Visualization and simulated animations of pathology and symptoms of Parkinson's disease

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1. *Introduction*
2. *Biochemistry of Parkinson's disease*
3. *Course Design*
4. *Student's need and the Visualization and simulations of the life cycle of Parkinson's disease*
5. *Conclusion*

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Introduction

Several diseases, including Parkinson's disease, have been selected as examples in the syllabus of BISC 395. To enhance student learning, we have developed a ***Simulated Learning Aid (SLA)*** using Parkinson's disease as the first selected example.

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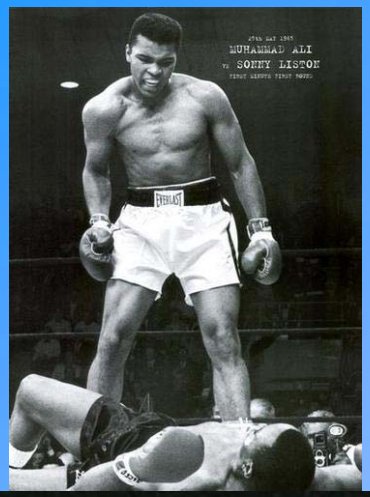

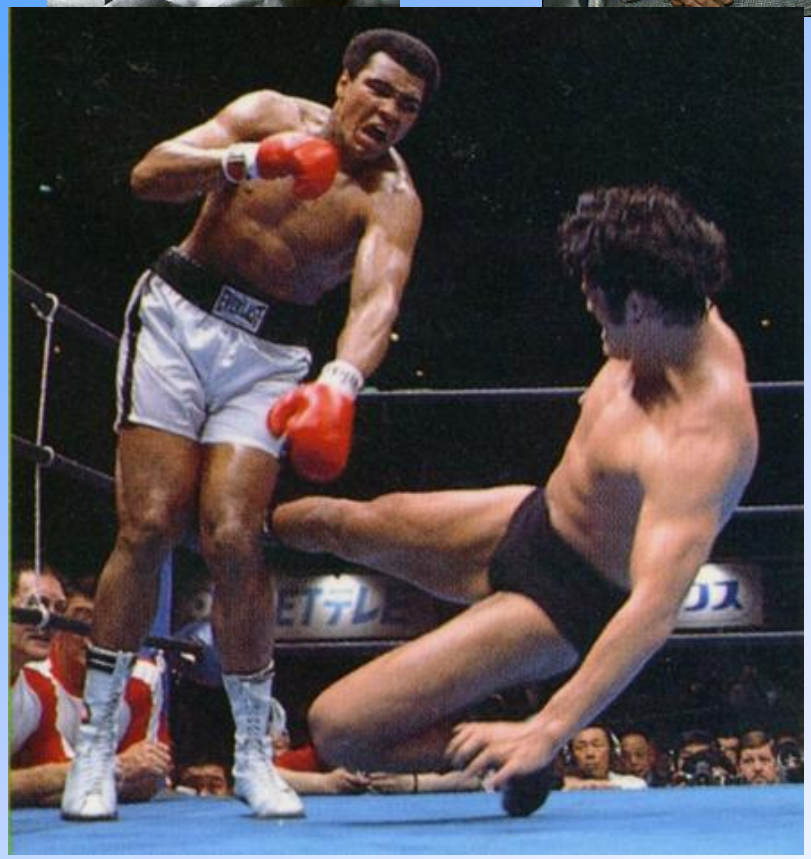

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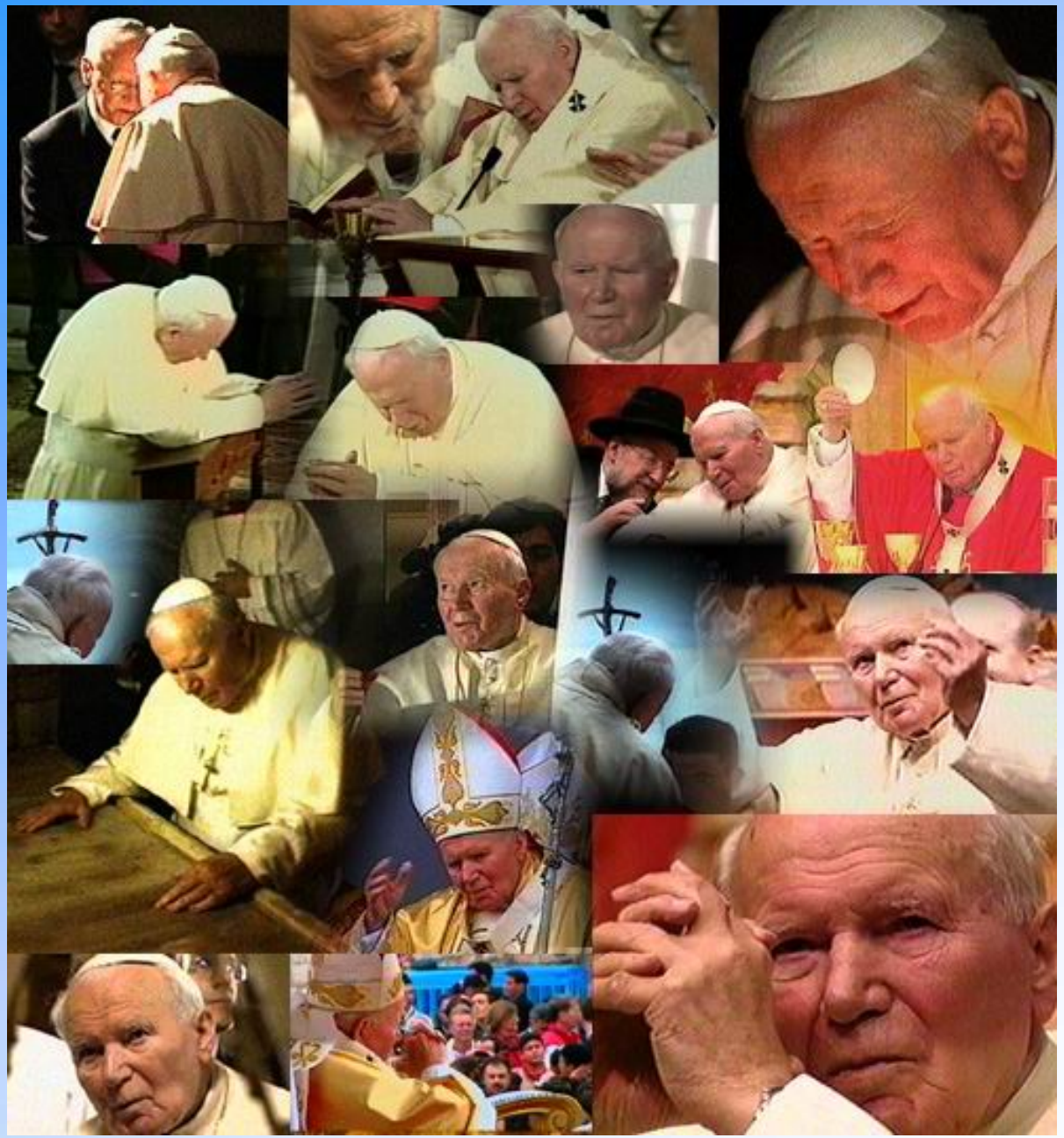

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Outline

- **Introduction**
- **Clinical signs (TRABP)**
- **Progression changes (I → IV)**
- **Etiology**
  - **Familiar (≤5%)**
  - **Idiopathic (majority)**
- **Biochemical hypothesis**
  - **MPTP**
  - **Free radicals**
  - **DA-Neuronal death in SN**

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Visualization and simulated animations of pathology and symptoms of Parkinson's disease

- 2D animated simulation of biochemical pathway
- Video of movement
- Label of importance parts
- Reference
- Glossary
- Short test

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Introduction

- Parkinson's disease was first described by **Dr. James Parkinson** in 1817 as "**shaking palsy**."

