Beyond Alzheimer's disease: overview of other major forms of neurodegenerative dementia

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Disclosure

- I receive research support from
  - NIH K08 AG052648
  - Tau Consortium
  - Bluefield Consortium for Frontotemporal Dementia Research
  - Chan-Zuckerberg Initiative

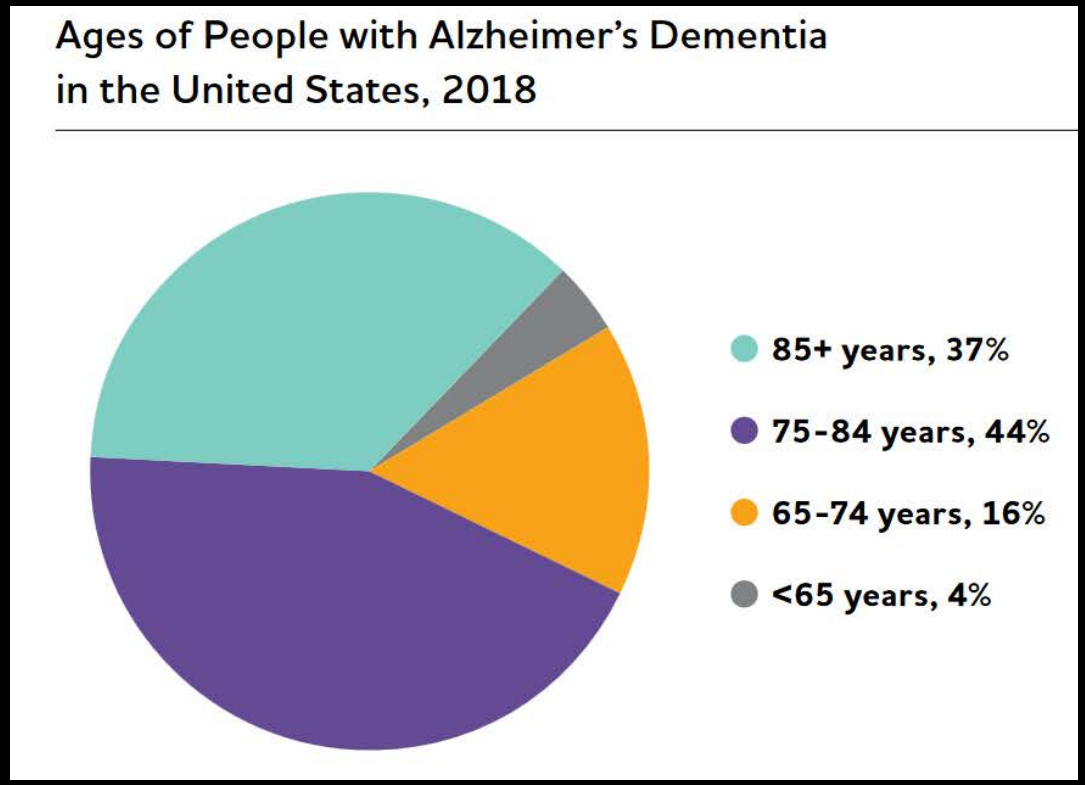
- I have no conflicts of interest related to this presentation

Overview

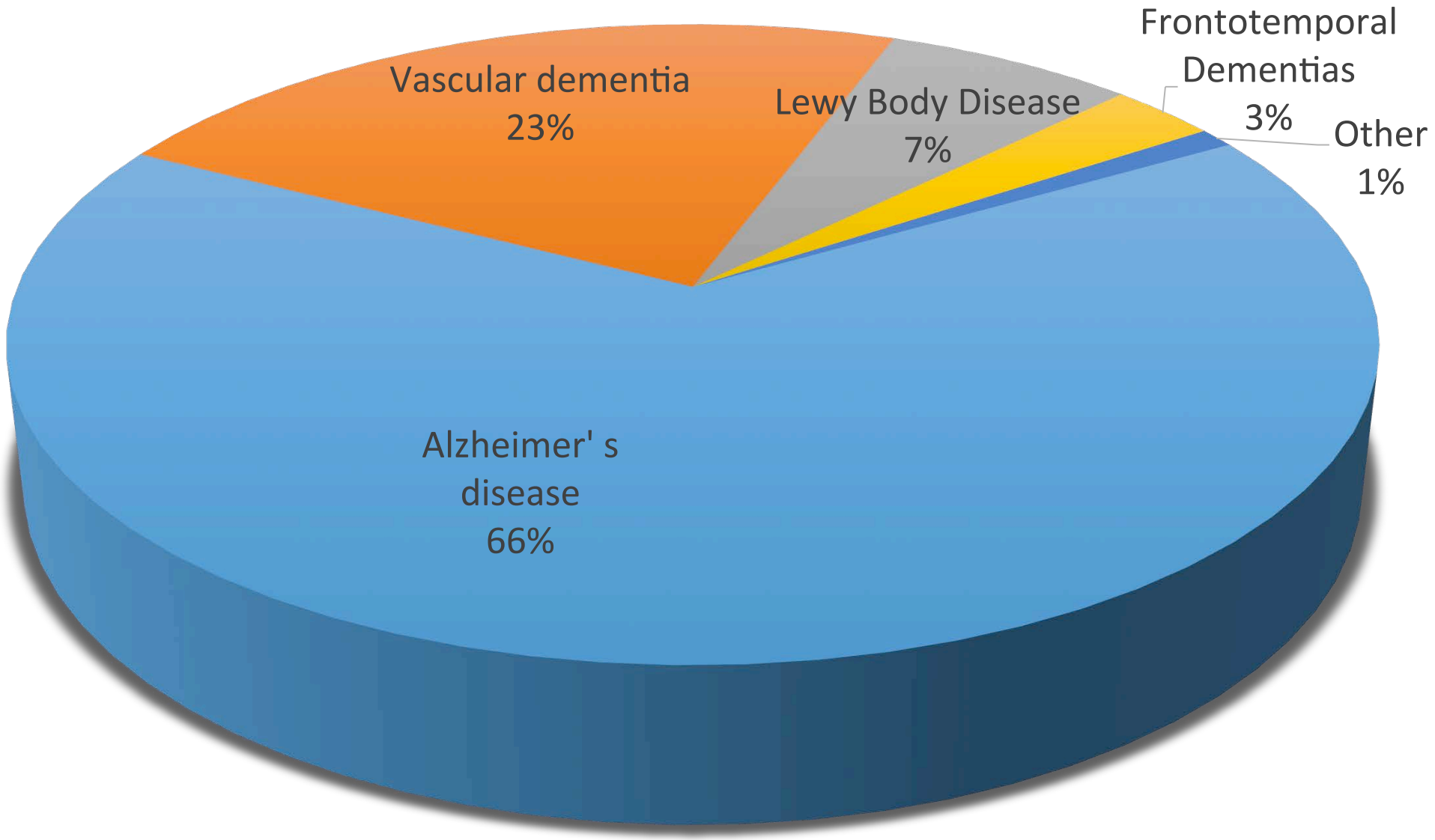
- Prevalence of the most common neurodegenerative dementias
- Lewy-body disease
  - Parkinson's disease & Dementia with Lewy bodies
- The frontotemporal lobar degenerations
- Neurodegenerations of aging
  - Hippocampal sclerosis and LATE
- Is dementia one or multiple diseases?
- Chronic traumatic encephalopathy

Prevalence of Alzheimer's disease

Total prevalence	1800/100,000
<65 yo	72
Age 65-74	288
Age 75-84	792
>85 yo	666



Prevalence of neurodegenerative dementias



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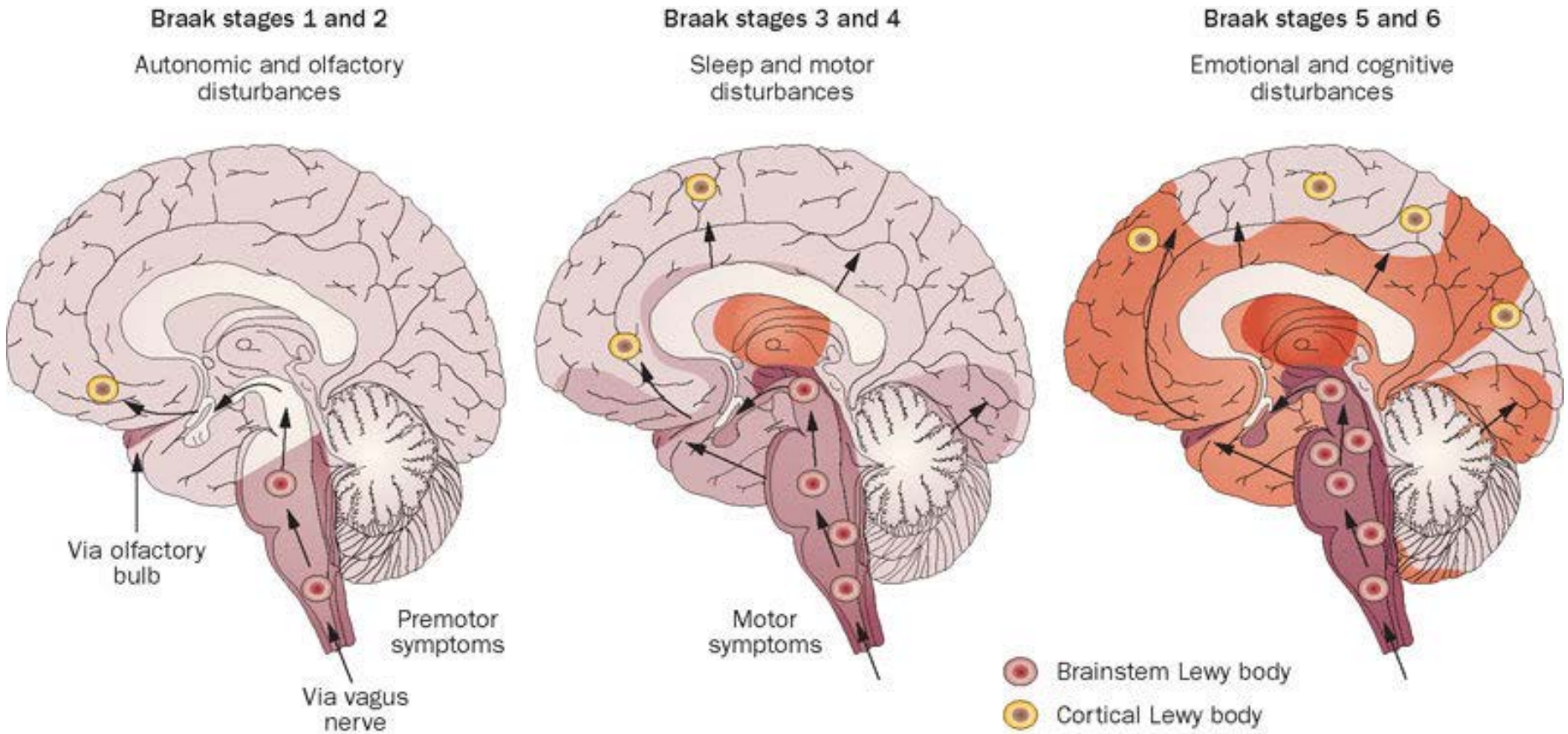
Lewy body disease – alpha-synucleinopathy

- Parkinson's disease
  - Resting tremor
  - Rigidity
  - Bradykinesia
  - Postural instability
  - Asymmetric onset
  - Responsiveness to L-DOPA
- Prevalence:
  - 41/100.000 at age 40-49
  - 1900/100.000 >80 years
- PD dementia
  - 30-40% of all PD cases
  - 80% after 20-years duration

- Dementia with Lewy bodies
  - Attention/executive and visuospatial deficit
  - Cognitive fluctuations
  - Visual hallucinations
  - REM-sleep behavior disorder
  - Parkinsonism
- Prevalence: 7% of all cases of dementia

Other common symptoms of LBD

- Symptoms of autonomic dysfunction (constipation, sweating abnormalities, sexual dysfunction, etc.)
- Decreased sense of smell
- Seborrheic dermatitis
- Anxiety/depression
- Hypophonia
- Decreased facial expression
- Delusional thinking


Braak stages 1 and 2
Autonomic and olfactory disturbances
Via olfactory bulb
Premotor symptoms
Via vagus nerve
Braak stages 3 and 4
Sleep and motor disturbances
Motor symptoms
Braak stages 5 and 6
Emotional and cognitive disturbances
Brainstem Lewy body
Cortical Lewy body

Braak Stages of PD

- Stage I — Olfactory bulb
  Nuclei IX and X in medulla
- Stage II — Intermediate reticular zone, lower raphe, coeruleus-complex
- Stage III — Substantia nigra,amygdala,hippocampus
- Stage IV — Temporal mesocortex and allocortex
- Stages V,VI — High order sensory association areas of neocortex and prefrontal cortex.

