PARKINSON'S DISEASE:

current aspects of ETIOLOGY, DIAGNOSIS and TREATMENT

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Parkinson's disease

Definition

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

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

James Parkinson (1817)

Milestones in Parkinson's research

- **1817:** **J. Parkinson** – "Essay on the Shaking Palsy"
- **1873:** **Charcot** – Description of the clinical picture and and first attempts at treatment
- **1919:** **Trétiakoff** – Discovery of cell degeneration in the substantia nigra as anatomical substrate
- **1957:** **Carlsson** – Discovery of dopamine deficiency in the striatum as biochemical substrate (Nobel Prize 2000)
- **1979:** **Davis** – Research into the pathological mechanism using the MPTP model
- **Ongoing** Research into genetic and neuroprotective factors

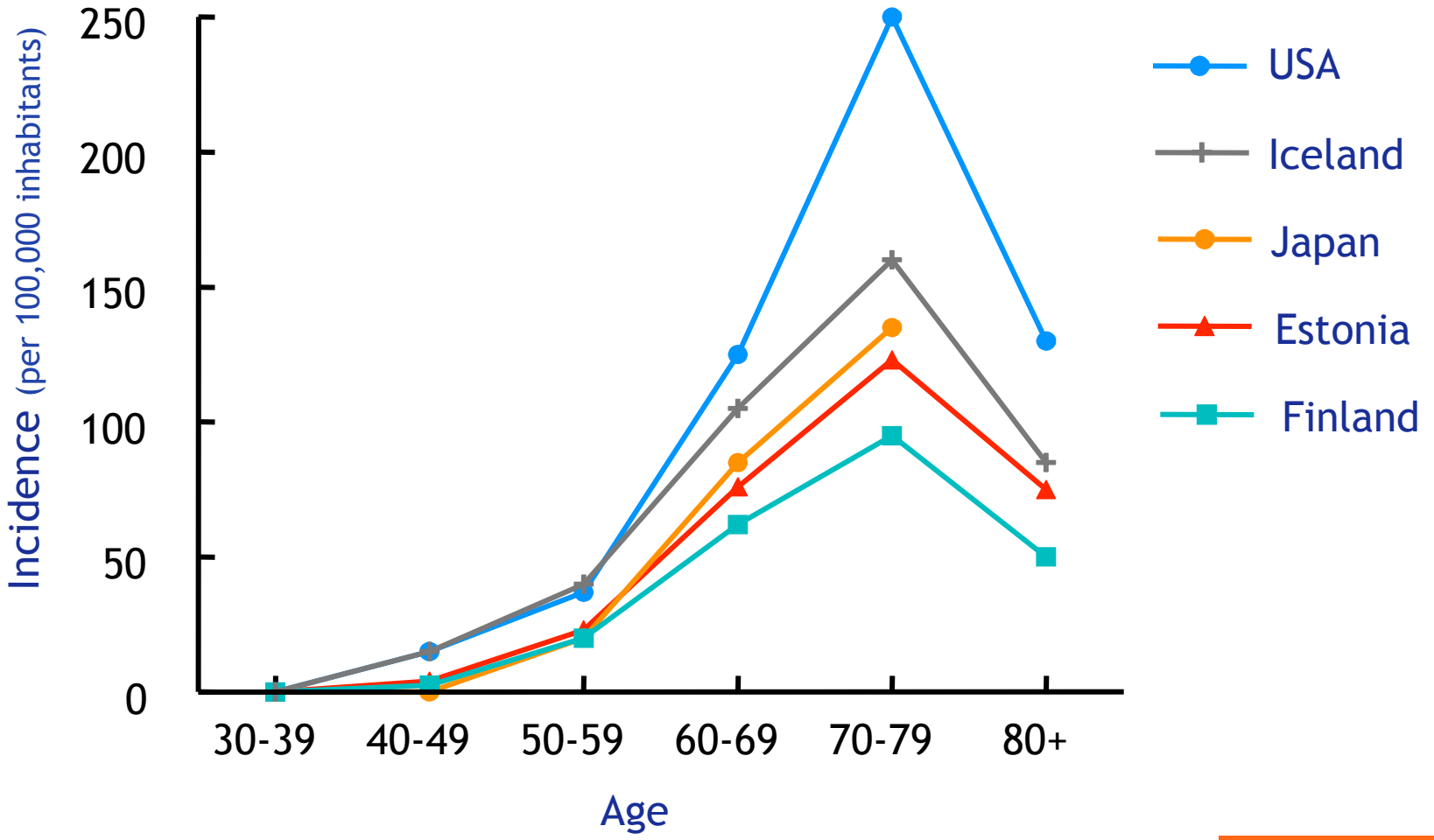
Milestones in therapy – Drug therapy

- **1946:** First synthetic **anticholinergics**
- **1961:** **Birkmayer & Hornykiewicz** – Clinical use of **L-dopa**
- **1969:** **Schwab** – Discovery of the antiparkinson effect of **amantadine**
- **1963:** **Birkmayer** – Clinical use of **L-dopa + decarboxylase inhibitor**
- **1974:** **Calne** – Introduction of **dopamine agonists**
- **1975:** **Birkmayer** – Use of **MAO-B inhibitors**
- **1997:** Introduction of **COMT inhibitors** to clinical treatment

Epidemiology – Facts

- In Europe the age-correlated prevalence (per 100,000 inhabitants) is **1.6** (Europarkinson Study, 1997)
- Roughly **1%** of all over-65s are affected
- Roughly **25%** of Parkinson patients remain undiagnosed
- Average life expectancy is slightly reduced

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



Risk factors

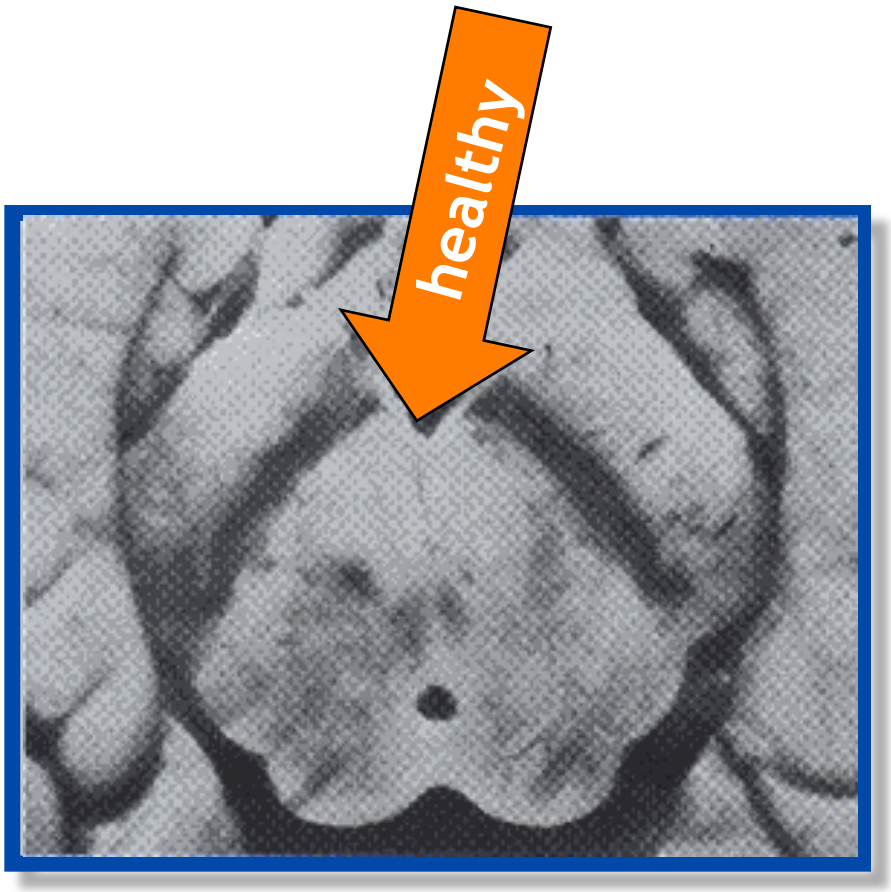
- Age
- Positive family history
- Possible: Poisoning with herbicides, pesticides, heavy metals
- Doubtful: Personality

