Parkinson's Disease:
A Brief Overview

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Cardinal Features of Parkinsonism

- Tremor
- Rigidity
- Bradykinesia
- Postural imbalance

Differential Diagnosis of Parkinsonism

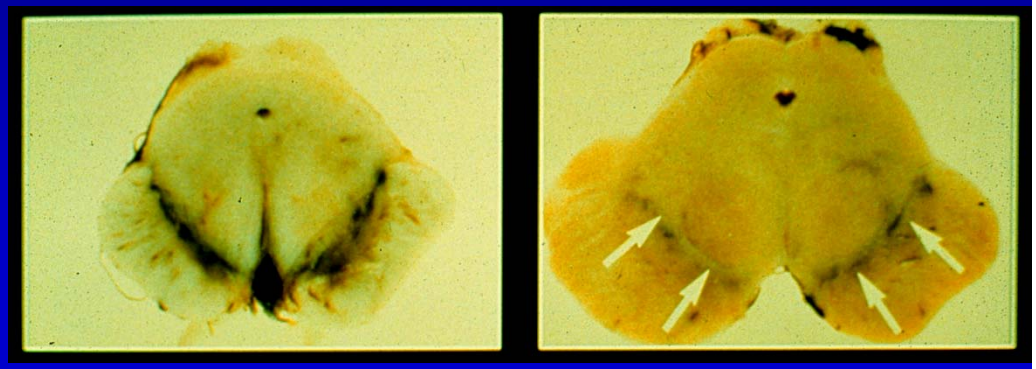
- Primary Parkinsonism – Parkinson's disease
- Degenerative
  - Progressive supranuclear palsy
  - Multiple system atrophy
    - Striatonigral degeneration
    - Cerebellar degeneration (olivopontocerebellar atrophy; OPCA)
    - Autonomic failure (Shy-Drager syndrome)
  - Diffuse Lewy Body disease
  - Corticobasal degeneration
- Heredodegenerative
  - Wilson's disease
  - DRPLA
- Secondary Parkinsonism
  - Drug-induced (haloperidol, metoclopramide)
  - Toxins: carbon monoxide, manganese, pesticides
  - Structural: vascular, hydrocephalus

Clinical Features suggestive of Atypical Parkinsonism

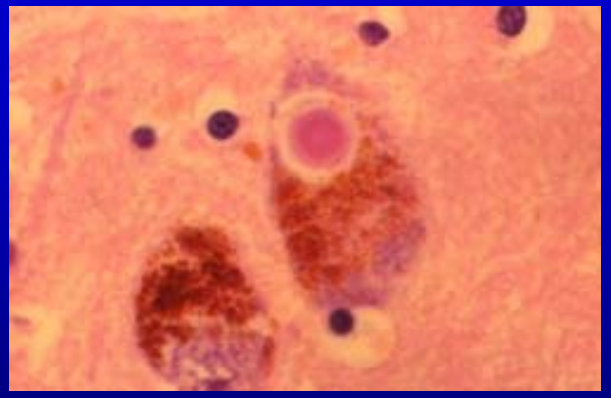
- Falls at presentation
- Symmetry at onset
- Rapid progression
- Lack of tremor
- Early dysautonomia
- Poor response to levodopa

Pathology of Parkinson's Disease

- Progressive loss of DA neurons from the substantia nigra pars compacta
- Marked depletion of striatal DA
- Lewy bodies = pathologic hallmark of PD

