Imperial College London

BSc Neuroscience and Mental Health
2011/2012

MODULE 2
Neurological and Psychiatric Disorders

Huntington's disease

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Consultant Neurologist

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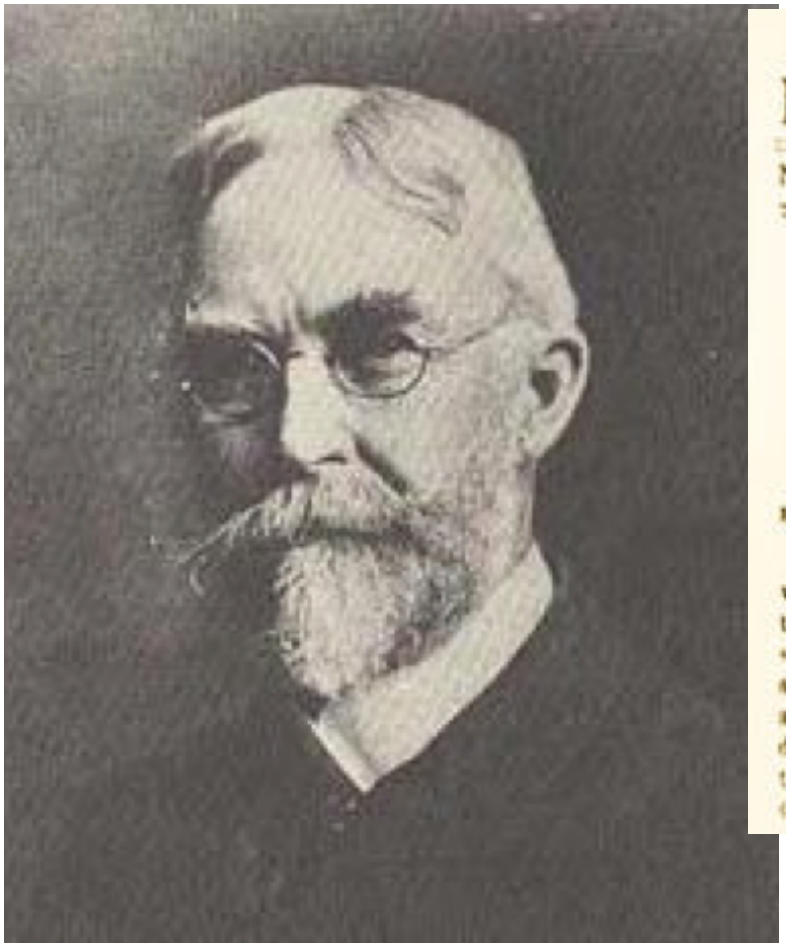
CHOREA



THE

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT

Chorea is es… a disease of … nerv…

The dis… means a da… as of … serious affec… however distressing it may be

The name 'chorea' is given to the disease on account of the 'dancing' propensities of those who are affected by it

…y be the first …unly. All the … to be affected, …exempted. …rude the tongue …t deal of diffi… …ncertainty. The hands are kept …t the palms upward, and then the …e shoulders are shrugged, and the …gs kept in perpetual motion; the …ned in, and then everted; one foot …cross the other, and then suddenly …withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete de-cription of

Chorea …
vous system …
the disea-e …
…ities of tho…
a very appr…
as it is commonly … by no means a …
dangerous or seri… …ection, however dis… tressing it may be … the one suffering from it, or to his friends. Its most marked and char…

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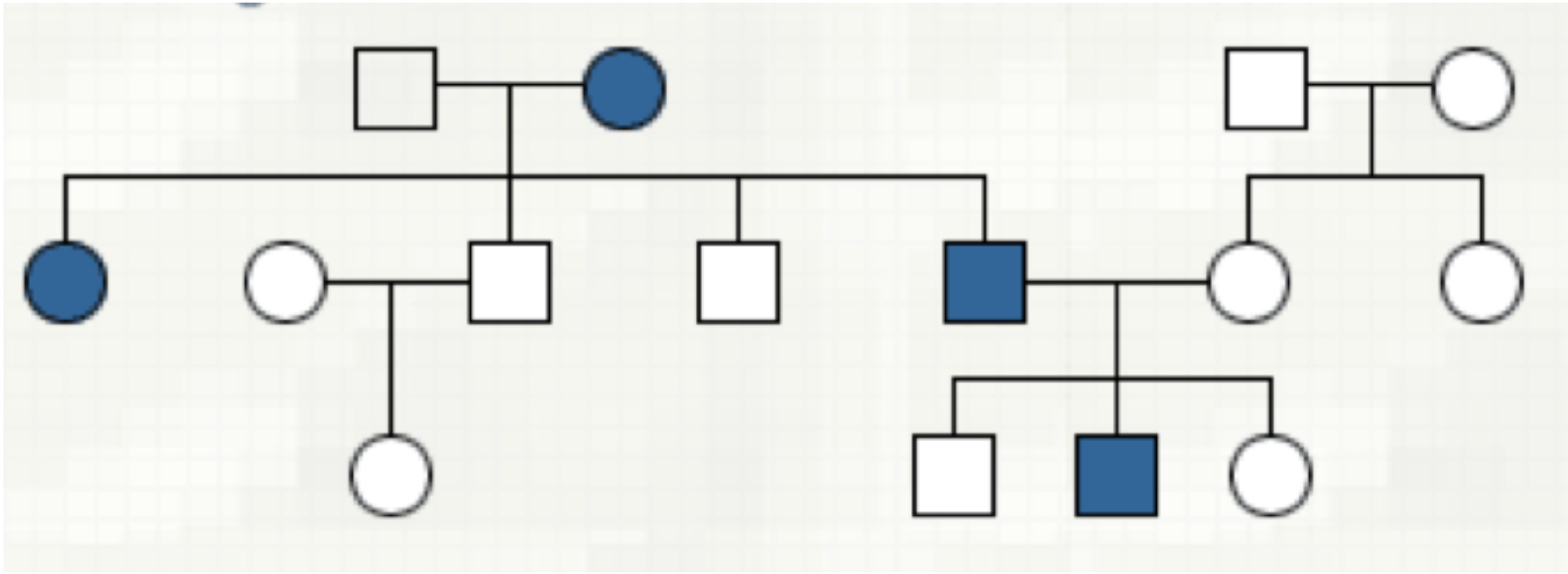
Huntington's disease

HD is caused by a mutation of the ***Huntingtin gene (HTT)*** on the short arm of **chromosome 4 (4p16.3).**

The mutation is expressed as an autosomal dominant disease.



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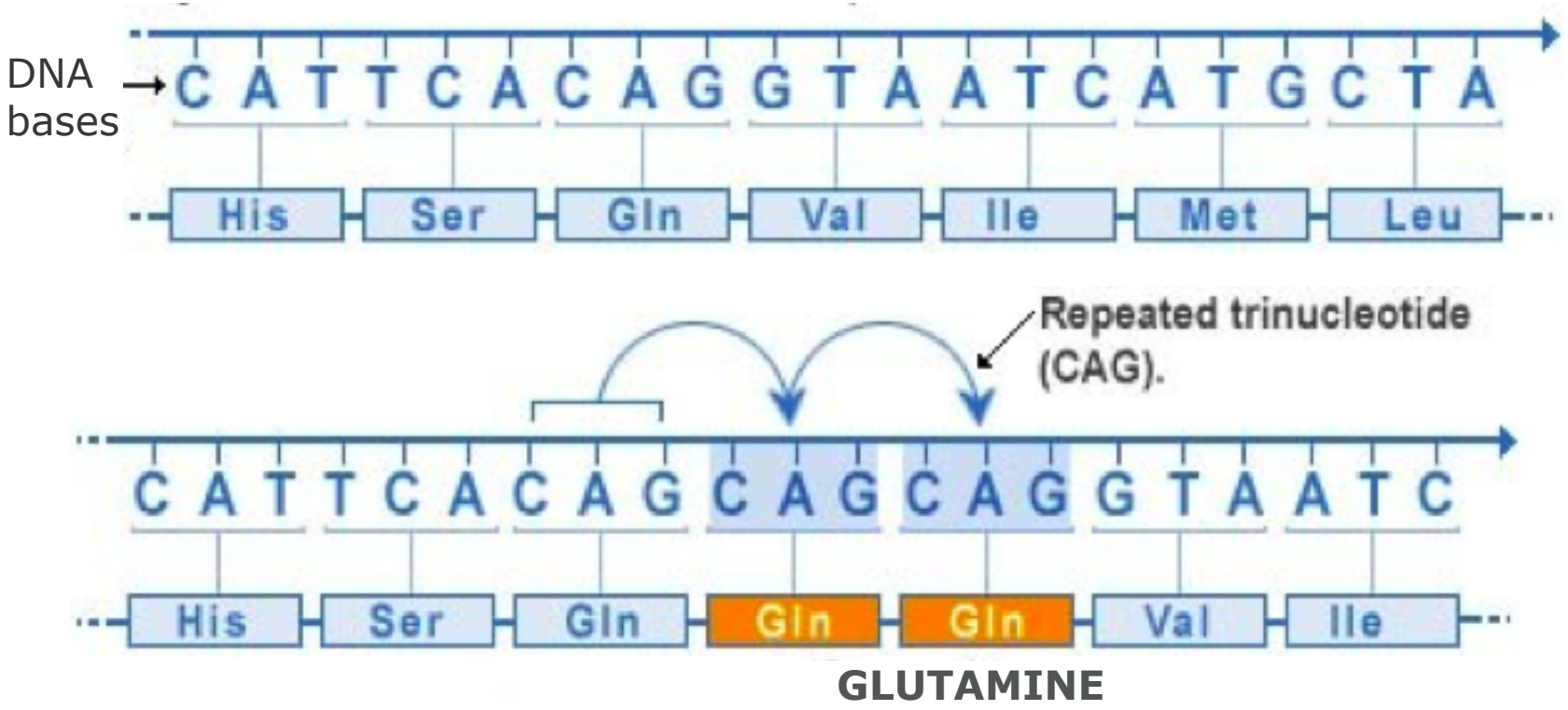
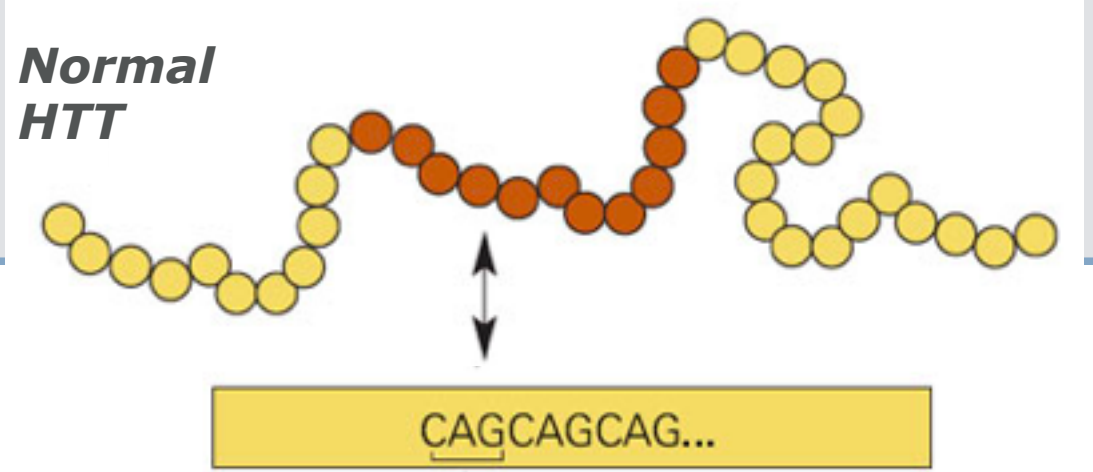
GENETIC DEFECT

The underlying mutation responsible for the disease involves an improper expansion of a CAG trinucleotide region in the gene **HUNTINGTIN-HTT.**

In people with HD, the CAG sequence abnormally repeats itself dozens of times.