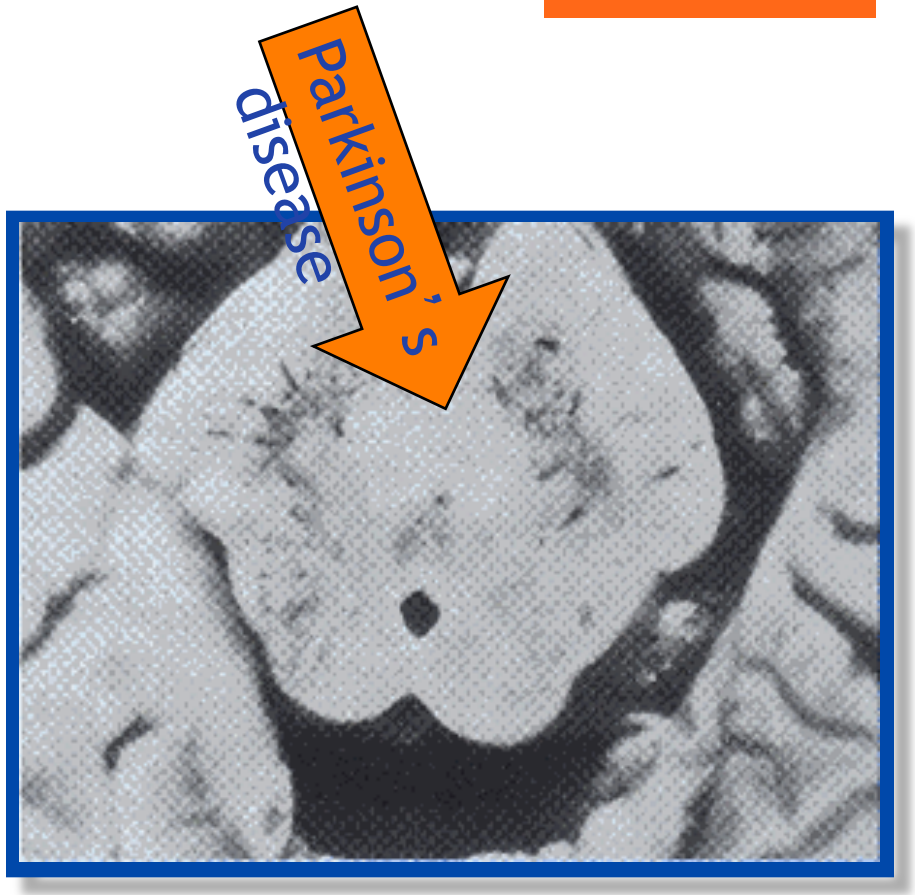
  Living in the countryside

Possible protective factors:

- Consumption of tea and coffee
- Nicotine

Cell degeneration in the substantia nigra





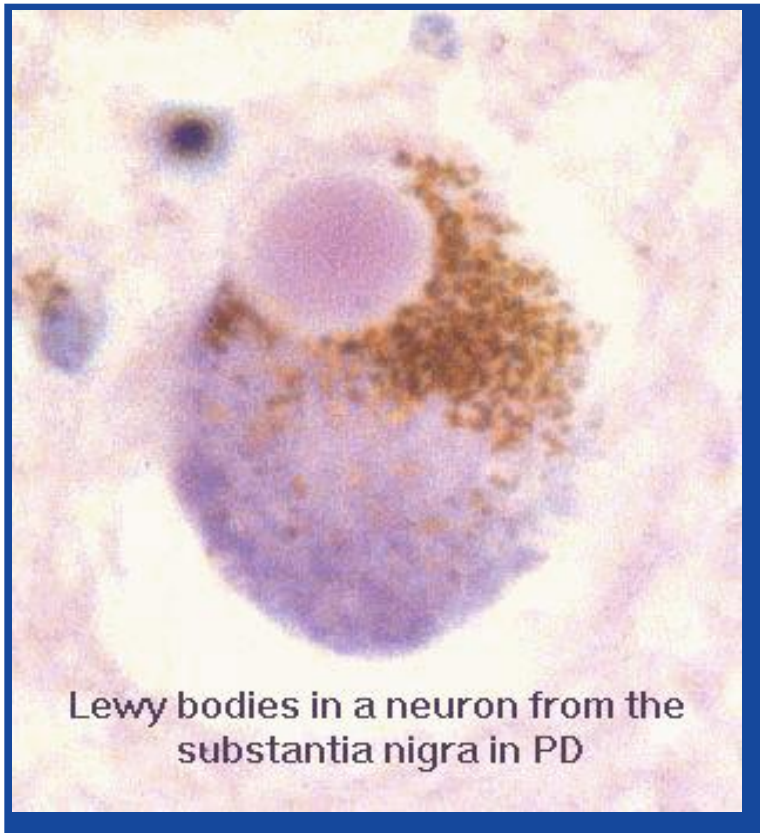
Schneider E.: Diagnostik und Therapie des M. Parkinson [Diagnosis and treatment of Parkinson's disease], de Gruyter, 1991.

Genetic causes

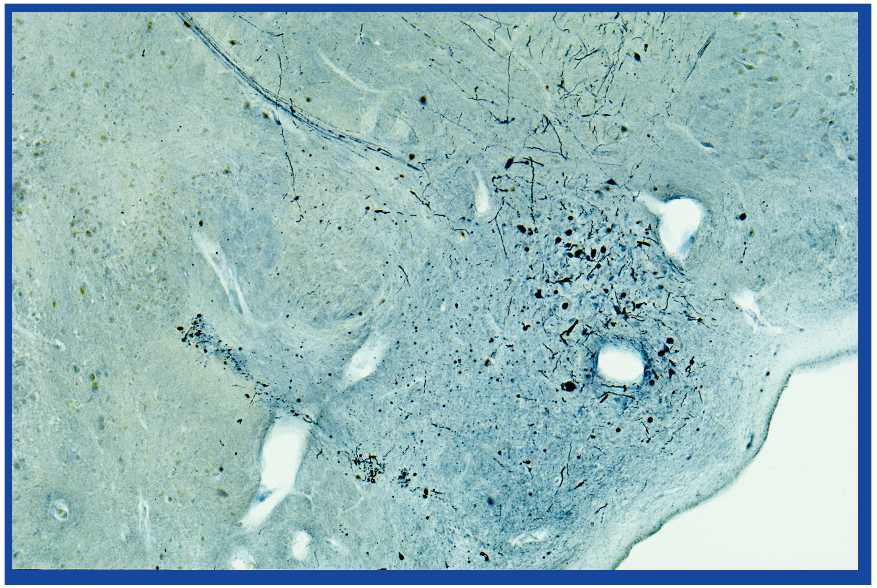
- **PARK 1**
  Locus: Chromosome 4q21
  Gene product: α-Synuclein (Polymeropoulos et al., 1997)
- **PARK 2**
  Locus: Chromosome 6q25
  Gene product: Unknown (Kitada et al., 1998)
- **PARK 3**
  Locus: Chromosome 2p13
  Gene product: Unknown (Gasser et al., 1998)

PARK 4 - 10

Lewy bodies – Microscopic findings



Lewy bodies in a neuron from the substantia nigra in PD



By kind permission of Prof. H. Braak

Center for Morphology, Frankfurt University Hospital

Lewy bodies – Pathoanatomical cascade model

(Braak et al., 2002)

Stages of Lewy body formation:

I. Dorsal vagal nucleus/olfactory bulb

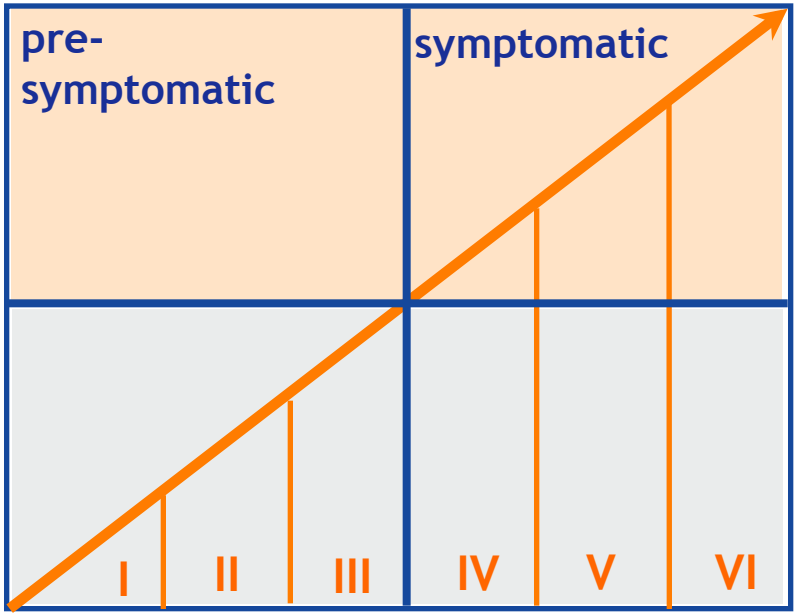
II. Brain stem/reticular formation

III. Basal prosencephalon/ amygdala/substantia nigra

IV. Mesocortex

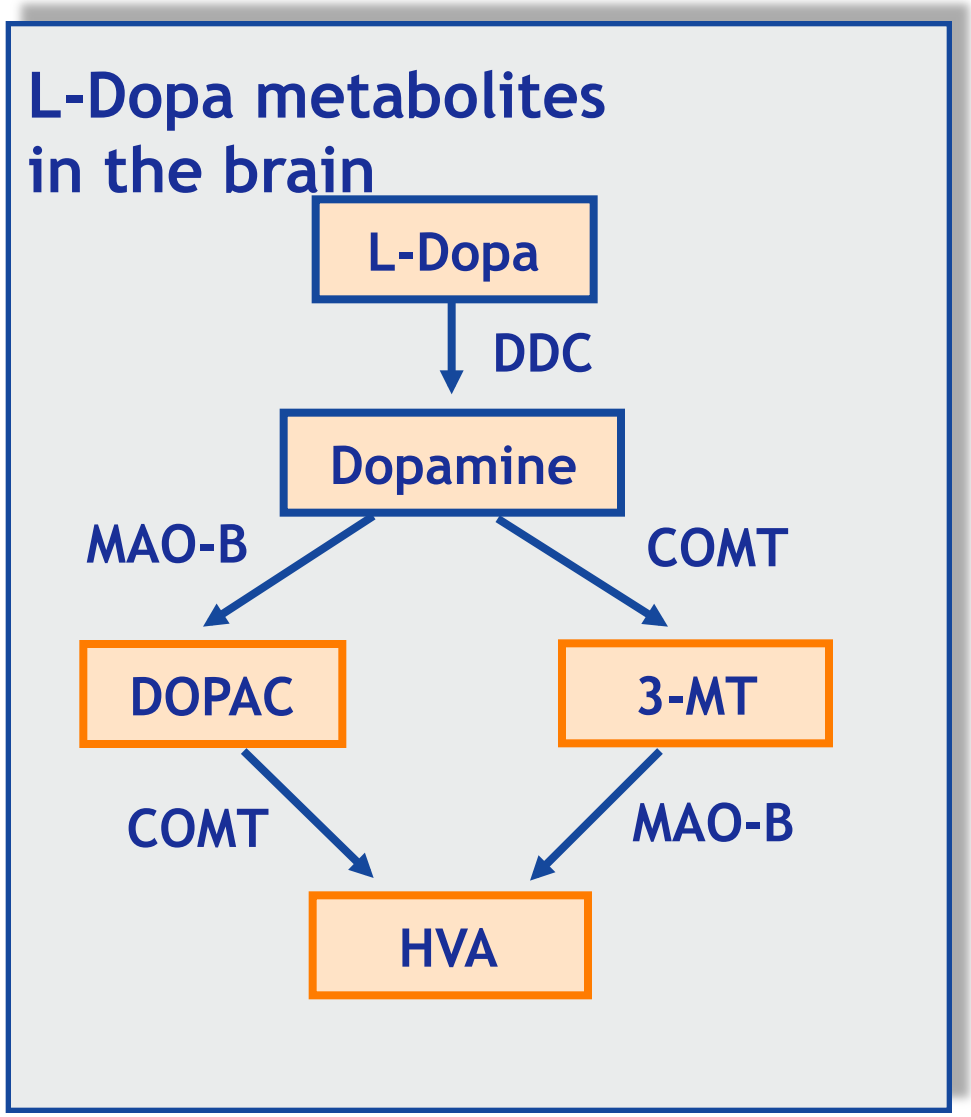
V. Neocortex – association areas

VI. Neocortex – sensory and motor areas

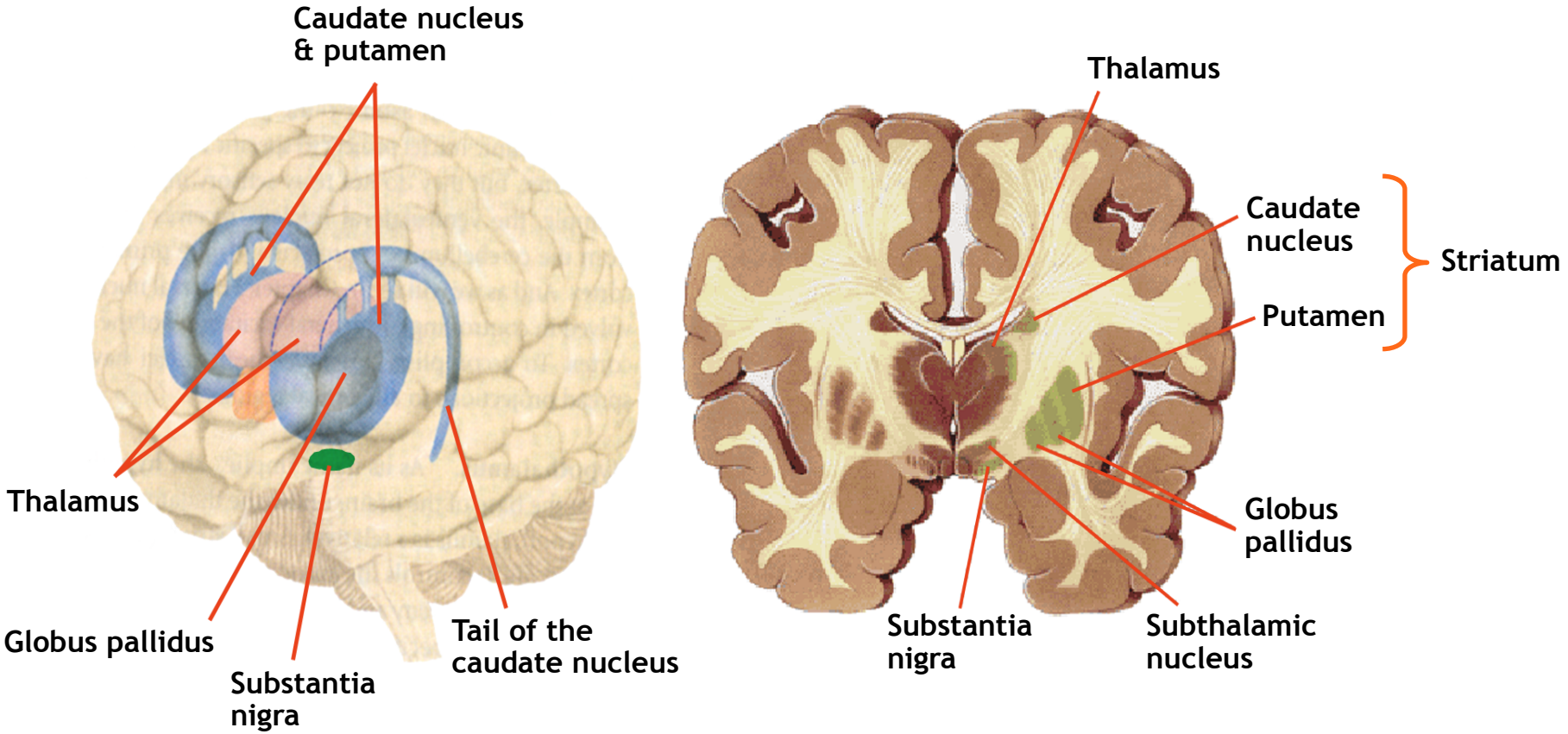


