Development of Drugs for Neurodegenerative Diseases

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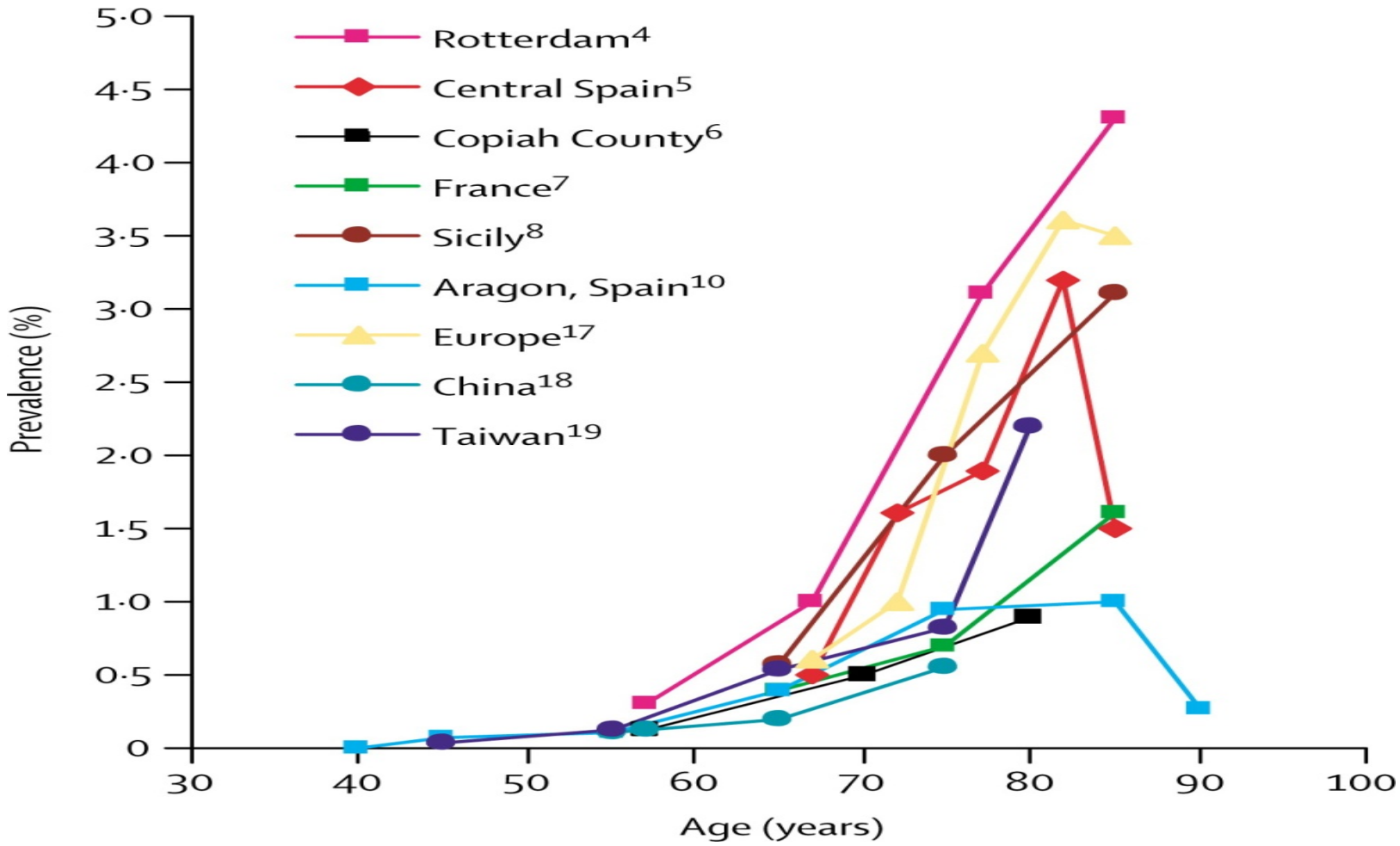
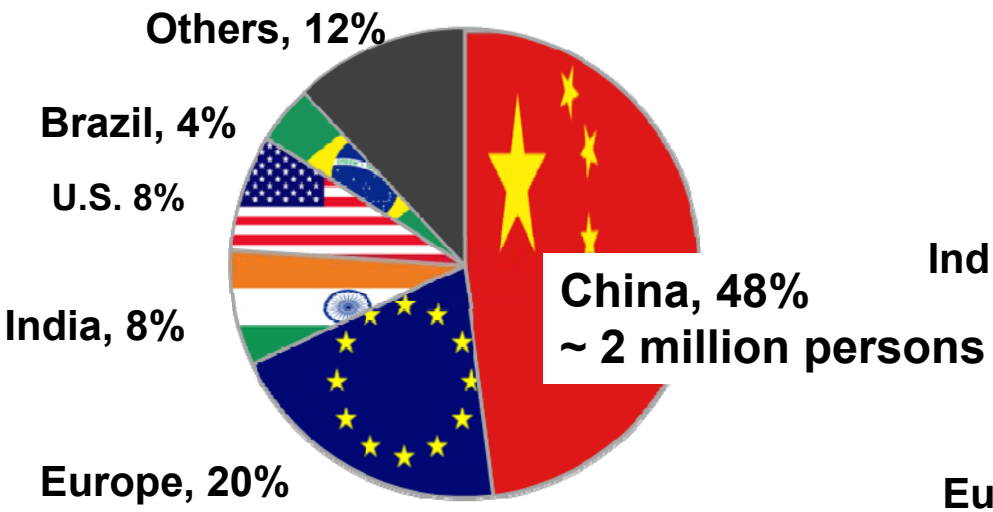
Parkinson's disease (PD): big challenge for population aging

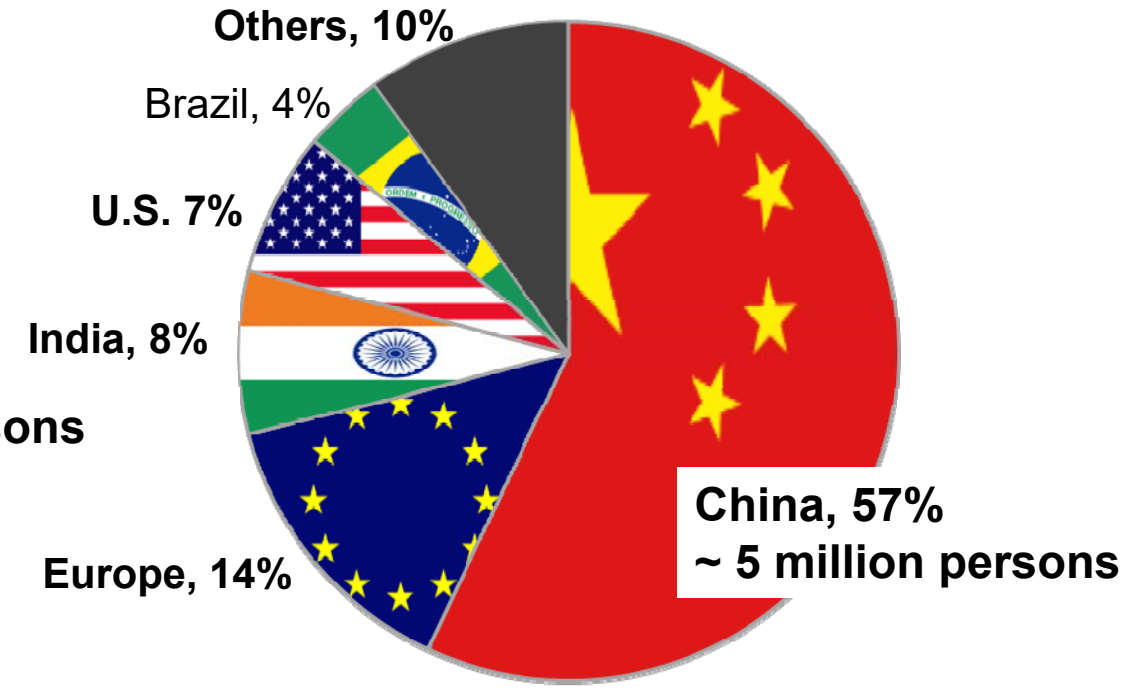


PD prevalence projected for China

2005
100% = 4.1 million individuals



2030
100% = 8.7 million individuals

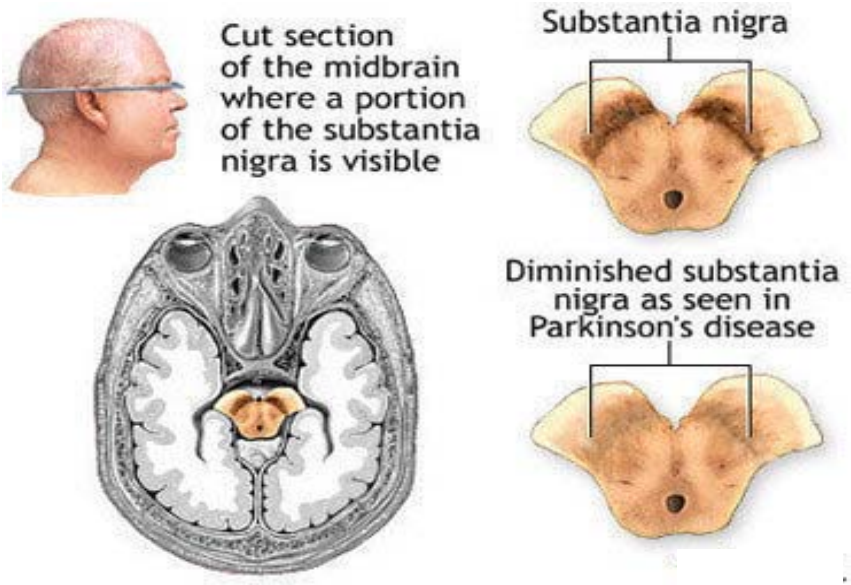


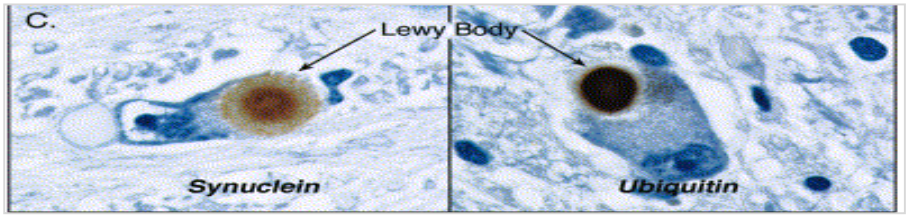
Persons aged > 50 in the world's ten most and Western Europe's five most populous nations

(Dorsey et al, 2007)