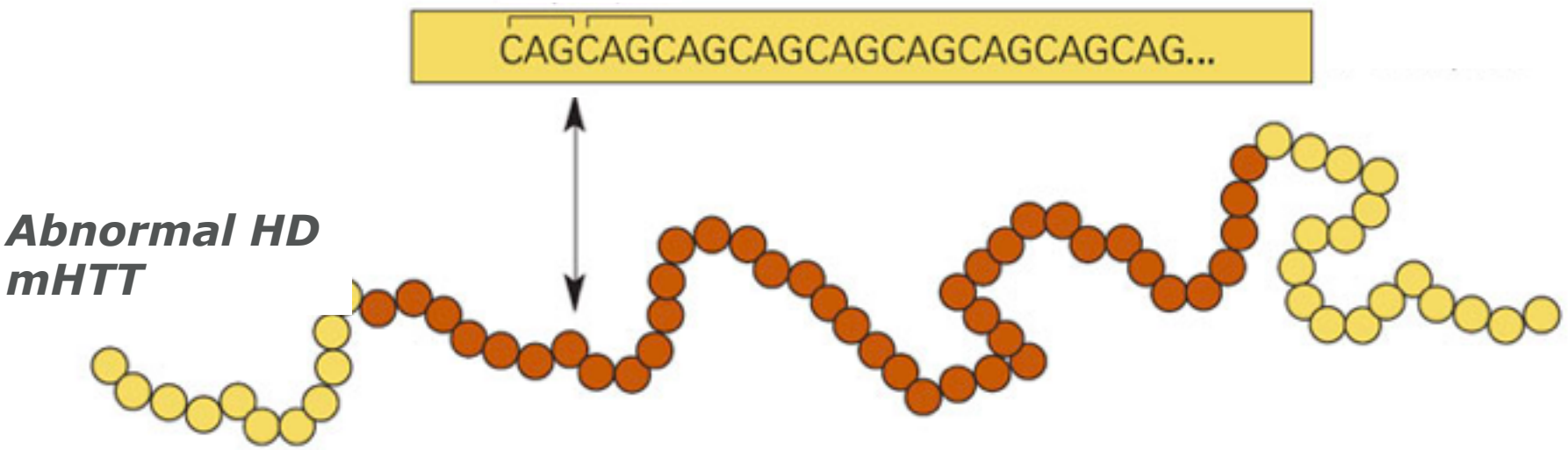


C=*cytosine* ***A***=*adenosine* ***T***=*Thymine* ***G***=*Guanine*

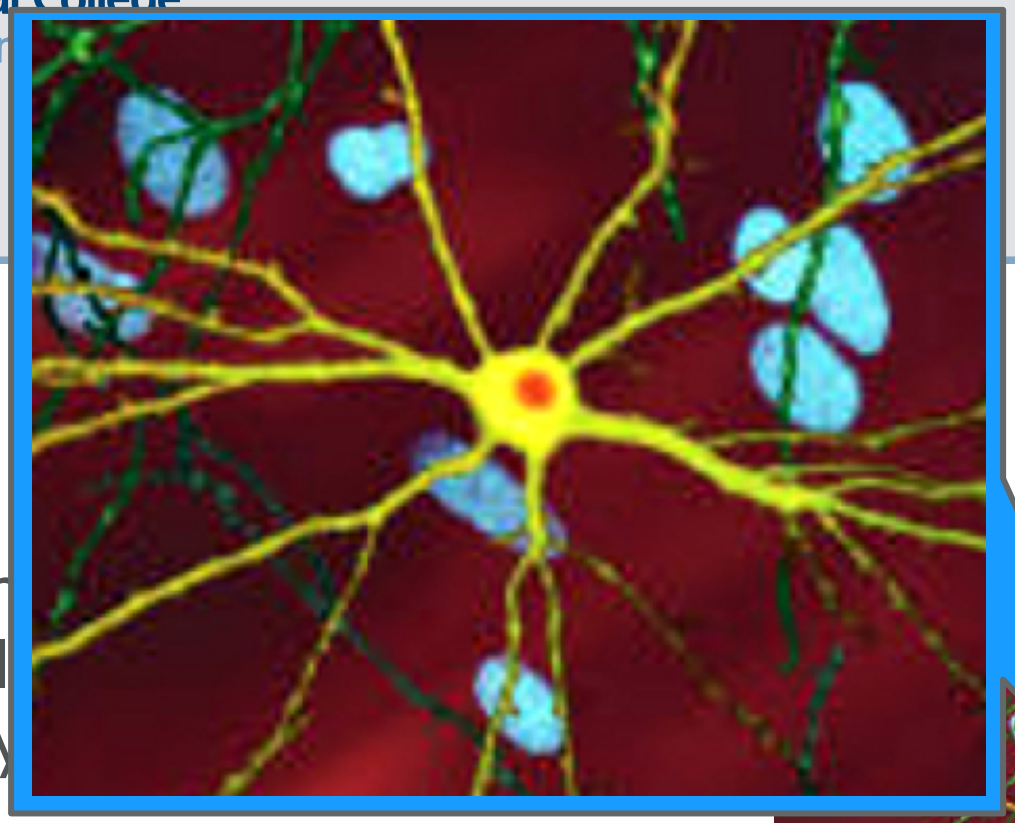


The *Huntingtin* gene normally provides the genetic information for a protein that is also called "*Huntingtin*".

HTT mutation ➔ expansion of CAG repeats

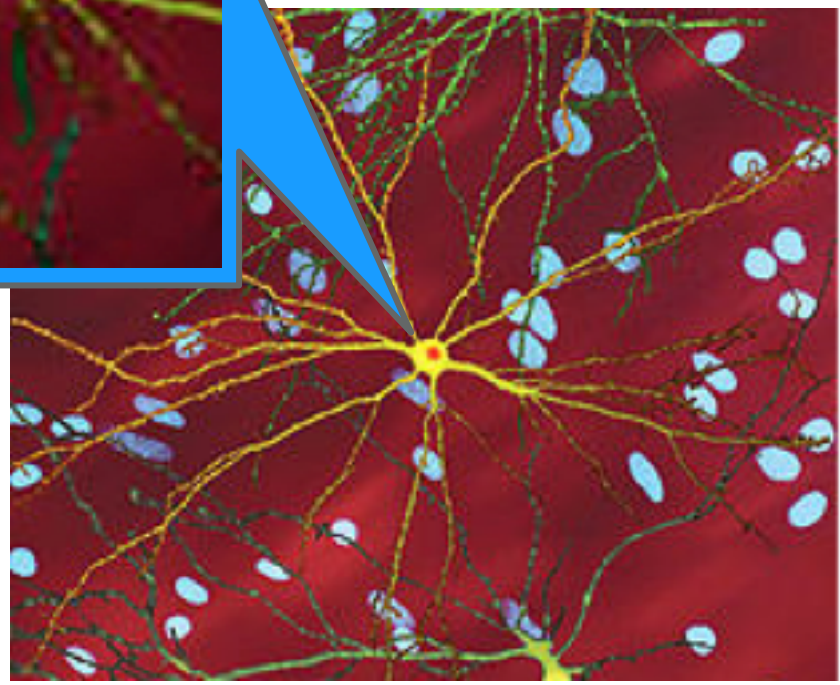


The mutation of the *Huntingtin* gene codes for a abnormal form of the protein with large glutamine blocks.



Abnorm
gradual
possibly

Main pathology: degeneration and death of medium spiny GABAergic neurons in the caudate and putamen



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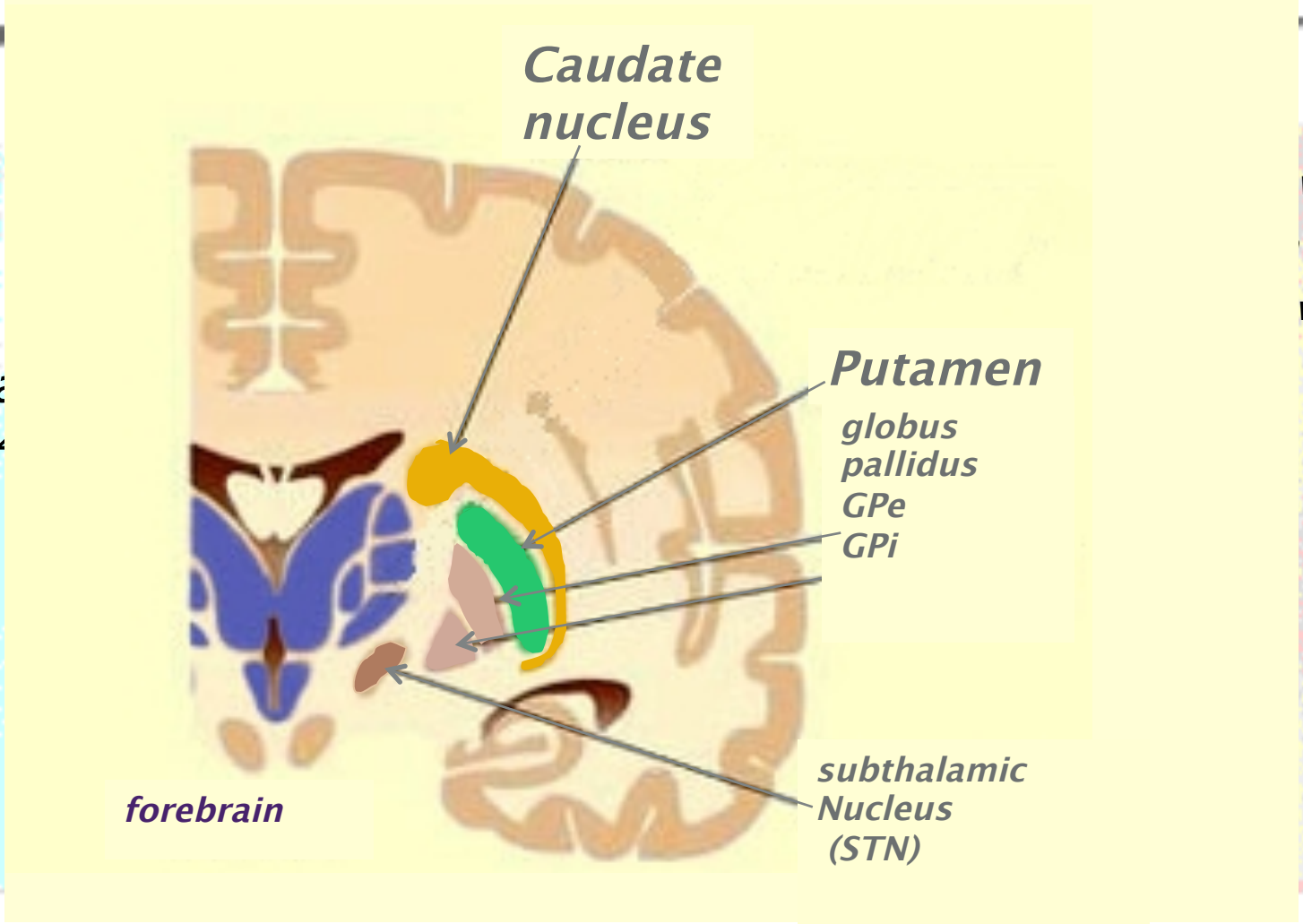
Huntington's disease



