Parkinson's Disease – An Introduction

Codrin Lungu, MD
Chief, NIH Parkinson Clinic
Office of the Clinical Director
National Institute of Neurological Disorders and Stroke
NIH

Disclosures

- Some brand names will be used, none are specifically endorsed
- Some illustrations and videos are either public domain or provided for teaching activities
- Reference is made to confidential work in progress
- All patients appearing in videos and photos have provided informed consent
- Some public figures appear for illustrative purposes; all the discussions related to these persons are hypothetical and for illustration only
- I have active research collaborations with Medtronic, Inc., BCN Peptides, Inc., the Kinetics Foundation, Convergent Medical Devices.

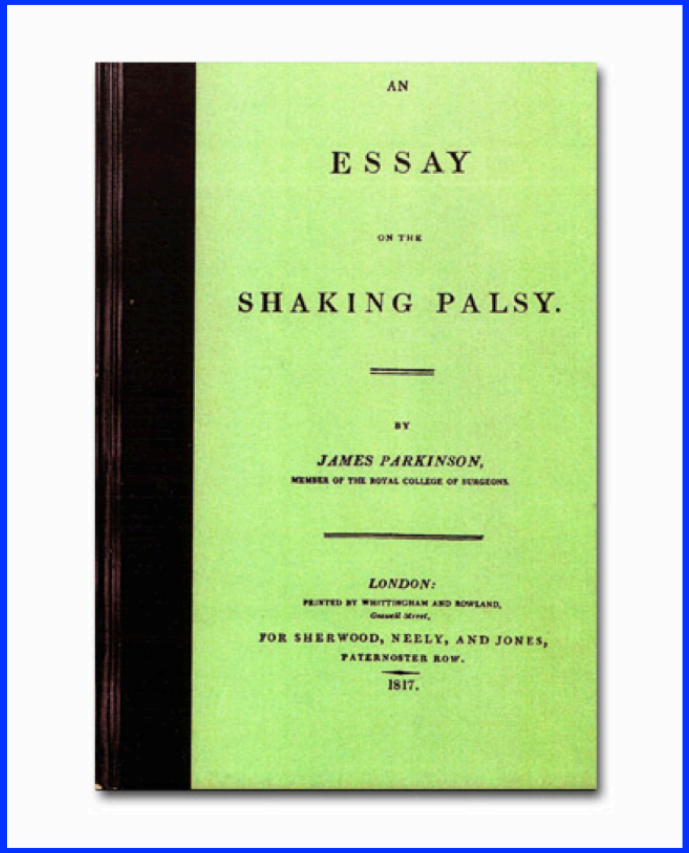
Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Outline

- **Definition, features, diagnosis and pathology**
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Parkinson 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,

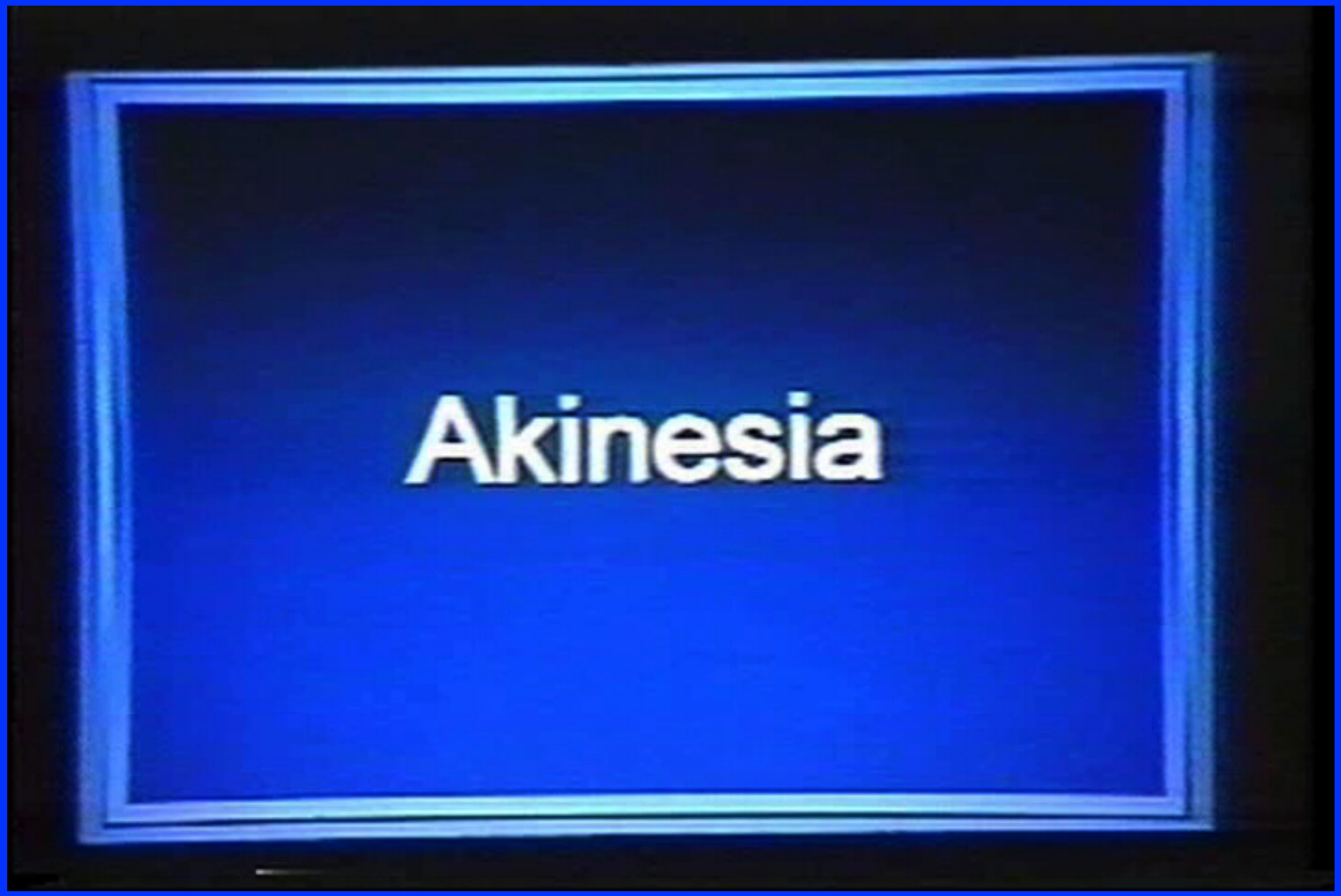
PATERNOSTER ROW.

