Neurodegenerative diseases

Dementing disorders

- **Alzheimer disease**
- **Frontotemporal dementia**
  Pick disease
  Chromosome 17-linked dementias

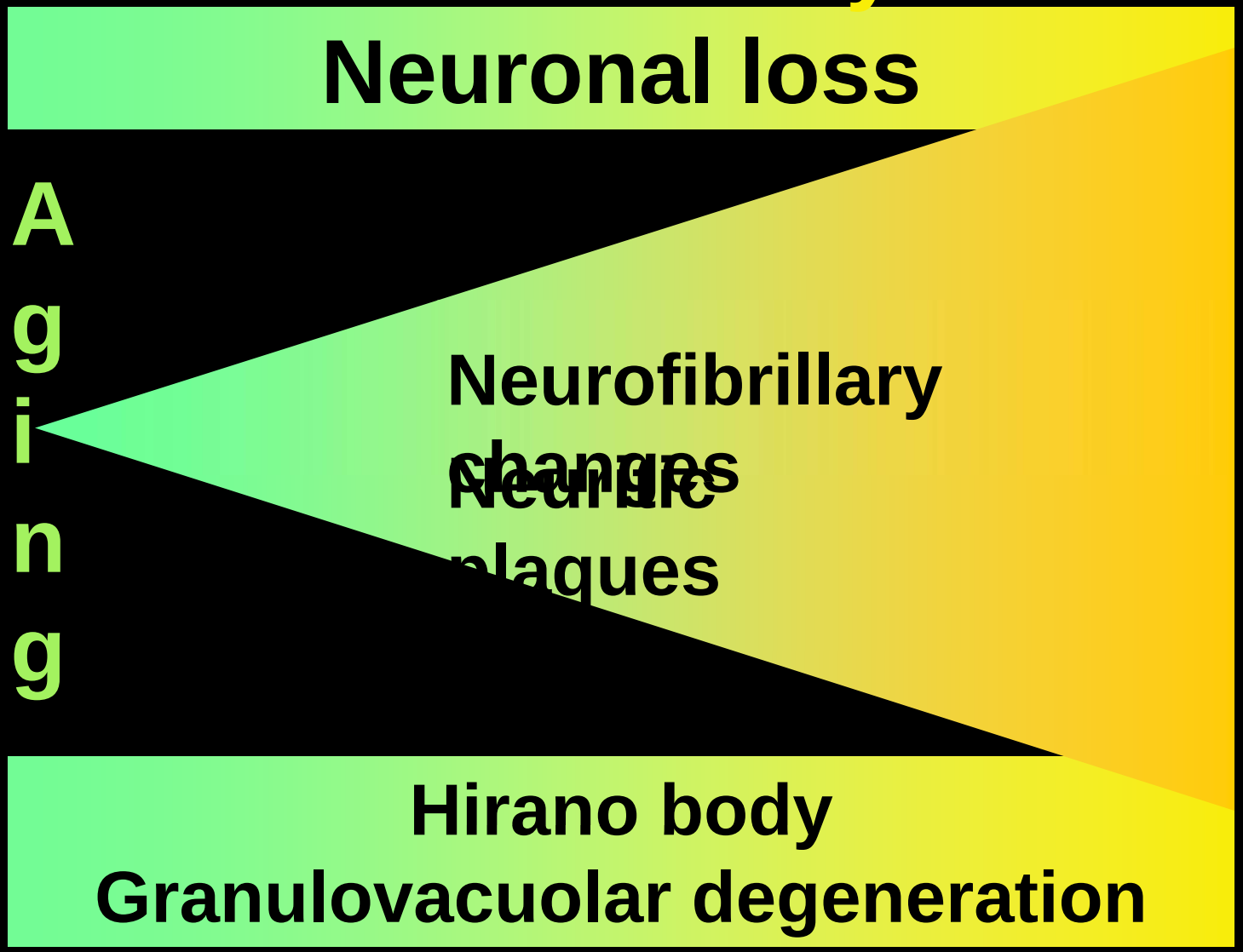
Movement disorders

- **Parkinson disease (PD) (30% develop dementia)**

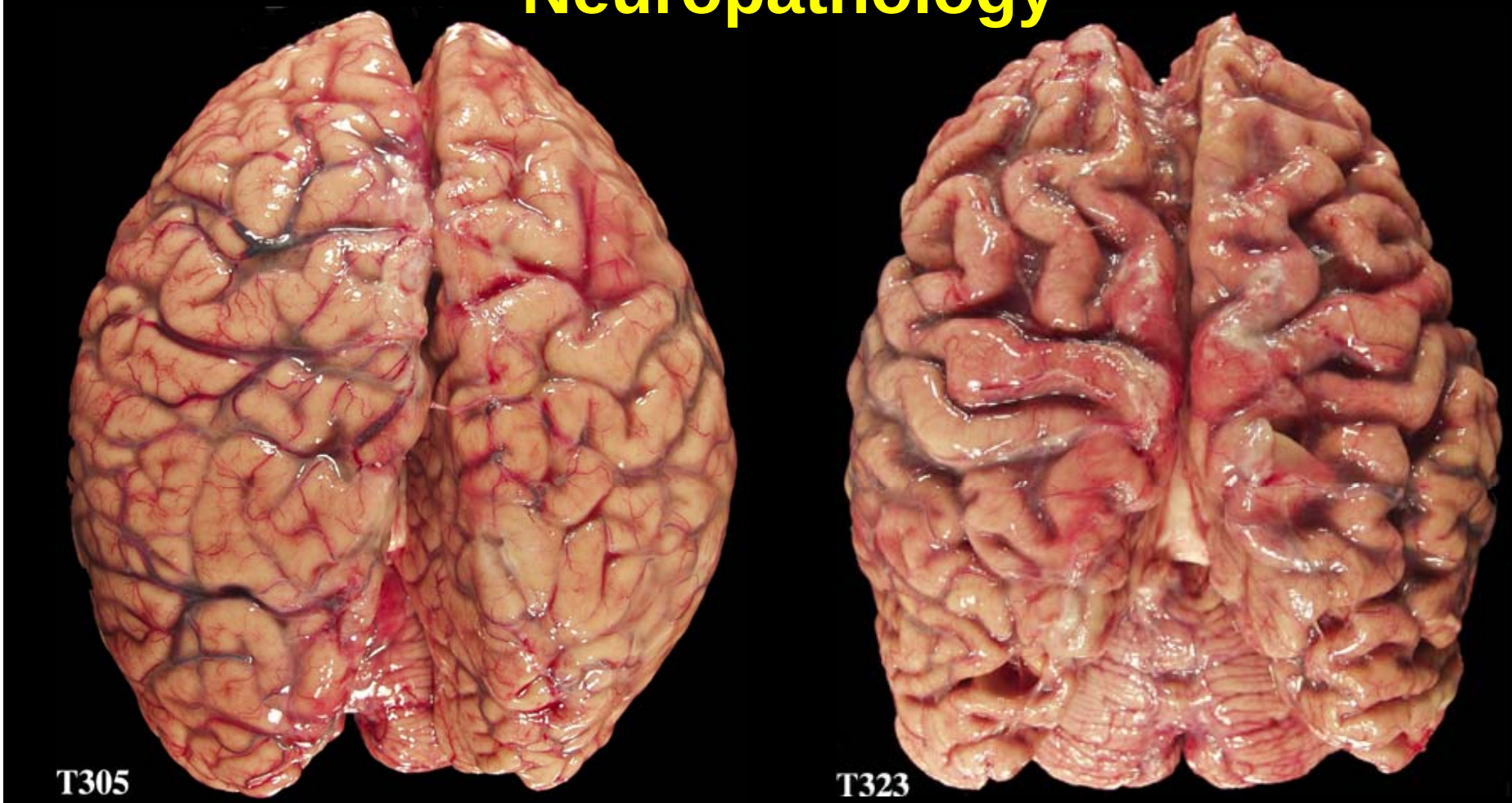
Movement disorders & dementia

- **Dementia with Lewy bodies**
  Diffuse Lewy body disease (DLBD)
  Alzheimer disease Lewy body (ADLBV)
- **Huntington disease (HD)**

Usual aging vs. morbidity



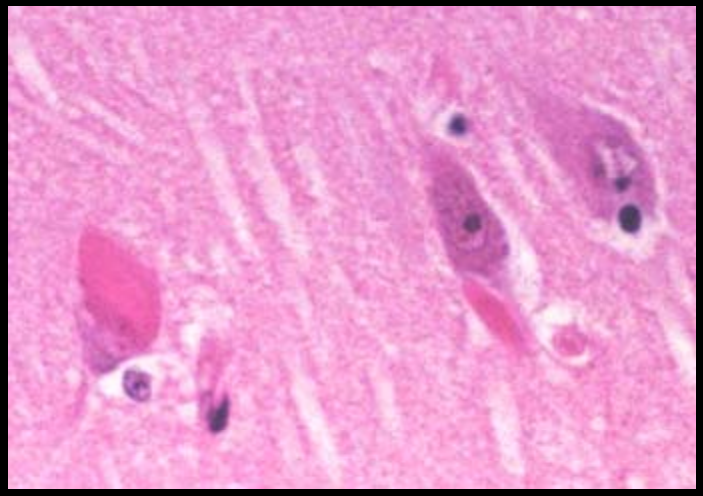
Usual aging v.s Alzheimer disease (AD) Neuropathology



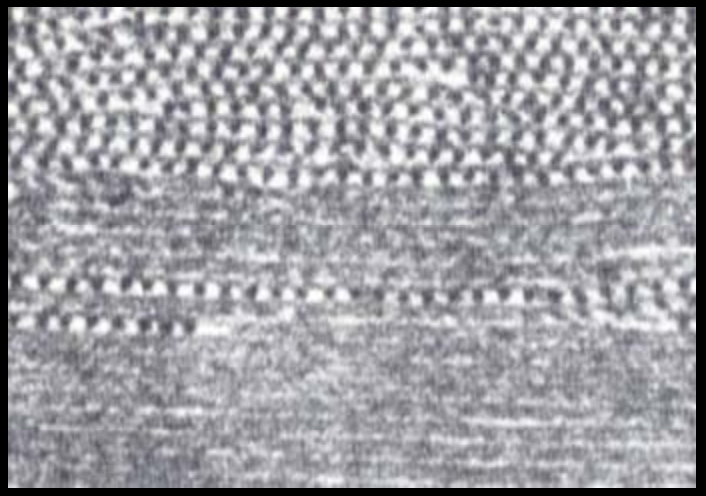
74 year-old, Contro

89 year-old, AD

Hirano body

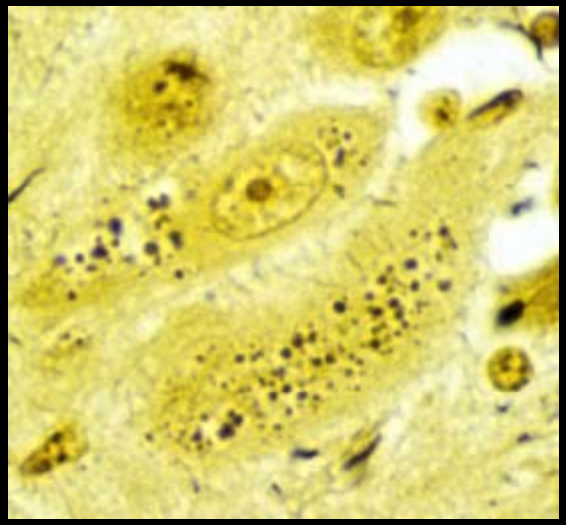


10 - 30 µm
adjacent or
within
cytoplasm
pyramidal
neurons of
hippocampus



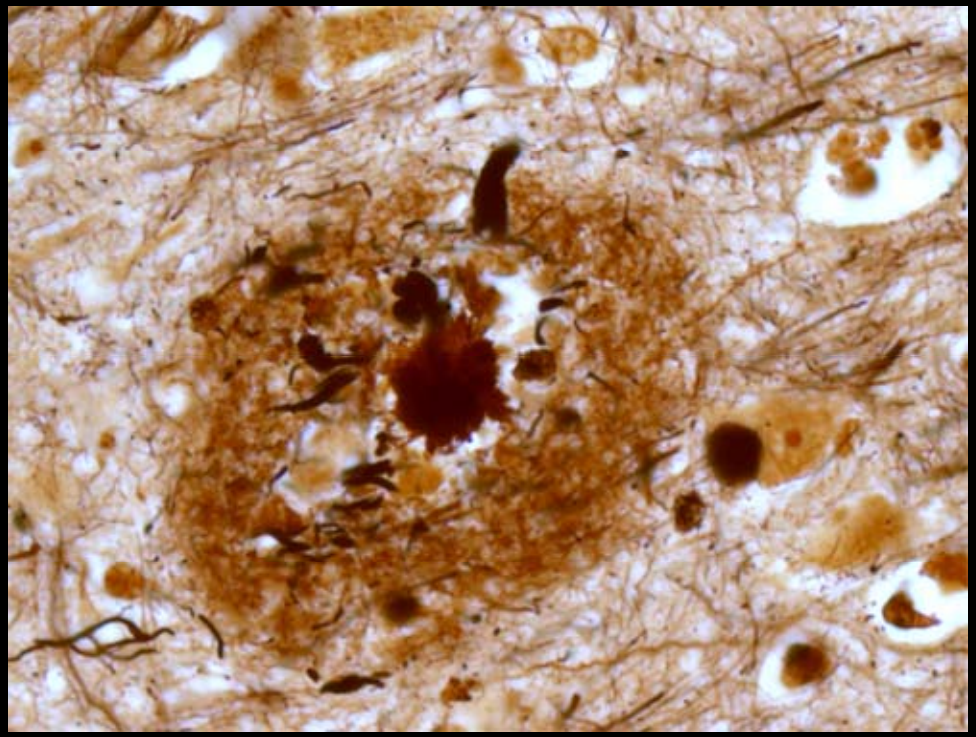
Granulovacuolar degeneration

Vacuole: 3 - 5 µm
Granule: 1 - 2 µm
Cytoplasmic
especially seen in
pyramidal neurons
of hippocampus



