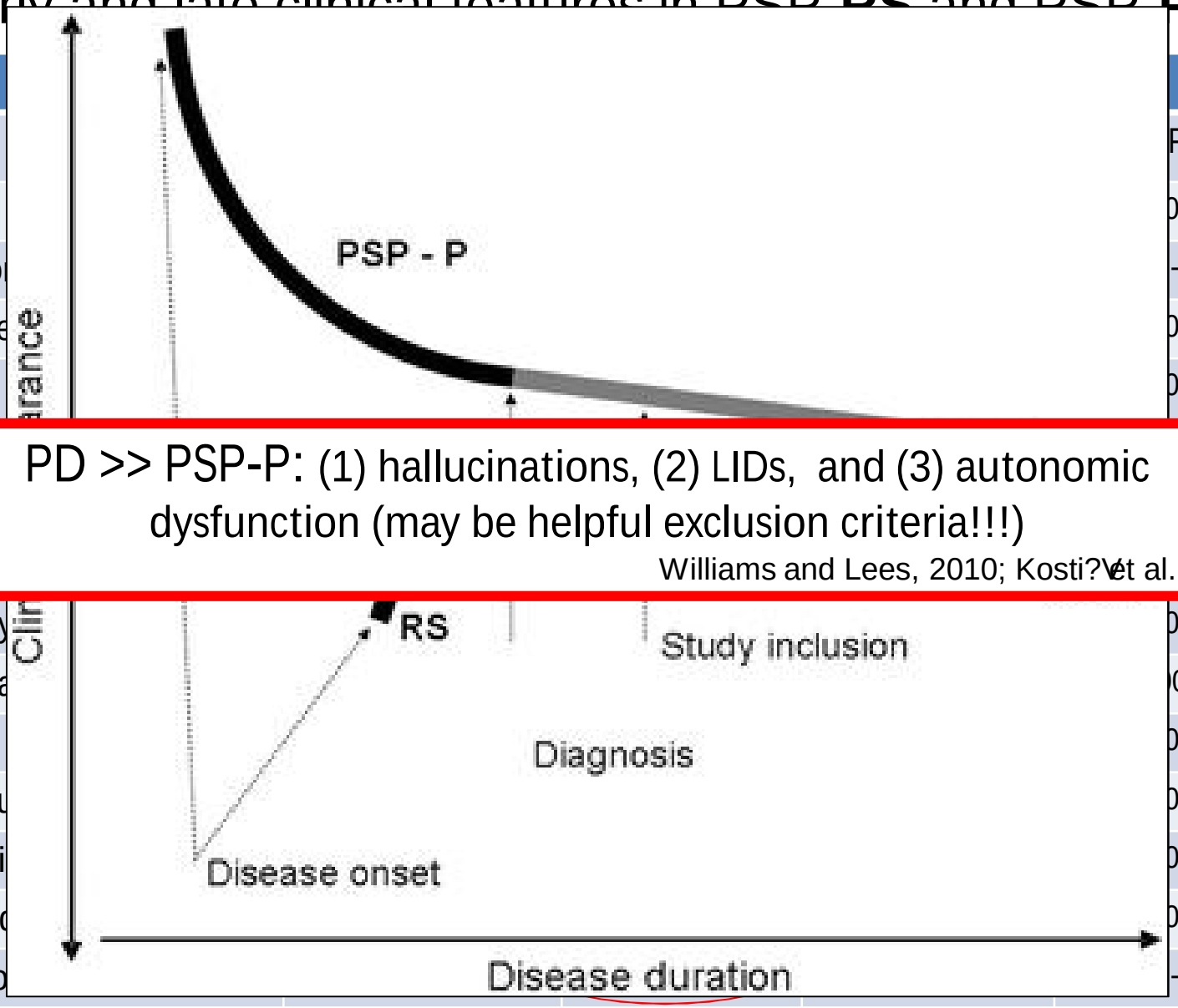
- List of symptoms from Williams et al., 2005

- ***PSP-RS***: falls, cognitive dysfunction, supranuclear gaze palsy, abnormalities of saccadic eye movements, and postural instability predominant in the first 2 years
- ***PSP-P***: at least three out of four (asymmetric bradykinesia of the limbs, a positive initial levodopa response, tremor or limb dystonia) during the same period

- Williams et al., 2005; Agosta et al., 2010; Longoni et al., 2011; Srulijes et al., 2011; Wittstock et al., 2013

