

TAUOPATHIES

Cognitive Syndromes

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OUTLINE

Diagnosis

Cognitive phenotypes

Testing Challenges

Therapies

Parkinsonism

Synucleinopathies

(RBD)

Parkinson's
disease, DLB

MSA

Tauopathies

(Eye movement)

PSP

CBD

Picks



Progressive supranuclear palsy



PSP CRITERIA

Hoglinger et al 2017

Sporadic
occurrence

Age 40 or older at
onset

Gradual
progression of PSP-
related symptom

Core features:

Oculomotor
dysfunction

Postural Instability

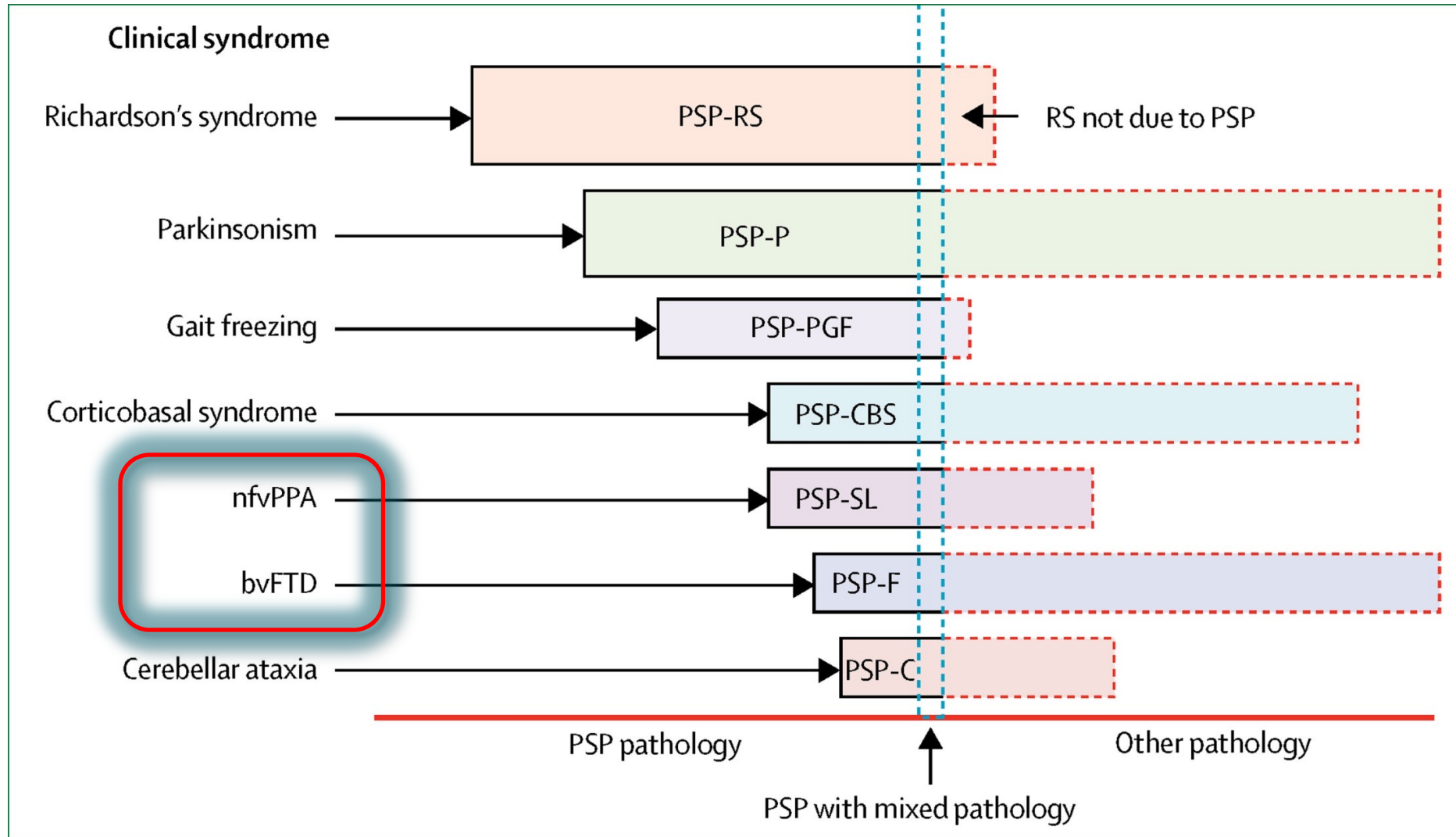
Akinesia

Cognitive
dysfunction

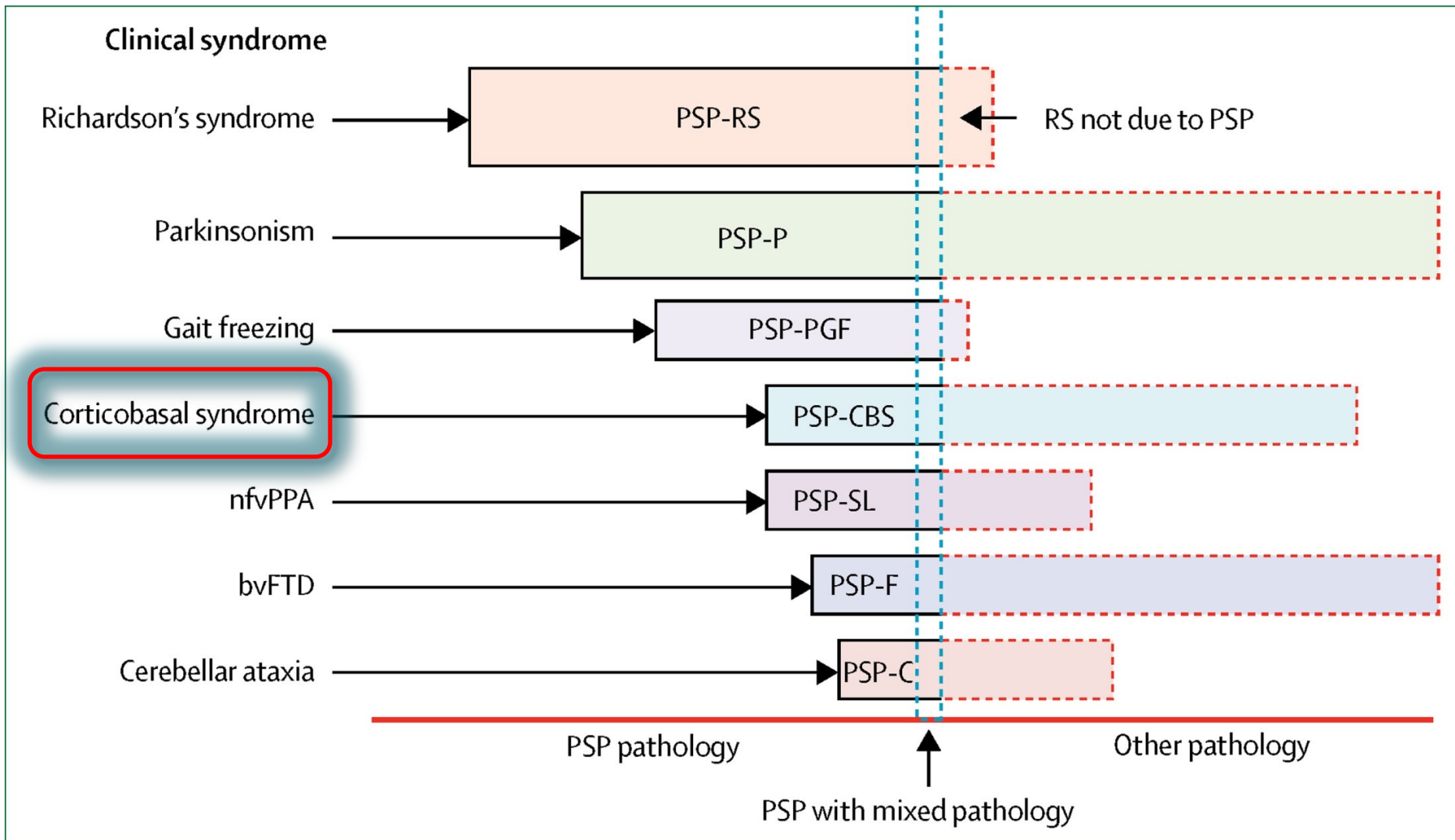
DIAGNOSIS OF PSP

Certainty	Oculomotor	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 year	C1: Speech/language disorder (nf/agrammatic PPA or AOS)
