PARKINSON'S DISEASE
Clinical aspects

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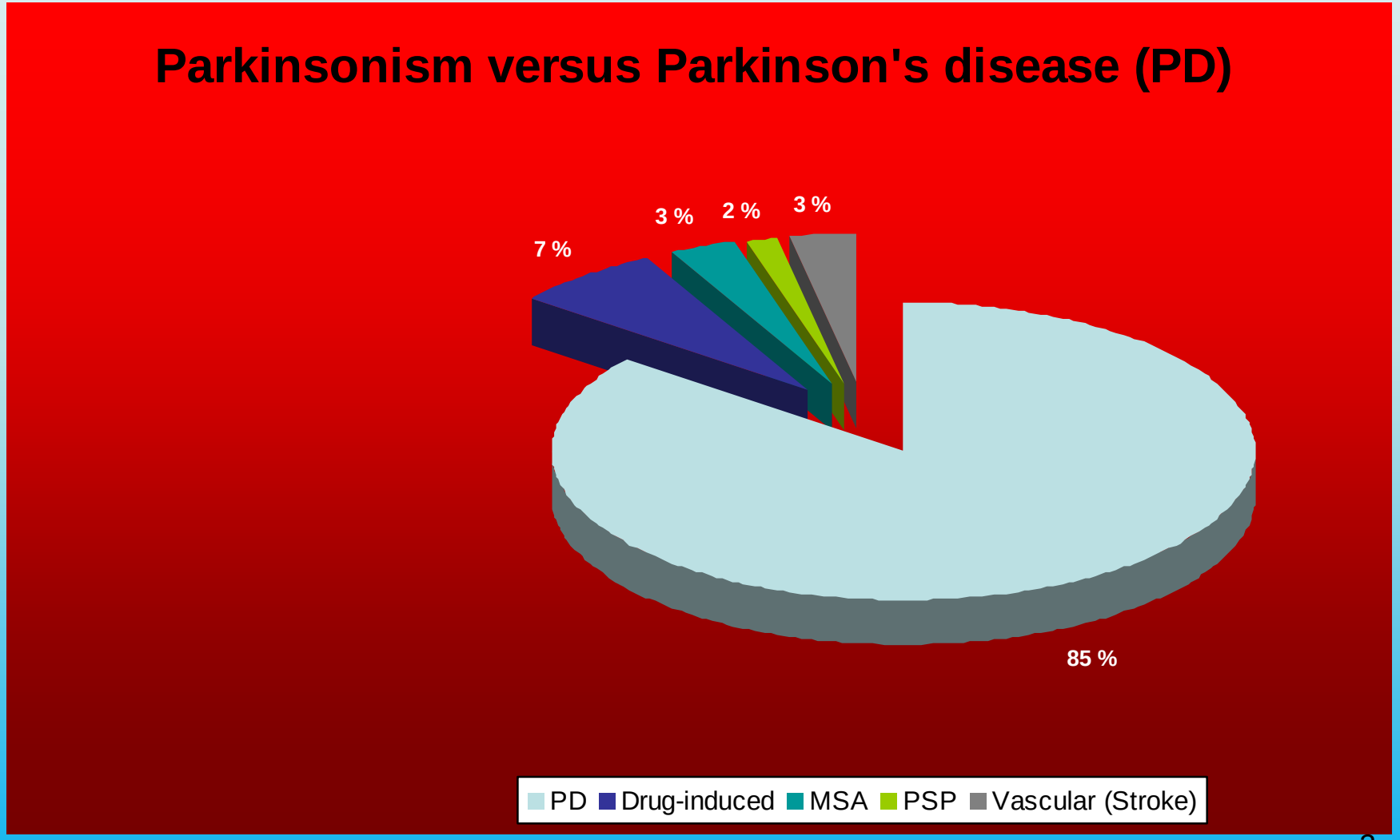
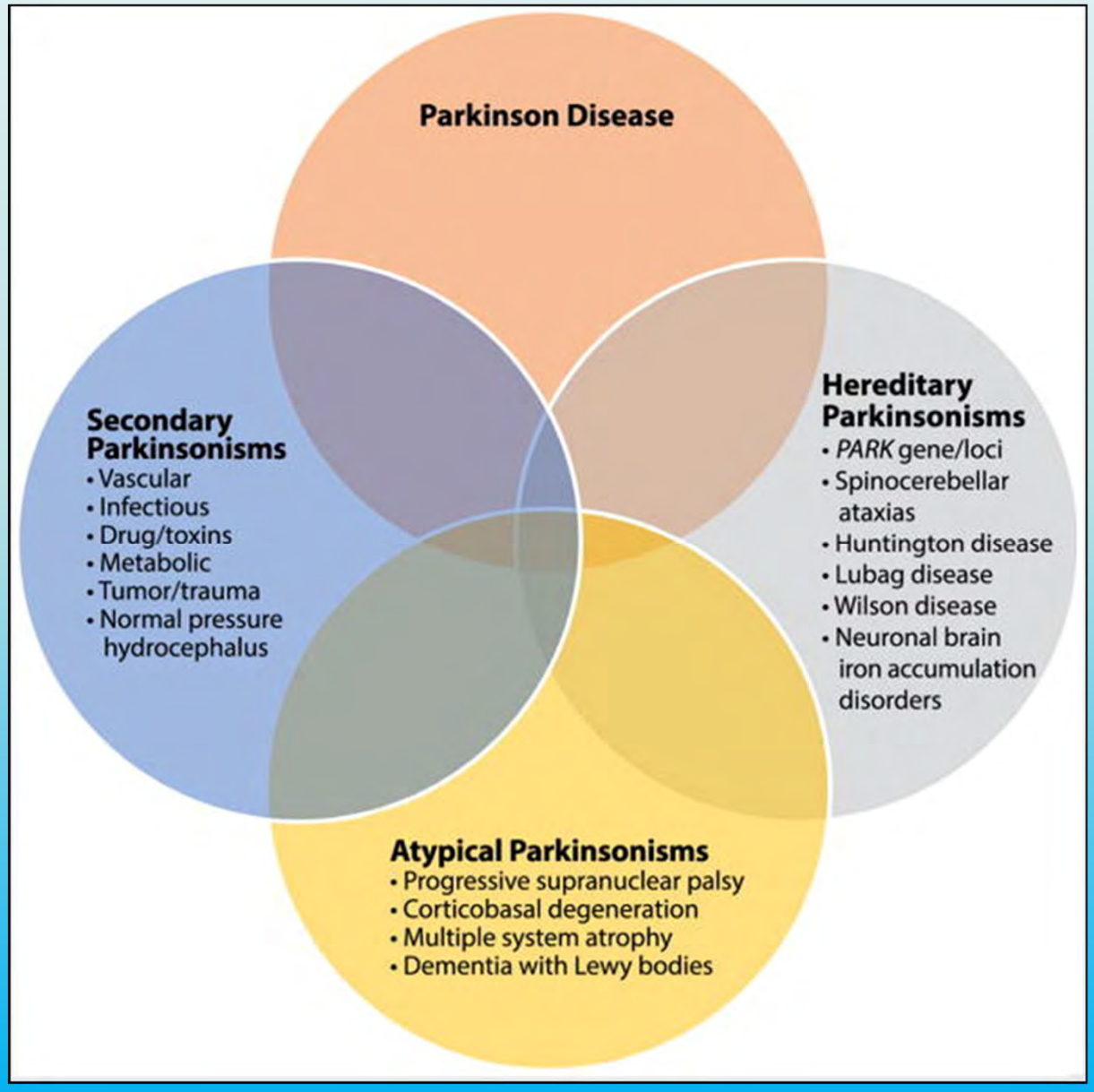
PARKINSONISM

- A clinical syndrome characterized by
  - bradykinesia / hypokinesia (slowness and poverty of movement)
  - tremor
  - rigidity (stiffness)
- Can have many causes
  - Parkinson's disease & other degenerative diseases
  - drug-induced, toxic, metabolic
  - vascular, traumatic, post-infectious, normal pressure hydrocephalus, etc.

