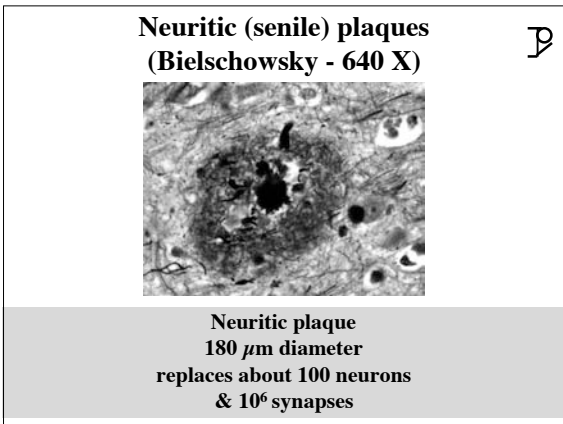
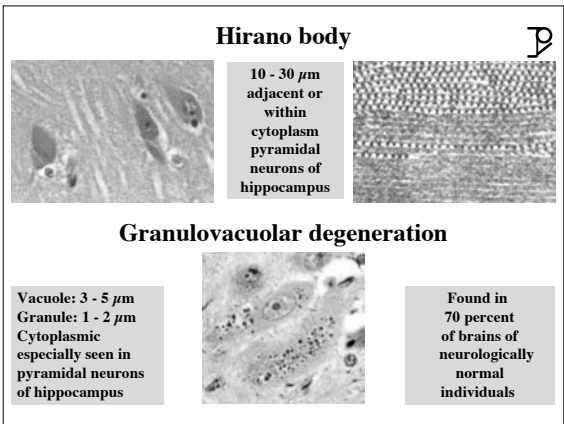
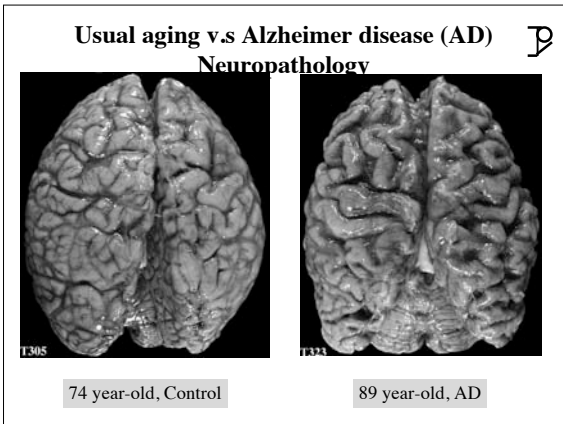
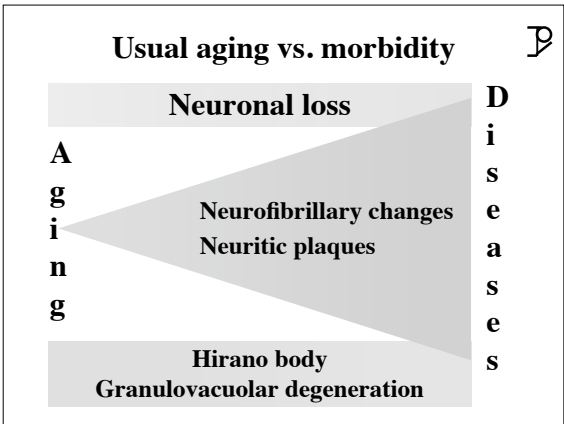



# Neurodegenerative diseases

- 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 variant (ADLBV)
  - Huntington disease (HD)



### Amyloid

**$\beta$ -pleated sheet conformation, insoluble**




Salmon pink

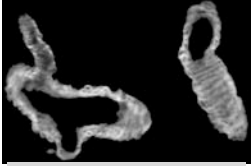
Congo red stain

Under polarized light

birefringent

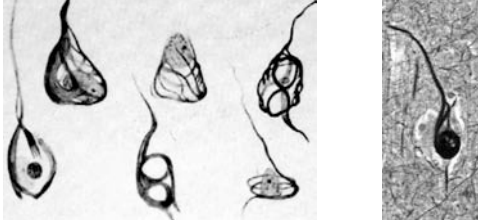


Apple green



Fluorescent with Thioflavine stain

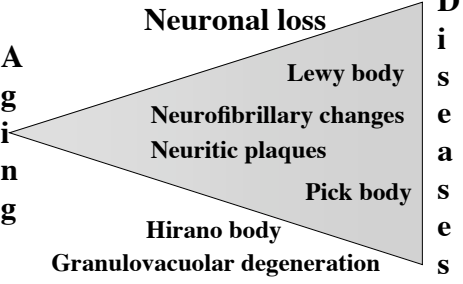
### Neurofibrillary tangles of Alzheimer



