# *Parkinson Disease Update*



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**Nov 2026**

# *Conflict of Interest Statement*

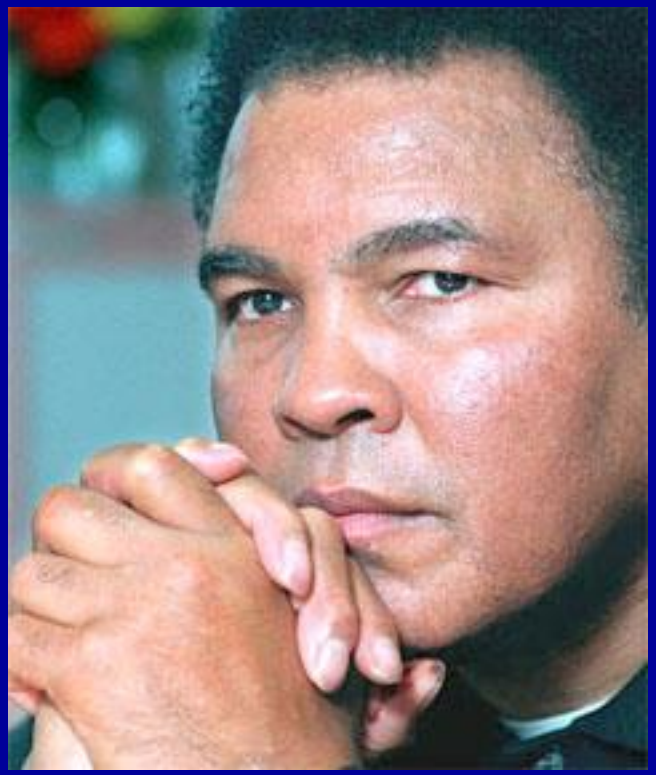
**No drug (or medical device) company pays me any money**

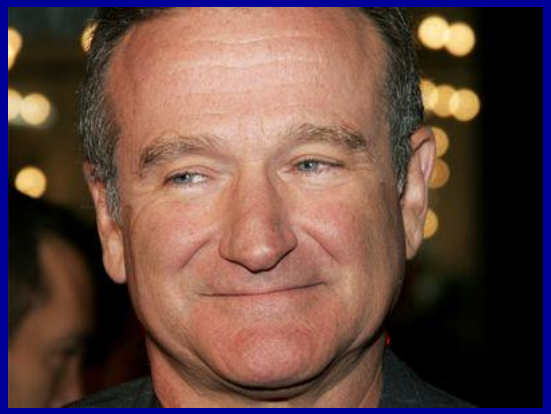
# *Parkinson Disease Update*

- **Epidemiology**
- **Pathology**
- **Medical treatment**

- **Surgical treatment**

# *Parkinson Disease Does Not Spare Anyone*












# *History of Parkinson Disease*

- **1817: James Parkinson describes “Shaking Palsy”**
- **1951: Apomorphine injection improved symptoms in a PD patient**
- **1947: Surgical destruction of internal globus pallidus (GPi) and Vim thalamic nucleus (Ernst A. Spiegel)**
- **1960: Parkinson disease is a state of dopamine deficiency (Herbert Ehringer* & Oleh Hornykiewicz)**
- **1961: First trial of IV levodopa in a PD patient (Birkmayer)**
- **1964: Progressive supranuclear palsy: clinical and pathologic description (Steele, Richardson, Olszewski)**
- **1968: Corticodentatonigral degeneration with neuronal achromasia (Rubeiz, Kolodny, Richardson)**
- **1991: DBS of ventral intermediate thalamic (Vim) nucleus (Alim Benabid)**
- **1995: DBS for subthalamic nucleus (STN) in PD (Patricia Limousin)**

# *Prevalence of PD in the World*

- **Second most common neurodegenerative disorder after Alzheimer disease**
- **World PD prevalence doubling every 25 years:**
  - **1990: 2.5 million**
  - **2016: 6.1 million**
  - **2021: 11.8 million**
  - **2050: 25.2 million (estimated) - 89% of growth due to aging population**
- **Prevalence in the USA:**
  - **1 million PD patients in the USA (~1/300): expected to triple by 2040**
  - **Prevalence by age: 0.4% at ages 60–69 vs 1.4% at ages 80–89**

# *Epidemiology of Parkinson Disease*

- **Etiology: Genetic vs Environmental**
  - **Man/Woman ratio ~ 2:1**
  - **Age: 47 to 77 /100,000 in >45 yrs, 108 to 212 /100,000 >65yrs**
  - **Race: Whites ~ Hispanics > Blacks/Asians (Willis 2010)**
  - **Urban > Rural (Willis 2010)**
  - **Chemicals:**
    - **Pesticides: paraquat, rotenone, organochlorines and organophosphates**
    - **chlorinated solvents: trichloroethylene, perchloroethylene**
    - **MPTP (1983), Manganese**
    - **Ultra-processed foods**
  - **Head trauma**
  - **High dairy consumption (organochlorine heptachlor builds up in milk)**
  - **Genes: few "causative" genes vs >90 common variant "risk-factor" genes**
- **Neuro-protective factors: Caloric restriction, exercise, antioxidants (?), smoking (???), caffeine (?), alcohol (?), …**

# ULTRA-PROCESSED FOOD LIST

Ultra-processed foods are industrial formulations made mostly from substances extracted from foods or synthesized in a lab.

## 1. SUGARY SNACKS




- Candy bars
- Sugary breakfast cereals
- Fruit-flavored snacks (gummies, fruit chews)
- Pastries (cookies, cakes, donuts)
- Sugary drinks (sodas, energy drinks, sweetened juices)

## 2. PROCESSED MEATS



- Hot dogs
- Sausages
- Bacon
- Deli meats (ham, turkey, salami)
- Chicken nuggets

## 3. CONVENIENCE FOODS




- Frozen pizzas
- Microwaveable meals
- Instant noodles
- Frozen dinners
- Boxed macaroni and cheese

## 4. PACKAGED SNACKS




- Potato chips
- Cheese puffs
- Crackers (especially flavored varieties)
- Pretzels
- Packaged cookies

## 5. FAST FOOD



- Hamburgers
- French fries
- Fried chicken
- Chicken nuggets
- Onion rings

## 6. BAKED GOODS



- Store-bought bread (especially white bread)
- Bagels
- Croissants
- Muffins
- Packaged baked desserts

## 7. PACKAGED SWEETS




- Candies (gummy bears, hard candies)
- Chocolate bars
- Packaged ice cream treats (ice cream bars, novelty cones)
- Cookies and cakes

## 8. INSTANT FOODS




- Instant soups
- Instant noodles
- Instant mashed potatoes
- Instant rice

## 9. CONDIMENTS & SAUCES




- Bottled salad dressings
- BBQ sauce
- Ketchup
- Mayonnaise
- Sauces and dips

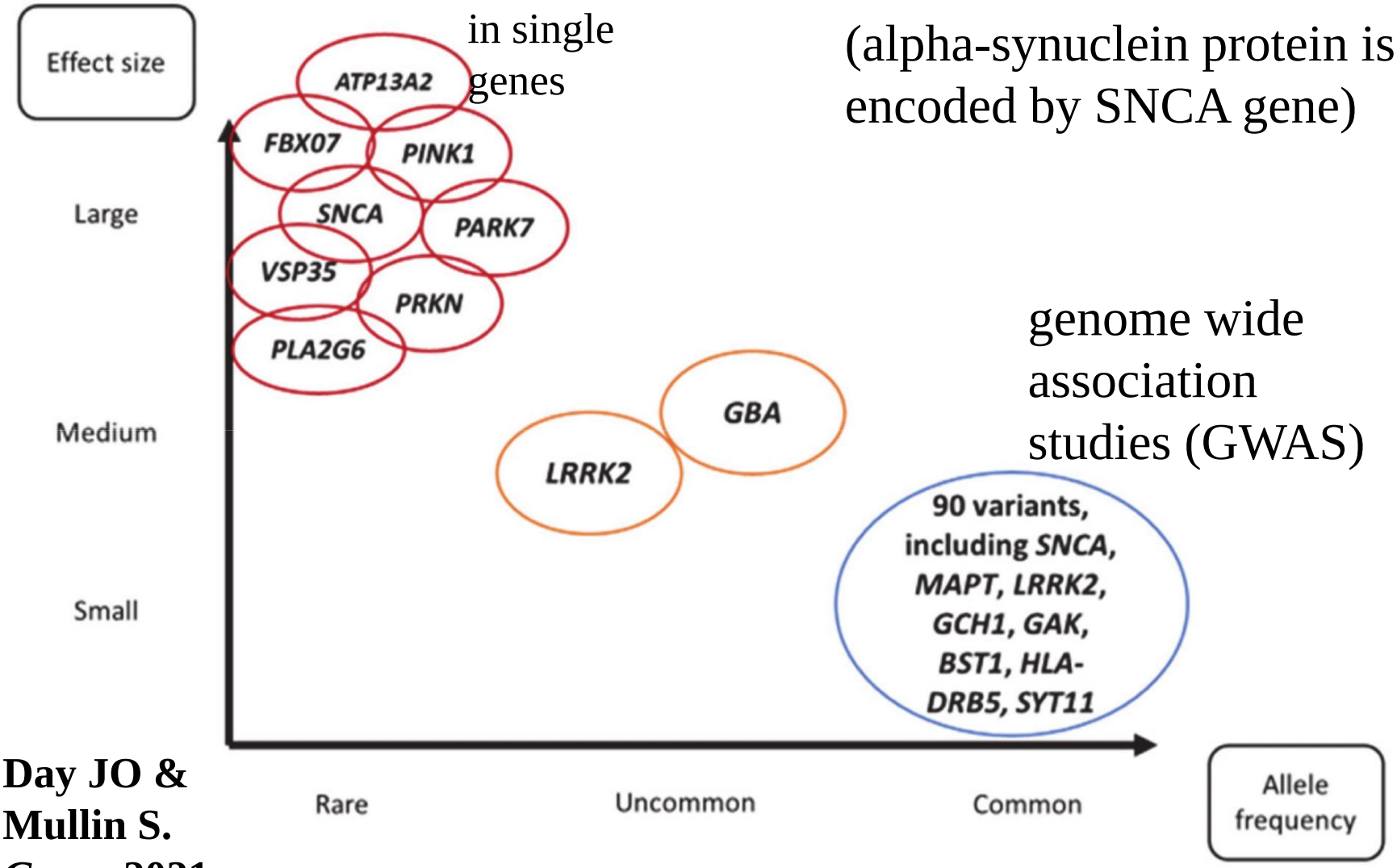
## WHY LIMIT ULTRA-PROCESSED FOODS?

- Supports better overall health
- Helps maintain a healthy gut
- May help manage weight
- Reduces risk of chronic diseases
- Supports better mood & energy

Choose whole foods, cook at home when possible, and read labels to make informed choices.

WelloraDesigns
-Etsy

# *Genetic Variants in PD: Allele Frequency vs Risk of PD*




rare variants in single genes

(alpha-synuclein protein is encoded by SNCA gene)

genome wide association studies (GWAS)

**Day JO & Mullin S.** ***Genes*** **2021**

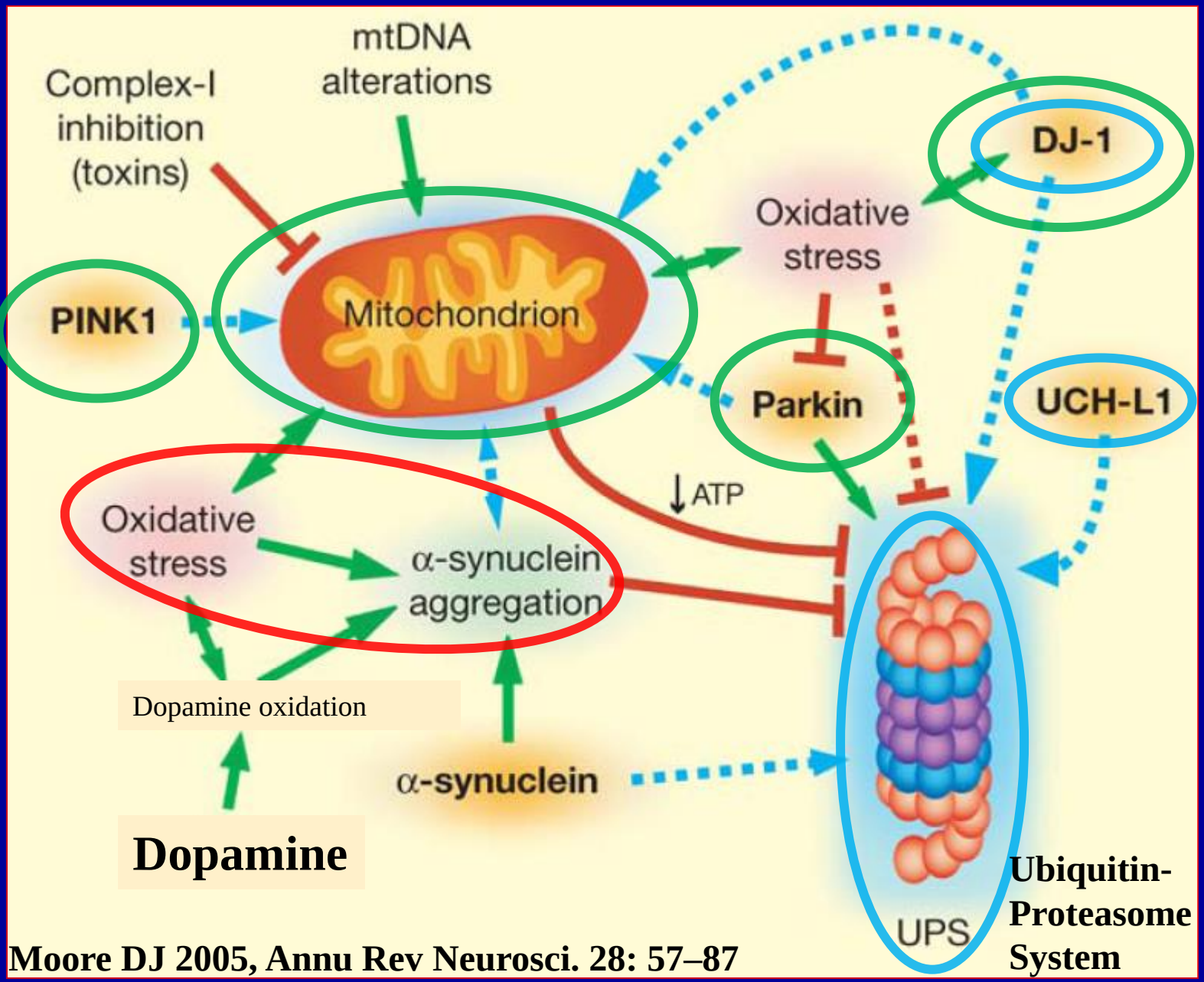
# Monogenic Variants Associated With Familial PD (2021)

