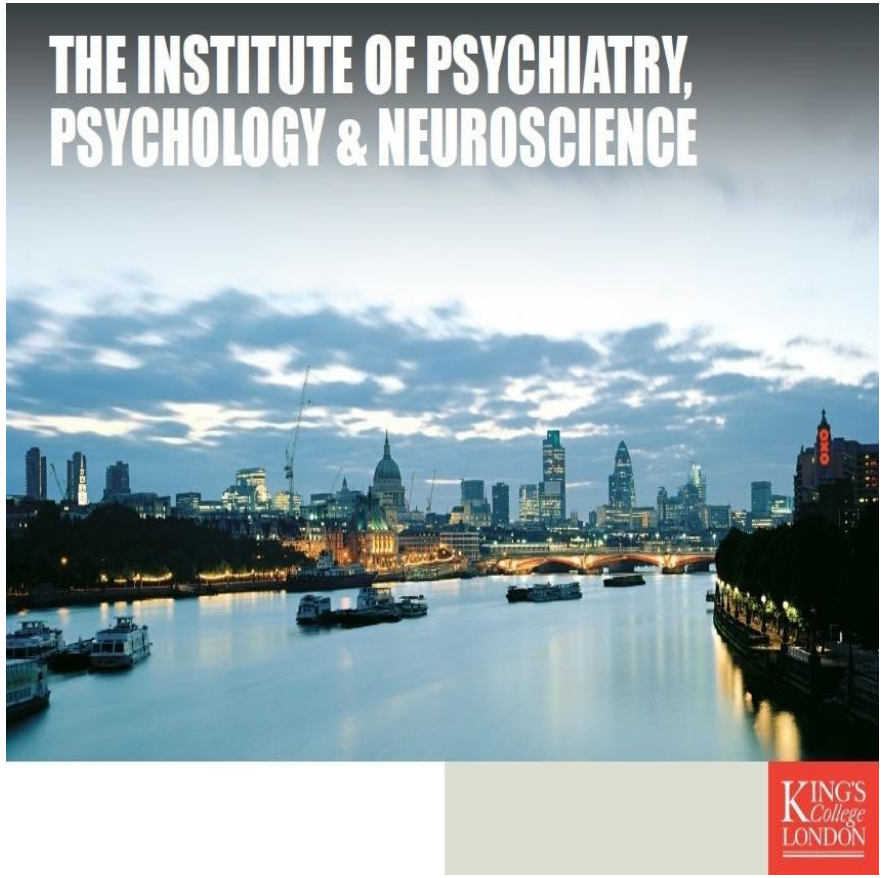
The Parkinson's Syndrome

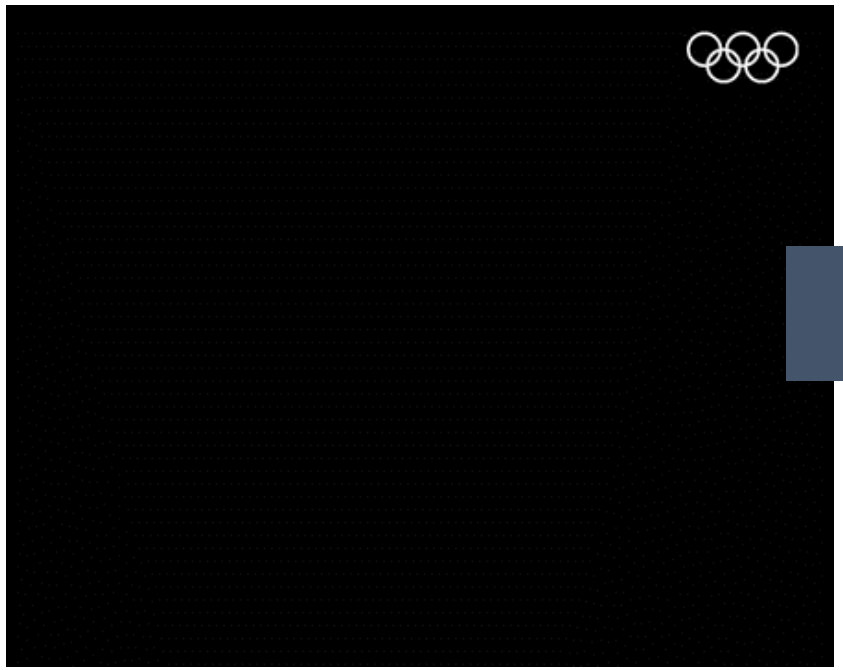
K RAY CHAUDHURI (RAY CHAUDHURI)

National Parkinson Foundation International Centre of Excellence, Kings College Hospital, Kings College, London



MOTOR

NONMOTOR



Neuropsychiatric and Cognitive
e.g. depression, anxiety, apathy and dementia

Autonomic dysfunction

Drug induced
e. g. Hallucinations, ICD/DAWS

Gastrointestinal disorders

Non-motor symptoms

Sensory disorders
e. g. pain, RLS, olfaction vision

Sleep disorders

Urinary disorders

Fatigue, Sexual dysfunction

Chaudhuri et al. Lancet Neurol 2006; Chaudhuri and Schapira Lancet Neurol 2009

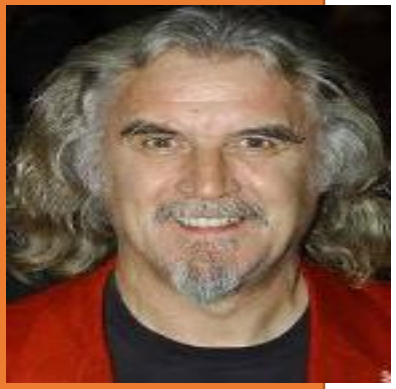
Reference: New Stem Cell Research Offers hope for Parkinson's disease, a Disorder Linked to Mitochondrial Dysfunction
Posted on August 15, 2013 by FMM General

Famous people affected by Parkinson´s disease

- Muhammad Ali
- Michael J. Fox
- Johnny Cash
- Billy Graham
- Billy Connolly
- Barbara Thompson
- Estelle Getty






The Parkinson Pandemic—A Call to Action

Dorsey. JAMA Neurology 2018

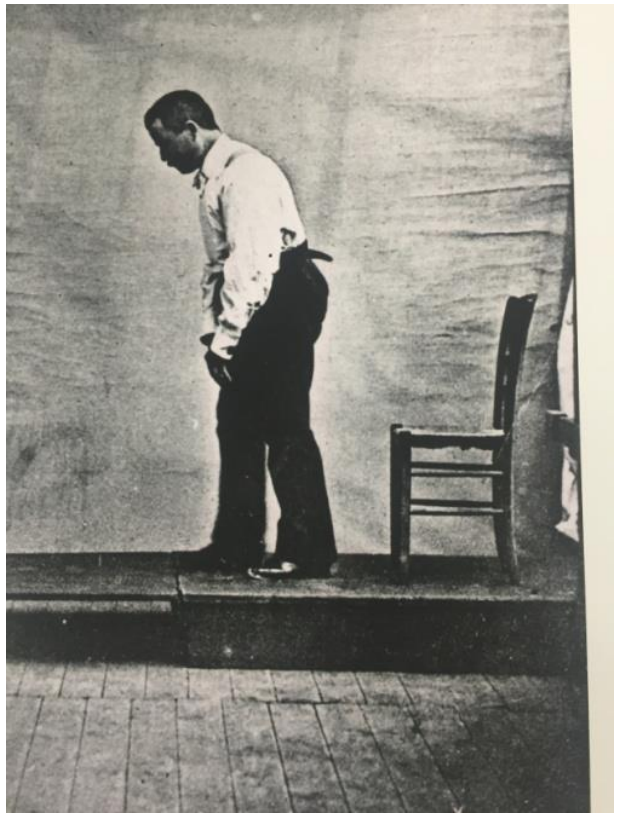
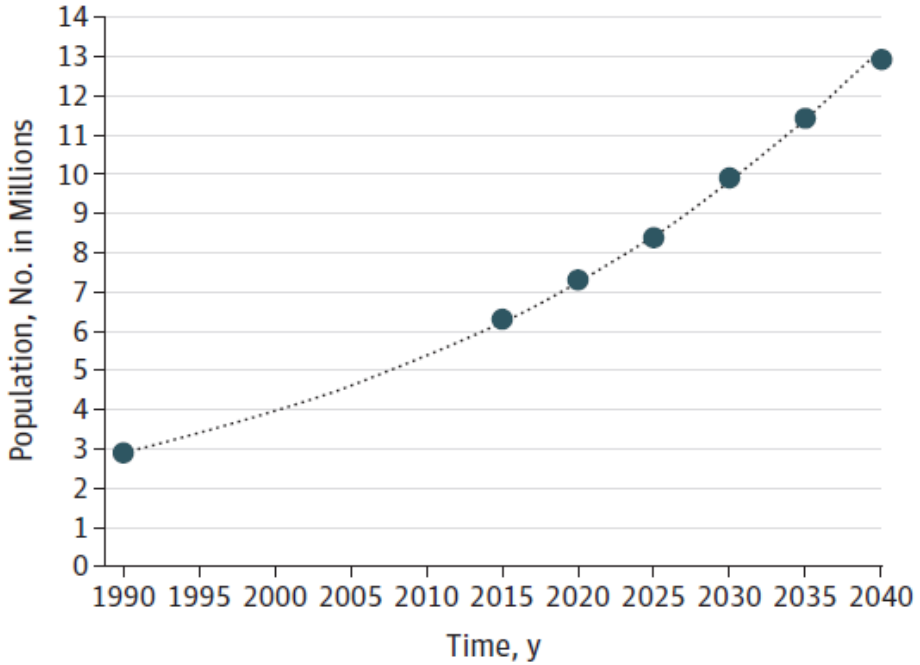


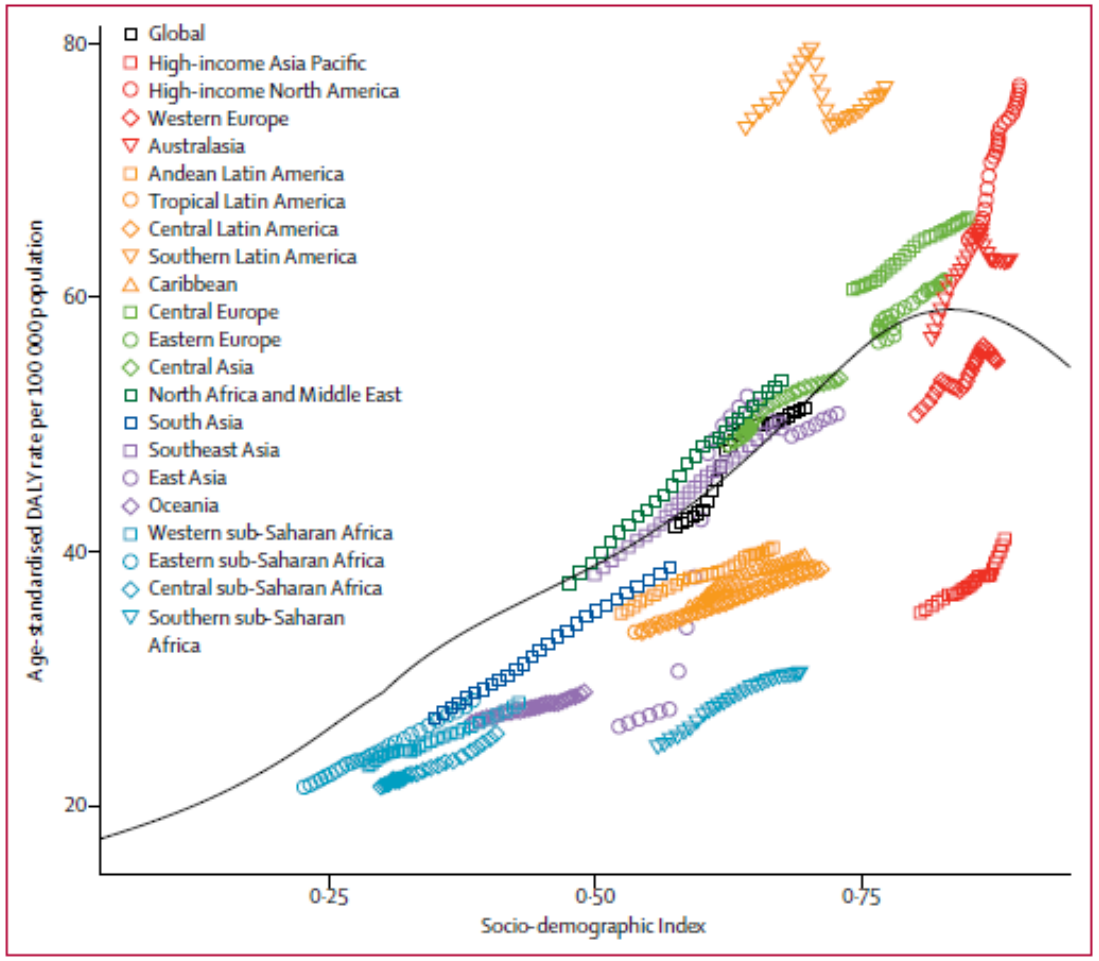
Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040



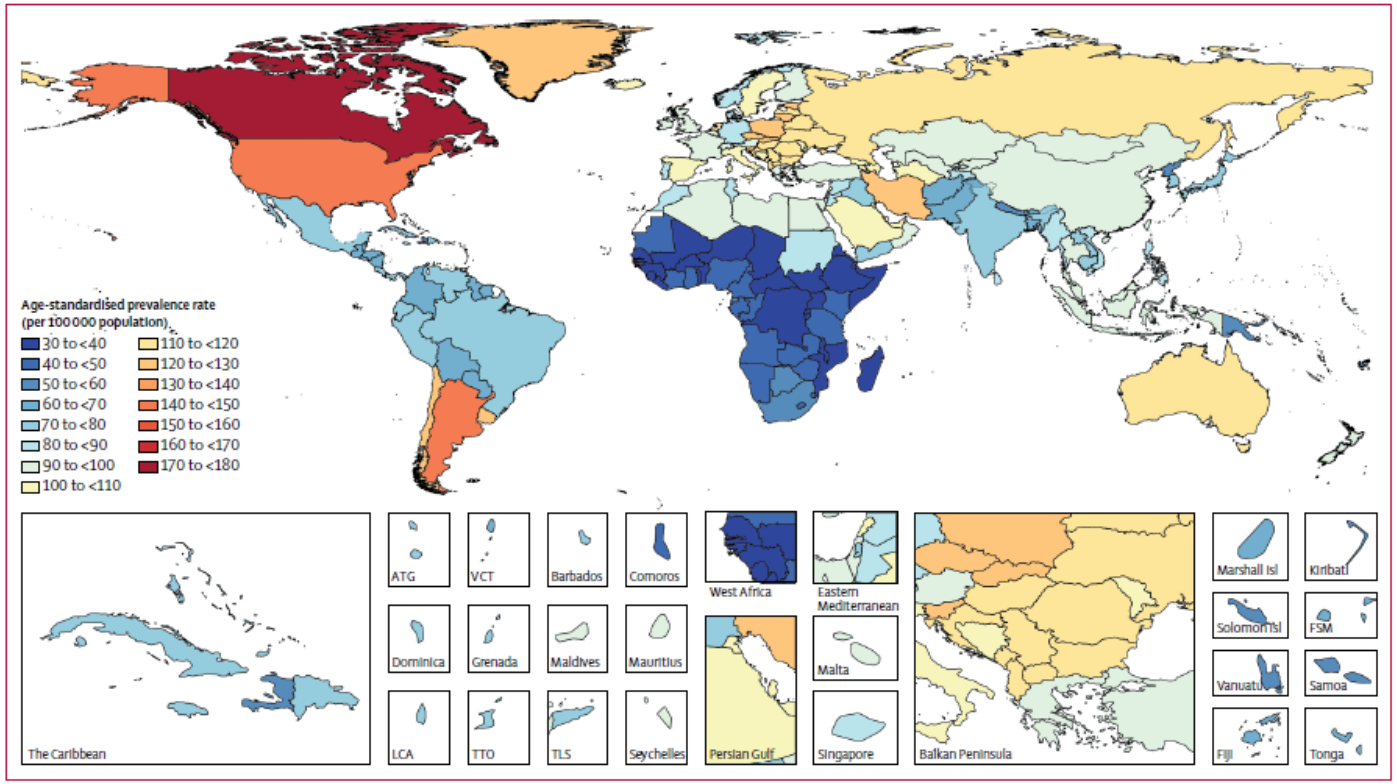
Sources: Global Burden of Disease Study (1990 and 2015) and projections based on published[2] and public[3] sources.