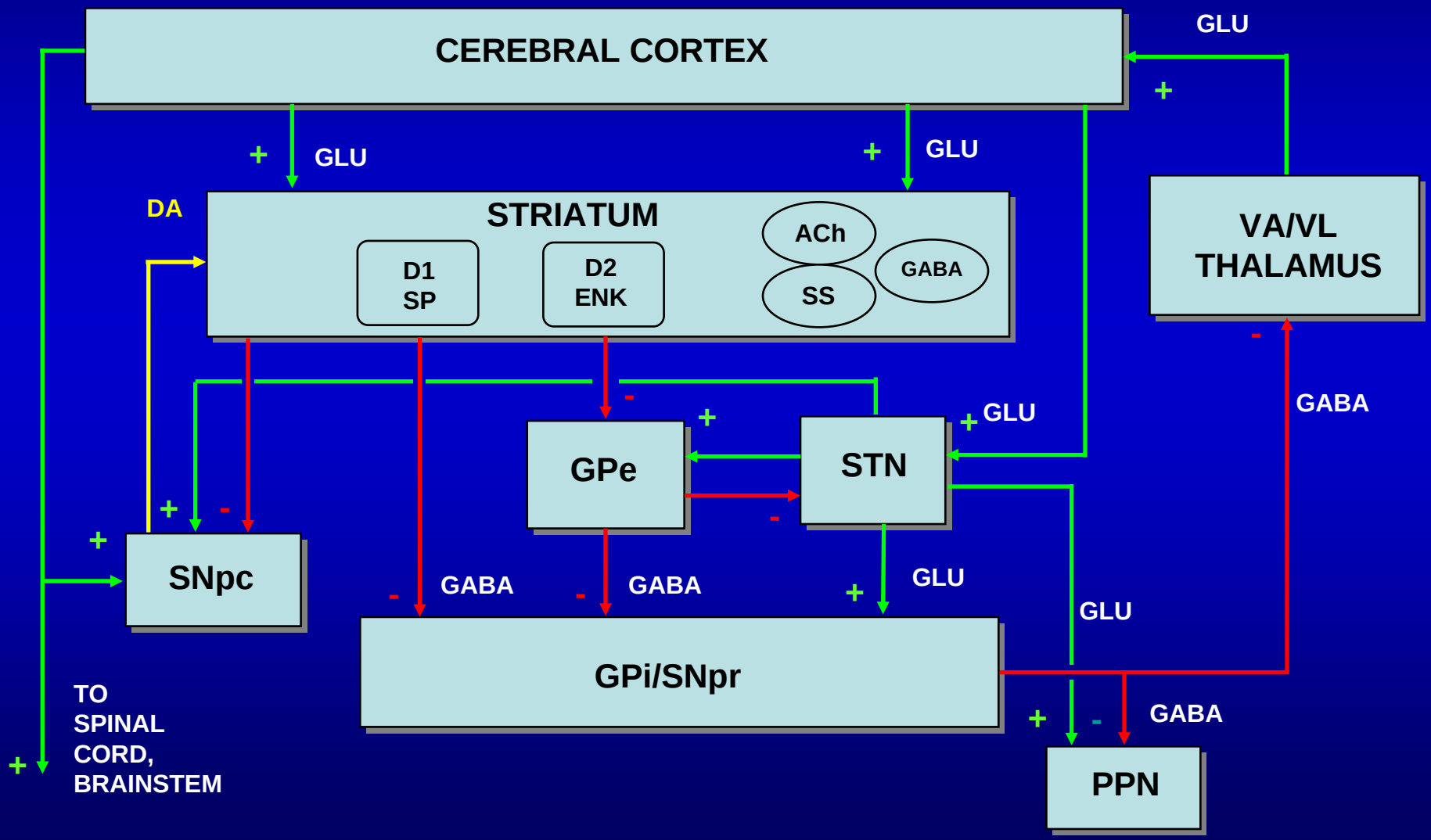


Normal Parkinson's

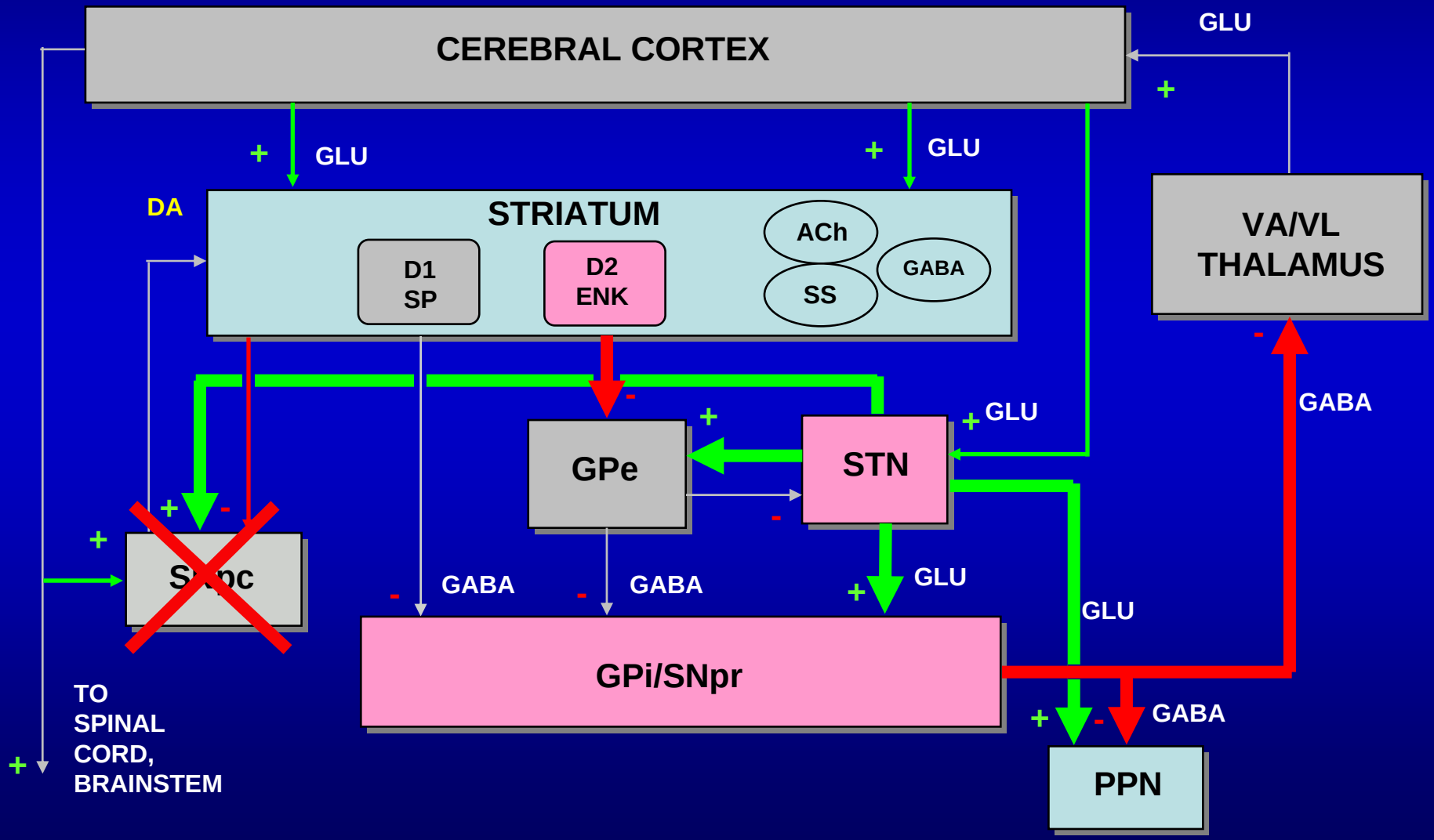


Lewy bodies

Functional Anatomy of the Basal Ganglia



Functional Anatomy of the Basal Ganglia: Parkinsonism



Genetics and PD: Evidence from Twin Studies

- Tanner et al., 1999: WWII Veterans Twins Registry
  - 19,842 twins, 193 pairs where at least one had PD
  - Concordance depends on age of onset
    - Pairwise concordance similar for all MZ and DZ twins; equal for onset > age 50
    - For onset < age 50, 6-fold increase in concordance for MZ twins

→ Early onset cases have a stronger genetic component

Genetic Causes of Parkinson's Disease

Locus	*Protein or Location*	*Function*	*Inheritance*	*Population*
PARK 1	alpha-synuclein mutation	Unknown – ? vesicle transport	AD	Italian, Greek, German
PARK 2	Parkin	Ubiquitin E3 ligase	mainly AR	Global
PARK 3	2p13		AD, reduced penetrance	N. European kindred
PARK 4*	alpha-synuclein triplication		AD, reduced penetrance	Iowa kindred
PARK 5	UCH-L1	Ubiquitin hydrolase	AD	German kindred
PARK 6	PINK1	Mitochondrial protein kinase	AR	Italian
PARK 7	DJ-1	Unknown – ? antioxidant	AR	Dutch
PARK 8	leucine-rich repeat kinase (LRRK2)	Vesicle dynamics, cell signaling	AD, reduced penetrance	multiple
PARK 9	1p36		AR	
PARK 10	1p32		?	Icelandic

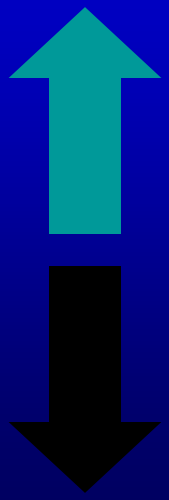
Non-genetic Factors in the Etiology of PD

