29 febrer 2016 DIA MUNDIAL DE LES MALALTIES MINORITÀRIES

Recerca de biomarcadors a la malaltia de Huntington preclínica

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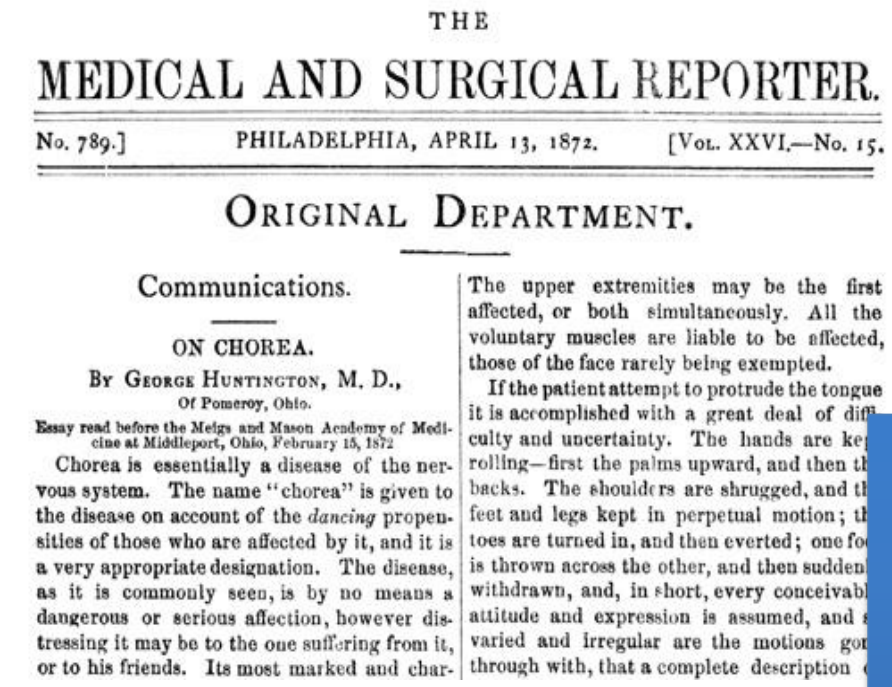
Unitat de Parkinson i Trastorns del Moviment.
Servei de Neurologia
Hospital Clínic de Barcelona

MALALTIA DE HUNTINGTON



THE

MEDICAL AND SURGICAL REPORTER.

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

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

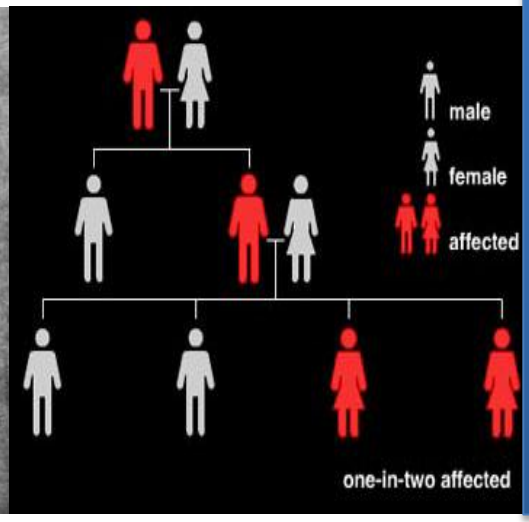
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

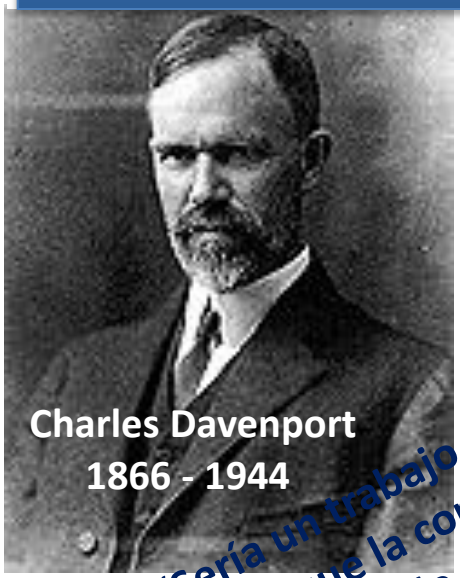
The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of diff- culty and uncertainty. The hands are ke rolling—first the palms upward, and then th backs. The shoulders are shrugged, and th feet and legs kept in perpetual motion; th toes are turned in, and then everted; one fo is thrown across the other, and then sudden withdrawn, and, in short, every conceivabl attitude and expression is assumed, and varied and irregular are the motions go through with, that a complete description



- Malaltia hereditària autosòmica dominant. Risc: 50% de la descendència
- Edat mitja d'inici: 35-40 anys (2-80 anys)
- Alt grau de dependència als 10 anys d'inici Supervivència mitja: 20 anys
- Prevalença: 5-10 per 100.000 hab. Catalunya: 350-700 casos ??

“Todos estos diablos de nuestro estudio proceden de una media docena de individuos con tres hermanos incluidos, que migraron (desde Inglaterra) a este país durante el siglo XVII. Sí esta media docena de individuos hubieran sido mantenidos alejados de este país se habría evitado mucha miseria” (Charles Davenport, New England)

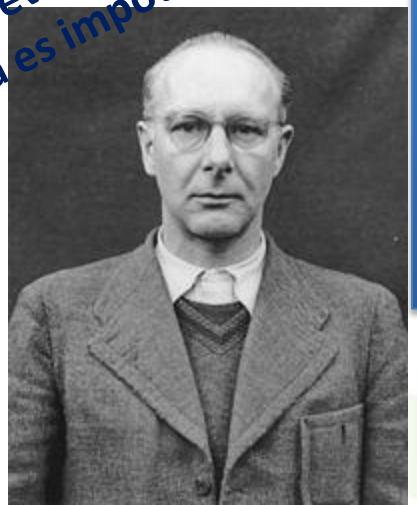


Charles Davenport
1866 - 1944

“Sería un trabajo de filantropía esterilizar a todos aquellos en los que la corea crónica ya se haya desarrollado y asegurarse de que aquellos descendientes que muestran síntomas prematuramente no se reproduzcan..... Un Estado que conoce quienes son sus coreicos y sabe que la mitad de los hijos de cada uno de ellos (de media) llegará a ser coreico y no hace las cosas obvias para prevenir la propagación de esta horrible enfermedad hereditaria es impotente, estúpido, ciego e invita al desastre” (Davenport and Muncey, 1916)

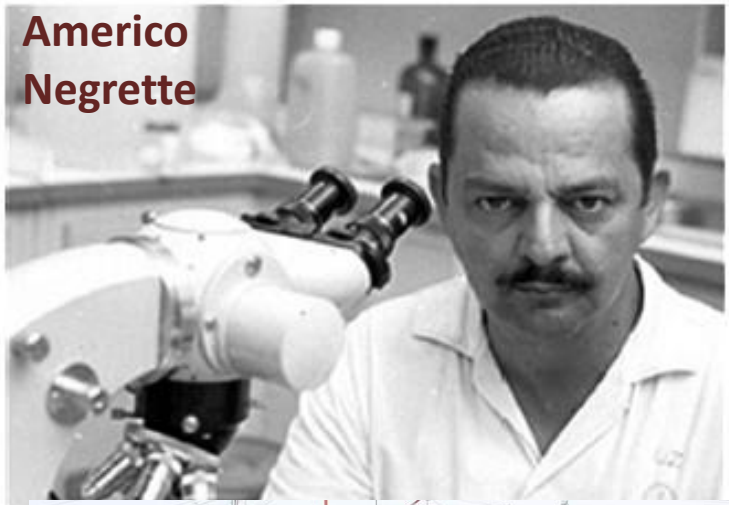
Nazi propaganda for their compulsory euthanasia program. **'This person suffering from hereditary defects costs the community 60,000 reichsmark during his lifetime. Fellow German, that is your money too.'**

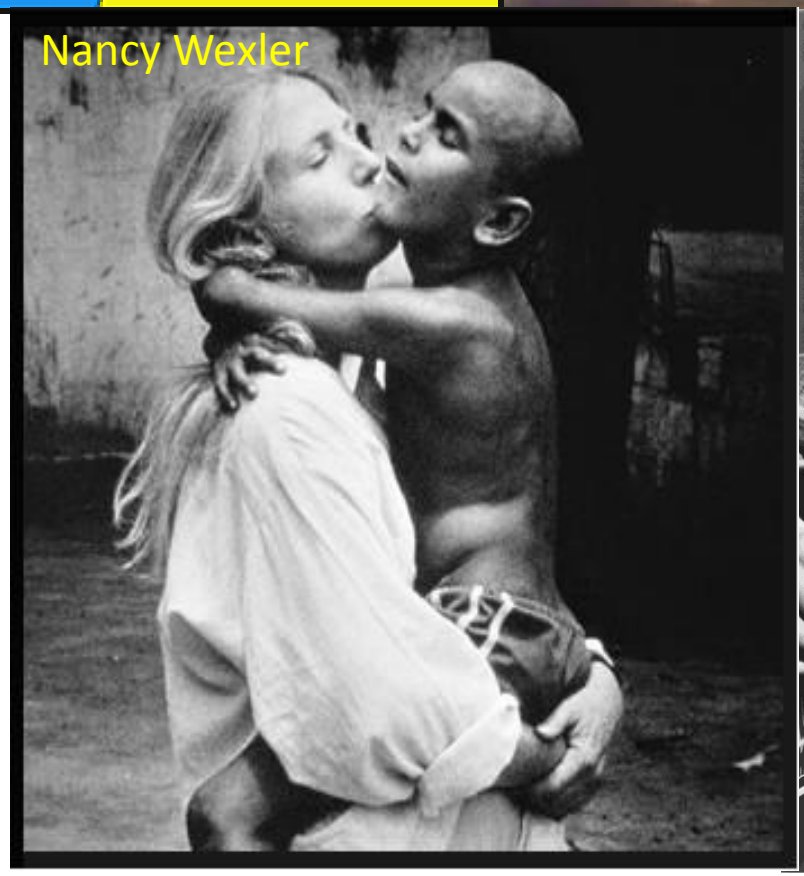
During the official stage of Action T4, **70,273 people were killed**

