

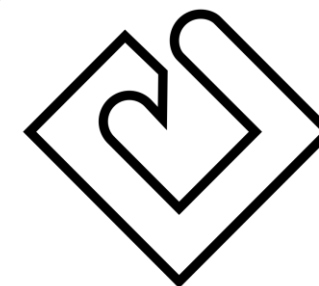
Parkinson Disease

from cell to clinic...

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NeuroMaPC

Center for Neuromodulation and Pain

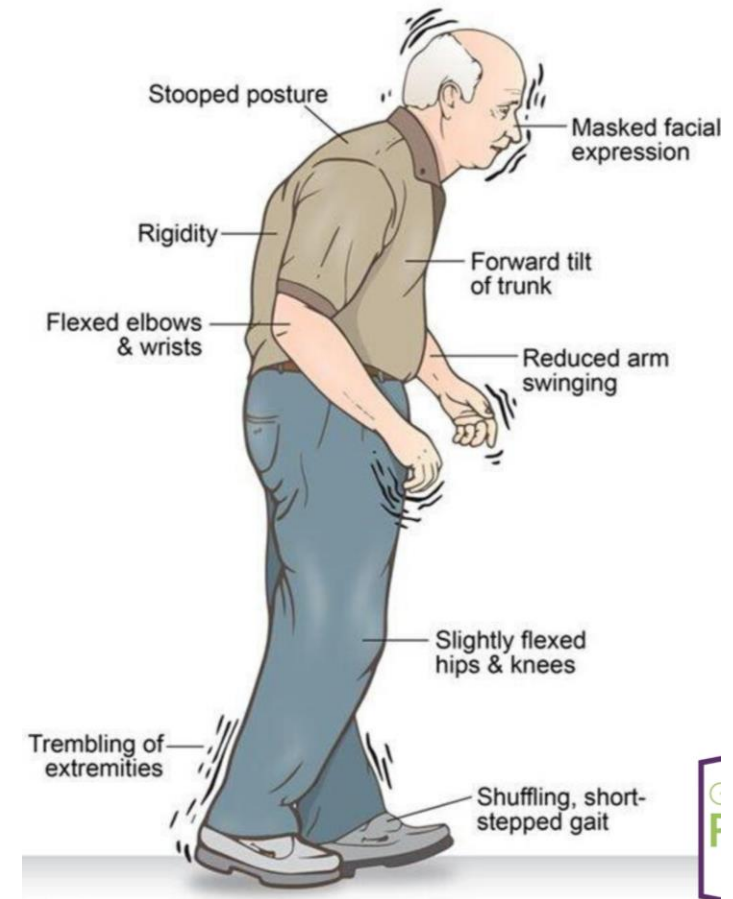
The Parkinson Disease

- **James Parkinson** on his “*Essay on the Shaking Palsy*” in **1817**
 - Rest tremor + Stooped posture + Excessive salivation + Festination
- **Charcot’s** lectures in **1860s**
 - Added Rigidity and Akathisia to the list
- In **1893** the main features were added as separate characteristics
 - **Rigidity**: fixity of limbs and motions
 - **Bradykinesia**: slowness of movements
- **1960s**
 - Discovery of **L-Dopa**, a potent drug for treatment of PD
- **1980s**
 - **IV drug addicts** injecting **MPTP** developed **profound and irreversible PD**
 - Development of “**Rate model**” for pathophysiology of PD



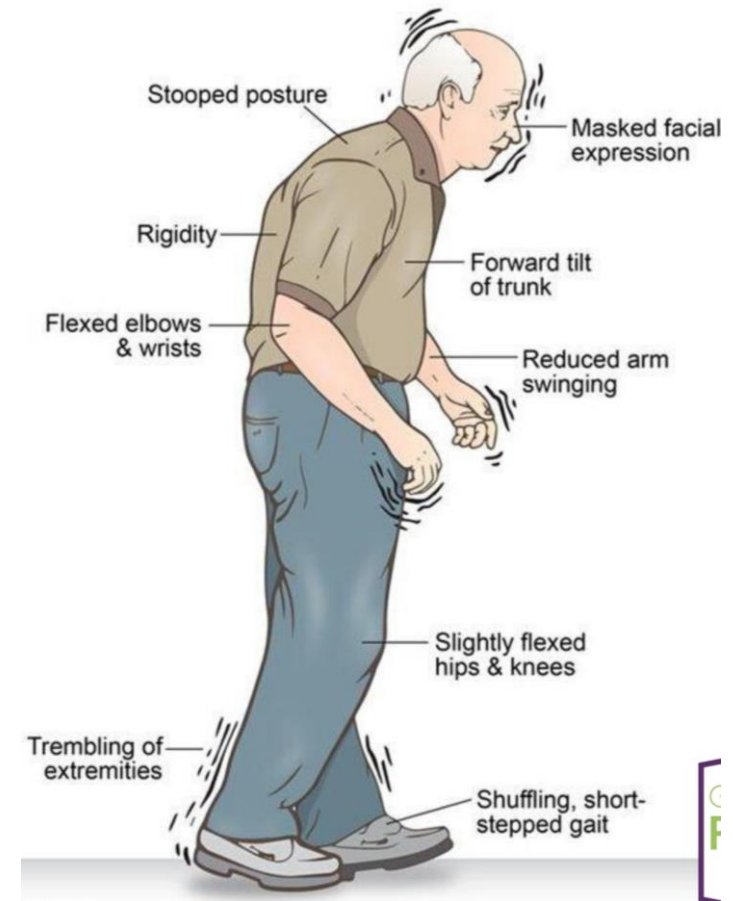
The Parkinson Disease

- **Four cardinal features**
 - **Bradykinesia**
with any of the below signs
 - **Rest tremor**
 - **Rigidity**
 - **Posture and gait instability**
- **Other important clinical features**
 - **Loss of automaticity**
 - **Increased need for voluntary control** in simultaneous movements (impairment in **procedural learning**)