1817.

- Progressive degenerative neurological disorder, characterized by a large number of motor and non-motor features.
- The classic cardinal features are tremor, bradykinesia, rigidity and loss of postural reflexes
- Parkinson's is the earliest detailed description, features present in the literature before, the entity was subsequently refined

Cardinal Features:
Tremor

Cardinal Features: Bradykinesia



Cardinal Features:
Gait and Postural Impairment

Cardinal Features:
Masked Face

Clinical Manifestations (Abbreviated Selection)

Cardinal Features: Tremor
Bradykinesia
Rigidity
Postural instability

Other motor features

Craniofacial

Hypomimia (masked facial expression)
Decreased eye blinking
Speech disturbances: hypokinetic dysarthria
hypophonia
Dysphagia
Sialorrhea

Visual

Blurred vision
Impaired contrast sensitivity
Impaired color discrimination
Hypometric saccades
Impaired vestibuloocular reflex
Impaired upward gaze and convergence
Lid apraxia

Musculoskeletal

Micrographia
Dystonia
Myoclonus
Stooped posture
Kyphosis
Scoliosis
Difficulty turning in bed

Gait

Shuffling, short-stepped gait
Freezing
Festination

Non-motor Features:

Cognitive dysfunction
Psychosis
Mood disorders: depression
anxiety
apathy/abulia
Sleep disturbances: RBD
PLMS
Fatigue
Autonomic dysfunction: urinary urgency/frequency
constipation
orthostasis
erectile dysfunction
Olfactory dysfunction
Pain and sensory disturbances
Dermatologic findings: seborrhea
seborrheic dermatitis

Complications of Therapy:

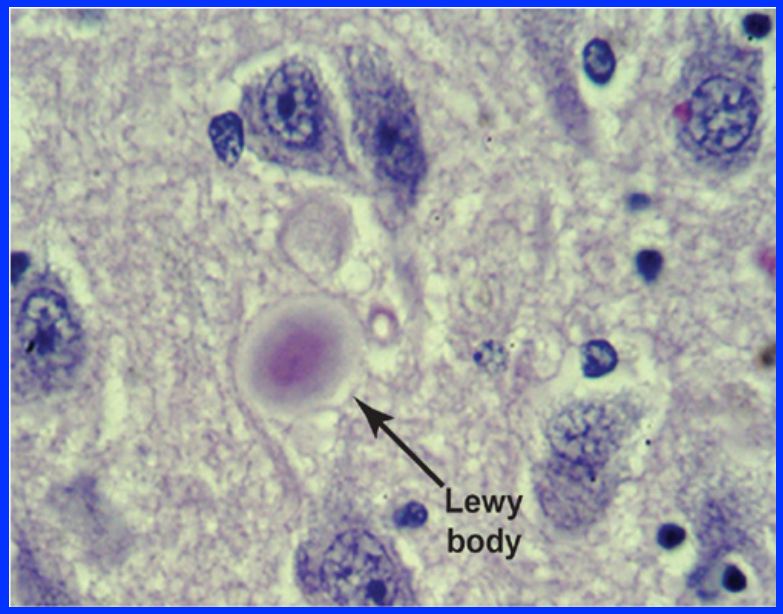
Dyskinesia
Motor fluctuations
Sudden off states
Failed doses
Impulse control disorders
Psychosis

UK Brain Bank Criteria

(Hughes et al JNNP 1992)

- Bradykinesia
- At least one of:
  - Rigidity
  - 4-6Hz resting tremor
  - Postural instability
- No other cause of parkinsonism present
- At least 3 of:
  - Unilateral onset
  - Rest tremor
  - Progressive
  - Persistent asymmetry
  - Excellent response to L-DOPA
  - Severe dyskinesia
  - L-DOPA response 5 years or more
  - Clinical course 10 years or more

