Parkinson Disease
Motor aspects

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TOPICS

* CARDINAL MOTOR FEATURES OF PD

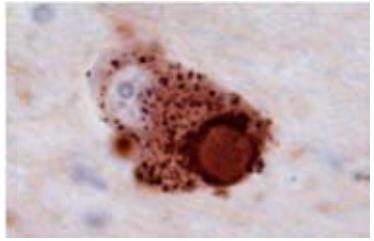
* LD-RELATED MOTOR COMPLICATIONS

* MOTOR ASYMMETRY IN PD

What is Parkinson’s disease ?

- **a clinical syndrome**
  * defined by the presence of cardinal motor features

- **a neuropathological entity**
  * defined by ?-synuclein positive neuronal cytoplasmic (Lewy bodies) and axonal (Lewy neurites) inclusions and cell loss in the SNc)



PDS BRC Criteria for Idiopathic Parkinson's Disease *Definition of a Parkinsonian Syndrome*

Bradykinesia,

plus one of

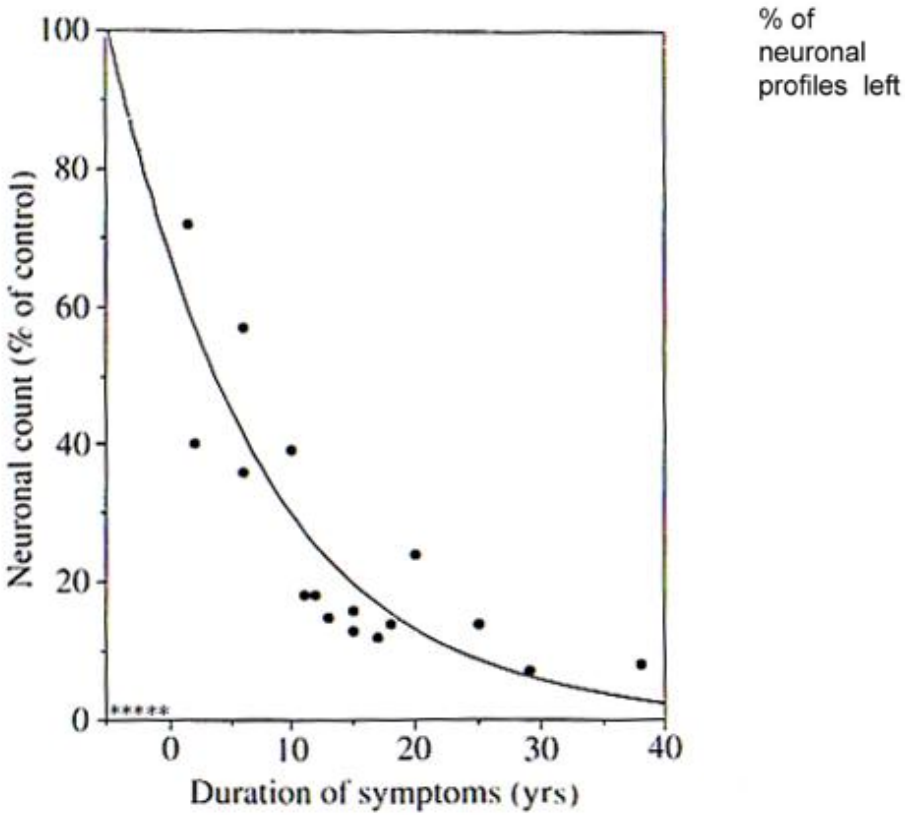
- **Rigidity**
- **4 - 6 Hz rest tremor**
- **Postural instability, not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction**

PDS BRC = Parkinson's Disease Society Brain Research Center.
Gibb WR, et al. *J Neurol Neurosurg Psychiatry.* 1988;51:745-752.

CLINICAL FEATURES OF BRADYKINESIA IN PD

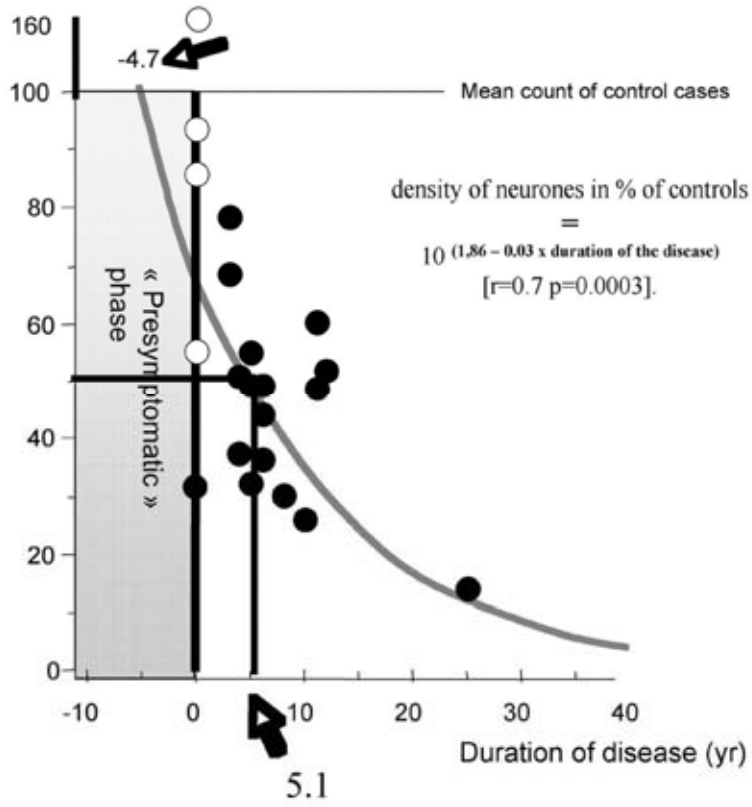
- **Bradykinesia = reduced speed of movement**
- **Hypokinesia = reduced and decrementing movement amplitude**
- **Akinesia = dysfunctional movement initiation**

Total nigral age-adjusted count vs Symptom Duration (Fearnley and Lees Brain 1991)

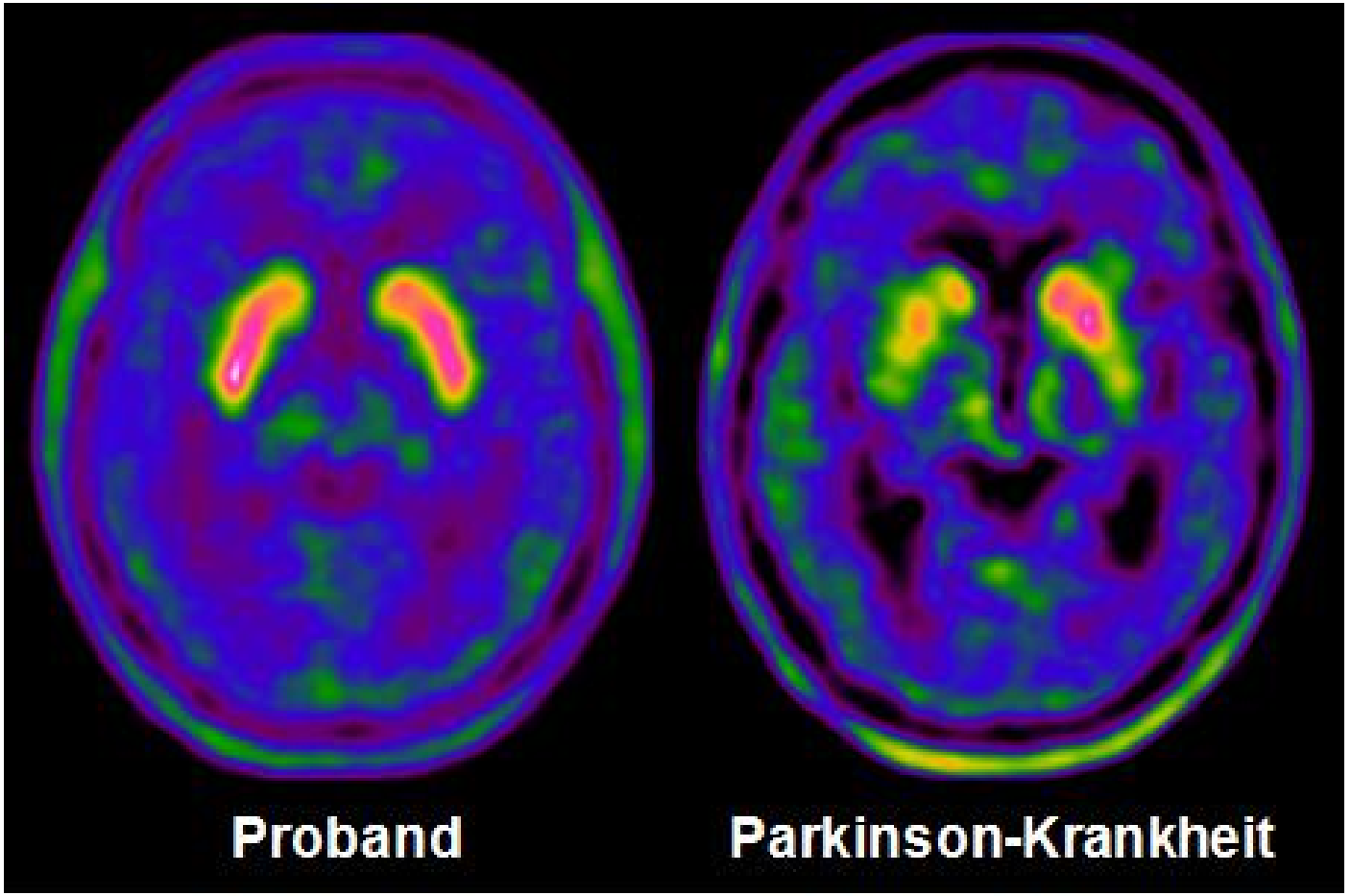


% of neuronal profiles left

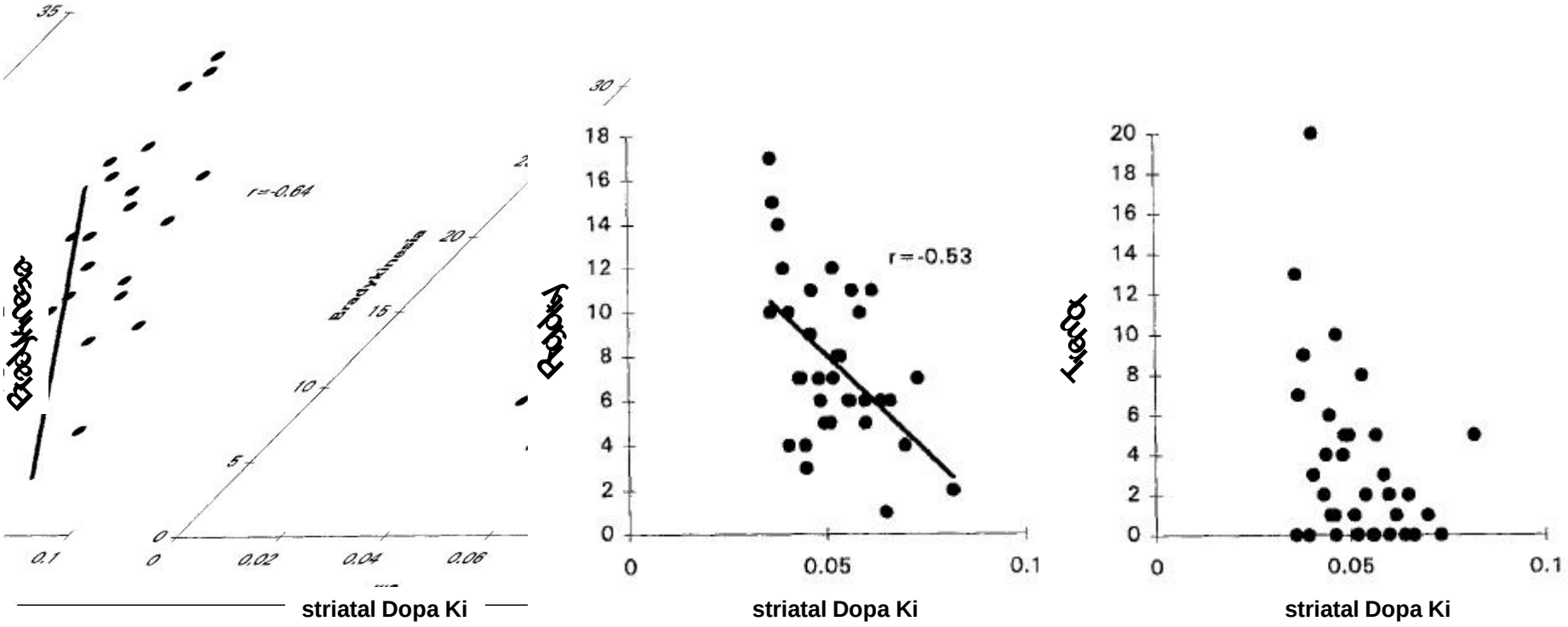
Total nigral age-adjusted count vs Symptom Duration (Duyckaerts et al, 2005)



Asymmetric reduction of putaminal [^{18}F]Dopa uptake in PD

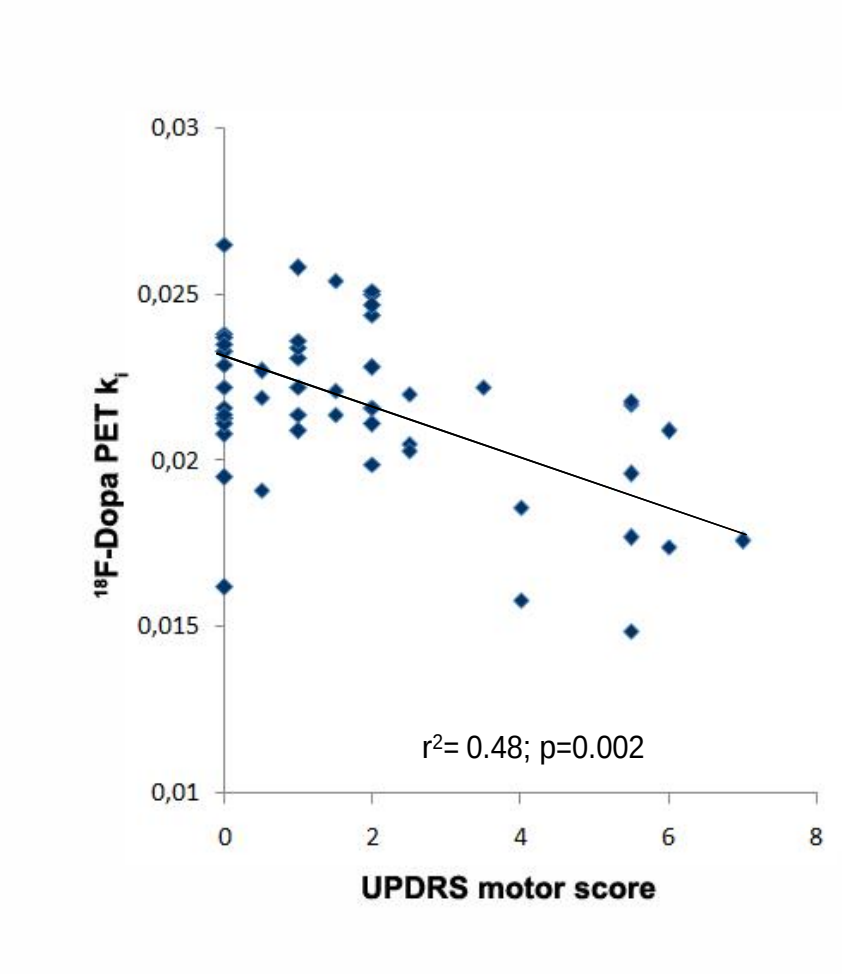


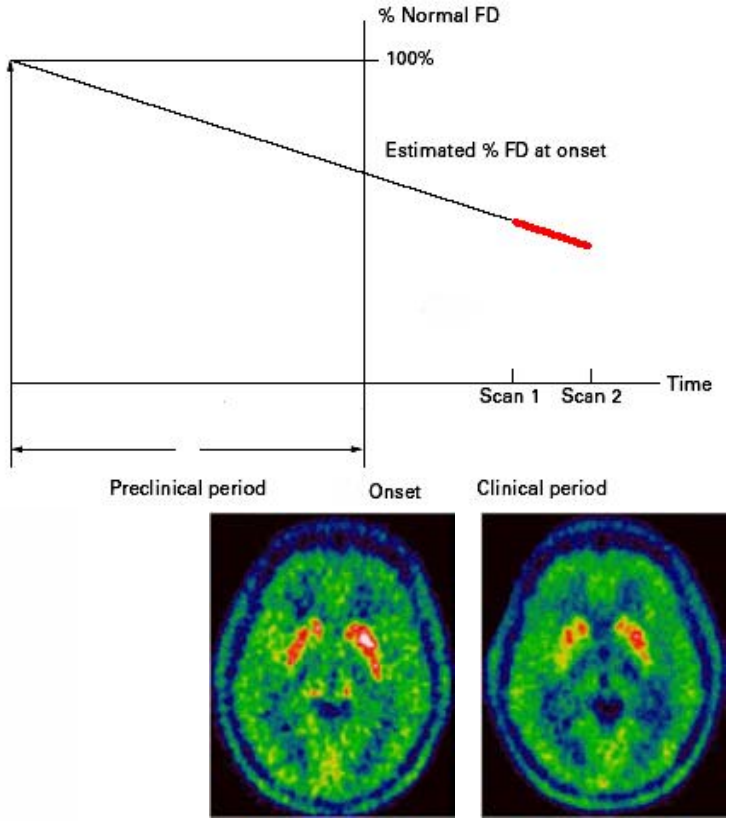
Correlations of motor symptoms and striatal Dopa PET uptake in Parkinson‘s disease



Vingerhoets et al., Ann Neurol 1997

[^{18}F]Dopa PET in PD risk subjects – correlation with UPDRS motor score





PDS BRC Criteria for Idiopathic Parkinson's Disease *Supportive Prospective Criteria*

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

PDS BRC = Parkinson's Disease Society Brain Research Center.
Gibb WR, et al. *J Neurol Neurosurg Psychiatry.* 1988;51:745-752.

NON-DOPAMINERGIC MOTOR SYMPTOMS IN PD ?

* **Posture, gait and balance**
  - **postural instability**
  - **falls**
  - **freezing**
  - **camptocormia**
  - **trunk lateroflexion**
  - **deformities of the hands and feet**

* **Speech problems**
  - **dysarthria**
  - **hypophonia**
  - **palilalia**

* **Dysphagia**

MOTOR COMPLICATION RATES WITH INITIAL L-DOPA-THERAPY

Retrospective uncontrolled studies	**50 - 80 %**
(Poewe et al, 1986)	**after 5 - 6 yrs**
Community-based studies	**30 - 40 %**
(Schrag et al, 2000)	**after 5 yrs**
Young-onset PD	**90 % after 5 yrs**
(Quinn et al, 1987; Schrag et al, 1998)	
RCT‘s	**16 % after 9 mths**
(PSG 2000; Whone et al, 2003; ELLDOPA)	**30 - 40 % after 2 yrs**

LD-RELATED MOTOR COMPLICATIONS IN PD

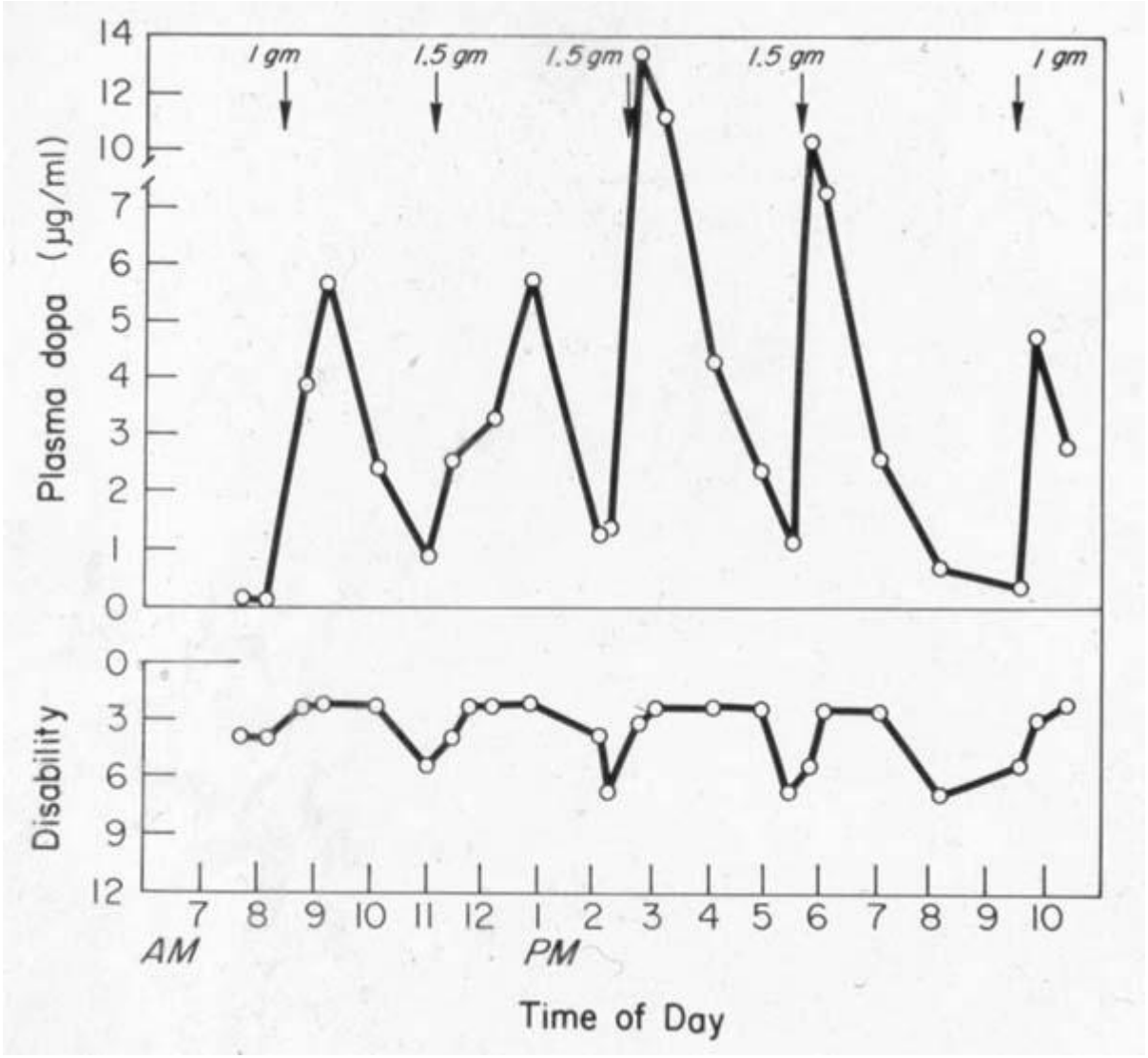
MOTOR RESPONSE FLUCTUATIONS

- wearing-off
- early morning akinesia
- random ON-OFF

LD-INDUCED DYSKINESIAS (LID‘S)

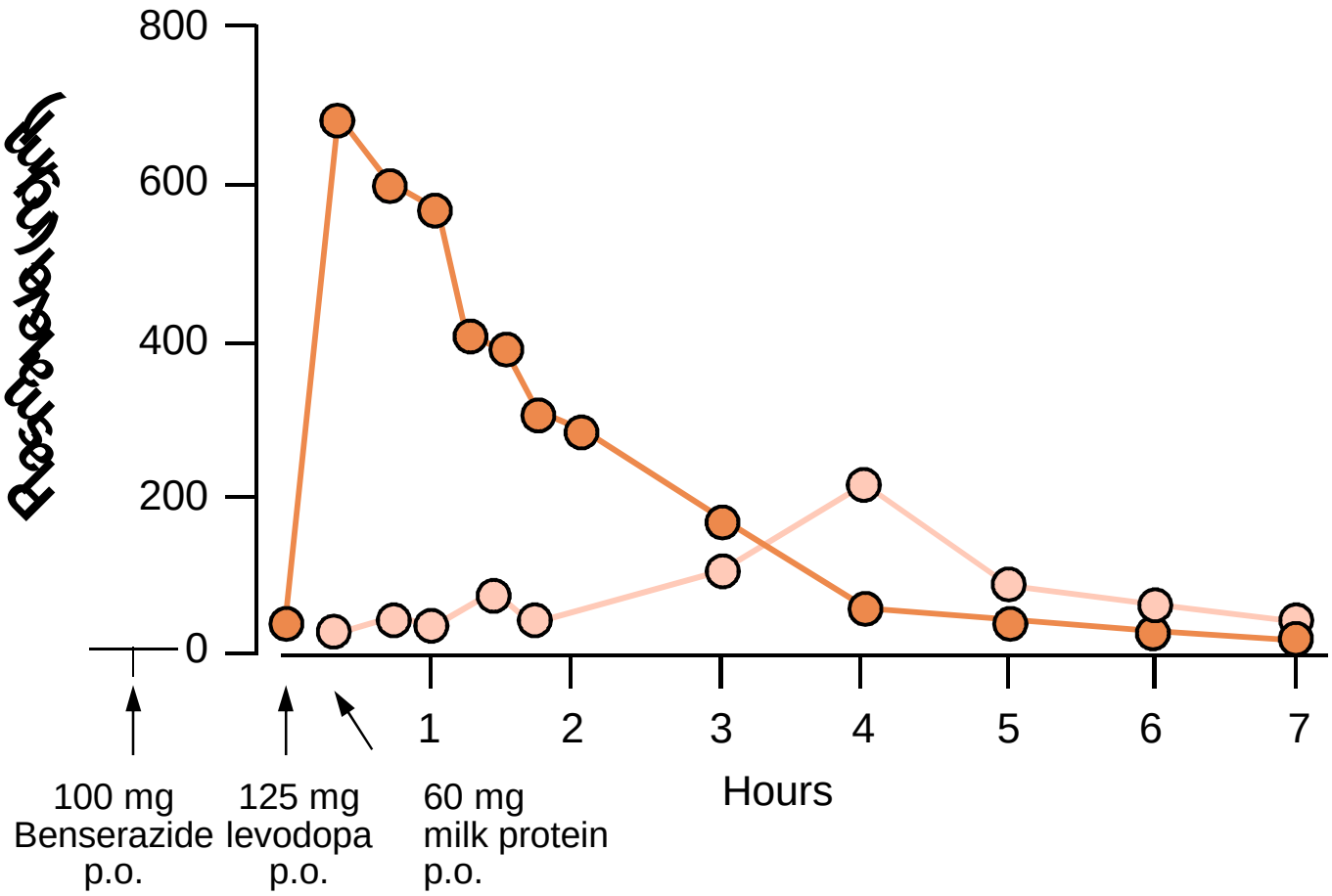
- on-period chorea
- off-period dystonia
- biphasic dyskinesias