6.1 million people with PD worldwide in 2016, compared with 2.1 million in 1990.

PD was estimated to cause 3.2 million disability-adjusted life years (DALYs) and this impact was greatest in high SDI countries



Greater proportions with PD in regions with a high income (e.g. Canada, US, Western Europe, 90 – <180/100,000) compared with low income (e.g. sub-Saharan Africa, 30 - <70/100,000)



GBDPsD. Lancet Neurol 2018

No Cure

No disease modification

No neuroprotection

Levodopa (1962) is still the best drug

Billions spent in clinical trials

J Neural Transm
DOI 10.1007/s00702-016-1667-6

Parkinson's: a syndrome rather than a disease?

Nataliya Titova[1] · C. Padmakumar[2] · Simon J. G. Lewis[3] · K. Ray Chaudhuri[4,5]

Table 1 List of proposed mechanisms and pathophysiological basis for the expression of clinical signs of Parkinson's disease

Genetics and epigenetics
LRRK2, GBA mutations, and higher rates of PD in certain ethnic groups, such as Ashkenazi Jews, Inuit populations
Dietary or occupational exposure to organic toxins (insecticides for example)
Gene interaction with environment (higher risk in agricultural communities, lower risk in smokers, head trauma)
Alpha-synuclein abnormalities
Misfolding, oligomeric form, and altered proteostasis and neurotoxicity
Susceptibility of ageing brain
Synaptic dysfunction and loss of synaptic level functioning
Prion-like intra axonal transport (gut to brain)
Amyloid and Tau deposition particularly in older PD and dementia
Mitochondrial dysfunction (reduced complex 1 activity)
Oxidative stress causing cell damage and death
Neuroinflammation which may trigger misfolding of alpha-synuclein
Altered gut microbiota and reduced mucin increasing gut permeability and possible inflammatory spread to brain
Neurotransmitter linked abnormalities (selective or in combination as detailed in the paper)
Alteration in cerebral functional network and signaling function
Adenosine receptor abnormalities

DOI: 10.1002/hbm.24585

RESEARCH ARTICLE

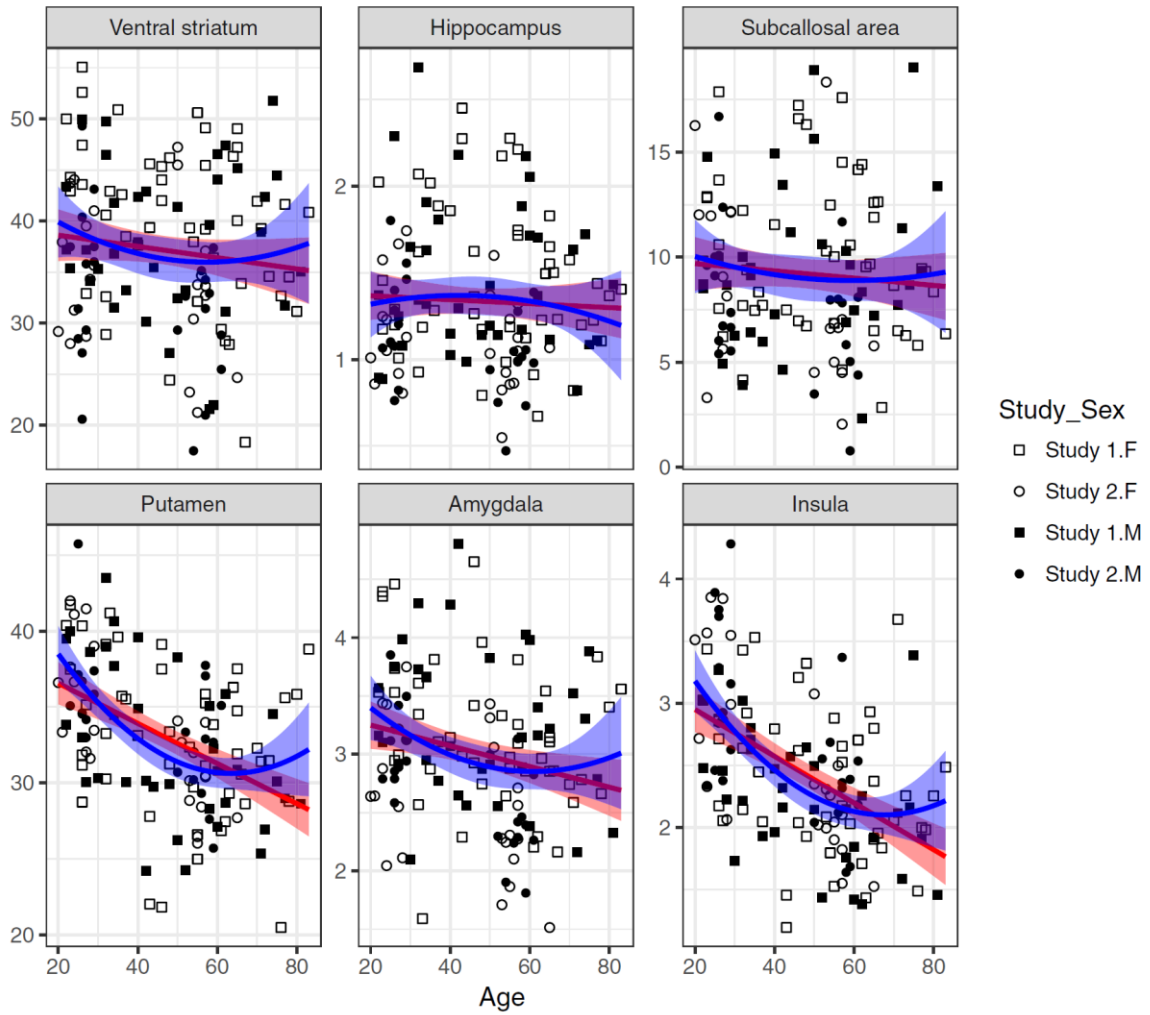
WILEY

Hum Brain Mapp. 2019;1–14.

Differential regional decline in dopamine receptor availability across adulthood: Linear and nonlinear effects of age

Kendra L. Seaman[1,2] | Christopher T. Smith[3] | Eric J. Juarez[4] | Linh C. Dang[3] | Jaime J. Castrellon[4] | Leah L. Burgess[3] | M. Danica San Juan[3] | Paul M. Kundzicz[3] | Ronald L. Cowan[3] | David H. Zald[3] | Gregory R. Samanez-Larkin[2,4]

regions showed linear effects of age while many showed curvilinear effects such that binding potential declined from young adulthood to middle age and then was relatively stable until old age. Overall, these data indicate that the rate and pattern of decline in D2 receptor availability is regionally heterogeneous. However, the differences across regions were challenging to organize within existing theories of brain development and did not show the same pattern of regional change that has been observed in gray matter volume, white matter integrity, or cognitive performance. This variation suggests that existing theories of adult brain development may need to be modified to better account for the spatial dynamics of dopaminergic system aging.



Journal of Neurology
https://doi.org/10.1007/s00415-018-9100-8

REVIEW

Amyloid-β and Parkinson's disease

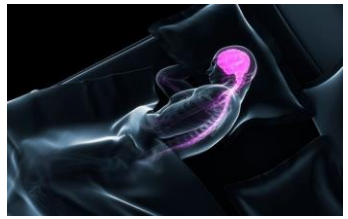
Ee Wei Lim[2,3,4] · Dag Aarsland[1] · Dominic Ffytche[1] · Raquel Natalia Taddei[2] · Daniel J. van Wamelen[1,2,5] · Yi-Min Wan[1,2,6] · Eng King Tan[3,4] · Kallol Ray Chaudhuri[1,2] on behalf of Kings Parcog groupMDS Nonmotor study group

Rainey-Smith et al. *Translational Psychiatry* (2018)8:47
DOI 10.1038/s41398-018-0094-x

Translational Psychiatry

ARTICLE Open Access

Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-amyloid burden



NMRC FELLOWSHIP WITH E K TAN

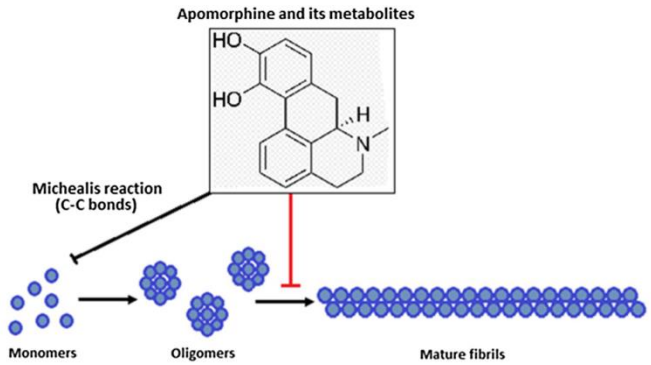
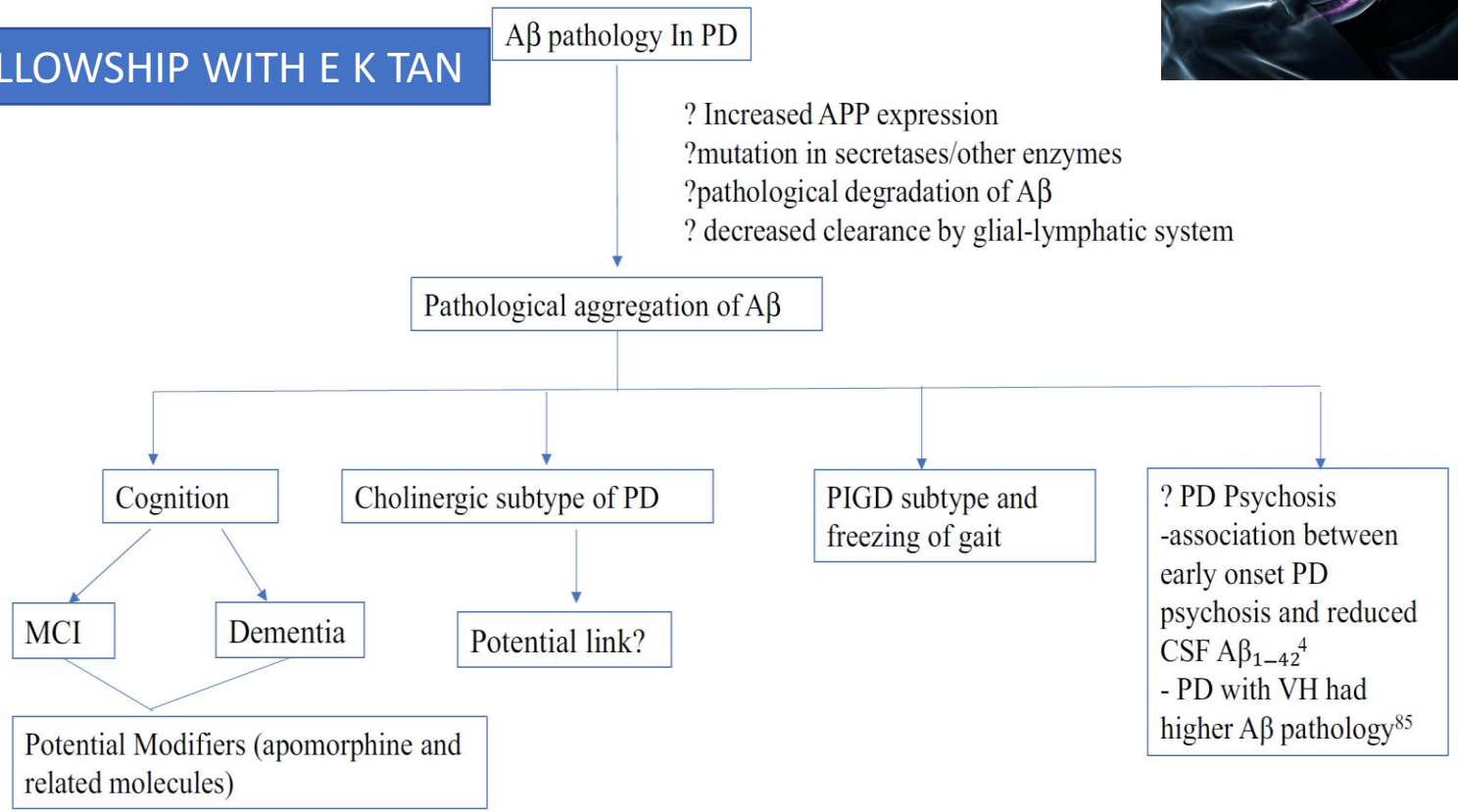
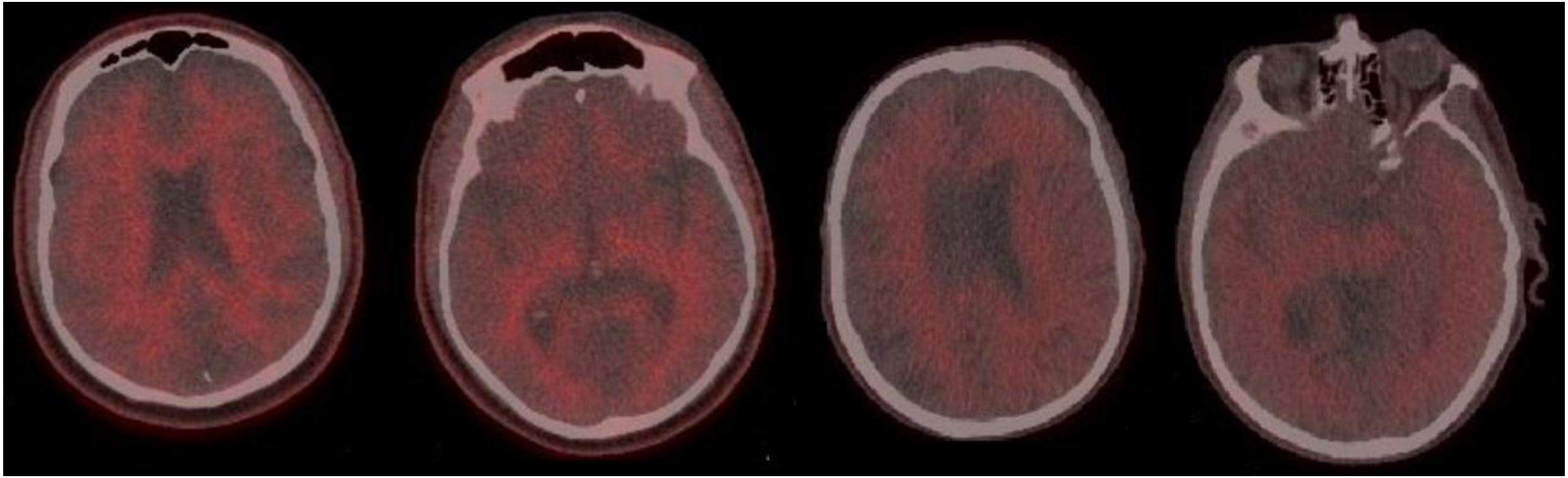


