

MPP en enfermedad de Parkinson y otros trastornos del movimiento

Pablo Mir

Unidad de Trastornos del Movimiento. Servicio de Neurología y Neurofisiología Clínica. UGC Neurociencias

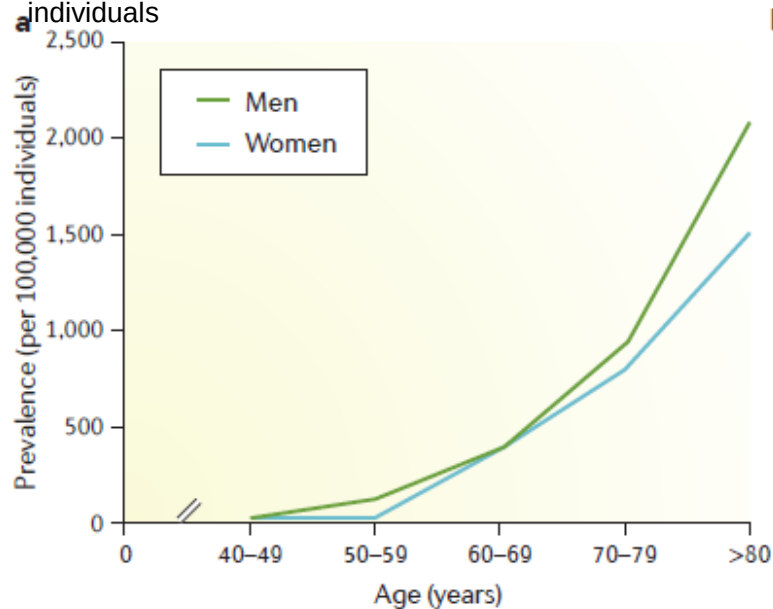
Instituto de Biomedicina de Sevilla – IBiS.

Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla

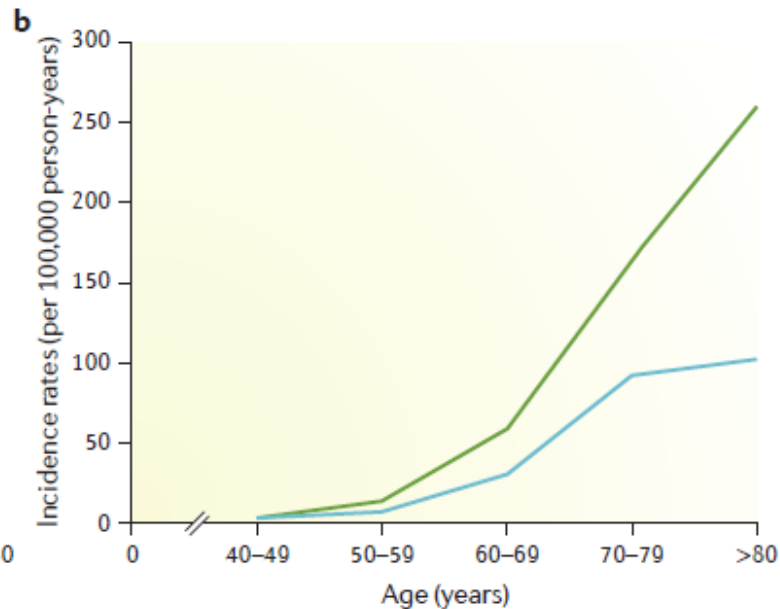


Parkinson's disease (PD)

Prevalence of PD in men and women per 100.000 individuals

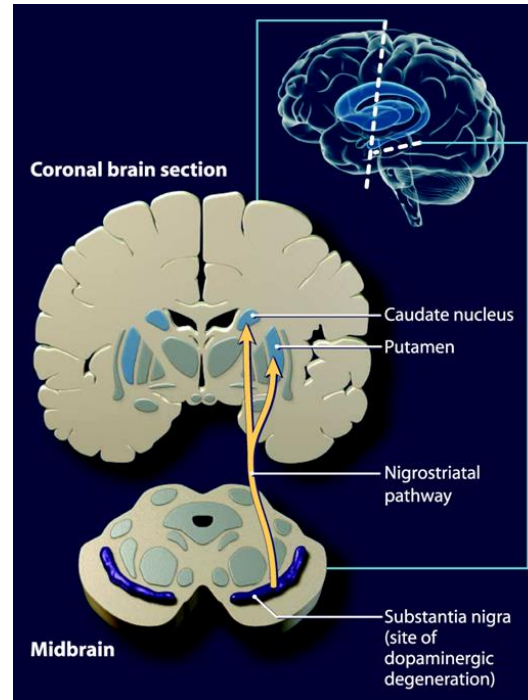


Incidence rate of PD per 100.000 person-year.



Enfermedad de Parkinson

Pérdida neuronal progresiva en la sustancia nigra



Guttman M et al. CMAJ 2003;168:293-301

Características clínicas de la EP

4

Acinesia/Bradicinesia

Rigidez

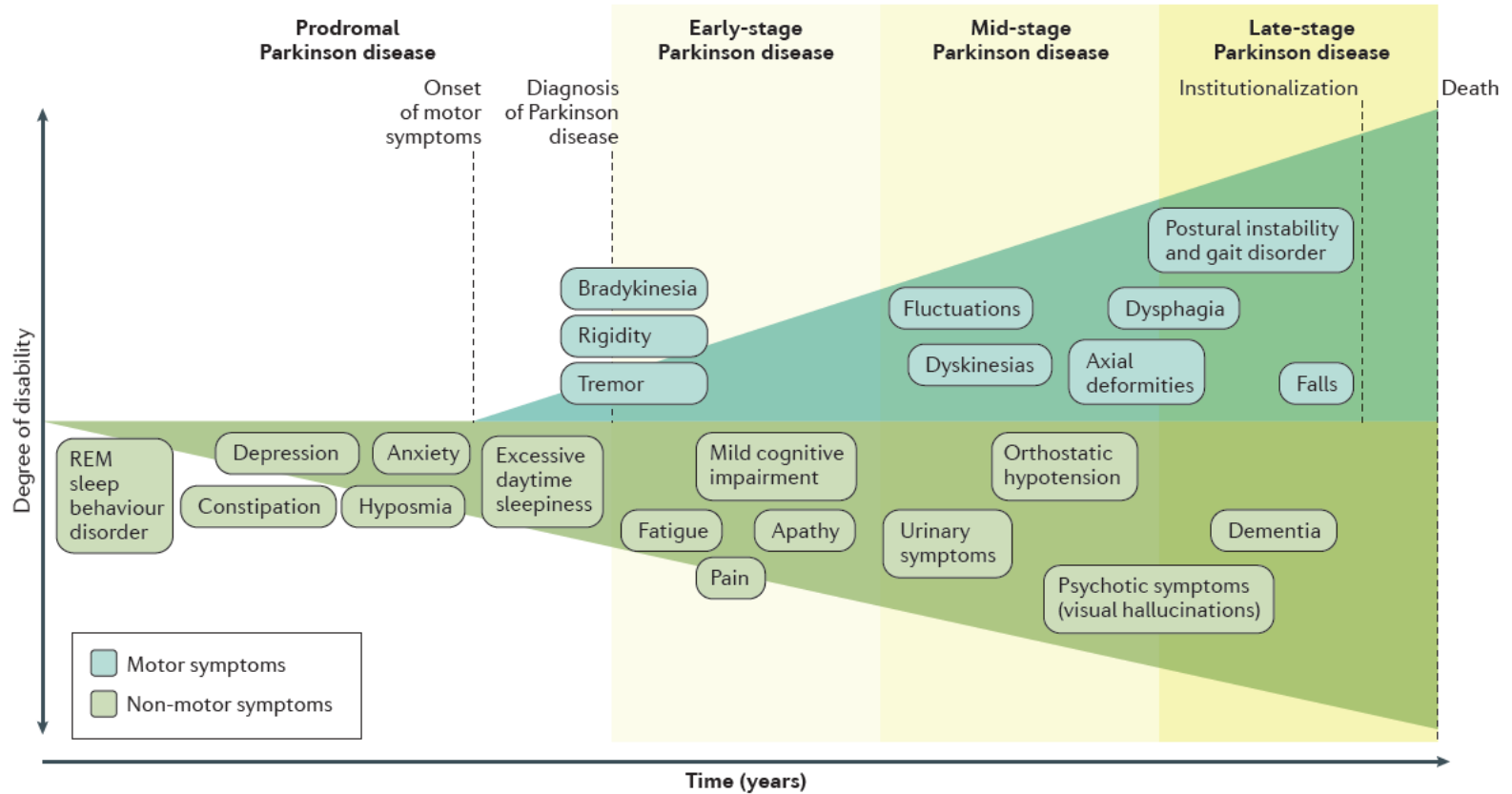
Temblor

Alteraciones posturales

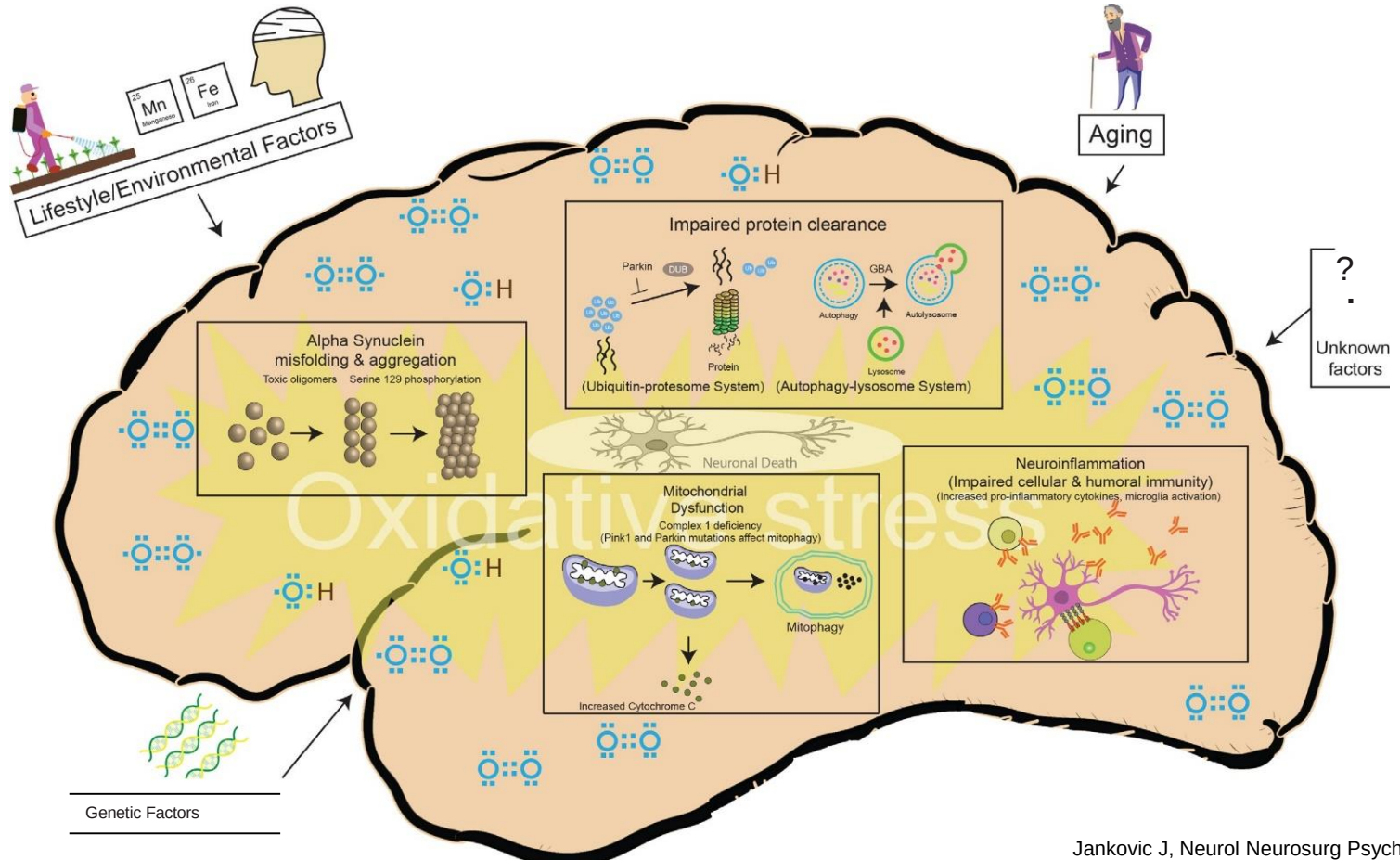
Estos síntomas típicamente se presentan asimetricamente



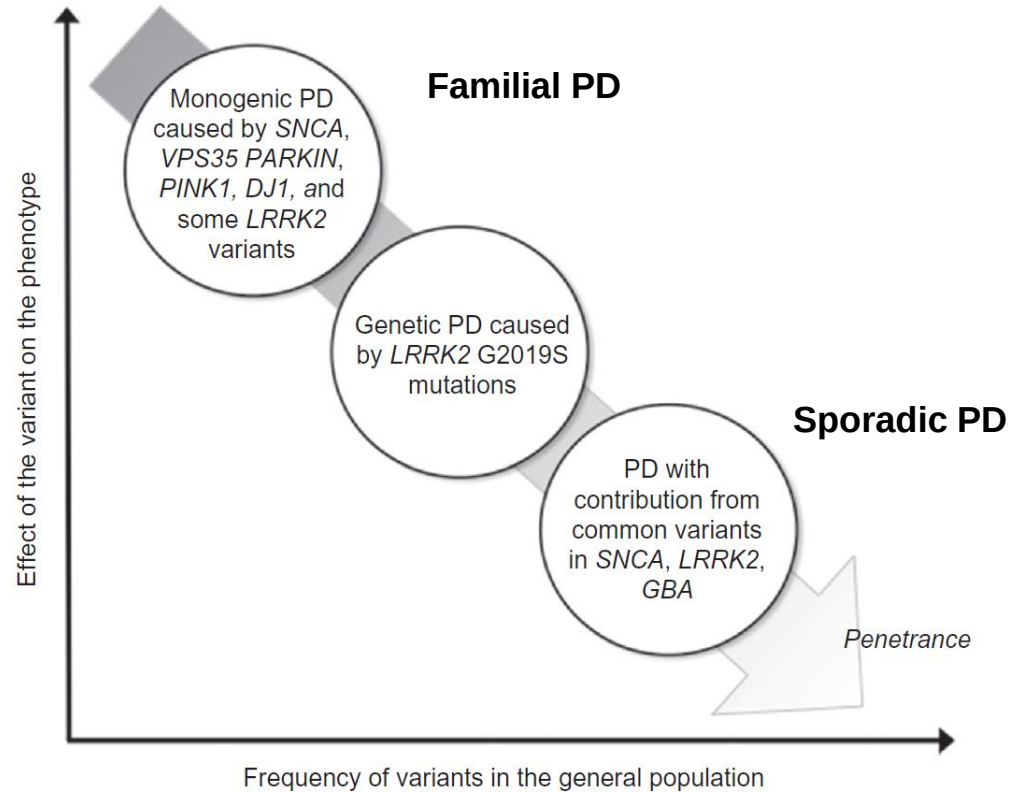
PD as a clinical syndrome



Pathogenesis of PD

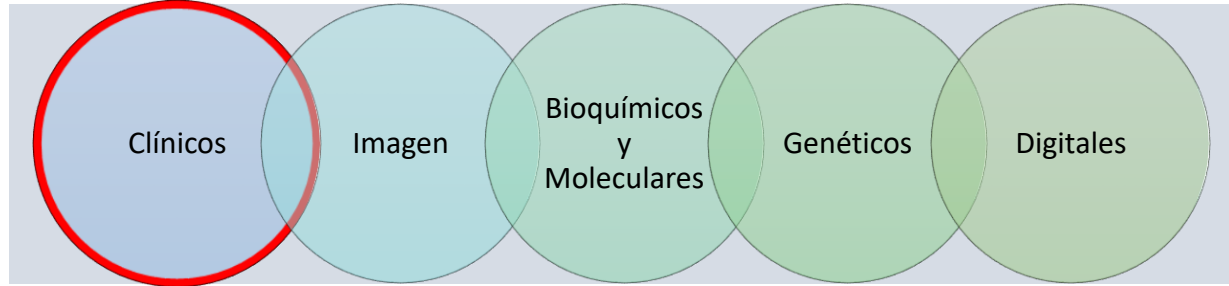


Etiology - Genetic factors



Biomarcadores y enfermedad de Parkinson

La fuente de biomarcadores en la enfermedad de Parkinson es amplia y sigue incrementándose incluyendo:



[PERO ninguno ha mostrado por sí solo ser suficientemente sensible y específico para el diagnóstico o pronóstico de la EP.](#)

Modelos multimodales: integración de distintos biomarcadores procedentes de distintas fuentes.

Tipos de Biomarcadores:

- De susceptibilidad de riesgo
- Diagnóstico
- De monitorización
- Pronóstico
- Predictivo

Objetivo:

- Identificar EP prodrómica: Intervención precoz y tratamientos neuroprotectores.
- Diagnóstico certero, especialmente en estadios precoces, y diagnóstico diferencial con otras entidades.
- Monitorizar tratamientos
- Medicina personalizada

Características clínicas de la EP

Acinesia/Bradicinesia

Rigidez

Temblor

Alteraciones posturales

Estos síntomas típicamente se presentan asimétricamente

Características clínicas de la EP

Acinesia/Bradicinesia

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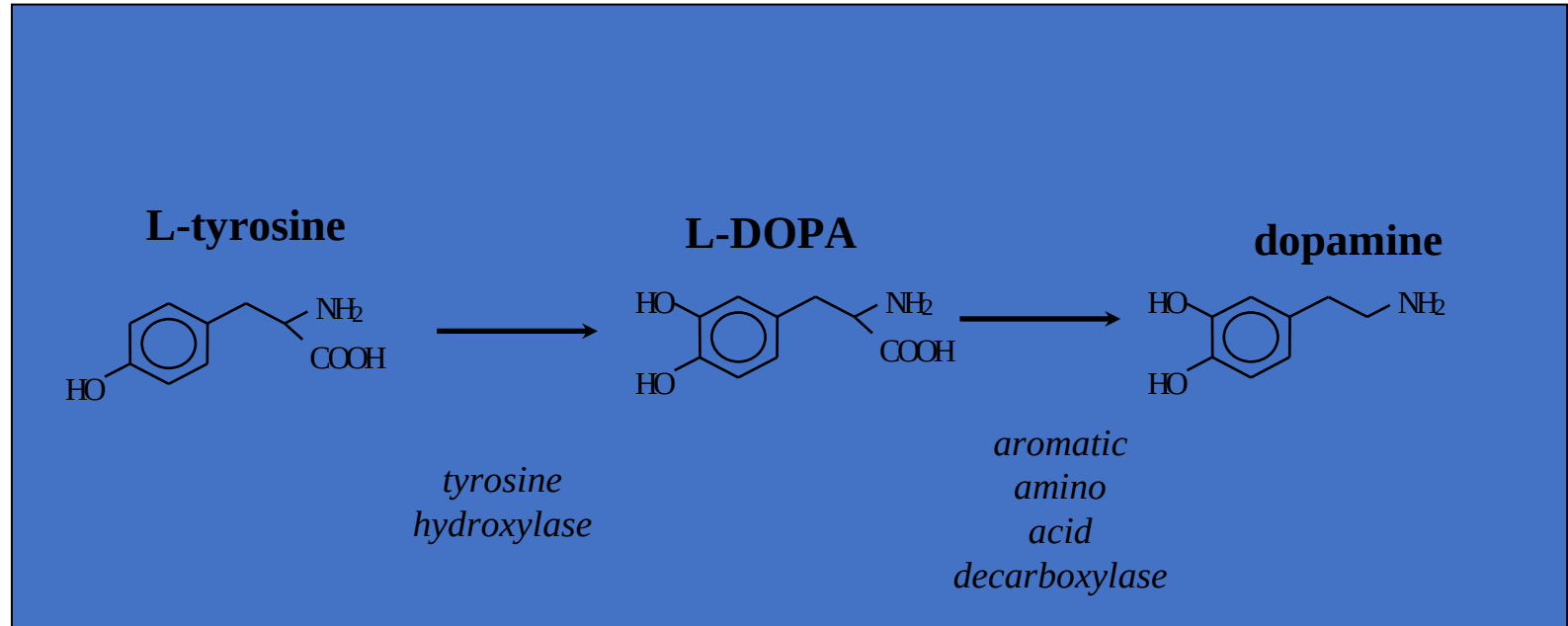
Alteraciones posturales

Estos síntomas típicamente se presentan asimetricamente

Bradicinesia

Manejo clínico paciente con EP

Levodopa y la síntesis de dopamina



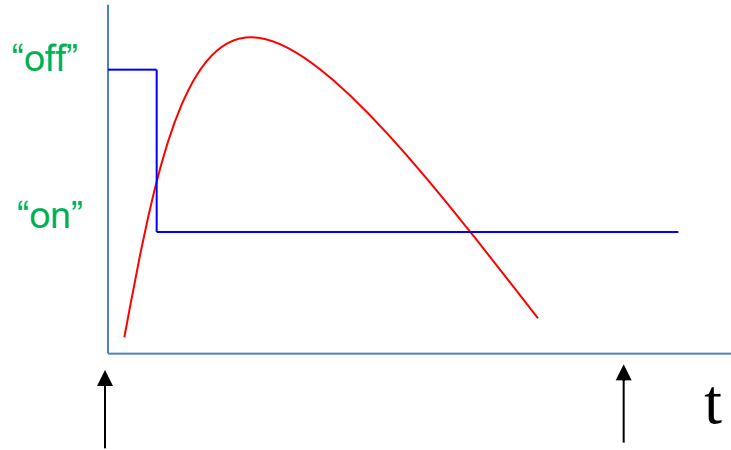
Manejo clínico paciente con EP

Luna de miel de la levodopa

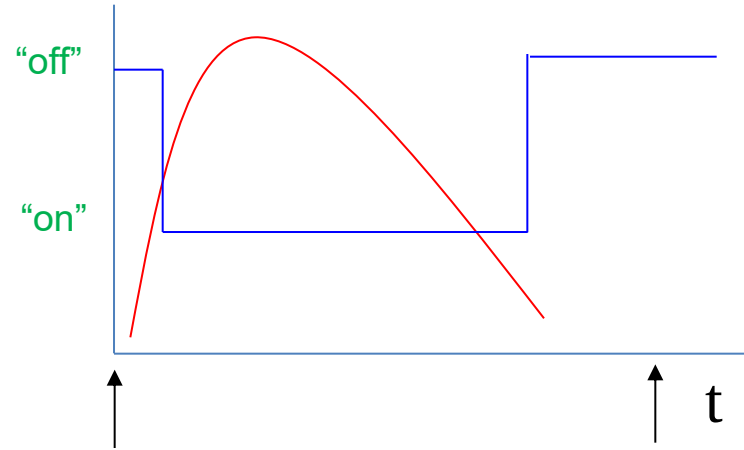


Manejo clínico paciente con EP

Respuesta a levodopa



Respuesta estable



Respuesta fluctuante

Manejo clínico paciente con EP

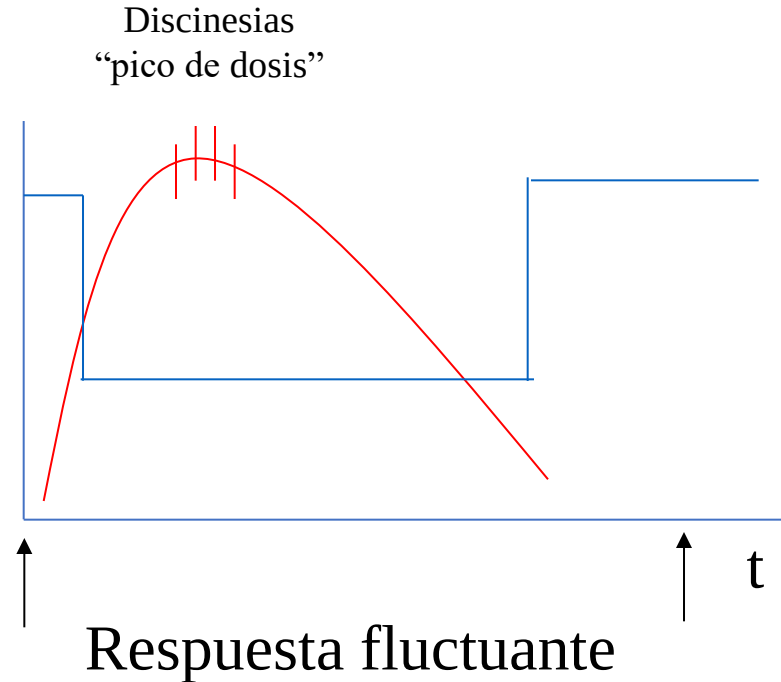
Fluctuaciones motoras

OFF

ON

Complicaciones del tratamiento

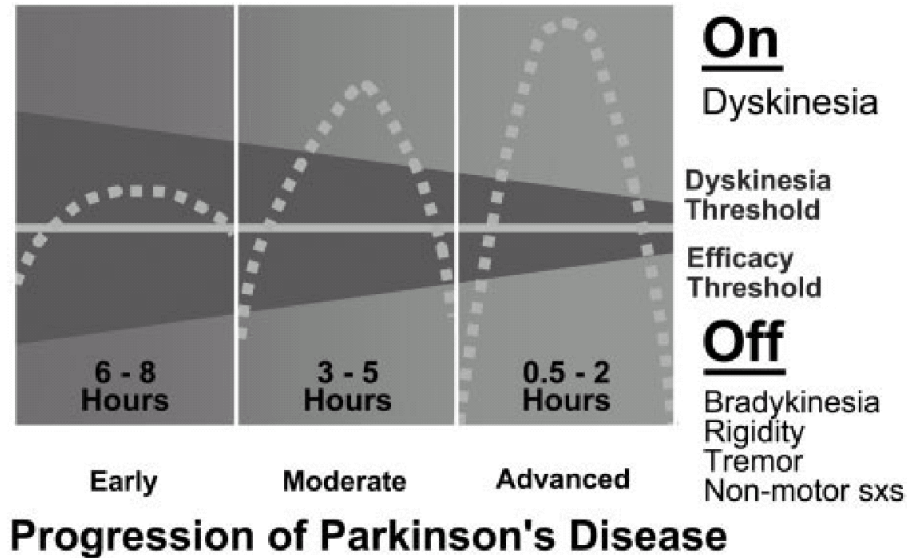
Discinesias inducidas por levodopa



Complicaciones del tratamiento

Discinesias “pico de dosis”

Complicaciones del tratamiento



Jankovic J. Movement Disorders 2005; 20 (Suppl 11): S11–S16

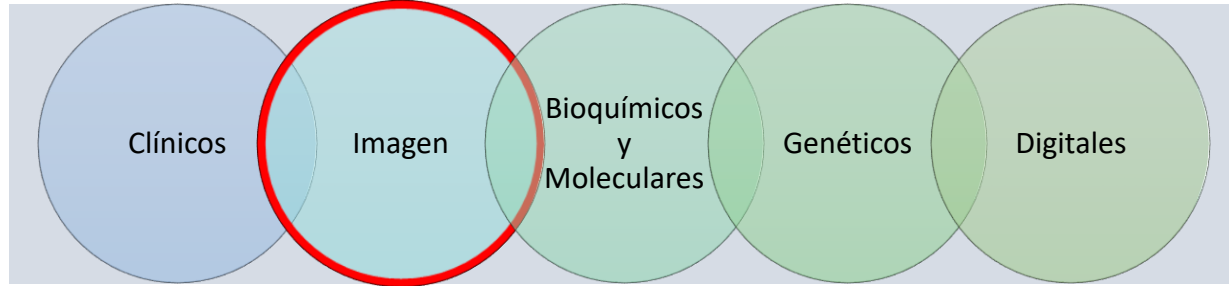
Complicaciones del tratamiento

19

	Treatment of motor symptoms		Treatment of motor complications	
	Monotherapy	Adjunct to levodopa	Fluctuations	Dyskinesia*
Levodopa				
Levodopa-carbidopa	+	..	+	-
Levodopa-benserazide	+	..	+	-
Dopamine agonists (non-ergot)				
Apomorphine	-	+	+	-
Piribedil	+	+	-	-
Pramipexole	+	+	+	-
Ropinirole	+	+	+	-
Rotigotine	+	+	+	-
Dopamine agonists (ergot)				
Bromocriptine	+	+	+	-
Cabergoline	+	+	+	-
Monoamine oxidase type B inhibitors				
Rasagiline	+	+	+	-
Selegiline	+	-§	-§	-
Catechol-O-methyltransferase inhibitors				
Entacapone	..	+	+	-
Tolcapone	..	+	+	-
Others				
Amantadine	+	+	-	+
Anticholinergics†	+‡	+‡	-	-
Clozapine	+‡	+‡	-	+
+ indicates efficacious or likely efficacious. - indicates non-efficacious or insufficient evidence. .. indicates not applicable. *Responses to peak dose dyskinesia (diphasic dyskinesia might respond to drugs used for motor fluctuations, particularly dopamine agonists). †Includes benztropine, ethopropazine, trihexyphenidyl, and others. ‡For treatment of tremor. §There is insufficient evidence but, in practice, selegiline is used and can be effective.				
Table 2: Pharmacological treatments for motor symptoms and complications				

Biomarcadores y enfermedad de Parkinson

La fuente de biomarcadores en la enfermedad de Parkinson es amplia y sigue incrementándose incluyendo:



[PERO ninguno ha mostrado por sí solo ser suficientemente sensible y específico para el diagnóstico o pronóstico de la EP.](#)

Modelos multimodales: integración de distintos biomarcadores procedentes de distintas fuentes.

