European Reference Network
for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

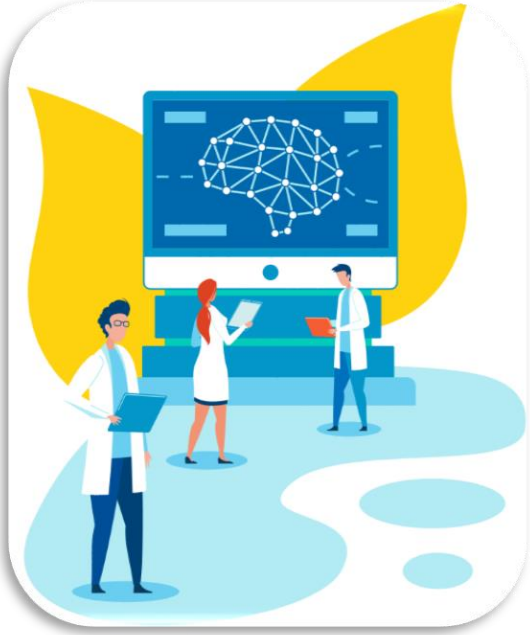
ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

26. January 2021

Joint webinar series



‘Progressive Supranuclear Palsy - Update on Diagnostics, Biomarkers, Therapies ’

by Günter Höglinger

Medical University Hannover, Germany

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European Reference Network for RARE Neurological Diseases (ERN-RND)

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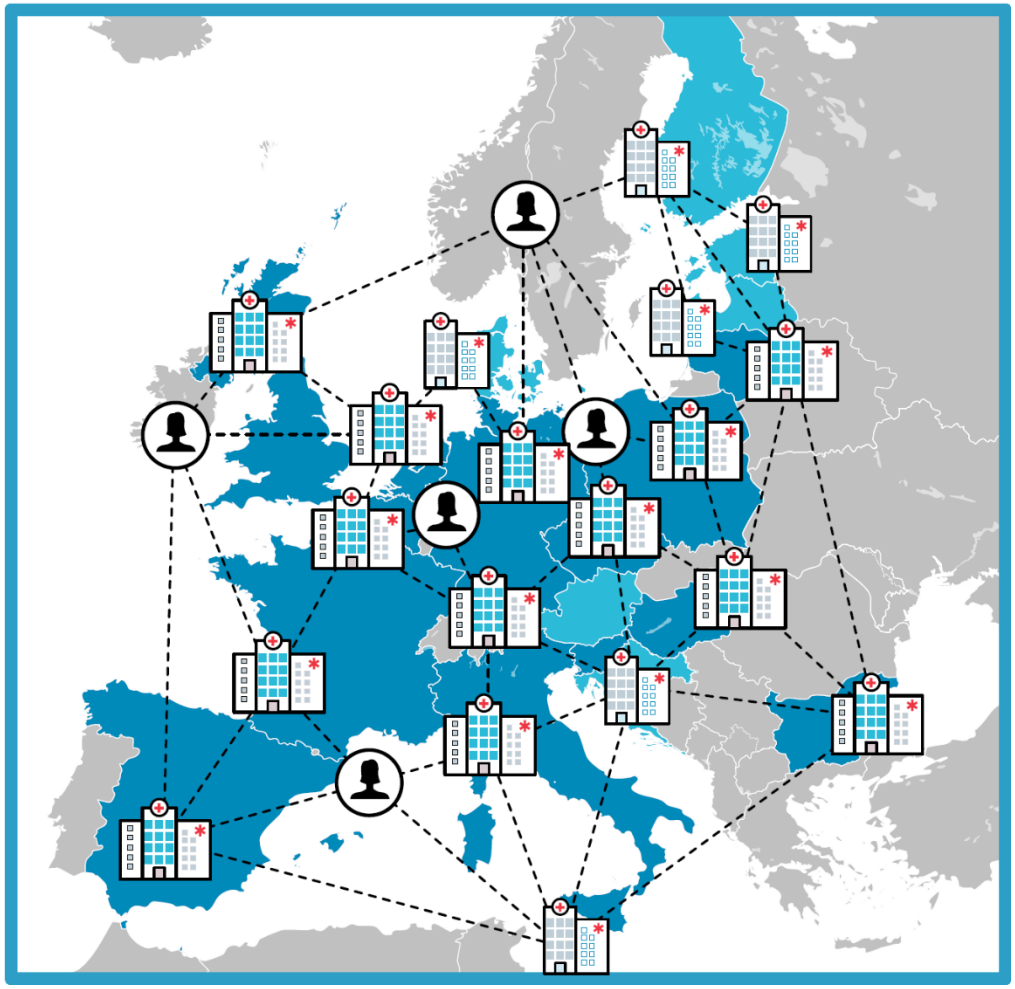

ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical Parkinsonism

General information about the webinars

- Focus on : RARE neurological, neuromuscular and movement disorders & neurorehabilitation
- Alternating adult and paediatric topics
- 40-45min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- ***NEW*** - upcoming webinars for 2021: http://www.ern-rnd.eu/education-training/webinars/
- Post-webinar survey (2-3min): satisfaction, topic/speaker ideas for next webinars

Speaker: Günter Höglinger

Short biosketch

- **Training:**

  MD Student, Universities Regensburg, Würzburg, Munich
  Postdoc, INSERM, Unit 679, Hôpital Salpêtrière, Paris, France
  Consultant in Neurology, Marburg University, Germany
  Consultant in Neurology, Technical University Munich, Germany
  W3, German Center for Neurodegenerative Diseases, Munich, Ger.

- **Current position:**

  Director, Dept. of Neurology, Hannover Medical School (MHH), Germany

- **Other key activities:**

  President, German Parkinson's and Movement Disorders Society

- **Research focus:**

  Translational research into tauopathies and synucleinopathies
  - Diagnosis and therapy of Parkinson's disease
  - Molecular biology of Parkinson's disease
  - Atypical Parkinson Syndromes (MSA, PSP, CBD)

Institutional Logo, ‚Speakers' picture or disease related picture

Webinar outline

1. PSP: high level overview
2. Tauopathies: key facts & classifications
3. PSP diagnostic criteria: challenges and solutions
4. PSP: video illustrations
5. Molecular diagnostics
6. Molecular disease mechanisms
7. Therapeutic trials

Institutional Logo,
‚Speakers' picture or disease related picture

Learning objectives

By the end of this webinar you will be able to:

- reliably diagnose PSP
- know the current status on diagnostic modalities
    - MR imaging
    - TAU PET
    - Fluid biomarkers
- understand the molecular pathogenesis
- know about ongoing / upcoming clinical trials

DZNE
Deutsches Zentrum für
Neurodegenerative Erkrankungen
in der Helmholtz-Gemeinschaft

Medizinische Hochschule
Hannover

Progressive Supranuclear Palsy (PSP): Update on Diagnostics, Biomarkers and Therapies'

ERN-RND, EAN lecture

January 26, 2021

Univ.-Prof. Dr. med. Günter Höglinger
Hannover / München

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Deutsches Zentrum für Neurodegenerative Erkrankungen
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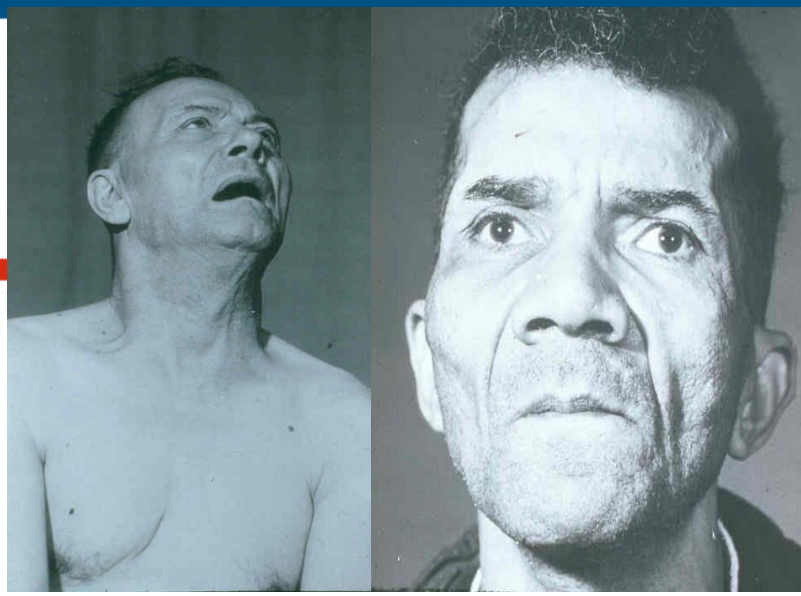


Progressive Supranuclear Palsy

A Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum With Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia

JOHN C. STEELE, MD
J. CLIFFORD RICHARDSON, MD
AND
JERZY OLSZEWSKI, MD
TORONTO

Introduction

In this report we are describing a progressive brain disease featured by supranuclear ophthalmoplegia affecting chiefly vertical gaze, pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, and other less constant cerebellar and pyramidal symptoms. Dementia has usually remained mild. This disease would appear to be predominantly a nerve cell degeneration centered chiefly in the brain stem.

Archives of Neurology, 1964;10:333-359

Distribution of lesions in PSP

Caudate
Putamen
Pallidum
STN

Tectum

SNc

Periaquedictal Grey

Pontine Nuclei

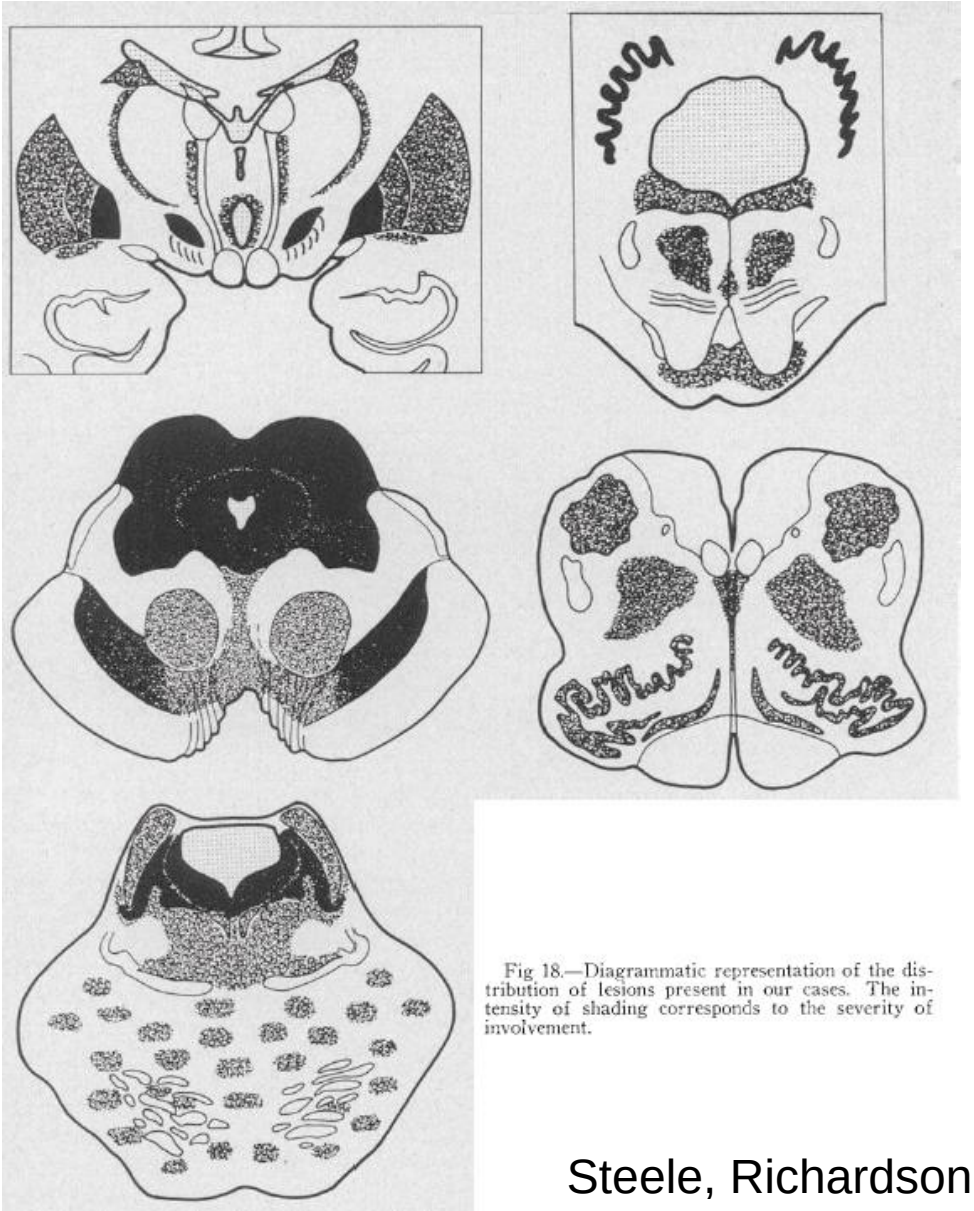
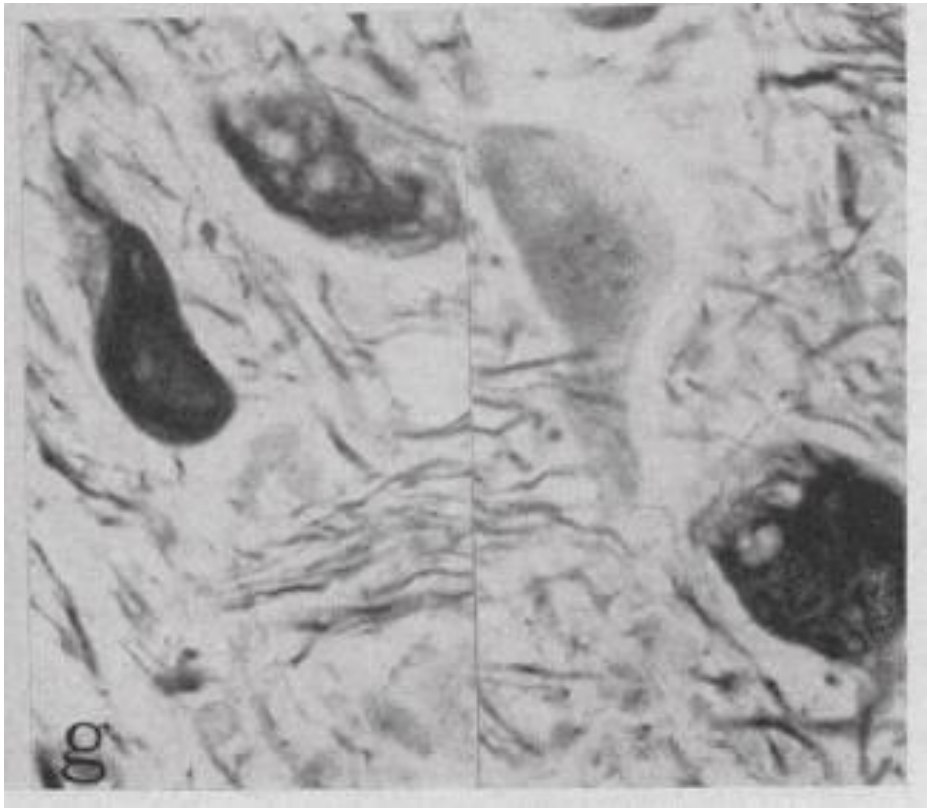


Fig 18.—Diagrammatic representation of the distribution of lesions present in our cases. The intensity of shading corresponds to the severity of involvement.

Steele, Richardson, Olszewski.
Archives of Neurology, 1964;10:333-359

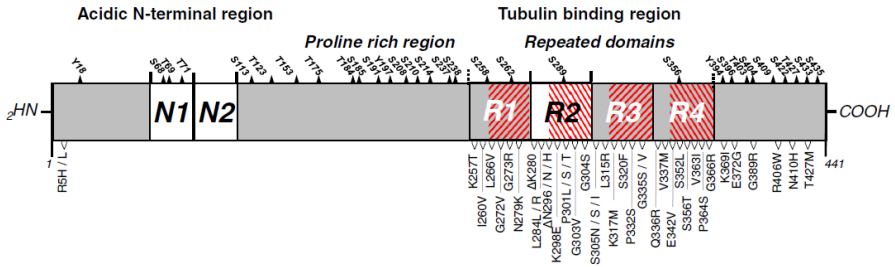
Microscopic lesions in PSP



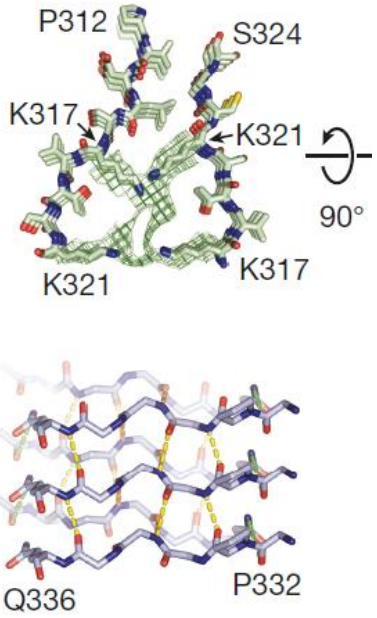
Bielschowsky pos. NFTs

Steele, Richardson, Olszewski.
Archives of Neurology, 1964;10:333-359

Tau



Moussaud et al. **Molecular Neurodegeneration** 2014

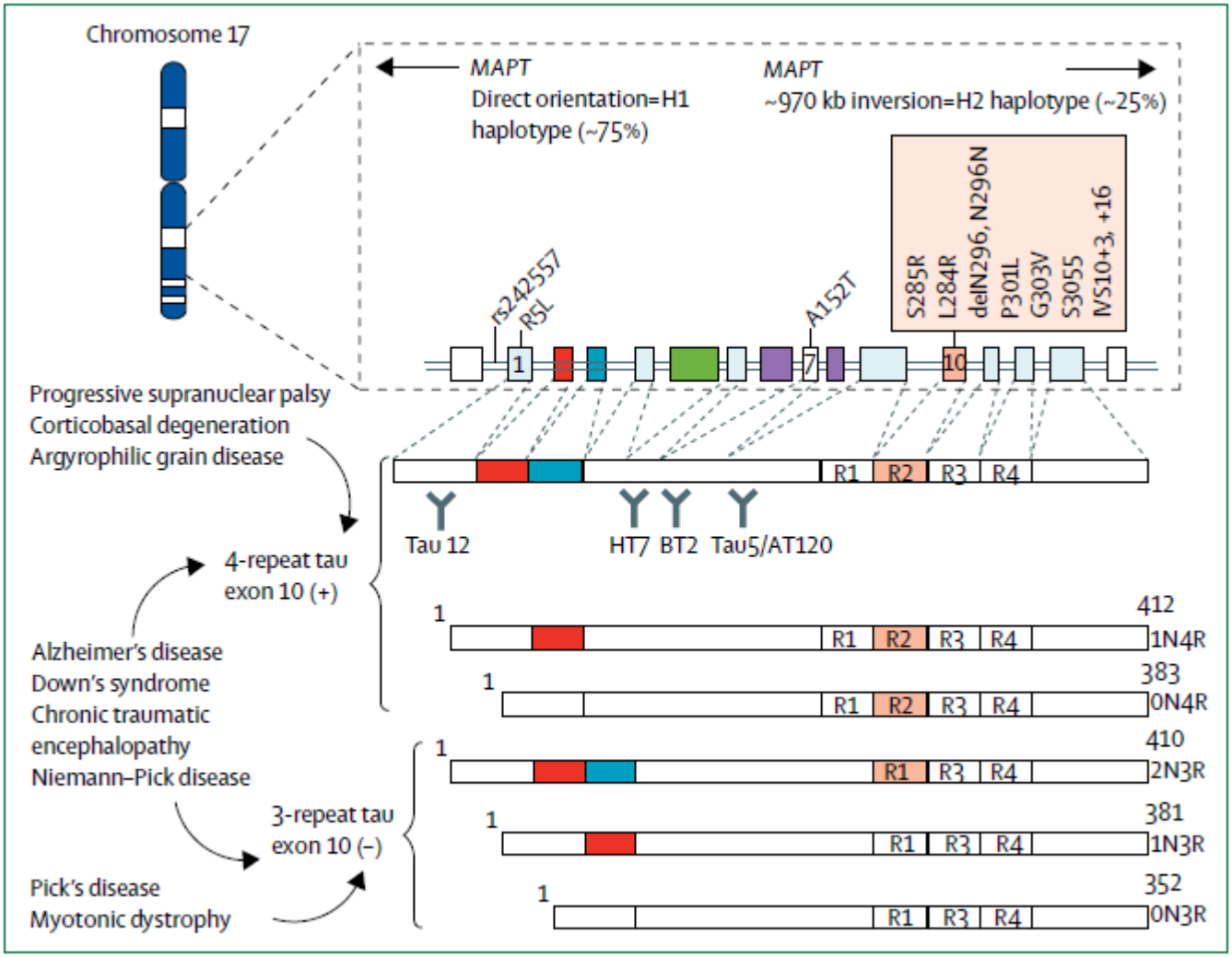


Fitzpatrick et al., **Nature** 2017

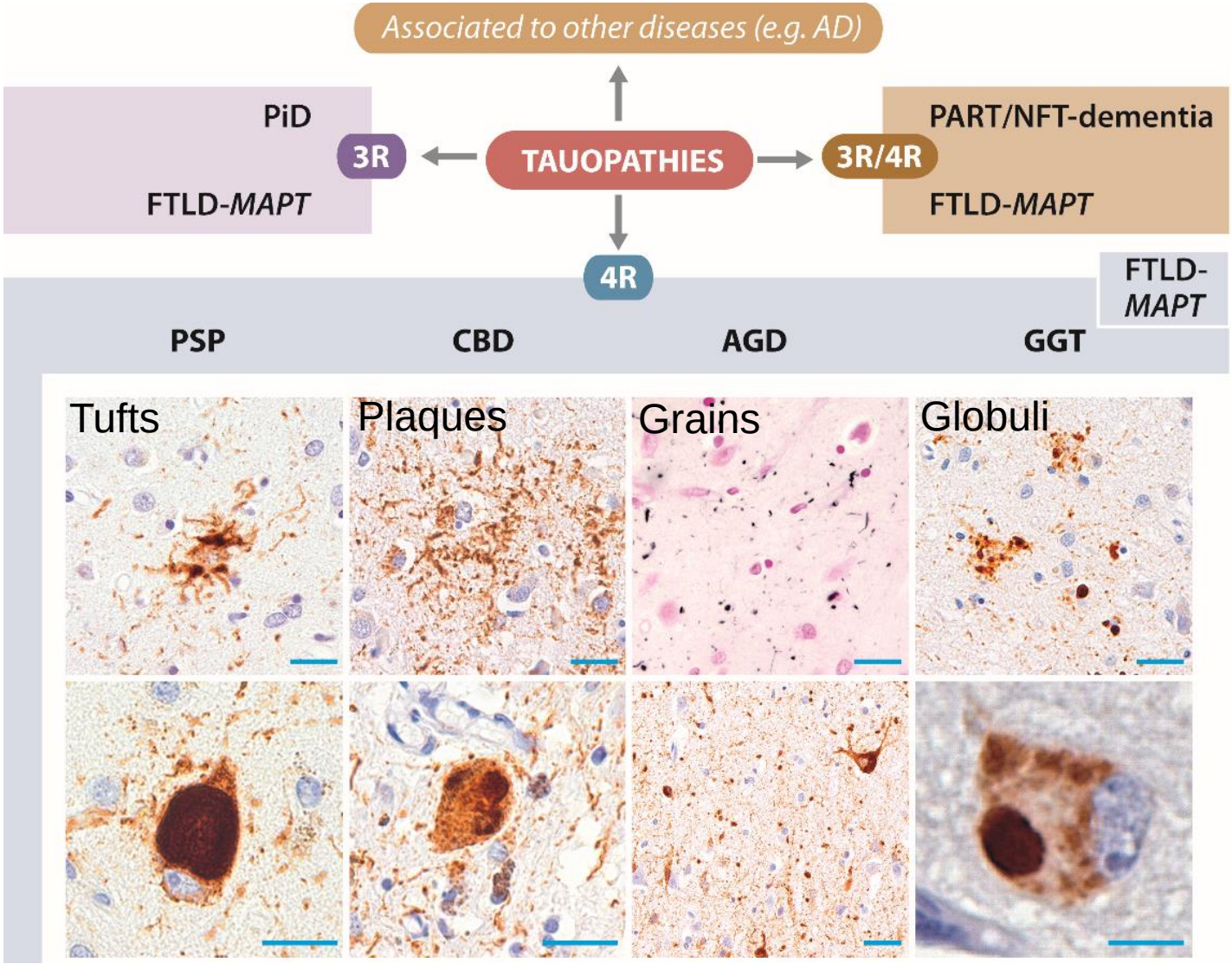
Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches

Adam L Boxer, Jin-Tai Yu, Lawrence I Golbe, Irene Litvan, Anthony E Lang, Günter U Höglinger

Lancet Neurol 2017; 16: 552–63



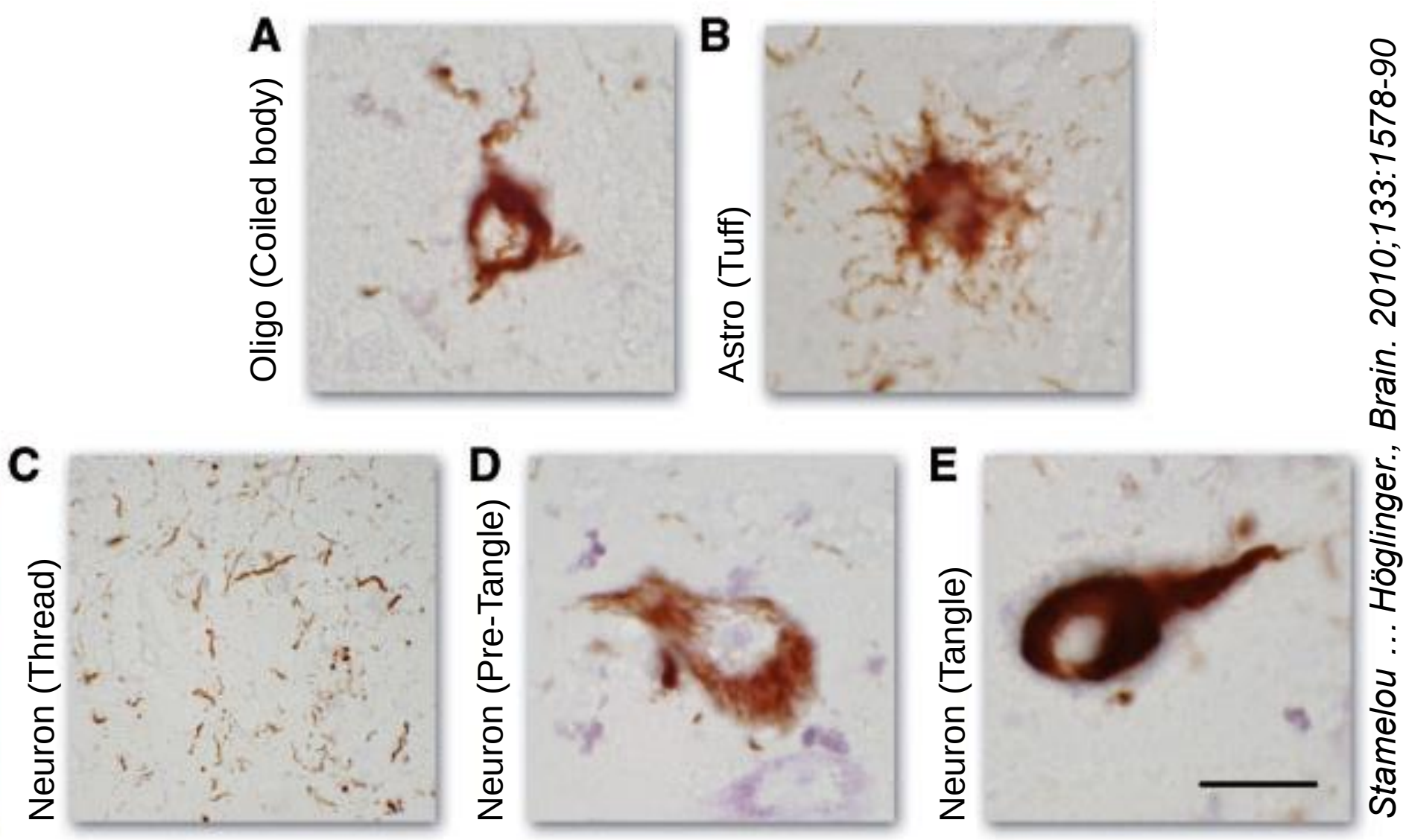
Tau Pathology



Tau Pathology
Rösler / Brendl / Höglinger, 2019

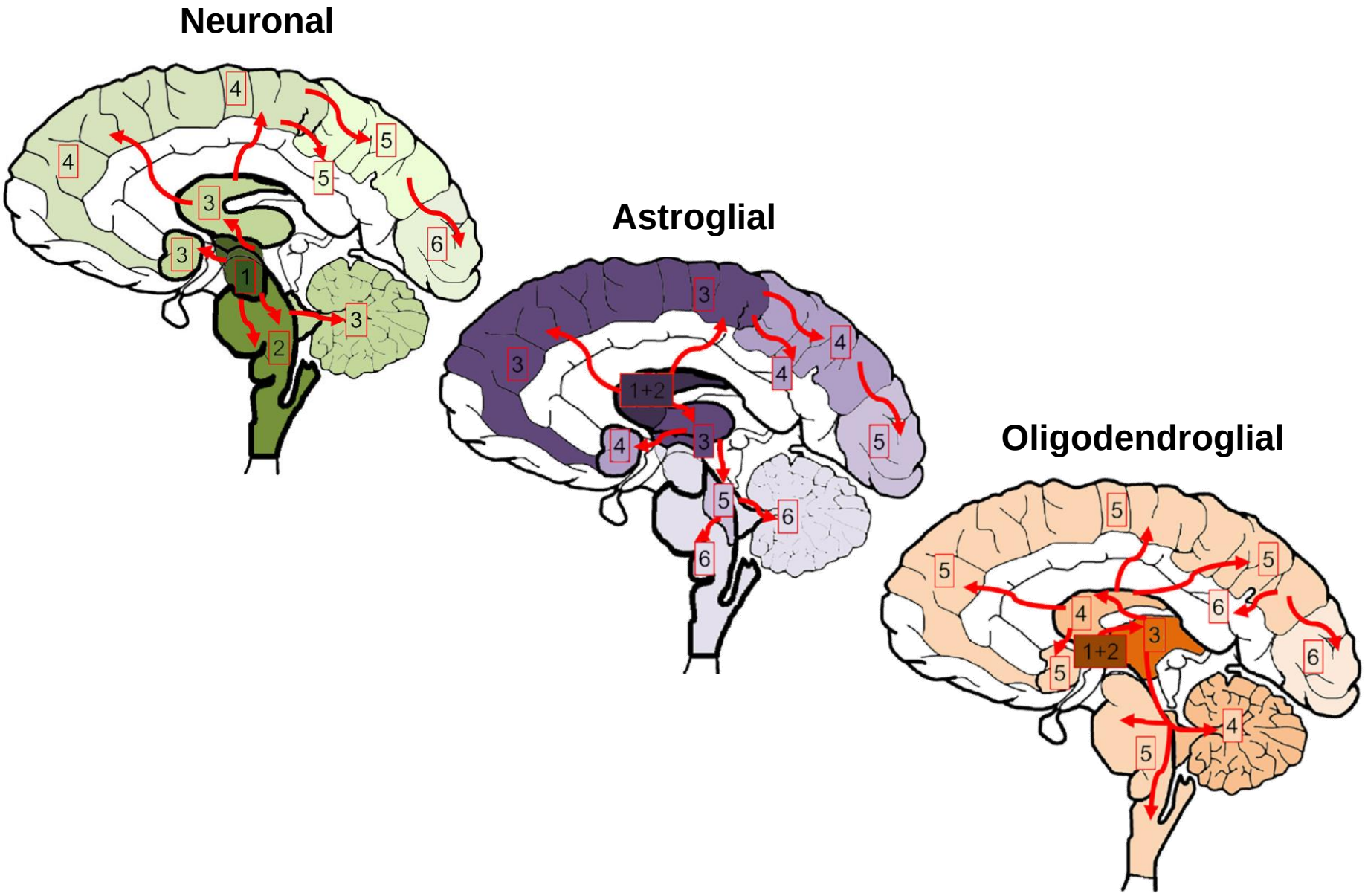
Progressive Supranuclear Palsy (PSP)

AT8 (phospho-Tau)$^{+}$ glial and neuronal inclusions



Stamelou … Höglinger., Brain. 2010;133:1578-90

Tau Spreading bei PSP



Kovacs, … Höglinger, **Acta Neuropath,** 2020

Q1: *MAPT* encodes

- One 3R isoform of the tau protein
- Three 3R isoforms of the tau protein
- One 4R isoform of the tau protein
- Three 4R isoforms of the tau protein
- One 3R and 4R isoform of tau each
- Three 3R and 4R isoforms of tau each

Q1: *MAPT* encodes

- One 3R isoform of the tau protein
- Three 3R isoforms of the tau protein
- One 4R isoform of the tau protein
- Three 4R isoforms of the tau protein
- One 3R and 4R isoform of tau each
- **Three 3R and 4R isoforms of tau each (CORRECT)**

Q2: PSP and CBD are

- Secondary mixed 3R / 4R tauopathies
- Secondary pure 3R tauopathies
- Secondary pure 4R tauopathies
- Primary mixed 3R / 4R tauopathies
- Primary pure 3R tauopathies
- Primary pure 4R tauopathies

Q2: PSP and CBD are

- Secondary mixed 3R / 4R tauopathies
- Secondary pure 3R tauopathies
- Secondary pure 4R tauopathies
- Primary mixed 3R / 4R tauopathies
- Primary pure 3R tauopathies
- **Primary pure 4R tauopathies (CORRECT)**

CLINICAL SCPECTUM: PSP PREDOMINANCE TYPES

Richardson's Syndrome

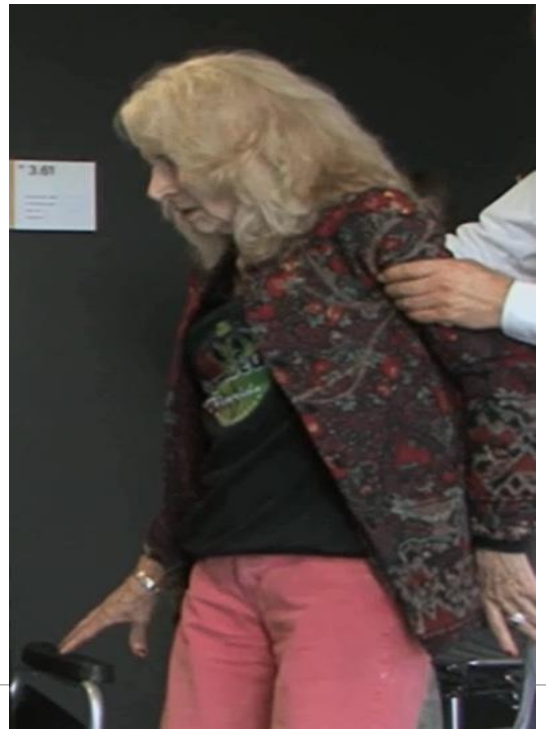
PSP clinical presentations

A **Ocular motor dysfunction**
- **Vertical supranuclear gaze palsy**
- **Slow velocity of vertical saccades**
- **Frequent macro square wave jerks**

https://www.youtube.com/watch?v=wUz1GaAS_-I

B **Postural instability**
- **Repeated unprovoked falls**
- **Tendency to fall on the pull-test**

> 2 steps backward on the pull-test



Höglinger, …, Mov Disord. 2017;32:853-864.

Astrocytic Tuft:
The defining lesion in PSP
Stamelou et al., Brain. 2010;133:1578-90

Richardson‘s syndrome
(RS, clinical diagnosis)

Supranuclear gaze palsy

Definite PSP
(PSP, neuropathological diagnosis)

Astrocytic Tuft

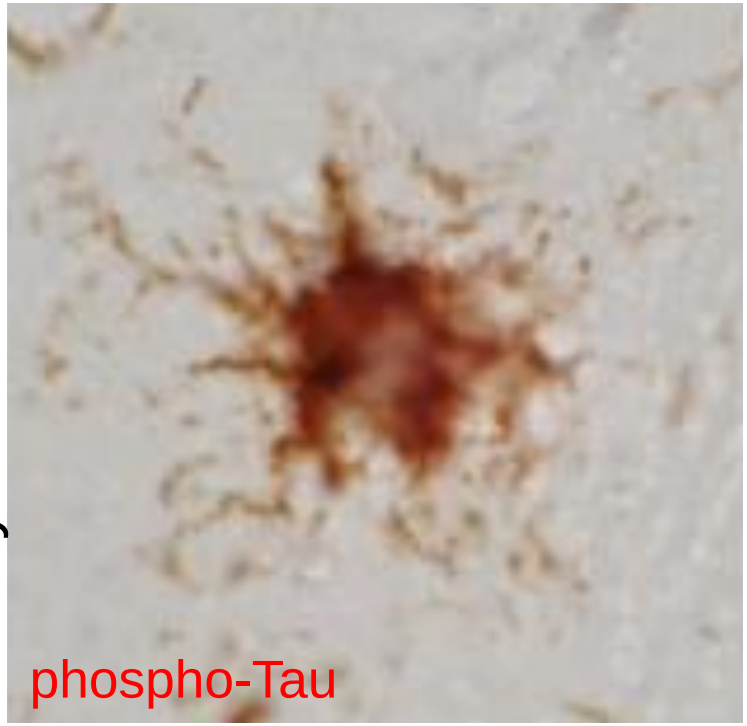
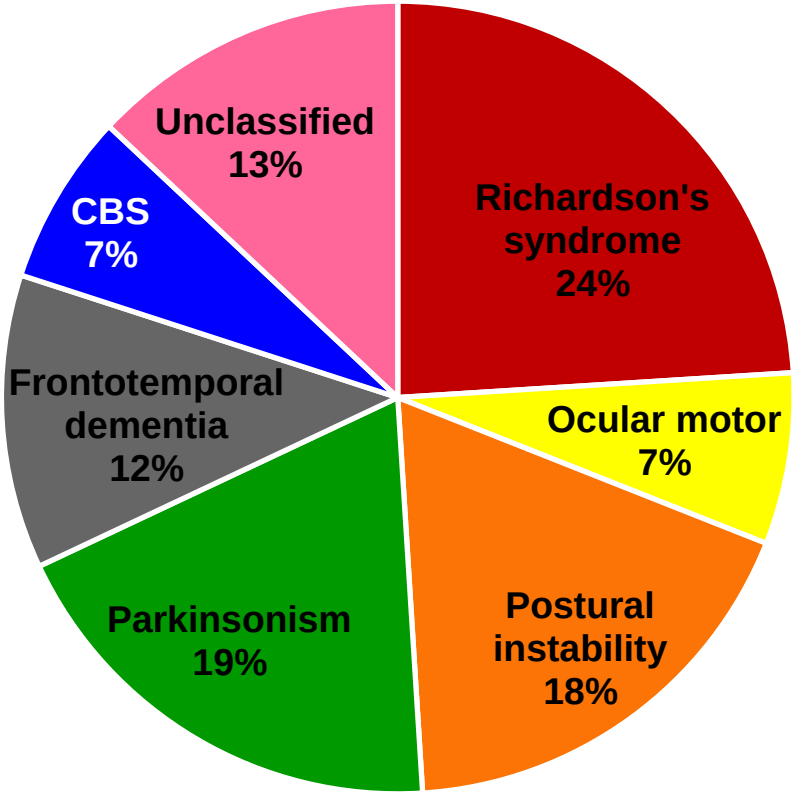


Photo: T. Arzberger / G. Höglinger

Astrocytic Tuft:
The defining lesion in PSP
Stamelou et al., Brain. 2010;133:1578-90

Full Clinical Spectrum



Respondek, … Höglinger, **Mov Dis.** 2014

Definite PSP

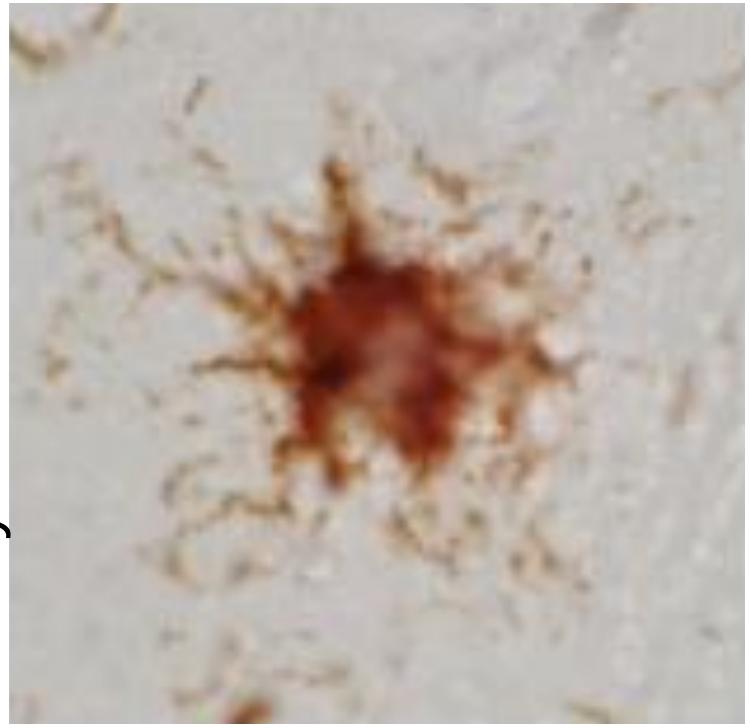


Photo: T. Arzberger / G. Höglinger

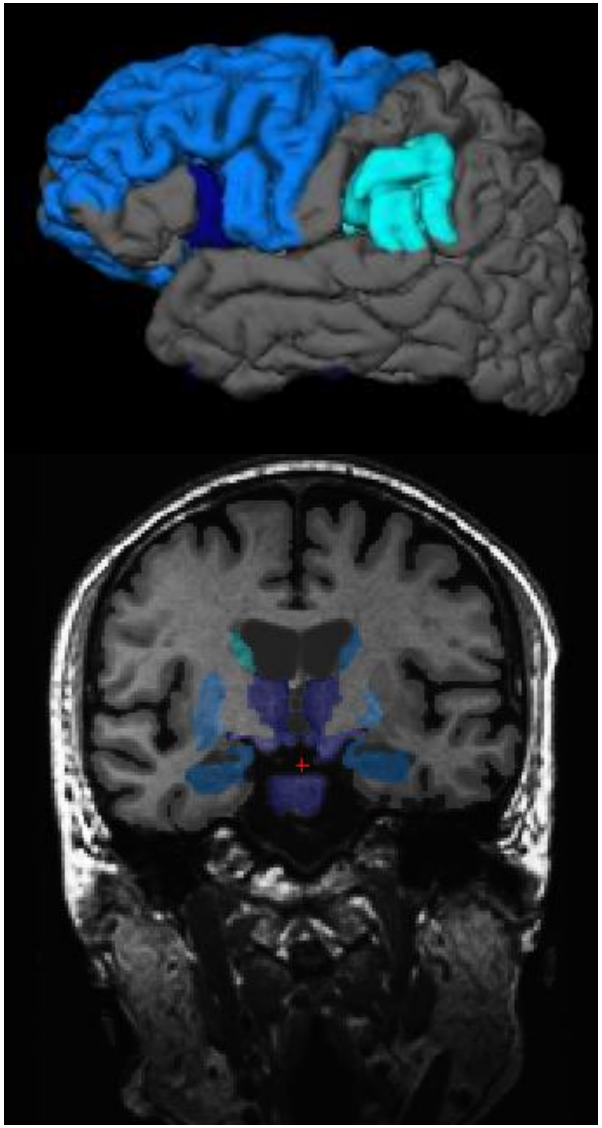
PSP clinical presentations

Classic	• PSP-RS	Richardson Syndrome
	• PSP-PI	Postural Instability
	• PSP-OM	Oculomotor Dysfunction
Motor	• PSP-P	Parkinsonism
	• PSP-PGF	Progressive Gait Freezing
	• PSP-CBS	Corticobasal Syndrome
Cognitive	• PSP-FTD	Frontotemporal Dementia
	• PSP-PNFA	Progressive Non-Fluent Aphasia
	• PSP-AOS	Apraxia of Speech
Other	• PSP-PLS	Primary Lateral Sclerosis
	• PSP-C	Cerebellar Ataxia

Höglinger, …, Mov Disord. 2017;32:853-864.
Rösler, …, Prog. Neurobiol 2019;180:101644.

