Parkinson's disease

Angelo Antonini
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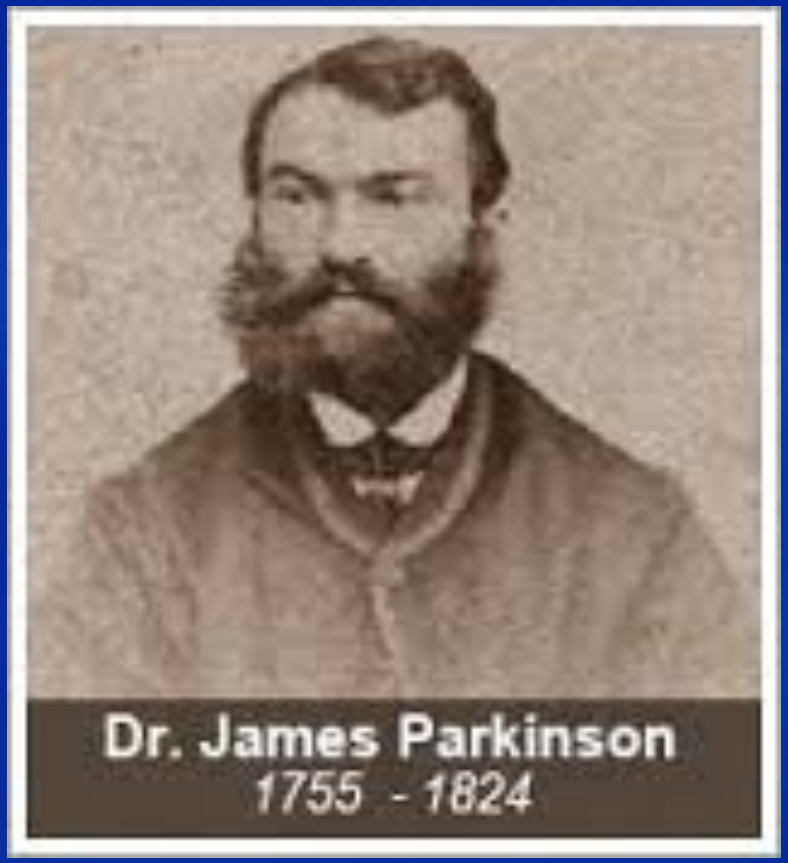
Dr James Parkinson
(1755–1824)
Politician, Geologist, Artist, Doctor



James Parkinson was the son of John Parkinson, an apothecary and surgeon practicing in Hoxton Square, London.

Where James studied is not known, but in 1784 his name appeared on a list of surgeons approved by the Corporation of London.

On May 21, 1783, he married Mary Dale of Hoxton Square; they had six children. James eventually succeeded his father in his practice in Hoxton Square.

James Parkinson died in Kingsland Road on December 21, 1824.

AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.
1817.

Parkinson's most important medical work was An Essay on the Shaking Palsy (1817). In this short essay Parkinson established the disease as a clinical entity:

"Involuntary tremolous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forewards, and to pass from a walking to a running pace: the senses and intellect being uninjured."

Four decades later Jean-Martin Charcot added rigidity to Parkinson's excellent clinical description and attached the name Parkinson's disease to the syndrome.

Although Parkinson's disease is one of the best known medical eponyms, Parkinson himself received little attention from his english-speaking collegues, until an article written by the american J. G. Rowntree in 1912 appeared in volume 23 of the Bulletin of the Johns Hopkins Hospital, titled:

"English born, English bred, forgotten by the English and the world at large, such was the fate of James Parkinson".

PARKINSON	1817
CHARCOT	1876

ŒUVRES COMPLÈTES
DE
J.-M. CHARCOT

LEÇONS
SUR LES
MALADIES DU SYSTÈME NERVEUX

RECUEILLIES ET PUBLIÉES
PAR
BOURNEVILLE

TOME I

avec 12 figures dans le texte et 12 planches

PARIS

AUX BUREAUX DU PROGRÈS MÉDICAL
14, rue des Carmes

A. DELAHAYE & E. LECROSNIER
Place de l'École-de-Médecine

1886

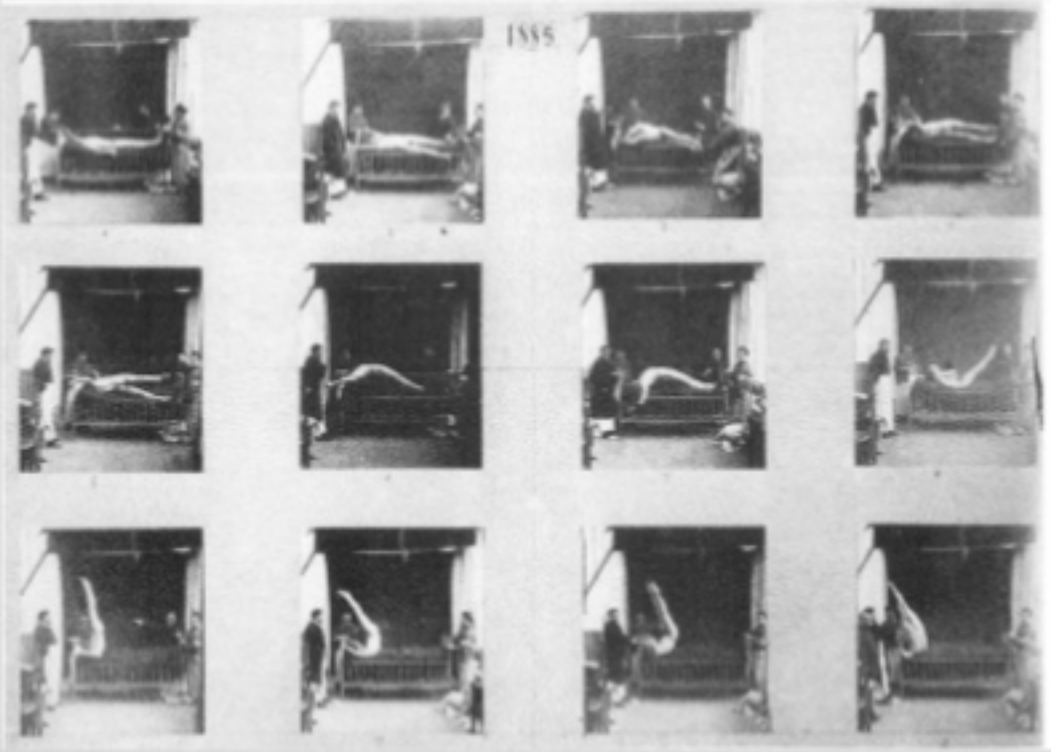
Jean-Martin Charcot (1825-1893)

Neurologist,
Salpêtrière Hospital,
Paris

-- Freud visited his clinic for four months, 1885-1886

Images of hysterical patients from Salpêtrière hospital

Clip slide



Wikimedia commons (Italy), public domain

Wikimedia commons, Public domain

Freud and Hysteria

- Repression: Particular memories, feelings, desires, fantasies (always having some sexual component (*Dora* 39)) are pushed out of consciousness into the unconscious

- Return of the repressed: But these repressed contents seek to emerge into consciousness some other way: they "speak" one's inner secrets through a different language, in dreams or bodily symptoms

- Role of analyst is to translate this language, re-tell the patient's own secrets to him/her. Once brought to consciousness, symptoms resolve.

Hysterical symptoms

- "Conversion" (*Dora* 46): psychological energy is converted, translated into physiological expression, a symptom
  - Symptoms repeat because the unconscious material still striving for expression
- "Somatic compliance" (*Dora* 33-34): psychological energy attaches to a physiological experience or symptom that the patient already had.
  - e.g., physiological basis of Dora's cough (74)
  - psychological meanings of it (74, 31-32, 41, 48)

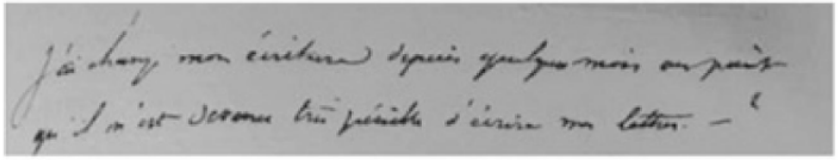
CINQUIÈME LEÇON

DE LA PARALYSIE AGITANTE.

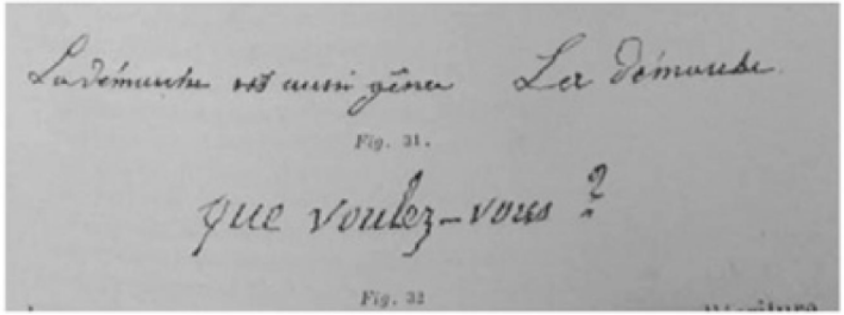
A

B

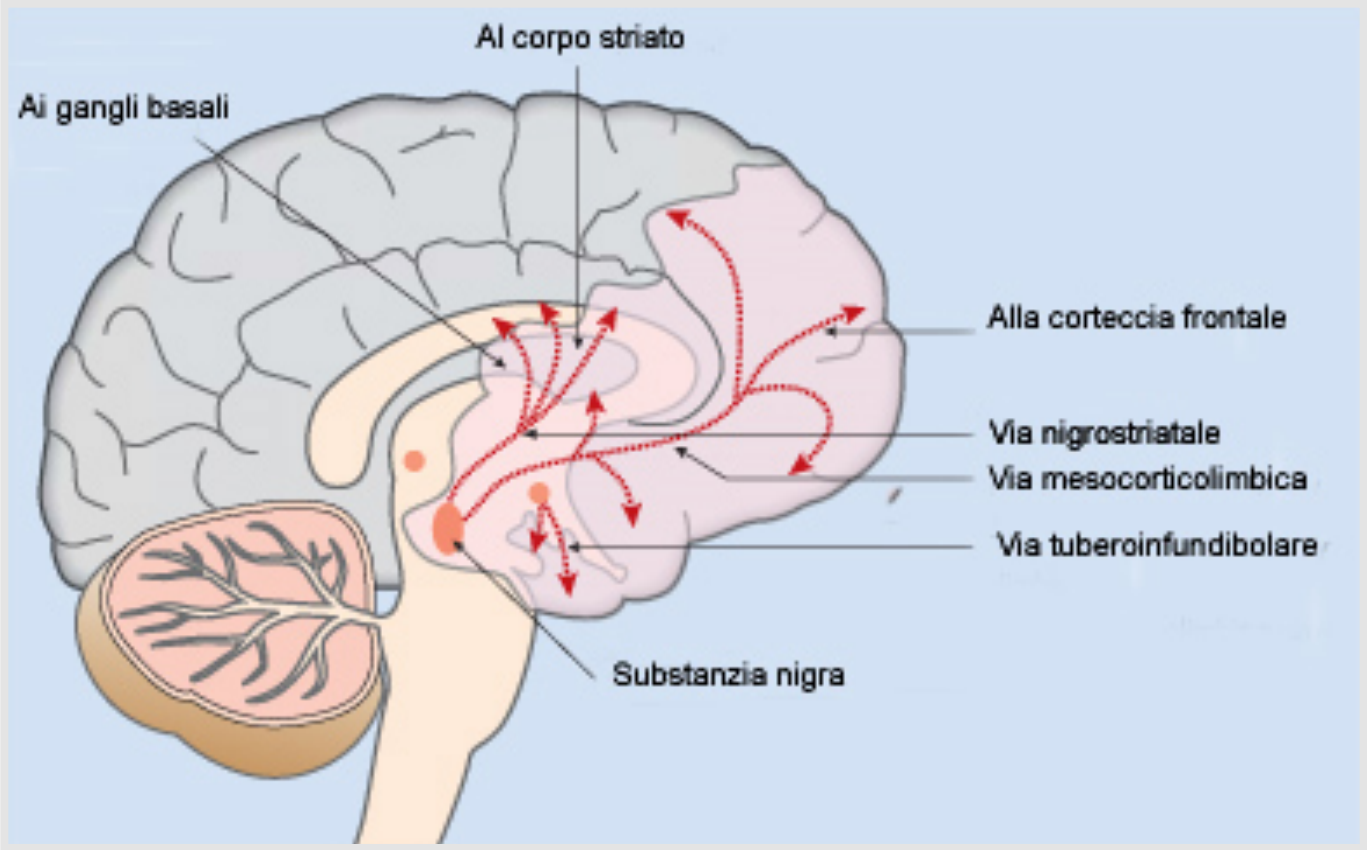
C

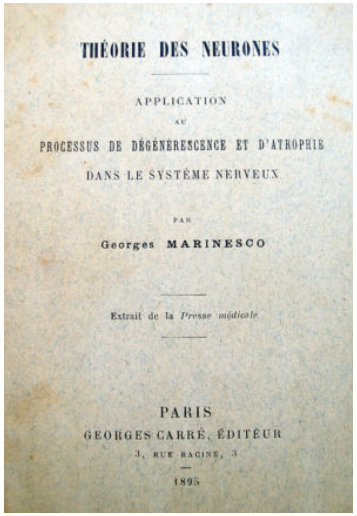


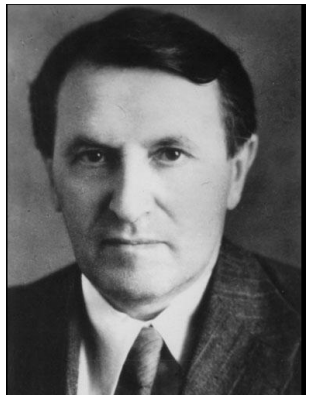
D



I circuiti alterati nel Parkinson





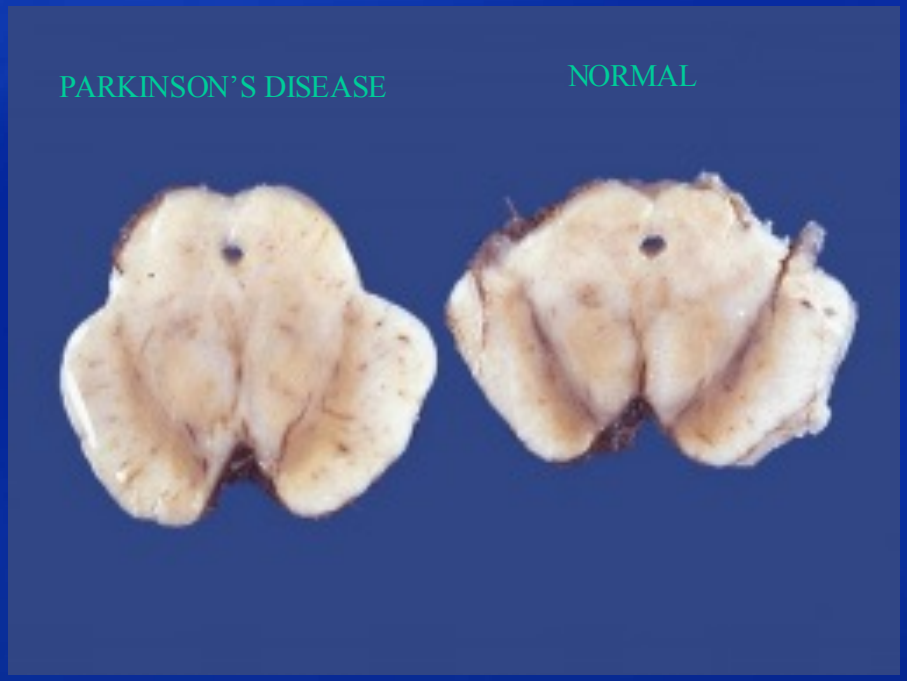


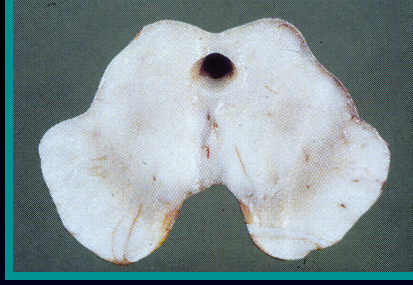
- The substantia nigra was discovered in 1786 by Félix Vicq d'Azyr, but it took more than a century before Paul Blocq and Georges Marinesco alluded to a possible link between this structure and Parkinson's disease. The insight came from the study of a tuberculosis patient admitted in Charcot's neurology ward at la Salpêtrière because he was suffering from unilateral parkinsonian tremor.
- At autopsy, Blocq and Marinesco discovered an encapsulated tumor confined to the substantia nigra, contralateral to the affected side, and concluded that tremor in that particular case resulted from a midbrain lesion.
- This pioneering work, published in 1893, led Edouard Brissaud to formulate, in 1895, the hypothesis that the substantia nigra is the major pathological site in Parkinson's disease.
- Brissaud's hypothesis was validated in 1919 by Constantin Trétiakoff in a thesis summarizing a post-mortem study of the substantia nigra conducted in Marinesco's laboratory.

What is Parkinson's?

The traditional view !

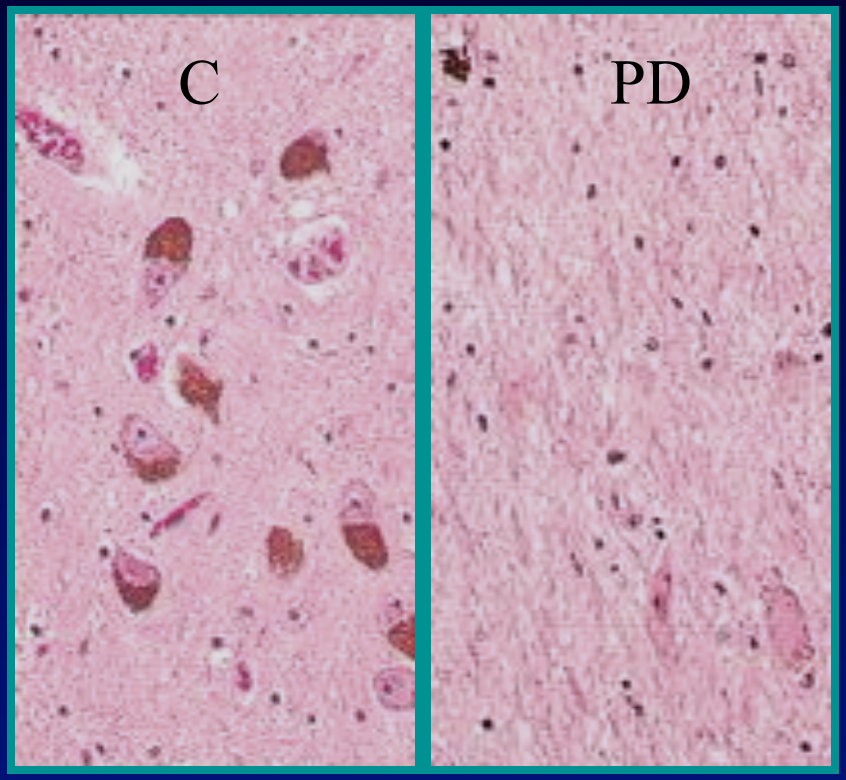
- Parkinson's disease is one of the most common neurodegenerative diseases
- First described by James Parkinson in 1817 in *An Essay on the Shaking Palsy*
- The main pathological feature is the degeneration of neuromelanin-containing neurones in the pars compacta of the substantia nigra; resulting in depleted levels of dopamine within the brain

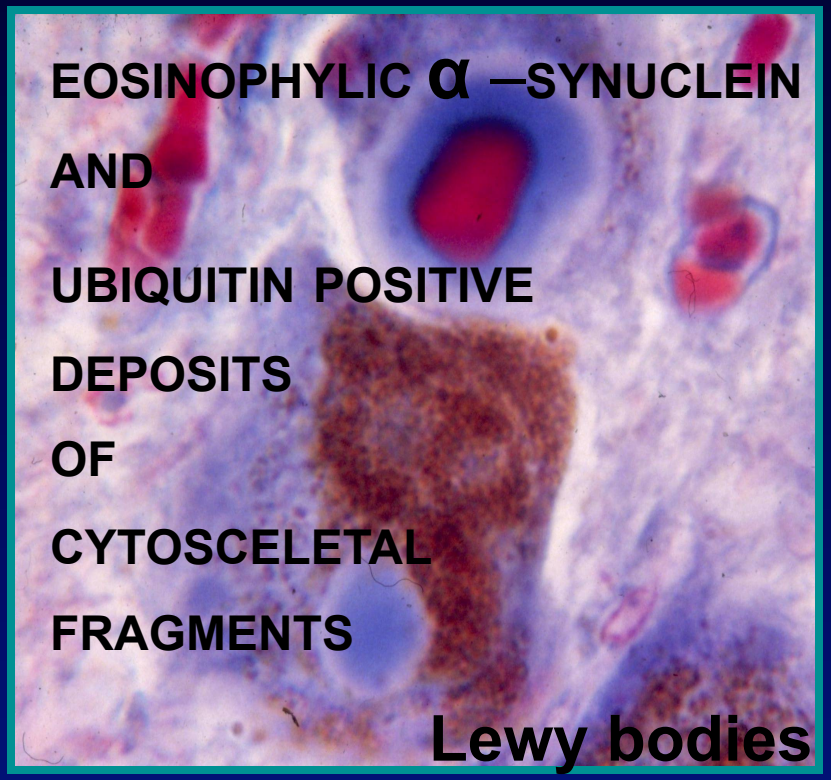




MOTOR PARKINSONISM DEVELOPS AS CONSEQUENCE OF DEGENERATION IN THE DOPAMINE-PRODUCING CELLS IN THE NIGRAL SUBSTANCE

leading to a dopaminergic denervation of the basal ganglia





ARVID CARLSON
Premio Nobel per la medicina nel 2000

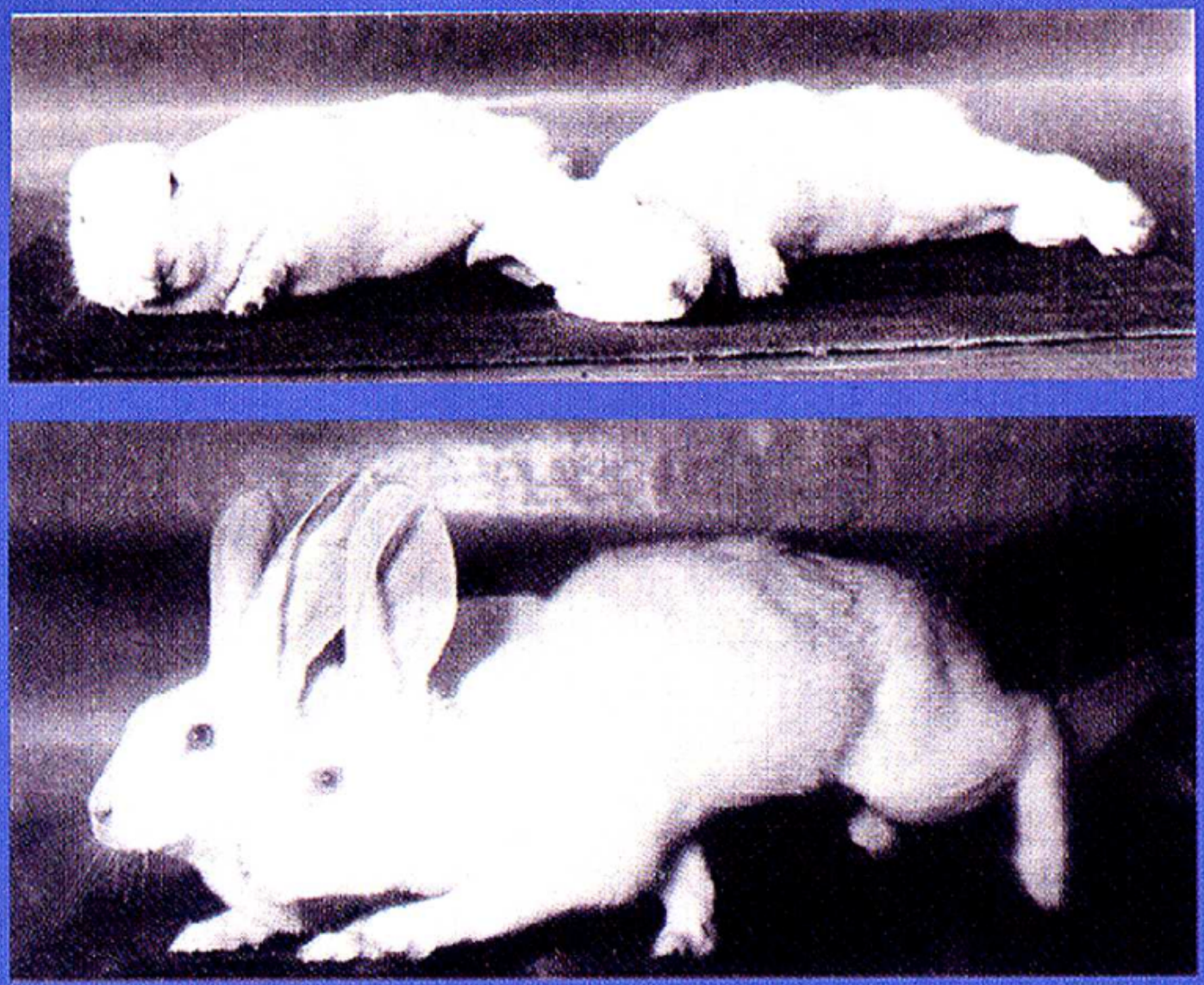
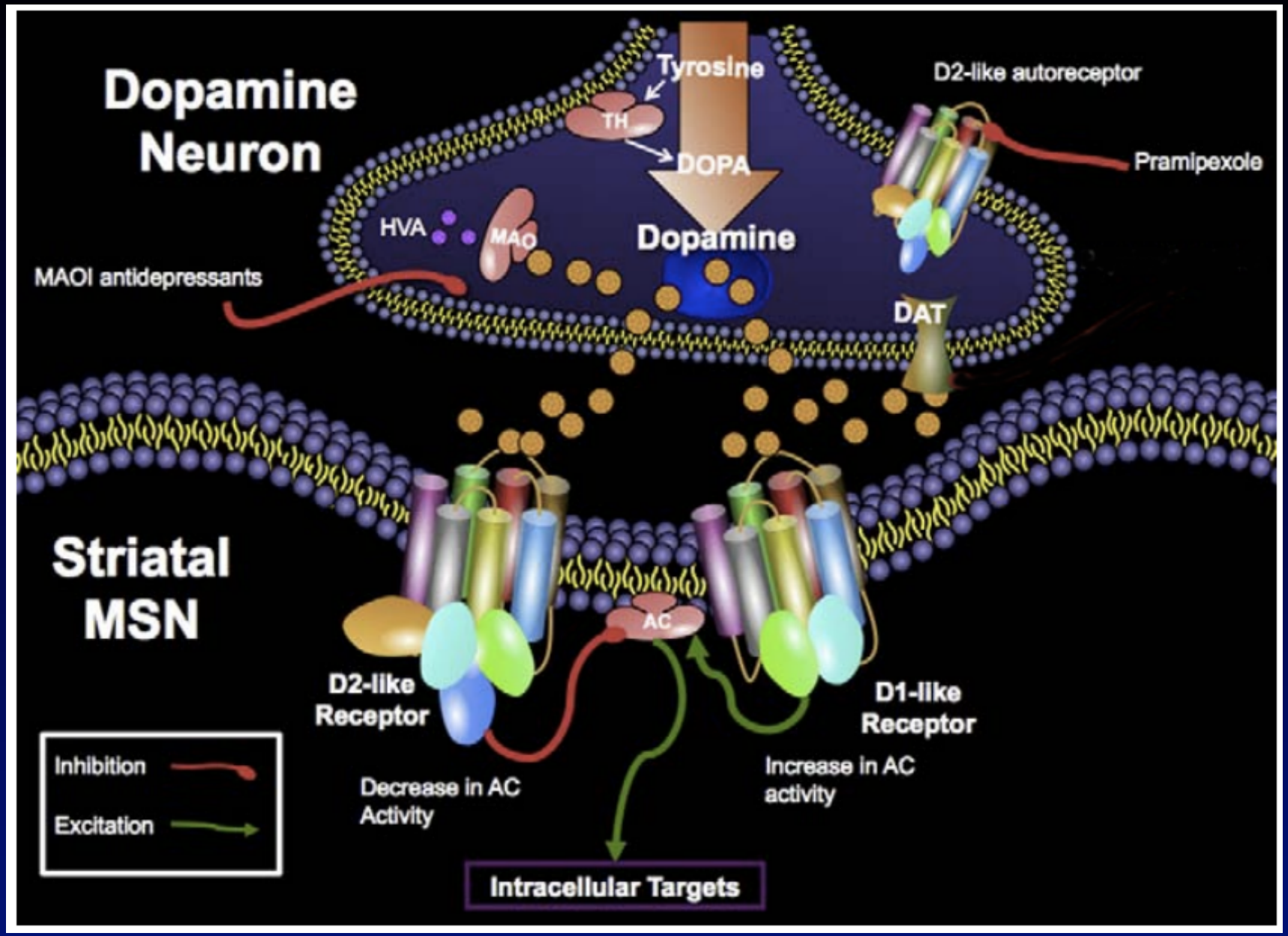
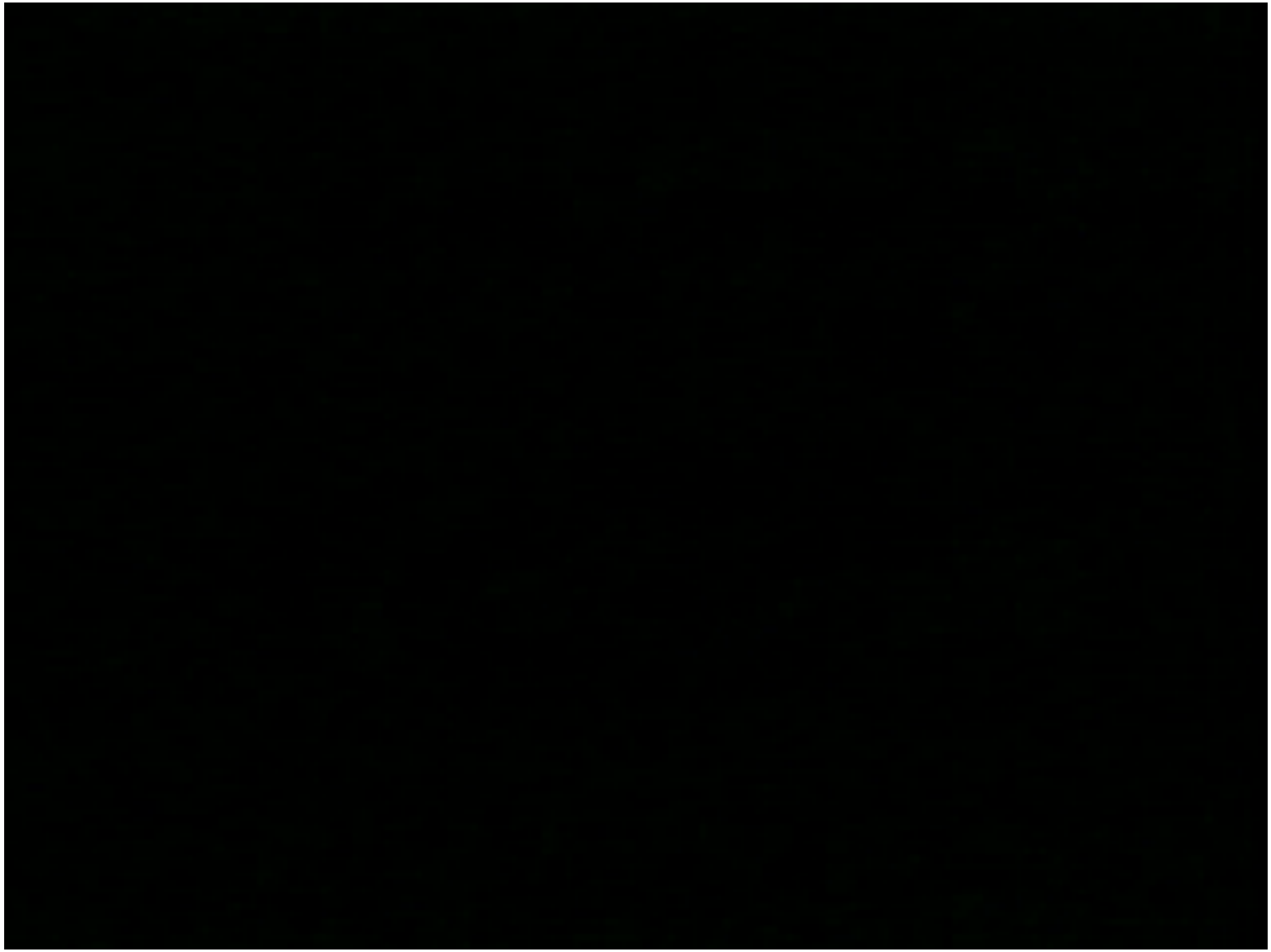


Figure 4. Rabbits treated with reserpine (5 mg/kg intravenously).before (top) and after DL-DOPA (200 mg/kg intravenously, bottom). From Carlsson (1960). Photo: Tor Magnusson.


