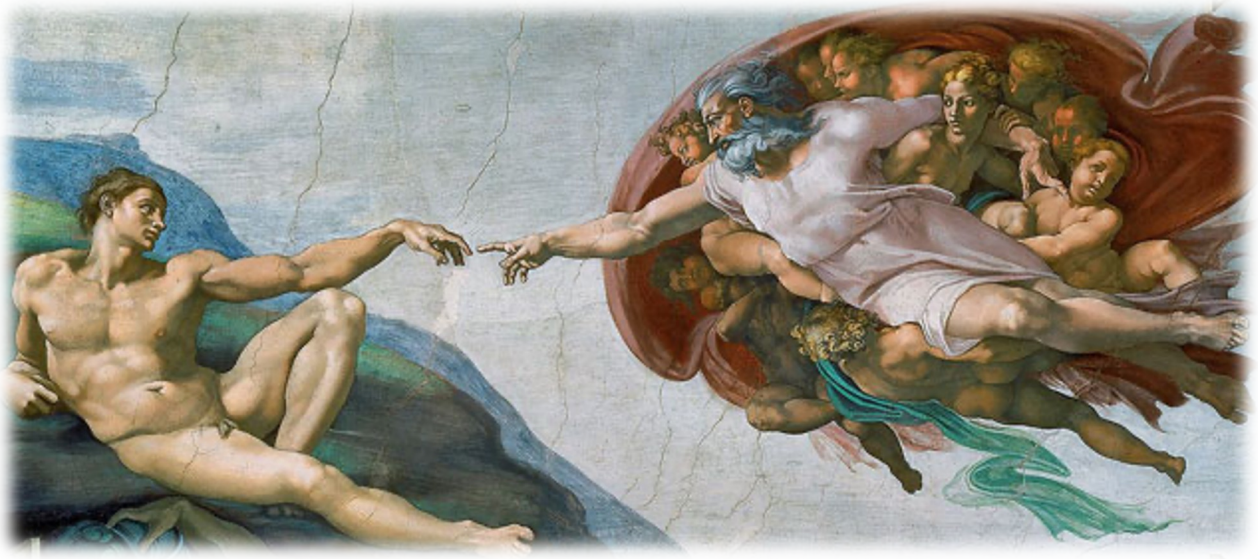
Neuroimaging in Huntington Disease



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QUESTION 1

To diagnose Huntington disease, it is essential to perform:

a. Brain MRI
b. Brain PET with ligands to mutant huntingtin
c. DATSCAN
d. Brain imaging is not part of a mandatory workup in HD

QUESTION 2

In Huntington disease, brain MRI may show everything except:

a. Striatal atrophy
b. Cortical atrophy
c. T2-/T2*-/SWI-hypointensity from the basal ganglia
d. Prominent infratentorial atrophy

QUESTION 3

Routinely, the following PET study may be conducted in HD patients:

a. FDG-PET
b. PET with ligands to mutant huntingtin
c. PET with ligands to PDE10A
d. PET with ligands to activated microglia markers

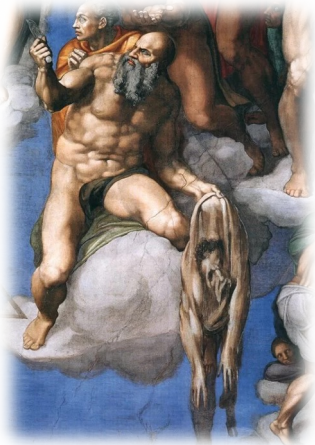
QUESTION 4

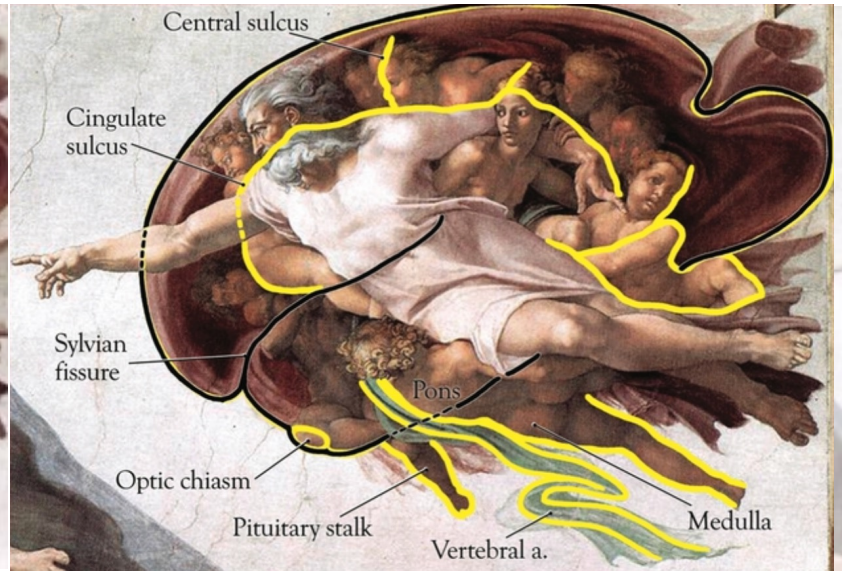
In differentiating autoimmune (non-HD) chorea, PET is practically useless:

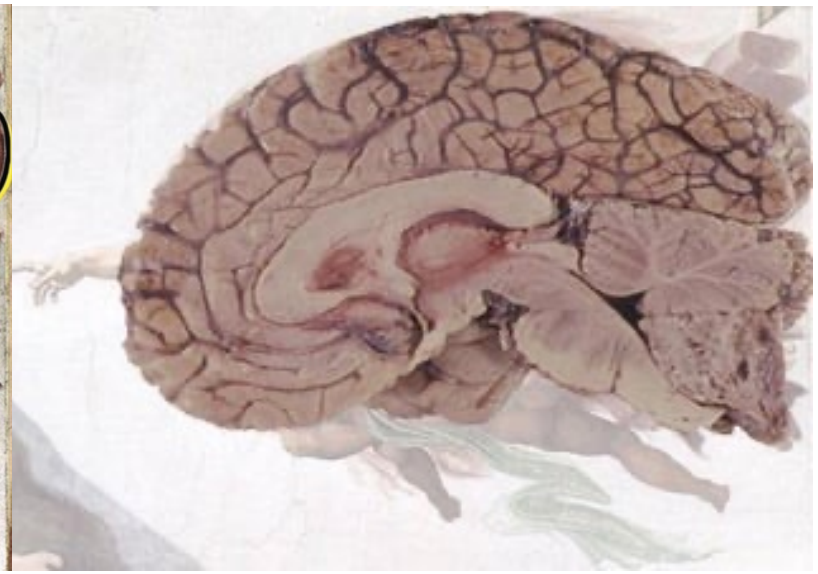
a. False

b. True

Neuroimaging in Michelangelo's Creation of Adam







Meshberger FL. *JAMA.*1990;264(14):1837–1841

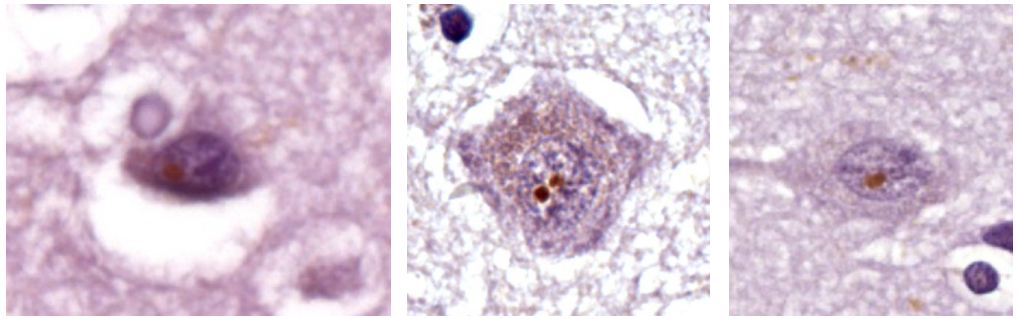
https://www.pinterest.de/pin/mri-scan--451908143860982183/

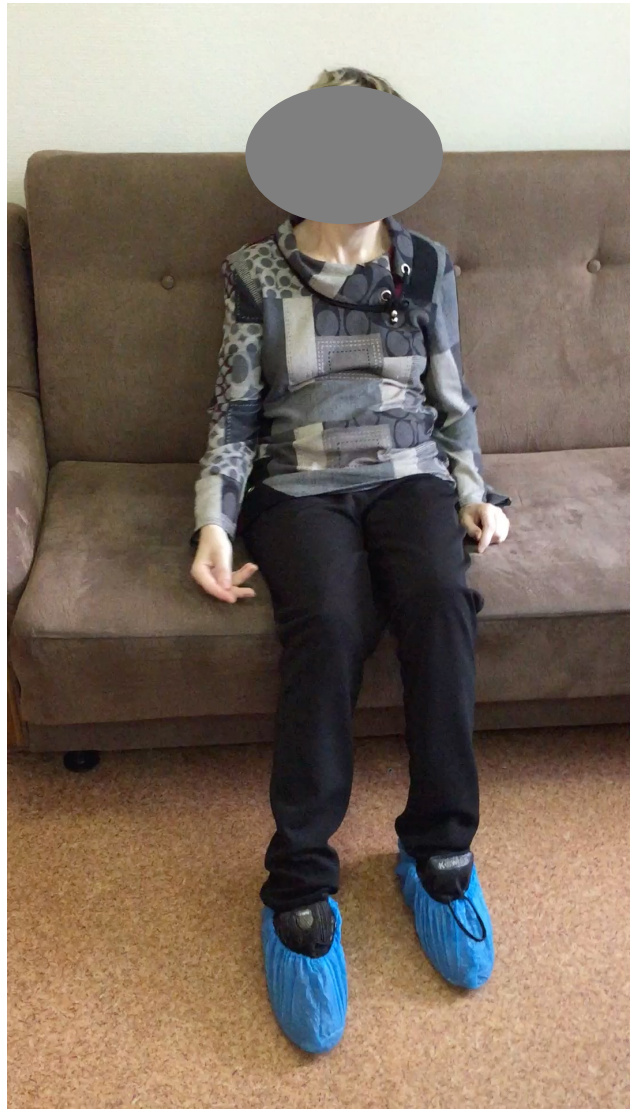
Neuroimaging in Huntington Disease: Learning Objectives

- Know what is Huntington disease
- Know the most commonly used neuroimaging biomarkers for HD
- State the recommended sequences, identify common imaging features
- Recognize the MRI patterns and know red flags when to apply neuroimaging in HD
- Describe the importance of disease stage and age of onset for pattern recognition
- Decide when to conduct neuroimaging and repeat as needed
- Decide when to conduct specialized neuroimaging and which type (e.g. functional, metabolic, post-processing, etc .)
- Interpret and apply the results of specialized neuroimaging accurately in the clinical context

Huntington Disease

- Autosomal dominant progressive neurodegenerative disorder caused by a pathological CAG repeat expansion in *HTT*
- Symptoms manifest at a mean age of 45 (range 2–87) years
- Death in 15–20 years from the time of symptomatic onset
- In natural environment, only in humans
- Prevalence of ~12 per 100,000 individuals in populations of European descent



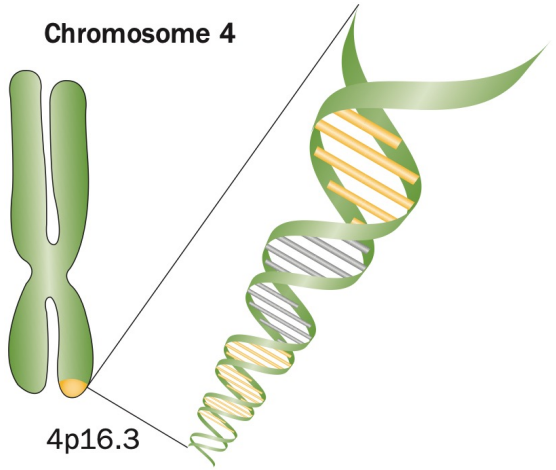


Personal observation

The Huntington Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington disease chromosomes. *Cell* 1993;**72**(6):971–983. https://www.openaccessgovernment.org/huntingtons-disease-hd-research/107601/

Tabrizi, S.J., Flower, M.D., Ross, C.A. et al. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. Nat Rev Neurol 16, 529–546 (2020). https://doi.org/10.1038/s41582-020-0389-4

Genetics of Huntington Disease

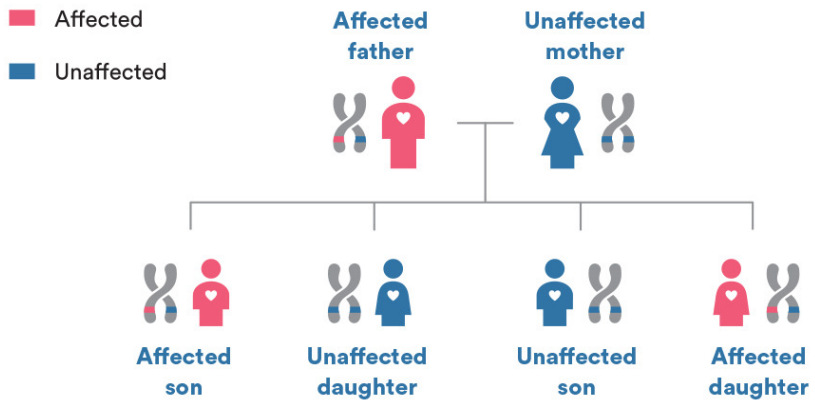


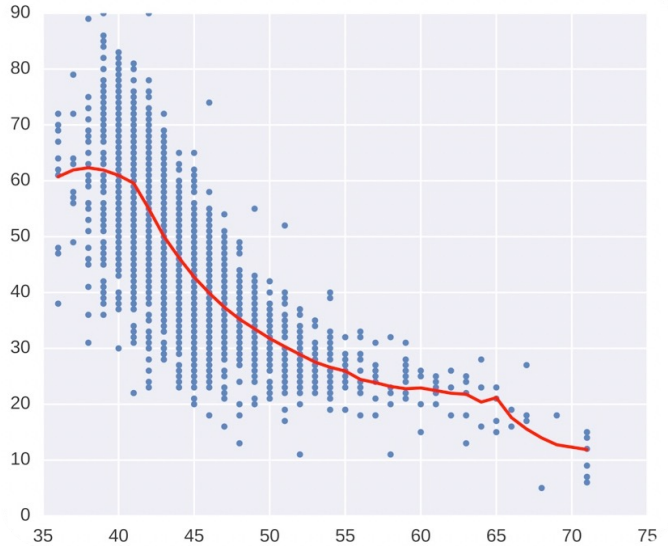
27–35 CAG	36–39 CAG	40–55 CAG	≥56 CAG
Intermediate alleles	Reduced penetrance	Huntington's disease	Juvenile Huntington's disease
~0% likelihood of developing disease phenotype	Higher likelihood of developing disease phenotype	~100% likelihood of developing disease phenotype	Probable early onset and severe progressive phenotype

Increased propensity to pass on to offspring an enlarged CAG expansion

Tabrizi et al. The Lancet. Neurology. 21: 632-644

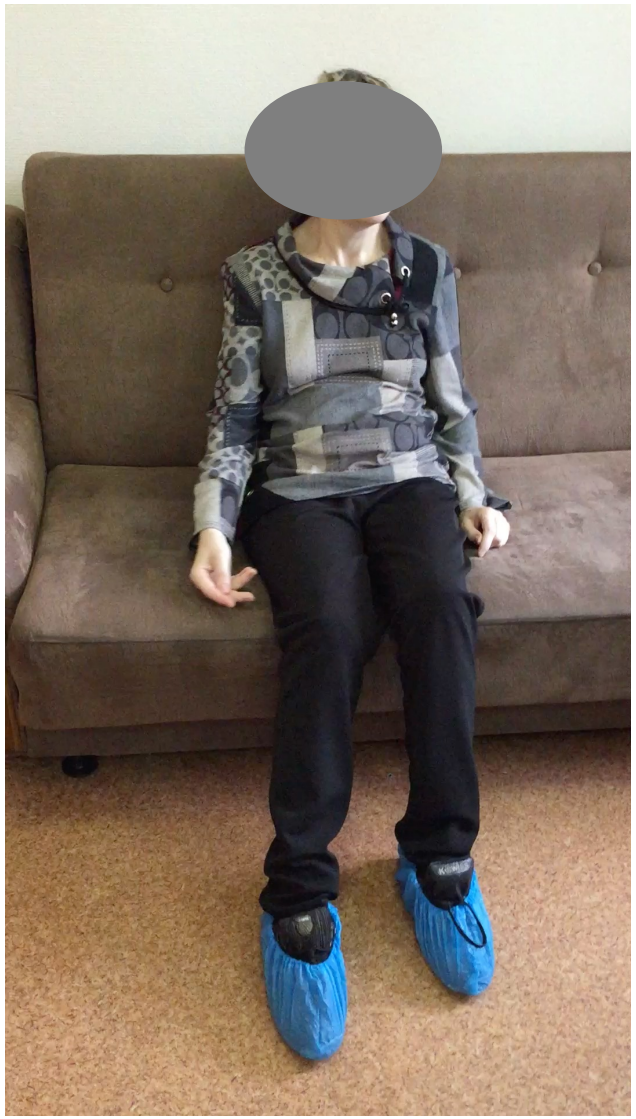
Squitieri, F. 'Fifty shades of grey' in the Huntington disease gene. *Nat Rev Neurol* **9,** 421–422 (2013). https://doi.org/10.1038/nrneurol.2013.128

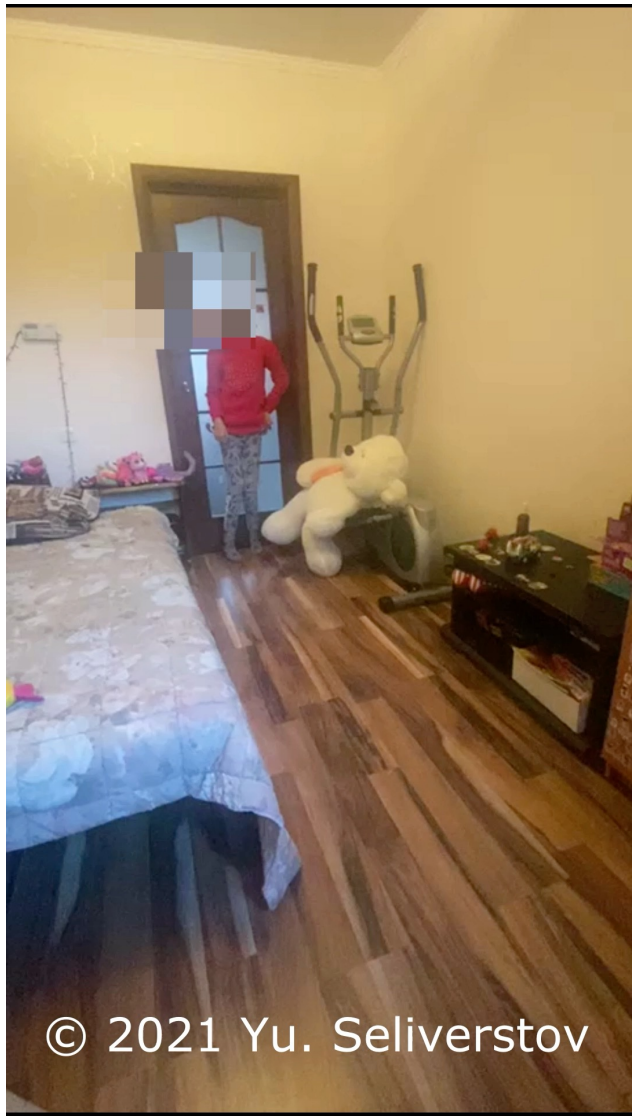




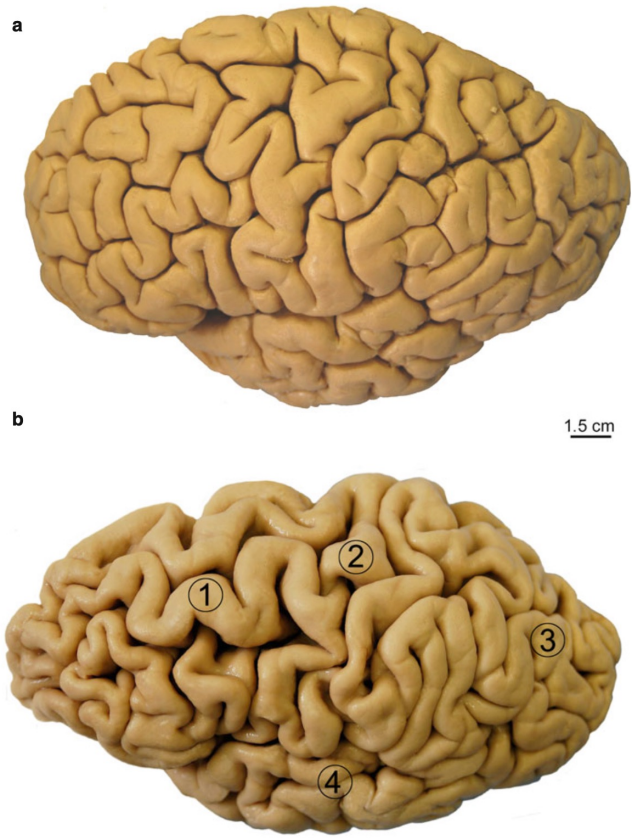
Y. Seliverstov, E. Shulgina, S. Illarioshkin, M. Belyaev. A modified model for prediction of Huntington disease age of onset based on length of CAG repeat expansion. Mov Disord. 2017; 32 (suppl 2).

