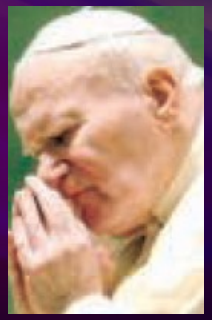
pietro.cortelli@unibo.it

IRCCS Istituto delle Scienze Neurologiche di Bologna
DIBINEM, Alma Mater Studiorum - Università di Bologna

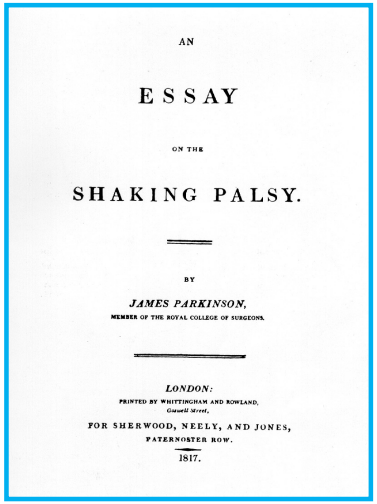
I disturbi Motori e Non Motori








Parkinson's disease


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

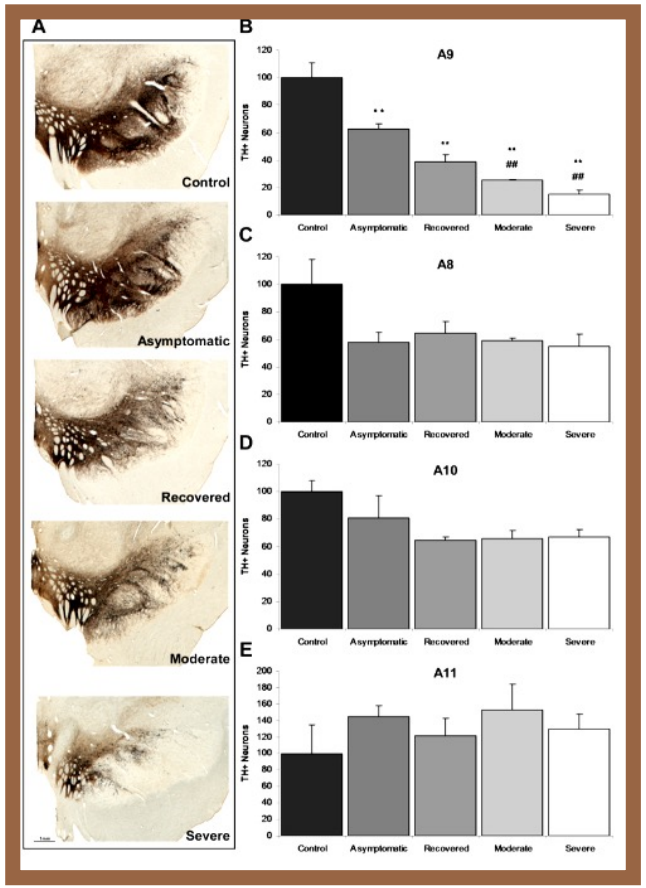
PATERNOSTER ROW.

1817.

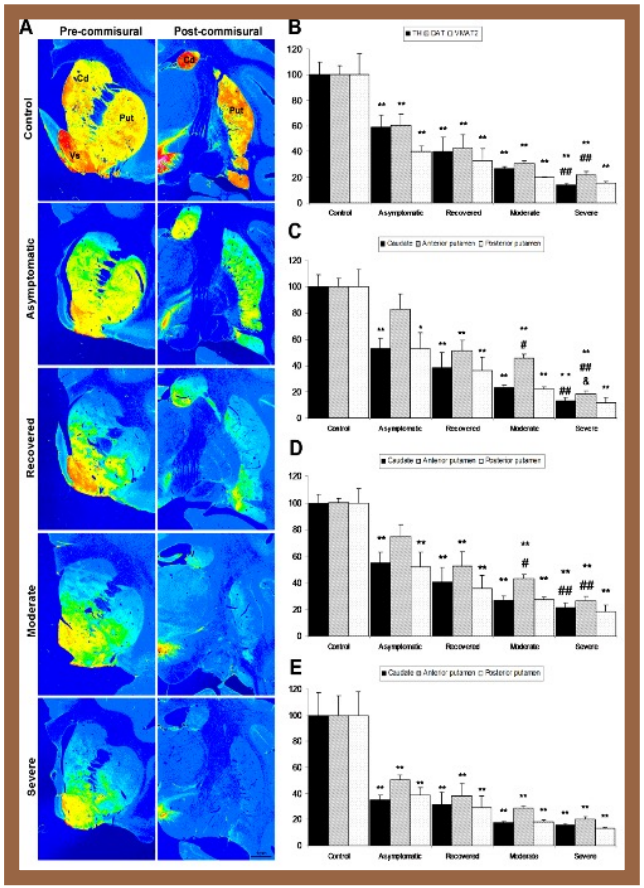
- **Clinical symptoms:** Neurodegenerative syndrome with chronic, progressive course (hypokinetic-hyperrigid/tremor-dominant)
- **Pathogenesis:** Degeneration of the nigrostriatal dopamine neurons
- **Etiology:** Idiopathic vs. symptomatic forms

"Involuntary tremulous motion, with lessened muscular power, in parts not in action even when supported; with a propensity to bend the trunk forward [...], the senses and the intellects being uninjured." James Parkinson (1817)

