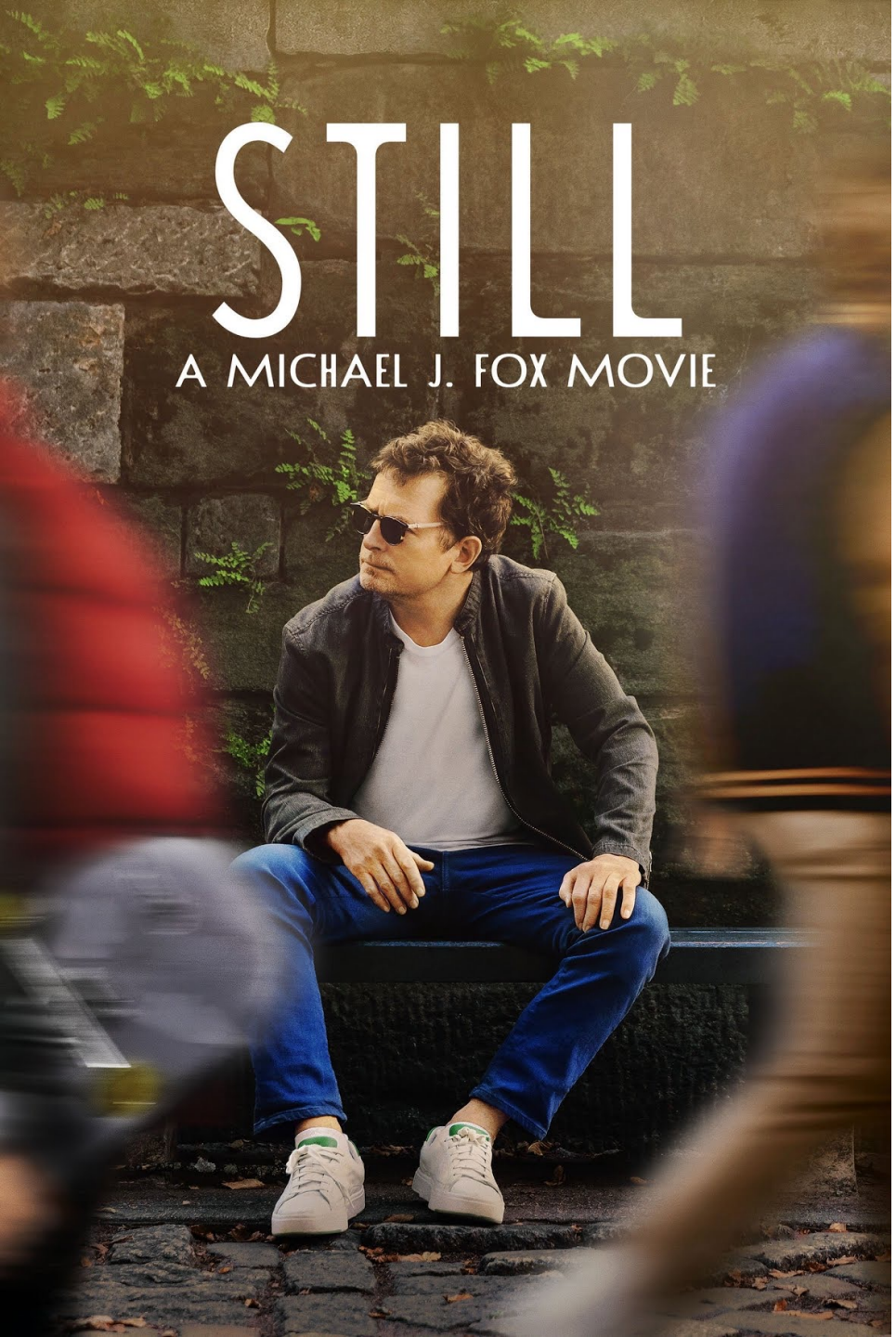
Neuro-X

Translational Neuroengineering

Parkinson's disease III

April 15, 2025

Juan Carlos Farah & Olaf Blanke

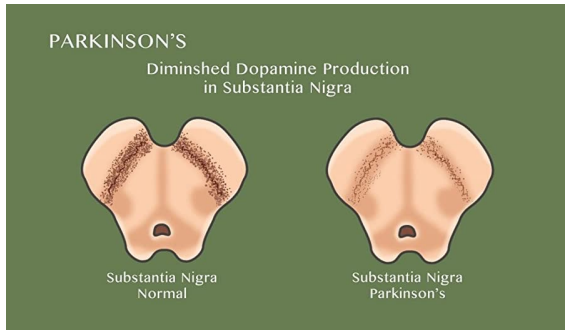


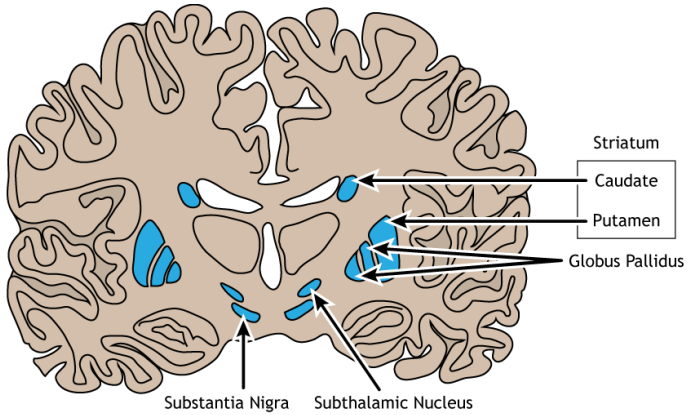
https://www.youtube.com/watch?v=lpz6QpJOkZE
(recent interview with Fox)

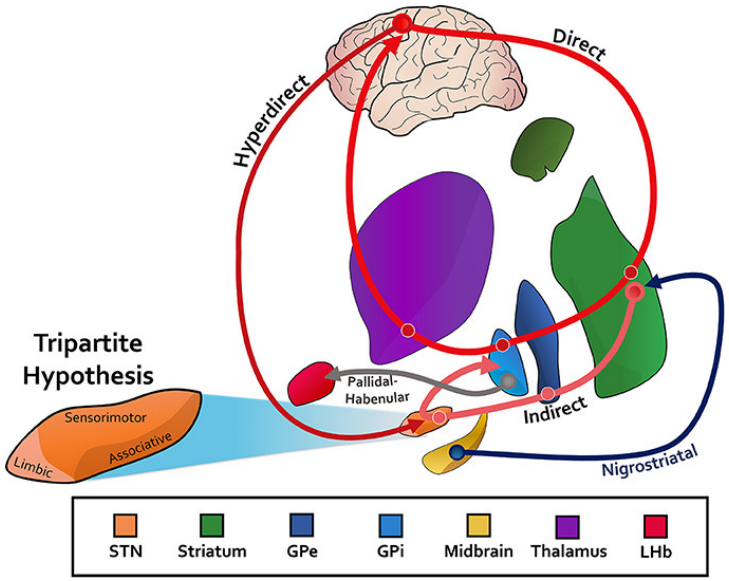
Documentary about Fox's life
Fox was diagnosied with PD at age 31 and
started the world's largest Parkinson foundation

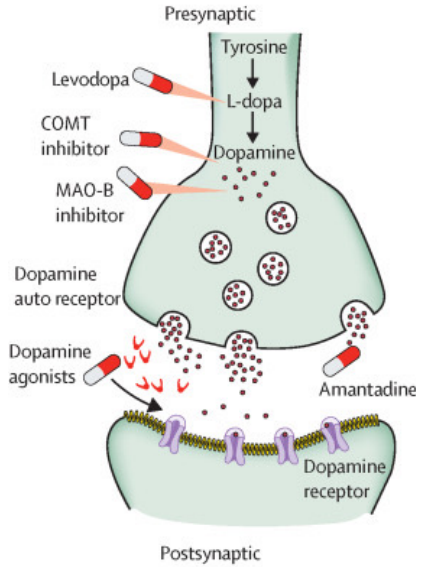
Parkinson's disease is a disorder of the basal ganglia …

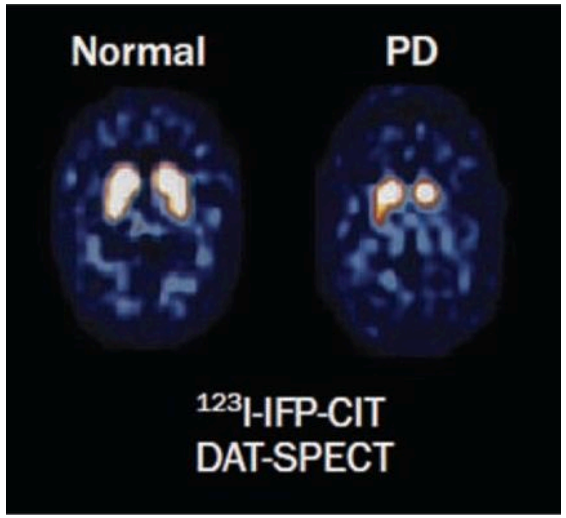
… is a movement disorder, caused by the loss of dopaminergic neurons in the substantia nigra, degeneration of the nigro-striatal pathway, and characterized by dopamine depletion in the striatum, leading to basal ganglia abnormality