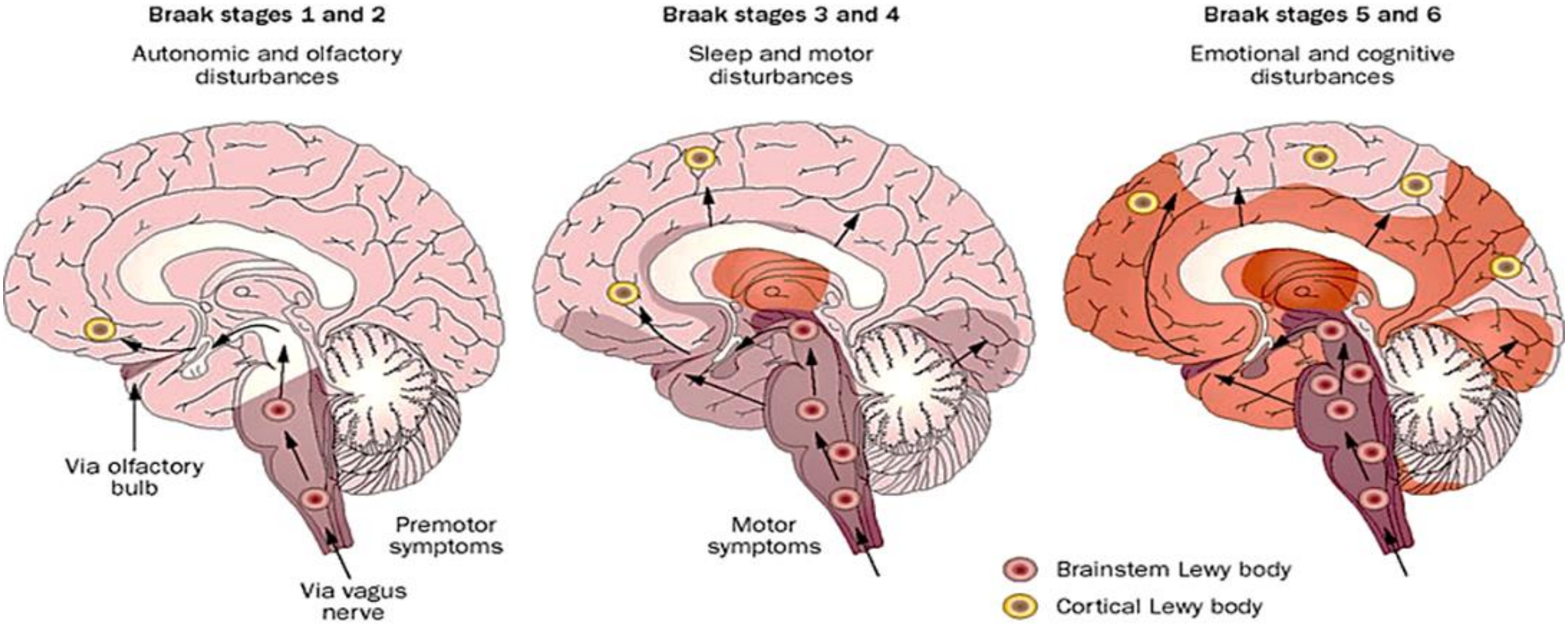
Fig. 3 Possible effects of apomorphine on Aβ which include decreased formation of amyloid oligomers from monomers via Michealis reaction and interfered amyloid fibrils formation from oligomers



PET scan

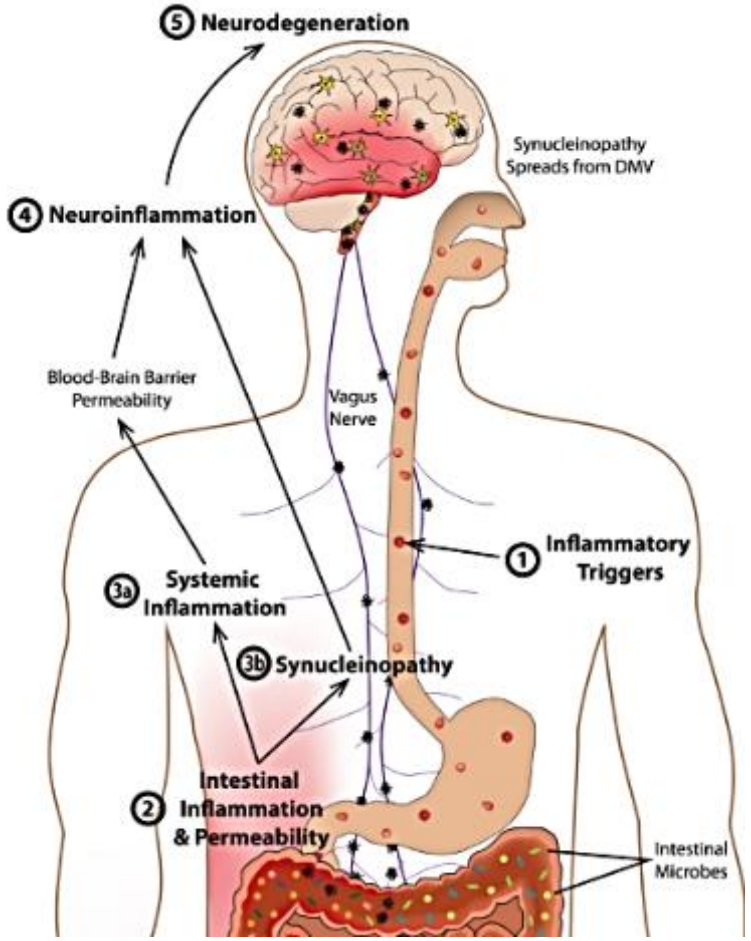


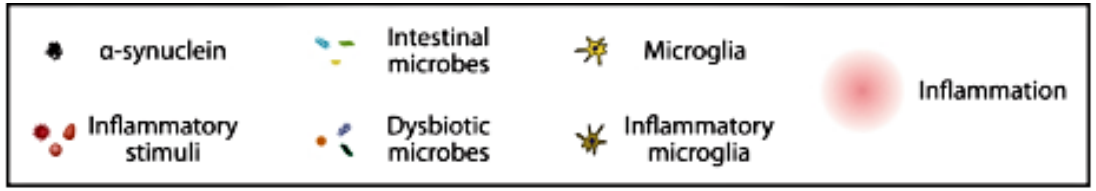
Braak staging and the dual-hit mechanism



Braak et al. J Neurology. 2002;24:1432-1459.

Gut-originating, inflammation-driven PD pathogenesis





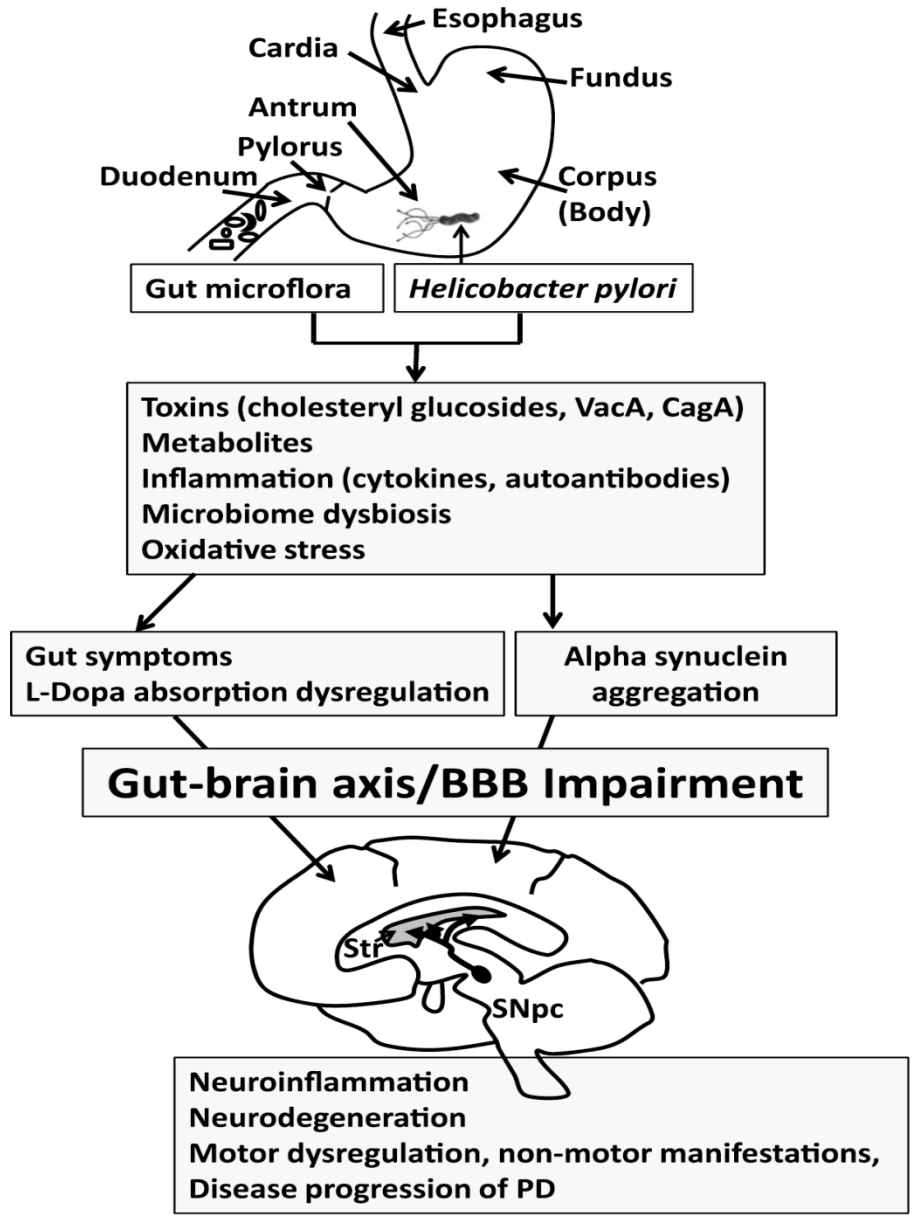
Houser and Tansey. NPJ Parkinsons Dis. 2017.11;3:3.

Journal of Parkinson's Disease 8 (2018) 367–374
DOI 10.3233/JPD-181327
IOS Press

Review

Stomaching the Possibility of a Pathogenic Role for *Helicobacter pylori* in Parkinson's Disease

David J. McGee[a,*], Xiao-Hong Lu[b] and Elizabeth A. Disbrow[b,c]



One disease ????

Parkinson's Heterogeneity

Motor and Nonmotor Subtypes

Annals of Medicine, 2013; 45: 511–521
© 2013 Informa UK, Ltd.
ISSN 0785-3890 print/ISSN 1365-2060 online
DOI: 10.3109/07853890.2013.849003

REVIEW ARTICLE

Glucocerebrosidase mutations and the pathogenesis of Parkinson disease

Michelle S. Beavan & Anthony H. V. Schapira

Rapid progression
Cognitive failure
No Ldopa response noted

PD

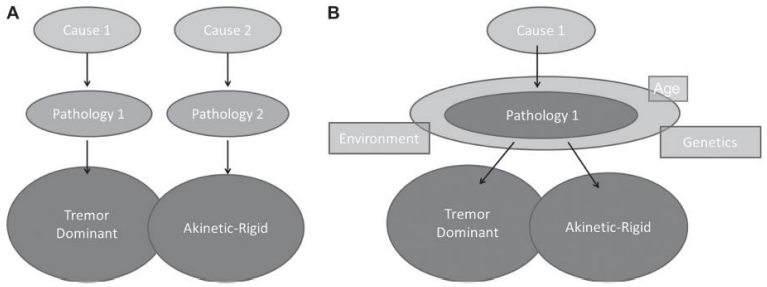


Figure 1 Possible reasons for distinct subtypes of Parkinson's disease. (A) Subtypes of Parkinson's disease may have separate causes and pathophysiology. (B) Subtypes of Parkinson's disease may share aetiological factors and pathophysiological processes, in which cases patient specific modifying factors (eg, age, environment, genetics) must account for the different manifestations.

Movement disorders

REVIEW

Parkinson's disease subtypes: lost in translation?