Oxidative stress

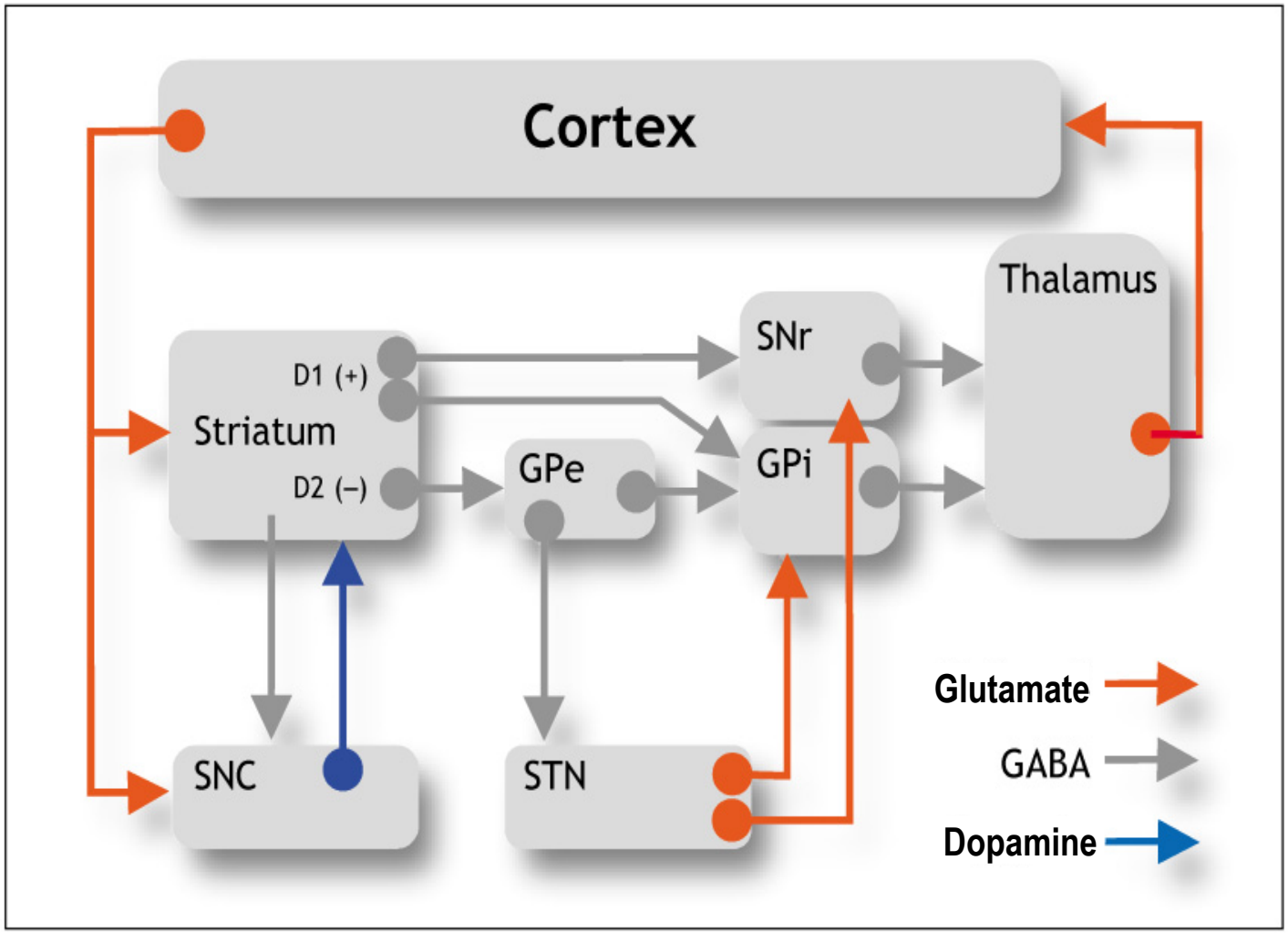
- Disturbed cell homeostasis through:
  - inefficient detoxification
  - impaired mitochondrial function
- Results:
  - increased radical formation
  - reduced ATP production
  - DNA damage


L-Dopa metabolites in the brain
L-Dopa
DDC
Dopamine
MAO-B
COMT
DOPAC
3-MT
COMT
MAO-B
HVA

