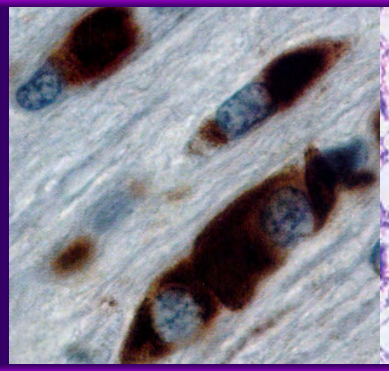
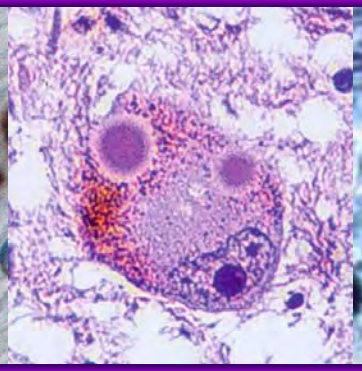
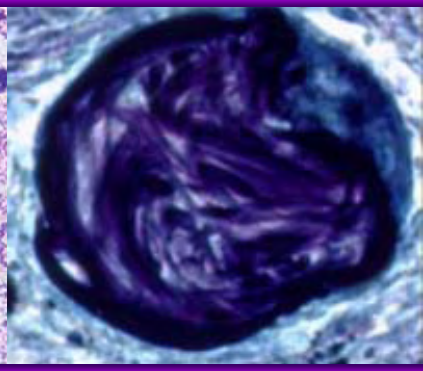
Distinguishing Parkinsonian disorders based on their pathology







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Neurodegenerative disorders with parkinsonian features

I. α-Synucleinopathies

1. Lewy body disease

- Idiopathic Parkinson's disease (brainstem type of LBD)
  sporadic
  familial (α-Syn., Parkin mutation)
- Incidental Lewy body disease
- Dementia with Lewy bodies
  "Pure" DLB (no/little AD)
- Lewy body variant of AD (LBV/AD)

2. CGI-associated

- Mult. system atrophy (MSA-P/-C)
  Striatonigral degen.
  Olivopontocerebellar atrophy
  Sly-Drager syndrome
- Hallervorden-Spatz disease

Neurodegenerative disorders with parkinsonian features

II. Tauopathies

- Progressive supranuclear palsy (4 repeat tau + exon 19)
- Corticobasal degeneration (CBD) (same)
- Parkinson-dementia/ALS complex of Guam (3+4 R triplet)
- Postencephalitic parkinsonism (3+4 R triplet)
- Alzheimer disease (3+4 R triplet + amyloid)
- Chromosome 17-linked familial dementia (FTDP-17)
- Pallido-ponto-nigral degeneration (PPND) (4 R tau)
- Multiple system tauopathy with presenile dementia (MSTD)
- Pick's disease (3 R tau doublet without exon 10)

Neurodegenerative disorders with parkinsonian features

III

Polyglutamine repeat (CAG) disorders

- Huntington's disease (rigid type)
- Choreoacanthocytosis (neuroacanthocytosis)
- Spinocerebellar ataxia (SCA 2, SCA 3)
- Dentatorubropallidoluysian atrophy (DRLPA)

Other heredodegenerative disorders

- (Non)hereditary striatal degeneration
- Pallidal degeneration and related variants
- Wilson's disease
- Inherited dystonias
- X-linked dystonia parkinsonism (Lubag)

Symptomatic Parkinsonism

- Vascular (pseudo)parkinsonism (lacunes, WMLs)
- Drug-induced parkinsonism (phenothiazines, etc.)
- Toxic parkinsonism
- Infectous and post-infectous disorders:
  - Japanese B encephalitis and other viral encephalitis
  - Creutzfeldt-Jakob disease, Neurosyphilis
- Other disorders:
  - Normal pressure hydrocephalus, frontal lobe tumor
  - Post-traumatic parkinsonism - Boxer's encephalop.

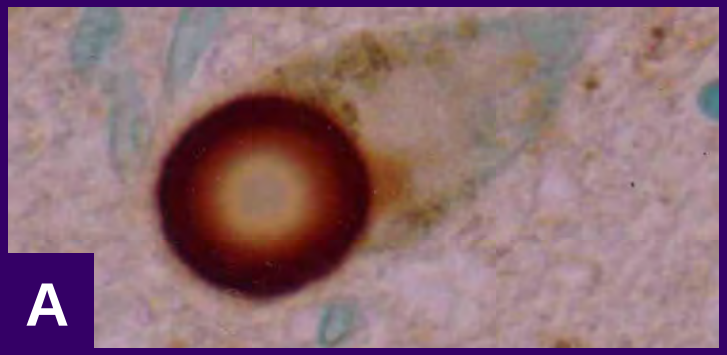
Pathology findings in 800 autopsy cases with clinical diagnosis of Parkinsonism (1962-2004)

Neuropathology	Total	%
Id. Parkinson dis. (IPD)	334	41.8
IPD + lacunar state / infarcts (114/12)	126	15.7
IPD + AD pathology	95	11.9
Lewy body variant AD	29	3.6
DLB (without AD)	33	4.1
IPD + MIE	16	2.0
IPD + other pathology	5	0.6
Prim. Lewy body dis.	*657*	*82.1*

Neuropathology	Total	%
AD/DAT	37	4.6
MIE/SAE/MIX	36	4.5
PSP	25	3.5
MSA	20	2.5
CBD. Pick's disease	5	0.6
Nigral lesion unclassif.	6	0.75
Postenceph. park.	2	0.3
Others, negative	12	0.5
Second. Park. syndr.	*143*	*17.9*
Total	***800***	***100.0***

Types of Parkinsonism in autopsy series (percentage)

	Schrag et al (Clin. PD)	Hughes et al (1990-99)	Jellinger (1957-70)	Jellinger (1971-88)	Jellinger (1989-2004) n	Jellinger (1989-2004) %
Lewy body disease			**78.0**	**82.8**	**309**	**85.7**
Idiopathic Parkinson disease	61.4	50.0	75.3	77.0	188	52.2
PD + AD / cer. vasc. lesions					65	18.0
Lewy body dem. (DDLB+LBV/AD		–	2.7	5.8	56	15.5
Other degenerative Parkinsonisms		**33.0**	**10.0**	**8.9**	**33**	**9.2**
MSA	1.5	22.0	4.6	2.3	7	
PSP	3.0	11.0	3.6	2.6	10	
Pick dis., Corticobasal degen.	–	?	0.9	0.5	1	
Alzheimer disease (AD)	–	?	0.9	3.5	15	
Secondary Parkinsonism (P.)		**17.0**	**12.0**	**8.3**	**18**	**5.1**
Vascular P. (MIE. SAE. MIX)	5.5	?	3.0	4.2	10	
Postencephalitic P.	–	?	6.3	1.9	0	
Sympt. (JCD, tumors, drugs)	3.5	?	0.9	0.6	3	
Posttraumatic/boxer dem.	–	?	0.9	0.3	0	
Unclassif./no lesion ("tremor")	22.8	?	0.9	1.3	5	
Total n:	*202*	*143*	*110*	*380*	*360*	*100.0*



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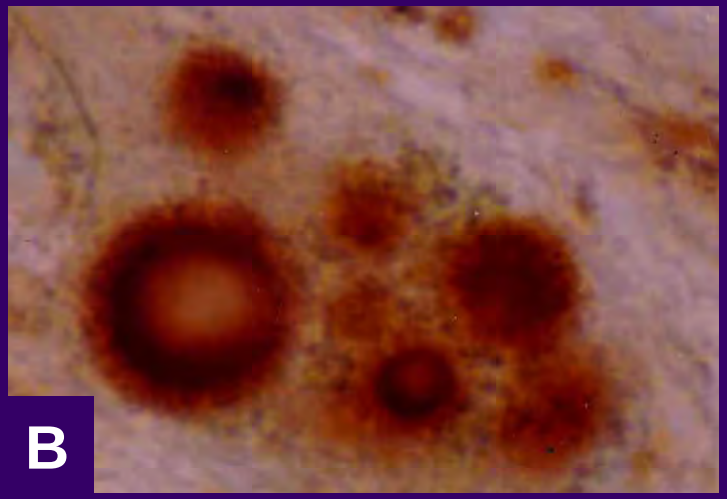

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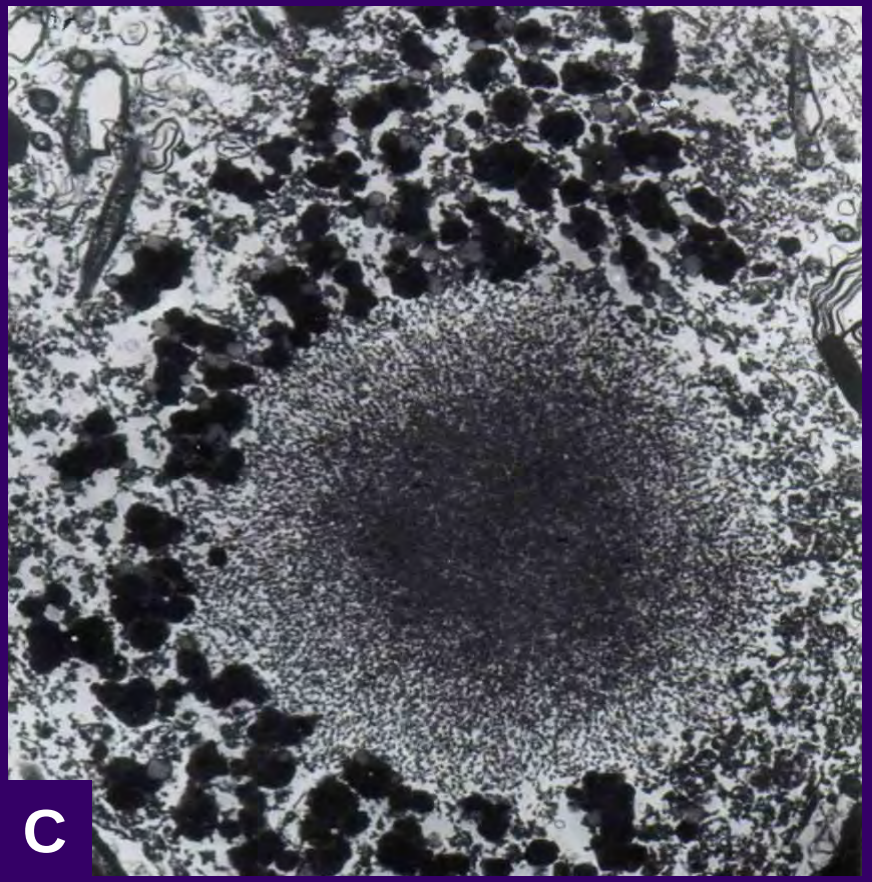

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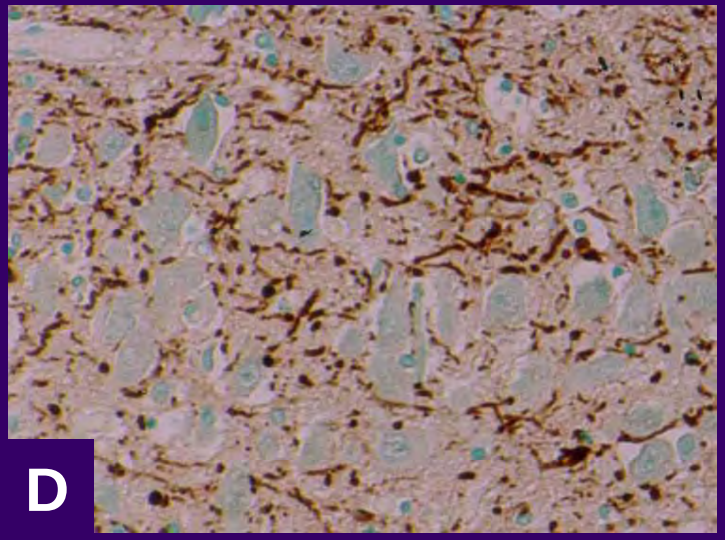

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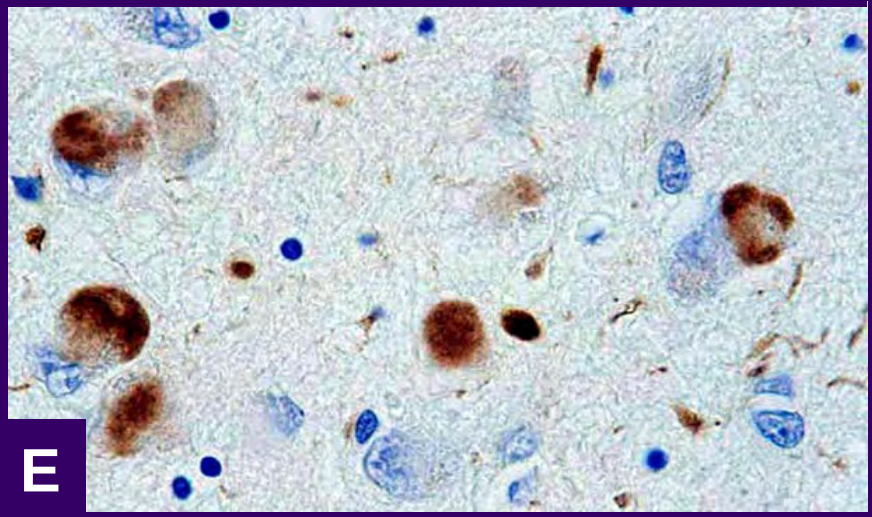
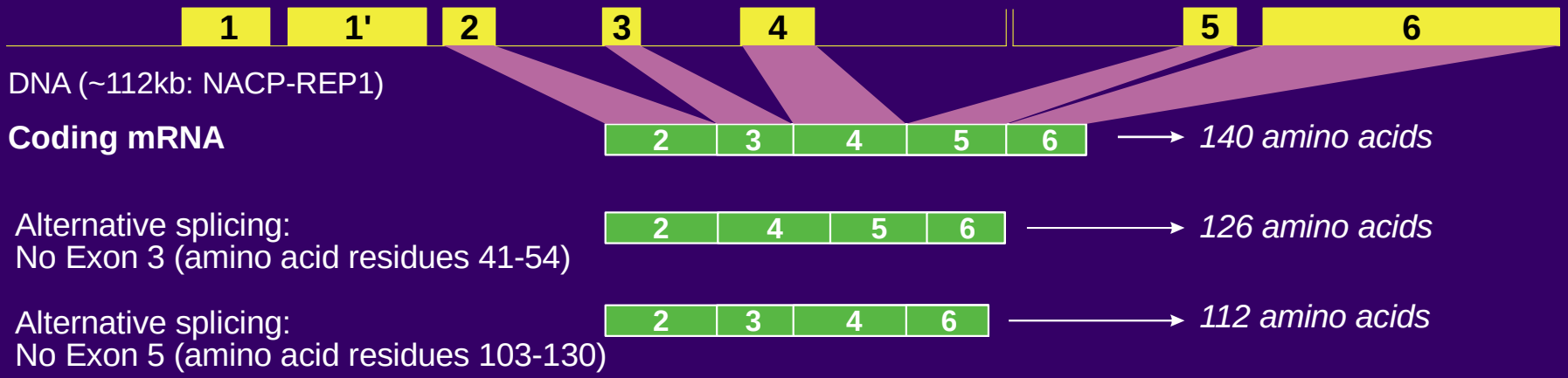


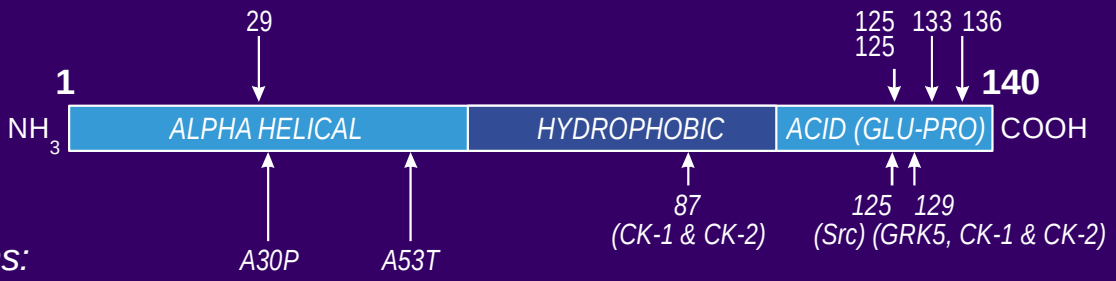
E

ALPHA-SYNUCLEIN



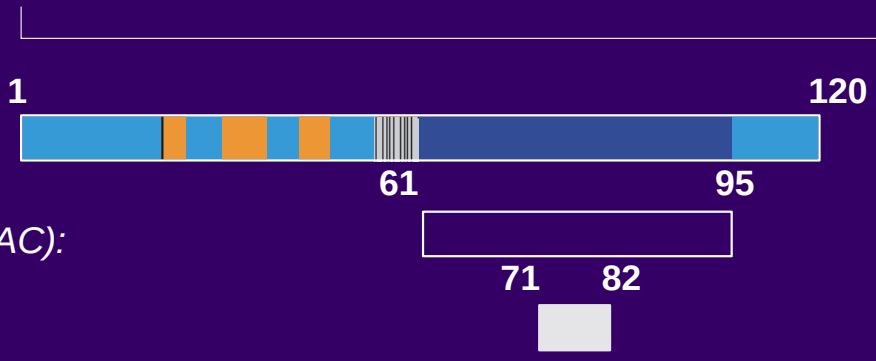
Tyrosine nitration sites:
o,o'-Dityrosine crosslinks:

Protein (structural domains):



Phosphorylation sites (kinases):
Familial Parkinson disease mutations:

Sporadic PD, DLB, LBV/AD, MSA



Hydrolytic fragment:

Non-amyloid component of plaques (NAC):