Classical concept of PD

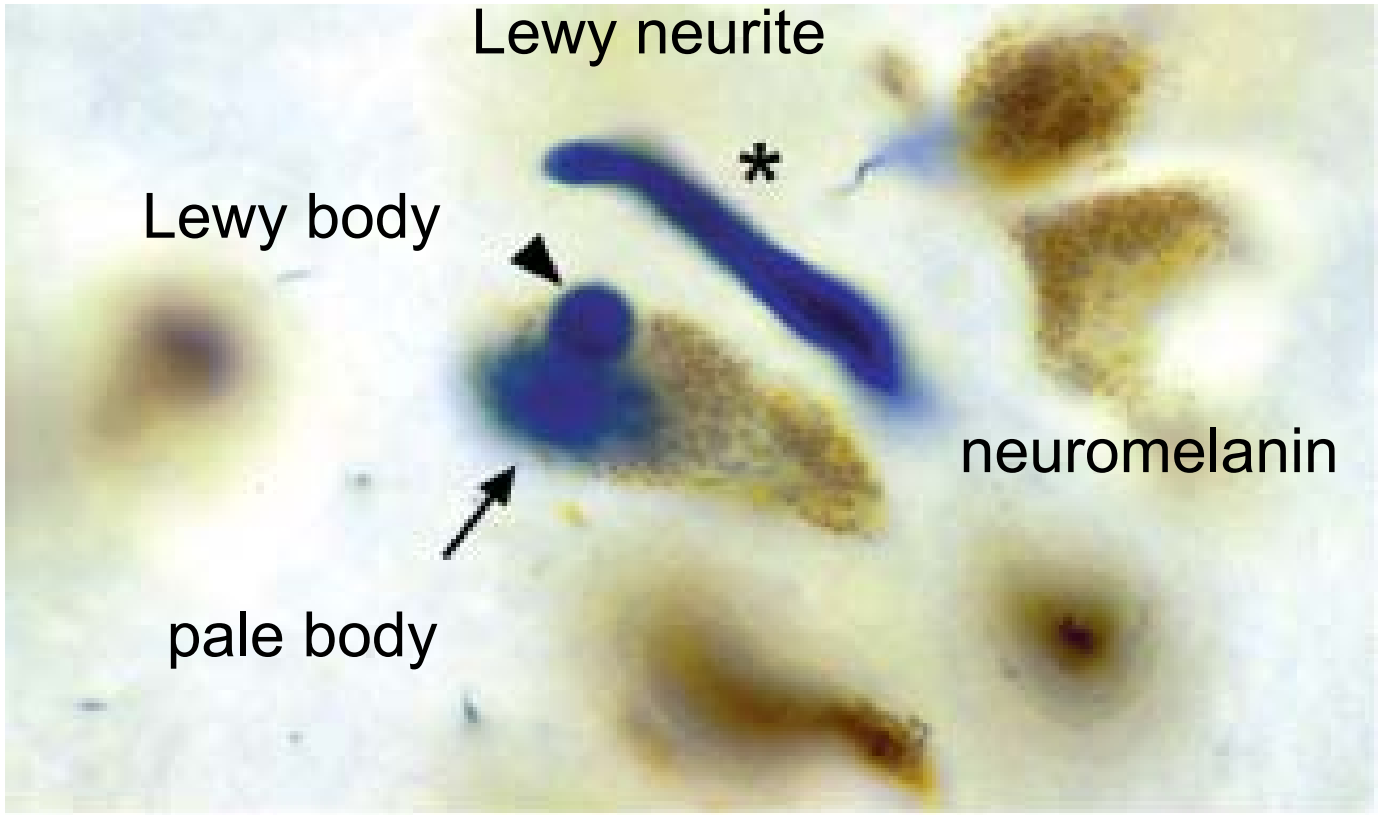
Loss of dopamine neurons + motor dysfunction





- ✓Resting tremor
- ✓bradyskinesia
- ✓rigidity
- ✓Loss of balance

α-Syn: pathological hallmark for PD



Braak H et al. J Neurol 2002, 249 (Suppl 3):III/1-5

Braak pathologic staging of PD

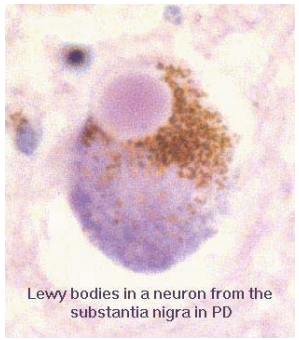
Based on Lewy body & neurite localization

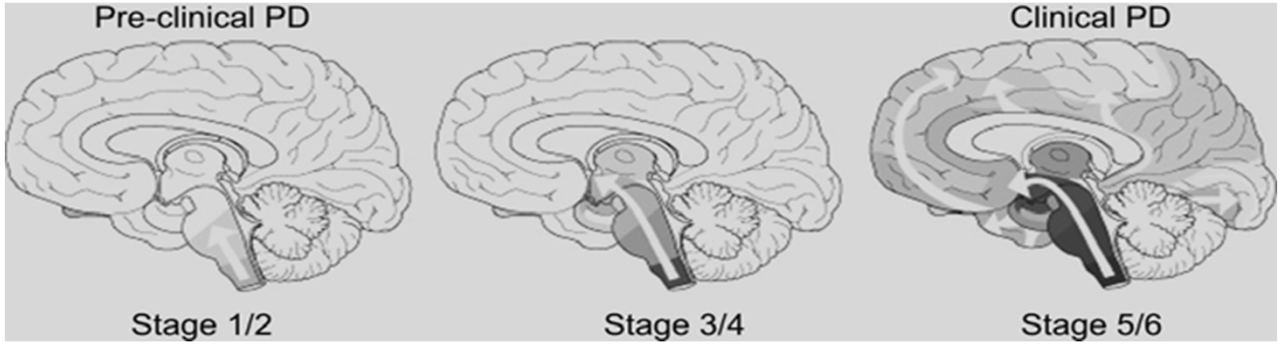
Suggests that Lewy body pathology does not begin in substantia nigra

Begins in dorsal motor nucleus of glossopharyngeal and vagus nerves, anterior olfactory nucleus, and enteric nerve cell plexus

Proceeds in rostral direction toward neocortex

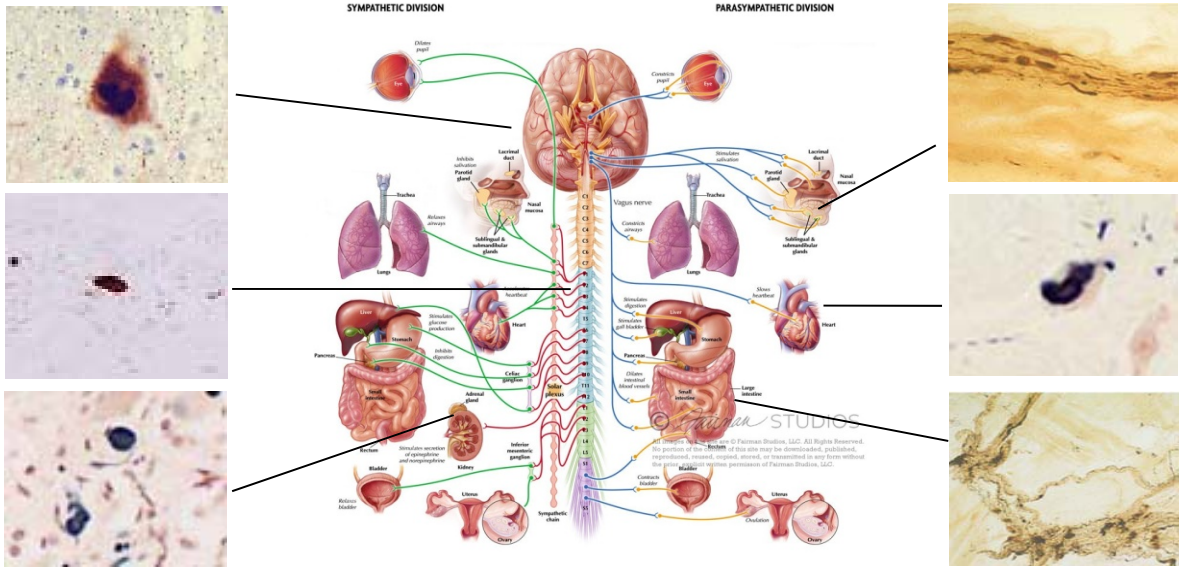
Progression of Parkinson's Disease may not always comply with this model


Lewy bodies in a neuron from the substantia nigra in PD



1. Braak et al. *Neurobiol Aging.* 2003;24:197-211. **2.**Braak et al. *Neurosci Lett.* 2006;396:67-72. **3.** Braak et al. *Cell Tissue Res.* 2003;318:121-134.
4. Braak et al. *Neurology.* 2005;64:1404-1410. **5.** Halliday et al. *Acta Neuropathol.* 2008;115:409-415. **6.** Parkkinen et al. *Acta Neuropathol.* 2008;115:399-407. **7.** Kalaitzakis et al. *Neuropathol Appl Neurobiol.* 2008;34:284-295. **8.** Parkkinen et al. *Ann Neurol.* 2005;57:82-91. **9.** Attems et al. *Neuropathol Appl Neurobiol.* 2008;34:466-467.

Extensive distribution of α-Syn pathology and non-motor symptoms

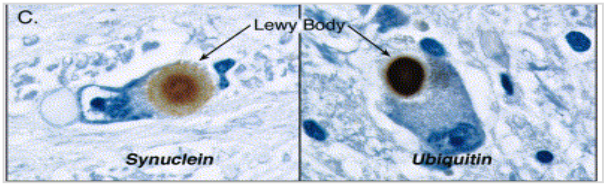


- Constipation
- Bradycardia
- orthostatic hypotension
- Sleep dysfunction
- Smell Dysfunction
- Depression
- Cognitive impairment

α-Syn advanced the earlier diagnosis

α-Synuclein identified in 1997

MDS Diagnostic criteria in 2015



Prodromal stage（5~20 yrs）

Clinical stage（15~30 yrs)

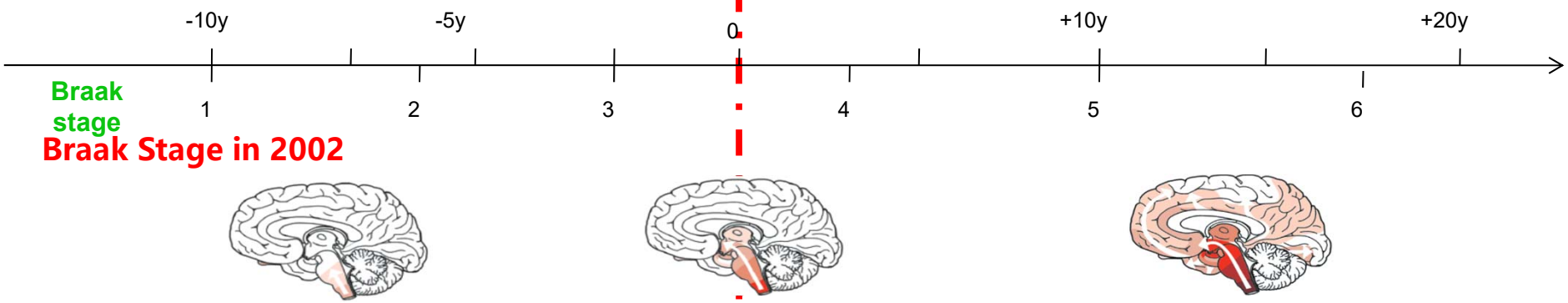
MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1*] Ronald B. Postuma, MD, MSc,[2*] Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

