

# Parkinsonism

(plus little intro to basal ganglia physiology)

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Médecin adjoint

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Neurology

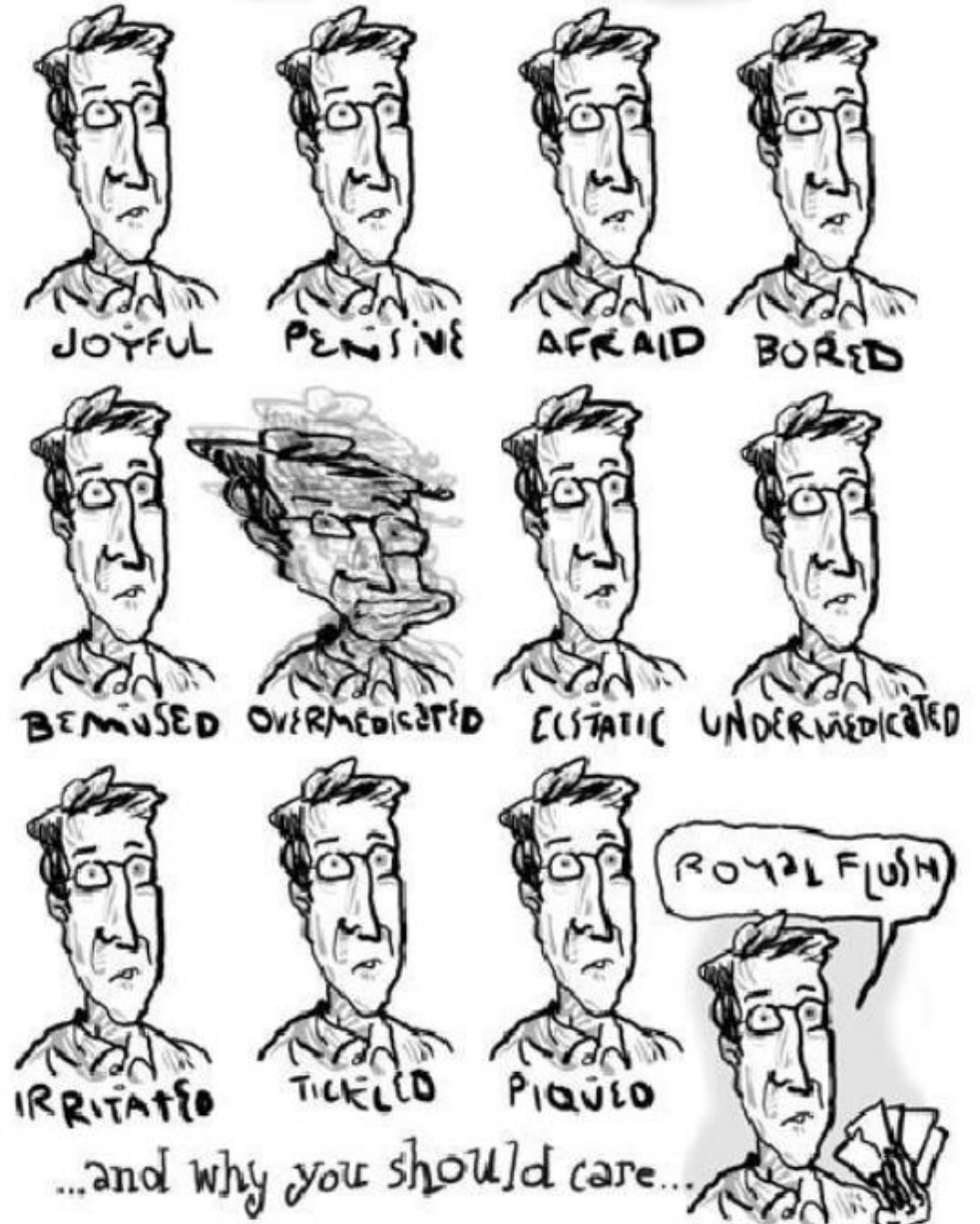


*Unil*

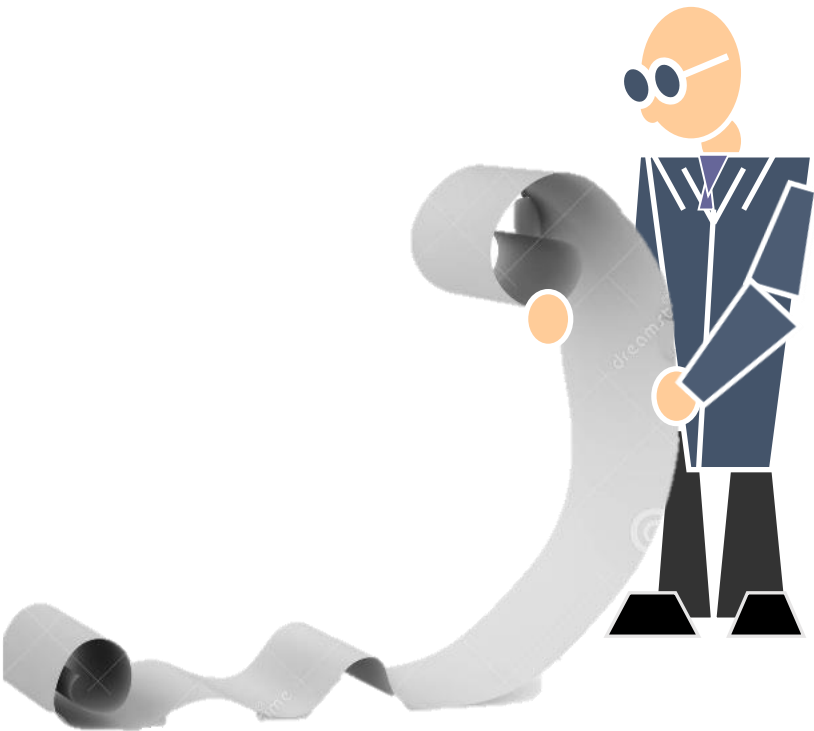
UNIL | Université de Lausanne  
Faculté de biologie  
et de médecine  
École de médecine

Cours EPFL – November 7<sup>th</sup>, 2025

POCKET GUIDE to DECODING  
THE PARKINSONIAN FACE...



- Thank you to Dr Sean J. Udow
  - Winnipeg, Manitoba, Canada



# Movement disorders?

- Ancient greek: ***dyskinesia***
- Dyskinesia:
  - **Too much** movement: **hyperkinesia**
  - **Too few** movement: **hypokinesia**

# Movement Disorders Phenomenology

Hypokinetic



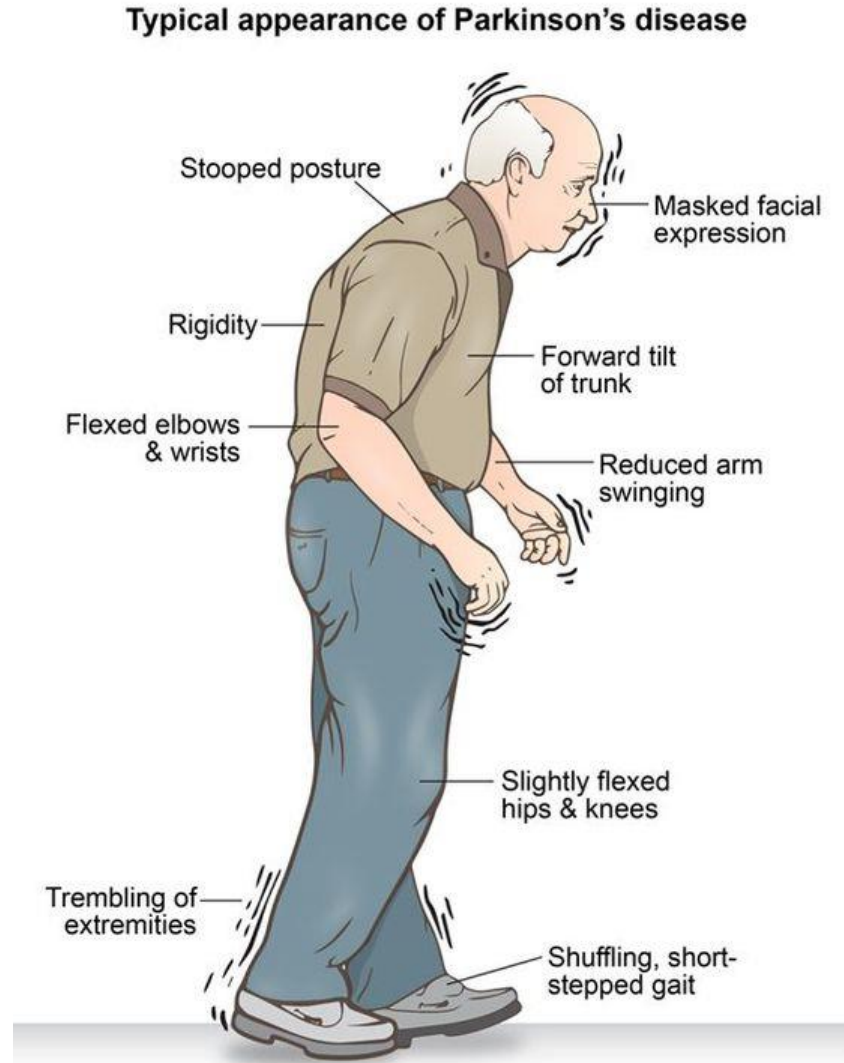
“Parkinsonism”

Hyperkinetic



# Too few movement: hypokinesia

- parkinsonism



# Too much movement: hyperkinesia

- ataxia
- dystonia
- tremor
- chorea
  - ballism
  - athetosis
- Myoclonus
  
- (Tics)
- (Stereotopies)
- (Functional mov disorders)



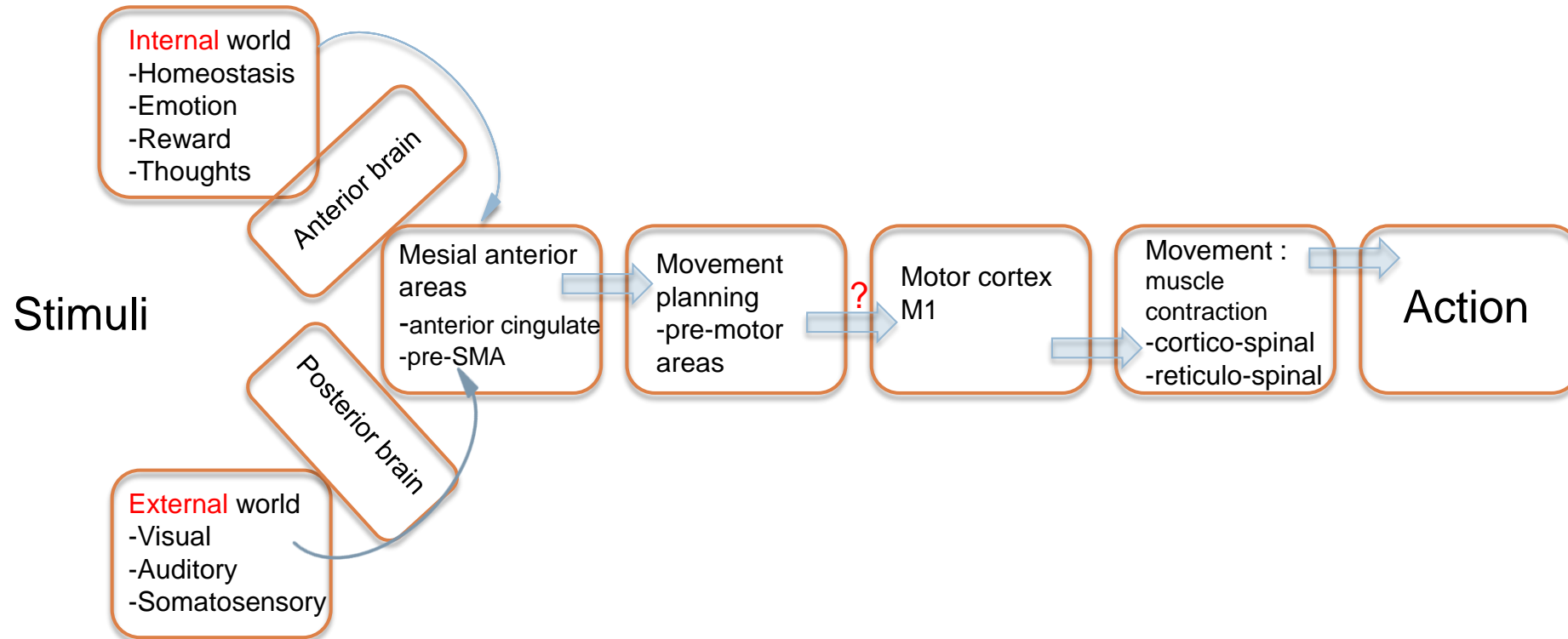
# List of Mov Dis Phenomenologies

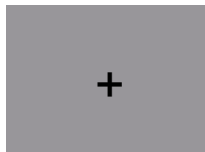
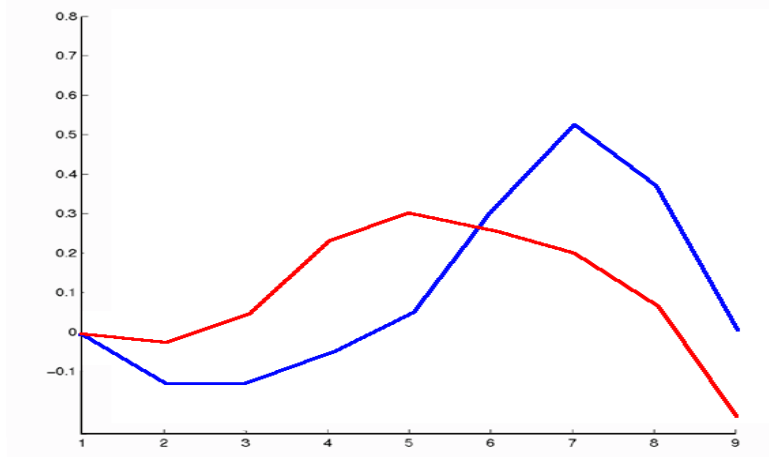
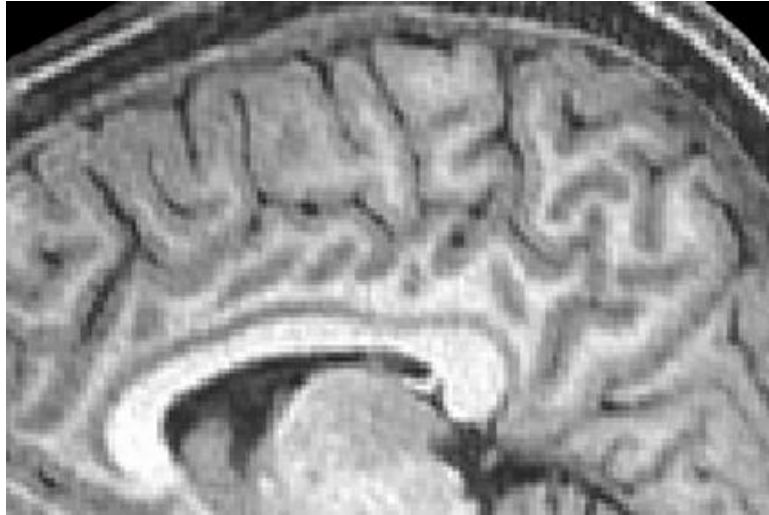
		Phenomenon	Definition
<b>Involuntary</b> (not distractible)	<b>hypokinetic</b>	parkinsonism	<b>Akinesia</b> +/- rigidity or rest tremor
		ataxia	Literally " <i>without order</i> ": <b>loss</b> of full <b>control</b> of bodily movements, which become clumsy and irregular due to decreased coordination
<b>Unvoluntary</b> (distractible)	<b>hyperkinetic</b>	dystonia	<b>sustained</b> muscle contractions, frequently causing twisting and repetitive movements or <b>abnormal postures</b>
		tremor	<b>Rhythmic oscillation</b> around an <b>axis</b> /joint
		Chorea (ballism, athetosis)	brief, abrupt, irregular, <b>unpredictable (random)</b> , <b>non-stereotyped</b> movements
		Myoclonus	Sudden, <b>brief, shock-like</b> involuntary movement caused by muscular contraction or inhibition
		Myorhythmia (rhythmic myoclonus)	Repetitive, <b>semirhythmic</b> , jerky or oscillatory, slow frequency (1-4 Hz) rapid movement, at rest and <b>very mildly modulated by actions</b>
		Tics	Spontaneous, repetitive, involuntary movements, <b>stereotyped</b> , motor or vocal, simple or complex, <b>preceded by a sensation</b> or urge
		Stereotypies	a <b>non-goal-directed</b> movement pattern that is repeated <b>continuously for a period of time</b> in the same form and on multiple occasions,
		Functional Mov Dis	abnormal movements <b>incongruent</b> with a known neurologic cause

# BEHAVIOUR

8

- Range of **action** made by organisms
- Response of the organism to various **stimuli**



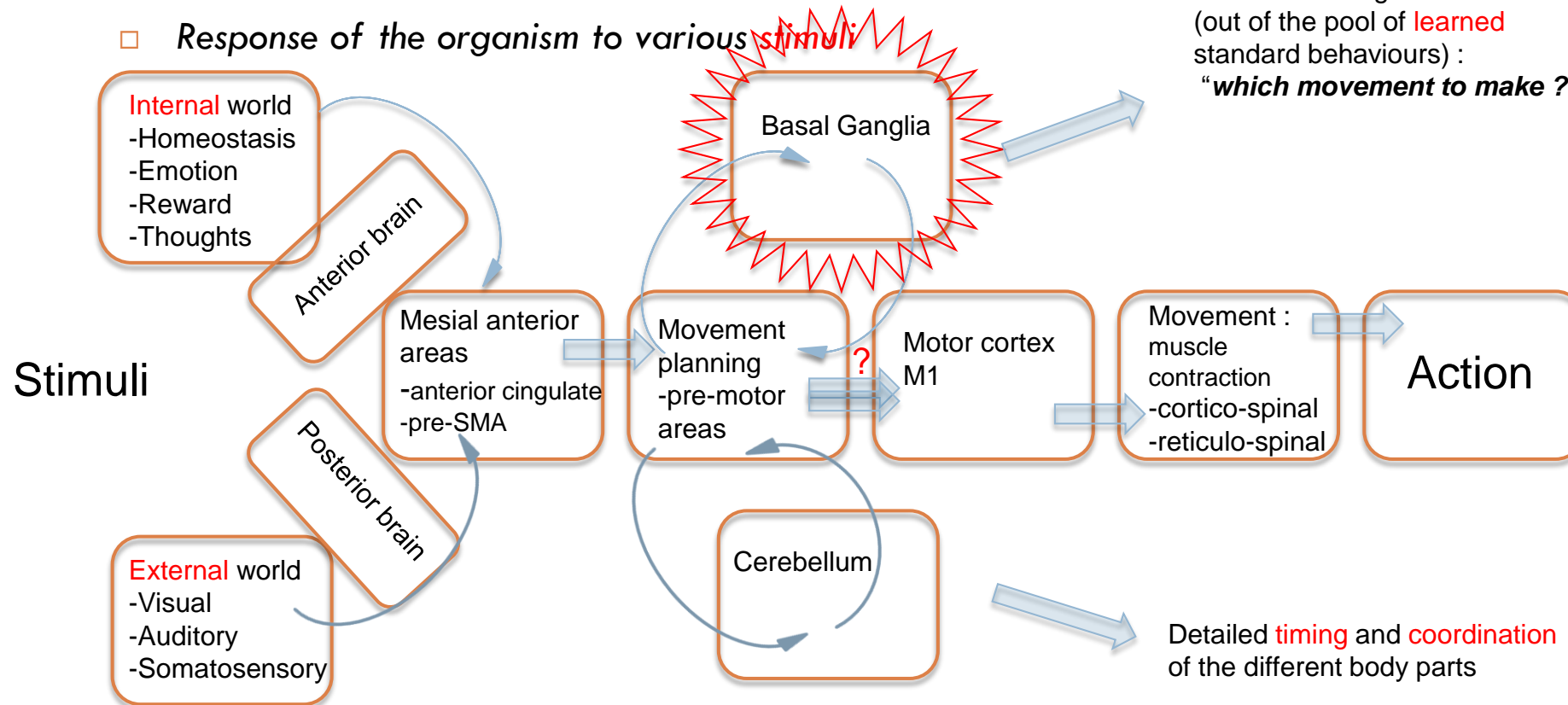


# BEHAVIOUR

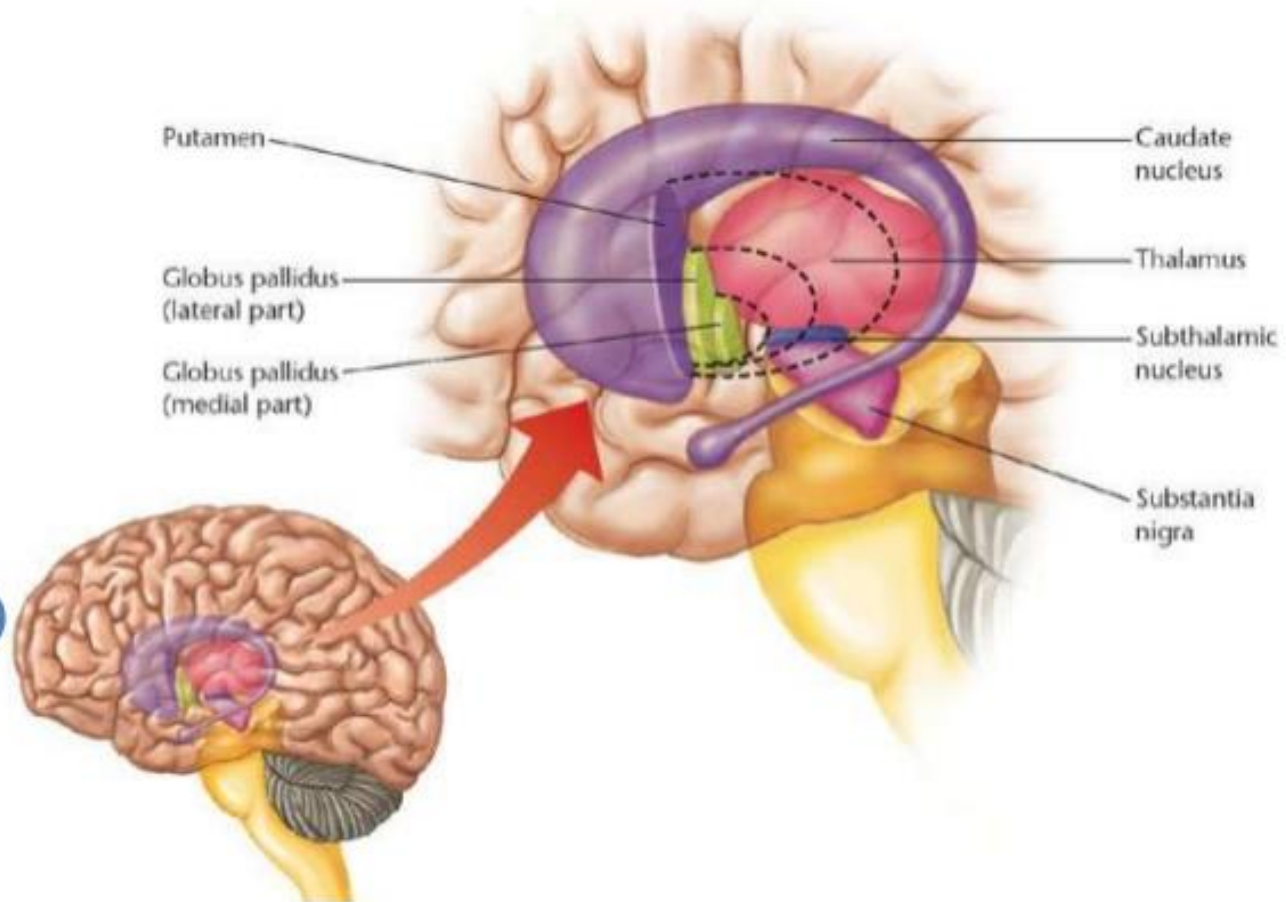
10

- Range of **action** made by organisms
- Response of the organism to various **stimuli**