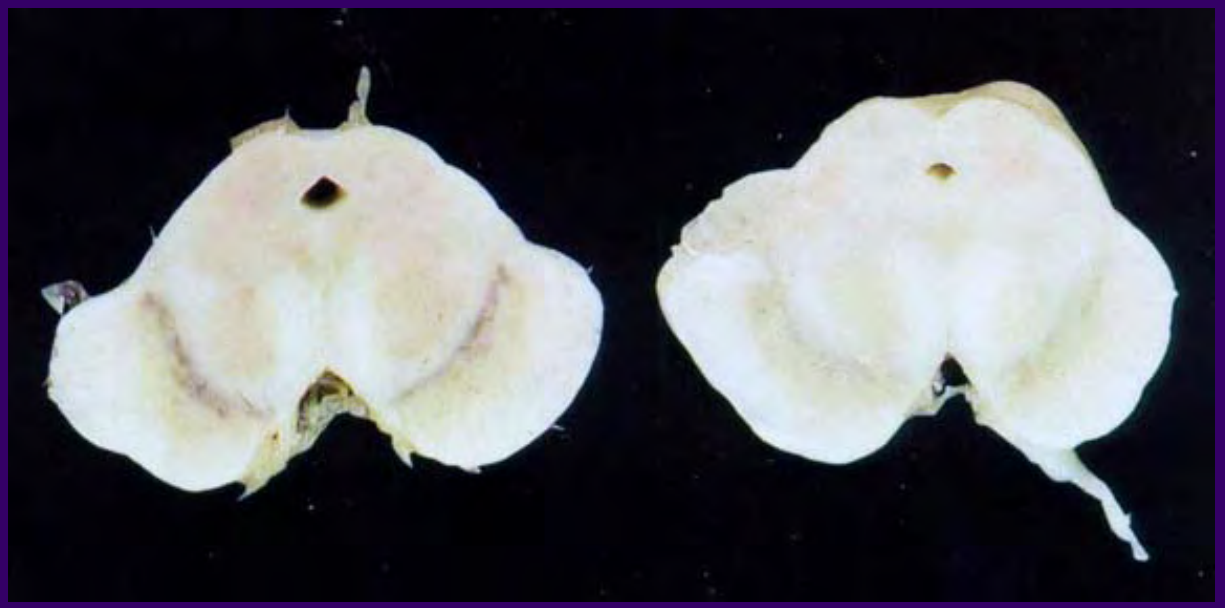
Minimal fibrillogenic domain:

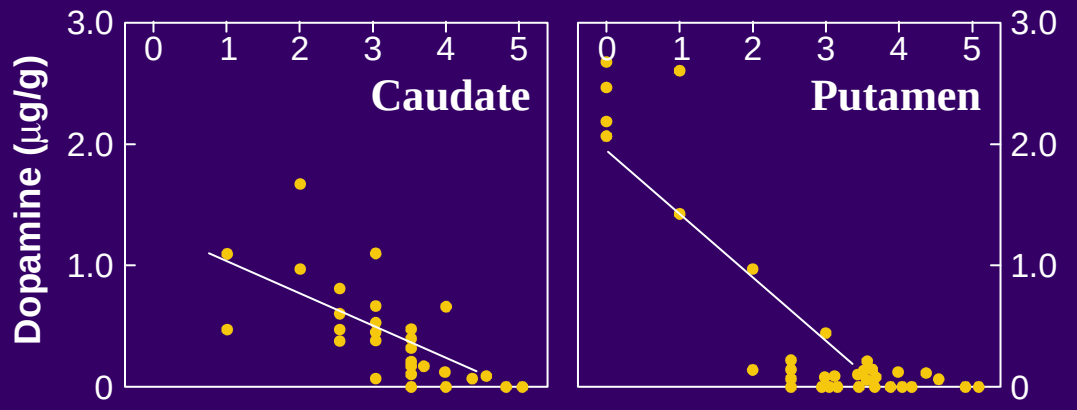
Spectrum of "Lewy body Diseases"

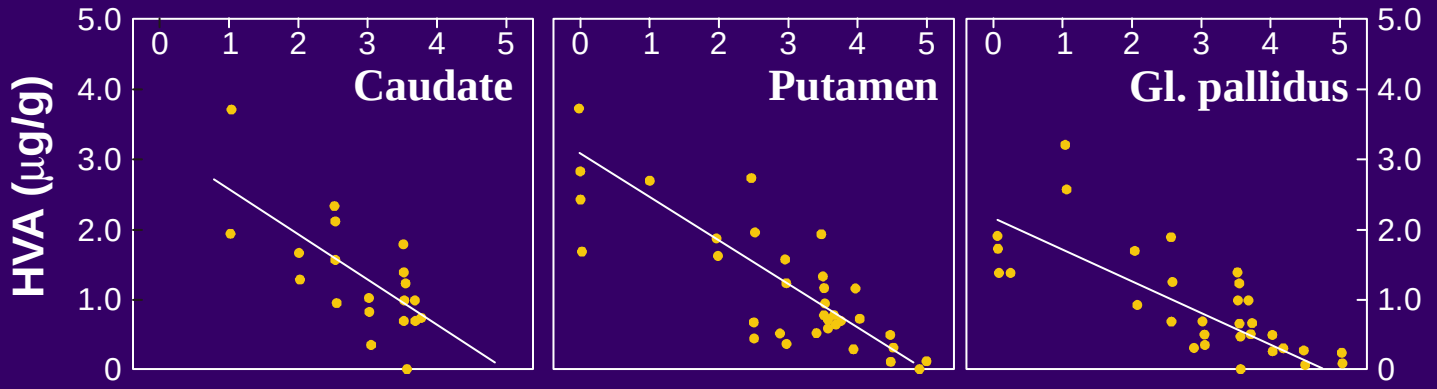
(adapted from Ince et al, 2001)

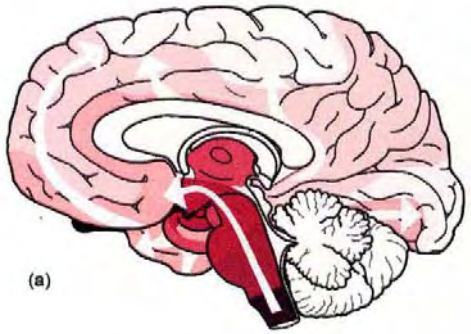
	neocortex cortex	limbic cortex N.basali M.	Substantia nigra	dorsal/vagal nucleus	lateral grey horn/ sympathetic ganglia	myenteric ganglia
Dementia w. Lewy bodies	2+/3+	3+	+/2+	+/3+	?	?
Parkinson's disease	+/2+	2+/3+	3+	+/3+	+/2+	+/2+
Pure autonomic failure	0	2+	+	3+	2+/3+	3+
Lewy body dysphagia	0	0	0/+	0	?	3+

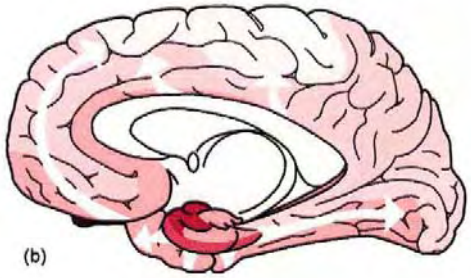
Neuron loss in substantia nigra

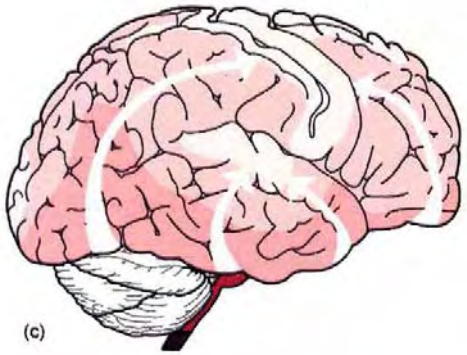


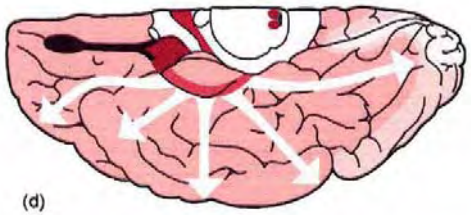


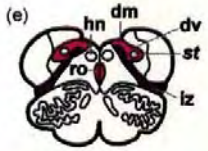


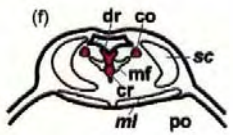


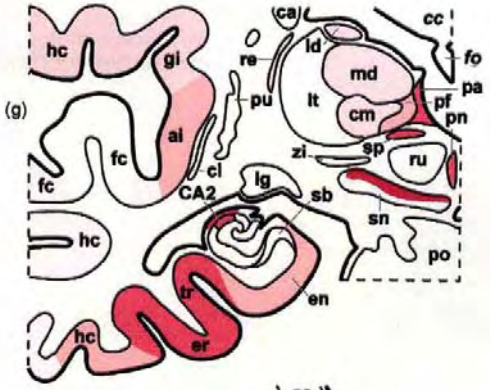


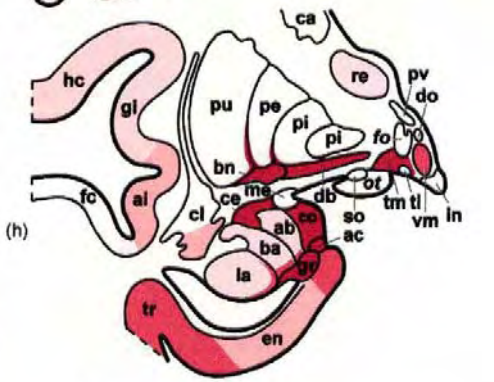






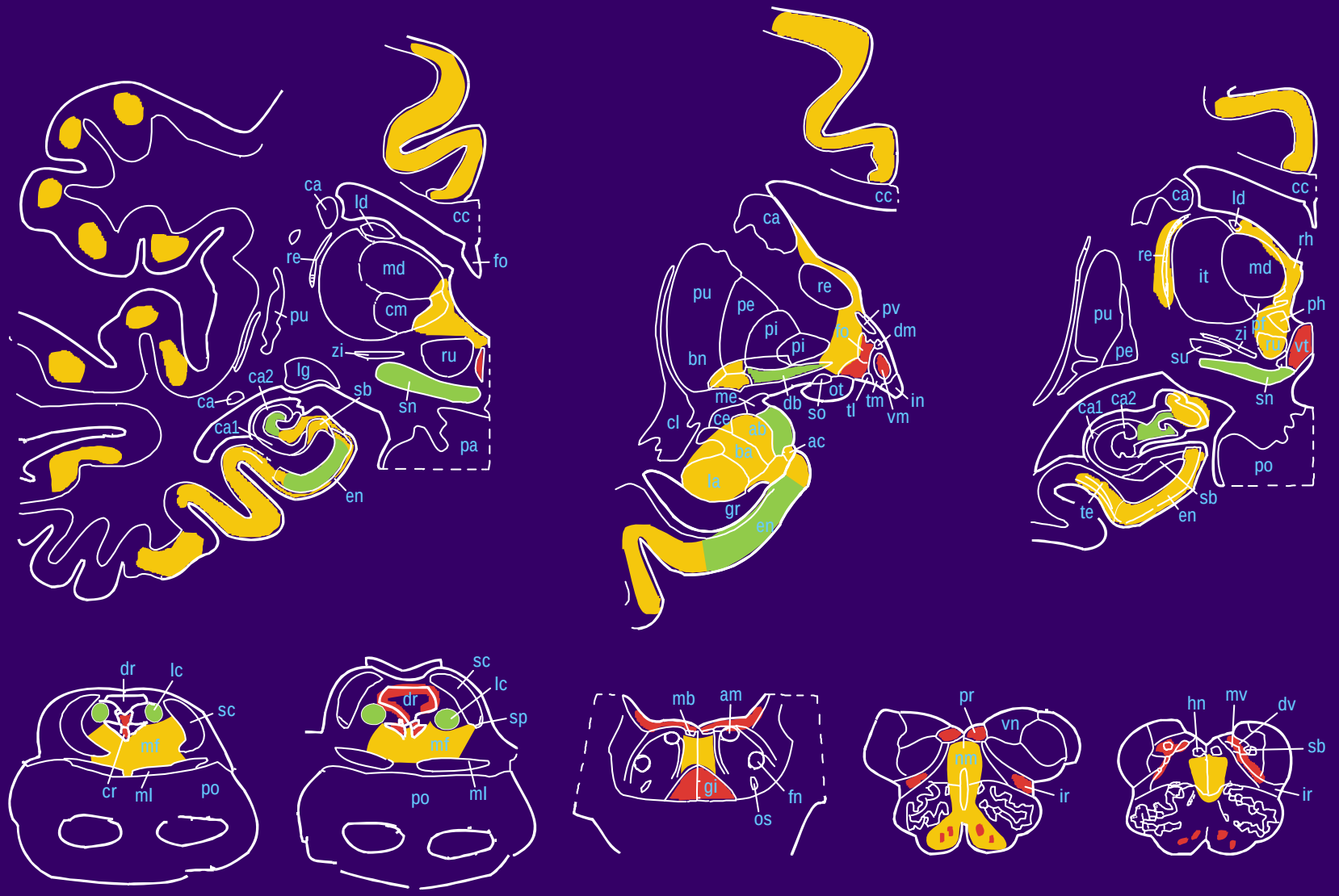






(i)

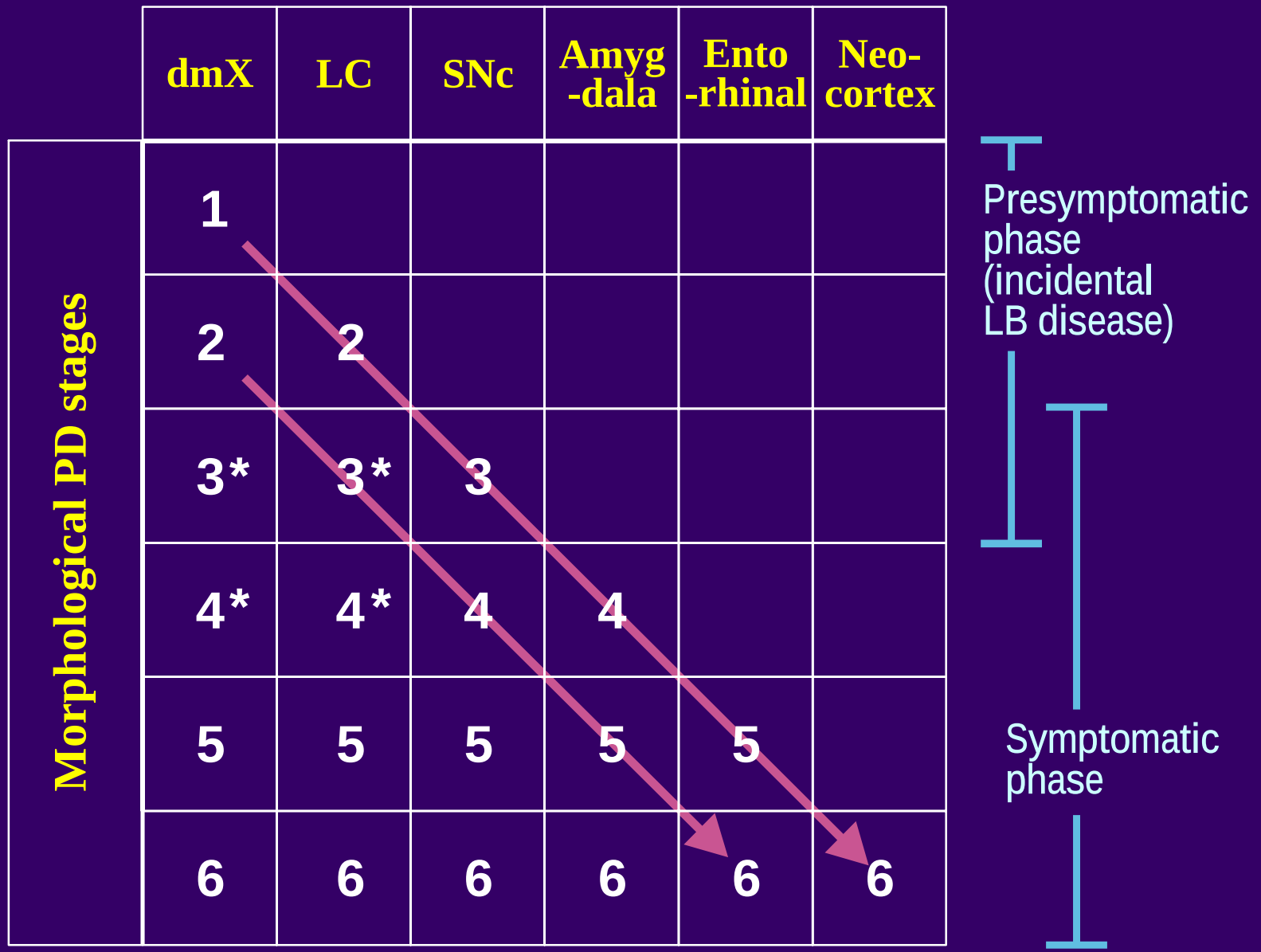
PD-stages	dm	co	sn	mc	hc	fc
1						
2						
3						
4						
5						
6						



Parkinson disease

- Stage 1-2
- Stage 3-4
- Stage 5-6

Progression of PD-related pathology



Symptom-related lesion pattern in PD

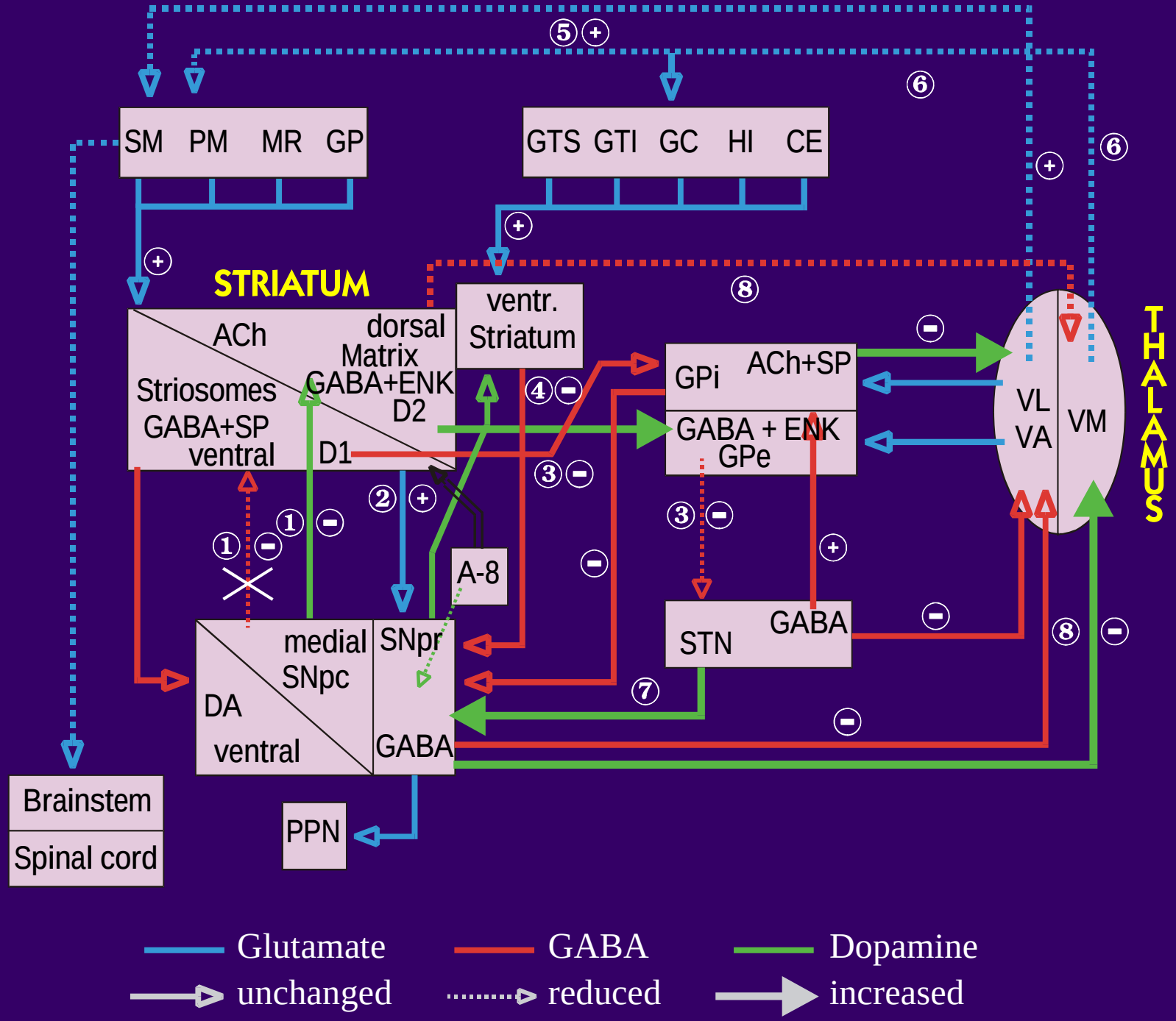
PD is a progressive multisystem degeneration involving many neuronal nuclei/loops causing complex clinical picture:

Dopaminergic striatonigral system

a) In PD, loss of nigral neurons causing striatal dopamine deficiency is related to both duration and clinical stages (severity) of the disease.

b) Clinical subtypes show different lesion patterns:

- **Rigid-akinetic PD**: severe cell loss in ventrolateral SNZC projecting to caudate and anterior putamen → overactivity of GABA inhibitory loop via SNZR and GPI → increased glutamatergic SIN activity → inhibition of thalamo-cortical motor loop → reduced cortical activation.
- **Tremor-dominant PD**: more severe cell loss in medial SNZC and area A8 → overactivity of VIM thalami and cerebellar connections.