Dopamine Neuron
Tyrosine
TH
DOPA
Dopamine
HVA
MAO
MAOI antidepressants
D2-like autoreceptor
Pramipexole
DAT
Striatal MSN
AC
D2-like Receptor
D1-like Receptor
Inhibition
Excitation
Decrease in AC Activity
Increase in AC activity
Intracellular Targets



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AROMATIC AMINO ACIDS AND MODIFICATION OF PARKINSONISM*

GEORGE C. COTZIAS, M.D.,† MELVIN H. VAN WOERT, M.D.,‡ AND LEWIS M. SCHIFFER, M.D.‡

UPTON, NEW YORK

THE known biochemical abnormalities in Parkinson's disease consist of a decrease of melanin pigment in the substantia nigra[1,2] and a decrease of some biogenic amines in the substantia nigra and the corpus striatum.[3] These 2 defects might be interrelated, as suggested by the fact that in both melanocytes[4] and sympathetic cells[5] tyrosine is hydroxylated to dihydroxyphenylalanine, a common precursor in the synthesis of both melanin and catecholamines. Furthermore, both melanocytes and sympathetic cells originate from the neural crest.[6]

It was suggested earlier[7,8] that the interrelations between melanogenesis and extrapyramidal disease might be of fundamental importance. It was noted that chronic exposure to at least 2 chemicals, manganese and phenothiazine compounds, may induce extrapyramidal manifestations. Manganese was shown to accumulate in the various melanin granules analyzed,[9,10] a property that is shared by phenothiazines.[11] In addition, metals such as manganese interact in vitro with phenothiazines to give semiquinone-free radicals, similar to those present in normal melanin.[12]

In the present work an effort was made to ameliorate the known biochemical abnormalities in patients with Parkinson's disease. Initially the effect of melanocyte-stimulating hormone was investigated. This agent increases melanin deposition at least in the integumental melanocytes,[13] and it was hoped that it might similarly affect the pigmented cells of the brain. Furthermore, this peptide has increased the amplitude of evoked monosynaptic potentials in the spinal cord of the cat.[14] It became apparent, however, that the Parkinsonian state was reversibly aggravated by the administration of this hormone. A serviceable working hypothesis compatible with this finding might be that the hormone was shifting dihydroxyphenylalanine (DOPA), the precursor of melanins and biogenic amines, from the brain to the integument. Therefore, it was considered desirable to investigate the therapeutic potential of DOPA, particularly since the early reports of short-lived improvement[15] were disputed by later studies.[16-18] Administration of higher doses than previously reported effected a striking, sustained improvement in several patients. In some of the patients depression of the circulating granulocytes and marked vacuolization of the corresponding bone-marrow cell developed. Similar hematologic complications associated with either phenylalanine deficiency or chloramphenicol toxicity have been reversed by phenylalanine.[19,20] Excesses of this amino acid have also increased the dopamine concentration in rat brain,[21] and low dopamine concentrations have been linked with the pathogenesis of Parkinsonism in human beings.[3] Therefore, this amino acid was also administered. The present paper summarizes these findings and discusses their relation to the therapy of Parkinsonism.

*From the Medical Research Center, Brookhaven National Laboratory.

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‡Associate scientist, Medical Research Center, Brookhaven National Laboratory; associate attending physician, Brookhaven National Laboratory Hospital.

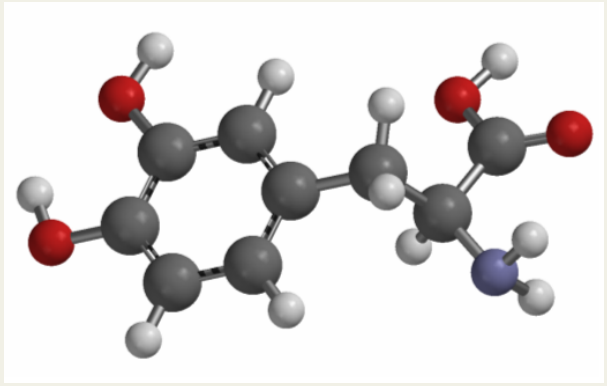
MATERIALS AND METHODS

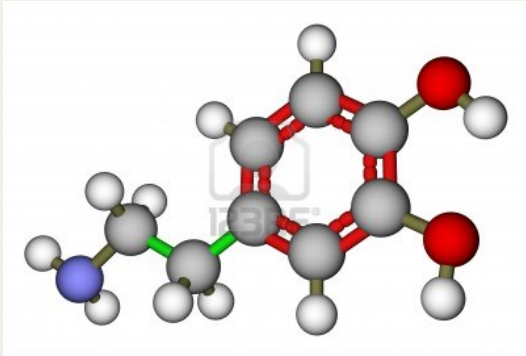
Clinical Material

Seventeen patients with Parkinsonism were admitted to this study. All had been referred to us by their physicians, after treatment with several stand-

L- DOPA

- **L-DOPA**, o **Levodopa** (3,4-diidrossi-l-fenilalanina), è un intermedio nella via biosintetica della dopamina.





Pharmacological properties of dopamine agonists

	D2/D3 receptor affinity	D1 receptor affinity	NE receptor affinity	5-HT_{2B} receptor affinity	Half-life (h)
Ergot agonists					
Bromocriptine	D2	–	+	+/–	3–6
Cabergoline	D3>D2	–	+	+	65
Dihydroergocriptine	D2	+/–	+	+	12–16
Lisuride	D2	–	+	+*	2–3
Pergolide	D3>D2	+	+	+	15–20
Non-ergot agonists					
Apomorphine	D3>D2	+	–	–	0·5
Piribedil	D3>D2	–	+/–	–	20
Pramipexole	D3>D2	–	+/–	–	10
Ropinirole	D3>D2	–	–	–	6
Rotigotine	D3>D2	+	–	–	5–7†

–=no affinity. +=high affinity. +/–=moderate affinity. NE=norepinephrine. *Antagonist. †After transdermal application.

Table 1: **Pharmacological properties of the dopamine agonists**

Antonini, Tolosa, Mizuno, Yamamoto & Poewe Lancet Neurol 2009

Oral levodopa therapy
Hurdles on route from the mouth to the brain

① **Swallowing oral therapy**
Impaired swallowing (dysphagia) in advanced disease

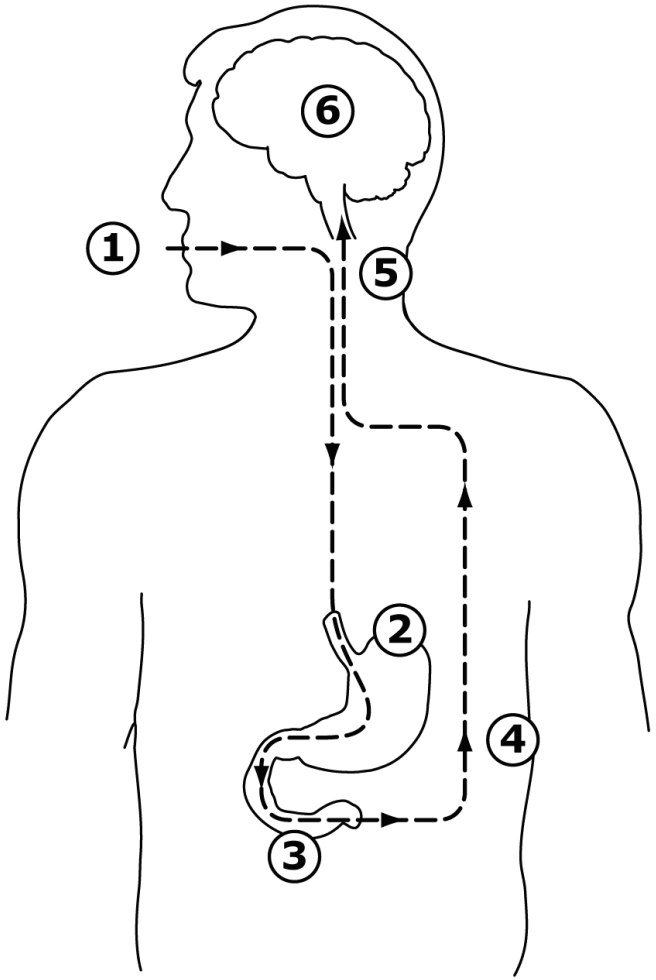
② **Stomach**
Variable absorption of levodopa due to irregular gastric emptying

③ **Jejunum**
Competition with dietary amino acids for active transport across the intestinal wall

④ **Peripheral tissues**
Reduced levodopa bioavailability due enzymatic breakdown by AADC and COMT

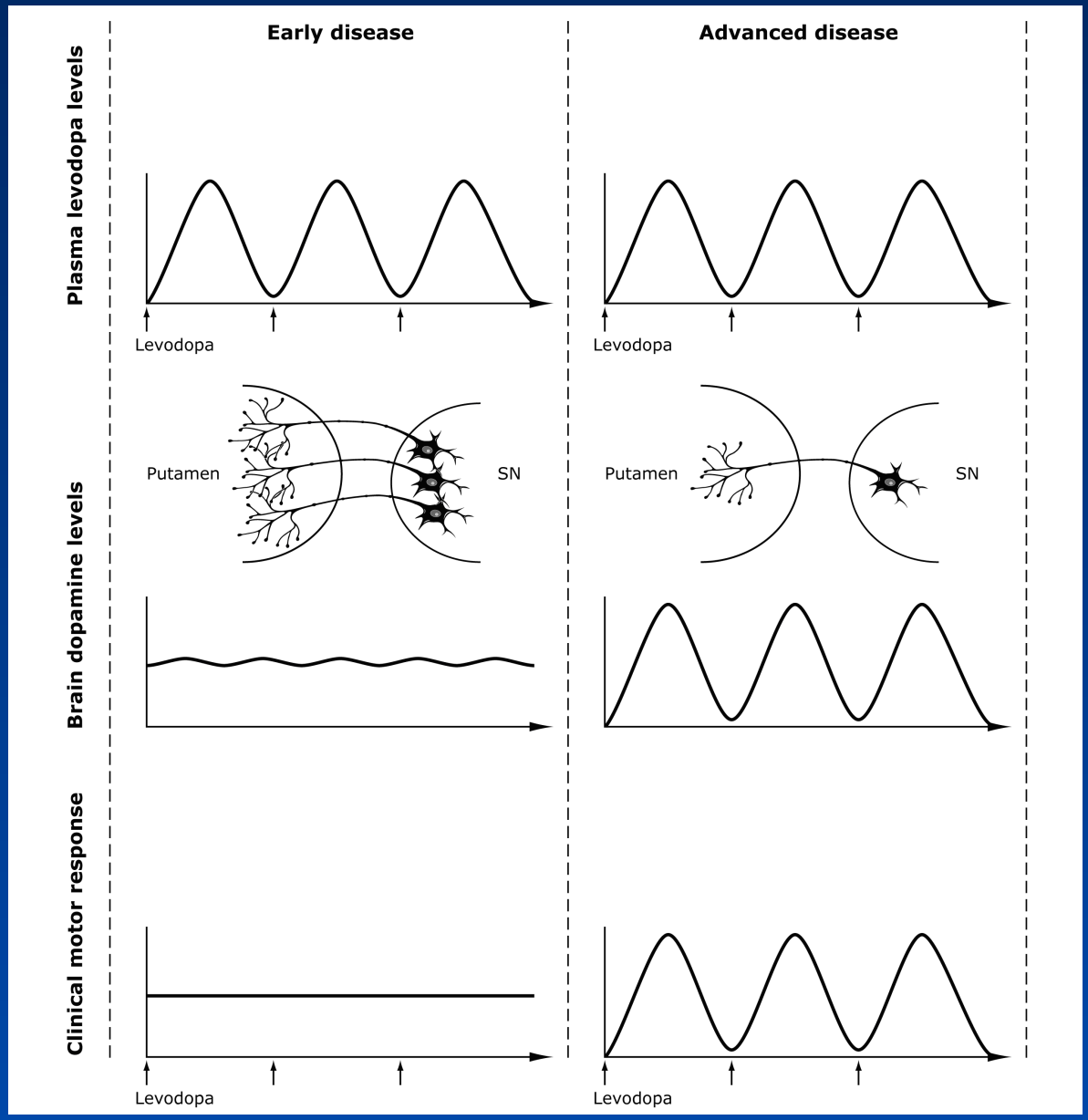
⑤ **Blood–brain barrier**
Competition for transport across the blood–brain barrier with large neutral amino acids limits the amount of levodopa reaching the striatum

⑥ **Striatum**
Conversion of levodopa to dopamine



Poewe et al. 2010

The evolution of levodopa-associated motor fluctuations



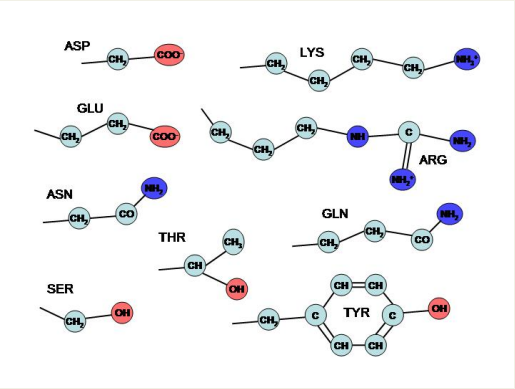
Poewe et al. 2010

ASSORBIMENTO

- Un rallentamento dello svuotamento gastrico è, quindi, responsabile di una maggiore permanenza della levodopa nello stomaco: qui l'ambiente acido e gli enzimi prodotti dalle pareti dello stomaco (decarbossilasi) causano la degradazione della levodopa in dopamina. Più a lungo la levodopa rimarrà nello stomaco, più verrà degradata con una riduzione del suo assorbimento da parte del duodeno e, di conseguenza, una minore quantità di levodopa arriverà al cervello perdendo così la sua efficacia terapeutica.

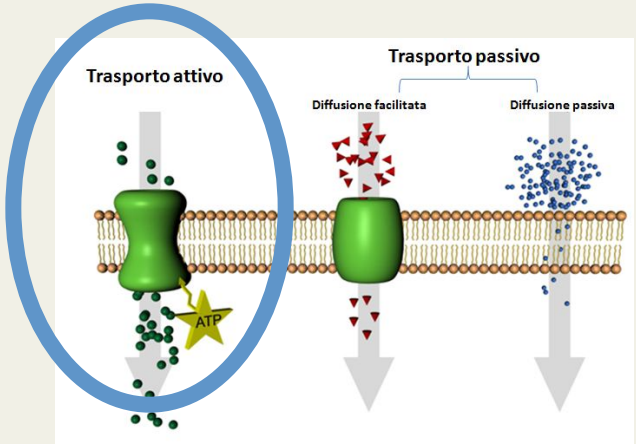
TRASPORTO L-DOPA

- Esistono sistemi di trasporto attivo diversi per i diversi tipi di amminoacidi basici, acidi, neutri e aromatici; questi sistemi utilizzano energia e sono specifici per classi di amminoacidi, di conseguenza



tutti gli amminoacidi aromatici (isoleucina, leucina, valina, fenilalanina, triptofano e tirosina), provenienti dalle proteine ingerite con il pasto utilizzano lo stesso sistema di trasporto della levodopa e si pongono in competizione con essa.

Pasti ricchi di proteine, e in particolar modo di questi amminoacidi, possono quindi interferire nell'attività farmacologica della levodopa rendendo indisponibili i carriers necessari al trasporto.



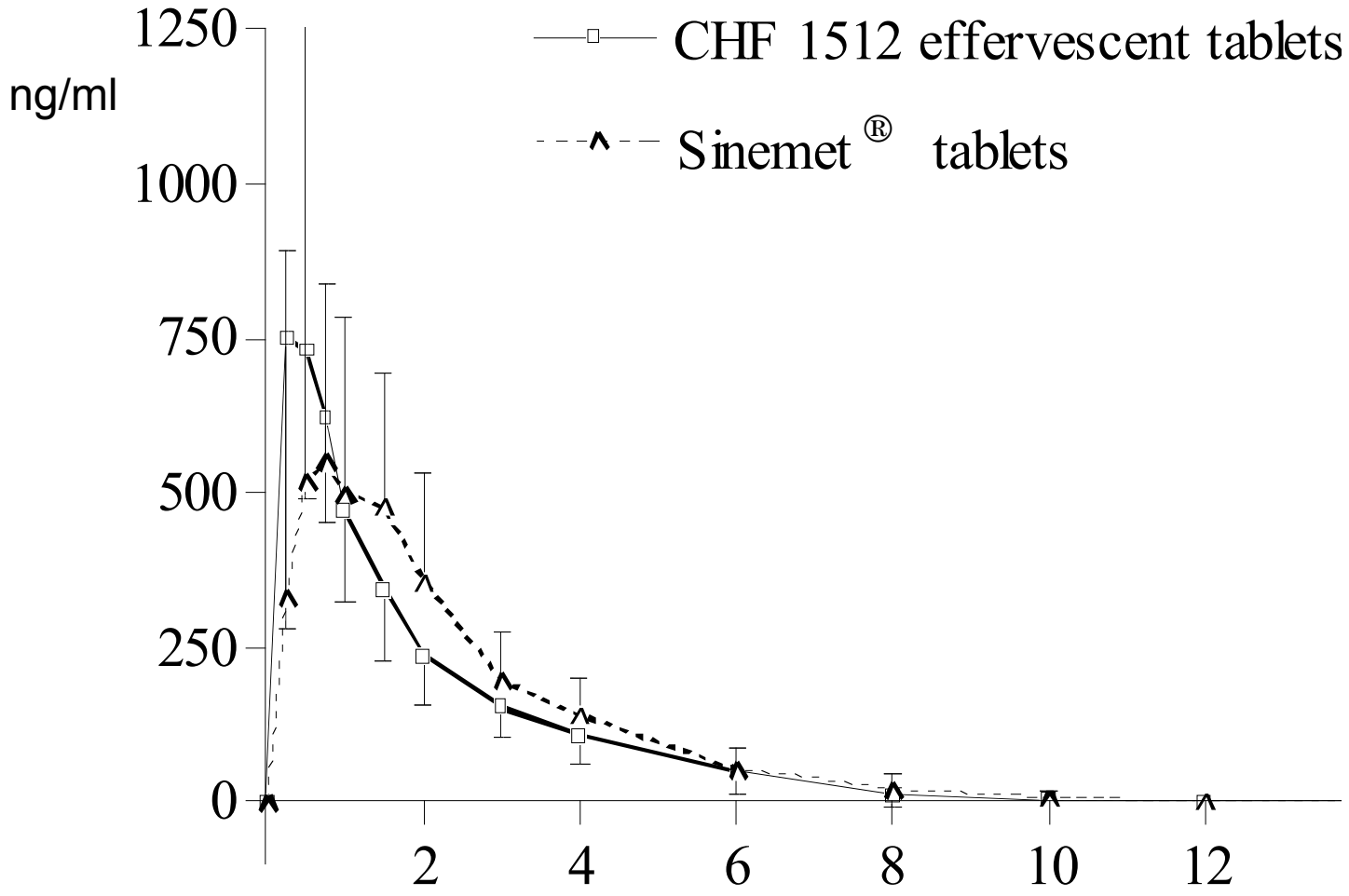
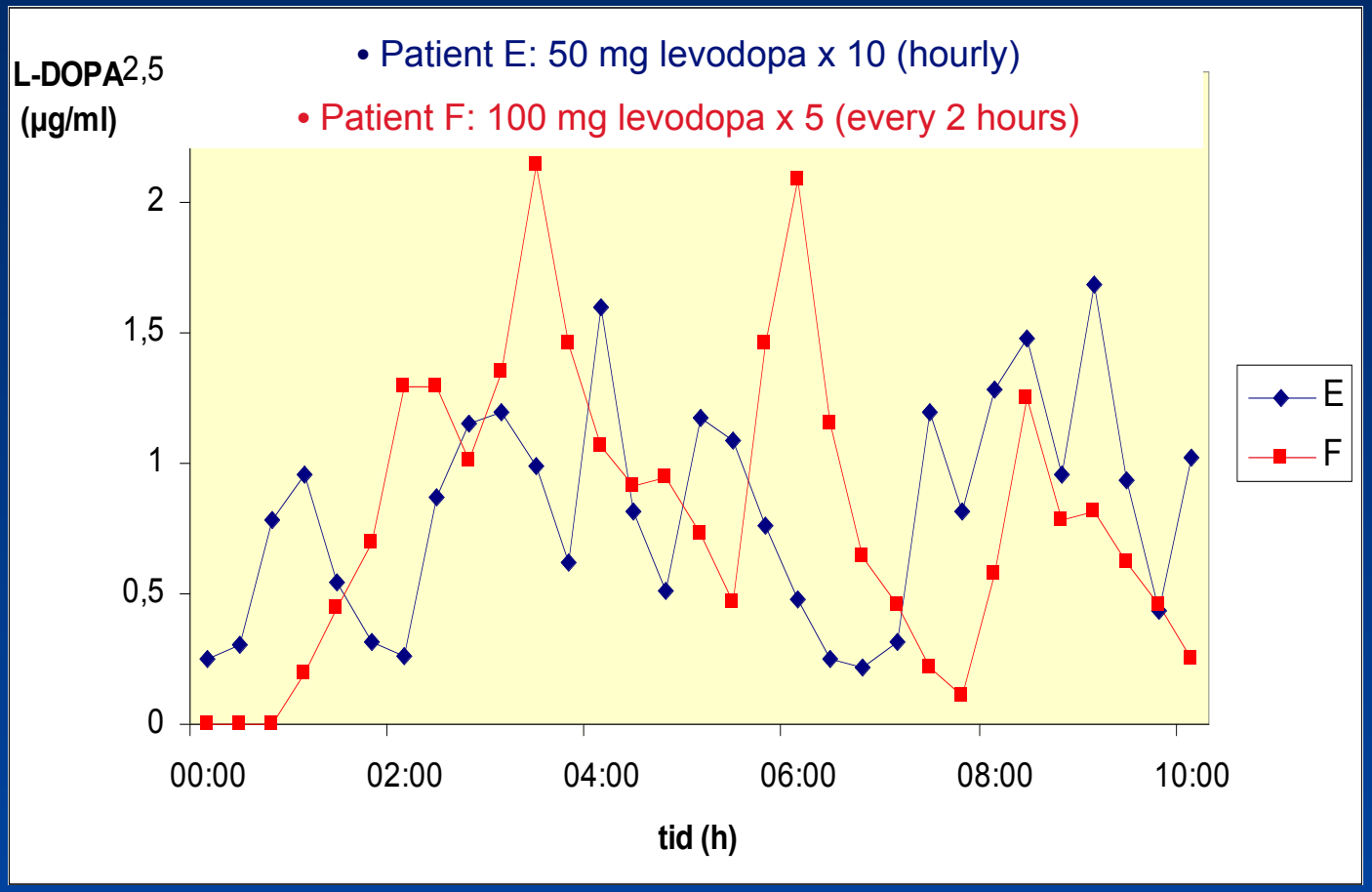

ng/ml
1250
1000
750
500
250
0
2
4
6
8
10
12
CHF 1512 effervescent tablets
Sinemet ® tablets

Figure 1

	T_{max} bioavailability (%)	***$T_{1/2}$ (min)***	***Protein binding (Hours)***	***(%)***
L-Dopa	n.d.	0,6 - 0,9	n.d.	99
L-Dopa + IDD	30 - 120	1 - 3	n.d.	99
L-Dopa + carbidopa CR	120 - 180	4 - 5	n.d.	70
L-Dopa + benserazide HBS	120 - 240	6 - 8	n.d.	60
L-Dopa metilestere	24 - 60	0,2 - 0,6	n.d.	99
DDI				
Benserazide	60	<2	n.d.	n.d.
Carbidopa	30 - 300	2	n.d.	n.d.