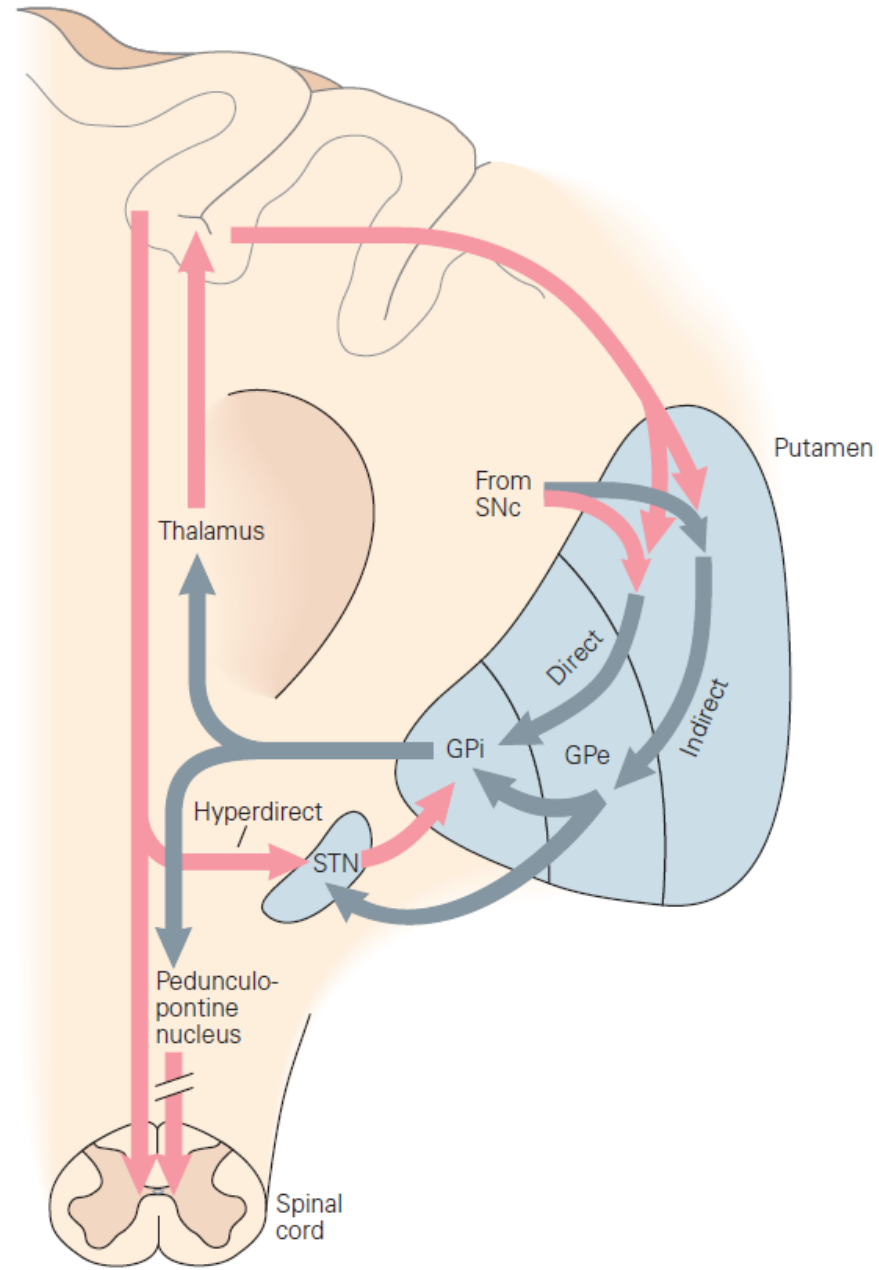


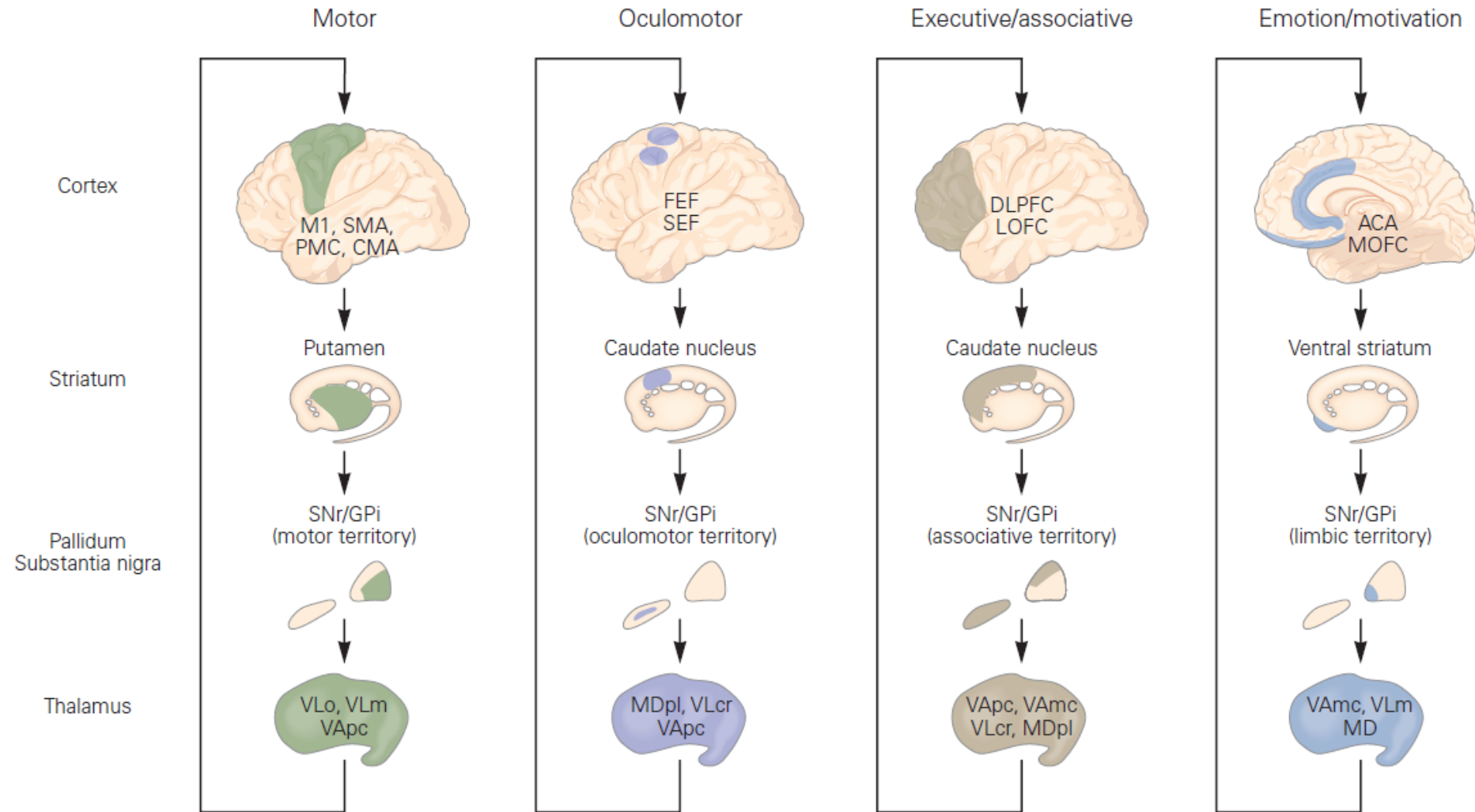
The Parkinson Disease

- **Nonmotor features**
 - **Cognitive impairment**
 - **Mood disorders**
 - Depression
 - Anxiety
 - **Sleep disturbances**
 - **Autonomic dysfunction**



The Basal Ganglia Functional Circuitry





Motor

Cognitive

Limbic

The Parkinson Disease

- **Pathophysiology**
- **Degenerative disorder of the CNS**
 - **Dopaminergic system**
 - **Mostly affected** system in the basal ganglia circuits
 - Responsible for **motor features** of the disease
 - **Other widespread systems** in the CNS
 - Less affected
 - Responsible for other features of the disorder