SM PM MR GP
GTS GTI GC HI CE
STRIATUM
ACh
dorsal Matrix
GABA+ENK
D2
Striosomes
GABA+SP
ventral
D1
ventr. Striatum
A-8
GPi
ACh+SP
GABA + ENK
GPe
VL
VA
VM
THALAMUS
STN
GABA
medial SNpc
DA
ventral
SNpr
GABA
Brainstem
Spinal cord
PPN
Glutamate
GABA
Dopamine
unchanged
reduced
increased

Extra striato-nigral degeneration in PD

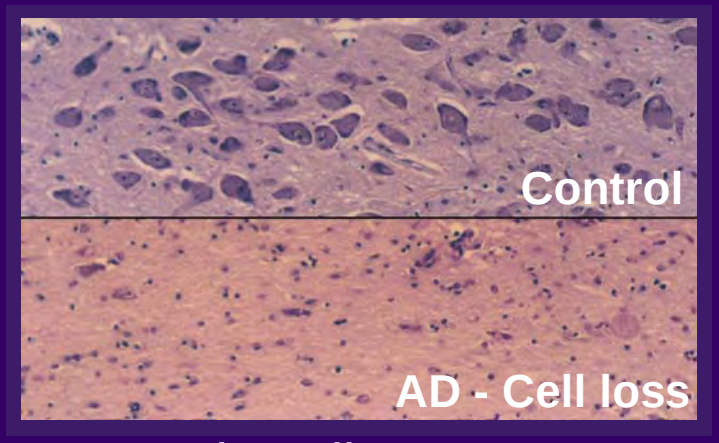
- Mesocortical dopaminergic system (VTA, limbic areas)
- Noradrenergic systems (l. coeruleus, motor vagal nucl.)
- Serotonergic system (dorsal raphe nucleus)
- Cholinergic systems (nucl. basalis of Meynert, nucl. tegmenti pedunculopont., Westphal-Edlinger nucl.)
- Amygdala-limbic system
- Peptidergic systems (striatum, SN, medulla etc)
- Limbic thalamic nuclei (prefrontal projections)
- Peripheral autonomic nervous system
- Adrenal medulla

Brain lesions associated with mental impairment in parkinsonism

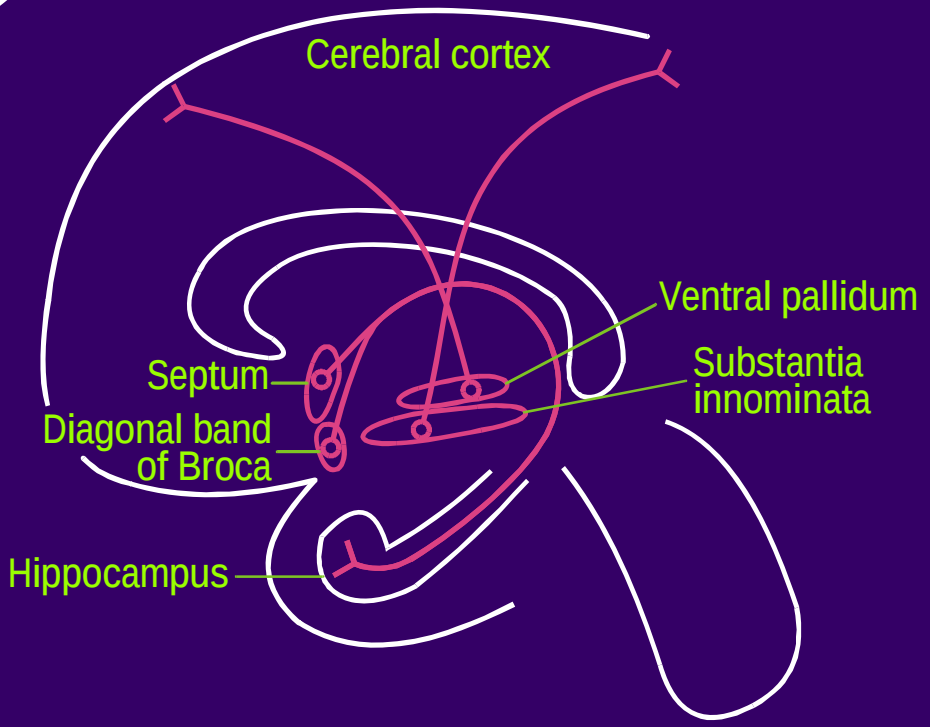
1. **Dysfunction of subcortico-cortical neuronal systems**
   a) Degeneration of nigrostriatal dopaminergic pathway ⇨ deafferentation of striato-(pre)frontal loops
   b) Cell loss in medial substantia nigra and VTA ⇨ mesocorticolimbic dopamine deficiency
   c) Degeneration of noradrenergic systems (locus coeruleus)
   d) Degeneration of serotonergic systems (dorsal raphe nuclei)
   e) Degeneration of cholinergic systems (nucleus basalis of Meynert)
   f) Degeneration of amygda + limbic system (thalamus, hippocampus)
   g) Combined degeneration of subcortical ascending systems
2. **Cortical pathologies**
   a) Cortical Lewybodies (93-100% in PD, 100% in DLB)
   b) Limbic and/or neocortical neuritic Alzheimer-type lesions + synapse loss
   c) Combination of Alzheimer and Lewy body pathologies (limbic system!)
3. **Combination of cortical, subcortical and other pathologies**

Transmitter systems vulnerable in PD

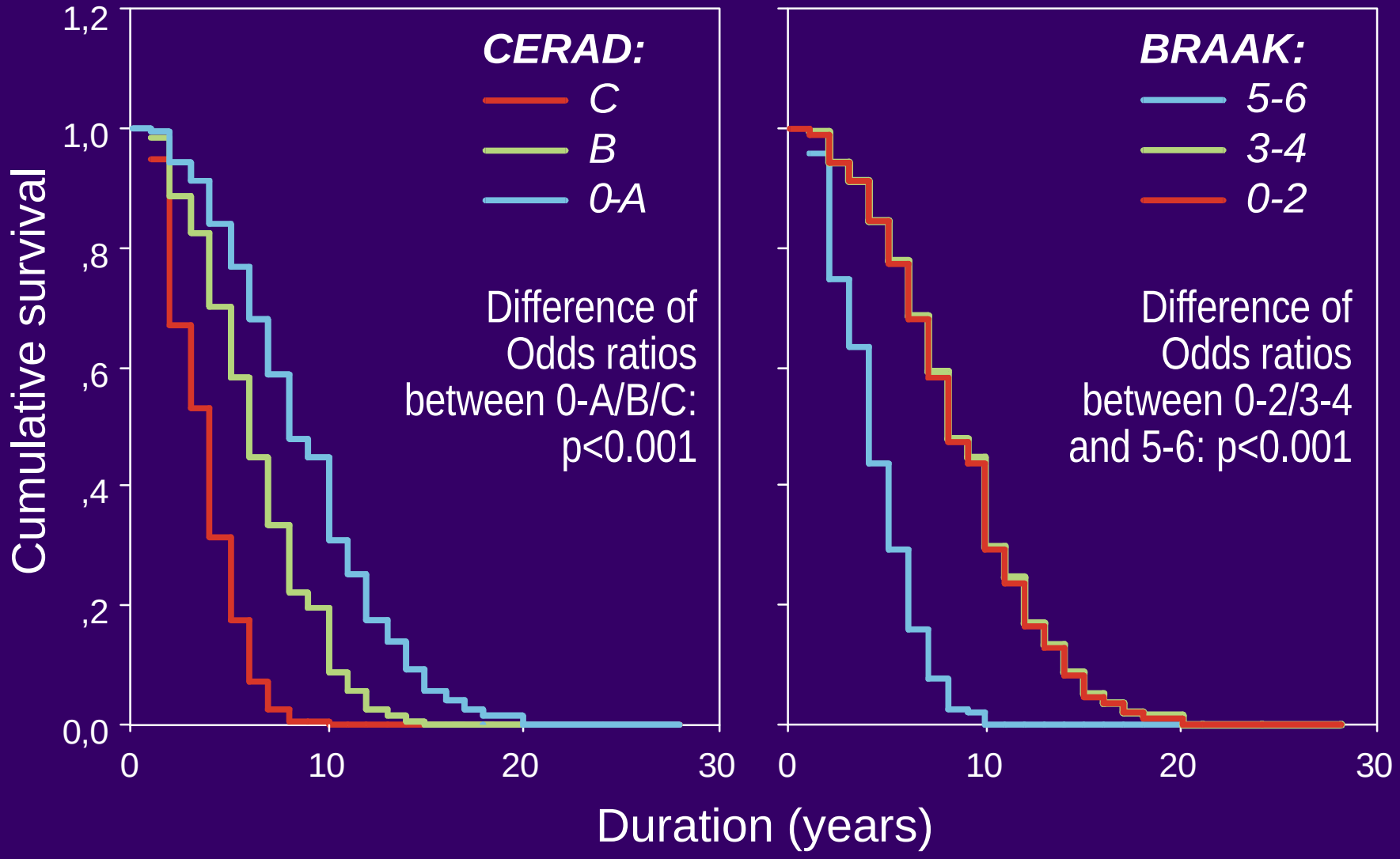
- Cortical systems
- Hippocampal circuits
- Limbic thalamocortical system
- Monoamine systems
- Basal forebrain cholinergic system

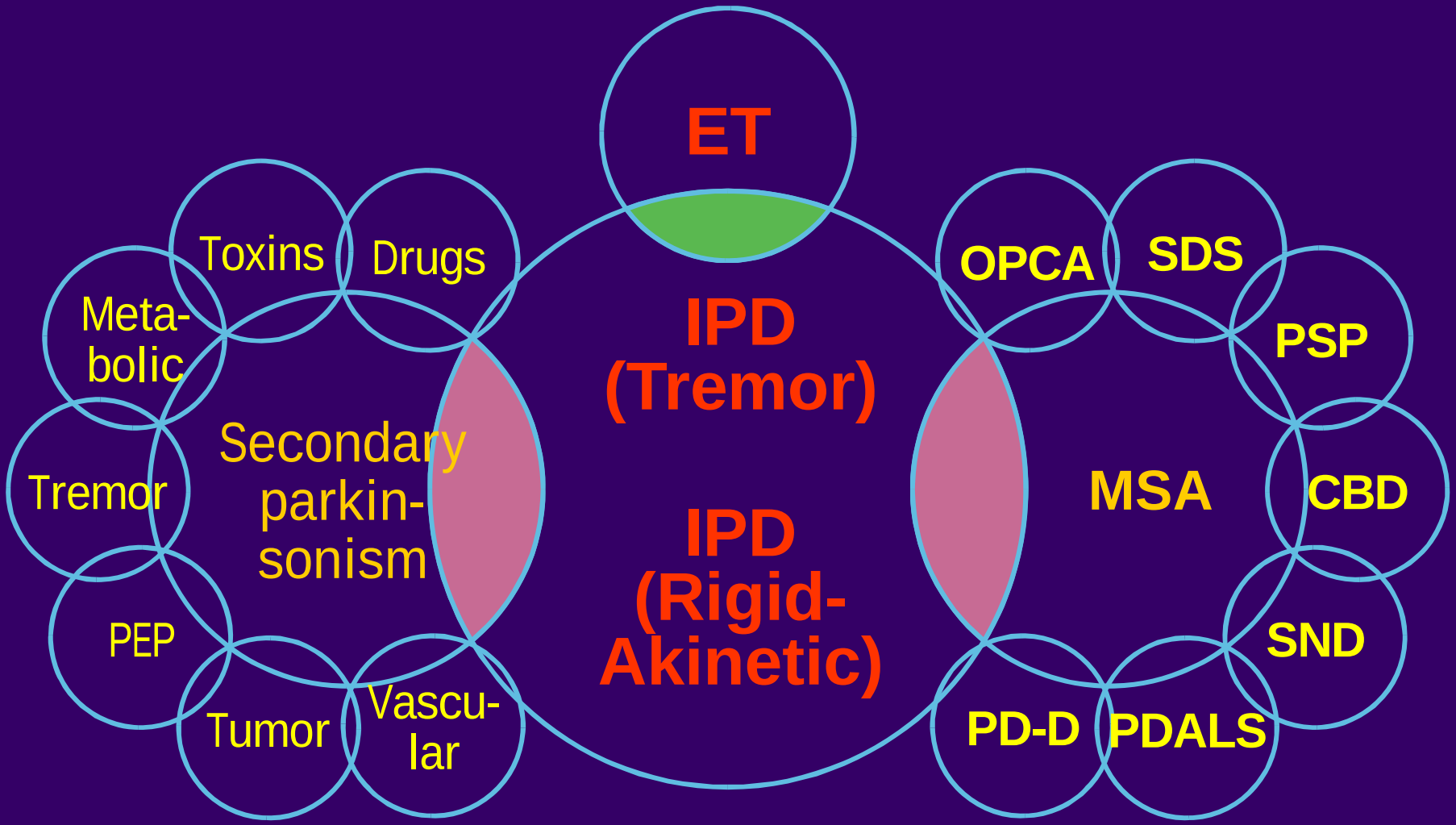


N. basalis Meynert



Kaplan-Meyer curves of survival in 200 PD patients with different AD stages




ET
IPD (Tremor)
IPD (Rigid-Akinetic)
Secondary parkin-sonism
Toxins
Drugs
Meta-bolic
Tremor
PEP
Tumor
Vascu-lar
MSA
OPCA
SDS
PSP
CBD
SND
PD-D
PDALS

Clinical criteria for dementia with Lewy bodies (DLB)

CERAD criteria

CDR 0.5-2 and any two:

- Delusions or hallucinations
- Extrapyramidal signs
- Unexplained falls / transient clouding of consciousness

Supportive features:

- Fluctuating course
- Levodopa failure
- Dementia > extrapyr. signs
- Weight loss, dysphagia, decreased mood

Exclude other dementias

McKeith criteria

Fluctuation in at least one:

- Test performance
- Activities of daily living
- Episodic confusion

Secondary (at least one):

- Hallucinations
- Extrapyr. sings or neuroleptic sensitivity
- Unexplained falls or transient clouding of consciousness
- Rapid decline

