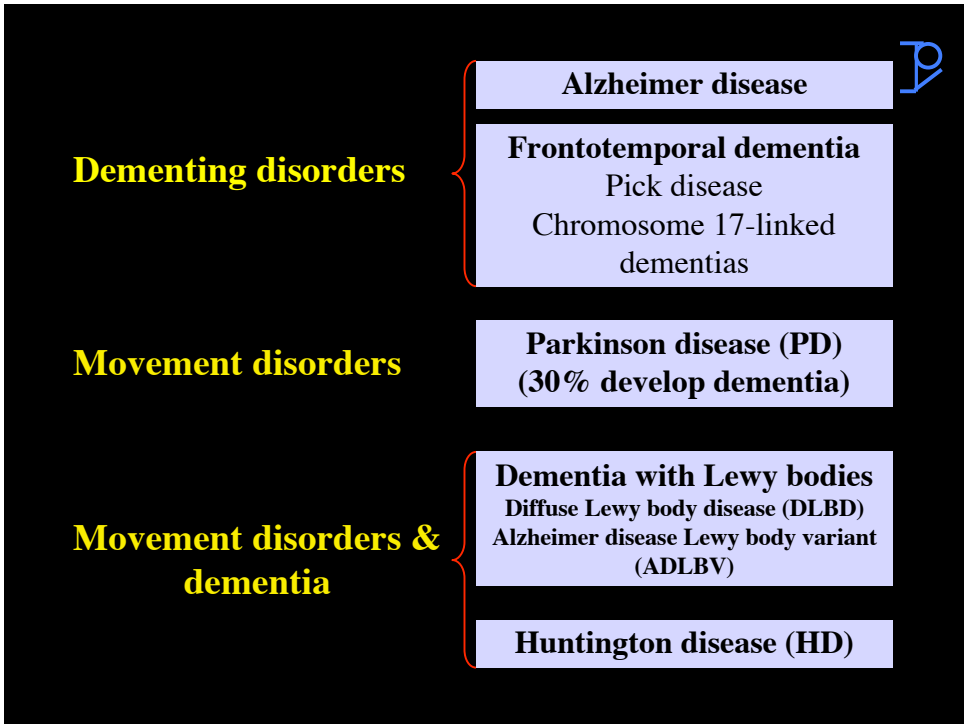
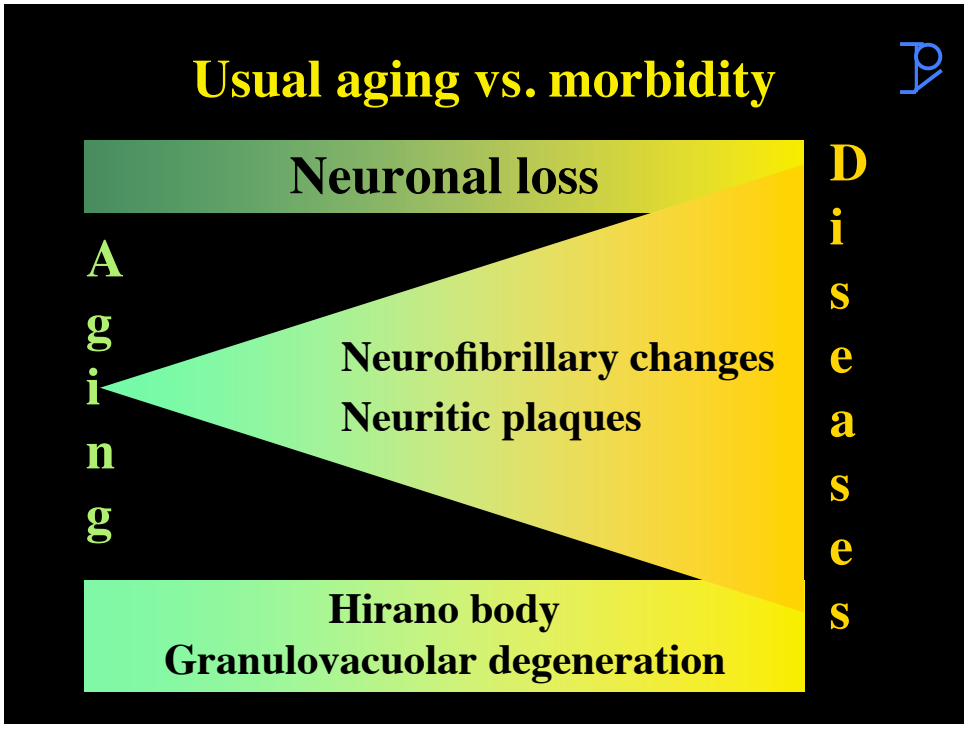
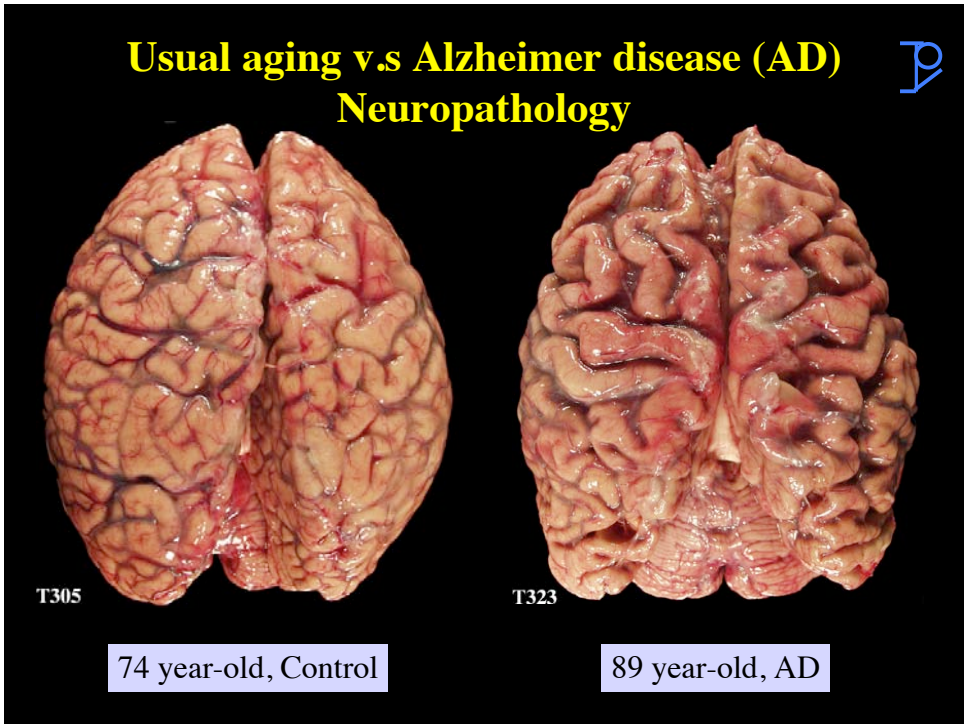
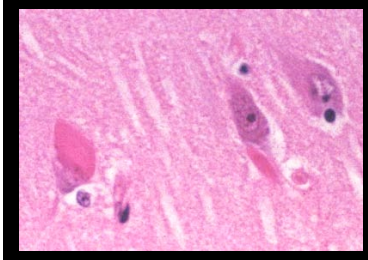
Neurodegenerative diseases



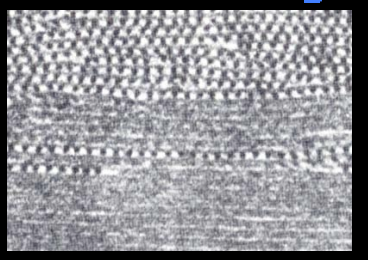

Usual aging vs. morbidity
Neuronal loss
Aging
Neurofibrillary changes
Neuritic plaques
Diseases
Hirano body
Granulovacuolar degeneration