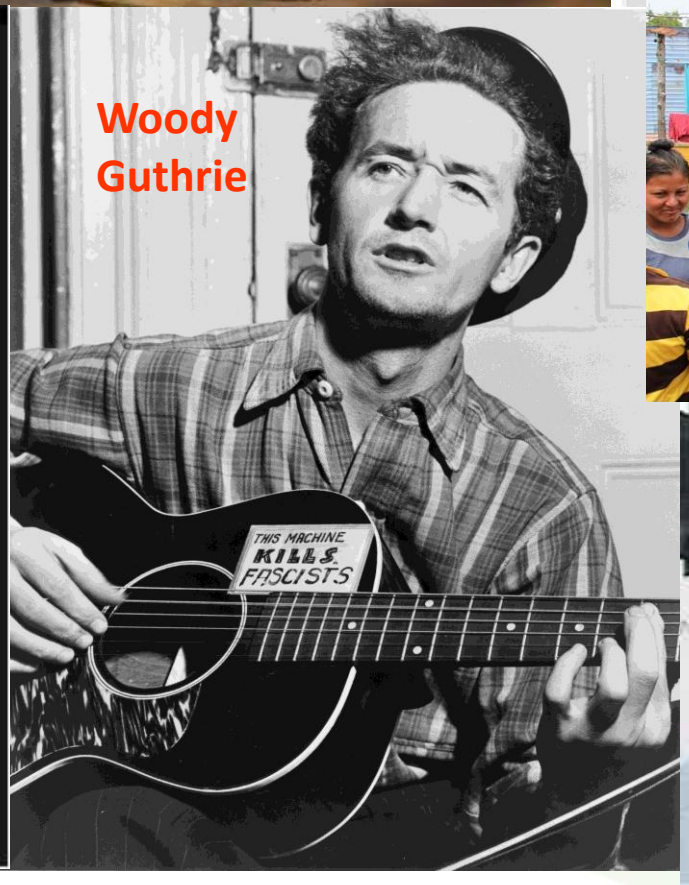


Viktor Brack
organiser of the **T4 Programme**

Venezuela
Colombia
Colombia
Maracaibo
Venezuela
Lake Maracaibo


Americo
Negrette


Nancy Wexler


Woody
Guthrie
THIS MACHINE
KILLS
FASCISTS

James F. Gusella

CLINICA

Trastorns motors

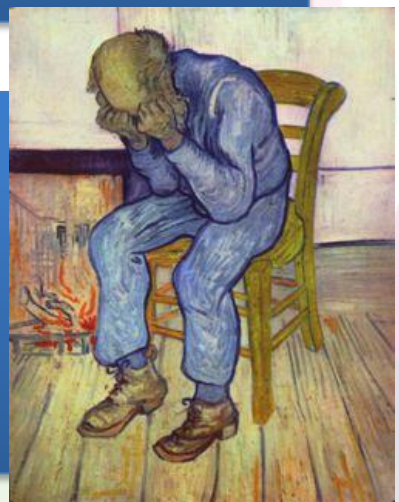
- Corea
- Distonia
- Lentitud motora
- Trastorn de la marxa
- Pèrdua d'equilibri
- Tics
- Mioclònies
- Disàrtria
- Disfàgia

Deteriorament cognitiu

- Funcions executives
- Alt. visuoespacials
- Memòria
- Llenguatge

Trastorns psiquiàtrics

- Canvis personalitat
- Depressió, ansietat, apatia, obsessions, psicosi

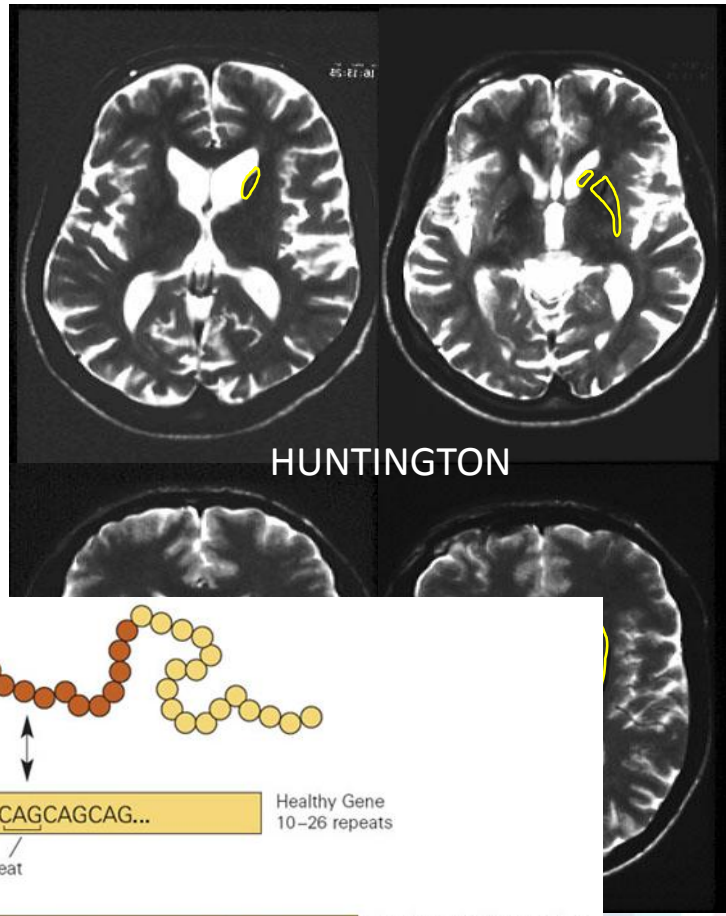


DIAGNÒSTIC

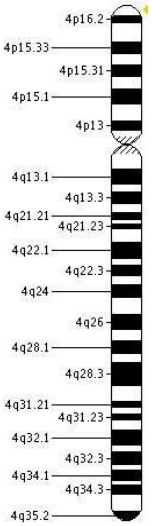
Clínic

Trastorns motors
Alteracions psiquiàtriques
Deteriorament cognitiu
Herència

Neuroimatge

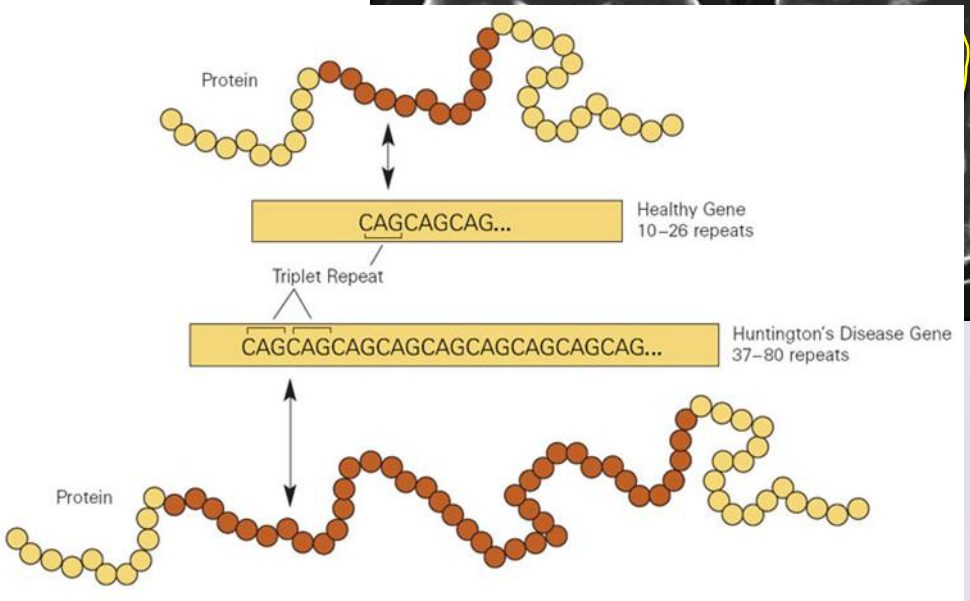


Genètic



Gen *HTT*.
CAGCAGCAGCAGCAGCAG....

- ≤ 29: Normal
- 30-34: Al·lel premutat
- 35-39: Reduïda penetrància
- ≥ 40: Afecte