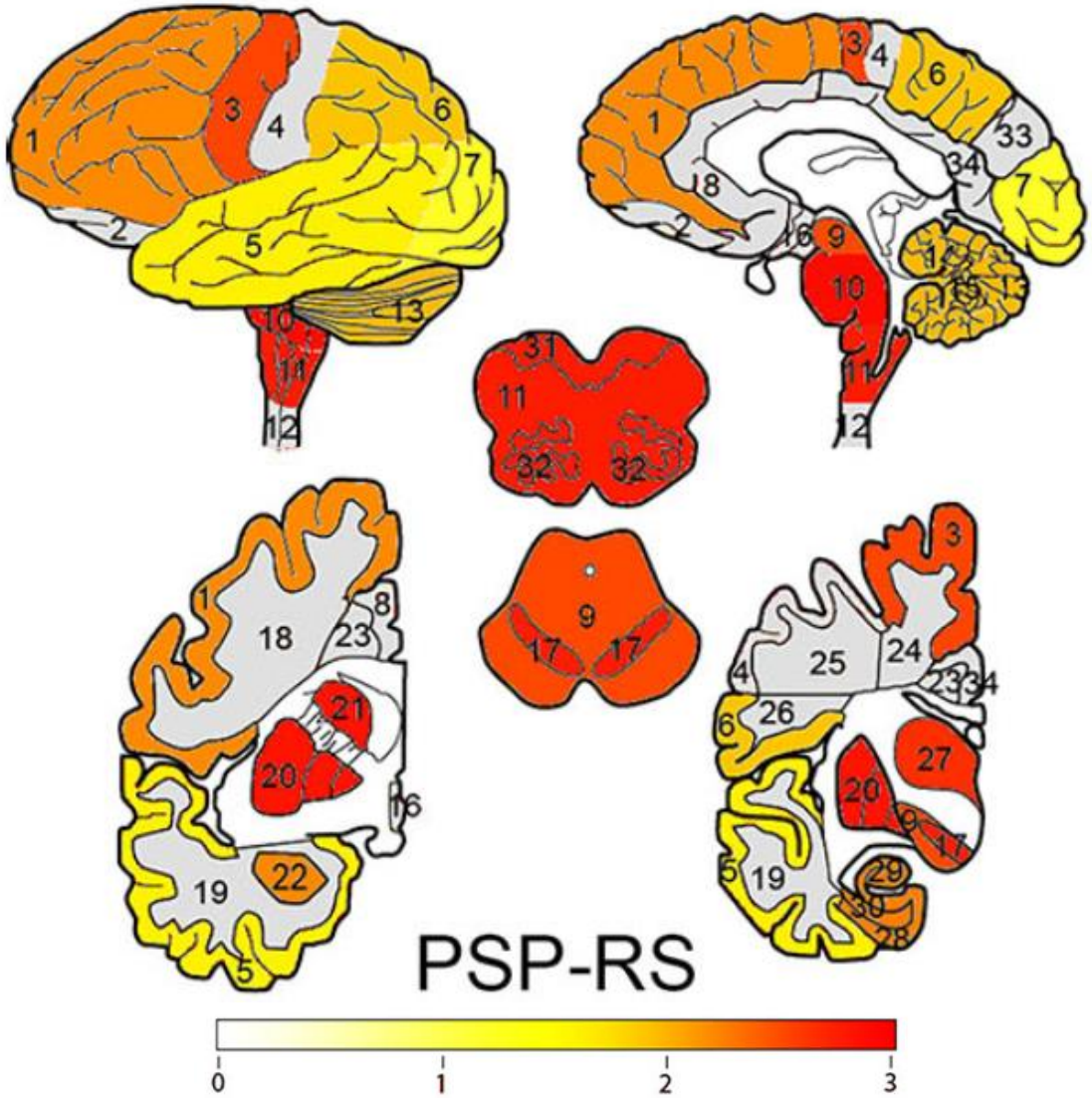
PSP-RS

MRI Atrophy



Höglinger, unpublished

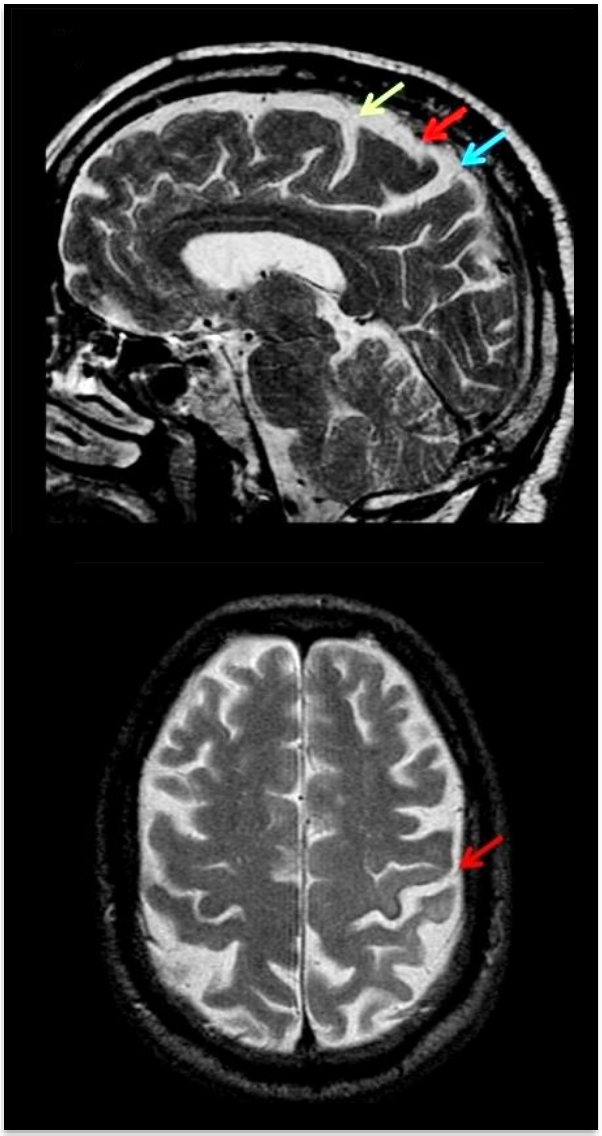
Tau Pathology



Kovacs, … Trojanowski, Höglinger, 2020

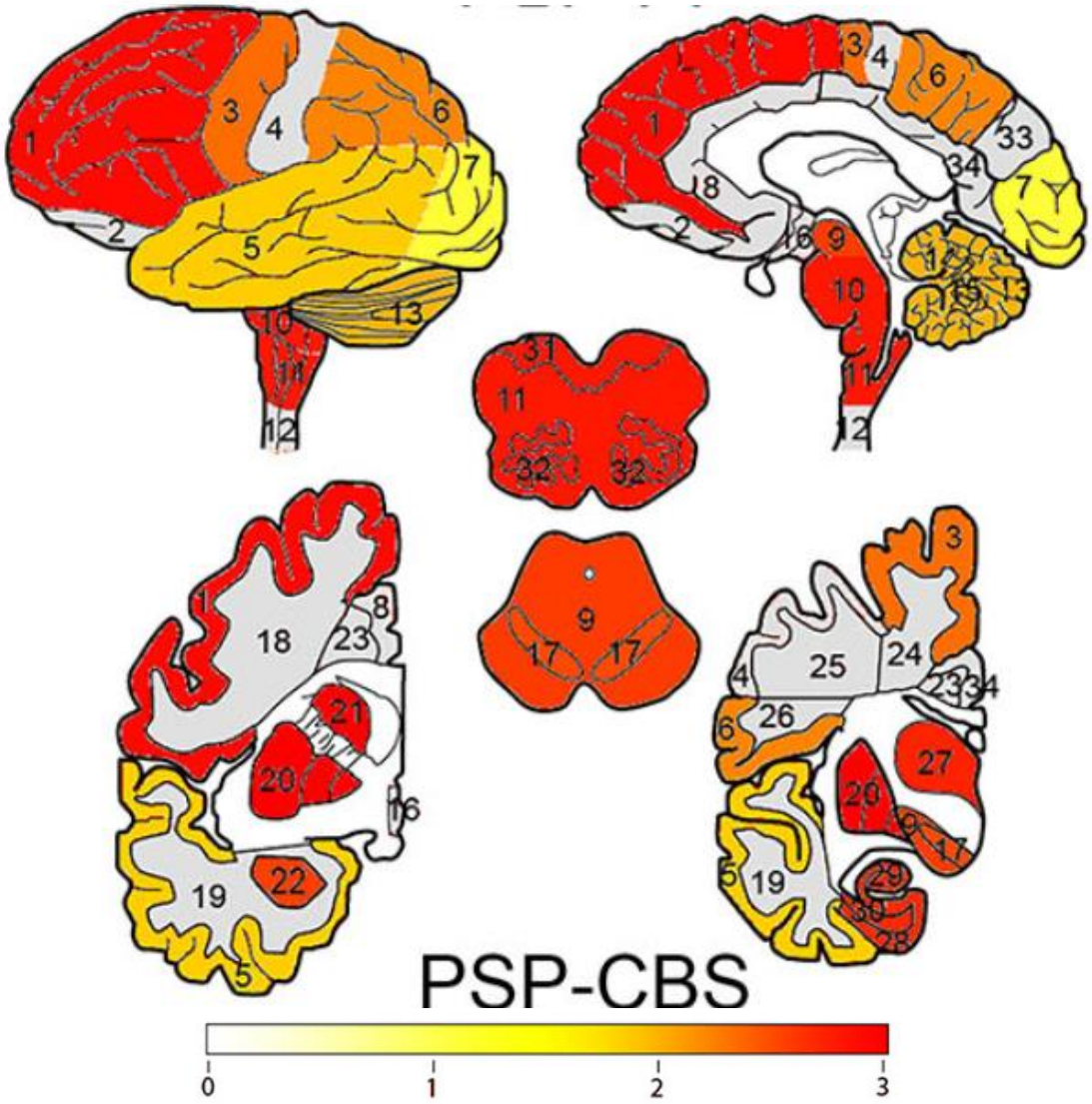
PSP-CBS

MRI Atrophy



Höglinger, 2011

Tau Pathology



Kovacs, … Trojanowski, Höglinger, 2020

Q3: Which of the following is NOT a typical clinical phenotype of PSP

- Posterior cortical atrophy
- Richardson’s syndrome
- Corticobasal syndrome
- Progressive gait freezing
- PSP with predominant Parkinsonism

Q3: Which of the following is NOT a typical clinical phenotype of PSP

- **Posterior cortical atrophy (FALSE)**
- Richardson's syndrome
- Corticobasal syndrome
- Progressive gait freezing
- PSP with predominant Parkinsonism

Q5: The clinical phenotype of tauopathies is primarily driven by

- Genetic variants at *MAPT*
- The histopathological hallmarks
- The topography of cerebral tau aggregation (CORRECT)
- The age at onset

Q5: The clinical phenotype of tauopathies is primarily driven by

- Genetic variants at *MAPT*
- The histopathological hallmarks
- **The topography of cerebral tau aggregation (CORRECT)**
- The age at onset

CLINICAL DIAGNOSIS

NINDS-SPSP Kriterien (*Litvan et al., 1996*)

NINDS-SPSP

All of the following:

- Age at disease onset ≥40 years;
- Gradually progressive disorder

Probable

A. Vertical supranuclear palsy

And

B. Postural instability with falls within 1 year of disease onset

Possible

A. Vertical supranuclear palsy

Or

B. 1. Slowing of vertical saccades

And

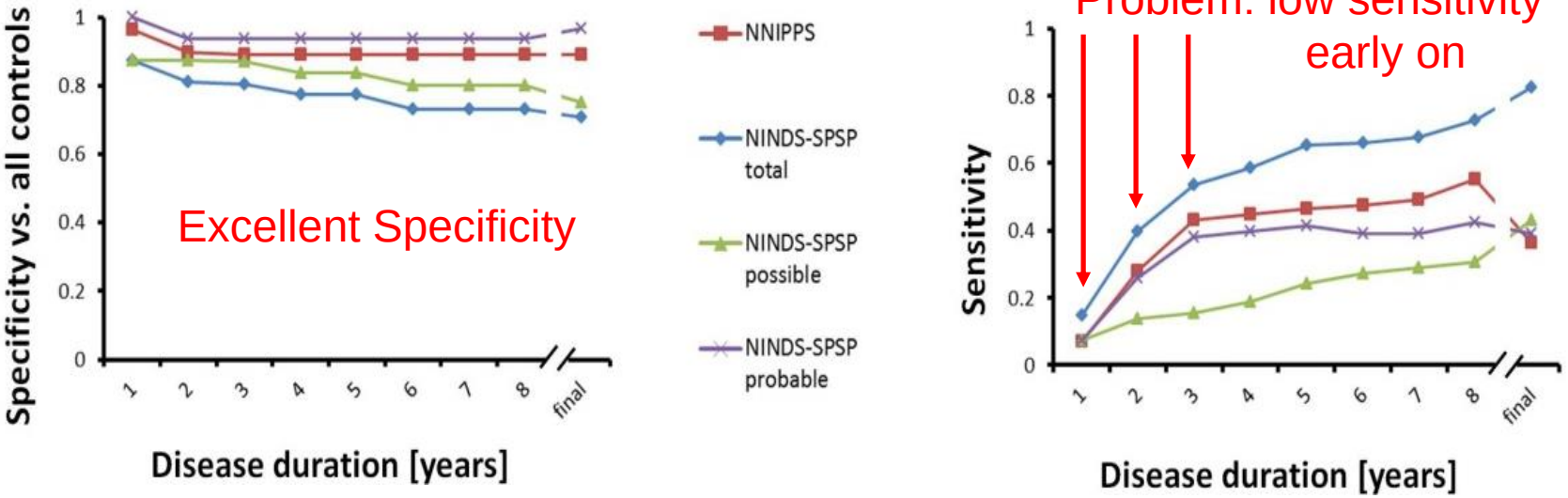
2. Postural instability with falls within 1 year of disease onset

Mov Disord. 2013;28:504-9

Accuracy of the National Institute for Neurological Disorders and Stroke/Society for Progressive Supranuclear Palsy and Neuroprotection and Natural History in Parkinson Plus Syndromes Criteria for the Diagnosis of Progressive Supranuclear Palsy

Gesine Respondek, MD,[1,2,3] Sigrun Roeber, MD,[4] Hans Kretzschmar, MD,[4] Claire Troakes, PhD,[5] Safa Al-Sarraj, FRCPath,[5] Ellen Gelpi, MD,[6] Carles Gaig, MD,[6] Wang Zheng Chiu, MD,[7] John C.van Swieten, MD,[7] Wolfgang H. Oertel, MD,[1] Günter U. Höglinger, MD[1,2,3]*

Clinicopathological study of
100 PSP-patients and 50 controls



The Need to Revise Diagnostic Criteria for PSP

Problem: low sensitivity for variant PSP

	All	PSP-RS	PSP-PI	PSP-OM	PSP-P	PSP-CBS	PSP-FTD	Unclassified
Diagnosis of PSP in first clinical record	26.2	66.7$^{\#\#}$	16.7	66.7$^{\#}$	5.3**	0.0*	10.0*	38.5
Diagnosis of PSP in last clinical record	70.0	100.0$^{\#\#\#}$	77.8$^{\#}$	100.0$^{\#}$	31.6***	57.1	33.3	84.6$^{\#}$
NNIPPS	28.0	62.5$^{\#\#\#}$	50.0$^{\#\#}$	14.3	0.0***	0.0*	0.0**	23.1
NINDS-SPSP possible	25.5	25.0	5.6	71.4	26.3	0.0	33.3	46.2
NINDS-SPSP probable	35.0	75.0$^{\#\#\#}$	77.8$^{\#\#\#}$	0.0	0.0***	0.0	0.0	7.7
NINDS-SPSP total	60.0	95.8$^{\#\#\#}$	77.8$^{\#}$	71.4	26.3***	0.0***	33.3***	53.3*

Frequency (%) of correct clinical diagnosis of all analyzed definitive PSP patients and of the patients subgrouped according to clinical predominance types: RS, Richardson's syndrome; PI, postural instability; OM, oculomotor; P, parkinsonism; CBS, corticobasal syndrome; FTD, frontotemporal dysfunction; Unclassified, patients not fitting any of these predominance types. Fulfillment of the NNIPPS, NINDS-SPSP possible, NINDS-SPSP probable, or NINDS-SPSP total (= possible or probable) criteria was verified by retrospective chart review.
Chi-squared test and Bonferroni adjustment: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, vs. RS; $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, vs. PSP-P.

Respondek et al., Mov Disord. 2013;28:504-9

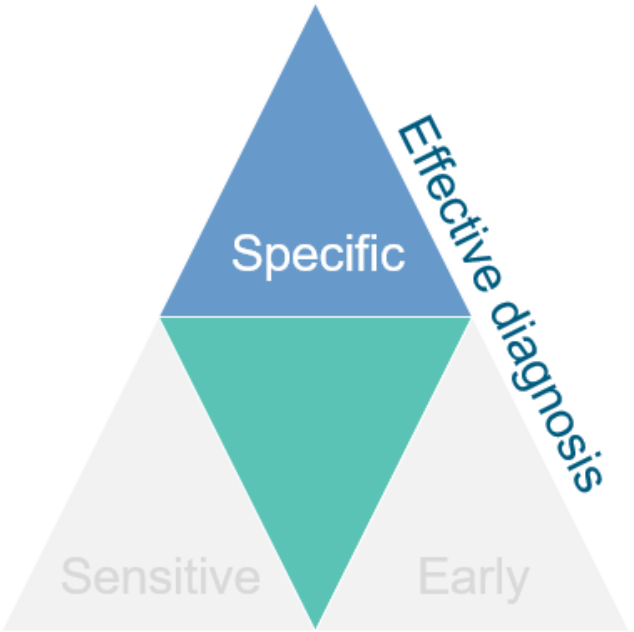
The 1996 NINDS-SPSP Criteria Are Highly Specific for Typical PSP Presentation[1]

Advantages

- Highly specific for typical PSP disease presentation[1]
- Provided guidelines to better understand the natural history of PSP

Disadvantages

- Sensitivity is low during early years[1]
  - A person needs to be relatively advanced in their course to be diagnosed[2]
- Sensitivity for variant manifestations is low[1]
  - Guidelines fail to identify all phenotypes of PSP[2]



NINDS-SPSP, National Institute of Neurological Disorders and Stroke/Society for PSP; PSP, progressive supranuclear palsy.

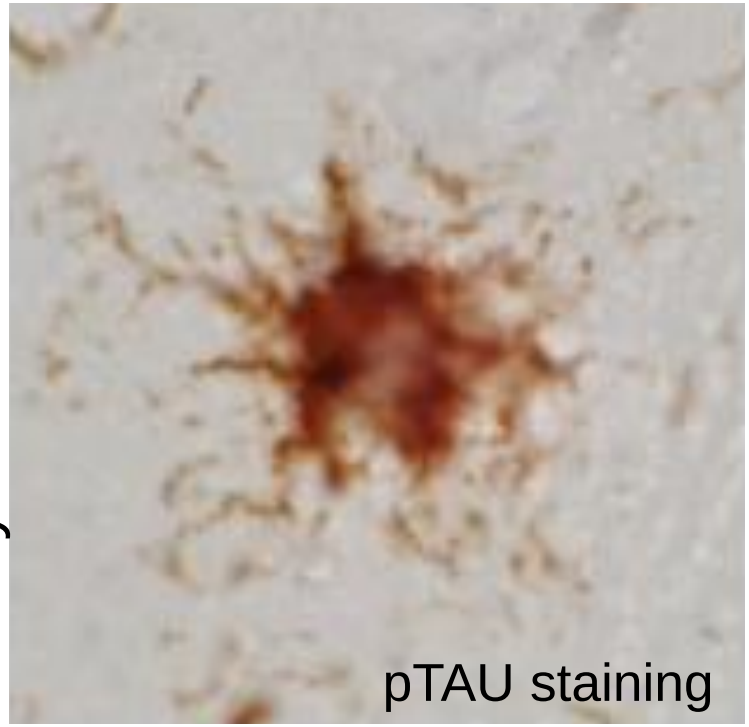
1. Movement Disorders. https://www.movementdisorders.org/MDS-Files1/Education/PDFs/NINDS-SPSPCriteria_Whydoweneedtoupdatethem_.pdf. Accessed September 11, 2018.
2. Alzforum. https://www.alzforum.org/news/research-news/revised-guidelines-diagnosing-progressive-supranuclear-palsy. Accessed September 11, 2018.

Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches

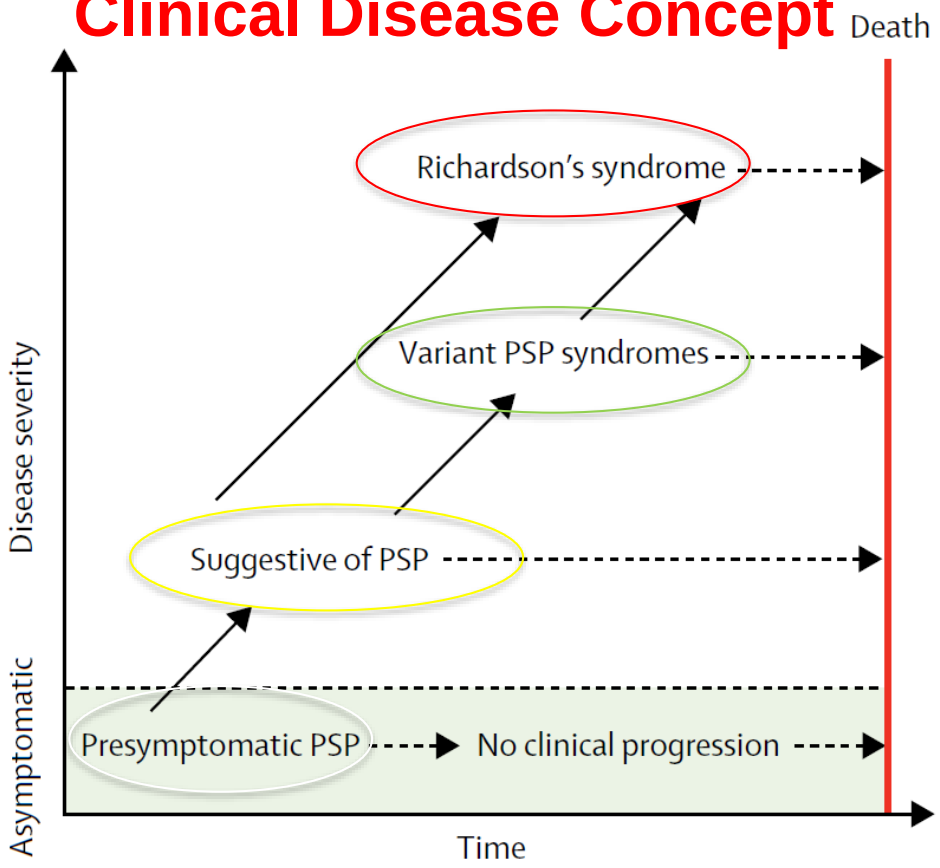
Adam L Boxer, Jin-Tai Yu, Lawrence I Golbe, Irene Litvan, Anthony E Lang, Günter U Höglinger

Lancet Neurol 2017; 16: 552–63

Definite PSP



Clinical Disease Concept



Boxer, … Höglinger, **Lancet Neurol.** 2017

RESEARCH ARTICLE

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Movement Disorders, Vol. 00, No. 00, 2017

Günter U. Höglinger, MD,[1,2*] Gesine Respondek, MD,[1,2] Maria Stamelou, MD,[3] Carolin Kurz, MD,[4] Keith A. Josephs, MD, MST, MSc,[5] Anthony E. Lang, MD,[6] Brit Mollenhauer, MD,[7] Ulrich Müller, MD,[8] Christer Nilsson, MD,[9] Jennifer L. Whitwell, PhD,[10] Thomas Arzberger, MD,[2,4,11] Elisabet Englund, MD,[12] Ellen Gelpi, MD,[13] Armin Giese, MD,[11] David J. Irwin, MD,[14] Wassilios G. Meissner, MD, PhD,[15,16,17] Alexander Pantelyat, MD,[18] Alex Rajput, MD,[19] John C. van Swieten, MD,[20] Claire Troakes, PhD, MSc,[21] Angelo Antonini, MD,[22] Kailash P. Bhatia, MD,[23] Yvette Bordelon, MD, PhD,[24] Yaroslau Compta, MD, PhD,[25] Jean-Christophe Corvol, MD, PhD,[26] Carlo Colosimo, MD, FEAN,[27] Dennis W. Dickson, MD,[28] Richard Dodel, MD,[29] Leslie Ferguson, MD,[19] Murray Grossman, MD,[14] Jan Kassubek, MD,[30] Florian Krismer, MD, PhD,[31] Johannes Levin, MD,[2,32] Stefan Lorenzl, MD,[33,34,35] Huw R. Morris, MD,[36] Peter Nestor, MD,[37] Wolfgang H. Oertel, MD,[38] Werner Poewe, MD,[31] Gil Rabinovici, MD,[39] James B. Rowe, MD,[40] Gerard D. Schellenberg, PhD,[41] Klaus Seppi, MD,[31] Thilo van Eimeren, MD,[42] Gregor K. Wenning, MD, PhD,[31] Adam L. Boxer, MD, PhD,[39] Lawrence I. Golbe, MD,[43] and Irene Litvan, MD[44]; for the Movement Disorder Society–endorsed PSP Study Group.