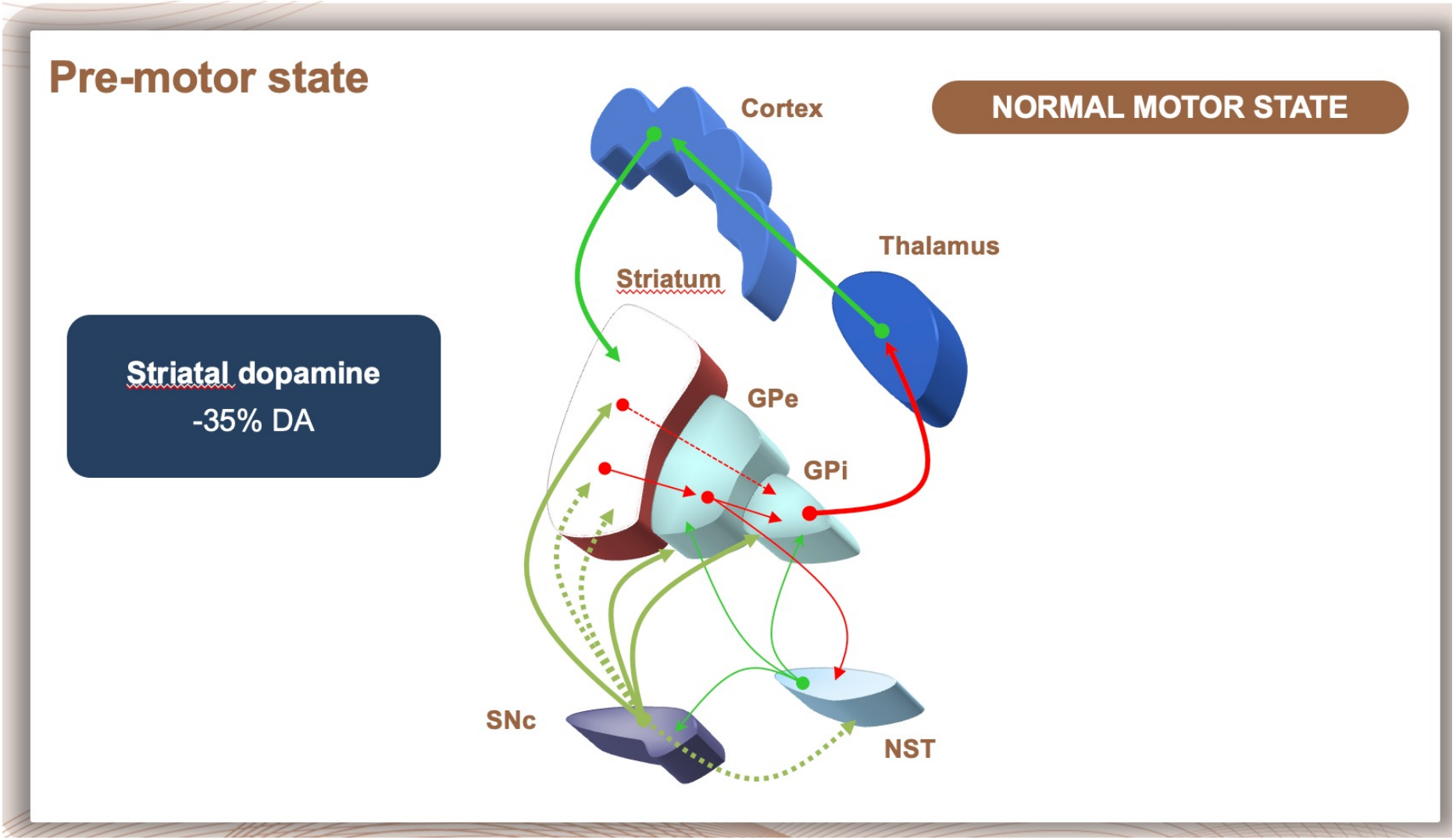
Cell loss in mesencephalic nuclei



Dopaminergic striatal innervation



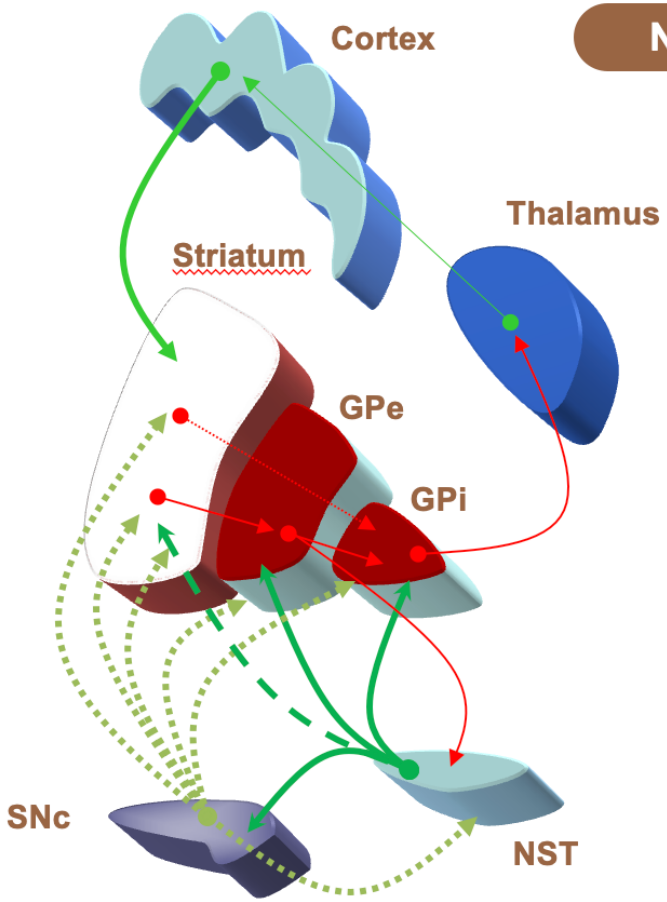
Mild striatal dopaminergic depletion



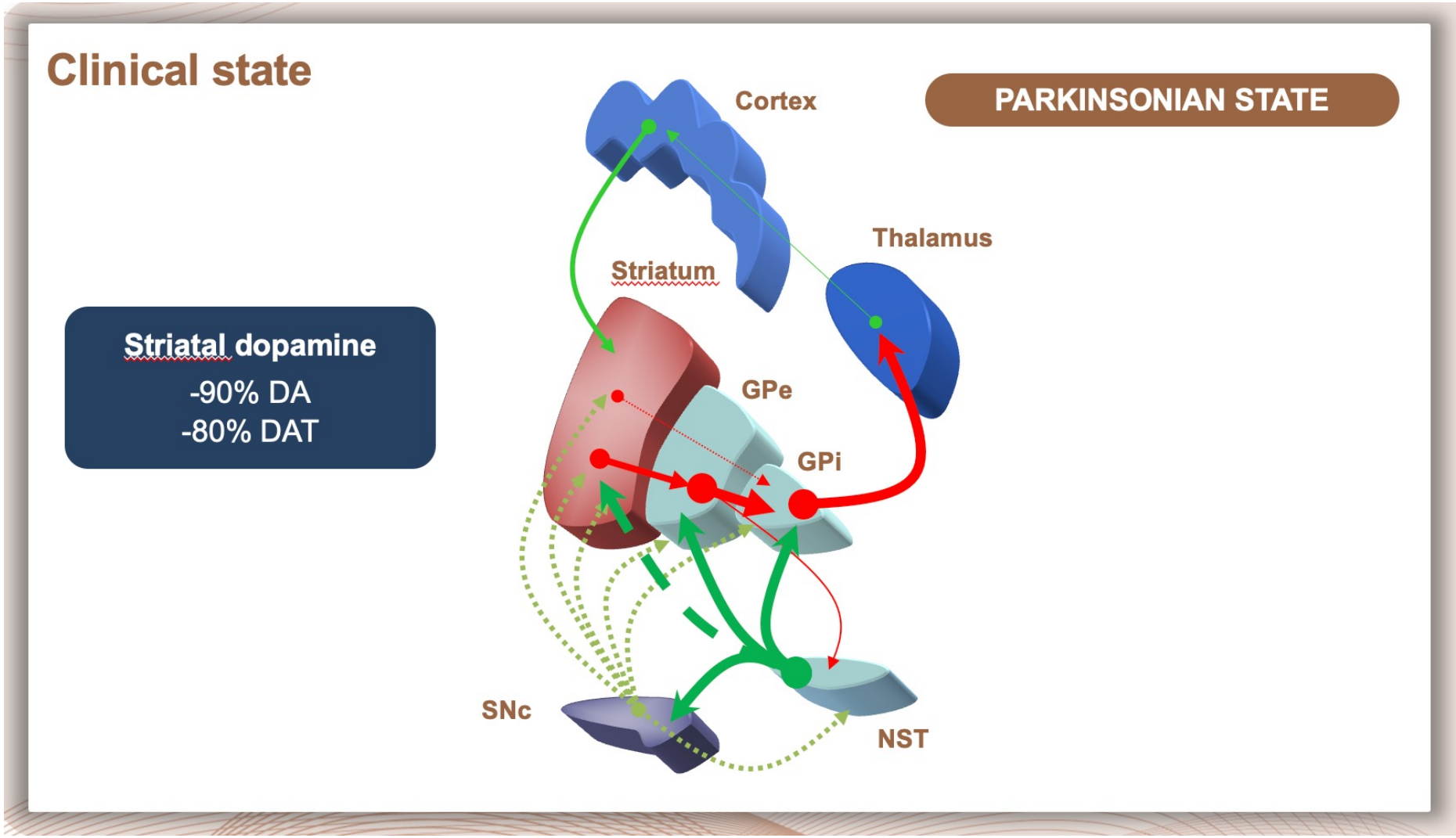
Mild striatal dopaminergic depletion

Pre-clinical state

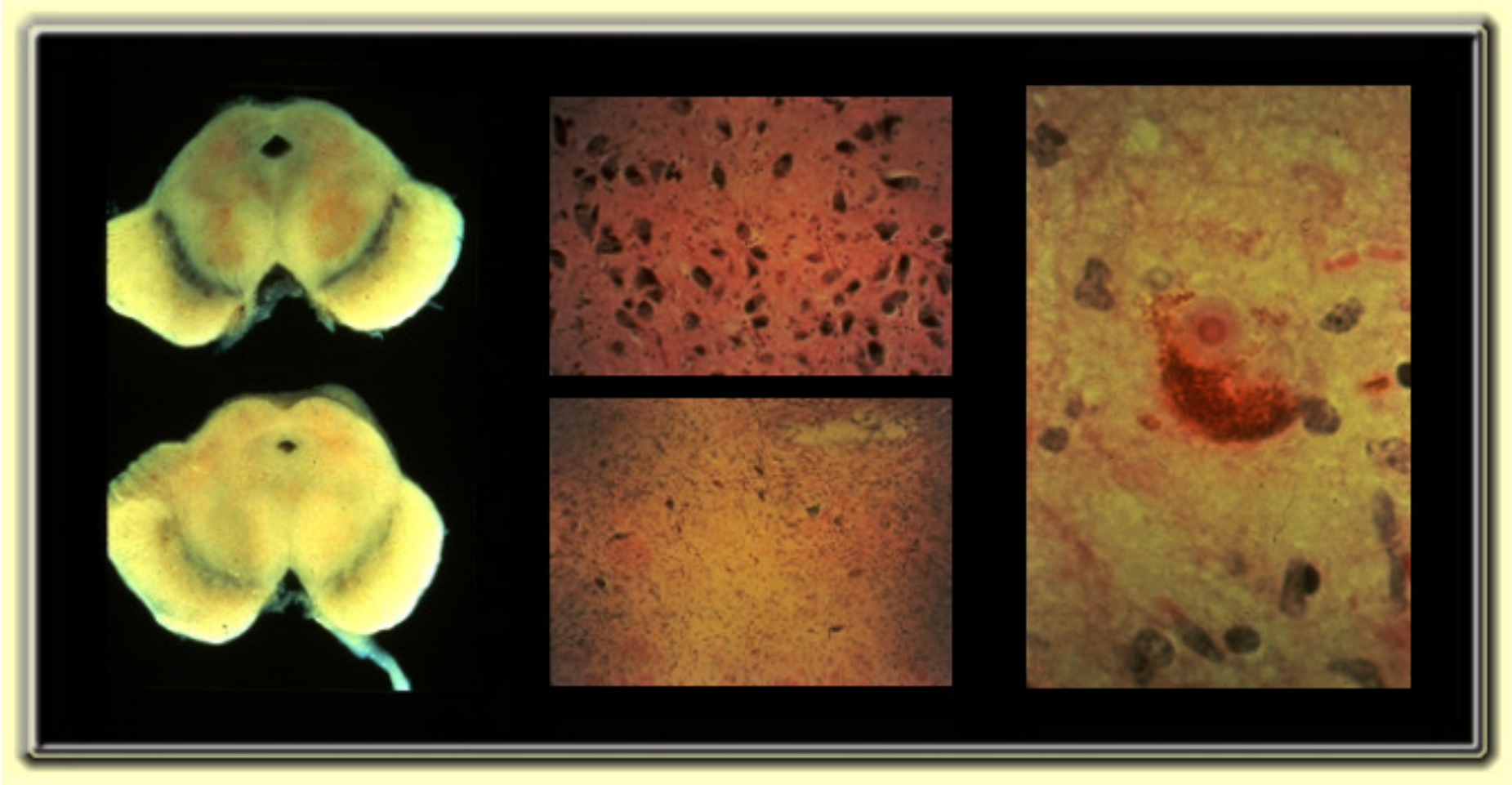
Striatal dopamine
-90% DA
-50% DAT



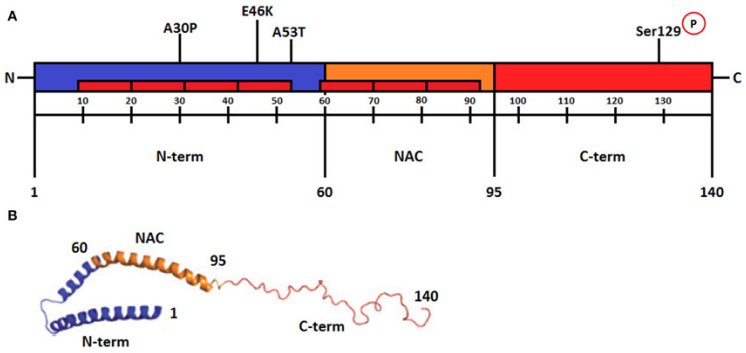
Severe striatal dopaminergic depletion



Pathology of Parkinson's Disease

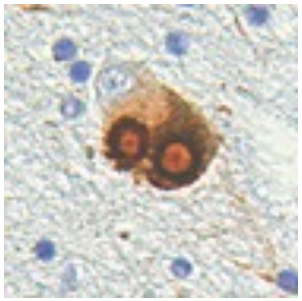


α-SYNUCLEIN

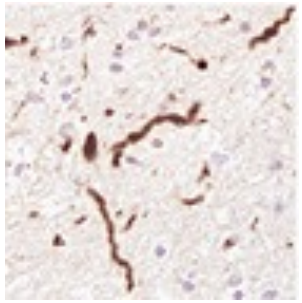


- Parkinson's disease (PD)
- Dementia with Lewy bodies (DLB)
- Multiple system atrophy (MSA)
- Pure autonomic failure (PAF)

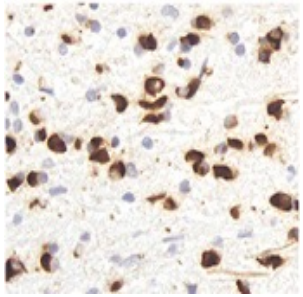
Lewy bodies



Lewy neurites



Glial cytoplasmic inclusions



EVOLUTION OF α-SYNUCLEIN CONCEPT

1817- James Parkinson describes the disease that Charcot named after him

1912- Friedrich Lewy describes inclusion body pathology

1960s- Loss of dopamine as core pathological event in PD is first described with successful treatment of patients with L-dopa

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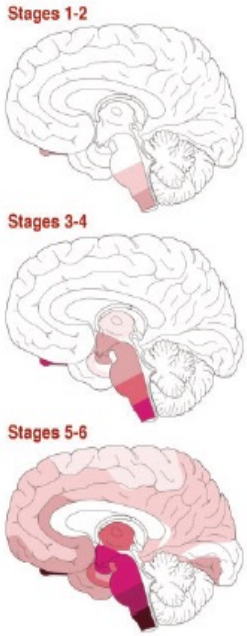
2008- Synuclein pathology in fetal neural grafts



BRIEF COMMUNICATIONS

nature medicine

Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

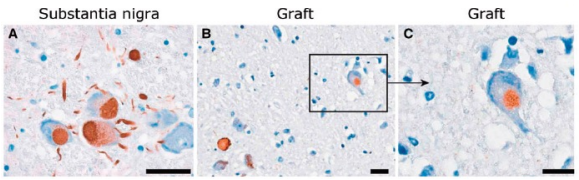
Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[3] & C Warren Olanow[4]

Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years

Ivar Mendez[1,6], Angel Viñuela[2,6], Arnar Astradsson[2], Karim Mukhida[1], Penelope Hallett[2], Harold Robertson[1], Travis Tierney[2,3], Renn Holness[1], Alain Dagher[4], John Q Trojanowski[5] & Ole Isacson[2]

Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation

Jia-Yi Li[1], Elisabet Englund[2], Janice L Holton[3], Denis Soulet[1], Peter Hagell[4], Andrew J Lees[3], Tammaryn Lashley[3], Niall P Quinn[5], Stig Rehncrona[6], Anders Björklund[7], Håkan Widner[4], Tamas Revesz[3,9], Olle Lindvall[4,8,9] & Patrik Brundin[1,9]



Goedert 2016

EVOLUTION OF α-SYNUCLEIN CONCEPT

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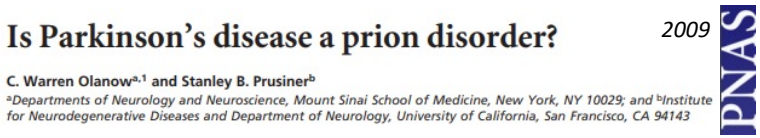
2008- Synuclein pathology in fetal neural grafts

2009- PD as a prion disorder?

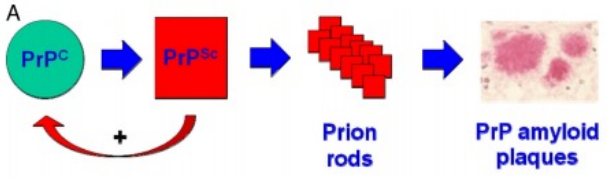

Is Parkinson's disease a prion disorder?

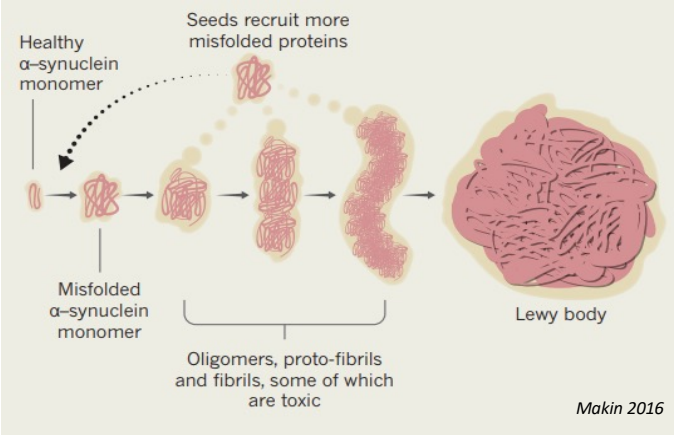
2009

PNAS

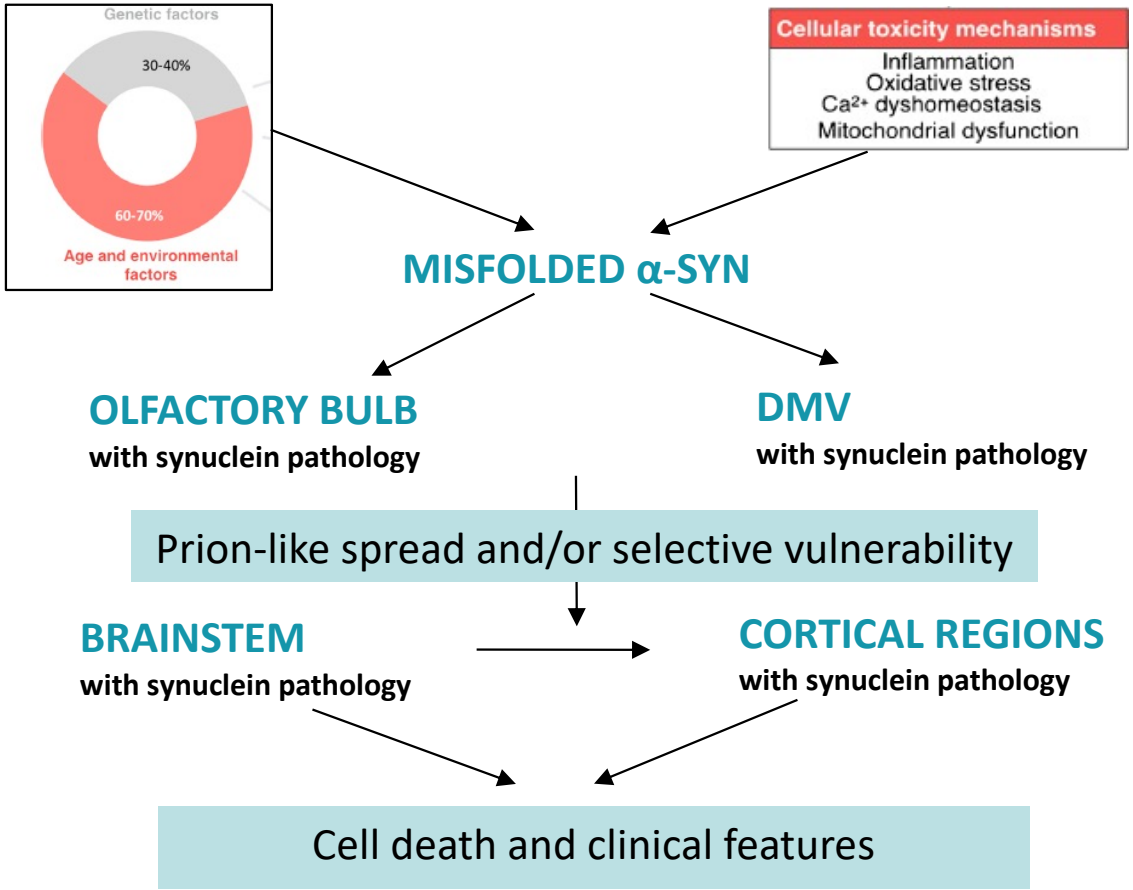
C. Warren Olanow[a,1] and Stanley B. Prusiner[b]

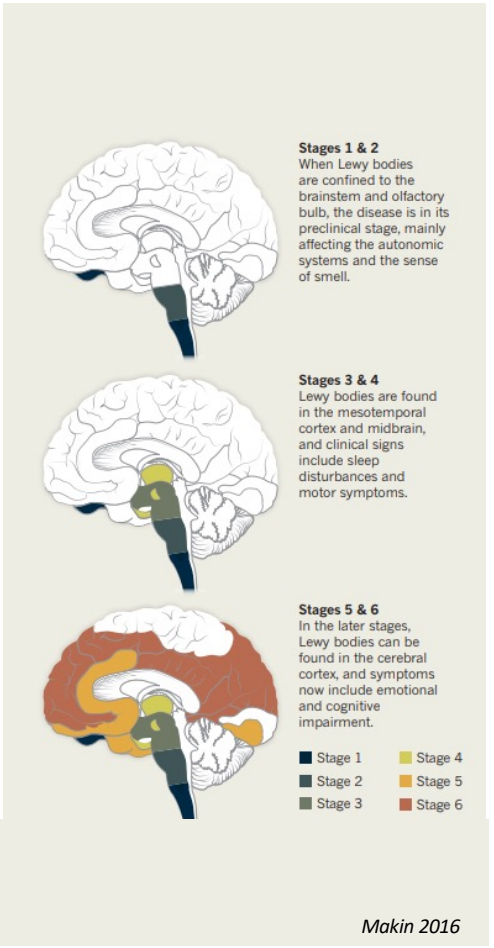
[a]Departments of Neurology and Neuroscience, Mount Sinai School of Medicine, New York, NY 10029; and [b]Institute for Neurodegenerative Diseases and Department of Neurology, University of California, San Francisco, CA 94143