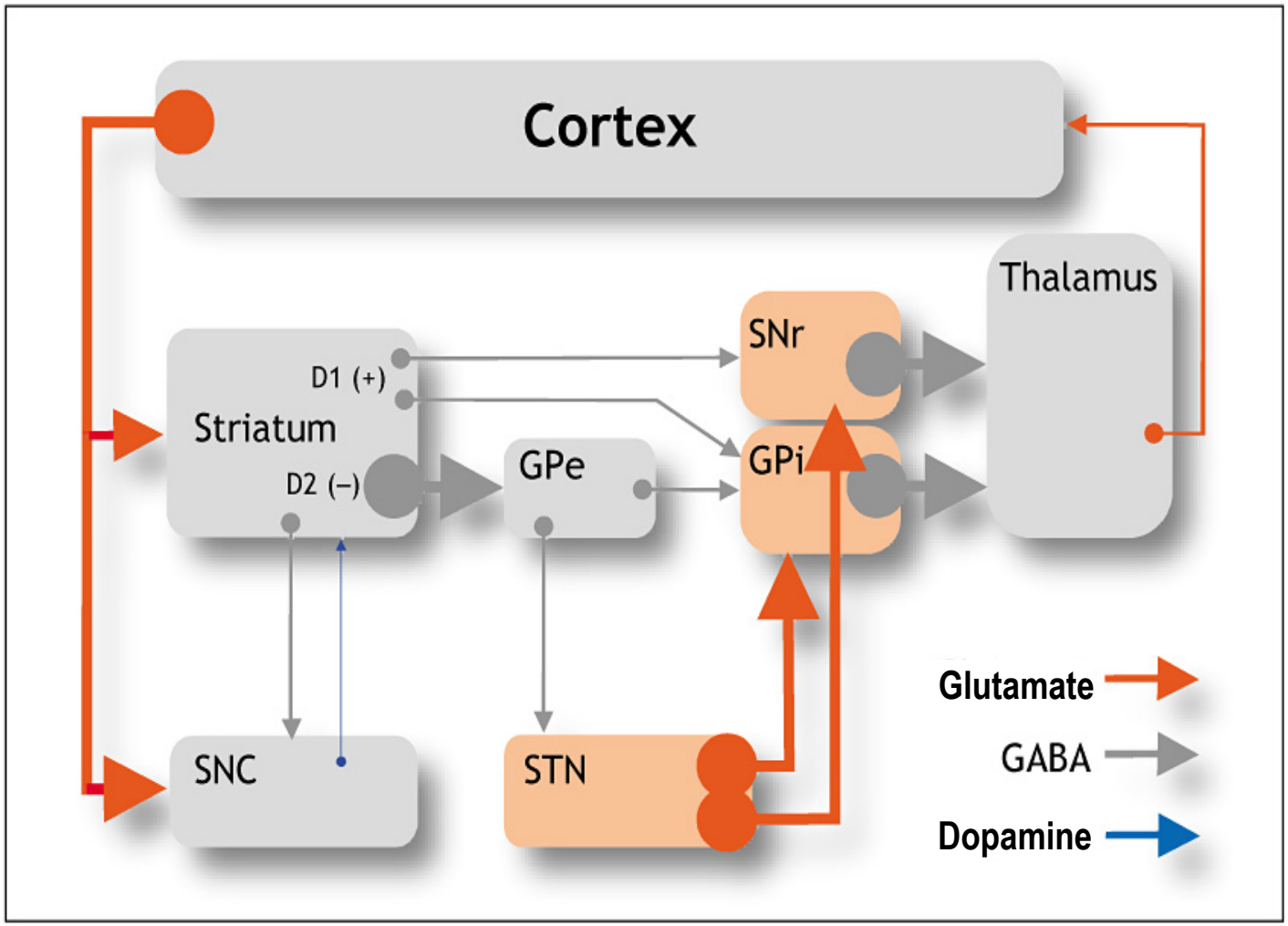
Core structures of the basal ganglia



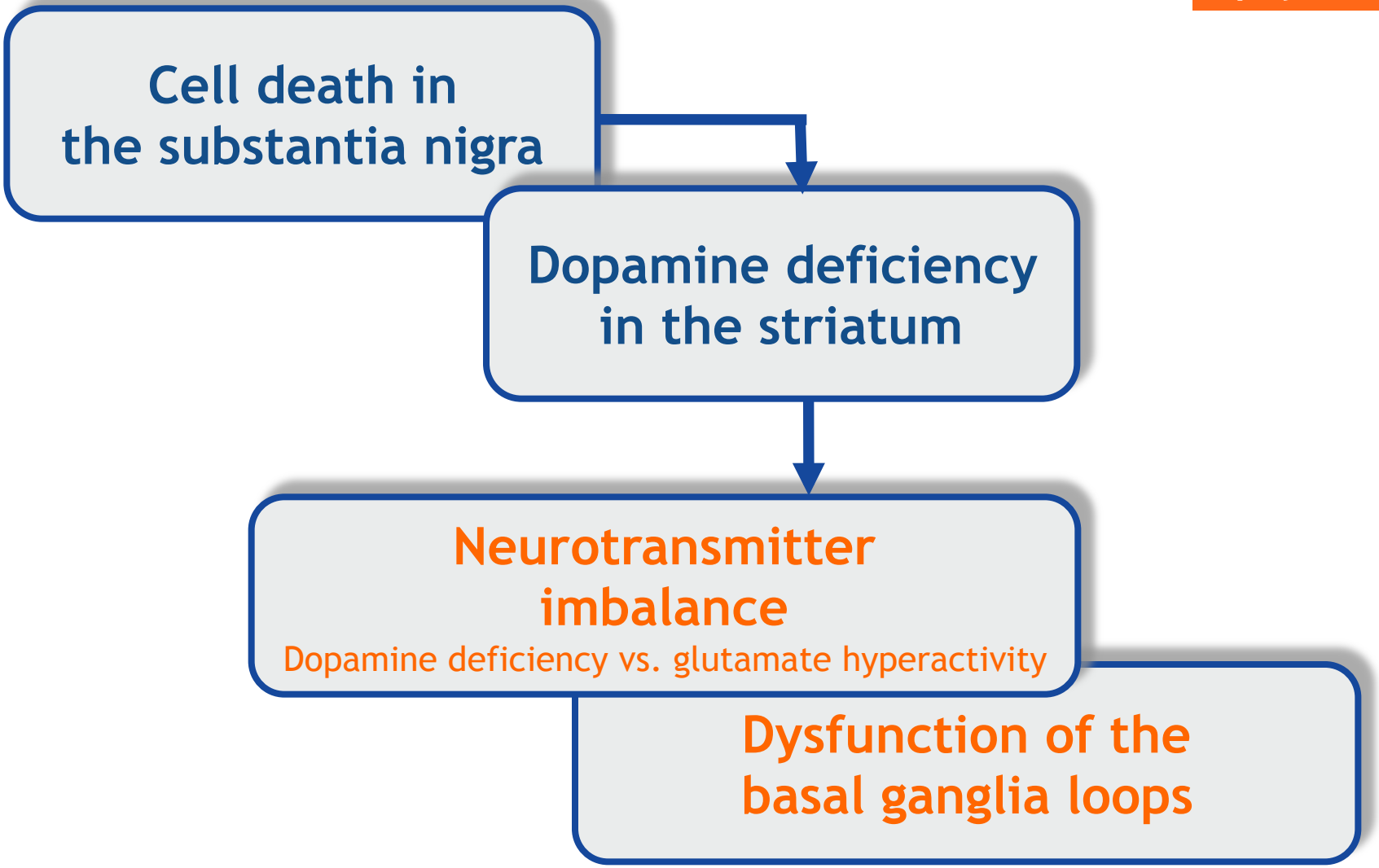
Basal ganglia loops – Physiological state



Basal ganglia loops – State in Parkinson's disease



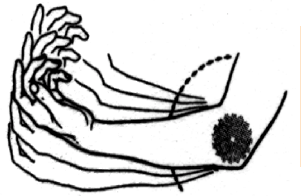
Development of Parkinson's symptoms



Main symptoms

Bradykinesia

Rigor



Tremor

Postural instability

Clinical diagnostic criteria (at least three must be satisfied)

- Unilateral onset of the disease
- Resting tremor and/or at least two of the main symptoms
- Progressive course
- Very good response to L-dopa
- L-Dopa-induced dyskinesia and fluctuations in efficacy
- No atypical signs

Gerlach, Reichmann & Riederer, Springer Verlag, 2003

Accompanying symptoms

Vegetative

- Post-encephalitic seborrhea (seborrhea)
- Sialorrhea
- Digestive disturbances
- Disturbed micturition and potency
- Orthostatic hypotension
- Disturbed thermoregulation

Psychopathological

- Depression
- Bradyphrenia
- Dementia

Exclusion criteria for Parkinson's disease

- Acute onset
- Oculogyric crises/gaze palsy
- Remission
- Neuroleptics
- Cerebellar symptoms
- Babinski's sign positive
- Early signs of dementia or autonomic dysfunction
- No response to L-dopa

Gerlach, Reichmann & Riederer, Springer Verlag, 2003

Parkinson Plus syndrome I

- Multisystem atrophy
  - Cerebellar symptoms (disturbances of equilibrium, unsteady gait, coordination disturbances) **or**
  - Autonomic disturbances (drop in blood pressure, bladder disorders, impotence)

- Progressive supranuclear gaze palsy
  - Postural instability as an early symptom
  - Vertical gaze palsy (upwards or downwards)
  - Unsteady gait
  - Symmetrical symptoms
  - No resting tremor

Parkinson Plus syndrome II

- Lewy body dementia
  - Early development of dementia
  - Fluctuating psychotic symptoms
  - Agitation
  - Paradoxical neuroleptic sensitivity
- Corticobasal degeneration
  - Dystonia (mainly flexion dystonia of the arm)
  - Irregular, unilateral tremor
  - "Alien limb" phenomenon
  - Cortical sensitivity disturbances
  - Pyramidal tract signs

Secondary (symptomatic) parkinsonism

Drug-induced:

- Neuroleptics
- Antihypertensives
- Antiemetics
- Cerebral calcium-channel blockers

Reversible

Toxic in origin:

- Carbon monoxide
- Lead
- Manganese
- Cyanide
- Methanol
- MPTP

Not progressive

Other etiology:

- Metabolic
- Postencephalitic
- Traumatic
- Compressive

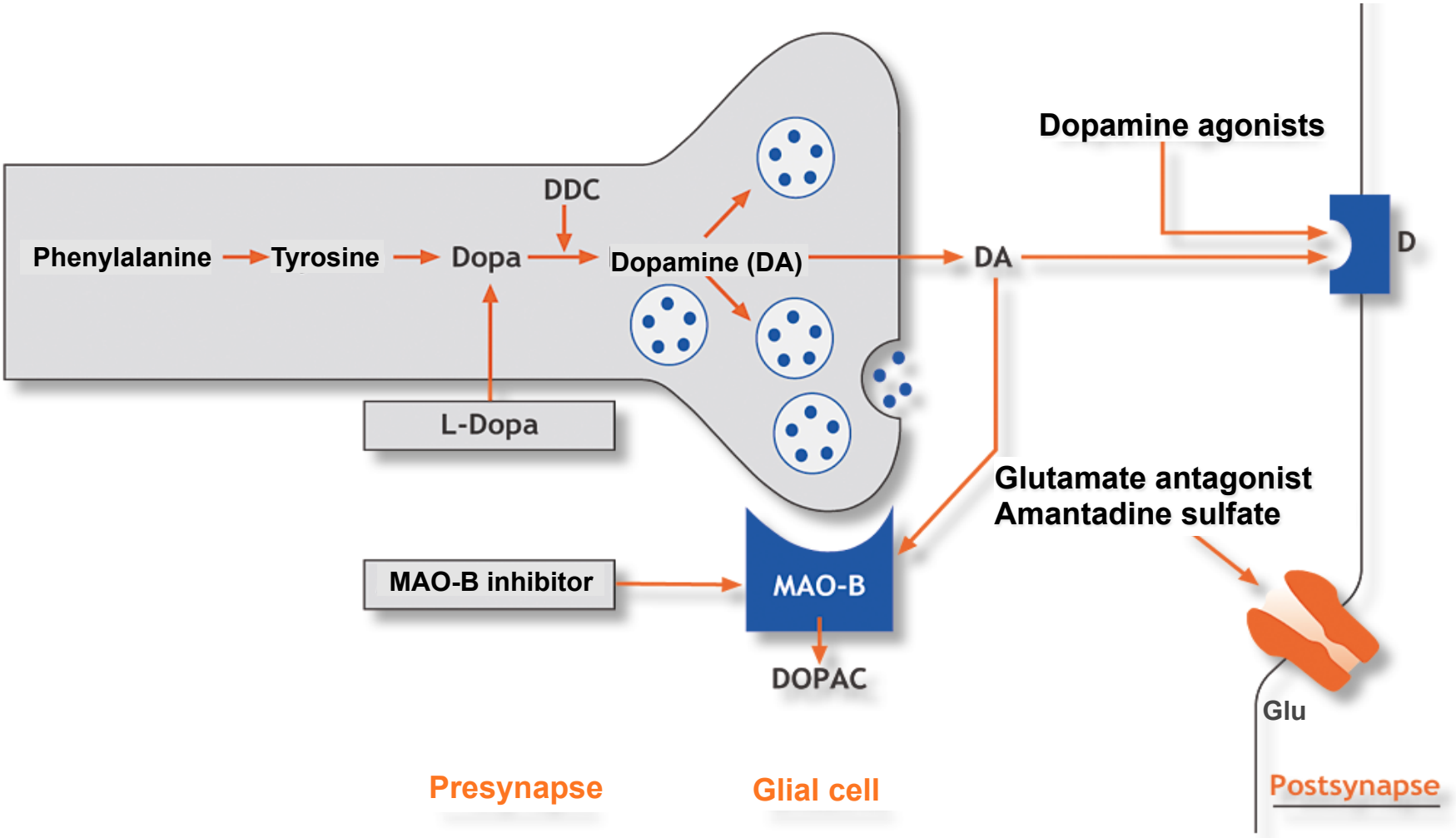
Treatable

Therapeutic options – Drug therapy

- L-Dopa therapy/dopamine agonists
  - Dopamine replacement

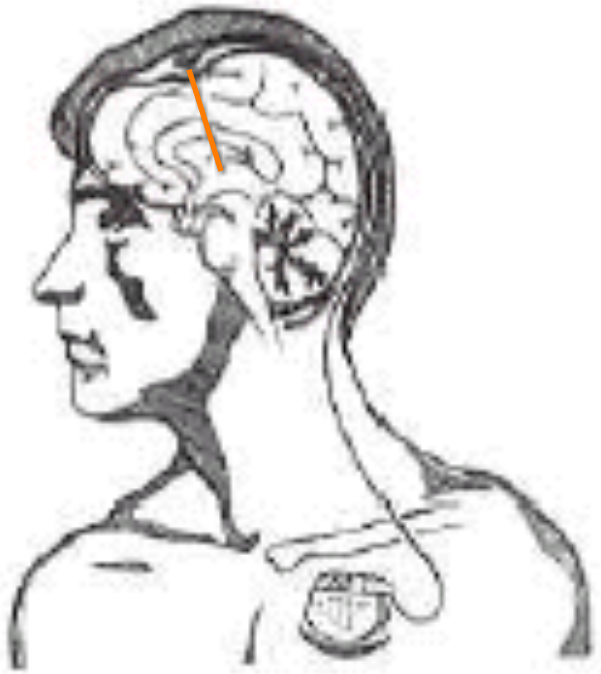
  Glutamate antagonist (amantadine)
  - Inhibition of glutamatergic hyperactivity
- MAO-B inhibitors
  - Central inhibition of dopamine breakdown
- COMT inhibitors
  - Peripheral inhibition of L-dopa breakdown

Points of attack of drug therapies



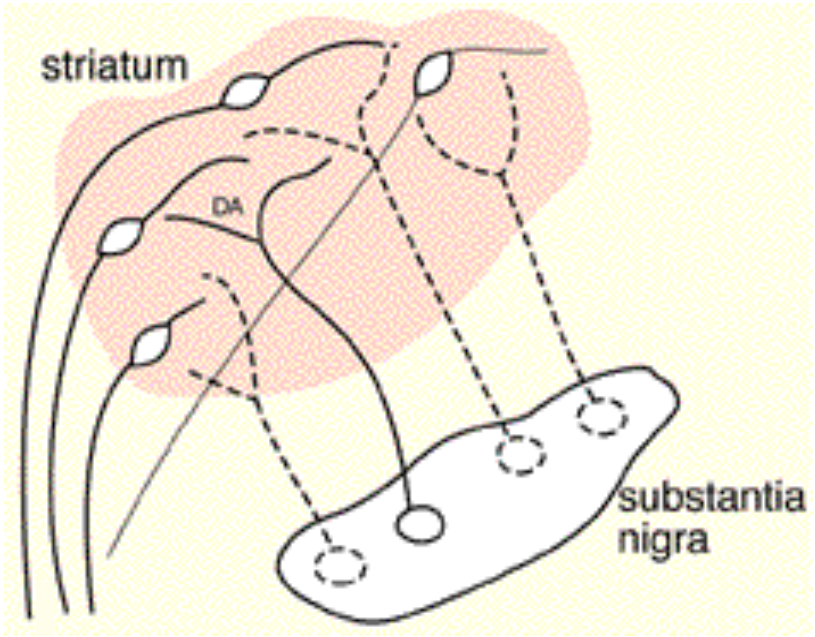
Therapeutic options – Deep brain stimulation

- Hyperstimulation (120 Hz) in affected regions of the brain:
  - Subthalamic nucleus
  - Globus pallidus
  - Thalamus
- Symptom and drug reduction
  - Tremor
  - Hypo-/hyperkinesia
  - L-Dopa-sparing effect
- Invasive, reversible