TRACTAMENTS

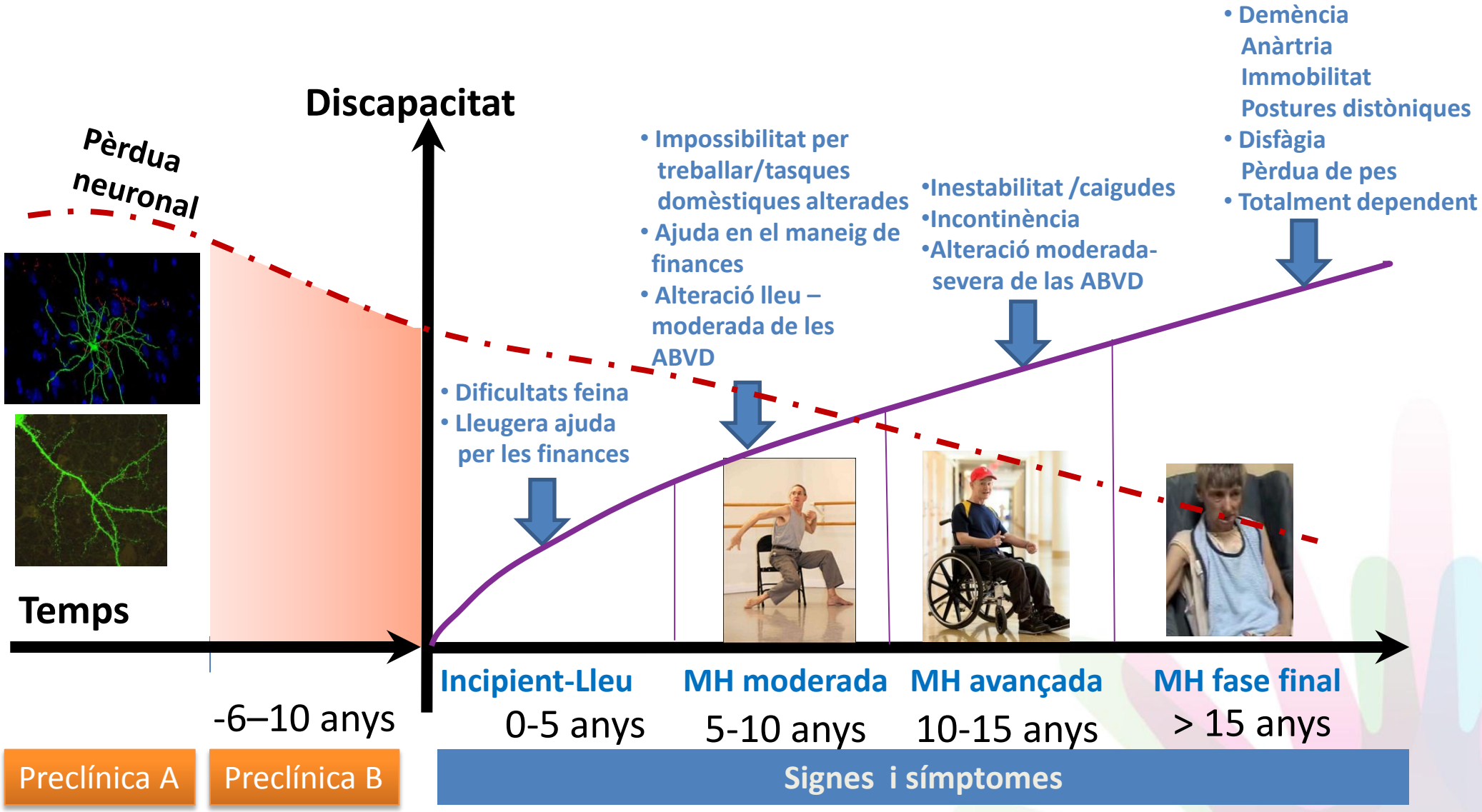
1. Simptomàtics

   - Farmacològics
   - Estimulació cerebral profunda
   - Fisioteràpia, teràpia cognitiva, ocupacional, logopèdia

2. Modificadors del curs de la malaltia

   - Tractaments “neuroprotectors”
   - Teràpia cel·lular
   - Teràpia gènica

EVOLUCIÓ DE LA DISCAPACITAT EN LA MH



CONCEPTE de BIOMARCADOR

- **Indicador** de la presència d'una malaltia que proporciona informació sobre el seu grau d'afectació des dels estadis preclínics fins les fases avançades.

- **Característiques ideals**:

  ✓Quantificable
  ✓Reproduïble
  ✓Fàcil
  ✓Barat
  ✓Técnica no invasiva

- **"Utilitat" principal**: Avaluar l'eficàcia de tractaments que potencialment podrien modificar l'inici i la progressió de la malaltia.

POTENCIALS BIOMARCADORS

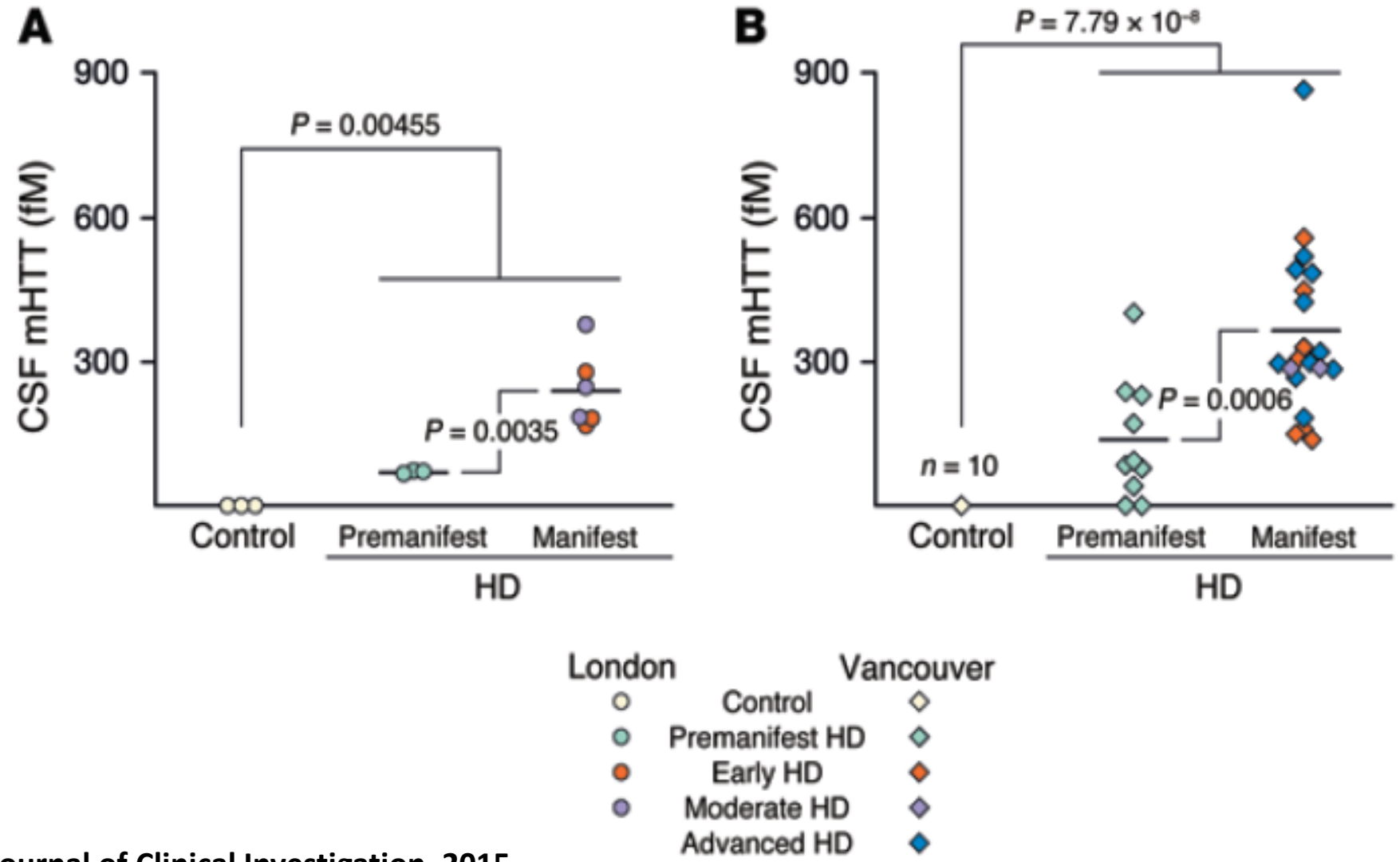
- Clínics: Test d'avaluació motora, cognitiva i de la conducta.

  - ✓Avantatges: Generalment barats
    Fàcils de realitzar
    Rarament requereixen aparells sofisticats
    Poden proporcionar una millor caracterització de la variabilitat fenotípica.
  - ✓Desavantatges: Potencial variabilitat intra i inter-avaluador.

- Neuroimatge
  - ✓Potencialment sensibles a la detecció d'alteracions estructurals, funcionals o metabòliques.
  - ✓No invasives .
  - ✓Els resultats poden ser reproduïbles o duplicats i poden enviar-se quasi instantàniament al centre de referència per a ser analitzats.

- Bioquímics

DETERMINACIÓ DE LA HUNTINGTINA MUTADA AL LCR



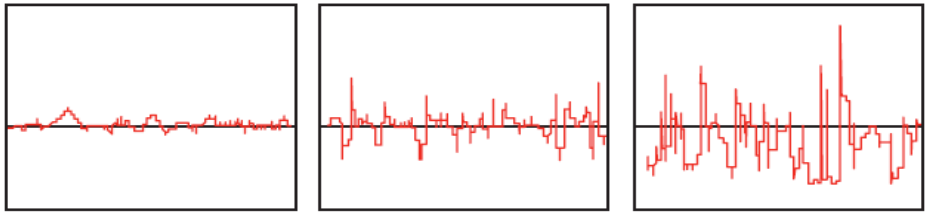
Wild et al. Journal of Clinical Investigation, 2015

Bradicinèsia i disrítmia en el “tapping” digital

Variabilitat de la força de prensió

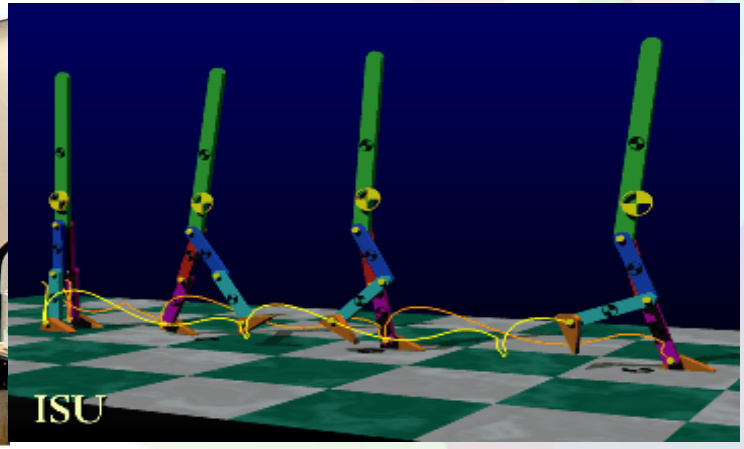
BIOMARCADORS CLÍNICS

B Tongue force



Variabilitat de la longitud de pas

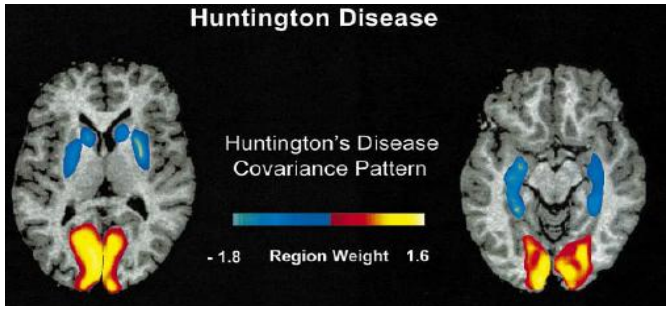
Impersistència motora de la protrusió lingual