Found in
70 percent
of brains of
neurologically
normal
individuals

Neuritic (senile) plaques (Bielschowsky - 640 X)



Neuritic plaque
180 µm diameter
replaces about 100 neurons
& 10^6 synapses

Amyloid

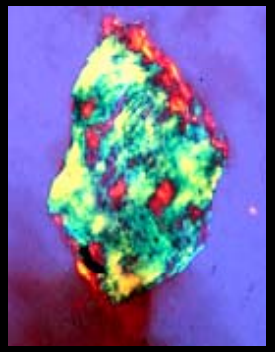
β– pleated sheet conformation, insoluble

Salmon pink

Congo red stain

Under polarized light

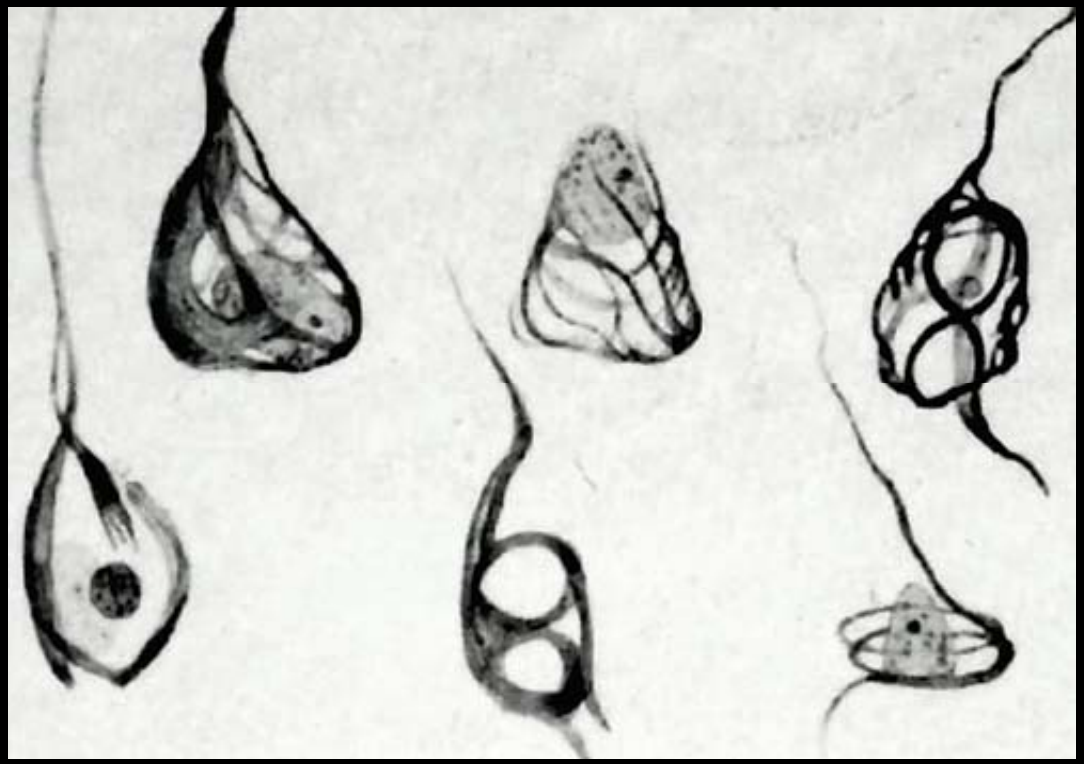
birefringent



Apple green

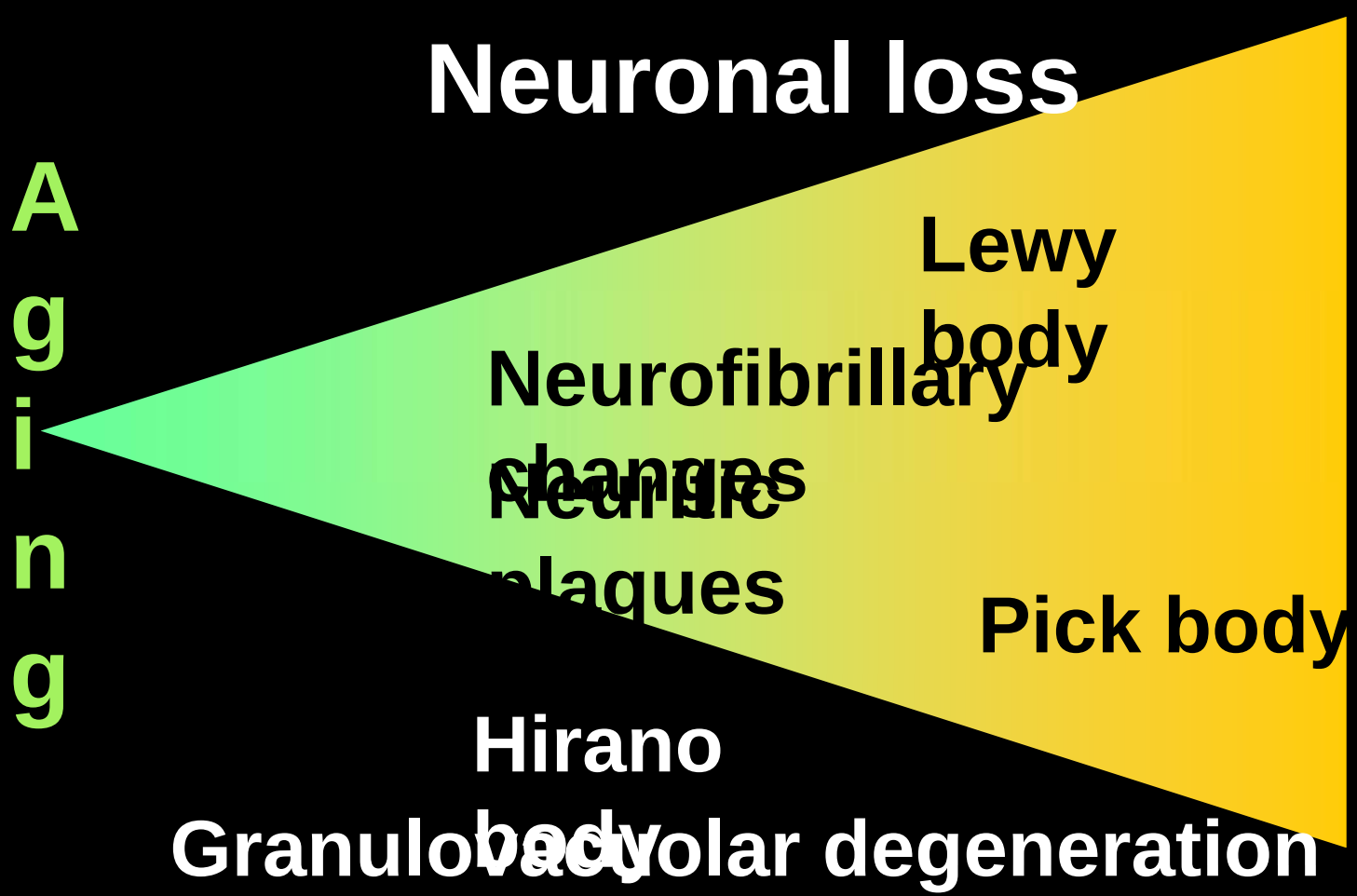
Fluorescent with Thioflavine sta

Neurofibrillary tangles of Alzheimer



Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. Zeitschrift für die gesamte Neurologie und Psychiatrie (Berlin) **1911**;4:356-85. (“Fortgeschrittene Erkrankung”)

Usual aging vs. morbidity



Alzheimer disease (AD)

- Irreversible neurodegenerative disease
- Causes memory loss
- Decreases ability to think
- Insidious onset
- Continuous, slow decline in cognition
- Currently, no cure
- Definite diagnosis: Neuropathologic examination

Alzheimer disease in the US

Most common cause of dementia

90 percent are sporadic; 10 percent are familial

Prevalence rate over the age of 60 years (y)
1900-5500 patients per 100,000 population
> 50 percent of nursing home residents

Annual incidence rate
increases exponentially with advancing age
2.4 patients / 100,000 population aged between 40 & 60 y
127 patients / 100,000 population aged 80 y & over

Alzheimer disease (AD) in the US

In 2000, there were
4.5 million persons with AD (*)

By 2050 -> 13.2 million AD patients (*)

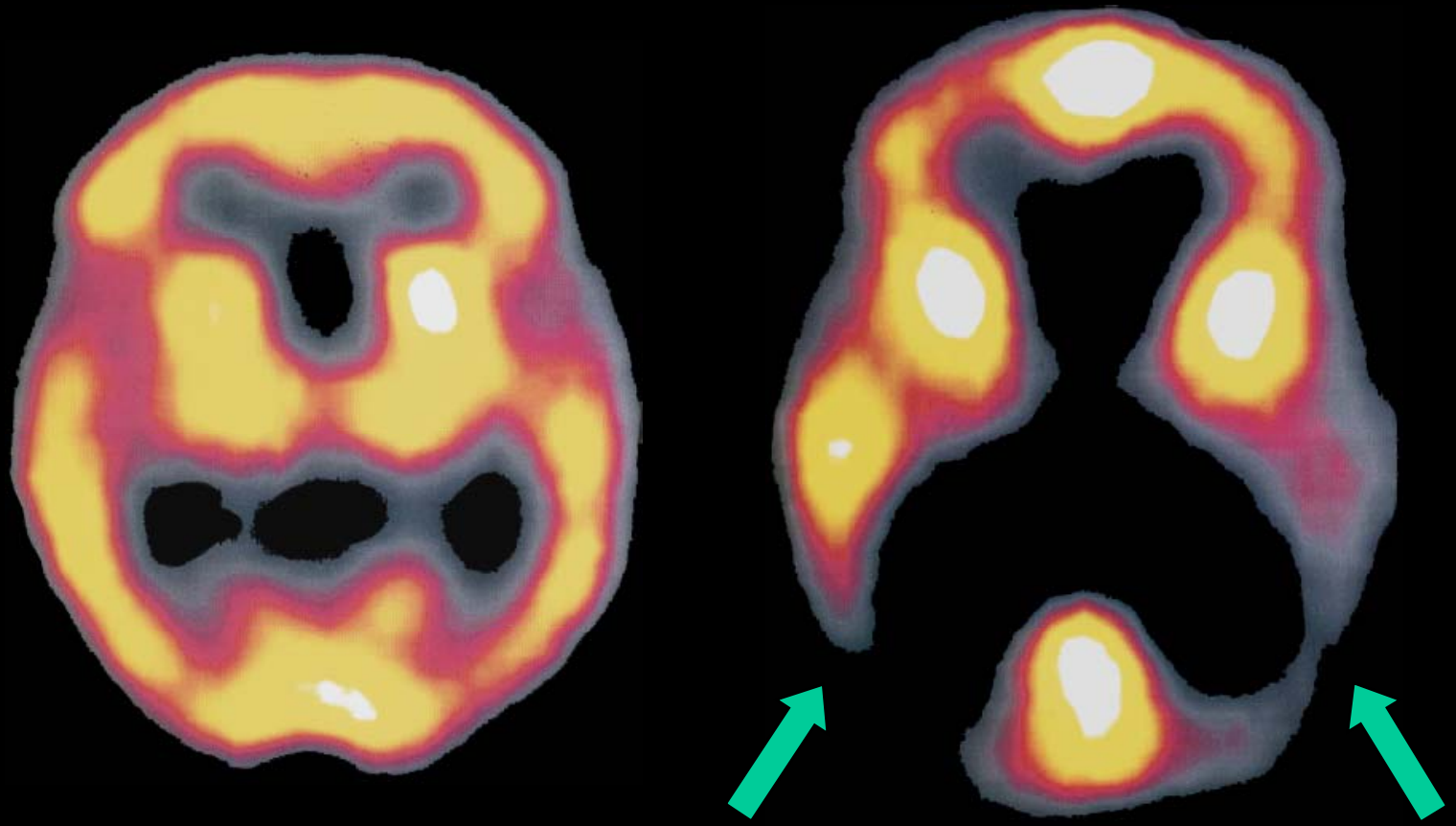
Estimated cost of AD
$100 billion / year (1993)