- Oxidative stress and mitochondrial dysfunction

$$DA + O_2 + H_2O \xrightarrow{MAO} DOPAC + NH_2 + H_2O_2$$

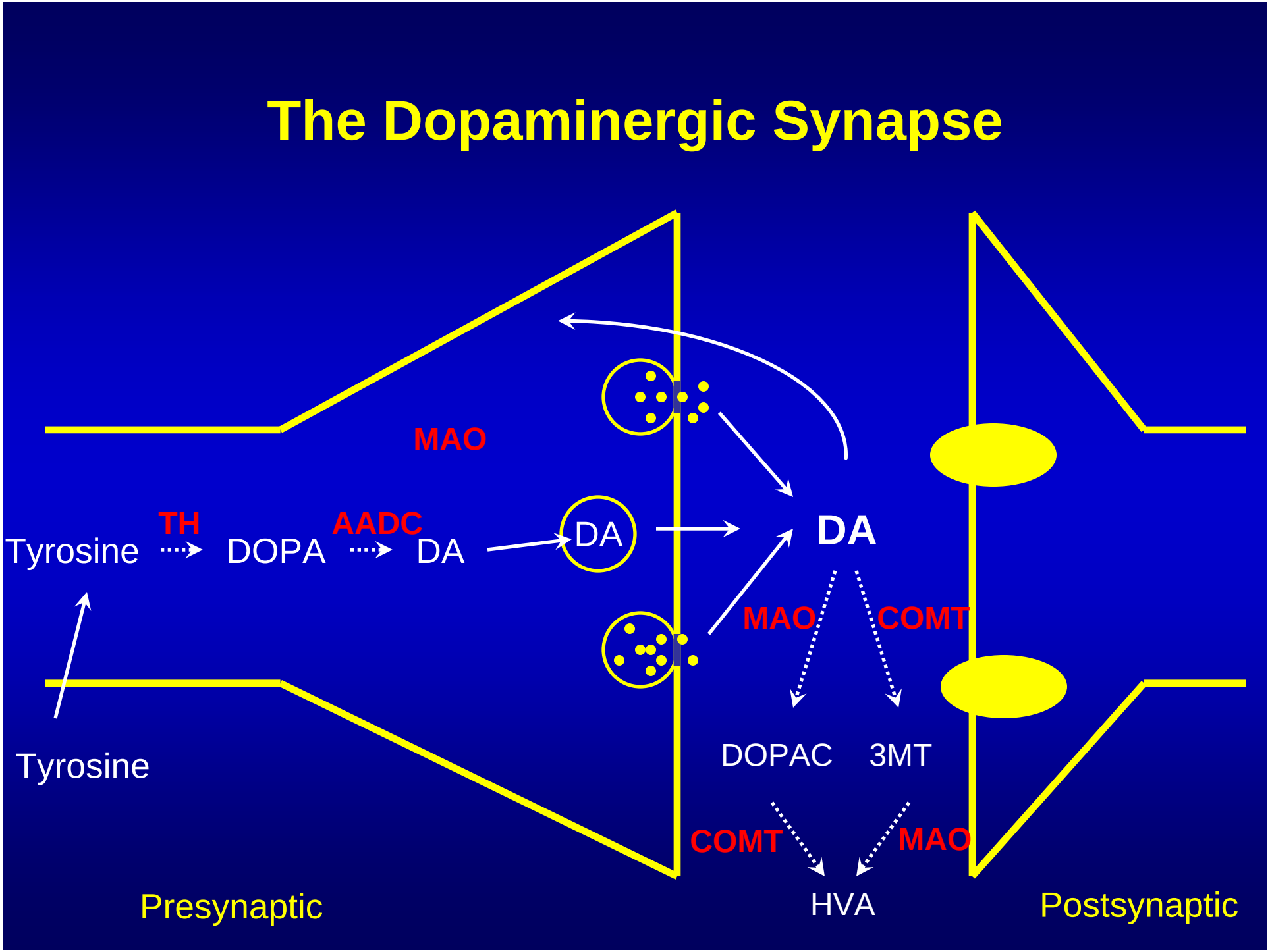
$$MPTP + O_2 + H_2O \longrightarrow MPP^+ + NH_2 + H_2O_2$$