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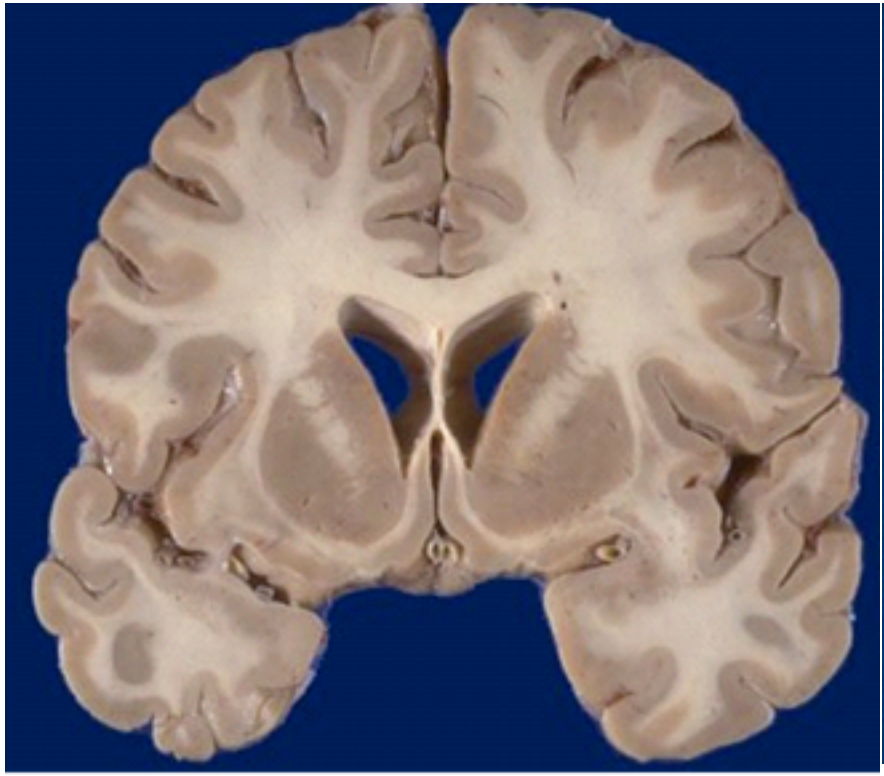
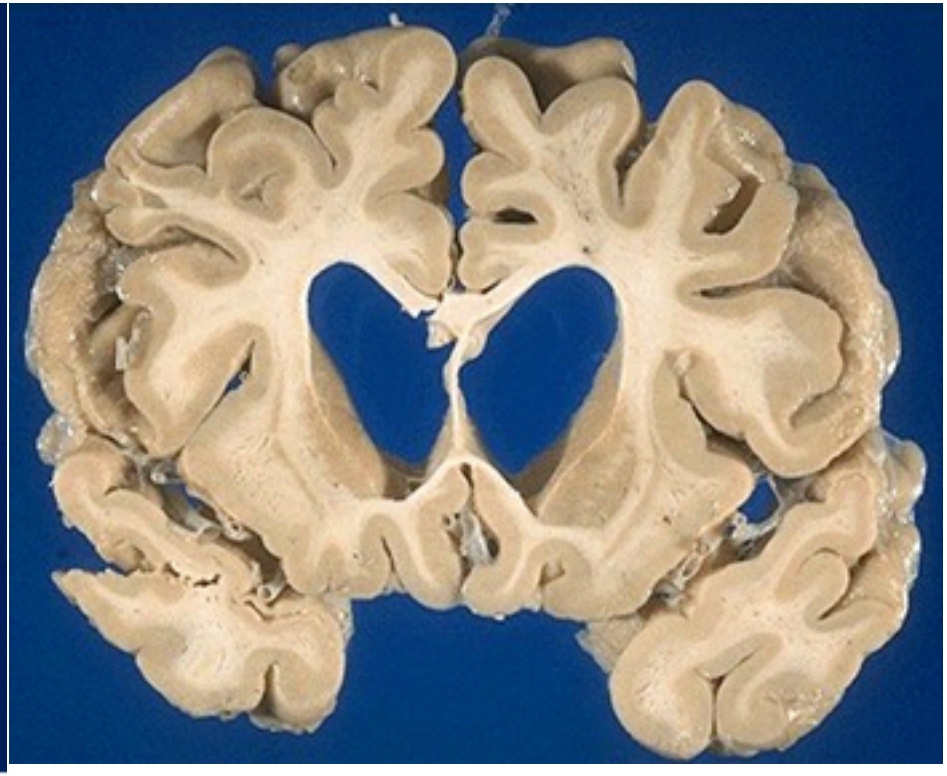
Huntington's disease



NORMAL BRAIN



HUNTINGTON'S DISEASE BRIAN

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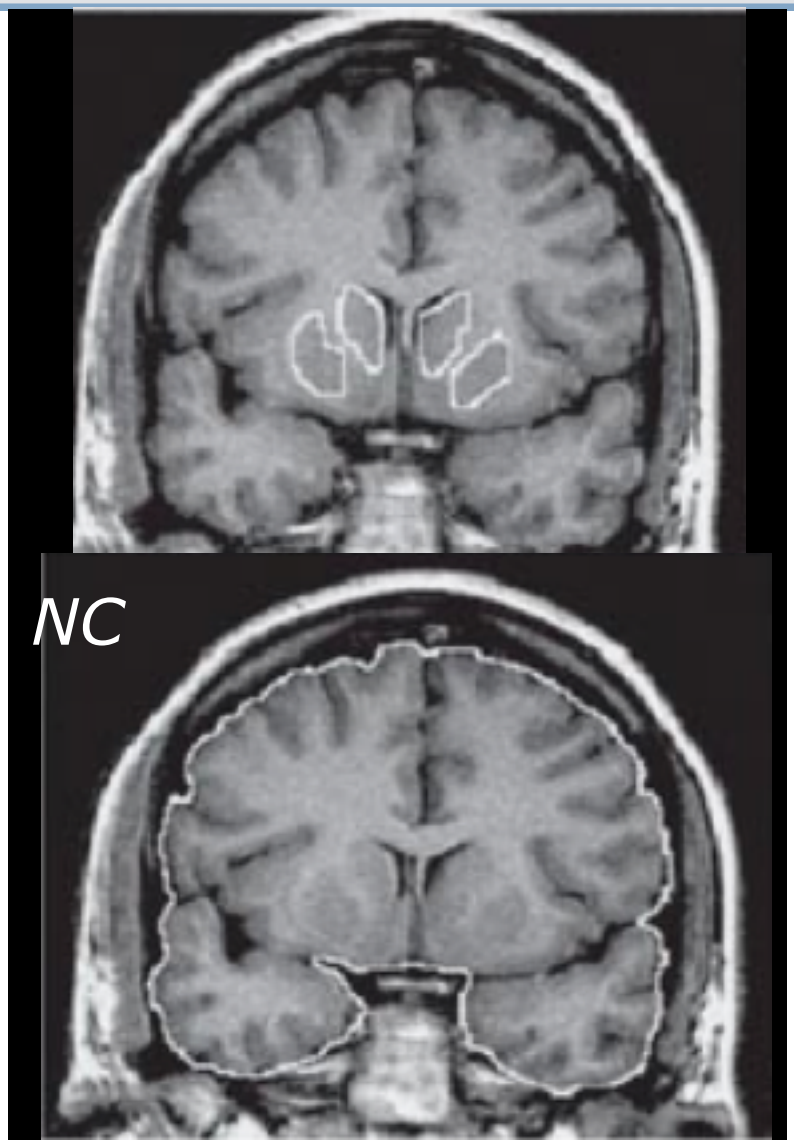
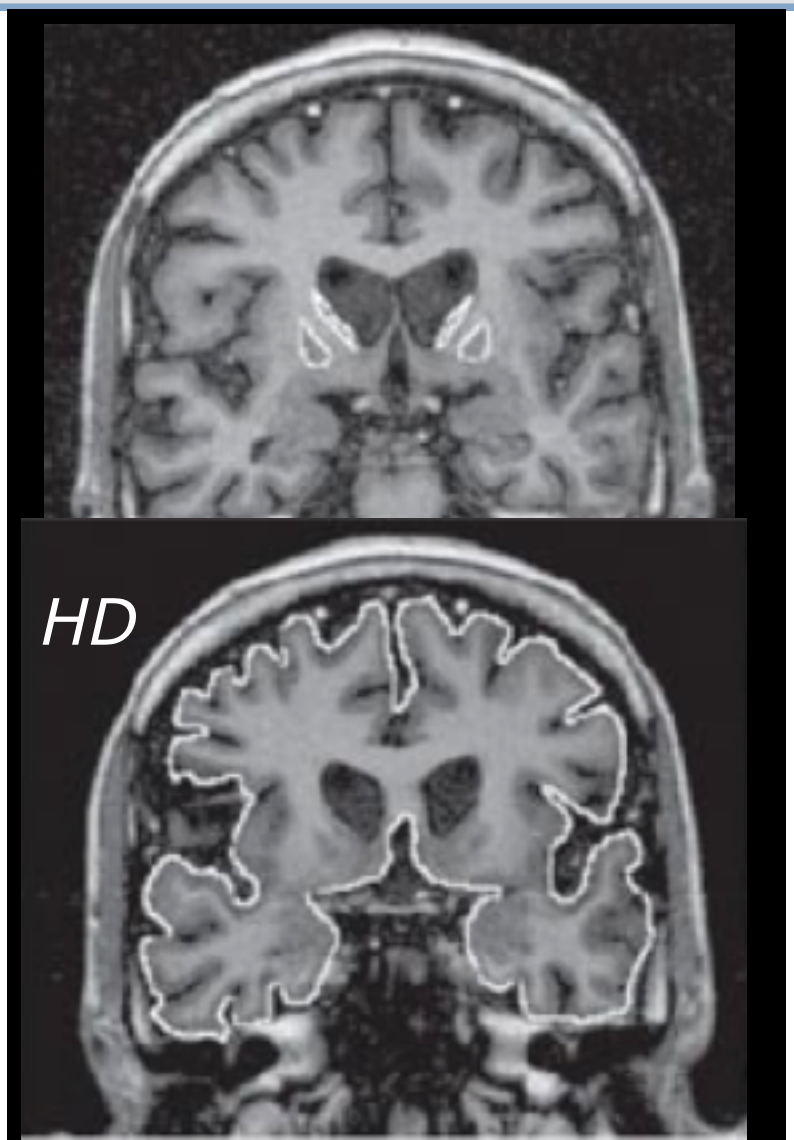
Huntington's disease MRI





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Huntington's disease: Symptoms

- Choreic movements : Rapid jerky involuntary movements of the body
- These movements usually affect the hands and the face at first.
- Early in the course of the disease patients can mask the involuntary movements by incorporating them into socially acceptable movements.
- They gradually increase overtime until the patients become totally incapacitated by them.
- Later on cognitive decline and dementia
- Death usually 10-15 years from symptoms onset

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Huntington's disease

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Clinical assessment

UHDRS: Unified Huntington Disease Rating Scale

TONGUE PROTRUSION
- 0 = can hold tongue fully protruded for 10 seconds
- 1 = cannot keep fully protruded for 10 seconds
- 2 = cannot keep fully protruded for 5 seconds
- 3 = cannot fully protrude tongue
- 4 = cannot protrude tongue beyond lips

DYSARTHRIA
- 0 = normal
- 1 = unclear, no need to repeat
- 2 = must repeat to be understood
- 3 = mostly incomprehensible
- 4 = mute

MAXIMAL CHOREA (face, mouth, trunk and extremities)
- 0 = absent
- 1 = slight/intermittent
- 2 = mild/common or moderate/intermittent
- 3 = moderate/common
- 4 = marked/prolonged

RETROPULSION PULL TEST
- 0 = normal
- 1 = recovers spontaneously
- 2 = would fall if not caught
- 3 = tends to fall spontaneously
- 4 = cannot stand

GAIT
- 0 = normal gait, narrow base
- 1 = wide base and/or slow
- 2 = wide base and walks with difficulty
- 3 = walks only with assistance
- 4 = cannot attempt

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Clinical assessment

COGNITIVE ASSESSMENT

BEHAVIORAL ASSESSMENT

Sad/Mood: feeling sad, sad voice/expression, tearfulness, inability to enjoy anything.
Low Self-Esteem/Guilt: self blame, self deprecation including feelings of being a bad or unworthy person, feelings of failure.
Anxiety: worries, anticipation of the worst, fearful anticipation.
Suicidal Thoughts: feels life not worth living, has suicidal thoughts, active suicidal intent, preparation for the act.
Disruptive or Aggressive Behavior: threatening behavior, physical violence, verbal outbursts, threatening, foul, or abusive language.
Irritable Behavior: impatient, demanding, inflexible, driven and impulsive, uncooperative.
Obsessions: recurrent and persistent ideas, thoughts or images
Compulsions: repetitive, purposeful, and intentional behaviors.
Delusions: Fixed false beliefs, not culturally shared
Hallucinations: a perception without physical stimulus: Auditory, Visual, Tactile, Gustatory and Olfactory