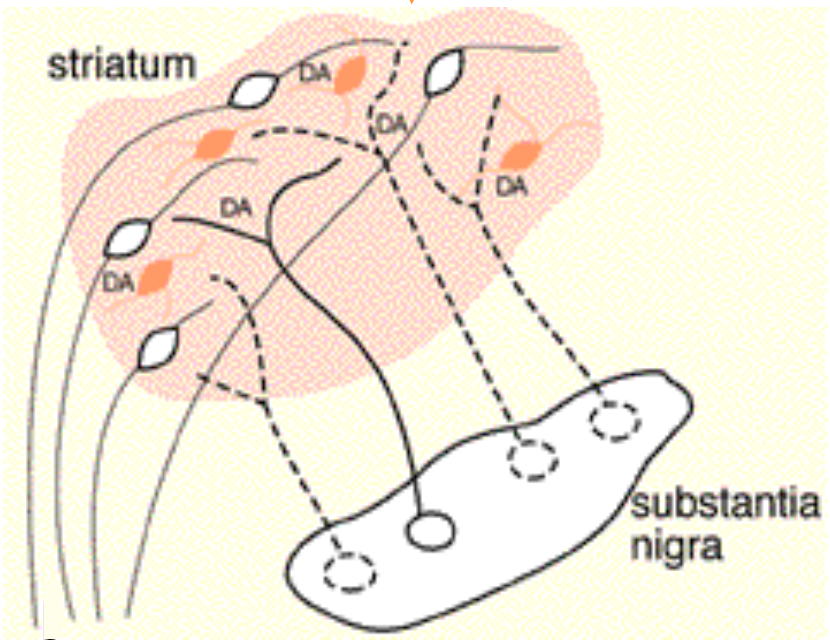


Therapeutic options – Transplantation

TRANSPLANTATION



Decrease in dopaminergic input in the striatum



Dopaminergic reinnervation of the striatum

OTHER MOVEMENT DISORDERS

Movement disorders

- Hyperkinetic

Chorea

Ballism

Tremor

Myoclonus

Tics

dystonia

- Hypokinetic

Parkinsonism: PD and All Parkinsonian Syndromes

DYSTONIA

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting movements and postures (Fahn 1987). Agonist and antagonist muscles contract simultaneously to produce the abnormal postures of dystonia. Dystonic movements may be slow and continuous, or fast and brief.

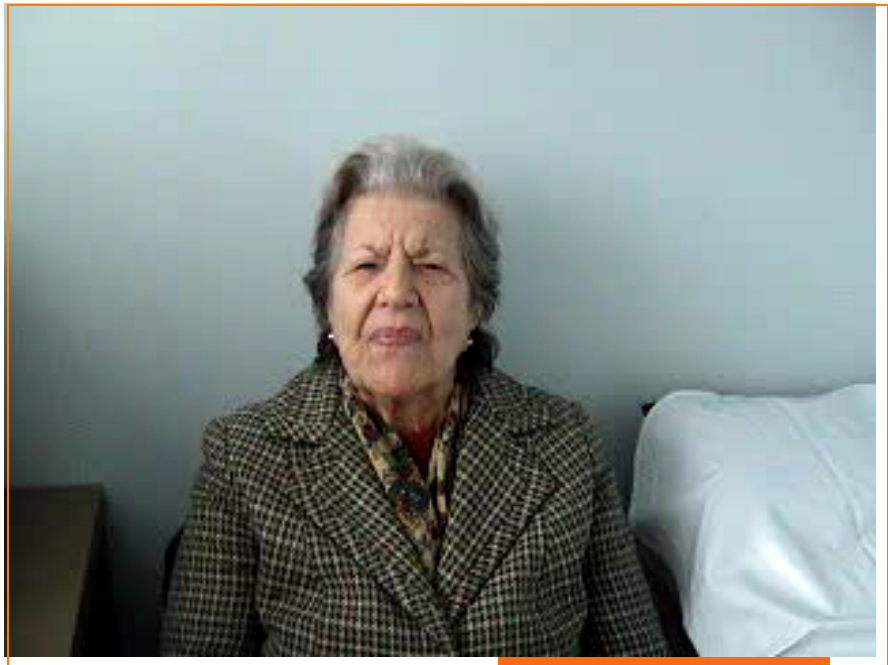
Dystonia may be **classified by**

•*age of onset,*

•*distribution* and

•*etiology*.

By region of distribution, dystonia is subdivided into *focal, segmental, hemi-body, and generalized* dystonia. Childhood-onset dystonia may begin in a body part, presenting as focal dystonia, but typically becomes generalized, especially if the underlying cause is a genetically-based or metabolic disorder



CHOREA

•**Chorea,** from the Greek word meaning *dance*, describes involuntary, random, abrupt, rapid, arrhythmic, unsustained movements and twitches that seem to flow from one body part to another.

•The timing, direction, and distribution of choreic movements varies from moment to moment, and cannot be predicted by an observer.

chorea

ATHETOSIS

Athetosis, meaning "no fixed position," describes a pattern of continuous writhing movements.

First coined by Hammond in 1871, the original description of athetosis was "an inability to retain the fingers and toes in any position in which they may be placed."

Athetosis is often linked with chorea, as in *choreoathetosi*s, to give a sense of its continuous, writhing, twisting aspect. Athetoid movements affect the limbs, especially **distally, but also the trunk and cranial structures.**

MYOCLONUS

Myoclonic jerks are sudden, brief muscle contractions that produce a simple quick movement. Myoclonic jerks may be repetitive and rhythmic or random and unpredictable.

Myoclonus may occur at rest, with posture-holding, directed movement (“action myoclonus”), or be triggered by external stimuli (“reflex myoclonus”), whether auditory, visual or tactile.

Myoclonus may be classified on the basis of

1. its distribution:focal, segmental, multifocal, or generalized or
2. site of origin: cortex, brain stem, spinal cord

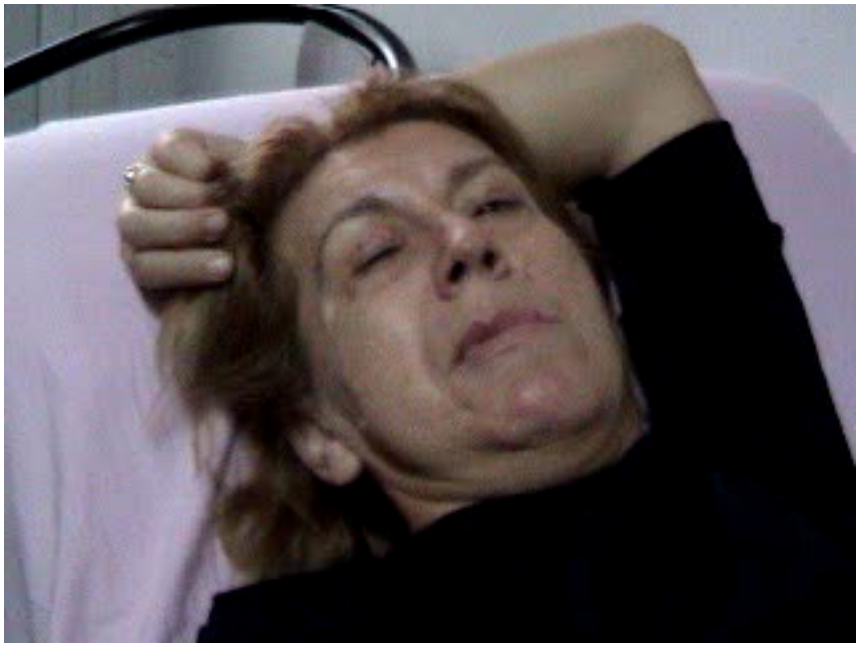
- **HEMIFACIAL SPASM:**

involuntary tonic or clonic contraction of muscles innervated by 7th cranial nerve