Tipos de Biomarcadores:

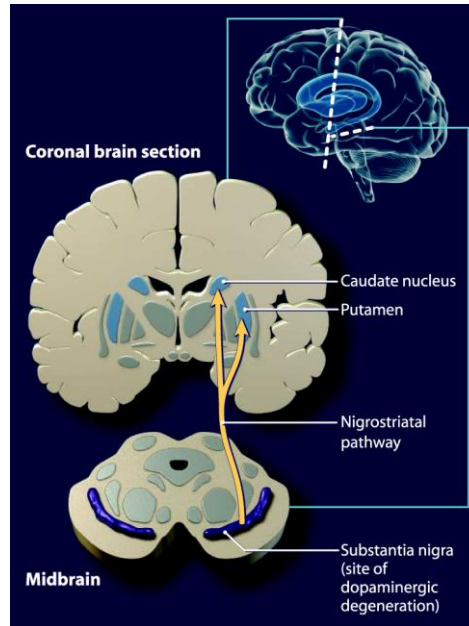
- De susceptibilidad de riesgo
- Diagnóstico
- De monitorización
- Pronóstico
- Predictivo

Objetivo:

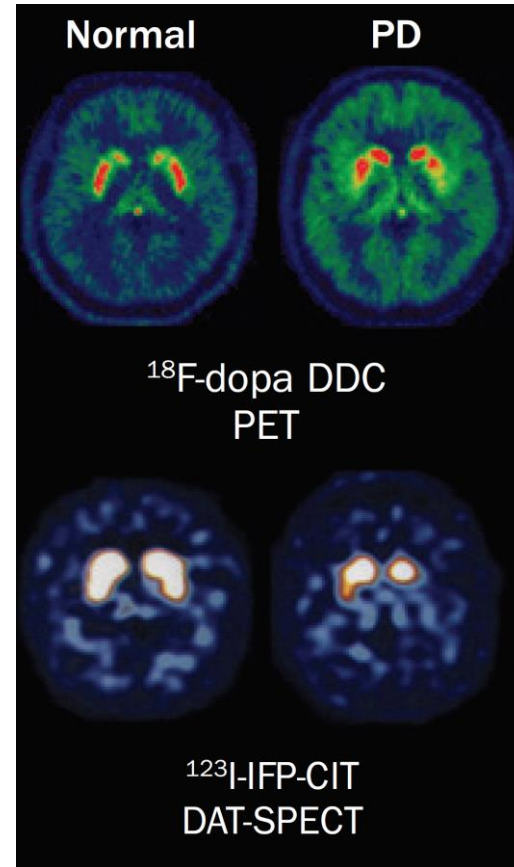
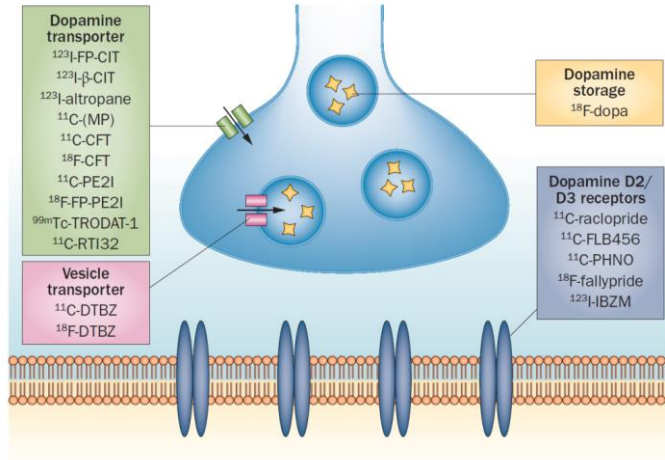
- Identificar EP prodrómica: Intervención precoz y tratamientos neuroprotectores.
- Diagnóstico certero, especialmente en estadios precoces, y diagnóstico diferencial con otras entidades.
- Monitorizar tratamientos
- Medicina personalizada

Parkinson disease

Progressive neuronal loss of the substantia nigra

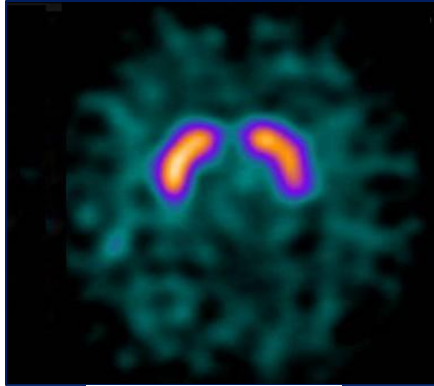


Radiotracers for dopaminergic imaging



SPECT con FP-CIT o DAT-SCAN

EVALUACIÓN CUALITATIVA: Interpretación visual



EVALUACIÓN SEMICUANTITATIVA: Índices de captación en subregiones estriatales

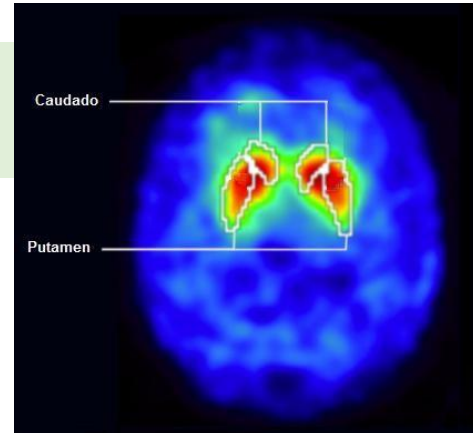
Ratio de unión específica (Specific Binding Ratio, SBR)



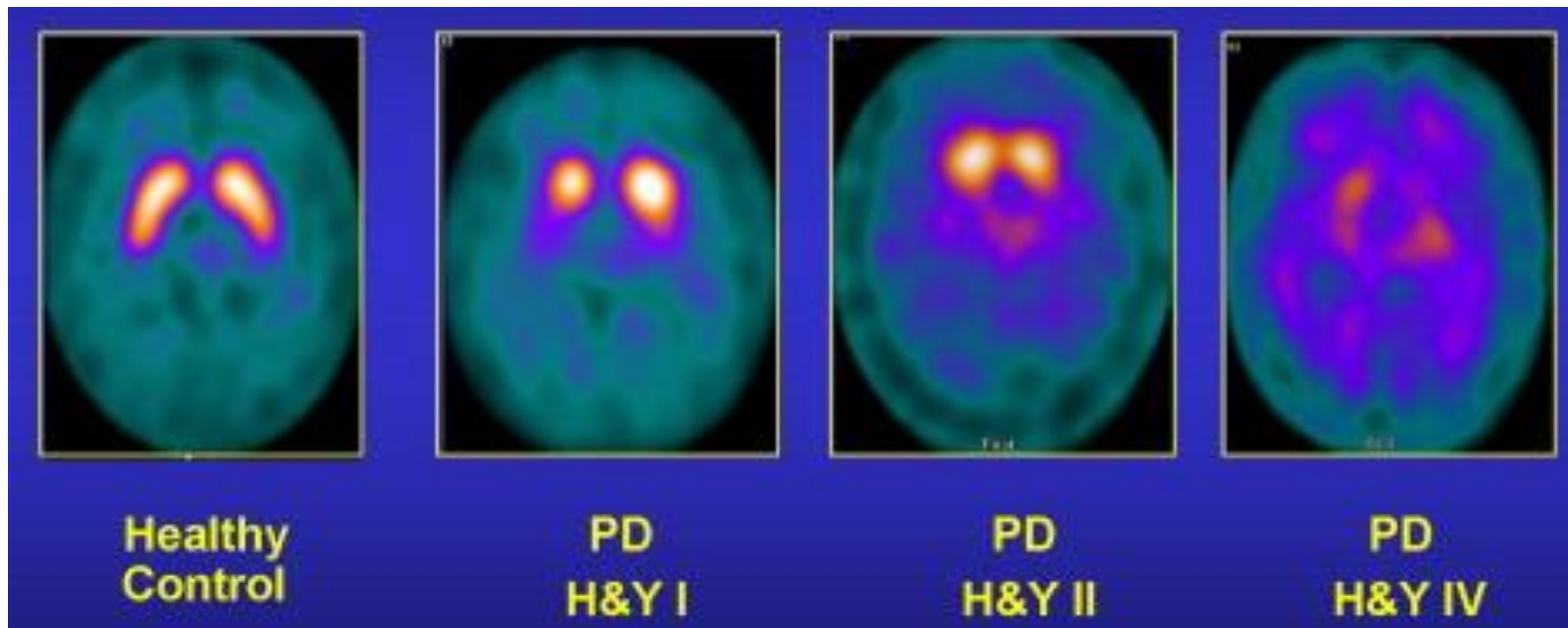
Parámetros numéricos que evalúan la relación de captación entre diferentes subregiones estriatales

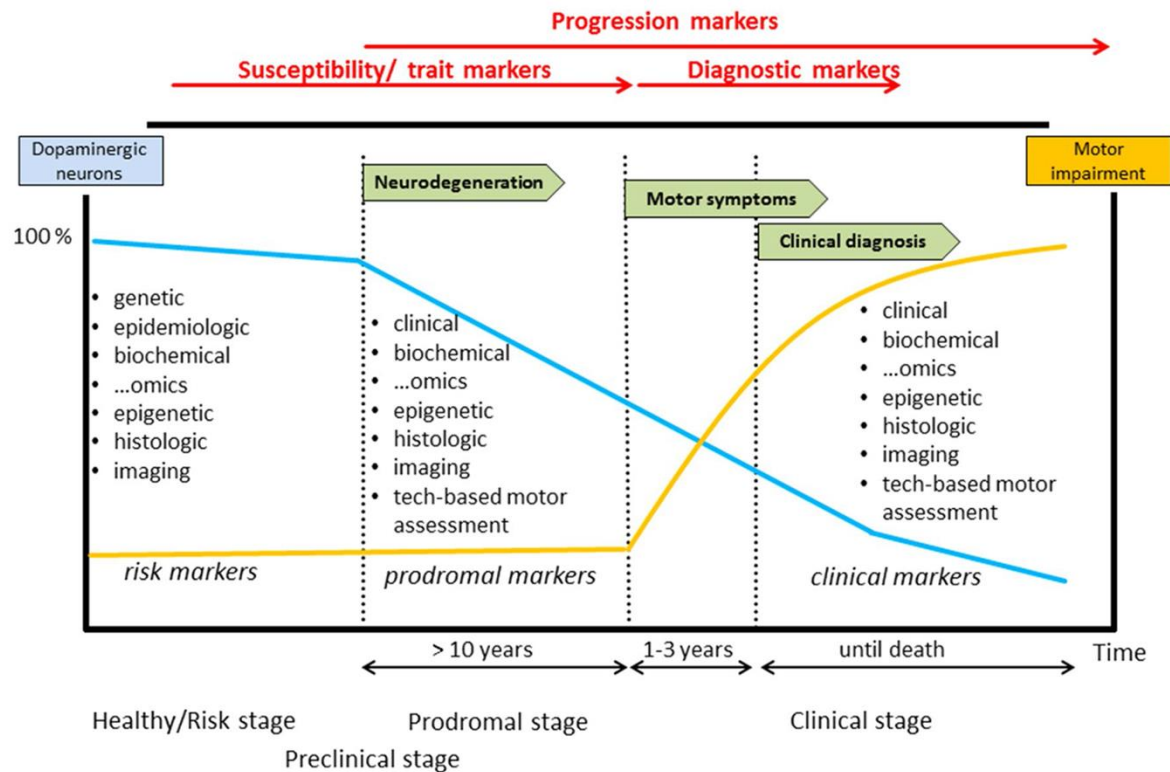


- Ratio estriado/fondo
- Ratio putamen/caudado
- Índices de asimetría estriatal



SPECT con FP-CIT o DAT-SCAN



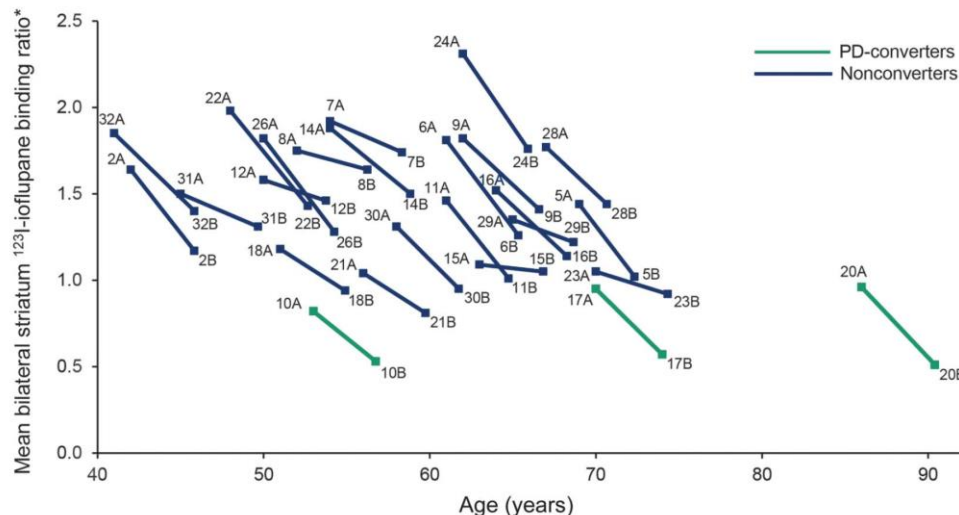


Prospective clinical and DaT-SPECT imaging in premotor *LRRK2* G2019S-associated Parkinson disease

Neurology® 2017;89:439-444

María Sierra, MD
Isabel Martínez-
Rodríguez, MD
Pascual Sánchez-Juan,
MD
Isabel González-
Aramburu, MD
Mikel Jiménez-Alonso,
MD
Antonio Sánchez-
Rodríguez, MD
José Berciano, MD
Ignacio Banzo, MD
Jon Infante, MD

Figure Individual decline of mean bilateral striatum ^{123}I -ioflupane binding ratio between baseline and 4 years

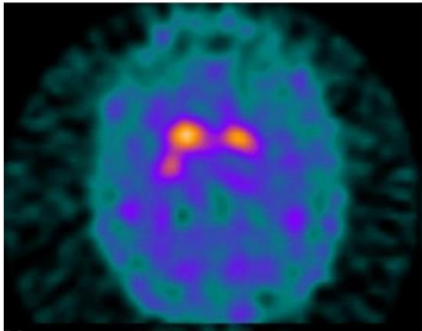


Síndromes parkinsonianos



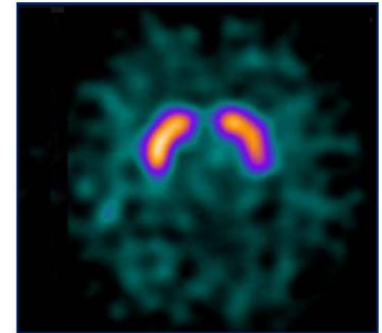
**DEGENERACIÓN DE NEURONAS
DOPAMINÉRGICAS PRESINÁPTICAS**

DaT ↓

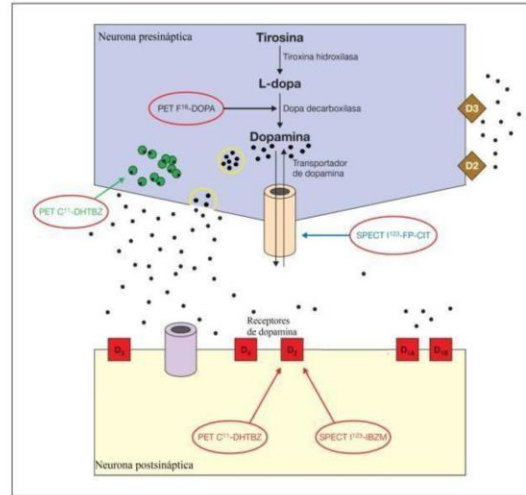


NO DEGENERACIÓN

DaT +/-



SPECT cerebral con [123I]FP-CIT



Transportadores de dopamina (DaT)

Esquema de la sinapsis dopaminérgica estriatal. Adaptado de Solís DG (2005).

Clinical features and ^{123}I -FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease

Francisco J. Diaz-Corrales • Salome Sanz-Viedma •
David Garcia-Solis • Teresa Escobar-Delgado •
Pablo Mir

SPECT con FP-CIT PIF vs EP	Cualitativo	Semicuantitativo
Sensibilidad (%)	90.6	87.5
Especificidad (%)	100	84
Valor predictivo positivo (%)	100	87.5
Valor predictivo negativo (%)	89.3	84

RESEARCH PAPER

Clinical features and ^{123}I -FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease

Sonia Benítez-Rivero,¹ Víctor A Marín-Oyaga,² David García-Solís,^{2,3}
Ismael Huertas-Fernández,¹ Francisco J García-Gómez,² Silvia Jesús,¹
María Teresa Cáceres,¹ Fátima Carrillo,¹ Ana M Ortiz,² Manuel Carballo,¹ Pablo Mir^{1,3}

J Neurol Neurosurg Psychiatry 2013;**84**:122–129. doi:10.1136/jnnp-2012-302618

Editorial commentary

Using biomarkers to disentangle different causes of Parkinsonism

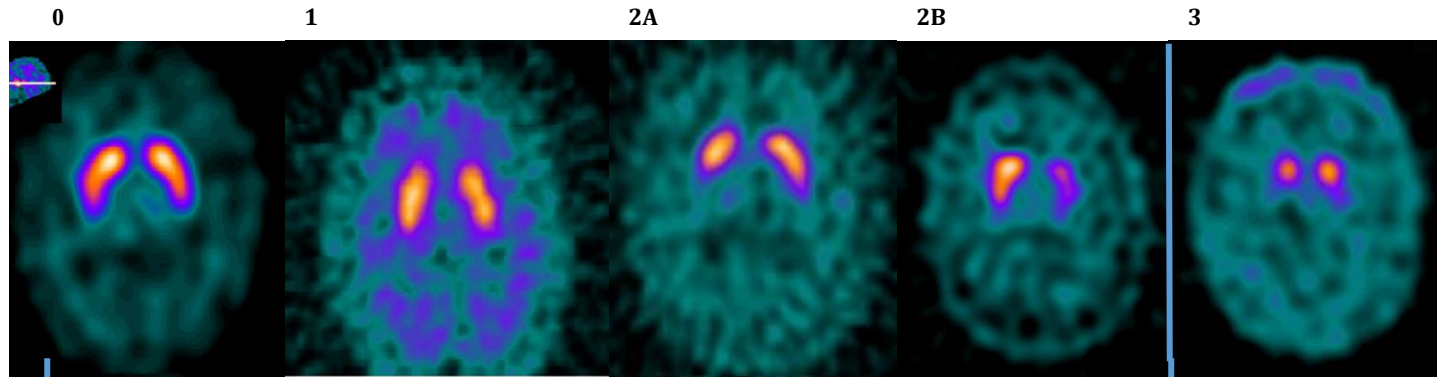
Dag Aarsland,^{1,2,3} Per Svenningsson^{1,2}

J Neurol Neurosurg Psychiatry 2012;**■**:1.
doi:10.1136/jnnp-2012-303025

“... provide new evidence suggesting that dopamine transporter single-photon emission computed tomography (SPECT) can aid in the differentiation between VP and PD, with important prognostic and treatment implications.”

^{123}I -FP-CIT SPECT en el parkinsonismo vascular (VP) vs enfermedad de Parkinson (EP)

^{123}I -FP-CIT SPECT ESCALA VISUAL	PV (n=80)	EP (n=171)
0	26 (100%)	0 (0%)
1	14 (93.3%)	1 (6.7%)
2	27 (100%)	0 (0%)
3	13 (7.1%)	170 (92.9%)

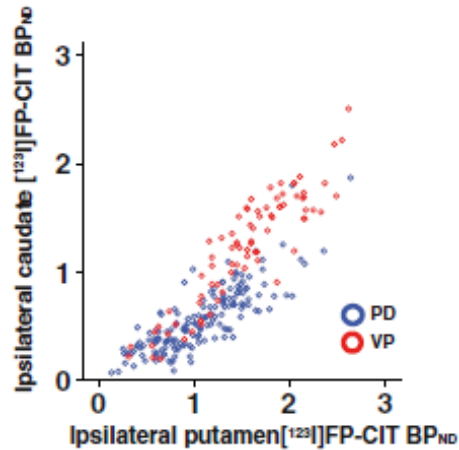


PATRONES BASADOS EN ESCALA VISUAL	PV (n=80)	EP (n=171)
PATRÓN PV	67 (98.5%)	1 (1.5%)
PATRÓN EP	13 (7.1%)	170 (92.9%)

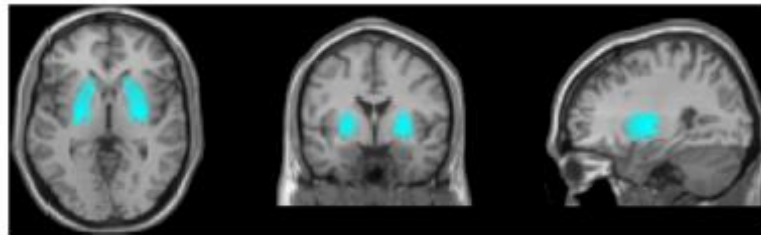
← Enfermedad de Parkinson

Machine learning models for the differential diagnosis of vascular parkinsonism and Parkinson's disease using [123 I]FP-CIT SPECT

I. Huertas-Fernández • F. J. García-Gómez • D. García-Solís • S. Benítez-Rivero •
V. A. Marín-Oyaga • S. Jesús • M. T. Cáceres-Redondo • J. A. Lojo •
J. F. Martín-Rodríguez • F. Carrillo • P. Mir



Method	AUC
LR	0.951 $\pm$ 0.046
LDA	0.940 $\pm$ 0.042
SVM	0.950 $\pm$ 0.045



Method	AUC
PLR	0.960 $\pm$ 0.039
PDA	0.878 $\pm$ 0.073
SVM	0.954 $\pm$ 0.057



Contents lists available at ScienceDirect

NeuroImage: Clinical

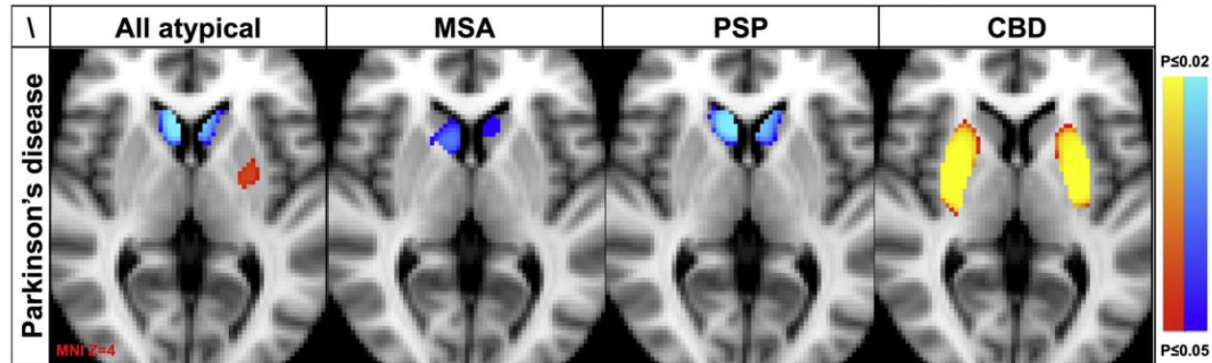
journal homepage: www.elsevier.com/locate/ynicl



Discriminating among degenerative parkinsonisms using advanced ^{123}I -ioflupane SPECT analyses



Simon Badoud^{a,b,c}, Dimitri Van De Ville^{d,e}, Nicolas Nicastro^a, Valentina Garibotto^{c,f},
Pierre R. Burkhard^{a,c}, Sven Haller^{c,g,h,i,*}



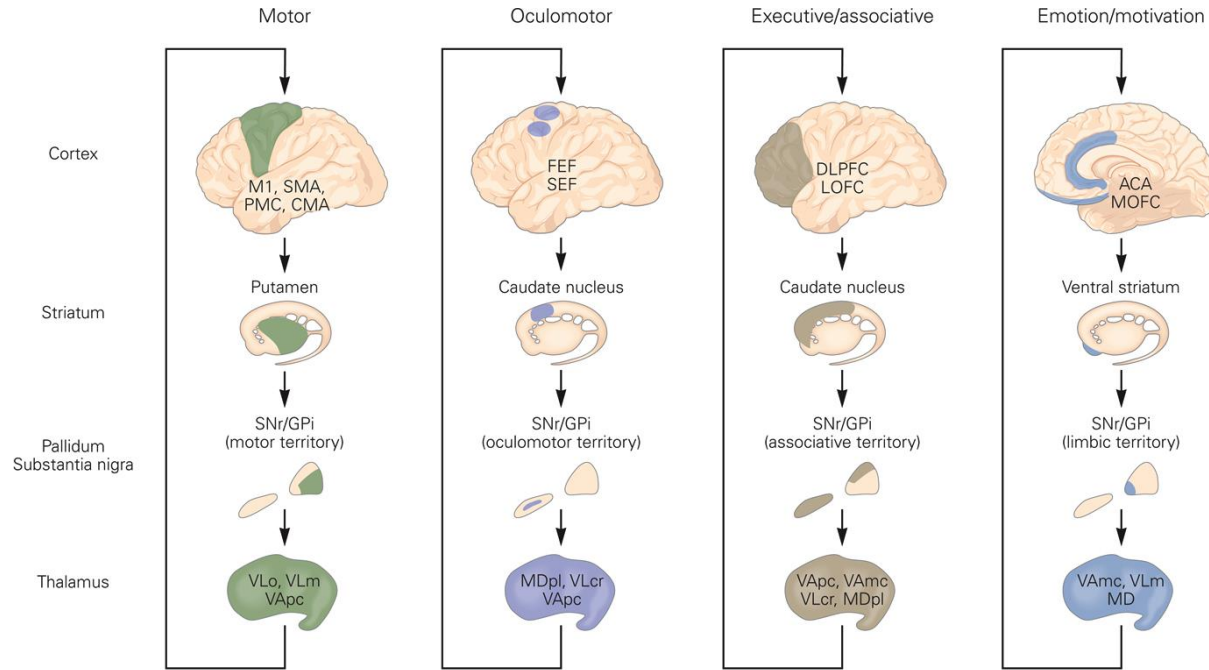
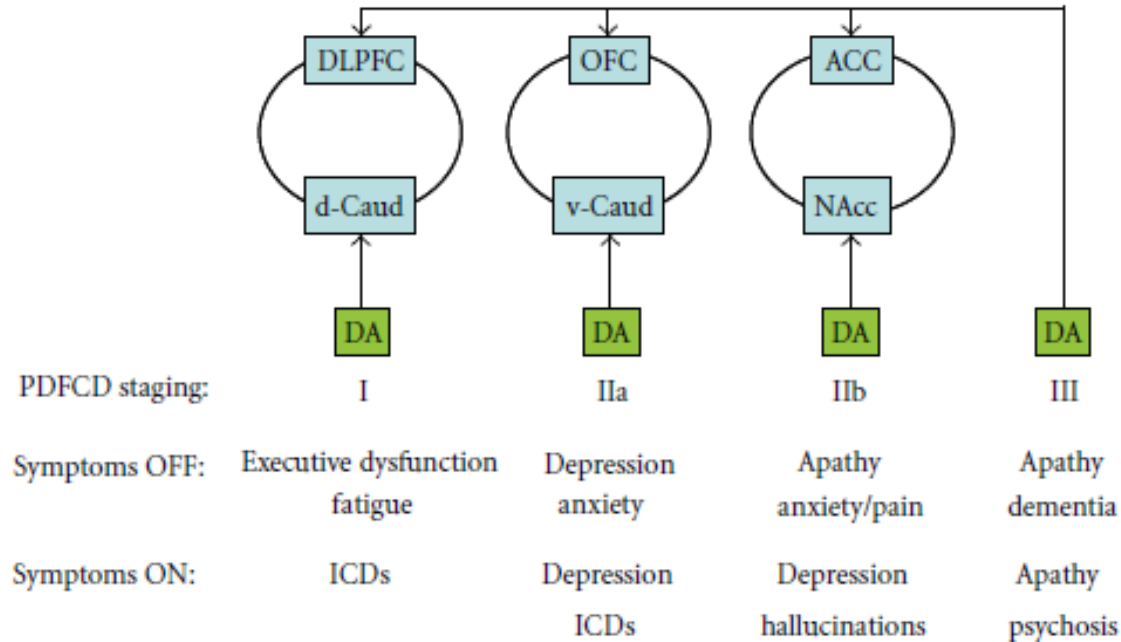


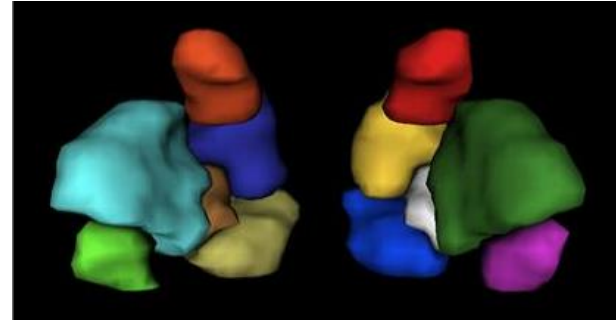
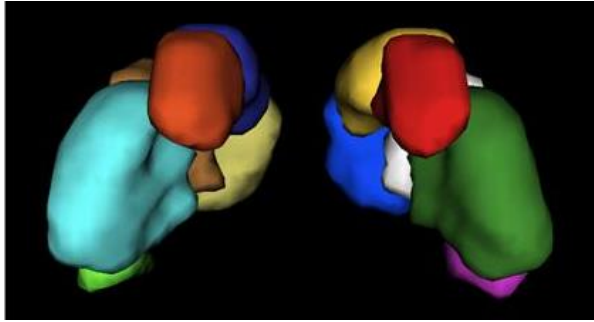
Figure 43–5 Global anatomy of cortico–basal ganglia–thalamocortical circuits. (ACA, anterior cingulate area; CMA, cingulate motor area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; GPi, internal segment of the globus pallidus; LOFC, lateral orbitofrontal cortex; M1, primary motor cortex; MD_{pl}, mediodorsal nucleus of thalamus, lateral part; MOFC, medial orbitofrontal cortex; PMC, premotor cortex; SEF, supplementary eye field; SMA, supplementary motor

area; SNr, substantia nigra pars reticulata; VA_{mc}, ventral anterior nucleus of thalamus, magnocellular part; VA_{pc}, ventral anterior nucleus of thalamus, parvocellular part; VL_{cr}, ventrolateral nucleus of thalamus, caudal part, rostral division; VL_m, ventrolateral nucleus of thalamus, medial part; VL_o, ventrolateral nucleus of thalamus, pars oralis.) (Adapted, with permission, from Wichmann and DeLong 2006.)