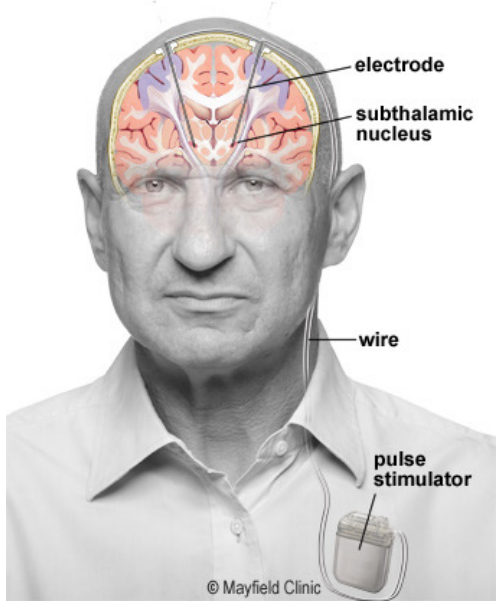


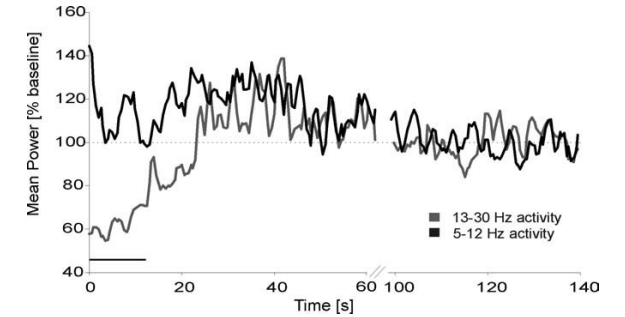


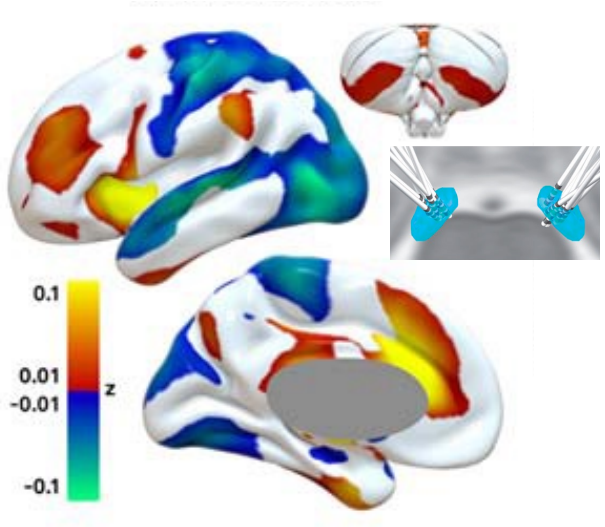
Neuropathology
Neuroanatomy
Chemical Neurotransmission
Clinical Neurology

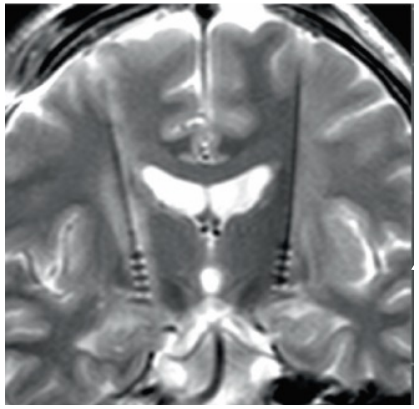
Parkinson's disease is not only a disorder of the basal ganglia, but also of the cortex …

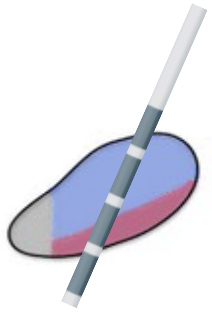
… brain oscilations (beta and gamma band) involve all parts of the basal ganglia and also involve many cortical systems in motor, premotor, supplementary motor cortex, as well as posterior cortical regions; DBS (and dopamine replacement therapy) normalize these distributed pathological oscillations

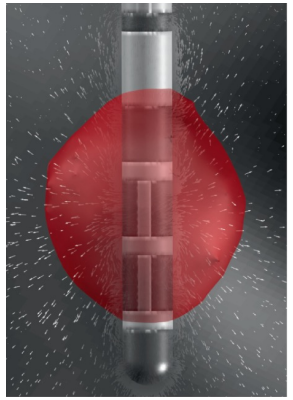


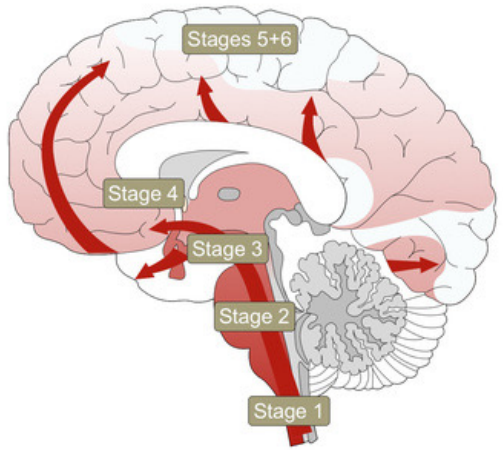




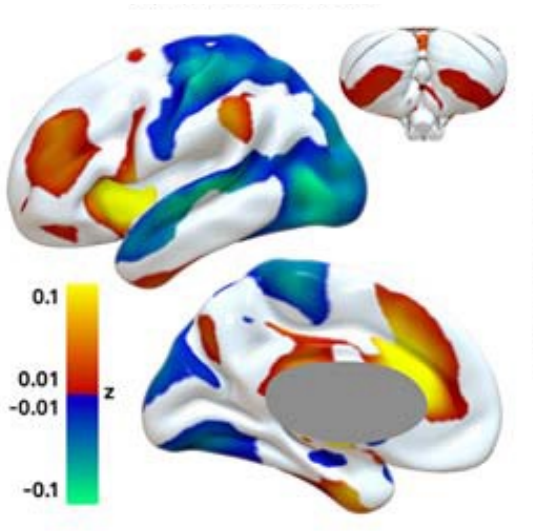






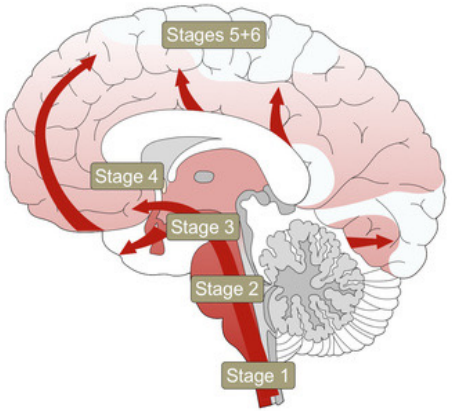


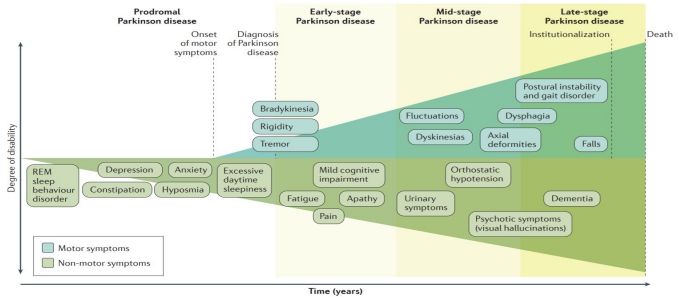
PD is also a distributed disease



Even though pathological changes and neurochemical changes are - at least initially focal (SN, striatum) - the associated electrophphysiological changes (beta and gamma oscillations) affect many of the structures in the basal ganglia as well as the cortex and so do the main PD treatments (dopamine and DBS)

(additionally as PD progresses these cortical systems are affected more prominently by Lewy body pathology)





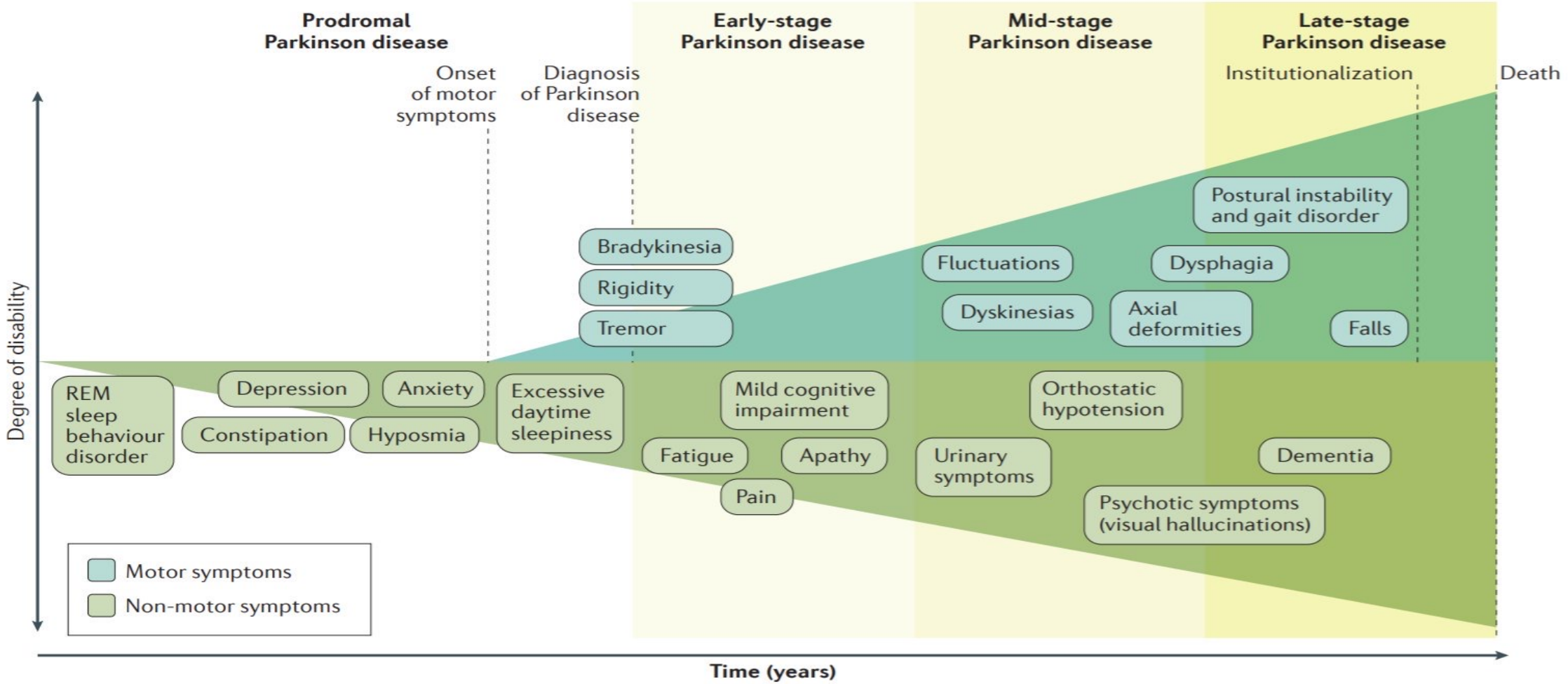
Many of the non-motor symptoms of PD are also compatible with PD as a disease that affects more then the nigro-striatal pathway and basal ganglia

Non-motor symptoms in PD

-Motor symptoms are used to define PD (diagnosis), but many non-motor symptoms are very frequent in PD