4th or 5th leading cause of death

n AD patients will continue to increase unless discoveries contribute prevention of the disease (*)

(*) Archives of Neurology, 2003. 60:1119-1122
Neurology, 2005(Suppl 3). 65:S31-S32)

Control **Alzheimer disease (AD)**



Single photon emission computerized tomography (SPECT)
In AD: Parietal hypoperfusion

From: The Neuropathology of Dementia, M. Esiri & J. Morris
Cambridge University Press. 1997

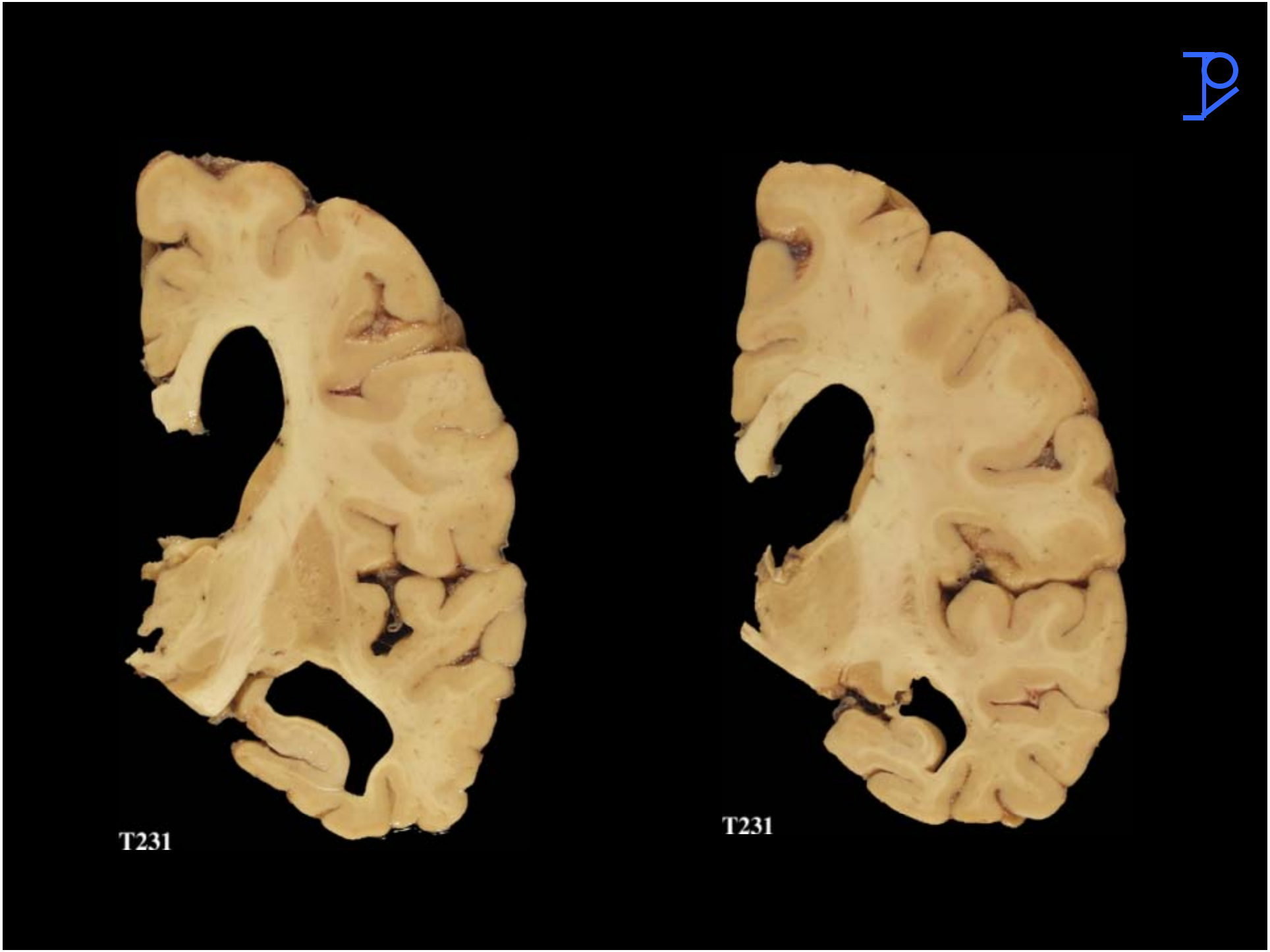
Alzheimer disease (AD) : Neuropathology

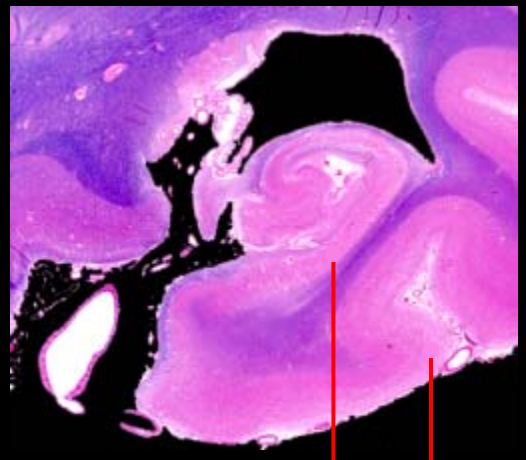
Cerebral atrophy

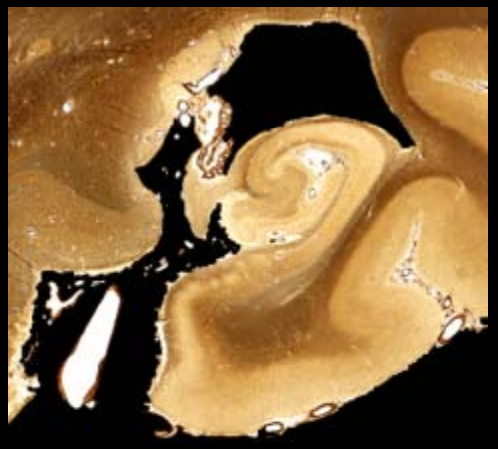
Atrophy = Widening of sulci + Narrowing of g

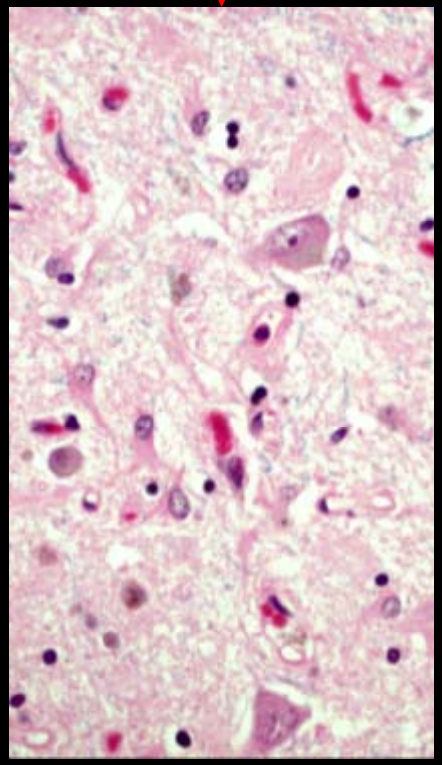
Permanent loss of predominantly glutamatergic, pyramidal neurons of neocortex

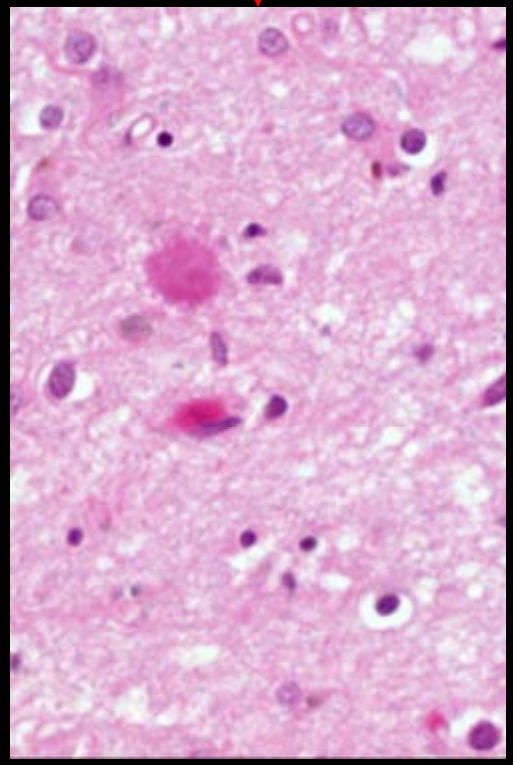
Basal nucleus of Meynert (cholinergic system)


T231
T231

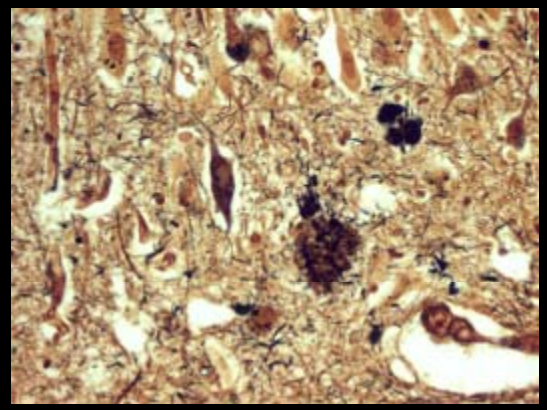




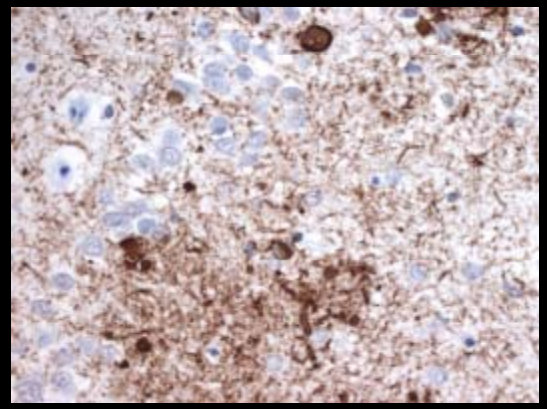




CA1



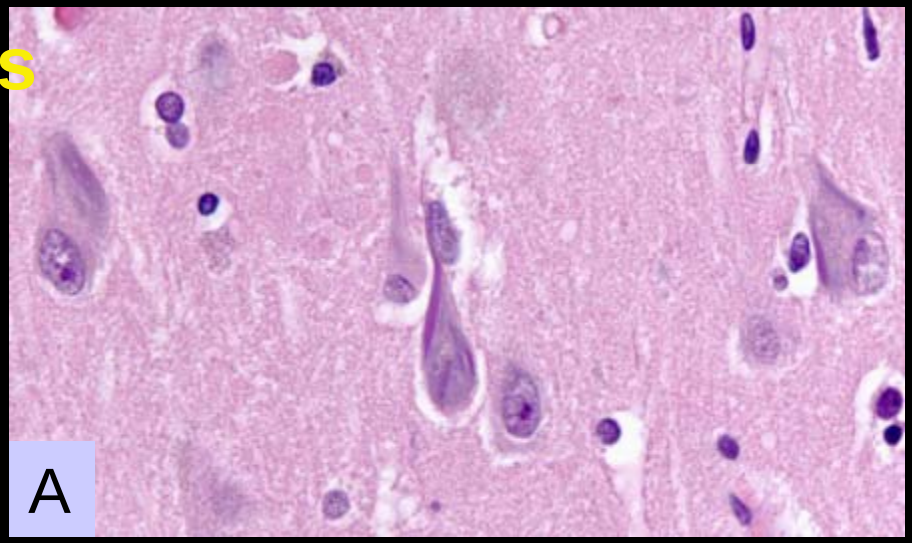
CA4



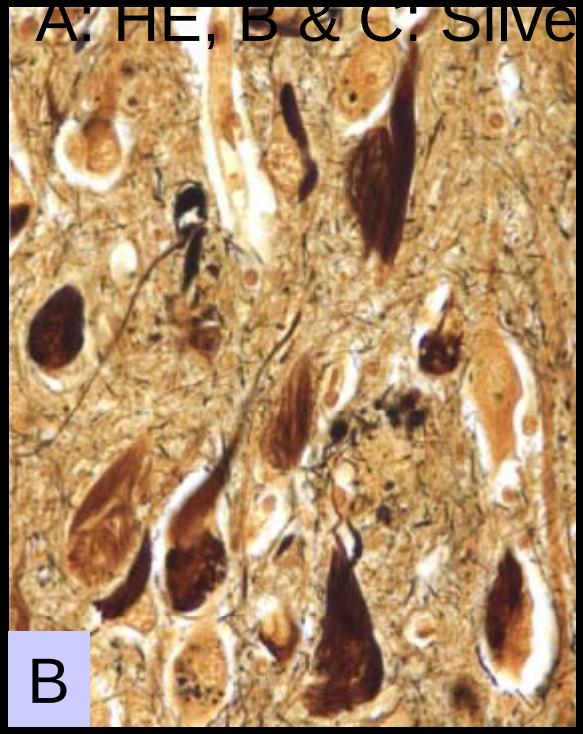
St. gr.