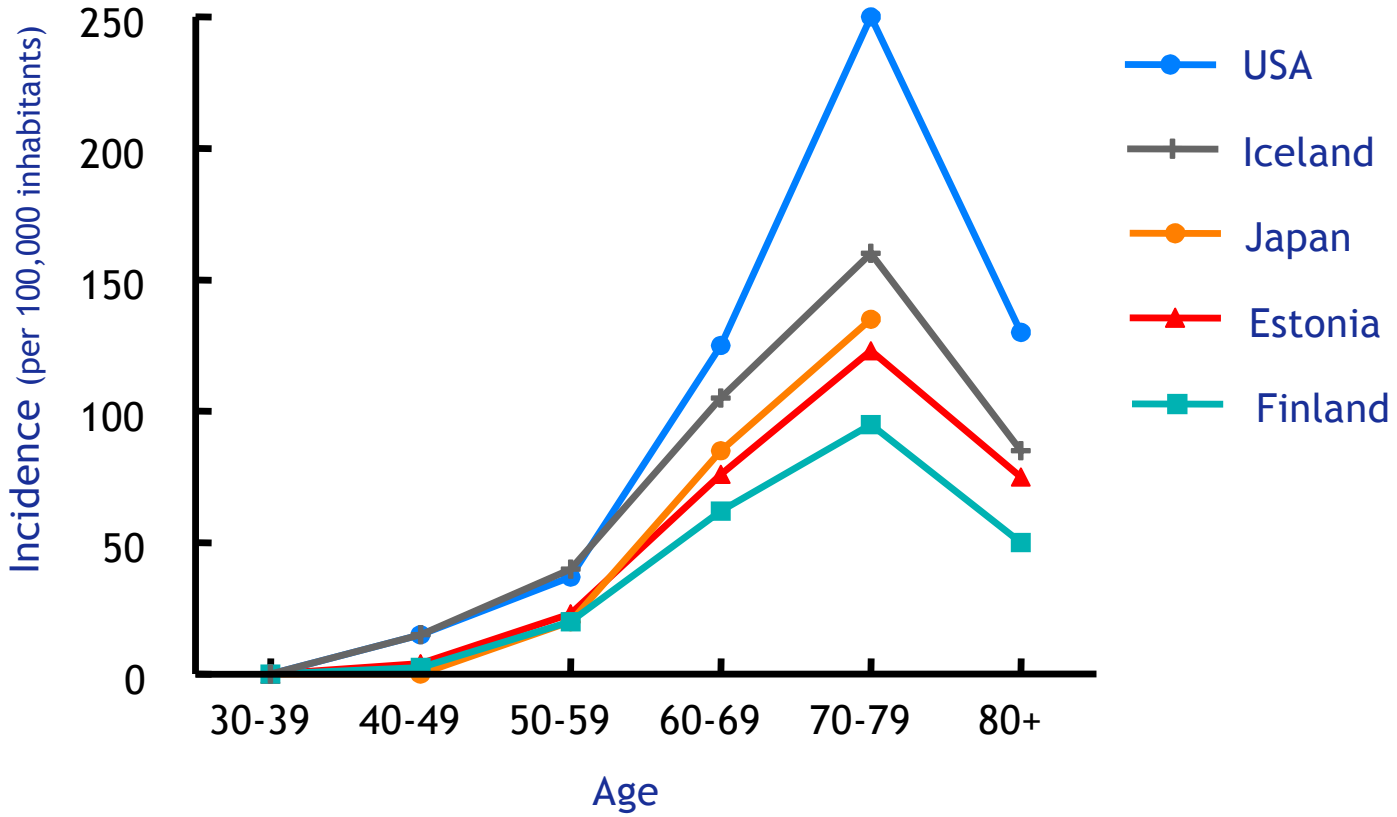


α-SYN SPREAD

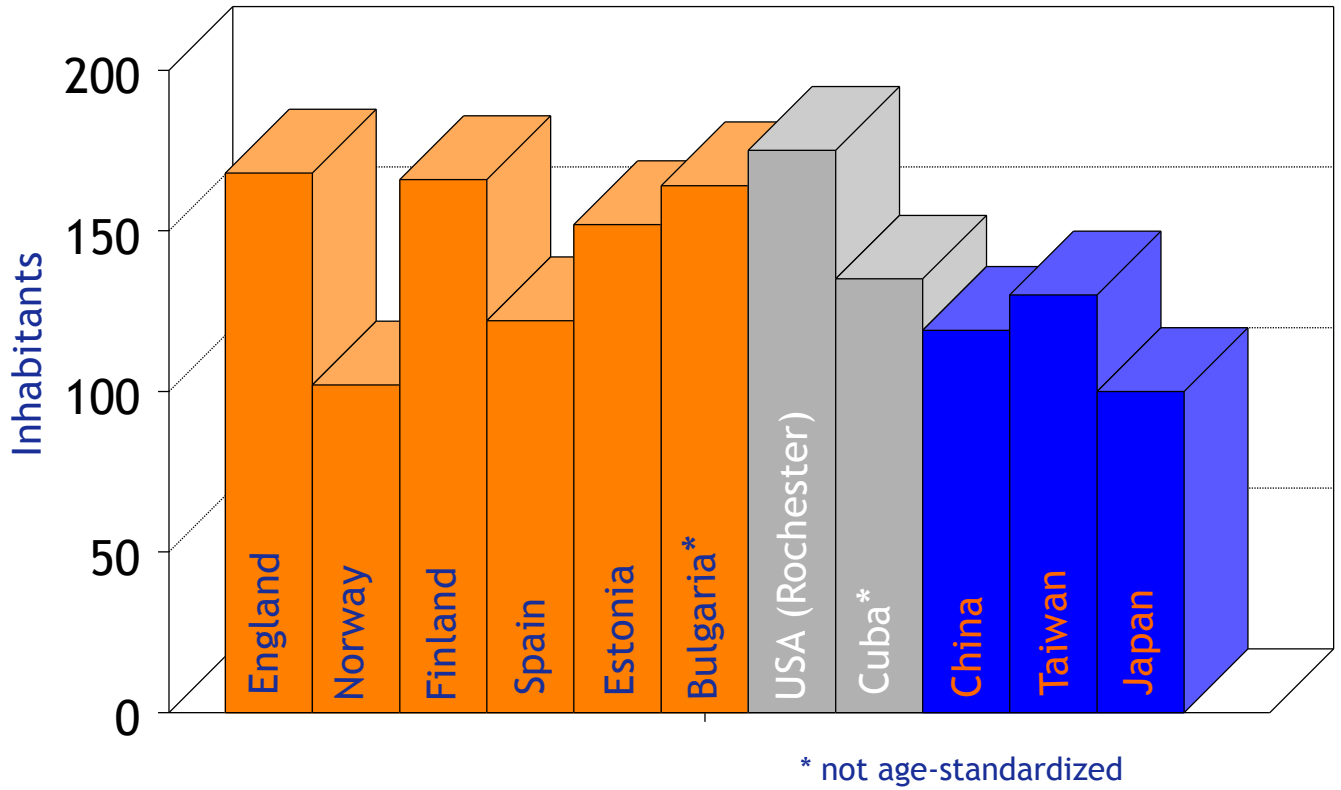

Genetic factors
30-40%
60-70%
Age and environmental factors
Cellular toxicity mechanisms
Inflammation
Oxidative stress
Ca2+ dyshomeostasis
Mitochondrial dysfunction
MISFOLDED α-SYN
OLFACTORY BULB
with synuclein pathology
DMV
with synuclein pathology
Prion-like spread and/or selective vulnerability
BRAINSTEM
with synuclein pathology
CORTICAL REGIONS
with synuclein pathology
Cell death and clinical features


Stages 1 & 2
When Lewy bodies are confined to the brainstem and olfactory bulb, the disease is in its preclinical stage, mainly affecting the autonomic systems and the sense of smell.
Stages 3 & 4
Lewy bodies are found in the mesotemporal cortex and midbrain, and clinical signs include sleep disturbances and motor symptoms.
Stages 5 & 6
In the later stages, Lewy bodies can be found in the cerebral cortex, and symptoms now include emotional and cognitive impairment.
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Makin 2016

Age-specific incidence of new cases of Parkinson's disease



Prevalence of Parkinson's disease (per 100,000 inhabitants)

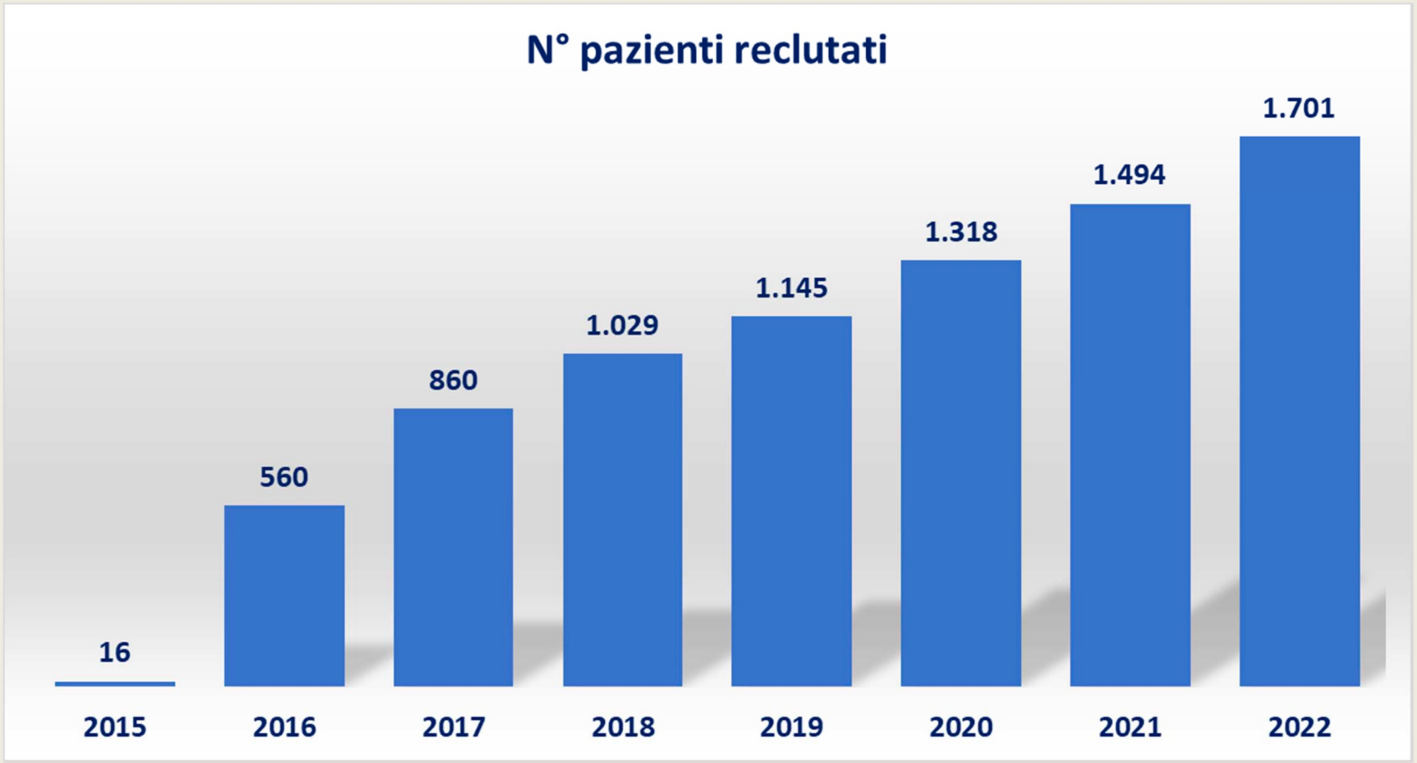


Epidemiology – Facts

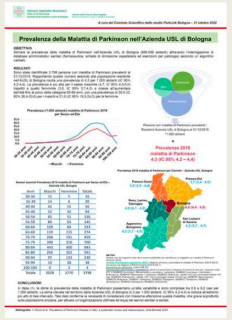
Reclutamento ParkLink

Dati aggiornati al **31 dicembre 2022**

Anno	N° x anno	N tot
2015	16	16
2016	544	560
2017	300	860
2018	169	1.029
2019	116	1.145
2020	173	1.318
2021	176	1.494
2022	207	1.701

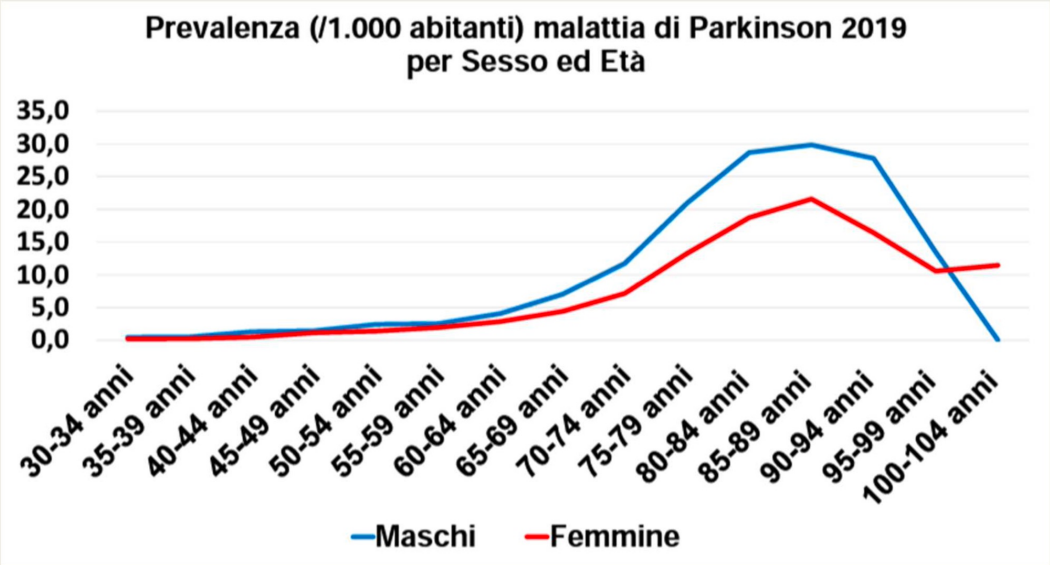


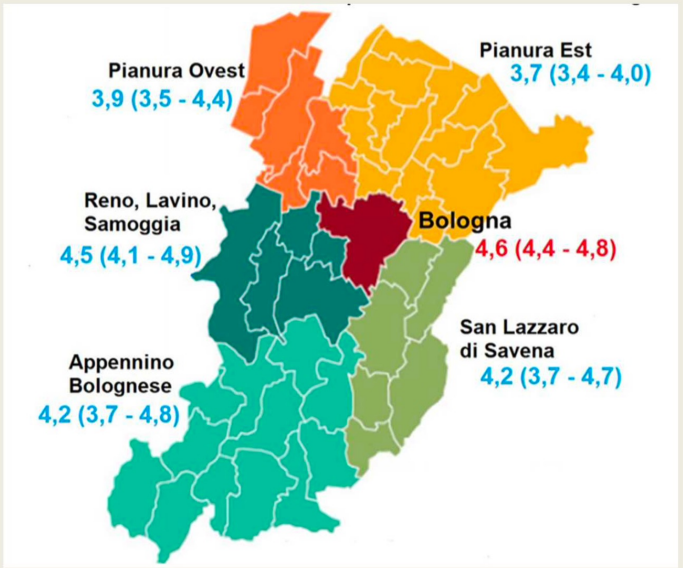
Prevalenza della Malattia di Parkinson nell'Azienda USL di Bologna