- Parkinson's disease is a slowly progressive degenerative neurologic disease characterized by: (**TRABP**)
  1. **tremor**,
  2. **rigidity**,
  3. **akinesia** (difficult in initiation movements)
  4. **bradykinesia** (sluggish neuromuscular responsiveness), and
  5. **postural** instability.

- It is one of the most common hypokinetic disorders occurred after age 50 (with an incidence of 100~150/100,000 population). Onset generally occurs between ages 50 and 65;

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Signs and symptoms

1. **Tremor**
   a) Tremor may be the **initial** complaint in some patients. It is most evident at rest (**resting tremor**) and with low-frequency movement. When the thumb and forefinger are involved, it is known as the **pill-rolling tremor**. Before polls were made by machine, pharmacists made tablets (pills) by hand, which is how this action was named.
   b) Some patients experience **action tremor** (most evident during activity), which can exist with or **prior** to the development of **resting tremor**.

2. Limb Rigidity is present in almost all patients. It is detected clinically when the arm responds with a ratchet-like (i.e. **cogwheeling**) movement when the limb is moved passively. This is due to a tremor that is superimposed on the rigidity.

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Signs and symptoms

3. **Akinesia** and **bradykinesia**. Akinesia is characterized by **difficulty** in **initiating movements**, and bradykinesia is a **slowness** in performing common voluntary movements, including standing, walking, eating, writing, and talking. The lines of the patient's face are smooth, and the expression is fixed (**masked face**) with little evidence of spontaneous emotional responses.

4. **Gait** and **postural difficulties**. Characteristically, patients walk with a stooped, flexed posture; a small shuffling stride; and a diminished arm swing in rhythm with the legs. There may be a tendency to accelerate or festinate.

5. Changes in mental status. Mental status changes, including depression (50%), dementia (25%), and psychosis, are associated with the disease and may be precipitated or worsened by drugs.

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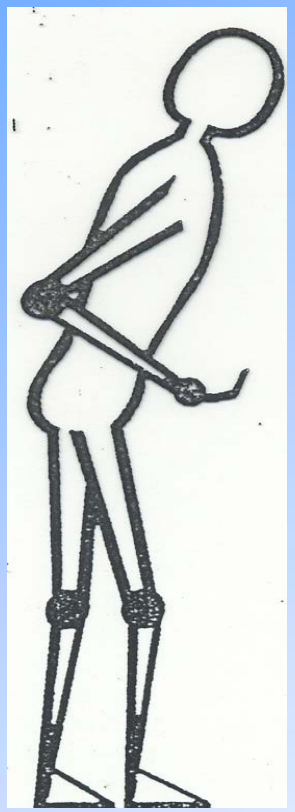
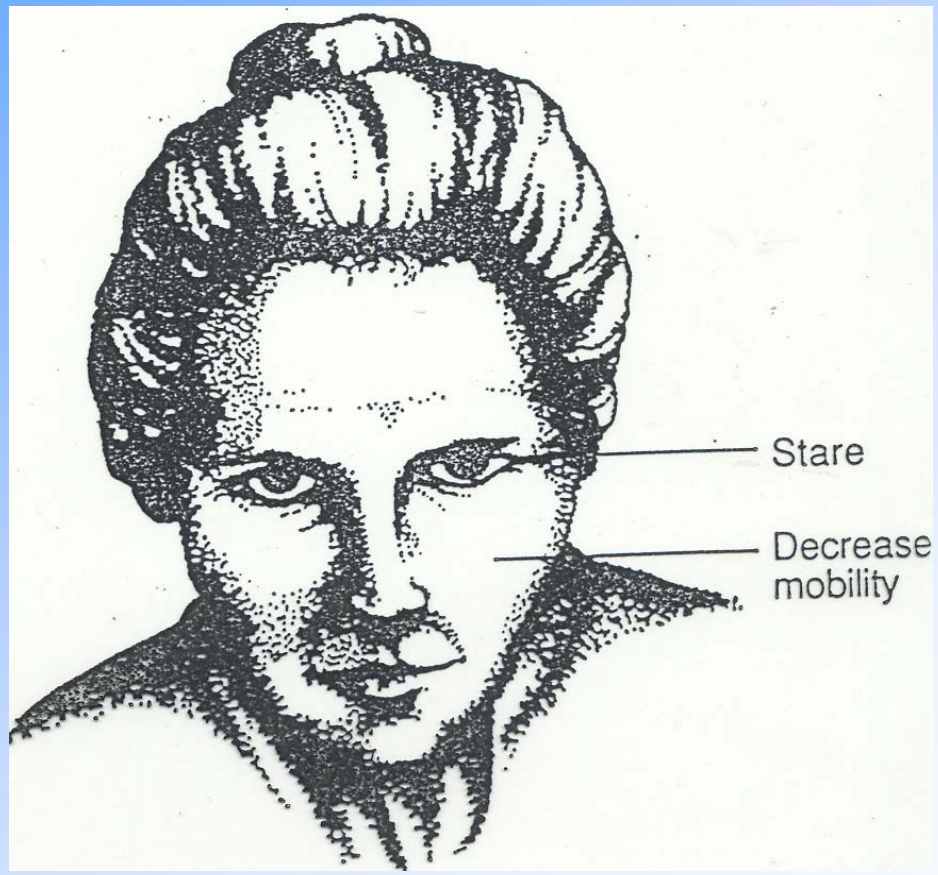


Characteristic walk of patients with Parkinson's disease



Masked face

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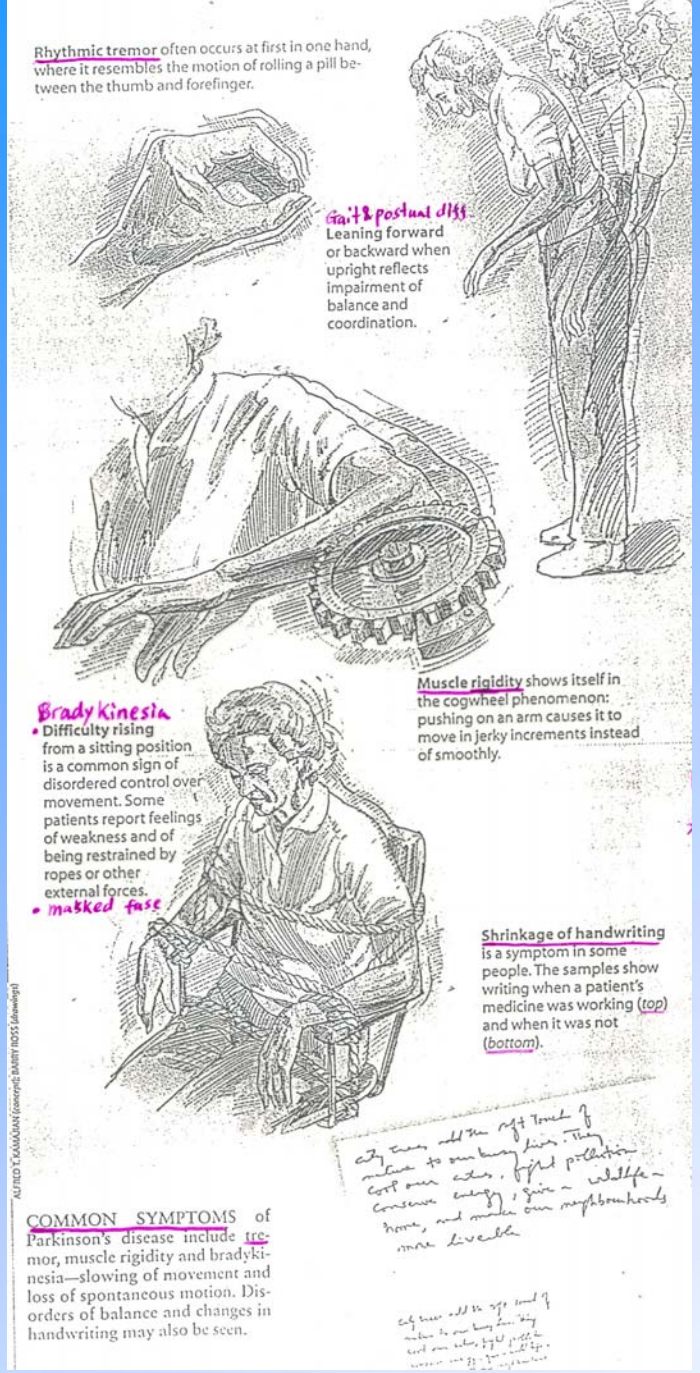