Usual aging v.s Alzheimer disease (AD)
Neuropathology
T305
T323
74 year-old, Control
89 year-old, AD

Hirano body

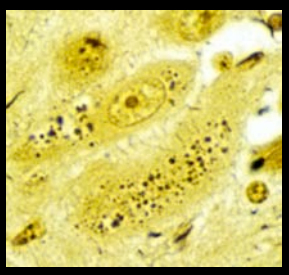


10 - 30 μm
adjacent or within cytoplasm pyramidal neurons of hippocampus



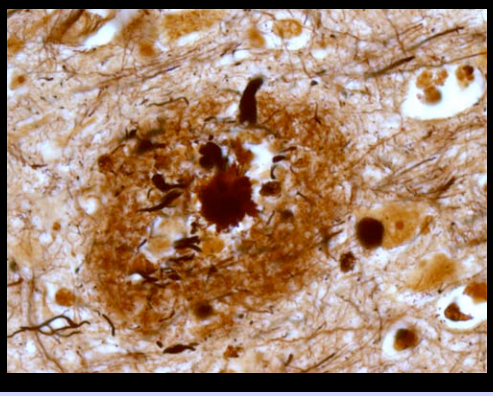
Granulovacuolar degeneration

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

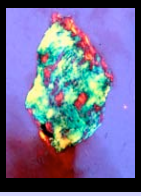
β– pleated sheet conformation, insoluble

Salmon pink

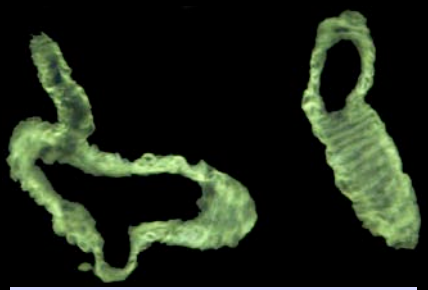
Congo red stain

Under polarized light

birefringent

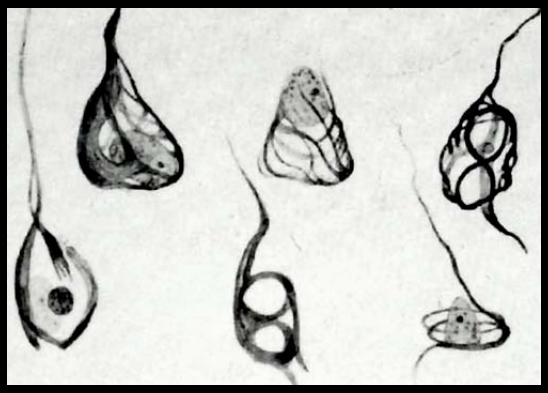


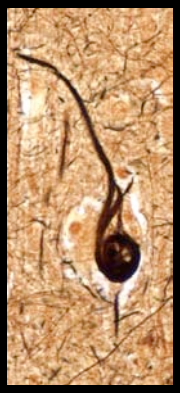
Apple green



Fluorescent with Thioflavine stain

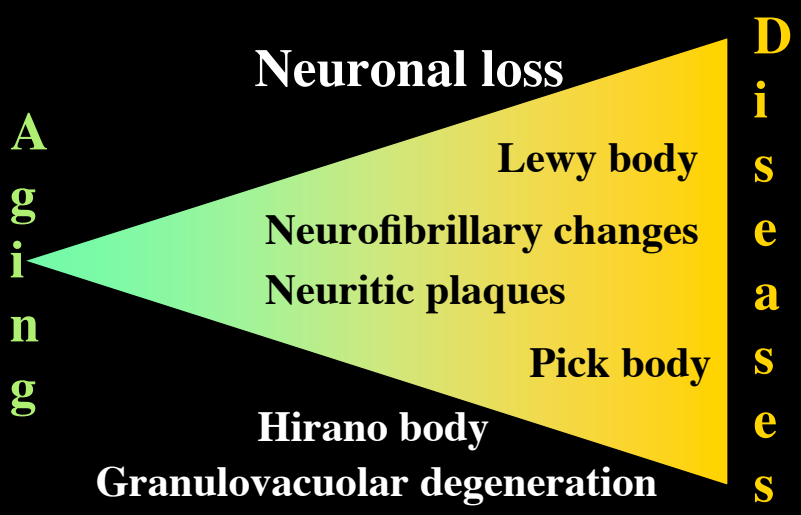
Neurofibrillary tangles of Alzheimer





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 (*)

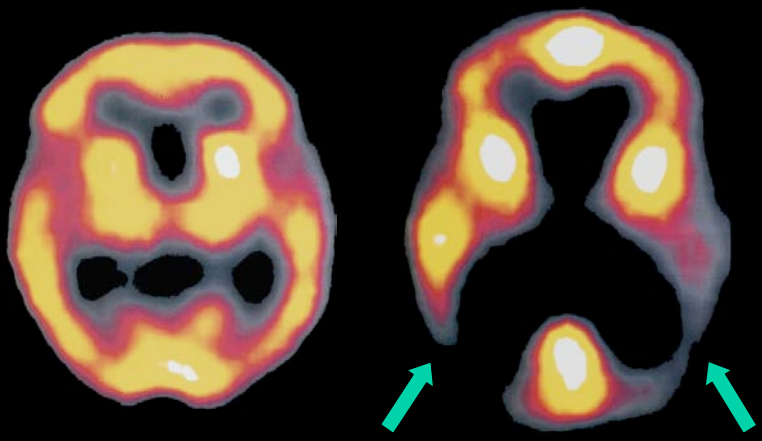
Estimated cost of AD
$100 billion / year (1993)

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)

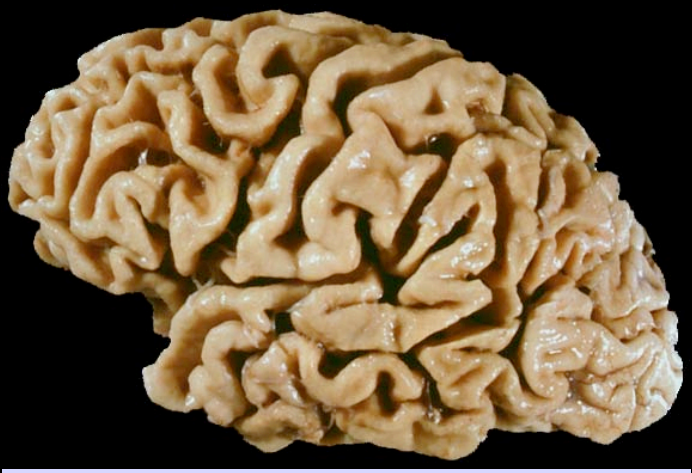


Single photon emission computerized tomography (SPECT)
In AD: Parietal hypoperfusion