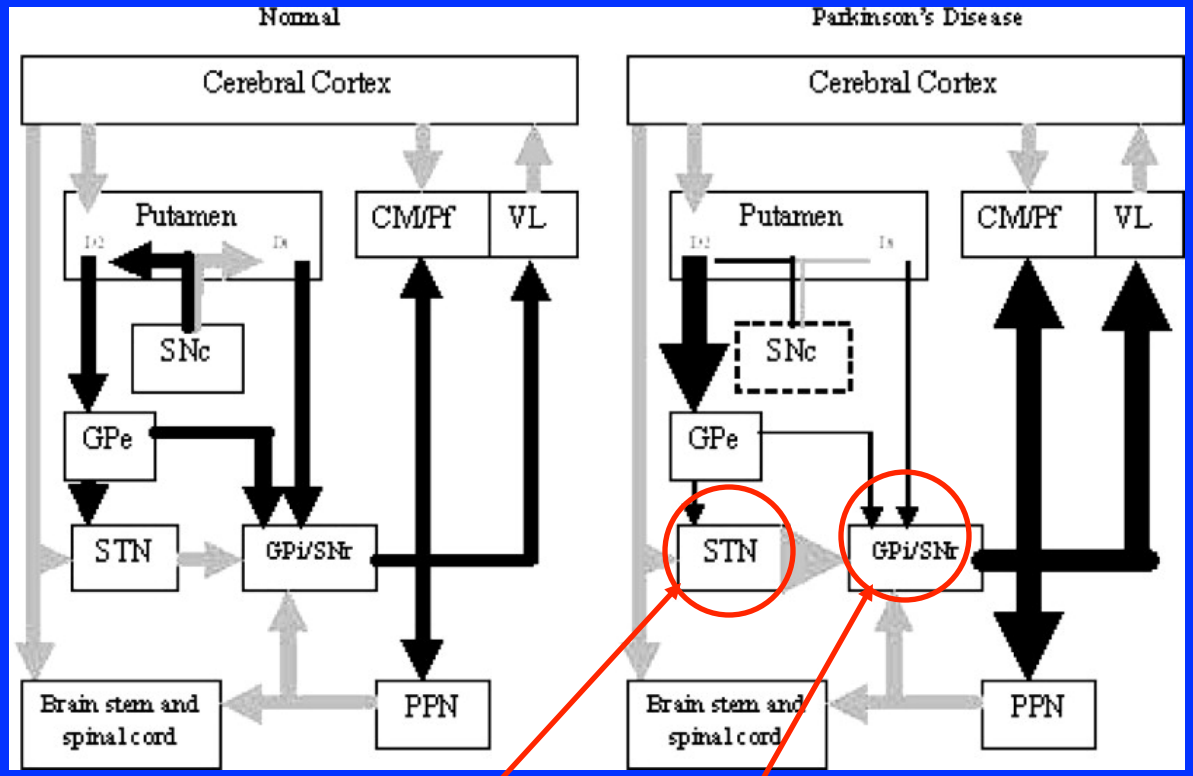
Pathology



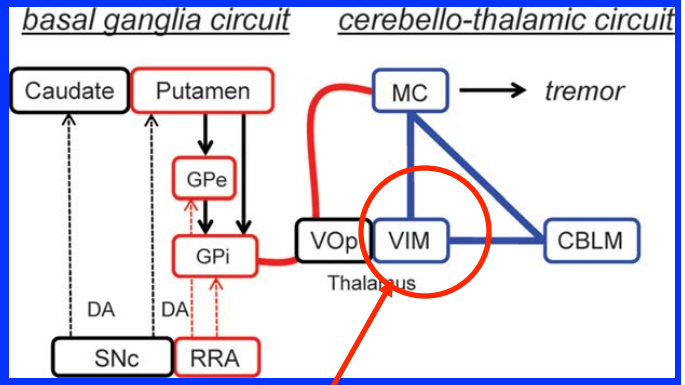
www.genome.gov

University of Rochester Dept. of Pathology

Pathophysiology and Possible Targets



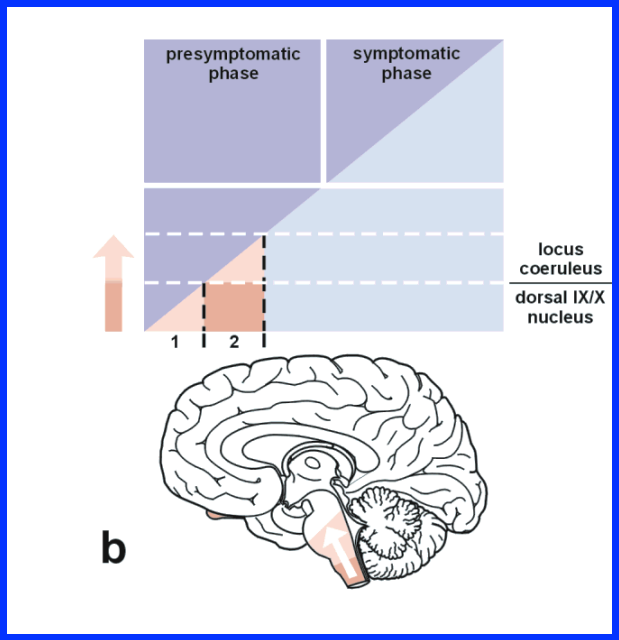
Cozzens, Dis Mon 2007

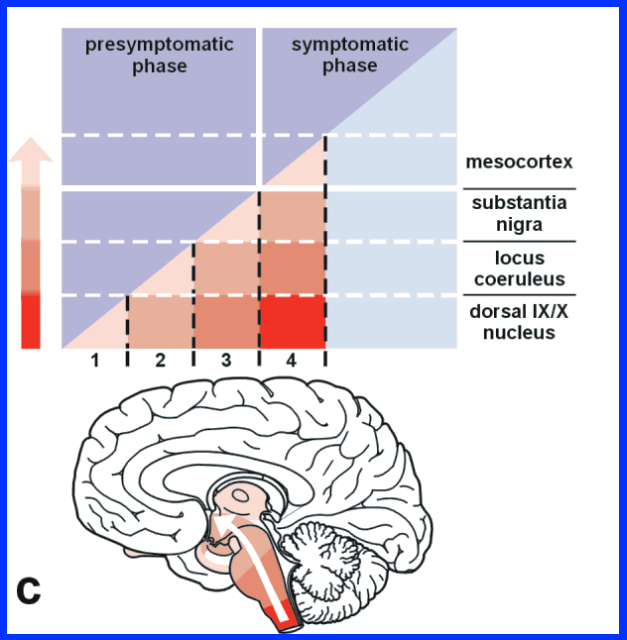


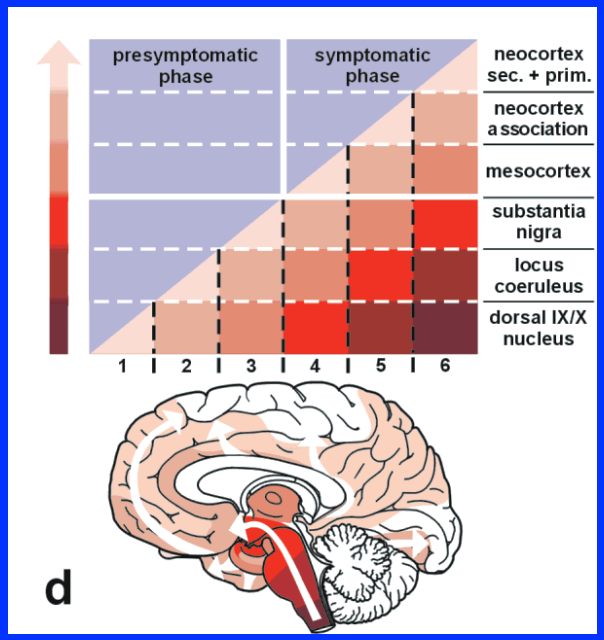
Helmich et al., Ann Neurol 2011

Pathology: Braak Stages

Braak H et al, J Neurol 2002







Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Outline

- Definition, features, diagnosis and pathology
- **Genes, environment, or both?**
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Historic note

- In the modern era, traditionally considered predominantly due to environmental factors
  - Absence of family history in most cases
  - Link to infectious etiology - 1918 flu pandemic (Poskanzer DC et al, J Chronic Dis 1963)
  - Link to toxins - MPTP etc. (Langston JW et al, Science 1983)
- Leroux & Lhirondel, 1880: regarding the etiology of PD, "a true cause of paralysis agitans, and may be the only cause, is heredity". (Leroux PD, Thesis, Paris 1880)
- Mjones, 1949: AD transmission with reduced penetrance (Mjones H, Acta Psych Neurol Scand Suppl 1949)
- Since 1996: identification of genes causing familial PD. First identified: α-synuclein (Polymeropoulos MH et al, Science 1996)
- Recently, LRRK2 mutations found in both AD PD (Paisan-Ruiz C et al, Neuron 2004), and "sporadic" PD (Gilks WP et al, Lancet 2005), pointing to a possible false dichotomy of "genetic" and "sporadic"