Tau Consortium

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

DFG

Heisenberg-Programm Deutsche Forschungsgemeinschaft

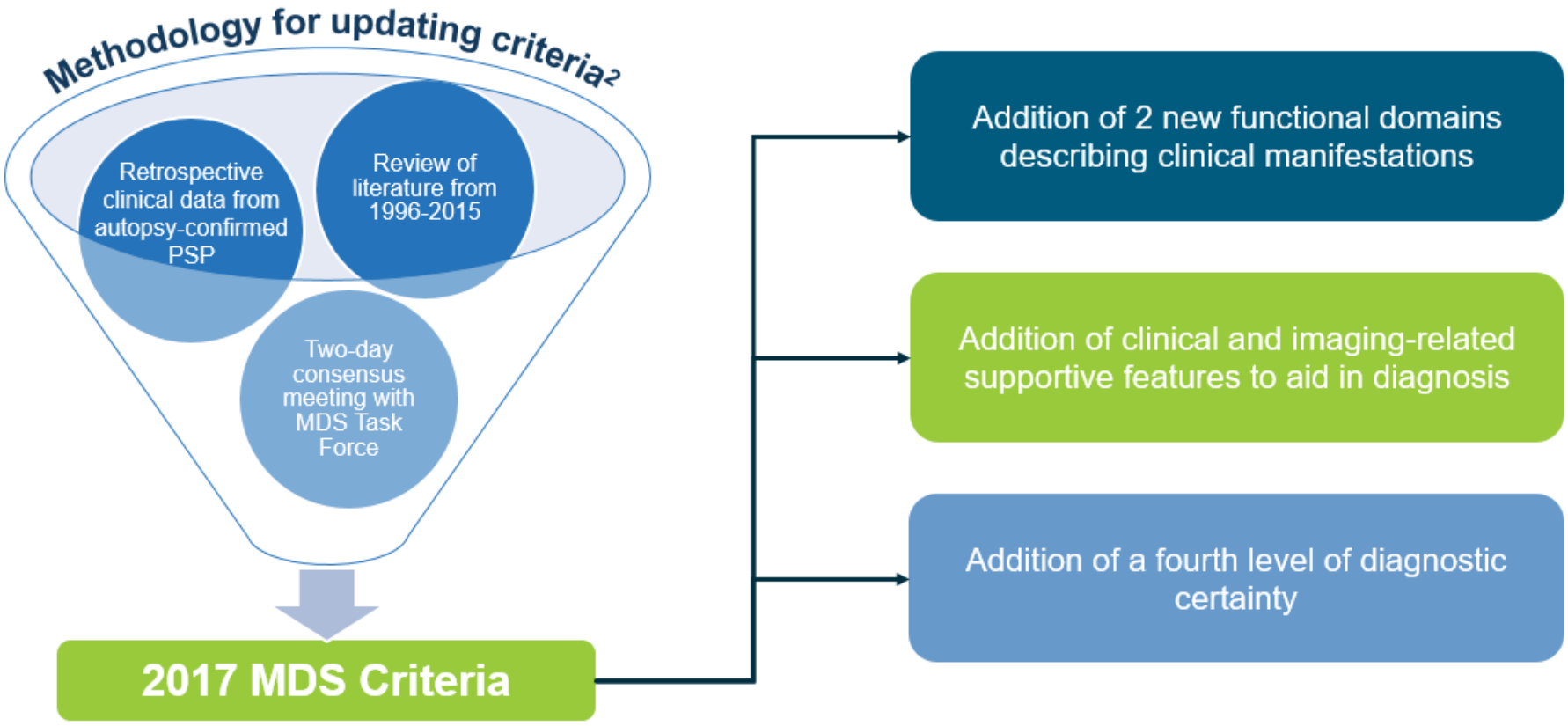
International Parkinson and Movement Disorder Society

Progressive Supranuclear Palsy PSPA

Deutsche PSP Gesellschaft e.V.

curePSP Society for Progressive Supranuclear Palsy

The 2017 MDS Criteria Were Developed to Identify a Broader Patient Population[1]



MDS, International Parkinson and Movement Disorder Society; PSP, progressive supranuclear palsy.
1. Movement Disorders. https://www.movementdisorders.org/MDS-Files1/Education/PDFs/NINDS-SPSPCriteria_Whydoweneedtoupdatethem_.pdf. Accessed September 11, 2018. **2.** Höglinger et al. *Mov Disord.* 2017;32:853-864.

Basic features

B1: *Basic features*	*Sporadic* occurrence, *Age 40 or older* at onset, *Gradual progression* of PSP-related symptoms
B2: *Mandatory exclusion criteria*	*Clinical or imaging findings* occurring before or within the first year following the onset of PSP-related symptoms *suggestive of other conditions, which may mimic aspects of PSP clinically*
B3: *Context dependent exclusion criteria*	Imaging, laboratory, or genetic findings suggestive of other conditions, which may mimic aspects of PSP clinically; *they are mandatory only if suggestive clinical findings are present*

Exclusion criteria

B2: Mandatory exclusion criteria	**Clinical findings** **1. Predominant, otherwise unexplained impairment of episodic memory, suggestive of Alzheimer's disease** **2. Predominant, otherwise unexplained autonomic failure, e.g. orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing ≥ 30 mmHg systolic or ≥ 15 mmHg diastolic), suggestive of multiple system atrophy or Lewy body disease** **3. Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness, suggestive of dementia with Lewy bodies** **4. Predominant, otherwise unexplained multisegmental upper and lower motor neuron signs, suggestive of motor neuron disease (pure upper motor neuron signs are not an exclusion criterion)** **5. Sudden onset or stepwise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies or prion disease** **6. History of encephalitis** **7. Prominent appendicular ataxia** **8. Identifiable cause of postural instability, e.g. primary sensory deficit, vestibular dysfunction, severe spasticity or lower motor neuron syndrome** **Imaging findings** **1. Severe leukoencephalopathy, evidenced by cerebral imaging** **2. Relevant structural abnormality, e.g. normal pressure or obstructive hydrocephalus; basal ganglia, diencephalic, mesencephalic, pontine or medullary infarctions, hemorrhages, hypoxic-ischemic lesions, tumors or malformations**

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Exclusion criteria

International Parkinson and Movement Disorder Society

B3: Context dependent exclusion criteria[#, ##]	**Imaging findings** **1. In syndromes with sudden onset or stepwise progression, exclude stroke, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) or severe cerebral amyloid angiopathy, evidenced by DWI , FLAIR or T2*-MRI** **2. In cases with very rapid progression, exclude cortical and subcortical hyperintensities on DWI-MRI suggestive of prion disease** **Laboratory findings** **1. In patients with PSP-CBS, exclude primary Alzheimer's disease pathology (typical CSF constellation [i.e. both elevated total tau / phospho-tau protein and reduced β-amyloid 42] or pathological β-amyloid PET imaging)** **2. In patients < 45 years of age, exclude** **a. Wilson's disease (e.g. reduced serum ceruloplasmin, reduced total serum copper, increased copper in 24 hour urine, Kayser-Fleischer corneal ring)** **b. Niemann-Pick disease, type C (e.g. plasma cholestan-3ß,5a,6ß-triol level, filipin test on skin fibroblasts)** **c. Hypoparathyroidism** **d. Neuroacanthocytosis (e.g. Bassen-Kornzweig, Levine Critchley, McLeod disease)** **e. Neurosyphilis** **1. In rapidly progressive patients, exclude** **a. Prion disease (e.g. elevated 14-3-3 , NSE, very high total tau protein [>1200 pg/ml], or pos. RT-QuIC in CSF)** **b. Paraneoplastic encephalitis (e.g. anti-Ma1, Ma2 antibodies)** **1. In patients with suggestive features (i.e. gastrointestinal symptoms, arthralgias, fever, younger age, atypical neurological features such as myorhythmia), exclude Whipple's disease (e.g. T. Whipplei DNA PCR in CSF)** **Genetic findings [§]** **1. MAPT rare variants (mutations) are no exclusion criterion, but their presence defines inherited, as opposed to sporadic PSP.** **2. MAPT H2 haplotype homozygosity is not an exclusion criterion, but renders the diagnosis unlikely** **3. LRRK2 and Parkin rare variants have been observed in patients with autopsy confirmed PSP, but their causal relationship is unclear so far** **4. Known rare variants in other genes are exclusion criteria, since they may mimic aspects of PSP clinically, but differ neuropathologically; these include** **a. Non-MAPT associated frontotemporal dementia (e.g. C9orf72, GRN, FUS, TARDBP, VCP, CHMP2B)** **b. Parkinson's disease (e.g. SYNJ1 ,GBA)** **c. Alzheimer's disease (APP, PSEN1, PSEN2)** **d. Niemann Pick disease, type C (NPC1, NPC2)** **e. Kufor Rakeb syndrome (ATP13A2)** **f. Perry syndrome (DCTN1)** **g. Mitochondrial diseases (POLG, mitochondrial rare variants)** **h. Dentatorubral pallidoluysian atrophy (ATN1)** **i. Prion-related diseases (PRNP)** **j. Huntington's disease (HTT)** **k. Spinocerebellar ataxia (ATXN1, 2, 3, 7, 17)**

1996 NINDS-SPSP Criteria Include Evaluation of Ocular Motor Dysfunction and Postural Instability

NINDS-SPSP Criteria,1996

Level of certainty[1]	Ocular motor dysfunction[1,2]	Postural instability[1,2]
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years

Diagnostic certainty

NINDS-SPSP, National Institute of Neurological Disorders and Stroke/Society for PSP; PSP, progressive supranuclear palsy.

1. Höglinger et al. *Mov Disord.* 2017;32:853-864. **2.** Litvan et al. *Neurology.* 1996;47:1-9. Figure adapted from Höglinger et al. *Mov Disord.* 2017;32:853-864. With permission from the International Parkinson and Movement Disorder Society.

Addition of 2 Functional Domains Allows Diagnosis to Encompass Broader Range of PSP Phenotypes

	NINDS-SPSP Criteria,1996		MDS Updates to NINDS-SPSP Criteria, 2017	
Level of certainty[1]	**Ocular motor dysfunction[1,2]**	**Postural instability[1,2]**	**Akinesia[1]**	**Cognitive dysfunction[1]**
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/Language disorder[a]
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years	**A2:** Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2:** Frontal cognitive/behavioral presentation
Level 3	**O3:** Frequent macro square wave jerks or "eyelid opening apraxia"	**P3:** >2 steps backward on the pull-test within 3 years	**A3:** Parkinsonism with tremor and/or asymmetric and/or levodopa responsive	**C3:** Corticobasal syndrome

Diagnostic certainty ↑

MDS, International Parkinson and Movement Disorder Society; NINDS-SPSP, National Institute of Neurological Disorders and Stroke/Society for PSP; PSP, progressive supranuclear palsy.
[a]Can include nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech.
1. Höglinger et al. *Mov Disord.* 2017;32:853-864. **2.** Litvan et al. *Neurology.* 1996;47:1-9. Figure adapted from Höglinger et al. *Mov Disord.* 2017;32:853-864. With permission from the International Parkinson and Movement Disorder Society.

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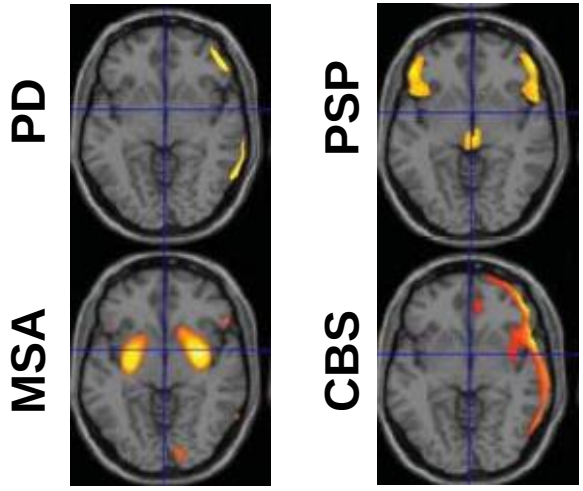
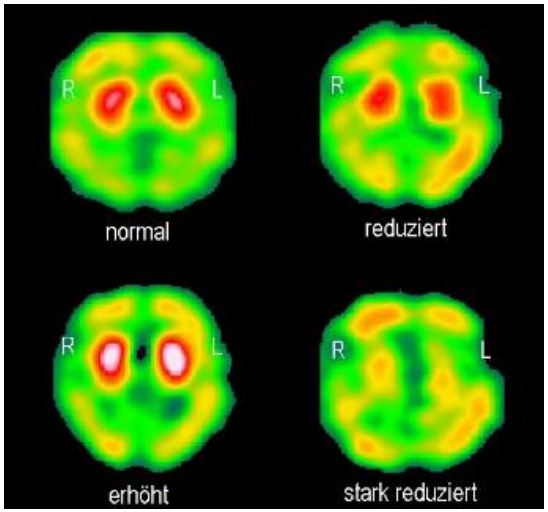
Supportive Features:

	Feature	
Imaging findings		
IF1	**Predominant midbrain atrophy or hypometabolism**	Atrophy or hypometabolism predominant in midbrain relative to pons, as demonstrated e.g. by MRI or [18F]DG-PET
IF2	**Postsynaptic striatal dopaminergic degeneration**	Postsynaptic striatal dopaminergic degeneration, as demonstrated e.g. by [123I]IBZM-SPECT or [18F]-DMFP-PET



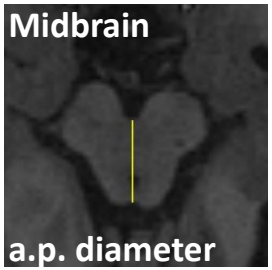
Teune et al., Mov Disord. 2010;25:2395-404.

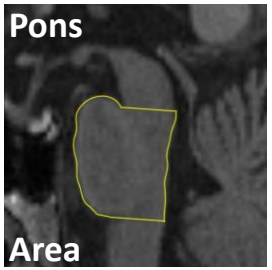


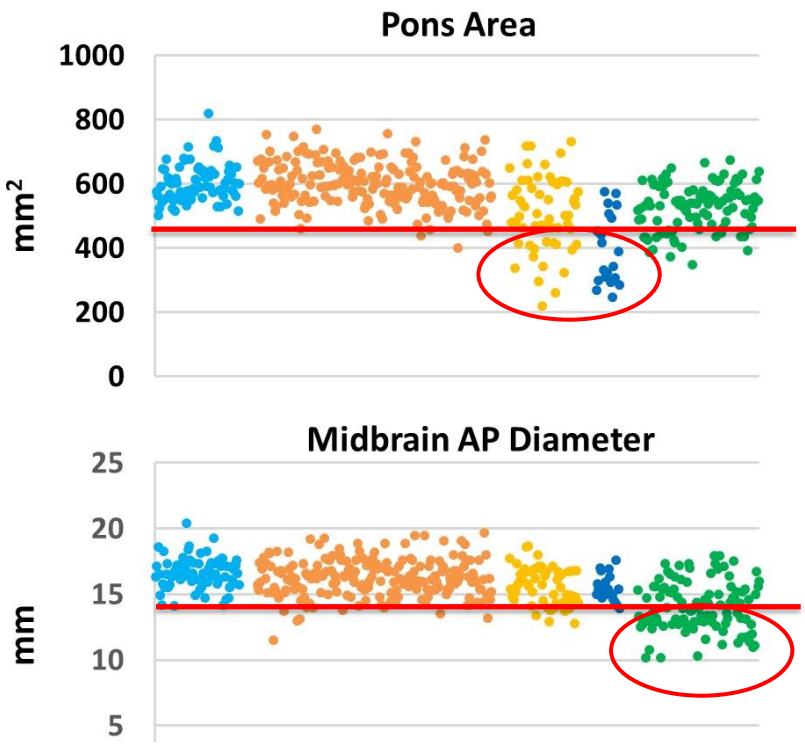
Manual MRI Morphometry in Parkinsonian Syndromes

Leona Möller, MD,[1] Jan Kassubek, MD,[2]
Martin Südmeyer, MD,[3,4] Rüdiger Hilker, MD,[5]
Elke Hattingen, MD,[6] Karl Egger, MD,[7] Florian Amtage, MD,[8]
Elmar H. Pinkhardt, MD,[2] Gesine Respondek, MD,[1,9,10]
Maria Stamelou, MD,[1,11] Franz Möller, MD,[12]
Alfons Schnitzler, MD,[3] Wolfgang H. Oertel, MD,[1]
Susanne Knake, MD,[1] Hans-Jürgen Huppertz, MD,[13] and
Günter U. Höglinger, MD[1,8,9*]

Movement Disorders, Vol. 00, No. 00, 2017

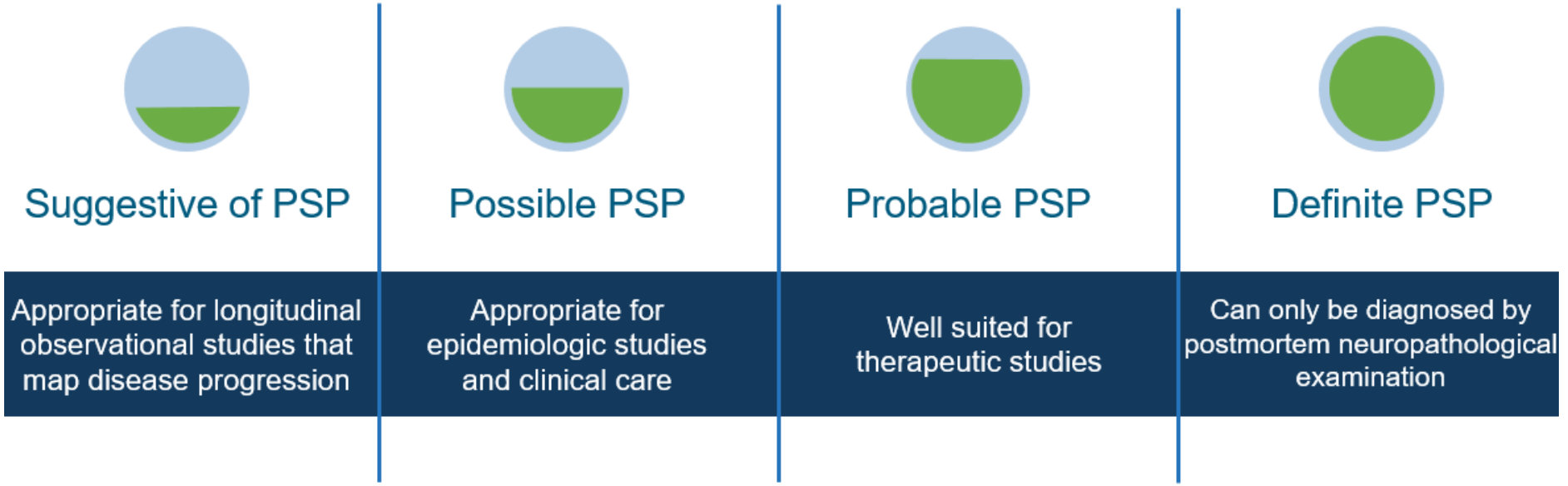






MDS Criteria Added a Fourth Level of Diagnostic Certainty[1]

These updates help identify patients with subtle clinical symptoms in a milder disease state[2,3]



MDS, International Parkinson and Movement Disorder Society; PSP, progressive supranuclear palsy.

1. Höglinger et al. *Mov Disord.* 2017;32:853-864. 2. Boxer et al. *Lancet Neurol.* 2017;16:552-563. 3. Alzforum. https://www.alzforum.org/news/research-news/revised-guidelines-diagnosing-progressive-supranuclear-palsy. Accessed September 11, 2018.