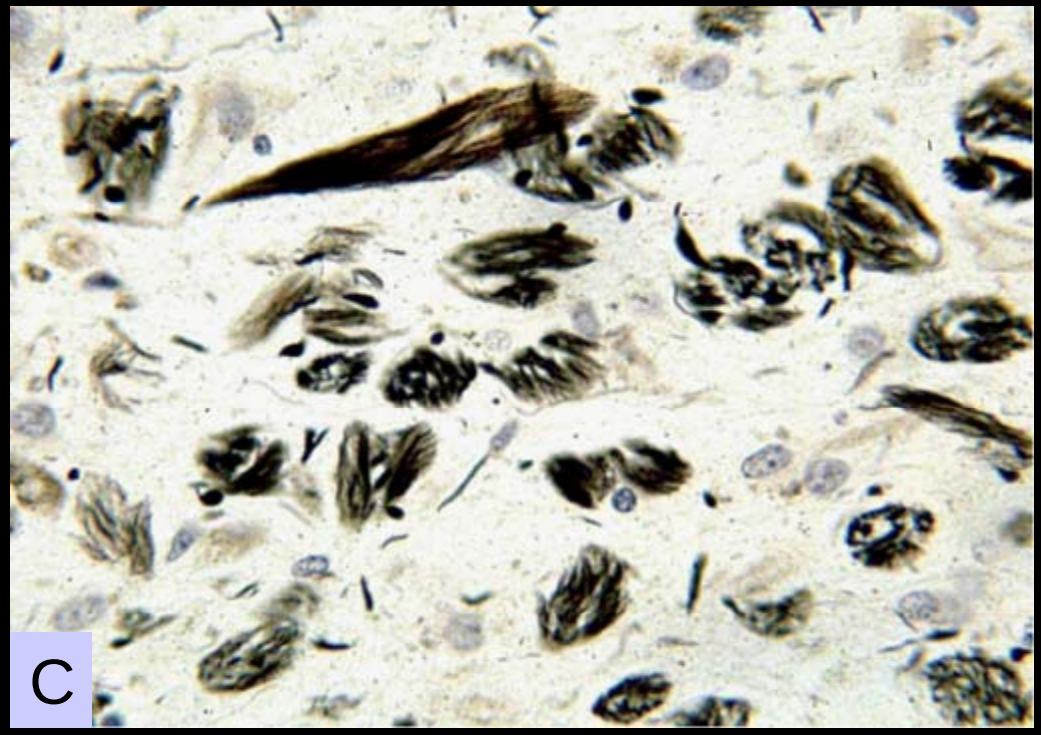
Neurofibrillary tangles

A: Early stage
B: Intermediate stage
C: End stage

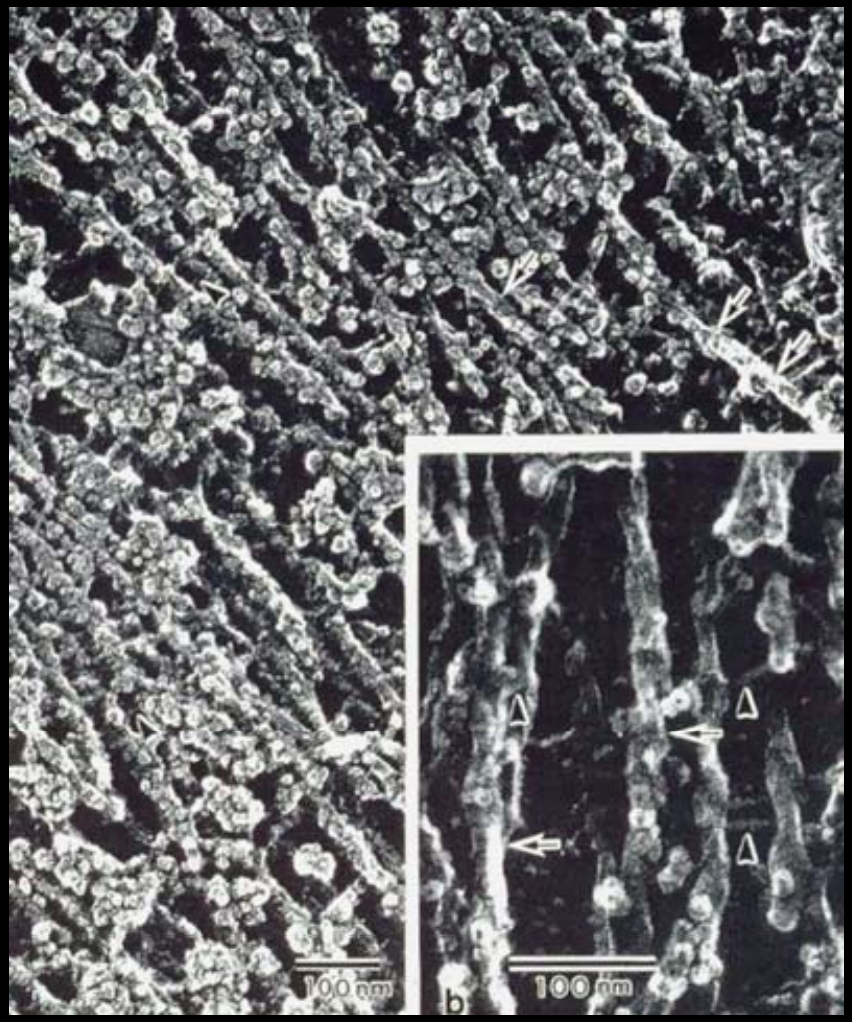


A: HE, B & C: Silve





Neurofibrillary tangles: ultrastructure

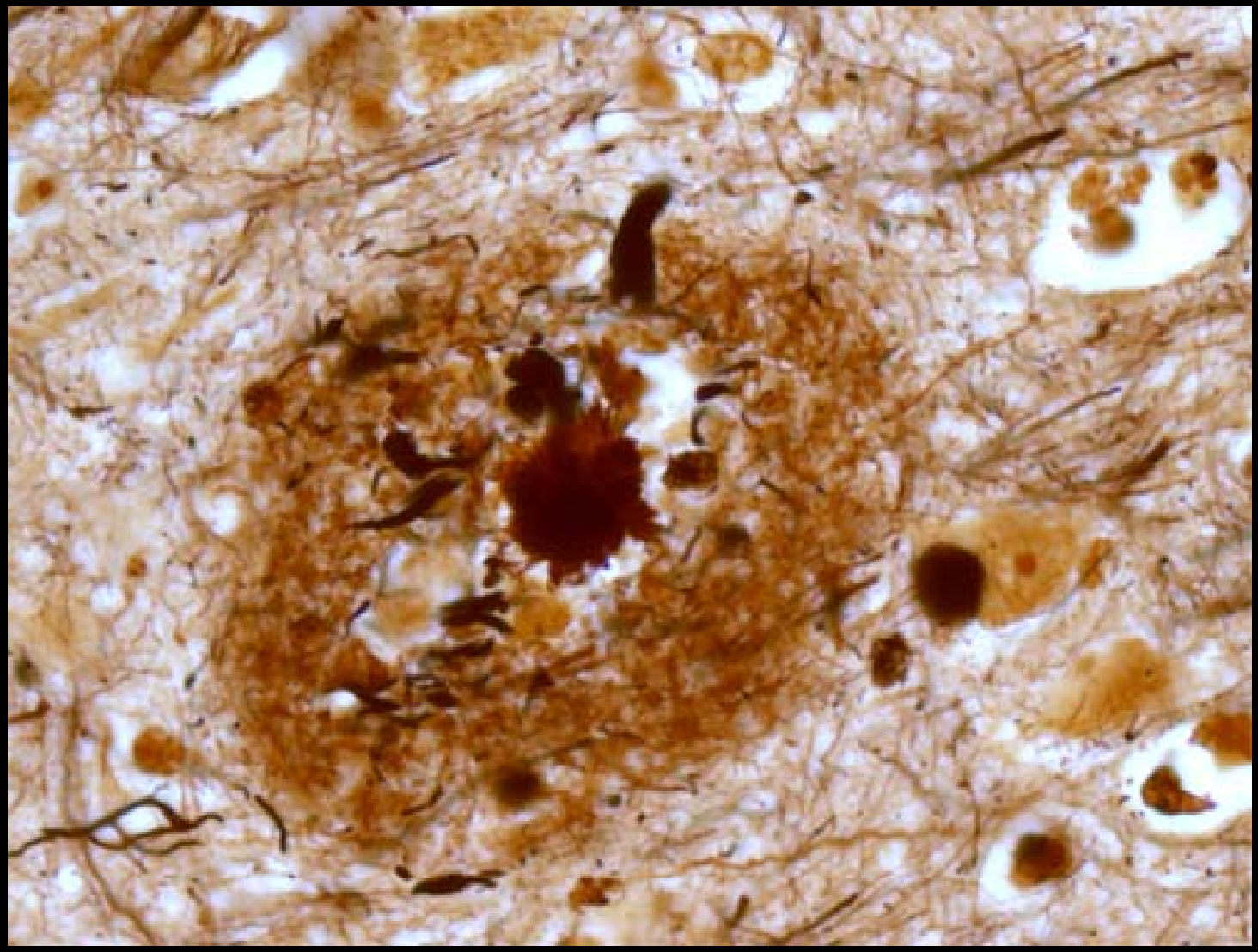


Paired helical filaments
8 - 12 nm, helically wound
Insoluble
React with silver stains

Hyperphosphorylated Tau
? Abnormal kinase or phosphatase activities

Tau: normal neuronal proteins, bind to microtubules regulate their assembly

Neuritic (senile) plaques (Bielschowsky)