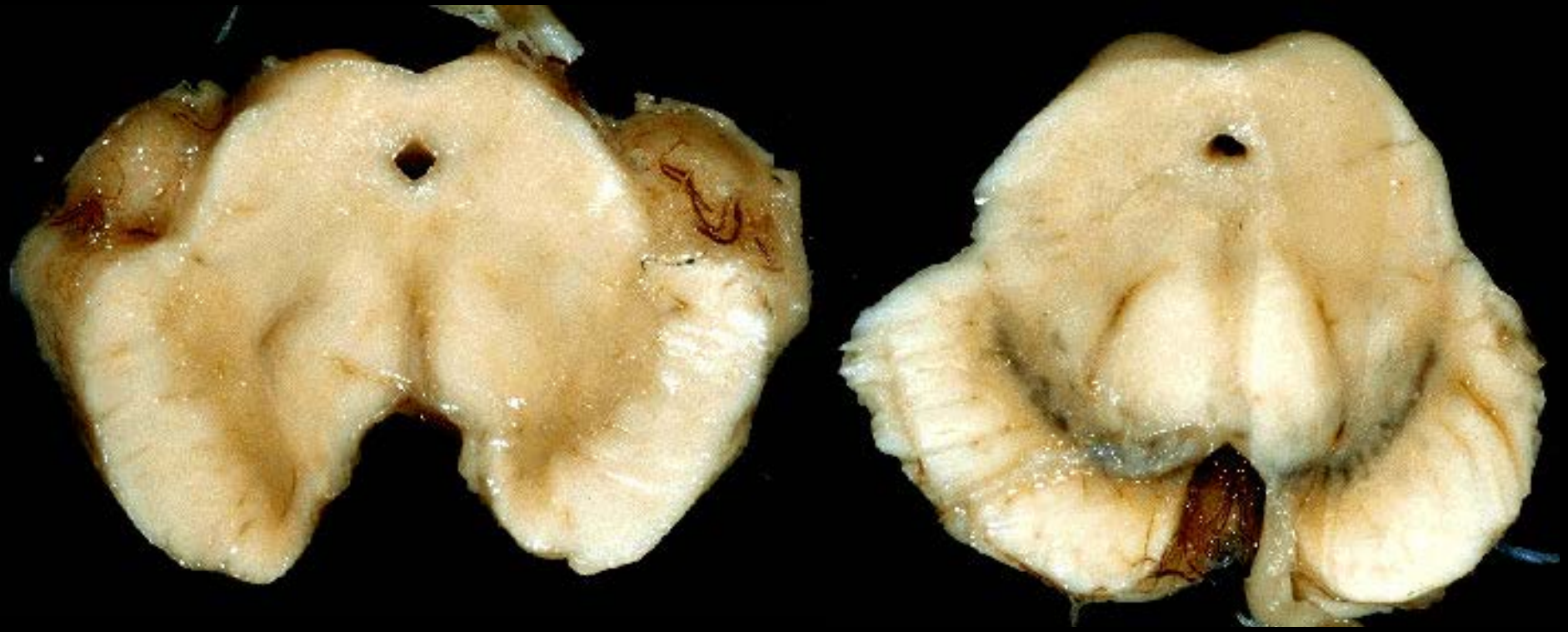
Non-motor signs

Motor signs

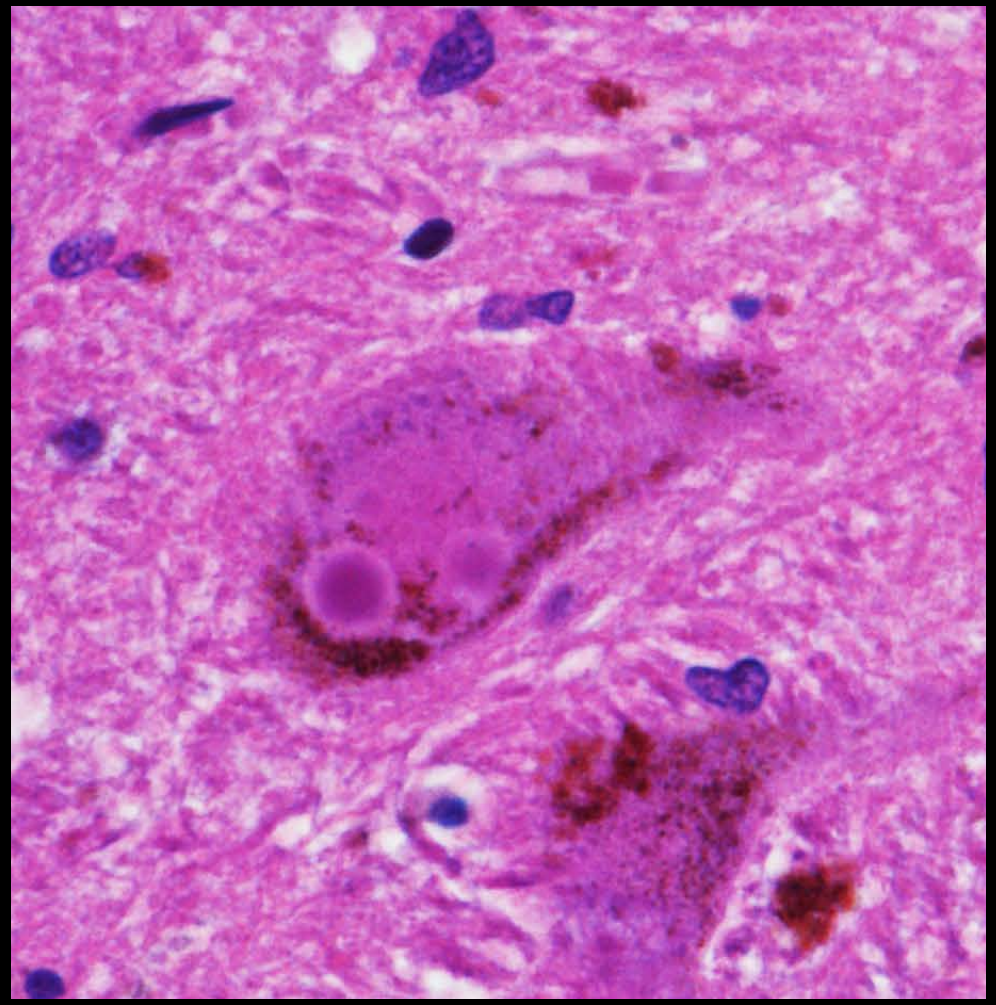
Cognition, emotion

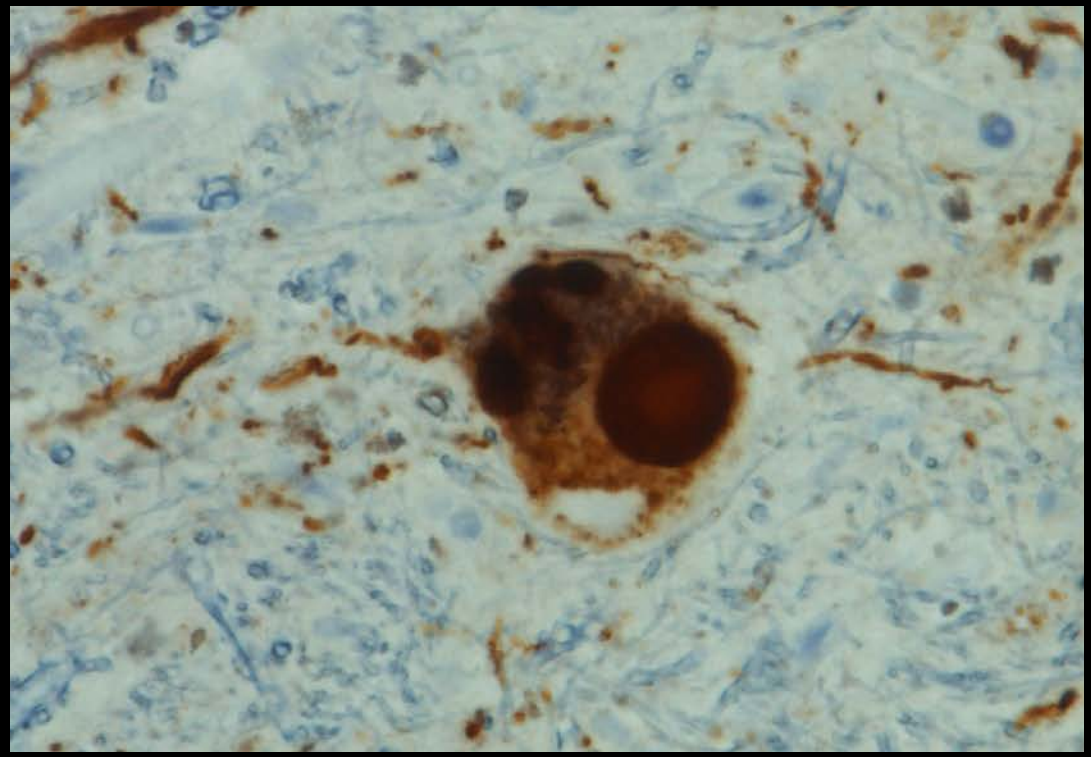
Braak H et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003

Substantia nigra degeneration



Lewy bodies





alpha-synuclein immunohistochemistry

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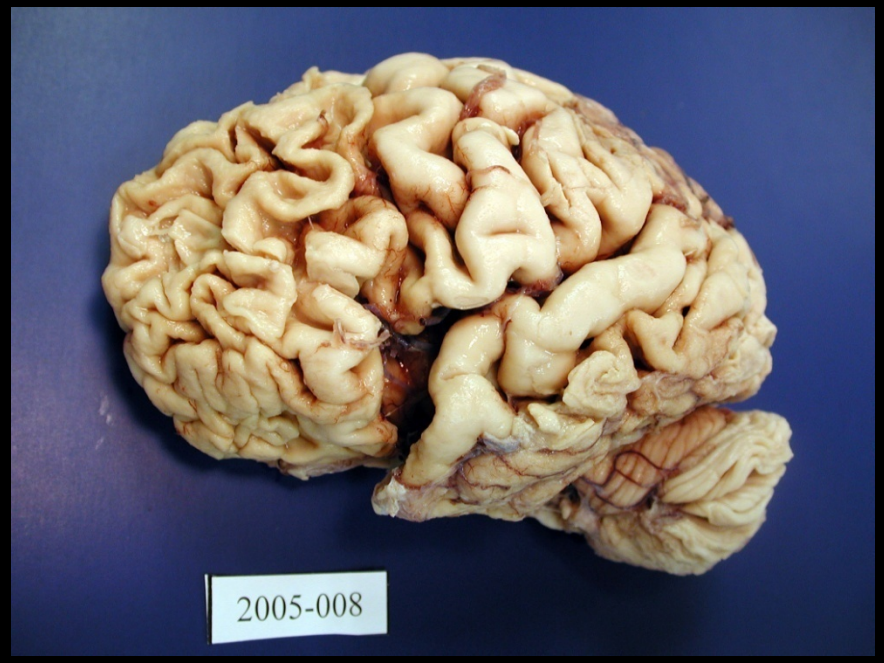
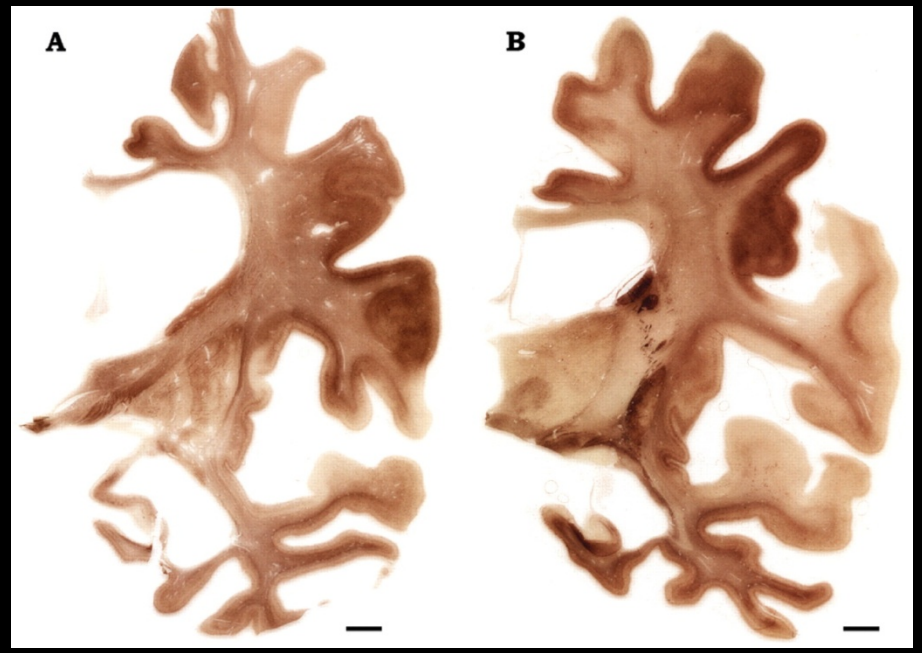
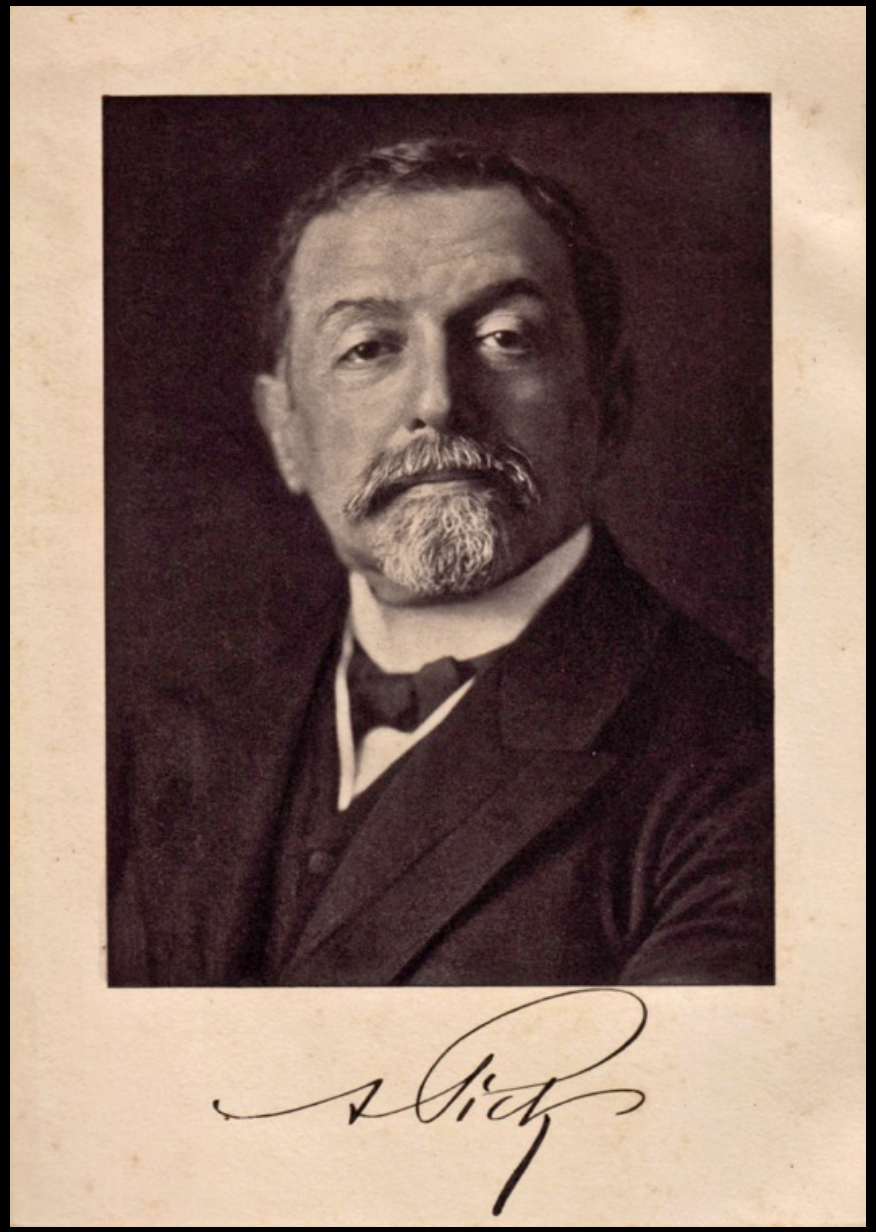
Frontotemporal Lobar Degeneration (FTLD)

- Neurodegenerative process characterized by predominant neuronal loss and gliosis (atrophy) of the frontal and temporal lobes of the brain





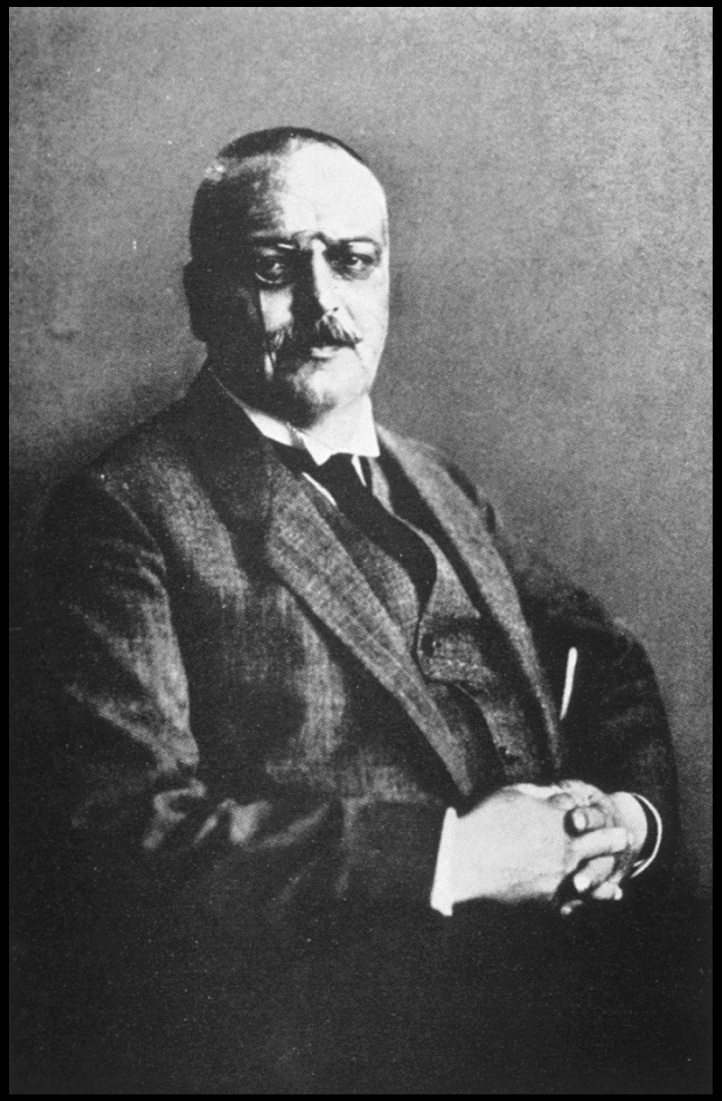


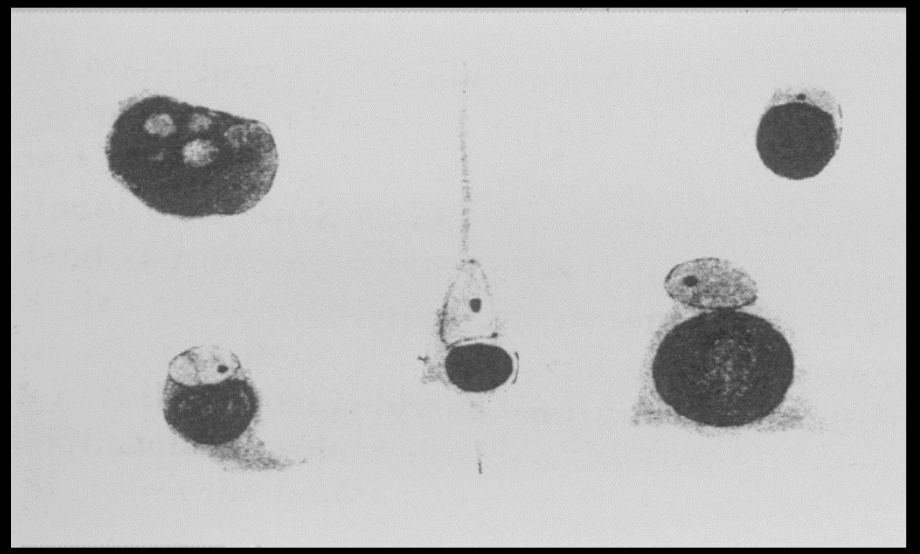
Arnold Pick

- …. circumscribed lobar (frontotemporal) atrophy ….

Pick A. *Prager Med Wochenschr* 1892;17:165-167

Alois Alzheimer defines Pick's disease





- …. absence of plaques, presence of round-shaped neurofibrillary tangles (Pick bodies), and swollen neurons ….