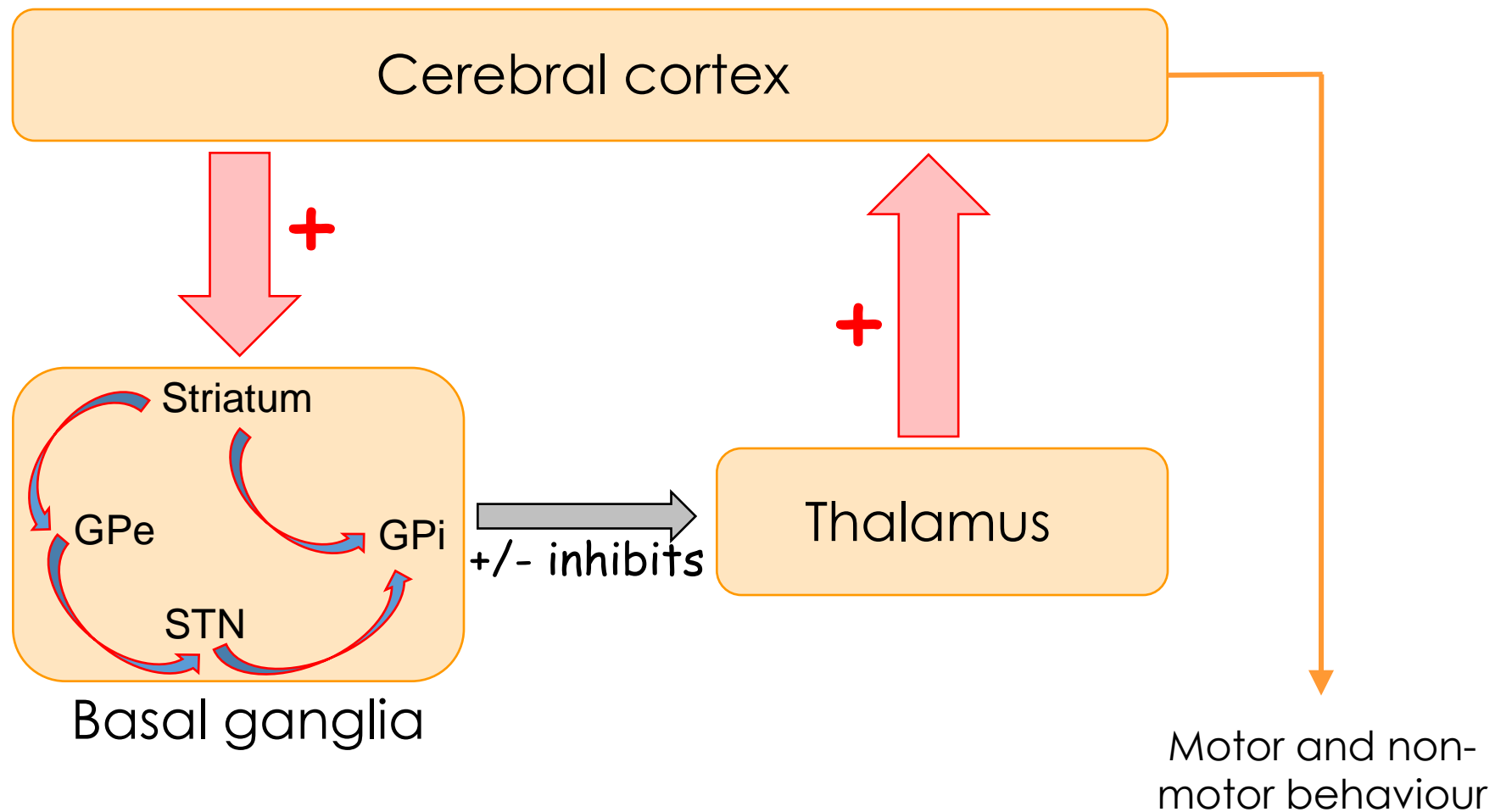
-Appropriate **selection** of behavioural fragments (out of the pool of **learned** standard behaviours) :  
“**which movement to make ?**”



# BASAL GANGLIA



# The cortico-BG-thalamo-cortical loop





# The car metaphor

Hyperdirect &  
indirect pathways  
are  
**the brake**

inhibition of the  
movement

= inhibition of  
unwanted  
behavioural  
outputs

Direct pathway  
is **the  
accelerator**

selection of the  
movement

= selection of  
desired  
behavioural  
outputs

# Dopamine : favors movement

17

- 1. hyperdirect
  - ▣ No action of Dopamine
  
- 2. direct
  - ▣ Dopamine favors the direct pathway, hence favors movement
  
- 3. indirect
  - ▣ Dopamine inhibits the indirect pathway, hence favors movement

# MPG: Motor pattern generators

18

## □ Introduction to the concept of “Motor pattern generators”

Example of a **learned** motor pattern

Writing using muscles from :  
A) The hand,  
B) The forearm,  
C) The arm/shoulder.

Parkinson's Disease Clinic  
King's College Hospital  
A

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Parkinson's Disease Clinic  
King's College Hospital  
B

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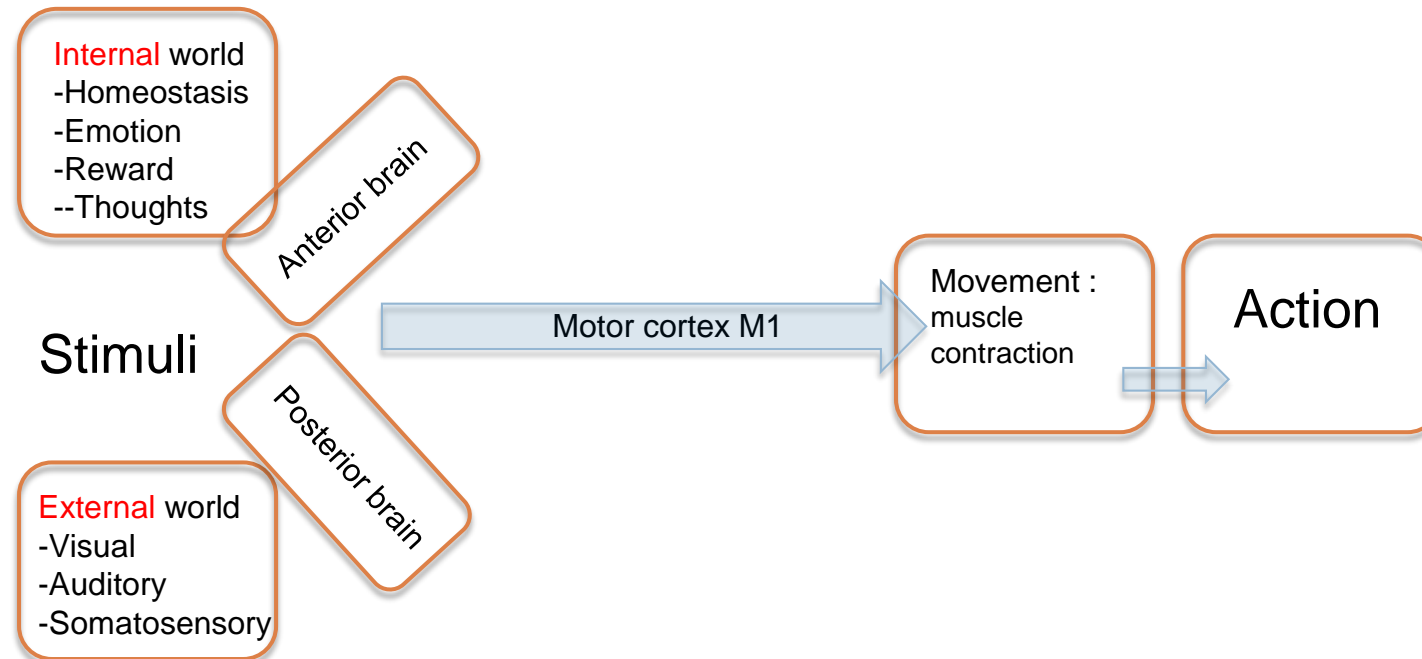
Parkinson's Disease Clinic  
King's College Hospital  
C

Marsden 1982

# Selection of a MPG

19

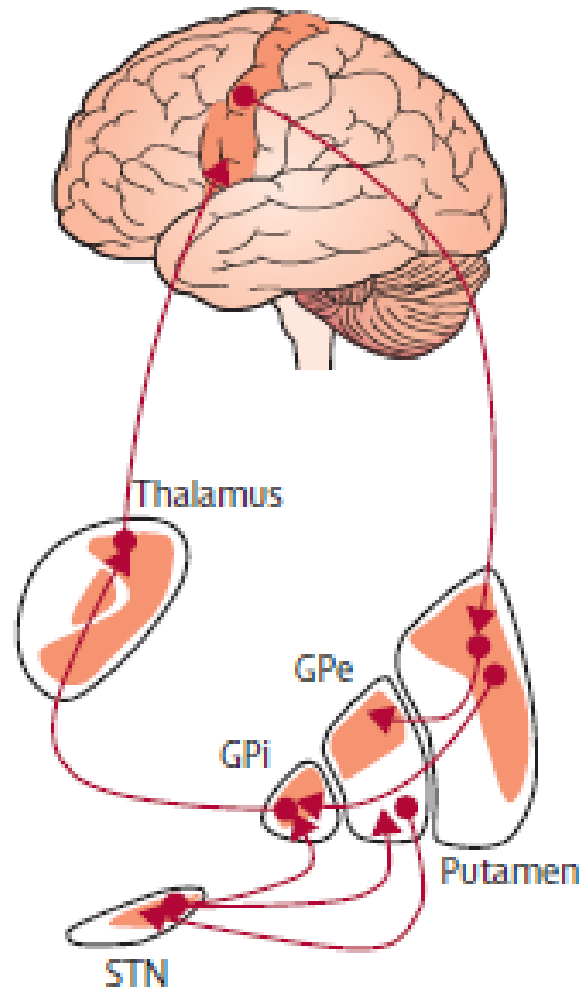
- Concept of “Multiple parallel-processing sensory, cognitive and affective systems”



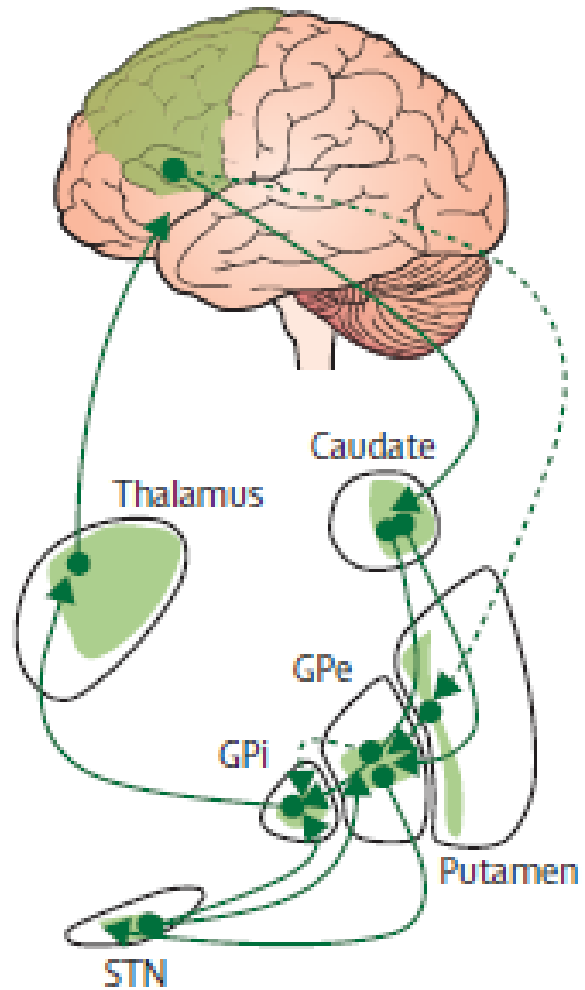
- Simultaneously seek access to limited attentional and motor resources : there is only **one** single common effector : **an action** !
- Need for **selection** of a MPG ! **This is the role of the basal ganglia !!!**

# Parallel, functionally segregated BG-thalamo-cortical loops

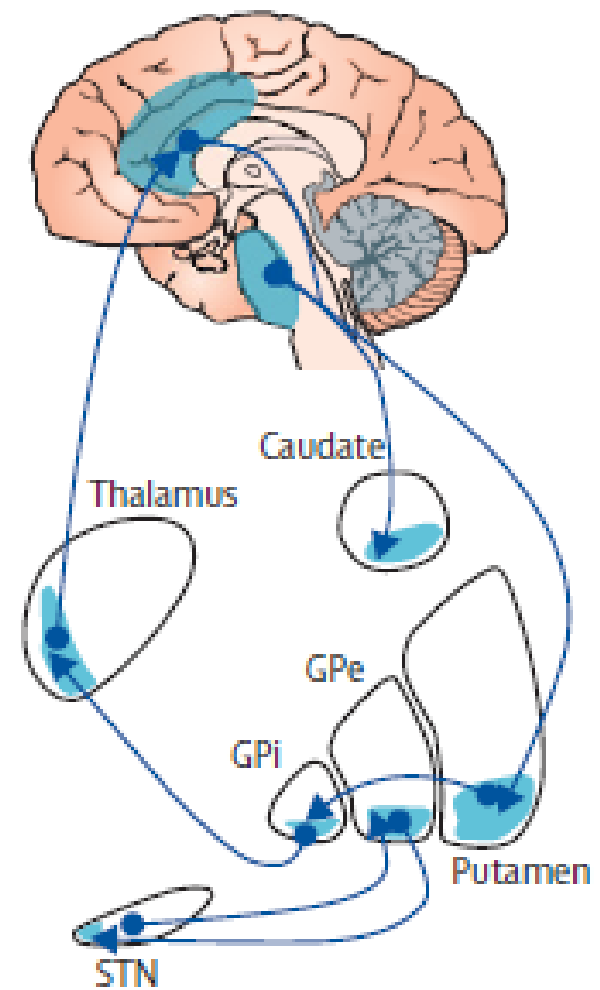
Motor circuit



Associative circuit



Limbic circuit



# Missing slides

21

- From «conscious» goal-directed movements to the creation of habits!
  - ▣ Automatism
    - Limbic then cognitive then sensori-motor
  
- Interaction of the different parallel loops
  - ▣ Via dopamine signaling
  - ▣ To create the habit

# What have I told you ?

22

- **Behaviour** is the range of **actions** made in **response** to various stimuli in a precise context
- **direct** and **indirect** pathways
  - Direct : **promoting** movement
  - Indirect : **suppressing** undesired motor programs
- Dopamine : **modulation** of the **direct** and **indirect** pathways
- There are many different **parallel**, functionally segregated, BG-thalamo-cortical loops
  - Limbic
  - Associative
  - Motor
- These parallel and functionally segregated loops **interact** with each others

# Conclusion : roles of the BG

23

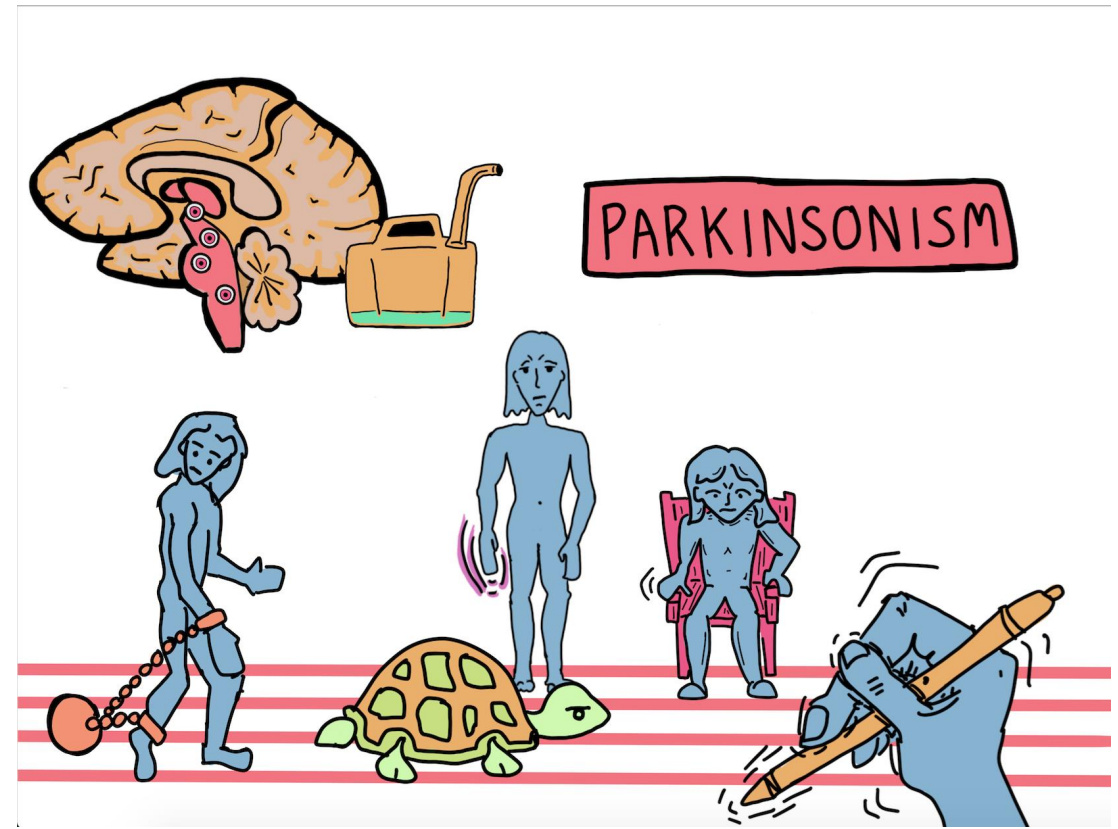
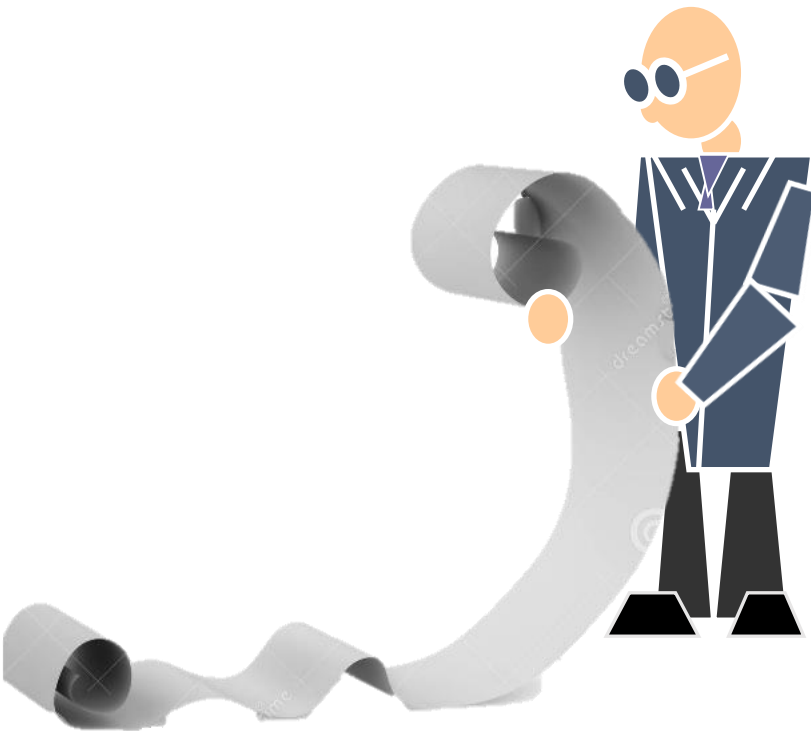
- The basal ganglia are responsible for the **automatic** execution of **learned *motor, cognitive and emotional*** plans
- The BG assist the (pre-frontal) cortex in **selecting** the most appropriate behavioural output (motor, executive, emotional) in a particular context
  - ▣ The “**stop**” component of their function being as important as the “**go**” component: suppression of unwanted motor/behavioral plans

# Today's Learning Objectives

- Hypokinesia
  - Parkinsonism

## • Parkinson's disease

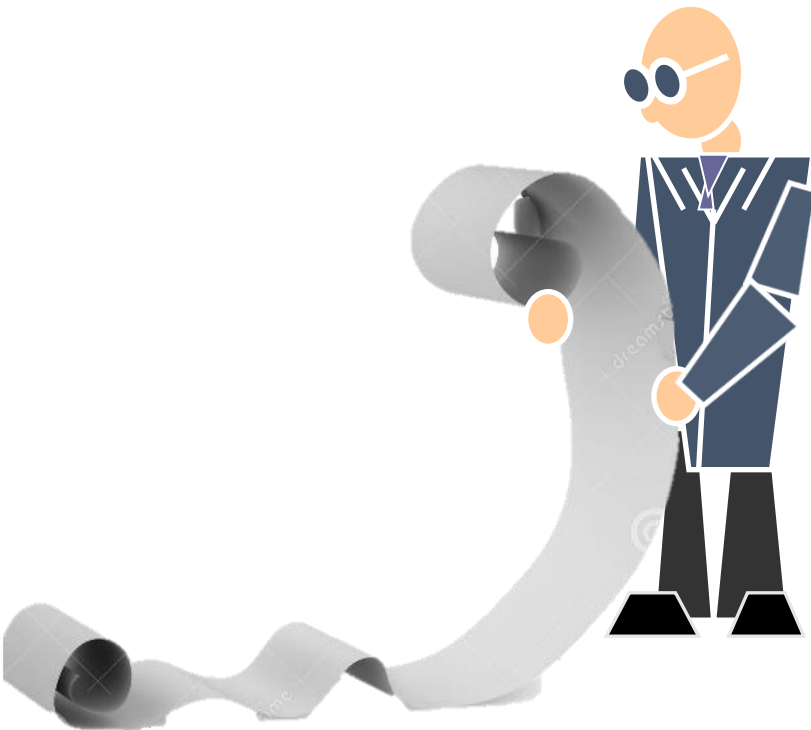
- Atypical parkinsonisms
- Secondary parkinsonisms
- Zebras...



