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Brain and Mind
The University of Western Ontario

Parkinson's Disease

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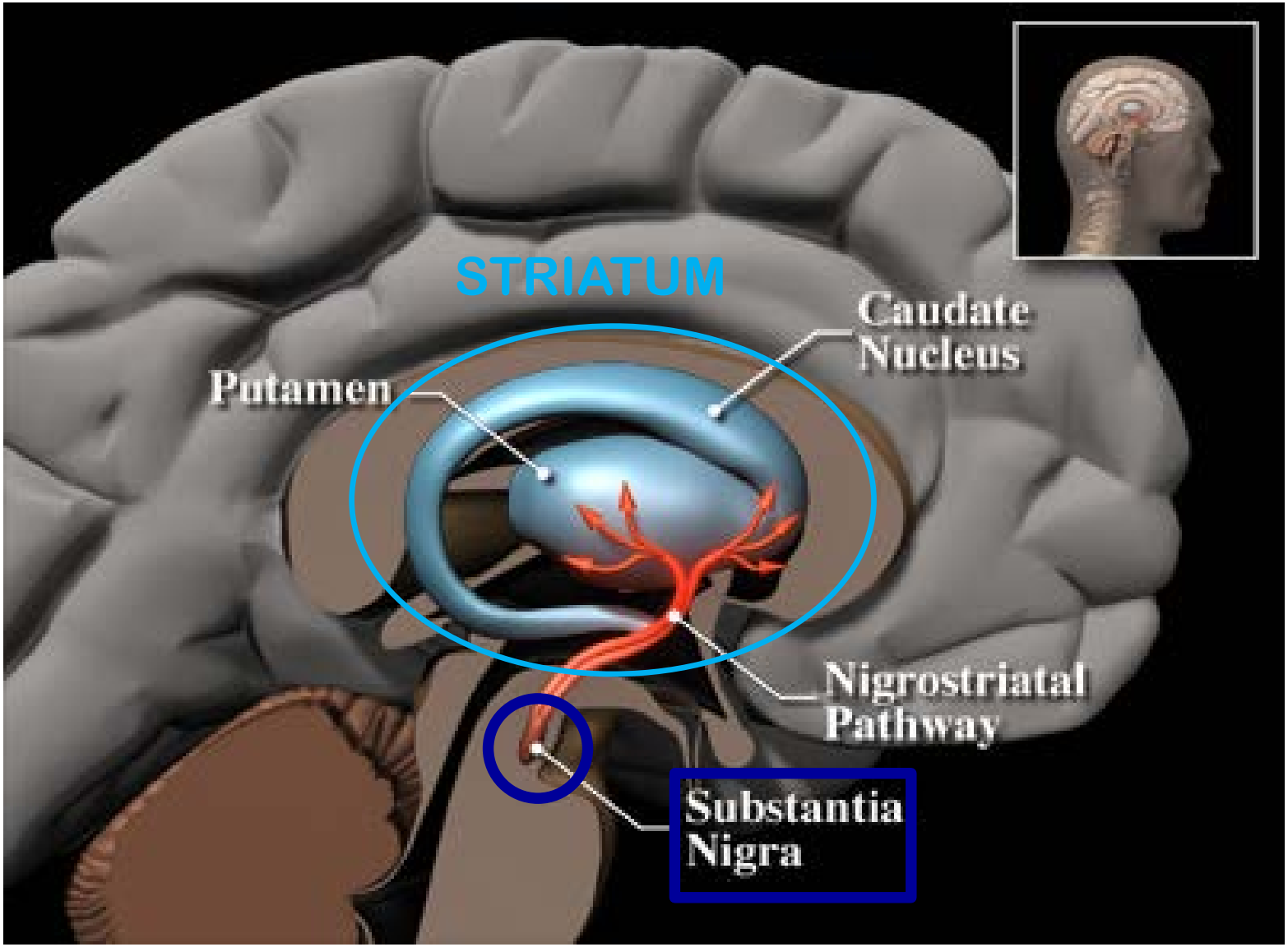
Overview

- review the epidemiology
- pathophysiology of motor symptoms
- motor symptoms
- non-motor symptoms
- effect of dopaminergic therapy
- effect of DBS
- research

PD: Definition & Epidemiology

- progressive multi-symptom illness
- premature, focal neurodegeneration
- cardinal, motor symptoms 2° loss of dopamine-producing cells in SN that supply the (dorsal) striatum
- prevalence 1-2% over age 60 in industrialized countries
- 85% of parkinsonism presentations
- M:F ~ 1.5:1
- Average age of onset ~ 60 years of age (wide range)
- disease duration is complicated, influenced by a number of factors such as age of onset and presence of dementia