PARKINSONIAN SYNDROMES



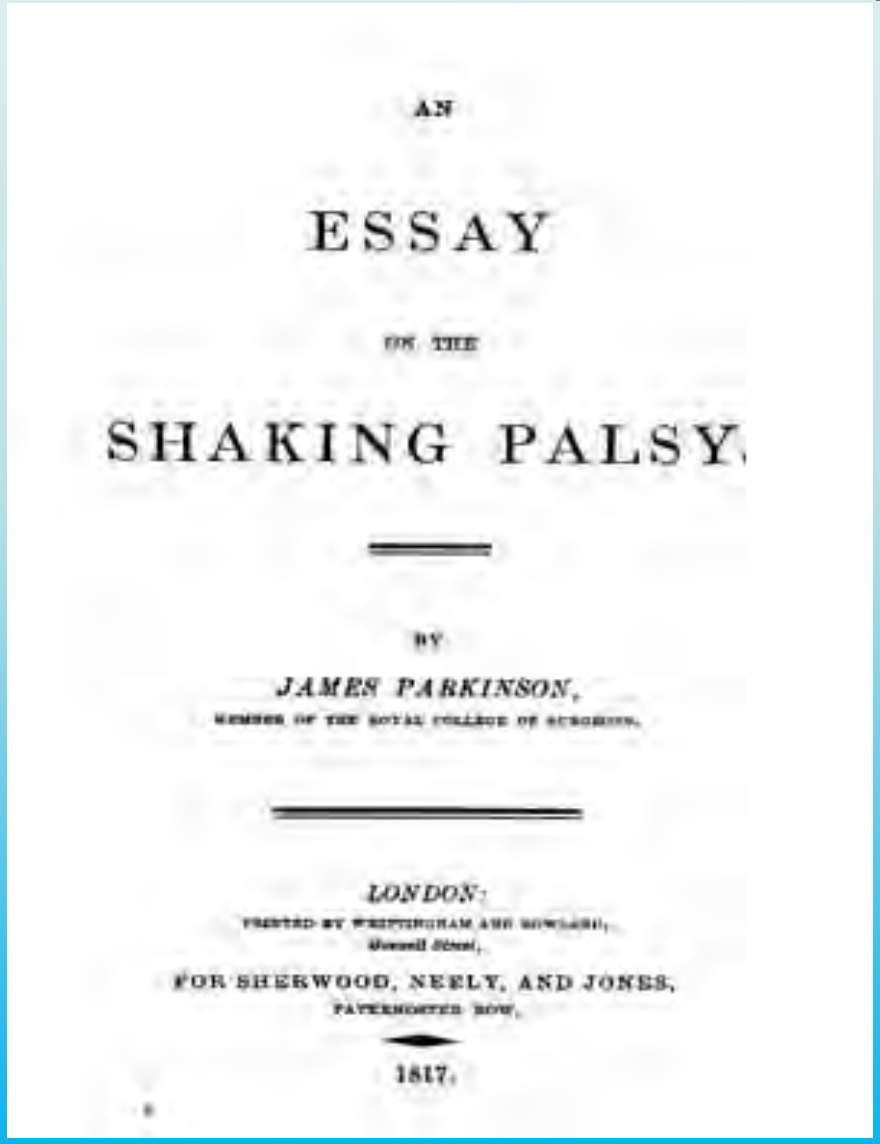
Parkinsonisms



Diagnostic Approach to Atypical Parkinsonian Syndromes.
McFarland, Nikolaus; MD, PhD

CONTINUUM: Lifelong Learning in Neurology. 22(4, Movement Disorders):1117-1142, August 2016.
DOI: 10.1212/CON.0000000000000348

History of Parkinson's disease: First description 1817



AN

ESSAY

ON THE

SHAKING PALSY.

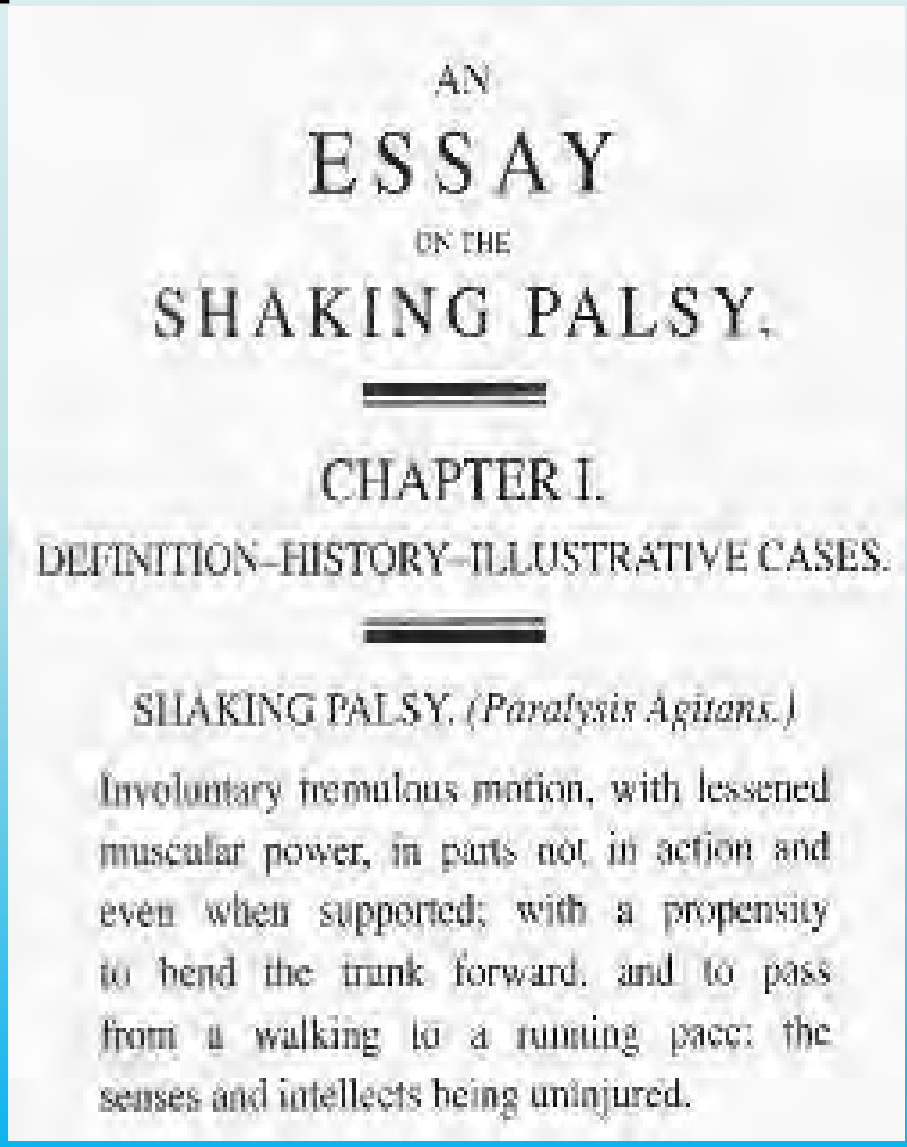
BY

JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

1817.



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Epidemiology

- Prevalence in white population 100-180/100000 and incidence 10-15/100000/v
  - In Finland 1992 prev . 166/100000 ja ins. 15/100000/v
  - In Finland ~15000 PD patients
- increasing prevalence after 50 years of age, 1-1.5% of > 70 y population
- Men > women

PARKINSON'S DISEASE

- Degeneration of *substantia nigra*
  - causes the motor symptoms
  - apoptosis
  - non-linear rate of cell death
- Initially, remaining cells compensate
- A *premotor phase* of several years
- Motor symptoms emerge after
  - ~50% of nigral cell loss
  - ~80% of striatal DA loss
- Insidious onset, slow progression

NEUROPATHOLOGY OF PD

- Widespread, not only substantia nigra
  - cerebral cortex
  - multiple brainstem & basal forebrain nuclei
    - dorsal motor of vagus, raphe, ceruleus, pedunculopontine, Meynert, olfactory
  - hypothalamus
  - spinal cord (intermediolateral cell horn)
  - peripheral autonomic nervous system
    - paraspinal ganglia, cardiac plexus, sacral nuclei
  - visceral (*enteric*) nervous system

  - → also non-motor symptoms

Neuropathology of PD

Clinico-pathological correlations of PD stages

Clinical phase	Pathology
Preclinical	Medulla oblongata, pontine tegmentum, olfactory bulb, autonomic? (Stages1-2)
Early- moderate PD	Medulla oblongata, pontine tegmentum, olfactory bulb, autonomic?, substantia nigra (Stages 3-4)
Severe PD, PDD	Medulla oblongata, pontine tegmentum, olfactory bulb, autonomic, substantia nigra, cortex (Stages 5-6)