The Short Duration Response

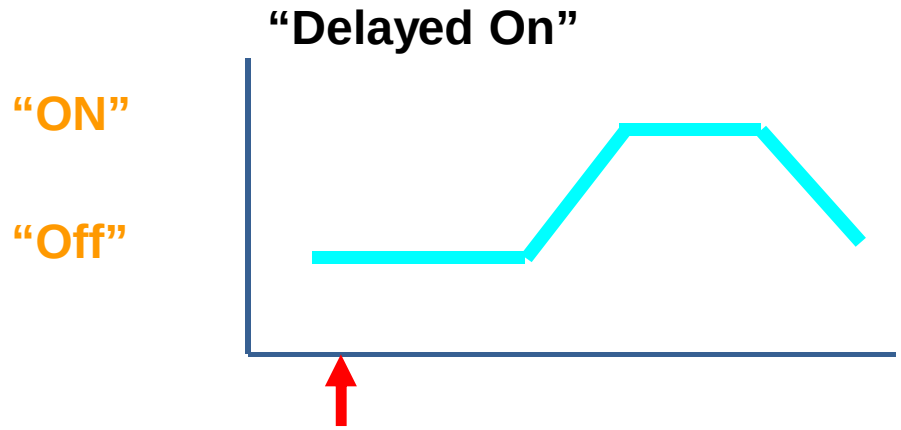


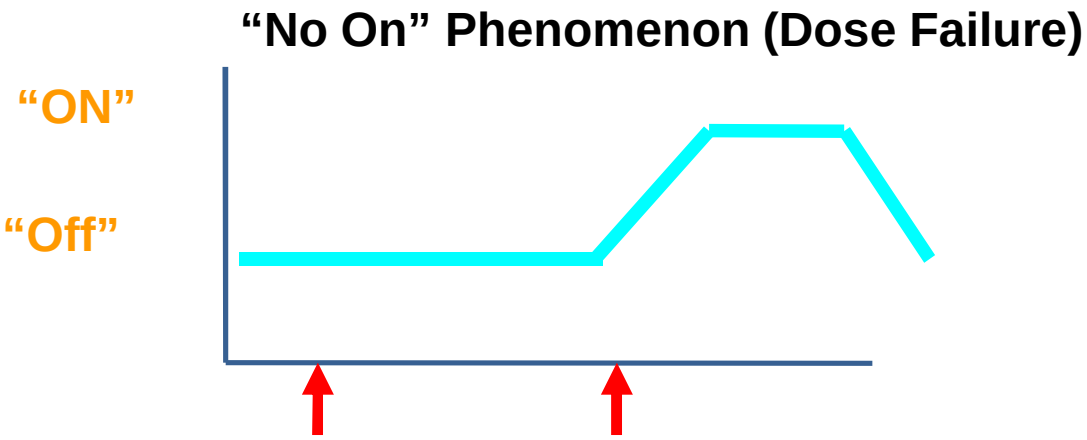
Tolosa et al, 1975

Protein load effect on levodopa absorption



Beginning of Dose Difficulties



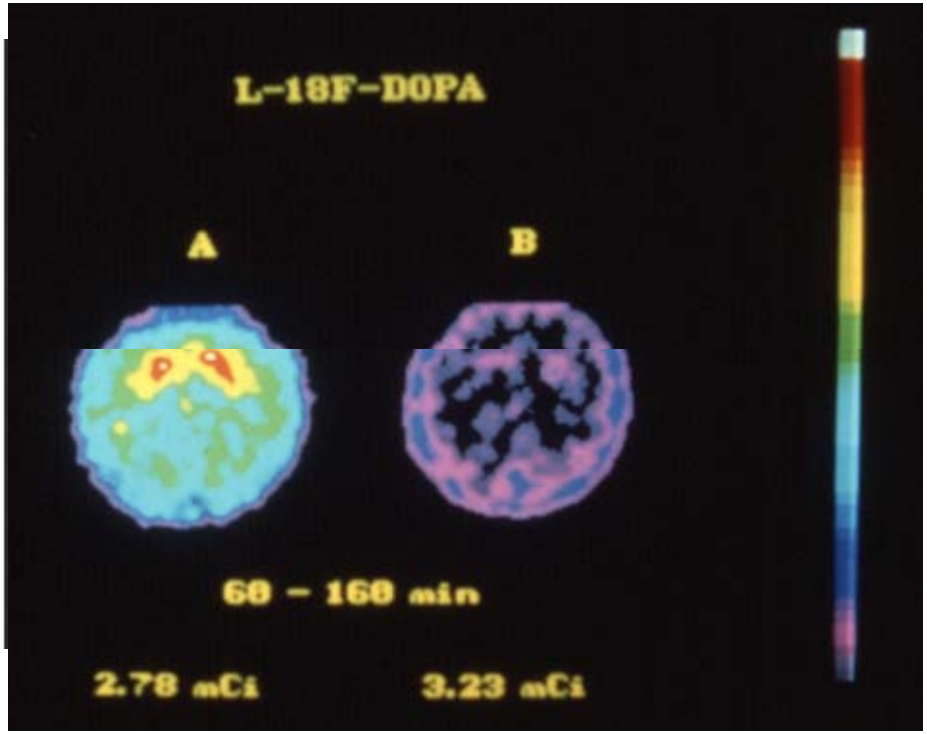


Mechanisms of wearing-off
- Effect of protein loading on LD uptake -

Inhibition of L-[^{18}F]Fluorodopa Uptake into Human Brain by Amino Acids Demonstrated by Positron Emission Tomography

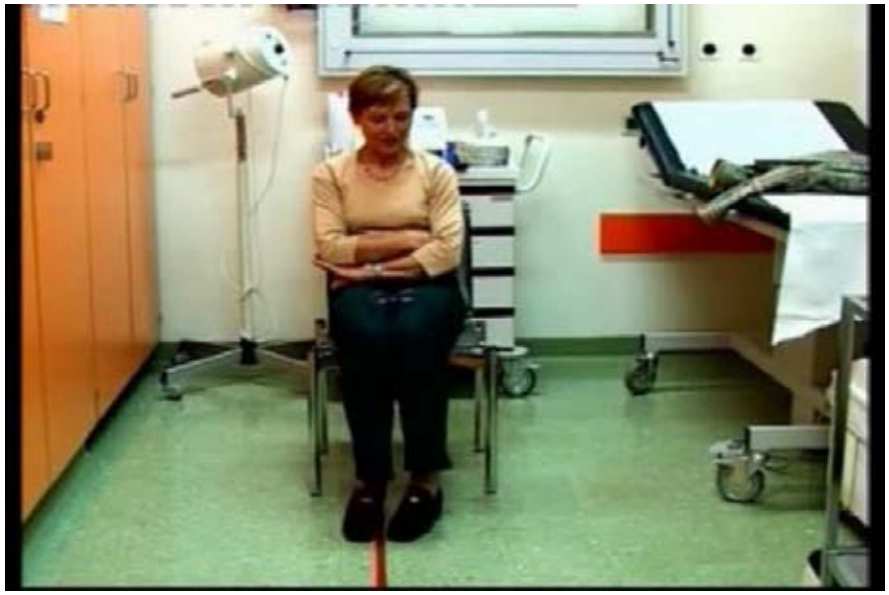
K. L. Leenders,* W. H. Poewe,† A. J. Palmer,*
D. P. Brenton,‡ and R. S. J. Frackowiak*

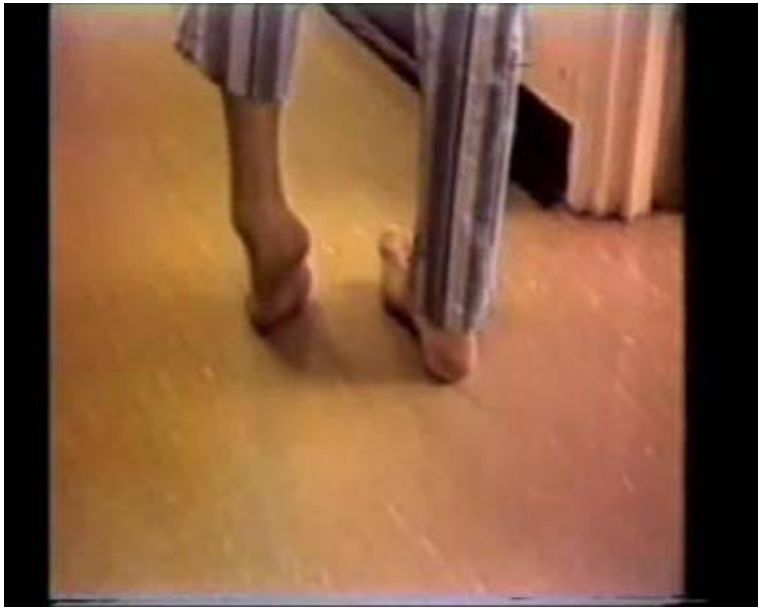
Leenders KL, Poewe WH, Palmer AJ, Brenton DP, Frackowiak RSJ: Inhibition of L-[^{18}F]fluorodopa uptake into human brain by amino acids demonstrated by positron emission tomography. Ann Neurol 20:258–262, 1986



Classification of levodopa-related motor fluctuations in PD

Clinical pattern	Mechanism
Wearing-off	levodopa - t 1/2 pre-synaptic storage
Delayed-on	gastric emptying intestinal absorption
Dose-failures (No-on)	gastric emptying intestinal absorption BBB-transport
Random ON-OFF	striatal pharmacodynamic changes





DRUG-INDUCED DYSKINESIAS IN PARKINSON‘S DISEASE

ON-PERIOD DYSKINESIAS („INTERDOSE“)

- phasic (choreic) limb movements
- dystonic craniocervical movements
- more pronounced on side initially affected by PD

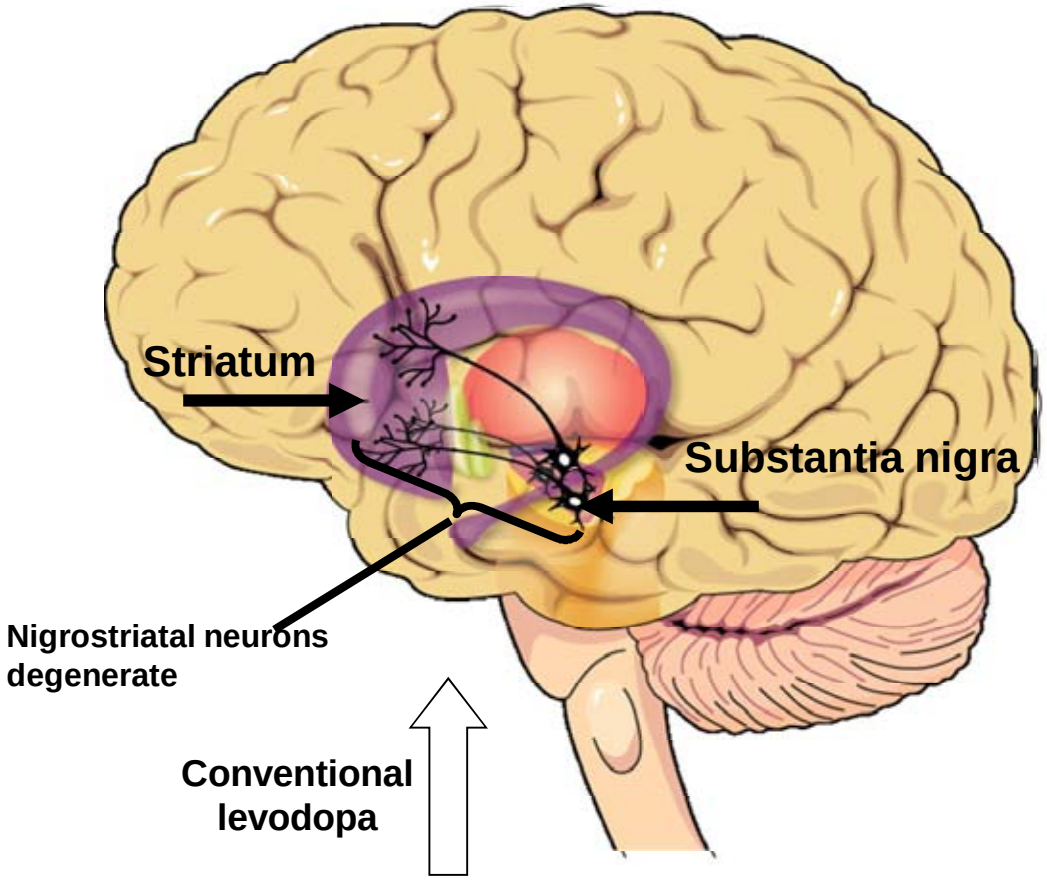
BIPHASIC DYSKINESIAS

- at onset or wearing-off of clinical benefit from a dose of levodopa (or both)
- mix of phasic and dystonic movements („mobile dystonia“)

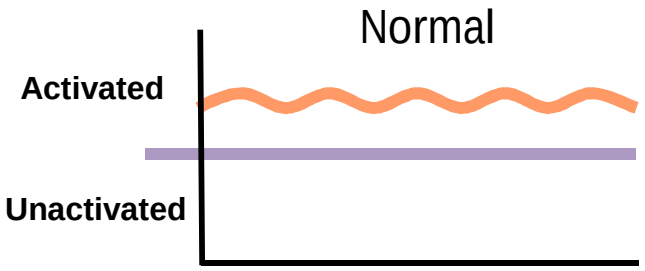
OFF-PERIOD DYSTONIA

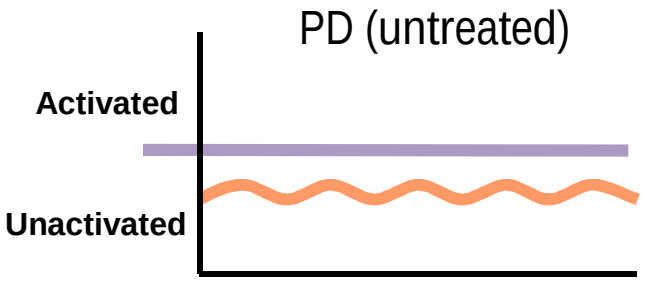
- most often distal limb (feet)
- painful

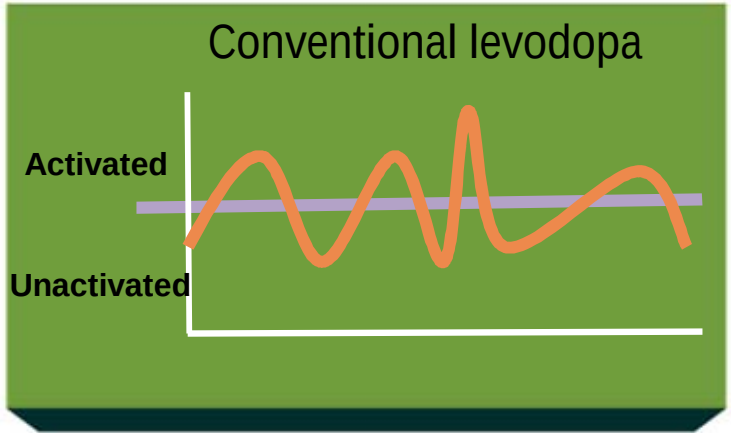
Discontinuous drug delivery and pulsatile stimulation of dopamine receptors



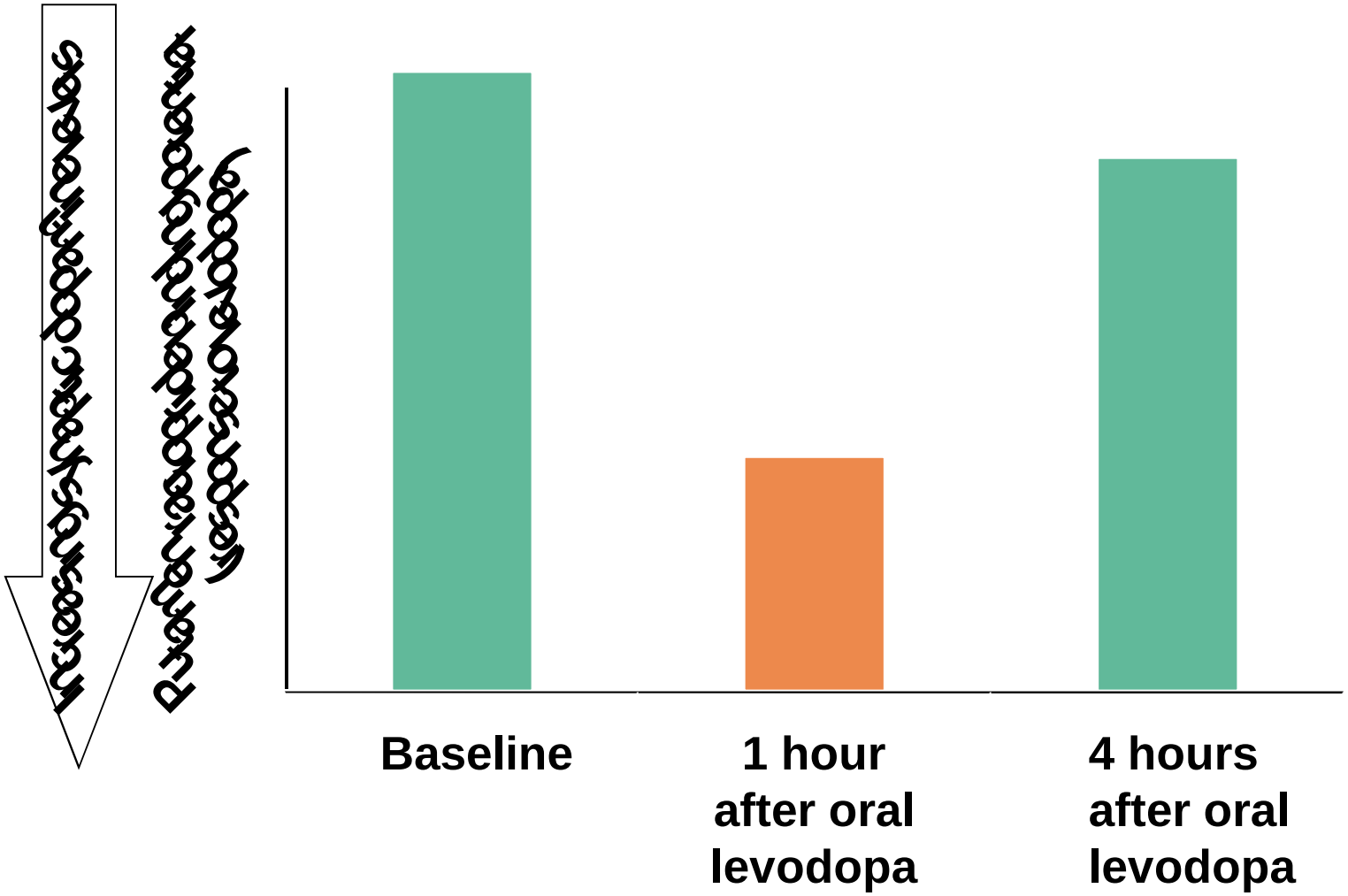
Dopamine receptor state





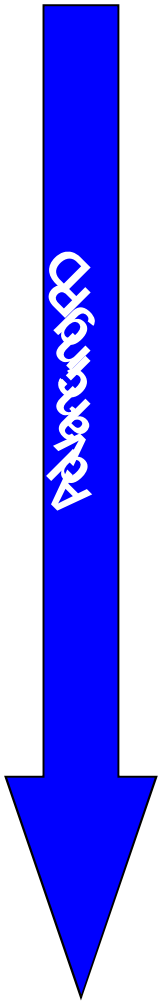


Mechanisms of wearing-off: Dose-dependent fluctuations in synaptic DA-concentrations



De la Fuente-Fernández et al, 2001

Development of motor complications



Progressive degeneration of dopamine neurones leads to reduced dopamine storage capacity in the striatum

Fluctuations in plasma levodopa levels because of the drug's short half-life can no longer be *'buffered'*

Pulsatile stimulation of striatal dopamine receptors

Downstream dysregulation of genes, proteins and second messenger systems

Altered basal ganglia firing patterns

Motor complications

L-DOPA-INDUCED DYSKINESIAS IN PD
- Risk factors -

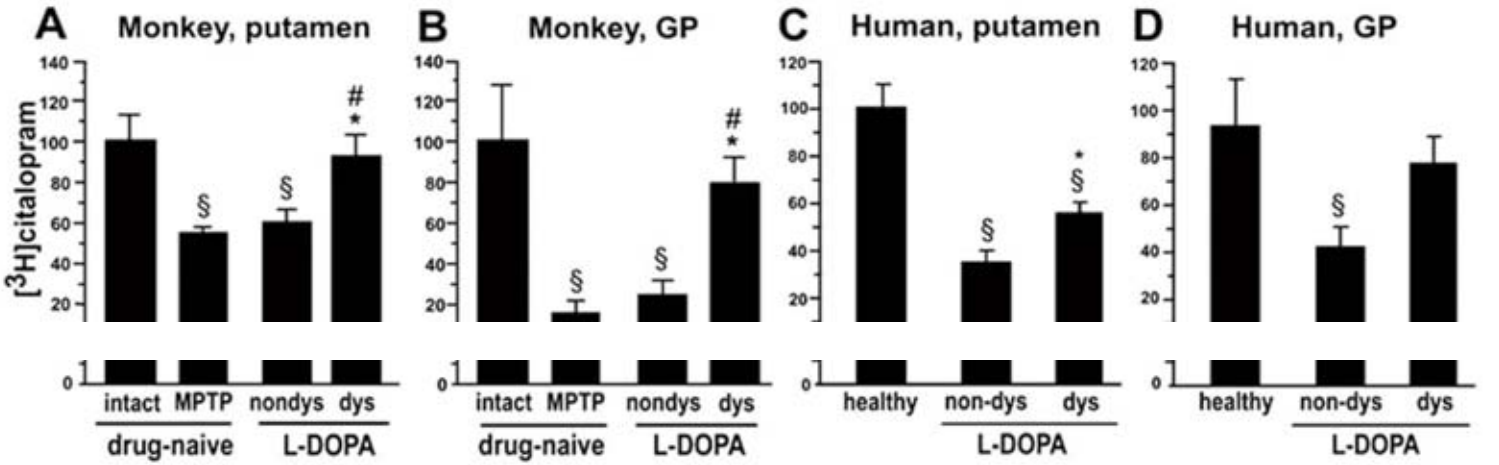
- **Well established**
  - **Younger age at onset**
  - **Treatment duration**
  - **LD-dose**

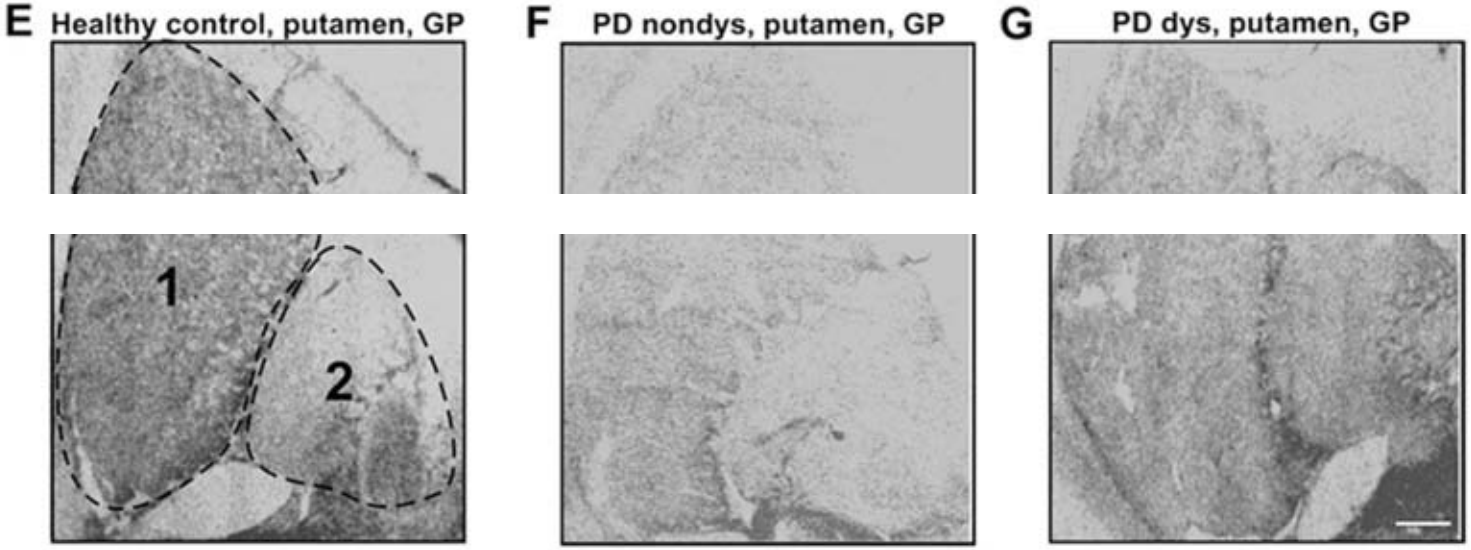
- **Less well established**
  - **Disease duration**
  - **Disease severity**

Maladaptive Plasticity of Serotonin Axon Terminals in Levodopa-Induced Dyskinesia