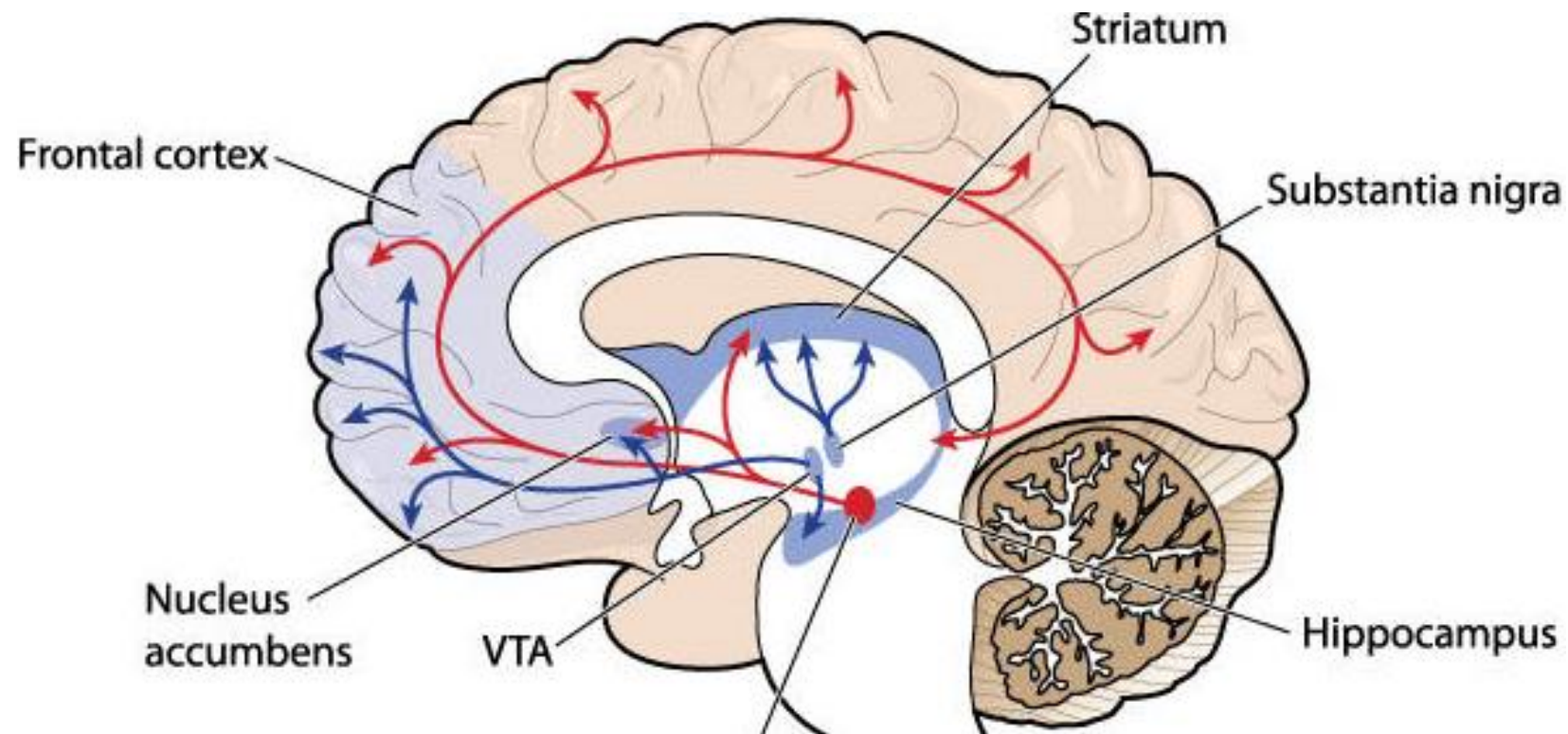


Dopaminergic Projections to The Striatum

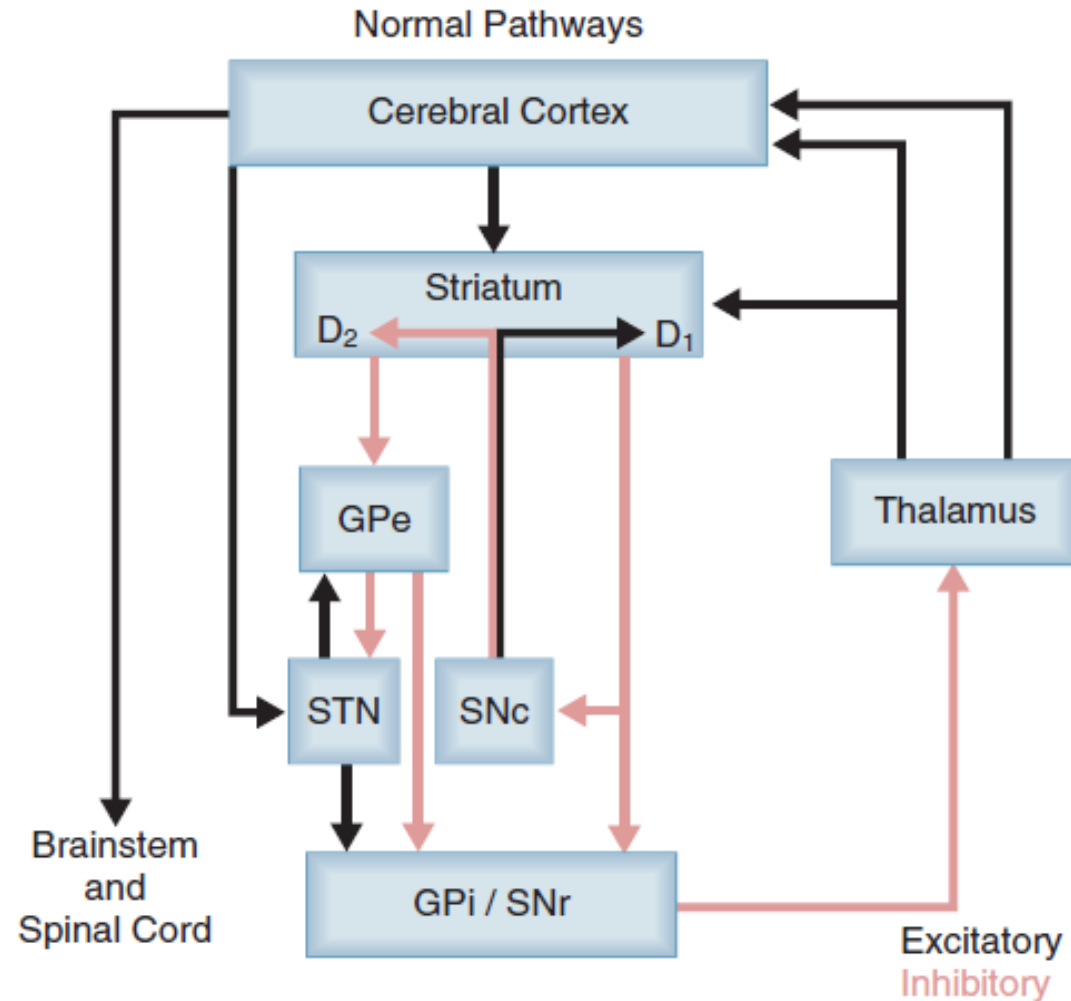
- **Dopaminergic neurons in the ventral midbrain**
 - I. **Retrosubthalamic field (RRF; A8 group)**
 - II. **Substantia nigra pars compacta (SNc; A9 group)**
 - III. **Ventral tegmental area (VTA; A10 group)**



Dopaminergic Projections to The Striatum



Dopaminergic Projections to The Striatum



Dopaminergic Projections to The Striatum

- **Nigro-striatal dopaminergic projections**
 - **Functionally segregated** projections from cortical areas to the striatum
 - **Motor**
 - **SNc-v** >>> Post-commissural putamen
 - **Limbic**
 - **SNc-d and VTA** >>> Nuc. Accumbens
 - **Associative/cognitive**
 - **SNc-v** >>> Caudate n. and Pre-commissural putamen