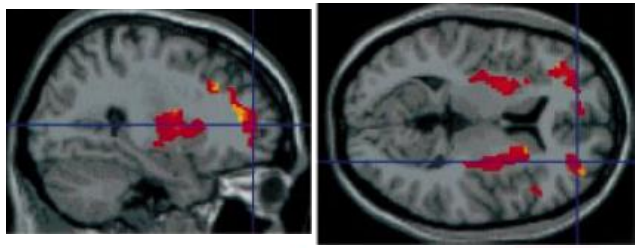


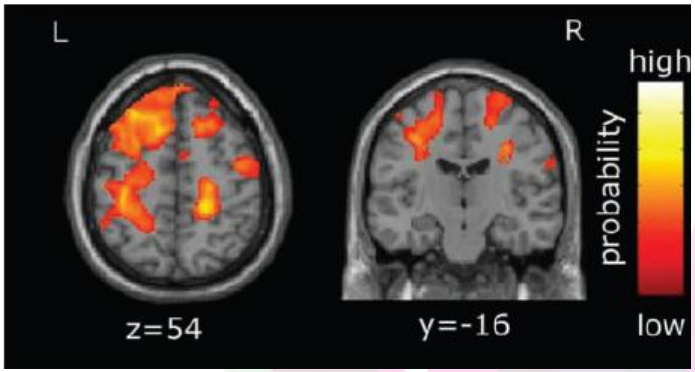
David W Weir, Aaron Sturrock*, Blair R Leavitt. Lancet Neurol. 2011*

BIOMARCADORS DE NEUROIMATGE

- ESTRUCTURALS I METABOLICS (RM)
  - Estudis volumètrics
  - Estudis de difusió
  - Estudis espectroscòpics
- FUNCIONALS
  - Ressonància magnètica funcional
  - Tomografia de emissió de positrons (PET)

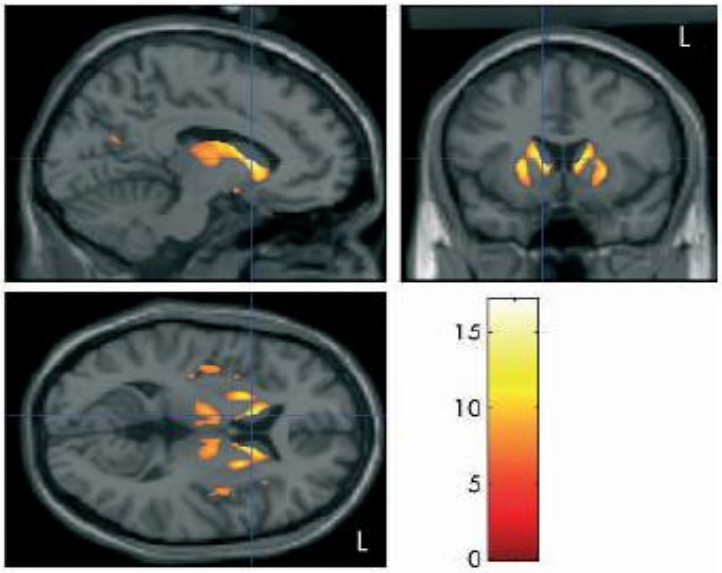


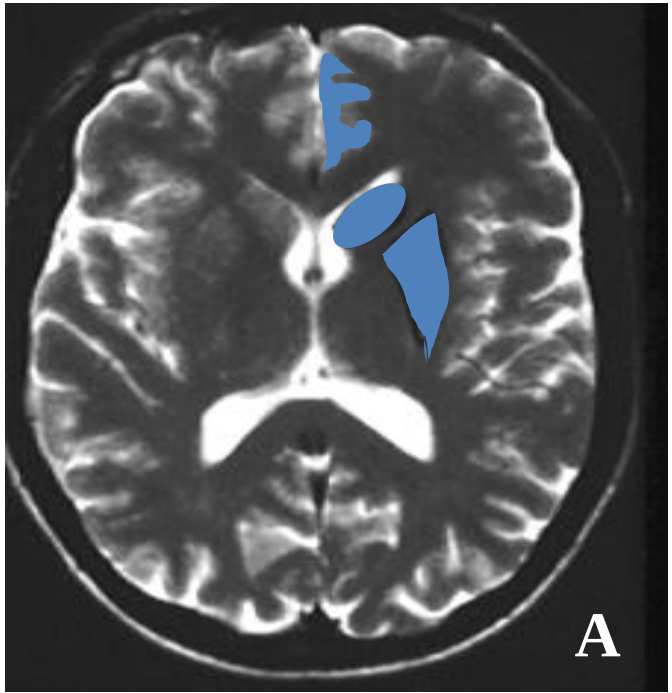


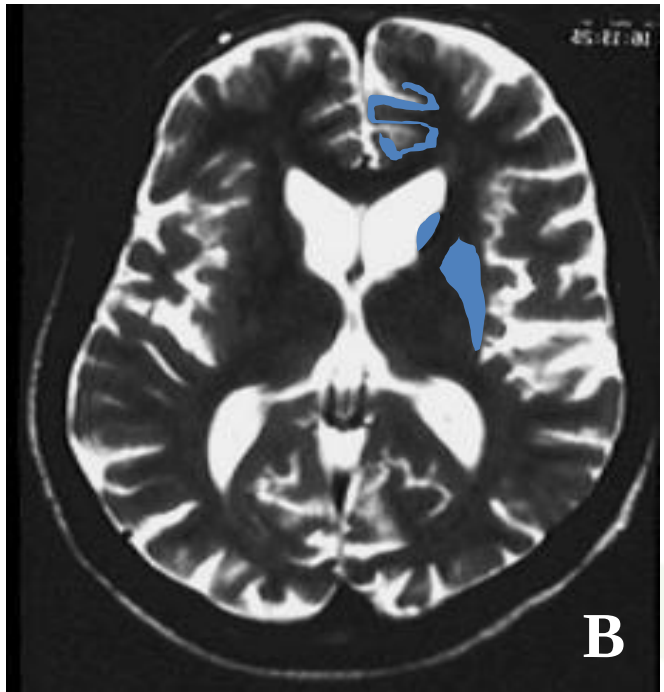


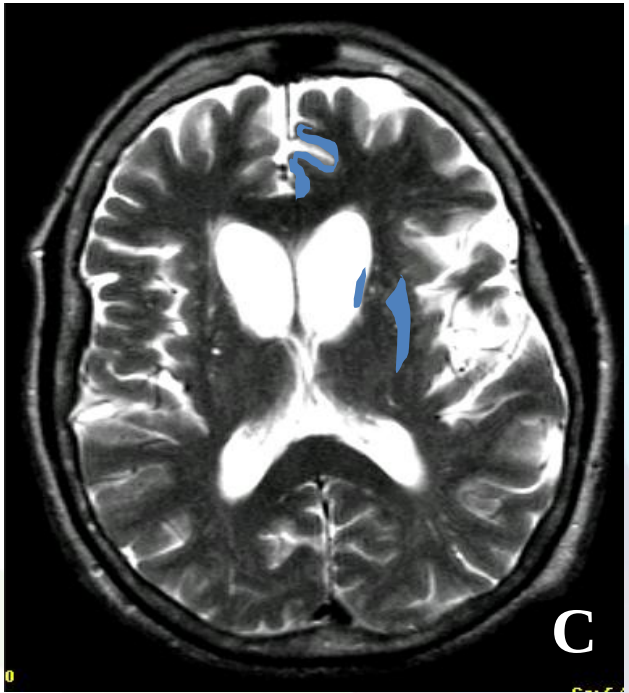
Estudis volumètrics

- ROI (regions of interest)
- VBM (voxel morphometry)
- Grossor cortical
- Substància blanca cerebral









Estudis volumètrics en subjectes presimptomàtics

Table 2. Results from General and Regional Brain Structure Analysis Means (SD) in Cubic Centimeters

	PreHD (n = 24)	Control Subjects (n = 24)	F	p
General Measures[a]				
Intracranial volume	1.403 (135.3)	1.413 (169.8)	.1	.723
Total brain tissue	1.263 (124.1)	1.302 (162.4)	.4	.532
Cerebral volume	1.227 (123.6)	1.223 (151.2)	.5	.465
Cerebellar volume	125.7 (12.5)	127.1 (15.2)	.0	.953
Total CSF	140.5	110.7	4.9	.032
CSF Measures[b]				
Infratentorial CSF	19.1 (4.83)	19.6 (7.85)	0.04	.850
Supratentorial CSF	121.4 (56.9)	94.1 (36.1)	5.2	.027
Surface CSF	102.3 (52.2)	75.6 (33.2)	5.0	.030
Ventricular CSF	19.1 (20.45)	18.4 (6.85)	0.4	.520
Cerebral Measures[b]				
Gray matter (cortex)	635.4 (71.3)	588.8 (70.3)	40.85	<.0001
White matter	420.2 (49.7)	455.9 (79.5)	22.20	<.0001
Subcortical Structures[c]				
Caudate	4.55 (1.11)	5.23 (0.77)	10.6	.002
Putamen	6.36 (1.44)	8.93 (1.46)	44.03	<.0001
Thalamus	11.8 (1.14)	12.4 (1.90)	5.8	.019

Paulsen et al. Brain Structure in Preclinical Huntington's Disease. Biol Psychiatry 2006

Parkinsonism and Related Disorders 15 (2009) 213–219

Prefrontal cortex volume reduction on MRI in preclinical Huntington's disease relates to visuomotor performance and CAG number

B. Gómez-Ansón [a,b,*], M. Alegret [c], E. Muñoz [b,d,f], G.C. Monté [e], E. Alayrach [e], A. Sánchez [b,g], M. Boada [c], E. Tolosa [b,d,f]

Table 1
Demographic and clinical data of preclinical HD carriers ($n = 20$) and controls ($n = 21$)