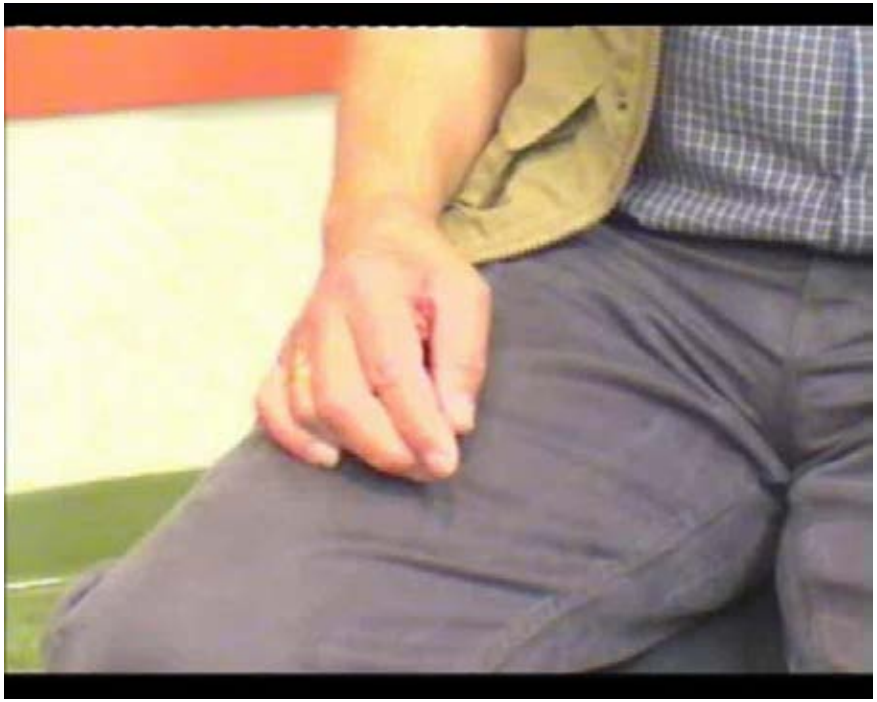
Daniella Rylander, PhD,[1] Martin Parent, PhD,[2] Sean S. O'Sullivan, MB, MRCPI,[3] Sandra Dovero, PhD,[4] Andrew J. Lees, MD, FRCP,[3] Erwan Bezard, PhD,[4] Laurent Descarries, MD, FRCP(C),[5,6] and M. Angela Cenci, MD, PhD[1]

ANN NEUROL 2010;68:619–628





The enigma of motor asymmetry in Parkinson‘s disease



Hoehn and Yahr Scale

1: Unilateral involvement only, usually with minimal or no functional disability

2: Bilateral or midline involvement without impairment of balance

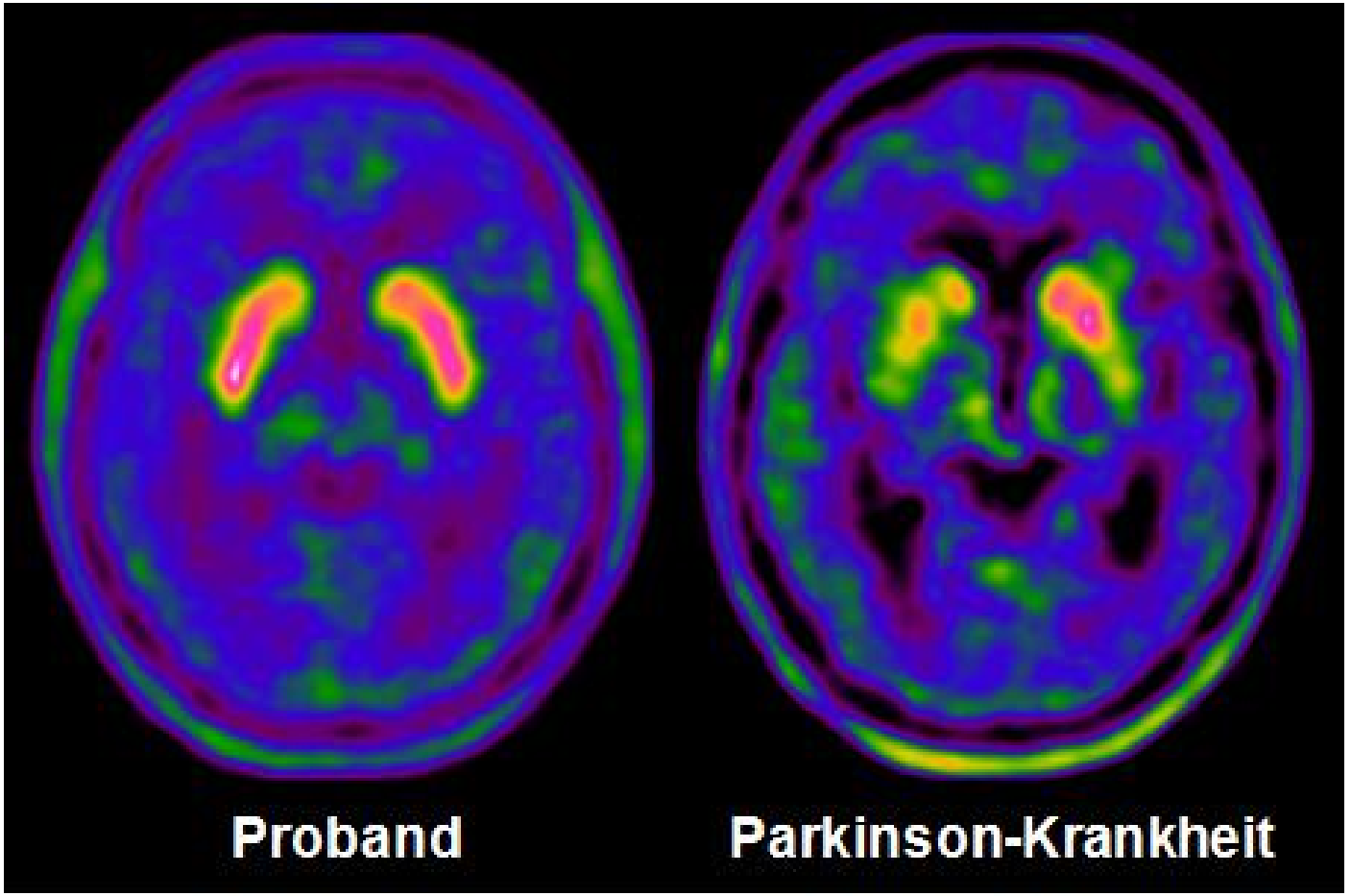
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent*

4: Severely disabling disease; still able to walk or stand unassisted

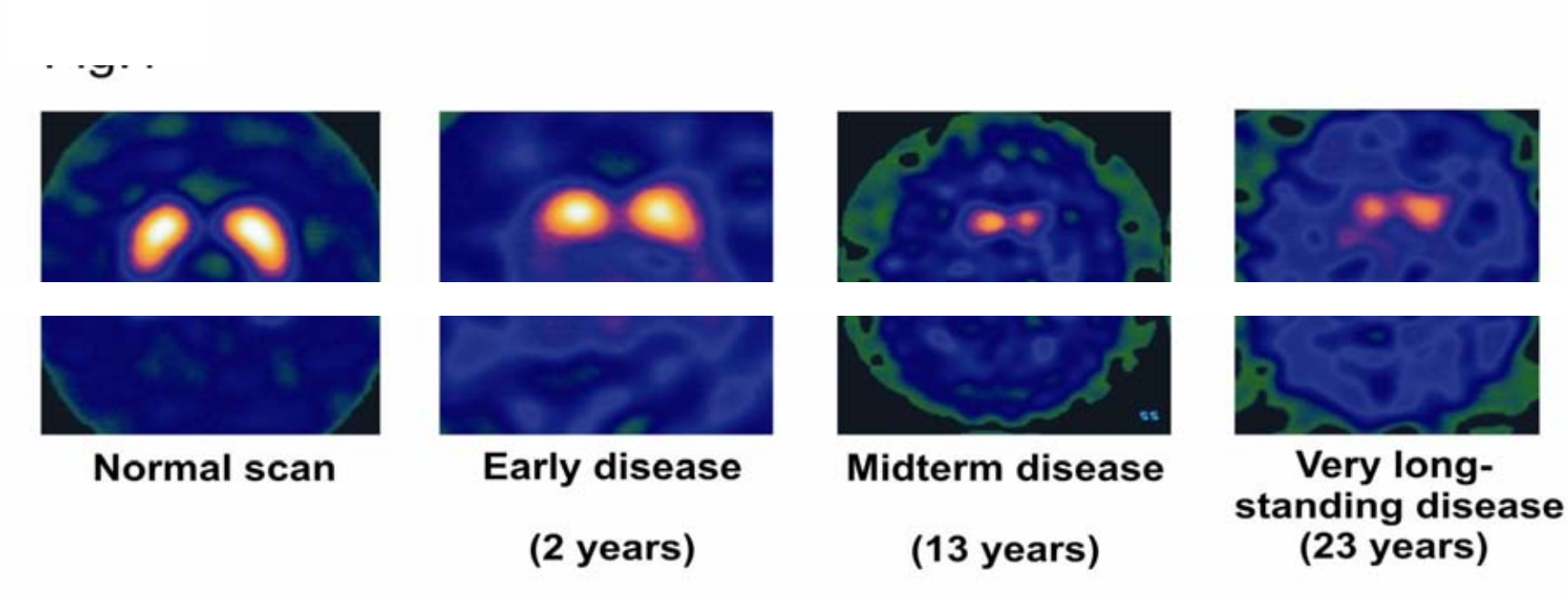
5: Confinement to bed or wheelchair unless aided

* Stage 3 is a summary of the author‘s original, more narrative description

Asymmetric reduction of putaminal [^{18}F]Dopa uptake in PD



Persistent asymmetry of nigrostriatal dysfunction (FP-CIT-SPECT) in PD



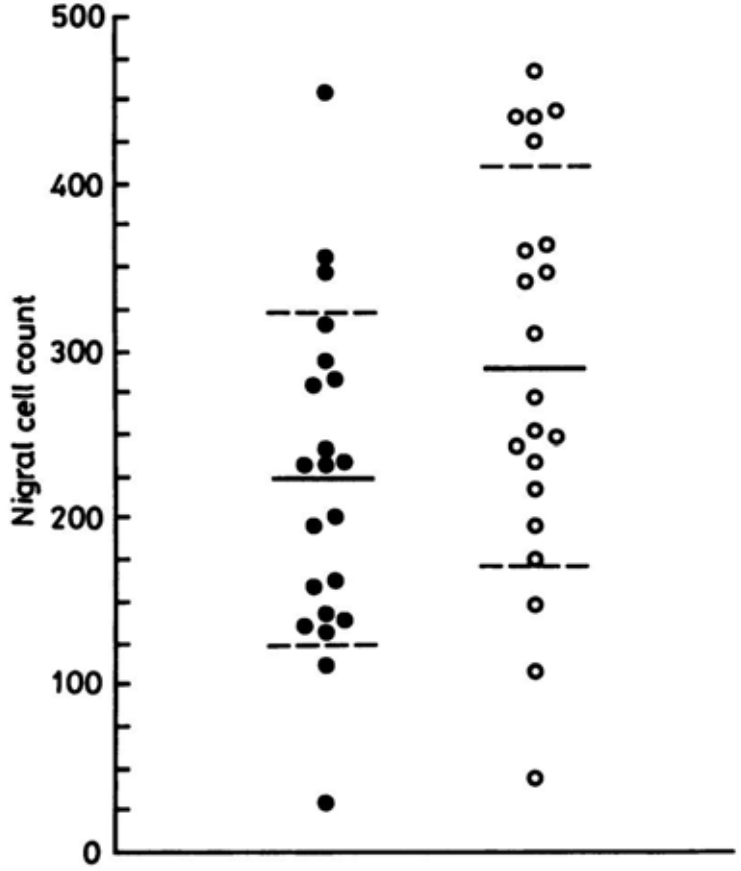
Djaldetti et al, Mov Disord 2010

Journal of Neurology, Neurosurgery, and Psychiatry 1989;52:72–76

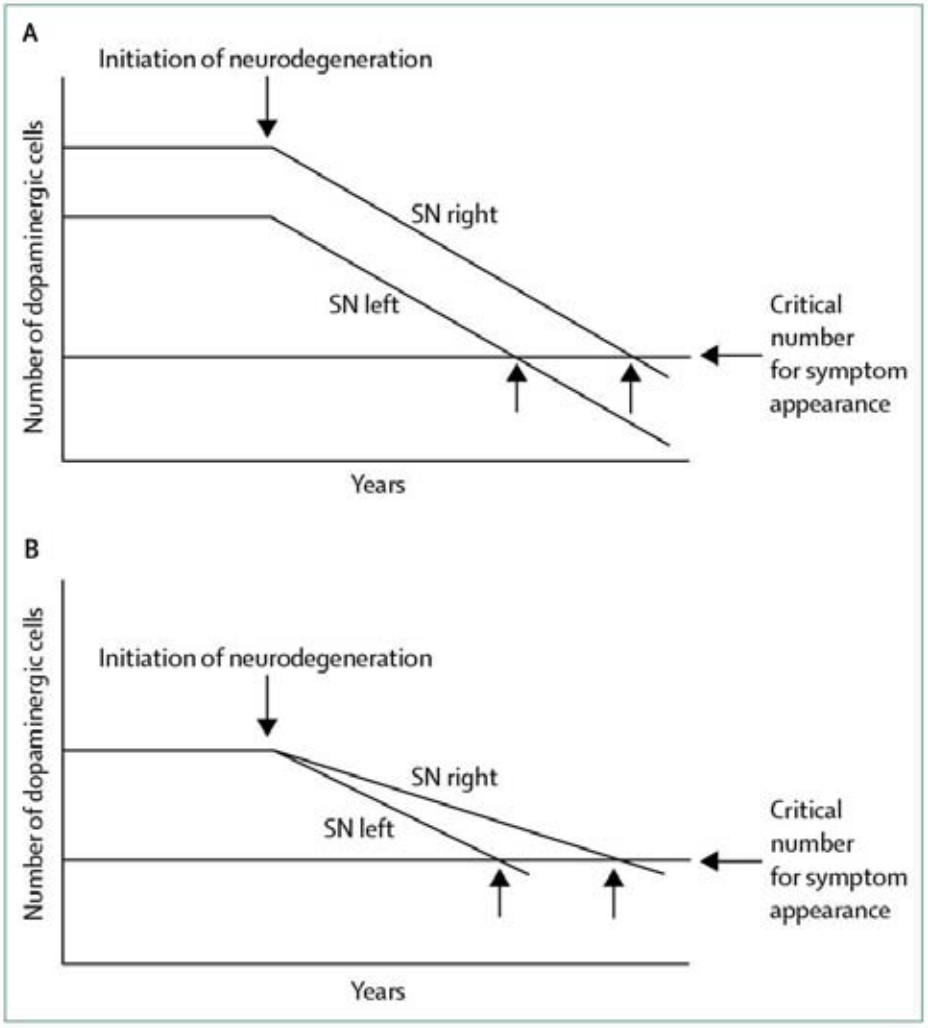
Asymmetry of substantia nigra neuronal loss in Parkinson's disease and its relevance to the mechanism of levodopa related motor fluctuations.

P A KEMPSTER,* W R G GIBB,† G M STERN,* A J LEES*†

From the Department of Neurology, Middlesex Hospital and Department of Neuropathology, National Hospital for Nervous Diseases, Maida Vale,† London, UK*



WHY ARE PD MOTOR SIGNS ASYMMETRIC ?



Djaldetti und Melamed, 2006

HYPOTHETICAL MECHANISMS UNDERLYING MOTOR ASYMMETRY IN PD

ANATOMICAL

- R/L differential in SN neuronal count
- hemispheric asymmetry of motor circuits

FUNCTIONAL

- asymmetric dopamine concentrations
- asymmetric dysfunction of blood-brain-barrier
- asymmetric progression of synuclein pathology
- *effects of hemispheric dominance*

GENETIC

- genetically determined lateralised vulnerability and/or organisation of motor circuits

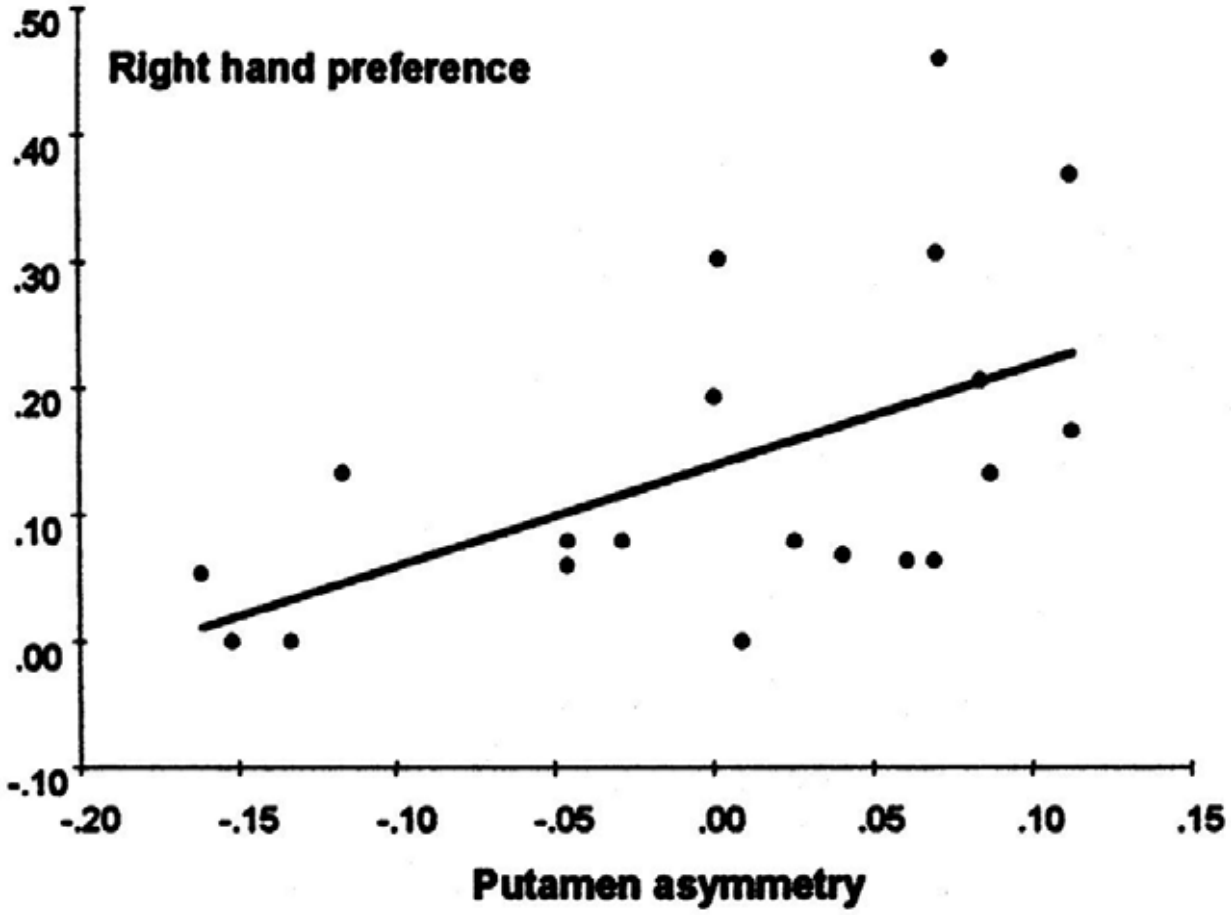
HEMISPHERIC ASYMMETRY AND PD
- Anatomical and functional findings in healthy subjects -

* ***MR Volumetry*** – Basal ganglia volume L > R
  (*Murphy et al, 1992*)

* ***DAT-SPECT*** – greater tracer binding in L Striatum
  (*Dyck et al, 2002*)

* ***Neurotransmitter levels*** – striatal DA-concentrations L > R
  (*Glick et al, 1982)*

Correlation between R-Handedness and putaminal F-DOPA-K_i (N=20)

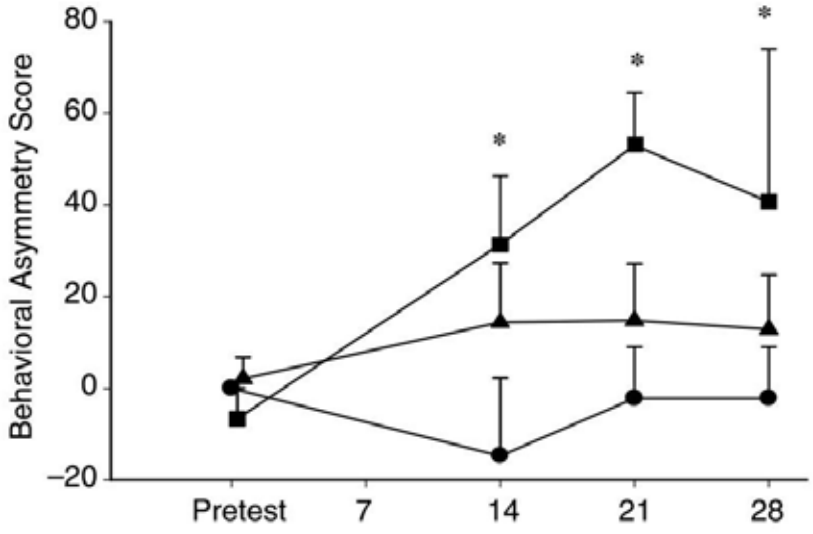


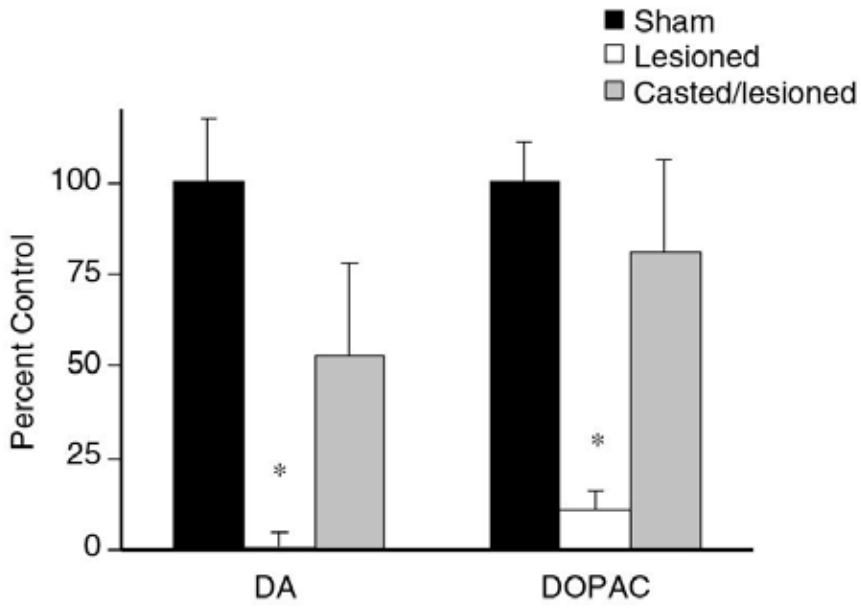
De la Fuente-Fernández et al, 2000

Journal of Neurochemistry, 2003, **85**, 299–305

Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF

Ann D. Cohen,*,† Jennifer L. Tillerson,† Amanda D. Smith,* Timothy Schallert†,‡ and Michael J. Zigmond*

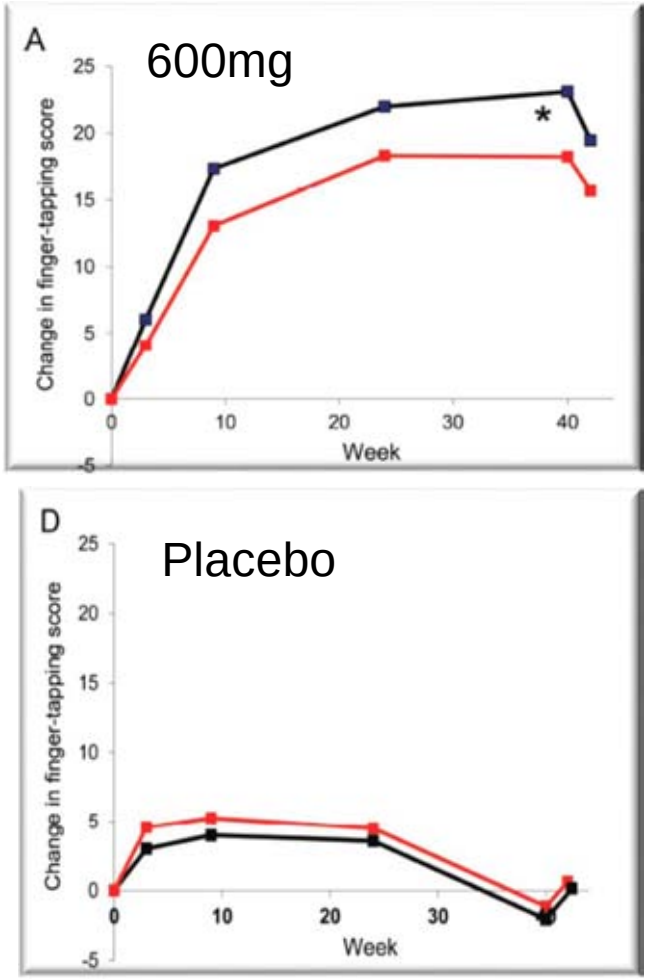




Un Jung Kang, MD
Peggy Auinger, MS
On behalf of the
Parkinson Study
Group ELLDOPA
Investigators

Activity enhances dopaminergic long-duration response in Parkinson disease

Improvement of long duration response dependent on L-Dopa and motor activity (greater improvement in dominant hand)



Neurology® 2012;78:1146-1149

Handedness Correlates with the Dominant Parkinson Side: A Systematic Review and Meta-analysis

Anouk van der Hoorn, BSc,[1*] Huibert Burger, MD, PhD,[2,3] Klaus L. Leenders, MD, PhD,[1] and Bauke M. de Jong, MD, PhD[1]

[1]*Department of Neurology, University Medical Center Groningen, University of Groningen, The Netherlands*
[2]*Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands*
[3]*Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands*

Mov Disord 2012;27:206-10

- **10 studies with sufficient information on handedness and motor asymmetry**
- **N = 4405 Patients (*92.1% R-Handed*)**
- **R-Handed (N=4057)**
  - ***59.5 % R > L***
  - ***40.5 % L > R***
- **L-Handed (N=348)**
  - ***40.8 % R > L***
  - ***59.2 % L > R***

doi:10.1093/brain/aws253 Brain 2012: 135; 3348–3354 | 3348

BRAIN
A JOURNAL OF NEUROLOGY

Left hemispheric predominance of nigrostriatal dysfunction in Parkinson's disease