**Day JO & Mullin S.**
***Genes* 2021**

| | Gene (HGNC Approved Name) | Alternative Gene Names | Inheritance | Pathogenicity | PD Phenotype | Function |
|---|---|---|---|---|---|---|
| High penetrance | *SNCA* | *PARK1, PARK4, NCAP* | AD | Pathogenic | Early-onset | Uncertain (encodes α-synuclein) |
| | *VPS35* | *PARK17, MEM3* | AD | Pathogenic | Typical | Retromer and endosomal trafficking |
| | *PINK1* | *PARK6* | AR | Pathogenic | Early-onset | Mitochondrial |
| | *PARK7* | *DJ-1* | AR | Pathogenic | Early-onset | |
| | PRKN | *PARK2, PARKIN* | AR | Pathogenic | Early-onset | |
| | *PLA2G6* | *PARK14, IPLA2* | AR | Pathogenic | Early-onset, atypical | Cell membrane |
| | *ATP13A2* | *PARK9* | AR | Pathogenic | Early-onset, atypical | Lysosomal |
| | *FBXO7* | *PARK15, FBX7* | AR | Pathogenic | Early-onset, atypical | Mitochondrial |
| | *POLG* | *POLG1, POLGA* | AD | Pathogenic | Early-onset, atypical | Mitochondrial DNA maintenance |
| | *DNAJC6* | *PARK19, DJC6* | AR | Likely pathogenic | Early-onset | Synaptic vesicle formation and trafficking |
| | *DNAJC13* | *PARK21, RME8* | AD | Conflicting reports | Typical | |
| | *TMEM230* | *C20ORF30* | AD | Conflicting reports | Typical | |
| | *SYNJ1* | *PARK20* | AR | Pathogenic | Early-onset, atypical | |
| | *VPS13C* | *PARK23* | AR | Pathogenic | Early-onset | Mitochondrial |
| | *CHCHD2* | - | AD | Pathogenic | Typical | Uncertain |
| | *DCTN1* | - | AD | Pathogenic | Atypical | Microtubule |
| Variable penetrance | *LRRK2* | *PARK8, DARDARIN* | AD | Pathogenic | Typical | Lysosomal, mitochondrial, microtubule |
| | *GBA* | *GBA1* | AD | Pathogenic | Typical | Lysosomal |
| Associated with PD but unlikely to be pathogenic | *HTRA2* | - | AD | Uncertain/likely benign | - | Mitochondrial |
| | *UCHL1* | *PARK5* | AD | Uncertain/likely benign | - | Ubiquitin-proteasome |
| | *GIGYF2* | *PARK11* | AD | Uncertain/likely benign | - | Uncertain |
| | *EIF4G1* | - | AD | Benign | - | mRNA translation |
| | *LRP10* | *LRP9* | AD [1] | Uncertain | - | Uncertain |

[1] AD = autosomal dominant, AR = autosomal recessive, HNGC = HUGO Gene Nomenclature Committee.

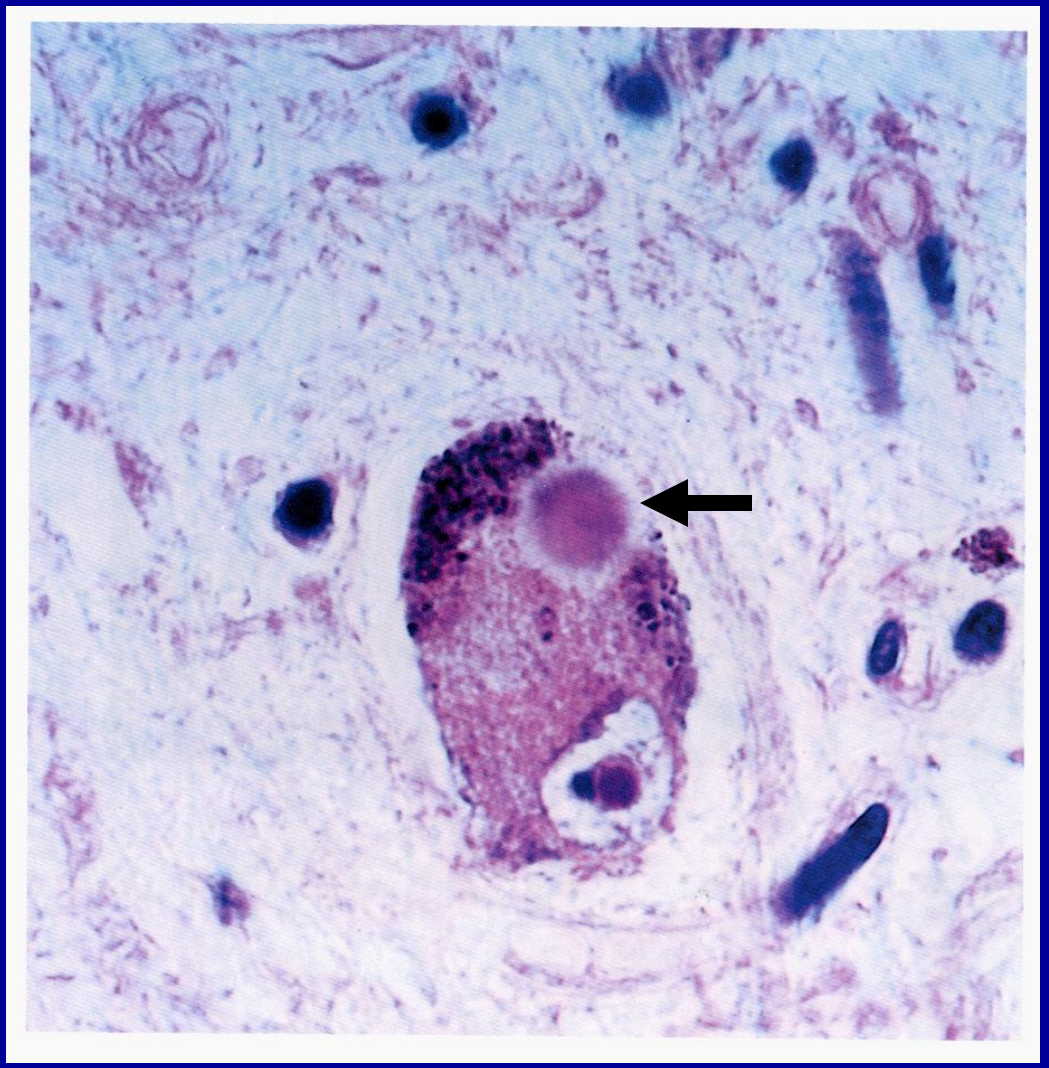
# *Pathophysiology of PD: Synucleinopathy*




Moore DJ 2005, Annu Rev Neurosci. 28: 57–87

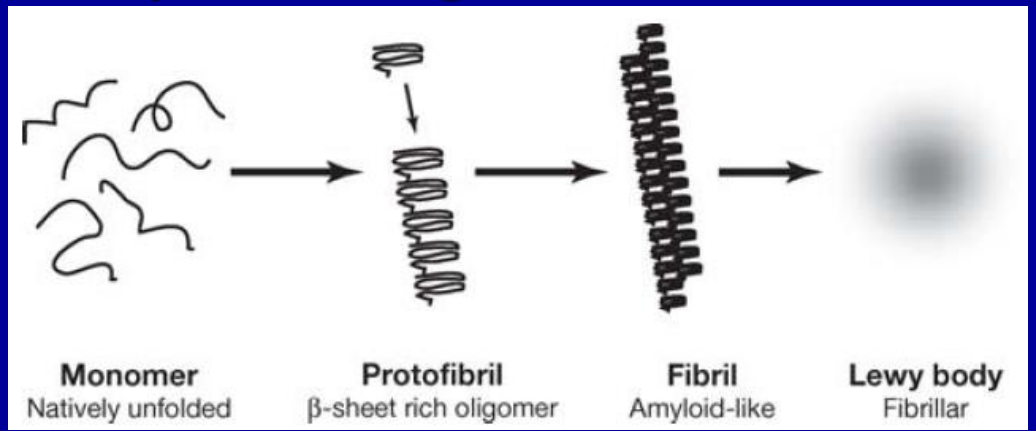
# *Hallmark of Parkinson Disease & Lewy Body Disease: Lewy Bodies*

- **Eosinophillic inclusions in nigral dopaminergic neurons**
- **Contains ubiquitin & α-synuclein**



# *Alpha-Synuclein*

- **Normal α-synuclein (SNCA gene):**
  - **Location: presynaptic membranes and vesicular structures**
  - **Function: synaptic vesicle recycling (?) + affects lysosomal function, mitochondrial function and inflammation**
- **Aggregated α-synuclein:**
  - **aggregation process is accelerated by SNCA pathogenic variants and/or by an increase in intracellular α-synuclein concentration**
  - **disrupts proteasome function and exacerbates oxidative stress**
  - **major component of Lewy bodies (with ubiquitin) & Lewy neurites**
  - **α-synuclein oligomer can transfect neurons, mediating toxicity**