Connie Marras,[1,2] Anthony Lang[1,2]

Editor's choice
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npj | Parkinson's Disease
www.nature.com/npjparkd

ARTICLE OPEN

Parkinson's disease associated with pure *ATXN10* repeat expansion

Birgitt Schüle[1], Karen N. McFarland[2], Kelsey Lee[1], Yu-Chih Tsai[3], Khanh-Dung Nguyen[4], Chao Sun[4], Mei Liu[4], Christie Byrne[1], Ramesh Gopi[5], Neng Huang[6], J. William Langston[1], Tyson Clark[3], Francisco Javier Jiménez Gil[7] and Tetsudo Ashizawa[8]

npj Parkinson's Disease (2017)3:27 ; doi:10.1038/s41531-017-0029-x

Journal of Parkinson's Disease xx (20xx) x–xx
DOI 10.3233/JPD-140515
IOS Press

The Profile of Long-term Parkinson's Disease Survivors with 20 Years of Disease Duration and Beyond

Anhar Hassan[a,c,*], Samuel S. Wu[b], Peter Schmidt[d], Tanya Simuni[e], Nir Giladi[f], Janis M. Miyasaki[g], Bastiaan R. Bloem[h], Irene A. Malaty[a], Michael S. Okun[a] and on behalf of the NPF QII Investigators

Conclusions: PD-20 subjects reflect an elite group of PD survivors with early-onset disease and relatively mild cognitive disability despite long disease duration. Interventions for caregivers, mobility, and activities of daily living are areas that could improve caregiver burden and patient quality of life.

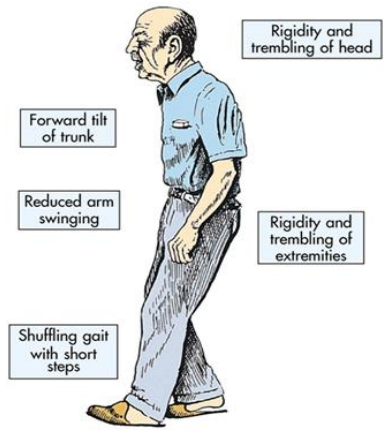

Bills
JAMES
PARKINSON
1755-1824
Physician and
Geologist
lived here


JAMES
PARKINSON
1755-1824
Physician and
Geologist
lived here

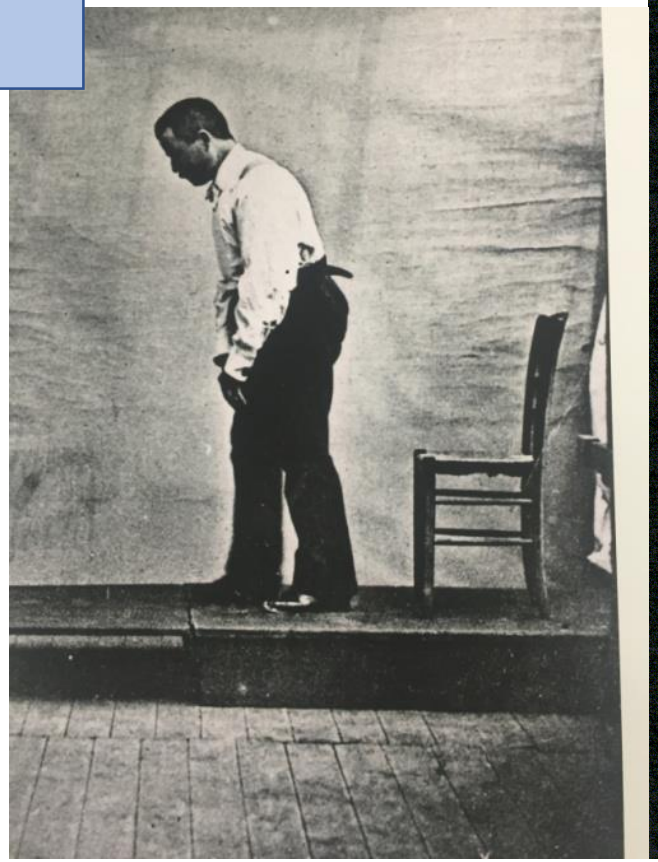
Dr James Parkinson recognised a mixture of a Motor Syndrome with NMS ! (1755–1828)

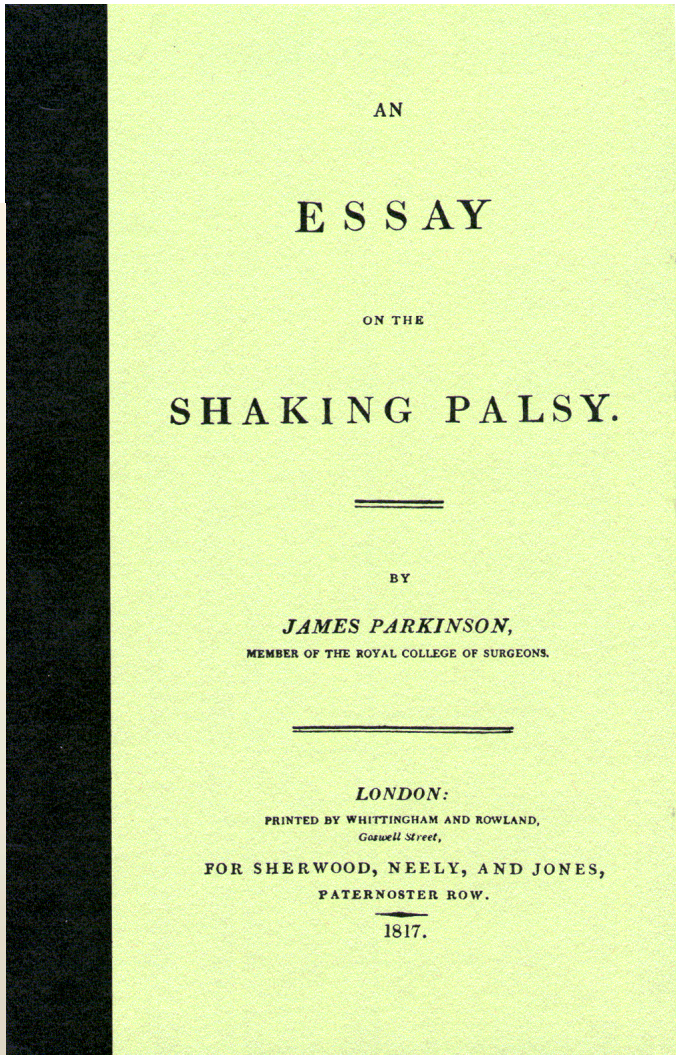
Described

- Pain
- Sleep dysfunction
- Dysautonomia
- Constipation
- Delusion



Prodromal PD: Pain




AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

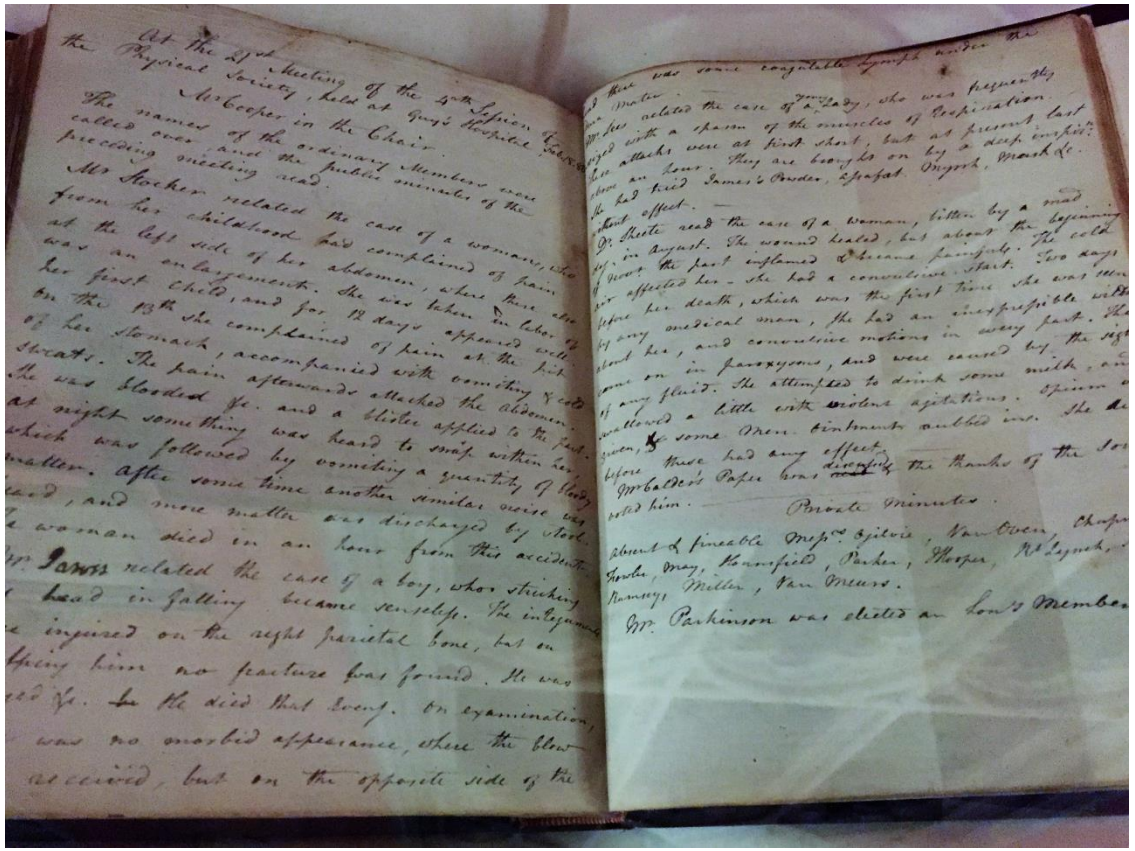
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

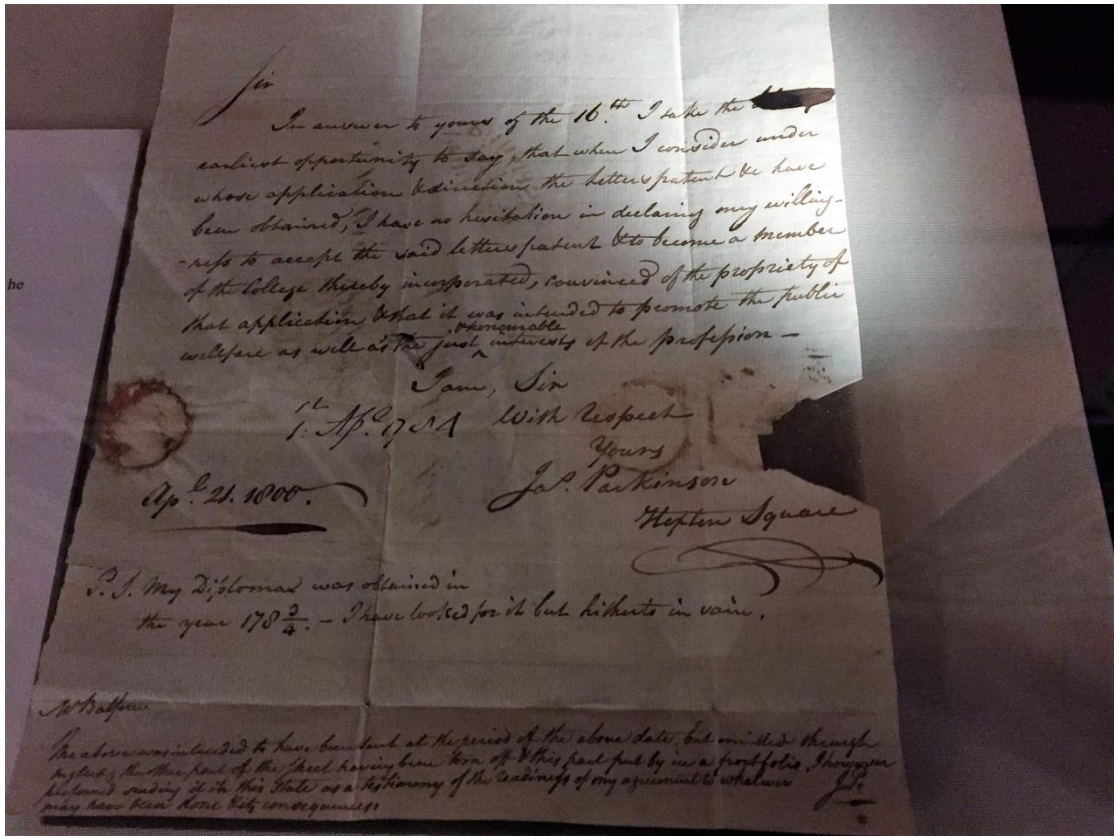
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.



Medical historians feel that the first case he described was in all probability one of multiple system atrophy.



last case was of considerable interest, since tremor disappeared following an attack of apoplexy.

James Parkinson Described the Hidden Face well inlcuding prodromal pain, but we chose to ignore !!!!

Table 1. Parkinson's description of non-motor symptoms [1]

Non-motor symptom	Parkinson's original description
Sleep	'In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm'
Constipation	'The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power: the expulsion of the faeces from the rectum sometimes requiring mechanical aid…'
Speech disturbance	'His words are now scarcely intelligible'
Dysphagia	'…and he is not only no longer able to feed himself, but when the food is conveyed to the mouth, so much are the actions of the muscles of the tongue, pharynx, impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the month until masticated; and then as difficultly swallowed.'
Sialorrhea	'the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth'
Incontinence	'The urine and faeces are passed involuntarily'

McDonald C, Gordon G, Hand A, Walker RW, Fisher JM. 200 Years of Parkinson's disease: what have we learnt from James Parkinson? Age Ageing. 2018 Mar 1;47(2):209-214. doi: 10.1093/ageing/afx196.

J Neural Transm
DOI 10.1007/s00702-016-1667-6

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Parkinson's: a syndrome rather than a disease?