Sintomatología asociada EP



Subregiones del estriado

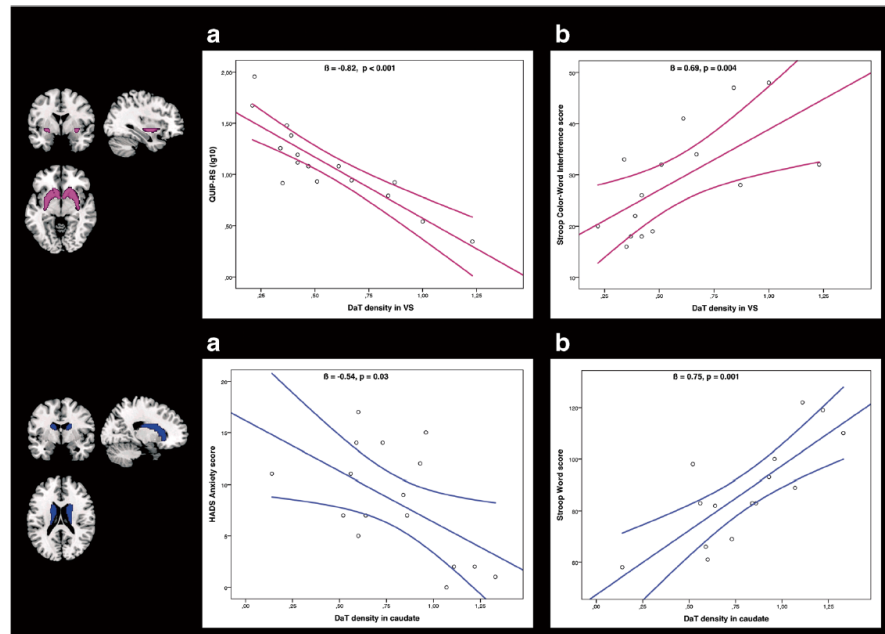


 L Posterior Caudate	 L Anterior Putamen	 R Posterior Caudate	 R Anterior Putamen
 L Anterior Caudate	 L Posterior Putamen	 R Anterior Caudate	 R Posterior Putamen
 L Ventral Striatum	 L Ventral Putamen	 R Ventral Striatum	 R Ventral Putamen



Nigrostriatal dopamine transporter availability, and its metabolic and clinical correlates in Parkinson's disease patients with impulse control disorders

I. Navalpotro-Gomez^{1,2} · R. Dacosta-Aguayo^{1,2} · F. Molinet-Dronda³ · A. Martin-Bastida⁴ · A. Botas-Peñín⁵ · H. Jimenez-Urbieto^{1,2} · M. Delgado-Alvarado^{1,2,6} · B. Gago^{1,2} · A. Quiroga-Varela^{1,2,7} · Maria C. Rodriguez-Oroz^{2,4,7,8,9} 



SUBREGIONES FUNCIONALES (Límbica, ejecutiva, sensoriomotora)

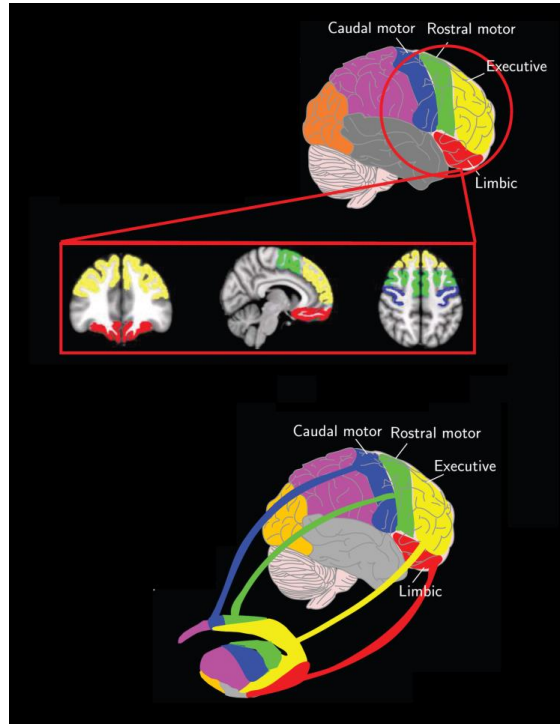
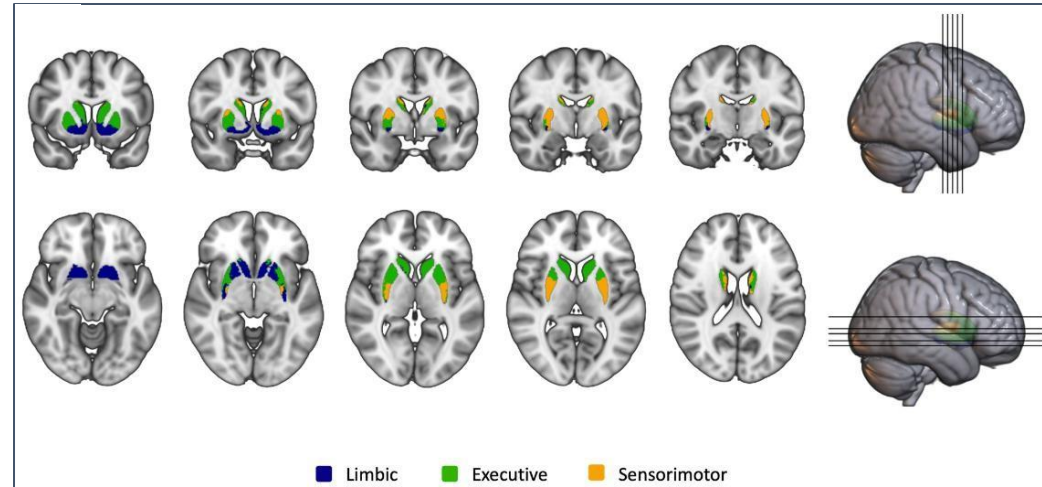


Imagen de las subregiones funcionales estriatales basadas en circuitos de conectividad corticoestriatal. Adaptado del atlas de *Tziortzi et al.*

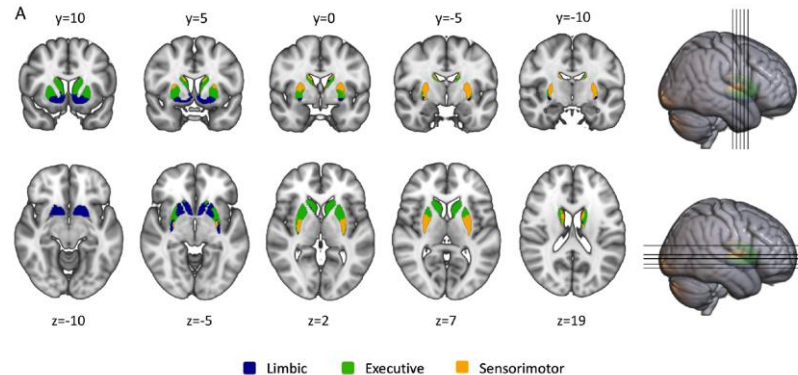


Representación del atlas de subdivisiones funcionales del estriado superpuestas en una plantilla de RMN.

Levodopa-Induced Dyskinesia in Parkinson Disease Specifically Associates With Dopaminergic Depletion in Sensorimotor-Related Functional Subregions of the Striatum

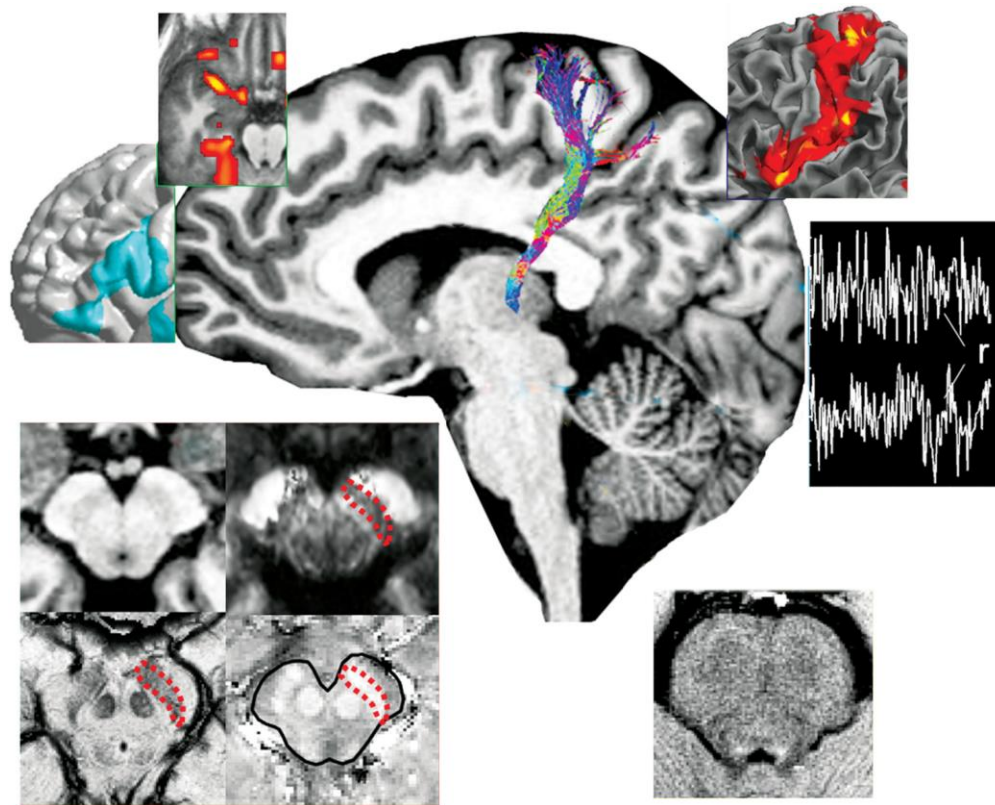
Miguel A. Labrador-Espinosa, MSc,*† Michel J. Grothe, PhD,*† Daniel Macías-García, MD,*†
 Silvia Jesús, PhD,*† Astrid Adarmes-Gómez, MD,*† Laura Muñoz-Delgado, MD,†
 Paula Fernández-Rodríguez, MD,‡ Juan Francisco Martín-Rodríguez, PhD,*†§ Ismael Huertas, PhD,*
 David García-Solís, MD,‡ and Pablo Mir, PhD*†

(*Clin Nucl Med* 2021;46: e296–e306)



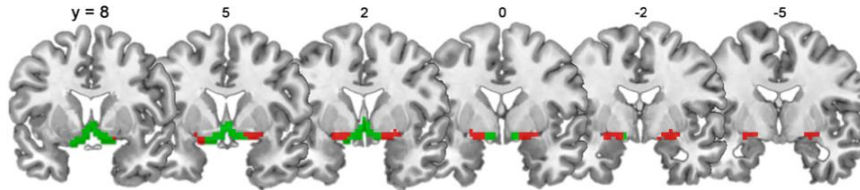
Measuring DAT depletion in functionally defined **sensorimotor-related striatal regions** of interest may provide a more sensitive tool to detect **LID-associated dopaminergic changes** at an early disease stage and could improve individual prognosis of this common clinical complication in PD

MRI methods used to study Parkinson's disease

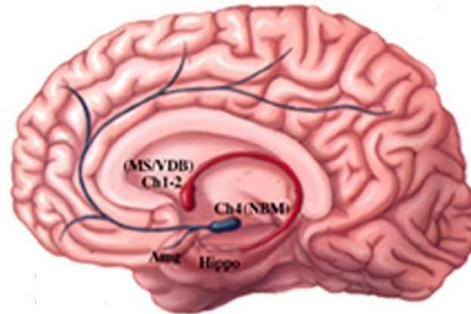


Basal Forebrain

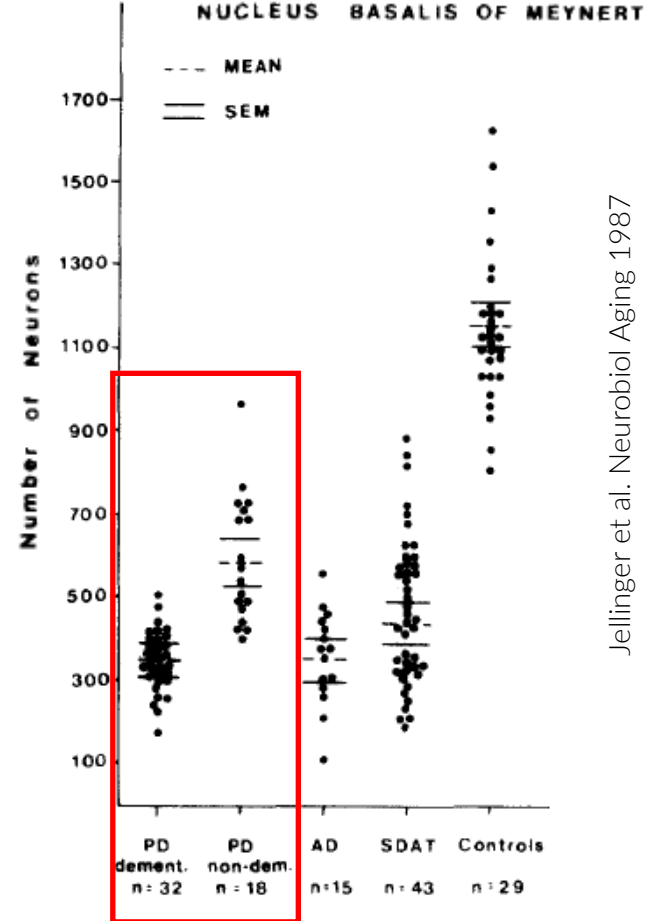
- **Cholinergic basal forebrain (BF)** is the main source of cholinergic innervation of the cerebral cortex and implicated in cognitive functions.
- BF degeneration is an established pathologic feature of both Alzheimer's disease (AD) and Parkinson's disease (PD) and associates with cognitive impairment.



Fritz et al. HBM 2019

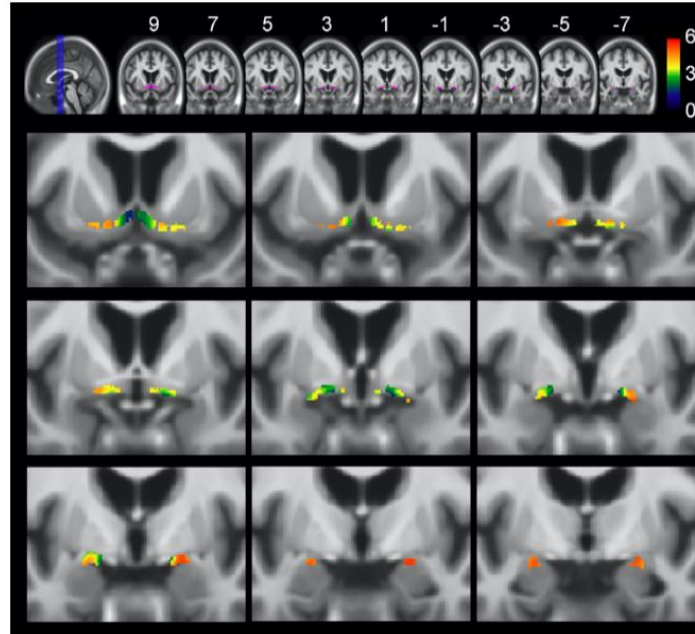


Mufson et al. J Chem Neuroanat 2003



BF atrophy in AD

Cross-sectional study BF atrophy in early stages of AD



Grothe et al. Biol Psychiatry. 2012

BF atrophy - PD

Automated magnetic resonance imaging (MRI)
morphometry techniques



In vivo MRI-based biomarkers of cBF atrophy

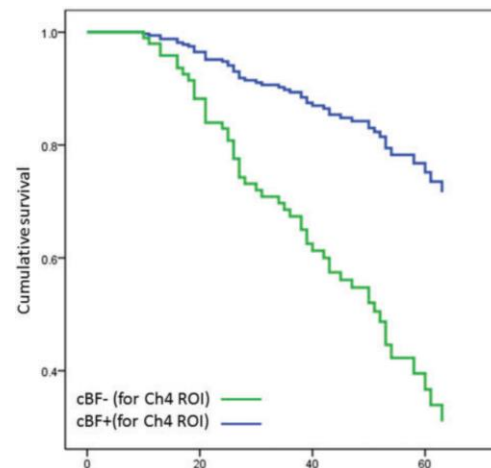
PPMI | 168 *de novo* PD patients with:

- High-resolution structural MRI (3T)
- Longitudinal assessment of cognitive impairment

In vivo cholinergic basal forebrain atrophy predicts cognitive decline in *de novo* Parkinson's disease

Nicola J. Ray,¹ Steven Bradburn,² Christopher Murgatroyd,² Umar Toseeb,³ Pablo Mir,^{4,5} George K. Kountouriotis,¹ Stefan J. Teipel^{6,7} and Michel J. Grothe⁷

BF volume as predictive biomarker



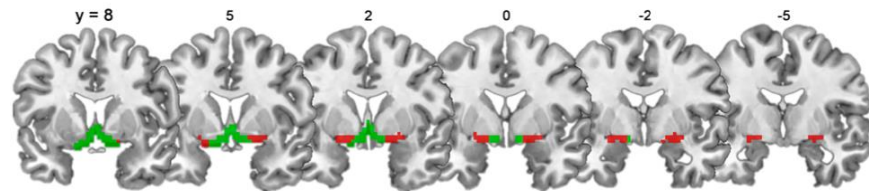
HR = 3.0
p = 0.02

BF atrophy - PD

Automated MRI morphometry techniques

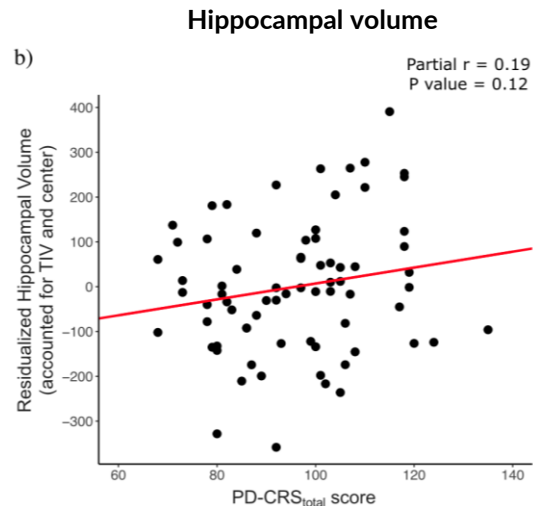
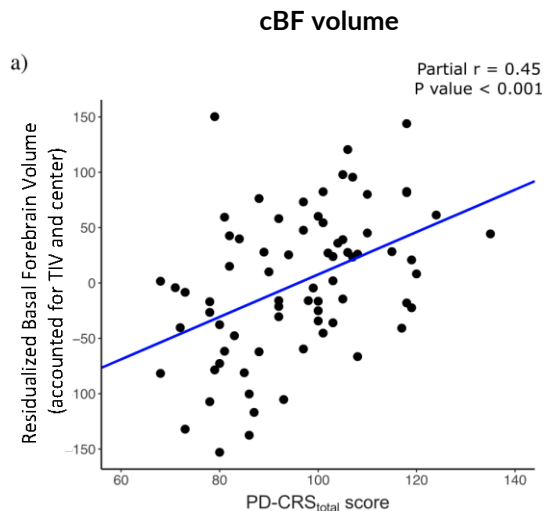


In vivo MRI-based biomarkers of cBF atrophy



Fritz et al. HBM 2019

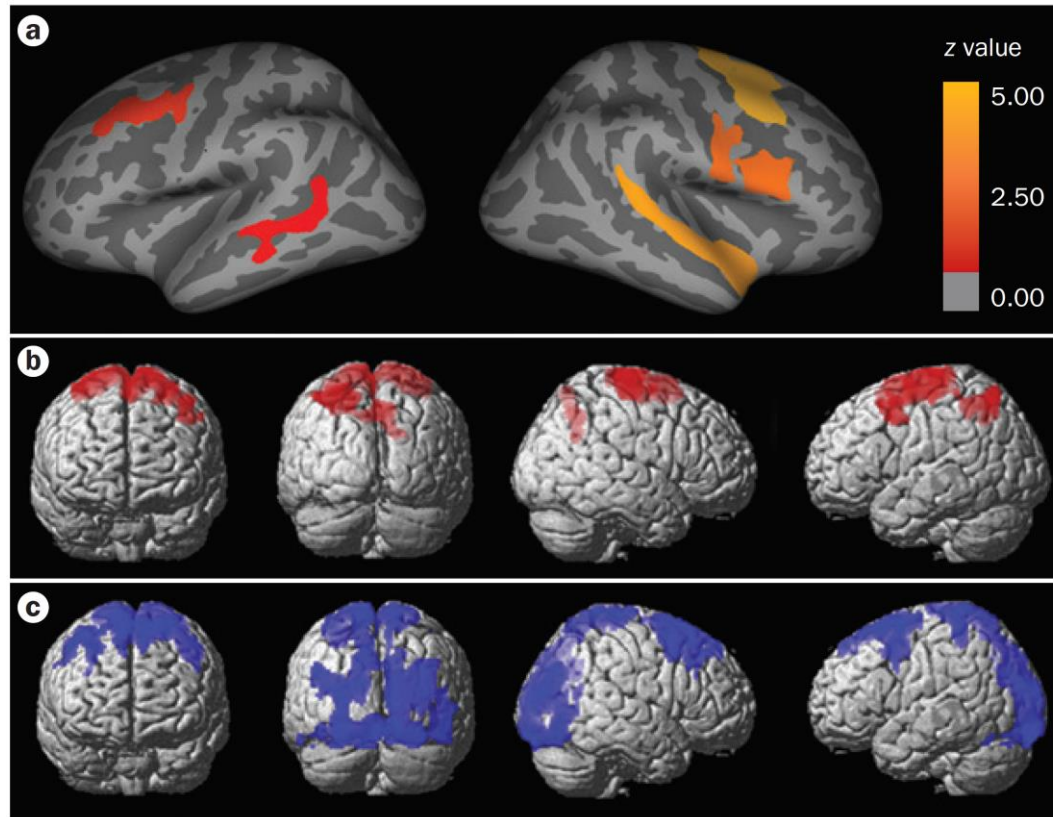
COPPADIS | 180 non-demented PD patients with structural MRI and PD-CRS



Grothe*, Labrador-Espinosa* et al. Parkinsonism and related disorders. 2021



Cortical imaging in Parkinson's disease

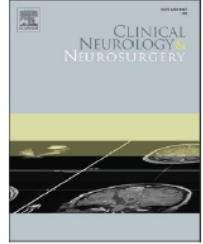




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Cortical macro and microstructural correlates of cognitive and neuropsychiatric symptoms in Parkinson's disease

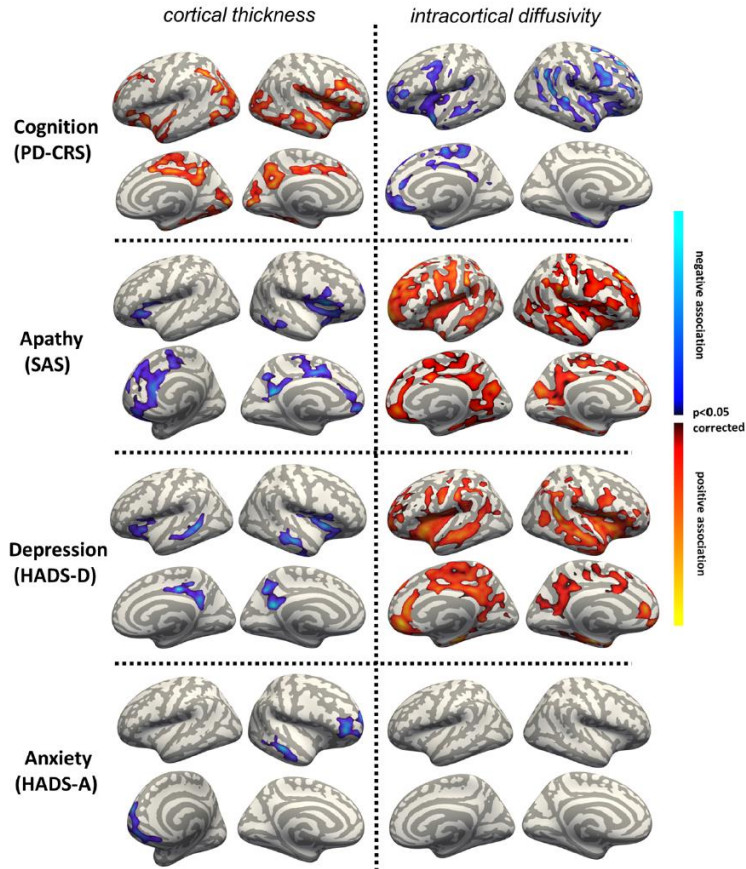
Frederic Sampedro ^{a,b,c,d,1}, Arnau Puig-Davi ^{a,b,c,e,1}, Saul Martinez-Horta ^{a,b,c},
Javier Pagonabarraga ^{a,b,c}, Andrea Horta-Barba ^{a,b,c,f,g}, Ignacio Aracil-Bolaños ^{a,b,c},
Jaime Kulisevsky ^{a,b,c,*}



Cortical macro and m neuropsychiatric sym

Frederic Sampetro ^{a,b,c,d,1},
Javier Pagonabarraga ^{a,b,c},
Jaime Kulisevsky ^{a,b,c,*}

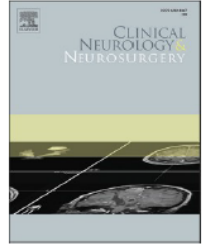
Cortical macro and microstructural correlates of non-motor symptoms in PD



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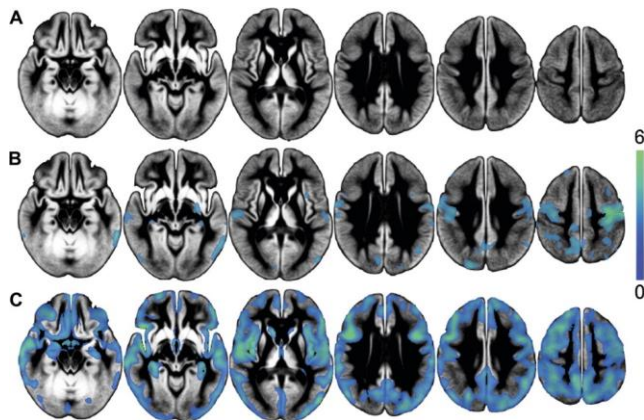
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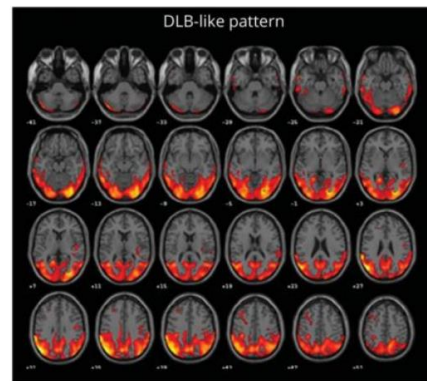
RM y PET-FDG como marcadores de la degeneración cortical asociada al deterioro cognitivo en EP

MRI:



Melzer et al. *JNNP*. 2012

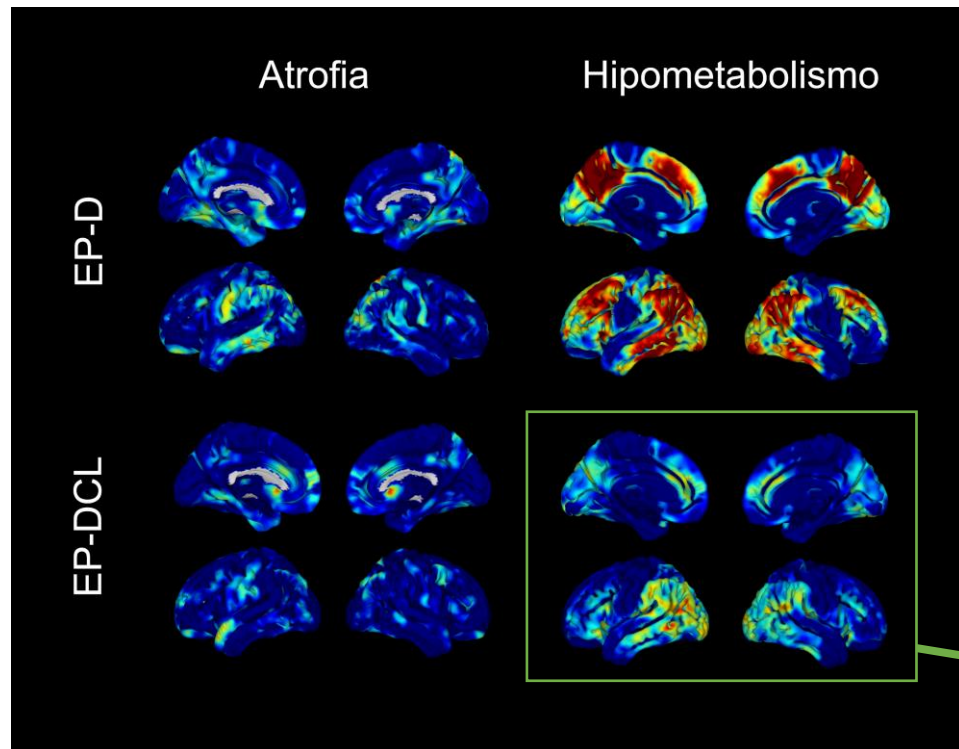
PET-FDG:



Pilotto et al. *Neurology*.
2018

Conclusion: FDG → Un patron similar a DLB (parieto-occipital predice el desarrollo de DCL en EP)

RM vs PET-FDG como marcadores de la degeneración cortical asociada al deterioro cognitivo en EP



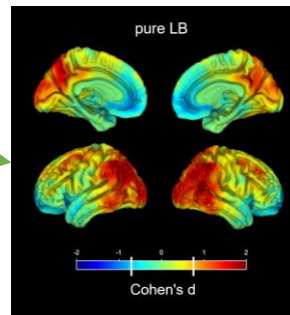
Silva-Rodríguez J et al. (manuscript in preparation)

En pacientes con DCL:

No se observa un patrón de atrofia consistente en DCL

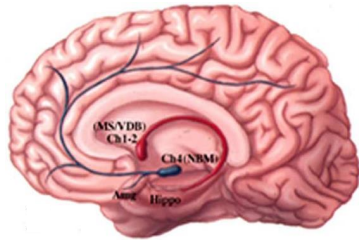
Si se observa un patrón de hipometabolismo postero-occipital.