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

A  
g  
i  
n  
g



D  
i  
s  
e  
a  
s  
e

### 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

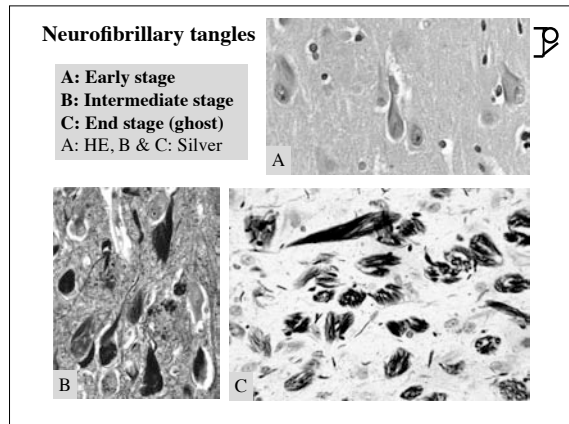
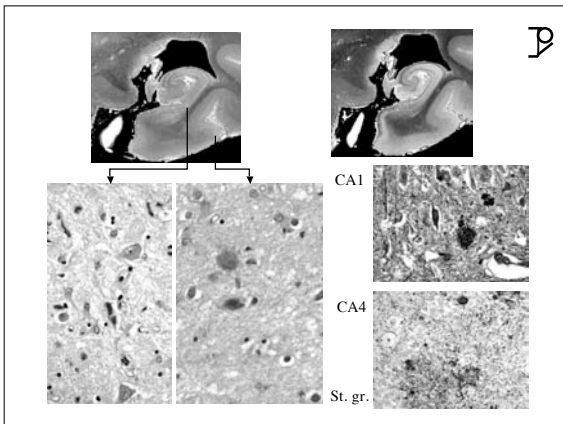
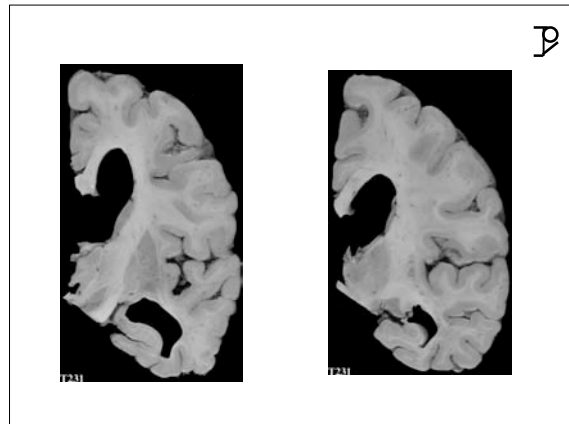
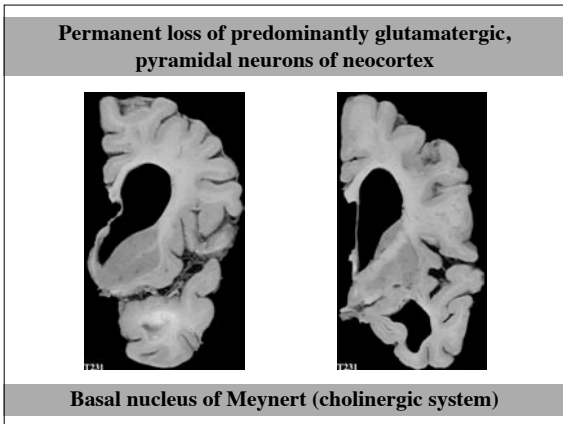
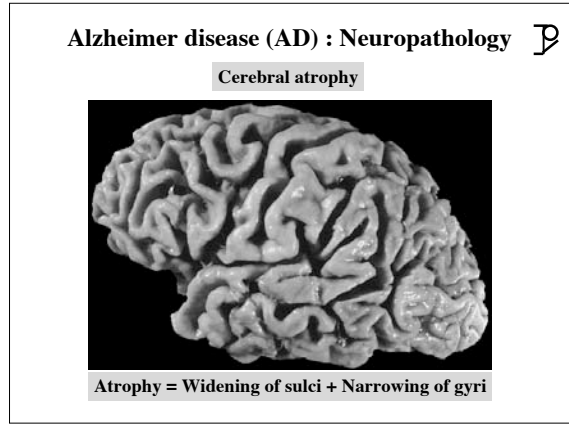
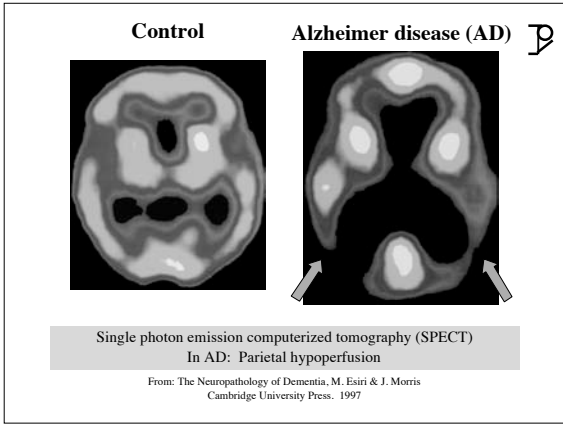
### Alzheimer disease in the US