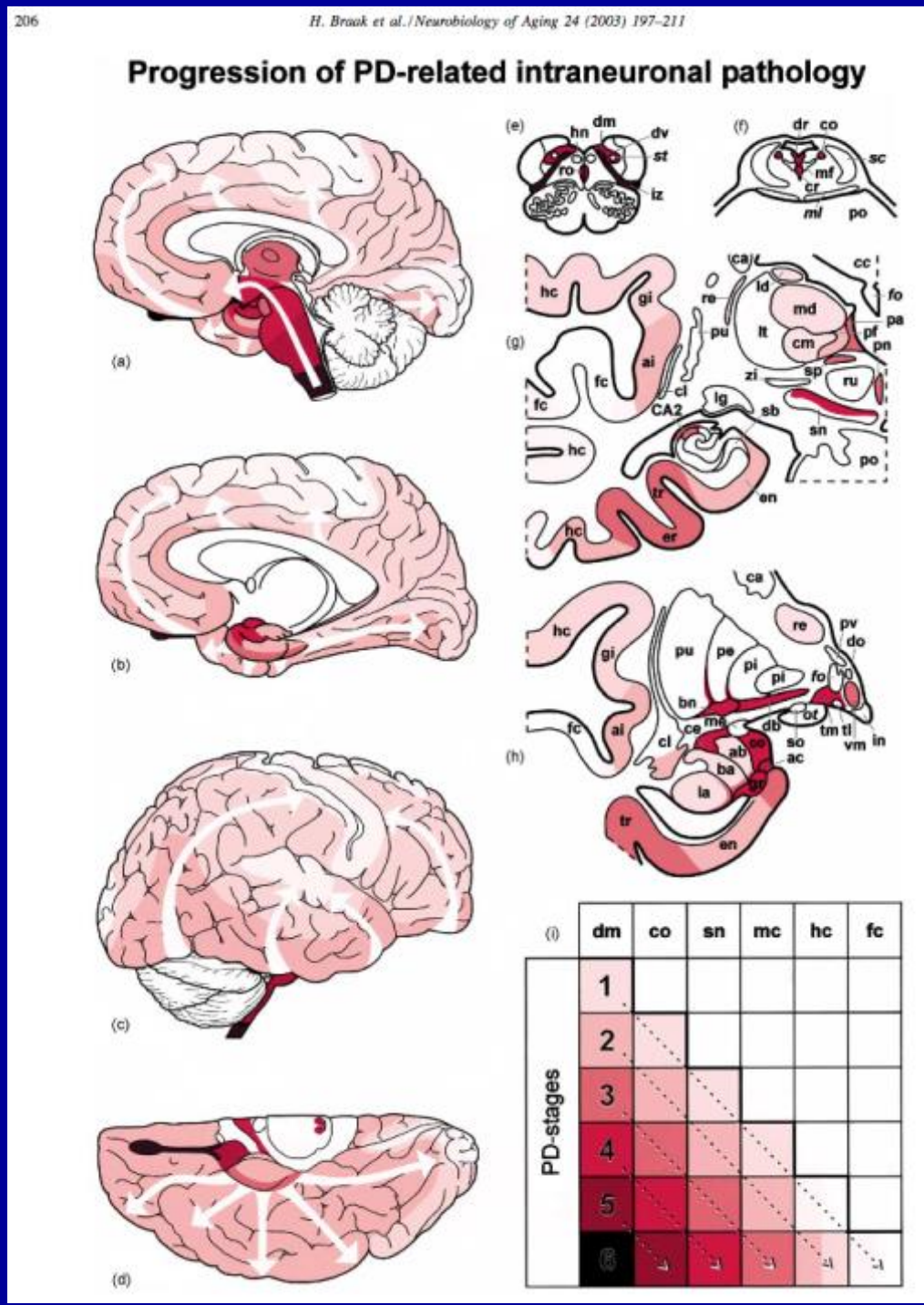



**Moore DJ 2005, Annu Rev Neurosci. 28: 57–87**

# *Braak Staging of PD: Spread of Lewy Body*

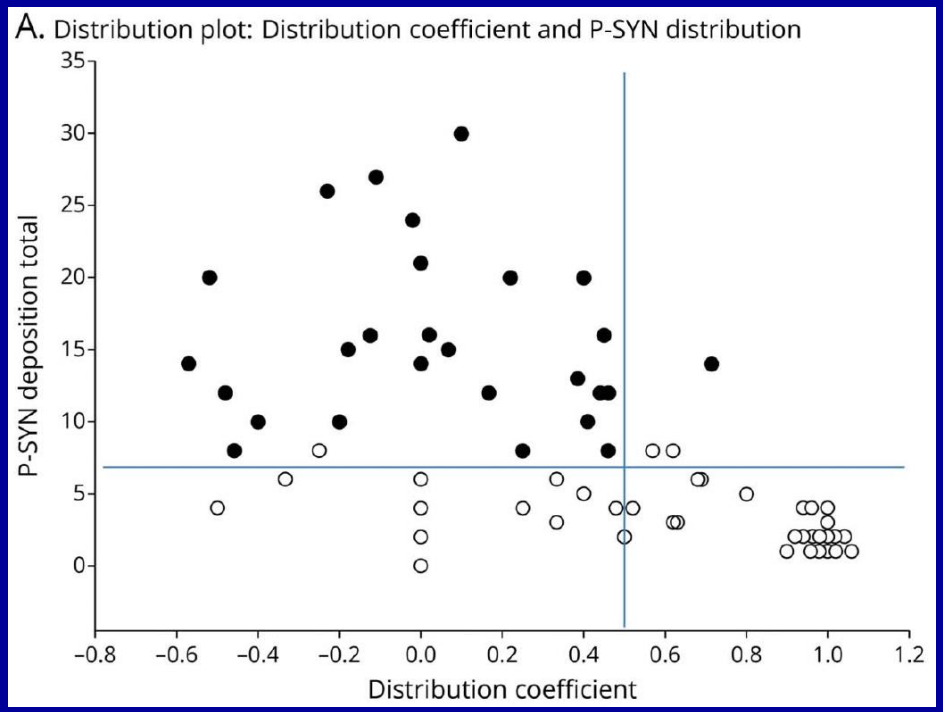
1) Anterior olfactory nerve
   Dorsal motor nuclei of:
   - glossopharyngeal nerve
   - vagal nerve
2) Ascends in the brain stem:
   - caudal raphe nuclei
   - gigantocellular reticular nucleus
   - coeruleus–subcoeruleus complex
3) Substantia nigra pars compacta
4) Anteromedial temporal mesocortex
5) Neocortex high order sensory association & prefrontal areas
6) First order sensory association/premotor areas & primary sensory/motor fields

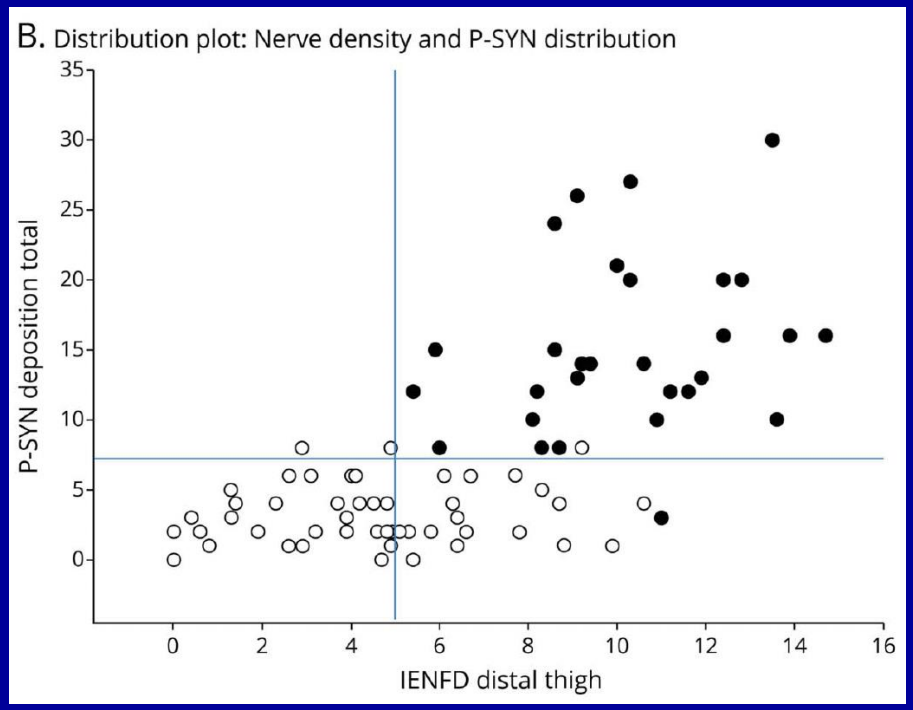
Braak H 2003, *Neurobiol of Aging*



# *Skin Biopsy for Phosphorylated α-Synuclein (P-SYN)*

- **Skin biopsy from distal thigh, posterior cervical and proximal thigh**
- **MSA had greater deposition ($p < 0.0001$) and more widespread peripheral distribution of P-SYN ($p < 0.0001$) than PD.**
- **No P-SYN in controls**




Gibbons C et al, 2023, *Neurology*, 100: e1529-e1539

# *Pathophysiology of PD*

- **Protein handling: ubiquitin & α-synuclein**
- **Mitochondrial dysfunction:**
  - **complex I activity is decreased in substantia nigra**
  - **complex I inhibition induces Lewy body-like inclusions *in vivo***
  - **MPTP and rotenone inhibit complex I**
  - **Mitochondrial dysfunction increases oxidative and nitrosative stress**
  - **Mitochondrial dysfunction promotes α-synuclein aggregation**
  - **PINK1, parkin and DJ-1 contribute to normal mitochondrial function**
- **Oxidative stress: free radicals & iron**
- **Nitrosative stress: Nitric oxide, peroxynitrite & protein nitration**
- **Excito-toxicity: glutamate & calcium**
- **(Glial cells: decreased GDNF & BDNF)**
- **(Apoptosis )**

# *Current Studies on Neuroprotection*

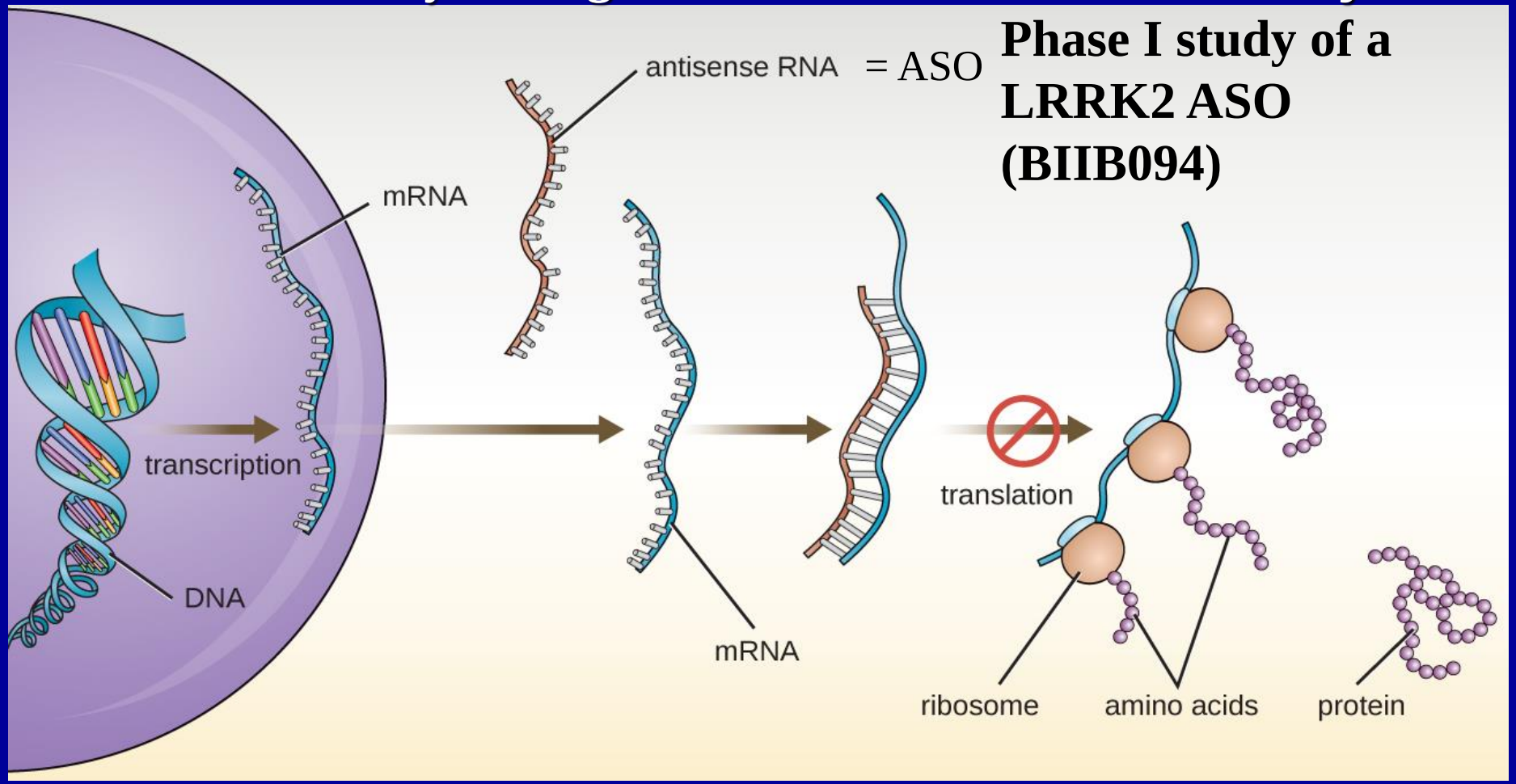
- **Immunotherapy to remove toxic forms of synuclein using:**
  - **antibodies: prasinezumab, cinpanemab (phase II)-Failed**
  - **synuclein peptide mimic which stimulates an immune response: PD01A (passed phase I clinical trial)**
  - **Nilotinib (accelerates synuclein degradation) -Failed**
- **Mitochondrial agents (all phase II):**
  - **ursodeoxycholic acid (phase II)**
  - **terazosin (passed phase I)**
  - **nicotinamide (passed phase I)**
  - **EPI-589 (novel agent)**
- **Antisense Oligonucleotides**

# *Prasinezumab*

- Binds to C-terminus of aggregated α-synuclein and may block cell-to-cell spread of the protein
- It binds aggregated α-synuclein far more tightly than monomeric α-synuclein
- Phase IIb dose was 1500 mg IV every 4 weeks
  - Lowered free serum α-synuclein by up to 97%; CSF α-synuclein did not change
  - Adverse events: constipation, diarrhea, peripheral edema, headache, post-lumbar puncture Sd, allergic reactions (2 pts)
- Phase II studies (n= 316 + 586):
  - No change in MDS-UPDRS Parts I+II+III at 52 weeks
  - But less decline on MDS-UPDRS Part III (motor) scores
  - Larger benefit in patients with faster-progressing disease or those taking MAO-B inhibitors… Now Phase III study