Symptoms

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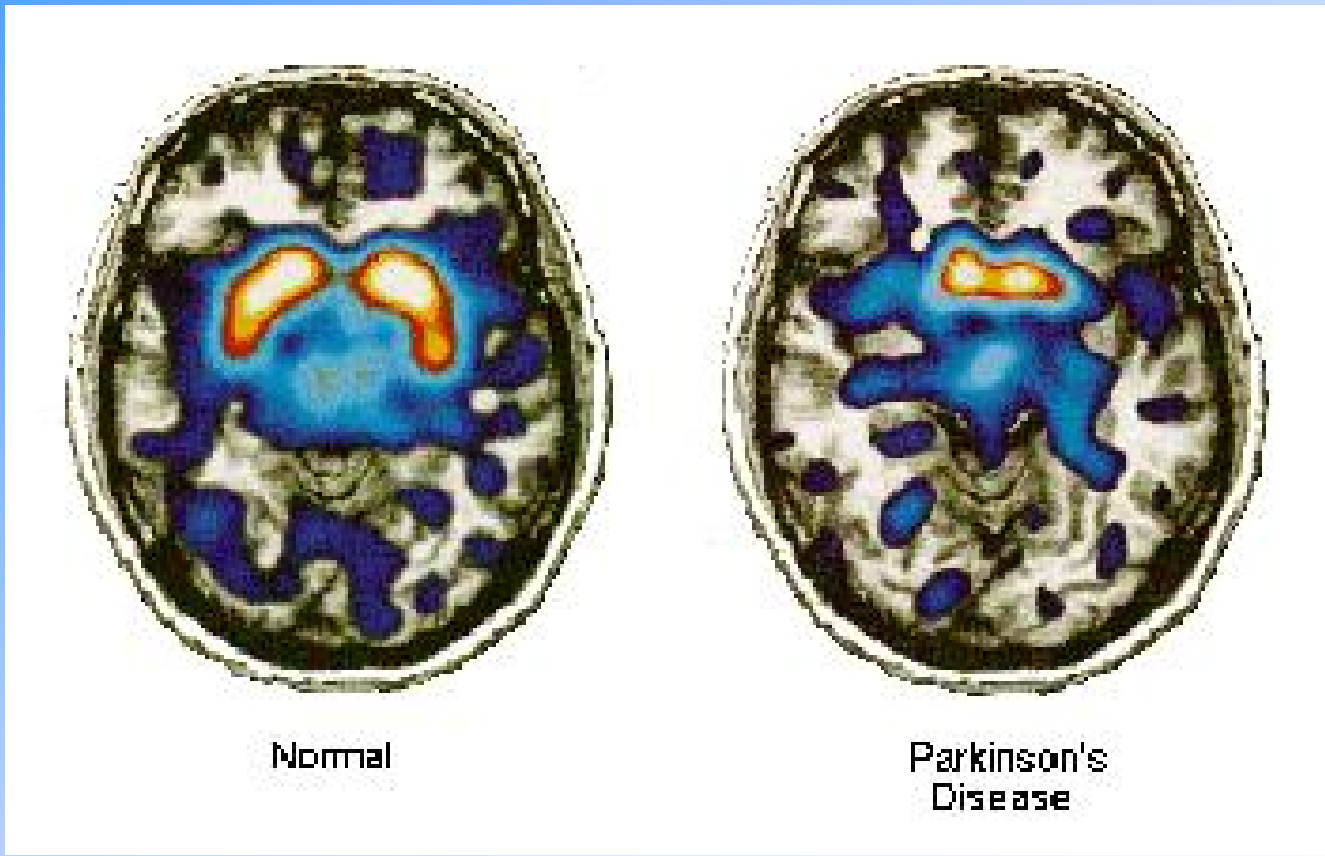
The changing brain in Parkinson's disease



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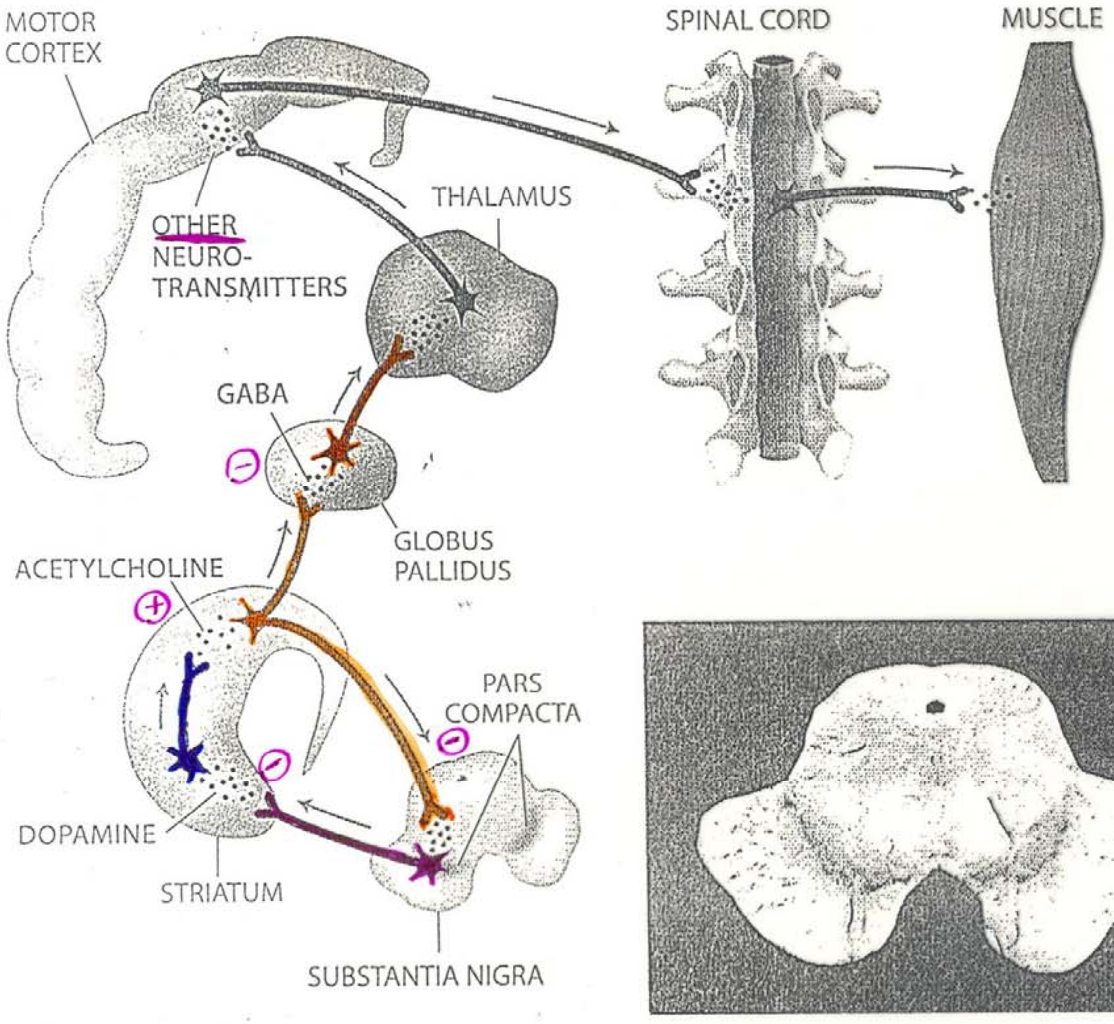
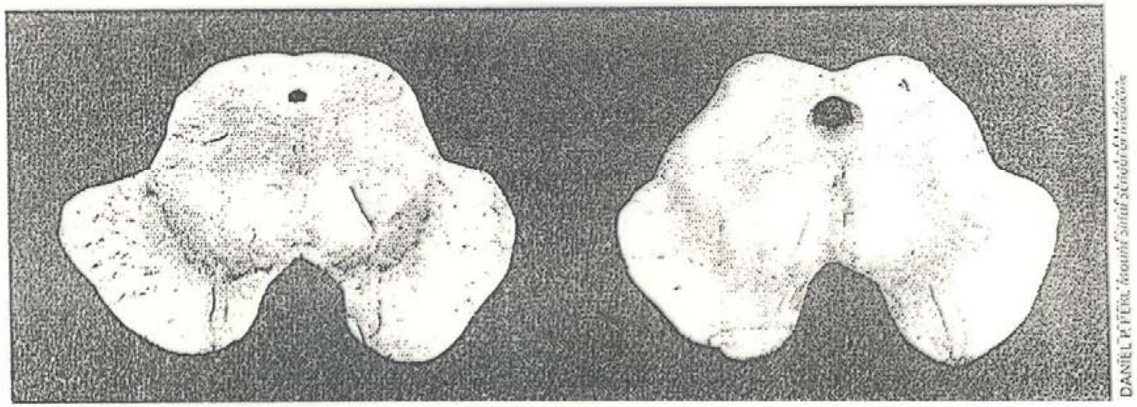
Neuronal circuit disrupted in Parkinson's disease



