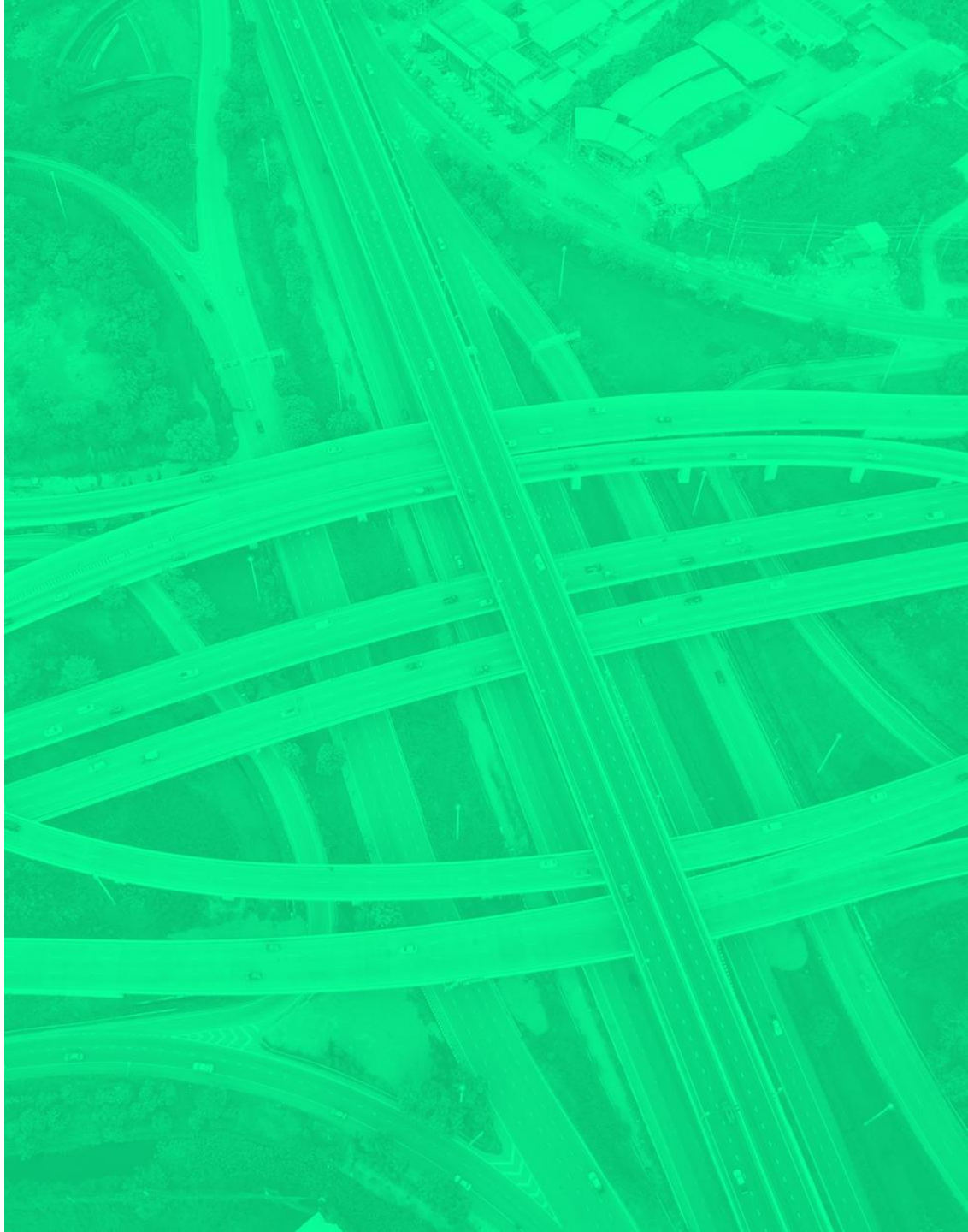
Cerebro e Inflamación:
Diferentes Vías, un Mismo Destino

ORGANIZADO POR

Fundación Lucha contra las Infecciones

ScienHub



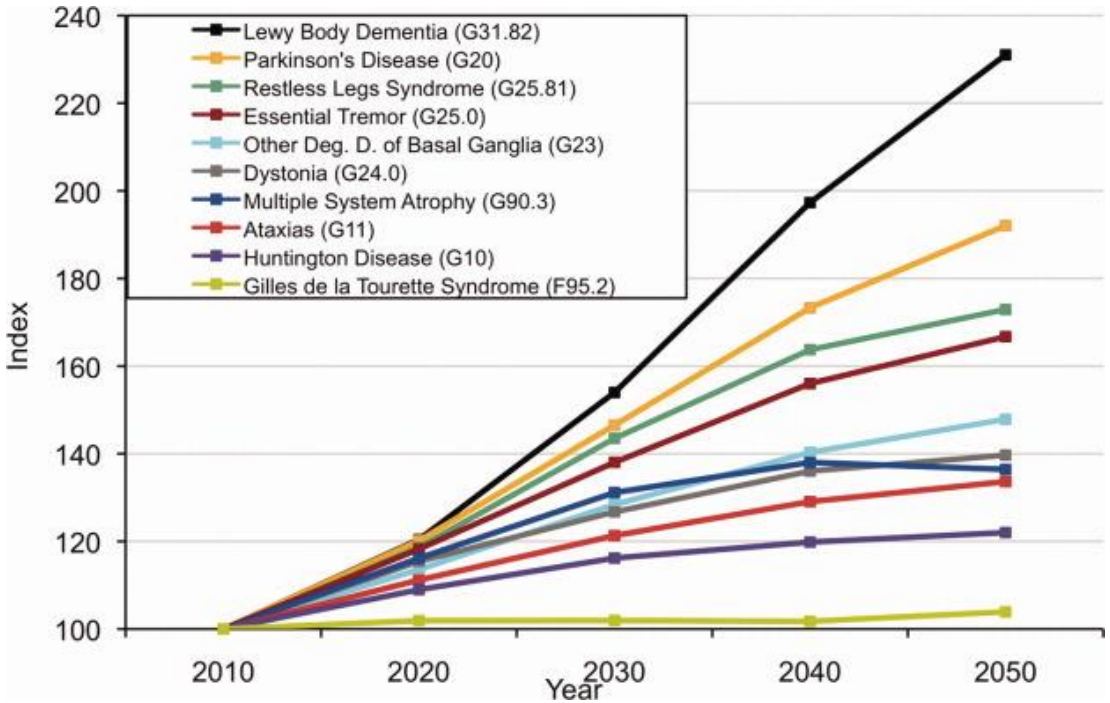
20 Febrero 2025

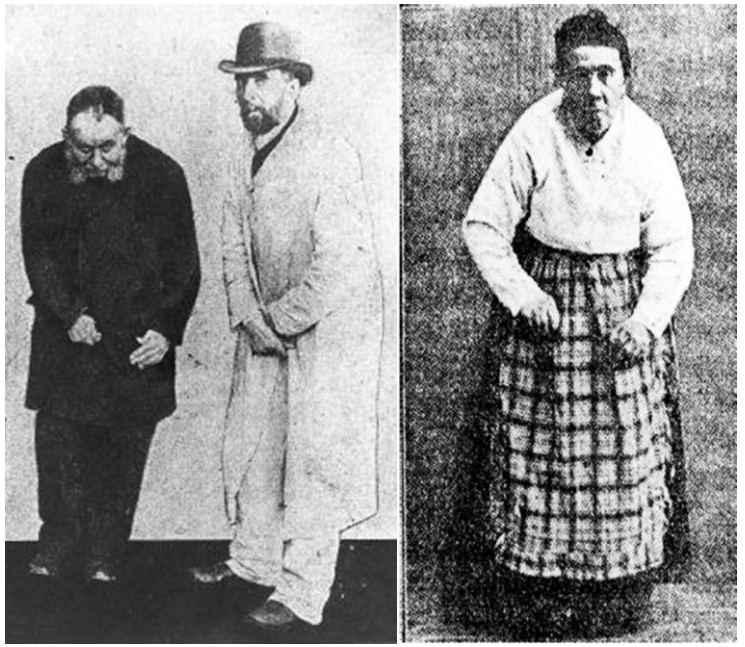
Enfermedad de Parkinson e inflamación

Dolores Vilas Rolán
Neuróloga
Unidad Trastornos del Movimiento
Hospital Germans Trias i Pujol
Badalona

Enfermedad de Parkinson

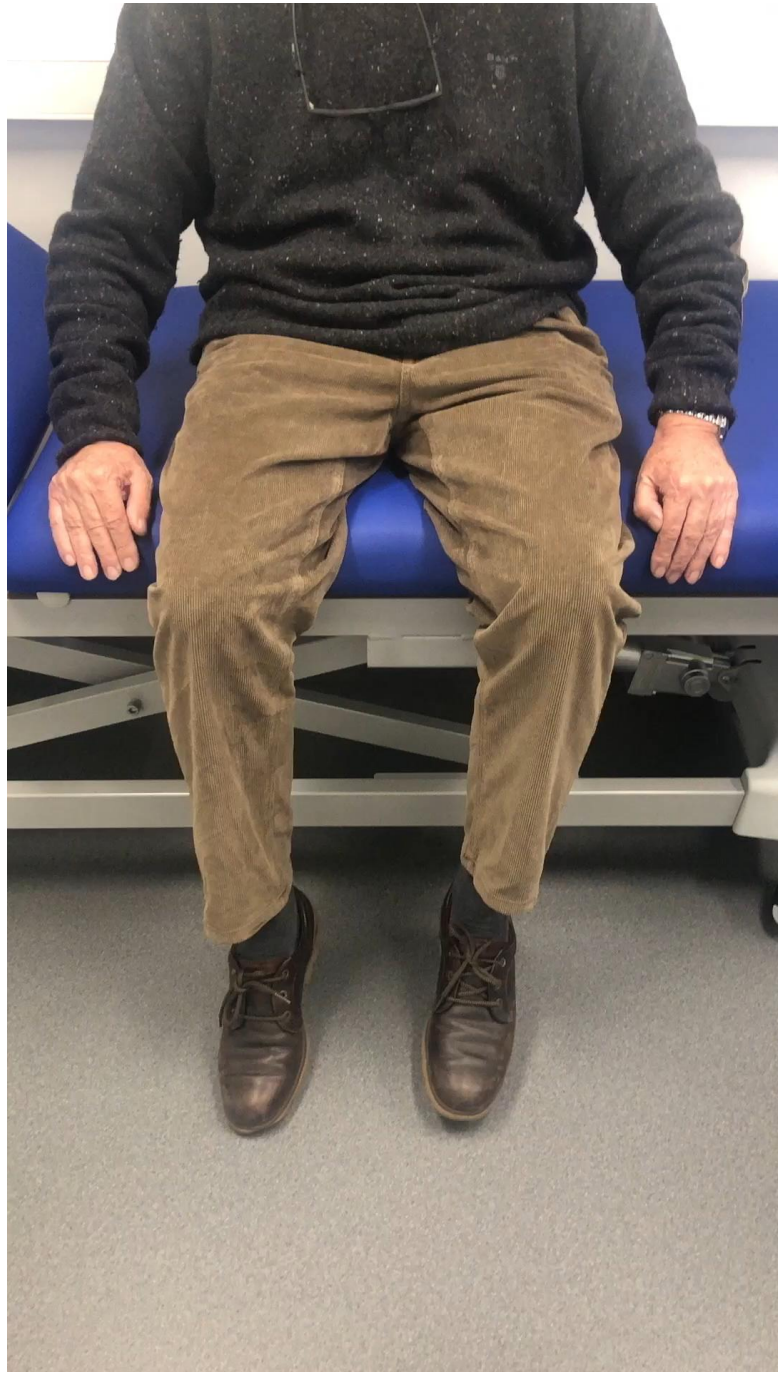
Enfermedad neurodegenerativa
1-2 % población> 65 años
Hombres>mujeres





James Parkinson, 1817

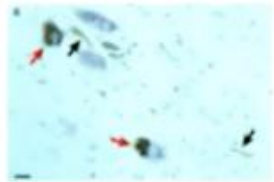
https://doi.org/10.1002/mds.23878



α–Synuclein aggregates in Lewy pathology

Goedert et al 2012

Lewy 1923



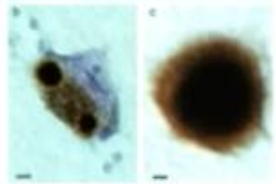
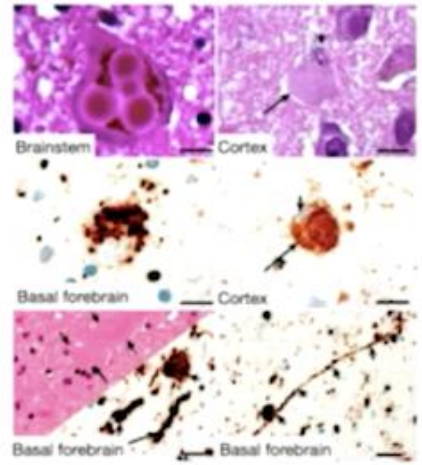


Fig. 1 Twenty years ago: Ross Jakes, Maria Grazia Spillantini and Michel Goedert (from left to right) in 1997.