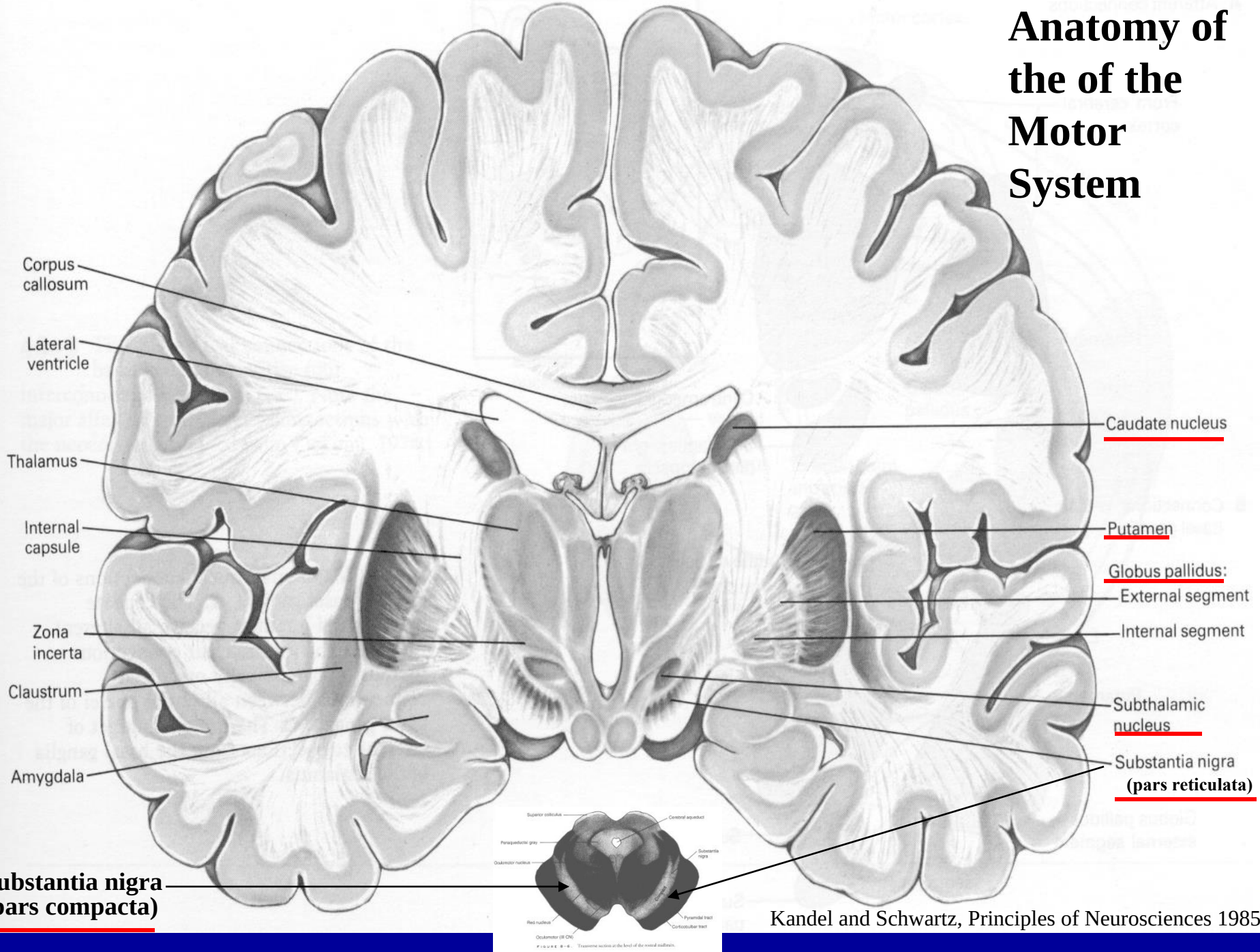
# *Antisense Oligonucleotides (ASOs)*

- **Single-stranded DNA, 8 to 50 base pairs length**
- **Highly charged and large molecule**
- **Distribute widely throughout the CNS after intrathecal injection**




**Phase I study of a LRRK2 ASO (BIIB094)**

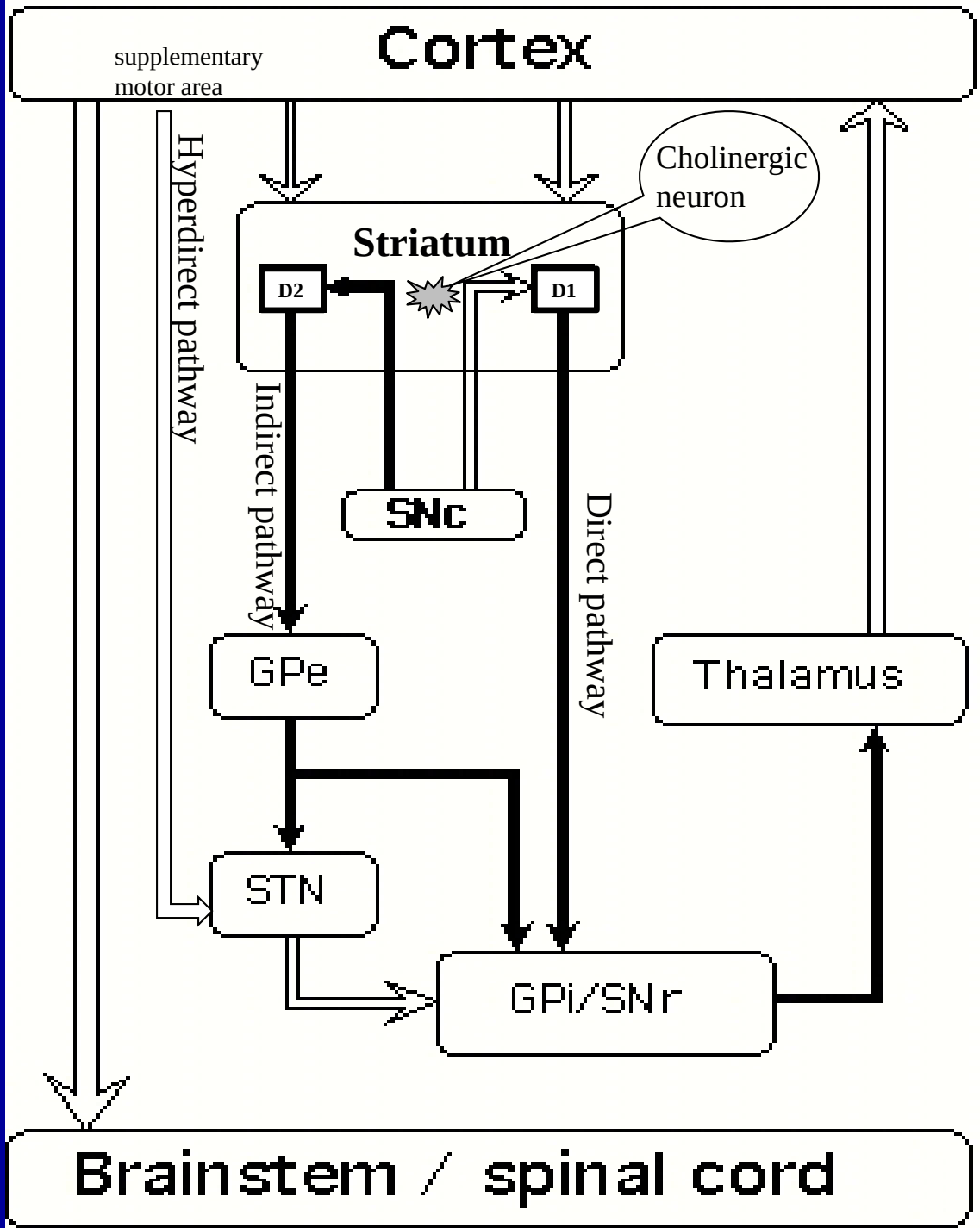
# Anatomy of the of the Motor System



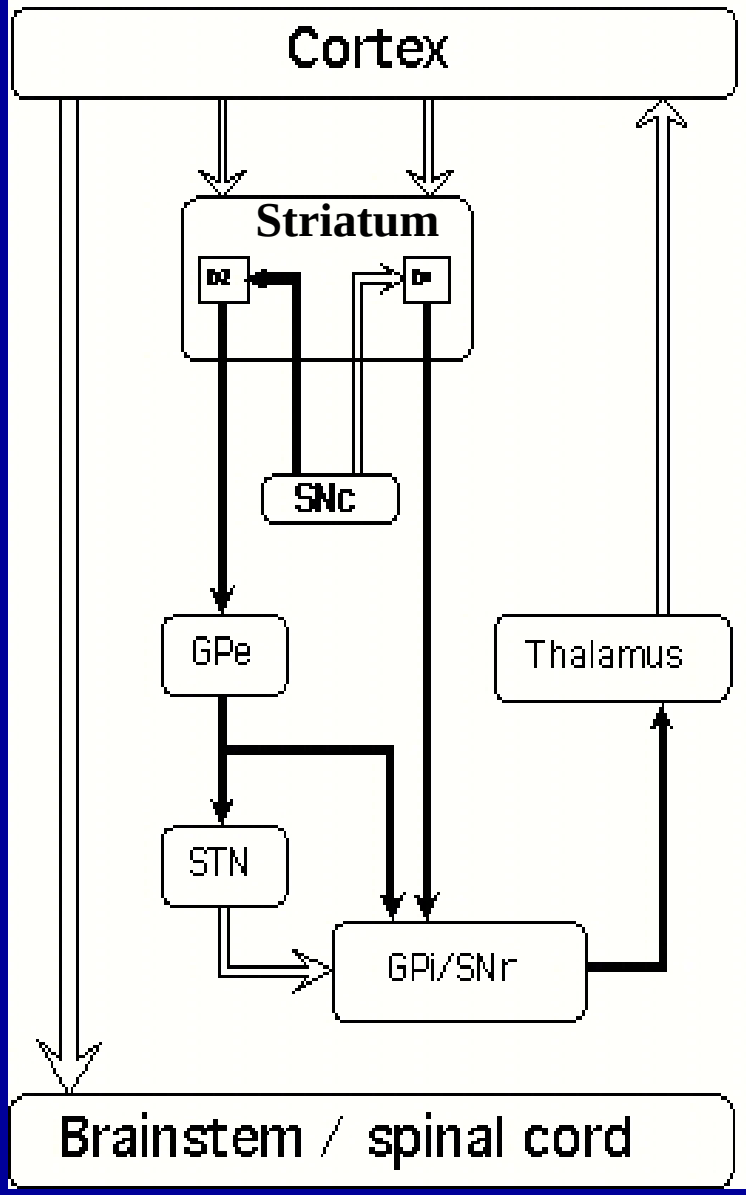

Kandel and Schwartz, Principles of Neurosciences 1985

# Normal Basal Ganglia Circuitry

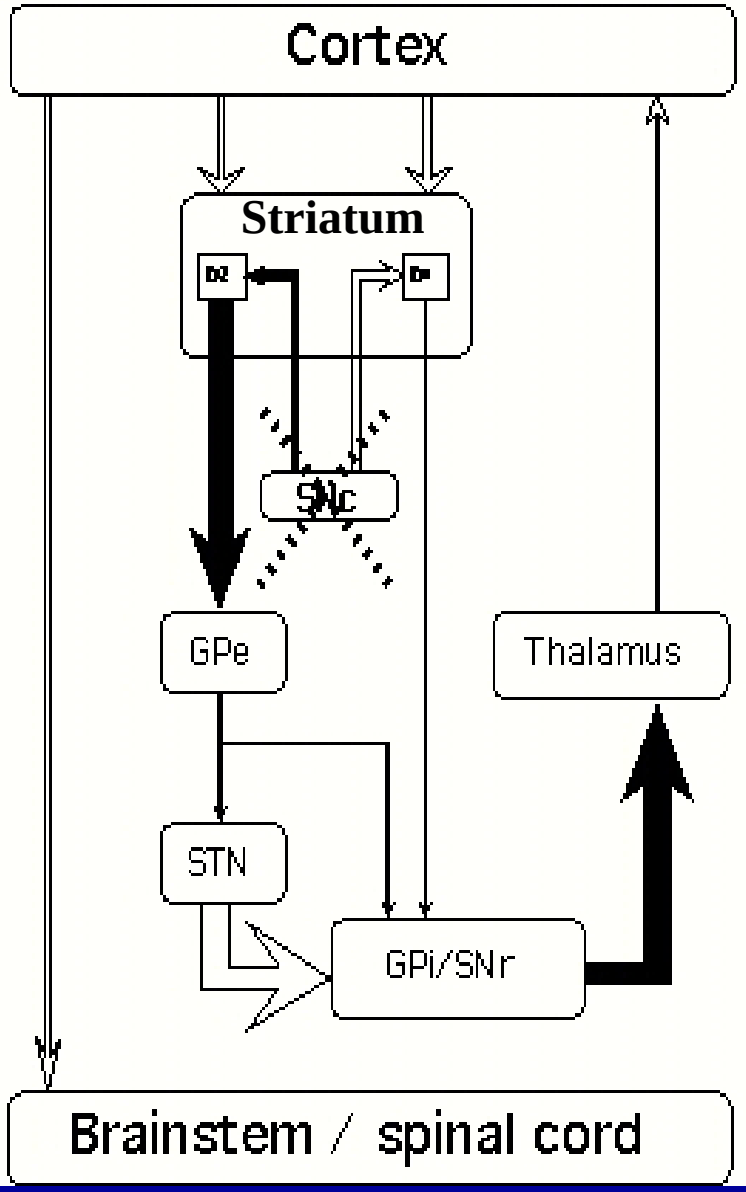
- **Role of basal ganglia:**
  - **Facilitate wanted movements**
  - **Suppress unwanted movements**
  - **Initiate and maintain movements**
- **Two major motor pathways in the basal ganglia:**
  - **Direct pathway: promotes movement**
  - **Indirect pathway: inhibits movement**
- **Also, hyperdirect pathway: cortex-to-STN**
- **Inhibiting cholinergic neurons promote movement**