Patrón muy similar a DLB



Silva-Rodríguez J et al. JNM 2023

CORTICAL DENERVATION - AD



Mufson et al. J Chem Neuroanat 2003

Experimental Neurology **170**, 36–47 (2001)

doi:10.1006/exnr.2001.7700, available online at <http://www.idealibrary.com> on **IDEAL**®

Selective Antibody-Induced Cholinergic Cell and Synapse Loss Produce Sustained Hippocampal and Cortical Hypometabolism with Correlated Cognitive Deficits

Susan E. Browne,* Ling Lin,† Anna Mattsson,† Biljana Georgievska,† and Ole Isacson†¹

Is the association between cBF atrophy and cognitive impairment mediated by cortical hypometabolism in humans?

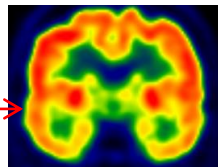
Multimodal study to assess the association between cBF atrophy and cortical FDG-PET signal (cortical function)

- 132 MCI subjects (MMSE = 27.5 ± 1.9 ; age = 72 ± 8)



cBF volume using MRI T1

?



Cortical hypometabolism using FDG-PET



ORIGINAL ARTICLE

Cognitive Correlates of Basal Forebrain Atrophy and Associated Cortical Hypometabolism in Mild Cognitive Impairment

Michel J. Grothe¹, Helmut Heinsen², Edson Amaro Jr³, Lea T. Grinberg^{4,5}, and Stefan J. Teipel^{1,6} for the Alzheimer's Disease Neuroimaging Initiative

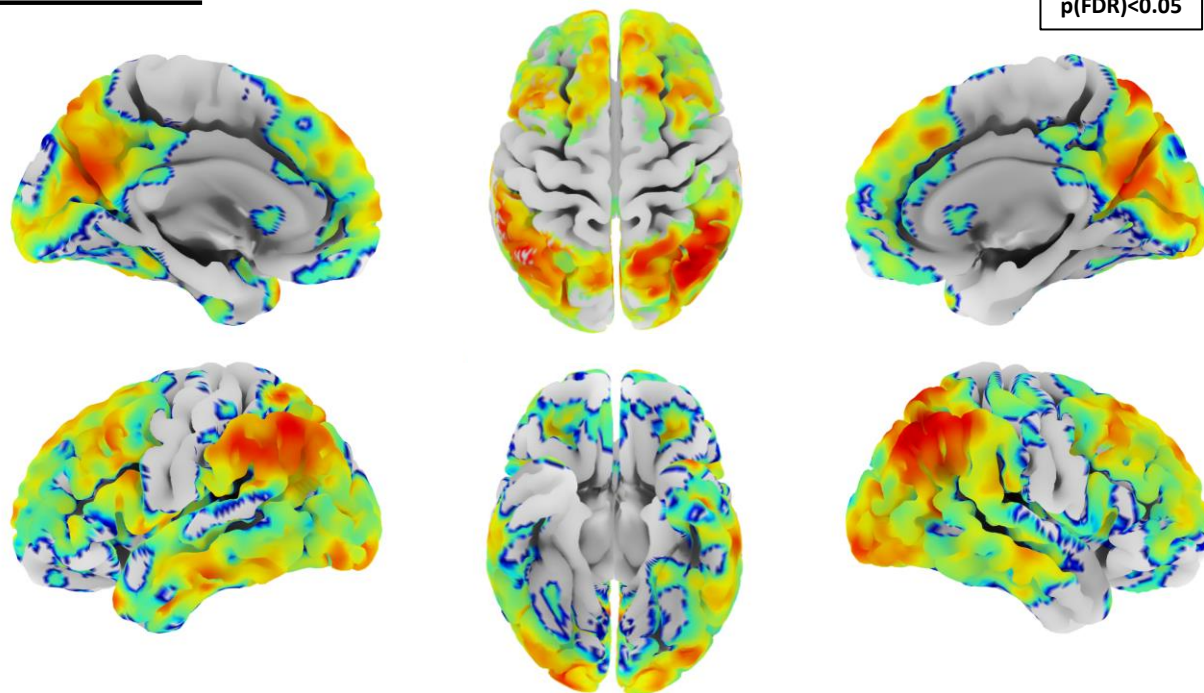
Grothe et al. Cerebral cortex. 2016

Association between cBF atrophy and cortical hypometabolism in PD

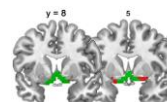
Posterior cBF

$p(\text{FDR}) < 0.05$

cBF atrophy associated with
widespread cortical
hypometabolism
in cognition-relevant regions



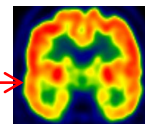
$p(\text{FDR}) < 0.05$ Correlation coefficient



Fritz et al. HBM 2019



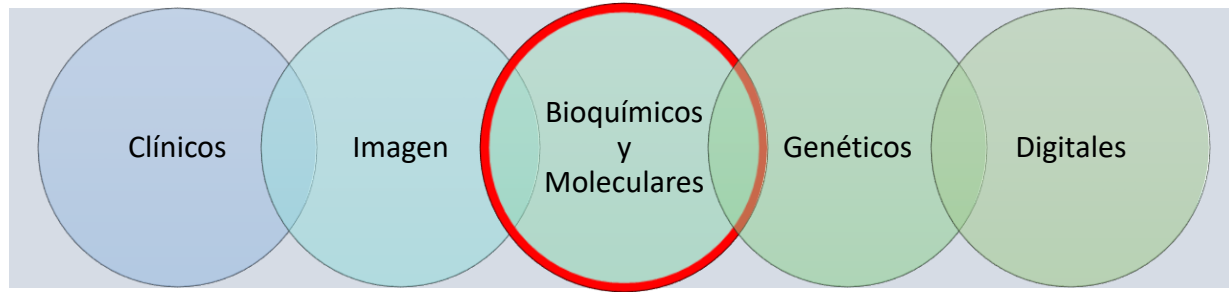
cBF volume using
MRI T1



Metabolism
using FDG-PET

Biomarcadores y enfermedad de Parkinson

La fuente de biomarcadores en la enfermedad de Parkinson es amplia y sigue incrementándose incluyendo:



PERO ninguno ha mostrado por sí solo ser suficientemente sensible y específico para el diagnóstico o pronóstico de la EP.

Modelos multimodales: integración de distintos biomarcadores procedentes de distintas fuentes.

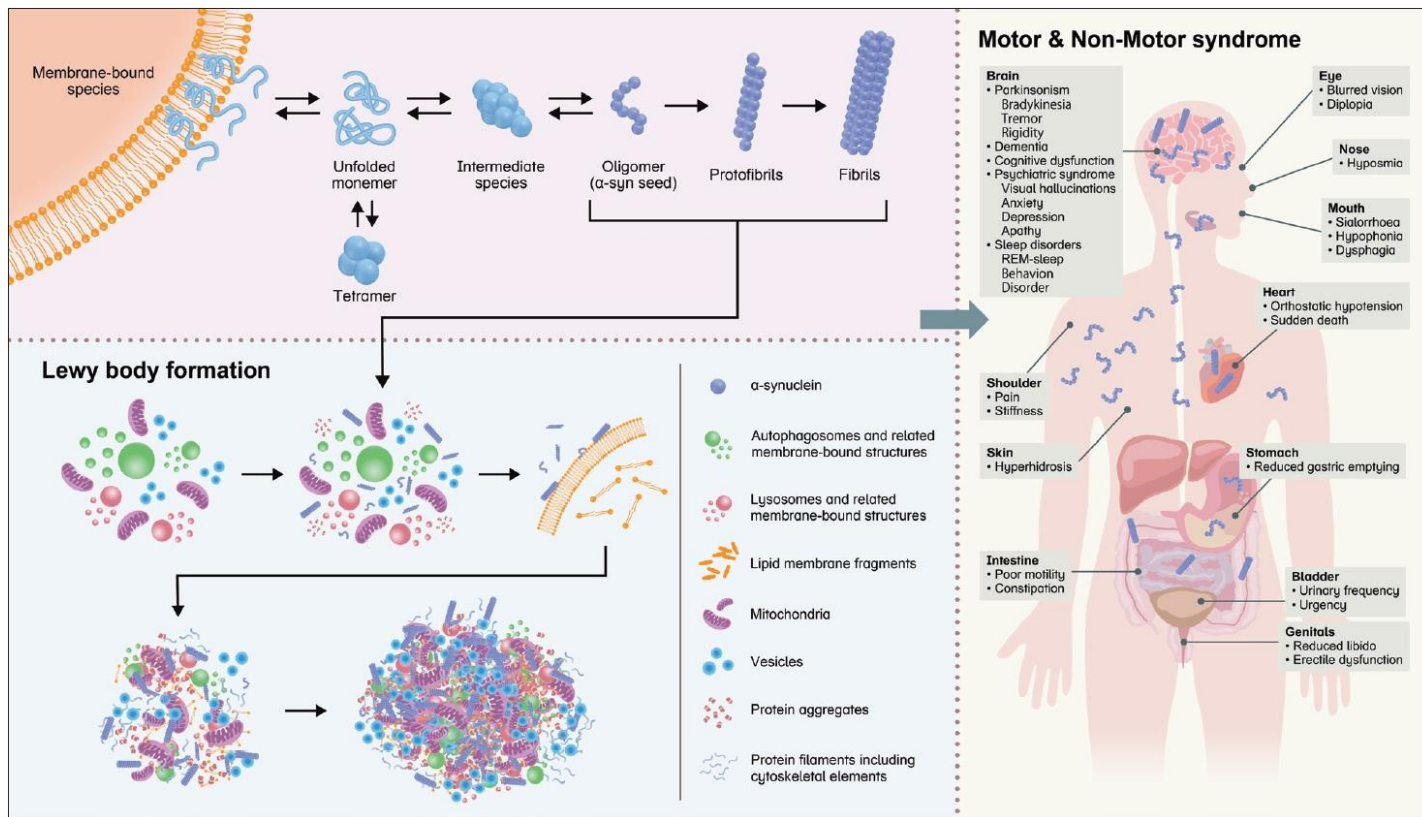
Tipos de Biomarcadores:

- De susceptibilidad de riesgo
- Diagnóstico
- De monitorización
- Pronóstico
- Predictivo

Objetivo:

- Identificar EP prodrómica: Intervención precoz y tratamientos neuroprotectores.
- Diagnóstico certero, especialmente en estadios precoces, y diagnóstico diferencial con otras entidades.
- Monitorizar tratamientos
- Medicina personalizada

Systematic distribution and pathogenic mechanisms of α -synucleinopathies



Detección de α -sinucleína malplegada y con tendencia a agregarse de forma patológica.

Técnicas ultrasensibles que permiten detectar la agregación de proteínas mal plegadas

- RT-QuIC (Real-Time Quaking-Induced Conversion)
- PMCA (Protein-misfolding Cyclic Amplification o amplificación cíclica del plegamiento incorrecto de proteínas)

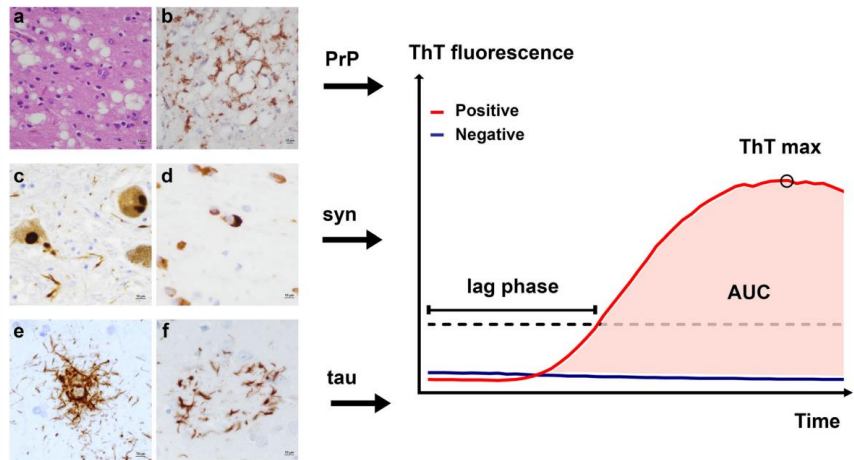


Fig. 2 Main fields of application of the RT-QuIC assay and kinetic parameters analysed. Prion disease (a, b): spongiform change (a) and perivascular pattern of PrP^{Sc} deposition (b) in the occipital cortex of sCJD MM2C. Synucleinopathies (c, d): Lewy bodies and neurites in the substantia nigra of a DLB patient (c); glial cytoplasmic inclusions in the cerebellar with matter of a MSA case (d). 4R-tauopathies (e, f): tufted astrocyte (e), and astrocytic plaque (f) in the striatum of PSP and CBD cases. Hematoxylin and eosin stain (a), immunohistochemistry for PrP (mAb 3F4, dilution 1:400, Signet Labs), (b), α -Syn (LB509, dilution 1:100, Thermo Fisher), (c, d), hyperphosphorylated tau (AT8, dilution 1:100, Innogenetics), (e, f). Lag phase is defined as the time interval between the beginning of the reaction and the time in which the curve of the fluorescent signal crosses the threshold (dot line); ThT max (circle) is defined as the maximum fluorescence value reached by the curve; AUC (area under the curve)

Principales campos de aplicación del ensayo RT-QuIC

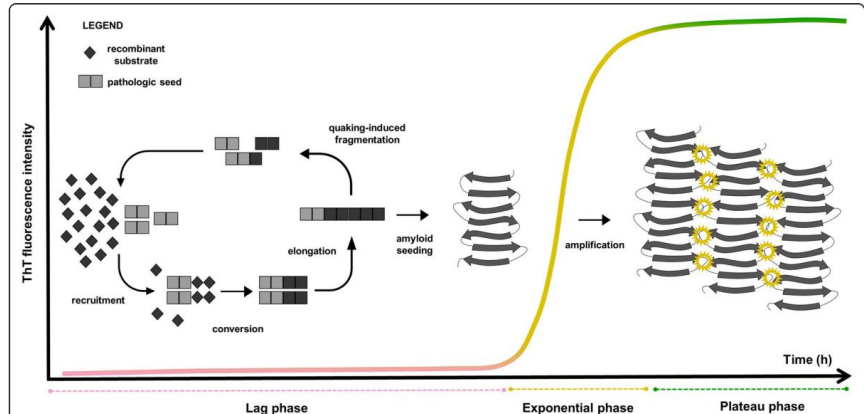


Fig. 1 Schematic representation of the RT-QuIC reaction. The RT-QuIC reaction may be divided into temporal stages: the lag phase, the exponential phase and the plateau phase. The lag phase represents the time required for the reaction to take place. During this step, the seed is allowed to contact the substrate and to trigger the conformational change. Once enough energy is received by the system, ThT sensitive oligomers emerge, which incorporate the monomers into small aggregates (exponential phase). Eventually, when all the substrate is incorporated into fibrils, a plateau phase is observed

Representación esquemática de la reacción RT-QuIC. La reacción RT-QuIC se puede dividir en etapas temporales: la fase de retraso, la fase exponencial y la fase de meseta.

Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies

Graham Fairfoul¹, Lynne I. McGuire¹, Suvankar Pal^{1,2}, James W. Ironside¹, Juliane Neumann³, Sharon Christie⁴, Catherine Joachim⁴, Margaret Esiri⁴, Samuel G. Evetts³, Michal Rolinski³, Fahd Baig³, Claudio Ruffmann³, Richard Wade-Martins⁵, Michele T. M. Hu², Laura Parkkinen² & Alison J. E. Green¹

1. COHORTE EXPLORATORIA

Objetivo:

- Investigar sensibilidad y especificidad
- Calcular el óptimo volumen de LCR

99 muestras de LCR de pacientes con enf neurodegenerativas con dx AP en 3 volúmenes diferentes (5, 10 y 15 uL)

Con 15 uL, sensibilidad del 92% en DCL y del 65% en patología mixta DCL/EA.

Ninguno de los CS, o puros EA, DCB o PSP fueron positivos para agregados de alfasinucleína.

2. COHORTE DE VALIDACIÓN (Cohorte Oxford Discovery):

15 CS, 20 EP y 3 en riesgo con TCSREM

Table 2. Positive RT-QuIC reactions seeded with CSF samples from patients with neuropathologically confirmed DLB, mixed DLB/AD, AD with incidental LB, AD, PD, and healthy controls (Exploratory group) and patients with clinically diagnosed PD, at-risk PD, neuropathologically confirmed corticobasal degeneration and supranuclear palsy and PD controls (Confirmatory group).

	Number of positive RT-QuIC (%) using 5 μ L	Number of positive RT-QuIC (%) using 10 μ L	Number of positive RT-QuIC (%) using 15 μ L
Exploratory patient group (n)			
AD with incidental LB (13)	2 (15%)	4 (31%)	2 (15%)
Healthy Controls (20)	0 (0%)	0 (0%)	0 (0%)
Mixed DLB/AD (17)	9 (53%)	11 (65%)	11 (65%)
Parkinson's disease (2)	2 (100%)	2 (100%)	2 (100%)
Progressive supranuclear palsy (2)	0 (0%)	0 (0%)	0 (0%)
Corticobasal degeneration (3)	0 (0%)	0 (0%)	0 (0%)
Pure AD (30)	2 (7%)	1 (3%)	0 (0%)
Pure DLB (12)	10 (83%)	11 (92%)	11 (92%)
Sensitivity (DLB)	83%	92%	92%
Specificity (vs. controls)	100%	100%	100%
Specificity (vs. AD)	93%	97%	100%
Specificity (vs. controls + AD)	96%	98%	100%
Confirmatory patient group (n)			
Parkinson disease (20)	—	—	19 (95%)
At-risk PD patients (3)	—	—	3 (100%)
Parkinson's disease controls (15)	—	—	0 (0%)
Sensitivity (PD)	—	—	95%
Specificity	—	—	100%

A positive RT-ASA response was classified as a relative fluorescence unit (rfu) value of >2SD above the mean of the negative controls at 120 h of at least one of the CSF duplicates.

Conclusiones:

Sensibilidad del **95% y 92% en EP y DCL, respectivamente, y 100% de especificidad** para la detección de alfa-sinucleína anormal.

Además los 3 pacientes con TCSREM mostraban respuesta positiva en la RT-QuIC (BM de susceptibilidad de riesgo en EP prodrómica?)

Ni PSP ni DCB tuvieron respuesta positiva en la RT-QuIC (BM de diagnóstico diferencial?)

Detection of α -synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study

Alex Iranzo, Graham Fairfoul, Anutra Chumbala Na Ayudhaya, Monica Serradell, Ellen Gelpi, Isabel Vilaseca, Raquel Sanchez-Valle, Carles Gaig, Joan Santamaria, Eduard Tolosa, Renata L Riha, Alison J E Green

Objetivo: analizar si RT-QuIC puede detectar alfa-sinucleina en LCR de personas con TCSREM y pudiera ser útil como biomarcador prodrómico.

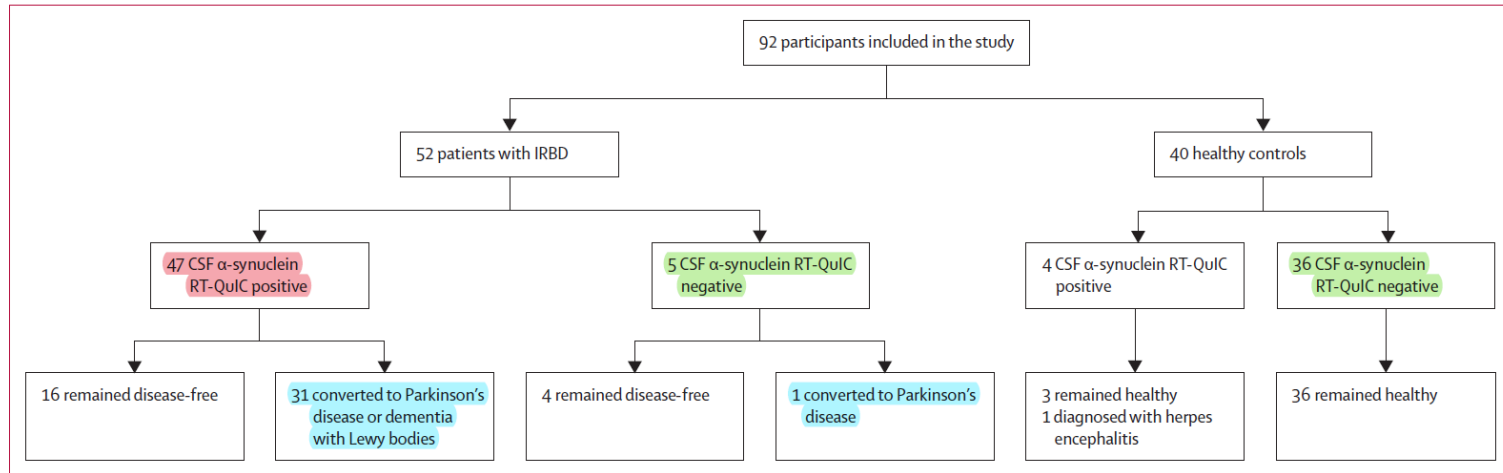


Figure 2: Baseline CSF α -synuclein RT-QuIC responses in patients with IRBD and healthy controls

La RT-QuIC fue positiva para alfasinucleina en LCR en **47 de 52 pacientes con TCSREM (90%)** y en **4 de 40 CS (10%)** → S 90.4% y E 90%.

En pacientes con TCSREM, la detección de alfasinucleina en LCR por RT-QuIC como BM de conversión a EP / DCL → **S 96.9%, E 20%**, VPP del 66% y VPN 80%.

El % de pacientes con TCSREM que tenían más del 80% de ser EP prodrómicos fue mayor en los que eran alfa-sinucleina + y convirtieron a EP, respecto a los que eran alfa-sinucleina + y permanecieron libres de enfermedad (94% vs 63%, $p=0.013$). – ¿BM de susceptibilidad de riesgo?

Discriminating α -synuclein strains in Parkinson's disease and multiple system atrophy

Mohammad Shah Nawaz¹, Abhisek Mukherjee¹, Sandra Pritzkow^{1,6}, Nicolas Mendez^{1,6}, Prakruti Rabadia¹, Xiang Liu², Bo Hu², Ann Schmeichel³, Wolfgang Singer³, Gang Wu⁴, Ah-Lim Tsai⁴, Hamid Shirani⁵, K. Peter R. Nilsson⁵, Phillip A. Low³, Claudio Soto^{1,*}

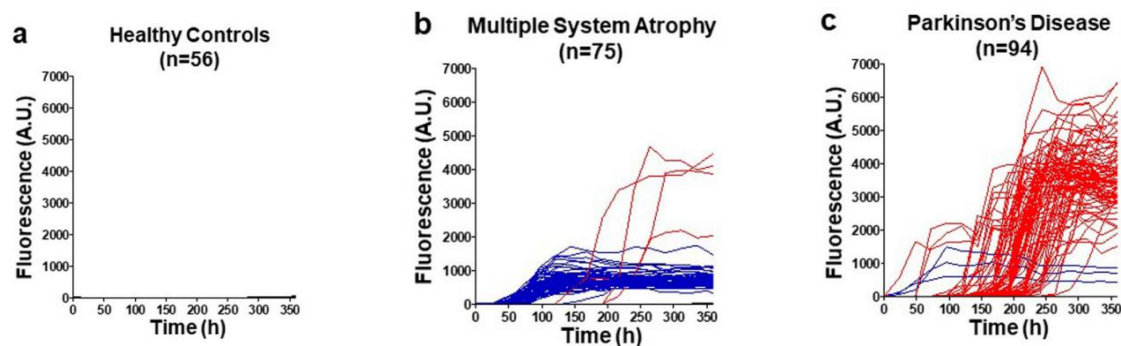


Figura. Cinética de la agregación de la alfasinucleína presente en LCR de pacientes con EP, AMS y controles sanos.

Los pacientes con AMS presentan una agregación más rápida, pero alcanzan una menor señal plateau de fluorescencia.

El mismo estudio muestra que los agregados de alfa sinucleína en AMS y EP muestran distintas propiedades estructurales y bioquímicas.

RESEARCH

Open Access



Efficient RT-QulC seeding activity for α -synuclein in olfactory mucosa samples of patients with Parkinson's disease and multiple system atrophy

Chiara Maria Giulia De Luca^{1†}, Antonio Emanuele Elia^{2†}, Sara Maria Portaleone³, Federico Angelo Cazzaniga¹, Martina Rossi⁴, Edoardo Bistaffa¹, Elena De Cecco⁴, Joanna Narkiewicz⁴, Giulia Salzano⁴, Olga Carletta¹, Luigi Romito², Grazia Devigili², Paola Soliveri², Pietro Tiraboschi¹, Giuseppe Legname⁴, Fabrizio Tagliavini⁵, Roberto Eleopra², Giorgio Giaccone¹ and Fabio Moda^{1*}

JAMA Neurology | Original Investigation

Skin α -Synuclein Aggregation Seeding Activity as a Novel Biomarker for Parkinson Disease

Zerui Wang, MD, PhD; Katelyn Becker, MS; Vincenzo Donadio, MD, PhD; Sandra Siedlak, MS; Jue Yuan, MS; Masih Rezaee, MD; Alex Incensi, MSc; Anastasia Kuzkina, MD; Christina D. Orrú, PhD; Curtis Tatsuoka, PhD; Rocco Liguori, MD; Steven A. Gunzler, MD; Byron Caughey, PhD; Maria E. Jimenez-Capdeville, PhD; Xiongwei Zhu, PhD; Kathrin Doppler, MD; Li Cui, MD, PhD; Shu G. Chen, PhD; Jiyun Ma, MD, PhD; Wen-Quan Zou, MD, PhD

doi:10.1093/brain/awb005

BRAIN 2021; 144: 1118–1126 | 1118

BRAIN
A JOURNAL OF NEUROLOGY

Alpha-synuclein seeds in olfactory mucosa of patients with isolated REM sleep behaviour disorder

Ambra Stefani,¹ Alex Iranzo,² Evi Holzknecht,¹ Daniela Perra,³ Matilde Bongianini,³ Carles Galg,² Beatrice Heim,¹ Monica Serradell,² Luca Sacchetto,⁴ Alicia Garrido,² Stefano Capaldi,² Almudena Sánchez-Gómez,² Maria Paola Cecchini,⁶ Sara Mariotto,³ Sergio Ferrari,³ Michele Fiorini,³ Joachim Schmutzhard,⁷ Pietro Cocchiara,³ Isabel Vilaseca,⁸ Lorenzo Brozzetti,³ Salvatore Monaco,³ M. Jose Martí,² Klaus Seppi,¹ Eduardo Tolosa,² Joan Santamaria,² Birgit Högl,¹ Werner Poewe^{1,2} and Gianluigi Zanusso³ for the SINBAR (Sleep Innsbruck Barcelona) group

	Diagnostic potential			Disease progression	Comments
	Prodromal Parkinson's disease	Manifest Parkinson's disease	Differential diagnosis (non-Parkinson's disease)		
Tissue biopsies					
Dermal α-synuclein immunohistochemistry ⁸⁶	Informative	Informative	Not informative	Unknown	Requires multi-site sampling; limited sensitivity, not specific to Parkinson's disease vs other synucleinopathies
Dermal α-synuclein seeding activity (RT-QulC; PMCA) ⁹³	Unknown	Informative	Informative	Unknown	Limited in vivo information
Olfactory mucosa α-synuclein seeding activity (RT-QulC) ⁹⁶	Possibly informative	Informative	Unknown	Unknown	Few studies
Gastrointestinal α-synuclein ⁸⁷	Unknown	Insufficient data	Not informative	Unknown	Invasive; requires multi-site sampling; limited sensitivity
Salivary gland α-synuclein ^{87,88}	Informative	Informative	Not informative	Not informative	Invasive; limited sensitivity



Propagative α -synuclein seeds as serum biomarkers for synucleinopathies

Received: 1 July 2022

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Check for updates

Ayami Okuzumi¹, Taku Hatano¹, Gen Matsumoto², Shuko Nojiri³,
Shin-ichi Ueno¹, Yoko Imamichi-Tatano¹, Haruka Kimura¹,
Soichiro Kakuta⁴, Akihide Kondo⁵, Takeshi Fukuhara⁶, Yuanzhe Li¹,
Manabu Funayama¹, Shinji Saiki^{1,7}, Daisuke Taniguchi¹, Taiji Tsunemi¹,
Deborah McIntyre⁸, Jean-Jacques Gérardy⁹, Michel Mittelbronn⁹,
Rejko Kruger^{8,10}, Yasuo Uchiyama¹¹, Nobuyuki Nukina¹² & Nobutaka Hattori^{1,6}✉

α -syn SAA amplifying pathological α -syn derived from neuronal extracellular vesicles (NE) in blood