α-Synuclein in Lewy bodies

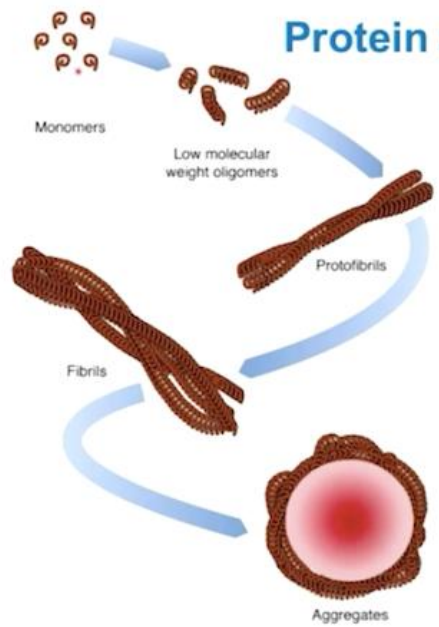
NATURE | VOL 388 | 28 AUGUST 1997

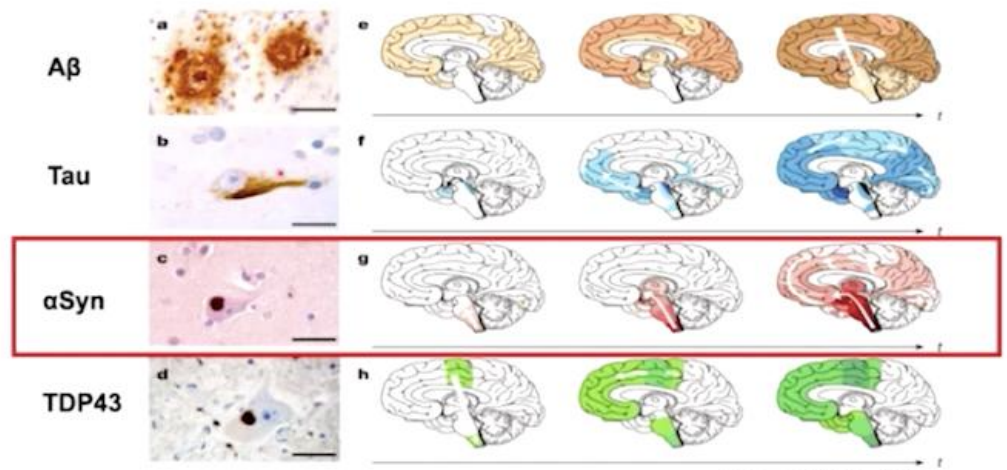
Maria Grazia Spillantini
Medical Research Council Centre for Brain Repair and Department of Neurology, University of Cambridge, Robinson Way, Cambridge CB2 2PY, UK
Marie Luise Schmidt
Virginia M.-Y. Lee
John Q. Trojanowski
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6283, USA
Ross Jakes, Michel Goedert
Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK



Chartier and Duyckerts 2018

Protein aggregation in synucleinopathies



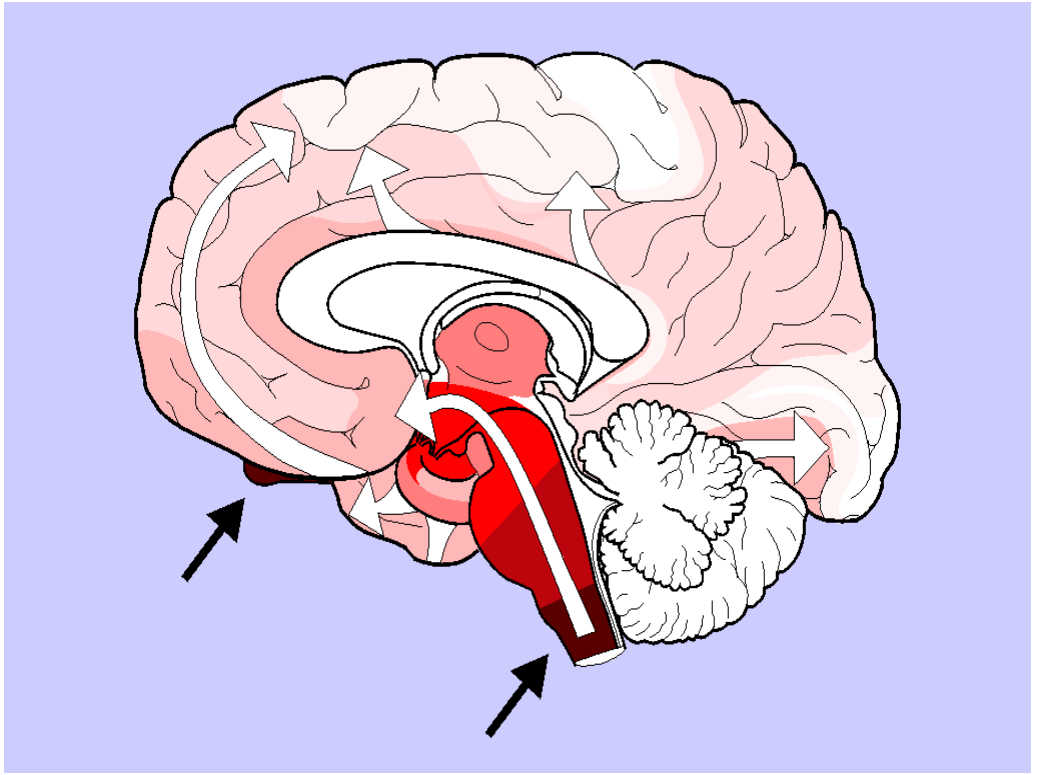


Jucker and Walker 2013

Adapted from Eisbach and Outeiro, JMM, 2013

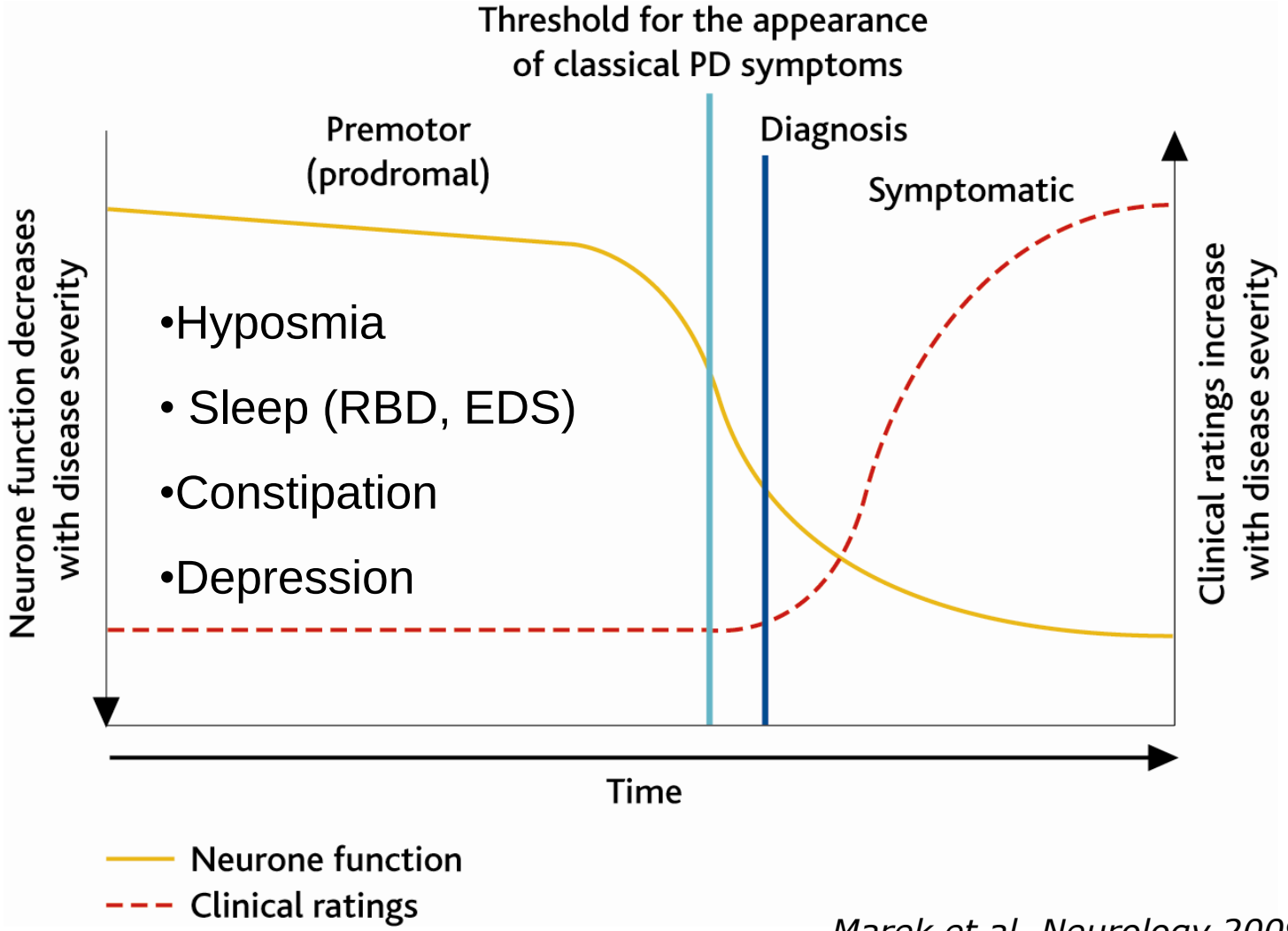
Braak PD CNS neuropathological staging

- **Stage 1: Medulla and olfactory bulb**
- **Stage 2: Pontine tegmentum and locus coeruleus**
- **Stage 3: Midbrain (substantia nigra) and basal forebrain**
- **Stage 4: Medial temporal cortex and amygdala**
- **Stage 5: Higher order association cortices**
- **Stage 6: Primary cortices**