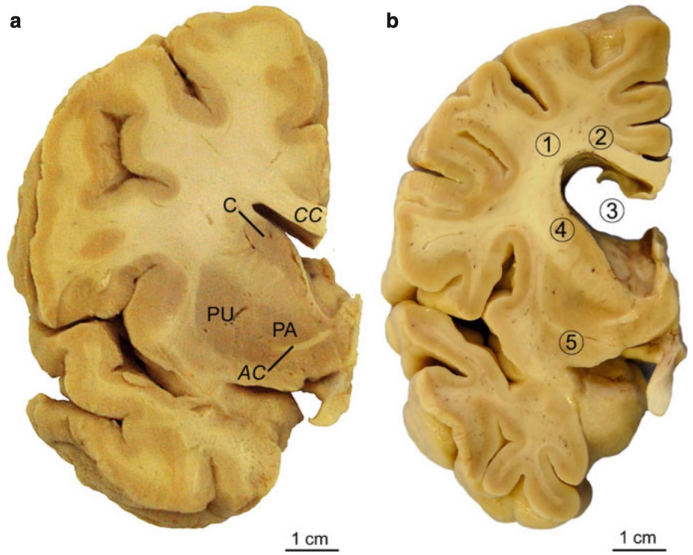
Adult VS pediatric onset of Huntington disease

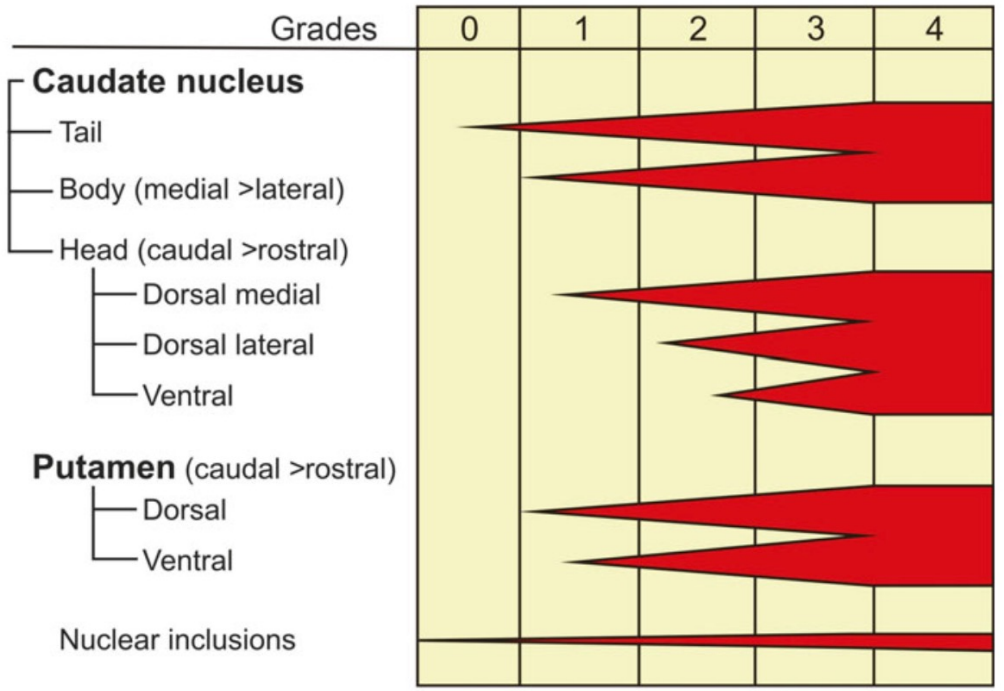




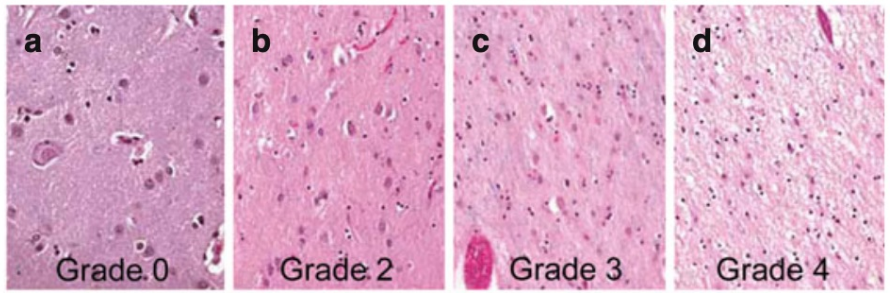
PROGRESSIVE NEURODEGENERATION







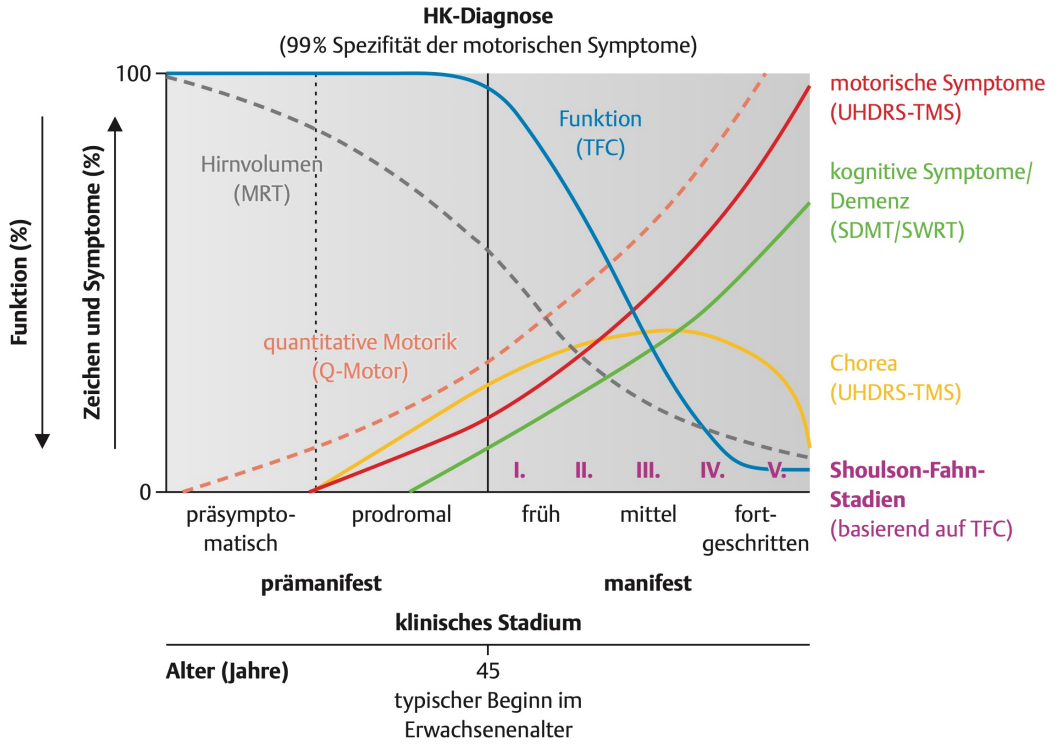
Caudate nucleus

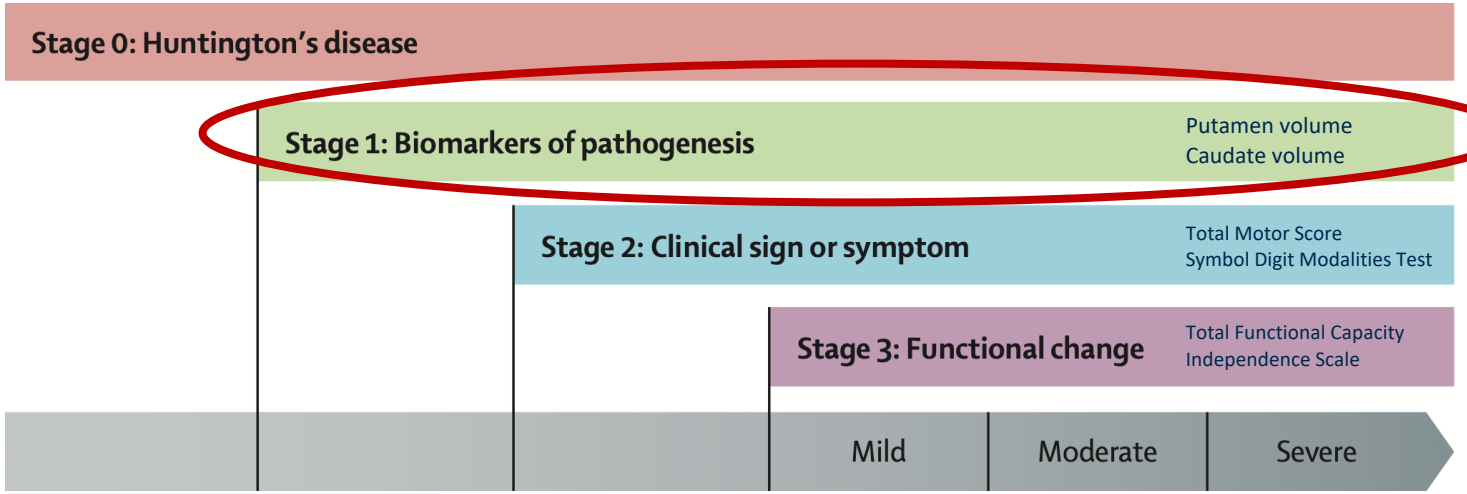


Rüb, U., Vonsattel, J.P.G., Heinsen, H., Korf, HW. (2015). The Neuropathological Grading of Huntington's Disease

CLINICAL FEATURES OF HD

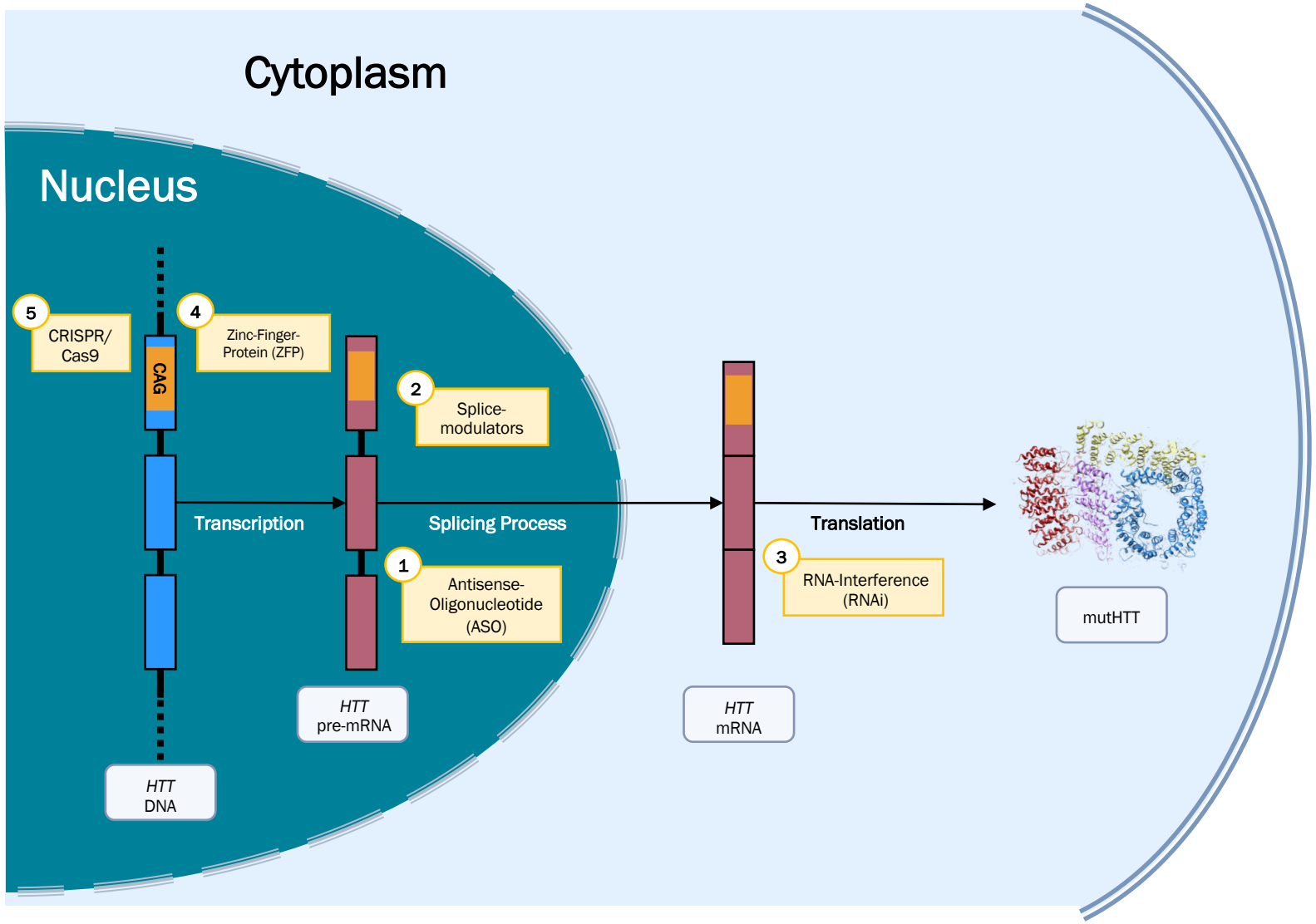
- **Movement disorders:** chorea, dystonia, bradykinesia, etc.
- **Behavioural and psychiatric disturbances** (depression, psychosis, and obsessive–compulsive disorder, suicidality, etc.)
- **Cognitive disturbances, dementia**
- **Non-neurological features**





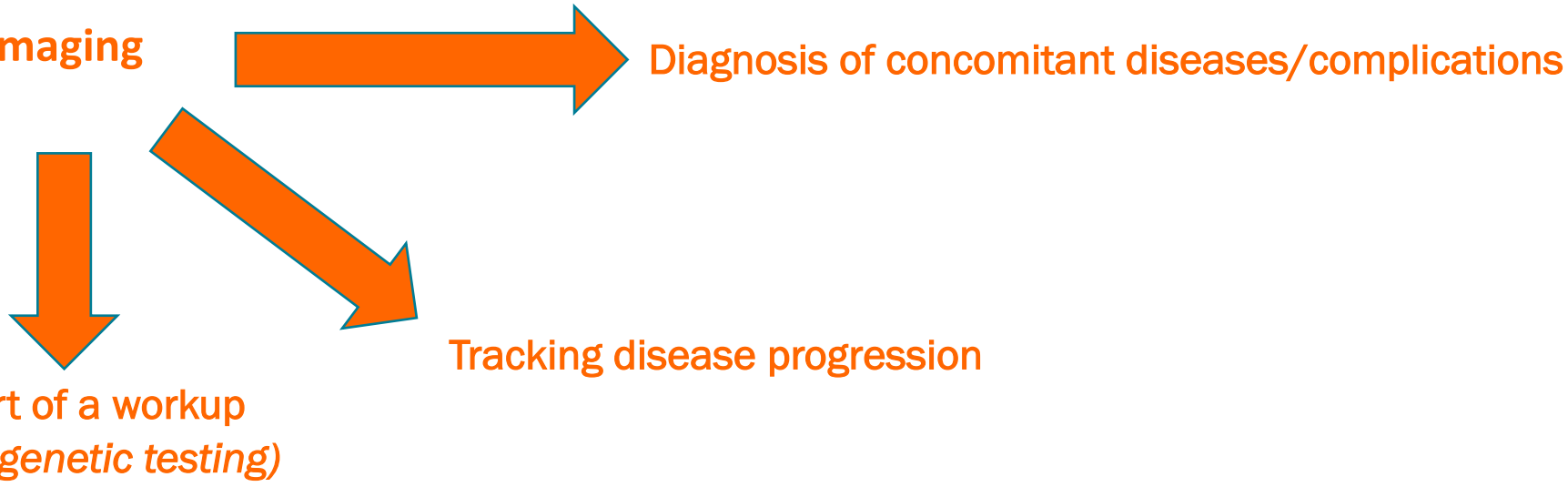
Tabrizi et al. The Lancet. Neurology. 21: 632-644

Tools for Potentially Disease Modifying Treatment in HD



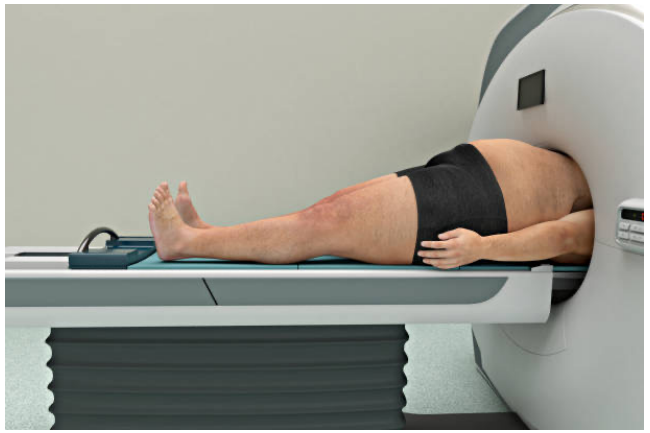
DIAGNOSTIC FLOWCHART FOR HUNTINGTON DISEASE

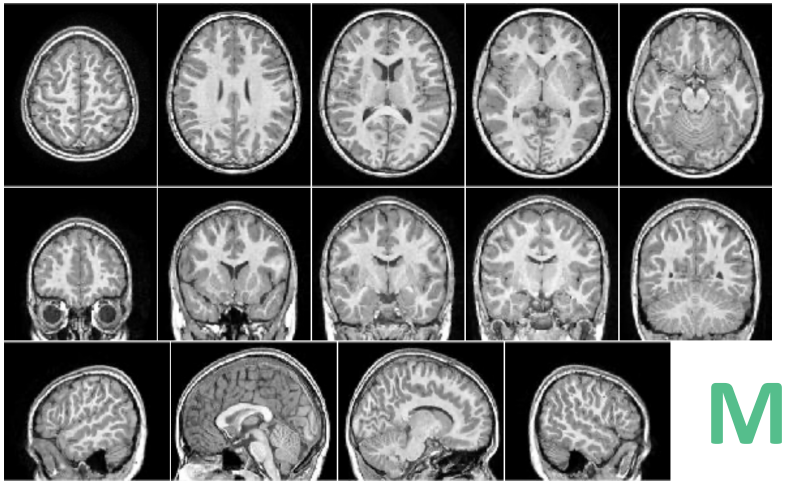
- Huntington disease HD is **the most frequent inherited chorea in adults**
- Identification of the HD phenotype: **MOTOR + COGNITIVE + NEUROPSYCHIATRIC SYMPTOMS**
- Extensive clinical examination
- Comprehensive history taking
- Family history
- **Targeted genetic testing**
- **Neuroimaging**



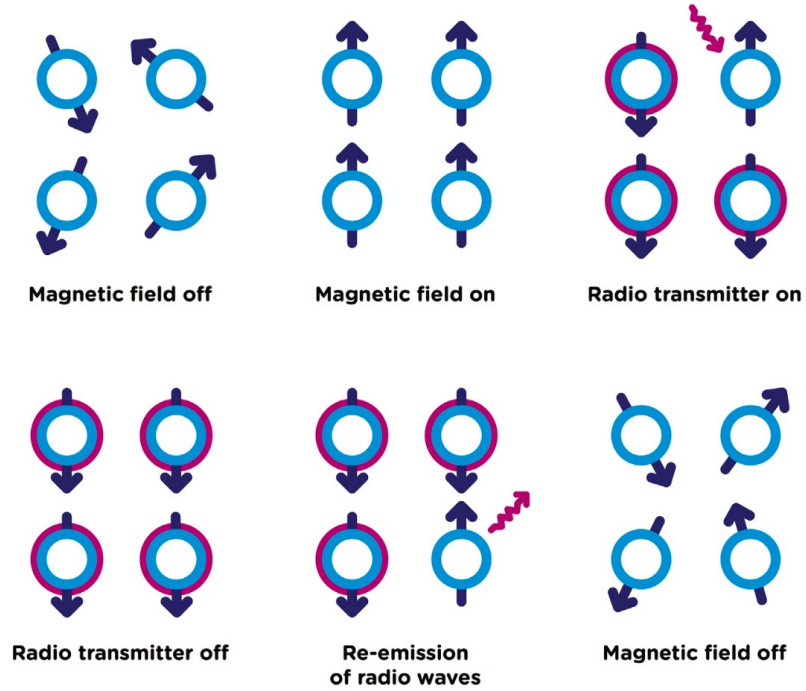
Neuroimaging modalities used in HD

- Sonography: outdated for application in HD
- **MRI:** *in vivo* method of quantifying structural and functional brain changes during HD progression
  - structural MRI: T1, T2, FLAIR, SWI/T2*
  - diffusion MRI: DWI, tractography
  - functional MRI: resting-state, task-based
- **CT:** when MRI cannot be applied (but pregnancy!)
- **PET:** *in vivo* molecular imaging

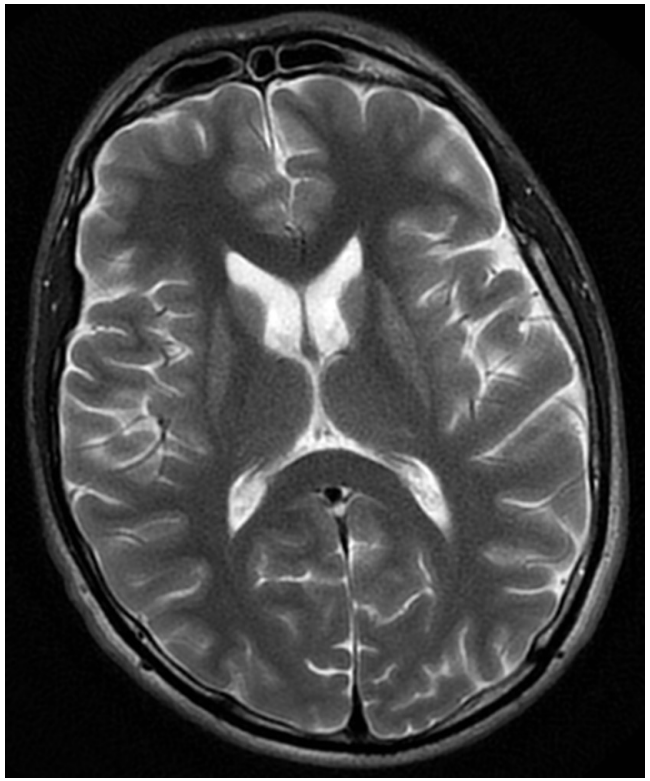


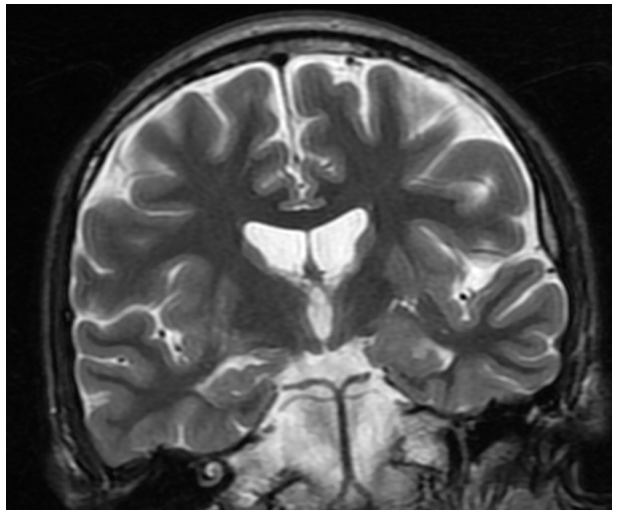


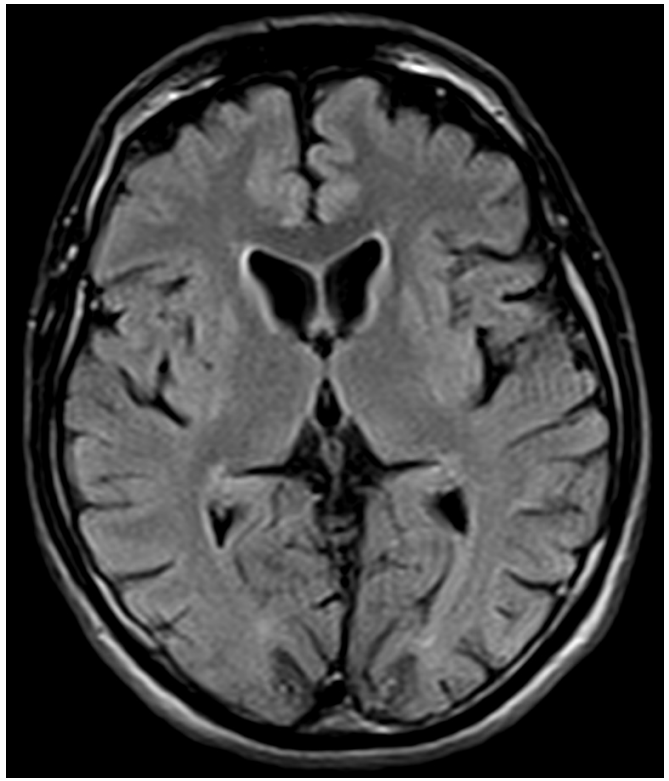
MAGNETIC RESONANCE IMAGING



Structural MRI in Huntington disease: atrophy



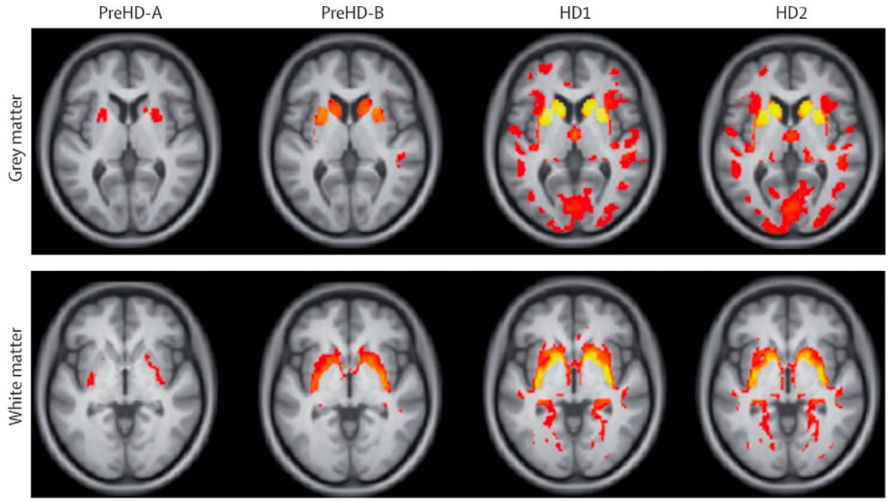


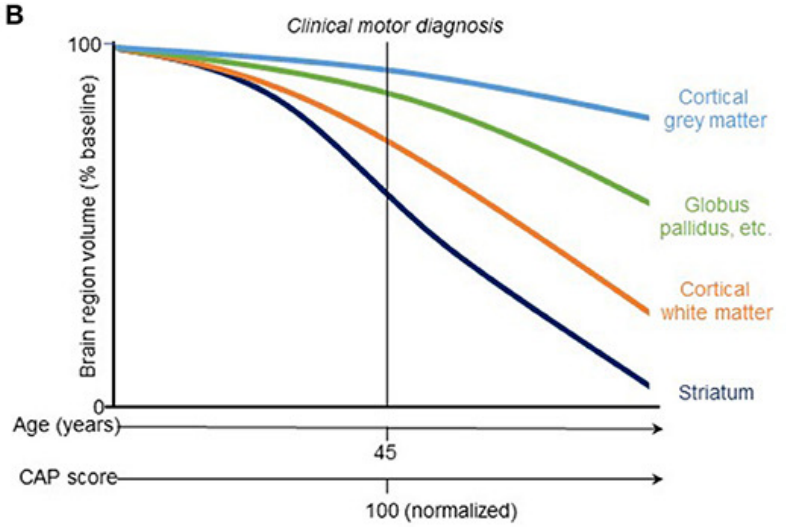


Personal observations

LONGITUDINAL STRUCTURAL MRI

Study Name	Principal Investigator	Study Years	Disease Stage Relative to Clinical Diagnosis	Total Sample Size	MRI Sites	Field Strength
TRACK-HD	S. Tabrizi (UCL)	2008 – 2014	Before HD clinical motor diagnosis, Clinically diagnosed HD (with TFC 7-13)	366	4	3T
TrackOn-HD	S. Tabrizi (UCL)	2012 – 2014	Before HD clinical motor diagnosis	239	4	3T
IMAGE-HD	N. Georgiou-Karistianis (Monash)	2008 – 2012	Before HD clinical motor diagnosis, Clinically diagnosed HD (with TMS > 5)	108	1	3T
PREDICT-HD	J. Paulsen (Iowa)	2001 – 2012	Before HD clinical motor diagnosis	1314	33	3T
PADDINGTON	B. Landwehrmeyer (Ulm)	2011 – 2013	Clinically diagnosed HD (with TFC ≥ 11)	61	4	3T