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MDS-PSP Kriterien (Höglinger et al., Mov. Disord. 2017)

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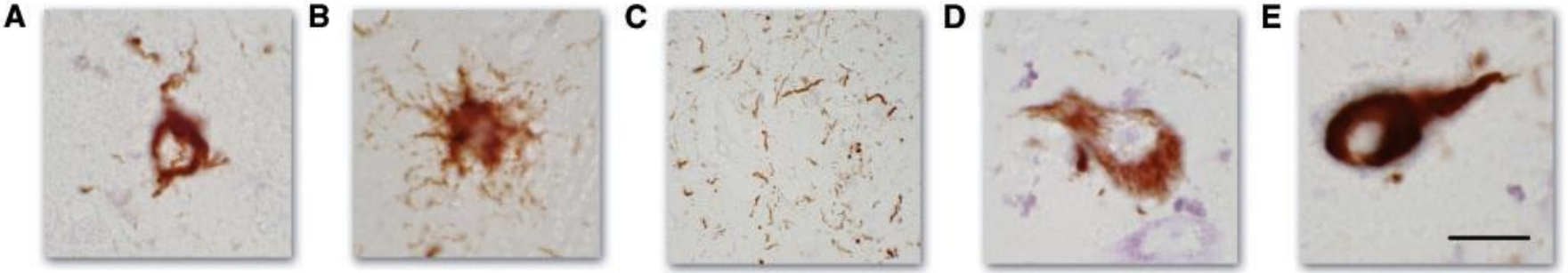
Diagnostic certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/Language disorder
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years	**A2:** Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2:** Frontal cognitive/behavioral presentation
Level 3	**O3:** Frequent macro square wave jerks or "eyelid opening apraxia"	**P3:** >2 steps backward on the pull-test within 3 years	**A3:** Parkinsonism with tremor and/or asymmetric and/or levodopa responsive	**C3:** Corticobasal syndrome

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

Aim: Clinical Prediction of 4R-Tau Pathology



Stamelou … Höglinger., Brain. 2010

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Diagnostic certainty ↑

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/Language disorder
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years	**A2:** Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2:** Frontal cognitive/behavioral presentation
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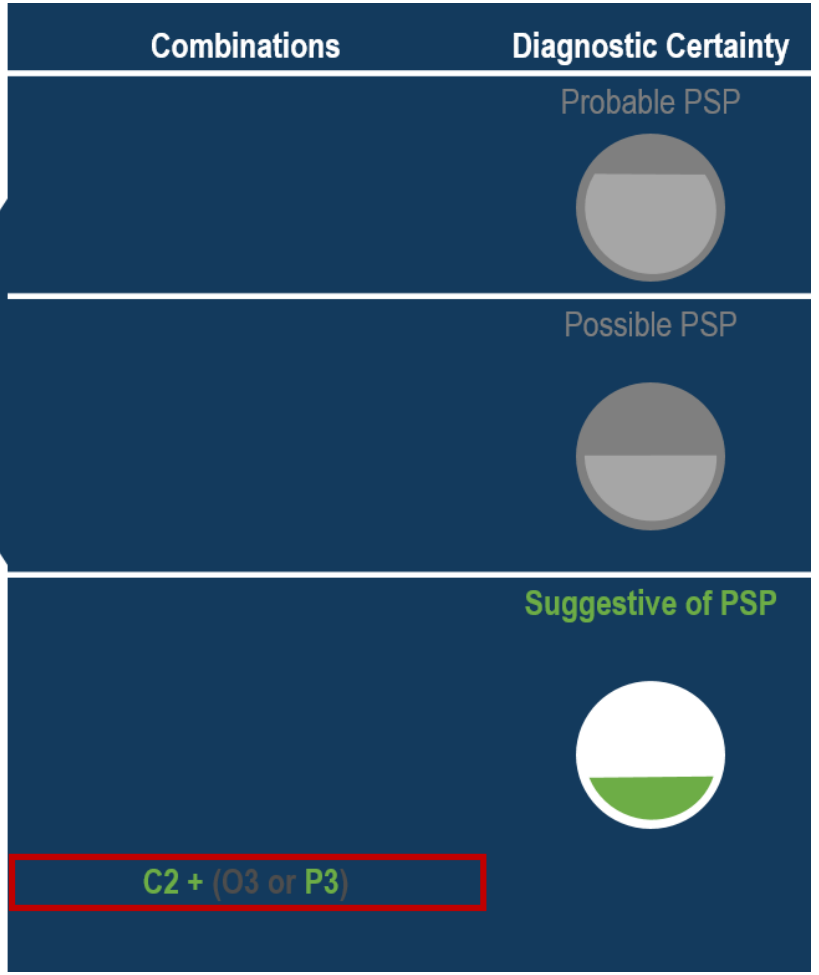

PSP, progressive supranuclear palsy.

Höglinger et al. *Mov Disord.* 2017;32:853-864.

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Diagnostic certainty ↑

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
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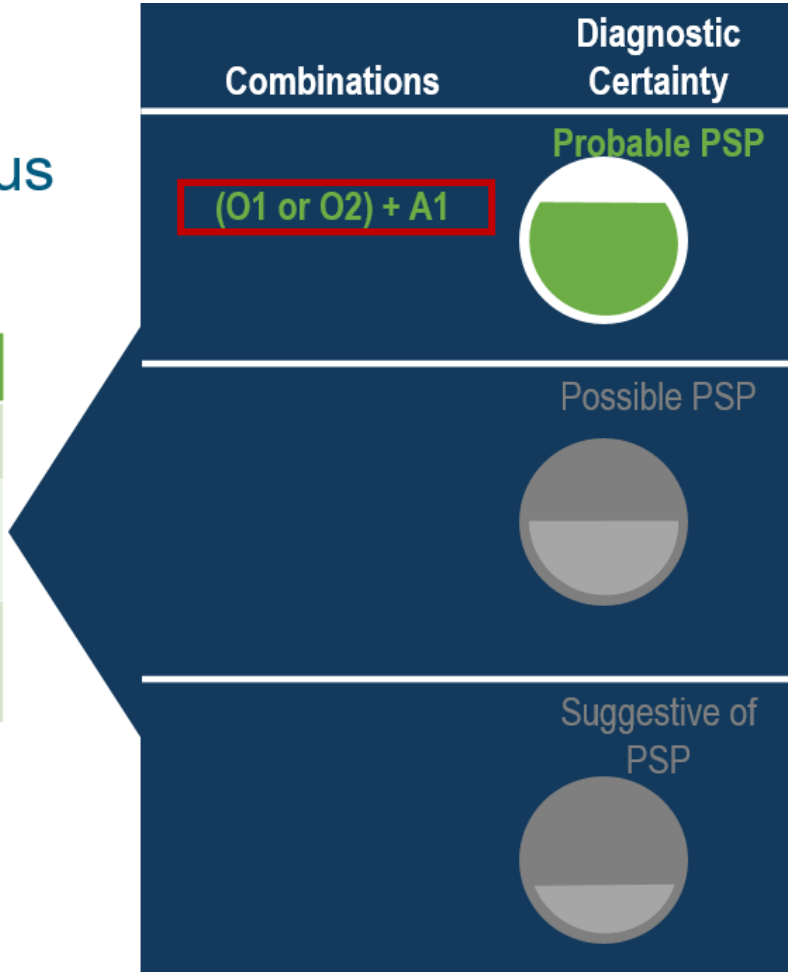
PSP, progressive supranuclear palsy.

Höglinger et al. *Mov Disord.* 2017;32:853-864.



Combinations of these features define **diagnostic criteria**, stratified by **diagnostic certainty**

Diagnostic certainty	Definition	Combinations	Predominance type	Abbreviation
Definite PSP	**Gold standard** defining the disease entity	neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	**Highly specific**, but not very sensitive for PSP Suitable for therapeutic and biologic studies	(O1 or O2) + (P1 or P2)	PSP-Richardson Syndrome	prob. PSP-RS
		(O1 or O2) + A1	PSP with Progressive Gait Freezing	prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with Predominant Parkinsonism	prob. PSP-P
		(O1 or O2) + C2	PSP with Predominant Frontal Presentation	prob. PSP-F
Possible PSP	**Substantially more sensitive**, but less specific for PSP Suitable for descriptive epidemiologic studies and clinical care	O1	PSP with Predominant Ocular Motor Dysfunction	poss. PSP-OM
		O2 + P3	PSP with Richardson Syndrome	poss. PSP-RS
		A1	PSP with Progressive Gait Freezing	poss. PSP-PGF
		(O1 or O2) + C1	PSP with Predominant Speech/Language Disorder *	poss. PSP-SL
		(O1 or O2) + C3	PSP with Predominant Corticobasal Syndrome *	poss. PSP-CBS
Suggestive of PSP	Suggestive of PSP, but **not passing the threshold for possible or probable PSP** Suitable for early identification	O2 or O3	PSP with Predominant Ocular Motor Dysfunction	s.o. PSP-OM
		P1 or P2	PSP with Predominant Postural Instability	s.o. PSP-PI
		O3 + (P2 or P3)	PSP with Richardson Syndrome	s.o. PSP-RS
		(A2 or A3) + (O3, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with Predominant Parkinsonism	s.o. PSP-P
		C1	PSP with Predominant Speech/Language Disorder	s.o. PSP-SL
		C2 + (O3 or P3)	PSP with Predominant Frontal Presentation	s.o. PSP-F
		C3	PSP with Predominant Corticobasal Syndrome	s.o. PSP-CBS

ELSEVIER

Parkinsonism & Related Disorders

Volume 78, September 2020, Pages 200-203

Video-tutorial for the Movement Disorder Society criteria for progressive supranuclear palsy

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Videos: https://pubmed.ncbi.nlm.nih.gov/32988736

1. Core clinical features	
Domain: Ocular motor dysfunction	
O1	Vertical supranuclear gaze palsy
O2	Slow velocity of vertical saccades
O3	Subtle ocular motor dysfunction, *i.e.*
O3-1	frequent macro square wave jerks, *or*
O3-2	"eyelid opening apraxia"
Domain: Postural instability	
P1	Repeated unprovoked falls within 3 years
P2	Tendency to fall on the pull-test within 3 years
P3	More than 2 steps backward on the pull-test within 3 year
Domain: Akinesia	
A1	Progressive gait freezing within 3 years
A2	Parkinsonism, akinetic-rigid, predominantly axial and levodopa-resistant
A3	Parkinsonism, with tremor and/or asymmetric and/or levodopa-responsive
Domain: Cognitive dysfunction	
C1	Speech/language disorder, *i.e.* at least 1 of the following features:
C1-1	Nonfluent agrammatic variant of primary progressive aphasia (nfaPPA), *or*
C1-2	progressive apraxia of speech (AOS)
C2	Frontal cognitive/behavioral presentation, *i.e.* at least 3 of the following features:
C2-1	Apathy
C2-2	Bradyphrenia
C2-3	Dysexecutive syndrome (e.g., pathological Luria sequence)
C2-4	Reduced phonemic verbal fluency (e.g., reduced "D, F, A or S" words per minute)
C2-5	Impulsivity, disinhibition, or perseveration (e.g., socially inappropriate behaviors, overstuffing the mouth when eating, motor recklessness, applause sign, palilalia, echolalia)
C3	Corticobasal syndrome, i.e. at least 1 sign each from the following 2 groups
C3-1	Cortical signs
C3-1a	Orobuccal or limb apraxia
C3-1b	Cortical sensory deficit
C3-1c	Alien limb phenomena (more than simple levitation)
C2-2	Movement disorders signs
C3-2a	Limb rigidity
C3-2b	Limb akinesia
C3-2c	Limb myoclonus
C3-2d	Limb dystonia
2. Clinical clues	
CC1	Levodopa-resistance
CC2	Hypokinetic, spastic dysarthria
CC3	Dysphagia
CC4	Photophobia

Validation of the MDS-PSP criteria on neuropathologically-confirmed PSP and other forms of frontotemporal lobar degeneration.

Stefano Gazzina[1,2], MD; Gesine Respondek[3], MD; Yaroslau Compta[4], MD, PhD; Kieren S.J. Allinson[5], MD; Maria G. Spillantini[1], PhD; Laura Molina-Porcel[6], MD, PhD; Mar Guasp-Verdaguer[4], MD; Shirin Moftakhar[7], BS; Stephen G. Reich[8], MD; Deborah Hall[9], MD; Irene Litvan[7], MD; Günter U. Höglinger[3], MD; Movement Disorder Society-endorsed PSP Study Group, James B. Rowe[1], MD, PhD.

Submitted, https://www.biorxiv.org/content/10.1101/520510v1

	PSP cohort		
	Cambridge (N=65)	Barcelona (N=21)	ENGENE-PSP (N=22)
Sex, female, %	43.1	61.9	45.5
Age at onset, yrs	67.0±7.2	69.8±6.5	63.6±6.2
Age at first visit, yrs	69.8±7.1	74.7±4.5	67.3±6.4
	FTLD cohort		
	bvFTD (N=38)	nfvPPA (N=14)	CBD (N=29)
Sex, female, %	23.7	28.6	41.4
Age at onset, yrs	58.3±9.1	61.1±8.6	64.3±6.9
Age at first visit, yrs	61.7±9.3	63.6±7.8	66.9±6.8
Age at death, yrs	67.5±10.1	70.1±8.3	71.6±7.1
Disease duration, yrs	9.2±4.6	9.0±3.5	7.3±3.9

	NINDS-SPSP			MDS-PSP	
	Sensitivity	Specificity		Sensitivity	Specificity
Probable PSP	48.1	100		72.2	95.1
Possible PSP	61.1	97.5		81.5	88.9
Suggestive of PSP				100	53.1

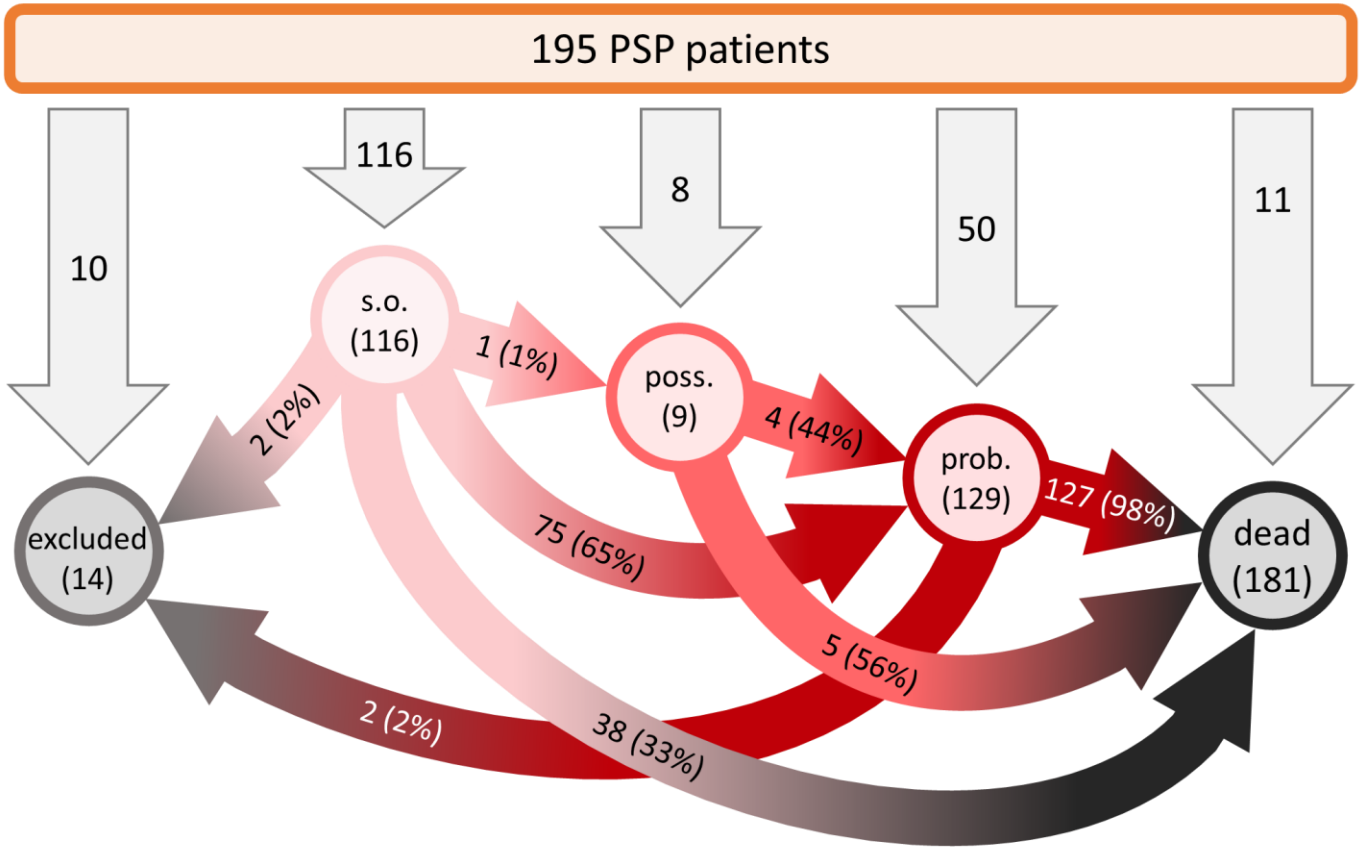
Clinical Conditions "Suggestive of Progressive Supranuclear Palsy"-Diagnostic Performance.

Grimm MJ, Respondek G, Stamelou M, Arzberger T, Ferguson L, Gelpi E, Giese A, Grossman M, Irwin DJ, Pantelyat A, Rajput A, Roeber S, van Swieten JC, Troakes C, Meissner WG, Nilsson C, Piot I, Compta Y, Rowe JB, Höglinger GU

for the Movement Disorder Society-endorsed PSP study group.

Mov Disord. 2020 Dec;35(12):2301-2313

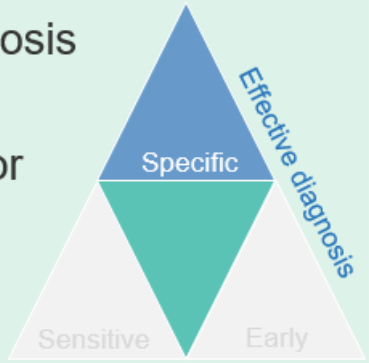
S.o. PSP is the most frequent first diagnosis



MDS Updates to NINDS-SPSP Criteria Increase Diagnostic Sensitivity While Maintaining Specificity[1]

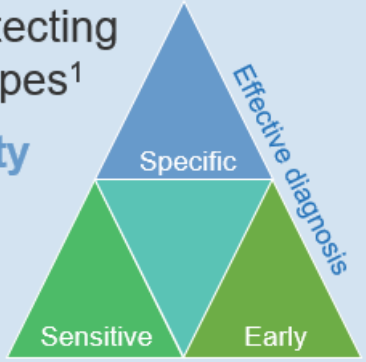
1996 NINDS-SPSP Criteria

- 2 functional domains[1]
- 3 levels of diagnostic certainty[2]
- Highly **specific** for diagnosis of typical PSP[3]
- Low sensitivity for early or variant PSP[3]



2017 MDS Criteria

- 4 functional domains[1]
- 4 levels of diagnostic certainty[1]
- Better **sensitivity** for detecting **early** PSP and variant types[1]
- Maintains high **specificity** to differentiate from other diagnoses[1]



Clinical validation of the updated criteria is ongoing

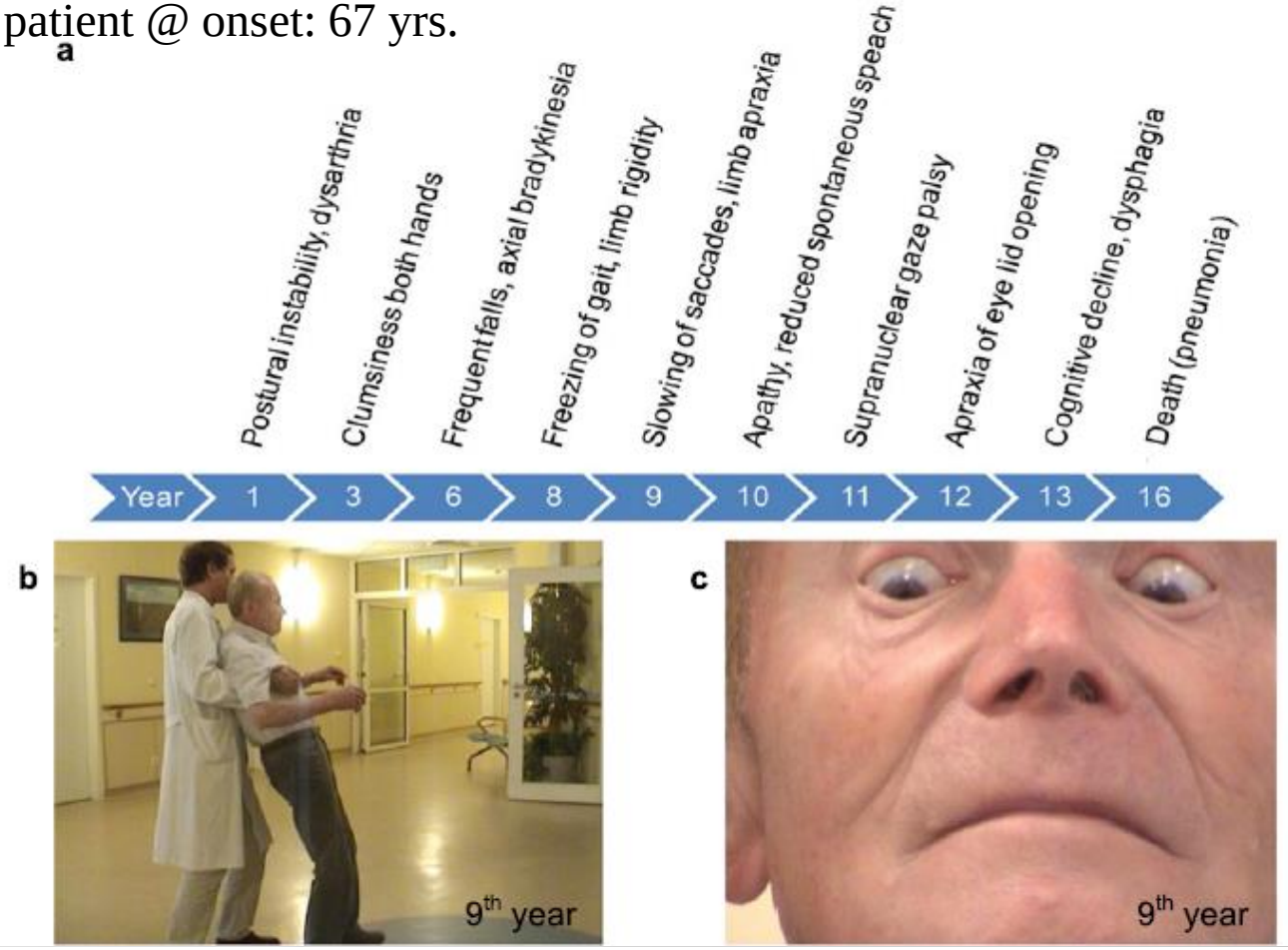
MDS, International Parkinson and Movement Disorder Society; NINDS-SPSP, National Institute of Neurological Disorders and Stroke/Society for PSP; PSP, progressive supranuclear palsy.

1. Höglinger et al. *Mov Disord.* 2017;32:853-864. **2.** Litvan et al. *Neurology.* 1996;47:1-9. **3.** Movement Disorders. https://www.movementdisorders.org/MDS-Files1/Education/PDFs/NINDS-SPSPCriteria_Whydoweneedtoupdatethem_.pdf. Accessed September 11, 2018.

EXAMPLE CASE: HOW TO APPLY THE MDS-PSP DIAGNOSTIC CRITERIA.

Kurz … Höglinger, Acta Neuropath Comm 2016; https://pubmed.ncbi.nlm.nih.gov/27842578/

Age of the patient @ onset: 67 yrs.



MDS PSP Diagnostic Criteria

Diagnostic certainty ↑

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/Language disorder[a]
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Level 3	**O3:** Frequent macro square wave jerks or “eyelid opening apraxia”	**P3:** >2 steps backward on the pull-test within 3 years	**A3:** Parkinsonism with tremor and/or asymmetric and/or levodopa responsive	**C3:** Corticobasal syndrome

PSP, progressive supranuclear palsy.
Figure adapted from Höglinger et al. *Mov Disord*. 2017;32:853-864.
With permission from the International Parkinson and Movement Disorder Society.