Braak 2003

Natural history of idiopathic PD



Marek et al. Neurology 2009; 72: S21

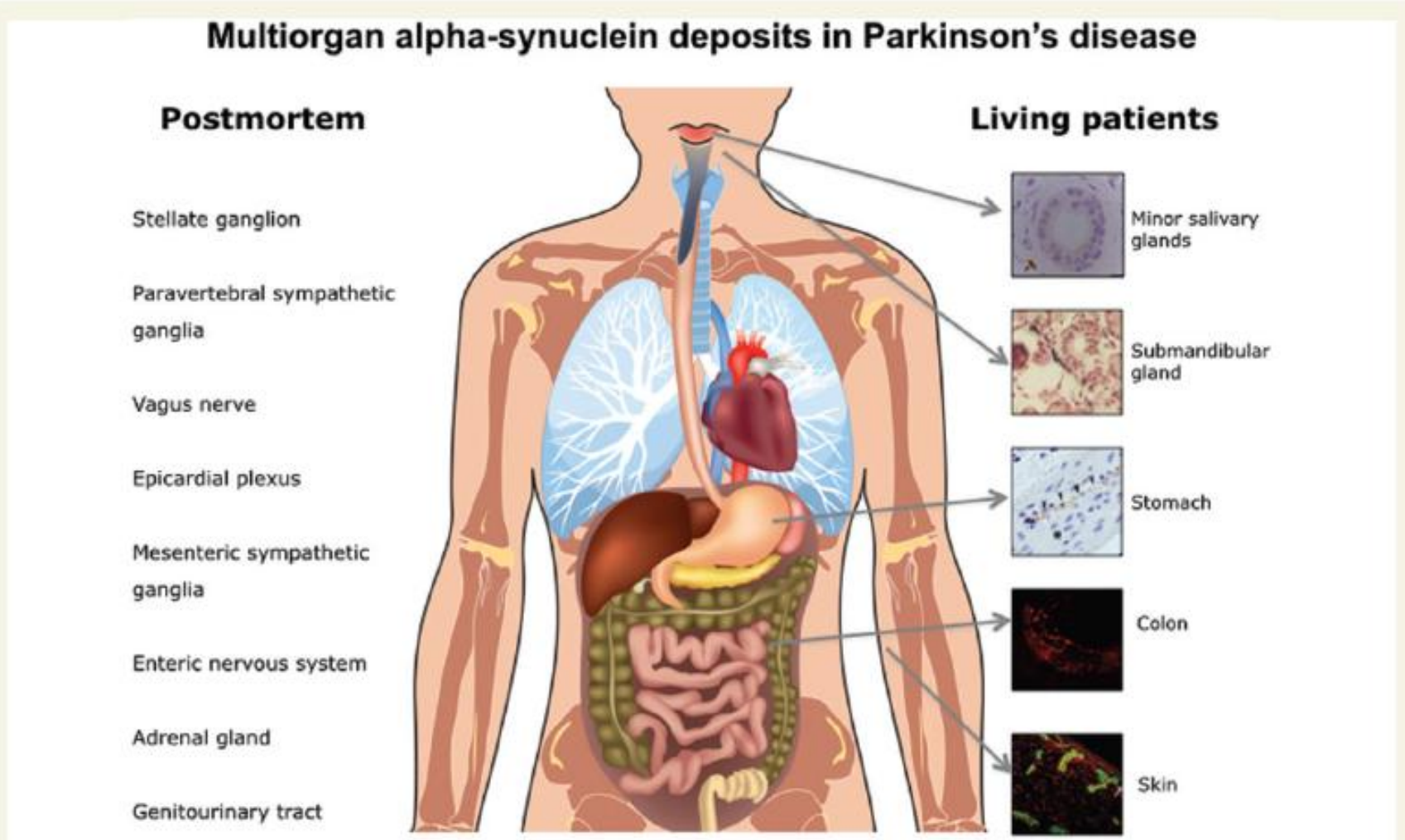
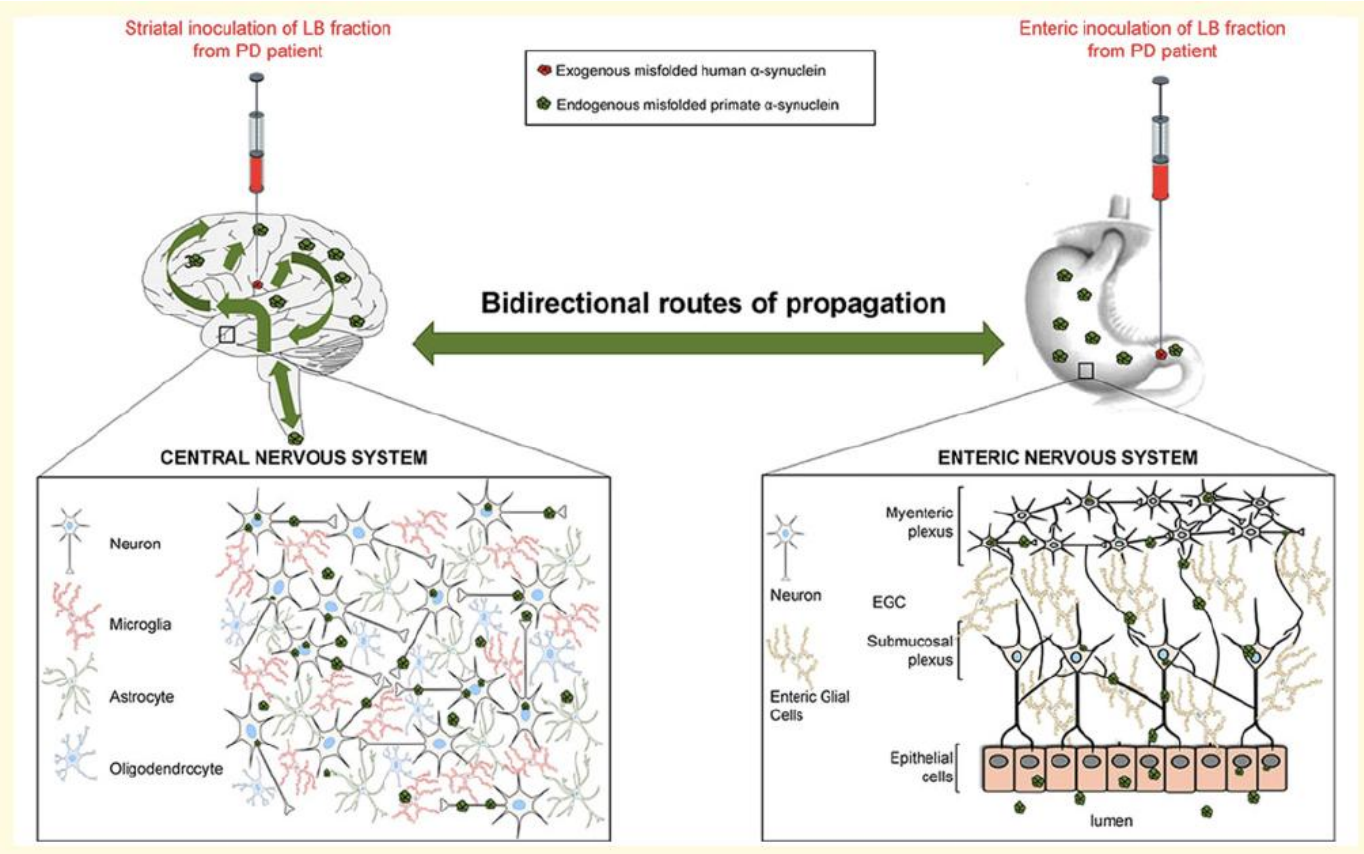


Figure 1 Peripheral tissues in which pSNCA deposits have been reported to occur in Parkinson's disease. Modified from image by Yoko Design, Shutterstock.

Tolosa E, Vilas D. Brain 2015

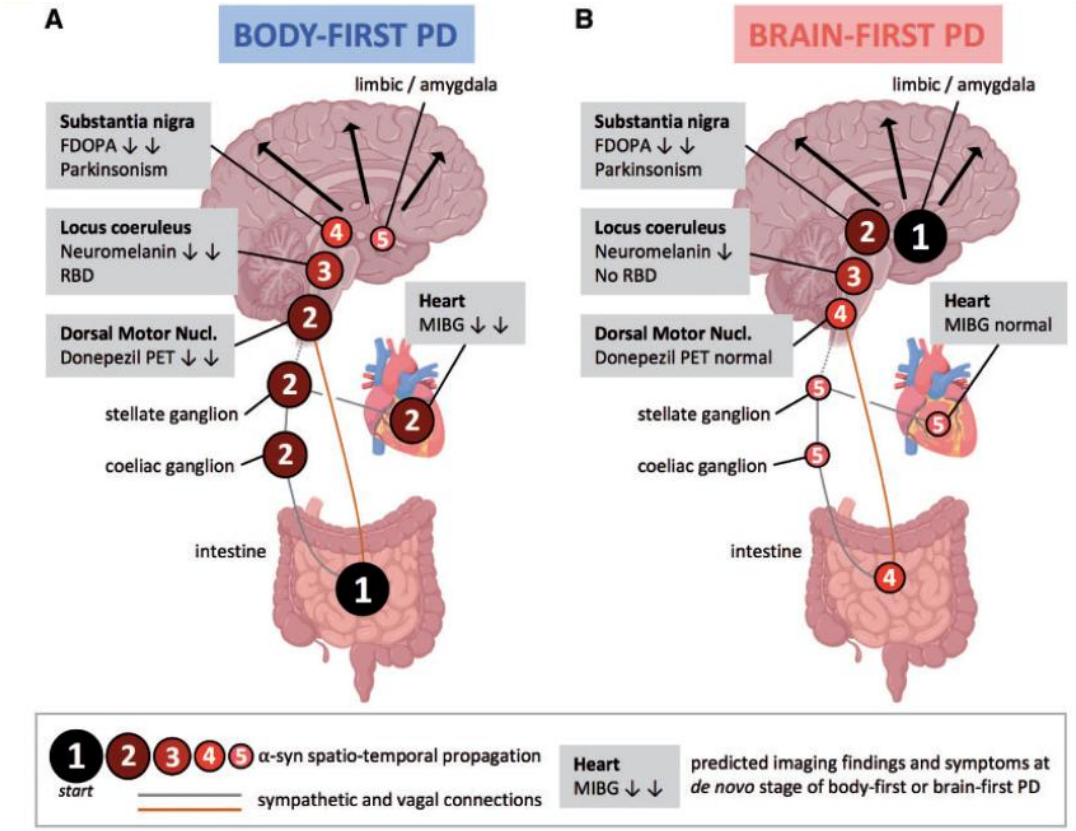
doi:10.1093/brain/awaa096 BRAIN 2020: Page 1 of 14 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Bidirectional gut-to-brain and brain-to-gut propagation of synucleinopathy in non-human primates



doi:10.1093/brain/awaa238 BRAIN 2020: Page 1 of 12 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study



¿Enfermedad de Parkinson e inflamación?