- 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

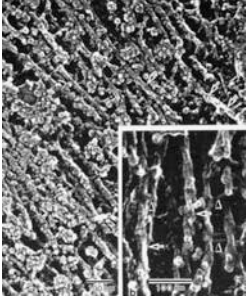
### Alzheimer disease (AD) in the US

- 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)**
- 4<sup>th</sup> or 5<sup>th</sup> 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)



### Neurofibrillary tangles: ultrastructure $\mathcal{P}$

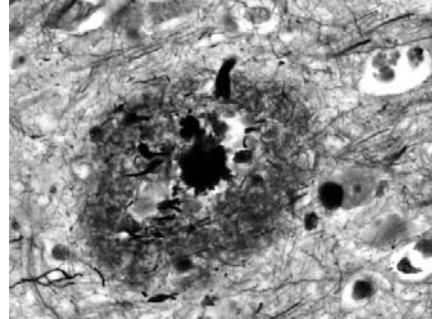


Paired helical filaments  
8 - 12 nm, helically wound  
Insoluble  
React with silver stains

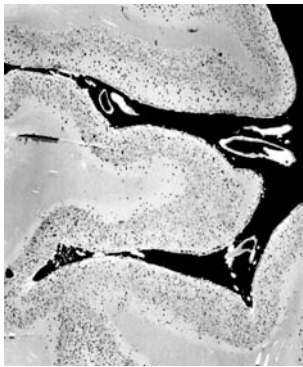
Hyperphosphorylated Tau  
? Abnormal kinase or  
phosphatase activities

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

### Neuritic (senile) plaques (Bielschowsky) $\mathcal{P}$



640 X

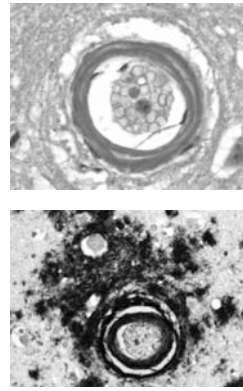


$\beta$ -amyloid

Precuneus

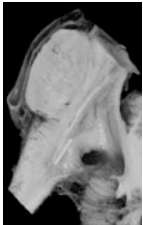
Cuneus

Calcarine



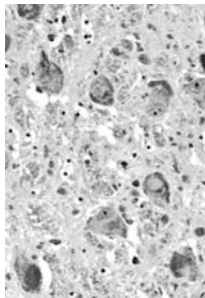
$\beta$ -amyloid

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

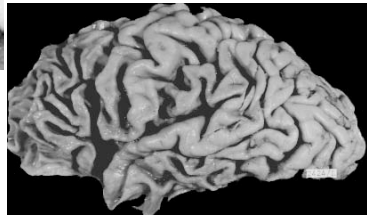


Coeruleus  
Norepinephrine  
Paradoxical sleep  
Cortical activation

Dorsal n. X



### Pick disease $\mathcal{P}$



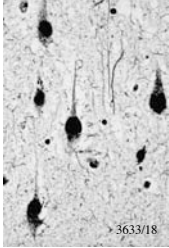
**Pick body** P

Cytoplasmic, round, argyrophilic,  
tau positive, ubiquitin positive,  
10 - 15  $\mu\text{m}$  across  
 $\alpha$ -synuclein negative