Tren
radyk
Rigi

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[11*] Daniela Berg, MD,[21*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

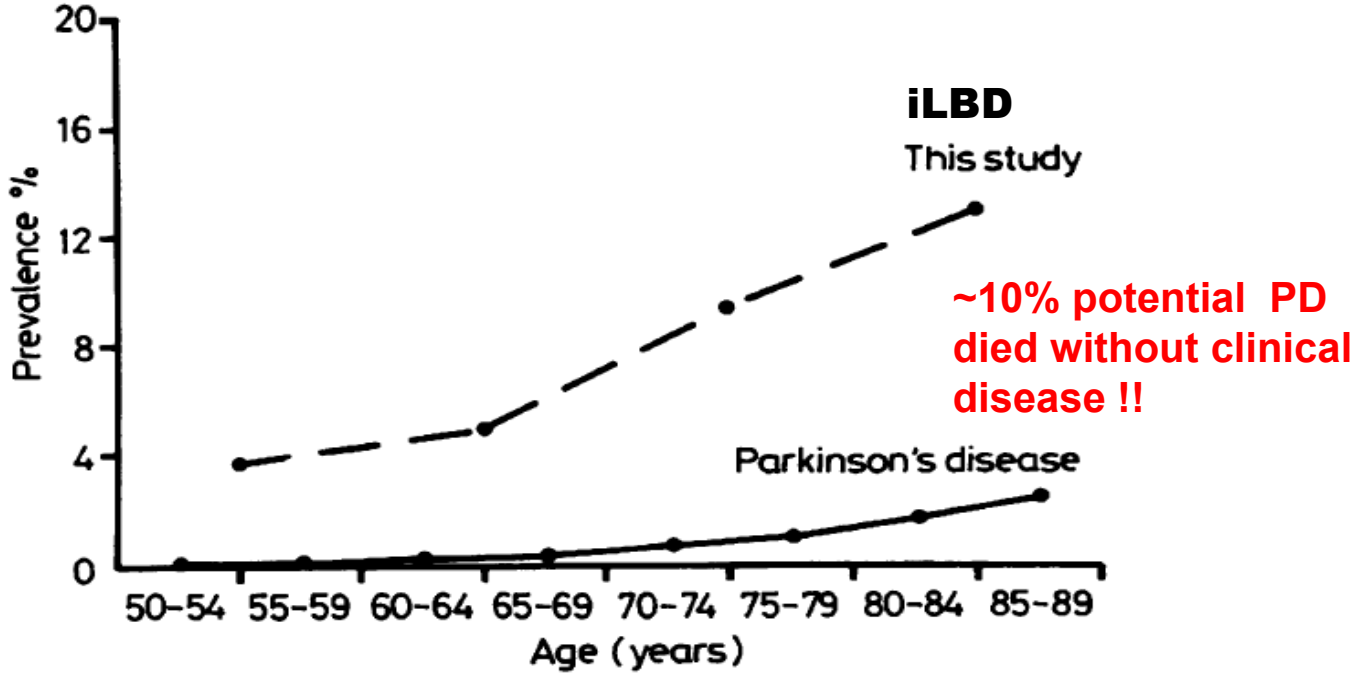


Braak Stage in 2002

Hawkes CH,et al. Parkinsonism and Related Disorder, 2010,16:79-84.

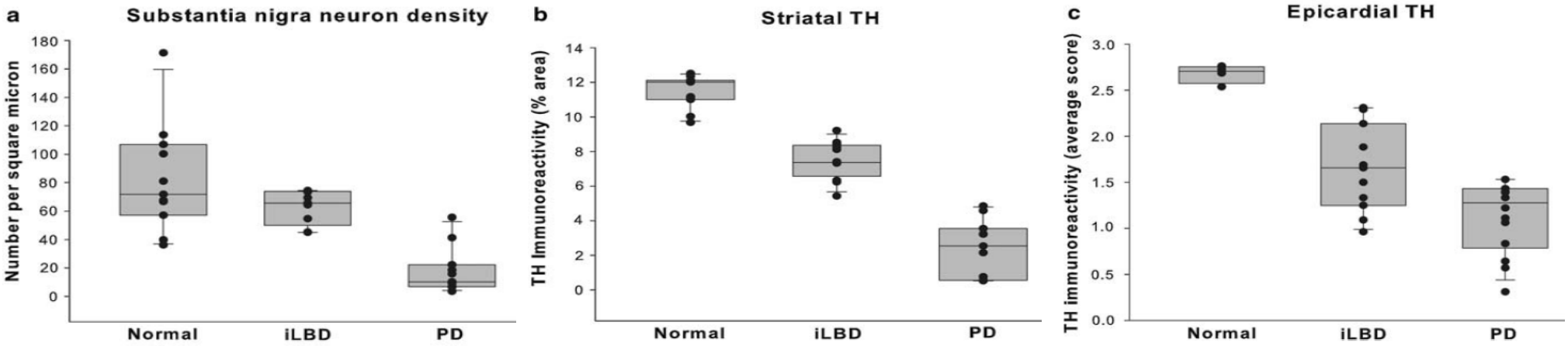
Incidental Lewy body disease (iLBD): prodromal stage of PD?

Clinically normal individuals over age 60 years have Lewy bodies in brainstem nuclei with routine histologic methods, which is often termed coincidental or incidental Lewy body disease (iLBD)



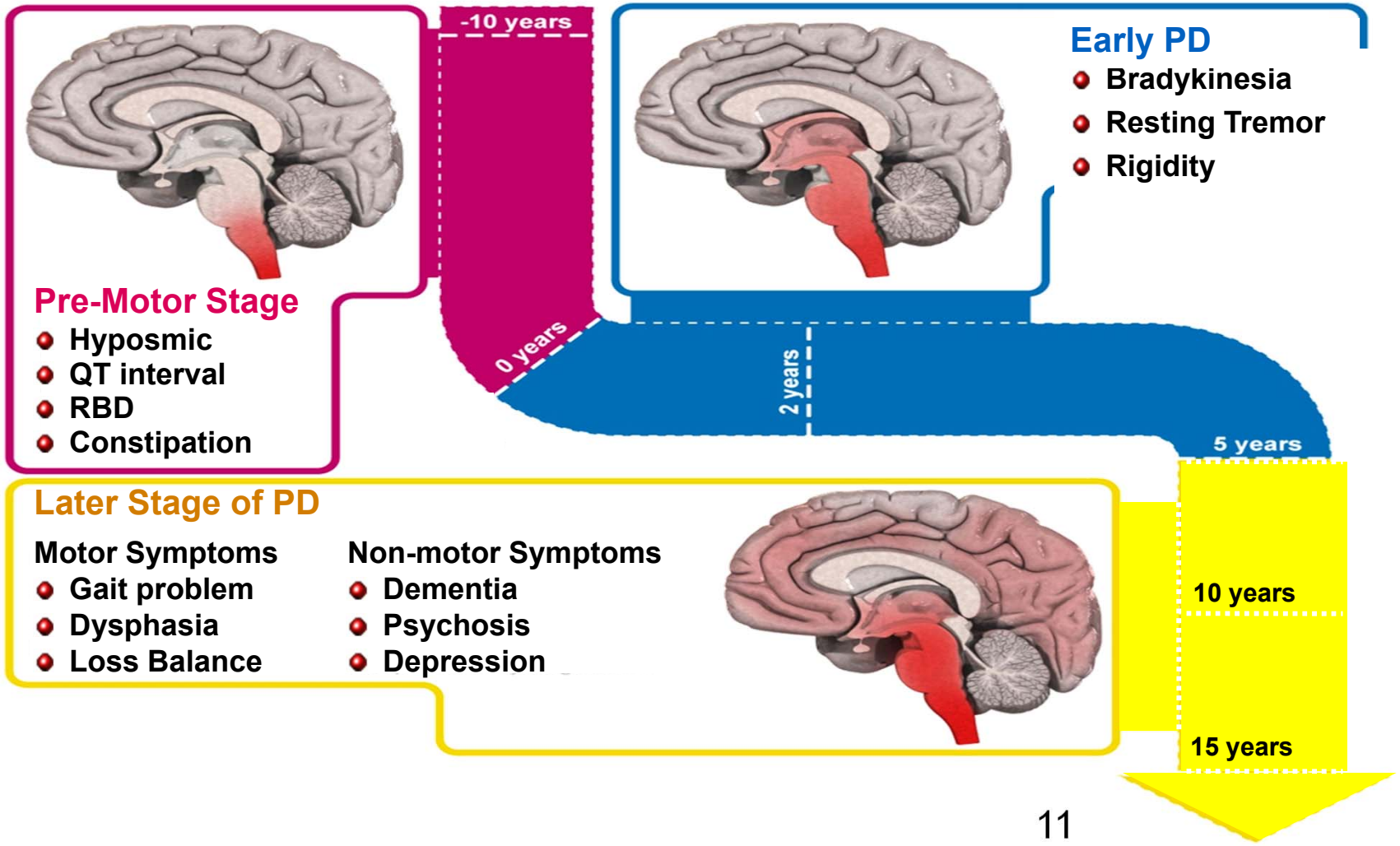
J Neurol Neurosurg Psychiatry 1988, 51:745–752
Fono LS. J Am Geriatr Soc 1969, 17:557–575