<https://doi.org/10.1093/brain/awac115>

BRAIN 2022; 145; 3058–3071 | 3058

BRAIN
ORIGINAL ARTICLE



Detection of neuron-derived pathological α -synuclein in blood

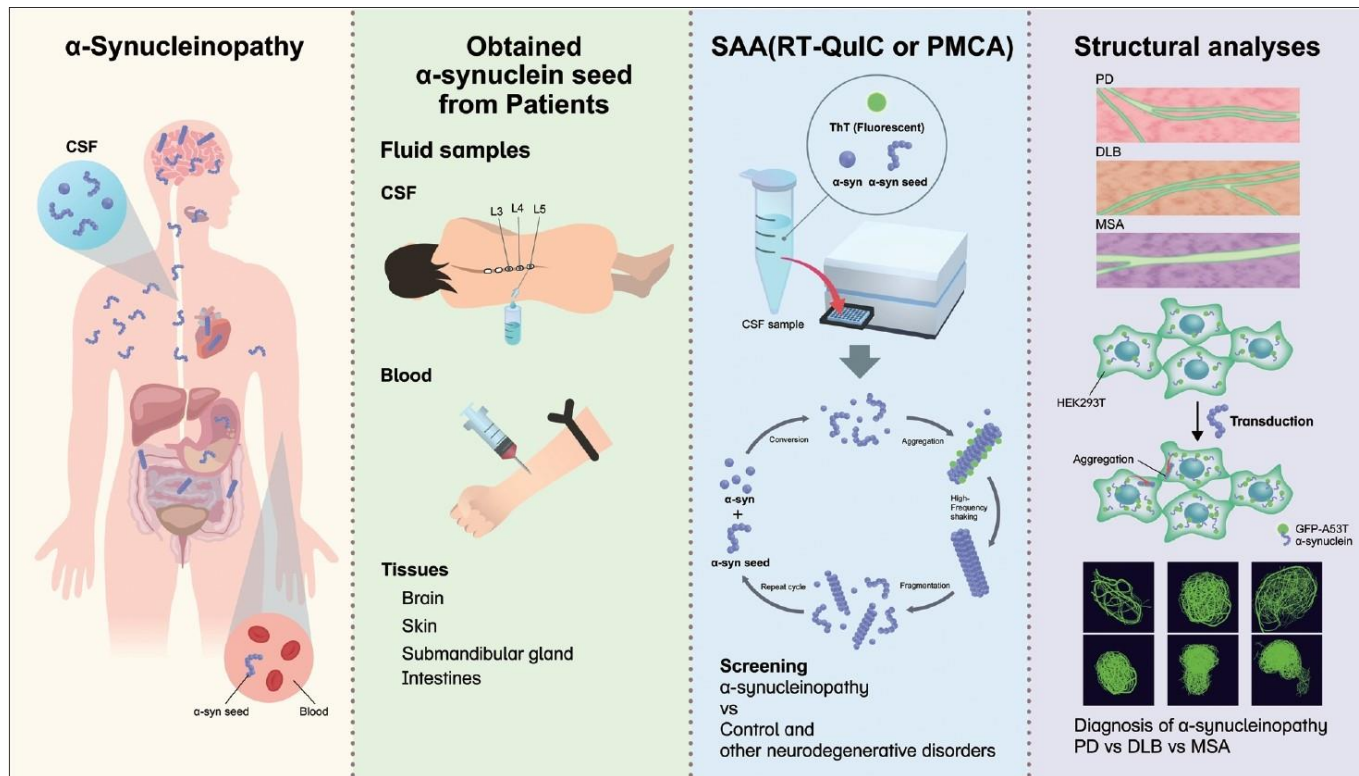
Annika Kluge,¹ Josina Bunk,² Eva Schaeffer,¹ Alice Drobny,³ Wei Xiang,³ Henrike Knacke,¹ Simon Bub,³ Wiebke Lückstädt,⁴ Philipp Arnold,⁵ Ralph Lucius,⁴ Daniela Berg^{1,†} and Friederike Zunke^{3,†}

RESEARCH ARTICLE

Detecting Misfolded α -Synuclein in Blood Years before the Diagnosis of Parkinson's Disease

Annika Kluge, MD,^{1*} Eva Schaeffer, MD,¹ Josina Bunk, MD,¹ Michael Sommerauer, MD,^{2,3} Sinah Röttgen, MSc,^{2,3} Claudia Schulte, MSc,^{4,5} Benjamin Roeben, MD,^{4,5} Anna-Katharina von Thaler, PhD,¹ Julius Welzel, MSc,¹ Ralph Lucius, MD, PhD,⁶ Sebastian Heinzl, PhD,¹ Wei Xiang, PhD,⁷ Gerhard W. Eschweiler, MD,^{8,9} Walter Maetzler, MD,¹ Ulrike Suenkel, MD,^{9,10} and Daniela Berg, MD¹

Diagnostic potential of α -synuclein seeds as biomarkers for α -synucleinopathies





A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria

Günter U Höglinger, Charles H Adler, Daniela Berg, Christine Klein, Tiago F Outeiro, Werner Poewe, Ronald Postuma, A Jon Stoessl, Anthony E Lang

Lancet Neurol 2024; 23: 191–204



A biological definition of neuronal α -synuclein disease: towards an integrated staging system for research

Tanya Simuni, Lana M Chahine*, Kathleen Poston, Michael Brumm, Teresa Buracchio, Michelle Campbell, Sohini Chowdhury, Christopher Coffey, Luis Concha-Marambio, Tien Dam, Peter DiBiaso, Tatiana Foroud, Mark Frasier, Caroline Gochanour, Danna Jennings, Karl Kiebertz, Catherine M Kopil, Kalpana Merchant, Brit Mollenhauer, Thomas Montine, Kelly Nudelman, Gennaro Pagano, John Seibyl, Todd Sherer, Andrew Singleton, Diane Stephenson, Matthew Stern, Claudio Soto, Caroline M Tanner, Eduardo Tolosa, Daniel Weintraub, Yuge Xiao, Andrew Siderowf, Billy Dunn, Kenneth Marek*

Lancet Neurol 2024; 23: 178–90



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Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis



Review article

Loss of monomeric alpha-synuclein (synucleinopenia) and the origin of Parkinson's disease

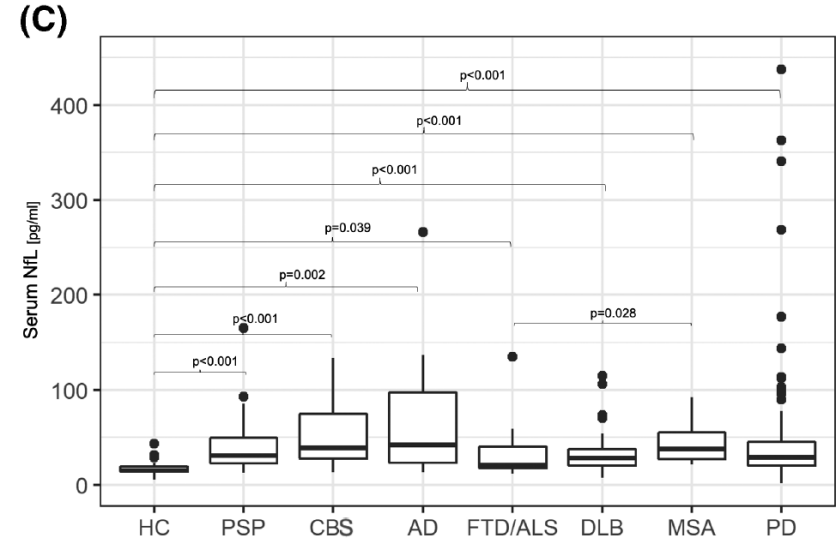
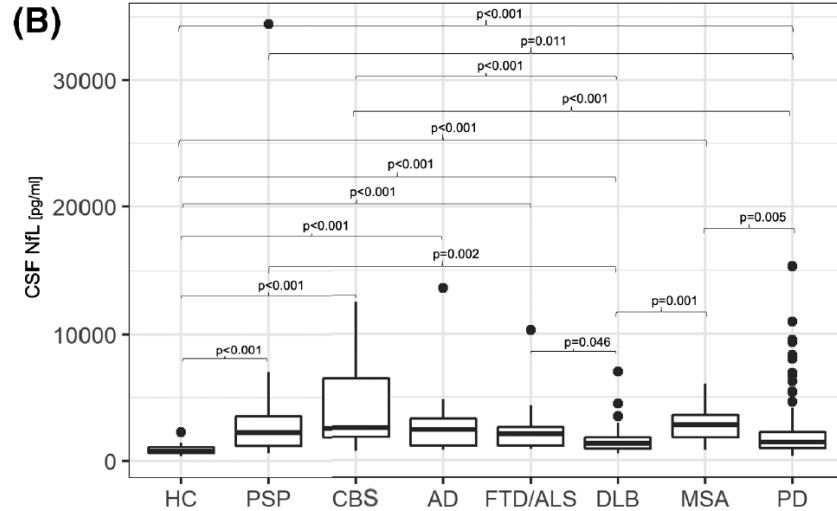
Alberto J. Espay^{a,*}, Andrew J. Lees^b



2.5. Myth 5. A positive seed amplification assay indicates proteins seed in the brain

Neurofilamentos de cadena ligera (NfL)

Es un biomarcador de degeneración axonal



Los niveles de NFL están ↑ en LCR y suero en todos los grupos diagnósticos frente a CS ($p < 0.001$)

Capacidad diagnóstica:

- **EP vs CS:**

Biomarcadores útiles en suero: sTREM (receptor desencadenante soluble expresado en células mieloides 2)(AUC 0.879), S100 (proteína B fijadora de calcio) (AUC 0.873), **NfL (caedena ligera de neurofilamento)(AUC 0.769)**, aSyn (AUC 0.746)

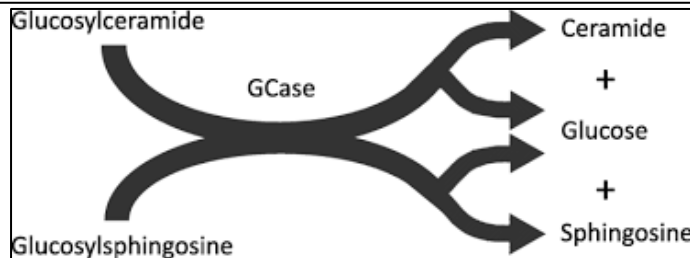
- **Diagnóstico diferencial** entre sinucleinopatías y taupatías:

~~En LCR, el mejor fue el NfL.~~

En suero, ningún biomarcador mostró diferencias significativas.

Cerebrospinal Fluid β -Glucocerebrosidase Activity Is Reduced in Parkinson's Disease Patients

Lucilla Parnetti, MD, PhD,^{1†*} Silvia Paciotti, PhD,^{1b,2†} Paolo Eusebi, PhD,¹ Andrea Dardis, PhD,³ Stefania Zampieri, PhD,³ Davide Chiasserini, PhD,¹ Anna Tasegian, PhD,² Nicola Tambasco, MD, PhD,¹ Bruno Bembi, MD,³ Paolo Calabresi, MD,¹ and Tommaso Beccari, PhD²



ENZIMAS LISOSOMALES –
 β -glucocerebrosidasa (Gcase)

Una de las vías implicadas asociadas en la acumulación de alfa-sinucleína agregada es la vía autofagia-lisosomal, que representa una de las rutas intracelulares de degradación de la alfasinucleína. (Zunke *et al*, 2019)

↓ **Actividad Gcase en EP frente a CS** – (Parnetti *et al.*, 2014a; Lerche *et al.*, 2021, Huebecker *et al*, 2019)

- Aproximadamente 5-20% de EP esporádico o idiopático se asocia con variantes en el gen *GBA*.
- Disminución se encuentra presente de forma independiente a ser portador de variantes en el gen *GBA*.
- ¿Terapias modificadoras de enfermedad con diana en la actividad Gcase?

Biomarcadores Inflamatorios - Citoquinas

Table. Summary of Comparative Outcomes for Measurements of Peripheral Blood Cytokine Levels

Cytokine	No. of Studies	No. With PD/Controls	Main Effect			Heterogeneity			Publication Bias		
			Hedges g (95% CI)	z Score	P Value	Q Statistic	df	P Value	I ² Statistic	Egger Intercept	P Value
IL-6	13	898/678	0.325 (0.007 to 0.643)	2.002	.045	100.328	12	<.001	88.039	0.57	.81
TNF	9	809/528	0.354 (0.144 to 0.563)	3.31	.001	21.968	8	.005	63.583	0.83	.63
IL-1 β	6	623/339	0.382 (0.142 to 0.621)	3.124	.002	12.098	5	.03	58.670	0.90	.66
CRP	6	696/411	0.323 (0.052 to 0.593)	2.338	.02	22.317	5	<.001	77.595	3.11	.42
IL-10	5	376/181	0.329 (0.051 to 0.607)	2.323	.02	7.193	4	.13	44.390	0.41	.83
RANTES	5	171/154	0.605 (0.111 to 1.099)	2.402	.02	15.361	4	.004	73.961	2.47	.38
IFN- γ	5	432/293	0.745 (-0.192 to 1.682)	1.558	.12	101.479	4	<.001	96.058	4.08	.43
IL-2	3	282/138	0.789 (0.105 to 1.472)	2.261	.02	12.274	2	.002	83.706	4.11	.32
IL-4	3	269/126	0.031 (-0.191 to 0.253)	0.273	.79	2.046	2	.36	2.244	0.03	.99
IL-8	3	298/130	0.072 (-0.136 to 0.279)	0.677	.50	1.078	2	.58	0	-0.44	.79

Abbreviations: CRP, C-reactive protein; *df*, degrees of freedom; IFN- γ , interferon γ ; IL, interleukin; PD, Parkinson disease; RANTES, regulated on activation, normal T-expressed, and presumably secreted; TNF, tumor necrosis factor.

Moléculas que comunican y modulan los compartimentos inmunes central y periférico. Alteración en **sangre, líquido cefaloraquídeo y cerebros** de pacientes con EP vs controles sanos.

Meta-análisis: **perfil proinflamatorio de citoquinas en EP**, apoyando una respuesta inmune inflamatoria aumentada.

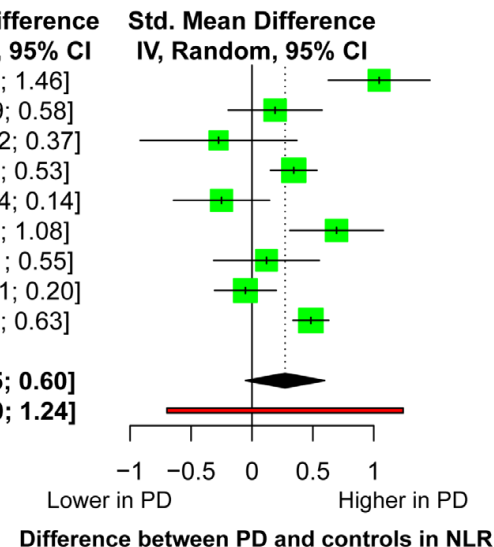
Biomarcadores inflamatorios – Ratio Neutrófilo/Linfocito en sangre periférica

Peripheral Immune Profile and Neutrophil-to-Lymphocyte Ratio in Parkinson's Disease

Study ID and year	PD patients			Healthy controls			Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Akil et al. 2015	3.10	1.30	51	2.10	0.32	50	10.5%	1.04 [0.63; 1.46]
Atag Ugar et al. 2017	2.66	1.05	46	2.46	1.04	60	10.9%	0.19 [-0.19; 0.58]
Buyukkoyuncu Pekel et al. 2018	2.22	0.76	17	2.56	1.48	21	8.0%	-0.27 [-0.92; 0.37]
Sanjari et al. 2018	2.50	0.90	388	2.20	0.80	148	12.9%	0.34 [0.15; 0.53]
Jiang et al. EOPD 2019	1.73	0.56	61	1.89	0.77	42	10.8%	-0.25 [-0.64; 0.14]
Jiang et al. LOPD 2019	2.04	0.89	54	1.53	0.53	57	10.9%	0.69 [0.31; 1.08]
Inci et al. 2020	2.24	1.03	42	2.13	0.77	40	10.3%	0.12 [-0.31; 0.55]
Jin et al. 2020	2.91	1.74	183	3.00	1.50	89	12.4%	-0.05 [-0.31; 0.20]
Muñoz-Delgado et al. 2020	2.47	1.10	377	1.98	0.91	355	13.2%	0.48 [0.34; 0.63]

Total (95% CI) 1219 862 100.0% 0.27 [-0.05; 0.60]
Prediction interval [-0.70; 1.24]

Heterogeneity: $\text{Tau}^2 = 0.15$; $\text{Chi}^2 = 40.84$, $\text{df} = 8$ ($P < 0.01$); $I^2 = 80\%$



↑ Ratio neutrófilo / linfocito en EP frente a CS = biomarcador de inflamación sistémica

No se encontró asociación con la edad de inicio, severidad motora de la enfermedad o duración de la enfermedad.

Otros Biomarcadores Séricos presentes en pacientes con EP vs CS

↓ **niveles de Apolipoproteína A1** (Lawton et al, 2020; Chahine et al, 2014).

Plasma Apolipoprotein A1 as a Biomarker for Parkinson Disease

Judy K. Qiang,¹ Yvette C. Wong,¹ Andrew Siderowf, MD,²

American Neurological Association, 2013

Se evalúan 90 biomarcadores en plasma

1. Cohorte exploratoria

152 pacientes con EP

2. Cohorte de validación

187 pacientes con EP

134 sujetos en riesgo de la cohorte PARS

En pacientes sintomáticos (EP), niveles bajos de ApoA1 se asocian con:

- Edad de inicio menor (independientemente de la medicación o de la severidad motora).
- Severidad motora mayor

En asintomáticos, niveles más bajo de ApoA1 en plasma se correlacionan con mayor déficit en la captación putaminal por DATscan → ¿Biomarcador de susceptibilidad de riesgo?

Otros Biomarcadores Séricos presentes en pacientes con EP vs CS



ELSEVIER

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Increased bilirubin levels in Parkinson's disease

Daniel Macías-Gar
Astrid Adames-G
Pablo Mir^{a,b,*}

^a Unidad de Trastornos del Movt
Universidad de Sevilla, Sevilla, S
^b Centro de Investigación Bioméd

European Journal of Neurology 2013, 20: 208–210

SHORT COMMUNICATION

Low serum uric acid concentration in Parkinson's disease in southern Spain

S. Jesús^a, I. Pérez^a, M. T. Cáceres-Redondo^a, F. Carrillo^a, M. Carballo^a, P. Gómez-Garre^a and P. Mir^{a,b}

^aUnidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain; and ^bCentro de Investigación Biomédica en Red sobre Enfer

↑ **Bilirrubina** (Macías-García et al, 2019)

doi:10.1111/j.1468-1331.2012.03745.x

↓ **Ácido úrico** (Jesús et al, 2013)

Blood Biomarkers With Parkinson's Disease Clusters and Prognosis: The Oxford Discovery Cohort

Michael Lawton, BSc, MPhil, MSc,^{1*} Fahd Baig, DPhil,^{2,3} Greg Toulson, PhD, MSc,⁴ Alireza Morovat, PhD, FRCPATH,⁴ Samuel G. Evetts, MSc,^{2,3} Yoav Ben-Shlomo, PhD, MSc,¹ and Michele T. Hu, PhD, FRCP^{2,3,5}

¹Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

²Nuffield Department of Clinical Neurosciences, Division of Clinical Neurology, University of Oxford, Oxford, UK

³Oxford Parkinson's Disease Centre, University of Oxford, Oxford, UK

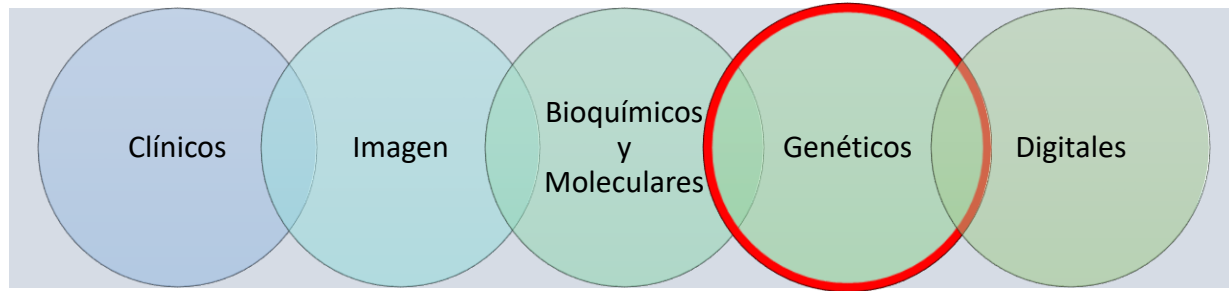
⁴Department of Clinical Biochemistry, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

⁵Department of Clinical Neurology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

)
↓ **Vitamina D** (Lawton et al, 2020)

Biomarcadores y enfermedad de Parkinson

La fuente de biomarcadores en la enfermedad de Parkinson es amplia y sigue incrementándose incluyendo:



PERO ninguno ha mostrado por sí solo ser suficientemente sensible y específico para el diagnóstico o pronóstico de la EP.

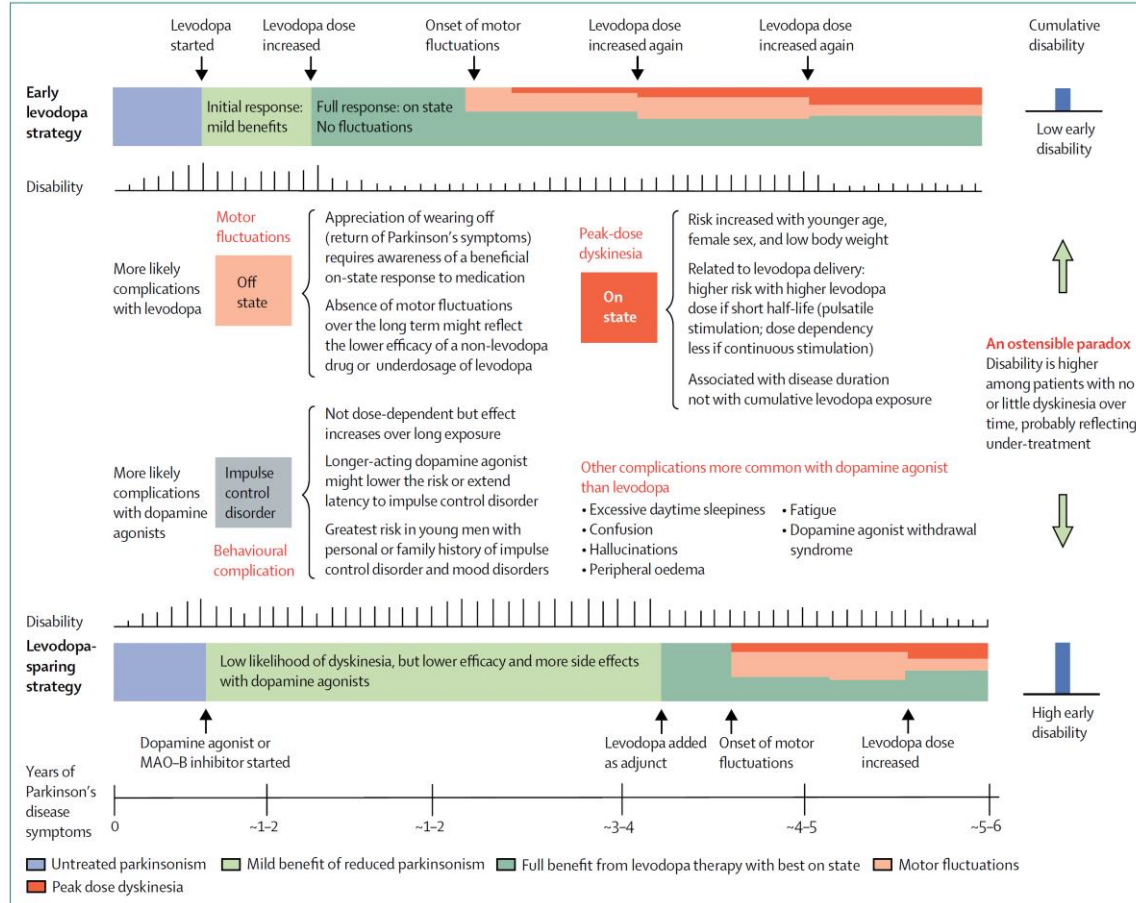
Modelos multimodales: integración de distintos biomarcadores procedentes de distintas fuentes.

Tipos de Biomarcadores:

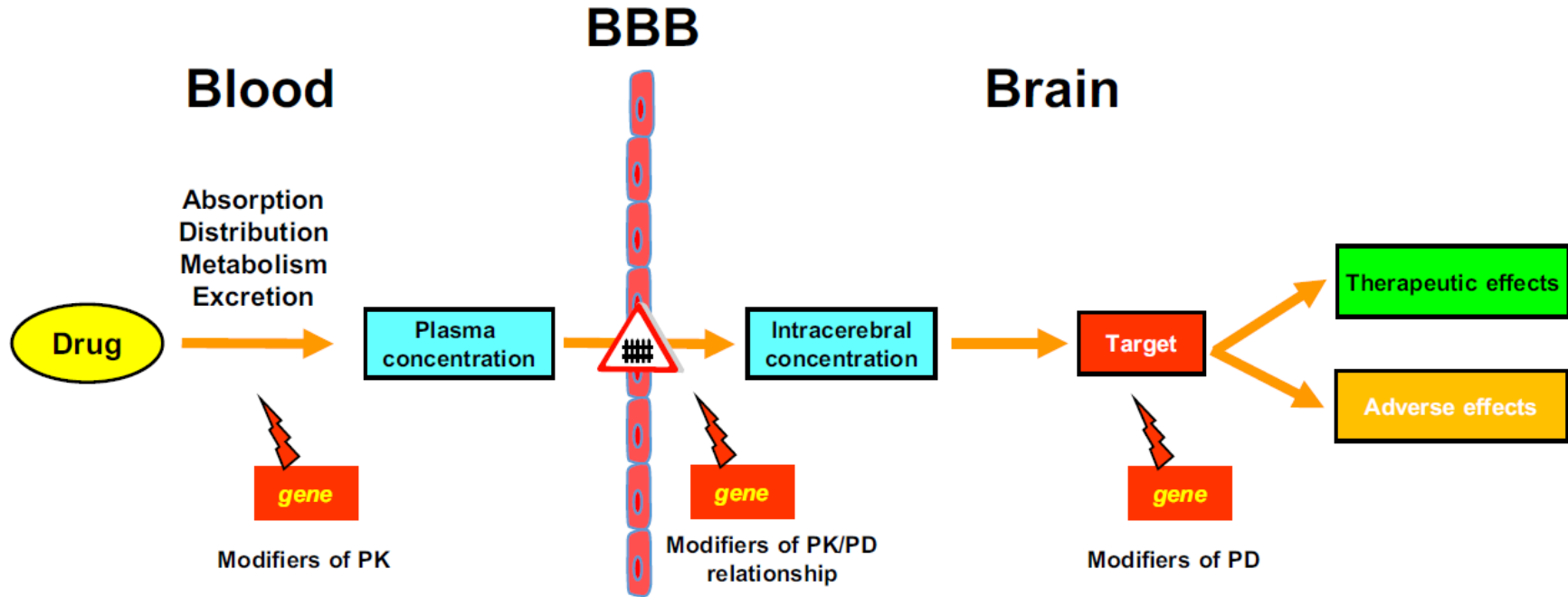
- De susceptibilidad de riesgo
- Diagnóstico
- De monitorización
- Pronóstico
- Predictivo

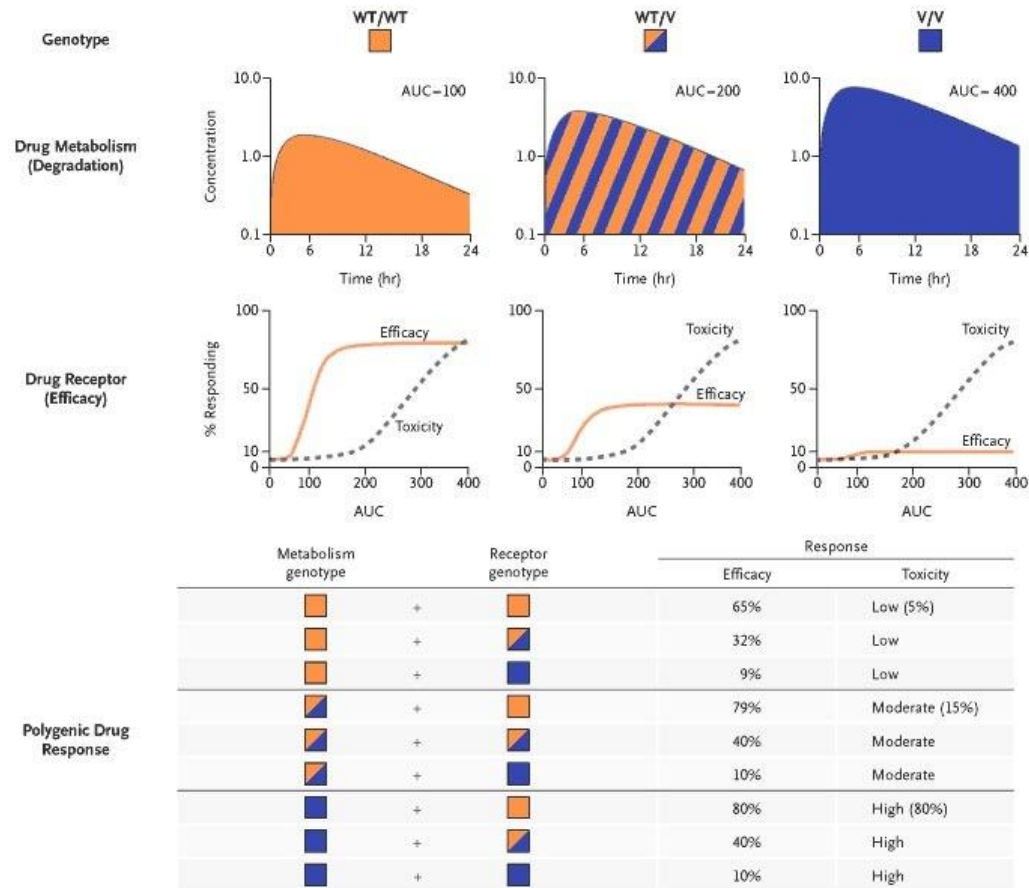
Objetivo:

- Identificar EP prodrómica: Intervención precoz y tratamientos neuroprotectores.
- Diagnóstico certero, especialmente en estadios precoces, y diagnóstico diferencial con otras entidades.
- Monitorizar tratamientos
- Medicina personalizada