–Non-motor symptoms determine life quality for many patients

-Several non-motor symptoms appear years (decades) before the onset of bradykinesia, rigidity, or tremor



Poewe et al., 2017

Parkinson's disease

Non-motor symptoms

Many non-motor symptoms

Depression-anxiety
Fatigue
REM sleep behavioral disorder (RBD)
Hyposmia (loss of smell)
Orthostatic hypotension
Dementia
Psychosis
Urinary symptoms
…

Major non-motor symptoms

Mental-psychiatric: Hallucinations & Psychosis

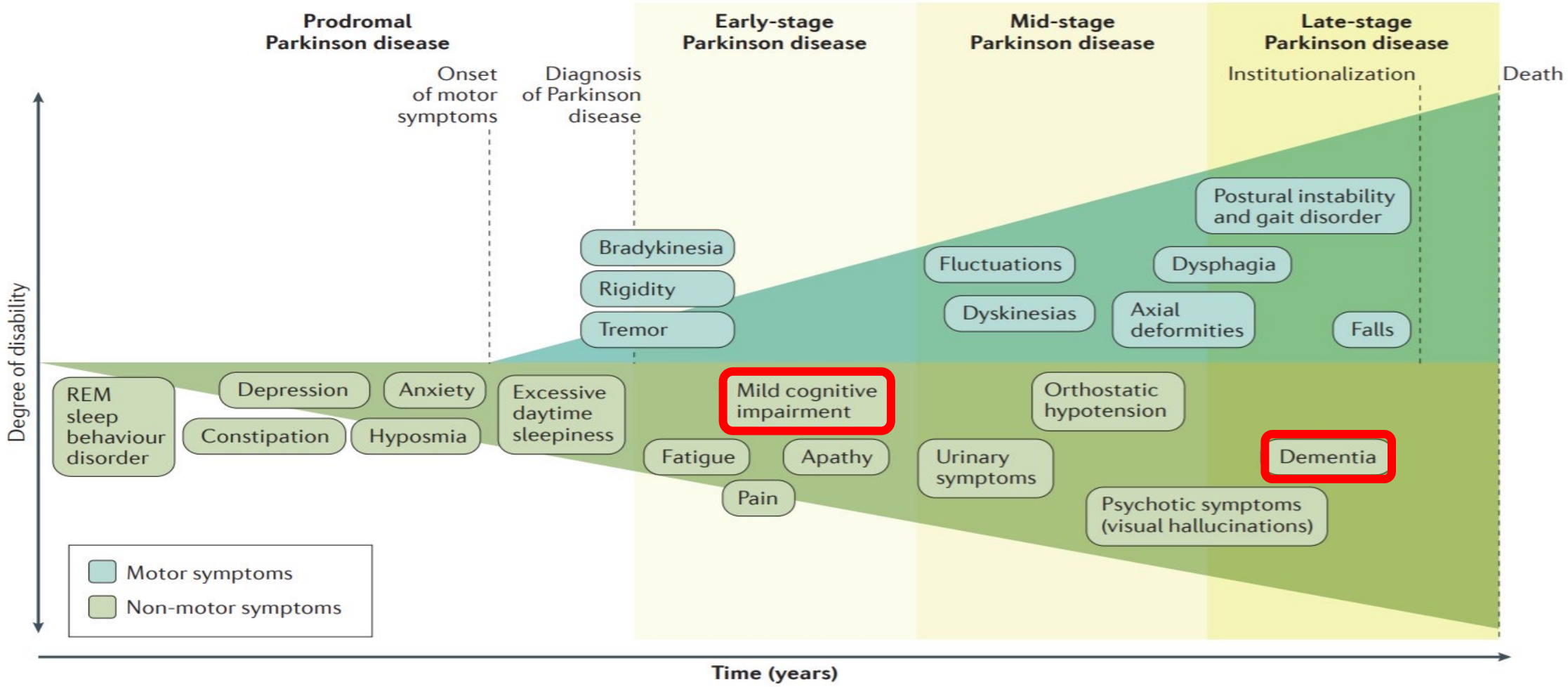
Cognitive: Mild cognitive decline & Dementia

Sleep-wake cycle: REM sleep behavior disorder

Apathy
Impulse Control Disorder
Decision making

Cognitive Impairment & Dementia in PD

A frequent non-motor symptom



Poewe et al., 2017

Cognitive impairment in PD

… concerns mainly cognitive functions mediated by frontal-subcortical networks

Cognitive impairment in PD is frequent
-cognitive impairment is intrinsically linked to PD (i.e., it is not a treatment complication or induced by therapy)

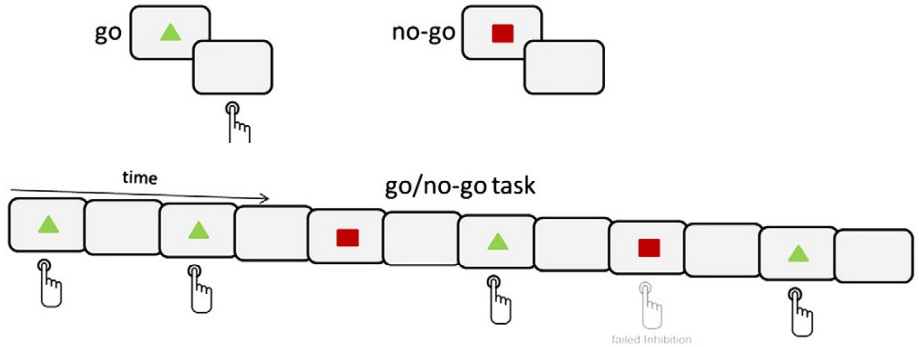
- 6x more frequent than in healthy aged matched people

-about **80% of PD patients have a cognitive impairment** at the moment the diagnosis is made (based on motor symptoms), but the deficit may be subtle and only be detected by specialized tests

Main impaired functions are involving attention-related and executive functions. These impaired functions are generally referred to as frontal lobe functions.

Impaired cognitive functions are:
-fluency tasks (semantic, phonological)
-set shifting
-complex problem solving
-response initiation
-response inhibition
-working memory

Inhibitory processes are deficient in PD
Go/no-go task tests inhibition (subject asked to press or not to press a response button as fast as possible)



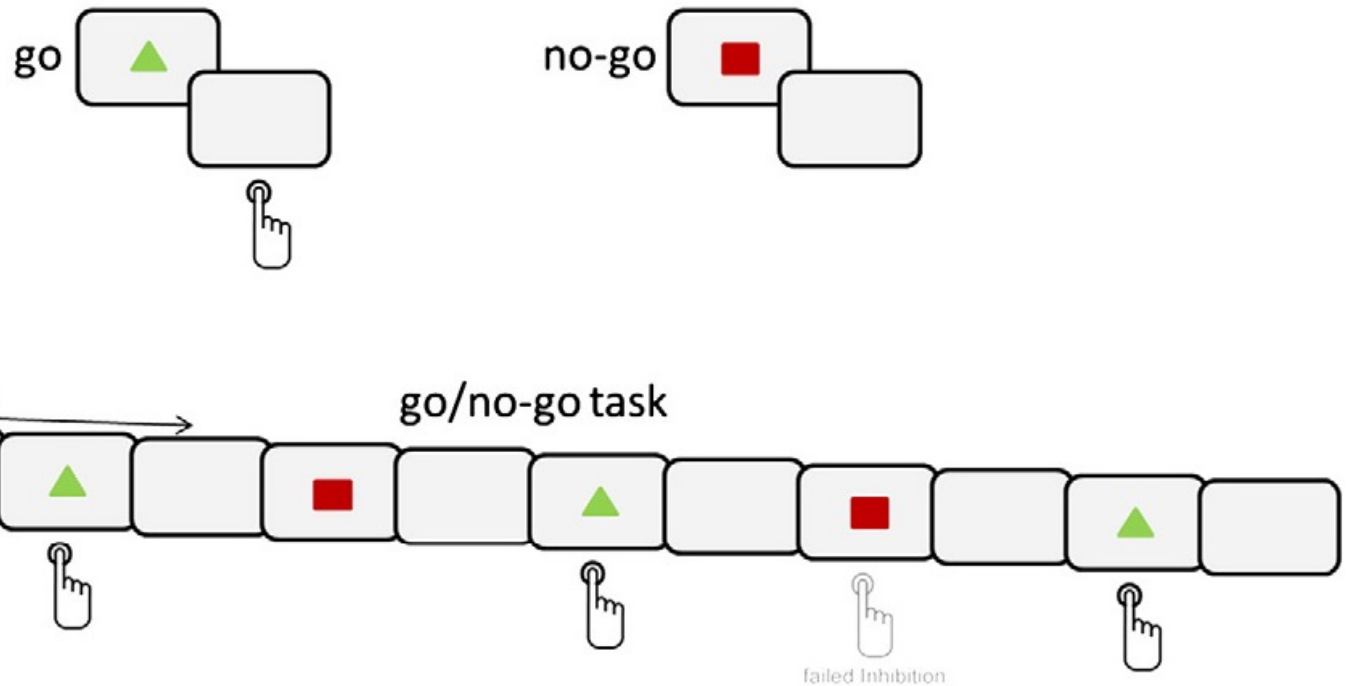
Verbal fluency is deficient in PD
Rapid generation of words in specific period of time

Semantic fluency: words from semantic category (animals, fruit)
Phonological fluency: words staring with the letter S
Alternating category fluency: if semantic fluency is alternating between animals and fruit

Kulisevsky et al., 2013

Response inhibition

Go/no-go task tests inhibition (subject asked to press or not to press a response button as fast as possible)