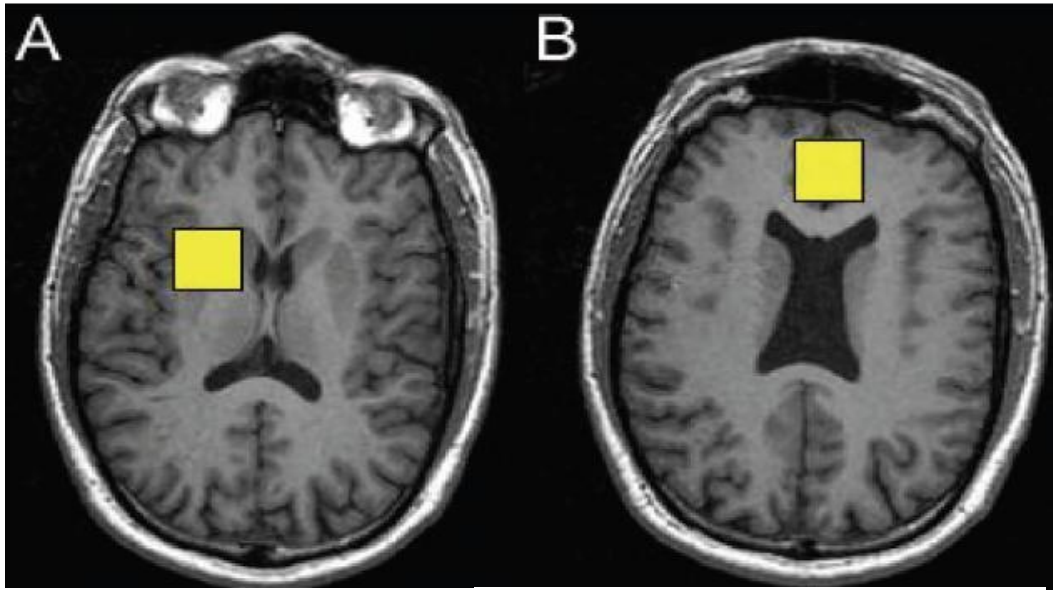
	Preclinical HD carriers		Controls
	Motor-UHDRS = 0	Motor-UHDRS > 0	
Number	12	8	21
Gender	6M/6F	5M/3F	11M/10F
Age	32.4 ± 9.4	34 ± 8.6	33.2 ± 8.8
CAG	42.8 ± 1.6	45.5 ± 3.6[a]	–
UHDRS motor score	0	4.9 ± 2.9	–

[a] $p \leq 0.05$, Student's t-test.

Decreased frontal choline and neuropsychological performance in preclinical Huntington disease

B. Gómez-Ansón, MD, PhD, FRCR; M. Alegret, PhD; E. Muñoz, MD, PhD; A. Sainz; G.C. Monte; and E. Tolosa, MD, PhD

NEUROLOGY 2007;68:906–910



17 PreHD
17 Controles

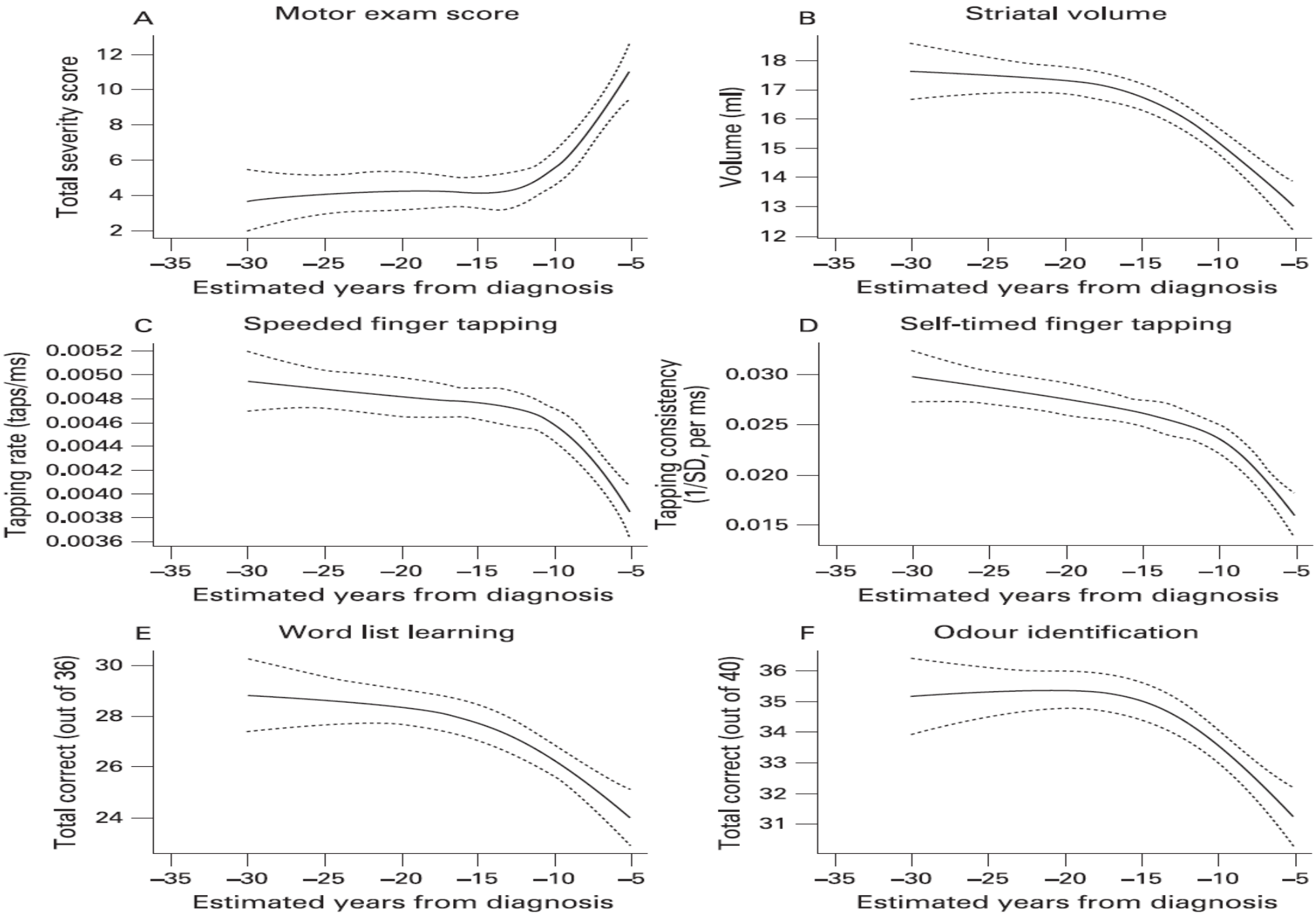
Metabolites
NAA
CRE
CHO P=0.008
INO
GLU
GLN
(GLU+GLN+GABA)−(GLU+GLN)

Test
The 15-Objects Test (seconds) p =0.0001
RAVLT total trials
Rey Complex Figure
Luria motor alternances (dominant hand)
Luria motor alternances (nondominant hand)
Luria motor alternances (right + left)
Stroop Interference
Trail Making B
Phonetic verbal fluency
Semantic verbal fluency
Arithmetic WAIS-III
Stroop Reading
Stroop Naming
Trail Making A
Symbol Digit WAIS-III
Judgment of Line Orientation
Beck Depression Questionnaire
Leyton

ESTUDIS DE BIOMARCADORS A LA MALALTIA DE HUNTINGTON

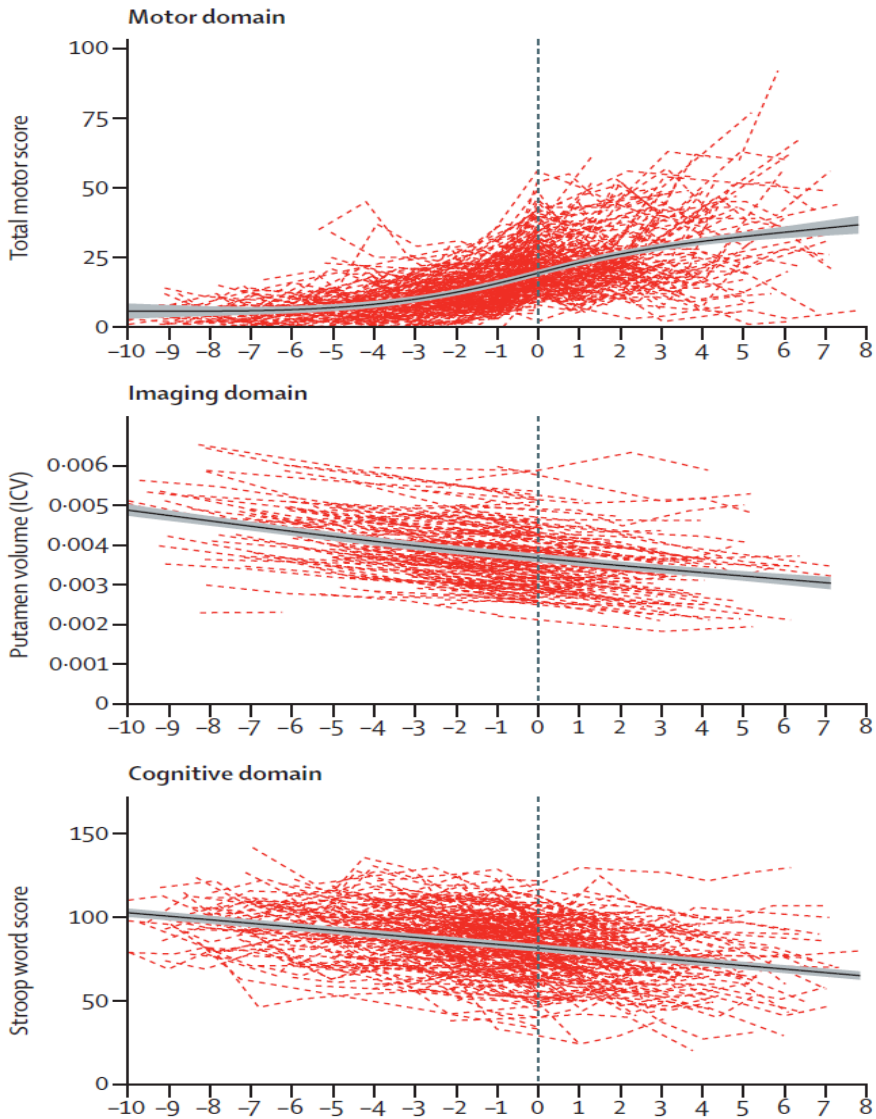
PREDICT: The objective of the Predict-HD study is to use genetic, neurobiological and refined clinical markers to understand the early progression of Huntington's disease (HD), prior to the point of traditional diagnosis, in persons with a known gene mutation.