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/Language disorder
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years **Y-1**	**A2:** Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2:** Frontal cognitive/behavioral presentation
Level 3	**O3:** Frequent macro square wave jerks or "eyelid opening apraxia"	**P3:** >2 steps backward on the pull-test within 3 years **Y-1**	**A3:** Parkinsonism with tremor and/or asymmetric and/or levodopa responsive	**C3:** Corticobasal syndrome

Diagnostic certainty ↑

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

Year 1:
s.o. PSP-PI

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years Y-6	A1: Progressive gait freezing within 3 years	C1: Speech/Language disorder
Level 2	O2: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years Y-1	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant Y-6	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: >2 steps backward on the pull-test within 3 years Y-1	A3: Parkinsonism with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Diagnostic certainty

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

Year 6:
s.o. PSP-P
(poss. PSP-PGF)

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years Y-6	A1: Progressive gait freezing within 3 years Y-9	C1: Speech/Language disorder Y-9
Level 2	O2: Slow velocity of vertical saccades Y-9	P2: Tendency to fall on the pull-test within 3 years Y-1	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant Y-6	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: >2 steps backward on the pull-test within 3 years Y-1	A3: Parkinsonism with tremor and/or asymmetric and/or levodopa responsive Y-9	C3: Corticobasal syndrome

Diagnostic certainty

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

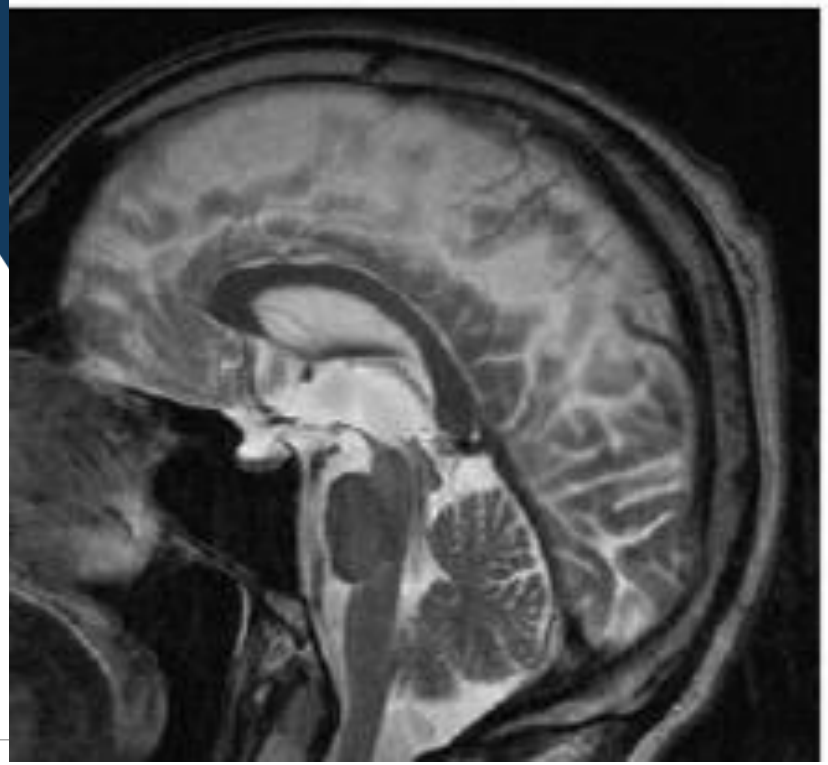
Year 9:
prob. PSP-RS

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years Y-6	A1: Progressive gait freezing within 3 years Y-9	C1: Speech/Language disorder Y-9
Level 2	O2: Slow velocity of vertical saccades Y-9	P2: Tendency to fall on the pull-test within 3 years Y-1	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant Y-6	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: >2 steps backward on the pull-test within 3 years Y-1	A3: Parkinsonism with tremor and/or asymmetric and/or levodopa responsive Y-9	C3: Corticobasal syndrome

Diagnostic certainty

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2)	Probable PSP
(O1 or O2) + A1	
(O1 or O2) + (A2 or A3)	
(O1 or O2) + C2	



Year 9:
prob. PSP-RS

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy (Y-10)	P1: Repeated unprovoked falls within 3 years (Y-6)	A1: Progressive gait freezing within 3 years (Y-9)	C1: Speech/Language disorder (Y-9)
Level 2	O2: Slow velocity of vertical saccades (Y-9)	P2: Tendency to fall on the pull-test within 3 years (Y-1)	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant (Y-6)	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: >2 steps backward on the pull-test within 3 years (Y-1)	A3: Parkinsonism with tremor and/or asymmetric and/or levodopa responsive (Y-9)	C3: Corticobasal syndrome

Diagnostic certainty

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

Year 10:
prob. PSP-RS

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy Y-10	P1: Repeated unprovoked falls within 3 years Y-6	A1: Progressive gait freezing within 3 years Y-9	C1: Speech/Language disorder Y-9
Level 2	O2: Slow velocity of vertical saccades Y-9	P2: Tendency to fall on the pull-test within 3 years Y-1	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant Y-6	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia" Y-12	P3: >2 steps backward on the pull-test within 3 years Y-1	A3: Parkinsonism with tremor and/or asymmetric and/or levodopa responsive Y-9	C3: Corticobasal syndrome

Diagnostic certainty

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

Year 12:
prob. PSP-RS

Combinations of Symptoms Can Be Used to Diagnose Patients With Various Diagnostic Certainty

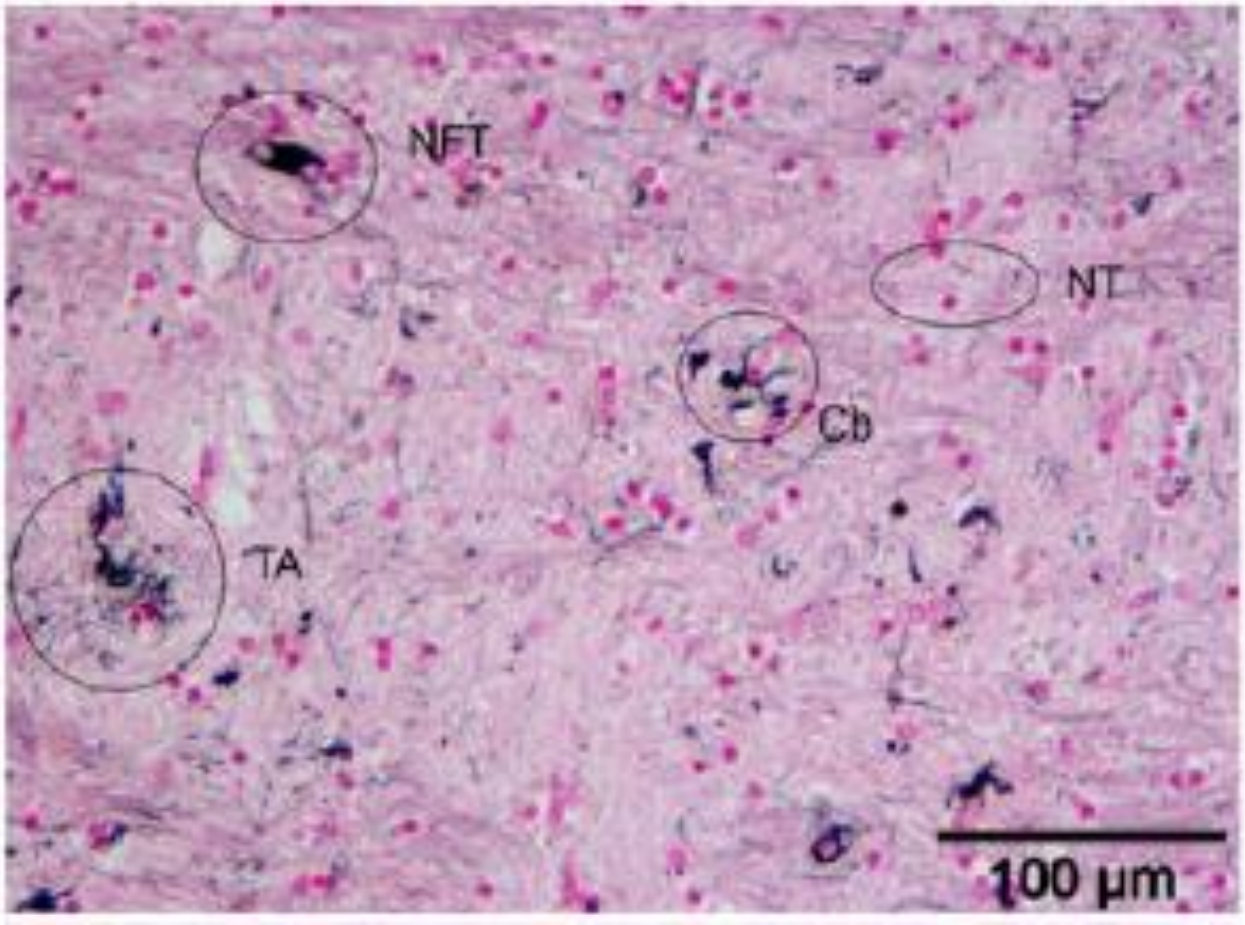
Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy Y-10	P1: Repeated unprovoked falls within 3 years Y-6	A1: Progressive gait freezing within 3 years Y-9	C1: Speech/Language disorder Y-9
Level 2	O2: Slow velocity of vertical saccades Y-9	P2: Tendency to fall on the pull-test within 3 years Y-1	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant Y-6	C2: Frontal cognitive/behavioral presentation Y-13
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia" Y-12	P3: >2 steps backward on the pull-test within 3 years Y-1	A3: Parkinsonism with tremor and/or asymmetric and/or levodopa responsive Y-9	C3: Corticobasal syndrome

Diagnostic certainty

Combinations	Diagnostic Certainty
(O1 or O2) + (P1 or P2) (O1 or O2) + A1 (O1 or O2) + (A2 or A3) (O1 or O2) + C2	Probable PSP
O1 O2 + P3 A1 (O1 or O2) + C1 (O1 or O2) + C3	Possible PSP
O2 or O3 P1 or P2 O3 + (P2 or P3) (A2 or A3) + (O3, P1, P2, C1, C2)[a] C1 C2 + (O3 or P3) C3	Suggestive of PSP

Year 13:
prob. PSP-RS

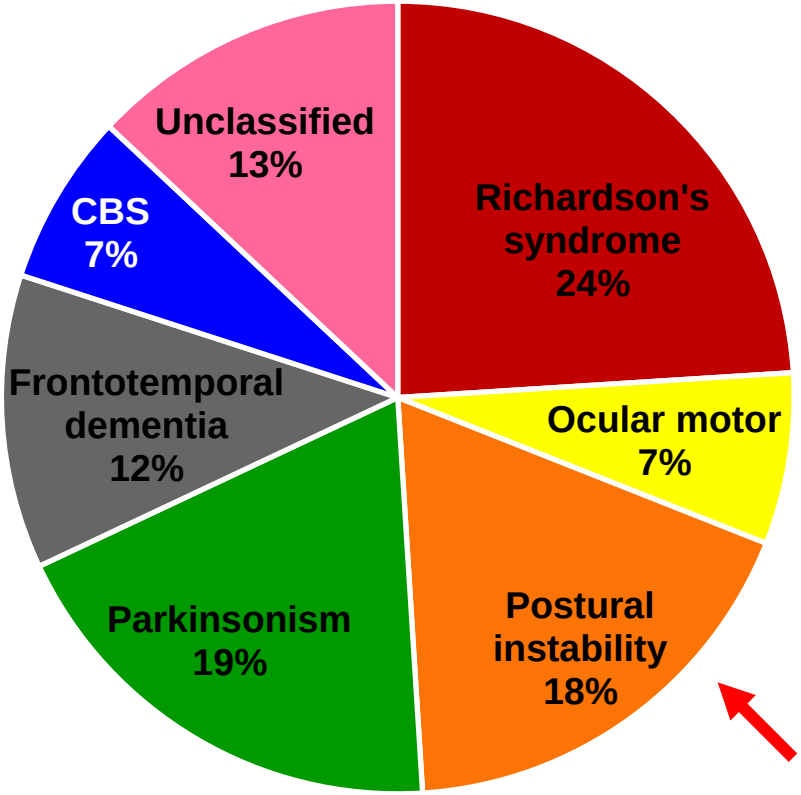
Kurz … Höglinger, Acta Neuropath Comm 2016; Age of the patient @ onset: 67 yrs.



Year 16:
def. PSP

Summary:
This case presents the typical course of a patient with PSP-PI

Full Clinical Spectrum



Respondek, … Höglinger, **Mov Dis.** 2014

Definite PSP

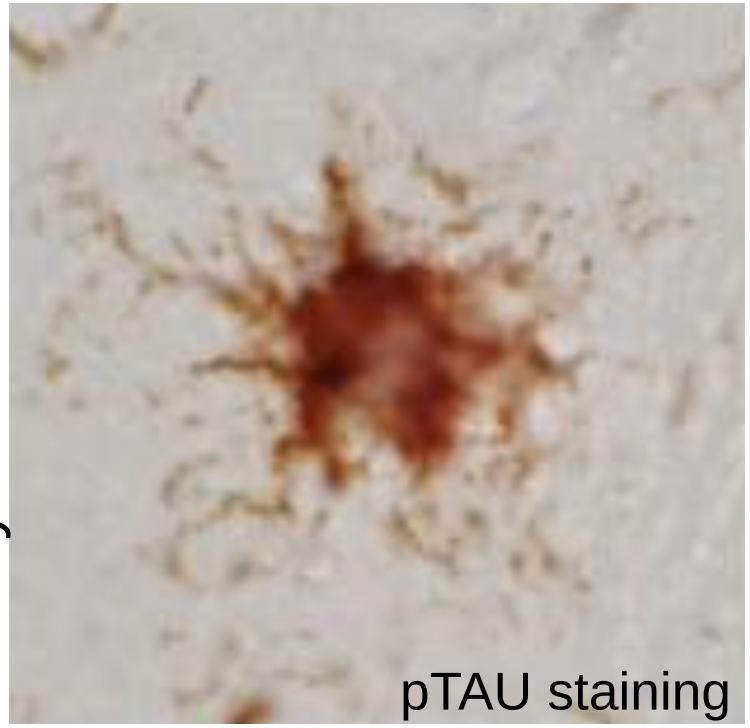


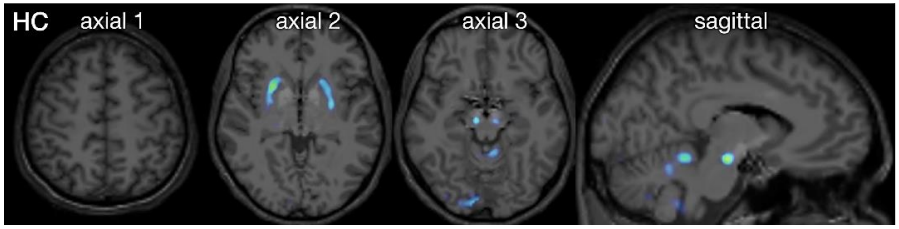
Photo: T. Arzberger / G. Höglinger

MOLECULAR DIAGNOSIS
4RT CONCEPT

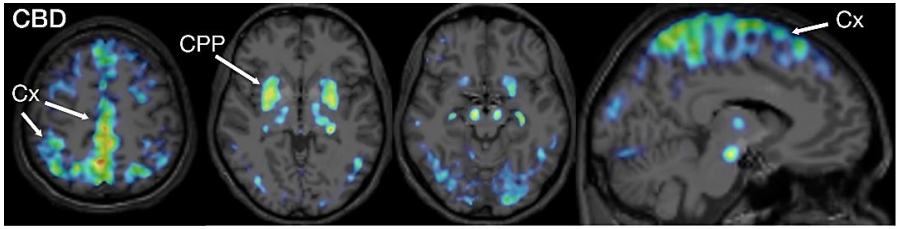
Tau PET
Is not (yet) a supportive feature

PET images using the tau tracer ^{18}F-PI-2620 in 4-repeat tauopathies

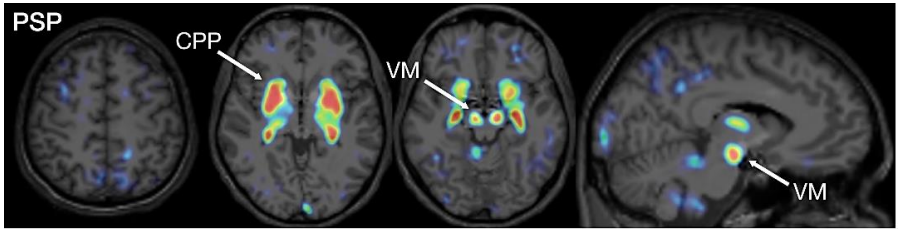
Healthy control



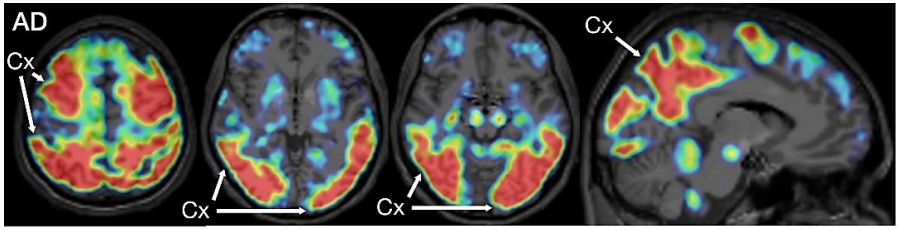
Corticobasal degeneration



Progressive supranuclear palsy



Alzheimer's disease



CPP, caudate nucleus, globus pallidus, and putamen; Cx,cortex; VM, ventral midbrain.

Rösler TW, … Höglinger. Prog Neurobiol, 2019101644.
Brendel M, … Höglinger GU, et al. JAMA Neurol. 2020;77(11):1408-1419.

CSF neurofilament light chain and phosphorylated tau 181 predict disease progression in PSP

Julio C. Rojas, MD, PhD, Jee Bang, MD, Iryna V. Lobach, PhD, Richard M. Tsai, MD, Gil D. Rabinovici, MD, Bruce L. Miller, MD, and Adam L. Boxer, MD, PhD On behalf of AL-108-231 Investigators

Neurology® 2018;90:e1-9. doi:10.1212/WNL.0000000000004859

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Dr. Rojas
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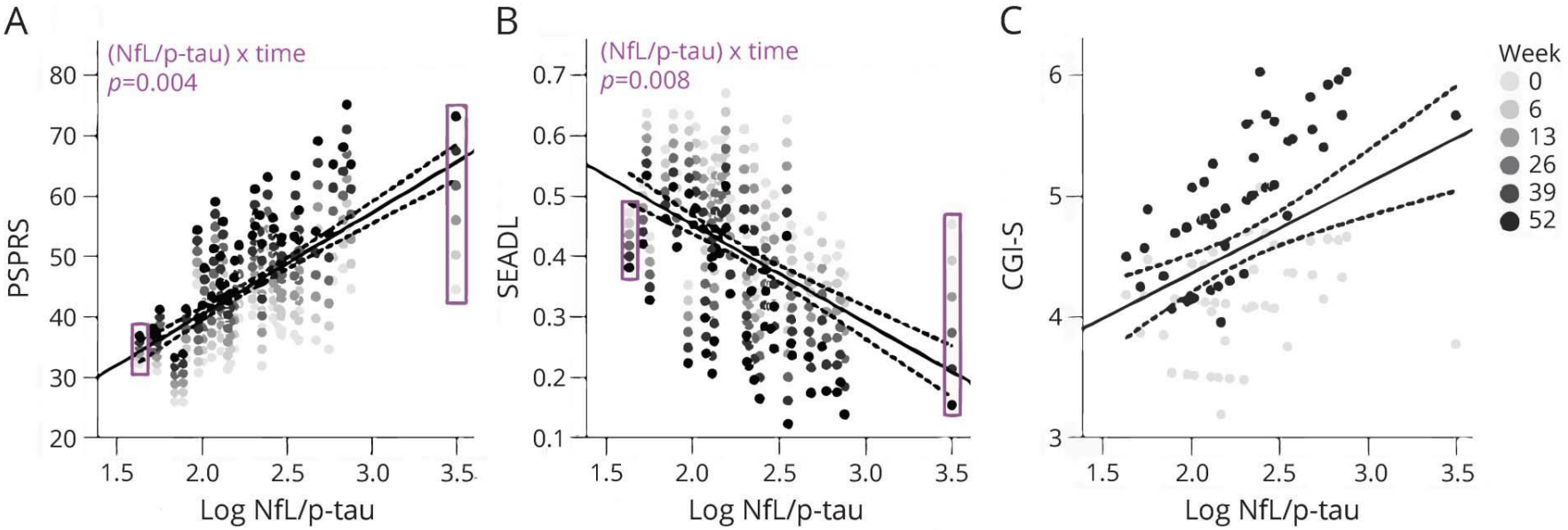
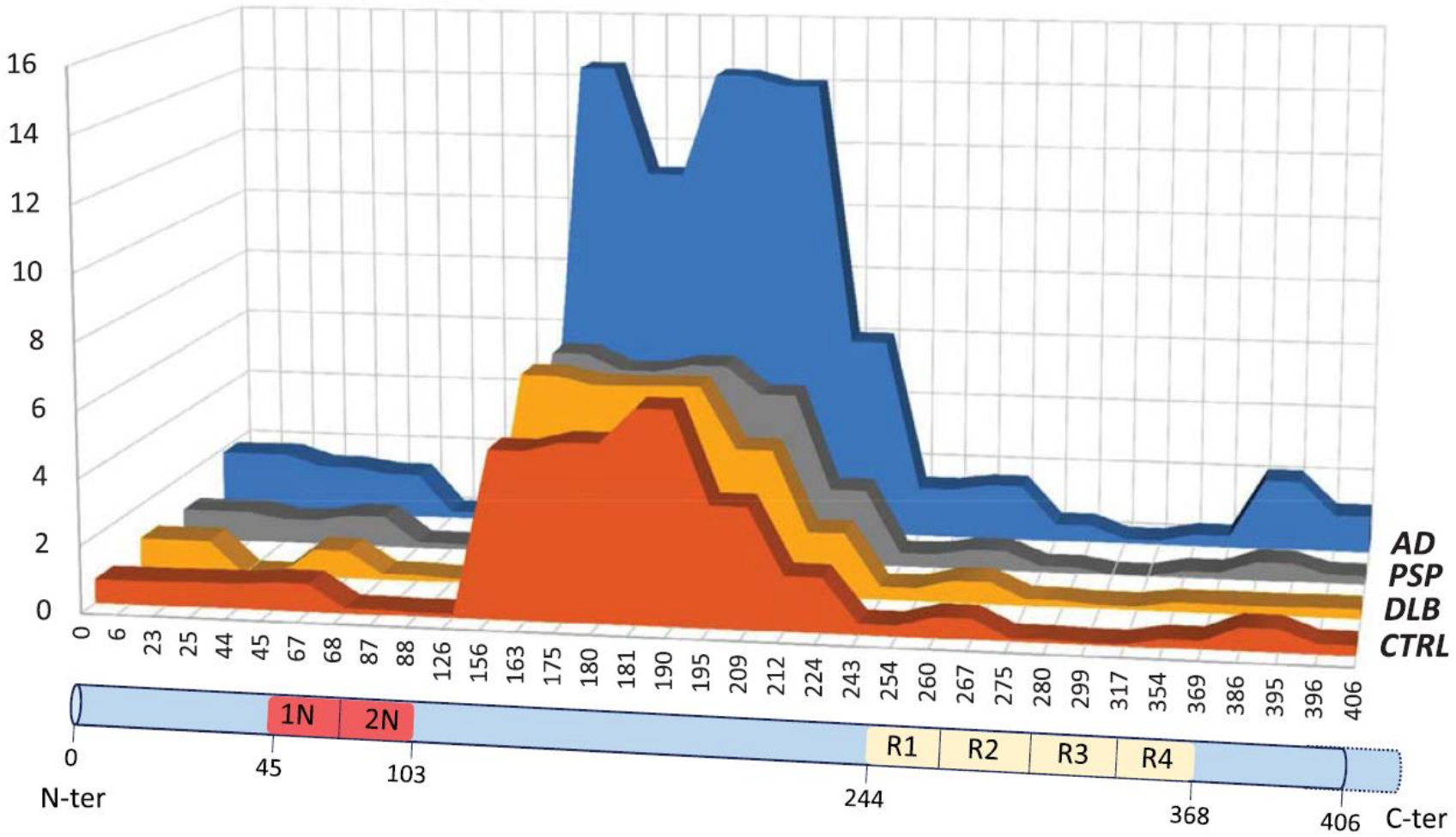