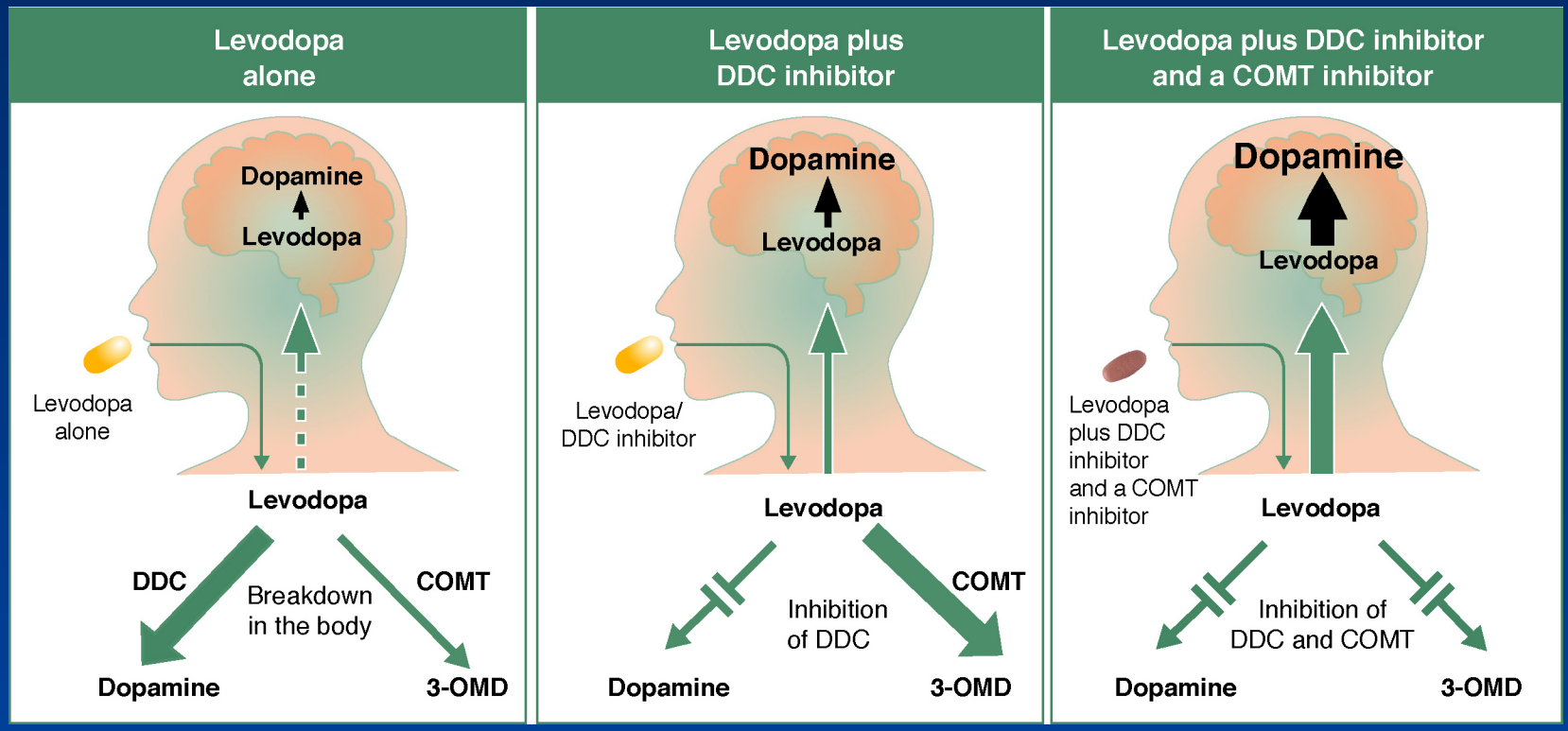
Excessive fragmentation of oral levodopa makes plasma levels more erratic and unpredictable



Nyholm et al. 2002

Ottimizzazione farmacocinetica della levodopa (Stalevo)

→ ampliamento della finestra terapeutica

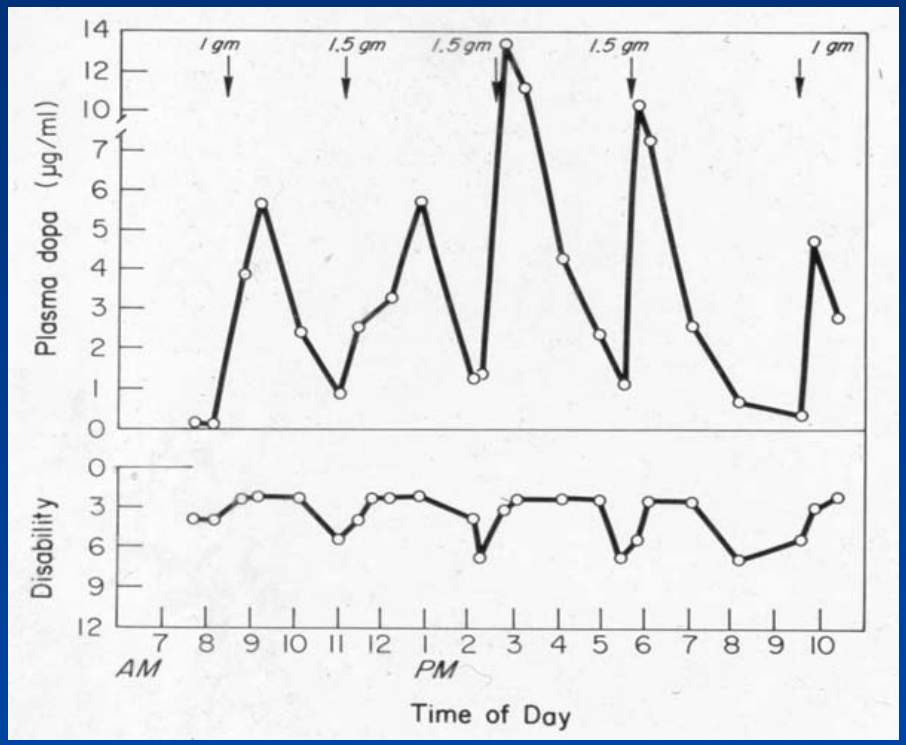


Inibizione duplice DDC e COMT
massimo ingresso di levodopa nel cervello

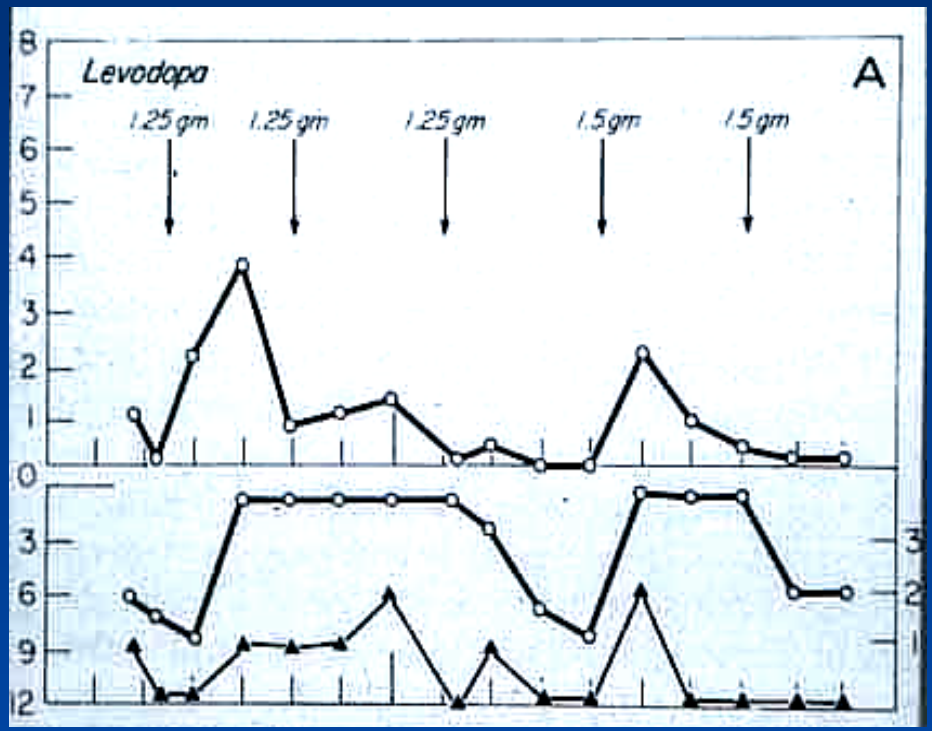
Factors associated with development of motor complications
2) Peripheral pharmacokinetic of levodopa

Patterns of clinical response and plasma levodopa levels in PD

Short half-life



Erratic gastric emptying



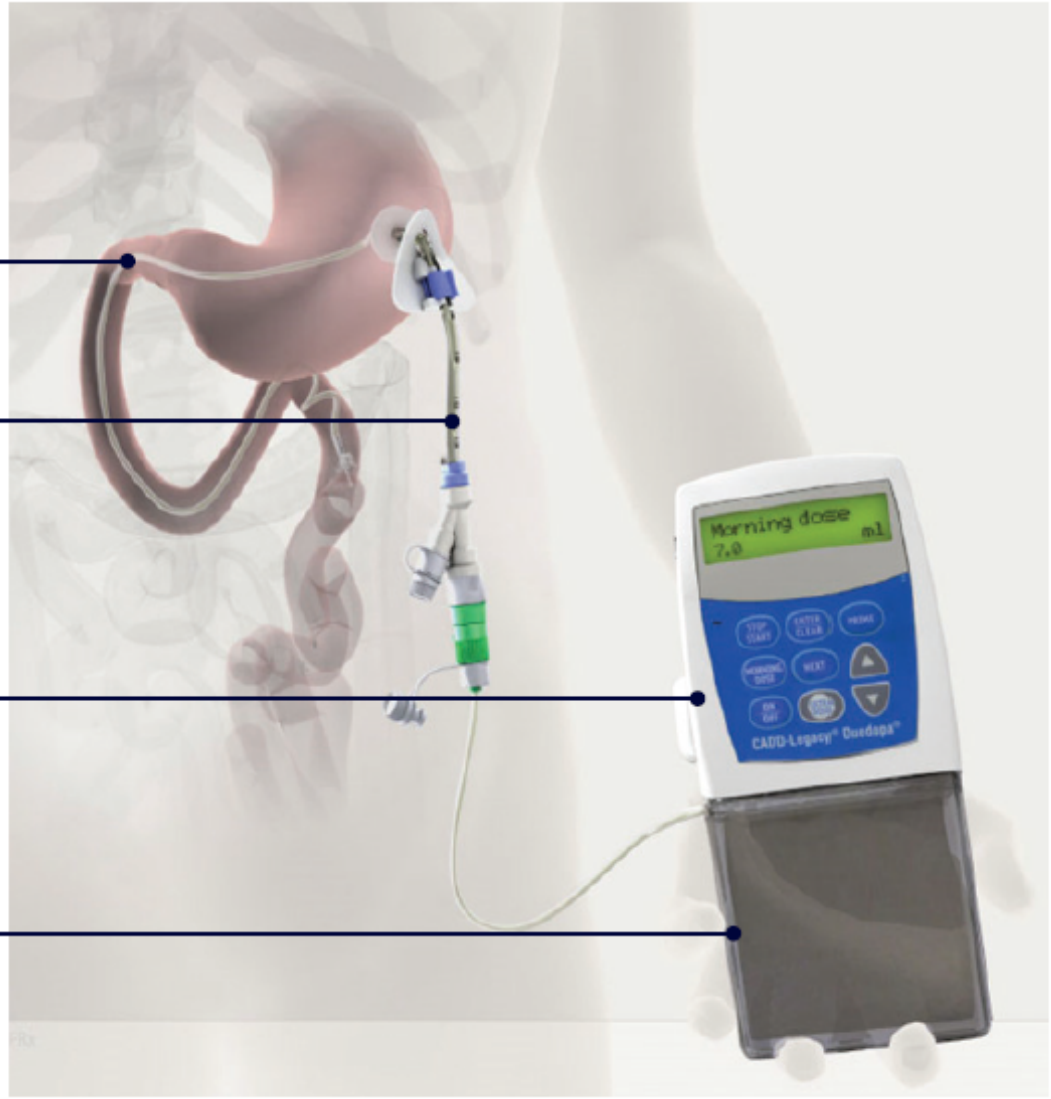
Tolosa et al, 1975

J Tube
(i.e. intestinal tube)

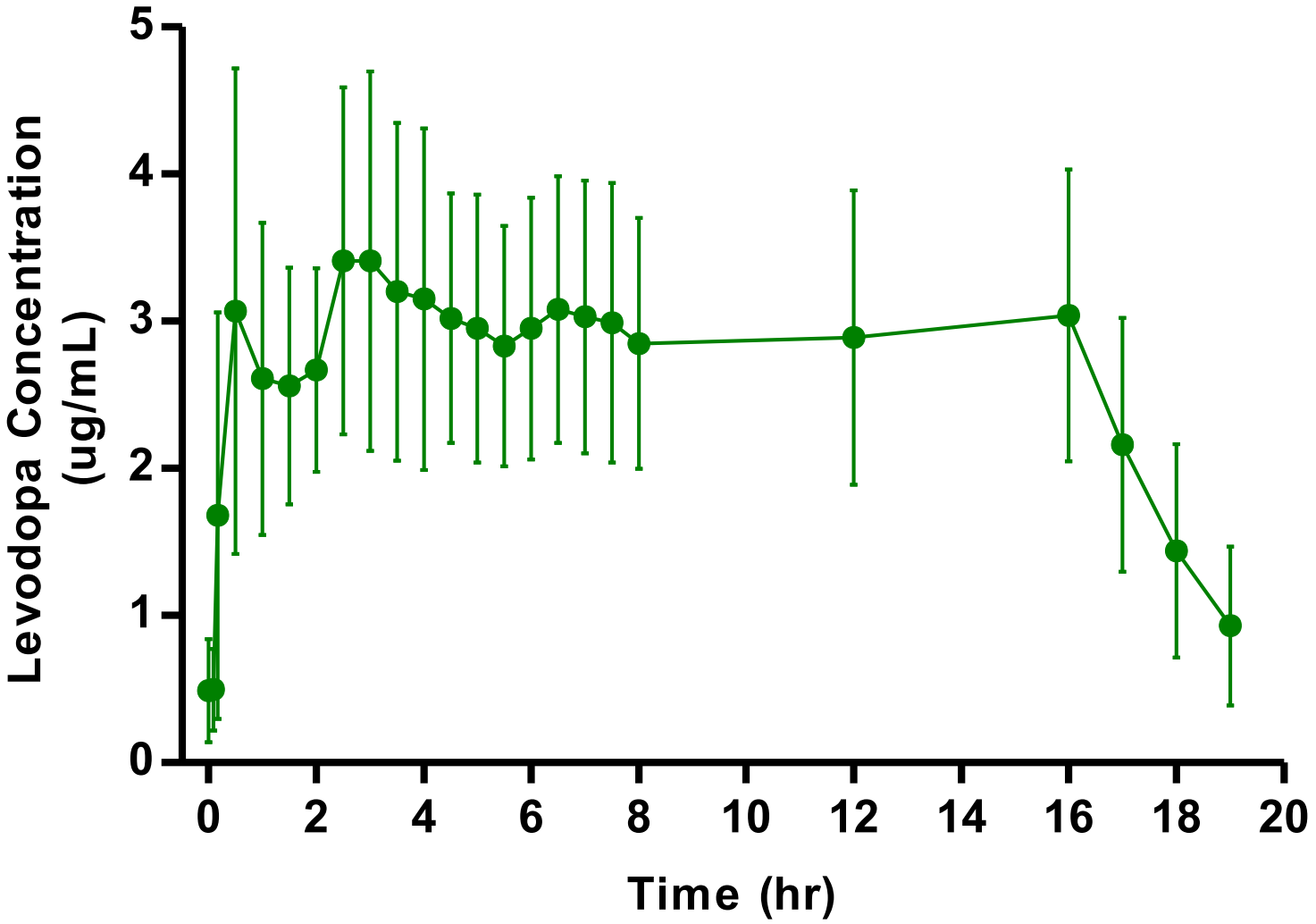
PEG tube

Pump

Cassette



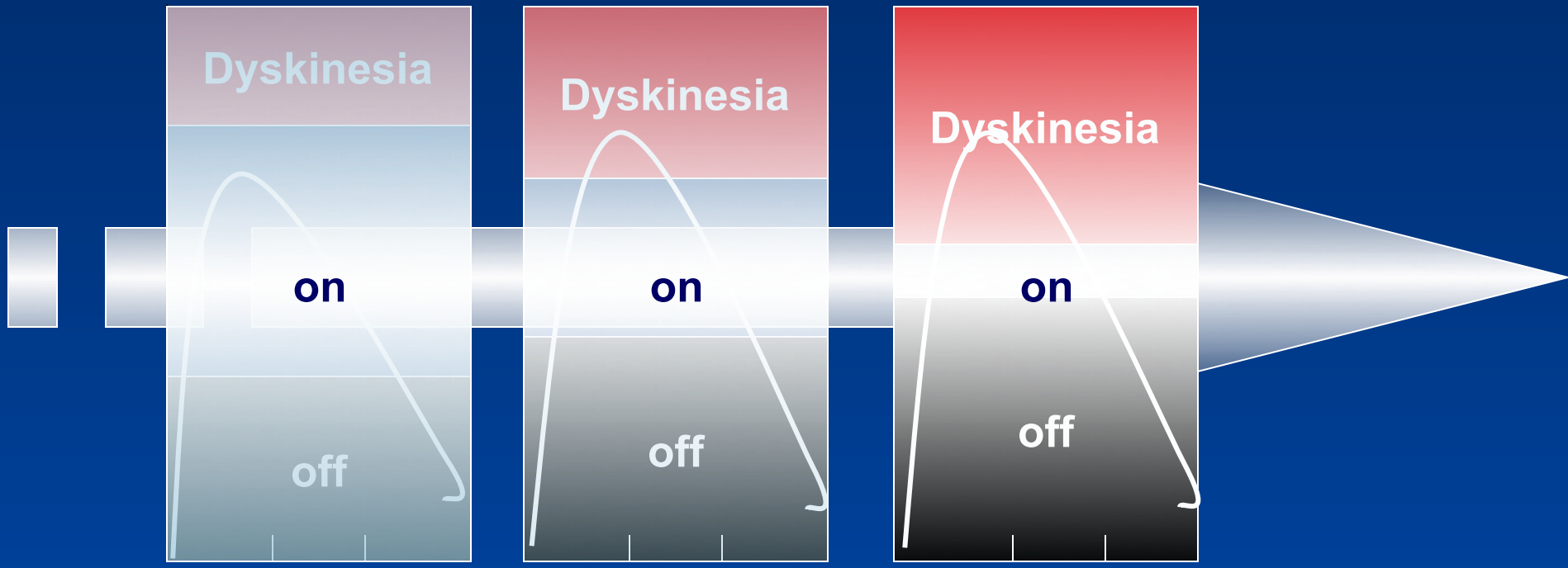
Plasma Levodopa Concentration over time during Duodenal infusion



S187.1.001

Nyholm D, Odin P, Johansson A et al. Stable Levodopa Plasma Levels with Jejunal Infusion of Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease Patients. International Congress on Parkinson´s disease and Movement Disorders, Dublin, 2012

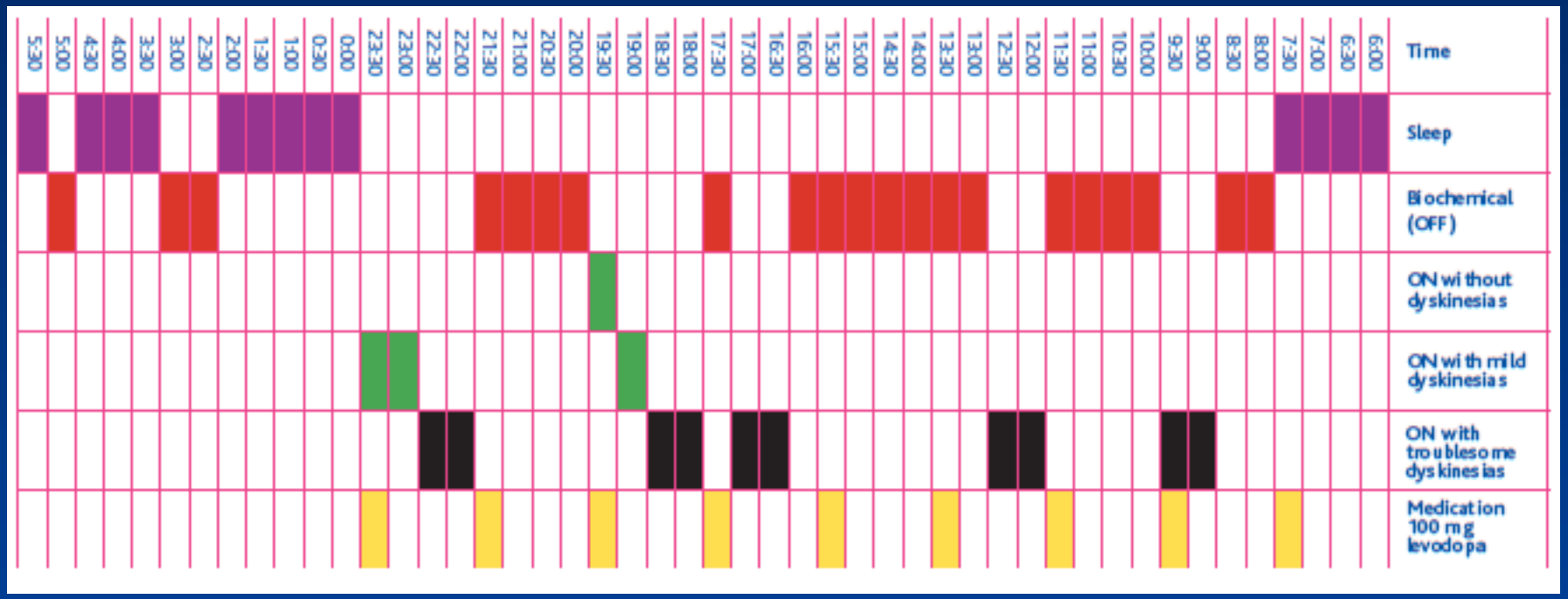
As PD progresses patient mobility becomes increasingly dependent from peripheral levodopa bioavailability



https://www.youtube.com/watch?v=pOhBtTYfSE4https://youtu.be/pOhBtTYfSE4

https://www.youtube.com/watch?v=koL0PWCJ4lo

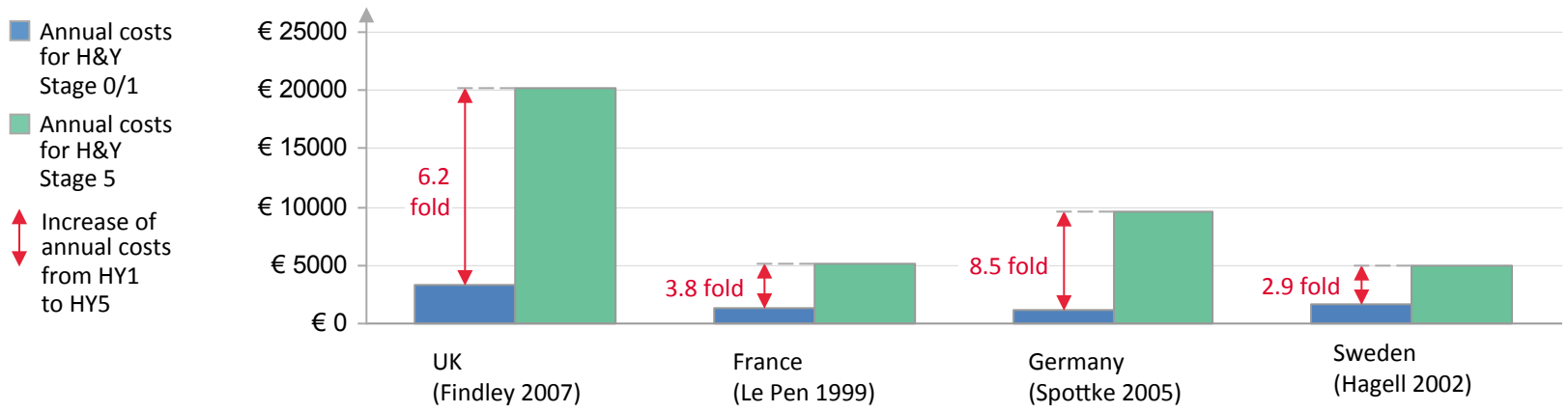
Motor fluctuations in advanced Parkinson



An example of severe end-of-dose dyskinesia

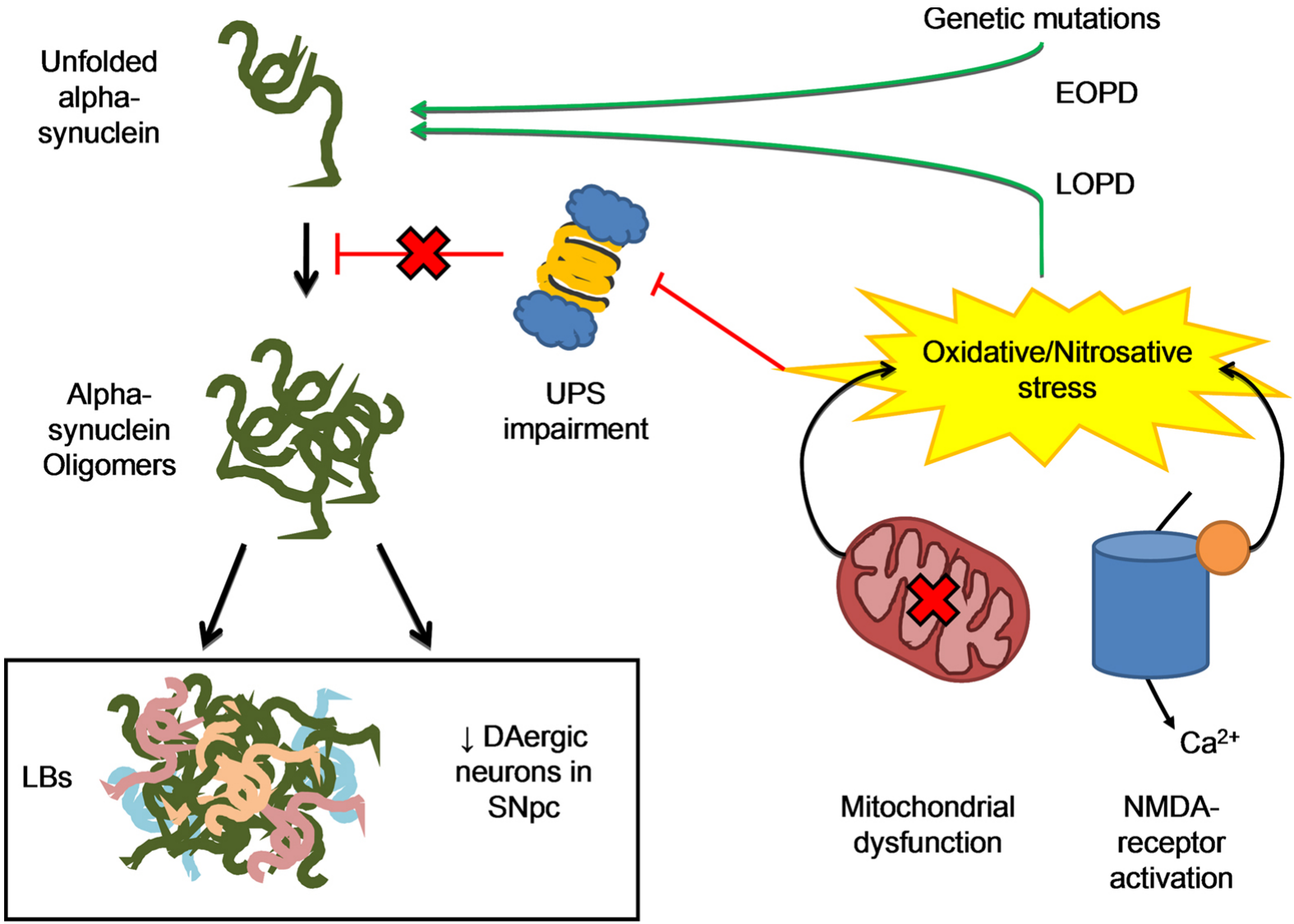
Severe peak dose dyskinesia in an Early-onset PD with Dopamine Disregulation Syndrome

Cost of illness according to disease stages in different countries

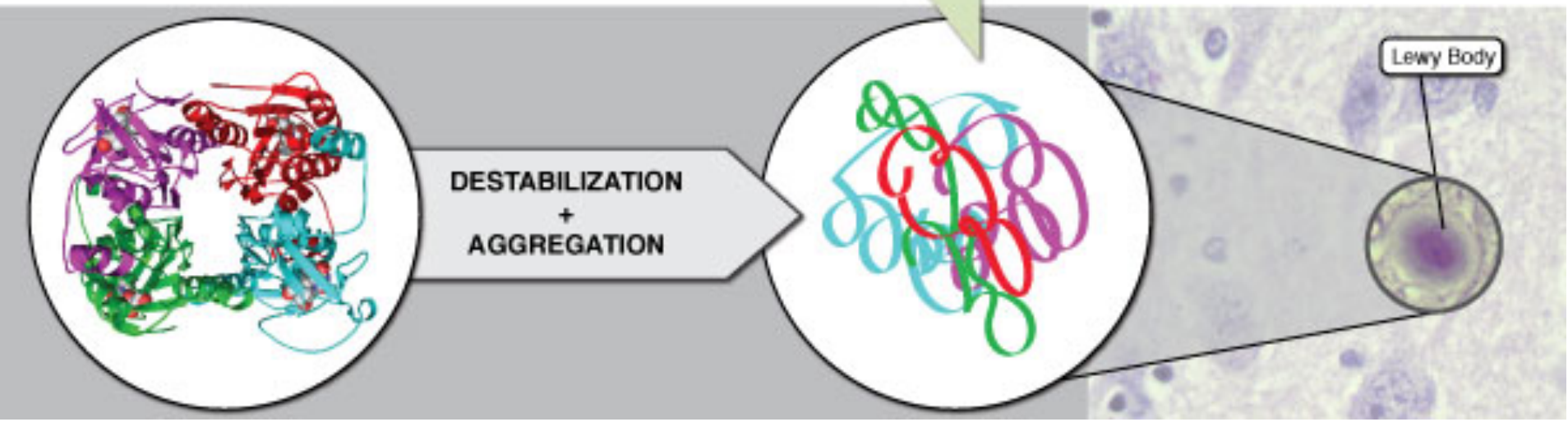


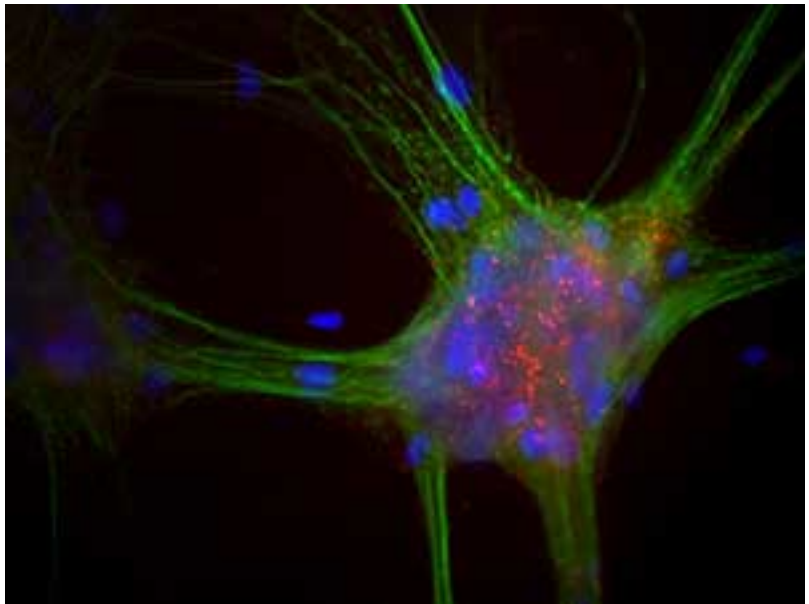
	UK (Findley 2007)	France (Le Pen 1999)	Germany (Spottke 2005)	Sweden (Hagell 2002)
Direct health costs	✓	✓	✓	✓
Non-health related direct costs	✓		✓	✓
Indirect costs		Partly	✓	✓

Note: Comparison is possible per country and not between countries as different costs were included in different countries


Genetic mutations
EOPD
LOPD
Unfolded alpha-synuclein
Alpha-synuclein Oligomers
UPS impairment
Oxidative/Nitrosative stress
LBs
↓ DAergic neurons in SNpc
Mitochondrial dysfunction
NMDA-receptor activation
Ca2+

New insight into protein structure can help researchers understand the pathophysiology of Parkinson's.