Exclude other causes of fluctuation and cerebral vascular events

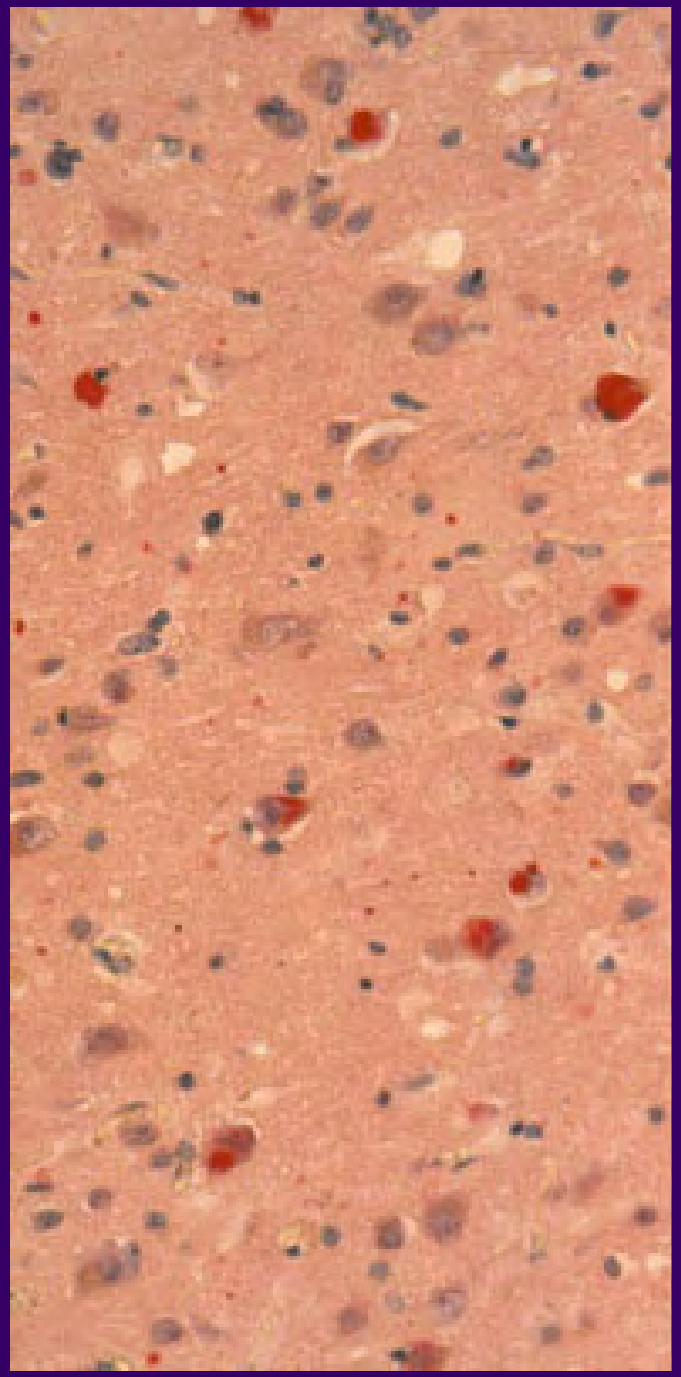
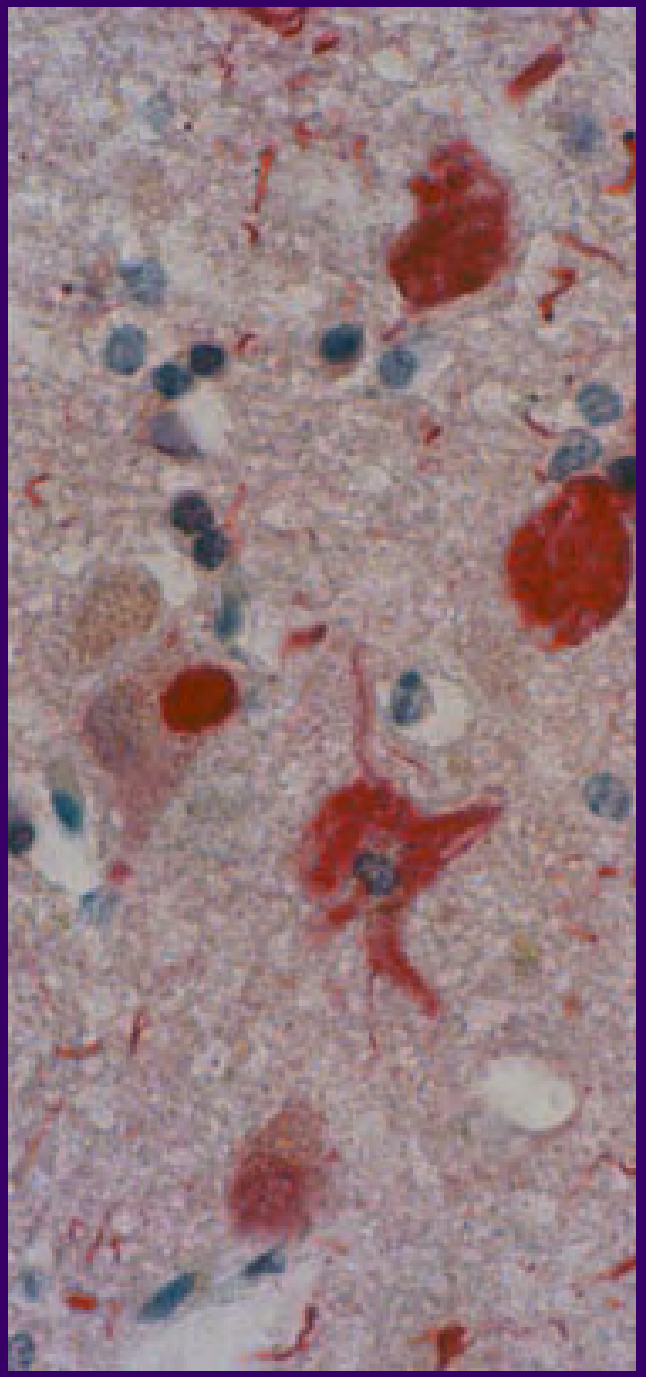
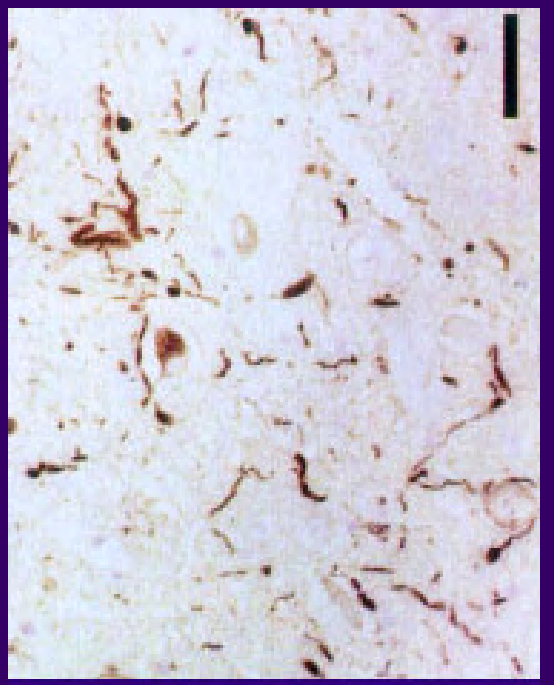
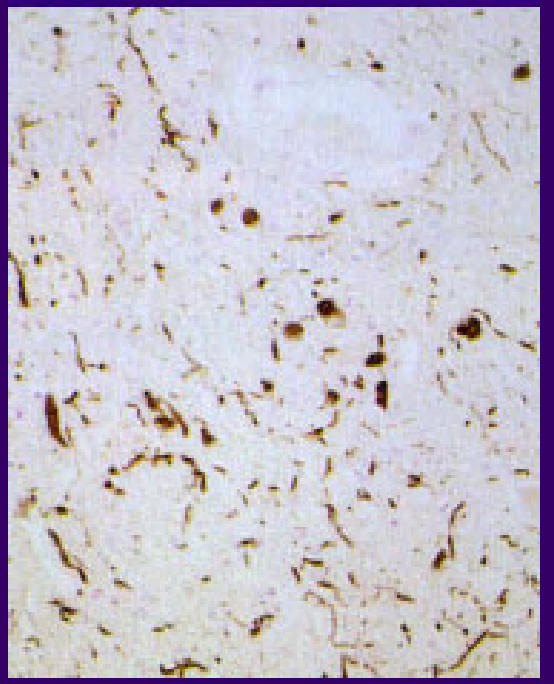
CDLB criteria

Two of the following for probable DLB (one of the following for possible):

- Fluctuating cognition, attention, alertness
- Visual hallucinations
- Extrapyramidal signs

Supportive features:

- Repeated falls, syncope
- Trans. loss of consciousness
- Neuroleptic sensitivity
- Systematized delusions
- Hallucinations

Lewy body scoring guidelines

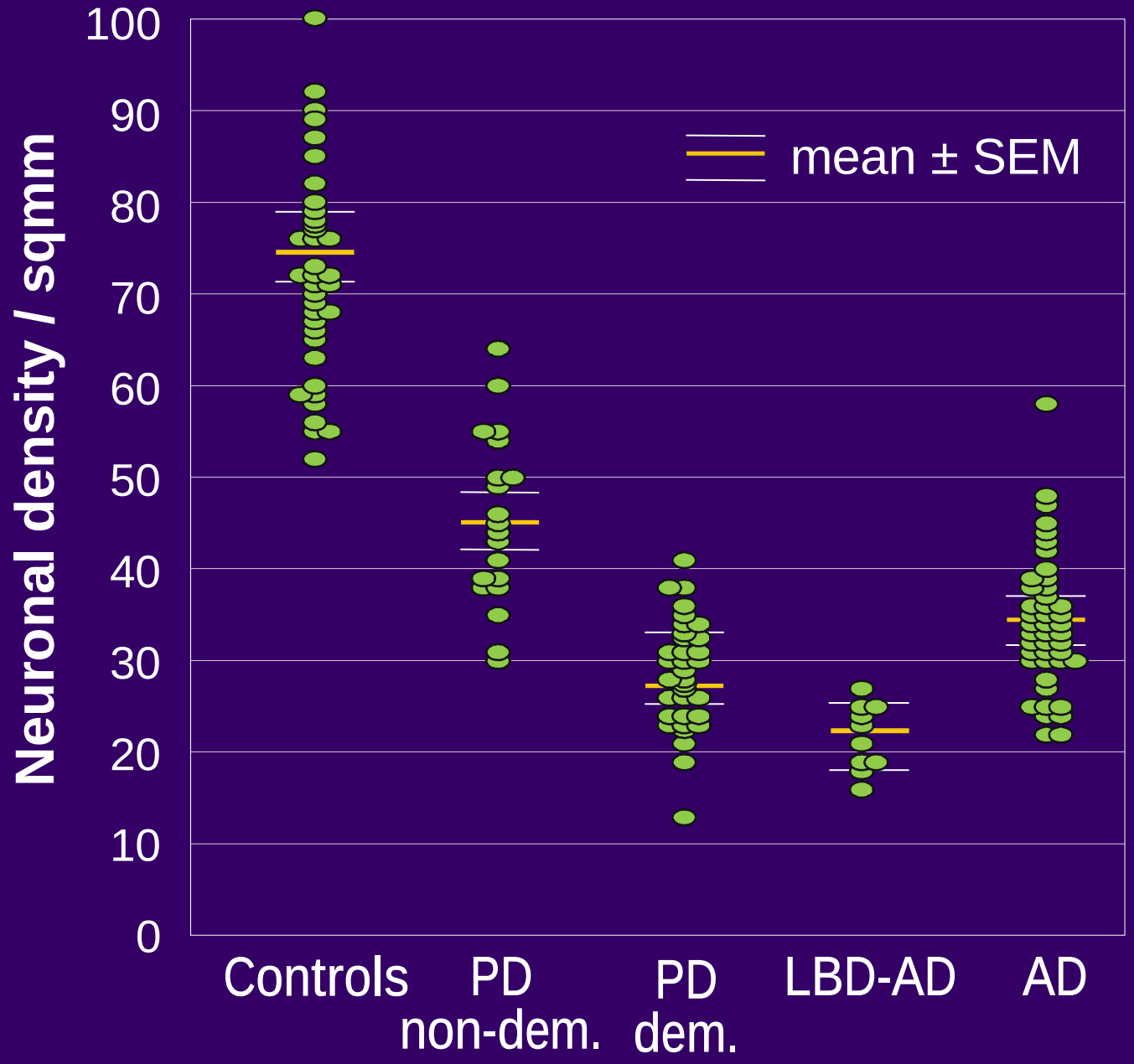
Cortical region	Anatomy	Score
Entorhinal cortex	medial flank of collateral sulcus	0 1 2
Cingulate gyrus	whole gyral complex	0 1 2
Mid-Frontal cortex	lateral flank of super. front. sulcus	0 1 2
Mid-Temporal cortex	inferior surface of super. front. sulcus	0 1 2
Inferior parietal lobule	lateral flank of parietal sulcus	0 1 2

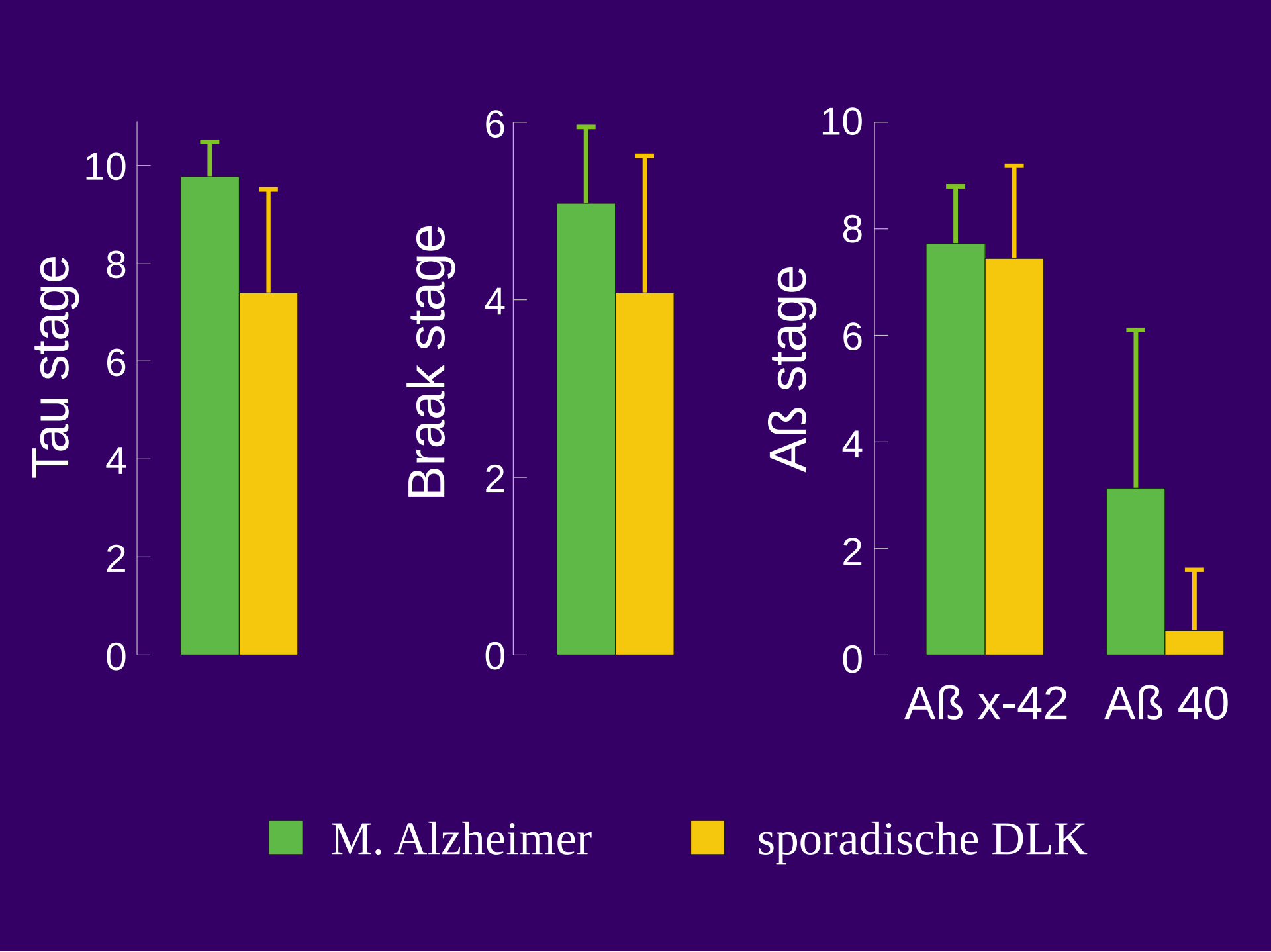
0-2	Brainstem-predominat
3-6	Limbic or 'transitional'
7-10	Neocortical