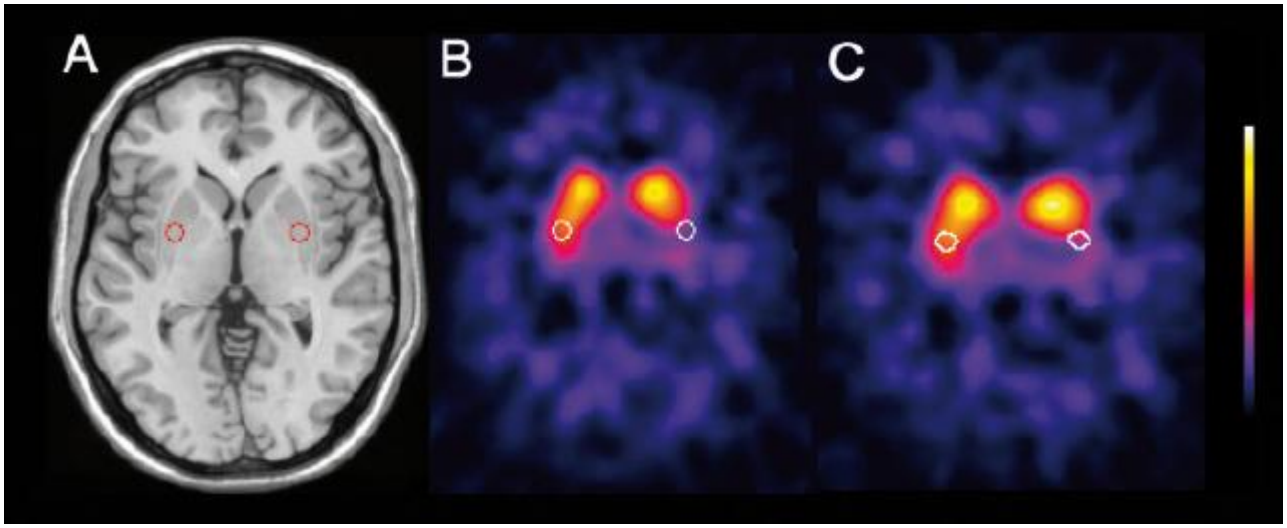
Christoph Scherfler,[1] Klaus Seppi,[1] Katherina J. Mair,[1] Eveline Donnemiller,[2] Irene Virgolini,[2] Gregor K. Wenning[1] and Werner Poewe[1]

N = 68 patients

- UK PDSBB Criteria
- symptom onset > 50 a
- positive DAT-SPECT (ß-CIT)
- positive LD response
- mean age 63 a
- mean disease duration 2 a

- UPDRS III Score „ON“
- Edinburgh Handedness Inventory
- side of symptom onset
- UPDRS III AI

Template-based ROI-Analysis



ROIs in MRI template space

DAT SPECT and ROIs in MRI template space

Inverse projection of ROIs onto the single DAT SPECT

Scherfler et al, Brain 2012

L-HEMISPHERIC PREDOMINANCE OF NIGROSTRIATAL DYSFUNCTION IN PD

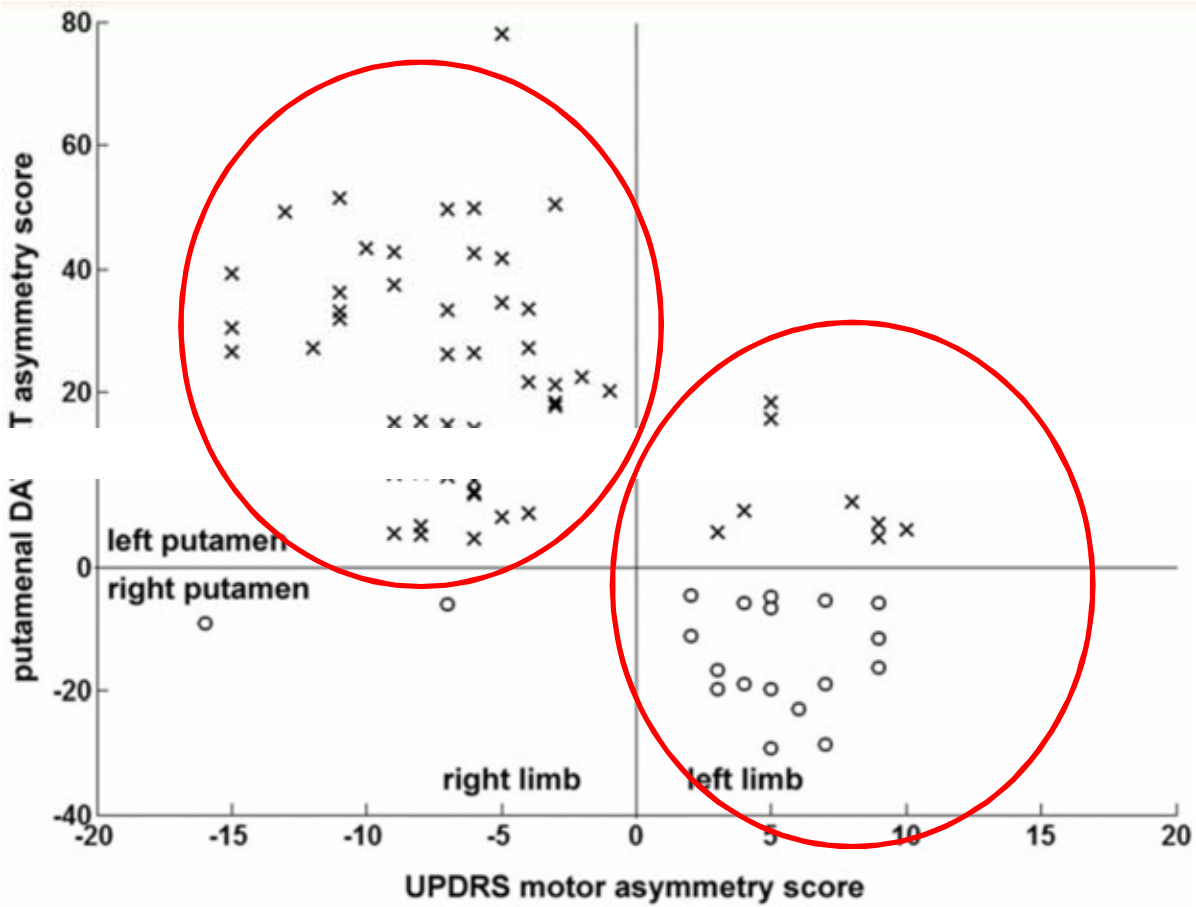
Inclusion criteria: Diagnosis according to UK PDSBB Criteria
Age > 50 yrs
Levodopa responsiveness
Decreased striatal DAT binding (SPECT)

Exclusion criteria: Clinical signs of atypical parkinsonism
Basal ganglia lesions in CT/MRI

	PD-LEFT patients [$n = 49^{*}$ (72%)]	PD-RIGHT patients [$n = 19$ (28%)]
Gender, female/male	19/30	6/13
Age at DAT SPECT (years)	62.2 ± 7.4	63.9 ± 6.3
Disease duration until DAT SPECT (years)	2.2 ± 1.5	2 ± 1.5
UPDRS motor score	20 ± 7.1	$30.2 \pm 9.9^{**}$
Time period between DAT SPECT and UPDRS (years)	0.8 ± 1.2	1 ± 1.3
UPDRS asymmetry subscore[a]	7.2 ± 3.4	6 ± 3.3
Right-side	41 (83.7)	2 (10.5)
Left-side	8 (16.3)	17 (89.5)

Scherfler C, Seppi K, Mair KJ, Donnemiller E, Virgolini I, Wenning G, Poewe W - Brain 2012

L-HEMISPHERIC PREDOMINANCE OF NIGROSTRIATAL DYSFUNCTION IN PD



Scherfler et al, Brain 2012

MOTOR ASPECTS OF PD
- Summary -

*** Close correlation between bradykinesia and striatal dopaminergic denervation**

*** Postural instability and motor blocks (FOG) of advanced PD probably due to additional dysfunction in non-dopaminergic pathways**

*** LD-related motor complications reflect pharmacokinetics of levodopa and „maladaptive“ neuroplasticity**

*** Asymmetry of motor signs in PD partially related to hemispheric dominance**

Effects of laterality on degree of loss of dexterity

- Haaxma et al, Neuroscience 2010 -

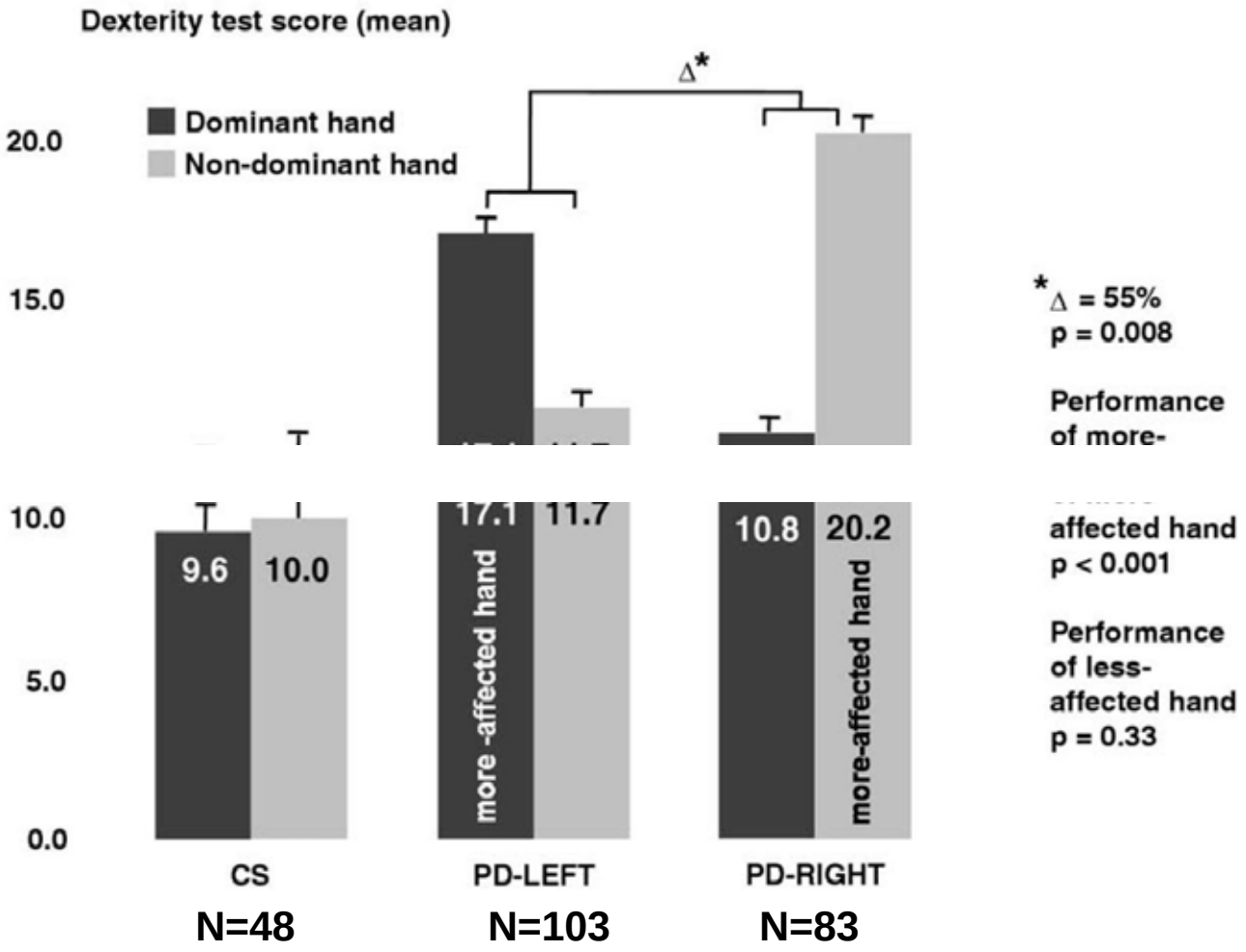
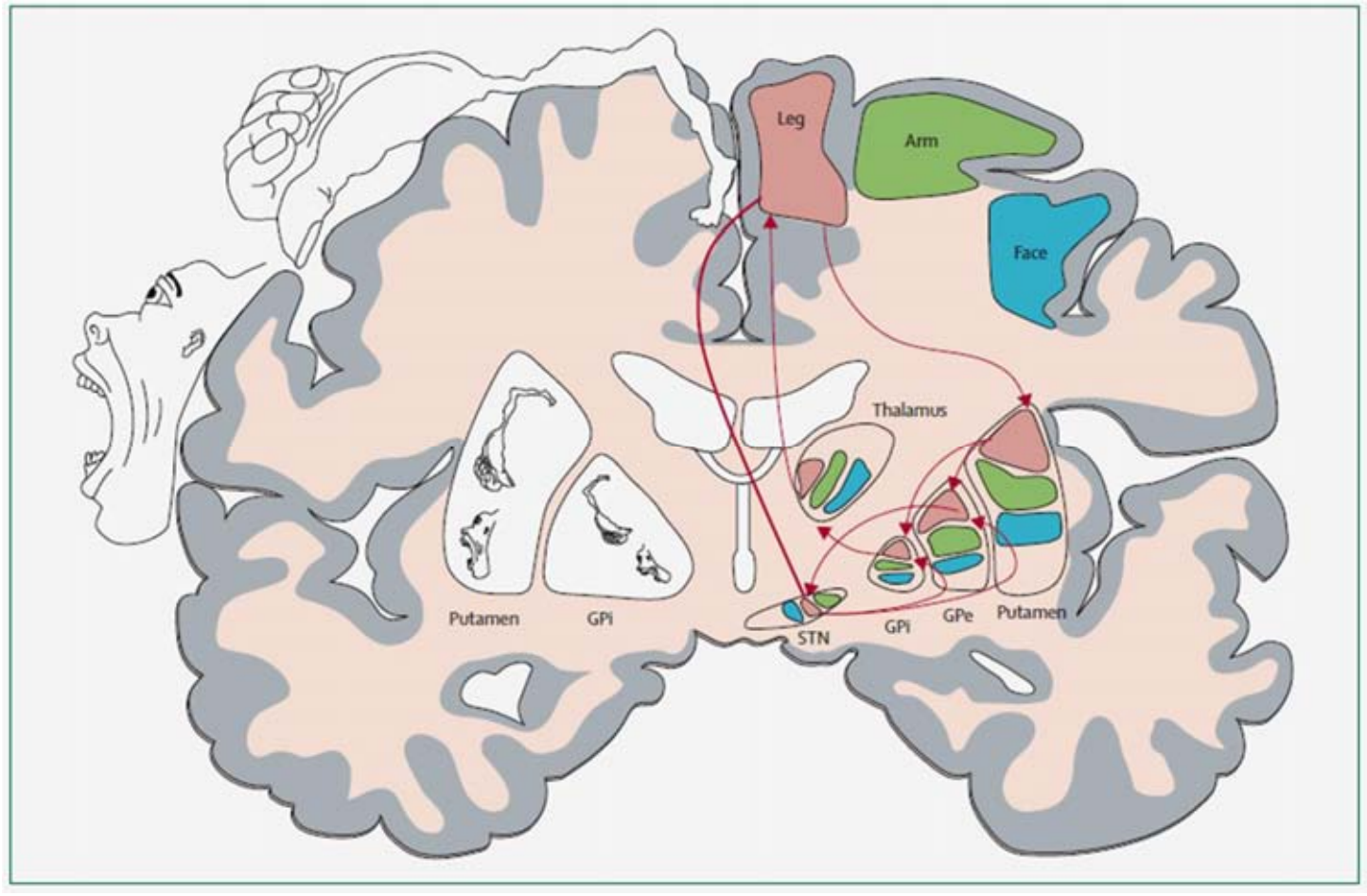


Table 2. Topography of L-Dopa-Induced Dystonia in Parkinson's Disease (n = 56)

Body Area Involved	Off-Period (n = 46)	Biphasic (n = 7)	Peak-Dose (n = 9)
Foot	46	7	1
Proximal leg	5	5	0
Ipsilateral arm	6	5	1
Trunk	1	1	0
Face/neck	1	4	9

Poewe et al, Ann Neurol 1988

Motor loop somatotopic organisation

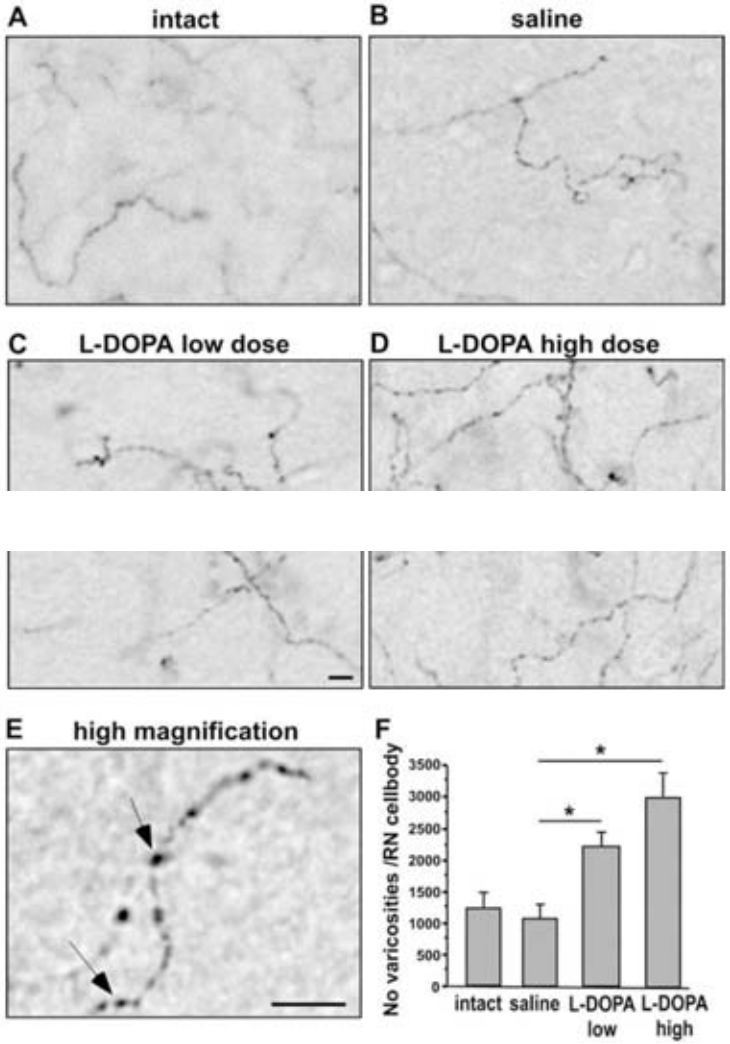


Rodriguez-Oroz et al, Lancet Neurol 2009

Maladaptive Plasticity of Serotonin Axon Terminals in Levodopa-Induced Dyskinesia

Daniella Rylander, PhD,[1] Martin Parent, PhD,[2] Sean S. O'Sullivan, MB, MRCPI,[3] Sandra Dovero, PhD,[4] Andrew J. Lees, MD, FRCP,[3] Erwan Bezard, PhD,[4] Laurent Descarries, MD, FRCP(C),[5,6] and M. Angela Cenci, MD, PhD[1]

ANN NEUROL 2010;68:619–628



HYPOTHETICAL MECHANISMS UNDERLYING MOTOR ASYMMETRY IN PD

ANATOMICAL

- R/L differential in SN neuronal count
- hemispheric asymmetry of motor circuits

FUNCTIONAL

- asymmetric dopamine concentrations
- asymmetric dysfunction of blood-brain-barrier
- asymmetric progression of synuclein pathology
- effects of hemispheric dominance

GENETIC

- genetically determined lateralised vulnerability and/or organisation of motor circuits

Genetic determinance of laterality ?
- Evidence from twin studies -

- F-DOPA-PET studies in monocygotic PD twins show lateralised signal reductions in asymptomatic twins

- ^{18}F-DOPA-PET in 6 monocygotic twin pairs show concordance for lateralised symptoms in 5 of 6 (Piccini, personal communication)

- Discordant laterality in 4 of 7 monocygotic twin pairs (Chade, Mov Disord 2006)

- Inconsistent asymmetry in 7 patients from large Austrian VPS-35 family (4 R, 3 L) (Struhal, personal communication)

L-HEMISPHERIC PREDOMINANCE OF NIGROSTRIATAL DYSFUNCTION IN PD - Mean regional [^{123}I]ß-CIT BP_{ND} -

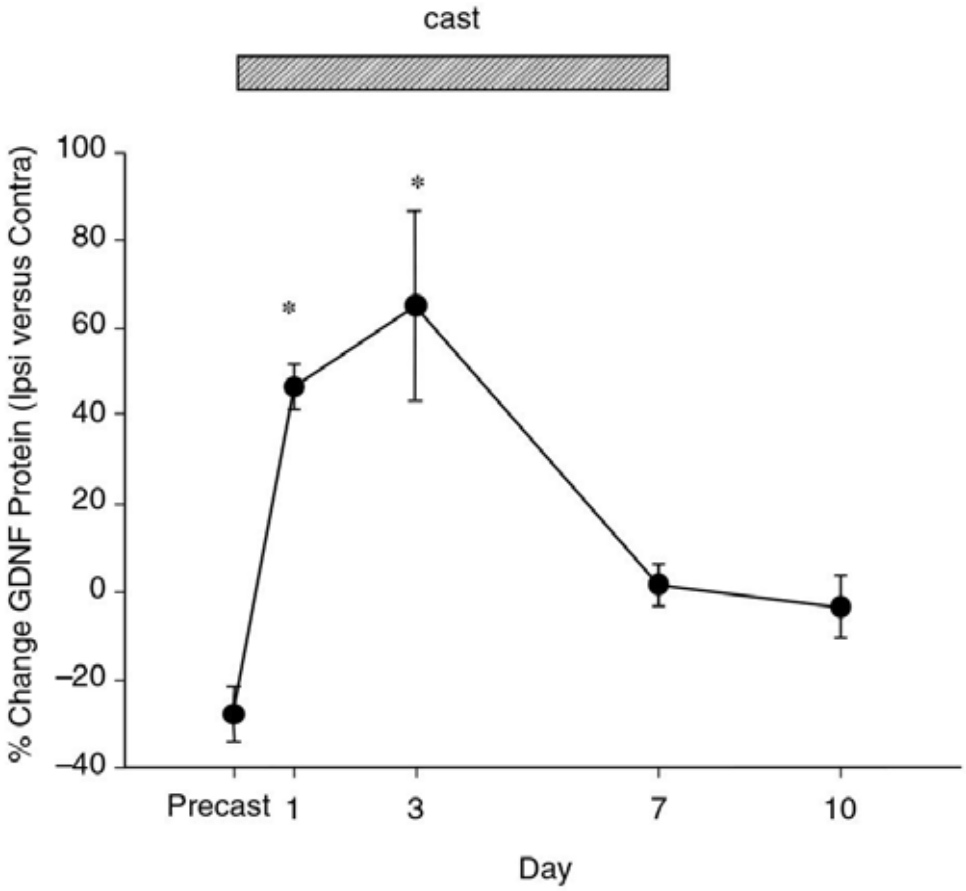
	PD-LEFT patients ($n = 49^{\dagger\dagger\dagger}$)	PD-RIGHT patients ($n = 19$)
Left caudate	$7.2 \pm 1.9^{***}$	$7.5 \pm 1.5^{***}$
Right caudate	$7.4 \pm 1.9^{***}$	$6.6 \pm 1.5^{***}$
Left posterior putamen	$3.9 \pm 1.32^{**}$	$4 \pm 0.9^{***}$
Right posterior putamen	$5 \pm 1.4^{***}$	$3.6 \pm 0.8^{***,\dagger\dagger\dagger}$
Mean caudate	$7.3 \pm 1.8^{***}$	$7 \pm 1.6^{***}$
Mean posterior putamen	$4.5 \pm 1.2^{***}$	$3.8 \pm 0.9^{***,\dagger}$
Asymmetry index of caudate	$13.6 \pm 8.8^{***}$	$15.1 \pm 9.1^{***}$
Asymmetry index of posterior putamen	$25.2 \pm 16.5^{***,\dagger\dagger}$	$13.8 \pm 8.1^{*}$
Ratio of caudate/posterior putamen left	$2 \pm 0.8^{**}$	$1.9 \pm 0.5^{**}$
Ratio of caudate/posterior putamen right	$1.6 \pm 0.6^{\dagger,\#}$	$1.9 \pm 0.6^{**}$

Scherfler et al, Brain 2012

Journal of Neurochemistry, 2003, **85**, 299–305

Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF

Ann D. Cohen,*,† Jennifer L. Tillerson,† Amanda D. Smith,* Timothy Schallert†,‡ and Michael J. Zigmond*



Clinical and imaging asymmetry index (AI)

UPDRS motor asymmetry index

$$a - b \; ?\grave{I}2$$

a, b … R and L scores of UPDRS items 20-26

DAT asymmetry (%) caudate and posterior putamen

$$[(a - b)/(a+b)] \times 2 \times 100$$

a, b … R and L putamen or caudate

Uitti et al., Neurology 2005; Zijlmans et al., 2007

ASYMMETRY OF MOTOR SIGNS IN PD

Study	N	% with asymmetry	Criterion
Uitti et al, 2006	1277	46 %	UPDRS R-L $\geq$ 5
Stocchi et al, 2009	472	84 %	clinical
Barrett et al, 2010	1173	86.5 %	clinical