Dopaminergic Projections to The Striatum

- **Nigro-striatal dopaminergic projections roles**
 - I. **Neuromodulation** of glutamatergic and cholinergic transmissions in the striatum
 - **Pre-synaptically**
 - **Post-synaptically**
 - II. Regulating the **abundance** and **plasticity** of dendritic spines on **D2-expressing MSNs**



Dopaminergic Projections to The Striatum

- **Dopaminergic modulation in Striatal projection neurons**
 - **Acute**
 - **Potentialiation in dMSNs (via PKA-associated pathway)**
 - **Depression in iMSNs (via PKC-associated pathway)**
 - **Long-term**
 - **LTD in iMSNs**
 - **LTP in dMSNs**



Dopaminergic Projections to The Striatum

- **Selective and sequential** denervation in Parkinson's disease
 - **VTA** projections degeneration **much less** than **SNc** projections
 - **Motor** projections **before** limbic and associative ones

- **SNc-v (ventral tier)**
 - **Low** levels of **Calbindin**
 - **Preferential vulnerability** in Parkinson's disease



Dopaminergic Projections to The Striatum

- Symptoms present when
 - **~30%** loss in SNc dopaminergic **neurons**
 - **~50%** loss in striatal dopaminergic **axons**
 - **~80%** loss in striatal **dopamine content**



Dopaminergic Projections to The Striatum

- **Homeostatic plasticity** in striatal circuitry in **Parkinson disease**
 - **Presynaptically**
 - ▼ in DA concentration and constancy – surges following DA therapy
 - Dopamine release from 5-HT cells
 - **Postsynaptically**
 - **Supersensitivity** (hyperexcitability) of DA receptors – more in D1-MSNs
 - **Structural changes**
 - **Pruning** of dendritic spines – selectively D2-MSNs

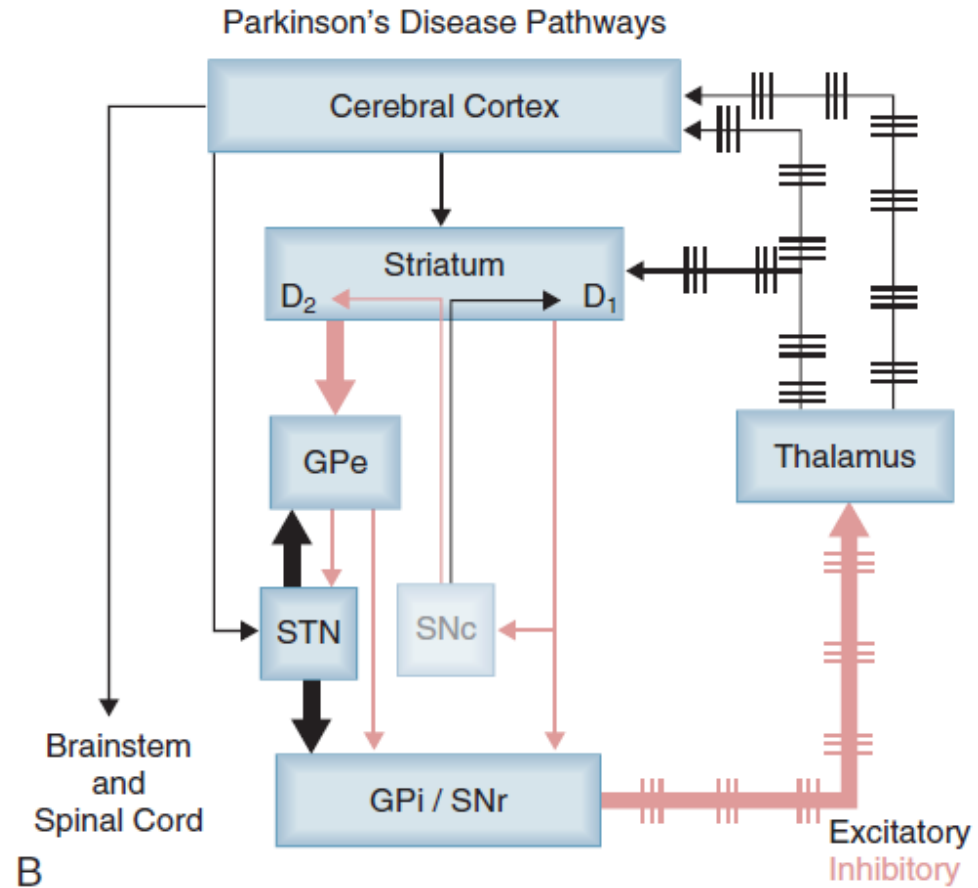
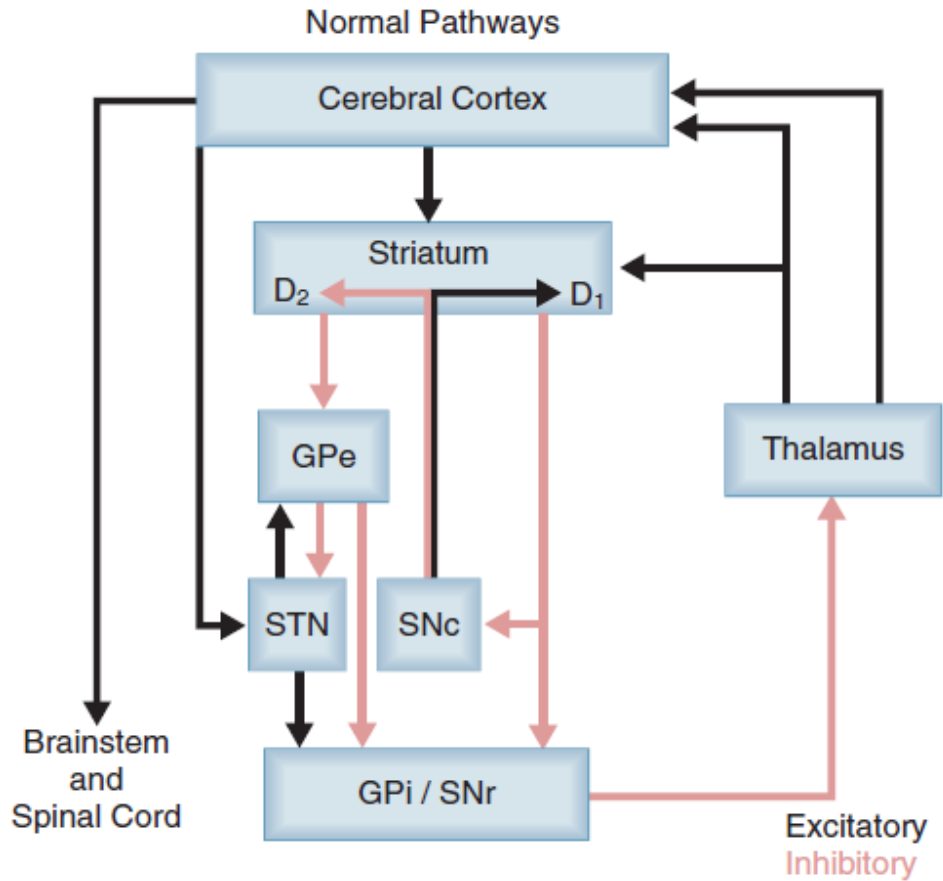