FUNCTIONAL CAPACITY

OCCUPATION
0 = unable
1 = marginal work only
2 = reduced capacity for usual job
3 = normal

FINANCES
0 = unable
1 = major assistance
2 = slight assistance
3 = normal

DOMESTIC CHORES
0 = unable
1 = impaired
2 = normal

ADL
0 = total care
1 = gross tasks only
2 = minimal impairment
3 = normal

CARE LEVEL
0 = full time skilled nursing
1 = home or chronic care
2 = home

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Huntington's disease: diagnosis

Genetic test analyses DNA for the HD mutation by counting the number of CAG repeats in the *Huntingtin* gene

No. of CAG repeats	Outcome
≤ 28	Normal range; individual will not develop Huntington's disease
29-34	Individual will not develop Huntington's disease but the next generation is at risk
35-39	Some, but not all, individuals in this range will develop Huntington's disease; next generation is at risk
≥ 40	Individual will develop Huntington's disease

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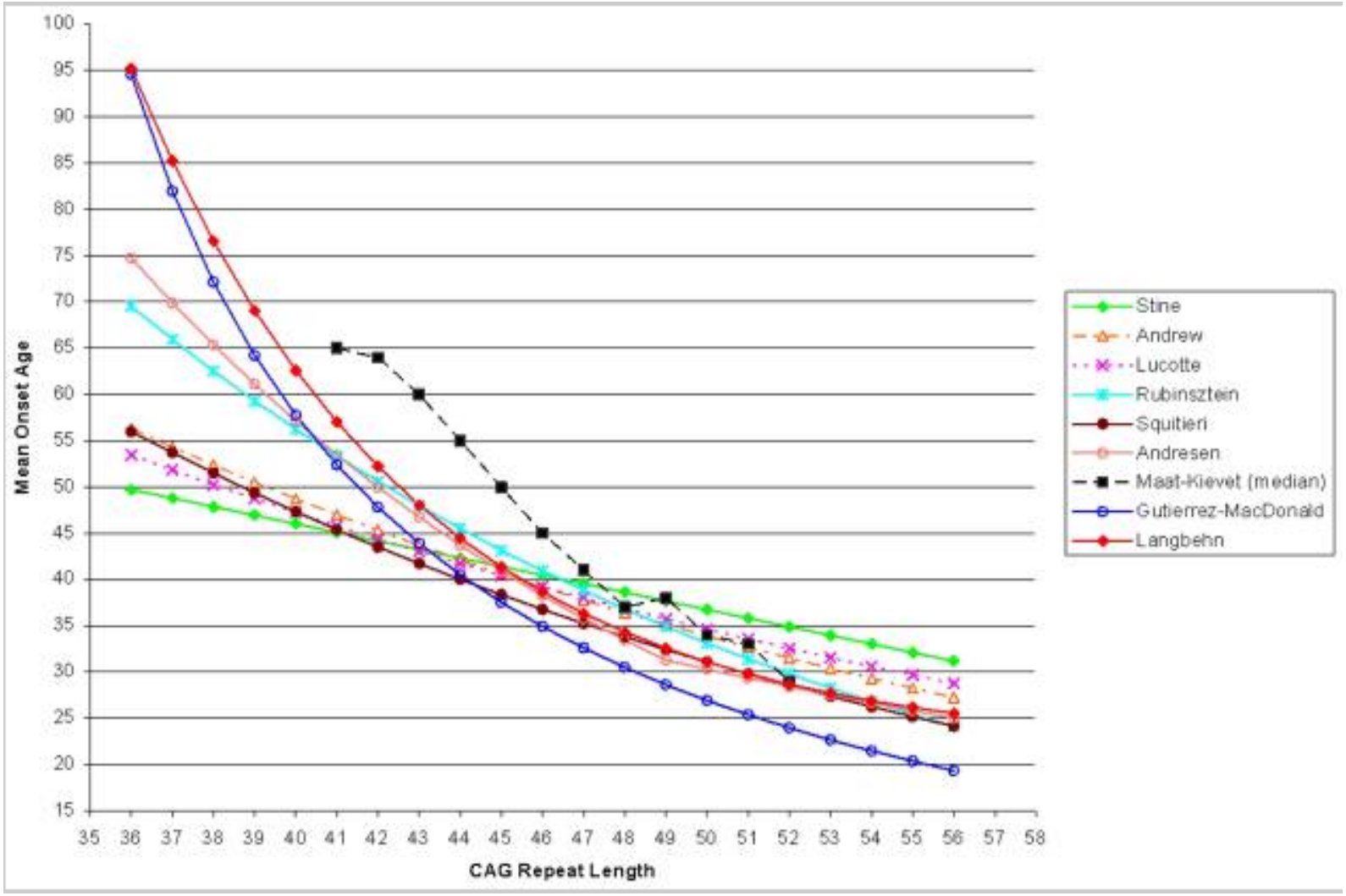
CAG repeat lengths and age of onset



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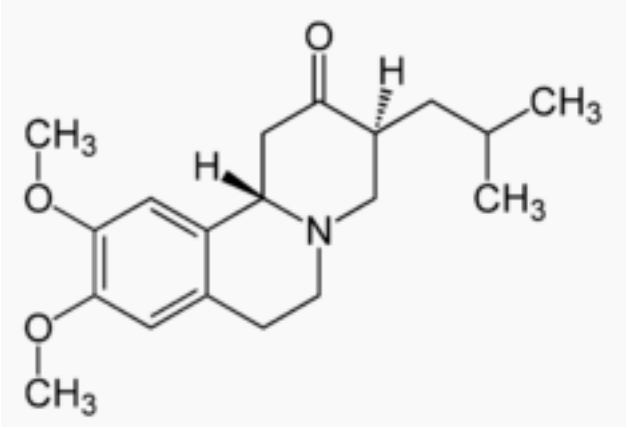
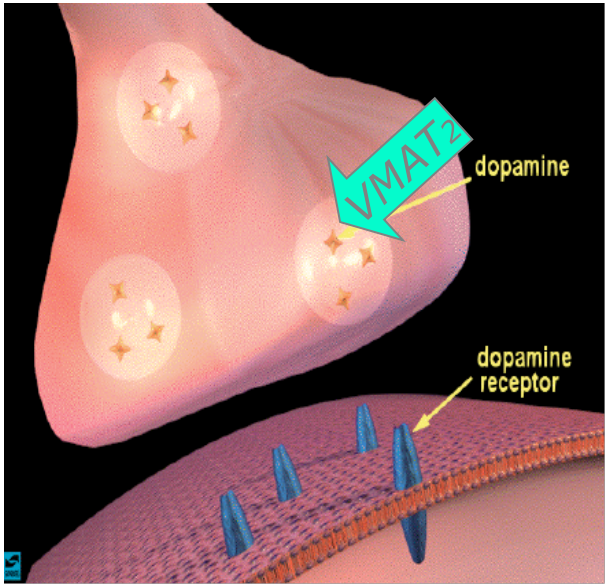
Pharmacological treatment

Only drug for HD approved by the US Food and Drug administration (2008) is **TETRABENAZINE**





It works as **VMAT inhibitor** and promotes metabolic degradation of monoamines particularly Dopamine

Mostly used to reduce **choreic movements**

Side effects

- *Depression*
- *Drowsiness, fatigue, dizziness*
- *Akatisia and anxiety*
- *Parkinsonism*

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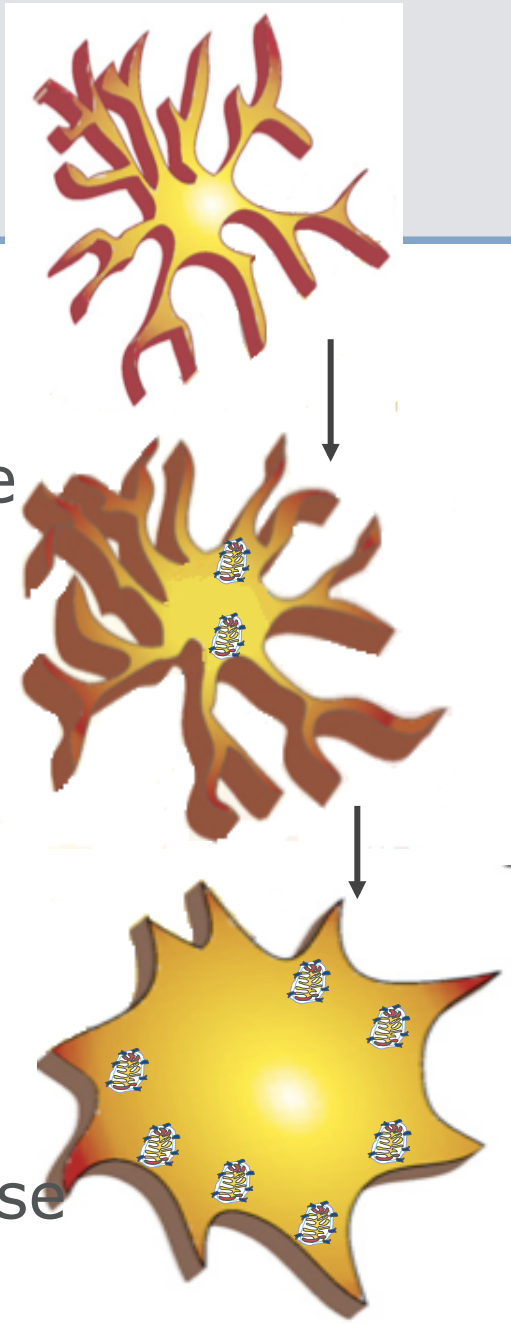
Role of Microglia in HD

- Microglia constitute up 10% of the total cell population of the brain
- In normal brain : microglia thought to be resting, quiescent
- Microglia change in response to CNS insults
- Undergo morphological changes with expression of new surface markers and proliferation: **activated microglia**
- Main role : defensive
- present foreign antigens and phagocytose cellular debris



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Role of Microglia in HD

However…

- Activated microglia synthesize and secrete potential neurotoxins
  - Free radicals
  - Nitric oxide
  - Proteinase
  - Cytokines interleukin-1 and interleukin-2
  - Chemokines

May cause neuronal damage, influence neuronal function and viability⇝⇝ aggravate underlying pathology