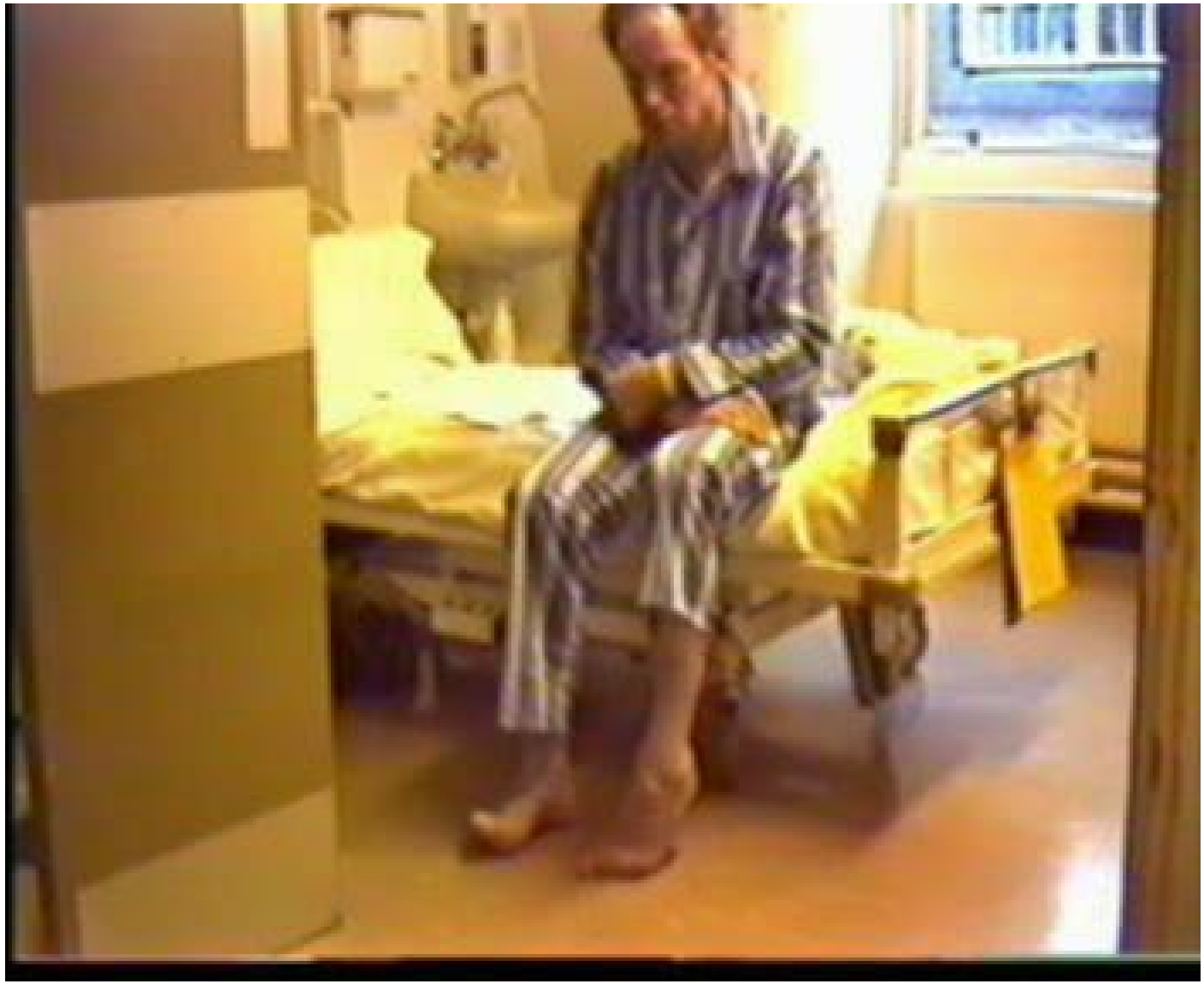
TOPICS

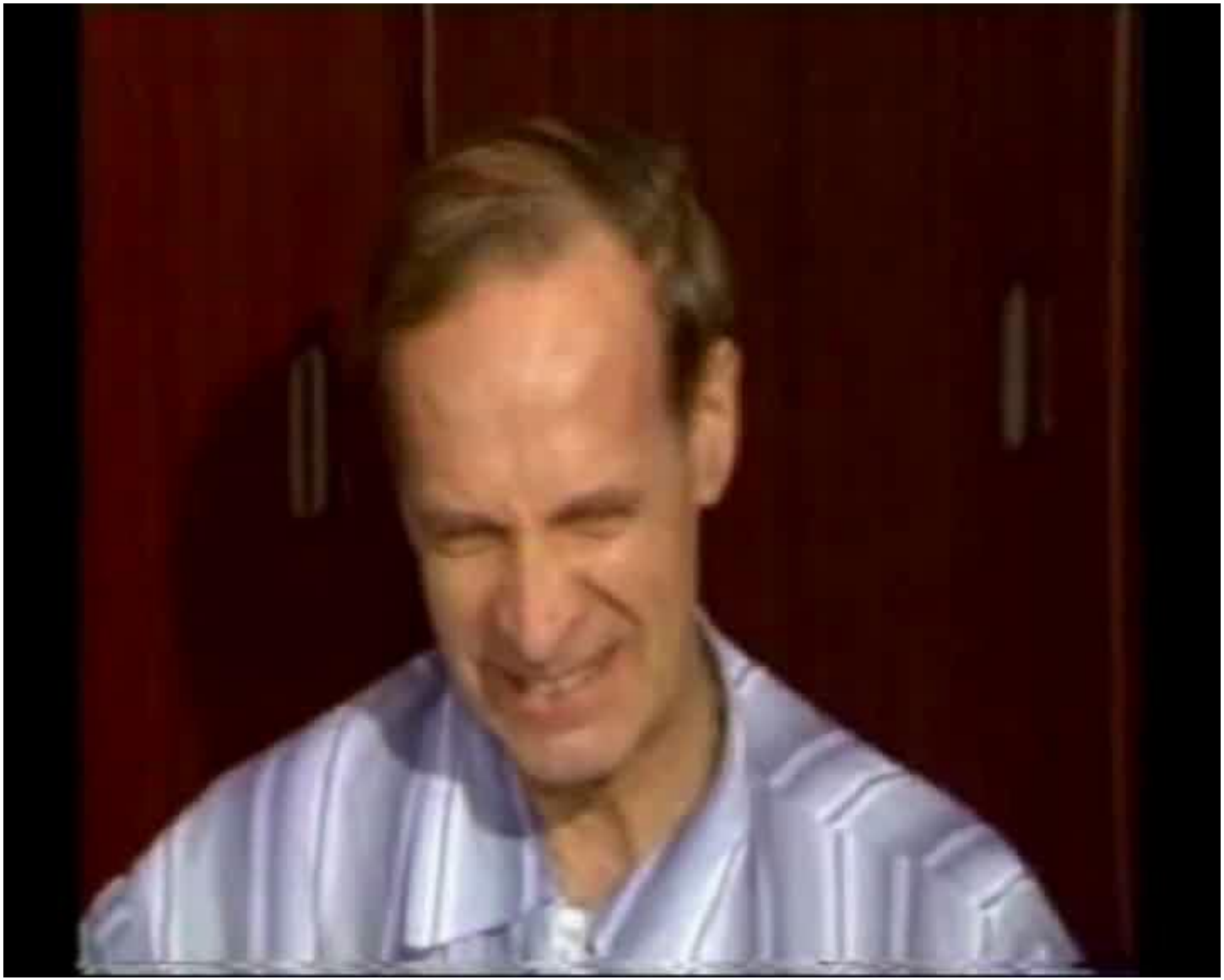
* CARDINAL MOTOR FEATURES OF PD

* LD-RELATED MOTOR COMPLICATIONS

* LD-INDUCED DYSTONIA

* MOTOR ASYMMETRY IN PD



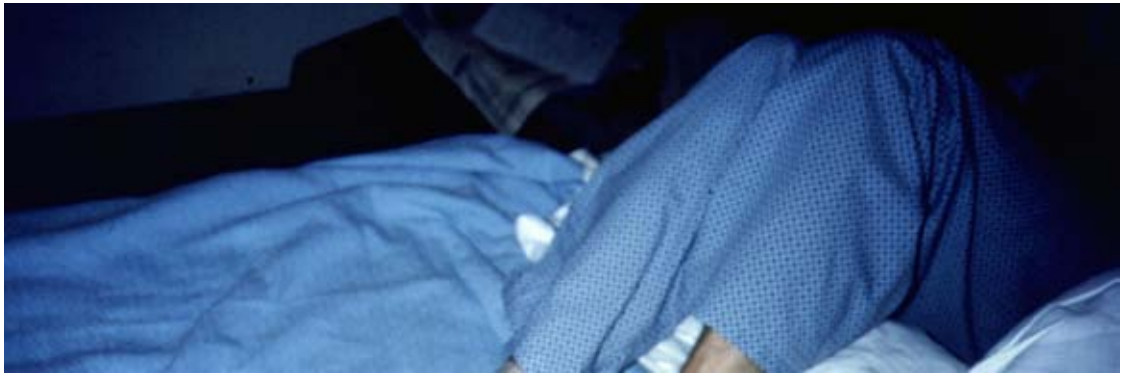


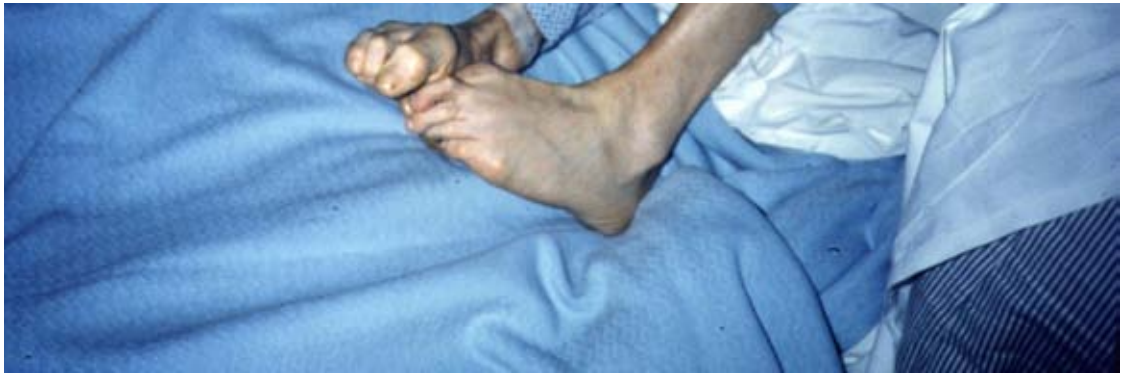
Topography of parkinsonian initial symptoms and levodopa-induced dyskinesia in 20 patients with Parkinson‘s disease

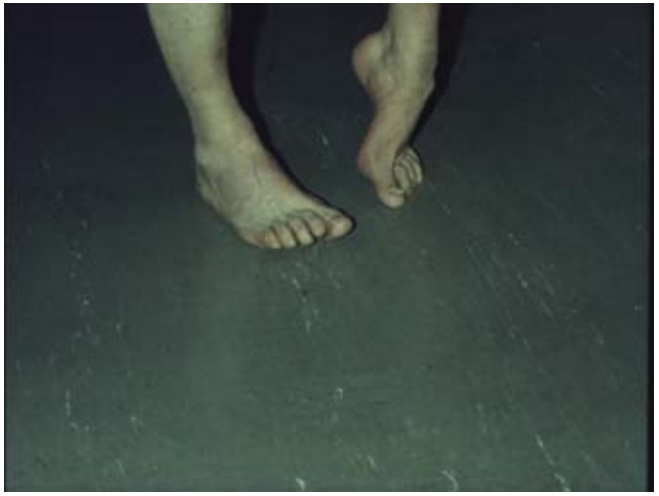
- Vidailhet et al, Neurology 1994 -

Body area involved	Initial symptoms of parkinsonism	Levodopa-induced dyskinesia during the levodopa test	
		Onset-of-dose	mid-dose
Foot and lower limb	6	20 (dystonia)	0
Upper limb	14	0	4 (chorea)
Trunk / Neck	0	0	7 (chorea)
Face	0	0	2 (chorea)

Why does OFF-period dystonia affect the foot ?







PDS BRC Criteria for Idiopathic Parkinson's Disease *Supportive Prospective Criteria*

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

PDS BRC = Parkinson's Disease Society Brain Research Center.
Gibb WR, et al. *J Neurol Neurosurg Psychiatry.* 1988;51:745-752.

JOINT AND SKELETAL DEFORMITIES IN PARKINSONISM

	PD (N=164)	MSA (N=19)	PSP (N=19)
Striatal limb deformities	12.8% (21)	26.3% (5)	5.3% (1)
Involuntary trunk flexion	12.2% (20)	26.3% (5)	5.3% (1)
Anterocollis	5.5% (9)	42.1% (8)	10.5% (2)
Scoliosis	8.5% (14)	10.5% (2)	5.3% (1)
All deformities	33.5% (55)	68.4% (13)	26.3% (5)

Pts. with deformities vs. without

- younger age (60.4 vs. 68.6 yrs)
- earlier onset age (55 vs. 62 yrs)
- higher UPDRS (57 vs. 46)
- more frequent LD (70% vs. 50%)

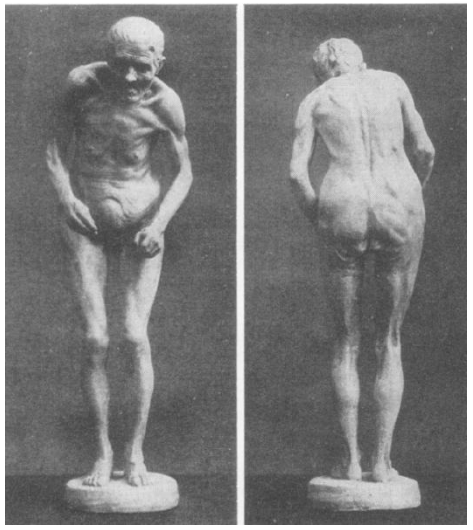
Ashour and Jankovic, Mov Disord 2006

Axial deformities in Parkinson‘s disease

- Lateral flexion of the trunk common in advanced PD

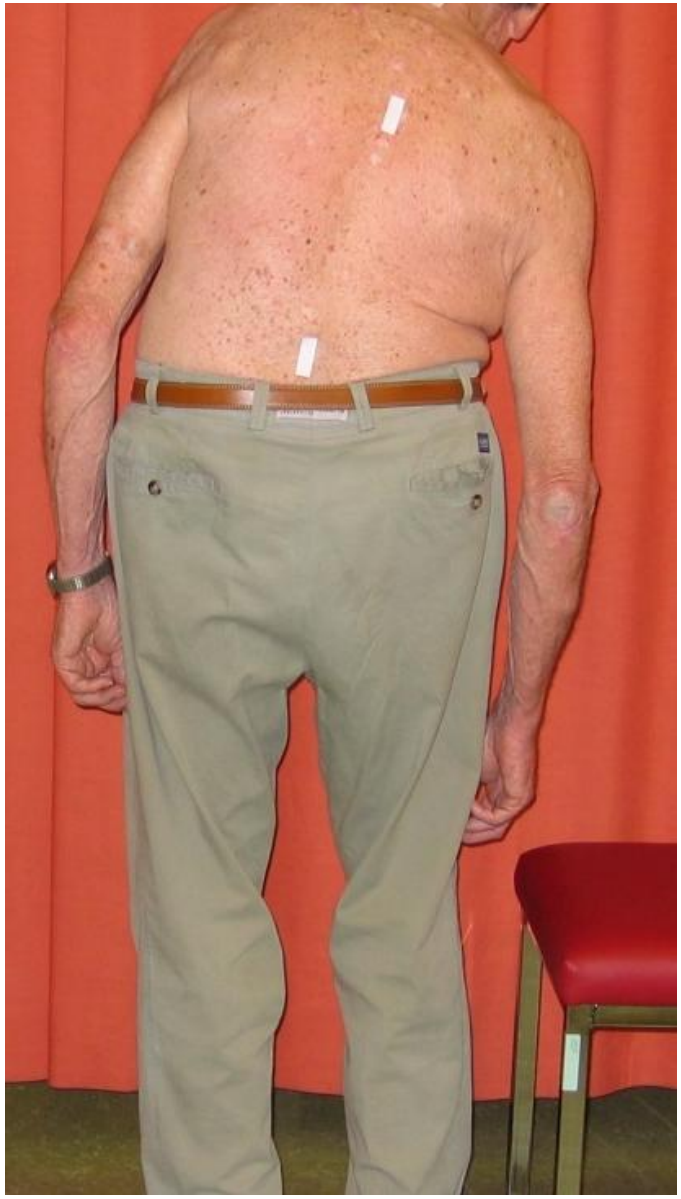
- Duvoisin und Marsden 1975, JNNP

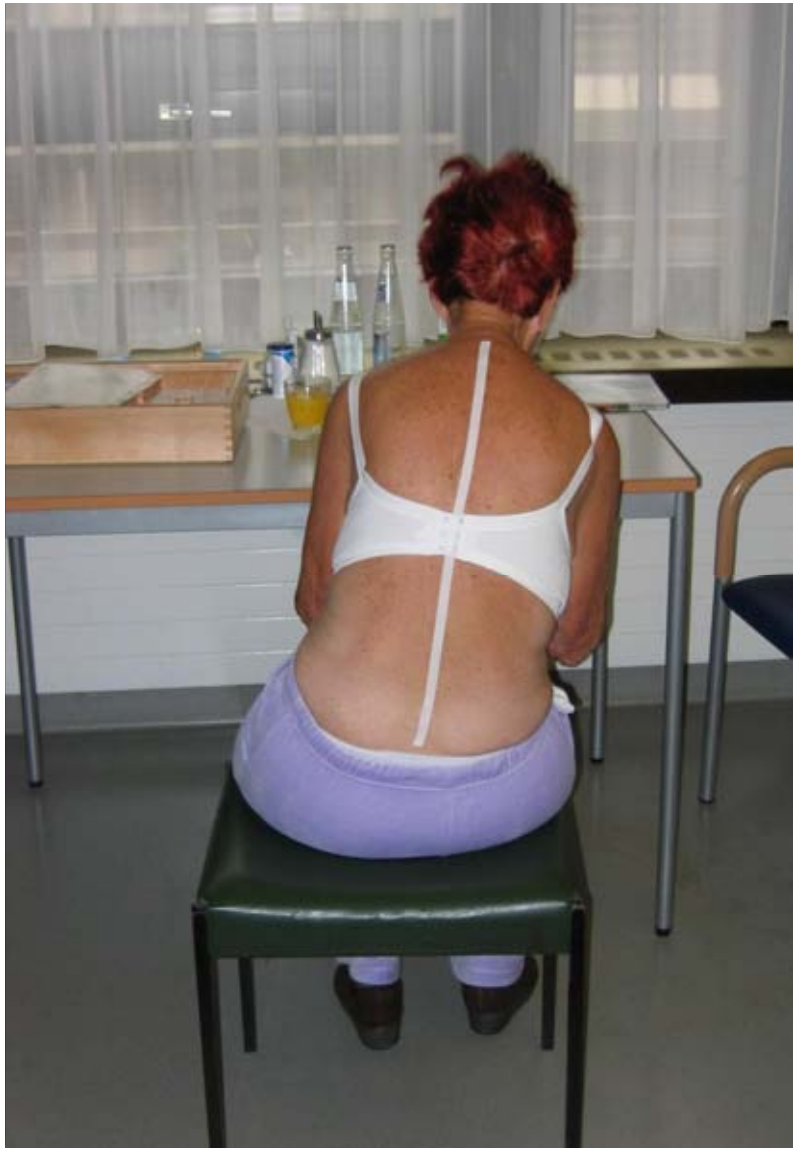
  19 PD patients with lateral flexion of the trunk
  contralateral to initially affected side
  „Scoliosis of PD“
  few recent studies



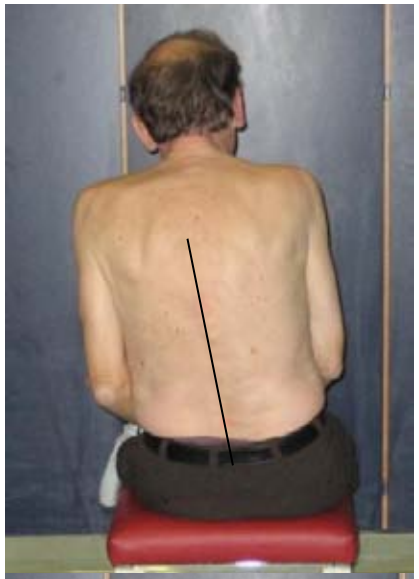
Richer und Meige 1895

Lateral flexion of the trunk in PD

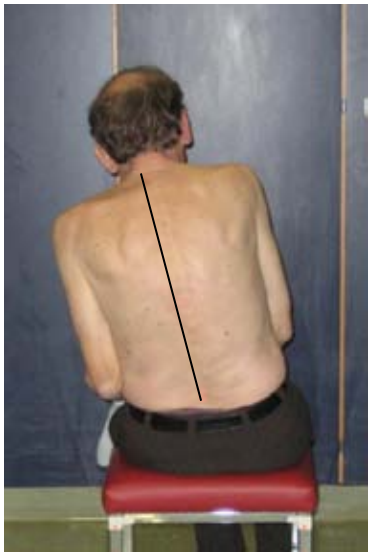




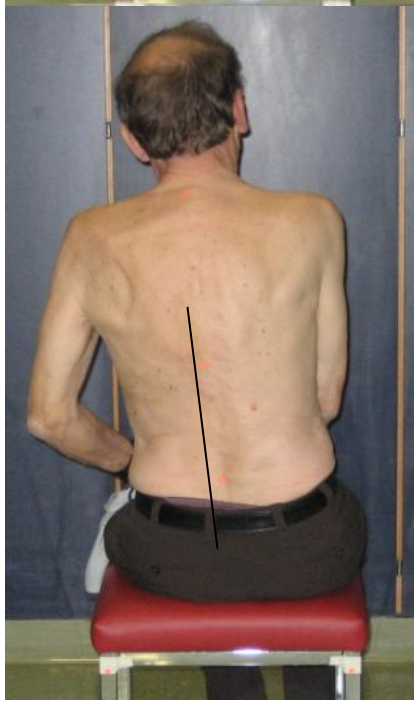
Lateral trunk flexion: quantitative assessment



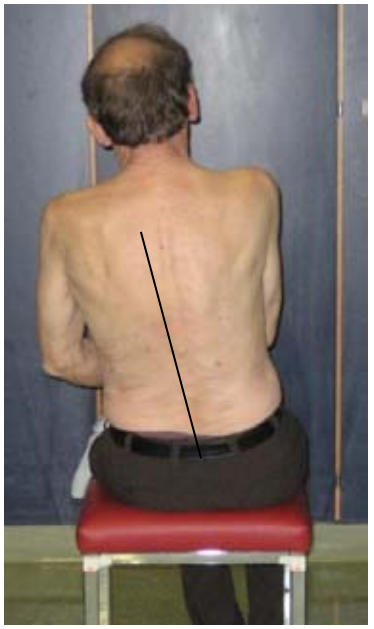
WINKEL 1: 8,7°



WINKEL 2: 11°



WINKEL 3: 7,3°



WINKEL 4: 9,5°

Lateral trunk flexion in PD

- a descriptive study -

	Patients	Controls
n	99	33
Age	68,2a (51-80)	66,2a (53-88)
Gender	33w/66m	19w/14m

Lateral trunk flexion in PD

- a descriptive study -

	Patients	Controls
UPDRS III	21	0.9
H&Y	2,4	-
MMSE	27,4	29,2
	(11 <24)	(0 <24)
FOG	6,5	0
OH	34	9

Lateral trunk flexion in PD

- Frequency -

	Patients	Controls
Cut-off ≥ 3°	32 %	3 %
Cut-off ≥ 5°	13 %	0 %

Lateral trunk flexion in PD

- Laterality -

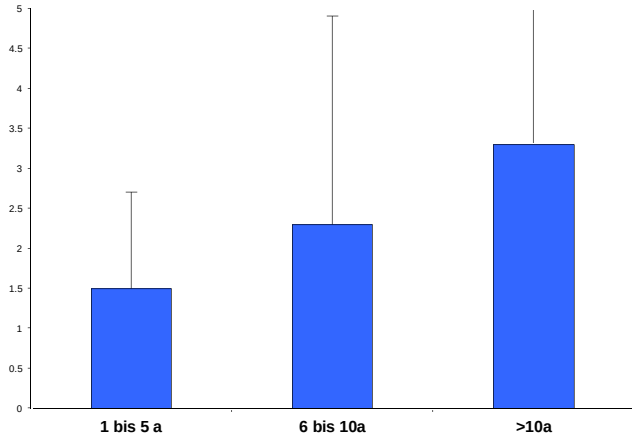
Flexion towards most affected side 47 %

Flexion away from most affected side 47.5 %

Lateral trunk flexion in PD
- Correlations -

- Univariant analysis
  - Disease duration (p=0.004)
  - Presence of dyskinesias (p=0.005)

- Multivariant analysis
  - **Disease duration (p=0.006)**



Lateral trunk flexion in PD
- Correlations -

- No significant correlation with

- Age	(p=0,63)
- UPDRS III	(p=0,74)
- Motor fluctuations	(p=0.69)
- Freezing	(p=1.0)
- OH	(p=0.43)
- Visual hallucinations	(p=0.20)
- MMSE	(p=0.17)

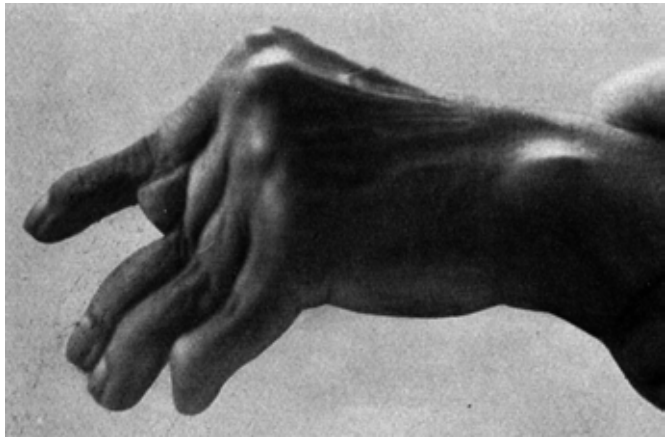
Axial deformities in PD

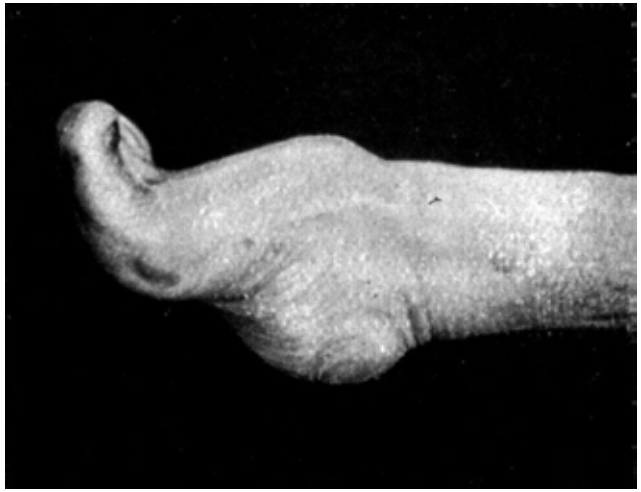
	Country	Number of patients with PD	Prevalence (%)	Diagnostic criteria
Camptocormia				
Abe et al[8]	Japan	153	18%	45° TL flexion
Tiple et al[6]	Italy	275	7%	45°TL flexion
Lepoutre et al[9]	France	700	3%	TL flexion
Ashour and Jankovic[1]	USA	164	12%	45° TL flexion
Antecollis				
Ashour and Jankovic[1]	USA	164	6%	>45° neck flexion
Yamada et al[10]	Japan	126	6%	NA
Kashihara et al[11]	Japan	252	6%	Neck flexion
Fujimoto[12]	Japan	131	5%	NA
Pisa syndrome				
Bonanni et al[13]	Italy	1400	2%	>15° lateral flexion
Scoliosis				
Baik et al[14]	Korea	97	33%	Radiograph (Cobb method)
Ashour and Jankovic[1]	USA	164	9%	Lateral curvature
Grimes et al[15]	UK	103	60%	Clinical, radiography in 50%
Duvoisin and Marsden[16]	UK	21	91%	Clinical examination
Indo and Ando[17]	Japan	70	31%	Clinical examination
Serratrice and Schiano[18]	France	140	13%	Clinical then radiography
Sicard[19]	France	17	47%	NA
Onuaguluchi[20]	UK	33	15%	NA

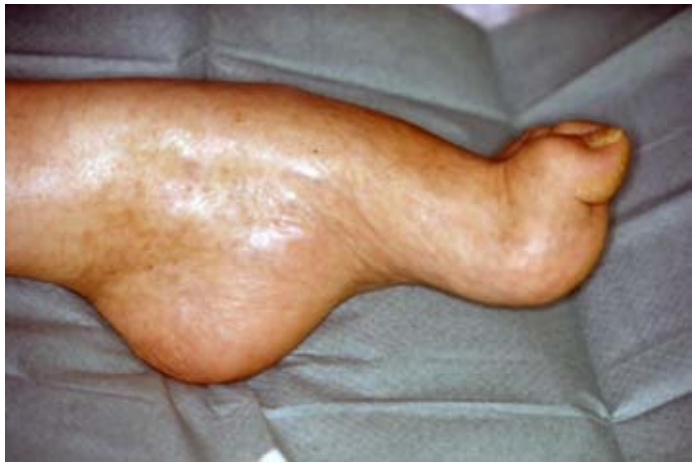
TL=thoracolumbar. NA=data not available.