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

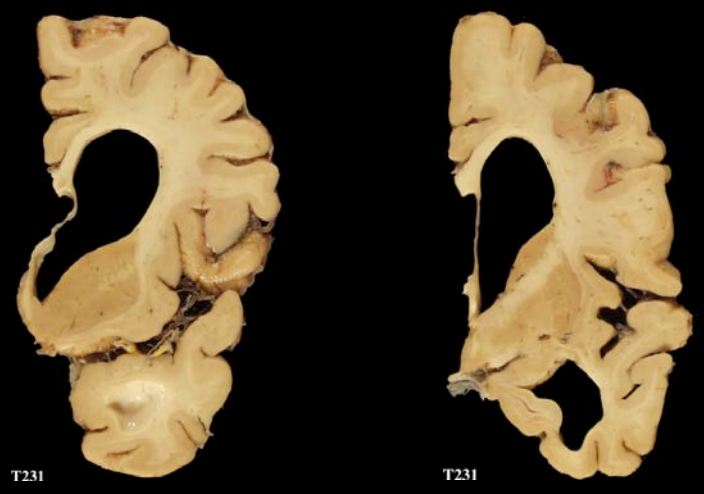
Alzheimer disease (AD) : Neuropathology

Cerebral atrophy

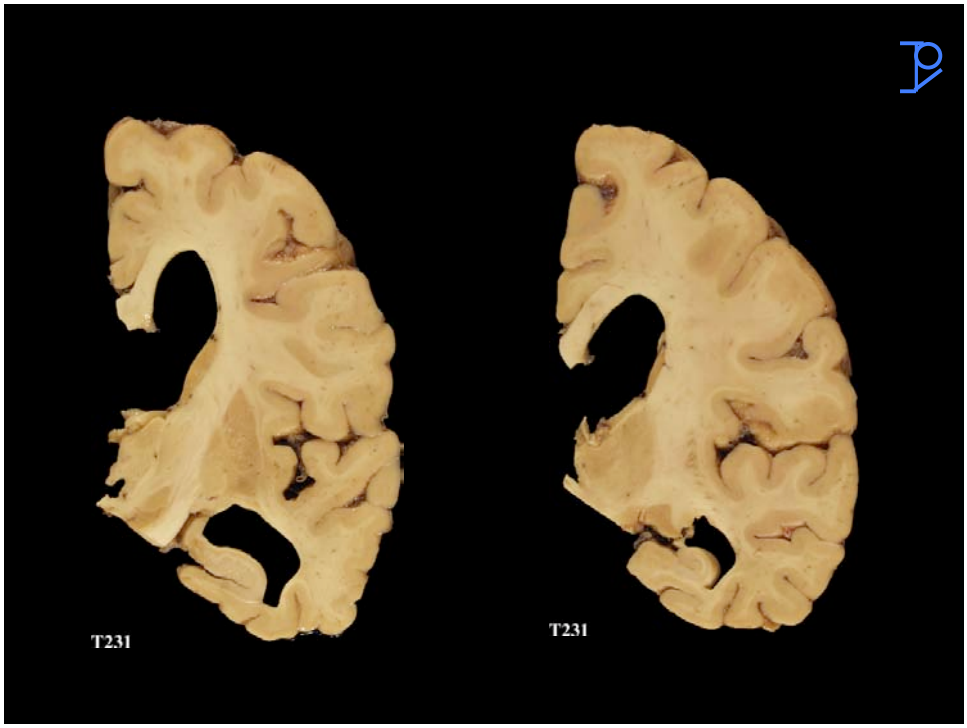


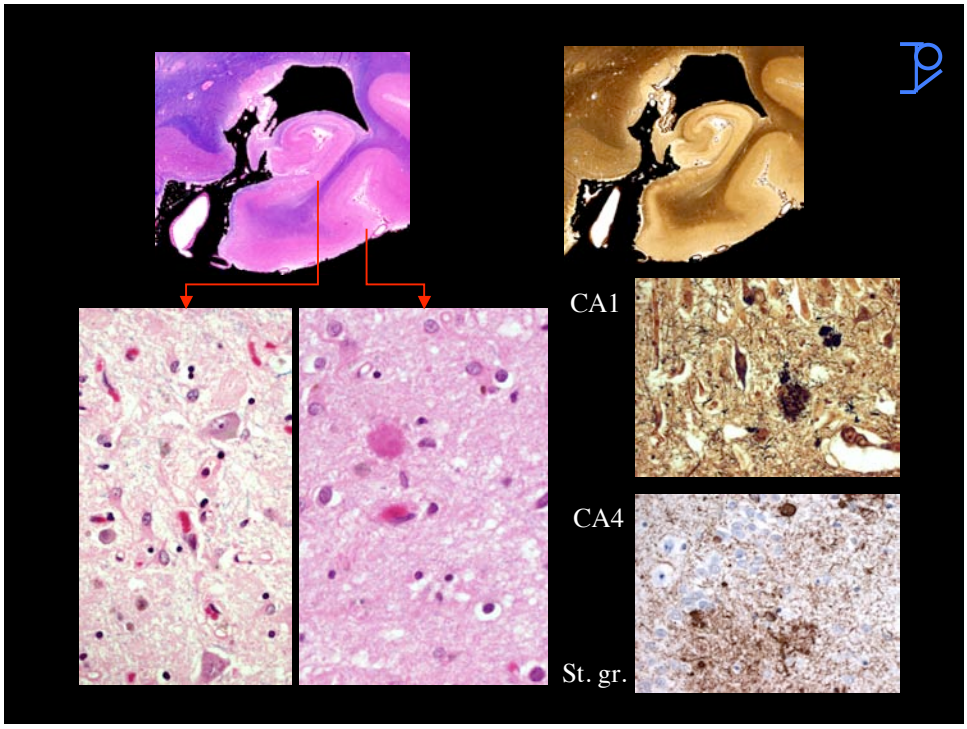
Atrophy = Widening of sulci + Narrowing of gyri

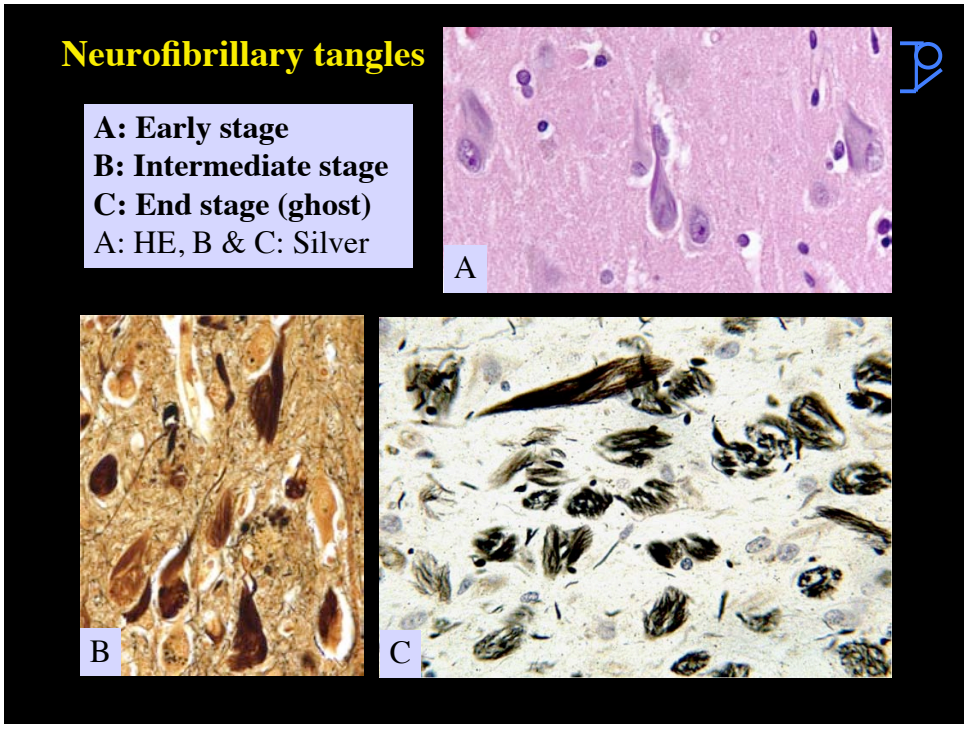
Permanent loss of predominantly glutamatergic, pyramidal neurons of neocortex



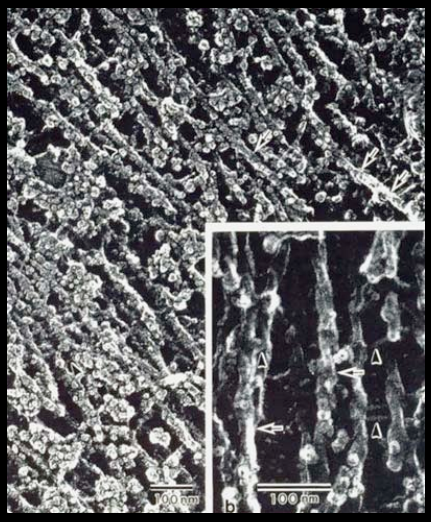
Basal nucleus of Meynert (cholinergic system)




CA1
CA4
St. gr.