- Environmental factors



  - Well water and rural living
  - Pesticides, toxins

  - Smoking
  - Caffeine

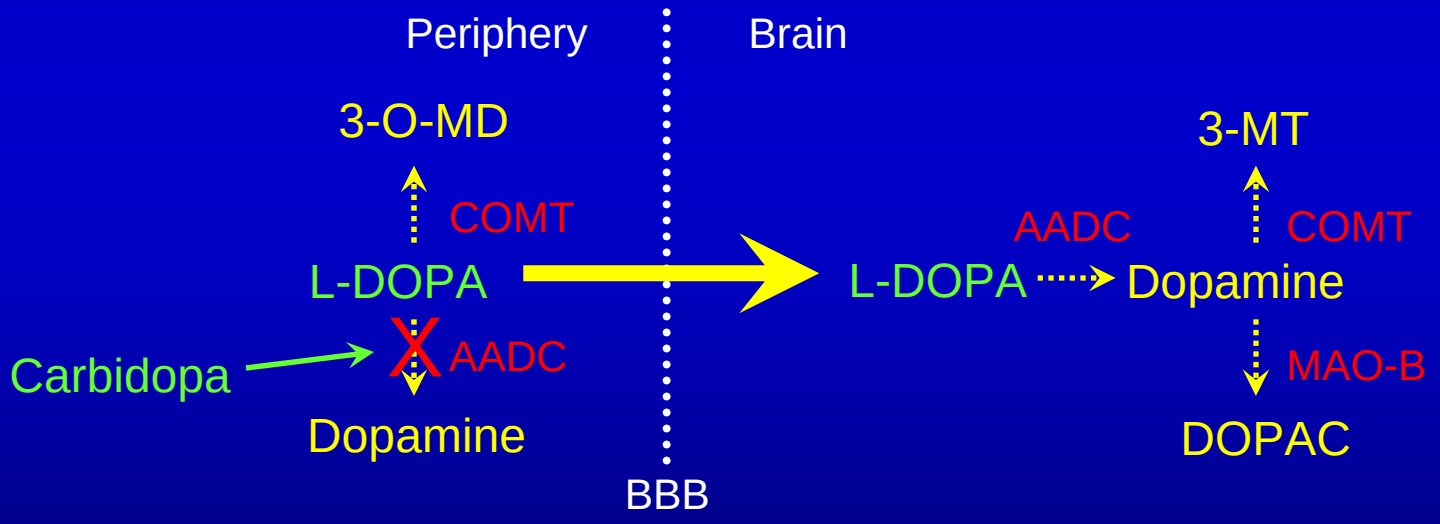

The Dopaminergic Synapse
MAO
TH
AADC
Tyrosine
DOPA
DA
DA
DA
MAO
COMT
Tyrosine
DOPAC
3MT
COMT
MAO
HVA
Presynaptic
Postsynaptic

Pharmacologic Treatment of Parkinson's Disease

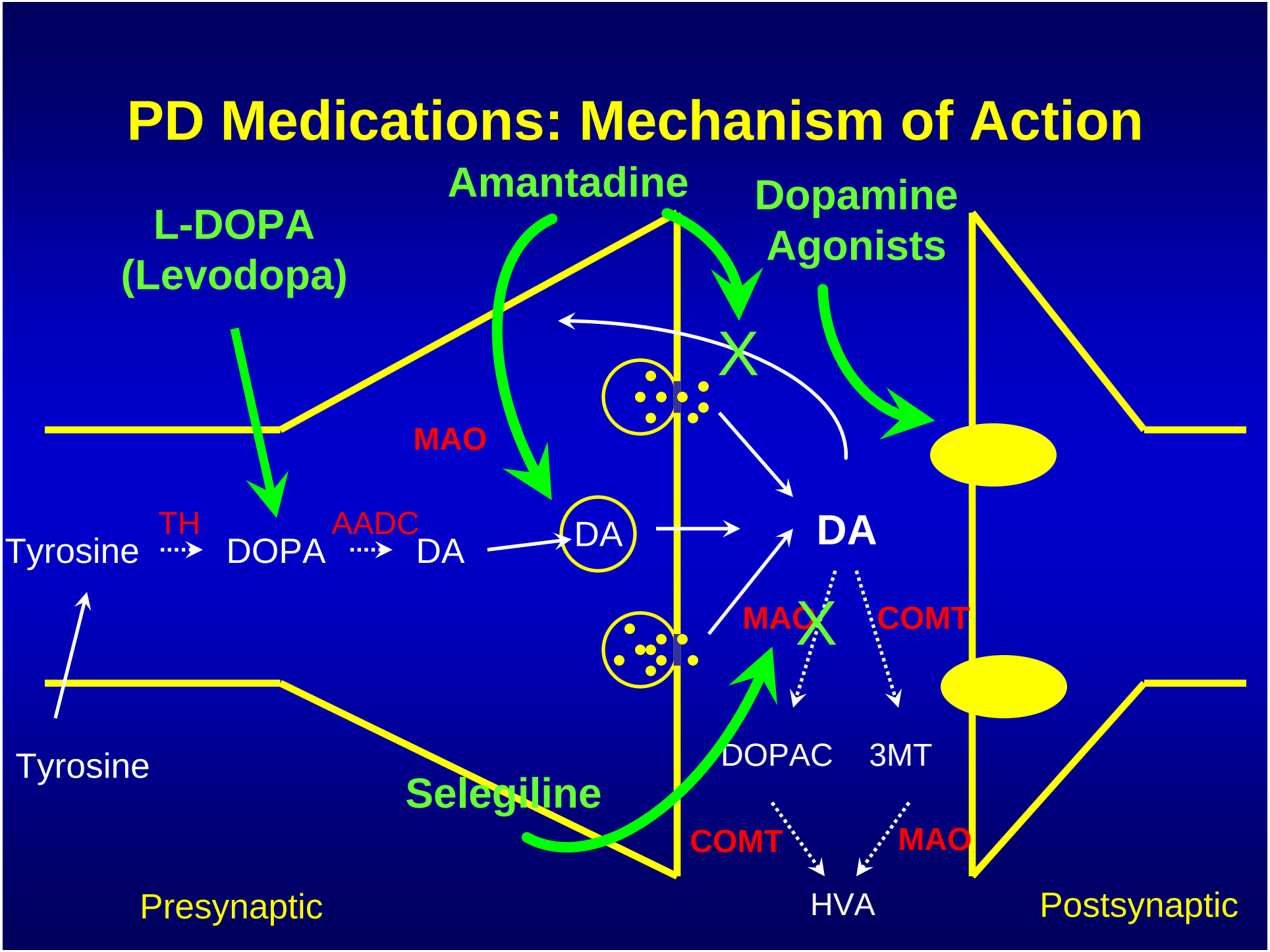
- Dopaminergic agents
  - Levodopa
  - Dopamine agonists
- COMT inhibitors
- MAO-B inhibitors
- Anticholinergics
- Amantadine

