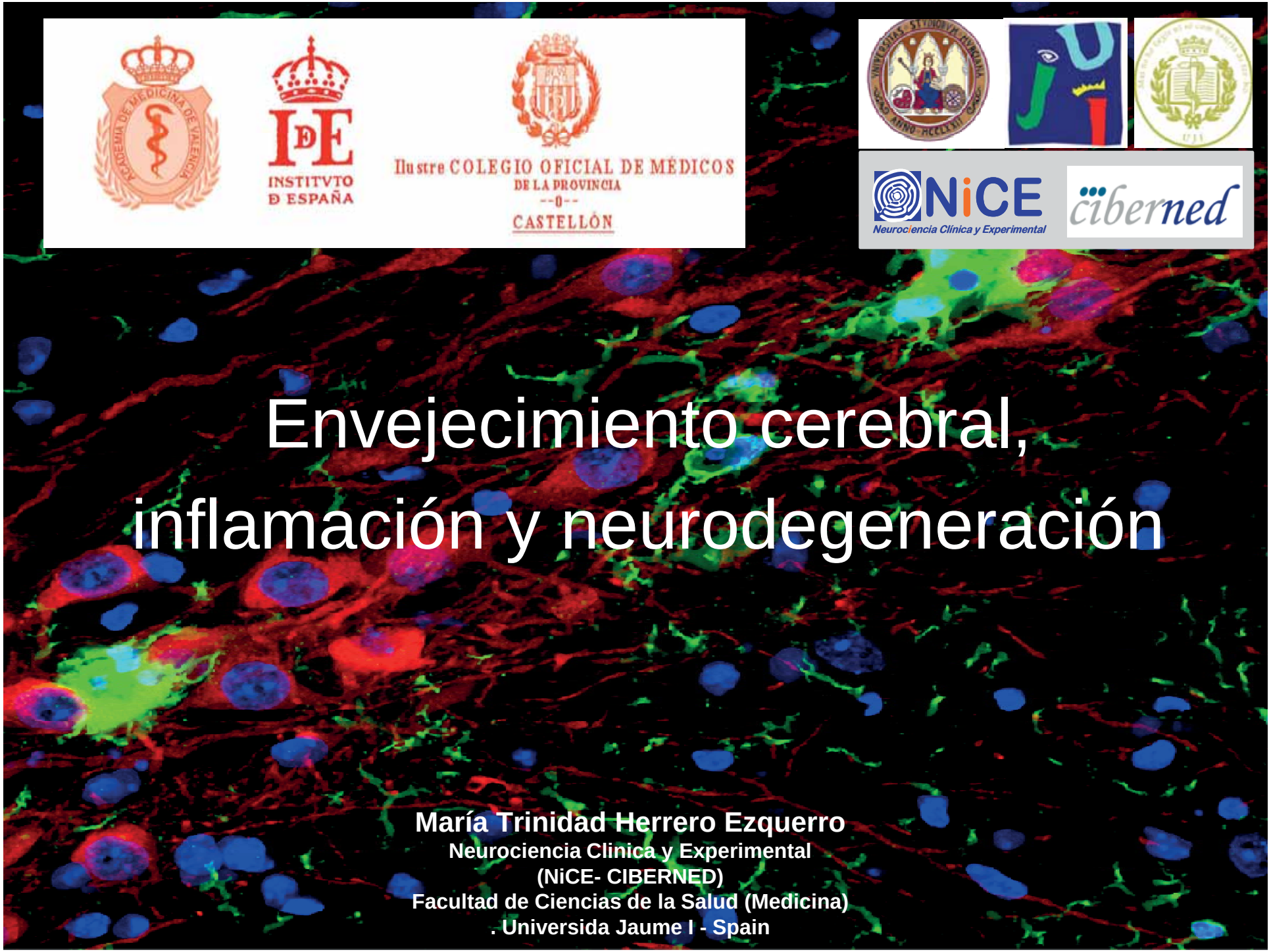
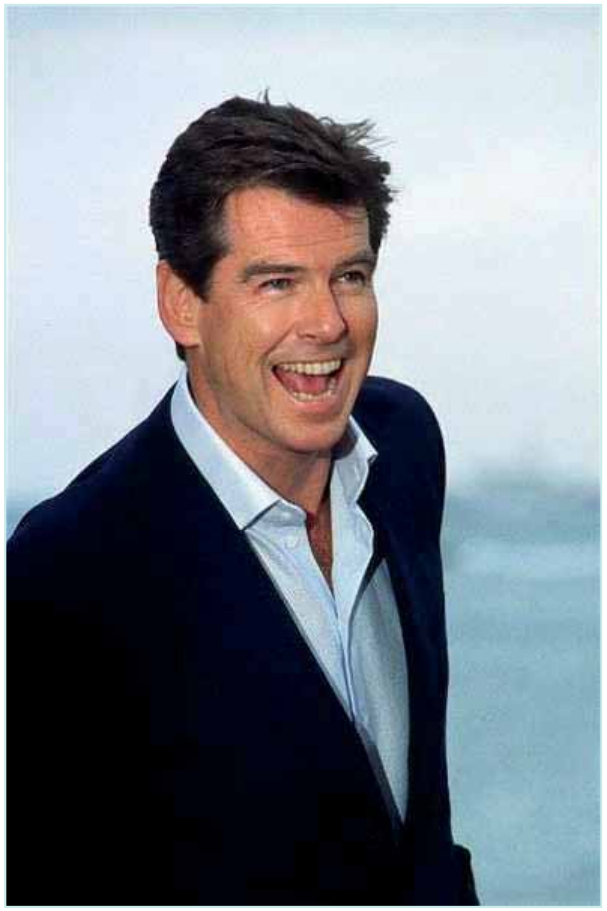


# Envejecimiento cerebral, inflamación y neurodegeneración

**María Trinidad Herrero Ezquerro**
**Neurociencia Clinica y Experimental**
**(NiCE- CIBERNED)**
**Facultad de Ciencias de la Salud (Medicina)**
**. Universida Jaume I - Spain**

Siglo XVIII

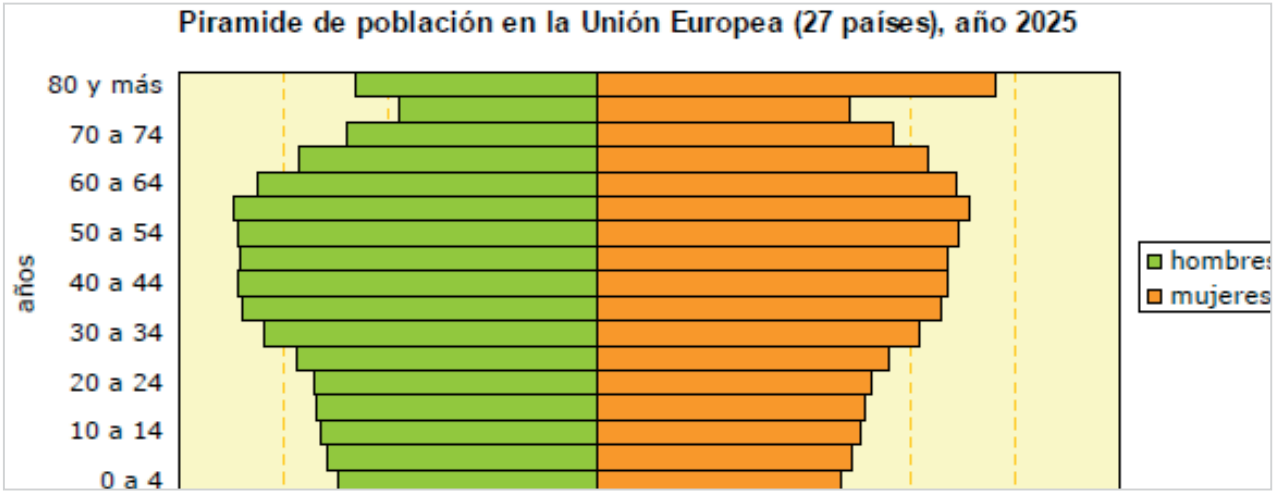
Siglo XXI



# Dos “jóvenes de 50 años”

Carlos IV de España (1798)

Pierce Brosnan (2008)




| Unión Europea (27 países) Población total y adultos mayores en 2000, 2008, 2025 y 2050 | | | | |
|---|---|---|---|---|
| | 2000 | 2008 | 2025 | 2050 |
| POBLACIÓN TOTAL | | | | |
| Total | 482.760.665 | 495.394.020 | 517.810.844 | 515.303.488 |
| Hombres | 235.080.335 | 241.849.000 | 253.876.528 | 253.363.762 |
| Mujeres | 247.680.330 | 253.545.020 | 263.934.316 | 261.939.726 |
| Hombres % | 48,7% | 48,8% | 49,0% | 49,2% |
| Mujeres % | 51,3% | 51,2% | 51,0% | 50,8% |
| PERSONAS DE 60 AÑOS Y MÁS | | | | |
| Total | 100.946.181 | 111.490.629 | 146.798.439 | 181.420.615 |
| Hombres | 42.528.674 | 48.113.311 | 65.744.892 | 83.196.635 |
| Mujeres | 58.417.503 | 63.377.318 | 81.053.547 | 98.223.980 |
| Proporción s/ la población total % | 20,9% | 22,5% | 28,3% | 35,2% |
| Hombres % | 42,1% | 43,2% | 44,8% | 45,9% |
| Mujeres % | 57,9% | 56,8% | 55,2% | 54,1% |

# ¿cuándo viviremos hasta los 100 años?


| | |
|---|---|
| 2030 ➔ | 85 años varones<br>90 años mujeres |

| | |
|---|---|
| Ritmo de crecimiento ➔ | de 4 cada 20 años mujeres<br>de 5 años cada 20 años varones |
| 100 años de vida ➔ | 2070 mujeres<br>2090 varones |

# CEREBRO: MOTOR NUESTRO CUERPO

Exterior

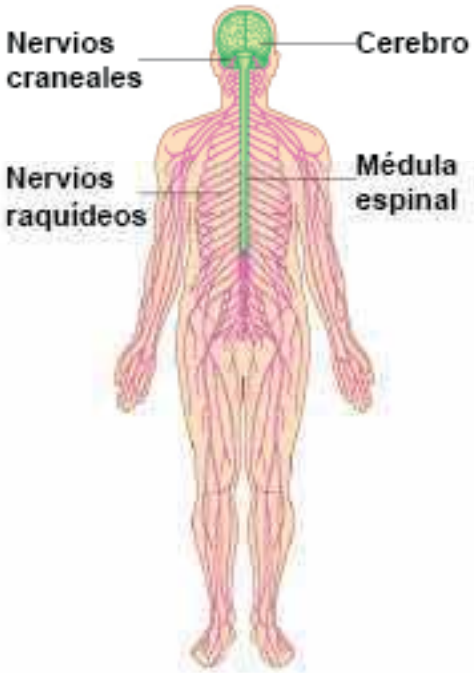
ORGANOS DE LOS SENTIDOS

Información

Interior cuerpo

Médula Espinal

Información




CEREBRO

Memoria

Procesamiento de información

Respuesta

TODAS LAS FUNCIONES del cuerpo humano

Degeneración progresiva de huesos y articulaciones

Pérdida progresiva de los sistemas homeostáticos

Aumento de la Tensión Arterial

Pérdida progresiva de la capacidad del sistema inmunitario

Pérdida progresiva de la líbido

**Aspectos del envejecimiento humano**

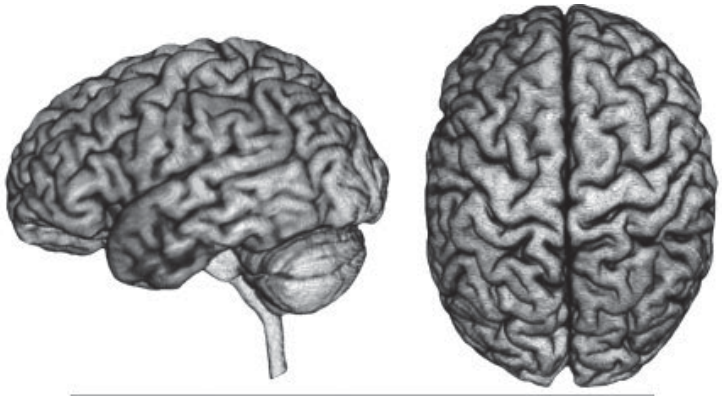
**Pérdida de Plasticidad**

Pérdida progresiva de olfato, gusto y audición

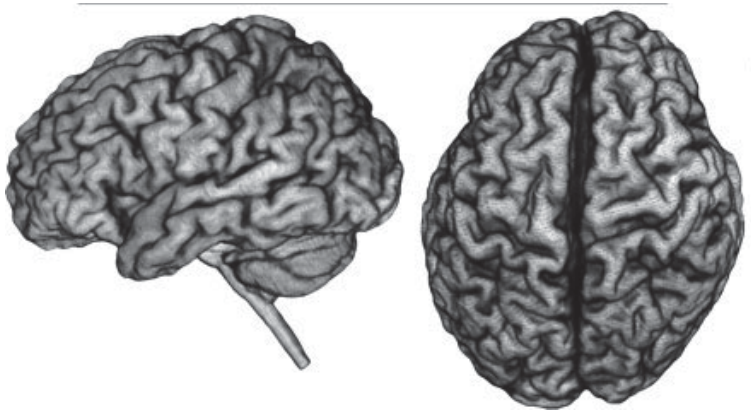
Pérdida progresiva de la capacidad visual

**Pérdida progresiva de la capacidad y coordinación motora**

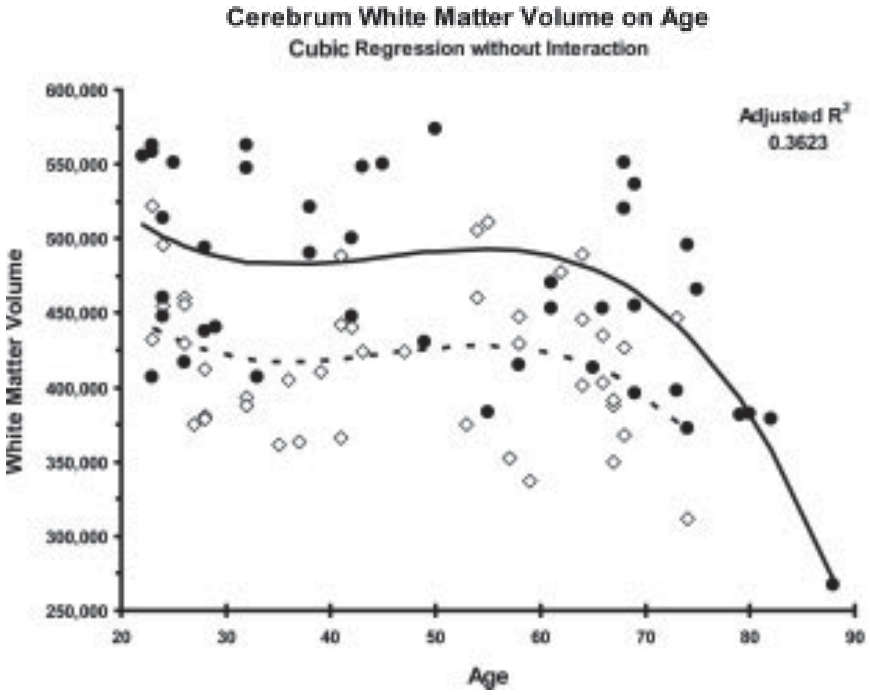
**Pérdida progresiva de la memoria y de la cognición**

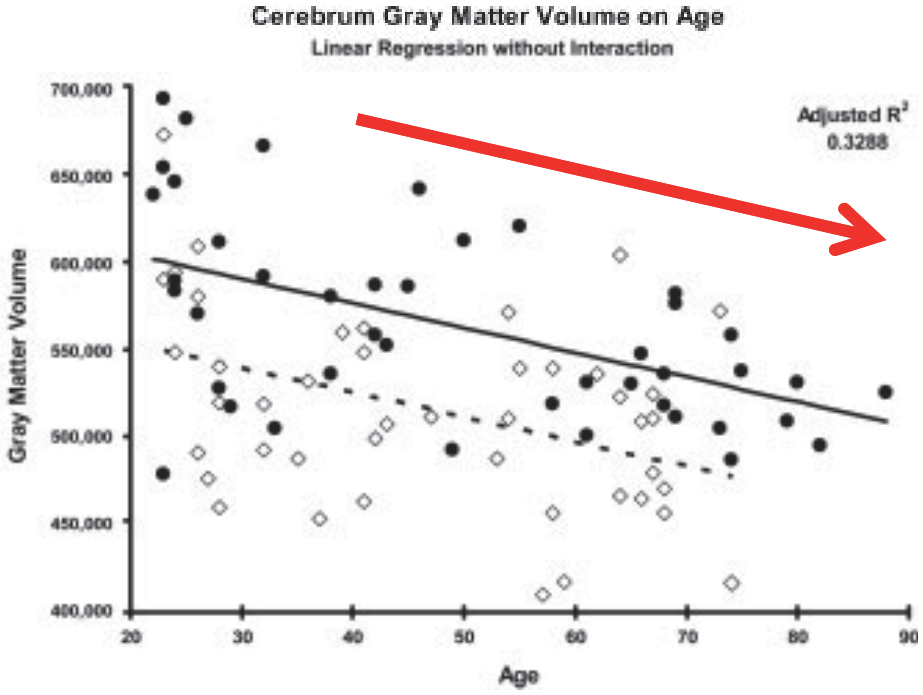


28-year-old male



88-year-old male



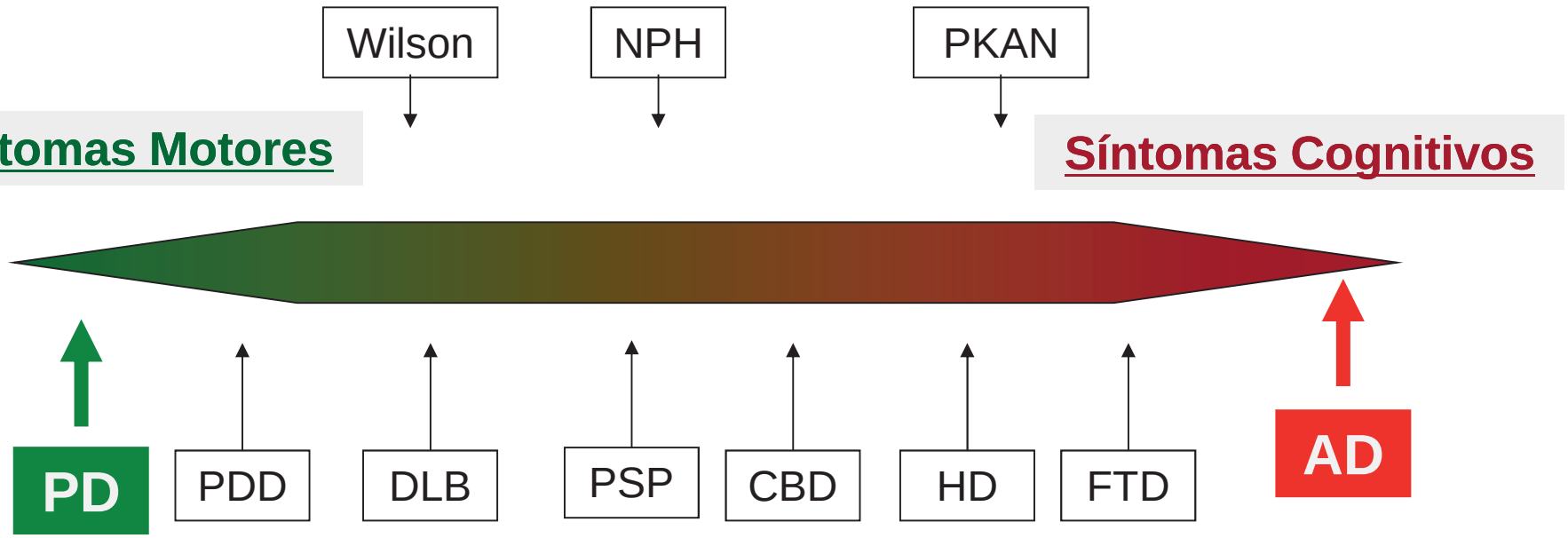



**DE LOS MOVIMIENTOS ANORMALES ➔ A LA DEMENCIA**

**DE LOS SÍNTOMAS MOTORES ➔ A LOS COGNITIVOS**

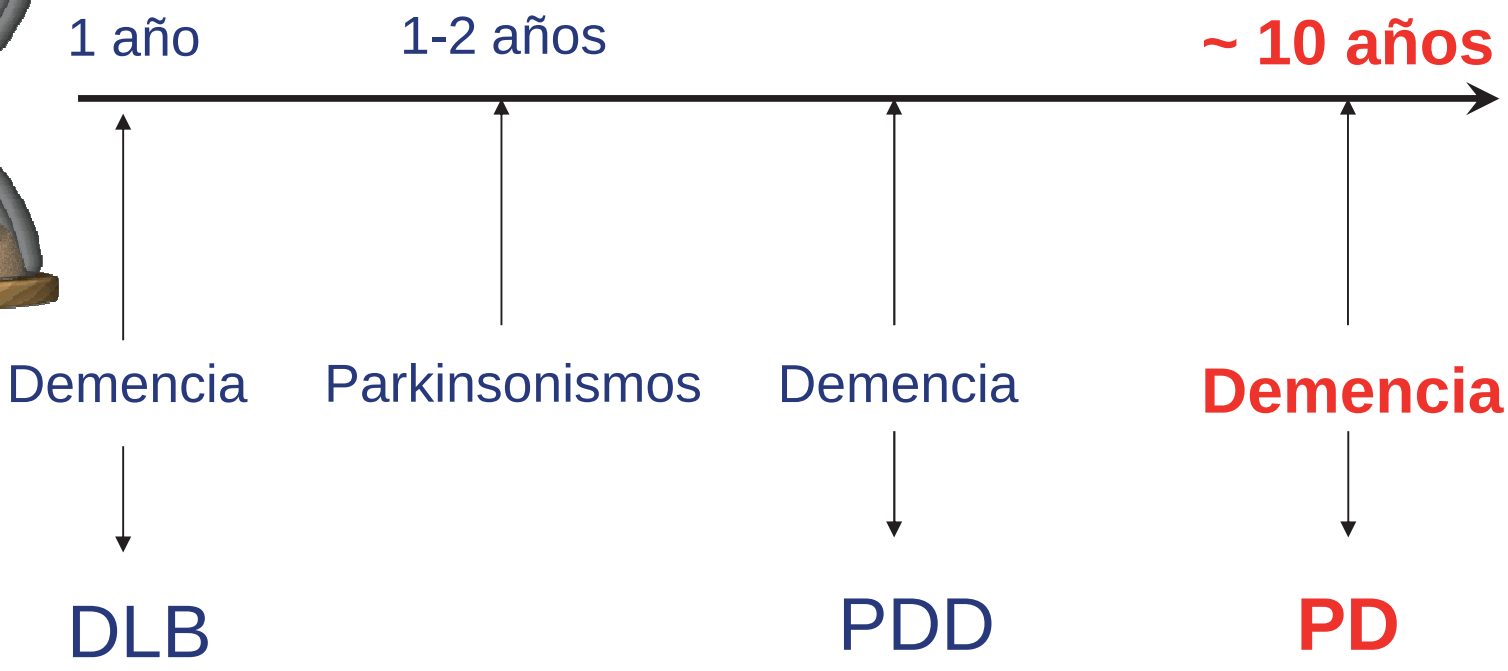
**Trastornos del Movimiento**

**Demencias**

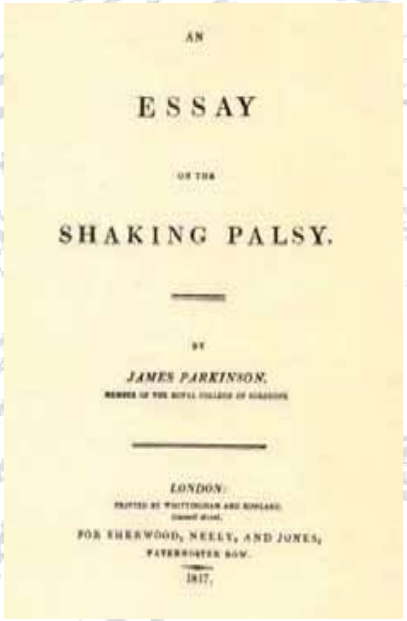


# Parkinsonismo y demencia: el factor tiempo

## Curso de la enfermedad



# Enfermedad de Párkinson


AN

ESSAY

ON THE

SHAKING PALSY.

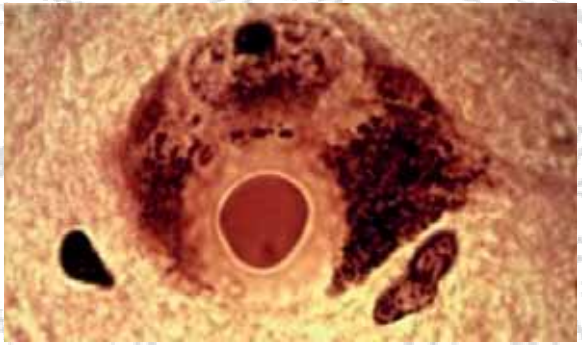
BY

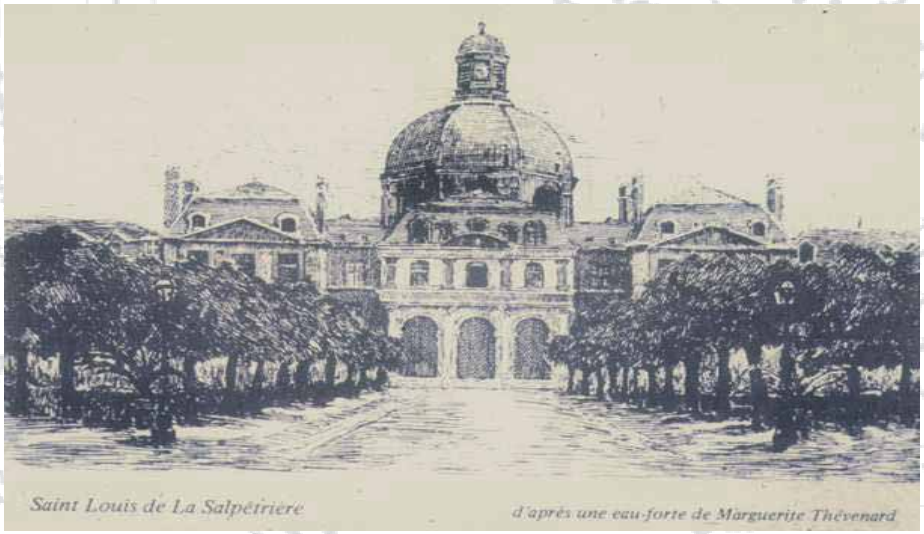
JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

1817.






## Es una entidad clínica

# Parkinson's disease

Lancet 2009; 373: 2055–66

Andrew J Lees, John Hardy, Tamas Revesz

Parkinson's disease is a common progressive bradykinetic disorder that can be accurately diagnosed. It is characterised by the presence of severe pars-compacta nigral-cell loss, and accumulation of aggregated α-synuclein in specific brain stem, spinal cord, and cortical regions. The main known risk factor is age. Susceptibility genes including α-synuclein, leucine rich repeat kinase 2 (*LRRK-2*), and glucocerebrosidase (*GBA*) have shown that genetic predisposition is another important causal factor. Dopamine replacement therapy considerably reduces motor handicap, and effective treatment of associated depression, pain, constipation, and nocturnal difficulties can improve quality of life. Embryonic stem cells and gene therapy are promising research therapeutic approaches.

# Parkinson's disease

*Lancet* 2009; 373: 2055–66

*Andrew J Lees, John Hardy, Tamas Revesz*

## Queen Square brain bank clinical diagnostic criteria

**Step 1 Diagnosis of parkinsonian syndrome**

Bradikinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)

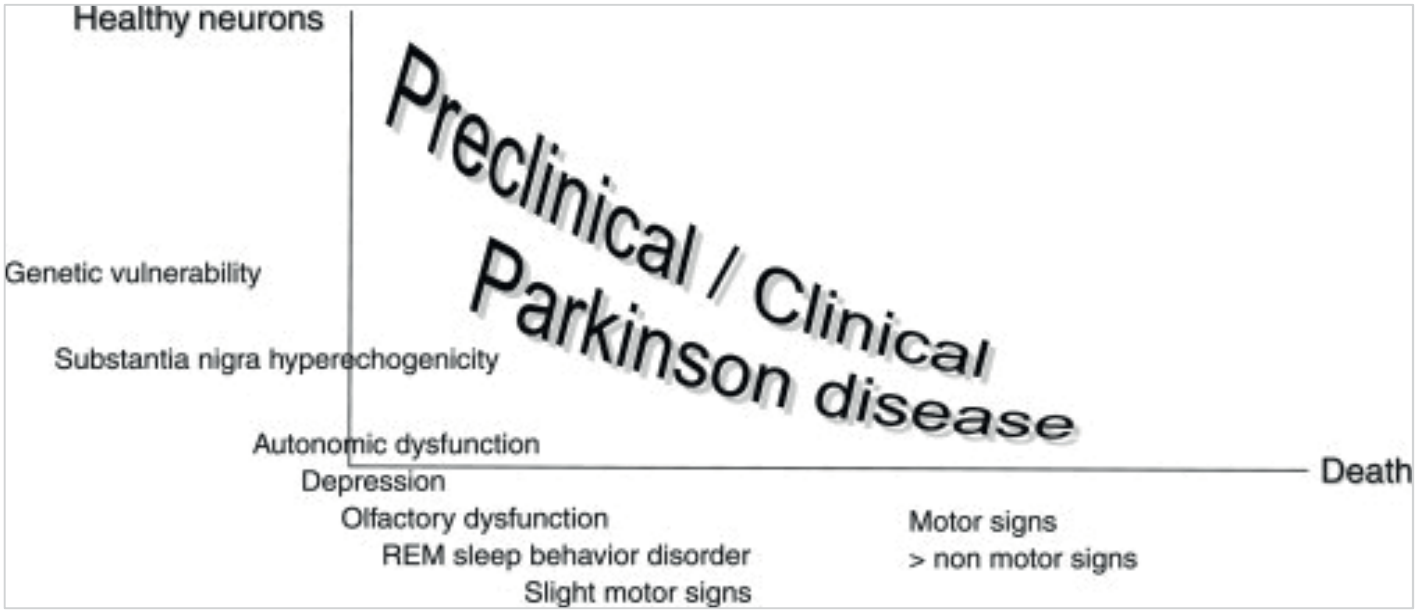
And at least one of the following:

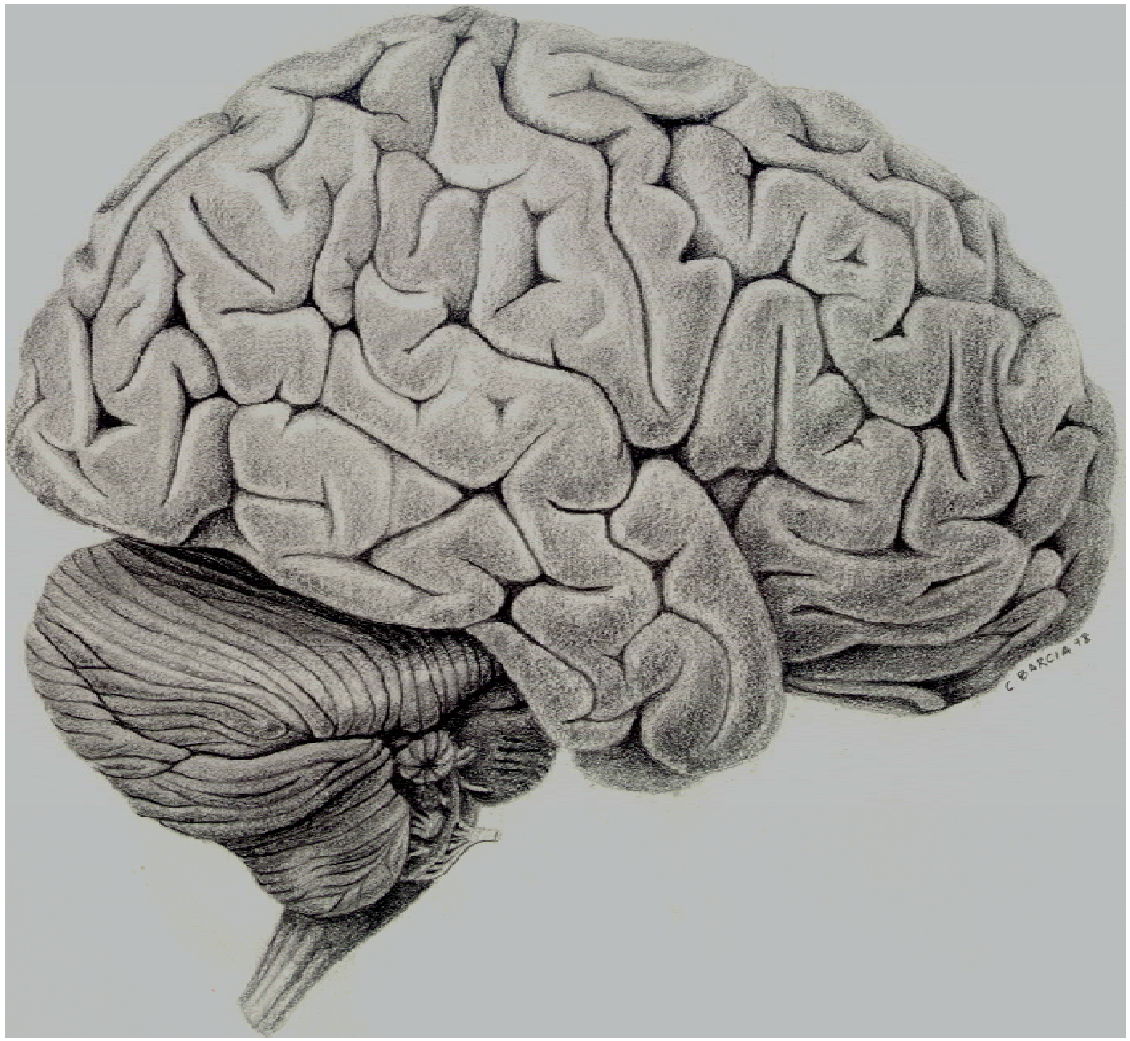
- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