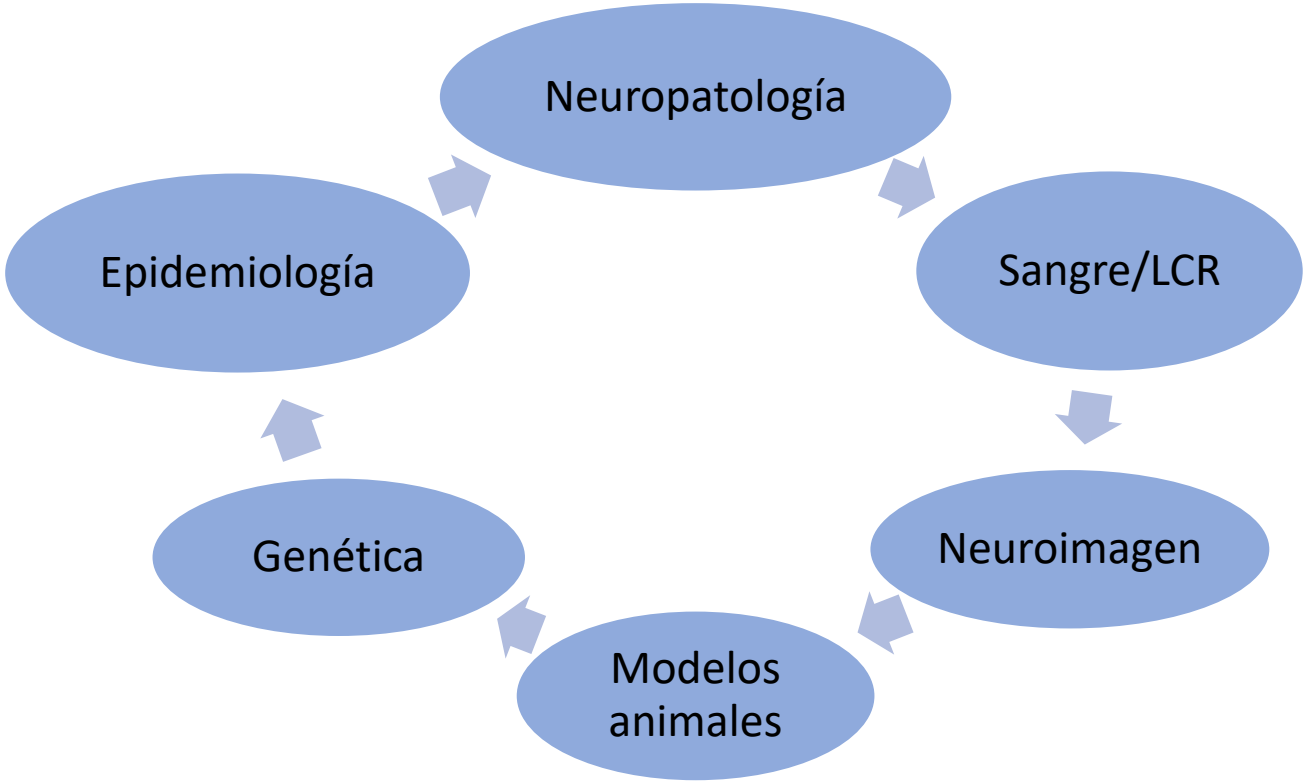
Neuroinflamación

- La **neuroinflamación** es una respuesta dinámica y compleja del SNC al daño, infección y enfermedad

- **Inflamación aguda:** papel protector (preservación de la homeostasis del SNC)
  - Aclaramiento del patógeno
  - Reparación del daño tisular

- **Inflamación crónica/inflamación "desregulada"**
  - Progresión de enfermedades neurodegenerativas
    E. Alzheimer, E Parkinson, Esclerosis Múltiple
  - Activación de las células inmunológicas en el SNC
  - Circuitos de señalización aberrantes
  - Infiltración de células inmunes periféricas
  - Daño neuronal progresivo
  - Daño funcional

Enfermedad de Parkinson e inflamación

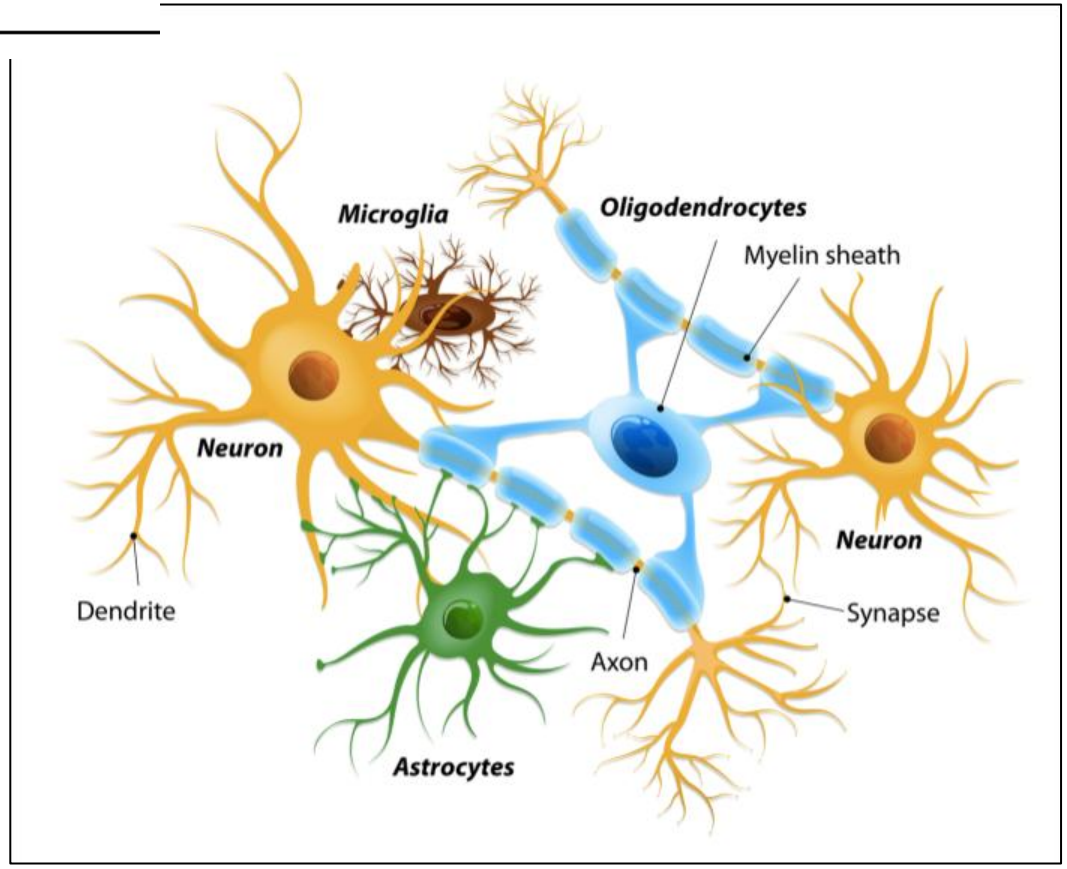


“Tormenta perfecta”

Predisposición genética → Factores ambientales → Sistema inmune alterado → **E. Parkinson**

Table 1. Key Cellular components and their roles in neuroinflammation.

Component	Role	Key Features
Microglia	Primary immune cells in CNS	Respond to amyloid beta, alpha synuclein, and injury; pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes
Astrocytes	Support neurons and modulate neuroinflammation	Pro-inflammatory (A1) vs. anti-inflammatory (A2); secrete cytokines (IL-1, IL-6) and chemokines
Peripheral Cells	Mediate immune–CNS interactions during BBB disruption	T cells and macrophages contribute to inflammation; Tregs regulate responses via IL-10 and TGF-β



Kim and Lee. Curr Issues Mol biol. 2025, 47, 8

Microglía

Fenotipo M1 (*Proinflamatorio*)

Liberación citoquinas pro-inflamatorias

TNF-alfa
IL-1 beta
IL-6

Liberación especies reactivas O2 (ROS) y óxico nítrico (NO)

Daño neuronal

Fenotipo M2 (antiinflamatorio)

Liberación citoquinas anti-inflamatorias

IL-10
TGF-beta

Enfermedades neurodegenerativas: Un estado proinflamatorio prolongado o incontrolado

Factores moleculares que modulan el equilibrio entre estos 2 estados:

- Factor de transcripción NF-kB: proinflamatorio
- STAT6: antiinflamatorio

E Parkinson: papel de la microglía

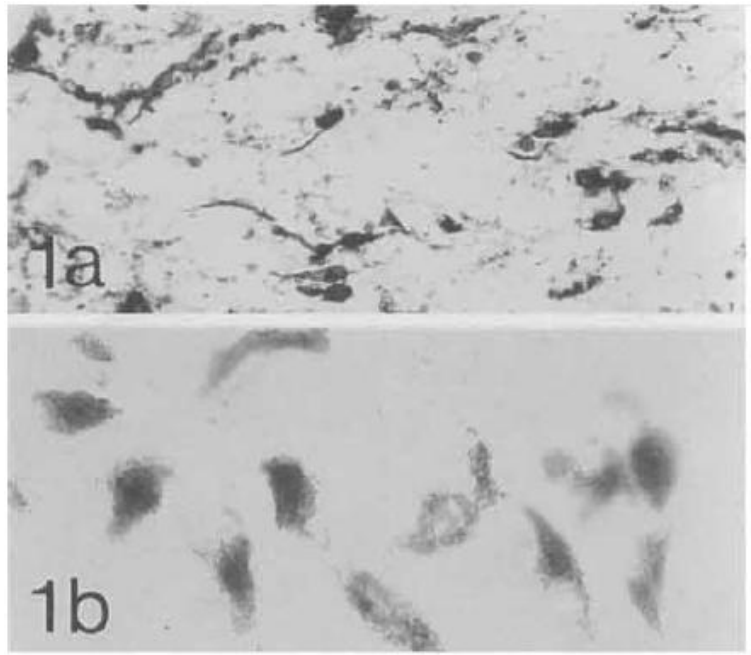
- La microglía está densamente poblada en la SNpc y estriado, áreas afectadas en la E Parkinson

Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains

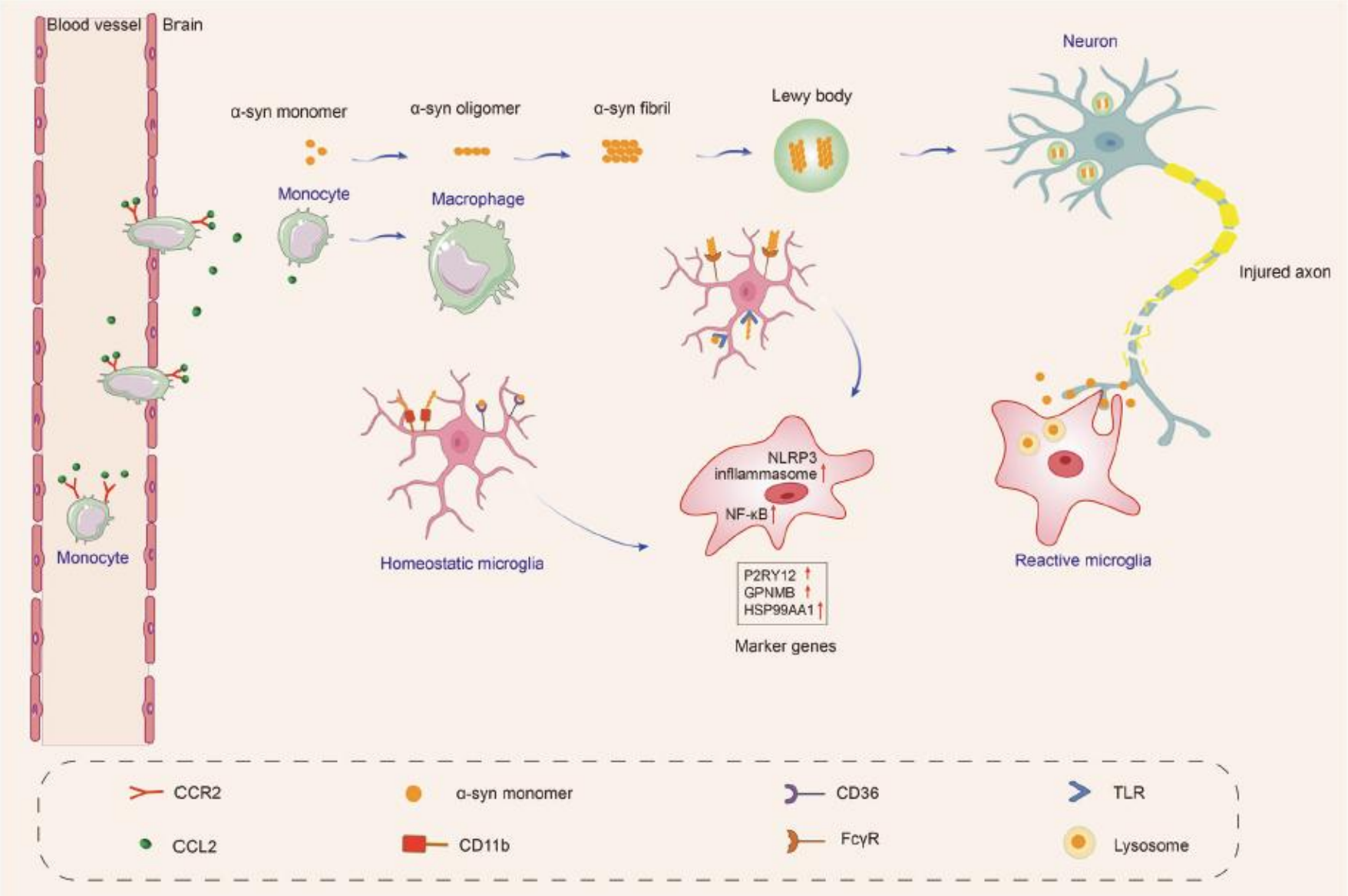
P.L. McGeer, MD, PhD; S. Itagaki, MD; B.E. Boyes, MSc; and E.G. McGeer, PhD