The Parkinson Disease

- **Pathophysiology**
- **Abnormalities in basal ganglia circuits**
 - **Abn. in “firing rate”**
 - **Decreased** activity in the “**direct pathway**”
 - **Increased** activity in the “**indirect pathway**”
 - **Abn. in “firing patterns”**
 - **Abn. Beta-band** synchronized oscillations ▲
 - **Normal gamma-band** oscillations ▼



The Parkinson Disease



The Parkinson Disease

- **Pathophysiology**
- **Abnormalities in firing patterns esp. in the “indirect pathway”**
 - ▲ High amplitude **beta-band (10-30Hz)** synchronized oscillations in
 - **STN**
 - **GPi / SNr**
 - **Frontal motor cortices**
 - ▼ Normal **gamma-band (60-90Hz)** oscillations in **frontal cortices**

Early PD:

1. ▼ Dopamine reserve due to ▼ dopamine nerve terminals in striatum
2. Dependence on L-dopa
3. Conversion to dopamine and storage >>> Release

After 5-10 years:

1. Further nerve terminal loss and ▼ in vesicular storage capacity
2. Shortening of response time to L-dopa
3. “**Wearing off**” phenomenon and “**Motor fluctuations**”

Progressive stage:

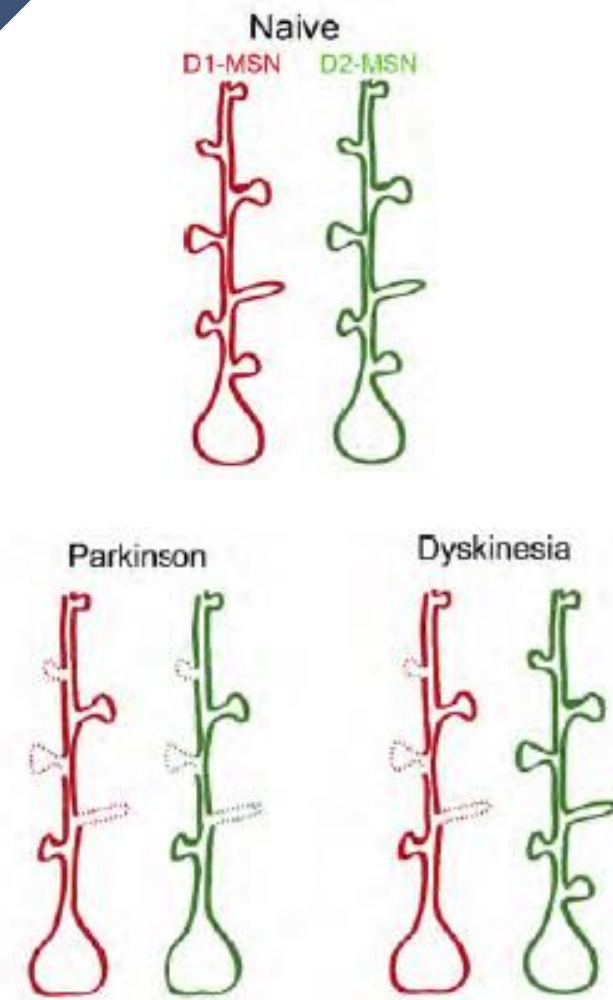
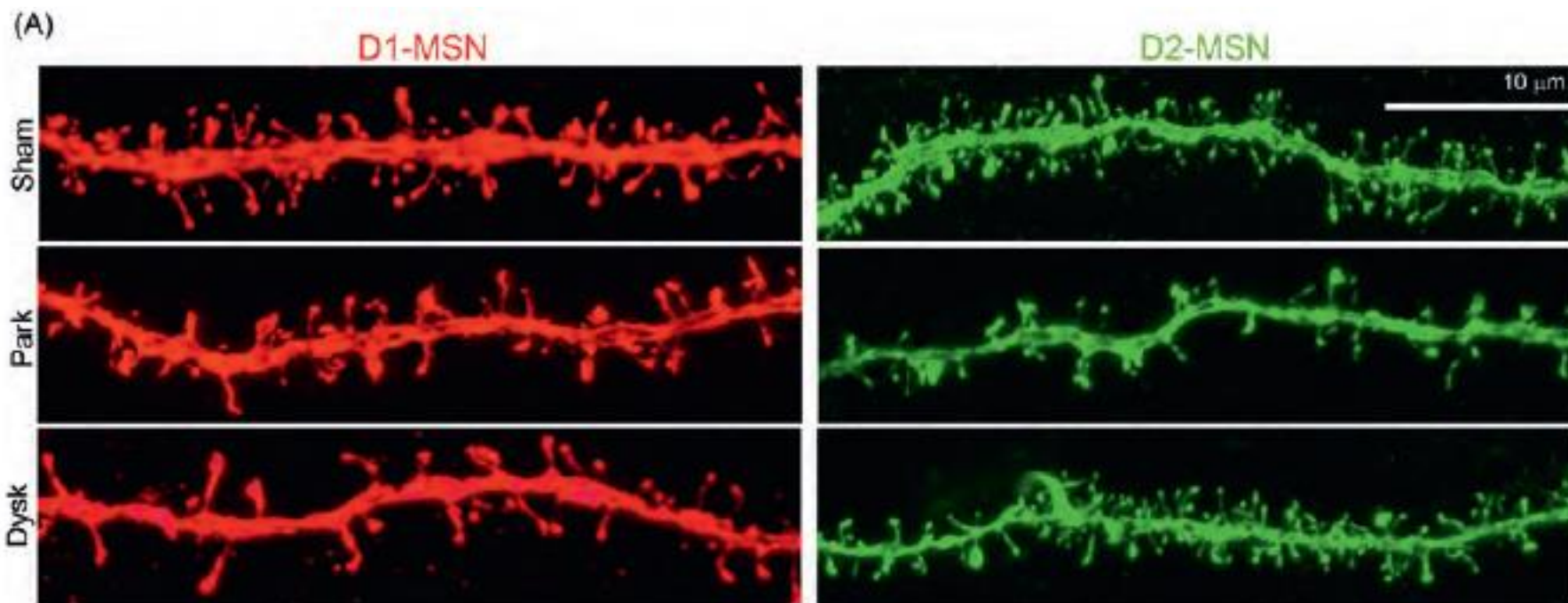
1. Post-synaptic remodeling and sensitization of receptors
2. **Tolerance**
3. **Drug-induced dyskinesia**



L-Dopa-induced Dyskinesia

- **Prevalence**
 - **40% after 4-6 years**
 - **90% after 10 years**
- **Main forms**
 - **Motor fluctuations**
 - **Abnormal involuntary movements**