Alzheimer A. *Z ges Neurol Psychiat* 1911;4:356-385

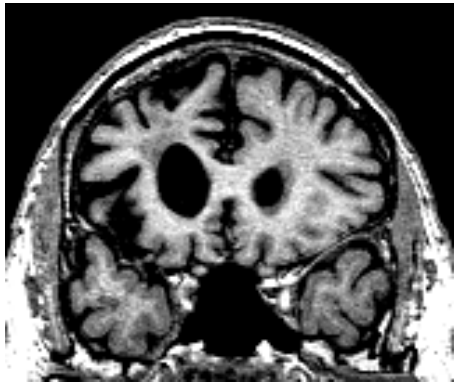
Prevalence of neurodegenerative dementias

Pathological entity	Prevalence
Alzheimer's Disease	1800/100,000
<65 yo	72
Age 65-74	288
Age 75-84	792
>85 yo	666
PDD-LBD	~800
Frontotemporal dementias	15-50

- Common cause pre-senile dementia
  - 1:1 with AD 45–64 years (Ratnavalli 2002)
  - More common than AD <60 years (Knopman 2004)
- Common in elderly?
  - 3% prevalence 80–90 (2003 Skoog)

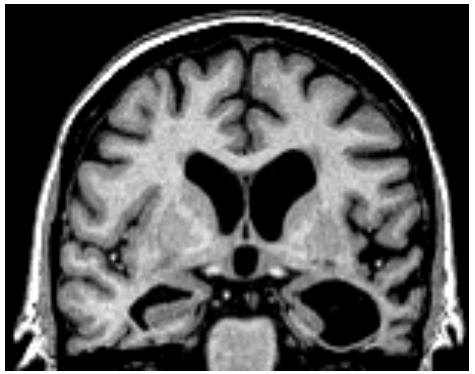
3 types frontotemporal dementia

Behavioral variant

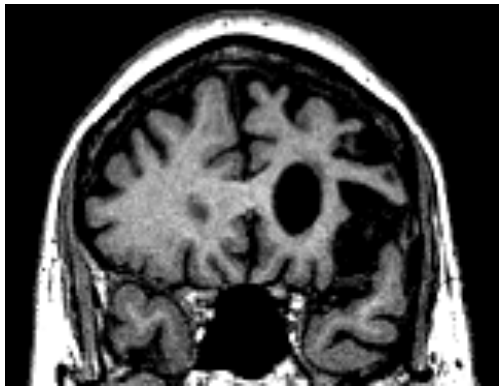


Language variants

Semantic variant



Non-fluent variant



International Research Criteria for Behavioral Variant FTD

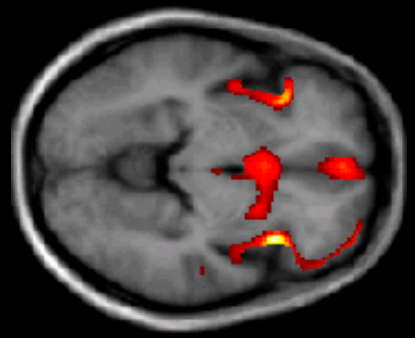
1. Early (2-3 yrs) behavioral disinhibition
2. Early (2-3 yrs) apathy or inertia
3. Early (2-3 yrs) loss of emotional reactivity/sympathy and empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile

7. Frontal or anterior temporal atrophy on MRI
8. Presence of known mutation

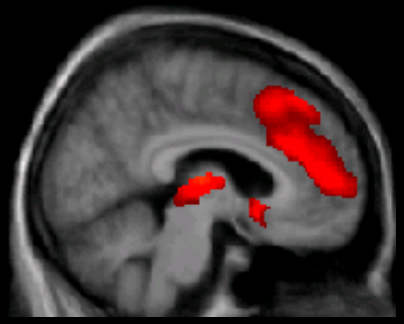
Rascovsky et al. Brain 2011

Regions Involved in Emotion

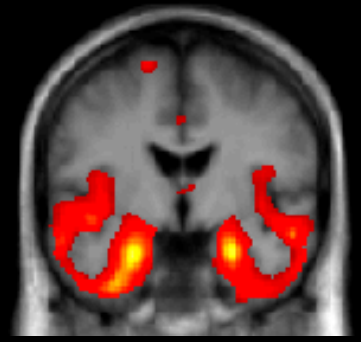
Insula

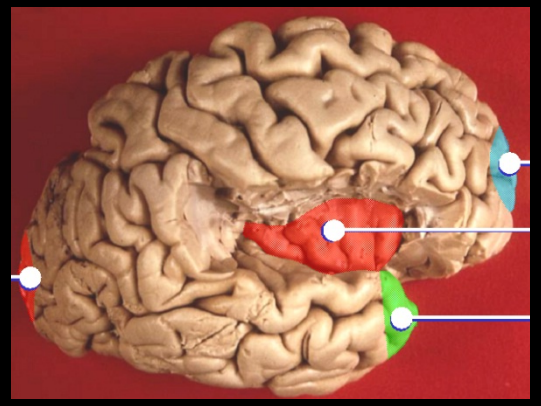


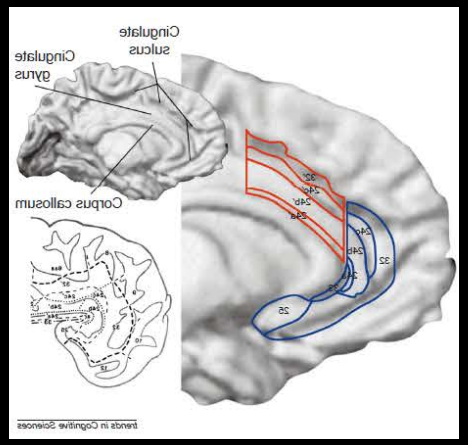
Anterior

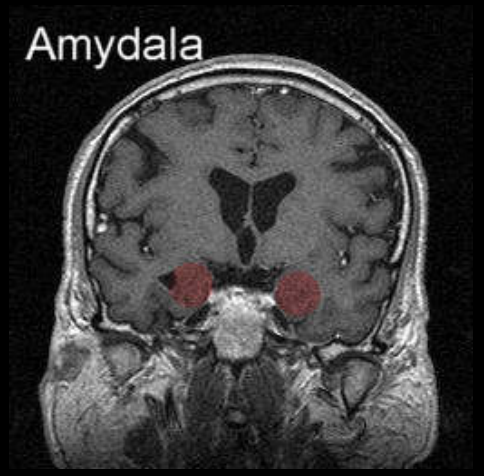


Amygdala









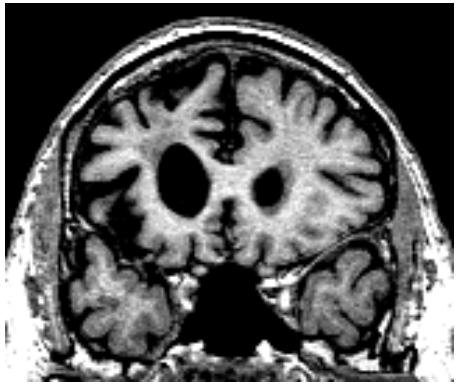
Emotional Deficits in FTD

- Lack of concern for loved one's illness
- Cruelty to children, animals elderly
- Lack of concern when others are sad
- Rude comments to others
- Lose respect for intrapersonal space
- "Disgusting" behaviors
- Diminished response to pain

Behavioral Variant FTD

3 types frontotemporal dementia

Behavioral variant



Language variants

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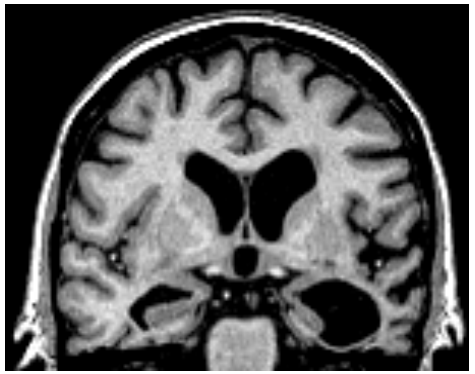
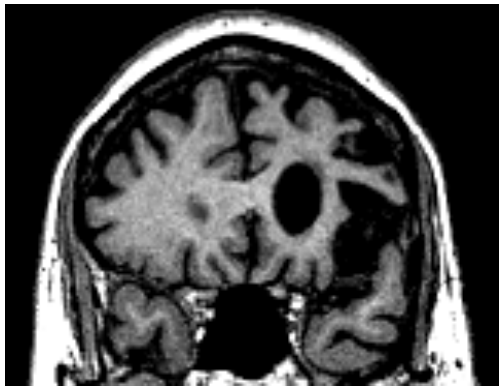
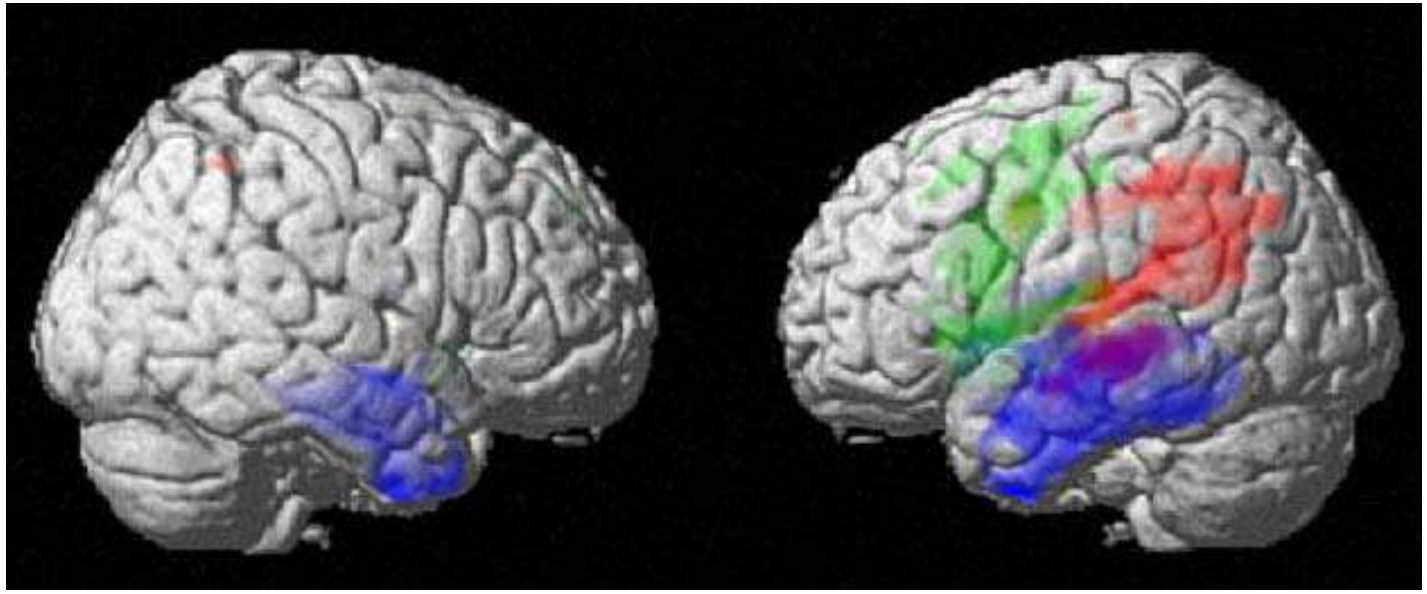


Non-fluent variant



Primary Progressive Aphasia (PPA)



= Semantic dementia FTD (TDP-43)

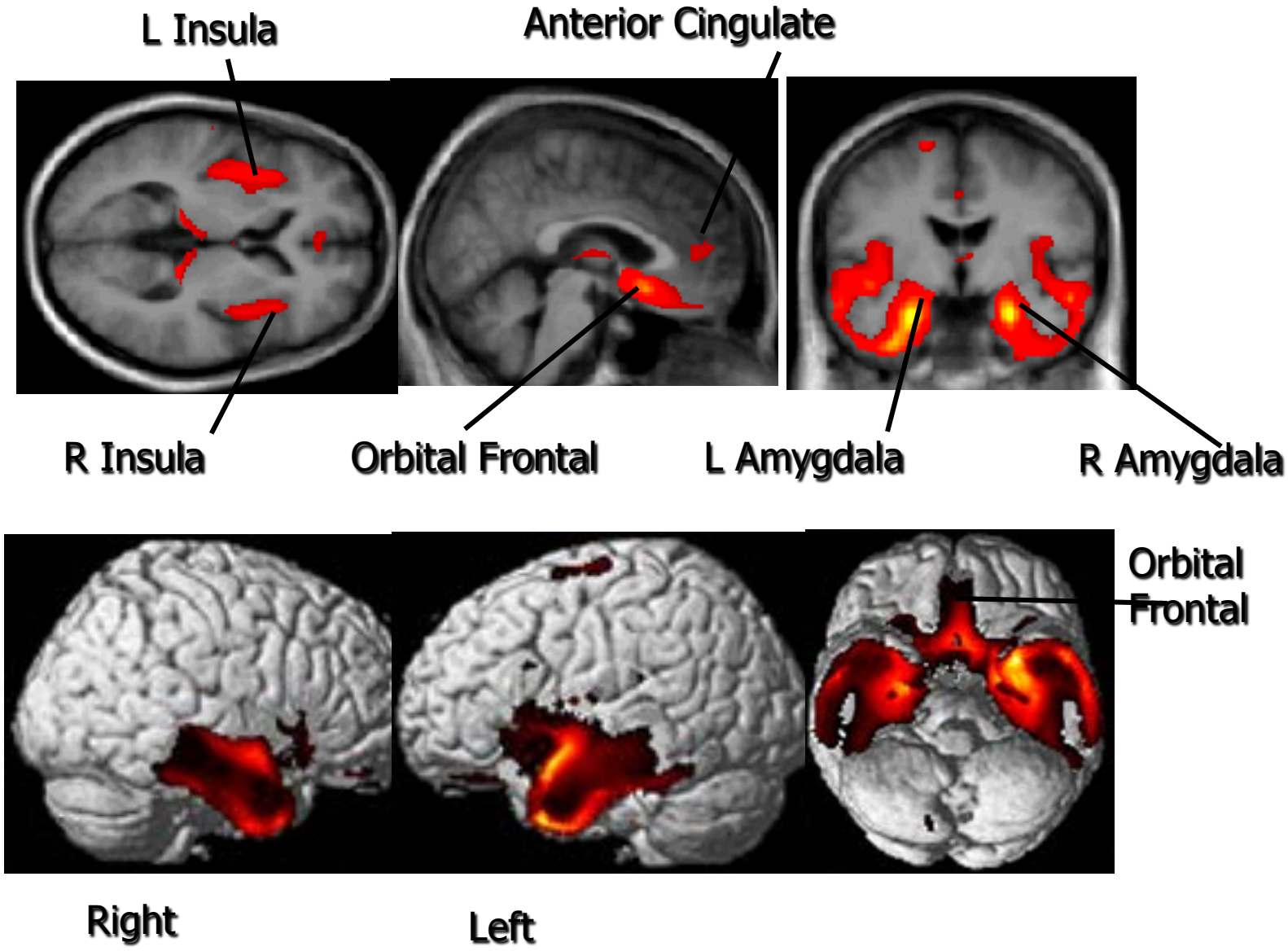
= Logopenic – AD (AB42, tau)

= Non-fluent CBD, PSP (tau)