A. Normal Basal Ganglia Circuitry




B. In Parkinson disease



# *Idiopathic Parkinson Disease*

- **Definition:**
  - **Parkinsonism**
  - **Lewy bodies in degenerating dopaminergic neurons**
- **Diagnosis of parkinsonism: 2/3 Cardinal Symptoms**
  - **Bradykinesia**
  - **Tremor at rest (60% of PD patients)**
  - **Rigidity (lead-pipe)**

  **(PET, DaTscan or skin biopsy NOT required for Dx)**
- **Rule out Parkinson Plus Syndromes (atypical parkinsonism):**
  - **10% of parkinsonian patients**
  - **Rapidly disabling, poorly treatable**

# *Differential Diagnosis of Parkinsonism*

## PD vs Parkinson Plus Syndromes

Synucleinopathy

- **Multiple system atrophy**: MSA-P vs MSA-C (cerebellar)
  - Striatonigral degeneration (P + poor response to levodopa)
  - Shy-Drager Sd (P + autonomic Sx)
  - Olivo-ponto-cerebellar atrophy-OPCA (P + cerebellar Sx)

Tauopathy

- **Progressive supranuclear palsy**
  (P + early imbalance + eyes movement abnormalities)
- **Corticobasal ganglionic degeneration**-CBGD
  (P + unilateral dystonia + cortical sensation loss)

Synucleinopathy

- **Parkinsonism + early dementia:**
  - Alzheimer disease + parkinsonian features
  - Diffuse Lewy body disease
  - Vascular dementia + Parkinsonism (white matter disease)
- **Lower body Parkinsonism:**
  - Vascular Parkinsonism (white matter disease)
  - Normal pressure hydrocephalus
- **Drug-induced parkinsonism (D2-receptors blockers)**

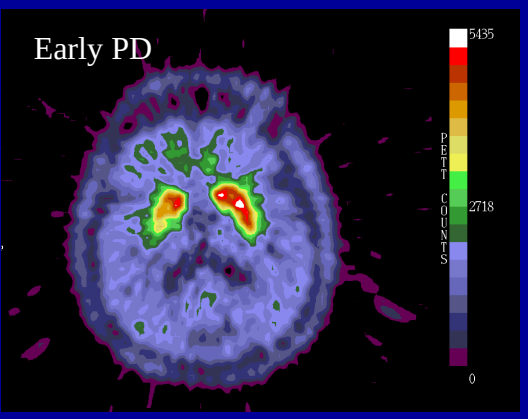
# *The Red Flags of Atypical Parkinsonism*

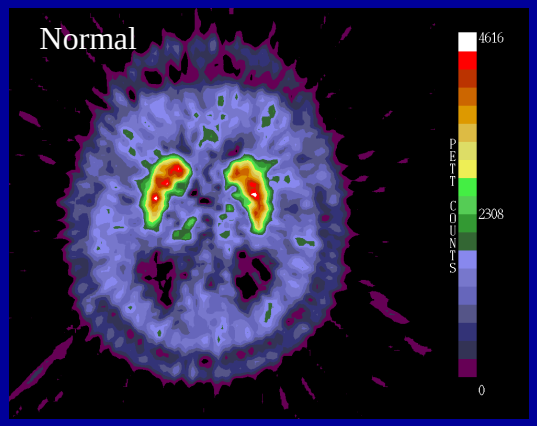
- **Rapid disease progression**
- **Early gait instability and falls**
- **Absence of rest tremor (40% of Parkinson disease)**
- **Symmetry of onset – MSA, PSP, vascular parkinsonism**
- **Poor or absent response to levodopa**
  - **eye movements abnormality - PSP**
  - **pyramidal tract (Babinski sign, ankle clonus, hyperreflexia) – MSA, CBD**
  - **cerebellar signs (ataxia) – MSA-c**
  - **prominent autonomic dysfunction (constipation, incontinence, impotence, orthostatic hypotension) – MSA, DLBD**
  - **severe dysarthria, dysphonia, laryngeal stridor - MSA**
  - **myoclonus - CBD**
  - **alien limb - CBD**
  - **apraxia - CBD**
  - **early dementia - DLBD, PSP, CBD**

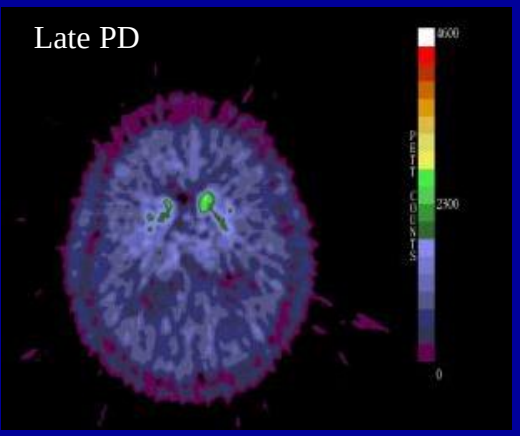
# *Alpha-Synuclein Skin Biopsy*

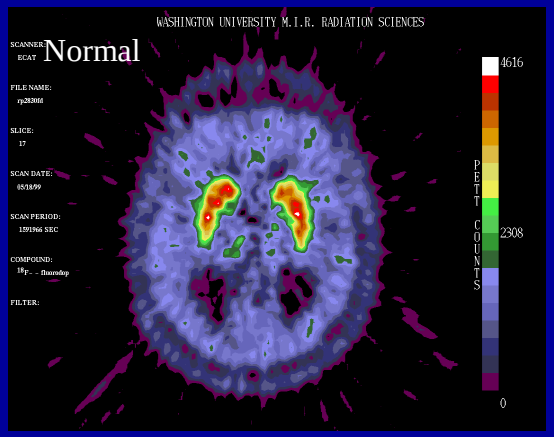
| Diagnosis | Detection (sensitivity) | False-negative rate |
|---|---|---|
| Parkinson disease | 92.7% | ~7.3% |
| Multiple system atrophy | 98.2% | ~1.8% |
| Dementia with Lewy bodies | 96.0% | ~4.0% |
| Pure autonomic failure | 100% | ~0% |

# *18-Fluorodopa Positron Emission Tomography in (PET)*

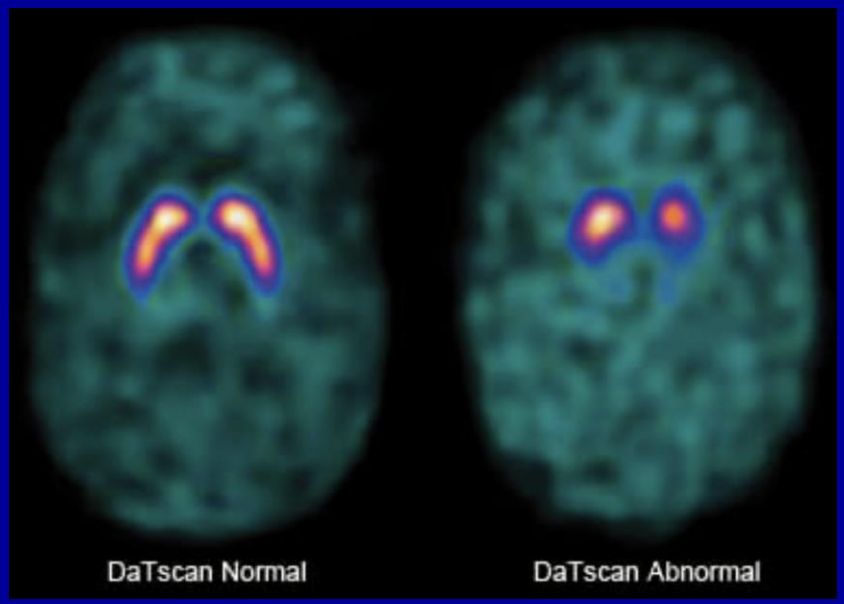



# *DaTscan (123I-ioflupane SPECT)*



# *DaTscan ($^{123}$I-ioflupane SPECT)*

- **DaTscan highly sensitive for presynaptic dopaminergic degeneration (PD, MSA, PSP, DLB) ~78–100%**
  - **Abnormal in PD, MSA, PSP, DLB**
  - **Normal in CBD**
- **Normal DaTscan practically rules out PD and would imply other dx (essential tremor, drug-induced, psychogenic or usually vascular parkinsonism)**
- **FDA-approved for "distinguishing PD from essential tremor"**
- **Not useful to track progression of illness (does not correlate with motor sx; looks worse if patient on levodopa, looks better if on dopamine agonists)**

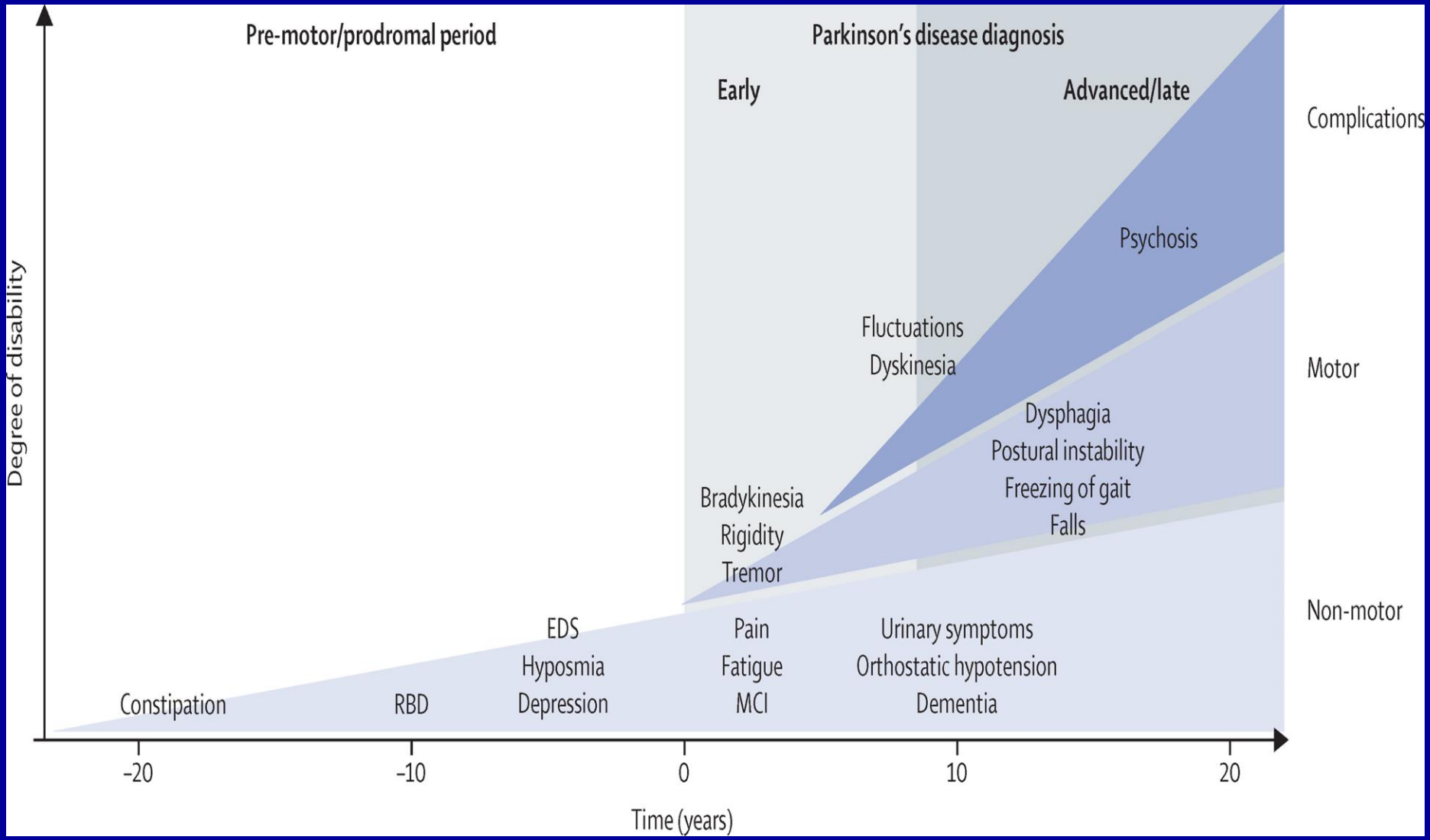
# *Natural History of Parkinson Disease*

- **Before levodopa: Death within 10 years**
- **After levodopa:**
  - **"Honeymoon" period (~ 5-7 years)**
  - **Drug-induced motor (ON/OFF) fluctuations & dyskinesias:**
    - **Drug therapy effective initially**
    - **Surgical intervention by 10-15 years**
      - **Deep brain stimulation (DBS) therapy**
  - **Prominent gait impairment and autonomic symptoms by 20-25 years (Merola 2011)**
- **Dementia and psychosis at anytime during the illness:**
  - **When late: Parkinson disease with dementia**
    - **Psychosis is drug-induced**
  - **When early: diffuse Lewy body disease/dementia**
    - **Associated with Lewy bodies in the substantia nigra AND throughout the cortex**
    - **~30% have psychosis even off dopaminergic drugs**
    - **Very prone to drug-induced psychosis**