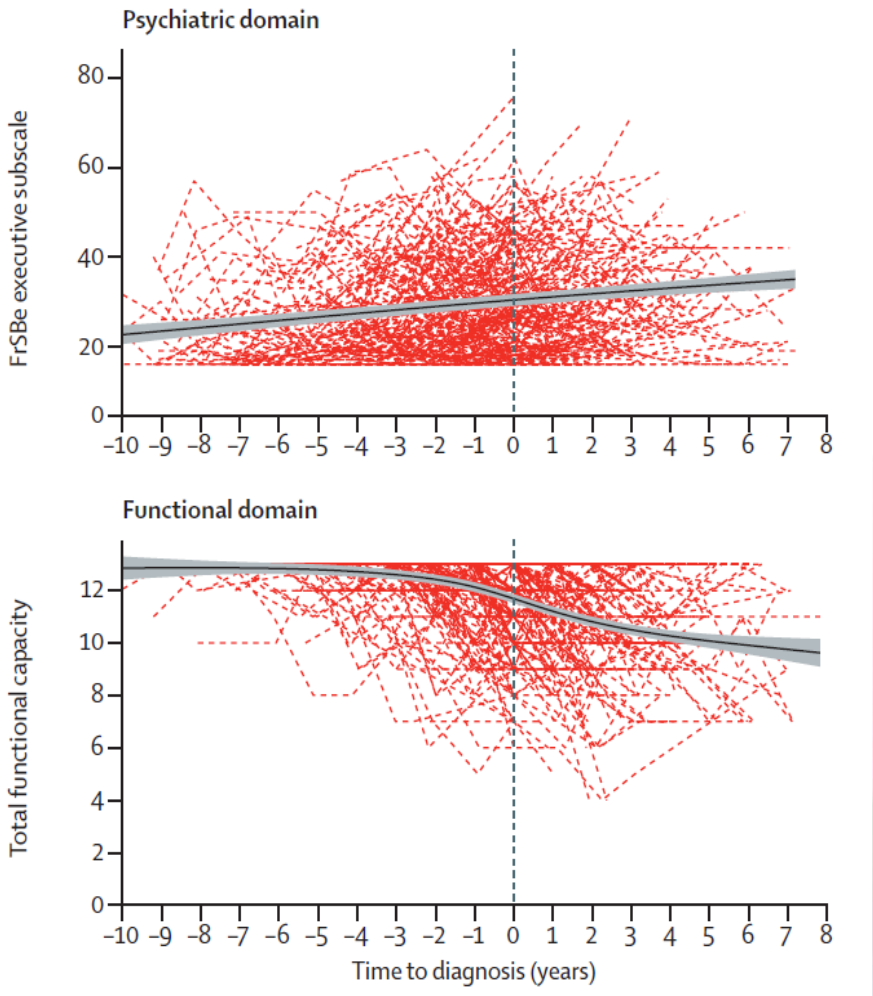
TRACK-HD is a multinational prospective observational study of Huntington's disease (HD) that examines clinical and biological findings of disease progression in individuals with premanifest HD (preHD) and early-stage HD.


A
Motor exam score
Total severity score
12
10
8
6
4
2
–35 –30 –25 –20 –15 –10 –5
Estimated years from diagnosis
B
Striatal volume
Volume (ml)
18
17
16
15
14
13
12
–35 –30 –25 –20 –15 –10 –5
Estimated years from diagnosis
C
Speeded finger tapping
Tapping rate (taps/ms)
0.0052
0.0050
0.0048
0.0046
0.0044
0.0042
0.0040
0.0038
0.0036
–35 –30 –25 –20 –15 –10 –5
Estimated years from diagnosis
D
Self-timed finger tapping
Tapping consistency (1/SD, per ms)
0.030
0.025
0.020
0.015
–35 –30 –25 –20 –15 –10 –5
Estimated years from diagnosis
E
Word list learning
Total correct (out of 36)
30
28
26
24
–35 –30 –25 –20 –15 –10 –5
Estimated years from diagnosis
F
Odour identification
Total correct (out of 40)
36
35
34
33
32
31
–35 –30 –25 –20 –15 –10 –5
Estimated years from diagnosis

Prediction of manifest Huntington's disease with clinical and imaging measures: a prospective observational study

Lancet Neurol 2014; 13: 1193–201





N=1078 presimptomàtics → 225 simptomàtics

Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data

Sarah J Tabrizi, Douglas R Langbehn, Blair R Leavitt, Raymund A C Roos, Alexandra Durr, David Craufurd, Christopher Kennard, Stephen L Hicks, Nick C Fox, Rachael I Scahill, Beth Borowsky, Allan J Tobin, H Diana Rosas, Hans Johnson, Ralf Reilmann, Bernhard Landwehrmeyer, Julie C Stout, and the TRACK-HD investigators

Lancet Neurol 2009; 8: 791–801

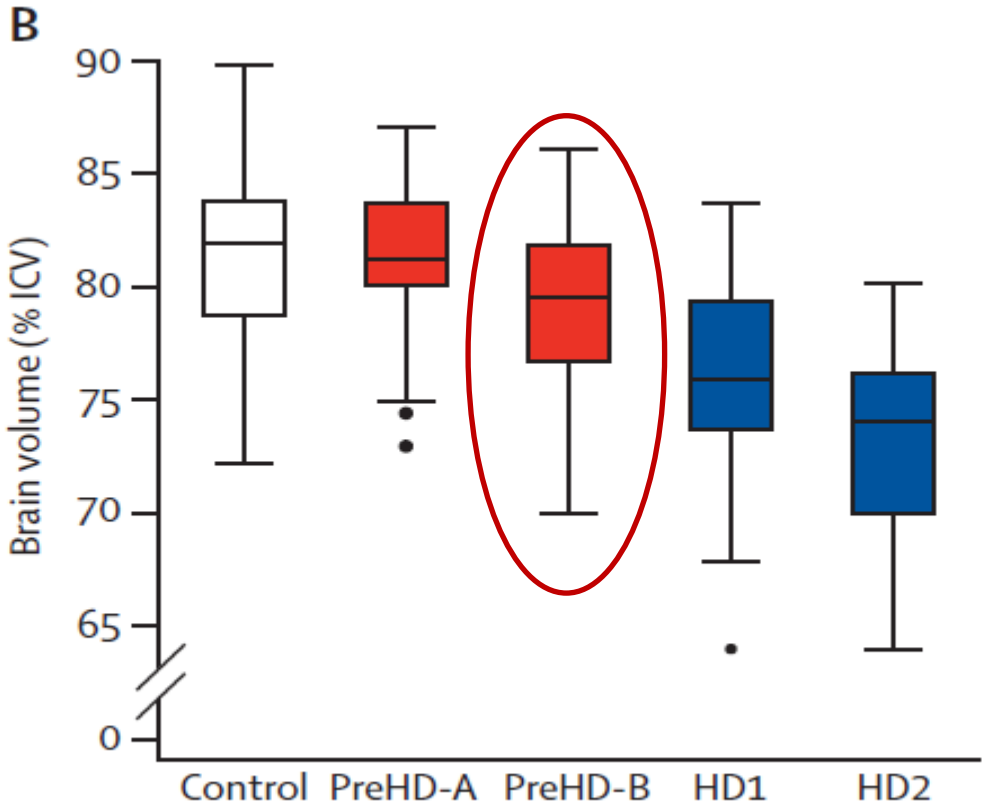
	Controls (n=123)	PreHD			HD		
		PreHD-A (n=62)	PreHD-B (n=58)	Combined (n=120)	HD1 (n=77)	HD2 (n=46)	Combined (n=123)
Age (years)	46·1 (10·2, 23·0–65·7)	41·1 (8·6, 18·6–59·4)	40·6 (9·2, 22·3–64·1)	40·8 (8·9, 18·6–64·1)	47·2 (10·3, 22·8–64·1)	51·4 (8·6, 33·3–63·3)	48·8 (9·9, 22·8–64·1)
Women	68 (55%)	33 (53%)	33 (57%)	66 (55%)	46 (60%)	21 (46%)	67 (55%)
Education (years)	4·0 (1·3)	4·1 (1·1)	3·8 (1·3)	3·9 (1·2)	3·8 (1·3)	3·2 (1·4)	3·6 (1·3)
Disease-burden score*	..	259·1 (30·1)	333·1 (30·0)	294·8 (47·7)	364·1 (74·3)	397·6 (67·5)	376·6 (73·3)
Centres							
Leiden	30	16	14	30	16	14	30
London	30	14	16	30	19	11	30
Paris	30	14	16	30	26	4	30
Vancouver	33	18	12	30	16	17	33

Data are mean (SD, range) or number (%). *Disease-burden score=age×(CAG length–35·5).