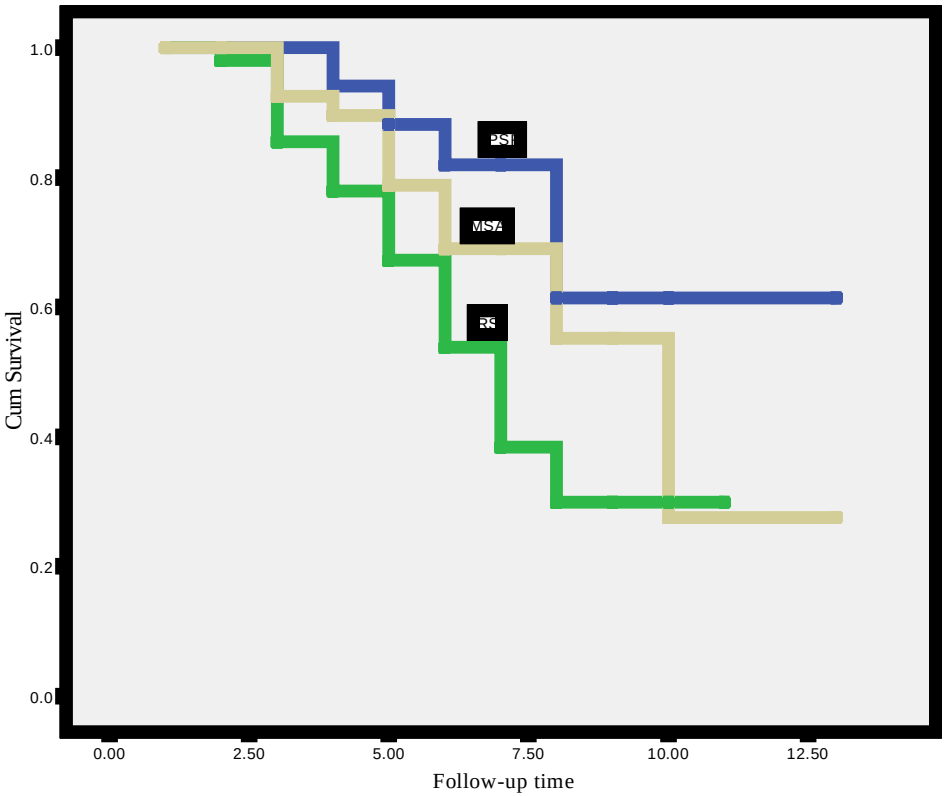
Early and late clinical features in PSP-**RS** and PSP-**P**

				P-P
Falls				0%
Asymetric o				-
Vertical gaze				0%
Tremor				0%
Rigid				
Post				
Abn				
Extraaxial dy				0%
Bradykinesia				00%
Dysphagia				0%
Speech distu				0%
Pyramidal si				0%
Autonomic d				0%
Response to				-
LID	-	-	10%	10%



PD >> PSP-P: (1) hallucinations, (2) LIDs, and (3) autonomic dysfunction (may be helpful exclusion criteria!!!)

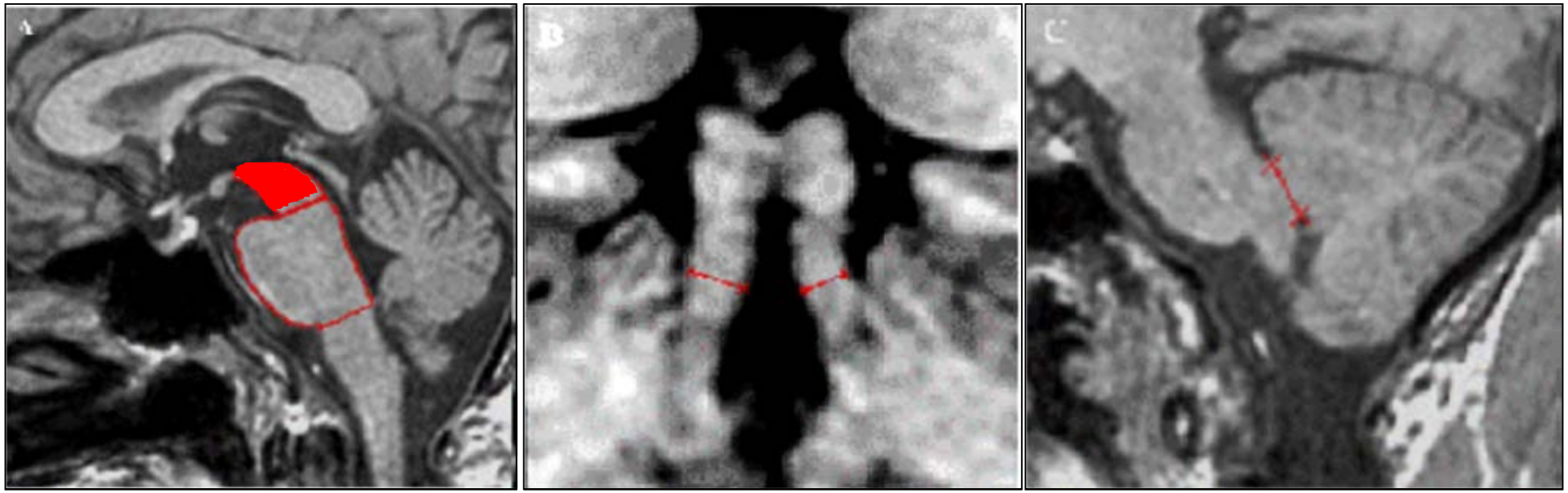
Williams and Lees, 2010; Kosti?V et al., 2011



	PSP-P (18)	PSP-RS (51)	MSA-P (49)	p
Mean survival time (yrs)	**10.5**	**7.1**	**8.5**	**0.034**
95% CI	8.8-12.3	6.1-8.1	7.1-10.7	
5 years survival probability (%)	**81.9±9.5**	**67.2±7.3**	78.9±7.3	0.034
10 years survival probability (%)	**61.4±14.4**	**29.9±8.7**	55.2±14.3	