Levodopa

- Most effective drug for Parkinsonian symptoms
- Given with carbidopa, which blocks peripheral decarboxylase (Sinemet® = carbidopa/levodopa)



- Most important limitation: Development of "motor fluctuations" and "dyskinesias"


PD Medications: Mechanism of Action
Amantadine
L-DOPA
(Levodopa)
Dopamine
Agonists
MAO
TH
AADC
Tyrosine
DOPA
DA
DA
DA
MAO
COMT
Tyrosine
Selegiline
DOPAC
3MT
COMT
MAO
HVA
Presynaptic
Postsynaptic

Dopamine Agonists

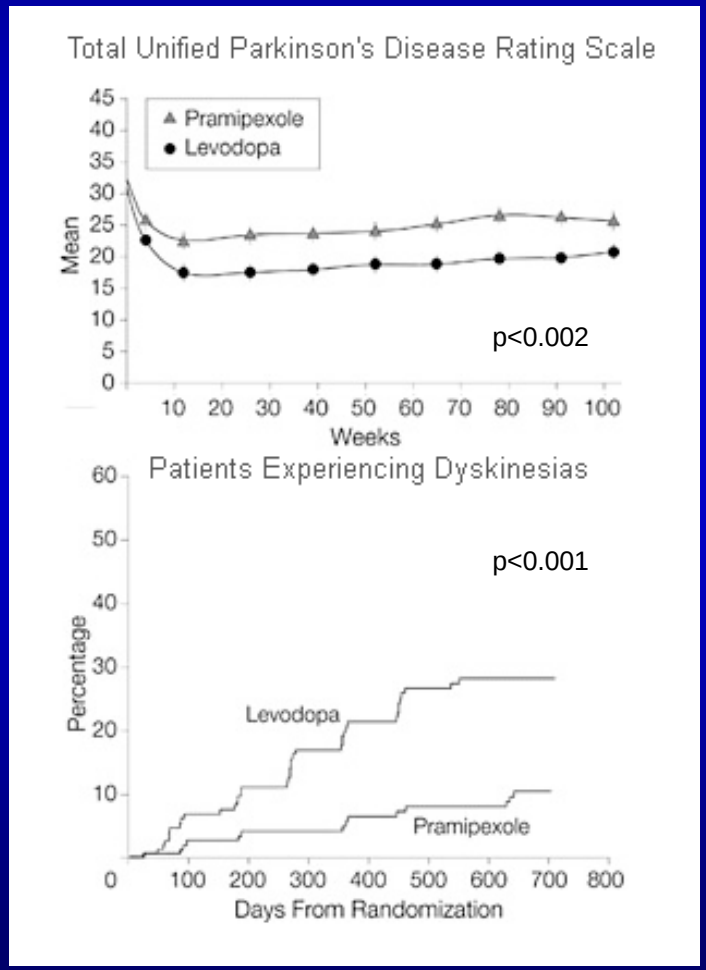
- Directly stimulate postsynaptic DA receptors
- May be used as monotherapy or as adjunct to levodopa
- Longer half-life
- Older Agents:
  - Bromocriptine (Parlodel®)
  - Pergolide (Permax®)
- Newer Agents:
  - Pramipexole (Mirapex®)
  - Ropinirole (Requip®)

Neuroprotective treatments in Parkinson's disease?