3.798 soggetti

Prevalenza 2019
4,3 / 1.000 (IC 95% 4,2 – 4,4)





Risk factors

- Age
- Positive family history
- Possible: Poisoning with herbicides, pesticides, heavy metals
- Doubtful: Personality, Living in the countryside

Possible protective factors:

- Consumption of tea and coffee
- Nicotine

PROPAG-AGEING

The continuum between healthy ageing and idiopathic Parkinson Disease within a propagation perspective of inflammation and damage: the search for new diagnostic, prognostic and therapeutic targets

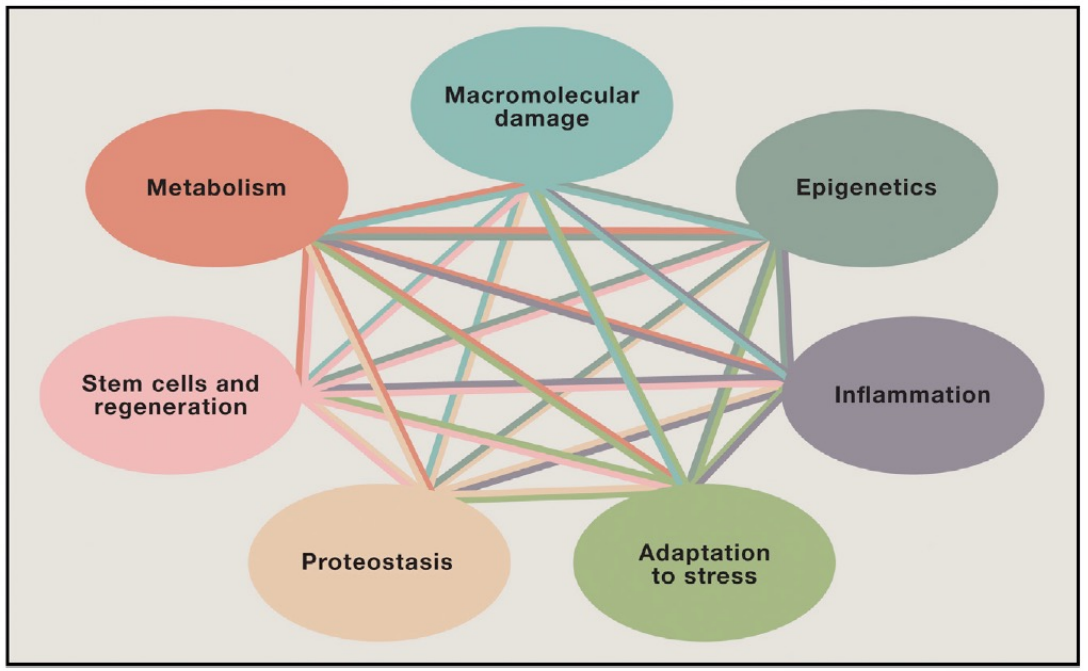


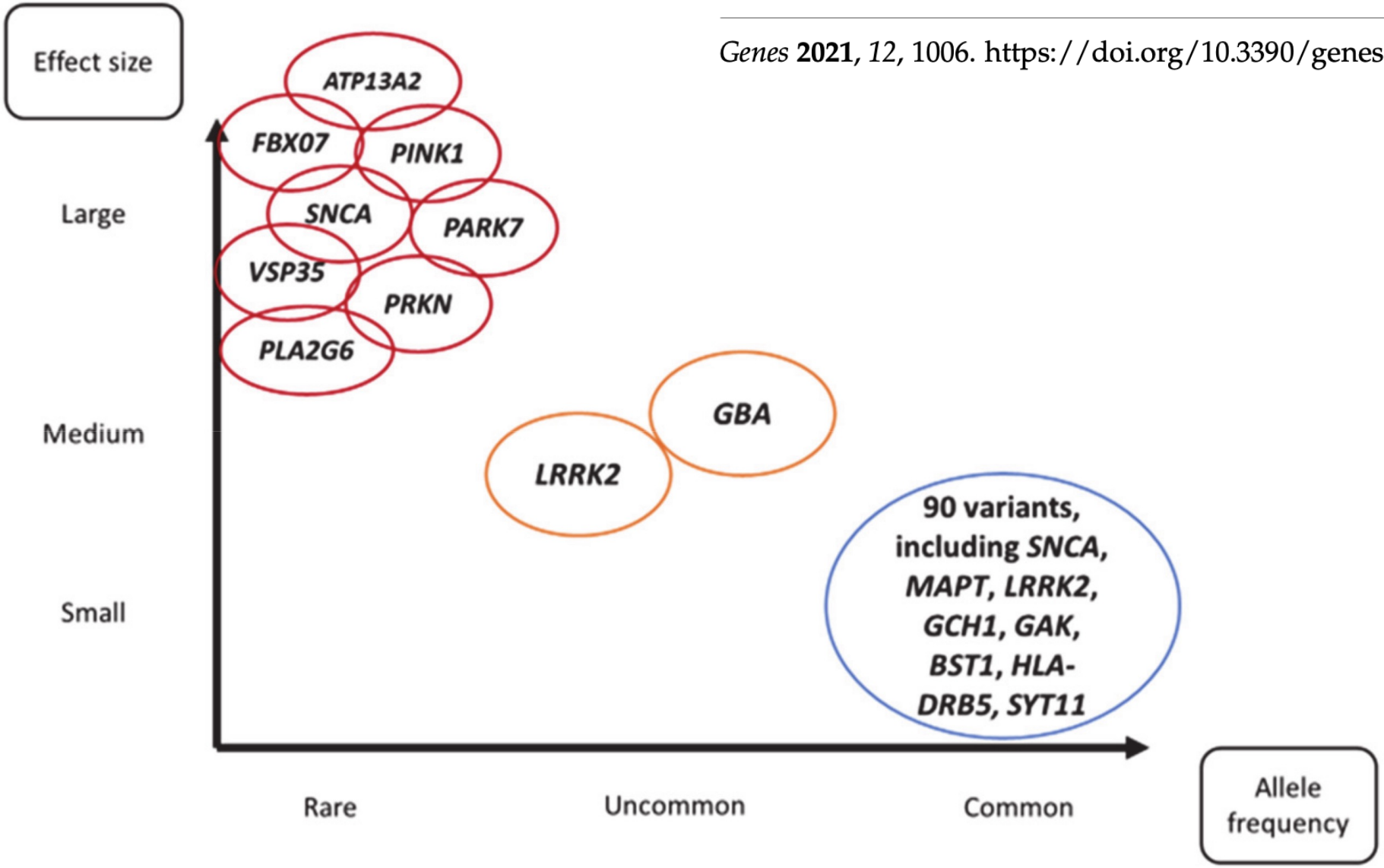
Figure 1. The Seven Pillars of Aging

Genetic causes

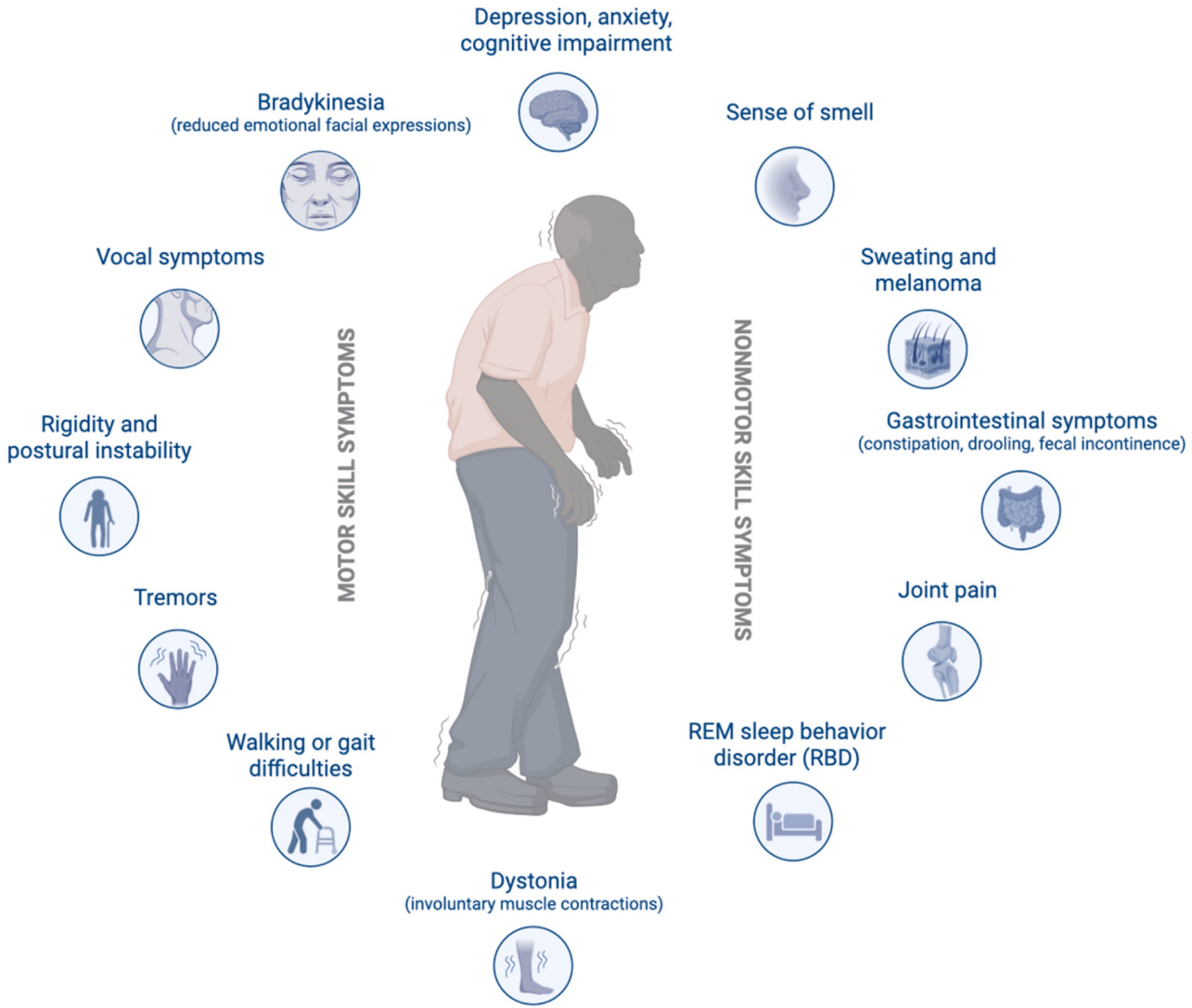
- **PARK 1**
  Locus: Chromosome 4q21
  Gene product: α-Synuclein (Polymeropoulos et al., 1997)
- **PARK 2**
  Locus: Chromosome 6q25
  Gene product: Unknown (Kitada et al., 1998)
- **PARK 3**
  Locus: Chromosome 2p13
  Gene product: Unknown (Gasser et al., 1998)

PARK 4 – 10

Genes **2021**, *12*, 1006. https://doi.org/10.3390/genes12071006

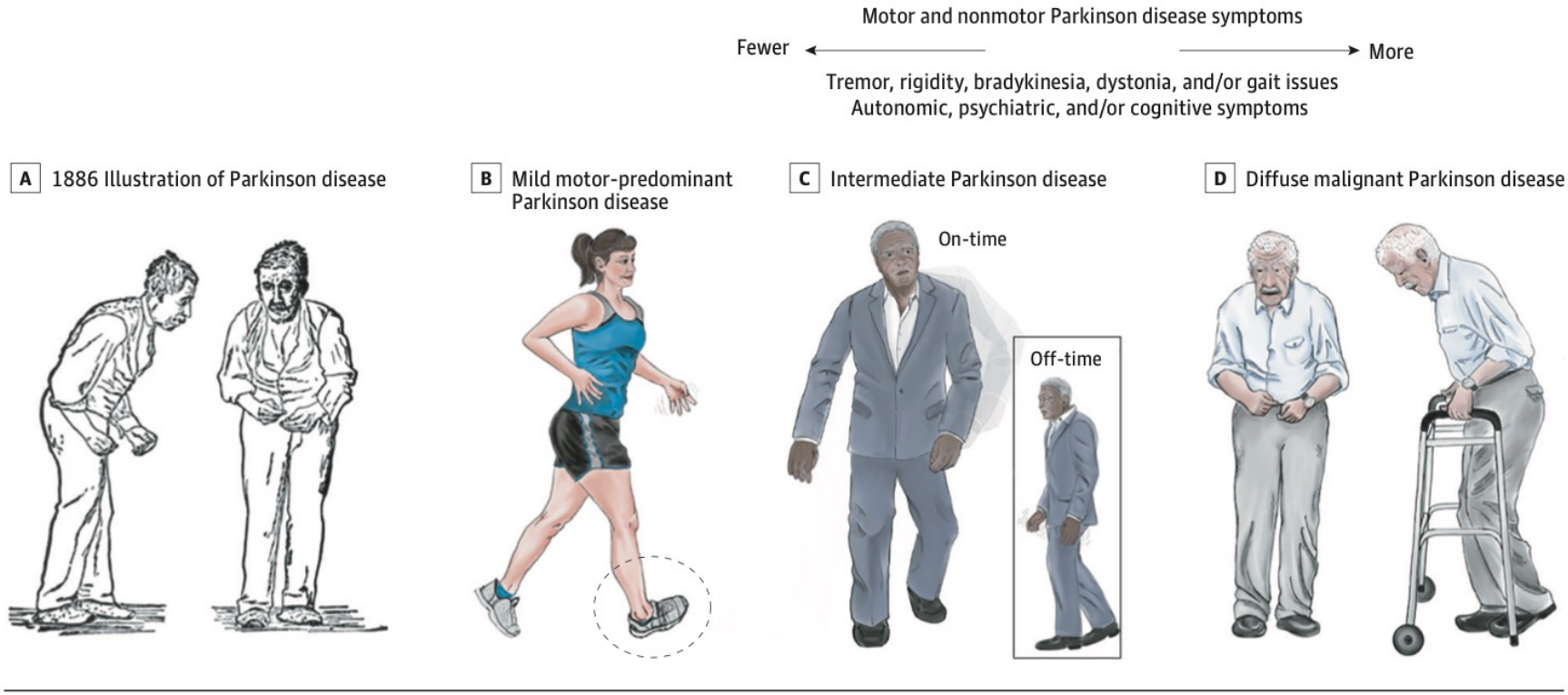


Symptoms of Parkinson's Disease



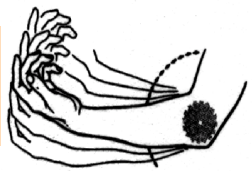
Time for a new Image of Parkinson's Disease