Mesulam et al. *Ann Neurol.* 2001

Gorno-Tempini ML et al. *Ann Neurol*. 2004

Semantic Dementia vs Controls

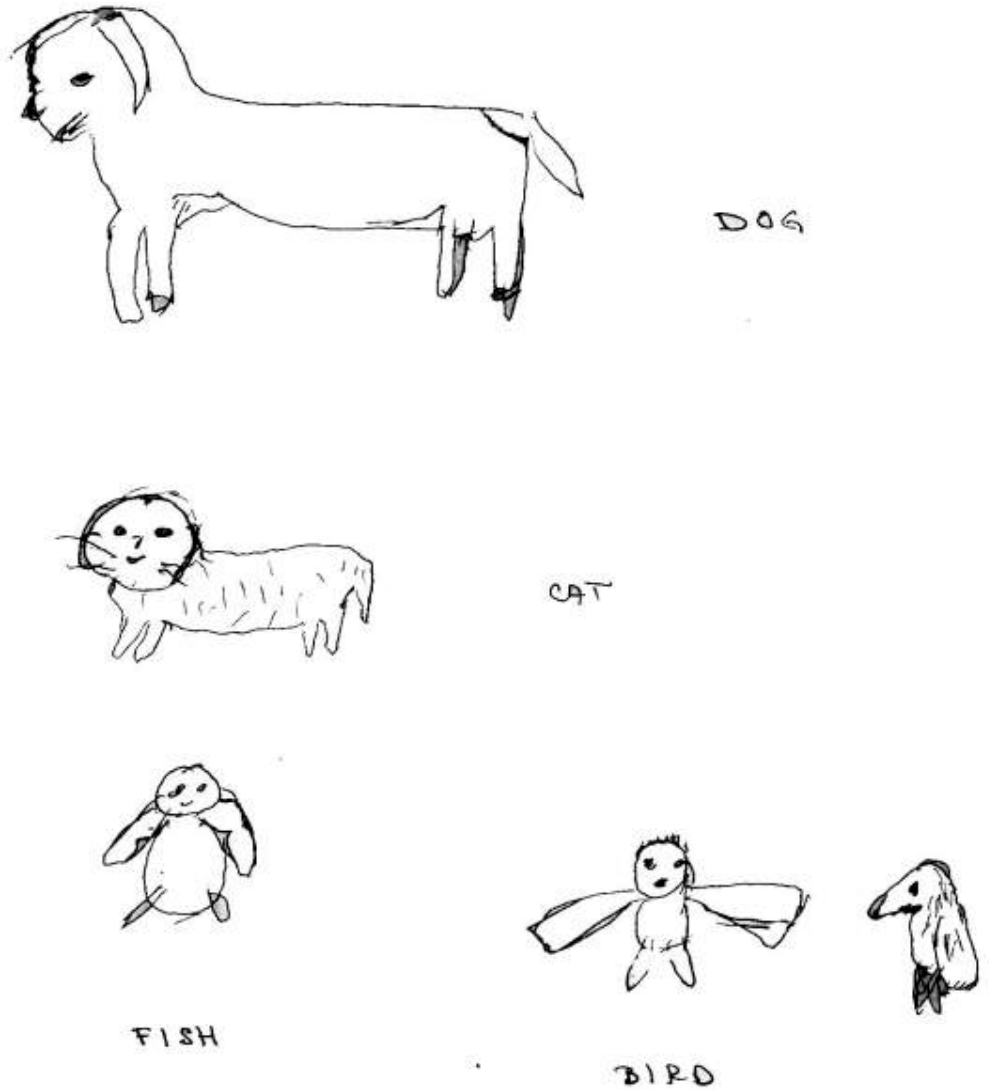


Rosen et al. *Brain* 2002;125:2286-2295

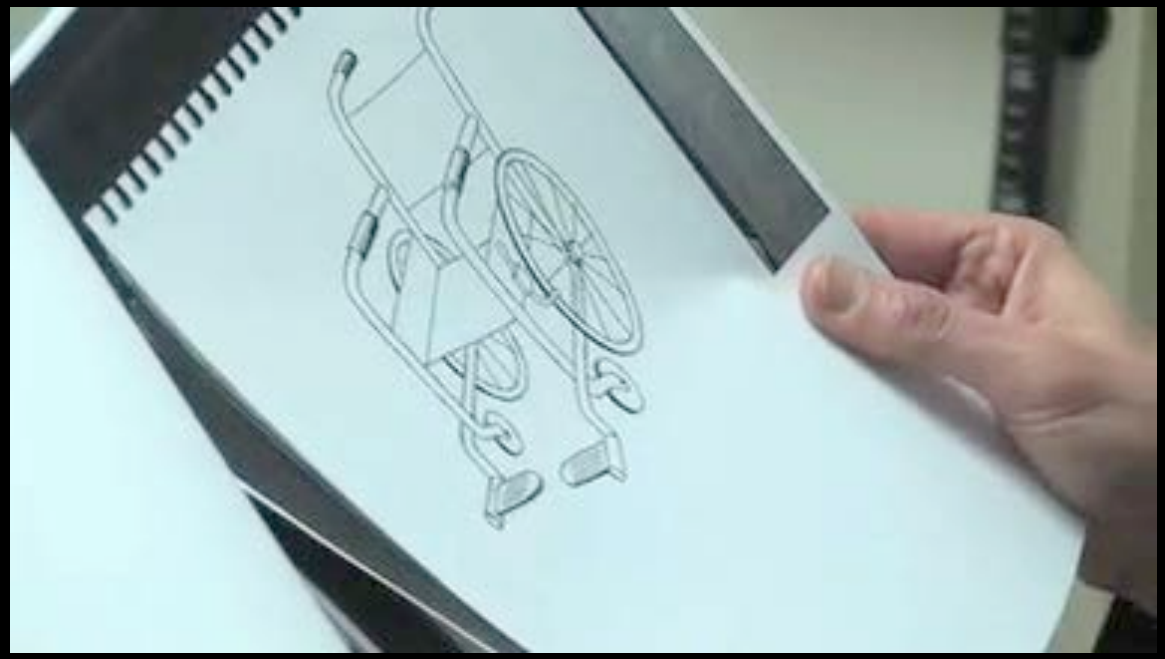
Semantic variant PPA (svPPA)
left-temporal pole degeneration

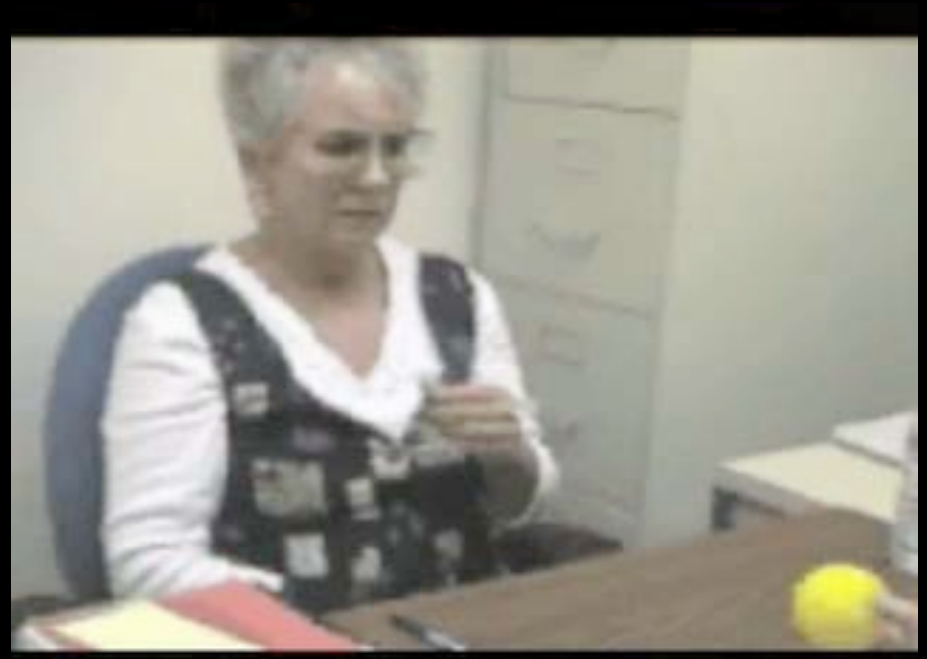
- Impaired confrontation naming
- Loss of word meaning (more severe for low frequency words)
- Impaired object knowledge (more severe for low frequency items)
- Surface dyslexia (regularization of irregular phonetic words)
  - Colonel, knight, yacht, etc.
- Spared repetition
- Spared grammar
- Often hyper-verbal, fluent aphasia

Animals Become Prototypical



Semantic dementia



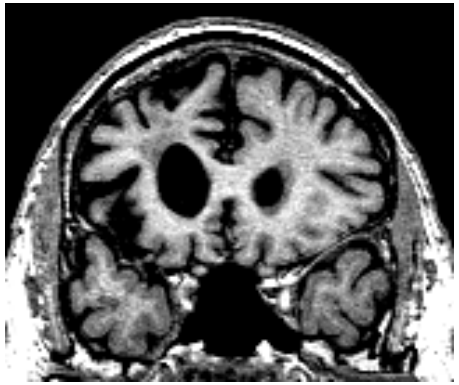


Right-temporal pole degeneration
Behavioral variant FTD with additional peculiar features

- Loss of knowledge of famous faces
- increased interest towards word-search games
- Extremely rigid and stereotypic behavior
- Often cold, distinct, anti-social personality
- Hyper-religiosity

3 types frontotemporal dementia

Behavioral variant



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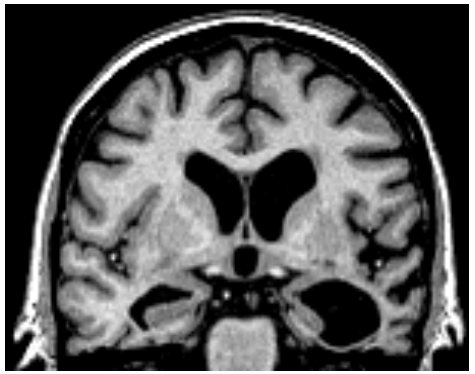
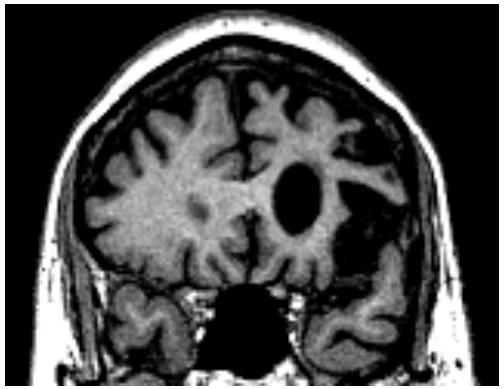


Non-fluent variant



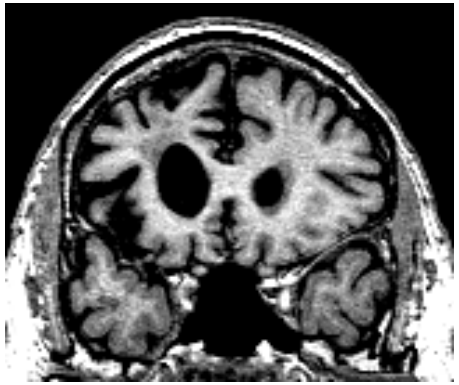
Nonfluent variant PPA (nfvPPA)
left posterior frontoinsular atrophy

- Agrammatism
- Effortful , halting speech with sound errors and distortions
- Impaired comprehension of complex sentences
- Spared single word comprehension
- Spared object knowledge

Nonfluent variant PPA (nfvPPA)

3 types frontotemporal dementia

Behavioral variant



Language variants

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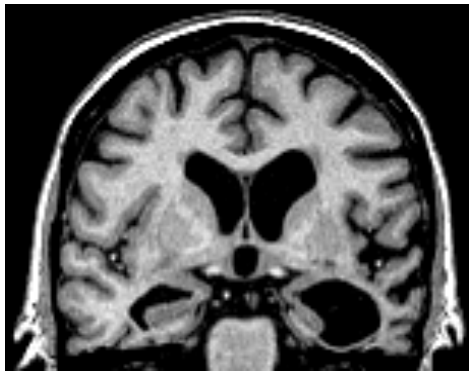

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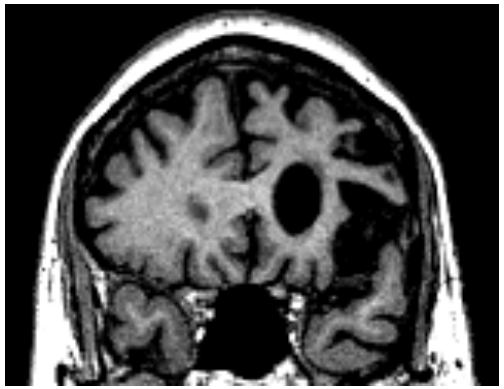


3 more types of frontotemporal dementia…

- FTD with motor neuron disease (FTD-MND)
- Progressive supranuclear palsy syndrome (PSP-S)
- Corticobasal syndrome (CBS)

FTD with motor neuron disease (FTD-MND)

- Amyotrophic lateral sclerosis (ALS)
  - 10% of FTD patients develop ALS
  - Most ALS patients develop cognitive impairment

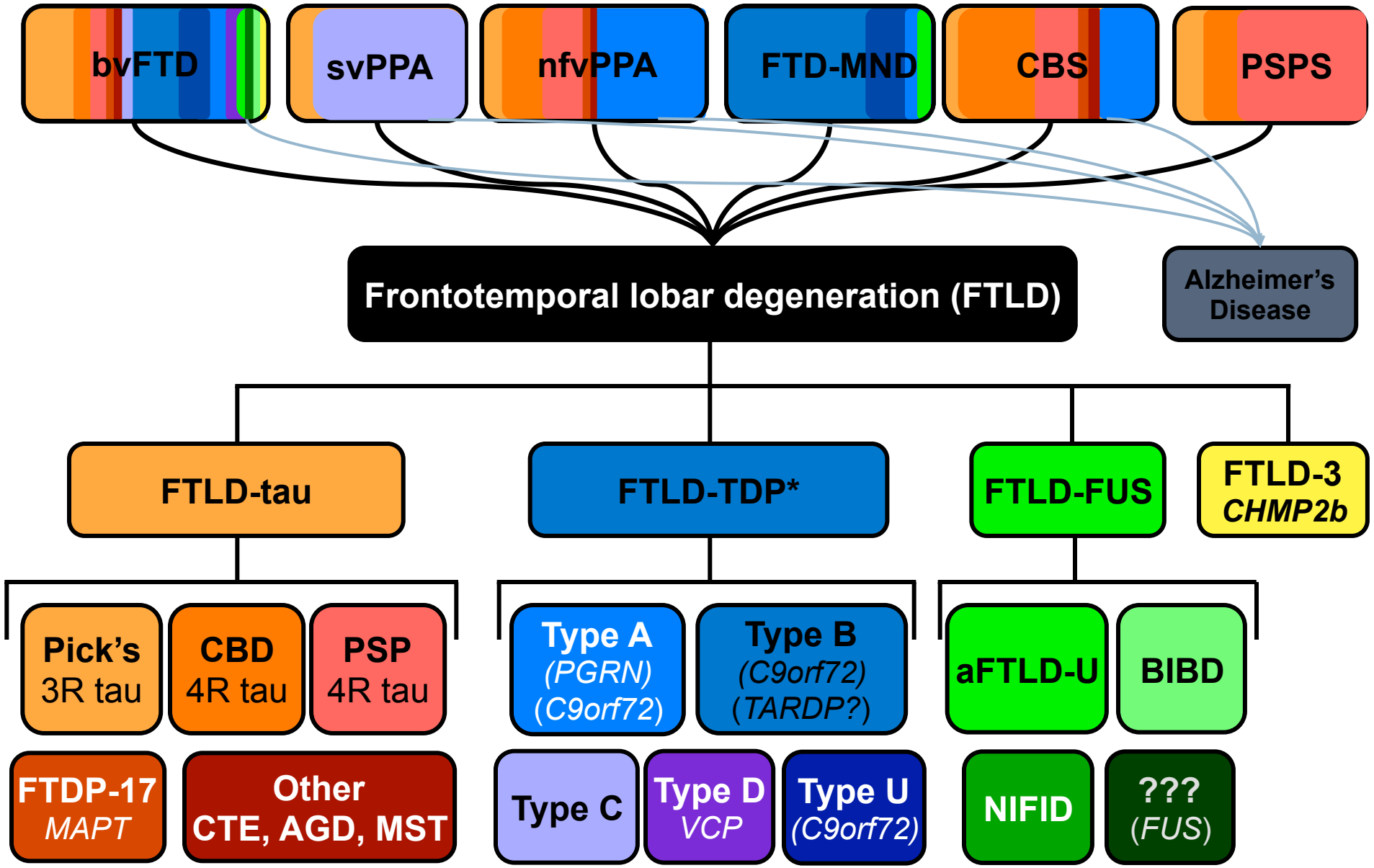
- Progressive muscle weakness and degeneration leading to death within 3 years on average

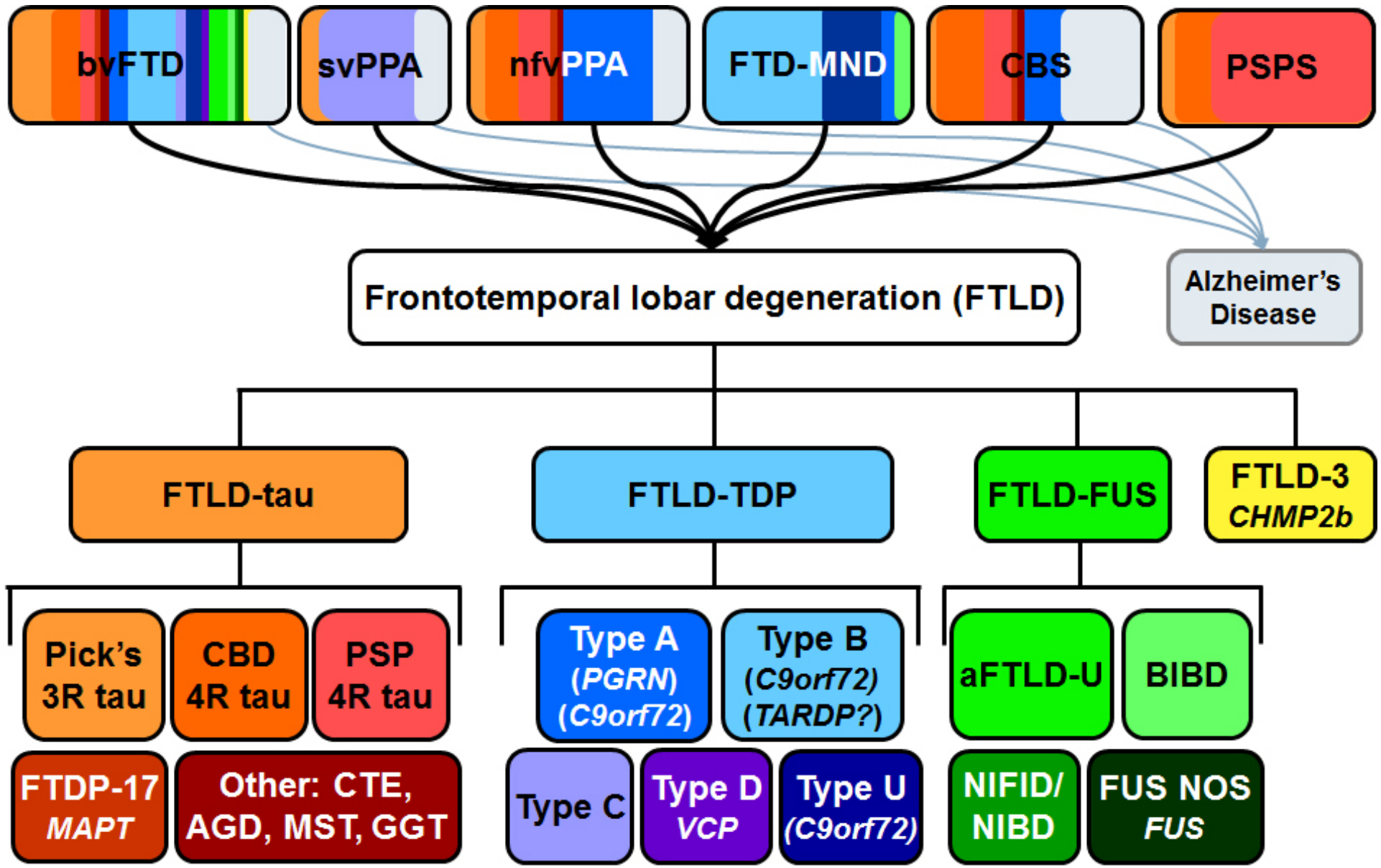
Progressive supranuclear palsy syndrome (PSP-S)
Richardson's syndrome