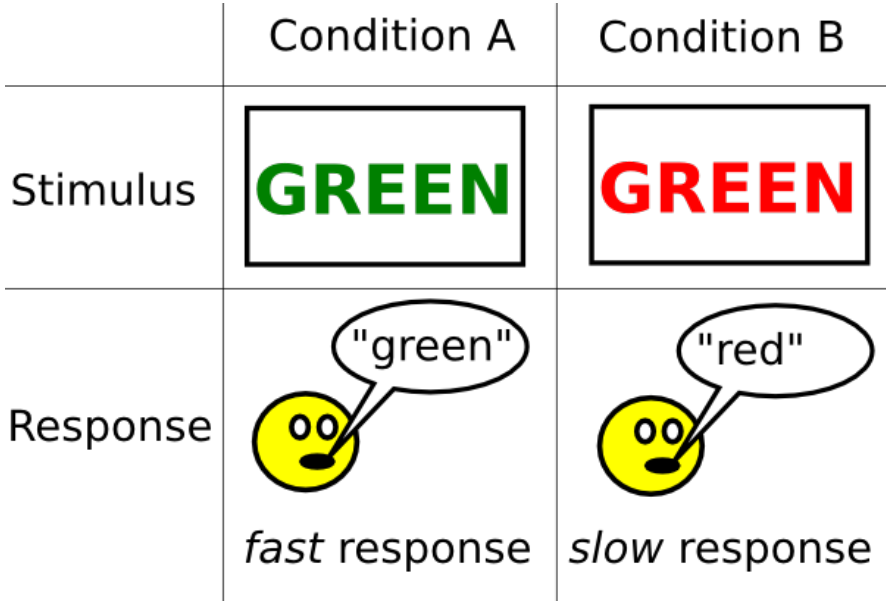
Inhibitory processes are deficient in PD (many failed inhibitory responses)

Response inhibition in the Stroop task

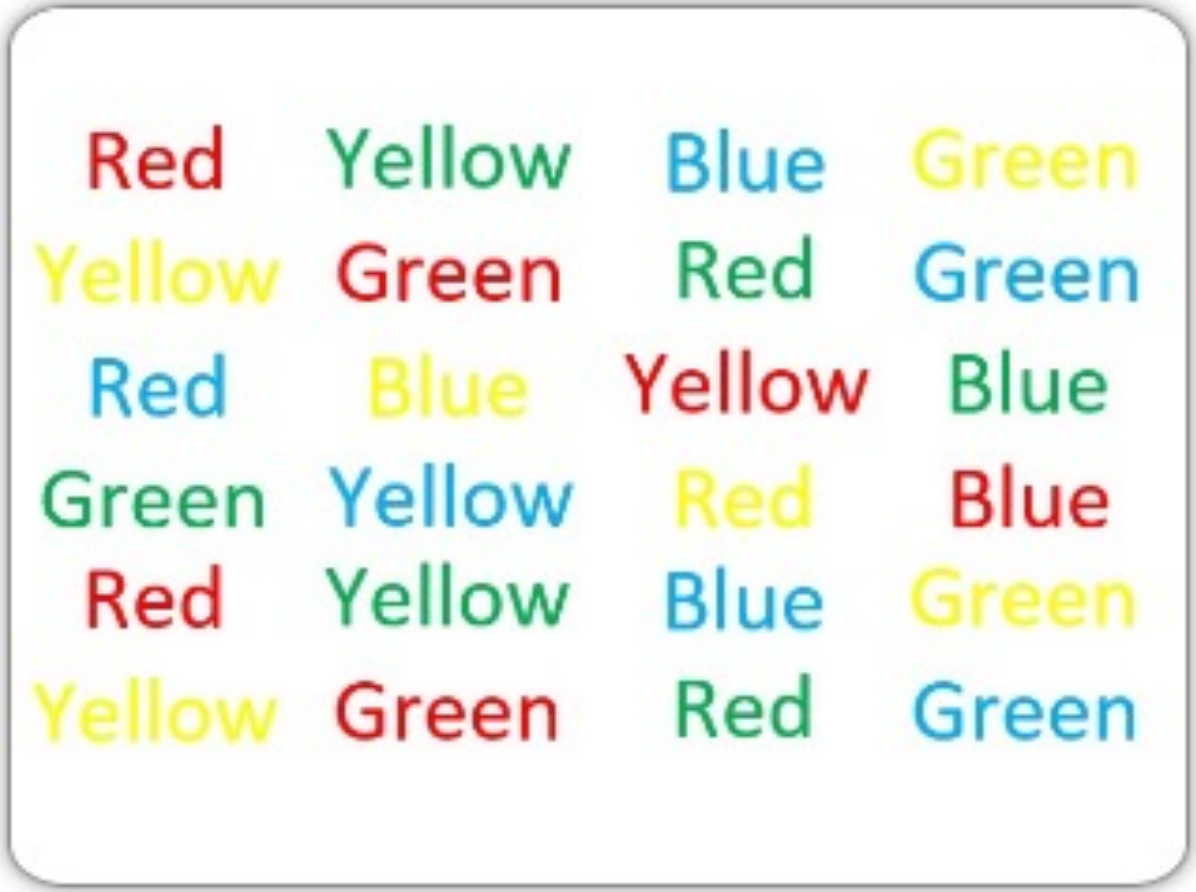
Another test that investigates inhibition

Subjects are asked to name the color of the ink/font (and to not 'read' the word) and to do this as fast as possible.

Reaction time and errors are measured



PD patients are slower than controls and make errors in this task



1	control
	dog
	chair
	boat
	window
	block
	fan
	wheel
	tray
	bottle
	fence

2	compatible
	red
	yellow
	green
	blue
	red
	blue
	yellow
	green
	blue
	red

3	incompatible
	red
	yellow
	green
	blue
	red
	blue
	yellow
	green
	blue
	red

Cognitive impairment in PD

… language and memory are generally not impaired

Important:
Other major cognitive functions (aparts from frontal lobe functions) are typically **NOT** impaired, at least not until later phases of PD.

-**Language functions are preserved** (PD impairment is a non-aphasic cognitive impairment)

-**Memory (long-term) is preserved**, especially long-term memory is normal (verbal and visuo-spatial memory) (PD impairment is a non-amnestic cognitive impairment)

-Eventually 40-50% of PD patients will develop dementia over 7-20 years

A detailed neuropsychological examination allows to distinguish the PD-related cognitive impairment from the impairment of other neurodegenerative diseases.

For example Alzheimer's disease, characterized clasically by an predominant amnestic cognitive impairment.

If the cognitive deficits are very strong at diagnosis with existing parkinsonian motor symptoms (bradykinesia, tremor, rigidity)
→ probably not PD, but DLB (see later).

Cognitive impairment in PD

Concerns functions mediated by frontal-subcortical networks

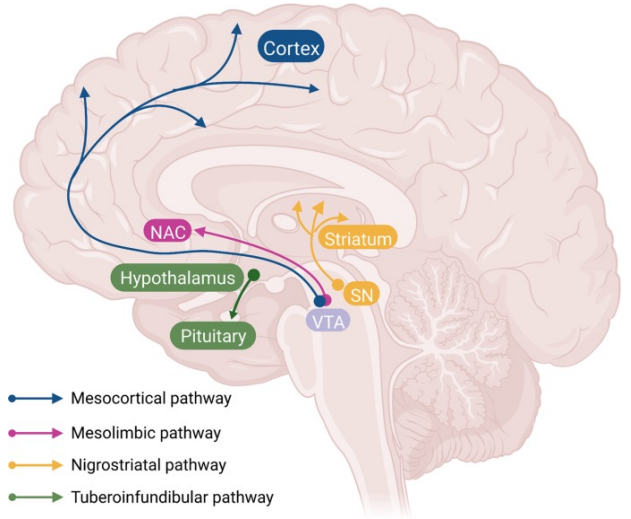
Cognitive impairment in PD has been linked to nigro-striatal-frontal pathology (impairment and slowness in fluency for example has been described as **bradyphrenia** (slowness of the mind), a slowness of initiation, alternation, and learning in cognition)**.**

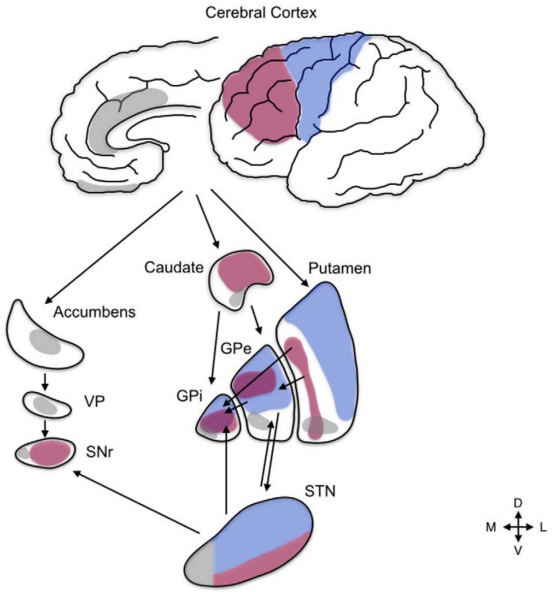
-Striatal dopamine depletion linked to the nigro-striatal projections to the striatum and to premotor and frontal cortex is involved in cognitive deficits in PD.

This was shown by ...
... **initiation of dopamine replacement therapy at the beginning of PD leads to incomplete but significant improvement of frontal lobe cognitive dysfunctions** (i.e., Kulisevsky et al., 2000).

- **significant improvement of frontal lobe cognitive dysfunctions** also observed when comparing PD patients in **ON vs. OFF dopamine medication** phases, later in the disease (Cools et al., 2002)

Alterations in dopamine pathways and frontal-basal ganglia pathways in PD cause cognitive impairments





Kulisevsky et al., 2013

Cognitive impairment in PD

… MCI in PD versus PD Dementia and their clinical relevance

Degree of cognitive impairment: MCI vs. dementia in PD (PDD)

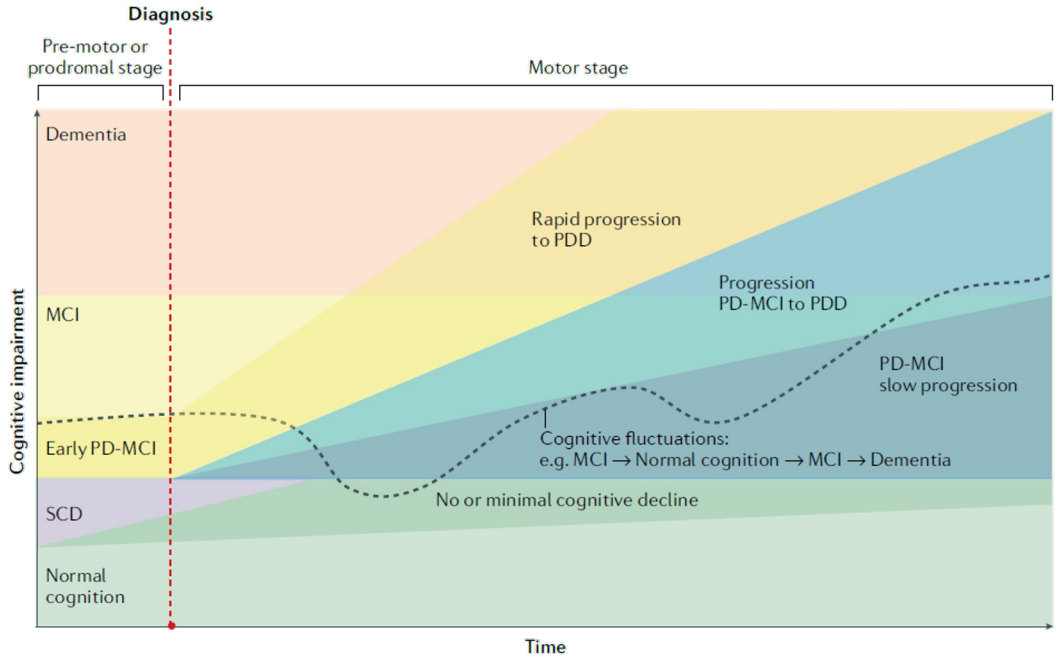
MCI (PD-MCI; 80%)
Mild cognitive impairment
-1 significant cognitive deficit detected by specific neuropsychological test
-**Impairment does not impact daily life and functioning of patient**