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

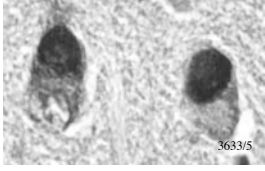
**Pick body** P

Bielschowsky



3633/18

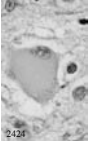

Tau



3633/5

**Tau positive**  
**Ubiquitin positive**  
 **$\alpha$ -synuclein negative**

**Ballooned neurons** P

Pick disease  
Primary progressive aphasia  
Chromosome 17-linked dementia  
Corticobasal degeneration  
Alzheimer disease  
Progressive supranuclear palsy  
Creutzfeldt-Jakob disease

**Parkinson disease** P

**And**

**Dementia with Lewy bodies**

**Dementing disorders** P

- 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)

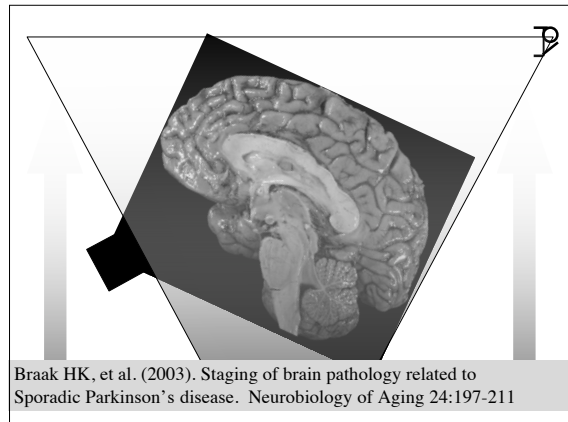
**Parkinson disease** P



**1919: Trétiakoff, C.**

**50,000 Americans / year -> diagnosed with PD**


<b>Parkinson disease (PD)</b>	
<b>Bradykinesia</b> <b>Rigidity</b> <b>Resting tremor</b> <b>Postural instability</b>	
<b>Neuronal loss</b> <b>Cytoplasmic inclusion: Lewy body</b>	
<b>Pars compacta of substantia nigra</b> <b>Nucleus coeruleus</b> <b>Substantia innominata</b> <b>Hypothalamus</b> <b>Dorsal nucleus of vagus</b>	



<b>Neuronal loss</b> <b>Cytoplasmic inclusion: Lewy body</b>	
<b>Dorsal nucleus of vagus</b> <b>Nucleus coeruleus</b> <b>Pars compacta of substantia nigra</b> <b>Hypothalamus</b> <b>Substantia innominata -&gt; Mesolimbic cortex</b>	<b>Parkinson disease</b>
<b>If, in addition,</b> <b>neurons with Lewy body in cerebral neocortex (-&gt; dementia)</b>	
<b>If, in addition,</b> <b>neuritic plaques or neurofibrillary tangles or both in cerebral cortex (as seen in Alzheimer disease)</b>	<b>Alzheimer Disease</b> <b>Lewy body variant</b>