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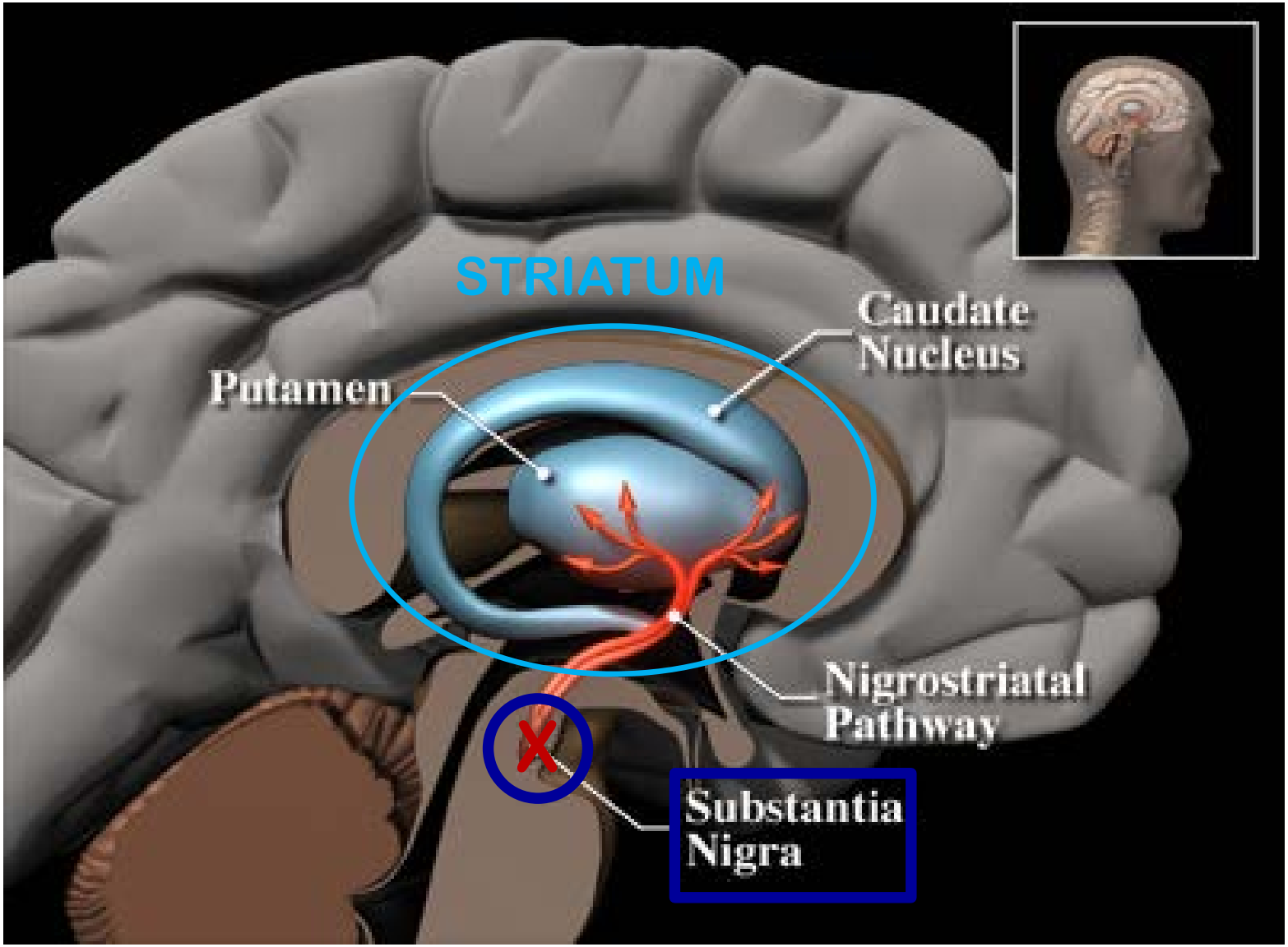