MRI brainstem measurements in healthy subjects

sagittal and coronal 3D-T1 weighted images

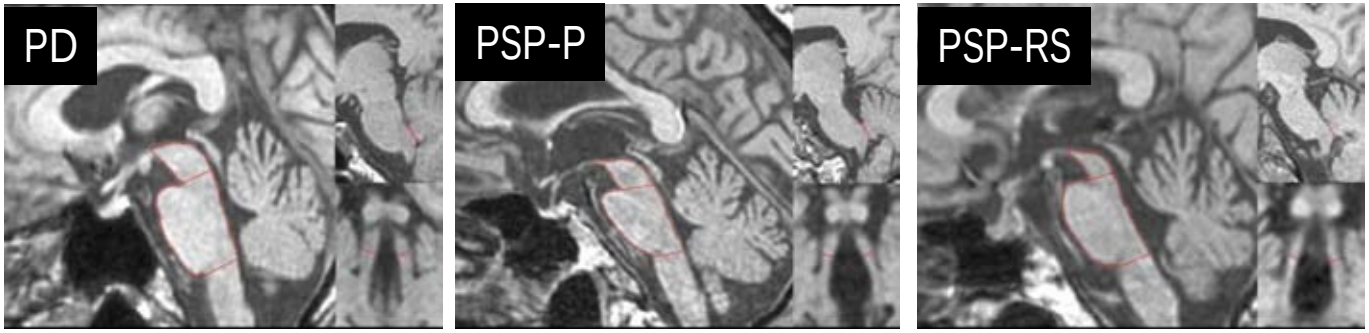


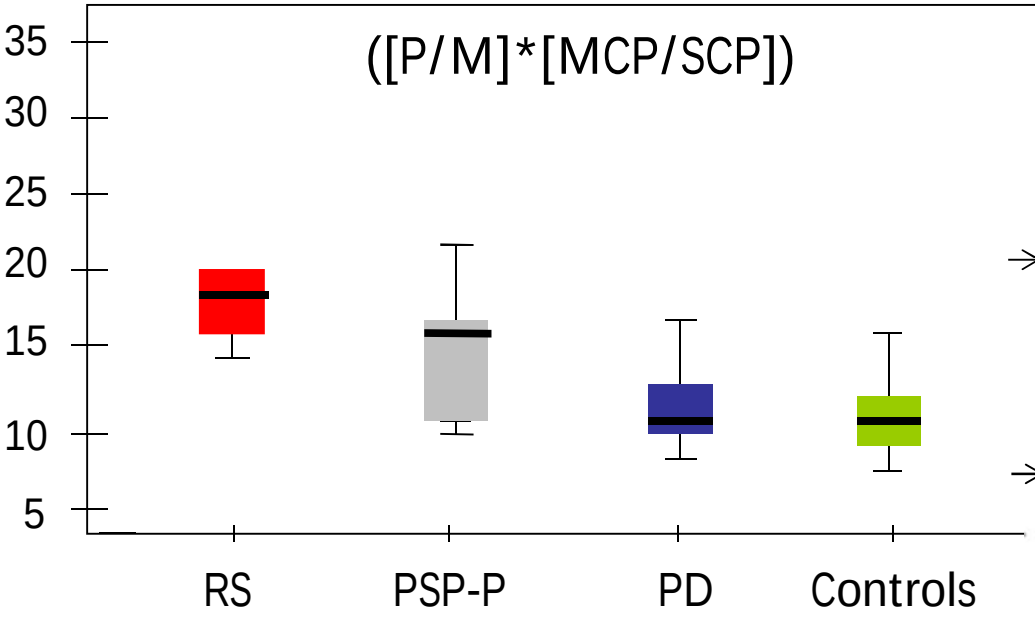
Pons area (P) Midbrain area (M)	Superior cerebellar peduncle (SCP) width	Middle cerebellar peduncle (MCP) width

- ü P/M ratio
- ü MCP/SCP ratio
- ü MR parkinsonism index ([P/M]*[MCP/SCP])