- Significantly reduced striatal volume is detectable more than 20 years prior to clinical motor diagnosis, whereas losses in other brain structures are more apparent in later disease stages
- At the time of clinical motor diagnosis, striatal volumes are markedly reduced compared to age-matched normal volumes — caudate: 52–70% loss; putamen: 43–67% loss; nucleus accumbens: 59–60% loss

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LONGITUDINAL STRUCTURAL MRI

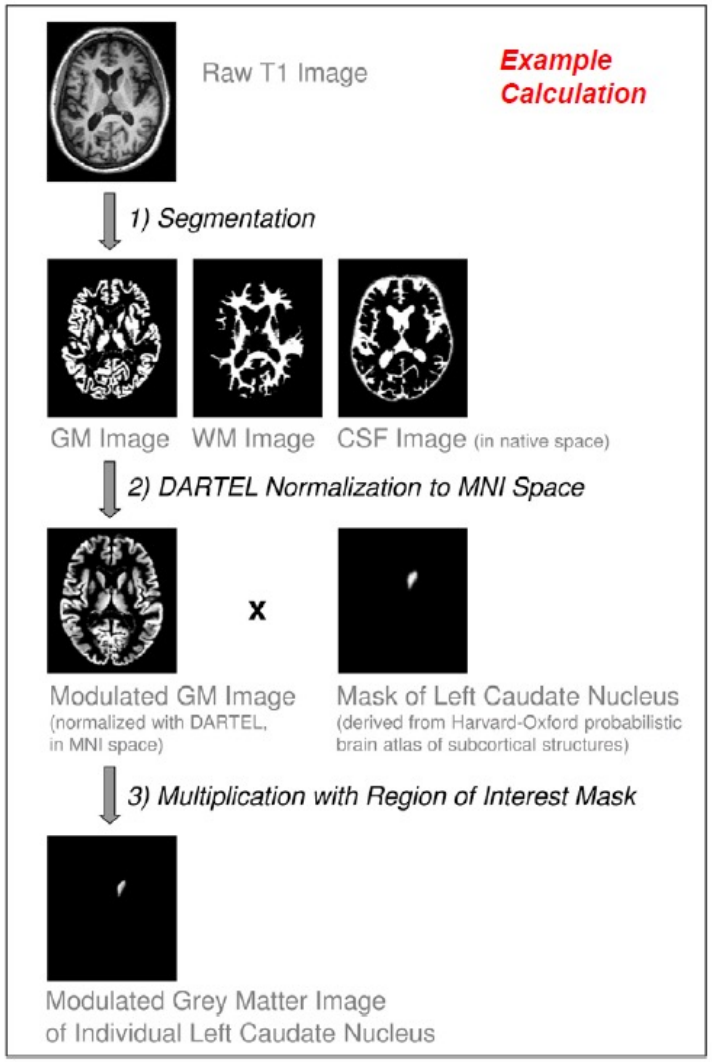
Length	Study	Reference	Detection	Shoulson-Fahn disease stage	Sample size [95% CI]
1 year	TRACK-HD	Frost et al. (65)	20% slowing of rate of whole-brain atrophy	TFC 11-13 & TFC 7-10	636 [454, 1,001]
1 year	TRACK-HD	Frost et al. (65)	40% slowing of rate of whole-brain atrophy	TFC 11-13 & TFC 7-10	159 [114, 251]
2 years	TRACK-HD	Frost et al. (65)	20% slowing of rate of whole-brain atrophy	TFC 11-13 & TFC 7-10	289 [211, 435]
2 years	TRACK-HD	Frost et al. (65)	40% slowing of rate of whole-brain atrophy	TFC 11-13 & TFC 7-10	73 [53, 109]
3 years	TRACK-HD	Frost et al. (65)	20% slowing of rate of whole-brain atrophy	TFC 11-13 & TFC 7-10	225 [158, 355]
3 years	TRACK-HD	Frost et al. (65)	40% slowing of rate of whole-brain atrophy	TFC 11-13 & TFC 7-10	57 [40, 89]
1 year	TRACK-HD	Frost et al. (65)	20% slowing of rate of caudate atrophy	TFC 11-13 & TFC 7-10	484 [363, 777]
1 year	TRACK-HD	Frost et al. (65)	40% slowing of rate of caudate atrophy	TFC 11-13 & TFC 7-10	121 [91–195]
2 years	TRACK-HD	Frost et al. (65)	20% slowing of rate of caudate atrophy	TFC 11-13 & TFC 7-10	197 [145, 350]
2 years	TRACK-HD	Frost et al. (65)	40% slowing of rate of caudate atrophy	TFC 11-13 & TFC 7-10	50 [37, 90]
3 years	TRACK-HD	Frost et al. (65)	20% slowing of rate of caudate atrophy	TFC 11-13 & TFC 7-10	144 [98, 284]
3 years	TRACK-HD	Frost et al. (65)	40% slowing of rate of caudate atrophy	TFC 11-13 & TFC 7-10	36 [25, 71]
6-month	PADDINGTON	Hobbs et al. (5)	50% slowing of rate of ventricular expansion	TFC ≥ 11	134 [64, 495]
9-month	PADDINGTON	Hobbs et al. (5)	50% slowing of rate of ventricular expansion	TFC ≥ 11	98 [51, 275]
15-month	PADDINGTON	Hobbs et al. (5)	50% slowing of rate of ventricular expansion	TFC ≥ 11	80 [48, 186]
6-month	PADDINGTON	Hobbs et al. (5)	50% slowing of rate of caudate atrophy	TFC ≥ 11	173 [81, 652]
9-month	PADDINGTON	Hobbs et al. (5)	50% slowing of rate of caudate atrophy	TFC ≥ 11	207 [87, 801]
15-month	PADDINGTON	Hobbs et al. (5)	50% slowing of rate of caudate atrophy	TFC ≥ 11	59 [30, 153]

	Motor (*N* = 504)						Cognitive (*N* = 486)					Functional (*N* = 516)	
	Speeded tapping	UHDRS total motor	UHDRS oculomotor	UHDRS bradykinesia	UHDRS chorea	UHDRS dystonia	Symbol-digit modalities	Hopkins verbal learning	Emotion recognition	Self-paced timing	Letter-number sequencing	Total functional capacity	Functional assessment scale
Putamen	−0.42	−0.27	−0.18	−0.22	−0.22		0.33	0.23	0.31	0.32	0.15		
Caudate	−0.42	−0.29	−0.2	−0.25	−0.21		0.31	0.33	0.33	0.32	0.2		
Globus pallidus	−0.36	−0.3	−0.2	−0.24	−0.27		0.35	0.29	0.33	0.34	0.18		
Thalamus	−0.14						0.12						
Nucleus accumbens	−0.2	−0.14	−0.13				0.13		0.15				
Hippocampus													
Frontal white	−0.15	−0.15	−0.12	−0.16									
Parietal white	−0.21	−0.12		−0.17			0.23		0.16	0.18	0.13		
Occipital white				−0.13			0.19		0.13				
Temporal white		−0.13		−0.17			0.12						
Frontal gray													
Parietal gray													
Occipital gray													
Frontal gray													

Only correlations that remained statistically significant following false discovery rate multiplicity correction are shown. The directionality of the associations was such that smaller tissue volumes were associated with greater impairment (higher scores on motor tasks, lower scores on cognitive tasks). Significant positive correlations are highlighted in a red color scale, significant negative correlations in a blue color scale, and darker shades are associated with stronger correlation coefficients.

Kinnunen et al. Front. Neurol. 12:712555

POSTPROCESSED STRUCTURAL MRI IN DIFFERENTIAL DIAGNOSIS

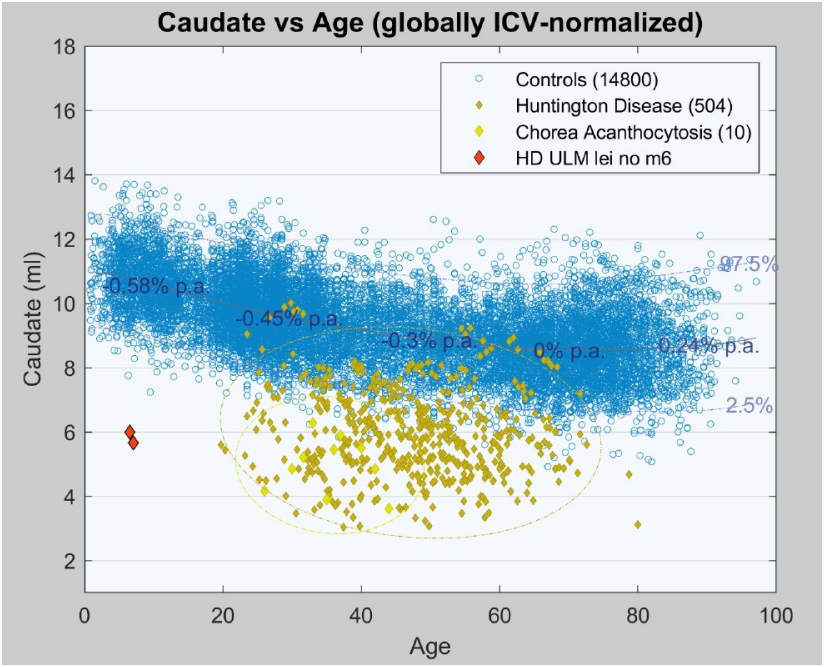


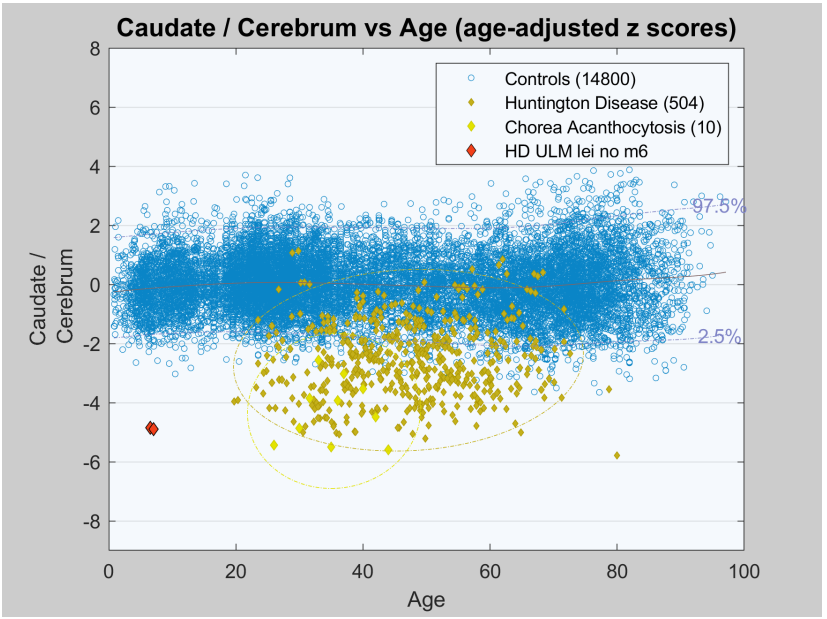
Atlas-based Volumetry (ABV)

- voxel- and atlas-based method for automated volumetric MRI analysis
- using algorithms of the software for Statistical Parametric Mapping (SPM)
  (Wellcome Trust Centre for Neuroimaging, London, UK, www.fil.ion.ucl.ac.uk/spm)
- …and probabilistic brain atlases

- Processing steps:
  - Segmentation into gray matter (GM), white matter (WM) & CSF compartments
  - Normalization to MNI space
  - Multiplication with region-of-interest mask derived from a probabilistic brain atlas
  - Volume calculation by summing up the values of remaining voxels

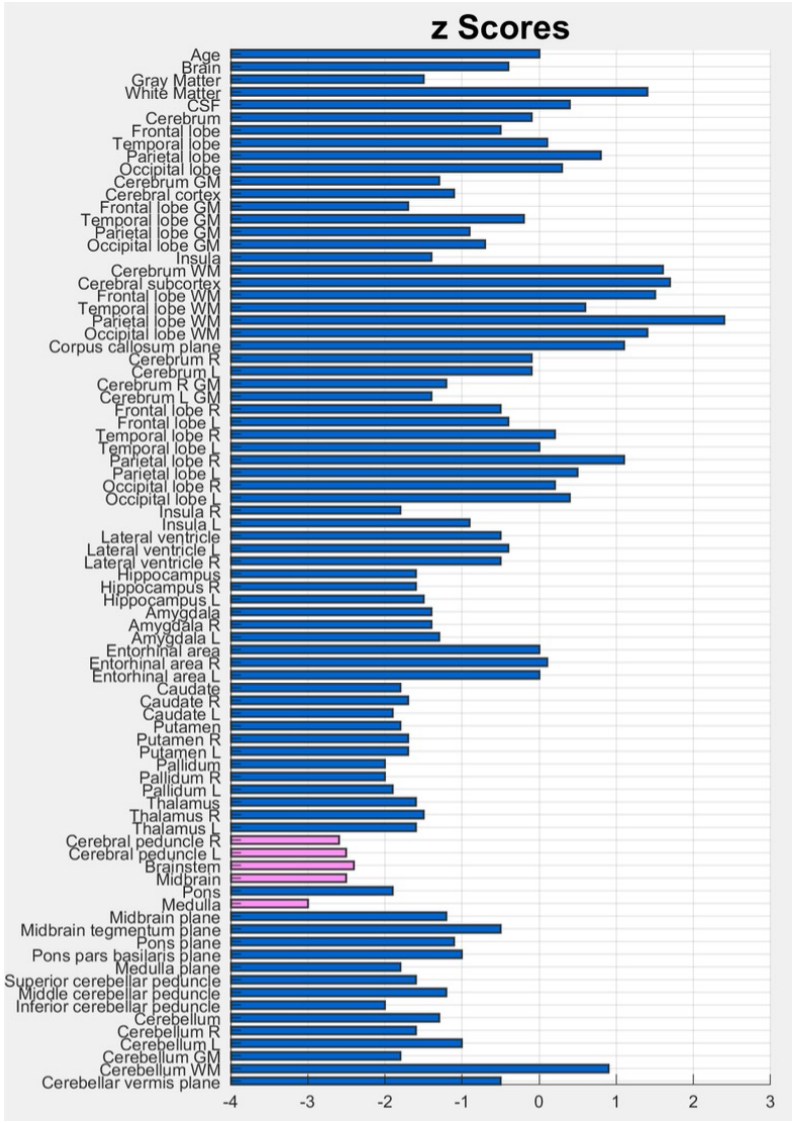
(cf.: Huppertz HJ, Kröll-Seger S, Klöppel S, Ganz RE, Kassubek J: Intra- & interscanner variability of automated voxel-based volumetry based on a 3D probabilistic atlas of human cerebral structures. NeuroImage 2010)

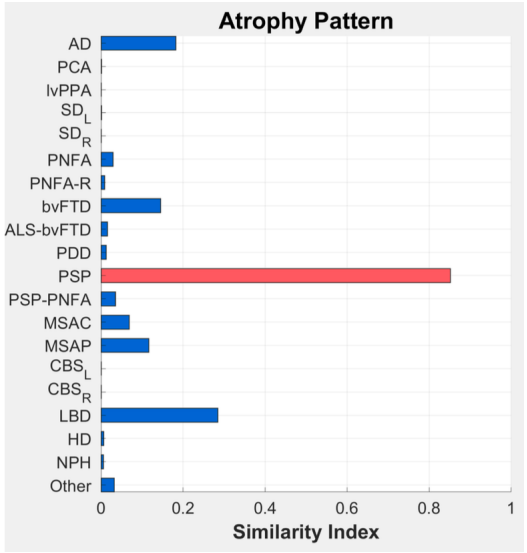


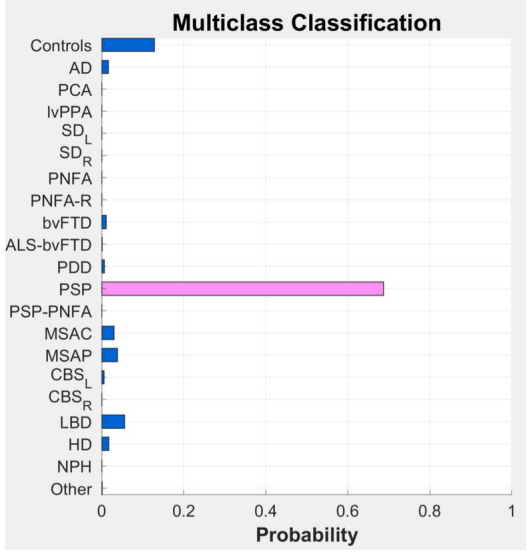


In collaboration with Prof. Dr. med. Hans-Jürgen Huppertz

POSTPROCESSED STRUCTURAL MRI IN DIFFERENTIAL DIAGNOSIS







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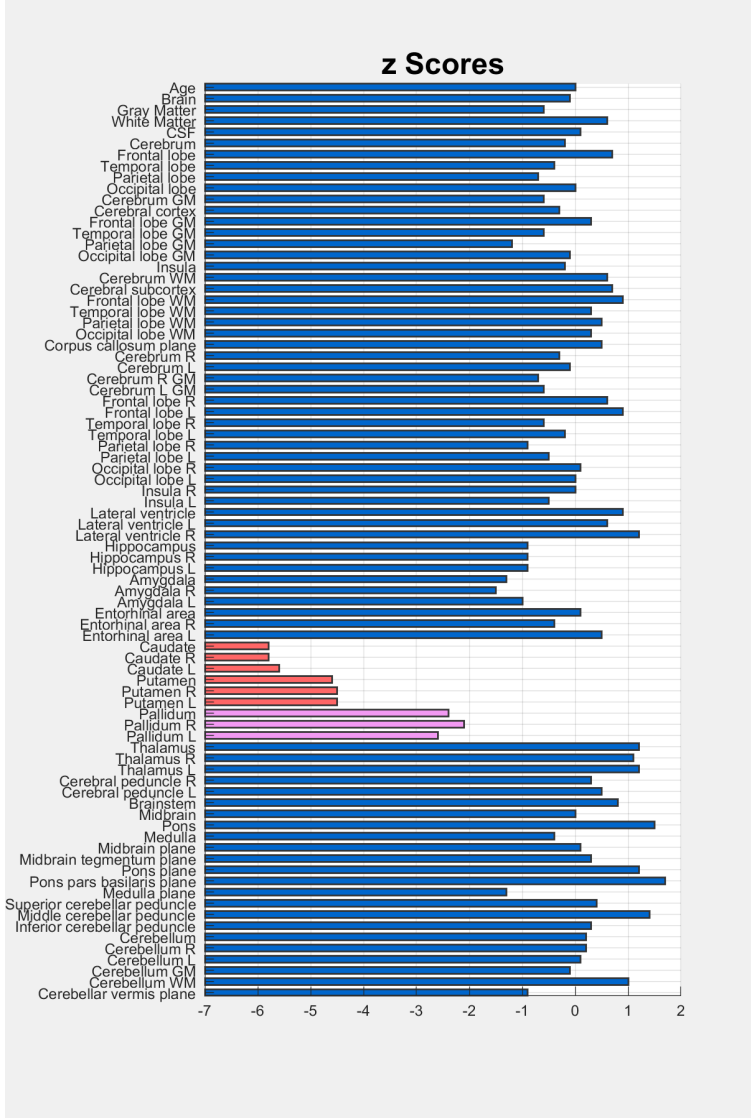
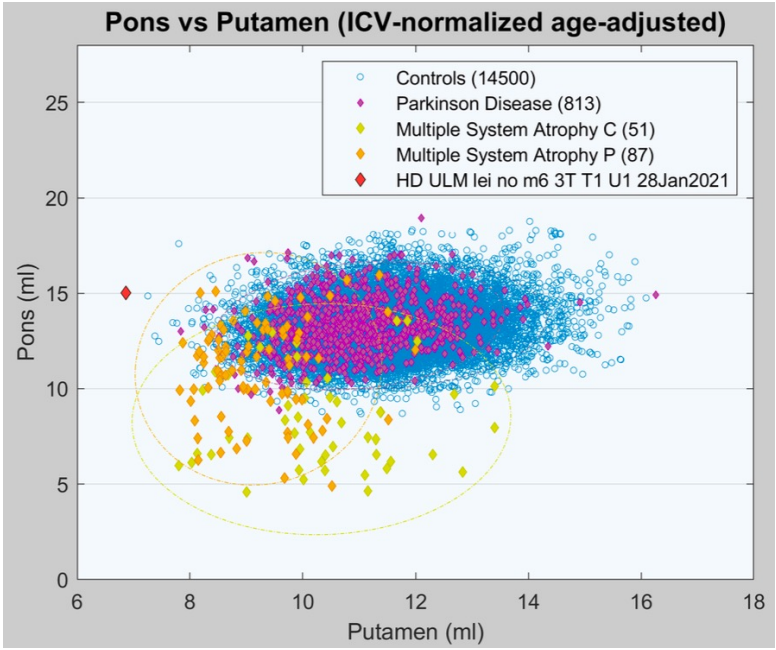
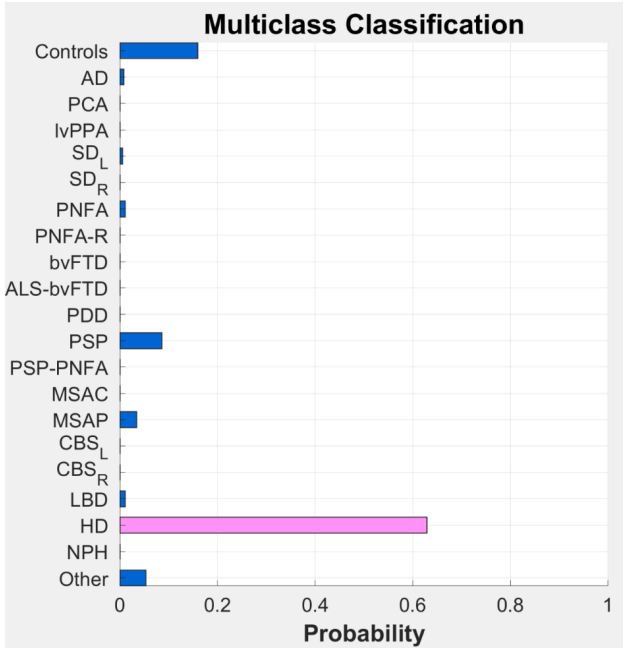
POSTPROCESSED STRUCTURAL MRI IN DIFFERENTIAL DIAGNOSIS