Simplified from Braak H et al 2003, Probst A et al 2008.
PDD= PD with dementia

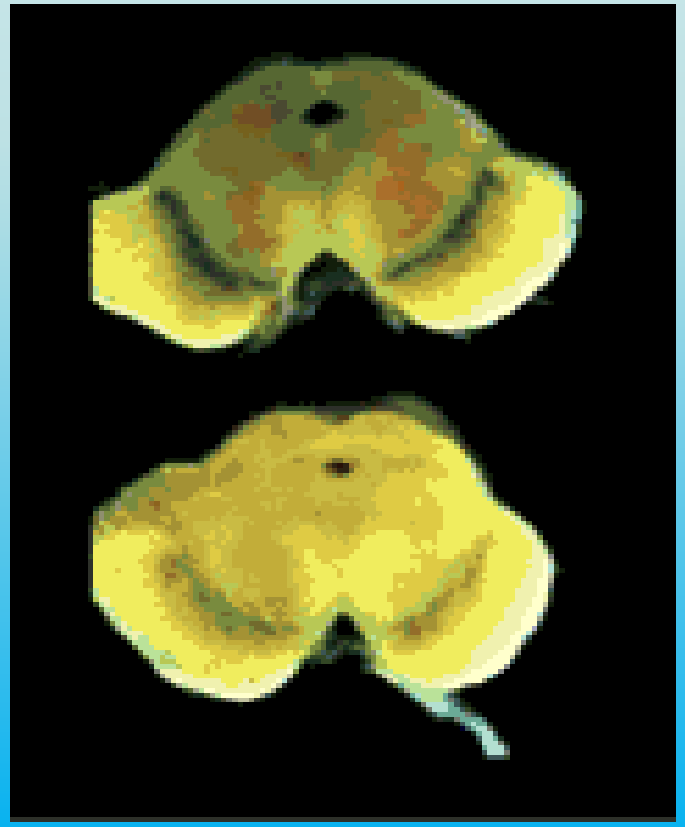
PD neuropathology

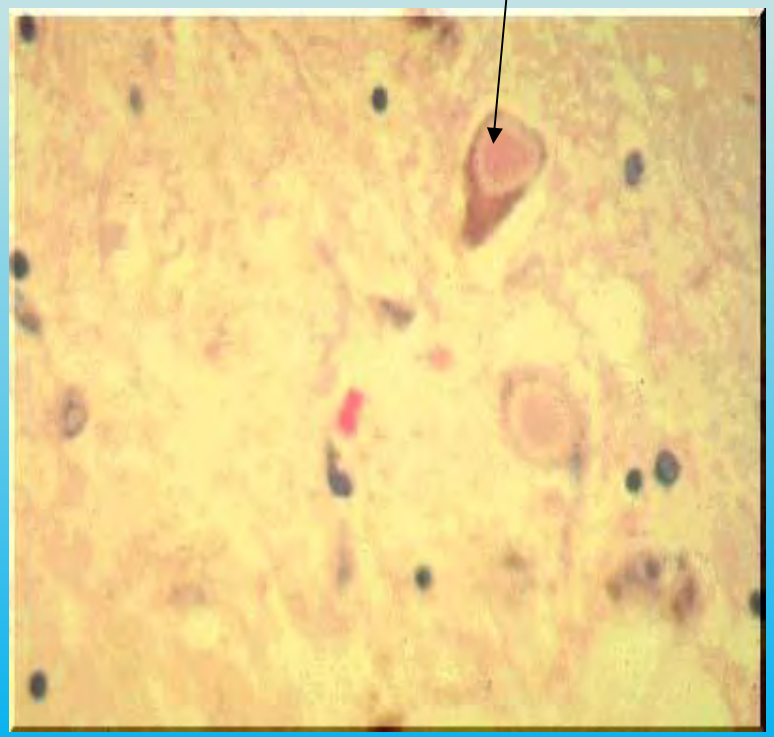
Characteristic: *substantia nigra*

- macroscopic: depigmentation, paleness
- microscopic: neuronal loss, gliosis, intraneuronal *Lewy bodies* which mainly consist of *a-synuclein*

Normal substantia nigra

Pale substantia nigra of a PD patient





PD - RISK FACTORS

- Age is the most important
- Family / genetic factors
  - affected 1st degree relative: 2.9x (Autere, 2000)
- Gender
  - slightly higher risk in men: 1.2-1.5x
- Suspected environmental risk factors (no consistent evidence)
  - well water use?
  - rural dwelling?
  - mining?
  - herbi- / pesticides?
- Protective environmental factors:
  - coffee
  - smoking cigarettes

Is PD hereditary?

- Small part (10-15 %) have positive family history
- Genetic susceptibility has been shown also in ”normal” sporadic PD

Twin studies, e.g.:

- **<u>Tanner et al 1999</u>**:
- similar concordance for MZ and DZ twins but if dg <50 v concordance MZ 1.0 vs. DZ 0.167

→”.. typical PD diagnosed after 50 years has no genetic component”

- **<u>Piccini et al 1999</u>**,
- PET study, concordance
  75% in MZ vs 22 % in DZ twins
- ==> **significant genetic effect** in nigrostriatal dopaminergic dysfunction

MOTOR SYMPTOMS & SIGNS

- Bradykinesia / Hypokinesia
  - slowness / poverty of movement
  - akinesia
- Rigidity
  - increase in muscle tone
  - cogwheel or leadpipe
- Tremor
  - rhythmic, oscillatory motion of a body part
- Postural instability
  - forward bent posture
  - impaired balance
  - later phenomenon

Rigidity (cogwheel phenomenon)

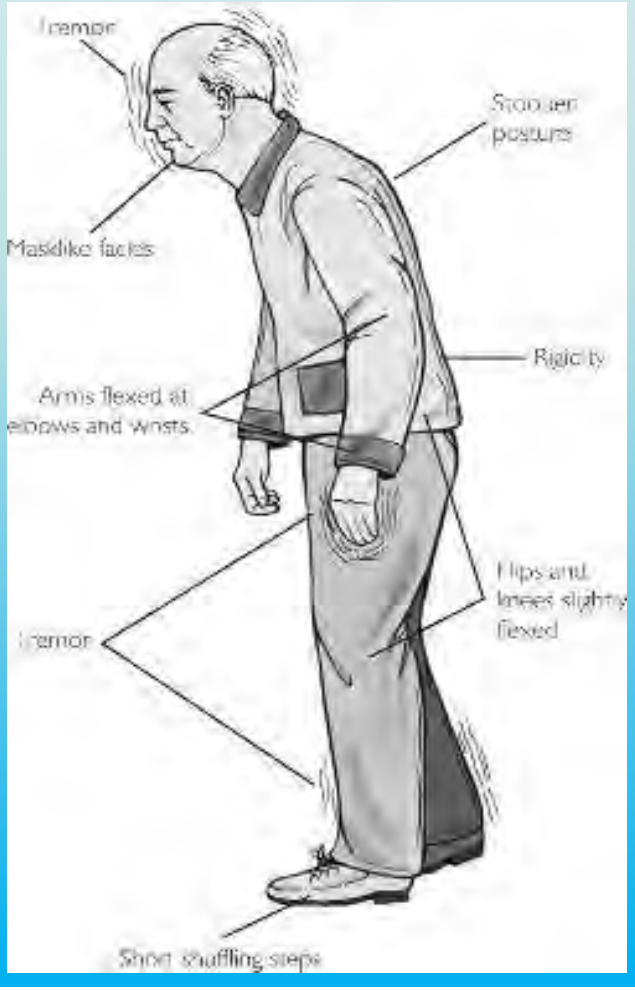
PD

Clinical manifestations

- The patients may complain or present with
  - impairment (“clumsiness”) in manual tasks
  - small hand writing *(micrographia)*
  - masked face & reduced blinking *(hypomimia)*
  - short-stepped, shuffling gait
  - stooped posture
  - muscle cramps
  - slurred speech with reduced volume *(hypophonic dysartria)*