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Role of Microglia in HD

☞ *at post mortem in HD brain extensive microglia activation*

? Late stage reaction to extensive neuronal death or early phenomenon

? Contribution to further disease progression

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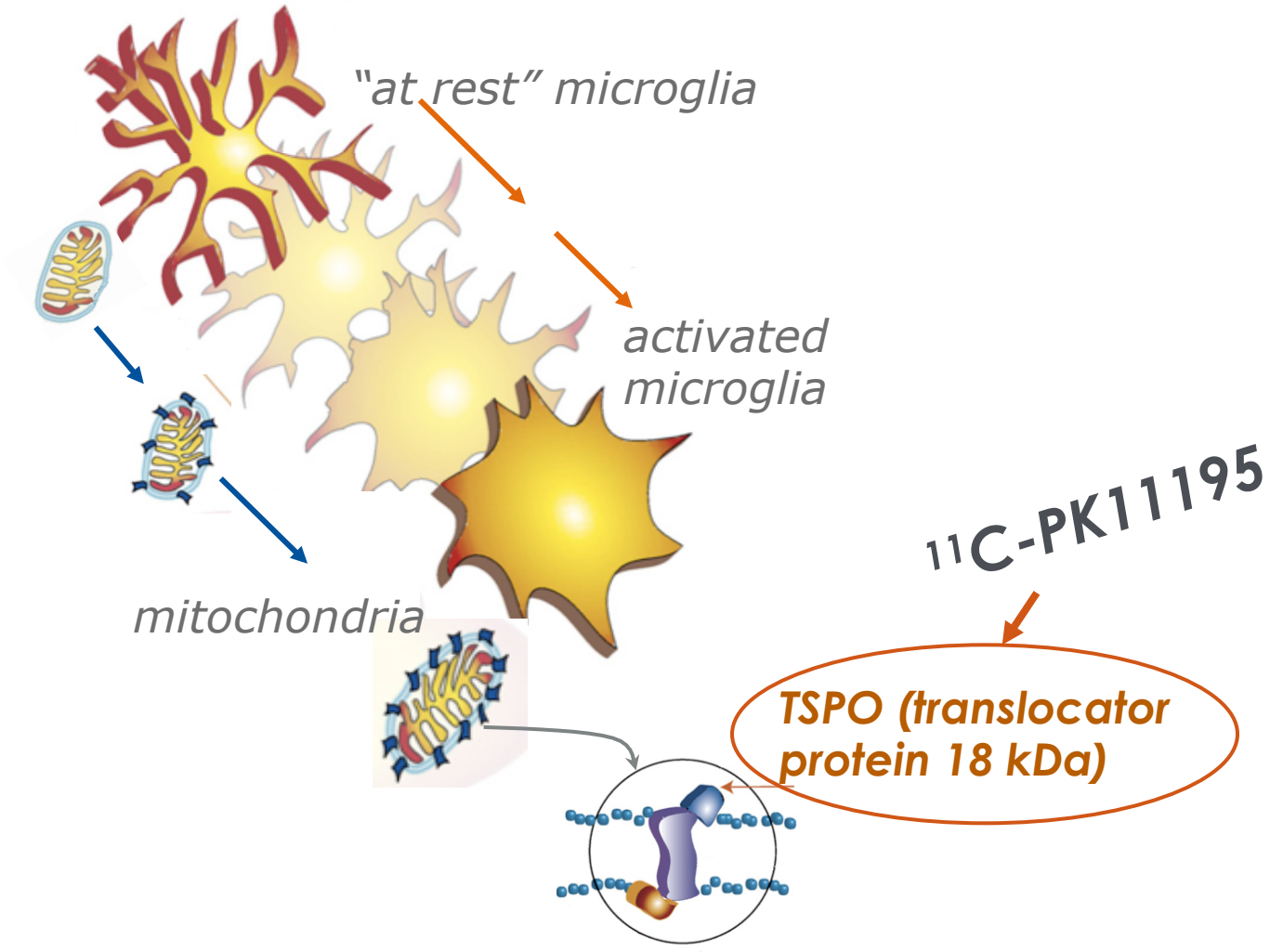
IN VIVO IMAGING of MICROGLIA ACTIVATION IN HD

Positron Emission Tomography (PET)



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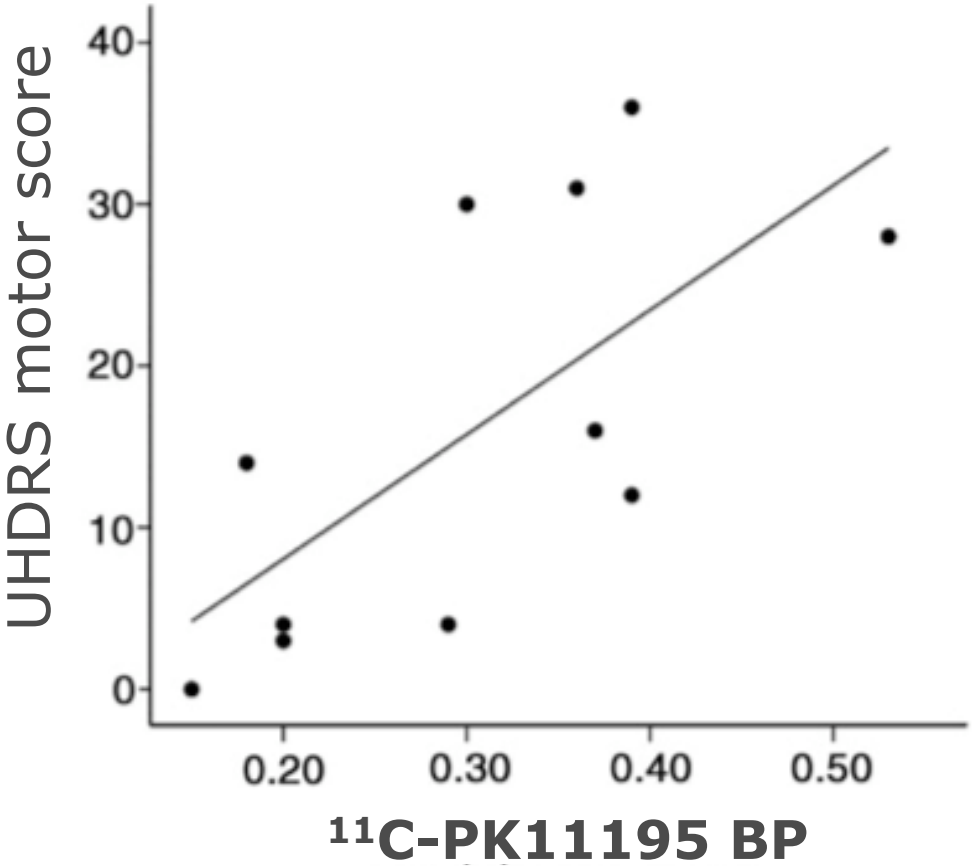
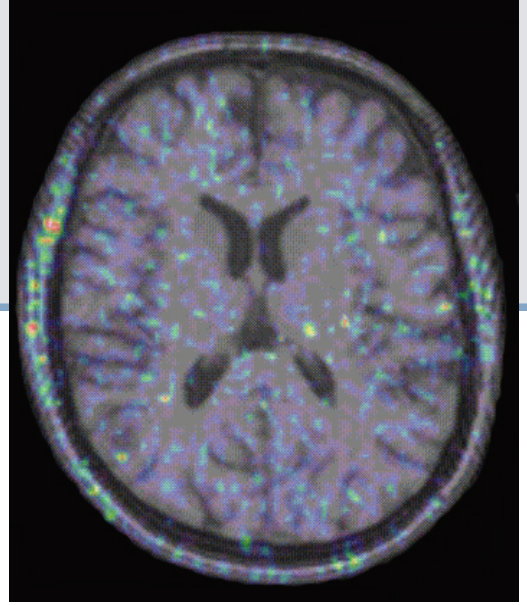
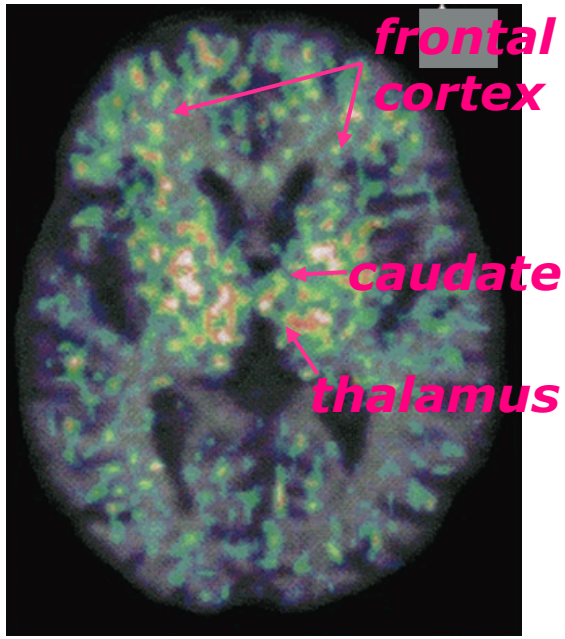
^{11}C-PK11195 PET





Normal subject



HD patient

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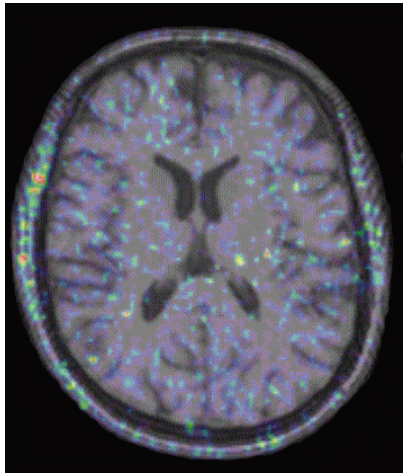
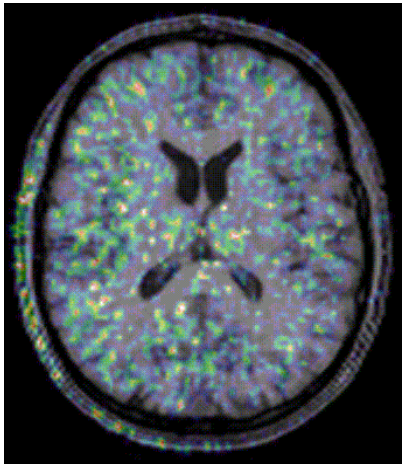
Role of Microglia in HD

Pre-manifest gene carrier subjects

	age	CAG repeat	HD diagnostic confidence	5-yr probability of developing HD
1	41	43/38[c]	0	0.26
2	44	40/17	0	0.06
3	33	47/11	1	0.45
4	43	39/17	0	0.03
5	41	44/20	1	0.40
6	37	48/25	2	0.67
7	61	40/18	1	0.34
8	40	46/17	1	0.60
9	32	46/19	0	0.29
10	46	41/17	0	0.15
11	46	41/10	0	0.15



Normal subject



Pre-manifest gene carrier

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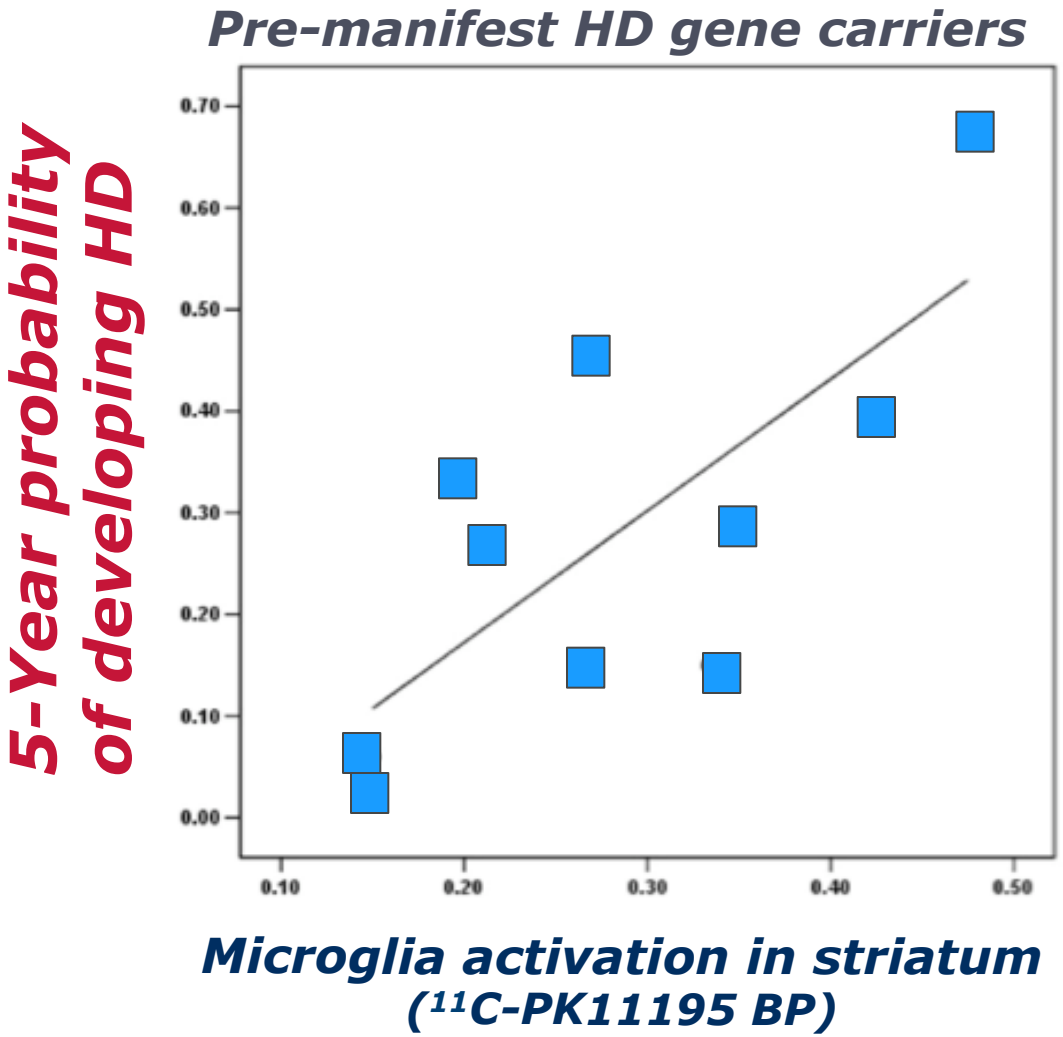
Role of Microglia in HD