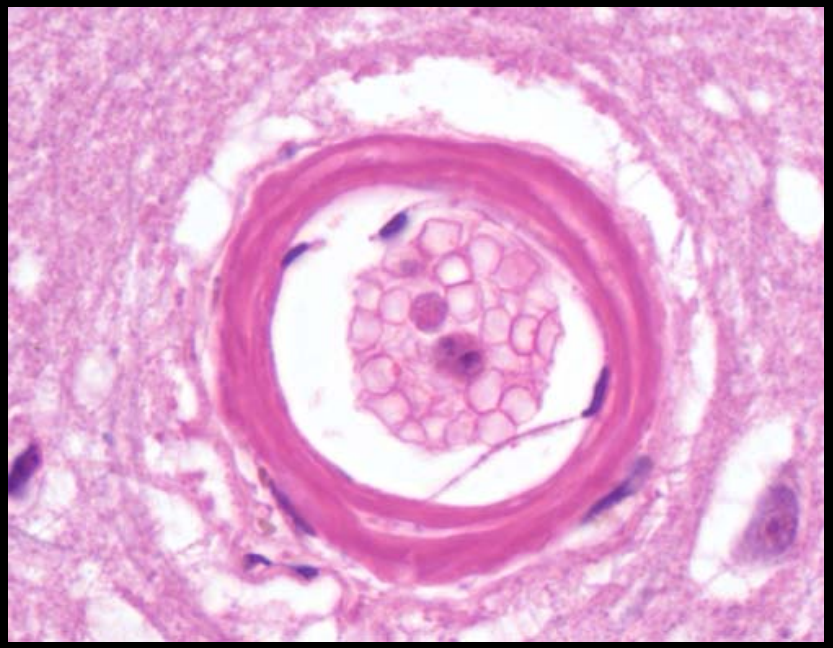
640 X

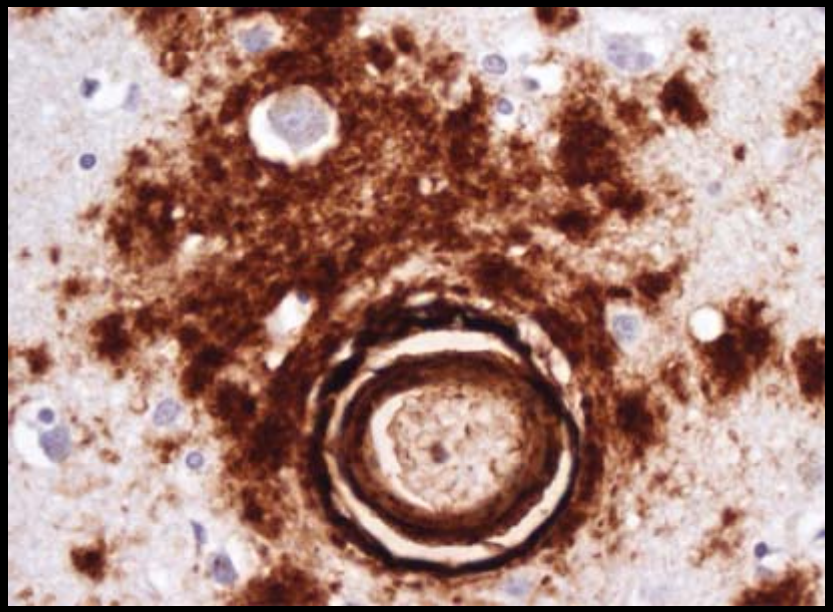
Precuneus

Cuneus

Calcarine

β–amyloid





β-amyloid

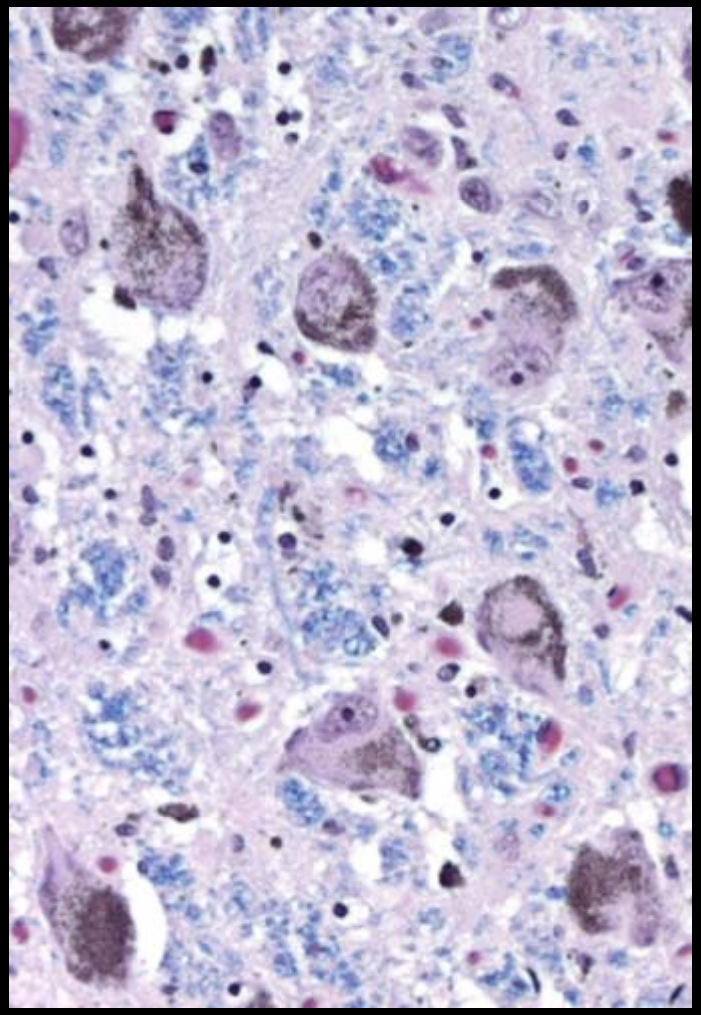
Substantia nigra pars reticulata (SNr), & compacta (SNc)

Coeruleus
Norepinephrine

Paradoxical sleep

Cortical activation

Dorsal n. X



LHE

Pick disease

Pick body

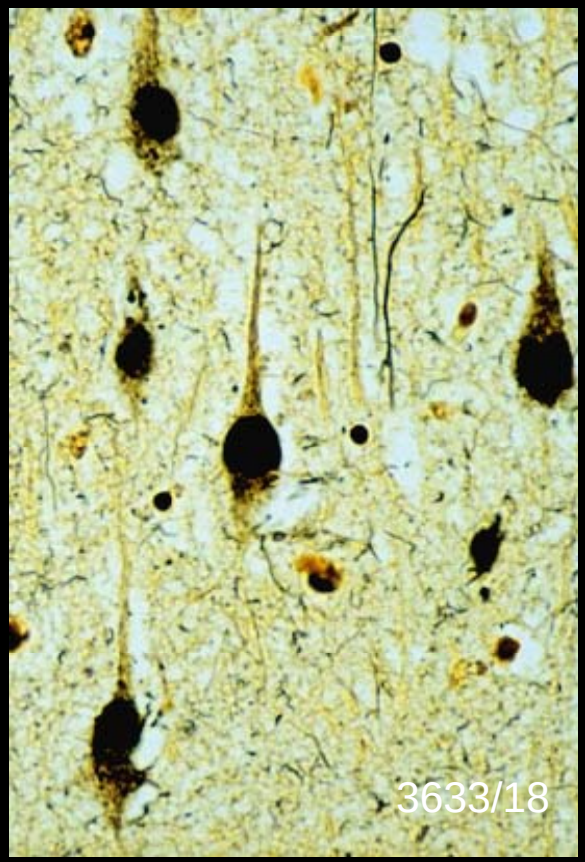
Cytoplasmic, round, argyrophilic,
tau positive, ubiquitin positive,
10 - 15 µm across
α–synuclein negative

Pick bodies usually involve

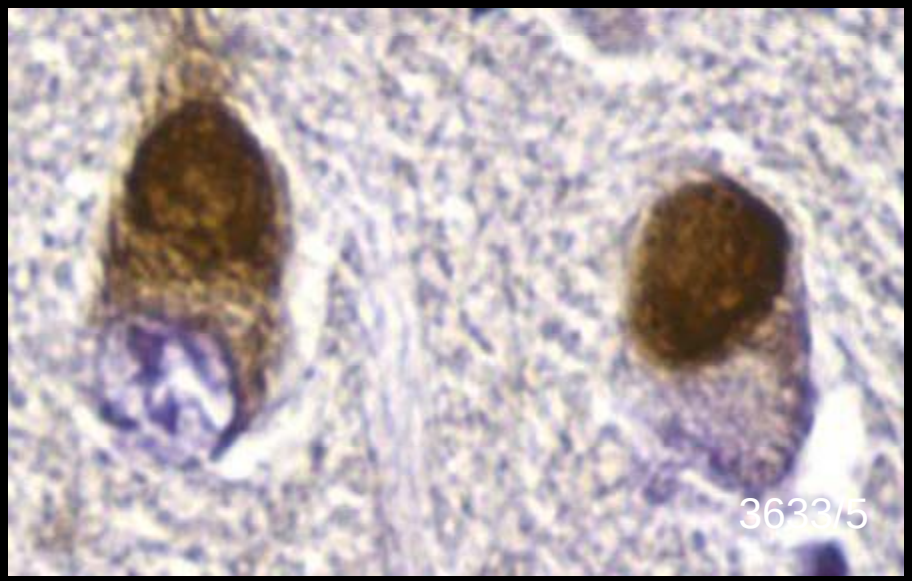
- **neocortical, pyramidal neurons**
- **hippocampal, pyramidal neurons**
- **stratum granulosum of dentate gyrus**
- **amygdala**
- **striatum**
- **brainstem**

Pick body

Bielschowsky

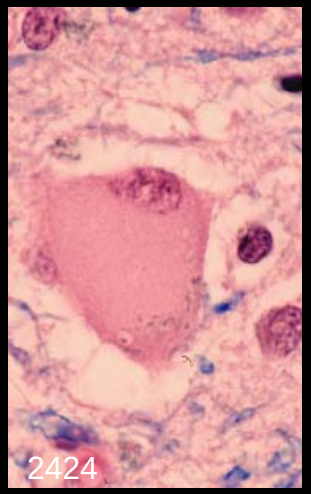


Tau



Tau positive
Ubiquitin positive
α-synuclein negative

Ballooned neurons

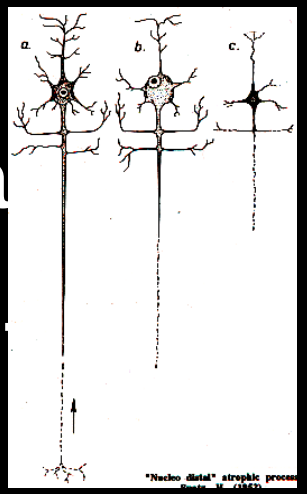


Pick disease

Primary progressive aphasia

Chromosome 17-linked dement

Corticobasal degeneration



Alzheimer disease

Progressive supranuclear palsy

Creutzfeldt-Jakob disease

Parkinson disease

And

Dementia with Lewy bodies

Dementing disorders

- **Alzheimer disease**
- **Frontotemporal dementia**
  Pick disease
  Chromosome 17-linked dementias

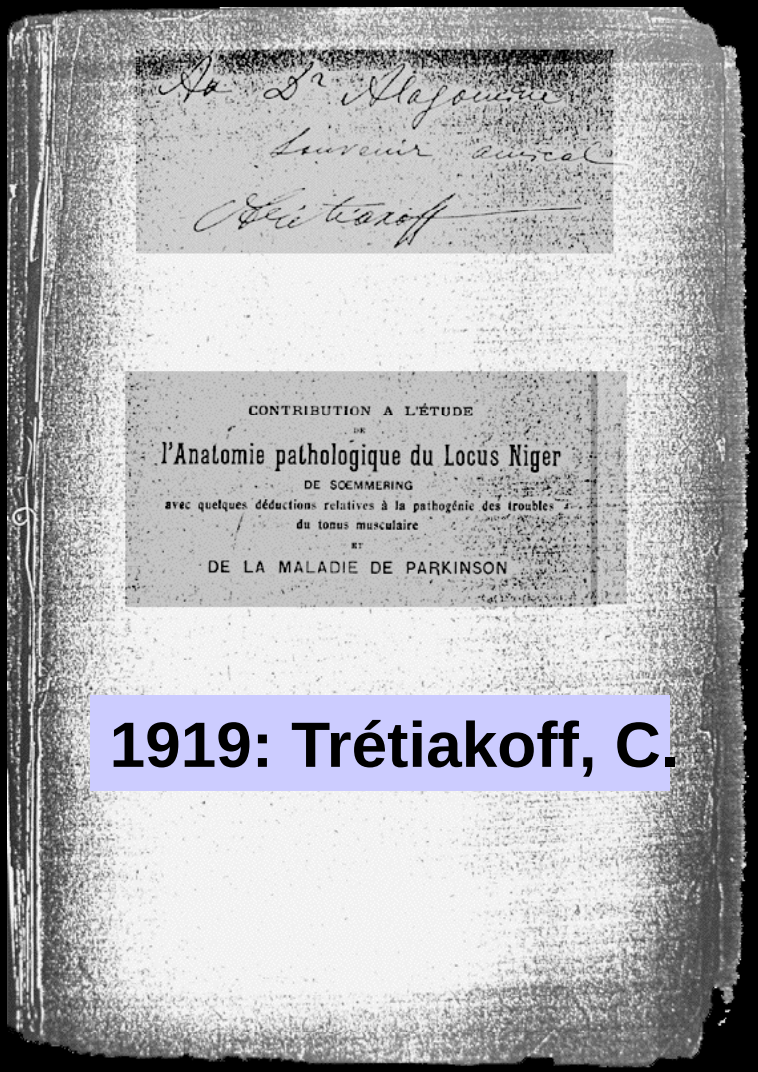
Movement disorders

- **Parkinson disease (PD) (30% develop dementia)**

Movement disorders & dementia

- **Dementia with Lewy bodies**
  Diffuse Lewy body disease (DLBD)
  Alzheimer disease Lewy body (ADLBV)
- **Huntington disease (HD)**

Parkinson disease



1919: Trétiakoff, C.