Dementia (PDD; 50%)
-Significant cognitive deficit detected by specific neuropsychological test in at least 2 of 4 cognitive domains (executive functions, attention, visuo-spatial functions, memory)
-**Impairment significantly impacts daily life**

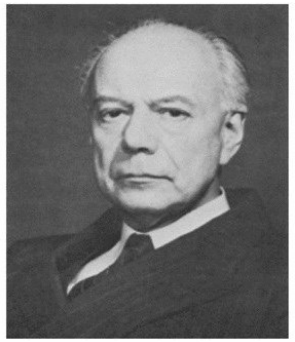
PD patients advancing from MCI to dementia (PDD) show significant disturbances in additional cognitive functions other than frontal-subcortical functions, involving parietal and temporal cortex:
-perceptual tasks
-visuo-spatial tasks
-memory

Clinical relevance of cognitive impairments in PD

Cognitive impairments, even MCI, have been linked to ...
...lower quality of life
... a more severe and more rapidely advancing form of PD
... earlier nursing home placement
... Higher mortality



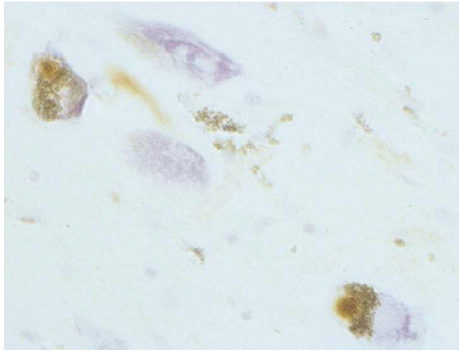
Aarsland et al., 2021; Heinzel et al., 2019; Kulisevsky et al., 2013



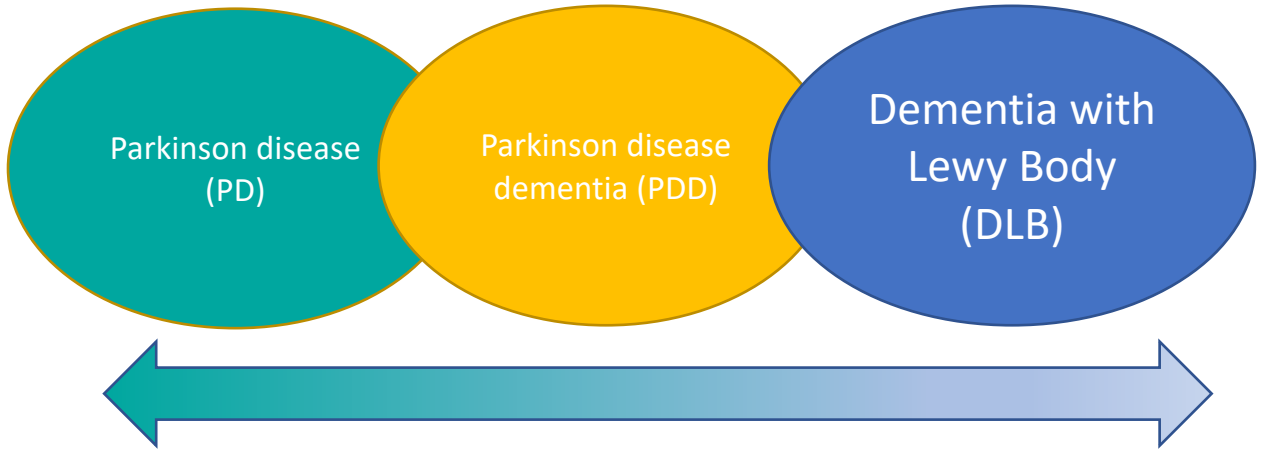
Fritz Lewy
(1885-1950)

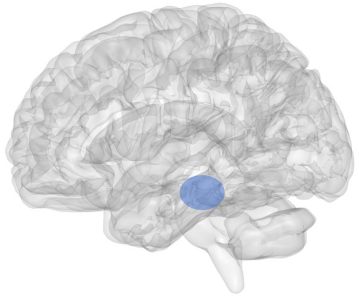
Dementia in PD and its distinction from dementia with Lewy bodies (LBD)

Three diseases on the Lewy body spectrum

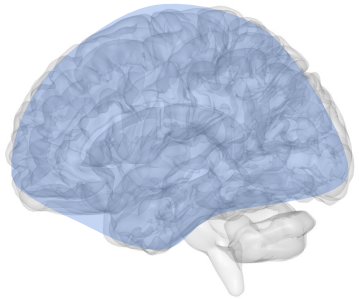


Godaert, Science 2015





Predominant early neurodegeneration is in the basal ganglia, but neurophysiological and network changes also involve the cortex



Global distributed pathology, from onset

Dementia in PD and its distinction from dementia with Lewy bodies (DLB)

Three diseases on the Lewy body spectrum

Robin Williams
Susan Schneider Williams (Neurology, 2016)

PD

Central clinical feature:
-always with **parkinsonian motor symptoms** (bradykinesia, rigidity, tremor)
-no dementia at moment of PD diagnosis, no dementia within the first year after PD diagnosis
-MCI develops progressively over many years, involving mainly frontal loby dysfunction (see previous slides)

PDD

Central clinical feature:
-always with **parkinsonian motor symptoms** (bradykinesia, rigidity, tremor)

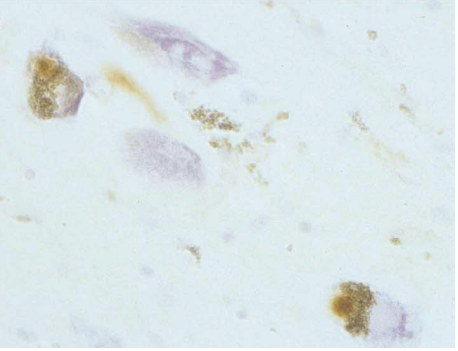
Core clinical PDD feature:
-**Dementia develops more quickly** than in PD, but **never earlier than 1 year** after diagnosis of PD (motor symptoms)
-frontal loby dysfunction (see previous slides) and progressively other posterior functions

DLB

Central clinical feature:
If parkinsonian symptoms are also present dementia is already present or starts within the first year after the motor symptom onset; DLB can also present/start without PD motor symptoms and only with dementia.
-frontal lobe dysfunction (similar but more severe/advanced then PDD, memory not impaired in early phase)

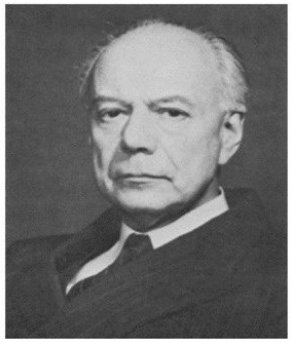
Core clinical DLB features:
-**Hallucinations** (more frequent than in PD or PDD; Aarsland et al., 2001)
-**Parkinsonian motor symptoms** (bradykinesia, rigidity, tremor), but they can also be absent in DLB (not needed for diagnosis)
-**Fluctuating cognition** and alertness (more prominent than in PDD)

Londos, 2013

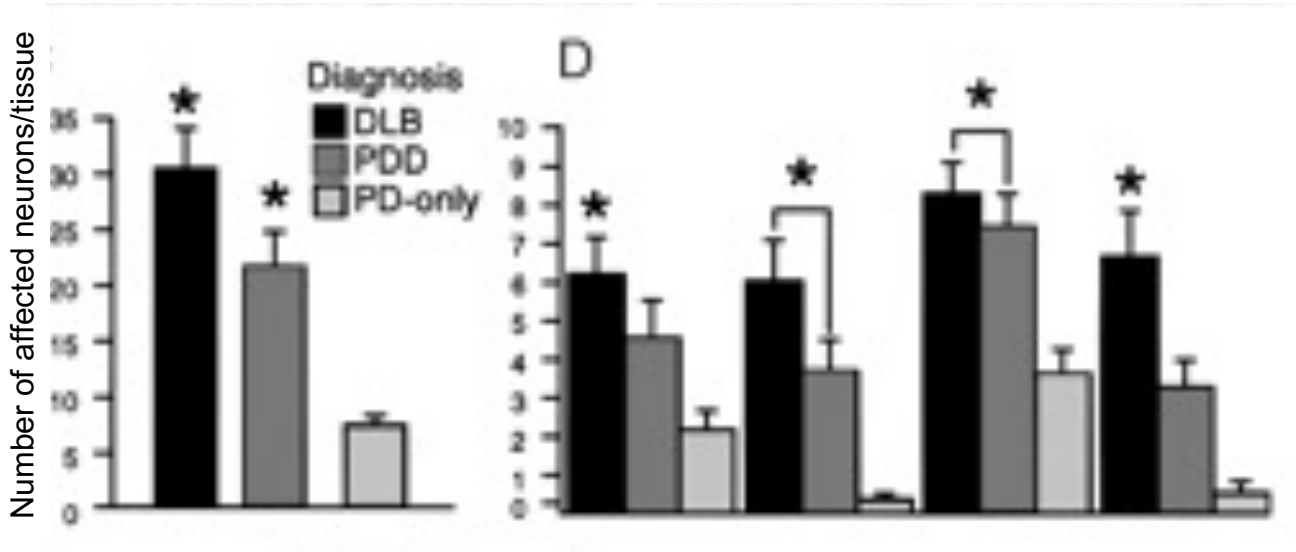


Godaert, Science 2015

PD, PDD & DLB have different Lewy body pathology, highest in DLB (pathology, post mortem)



Fritz Lewy
(1885-1950)



DLB patients have higher number of neurons affected by Lewy body pathology than PDD or PD, globally (full brain) and per investigated region.