# *Non-Motor Symptoms of PD*

- **Sensory Sx**
  - Olfactory: hyposmia/loss of smell
  - Gustatory: taste sensation change
  - Visual: diplopia, blurred vision, reading difficulty
  - Pain syndromes
- **Sleep disorders**
  - Insomnia
  - Restless legs syndrome (RLS)
  - REM-sleep behavior disorder (RBD)
  - Excessive daytime sleepiness
- **Autonomic Sx**
  - Cardiac: Orthostatic hypotension
  - Urinary: urgency, frequency, nocturia
  - Genital: erectile dysfunction
  - GI: constipation, hypersalivation
  - Skin: Seborrhoea, hyper/hypohidrosis
- **Neuro-psychiatric Sx:**
  - depression, anxiety, apathy...
  - Psychosis, dementia...
- **Fatigue**

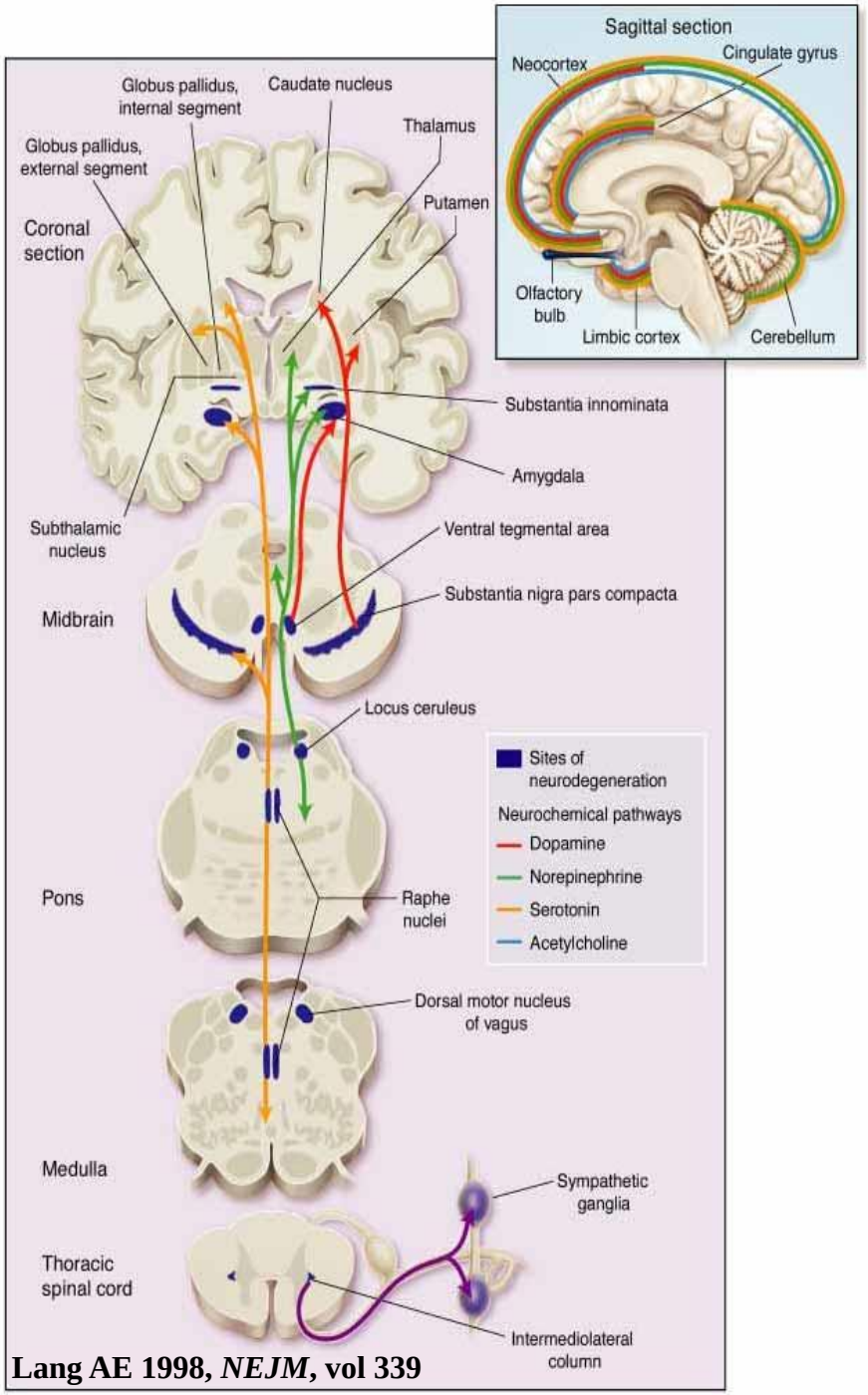
# Parkinson Disease
# Clinical Progression




Kalia & Lang 2015, *Lancet*, 386: 896–912

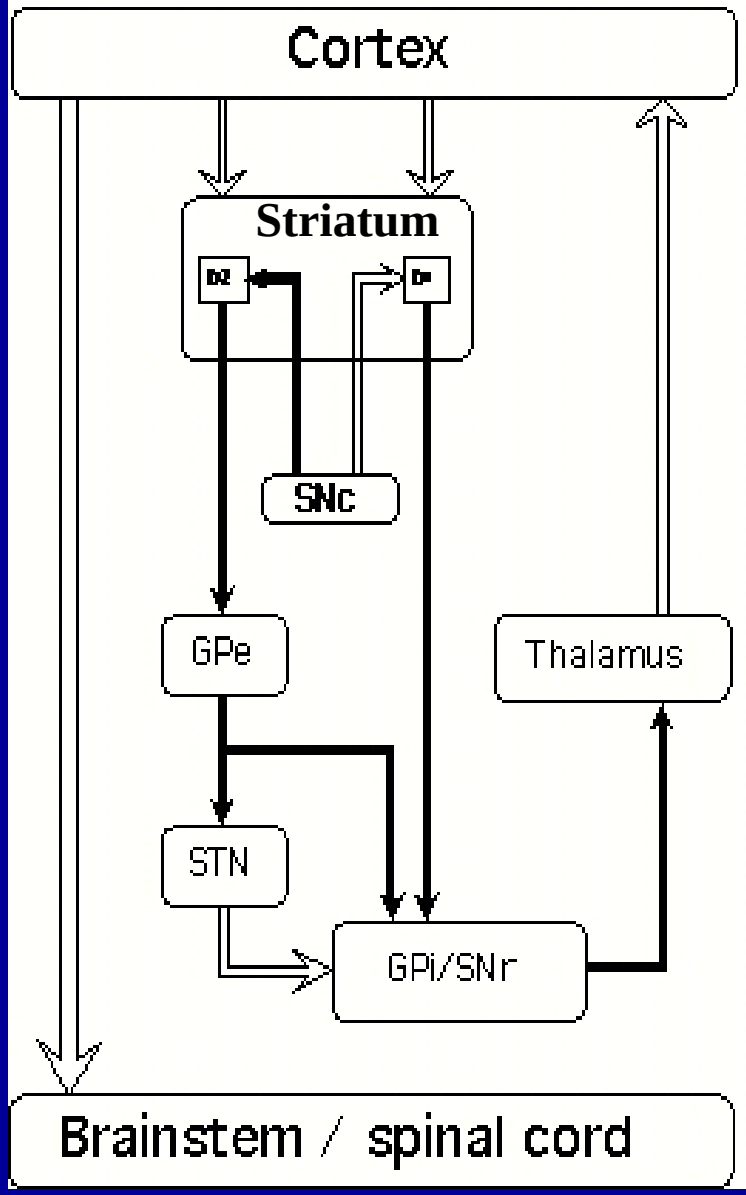
# Sites of Neurodegeneration in Parkinson Disease

- Substantia nigra pars compacta
- Substantia innominata
- Amygdala
- Ventral tegmental area
- Locus ceruleus
- Raphe nuclei
- Dorsal motor nucleus of vagus nerve
- Intermediolateral column/Sympathetic ganglia