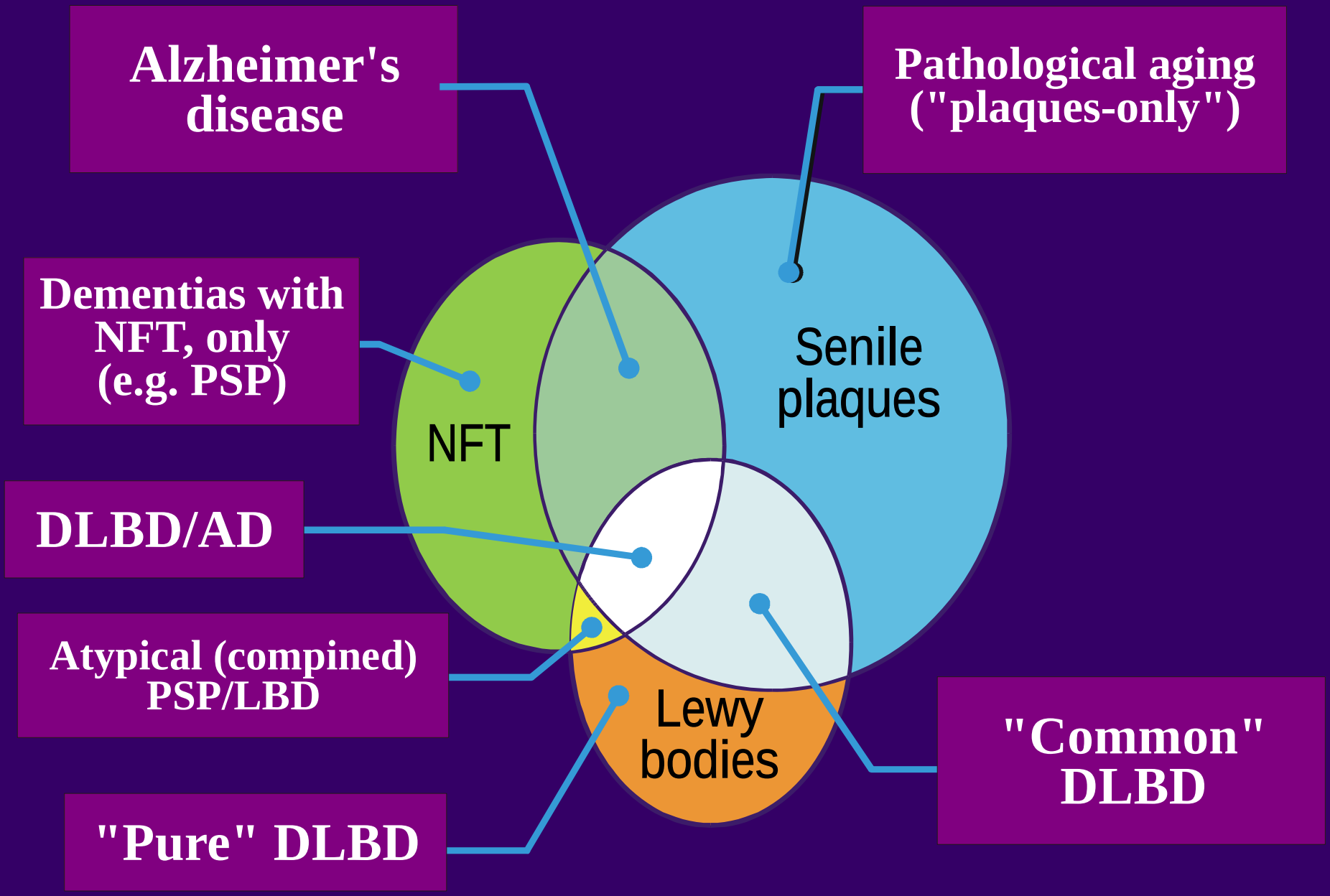
Score 1: ≤ to 5 LBs per region

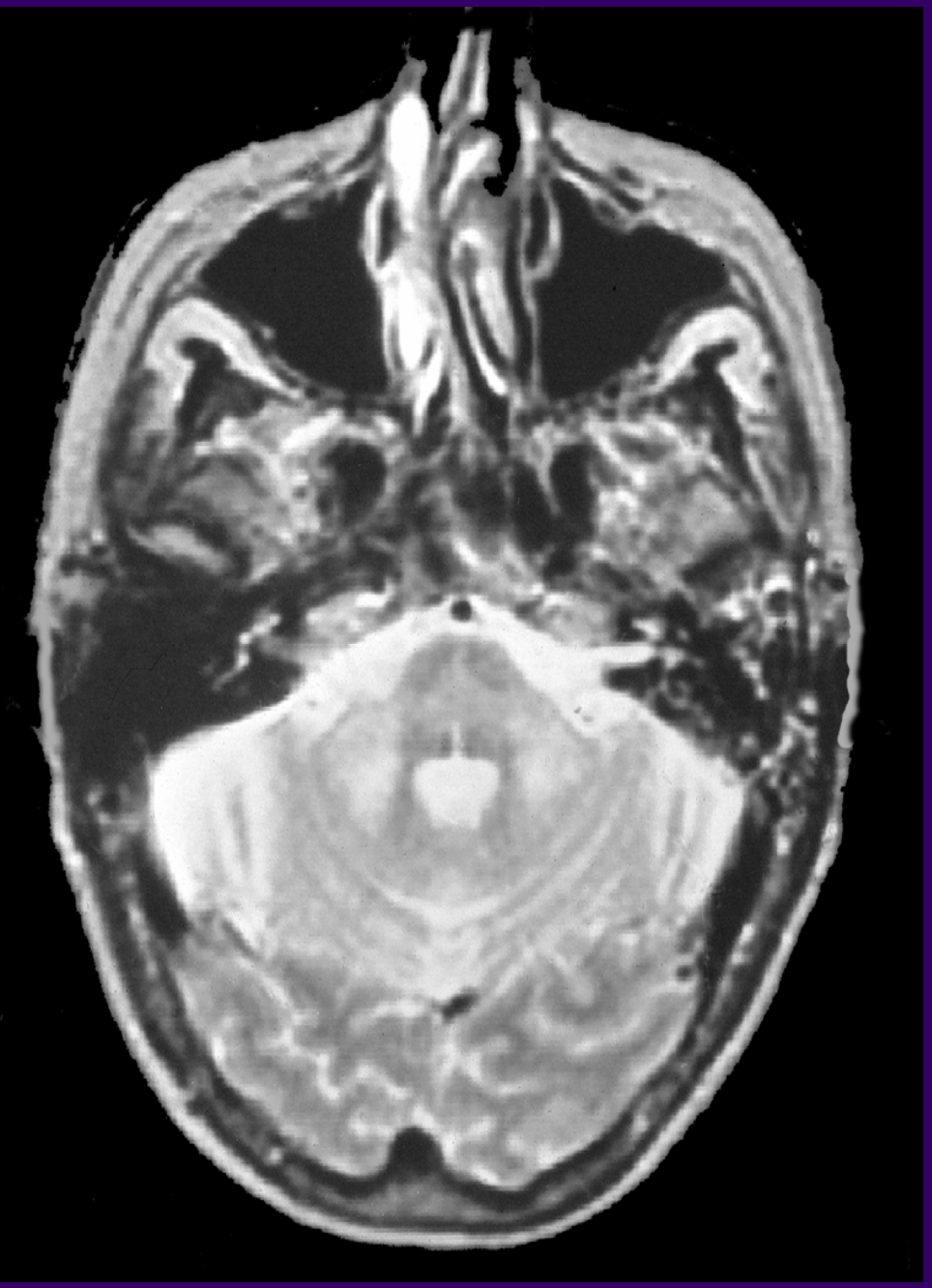
Score 2: > 5 LBs per region

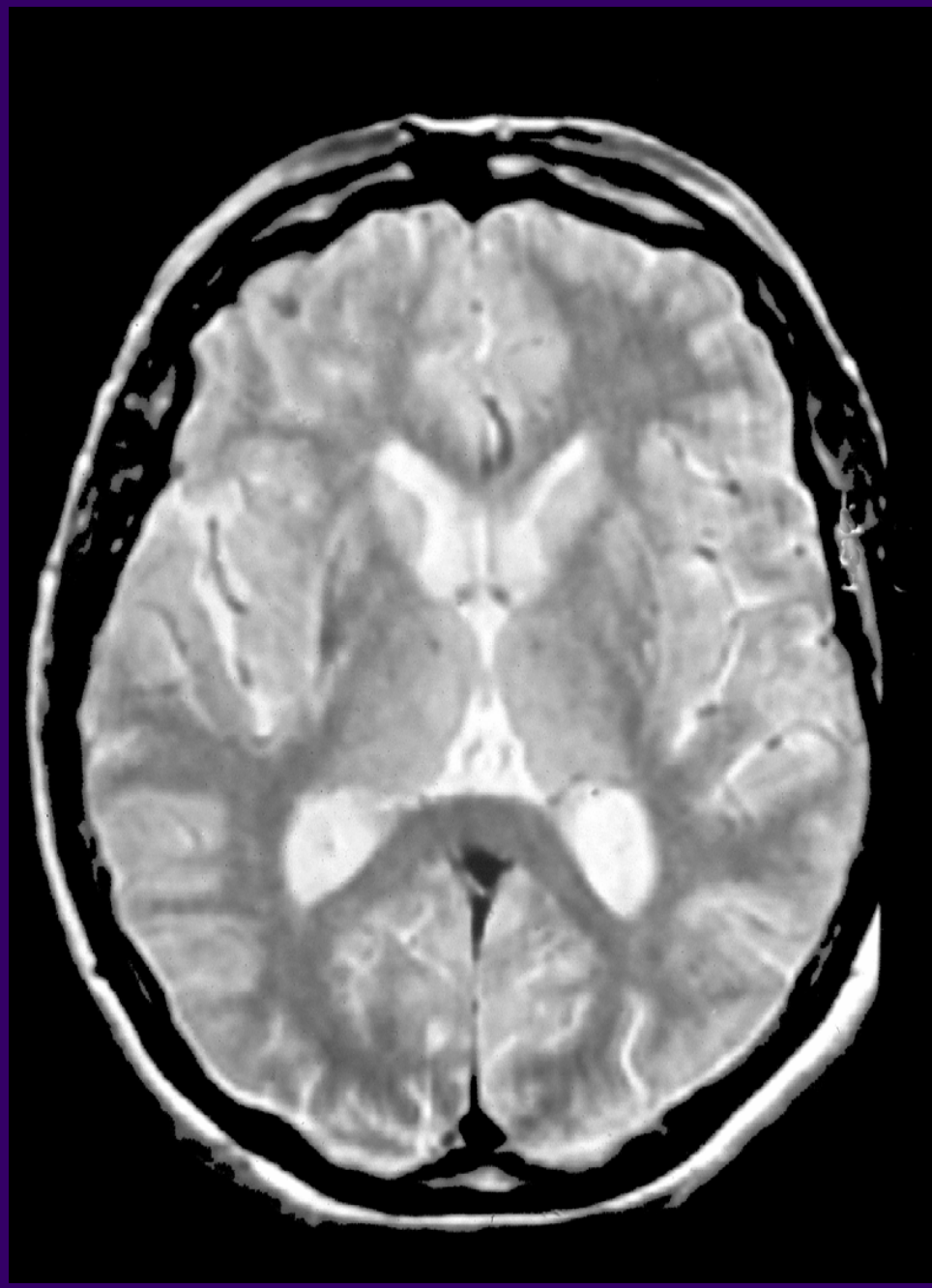
Nucleus basalis of Meynert (Magnocellular part)



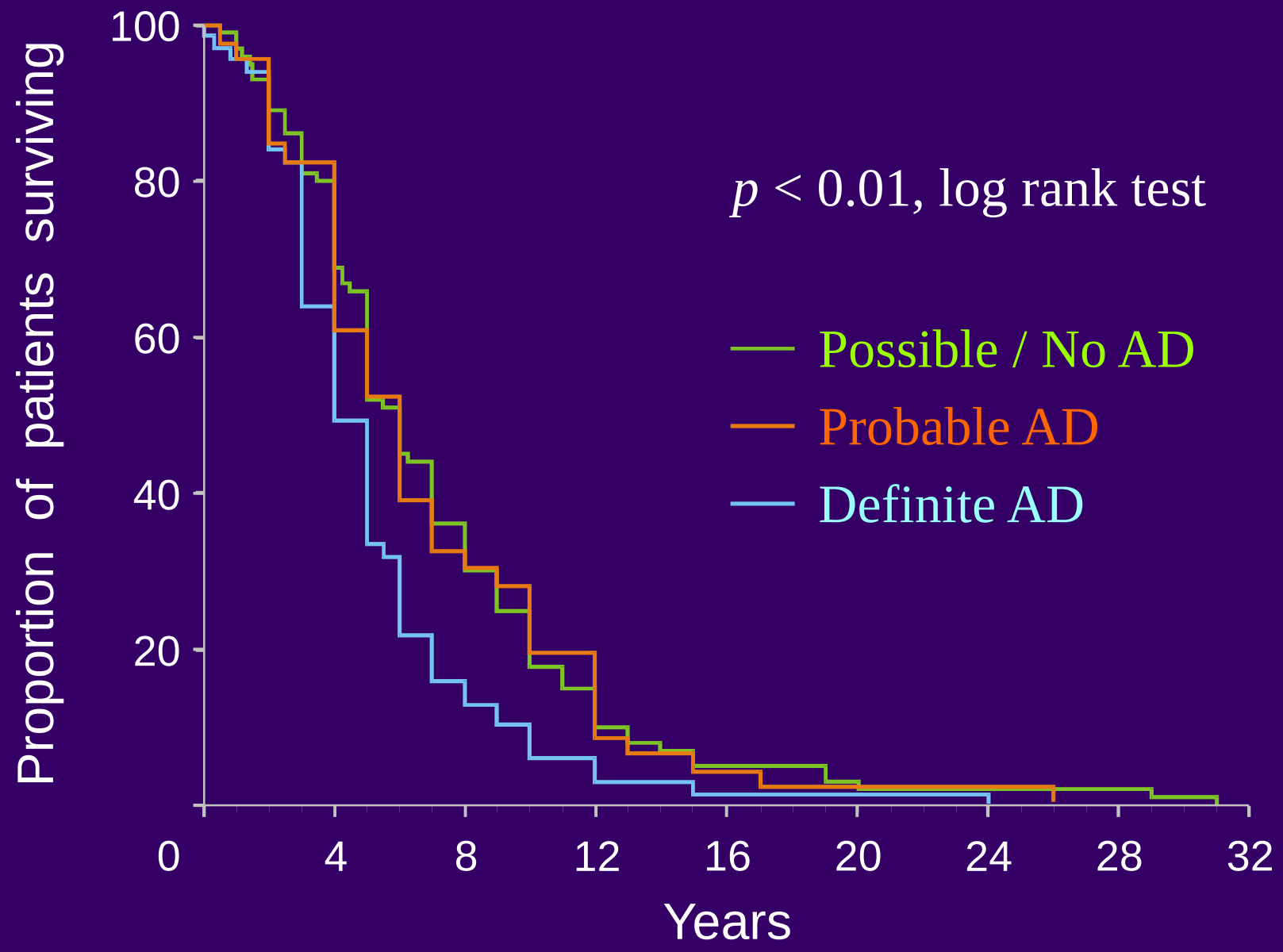

Tau stage
0
2
4
6
8
10
Braak stage
0
2
4
6
Aß stage
0
2
4
6
8
10
Aß x-42
Aß 40
M. Alzheimer
sporadische DLK


Alzheimer's disease
Pathological aging ("plaques-only")
Dementias with NFT, only (e.g. PSP)
NFT
Senile plaques
DLBD/AD
Atypical (compined) PSP/LBD
Lewy bodies
"Common" DLBD
"Pure" DLBD





AD pathology and survival in DLB



Diagnostic categories of MSA

(Gilman et al. 1999)

1. **Possible MSA**

One criterion + 2 clinical features from other domains
Poor L-dopa response for parkinsonism

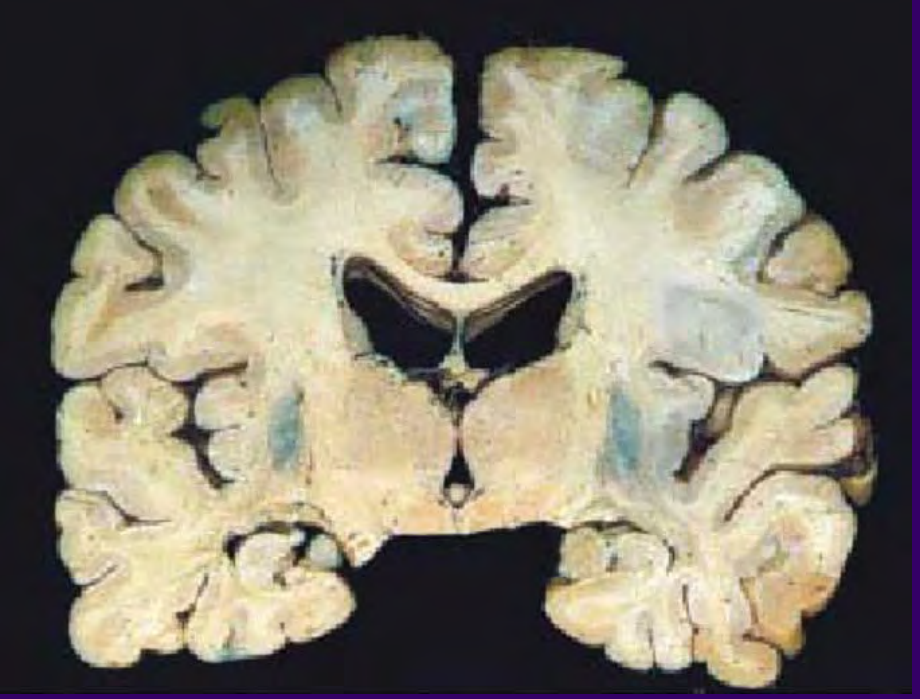
2. **Probable MSA**

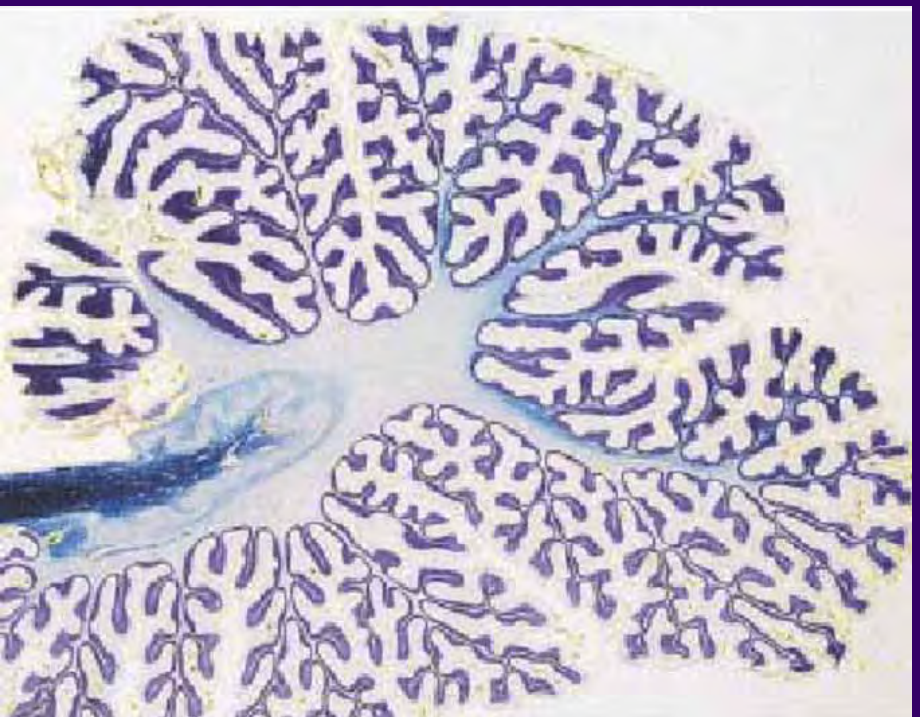
Criterion for autonomic failure / urinary dysfunction + poorly L-dopa responsive parkinsonism or cerebellar dysfunction

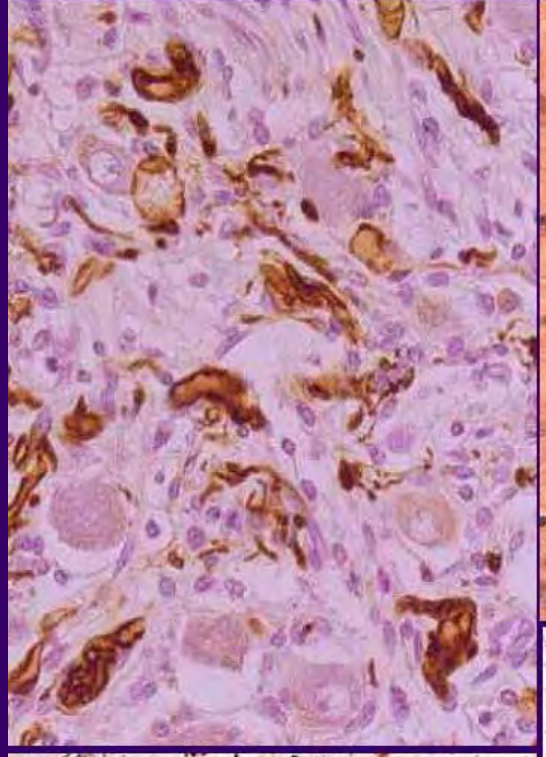
3. **Definite MSA**

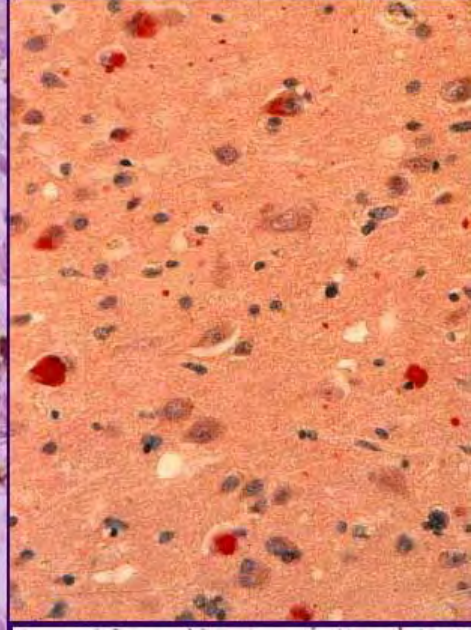
Pathologically confirmed: glial cytoplasmic inclusions + comb. degeneration of nigrostriatal and olivopontocerebellar systems