Nataliya Titova[1] · C. Padmakumar[2] · Simon J. G. Lewis[3] · K. Ray Chaudhuri[4,5]

Modern concept of PD is that it is a syndromic condition[1]

Clinical subtypes and genetic heterogeneity: of lumping and splitting in Parkinson disease

Rainer von Coelln and Lisa M. Shulman

POINTS OF VIEW

The Parkinson's Complex: Parkinsonism Is Just the Tip of the Iceberg

J. William Langston, MD

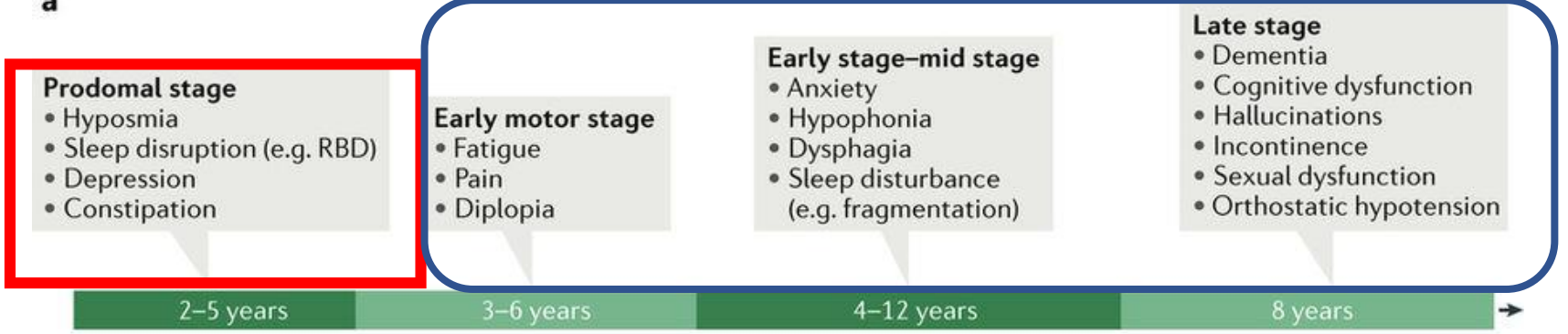
1. Titova N, et al. J Neural Transm (Vienna). 2017 doi: 10.1007/s00702-016-1667-6.
2. Chaudhuri KR, et al. Parkinsonism Rel Disord. 2011;17:717-23.
3. Langston . Ann Neurol 2006

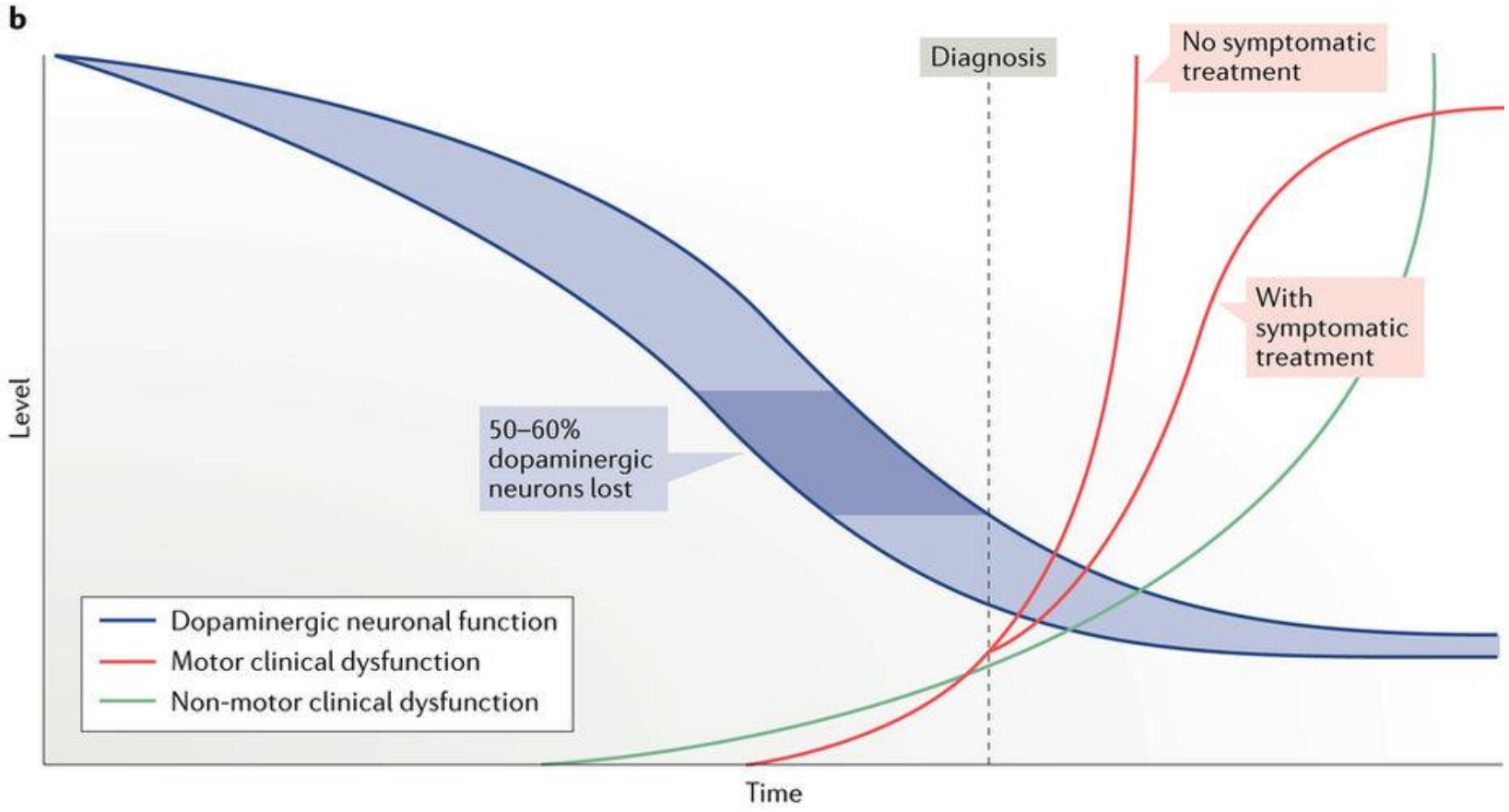
Calne DB. Is 'Parkinson's disease' one disease? J Neurol Neurosurg Psychiatry 1989; 52 (Suppl):18–21.
Weiner WJ. There is no Parkinson disease. Arch Neurol 2008; 65:705–708.

NATURE REVIEWS | NEUROSCIENCE
2017
REVIEWS

Non-motor features of Parkinson disease

Anthony H.V. Schapira[1], K. Ray Chaudhuri[2] and Peter Jenner[3]





Schapira, Chaudhuri, Jenner

Nature Reviews | Neuroscience

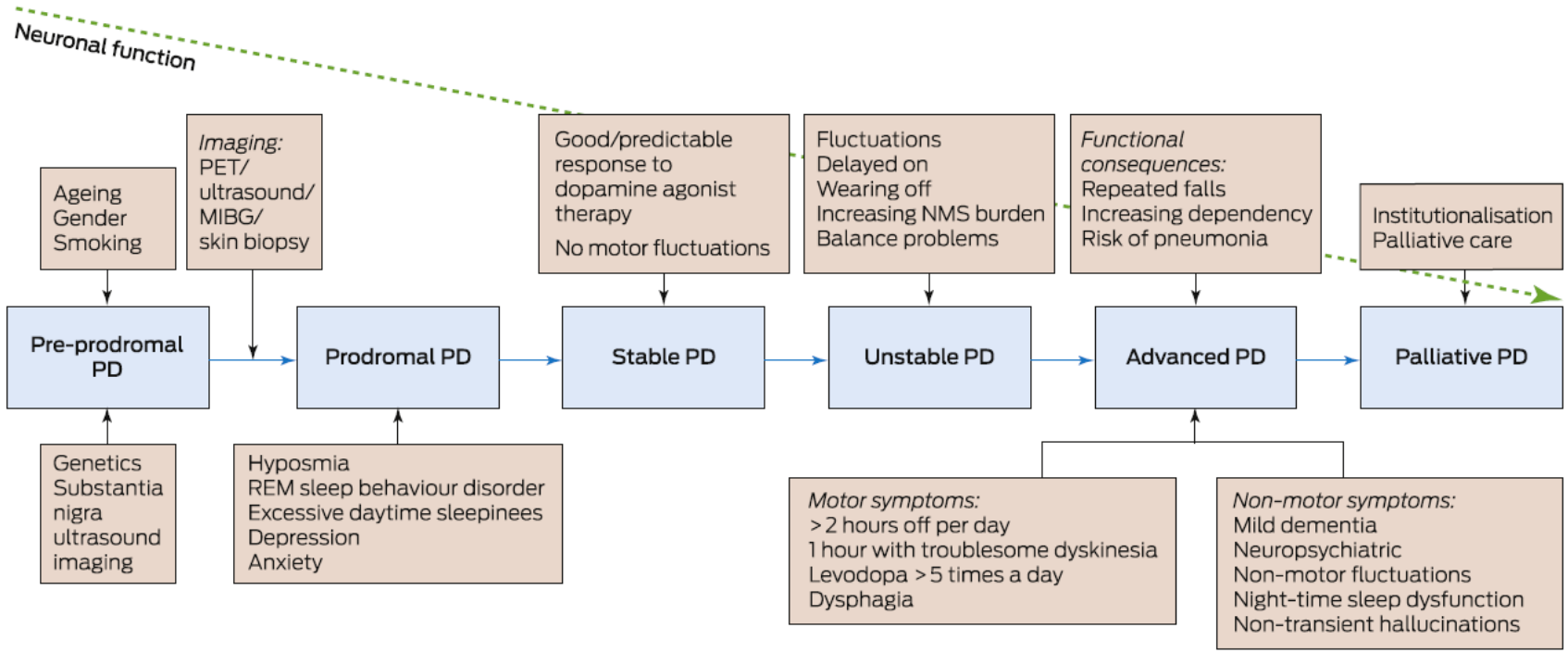
Narrative review

Non-motor Parkinson disease: new concepts and personalised management

2018

Nataliya Titova[1], K Ray Chaudhuri[2]

1 Natural history pattern of Parkinson disease (PD)



MIBG = meta-iodobenzylguanidine. NMS = non-motor symptoms. PET = positron emission tomography. REM = rapid eye movement. Note that the neuronal loss in PD is unlikely to follow a linear pattern (as suggested in the figure) and the relevant dotted line is a schematic representation. Imaging using transcranial ultrasound, PET and MIBG scans may be useful as markers in the prodromal period and possibly the pre-prodromal period. Skin biopsy may also be useful in patients with REM sleep behaviour disorder. Reproduced with permission from Titova et al.[11] ◆

CHAPTER FIVE

In. Nonmotor Parkinson'sThe Hidden Face. Chaudhuri, Titova, 2017

Genes and Nonmotor Symptoms in Parkinson's Disease

Ee-Wei Lim, Eng-King Tan[1]
National Neuroscience Institute, Duke NUS Medical School, Singapore, Singapore
[1]Corresponding author: e-mail address: tan.eng.king@singhealth.com.sg

Duke NUSM and King's

Table 1 Genetic Risk Factors for Cognitive Impairment in PD

Gene	Cognitive Impairment
GBA	+
ApoE	± (mostly positive)
MAPT	±
COMT	±
Inflammatory genes: IL10, IL17A	±
SNCA	± (sporadic), + (monogenic)
BDNF	±
FMR1	−
UBQLN1	−
LRRK2	No association or reduced prevalence

+: Positive association; −: no association; ±: mixed findings.

Table 2 Genetic Risk Factors for Psychosis in PD

Gene	Psychosis
GBA	+
MAPT	±
ACE	±
SLC6A3 (DAT1)	±
DRD2	±
HOMER1	±
CCK	±
ApoE	Mostly no association
COMT	−
HTR2A	−
DRD3	−
DRD4	−

+: Positive association; −: no association; ±: mixed findings.

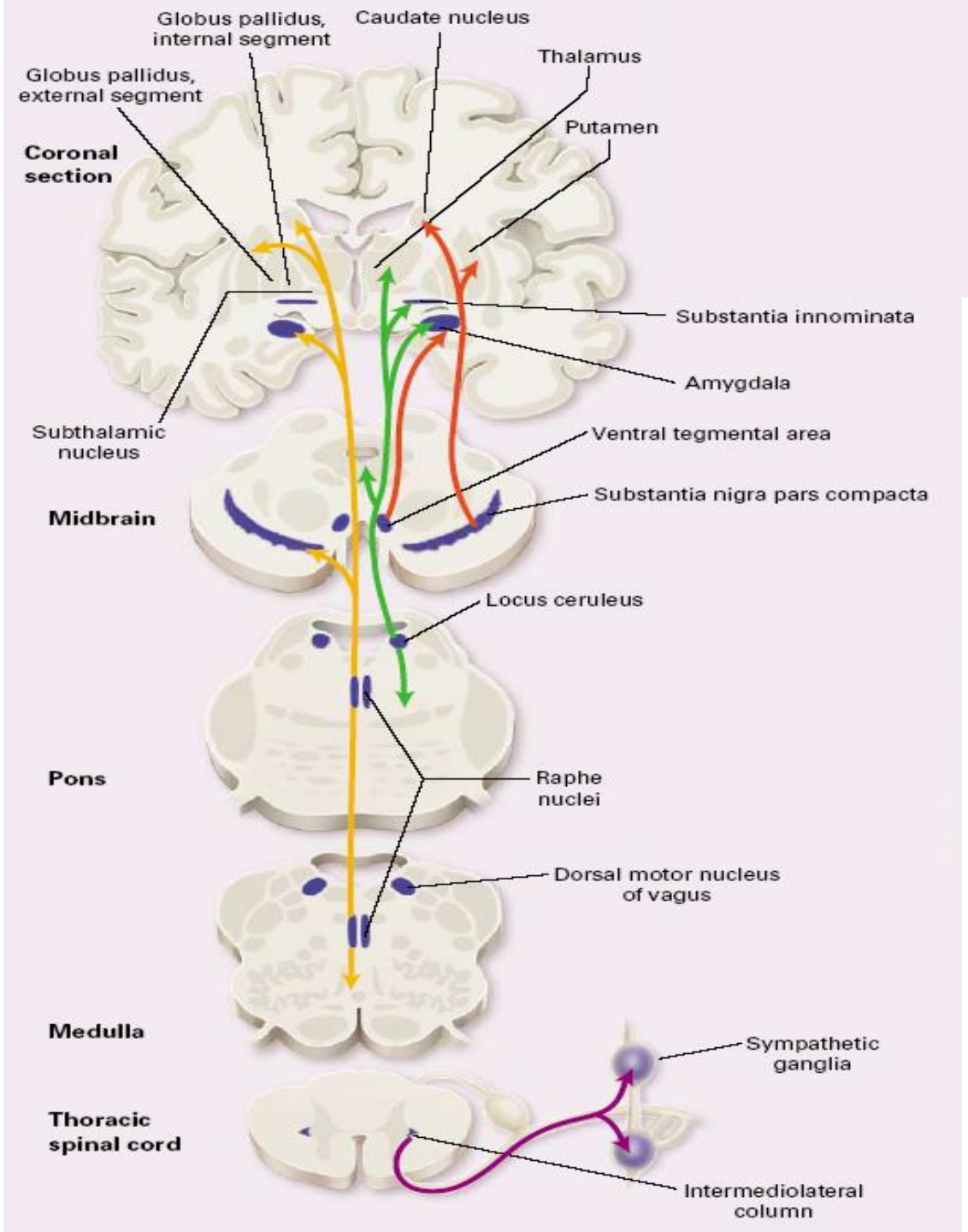
Nonmotor Signs in Genetic Forms of Parkinson's Disease