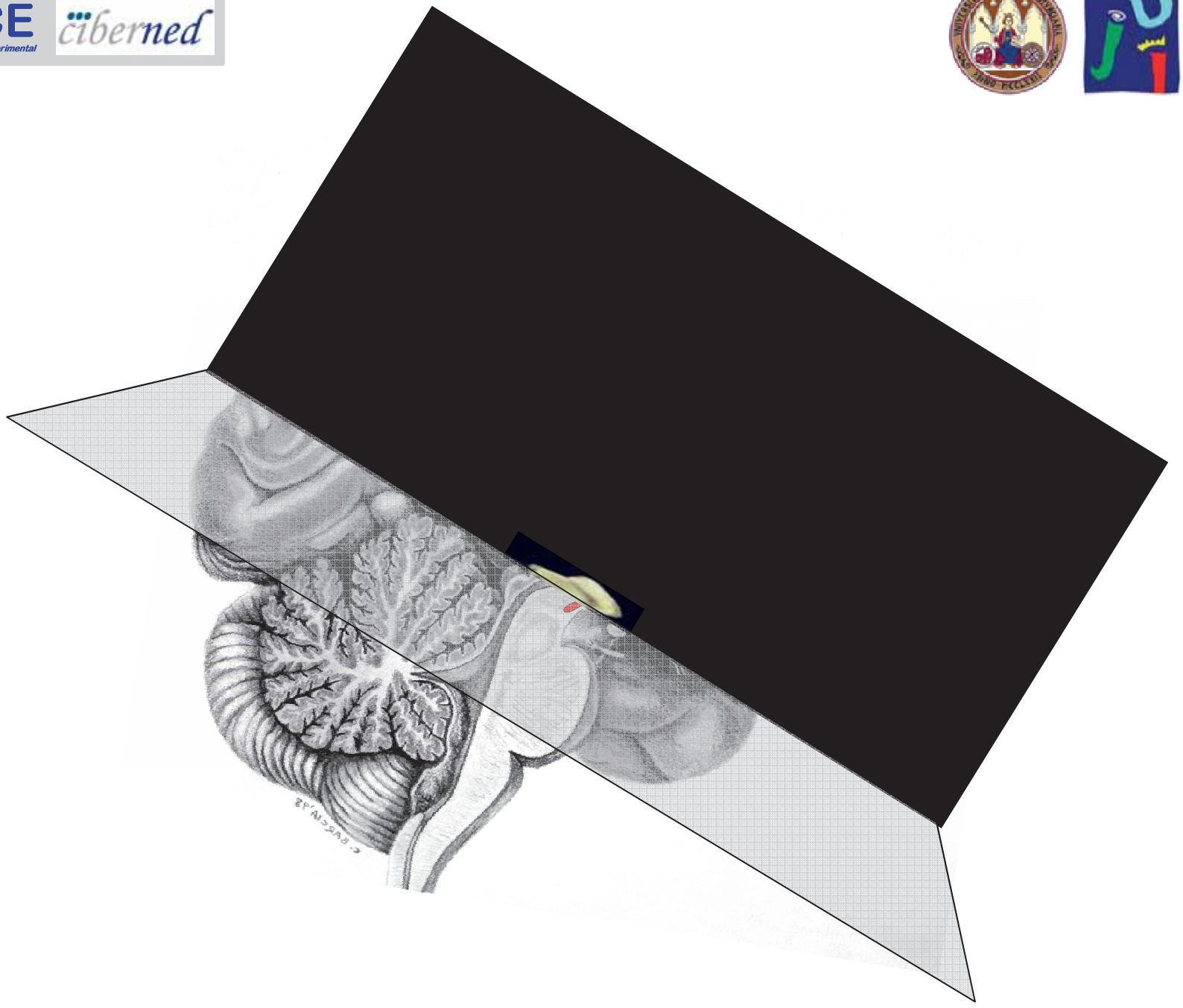
# PACIENTE DE 64 AÑOS

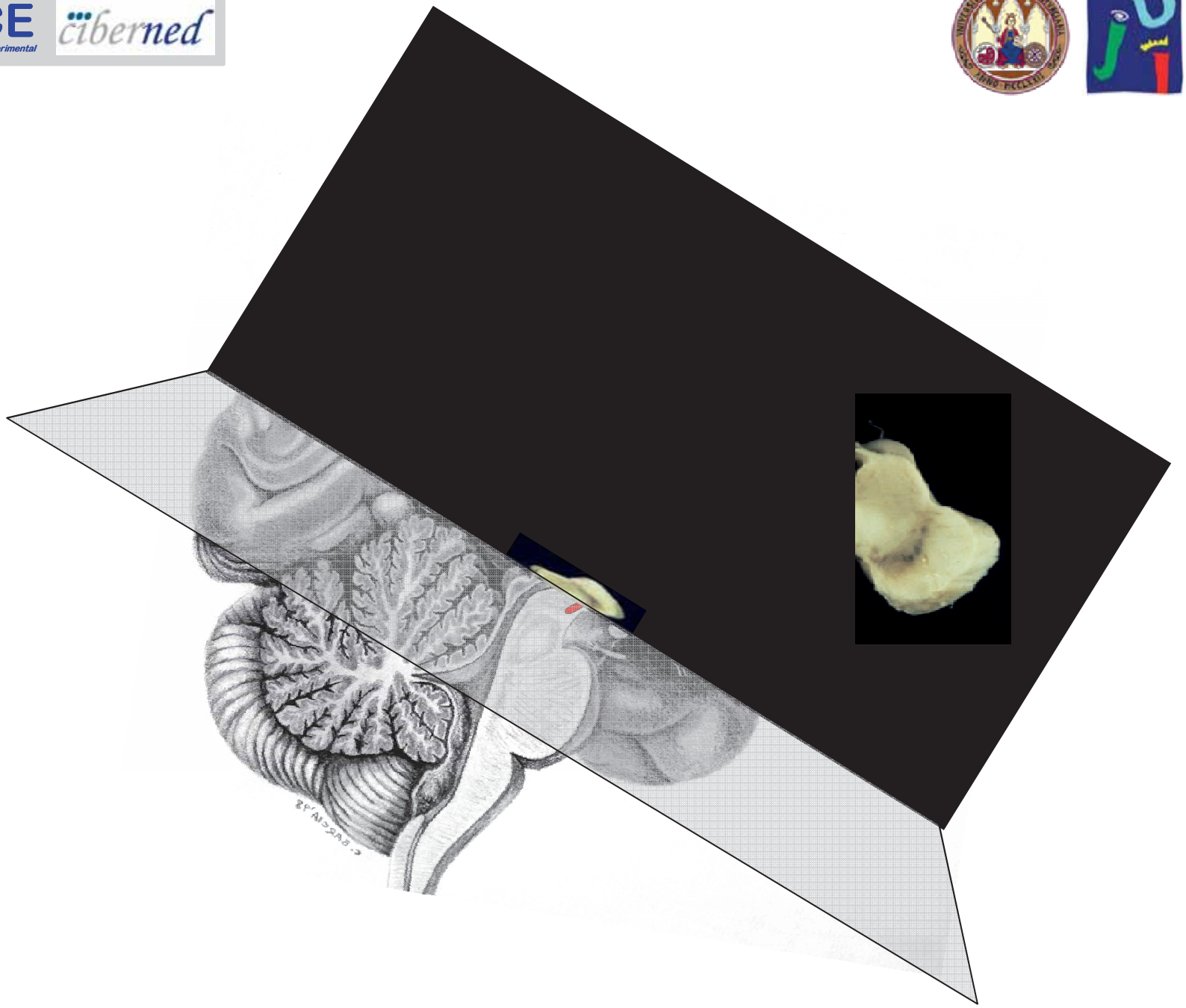
# PACIENTE DE 44 AÑOS

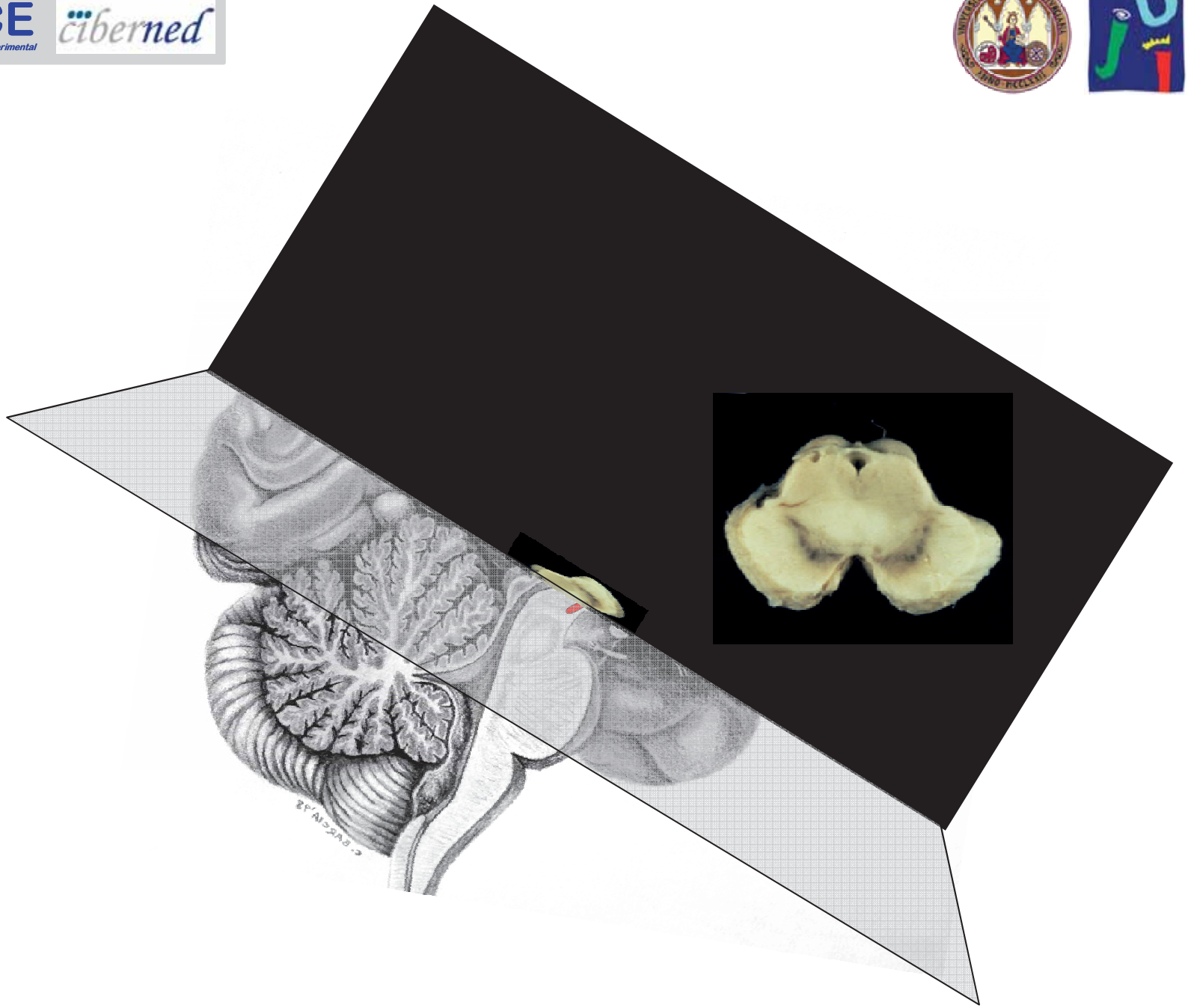

# Es una enfermedad sistémica

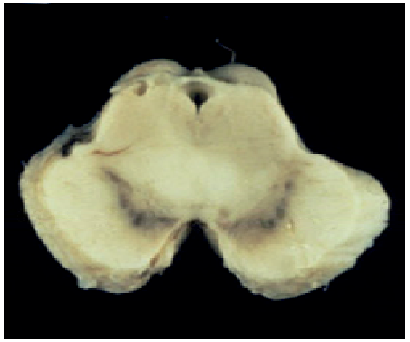


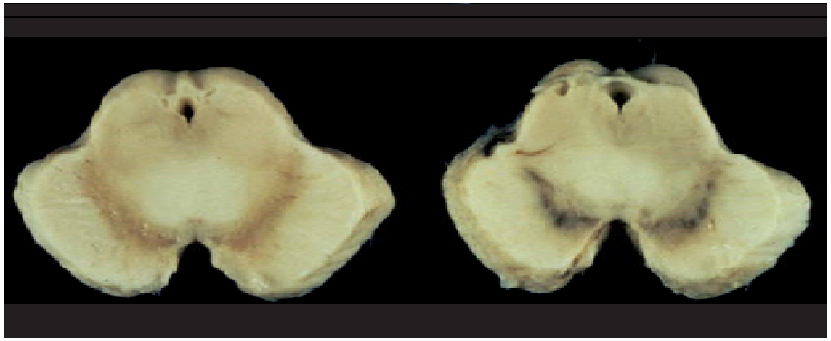








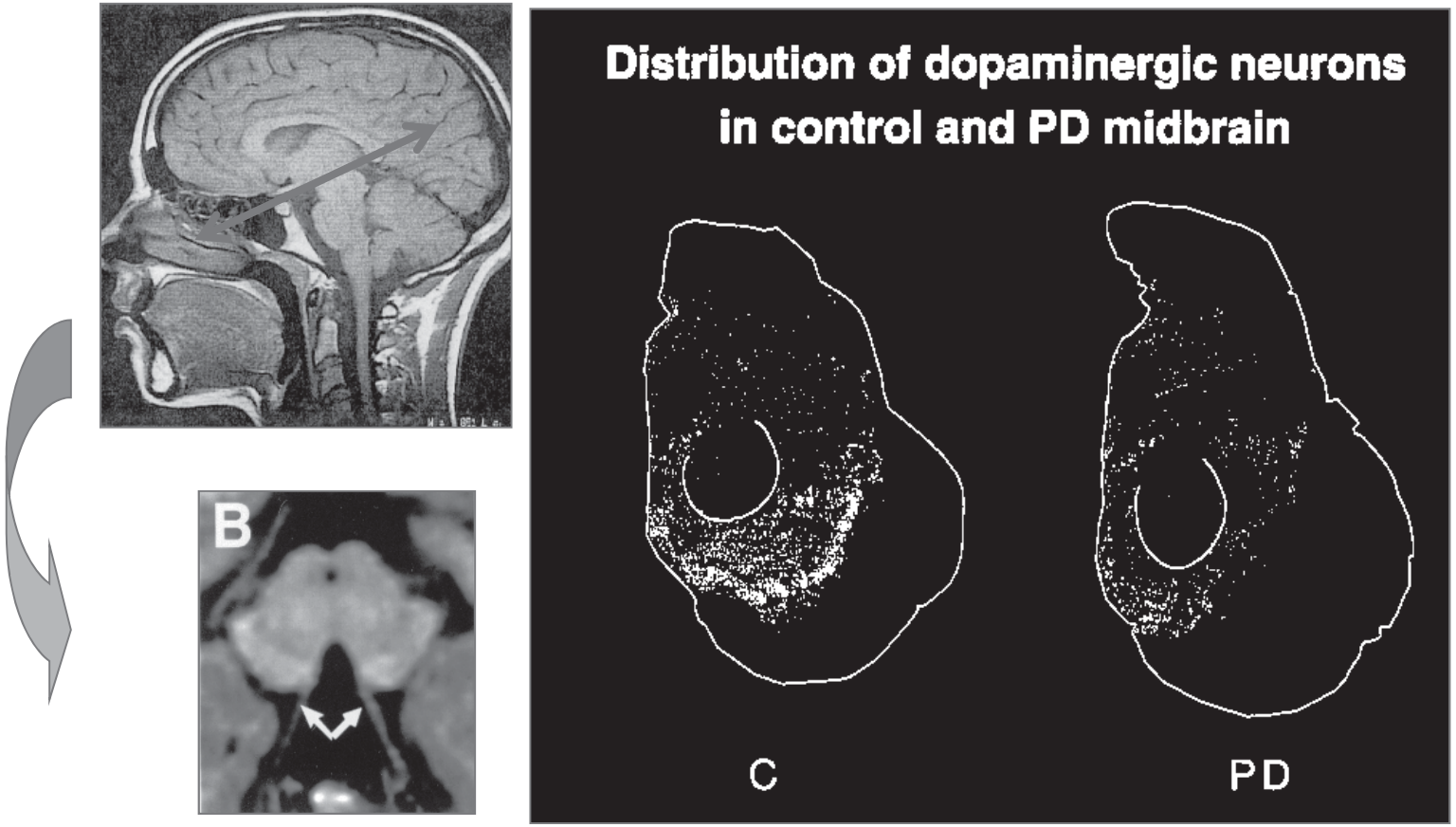


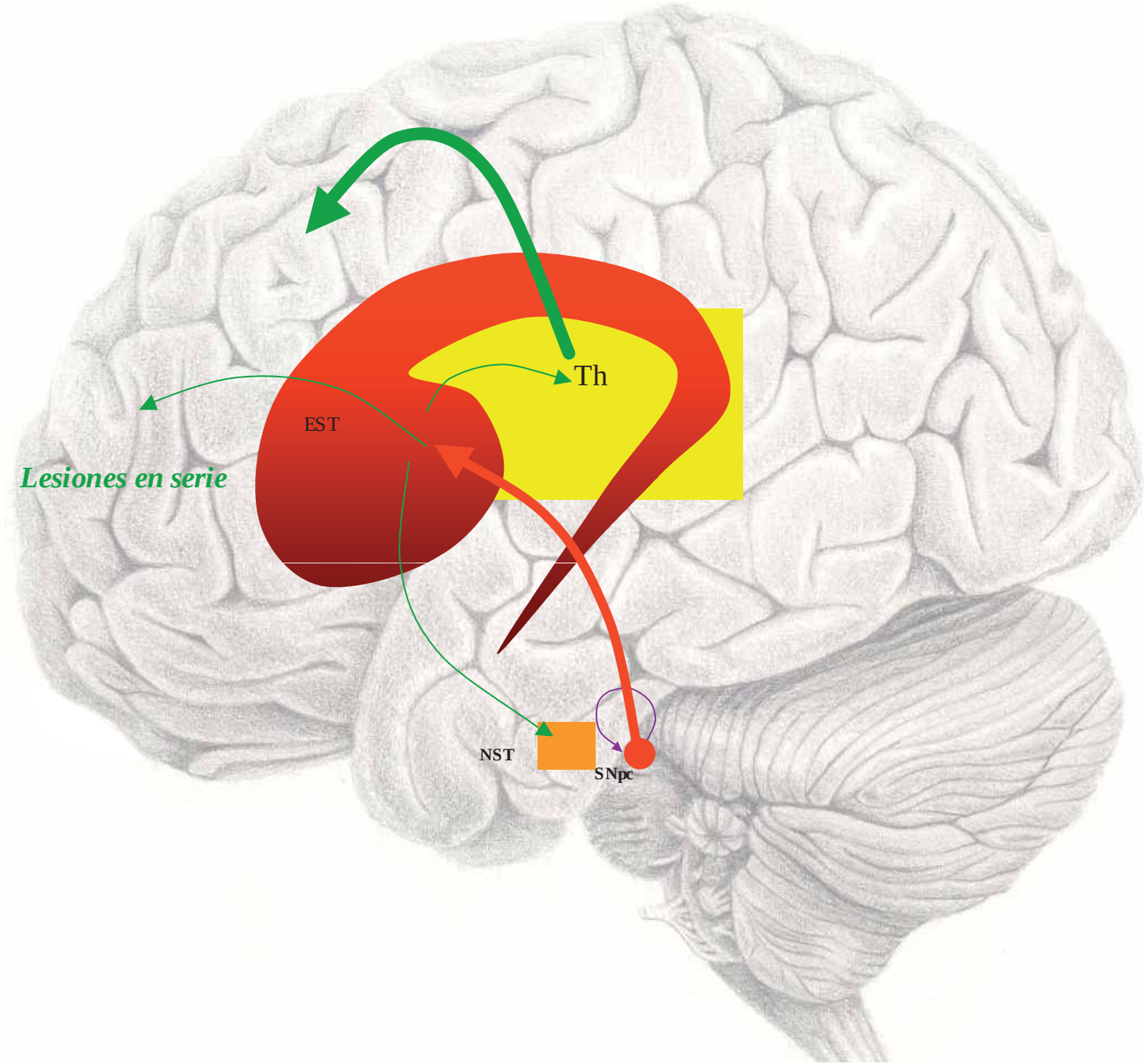


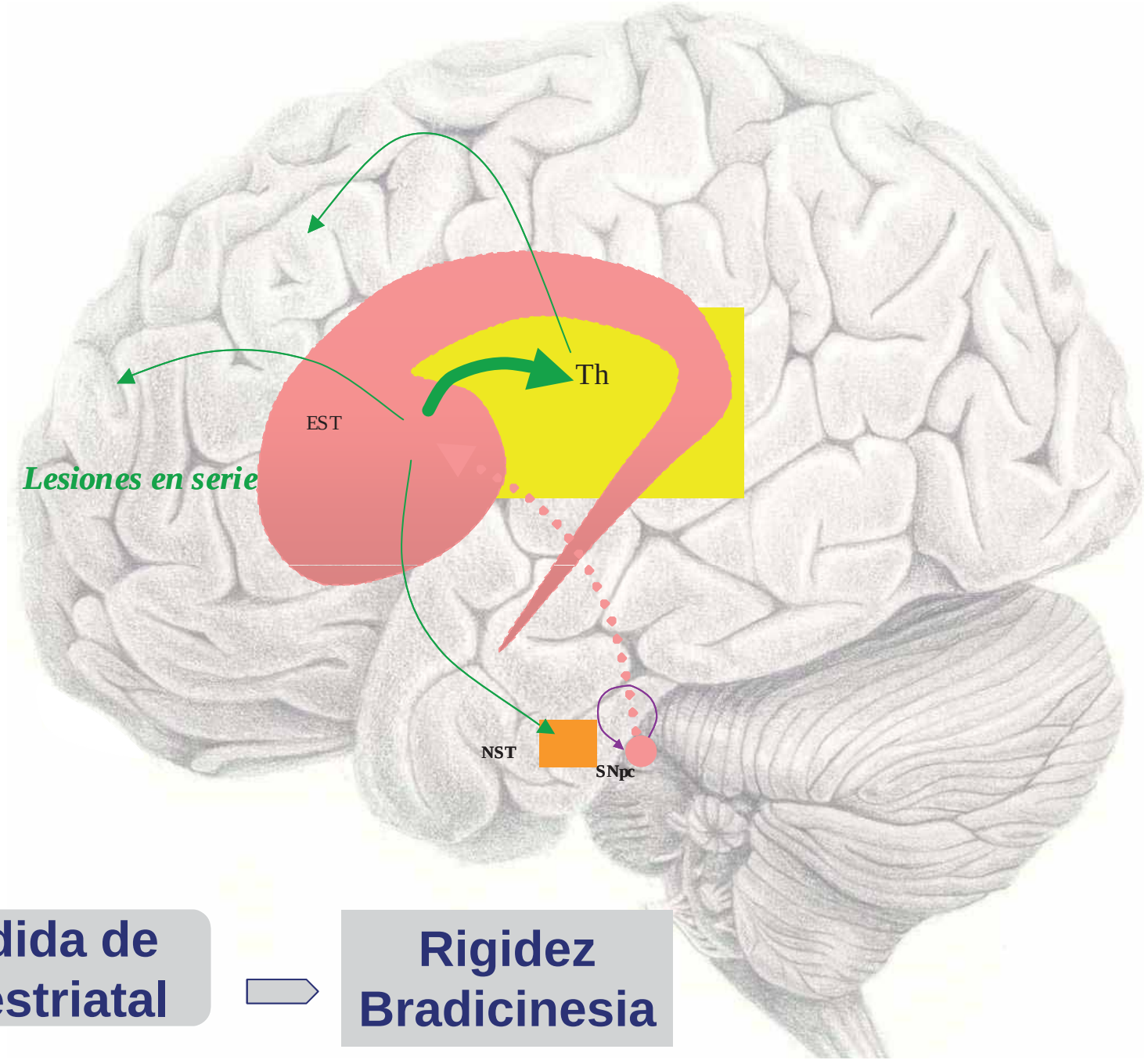
# Muerte neuronal dopaminérgica

(Tetriakoff, 1919)

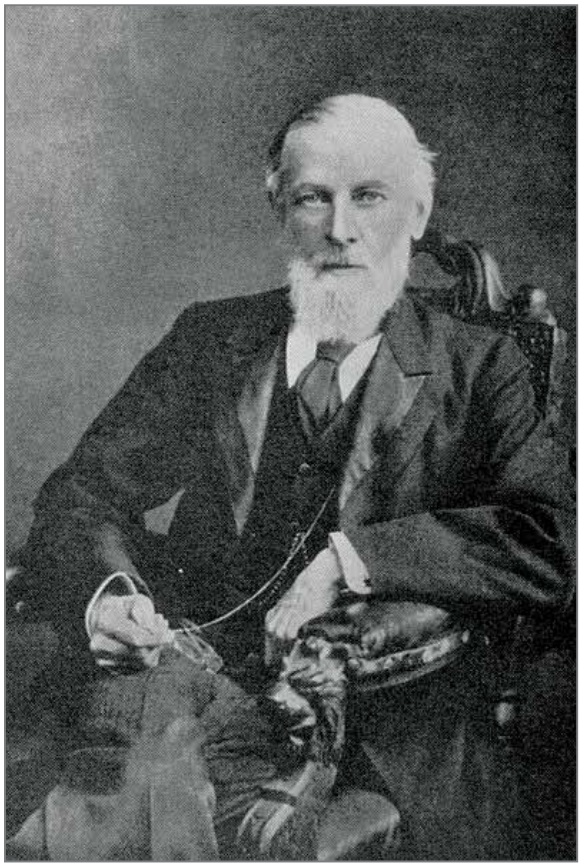
# Degeneración de neuronas dopaminérgicas: MASIVA pero HETEROGENEA




Th
EST
Lesiones en serie
NST
SNpc




**Pérdida de DA estriatal** → **Rigidez Bradicinesia**



**Sir William Richard Gowers**
**neurologist, researcher & artist**

Prof. Gowers drew this illustration in 1886 as part of his documentation of Parkinson's Disease The image appeared in his book, **A Manual of diseases of the Nervous System**, still used today by medical professionals as a primary reference for this disease.