# Learning Objectives

- **Parkinson's disease**

- The syndrome
- Epidemiology
- Etiology
- Pathophysiology
  - Substantia nigra compacta - neuronal loss
- Clinical signs & symptoms
- Treatment
  - Dopamine & other drugs
  - Motor fluctuations
  - Advanced therapies
    - Deep brain stimulation (DBS) = stimulation cérébrale profonde
- Non-motor symptoms



# Parkinsonism

- Association of **bradykinesia** and
  - **Rigidity** and/or
  - Rest **tremor**
  - +/- Postural instability
- Parkinsonism = parkinsonian syndrome
  - A syndrome is a set of symptoms and signs
- Syndromes have a DDx (differential diagnosis)

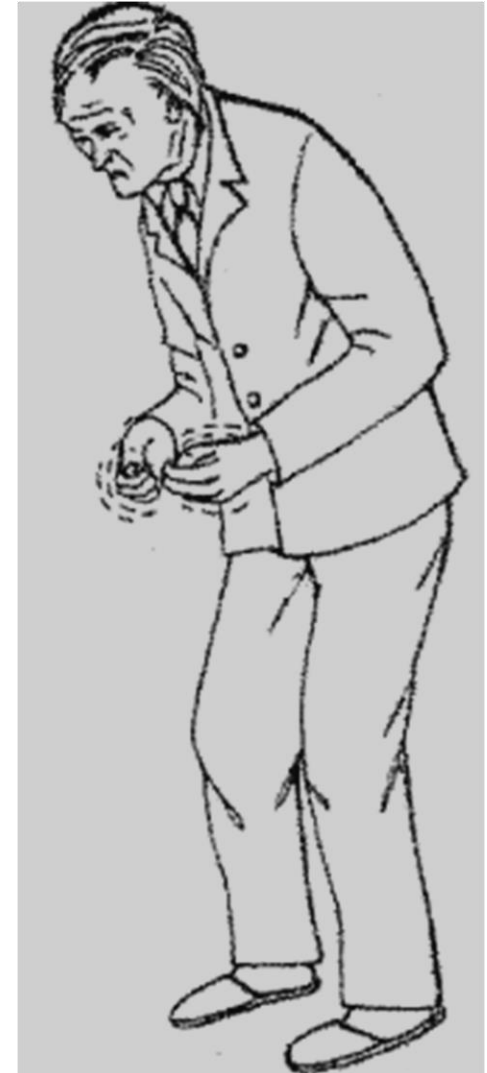


# Parkinsonism (PKism) : the “5-2-100 rule”

- DDX: Differential diagnosis
  - **Parkinson’s disease (PD)**
  - atypical parkinsonisms
    - Multiple System Atrophy MSA
    - Progressive Supranuclear Palsy PSP
    - Corticobasal Degeneration CBD
    - Lewy Body Dementia LBD
- **Two** main **secondary** parkinsonisms
  - **Drug-induced** (neuroleptics)
  - Vascular parkinsonism
- Zebras... (more than 100, including genetic degenerative & genetic metabolic causes, or secondary...)
  - A lot of rare diseases, not primarily classified among the parkinsonisms, **may present with parkinsonism**, among other symptoms, e.g.:
    - Huntington, Wilson, Brain Iron accumulations, familial brain calcifications, some genetic ataxias, metabolic diseases (Niemann-Pick type C), Normal pressure Hydrocephalus, toxic causes, infectious causes

*2 thirds of the cases*

*Five (main) degenerative parkinsonisms*



# Atypical Parkinsonian Syndromes = “Parkinson-plus”

- **Less likely to be levodopa responsive**
- **Progress faster, more severe, worse prognosis**
- **Additional clinical features**
  - Multiple System Atrophy
    - **Dysautonomia**, Ataxia and PKism
  - Progressive Supranuclear Palsy
    - Supranuclear **gaze** palsy, **falls**, axial PKism signs
  - Corticobasal Degeneration
    - **Apraxia**, dystonia, **unilateral** PKism, cortical sensory signs
  - Dementia with Lewy Bodies
    - **Dementia** +/- cognitive fluctuations, or PKism, or hallucinations

# Multiple System Atrophy



Parkinsonism

Stooped neck early

Autonomic failure

Hypotension

Incontinence

Impotence

Ataxia

Pyramidal involvement

Rather poor med response

# Vidéo MSA



2016 OFF-dopa  
Début maladie 2010 à 46 ans

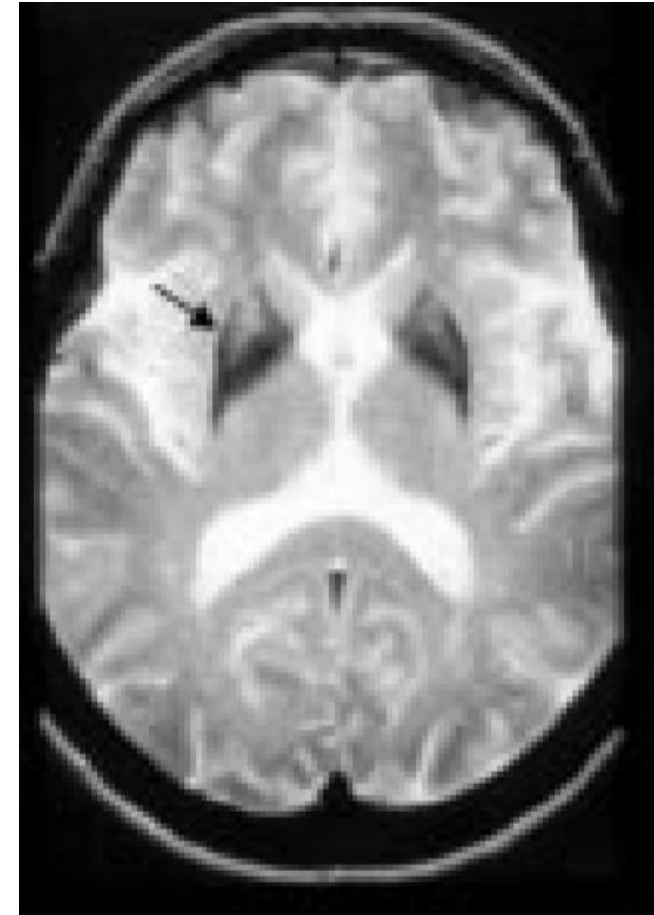
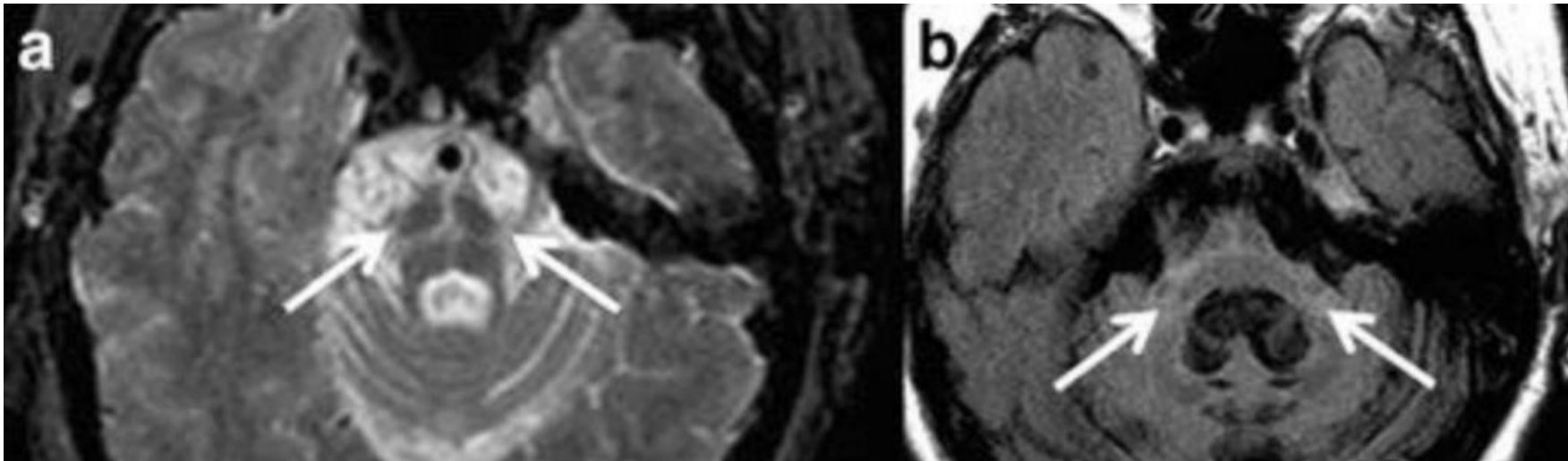
MSA: colored /discolored hands and feet:  
dysautonomia



# Brain imaging in MSA

- Parkinson's disease : fairly **normal**
- Atypical parkinsonisms : **abnormal**

**MSA:** MSA: **pontine** atrophy and **putaminal** T2-hypointensity



# Progressive Supranuclear Palsy



Wide open eyes

Neck rigidity

Poor Up & Down gaze

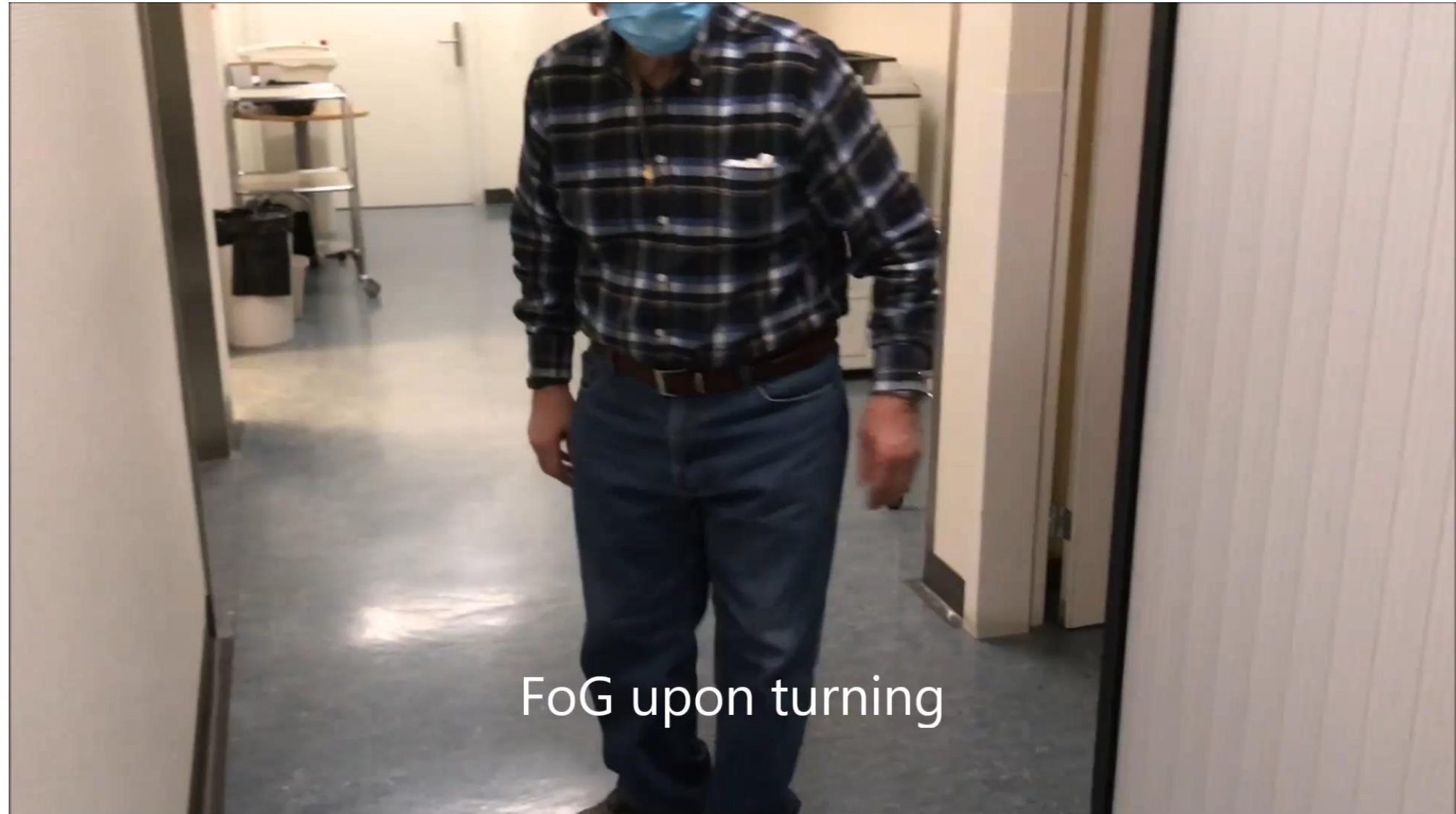
Falls within a year of Dx

Early pharyngeal dysfunction

Dementia early

Very poor med response

# Vidéo PSP



# Vidéo PSP : square wave jerks, supranuclear gaze palsy (that gets better after Oculo-cephalic reflex)

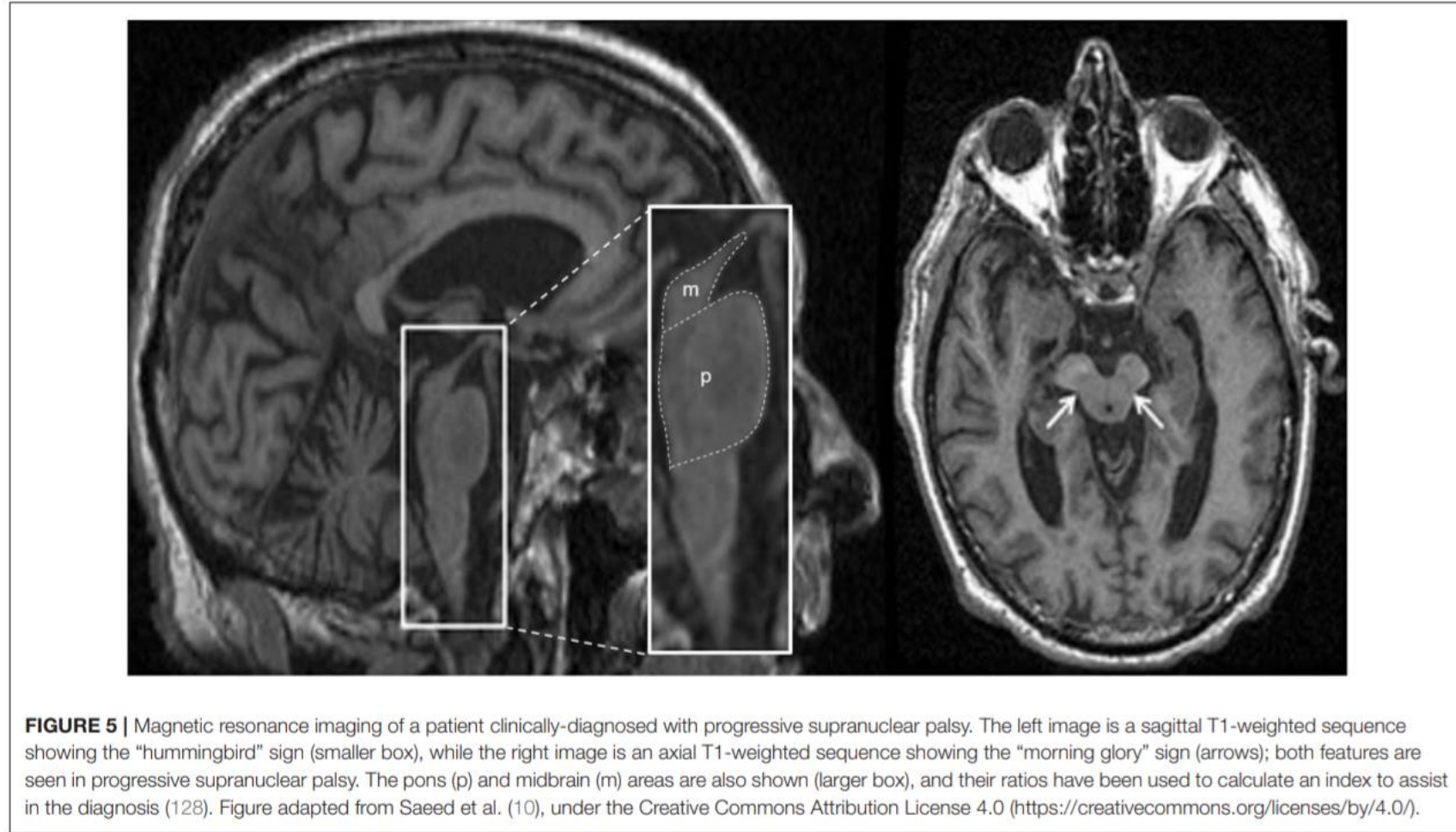


Macro square wave jerks

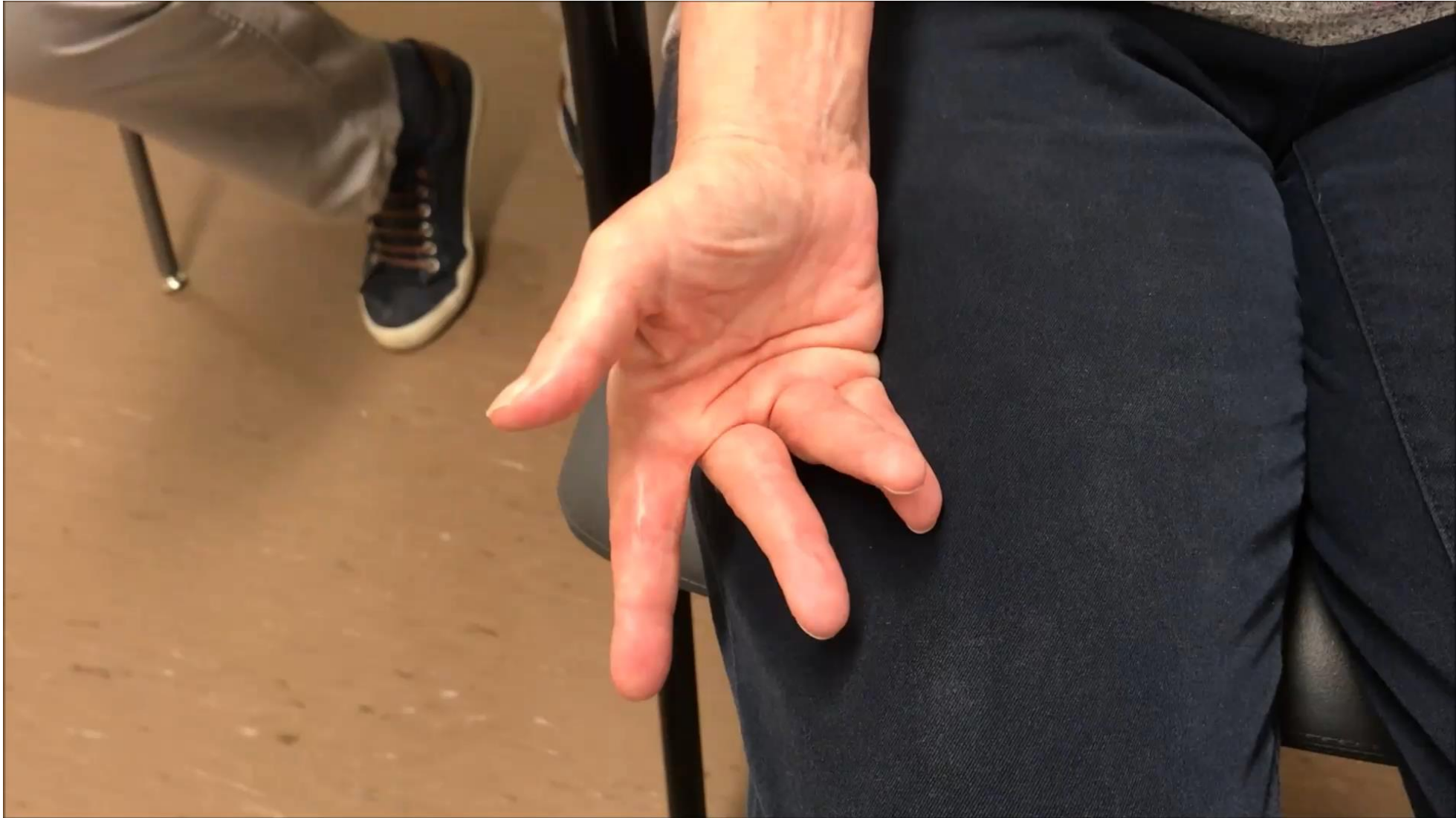
# Brain imaging in PSP

- Parkinson's disease : fairly **normal**
- Atypical parkinsonisms : **abnormal**

**PSP**: midbrain atrophy = colibri sign



# Vidéo CBD : major dystonia and parkinsonism (unilateral at first), ideomotor apraxia



## Panel 1 Secondary parkinsonism

### Infectious

Encephalitis lethargica and other viral infections (eg, AIDS, PML)  
Prion disease  
Neurosyphilis  
Toxoplasmosis

### Toxic

Carbon monoxide  
Cyanide  
Carbon disulphide  
MPTP  
Manganese  
Solvents

### Drug induced

Dopamine-receptor blockers  
Classic neuroleptics (eg, phenothiazines, butyrophenones)  
Atypical antipsychotics (eg, risperidone, olanzapine)  
Dopamine-depleting drugs (eg, tetrabenazine)  
Other drugs (eg, valproic acid, calcium channel blockers)

### Anti-vomiting drugs :

**metoclopramide**

### Brain tumours

Supratentorial and brainstem tumours  
Arteriovenous malformations

### Cranial trauma

Striatal variant of dementia pugilistica  
Chronic subdural haematoma  
Mid-brain trauma

### Vascular lesions

### Metabolic

Hypoxia  
Hypoparathyroidism  
Familial basal ganglia calcification  
Extrapontine myelinolysis  
Chronic liver failure  
Wilson's disease

### Miscellaneous

Huntington's disease  
SCA mutations  
FTDP-17  
Neuroacanthocytosis  
Dentatorubropallidal-luysian atrophy  
Normal pressure hydrocephalus  
Haemiatrophy-hemiparkinson syndrome  
Psychogenic

# Neuroleptic-Induced Movement Disorders



Oculogyric Crisis



Parkinsonism

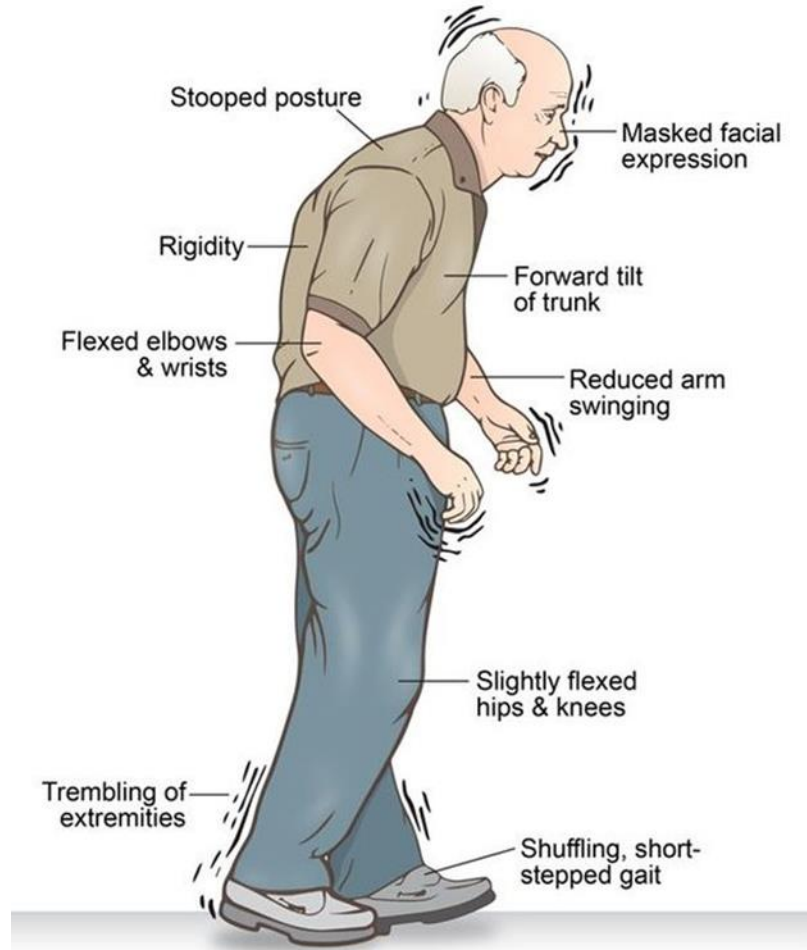


Tardive Dyskinesia

Tardive dystonia

# Parkinson Disease – Motor Symptoms

Typical appearance of Parkinson's disease



- **Bradykinesia, plus**
  - Rest tremor, and/or
  - Rigid hypertonia
- Hypomimia (masked facies)
- Micrographia
- Stooped posture
- Diminished arm swing
- Gait difficulty including freezing of gait
- Hypophonia (early), dysarthria (late)
- Balance issues & falls

# Parkinson's Disease (PD) - Epidemiology

- Second most common neurodegenerative disease (after Alzheimer's disease)
- More common in men than women
- Worldwide incidence estimates
  - 5 to >35 new cases per 100,000 individuals per year
- Rare before 50 years of age
  - But exists !!! We follow a dozen of young-onset PD patients in our clinic
  - Young-onset PD: almost always **genetic PD**
- Incidence increases 5-10 fold from the 6<sup>th</sup> to 9th decades
- Global prevalence 0.3% for all ages
  - But >3% in those >80 years of age

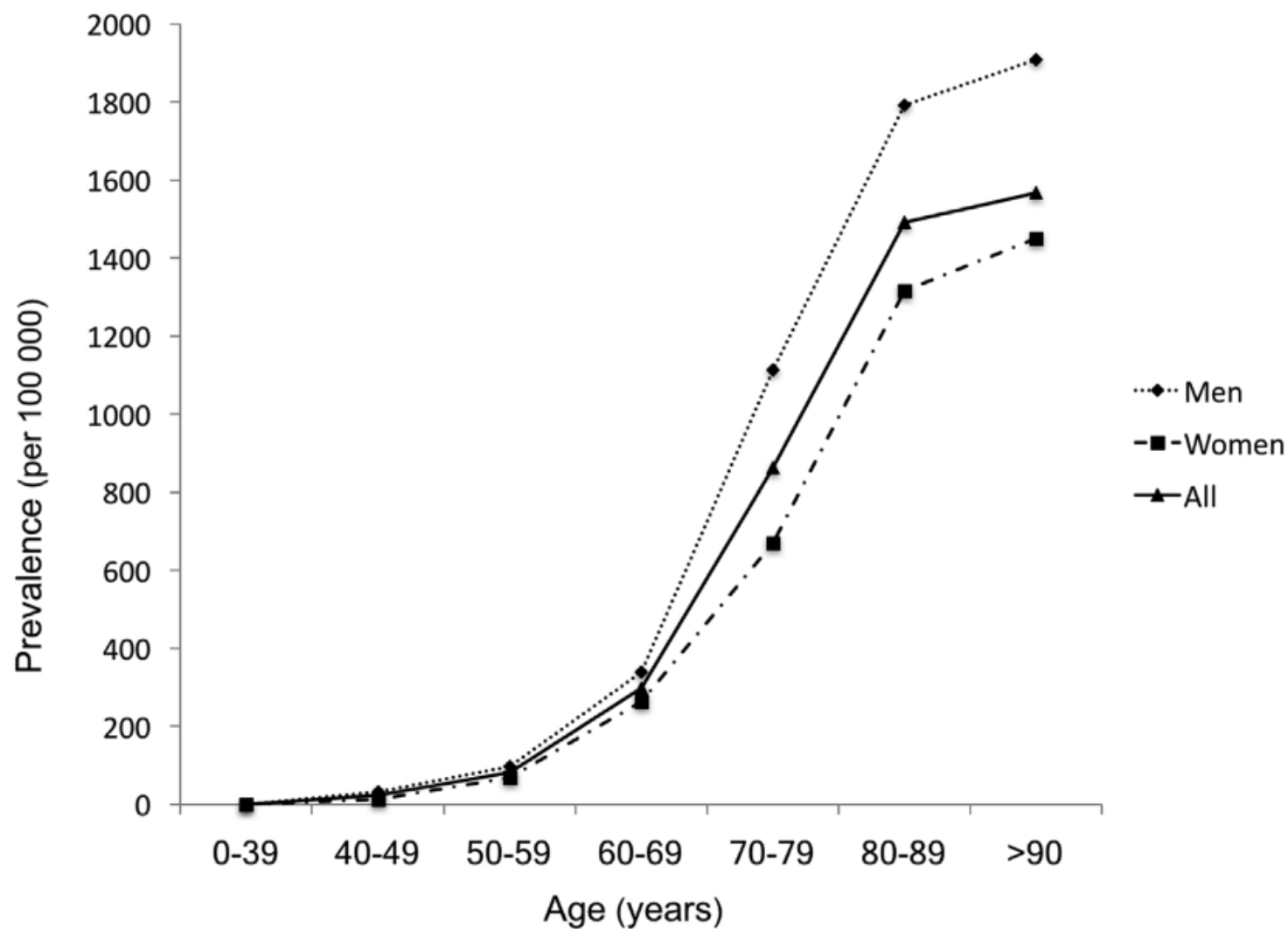
Vanessa Fleury

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Parkinson's disease	
0–39	0
40–49	17
50–59	50
60–69	138
70–79	275
80–89	268
≥90	64
All ages	812