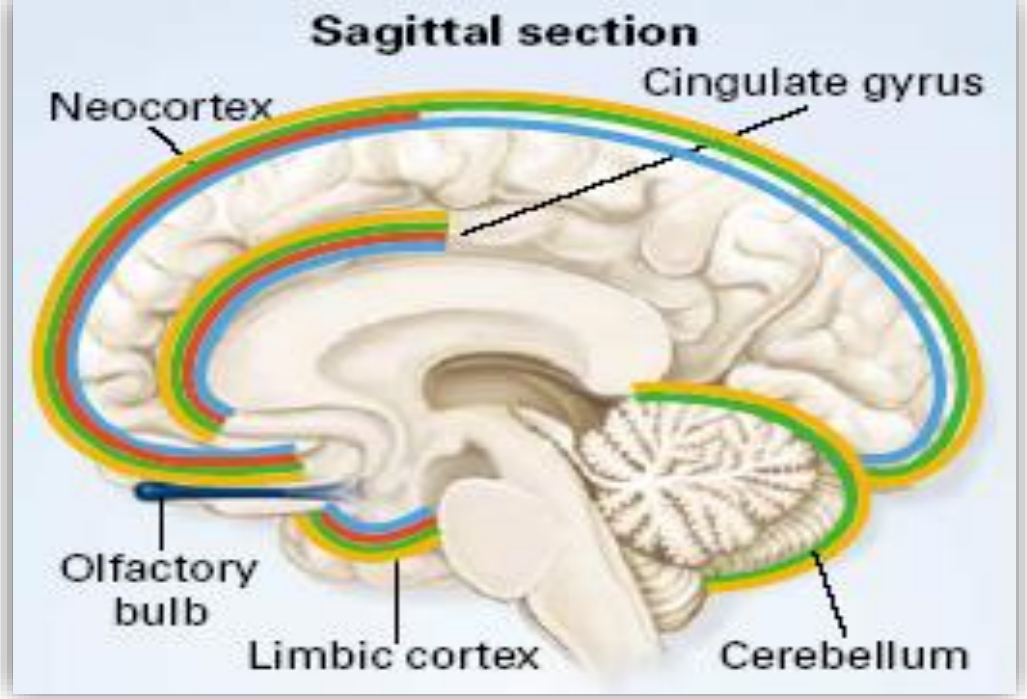
Meike Kasten*, Connie Marras†, Christine Klein‡,1

In. Nonmotor Parkinson'sThe Hidden Face. Chaudhuri, Titova, 2017

Table 7.7 *LRRK2*

Symptom	Frequency of symptom	Availability of information
Depression	127/363 (35%)	363/866 (42%)
Anxiety	60/210 (29%)	210/866 (24%)
Hallucinations	58/354 (16%)	354/866 (41%)
Dementia	71/425 (17%)	425/866 (49%)
Autonomic	55/224 (25%)	224/866 (26%)
Sleep	106/174 (61%)	174/866 (20%)
Other/comments	Two completed suicides reported, one in the context of severe recurrent depression	



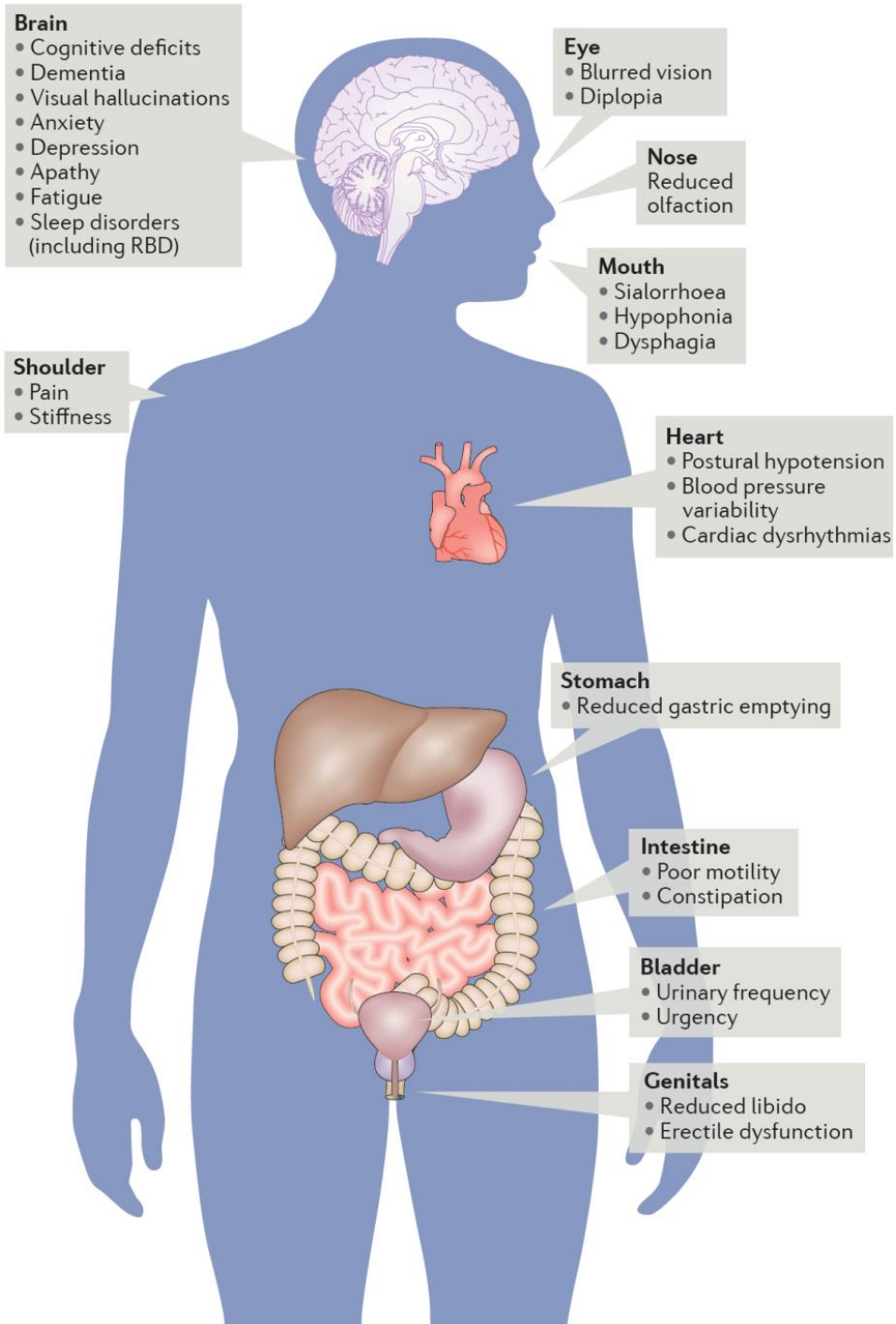


Sites of neurodegeneration

Neurochemical pathways

- Dopamine
- Norepinephrine
- Serotonin
- Acetylcholine

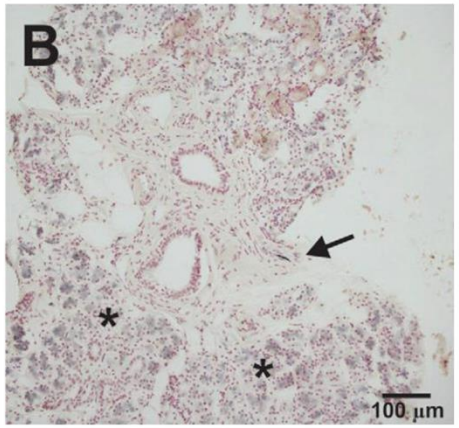
Kalia and Lang *Lancet* 2015; 386: 896–912;
Obeso et al. *Move Disord* 2017; 32: 1264–1310

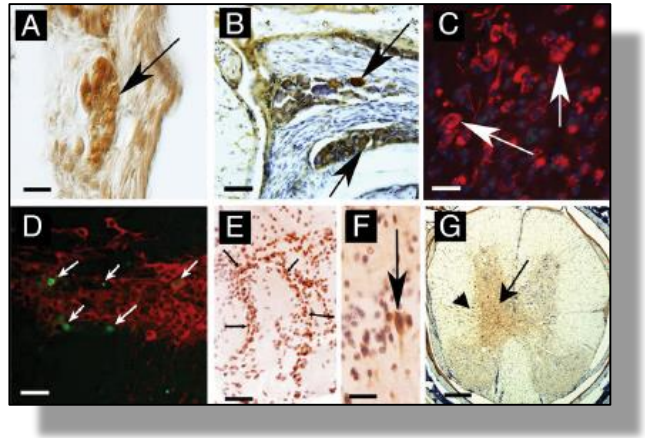


Non-motor features of Parkinson disease

Anthony H.V. Schapira[1], K. Ray Chaudhuri[2] and Peter Jenner[3]

Abstract | Many of the motor symptoms of Parkinson disease (PD) can be preceded, sometimes for several years, by non-motor symptoms that include hyposmia, sleep disorders, depression and constipation. These non-motor features appear across the spectrum of patients with PD, including individuals with genetic causes of PD. The neuroanatomical and neuropharmacological bases of non-motor abnormalities in PD remain largely undefined. Here, we discuss recent advances that have helped to establish the presence, severity and effect on the quality of life of non-motor symptoms in PD, and the neuroanatomical and neuropharmacological mechanisms involved. We also discuss the potential for the non-motor features to define a prodrome that may enable the early diagnosis of PD.





CHAPTER SEVEN

Biomarkers of Parkinson's Disease: An Introduction

Nataliya Titova[*,1], **Mubasher A. Qamar**[†,‡,§], **K. Ray Chaudhuri**[†,‡,§]

[*]Federal State Budgetary Educational Institution of Higher Education "N.I. Pirogov Russian National Research Medical University" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia
[†]National Parkinson Foundation International Centre of Excellence, Kings College and Kings College Hospital, London, United Kingdom
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[§]National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre (BRC) and Dementia Unit at South London and Maudsley NHS Foundation Trust, London, United Kingdom
[1]Corresponding author: e-mail address: nattitova@yandex.ru

Molecular biomarkers for PD – overview

Marker	Blood (serum, plasma)	CSF	Saliva	Urine
α-Synuclein	✓	✓	✓	
Phosphorylated α-Synuclein	✓	✓		
α-Synuclein oligomers		✓		
DJ-1	✓	✓	✓	
Flt3L		✓		
8-OH 2'deoxyguanosine				✓
Catecholamines and metabolites	✓	✓		✓
Uric acid	✓	✓		
Autoantibody profiles	✓			
α-Synuclein antibodies	✓			

Tissue biomarkers for PD – overview

Tissue type	Accessability in routine practice	Type of marker	Marker found in 'pre-clinical' cases
Colonic submucosa [1-6]	✓	• Phosphorylated α-SNC positive Lewy neurites [1-4] • α-SNC positive nerve fibres [5,6]	✓ [6]
Gastric submucosa [7]	✓	• Phosphorylated α-SNC positive Lewy neurites	
Skin [8]	✓	• α-SNC accumulation	
Minor salivary glands [9]	✓	• α-SYN inclusions	

[1] Lebouvier 2008, [2] Lebouvier 2010, [3] Pouclet 2012a, [4] Pouclet 2012b,
[5] Shannon 2012a, [6] Shannon 2012b, [7] Pouclet 2012c, [8] Miki 2010, [9] Cersosimo 2011

npj | Parkinson's Disease

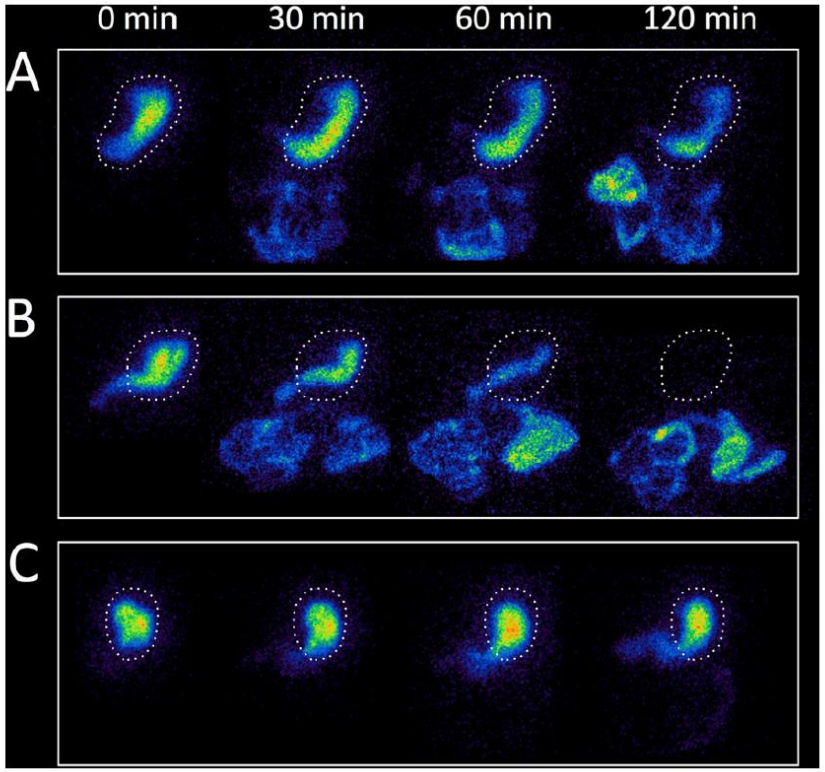
www.nature.com/npjparkd

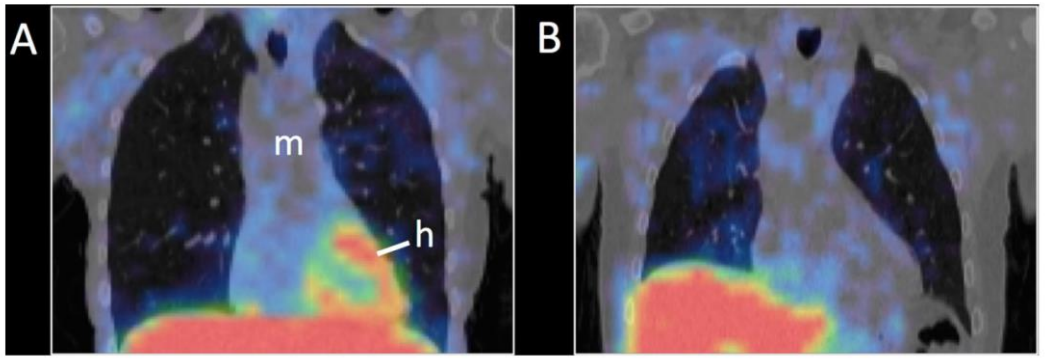
npj Parkinson's Disease (2017)3:15 ; doi:10.1038/s41531-017-0017-1