Most Relevant Putative Environmental Factors

Raising susceptibility or potential of causing distinct parkinsonian syndrome:

- Well water
- Rural residence and farming
- Pesticides
- Infection - post-encephalitic parkinsonism
- Trauma - traumatic parkinsonism, dementia pugilistica

Protective from sporadic PD:

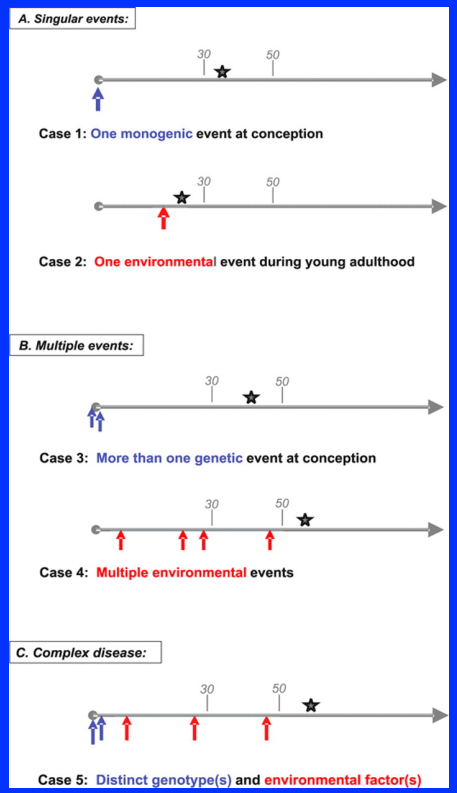
- Caffeine
- Smoking
- Some NSAIDS

Most Relevant Monogenic Causes

Gene / Product	Proposed Role	Typical Onset	Clinical Features	Pathology
α-synuclein PARK 1/4	Synaptic vesicle traffic	YOPD	Rapid progression; high rate of dementia	Lewy bodies, Tau pathology
LRRK2 PARK 8	Cytoplasmic kinase / signaling	LOPD	Similar to sporadic, less severe, less dementia	Variable, with/ without Lewy bodies
Parkin PARK 2	Ubiquitin ligase; mitochondrial integrity	YOPD	Slow progression, severe motor complications, non-motor features rare	Nigral degeneration without Lewy bodies
PINK1 PARK 6	Mitochondrial protein	YOPD	Slow progression, severe motor complications, non-motor features rare	Nigral degeneration without Lewy bodies
DJ1 PARK 7	RNA binding / oxidation	YOPD	Same as Parkin and PINK1	Unknown

Where This Leaves us

- Calne, 1989 (JNNP): "It is remarkably difficult to find a clear statement of what constitutes Parkinson's disease"
- Weiner, 2008 (Arch Neurol): "There is no Parkinson disease"
- Fahn, 1989 (Mov Disord): "Parkinson's disease, although of unknown etiology today, undoubtedly will be subdivided in the future into different varieties and etiologies".



Klein and Schlossmacher, Neurology 2007

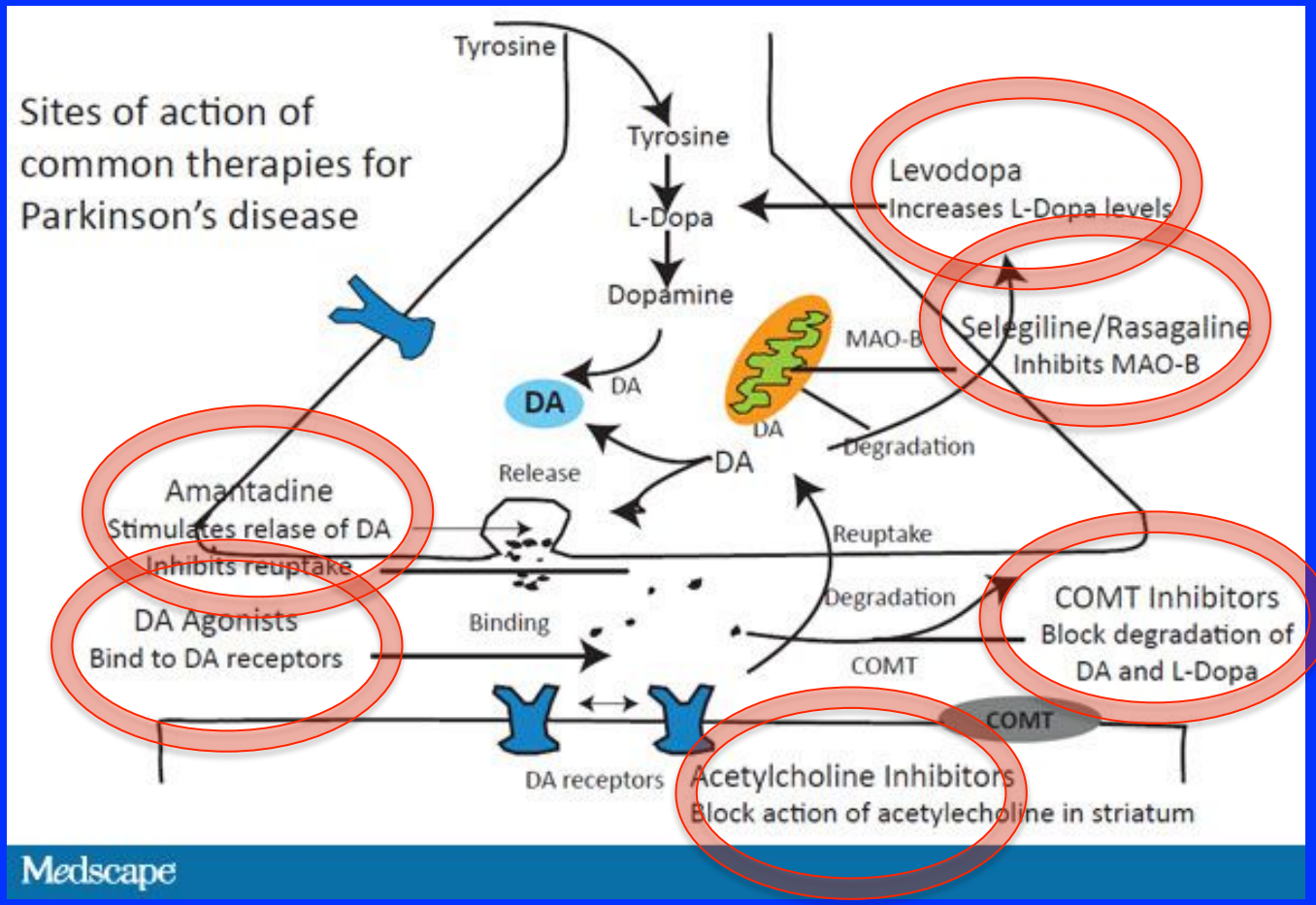
Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- **Symptomatic therapy, practical approaches and examples**
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Basis for Symptomatic Therapy