# Descriptive epidemiology of parkinsonism in the Canton of Geneva, Switzerland

Vanessa Fleury <sup>a, d, \*</sup>, Pauline Brindel <sup>b</sup>, Nicolas Nicastro <sup>c</sup>, Pierre R. Burkhard <sup>a, d</sup>



**Fig. 2.** Age- and sex-specific prevalence per  $10^5$  of Parkinson's disease.

# PD in Geneva

## 0.17%

Vanessa Fleury

Study period: From 01.01.2003 to 31.12.2012  
 Population on the 31.12.2012: 470512  
 Prevalence date: 01.01.2013

Case finding

Hospital medical records

Private neurologists

Homes for the elderly

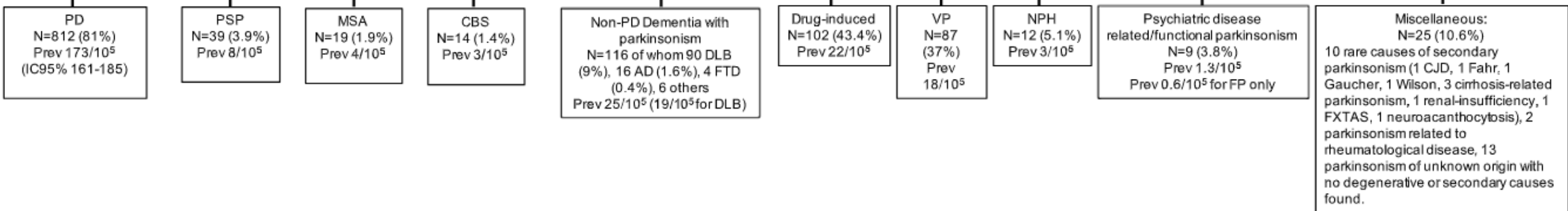
2312 patients with suspected parkinsonism

1077 patients excluded (830 deceased, 91 had left the canton at the prevalence date, 56 diagnosis made after the prevalence date, 34 coding errors, or 66 didn't meet criteria for parkinsonism after medical file review)

Parkinsonism  
N=1235

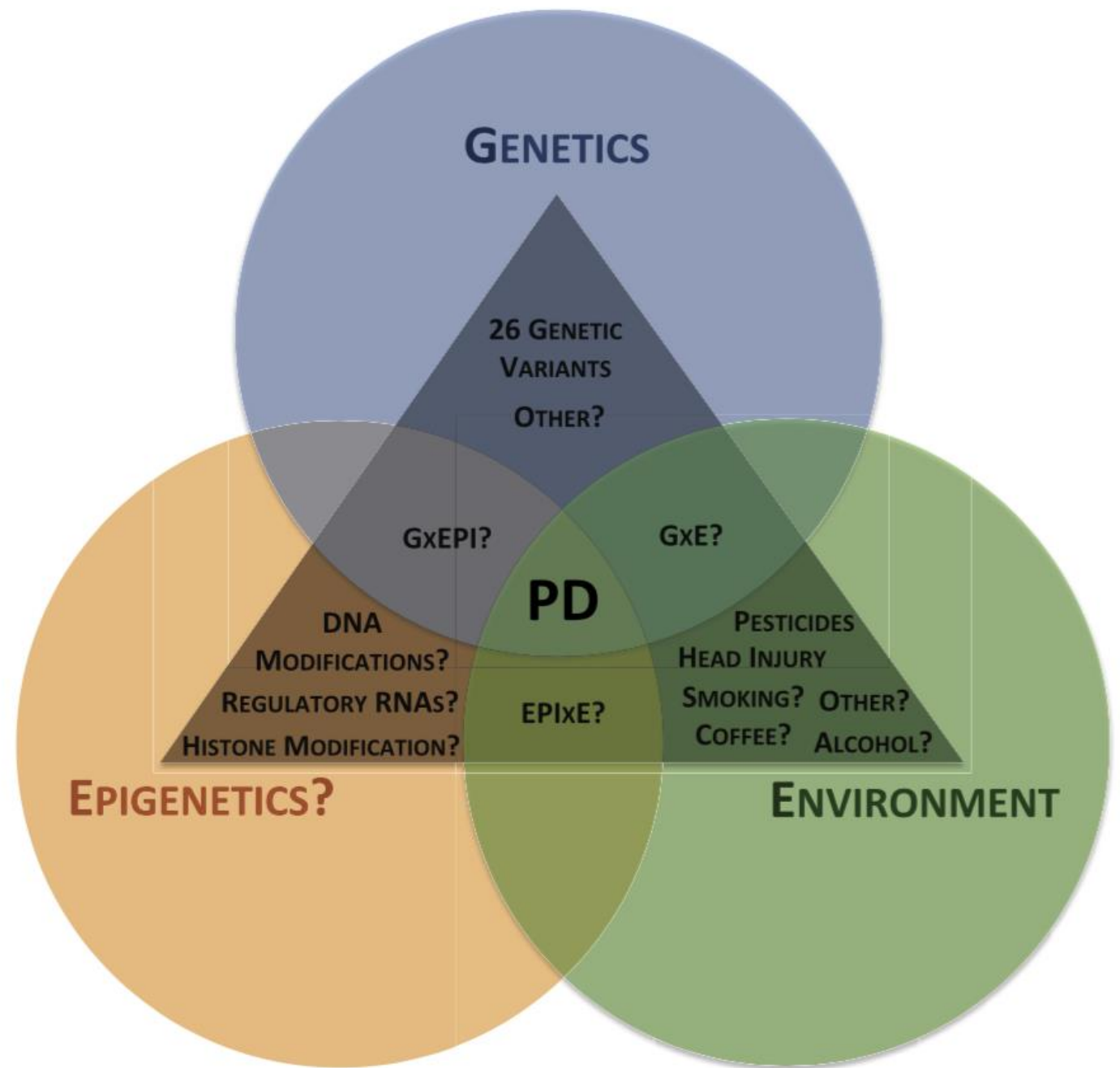
Degenerative parkinsonism  
N=1000 (81% of parkinsonism)  
Crude Prev=213/10<sup>5</sup> IC95%(200/10<sup>5</sup>-227/10<sup>5</sup>)

Non degenerative parkinsonism  
N=235 (19% of parkinsonism)  
Crude Prev=50/10<sup>5</sup> IC95%(43/10<sup>5</sup>-56/10<sup>5</sup>)



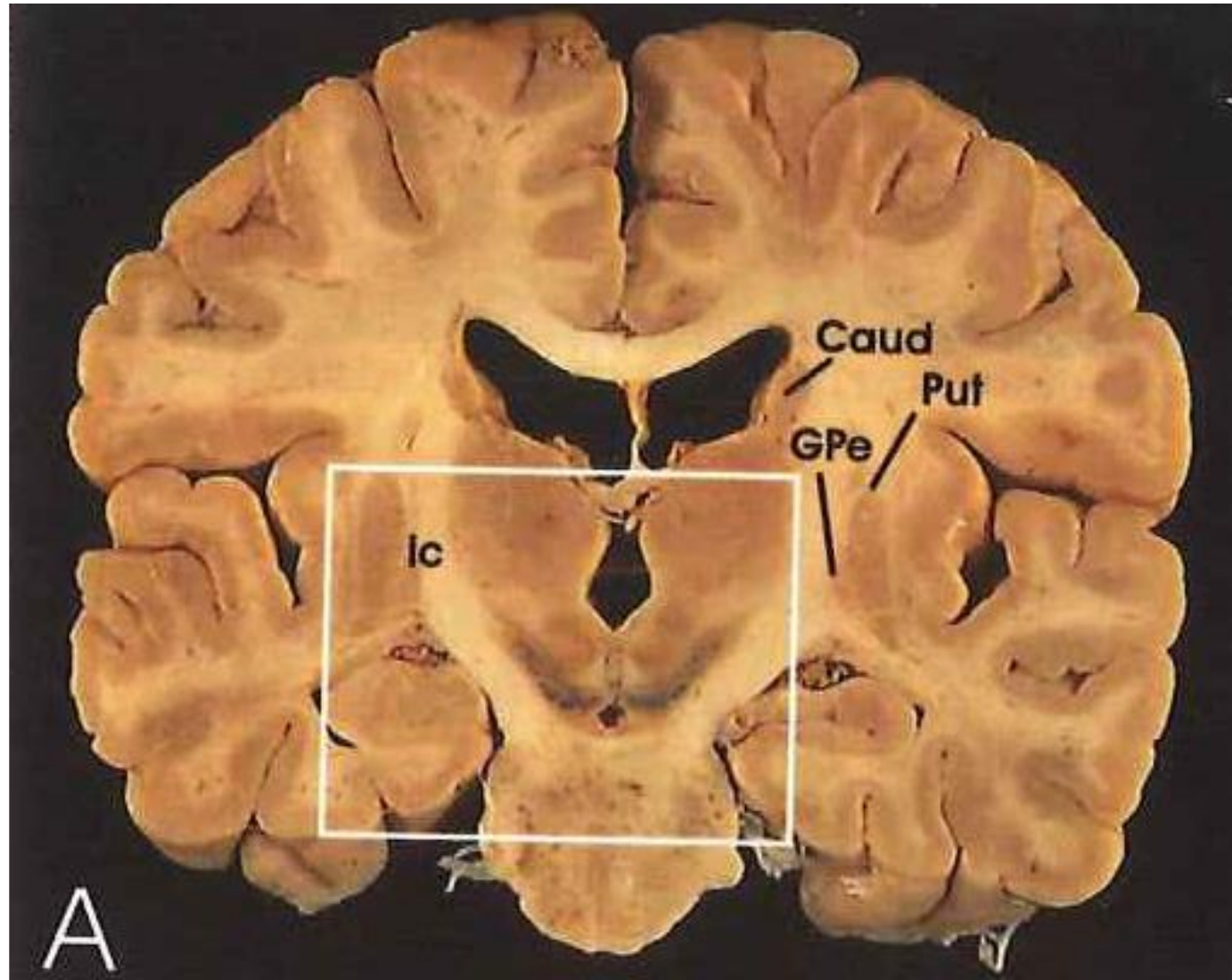
# Etiologies in PD

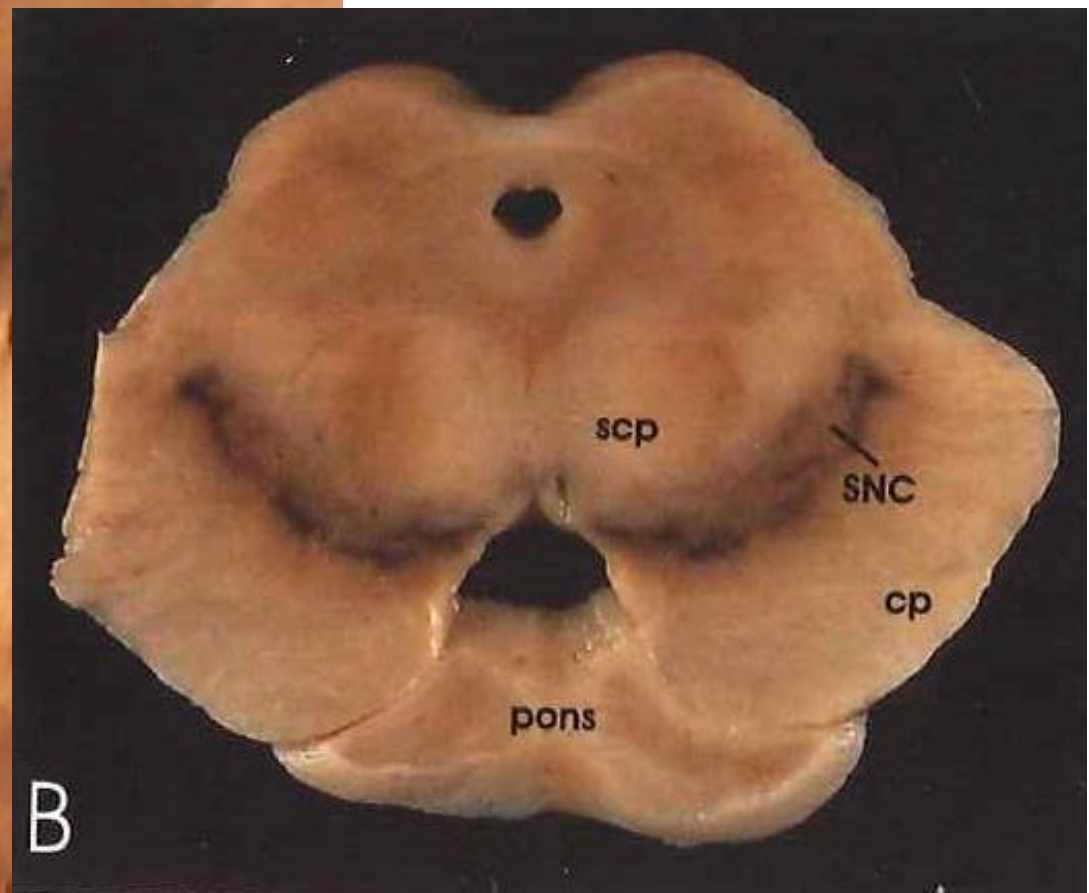
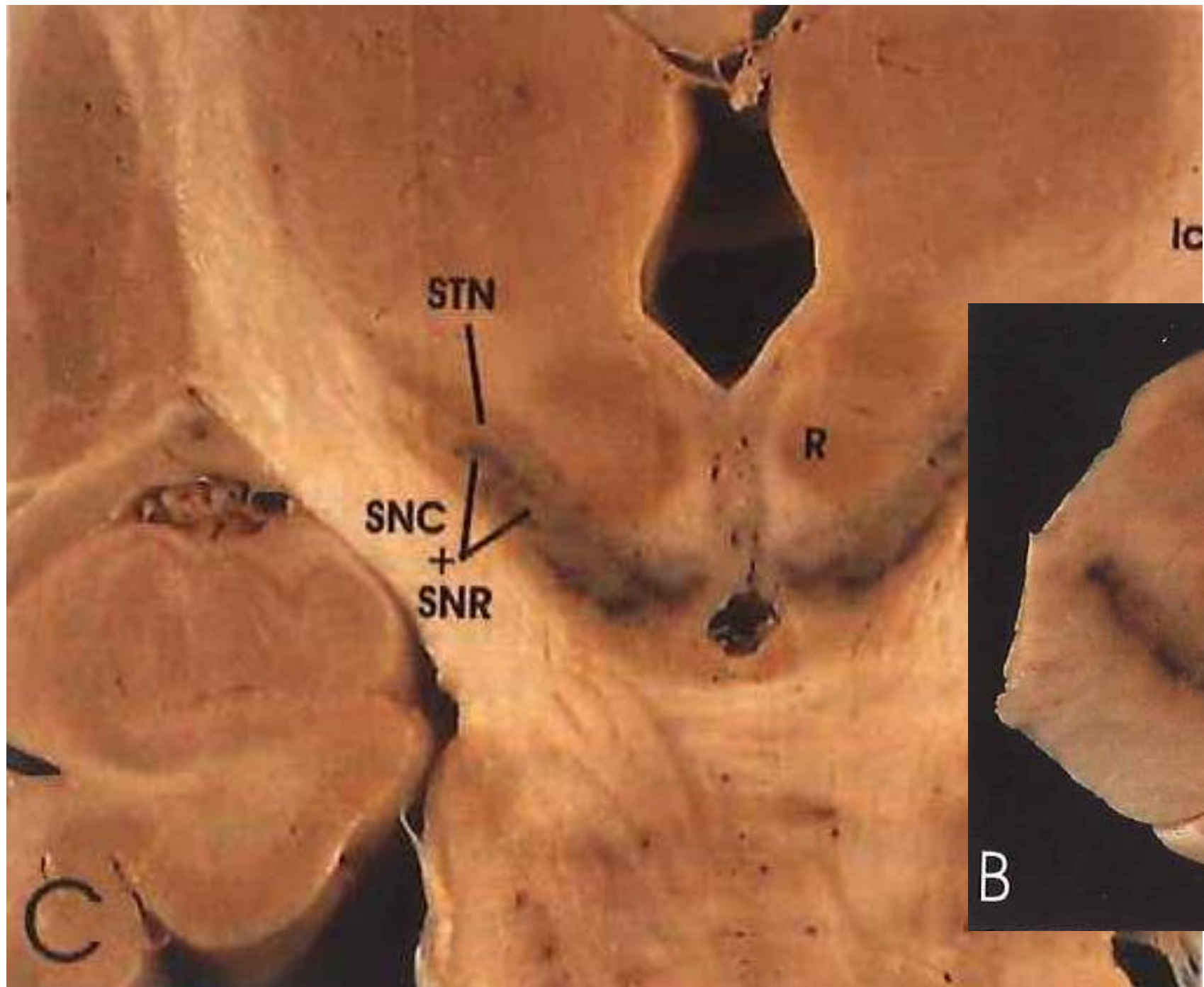
- Multifactorial
- **Mysterious**
- **Genetics:**
- Family history increases risk
- 15% have a family history
- 5-10% of cases are monogenetic
- >10% are monogenetic if 'young-onset' (<45 years)



# Pathophysiology of PD

## Substantia nigra





# PD = Neurodegenerative Disease

- Neuronal loss in the **substantia nigra Pars compacta (dopamine production)**
- **$\alpha$ -synuclein** aggregation forms Lewy bodies and lewy neurites
- Extra-nigral brain areas become affected over time

Introduction to non-motor symptoms

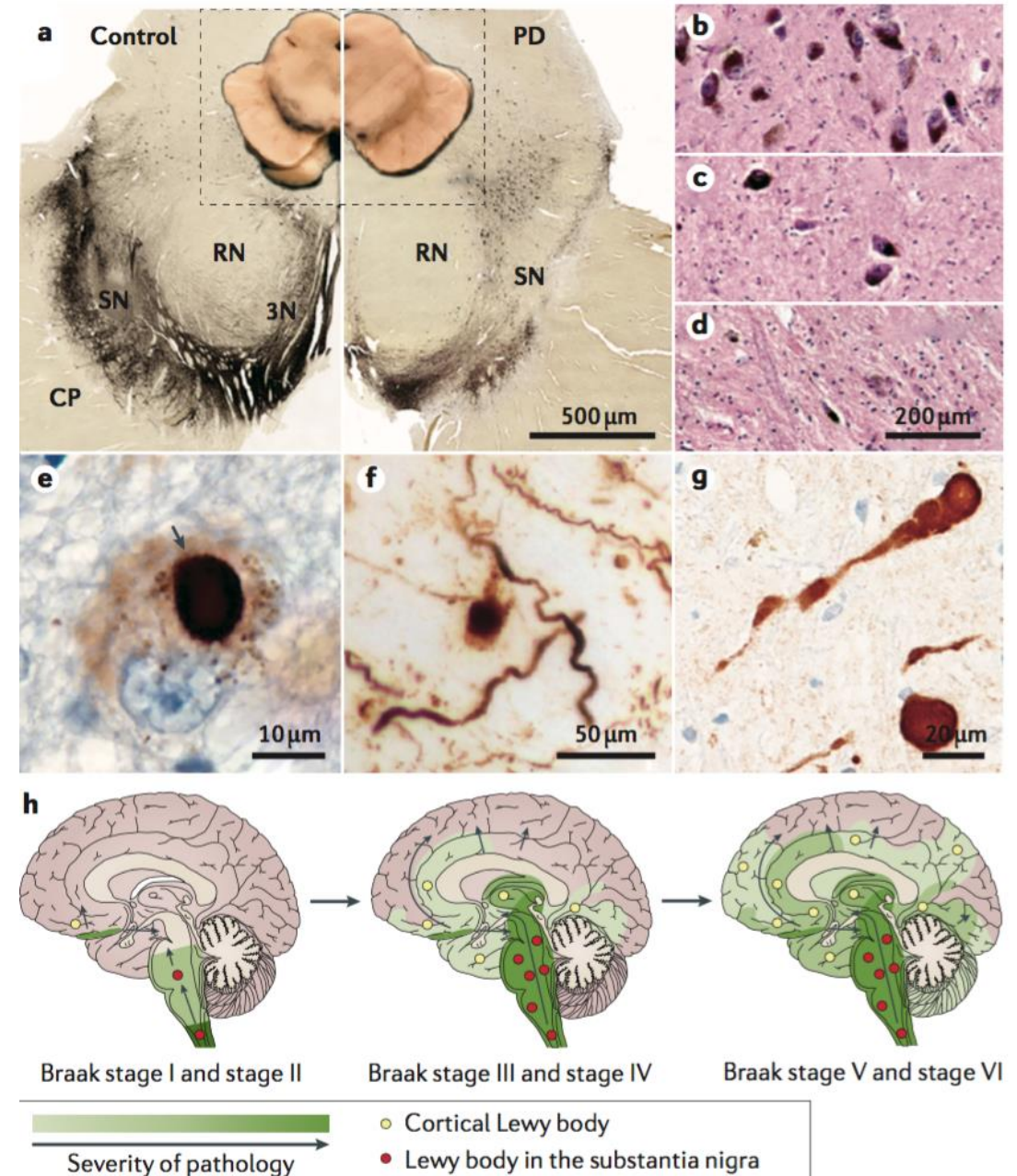
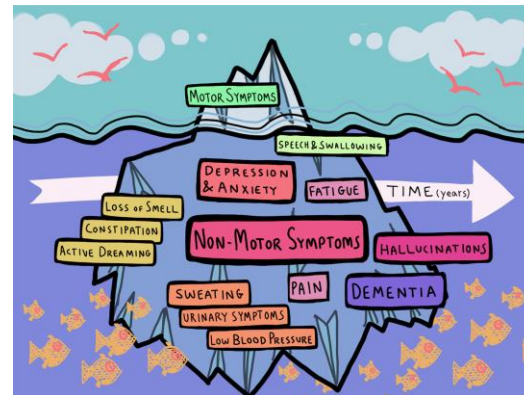


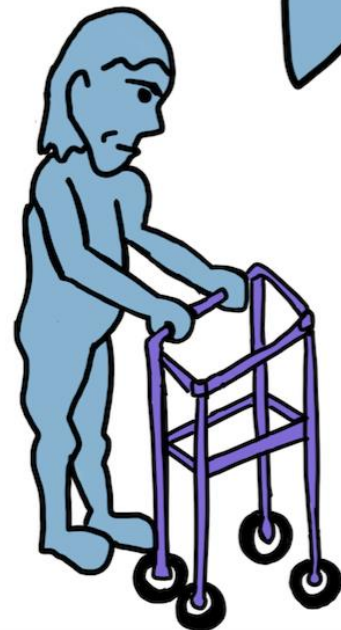
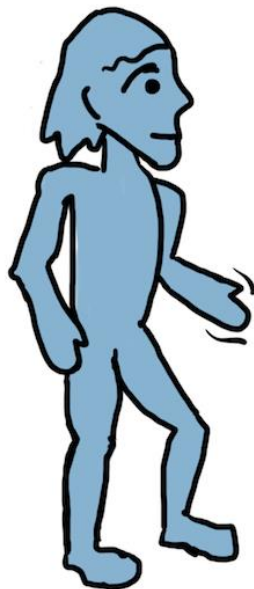
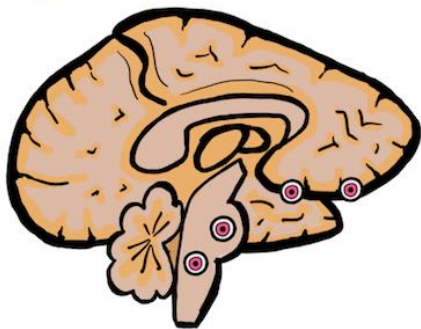
Figure 2 | The main diagnostic neuropathologies for Parkinson disease. a | Parkinson