Neurofibrillary tangles
A: Early stage
B: Intermediate stage
C: End stage (ghost)
A: HE, B & C: Silver
A
B
C

Neurofibrillary tangles: ultrastructure

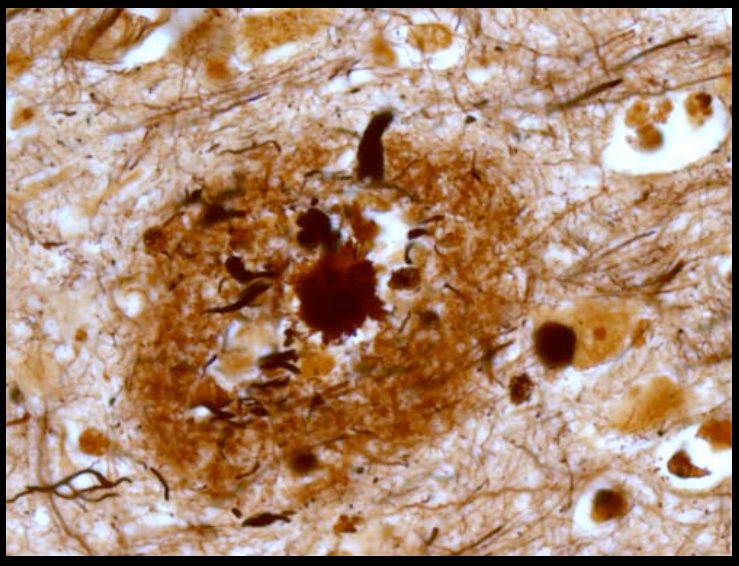


Paired helical filaments
8 - 12 nm, helically wound
Insoluble
React with silver stains

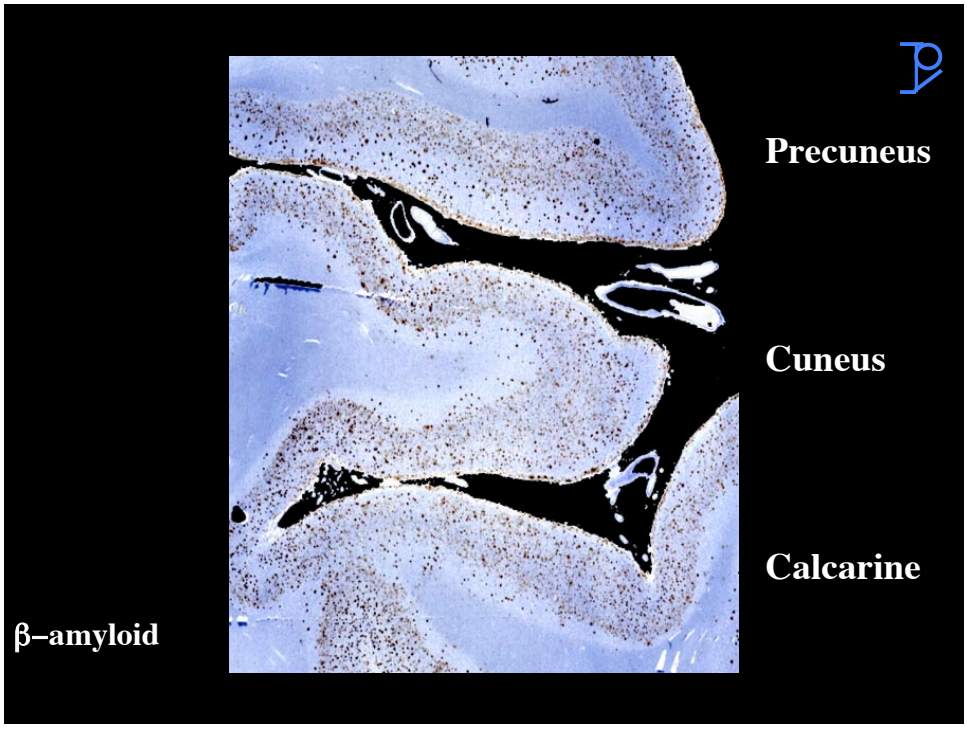
Hyperphosphorylated Tau
? Abnormal kinase or phosphatase activities

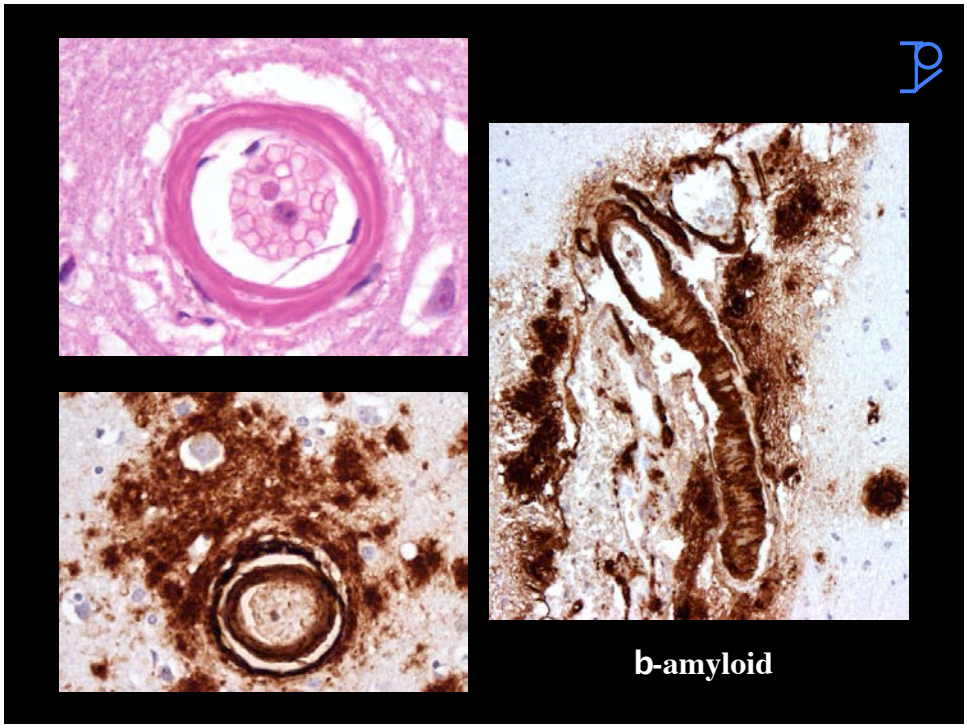
Tau: normal neuronal proteins, bind to microtubules regulate their assembly

Neuritic (senile) plaques (Bielschowsky)