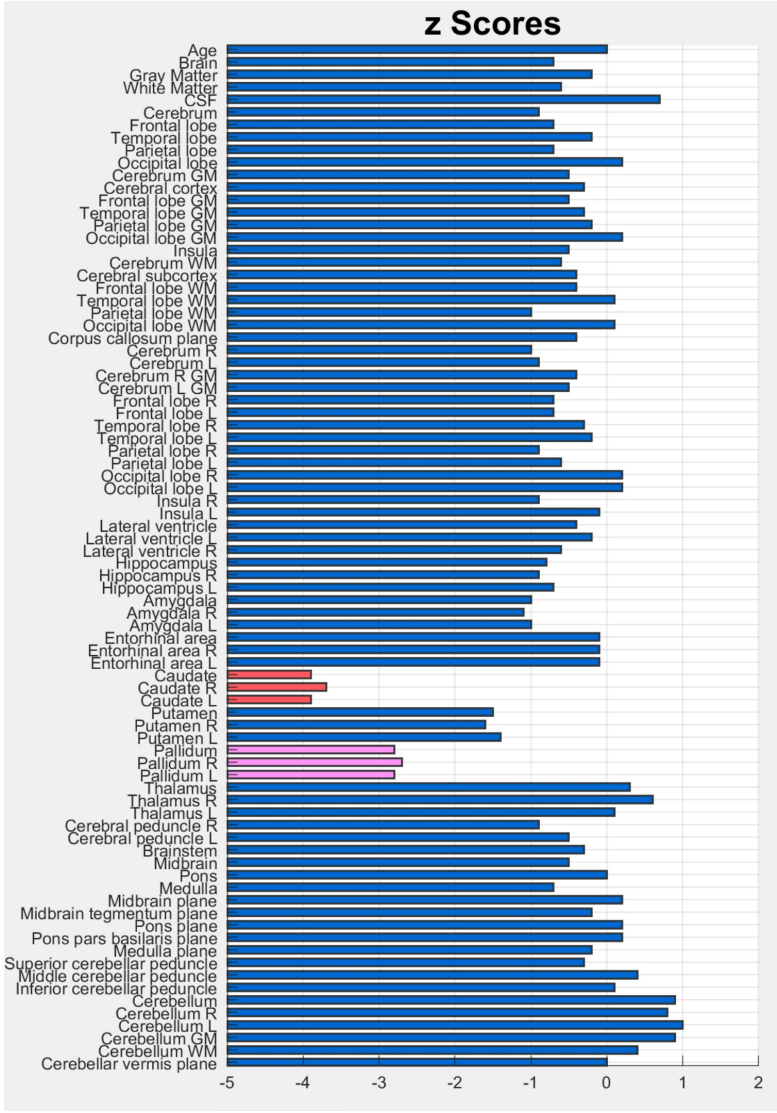


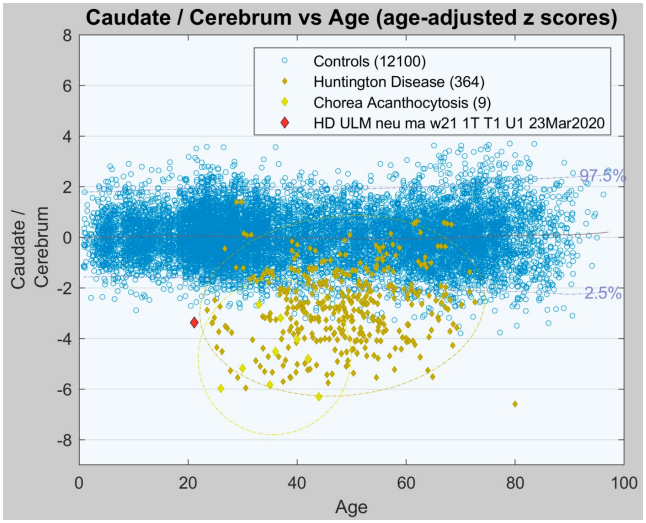
JHD, born 2014

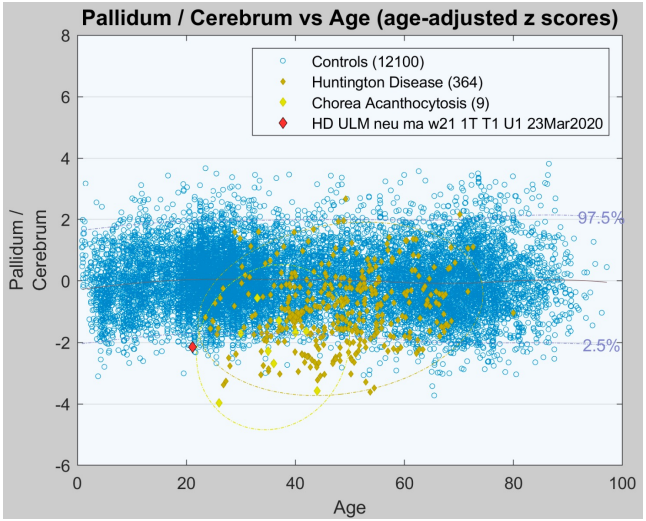
In collaboration with Prof. Dr. med. Hans-Jürgen Huppertz

Postprocessed Structural MRI in decision-making

- nCAG=58/18
- 20 years
- Facial hyperkineses, dysarthria, bradykinesia and myoclonias
- Dysexecutive syndrome, reduced concentration ability, lowered cognitive performance
- Apathy with increased irritability



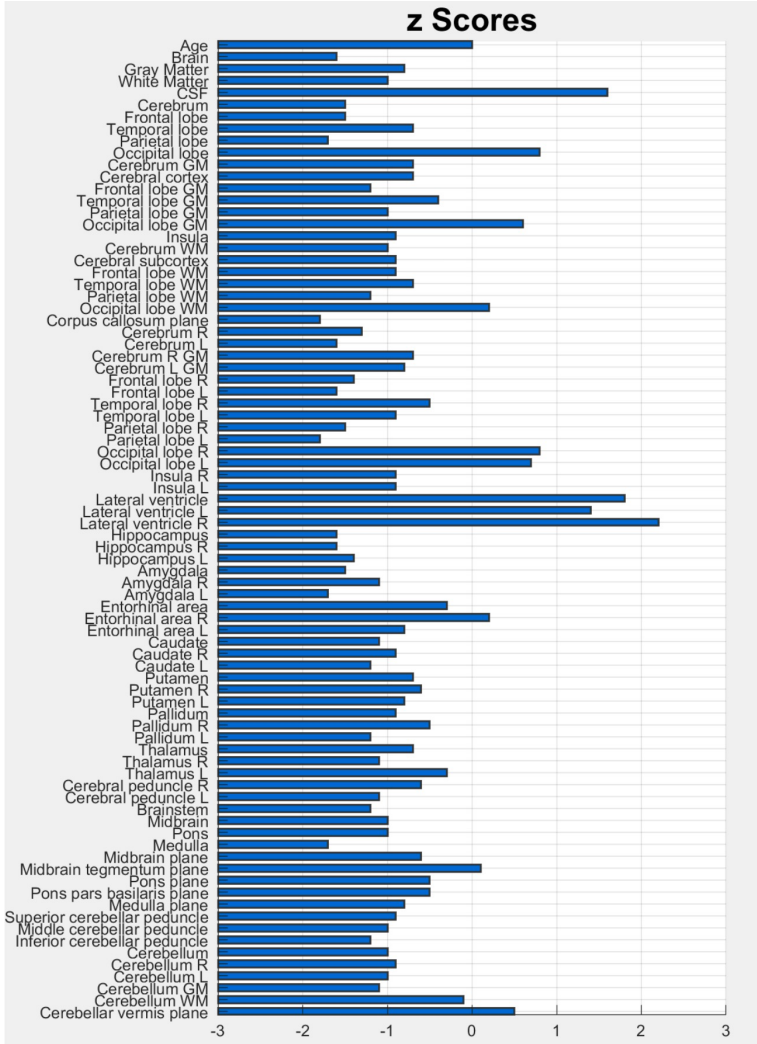




In collaboration with Prof. Dr. med. Hans-Jürgen Huppertz

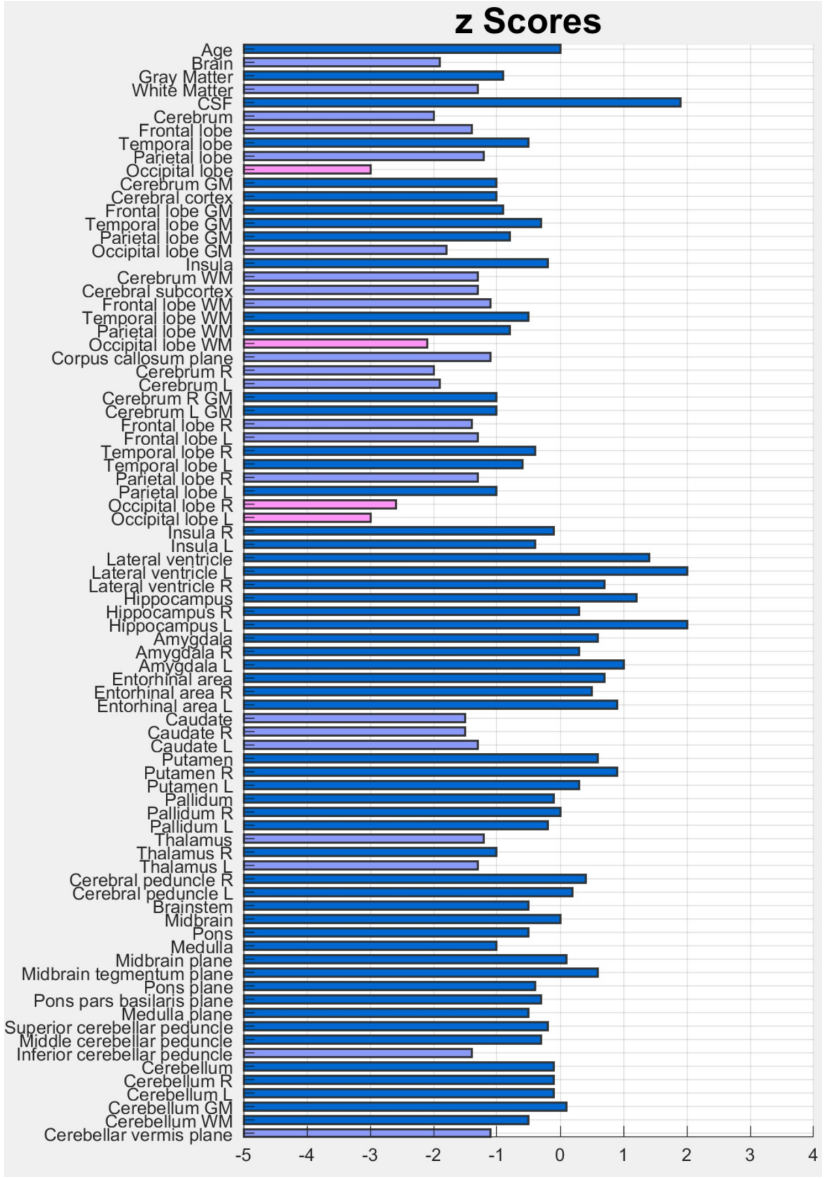
POSTPROCESSED STRUCTURAL MRI IN DECISION-MAKING

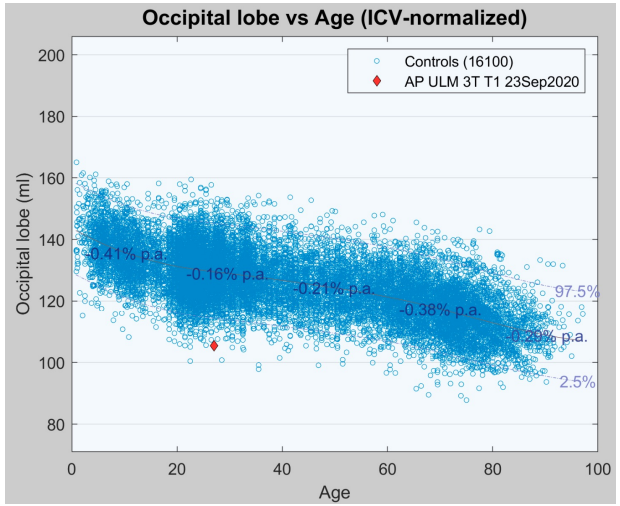
- nCAGmax=40
- 50 years
- Mild depression and anxiety

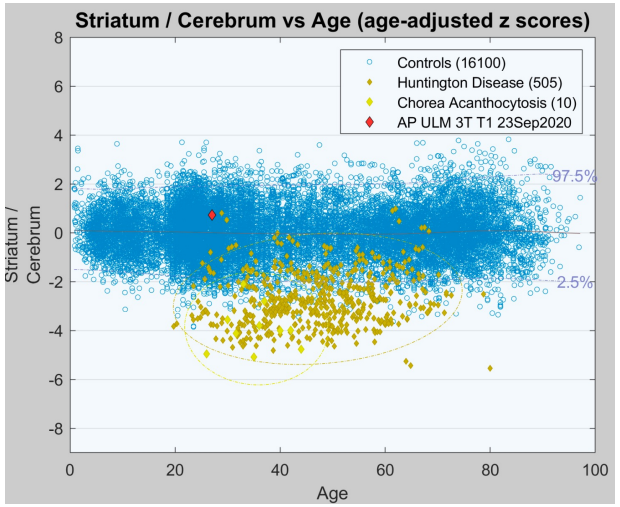


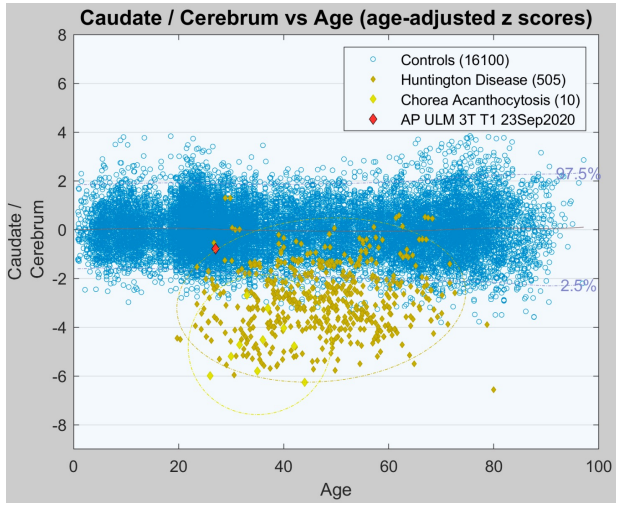
In collaboration with Prof. Dr. med. Hans-Jürgen Huppertz

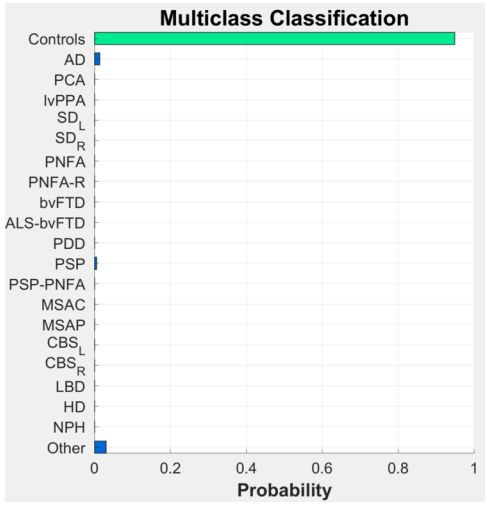
- nCAGmax=42
- 29 years
- No motor signs
- Since the age of 12: hyperactivity, OCD, inability to maintain an orderly daily structure, social withdrawal, decreased drive, and increased irritability
- Visual impairment is noticeable despite visual acuity correction with glasses with extreme diopter numbers.





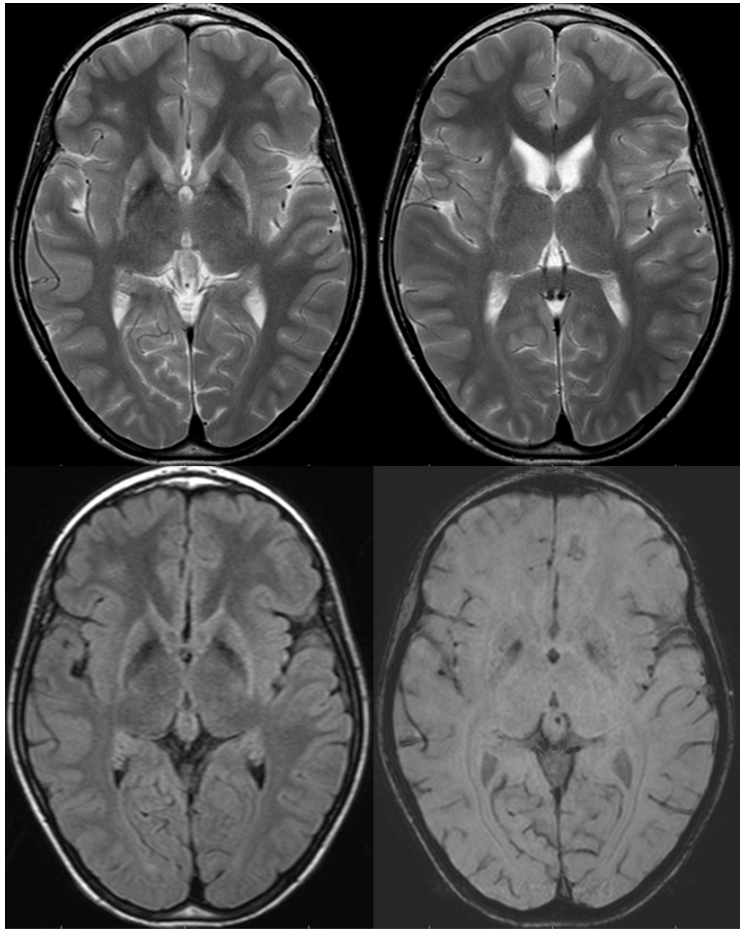


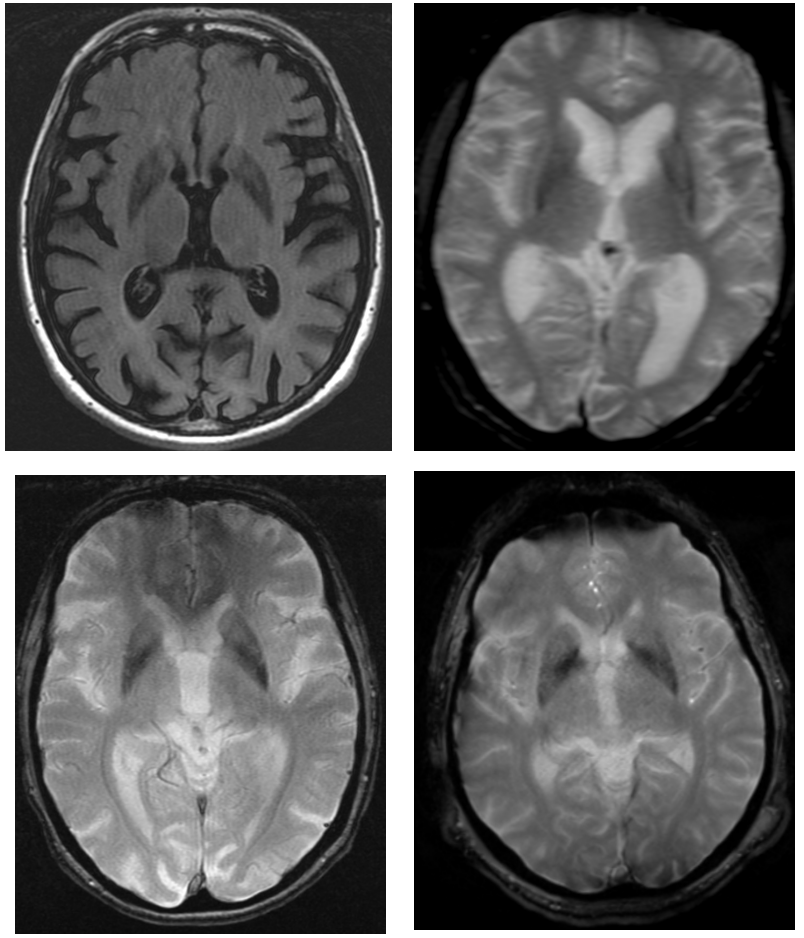




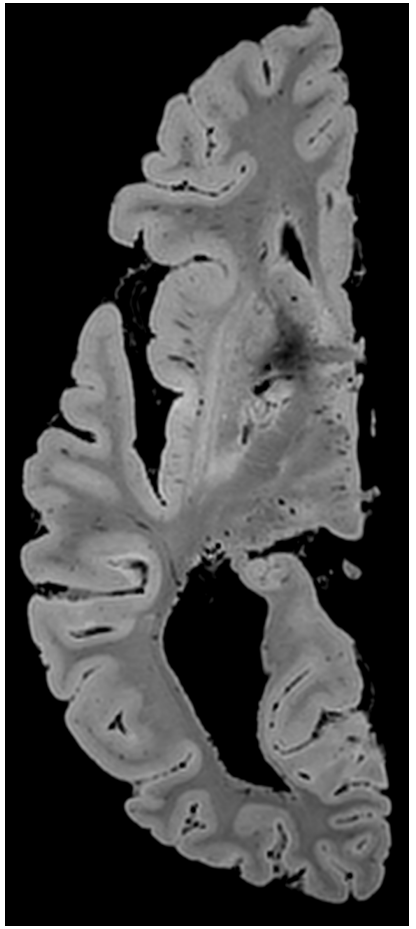
In collaboration with Prof. Dr. med. Hans-Jürgen Huppertz