Article abstract—We detected large numbers of HLA-DR-positive reactive microglia (macrophages), along with Lewy bodies and free melanin, in the substantia nigra of all cases studied with Parkinson's disease (5) and parkinsonism with dementia (PD) (5). We found similar, but less extensive, pathology in the substantia nigra of six of nine cases of dementia of the Alzheimer type (DAT) but in only one of 11 age-matched nonneurologic cases. All dementia cases with a premortem diagnosis of DAT or PD showed large numbers of HLA-DR-positive reactive microglia and significant plaque and tangle counts in the hippocampus, as well as reduced cortical choline acetyltransferase activity. One of 11 nondemented controls showed mild evidence of similar cortical pathology. These data indicate that HLA-DR-positive reactive microglia are a sensitive index of neuropathologic activity. They suggest a frequent coexistence of DAT- and Parkinson-type pathology in elderly patients.

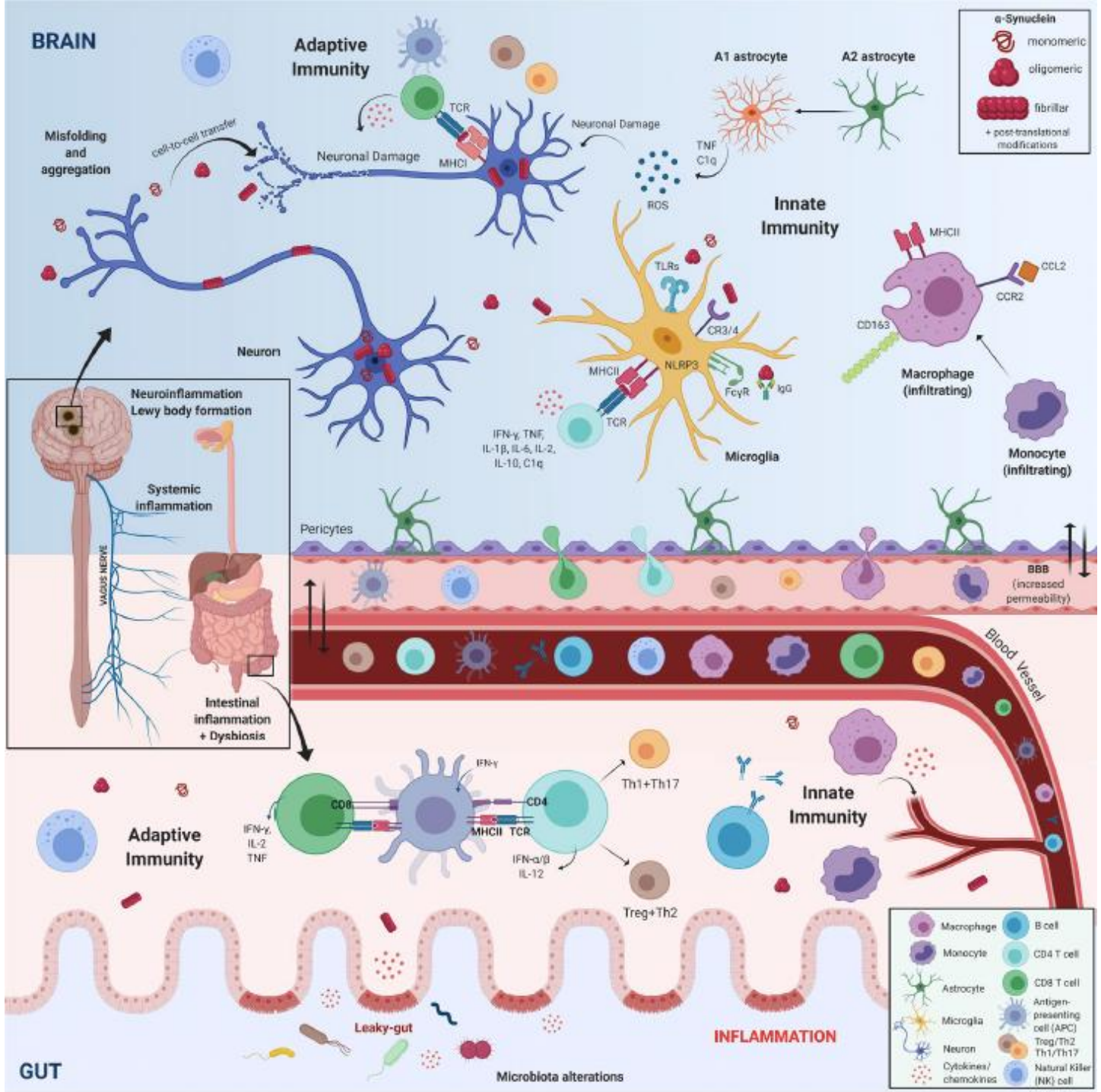
NEUROLOGY 1988;38:1285-1291



Microglía in EP

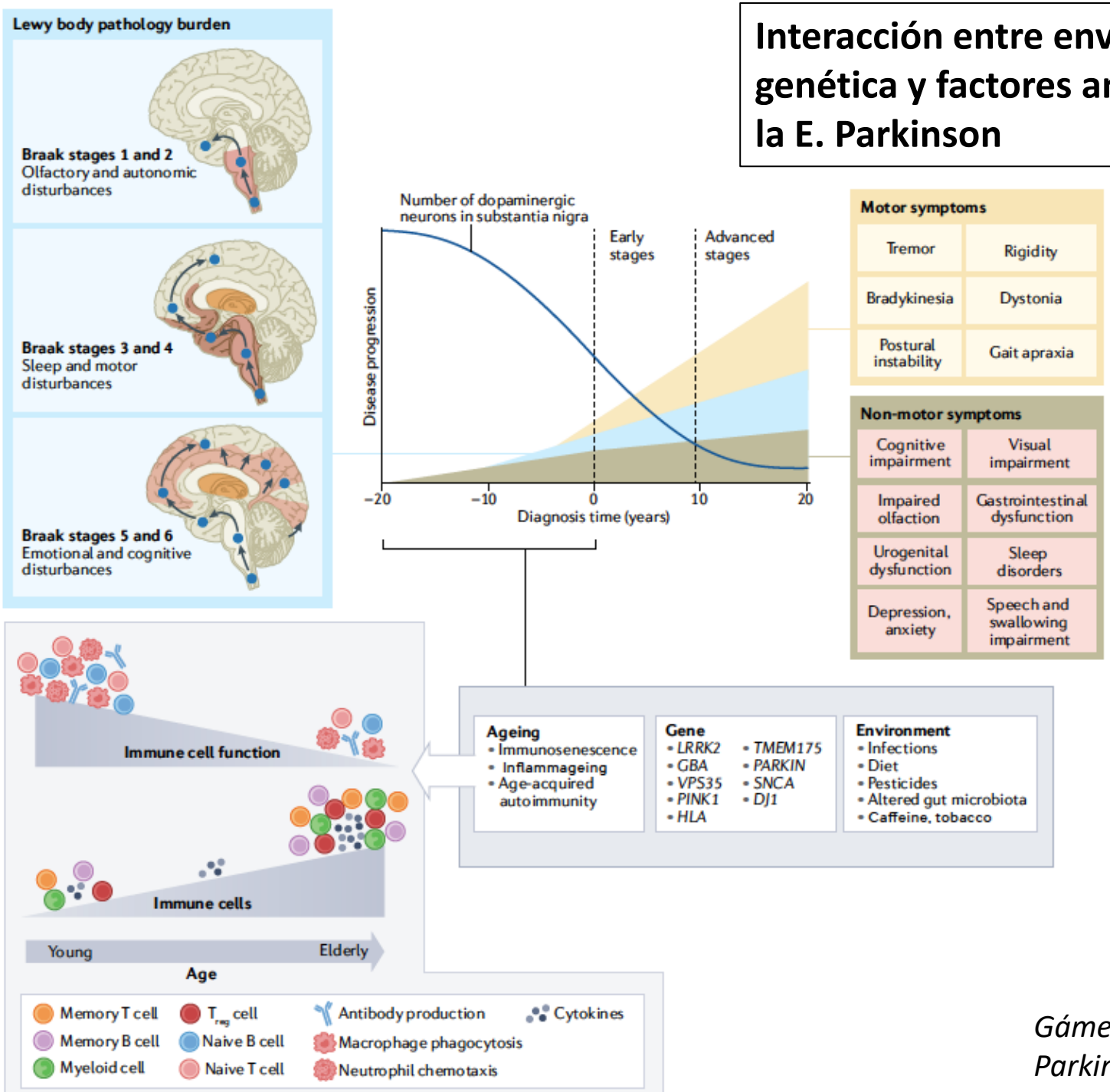


Gao et al. Signal Transduction and Targeted Therapy; 2023;8:359

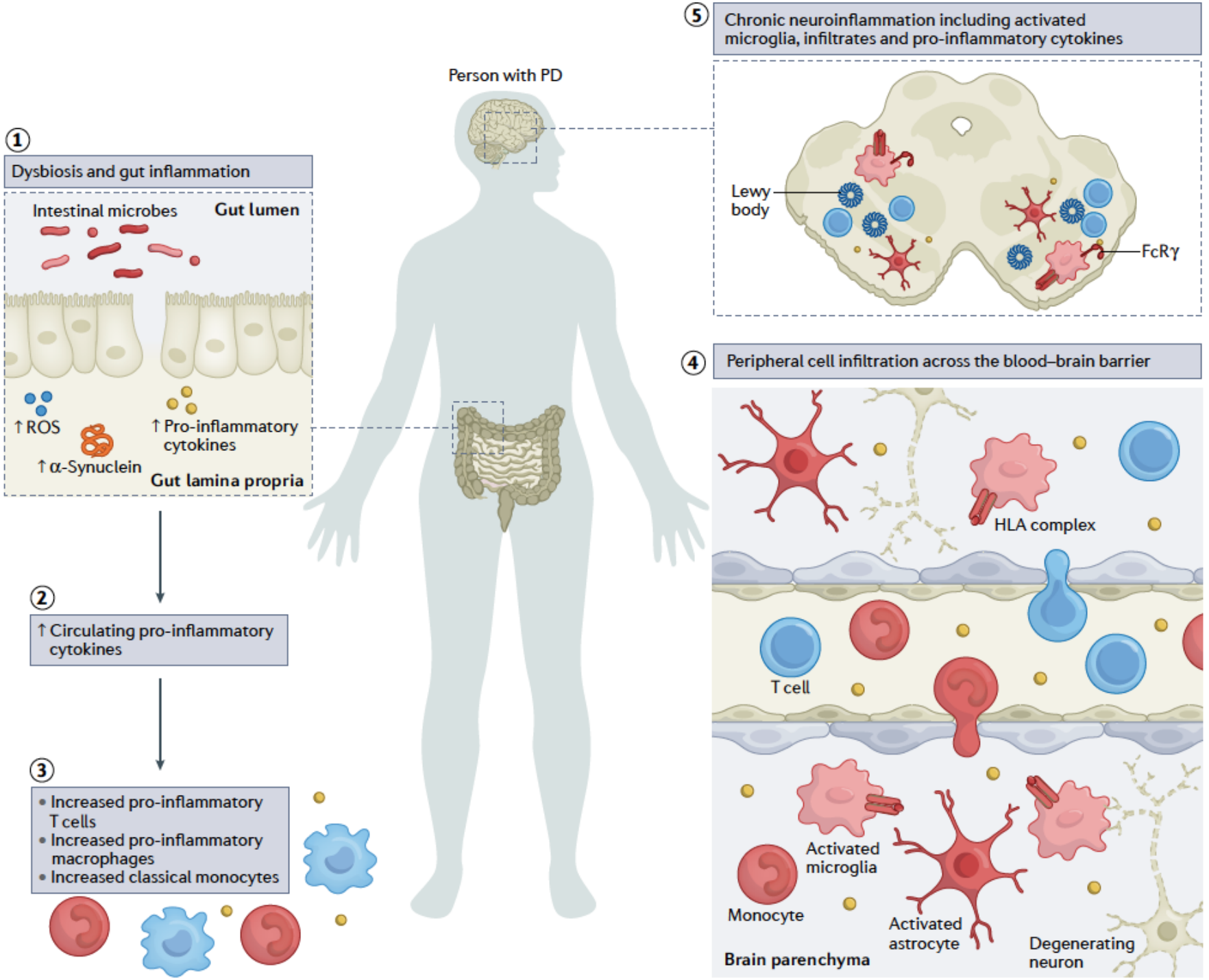


Harms et al. Acta Neuropathologica (2021); 141:527–545

Interacción entre envejecimiento de células inmunitarias, genética y factores ambientales y progresión de la patogenia de la E. Parkinson



Gámez-Tansey et al. Inflammation and immune dysfunction in Parkinson disease. Nature Reviews. 2022;vol 22;657-673



Manifestaciones de inflamación en la E Parkinson

Gámez-Tansey et al. Inflammation and immune dysfunction in Parkinson disease. Nature Reviews. 2022;vol 22;657-673

Actividad microglial ”in vivo” con PET en E Parkinson

[^{11}C]®-PK11195: unión a la proteína TSPO (translocator protein) (=receptor de benzodiacepina periférica) (selectivamente expresada en microglía activada)

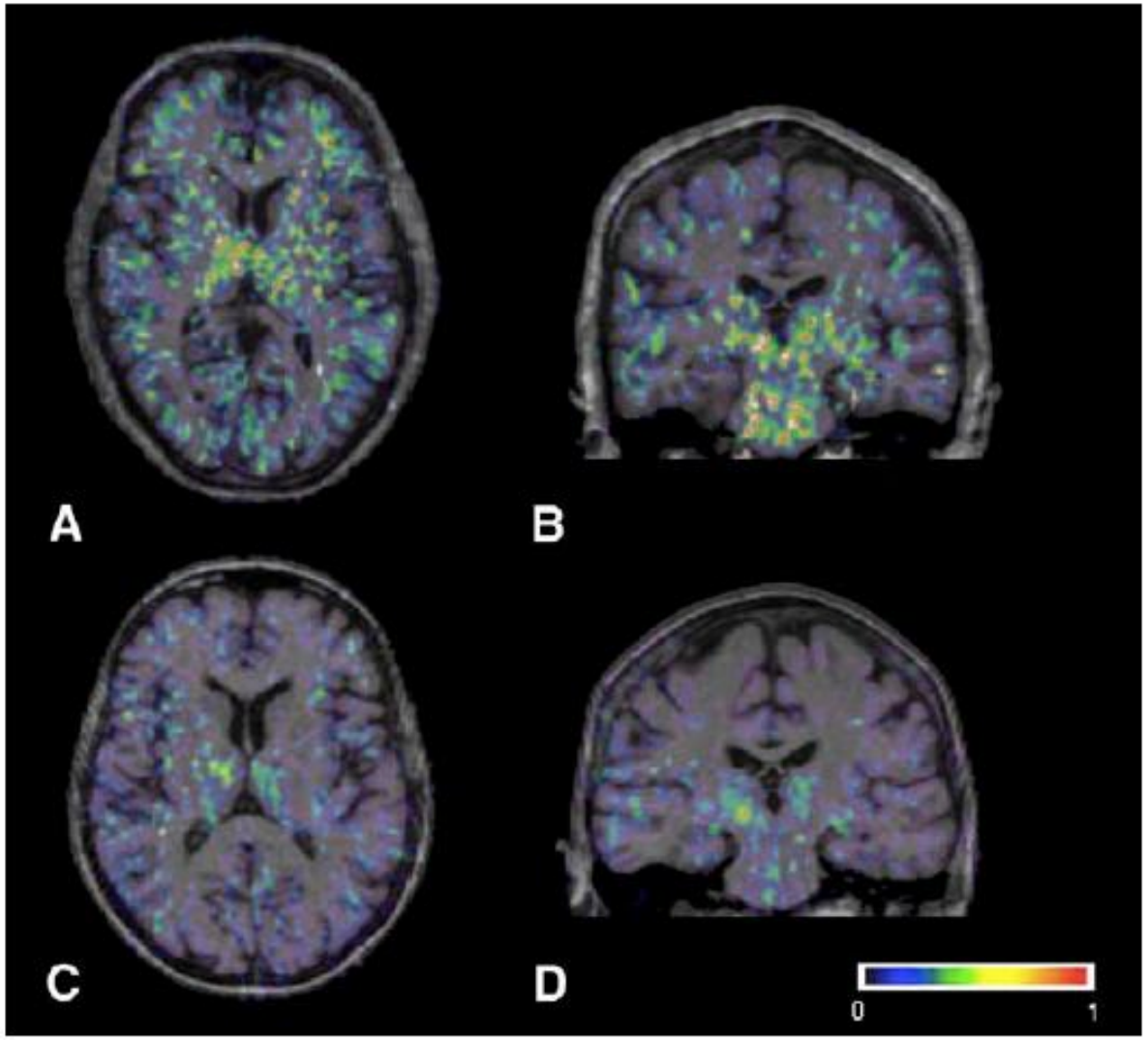
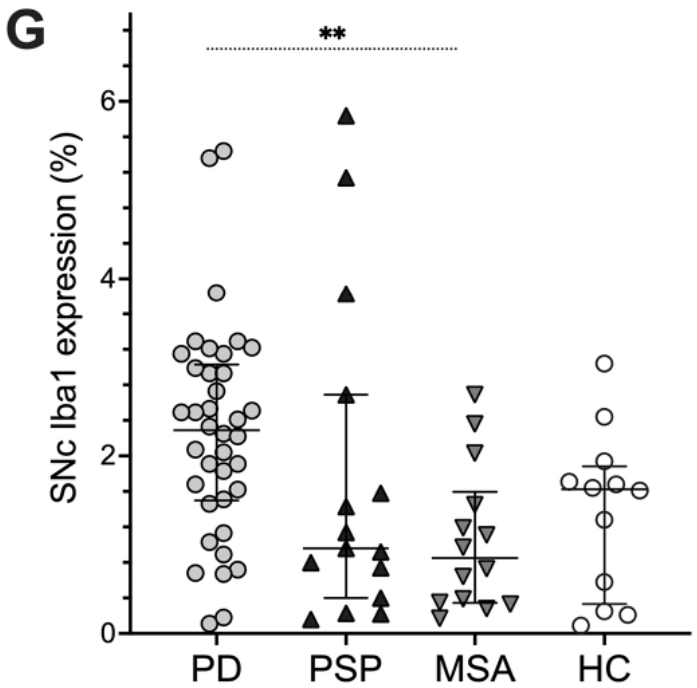


Fig. 1. Transverse and coronal sections of binding potential maps co-registered to the individual MRI. In the PD patient (A and B), binding is increased in the basal ganglia, pons and frontal regions, while the healthy control person (C and D) only shows constitutive [^{11}C](*R*)-PK11195 binding in the thalamus and pons. The color bar denotes binding potential values from 0 to 1.

Gerhard A, et al. Neurobiol Dis. 2006 Feb;21(2):404-12.

Nigral Neuroinflammation and Dopaminergic Neurons in Parkinson's Disease and Atypical Parkinsonisms