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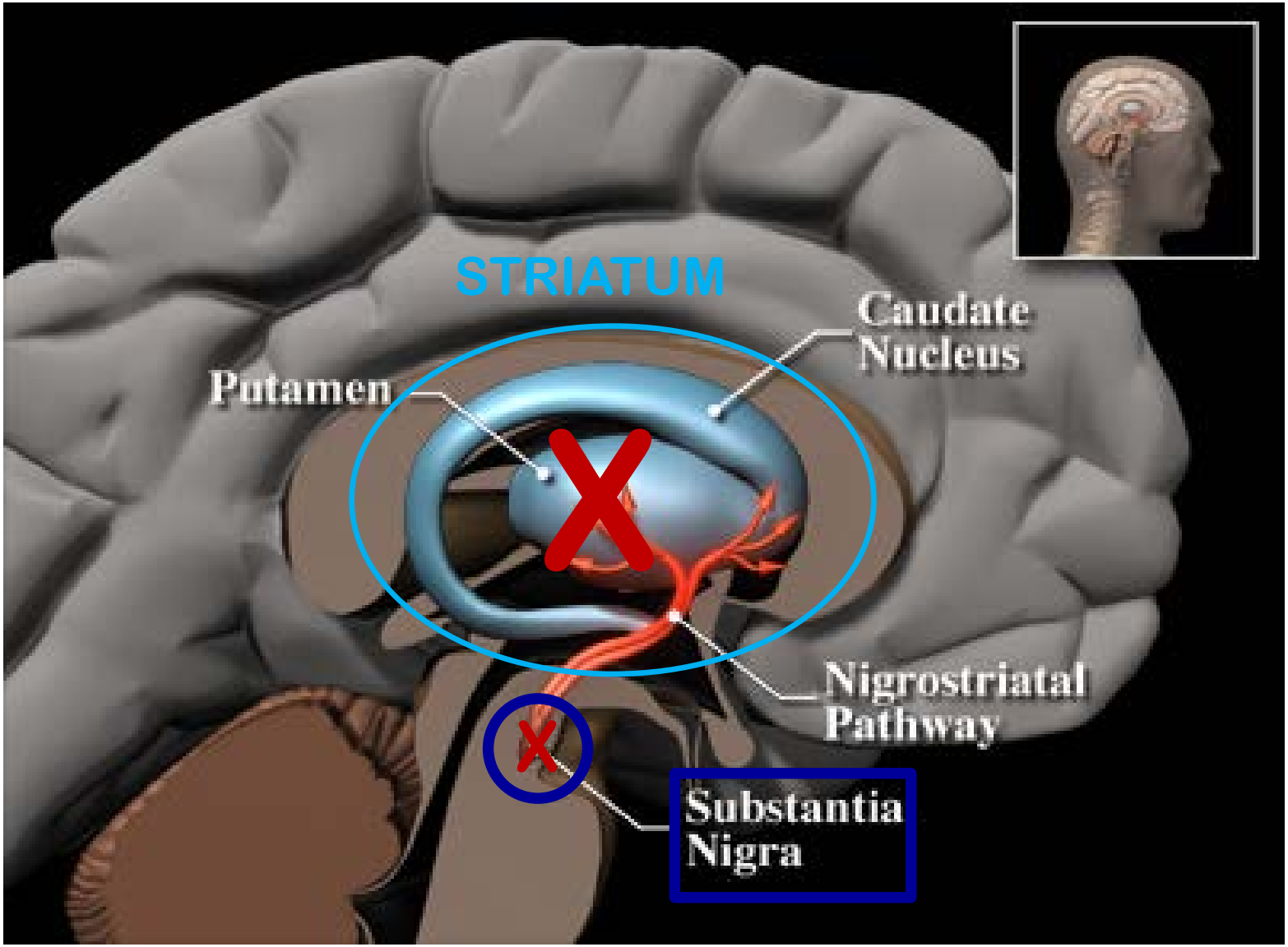

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Before diagnosis -

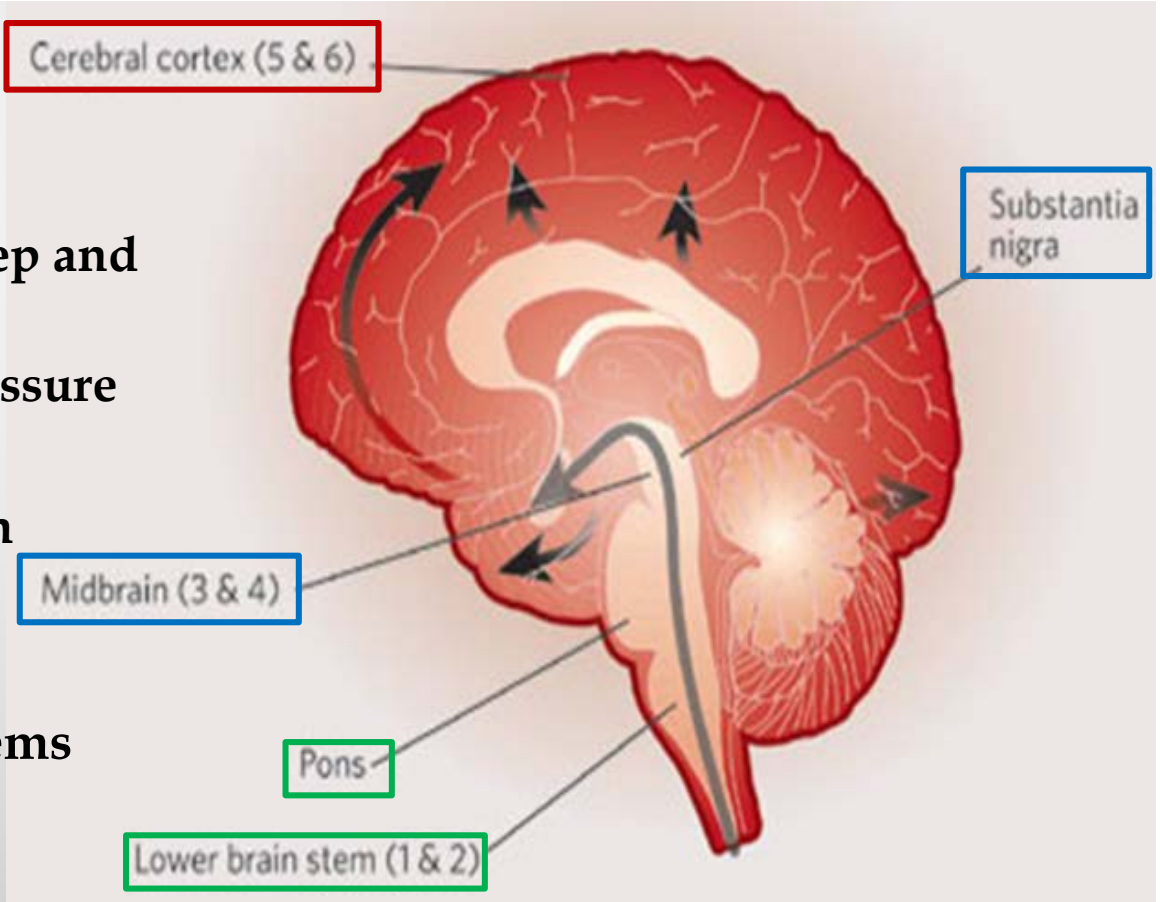
Stages 1 & 2 :