Figure 4 CSF neurofilament light chain (NfL)/phosphorylated tau 181 (p-tau) predicts clinical decline and stratifies patients by disease severity

Differential Mass Spectrometry Profiles of Tau Protein in the Cerebrospinal Fluid

Nicolas R. Barthélemy

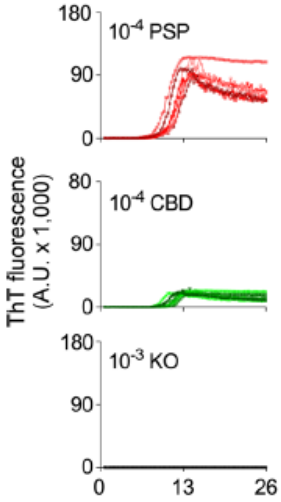
Journal of Alzheimer's Disease 51 (2016) 1033–1043

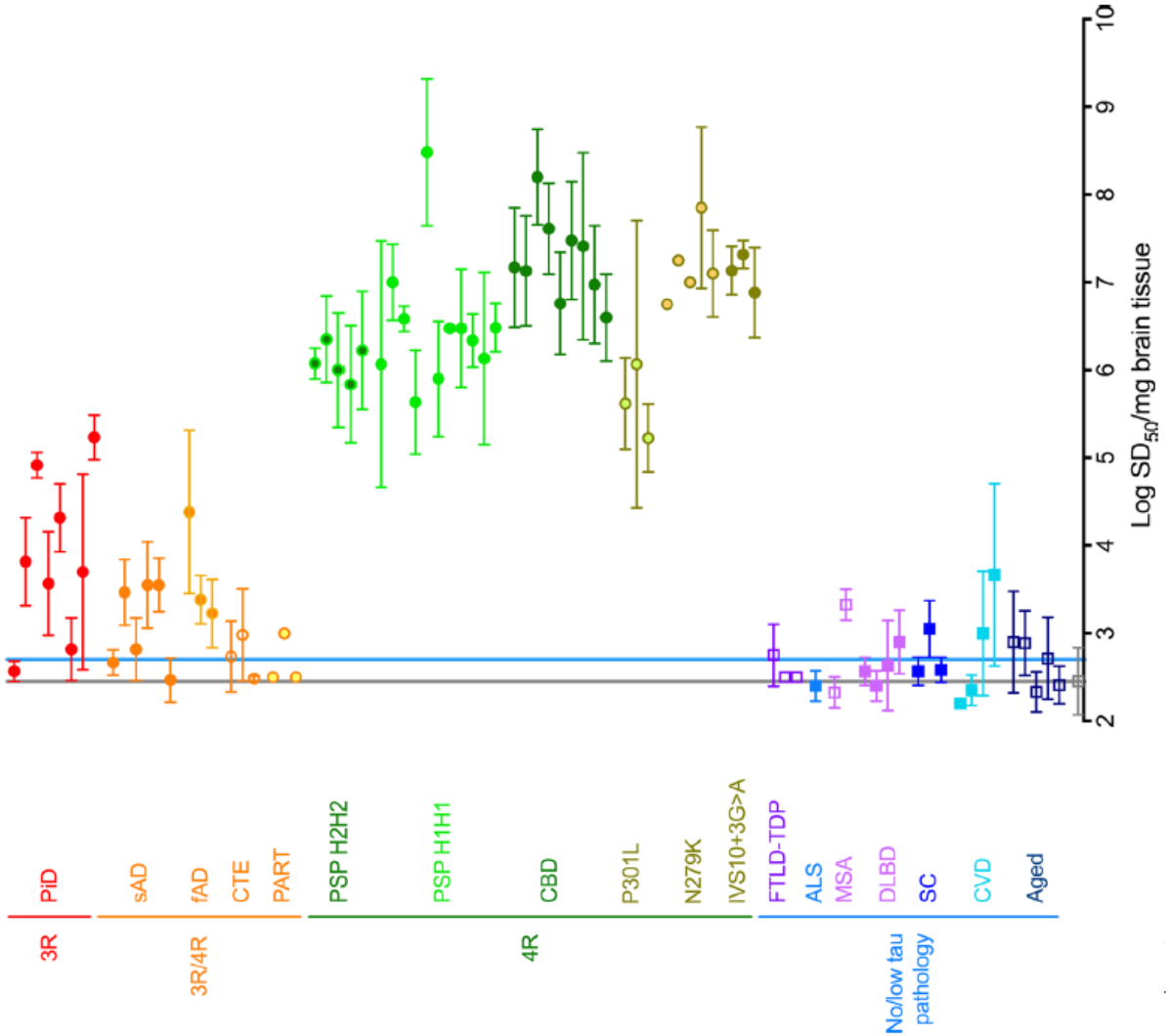


4-Repeat tau seeds and templating subtypes as brain and CSF biomarkers of frontotemporal lobar degeneration

Acta Neuropathologica
https://doi.org/10.1007/s00401-019-02080-2

Eri Saijo[1] · Michael A. Metrick II[1] · Shunsuke Koga[2] · Piero Parchi[3,4] · Irene Litvan[5] · Salvatore Spina[6] · Adam Boxer[6] · Julio C. Rojas[6] · Douglas Galasko[7] · Allison Kraus[1] · Marcello Rossi[3] · Kathy Newell[8] · Gianluigi Zanusso[9] · Lea T. Grinberg[6,10] · William W. Seeley[6] · Bernardino Ghetti[8] · Dennis W. Dickson[2] · Byron Caughey[1]





CURRENT THERAPY

A Review of Treatment Options for Progressive Supranuclear Palsy

Maria Stamelou[1,2,3] · **Günter Höglinger**[1,4,5]

CNS Drugs 24 May 2016
DOI 10.1007/s40263-016-0347-2

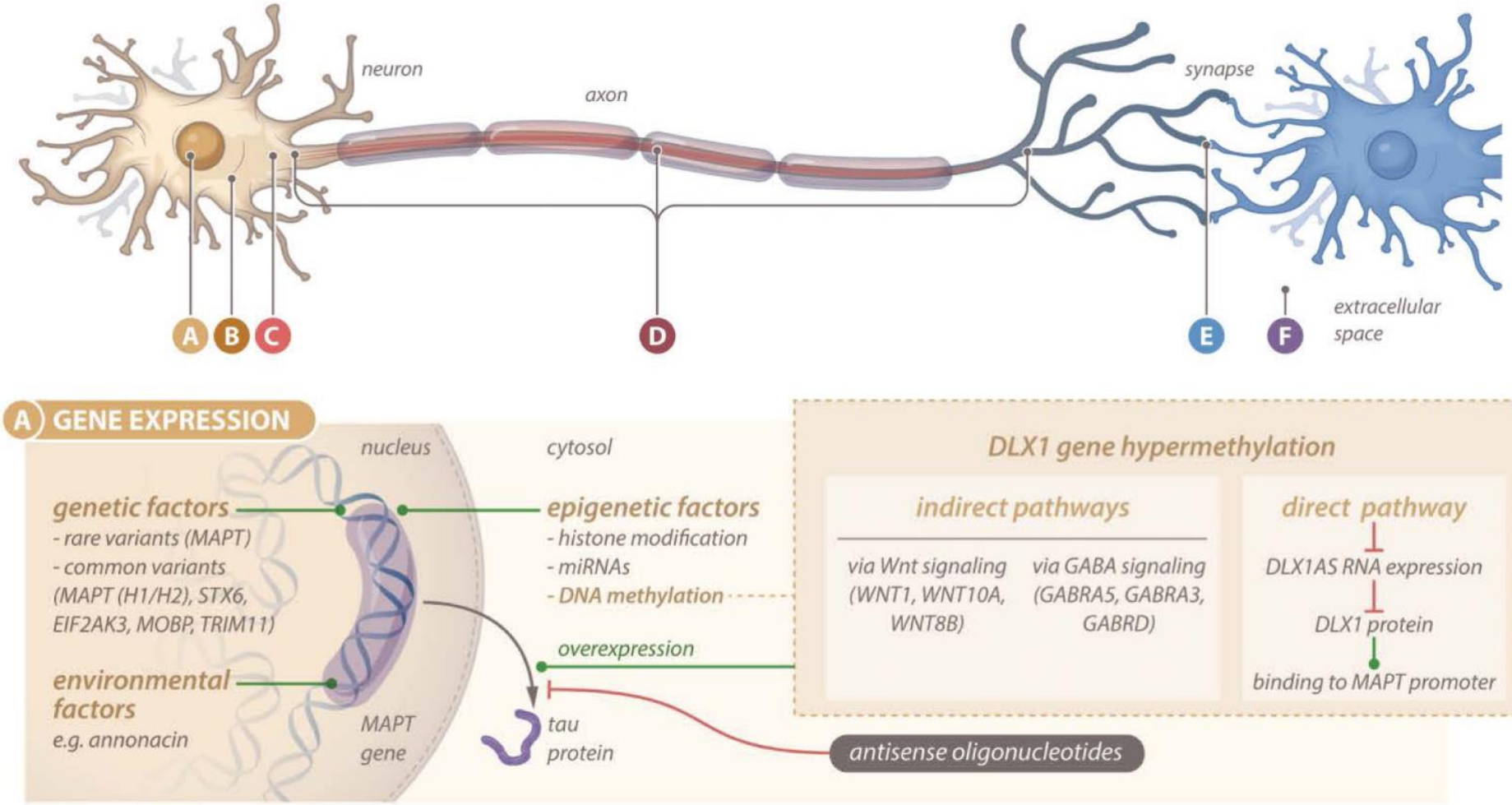
Table 1 Evidence levels and degrees of recommendation[a] for off-label pharmacological use in progressive supranuclear palsy

Treatment	Regimen	Target symptom	Effect size	Evidence level	Degree of recommendation
Levodopa	Up to 4 × 300 mg (in clinical practice, rarely >1000 mg/day)	Akinesia–rigidity, postural instability	Mild to moderate	2−	D
Amantadine	3 × 100–200 mg (in clinical practice, rarely >400–450 mg/day)	Akinesia–rigidity, postural instability	Mild to moderate	3	D
Amitriptyline	1 × 75–150 mg	Oculomotor dysfunction, depression	Mild to moderate	2−, 3	D
Zolpidem	1 × 5–10 mg	Insomnia	Moderate	4	–
		Motor and oculomotor dysfunction	Mild	1−	–
CoQ10	5 mg/kg body weight/day, nanoparticle emulsion	Motor and cognitive dysfunction	Mild	1+	B
Botulinum toxin A		Focal dystonia, including eyelid apraxia, blepharospasm	Good	3	D