Quattrone et al., Radiology 2008

PSP *vs.* PD / MRI brainstem measurements



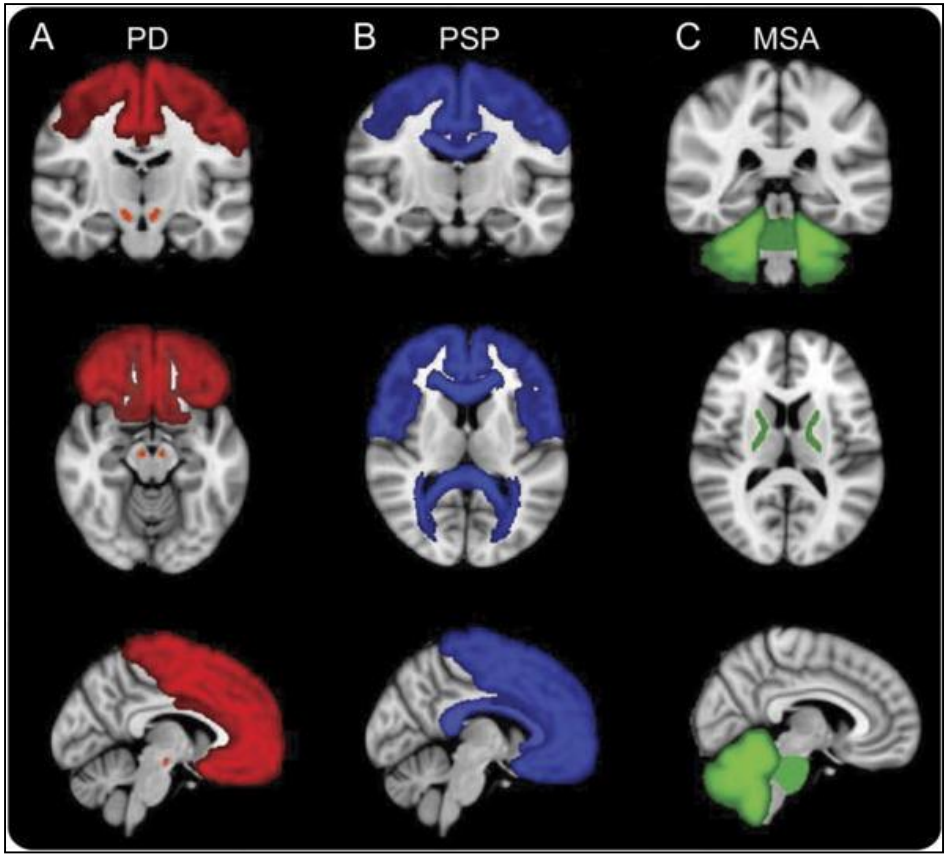


	Cut-off values	Sensitivity (%)	Specificity (%)	Accuracy (%)
→ Pons/midbrain ratio				
PSP-RS vs. controls	≥5.00	100	87.5	91
PSP-P vs. controls	≥4.52	80	67	47
PSP-RS vs. PD	≥6.01	90	96	94
PSP-P vs. PD	≥6.02	60	96	86
PSP-P vs. PSP-RS	<7.32	90	70	80
→ MR parkinsonism index				
PSP-RS vs. controls	≥13.44	100	92	94
PSP-P vs. controls	≥15.40	60	100	88
PSP-RS vs. PD	≥13.57	100	92	97
PSP-P vs. PD	≥ 11.07	70	68	40
PSP-P vs. PSP-RS	<17.50	80	70	75

Longoni, Filippi et al., Mov Disord 2011

Diffusion tensor imaging in parkinsonian syndromes: A systematic review and meta-analysis.

Cochrane C, Ebmeier K. *Neurology 2013;*80:857-864



? 3 studies individually detected a significant ($p < 0.05$) alteration in fractional anisotropy (FA) vs. healthy controls. (A) **PD**: substantia nigra and frontal lobe; (B) **PSP**: corpus callosum and frontal lobe; (C) **MSA**: cerebellum, middle cerebellar peduncle, pons, and internal capsule. All alterations were reductions in FA apart from 1 instance of increase in PSP in the corpus callosum.

Wolters Kluwer Health | OvidSP

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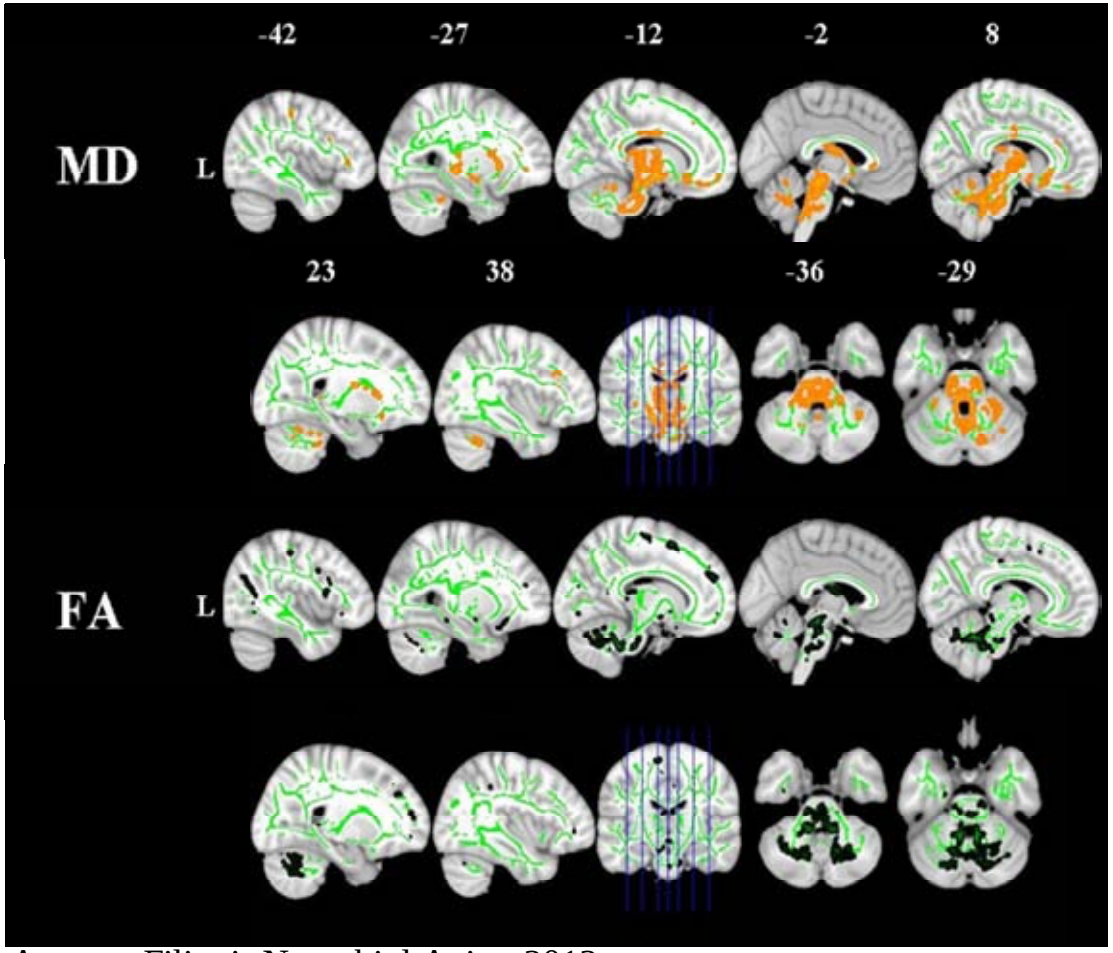
PSP-RS *vs.* PSP-P