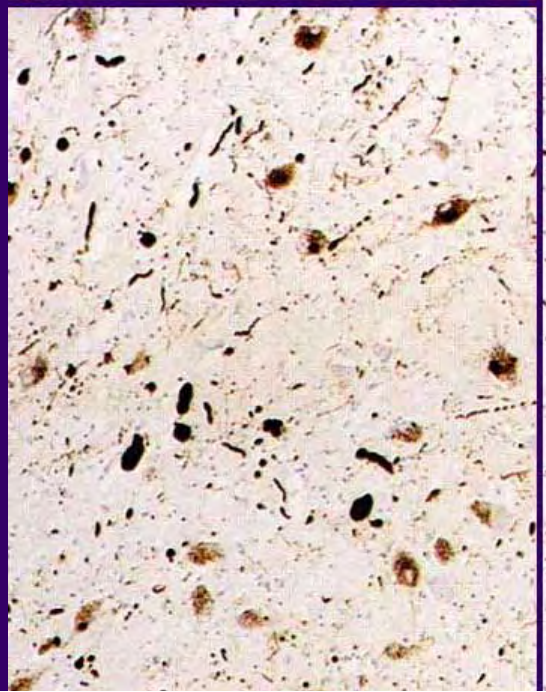
MSA-P - predominant parkinsonian features
MSA-C - predominant cerebellar features