- Early falls
- Eye movement abnormalities
- Axial rigidity
- Parkinsonian features not responsive to L-DOPA
- Executive dysfunction
- Increased impulsivity
- Disrupted sleep pattern

Corticobasal syndrome (CBS)

- Asymmetric limb rigidity, dystonia, myoclonus
- Oral or limb apraxia
- Cortical sensory deficits
  - astereognosis
  - agraphesthesia
- Alien-limb phenomenon


bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSPS
Frontotemporal lobar degeneration (FTLD)
Alzheimer's Disease
FTLD-tau
FTLD-TDP*
FTLD-FUS
FTLD-3
CHMP2b
Pick's
3R tau
CBD
4R tau
PSP
4R tau
Type A
(PGRN)
(C9orf72)
Type B
(C9orf72)
(TARDP?)
aFTLD-U
BIBD
FTDP-17
MAPT
Other
CTE, AGD, MST
Type C
Type D
VCP
Type U
(C9orf72)
NIFID
???
(FUS)


bvFTD
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Frontotemporal lobar degeneration (FTLD)
Alzheimer's Disease
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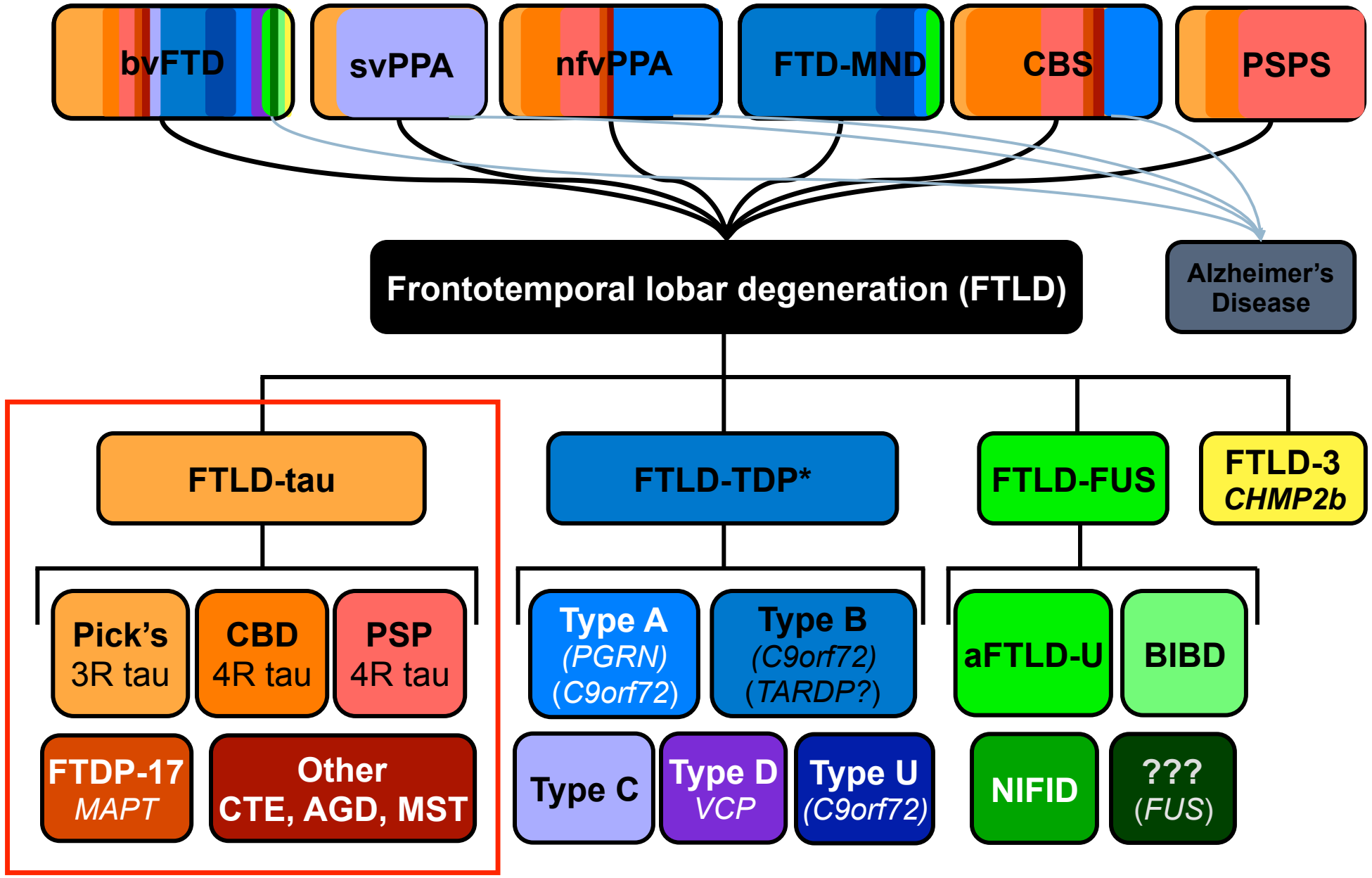
FTLD-TDP
FTLD-FUS
FTLD-3
CHMP2b
Pick's 3R tau
CBD 4R tau
PSP 4R tau
FTDP-17 MAPT
Other: CTE, AGD, MST, GGT
Type A (PGRN) (C9orf72)
Type B (C9orf72) (TARDP?)
Type C
Type D VCP
Type U (C9orf72)
aFTLD-U
BIBD
NIFID/ NIBD
FUS NOS FUS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Type U
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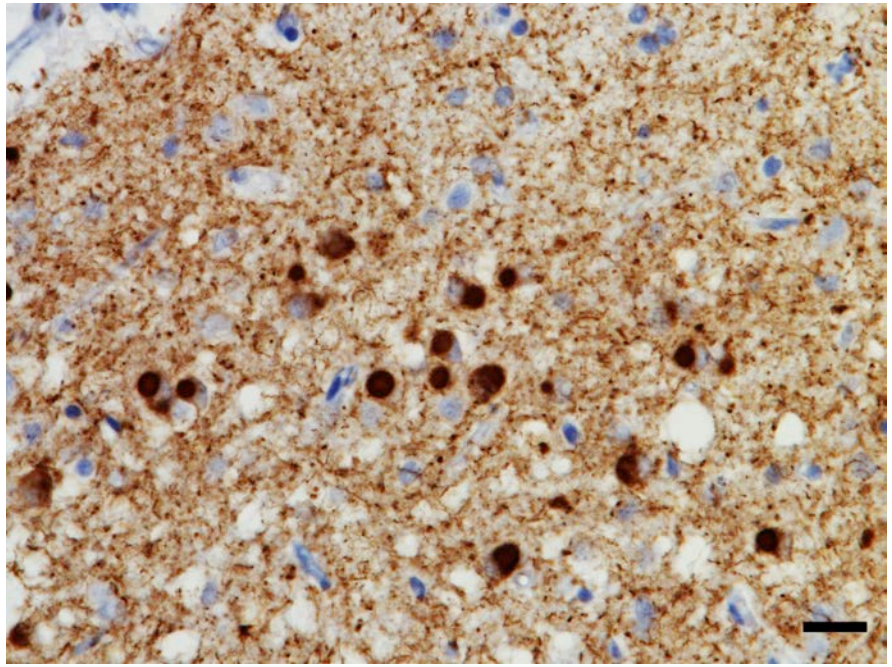
NIFID
???
(FUS)

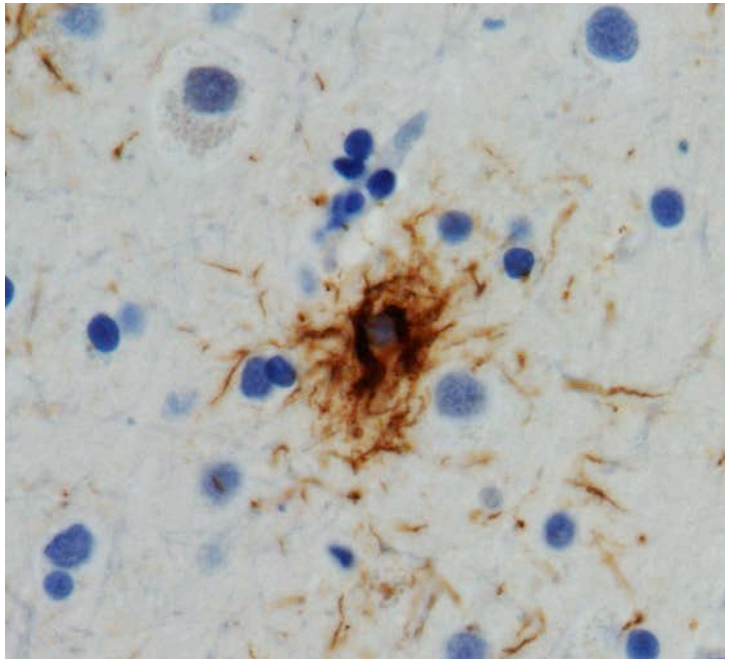
FTLD-tau: the tauopathies (40% of FTLD)

Pick's disease



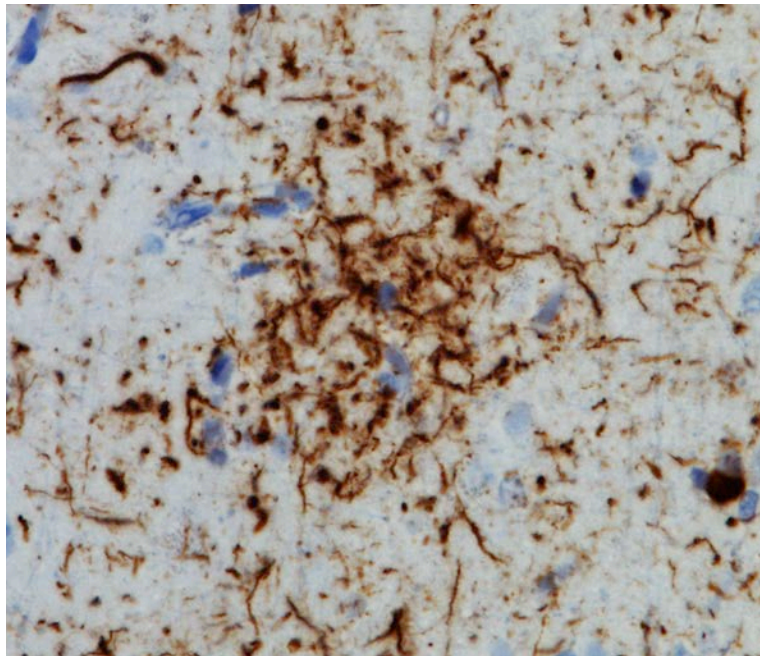
Pick bodies

Progressive supranuclear palsy

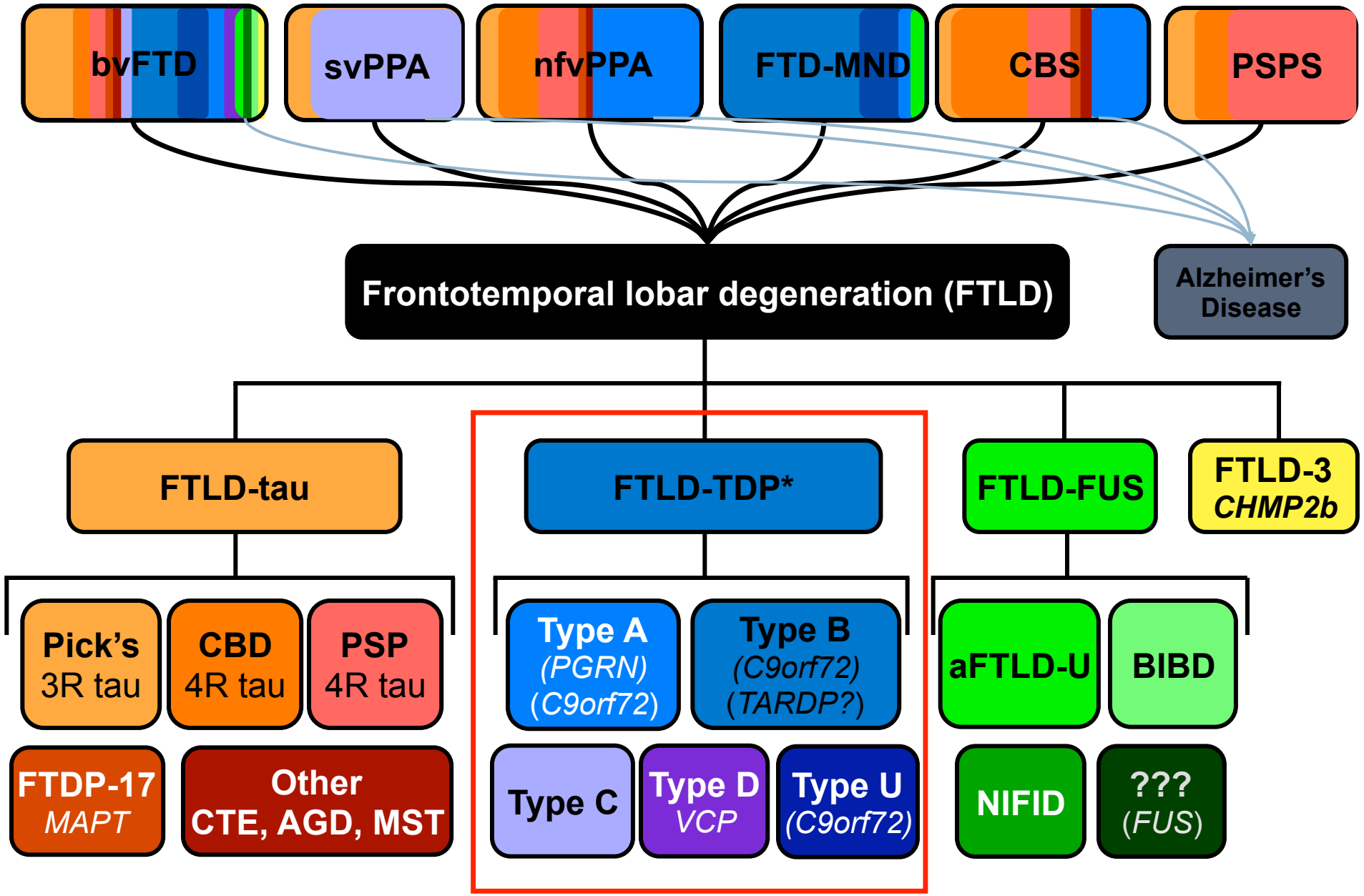


Tufted astrocyte

Corticobasal degeneration

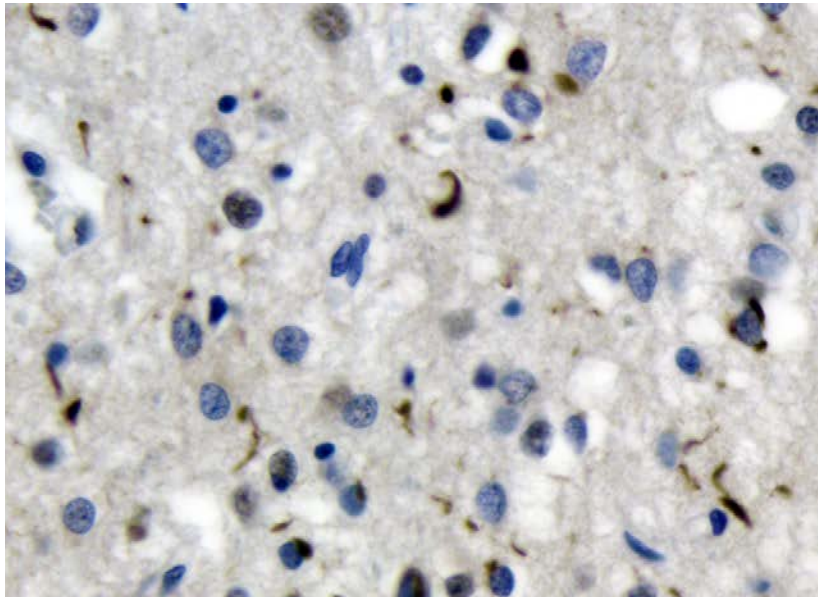


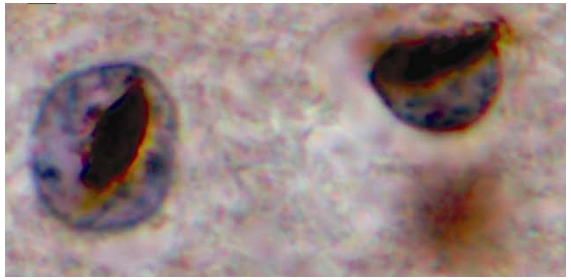
Astrocytic plaque


bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSPS
Frontotemporal lobar degeneration (FTLD)
Alzheimer's Disease
FTLD-tau
FTLD-TDP*
FTLD-FUS
FTLD-3
CHMP2b
Pick's
3R tau
CBD
4R tau
PSP
4R tau
Type A
(PGRN)
(C9orf72)
Type B
(C9orf72)
(TARDP?)
aFTLD-U
BIBD
FTDP-17
MAPT
Other
CTE, AGD, MST
Type C
Type D
VCP
Type U
(C9orf72)
NIFID
???
(FUS)