33 y.o

42 y.o

59 y.o

MONOGRAPHIEN AUS DEM GESAMTGEBIETE DER NEUROLOGIE UND PSYCHIATRIE

HERAUSGEGEBEN VON

O. FOERSTER-BRESLAU UND K. WILMANNS-HEIDELBERG

HEFT 34

DIE

LEHRE VOM TONUS UND DER BEWEGUNG

ZUGLEICH SYSTEMATISCHE UNTERSUCHUNGEN ZUR KLINIK, PHYSIOLOGIE, PATHOLOGIE UND PATHOGENESE DER PARALYSIS AGITANS

VON

F. H. LEWY

PROFESSOR AN DER UNIVERSITÄT BERLIN

MIT 569 ZUM TEIL FARBIGEN ABBILDUNGEN UND 8 TABELLEN

BERLIN

VERLAG VON JULIUS SPRINGER

1923

**ENFERMEDAD PROGRESIVA**

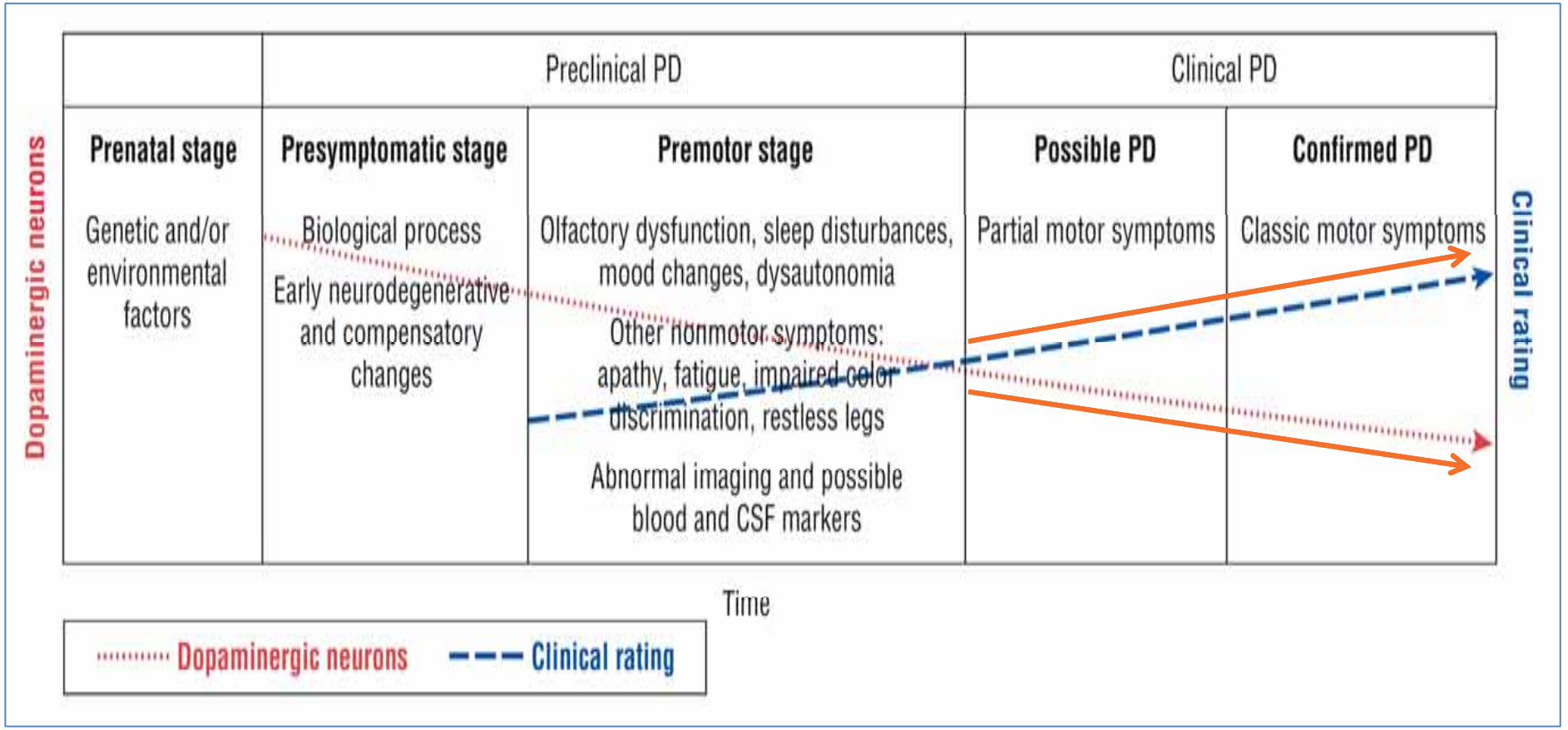
*Arch Neurol. 2011;68(1):22-30*

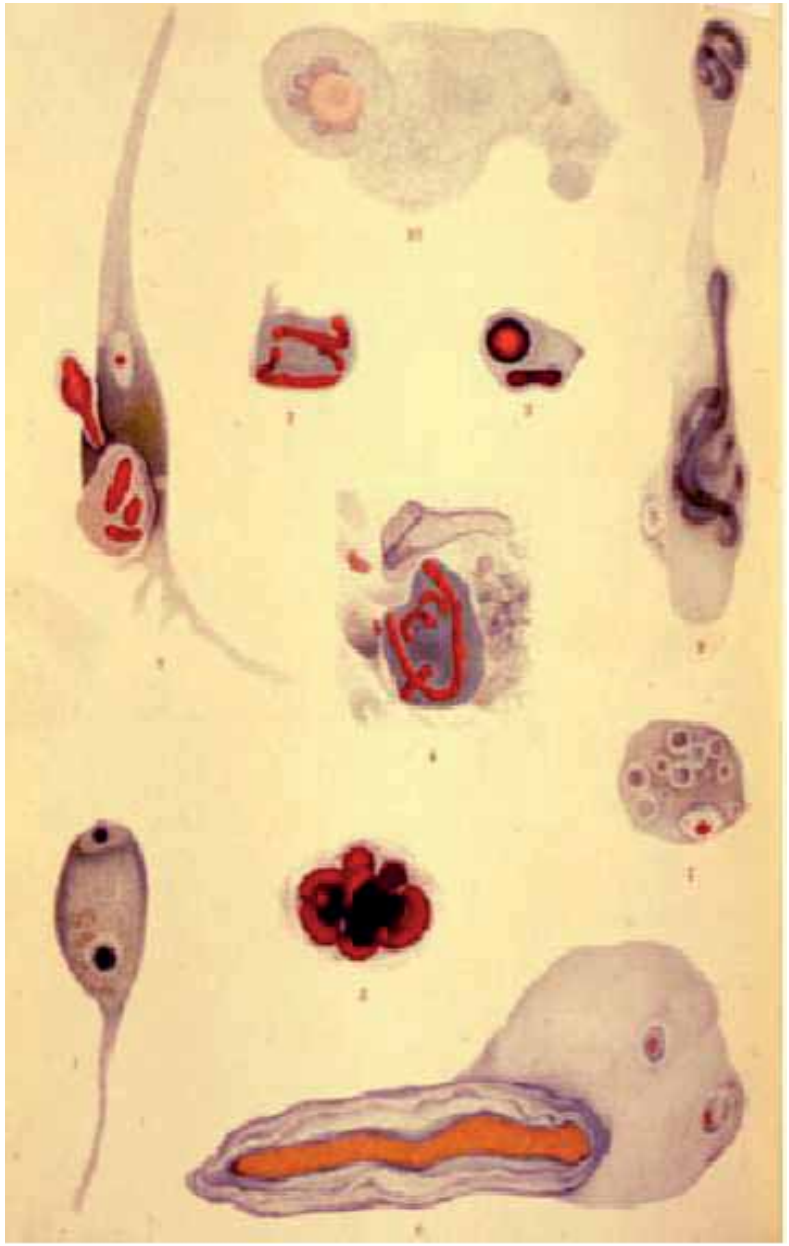
NEUROLOGICAL REVIEW

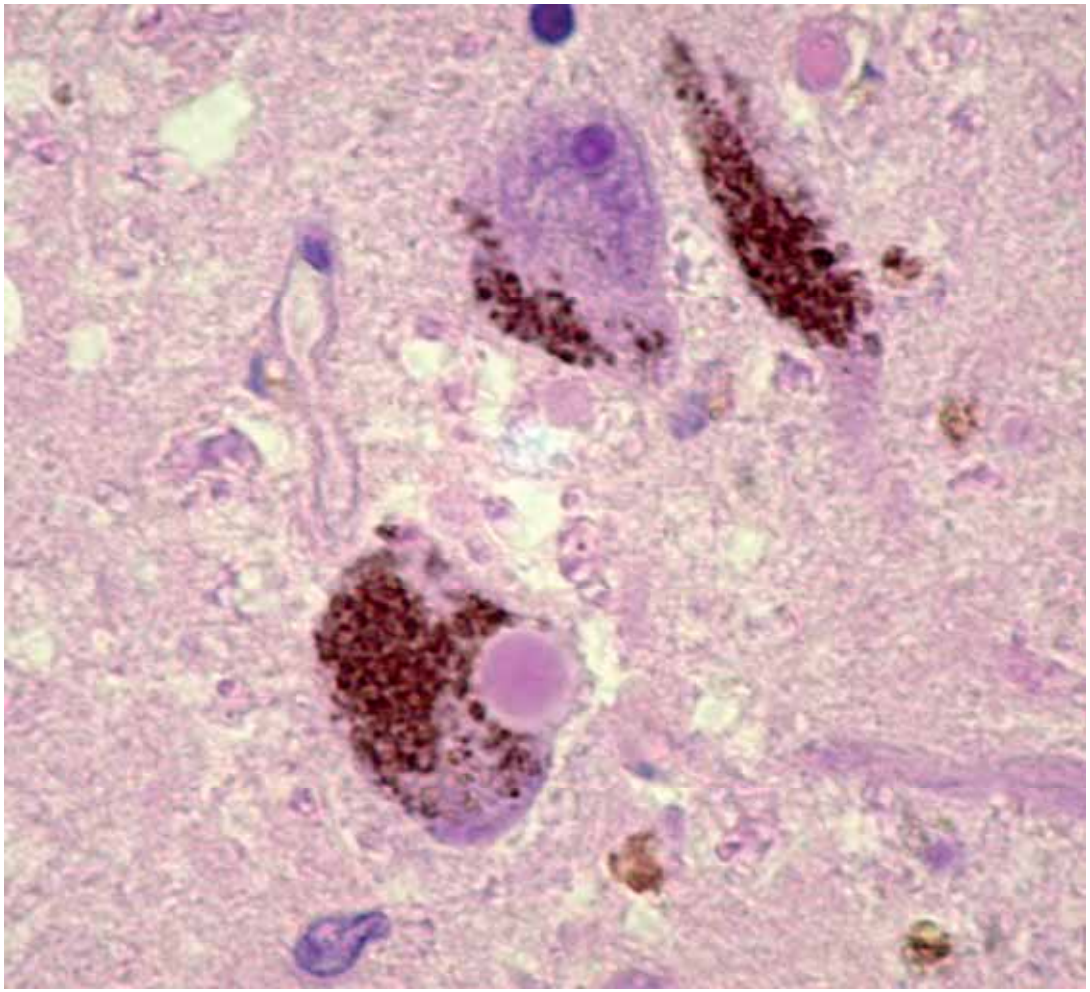
SECTION EDITOR: DAVID E. PLEASURE, MD

# Preclinical Biomarkers of Parkinson Disease

*Yuncheng Wu, MD, PhD; Weidong Le, MD, PhD; Joseph Jankovic, MD*





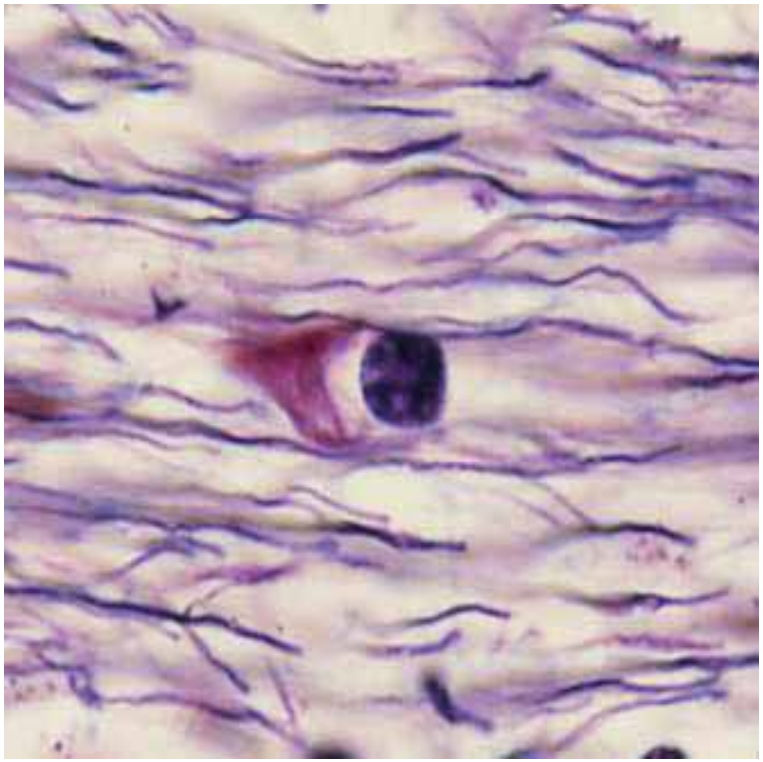


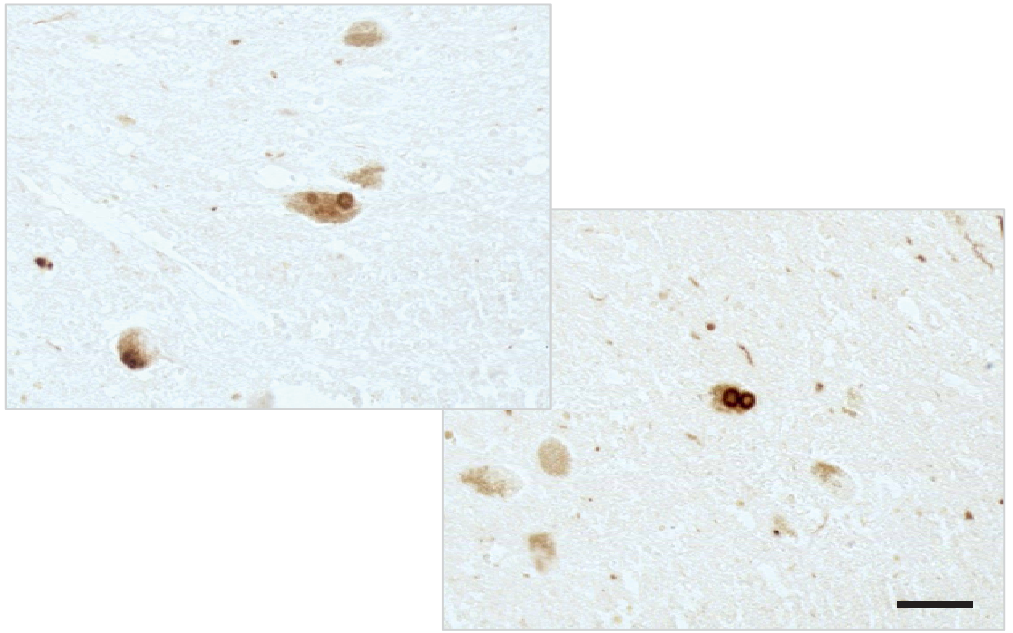
F. Lewy

# CUERPOS DE LEWY

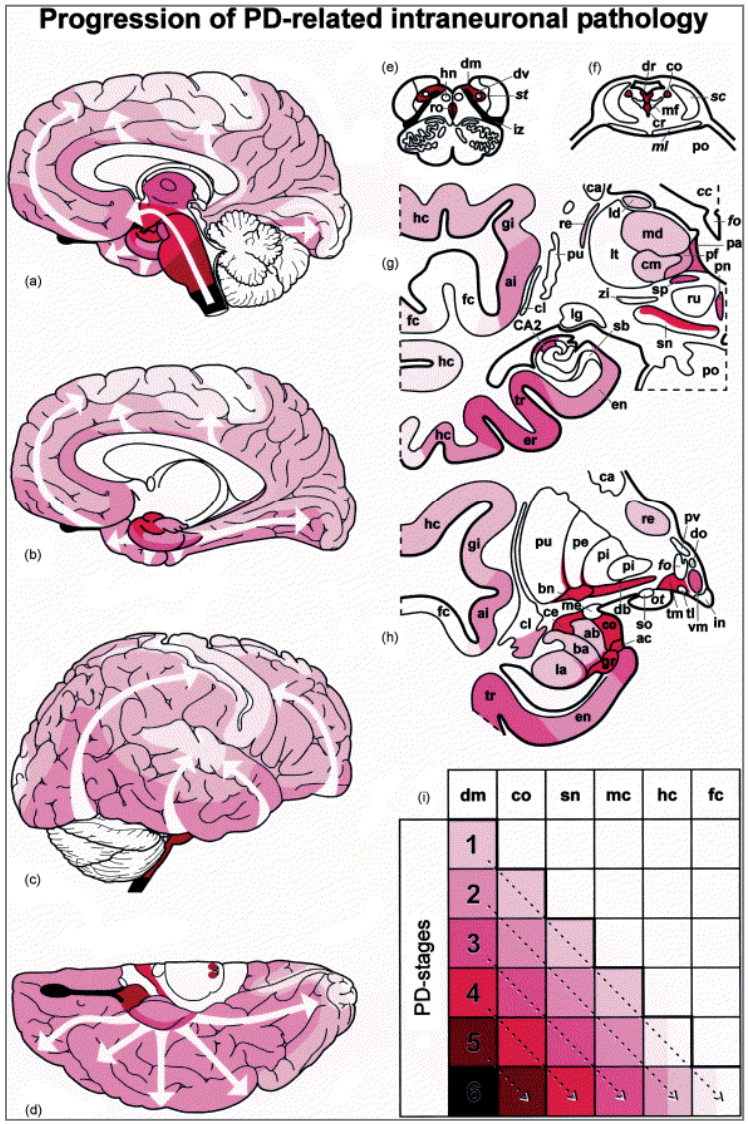
## α-sinucleína

Sinfilina-1
(Wakabayashi et al, 2002)
Ubicuitina
TAU no fosforilada
α y β-cristalina
α y β-tubulina





# Progresión de la muerte neuronal

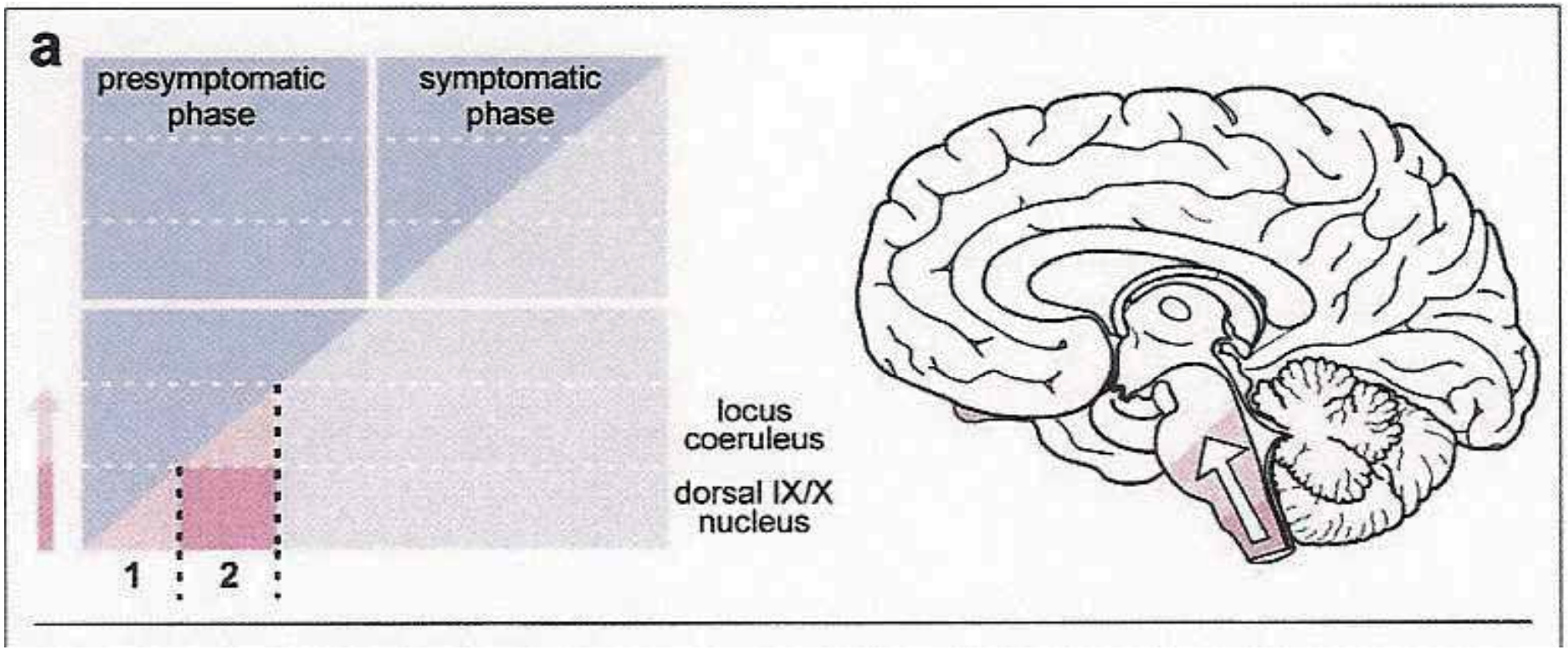


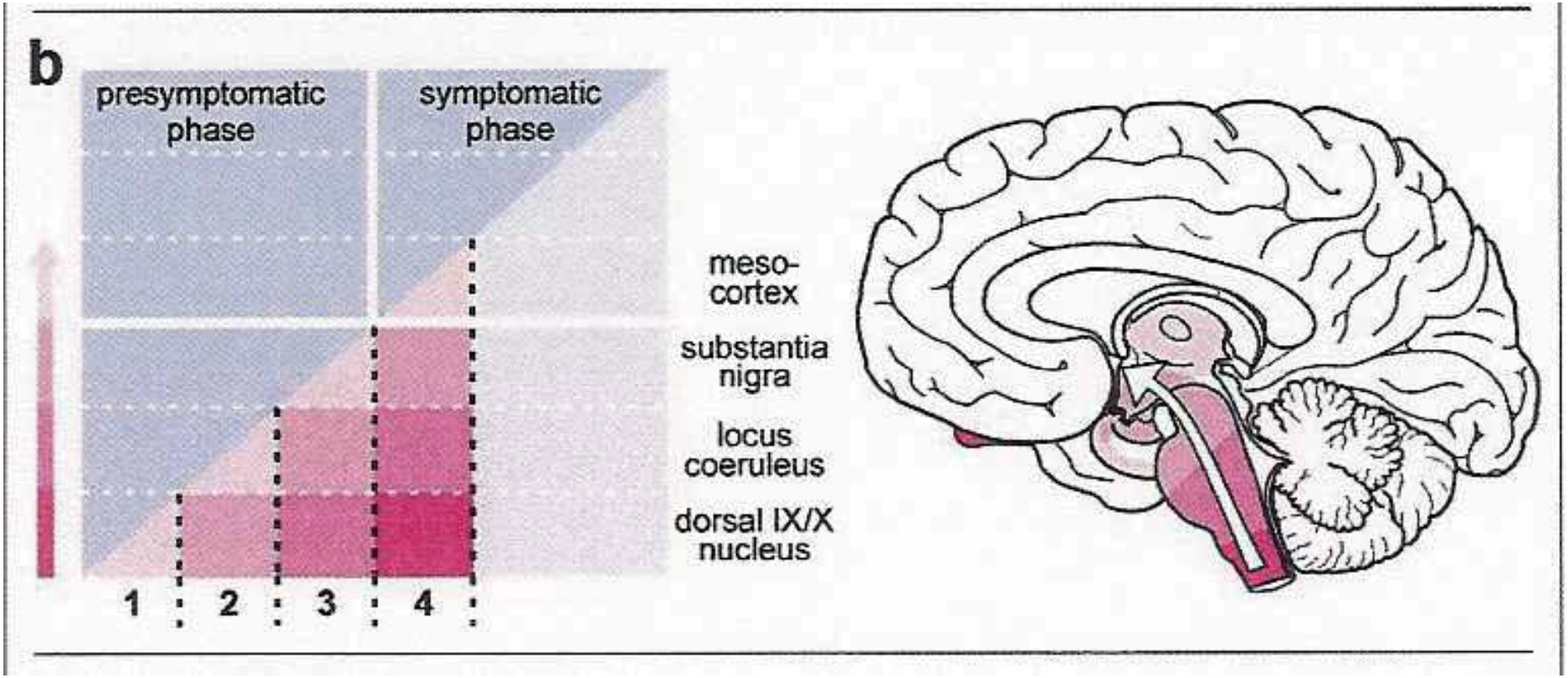

## MUERTE NEURONAL

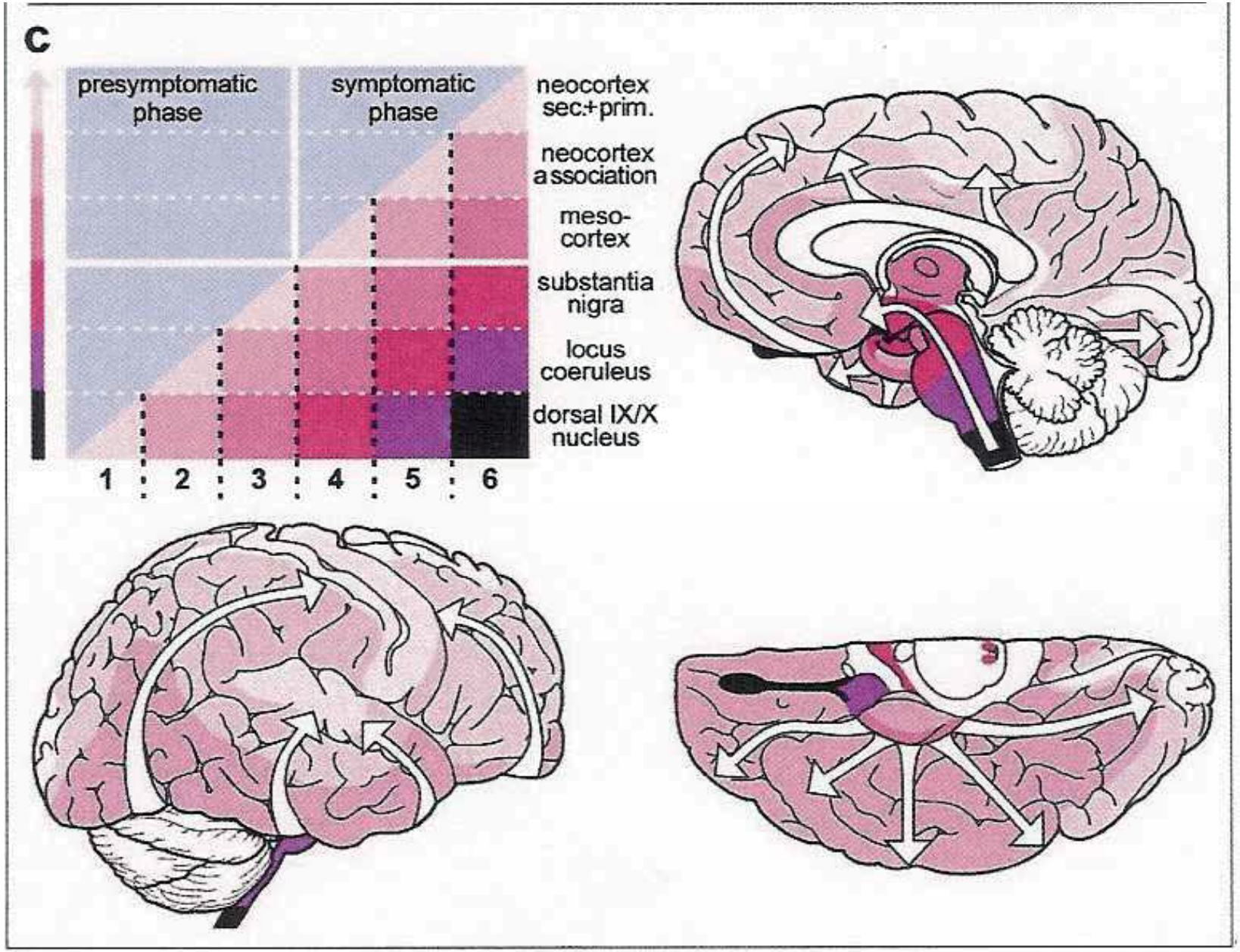
(Braak et al, 2003)

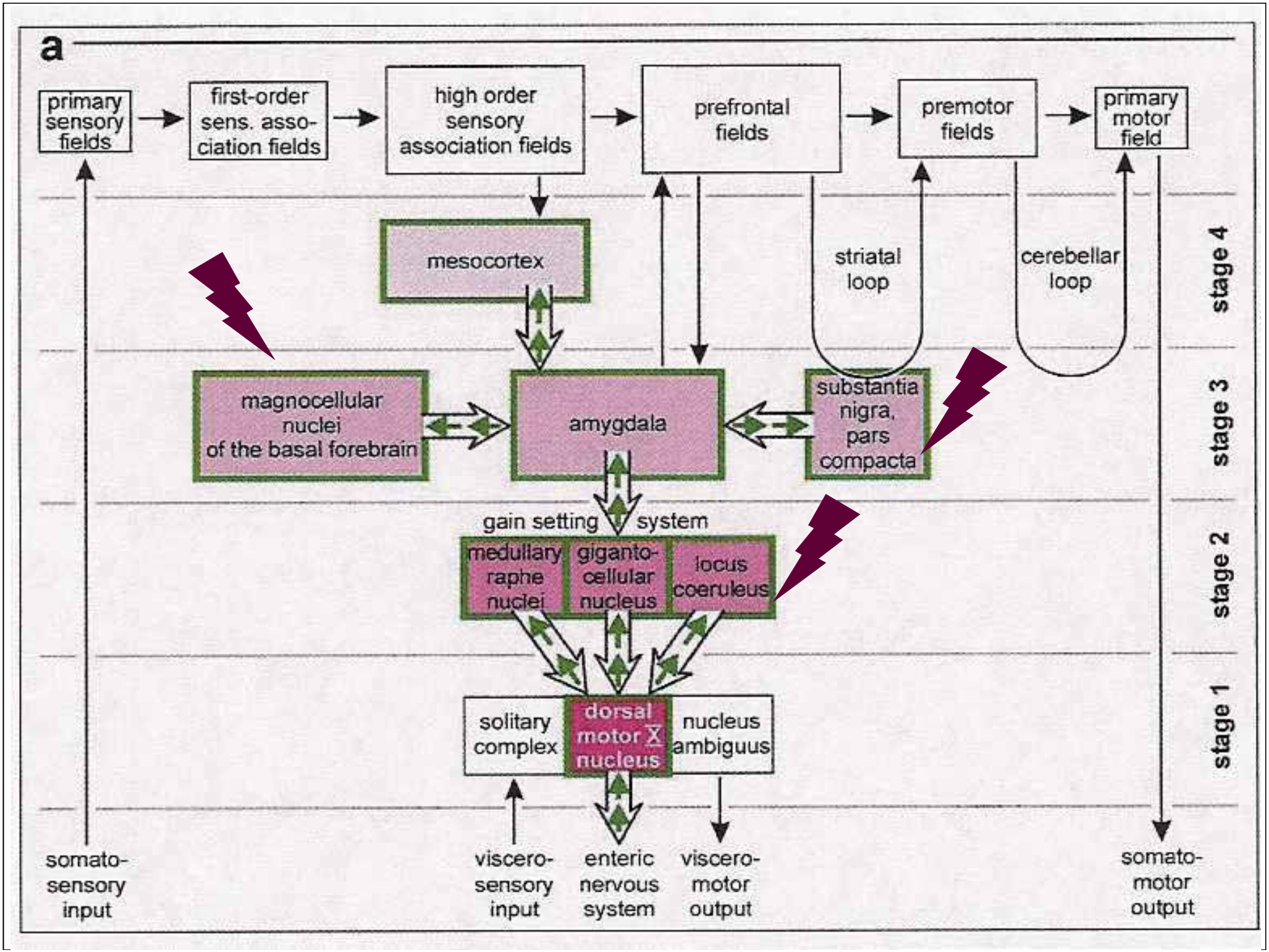
**Estereotipada**

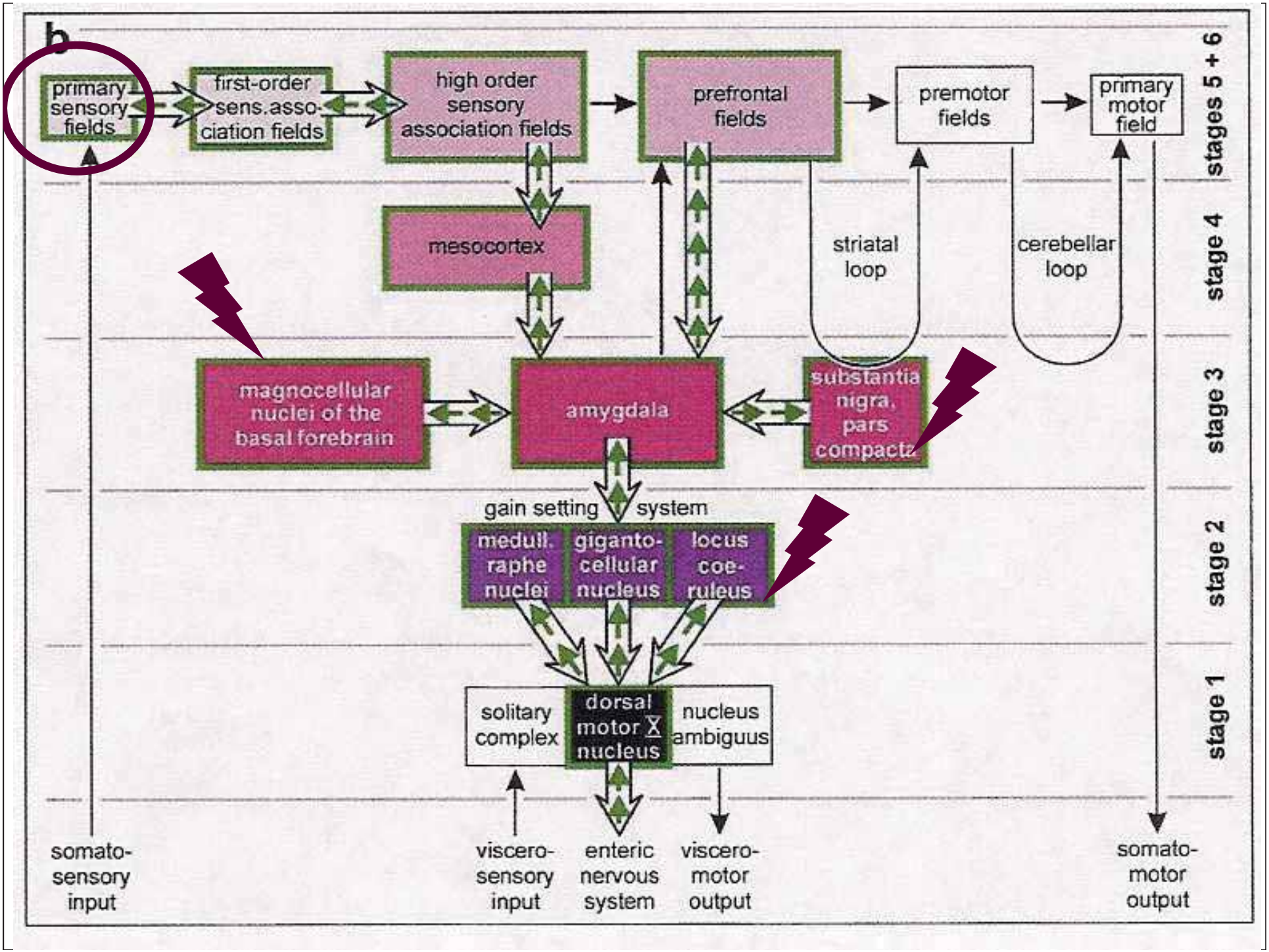
**Temporo-espacial**


a
presymptomatic phase
symptomatic phase
locus coeruleus
dorsal IX/X nucleus
1
2


b
presymptomatic phase
symptomatic phase
meso-cortex
substantia nigra
locus coeruleus
dorsal IX/X nucleus
1
2
3
4


C
presymptomatic phase
symptomatic phase
neocortex sec:+prim.
neocortex association
meso-cortex
substantia nigra
locus coeruleus
dorsal IX/X nucleus
1
2
3
4
5
6


a
primary sensory fields
first-order sens. asso-ciation fields
high order sensory association fields
prefrontal fields
premotor fields
primary motor field
mesocortex
striatal loop
cerebellar loop
magnocellular nuclei of the basal forebrain
amygdala
substantia nigra, pars compacta
gain setting system
medullary raphe nuclei
gigantocellular nucleus
locus coeruleus
solitary complex
dorsal motor X nucleus
nucleus ambiguus
somato-sensory input
viscero-sensory input
enteric nervous system
viscero-motor output
somato-motor output
stage 4
stage 3
stage 2
stage 1


b
primary sensory fields
first-order sens.asso-ciation fields
high order sensory association fields
prefrontal fields
premotor fields
primary motor field
stages 5 + 6
mesocortex
striatal loop
cerebellar loop
stage 4
magnocellular nuclei of the basal forebrain
amygdala
substantia nigra, pars compacta
stage 3
gain setting system
medull. raphe nuclei
giganto-cellular nucleus
locus coe-ruleus
stage 2
solitary complex
dorsal motor X nucleus
nucleus ambiguus
stage 1
somato-sensory input
viscero-sensory input
enteric nervous system
viscero-motor output
somato-motor output

# Ageing, neurodegeneration and Parkinson's disease

JOHN V. HINDLE

*Age and Ageing* 2010; **39:** 156–161

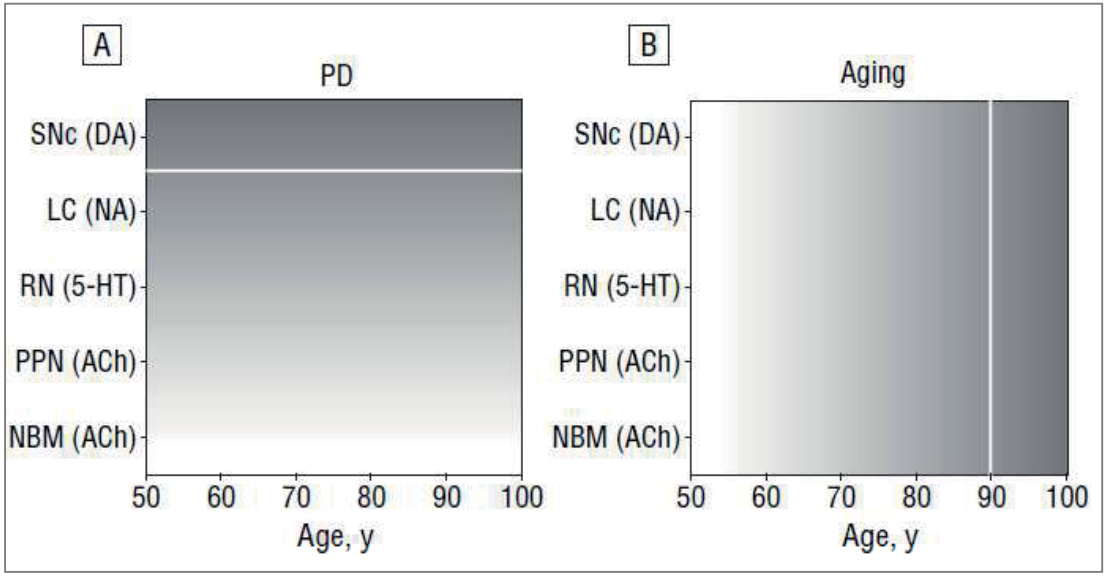
## Key points

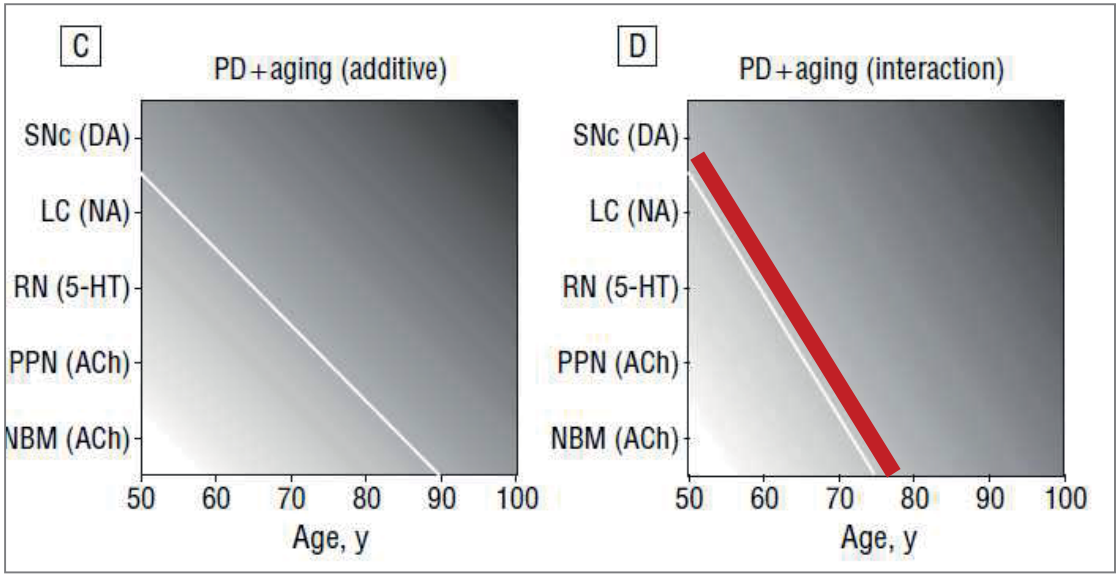
- The mechanisms of ageing and neurodegeneration are inter-related.
- Ageing is the single most significant factor influencing the clinical presentation, course and progression of PD.
- Age-related changes in cellular function and a reduced compensatory capacity predispose to the pathogenesis of PD.
- The formation of Lewy bodies may represent a marker of protective mechanisms against age-related degeneration of the nervous system.
- PD is one of the best examples of an age-related disease.