Hurtig H et al. Medscape Neurology 2010

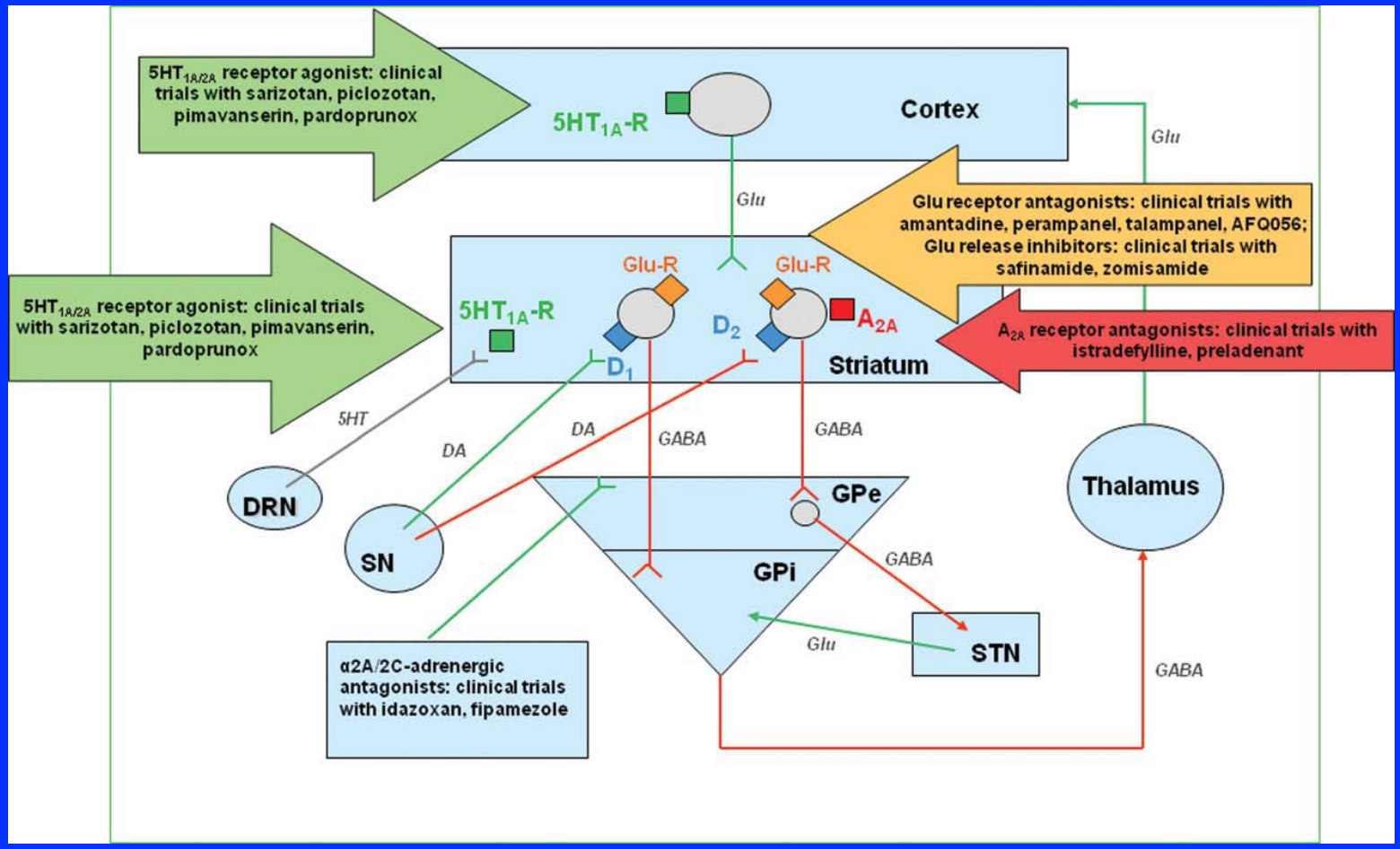
Treatment

- Levodopa: Carbidopa/Levodopa; Sinemet®: Provides the missing dopamine; can be combined with COMT inhibition. Short half-life. Side effects: dyskinesia; nausea
- DA agonists: Pramipexole – Mirapex®; Ropinirole – Requip® etc. Mimic the effects of dopamine by activating the same receptors. Longer half-life. Side-effects: psychiatric; sleep-related

Treatment

- Anticholinergics: Trihexyphenidyl – Artane® etc: Act on the cholinergic system, for tremor. Side-effects: cognitive slowing
- MAO-inhibitors: Rasagiline – Azilect®; Selegiline – Zelapar® etc.: prevent break-down of dopamine. Studied for disease-modifying effect. Side-effects: concern for interaction with anti-depressants
- Amantadine – Symmetrel®: unclear mechanism of action. Can help dyskinesia. Side-effects: cognitive slowing

Non-dopaminergic Symptomatic Therapy



Rascol O et al. Mov Disord 2011

Different Patients, Different Diseases, Different Approaches

Young patient, tremor dominant

Start treatment with DA agonists, tremor agents; MAO-inhibitors; Consider DBS surgery early; Discussion of genetic causes

Different Patients, Different Diseases, Different Approaches

Middle age patient, tremor and postural problems; possible question about atypical parkinsonism.

Treatment with agonists or levodopa; physical therapy; likely avoid DBS surgery

Different Patients, Different Diseases, Different Approaches

Elderly patient, slowness and stiffness dominant.