- No clearly proven neuroprotective agents
- Difficult to prove neuroprotection
- ? MAO inhibitors, ? dopamine agonists
- ? Coenzyme Q10

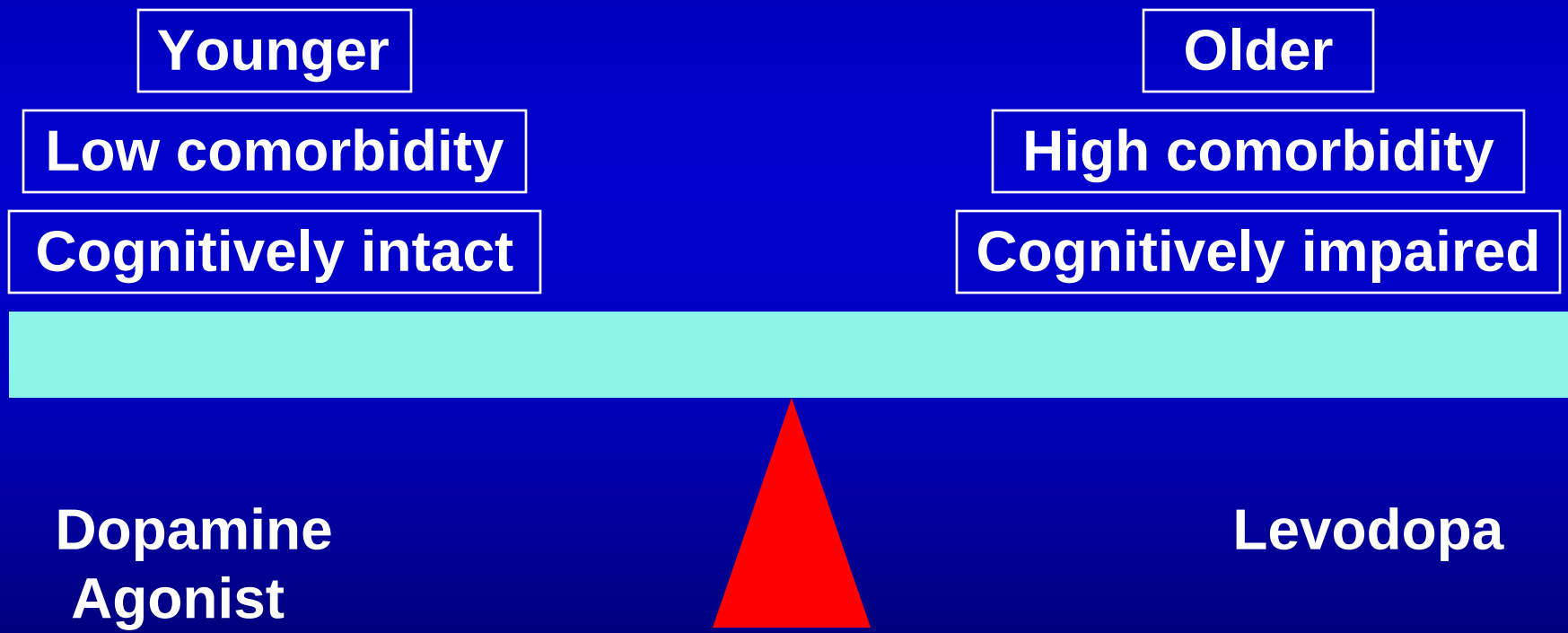
Dopamine agonists vs. Levodopa

- **CALM-PD**: Randomized trial of levodopa vs. pramipexole as initial treatment for PD
- Levodopa is more potent at reducing PD symptoms
- Initial treatment with pramipexole reduces development of wearing off and dyskinesias
- Higher incidence of adverse effects with pramipexole, including somnolence, edema, and hallucinations