- loss of smell
- disturbance of sleep and wakefulness
- lowered blood pressure
- constipation
- anxiety/depression

At diagnosis -

Stages 3 & 4:

- movement problems
- subtle thinking problems



Later disease - Stages 5 & 6:

- worsening movement problems
- more significant thinking problems/dementia
- worsening anxiety/depression
- hallucinations/paranoia/delusions (i.e., false beliefs)

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Familial Parkinsonism

AD

- Fahr's
- Early onset Parkinsonism
  - a-synuclein - PARK1/4 (1997); < 0.05%
  - LRRK2 - PARK8 (2004); 5-10%
- Juvenile Huntington's
- SCA2
- SCA3 (Machado-Joseph)

AR

- Early onset Parkinsonism
  - Parkin - PARK2 10-20%
  - DJ-1 - PARK7 1-2%
  - PINK1 - PARK6 2-7%
- Gaucher's Disease
- Wilson's Disease
- Parkinsonism-Dementia Complex of Guam+ ALS
- Guadeloupean Parkinsonism
- Lubag -dystonia(DYT 3)
- PKAN • Neuroaxonal dystrophy

Sporadic Parkinsonism

- **Idiopathic Parkinson's Disease**
- **Parkinson's Plus Syndromes**
  - **PSP, CBD, MSA, DLB**
- vascular
- Toxicity [MN; CO; methanol neuroleptics/tetrabenazine; MPTP; Parkinsonism-Dementia Complex of Guam+ ALS (cycad nut)]
- Post-encephalitic Parkinsonism (not since 1960)
- FTD with Parkinsonism –17
- Fahr's (bg ca^{2+} idiopathic; hypoparathyroidism, 2° hyperparathyroidism)
- Guadeloupean Parkinsonism (annoma muricata)
- recurrent trauma

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Motor symptoms

- rest tremor
  - maximal at rest, decreases or disappears when muscles are contracted/with actions
  - especially affects the thumb and index finger
  - ‘pill-rolling’ appearance, 4-6Hz
  - can appear in hands, legs, head, jaw, **chin**, voice/stuttering
- Rigidity (cogwheeling if patient has tremor)
  - limb, axial, stooped posture (camptocormia, pisa syndrome)

Aside: Essential Tremor

- essential tremor
  - postural + kinetic tremor
  - overflow tremor can make tremor seem to occur at rest
    - be sure patient is relaxed and muscles not contracted
  - should not affect legs
  - often slight tremor present many years (even decades) before assessment