Structural MRI in Huntington disease: iron deposition





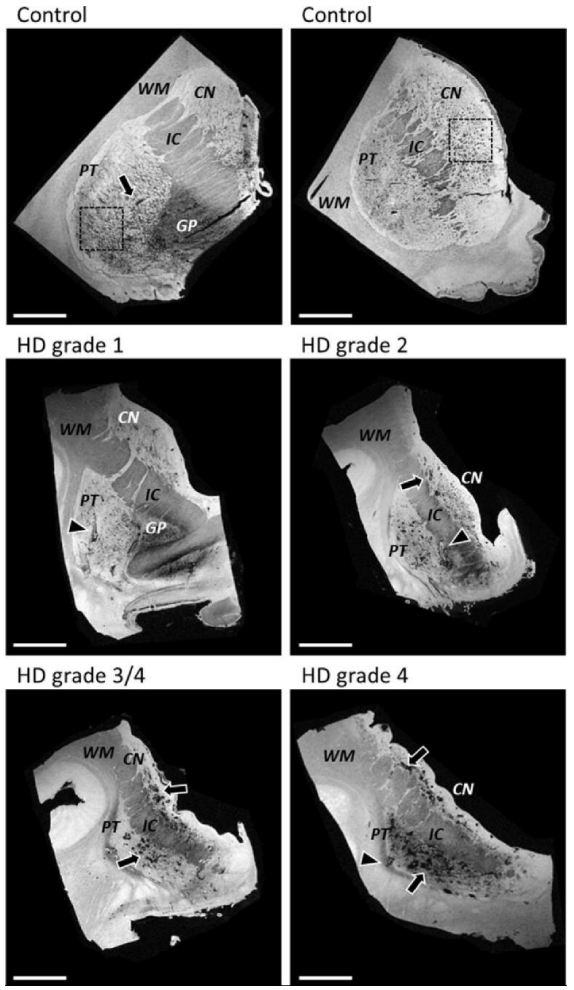
Personal observations

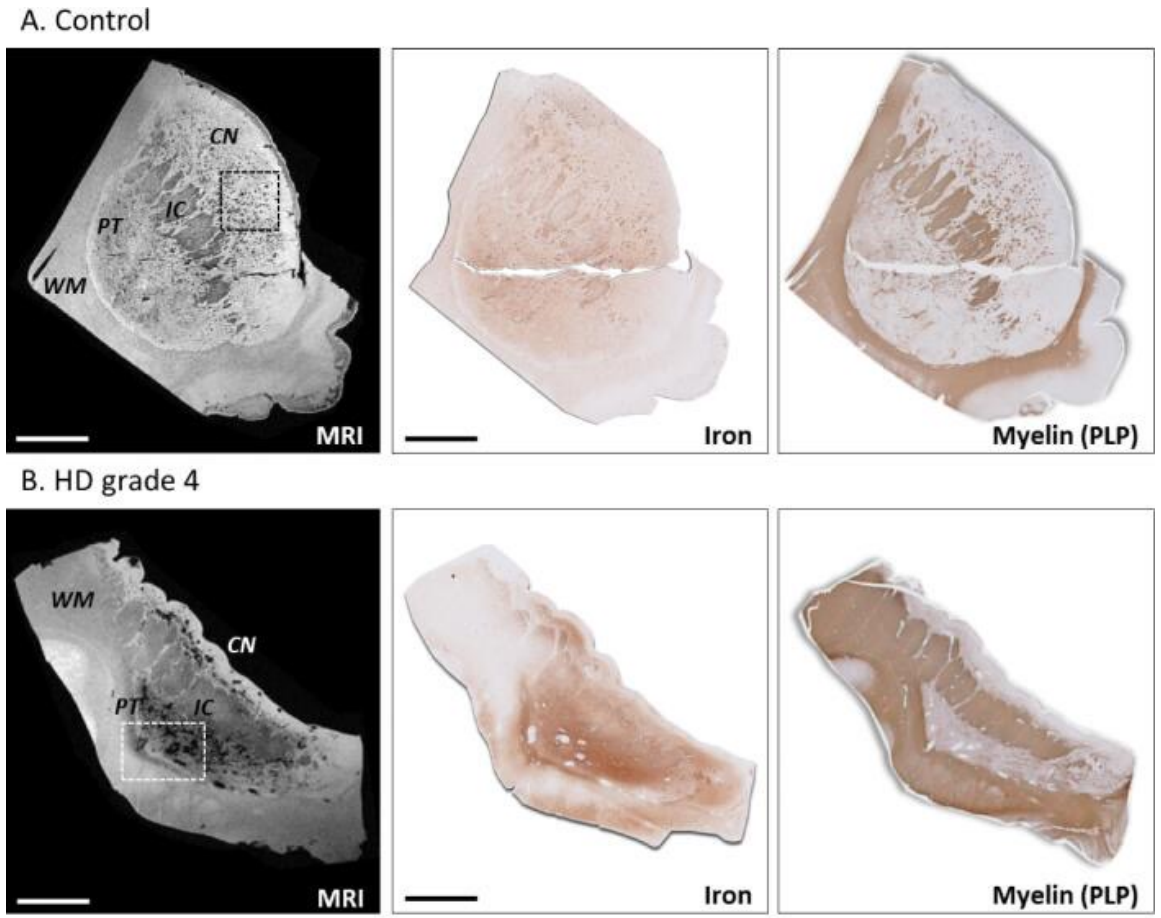


Obtained in collaboration with Prof. Dr. D. Yilmazer-Hanke

Structural MRI in Huntington disease: iron deposition

- 7T MRI on postmortem tissue of the striatum of 3 control subjects and 10 HD patients followed by histological examination
- Large focal hypointensities frequently colocalized with enlarged perivascular spaces and iron was found within the vessel wall and reactive astrocytes

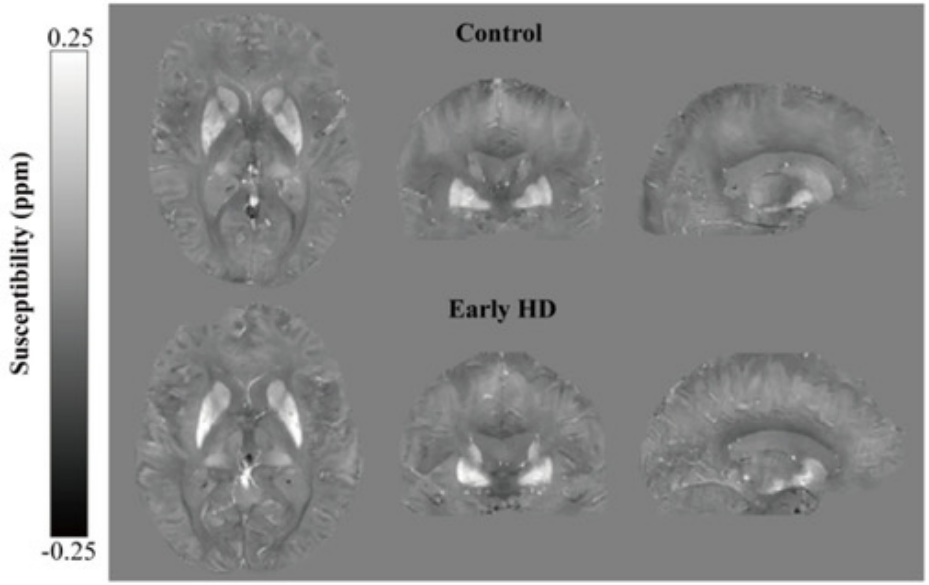




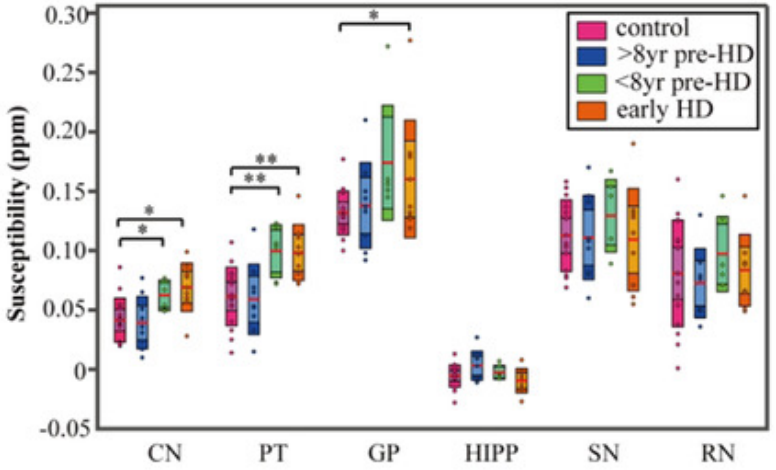
Bulk M, Hegeman-Kleinn I, Kenkhuis B, Suidgeest E, van Roon-Mom W, Lewerenz J, van Duinen S, Ronen I, van der Weerd L. Neuroimage Clin. 2020;28:102498

Structural MRI in Huntington disease: iron deposition

- Increased R2* in the putamen, globus pallidum and external capsule in PreHD
- Neuronal loss may lead to remyelination of white matter fibres and a congruent increase of iron-rich oligodendrocytes?
- Disrupted iron homeostasis?



Johnson, Eileanoir B. et al. EBioMedicine 65 (2021) 103266



Chen et al. J Neurosci Res. 2019 Apr;97(4):467-479

Neuroimaging in differentiating HD Phenocopies

CREDIT: Photo: AP

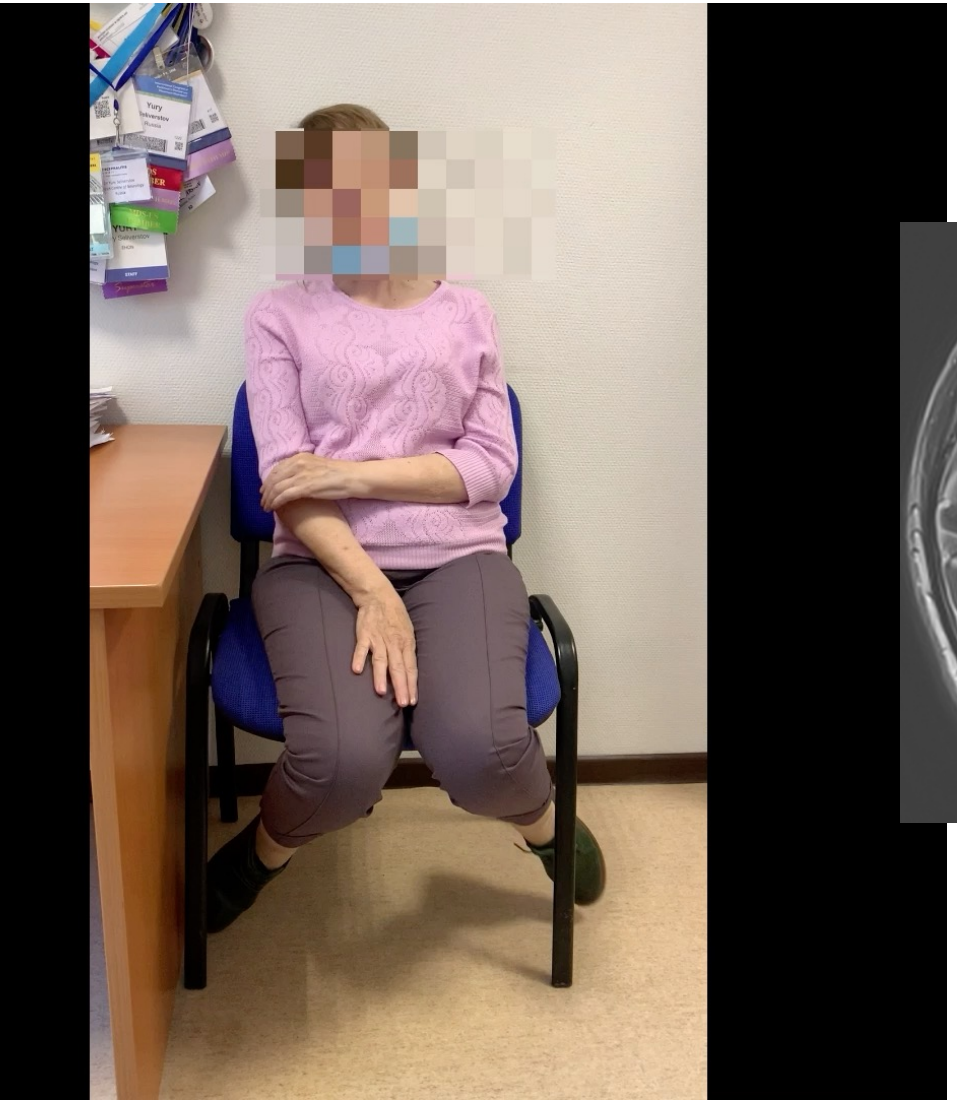
Chorea can be caused by a large number of conditions, including but not limited to inherited/degenerative diseases. Other causes are autoimmune, metabolic, and structural disorders as well as pharmacological treatments

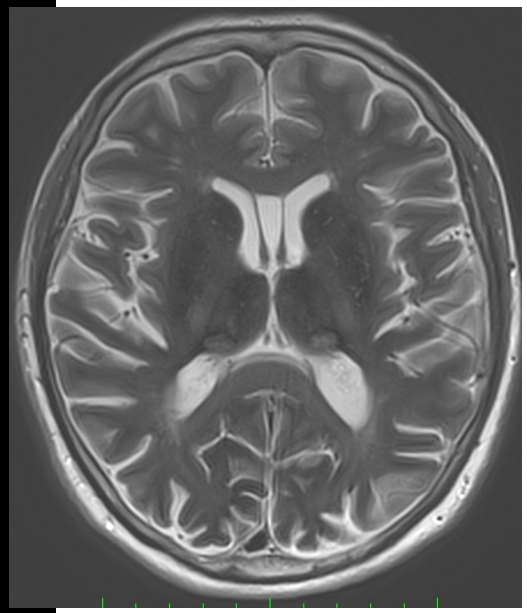
RED FLAGS OF NON-HD CHOREA

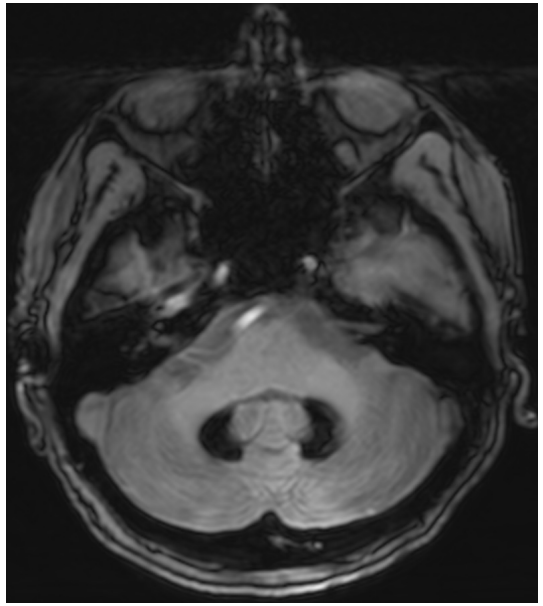
- African/Japanese ancestry
- Childhood-onset chorea
- Acute, subacute, paroxysmal nature
- Prominent orofacial and/or unilateral localization of chorea
- Concomitant neuropathy, myopathy, myoclonus, seizures (*NB! juvenile HD*)
- Prominent cerebellar, dystonia, parkinsonism, oculomotor signs (*NB! juvenile HD*)
- Non-HD pattern in neuroimaging

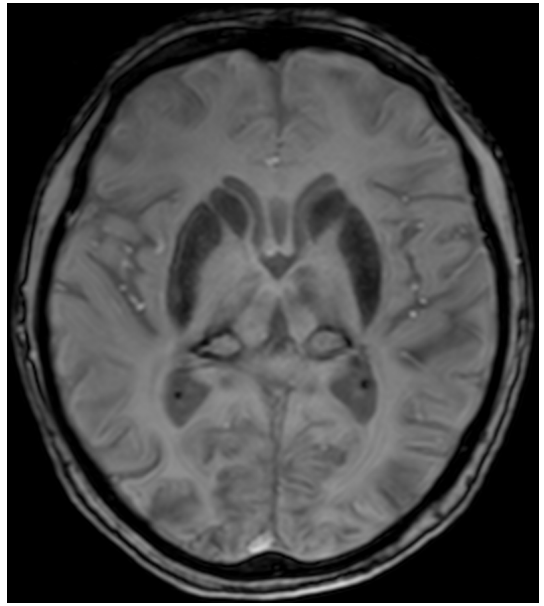
Nguyen QTR, Ortigoza Escobar JD, Burgunder J-M, Mariotti C, Saft C, Hjermind LE, Youssov K, Landwehrmeyer GB and Bachoud-Lévi A-C (2022) *Front. Neurol.* 13:817753

STRUCTURAL MRI IN DIFFERENTIAL DIAGNOSIS: *CP*



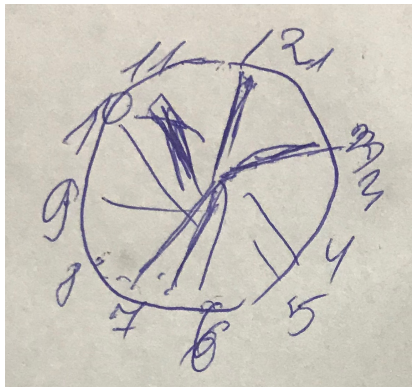


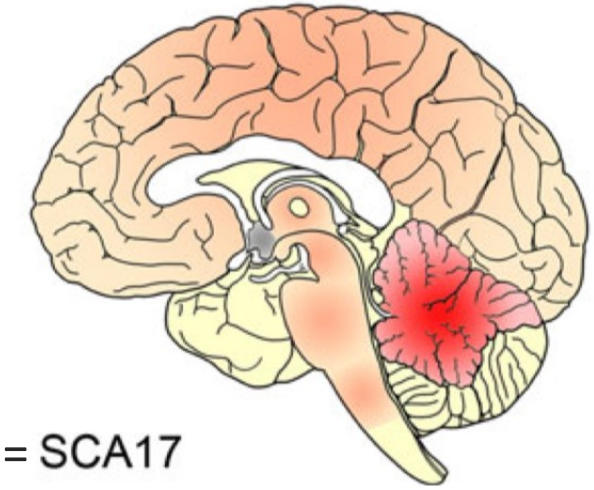




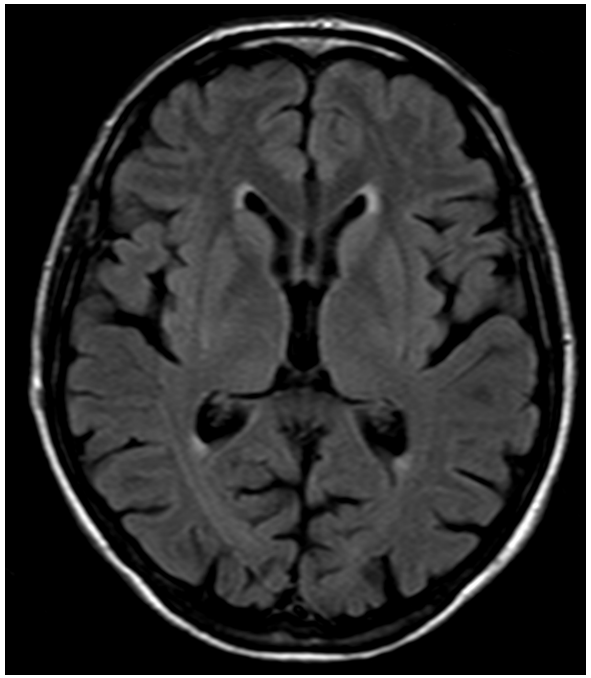
Personal observation

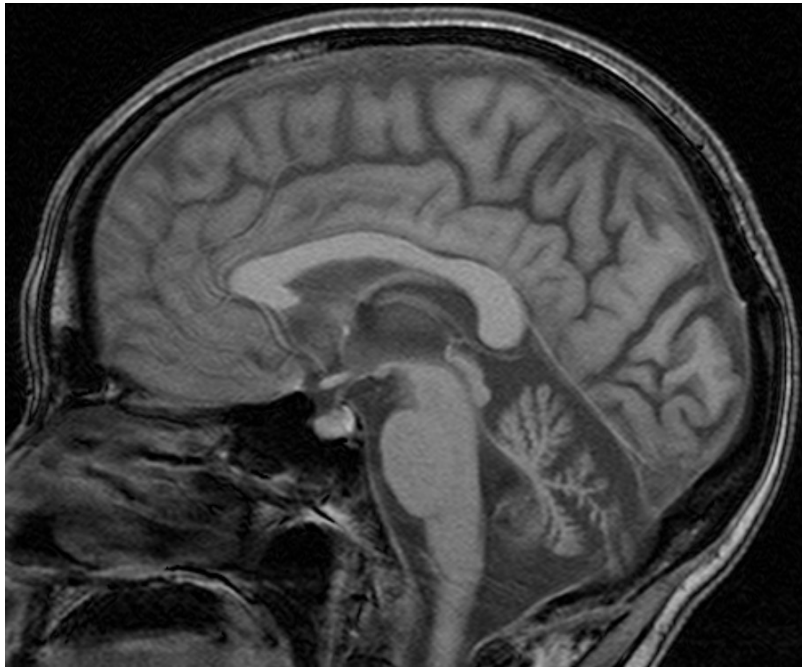
STRUCTURAL MRI IN DIFFERENTIAL DIAGNOSIS: *TBP*





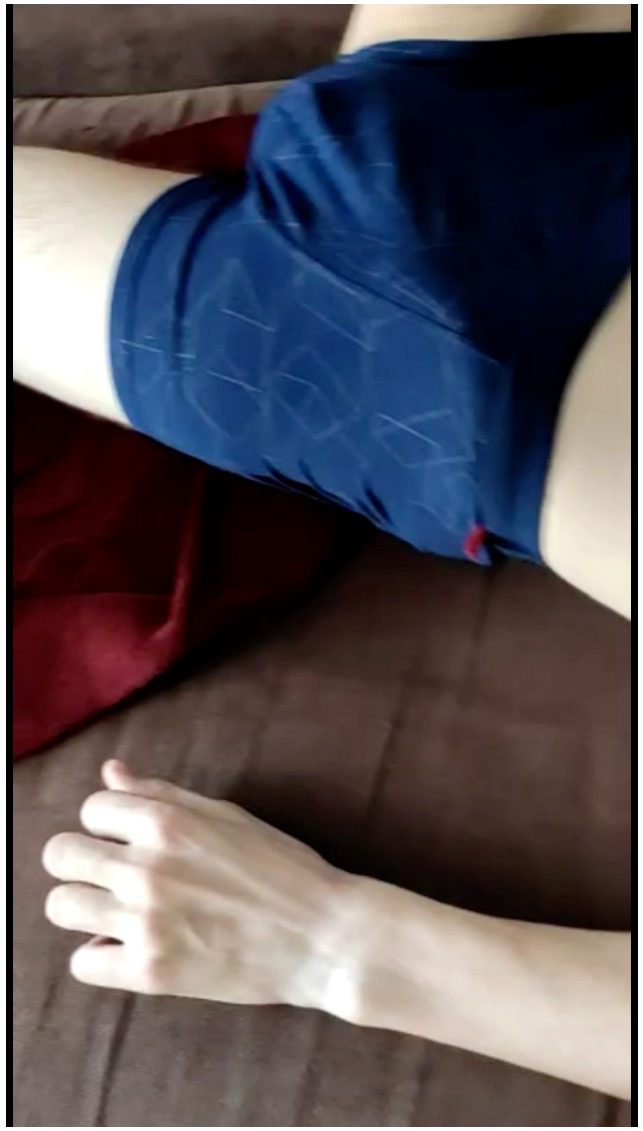
HDL-4 = SCA17

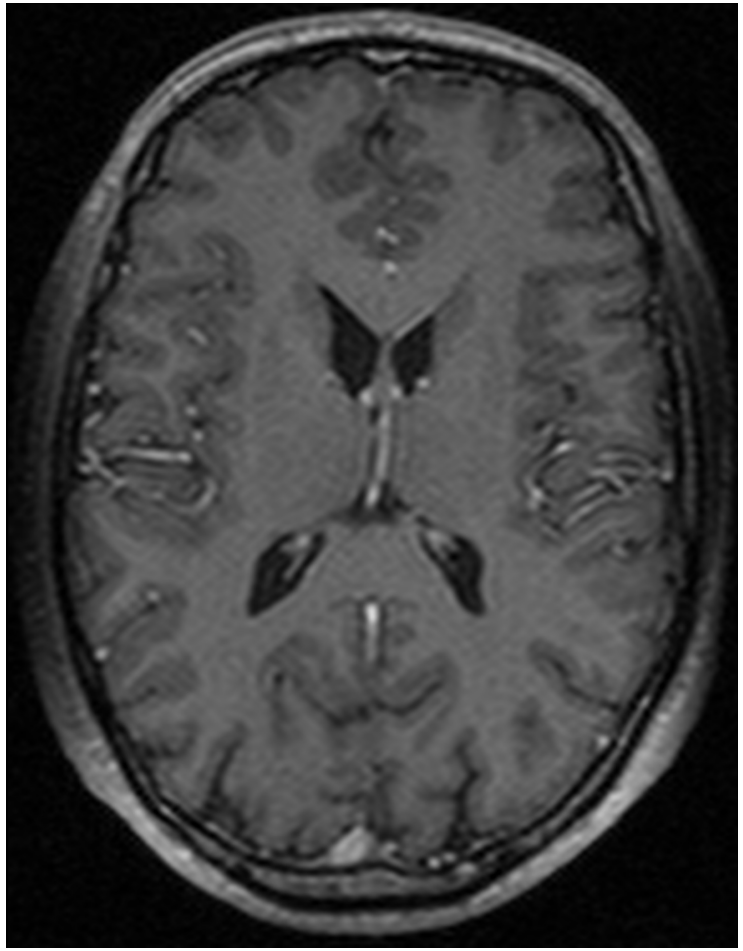




Personal observation

STRUCTURAL MRI IN DIFFERENTIAL DIAGNOSIS: *VPS13A*

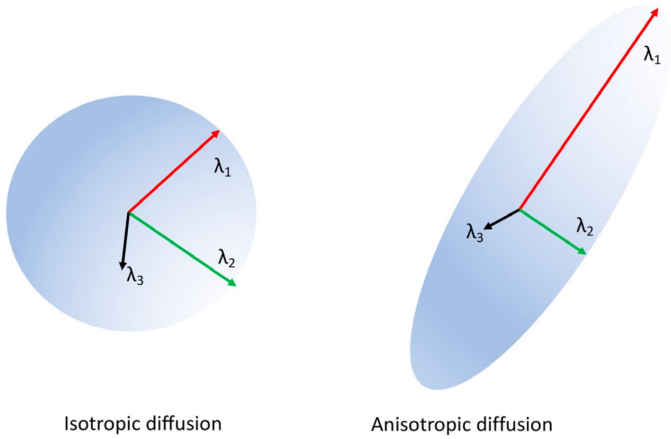




Personal observation

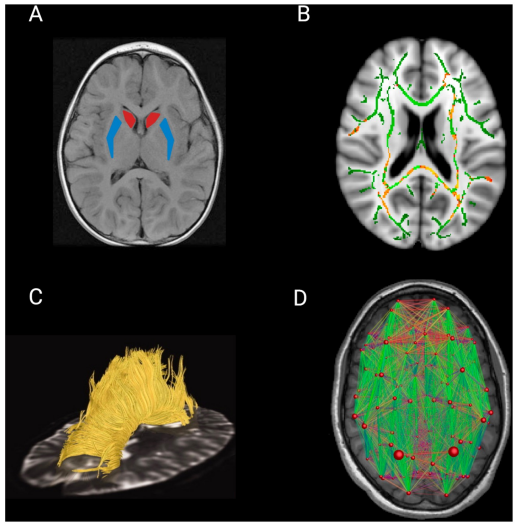
Diffusion MRI in Huntington disease

- Diffusion MRI allows to estimates brain fiber structures using water diffusion properties as a probe
- Anisotropy: coherent directionality of movement of the water molecules along the cell‘s processes
- Fractional anisotropy (FA): a scalar value that goes from 0 (diffusion is completely isotropic) to 1 (diffusion is completely anisotropic) → reflects fiber density, axonal diameter, and myelination in white matter