Agosta...Filippi. Neurobiol Aging 2012

	MRPI	MRPI and DT MRI measures	
	C-index (95% CI)	C-index (95% CI)	Relative IDI (%)
PSP-RS versus healthy controls	0.92 (0.85–0.99)	0.98 (0.94–1.00)	38
PSP-P versus healthy controls	0.70 (0.54–0.86)	0.82 (0.67–0.97)	141
PSP-RS versus PSP-P	0.77 (0.61–0.93)	0.84 (0.73–0.99)	96

C-index: discriminatory power; IDI: integrated discriminatory improvement

PSP: WM damage

- All PSP: diffusivity abnormalities in the corpus callosum, fronto-parietal and frontotemporo-occipital tracts
- Infratentorial WM and thalamic radiations were severely affected in PSP-RS and relatively spared in PSP-P

Schofield et al (2011): in a pathological study, thalamocortical atrophy was a defining feature of PSP-RS (did not correlate with any cardinal clinical feature!)

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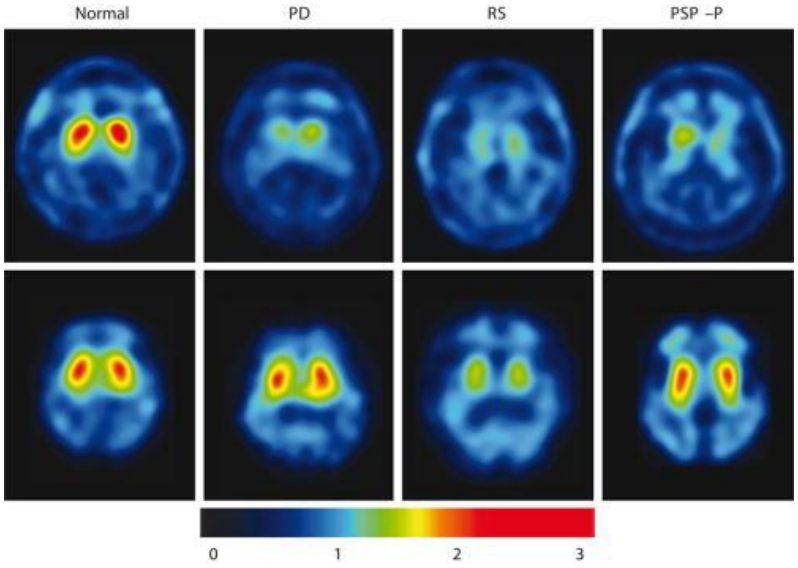
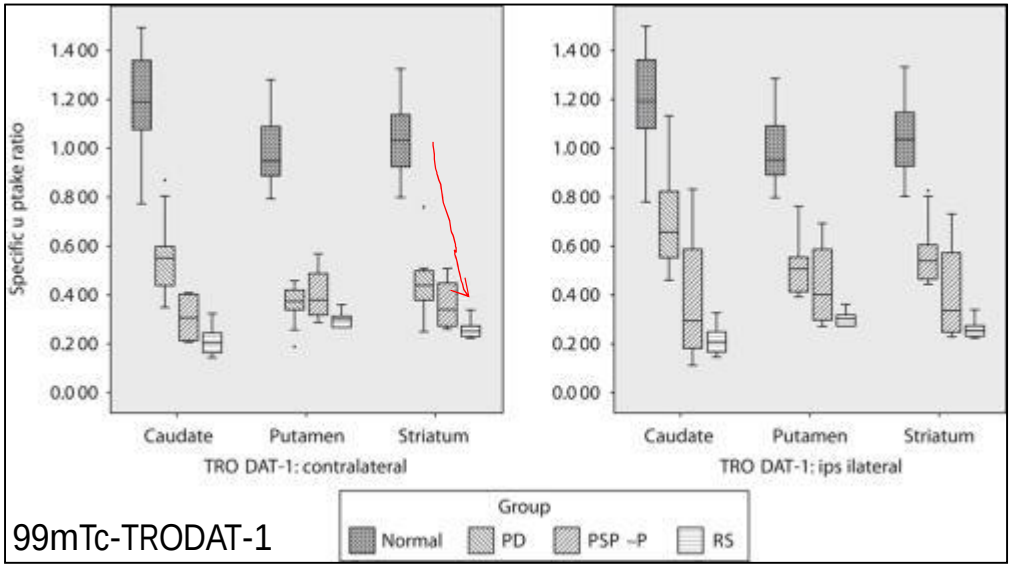
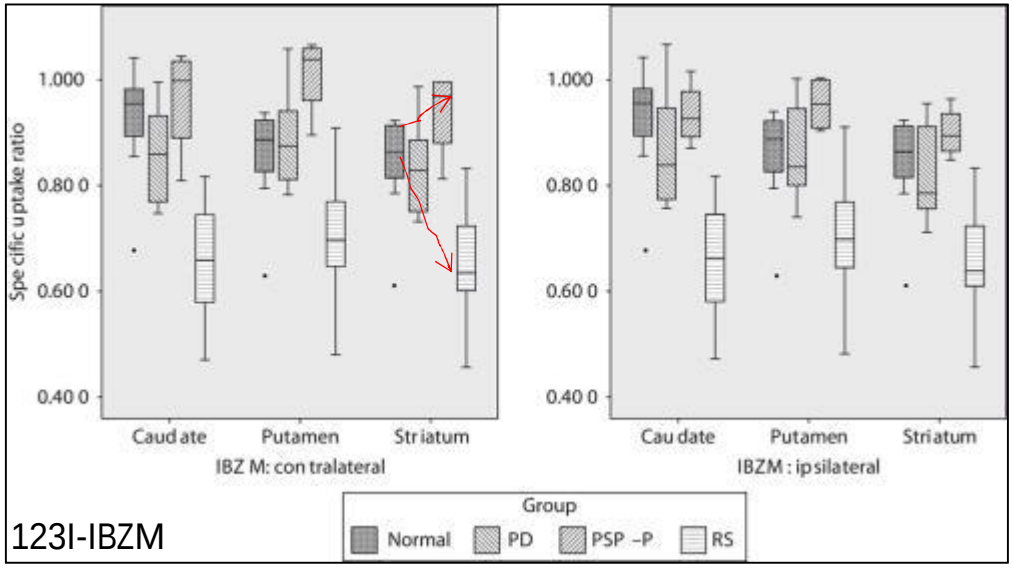
Differential DA impairments in subtypes of PSP