# The Relationship of Parkinson Disease With Aging

Gilberto Levy, MD, MS

*Arch Neurol*. 2007;64(9):1242-1246



Acta Neuropathol (2008) 115:409–415

# The progression of pathology in longitudinally followed patients with Parkinson's disease

Glenda Halliday · Mariese Hely · Wayne Reid
John Morris

Case details for patients at different times during the Sydney Multicenter Study of PD

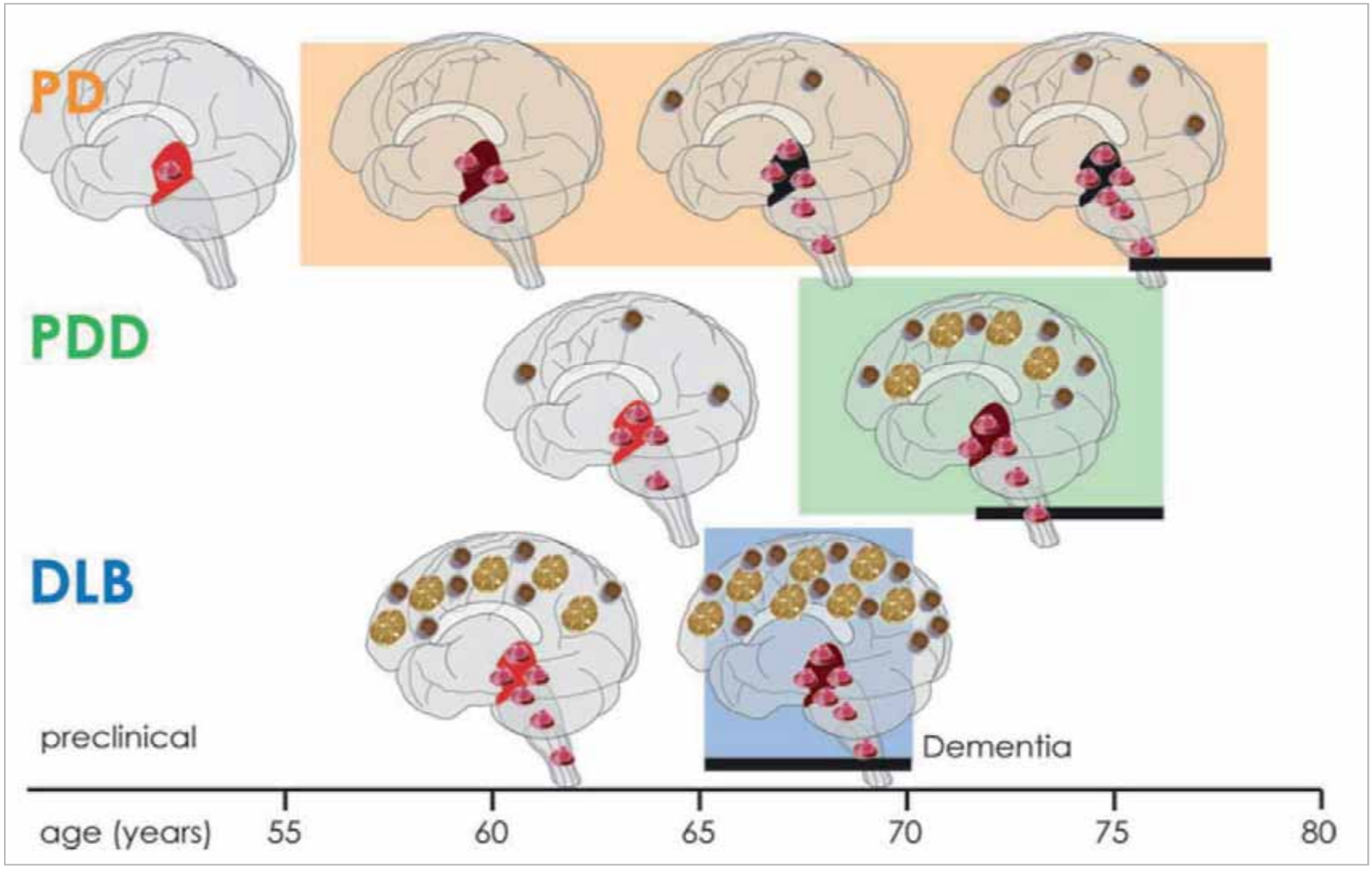
| End-stage clinical diagnosis | PD | PDD | DLB |
|---|---|---|---|
| N | 29 | 52 | 6 |
| ***During the first 5 years*** | | | |
| Age at onset | 70±8 | - | 65±6 |
| Disease duration | 5±0 | - | 3±2 |
| last H&Y score | 3±2 | - | 4±1 |
| last CDR score | 0±0 | - | 3±0 |
| Braak LB stage | mainly brainstem | - | mainly neocortical |
| % amyloid plaque | 0 | - | 83 |
| % NIA-Regan AD | 0 | - | 16 |
| ***Between 6 and 10 years*** | | | |
| Age at onset | 68±6 | 70±5 | - |
| Disease duration | 8±1 | 8±2 | - |
| [illegible] | 3±1 | 5±1 | - |
| [illegible] | 0±0 | 2±1 | - |
| [illegible] LB stage | mainly brainstem | limbic & neocortical | - |
| [illegible] amyloid plaque | 0 | 80 | - |
| % NIA-Regan AD | 0 | 10 | - |
| ***Between 11 and 15 years*** | | | |
| Age at onset | 59±11 | 67±6 | - |
| Disease duration | 13±1 | 13±1 | - |
| last H&Y score | 4±1 | 4±1 | - |
| last CDR score | 0±0 | 2±1 | - |
| Braak LB stage | brainstem & limbic | limbic & neocortical | - |
| % amyloid plaque | 0 | 56 | - |
| % NIA-Regan AD | 0 | 6 | - |
| ***Between 16 and 20 years*** | | | |
| Age at onset | 58±9 | 58±7 | - |
| Disease duration | 17±1 | 18±1 | - |
| last H&Y score | 4±1 | 5±0 | - |
| last CDR score | 0±0 | 2±1 | - |
| Braak LB stage | brainstem & limbic | limbic | - |
| % amyloid plaque | 7 | 44 | - |
| % NIA-Regan AD | 0 | 6 | - |
| ***20+ years*** | | | |
| Age at onset | - | 55±3 | - |
| Disease duration | - | 25±2 | - |
| last H&Y score | - | 4±1 | - |
| last CDR score | - | 2±1 | - |
| Braak LB stage | - | limbic & neocortical | - |
| % amyloid plaque | - | 13 | - |
| % NIA-Regan AD | - | 0 | - |

PARKINSON-DEMENCIA

# The progression of pathology in Parkinson's disease

Glenda Margaret Halliday and Heather McCann

Ann. N.Y. Acad. Sci. ISSN 0077-8923



# The progression of pathology in Parkinson's disease

Glenda Margaret Halliday and Heather McCann

Ann. N.Y. Acad. Sci. ISSN 0077-8923

bodies. PDD phenotype: an older-onset group with shorter disease durations and dementia by midstage disease have greater amounts of cortical Lewy bodies early in their disease and some coexisting Alzheimer's disease pathology appearing with the onset of dementia. DLB phenotype: a dominant dementia syndrome with severe cortical Lewy body loads often with coexisting Alzheimer's disease pathology, which must occur early in the disease process due to their short disease durations and early onset of dementia.

for more autopsy studies assessing closely followed cases over defined epochs is vital to elucidating the true progression of pathology in PD and any contributing factors such as age, disease duration, and coexisting illnesses.

**EDAD, DURACIÓN DE LA ENFERMEDAD**

**Y OTRAS ENFERMEDADES COEXISTENTES**

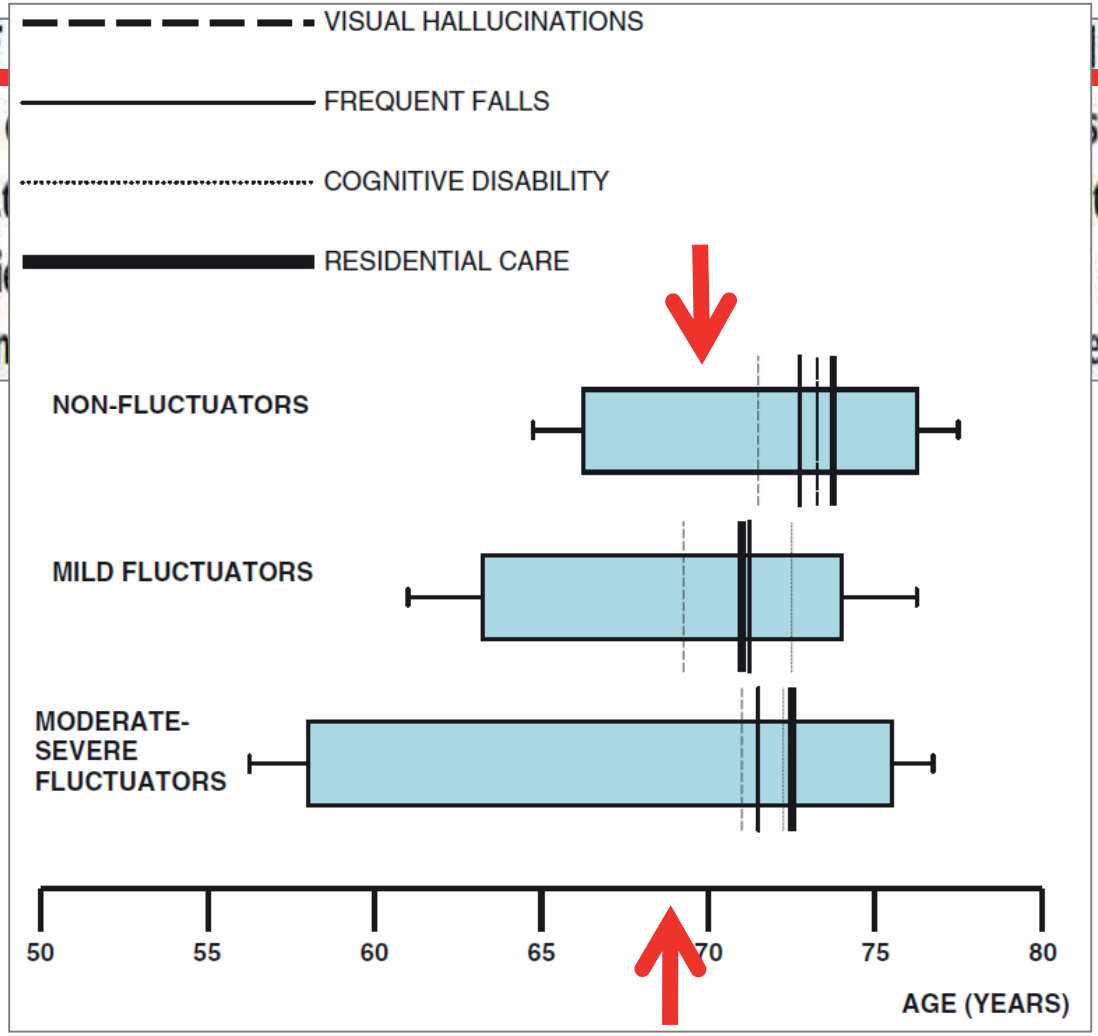
doi:10.1093/brain/awm142 *Brain* (2007), **130**, 2123–2128

# Patterns of levodopa response in Parkinson's disease: a clinico-pathological study

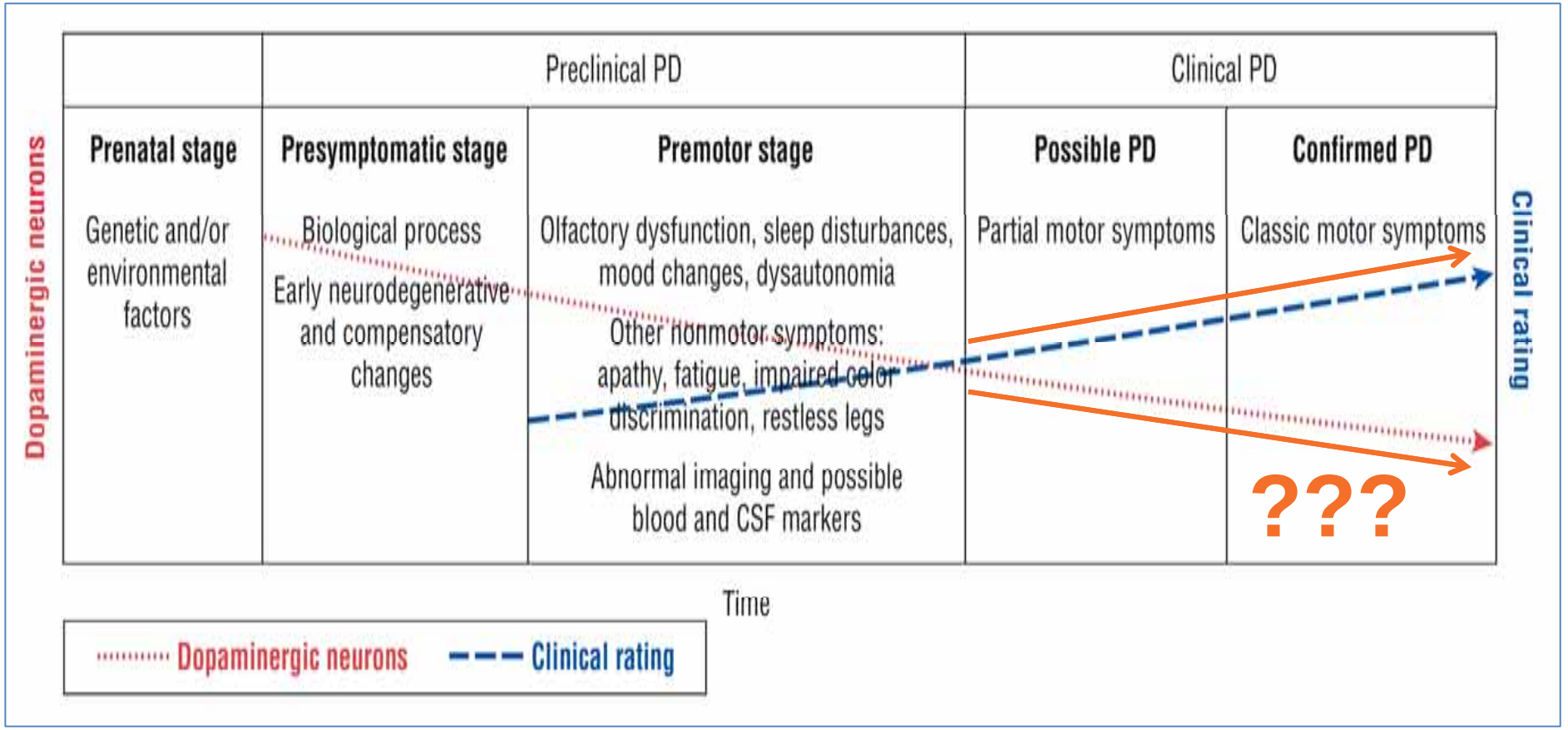
P. A. Kempster,[1,2] D. R. Williams,[1,3] M. Selikhova,[1] J. Holton,[1] T. Revesz[1] and A. J. Lees[1]

Four milestones of
for residential care)
to the disease durat
or other pathologi
pathological endpoin

lisability and need
s not proportionate
tion of Lewy body
reach a common
e disease are alike.



# PERO…
# ¿qué causa la progresión de la EP?



# Evidencia *In vivo* del aumento de microglia (PET-Scan PK11195)

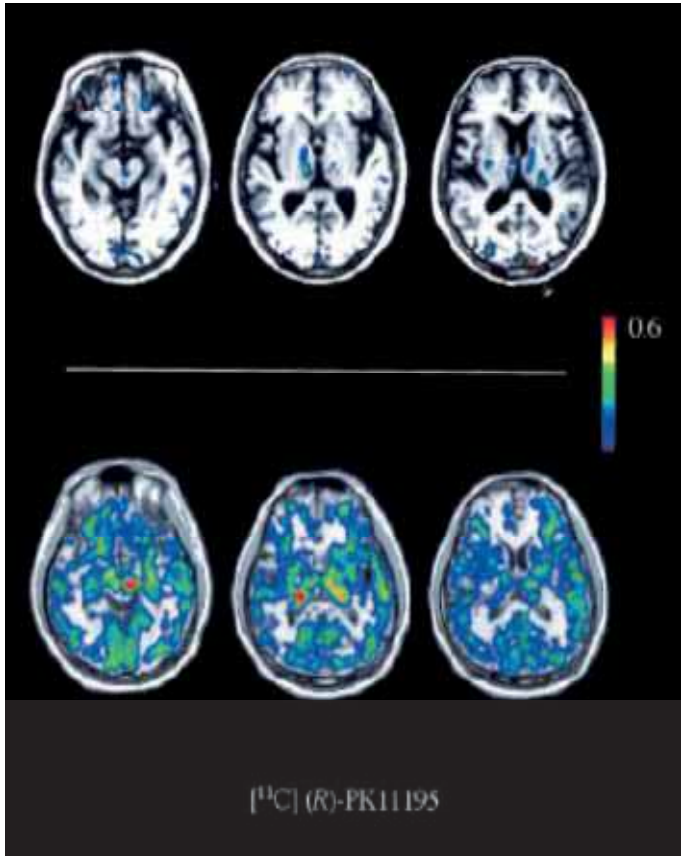
Microglial Activation and Dopamine Terminal Loss in Early Parkinson's Disease

Yasuomi Ouchi, MD, PhD,[1] Etsuji Yoshikawa, BA,[2] Yoshimoto Sekine, MD, PhD,[1,2]
Masami Futatsubashi, BA,[2] Toshihiko Kanno, RT,[1] Tomomi Ogusu, MA,[2] Tatsuo Torizuka, MD, PhD[1]

Ann Neurol 2005;57:168–175

**Control**

**PD**




*** <u>Correlation negativa</u> con la inervación dopaminérgica estriatal.**

*** <u>Correlación positiva</u> con los síntomas motores contralaterales.**

# HLA-DR susceptibilidad genética en rastreo del genoma

nature genetics

Received 9 March; accepted 15 July; published online 15 August 2010; doi:10.1038/ng.642

## Common genetic variation in the *HLA* region is associated with late-onset sporadic Parkinson's disease

Taye H Hamza[1], Cyrus P Zabetian[2,3], Albert Tenesa[4], Alain Laederach[1], Jennifer Montimurro[1], Dora Yearout[1–3], Denise M Kay[1], Kimberly F Doheny[5], Justin Paschall[6], Elizabeth Pugh[5], Victoria I Kusel[1], Randall Collura[1], John Roberts[7], Alida Griffith[8], Ali Samii[2,3], William K Scott[9], John Nutt[10], Stewart A Factor[11] & Haydeh Payami[1]

## Genome wide associaton studies: genetic susceptibility factors

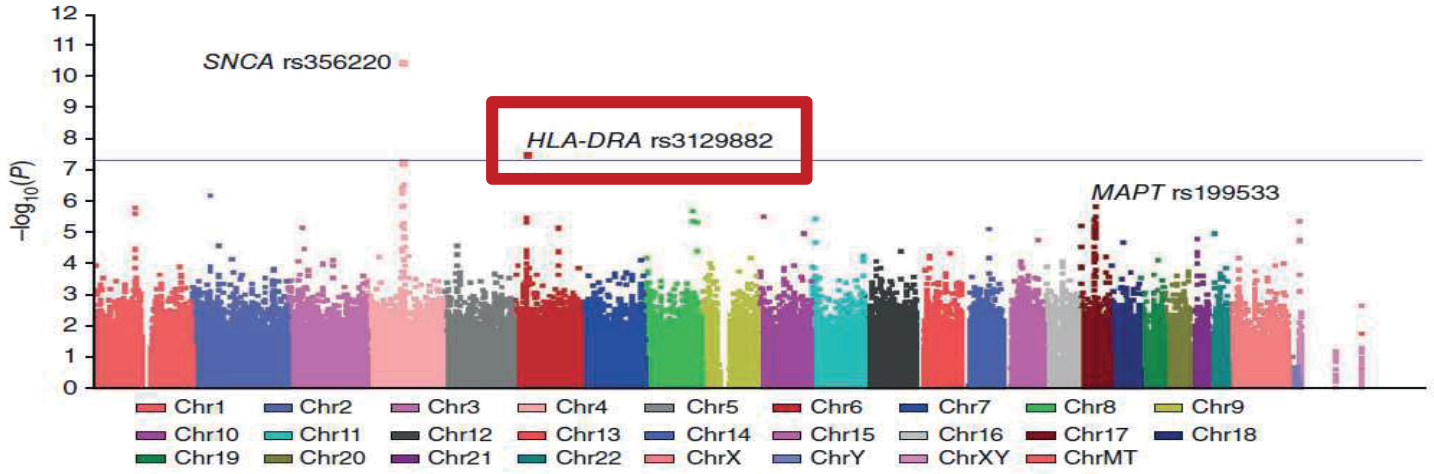



**Figure 1** Genome-wide association *P* values. The Manhattan plot shows the *P* values for association of 811,597 SNPs with Parkinson's disease. SNPs that surpassed genome-wide significance ($P < 5 \times 10^{-8}$) were on chromosomes 4 (*SNCA* region) and 6 (*HLA-DRA*). *SNCA* was known to be associated with Parkinson's disease; however, the association with *HLA* was not previously known. The other known Parkinson's disease–associated region is on chromosome 17 (*MAPT* region), which replicated at $P = 1.3 \times 10^{-6}$.

# HLA-DR susceptibilidad genética en rastreo del genoma

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Received 9 March; accepted 15 July; published online 15 August 2010; doi:10.1038/ng.642

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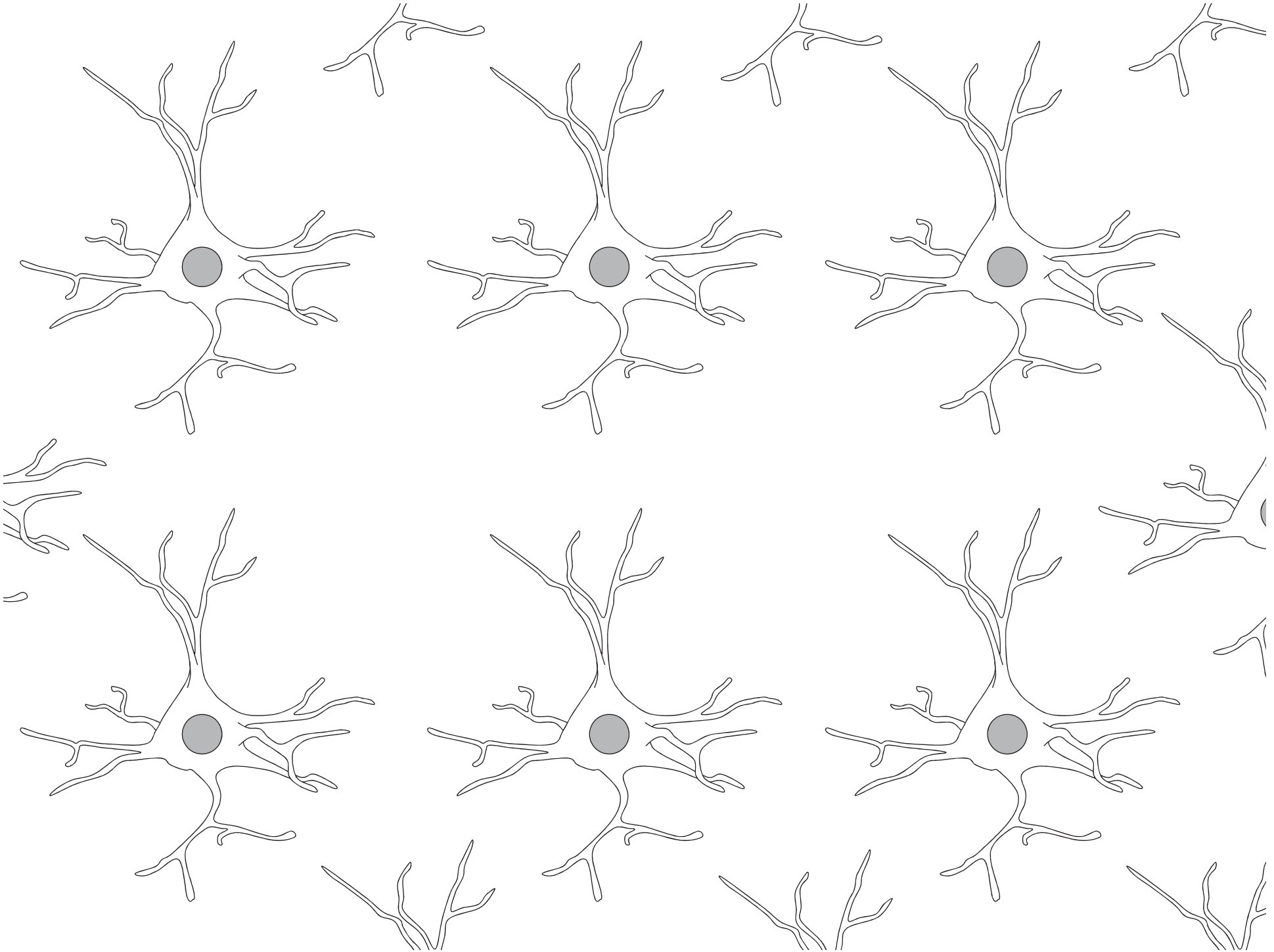
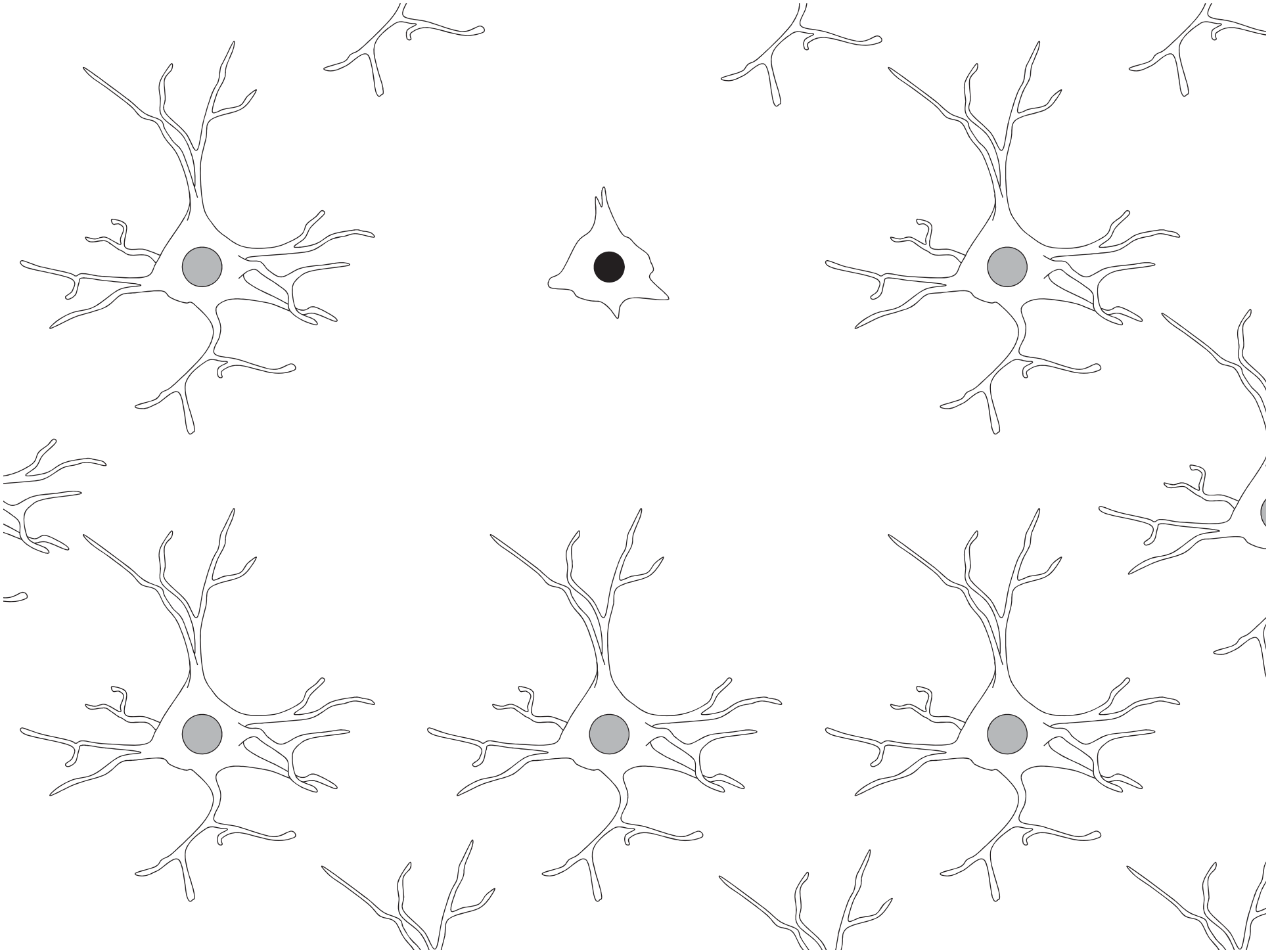
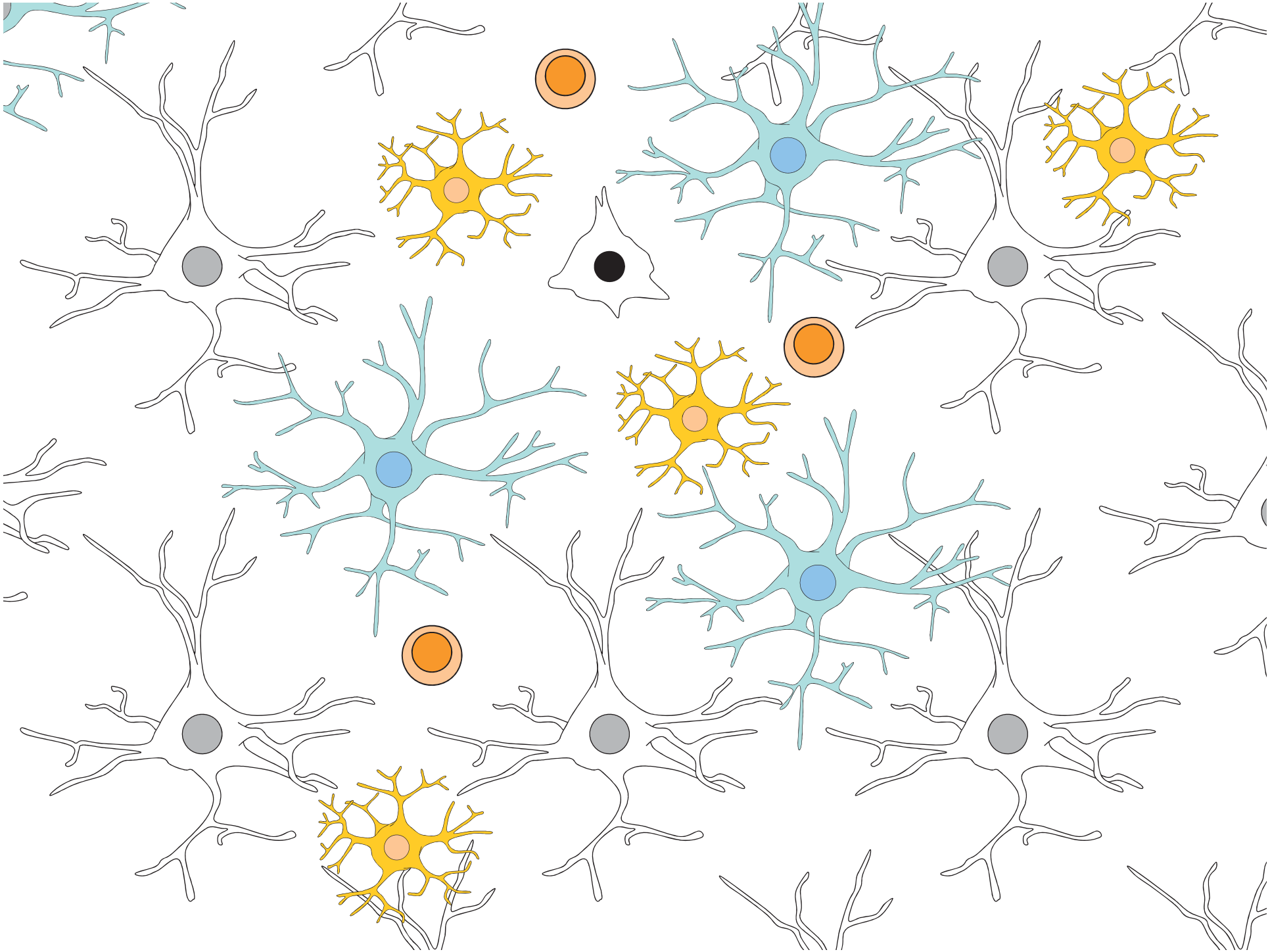
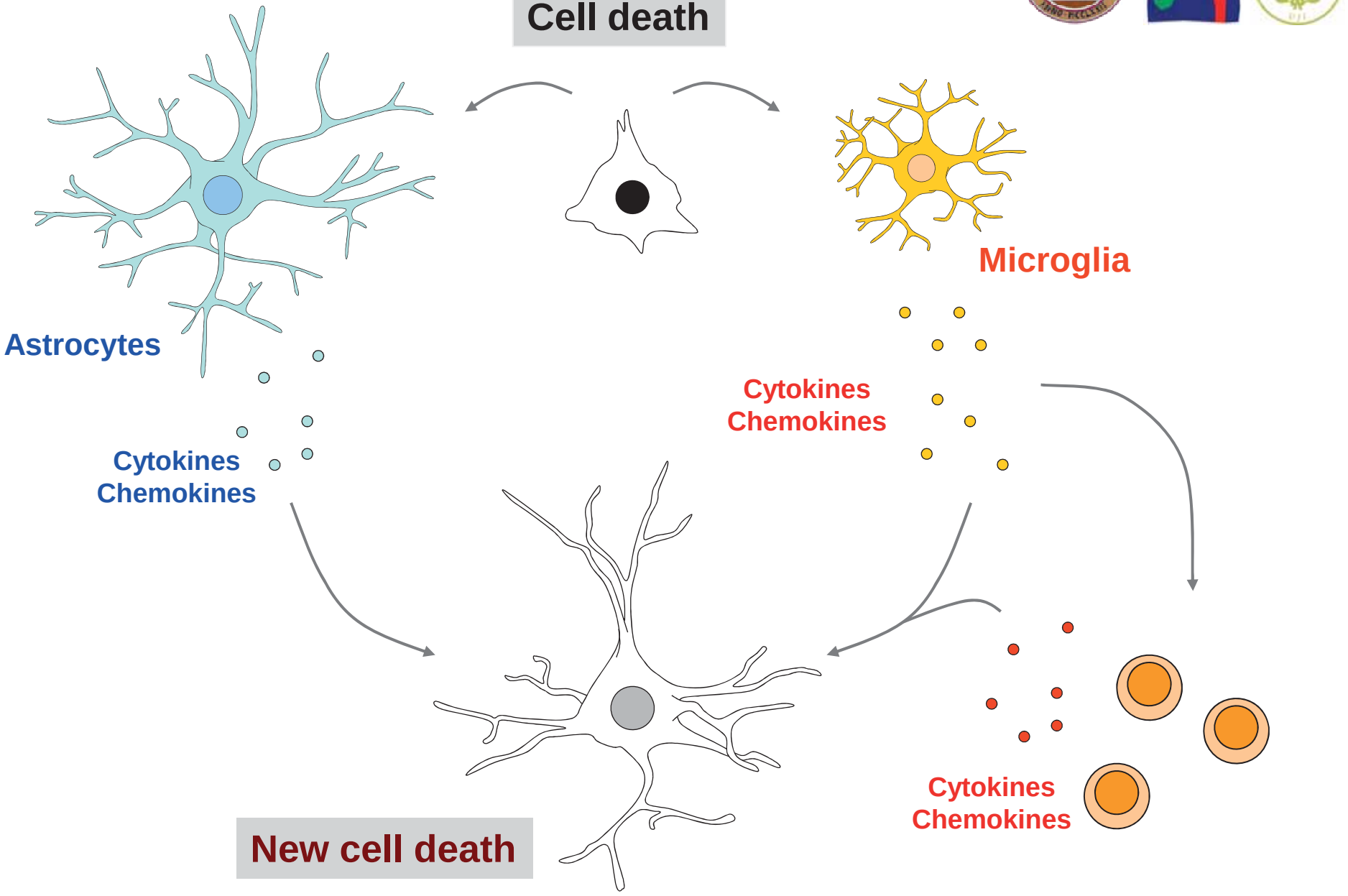
**The brains of individuals with Parkinson's disease show upregulation of DR antigens and the presence of DR-positive reactive microglia[12], and nonsteroidal anti-inflammatory drugs reduce Parkinson's disease risk[4,13]. The genetic association with *HLA* supports the involvement of the immune system in Parkinson's disease and offers new targets for drug development.**