NEURONAL CIRCUIT disrupted in Parkinson's disease is shown schematically. When dopamine-producing neurons die, loss of dopamine release in the striatum causes the acetylcholine producers there to overstimulate their target neurons, thereby triggering a chain reaction of abnormal signaling leading to impaired mobility. The pars compacta region of the substantia nigra in the normal brain appears dark (*left photograph*) because dopamine-producing neurons are highly pigmented; as neurons die from Parkinson's disease, the color fades (*right photograph*).



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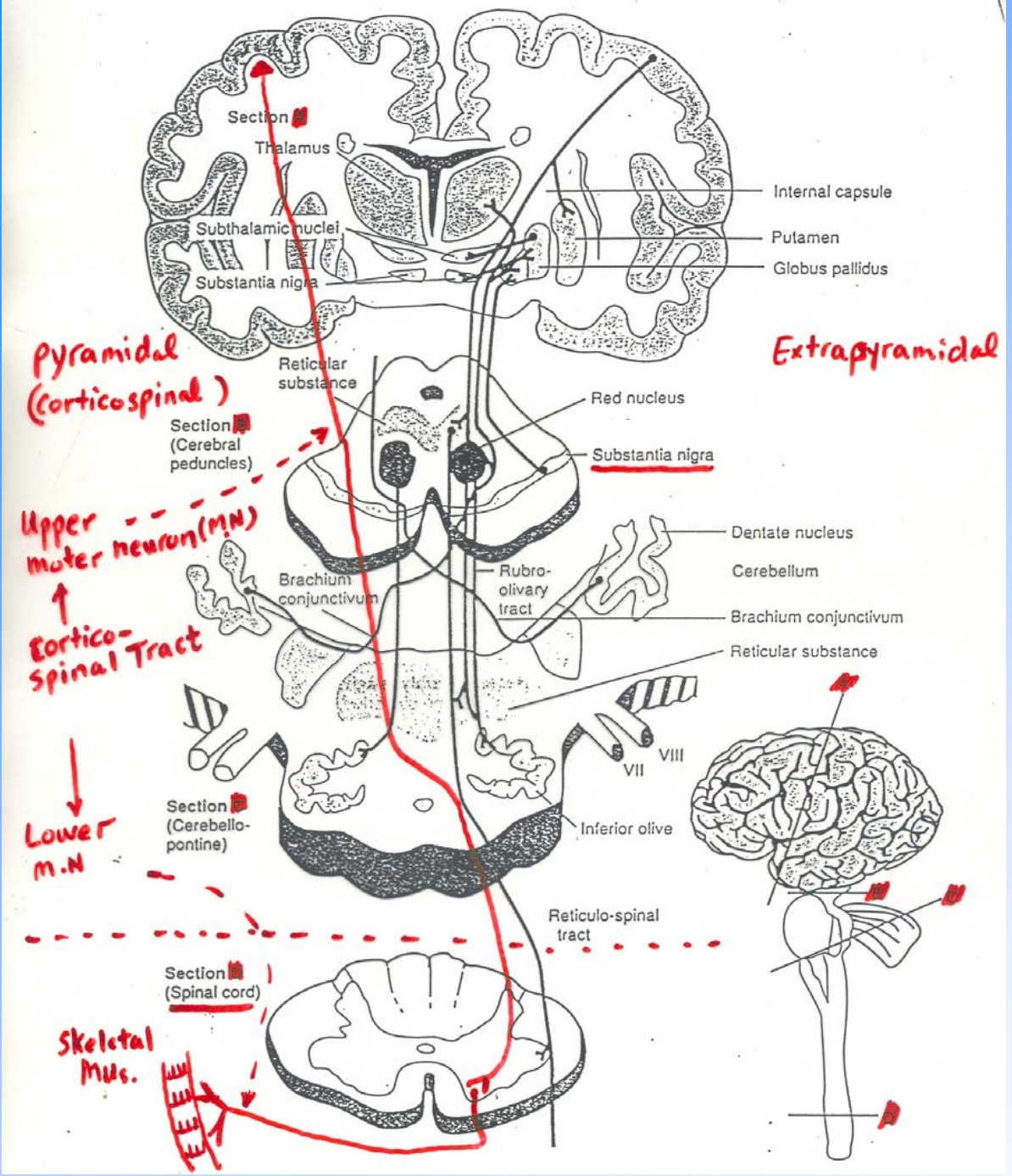
Extrapyramidal system involved in Parkinson's disease