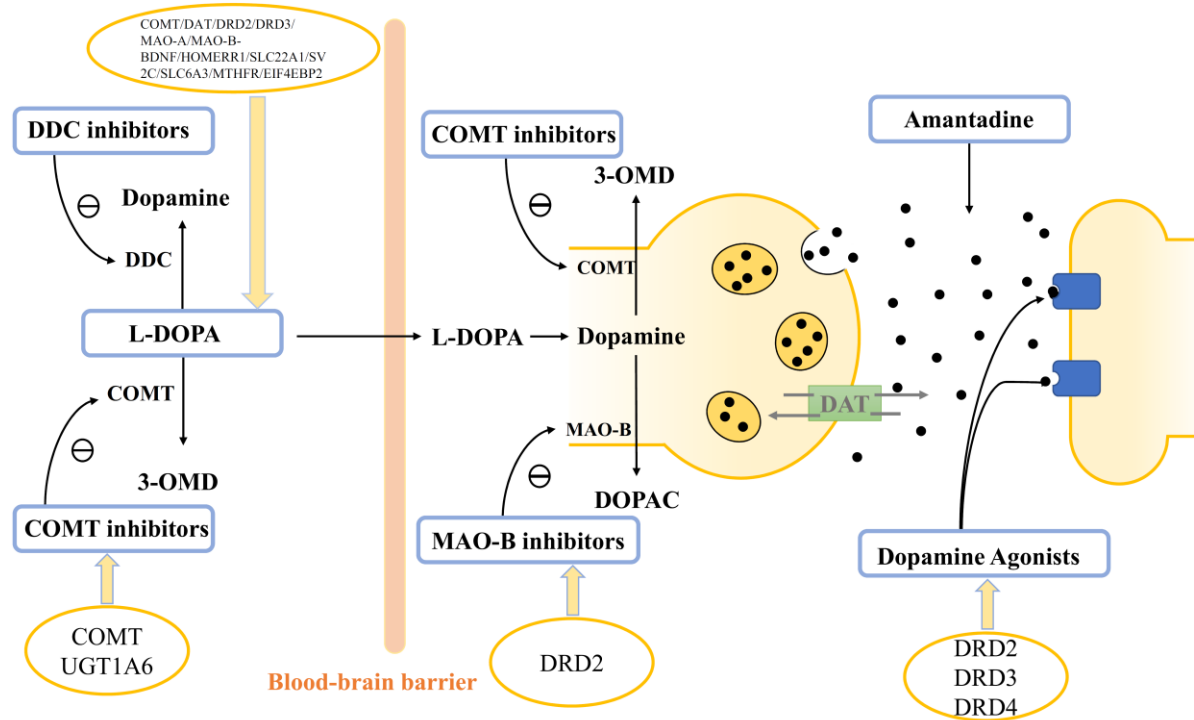


Pharmacogenetics in Neurology





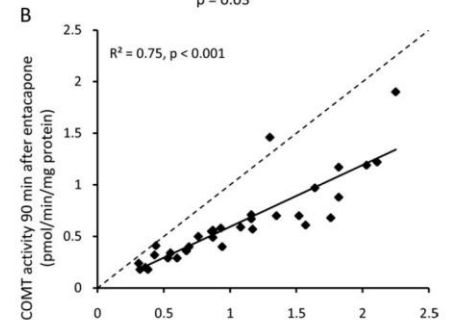
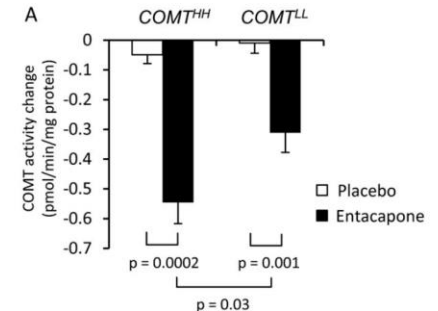
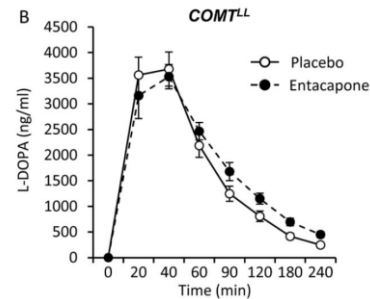
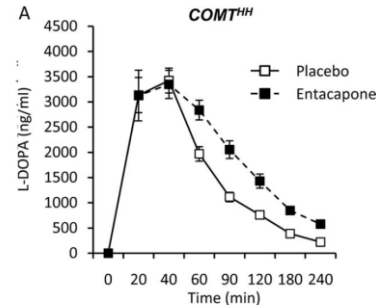
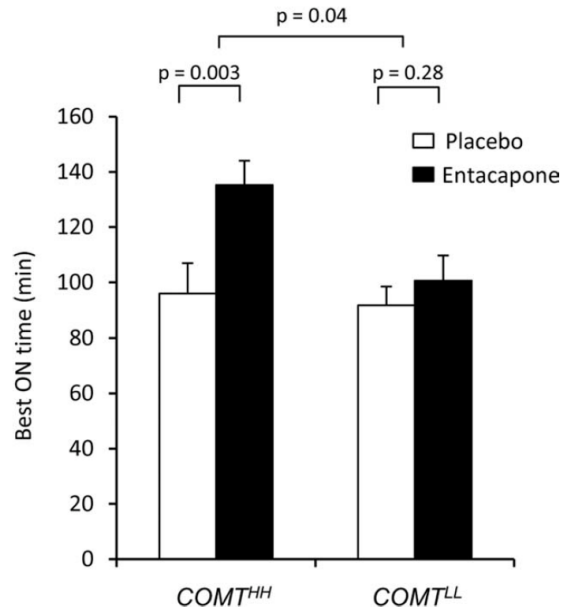
Parkinson's disease drugs and their associated gene polymorphisms



The COMT Val158Met Polymorphism Affects the Response to Entacapone in Parkinson's Disease: A Randomized Crossover Clinical Trial

Jean-Christophe Corvol, MD, PhD,^{1,2,3,4} Cécilia Bonnet, MD,¹
 Fanny Charbonnier-Beaupel, PharmD,¹ Anne-Marie Bonnet, MD,²
 Marie-Hélène Fiévet, PharmD,⁴ Agnès Bellanger, PharmD,⁴ Emmanuel Roze, MD, PhD,^{1,2,6}
 Gayané Meliksetyan, MD,¹ Mouna Ben Djebara, MD,¹ Andreas Hartmann, MD,^{1,2,6}
 Lucette Lacomblez, MD,^{3,5,7} Cédric Vignaud, BSc,³ Noël Zahr, PhD,³
 Yves Agid, MD, PhD,^{1,2,5} Jean Costentin, MD,⁸
 Jean-Sébastien Hulot, MD, PhD,^{3,5} and Marie Vidailhet, MD^{1,2,5,6}

ANN NEUROL 2011;69:111-118





Review

A Systematic Review of Parkinson's Disease Pharmacogenomics: Is There Time for Translation into the Clinics?

Vladimira Vuletić ^{1,2,*}, Valentino Rački ^{1,2}, Eliša Papić ¹ and Borut Peterlin ³

Int. J. Mol. Sci. **2021**, *22*, 7213.

Conclusions: This systematic review demonstrated that the evidence for **implementation of pharmacogenomics in clinical practice** is still lacking and that further research needs to be done to enable a more personalized approach to therapy for each patient.



FÁRMACOS	GENES	POLIMORFISMOS	ESTUDIOS PREVIOS
Levodopa	<i>COMT</i>	Haplotipo basado en los polimorfismos rs6263, rs4633, rs4818, rs4680	-Bialecka, M., et al., Pharmacogenetics and genomics, 18 (2008) 815 - Cheshire, P., et al., Neurodegenerative diseases, 13 (2014) 24
	<i>SLC22A1</i>	rs622342	Becker, M.L., et al., Neurogenetics, 12 (2011) 79
	<i>SLC6A3</i>	rs28363170, rs3836790	Moreau, C., et al., Brain, 138 (2015) 1271
	<i>DDC</i>	rs921451, rs3837091	Devos, D., et al., Parkinsonism & related disorders, 20 (2014) 170
Agonistas dopaminérgicos	<i>DRD3</i>	rs6280	Liu, Y.Z., et al., European journal of clinical pharmacology, 65 (2009) 679
Inhibidores enzimáticos	<i>COMT</i>	rs4680	Corvol, J.C., et al., Annals of neurology, 69 (2011) 111
	<i>ANKK1</i>	rs2283265, rs1076560	Masellis, M., et al., Brain, 139 (2016) 2050
	<i>UGT1A</i>	rs1105880	Acuna, G., et al., The pharmacogenomics journal, 2 (2002) 327

Effect of variants in *COMT* and *UGT1A* genes on clinical response in patients with Parkinson's disease treated with opicapone

Ojeda-Lepe, Elena¹; García-Díaz, Sergio¹; Díaz Belloso, Rafael¹; Muñoz-Delgado, Laura^{1,2}; Jesús, Silvia^{1,2}; Perinán, María Teresa^{1,2}; Benítez Zamora, Belén^{1,2}; Adarmes-Gómez, Astrid Daniela^{1,2}; Macías-García, Daniel^{1,2}; Martín-Bornez, Miguel¹; Bonilla-Toribio, Marta^{1,2}; Buiza-Rueda, Dolores^{1,2}; Pineda-Sánchez, Rocío^{1,2}; Carrillo, Fátima^{1,2}; Gómez-Garre, Pilar^{1,2}; Mir, Pablo^{1,2,3}.

We genotyped rs4818, rs4680, rs4633 in the **COMT** gene and rs1105880 in the UGT1A gene. The rs4680 variant was associated to a reduced risk of worsening in motor fluctuations, and the rs4818 heterozygosis state to a **clinical improvement** according to their CGI score.



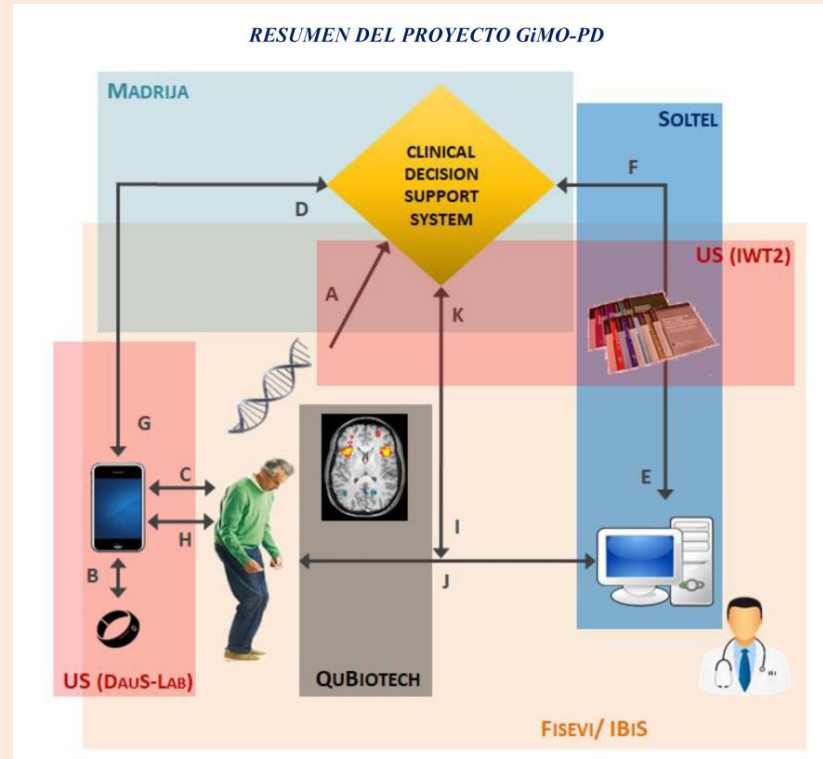
International Parkinson and
Movement Disorder Society

August 27-31, 2023
Copenhagen
DENMARK

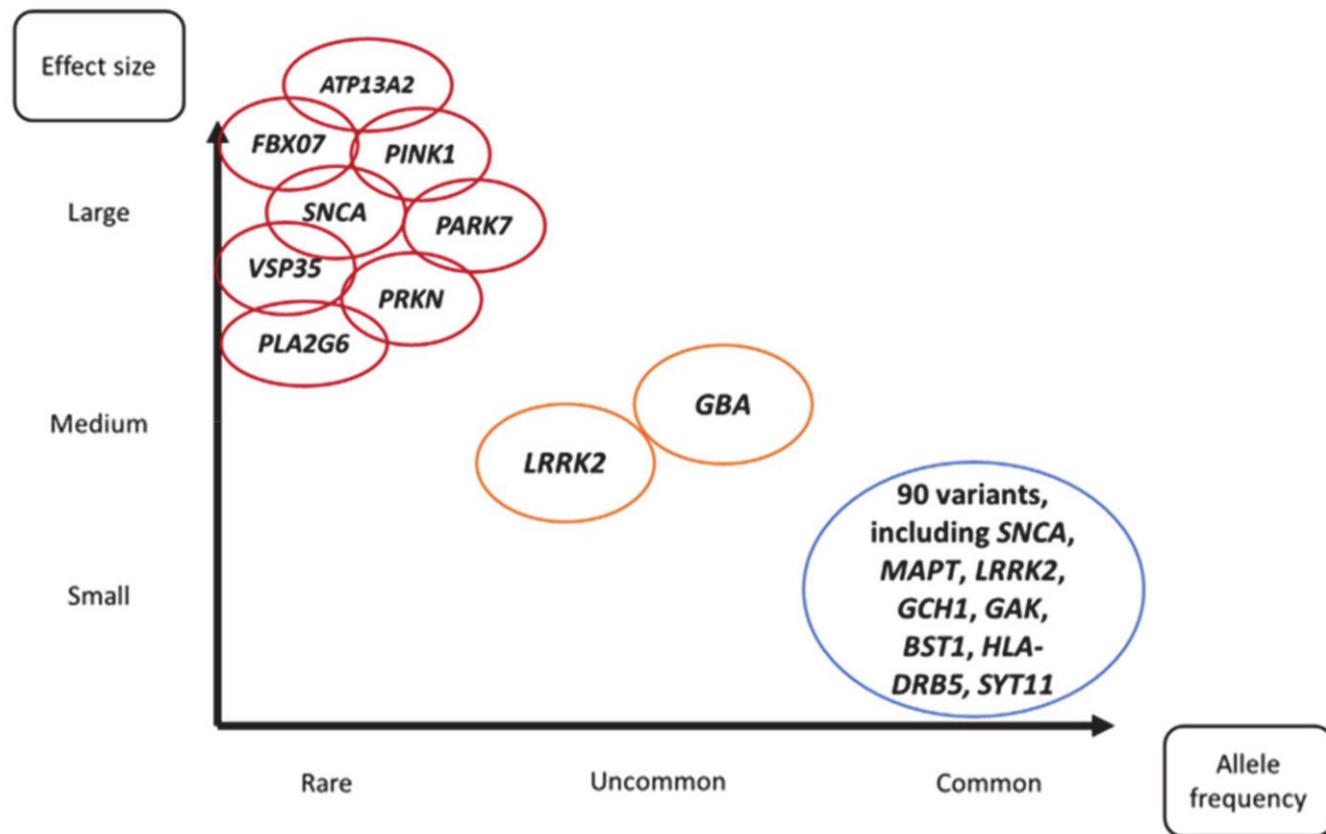


Mobile health solution based on Genetic profile, Imaging analysis and permanent symptoms Monitoring for personalized management of Parkinson Disease patients

GiMo-PD

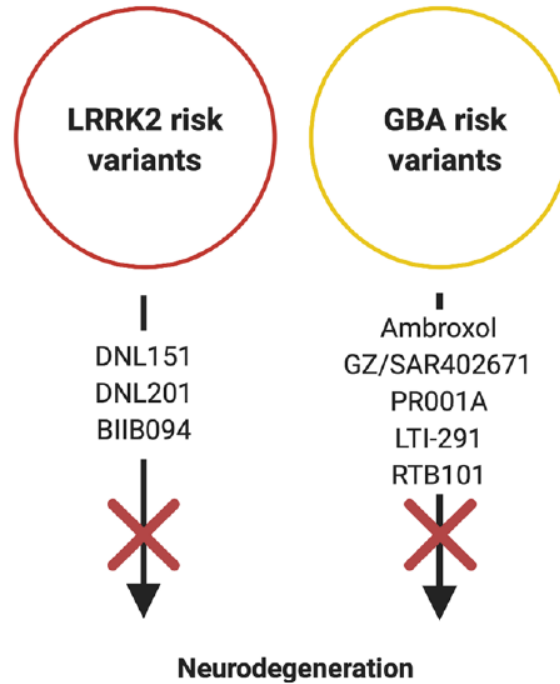


Genetic variants in Parkinson's disease grouped according to allele frequency and associated risk

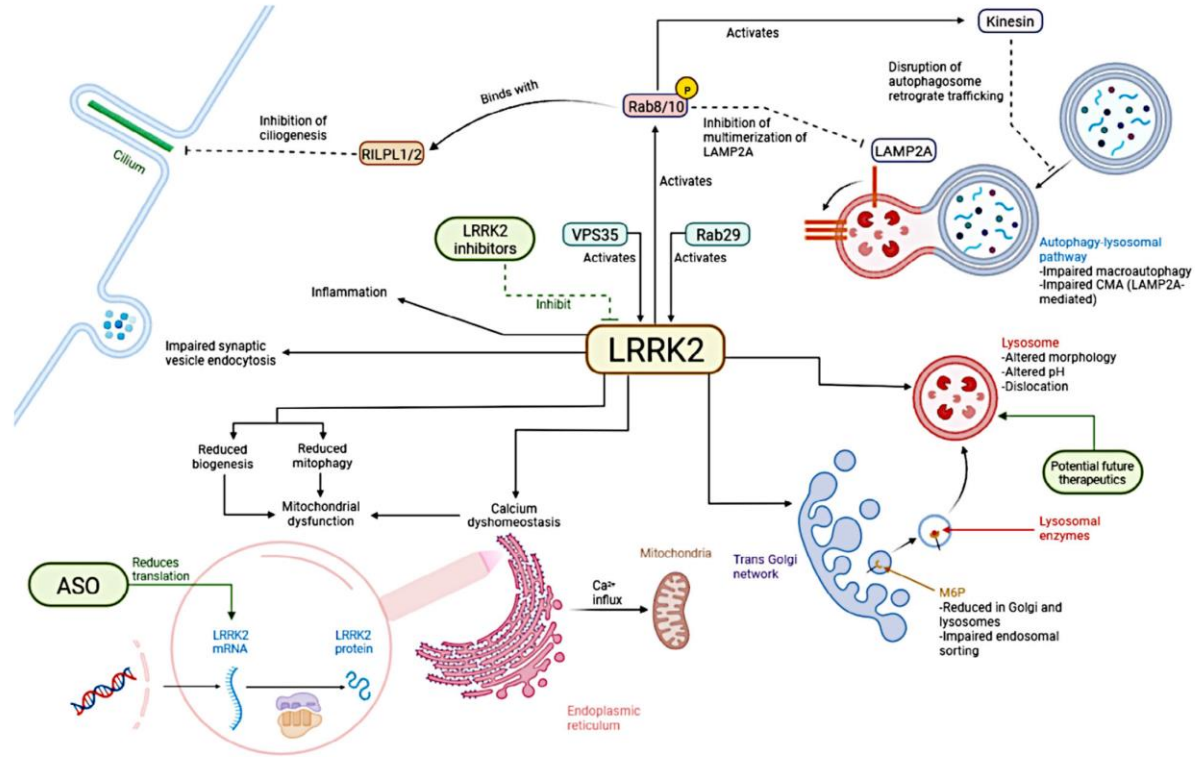


a

Precision medicine



Principal mechanisms where LRRK2 has been implicated in Parkinson's disease and therapeutic targets



Research Report

Safety, Pharmacokinetics, and Pharmacodynamics of Oral Venglustat in Patients with Parkinson's Disease and a *GBA* Mutation: Results from Part 1 of the Randomized, Double-Blinded, Placebo-Controlled MOVES-PD Trial

M. Judith Peterschmitt^{a,*}, Hidemoto Saiki^b, Taku Hatano^c, Thomas Gasser^d, Stuart H. Isaacson^e, Sebastiaan J.M. Gaemers^f, Pascal Minini^g, Stéphane Saubadu^g, Jyoti Sharma^h, Samantha Walbillic^g, Roy N. Alcalayⁱ, Gary Cutter^j, Nobutaka Hattori^c, Günter U. Höglinger^{k,l}, Kenneth Marek^m, Anthony H.V. Schapiraⁿ, Clemens R. Scherzer^o, Tanya Simuni^p, Nir Giladi^q, Sergio Pablo Sardi^q and Tanya Z. Fischer^a; on behalf of the MOVES-PD Investigators^l

Venglustat showed **favorable safety and tolerability** in MOVES-PD Part 1 and target engagement was achieved in CSF.

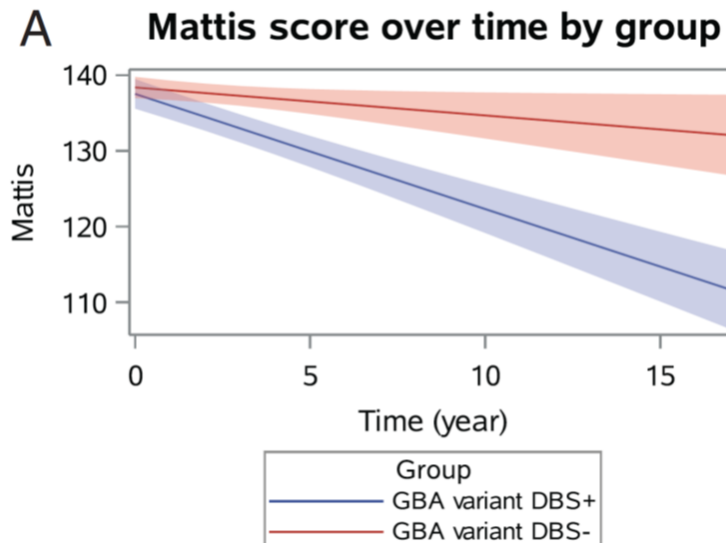


Parkinson Disease and Subthalamic Nucleus Deep Brain Stimulation: Cognitive Effects in *GBA* Mutation Carriers

Gian Pal, MD, MS ^{1,2} Graziella Mangone, MD, PhD,³ Emily J. Hill, MD,⁴ Bichun Ouyang, PhD,² Yuanqing Liu, MA,² Vanessa Lythe, BM BCh, MSc,⁵ Debra Ehrlich, MD,⁶ Rachel Saunders-Pullman, MD,⁷ Vicki Shanker, MD,⁷ Susan Bressman, MD,⁷ Roy N. Alcalay, MD, MS,⁸ Priscilla Garcia, MD,⁹ Karen S. Marder, MD, MPH,⁸ Jan Aasly, MD,¹⁰ M. Maral Mouradian, MD,^{1,11} Samantha Link, BS,² Marc Rosenbaum, MS,² Sharlet Anderson, PhD,² Bryan Bernard, PhD,² Robert Wilson, PhD,² Glenn Stebbins, PhD,² William C. Nichols, PhD,¹² Marie-Laure Welter, MD, PhD ^{3,13} Sepehr Sani, MD,¹⁴ Mitra Afshari, MD, MPH,² Leo Verhagen, MD, PhD,² Rob M.A. de Bie, MD, PhD,¹⁵ Tom Foltynie, MD, PhD, MRCP,⁵ Deborah Hall, MD, PhD ² Jean-Christophe Corvol, MD, PhD,³ and Christopher G. Goetz, MD ²

Parkinson Disease and Subthalamic Nucleus Deep Brain Stimulation: Cognitive Effects in *GBA* Mutation Carriers

ANN NEUROL 2022;91:424–435



Parkinson Disease and Subthalamic Nucleus Deep Brain Stimulation: Cognitive Effects in *GBA* Mutation Carriers

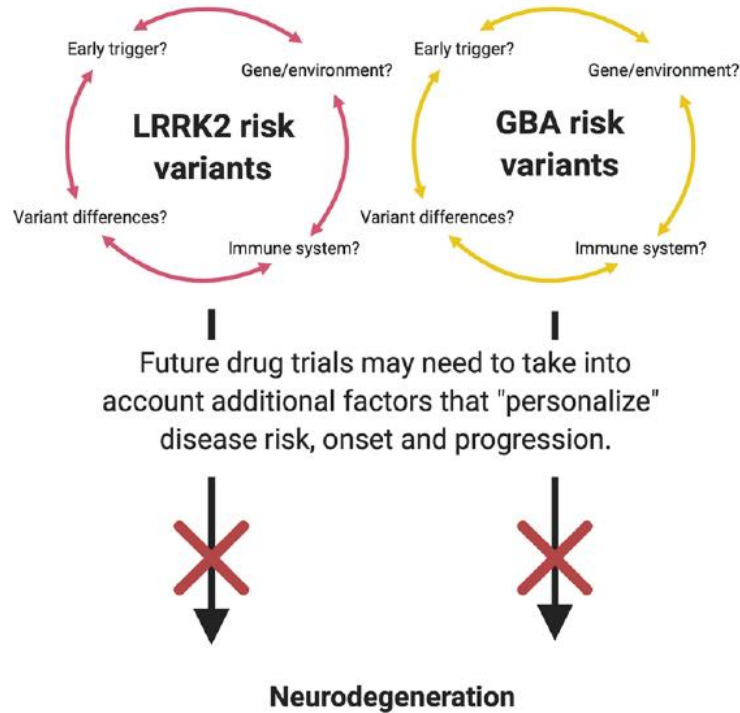
ANN NEUROL 2022;91:424–435

Authors' Interpretation: “Although not randomized, this composite analysis suggests that the **combined effects of *GBA* mutations and STN-DBS negatively impact cognition**. We advise that **DBS candidates be screened for *GBA* mutations** as part of the presurgical decision-making process. We advise that *GBA* mutation carriers be counseled regarding potential risks associated with STN-DBS so that alternative options may be considered.”



b

Precision medicine (More personal)





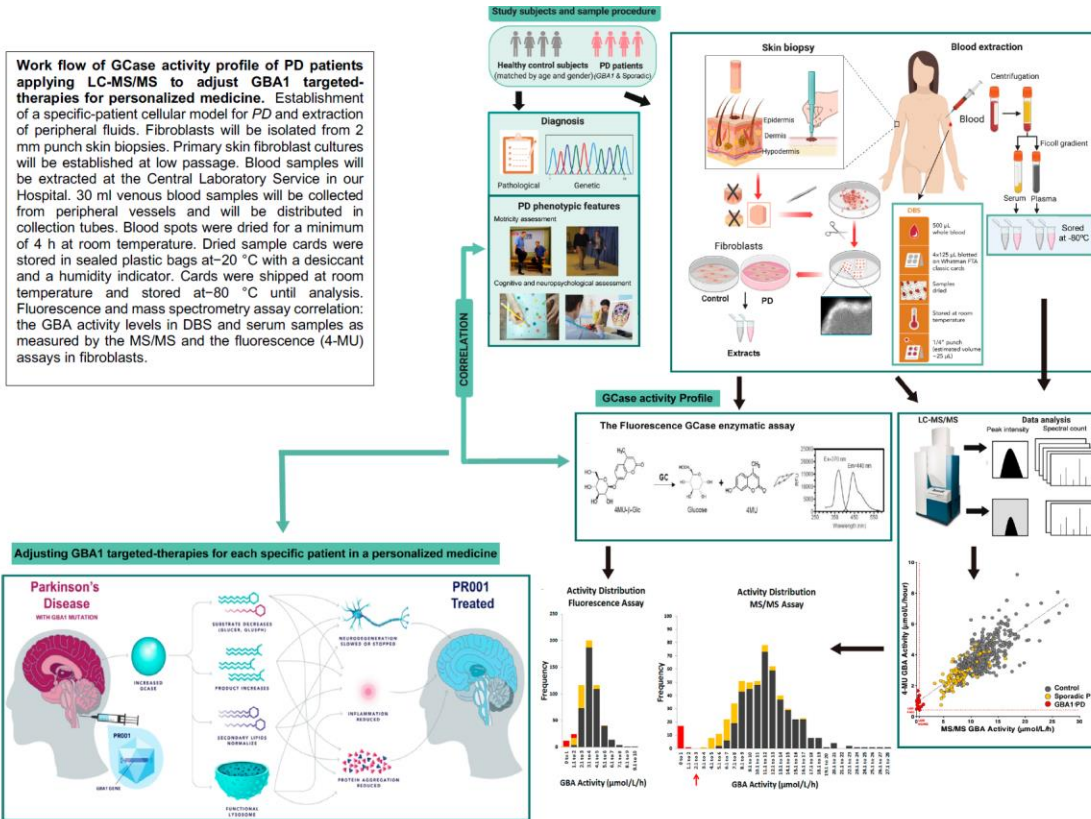
***GBA*-associated PD: chances and obstacles for targeted treatment strategies**

Günter Högl^{1,2} · Claudia Schulte^{3,4} · Wolfgang H. Jost⁵ · Alexander Storch^{6,7} · Dirk Voitalla⁸ · Rejko Krüger^{9,10,11} · Björn Falkenburger¹² · Kathrin Brockmann^{3,4} 

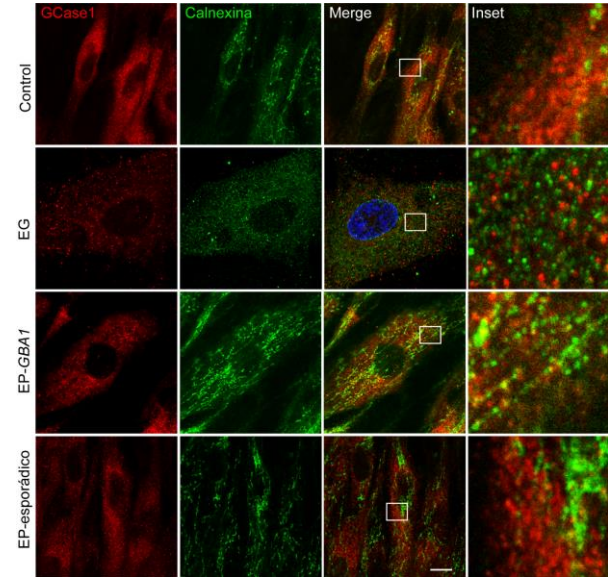
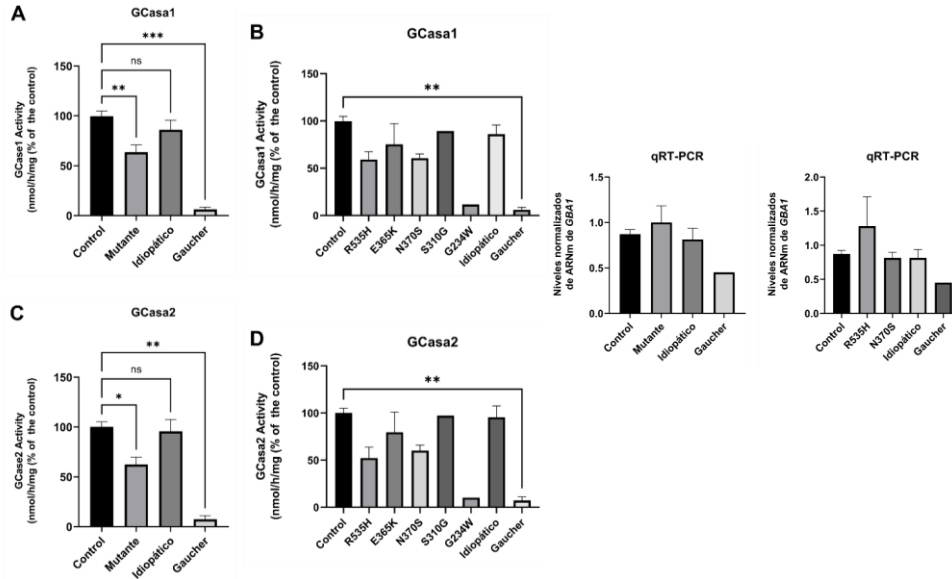
“...**differences** and characteristics based on **mutation severity** are recognized”