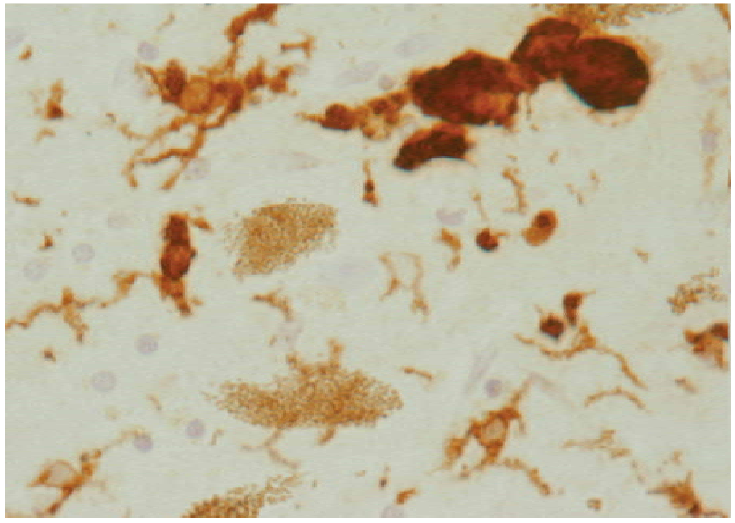


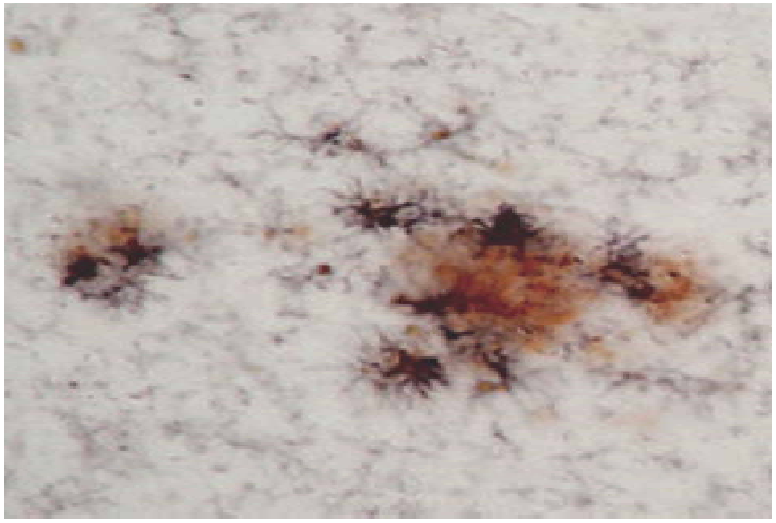

Cell death
Microglia
Astrocytes
Cytokines
Chemokines
Cytokines
Chemokines
Cytokines
Chemokines
New cell death

Estudios *post-mortem* en pacientes con PD o con AD

**presentaban microglía activa**

en las áreas de mayor muerte neuronal



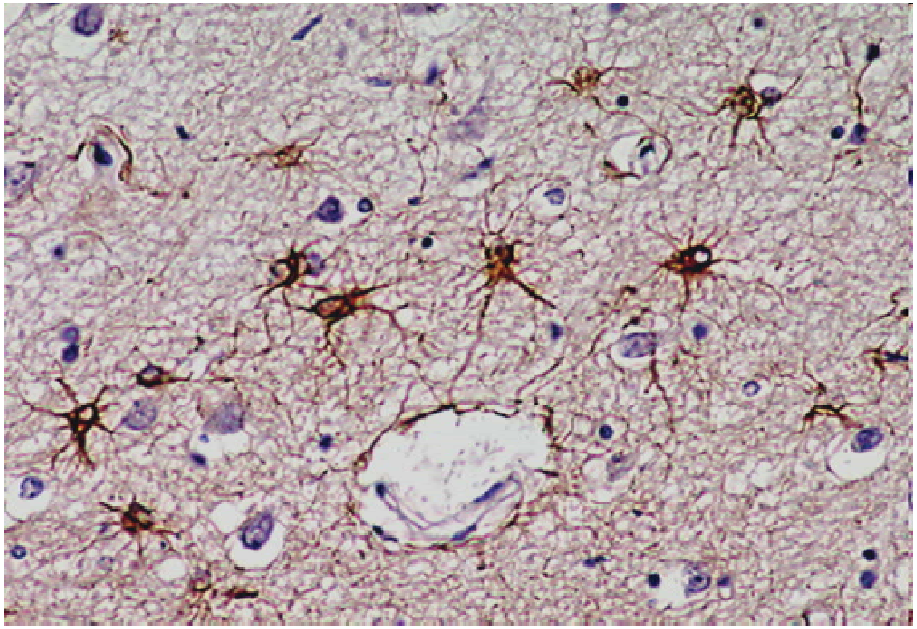


McGeer *et al*., Neurology 1988

Estudios *post-mortem* en pacientes con PD o con AD

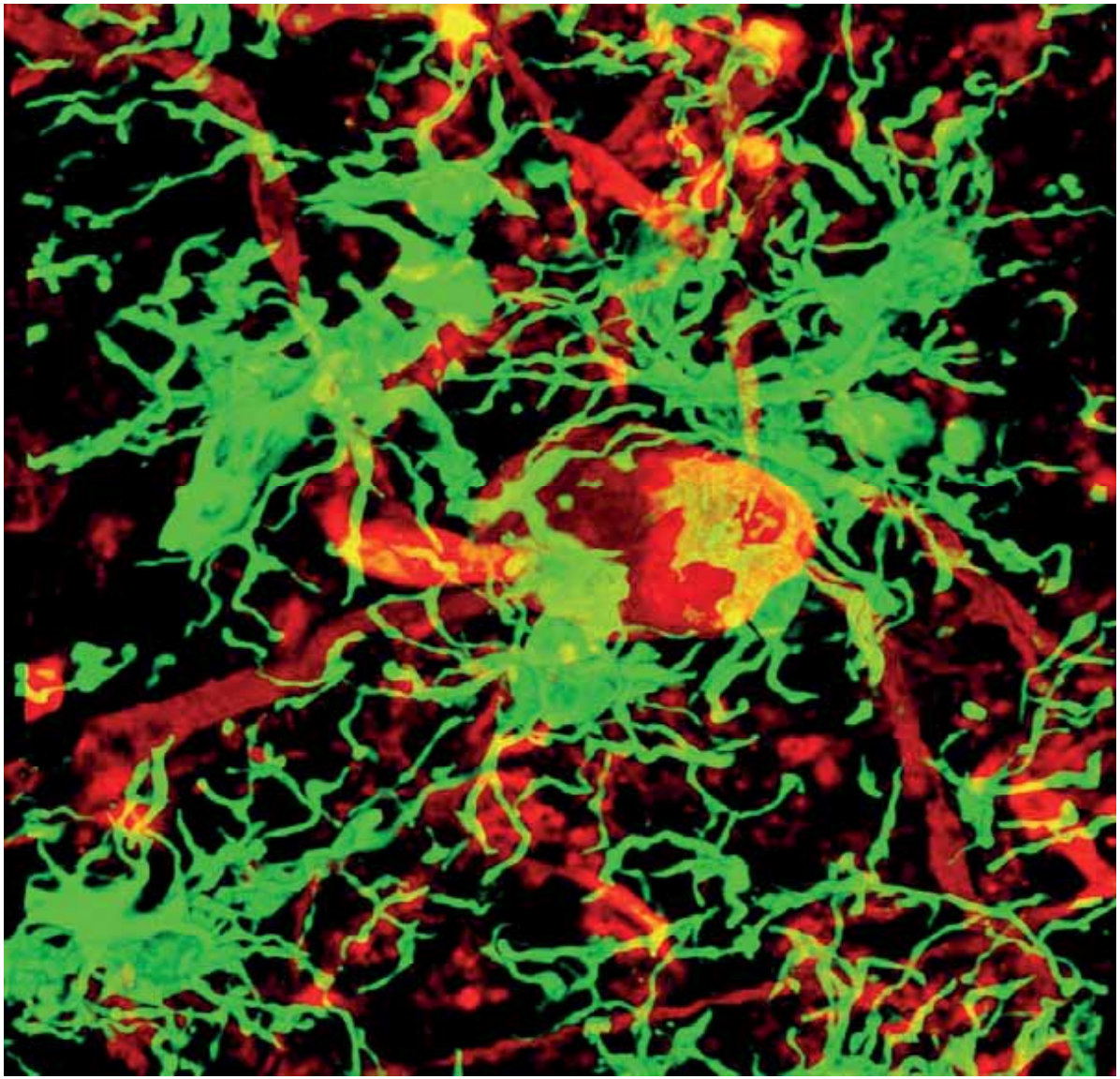
**presentaban astroglía activa**

en las áreas de mayor muerte neuronal



Forno *et al*., Prog Brain Res. 1992;
Yamaguchi et al., Acta Neuropathologica. 1987

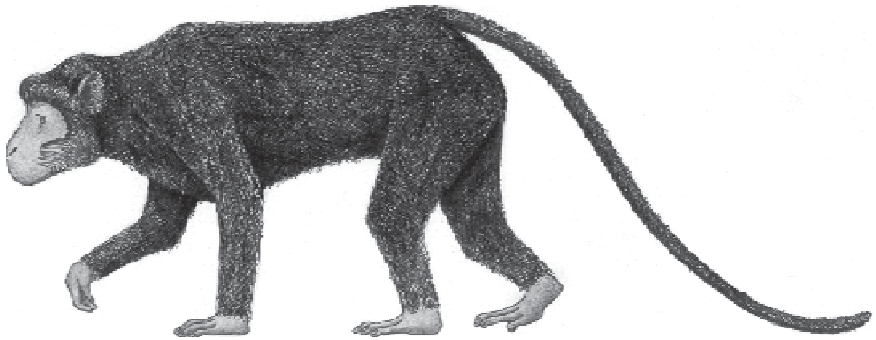
TH: Dopaminergic neurons
Iba-1: Microglia



# Modelo de parkinsonismo crónico en monos

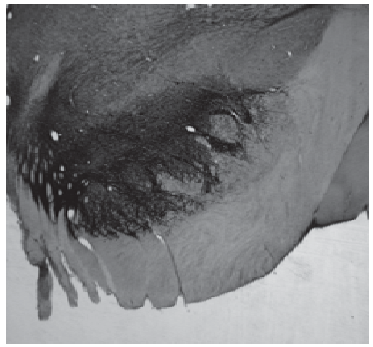
## Síndrome Parkinsoniano + Muerte Neuronal

Control

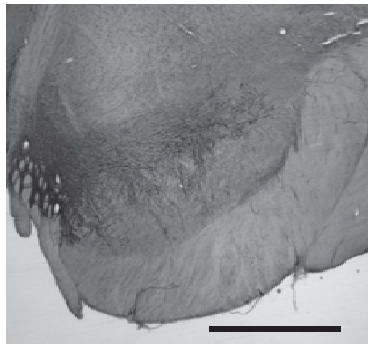


Parkinsonian

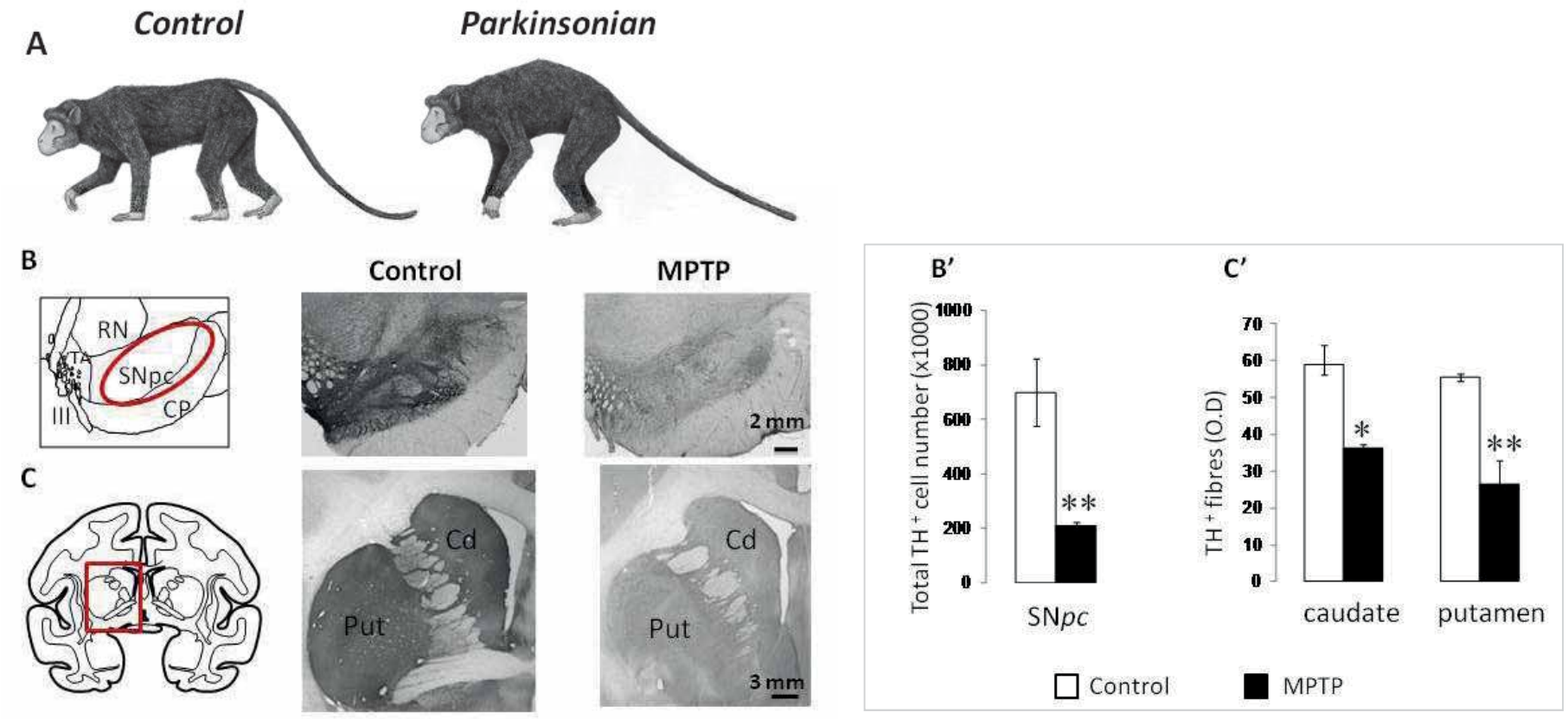
Control



Parkinsonian

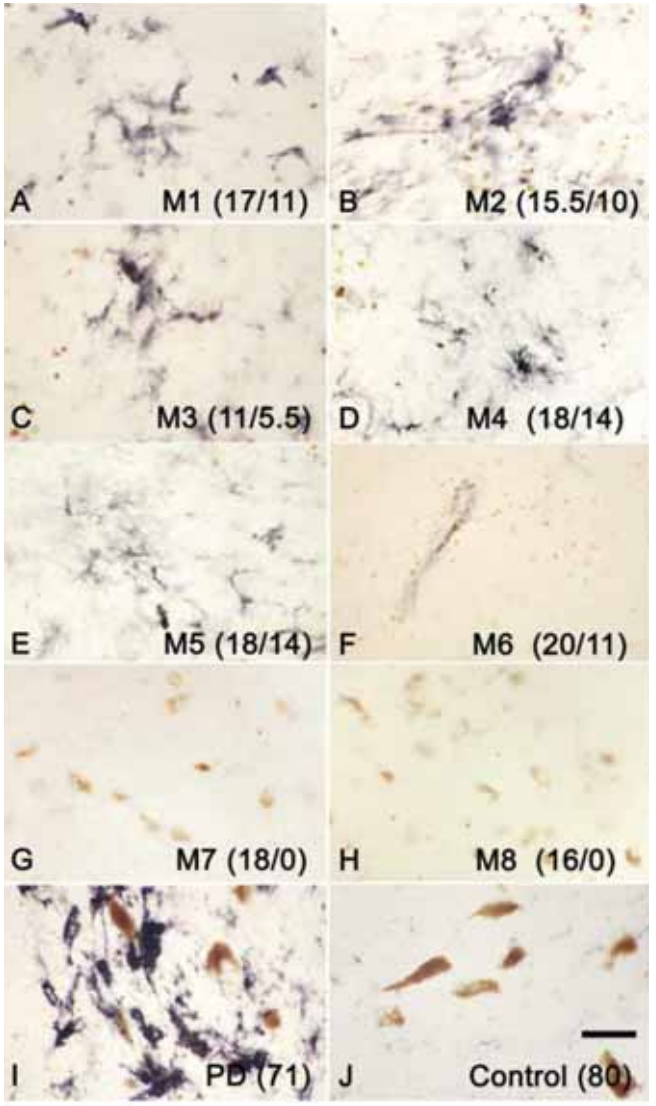


# La intoxicación crónica con MPTP induce una pérdida neuronal dopaminérgica persistente y progresiva en la sustancia negra, y de sus proyecciones al estriado



# Microglía y astroglía activas años después de la última dosis de MPTP

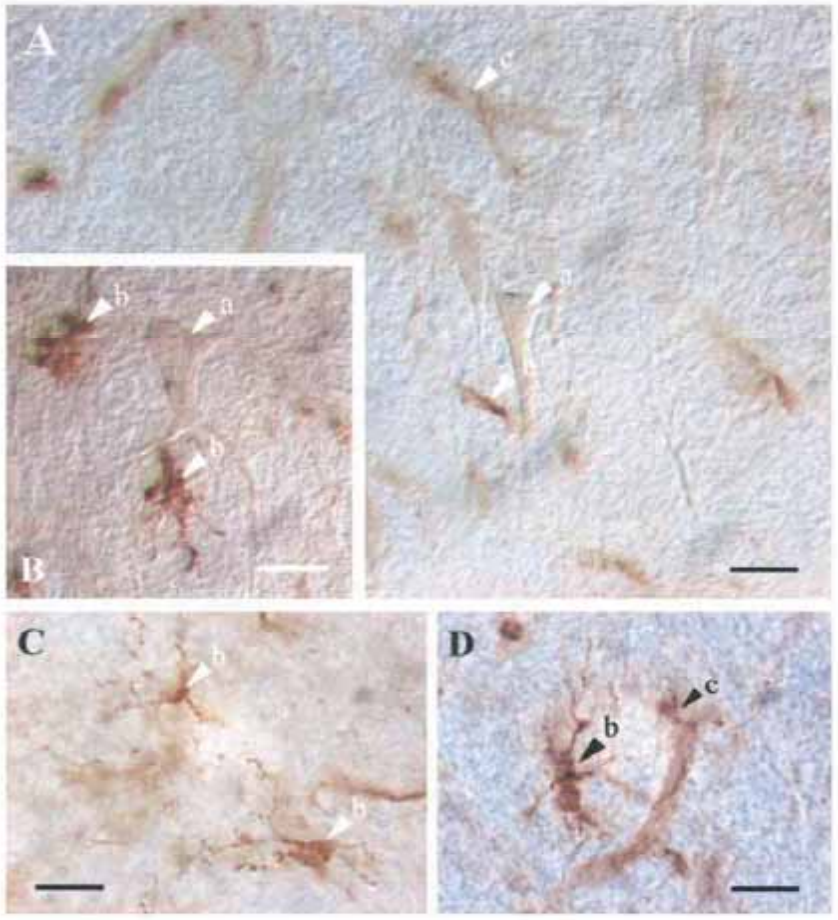
**PERO...**
**los monos estaban tratados con levodopa**

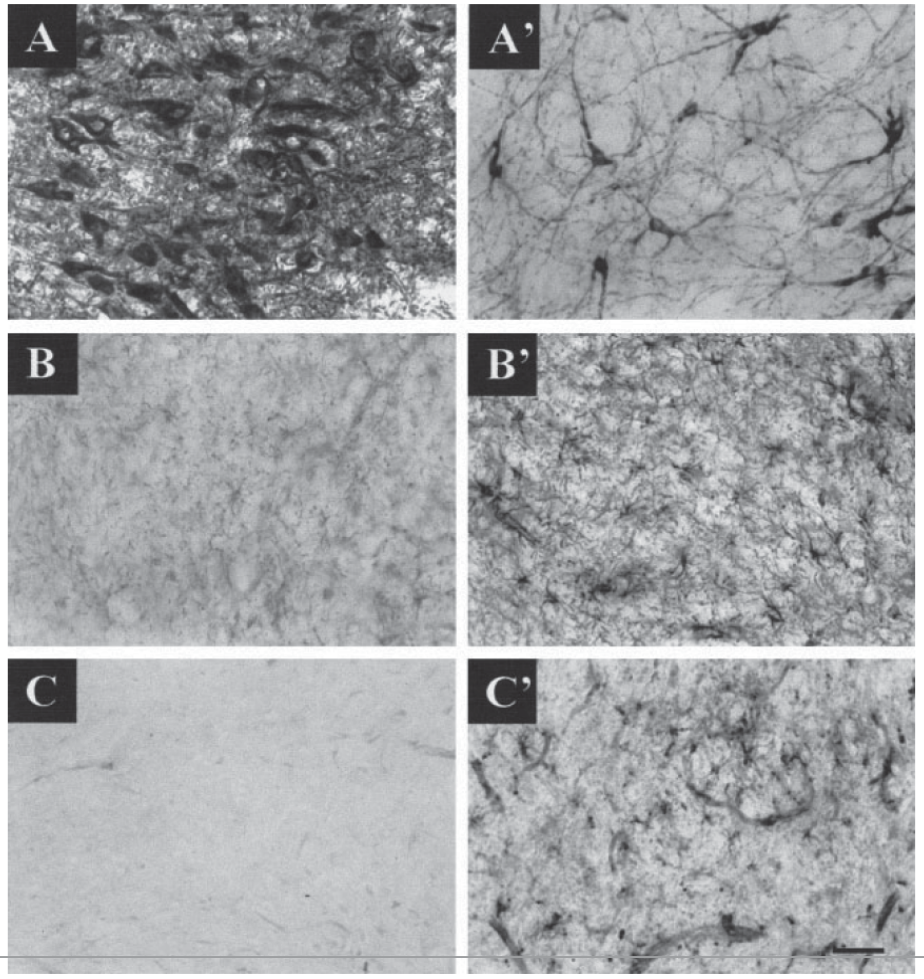



McGeer *et al*., Ann Neurol. 2003

# Monos parkinsonizados crónicamente

## Microglía activa 1 año después de la última dosis de MPTP y sin tratamiento con levodopa

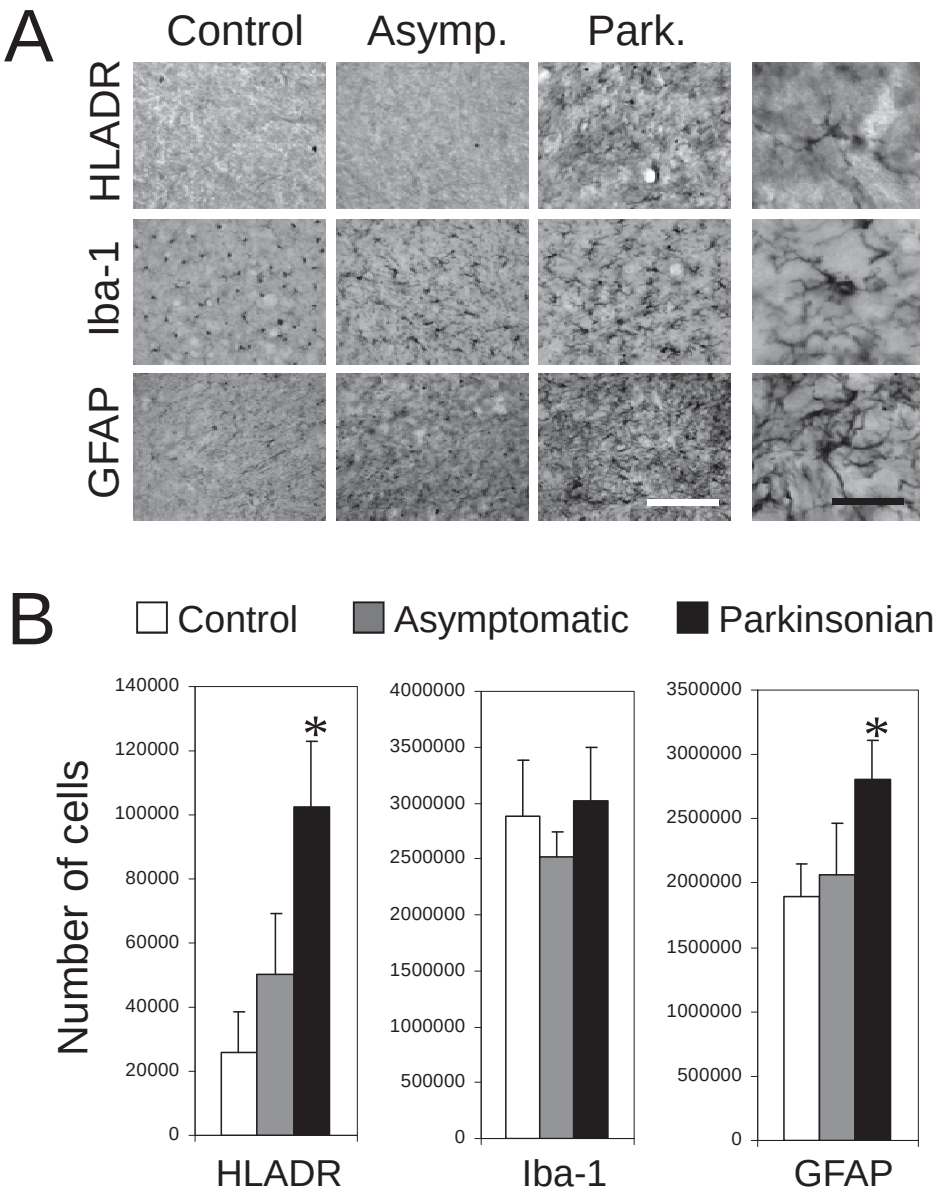



Barcia *et al.*, Glia 2004

# Parkinsonismo crónico en monos MPTP

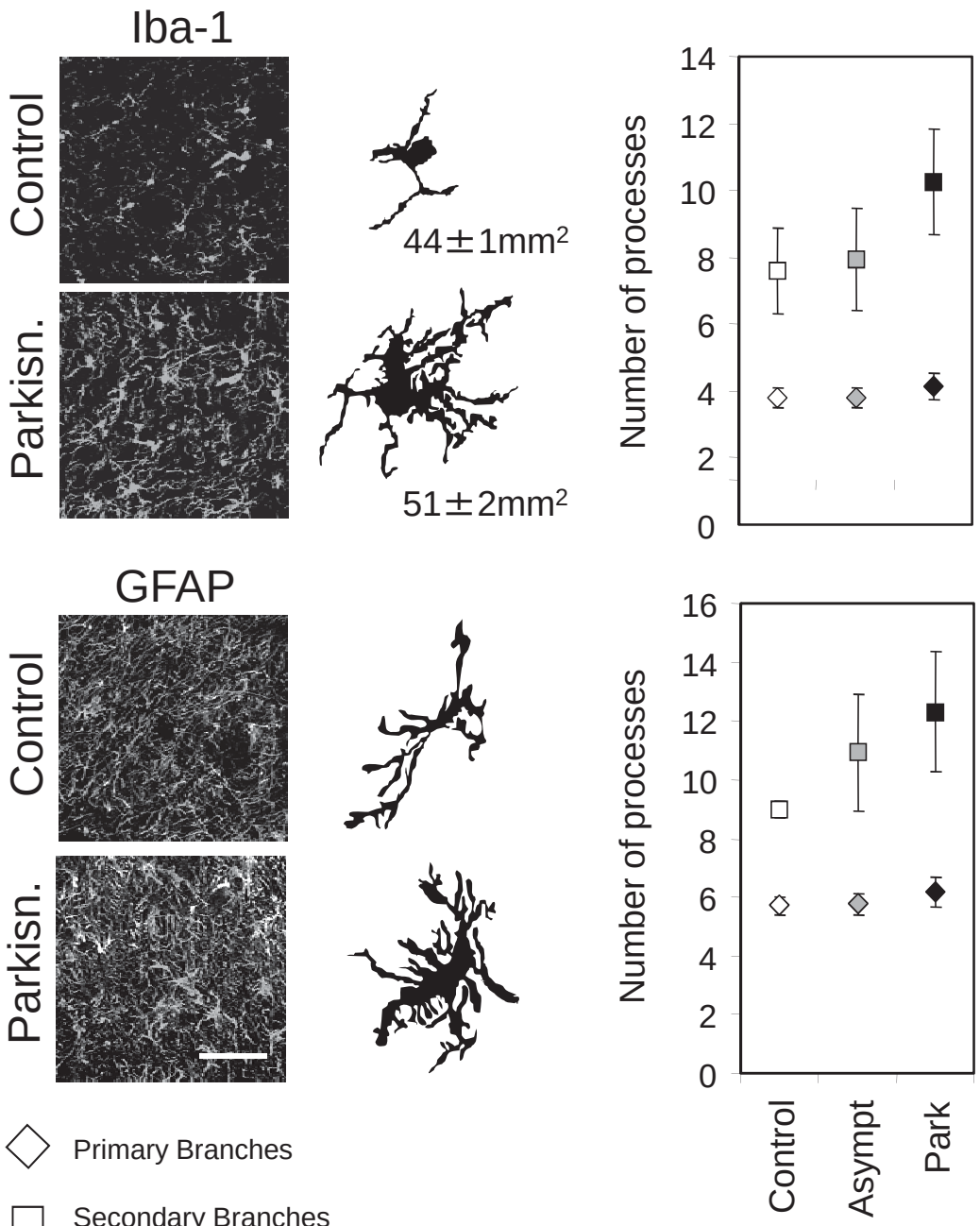
## Activación persiste años después de la última dosis de MPTP



**Parkinsonismo crónico en monos MPTP**

**Activación persiste años después de la última dosis de MPTP**

**Aumenta el tamaño y el número de ramificaciones**



# ¿Porqué y cómo continúa activa la microglía?

# Las candidatas son las CITOQUINAS

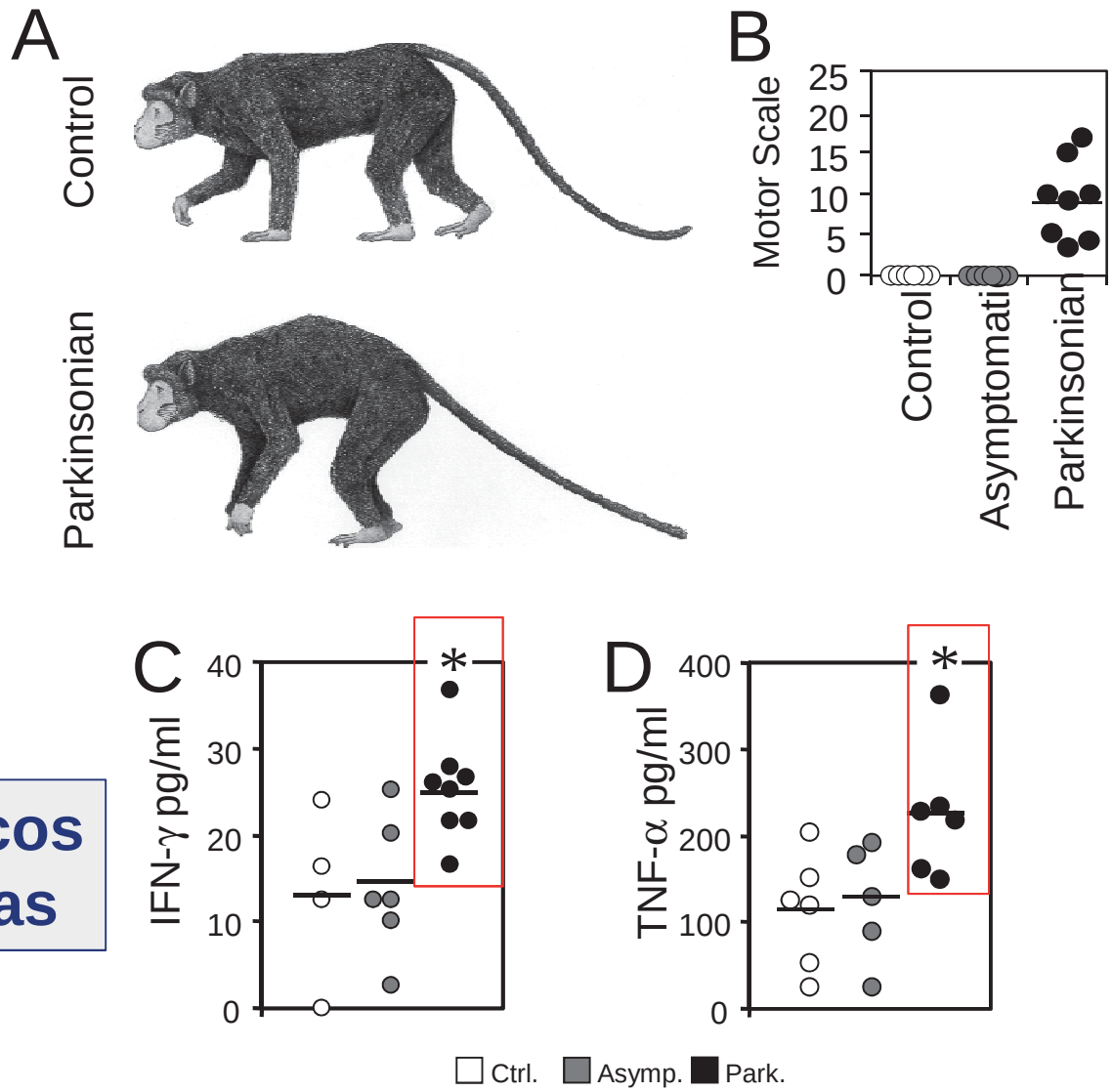
## TNF-α e IFN-γ

**Serum levels of TNF-α & IFN-γ increase in PD patients**
*(Mogi et al., 1994, Mount et al., 2007)*

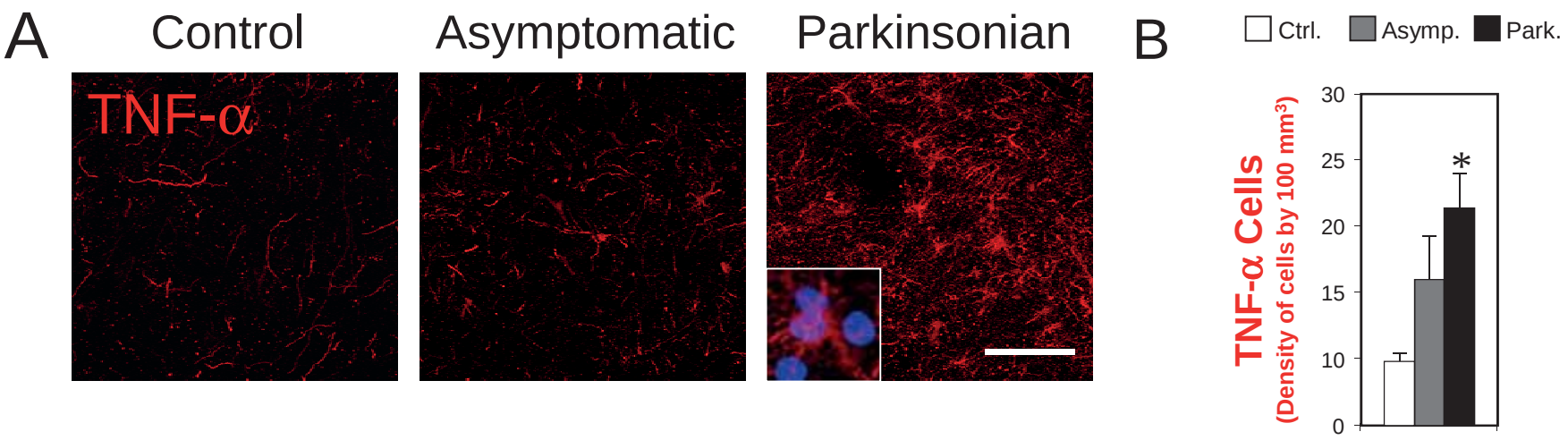
**IFN-γ KO mice are protected against MPTP**
*(Mount et al., 2007)*