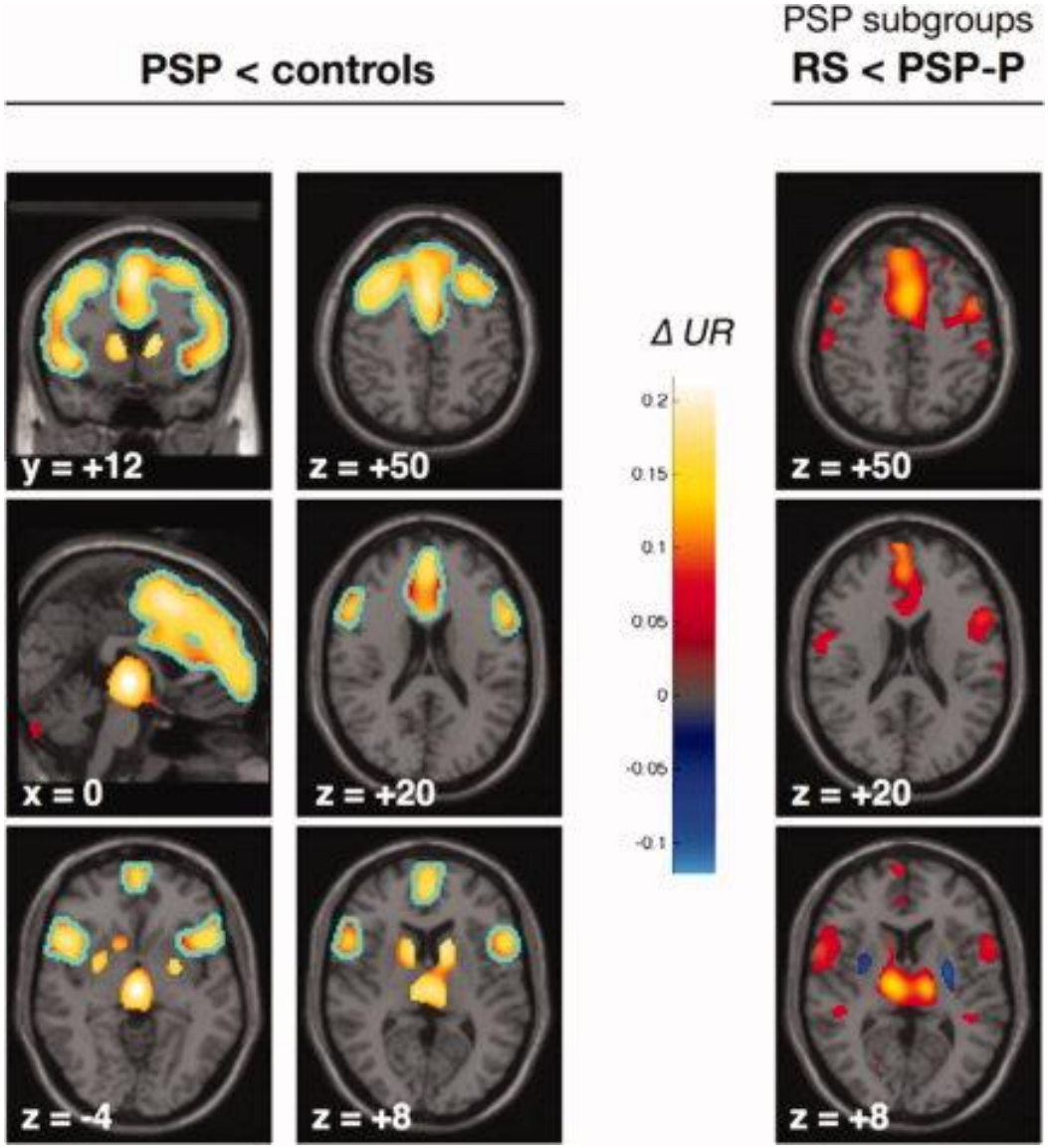
99mTc-TRODAT-1



123I-IBZM

Lin et al. Nucl Med Comm 2010

FDG PET in PSP-RS and PSP-P



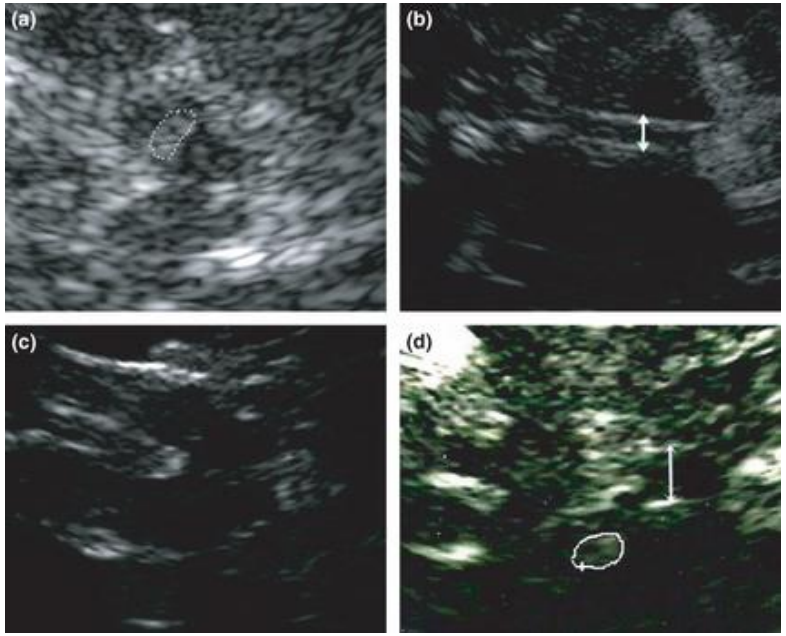
- ü PSP-RS: pronounced thalamic hypometabolism
- ü PSP-P: pronounced putaminal hypometabolism
- ü Putamen/thalamus uptake ratio differentiated PSP-P from PSP-RS and PD with acceptable accuracy
- ü Frontal hypometabolism predominantly found in PSP-RS

Srulijes et al. Mov Disord 2012

TCS in two main variants of **PSP**

	PSP-RS (n=21)	PSP-P (n=11)	*p*
Normal SN	18 (86%)	3 (27%)	0.020