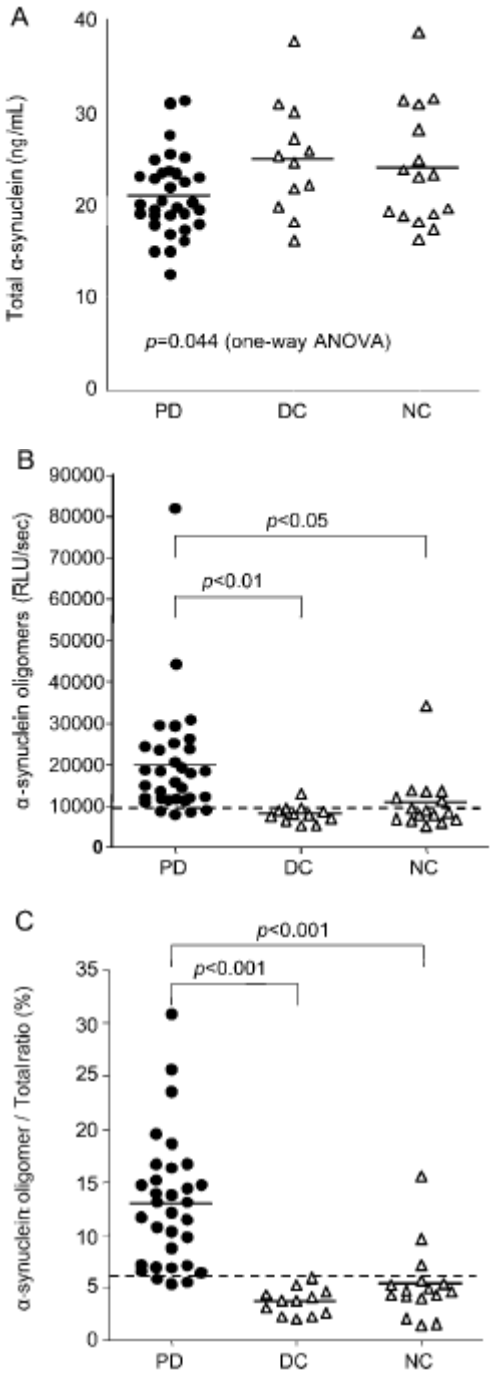




α-synuclein increase in CSF

<u>Tokuda et al. (2010):</u>

Significant difference in the oligomers/total α -synuclein-ratio in CSF



Tokuda et al. 2010: Detection of elevated levels of α–synuclein oligomers in CSF from patients with PD

Use of Saliva

Background

- Salivary glands are linked to the CNS and have been found to be involved in Parkinson's disease at relatively early stages of the disease
- Human submandibular gland produces 70% of total resting and 63% of stimulated salivary volume
- Phosphorylated α -Syn was investigated with immunohistochemical methods in different body sites
  - Submandibular gland
  - GIT

  -> Highest frequencies located in the lower oesophagus and the submandibular gland

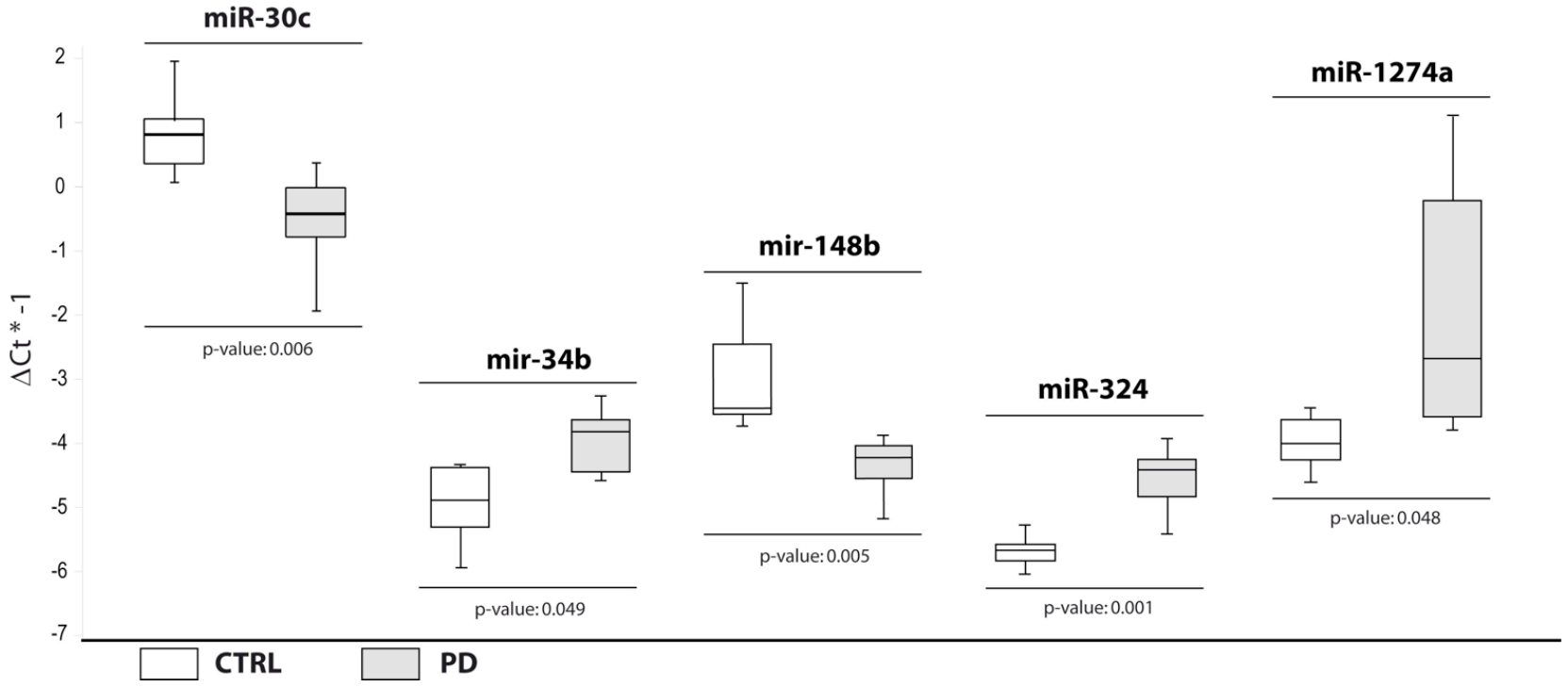
Del Tredici et al. 2010: Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease.
Silvers et al. 1998: Salivary glands
Blessing et al. 2004: Lower brain stem regulation of visceral, cardiovascular and respiratory function
Cook et al. 1994: Secretion by the major salivary glands

Saliva

- One study could demonstrate that anti-α-Syn antibodies and anti-DJ-1 antibodies can be detected in saliva
- It seems to be another ideal biofluid to study potential biomarkers for Parkinson's disease diagnosis and progression because it is typically free of blood contamination

Beach et al. 2010: Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders
Cersosimo et al. 2010: Alpha-synuclein immunoreactivity in minor salivary gland biopsies of Parkinson's disease patients
Devic et al. 2011: Salivary a-synuclein and DJ-1: potential biomarkers for Parkinson's disease

Identification of circulating microRNAs for the differential diagnosis of Parkinson's disease



Vallelunga et al. submitted

GENE MUTATIONS WITH LINKAGE TO PD

Most important autosomal dominant gene mutations

- α-synuclein gene (PARK 1$_{\text{chromosome 4q21}}$, PARK 4$_{\text{chromosome 4p15}}$)

  (α-synuclein expression) PD-LIKE PHENOTYPE
- UCH-L1 (PARK 5$_{\text{chromosome 4p14}}$)

  (key component of ubiquitin-proteasome system) PD-LIKE PHENOTYPE
- LRRK2: Leucine-rich repeat kinase 2 (PARK 8)

  (regulation of neuronal survival) PD-LIKE PHENOTYPE

Most important autosomal recessive gene mutations

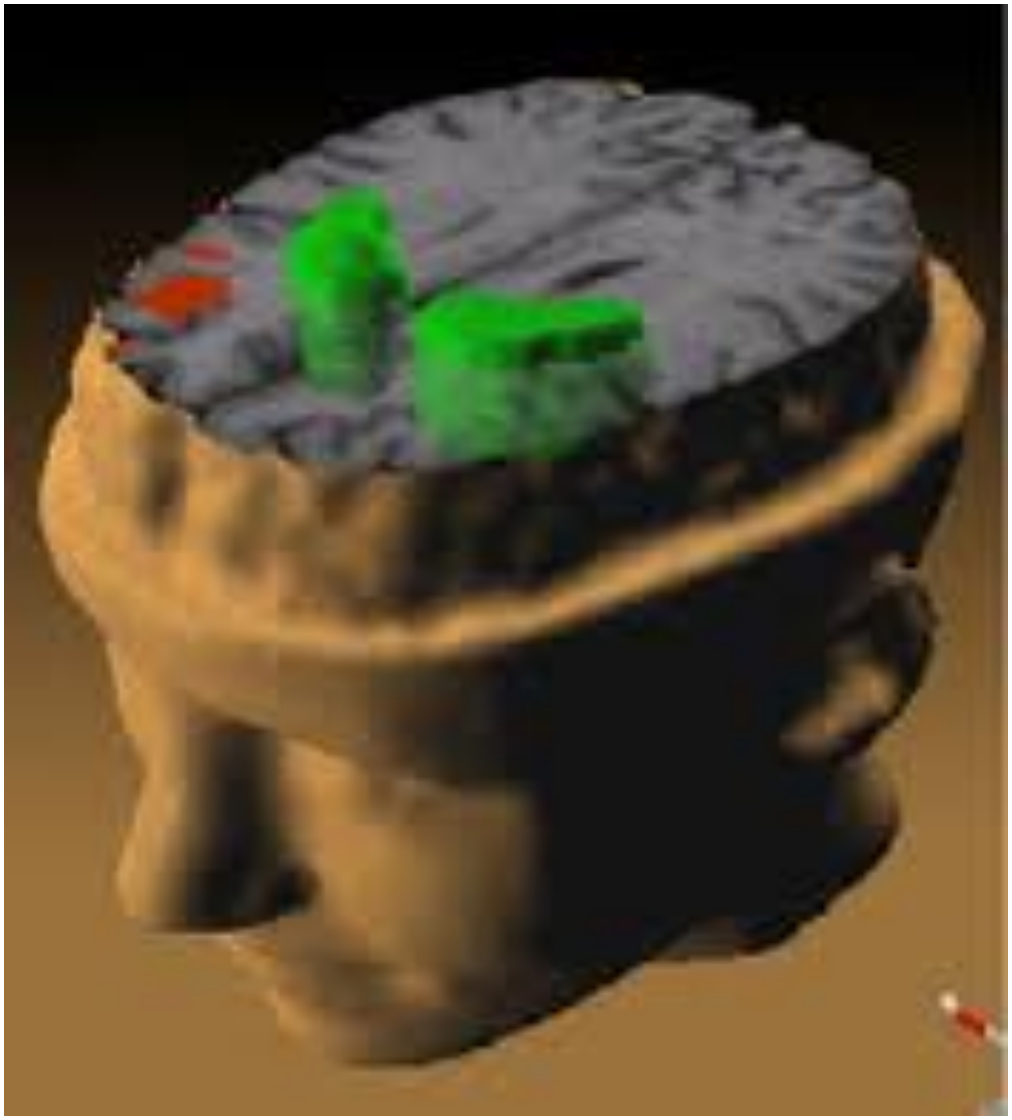
- Parkin (PARK 2$_{\text{chromosome 6q25.2-q27}}$)

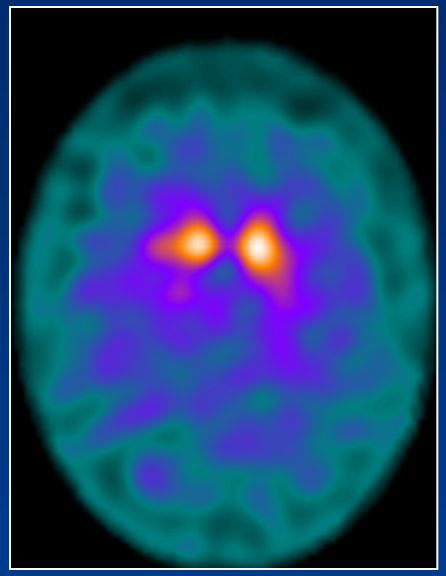
  (ubiquitin E3 ligase: targeting ubiquitin for proteasomal degradation) SLOW PROGRESS DYSTONIC PAR
- PINK 1 (PARK 6$_{\text{chromosome 1p}}$)

  (protection against Mt dysfunction-induced stress) SLOW PROGRESS DYSTONIC PARKINSONISM
- DJ-1 (PARK 7$_{\text{chromosome 1p36}}$)

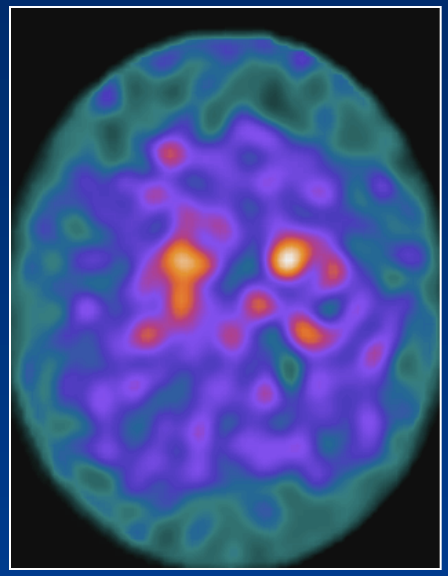
  (protection against oxidative stress) SLOW PROGRESS PARK + DYSTONIA + PSYCHIAT. SYMPTOMS
- ATP13A2 (PARK 9$_{\text{chromosome 1p36}}$)

  (lysosomal protein degradation) PARKINSONISM + SPASTICITY + DEMENTIA

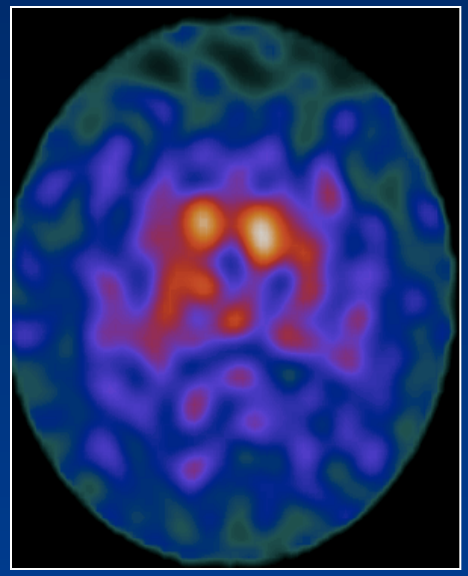




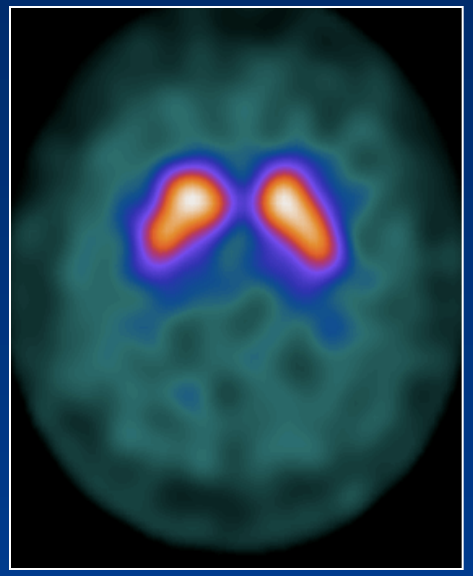
Non-genetic PD
Age 63
6 yrs disease



PARK 8
Age 62
6 yrs disease

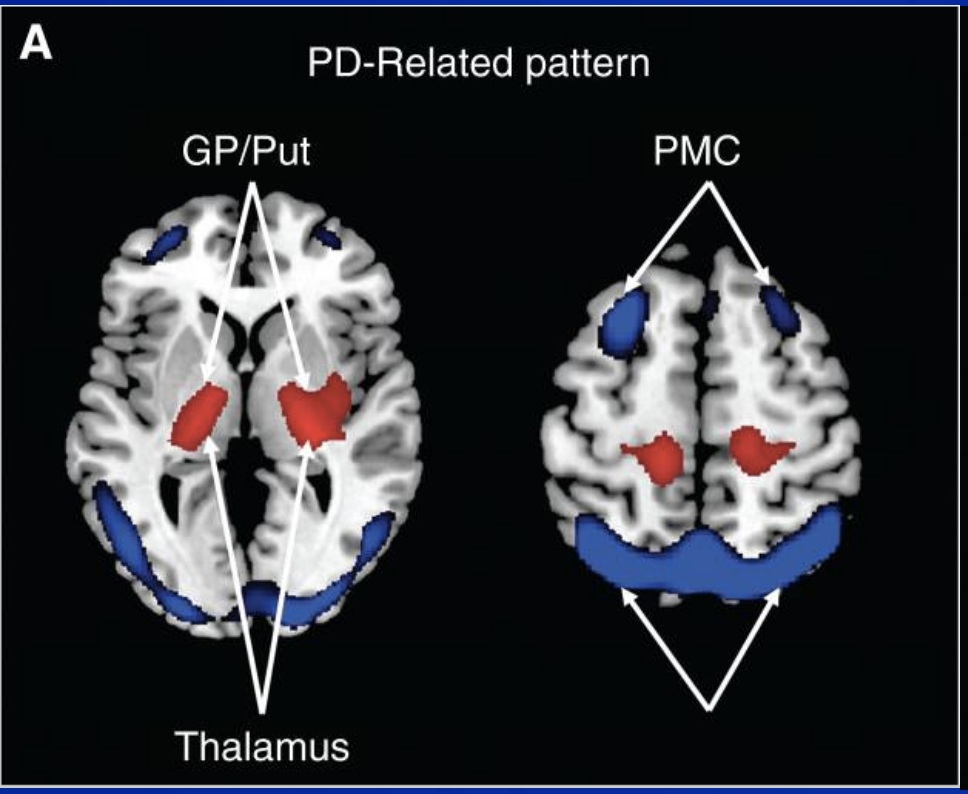


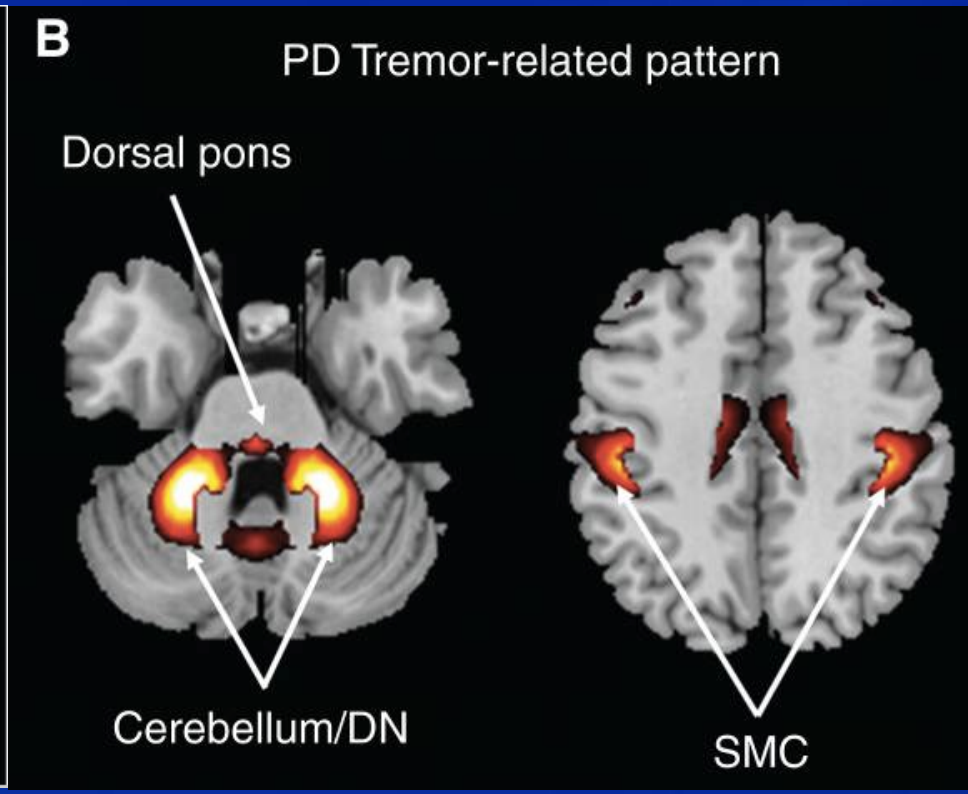
PARK 6
Age 60
6 yrs disease



Healthy
Control

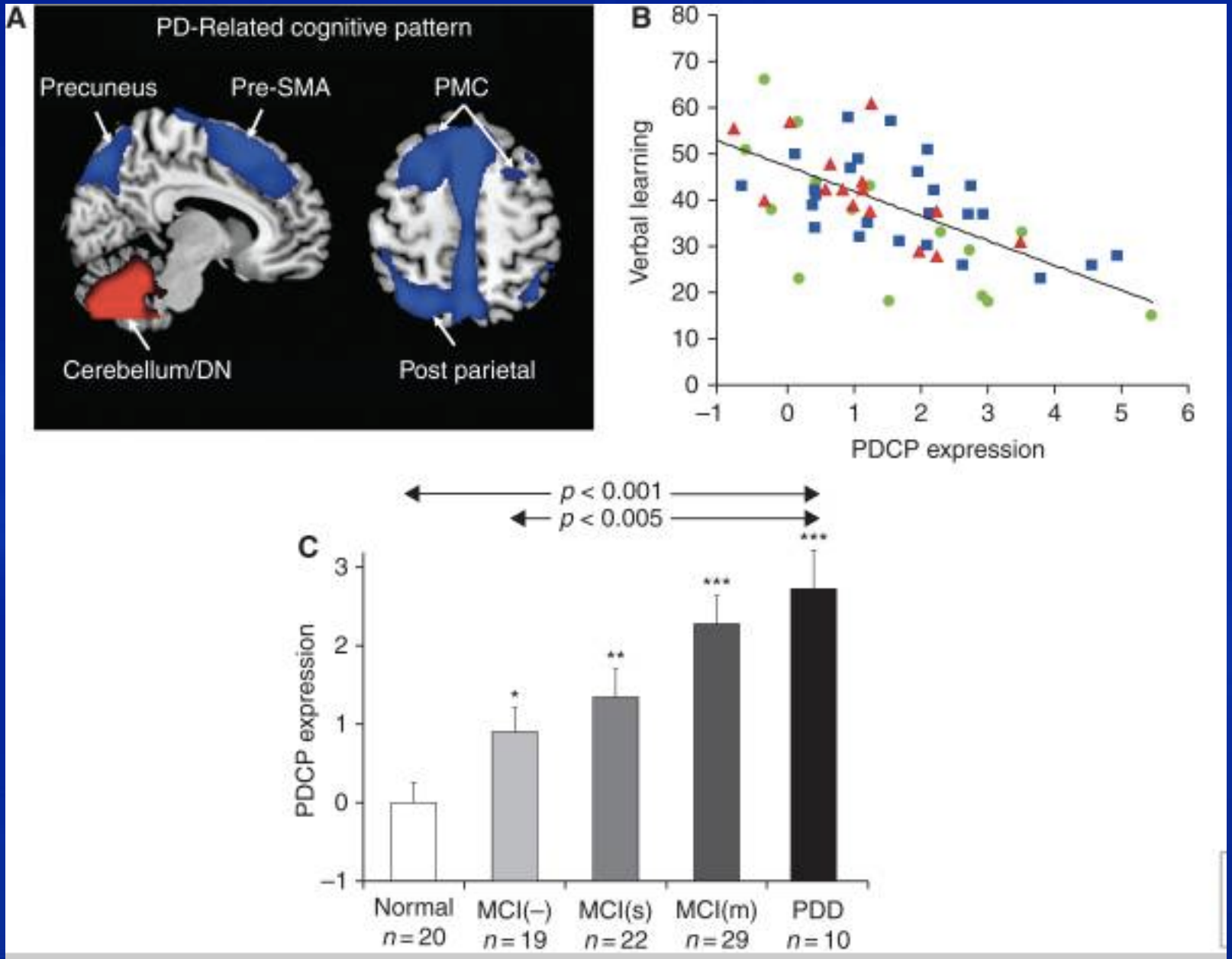
Abnormal metabolic networks in Parkinson's disease (FDG-PET)