Extensive pathological changes in iLBD

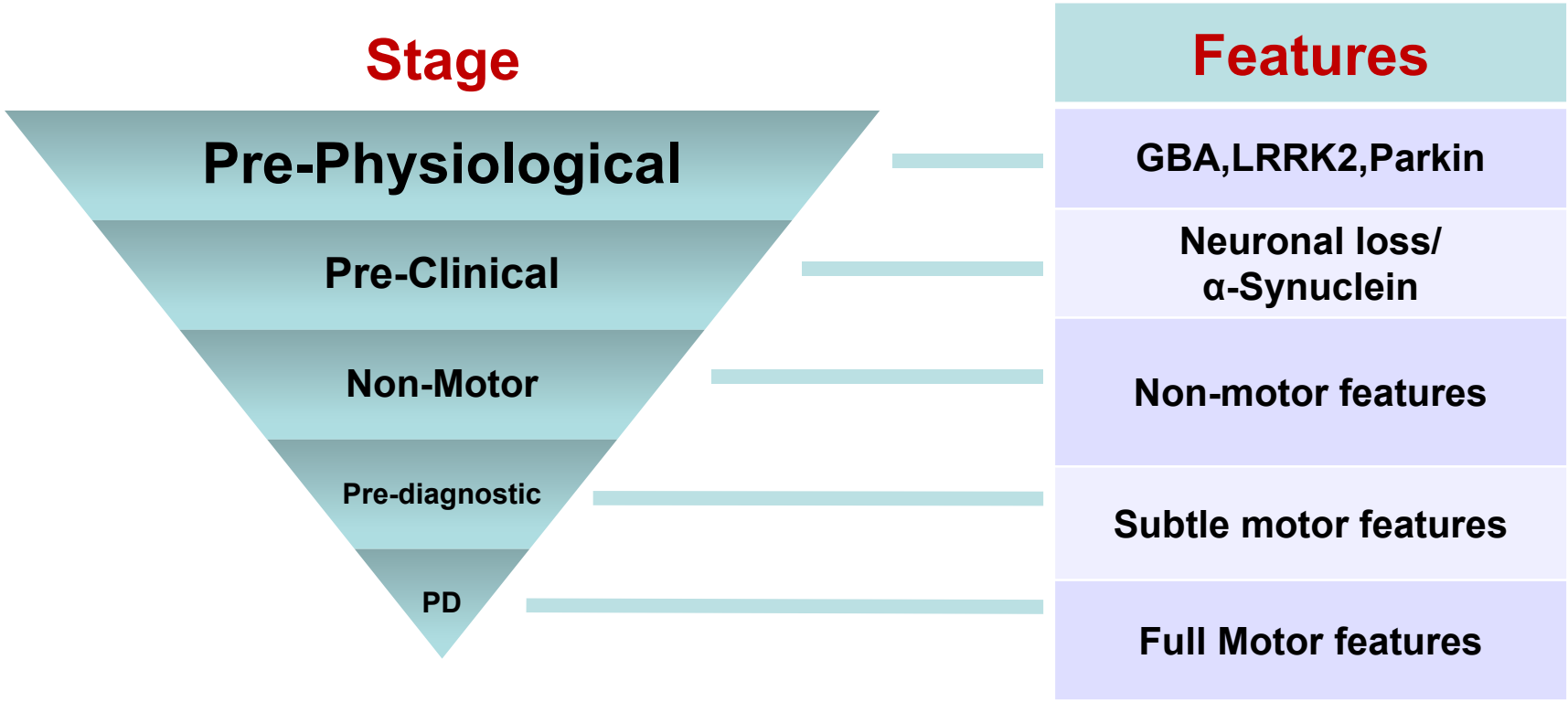


Dickson DW et al. Acta Neuropathol (2008) 115:437–444

Clinical and pathological stages for PD



Is pre-clinical diagnosis possible for PD?

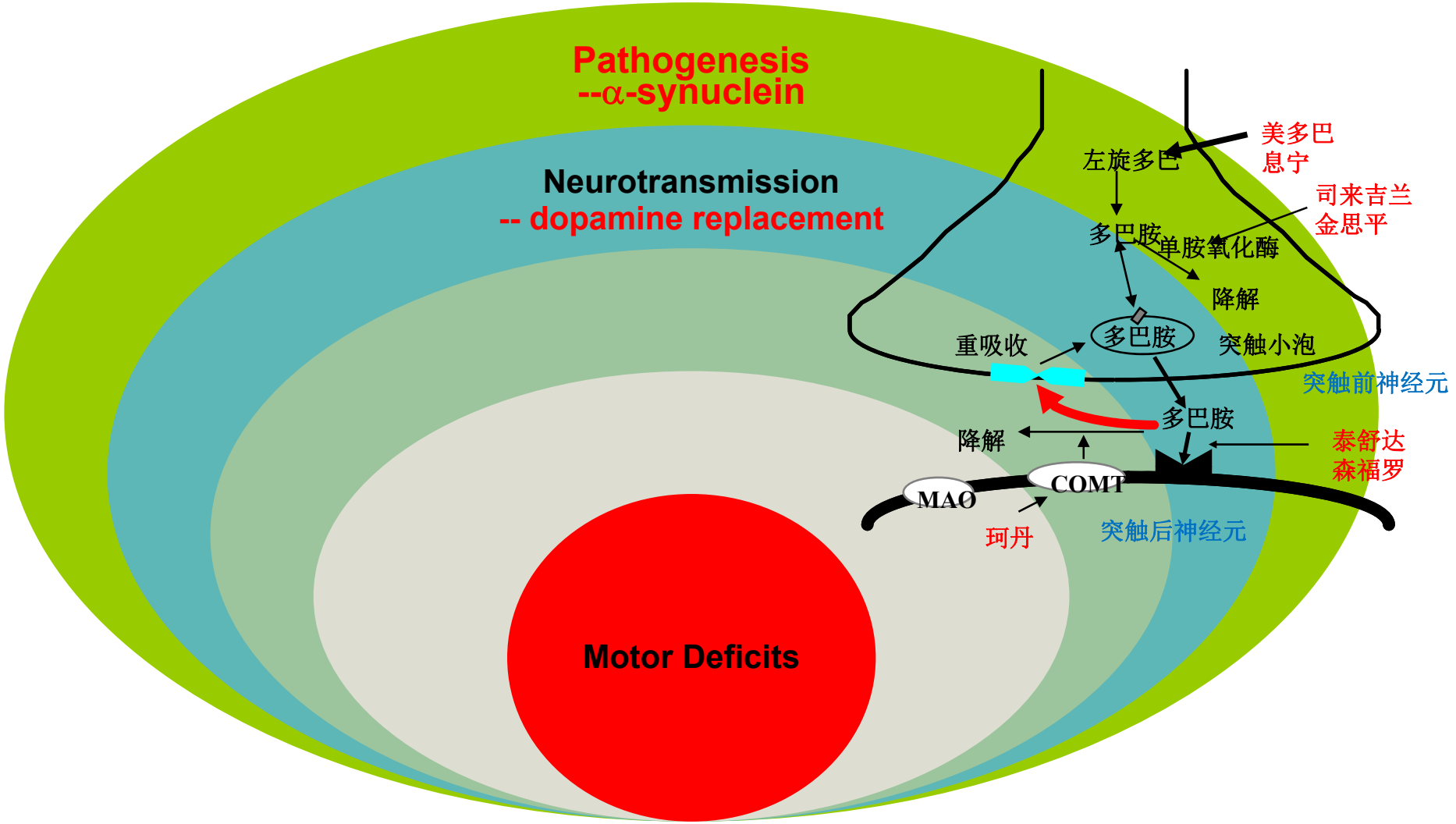


Siderowf A. Mov Disord. 2012; 27(5): 608–616

Therapy for Parkinson's Disease: 20th Century

- Loss of dopamine explained clinical motor features of Parkinson's disease.
- L-dopa replacement treatment is the most effective and standard therapy.

Therapeutic development for PD

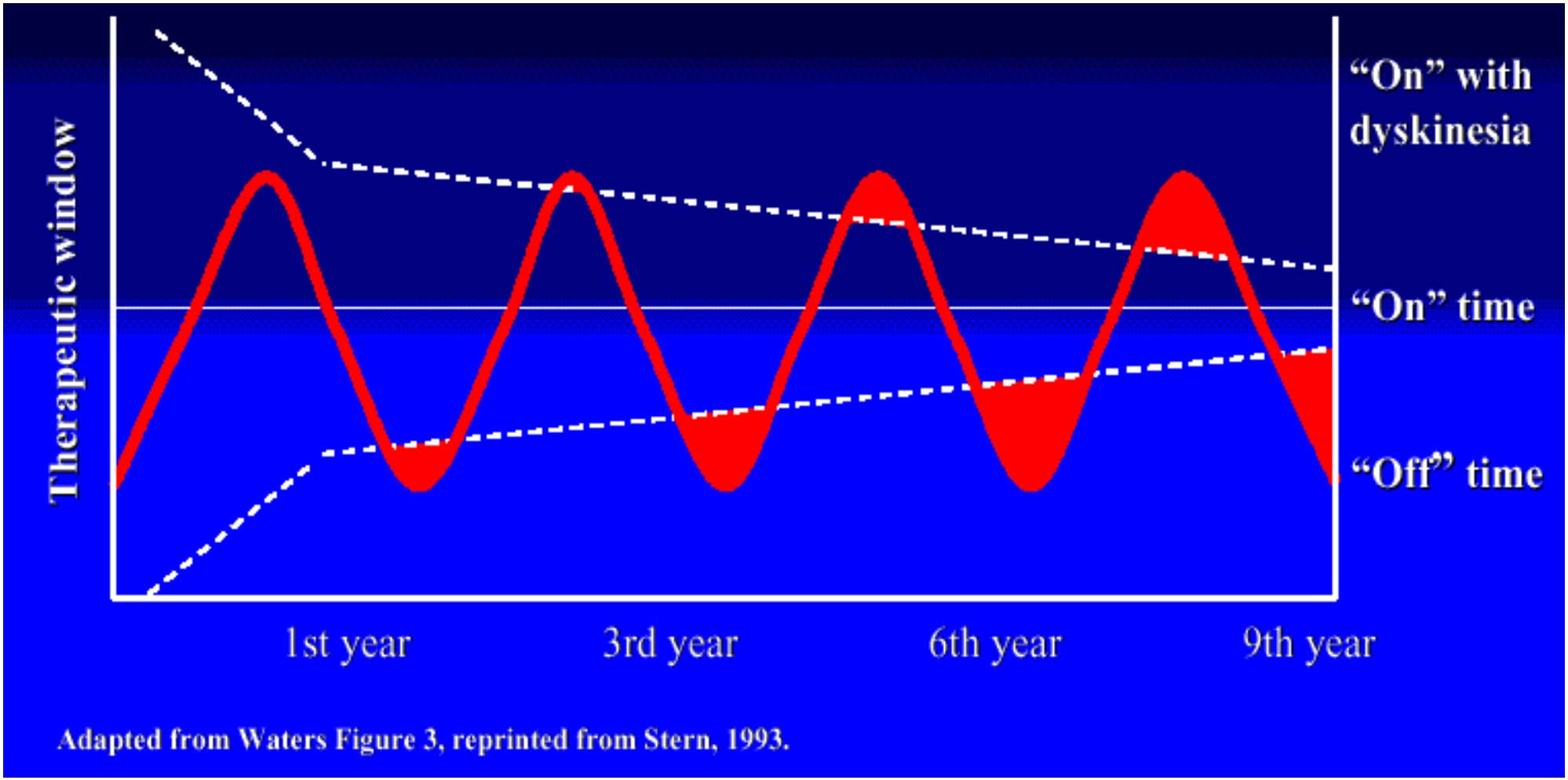


Current medicines for treating PD

Drug	Advantages	Disadvantages
Levodopa (L-dopa) + dopa decarboxylase inhibitor	• Probably the most potent dopaminergic drug for symptom relief • Generally well tolerated	• Motor complications (cumulative risk 10% per annum)
Catechol-O-methyl transferase inhibitors, for example, entacapone, tolcapone	• Increase levodopa half-life • Reduce 'off' time	• Tolcapone can cause liver damage. • Diarrhoea
Ergot dopamine agonists (for example, bromocriptine, pergolide, cabergoline Non-ergot dopamine agonists for example, pramipexole, ropinirole, rotigitine	• Good efficacy • Delay onset of motor complications • Generally well tolerated • Once-a-day preparations available with some • Transdermal patch for rotigitine • Theoretical neuroprotective action • Some antidepressant action with pramipexole	• Increased risk of somnolence, confusion, hallucinations, peripheral oedema and behavioural changes • Cardiac valve fibrosis with ergot drugs
Monoamine oxidase B inhibitor; selegiline; rasagiline	• Improve motor features in early and late disease • Easy to use, once-a-day • Well tolerated • Theoretical neuroprotective effect	• Relatively mild efficacy • Selegiline metabolized to amphetamines — potential cognitive effects
Amantadine	• Mild anti-Parkinsonian effect • Improves dyskinesias	• Cognitive disturbances • Peripheral oedema • Livedo reticularis
Anticholinergics	• Mild anti-Parkinsonian effect	• Limited by side effects such as confusion

Schapira et al., NATURE REVIEWS, DRUG DISCOVERY 5, 845 2006

Long-term treatment associated with Motor Complications



Therapy for Parkinson's Disease: for the 21st Century

Modification of Neuroplasticity??