Isotropic diffusion

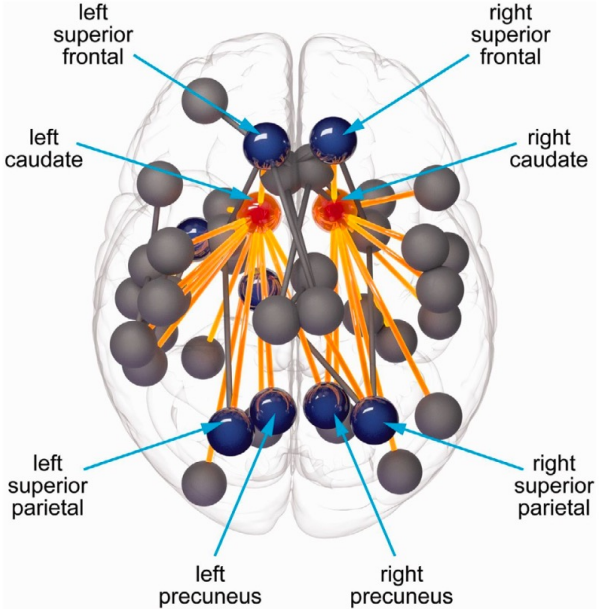
Anisotropic diffusion



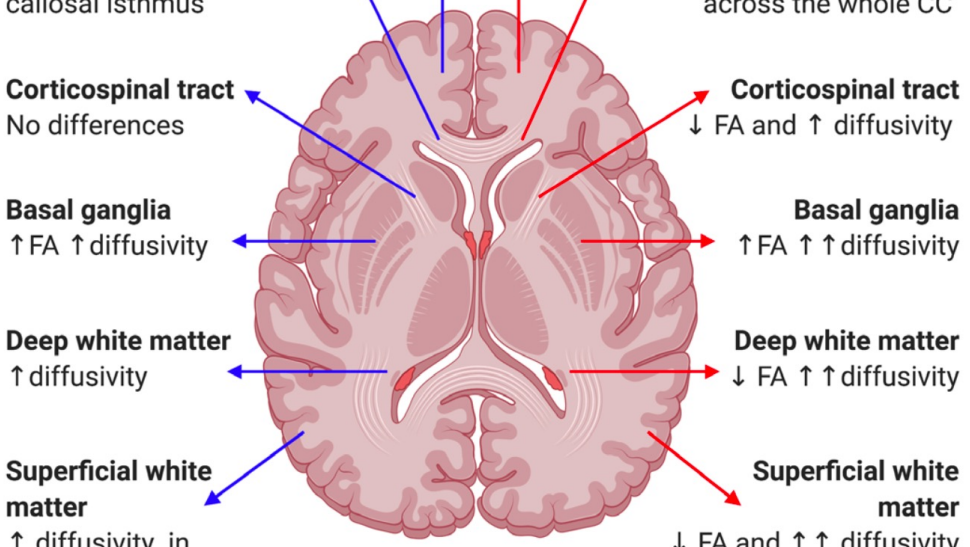
Estevez-Fraga C, Scahill R, Rees G, *et al. J Neurol Neurosurg Psychiatry* 2021;**92**:62–69

DIFFUSION MRI IN HUNTINGTON DISEASE

- Centrifugal pattern of degeneration with deeper brain areas being affected prior to superficial ones
- Loss of integration of neural networks



Eileanoir B. Johnson and Sarah Gregory. Progress in Molecular Biology and Translational Science. Volume 165, 2019, 321-369



PREMANIFEST HD

Prefrontal white matter tracts
↓ FA ↑ diffusivity in inferior and lateral regions

Corpus callosum
↑ diffusivity in the callosal isthmus

Corticospinal tract
No differences

Basal ganglia
↑FA ↑diffusivity

Deep white matter
↑diffusivity

Superficial white matter
↑ diffusivity in posterior areas

SYMPTOMATIC HD

Prefrontal white matter tracts
↓ FA ↑↑ diffusivity generalized

Corpus callosum
↓↓ FA and ↑↑ diffusivity across the whole CC

Corticospinal tract
↓ FA and ↑ diffusivity

Basal ganglia
↑FA ↑↑diffusivity

Deep white matter
↓ FA ↑↑diffusivity

Superficial white matter
↓ FA and ↑↑ diffusivity across the whole brain

Corticostriatal tract and sensorimotor network
↓ FA ↑ diffusivity between the putamen/caudate and prefrontal/premotor, motor/sensory areas

↑ diffusivity in the sensorimotor network associating with CAG repeats

Corticostriatal tract and sensorimotor network
↓ FA and ↑ diffusivity in M1 and S1 areas of the striatum

↓ FA and ↑ diffusivity between the striatum and thalamus with prefrontal, motor and parietal areas

Estevez-Fraga C, Scahill R, Rees G, *et al. J Neurol Neurosurg Psychiatry* 2021;**92**:62–69

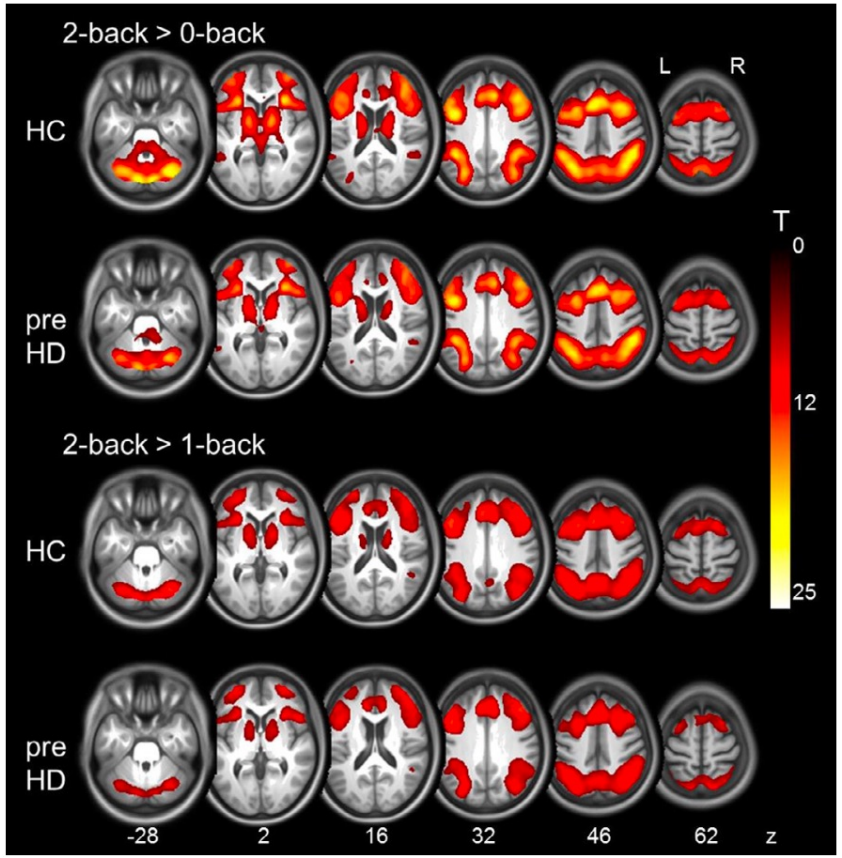
RESTING-STATE FUNCTIONAL MRI

- Bold oxygen level-dependent (BOLD) signal as a proxy of the brain activity
- Reduced connectivity between the premotor cortex and the caudate in HD
- Disrupted DMN (default mode network) connectivity within HD gene carriers
- Increased connectivity within the DMN and basal ganglia were associated with higher levels of depression
- **Still difficult to interpret**

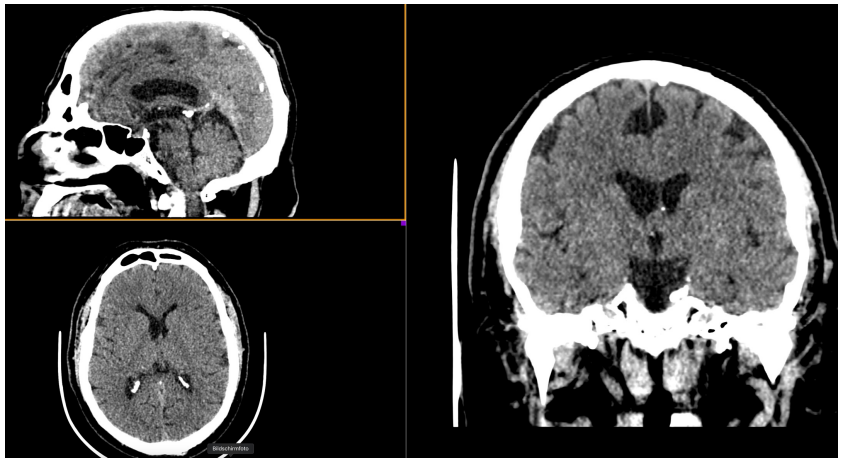
Eileanoir B. Johnson and Sarah Gregory. Progress in Molecular Biology and Translational Science. Volume 165, 2019, 321-369

TASK-BASED FUNCTIONAL MRI

- Measurement of the BOLD signal during task performance
- Considerable variation in results
- Compensatory mechanisms?



Eileanoir B. Johnson and Sarah Gregory. Progress in Molecular Biology and Translational Science. Volume 165, 2019, 321-369

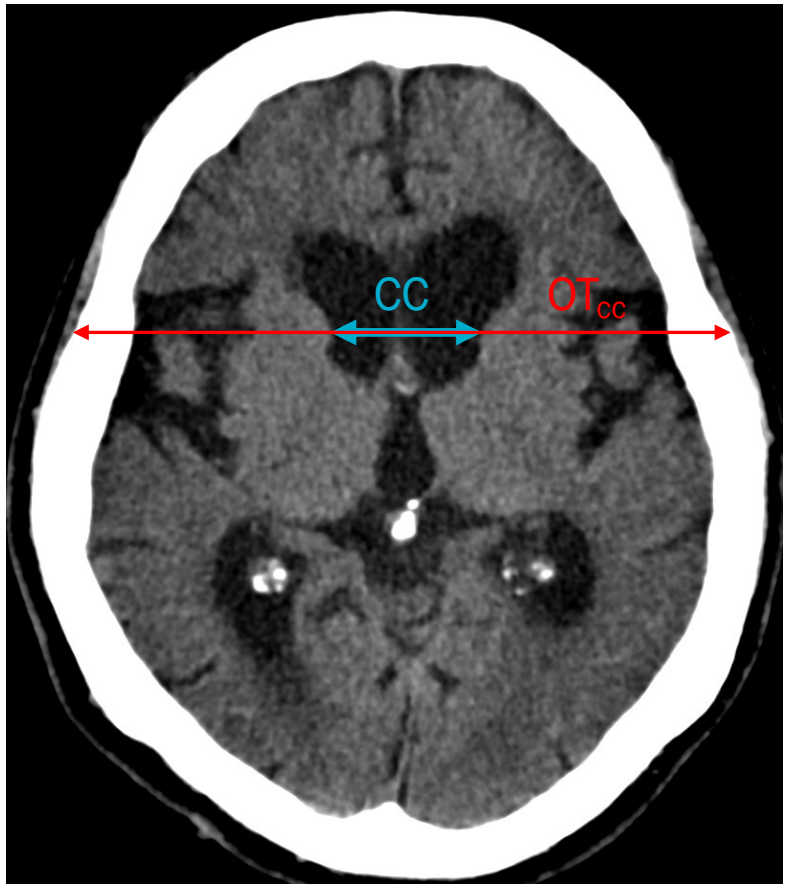


COMPUTED TOMOGRAPHY

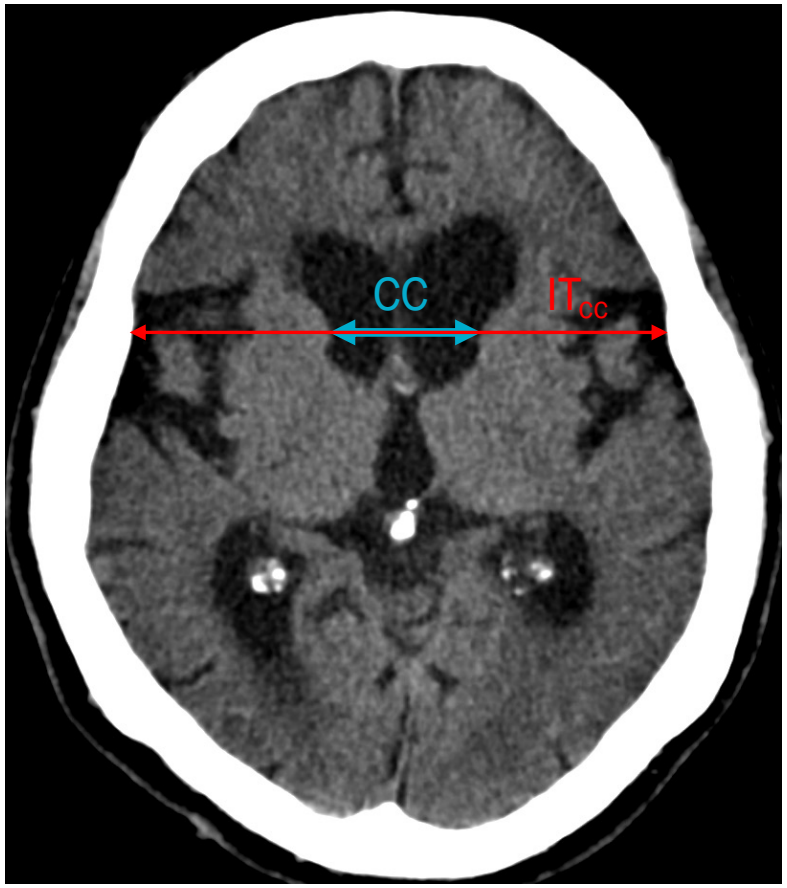
CT in Huntington disease

- Evidence of brain atrophy (if MRI is contraindicated)

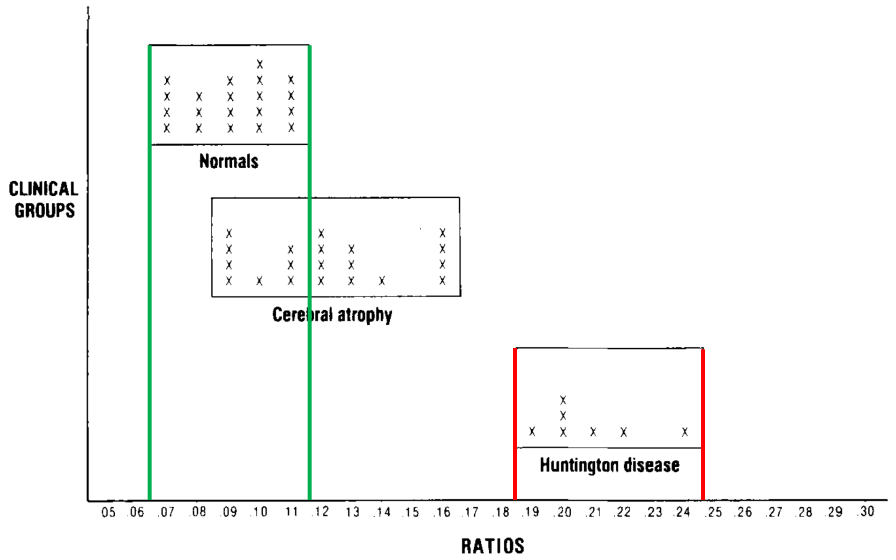
Bicaudate index (ratio): CC/OT_{cc} or CC/IT_{cc}



0.23



0.25

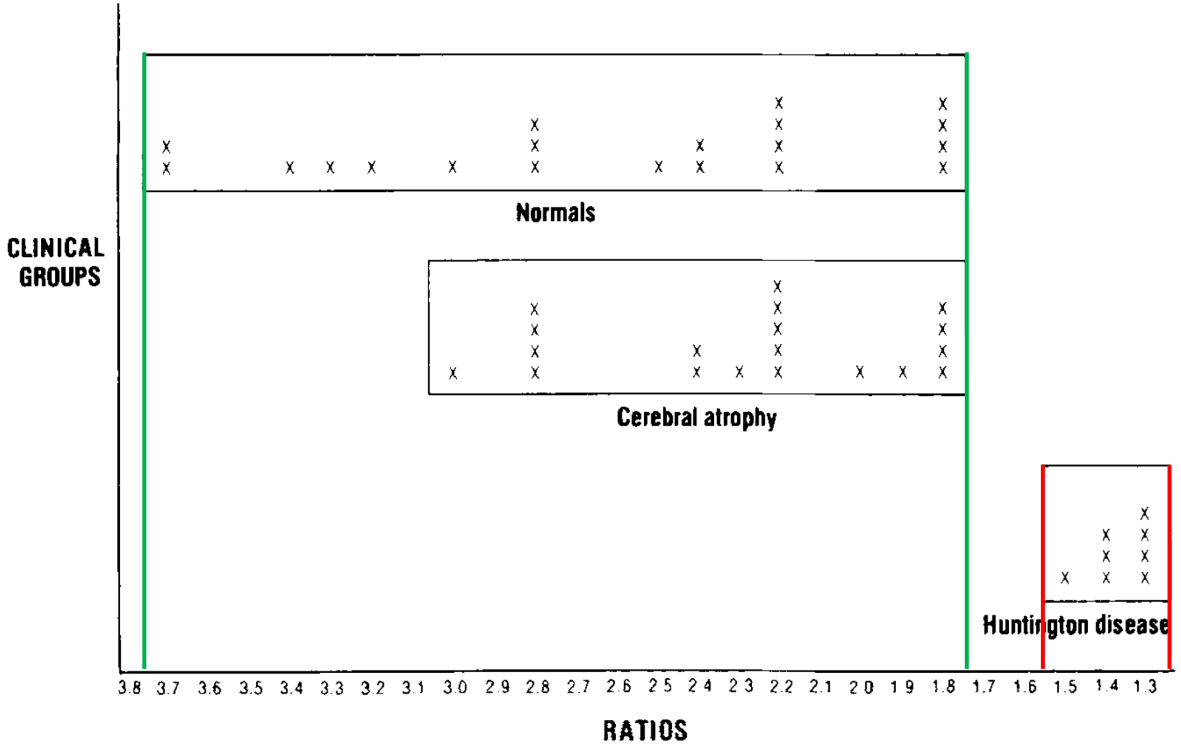


Barr AN et al. Bicaudate index in computerized tomography of Huntington disease and cerebral atrophy. Neurology. 1978 28(11):1196-1200

Normal CC/IT ratio range is 0.09 to 0.12

CT in Huntington disease

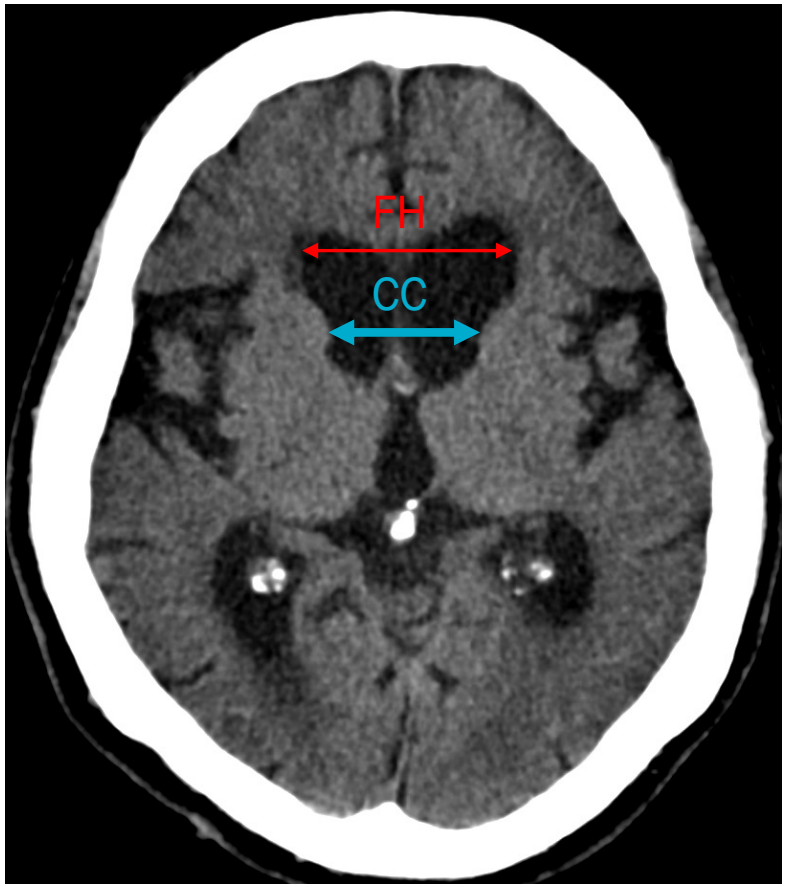
- Evidence of brain atrophy (if MRI is contraindicated)



Barr AN et al. Bicaudate index in computerized tomography of Huntington disease and cerebral atrophy. Neurology. 1978 28(11):1196-1200