Doherty et al, Lancet Neurol 2011

DYSTONIA IN UNTREATED P.D.
- Deformities of hands and feet -

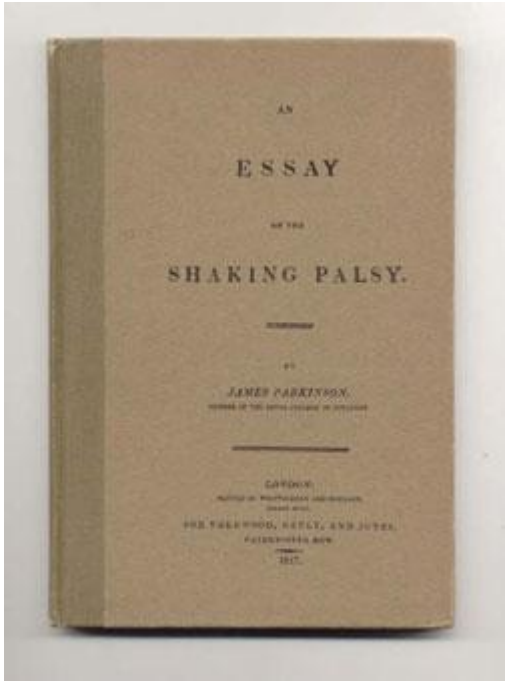


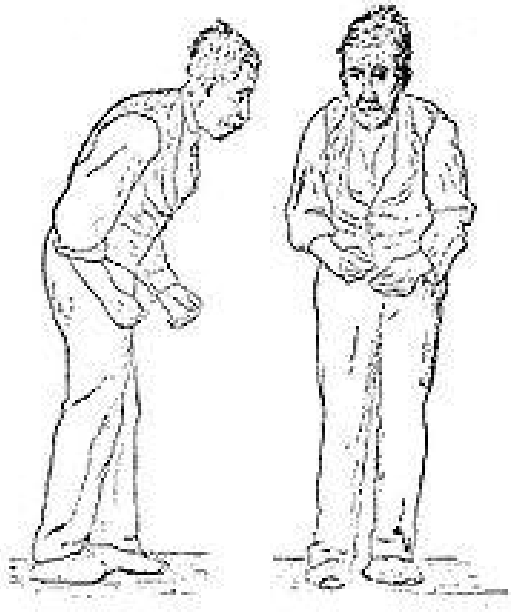




J. M. Charcot, 1877; W.R. Gowers, 1888; F.H. Lewy, 1913; P. Gortvai, 1963

Axial deformities in Parkinson‘s disease





„propensity to bend the trunk forward“

UPDRS III

28. Posture

0-normal erect

1-slightly stooped, could be normal for older person

2-definitely abnormal, mod. stooped, may lean to one side

3-severely stooped with kyphosis

4-marked flexion with extreme abnormality of posture

Extensor Muscle Myopathy in PD
- Possible causes -

(1) Primary Myopathy

- Focal Myositis
- Inclusion Body Myositis
- Dystrophic Myopathy
- Mitochondrial Myopathy

(2) Secondary Myopathy

- Aging
- Chronic stretch / overuse (flexor rigidity)
- Underuse (bradykinesia)

Camptocormia: Definition

- Camptocormia (gr.: kamptos = bent; kormos = trunk)
  - Severe unfixed forward flexion of the thoracolumbar spine
    - Worsening with standing and walking
    - Abates when sitting or recumbent
  - Different etiologies reported
    - E.g. myasthenia, psychogenic, ALS, myositis, GBS, tardive, GTS, DAT…PD

Camptocormia in PD

„..the body being so bowed and the head so forward..as to oblige him to employ a stick..to force him more to upright posture..“

James Parkinson 1817

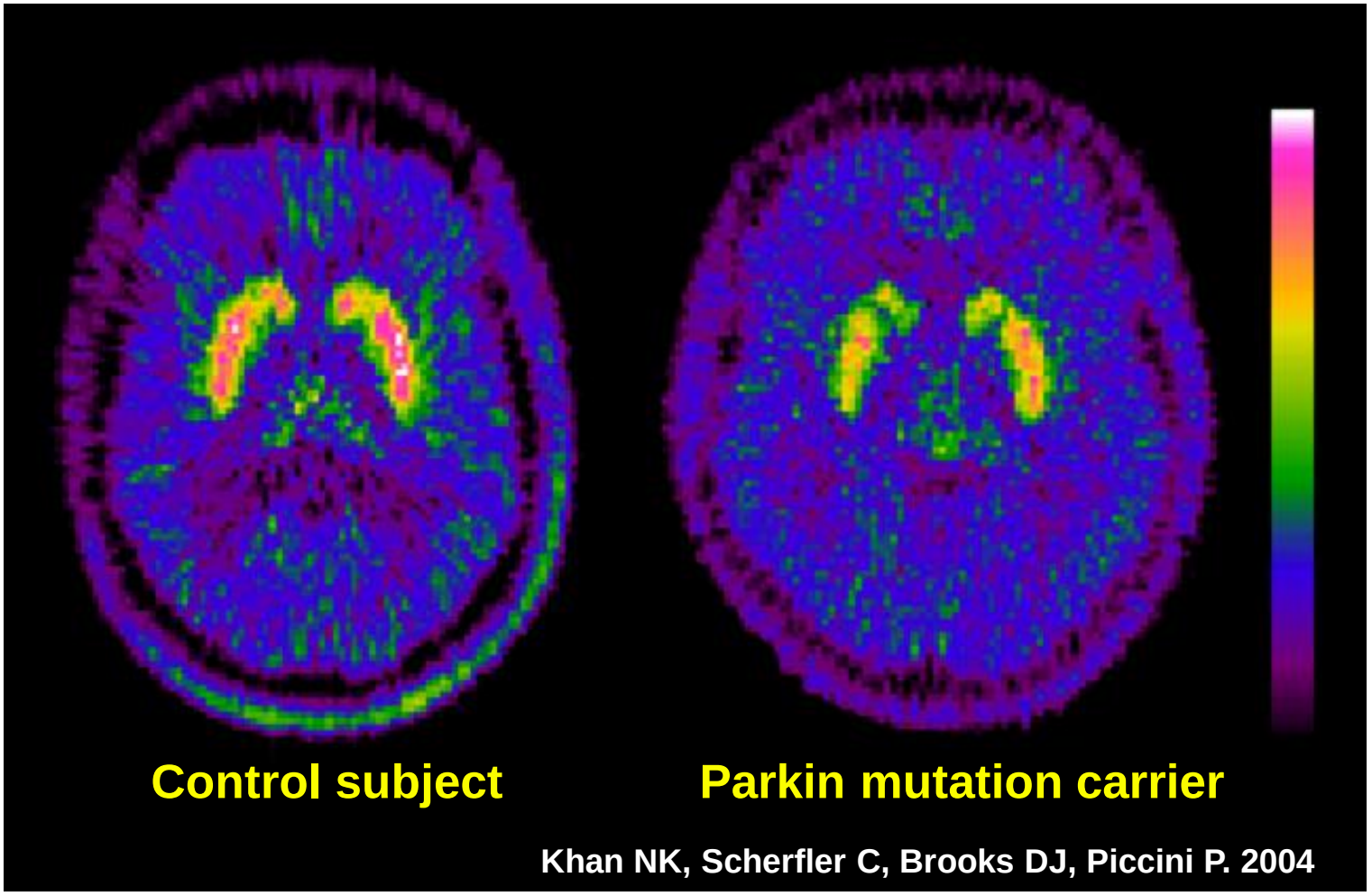
- First case series 1999 [1]

- More frequent in rigid-akinetic subtype
- Sub-acute or chronic
- Back pain common
- Prevalence 3-17% [2]

Drawing of a patient with Parkinson’s disease and camptocormia (Bibliothèque Charcot); from Bloch et al. 2006

[1]Djaldetti et al 1999 [2]Doherty et al 2011

Preclinical reduction in striatal [^{18}F]-Fluorodopa uptake



PRODROMAL MOTOR ABNORMALITIES IN PD-RISK GROUPS

TYPE OF ABNORMALITY	COHORT TESTED
Gait variability under challenge	LRRK2 mutation carriers [1]
Increased UPDRS scores	LRRK2 mutation carriers [2,3]
Acceleration of static sway	Healthy subjects with SN hyperechogenicity [4]
Unilateral reduced arm swing	Elderly subjects with SN hyperechogenicity [5]
Finger tapping, purdue peg board, timed up-and-go	Idiopathic RBD [6,7]

1 Mirelman et al, Ann Neurol 2011; 2 Marras et al, Neurology 2011; 3 San Luciano et al, Mov Disord 2010;
4 Maetzler et al, PLoS One 2012; 5 Liepelt et al, Neurobiol Aging 2011; 6 Postuma et al, Brain 2009; 7 Postuma et al, Neurology 2008

What is Parkinson's disease ?

Parkinson's disease (PD) – a clinicopathological entity

- **a clinical syndrome**
  * defined by the presence of cardinal motor features (BUT with many non-motor features !)

- **a neuropathological syndrome**
  * defined by ?-synuclein positive neuronal cytoplasmic (Lewy bodies) and axonal (Lewy neurites) inclusions and cell loss in the SNc)

- **a biomarker supported clinical syndrome ?**
  * imaging
  * molecular (genomic, proteomic)

Classification of Parkinsonism

- Neurodegenerative parkinsonism
  - Idiopathic Parkinson's disease (IPD)
    - Sporadic
    - Genetic
  - Atypical parkinsonian disorders

- Symptomatic parkinsonism
  - Drug-induced
  - Vascular parkinsonism
  - Basal ganglia lesions
  - Toxic (MPTP, CO, CN, MN)
  - Encephalitis
  - Frontal meningeoma

Common errors in the diagnosis of PD

Relate to:

- Essential Tremor
- Atypical Parkinsonian disorders
  - Multiple system atrophy
  - Progressive supranuclear palsy
- Vascular parkinsonism

Schrag et al. 2002 JNNP; Meara et al. 1999 Age Ageing; Hughes et al. 1992 Neurology/2001 Neurology/2002 Brain; Rajput et al. 1991 Can J Neurol Sci; Tolosa et al. 2006 Lancet Neurology

UKPDS brain Bank criteria

STEP 2: Exclusion criteria ?

- History:
  - repeated strokes
  - head injury
  - neuroleptic treatment
  - sustained remission
  - Negative response to large doses of levodopa

- Systematic neurological exam
  - Supranuclear gaze palsy
  - Cerebellar signs
  - Early severe autonomic involvement
  - Early severe dementia
  - Babinski sign
  - strictly unilateral features after 3 yrs

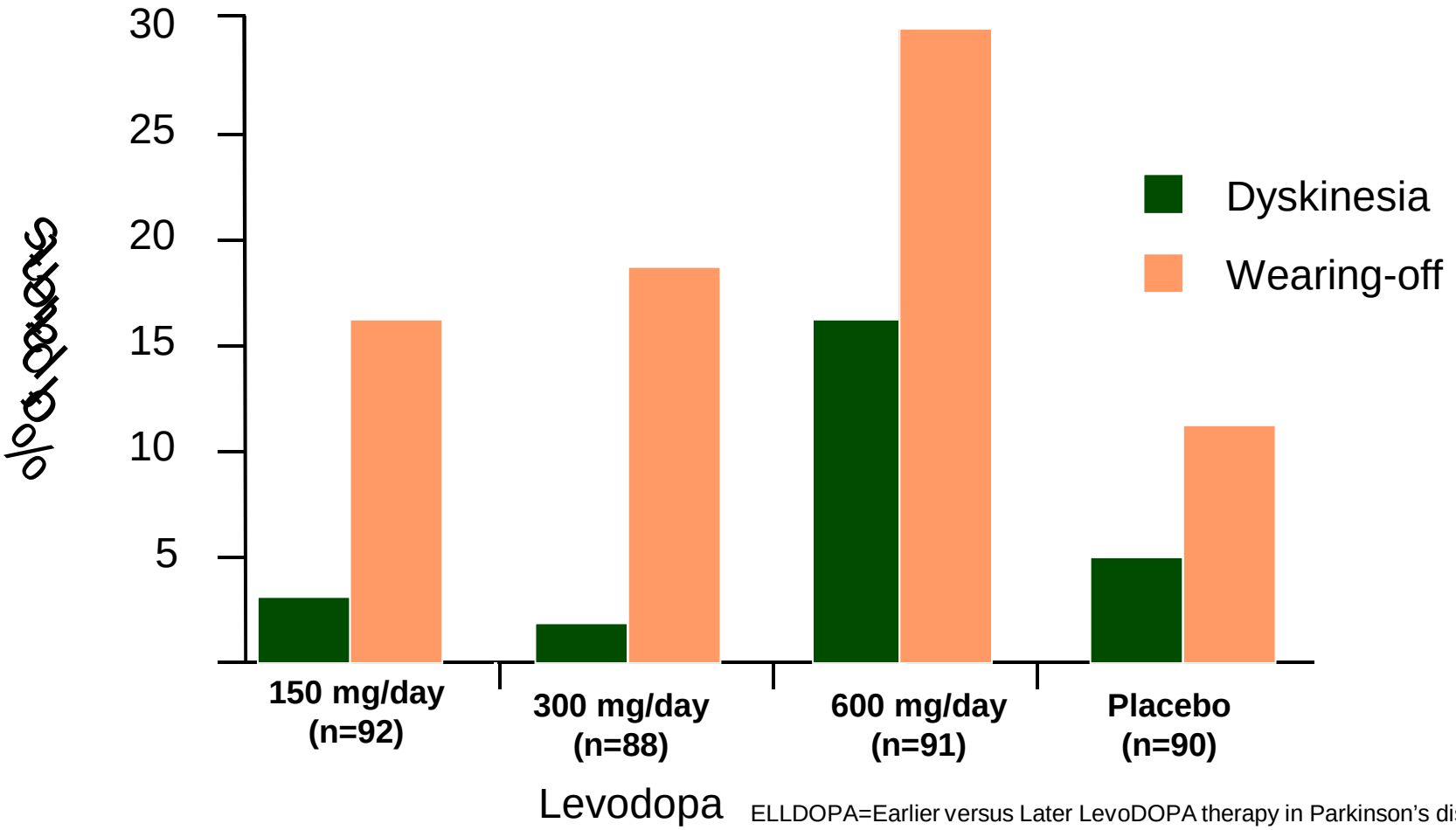
Gibb and Lees JNNP 1988

MOTOR PHENOTYPE IN YOUNG-ONSET PD

(Gibb and Lees, 1988)

	YOUNG-ONSET (N=46)	OLD-ONSET (N=52)
Median age at onset (yrs)	38 (24-45)	73 (70-90)
Median duration (yrs)	11 (1-34)	6 (1-11)
First symptom		
Rest tremor	19 (41%)	33 (63%)
Difficulty walking	2 (4%)	17 (33%)
Stiff muscles	20 (43%)	2 (4%)
Slowness	2 (4%)	0
Stiffness and tremor	2 (4%)	0
Weakness	1 (2%)	0
Mean dose of L-Dopa (mg)	590.8 (30)	595.8 (12)
Number of pts with dyskinesia	29 (91%)	9 (69%)
Number of pts with dystonia	11 (34%)	0/13

Motor complication rates in the ELLDOPA Trial



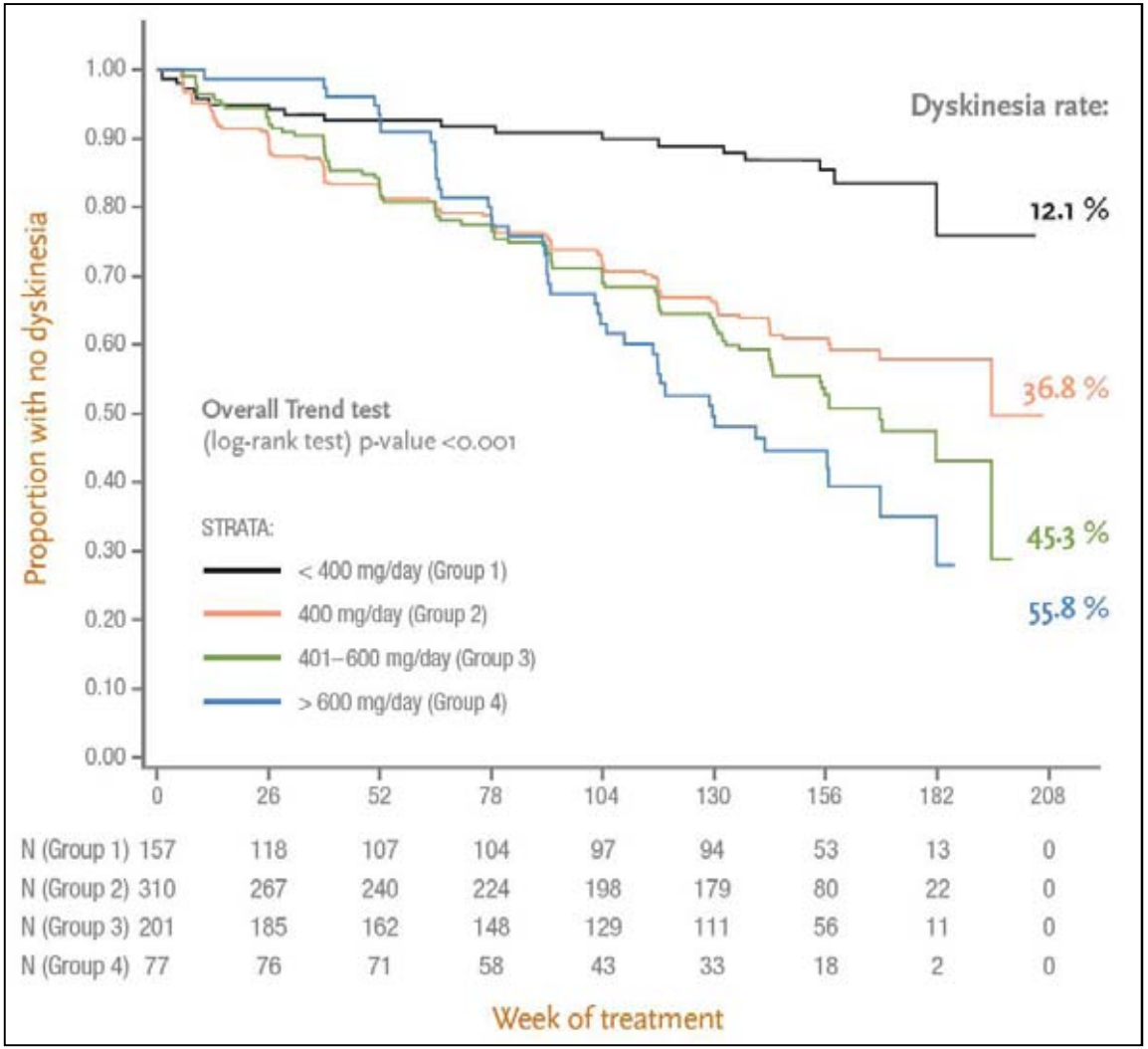
ELLDOPA=Earlier versus Later LevoDOPA therapy in Parkinson's disease

Fahn S, et al. *N Engl J Med* 2004; 351(24): 2498–2508

Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson's Disease

C. Warren Olanow, MD, FRCPC,[1,2*] Karl Kieburtz, MD, MPH,[3] Olivier Rascol, MD, PhD,[4] Werner Poewe, MD,[5] Anthony H. Schapira, MD, DSc, FRCP, FMedSci,[6] Murat Emre, MD,[7] Helena Nissinen, MD, PhD,[8] Mika Leinonen, MSci,[9] Fabrizio Stocchi, MD, PhD,[2] for the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) Investigators

Mov Disord 2013 (in press)



*for patients who did not get dyskinesia: dose at the end of study

for patients who got dyskinesia: pre-dyskinesia dose

Efficacious treatments for levodopa-related motor complications in PD

MOTOR FLUCTUATIONS

- DA-agonists (pramipexole, ropinirole, rotigotine, apomorphine, pergolide)
- L-Dopa (enteral infusions, rapid onset formulations)
- COMT inhibitors (entacapone, tolcapone)
- MAO-B inhibitors (rasagiline)
- DBS surgery (STN, GPi)
- Unilateral pallidotomy

DYSKINESIAS

- *Amantadine*
- DBS surgery (STN, GPi)
- Unilateral pallidotomy

DBS=deep brain stimulation; STN=subthalamic nucleus; GPi=Globus Pallidus pars interna

Fox et al, MDS Task Force 2011

Pharmacological management of motor fluctuations

- **Modify L-dopa delivery and pharmacokinetics**
  - Reduce inter-dose interval – increase dose frequency
  - Increase dose
  - Use sustained-release L-dopa
  - Add COMT inhibitor
  - Use intrajejunal infusions of L-dopa

- **Enhance striatal dopamine concentrations**
  - Use MAO-B inhibitors, e.g., rasagiline

- **Use dopamine agonists**
  - Oral agonists (non-ergot)
  - Transdermal (rotigotine)
  - s.c. (apomorphine)

Dyskinesias and motor fluctuations in a community-based study of PD

(Schrag et al, 2000)

R E S U L T S

*** Dyskinesias in 28 % of the patients**

*** Motor fluctuations in 40 % of the patients**

*** Predictors for the evolution of motor fluctuations:**

- **Disease duration**
- **LD dose**

***Predictors for the evolution of dyskinesias:**

- **Duration of treatment**

Medical Hypothesis

Neurology 1997;49:1432–1438

MPTP induces dystonia and parkinsonism

Clues to the pathophysiology of dystonia

J.S. Perlmutter, MD; L.W. Tempel, MD; K.J. Black, MD; D. Parkinson, PhD; and R.D. Todd, PhD, MD

Article abstract—The pathophysiology of dystonia is unclear, but several clues implicate striatal dopamine dysfunction. In contrast, the causal relationship between striatal dopamine deficiency and parkinsonism is well defined. We now suggest that parkinsonism or dystonia may occur following striatal dopamine deficiency. Baboons treated with intracarotid 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed transient hemidystonia prior to hemiparkinsonism. The day after MPTP treatment, most animals had spontaneous ipsilateral turning. Within a few days, all developed contralateral hemidystonia, with the arm and leg extended and externally rotated. This transient dystonia preceded hemiparkinsonism with flexed posture, bradykinesia, and postural tremor that persisted for up to 1.5 years. Dystonia corresponded temporally with a decreased striatal dopamine content and a transient decrease in D_2-like receptor number. The time course of dystonia and parkinsonism is analogous to lower limb dystonia as the first, frequently transient, symptom of Parkinson's disease in humans. The association of striatal dopamine deficiency with dystonia and parkinsonism implies that other factors influence clinical manifestations.

DYSTONIA IN UNTREATED PD
(N = 30 from 3 series*)

Dystonia preceding PD	21 / 30
Dystonia - PD latency < 10 yrs.	19 / 21
Mean age at onset of dystonia	< 50 yrs.