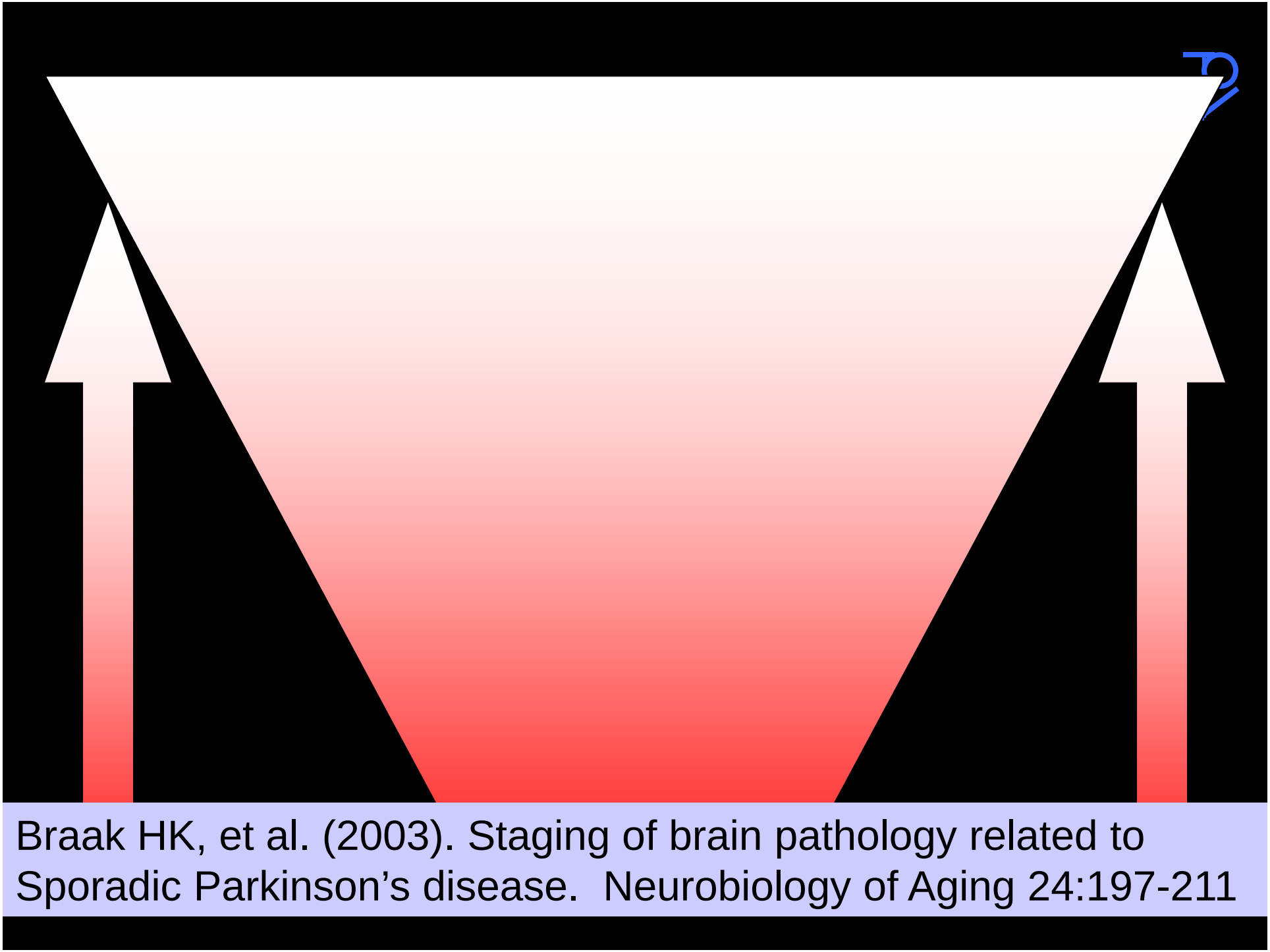
50,000 Americans / year -> diagnosed with PD

Parkinson disease (PD)

Bradykinesia
Rigidity
Resting tremor
Postural instability

Neuronal loss
Cytoplasmic inclusion: Lewy body

Pars compacta of substantia nigra
Nucleus coeruleus
Substantia innominata
Hypothalamus
Dorsal nucleus of vagus



Braak HK, et al. (2003). Staging of brain pathology related to Sporadic Parkinson's disease. Neurobiology of Aging 24:197-211

Neuronal loss
Cytoplasmic inclusion: Lewy

Dorsal nucleus of vagus
Nucleus coeruleus
Pars compacta of substantia nigra
Hypothalamus
Substantia innominata -> Mesolimbic cortex

Parkinson disease

If, in addition,
neurons with Lewy body in cerebral neocortex (-> dementia)

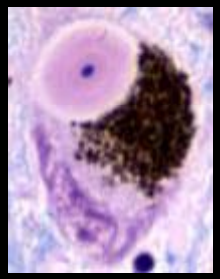
Diffuse Lewy body disease

If, in addition,
neuritic plaques or neurofibrillary tangles or both in cerebral cortex

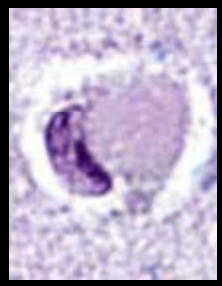
Alzheimer Disease Lewy body variant

Lewy body

Cytoplasmic inclusion, round, 8 - 30 µm



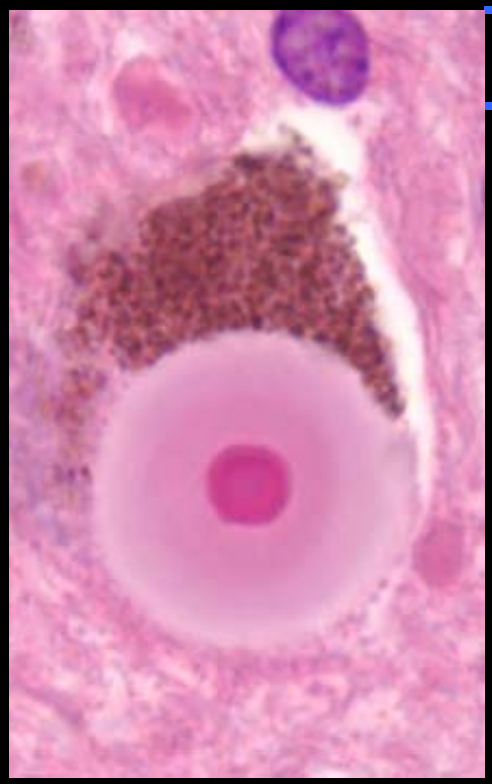
Brainstem type, discrete
Cortical type, ill-defined



Found in

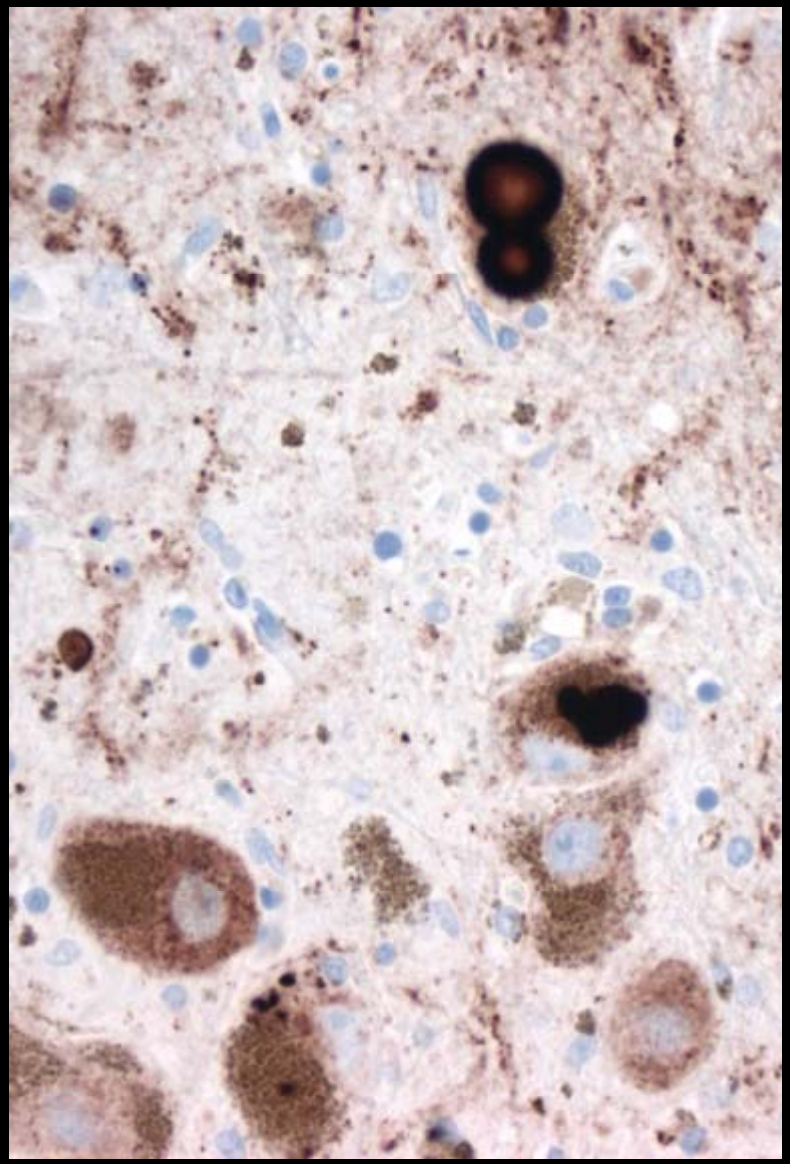
5% of asymptomatic, elderly subjects
100% of patients with Parkinson disease or with Lewy body dementia