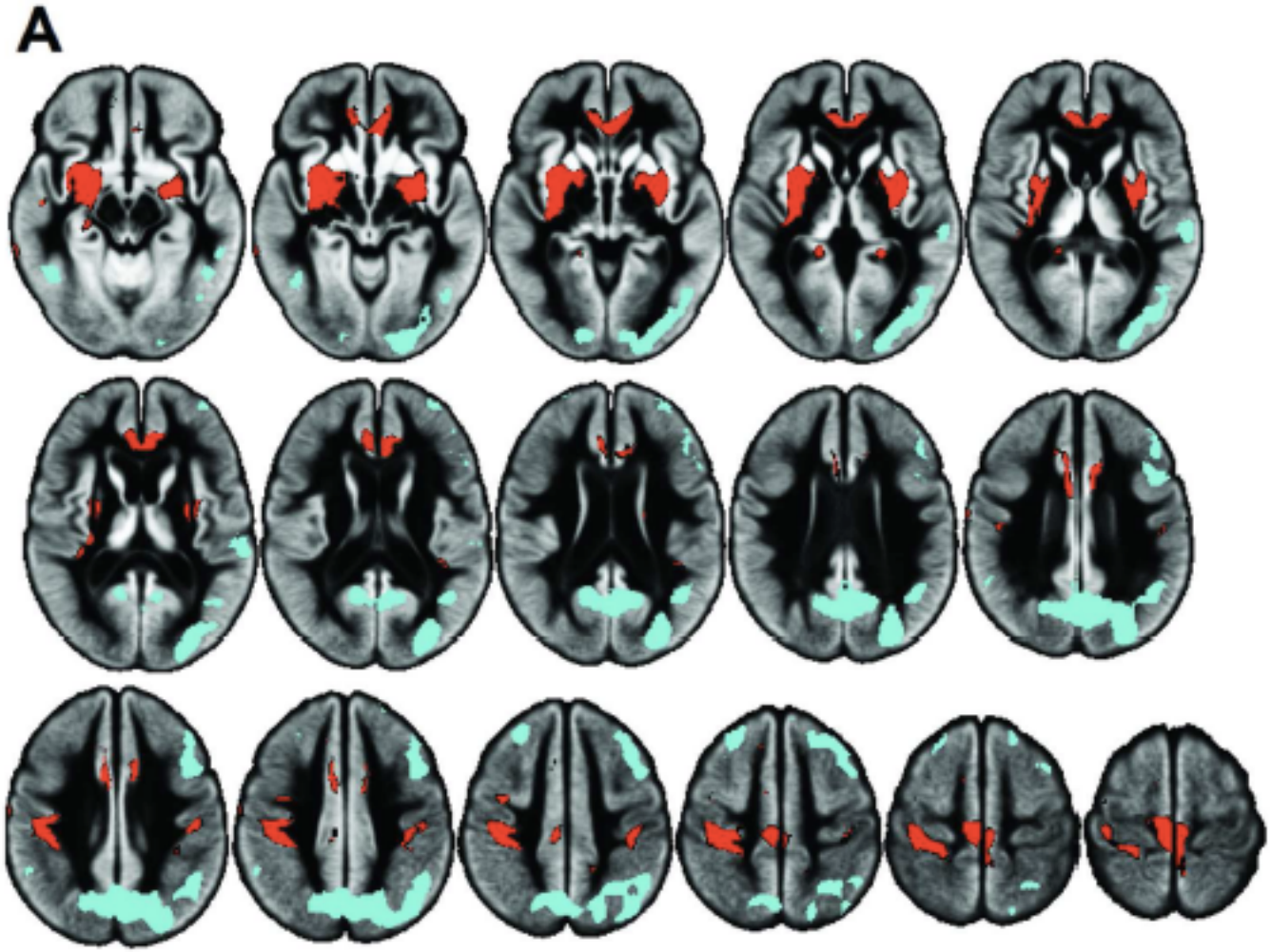


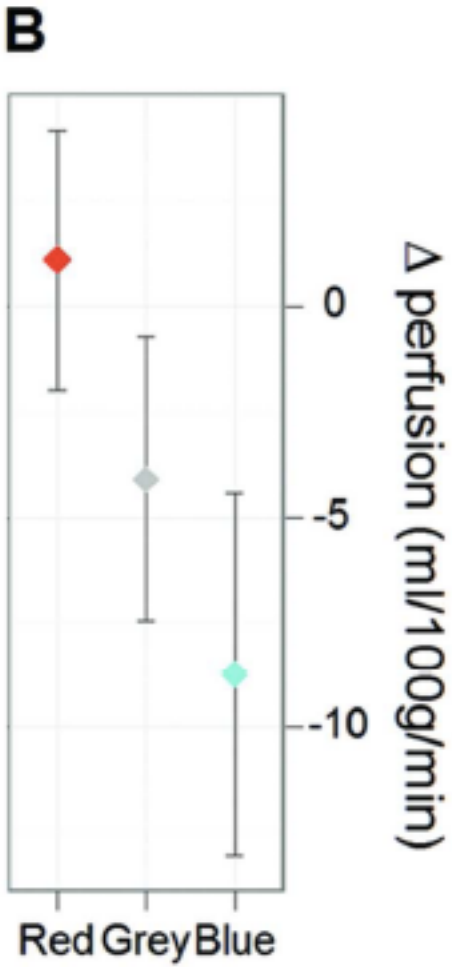
Eidelberg et al. Trends Neuroscience 2009

Parkinson's disease-related cognitive pattern: FDG-PET



PD-related perfusion network as identified by principal component analysis of Arterial Spin Labeling MRI. The spatial covariance network was identified from 61 PD subjects and 29 controls





Melzer et al Brain 2011

The Evolution of PD

Onset motor symptoms

Preclinical PD

olfactory loss
RBD,
constipation
anxiety,
depression,

Early treated PD (stable)

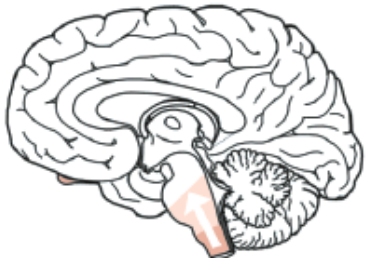
bradykinesia
rigidity
rest-tremor
(+/- non-motor-symptoms)

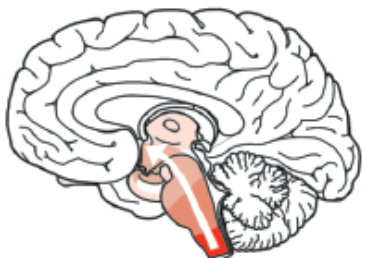
Advanced PD

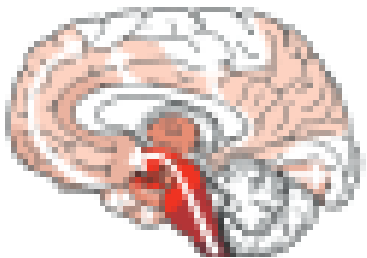
motor complications
wearing off/
dyskinesias
gait and balance
problems
axial deformities

non-motor complicatio
cognitive decline /
dementia, psychosis,
autonomic dysfunction
sleep-wake-dysregulati

-10a 0 2a 5a 10a 15a

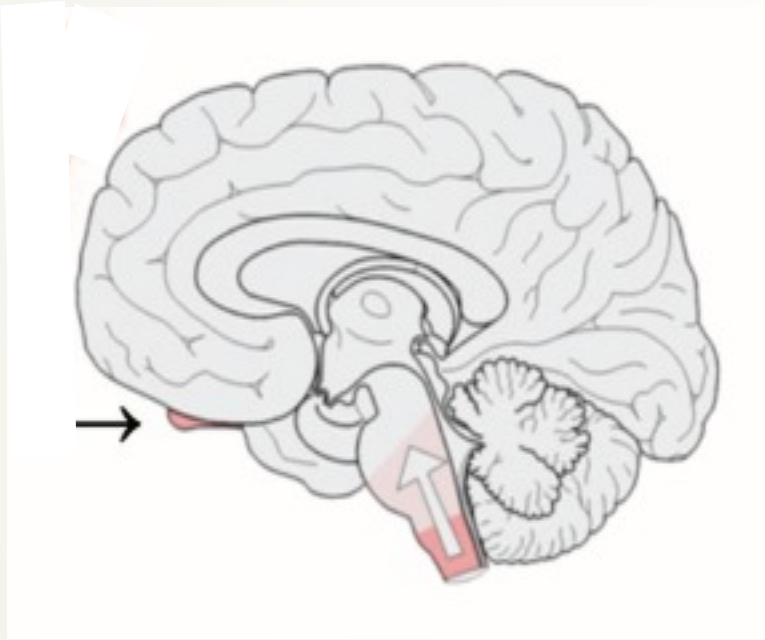






Braak PD stages 1-2 : Pre-clinical PD

Lewy Body Pathology



- Medulla, olfactory bulb
- Pontine tegmentum and locus ceruleus
- Enteric plexus of the gastrointestinal tract, sympathetic nerve fiber in the heart

Non-motor Symptoms

REM sleep behavioral disorder

Hyposmia

Constipation

Depression

Pain

Braak PD stages 3-4 : Clinical PD

Lewy Body Pathology

- Midbrain (substantia nigra)
- Basal forebrain
- Medial temporal cortex
- Amygdala

Symptoms

Bradykinesia/akinesia

Rigidity

Resting tremor

Mild cognitive impairment

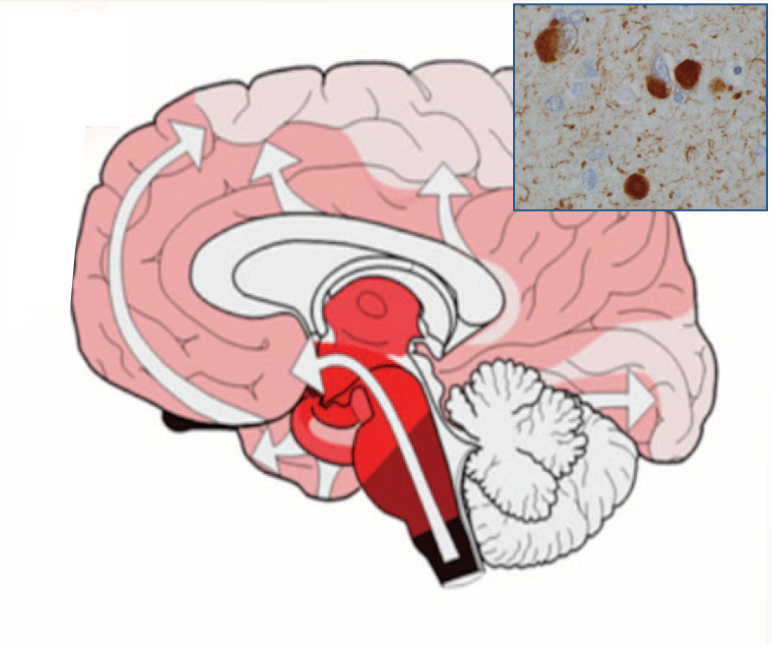
Apathy/anhedonia

Visual hallucination

Pain

Braak PD stages 5-6 : Advanced PD

Lewy Body Pathology



- Higher order association cortices (temporal and frontal)
- Primary cortices

Symptoms

Postural instability / Fall

Wearing-off /dyskinesia

Dysphagia

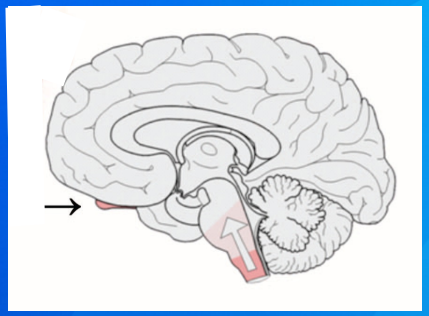
Moderate/severe cognitive impairment

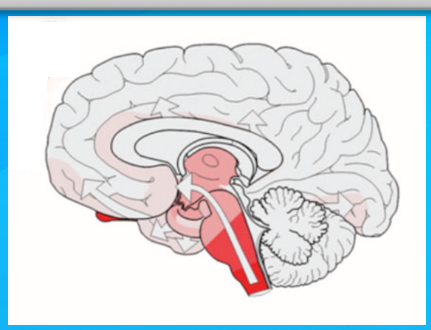
Daytime sleepiness/Sudden onset of Sleep

Visual hallucination/delusion

Disease progression and MS/NMS

Disease onset of PD





Resting tremor
Rigidity
Bradykinesia/Akinesia

Postural instability
Freezing of gait
Fall

Premotor stage

Early stage

Advanced stage

Impaired vision
Mild cognitive impairment

Dementia
Psychosis

REM sleep behavioral disorder
Hyposmia
Autonomic dysfunction
Depression

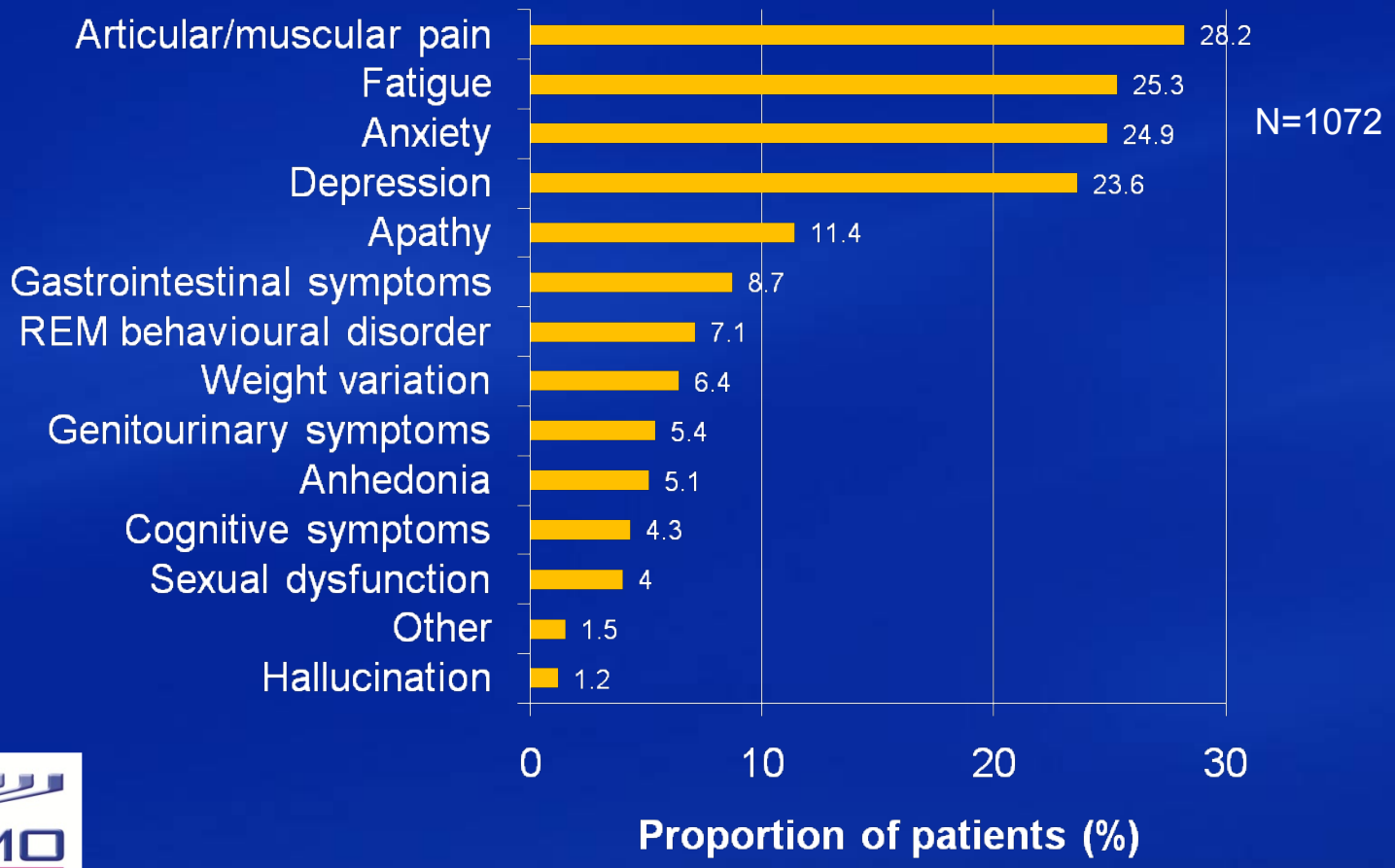
Non-motor symptoms (NMS) of PD

Neuropsychiatric symptoms	•Depression, apathy, anxiety, anhedonia, attention deficit, hallucinations •Delusions, dementia, obsessive behaviour
Sleep disorders	•Restless legs, periodic limb movements, REM behaviour disorder •Excessive daytime sleepiness, vivid dreaming, non-REM sleep-related movement disorders, insomnia
Autonomic symptoms	•Bladder disturbances, urgency, nocturia, frequency, sweating •Orthostatic hypotension (OH), falls related to OH, coat-hanger pain •Sexual dysfunction, hypersexuality, erectile impotence
Gastrointestinal symptoms (overlaps with autonomic)	•Dribbling of saliva, ageusia, dysphagia/choking, reflux, vomiting, •Nausea, constipation, unsatisfactory voiding of bowel, bowel incontinence
Sensory symptoms	•Pain, paraesthesia, olfactory disturbance
Other symptoms	•Fatigue, diplopia, blurred vision, seborrhoea, weight loss

Chaudhuri K R *et al.* Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment *Lancet Neurol* 2009;8:464-74.

An example of motor and non-motor off

First NMS at PD diagnosis



PRIAMO
PARKINSON AND NON MOTOR SYMPTOMS

Antonini A *et al*. The PRIAMO study: background, methods and recruitment. *Neurol Sci* 2008;29 (2):61–5. Barone P *et al*. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disorders* 2009;15;24(11):1641–9.

NMS frequency (%) and PD severity

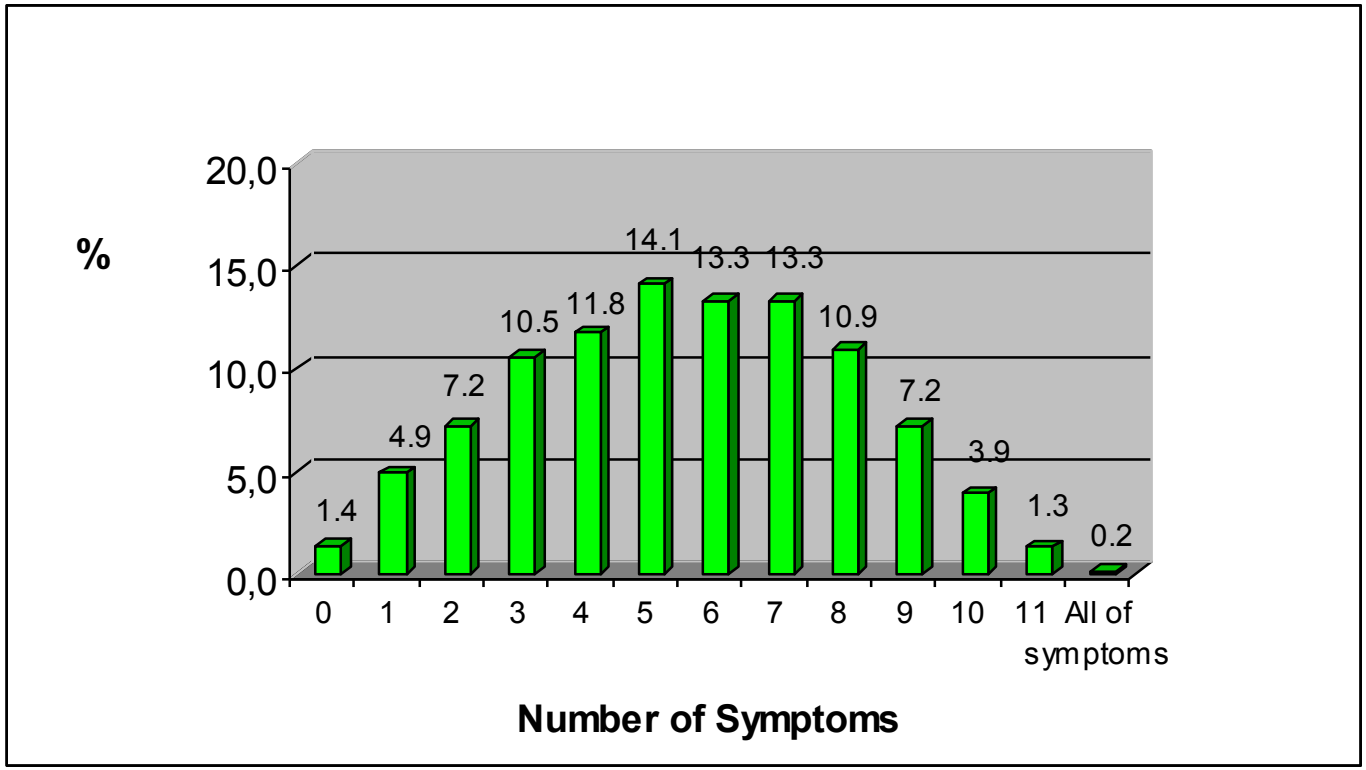
	Disease severity as Hoehn & Yahr score N=1072			
	1	1.5–2	2.5–3	4–5
Pain	50.9	58.6	67.1	79.6
Urinary	43.1	51.7	68.3	89.8
Sleep dysfunction	47.9	60.6	75.4	81.6
Fatigue	37.7	56.5	68.9	81.6
Apathy	24.6	26.8	36.6	49.0
Attention/memory	37.7	40.4	51.7	65.3
Skin	14.4	19.8	34.5	32.7
Psychiatric	61.1	63.3	73.2	83.7
Respiratory	9.6	15.5	22.8	30.6
Gastrointestinal	45.5	54.4	76.9	73.5

Adapted from:

Antonini A *et al.* The PRIAMO study: background, methods and recruitment. *Neurol Sci* 2008;29 (2):61–5.

Barone P *et al*. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disorders* 2009;15;24(11):1641–9.

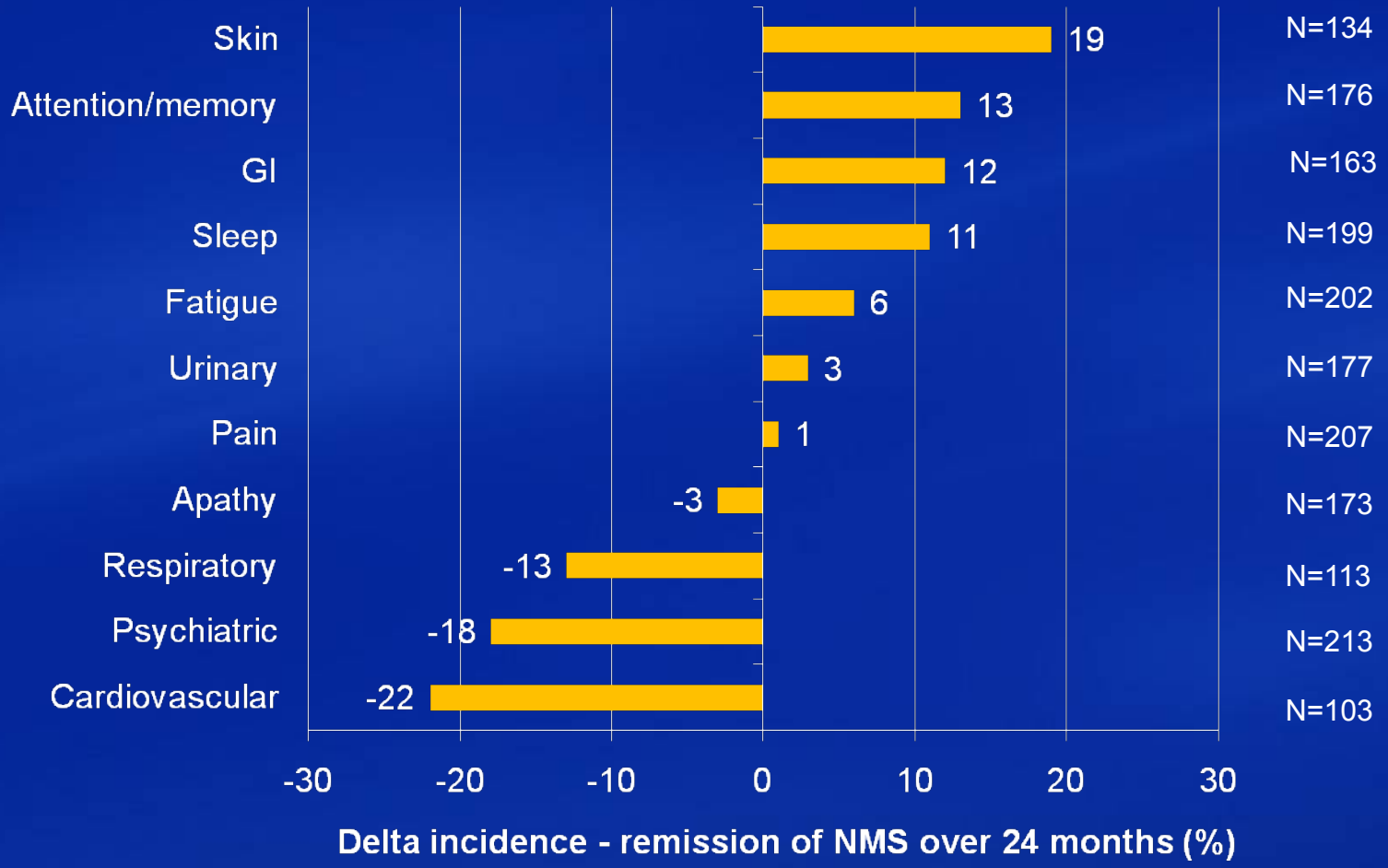
NMS Distribution in PD Patients



	Mean	SD	Median	25° percentile	75° percentile	Min	Max
Number of NMS/patient	5.49	2.54	6.00	4.00	7.00	0.00	12.00

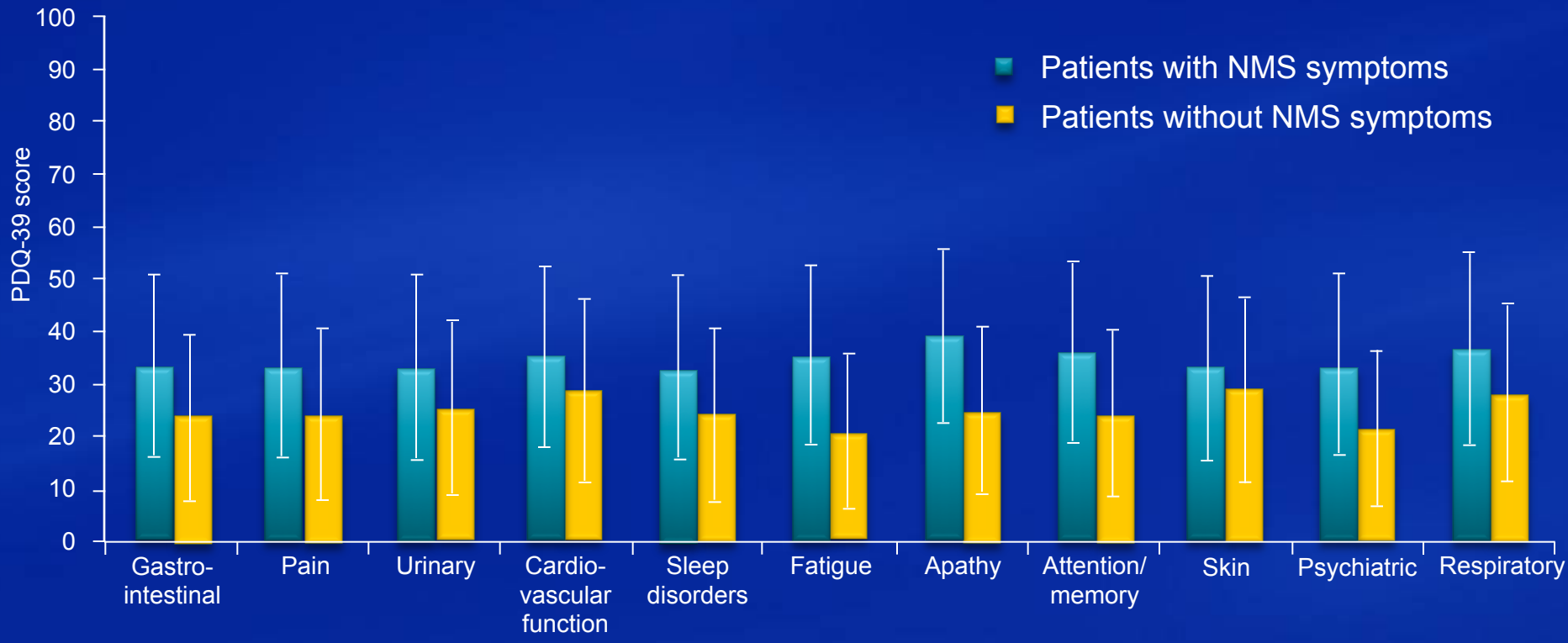
Barone *et al.* Mov Disord 2009

Progression of non-motor disability over 24 months in PD varies by domain



Antonini *et al*. Two-year clinical follow-up of a cohort with Parkinson's disease and other parkinsonisms: the PRIAMO study. *Mov Disord* 24, Suppl 1, 434 (Poster presented at the 13th International Congress of Parkinson's Disease and Movement Disorders, Paris, France; June7-11, 2009.)

Patients who have NMS have worse quality of life (PDQ-39 scores) than those without



N=1072; score range between 0 (best health state) and 100 (worst health state)

Adapted from:
Antonini A *et al.* The PRIAMO study: background, methods and recruitment. *Neurol Sci* 2008;29(2):61-65. Barone P *et al*. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disorders* 2009;15;24(11):1641-9.