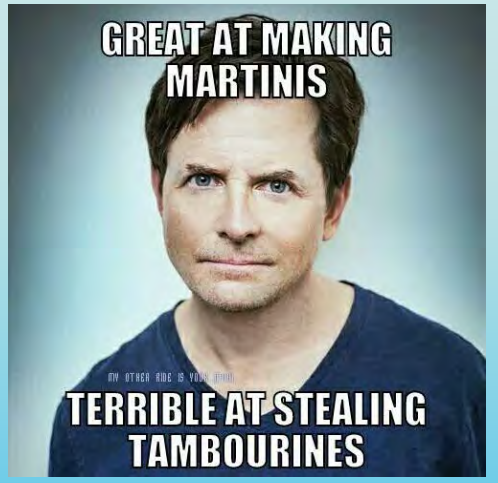
Parkinson's disease

more motor manifestations



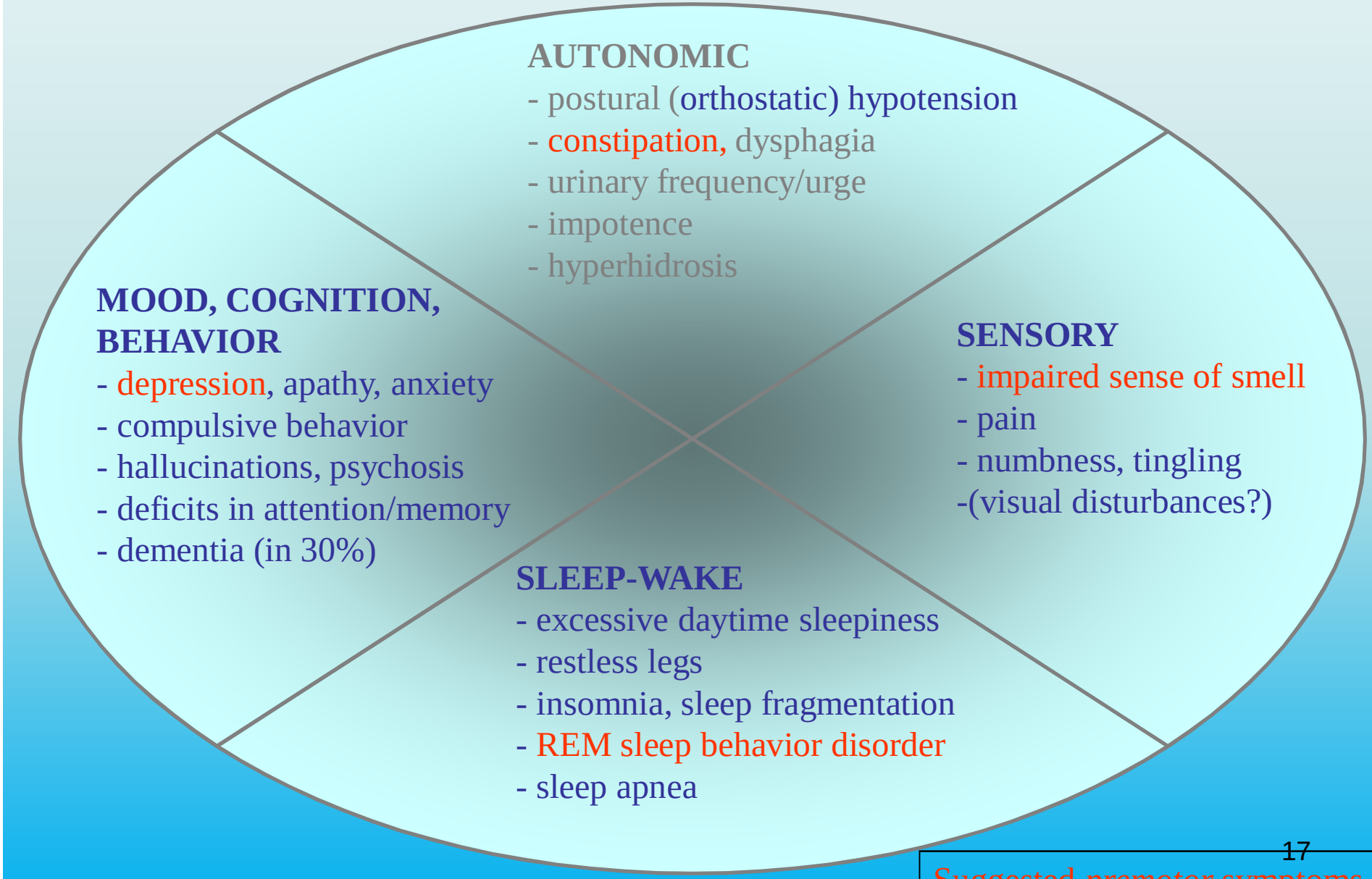
Micrographia

Hypomimia



Videos

NON-MOTOR SYMPTOMS IN PD



Suggested *premotor* symptoms

PD DIAGNOSIS

- History
- Clinical symptoms and signs
- Exclusion of other causes
- Follow-up
- No spesific biomarkers available
- false positives up to 15-25% !

MDS Clinical diagnostic criteria for Parkinson's disease

- PARKINSONISM MUST BE PRESENT
- Bradykinesia AND
- rigidity
- or resting tremor (or both)

MDS clinical criteria for PD
Exclusion criteria

1) cerebellar signs
2) vertical gaze palsy
3) Dg of diagnosis of behavioral variant frontotemporal dementia or primary progressive aphasia within first 5 y of disease
4) Parkinsonism restricted to lower limbs > 3 y
5) Drug-induced parkinsonism
6) Absence of response to levodopa
7) Unequivocal cortical sensory loss, clear limb apraxia or progressive aphasia
8) Normal functional neuroimaging of the presynaptic dopaminergic system
9) Documentation or expert opinion that other condition causes parkinsonism

MDS clinical criteria for PD Red flags

1) Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
2) Lack of progression of motor symptoms or signs > 5 y unless stability is related to (increasing) treatment
3) Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia within first 5 y
4) inspiratory stridor
5) severe autonomic failure < 5 y
6) recurrent falls < 3 y
7) Severe antrocollis or contractures of hand or feet <10 y
8) Absence of nonmotor features > 5 y
9) otherwise-unexplained pyramidal tract signs
10) Bilateral symmetric parkinsonism

MDS clinical criteria for PD Supportive criteria

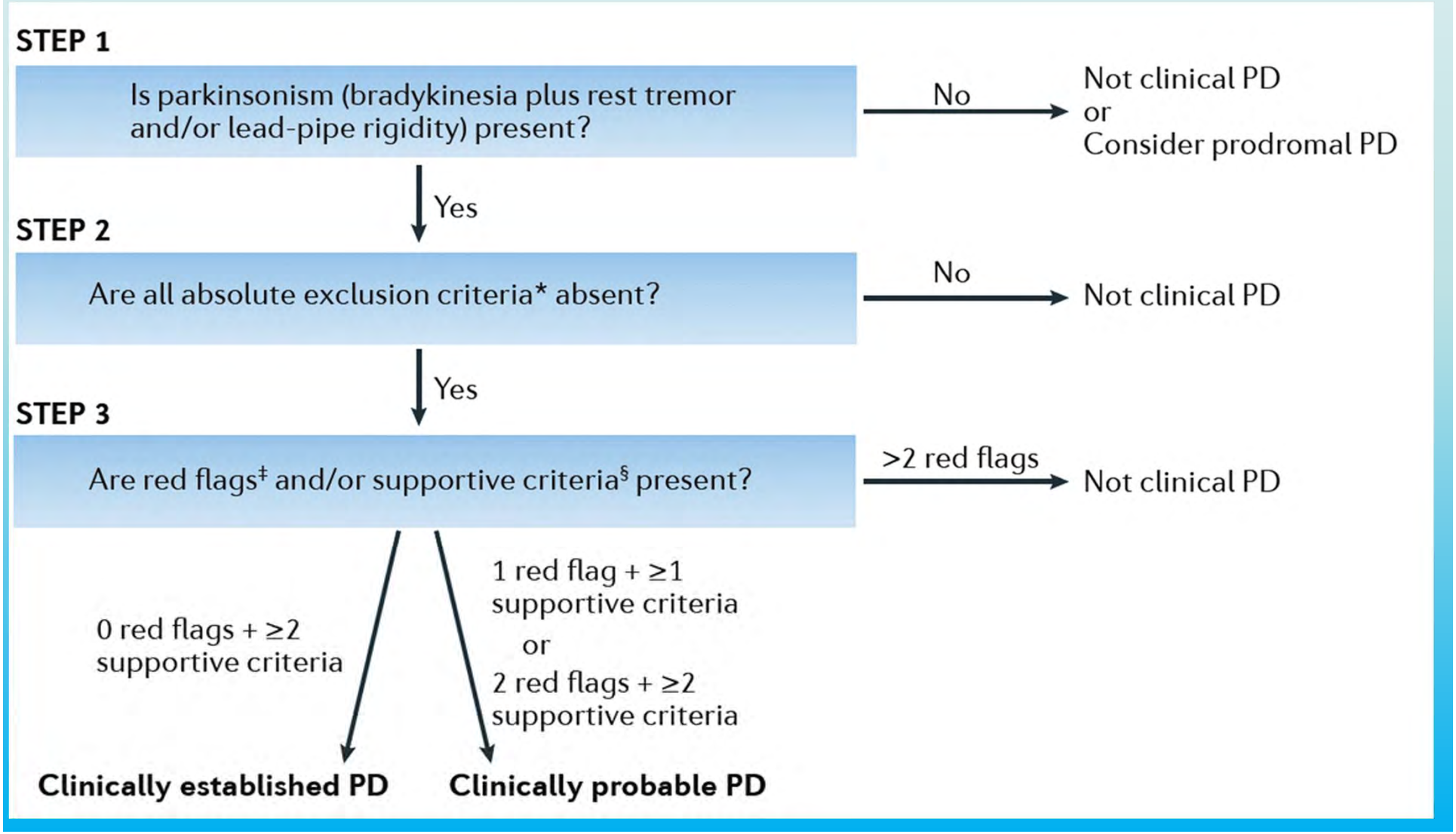
1)clear beneficial response to dopaminergic therapy

2)Presence of levodopa-onduced dyskinesi

3)rest tremor of a limb

4)olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

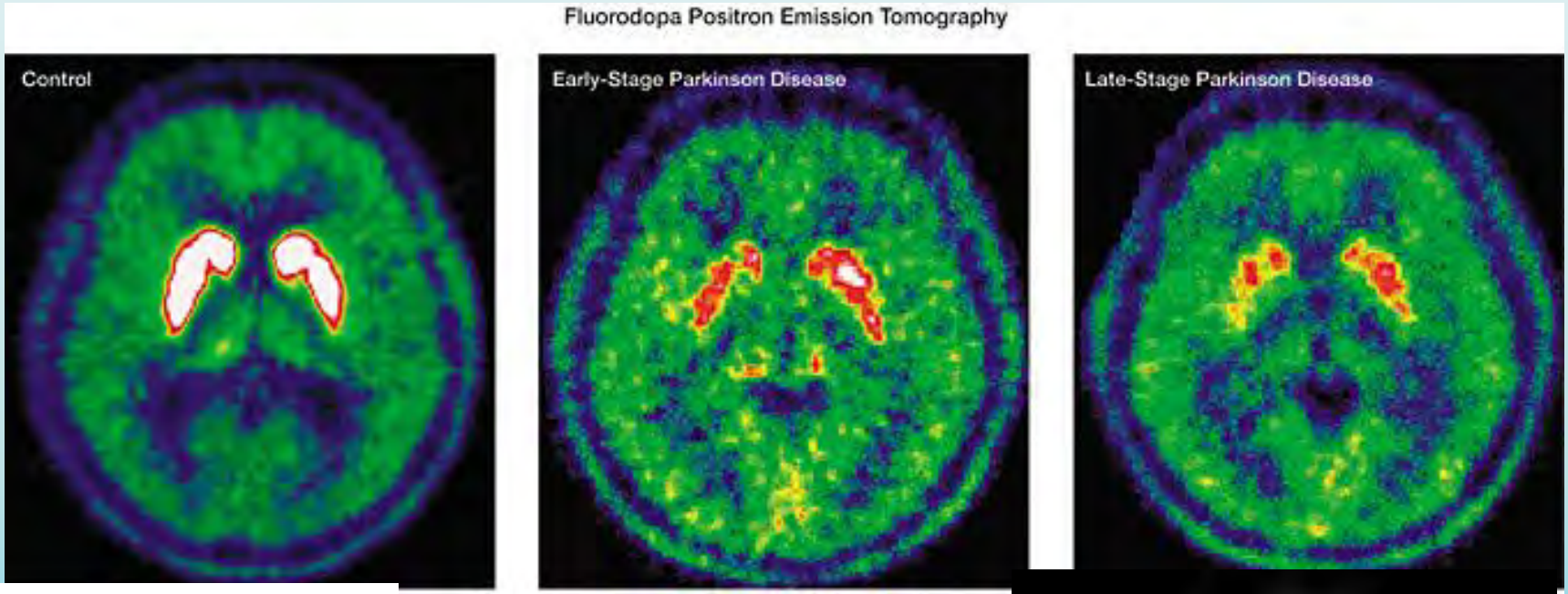
MDS Clinical diagnostic criteria for Parkinson's disease