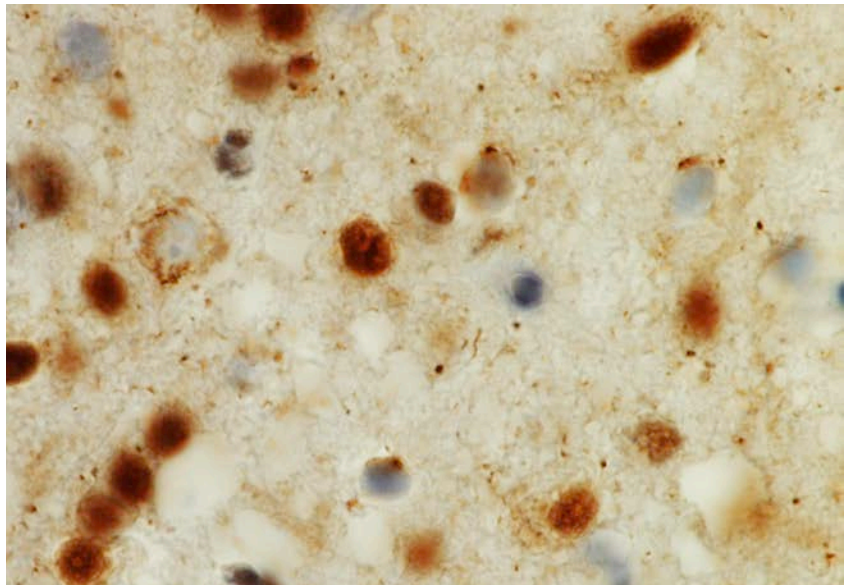
FTLD-TDP43 (55% of FTLD)

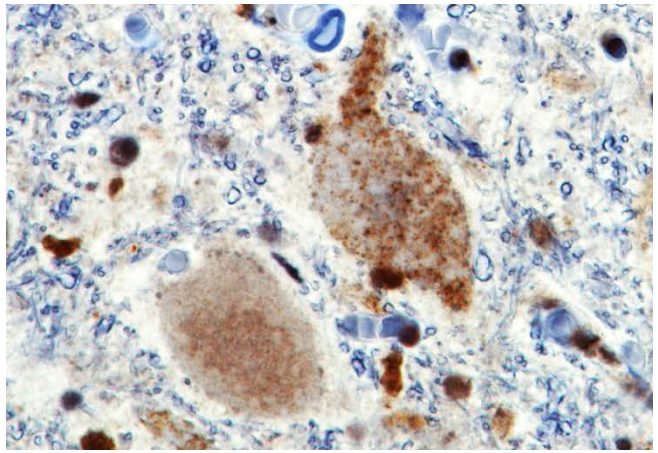
Type A



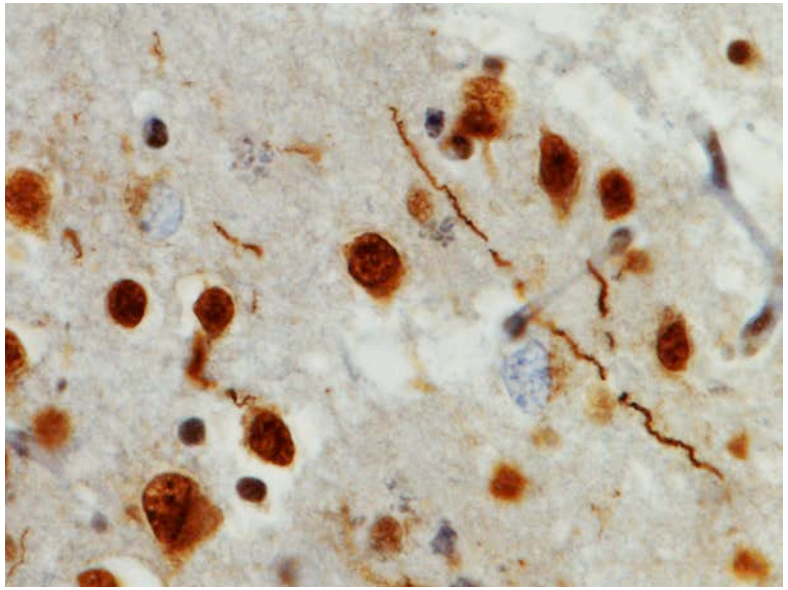


Type B

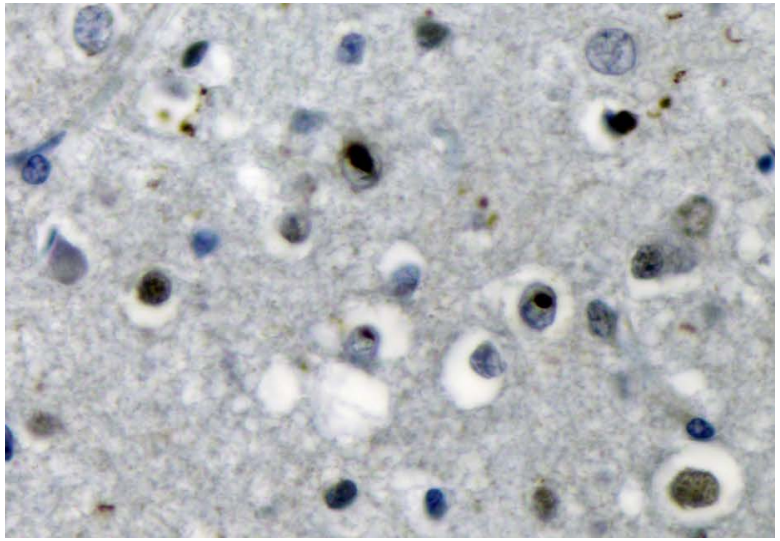


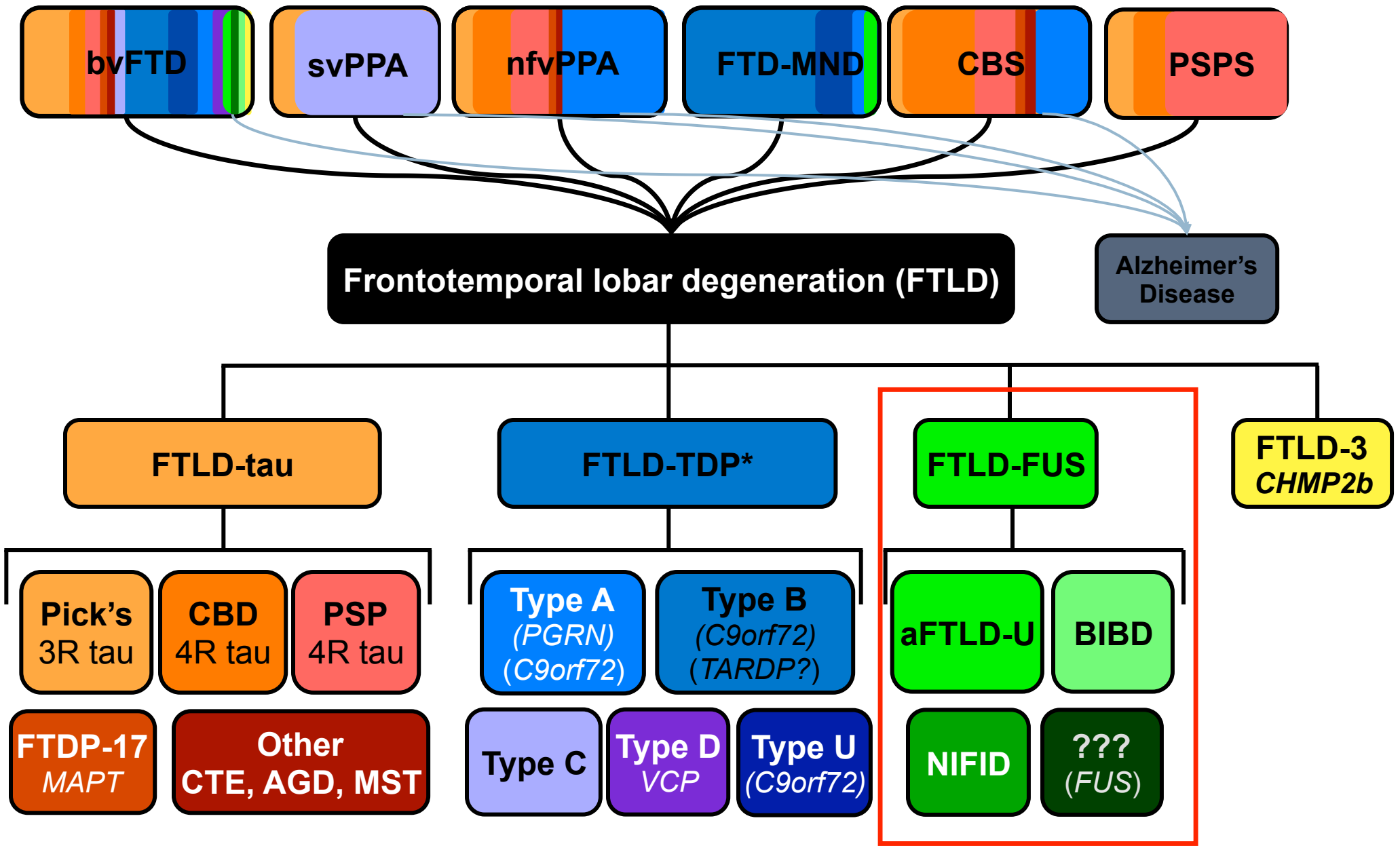


Type C



Type D

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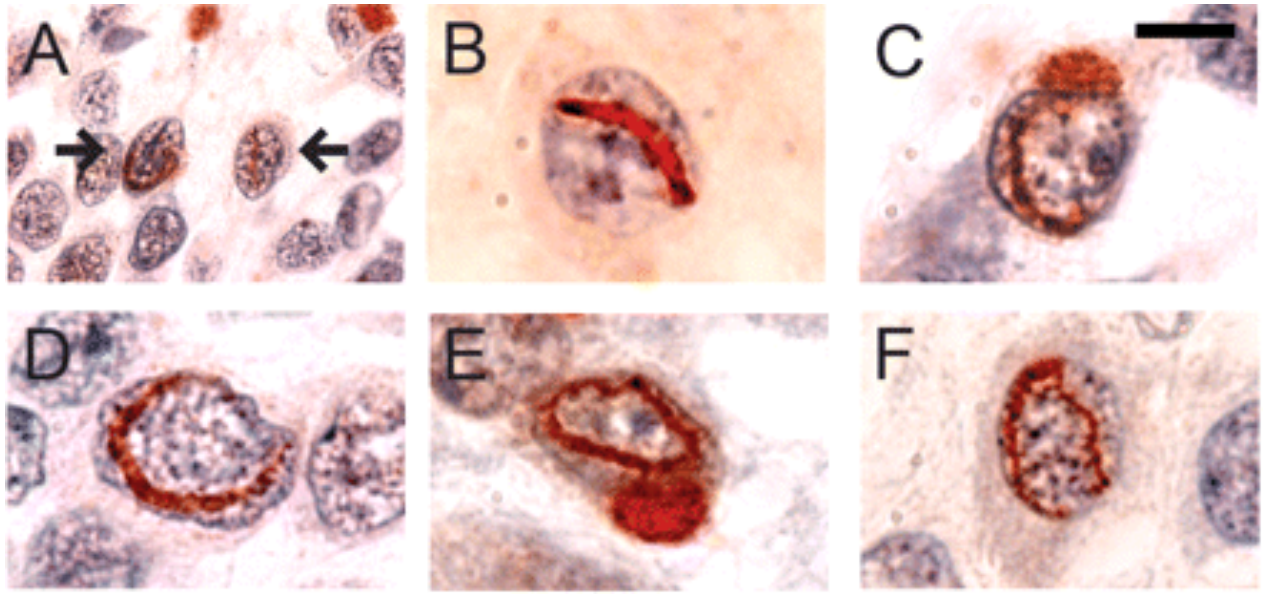
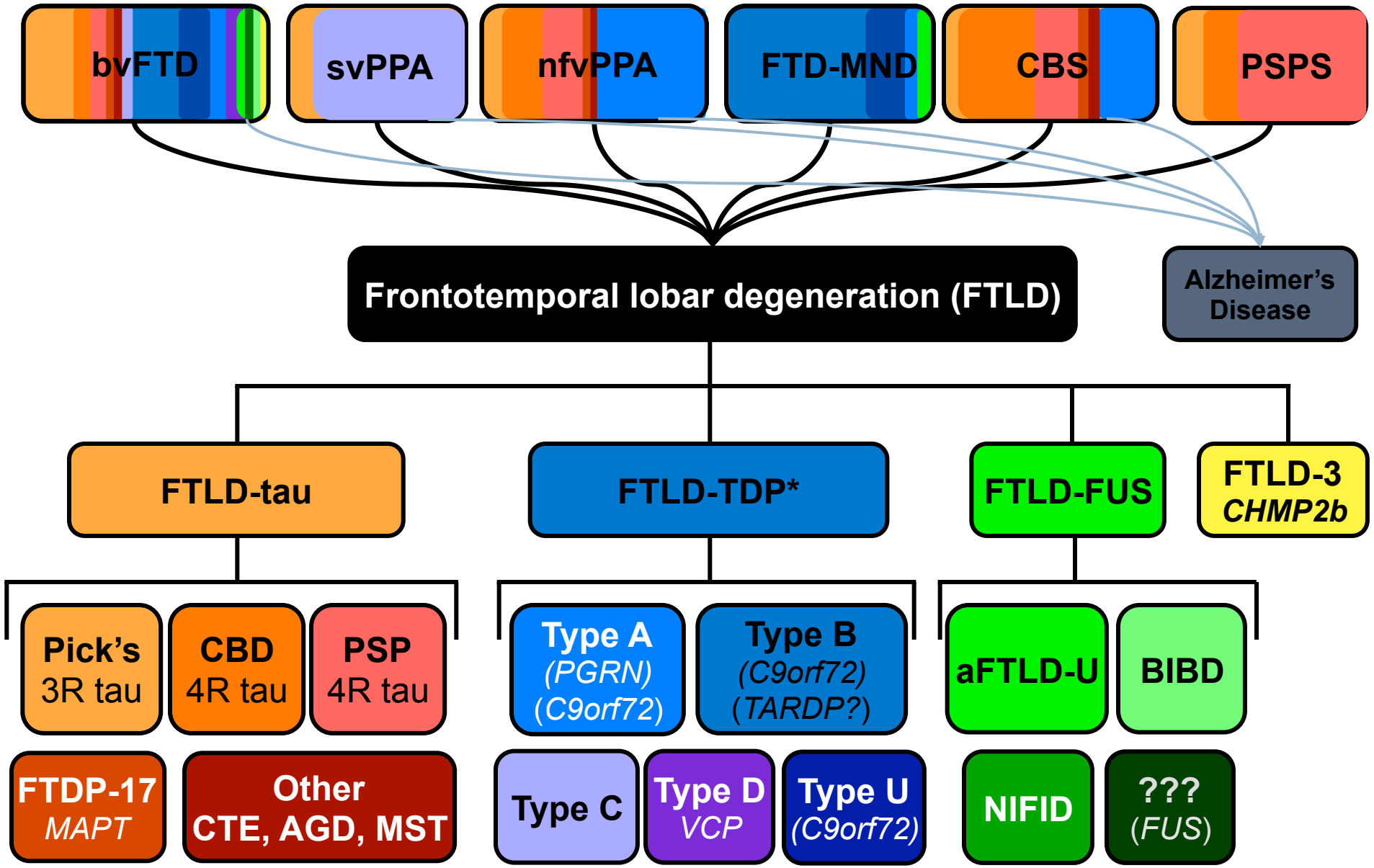
(C9orf72)
NIFID
???
(FUS)

FTLD-FUS: the FUS-opathies (<5% of FTLD)