Pre-manifest gene carrier subjects



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Role of Microglia in HD

Neuroinflammatory processes

- Occur very early in the disease
- Possibly contribute to propagation of and progression of the disease

- Role for anti-inflammatory agents in slowing down progression this neurodegenerative disease

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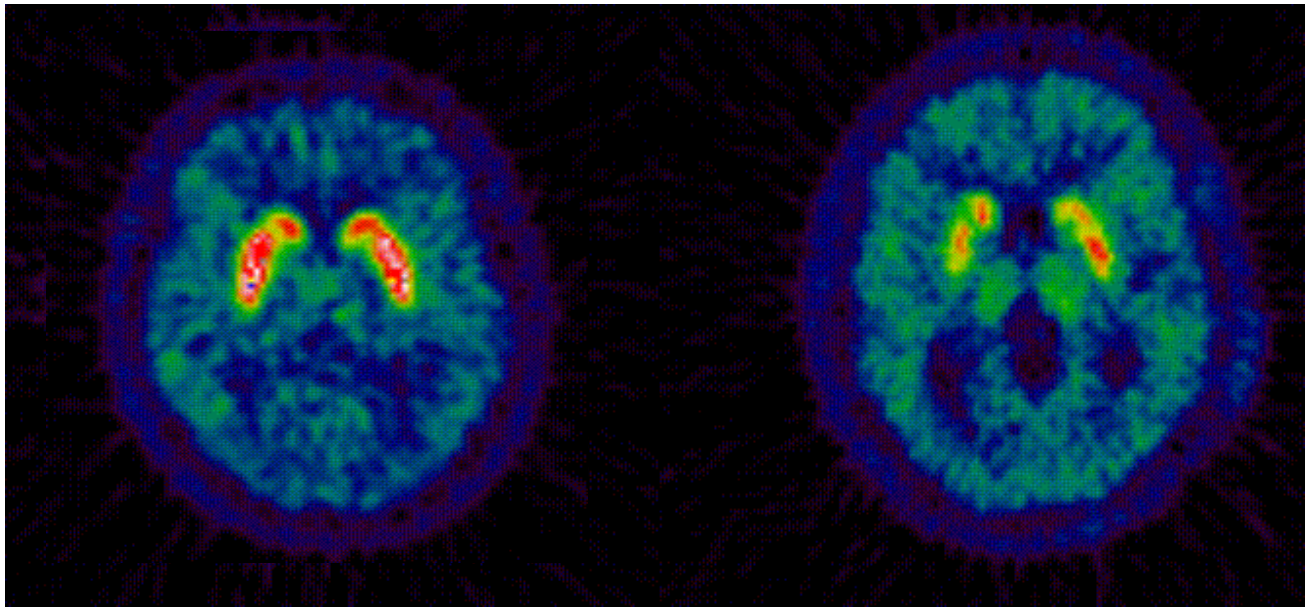
Imaging Huntington's disease
^{11}C-Raclopride PET

Loss of striatal medium spiny GABA neurons bearing **D2 receptors**

^{11}C-Raclopride specific ligand for D2 receptor and indirect marker of neuronal loss in HD



Normal subject **Huntington's disease**

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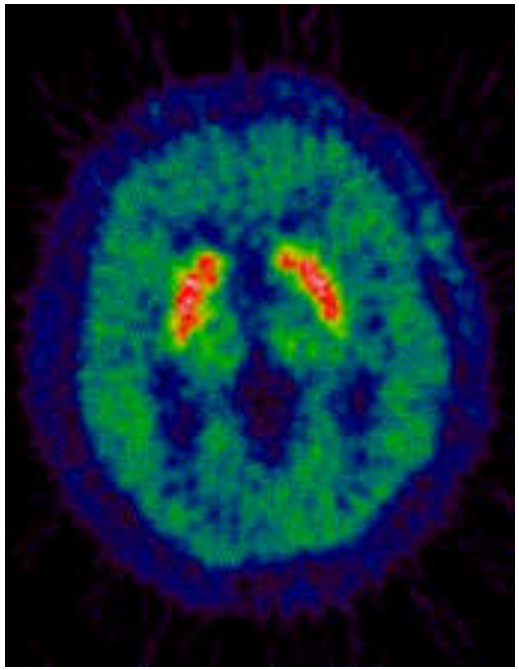
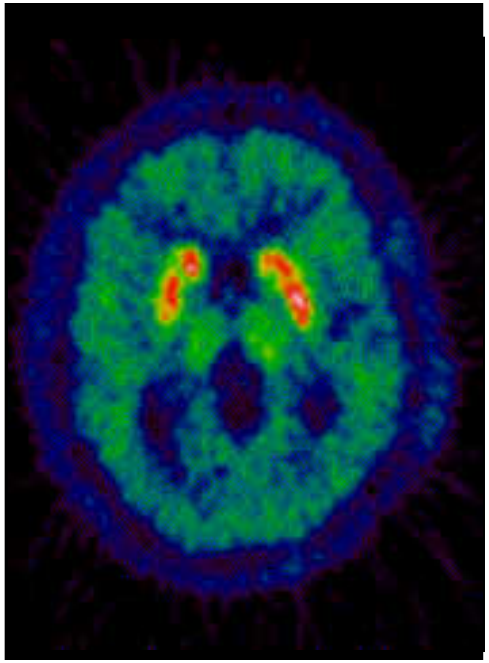
Imaging Huntington's disease

^{11}C-Raclopride

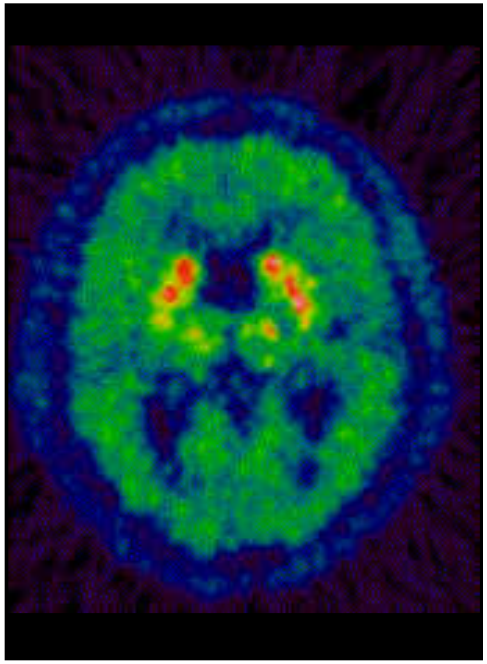
Serial scans in a patient with HD showing progressive loss of D2 receptors



baseline



+ 2 years



+ 4 years

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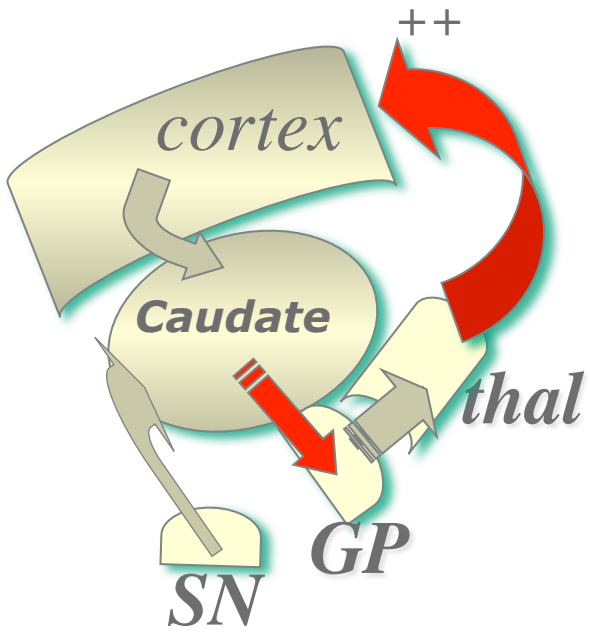
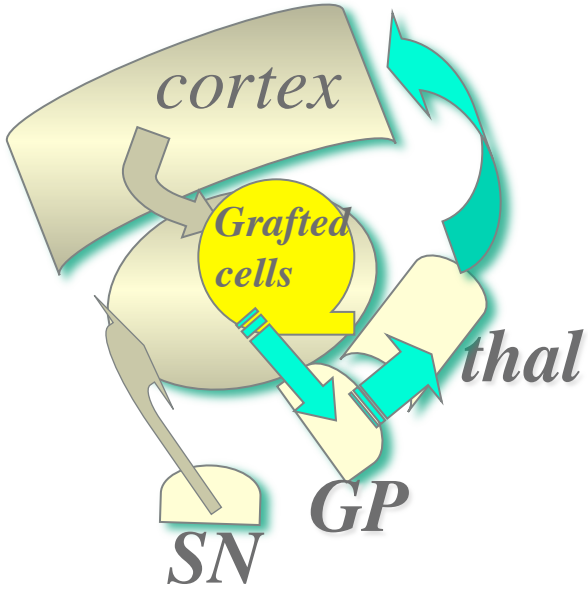
Cell transplantation therapy in HD

Death of caudate neurons and disruption of basal ganglia-cortical pathways





Restoration of down stream basal ganglia-cortical circuits and improvement of HD symptoms