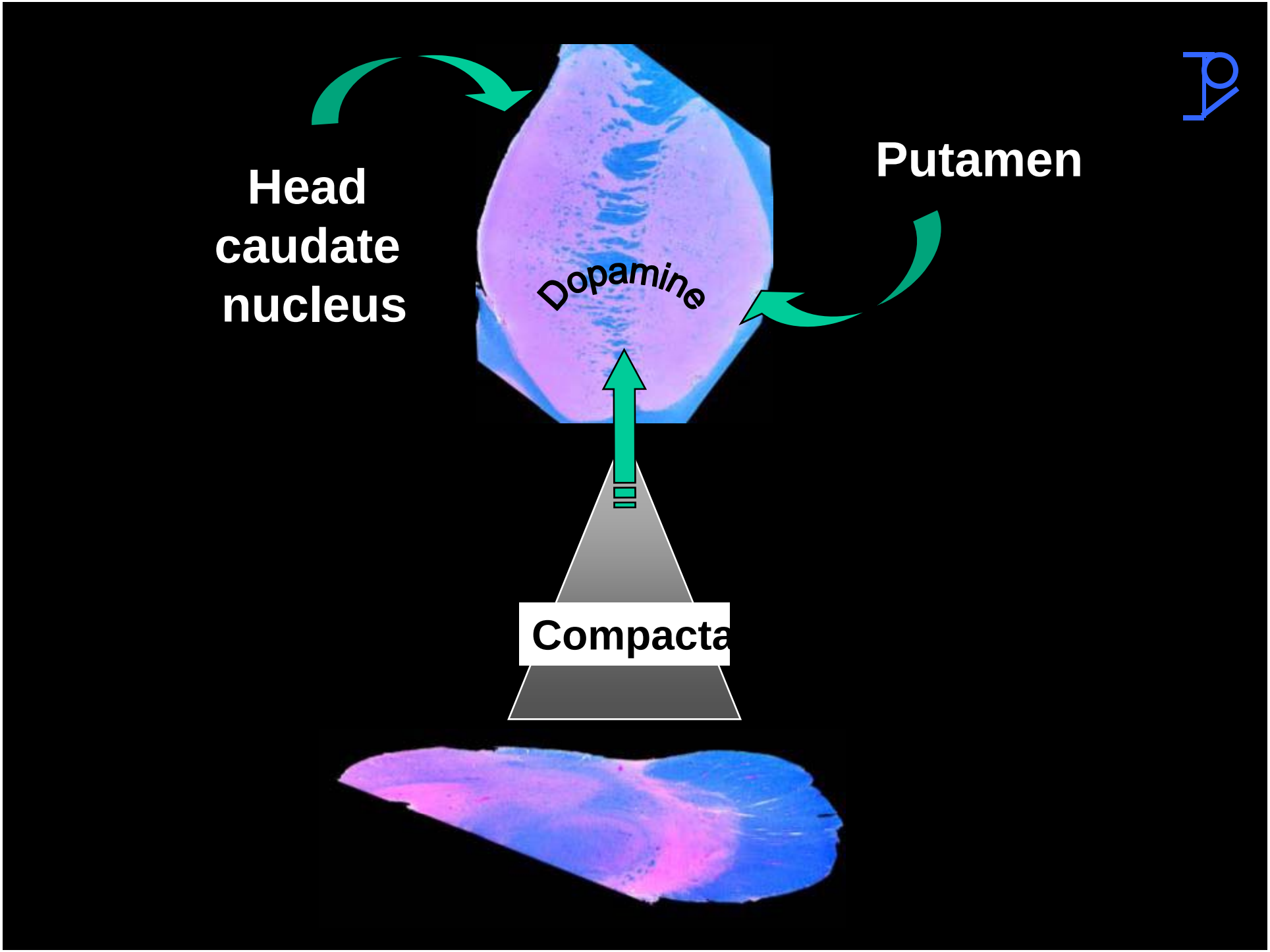
Parkinson disease



Control

2120




Head
caudate
nucleus
Putamen
Dopamine
Compacta

MPTP

MPTP

1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydropyridine

Not toxic

MPP^+

1-Methyl-4-Phenylpyridinium ion

Toxic

VIDEO

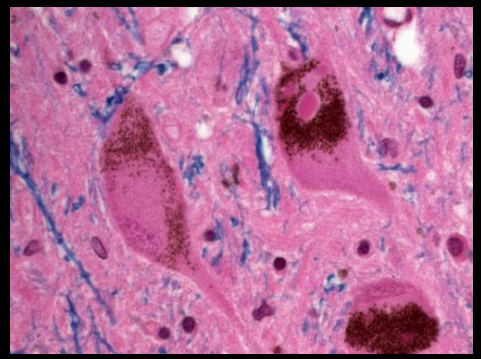
VIDEO

VIDEO

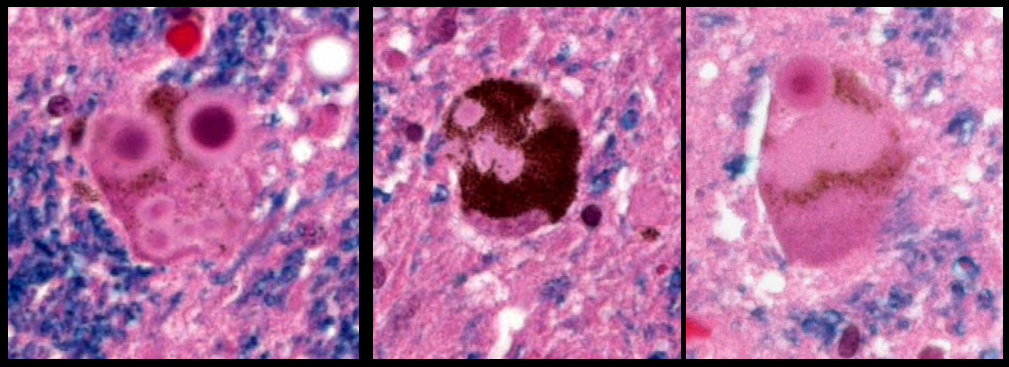
Dementia with Lewy body (LB)
Diffuse LB disease

Lewy bodies & Lewy neurites

***Neocortex*, hypothalamus, substantia innominata, substantia nigra (compacta), coeruleus, dorsal nucleus of vagus**



Substantia nigra



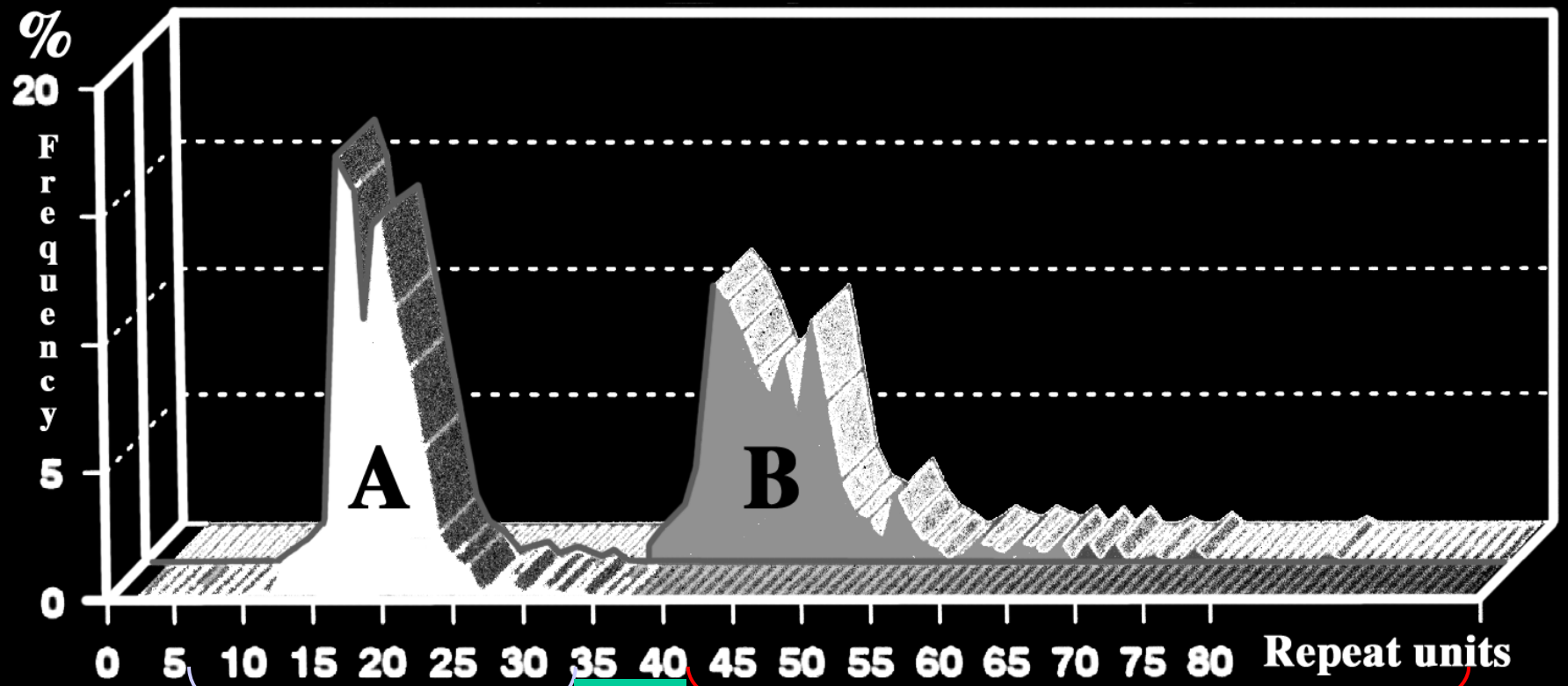
Nucleus coeruleus

Huntington disease

Huntington diseas

Early stage

CAG repeats



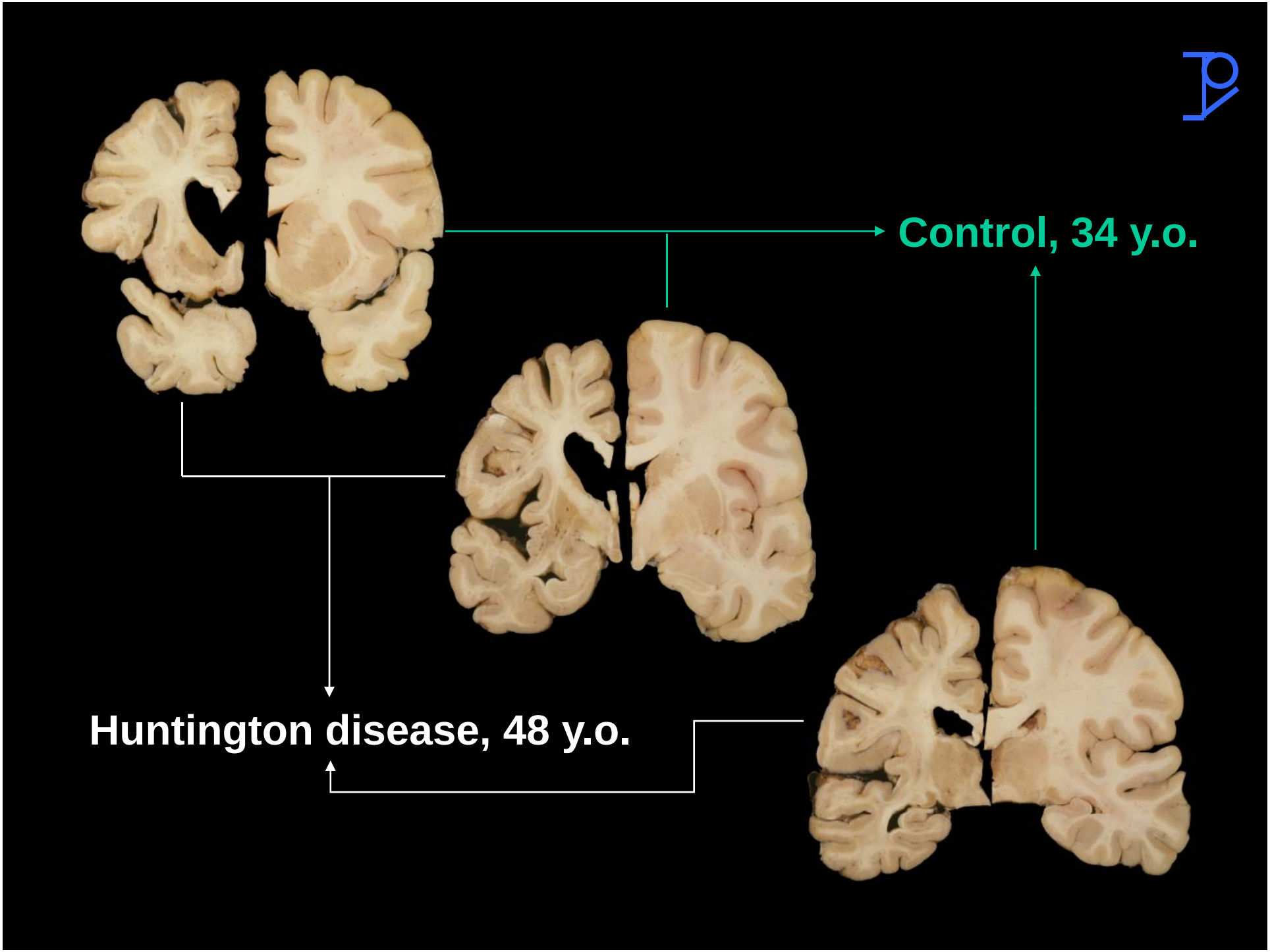
Normal allele

?

Abnormal allele

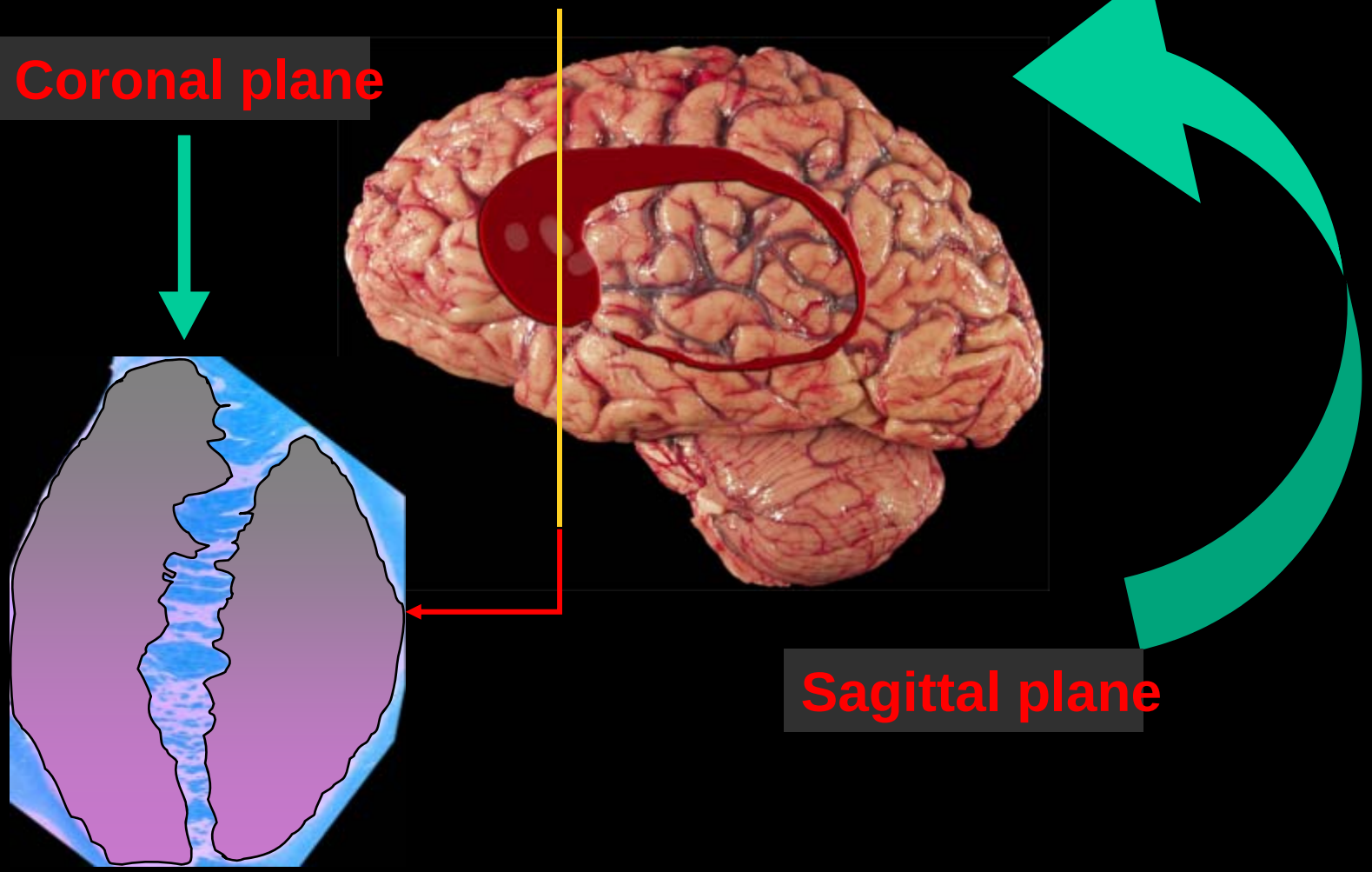
May or may not develop the disease

Huntington diseas


Control, 34 y.o.
Huntington disease, 48 y.o.