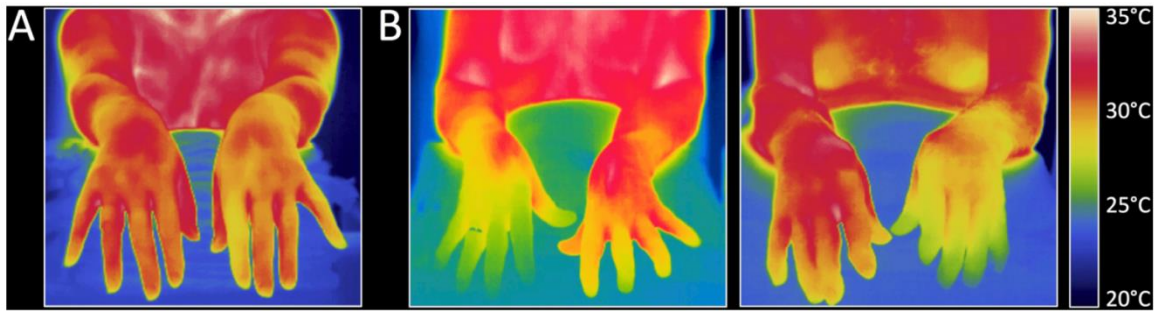
REVIEW ARTICLE OPEN

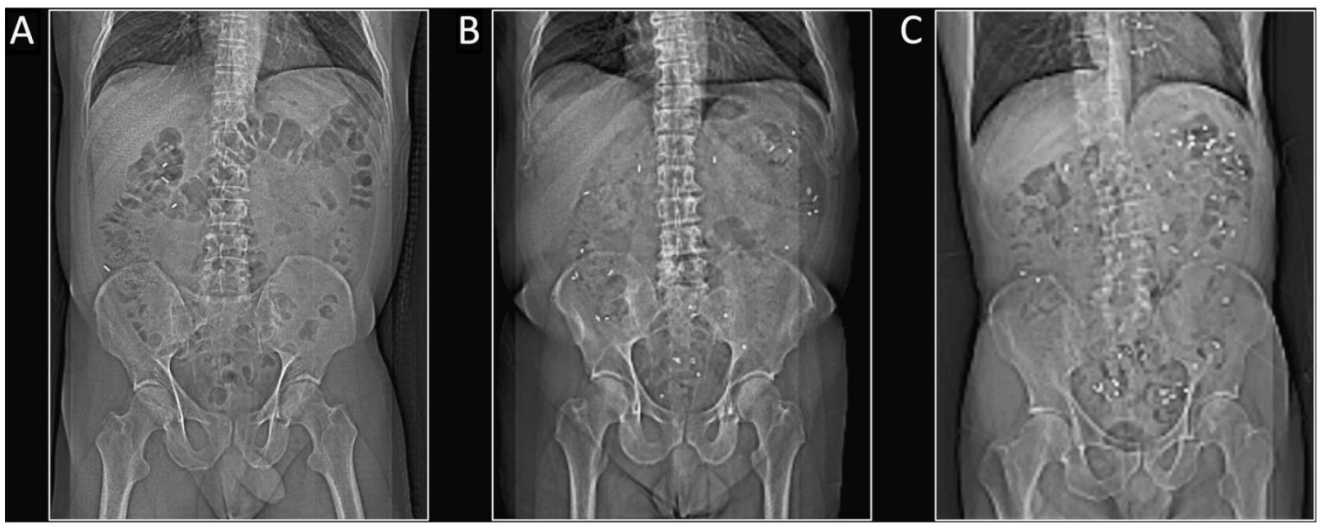
Imaging Parkinson's disease below the neck

Per Borghammer[1], Karoline Knudsen[1], Tatyana D. Fedorova[1] and David J. Brooks[1,2,3]









REVIEW

CME

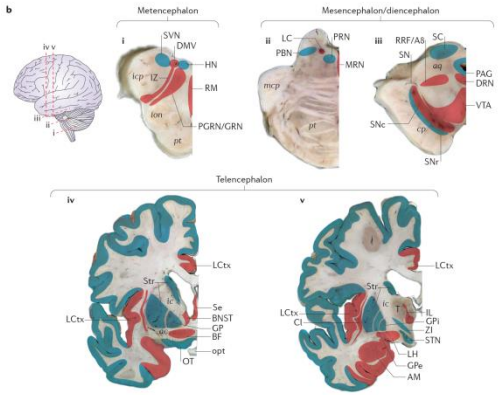
Neuropathology of Sporadic Parkinson's Disease: Evaluation and Changes of Concepts

Kurt A. Jellinger, MD*
Institute of Clinical Neurobiology, Vienna, Austria

1. Parkinson's is a multi-organ disorder: CNS and extra-CNS
2. Parkinson's is a multi-peptide dysfunction related disorder
3. Non-DA involvement may be greater than DA involvement

Selective neuronal vulnerability in Parkinson disease

D. James Surmeier[1], José A. Obeso[2,3] and Glenda M. Halliday[4,5]



Troublesome Symptoms: The Patient's Perspective

Rank of 10 most bothersome symptoms in 173 advanced patients with more than 6 years of disease duration

Rank	Symptom/condition	Total score
1	Fluctuating response to medication	115
2	Mood	96
3	Drooling	85
4	Sleep	83
5	Tremor	67
6	Pain	60
7	Bowel problems	46
8	Urinary problems	40
9	Falls	39
10	Appetite/weight	36

Movement Disorders
Vol. 25, No. 11, 2010, pp. 1646–1651

Parkinson's Disease Symptoms: The Patient's Perspective

Marios Politis, MD, MSc,[1,2]* Kit Wu, MRCP,[1,2] Sophie Molloy, MD,[3] Peter G. Bain, MD, FRCP,[3]
K. Ray Chaudhuri, MD, FRCP, DSc,[4] and Paola Piccini, MD, PhD, FRCP,[1,2]

CHAPTER

6

Anna Sauerbier and K. Ray Chaudhuri

Nonmotor Symptoms in Parkinson's Disease

2016

TABLE 6.1 Nondopaminergic Involvement in PD at a Premotor and Early Motor Stage

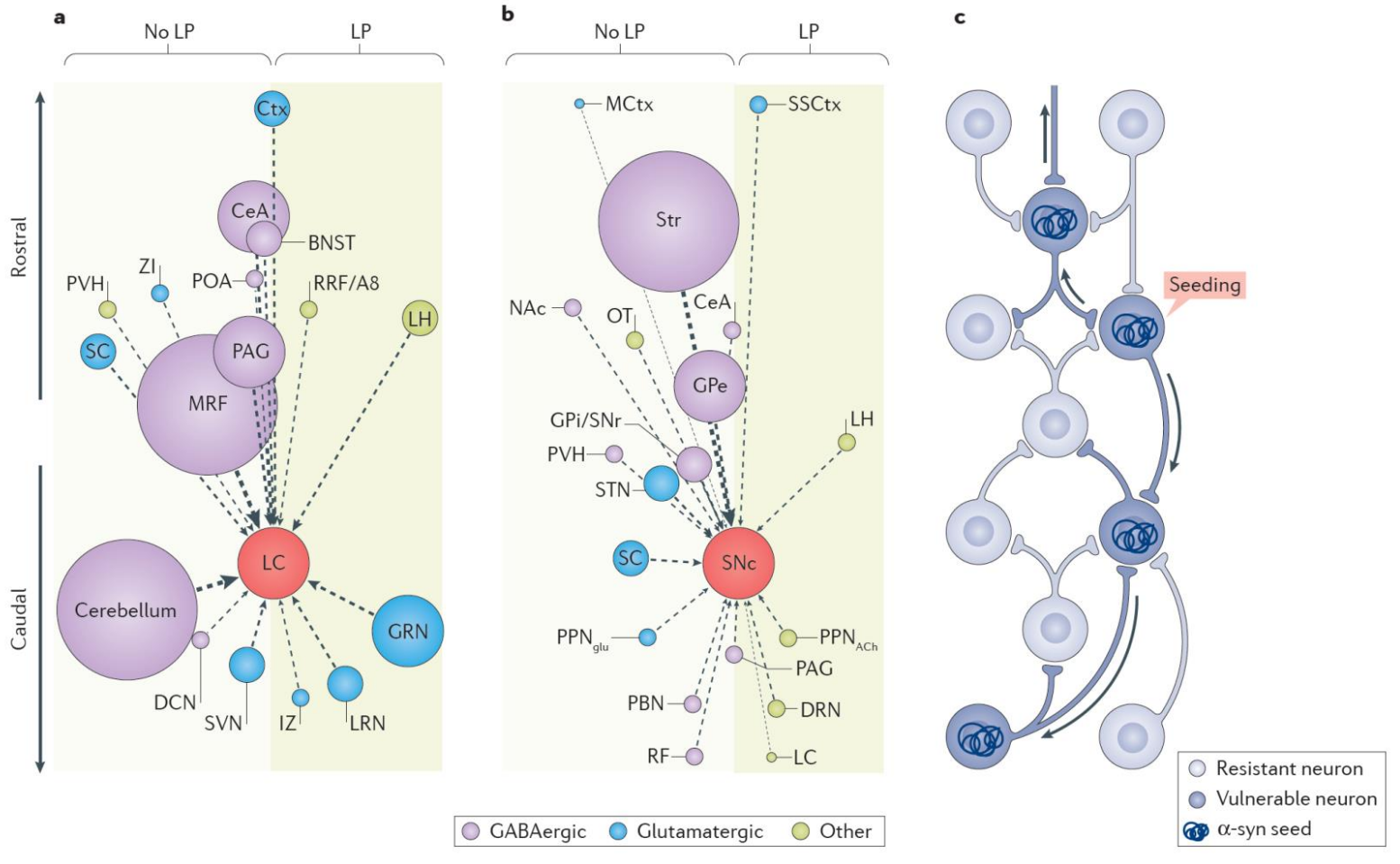
Author, year	Evidence of Nondopaminergic Involvement in PD at a Premotor and Early Motor Stage
Forno, 1996 (18)	Lewy bodies were first reported in nondopaminergic neurones.
Jellinger, 1987 (19) Halliday, 1990 (20) Hirsch, 1987 (21)	Cholinergic pedunculopontine nucleus neurones and substance P–containing neurones suffer 77% loss in dorsal motor nucleus of the vagus, while tyrosine hydroxylase–immunoreactive neurones appear spared (<5%) Neuronal loss in dorsal motor nucleus of the vagus is as marked as in the substantia nigra.
Saper, 1991 (22)	Complete sparing of medullary dopaminergic neurones described
Wakabayashi, 1997 (23)	Lewy body degeneration is prominent in the nondopaminergic anterior olfactory nucleus. Noncatecholaminergic neurones severely depleted in PD in the autonomic system: spinal intermediolateral nucleus 30%–40% loss of preganglionic autonomic neurones Lewy bodies are frequent in the vasoactive intestinal peptide neurones of the enteric nervous system but rare in catecholaminergic cells.
Wakabayashi,1997;Iwanaga, 1999 (23,24)	Lewy bodies present in both TH+ and TH− cells in the cardiac plexus.
Braak, 2003 (25)	Lewy body degeneration developing in lower brain stem neurones well before the substantia nigra.
Braak, 2004 (26)	Incidental Lewy bodies identified within pontomedullary neurones in the absence of substantia nigra pathology, but not vice versa

Source: Adapted from Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. *Pract Neurol* 2014;14:310–322.

Selective neuronal vulnerability in Parkinson disease

D. James Surmeier[1], José A. Obeso[2,3] and Glenda M. Halliday[4,5]

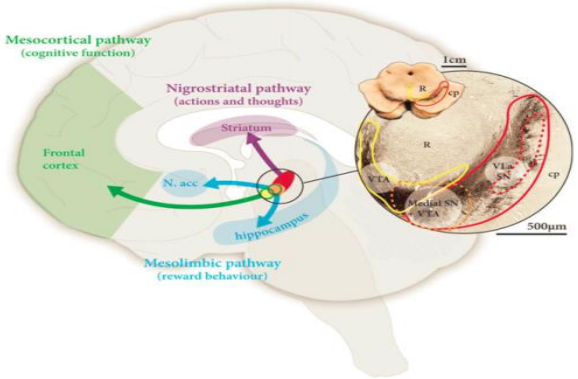
Abstract | Intracellular α-synuclein (α-syn)-rich protein aggregates called Lewy pathology (LP) and neuronal death are commonly found in the brains of patients with clinical Parkinson disease (cPD). It is widely believed that LP appears early in the disease and spreads in synaptically coupled brain networks, driving neuronal dysfunction and death. However, post-mortem analysis of human brains and connectome-mapping studies show that the pattern of LP in cPD is not consistent with this simple model, arguing that, if LP propagates in cPD, it must be gated by cell- or region-autonomous mechanisms. Moreover, the correlation between LP and neuronal death is weak. In this Review, we briefly discuss the evidence for and against the spreading LP model, as well as evidence that cell-autonomous factors govern both α-syn pathology and neuronal death.



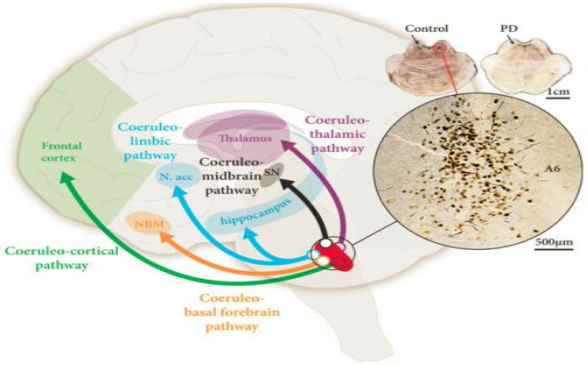
Contributors for different phenotypes in Parkinson‘s disease

Halliday et al., 2014; Titova et al 2017

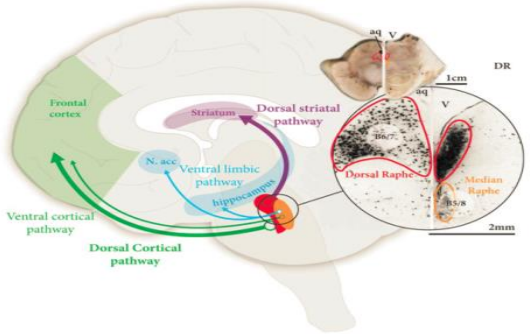
At least four disctinct neurotransmitter system are affected by α-synuclein pathology and contribute to the many symptoms in Parkinson‘s disease



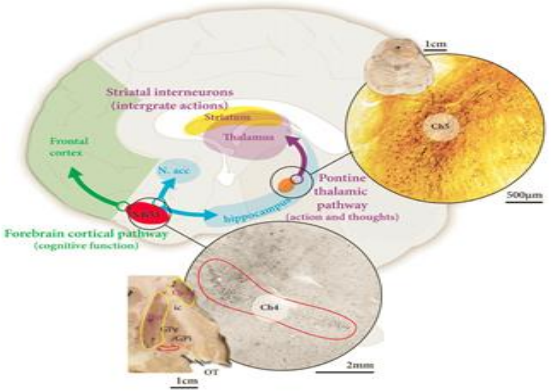
Dopamine pathway



Noradrenaline pathway



Serotonin pathway



Cholinergic pathway

J Neural Transm
DOI 10.1007/s00702-016-1667-6

CrossMark

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Parkinson’s: a syndrome rather than a disease?