L-Dopa-induced Dyskinesia

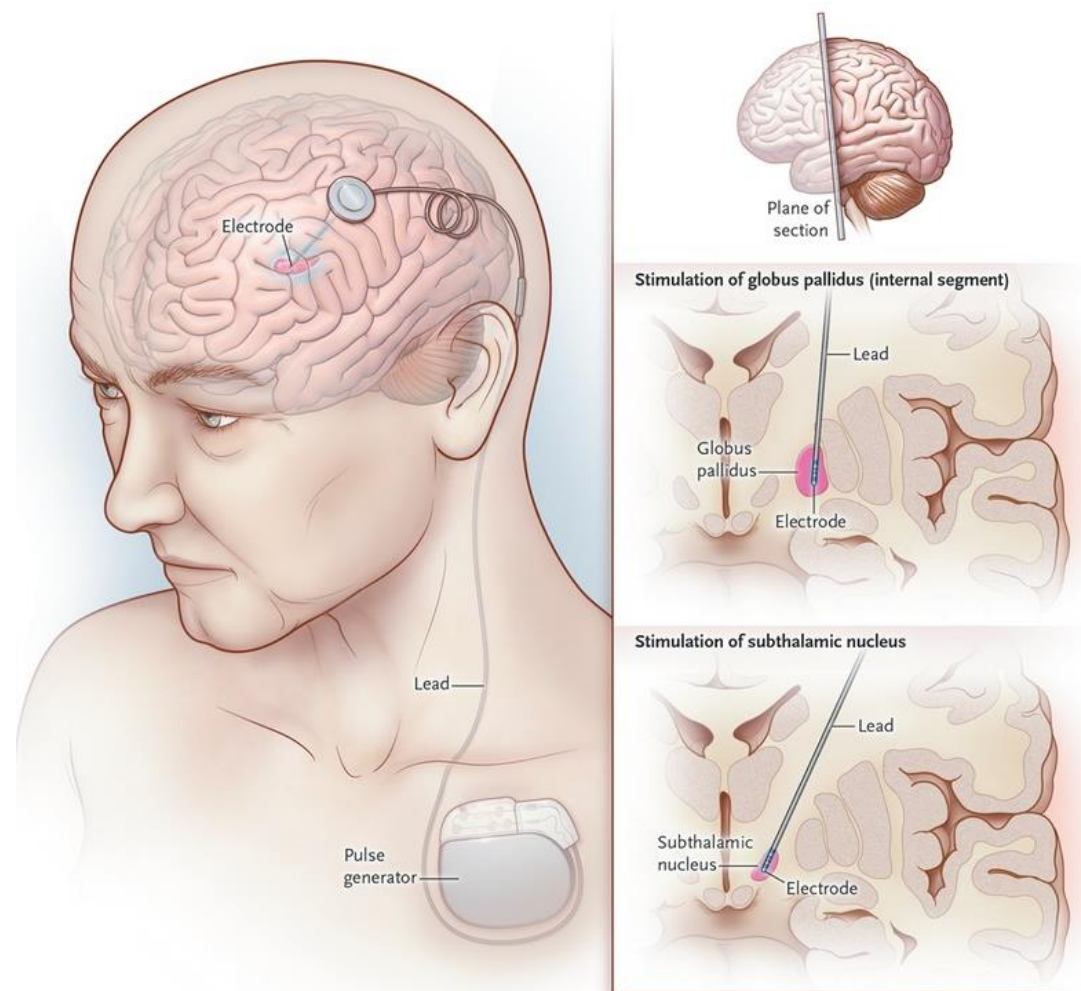


L-Dopa-induced Dyskinesia

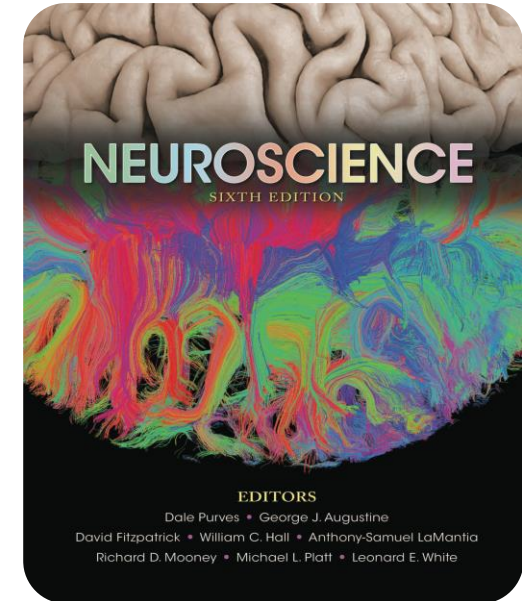
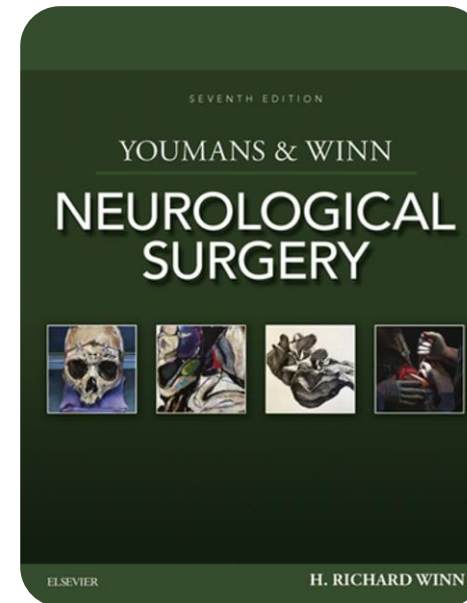
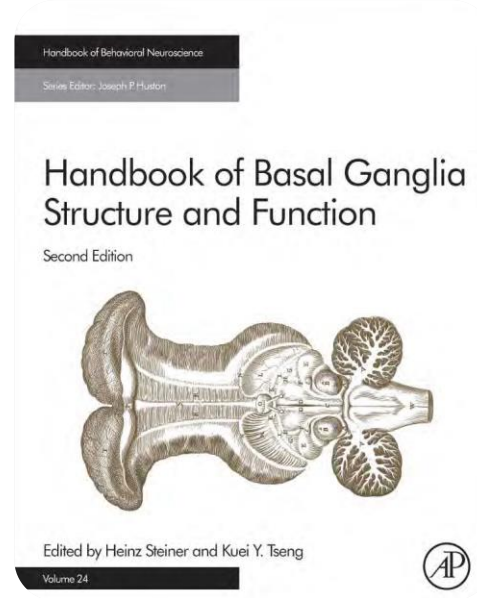
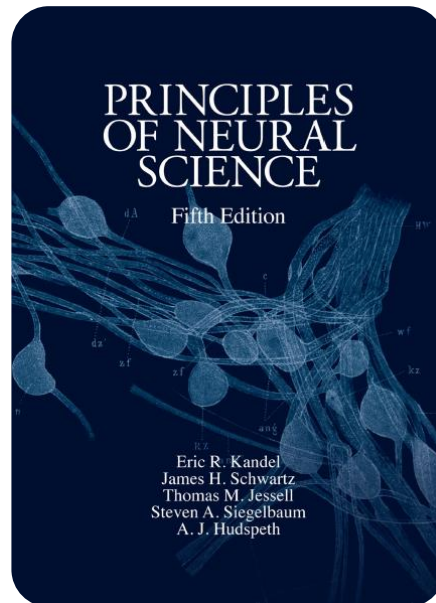
- **L-Dopa**
- **Selective restoration of spine density in indirect pathway (D2) MSNs**
 - **L-dopa blunts D2-MSNs increased responsiveness** to glutamatergic inputs
 - **Compensatory increase** in dendritic spines density on **D2-MSNs**
 - **Selective expression of A2a receptor** on D2-MSNs
- **Abnormal synaptic connections** for reborn spines

Neuromodulation

Deep Brain Stimulation (DBS)



References...





THANK YOU...

Any questions?