Figure. Images of Parkinson Disease: 1886 and 2020



Main symptoms are Motor symptoms

- Bradykinesia
- Rigor

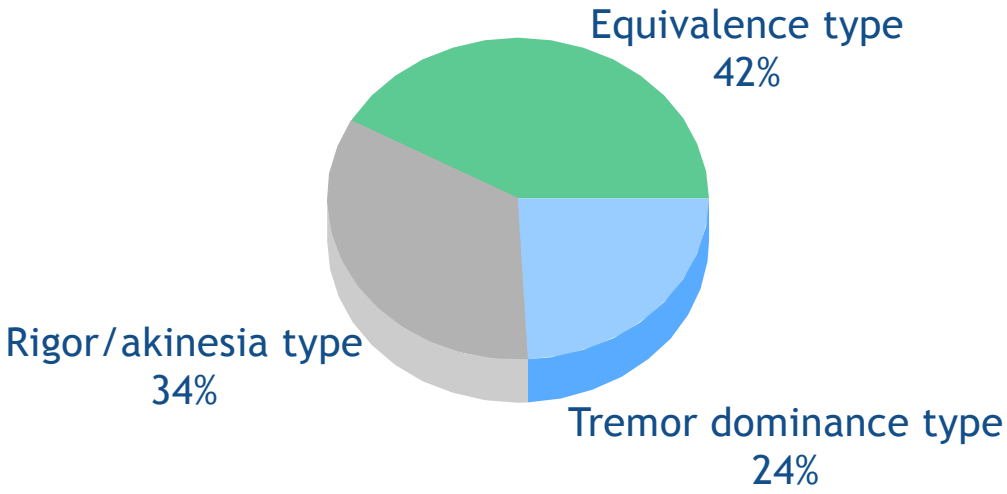


- Tremor

- Postural instability

Early symptoms

- Neck and shoulder pain
- Depression/reduced drive
- Sensory disturbances: e.g. disturbed sense of smell
- Change in handwriting
- Speech disturbances
- Problems walking



La diagnosi: difficoltà e importanza della diagnosi precoce

BMJ 2015;351:h6141 doi: 10.1136/bmj.h6141 (Published 14 December 2015)

"Gunslinger's gait": a new cause of unilaterally reduced arm swing

Rui Araújo *resident in neurology*[1], Joaquim J Ferreira *professor of neurology*[2], Angelo Antonini *professor of neurology*[3], Bastiaan R Bloem *professor of movement disorder neurology*[4]

Objective To postulate a new possible cause of a unilaterally reduced arm swing in addition to the known medical conditions such as shoulder pathology, Erb's palsy, stroke, and Parkinson's disease.

Methods Analysis of YouTube videos depicting the gait of highly ranked Russian officials.

Results We found a similar walking pattern in President Vladimir Putin, Prime Minister Dmitry Medvedev and three other highly ranked Russian officials, all presenting with a consistently reduced right arm swing in the absence of other overt neurological abnormalities.

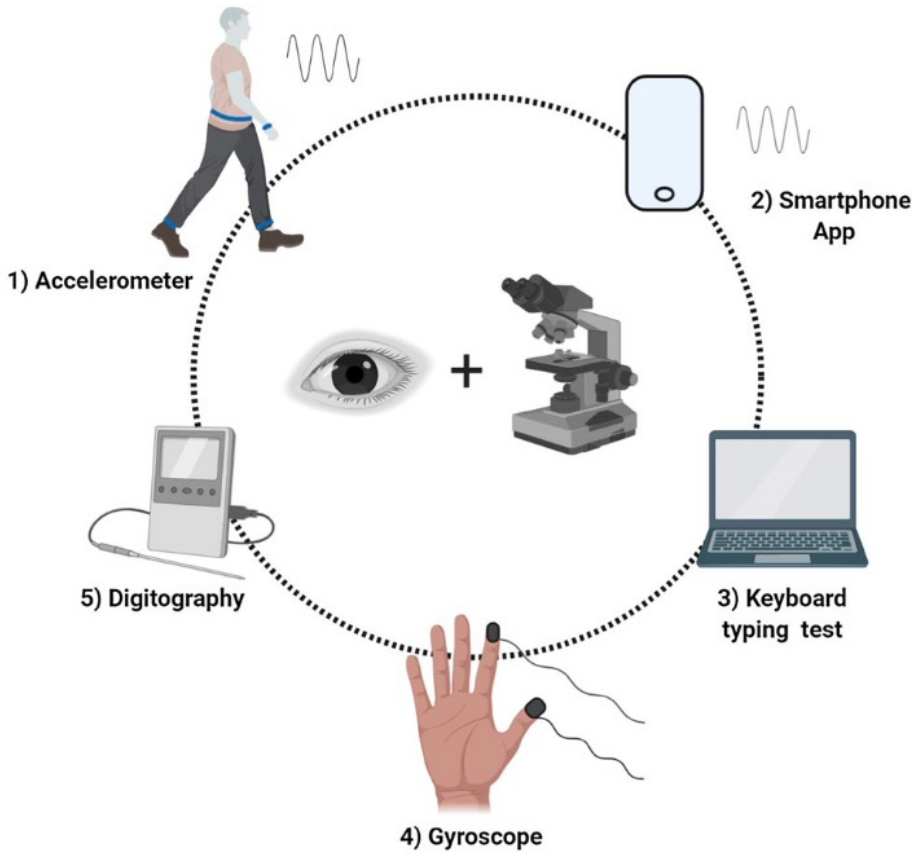
Conclusions We propose that this new gait pattern, which we term "gunslinger's gait," may result from a behavioural adaptation, possibly triggered by KGB or other forms of weapons training where trainees are taught to keep their right hand close to the chest while walking, allowing them to quickly draw a gun when faced with a foe. This should be included in the differential diagnosis of a unilaterally reduced arm swing.

Dott. Vincenzo Mastrangelo

Late symptoms

- Motor complications:
  - Fluctuations
  - L-Dopa-induced dyskinesia
  - Freezing
  - Akinetic crisis
- Increased vegetative disorders
- Neuropsychiatric problems

Revealing subtle motor dysfunction: prodromal phase of PD



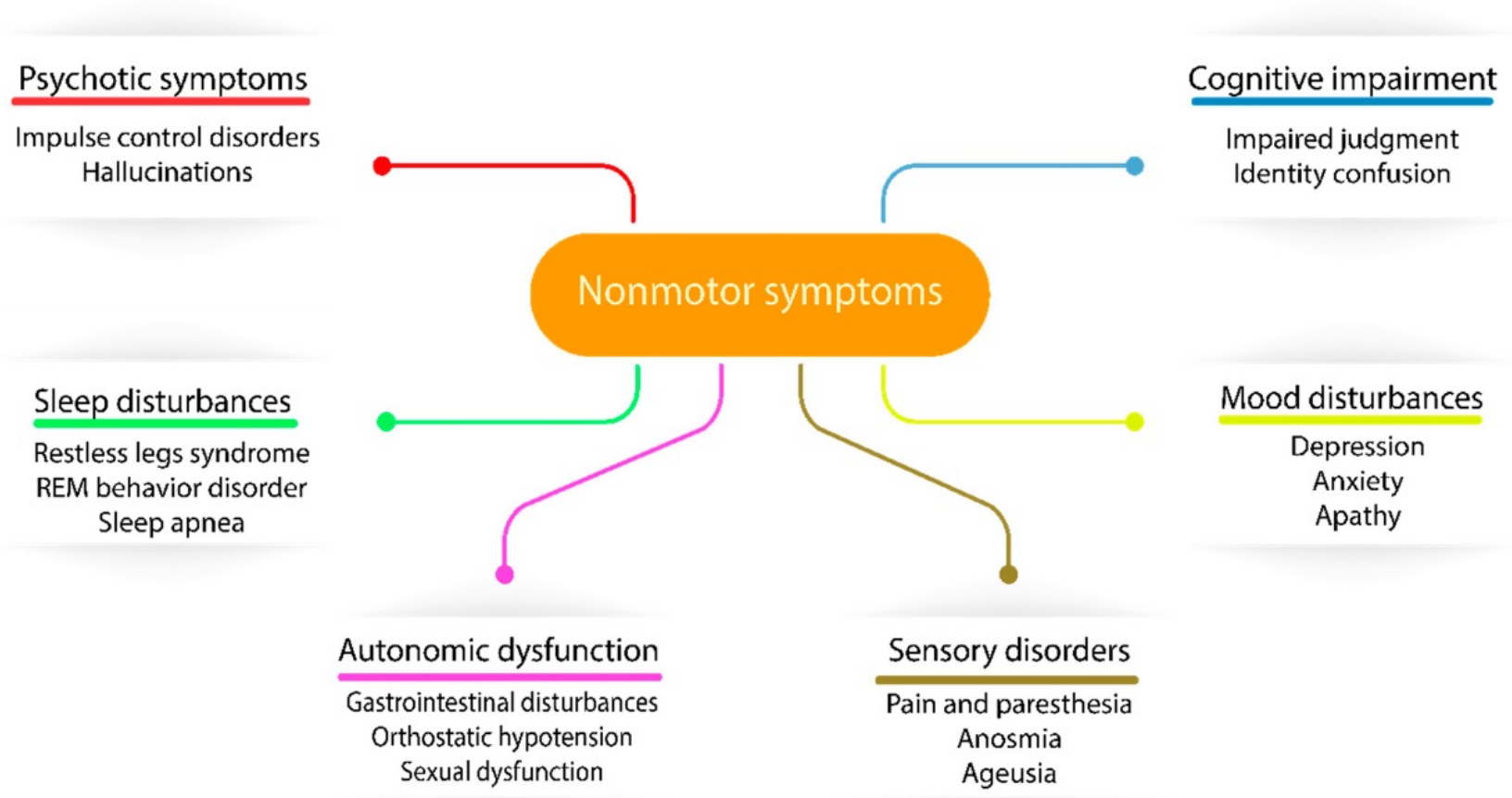


Figure 1. The diverse nature of nonmotor symptoms affecting Parkinson's disease (PD) patients.

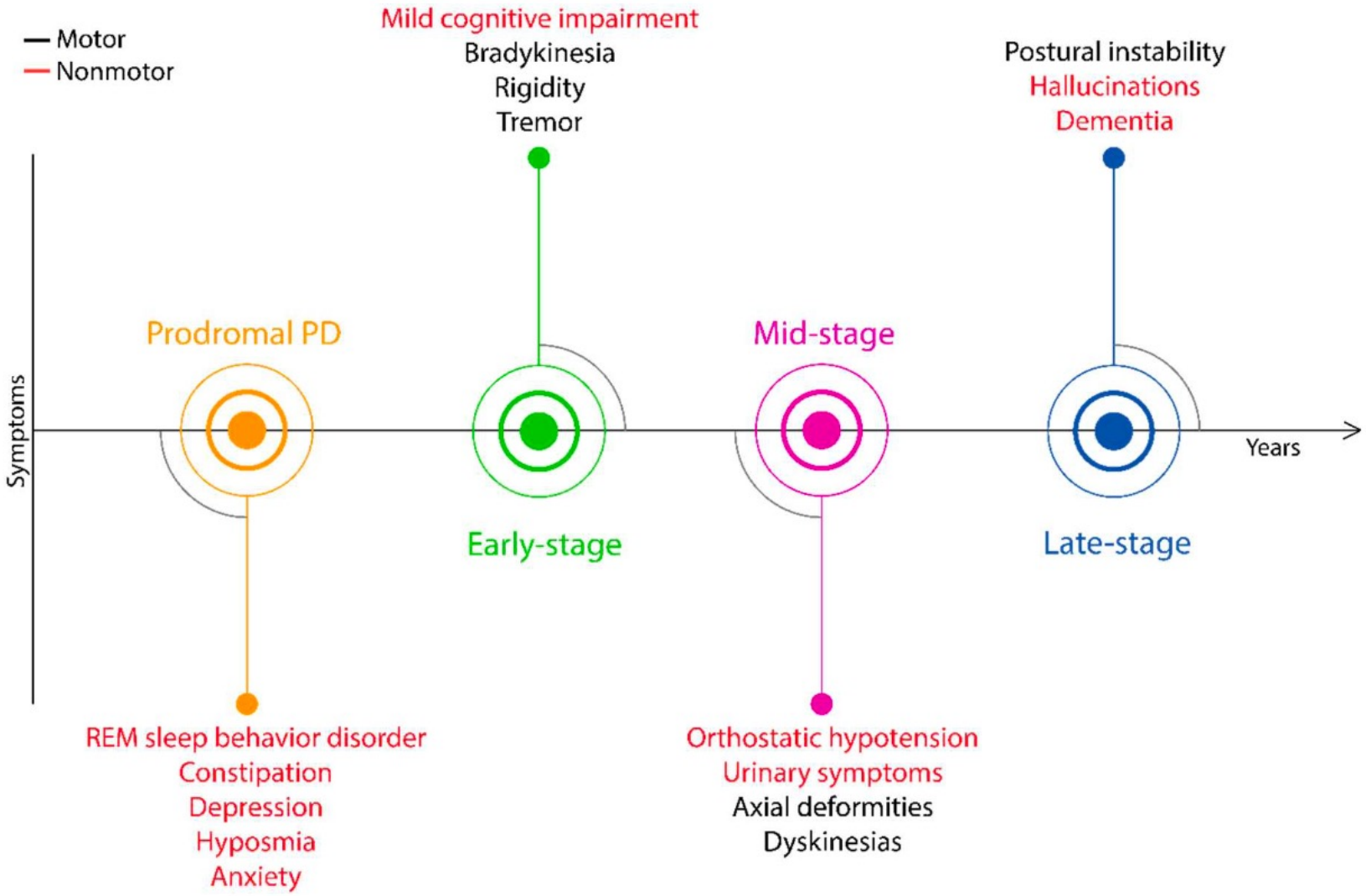
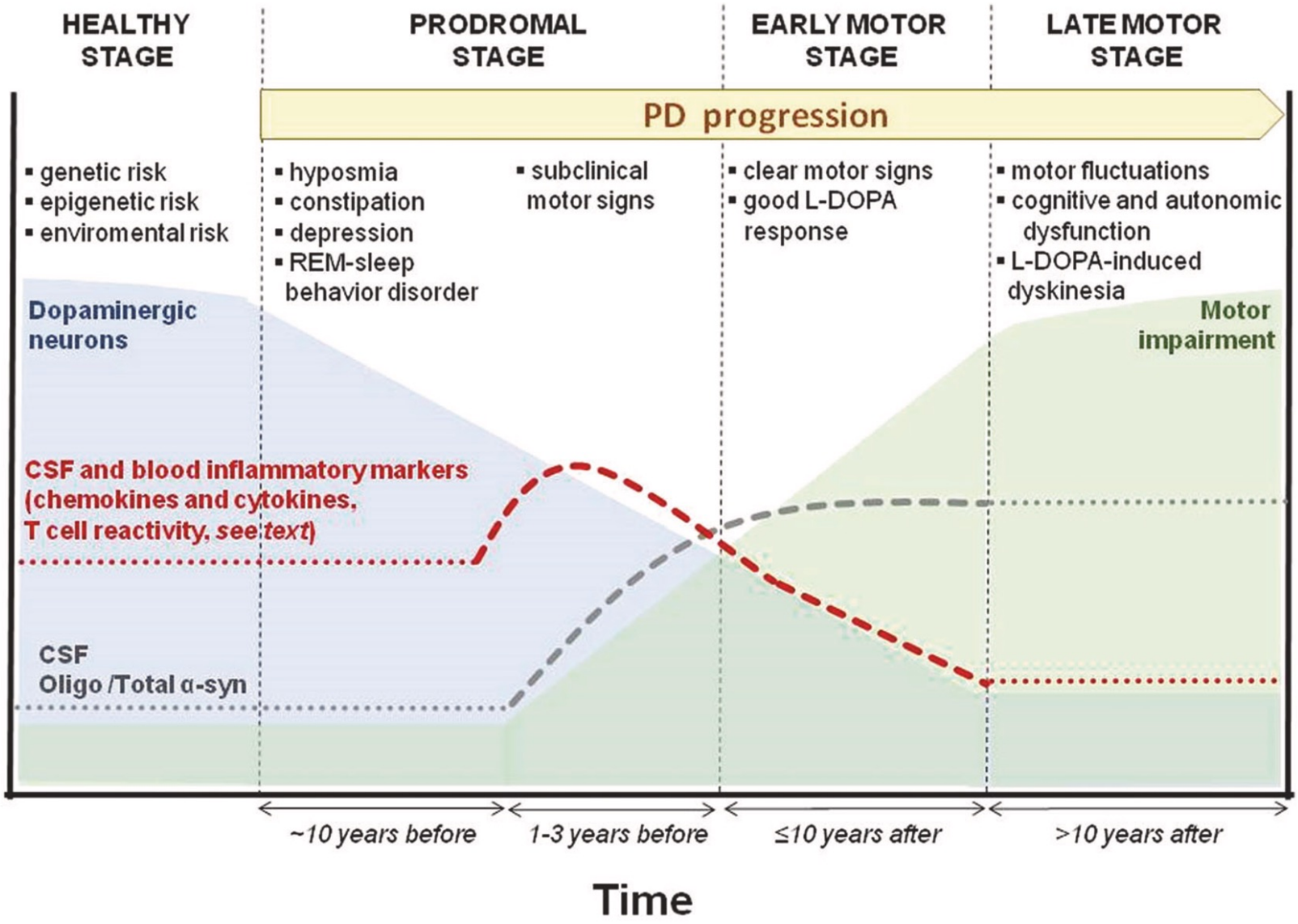