**TNF-α and TNF-αR KO mice are less sensitive to MPTP**
*(Ferger et al., 2004; McCoy et al., 2006; Sriram et al., 2006)*

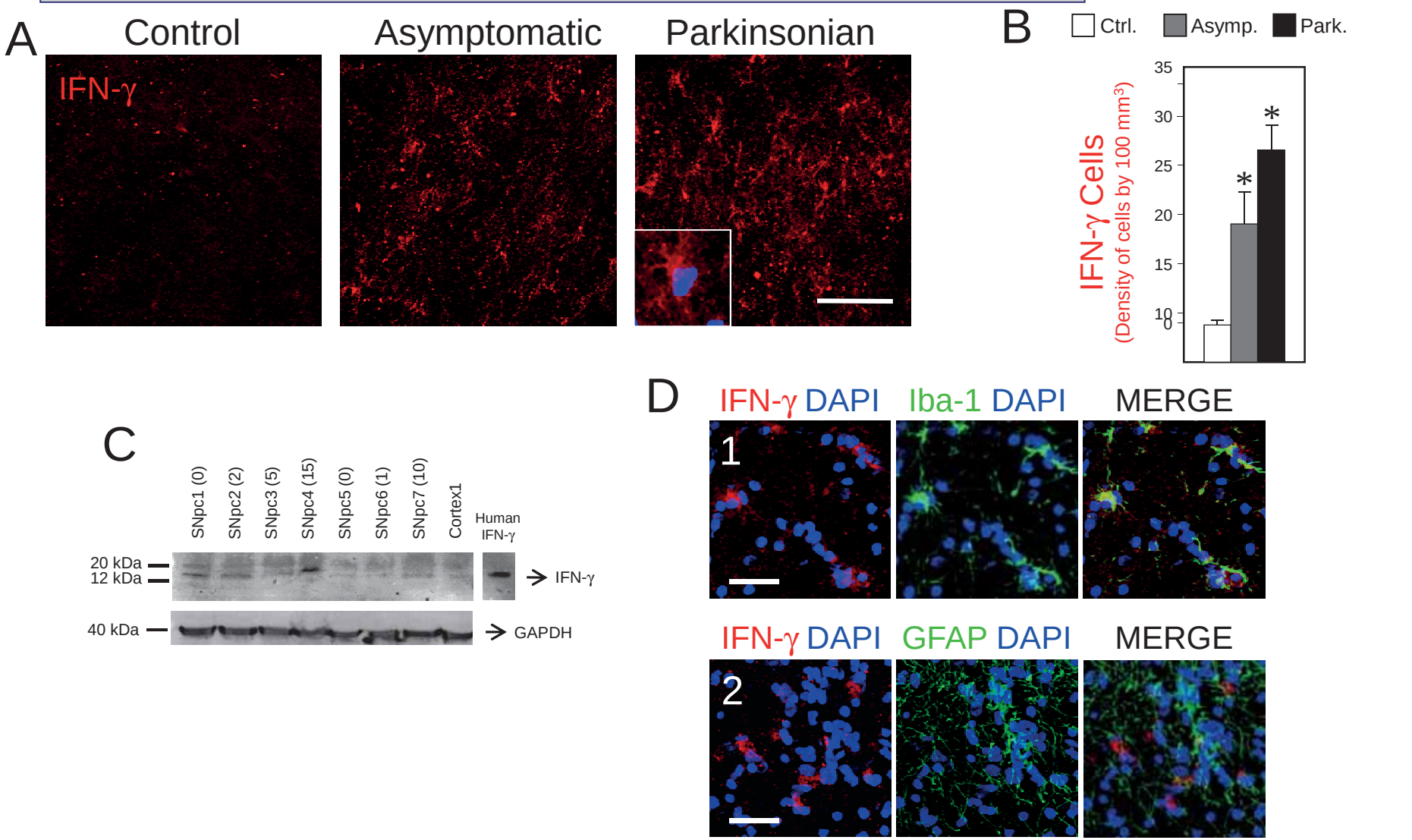
# Niveles séricos de citoquinas



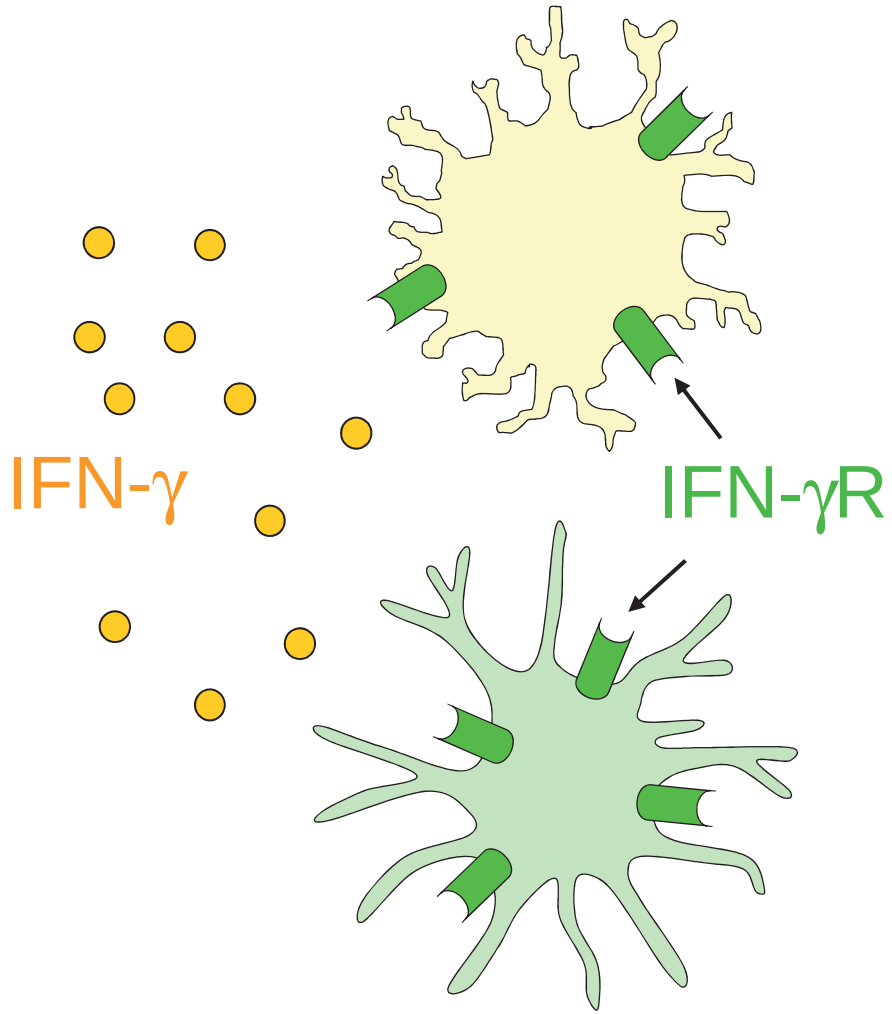
# TNF-α aumentado en monos parkinsonianos



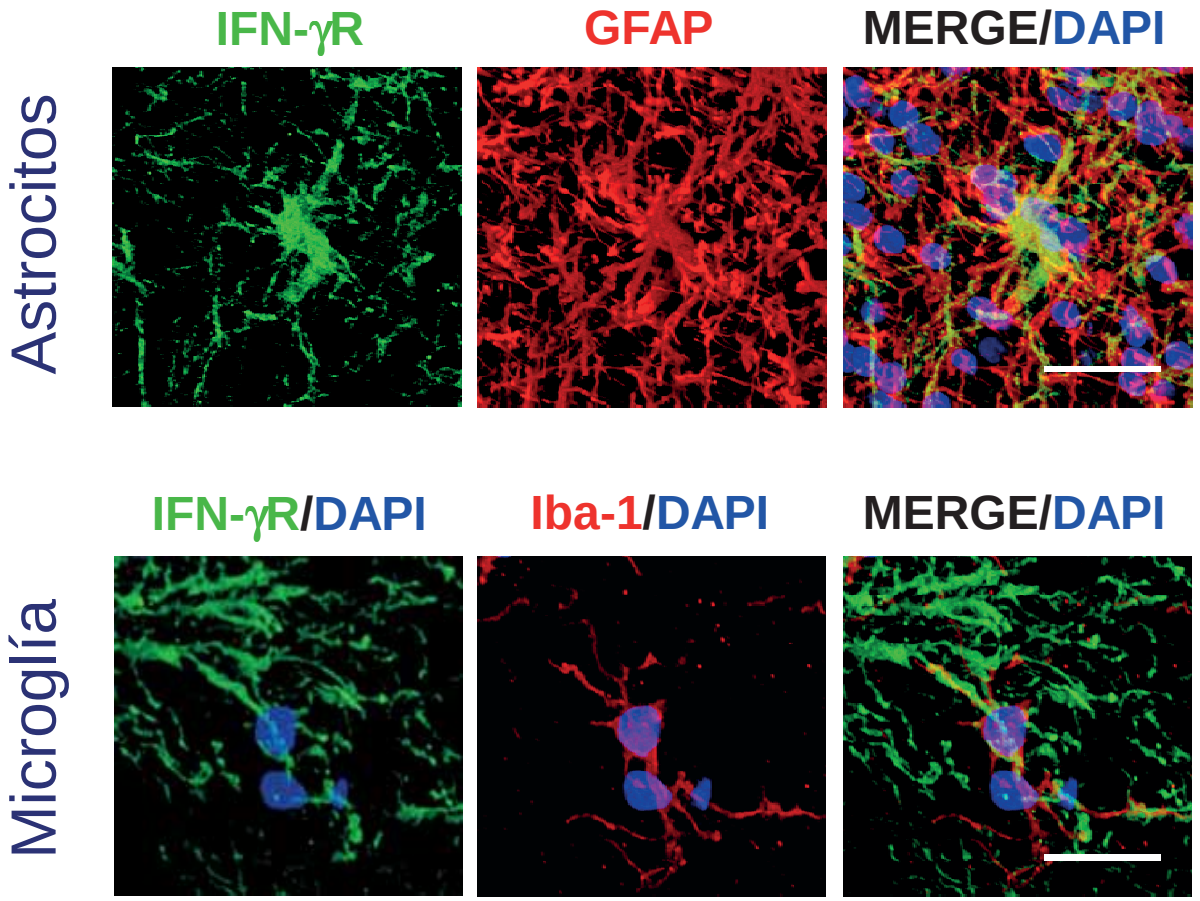
# IFN-γ aumentado en monos parkinsonianos



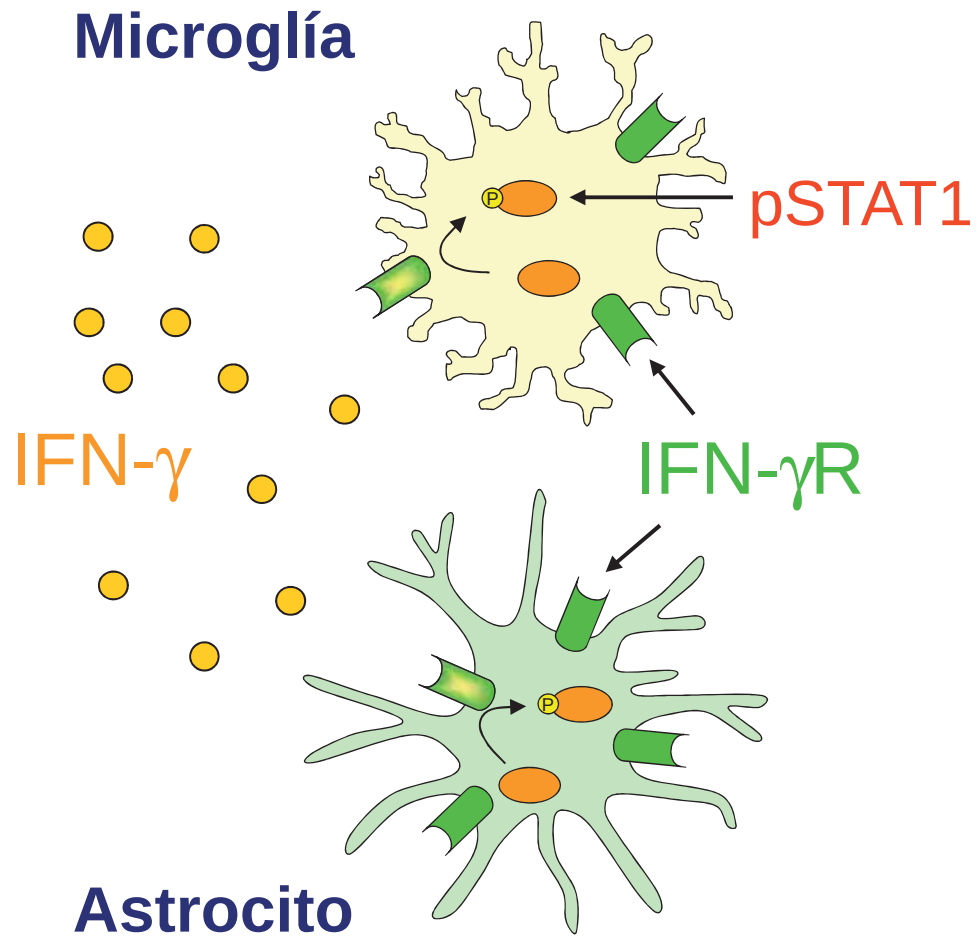
# ¿En que células se expresa el receptor de IFN-γ?



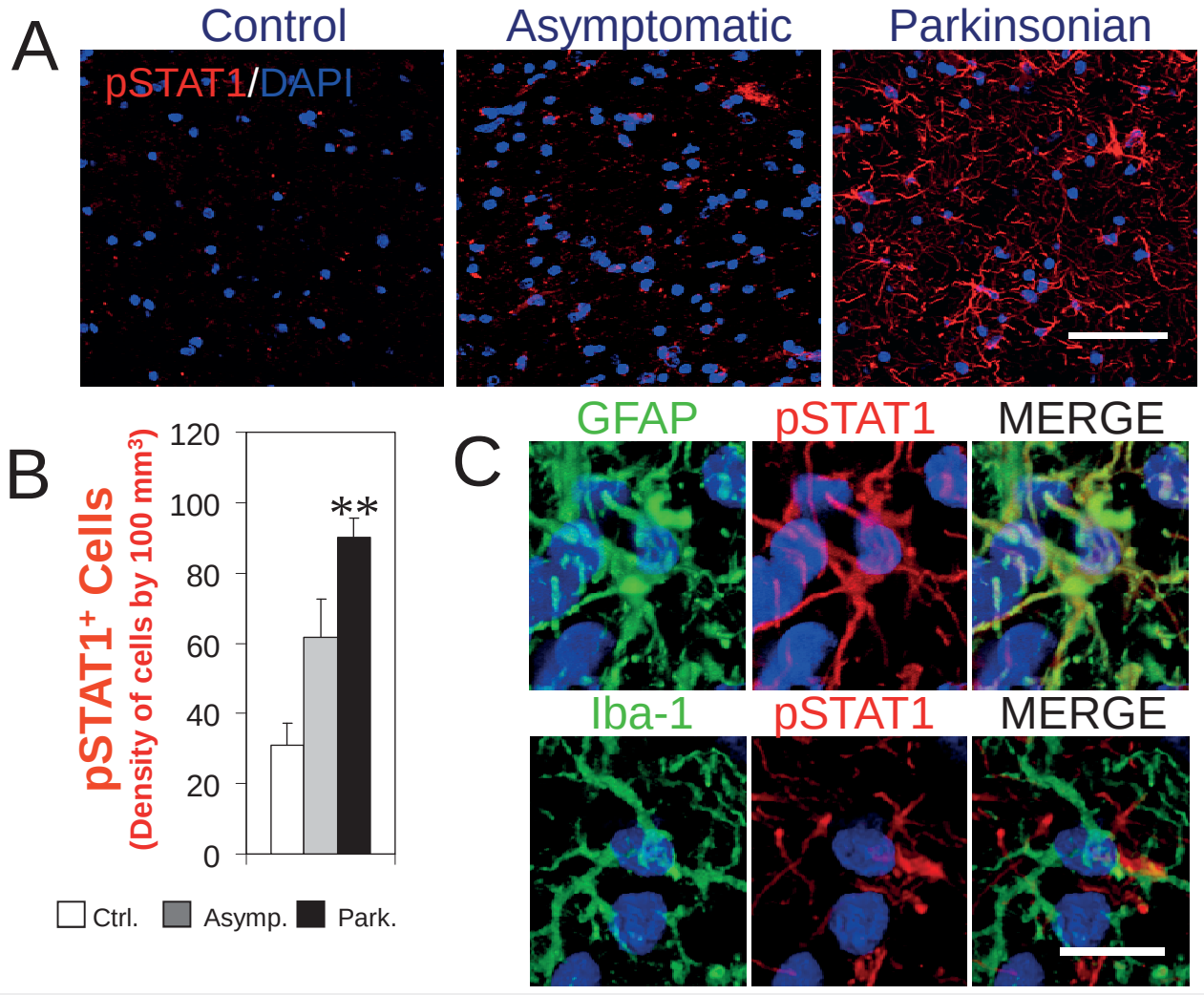
# El receptor de IFN-γ se expresa en microglía y astroglía



# El receptor de IFN-γ se expresa en microglía y astroglía



# La señal de IFN-γ aumenta en los monos parkinsonianos




**STAT1** ➔ member of the Signal Transducers and Activators of Transcription family. It is involved in upregulating genes due to a signal by IFN.

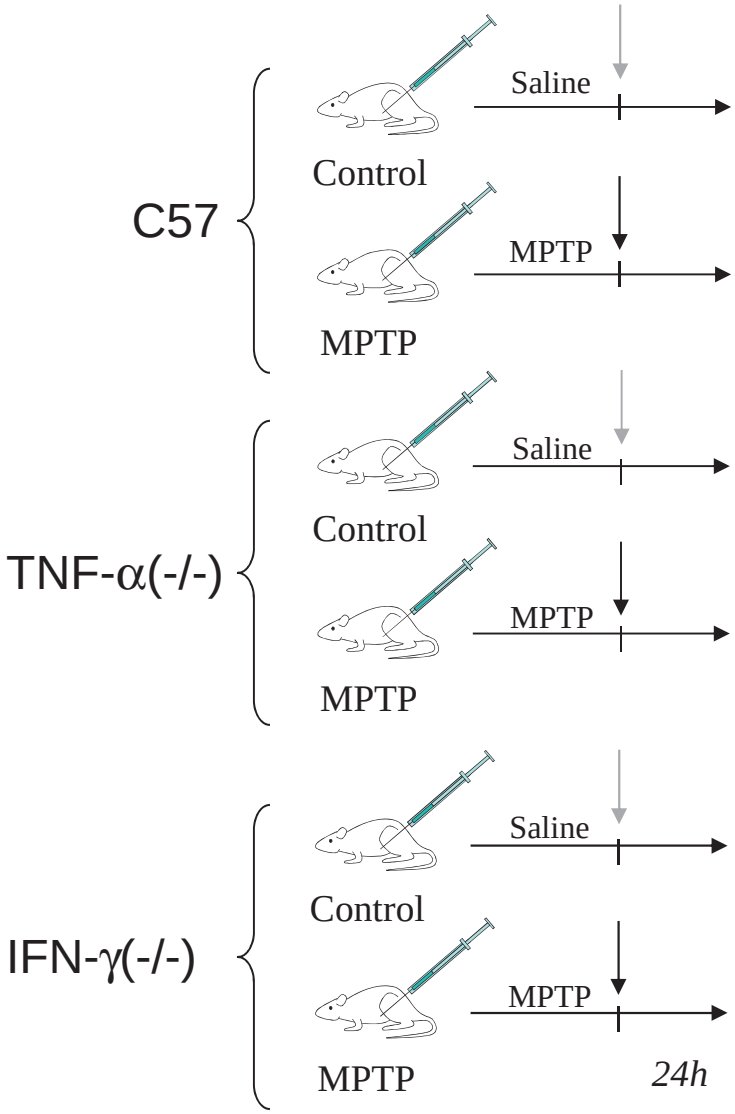
# ¿Cuál es el papel de IFN-γ y TNF-α en la activación glial?

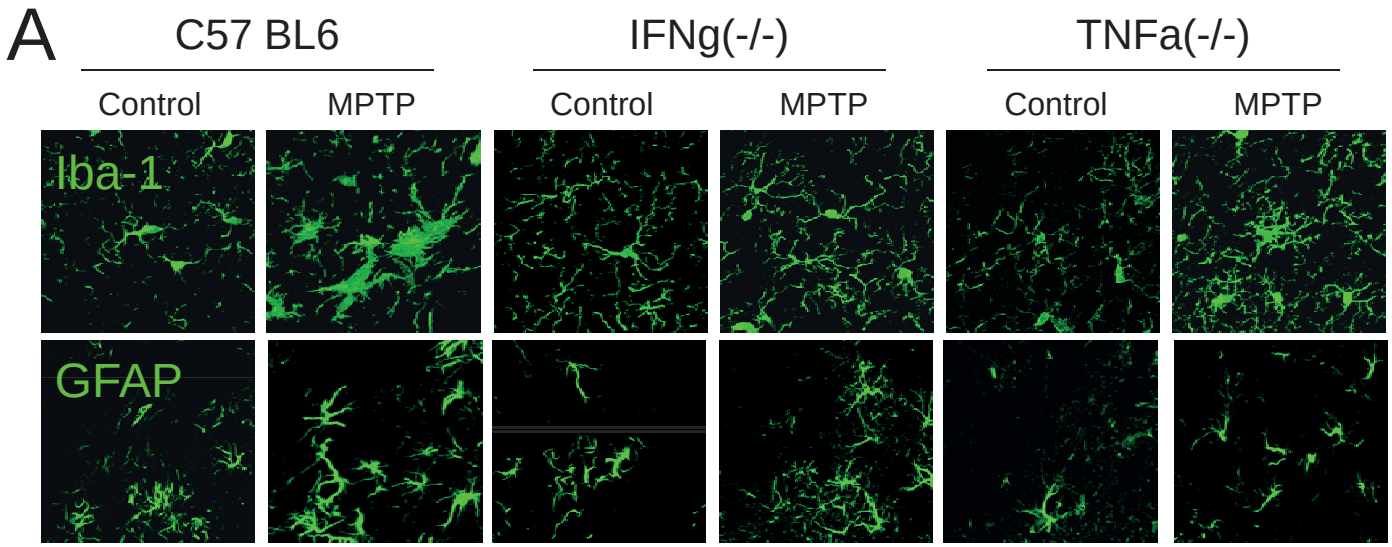
Citation: Cell Death and Disease (2011) 2, e142; doi:10.1038/cddis.2011.17

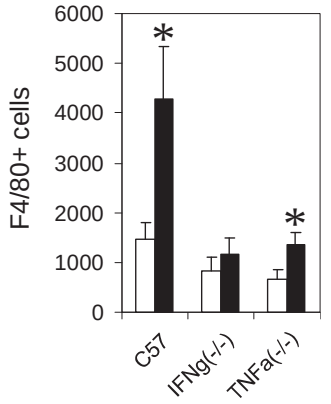
www.nature.com/cddis

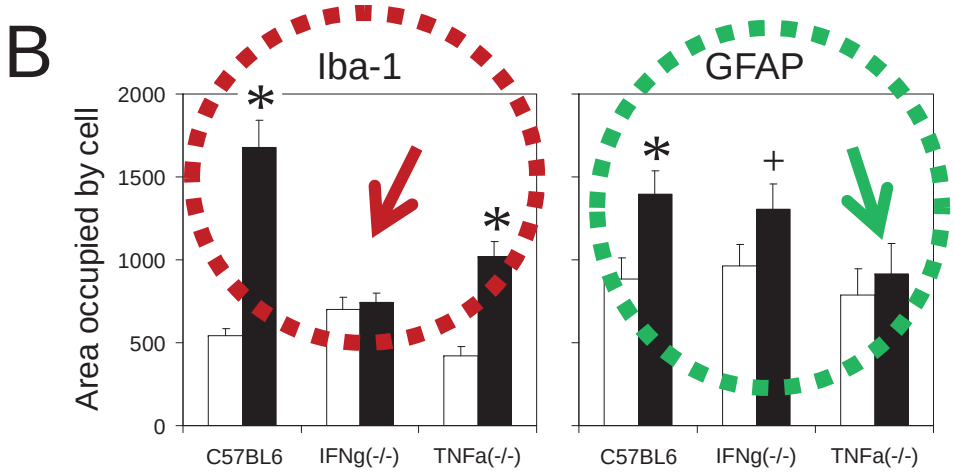
**IFN-γ signaling, with the synergistic contribution of TNF-α, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease**

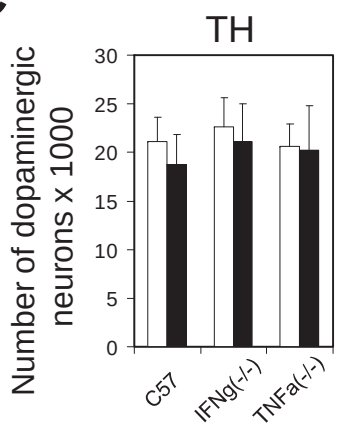
C Barcia[1,2], CM Ros[1,2], V Annese[1,2], A Gómez[1,2], F Ros-Bernal[1,2], D Aguado-Yera[1,2], ME Martínez-Pagán[1], V de Pablos[1,2], E Fernandez-Villalba[1,2] and MT Herrero*[,1,2]

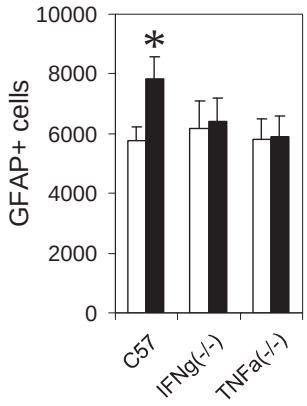

C57
Saline
Control
MPTP
MPTP
TNF-α(-/-)
Saline
Control
MPTP
MPTP
IFN-γ(-/-)
Saline
Control
MPTP
MPTP
24h

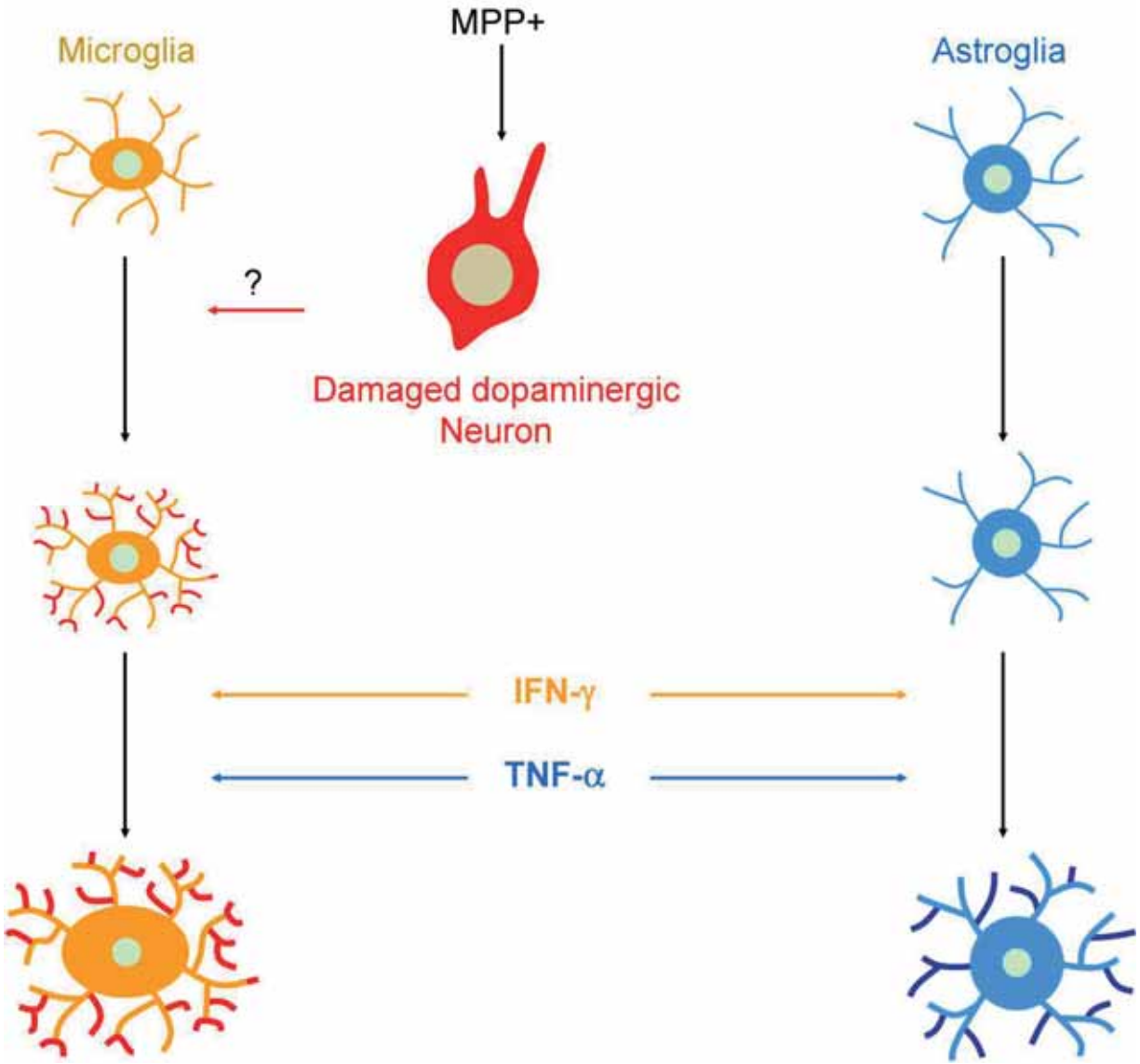

A
C57 BL6
IFNg(-/-)
TNFa(-/-)
Control
MPTP
Control
MPTP
Control
MPTP
Iba-1
GFAP

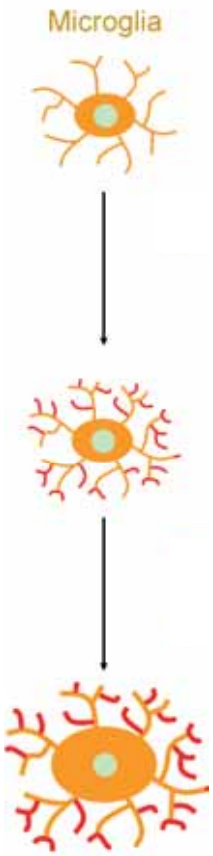

F4/80+ cells
6000
5000
4000
3000
2000
1000
0
C57
IFNg(-/-)
TNFa(-/-)


B
Iba-1
GFAP
Area occupied by cell
2000
1500
1000
500
0
C57BL6
IFNg(-/-)
TNFa(-/-)


C
TH
Number of dopaminergic neurons x 1000
30
25
20
15
10
5
0
C57
IFNg(-/-)
TNFa(-/-)