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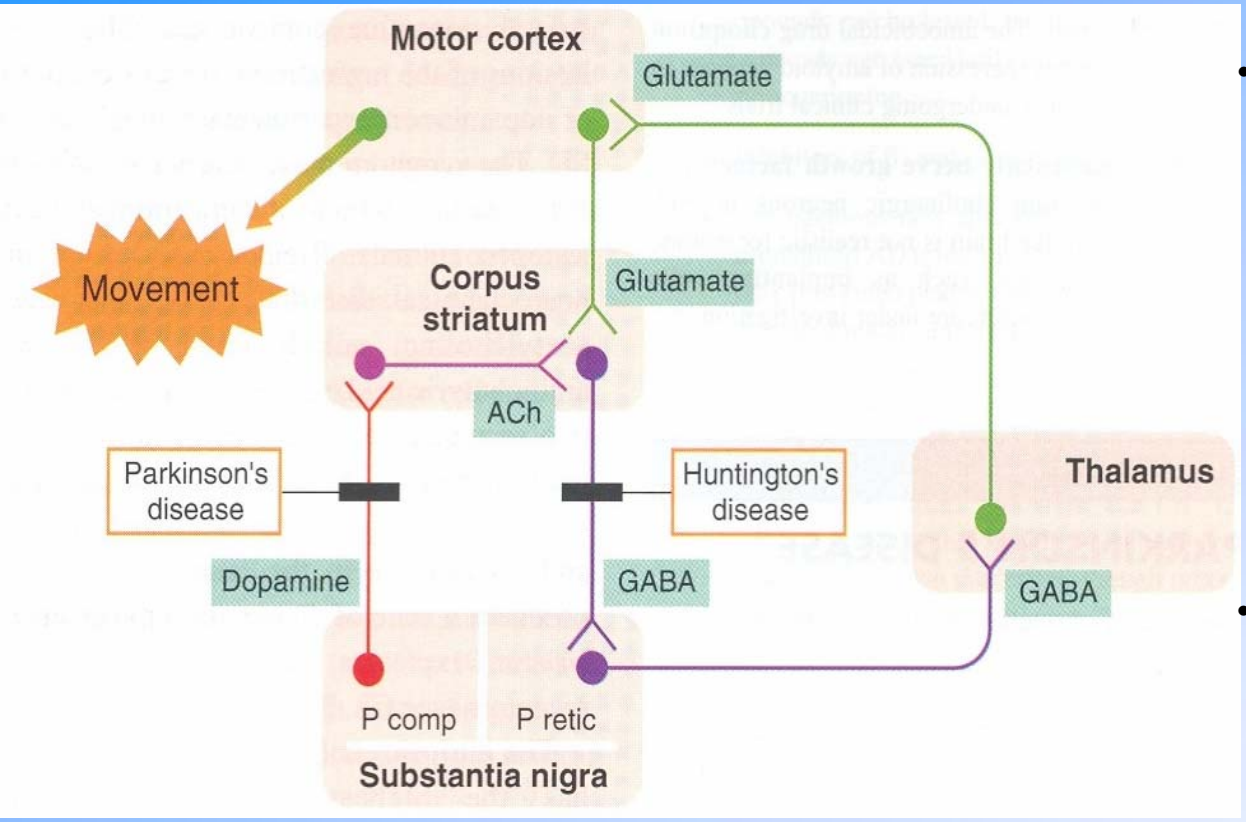
Simplified diagram of the extrapyramidal motor system, and defects that occur in Parkinson's disease



P comp, pars compacta;

P ret, pars reticulata;

- In the former, the **inhibitory dopaminergic** pathway from the substantia nigra to the striatum is impaired, increasing the activity of GABAergic cells in the stratum, which in turn inhibit GABAergic cells in the sunstantia nigra, thus **reducing the restraint** on the **thalamus** and **cortex**, causing **rigidity**.
- The dopaminergic inhibition of the striatal cells is opposed by excitatory cholinergic interneurons, the defect can be counteracted by dopamine agonists or by ACh (muscarinc) antagonists.

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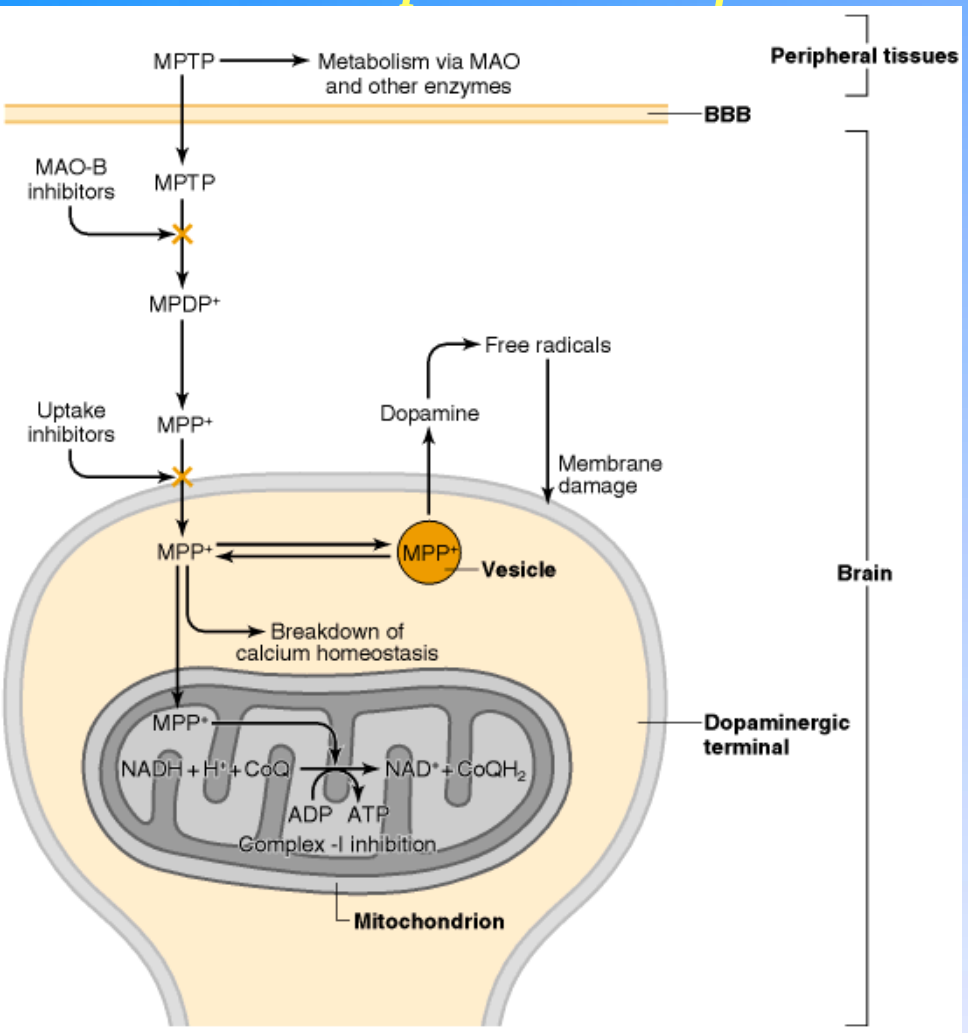
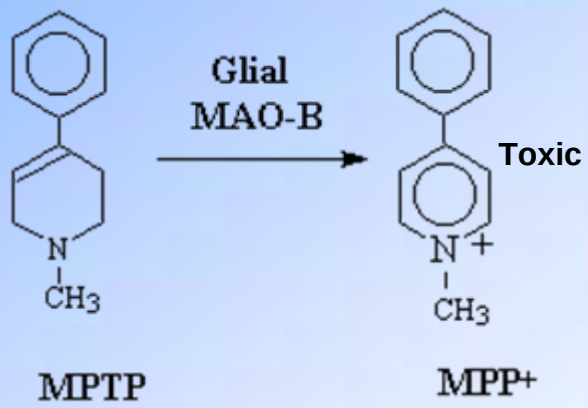
Schematic representation of the mechanisms involved in toxicity of MPTP





BBB: blood-brain barrier;
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine;
MPP$^+$: its four electron oxidation product N-methyl-4-phenylpyridinium

- **MPP$^+$ blocks mitochondrial oxidation, ↓ ATP formation ("complex I")**
- **↑ The release of superoxide anion radical (O^-_2)**
- **↓ Ion transportation**
- **↑ Cytosolic Ca^{2+} to toxic level**