Treat with levodopa; physical therapy; investigate cognitive function and treat; watch for complications; support structure; likely avoid surgery

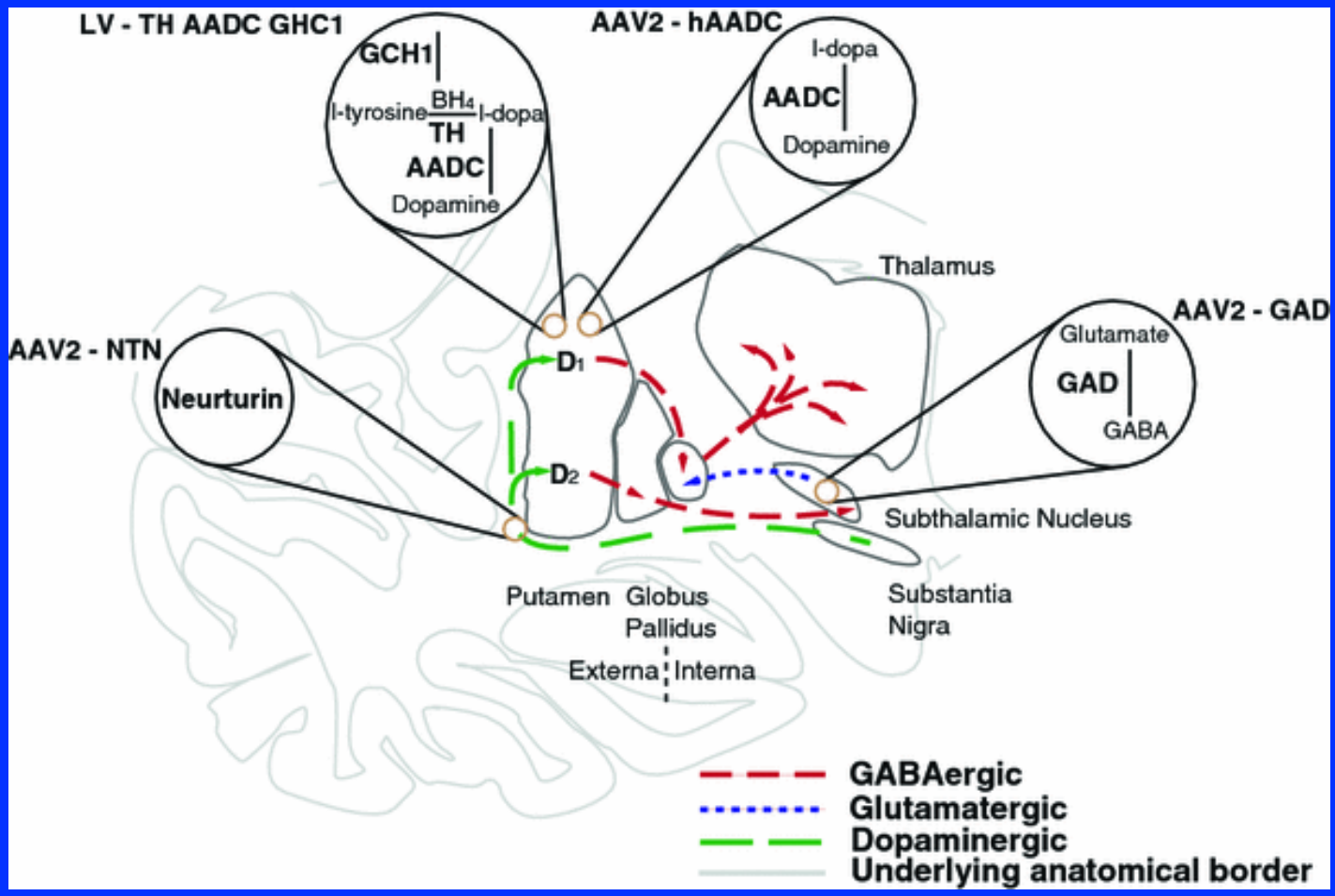
Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Outline

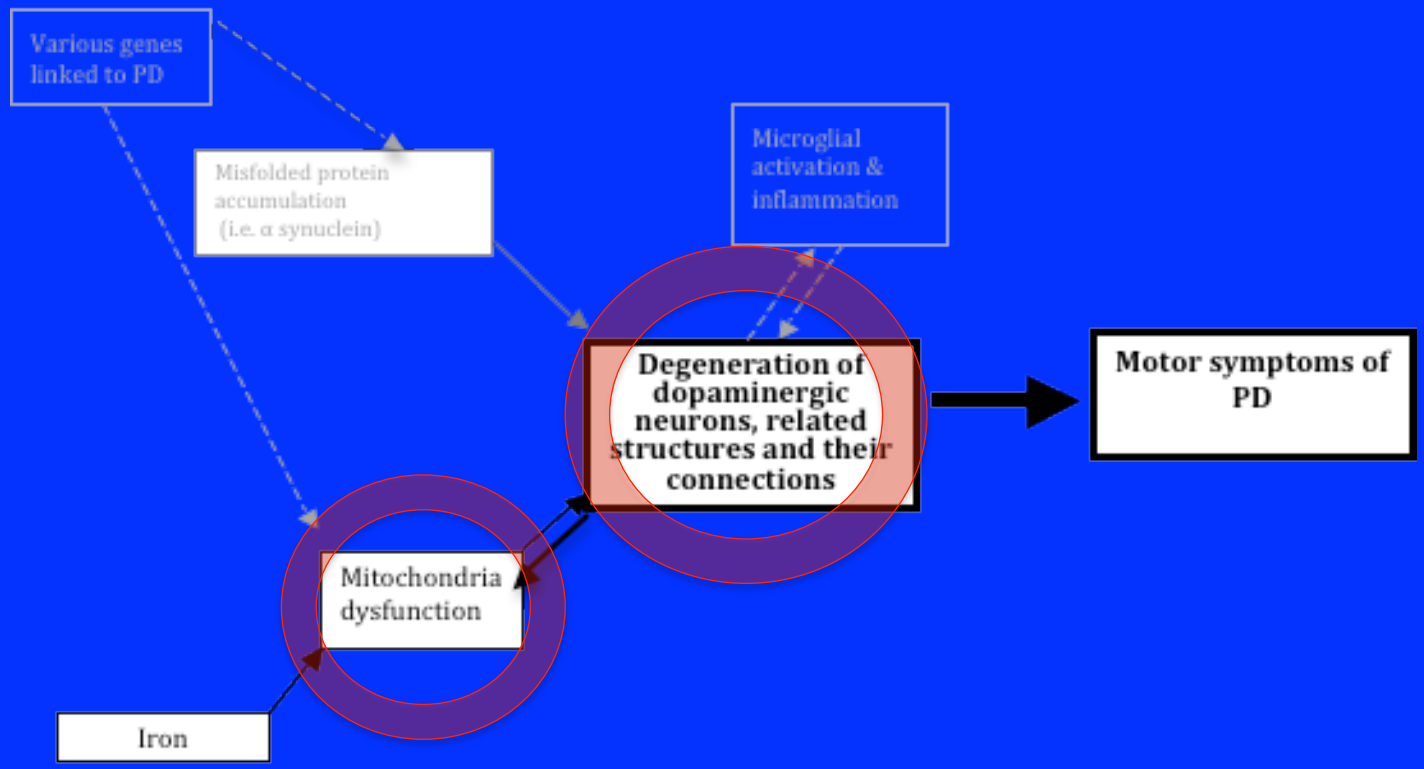
- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- **What basic research teaches us and gene-targeted therapy**
- Functional surgery and its role