Dystonia types

- foot dystonia	9
- cranial dystonia	7
- writer‘s cramp	6
- cervical dystonia	5
- hemidystonia	3

* LeWitt et al, 1986; Klawans and Paleologos, 1986; Poewe et al, 1988

DYSTONIA IN UNTREATED PD
- L-Dopa effect -
(N = 22 from 3 series*)

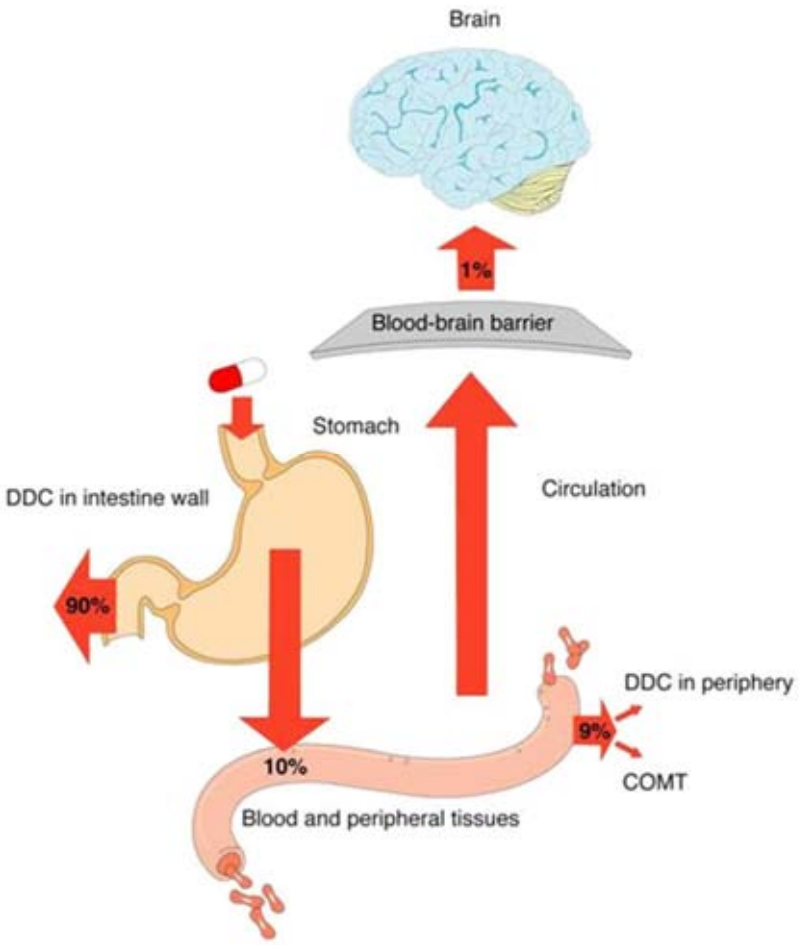
Effect on dystonia	
improvement	2
worsening	9
equivocal / nil	11
Effect on parkinsonism	
improvement	22

* LeWitt et al, 1986; Klawans and Paleologos, 1986; Poewe et al, 1988

Typical manifestations of bradykinesia in PD

- **Hypomimia**
- **Hypophonia**
- **Micrographia**
- **Small stepped gait**
- **Reduced arm swing**
- **Difficulties rising from a chair or turning in bed**

Clinical pharmacokinetics of levodopa



- **Levodopa/DDCI has poor bioavailability and short plasma half-life (60–90 min)**
- **Erratic gastric retention and/or absorption can lead to delays in oral levodopa uptake**
- **Competition with neutral amino acids (proteins) for transport across gastrointestinal tract and blood–brain barrier**

(modified from Nutt and Fellman, 1984)

Atypical Features in 100 Cases of Postmortem-Confirmed PD

Overall frequency	12 patients
Severe early dementia	5
No response to adequate levodopa	4
Early fluctuating confusional states	4
Myoclonus	2
Apraxia	2
Focal dystonia	2
Early marked dysautonomia	2

Coexistent pathology: cortical Lewy bodies (5); striatal infarcts (2); senile plaques/neurofibrillary tangles (1); none (4)

Hughes AJ, et al. *Arch Neurol.* 1993;50:140-148.

FREQUENCY OF MUTATIONS IN EARLY-ONSET PD

(Alcalay et al, Arch Neurol 2010)

- **N = 953 with clinically defined PD and onset younger than 51 yrs.**
- **Assessment for mutations in SNCA, PRKN, PINK1, DJ1, LRRK2, GBA**
- **16.6 % positive for mutations (*6.7% PRKN, 3.6% LRRK2, 6.7% GBA, 0.2% DJ1*)**
- **40.6 % with onset ≤ 30 yrs**

CLINICAL DIFFERENCES BETWEEN PARKIN+ and PARKIN- EOPD

(Lücking et al, N Engl J Med, 2000)

	PARKIN+	PARKIN-	P
Disease onset	32 a	42 a	< 0.001
Disease duration	17 a	13 a	0.002
Dystonia (presenting symptom)	42 %	22 %	0.02
Hyperreflexia	44 %	21 %	0.04
LID (after 5 yrs.)	77 %	63 %	0.04
Slow progression	88 %	72 %	

Case:
Male, 36 y, complaining of occasional tremor and unusual leg movements

- **Occasional tremor, while drinking, onset at 27 y**
- **“walking” problems, at 32 y**
- **Diagnosis of conversion**
- **Other cases of tremor or PD in the family**
- **N. Exam: Brisk reflex, slight rigidity.**

Courtesy Prof. P. Barone

A multidisciplinary study of patients with early-onset PD with and without parkin mutations
(Lohmann et al, Neurology 2009)

- 44 pts with young-onset PD (< 45 yrs)

	N=21 PRKN+	N=23 PRKN-
• Daily dose of LD	528 mg	778 mg
• Duration of tx	13.2 yrs	9.9 yrs
• Prevalence of dyskinesias	71.4 %	61 %
• Time to dyskinesia	12 yrs	10 yrs
• Prevalence of fluctuations	57 %	96 %
• Time to fluctuations	14 yrs	5 yrs

DOES DEFICIENT NIGROSTRIATAL DOPAMINERGIC TRANSMISSION CAUSE DYSTONIA ?

- **Symptomatic hemidystonia following putaminal lesions (i.e. stroke)**
- **Acute dystonic reaction following DA-blocking agents**
- **Dopa-responsive dystonia**

L-DOPA-INDUCED DYSTONIA IN P.D.

“D-I-D“-response	**Muenter et al, 1977**
“OFF-period dystonia“	**Lees et al, 1977**
“Early morning dystonia“	**Melamed, 1979**
“Dystonic foot response“	**Nausieda et al, 1980**
“Painful dystonic spasms“	**Ilson et al, 1984**

PREVALENCE OF LD-INDUCED DYSTONIA IN PD

STUDY	N	LD-INDUCED DYSTONIA		
		TOTAL	OFF-PERIOD	PEAK-DOSE
Schrag et al, 2000	87	?	10 %	?
Kidron and Melamed, 1987	207	28 %	25 %	7 %
Wickremaratchi et al, 2011	358	20 %	13 %	4 %

Dystonia in Parkinson's Disease: Clinical and Pharmacological Features

W. H. Poewe, MD,* A. J. Lees, MD,† and G. M. Stern, MD†

Ann Neurol 1988;23:73-78

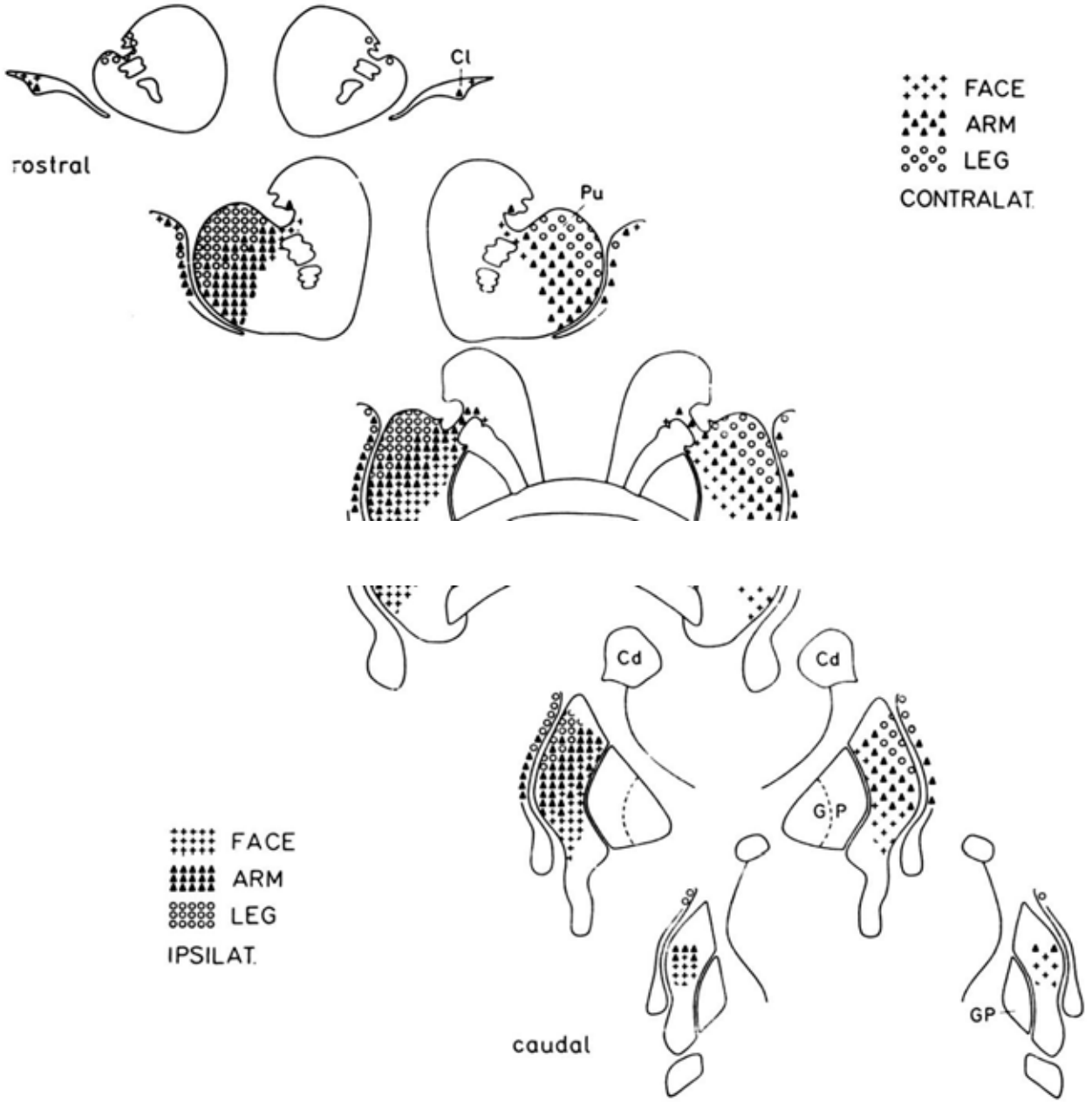
N	**56**
Age at PD onset	**48,7 (24 - 71) yrs.**
PD duration	**9,7 (2 - 20) yrs.**
L-Dopa	
- duration	**8,9 (0,25 - 17) yrs.**
- dose/d	**654 (300 - 2.000) mg**

L-DOPA-INDUCED DYSTONIA IN P.D.

(N = 56; Poewe et al, 1988)

- Relation to L-Dopa response cycle -

* **OFF-Period** **N = 46**
* **Biphasic** **N = 7**
* **Peak-dose** **N = 9**



Künzle H, Brain Research 1975

ETIOPATHOGENESIS OF PD
- Hypotheses -

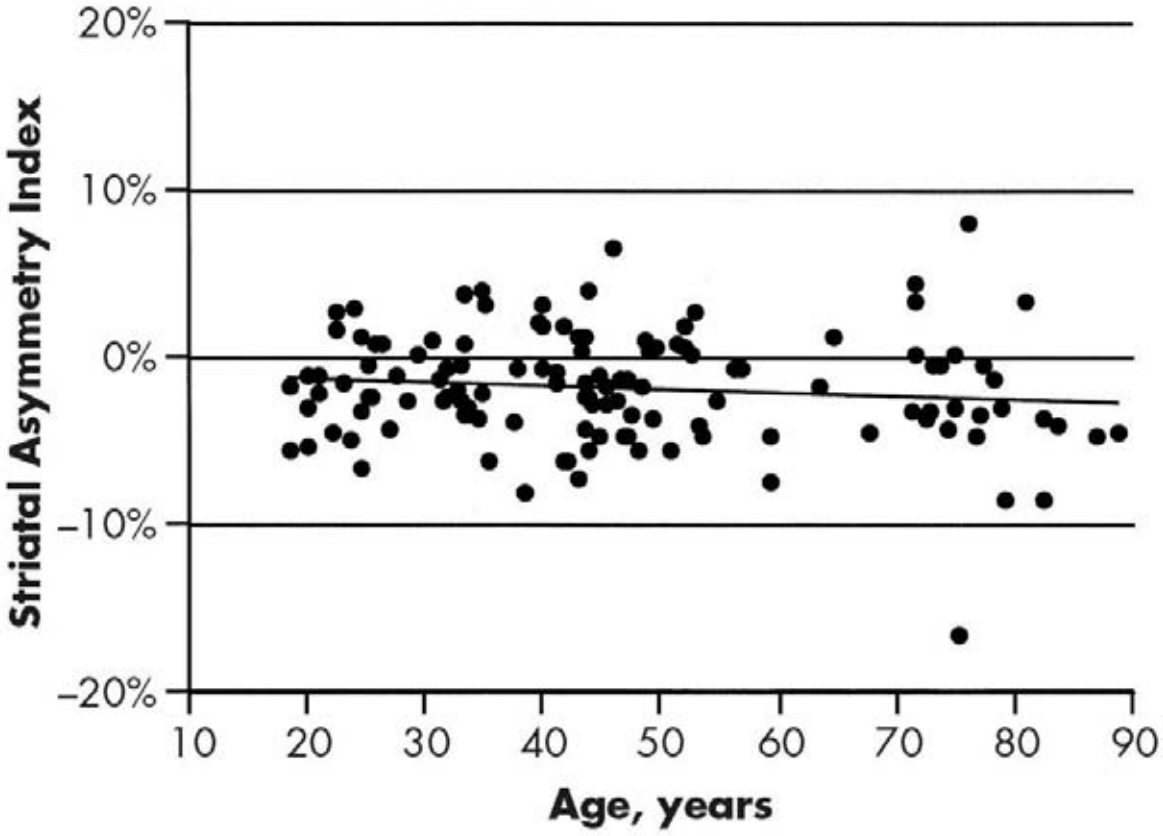
- **Environmental factors**
  - toxic
  - infectious
  - unknown

- **Genetic factors**
  - causative genes (LRRK2, SNCA, VPS35, PRKN, DJ1, PINK1)
  - risk genes (GBA)

- **Age**

Significantly higher DAT binding in L vs. R striatum

(V_3´´ L vs. R p<0.0001)



van Dyck et al, 2002

Handedness Correlates with the Dominant Parkinson Side: A Systematic Review and Meta-analysis

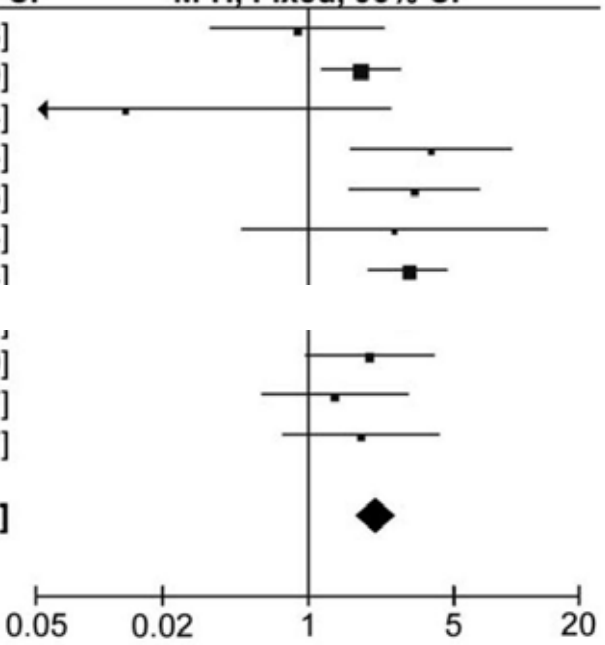
Anouk van der Hoorn, BSc,[1*] Huibert Burger, MD, PhD,[2,3] Klaus L. Leenders, MD, PhD,[1] and Bauke M. de Jong, MD, PhD[1]

[1]*Department of Neurology, University Medical Center Groningen, University of Groningen, The Netherlands*
[2]*Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands*
[3]*Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands*

Mov Disord 2012;27:206-10

	R-handed		L-handed			Odds Ratio
Study	**PD.R**	**PD.L**	**PD.R**	**PD.L**	**Weight**	**M-H, Fixed, 95% CI**
Akerman (2008)	78	70	10	8	3.3%	0.89 [0.33-2.38]
Barrett (2010)	524	403	37	51	23.3%	1.79 [1.15-2.79]
Reynolds (1971)	43	36	4	0	0.2%	0.13 [0.01-2.54]
Sawar (2010)	154	69	8	14	7.8%	3.91 [1.57-9.74]
Stewart (2009)	238	153	11	23	11.4%	3.25 [1.54-6.86]
Štochl (2009)	218	168	2	4	2.0%	2.60 [0.47-14.34]
Uitti (2005)	739	439	34	62	31.8%	3.07 [1.99-4.74]
[illegible]						
Van der Hoorn (2011)	158	96	15	18	8.8%	1.98 [0.95-4.10]
Van Rooden (2009)	129	104	12	13	5.7%	1.34 [0.59-3.07]
Yust-Katz (2008)	132	106	9	13	5.8%	1.80 [0.74-4.37]
Total (95% CI)	**2413**	**1644**	**142**	**206**	**100%**	**2.13 [1.71-2.66]**
Percentage %	**59.5**	**40.5**	**40.8**	**59.2**		

Heterogeneity: Chi^2 = 14.06, df = 9 (p = 0.12); I^2 = 36%
Test for overall effect: Z = 6.66 (p < 0.0001)

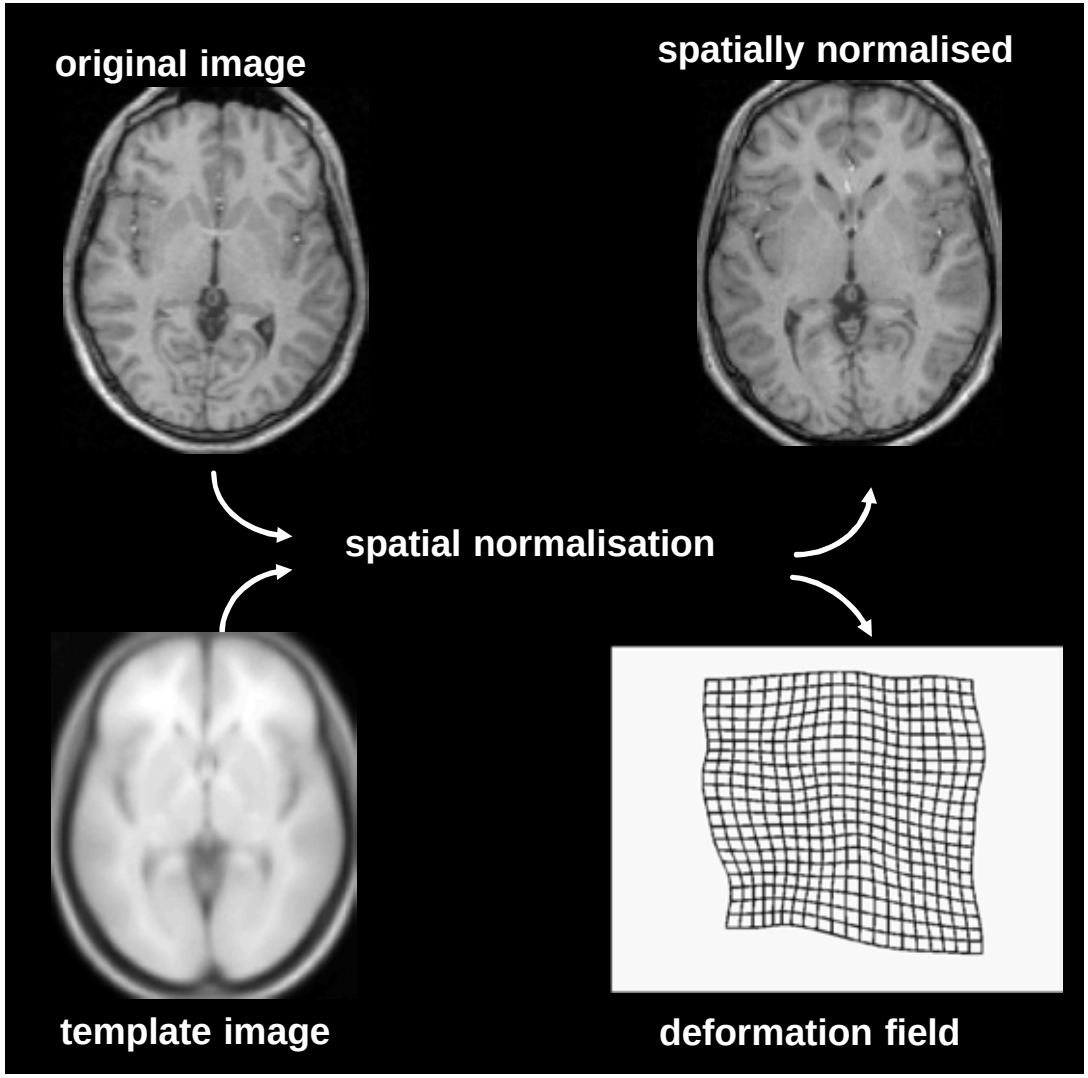


Handedness and motor symptom asymmetry in Parkinson‘s disease

- Barrett et al, JNNP 2011 -

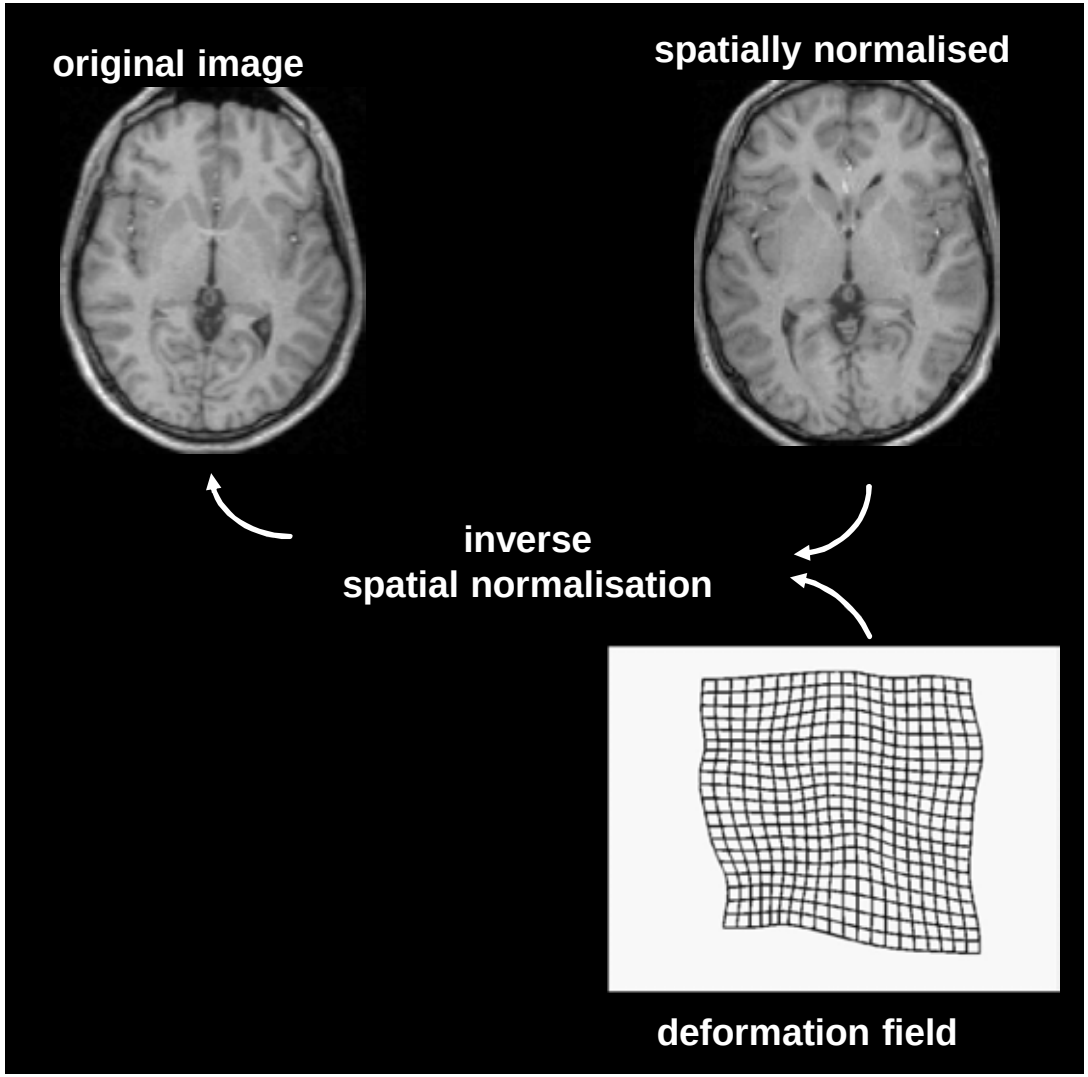
Pts. with asymm. onset (N=1015)	Side of onset Dominant (N=575)	Non-dominant (N=440)	p values
Initial motor symptom, N (%)			
Tremor	380 (66.1)	292 (66.4)	0.0001
Bradykinesia	101 (17.6)	40 (9.1)	
Rigidity	53 (9.2)	54 (12.3)	
Gait difficulty	23 (4.0)	40 (9.1)	
Other	18 (3.1)	14 (3.2)	