Therapeutic development for PD

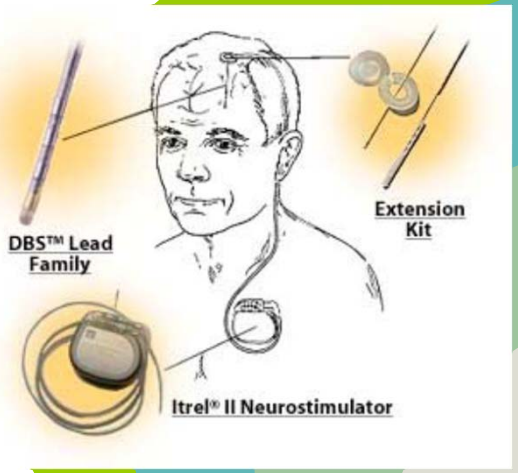
Pathogenesis
--α-synuclein

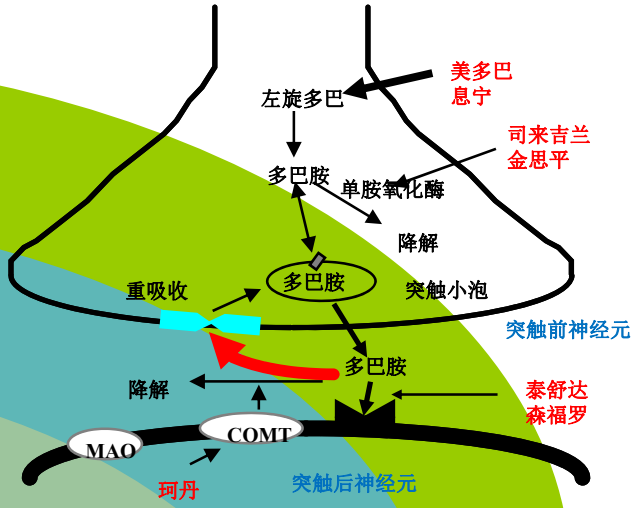
Neurotransmission
-- dopamine replacement

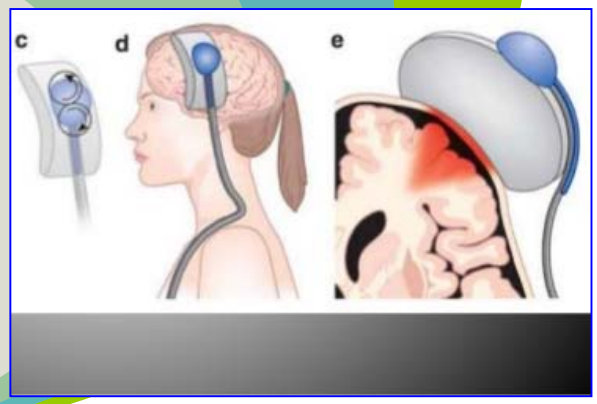
Basal Ganglia Circuit
-- DBS

Brain Connectivity
-- rTMS

Motor Deficits



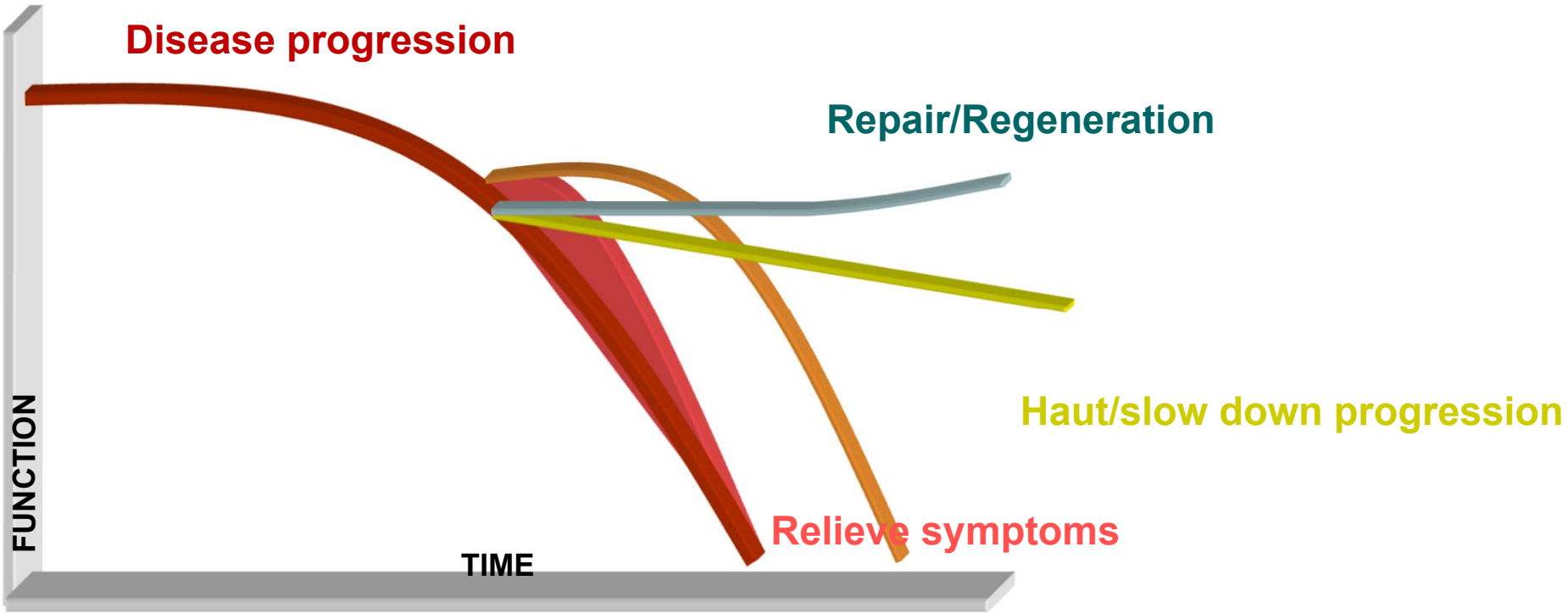




Therapy for Parkinson's Disease: for the future

Dopamine Denervation *vs* Abnormal Corticostriatal Plasticity

What approach to focus?



Unmet needs demand for new paradigm to translate "game-changing" science to disease-modifying medicines

What is neuroprotection

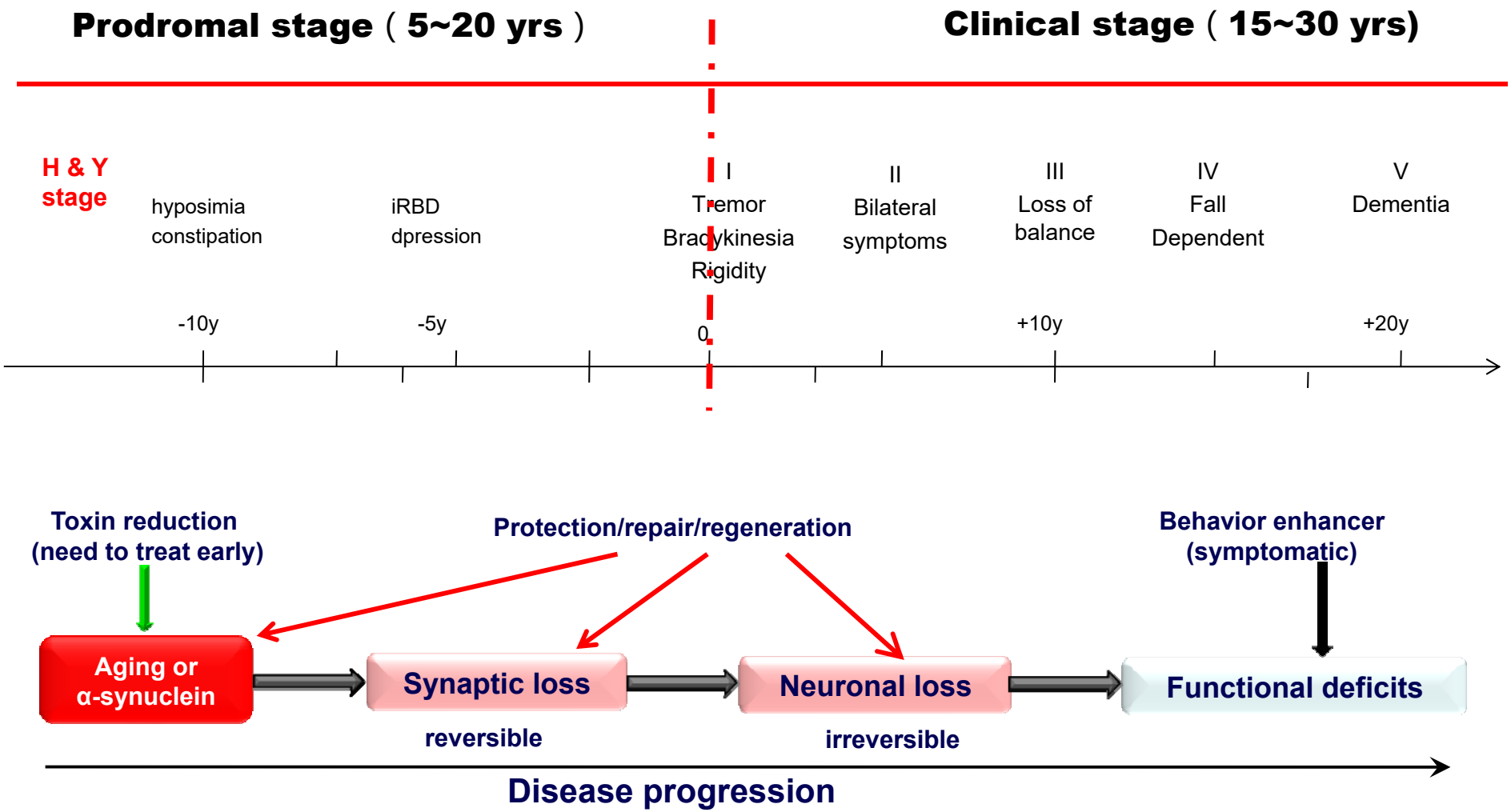
A therapy that slows, prevents, or reverses neuronal loss or dysfunction, leading to improved patient function.