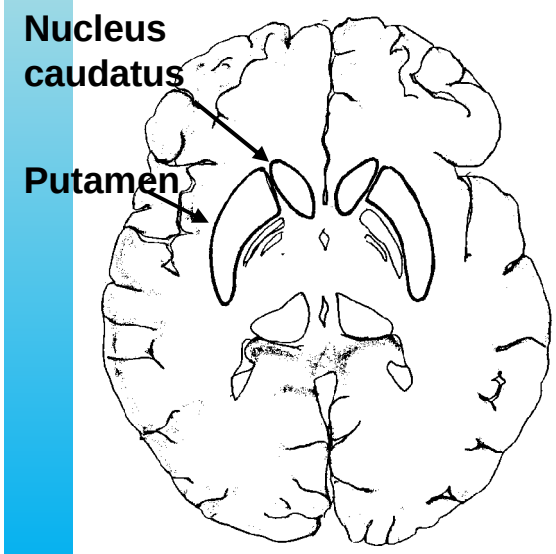


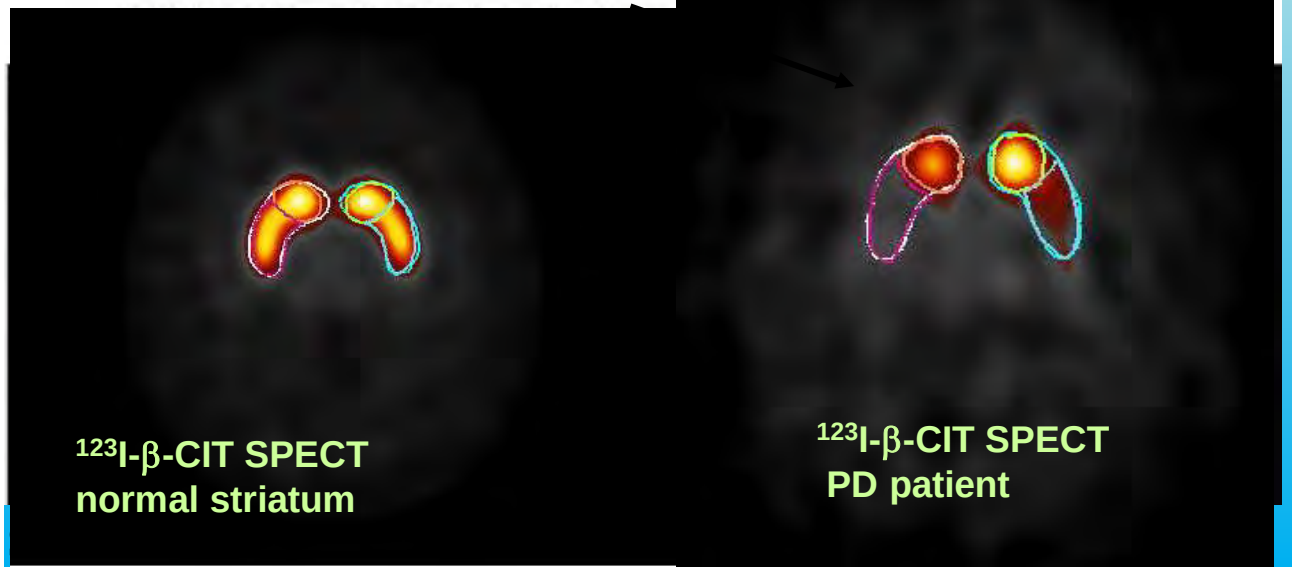
PD DIAGNOSIS - NEUROIMAGING

- Used to exclude other causes for parkinsonism routinely
  - computerized tomography (CT) or
  - magnetic resonance imaging (MRI)
- Functional neuroimaging in problematic cases
  - striatal dopaminergic terminals
  - single photon emission tomography (SPECT)
    - β-CIT binds to pre-synaptic dopamine transporter in the striatum
  - positron emission tomography (PET)
    - 6-[^{18}F]-dopa is taken up and stored pre-synaptically

^{18}FD PET, β-CIT SPECT

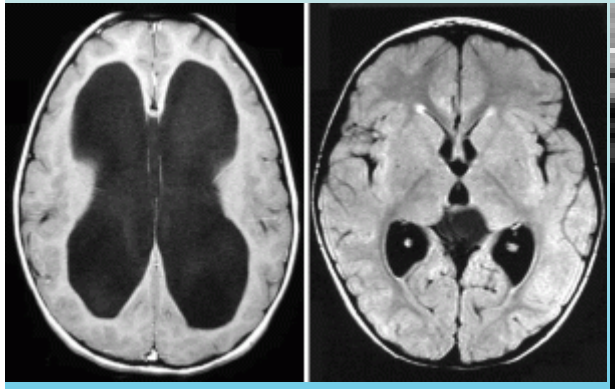




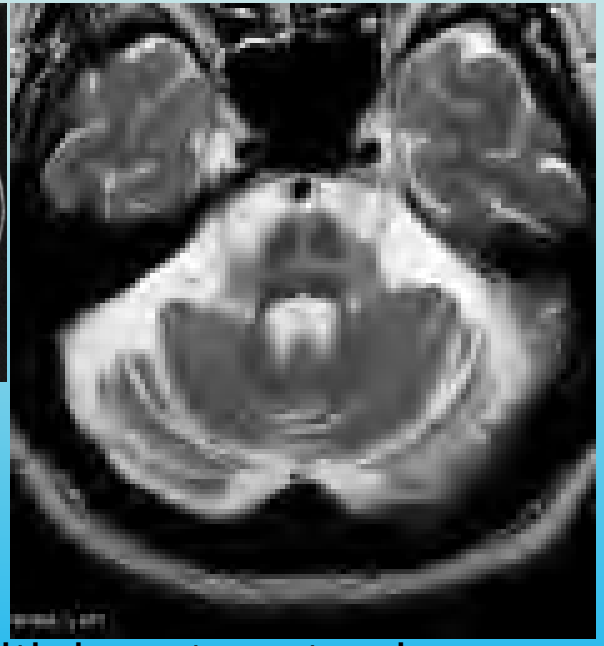


PD diagnosis - Imaging

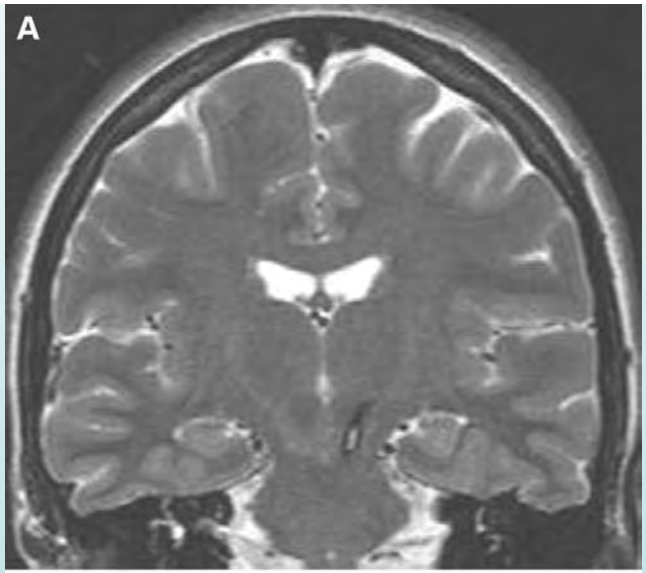
- Brain CT or MRI is normal in PD
- TO EXLUDE OTHER CAUSES
- Examples:

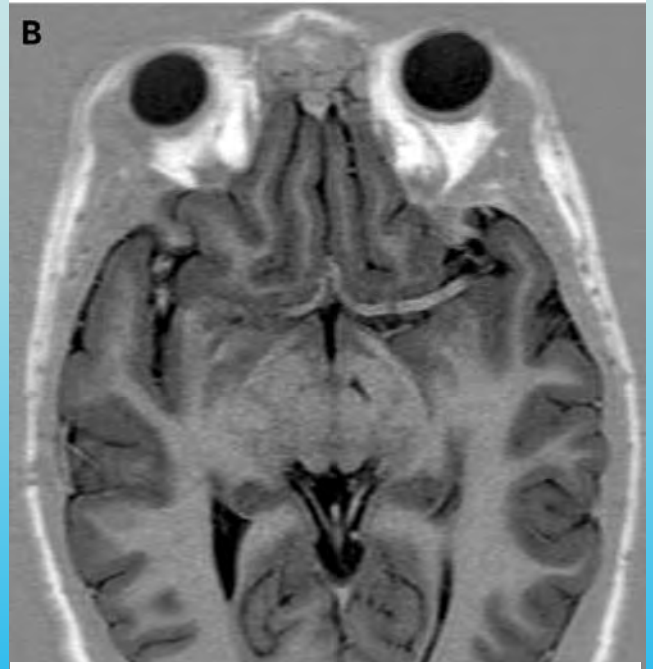


NPH



Multiple system atrophy:
Cerebellar and pontine atrophy
”Hot cross bun sign”