Huntington disease
Between early and late stages

Ordered and topographic distribution

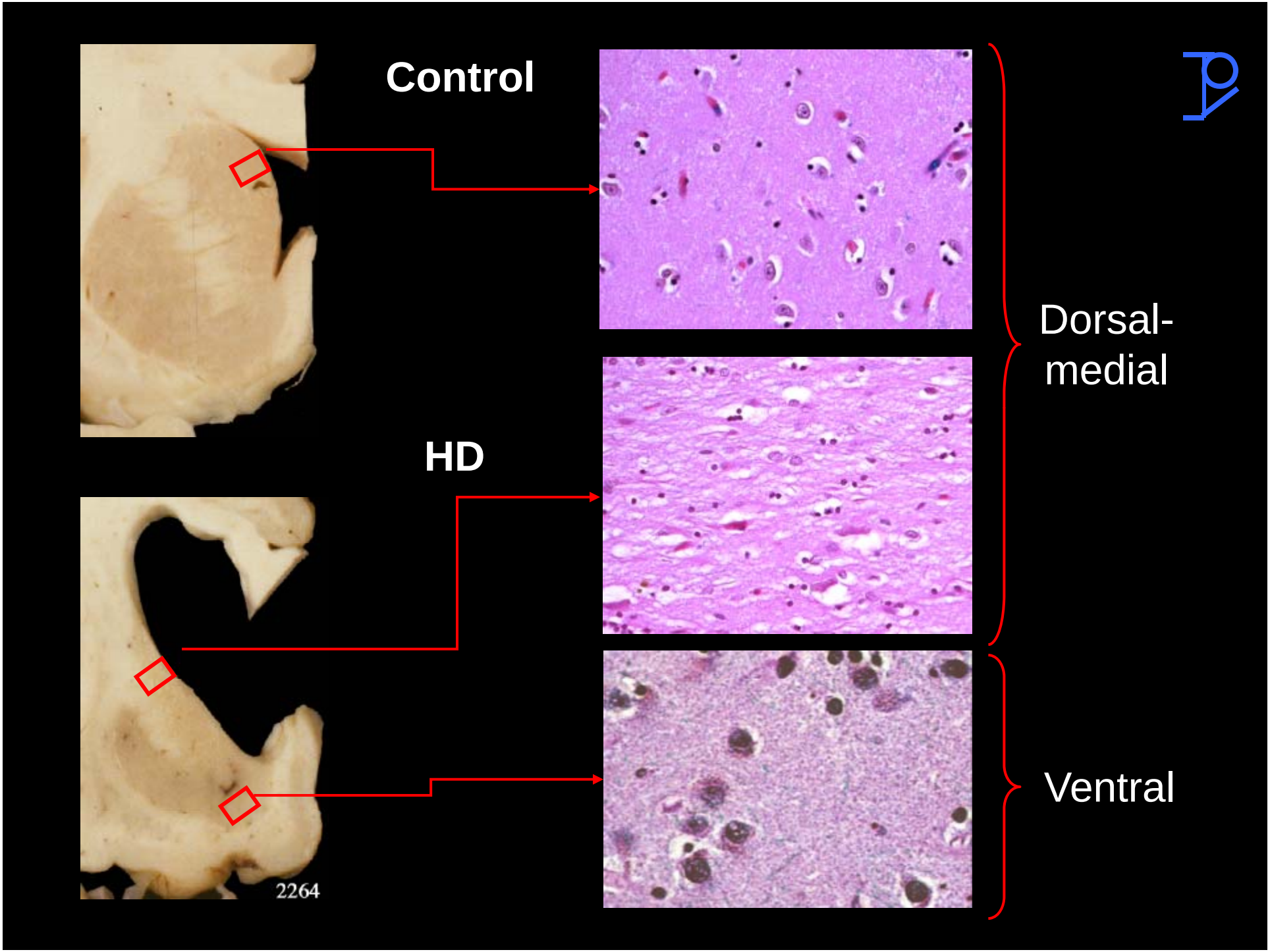


Huntington disease
Late stage

VIDEO

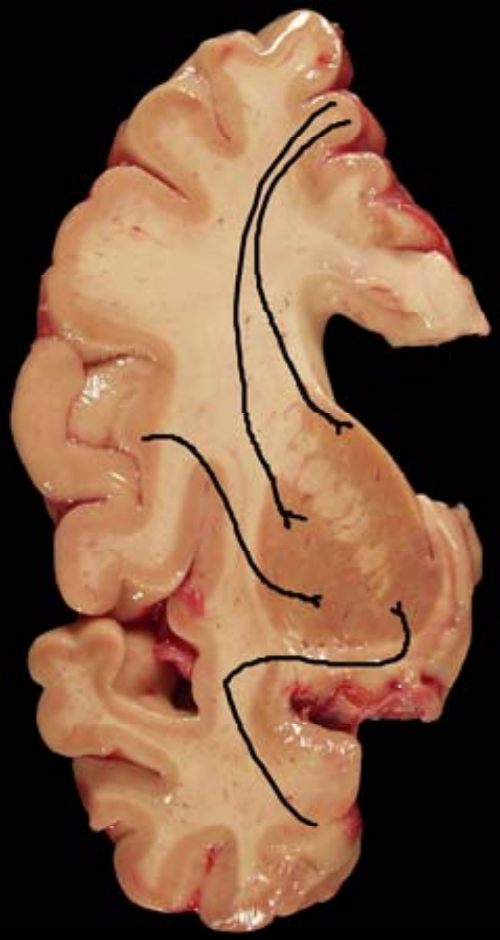
Huntington disease
Juvenile onset
End-stage (Grade 4/4

VIDEO


Control
HD
2264
Dorsal-medial
Ventral

Excitotoxicity

Glutamate

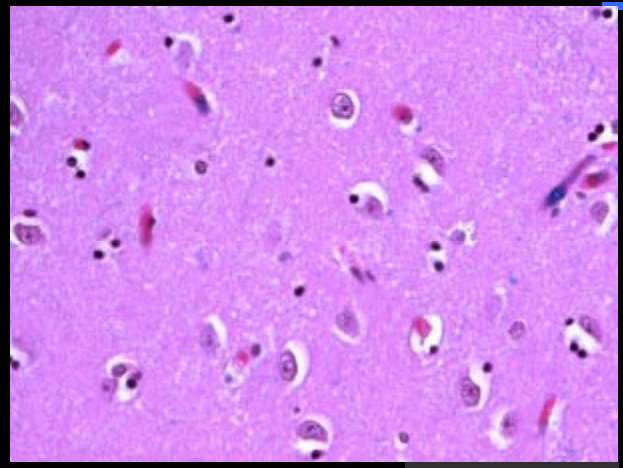


Receptors

NMDA
AMPA
Kainate
Metabotropic

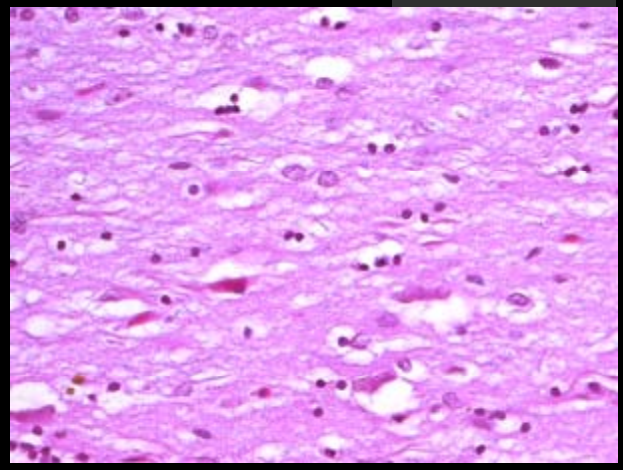
+

HDIT15 PolyQ

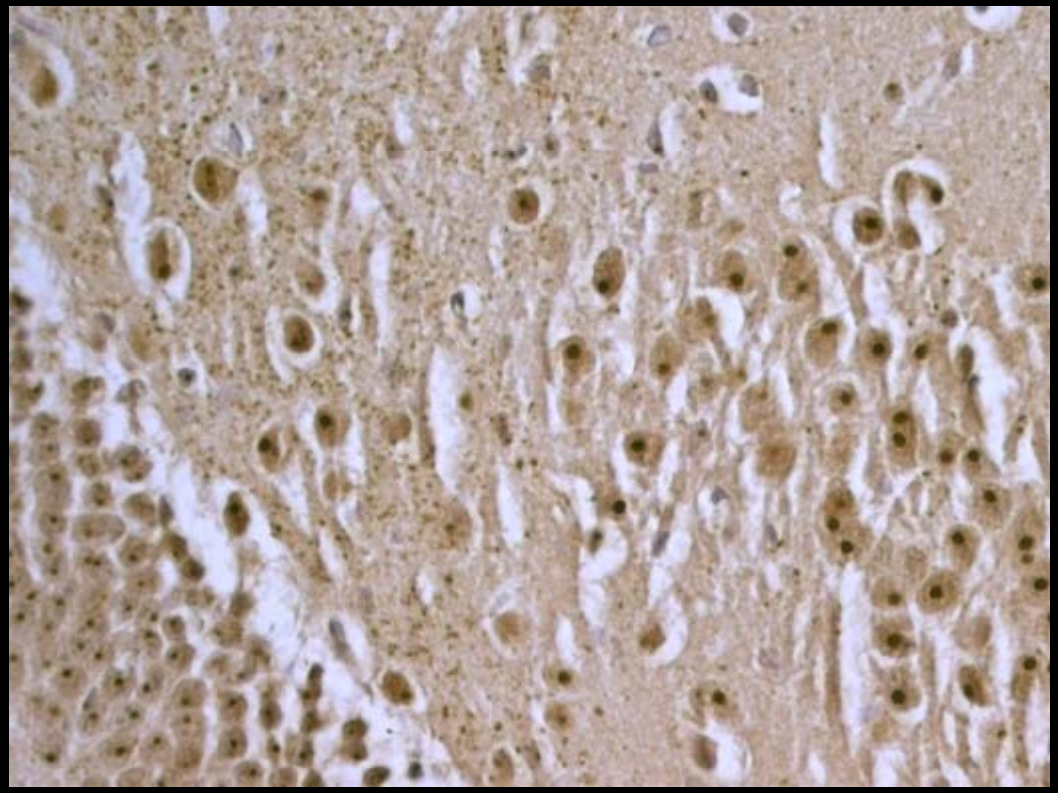


Normal

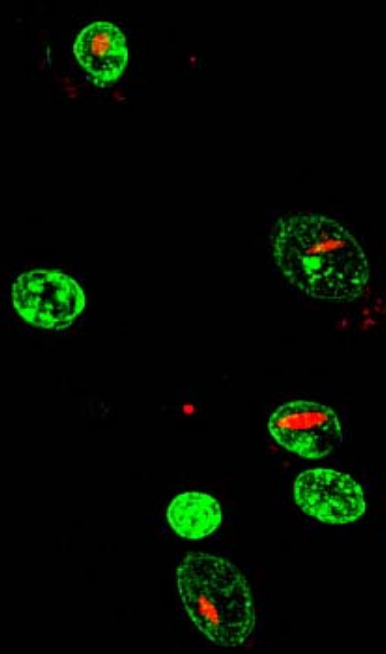
HD



Nuclear inclusions



Mouse R6/2
145 CAG



14 y.o. w
82/12 CAG

Huntington disease
Late onset
Relatively early stage
Slow progression