Emmilotta A. Backman, BM [1,2] Maria Gardberg, MD, PhD,[3] Laura Luntamo, MD, PhD,[1,2]
Markus Peurla, PhD,[4] Tero Vahlberg, MSc,[5] Per Borghammer, MD, PhD,[6,7]
Nadia Stefanova, MD, PhD,[8] Gregor Wenning, MD, PhD,[8‡] and
Valtteri Kaasinen, MD, PhD [1,2]



- Estudio neuropatológico de pacientes con EP, MSA y PSP.
- Patrones de neuroinflamación diferente en las distintas patologías
- Mayor activación microglial en la SN en pacientes con EP.
- **Mayor actividad inflamatoria en fases más precoces, disminuyendo con mayor pérdida neuronal.**

ANN NEUROL 2025;00:1–14

Evidencia epidemiológica

Reduced incidence of PD

- Caffeine consumption
- Exercise
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Smoking

Increased incidence of PD

- Pesticide exposure
- Traumatic brain injury
- Exposure to certain viral or bacterial infections
- Otras enfermedades AI (EM, Graves, Hashimoto, Polimialgia reumática)
- Gut dysbiosis and inflammatory bowel disease

Estos hallazgos sugieren que la **inflamación** puede hacer sinergia con la **predisposición genética** para desencadenar la patogénesis y progresión de la EP

Hernan, M. A., et al. Ann. Neurol. 52, 276–284 (2002); Yang, F. et al. Brain 138, 269–275 (2015); Ritz, B. et al. Arch. Neurol. 64, 990–997 (2007); Priyadarshi, A et al . Neurotoxicology 21, 435–440 (2000); Kenborg, L. et al. Neurology 84, 1098–1103 (2015); Park, M. et al. Neurology 64, 1047–1051 (2005); Brugger, F. et al. NPJ Parkinsons Dis. 1, 15014 (2015); Costa Sa, A. C., et al. Sci. Rep. 9, 8795 (2019).

Evidencia epidemiológica

Reduced incidence of PD

- Caffeine consumption
- Exercise
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Smoking

- Ibuprofeno: acción protectora neuronas dopaminérgicas in vitro
- Salicilato sódico, AAS y meloxicam: acción protectora de la neurotoxicidad inducida por MPTP en modelos animales
- Pacientes con consumo regular de AINEs (ibuprofeno): menor riesgo de EP
- AINEs: inhibición de la ciclooxigenasa 1 y 2 (COX1 y COX2), reduciendo la generación de radicales de óxido nítrico y estrés oxidativo

Hernan, M. A., et al. Ann. Neurol. 52, 276–284 (2002); Yang, F. et al. Brain 138, 269–275 (2015); Ritz, B. et al. Arch. Neurol. 64, 990–997 (2007); Priyadarshi, A et al . Neurotoxicology 21, 435–440 (2000); Kenborg, L. et al. Neurology 84, 1098–1103 (2015); Park, M. et al. Neurology 64, 1047–1051 (2005); Brugger, F. et al. NPJ Parkinsons Dis. 1, 15014 (2015); Costa Sa, A. C., et al. Sci. Rep. 9, 8795 (2019).