Haemorrhage in the left SN
-> acute onset right-sided hemiparkinsonism

DISEASE COURSE

- progressive, individual rate
- Prognosis prior to levodopa therapy
  - 80% dead or seriously crippled after 10-14 y
  - death rate *(mortality)*: 3x that of healthy
- Prognosis after levodopa therapy
  - changed dramatically
  - levodopa delays disability by several years
  - *mortality*: roughly equals that of healthy

DISEASE COURSE

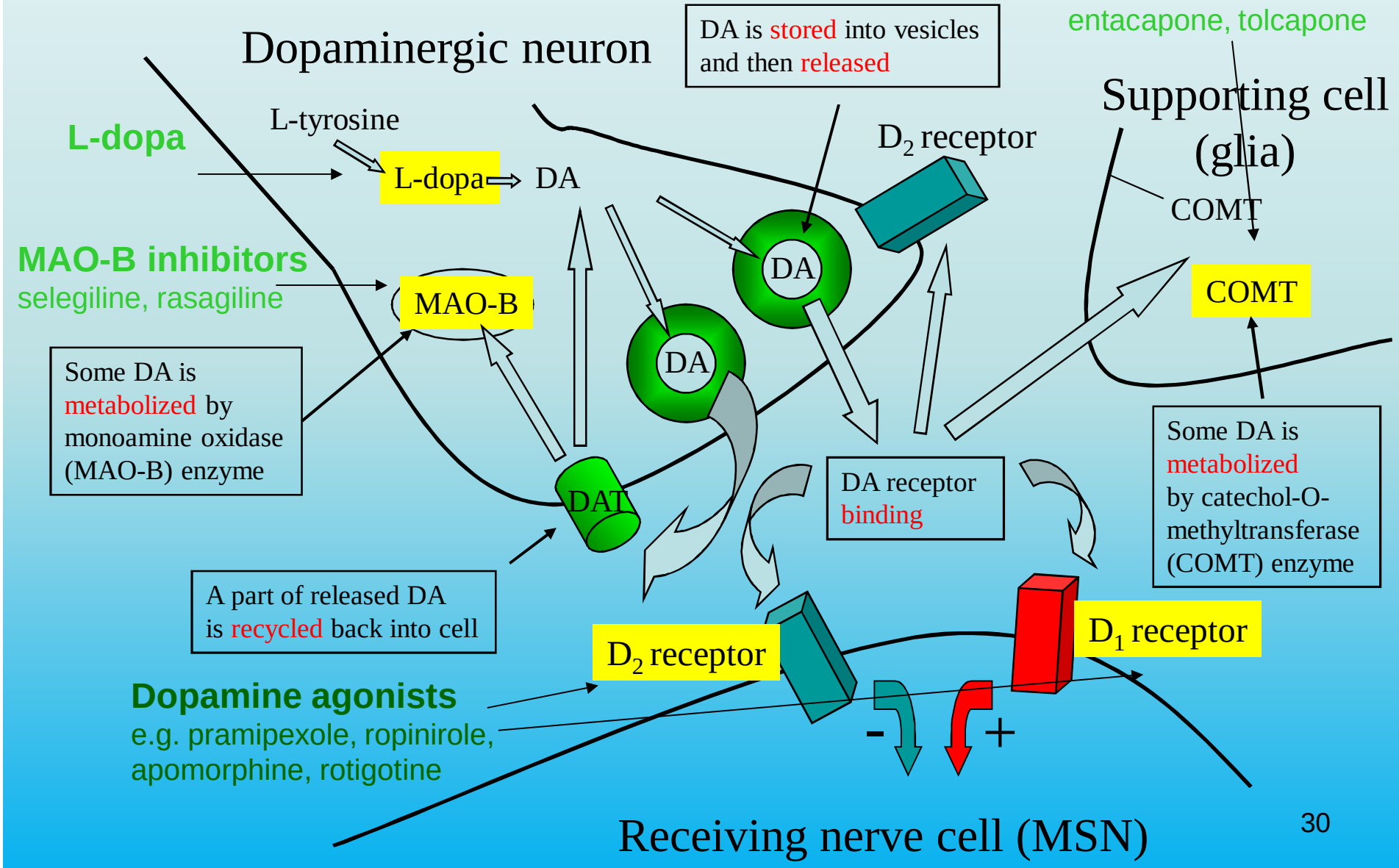
Patients with severe disability:	before L-dopa (1967)	after L-dopa (1992)
After 5 years	28%	9%
After 10 years	61%	22%
After 15 years	83%	51%

DRUG THERAPY IN BRIEF

- No therapy proven curative or disease modifying
- Only symptomatic
- Basic principle: enhancement of striatal dopaminergic activity
  - levodopa (DA replacement)
    - most effective, cheap
    - long-term motor complications
  - DA agonists (direct DA-receptor effect)
    - less long-term motor complications
    - less effective, more expensive
  - MAO-B inhibitors (inhibition of DA breakdown)
  - COMT inhibitors (combined with L-dopa) (inhibition of DA breakdown)
  - combinations