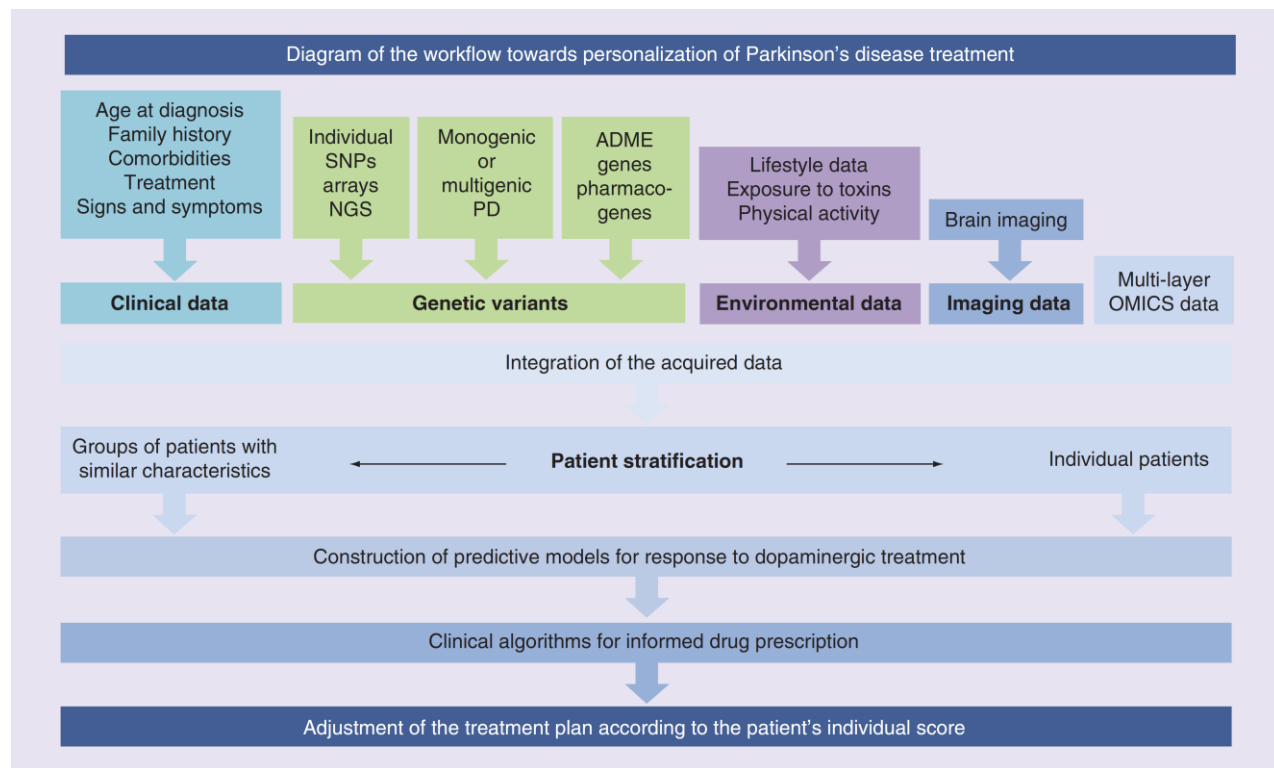


Título del proyecto: “Perfil de actividad diferencial de la glucocerebrosidasa de GBA1 y modelos de pacientes específicos de la enfermedad de Parkinson esporádica: preparándose para el advenimiento de la terapia personalizada”



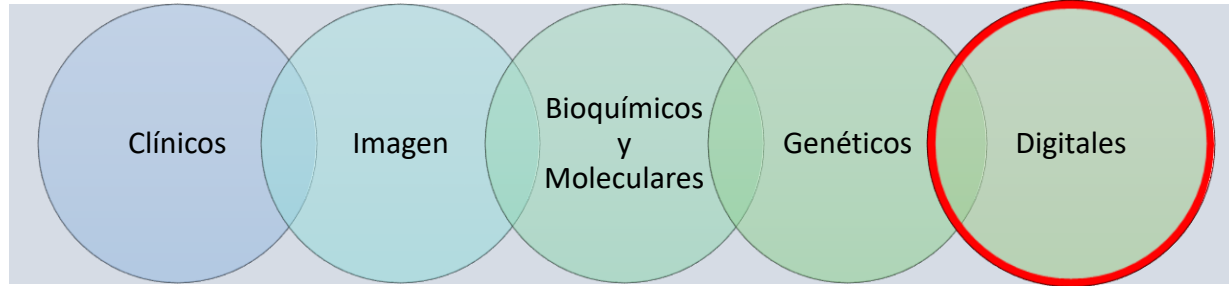
Título del proyecto: “Perfil de actividad diferencial de la glucocerebrosidasa de GBA1 y modelos de pacientes específicos de la enfermedad de Parkinson esporádica: preparándose para el advenimiento de la terapia personalizada”





Biomarcadores y enfermedad de Parkinson

La fuente de biomarcadores en la enfermedad de Parkinson es amplia y sigue incrementándose incluyendo:



PERO ninguno ha mostrado por sí solo ser suficientemente sensible y específico para el diagnóstico o pronóstico de la EP.

Modelos multimodales: integración de distintos biomarcadores procedentes de distintas fuentes.

Tipos de Biomarcadores:

- De susceptibilidad de riesgo
- Diagnóstico
- De monitorización
- Pronóstico
- Predictivo

Objetivo:

- Identificar EP prodrómica: Intervención precoz y tratamientos neuroprotectores.
- Diagnóstico certero, especialmente en estadios precoces, y diagnóstico diferencial con otras entidades.
- Monitorizar tratamientos
- Medicina personalizada

Características clínicas de la EP

Acinesia/Bradicinesia

Rigidez

Temblor

Alteraciones posturales

Estos síntomas típicamente se presentan asimetricamente

Bradicinesia

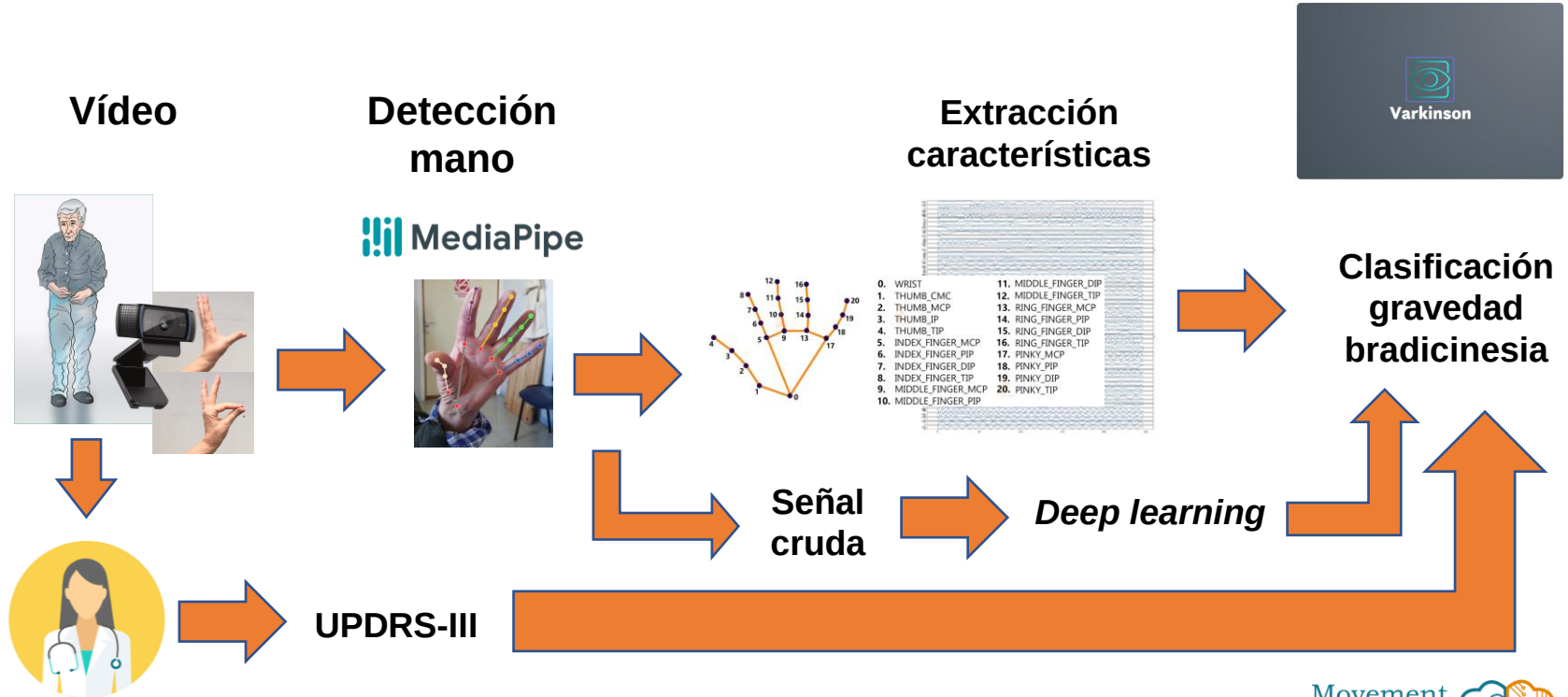
Visión artificial: intento de replicar la vision humana usando máquinas



VARKINSON

Visión Artificial en la Detección y Seguimiento de la Enfermedad de Parkinson

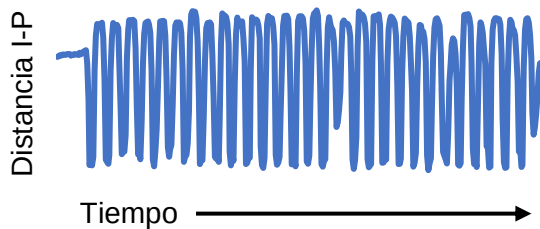
118



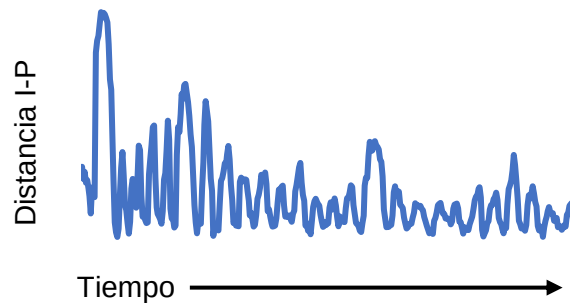
VARKINSON

Visión Artificial en la Detección y Seguimiento de la Enfermedad de Parkinson

UPDRS-III = 0
(no bradicinesia)



UPDRS-III = 3
(Bradicinesia moderada-grave)

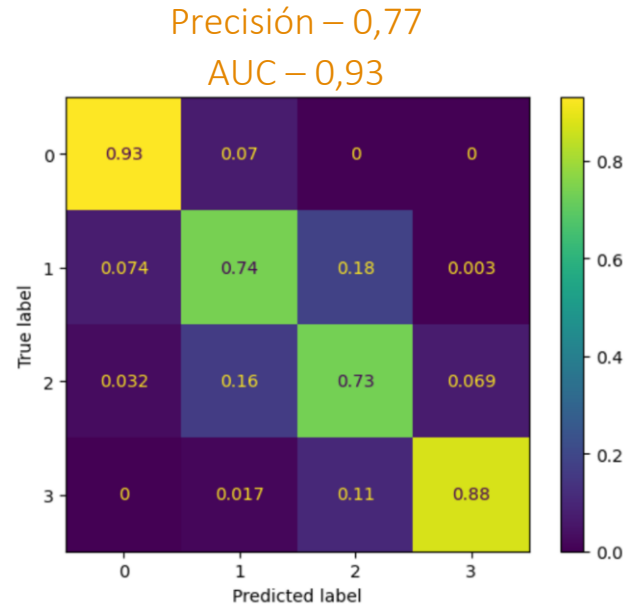
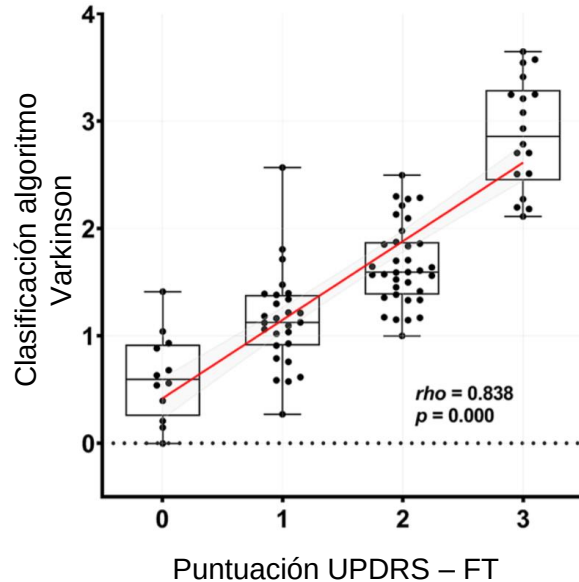


VARKINSON

Visión Artificial en la Detección y Seguimiento de la Enfermedad de Parkinson

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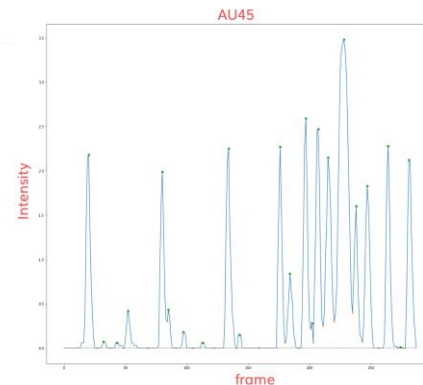
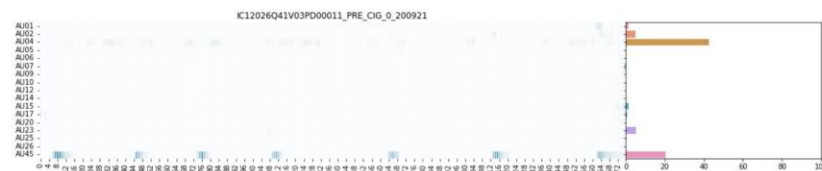
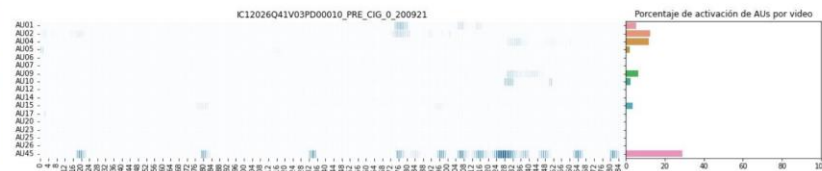
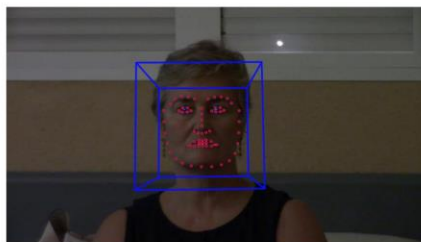
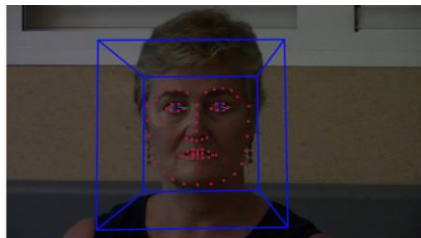
Correspondencia clasificación Varkinson - Clínica



VARKINSON

Visión Artificial en la Detección y Seguimiento de la Enfermedad de Parkinson

AU	Full name	Illustration
AU1	INNER BROW RAISER	
AU2	OUTER BROW RAISER	
AU4	BROW LOWERER	
AU5	UPPER LID RAISER	
AU6	CHEEK RAISER	
AU7	LID TIGHTENER	
AU9	NOSE WRINKLER	
AU10	UPPER LIP RAISER	
AU12	LIP CORNER PULLER	
AU14	DIMPLER	
AU15	LIP CORNER DEPRESSOR	
AU17	CHIN RAISER	
AU20	LIP STRETCHED	
AU23	LIP TIGHTENER	
AU25	LIPS PART	
AU26	JAW DROP	
AU28	LIP SUCK	
AU45	BLINK	



19. EXPRESIÓN FACIAL

0 = Normal.

1 = Mínima hipomimia, podría ser una cara inexpressiva (“cara de póker”) normal.

2 = Disminución discreta, pero claramente anormal, de la expresión facial.

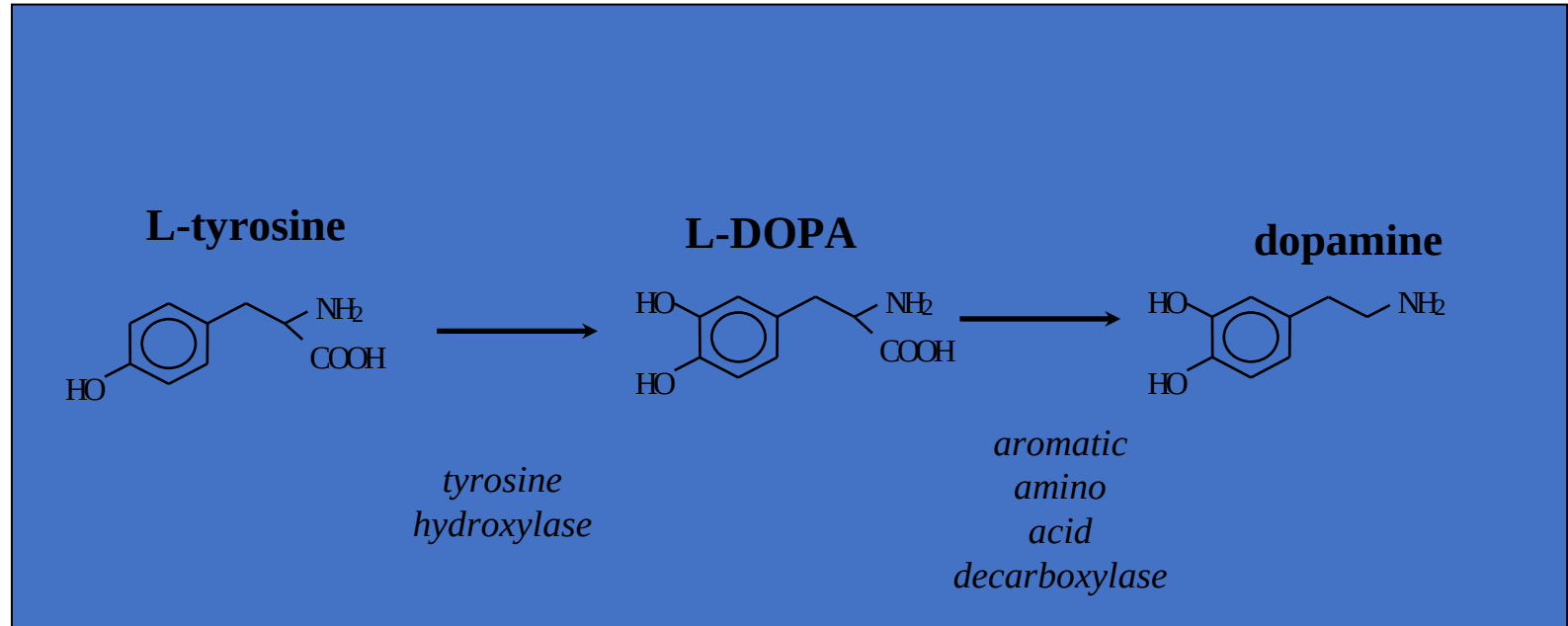
3 = Hipomimia moderada, labios separados la mayor parte del tiempo.

4 = Cara de “máscara” o expresión fija con pérdida acusada o completa de la expresión facial, labios separados más de 6mm.



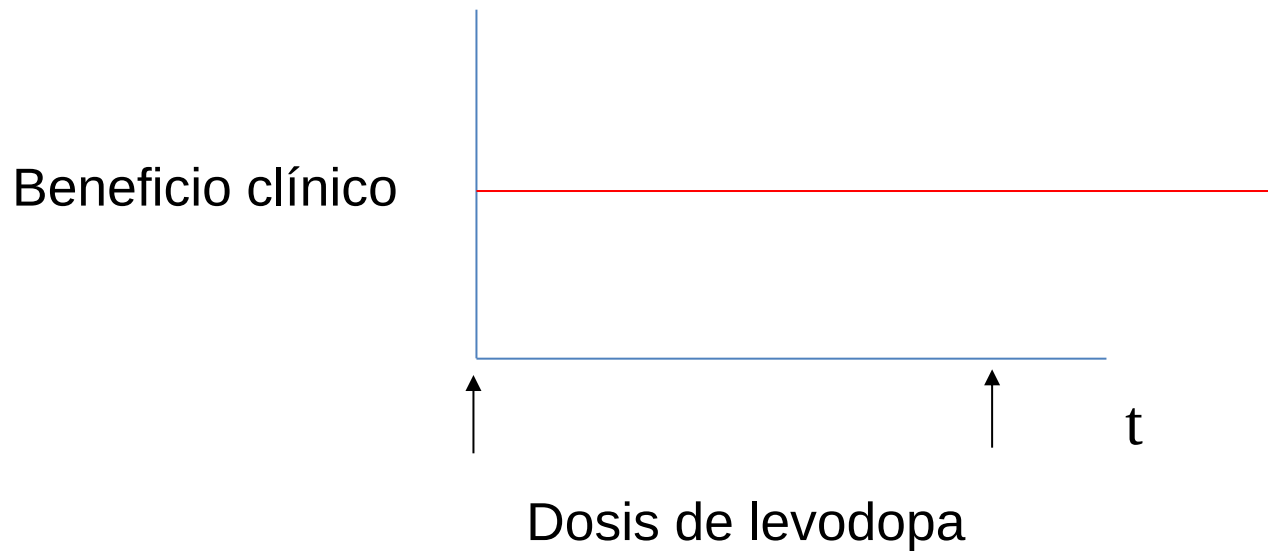
Manejo clínico paciente con EP

Levodopa y la síntesis de dopamina



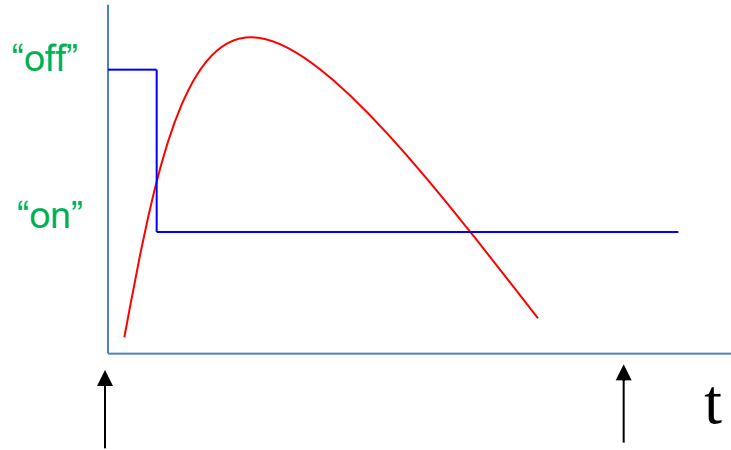
Manejo clínico paciente con EP

Luna de miel de la levodopa

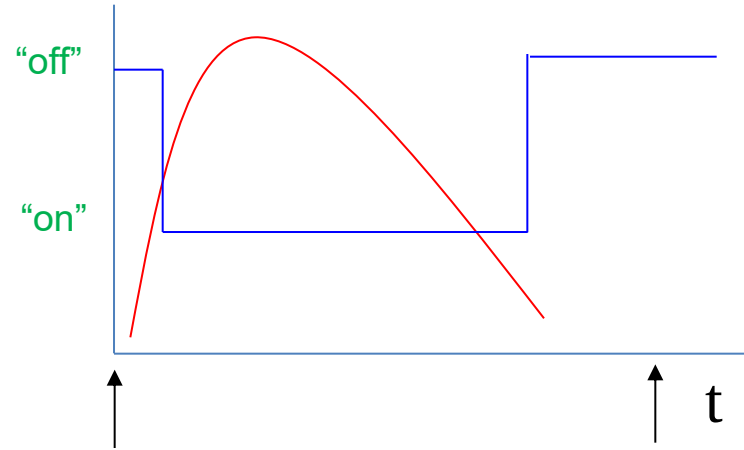


Manejo clínico paciente con EP

Respuesta a levodopa



Respuesta estable



Respuesta fluctuante

Manejo clínico paciente con EP

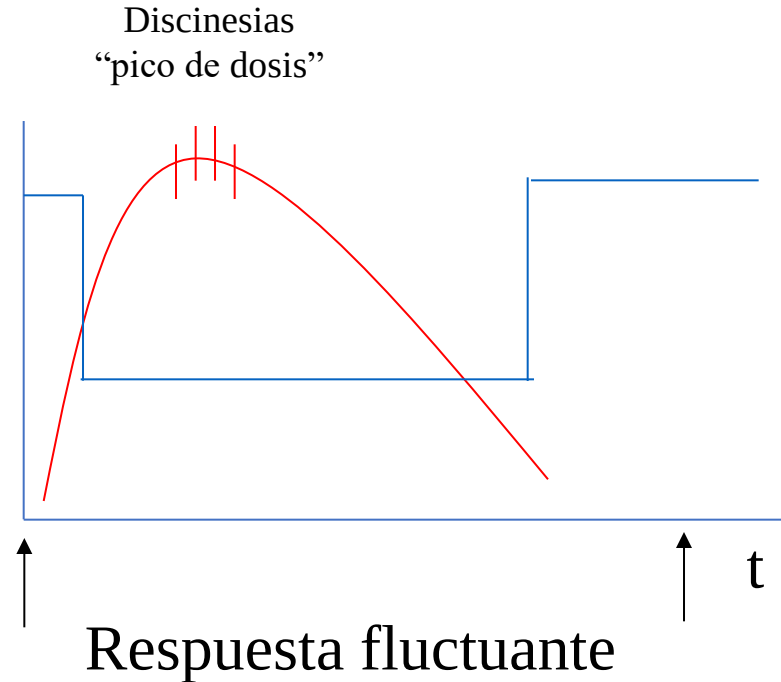
Fluctuaciones motoras

OFF

ON

Complicaciones del tratamiento

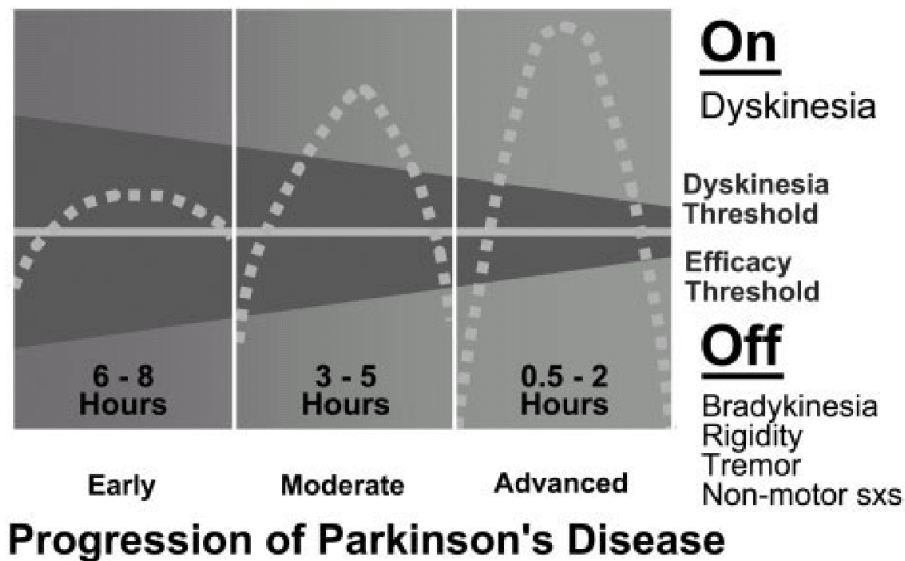
Discinesias inducidas por levodopa



Complicaciones del tratamiento

Discinesias “pico de dosis”

Complicaciones del tratamiento



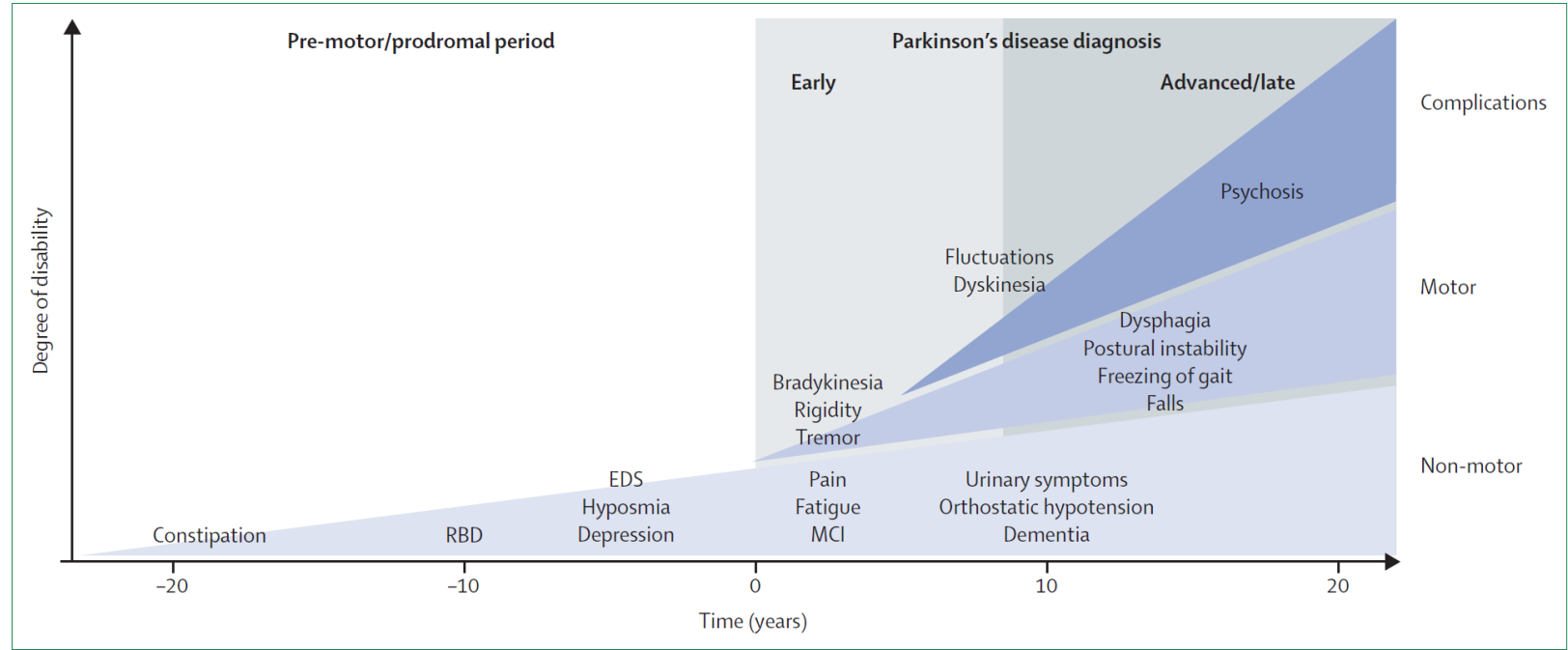
Jankovic J. Movement Disorders 2005; 20 (Suppl 11): S11–S16