Table 1: Demographics of the TRACK-HD participants at baseline

PreHD-A > 10 anys per l'inici teòric
PreHD-B < 10 anys per l'inici teòric

	PreHD vs controls	HD vs controls	PreHD vs HD	PreHD-A vs controls	PreHD-B vs preHD-A	HD1 vs PreHD-B	HD2 vs HD1
Neuroimaging measures							
Whole brain volume	-1·84% (-2·70 to -0·98) p<0·0001	-5·94% (-6·79 to -5·09) p<0·0001	-4·09% (-4·99 to -3·20) p<0·0001	-0·68% (-1·71 to 0·35) p=0·20	-2·41% (-3·6 to -1·21) p<0·0001	-2·23% (-3·40 to -1·06) p=0·0002	-1·61% (-2·87 to -0·34) p=0·01



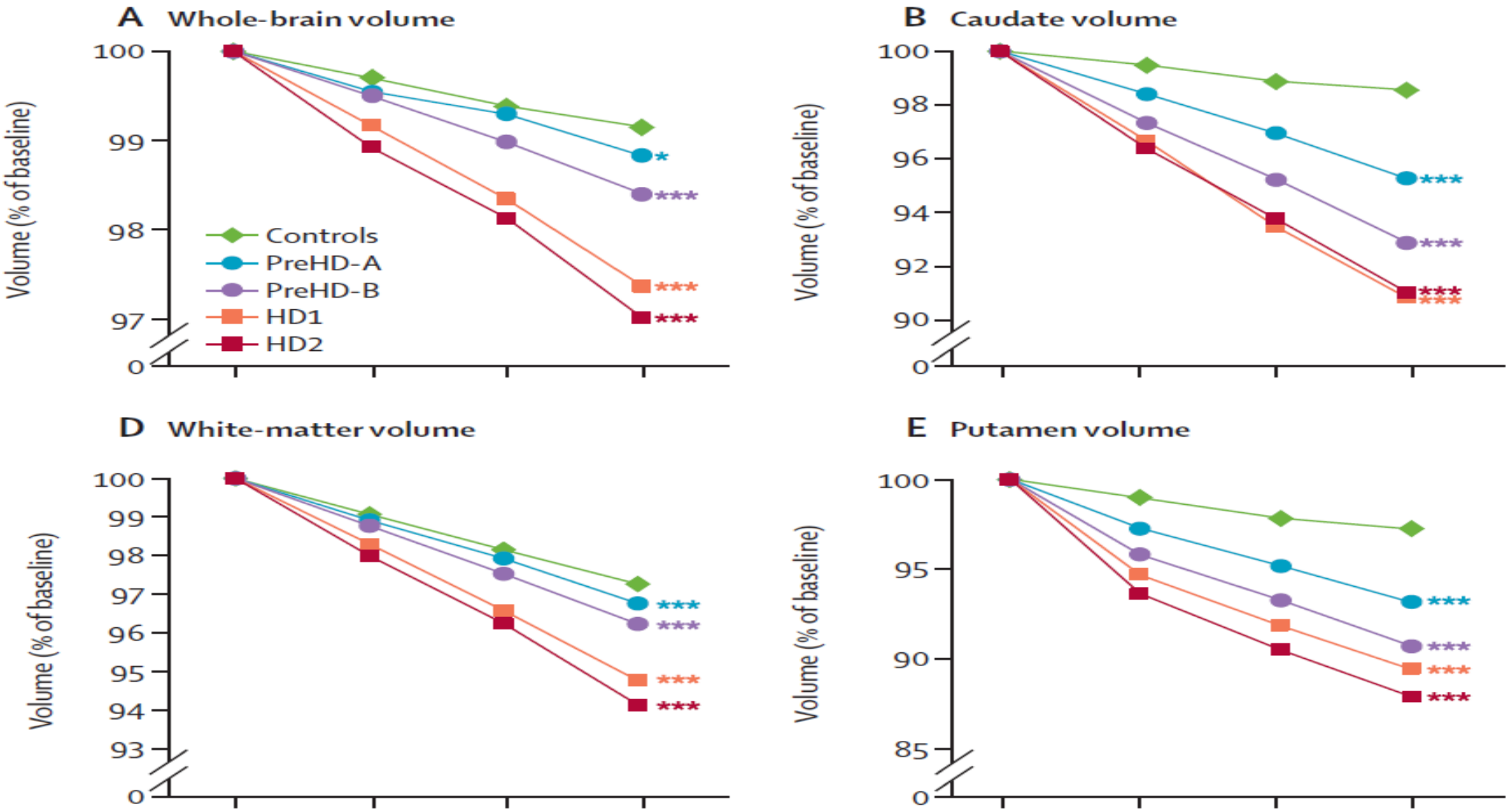
	PreHD vs controls	HD vs controls	PreHD vs HD	PreHD-A vs controls	PreHD-B vs preHD-A	HD1 vs PreHD-B	HD2 vs HD1
Quantitative motor and oculomotor measures							
Antisaccade error rate (%)	3·45 (-1·97 to 8·87) p=0·21	26·78 (21·44 to 32·13) p<0·0001	23·34 (17·72 to 28·96) p<0·0001	-0·50 (-7·02 to 6·02) p=0·88	8·17 (0·62 to 15·71) p=0·03	14·16 (6·84 to 21·48) p=0·0002	13·64 (5·61 to 21·67) p=0·0009
Tongue force heavy (log coefficient of variance)	0·30 (0·17 to 0·42) p<0·0001	1·10 (0·97 to 1·22) p<0·0001	0·80 (0·67 to 0·93) p<0·0001	0·19 (0·03 to 0·34) p=0·02	0·23 (0·05 to 0·40) p=0·01	0·64 (0·46 to 0·81) p<0·0001	0·13 (-0·06 to 0·32) p=0·18
Self-paced tapping precision non-dominant hand* (1/SD)	-9·84 (-12·92 to -6·77) p<0·0001	-27·53 (-30·43 to -24·64) p<0·0001	-17·69 (-20·43 to -14·95) p<0·0001	-5·64 (-9·34 to -1·94) p=0·003	-8·54 (-12·43 to -4·65) p<0·0001	-11·10 (-14·66 to -7·55) p<0·0001	-6·04 (-9·57 to -2·51) p=0·0009
Gaitrite stride length normal speed (log mean coefficient of variance)	0·12 (0·04 to 0·21) p=0·004	0·36 (0·28 to 0·44) p<0·0001	0·24 (0·15 to 0·32) p<0·0001	0·08 (-0·02 to 0·18) p=0·12	0·09 (-0·03 to 0·21) p=0·13	0·11 (-0·003 to 0·22) p=0·06	0·22 (0·1 to 0·34) p=0·0004

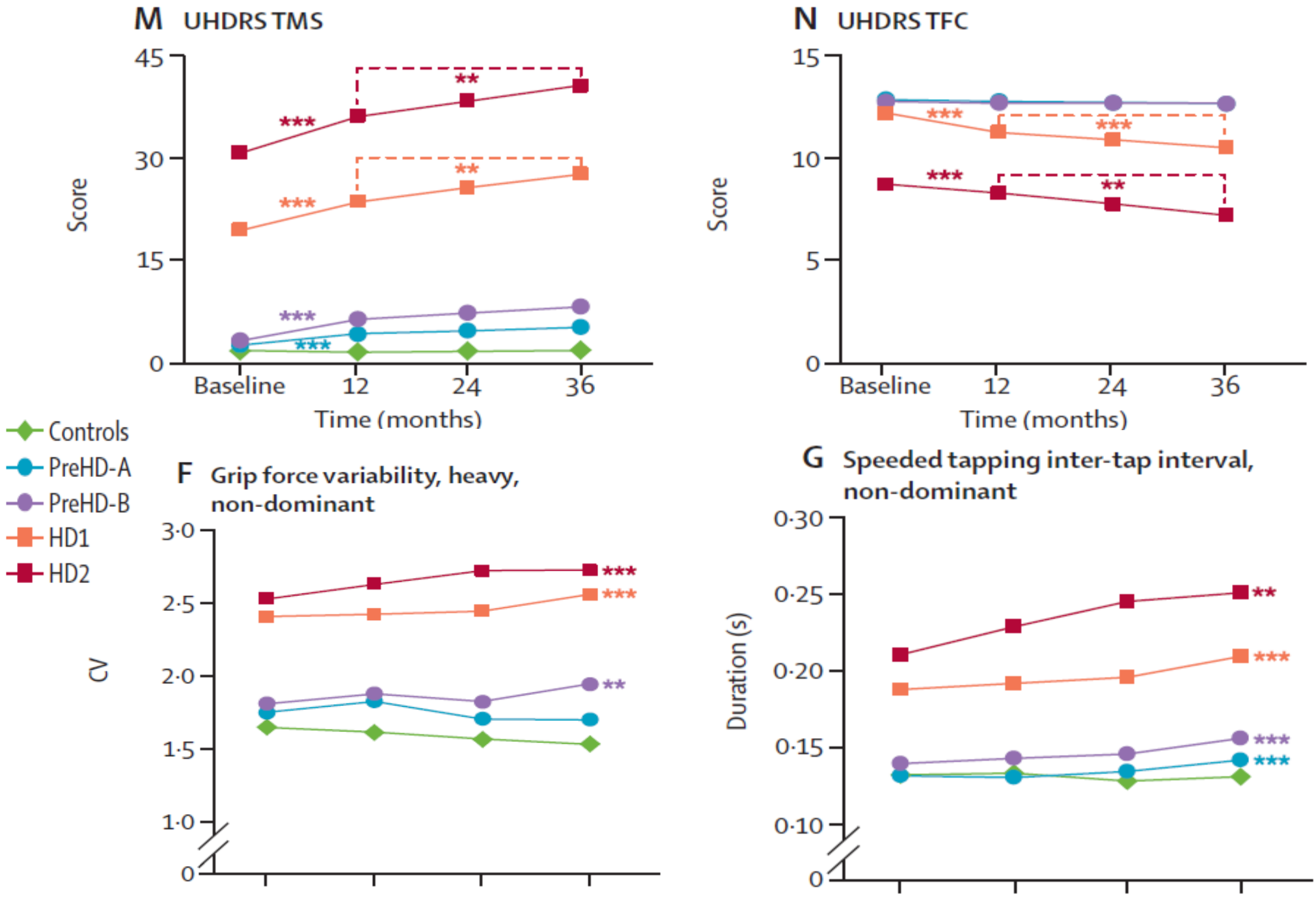
	PreHD vs controls	HD vs controls	PreHD vs HD	PreHD-A vs controls	PreHD-B vs preHD-A	HD1 vs PreHD-B	HD2 vs HD1
Cognitive measures							
Negative emotion recognition (number correct)	-2·76 (-4·21 to -1·32) p=0·0002	-9·08 (-10·52 to -7·64) p<0·0001	-6·31 (-7·82 to -4·81) p<0·0001	-2·36 (-4·08 to -0·64) p=0·007	-0·87 (-2·88 to 1·15) p=0·40	-5·44 (-7·42 to -3·47) p<0·0001	-1·13 (-3·29 to 1·03) p=0·30
Spot the change 5 sec ("K" number correct corrected for guessing)	-0·47 (-0·76 to -0·17) p=0·002	-1·39 (-1·69 to -1·10) p<0·0001	-0·93 (-1·24 to -0·62) p<0·0001	-0·25 (-0·61 to 0·10) p=0·16	-0·44 (-0·85 to -0·03) p=0·03	-0·66 (-1·07 to -0·26) p=0·001	-0·10 (-0·54 to 0·35) p=0·67
UPSIT smell identification* (number correct)	-0·88 (-1·42 to -0·35) p=0·001	-3·36 (-4·00 to -2·73) p<0·0001	-2·48 (-3·18 to -1·78) p<0·0001	-0·52 (-1·12 to 0·08) p=0·09	-0·75 (-1·58 to 0·07) p=0·08	-2·05 (-2·97 to -1·13) p<0·0001	-0·11 (-1·30 to 1·07) p=0·85
Neuropsychiatric measures							
PBA apathy† (points on PBA scale)	0·72 (0·18 to 1·27) p<0·01	2·38 (1·77 to 3·03) p<0·001	1·65 (0·89 to 2·39) p<0·001	0·47 (-0·06 to 1·29) p>0·05	0·54 (-0·34 to 1·61) p>0·05	0·68 (-0·52 to 1·66) p>0·05	1·79 (0·49 to 3·21) p=0·01
PBA irritability† (points on PBA scale)	1·50 (0·57 to 2·63) p<0·01	3·89 (2·82 to 5·09) p<0·001	2·38 (0·96 to 3·76) p<0·001	1·56 (0·51 to 3·20) P<0·01	-0·12 (-2·09 to 1·66) p>0·05	1·50 (-0·41 to 3·34) p>0·05	2·52 (0·50 to 4·59) p<0·01
PBA affect† (points on PBA scale)	1·23 (-0·15 to 2·58) p=0·08	1·92 (0·49 to 3·31) p<0·01	0·68 (-0·92 to 2·18) p>0·10	1·53 (-0·16 to 3·68) p=0·09	-0·62 (-3·01 to 1·24) p>0·10	0·38 (-1·47 to 2·25) p>0·10	1·65 (-0·48 to 4·08) p>0·10