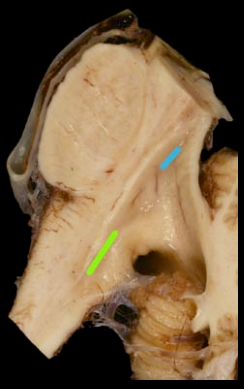


640 X


Precuneus
Cuneus
Calcarine
β–amyloid


b-amyloid

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

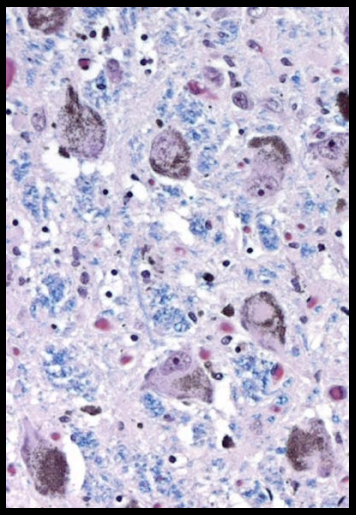


Coeruleus
Norepinephrine

Paradoxical sleep

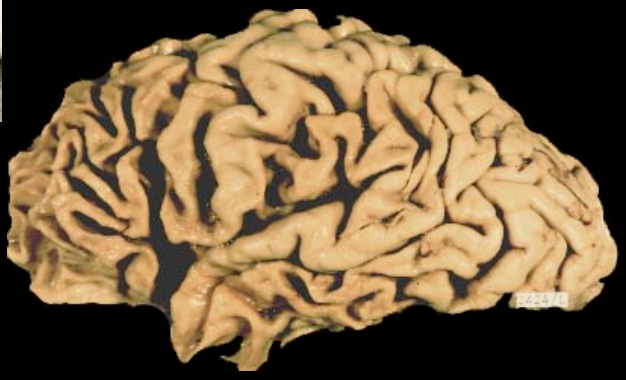
Cortical activation

Dorsal n. X



LHE

Pick disease



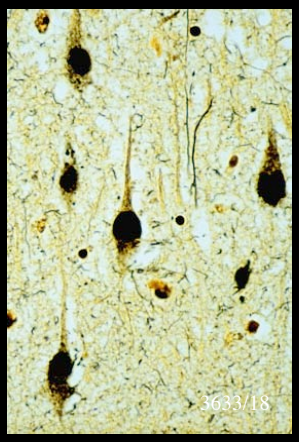
Pick body

Cytoplasmic, round, argyrophilic,
tau positive, ubiquitin positive,
10 - 15 μm across
a−synuclein negative

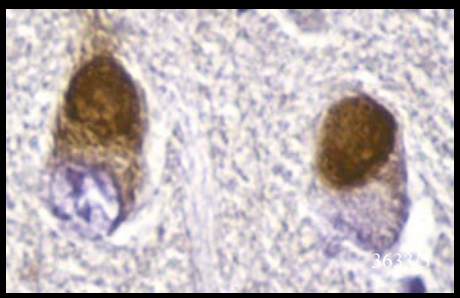
Pick bodies usually involve
- neocortical, pyramidal neurons
- hippocampal, pyramidal neurons
- stratum granulosum of dentate gyrus
- amygdala
- striatum
- brainstem

Pick body

Bielschowsky

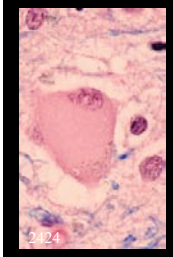


Tau



Tau positive
Ubiquitin positive
α-synuclein negative

Ballooned neurons

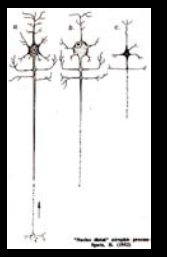


Pick disease

Primary progressive aphasia

Chromosome 17-linked dementia

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 variant (ADLBV)**
	Huntington disease (HD)

Parkinson disease

1919: Trétiakoff, C.

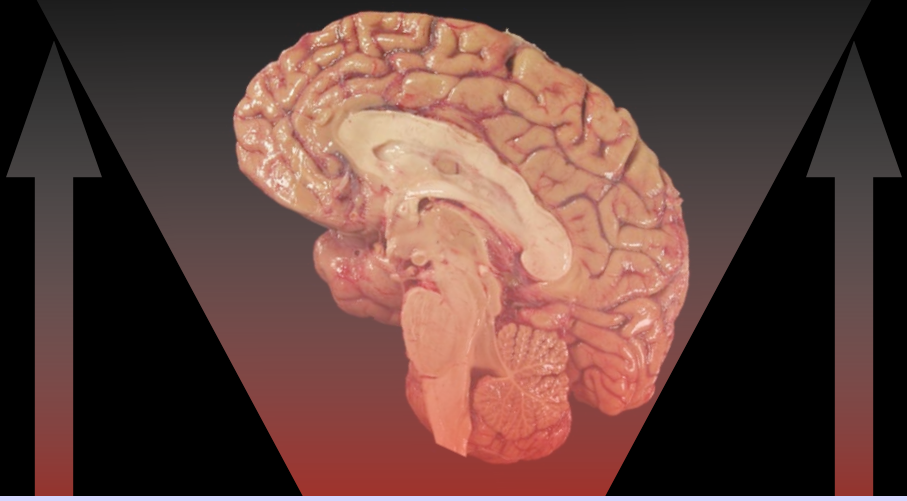
50,000 Americans / year -> diagnosed with PD

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 body

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

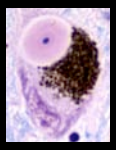
If, in addition,
neurons with Lewy body in
cerebral neocortex (-> dementia)

If, in addition,
neuritic plaques or neurofibrillary tangles or
both in cerebral cortex
(as seen in Alzheimer disease)

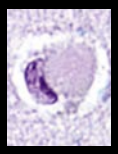
- Parkinson disease
- Diffuse Lewy body disease
- Alzheimer Disease Lewy body variant