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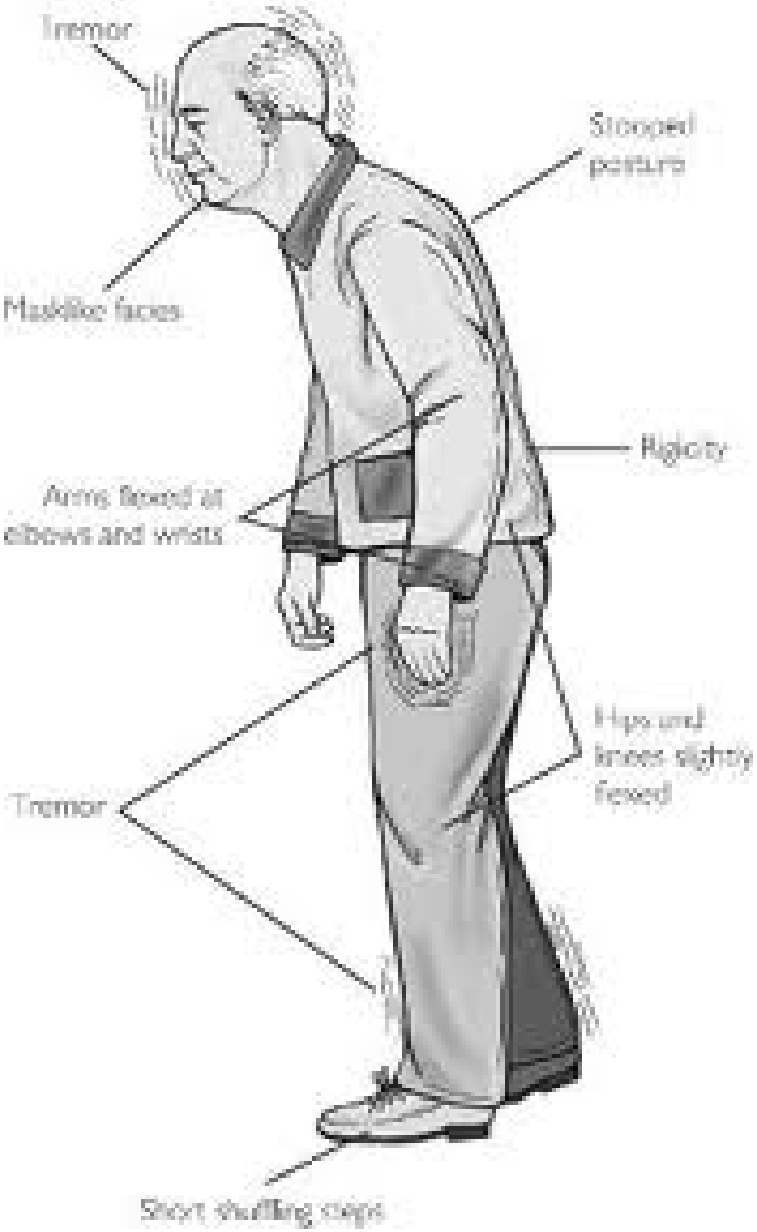
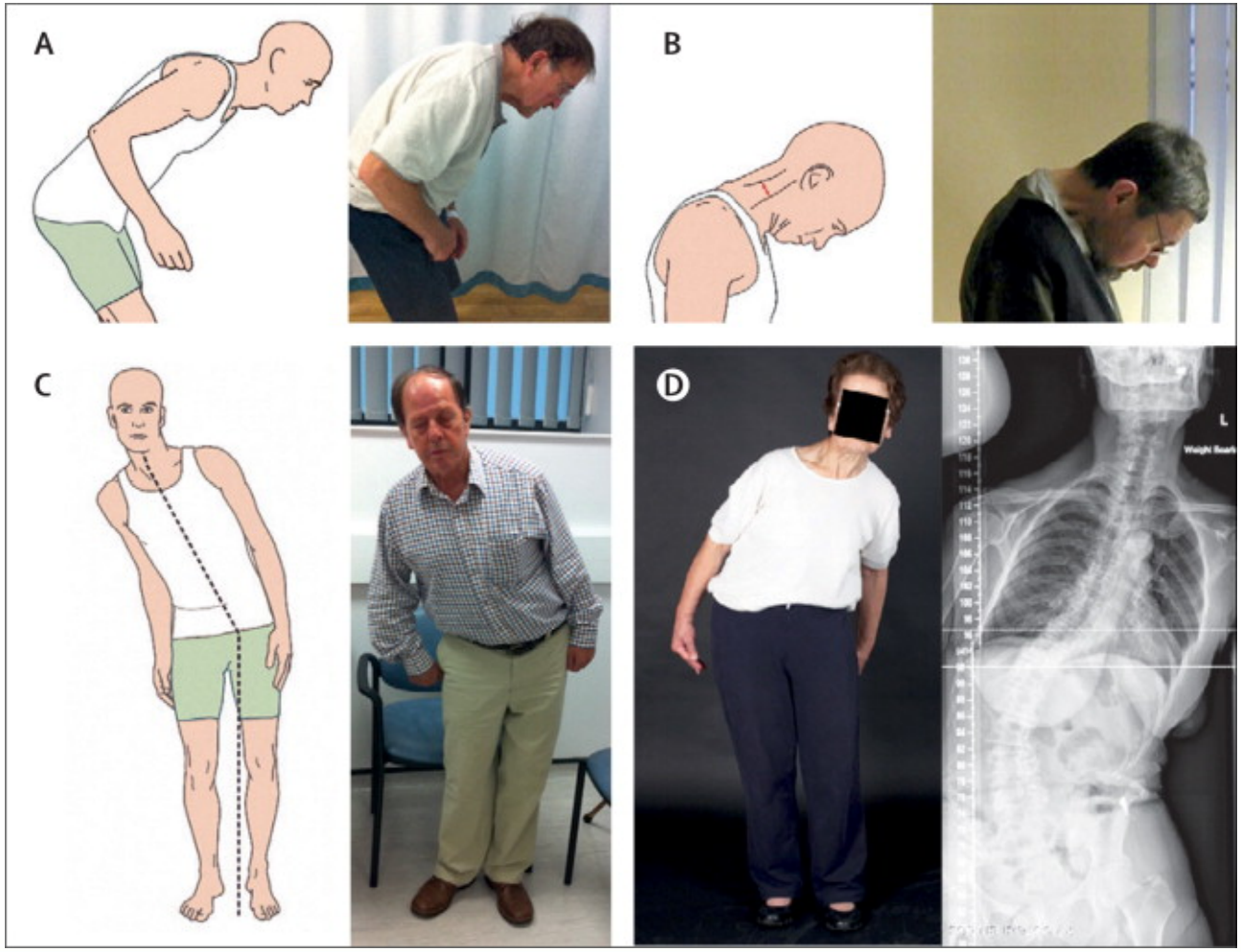
- Rigidity (cogwheeling if patient has tremor)
  - limb; axial (stooped posture, camptocormia, antercollis, pisa syndrome)