PRE-MOTOR

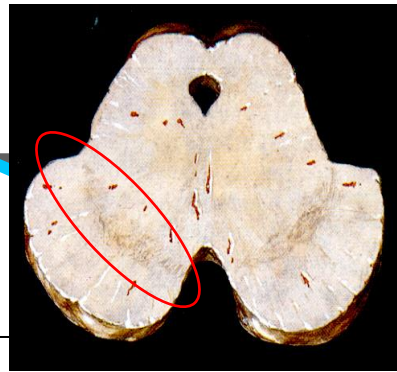
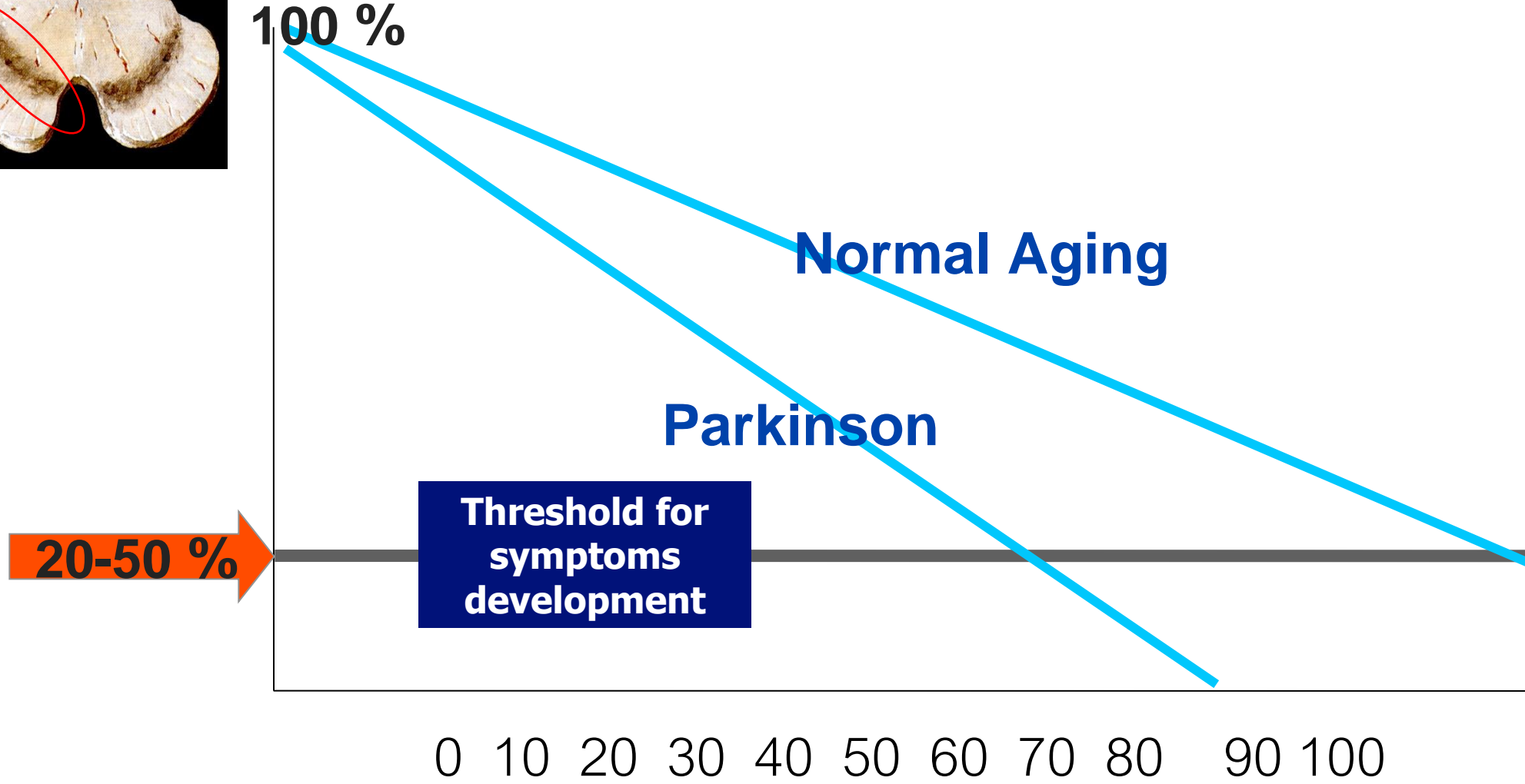
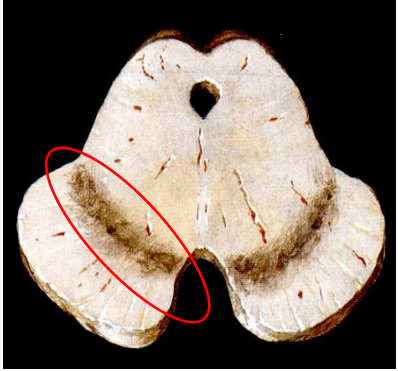
EARLY P.D.

ADVANCED P.D.

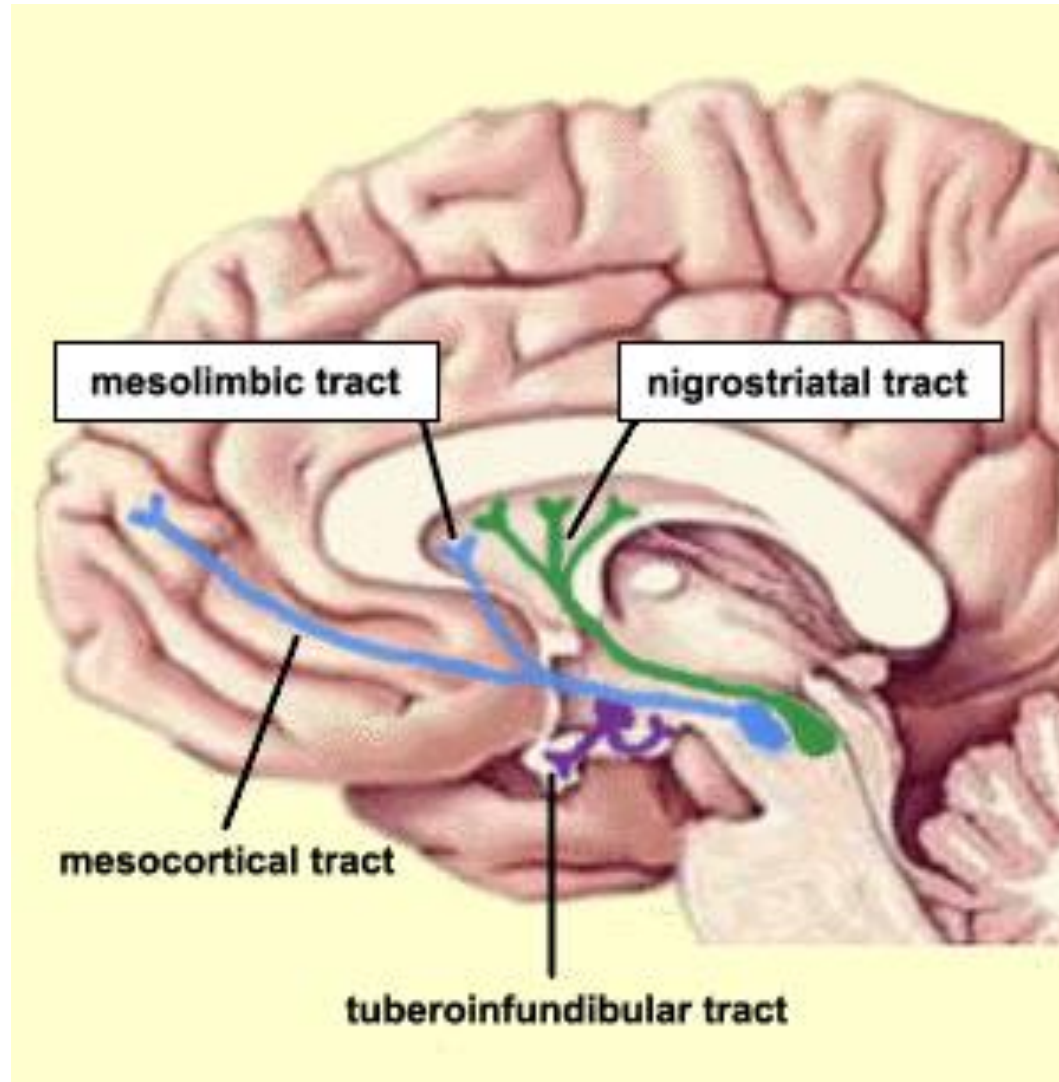
LATE P.D.



# Rate of SN neuron (dopamine neuron) loss with aging vs in PD



# Nigro-striatal pathway (dopamine!)



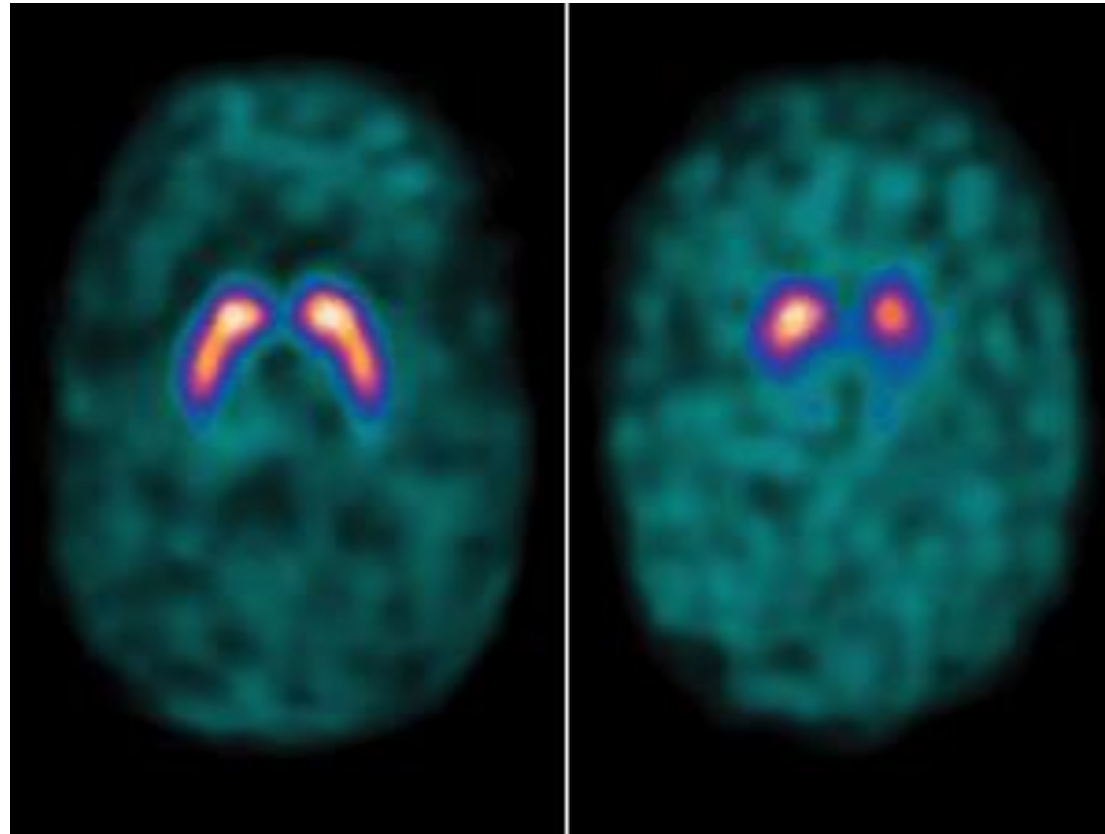
From Substantia nigra  
compacta...

...To Striatum

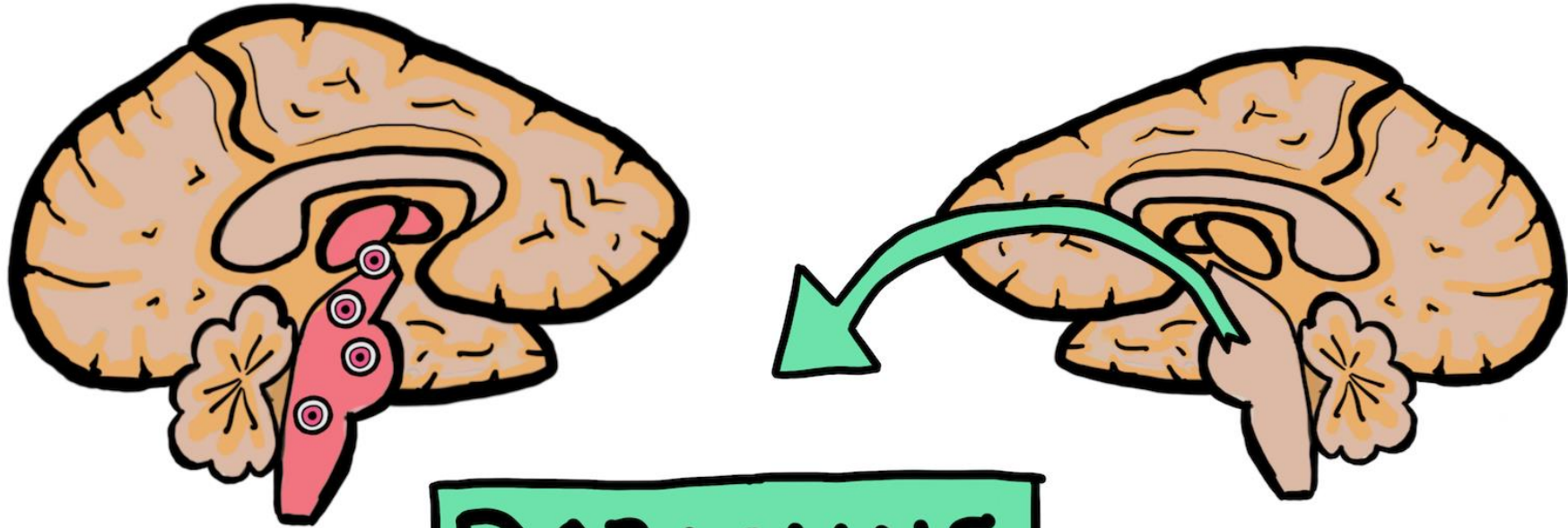
# Nigro-striatal denervation ? Can we see it ?

- DaT-scan = Dopamine Transporter ascan = **123I-FP-CIT SPECT**

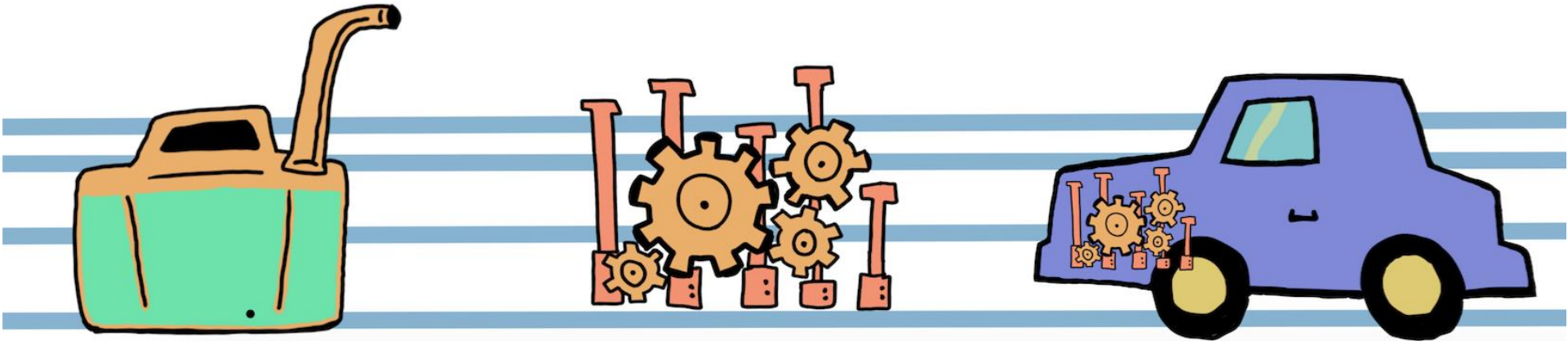
normal

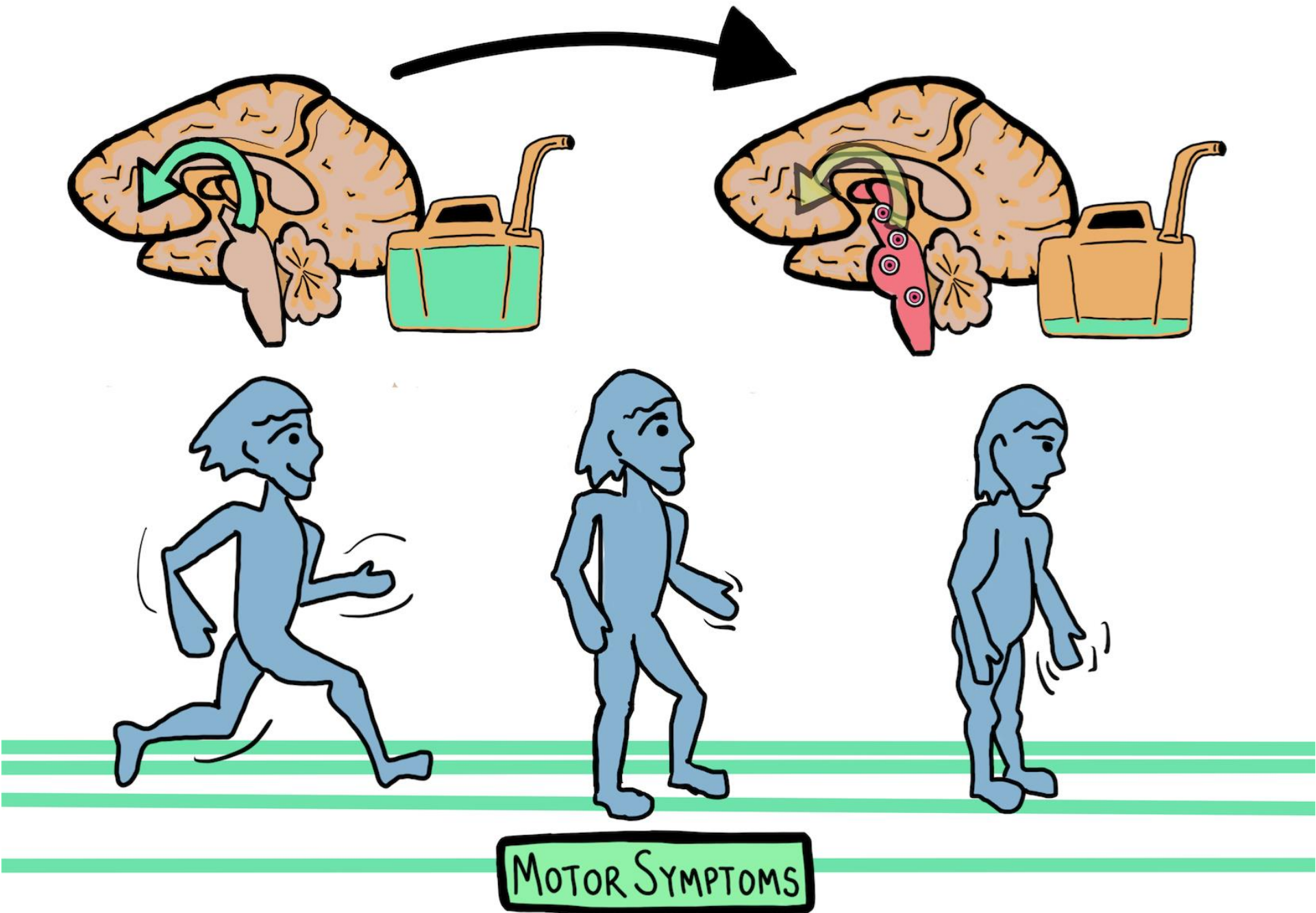


denervation

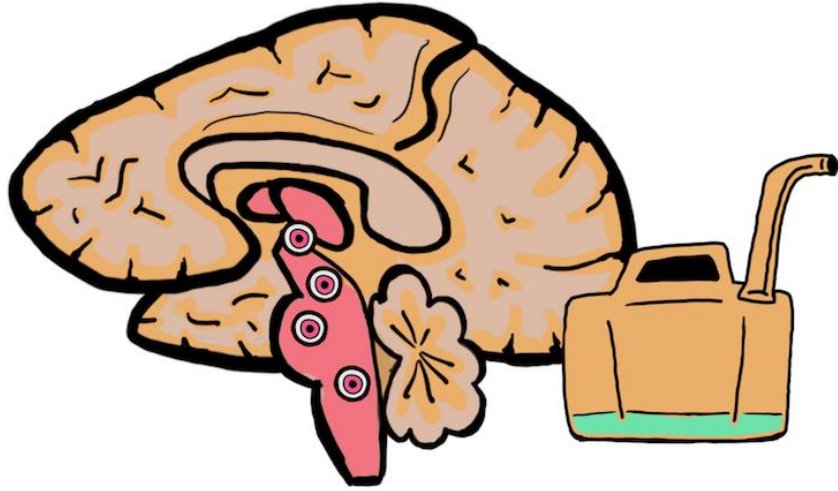


**DOPAMINE**

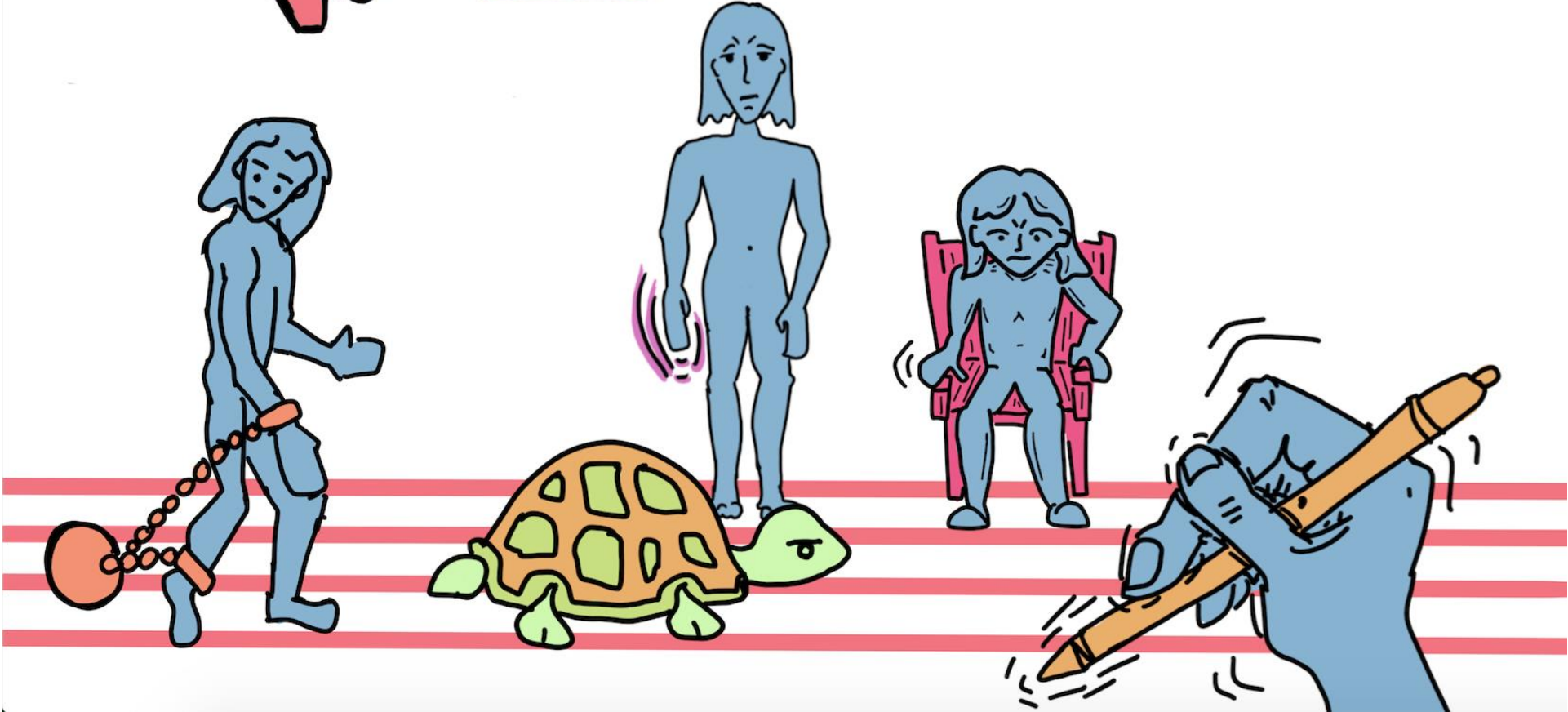




MOTOR SYMPTOMS



# PARKINSONISM



# What does the Patient notice?

Tremor

Unilateral muscle ache

Loss of dexterity

Fatigue

Constipation

Loss of sense of smell

Asked to repeat

Small writing

Excessive salivation

What does the Family notice?