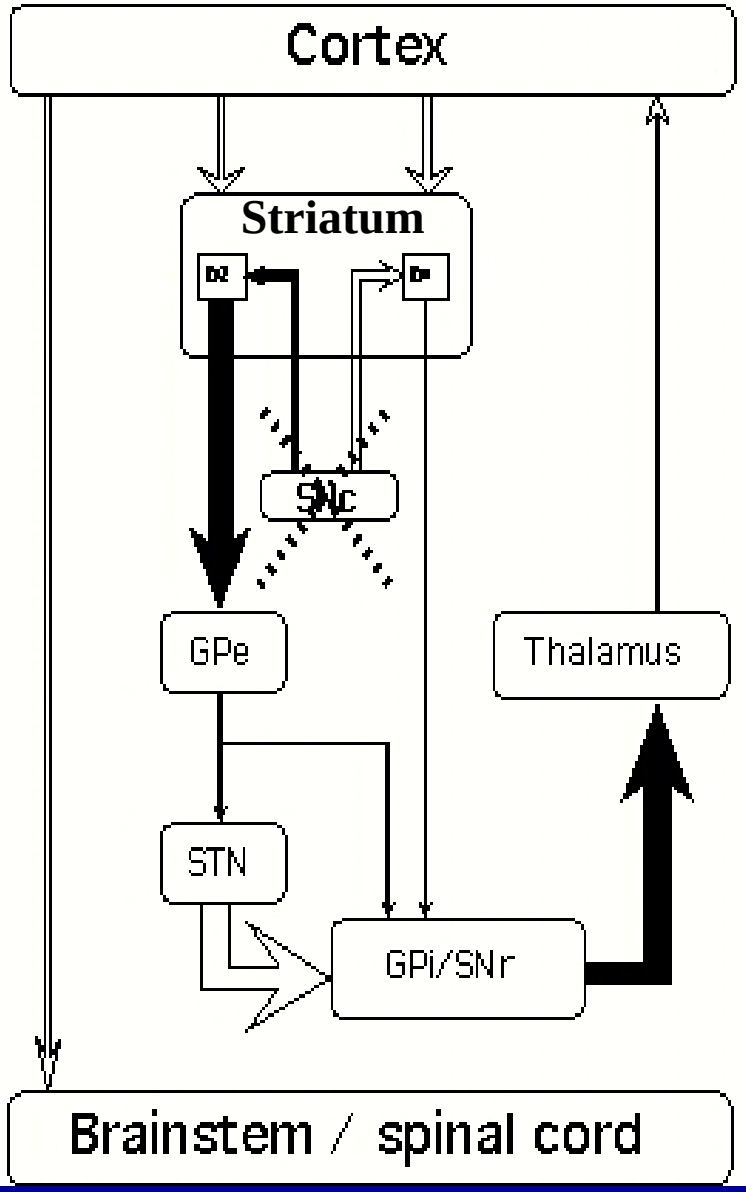


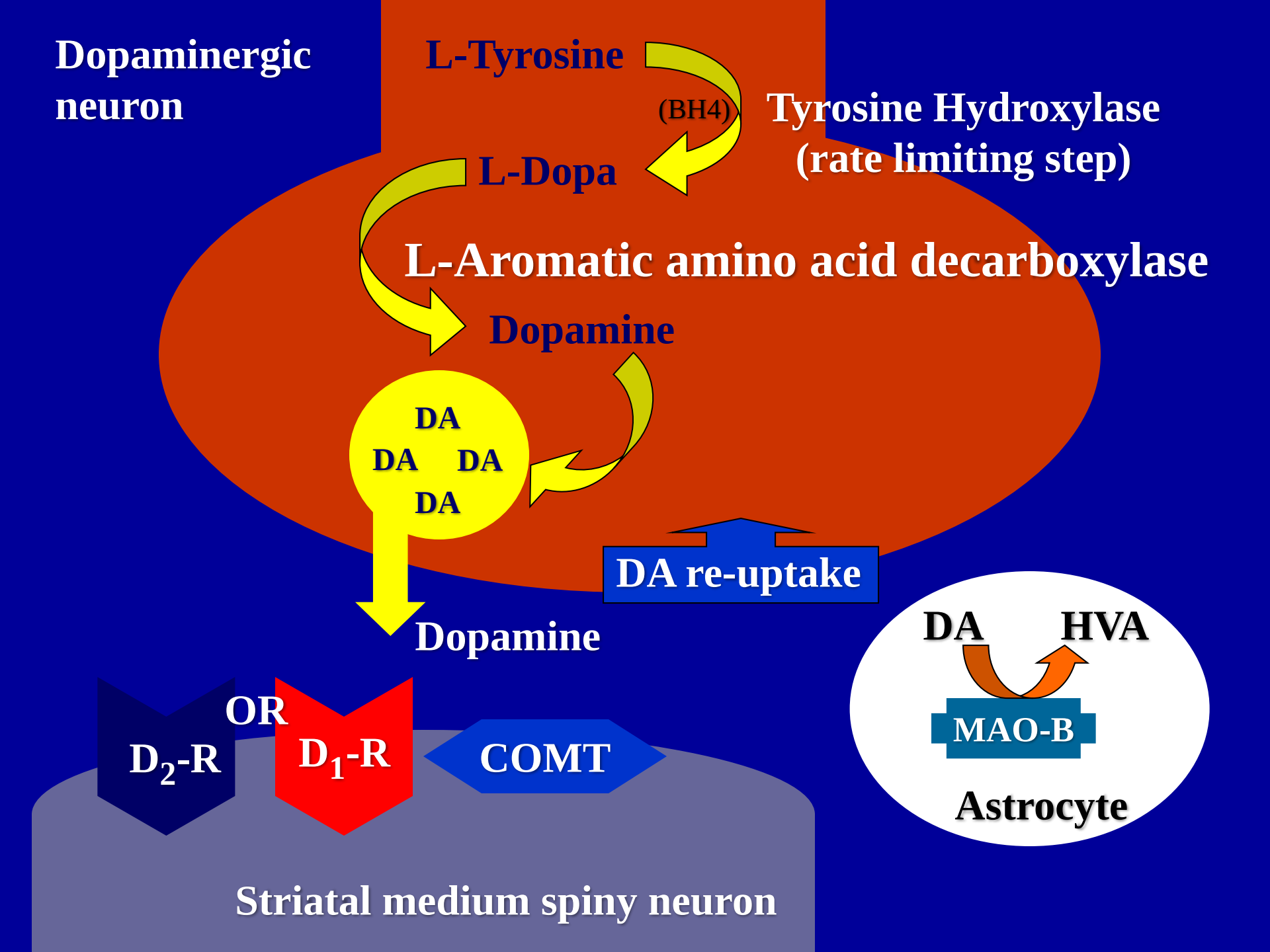

Lang AE 1998, *NEJM*, vol 339

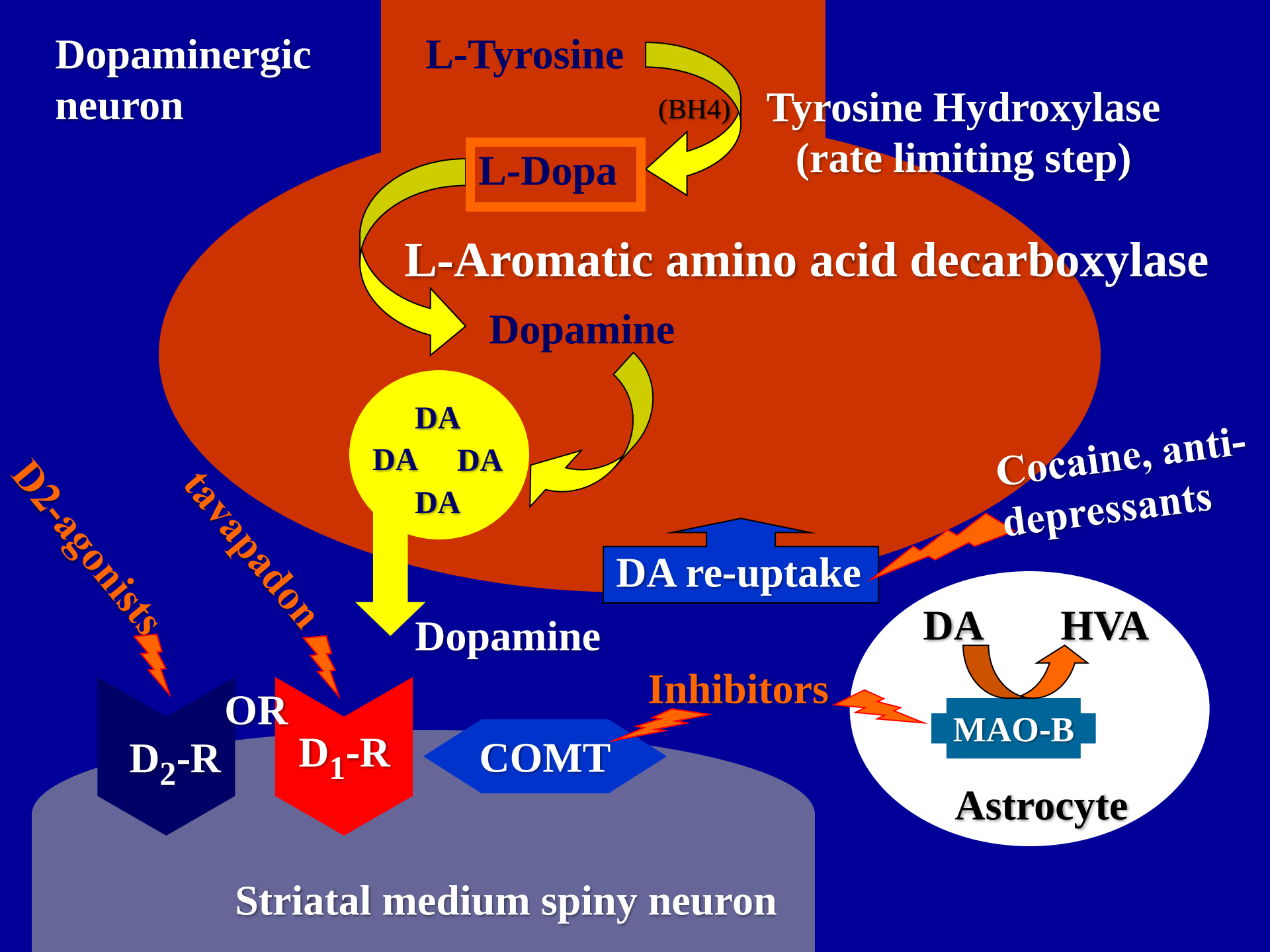
A. Normal Basal Ganglia Circuitry




B. In Parkinson disease




Dopaminergic neuron
L-Tyrosine
(BH4)
Tyrosine Hydroxylase (rate limiting step)
L-Dopa
L-Aromatic amino acid decarboxylase
Dopamine
DA
DA DA
DA
DA re-uptake
Dopamine
OR
D2-R
D1-R
COMT
DA
HVA
MAO-B
Astrocyte
Striatal medium spiny neuron


Dopaminergic neuron
L-Tyrosine
(BH4)
Tyrosine Hydroxylase (rate limiting step)
L-Dopa
L-Aromatic amino acid decarboxylase
Dopamine
DA
DA DA
DA
Cocaine, anti-depressants
D2-agonists
tavapadon
DA re-uptake
Dopamine
DA
HVA
Inhibitors
MAO-B
OR
D2-R
D1-R
COMT
Astrocyte
Striatal medium spiny neuron

# *Rx of Motor Symptoms of PD*

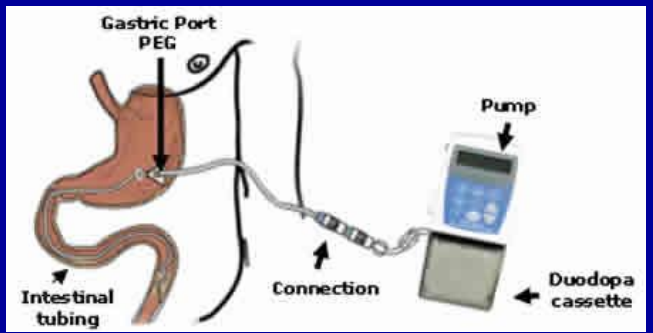
- **Dopamine Replacement:**
  - Levodopa with aromatic amino acid decarboxylase inhibitors (carbidopa or benserazide)
  - Catecholamine-O-methyl transferase (COMT) inhibitors: entacapone, opicapone
  - Dopamine agonists:
    - D2-receptors: bromocriptine, cabergoline, pramipexole, ropinirole, rotigotine patch, apomorphine (s/q injection or pump)
    - D1-receptors: tavapadon
- **Dopamine Releaser/NMDA-blocker:** amantadine
- **Mono-amine oxidase inhibitors (MAOI)-type B :**
  - selegiline, rasagiline, safinamide
- **Selective adenosine $A_{2a}$ receptor agonist:** istradefylline
- **Anticholinergic drugs:** trihexyphenidyl, benztropine, biperiden
- **Surgical Rx:** deep brain stimulation, high-intensity focused u/s

# *Treatment of Parkinson Disease: General Principles*

- **Start low & go slow**
- **Titrate symptoms**
- **Exercise for all before year 2030**

# *Levodopa*

- Most powerful anti-parkinsonian drug
- Formulation:
  - Carbidopa/levodopa
  - Carbidopa/levodopa/entacapone
  - Inhaled levodopa (Inbrija)
  - Carbidopa/levodopa beads (Rytary and Crexont)
  - Duodenal carbidopa/levodopa gel via Duodopa pump
  - Subcutaneous carbidopa/levodopa infusion via Vyalev pump
- Adverse effects:
  - Nausea: Rx with high-dose of carbidopa (Lodosyn 25-75 mg) or domperidone (Motilium) 10-30 mg tid, ½ hour before each dose of levodopa
  - Constipation, hypotension, peak-dose sedation/dizziness
  - Motor Fluctuations/Dyskinesia



# Rytary

- **Approved in January 2015 by the US FDA:**
  - **Rytary doses: 23.75/95, 36.25/145, 48.75/195, 61.25/245**
  - **beads of carbidopa and levodopa that dissolve at various rates**
  - **Max dose: 612/2450 mg**
  - **May open capsule and mix with food**
  - **70% bioavailable compared to carbidopa/levodopa**