Atypical FTLD with very early age at onset



Mackenzie et al. ***Brain*** 2008;131:1282–1293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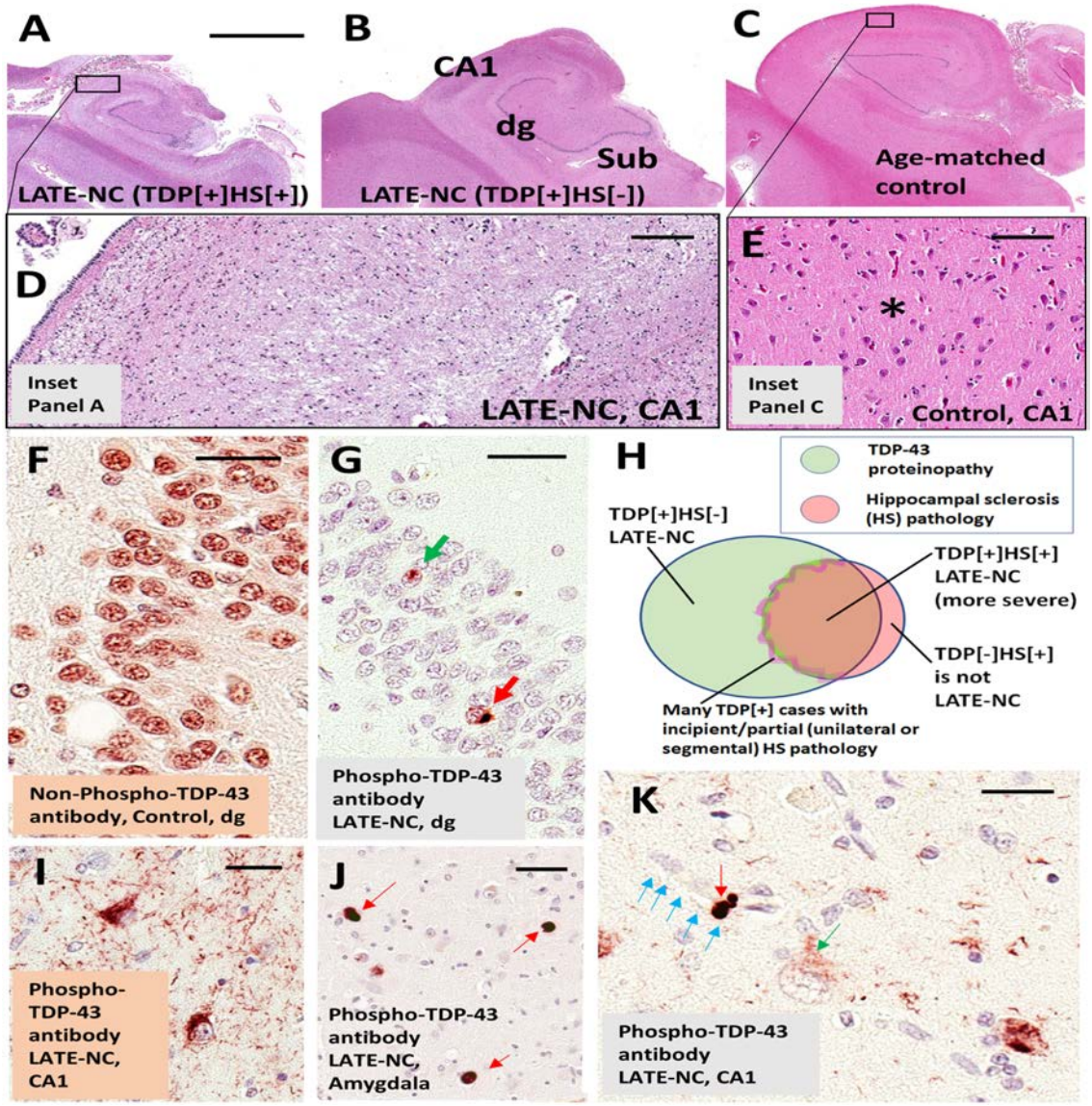
Overview

- Prevalence of the most common neurodegenerative dementias
- Lewy-body disease
  - Parkinson's disease & Dementia with Lewy bodies
- The frontotemporal lobar degenerations
- Neurodegenerations of aging
  - Hippocampal sclerosis and LATE
- Is dementia one or multiple diseases?
- Chronic traumatic encephalopathy

Neurodegeneration of aging

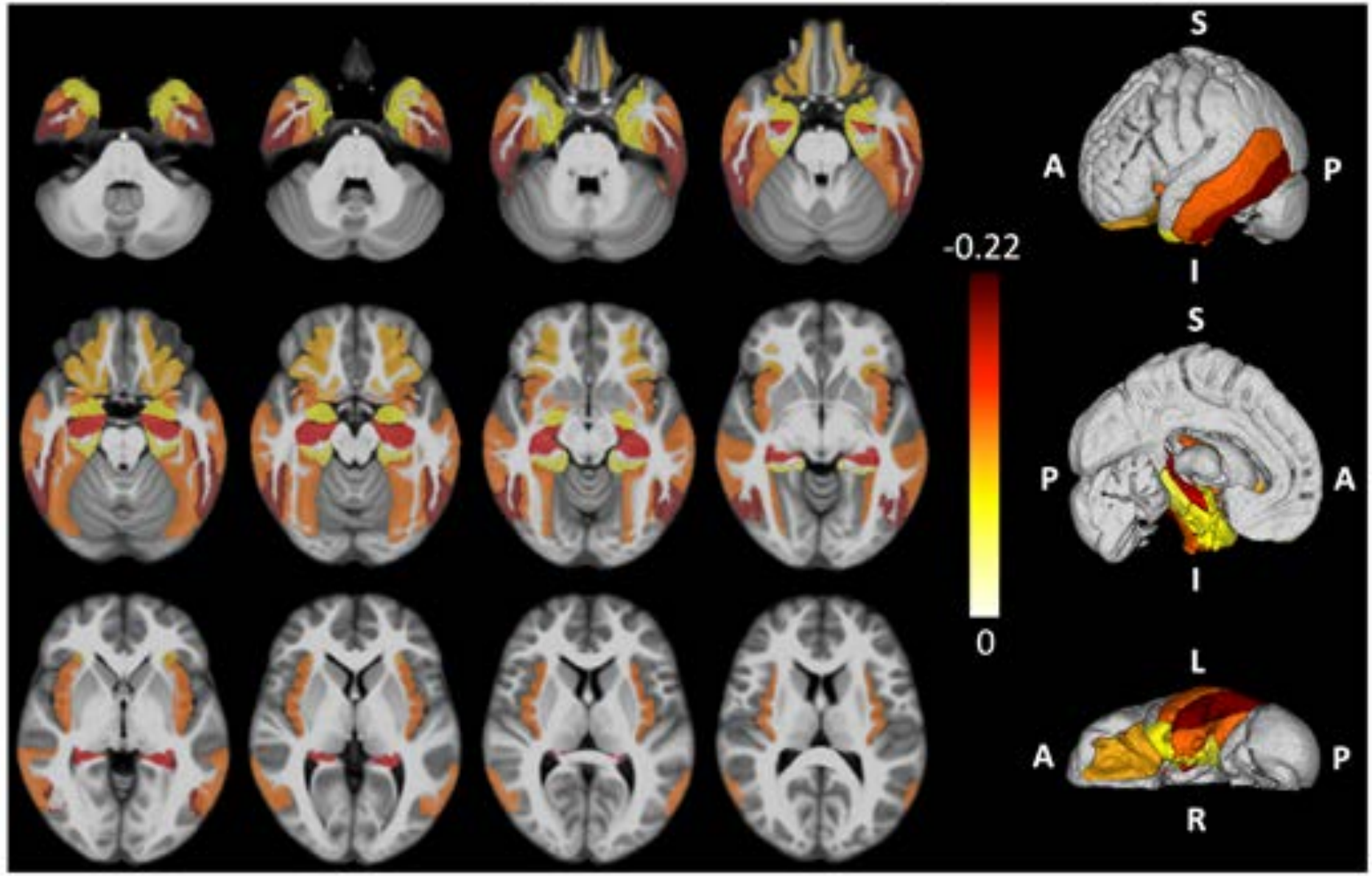


Limbic-predominant age-related TDP-43 encephalopathy (LATE)

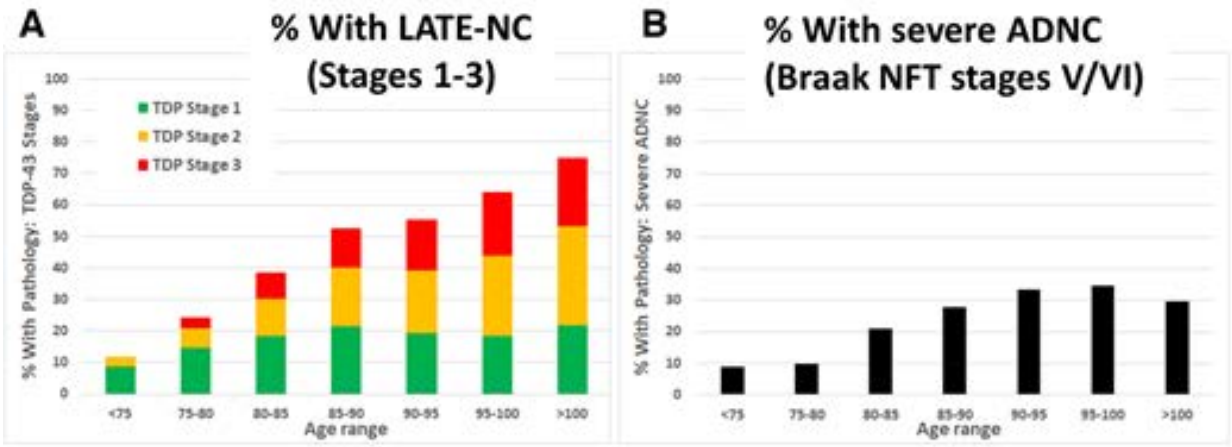
25% of cases in dementia autopsy series

Nelson et al. Brain 04/30/2019

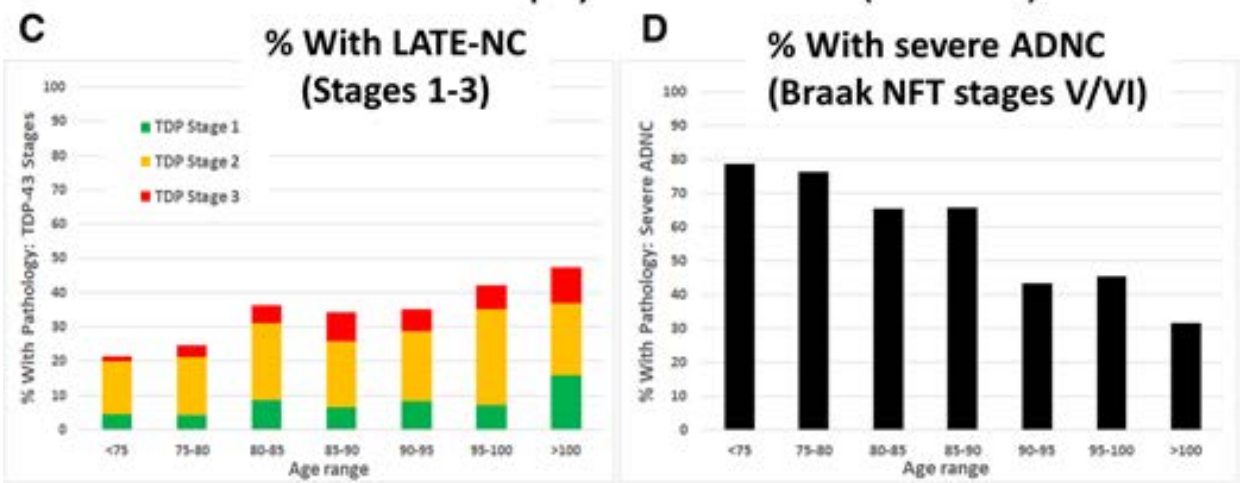
A **Brain atrophy associated with autopsy-confirmed LATE-NC:**
Data from Rush University ROS-MAP community-based autopsy cohorts

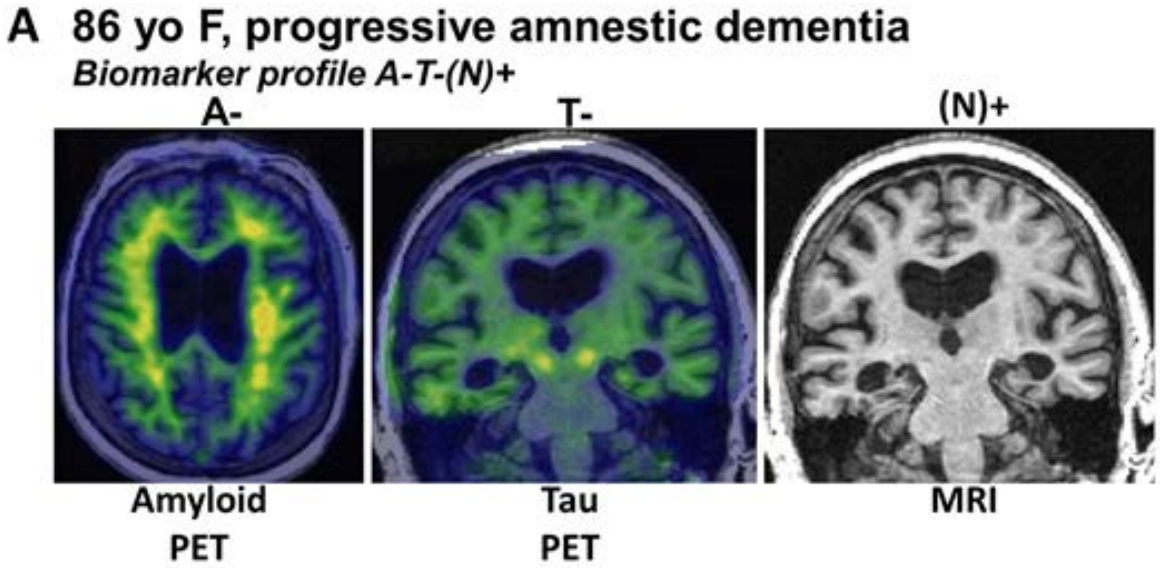


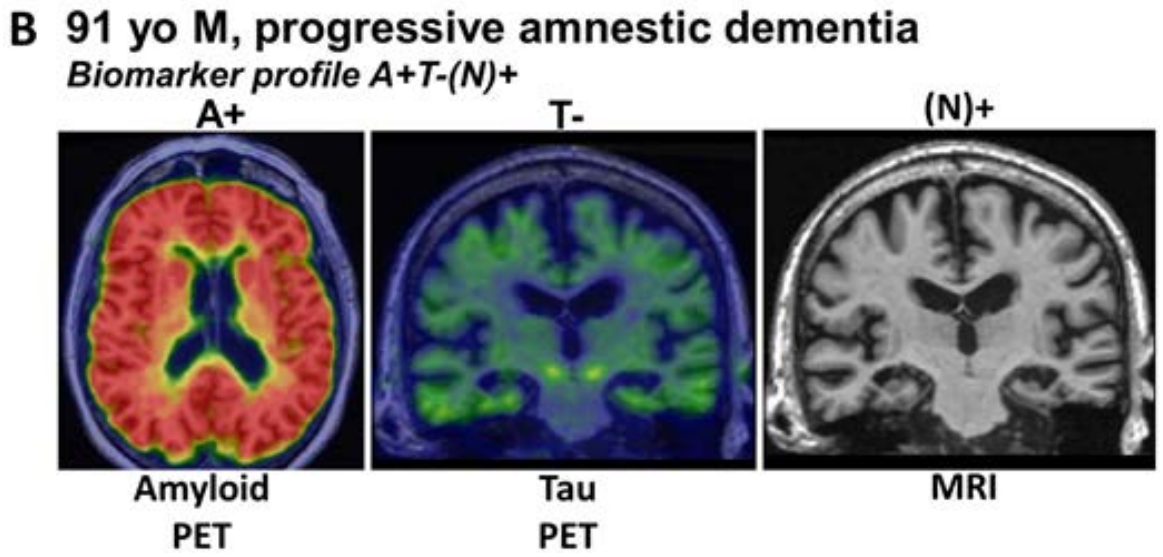
Rush University community-based cohort data (*n* = 1376)



NACC multicentre autopsy cohort data (*n* = 806)