Tremor

Depressed look

Old looking

Quiet voice

Slow gait

Change in writing

What does the MD need for Dx?

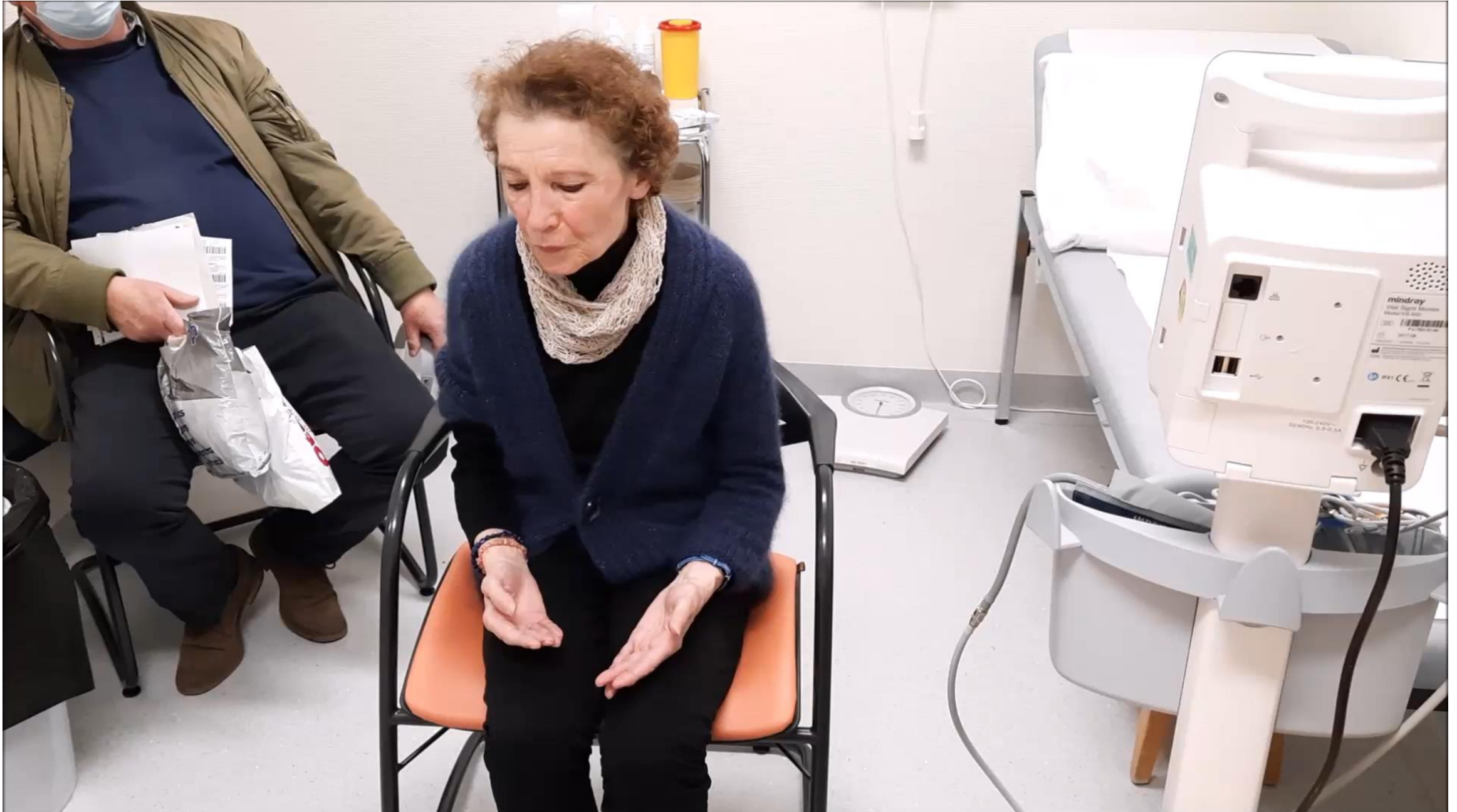
**Slowness**

and one of:

Tremor at rest / Rigidity

Typically starts on one side

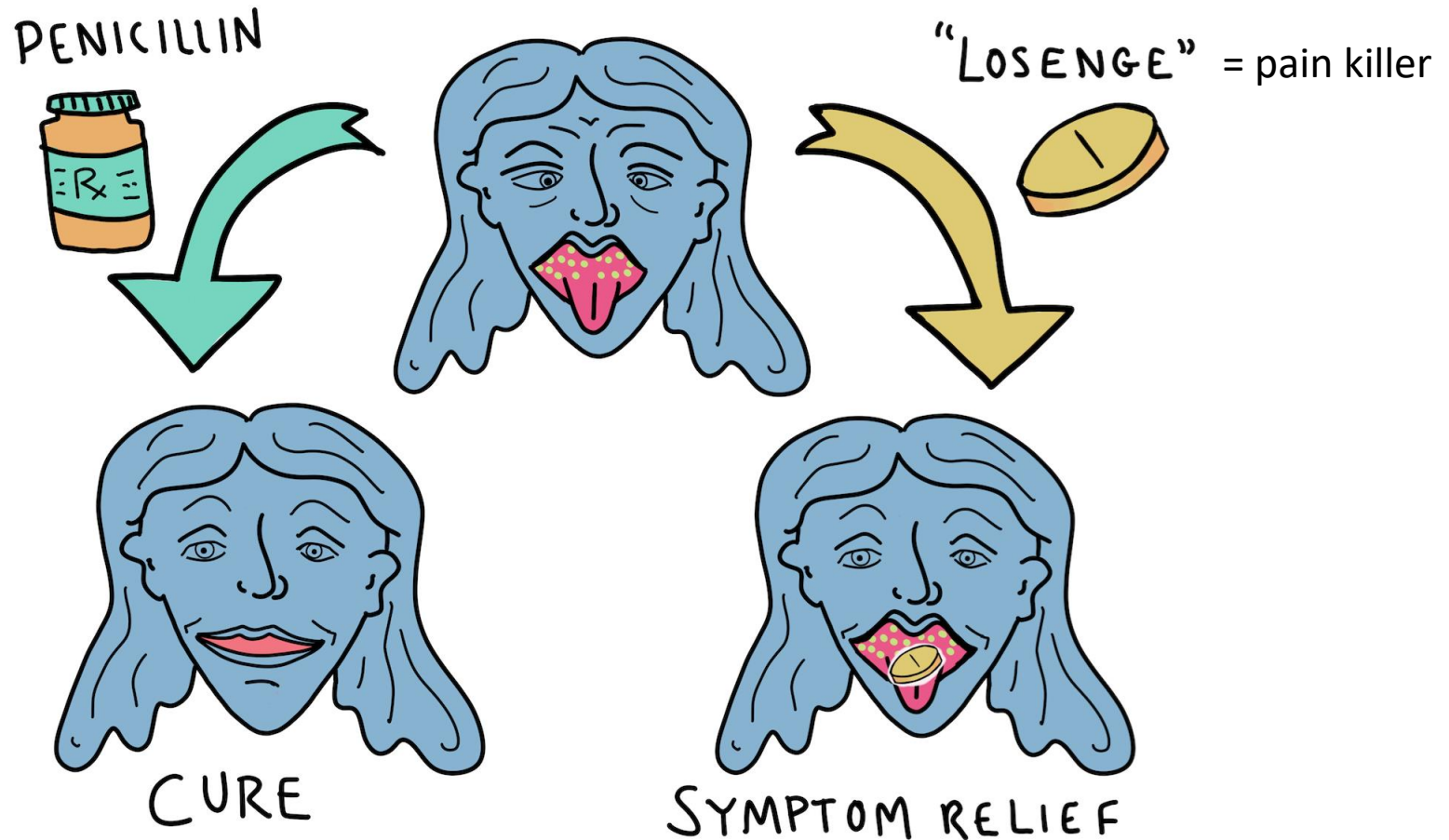
# Parkinson OFF-med (= no dopamine)



# Parkinson's Disease Treatment



Treatment : only symptomatic !  
(in 2025 at least...)



# Future: disease-modifying treatment

## Therapeutic strategies for Parkinson's disease: promising agents in early clinical development

Margherita Fabbri, Santiago Perez-Lloret & Olivier Rascol

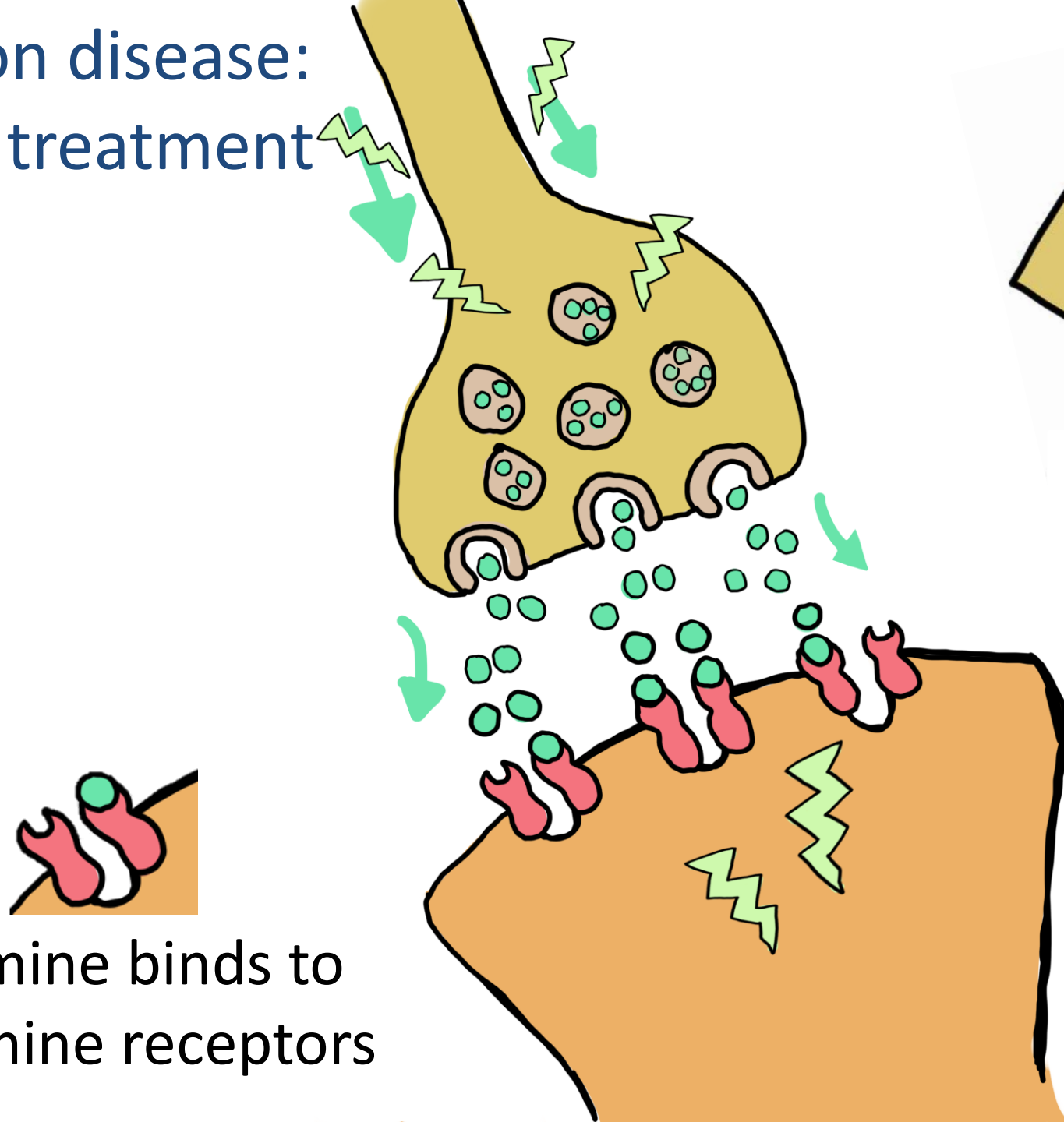
### Immunotherapy

#### $\alpha$ - Synuclein-targeting therapies

BIIB054 (SPARK)	binds to $\alpha$ -synuclein residues 1–10, with 800-fold higher affinity for aggregated over monomeric $\alpha$ -synuclein; inhibits $\alpha$ -synuclein spreading in cell-based assays	Phase I, recruiting Phase II, active not yet recruiting Phase I, completed 2019
RO7046015/PRX002 (PASADENA)	Monoclonal antibody derived from the murine monoclonal antibody 9E4 that targets both soluble and insoluble forms of $\alpha$ -synuclein	Phase II, not yet recruiting Phase I, completed 2016
BAN0805	Antibody targeting protofibrils of $\alpha$ -synuclein	Phase I, Recruiting
Affitope PD01A	$\alpha$ -synuclein-targeting vaccine	Phase I, completed 2016 Phase I, completed 2017
Lu AF82422	human IgG1 monoclonal antibody that inhibits $\alpha$ synuclein protein	Phase I, recruiting (Japan)
ABBV 0805	humanized monoclonal antibody targeting $\alpha$ -synuclein	Phase I, recruiting
MEDI1341	high-affinity monoclonal antibody to monomeric and aggregated $\alpha$ -synuclein	Phase I, recruiting
NPT200-11	orally bioavailable small molecule that binds to $\alpha$ -synuclein	Phase I, completed 2016

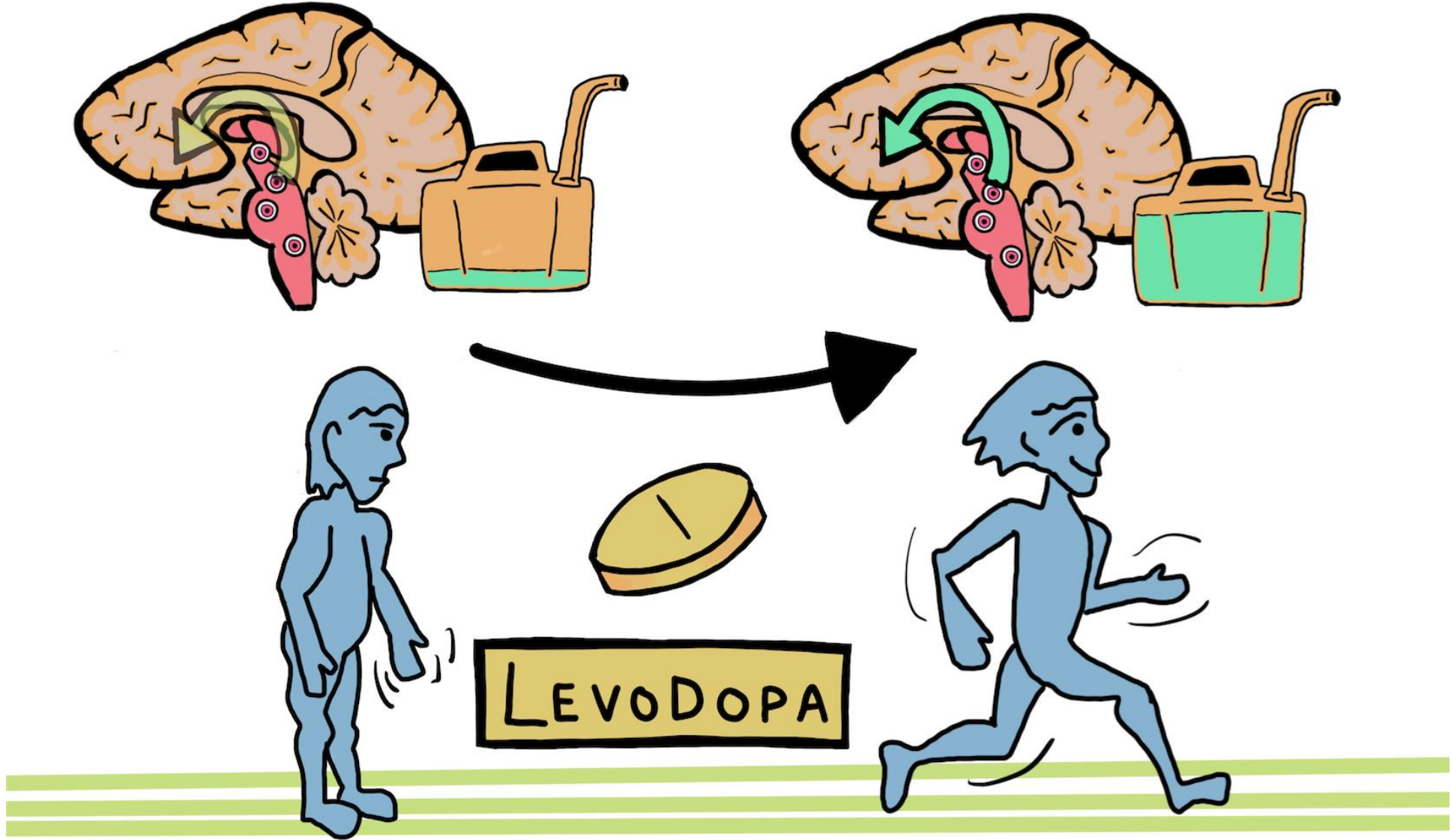
*It is still too early to predict what the role of immunotherapies centered on  $\alpha$ -synuclein will be in the future, as questions regarding efficacy and long-term safety are still open, but at the moment this approach is among the most promising ones (Fabbri et al., 2020)*

# Parkinson disease: medical treatment



Levodopa is turned into dopamine in the brain

Dopamine binds to dopamine receptors



# Levodopa Response



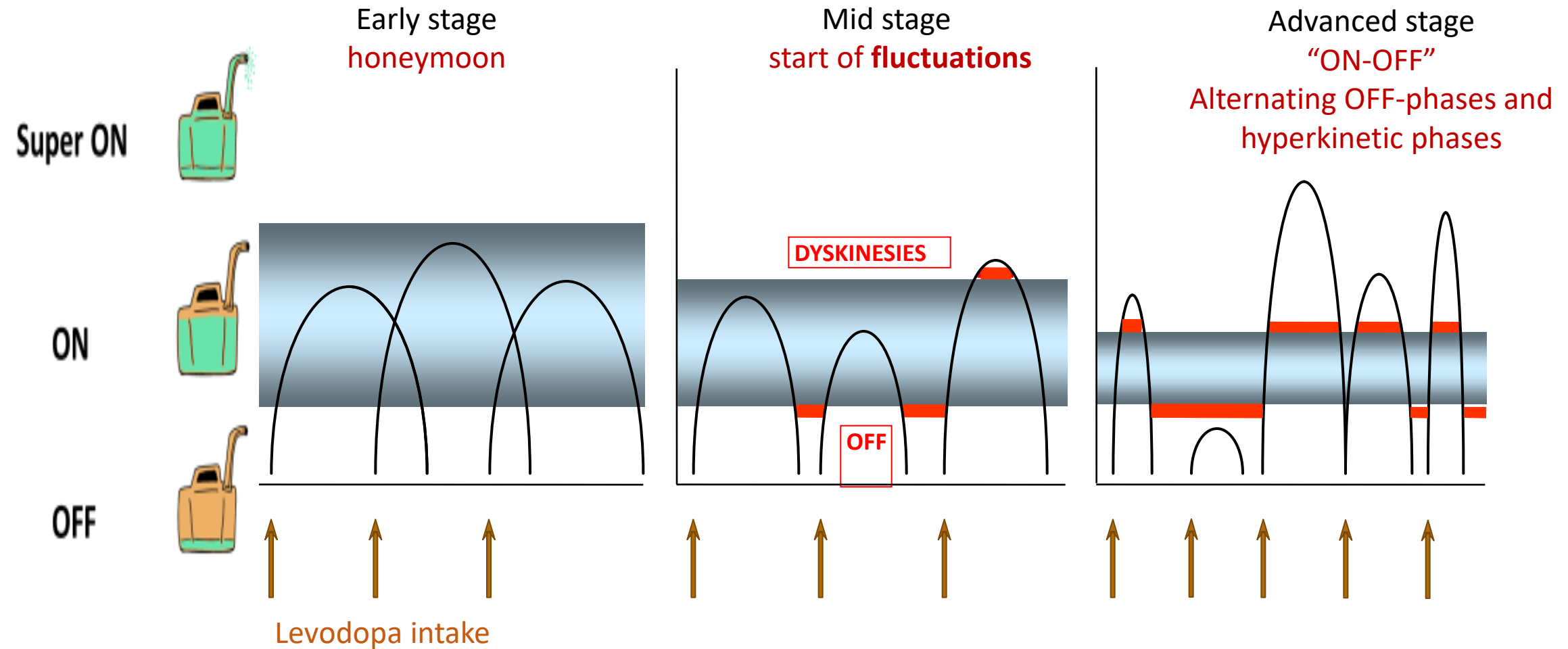
But it's not so easy...