Tremor
Stooped posture
Masklike faces
Rigidity
Arms flexed at elbows and wrists
Hips and knees slightly flexed
Tremor
Short shuffling steps

Camptocormia, Anterocollis, and Pisa Syndrome



Motor symptoms

- bradykinesia
  - slowed gait, position changes, hand/finger movements
  - postural instability–slowed righting
- hypokinesia/akinesia
  - masked facies, decreased blinking
  - drooling 2° decreased swallowing
  - decreased spontaneous movements
  - micrographia; hypophonia; dysarthria
- dysphagia
- dystonia (generalized, limb, task-specific)
- postural instability (late)

Non-motor symptoms

- anosmia
- autonomic dysfunction
  - constipation/nausea/early satiety
  - hypotension & orthostatic hypotension
  - sexual dysfunction
  - frequency/nocturia
  - runny nose; drooling
  - altered patterns of perspiration/flushing

Non-motor symptoms

- anxiety/depression (serotonin; noradrenaline)
- apathy/lack of interest or motivation
- cognitive impairment (subtle early; dementia late)
- psychosis (hallucinations, delusions, paranoia; late)

Non-motor symptoms

- disturbance of wakefulness
  - somnolence; increased daytime sleeping (noradrenaline, serotonin, histamine, orexin)
- disturbance of sleep
  - restless leg syndrome
  - increased dreaming/vivid dreams
  - REM sleep behaviour disorder
  - insomnia, difficulty maintaining sleep (acetylcholine, GABA, histamine, orexin)

Non-motor symptoms

- vision changes
  - impaired colour discrimination
  - glaucoma (need periodic ophtho
- skin problems
  - excessively oily skin
  - seborrheic dermatitis
  - increased risk of melanoma (educate patients about vigilance)
- pain

PD Diagnosis

At least THREE of the following supportive (prospective) criteria:

- unilateral onset
- persistent asymmetry primarily affecting side of onset
- progressive disorder
- excellent response (70–100%) to levodopa
- severe levodopa induced chorea (dyskinesia)**
- levodopa response for 5 years or more
- clinical course of 10 years or more

PD Plus Syndromes

Tauopathies (4-repeat tau)

- Progressive Supranuclear Palsy (PSP)
- Corticobasal Ganglionic Degeneration (CBGD)

α-synucleinopathies

- Multiple-System's Atrophy (MSA)
- Lewy Body Demential (DLB)*

(remember IPD is α-synucleinopathy)

* often also AD pathology

Red Flags: Consider 'PD Plus Syndrome' or Genetic Form

- early/prominent dementia
- early falls/postural instability
- early hallucinations
- eye-movement abnormalities
- symmetrical signs
- early or significant bulbar dysfunction
- early gait disorder
- wheelchair dependence within 5 years
- early autonomic failure
- sleep apnea/gasping respirations
- apraxia
- alien limb
- no response to L-dopa
- * numerous 1st degree relatives with PD
- * onset before age 40

PD & PD Plus: Presentation

- Motor > Cognitive
  - PD
  - MSA
  - CBD
- Cognitive > Motor
  - PSP
  - DLB
  - CBD

- Asymmetric
  - PD
  - CBD
  - DLB
- Symmetric
  - PSP
  - MSA
  - DLB

PD: Treatment of Motor Symptoms

Dopamine precursor [e.g., Levocarb (Sinemet); Parcopa]

- most effective treatment of *motor symptoms*

Dopamine agonists [e.g., pramipexole (Mirapex); ropinirole (Requip)]:

- effective medication to treat motor symptoms in PD

Both

- improve some aspects of **cognition**
  - attention/concentration, problem solving
- worsen other aspects of **cognition**
  - learning new skills/information
- improve restless leg syndrome (DA better than L-DOPA)
- frequency and dosages increase with disease progression

Dopaminergic Medications: Side Effects

Levocarb < Agonist

- nausea/dizziness
- postural hypotension
- somnolence
- confusion
- hallucinations
- paranoia
- ICDs/punding

Levocarb > Agonist

- dyskinesia

Dopaminergic Medications: Side Effects

Agonist

- sleep attacks
- peripheral edema
- nasal congestion
- can worsen constipation

Other Motor Treatments

Catechol-*O*-Methyltransferase inhibitors [COMT; entacapone(Comtan) or tolcapone(Tasmar)]

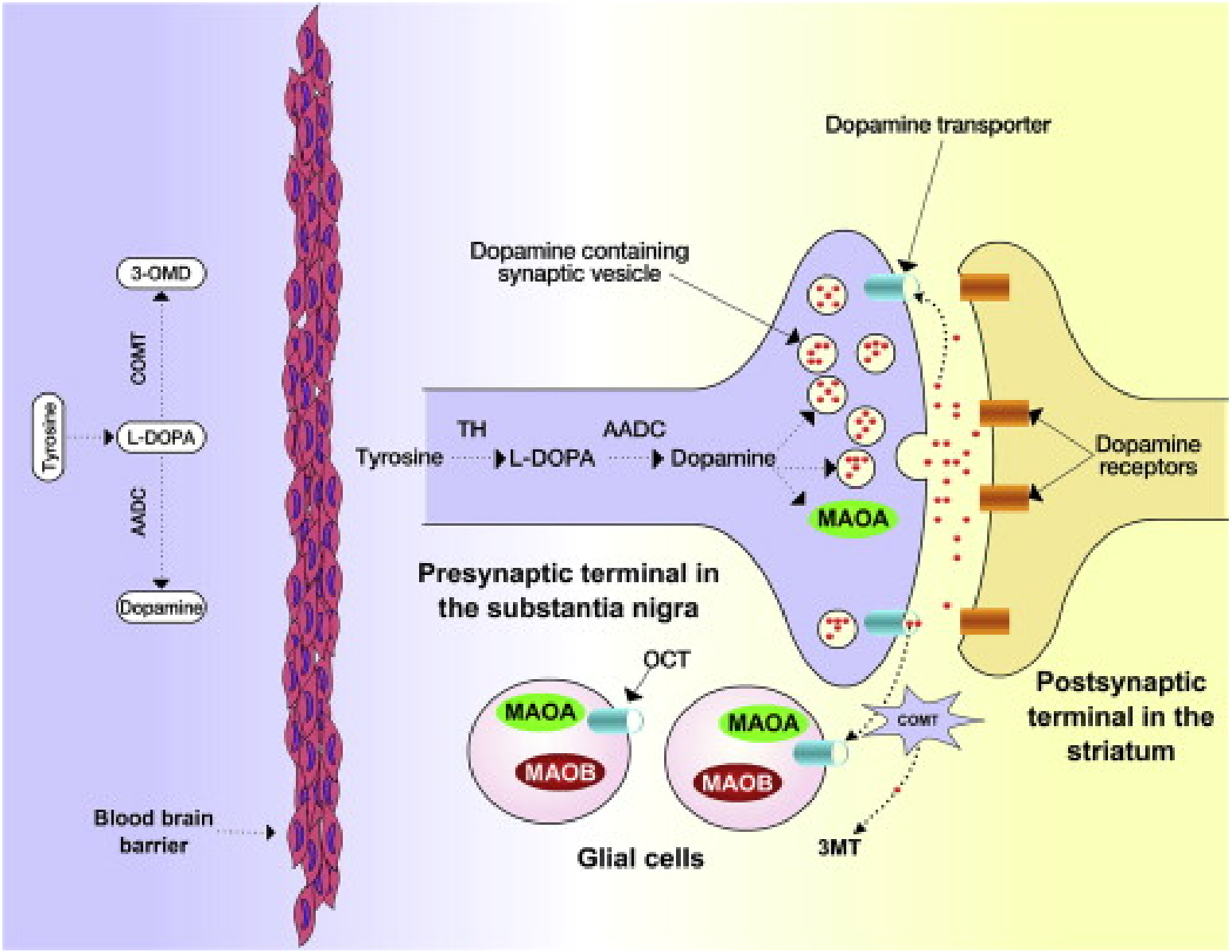
- slows the break-down of levodopa, thereby increasing the effect and duration of action of levodopa in the brain
- side effects:
  - increases all dopaminergic side effects
  - diarrhea
  - causes urine and sweat to have an orangey colour

*Note: **Stalevo** is a medication that combines **levocarb/Sinemet+ entacapone/Comtan** in one pill. The medication **tolcapone/Tasmar** is not used because of hepatic side effects.*