Normal mean FH/CC ratio range is 2.2 to 2.6

Frontal horn index (ratio): FH/CC

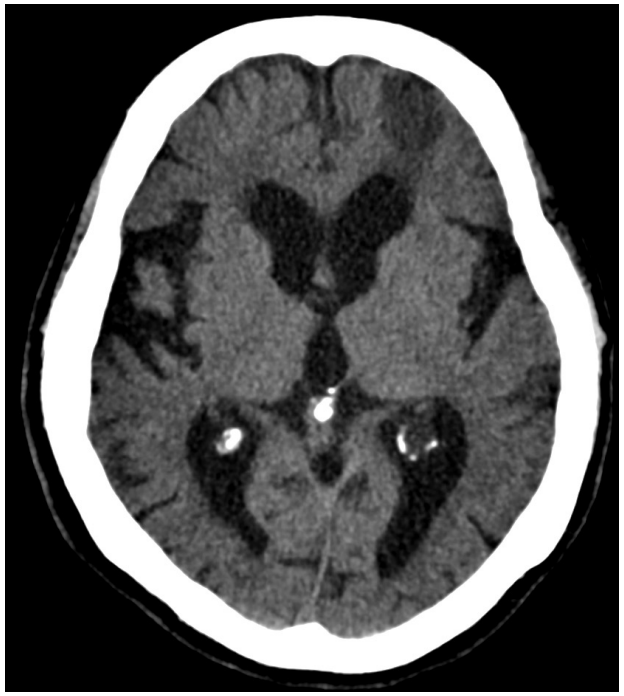


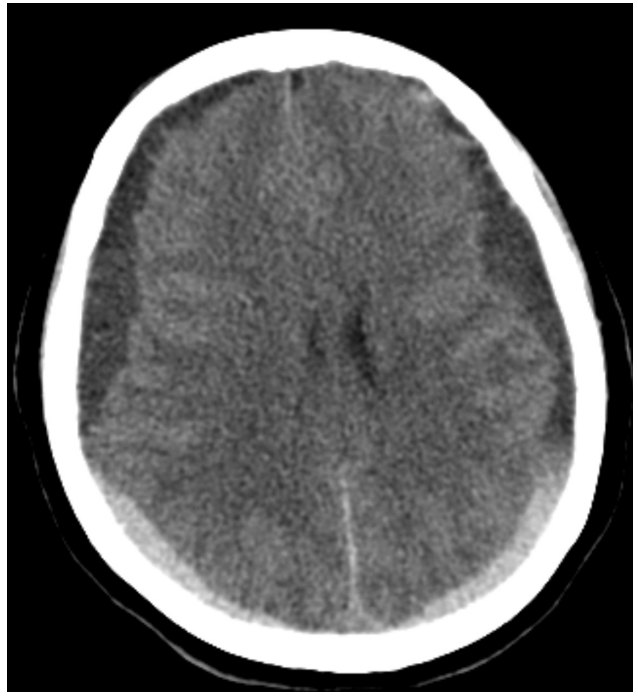
1.4

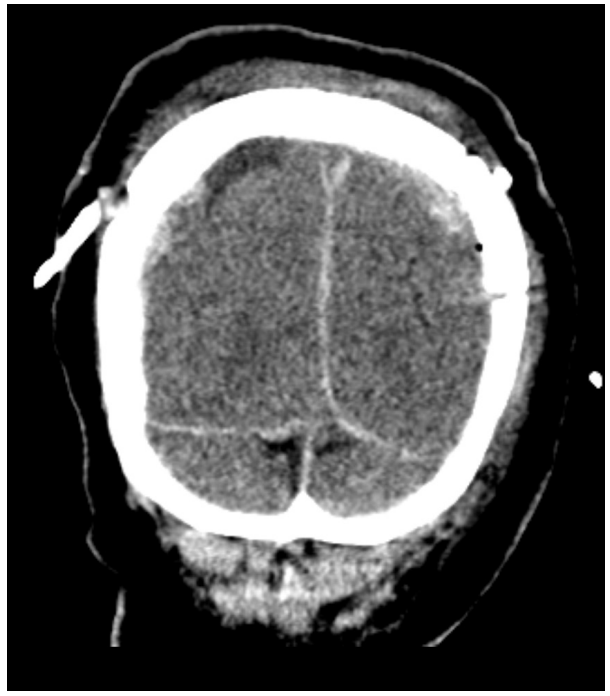
Personal observation

CT in Huntington disease

- Evidence of brain atrophy (if MRI is contraindicated)
- Screening for secondary complications or concomitant conditions (e.g., strokes, subdural hematomas)





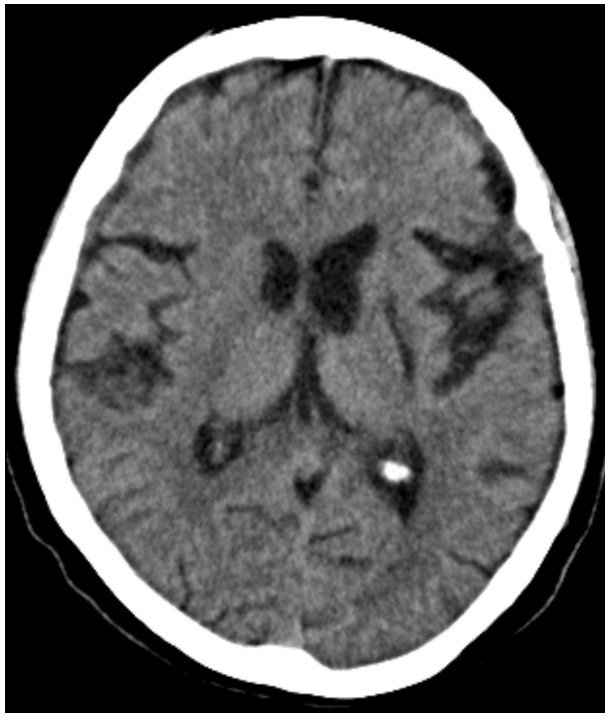


traumatic subdural hematomas and subarachnoid bleeding

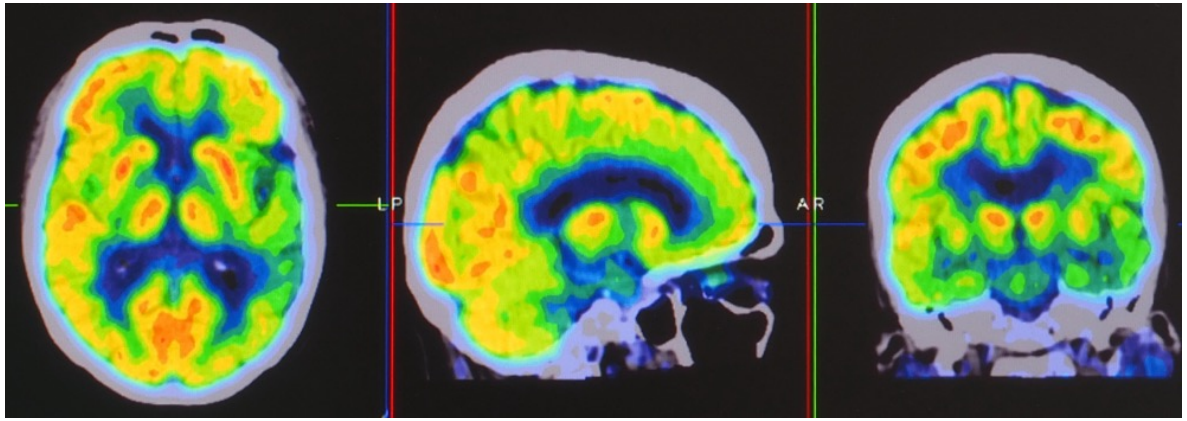
Personal observations

CT in Huntington disease

- Evidence of brain atrophy (if MRI is contraindicated)
- Screening for secondary complications or concomitant conditions (e.g., strokes, subdural hematomas)



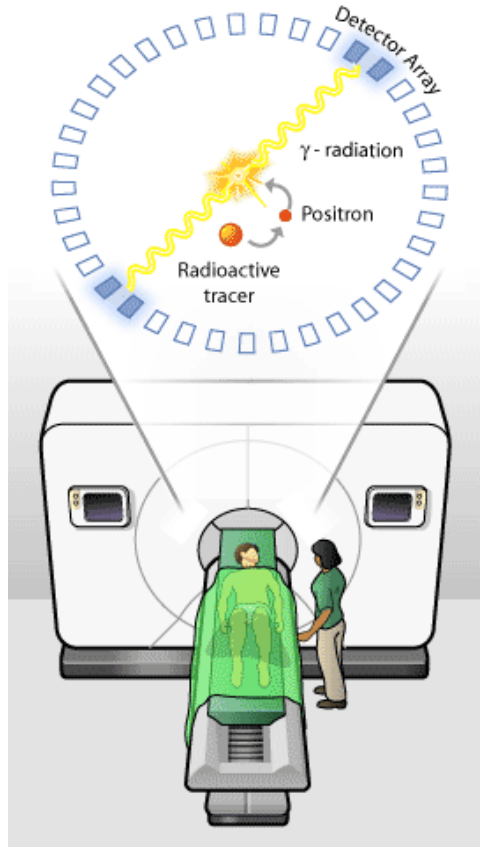
Personal observation



POSITRON EMISSION TOMOGRAPHY

PET LIGANDS USED IN HD

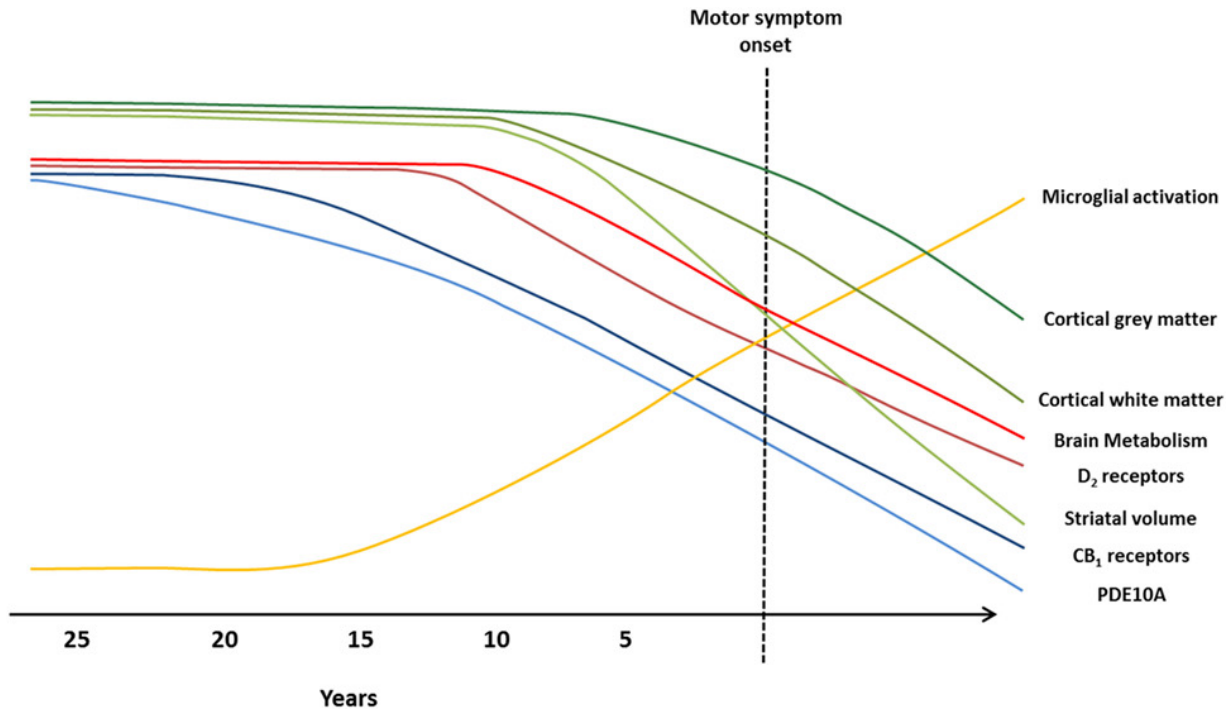
- **^{18}F-FDG**
- $H_2{}^{15}O$ *(tracer for studying brain perfusion)*
- For **dopamine/cannabinoid/** adenosine A_1/opioid/GABA/mGluR receptors
- For **PDE10A** *(coordinates cAMP signaling in striatal medium spiny neurons)*
- For **translocator protein, TSPO** *(located primarily on the outer mt membrane, microglial activation)*
- For **synaptic vesicle protein 2A**
- For **mutant huntingtin aggregates**

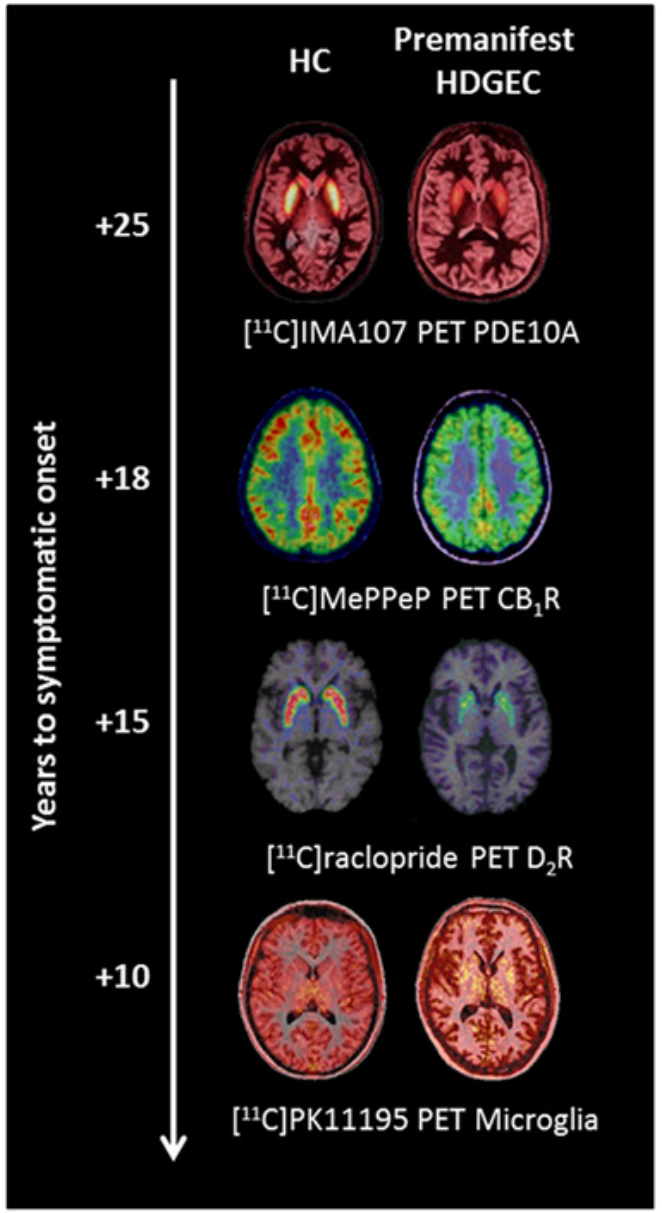


Courtesy of Bioteach at UBC

PET IN HUNTINGTON DISEASE

- Longitudinal studies revealed no changes in glucose metabolism
- Glucose metabolism has been shown to be a less sensitive marker of disease progression compared to [^{11}C]raclopride
- Alterations in PDE10A expression are the earliest biochemical change identified in HD
- Microglial activation alone it is unlikely to act as reliable marker to track HD progression

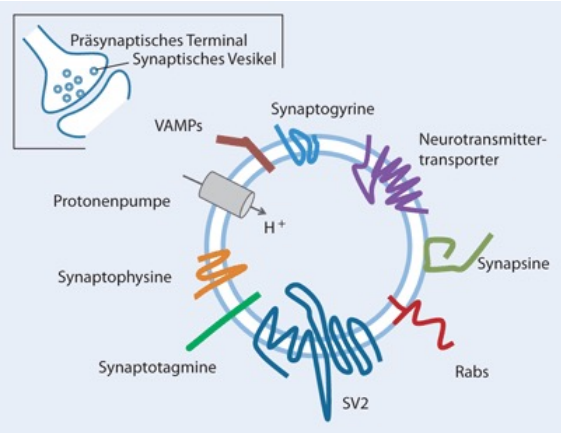




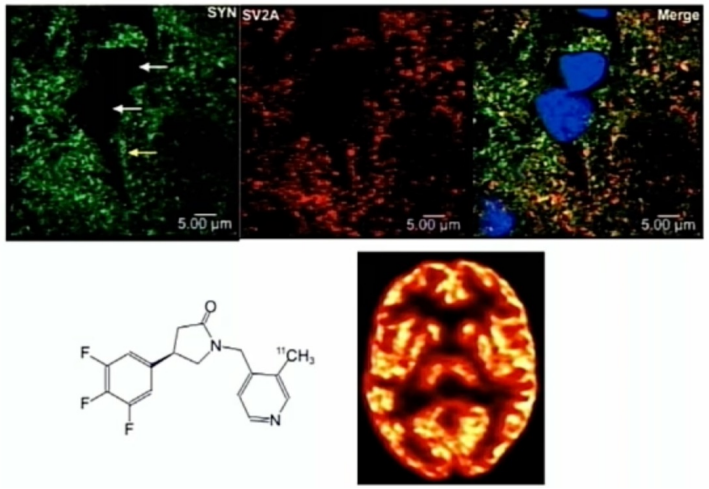
Wilson et al. (2017) Front. Neurol. 8:11

PRESYNAPTIC TERMINAL PET-IMAGING IN EARLY HD

- Q175 knock-in HD mouse: loss of corticostriatal and thalamostriatal terminals prior to MSN degeneration
- Humans: fMRI — impaired connectivity between cortex and striatum
- ^{11}C-UCB-J: PET radioligand for synaptic vesicle protein 2A (SV2A) **= may reflect synaptic density**
- SV2A is ubiquitously present in presynaptic terminals throughout the brain



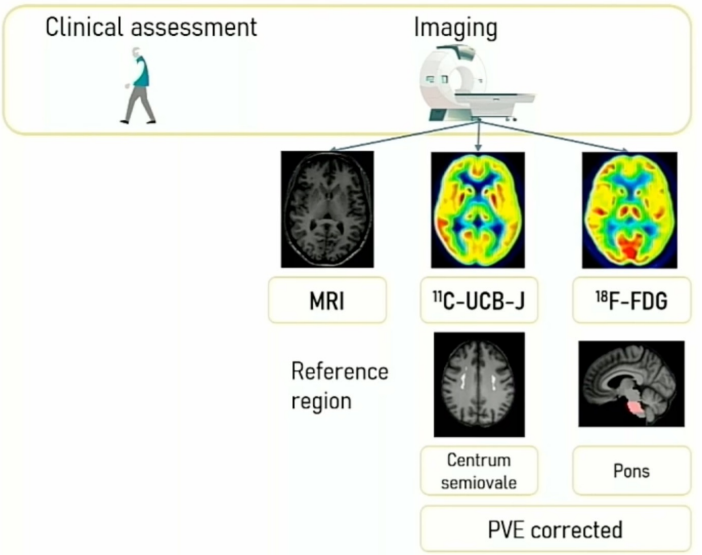
Surges, R., Schoch, S. & Elger, C. *Z. Epileptol.* **25**, 215–221 (2012)



Subjects

18 HD mutation carriers
- 7 premanifest
  - 6 late
  - 1 early
- 11 early manifest
  - 7 stage 1
  - 4 stage 2

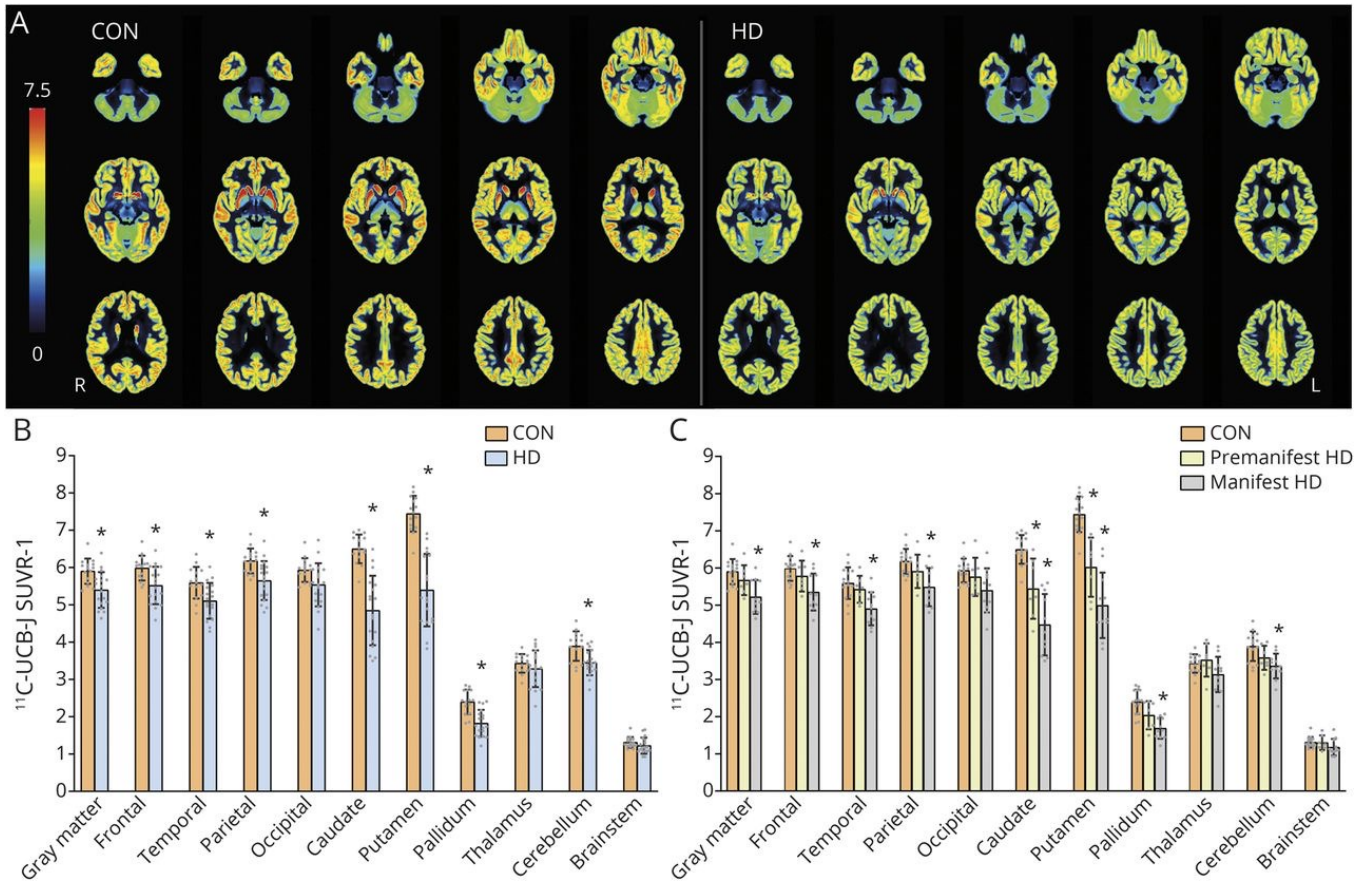
15 Healthy controls
Age- and sex-matched



Delva et al., Neurology Jan 2022, 98 (1) e83-e94

MULTIFOCAL LOSS OF SYNAPTIC INTEGRITY IN EARLY HD

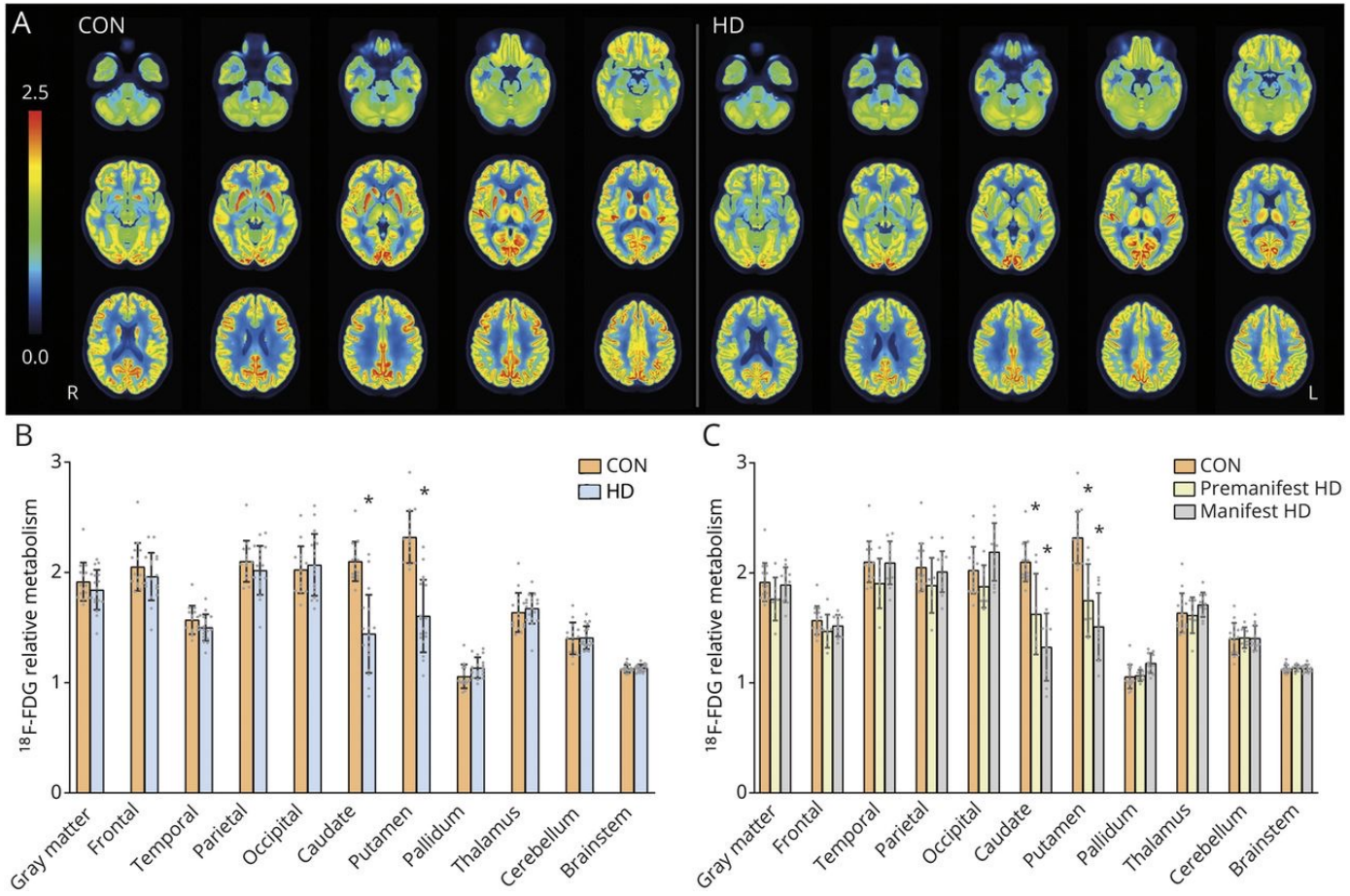
- "Evidence for cortico- and thalamostriatal denervation prior to MSNs degeneration" – hard to say!
- "SV2A loss in the cerebellum"