} **Cell Death**

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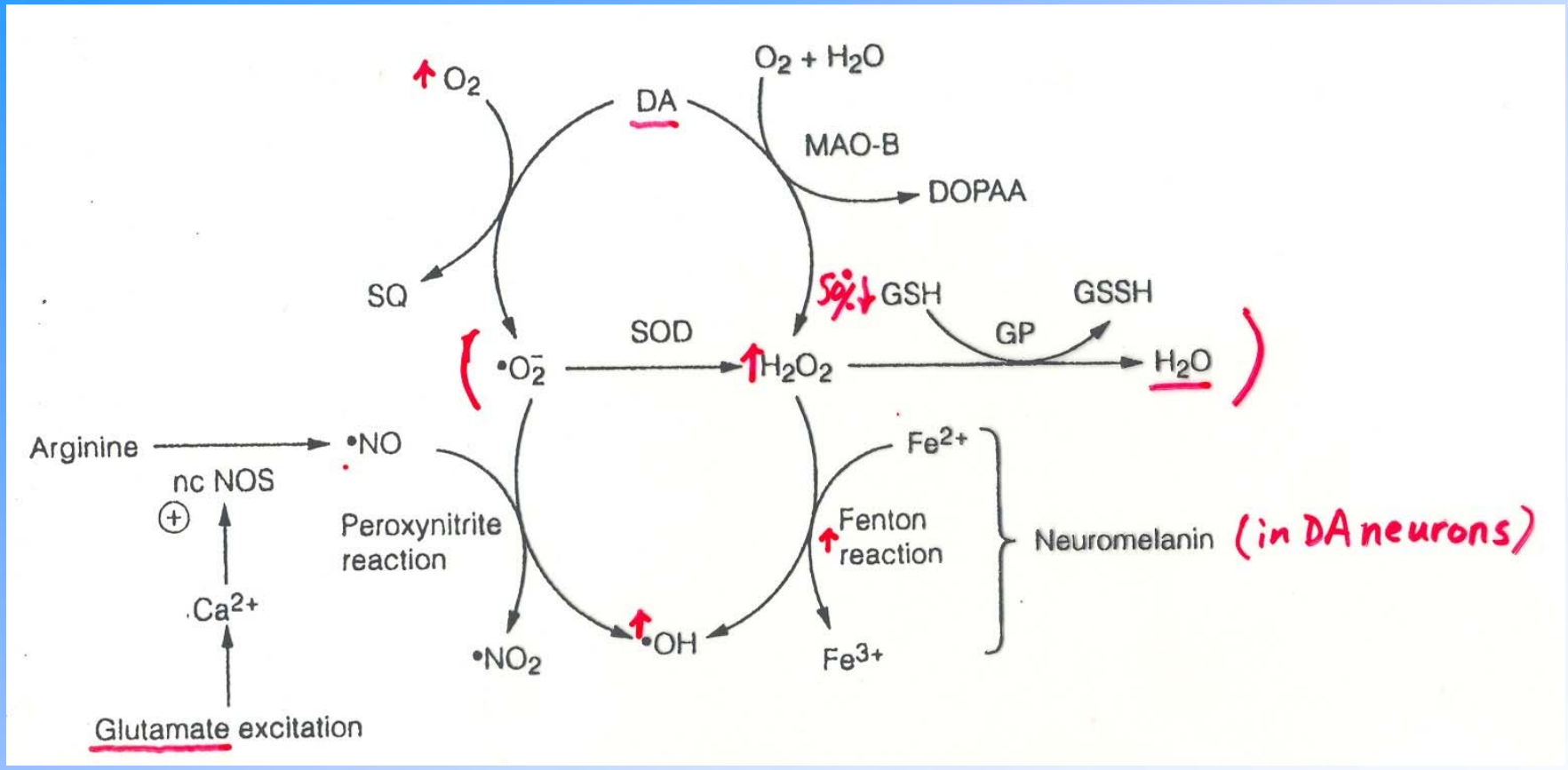
Free radical reactions in Parkinson's disease



DA: dopamine;

DOPAA: 3,4-dihydrophenyl-acetaldehyde;

GP: glutathione peroxidase;

GSH and GSSH: reduced and oxidized glutathione;

ncNOS: neuronal isoform of nitric oxide synthase;

SOD: superoxide dismutase;

SQ: semiquinone

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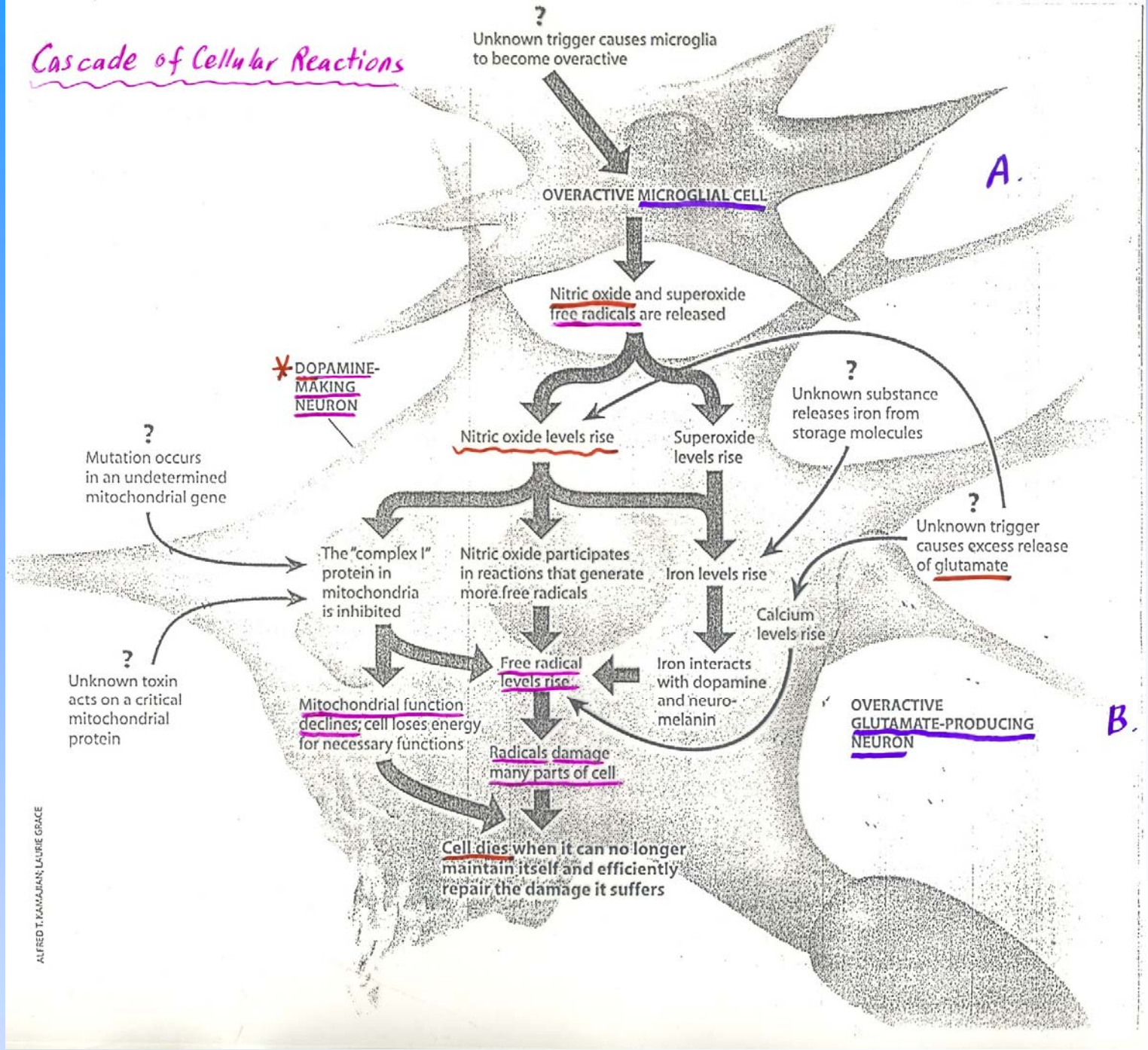