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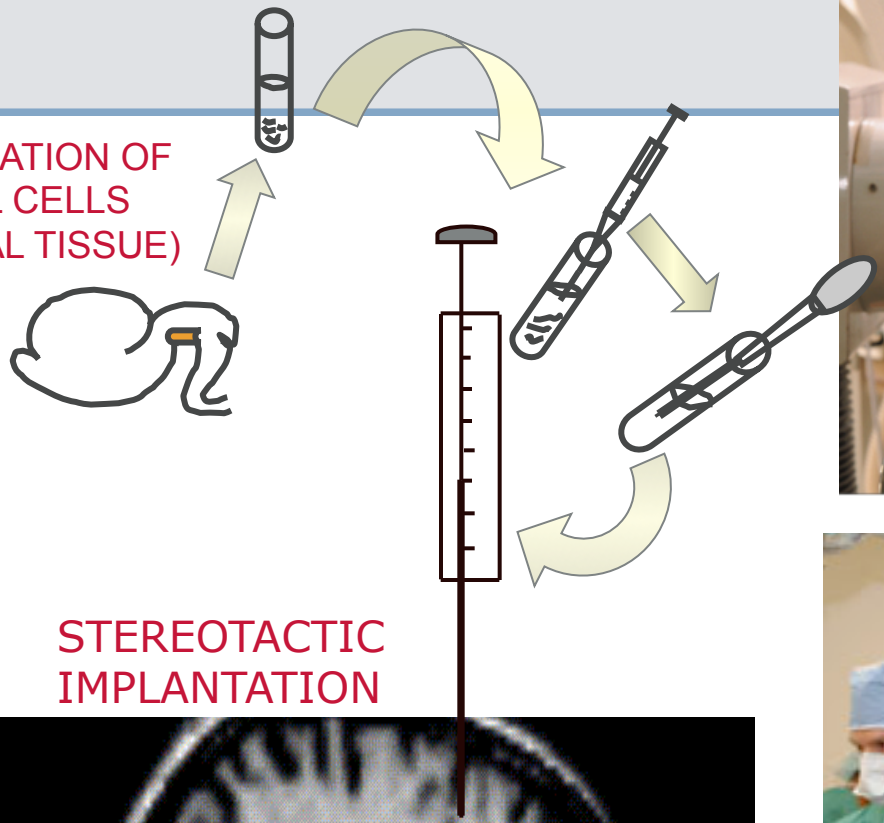
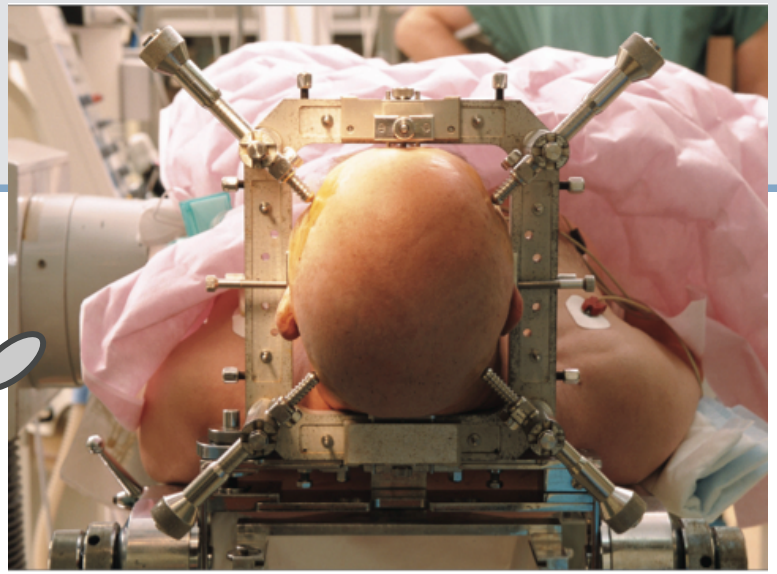
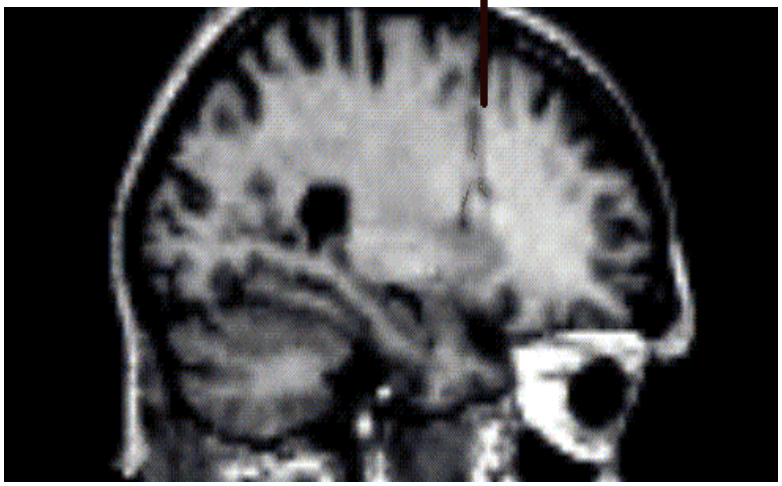
PREPARATION OF
FETAL CELLS
(STRIATAL TISSUE)





STEREOTACTIC
IMPLANTATION



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JNNP ONLINE

2008

Long-term clinical and positron emission tomography outcome of fetal striatal transplantation in Huntington's disease

I Reuter, Y F Tai, N Pavese, K R Chaudhuri, S Mason, C E Polkey, J Brooks, R A Barker and P Piccini

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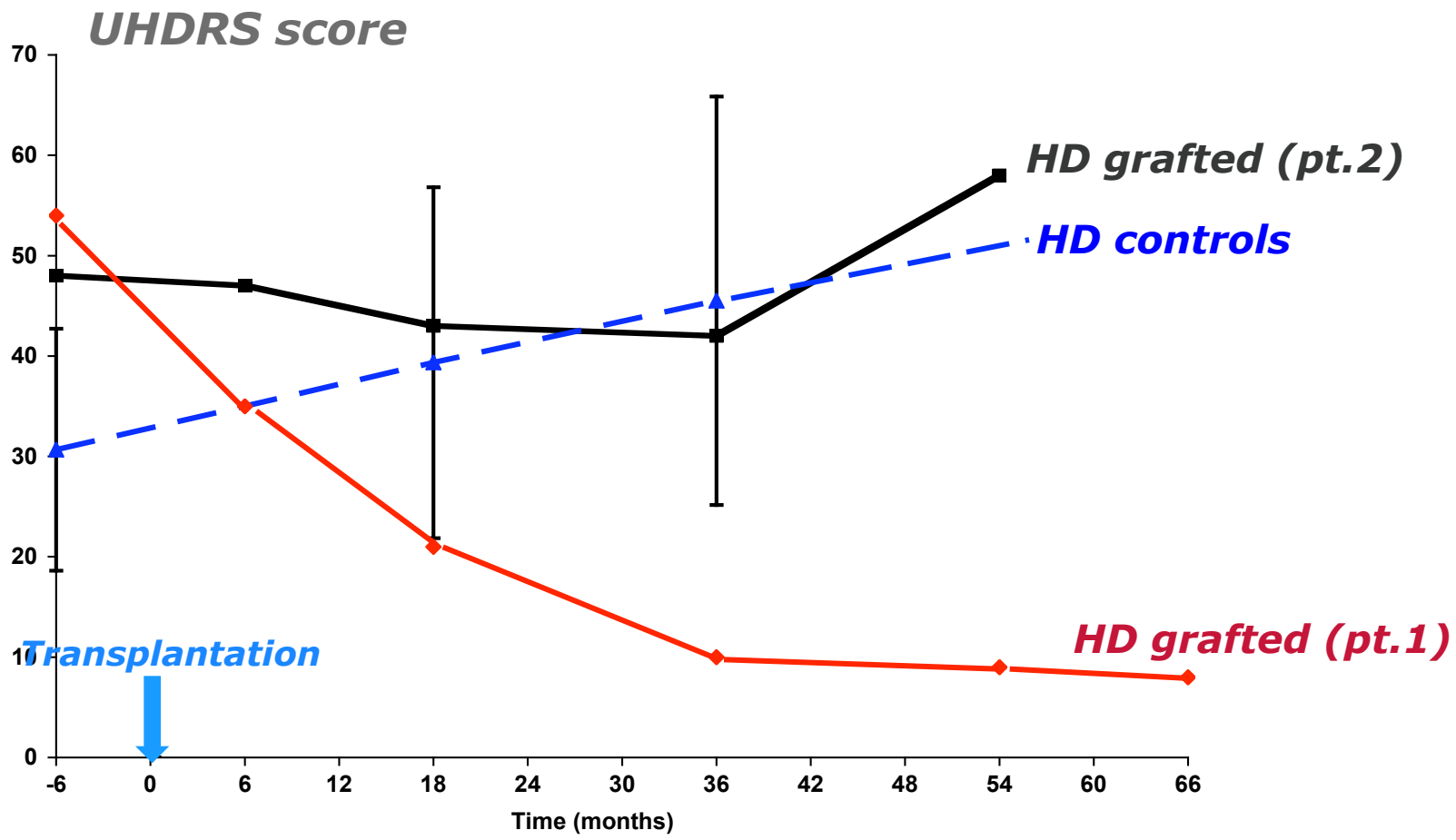
Clinical outcome following fetal striatal transplantation in two HD patient



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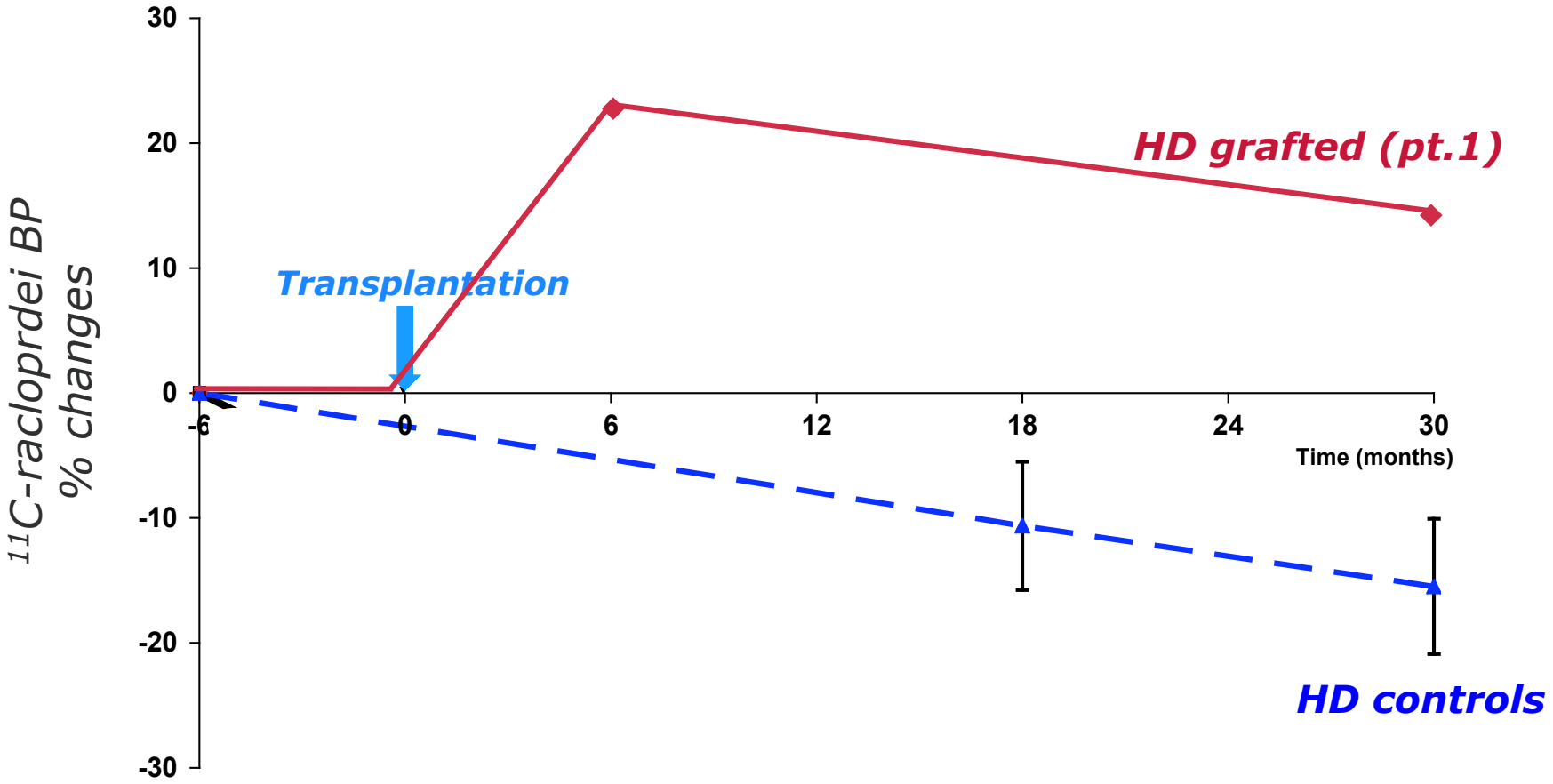
^{11}C-raclopride following fetal striatal transplantation in two HD patients