Lewy body

Cytoplasmic inclusion, round, 8 - 30 μm

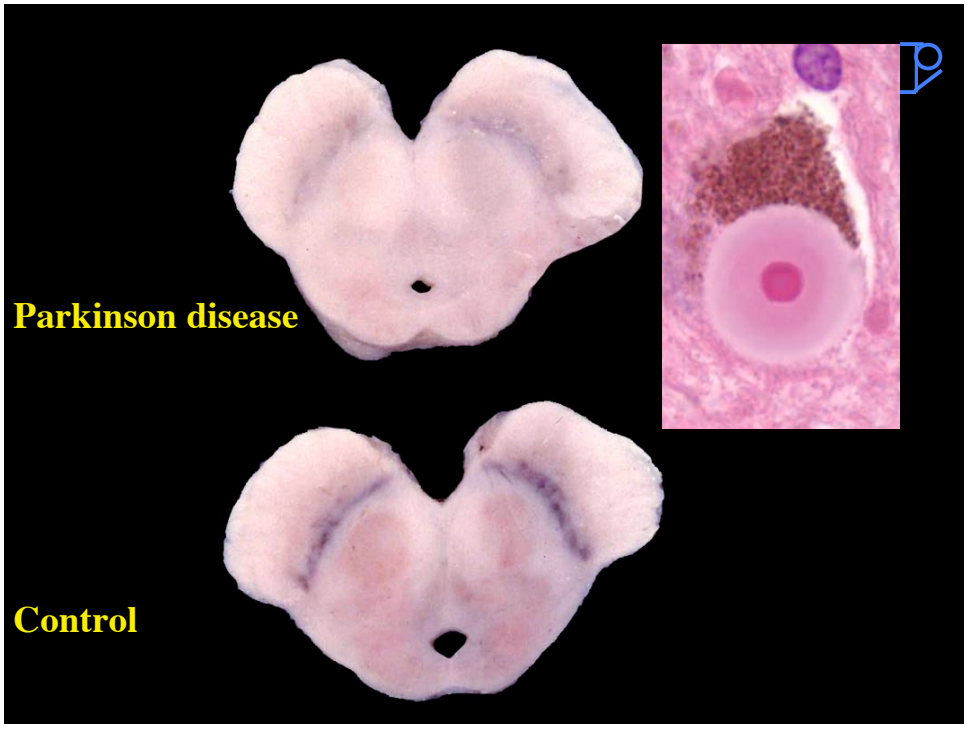


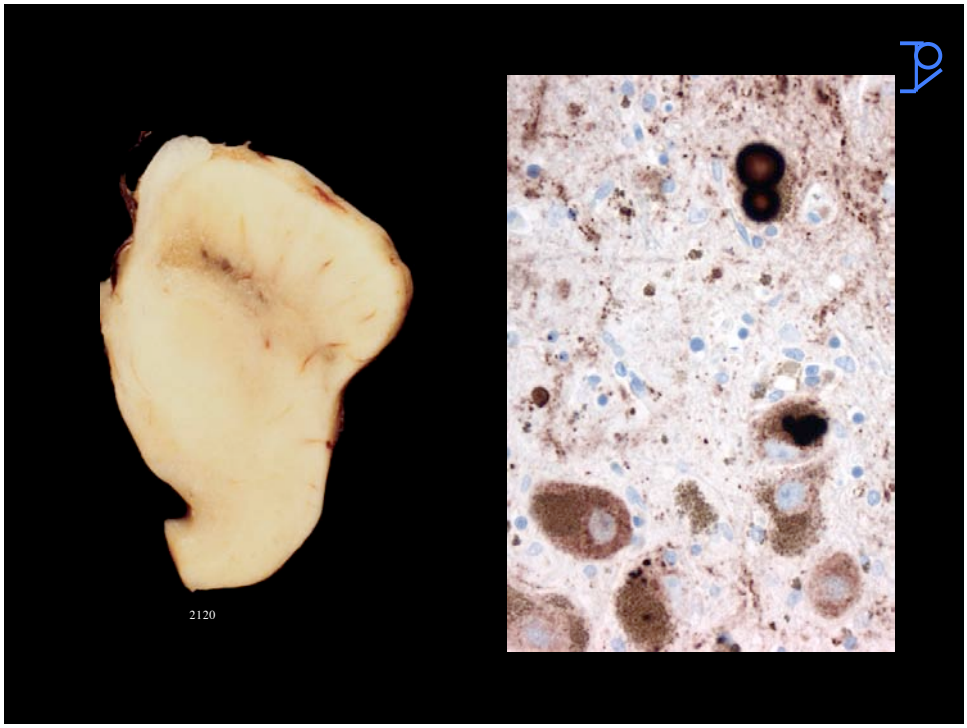
Brainstem type, discrete
Cortical type, ill-defined