Interventions favorably influencing the underlying **etiology** or **pathogenesis** of a neurodegenerative disorder

Prevent neuron death, thus slow, modify or halt disease progression

A sufficiently robust neuroprotective treatment = to a “**cure**”.

When to treat – the earlier the better



How to treat – a balance of multiple pathways

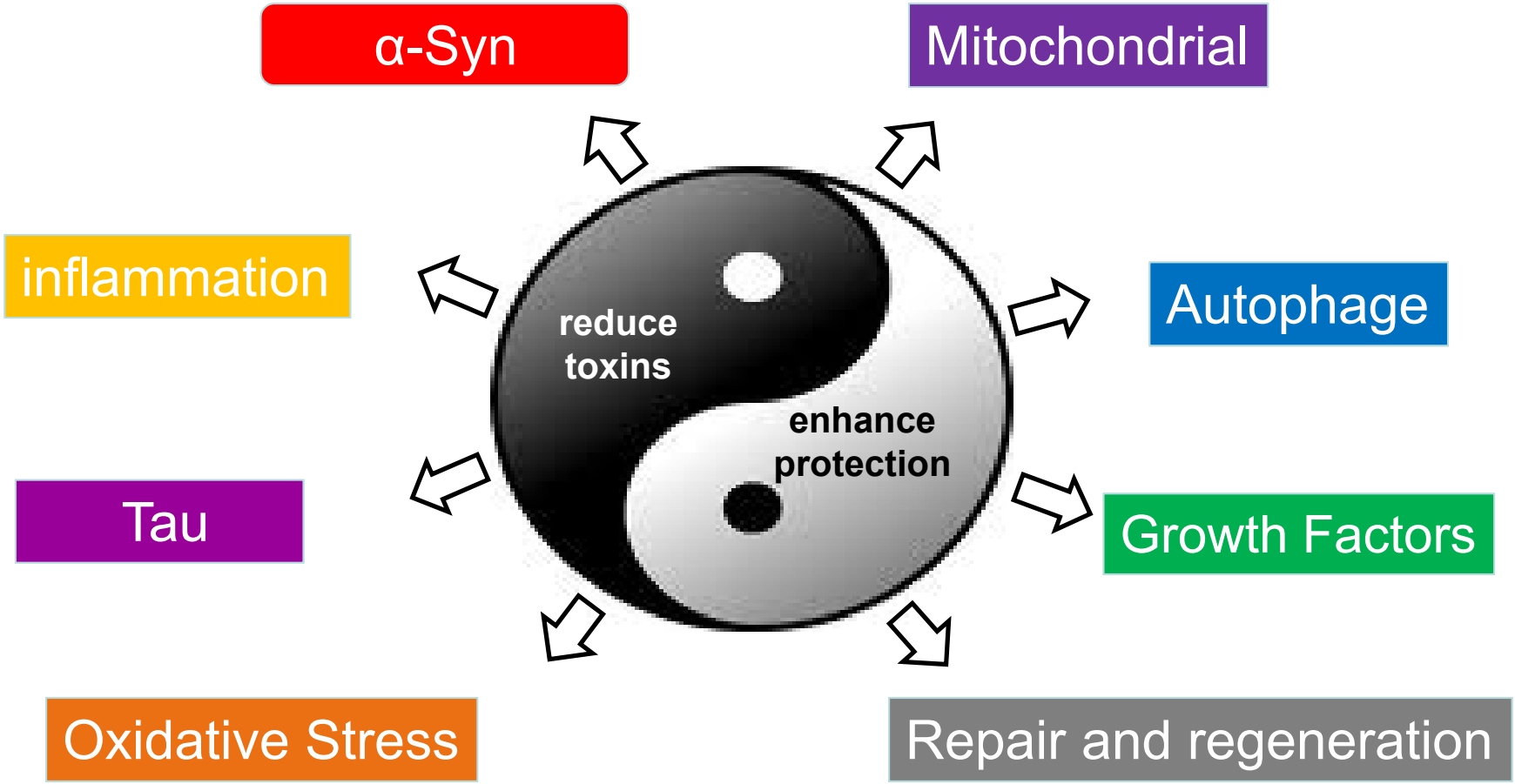


Table 4. Neuroprotective agents in PD

Neuropathology	Target	Investigational agents
Dopamine loss	Dopamine agonists; MAO-B inhibitors; catechol-O-methyl transferase inhibitors	IPX066, ND0612, tyrosine, rotigotine, pardoprunox; EMD1195686, rasagiline; BIA 9-1067
Neurotoxins	MPTP; metal chelators	MAO-B inhibitors: EMD1195686, rasagiline; deferiprone
Neurotransmitter/receptor signaling dysfunction	Adenosine A_{2A} receptor antagonists; 5-HT antagonists	SCH 420814, BIIB014, SCH 900800, ODT, KW-6002; [^{18}F]MPPF
Aggregation of α-synuclein in the form of Lewy bodies	α-Synuclein aggregation inhibitors	PD01A, SR57667B
Oxidative stress	Reactive oxygen species scavengers; antioxidants	Docosahexaenoic acid, GSH, MitoQ, N-acetylcysteine
Neuroinflammation	Anti-inflammatory agents; apoptosis inhibitors	TCH 346, CEP-1347
Excitotoxicity	(Antiglutamatergics); NMDA and AMPA antagonists; Ca^{2+} channel blockers; K^+ channel blockers; Cl^- channel blockers	ADX48621, AFQ056, topiramate, E2007, isradipine CR, zonisamide; dalfampridine; PYM50028

Challenge in new drug development

No proven drug

Mechanisms of neuronal death unknown

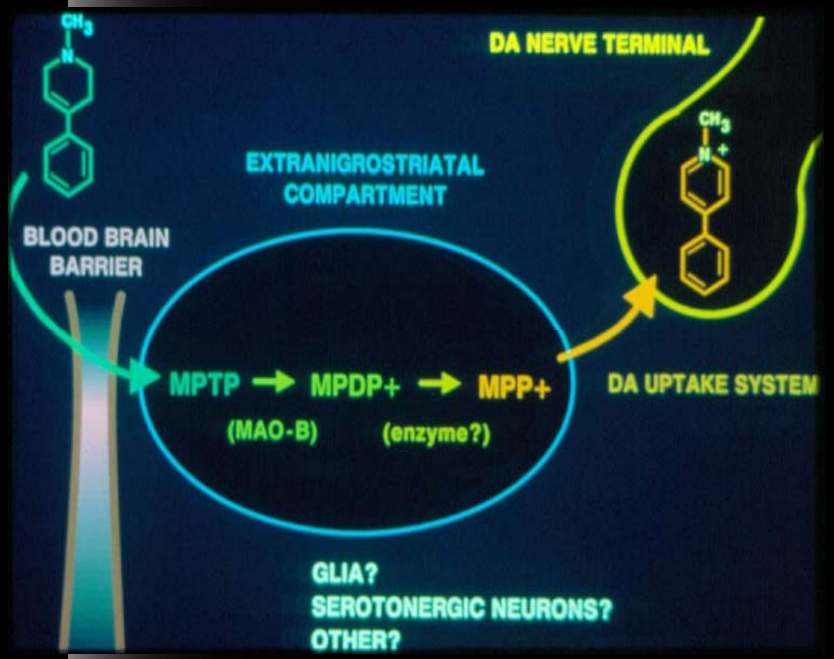
Challenge in defining and measuring neuroprotection

Potential clinical surrogate markers not validated

Long-term follow-up required to test possible neuroprotective benefit

Lack of good disease model

Disease Models



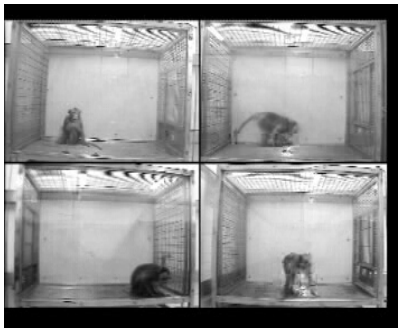
Classic and New Animal Models of Parkinson's Disease

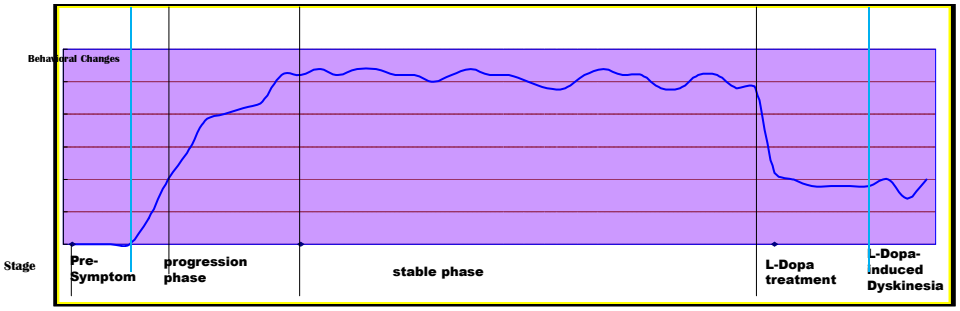
Model	Behavioral symptoms	Nigrostriatal damage	Synuclein aggregation/Lewy body formation	Uses of the model	Disadvantages
6-OHDA	Rotational behavior after unilateral injection	Loss of DA innervation at injection site (striatum)	No inclusions	Screen therapies that may improve PD symptoms. Study mechanisms of cell death	Requires intracerebral injection, very little synuclein involvement.
MPTP	Motor impairments in primates Less obvious motor impairments in acute rodent models	Loss of DA neurons dependent on dosing regimen, reaching 95% in acute high-dose conditions. Reduced DA levels in striatum concurrent with midbrain DA neuron loss	Inclusions not prevalent. Few cases of synuclein aggregation in nonhuman primates, as well as increased synuclein immunoreactivity in rodents.	Screen therapies that may improve PD symptoms. Study mechanisms of cell death	Nonprogressive model of cell death. Inclusiones are rare.
Rotenone	Reports of decreased motor activity in rodents	Loss of DA neurons accompanied by reduced DA innervation in striatum	Synuclein aggregation in DA neurons.	Test neuroprotective compounds	Substantial morbidity and mortality. Labor and time intensive.
Paraquat	No clear motor deficits	Decreased striatal TH immunoreactivity	No inclusions present, but increased synuclein immunoreactivity in DA neurons of the SN	Test neuroprotective strategies	Not extensively tested. Effects in other neurotransmitter systems.
α-synuclein	Severe motor deficits in the A53T model, less in the A30P model	Generally no DA neuron degeneration observed	Synuclein aggregation found in DA neurons, generally restricted to A53T model	Study the role of synuclein aggregation in PD, as well as the normal role of synuclein	Generally no DA neuron death observed with synuclein models
LRRK2	Few behavioral deficits seen in Drosophila mutation models	No effect on DA development or maintenance in knockouts, minimal levels of degeneration in mutation models	Generally not observed	Study the role of LRRK2 mutations related to PD	General lack of degeneration and general lack of synuclein aggregation.