Harding et al., 2015

Conventional (open-loop) DBS may have negative effects on cognitive function in PD (not covered in class)

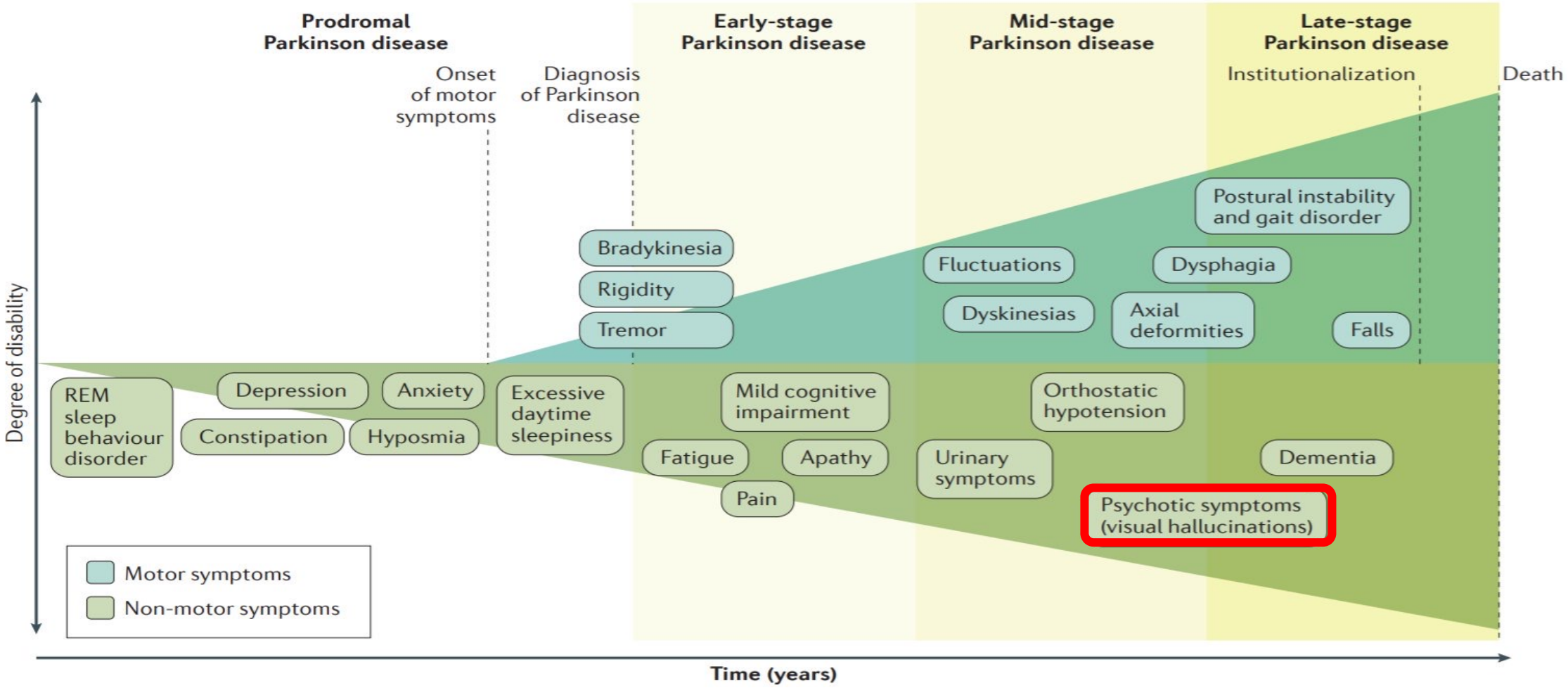
Saint-Cyr et al., 2002; Pal et al., 2022

Another major non-motor symptom in PD

Hallucinations (& illusions)

Hallucinations in PD

A frequent non-motor symptom that is very frequent in late PD

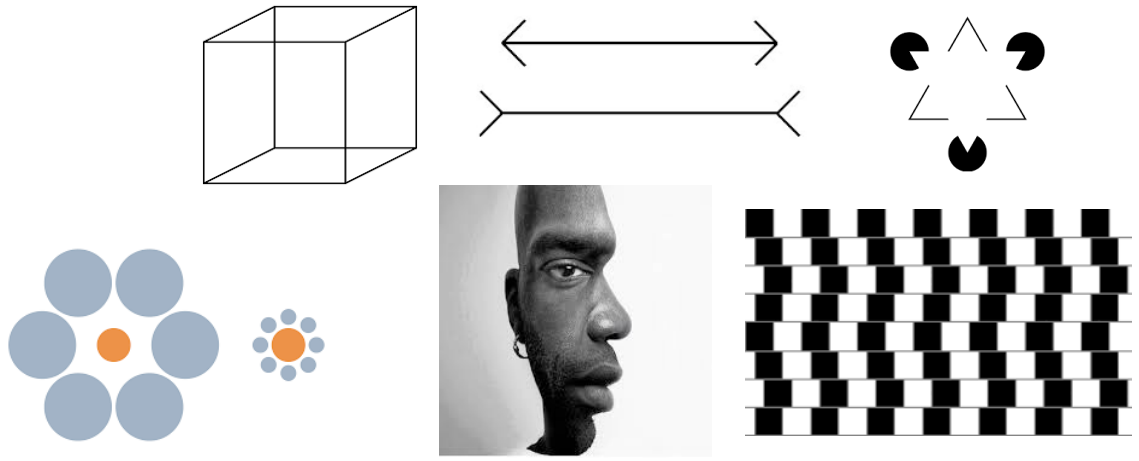


Poewe et al., 2017

Hallucinations & Illusions

Definitions, two types of false perception

Visual Illusions
(= errors in perception for a stimulus that is present)



Hallucinations

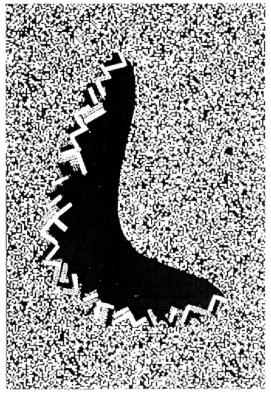
(= errors in perception for a stimulus that is NOT present)

Hallucinations are not specific to PD, but frequent …

Typical hallucinations in medicine

Auditory verbal hallucinations (voices) (schizophrenia)
Complex visual hallucinations (PD, Dementia with Lewy bodies)
Simple visual hallucinations (migraine)
Olfactory hallucinations (epilepsy)

Presence hallucinations (PD)