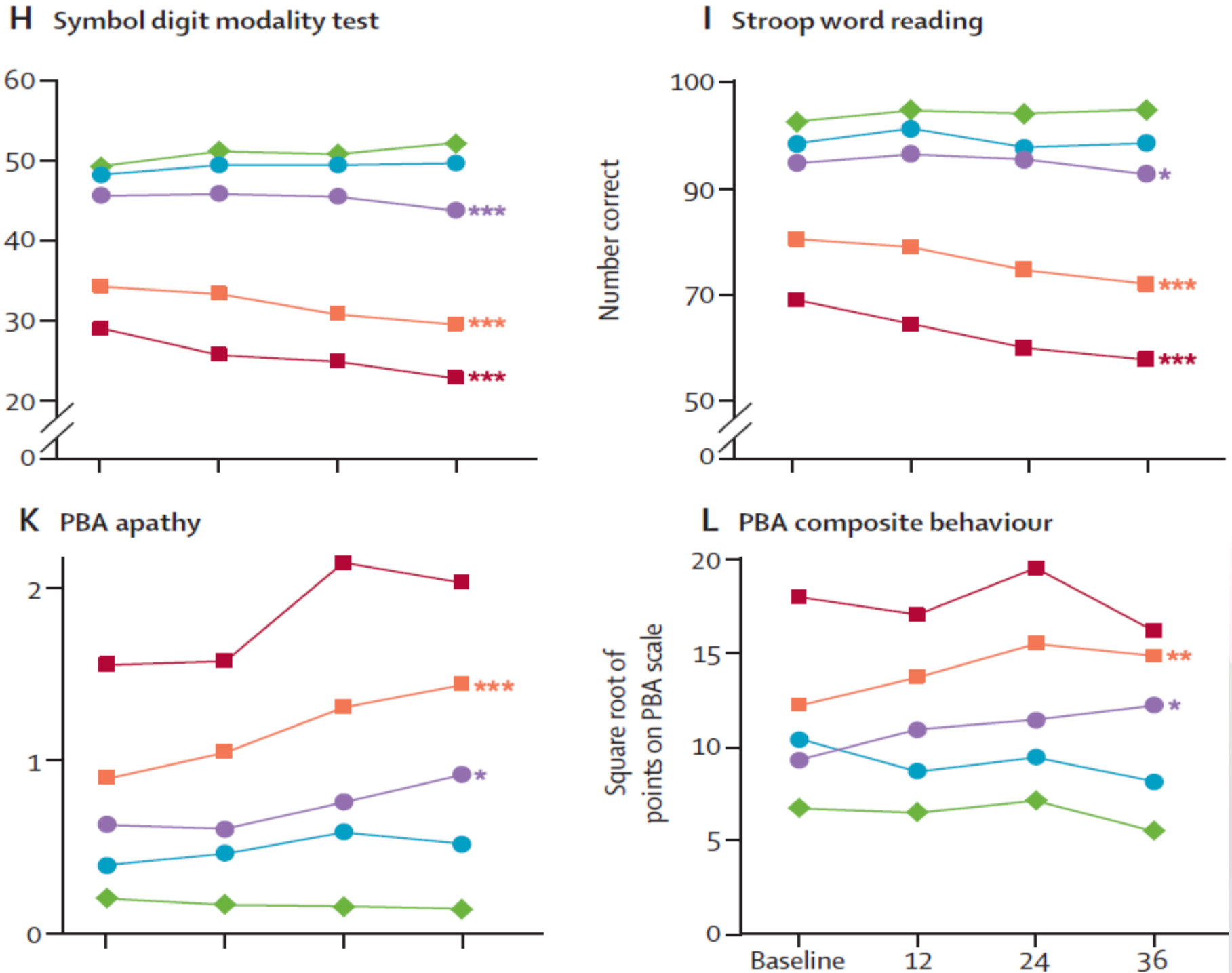
Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data

Sarah J Tabrizi, Rachael I Scahill, Gail Owen, Alexandra Durr, Blair R Leavitt, Raymund A Roos, Beth Borowsky, Bernhard Landwehrmeyer, Chris Frost, Hans Johnson, David Craufurd, Ralf Reilmann, Julie C Stout, Douglas R Langbehn, and the TRACK-HD Investigators*

Lancet Neurol 2013; 12: 637–49




M UHDRS TMS
Score
45
30
15
0
Baseline
12
24
36
Time (months)
***
**
***
**
***
***
N UHDRS TFC
Score
15
10
5
0
Baseline
12
24
36
Time (months)
***
***
***
**
Controls
PreHD-A
PreHD-B
HD1
HD2
F Grip force variability, heavy, non-dominant
CV
3·0
2·5
2·0
1·5
1·0
0
***
***
**
G Speeded tapping inter-tap interval, non-dominant
Duration (s)
0·30
0·25
0·20
0·15
0·10
0
**
***
***
***


H Symbol digit modality test
60
50
40
30
20
0
***
***
***
I Stroop word reading
Number correct
100
90
70
50
0
*
***
***
K PBA apathy
2
1
0
***
*
L PBA composite behaviour
Square root of points on PBA scale
20
15
10
5
0
**
*
Baseline
12
24
36

CONCLUSIONS

1. És possible detectar pèrdua de volum cerebral i alteracions motores, cognitives i conductuals a la fase preclínica de la malaltia

2. Aquestes alteracions es poden detectar fins i tot anys abans de l'inici clínic de la malaltia.

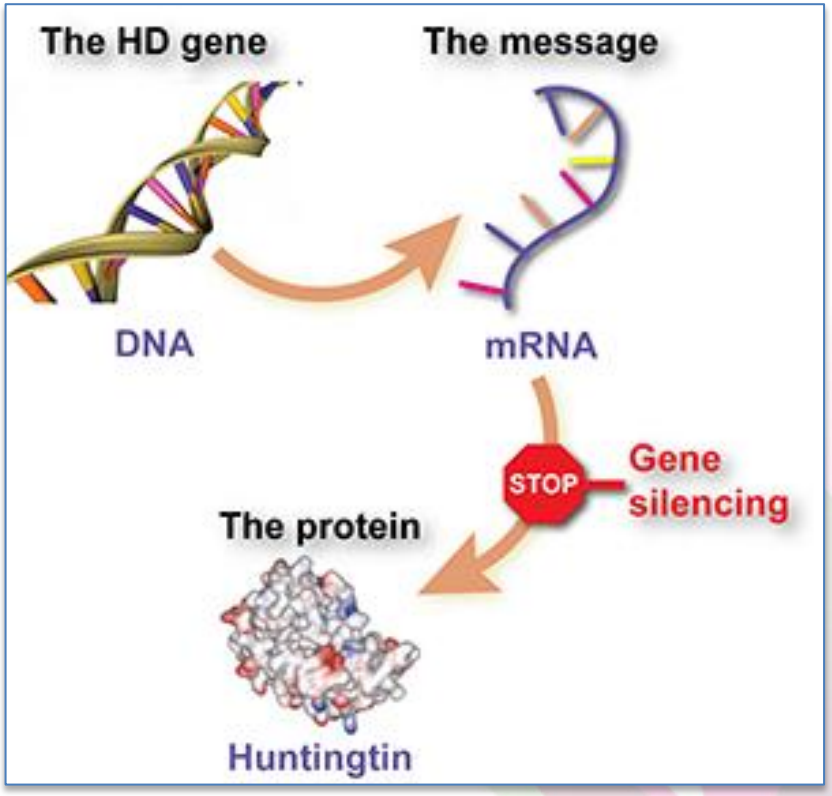
3. Els millors biomarcadors de la fase preclínica serien:

- ✓ La mesura del volum estriatal en la ressonància magnètica.
- ✓ La variabilitat en la força de prensió manual.
- ✓ La variabilitat en la ritmicitat del "tapping"
- ✓ La variabilitat en el manteniment de la força lingual

Liftoff: First humans treated with gene silencing drugs for HD!

Major Announcement: First HD patients treated with gene silencing drugs

By Dr. Jeff Carroll on October 22, 2015



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IDIBAPS Institut d'Investigacions Biomèdiques August Pi y Sunyer

Moltes gràcies!!

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