Hyperechogenic SN	3 (14%)	8 (73%)	
aSN max (cm^2)	0.16 ± 0.06	0.27 ± 0.14	0.005
Normal LN	7 (33%)	7 (64%)	0.101
Hyperechogenic LN	14 (67%)	4 (36%)	
III ventricle (mm^2)	11.8 ± 2.3	7.5 ± 1.4	0.001

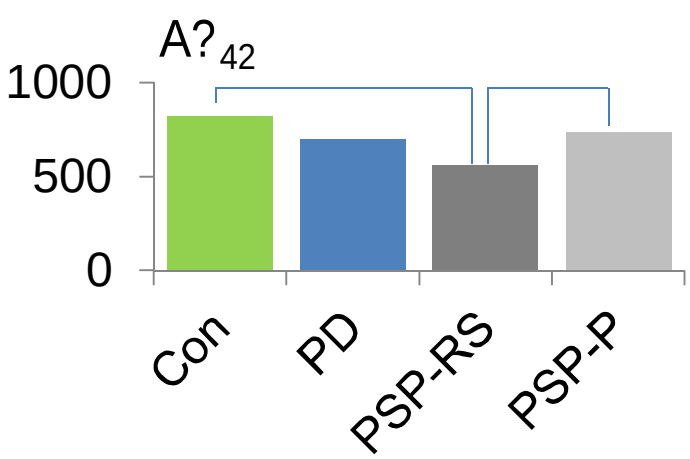
SN – substantia nigra; LN – nucleus lentiformis

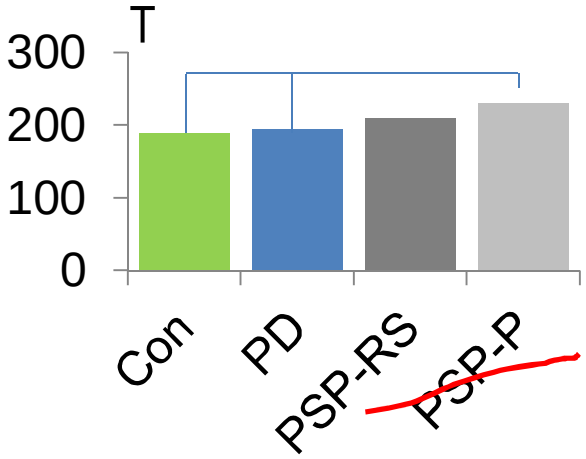


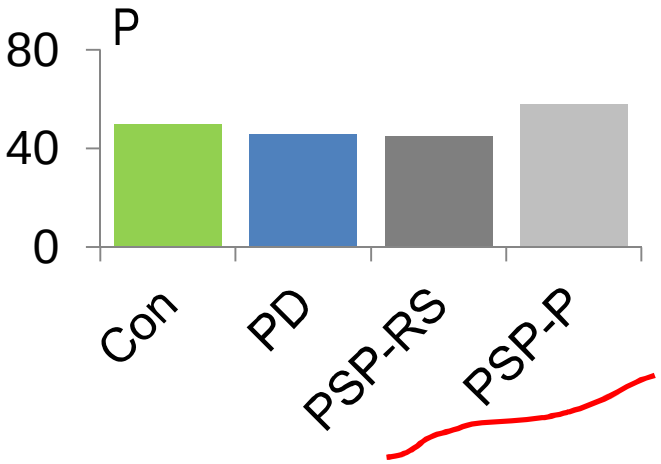
A patient with PSP-P with hyperechogenic SN (a) and normal III ventricle (b); and a patient with PSP-RS with normoechogenic SN (c) and enlarged third ventricle (d)