Figure 2. Timeline of clinical signs expressed throughout PD.


HEALTHY STAGE
PRODROMAL STAGE
EARLY MOTOR STAGE
LATE MOTOR STAGE
PD progression
▪ genetic risk
▪ epigenetic risk
▪ enviromental risk
▪ hyposmia
▪ constipation
▪ depression
▪ REM-sleep behavior disorder
▪ subclinical motor signs
▪ clear motor signs
▪ good L-DOPA response
▪ motor fluctuations
▪ cognitive and autonomic dysfunction
▪ L-DOPA-induced dyskinesia
Dopaminergic neurons
Motor impairment
CSF and blood inflammatory markers (chemokines and cytokines, T cell reactivity, see text)
CSF Oligo /Total α-syn
~10 years before
1-3 years before
≤10 years after
>10 years after
Time

Journal of Neurology, Neurosurgery, and Psychiatry 1988;**51**:745–752

Occasional review

The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease

W R G GIBB, A J LEES

From the Department of Neuropathology, National Hospitals for Nervous Diseases, Maida Vale, London, UK

SUMMARY The Lewy body is a distinctive neuronal inclusion that is always found in the substantia nigra and other specific brain regions in Parkinson's disease. It is mainly composed of structurally altered neurofilament, and occurs wherever there is excessive loss of neurons. It occurs in some elderly individuals and rarely in other degenerative diseases of the central nervous system. In 273 brains of patients dying from disorders other than Parkinson's disease, the age-specific prevalence of Lewy bodies increased from 3·8% to 12·8% between the sixth and ninth decades. Associated pathological findings suggest that these cases of incidental Lewy body disease are presymptomatic cases of Parkinson's disease, and confirm the importance of age (time) in the evolution of the disease. In view of the common and widespread occurrence of this disorder we propose that endogenous mechanisms operating in early life may be more important than environmental agents in the pathogenesis of Lewy bodies and Parkinson's disease.

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of 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.

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Journal of Neurology, Neurosurgery, and Psychiatry 1992;55:181–184

Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases

Andrew J Hughes, Susan E Daniel, Linda Kilford, Andrew J Lees

The retrospective application of recommended diagnostic criteria improved the diagnostic accuracy to 82%.

ARCH NEUROL/VOL 56, JAN 1999

SPECIAL ARTICLE

Diagnostic Criteria for Parkinson Disease

Douglas J. Gelb, MD, PhD; Eugene Oliver, PhD; Sid Gilman, MD

Table 1. Grouping of Clinical Features According to Diagnostic Utility

Group A features: characteristic of Parkinson disease
- Resting tremor
- Bradykinesia
- Rigidity
- Asymmetric onset

Group B features: suggestive of alternative diagnoses
- Features unusual early in the clinical course
  - Prominent postural instability in the first 3 years after symptom onset
  - Freezing phenomena in the first 3 years
  - Hallucinations unrelated to medications in the first 3 years
  - Dementia preceding motor symptoms or in the first year
- Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
- Severe, symptomatic dysautonomia unrelated to medications
- Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Criteria for POSSIBLE diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia

and

Either None of the features in Group B* is present

Or Symptoms have been present for less than 3 years, and none of the features in Group B* is present to date

and

Either Substantial and sustained response to levodopa or a dopamine agonist has been documented

Or Patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for PROBABLE diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A* are present

and

None of the features in Group B* is present (note: symptom duration of at least 3 years is necessary to meet this requirement)

and

Substantial and sustained response to levodopa or a dopamine agonist has been documented

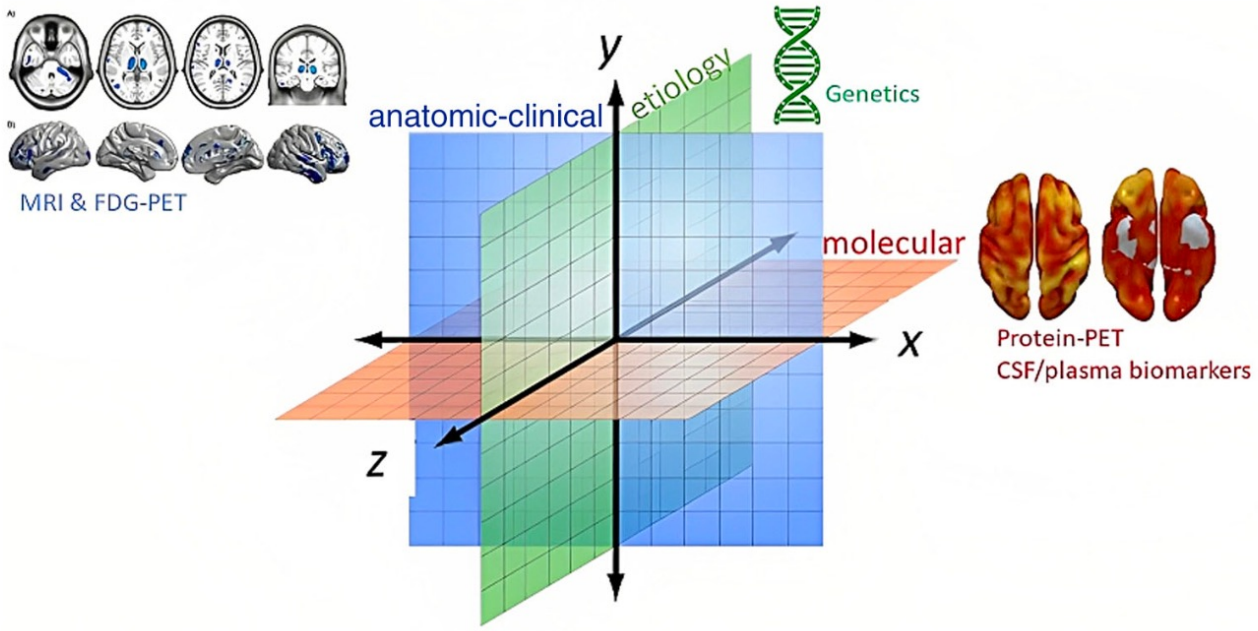
Criteria for DEFINITE diagnosis of Parkinson disease:

All criteria for POSSIBLE Parkinson disease are met

and

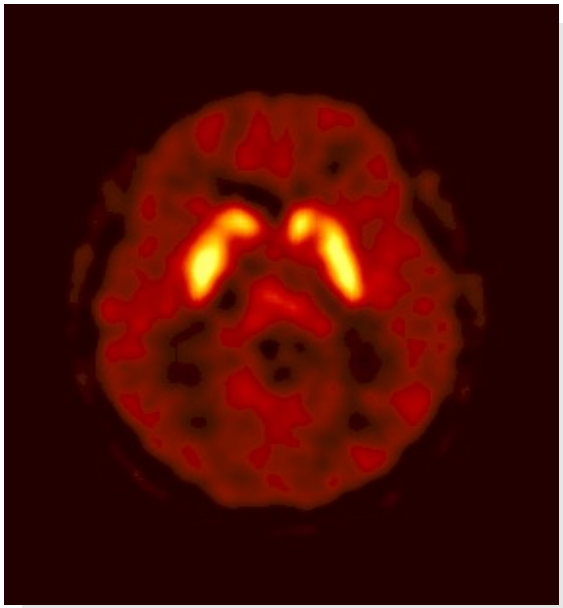
Histopathologic confirmation of the diagnosis is obtained at autopsy (see Table 3)

Neurodegenerative diseases can be studied and classified in a tridimensional scheme with three axes: anatomic–clinical, molecular, and etiologic

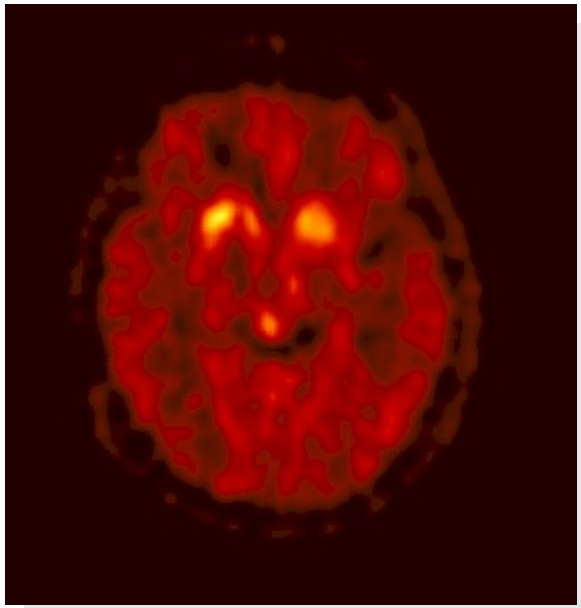


Machine-aided diagnosis PET

HEALTHY

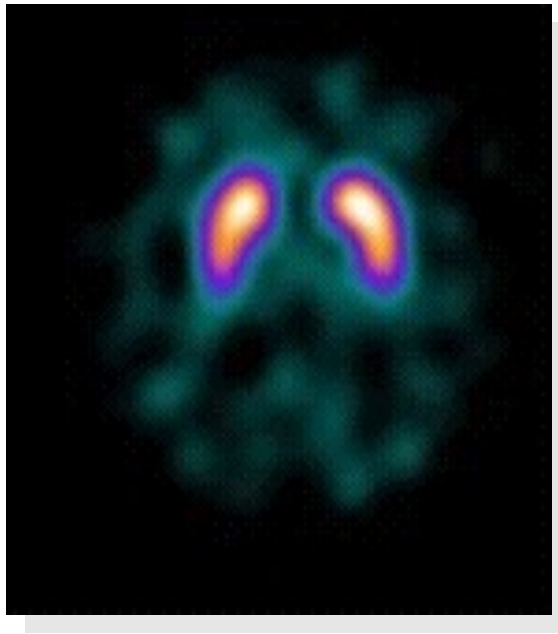


PARKINSON'S DISEASE

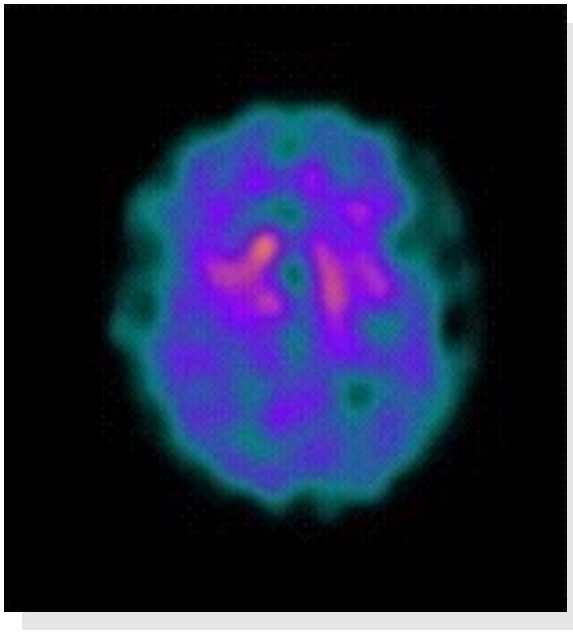


Machine-aided diagnosis SPECT (I^{123} beta-CIT)