**Lewy body**


**Cytoplasmic inclusion, round, 8 - 30  $\mu$ m**



←

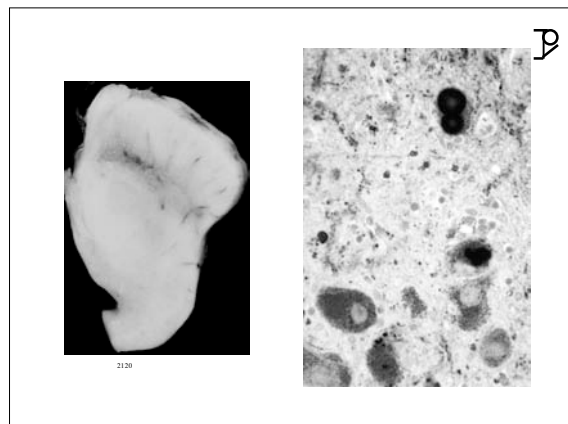
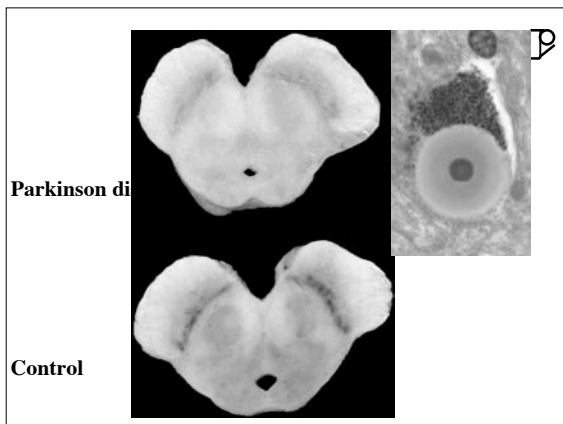
**Brainstem type, discrete**  
**Cortical type, ill-defined**

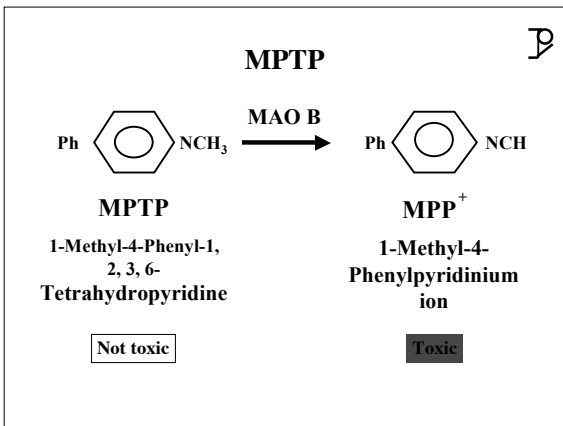
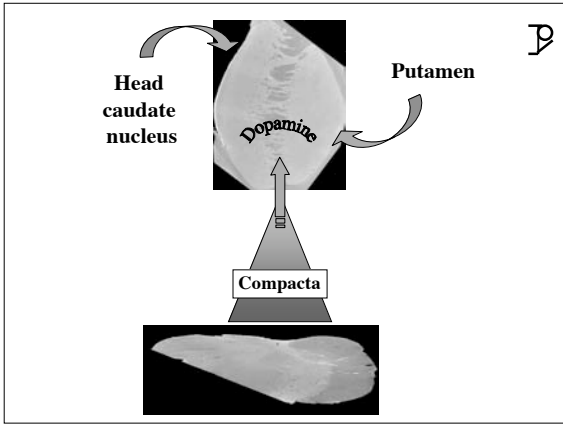
→




**Found in**

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

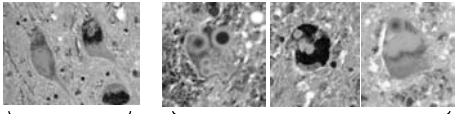




**Dementia with Lewy body (LB)** 

**Diffuse LB disease**

**Lewy bodies & Lewy neurites**  
*Neocortex, hypothalamus, substantia innominata, substantia nigra (compacta), coeruleus, dorsal nucleus of vagus*