Predictive validity for animal models of PD

Animal model	Reserpine	Haloperidol	6-OHDA	MPTP mouse	Rotenone	MPTP primate
L-DOPA ± carbidopa	✓	✓	✓	✓	✓	✓
Dopamine agonists						
Apomorphine	✓	✓ and X	✓	X	✓	✓
Bromocriptine	✓	✓	✓	✓	–	✓
Cabergoline	✓	–	✓	✓	–	✓
Pramipexole	✓	✓	✓	✓	–	✓
Pergolide	✓	–	✓	–	–	✓
Ropinirole	✓	–	✓	–	–	✓
Rotigotine	–	–	✓	–	–	✓
MAO-B inhibitors						
Selegiline	✓[a]	✓[a]	✓[a]	✓[a]	–	✓[a]
Rasagiline	✓[a]	✓	✓[a]	–	–	✓[a]
COMT inhibitors						
Entacapone	–	–	✓[a]	–	–	✓[a]
Tolcapone	✓[a,b]	✓[a]	✓[a]	✓[a]	–	✓[a]
Anticholinergics						
Trihexyphenidyl	✓[c]	✓	–	–	–	✓
Benztropine	✓[c]	✓[a]	–	–	–	✓
Orphenadrine	–	–	–	–	–	–
Procyclidine	–	–	–	–	–	–
Miscellaneous						
Amantadine	✓	✓	✓	✓[a]	–	✓

MPTP systemic parkinsonism model





- Behavior
- biochemistry
- neuroimaging

Baseline

Induction

- MPTP i.v.
- Continue until clinical signs obvious enough

- Behavioral signs stable for at least 2~3 months

Modeling

Drug response

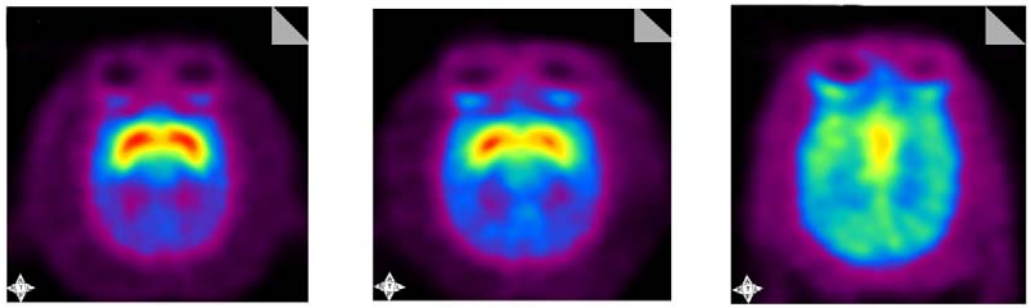
- Good response to Levodopa

- Abnormal motor movement after increased dose

Dyskinesia

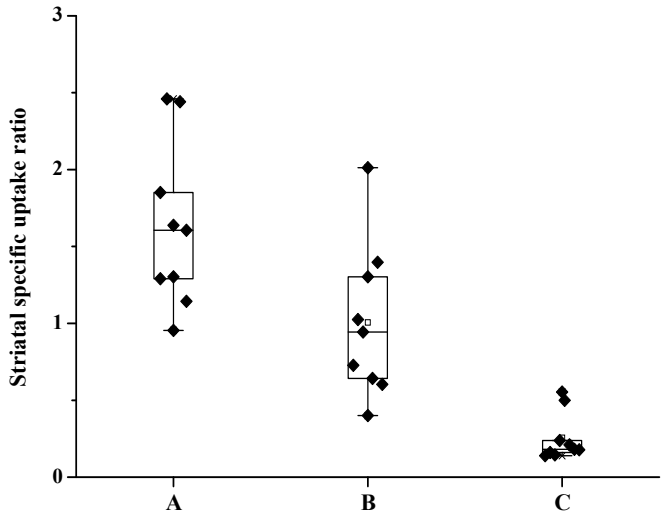
Clinical evaluation: [18F]AV-133 VMAT2 PET

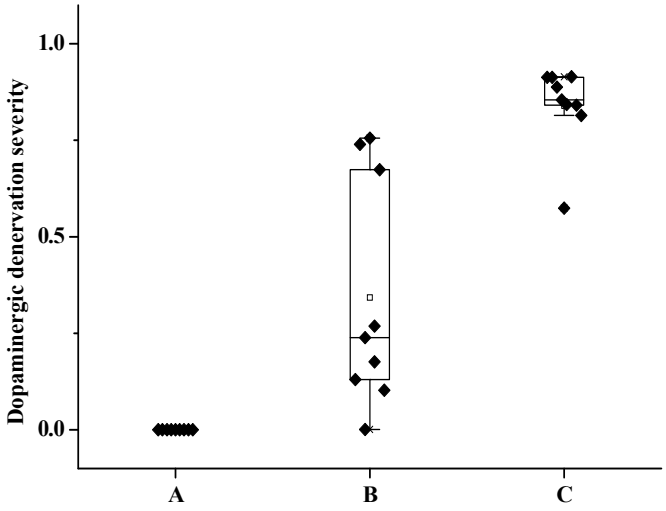
Before MPTP | After MPTP | Day 90



specific uptake ratio (SUr), calculated by (striatum uptake-cerebellum uptake)/cerebellum uptake;

dopaminergic denervation severity (DS) after MPTP treatment, calculated from SUr via ($SUr_{baseline}$-$SUr_{lesioned}$)/$Sur_{baseline}$





Liu Y et al., Neurosci Bull. 2014 Jun;30(3):409-16

A Randomized Double-Blind and Placebo-Controlled Study to Assess the Ability of Slowing Disease Progression and Safety and Tolerability of Green Tea Polyphenols in Patients with Early Parkinson's Disease

Chinese Parkinson Study Group

Supported by Michael J Fox Foundation

(ClinicalTrials. gov number, NCT00461942.)

Rational: Epidemiological Evidence

- A dose-dependent protective effect of PD in tea drinkers in ethnic Chinese and 3 cups/day for 10 years associated with a 28% risk reduction of PD (Chan et al., 1998 & 2003; Tan et al, 2003).
- Population-based incident studies in Caucasians have also found a 60% reduction in risk for PD, which were not confounded by smoking or coffee consumption (Checkoway et al 2002; Ascherio et al., 2001).

Rational: PD Animal Models

- EGCG can prevent MPTP-induced
  - depletion of DA, and TH protein and TH activity in the striatum
  - decrease in the number of DA neurons in the SN
  - increase of α-synuclein expression in the SN
- EGCG directly binds to unfolded polypeptide chains and inhibits β-sheet formation but form non-toxic oligomer assemblies.
- EGCG binding precedes the structural rearrangement of amyloid fibrils and does not stimulate the release of soluble monomers or oligomers
- EGCG remodels mature α-synuclein and amyloid-β fibrils and reduces cellular toxicity (Jan Bieschke et al., PNAS, 2010; 107:7710–7715)

TPs improved parkinsonism in NHPs

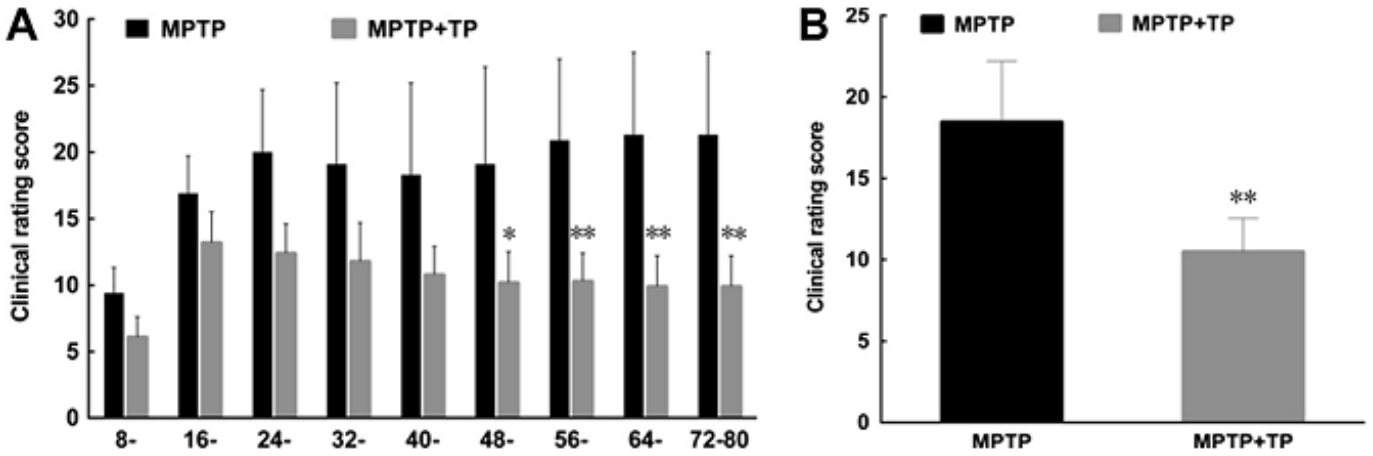
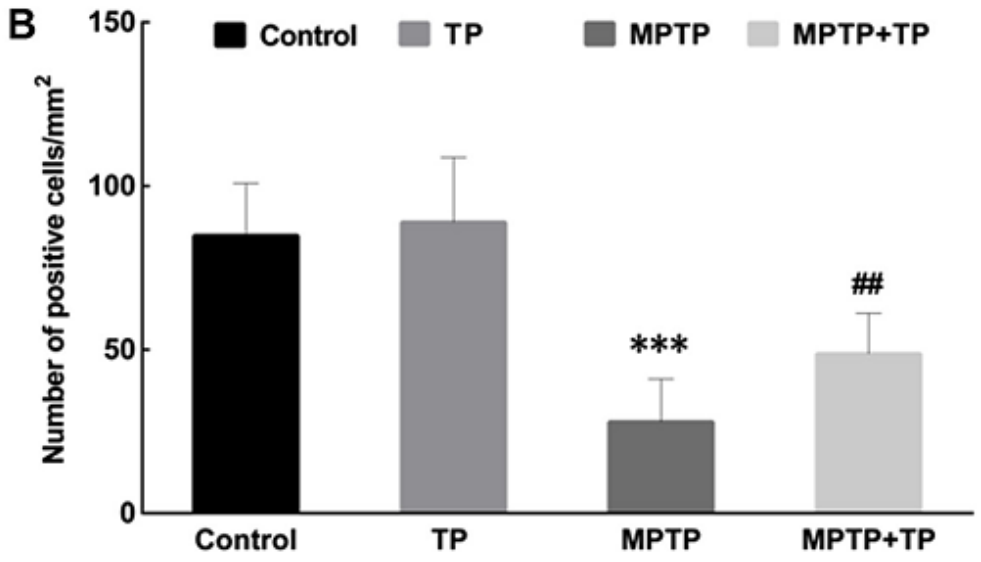


Fig. 2. Animal behavior assessed by clinical rating scores. (A) Time-dependent increase in clinical rating scores in MPTP-intoxicated monkeys (black column), indicating progressive motor impairment. Scores were stable until completion of the experiment. Clinical rating scores were markedly reduced by TP (gray column), and the reduction reached statistical significance by 48 days. Sidak's post hoc test after two-way ANOVA, $^{*}P < 0.05$ and $^{**}P < 0.01$, compared to MPTP-treated monkeys. (B) Integrated clinical rating scores for MPTP- and MPTP + TP-treated monkeys. Student *T* test, $^{**}P < 0.01$, compared to MPTP-treated monkeys. $n = 4$/group.