Relevant PD Pathogenic Pathways Including Symptomatic Approaches



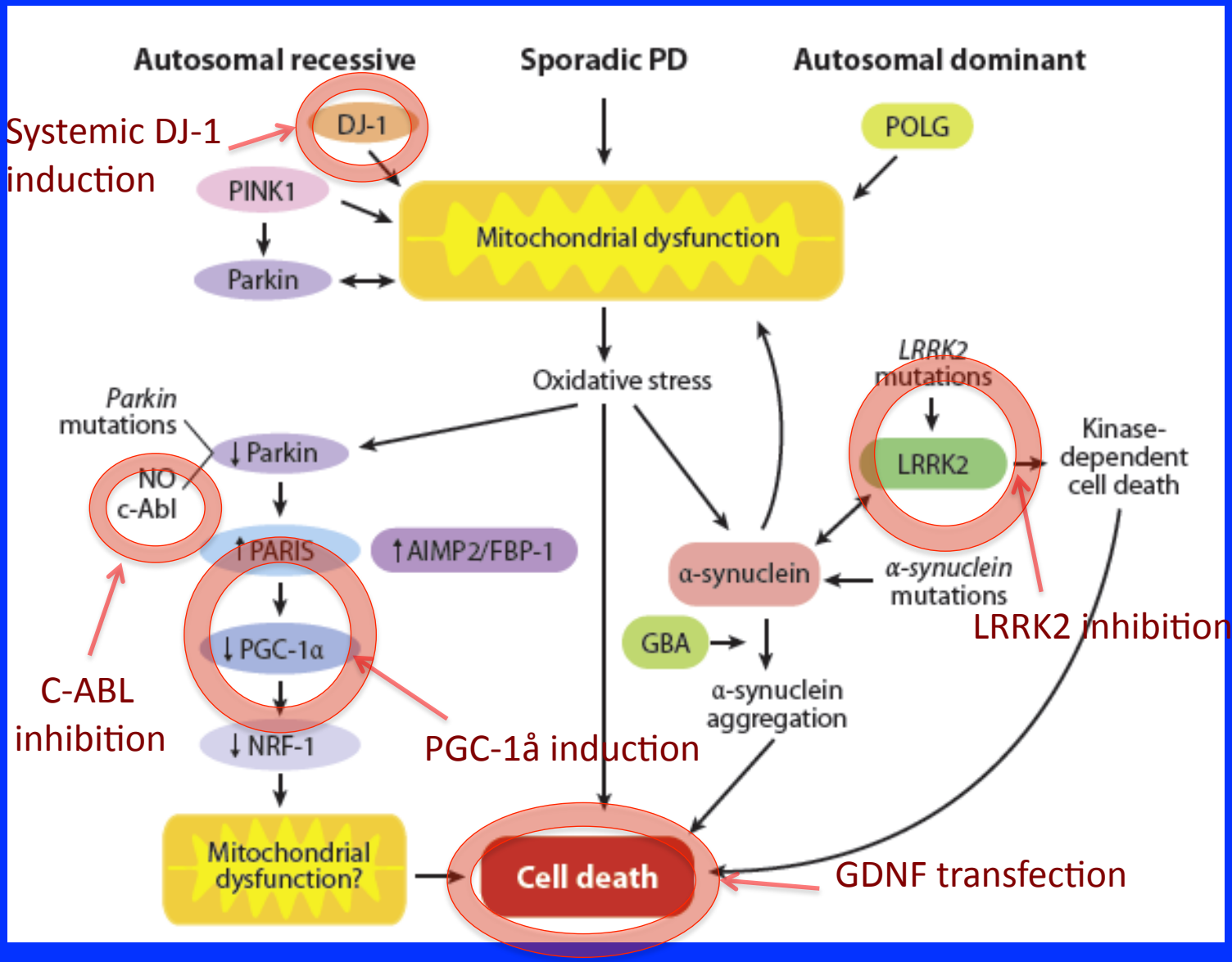
Berry and Foltynie, J Neurol 2011

Relevant PD Pathogenic Pathways Neurogenesis/Survival Approaches



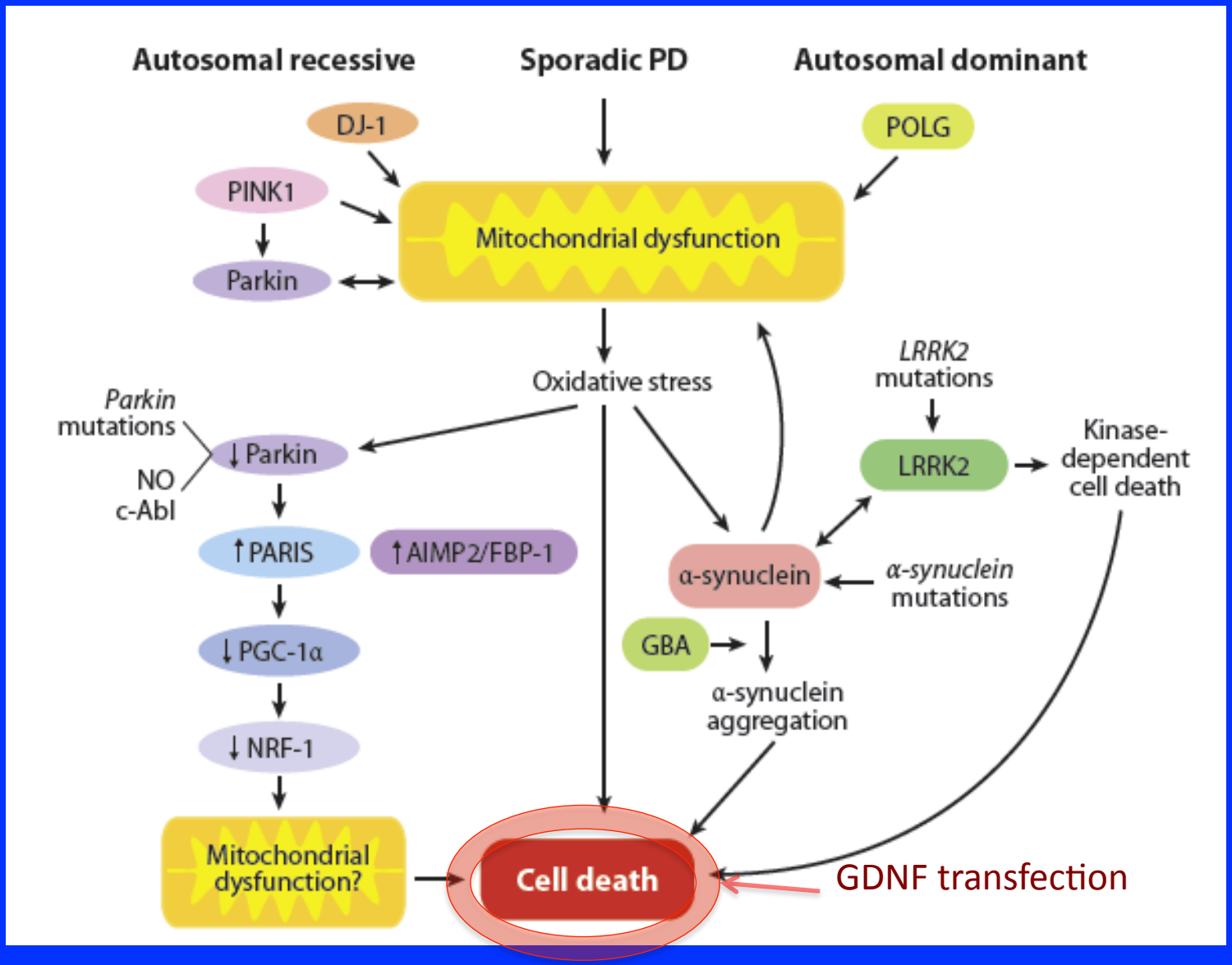
Courtesy of Dr Pritha Ghosh

Gene-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

Gene-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

GDNF Early Clinical Data and Next Steps

- 4 GDNF and 2 NTN trials conducted so far
- Variable efficacy, limited primarily by the efficacy of drug delivery

- New trial in preparation at the NIH, intramural – extramural collaboration
- Convention-enhanced delivery of AAV2-GDNF allows much better distribution of the gene product to the striatum
- 4 sequential dosing cohorts planned

Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role

Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- **Functional surgery and its role**

Deep Brain Stimulation Therapy
For Whom?

- Confirmed PD diagnosis
- Clear response to L-DOPA: at least 30% improvement in UPDRS with L-DOPA induced transition from off to on, by in-office evaluation
- Exclusion for severe medical conditions
- Exclusion for untreated depression, psychosis or dementia
- ? Failed medical therapy: appears superior to medical therapy in patients with motor complications
- ?Age: not a strict criterion

Deep Brain Stimulation Therapy When?

JAMA

Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease: A Randomized Controlled Trial

Frances M. Weaver, PhD; Kenneth Follett, MD, PhD; Matthew Stern, MD; Kwan Hur, PhD; Crystal Harris, PharmD; William J. Marks Jr, MD; Johannes Rothlind, PhD; Oren Sagher, MD; Domenic Reda, PhD; Claudia S. Moy, PhD; Rajesh Pahwa, MD; Kim Burchiel, MD; Penelope Hogarth, MD; Eugene C. Lai, MD, PhD; John E. Duda, MD; Kathryn Holloway, MD; Ali Samii, MD; Stacy Horn, DO; Jeff Bronstein, MD, PhD; Gatana Stoner, RN, CCRC; Jill Heemskerk, PhD; Grant D. Huang, PhD; for the CSP 468 Study Group

Enough Is Enough

Moving on to Deep Brain Stimulation in Patients With Fluctuating Parkinson Disease

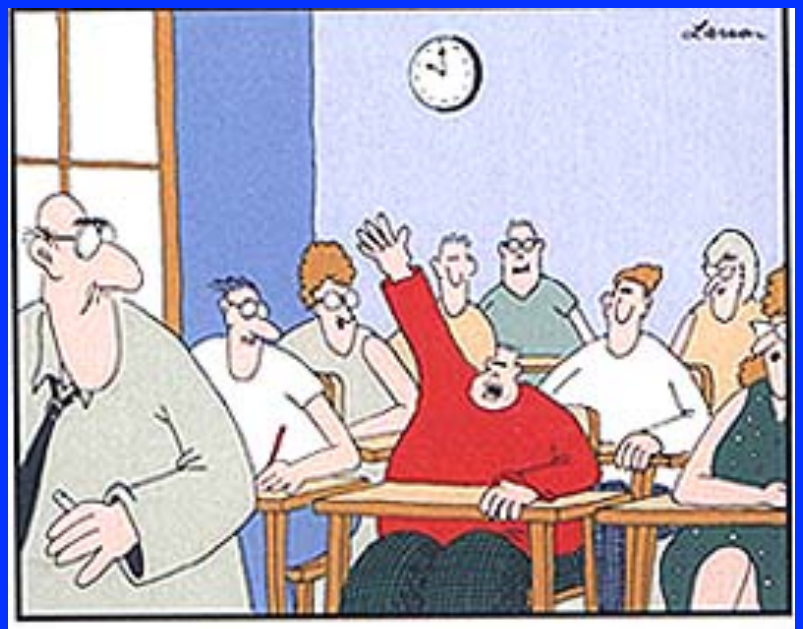
Michael S. Okun, MD
Kelly D. Foote, MD

ARCH NEUROL/VOL 66 (NO. 6), JUNE 2009

The time to refer to DBS is the time of fluctuations and dyskinesia

Deep Brain Stimulation Therapy
How?

- See Dr Zaghloul's lecture



"Mr. Osborne, may I be excused?
My brain is full."

Thank You

Thank you!

- NIH Parkinson Clinic
  - Dr Pritha Ghosh
  - Beverly McElroy
  - Mae Brooks
  - All our staff
- NIH OCD
  - Dr Avi Nath
  - Support staff
- NIH MNB
  - Dr Mark Hallett
  - Clinical and research fellows
  - Science, nursing and administrative staff
- NIH SNB
  - Dr Kareem Zaghloul
  - Dr Russell Lonser
  - Dr John Heiss
  - Research nurses and support staff
- **Patients and families**
- NIH, national and international collaborators