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: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

PERCENTAGE OF SYNDROME RELATED TO PSP PATHOLOGY



PERCENTAGE OF SYNDROME RELATED TO PSP PATHOLOGY



nfvPPA

Agrammatism

Effortful, halting speech with inconsistent speech sound errors and distortions (AOS)

22/25 nfvPPA in series found to have tau pathology post mortem Boxer et al. *Lancet Neurol* 2017

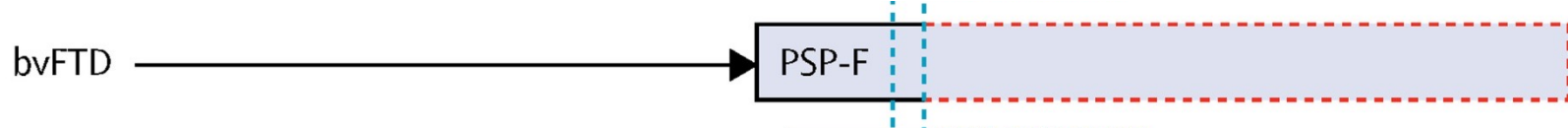
PSP-SL





C2-5 Affective Disinhibition
Pathological Laughing

PSP- F



bvFTD

- Apathy
- Disinhibition
- Hyperorality
- Executive dysfunction
- Compulsions
- Decreased empathy



PSP PATHOLOGY

Neurofibrillary tangles or neuropil threads, in the basal ganglia and the brainstem

Microscopic features:

Neuronal loss

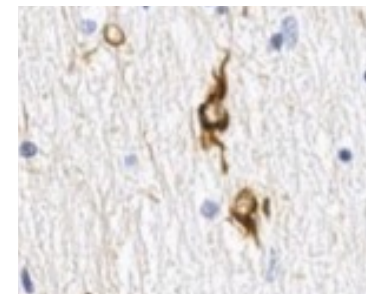
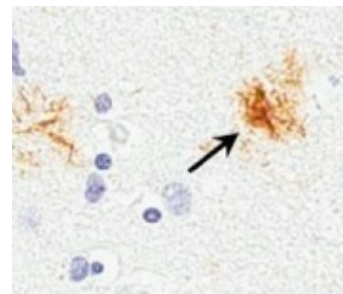
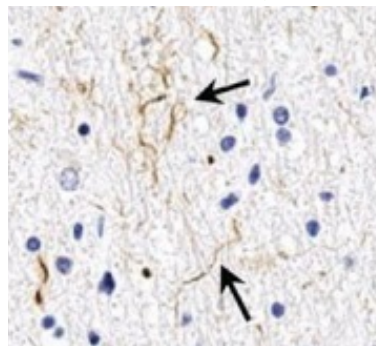
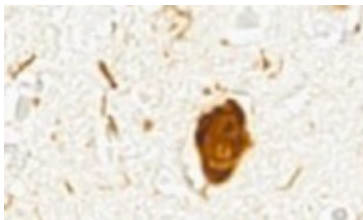
Gliosis


Neurofibrillary tangles

Neuropil threads

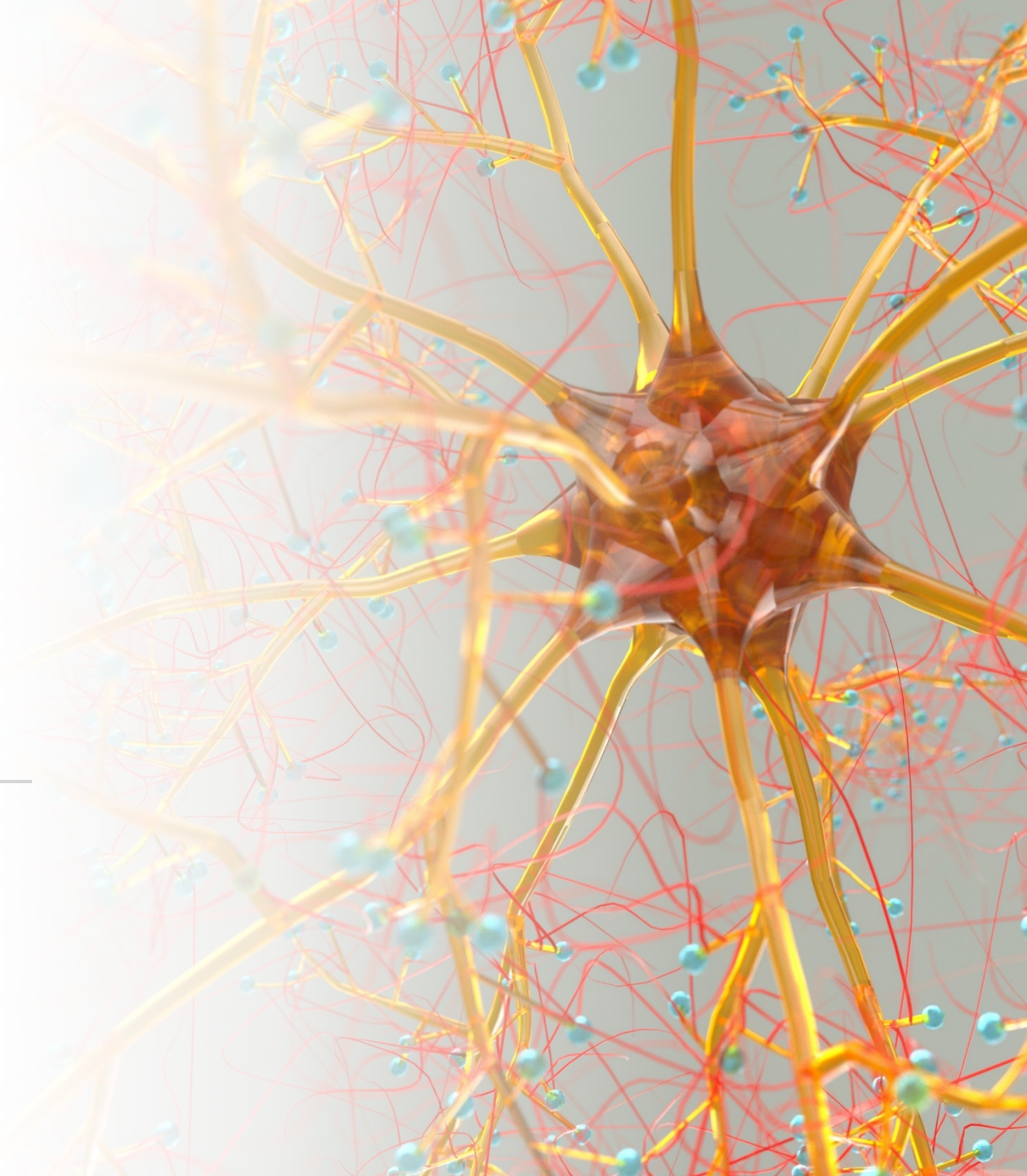
Tufted astrocytes

Oligodendroglial coiled bodies





Corticobasal
Syndrome
+
Corticobasal
Degeneration



CORTICOBASAL SYNDROME



Various symptoms:

Dystonia
Asymmetric parkinsonism
Apraxia
Cortical sensory loss
Loss of voluntary limb control

AND

CORTICOBASAL DISEASE



Syndrome caused by several pathologies:

CBD
PSP
DLB
AD
FTLD-TDP43
Prion disease



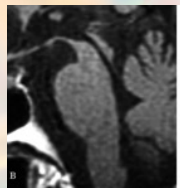
Several syndromes can be CBD pathology:

Bv FTD
Non-fluent aphasia
PSP syndrome
CBS

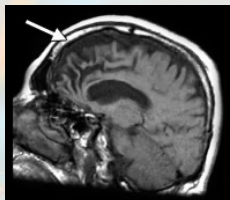
Syndrome



CBS



PSP



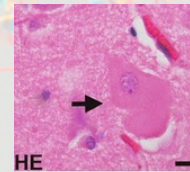
FTD



Non-fluent PPA

Pathology

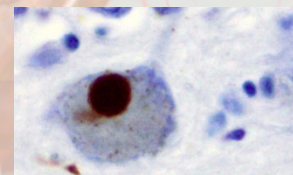
CBD



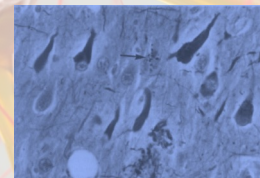
PSP



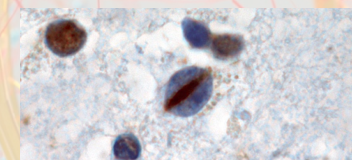
DLB



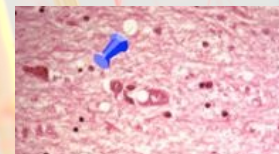
AD



TDP-43



Prion



Probable CBS Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)

Possible CBS May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)

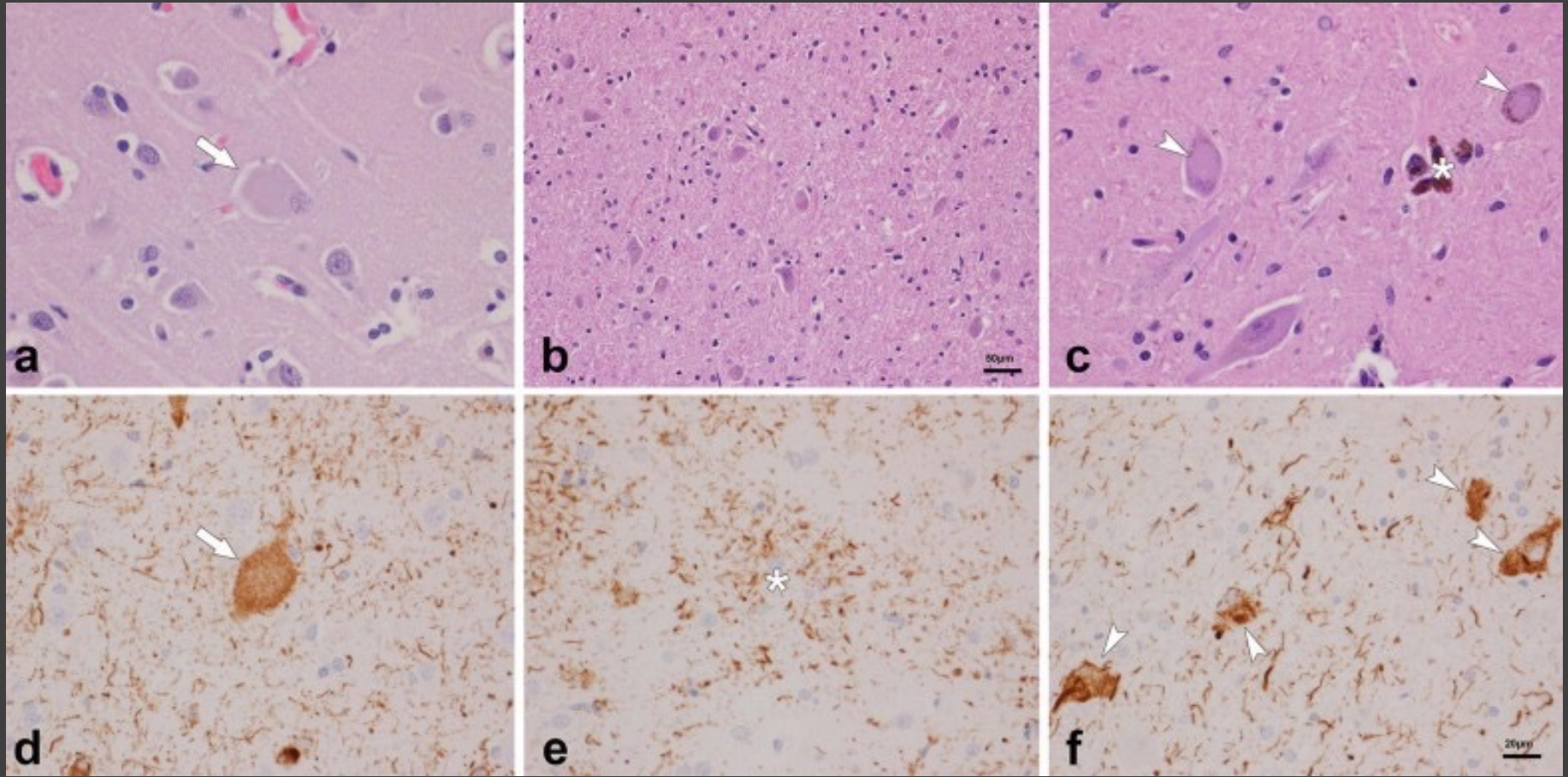
FBSS Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits

nfvPPA Effortful, agrammatic speech plus at least one of: a) impaired grammar/ sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)

PSPS Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

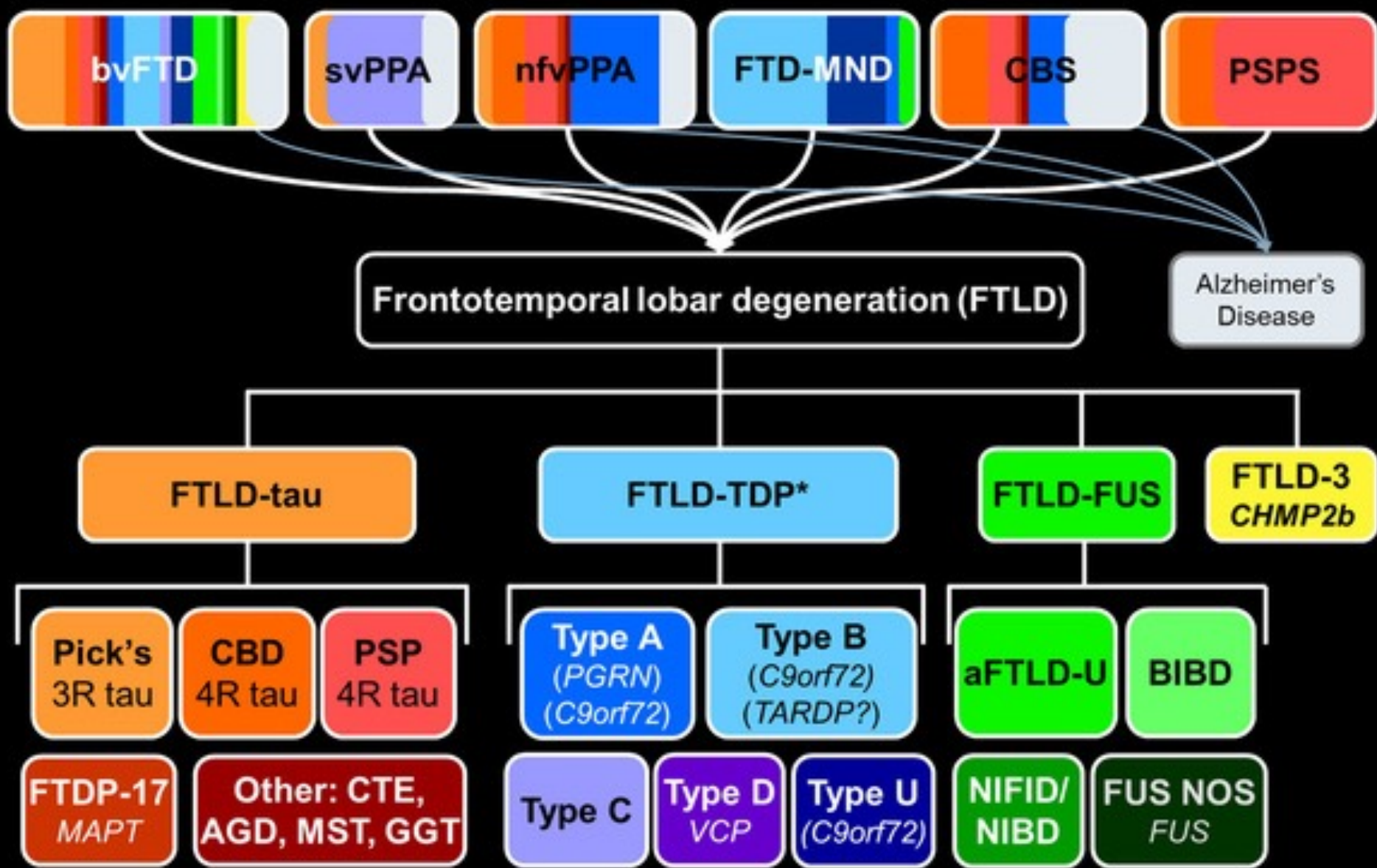
Proposed clinical phenotypes of CBD

Armstrong et al. *Neurology*, 2013



Microscopic findings CBD

- (a) H&E superior frontal gyrus shows **ballooned neurons (arrow)**
- (b) H&E subthalamic nucleus shows mild neuronal loss, but more gliosis
- (c) H&E substantia nigra shows focal neuronal loss (*extraneuronal neuromelanin); neurons with corticobasal bodies (arrowheads)
- (d) Phospho-tau IHC superior frontal gyrus shows neuropil threads, ballooned neuron with cytoplasmic tau immunoreactivity (arrow)
- (e) Phospho-tau IHC of caudate shows an astrocytic plaque (*)