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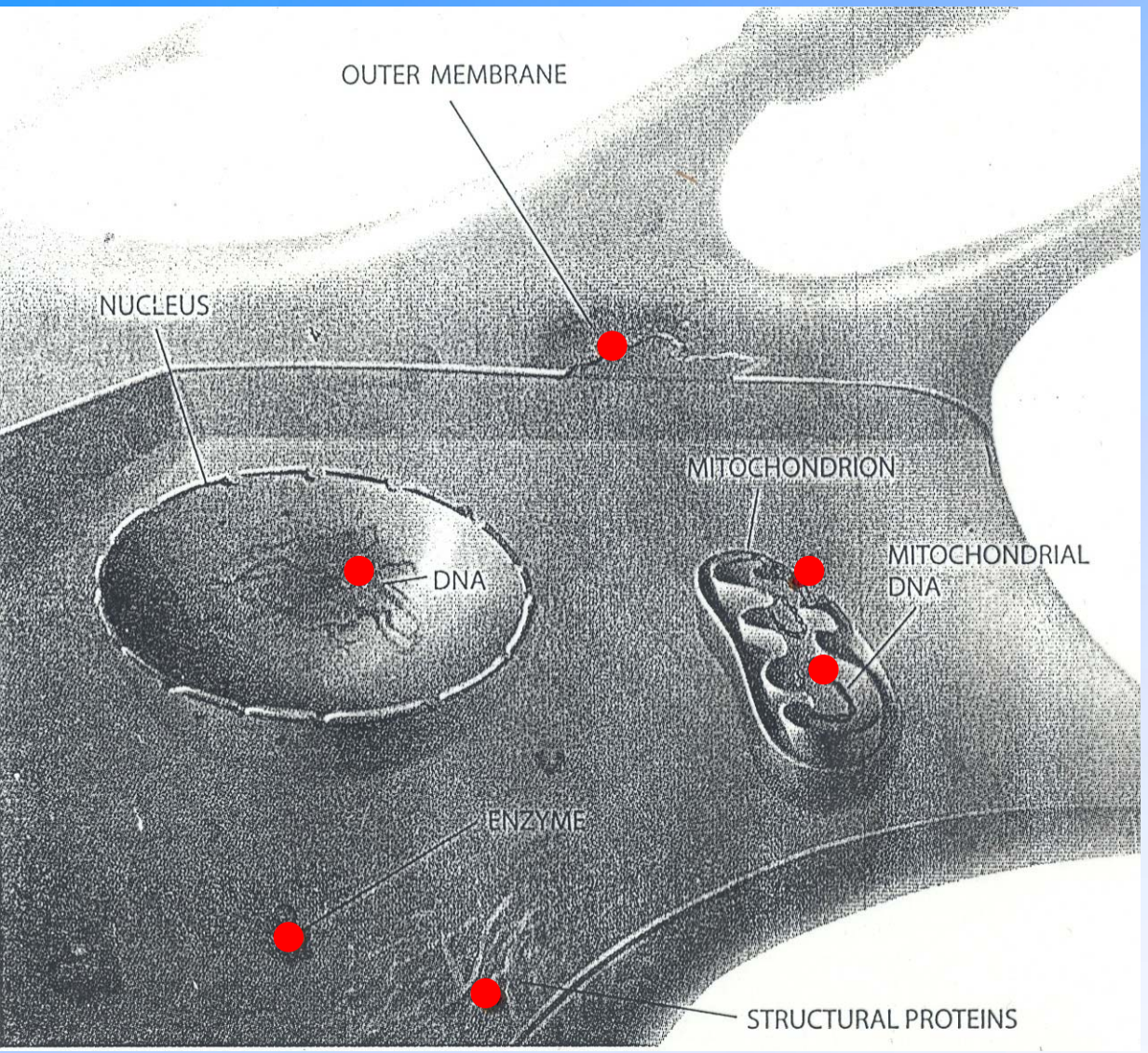
Free radical reactions in Parkinson's disease



- **Oxygen free radicals**, shown schematically as colored dots, can directly damage cells in many ways.
- They can injure nuclear and mitochondrial DNA, cell membranes and proteins.

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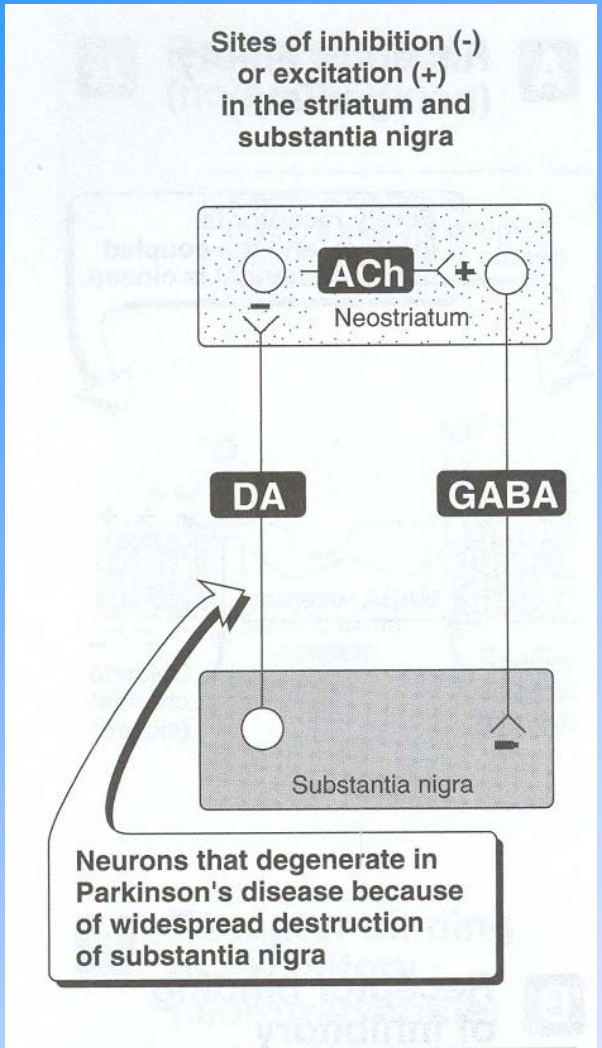
Sites of inhibition (-) or excitation (+) in the striatum and substantia nigra



1. **Substantia nigra**: the substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the striatum.

   – Each **dopaminergic** neuron makes **thousands** of **synaptic contacts** within the striatum and therefore modulates the activity of a large number of cells.

   – These dopaminergic projections from the substantia nigra fire tonically, rather than in response to specific muscular movements or sensory input.

   – Thus, the dopaminergic system apprears to serve as a **tonic**, **sustaining influence** on motor activity, rather than participating in specific movements.