^{11}C-UCB-J SUVR-1 in HD Mutation Carriers and Controls

^{18}F-FDG-PET IN EARLY HD

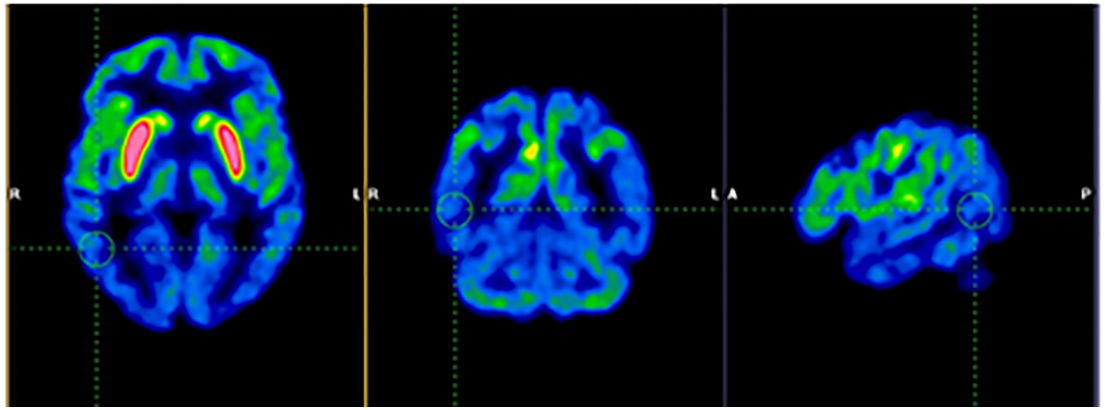
- Strongly reduced signal in the striatum in the HD group
- NO significant changes in pallidum, cerebral cortex, or cerebellum → discrepancy with ^{11}C-UCB-J



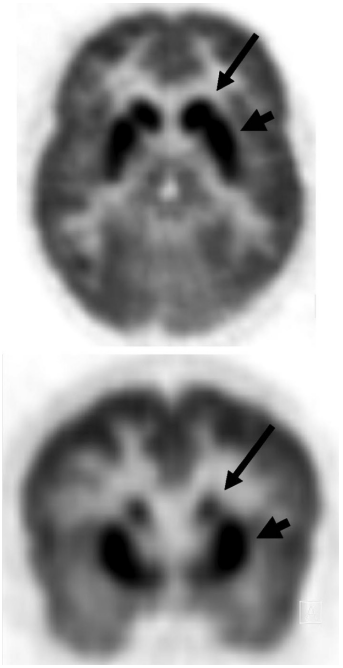
Striatal hypometabolism at has been also documented in other neurodegenerative choreas like chorea-acanthocytosis, McLeod syndrome, SCA-17

^{18}F-FDG-PET IN DIFFERENTIATING BETWEEN DEGENERATIVE AND AUTOIMMUNE CHOREA

- Striatal **hyper**metabolism in autoimmune chorea



Lerjefors, L., Andretta, S., Bonato, G., Mainardi, M., Carecchio, M. and Antonini, A. (2022) Mov Disord Clin Pract, 9: 516-521



Ho, Linh MD. Clinical Nuclear Medicine 34(2):p 114-116

Paraneoplastic (in order of prevalence)

- CRMP-5(CV2)
- ANNA-1(Hu)
- NMDAR
- Uncommon: ANNA-2(Ri), CASPR2, PDE-10A

Systemic disease

- SLE
- PAPS

Idiopathic autoimmune

- NMDAR
- GAD-65
- CASPR2
- LGI1

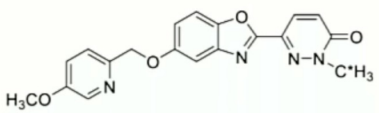
Idiopathic autoimmune and/or neurodegenerative

- IgLON5

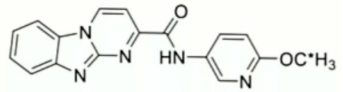
Kyle K, Bordelon Y, Venna N and Linnoila J (2022) Front. Neurol. 13:829076

[^{11}C]CHDI-180R AND [^{11}C]CHDI-626

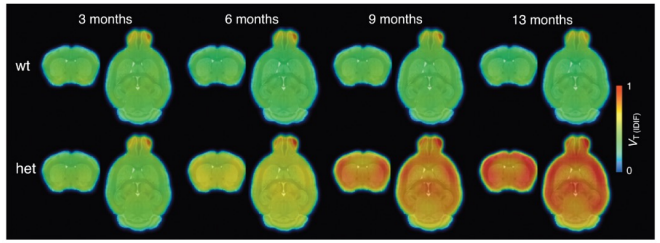
^{11}C-CHDI-180R



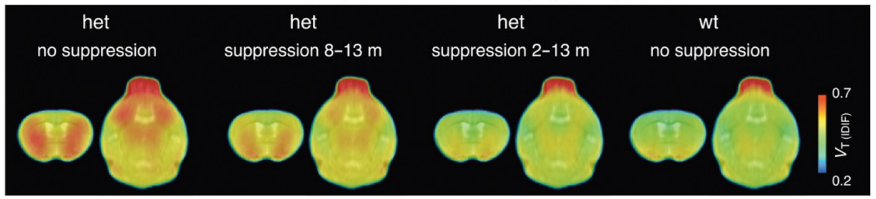
^{11}C-CHDI-626



[^{11}C]CHDI-180R PET imaging (mHtt)



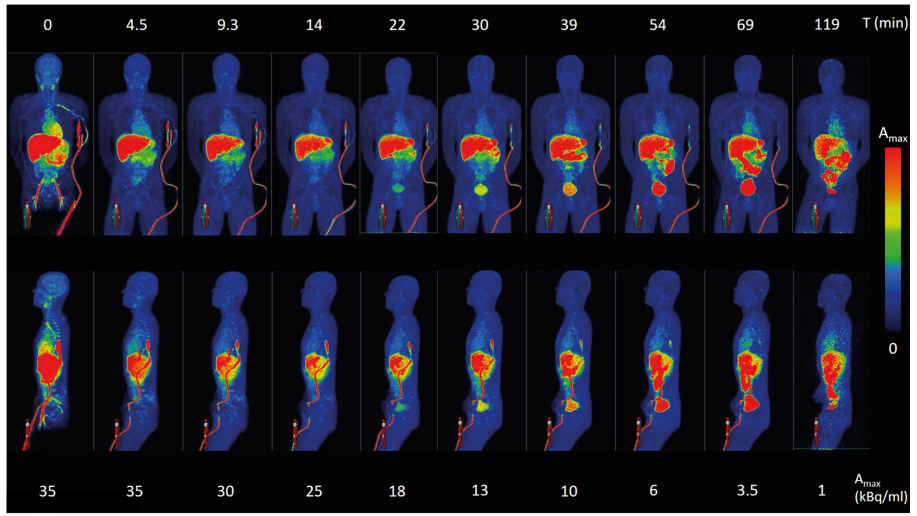
[^{11}C]CHDI-180R PET imaging (mHtt)



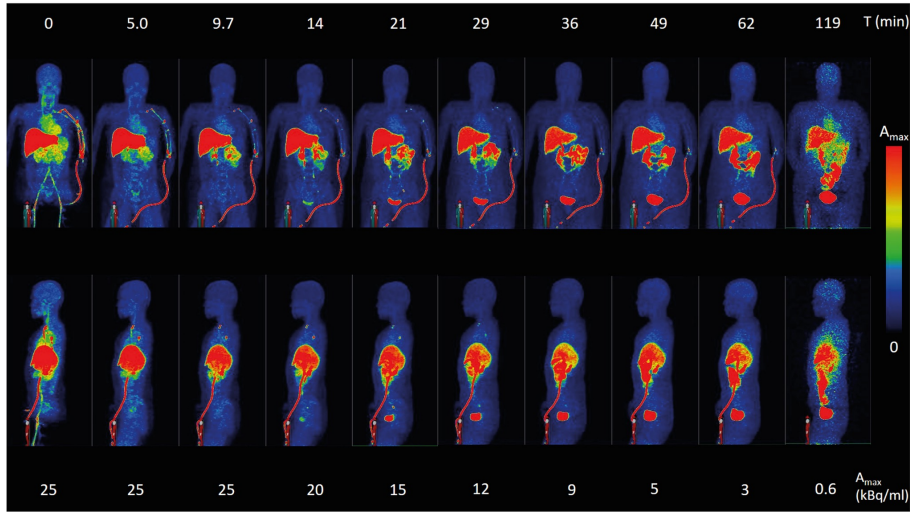
- Are safe for *in vivo* PET imaging in humans
- [^{11}C]CHDI-626 is not suitable for human *in vivo* mHTT PET due to the possibility of a radiometabolite accumulating in brain parenchyma
- **[^{11}C]CHDI-180R has promising kinetic properties in the brain targeting mHTT aggregates**

Whole-body time-activity distribution:

A



B



Delva, A., Koole, M., Serdons, K. *et al. Eur J Nucl Med Mol Imaging* **50**, 48–60 (2022)

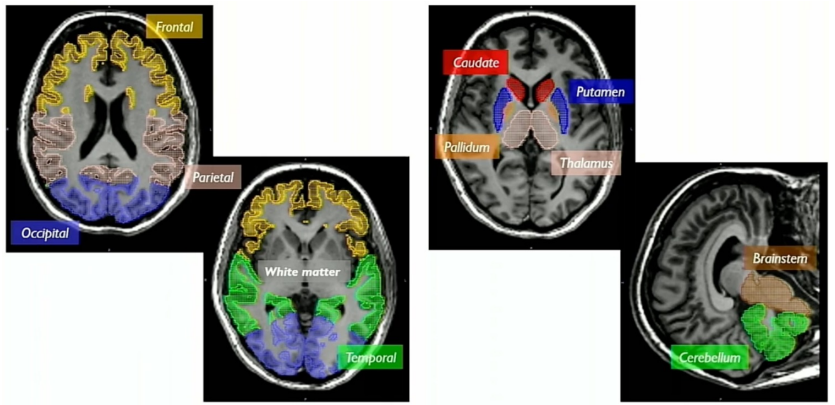
Aline Delva, CHDI's 17th Annual HD Therapeutics Conference, 2022

iMAGE*mHTT:* [^{11}C]CHDI-180R

- First in human evaluation of the radioligand [^{11}C]CHDI-180R targeting aggregated mutant huntingtin (Leuven, Belgium; sponsored by CHDI)

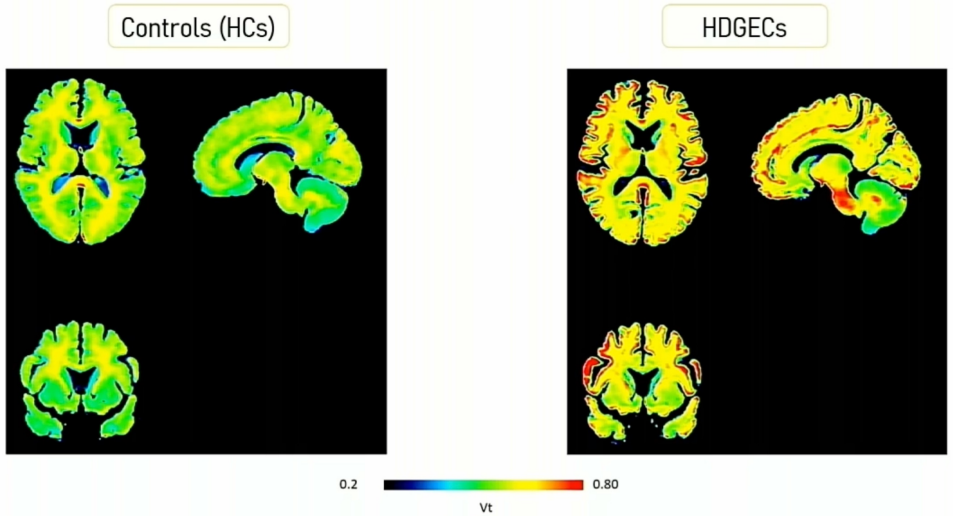
✓ Phase 1	a	3 healthy controls (**HCs**) <35y
	b	3 **HCs** <35y / 6 **stage 2** HD gene expansion carriers (**HDGECs**)
Phase 2	a	6 HCs / 6 **stage 2** HDGECs – **Age matched**
	b	6 HCs / 6 **stage 1** HDGECs – **Age matched**
	c	6 HCs / 6 **premanifest** HDGECs – **Age matched**
		+ test-retest for HDGECs

	HCs (n=6)	HDGECs (n=6)	*p*-value
Age (y)	26.8 ± 3.2	52.2 ± 7.7	< 0.001
F/M	4/2	5/1	NA
$(CAG)_n$ (mutant allele)	-	42.7 ± 1.7	NA
UHDRS total motor	-	26.5 ± 10.4	NA
UHDRS TFC	-	8 ± 1	NA
MoCA	29.2 ± 0.4	21.5 ±2.3	< 0.001
Tracer dose (MBq)	330 ± 53	351 ± 33	0.42

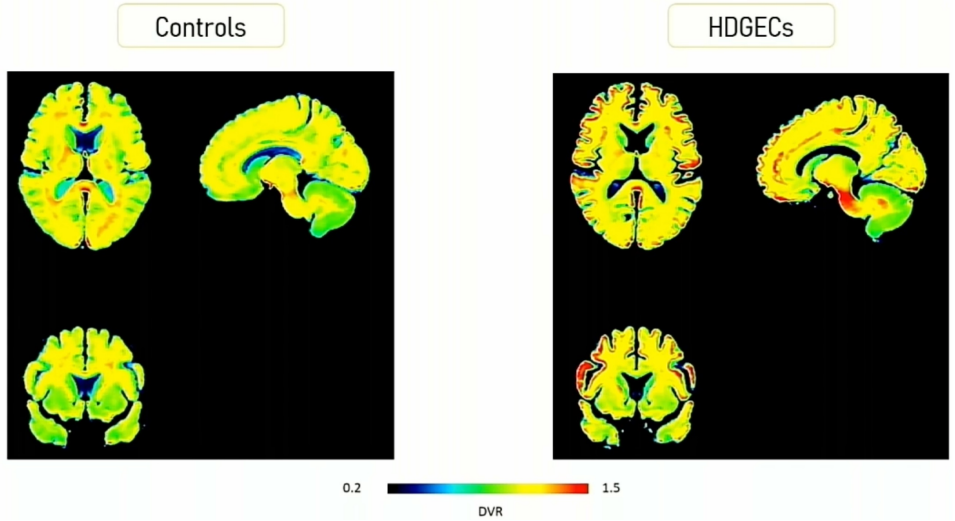


Aline Delva, CHDI's 17th Annual HD Therapeutics Conference, 2022

iMAGE*MHTT:* [^{11}C]CHDI-180R

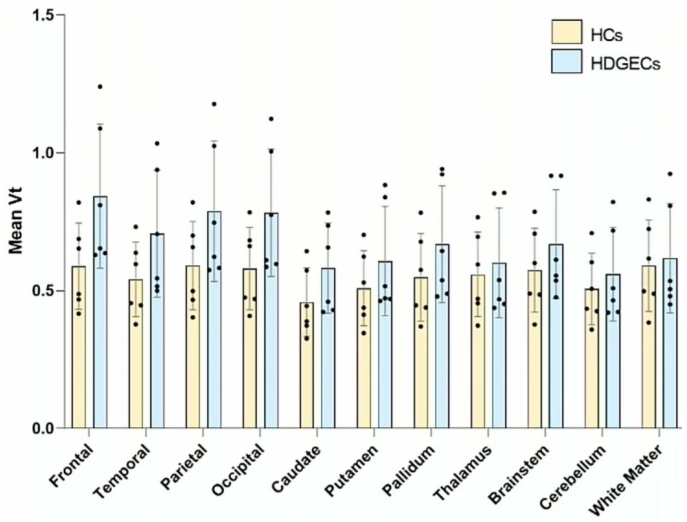


Average Distribution Volume PET images

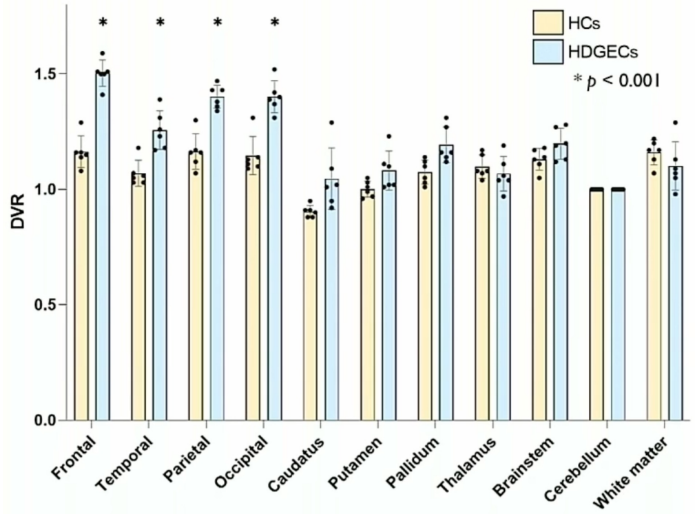


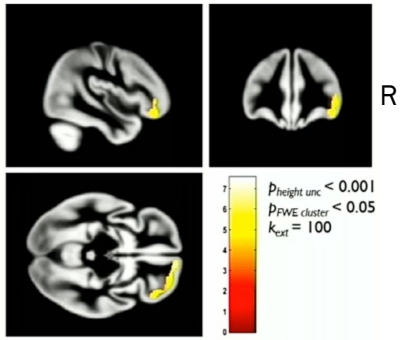
Average Distribution Volume Ratios with cerebellum as pseudo-reference region

Variability and overlap between groups



Significant differences in cerebral cortex





European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

FURTHER DEVELOPMENT…

Study of [^{11}C]CHDI-180R in HDGECs at different stages of the disease with age-matched controls

	^{18}F	↑ $t_{1/2}$	↑ Bmax	↑ HD binding	↓ AD	Status
CHDI-180	^{11}C					
CHDI-009	^{11}C	√	√	√	√	GLP tox
CHDI-650	√	√	-	-	√	Identifying Tox formulation.
CHDI-747	√	√	√	√	√	Pre-tox decision
CHDI-385	√	√	√√	√	√	NHP modeling
CHDI-386	√	√	√	√	√	Radio-chem

Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

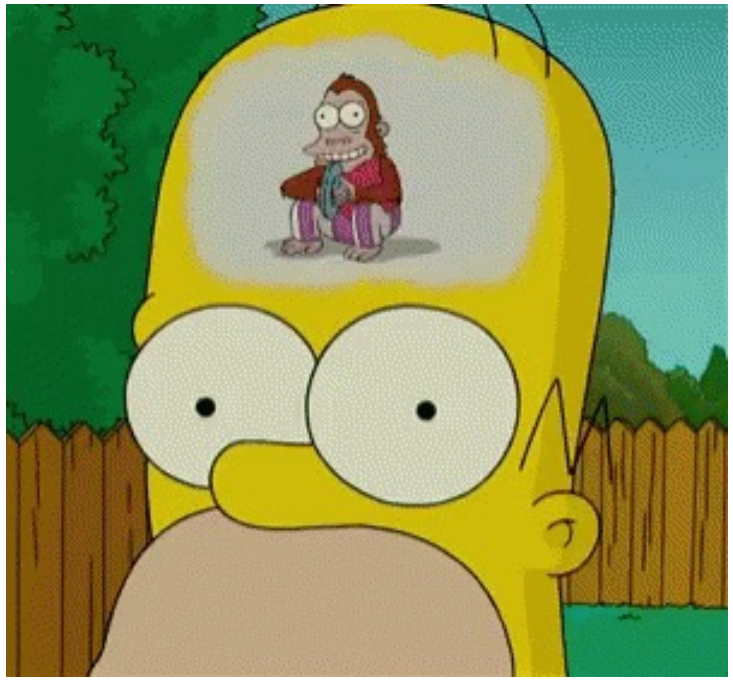
Design and Evaluation of [^{18}F]CHDI-650 as a Positron Emission Tomography Ligand to Image Mutant Huntingtin Aggregates

Published as part of the Journal of Medicinal Chemistry virtual special issue "Diagnostic and Therapeutic Radiopharmaceuticals".

Longbin Liu,* Peter D. Johnson,* Michael E. Prime, Vinod Khetarpal, Christopher J. Brown, Luca Anzillotti, Daniele Bertoglio, Xuemei Chen, Samuel Coe, Randall Davis, Anthony P. Dickie, Simone Esposito, Elise Gadouleau, Paul R. Giles, Catherine Greenaway, James Haber, Christer Halldin, Scott Haller, Sarah Hayes, Todd Herbst, Frank Herrmann, Manuela Heßmann, Ming Min Hsai, Yaser Khani, Adrian Kotey, Angelo Lembo, John E. Mangette, Gwendolyn A. Marriner, Richard W. Marston, Matthew R. Mills, Edith Monteagudo, Anton Forsberg-Morén, Sangram Nag, Laura Orsatti, Christine Sandiego, Sabine Schaertl, Joanne Sproston, Steven Staelens, Jack Tookey, Penelope A. Turner, Andrea Vecchi, Maria Veneziano, Ignacio Muñoz-Sanjuan, Jonathan Bard, and Celia Dominguez*

Cite This: *J. Med. Chem.* 2023, 66, 641−656 Read Online

Time for follow-up testing?



QUESTION 1

To diagnose Huntington disease, it is essential to perform:

a. Brain MRI
b. Brain PET with ligands to mutant huntingtin
c. DATSCAN
d. Brain imaging is not part of a mandatory workup in HD

QUESTION 1

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a. Brain MRI

b. Brain PET with ligands to mutant huntingtin

c. DATSCAN

d. Brain imaging is not part of a mandatory workup in HD

QUESTION 2

In Huntington disease, brain MRI may show everything except:

a. Striatal atrophy
b. Cortical atrophy
c. T2-/T2*-/SWI-hypointensity from the basal ganglia
d. Prominent infratentorial atrophy

QUESTION 2

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QUESTION 3

Routinely, the following PET study may be conducted in HD patients:

a. FDG-PET
b. PET with ligands to mutant huntingtin
c. PET with ligands to PDE10A
d. PET with ligands to activated microglia markers

QUESTION 3

Routinely, the following PET study may be conducted in HD patients:

a. **FDG-PET**
b. PET with ligands to mutant huntingtin
c. PET with ligands to PDE10A
d. PET with ligands to activated microglia markers

QUESTION 4

In differentiating autoimmune (non-HD) chorea, PET is practically useless:

a. False

b. True

QUESTION 4

In differentiating autoimmune (non-HD) chorea, PET is practically useless:

a. **False**

b. True

THANK YOU!