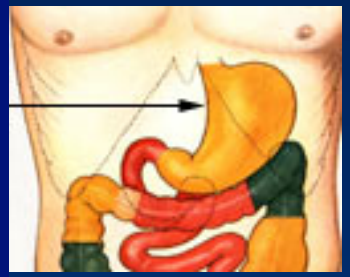
What we can learn from NMS in PD patients: Preclinical stage

- Possibility of early diagnosis and early treatment of PD

Premotor symptoms	Onset before motor symptoms
REM sleep behavioral disorder	12 yrs (up to 20 yrs)
Hyposmia	2-7 yrs
Constipation	10-18 yrs
Depression	3-6 yrs

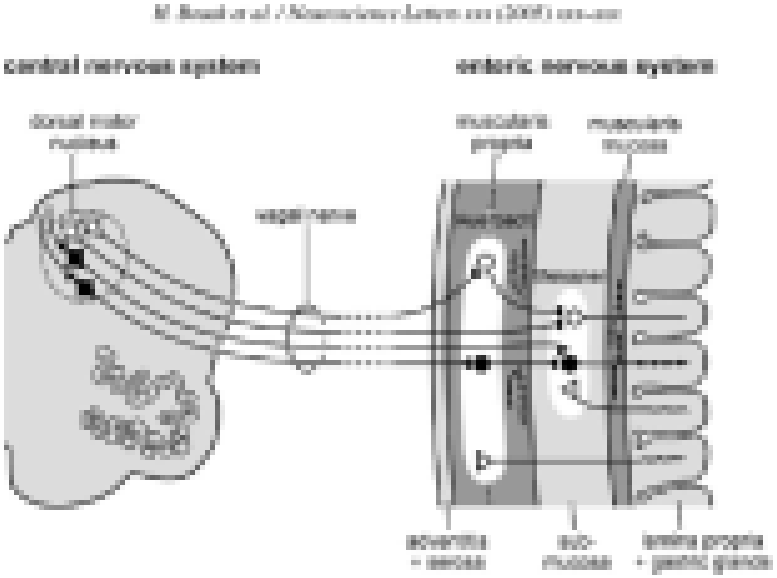
Gaig C and Tolosa E. Mov Disord 24; Supp 2, 2009: 656-664

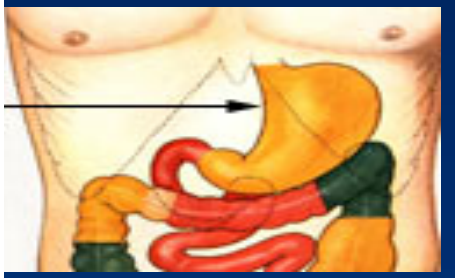
Early Involvement of the Upper GI in PD

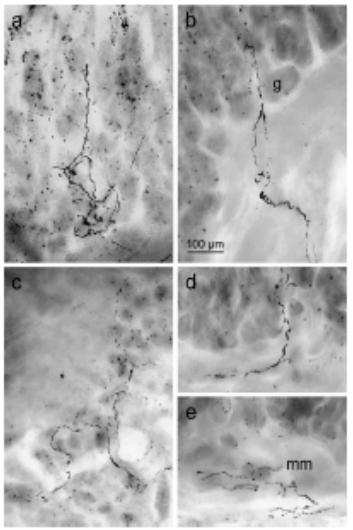


- Anorexia, upper abdominal fullness, bloating, pain, nausea, vomiting and reflux have been reported in naïve, recently diagnosed, PD patients (Eduards et al 1991; Harduff et al, 2001)

- Naïve patients had significantly slower gastric emptying (Djaldetti et al, 1995; Harduff et al, 2001)







Available online at www.sciencedirect.com
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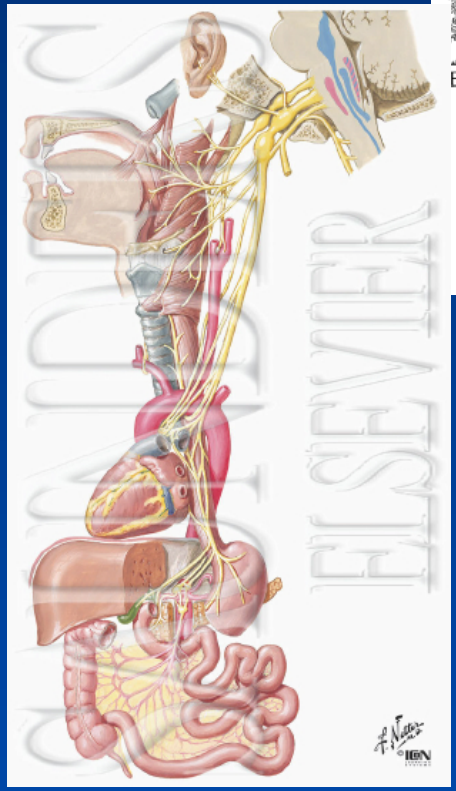
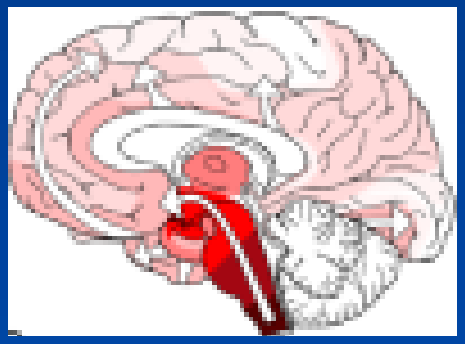
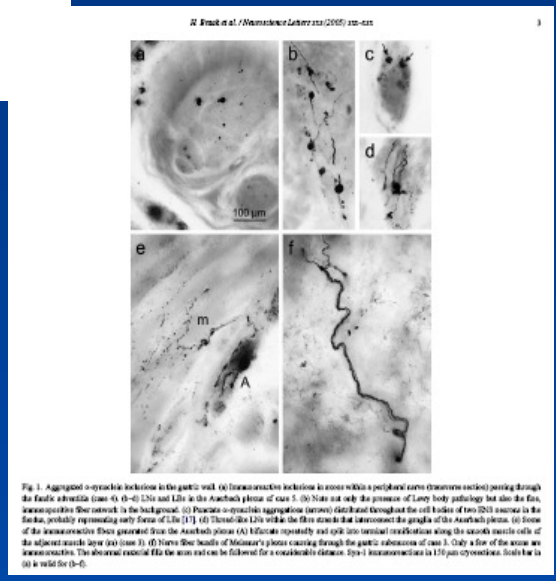
Neuroscience Letters xxx (2005) xxx–xxx
Neuroscience Letters
www.elsevier.com/locate/neulet



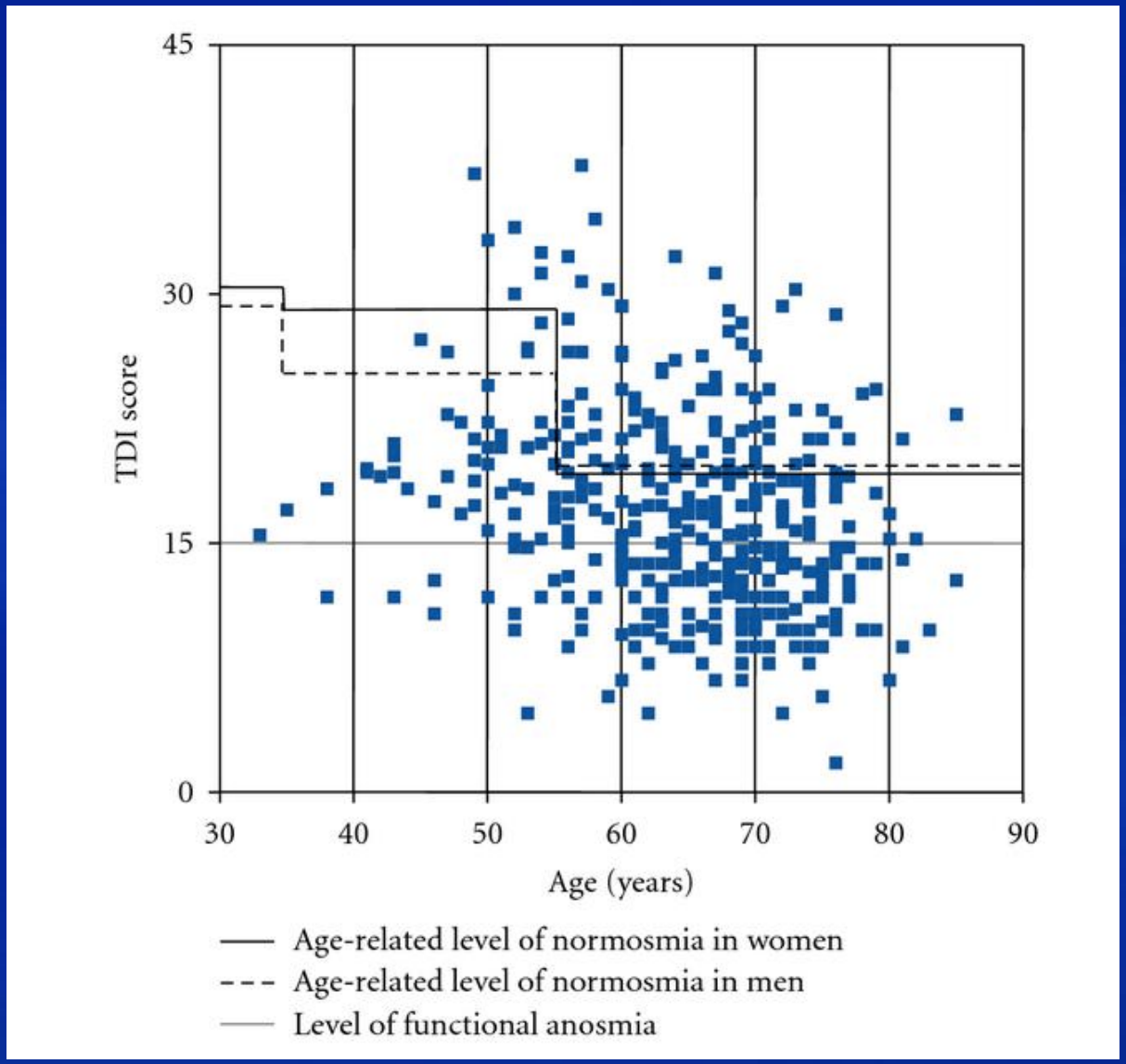
Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology

Heiko Braak[a,*], Rob A.I. de Vos[b], Jürgen Bohl[c], Kelly Del Tredici[a]



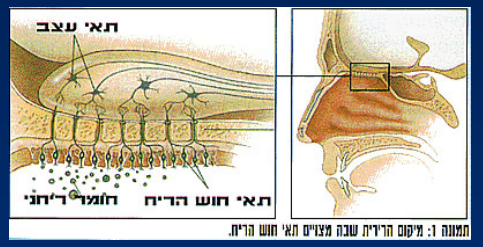


Smell function declines with age



Haehner et al Park Disease 2011

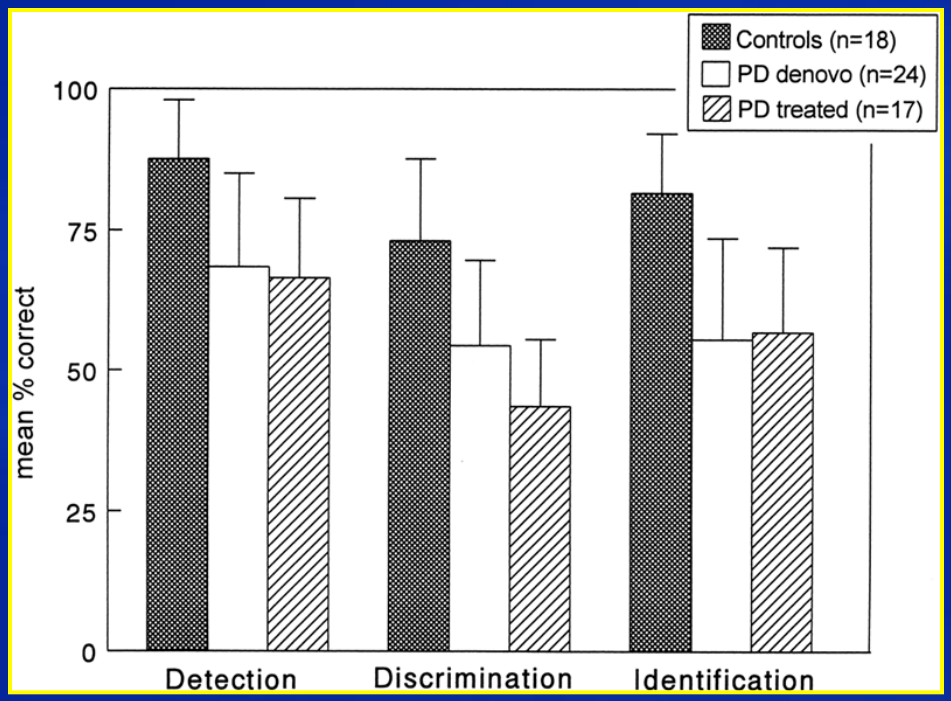
The Sense of Smell and Early PD

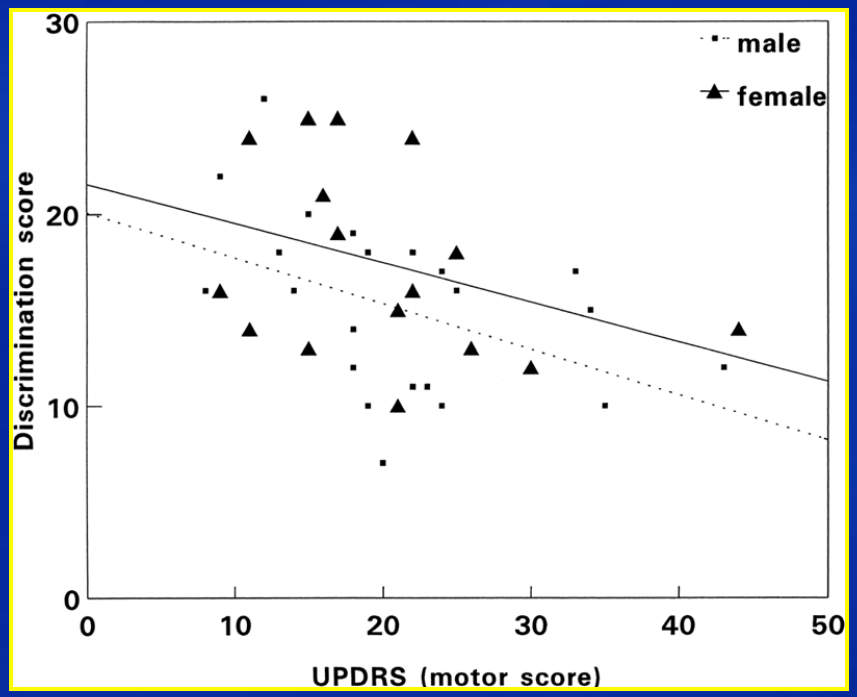


תמונה 1: מיקום הרירית שבה מצויים תאי חוש הריח.

- Olfactory deficit (detection, discrimination & identification) may precede PD motor symptoms by many years *(Dotty et al, 1988; Tissingh et al, 2001; Ponsen et al, 2004)*
- Abnormal olfaction in first degree relatives of PD patients *(Montgomery et al, 1999)*, unaffected twins who later developed PD *(Ward et al, 1988; Dickson et al, 2001)* and children of PD patients who later developed PD *(Berendse et al, 2001).*
- Using β CIT SPECT, healthy relatives with olfactory dysfunction had increased risk to develop dopaminergic dysfunction and PD *(Berendse et al, 2001; Siderowf et al, 2005)*

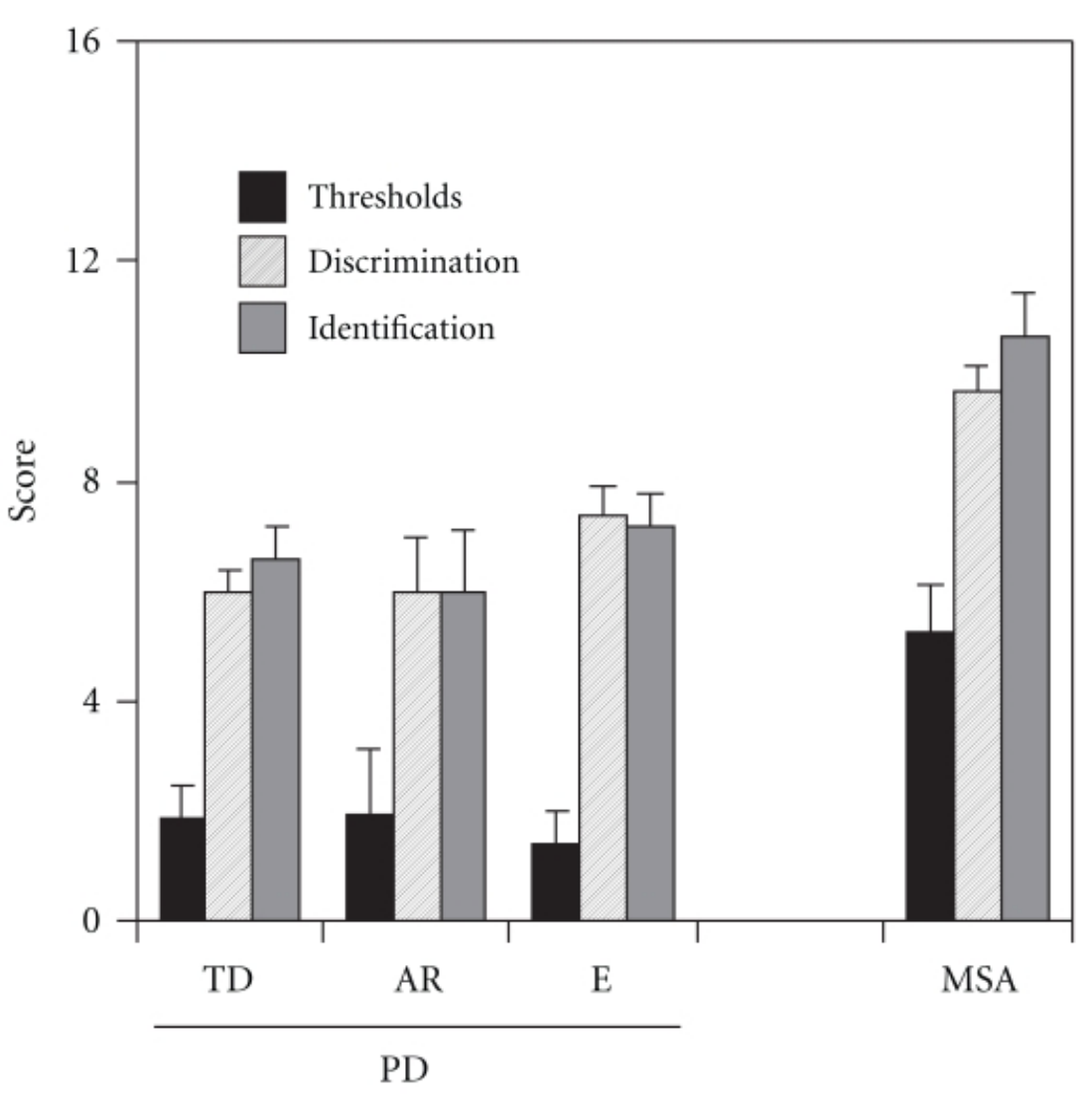
Smell and Parkinson





Tissingh Mov Dis 2001

Olfactory function in PD (TD: tremor-dominant, AR: akinetic-rigid, e: mixed type) and multiple system atrophy (MSA)



Haehner et al Park disease 2011

REVIEW

CME

Neuropathology of Sporadic Parkinson's Disease: Evaluation and Changes of Concepts

Kurt A. Jellinger, MD*
Institute of Clinical Neurobiology, Vienna, Austria

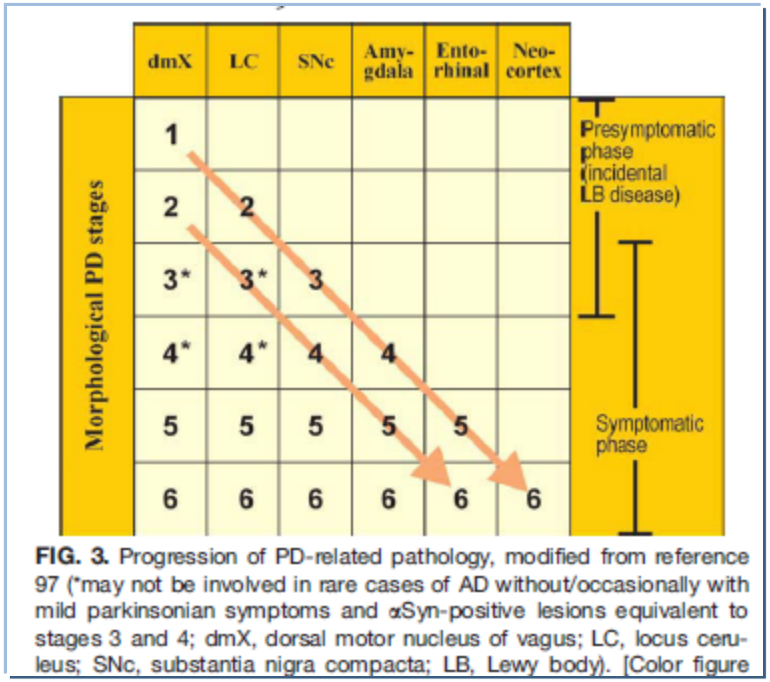


FIG. 3. Progression of PD-related pathology, modified from reference 97 (*may not be involved in rare cases of AD without/occasionally with mild parkinsonian symptoms and αSyn-positive lesions equivalent to stages 3 and 4; dmX, dorsal motor nucleus of vagus; LC, locus ceruleus; SNc, substantia nigra compacta; LB, Lewy body). [Color figure

Pathophysiology of Clinical Subtypes

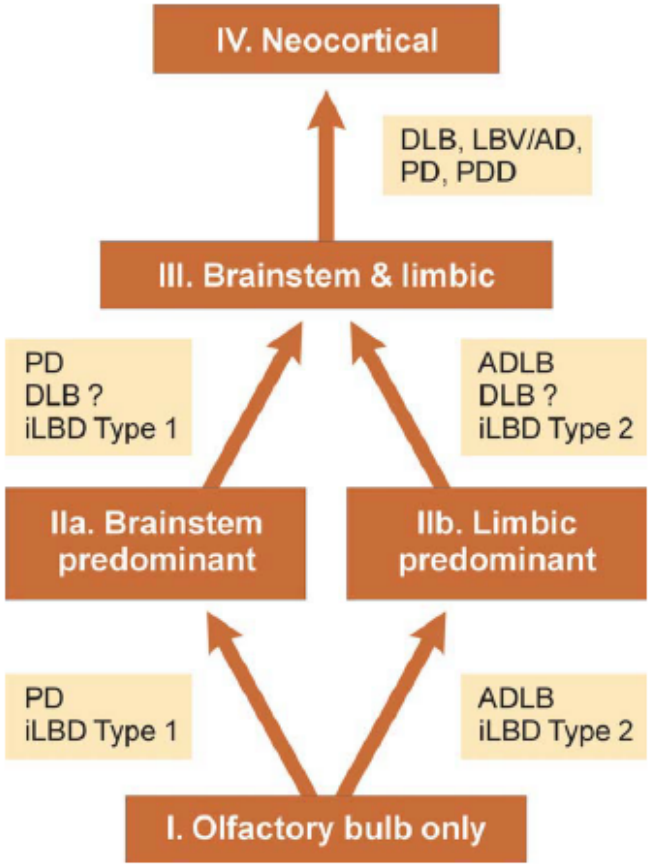
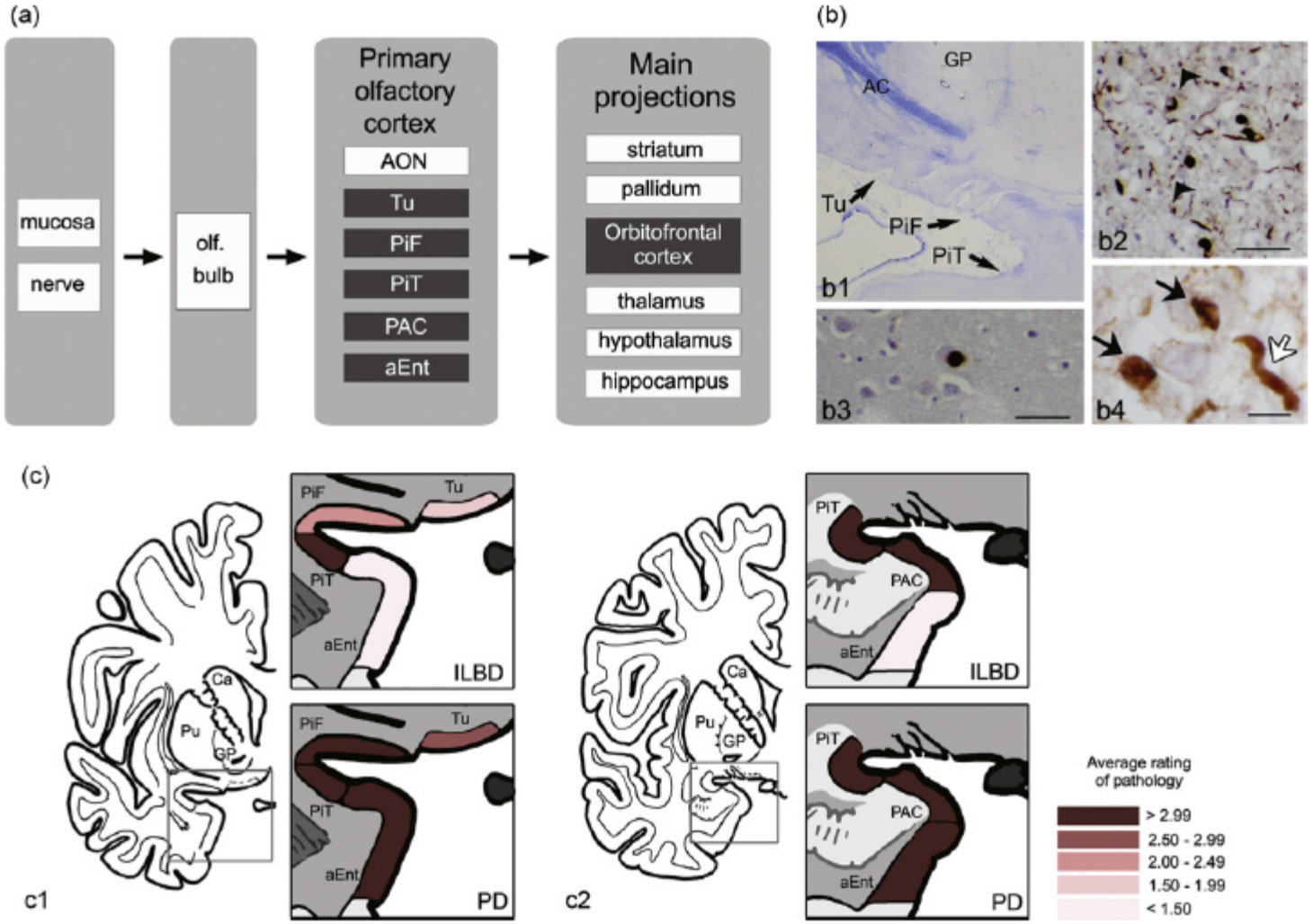


FIG. 4. Scheme of the hypothetic progression pathways and stages of Lewy body (LB) disorders. The pathway for Parkinson's disease (PD) is suggested to proceed through stage iia (brain stem predominant) and that for dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) with LBs probably pass through stage IIb. For incidental LB disease (iLBD), both pathways seem possible, whereas only PD/PD dementia (PDD), DLB, and the LB variant of AD (LBV/AD) progress to the neocortical stage.[202] [Color figure can be viewed in the online issue

Why Deficits in Olfaction and Cognition maybe Associated



Silveira-Moriyama, et al. Neurosci Lett (2009);453:77-80

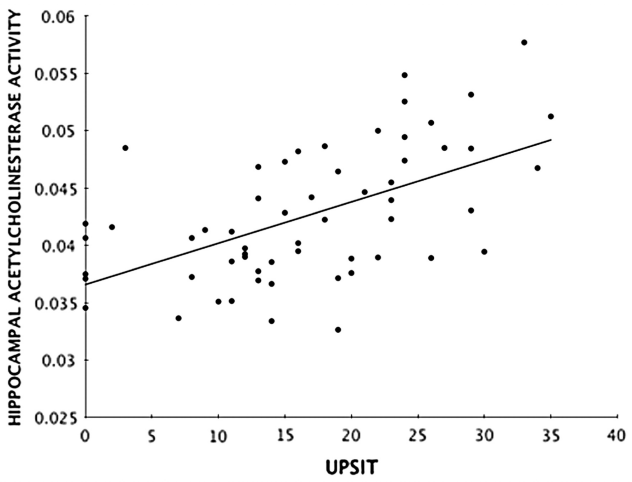
Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson's disease

Nicolaas I. Bohnen,[1,2,3] Martijn L. T. M. Müller,[1] Vikas Kotagal,[2] Robert A. Koeppe,[1] Michael A. Kilbourn,[1] Roger L. Albin[2,3] and Kirk A. Frey[1,2]

- 58 non-demented, moderate PD patients evaluated with UPSIT, neuropsychological assessment and AChE and VMAT2 PET imaging

•Higher UPSIT scores were associated with better scores on episodic verbal learning (r = 0.30, P = 0.023) but not visual non-verbal memory (r = 0.18, P = 0.17), visuospatial function (r = 0.001, P = 0.99), attention (r = –0.05, P = 0.80) or executive function (r = 0.1, P = 0.46) or Global function as assessed with MMSE (r = 0.25, P = 0.055)

- Multiple regression analysis controlling for age, dz duration and UPDRS score revealed a significant association between UPSIT scores correlated and limbic AChE activity (*F* = 8.1, *P*<0.0001)



Brain 2010;133:1747-54

RESEARCH ARTICLE

Olfactory Dysfunction Is Associated with Neuropsychiatric Manifestations in Parkinson's Disease

James F. Morley, MD, PhD,[1,2] Daniel Weintraub, MD,[1,2,3,4] Eugenia Mamikonyan, MS,[3] Paul J. Moberg, PhD,[1,2,3] Andrew D. Siderowf, MD,[1,2] and John E. Duda, MD[1,2*]