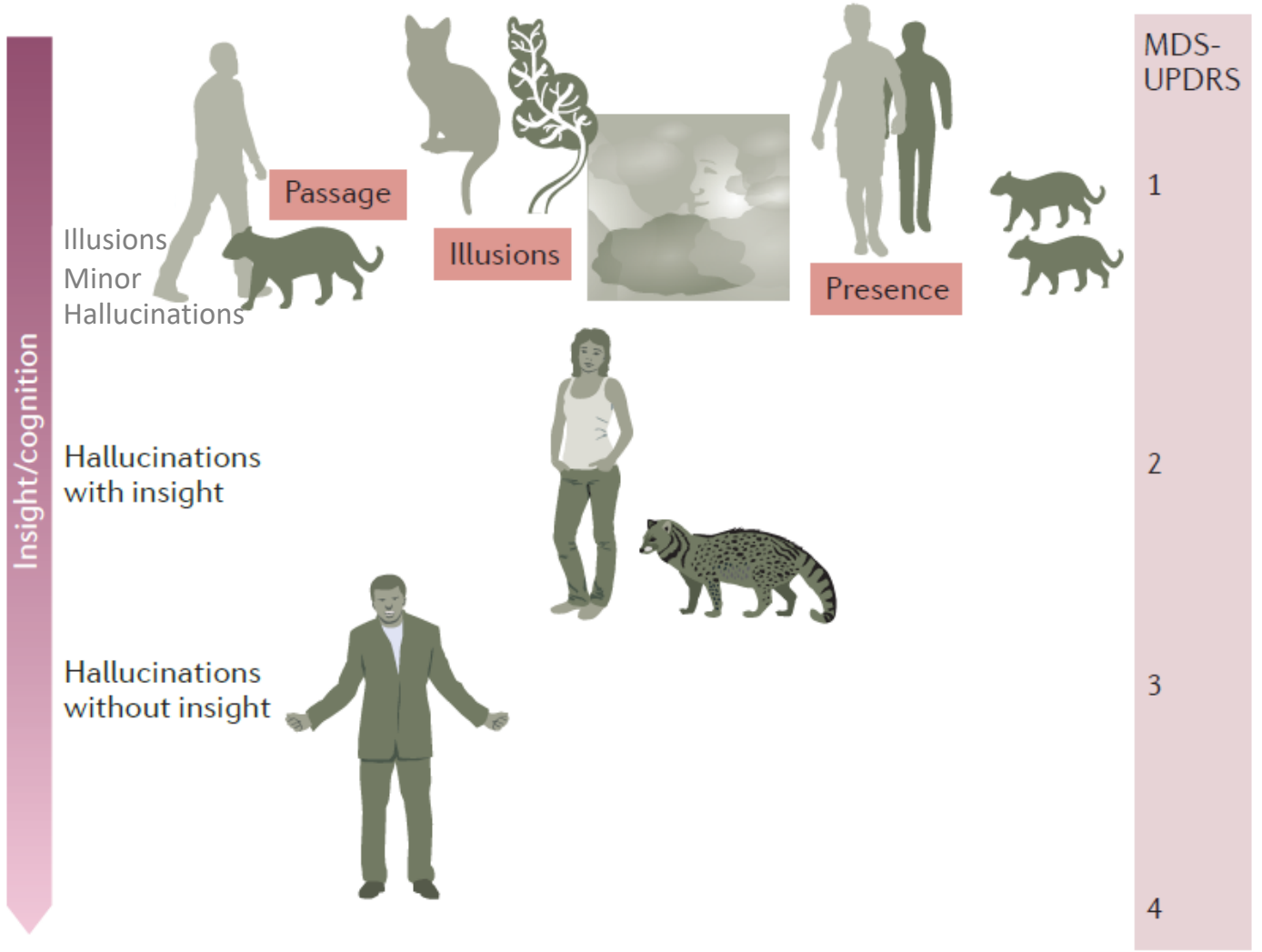


Hallucinations in PD

Illusions & minor hallucinations

Minor hallucinations
Presence Hallucination
Passage Hallucination

Complex visual hallucinations
People
Animals



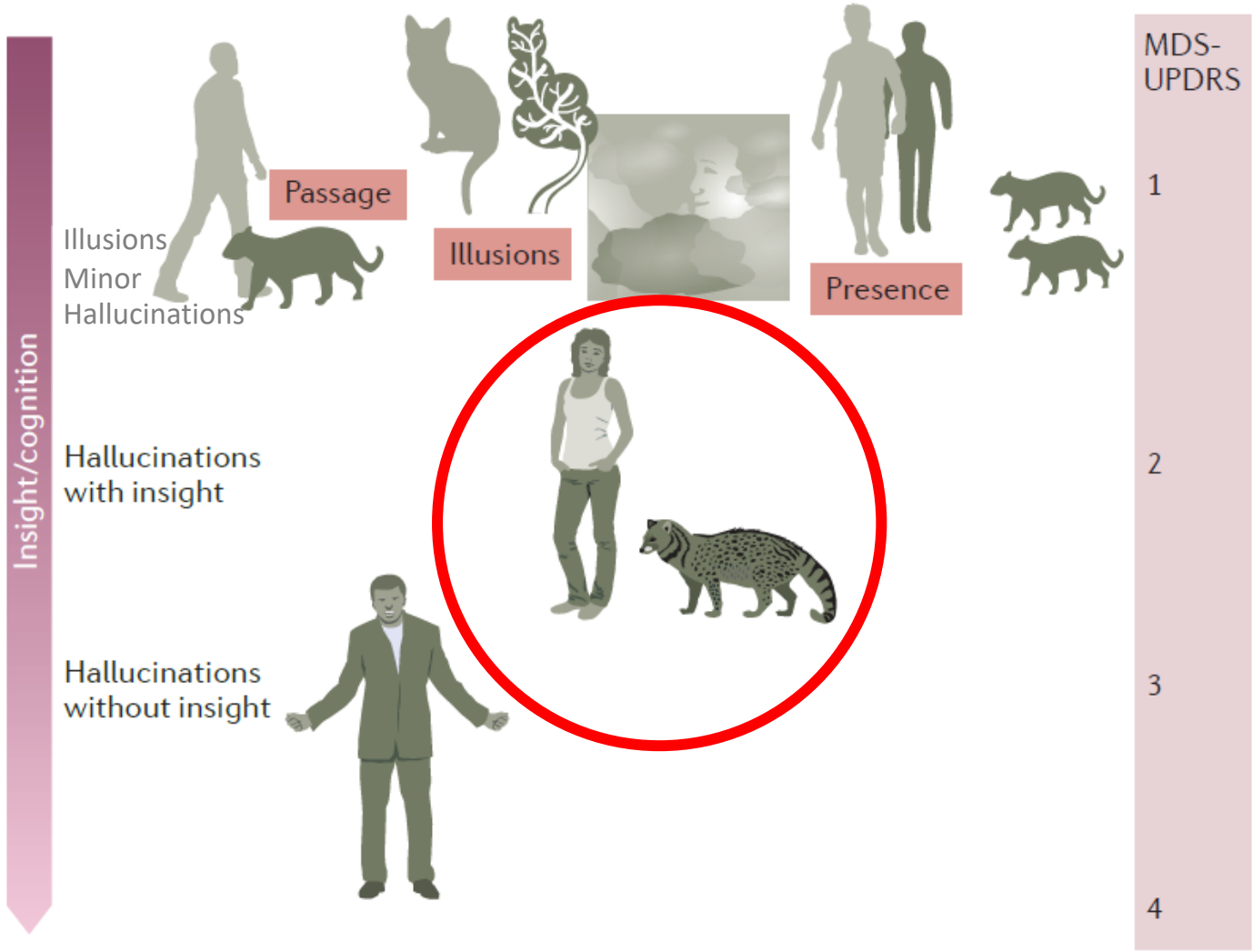
Visual Illusions
Pareidolia

Hallucinations in PD

Illusions & minor hallucinations

Minor hallucinations
Presence Hallucination
Passage Hallucination

Complex visual hallucinations
People
Animals



Visual Illusions
Pareidolia

Complex visual hallucinations (VH) in PD

Illusions & minor hallucinations

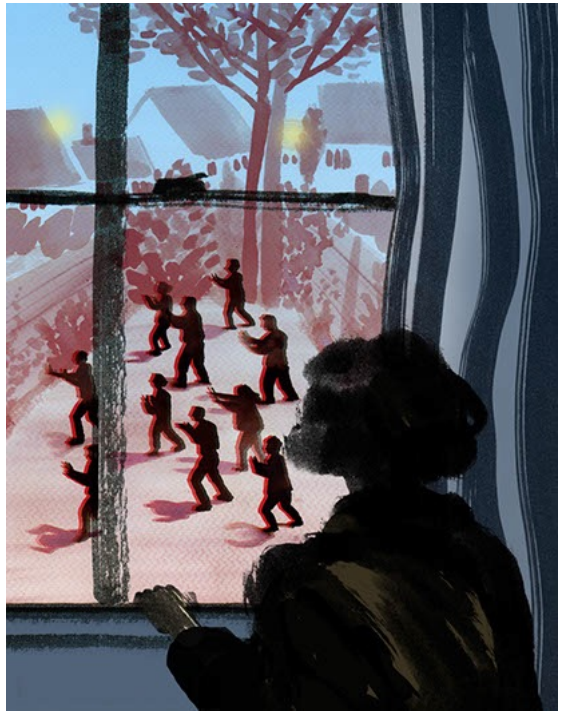
VH are …
-VH are complex VH and consist of “seeing” **humans** and/or **animals** (that can be moving)

-**chronic**, VH persist in patients
-**repetitive** in content (stereotypical)
-of **short duration** (seconds)

-more frequent under dim light conditions (evening at home) and in conditions of lightly reduced vigilance (evening, before going to bed), but otherwise clear sensorium

Complex Visual Hallucinations
-**develop late in the disease** course (= many years after diagnosis)
-occur after long-term-exposure to dopamine replacement therapy

-VH can also occur early on, but this is not typical for VH in PD (this is more typical for another neurodegenerative diseases, Dementia with Lewy Bodies or DLB)
-yet, the **phenomenology of VH is strikingly similar in PD and DLB**



Diederich et al., 2009

Animated short film (*Another Presence*) about visual hallucinations

Dementia with Lewy bodies (and PD)

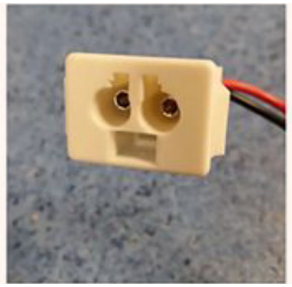
https://www.youtube.com/watch?v=tv4E0fU08hM

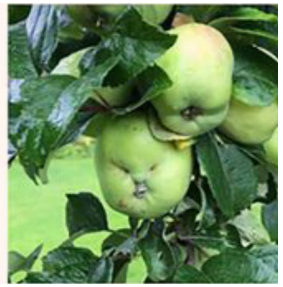
Visual illusions in PD

Visual illusions & Pareidolias

Visual illusions
-misperception of visual objects that are physically present
-need to be discriminated from VH
-**precede VH in the course of PD**
-examples: visual perseverations, inanimate objects are perceived as living beings or parts of living beings (show some examples)

Pareidolias
-illusion: identity/meaning is attributed to misperceived object
-needs to be discriminated from VH
-precede VH in the course of PD





Perceiving inanimate objects as animate (PD)

Visual perseveration (PD)

Complex visual hallucinations (VH) in PD

Prevalence

Frequency of VH
-present in **30-40% of PD patients**
-more in PD with dementia (PDD) = 50% (i.e. as frequent as in DLB)
-frequency of PD patients with hallucination-like phenomena is **40-75%** (if you include visual illusions and minor hallucinations, MH)
-**VH frequency increases over time**, reaching 75% after 20 years
-once a patient has VH, they persist
-**VH worsen over time**: more frequent, more intense, loss of insight (in only 3 years !)

Hallucinations are probably underreported because …
-Many patients do not spontaneously report their hallucinations (fear of stigma, fear of being considered as “crazy”)
-many researchers and clinicians do not ask about hallucinations in PD
-most studies involve patients in movement disorder clinics (selection bias)
-current questionaires and standard interviews lead to underestimation

Diederich et al., 2009

Complex visual hallucinations (VH) in PD

What causes hallucinations in PD ? There is evidence in favor of a medication-induced toxic syndrome

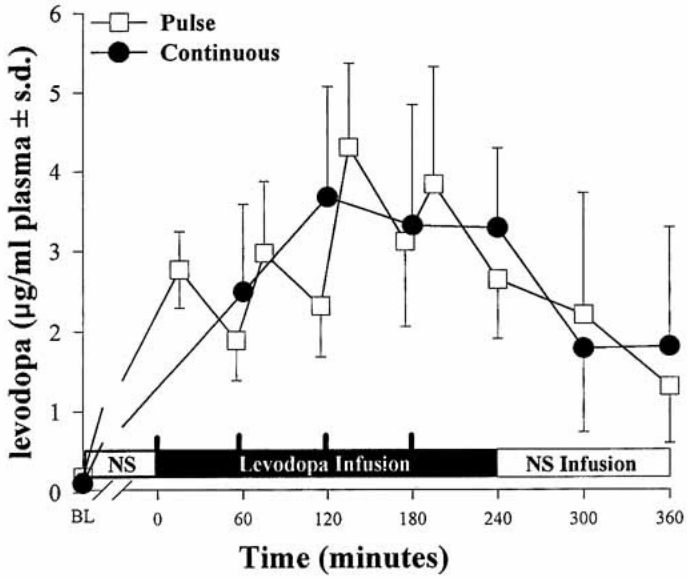
Dopamine
-PD leads to presynaptic striatal dopamine depletion caused by degeneration of the nigro-striatal pathway, which has been shown to lead to hypersensitive/upregulated postsynaptic dopamine receptors: →
Excess dopamine from medications could lead to VH

But ...
... daily dopamine dose by PD patients with VH does not differ from PD patients without VH (Merims et al., 2004; Sanchez-Ramos et al., 1996)
... High-dose intravenously injected dopamine does not induce hallucinations (Goetz et al., 1998)
... all types of dopaminergic treatments (also those targeting presynaptic dopamine) can exacerbate VH
... VH occurred in PD **before dopamine was discovered** and established as standard therapy

… anticholinergic drugs also involved (Goetz et al., 1982), but they differ from typical PD hallucinations (i.e., no clear sensorium).