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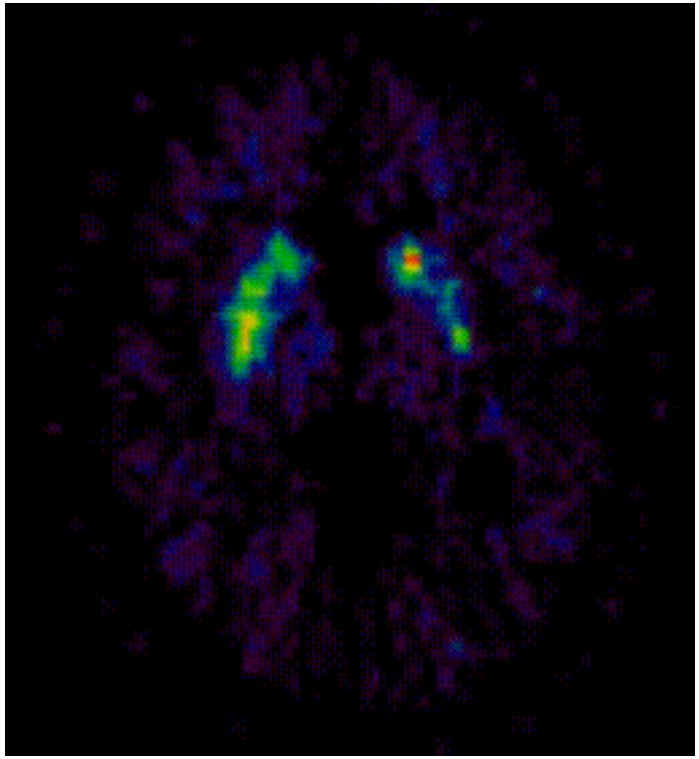
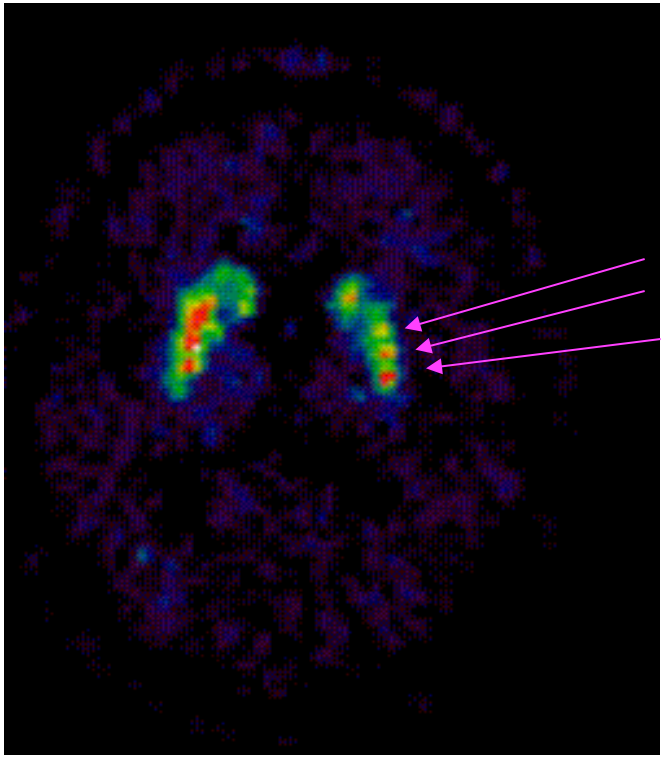
^{11}C-raclopride PET

HD patient n1 before and after implantation of foetal striatal cells in putamen and caudate



pre-graft



post-graft (12 months)

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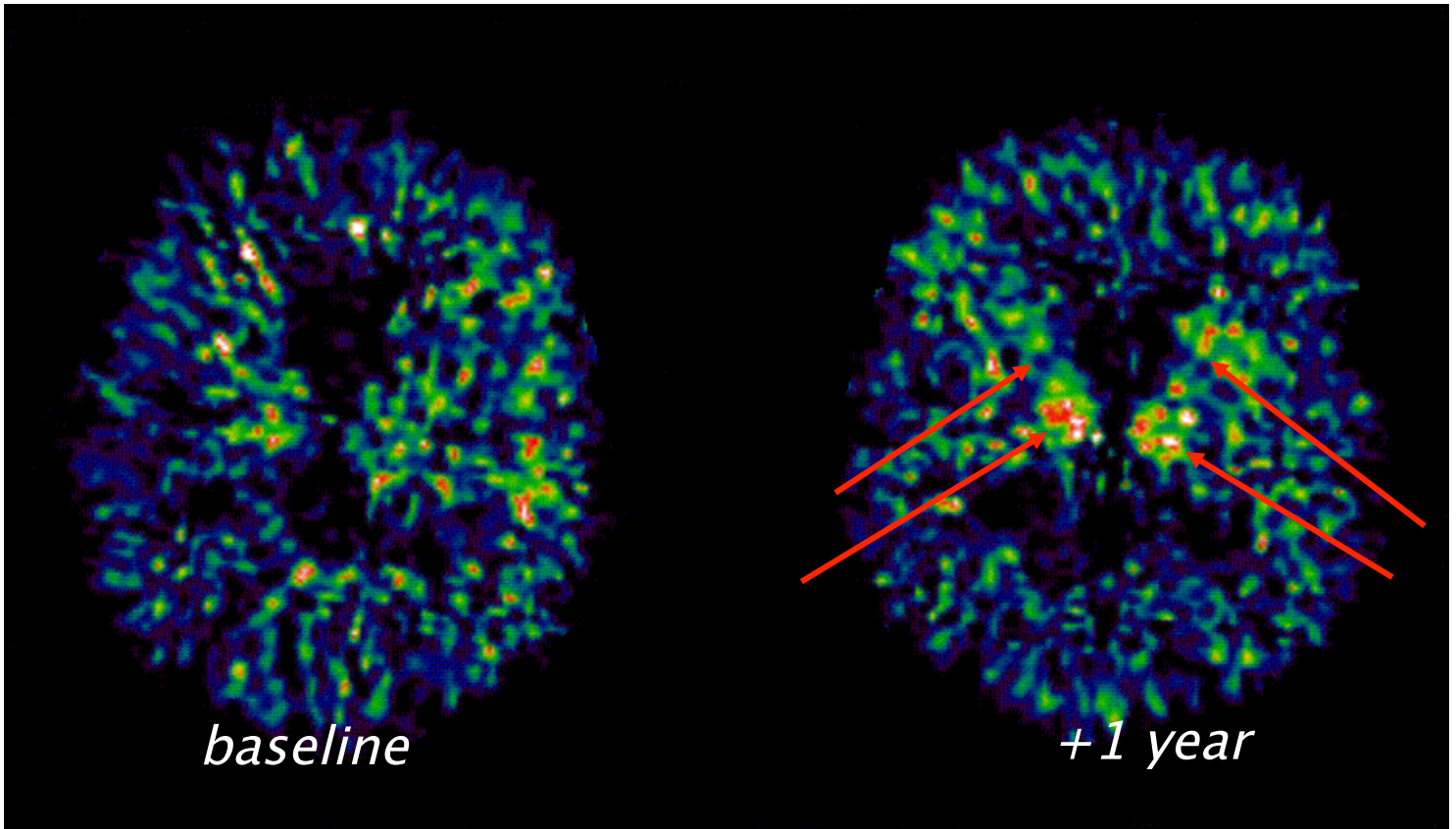
MICROGLIA ACTIVATION FOLLOWING FETAL TRANSPLANT IN HD

^{11}C-PK11195 PET

HD patient at baseline and 1 year after bilateral fetal striatal transplantation, showing significantly increased microglial activation in the striatum post-operatively



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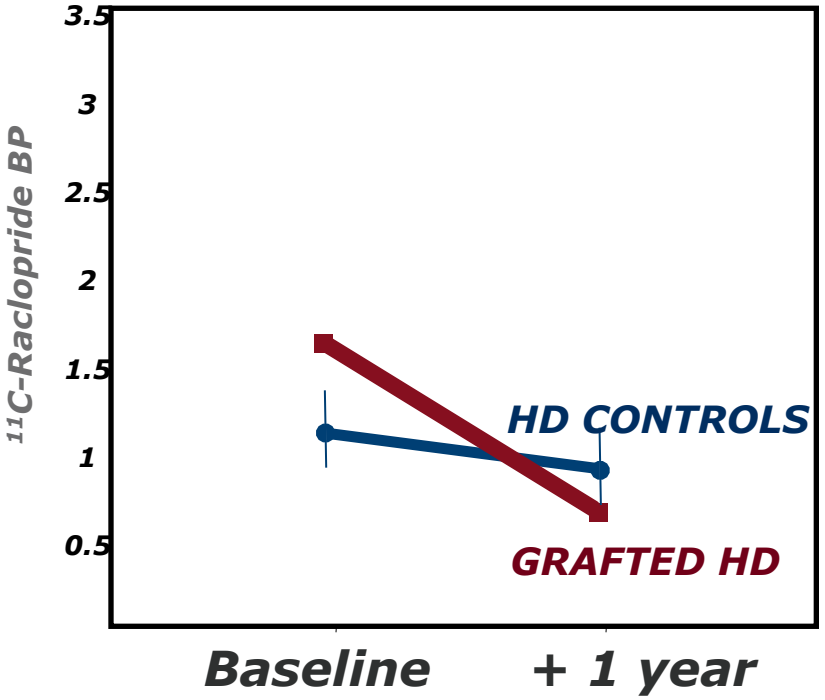
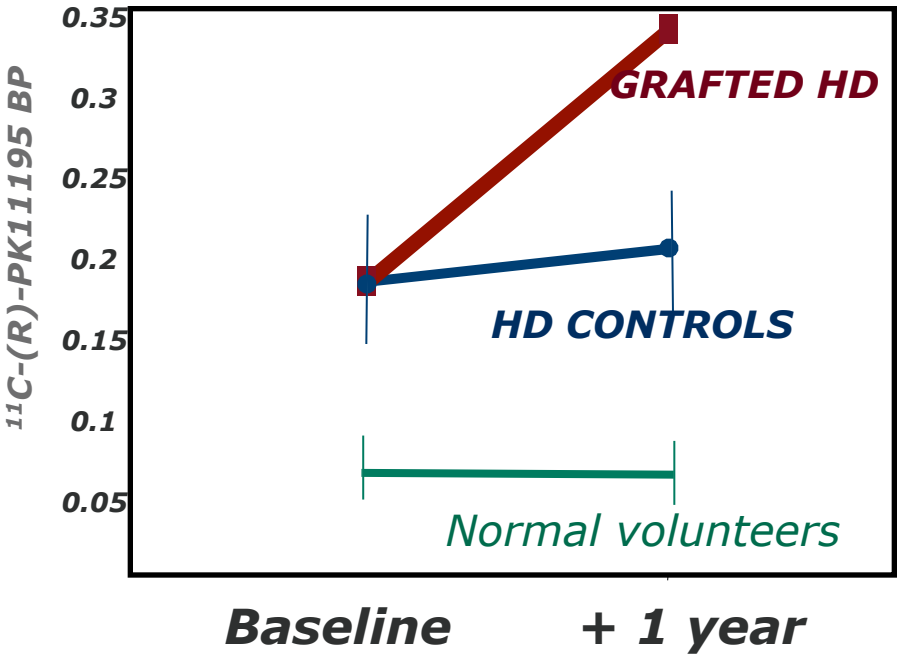
MICROGLIA ACTIVATION FOLLOWING FETAL TRANSPLANT IN HD

^{11}C-Raclopride
D2 receptor loss



^{11}C-PK11195
Microglia activation



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Conclusions

- Huntington's disease is genetic disorder caused by a mutation of the Huntingtin gene (HTT) on the short arm of chromosome 4
- The main pathology is the degeneration and death of medium spiny GABAergic neurons in the caudate and putamen
- Main clinical features are choreic movements
- No known cure and death usually occurs 10-15 years from symptoms onset
- Macroglia activation in the brain of HD possibly contributes to propagation of and progression of the disease. It can be assessed with PET and specific ligand for microglia activation
- Cell transplantation therapy may have a role in future for the treatment of HD

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THANKS