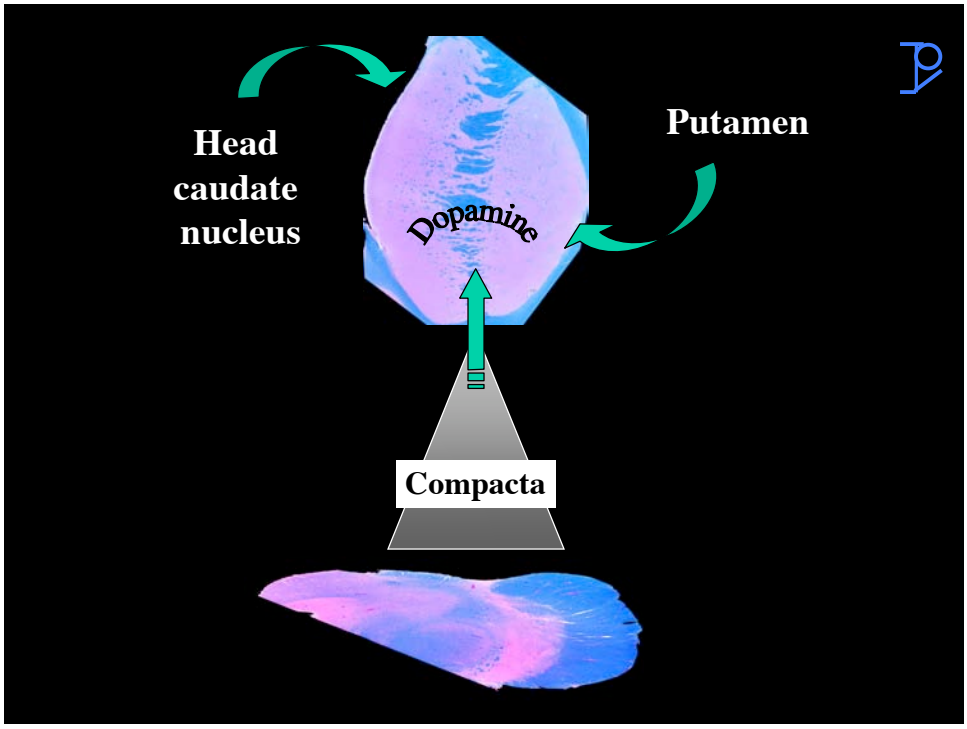


Found in

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


PLAY
DVD

MPTP

MPTP

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

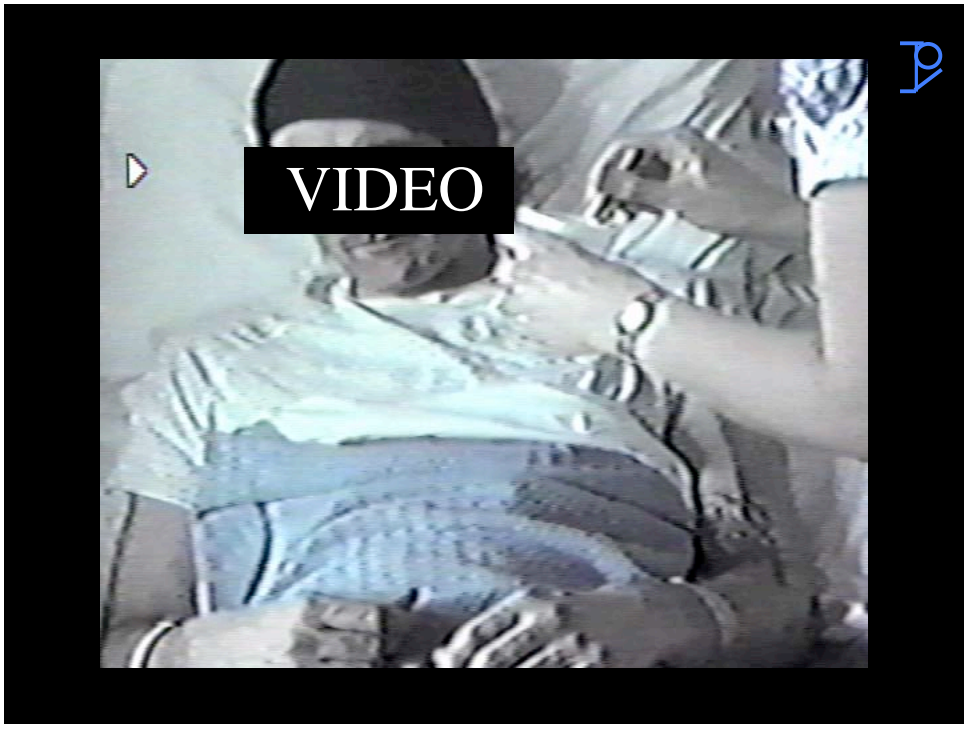
Not toxic

MPP$^+$

1-Methyl-4-Phenylpyridinium ion

Toxic

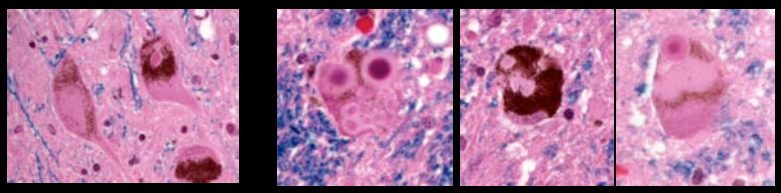

HOSPITAL TAPE:
GEORGE
VIDEO


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**

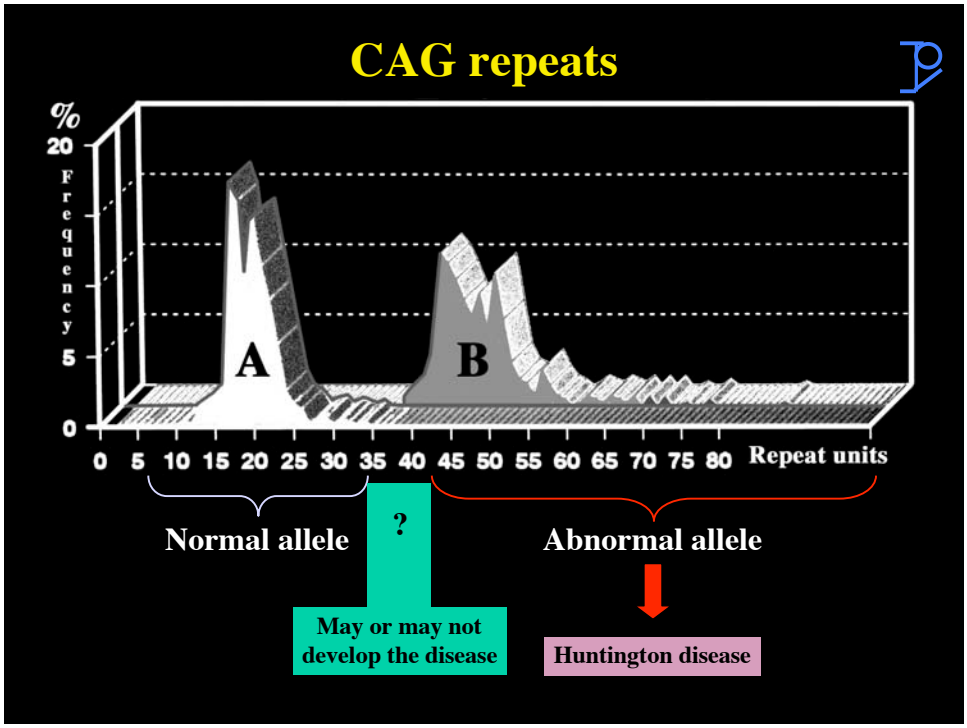


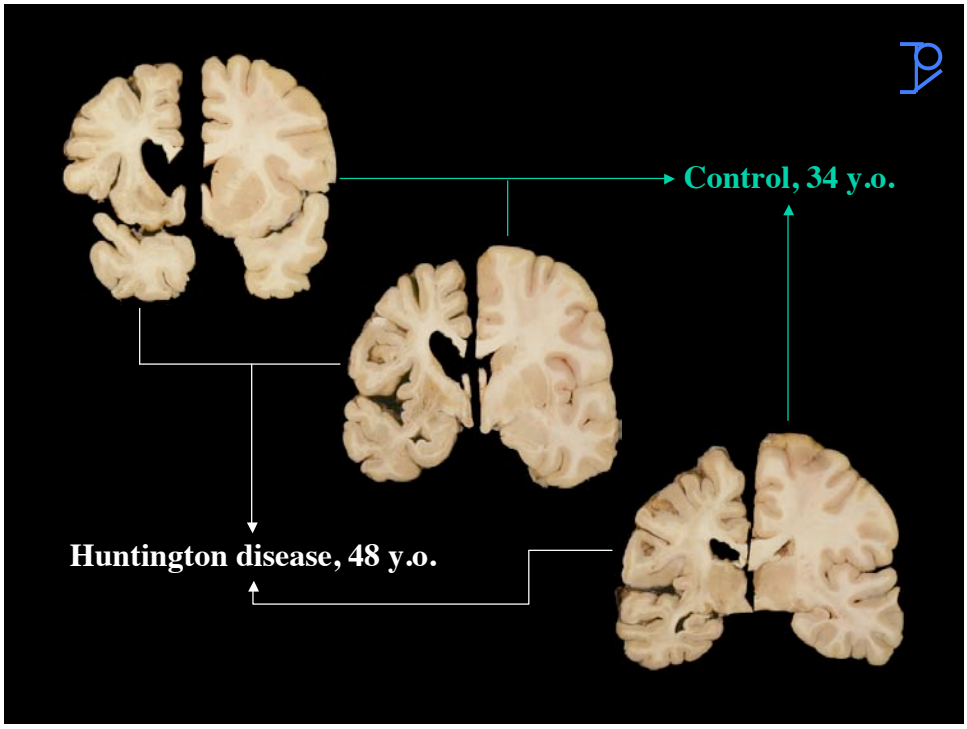
Substantia nigra

Nucleus coeruleus

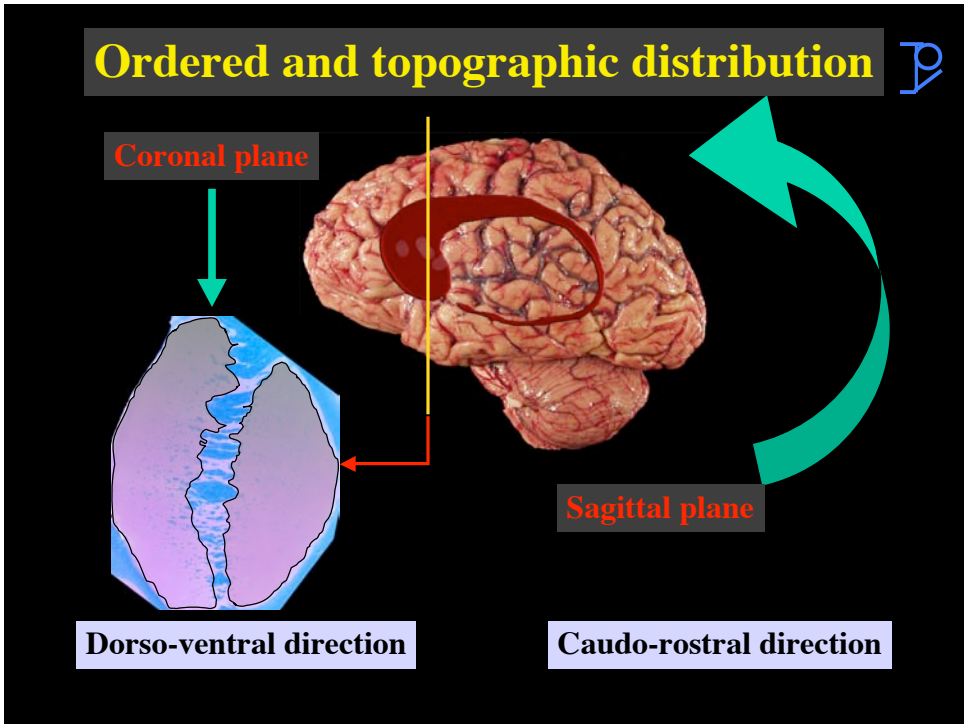
Huntington disease


Huntington disease
Early stage

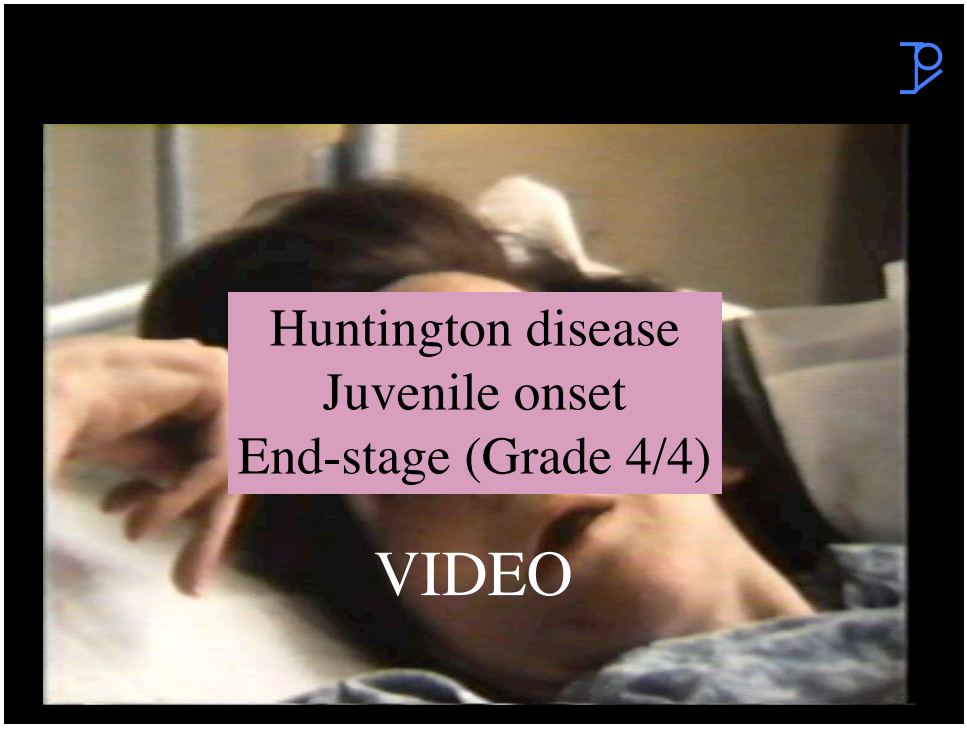

CAG repeats
%
20
Frequency
5
0
A
B
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80
Repeat units
Normal allele
?
Abnormal allele