Neurosci 2015

TPs prevent MPTP-induced loss of neurons in NHPs



Neurosci 2015

TPs prevent MPTP-induced loss of neurons and striatal dopmine in NHPs

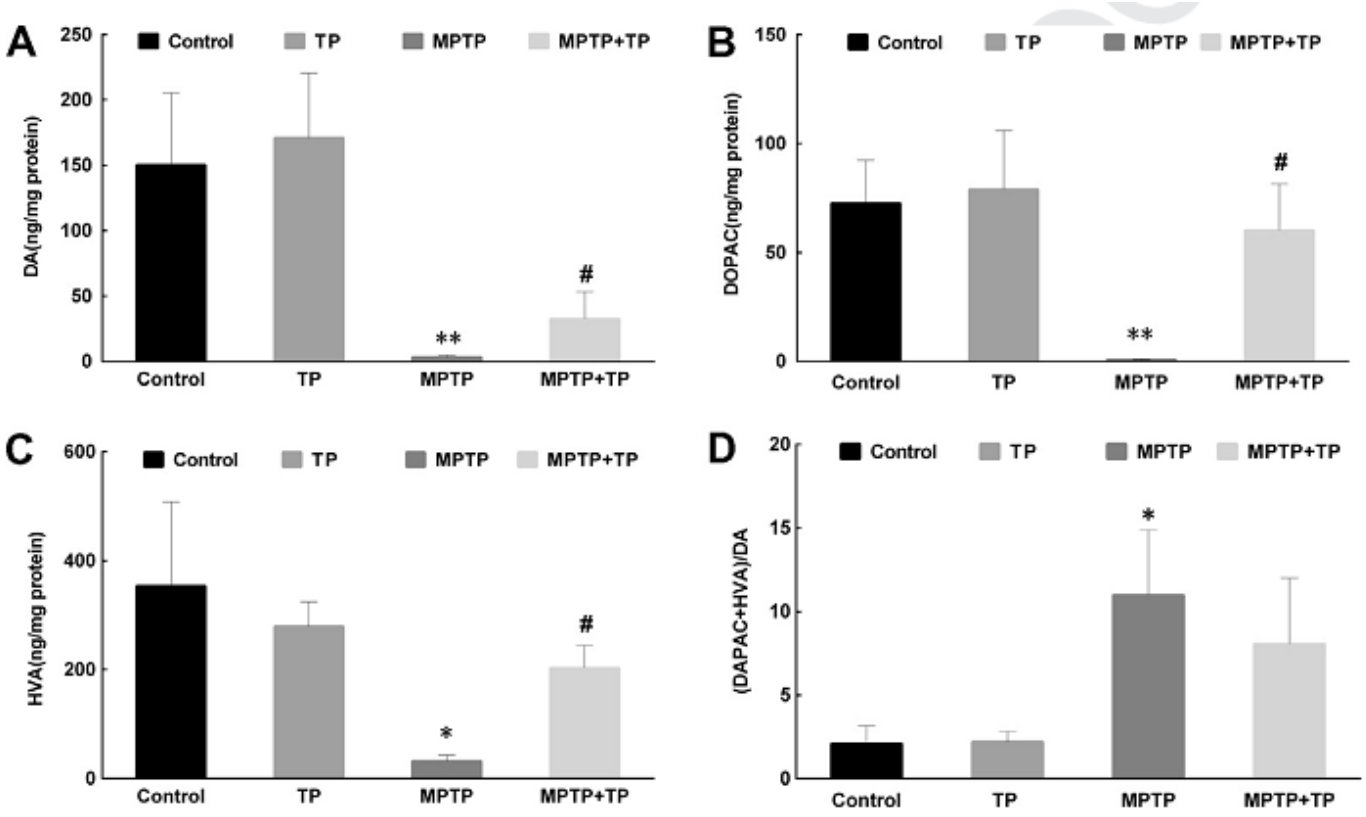


Fig. 3. Analysis of DA and DA metabolites in striatum. The levels of DA (A), DOPAC (B), and HAV (C) were significantly reduced in MPTP-treated monkeys and the reduction partially reversed by TP treatment. (D) The ratio of (DOPAC + HAV)/DA. Tukey's post hoc test after One-way ANOVA, $*P < 0.05$ and $**P < 0.01$, compared to control group; $^{\#}P < 0.05$, compared to MPTP group. $n = 4$/group.

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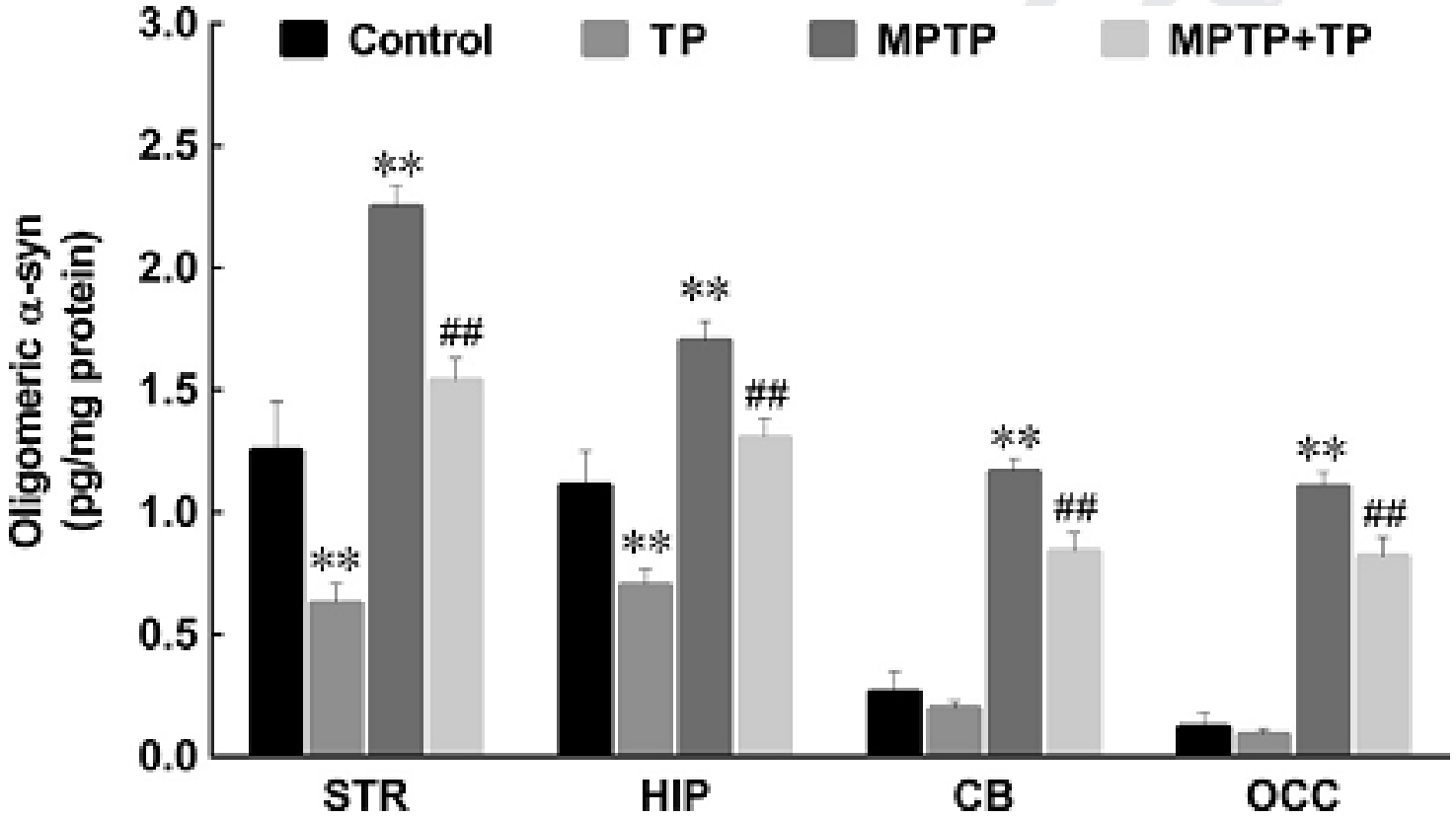
TPs decreased α-syn oligomers in brain after MPTP



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Examples of recently discontinued drug development for PD

COMPOUND	MECHANISM OF ACTION	PHASE	COMMENT
CEP-1347 (Cephalon/Lundbeck)	Kinase inhibitor	II	Lack of efficacy
E2007/perampenal (Eisai)	AMPA receptor antagonist	III	Lack of efficacy
GDNF (Amgen)	GDNF	II	Lack of efficacy and anti-drug antibody formation
MitoQ (Antipodean)	Mitochondria targeted antioxidant	II	Lack of efficacy
NS2330/tesofensine (NeuroSearch/BI)	Monoamine uptake inhibitor	III	Lack of efficacy
Sarizotan (EMD Serono)	Dopamine agonist	III	Lack of efficacy
SR57667/Paliroden (Sanofi)	Oral stimulator of NGF	II	Lack of efficacy
Vadova/levodopa (Impax)	dopamine	NDA	Non-approvable letter
Vipadenant/BIIB014 (Biogen)	Adenosine $A2_A$ antagonist	II	Toxicology issue

Wrong mechanism? Wrong target?
Wrong approach? Too little, too late or both?

How to be successful?

- **What to treat**
  - Symptoms vs disease modification
  - Target(s) and mechanism(s)
- **Who to treat**
  - Patient stratification
- **When to treat**
  - Early diagnosis and intervention (prevention?)
  - Opportunity/feasibility of treating moderate/advanced patients
- **How to enhance clinical success**
  - Value of preclinical models to predict clinical effectiveness?
  - Biomarkers: diagnosis, progression, mechanistic and early efficacy readout, when?
  - Sensitive/robust clinical trial paradigm to demonstrate clinical differentiation

Thanks for your attention!