Evidencia epidemiológica

Paraquato, rotenona y MPTP: inducen inflamación central y periférica y estrés oxidativo

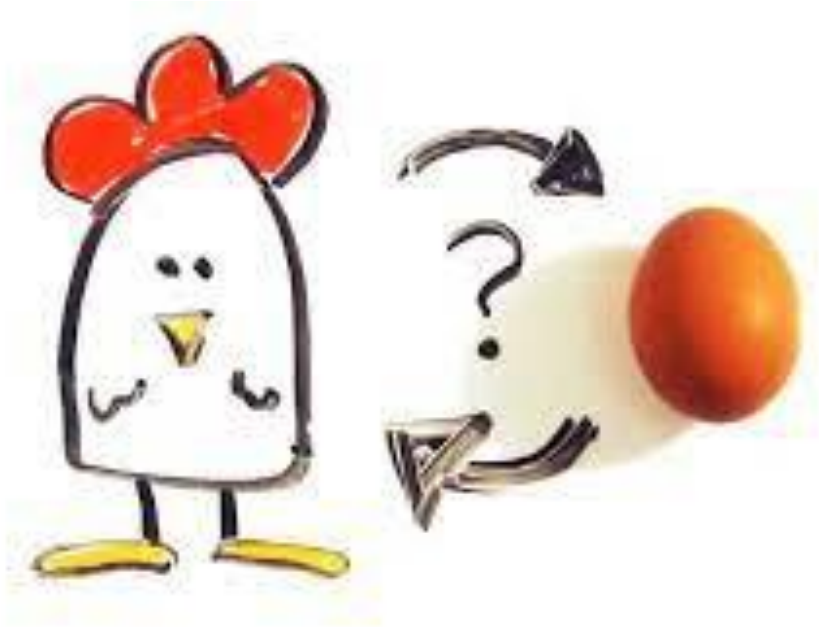
Estudio GWAS: se identificaron 17 loci comunes entre EP y 7 enfermedades autoinmunes (DM1, Crohn's disease, ulcerative colitis, rheumatoid arthritis, coeliac disease, psoriasis and multiple Sclerosis).

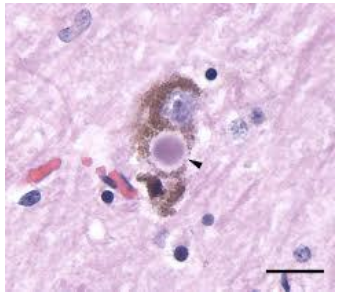
Increased incidence of PD

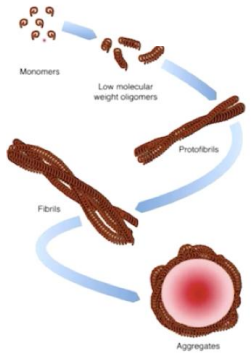
- Pesticide exposure
- Traumatic brain injury
- Exposure to certain viral or bacterial infections
- Otras enfermedades AI (EM, Graves, Hashimoto, Polimialgia reumática)
- Gut dysbiosis and inflammatory bowel disease

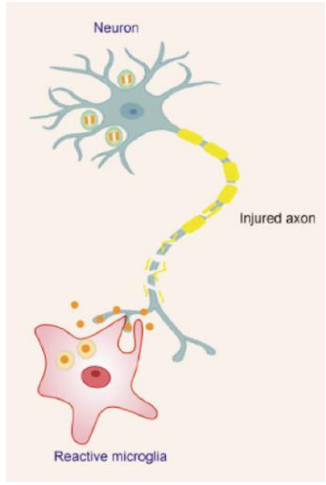
Hernan, M. A., et al. Ann. Neurol. 52, 276–284 (2002); Yang, F. et al. Brain 138, 269–275 (2015); Ritz, B. et al. Arch. Neurol. 64, 990–997 (2007); Priyadarshi, A et al . Neurotoxicology 21, 435–440 (2000); Kenborg, L. et al. Neurology 84, 1098–1103 (2015); Park, M. et al. Neurology 64, 1047–1051 (2005); Brugger, F. et al. NPJ Parkinsons Dis. 1, 15014 (2015); Costa Sa, A. C., et al. Sci. Rep. 9, 8795 (2019).

¿Causa o consecuencia? Sinucleína vs microglía







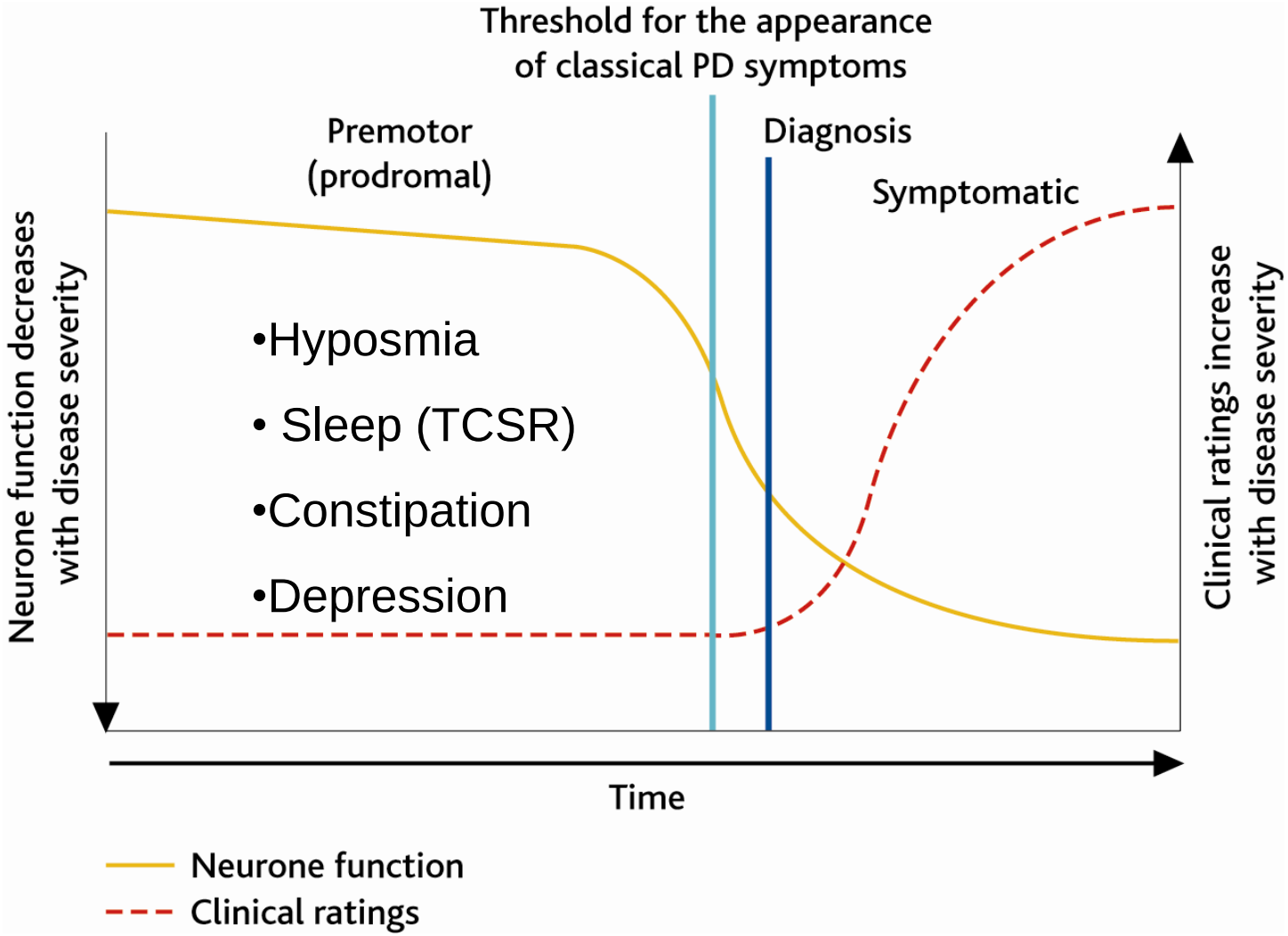


Joers, V., et al. Prog. Neurobiol. 155, 57–75 (2017); Sanchez-Guajardo, V et al. & Romero-Ramos, M. ASN Neuro 5, 113–139 (2013).

Schapansky, J., et al. Neuroscience 302, 74–88 (2015); Grozdanov, V. et al. Ann. Neurol. 86, 593–606 (2019).

Natural history of idiopathic PD

- **Trastorno conducta sueño REM (TCSR)**
- **EP-asociada mutaciones LRRK2**



Marek et al. Neurology 2009; 72: S21

E. de Parkinson (EP) asociada a mutaciones LRRK2

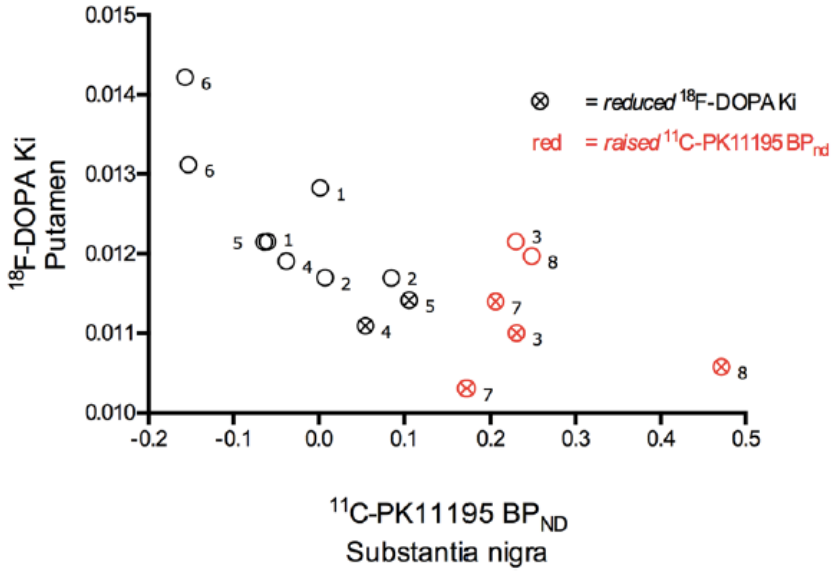
- Causa más frecuente de EP genética (4.6% de los pacientes con EP en Catalunya)
- **Herencia autosómica dominante**
- **Penetrancia incompleta, edad dependiente**
- En portadores asintomáticos de mutaciones LRRK2 se ha detectado un aumento de citoquinas pro-inflamatorias en sangre y CSF, lo que sugiere un papel de la inflamación en las fases presintomáticas