Template-based ROI-Analysis



Ashburner et al., Hum Brain Mapp 2001

Template-based ROI-Analysis



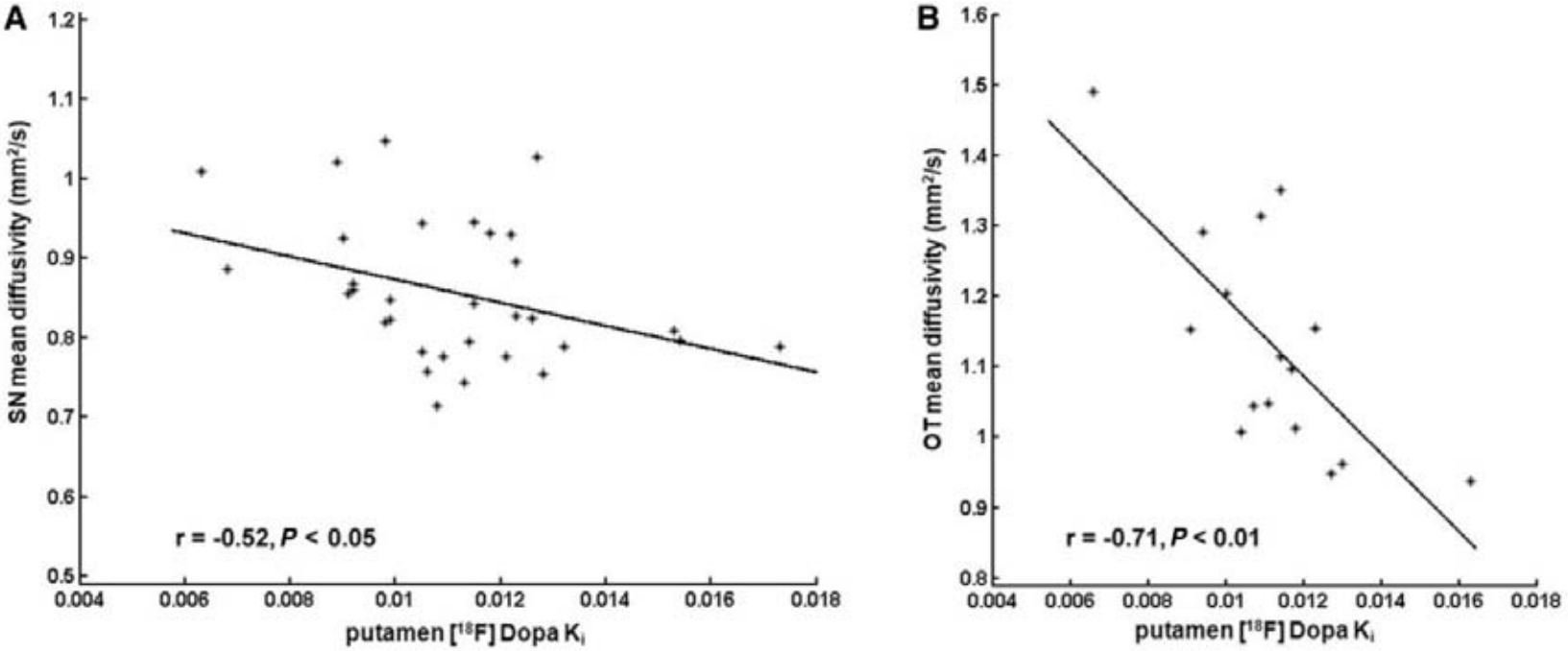
Ashburner et al., Hum Brain Mapp 2001

Correlations of nigral and olfactory MRI diffusivity and striatal Dopa PET uptake in Parkinson‘s disease – demographic data

	Parkinson's disease $n = 16$	Controls $n = 14$
Female/male (*n*)	10/6	8/6
Age at scan (years)		
Mean ± SD	68.1 ± 6.1 (54.8–76.3)	67.3 ± 3.7 (60–74.4)
Disease duration (years)		
Mean ± SD	3.7 ± 3.7 (0.1–15.2)	
UPDRS motor score		
Mean ± SD	20 ± 10.3 (8–42)	
Hoehn and Yahr staging		
Mean ± SD	2.3 ± 1 (1–4)	
Total odour score		
Mean ± SD	19.2 ± 4.4 (12.3–28.5)***	34.3 ± 2.2 (31.3–37.3)
Odour threshold		
Mean ± SD	3.8 ± 2.6 (1–9.8)***	7.3 ± 2.2 (4.3–12)
Odour discrimination		
Mean ± SD	8 ± 1.9 (5–13)***	13 ± 1.4 (10–15)
Odour identification		
Mean ± SD	7.4 ± 2.9 (3–13)***	13.9 ± 0.9 (12–15)

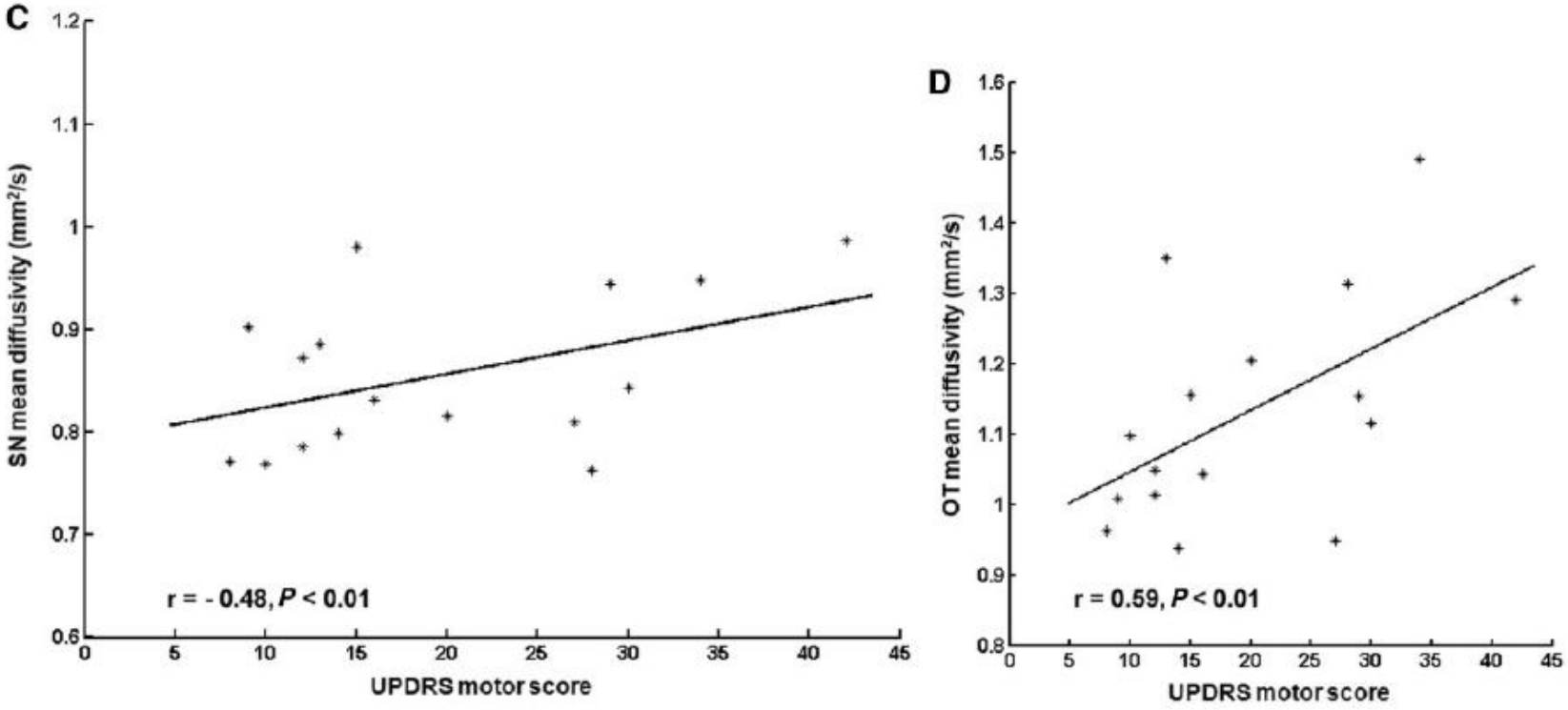
Scherfler et al., Brain 2013

Correlations of nigral and olfactory MRI diffusivity and striatal Dopa PET uptake in Parkinson‘s disease



Scherfler et al., Brain 2013

Correlations of nigral and olfactory MRI diffusivity and the UPDRS motor score in Parkinson‘s disease



Scherfler et al., Brain 2013

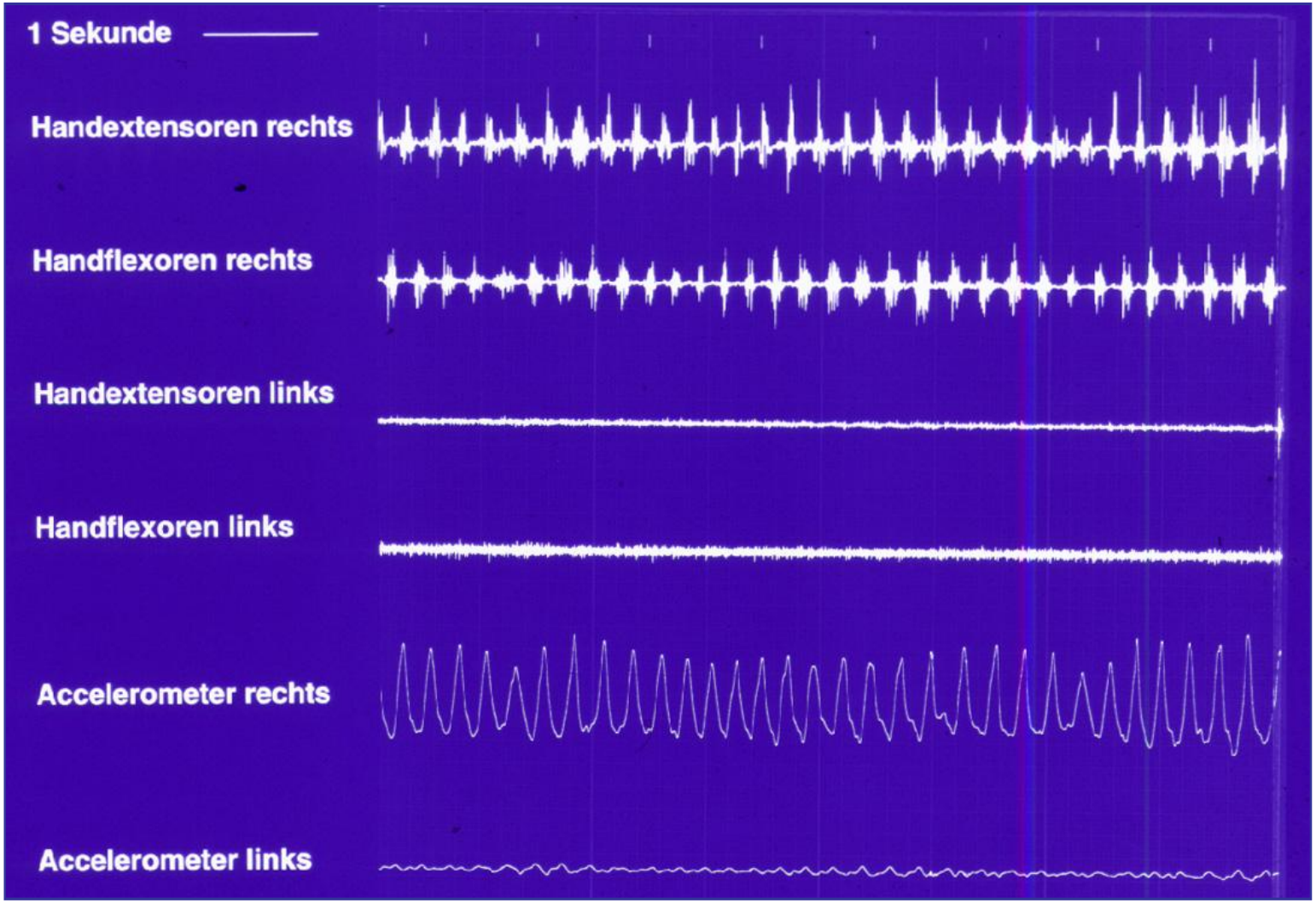
PARKINSON‘S DISEASE

- Differential clinical symptoms -

(Hughes et al, 1992)

- **Asymmetric onset**
- **Presence of classical rest tremor**
- **Absence of atypical features**
- **No evidence for alternative pathogenesis**

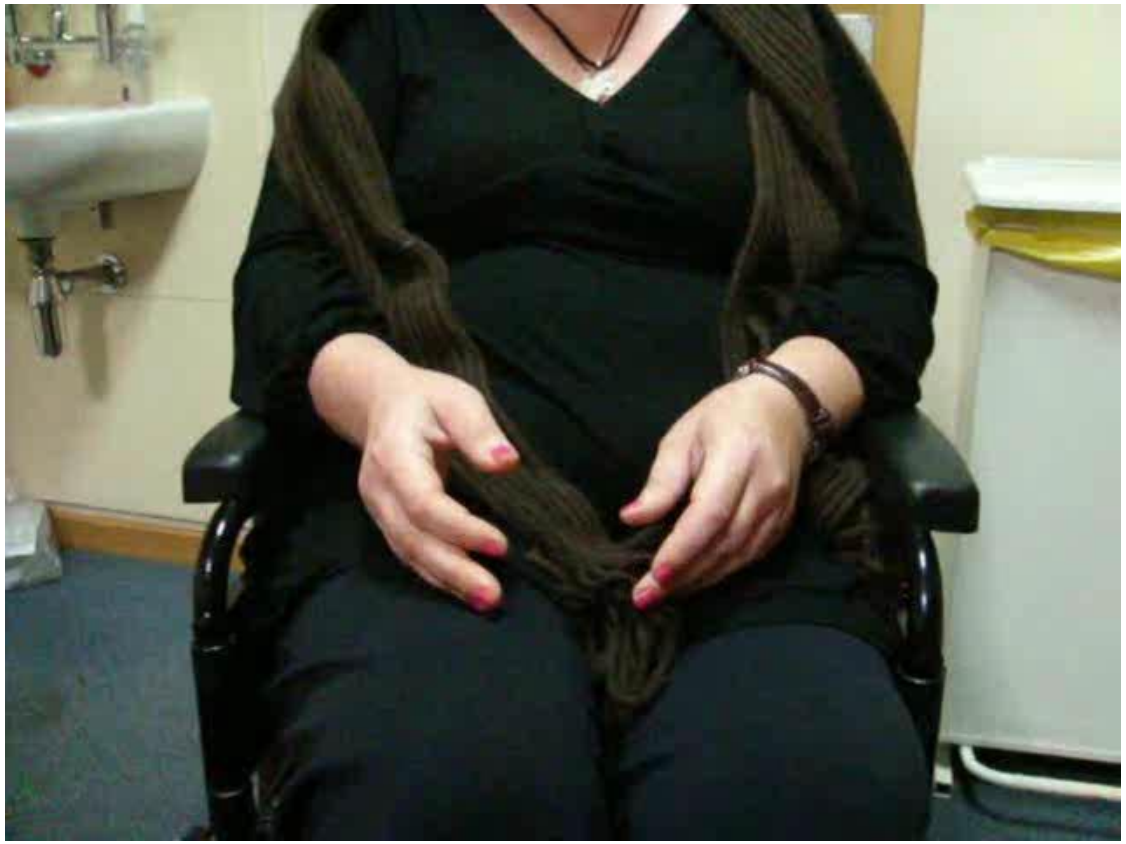
REST TREMOR IN PD

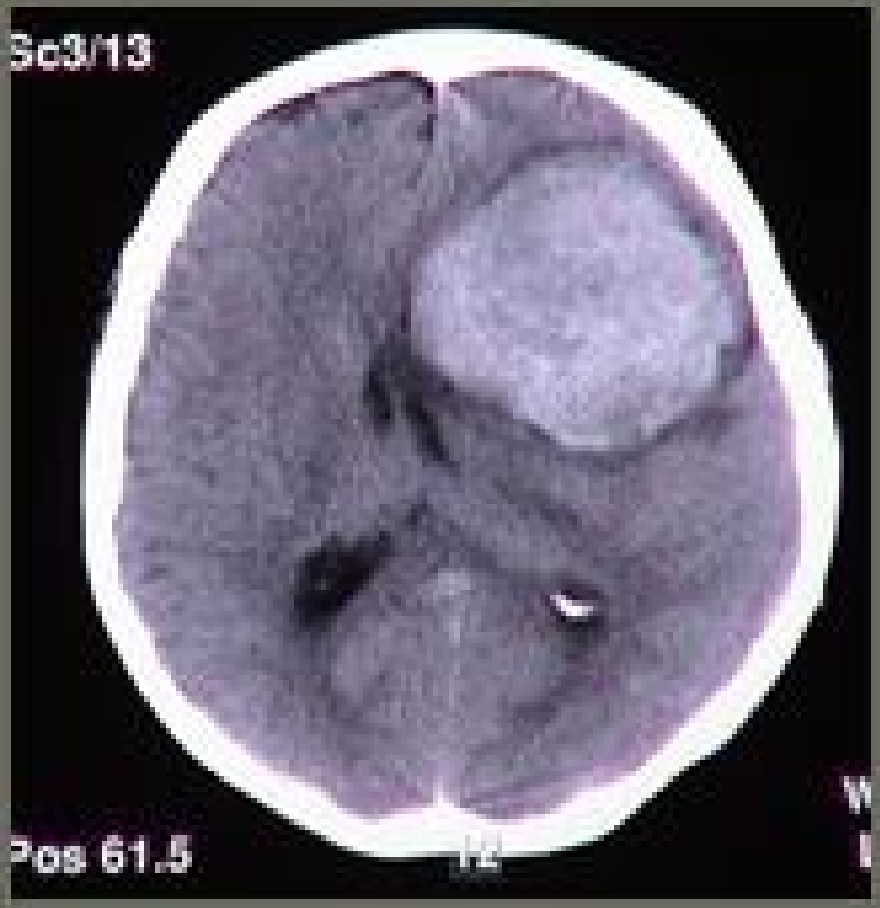


Decades of Delayed Diagnosis in 4 Levodopa-Responsive Young-Onset Monogenetic Parkinsonism Patients

Helen Ling, BScMed, BMBS, MSc,[1,2] Mark Braschinsky MD, PhD,[3] Pille Taba, MD,[3] Siiri-Merike Lüüs, MD,[3] Karen Doherty, MB, BCh, BAO, MRCP,[1,2] Anna Hotter, MD,[4] Werner Poewe, MD,[4] and Andrew J. Lees, MD FRCP[1,2]*

Movement Disorders, Vol. 26, No. 7, 2011




Sc3/13
Pos 61.5

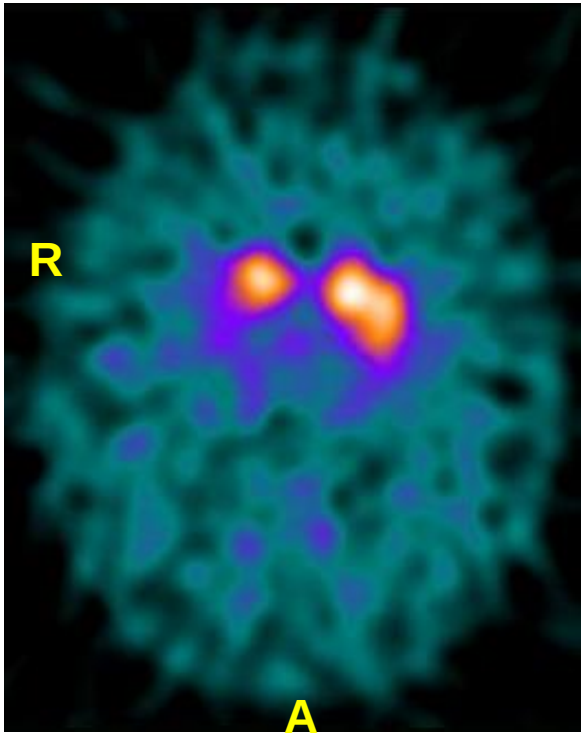
- **43 year old male**
- Involuntary cramping L foot for 9 mths.
- Occur exclusively following
  > 15 minutes of walking
- Painful
- Immediate cessation with rest
- Neurological findings outside of attacks normal

exercise-induced dystonia

Regina Katzenschlager, MD; Durval Costa, MD, PhD, FRCR; Svetislav Gacinovic, MD; and Andrew J. Lees, MD, FRCP

Abstract—Isolated foot dystonia following exercise is a rare manifestation of early PD. It may precede the onset of parkinsonism by years and can be clinically indistinguishable from familial exercise-induced dystonia. The authors present a patient with dystonic claudication where dopamine transporter SPECT using ^{123}I-FP-CIT allowed early diagnosis of PD and enabled effective symptomatic treatment with a dopamine agonist.

NEUROLOGY 2002;59:1974–1976



PARALYSIS AGITANS;

WITH AN ACCOUNT OF A NEW SYMPTOM.

By PURVES STEWART, M.A., M.D. Edin.,
M.R.C.P. Lond.,
SENIOR HOUSE PHYSICIAN TO THE NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC, QUEEN-SQUARE, BLOOMSBURY, LONDON, W.C.

The Lancet 1898

DYSTONIA IN PARKINSON‘S DISEASE

„The patient complains, when walking, that the toes of one foot occasionally become spontaneously strongly flexed and curled up under the sole in a cramp-like fashion, causing difficulty in walking. This „curling up“ of the toes is often so uncomfortable that the patient has to stand still for a minute or two until he can get his toes to relax and spread out flat again. All the toes, with the exception of the great toe, participate in this flexor contracture (…). In some cases the contraction may spread to the anterior tibial muscles, causing an inversion of the ankle as well.“

Purves-Stewart, 1898

DYSTONIA AS A PRESENTING SYMPTOM IN EARLY ONSET PD (EOPD)

STUDY	N	DYSTONIA AT ONSET	PTS. WITH AUTOSOMAL-RECESSIVE PD*
Schrag et al, 1998	139	14 %	nd
Lücking et al, 2000	186	22-42 %	54 % *
Chung et al, 2006	94	6 %	5 % *
Lohmann et al, 2009	44	52 %	50 % *
Wickremaratchi et al, 2011	70	20 %	29 % */**

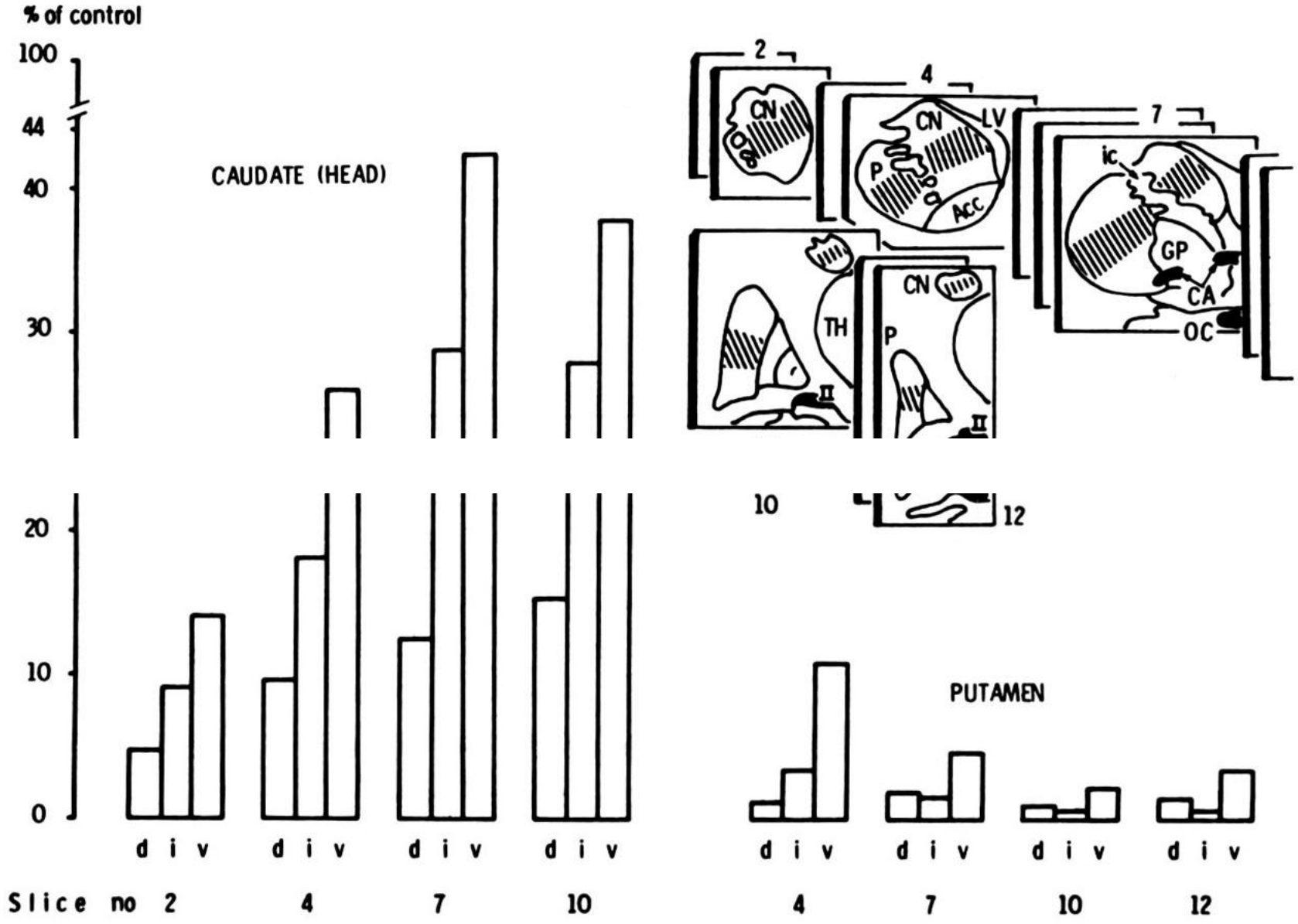
* Parkin; ** PINK-1

DYSTONIA IN PD
- Classification -

1. Focal Dystonia as a presenting symptom
- Sporadic PD
- Autosomal-recessive PD
  (Parkin, DJ-1, PINK1)

2. Drug-induced dystonia
- L-Dopa
- DA-agonists

3. Postural abnormalities in PD
- Deformities of the hands and feet
- Abnormal axial postures
  * „Antecollis“
  * Camptocormia
  * Lateroflexion (Pisa-Syndrome)



Kish et al, NEJM 1988