- (f) Phospho-tau IHC of STN shows heterogeneity of neuronal inclusions (arrowheads)



A background image of various laboratory glassware, including test tubes, flasks, and a burette, arranged on a stand. The glassware is illuminated with a blue and purple light, creating a scientific and clinical atmosphere.

CHALLENGE: Diagnostic tests are not yet available (Biomarkers)

Tau PET:

- Detects tau in AD
- Less binding in PSP/CBD, overlap with controls

CSF MTBR-tau243

P-tau (CSF, plasma) for AD

- Correlates with amyloid

NfL

- Non-specific marker of neuronal injury

Synuclein seeding assays (CSF, skin)

- Distinguish between tauopathy vs synuclein

DAT nonspecific-reduction in dopamine transporter

TREATMENTS ARE FOR SYMPTOMS

Language symptoms:

- Speech Therapy

Behavior:

- SSRI
- Dextromethorphan-quinidine for PBA

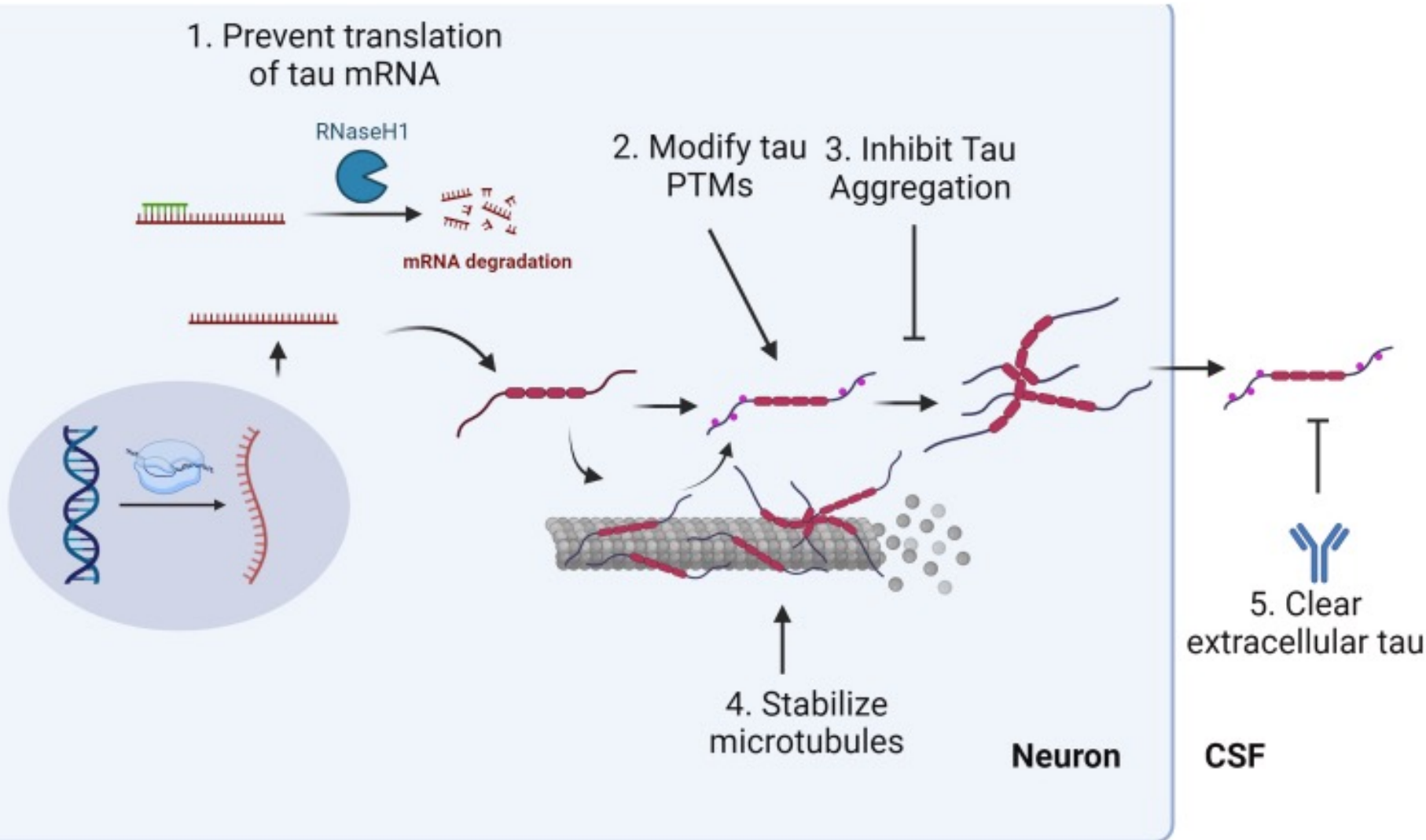
Apraxia:

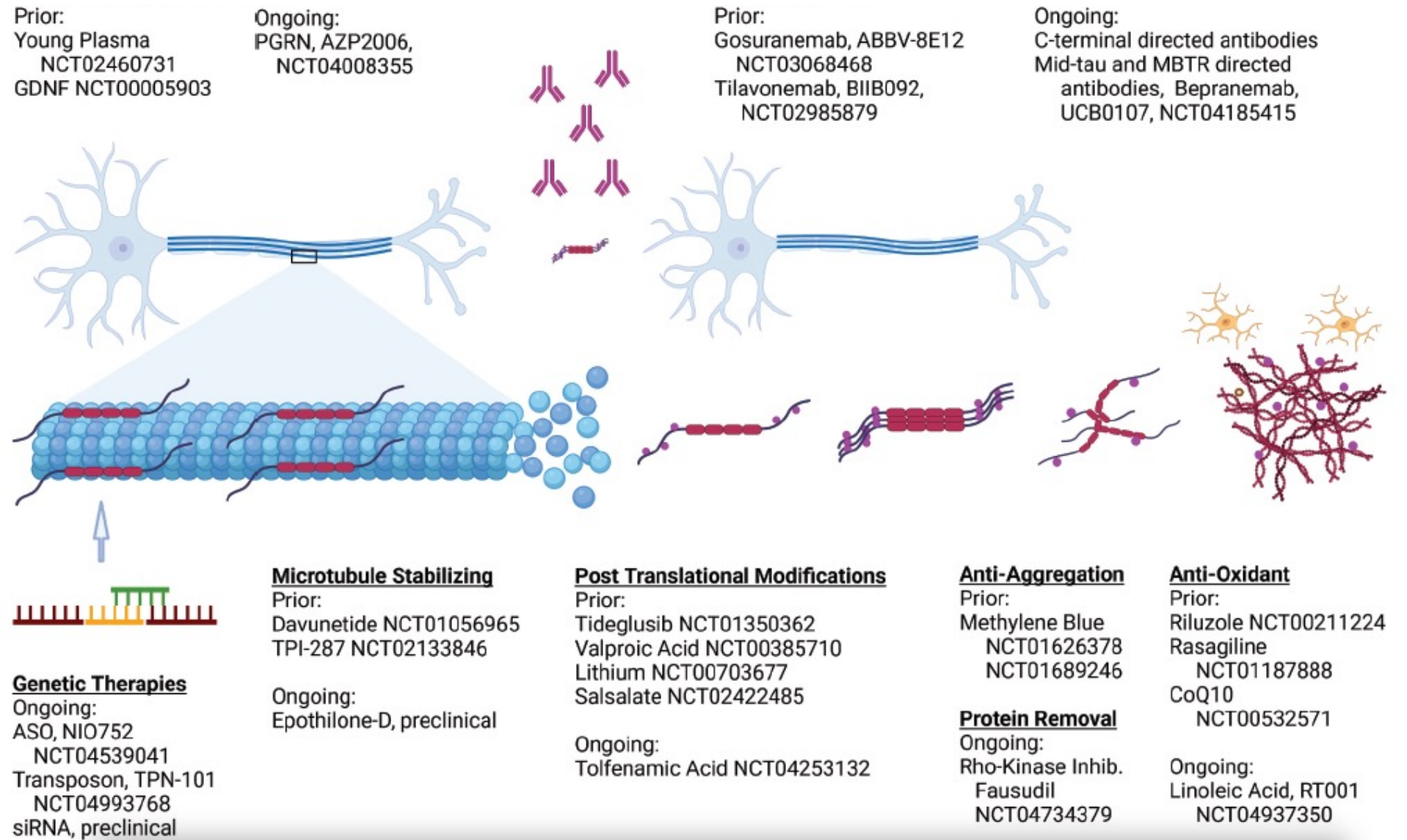
- Occupational Therapy

Cognition:

- Trial cholinesterase inhibitors (PSP-might worsen gait and dysphagia; FTD-might worsen behaviors)