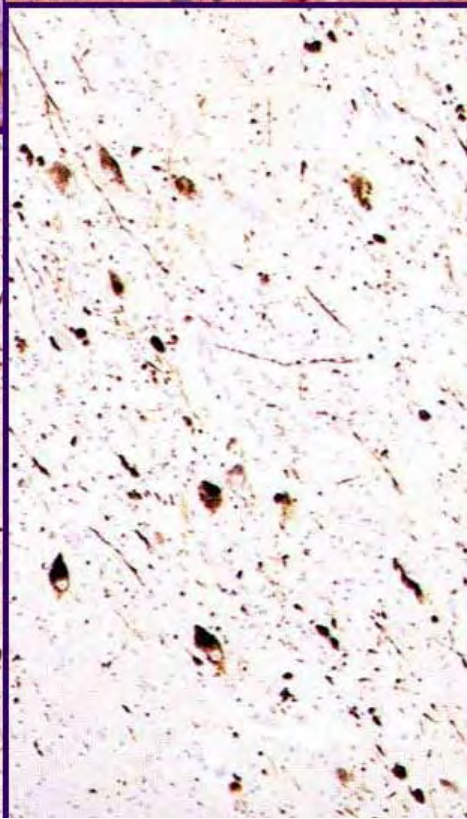




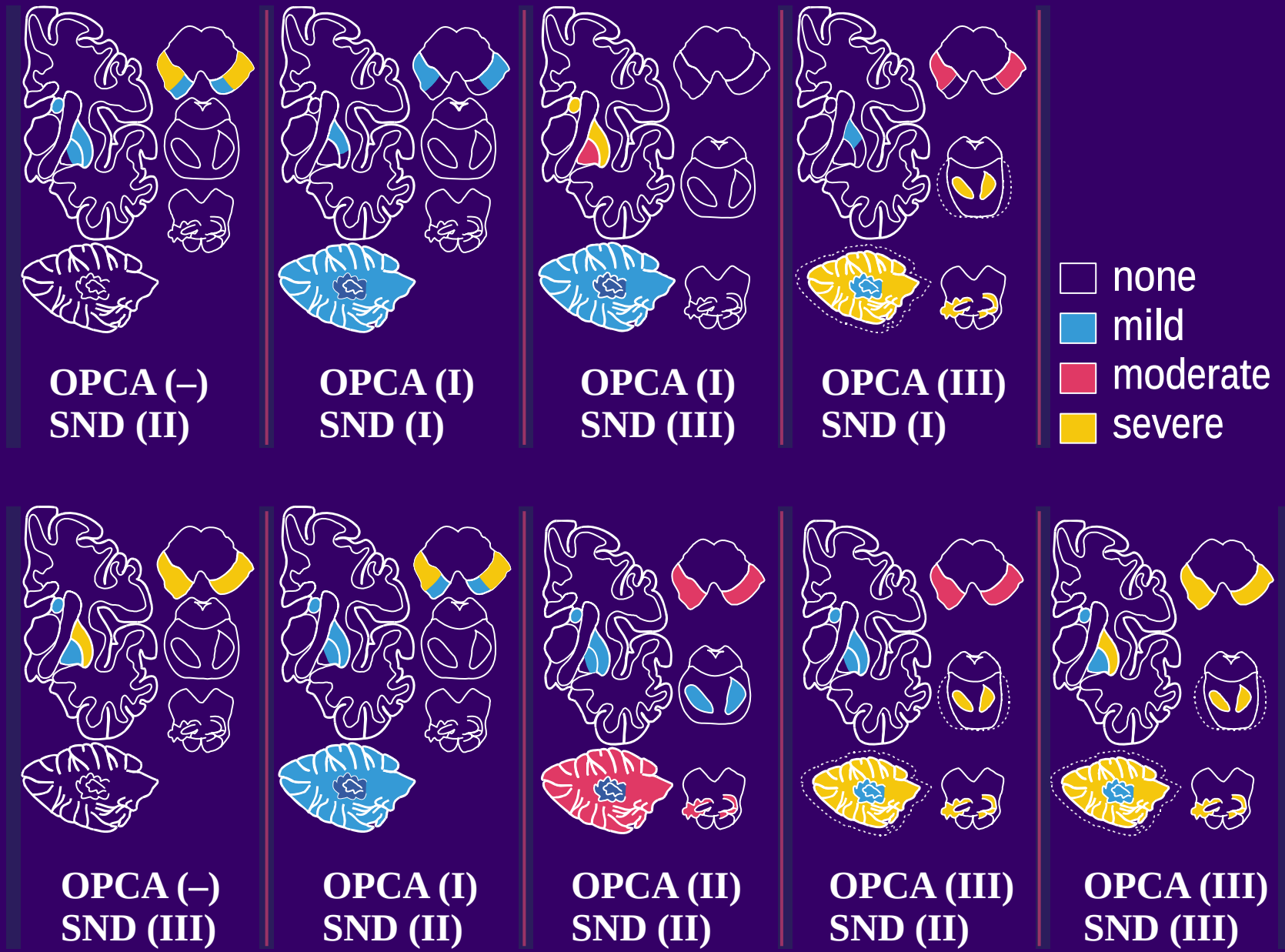




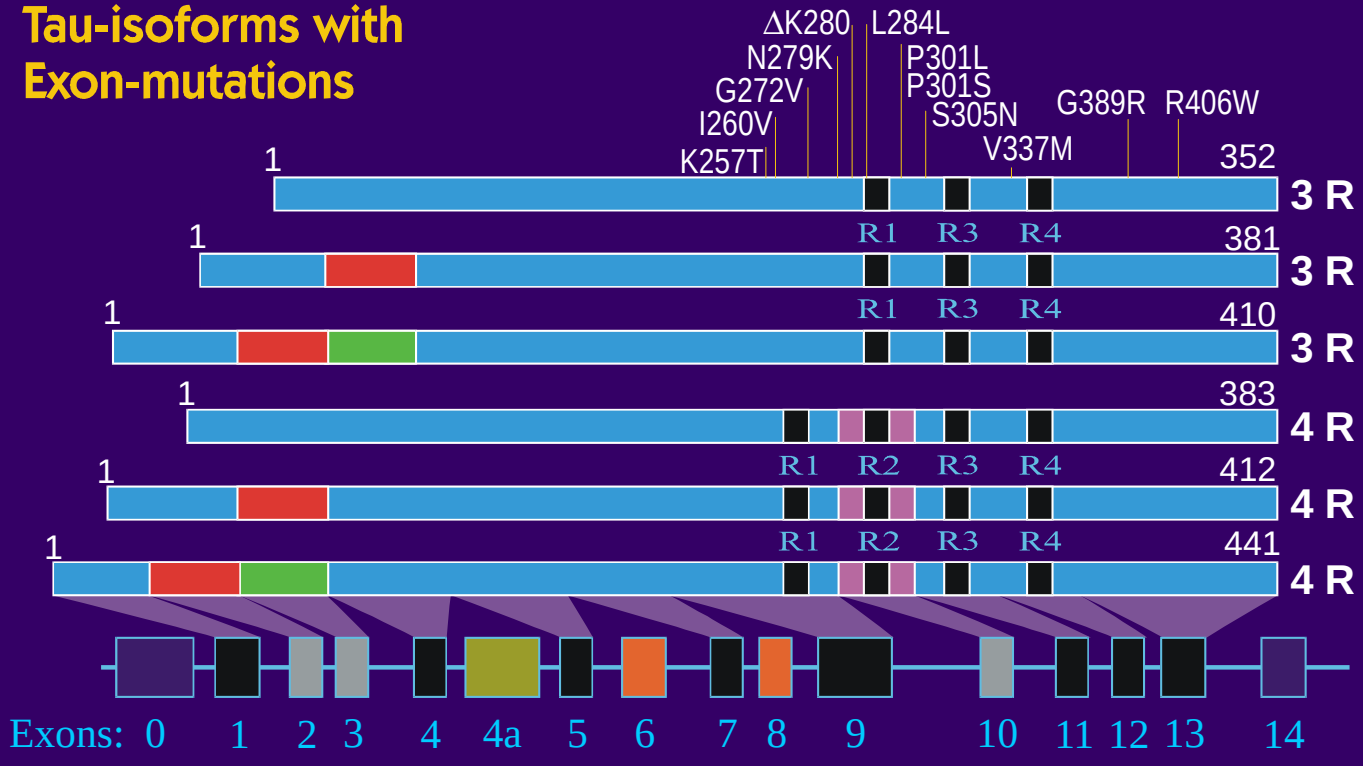


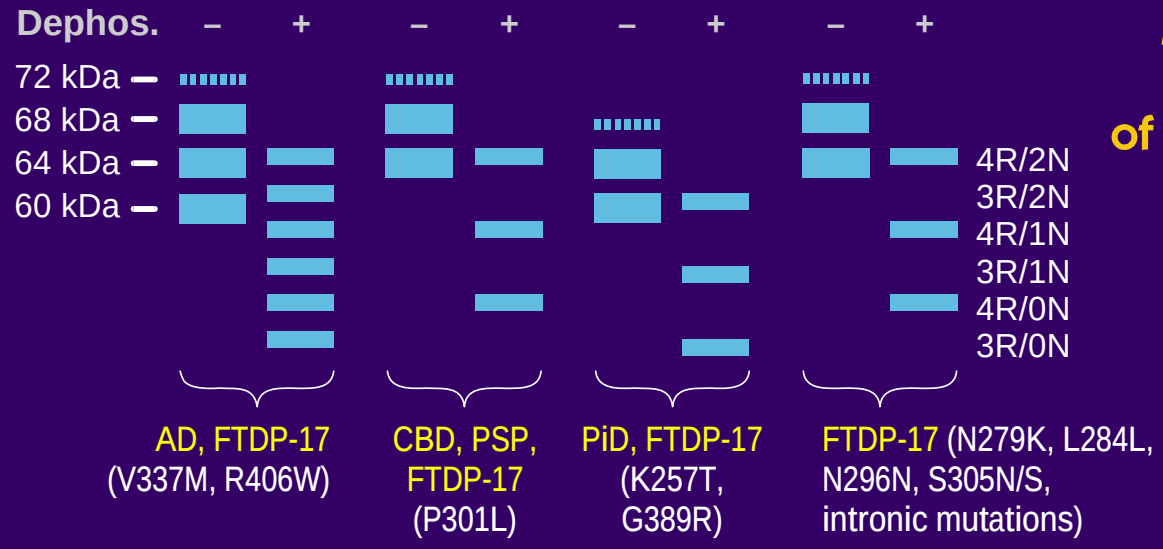


Neuropathological staging in MSA-P and MSA-C

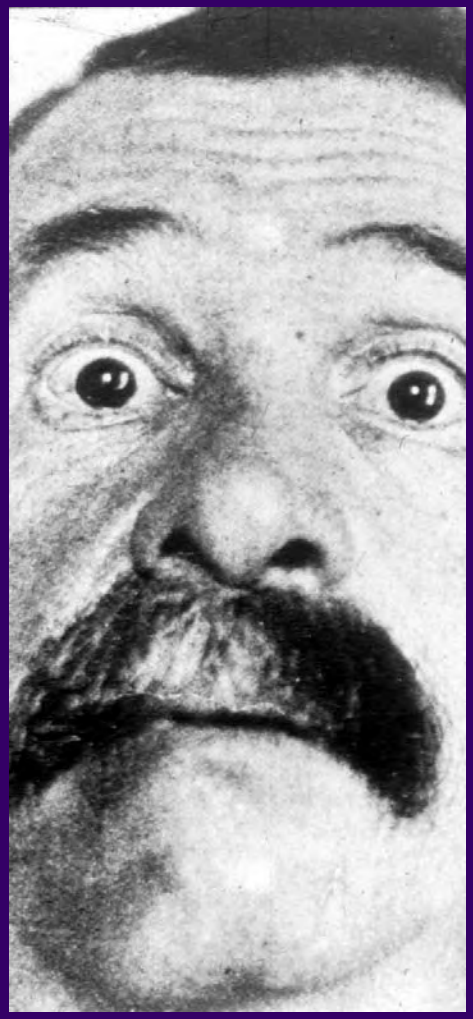


Tau-isoforms with Exon-mutations





Migration pattern of insoluble tau on SOS gel electro-phoresis

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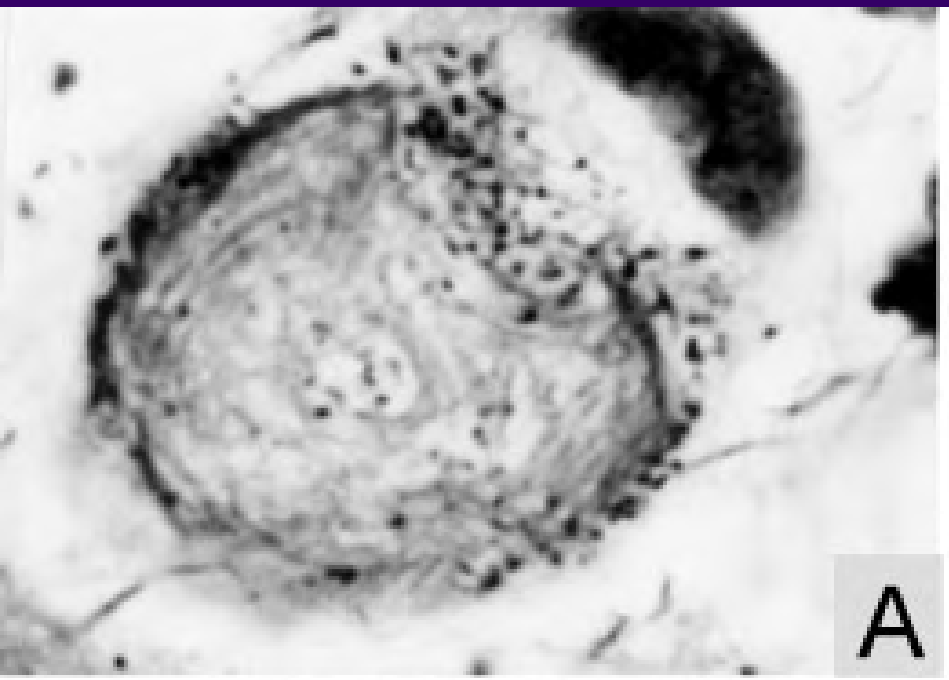
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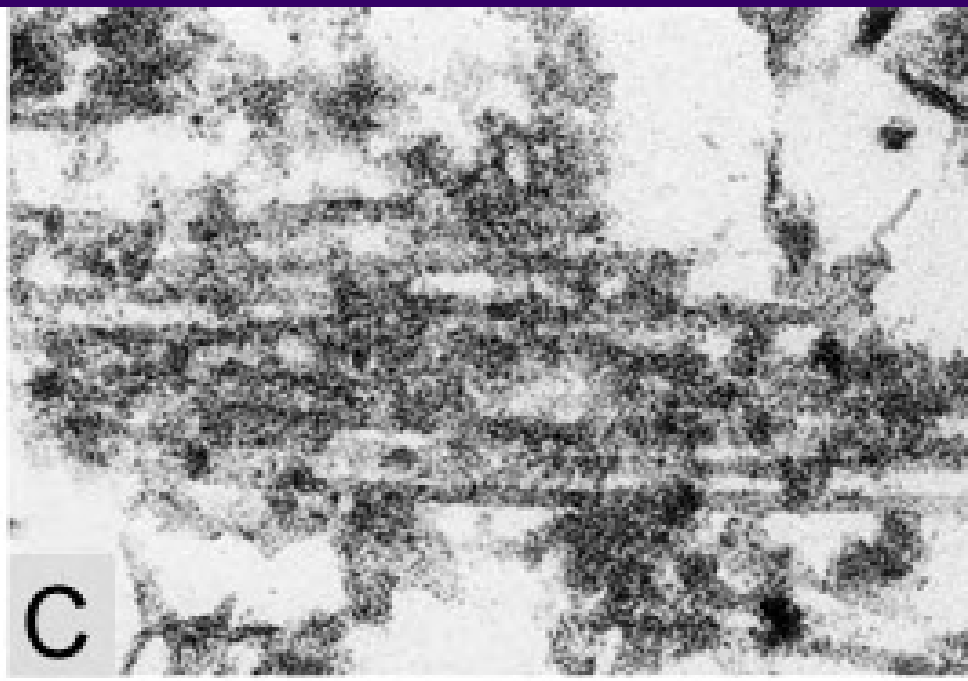
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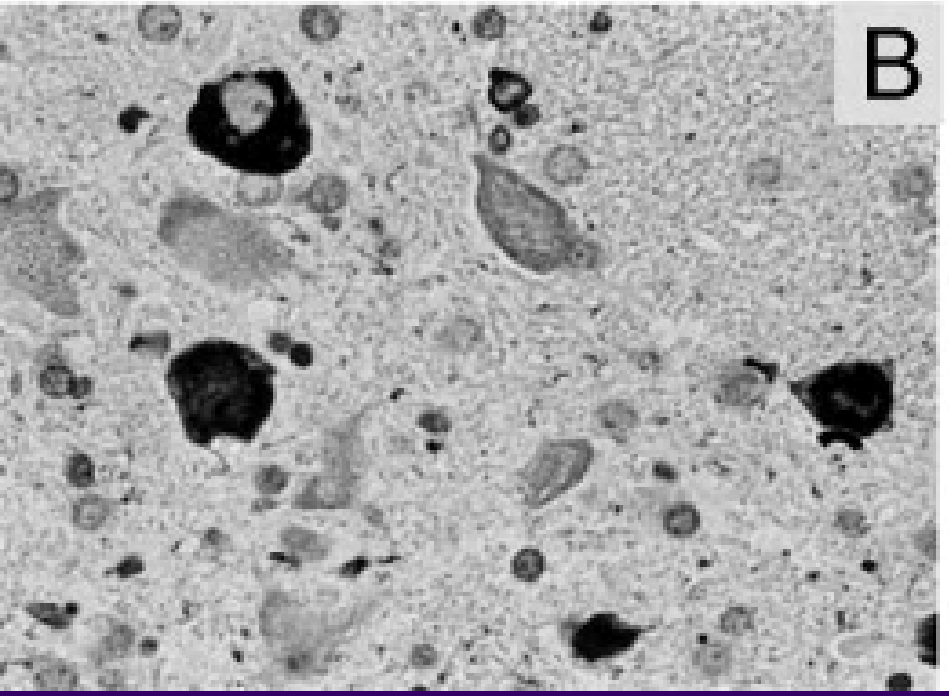
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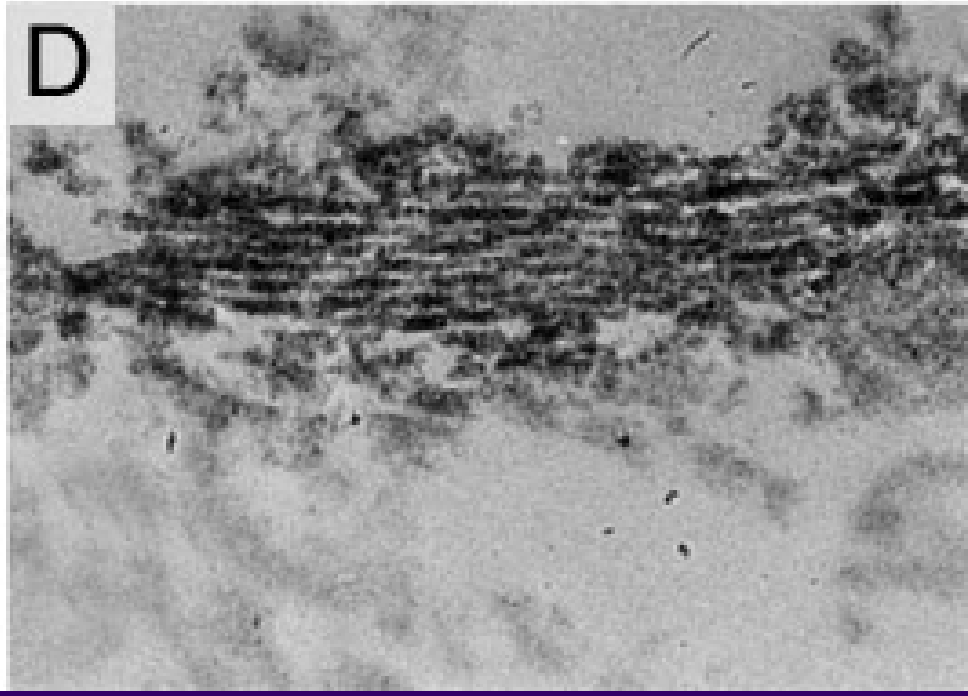
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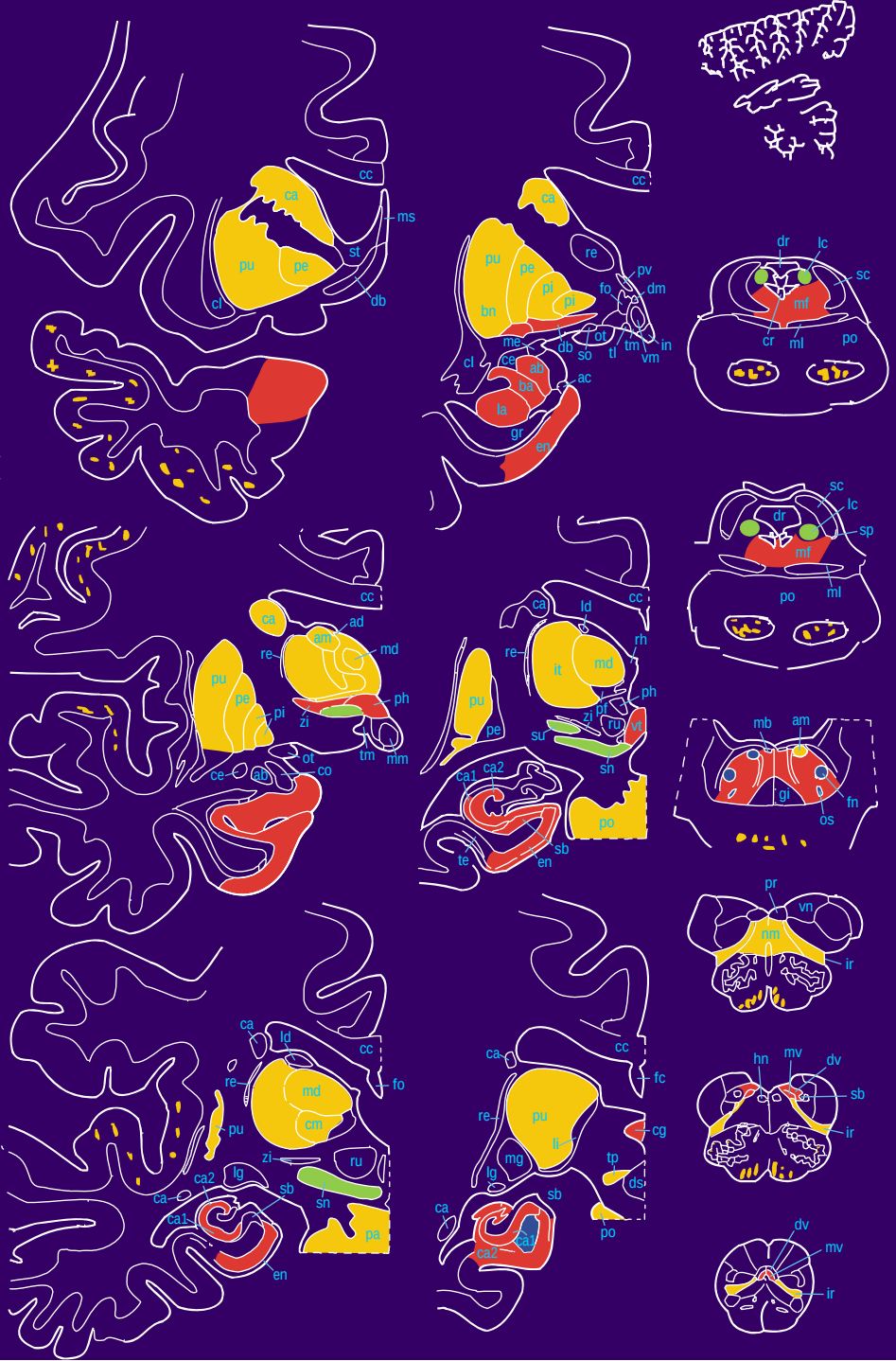
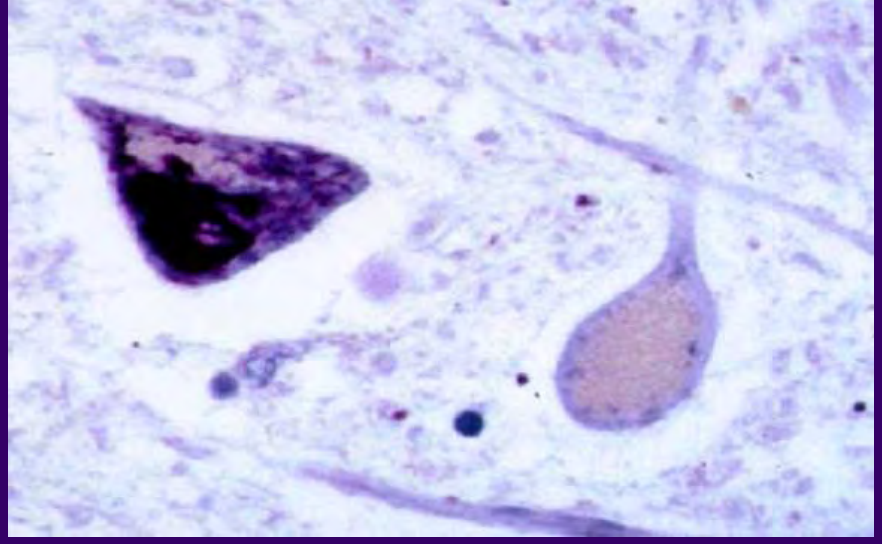
Distribution pattern of pathological lesions (neuron loss, tau-pathology, gliosis) in post-encephalitic Parkinsonism

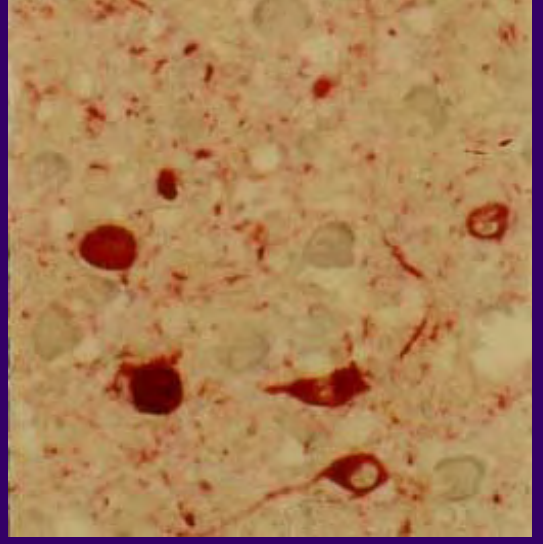
Severe lesions

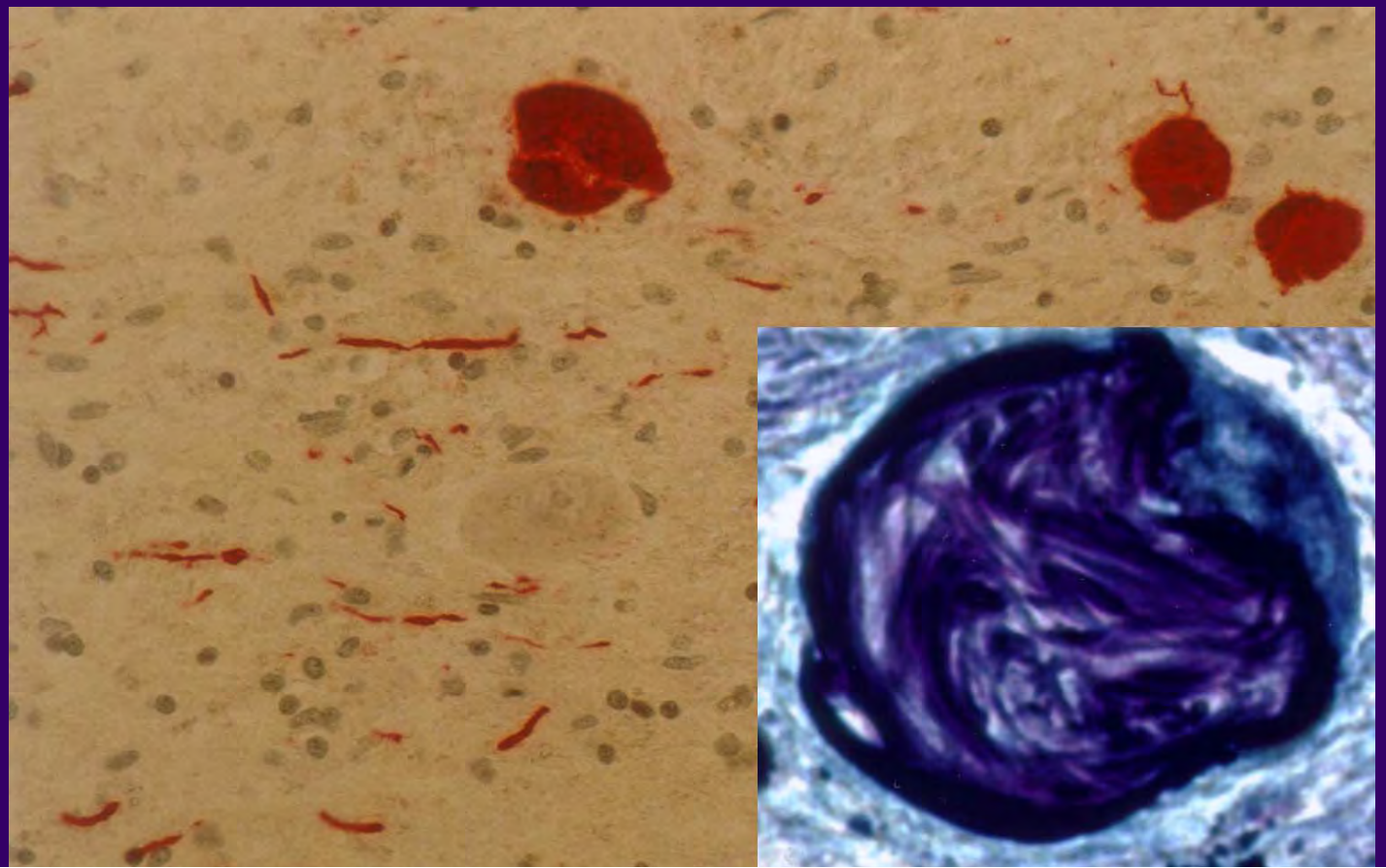
Moderate lesions

Mild lesions



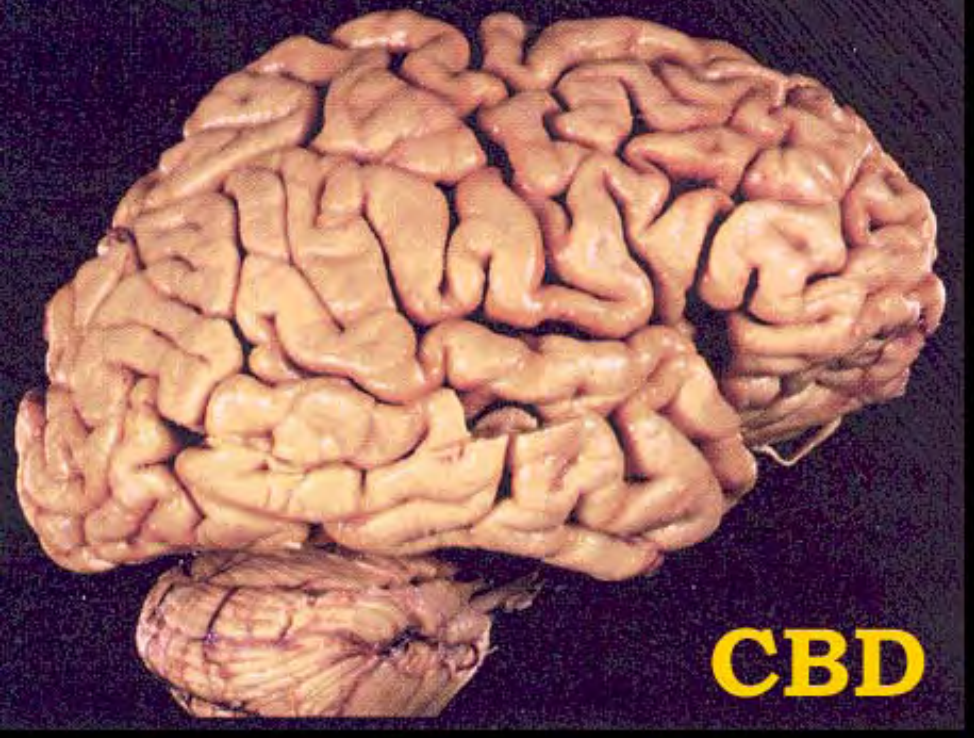






Histopathologic lesions in corticobasal degeneration

Lesion	Distribution	Comment
Neuronal inclusions	Cortex Basal ganglia+thalamus Basal nucleus of Meynert Subst. Nigra & locus cerul.	Neurons in the limbic structures (hippocampu, amygdala) usually spared, may have pre-tangles.
Threads & Coiled Bodies (Tau-positive)	White matter Centrum semiovale Long tracts, Pontine base Cortex, basal ganglia, Brainstem & cerebellum	In most cases the density of tau-immunopos. Threads in white matter equals or evan exceeds that in gray matter.
Astrocytic plaques	Cortex Basal ganglia	Diagnostic significance.
BALLONED OR ACHROMATIC NEURONS	Affected cortices (common) Basal ganglia (uncommon)	
NEURONAL LOSS	Affected cortices Substantia nigra, globus pallidus	Superficial spongiosis, gliosis, widespread inclusions.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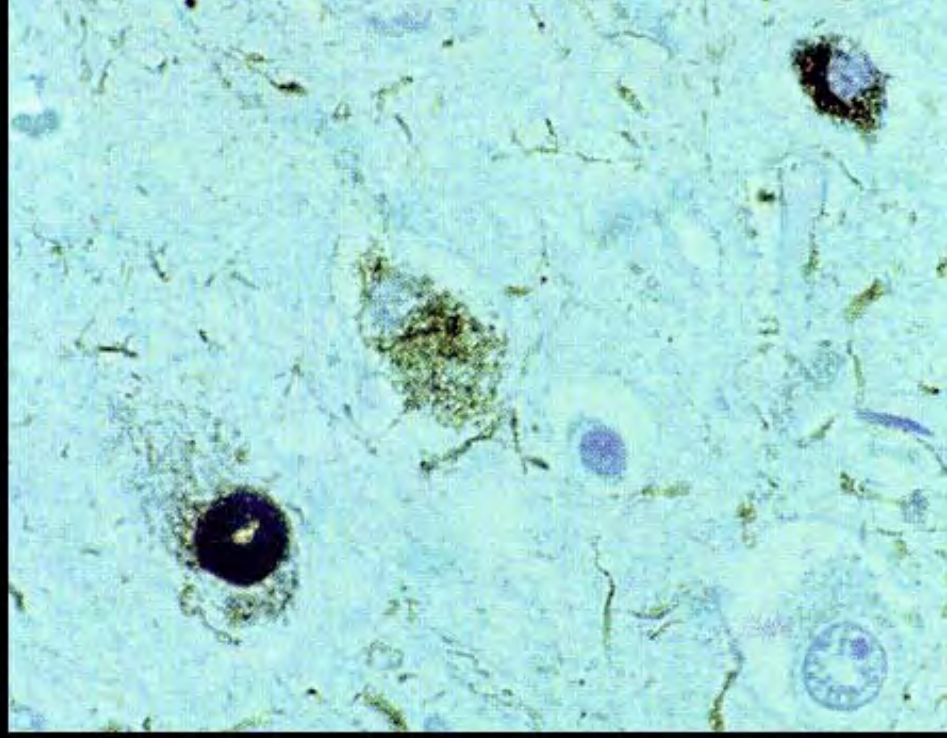