Parkinson Study Group, JAMA, 2000

Initial Therapy in PD



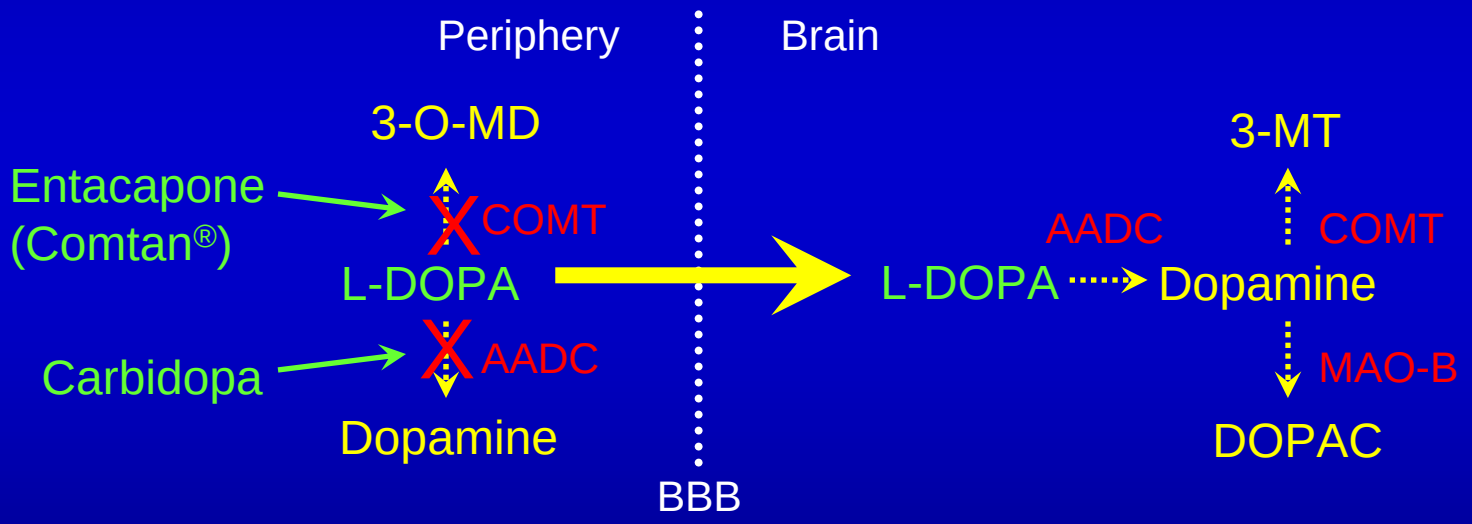
Management of Motor Fluctuations in Advanced PD

- Hypothesis: Non-physiologic variations in dopamine concentration induce motor complications

- Management Options:
  - Shorten dosing interval
  - Increase dose of dopamine agonist (longer half-life)
  - Addition of COMT inhibitor
  - Amantadine (treatment of dyskinesias)

COMT Inhibitors

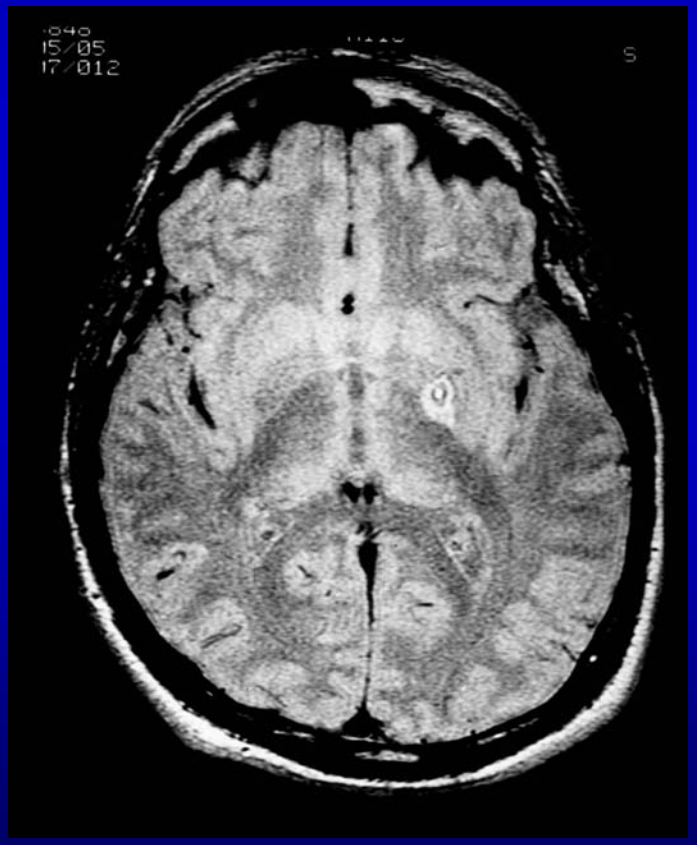
- Prolongs half-life of L-dopa by inhibiting catabolism by catechol-O-methyl transferase



- Reduces off-time and increases on-time in PD patients with motor fluctuations
- Stalevo® = carbidopa/levodopa + entacapone

Surgical Management of Parkinson's Disease

Pallidotomy



Deep Brain Stimulation