Idiopathic / vascular compression of facial nerve

treatment: BTX-A

pharmacologic agents



TREMOR

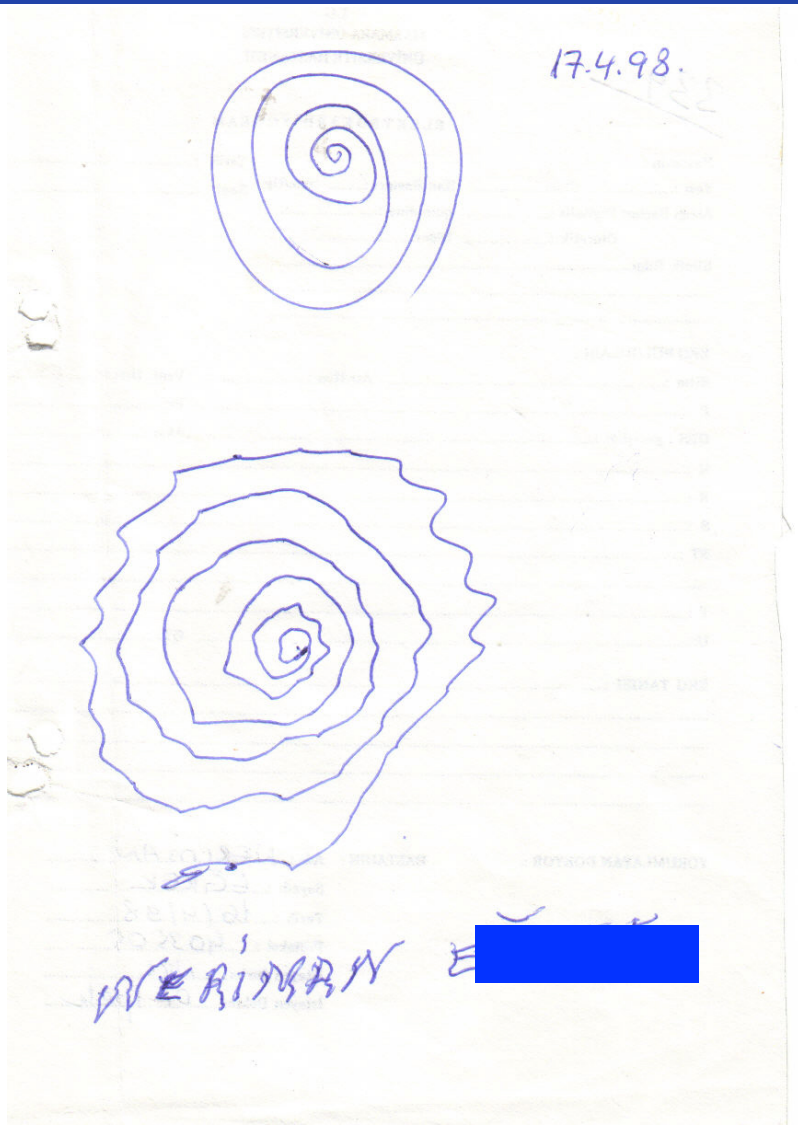
Tremor is a regular, rhythmic oscillation of one or more body parts produced by alternating or synchronous contractions of opposing muscles.

Phenomenologically, tremors are classified according to two main categories:

1. *tremors at rest* and
2. *tremors with action*.

•Rest tremors occur
when the affected body part is in complete repose, and fully supported. The classical tremor of parkinsonism is a tremor at rest.

•Action tremors occur with voluntary muscle contractions, and are subdivided into **postural, kinetic, task- or position-specific, and isometric tremors**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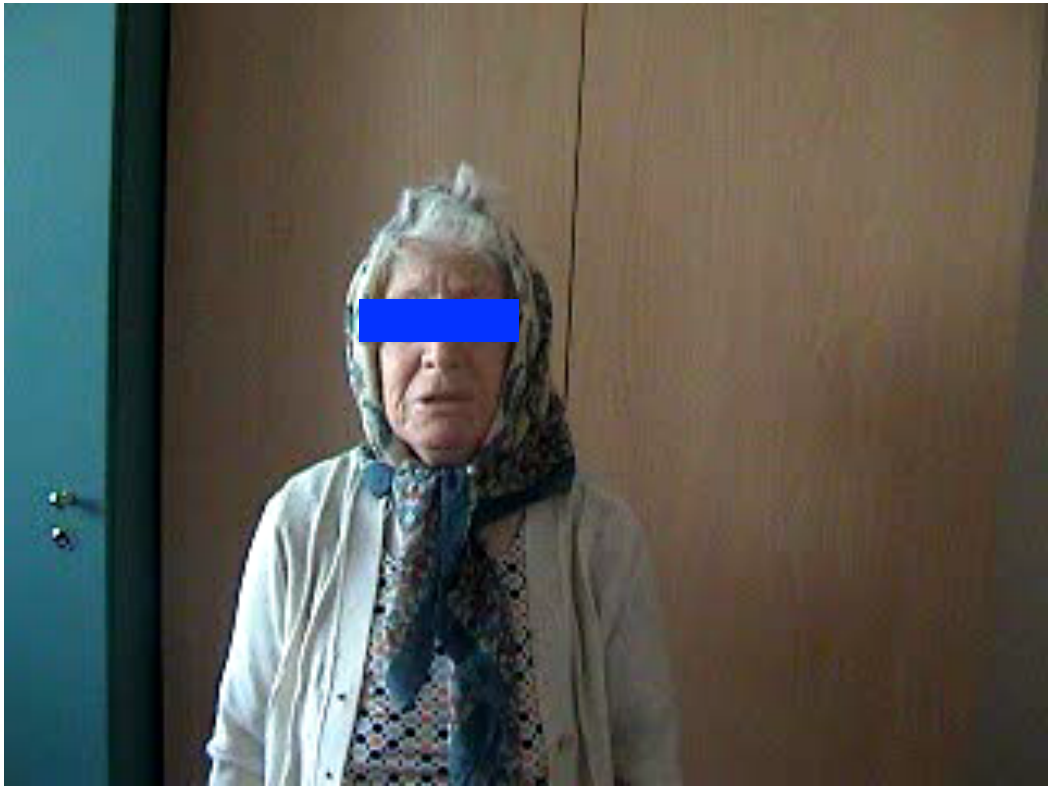

TICS

Tics are repetitive, stereotyped movements or phonations that occur abruptly against a background of normal motor activity and behavior.

Most tics are simple movements, such as an abrupt stereotyped ocular deviation, blink, facial grimace, or shoulder shrug.

Complex tics consist of coordinated patterns of sequential movement.

Tics are purposeless movements that are often preceded by an *inner urge or tension that is relieved by allowing the movement to occur.*

- **WILSON'S DISEASE**

curable movement disorder

AR, on chr 13q14.3 (Cu transporting ATPase)

failure to excrete Cu --- systemic Cu poisoning

- intestinal absorption is normal
- reduced biliary excretion
- result: increased Cu excretion in urine

initially Cu accumulates in liver

then in brain, eye, kidney, bones and blood tissues.

Symptoms: ages of 11-55 year

clinical types: 1. Akinetic-rigid syndrome

2. Generalized dystonic syndrome

3. Tremor+ ataxia+ dysarthria: pseudosclerotic

- **Diagnosis:** 24 hr urine cu excretion
- liver biopsy
- MRI
- genetic study
- **Treatment of Wilson disease**
- D-penicillamine + pyridoxine
- trientine
- Zinc
- BAL ?
- LIVER TRANSPLANTATION

HUNTINGTON'S DISEASE

- AD, chorea + dementia
- genetic defect: excessive trinucleotide repeat of CAG
- defected protein called huntingtin
- no established therapy
- symptomatic treatment

SYDENHAM'S CHOREA

- beta hemolytic streptococcus induced autoimmune disorder
- between ages of 5-15 years
- outcome is favorable
- prophylactic penicillin therapy prevents recurrences