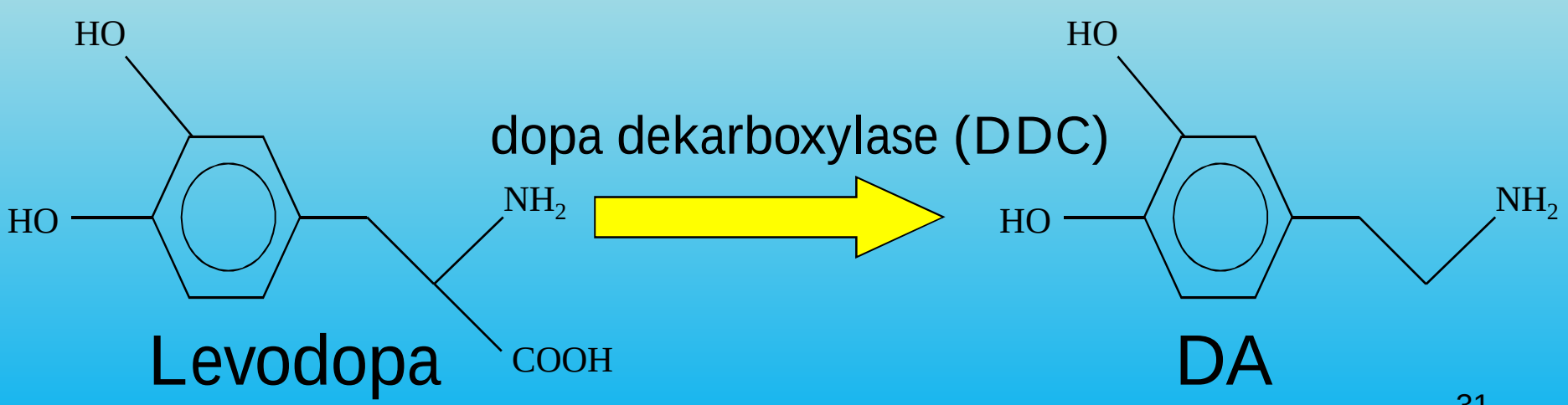
THE FATE OF DA

and PD medication



LEVODOPA REPLACEMENT

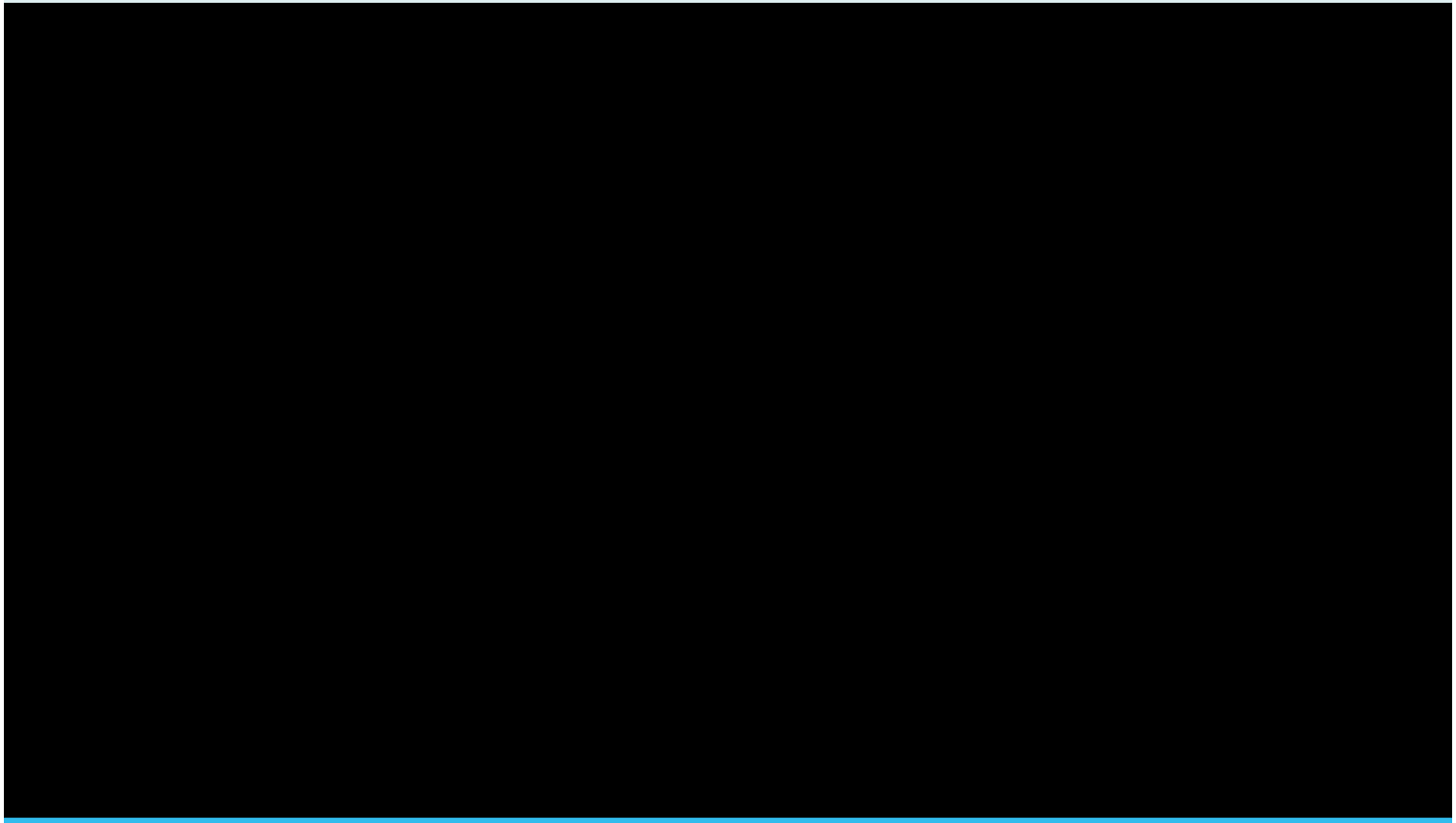
- Levodopa is a prodrug, precursor of DA
- Penetrates the blood-brain barrier
  - (DA does not)
- Metabolized to DA within the brain



MOTOR COMPLICATIONS
of long-term levodopa therapy

- Occur in
  - 20-50% after 5 y
  - 50-90% after 10 y
- Motor response fluctuations
  - drug effect wears off (”wearing-off”)
  - delayed or no drug effect
  - rapid fluctuations of motor state (”on-off”)
  - ”freezing”
- Involuntary movements, dyskinesia

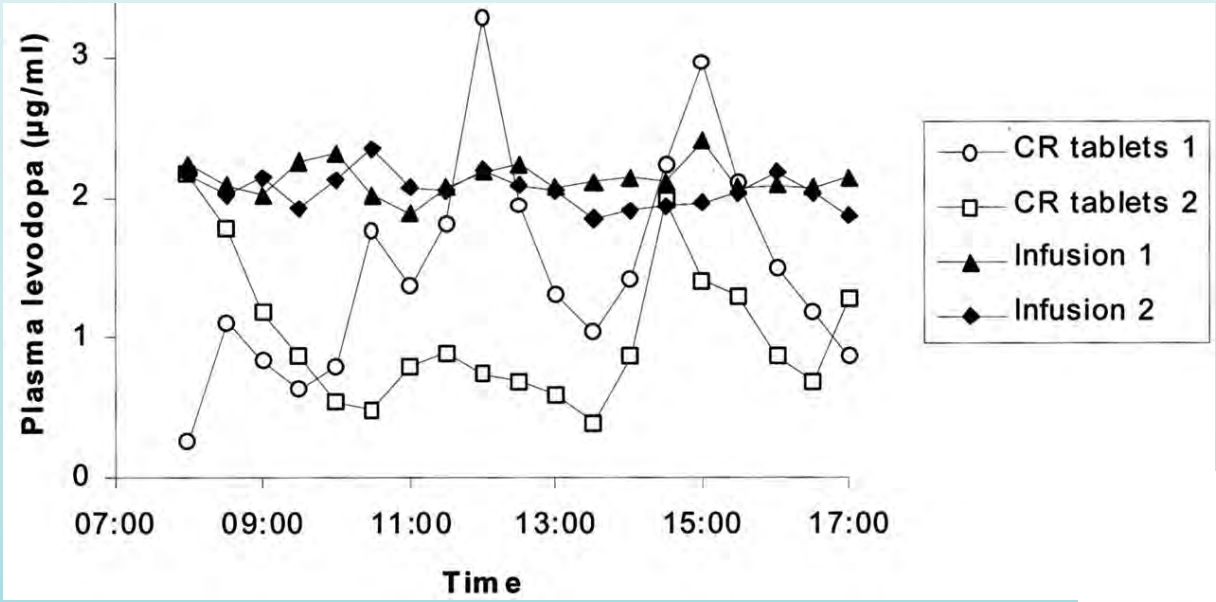
VIDEO PARKINSON DYSKINESIA

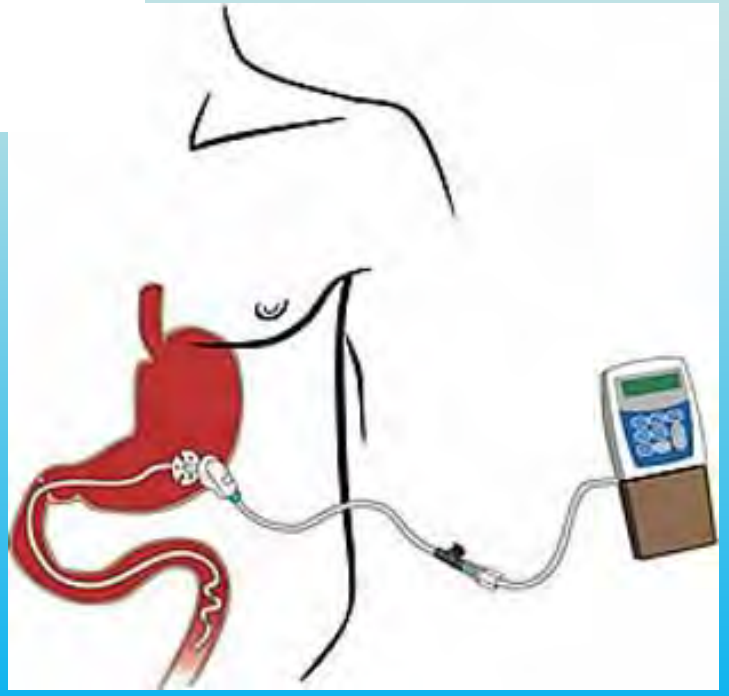


MOTOR COMPLICATIONS
Risk factors

- Age of onset
  - young at a higher risk
- Duration & severity of disease
- Duration & dosage of levodopa therapy
  - cumulative dosage

Duodenal levodopa



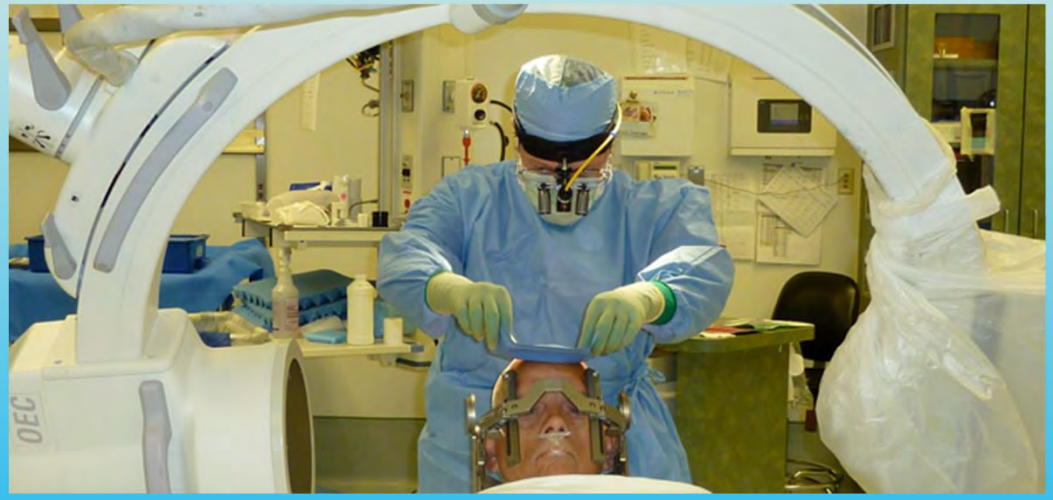


SURGICAL THERAPY IN PD

- Severe and disabling motor symptoms and / or motor response complications
  - not adequately managed by optimal drug therapy
  - patient does not tolerate drug therapy
- What is required?
  - 3D-mapping (*stereotaxis*, stereotactic frame)
  - intraoperative electrophysiologic monitoring
  - intraoperative clinical monitoring (patient fully aware & co-operative)

Surgical therapy of PD

- Ablation procedures→ deep brain stimulation (DBS)