Group Differences in Demographics and Disease Characteristics

	UPSIT Bottom (N = 123)	UPSIT Top (N = 125)	*P*
UPSIT score	13 (2.8)	26 (5.2)	<0.001
Demographic			
Age (y)	67 (9.5)	63 (10.3)	<0.001
Men (%)	84	66	0.001
Education (y)	16 (2.9)	16 (3.3)	0.20
Smokers (%)	4	6	0.41
Disease characteristics			
Hoehn and Yahr stage	2.3 (0.71)	2.1 (0.66)	0.001
UPDRS Part III	24 (12)	20 (8)	0.001
PD duration (y)	7.3 (5.2)	6.0 (5.4)	0.07
Levodopa dose (mg)	580 (330)	450 (430)	0.01

Mov Dis 2011; 26(11):2051-7

Poorer Olfactory Identification is Associated with Psychotic Symptoms, Poorer Verbal Memory and Executive function

	Adjusted OR (95% CI) for UPSIT Performance	*P*
Psychiatric		
Geriatric Depression Scale[a]	1.2 (0.70–2.3)	0.42
Inventory of Depressive Symptomatology[a]	1.5 (0.86–2.7)	0.15
State Anxiety Inventory[a]	0.97 (0.47–2.0)	0.94
Apathy Scale[a]	1.1 (0.61–1.9)	0.77
Psychosis[a]	2.1 (1.0–4.3)	0.05
Cognitive		
Mini–Mental State Examination[a]	1.0 (0.47–2.1)	0.99
Digit Span[a]	1.0 (0.52–2.1)	0.90
Stroop Color Word Test[b]	1.3 (0.50–3.2)	0.61
Tower of London-DX[b]	3.1 (1.5–6.2)	0.001
Hopkins Verbal Learning Test–Revised[b]	1.8 (1.1–3.7)	0.04

Adjusted for age, sex, disease severity, duration and medication status

Mov Dis 2011;26(11):2051-7

RESEARCH ARTICLE

Odor Identification Deficits Identify Parkinson's Disease Patients with Poor Cognitive Performance

Malene Flensborg Damholdt, PhD, MSc,[1]* Per Borghammer, MD, PhD,[2] Lars Larsen, PhD, MSc,[1] and Karen Østergaard, MD, PhD, DMSc[3]

- 63 PD patients divided up into:
  - 24 anosmic (B-SIT ≤ 5) – Mean B-SIT 3.7
  - 39 nonanosmic
    - 33 hyposmic (B-SIT < 9)
    - 6 normosmic (B-SIT ≥ 10)
  - 15 Controls
    - 4 hyposmic (B-SIT < 9)

Mov Dis (2011) 26:2045

Anosmic PD patients have Poorer Memory, Processing Speed and Language but not Executive Function Compared to Non-anosmic PD

TABLE 2. Cognitive domain and test *z*-scores of the 2 patient groups, mean (SD), Cronbach α, and comparisons

	Functionally anosmic PD (PDfa) n = 24, mean (SD)	Nonanosmic PD (PDna) n = 39, mean (SD)	Internal consistency Cronbach α, Spearman correlation	ANCOVA, $F_{2,86}$	Effect size, η_p^2	Direction of difference, Bonferroni post hoc
Verbal and visual memory	−1.55 (1.07)	−0.52 (0.73)	α = .812	17.603[a,c]	.290	PDfa < PDna, C
RAVLT recall trial 5	−1.42 (1.10)	−0.64 (1.01)				
RAVLT delayed recall	−1.56 (0.83)	−0.78 (0.91)				
RAVLT recognition	−2.11 (1.52)	−0.53 (1.25)				
LLT recall trial 5	−1.60 (2.60)	−0.16 (1.01)				
LLT delayed recall	−1.05 (1.65)	−0.01 (0.68)				
Processing speed	−1.60 (1.06)	−0.76 (0.89)	$r = 0.783$[a]	14.546[a,c]	.253	PDfa < PDna < C
Stroop word	−2.00 (1.38)	−0.95 (1.14)				
Stroop color	−1.18 (0.90)	−.056 (0.76)				
Language	−0.99 (1.25)	−0.62 (1.07)	$r = 0.385$[a]	5.073[b,d]	.104	PDfa < C, Pdna = C, Pdfa
Boston Naming Test	−1.19 (1.95)	−0.82 (1.62)				
Animal fluency	−0.80 (1.11)	−0.42 (0.93)				
Executive function	−0.97 (0.85)	−0.56 (0.90)	α = .783	7.424[a,c]	.155	PDfa, PDna < C
Stroop interference	−1.20 (1.27)	−0.59 (1.14)				
Alternating fluency	−1.24 (0.74)	−0.68 (0.77)				
Iowa gambling task	−0.37 (0.62)	−0.12 (0.91)				
WCST, categories	−0.77 (1.17)	−0.50 (1.19)				
WCST, total errors	−1.41 (1.73)	−0.92 (1.75)				

Mov Dis (2011) 26:2045

Parkinsonism and Related Disorders 18 (2012) 243–246

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

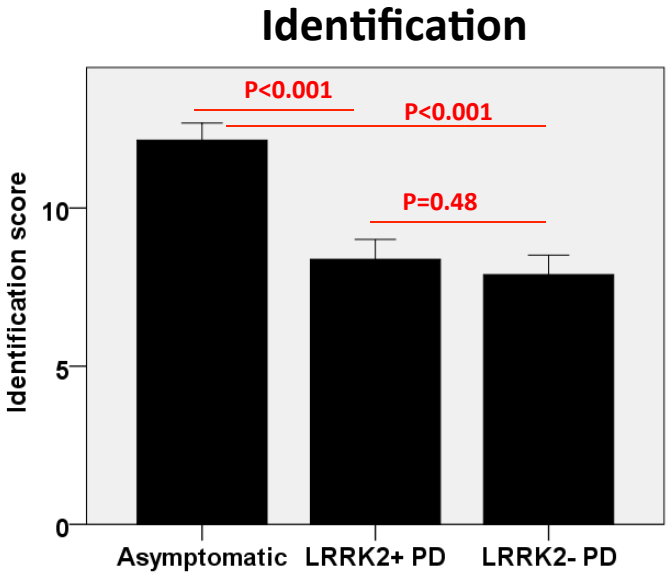
journal homepage: www.elsevier.com/locate/parkreldis

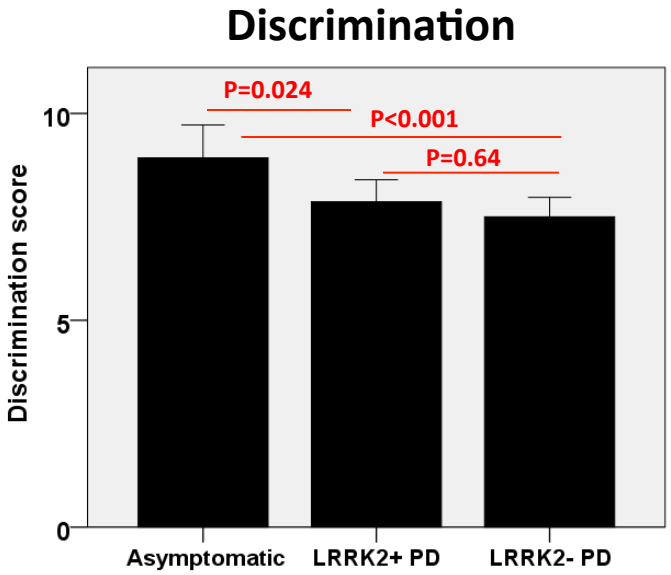
Cognitive dysfunction in Tunisian LRRK2 associated Parkinson's disease

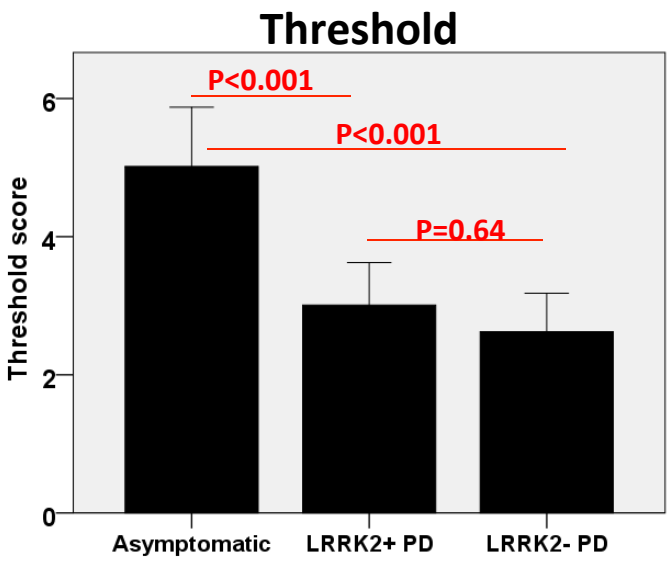
Samia Ben Sassi [a,*], Fatma Nabli [a], Emna Hentati [a], Houda Nahdi [a], Meriam Trabelsi [a], Hela Ben Ayed [a], Rim Amouri [a], John Eric Duda [b], Matthew John Farrer [c], Fayçal Hentati [a]

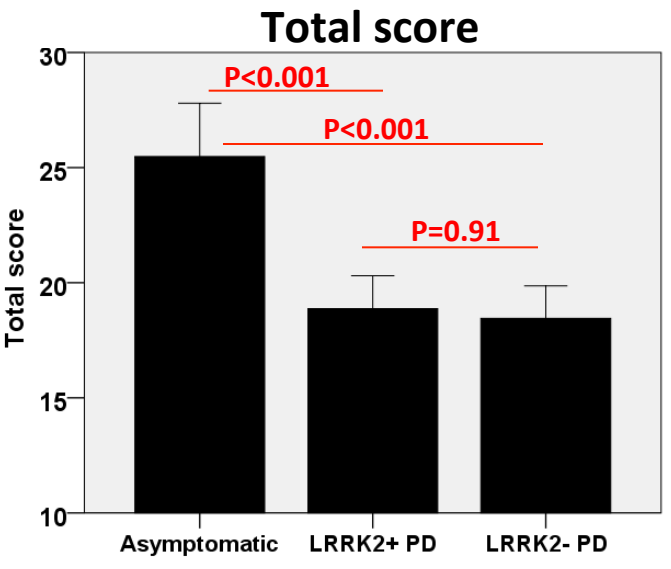
	Cohort N=272	PD		Asymptomatic	
		LRRK2- N=100	LRRK2+ N=89	LRRK2- N=53	LRRK2+ N=30
Age (y)	55 ± 12	58 ± 11	58 ± 10	52 ± 11	42 ± 13
Gender N(%) male	140 (52%)	62 (62%)	44 (50%)	21 (40%)	13 (43%)
Smokers N(%) current	44 (16%)	14 (16%)	10 (14%)	10 (24%)	10 (36%)
Duration (y)	8.6 ± 7.6	9.2 ± 8.3	7.9 ± 5.0	-	-

Olfactory impairment is not influenced by LRRK2 status in PD









doi:10.1093/brain/awr321 Brain 2012: 135; 161–169 | 16

BRAIN
A JOURNAL OF NEUROLOGY

Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study

Toru Baba,[1] Akio Kikuchi,[1] Kazumi Hirayama,[2,3] Yoshiyuki Nishio,[2] Yoshiyuki Hosokai,[2] Shigenori Kanno,[2] Takafumi Hasegawa,[1] Naoto Sugeno,[1] Masatoshi Konno,[1] Kyoko Suzuki,[2,4] Shoki Takahashi,[5] Hiroshi Fukuda,[6] Masashi Aoki,[1] Yasuto Itoyama,[1,7] Etsuro Mori[2] and Atsushi Takeda[1]

- 44 non-demented PD patients assessed at baseline and 3 years later with OSIT-J, cognitive battery, FDG-PET and MRI

PD patients with Severe Hyposmia have much greater Cognitive Decline over next 3 years

	Parkinson's disease without severe hyposmia		Parkinson's disease with severe hyposmia	
	t_0	t_3	t_0	t_3[a]
Number	20		24	
Age at t_0 (years)	65.5 ± 6.1		65.0 ± 6.2	
Sex (female/male), *n*	14/6		7/17	
OSIT-J score (max = 12)	7.1 ± 1.3		2.3 ± 1.4	
Duration (years)	5.8 ± 6.0		4.4 ± 3.3	
Hoehn and Yahr scale	2.4 ± 0.7	2.7 ± 0.4**	2.5 ± 0.5	3.2 ± 0.7***
UPDRS 3	18.2 ± 7.9	18.9 ± 7.1	18.9 ± 7.4	24.3 ± 11.6
Levodopa equivalent dose (mg)	360.7 ± 280.7	540.0 ± 282.9***	335.7 ± 248.1	554.9 ± 276.4***
Motor subtype (PIGD, TD, ID), *n*	14/4/2	18/1/1	19/4/1	22/0/2
CDR (0/0.5/1/2/3), *n*	18/2/0/0/0	15/5/0/0/0	17/7/0/0/0	9/8/3/1/3
MMSE	29.0 ± 1.2	28.3 ± 1.8	27.4 ± 1.9	22.5 ± 9.5*
Word recall score (max = 30)	20.0 ± 3.3	20.5 ± 4.1	17.0 ± 3.4	15.4 ± 7.3
Overlapping figure identification test				
Correct response score (max = 40)	32.6 ± 3.5	32.8 ± 4.4	29.8 ± 5.2	26.3 ± 7.2*
Illusory response score (max = 40)	2.3 ± 2.0	2.2 ± 1.7	4.0 ± 3.0	3.8 ± 2.8

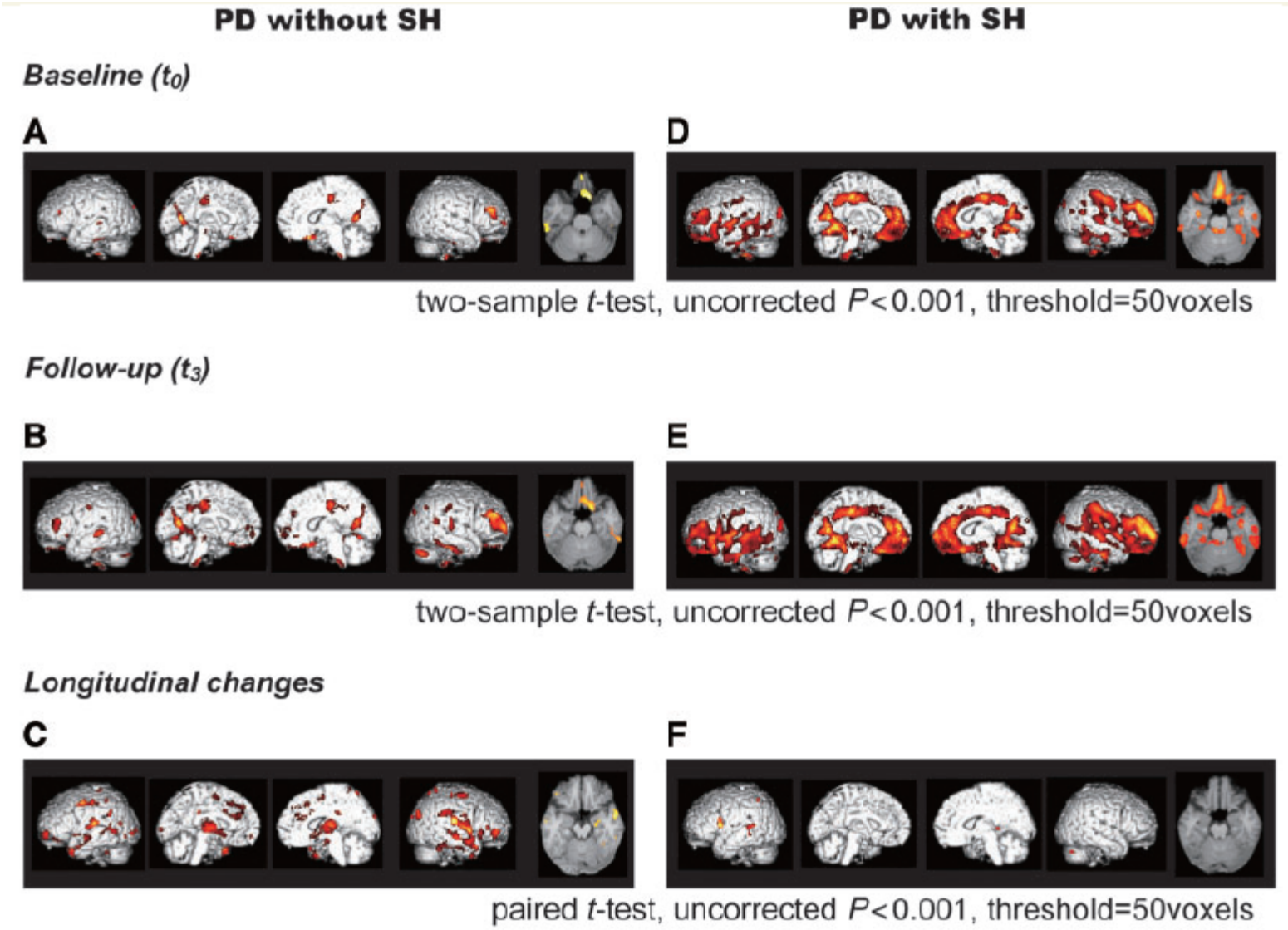
Subjects who Developed Dementia Similar to others except for Mild Cognitive Impairment and Severe Olfactory Dysfunction

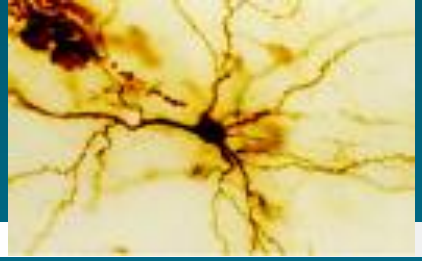
	Non-converters		Converters	
	t_0	t_3	t_0	t_3[a]
Number	34		10	
Age at t_0 (years)	64.7 ± 6.3		67.0 ± 5.1	
Sex (female/male), *n*	20/14		2/8	
OSIT-J score (max = 12)	5.2 ± 2.6		1.9 ± 1.5	
Duration (years)	5.0 ± 5.0		5.1 ± 4.1	
Hoehn and Yahr scale	2.4 ± 0.6	2.8 ± 0.4*	2.7 ± 0.4	3.9 ± 0.7*,[b]
UPDRS 3	18.5 ± 7.9	18.9 ± 7.0	18.9 ± 6.2	35.0 ± 11.8*,[b]
Levodopa equivalent dose (mg)	318.1 ± 257.8	549.2 ± 279.4*	445.4 ± 258.3	539.7 ± 281.2
Motor subtype (PIGD, TD, ID), *n*	25/6/3	30/1/3	8/2/0	10/0/0
CDR (0/0.5/1/2/3), *n*	30/4/0/0/0	24/10/0/0/0	5/5/0/0/0	0/3/3/1/3
MMSE	28.4 ± 1.6	28.0 ± 1.7	26.9 ± 2.0	15.3 ± 11.4*,[b,c]
Word recall score (max = 30)	19.1 ± 3.2	20.1 ± 3.6*	15.9 ± 4.2	9.6 ± 7.7[b,c]
Overlapping figure identification test				
Correct response score (max = 40)	31.4 ± 4.7	31.2 ± 5.4	30.0 ± 4.6	20.7 ± 6.2*,[b]
Illusory response score (max = 40)	2.8 ± 2.4	2.7 ± 2.3	4.7 ± 3.4	4.4 ± 2.7

Table 3 Relative risk of dementia according to the severity of hyposmia and illusory response

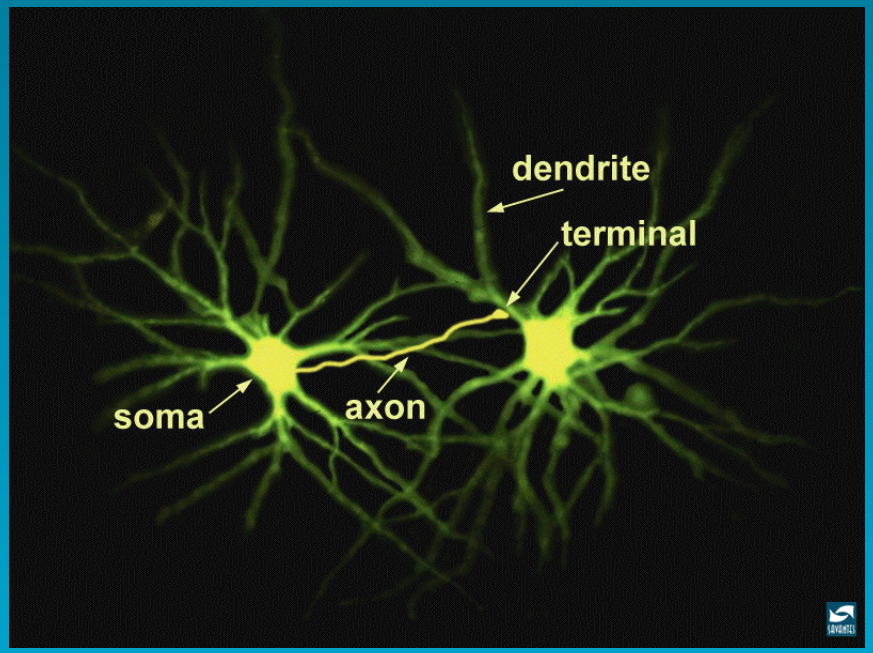
Variable	Standardized relative risk (95 % CI[a])	*P*-value[b]
OSIT-J score	18.7 (3.1–425.2)	0.02
Illusory response score	3.7 (1.3–18.0)	0.04

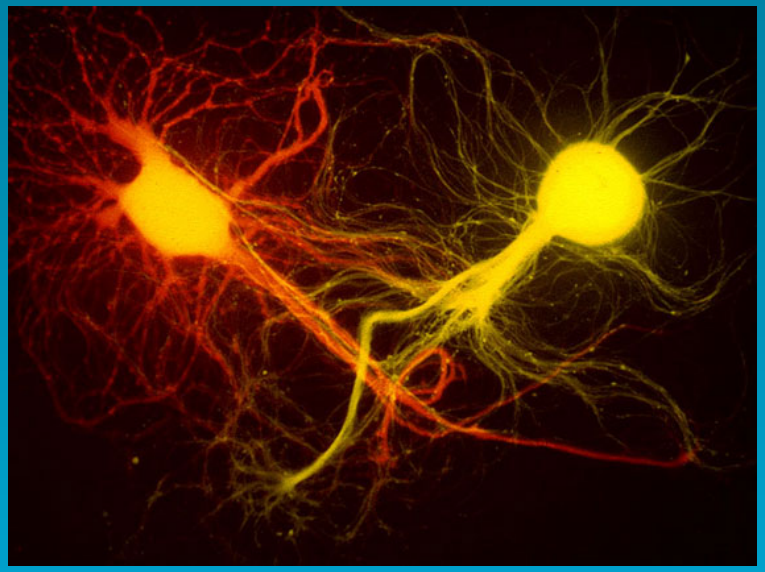
Severely Hyposmic PD Subjects have More Widespread Cortical Atrophy at Baseline





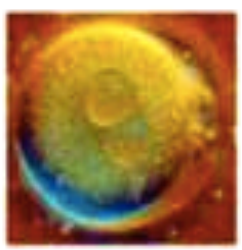
Sarà possibile curare il Parkinson con le cellule staminali?

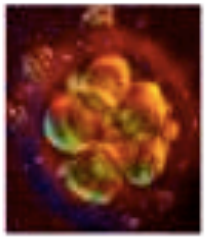


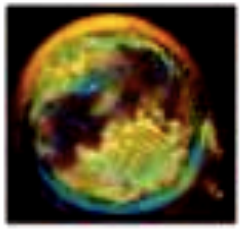


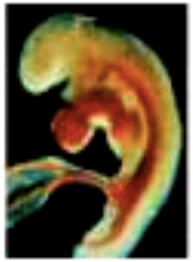
Stem Cells

Human Developmental Continuum →


Single-cell Embryo


3-day Embryo


5-7 day Embryo


4-week Embryo


6-week Embryo


Infant


Adult

Embryonic Stem (ES) cells
Totipotent

Embryonic Germ (EG) cells
(primordial germ cells)
Pluripotent

Fetal Tissue Stem cells
Pluripotent or Multipotent

Cord Blood Stem cells
Placental Stem cells
Pluripotent or Multipotent

"Adult" Stem cells
Pluripotent or Multipotent

Teratocarcinoma (germ cell tumor)

Bone marrow
Multipotent

Fetal mesencephalic cells- problems

- very low yield of dopaminergic cells
- very low tissue availability
- no proven efficacy in controlled trials

  Freed et al, NEJM 2001; Olanow et al, Ann Neurol 2003

- “off- medication” dyskinesia- a serious side- effect

Annals of Neurology

EXPEDITED PUBLICATION

A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease

C. Warren Olanow, MD,[1] Christopher G. Goetz, MD,[2] Jeffrey H. Kordower, PhD,[2] A. Jon Stoessl, MD,[3] Vesna Sossi, PhD,[3] Mitchell F. Brin, MD,[1] Kathleen M. Shannon, MD,[2] G. Michael Nauert, MD,[4] Daniel P. Perl, MD,[5] James Godbold, PhD,[6] and Thomas B. Freeman, MD[4]

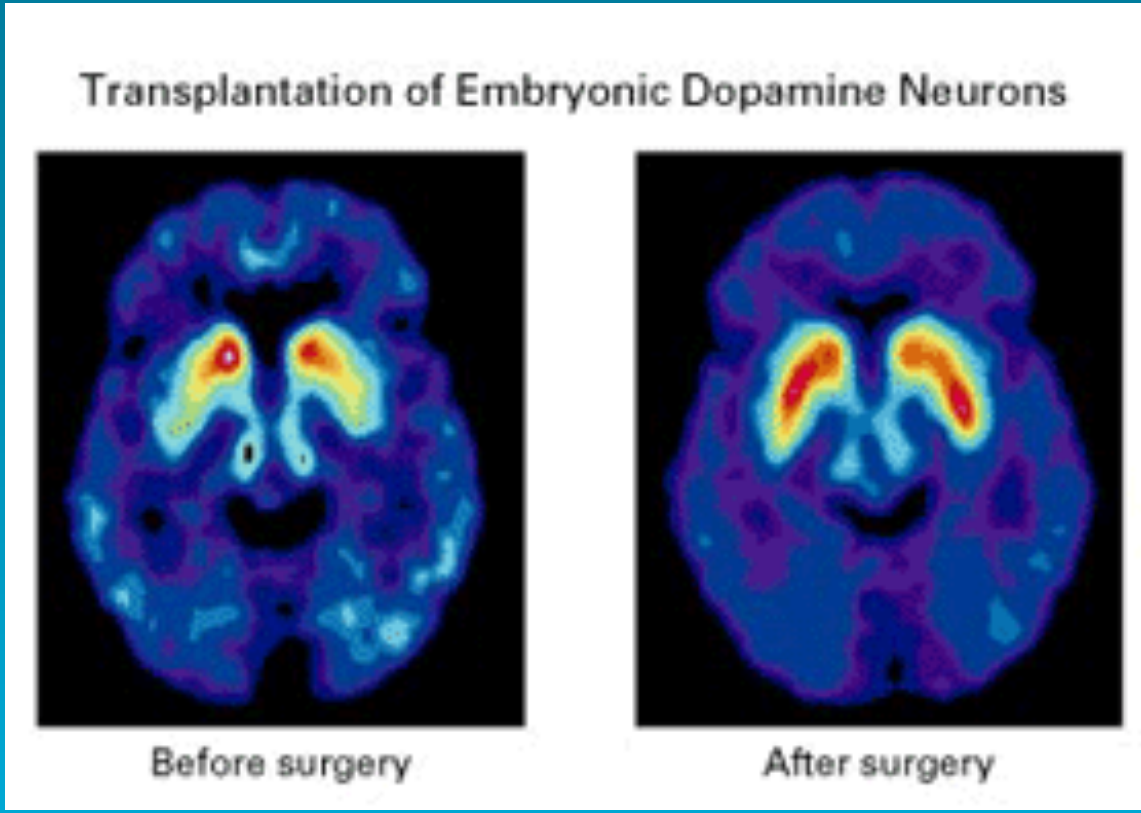
Thirty-four patients with advanced Parkinson's disease participated in a prospective 24-month double-blind, placebo-controlled trial of fetal nigral transplantation. Patients were randomized to receive bilateral transplantation with one or four donors per side or a placebo procedure. The primary end point was change between baseline and final visits in motor component of the Unified Parkinson's Disease Rating Scale in the practically defined off state. There was no significant overall treatment effect ($p = 0.244$). Patients in the placebo and one-donor groups deteriorated by 9.4 ± 4.25 and 3.5 ± 4.23 points, respectively, whereas those in the four-donor group improved by 0.72 ± 4.05 points. Pairwise comparisons were not significant, although the four-donor versus placebo groups yielded a p value of 0.096. Stratification based on disease severity showed a treatment effect in milder patients ($p = 0.006$). Striatal fluorodopa uptake was significantly increased after transplantation in both groups and robust survival of dopamine neurons was observed at postmortem examination. Fifty-six percent of transplanted patients developed dyskinesia that persisted after overnight withdrawal of dopaminergic medication ("off"-medication dyskinesia). Fetal nigral transplantation currently cannot be recommended as a therapy for PD based on these results.