## Parkinson's disease : 3 states

- OFF-state :
  - = **parkinsonian**
- ON-state:
  - = **normal** (thanks to the drug giving extra dopamine)
- Super-ON-state :
  - after a few years into the disease
  - involuntary hyperkinetic movements : levodopa-induced **dyskinesia**

# Disease progression

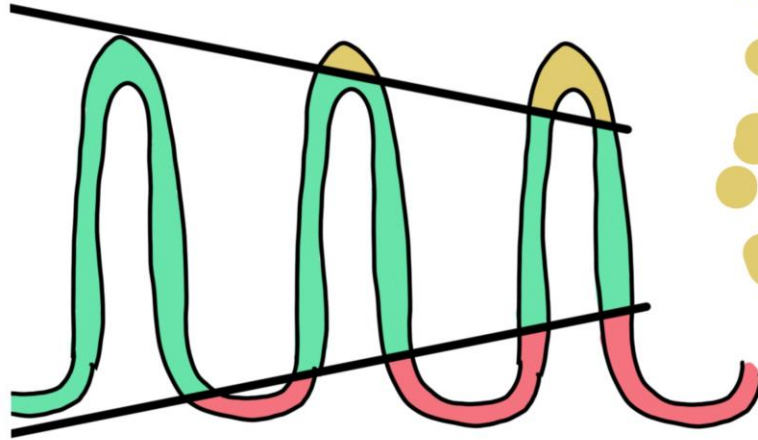
grey-blue: therapeutic window



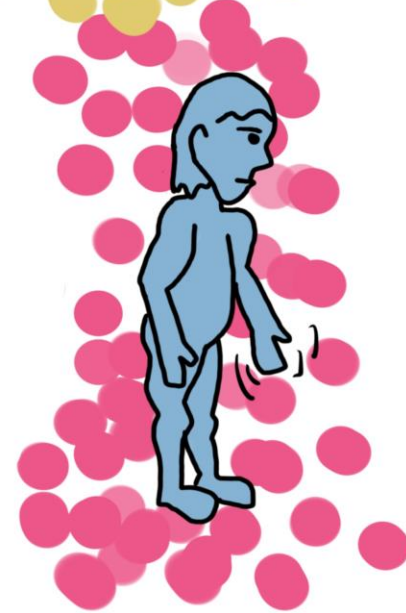
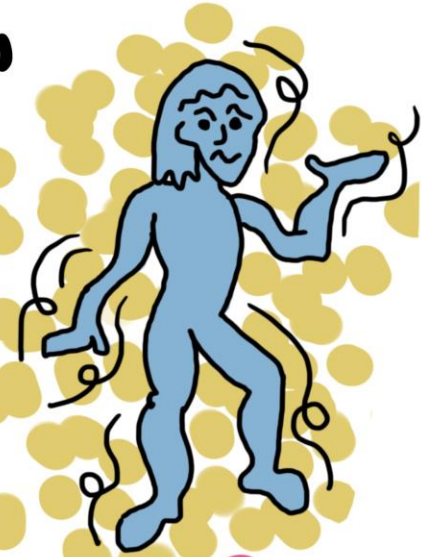
# "DYSKINESIA"



"ON"



"OFF"



# H3

## Tremor vs dyskinesia



I-dopa



Motor fluctuations



# Parkinson ON-med with dyskinesia

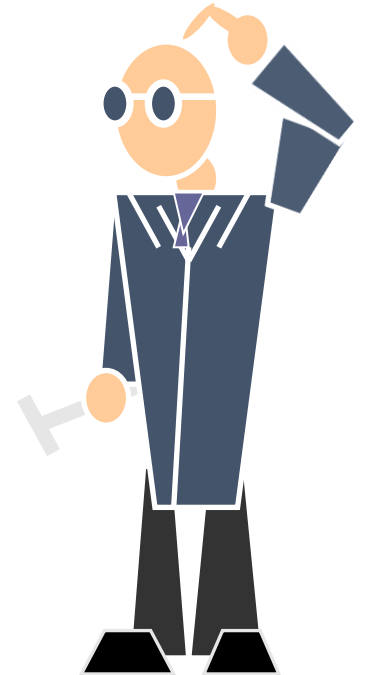
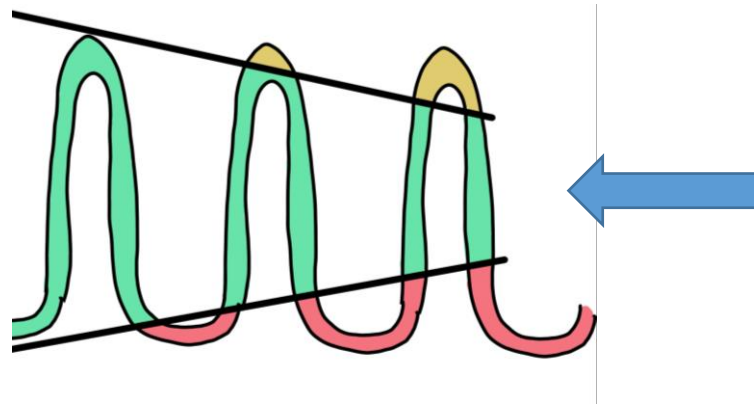


# Vidéo levodopa-induced chorea



# Treatment for PD Motor Fluctuations

- Increase the number of daily doses & reduce the unitary dose
  - “**fraction** the levodopa intake” !
- Advanced therapies
  - Continuous drug delivery
    - Apomorphine pump
    - Duodopa pump
  - Surgical treatment



# Advanced therapies !

- Continuous dopaminergic treatment



Duodopa®  
Level A

Apomorphine  
Level A



- Deep Brain Stimulation



Level A



# DBS = deep brain stimulation



Prof. Pierre Pollak –DBS pioneer in Grenoble in 1987

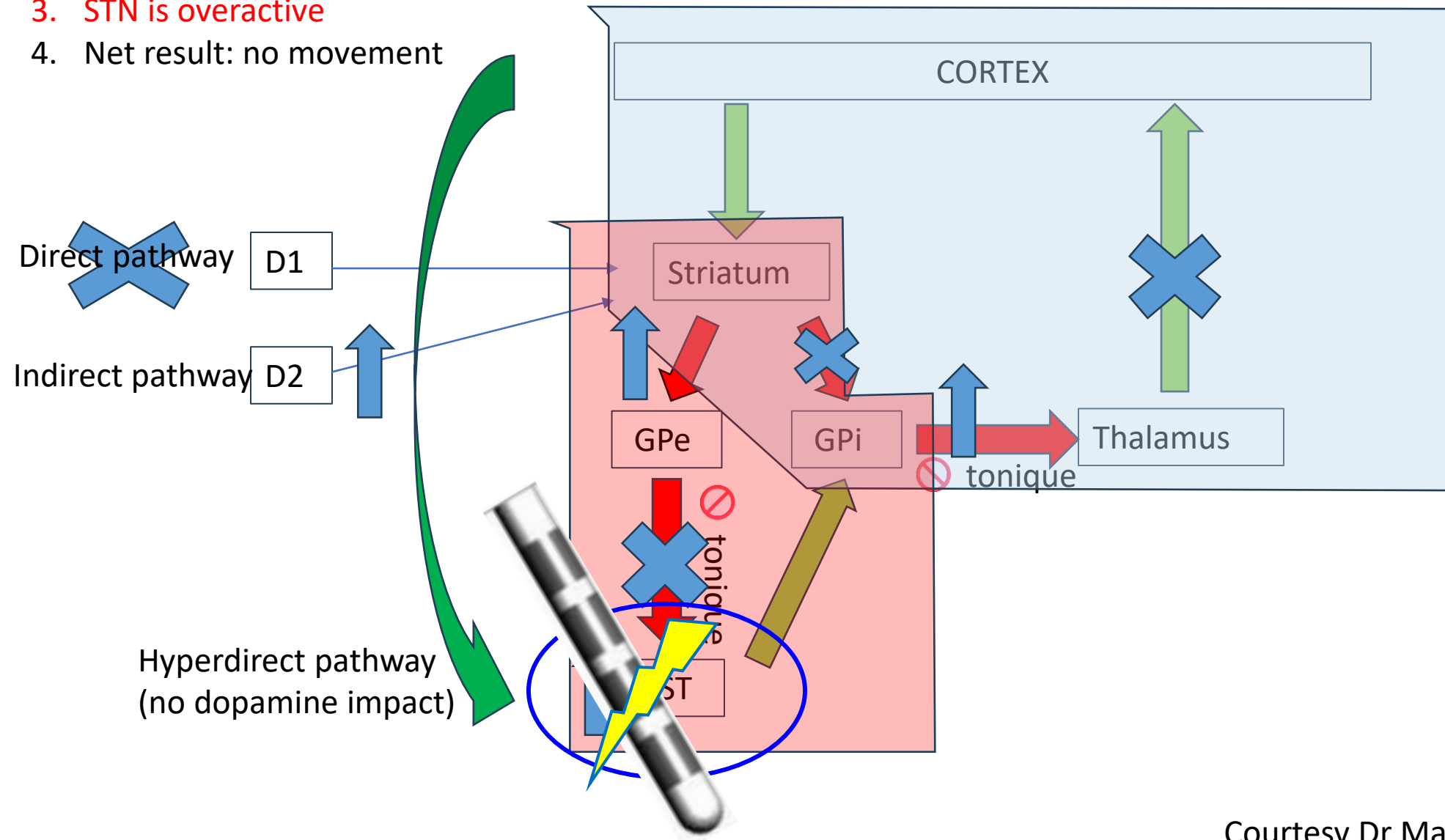
*Photo Sept 2020 – Ecublens VD*



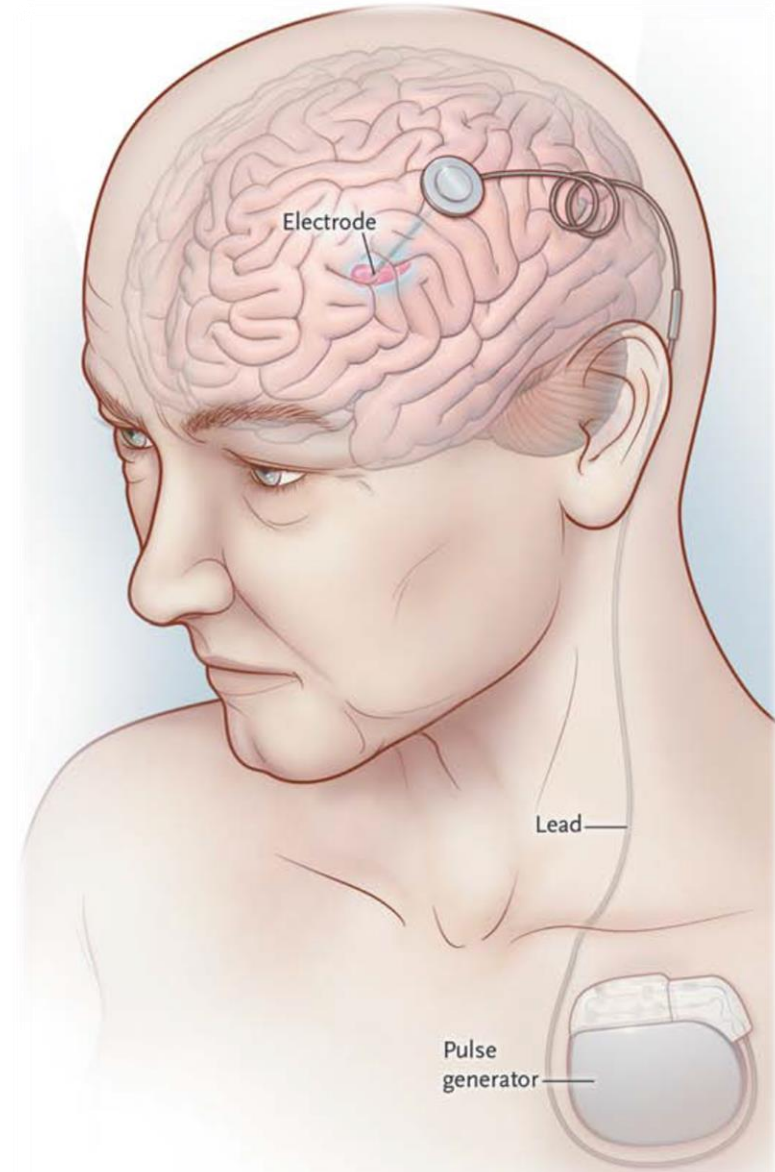
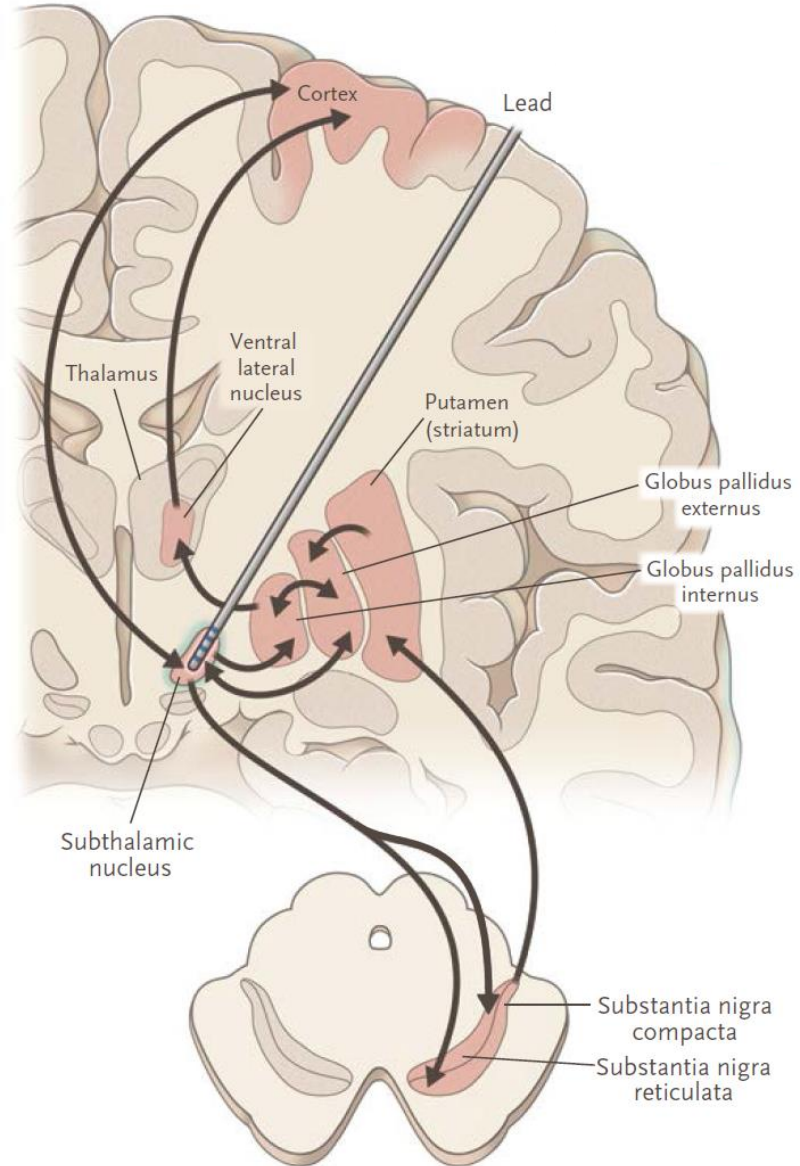
Profs A.L. Benabid et P. Pollak, Grenoble

What happens in PD? – lack of dopamine

1. No stimulation of direct pathway
2. No inhibition of indirect pathway
3. **STN is overactive**
4. Net result: no movement



# Deep brain stimulation (DBS)



LEGO

LEGO

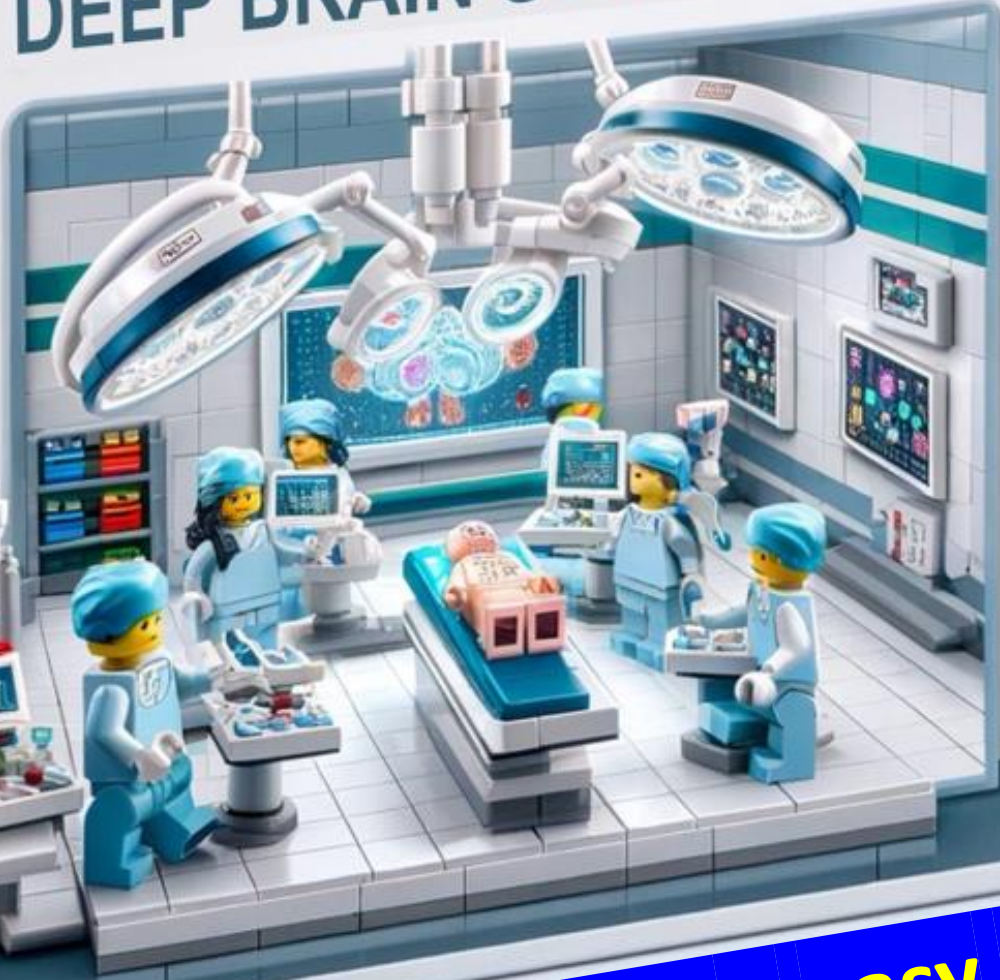
# DEEP BRAIN STIMULATION

SURGY  
**69**

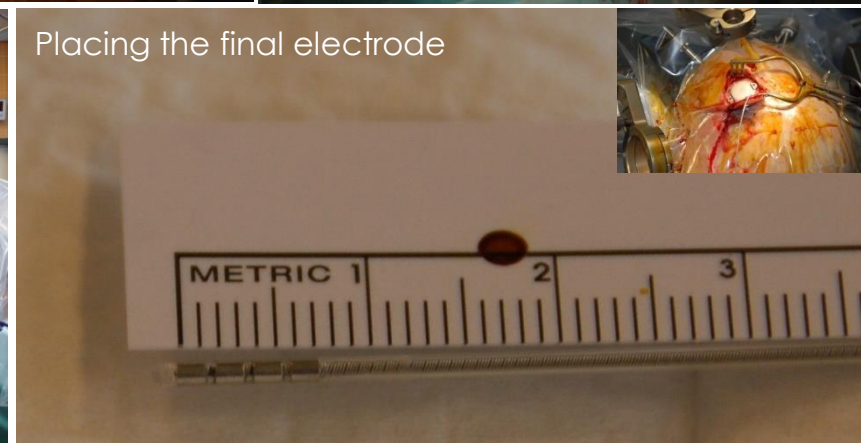
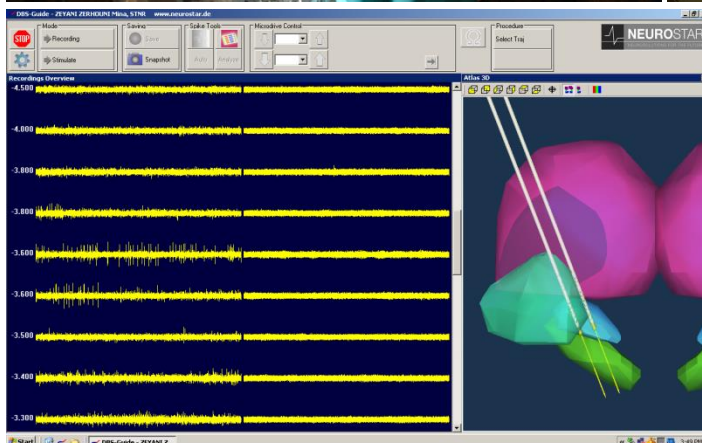
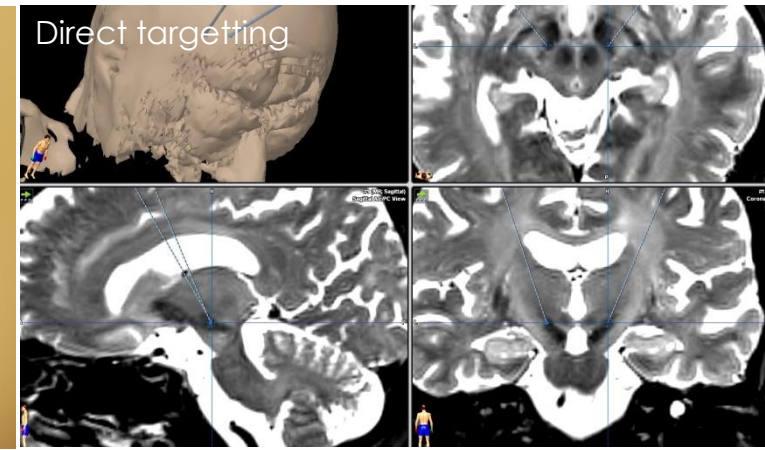
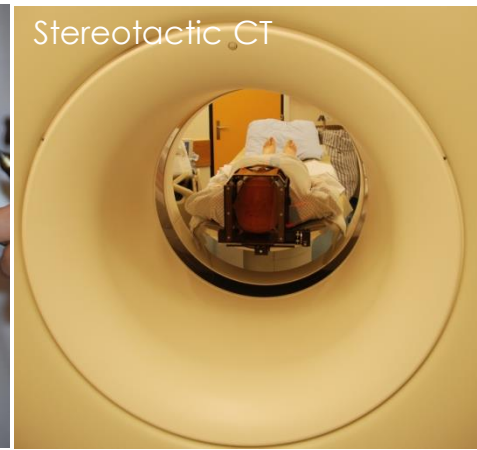
85 Pieces

85 Pieces

Essestochas enonengjarul



**DBS is easy !**

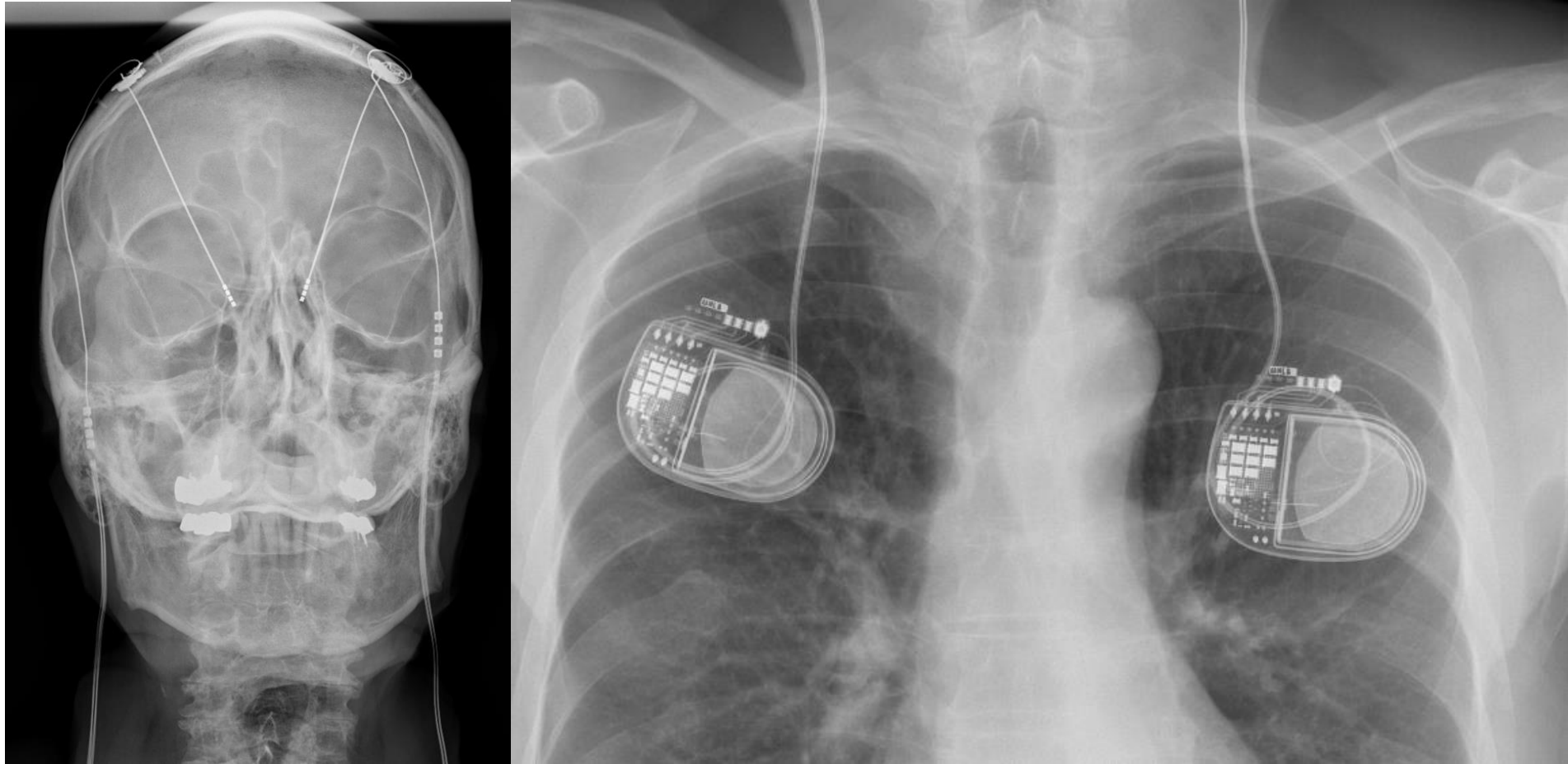


Prof.  
Jocelyne  
Bloch

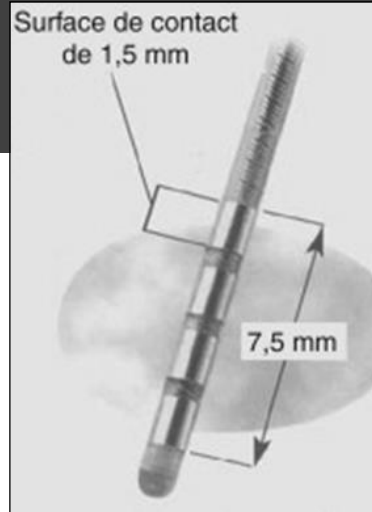
# Micro-electrode recording

**REGULAR NEURON**  
**STN**

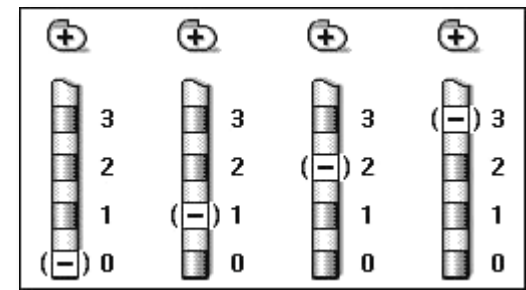
# DBS system in place



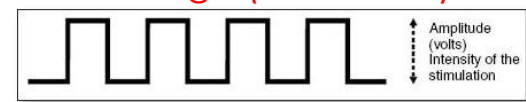
# DBS programming



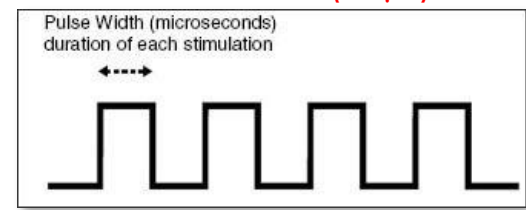
## Stimulation contacts



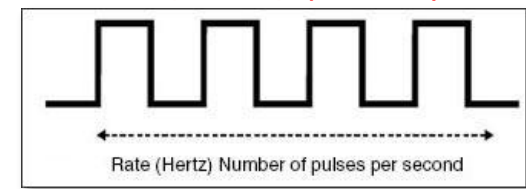
## Voltage (2.5 – 3.5 V)