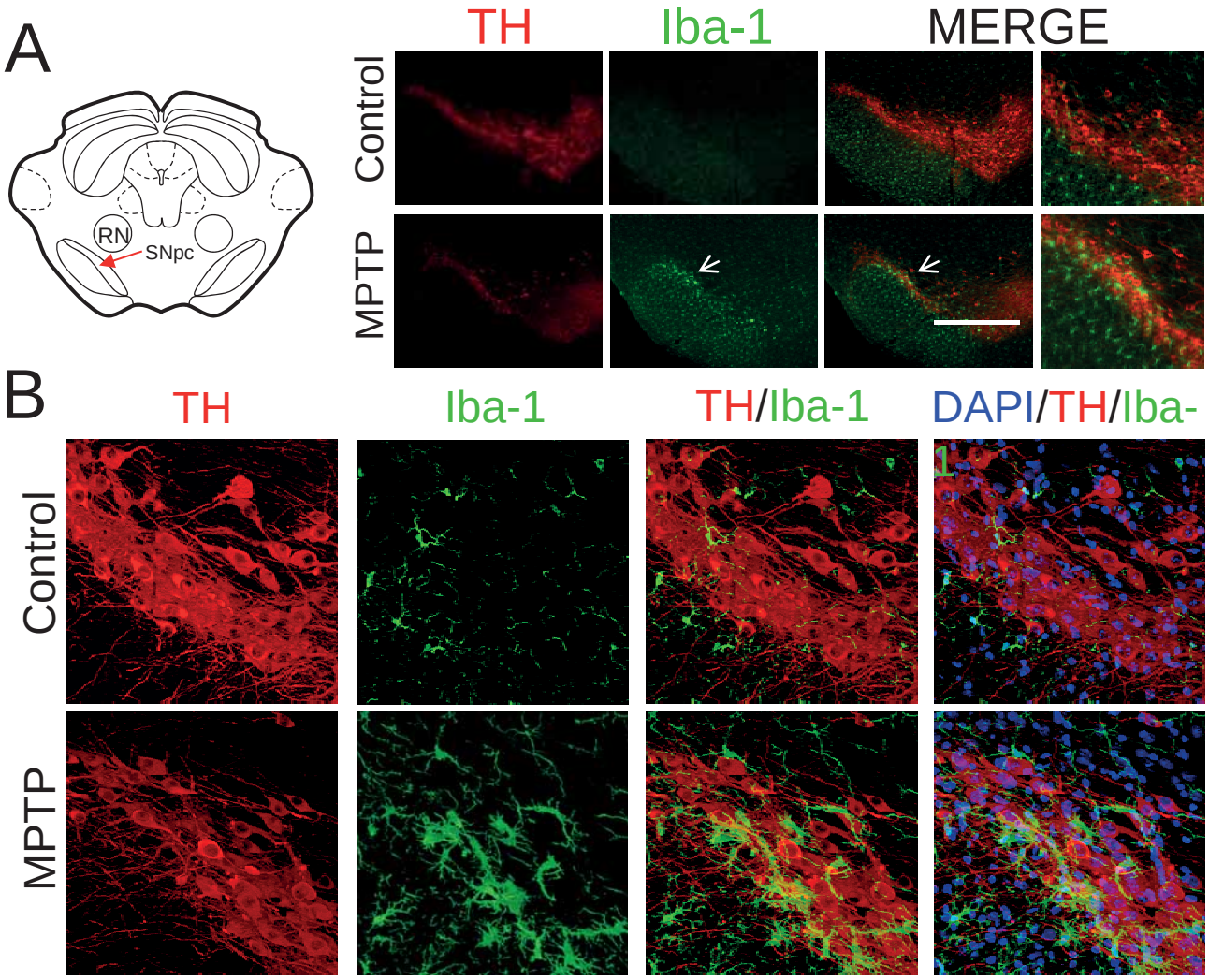

GFAP+ cells
10000
8000
6000
4000
2000
0
C57
IFNg(-/-)
TNFa(-/-)


MPP+
Microglia
Astroglia
?
Damaged dopaminergic
Neuron
IFN-γ
TNF-α

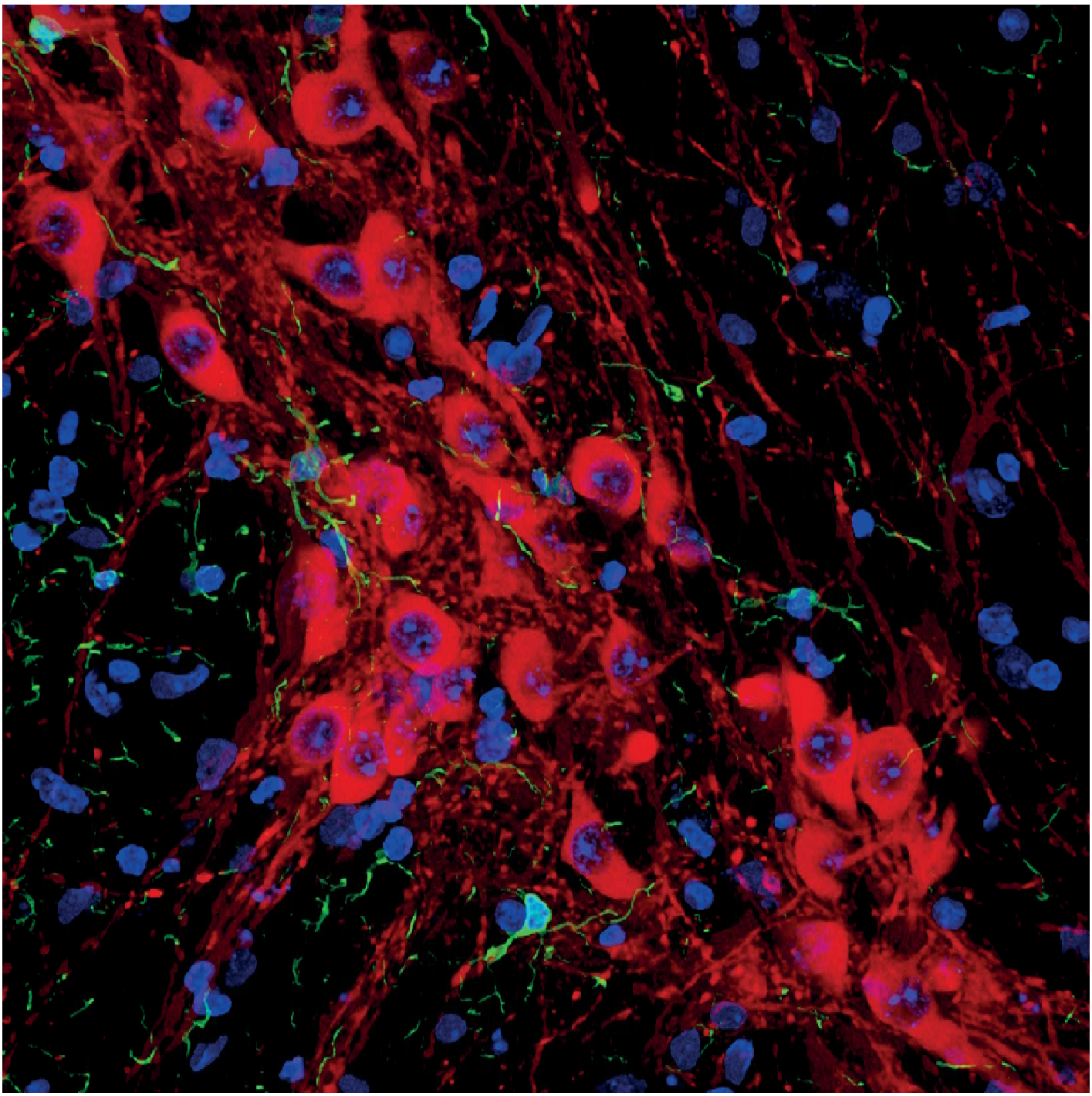



# ¿Cuál es el papel de la microglía en la enfermedad de Párkinson?

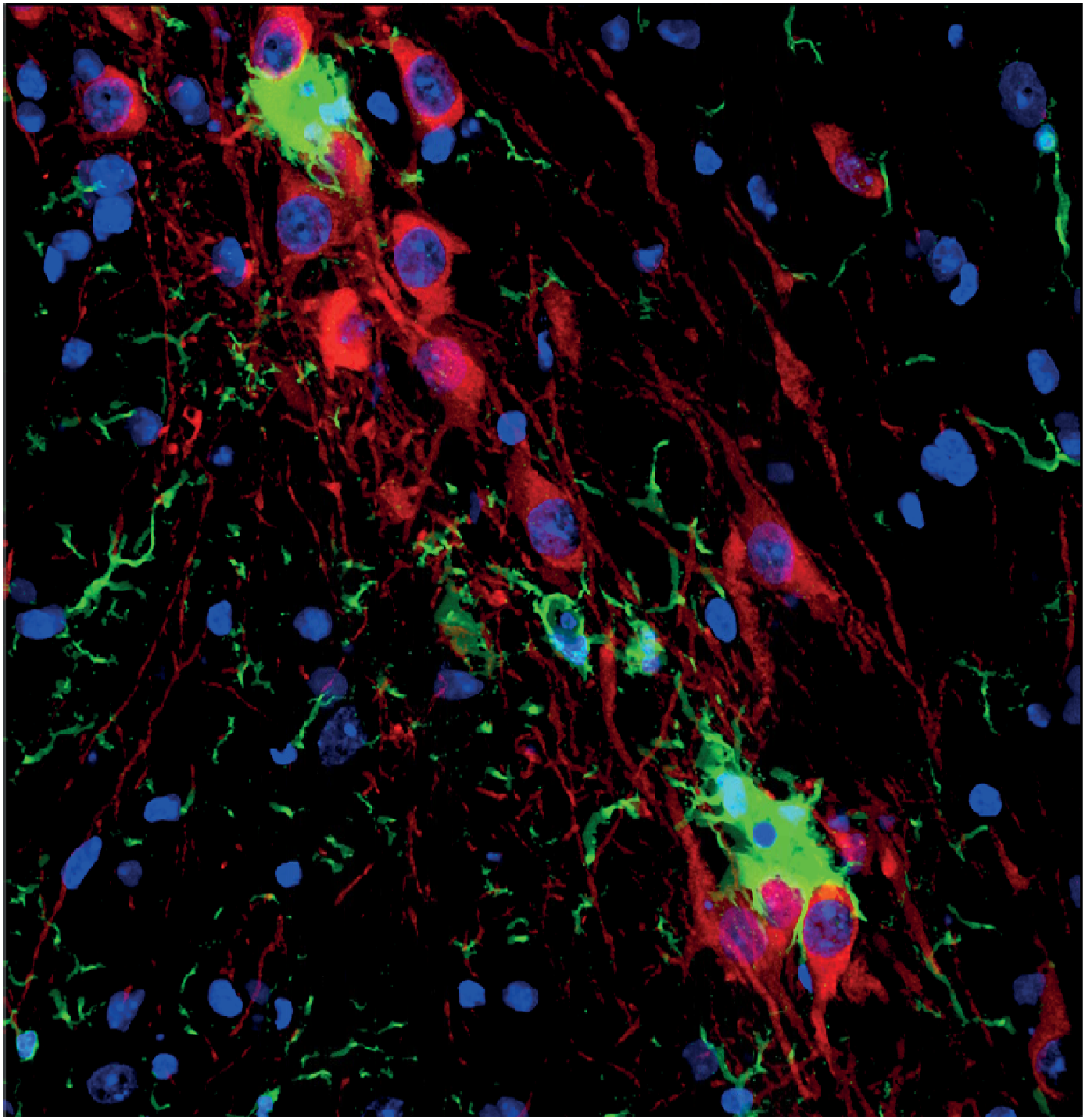
# Activación específica de microglía en ratones parkinsonizados



TH: Dopaminergic  neurons
Iba-1: Microglia
DAPI: Nuclei



TH: Dopaminergic  neurons
Iba-1: Microglia
DAPI: Nuclei



# ¿Es que la microglía hace contactos con las neuronas dopaminérgicas?

# ¿Y aumentan después del tratamiento con MPTP?

SCIENTIFIC REPORTS | 2 : 809 | DOI: 10.1038/srep00809

OPEN

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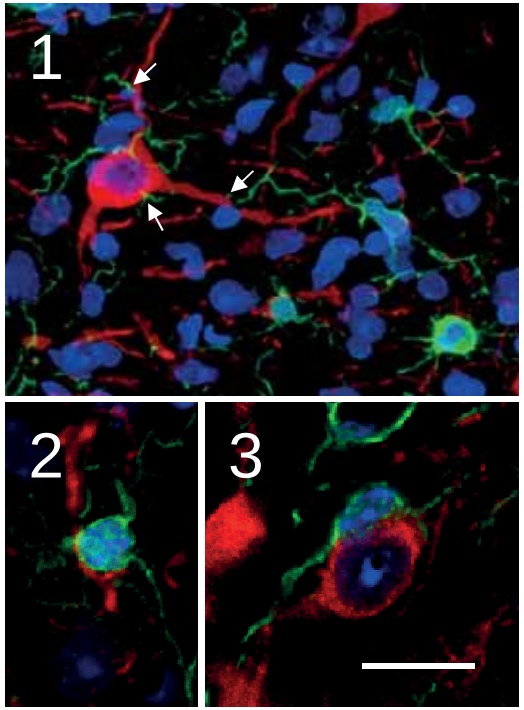
## SI ➔24 h después de la intoxicación con MPTP

## Aumentan los contactos entre las neuronas y la microglía

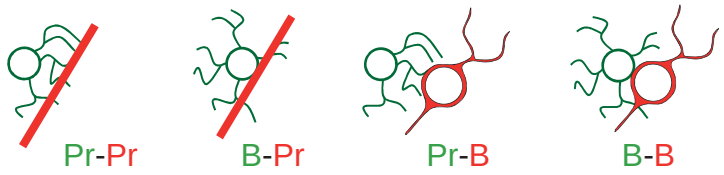
E

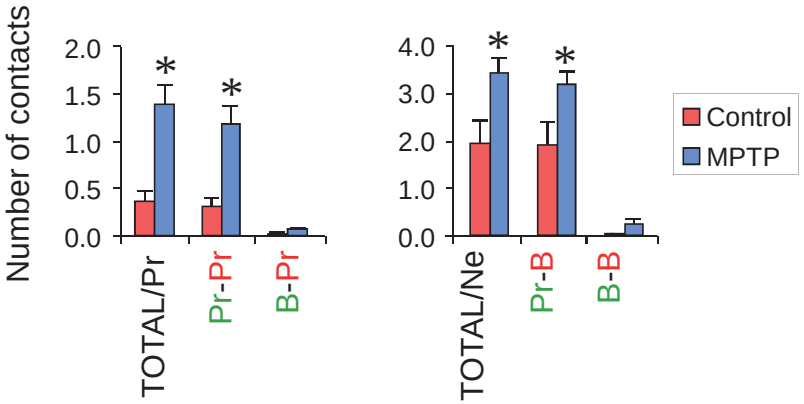
Iba-1/TH/DAPI




F

Microglia/dopaminergic neuron



# ¿Y en el parkinsonismo crónico?

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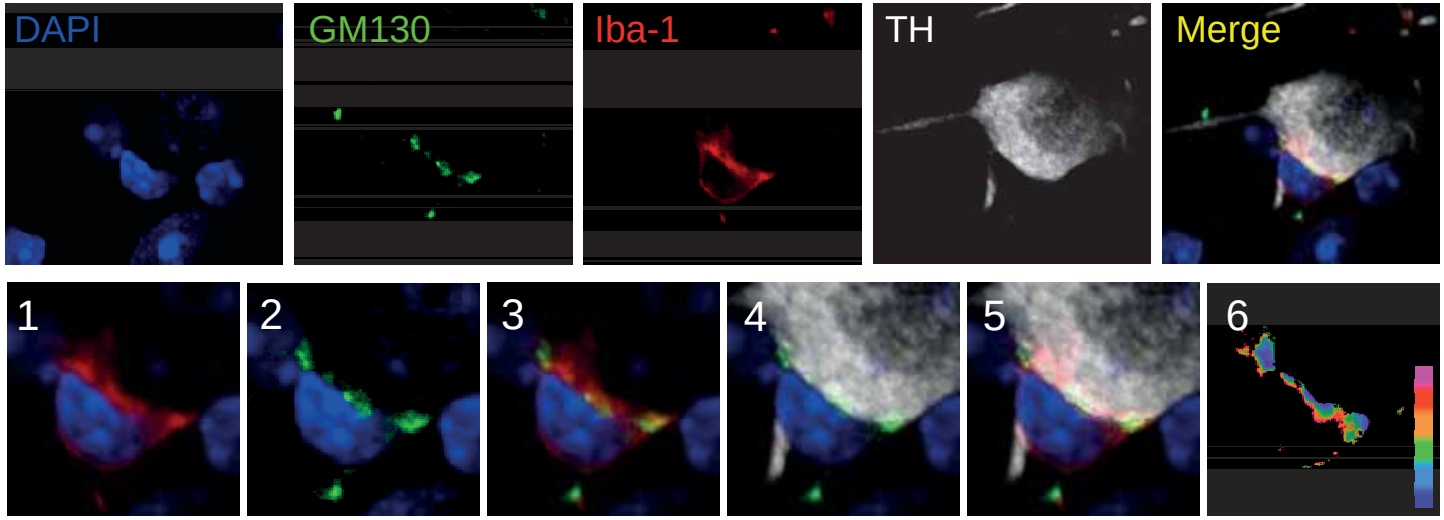
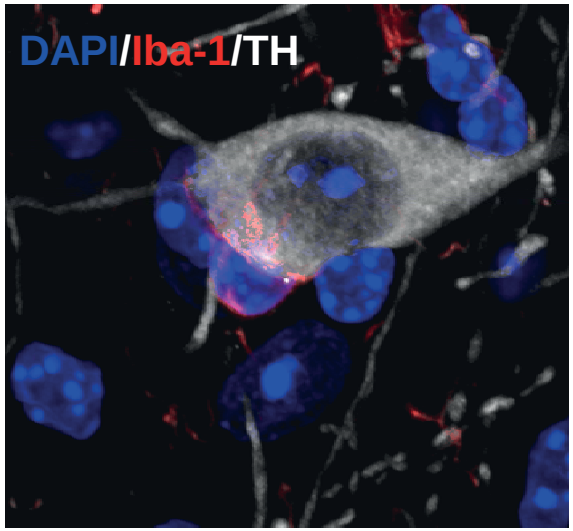
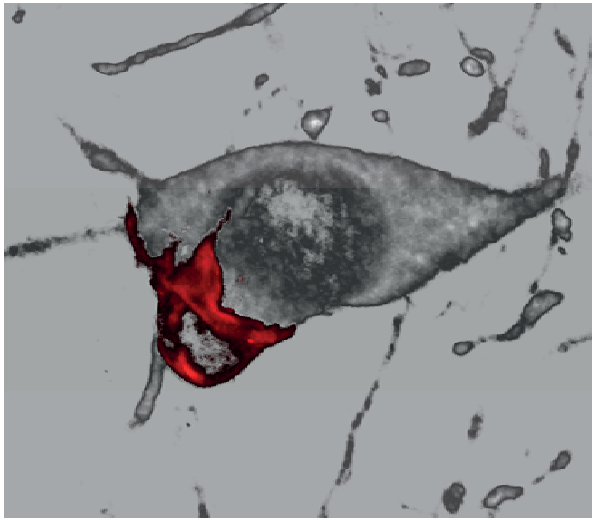
# GLIAPSIS: contactos microglía-neurona

Gliapse 1

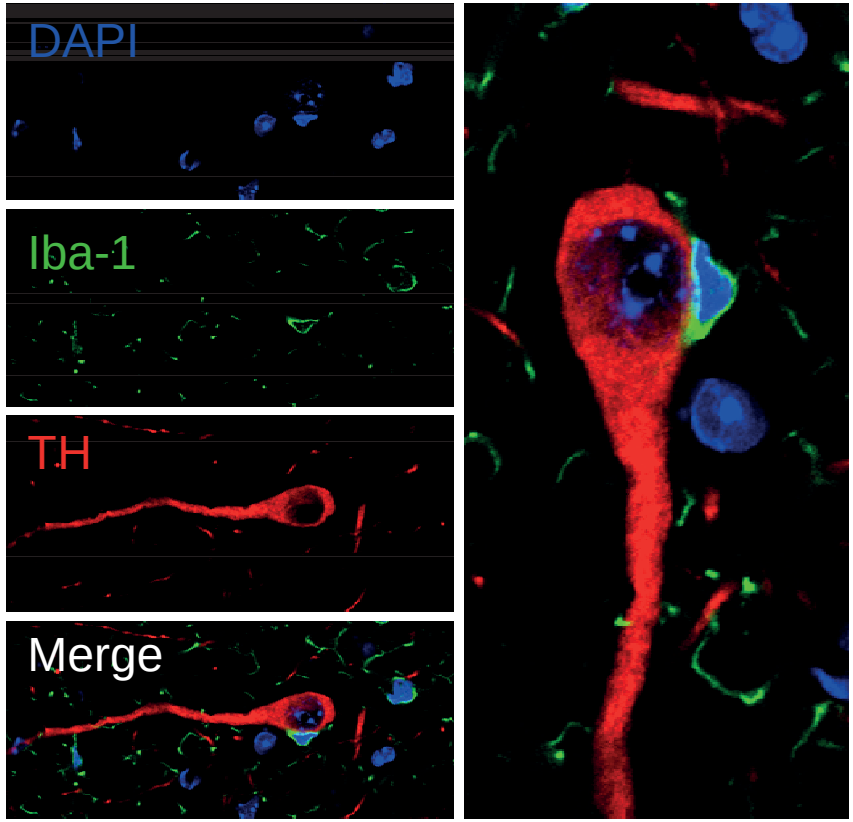


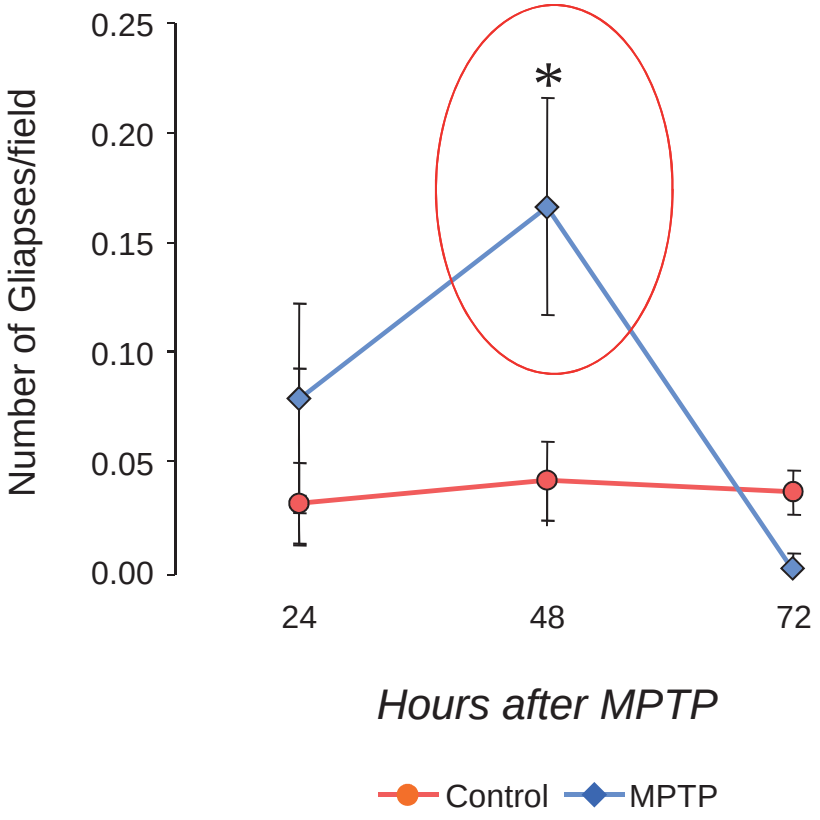



Iba-1/TH

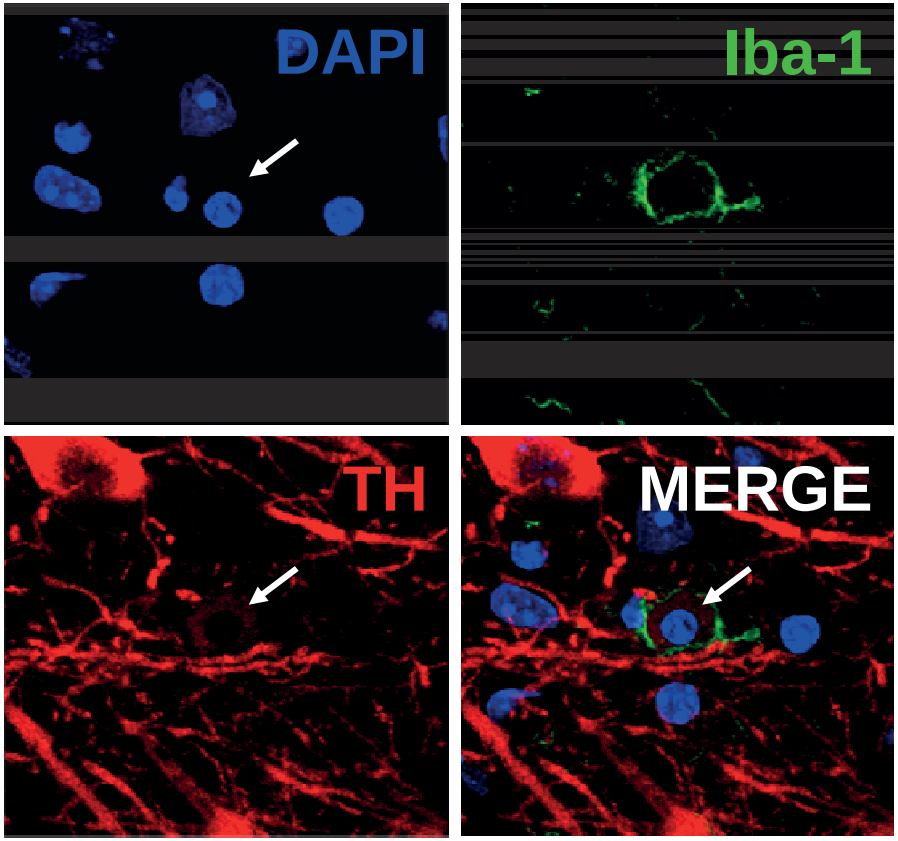
# GLIAPSIS: contactos microglía-neurona preceden a la muerte neuronal y fagocitosis

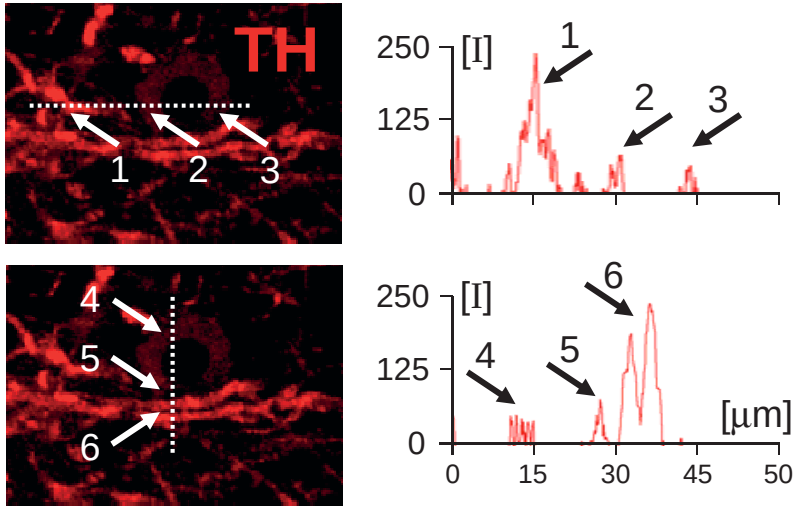


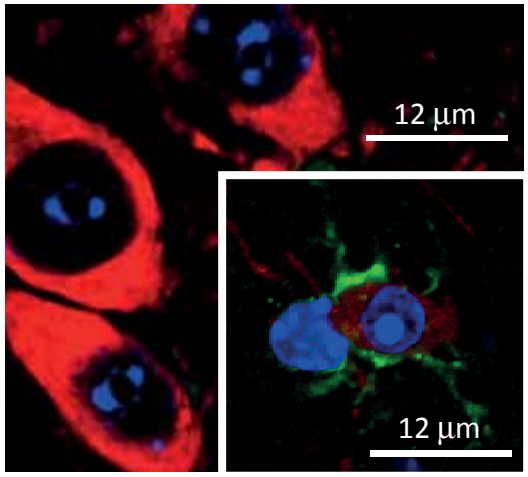
# ¿Se polariza la microglía?

# ¿Por qué?



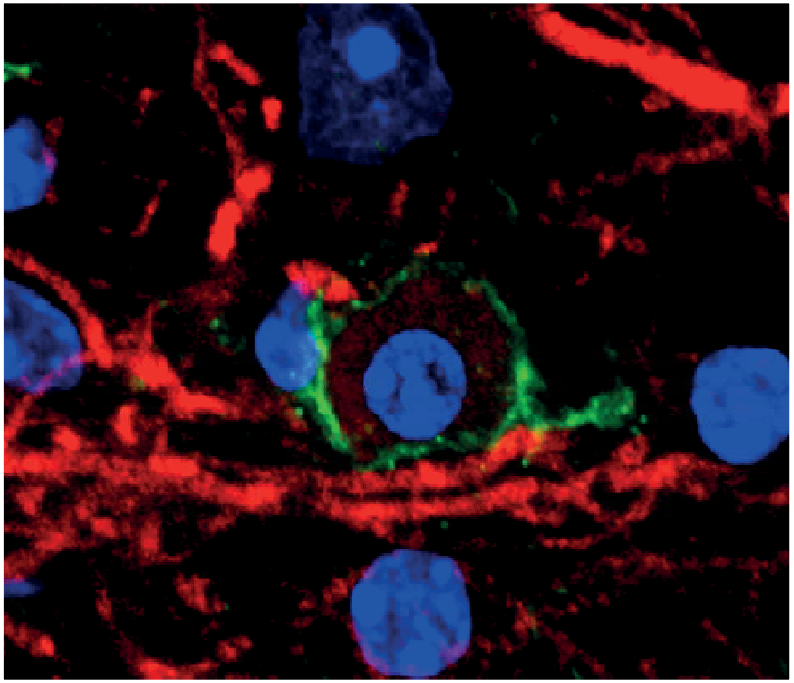



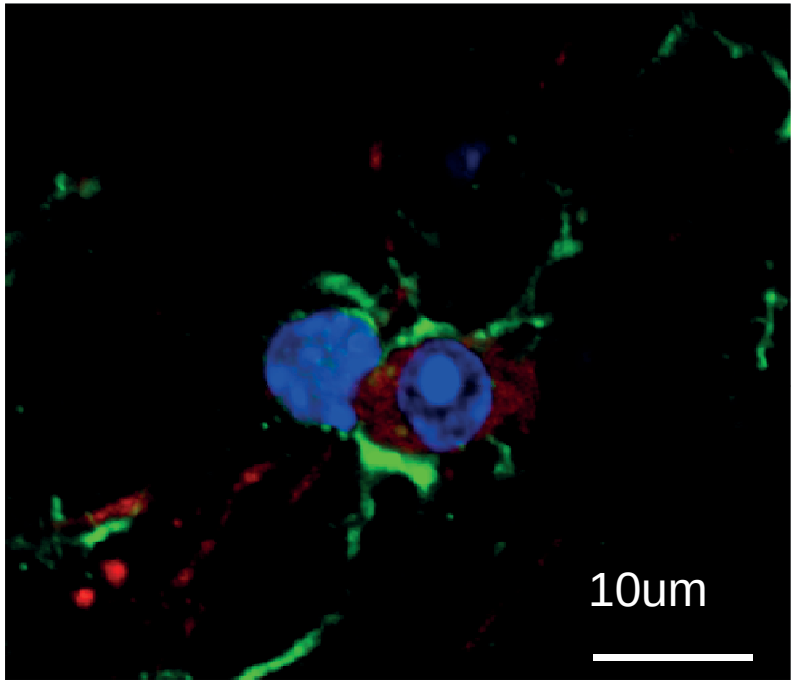

TH/Iba-1/DAPI




## Después de la intoxicación con MPTP se produce fagocitosis

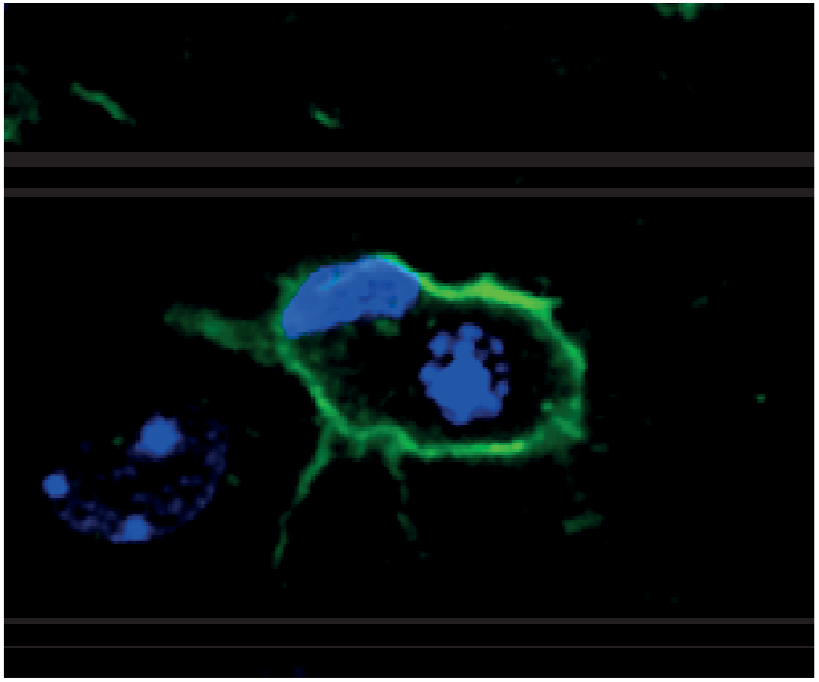
# Después de la intoxicación con MPTP se produce fagocitosis