Nataliya Titova[1] · C. Padmakumar[2] · Simon J. G. Lewis[3] · K. Ray Chaudhuri[4,5]

2017

Parkinsonism and Related Disorders xxx (2015) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Non motor subtypes and Parkinson's disease

Anna Sauerbier [a, b], Peter Jenner [c], Antoniya Todorova [a, b], K. Ray Chaudhuri [a, b, *]

Brainstem:

Park sleep

Park autonomic

Limbic:

Park fatigue

Park pain

Neocortical/ Cognitive:

Park cognitive

Park apathy

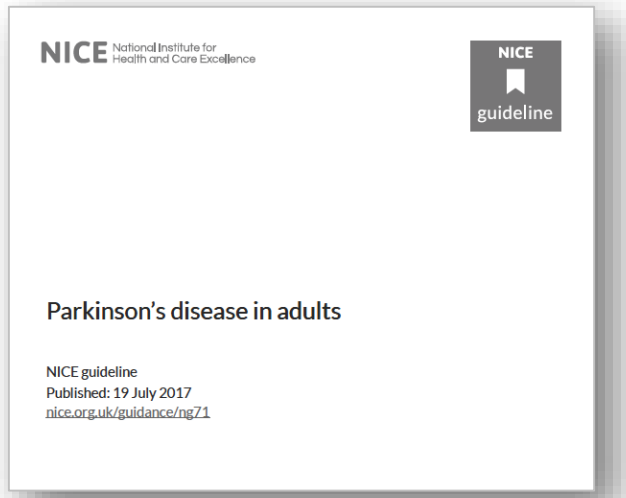
7 subtypes of PD

Park depression/anxiety

Guideline-driven medicine does not provide holistic care in Parkinson's

International Parkinson and Movement Disorder Society

AMERICAN ACADEMY OF NEUROLOGY



Guidelines

- ✓ Guidance for the less experienced
- ✓ Confidence
- ✓ Consistency
- ✓ Influence public policy
- ✓ Cost-efficacy

- ✗ May not apply in all situations and for all types of patients
- ✗ Mainly based on limited ('high' level) evidence
- ✗ Inflexible
- ✗ Lack of problem solving
- ✗ Focussed on DRT alone

Woolf et al. *BMJ*. 1999; 318(7182):527-30; Titova & Chaudhuri. *Mov Disorders*, 2017. doi: 10.1002/mds.27027;
NICE 2017. NG71 – Parkinson's disease in adults. Available from https://www.nice.org.uk/guidance/ng71. Last accessed November 2017.

A focus on Dopamine therapy **only tunnel vision** will not allow delivery of true personalised medicine for PD,
an approach that is required for every patient with PD

Toolkit for delivery of holistic personalised medicine for Parkinson's disease: first description of a personalised medicine checklist

Nataliya Titova[1,2] K Ray Chaudhuri[2,3]

HK MDS 2018

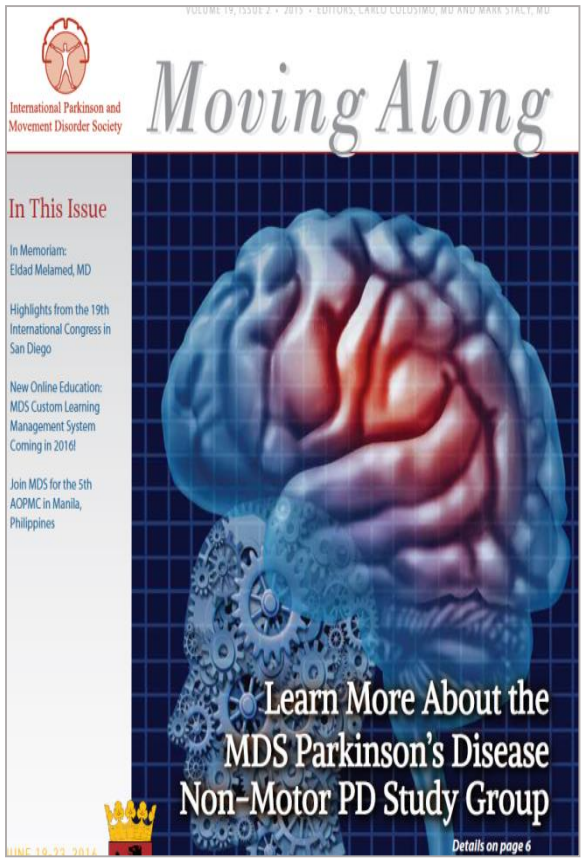
The Personalised Medicine Checklist

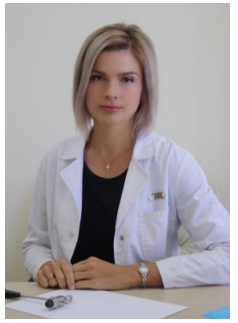
Personalised Medicine Domain	Have you considered the following? (tick if YES)	Explanatory notes
Age (*please tick the appropriate box*) <50 yrs ☐ 50-75yrs ☐ > 75yrs ☐		*important in relation to dyskinesias, ICD, and risk of neuropsychiatric problems and choice of dopamine replacement therapy*
Healthy aged (as judged by health care professional)		e.g. a fit active 80 year old with normal cognition and low nonmotor burden)
Lifestyle		focus on activities of daily living *(e.g. work, study, housework, family leisure activities, driving)*
Retired and sedentary		
Retired and active		
Working physical		
Working (office based/meetings)		e.g. company executive who might prefer nonoral therapies for rescue from off periods so as to function effectively during a high level meeting
Driving		anyone driving is at risk of sleep events with certain dopamine agonists particularly those with a history of falling asleep while driving
Bodyweight		
Low for age and height		low bodyweight is a risk factor for dyskinesias and also needs specific monitoring during levodopa infusion therapy
Obesity		obesity may be linked to sleepiness secondary to sleep apnoea and dosing of dopamine replacement therapy may need to be adjusted
Personality		
Anxious and/or depressed		Evidence suggests anxious depressed subtype is most associated with fluctuations and dyskinesias (Brown et al 2011)
ICD risk factors *(young onset, history of risk taking behaviours, addiction, single male)*		
Phobias *(levodopaphobia, needlephobia)*		
Comorbidity		
Diabetes		
Osteoporosis		
Peptic ulcer disease/Recurrent severe gastritis		
Constipation		
Arterial hypotension		
Clinical Subtypes		
Motor subtypes		
Tremor dominant		
PIGD (*overlap with cholinergic subtype*)		
Nonmotor subtypes		
Cholinergic		(cognitive, non-drug related hallucinations/psychosis, on freezing)
Noradrenergic		(autonomic (gasrointesitinal and postural hypotension), sleep dysfunction)
Serotonergic		(fatigue, sleep dysfunction (EDS), depression)
Mixed		
Consider Major Complications of DRT		can be managed by adjustment of DRT
Somnolence and sudden onset of sleep		
Hallucinations/Psychosis		
Postural hypotension		
Motor fluctuations (wearing off)		
Non motor fluctuations		
Dyskinesias		
Genetics (tick, only if known)		
LRRK 2 ☐ GBA ☐ Others ☐		

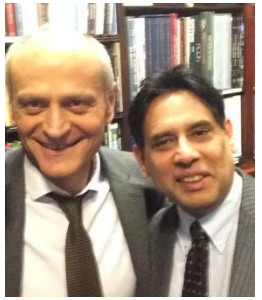
- Parkinson’s is a syndromic condition with clear phases:
  - Prodromal and pre prodromal PD
  - Manifest inlife motor PD
  - Manifest inlife nonmotor PD
  - Palliative
- NMS assessment in the clinic must be obligatory (NICE 2006/2017) as NMS is one of the key drivers of Quality of Life
- Management of PD therefore needs to be individualised and personalised to fit the subtypes.
  - The role of MDT and specifically PDNS is crucial
- Nonmotor subtyping and subtype specific treatment needs to be investigated
- The future of PD treatment is likley to be dominated by personalised medicine for PD focussing on a mixture of motor and nonmotor symptoms

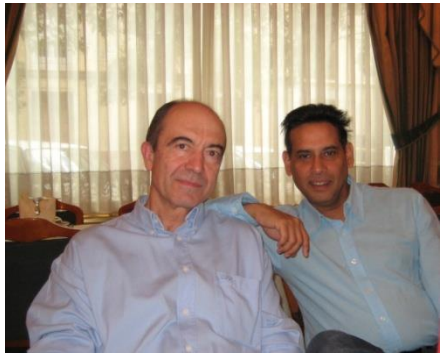
King's Parkinson's Research Team

Visit us at the Kings Parkinson's Centre: http://parkinsons-london.co.uk









Research:
London PEN
Kirby Laing Foundation
Herschel Post Fellowship
Britannia Fellowship
Parkinson's UK
NIHR, MRC, NMRC
MDS

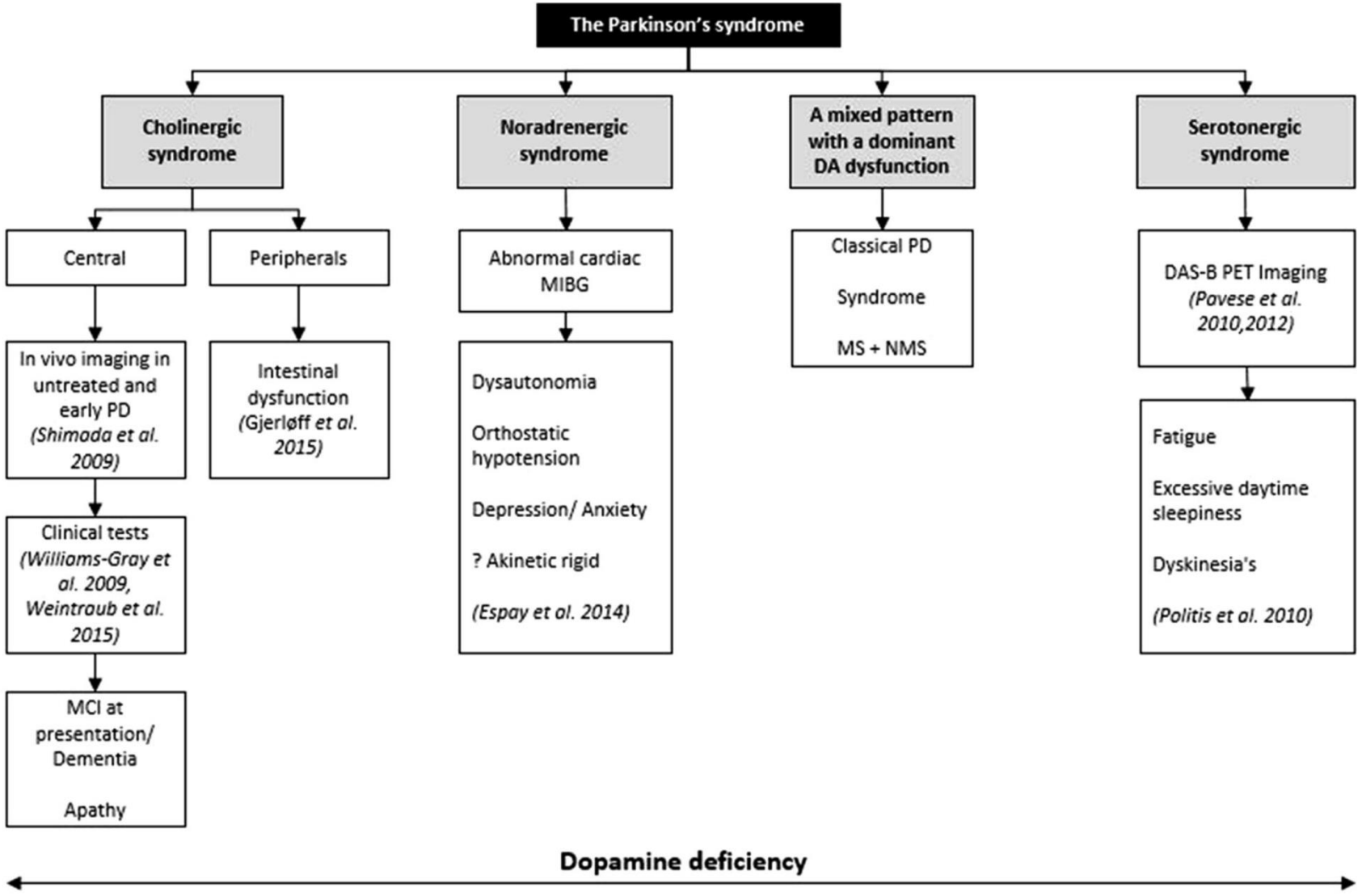
King's Parkinson's Research Team is an award winning research team recognised by the National Parkins
Foundation (NPF) for their dedication to research and care of Parkinson's patients and their carers.

J Neural Transm
DOI 10.1007/s00702-016-1667-6

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Parkinson's: a syndrome rather than a disease?

Nataliya Titova[1] · C. Padmakumar[2] · Simon J. G. Lewis[3] · K. Ray Chaudhuri[4,5]



REVIEW

Mov Disord 2016

Nonmotor Features of Parkinson's Disease Subtypes

Connie Marras, MD, PhD[1]* and K. Ray Chaudhuri, MD, FRCP, DSc[2]

TABLE 1. Clinical description of NMS-dominant phenotypic variants in well-characterized cohorts of PD (untreated and treated) as described in the literature (adapted from Sauerbier et al, 2015)

Nonmotor domain	Defining features of subtype	Ancillary features
Cognitive[29,63,64]	Early and dominant cognitive dysfunction	Older age (≥72 years) Non-tremor-dominant motor phenotype associated with falls Poor semantic fluency score (<20) Lower pentagon copying score (0 < 1 < 2) Microtubule-associated protein tau (MAPT) H1/H1 genotype possibly a biomarker
Neuropsychiatric	Anxiety/depression[65,66]: A. Anxious-depressed B. Depressed C. Anxious	 Postural instability gait disturbance Younger age Marked motor fluctuations
	Apathetic[67]	Relatively severe motor symptoms (out of proportion to disease duration) Concomitant depression Lower cognitive status Fatigue Good response to dopaminergic drugs
Sleep	REM sleep behavior disorder[60]	Symmetric disease onset Increased periods of freezing Autonomic dysfunction Prone to higher prevalence and severity of orthostatic symptoms Higher rate of depression Visual hallucinations Increased frequency of falls Impairment of color vision
Olfactory[68]	A. Severe loss of olfaction (anosmia)	Dyskinesias Progressive weight loss
	B. Moderate loss of olfaction	No further weight loss with disease progression
Autonomic	Urinary dysfunction[15]	Early noradrenergic deficit Postural hypotension