## Pulse width (60 $\mu$ s)



## Frequency (130 Hz)

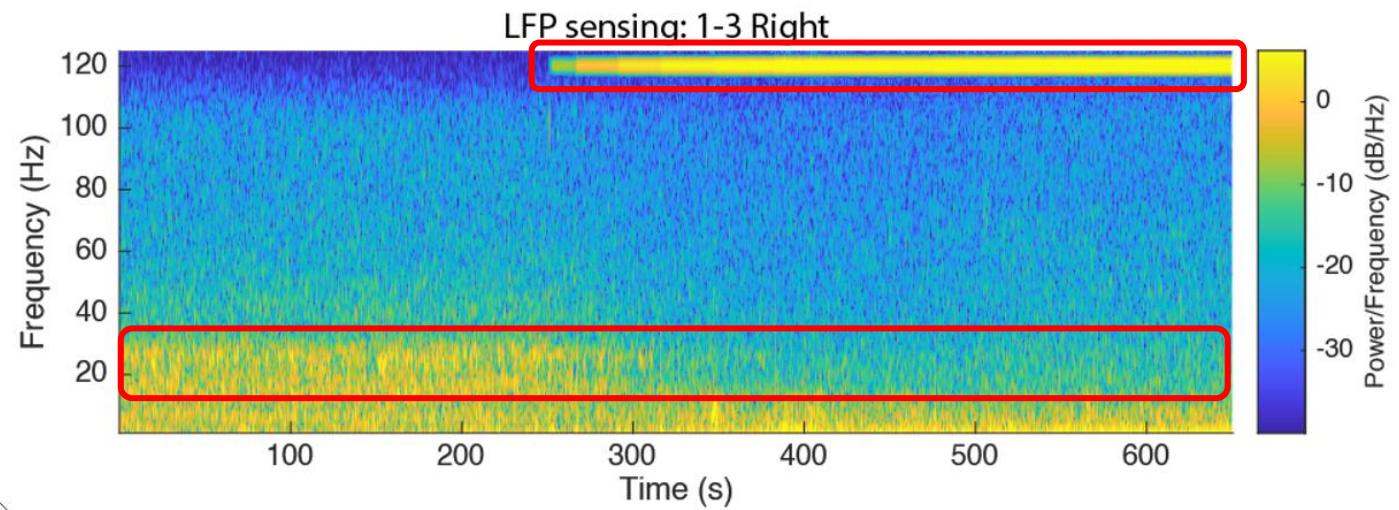
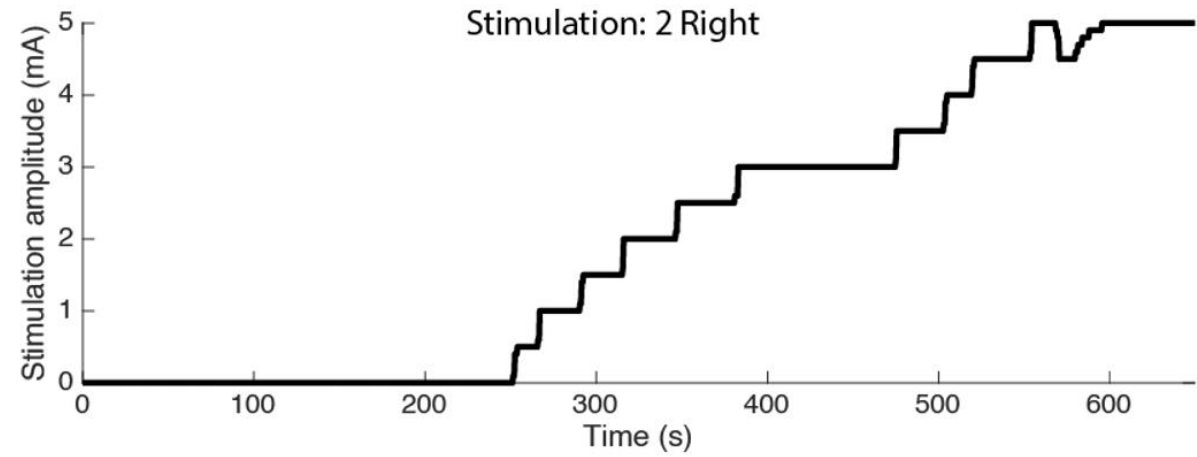


# Brain recordings





# Post-processing




# PD patient Post STN-DBS






20 jours après l'opération

A person wearing a green sweater is standing in a hallway. The hallway has white walls and a dark floor. To the left is a white door with a silver handle. To the right is a white wall with a small framed picture and a stack of firewood. The text "chorée d'origine toxique" is overlaid at the bottom of the image.

chorée d'origine toxique

A person wearing a dark blue long-sleeved shirt is standing in a kitchen. Their hands are held out in front of them, with fingers slightly curled, as if they are frozen in place. The background shows a kitchen with a white refrigerator and a white countertop. The lighting is somewhat dim, and the overall tone is clinical.

Parkinson en phase bloquée avec trouble  
sévère de la marche



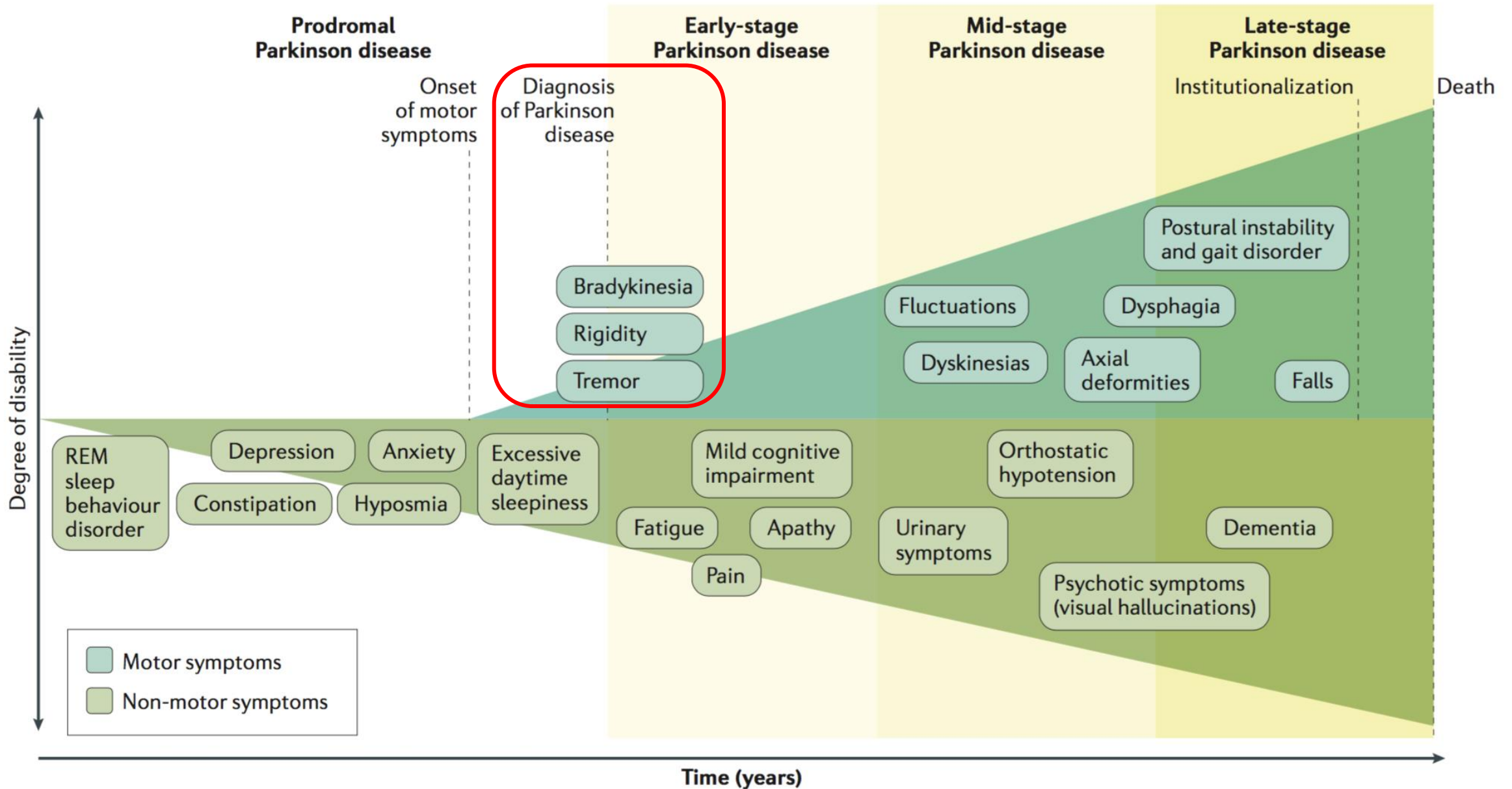


Figure 5 | **Clinical symptoms associated with Parkinson disease progression.** Diagnosis of Parkinson disease occurs with the onset of motor

throughout all stages of Parkinson disease. Progressive disability from Parkinson disease is driven by the combination of these non-motor

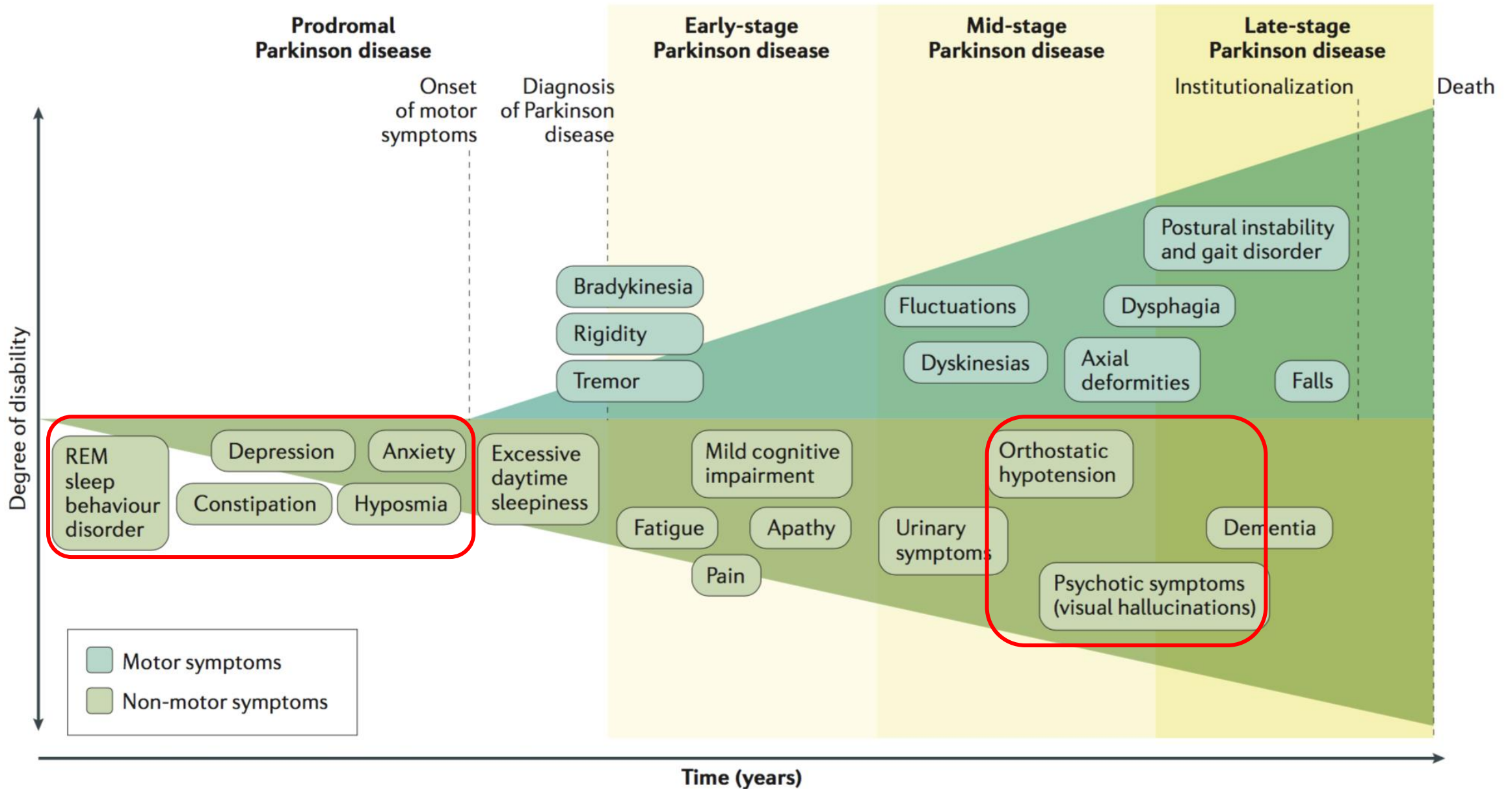
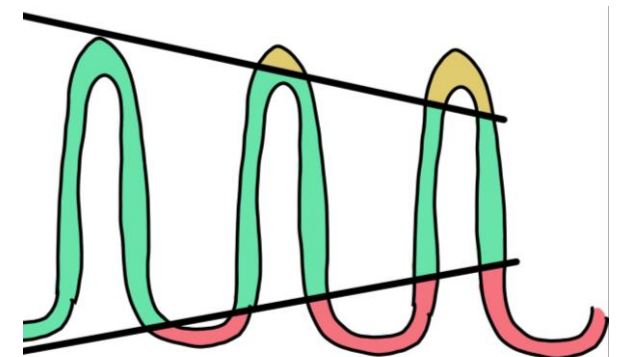
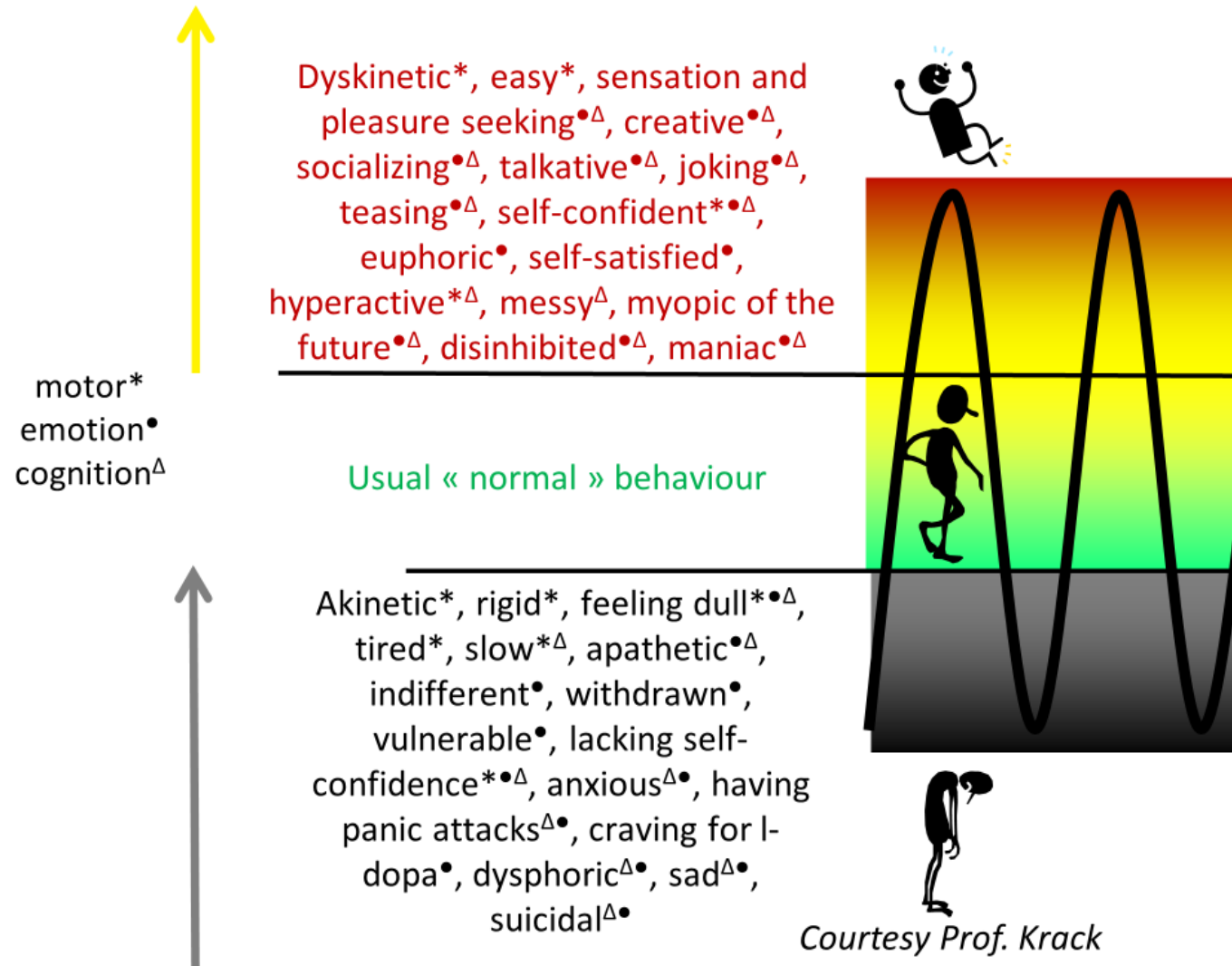


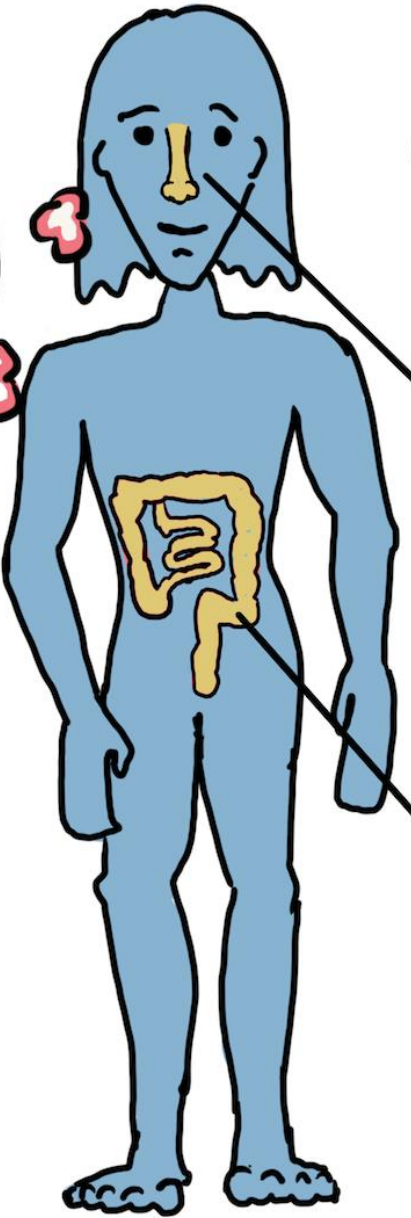
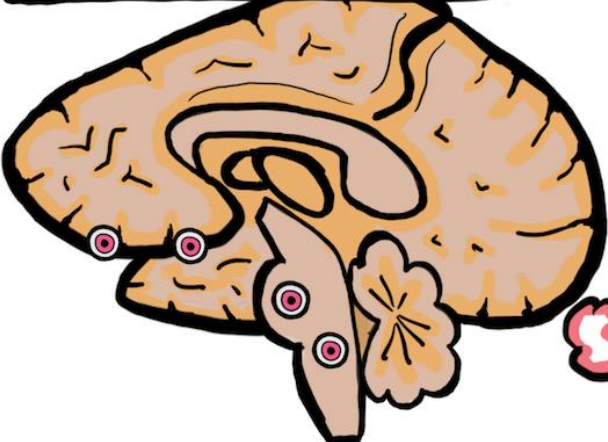
Figure 5 | **Clinical symptoms associated with Parkinson disease progression.** Diagnosis of Parkinson disease occurs with the onset of motor

throughout all stages of Parkinson disease. Progressive disability from Parkinson disease is driven by the combination of these non-motor

# Non-motor & motor fluctuations



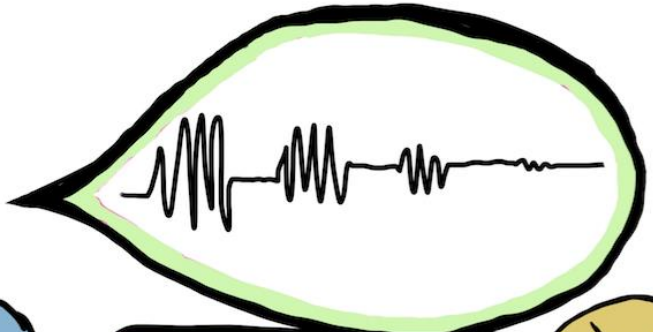
# PRE-MOTOR



LOSS OF SENSE OF SMELL

CONSTIPATION

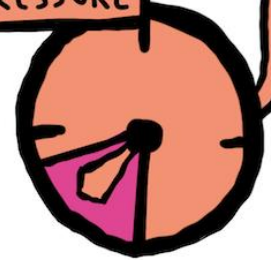
# ADVANCED P.D.



SPEECH & SWALLOWING



LOW BLOOD PRESSURE



URINARY SYMPTOMS

PAIN



## MOTOR FLUCTUATIONS



FATIGUE

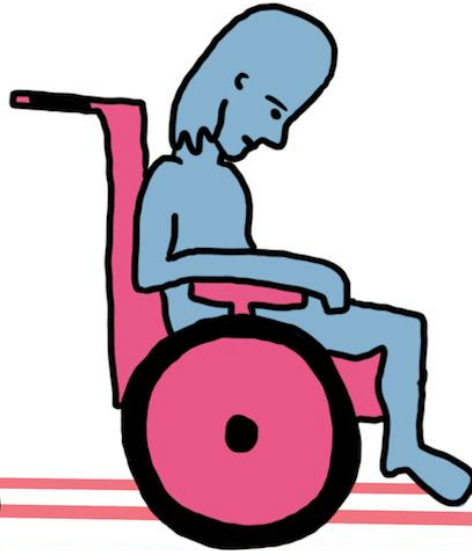
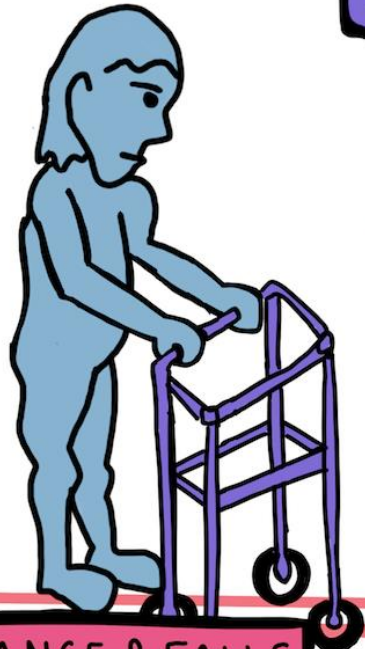
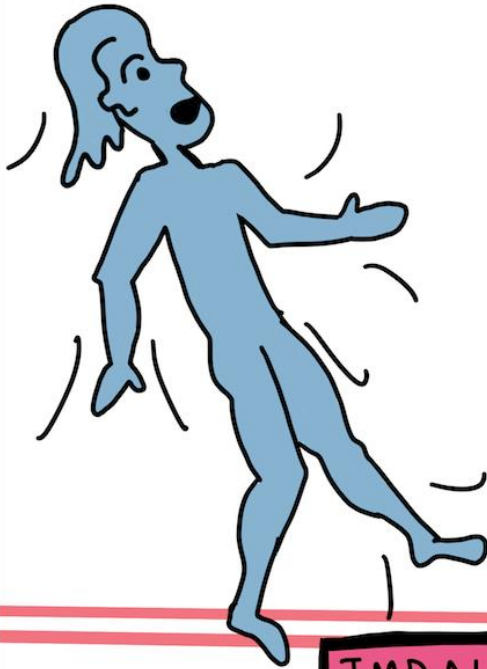
LATE P.D.



DEMENTIA



HALLUCINATIONS



IMBALANCE & FALLS

Thank you for your attention !





Tremblement - stimulation allumée