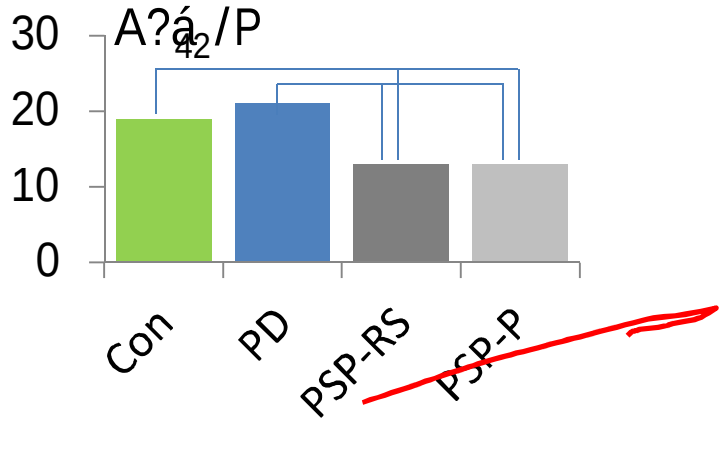
Kostic et al. European Journal of Neurology 2013 ; 20: 552-557.

CSF data (A?$_{42}$, T and P)





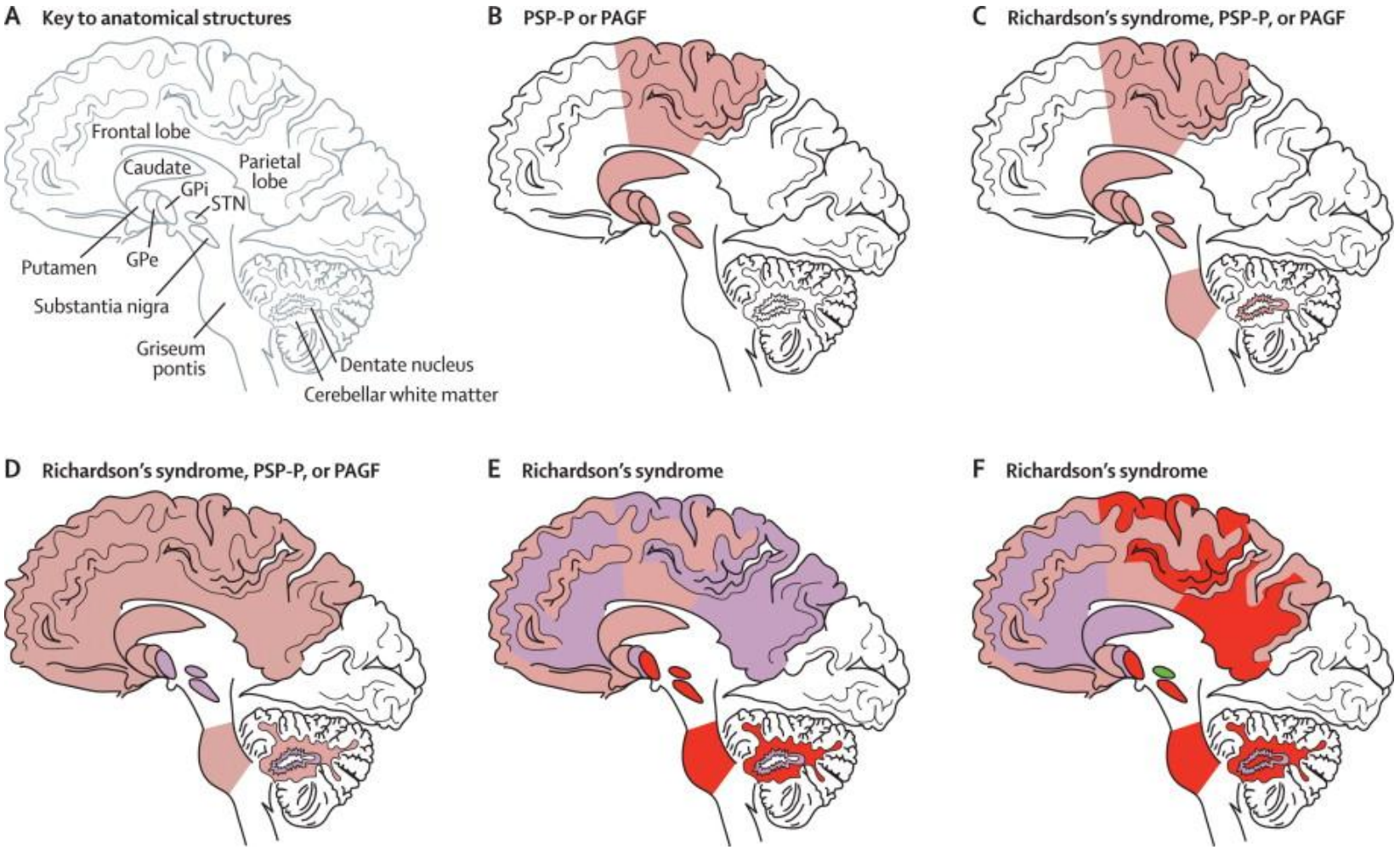




Kosti?<et al., in press

- Williams et al. Mov Disord 2007
  - Association of PSP-susceptibility haplotypes between PSP-RS and PSP-P
  - H1c in both groups
  - Routine screening for *MAPT* mutations in atypical PSP not recommended
- Pinkhardt et al. 2008
  - Eye movement recording
  - Clear-cut separation between PSP-P and PD obtained by measuring saccade velocity
- Wittstock et al. 2013
  - TMS transcallosal inhibition
  - Significantly more severe affection of TI in PSP-RS than in PSP-P and PD

Severity of PSP tau pathology varies according to distribution



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