CoQ10 coenzyme Q10

MOLECULAR MECHANISMS ⇨ DISEASE-MODIFYING THERAPIES

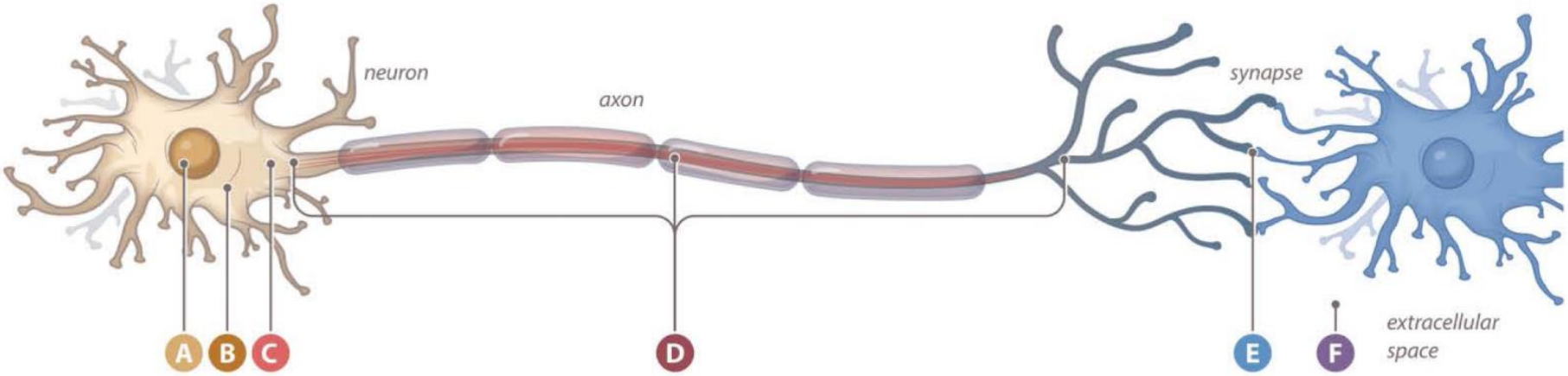
Disease Mechanisms & Targets

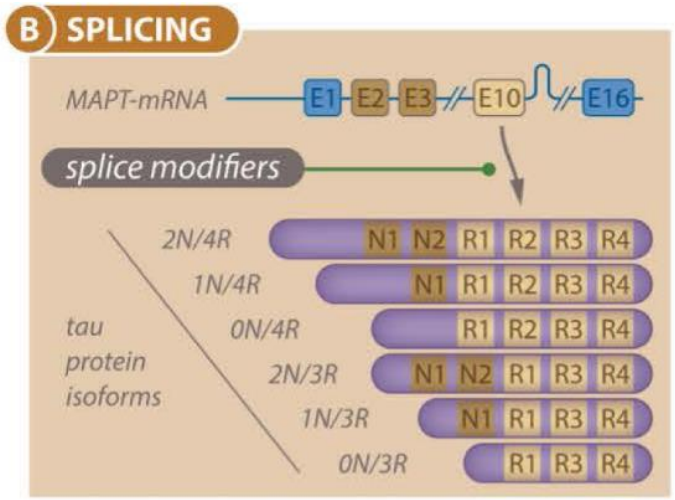


***MAPT* Expression**

Rösler, … Höglinger, ***Prog Neurobiol***. 2019

Disease Mechanisms & Targets

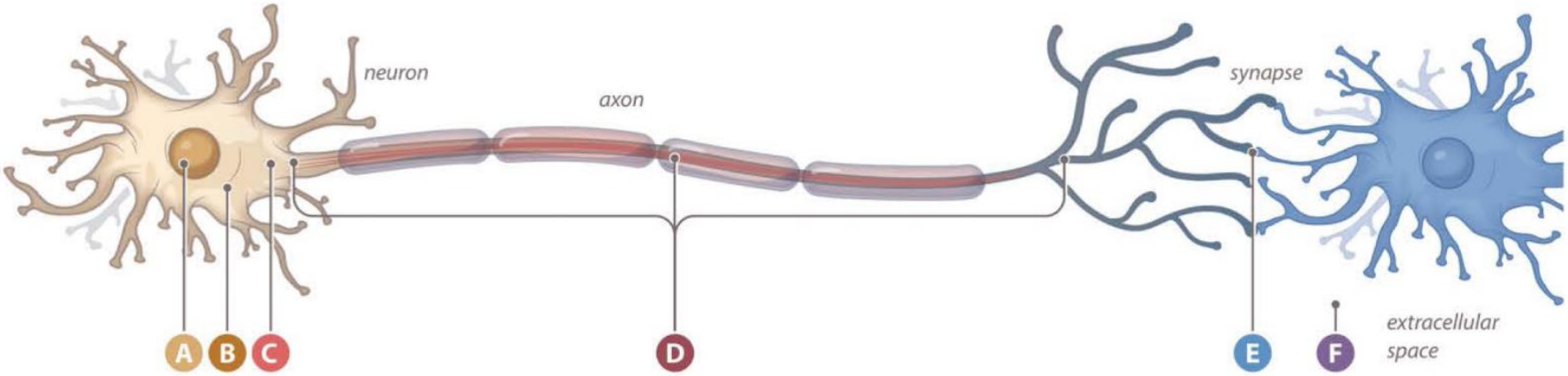


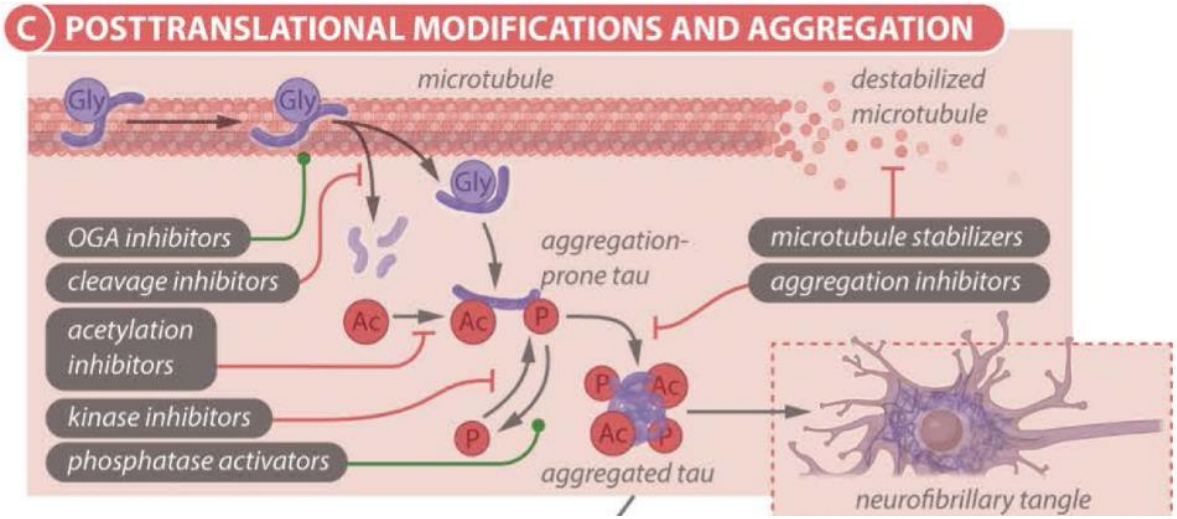


***MAPT* Isoform Composition**

Rösler, … Höglinger, ***Prog Neurobiol***. 2019

Disease Mechanisms & Targets

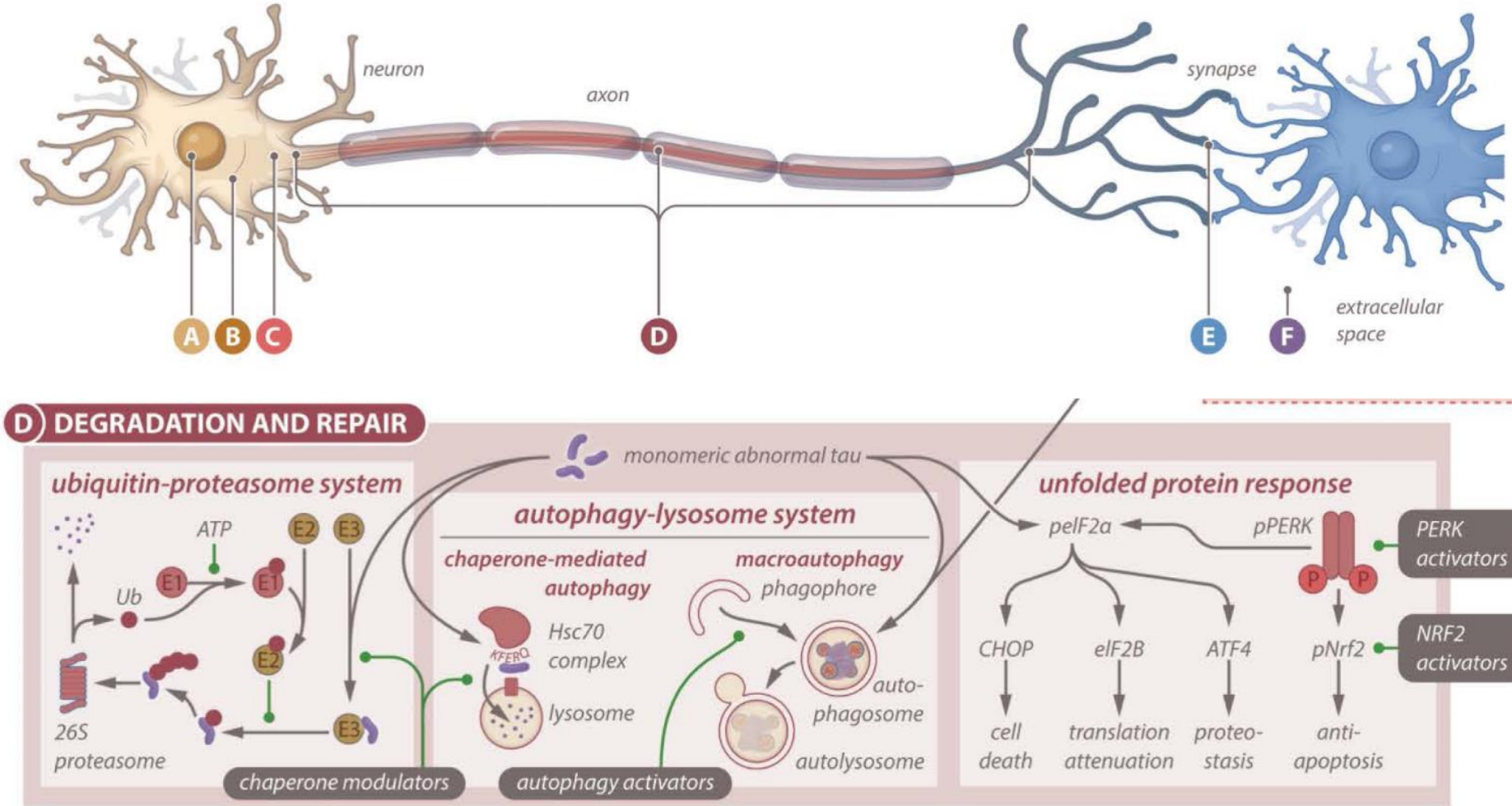




Tau PTMs

Rösler, … Höglinger, ***Prog Neurobiol***. 2019

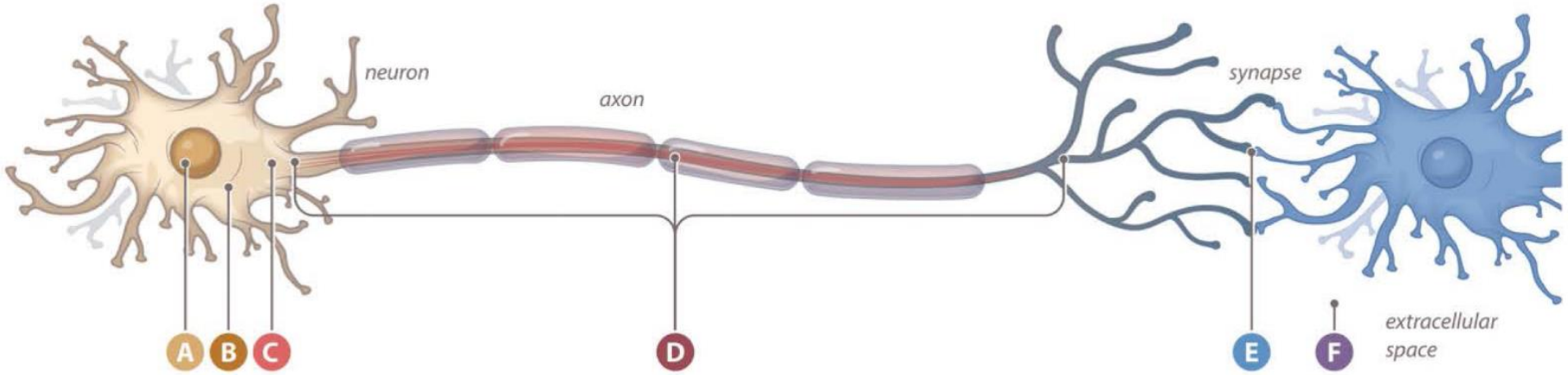
Disease Mechanisms & Targets

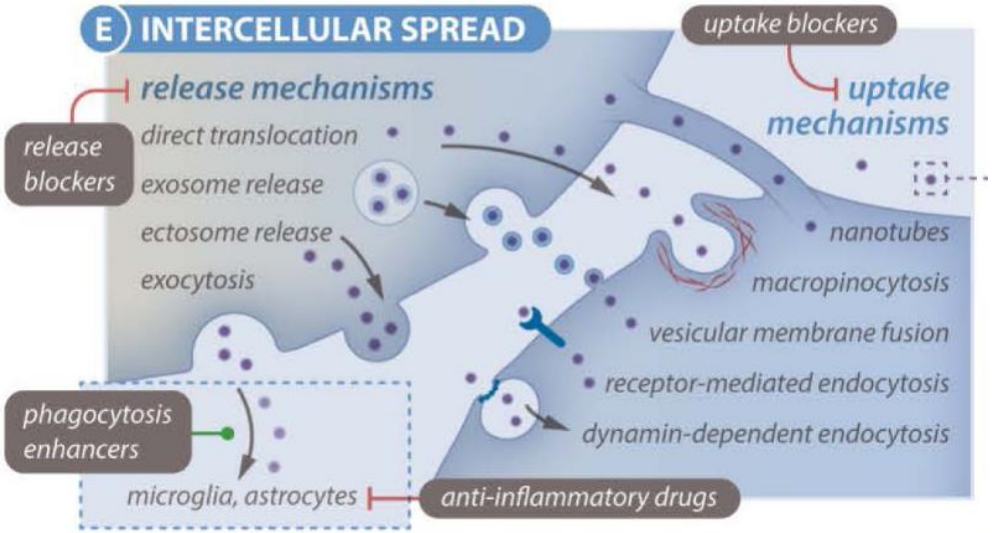


Tau Degradation

Rösler, … Höglinger, ***Prog Neurobiol***. 2019

Disease Mechanisms & Targets

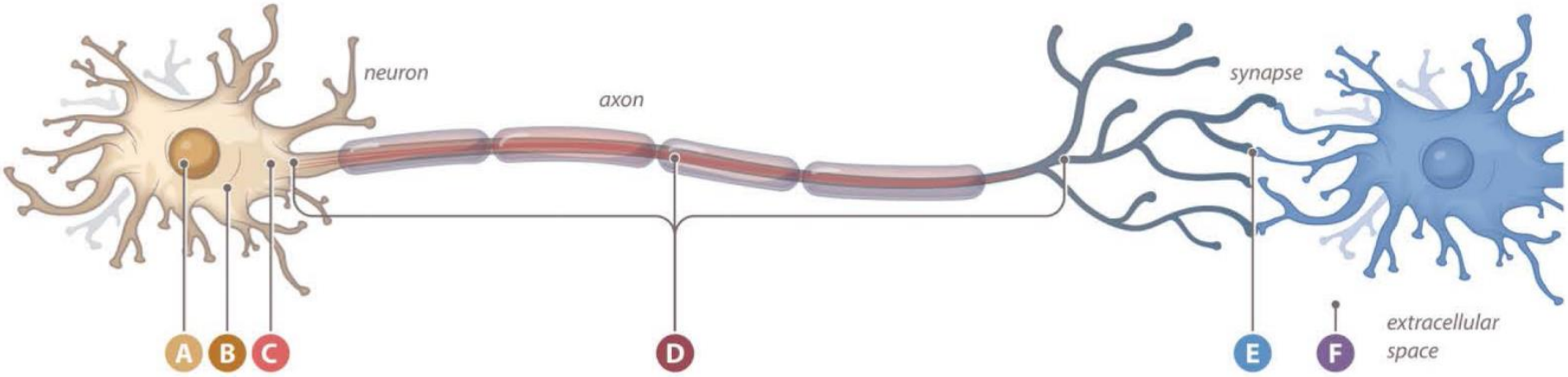


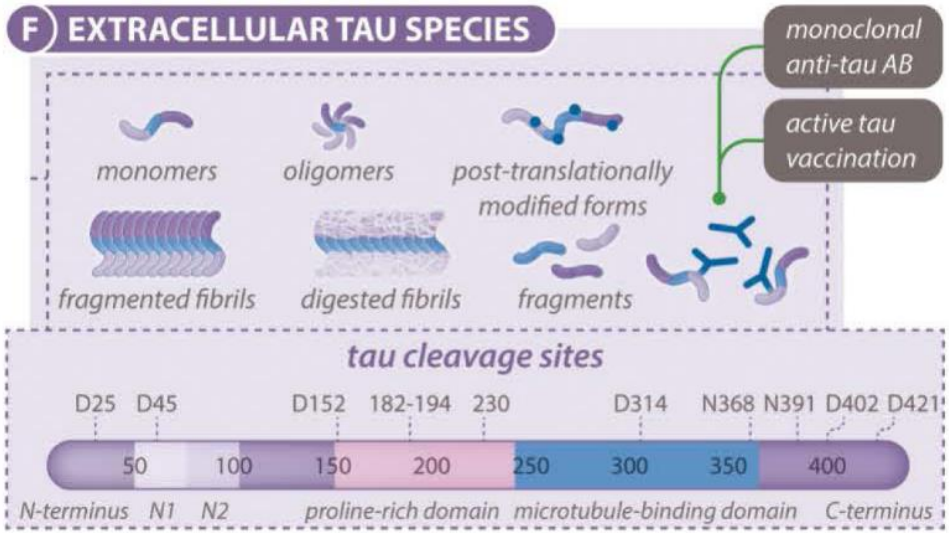


Tau Spreading

Rösler, … Höglinger, ***Prog Neurobiol***. 2019

Disease Mechanisms & Targets





eTau

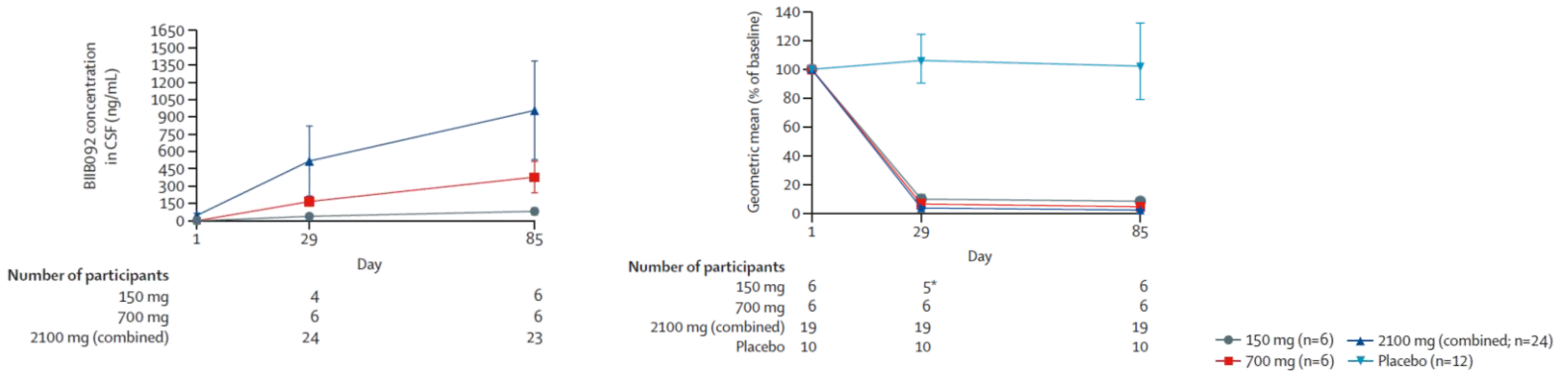
Rösler, … Höglinger, ***Prog Neurobiol***. 2019

BIIB092 (Gosuranemab)
Phase I Study in PSP

Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: a randomised, placebo-controlled, multiple ascending dose phase 1b trial

Adam L Boxer, Irfan Qureshi, Michael Ahlijanian, Michael Grundman, Lawrence I Golbe, Irene Litvan, Lawrence S Honig, Paul Tuite, Nikolaus R McFarland, Padraig O'Suilleabhain, Tao Xie, Giridhar S Tirucherai, Clifford Bechtold, Yvette Bordelon, David S Geldmacher, Murray Grossman, Stuart Isaacson, Theresa Zesiewicz, Tina Olsson, Kumar Kandadi Muralidharan, Danielle L Graham, John O'Gorman, Samantha Budd Haeberlein, Tien Dam

***Lancet Neurol* 2019; 18: 549–58**



ABBV-8E12 (Tilavonemab)
A monoclonal antibody that binds to the N-terminal of human tau.

Evaluation of tilavonemab (ABBV-8E12) in progressive supranuclear palsy: results from a phase 2, randomised, placebo-controlled, multicentre study

Günter Höglinger, Irene Litvan, Nuno Mendonca*, Deli Wang*, Hui Zheng*, Beatrice Rendenbach-Mueller*, Hoi Kei Lon*, Ziyi Jin, Nahome Fisseha*, Kumar Budur*, Michael Gold*, Davis Ryman*, Hana Florian*, on behalf of the ARISE Investigators.

Lancet Neurology, in press.

* Disclosure: Former or current employee of AbbVie Inc., North Chicago, IL, USA

UCB0107

A monoclonal antibody that binds to the mid-region of human tau.

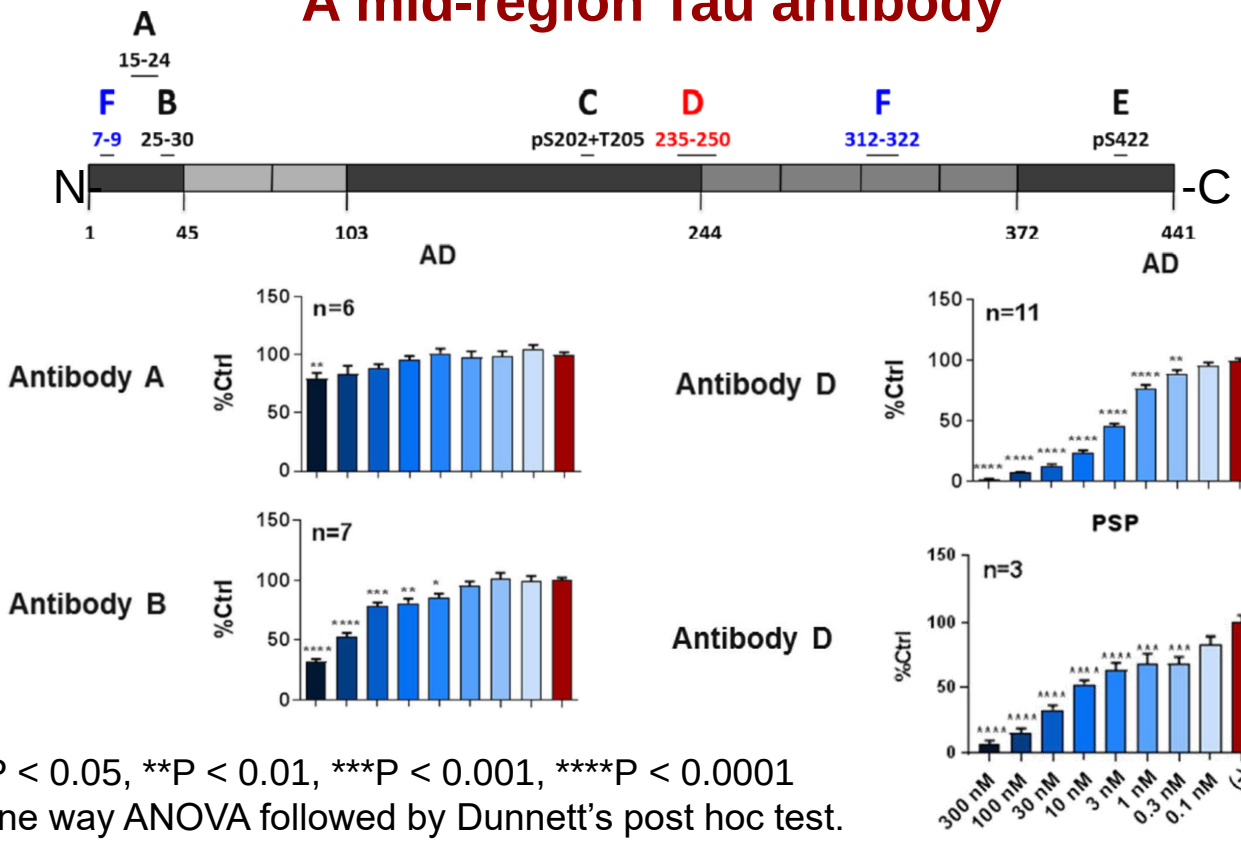
PSP003 Study:

A PARTICIPANT-BLIND, INVESTIGATOR-BLIND, PLACEBO-CONTROLLED, PHASE 1B STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF UCB0107 IN STUDY PARTICIPANTS WITH PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

Tim Buchanan*, Marie-Alix Bonny*, Steven De Bruyn*, Hans Van Tricht*, Massimiliano Germani*, Irene Rebollo Mesa*, Günter Höglinger

* Disclosure: Employee of UCB

UCB0107:
A mid-region Tau antibody



*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001
One way ANOVA followed by Dunnett's post hoc test.

Courade et al., Acta Neuropath. 2018

Inhibition of O-linked β-N-acetylglucosamine-ase

Medizinische Hochschule Hannover

nature chemical biology

ARTICLE

PUBLISHED ONLINE: 26 FEBRUARY 2012 | DOI: 10.1038/NCHEMBIO.797

Increasing *O*-GlcNAc slows neurodegeneration and stabilizes tau against aggregation

Scott A Yuzwa[1,5], Xiaoyang Shan[1,5], Matthew S Macauley[2,4], Thomas Clark[2], Yuliya Skorobogatko[3], Keith Vosseller[3] & David J Vocadlo[1,2*]

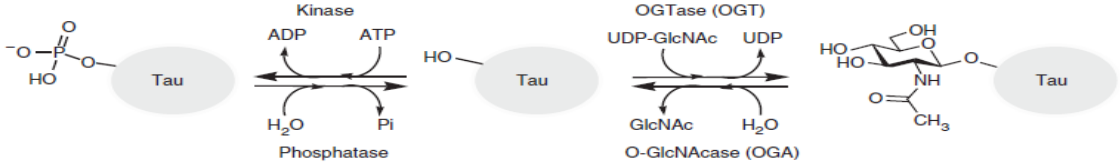
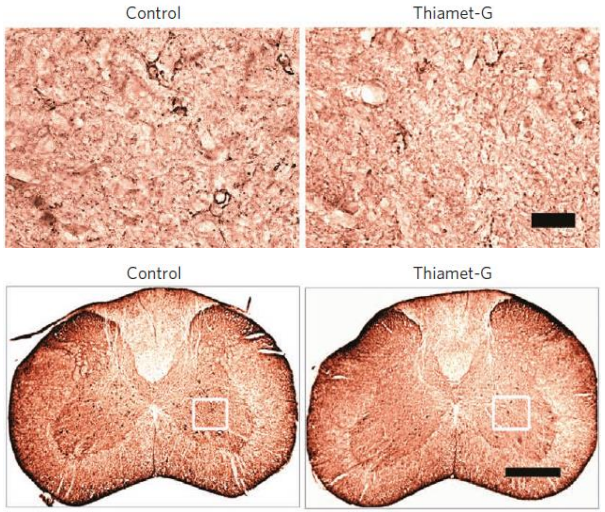


Figure 1 The relationship between phosphorylation and O-GlcNAcylation on tau is a dynamic equilibrium. The existence of serine or threonine residues that are known to be both phosphorylated and *O*-GlcNAc–modified dictates that such residues can exist in one of three different states: phosphorylated, glycosylated or free hydroxyl. The formation of these states is regulated by the appropriate enzymes.



Tau expression (Antisense Oligonucleotides, ASO)

Medizinische Hochschule Hannover

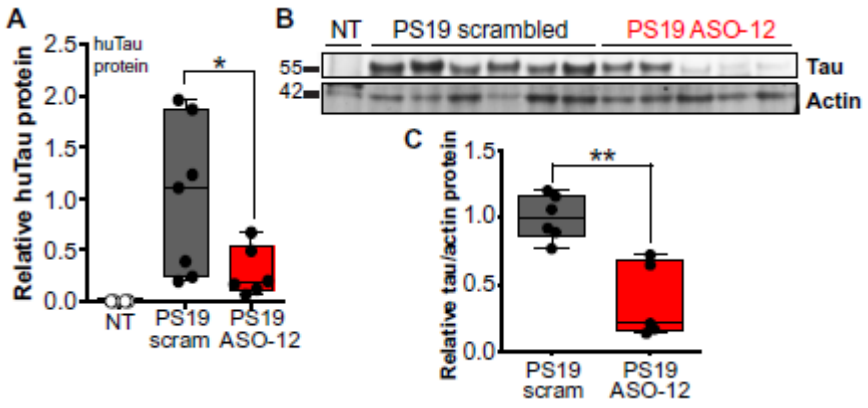
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

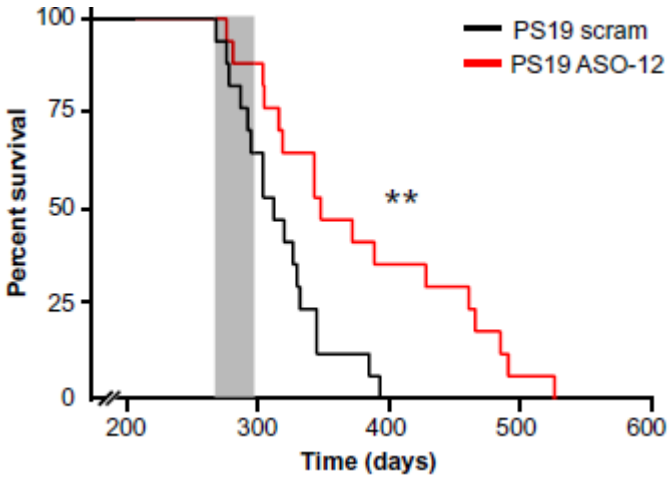
ALZHEIMER'S DISEASE

DeVos *et al.*, *Sci. Transl. Med.* **9**, eaag0481 (2017) 25 January 2017

Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy

Sarah L. DeVos,[1] Rebecca L. Miller,[1]* Kathleen M. Schoch,[1]* Brandon B. Holmes,[1] Carey S. Kebodeaux,[1] Amy J. Wegener,[1] Guo Chen,[1] Tao Shen,[1] Hien Tran,[2] Brandon Nichols,[2] Tom A. Zanardi,[2] Holly B. Kordasiewicz,[2] Eric E. Swayze,[2] C. Frank Bennett,[2] Marc I. Diamond,[3] Timothy M. Miller[1]†





Q4: The pathogenesis of 4R-tauopathies comprises

- Common genetic variation at *MAPT*
- Epigenetic changes at *DLX1*
- Altered *MAPT* splicing
- Posttranslational modification of Tau
- Alterations in the *PERK* pathway
- Intercellular spreading of Tau
- All of the above

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- Alterations in the *PERK* pathway
- Intercellular spreading of Tau
- **All of the above (CORRECT)**

Institutional Logo, ‚Speakers' picture or disease related picture

Webinar summary

1. PSP: prototypical primary 4R tauopathy
2. Tauopathies: classifications (prim sec / 3R / 4R)
3. PSP diagnostic criteria (NINDS / MDS)
4. PSP: video illustrations
5. Molecular diagnostics (fluid biomarker, Tau PET)
6. Molecular disease mechanisms
7. Therapeutic trials (AB, ASO, OGA)

DZNE
Deutsches Zentrum für Neurodegenerative Erkrankungen
in der Helmholtz-Gemeinschaft

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European Reference Network for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

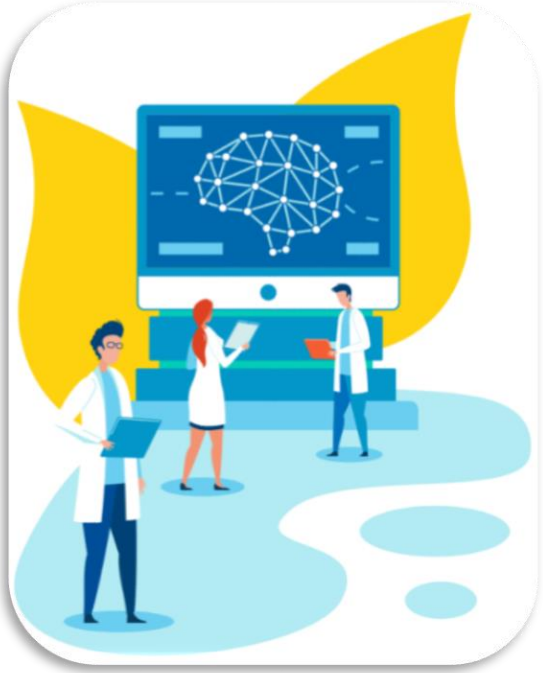
European Reference Network for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

26. January 2021

European Reference Network | Neurological Diseases (ERN-RND)

This webinar has been supported by ERN-RND , which is partly co-funded by the European Union within the framework of the Third Health Programme “ERN-2016 - Framework Partnership Agreement 2017-2021."



THANK YOU

Next webinar:

‚Genetic dystonia and treatment‘

2. February 2020