Other Motor Treatments

Monoamine oxidase Type B inhibitors [(MAOI-b; selegeline (Deprenyl), rasagiline(Azilect)]

- slows the break-down of levodopa/dopamine, thereby increasing the effect and duration of action of levodopa in the brain
- side effects
  - increases all dopaminergic side effects
  - nausea
  - insomnia
  - theoretical hypertensive crisis if combined with tyramine-rich foods/beverages/dietary supplements
    - not observed in the clinical trials so far



AADC = aromatic amino acid decarboxylase; COMT = catechol-o-methyltransferase ; MAOA/B = monoamine oxidase A/B; L-DOPA = L-3, 4-dihydroxyphenylalanine

Other Motor Treatments

Amantadine (Symmetrel)

- antiviral medication causing slight improvement in PD motor symptoms
- decreases dyskinesias
- side effects
  - hallucinations
  - confusion
  - nightmares
  - swelling of the limbs termed *peripheral edema*
  - purplish rash called *livedo reticularis*

Other Motor Treatments

Anticholinergic medications [e.g., trihexyphenidyl (Artane), benztropine (Cogentin)]

- blocks acetylcholine receptors
- minimally reduces tremor
- rarely used, poorly effective
- side effects
  - dry eyes and mouth
  - constipation
  - urinary retention
  - confusion; somnolence
  - hallucinations

Symptoms not Responsive to Dopaminergic Therapy

Motor symptoms

- falls, postural instability
- freezing
- swallowing
- speech

Non-motor symptoms

- all except for cognition, restless leg
- might improve depression but worsen anxiety

Treatment of non-motor symptoms

constipation

- diet, fibre
- docusate (Colace),
- Senna (Senokot),
- lactulose

sexual function

- sildenafil (Viagra)
- yohimbine
- no treatments proven for women

anxiety

- anxiolytic medications [e.g., citalopram (Celexa) venlafaxine (Effexor)]

Depression

- antidepressant medications [e.g., citalopram/(Celexa), venlafaxine/(Effexor)]

Treatment of non-motor symptoms

sleep and wakefulness deficits

- excessive somnolence
  - caffeine
  - modafinil
- vivid dreams/RBD
  - melatonin
  - clonazepam
- insomnia
  - zopiclone
- restless leg syndrome
  - dopamine agonist [e.g., pramipexole (Mirapex)] or precursor [(e.g., levocarb(Sinemet)]

urinary frequency/ urgency

- amitryptiline
- oxybutynin, flavoxate, tolterodrine
- DDAVP

Treatment of non-motor symptoms

sialorrhea

- amitriptyline
- 1 % atropine solution (sublingual)
- oral anticholinergics
- Botox injections

seborrhea

- steroid cream
- ketoconazole cream

DBS: Indications

- typical features of PD
- preferable that the disease duration be at least 5 years (except in cases of disabling tremor or disabling dyskinesias)
- failure of best medical therapy after good initial improvement
- wide fluctuations, difficult to control, but dopamine-reponsive (think of DBS as continuous Levocarb infusion)
- absence of significant medical problems
- absence of cognitive impairment
- appropriate age (STN surgery not recommended > 70

DBS Targets

Thalamus

- tremor

STN & GPi

- ↓ tremor/bradykinesia/rigidity, on-off fluctuations, dystonia (permit ↓ dopa med reduction ↓ dyskinesia)

STN

- possibly greater improvement in motor scores & med reduction
- smaller size → lower voltage stimulation & improved battery life

GPi DBS:

- possibly better for management of dyskinesias and less psychiatric side effect

Expectations of DBS

- does not cure
- bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking
- smooths out on-off fluctuations
- improves tremor, stiffness, bradykinesia
- decreased Levocarb dose leads to decreased dyskinesia
- never improves symptoms that are unresponsive to the patient's best "on"
- frequent programming visits, especially initially
- decreases medications in many, but not all, patients.

DBS Complications

Surgery related

- seizure
- hemorrhage
- infection
- permanent deficit (0 to 0.6%)
- misplaced leads

Hardware related

- device malfunction
- lead erosion/disconnection
- lead migration/fracture

Stimulation related

- paresthesias
- muscle contractions
- dysarthria
- diplopia
- cognitive changes
- depression/mania/suicide
- pseudobulbar affect
- obsessions/compulsions
- anxiety/panic attacks
- aggressive behaviour

Overview

- PD is a progressive, multi-system disorder.
- We do a good job of controlling motor symptoms.
- Non-motor symptoms are more difficult to address.
- DBS is an option for some patients only and it only can achieve what best ON state for that patient is with less dyskinesia.

Research

- Patients with early PD no cognitive problems as well as patients with REM Sleep Behaviour disorder no PD no MSA no cognitive impairment.
  - for longitudinal structural, functional MRI, genetic analysis, cognitive, real-world performance (e.g., driving simulation, VR gait studies)