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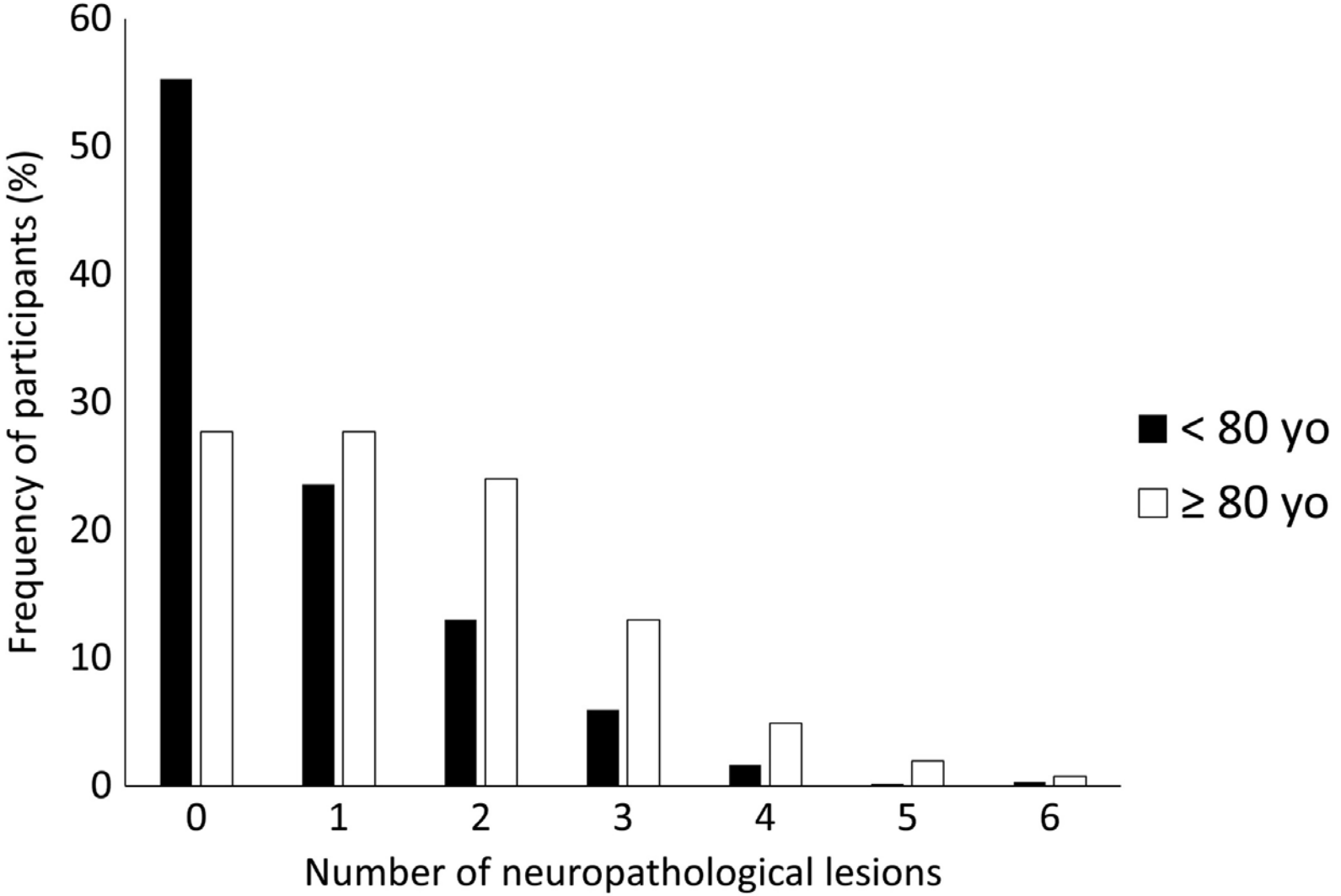
Neuropathological lesions in the very old: results from a large Brazilian autopsy study



Suemoto et al. Brain Pathology 2019

doi:10.1093/brain/awy146 BRAIN 2018: 141; 2181–2193 | 2181

BRAIN
A JOURNAL OF NEUROLOGY

Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated

John L. Robinson,[1,2,3,4] Edward B. Lee,[1,2,3,4] Sharon X. Xie,[1,2,3,4,5] Lior Rennert,[1,2,3,4,5] EunRan Suh,[1,2,3,4] Colin Bredenberg,[1,2,3,4] Carrie Caswell,[1,2,3,4,5] Vivianna M. Van Deerlin,[1,2,3,4] Ning Yan,[1,2,3,4,6] Ahmed Yousef,[1,2,3,4] Howard I. Hurtig,[1,2,3,7] Andrew Siderowf,[1,2,3,7] Murray Grossman,[1,2,3,7,8] Corey T. McMillan,[7,8] Bruce Miller,[9] John E. Duda,[3,10] David J. Irwin,[1,2,3,7,8] David Wolk,[1,2,3,7,8,11] Lauren Elman,[3,7] Leo McCluskey,[3,7] Alice Chen-Plotkin,[1,2,3,7] Daniel Weintraub,[2,3,12] Steven E. Arnold,[13] Johannes Brettschneider,[14] Virginia M.-Y. Lee[1,2,3,4,7] and John Q. Trojanowski[1,2,3,4,7]

Table 2 Prevalence of co-pathologies by neurodegenerative disease group

Group	*n*	Proteinopathy								Co-pathology prevalence					
		Tau		Amyloid-β		α-Synuclein		TDP-43		Single		Multiple		Total	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Minimal															
MPG	72	67	93	36	50	3	4	1	1	33	46	2	3	35	48
Amyloid-β															
iAD	46	46	100	46	100	19	41	15	33	26	57	4	9	30	65
hAD	201	201	100	201	100	111	55	81	40	90	45	51	25	141	70
Tau															
PiD	15	15	100	3	20	1	7	0	0	4	27	0	0	4	27
CBD	29	29	100	12	41	3	10	7	24	10	34	5	17	15	52
PSP	51	51	100	29	57	11	22	8	16	25	49	11	22	36	71
TDP-43															
ALS	108	95	88	39	36	12	11	108	100	35	32	8	7	43	40
FTLD-TDP	55	51	93	23	42	8	15	55	100	21	38	5	9	26	47
hTDP	25	25	100	8	32	4	16	25	100	8	32	2	8	10	40
α-Synuclein															
MSA	26	24	92	10	38	26	100	1	4	9	35	1	4	10	38
bLBD	20	19	95	10	50	20	100	0	0	10	50	0	0	10	50
lLBD	37	37	100	21	57	37	100	6	16	23	62	2	5	25	68
nLBD	81	81	100	65	80	81	100	18	22	49	60	17	21	59	81

MPG = minimal pathology group.

Table 2

A statistical analysis of attributable risk from research volunteers in two clinical-pathological studies of ageing from Rush University

Neuropathological indices	Fraction attributable % (95% CI)[a]
Alzheimer's disease (ADNC)	39.4 (31.5–47.4)
Vascular disease pathology[b]	24.8 (17.3–32.1)
LATE-NC	**17.3** (13.1–22.0)
α-Synucleinopathy/Lewy body pathology	11.9 (8.4–15.6)

Nelson et al. Brain 04/30/2019

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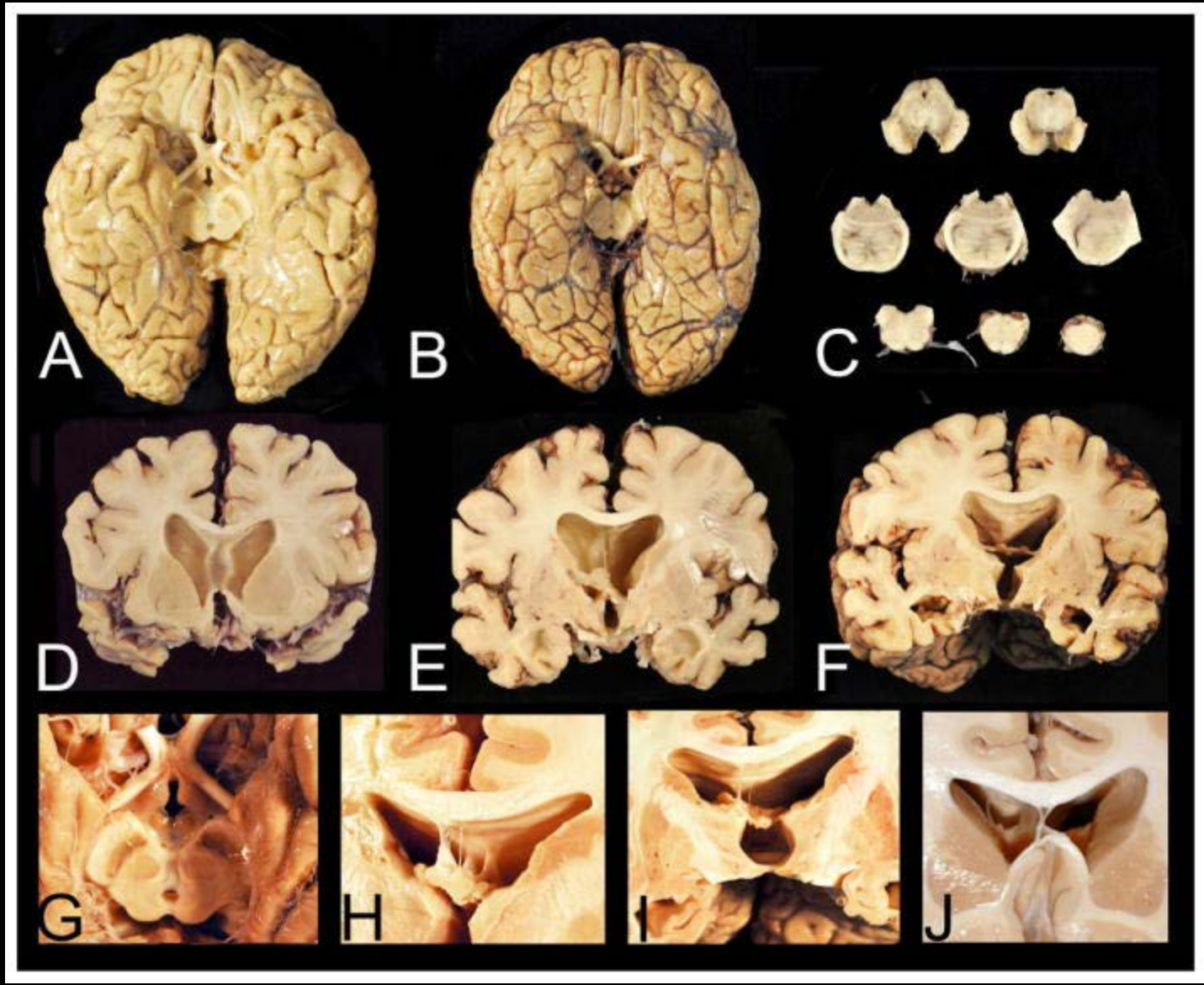
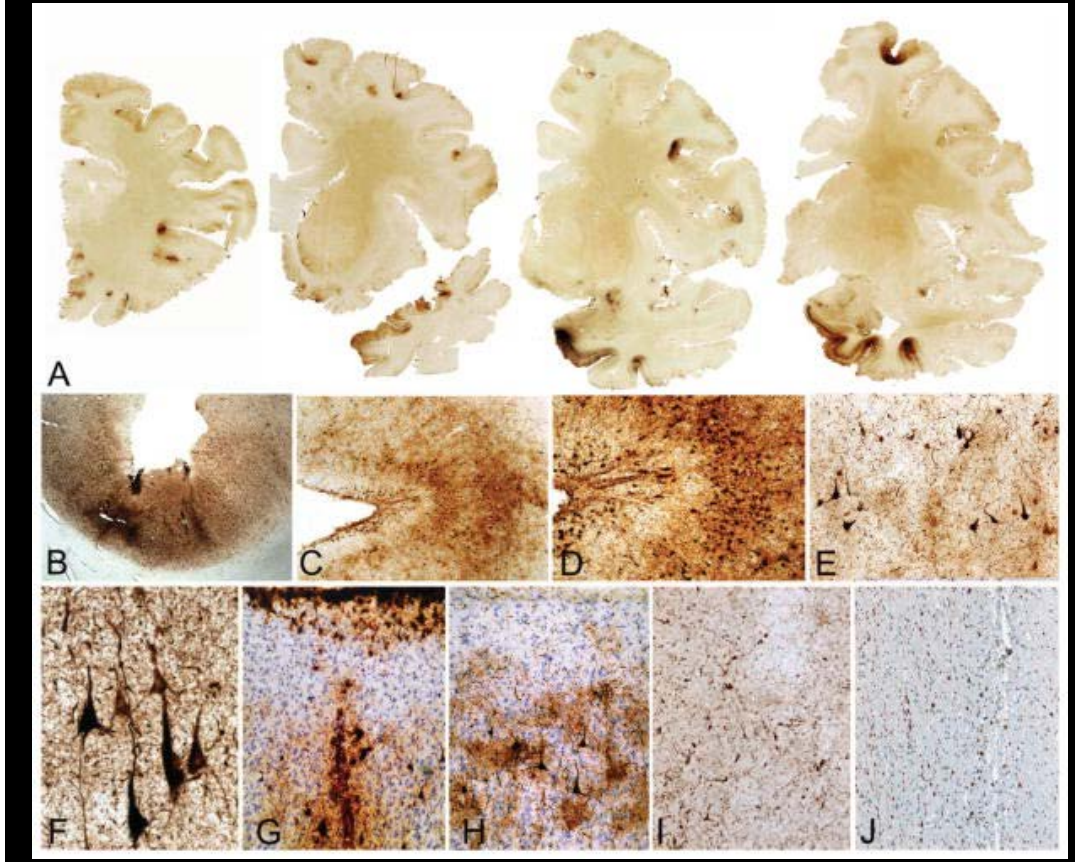
Chronic traumatic encephalopathy





McKee et al. Brain Pathology 2015

Chronic traumatic encephalopathy

- 99% autopsy prevalence among NFL players
- multiple repeated head trauma/concussions is highest risk factor
- can present as a behavioral syndrome
  - irritability
  - explosive aggressive behavior
  - depression leading to suicide
- can manifest as a late-onset amnestic syndrome indistinguishable from Alzheimer's disease
- Prevalence is possibly 1/3 in subject with significant h/o contact sport participation and virtually absent in subject with no contact sport history regardless of h/o single head trauma

Take home messages

- Alzheimer's disease is the most common but not the only cause of dementia throughout the lifespan
- Frontotemporal dementias are as common as AD in subjects aged 65 and more common than AD in people younger than 60-year old
- Dementia is very unlikely caused by a single pathologic process
- Coexistence of multiple pathologies is the rule, and their number increases with age
- The likelihood of developing cognitive symptoms is directly associated with the number of different diseases together affecting the same brain
- Chronic traumatic encephalopathy is a newly recognized cause of cognitive impairment. Its impact is high in subjects with h/o contact sports but likely minimal in subjects with no h/o repeated head trauma

Acknowledgments

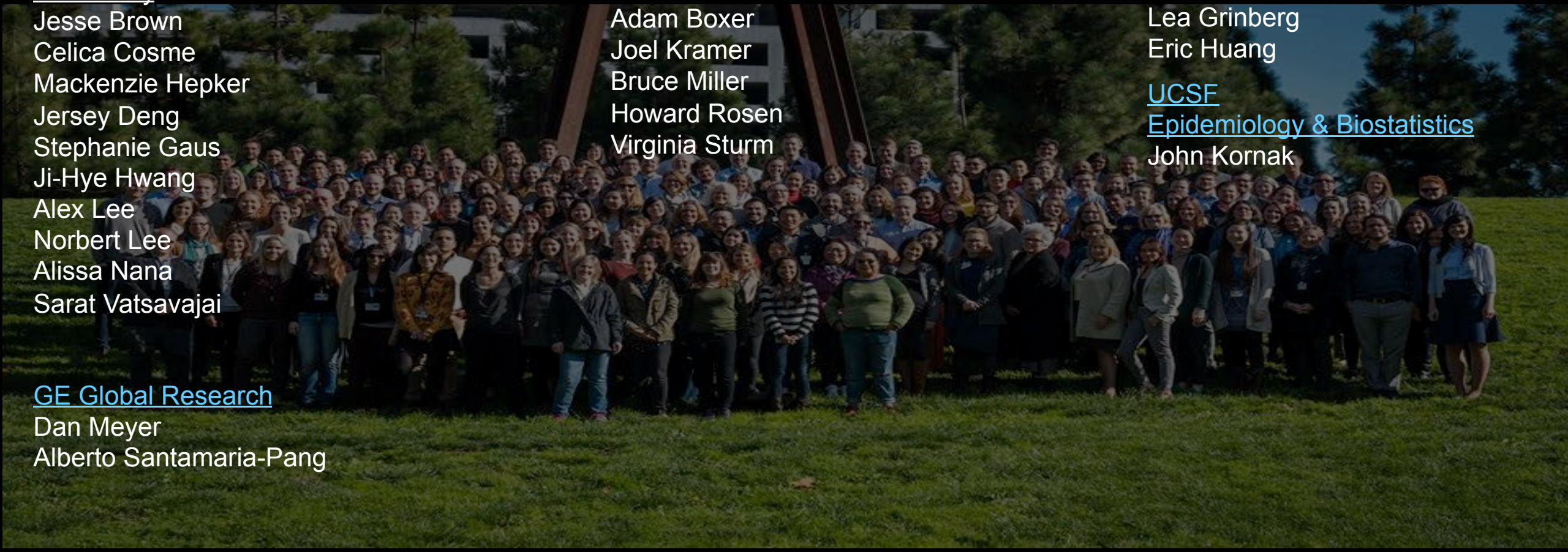
Seeley Lab
Bill Seeley
Jesse Brown
Celica Cosme
Mackenzie Hepker
Jersey Deng
Stephanie Gaus
Ji-Hye Hwang
Alex Lee
Norbert Lee
Alissa Nana
Sarat Vatsavajai

GE Global Research
Dan Meyer
Alberto Santamaria-Pang

UCSF Memory & Aging Center
Adam Boxer
Joel Kramer
Bruce Miller
Howard Rosen
Virginia Sturm

UCSF Brain Bank
Lea Grinberg
Eric Huang

UCSF Epidemiology & Biostatistics
John Kornak



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