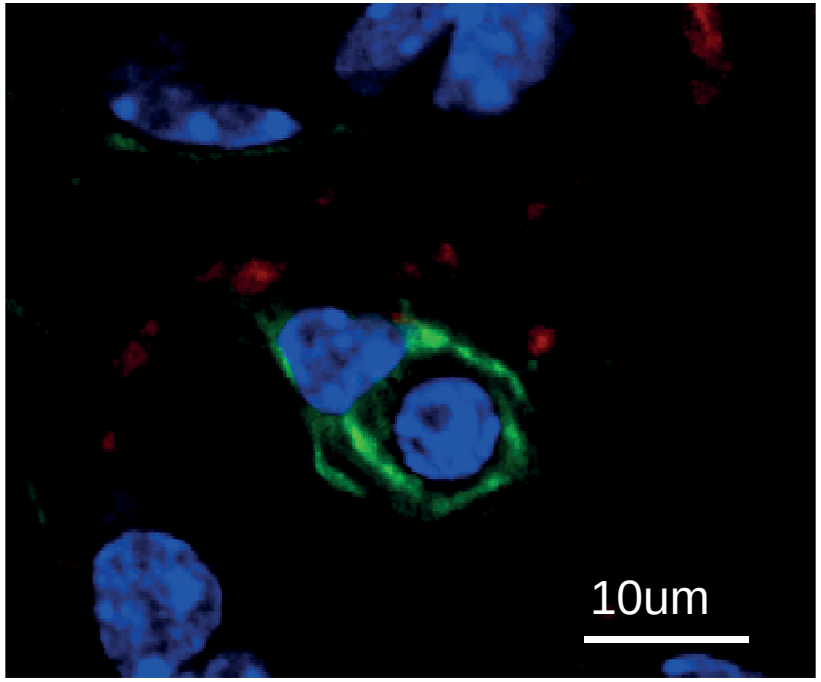





**TH/Iba-1/DAPI**

# Después de la intoxicación con MPTP se produce fagocitosis

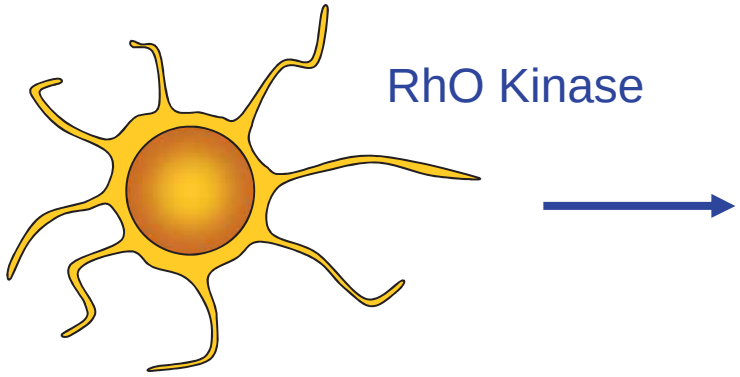




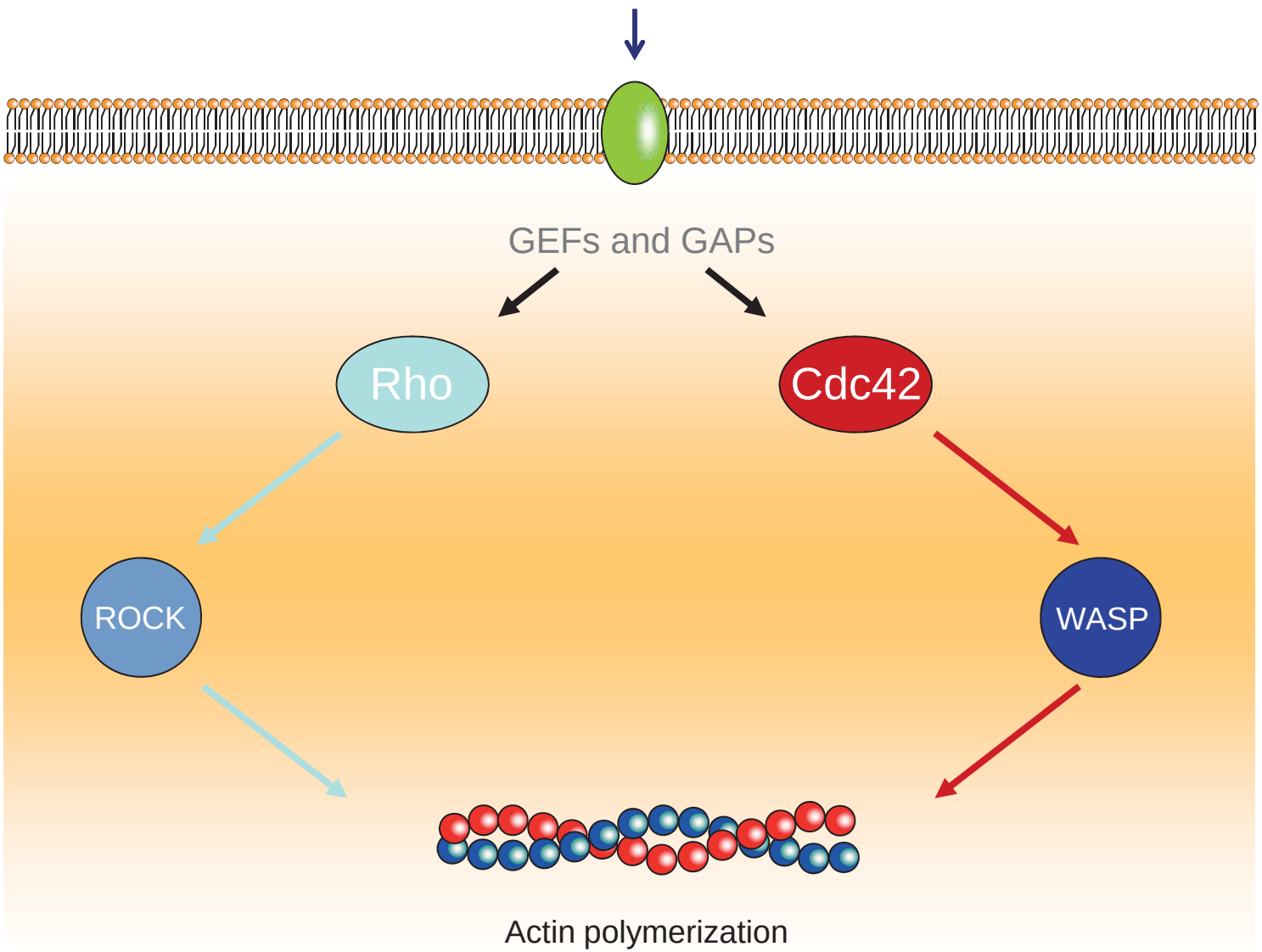

**TH/Iba-1/DAPI**

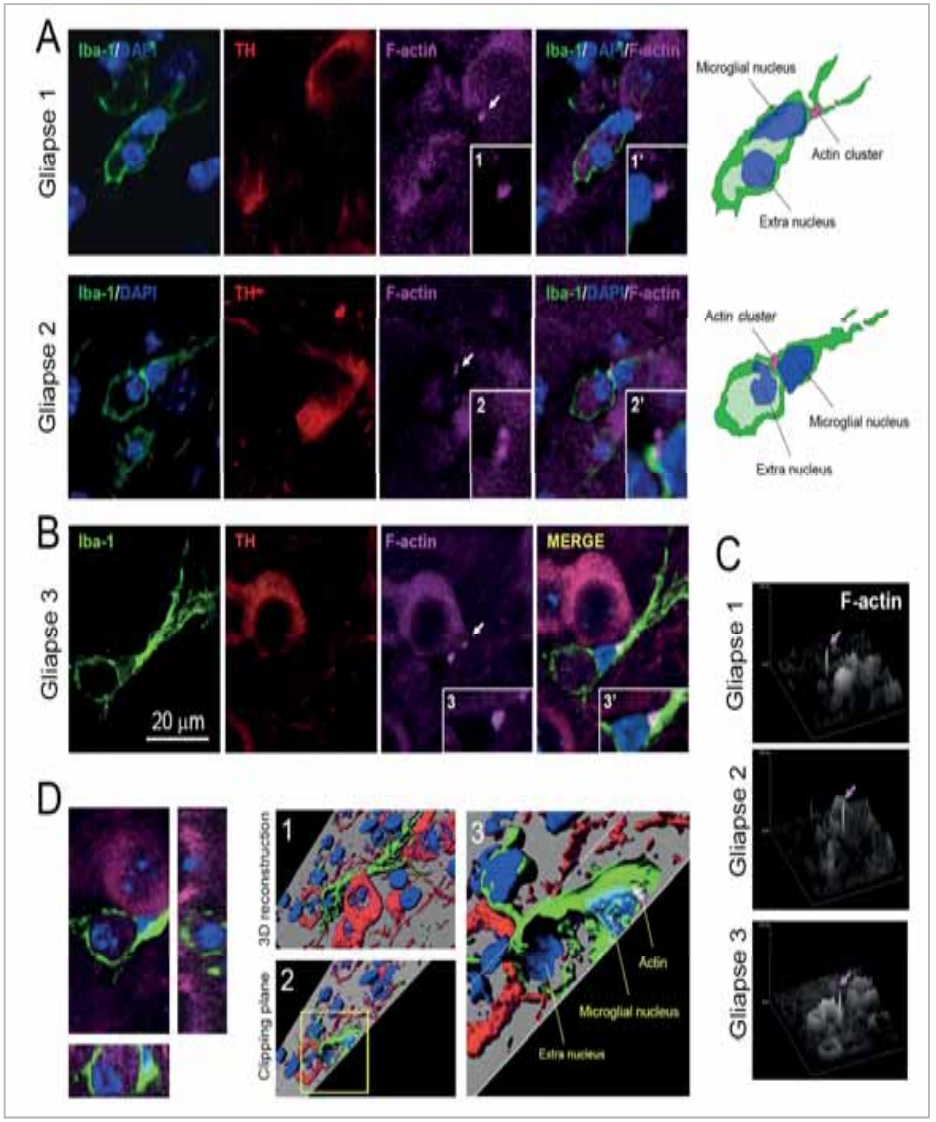
# Para fagocitar neuronas,

# la microglía debe polarizarse




## ¿Y si bloqueamos la polarización?


Signal
GEFs and GAPs
Rho
Cdc42
ROCK
WASP
Actin polymerization

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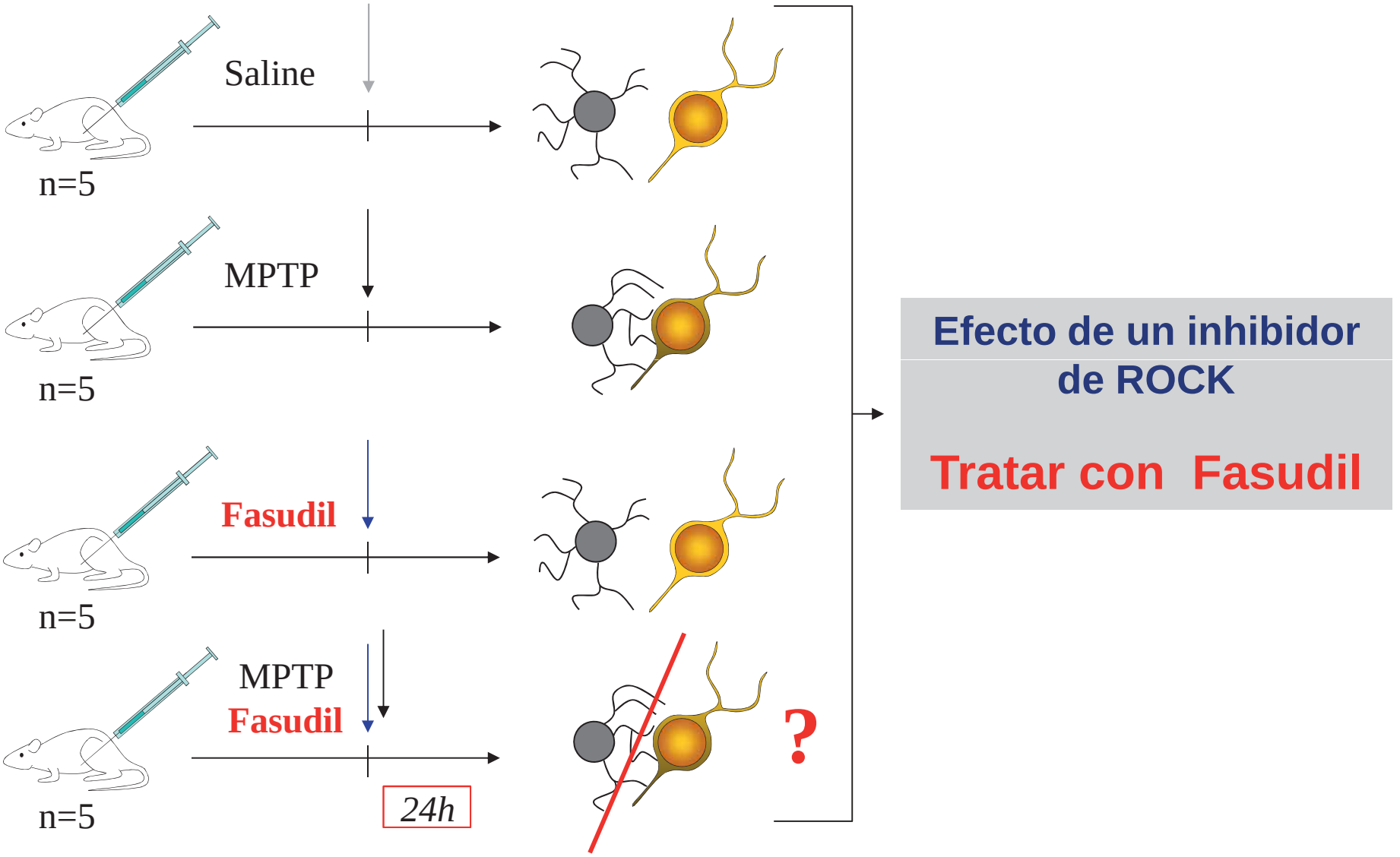
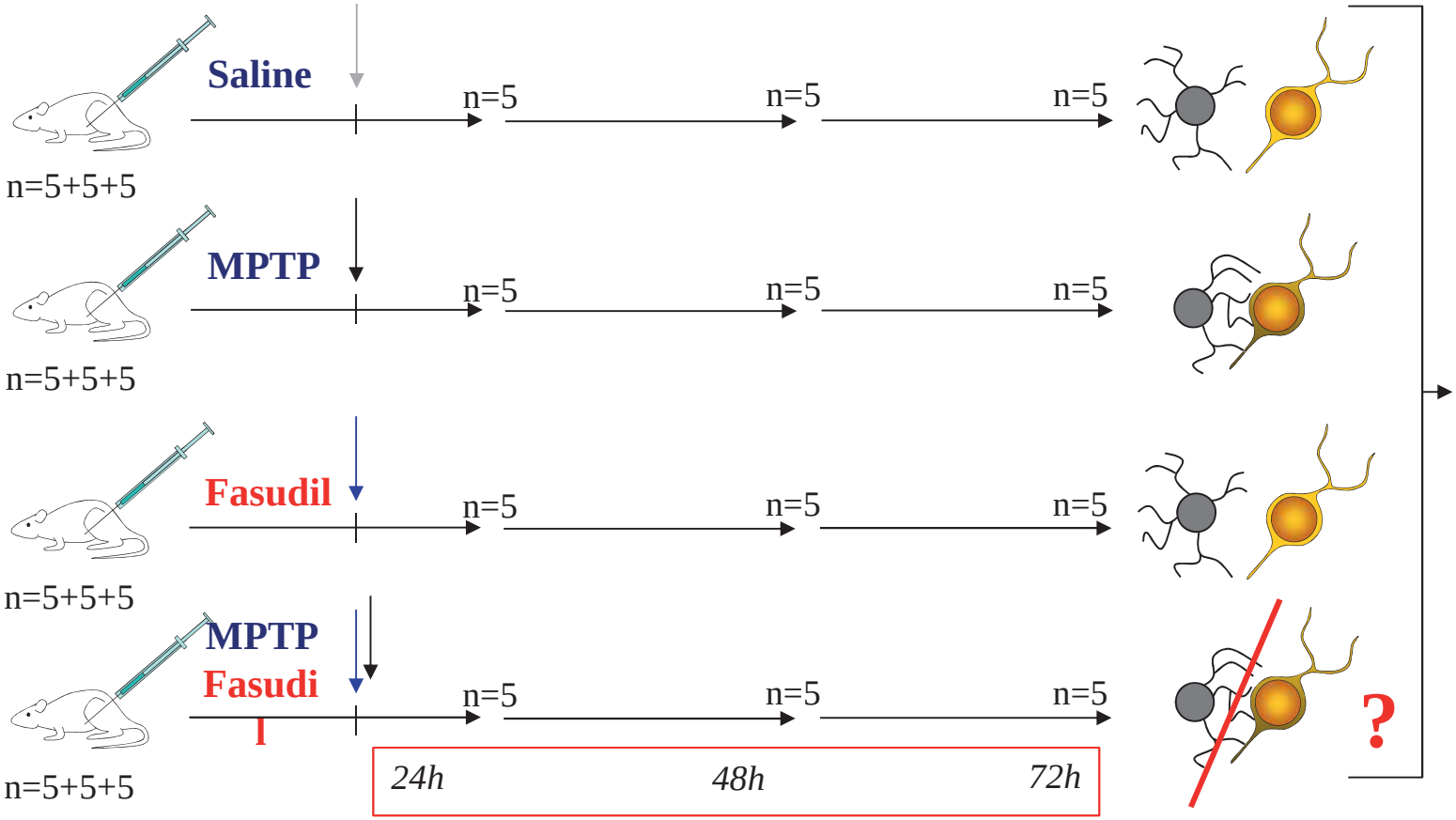
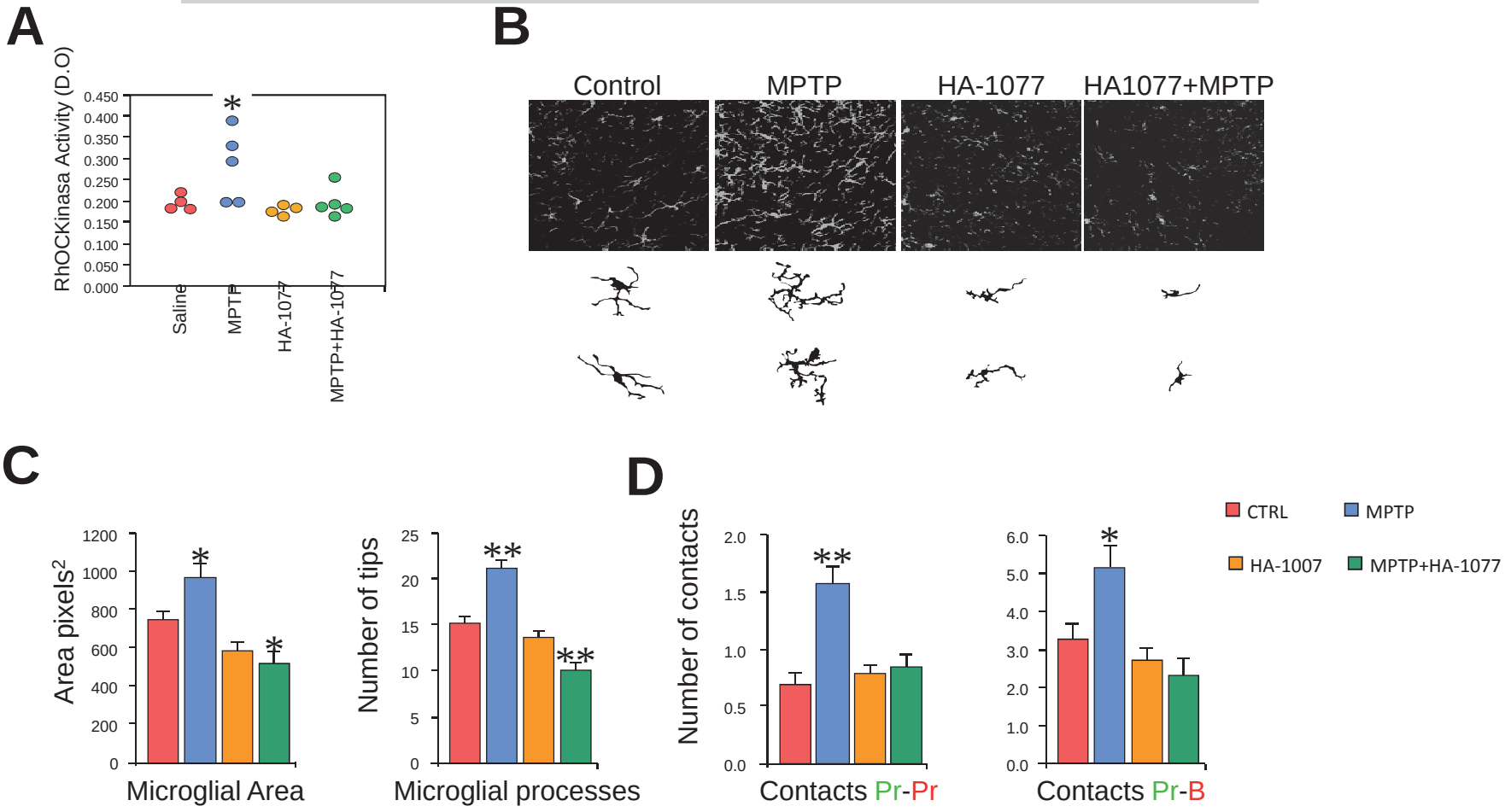
## ROCK media:

1. la motilidad de la Microglía
2. la formación de Gliapsis
3. la fagocitosis

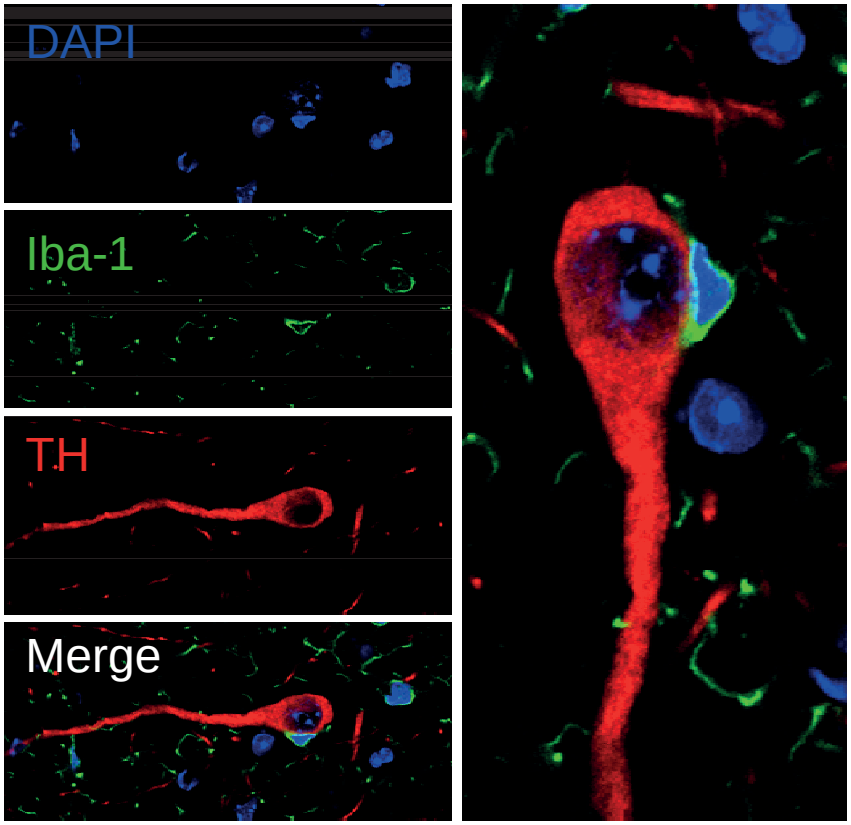

Saline
n=5
MPTP
n=5
Fasudil
n=5
MPTP
Fasudil
24h
n=5
?
Efecto de un inhibidor de ROCK
Tratar con Fasudil

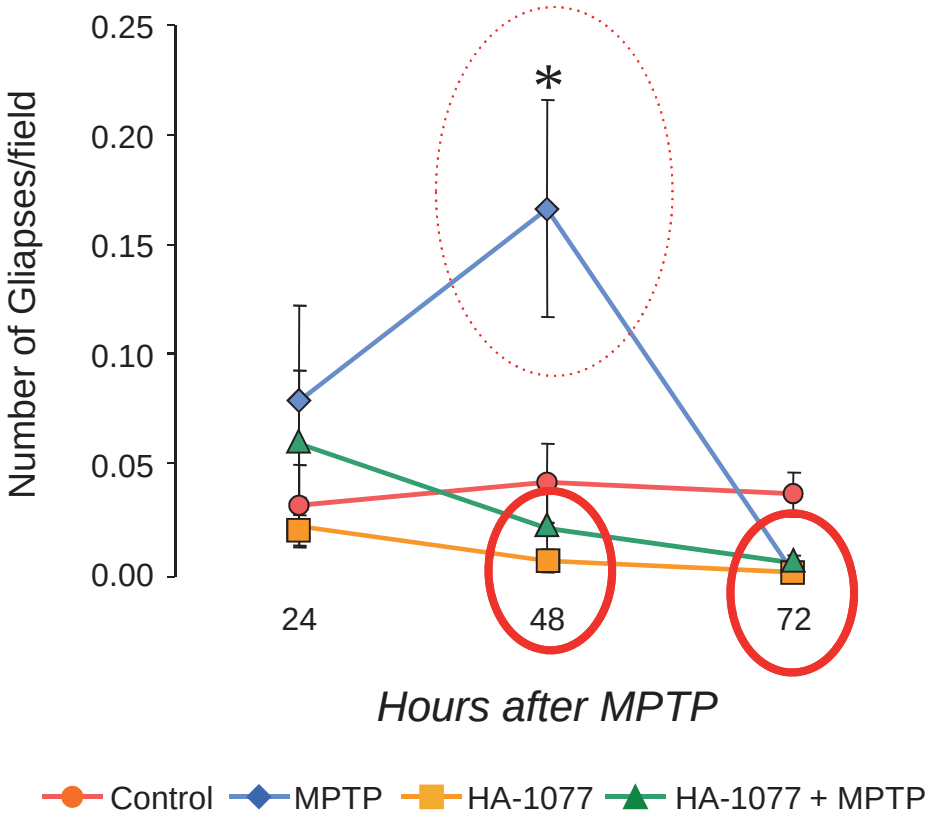

Saline
n=5
n=5
n=5
n=5+5+5
MPTP
n=5
n=5
n=5
n=5+5+5
Fasudil
n=5
n=5
n=5
n=5+5+5
MPTP
Fasudi
l
n=5
n=5
n=5
n=5+5+5
24h
48h
72h
?

# Fasudil (HA-1077 / inhibidor de ROCK)
## bloquea la polarización de la microglía

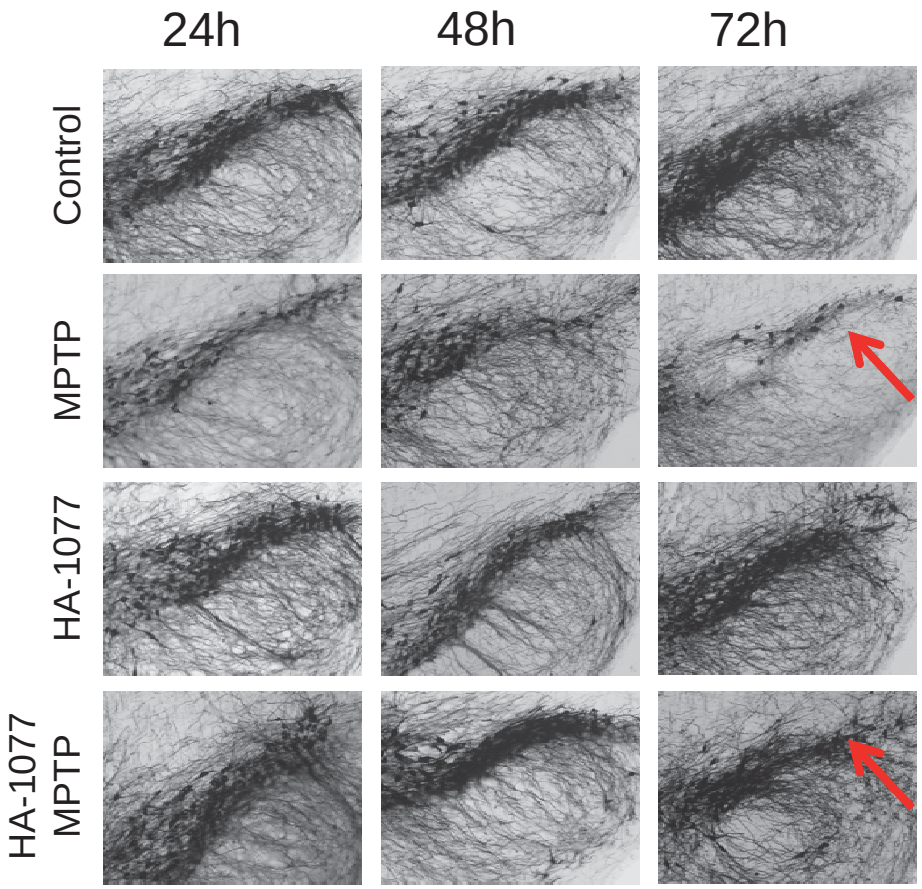


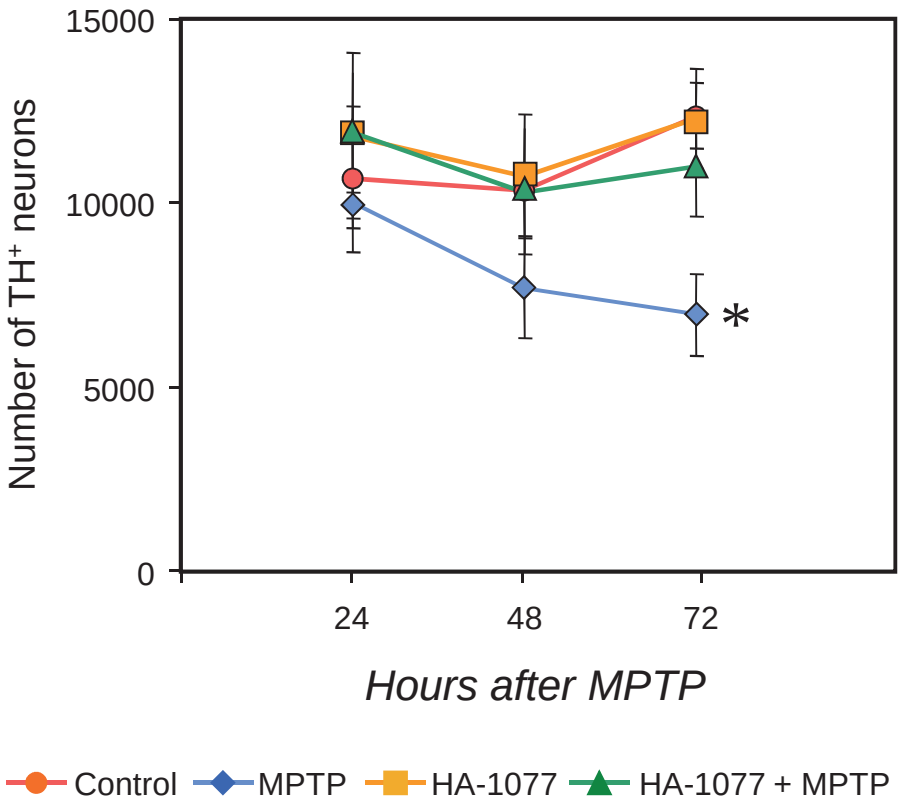
# Fasudil (HA-1077 / inhibidor de ROCK)
## disminuye el número de GLIAPSIS



# Fasudil (HA-1077 / inhibidor de ROCK) previene la muerte de neuronas dopaminérgicas tras intoxicación con MPTP



1. La microglía se polariza hacia las neuronas dopaminérgicas tras el tratamiento con MPTP **por un mecanismo dependiente de ROCK**.

1. Tras el tratamiento con MPTP la polarización microglial aumenta la formación de **contactos glia-neurona (gliapsis)** que preceden a la muerte neuronal dopaminérgica.

1. Las neuronas **dopaminérgicas dañadas son fagocitadas por células microgliales**.

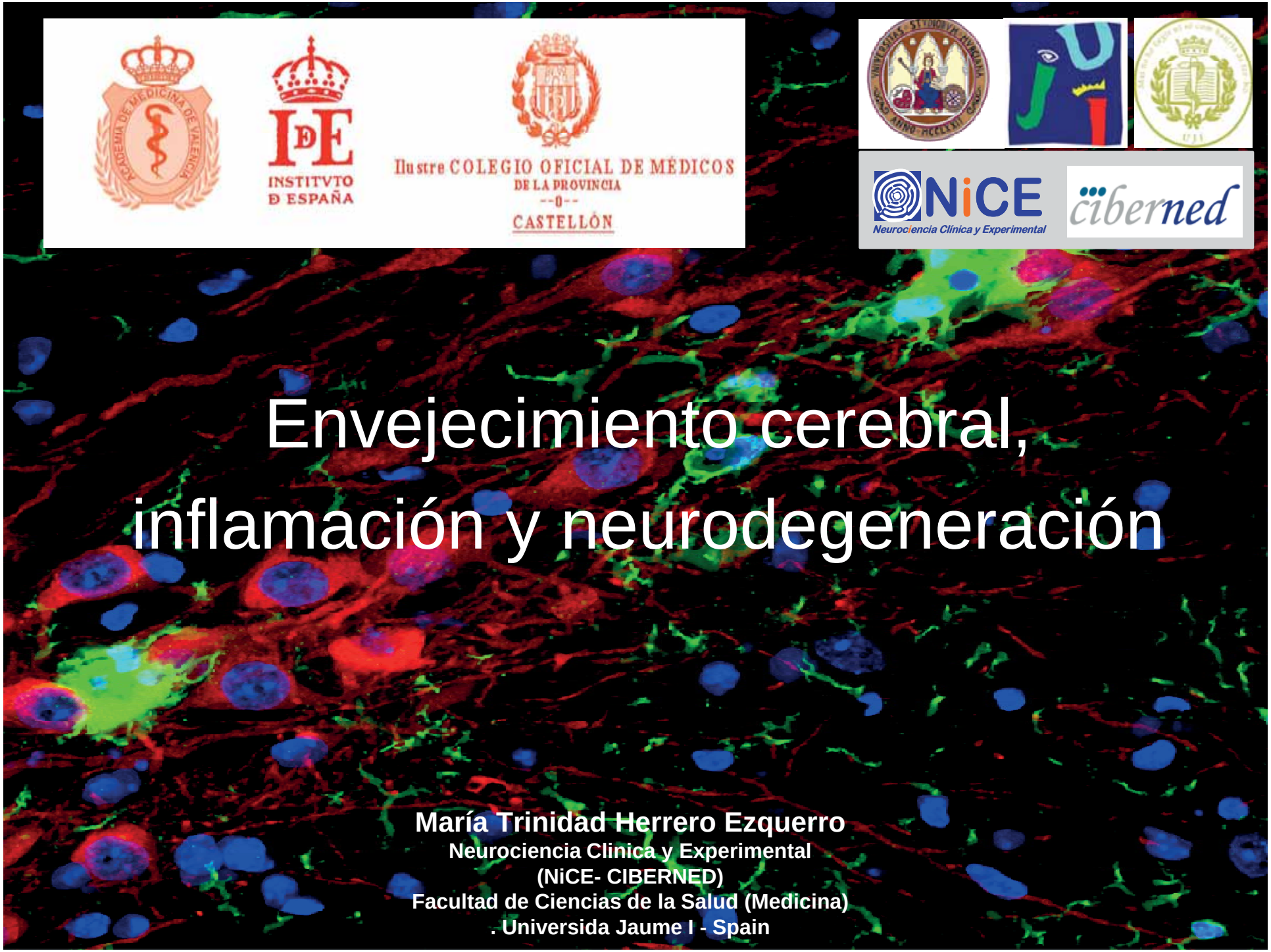
1. El **tratamiento con Fasudil** inhibe la polarización y la muerte dopaminérgica.

1. Esta estrategia podría ser beneficiosa para mantener las neuronas dopaminérgicas en la enfermedad de Párkinson y **prevenir efectos deletéreos asociados a envejecimiento cerebral fisiológico**.

**Nunca olvidamos que nosotros trabajamos por los pacientes, para mejorar su calidad de vida**


***La esperanza tiene formas redondeadas***
***Tremendos laberintos entre nueve letras***
***Un sinfín de contrariedades***
***Y vueltas al punto placentero***

**José María Delgado García**



# Envejecimiento cerebral, inflamación y neurodegeneración

**María Trinidad Herrero Ezquerro**
**Neurociencia Clinica y Experimental**
**(NiCE- CIBERNED)**
**Facultad de Ciencias de la Salud (Medicina)**
**. Universida Jaume I - Spain**