May or may not develop the disease
Huntington disease

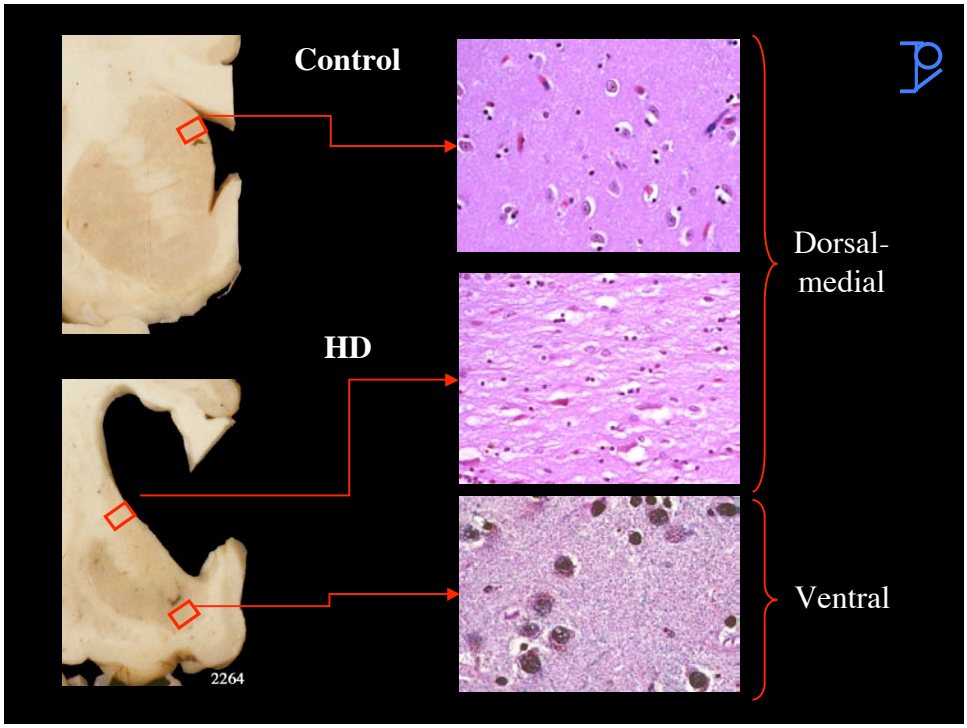


Huntington disease
Between early and late stages


Ordered and topographic distribution
Coronal plane
Sagittal plane
Dorso-ventral direction
Caudo-rostral direction

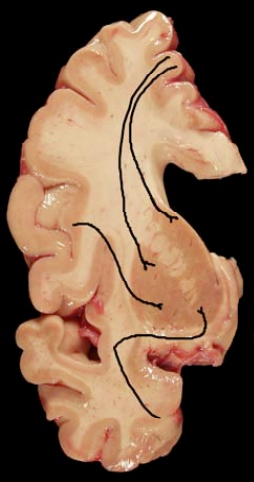

Huntington disease
Late stage
VIDEO


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


Control
HD
2264
Dorsal-medial
Ventral

Excitotoxicity

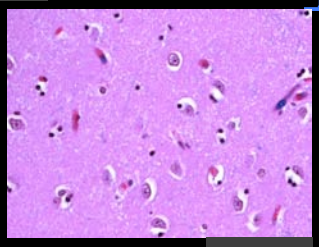
Glutamate



Receptors

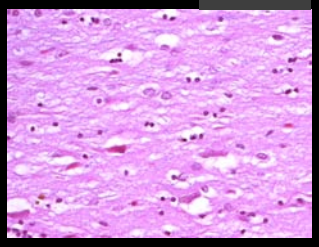
NMDA
AMPA
Kainate
Metabotropic

+
HDIT15
PolyQ

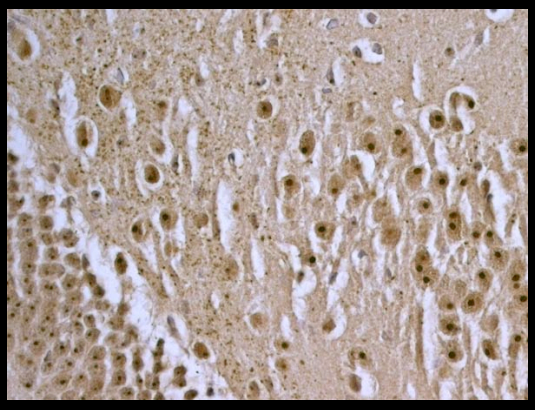


Normal

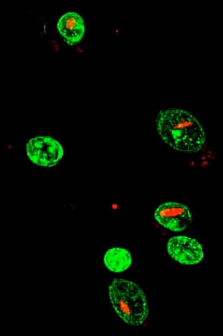
HD



Nuclear inclusions



Mouse R6/2
145 CAG



14 y.o. w
82/12 CAG

Huntington disease
Late onset
Relatively early stage
Slow progression