Ann Neurol 2003;54:403–414

Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease (Denver–Columbia trial)

Curt R. Freed, M.D., Paul E. Greene, M.D., Robert E. Breeze, M.D., Wei-Yann Tsai, Ph.D., William DuMouchel, Ph.D., Richard Kao, Sandra Dillon, R.N., Howard Winfield, R.N., Sharon Culver, N.P., John Q. Trojanowski, M.D., Ph.D., David Eidelberg, M.D., and Stanley Fahn, M.D.

NEJM 2001;344(10):710-719



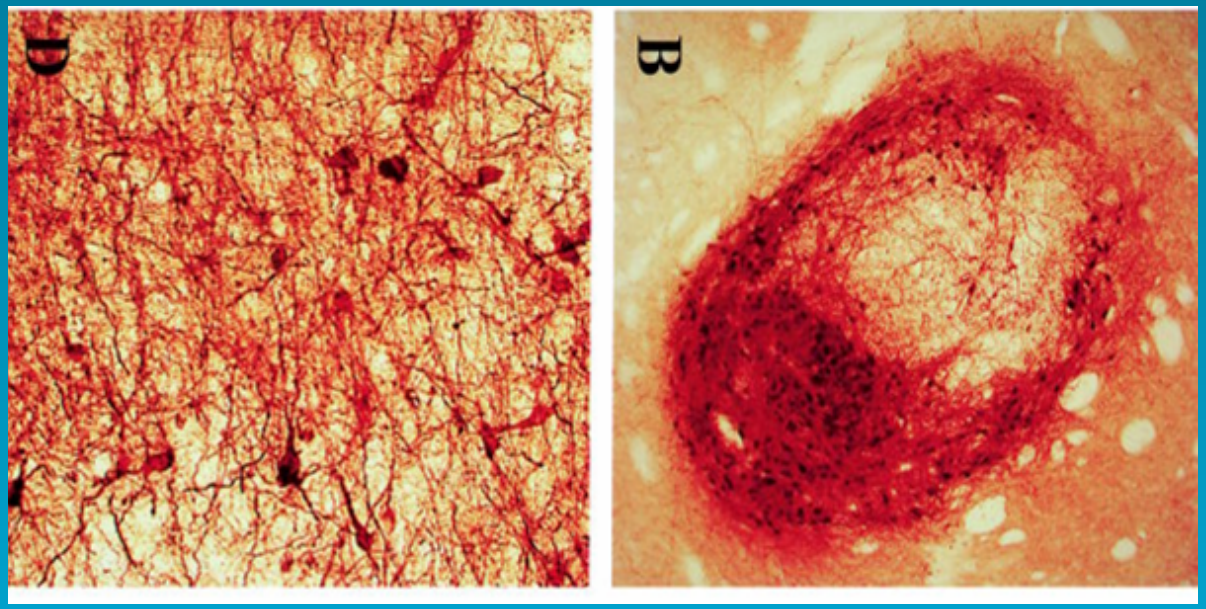
A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease

(Tampa–Mount Sinai trial)

C. Warren Olanow, MD, Christopher G. Goetz, MD, Jeffrey H. Kordower, PhD, A. Jon Stoessl, MD, Vesna Sossi, PhD, Mitchell F. Brin, MD, Kathleen M. Shannon, MD, G. Michael Nauert, MD, Daniel P. Perl, MD, James Godbold, PhD, Thomas B. Freeman, MD

Ann. Neurol. 2003;54(3):403-414

Tyrosine hydroxylase

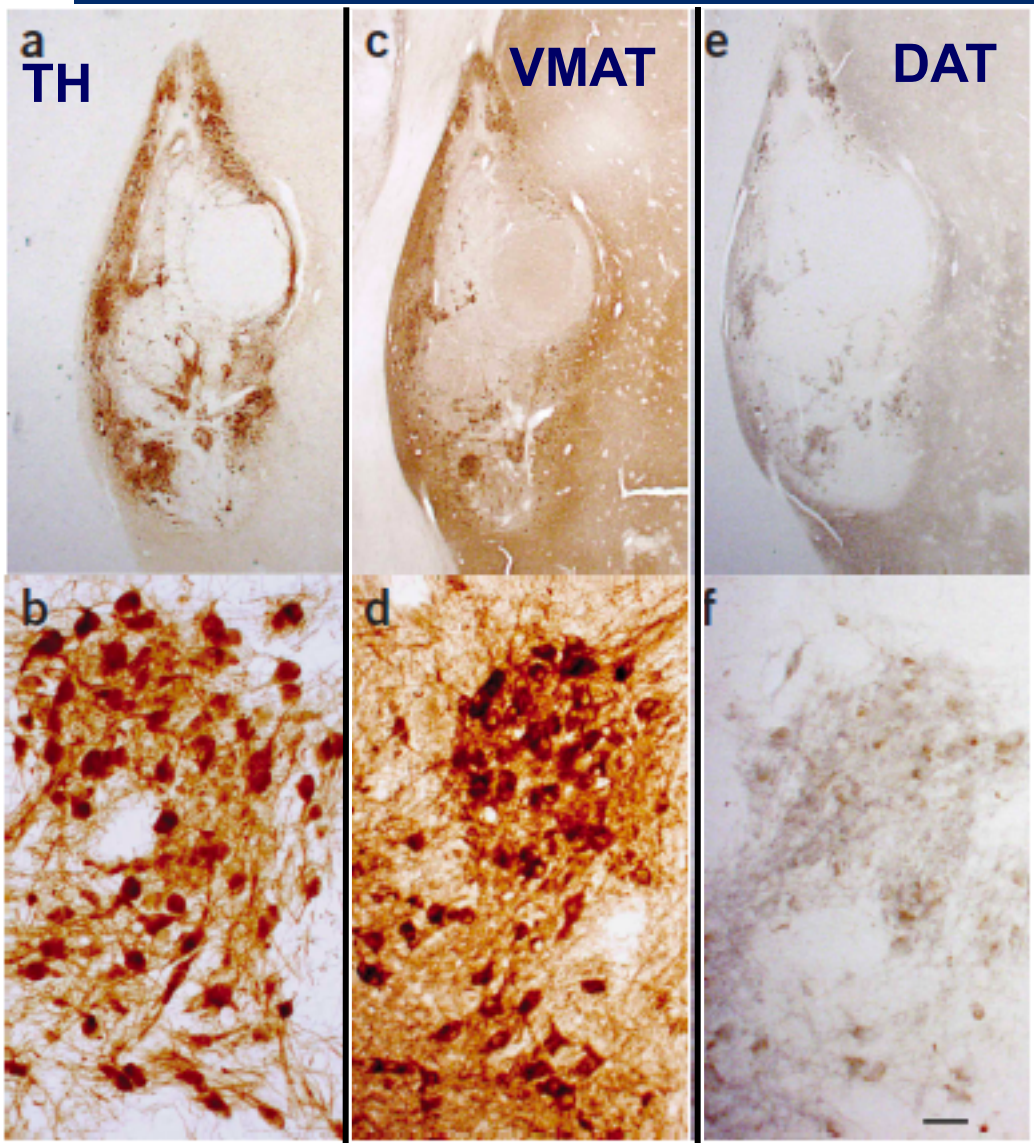


Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[3] & C Warren Olanow[4]

nature medicine

Is PD a "prion-like" disorder?



Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

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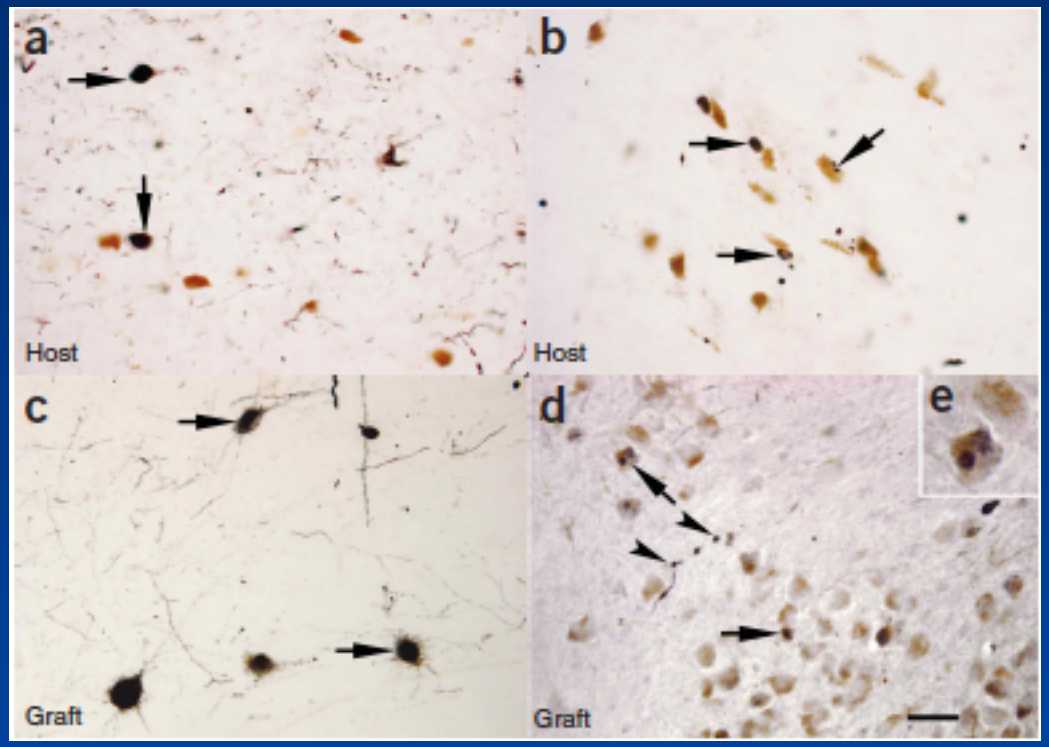


nature medicine

Many years later….

Nat Med. 2008 May;14(5):507-9. Epub 2008 Apr 6.

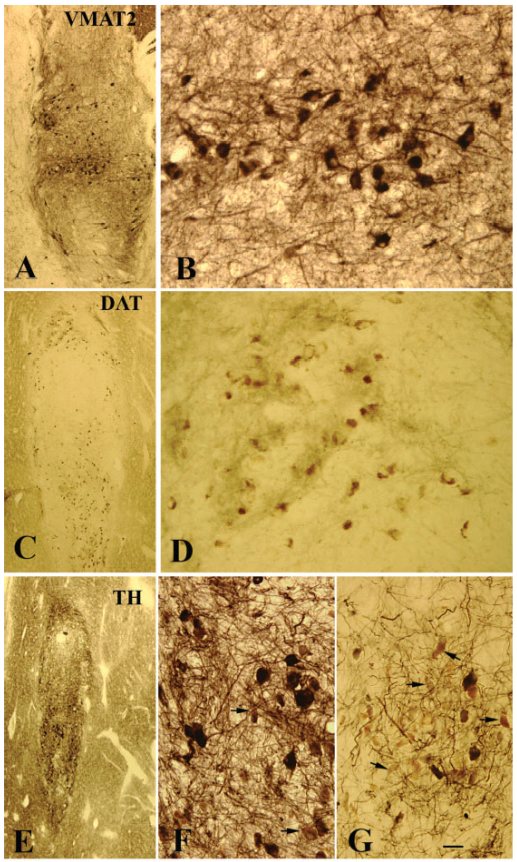
Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years.

Mendez I, Viñuela A, Astradsson A, Mukhida K, Hallett P, Robertson H, Tierney T, Holness R, Dagher A, Trojanowski JQ, Isacson O.

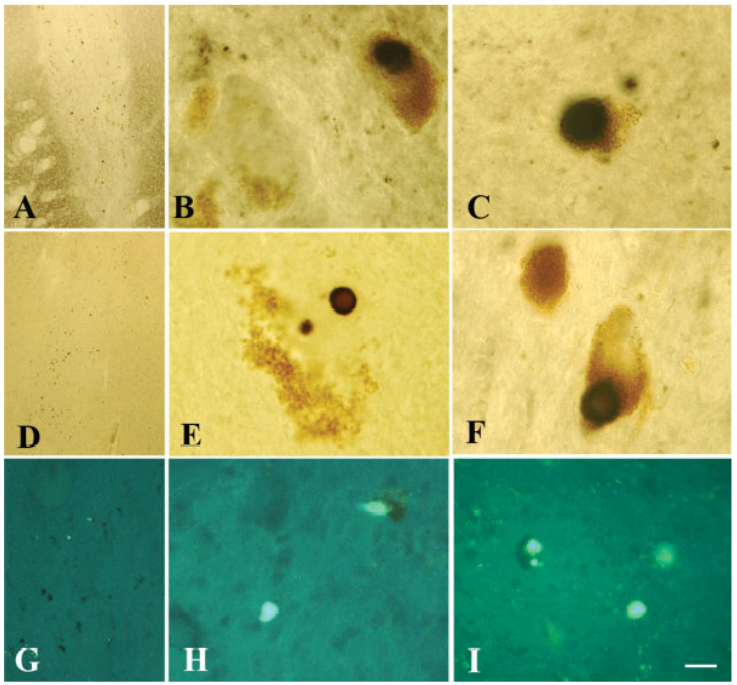
Postmortem analysis of five subjects with Parkinson's disease 9-14 years after transplantation of fetal midbrain cell suspensions revealed surviving grafts that included dopamine and serotonin neurons without pathology. These findings are important for the understanding of the etiopathogenesis of midbrain dopamine neuron degeneration and future use of cell replacement therapies.

Transplanted Dopaminergic Neurons Develop PD Pathologic Changes: A Second Case Report

Jeffrey H. Kordower, PhD,[1]* Yaping Chu, MD,[1]
Robert A. Hauser, MD,[2] C.Warren Olanow, MD,[3]
and Thomas B. Freeman, MD[4]

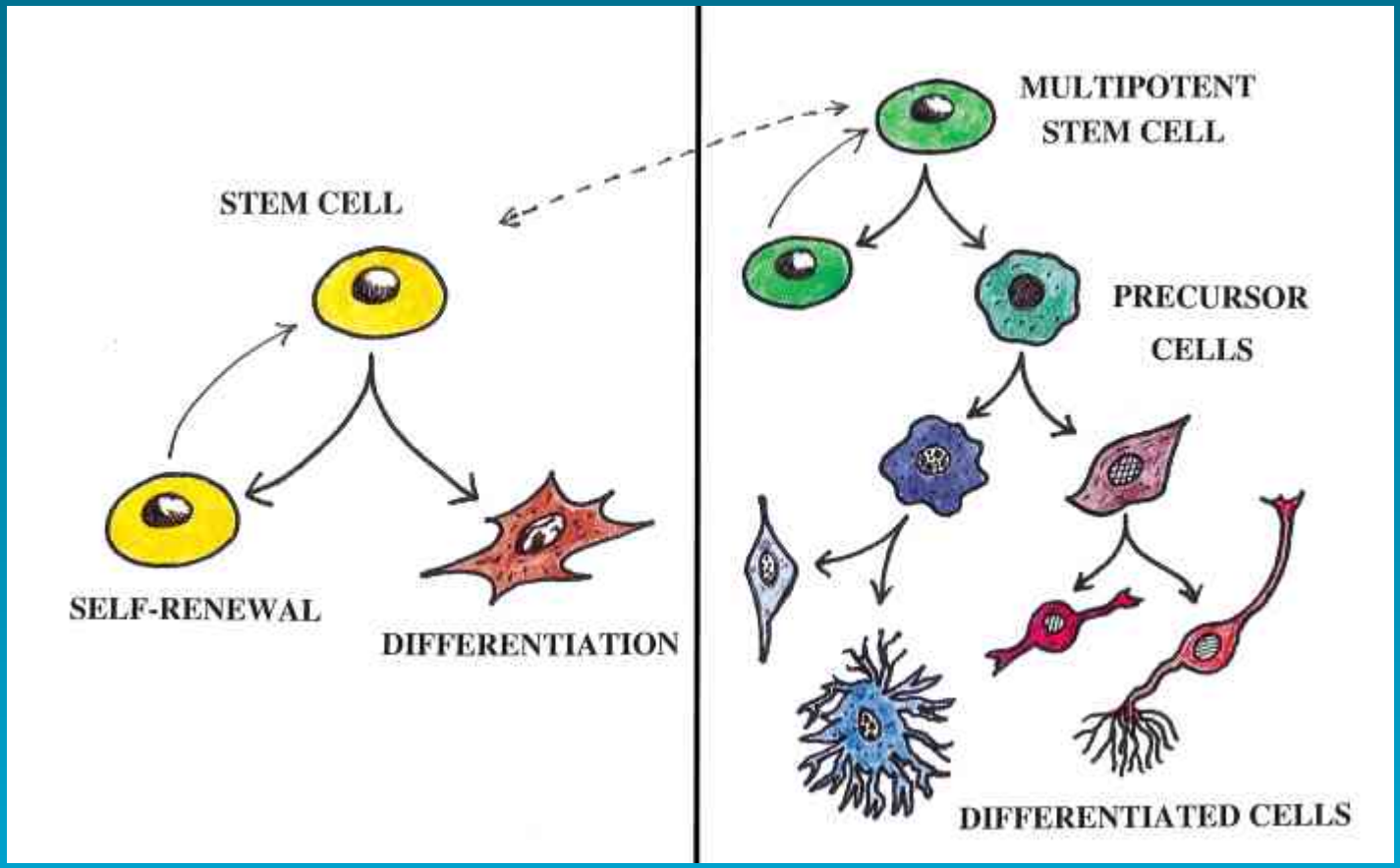


(A) and (B) high-power photomicrographs illustrating the robust immunoreactivity was seen within grafted neurons for VMAT2. (D) spare immunoreactivity was seen within grafted neurons stained for DAT. For the most part, grafted neurons displayed robust However, some melanin-containing grafted neurons failed to express TH (arrows). Scale bar in G represents the following magnifi- m for A and C; 320 μm for E; 25 μm for B, D, F, and G.



. Low- and high-power photomicrographs through the transplant stained for (**A**,**B**) alpha-synuclein, (**D**,**E**) ubiquitin, and (**G**,**H**) thioflavin-S are morphologically indistinguishable from nigral neurons stained for (**C**) alphasynuclein, (**F**) ubiquitin, and (**I**) thioflavin-S in the host Scale bar in I represents the following magnifications: A, D = 160 μm; 5 μm for B, C, E, and F = 5 μm; G = 80 μm, and H, I = 12 μm.

Stem Cells


STEM CELL
SELF-RENEWAL
DIFFERENTIATION
MULTIPOTENT
STEM CELL
PRECURSOR
CELLS
DIFFERENTIATED CELLS

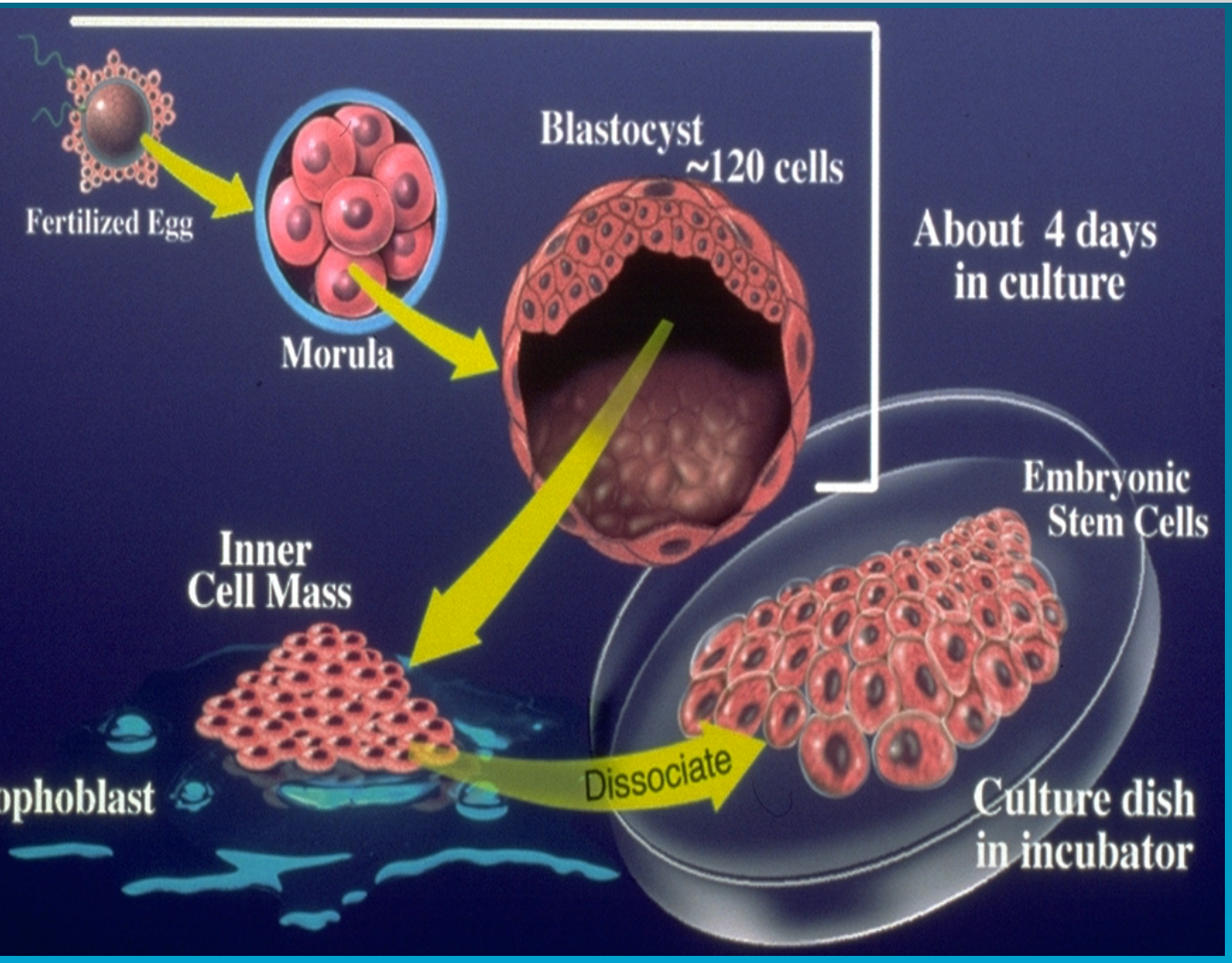
Science
1998;282(5391):1145-1147
REPORTS

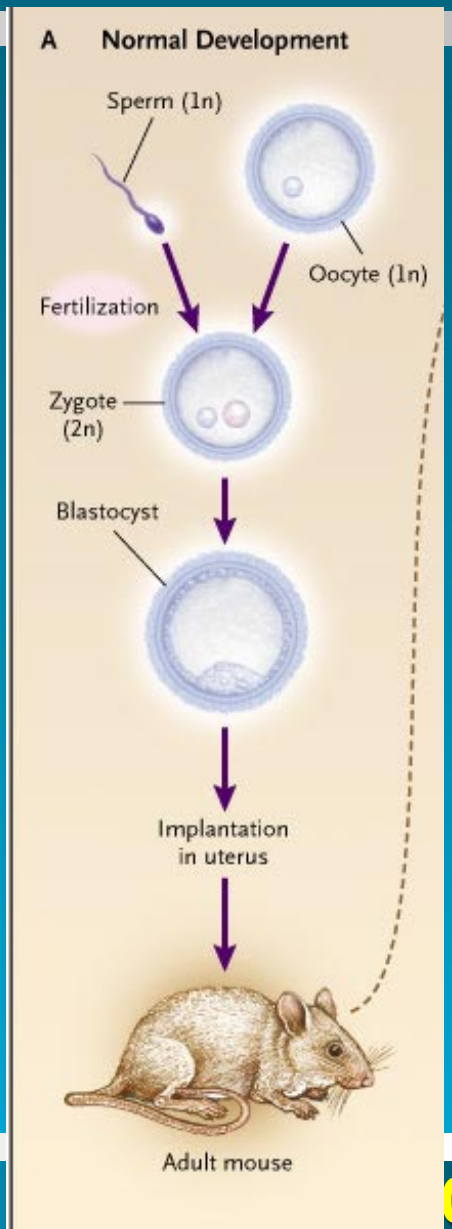
Embryonic Stem Cell Lines Derived from Human Blastocysts

James A. Thomson,* Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergiel, Vivienne S. Marshall, Jeffrey M. Jones

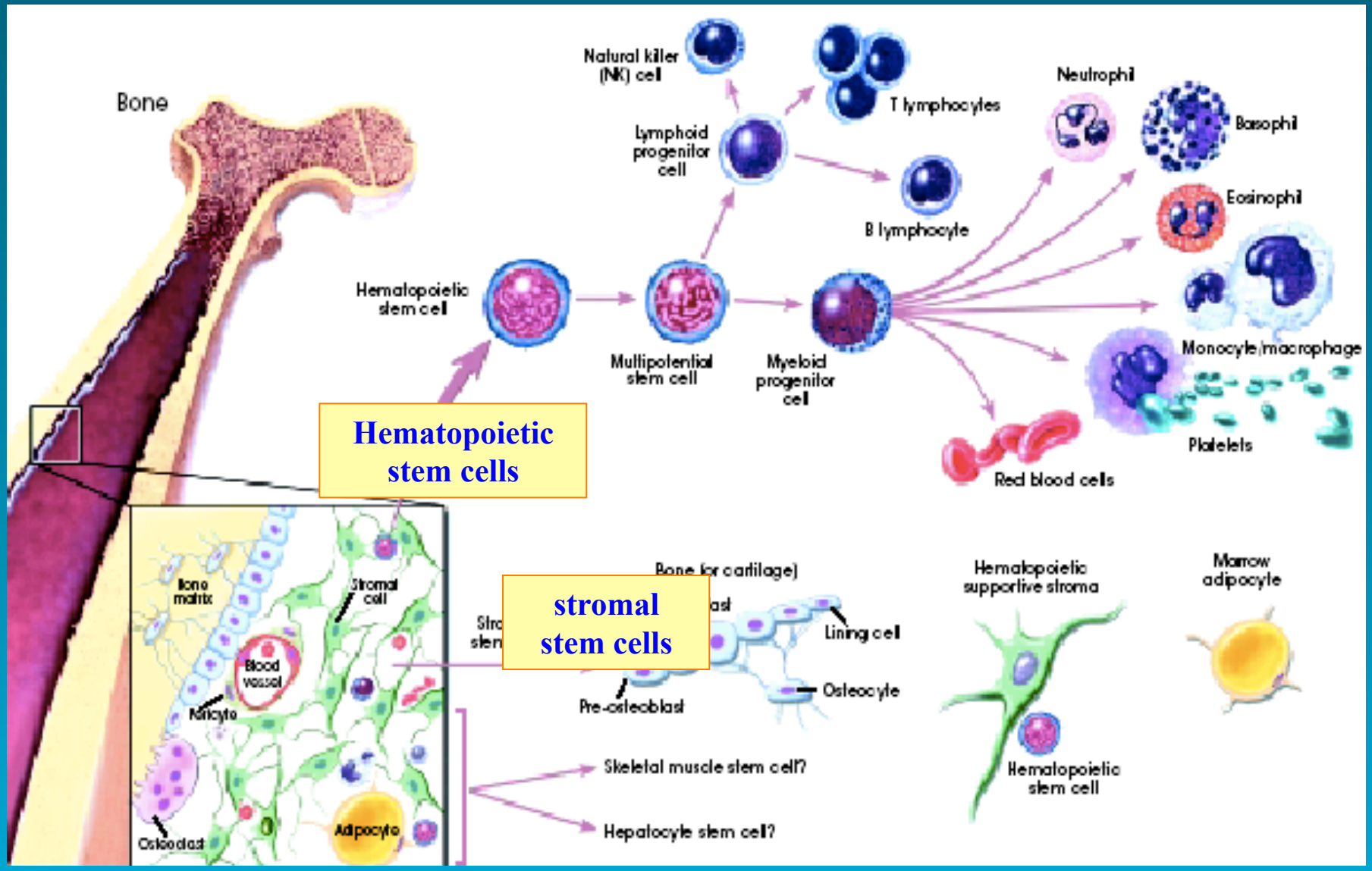
Human blastocyst-derived, pluripotent cell lines are described that have normal karyotypes, express high levels of telomerase activity, and express cell surface markers that characterize primate embryonic stem cells but do not characterize other early lineages. After undifferentiated proliferation in vitro for 4 to 5 months, these cells still maintained the developmental potential to form trophoblast and derivatives of all three embryonic germ layers, including gut epithelium (endoderm); cartilage, bone, smooth muscle, and striated muscle (mesoderm); and neural epithelium, embryonic ganglia, and stratified squamous epithelium (ectoderm). These cell lines should be useful in human developmental biology, drug discovery, and transplantation medicine.

Embryonic stem cells





Bone marrow cells



Mesenchymal stem cells potential

STEM CELLS AND DEVELOPMENT 15:141–164 (2006)

Original Research Report

Human Mesenchymal Stem Cells Express Neural Genes, Suggesting a Neural Predisposition

NETTA R. BLONDHEIM,[1,3] YOSSEF S. LEVY,[1,3] TALI BEN-ZUR,[1] ALEX BURSHTEIN,[1] TIRZA CHERLOW,[1] INNA KAN,[1] RAN BARZILAI,[1] MERAV BAHAT-STROMZA,[1] YAEL BARHUM,[1] SHLOMO BULVIK,[2] ELDAD MELAMED,[1] and DANIEL OFFEN[1]