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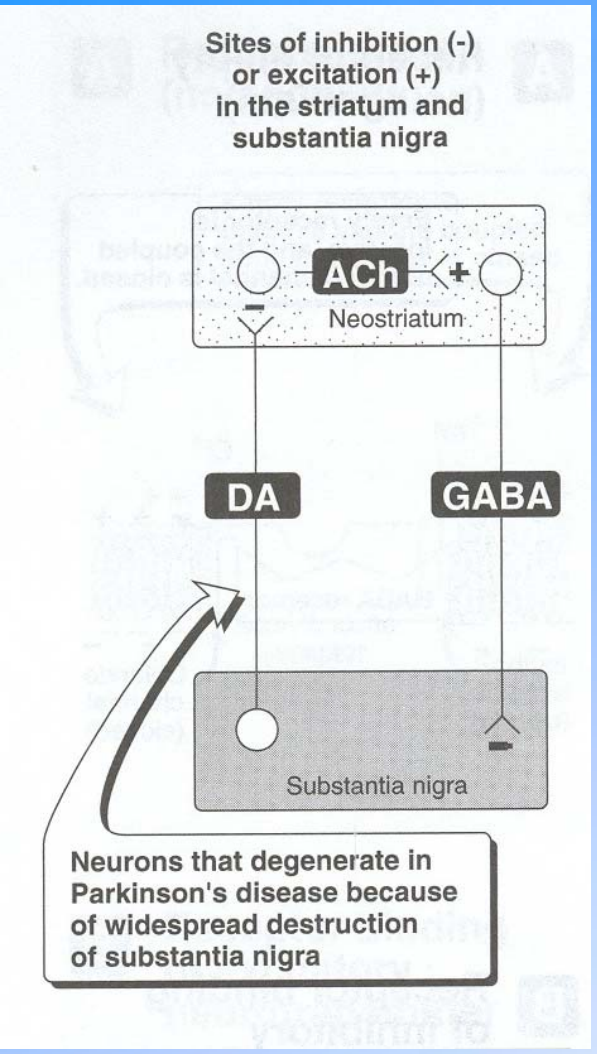
Sites of inhibition (-) or excitation (+) in the striatum and substantia nigra



2. **Striatum:** normally, the **striatum** is connected to the **substantia nigra** by neurons that secrete the inhibitory transmitter **GABA** at their termini in the substantia nigra.

- In turn, cells of the substantia nigra send neurons back to the striatum, secreting the inhibitory transmitter dopamine at their termini.
- This **mutual inhibitory pathway** normally maintains a degree of inhibition of the ***two*** separate areas. Nerve fibers from the cerebral **cortex** and **thalamus** secrete ACh in the neostriatum, causing excitatory effects that initiate and regulate gross intentional movements of the body.
- In Parkinson's disease, **destruction** of cells in the **substantia nigra** results in the **degeneration** of **neurons** responsible for secreting **dopamine** in the neostriatum.
- Normal aging: **5%** degeneration per **decade**; Parkinson's Disease: **12%** degeneration per year;
- Only 50% cell death ——▶PD syndromes;
- Thus the normal modulating **inhibitory** influence of **dopamine** on the neostriatum is significantly **diminished**, resulting in the parkinsonian degeneration of the control of muscle movement.

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Treatment of PD

A. Drug treatment and its strategy

- In addition to an abundance of (a) **inhibitory dopaminergic** neurons, the neostriatum is also rich in (b) **excitatory cholinergic** neurons that oppose the action of dopamine; (**causes**)

- Many of the symptoms of parkinsonism reflect an imbalance between the **excitatory cholinergic** neurons and the greatly diminished number of **inhibitory dopaminergic** neurons;

- Therapy is aimed at:

(1) **restoring dopamine** in the basal ganglia and;

(2) **antagonizing** the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine **balance**; (**therapy**)

(3) future pharmacological strategies include the use of **glutamate** or **adenosine receptor antagonists**.

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Treatment of PD

B. Surgical approaches

Surgical approaches involve **selective lesions** of the globus pallidus pars interna, subthalamus or ventrolateral tralamus, and the transplant of dopaminergic cells, harvested from the midbrain of human fetuses, into the striatum.

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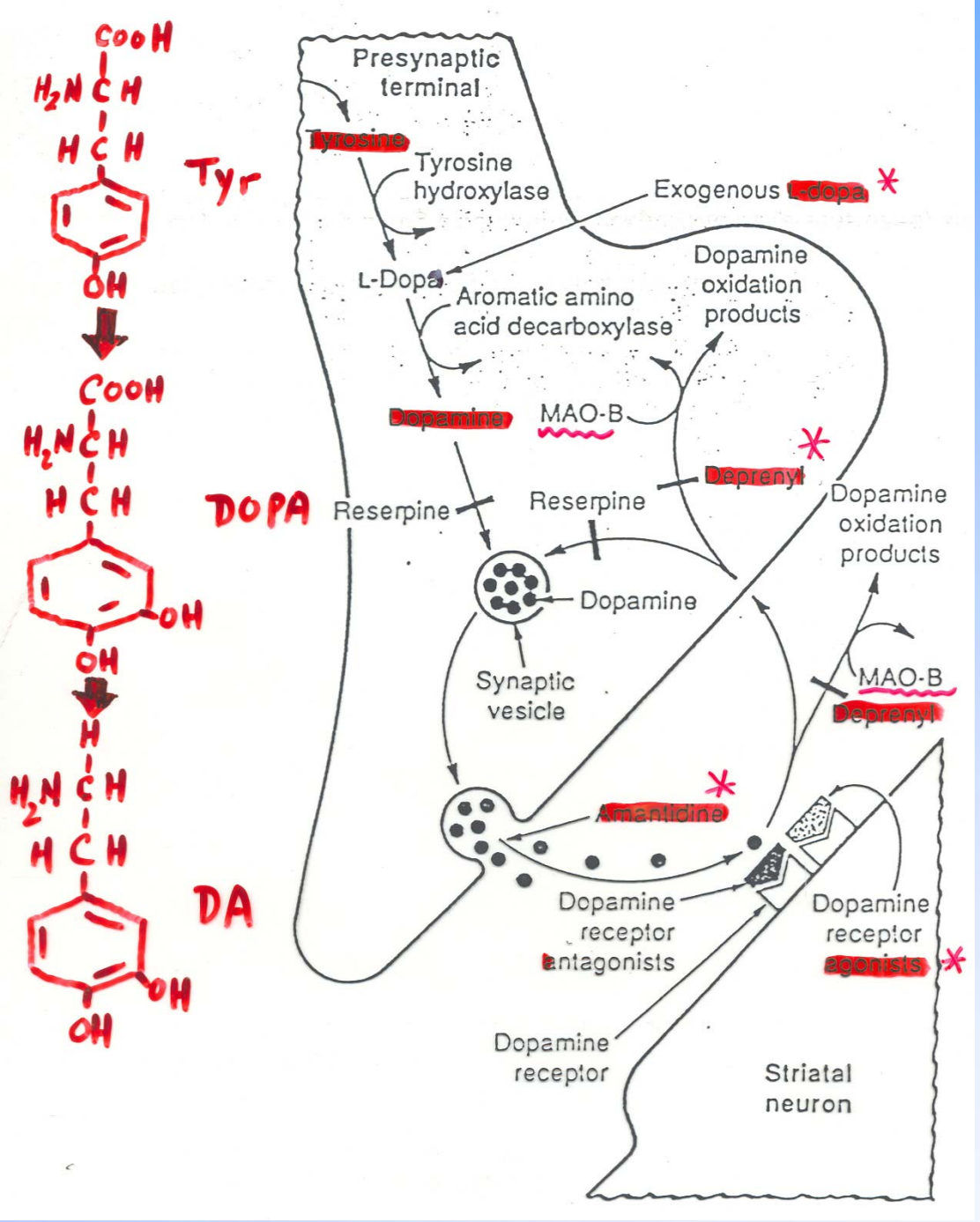

Schematic diagram illustrating:

1. **the release of dopamine by a neuron is the substantia nigra;**
2. **the sites of action of drugs that ameliorate or induce parkinsonism.**

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Conclusion

Using the SLAs, symptoms and pathology of Parkinson's disease can be simulated in the class. Students are expected to be given a clear impression of the framework and have a better understanding of Parkinson's disease. Next year, the SLAs programme will be implemented in the class.

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