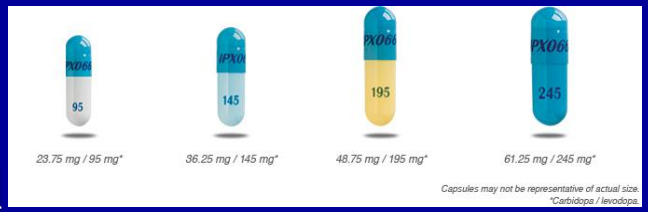


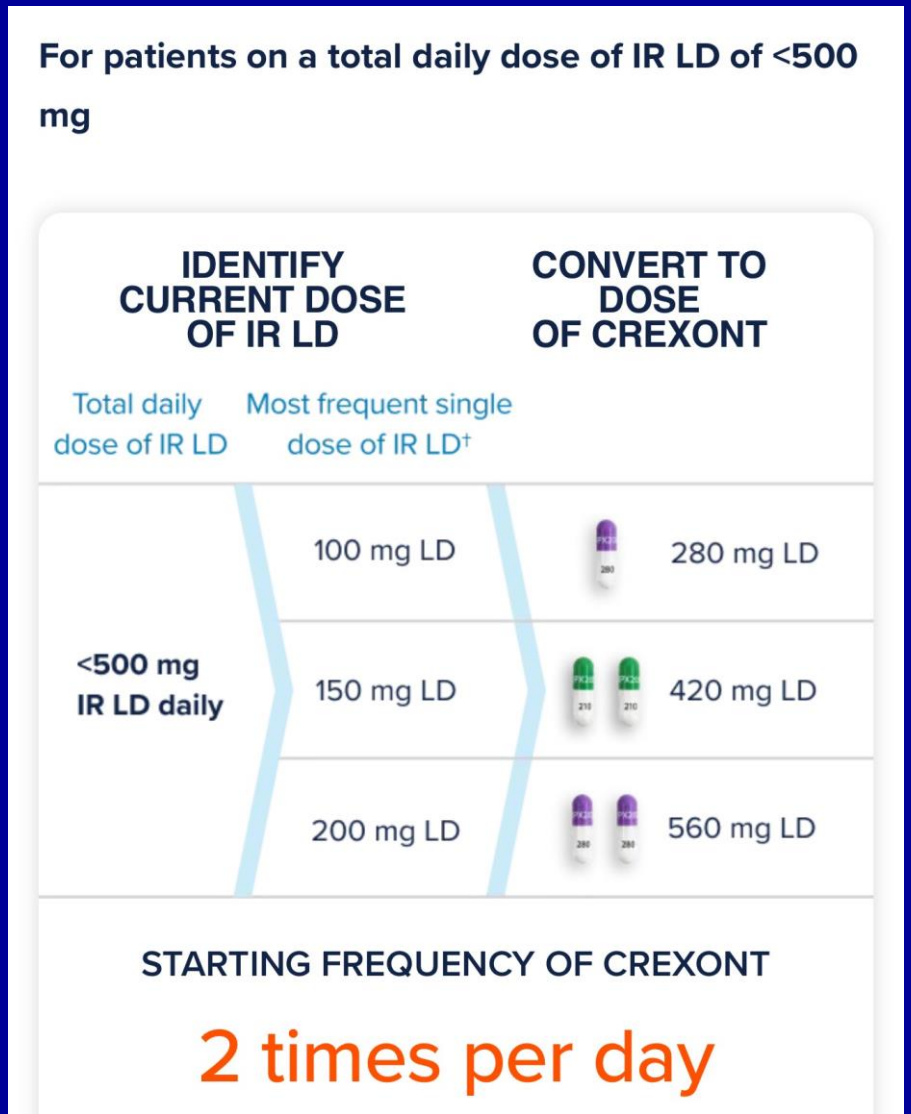

**Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to RYTARY**

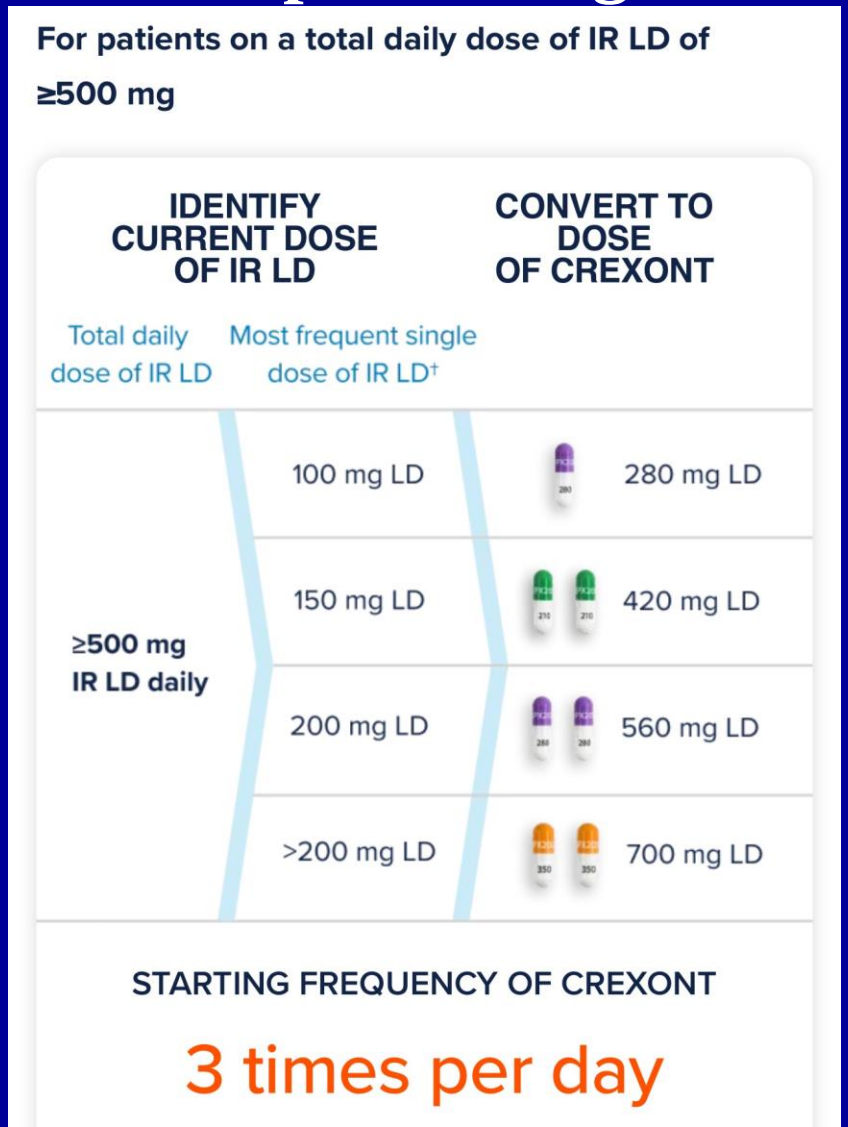
| Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa | Recommended Starting Dosage of RYTARY | | |
|---|---|---|---|
| | Total Daily Dose of Levodopa in RYTARY | RYTARY Dosing Regimen | |
| 400 mg to 549 mg | 855 mg | 3 capsules RYTARY 23.75 mg / 95 mg taken TID[a] | $630 |
| 550 mg to 749 mg | 1140 mg | 4 capsules RYTARY 23.75 mg / 95 mg taken TID | $830 |
| 750 mg to 949 mg | 1305 mg | 3 capsules RYTARY 36.25 mg / 145 mg taken TID | $660 |
| 950 mg to 1249 mg | 1755 mg | 3 capsules RYTARY 48.75 mg / 195 mg taken TID | $660 |
| Equal to or greater than 1250 mg | 2340 mg or | 4 capsules RYTARY 48.75 mg / 195 mg taken TID or | $830 |
| | 2205 mg | 3 capsules RYTARY 61.25 mg / 245 mg taken TID | $790 |

Levodopa dose x2 = Rytary dose

# Crexont

- **Crexont doses:** 35/140 mg, 52.5/210 mg, 70/280 mg, 87.5/350 mg
- Mucoadhesive polymer to stick to the proximal gut



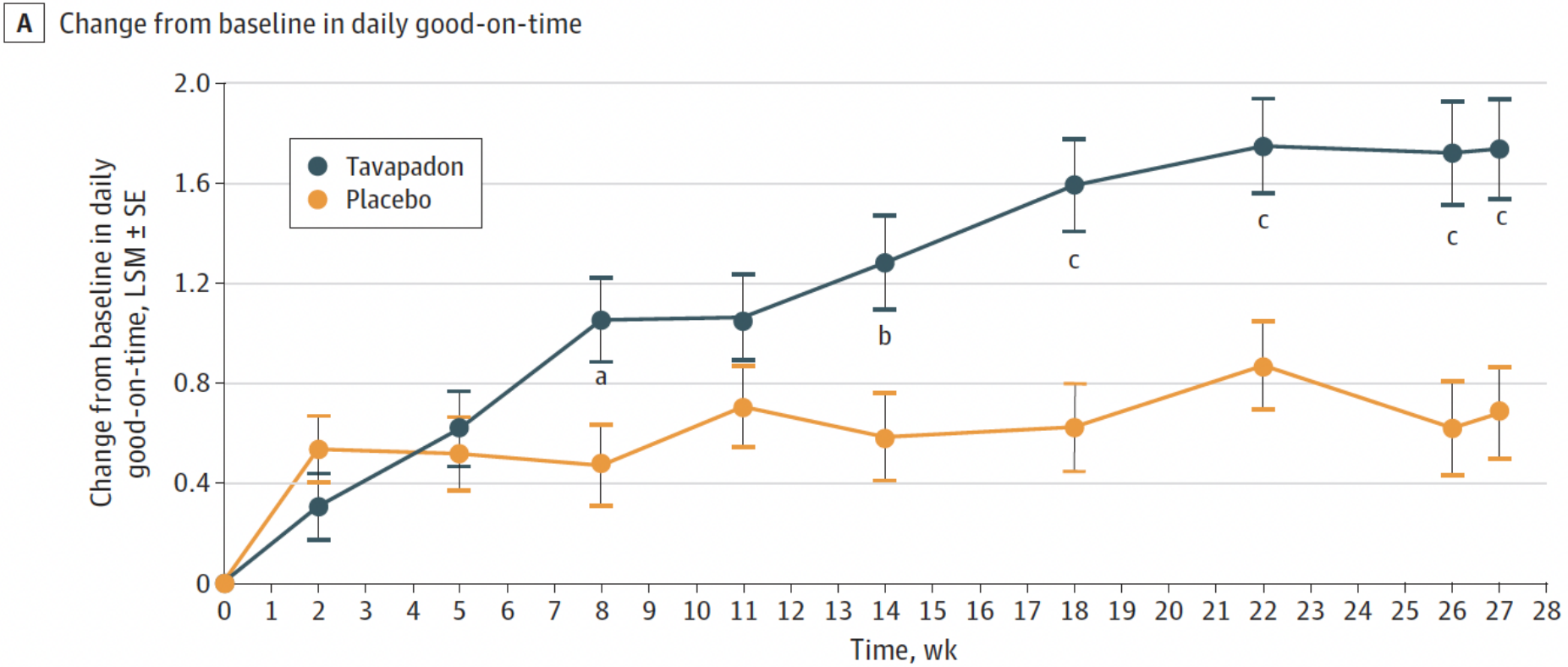



# *Levodopa vs D2-Receptor Dopamine Agonists*

| | Levodopa | Dopamine Agonists |
|---|---|---|
| **Motor benefit** | + + + | + |
| **Motor fluctuations at 10 years** | + + + | + |
| **Dyskinesia at 10 years** | + + + | + |
| **Mental adverse effects**<br>- **Hallucinations, delusions**<br>- **Impulse control (hypersexuality, gambling, compulsive shopping)**<br>- **Daytime sedation** | < 70yrs: +<br>> 70 yrs: + | < 70yrs: + +<br>> 70yrs: + + + |
| **Orthostasis at 10 years** | + + | + + + |

# *Tavapadon Increases Total Daily Good-ON-Time by 1.1 Hours (1.70 hr vs 0.60 hr)*

Figure 2. Line Graphs Showing the Least-Squares Mean Change From Baseline in Daily On-Time (Hours) Without Troublesome Dyskinesia (Good-on-Time) and Off-Time in the mITT Population




| Participants | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tavapadon | 242 | 239 | 223 | 206 | 192 | 182 | 174 | 163 | 153 | 151 |
| Placebo | 245 | 239 | 234 | 229 | 218 | 218 | 206 | 202 | 201 | 198 |

# *Tavapadon: Other End Points at week 26 Compared With Placebo*

- **1.2 point improvement in MDS-UPDRS part II scores (1.4 vs 0.1 points)**
- **2.4 points reduction in MDS-UPDRS part III scores at week 26 (7.0 s 4.6 points)**
- **3.7 points reduction in MDS-UPDRS part II+III combined scores at week 26 (8.4 vs 4.7 points)**

- **No notable differences in MDS-UPDRS part I, PDQ-39, or EQ-5D-5L Index and Visual Analogue Scale scores**

# *Tavapadon Summary of Adverse Events*

Table 2. Summary of Adverse Events (Safety Population)

| Safety outcomes | No. (%) Placebo QD (n = 254) | No. (%) Tavapadon 5-15 mg QD (n = 251) |
|---|---|---|
| AEs[a] | 140 (55.1) | 180 (71.7) |
| Mild | 65 (25.6) | 80 (31.9) |
| Moderate | 64 (25.2) | 82 (32.7) |
| Severe | 11 (4.3) | 18 (7.2) |
| AE related to study drug[b] | 54 (21.3) | 105 (41.8) |
| AEs by phase at onset, No./No. (%) | | |
| Titration | 83/254 (32.7) | 100/251 (39.8) |
| Adjustment | 54/237 (22.8) | 100/214 (46.7) |
| Maintenance | 65/220 (29.5) | 71/188 (37.8) |
| Serious AEs | 14 (5.5) | 17 (6.8) |
| AE leading to discontinuation | 23 (9.1) | 43 (17.1) |
| Death | 0 | 1 (0.4)[c] |

| Most common AEs (occurring with ≥5% incidence in tavapadon group), No. (%) | No. (%) Placebo QD (n = 254) | No. (%) Tavapadon 5-15 mg QD (n = 251) |
|---|---|---|
| Nausea | 11 (4.3) | 36 (14.3) |
| Dyskinesia | 4 (1.6) | 25 (10.0) |
| Dizziness | 8 (3.1) | 19 (7.6) |
| Headache | 7 (2.8) | 17 (6.8) |
| Fall | 13 (5.1) | 16 (6.4) |
| Orthostatic hypotension[d] | 3 (1.2) | 15 (6.0) |
| Hallucination, visual | 3 (1.2) | 14 (5.6) |
| COVID-19 | 9 (3.5) | 13 (5.2) |
| Somnolence | 11 (4.3) | 13 (5.2) |

**Presumably, no impulse control disorder… to date!**

# *Other Novel Delivery Systems of Dopaminergic Drugs*

- **VR040:**
  - **Inhalable apomorphine**
- **ND0611:**
  - **Transdermal levodopa ethyl ester**

# *Solengepras: GPR6 Inverse Agonist*

- **GPR6 is specifically expressed in the medium spiny neurons of the indirect pathway in the striatum**
- **Solengepras dampens the overactive indirect pathway, therefore promoting movements**

**Phase III study:**

- **Improved good-ON-time: 1.58 hour (vs 0.98 hour in placebo)**
- **Improved sleepiness: -0.98 point on Epworth sleepiness scale**
- **Improved quality of life: -2.87 point on PDQ-39**
- **Improved motor function: -1.91 point MDS-UPDRS part II**

# Treatment of Behavior in Advanced PD

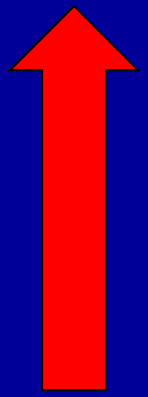
- **Behavioral symptoms:**
  - **Hallucinations with/without insight, paranoid delusions, confusion:**
    - **First, use levodopa as monotherapy if possible (discontinue MAO inhibitor, amantadine and dopamine agonists)**
    - **Drugs for psychosis:**
      - **(Quetiapine: proven NOT effective in PD)**
      - **Clozapine with weekly white blood cell count (1-2% risk of agranulocytosis)**
      - **Pimavanserin 34 mg daily (inverse agonist and antagonist of 5-HT2A and 5-HT2C serotonin receptors) ~ $1,000-2,000/month**
      - **Cholinesterase inhibitors: galantamine, donepezil, rivastigmine**
  - **Dementia: cholinesterase inhibitors**
- **Altered alertness/sleep:**
  - **Drowsiness after taking levodopa dose: give small doses more frequently**
  - **REM-sleep behavior disorder: low dose benzodiazepines (clonazepam 0.25 mg to 1 mg qhs)**
  - **Insomnia: melatonin (5-15 mg 4 hours before sleep), optimize nighttime dopaminergic replacement**

# *Motor Potency vs Mental Adverse Effects*

**Motor benefit:**

1. Levodopa
2. Dopamine agonists
3. MAO inhibitors, Anticholinergic drugs
4. Amantadine

More effects



Less effects

**Mental adverse effects:**

(in patients >70 years)

1. Anticholinergic drugs
2. Dopamine agonists
3. Amantadine (myoclonus), MAO inhibitors
4. Levodopa

- **For psychotic patients, the first medications to stop:**
  - Anticholinergic drugs, dopamine agonists, amantadine, then MAO inhibitors
  - then add cholinesterase inhibitors, then pimavanserin, then clozapine
  - then (decrease) levodopa

# *So:*

**Do NOT EVER give D2-receptor blocking agents to parkinsonian patients… (including haldol, risperidone, olanzapine, ziprasidone, …)**

# EVER!

**May withhold dopaminergic drugs for aggressiveness**

# *Long Live Dopamine !*