Complicaciones del tratamiento

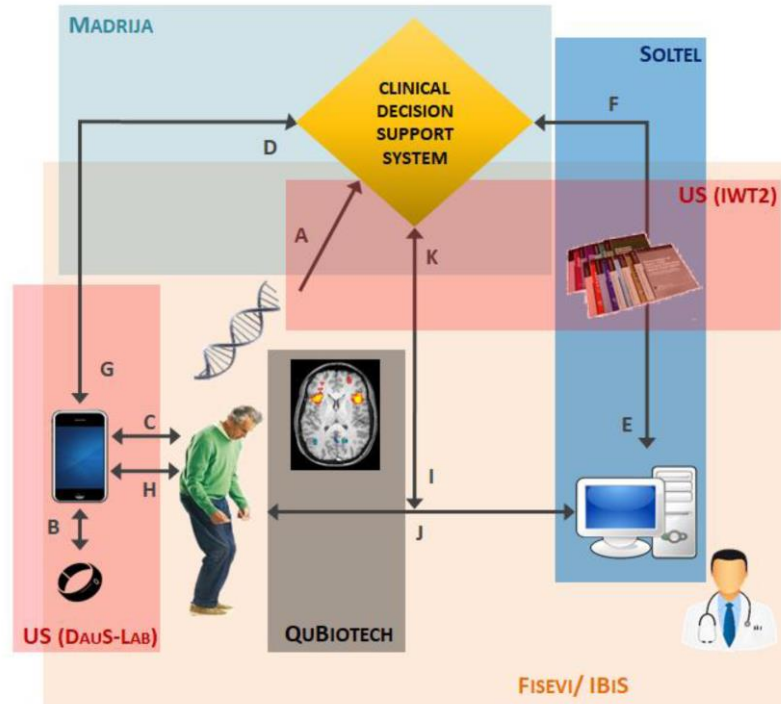
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	Treatment of motor symptoms		Treatment of motor complications	
	Monotherapy	Adjunct to levodopa	Fluctuations	Dyskinesia*
Levodopa				
Levodopa-carbidopa	+	..	+	-
Levodopa-benserazide	+	..	+	-
Dopamine agonists (non-ergot)				
Apomorphine	-	+	+	-
Piribedil	+	+	-	-
Pramipexole	+	+	+	-
Ropinirole	+	+	+	-
Rotigotine	+	+	+	-
Dopamine agonists (ergot)				
Bromocriptine	+	+	+	-
Cabergoline	+	+	+	-
Monoamine oxidase type B inhibitors				
Rasagiline	+	+	+	-
Selegiline	+	-§	-§	-
Catechol-O-methyltransferase inhibitors				
Entacapone	..	+	+	-
Tolcapone	..	+	+	-
Others				
Amantadine	+	+	-	+
Anticholinergics†	+‡	+‡	-	-
Clozapine	+‡	+‡	-	+
+ indicates efficacious or likely efficacious. - indicates non-efficacious or insufficient evidence. .. indicates not applicable. *Responses to peak dose dyskinesia (diphasic dyskinesia might respond to drugs used for motor fluctuations, particularly dopamine agonists). †Includes benztropine, ethopropazine, trihexyphenidyl, and others. ‡For treatment of tremor. §There is insufficient evidence but, in practice, selegiline is used and can be effective.				
Table 2: Pharmacological treatments for motor symptoms and complications				

Síntomas clínicos y evolución temporal de la progresión de la enfermedad de Parkinson

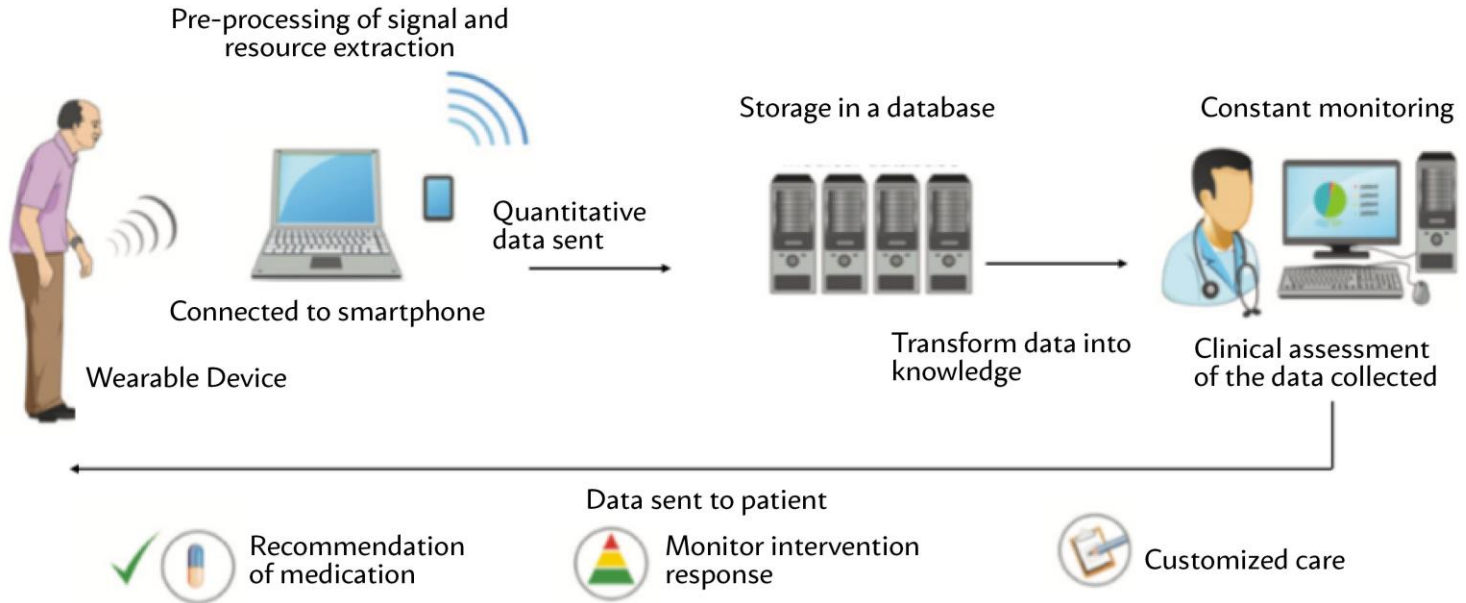


RESUMEN DEL PROYECTO GiMO-PD



GiMo-PD

Mobile health solution based on Genetic profile, Imaging analysis and permanent symptoms Monitoring for personalized management of Parkinson Disease patients



Mobile health solution based on Genetic profile, Imaging analysis and permanent symptoms Monitoring for personalized management of Parkinson Disease patients

Motores

- ❖ Temblor
- ❖ Discinesias
- ❖ Bradicinesia
- ❖ Trastornos de la marcha y del equilibrio



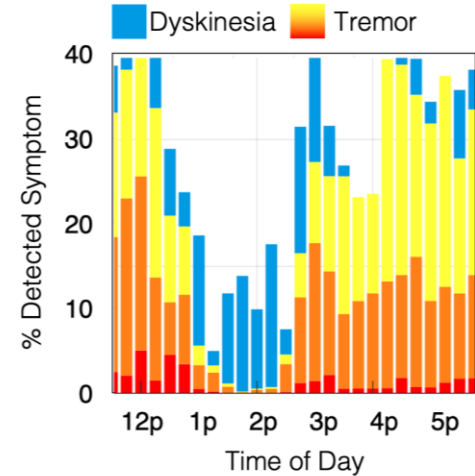
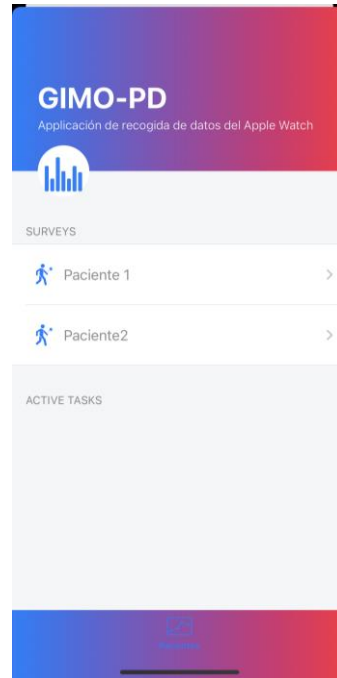
No motores

- ❖ Psicosis
- ❖ Trastornos del control de impulsos y conductas compulsivas
- ❖ Deterioro cognitivo/quejas cognitivas

GiMo-PD

Mobile health solution based on Genetic profile, Imaging analysis and permanent symptoms Monitoring for personalized management of Parkinson Disease patients

Solución mHealth 1: medición ubicua y continua del temblor y la discinesia a través de un smart watch

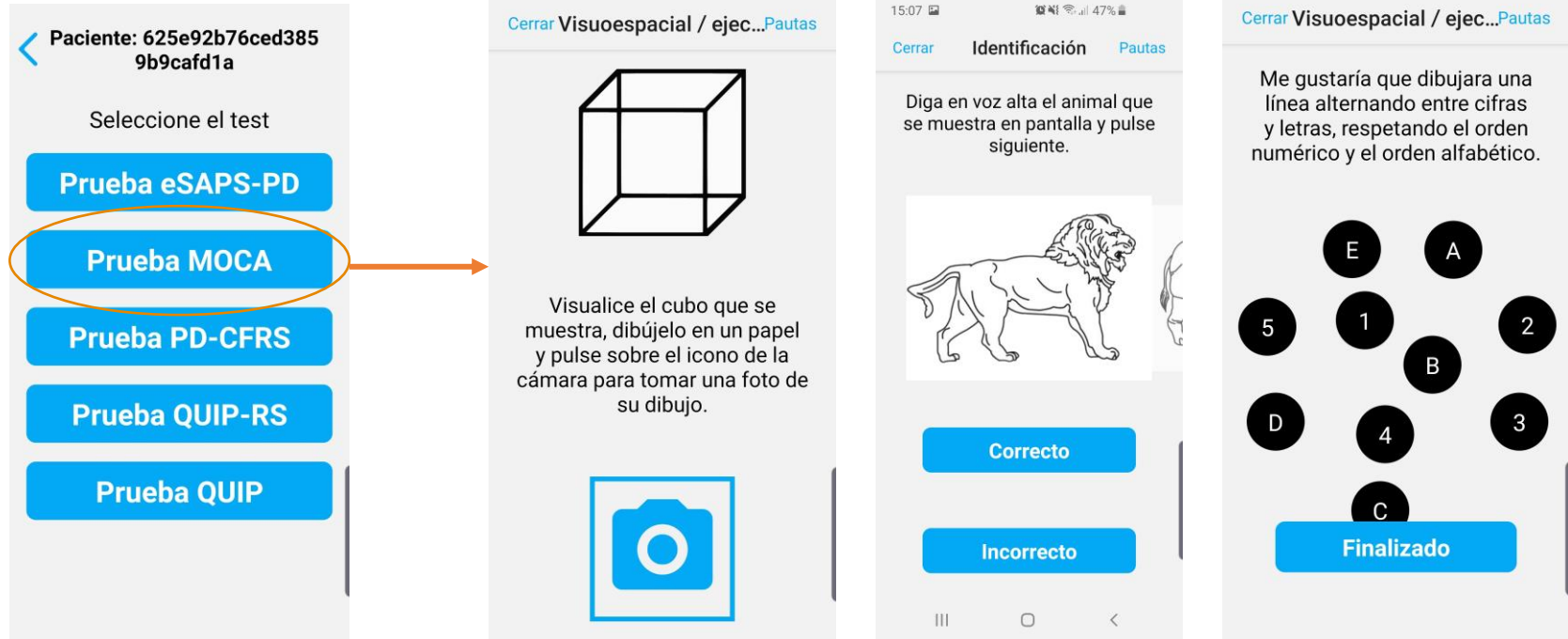


Mobile health solution based on Genetic profile, Imaging analysis and permanent symptoms Monitoring for personalized management of Parkinson Disease patients

Solución 2: Sistema de evaluación de remota para la evaluación de la bradicinesia, equilibrio/marcha y quejas cognitivas.

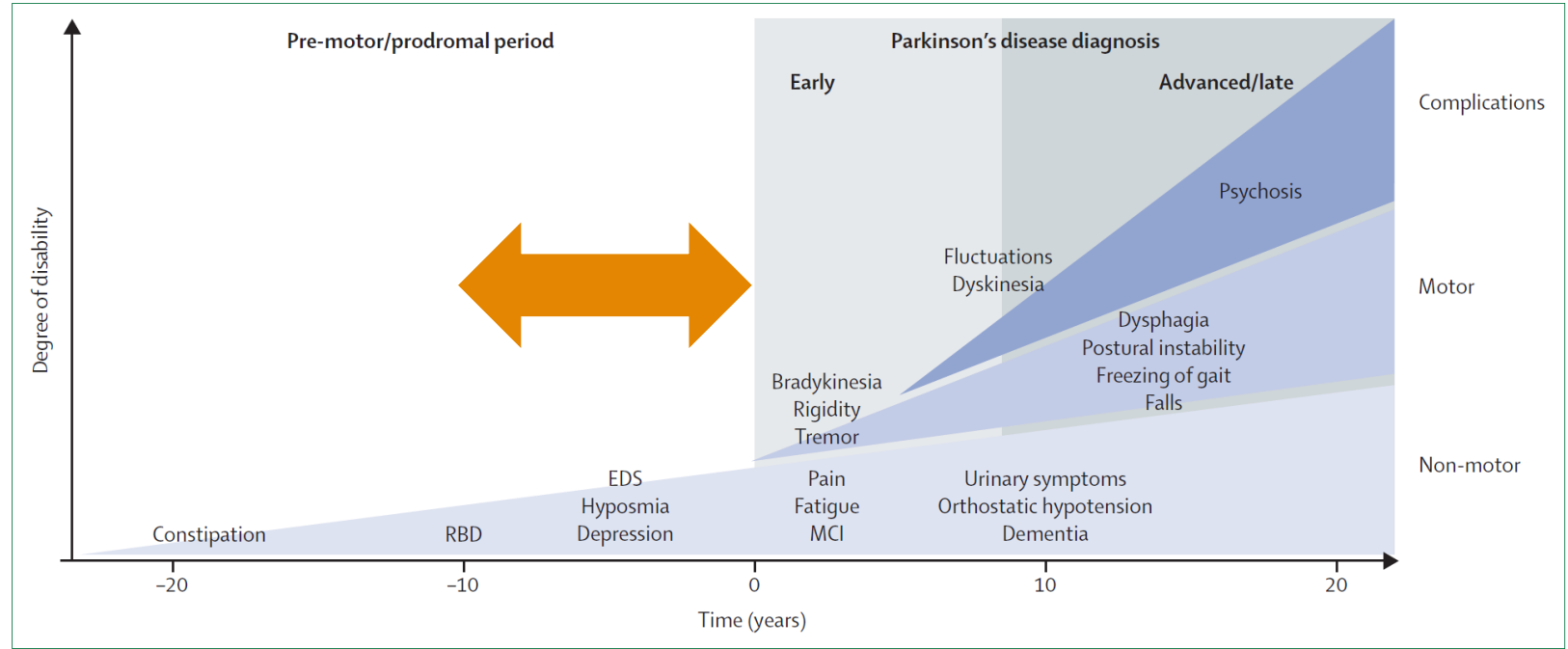


Solución 3: Sistema de evaluación de síntomas no motores

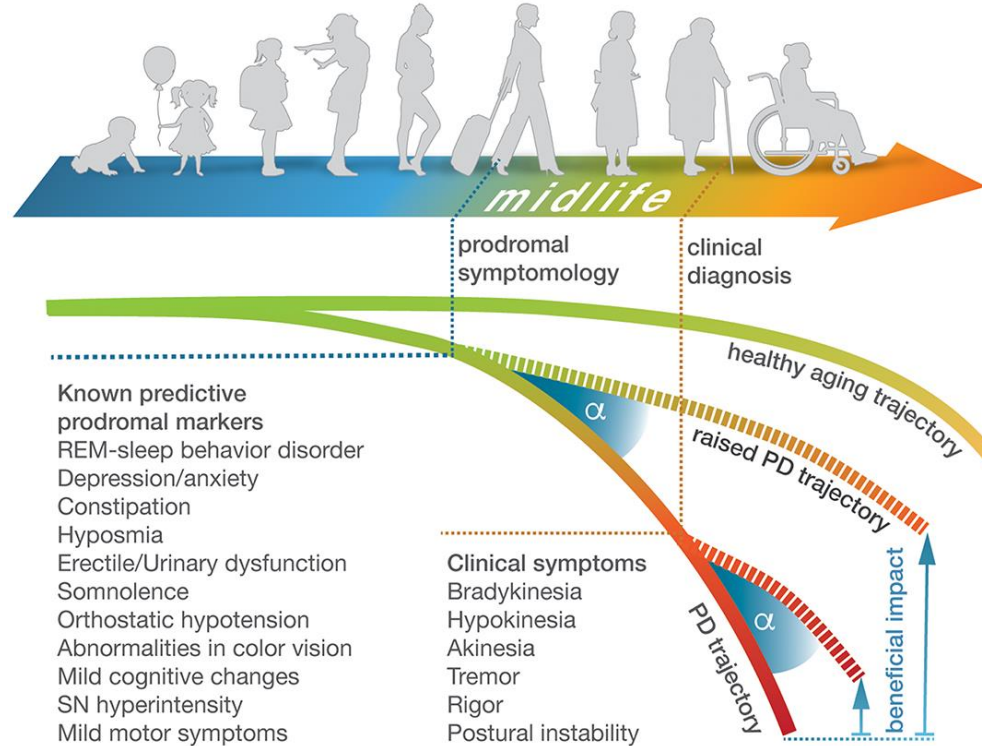


EP prodrómica

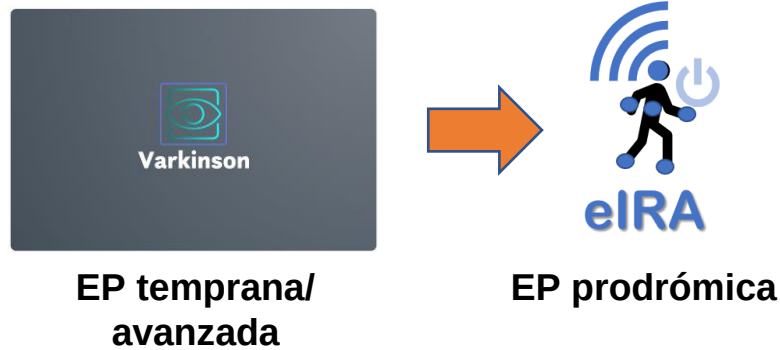
138



Retos y oportunidades de diagnosticar EP en etapas muy tempranas (mediana edad)



AI based Parkinson disease continuous diagnosis during prodroma state



European
Innovation
Council



SERVICIO ANDALUZ DE SALUD
Consejería de Salud y Familias

Asociación
ParKinson
Madrid

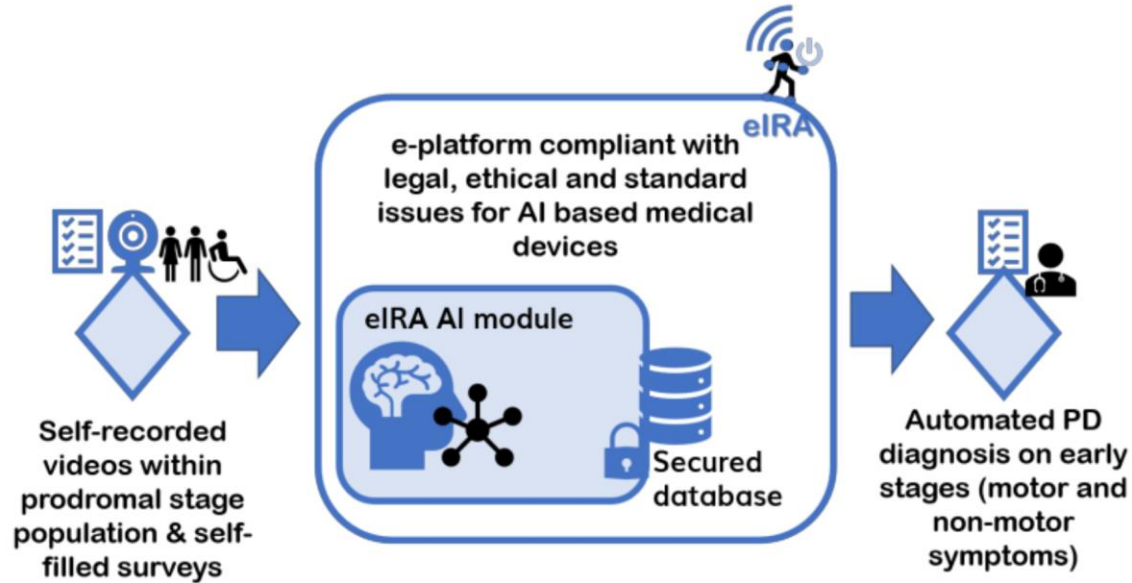
EIC Pathfinder Challenge: Towards the Healthcare Continuum: technologies to support a radical shift from episodic to continuous healthcare

izertis

KU LEUVEN

L2S2
TRANSFORMING DIGITAL HEALTH

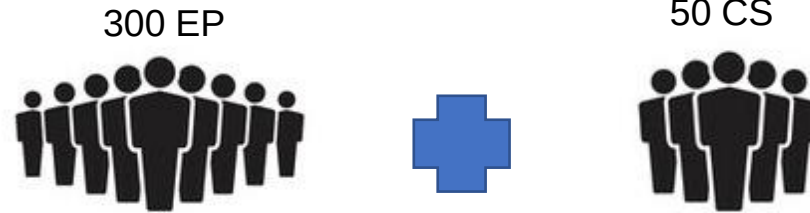
AI based Parkinson disease continuous diagnosis during prodroma state



AI based Parkinson disease continuous diagnosis during prodroma state

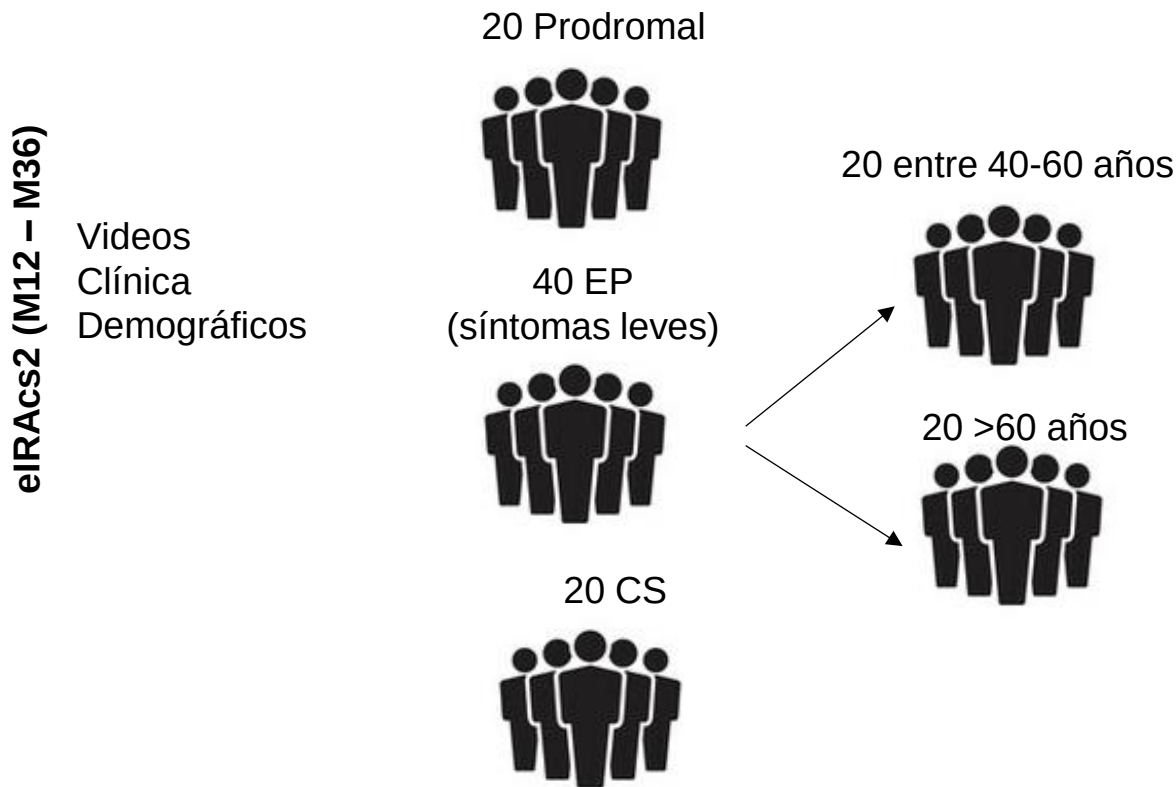
eIRAcS1 (M4 – M12)

Videos
UPDRS ON-OFF
Demográficos
Clínica



AI based Parkinson disease continuous diagnosis during prodroma state

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eIRA

AI based Parkinson disease continuous diagnosis during prodroma state

eIRacs3 (M30 – M48)

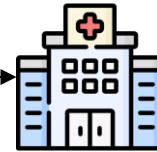
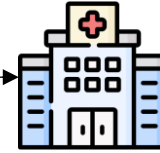
Population study: 1,000 pax



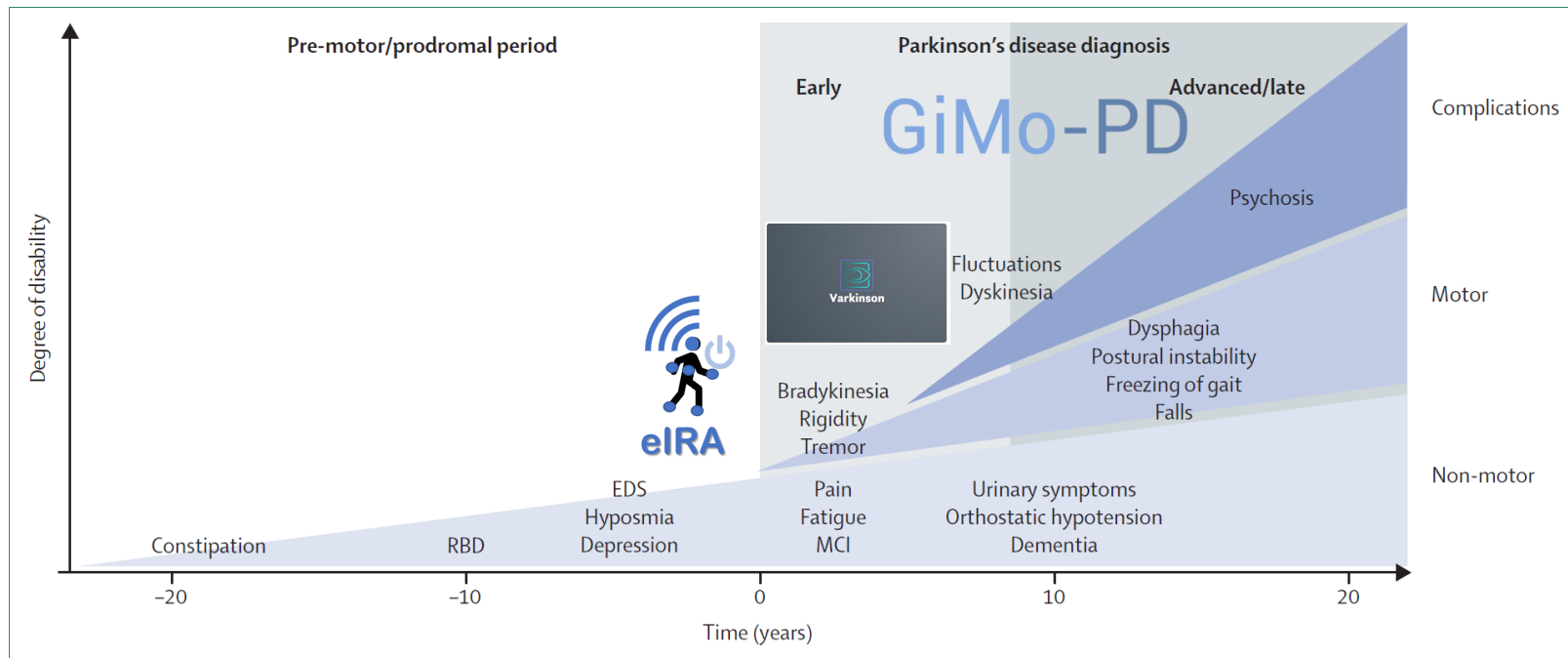
Test positivo

Test negativo

Confirmación clínica



Innovación tecnológica para la monitorización de síntomas clínicos y progression en la EP



“De la asistencia sanitaria episódica (reactiva al síntoma), a la continua”

IBiS

INSTITUTO DE BIOMEDICINA DE SEVILLA





THANKS!

Any questions?

You can find me at

▶ pmir@us.es