HEALTHY



PARKINSON'S DISEASE



FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

Daniela Berg, MD,[1*¶] Ronald B. Postuma, MD, MSc,[2¶] Bastiaan Bloem, MD, PhD,[3] Piu Chan, MD, PhD,[4] Bruno Dubois, MD, PhD,[5] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[6] Glenda M. Halliday, PhD,[7] John Hardy, PhD,[8] Anthony E. Lang, MD, FRCPC,[9] Irene Litvan, MD,[10] Kenneth Marek, MD,[11] José Obeso, MD, PhD,[12] Wolfgang Oertel, MD,[13] C. Warren Olanow, MD, FRCPC,[14] Werner Poewe, MD,[15] Matthew Stern, MD,[16] and Günther Deuschl, MD[17]

Movement Disorders, Vol. 29, No. 4, 2014

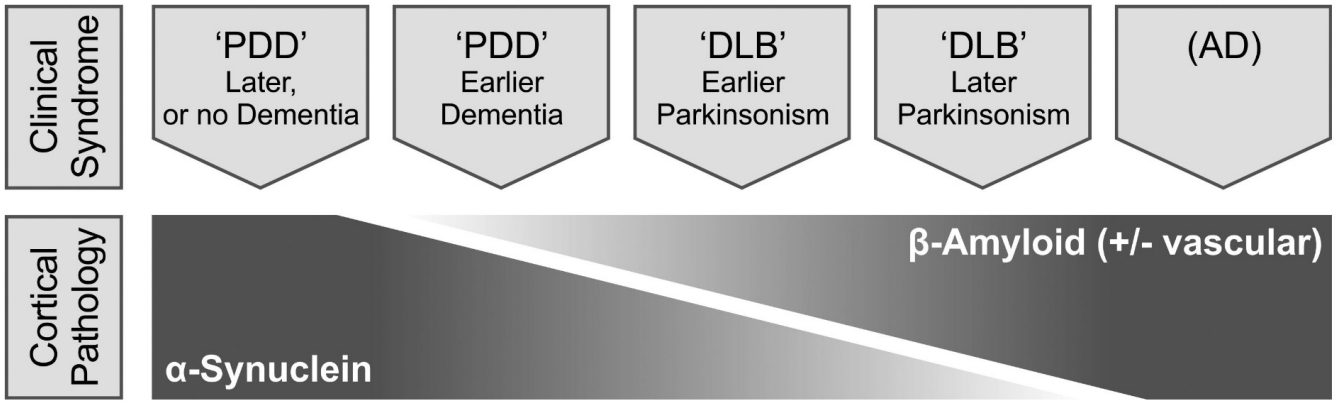
What Is the Gold Standard for the Definition of PD?

The issue: *A patient with classic clinical PD died without autopsy; can one never say they are "sure" she had PD? Why is autopsy the gold standard if it is almost never available (and might become outdated, once we have good biomarkers). Furthermore, don't genetic studies suggest that pathology can be inconclusive? A patient from a family of pathologically confirmed LRRK2 PD who meets clinical criteria for PD, but has no Lewy bodies (LB) on autopsy, or patients with parkin mutations without LB; do they not have PD?*

What Features Fit Under the PD Umbrella?

DLB

The issue: A patient developed cognitive impairment 18 months after PD diagnosis; he has PD dementia (PDD). Another developed cognitive impairment 10 months after PD diagnosis; according to current definitions, the initial diagnosis was "wrong," and she has DLB. Does this make sense?



PD Subtypes

The issue: A patient had unilateral tremor onset at age 40, robust L*-dopa response with fluctuations and, 20 years later, has few nonmotor features. A second developed bilateral bradykinesia and rigidity at age 80 and had no fluctuations, but had severe constipation, urinary dysfunction, sleep disturbance, and depression, eventually dying with dementia. Do these patients have the same disease?*

The Beginning of PD

The issue: A patient has RBD, olfactory loss, constipation, and depression, but no parkinsonism. Dopaminergic neuroimaging and SN ultrasound are abnormal. Doesn't this patient have PD?

Therefore ***the task force proposes*** the following:

1. Formal MDS diagnostic criteria should be created for the diagnosis of clinical PD.
2. Parkinsonism should remain a core feature of PD, based upon a combination of cardinal manifestations. The criteria should include clear definitions of what constitutes each cardinal manifestation, including explicit instructions for examination.
3. The benchmark of diagnostic criteria should be the expert clinical examination.
4. Criteria should incorporate both negative features (that argue against diagnosis) and positive features (that argue for diagnosis).
5. Criteria should be weighted, so that features that are highly specific for alternate conditions are differentiated from less specific "red flags."
6. Criteria should incorporate a time component, such that certainty can increase with longer disease duration, and individual diagnostic criteria can be applied differentially in early versus late disease.
7. Criteria should incorporate different levels of certainty, delineated as "clinical PD" (highly specific, but not necessarily sensitive or representative) and "possible PD" (balancing specificity and sensitivity).
8. Although ancillary diagnostic tests can be incorporated, only tests that have been extensively proven as specific diagnostic markers in PD should be included. Moreover, they should be considered as ancillary only and not be essential to making diagnosis.

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

Movement Disorders, Vol. 30, No. 12, 2015

Centrality of Motor Syndrome—Parkinsonism and PD

Criteria Benchmark—The Expert Examination

Full diagnostic certainty is impossible during life; between 75% and 95% of patients diagnosed with PD by experts have their diagnosis confirmed on autopsy.[8-12] Diagnostic accuracy varies considerably according to

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Bradykinesia

Bradykinesia is defined as slowness of movement AND decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued. Brady-

Rest Tremor

Rest tremor refers to a 4- to 6-Hz tremor in the fully resting limb, which is suppressed during movement initiation. Rest tremor can be assessed during the entire interview and examination (MDS-UPDRS 3.17, 3.18). Kinetic and postural tremors alone (MDS-UPDRS 3.15 and 3.16) do not qualify for parkinsonism criteria.

Rigidity

As outlined in the MDS-UPDRS, rigidity is judged on "slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck." Rigidity refers to "lead-pipe" resistance; that is, velocity-independent resistance to passive movement not solely reflecting failure to relax (ie, distinct from spasticity or paratonia).

Once Parkinsonism has been diagnosed

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive Criteria

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:

a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).

b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute Exclusion Criteria

- ☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- ☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- ☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
- ☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
- ☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
- ☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- ☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
- ☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
- ☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red Flags

- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Criteria Applications

1. Does the patient have parkinsonism, as defined by the MDS criteria? Yes ☐ No ☐
   If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes:*
2. Are any absolute exclusion criteria present? Yes ☐ No ☐
   If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no:*
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria *and* no red flags? Yes ☐ No ☐
   If yes, patient meets criteira for **clinically established PD**. *If no:*
6. Are there more than 2 red flags? Yes ☐ No ☐
   If "yes," probable PD *cannot* be diagnosed. *If no:*
7. Is the number of red flags equal to, or less than, the number of supportive criteria? Yes ☐ No ☐
   If yes, patient meets criteria for **probable PD**

REVIEW

CME

MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1*] Ronald B. Postuma, MD, MSc,[2*] Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

Movement Disorders, Vol. 30, No. 12, 2015

Likelihood-ratio of risk markers

Risk markers		
Male sex	1.2 (male)	0.8 (female)
Regular pesticide exposure	1.5	n/a
Occupational solvent exposure	1.5	n/a
Nonuse of caffeine	1.35	0.88
Smoking		
Current	n/a	0.45
Never	1.25	n/a
Former	n/a	0.8
Sibling had PD with age onset <50	7.5	n/a
or		
Any other first-degree relative with PD	2.5	n/a
or		
Known gene mutation	see Supporting Table II	n/a
SN hyperechogenicity	4.7	0.45

Likelihood-ratio of prodromal markers

Prodromal markers		
PSG-proven RBD	130	0.62
or		
Positive RBD screen questionnaire with >80% specificity	2.3	0.76
Dopaminergic PET/SPECT clearly abnormal (e.g., <65% normal, 2 SDs below mean)	40	0.65
Possible subthreshold parkinsonism (UPDRS >3 excluding action tremor)	10	0.70
or		
Abnormal quantitative motor testing	3.5	0.60
Olfactory loss	4.0	0.43
Constipation	2.2	0.80
Excessive daytime somnolence	2.2	0.88
Symptomatic hypotension	2.1	0.87
Severe erectile dysfunction	2.0	0.90
Urinary dysfunction	1.9	0.90
Depression (± anxiety)	1.8	0.85

Movement Disorders, Vol. 38, No. 4, 2023

RESEARCH ARTICLE

Clinical Diagnostic Accuracy of Parkinson's Disease: Where Do We Stand?

Sasivimol Virameteekul, MD, MSc,[1,2] Tamas Revesz, PhD, FRCPath,[1] Zane Jaunmuktane, MD, FRCPath,[1] Thomas T. Warner, FRCP, PhD,[1,2] and Eduardo De Pablo-Fernández, MD, PhD[1,2*]

[1]*Department of Clinical and Movement Neurosciences, Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, London, United Kingdom*
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PARKINSON'S DISEASE DIAGNOSTIC ACCURACY

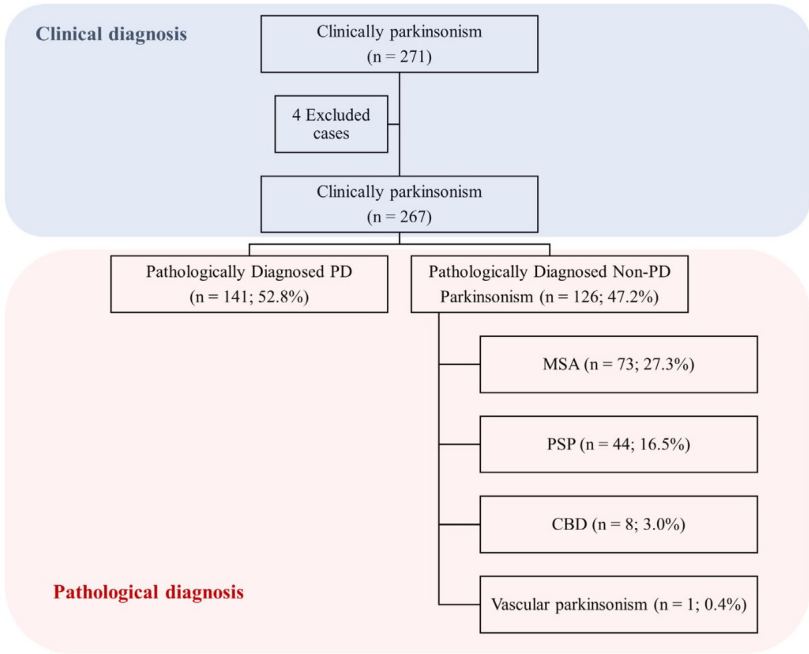

FIG. 1. Study design. PD, Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 *Sensitivity, specificity, predictive values, and accuracy of different diagnostic categories (and by type of clinician) for the diagnosis of Parkinson's disease at the early stage and after adequate follow-up*

	Sensitivity	Specificity	PPV	NPV	Accuracy
Early stage <5 years					
Clinical diagnosis	82.3 (74.9–88.2)	86.5 (79.3–91.9)	87.2 (80.3–92.4)	81.3 (73.7–87.5)	84.3 (79.3–88.4)
Expert clinical diagnosis	93.4 (86.2–97.5)	88.2 (76.1–95.6)	93.4 (86.2–97.5)	88.2 (76.1–95.6)	91.5 (85.7–95.6)
MDS clinically established early PD	68.8 (60.5–76.3)	98.4 (94.4–99.8)	98.0 (92.9–99.8)	73.8 (66.5–80.3)	NA[a]
MDS clinically probable PD	87.9 (81.4–92.8)	91.3 (84.9–95.6)	91.9 (85.9–95.9)	87.0 (80.2–92.3)	89.5 (85.2–92.9)
MDS clinically established PD	58.2 (49.6–66.4)	99.2 (95.7–100.0)	98.9 (93.5–100.0)	67.9 (60.7–74.6)	NA[a]
Final stage					
Clinical diagnosis	83.0 (75.7–88.8)	98.4 (94.4–99.8)	98.3 (94.1–99.8)	83.8 (76.8–89.3)	90.3 (86.1–93.5)
Expert clinical diagnosis	94.6 (87.8–98.2)	98.9 (93.8–100.0)	98.9 (93.8–100.0)	94.6 (87.8–98.2)	96.7 (92.9–98.8)
MDS clinically probable PD	87.9 (81.4–92.8)	97.6 (93.2–99.5)	97.6 (93.3–99.5)	87.9 (81.3–92.8)	92.5 (88.7–95.4)
MDS clinically established PD	63.1 (54.6–71.1)	99.2 (95.7–100.0)	98.9 (94.0–100.0)	70.6 (63.3–77.2)	NA[a]

Note: Data are presented as percentage (95% confidence interval).

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; MDS, International Parkinson and Movement Disorder Society; PD, Parkinson's disease; NA, not applicable.

[a]As MDS clinically established categories were designed to maximize specificity, a measure of global diagnostic accuracy is not considered appropriate.