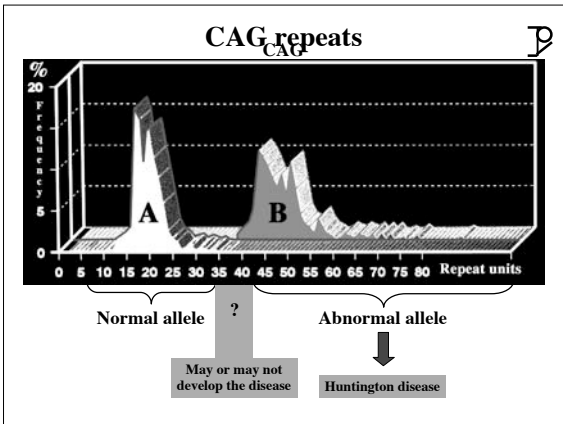



Substantia nigra      Nucleus coeruleus

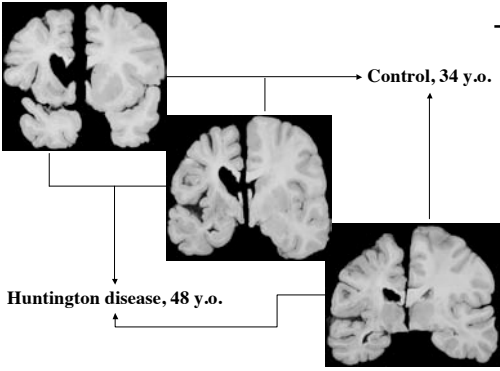
**Huntington disease** 

**Huntington disease** 

**Early stage**





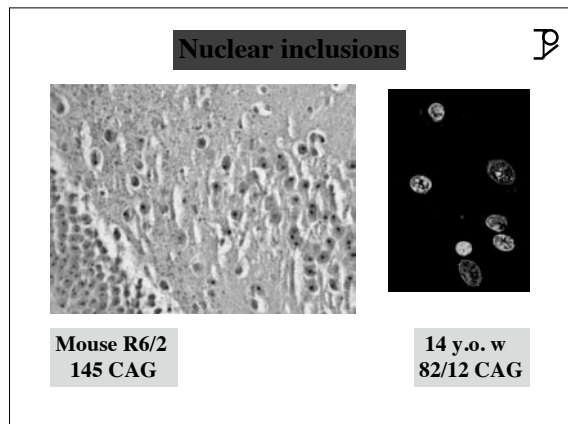
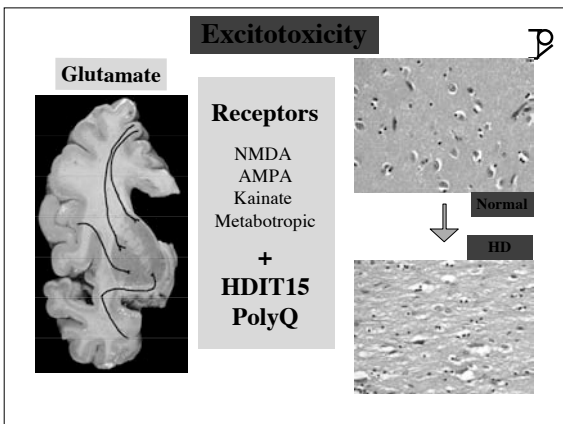
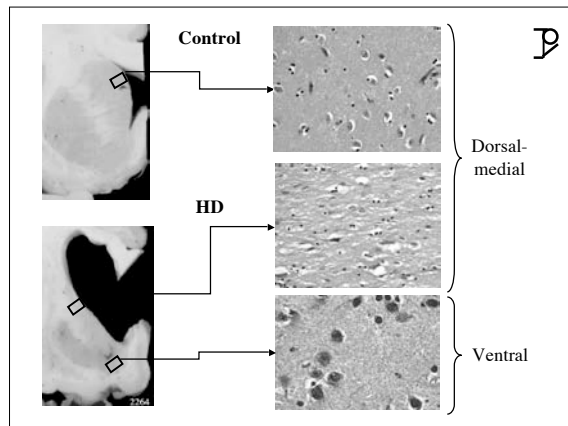
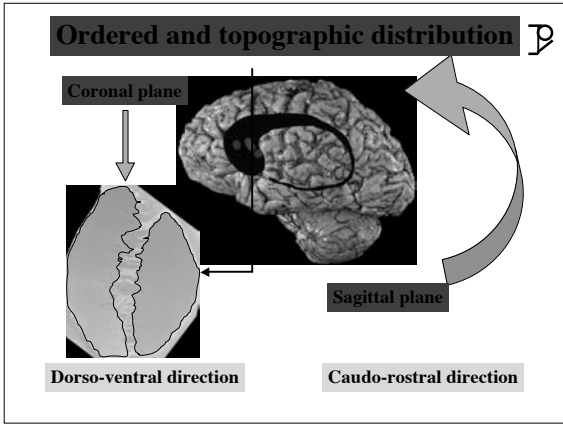
Control, 34 y.o.

Huntington disease, 48 y.o.

**Huntington disease**  
**Between early and late stages**







**Huntington disease**  
**Late onset**  
**Relatively early stage**  
**Slow progression**