Journal of Neurology
https://doi.org/10.1007/s00415-020-09830-3

ORIGINAL COMMUNICATION

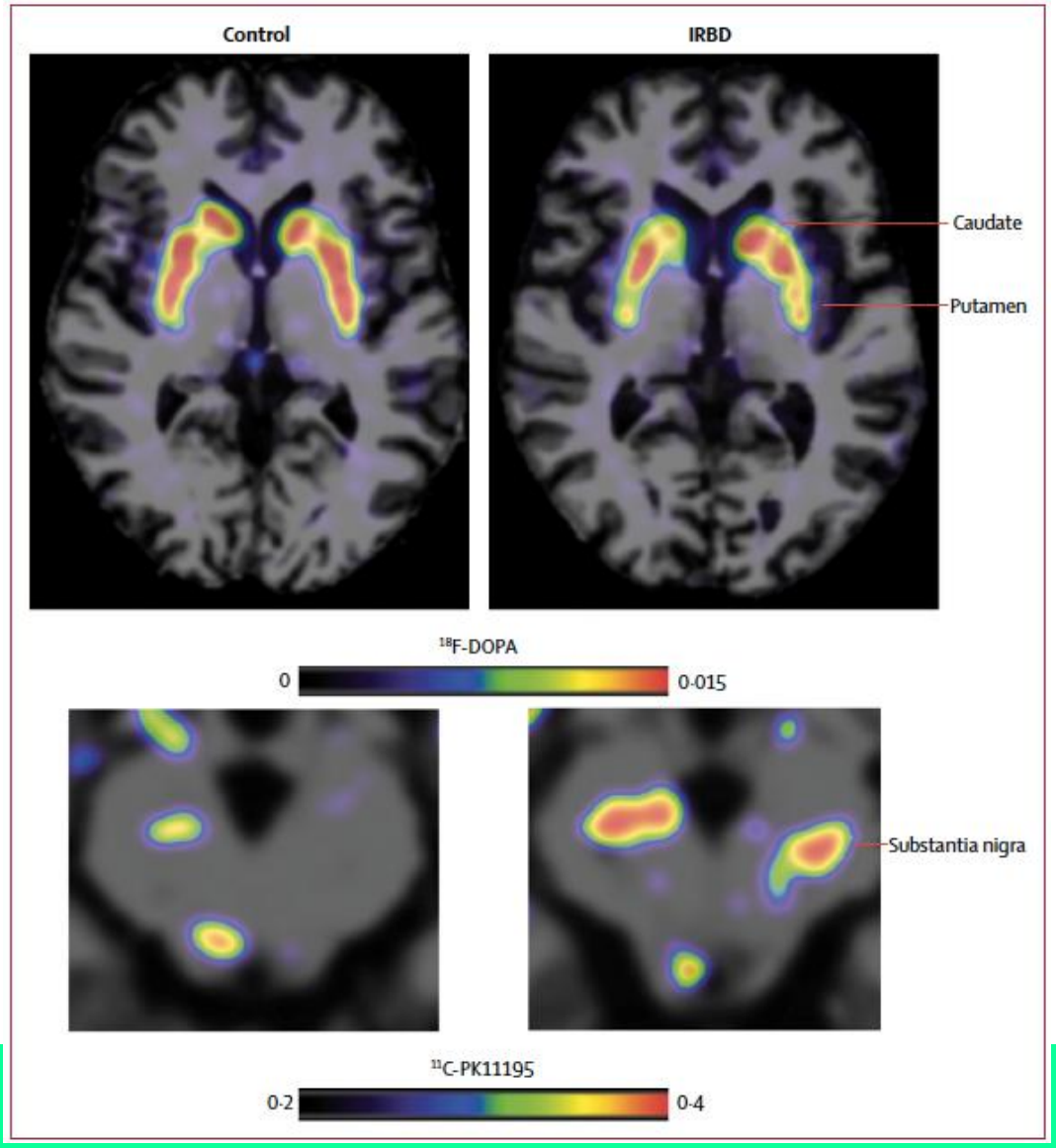
Imaging dopamine function and microglia in asymptomatic LRRK2 mutation carriers

Morten Gersel Stokholm[1] · Alicia Garrido[2,3] · Eduardo Tolosa[2,3,4] · Mónica Serradell[3] · Alex Iranzo[3,4] · Karen Østergaard[5] · Per Borghammer[1] · Arne Møller[1] · Peter Parbo[1] · Kristian Stær[1] · David J. Brooks[1,6] · Maria José Martí[3,4] · Nicola Pavese[1,6]



Gaig, Arch neurol 2006; Healy, Lancet Neurol 2008; Sierra, Mov Disord 2011; Dzamko N, et al. Mov Disord. 2016 Jun;31(6):889–97

TRASTORNO CONDUCTA SUEÑO REM

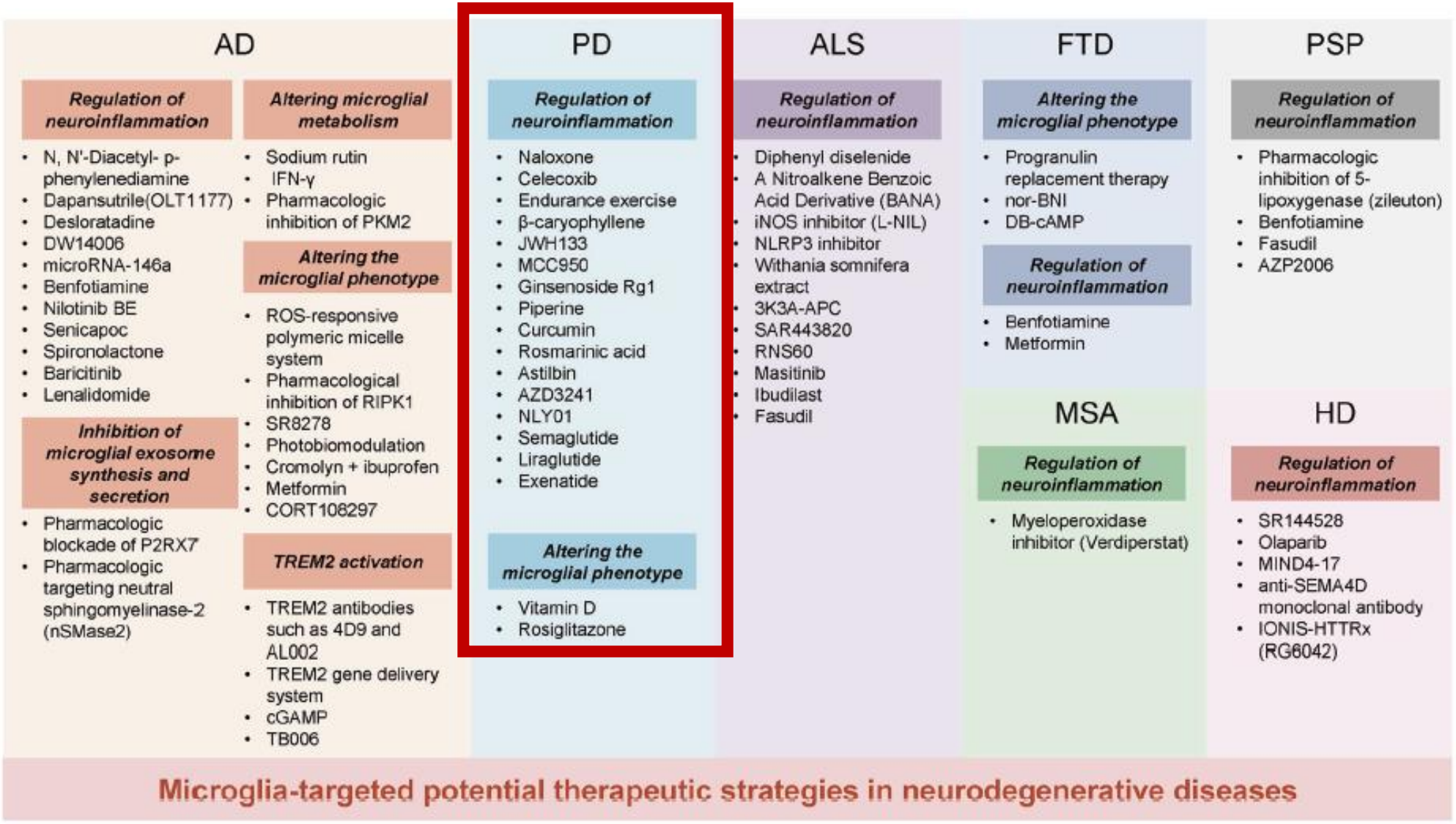


- **Estudio transversal:** los pacientes con TCSR tenían un aumento de la actividad microglial en la SN y esto se asociaba a la alteración de la vía nigroestriatal.

- **Estudio longitudinal:** los pacientes con TCSR y mayor actividad microglial en la SN tenían más alteración de la vía nigroestriatal en el seguimiento.

Stokholm M et al. Lancet Neurol. 2017 Oct;16(10):789-796;
Stær K, et al. Mov Disord. 2024 Aug;39(8):1323-1328..

IMPLICACIONES TERAPÉUTICAS



ScienHub

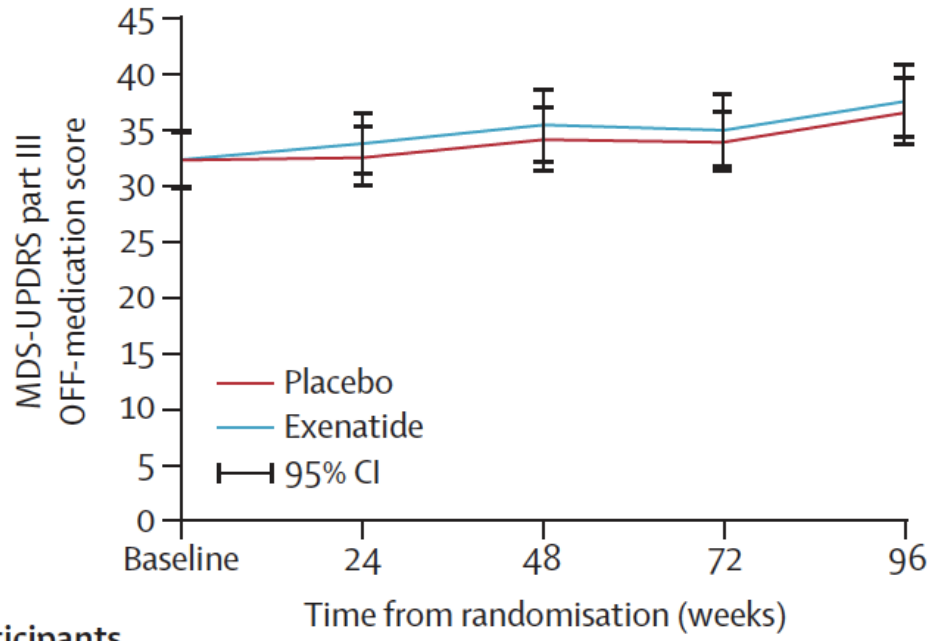
Gao et al. Signal Transduction and Targeted Therapy; 2023;8:359

Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial

Nirosen Vijiaratnam, Christine Girges, Grace Auld, Rachel McComish, Alexa King, Simon S Skene, Steve Hibbert, Alan Wong, Sabina Melander, Rachel Gibson, Helen Matthews, John Dickson, Camille Carroll, Abigail Patrick, Jemma Inches, Monty Silverdale, Bethan Blackledge, Jessica Whiston, Michele Hu, Jessica Welch, Gordon Duncan, Katie Power, Sarah Gallen, Jacqueline Kerr, K Ray Chaudhuri, Lucia Batzu, Silvia Rota, Edwin Jabbari, Huw Morris, Patricia Limousin, Nigel Greig, Yazhou Li, Vincenzo Libri, Sonia Gandhi, Dilan Athauda, Kashfia Chowdhury, Tom Foltynie

Ongoing trials of **semaglutide and liraglutide** in populations with Parkinson's disease (NCT03659682) and Alzheimer's disease (NCT04777396 and NCT01843075).

- EC fase 3 (exenatide vs placebo)
- 2 años
- Inyecciones de exenatide 2 mg sc/semana
- Endpoint primario: MDS-UPDRS III
- **Exenatide no superior a placebo** (similar empeoramiento en la MDS-UPDRS III en ambos grupos)
- Seguro y bien tolerado
- Penetrabilidad en el SNC?



Number of participants					
Exenatide	97	92	87	83	85
Placebo	97	96	94	95	93

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Conclusiones

- La **neuroinflamación** forma parte del **proceso fisiopatológico** de la E. Parkinson, tanto a nivel central como periférico.
- Existe una estrecha relación entre **alfa-sinucleína e inflamación**, en particular, activación microglial.
- La activación microglial está ya presente en **fases prodrómicas** de la E. Parkinson.
- Potencial terapéutico de fármacos que modulen la neuroinflamación.

Germans Trias i Pujol
Hospital

¡Muchas gracias por vuestra atención!