Choosing the right PD patient for DBS

LIKELY TO BENEFIT

- severe fluctuation of symptoms despite of adequate medication
- troublesome dyskinesias
- levodopa benefit
- cognitively intact patient, not too old

NOT LIKELY TO BENEFIT

- Uncorrect diagnosis
- no benefit from levodopa
- high age?
- Problems with speech or gait
- Cognitive problems
- severe psychiatric symptoms
- severe comorbidities
- Abnormalities in brain imaging

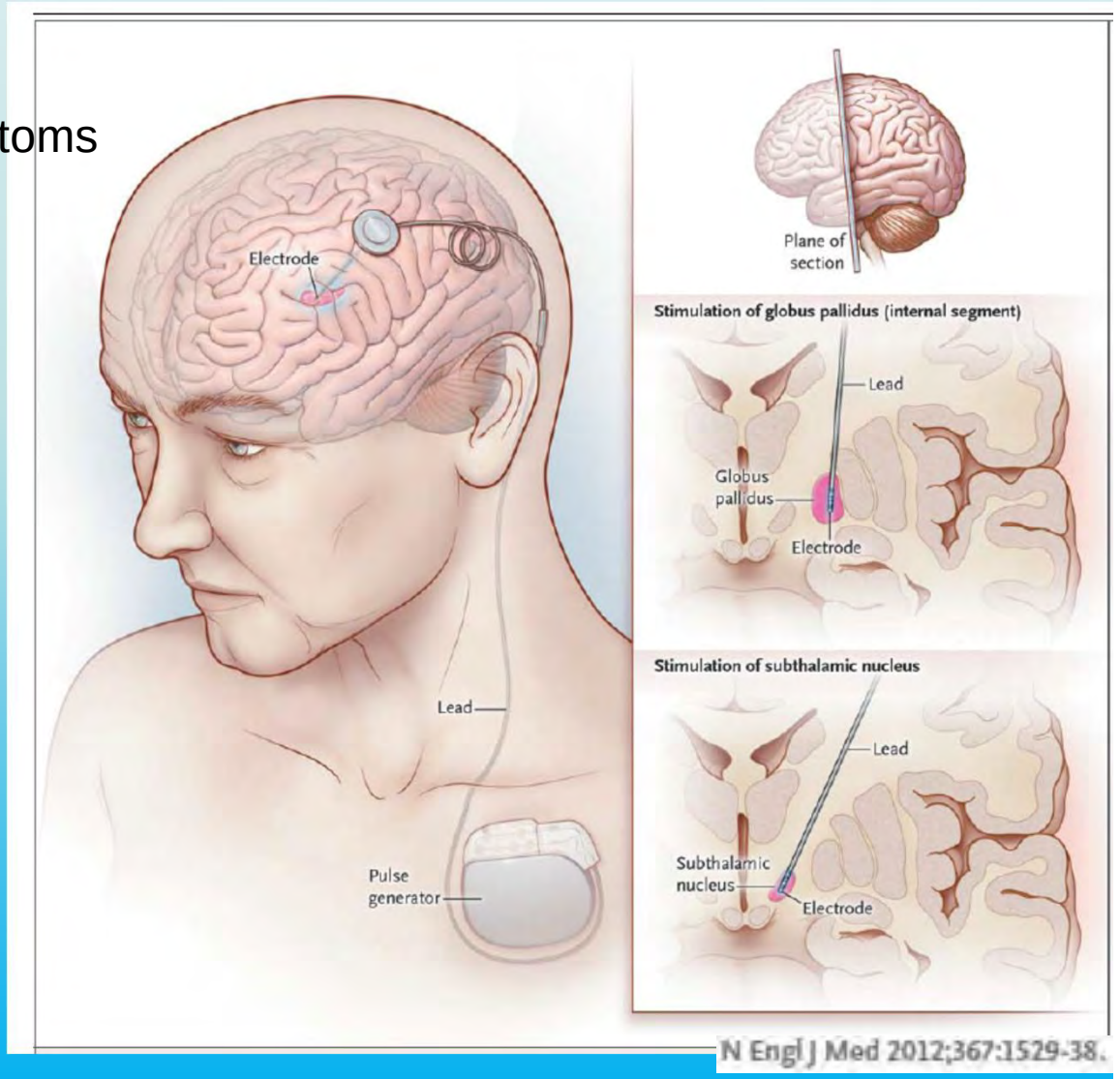
(atrophy, white matter degeneration, signs of (old)basal ggl ischemia)

Stimulation targets

-**Subthalamic nucleus (STN)**
* > 90% PD DBS
* reduces most PD motoric symptoms
* allows 25-50% levodopa dose reduction

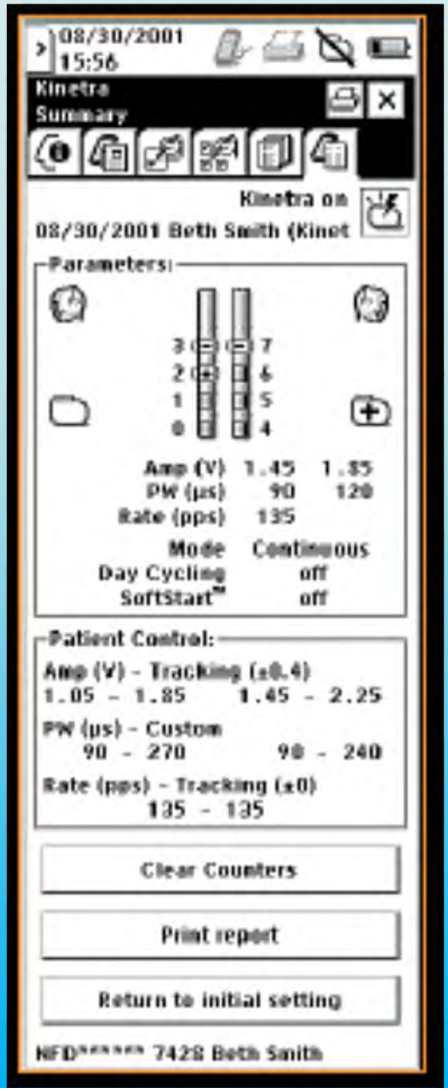
-Globus pallidus interna (GPi)
* reduction in most PD motoric symptoms
* no medication reduction
* possibly less depression

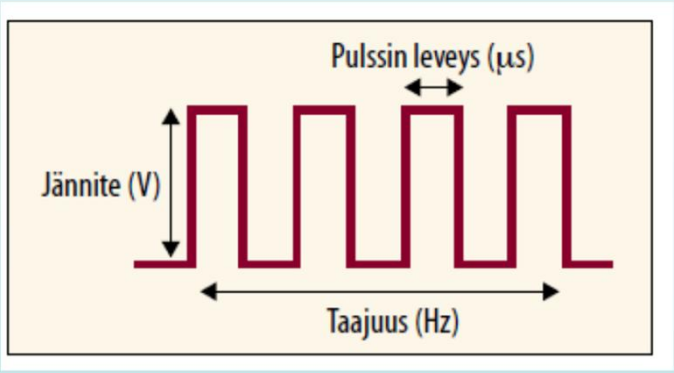
-Nucleus ventralis intermedius (Vim)of thalamus
* reduction of tremor only

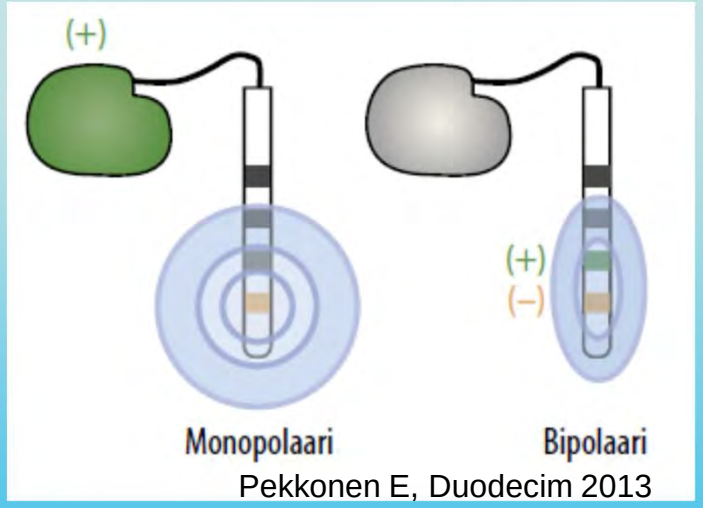


N Engl J Med 2012;367:1529-38.

DBS adjustment







Pekkonen E, Duodecim 2013

INTRODUCING THE ST. JUDE MEDICAL INFINITY™ DBS SYSTEM

- Directional lead technology
- App-based programming via Bluetooth® wireless communication
- Bilateral, independent frequency control
- User-friendly Apple™ mobile digital devices[1]
- Upgradeable technology platform

DBS
Risks and side effects

- The most serious risks
  - ICH n 1-3% (Pekkonen E, Duodecim 2013, Okun M, NEJM 2012)
  - infection 5 %(Okun NEJM 2012)
- Mild cognitive decline or decline of speech fluency, depression or mania, aggression or suicidal behavior ?
- Usually transient and mild, and respond to adjusting stimulation parameters:
  - dysarthria
  - paresthesia
  - diplopia
  - vertigo, balance problems
  - dystonia
- Lead fracture