POTENTIAL APPROACHES FOR TAU DRUGS





TAU CLINICAL TRIALS

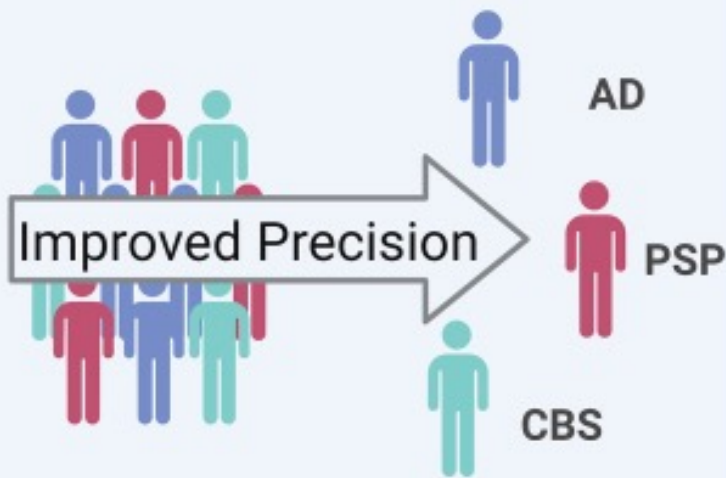
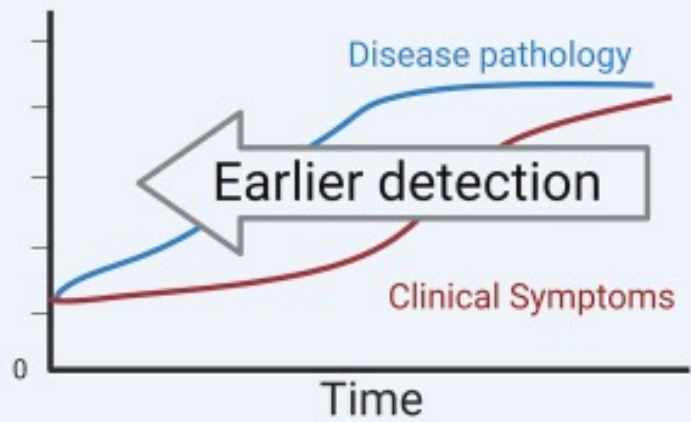
Coughlin & Litvan 2022

TAU ANTIBODY TRIALS

Younes and Sha. *Brain* 2023

Medication	Phase	Indication	Mechanism	Status	Sponsor/Collaborators
E2814	1/2	Mild-mod AD	IgG1 antibody recognizes an HVPGG epitope in the MTBR near the mid-domain of tau	Active, not recruiting	Eisai Inc.
JNJ-63733657	2	Early AD	IgG1 antibody recognizes the MTBR of tau. It has high affinity for tau phosphorylated at residue 217	Recruiting	Janssen
Lu AF87908	1	Early AD	IgG1 antibody to phosphorylated tau protein residues 386-408 and phosphorylated at serine 396 and 404	Recruiting	H. Lundbeck A/S
UCB0107 (Bepranemab)	2	Early AD	IgG4 antibody binds to the central region of tau, recognizing amino acids 235–250 near tau's MTBR	Active, not recruiting	UCB Pharma
APNmAb005	1	AD	Anti-tau IgG antibody recognizes a conformational epitope in tau oligomers	Recruiting	APRINOIA
MK-2214	1	AD	Anti-tau monoclonal antibody	Recruiting	Merck
NIO752	1	AD	Antisense oligonucleotide to tau	Recruiting	Novartis
BIIB080	2	AD	Antisense oligonucleotide to tau	Recruiting	IONIS, Biogen
OLX-07010	1	AD	Small molecule inhibitor of tau self-association	Enrolling by invitation	Oligomerix, Inc
LY3372689	2	Early AD	Small molecule O-GlcNAcase (OGA) enzyme inhibitor. Reduces tau propensity to form toxic aggregates	Active, not recruiting	Eli Lilly and Company
ACI-35	1/2	Early AD	Active vaccine	Active, not recruiting	AC Immune
BIIB076	1	Early AD	IgG1 antibody against mid-region tau	Completed	Biogen, Neurimmune, Eisai Co., Ltd.
BIIB092 (Gosuranemab)	2	PSP	IgG4 monoclonal anti-tau antibody	Completed	Biogen, Bristol-Myers Squibb
LY3303560 (Zagotenemab)	1	Early AD	IgG4 anti-tau antibody	Completed	Eli Lilly and Company
RO7105705 (Semorinemab)	2	Mild-mod AD	IgG4 anti-tau antibody	Completed	AC Immune SA, Genentech
LMTM (TRx0237, LMT-X, Methylene Blue)	3	AD	small-molecule inhibitor of tau aggregation	Completed	TauRx
ACI-3024 (Tau Morphomer™)	1	AD	small-molecule inhibitor of tau aggregation	Completed	AC Immune, Lilly
TPI 287	1	AD	small-molecule inhibitor of tau aggregation	Completed	UCSF
AADvac1	2	AD	Active vaccine	Completed	Axon Neuroscience SE

1. Better Biomarkers



2. Diverse Patient Populations



WAYS TO IMPROVE CLINICAL TRIALS





Summary

- Heterogeneous syndromes can lead to PSP pathology
- Heterogeneous syndromes can lead to CBD pathology
- Cognitive syndromes are non-fluent language, behavioral
- Diagnostic markers are developing
- Treatments are speech therapy, SSRI, OT
- Multiple tau trials occurring- join!