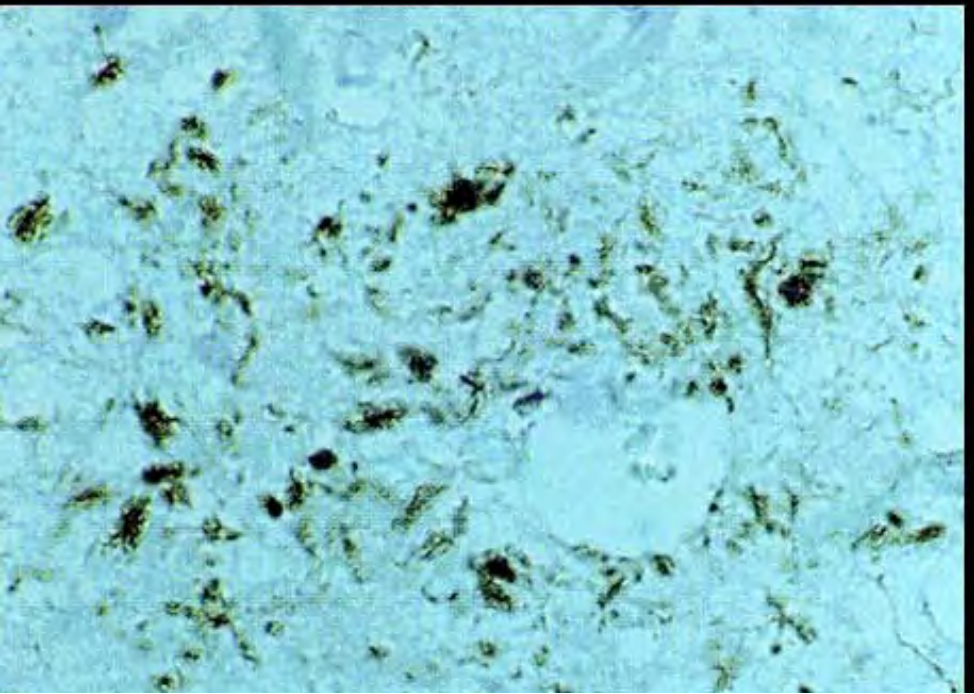

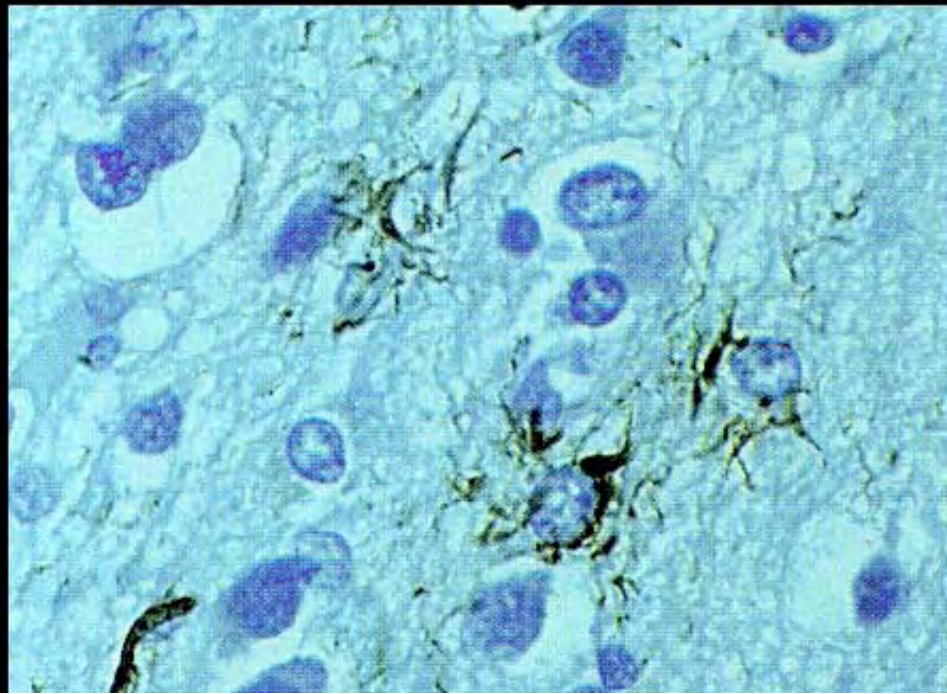

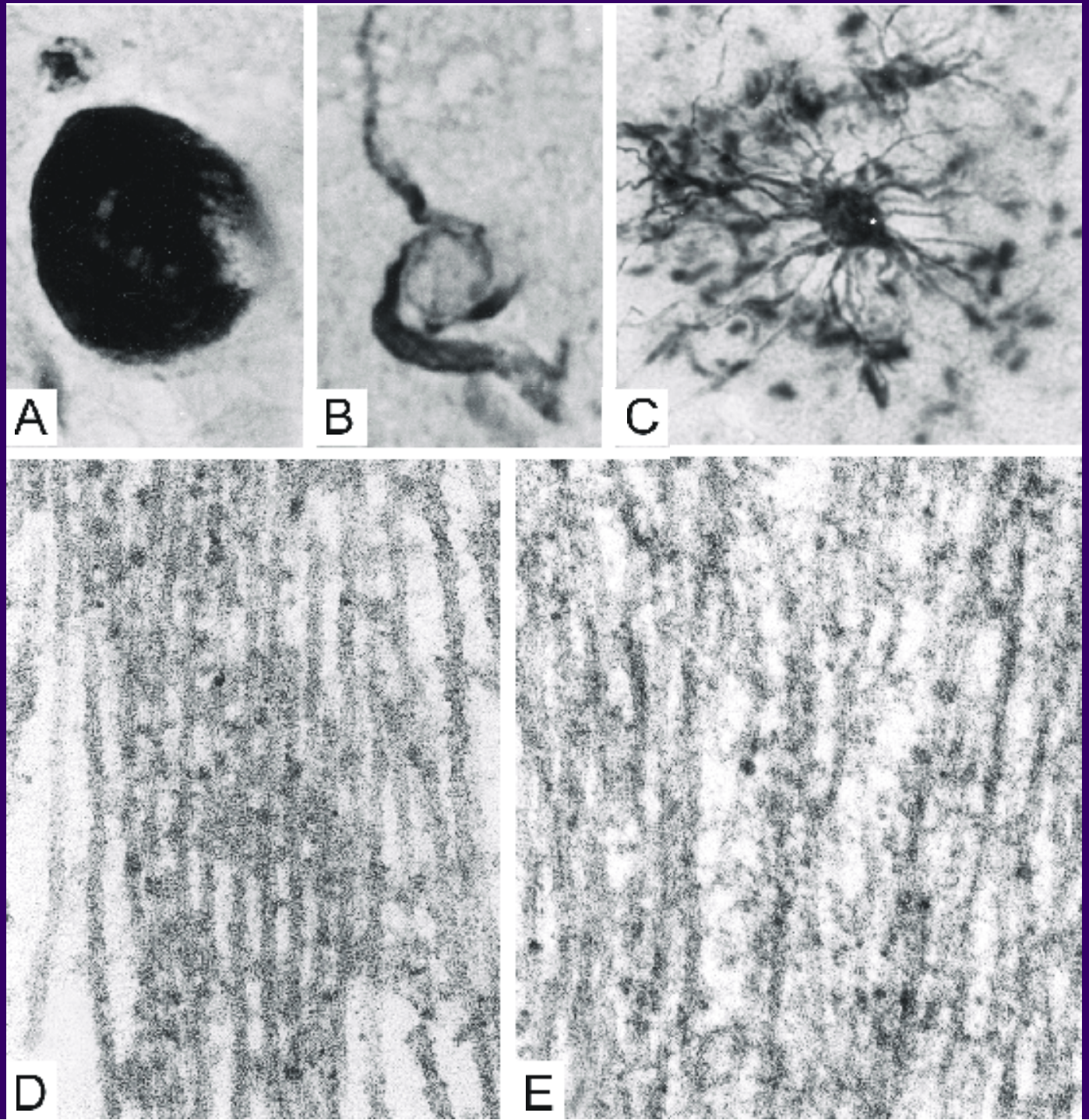
A
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Clinical classification of frontotemporal dementias

1. Syndrome-based clinical features and anatomy

- Frontal variant FTD. . . . . bilateral orbito-frontal
- Semantic dementia. . . . . left/bilateral temporal pole
- Progressive non-fluent aphasia . Left perisylvian

2. Familial FTD

- Chromosome 17 tauopathy with parkinsonism ± amyotrophy (FTDP-17)
- Chromosome 3-linked Danish variant
- Chromosome 9-linked FTD-MND
- Familial FTD with no known linkage (majority at present)

3. FTD with motor neuron disease

Pathologic classification of FTDs

1. With tau-pos. lesions (3R tau)

- Pick's disease (neuronal inclus.), usually non-familial
- FTDP-17 (neuronal tangles, tau-pos. glia)

2. With tau-pos. lesions (4R tau)

- Corticobasal degeneration (achromatic axons, astrocytic plaques)
- Progressive supranuclear palsy (subcort. NFTs, tau-pos. Astrocytes)
- FTDP-7 (see above)
- Argyrophilic grain disease (AGD) (tau+ grains ± NFTs)

3. With tau-pos. lesions (3+4R tau)

- Neurofibrillary tangle senile dementia (NFT-SD)
- FTDP-17 (see above)

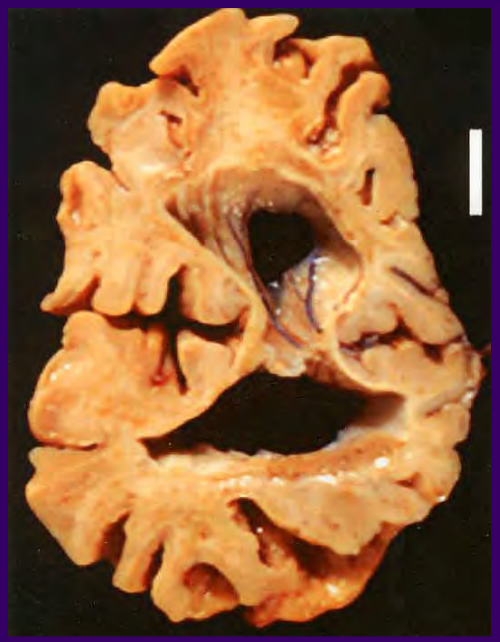
4. With ubiquitin-pos.(tau-neg.) inclusions +/- MND

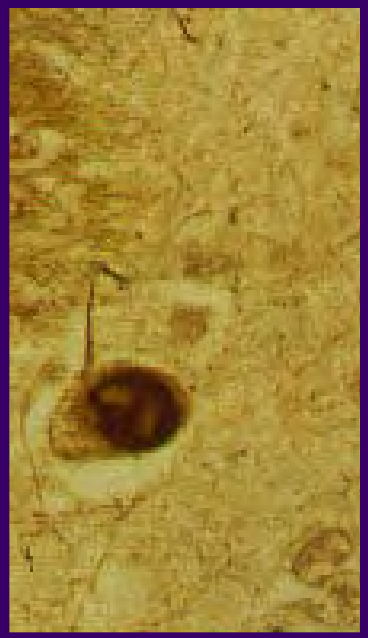
- FT lobar degeneration (FTLD) with MND / MND-like inclusions

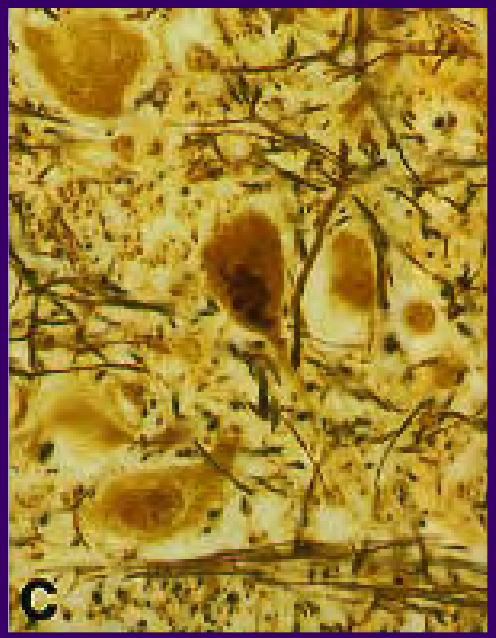
5. Frontotemporal neuron loss,spongiosis; no inclusions

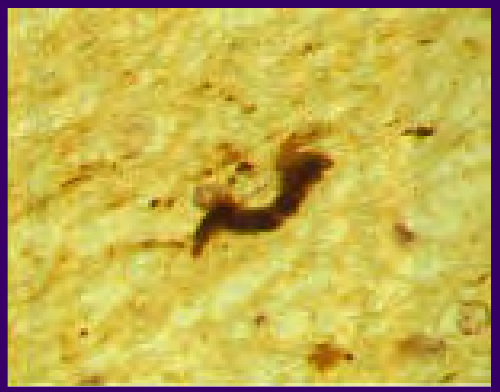
- Dementia lacking distinct histology (DLDH or FTLD)

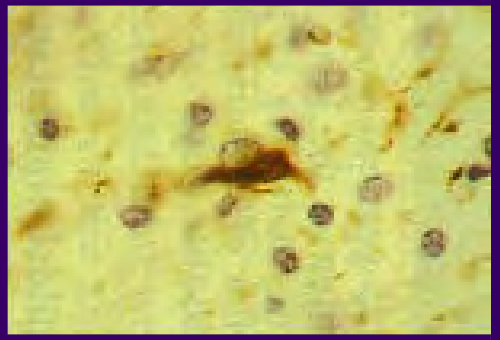
Familial FTD with P103 tau mutation

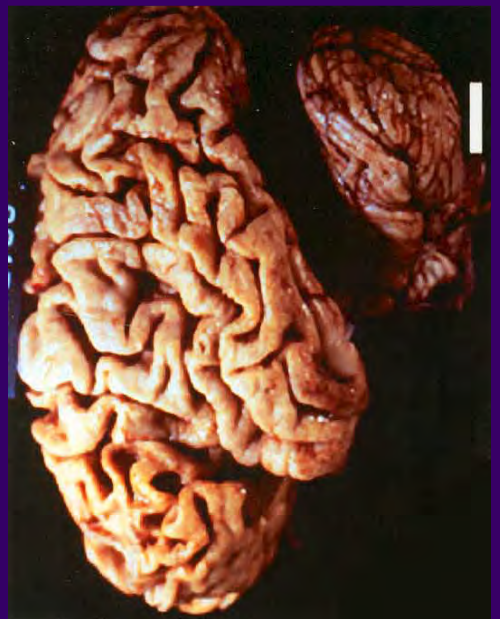


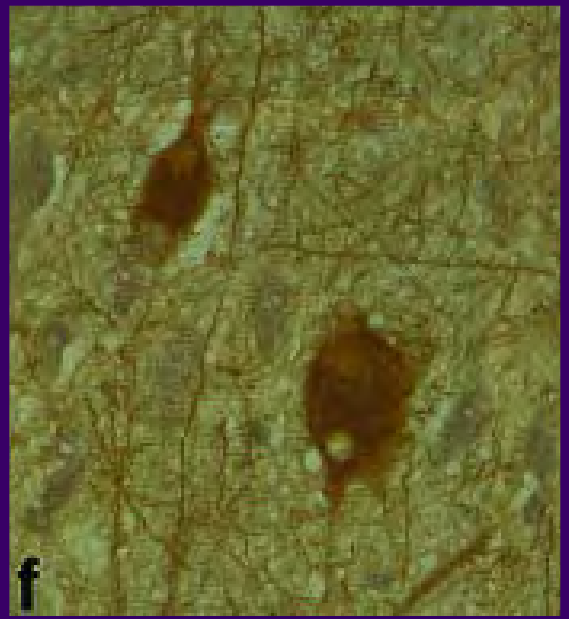


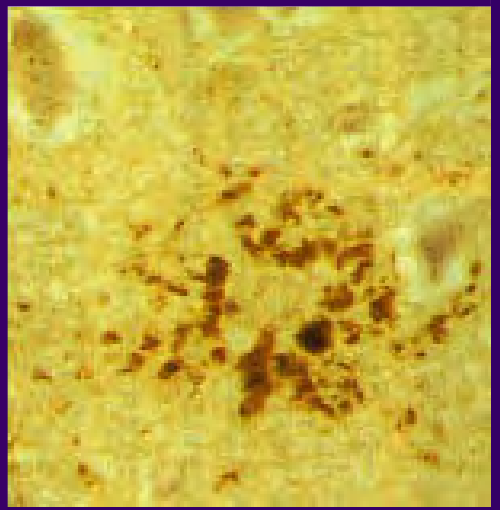












Clinico-pathologic correlations of some tauopathies

B.E. Boeve 2005

Syndrome	Major cortical topography
Mild cognitive impairment Progressive amnesia syndrome	Bilateral mesial temporal
Frontotemporal dementia Progress. neuropsychiatric syndrome Progress. frontal network syndrome Progress. dysexecutive syndrome	Focal / asymetric prefrontal and orbitofrontal
Primary progressive aphasia Progress. aphasia syndrome Progress. nonfluent aphasia syndrome Semantic aphasia and associative agnosia	Focal / asymetric frontotemporal (dominant hemisphere)
Corticobasal syndrome Progress. asymetric rigidity and apraxia syndrome Progress. perceptual motor syndrome	Focal / asymetric parietofrontal
Posterior cortical atrophy Progress. cortical visual dysfunction syndrome Progress. simultanagnosis / Balint's syndrome	Focal / asymetric parietooccipital

Histopathology / disease

- Alzheimer dis.
- Pick's dis.
- CBD
- PSP
- MND inclusion dementia
- NIBD
- DLDH
- CJD

Neurodegenerative disorders with protein filaments

Filamentous protein aggregates

Extracellular

- **PrP** Prion-diseases
- **Aβ** Aging, AD, Down syndr.

Intraneuronal

Intranuclear

Polyglutamine disorders
- Huntigton disease
- DRPLA u.a.

Cytoplasm / Neurites

"Ubiquitin Syndrome"
- ALS-dementia
- FLD (MND-type)

α-Synucleinopathies
- Parkinson disease
- Dementia w. Lewy bodies
- Multiple system atrophy (CGIs in glia)

Tauopathies

Triplet-Tauopathies
3 & 4-Repeats
(predominant neuronal)
- Aging, Alzheimer dis.
- M. Down
- GSS with NFD
- ALS/PDC on Guam

Doublet-Tauopathies

Mainly 4-Repeats
(neuronal and glial, Arg. grain dis.)
- PSP, CBD
- MSTD, PPND

Mainly 3-repeats
(neuronal)
- Pick disease