Major advances in the field of tissue and fluid-based bio- markers

- abnormal synuclein deposition in skin and digestive tract using immunohistochemistry

- synuclein seeding assays in CSF, skin and other body tissues,10 and perhaps even blood

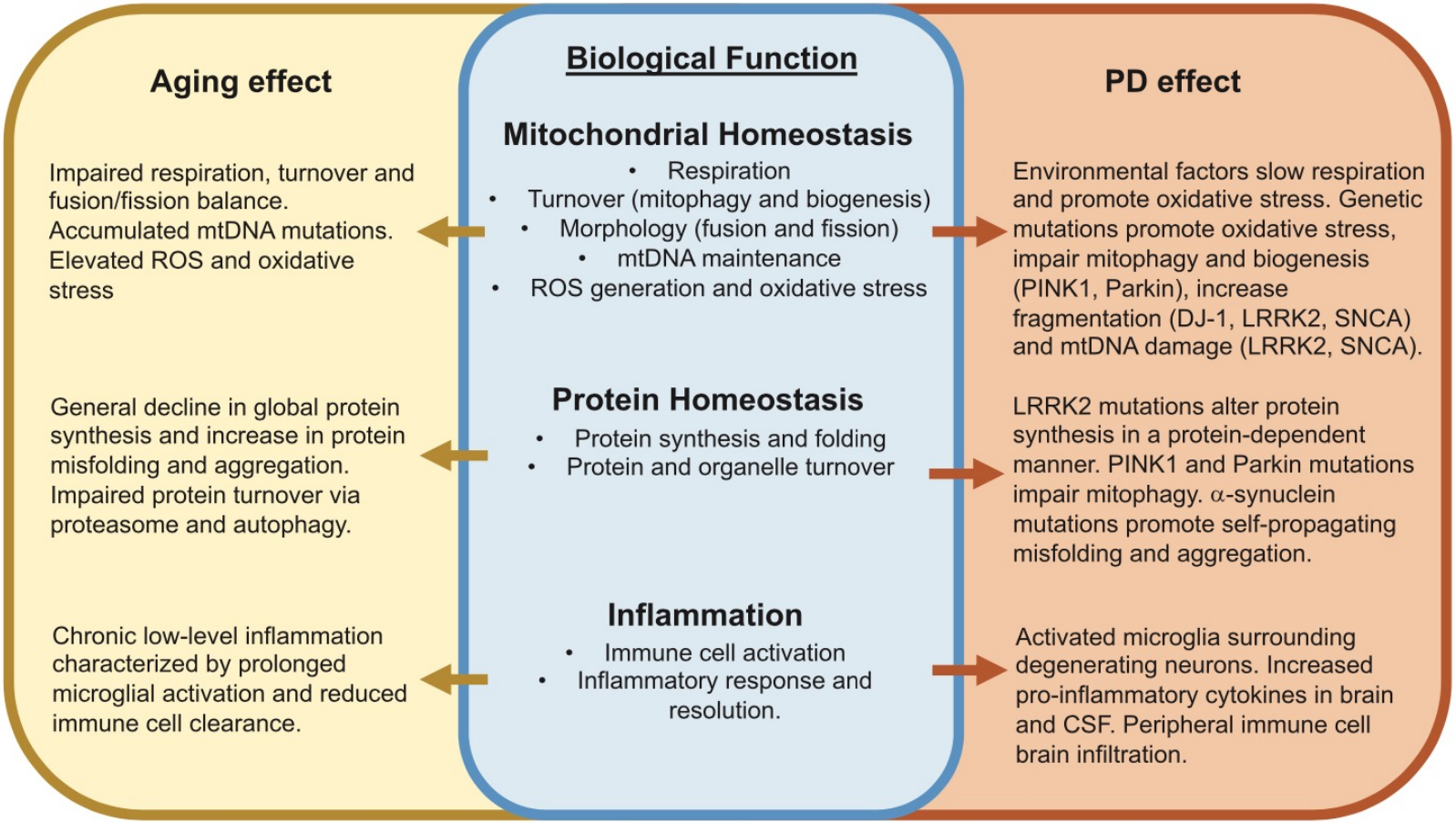

Fig. 1. Convergent effects of aging and Parkinson's disease development on key biological functions. Major overlapping effects of aging and PD on mitochondrial homeostasis, protein homeostasis and inflammation are described. See text for additional details. ROS, reactive oxygen species.

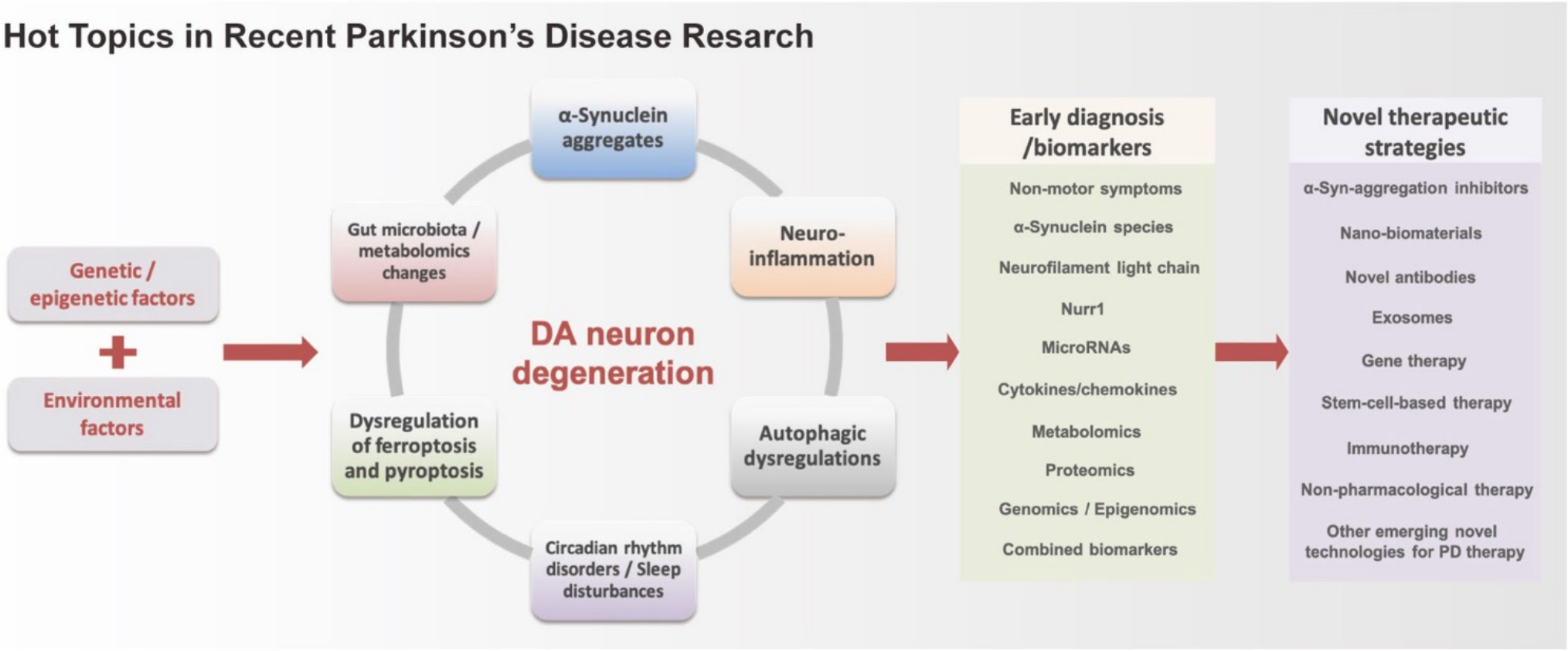

Fig. 1 Hot topics in recent Parkinson's disease research.

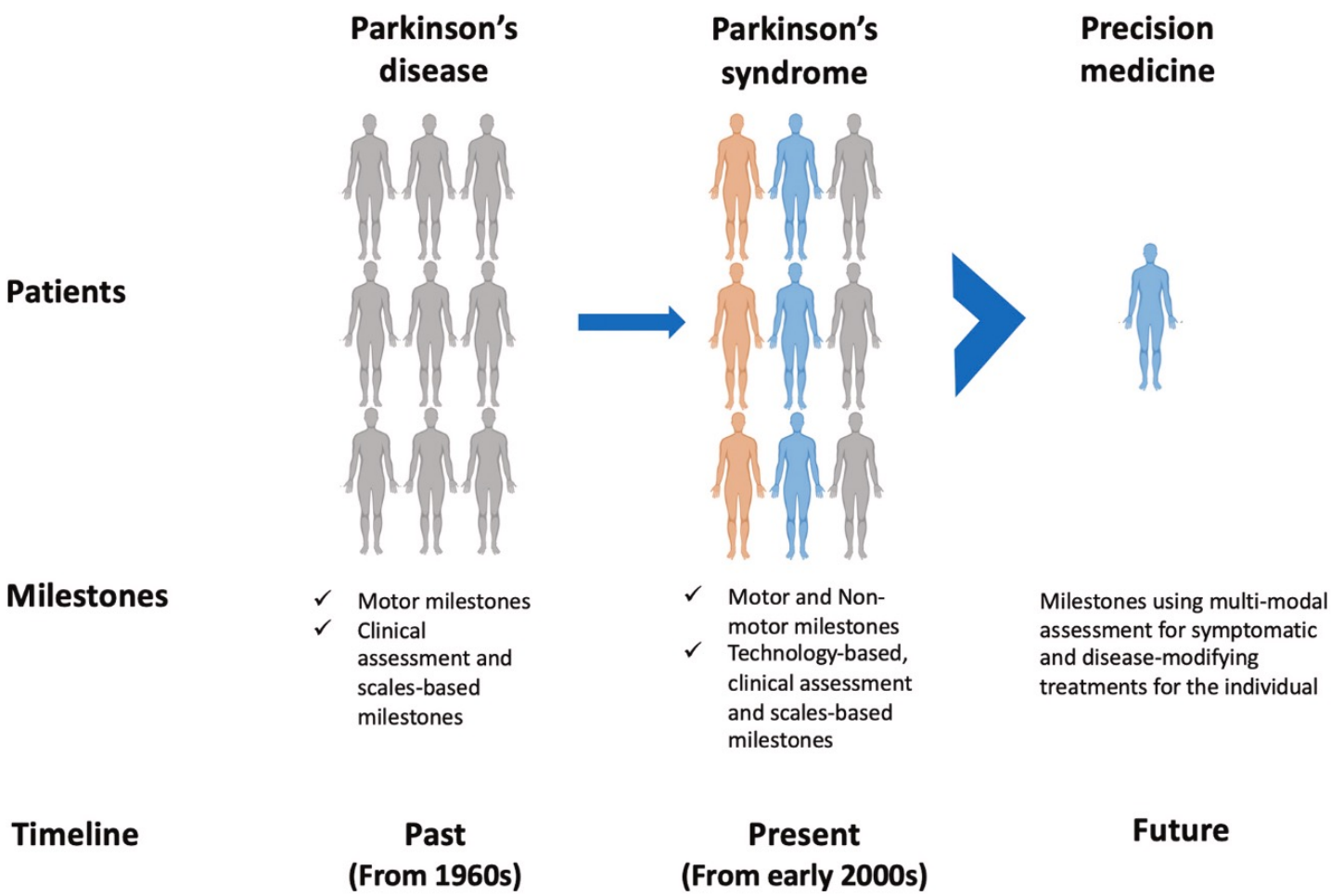

Fig. 1. Schematic representation of the main theme of the article. The concept Parkinson's disease has changed over time, from the past "one size fits all" era to the more recent "Parkinson's syndrome" approach (stratified medicine), and so have disease milestones. During the 1960s, motor milestones started to have importance in the assessment of disease progression. Later, non-motor disease milestones started to have their importance in the metric of disease progression. A current challenge is to assess disease milestones with technology-based objective measures (TOMs) to help clinicians in a more objective and easily recognition of these endpoints. In the future, precision medicine will allow to tackle different subgroups of Parkinson's diseases with different disease-modifying therapies, and disease milestones will be more important in assessing the effect of these treatments.

Concept Paper

Towards a Biological Definition of Parkinson's Disease

Günter U. Höglinger[1], Charles H. Adler[2], Daniela Berg[3], Christine Klein[4], Tiago F. Outeiro[5], Werner Poewe[6], Ronald Postuma[7], A. Jon Stoessl[8] and Anthony E. Lang[9]

pose a biologically based definition for the diagnosis of Parkinson's disease, initially to be used for research purposes. The criteria use a three-component 'G-S-N' system. The first is documentation of defined gene variants ('G'), which cause or strongly predispose to PD as the most upstream component. The second is α-synuclein pathology ('S'), currently defined as pathological α-synuclein deposition in tissue or positive α-synuclein seeding assays. The third is evidence of underlying neurodegeneration ('N'), currently defined by specific neuroimaging procedures. The associated clinical syndrome ('C') is defined by a single high-specificity feature or multiple lower-specificity features. Initiating this transition will enable the field to fuel both basic and clinical research and

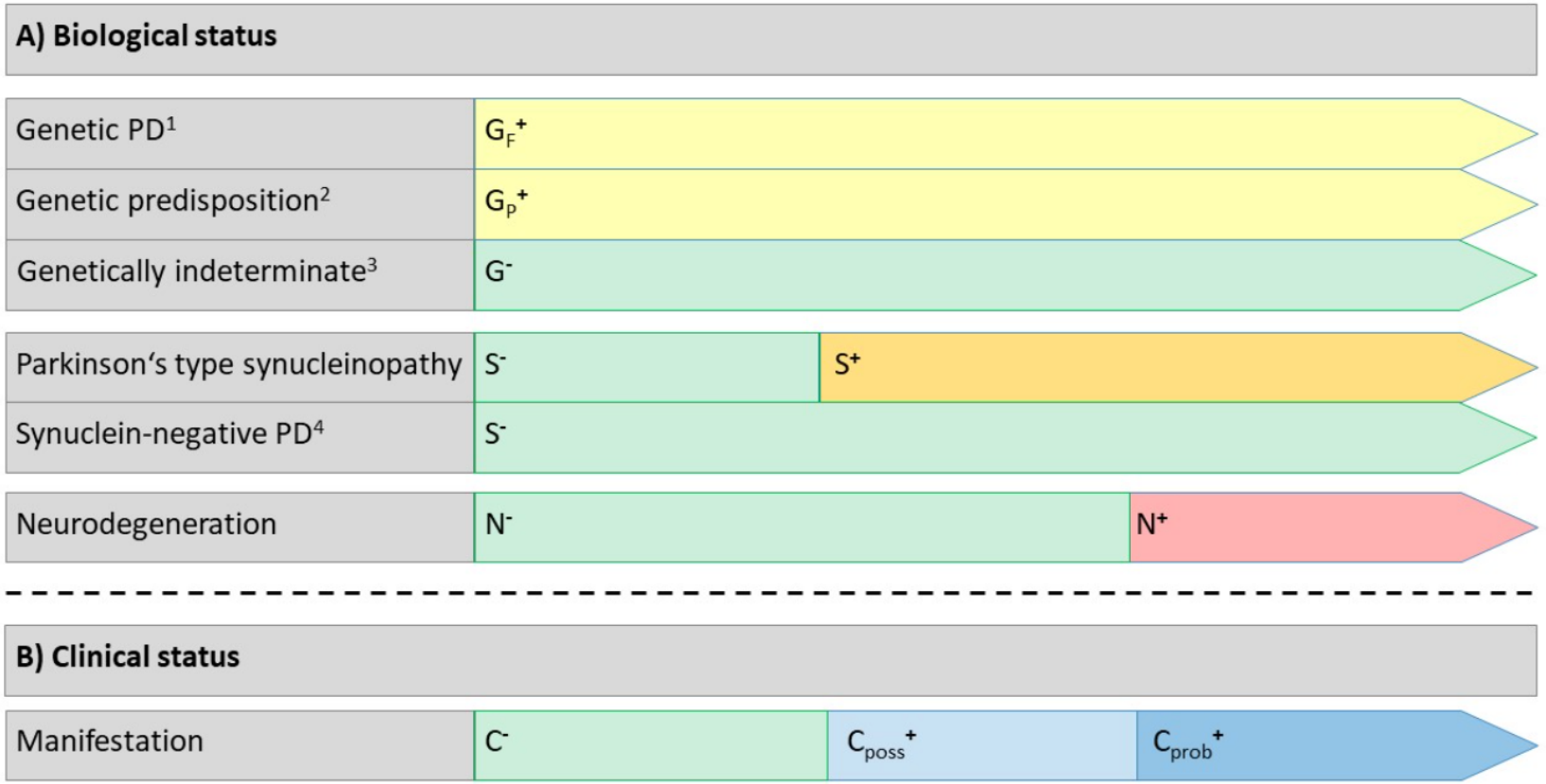

Figure 1. Research framework of PD biological definitions.

Temporal sequence and variability of the components contributing to the biological definition of PD. Green bars indicate a physiological condition, other colours indicate pathological conditions.


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