-VH are inherently linked to PD
-Dopamine can induce VH, but these do not reflect classical VH in PD
-Other important processes are also involved

In the study by Goetz (1998)
... all patients had daily VH (humans, animals)
... none had non-visual hallucinations
... none had dementia
→ Study administered dopamine i.v.

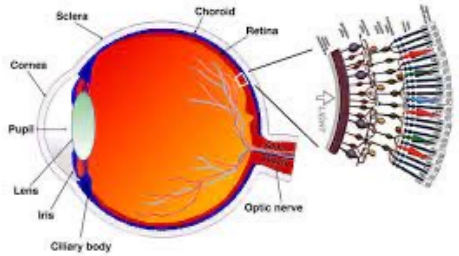


No habitual hallucinations were induced in any of the 5 tested patients (but 2 had their habitual dopamine side effects (dyskinesias)

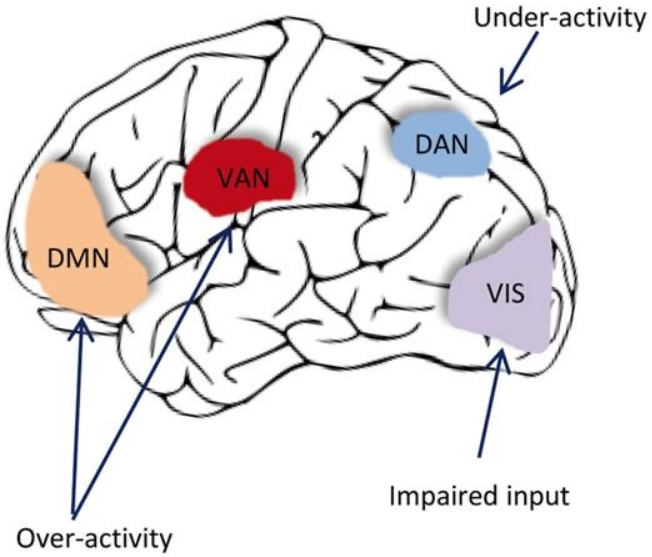
Goetz et al., 1998; Diederich et al., 2009

Several potential causes for complex visual hallucinations (VH) in PD

Visual deficits are reflected in structural changes at many levels

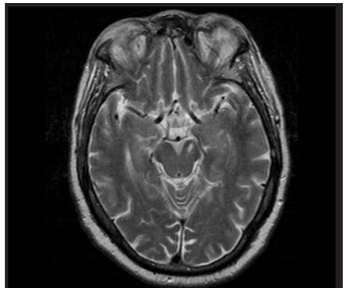


Retina
-retinal abnormalities have been described (not covered in this class)

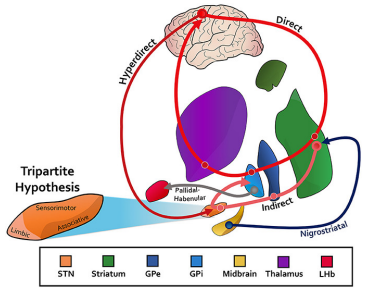


Cortex (this class)
-reductions in grey matter volume (MRI) in lingual gyrus (area 18), but also in extrastriate regions
-confirmed in pathological work (post-mortem)
-ventral pathway and the dorsal pathway of the visual system are impaired
-but also frontal cortex !

Brainstem
Lhermite syndrome with visual hallucinations
(post-brainstem stroke to sleep-regulating structures)
(not covered in this class)



Basal ganglia and thalamus
(not covered in this class)



Complex visual hallucinations (VH) in PD

Patients with PD and VH suffer from visual dysfunctions

Visual perceptual dysfunctions in PD and these are stronger in PD with VH

Impairments in ...

... color perception in PD patients with VH

... face perception

... form perception

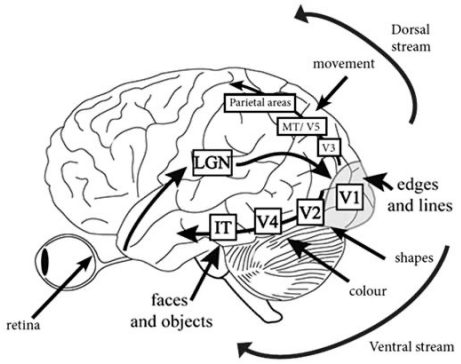
... visuo-spatial deficits

... bistable visual perception

... visual acuity

... contrast sensitivity

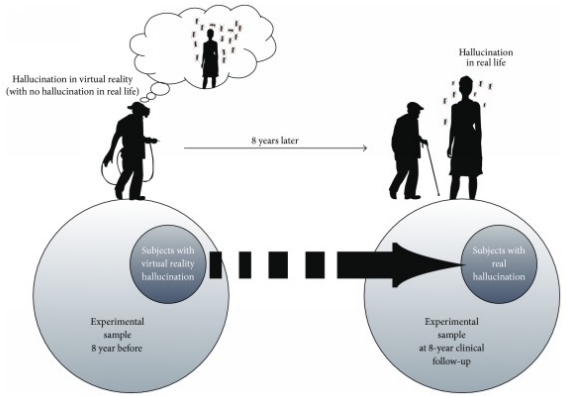
(Gallagher et al., 2011)



Virtual Reality may be able to induce VH in patients with PD

-35 minute session of VR induced in 6 of 23 PD patients VH (Onofrj et al., 2006)

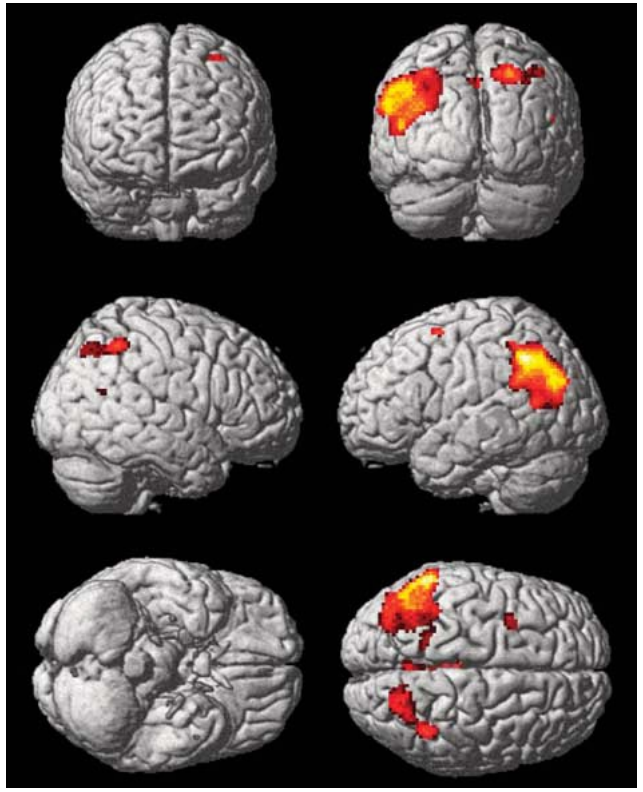
- If tested 8 years later, there is preliminary-anecdotal evidence that patients who had VH in VR, will develop VH in their real life (Albani et al., 2015)

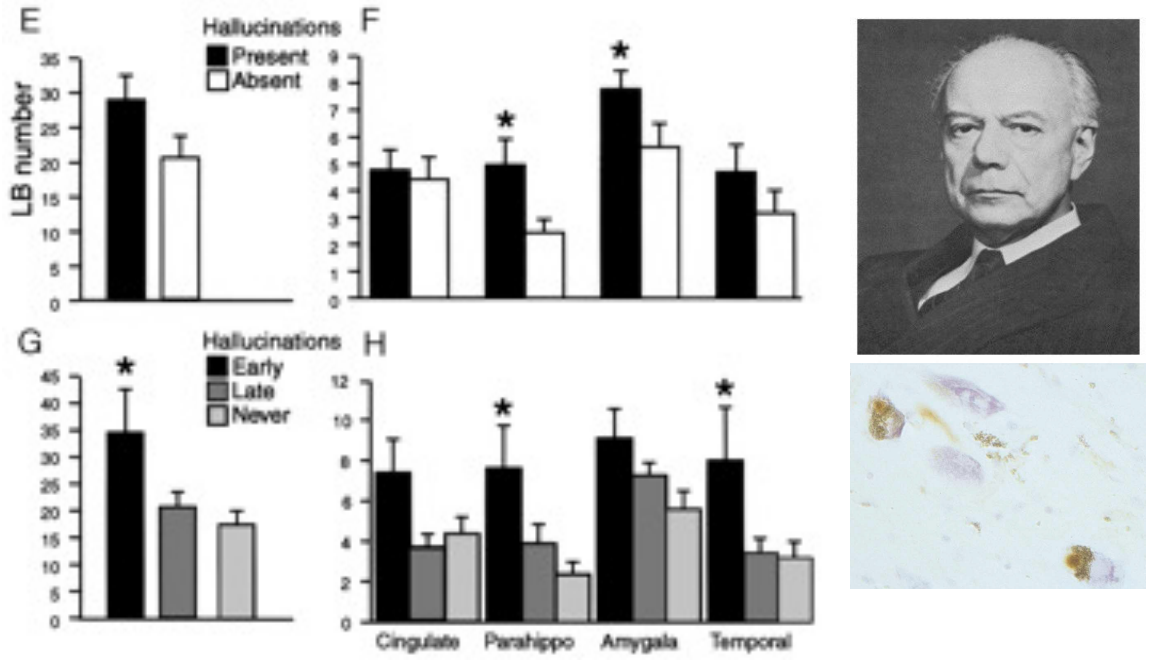


Shine et al., 2015; Weil et al., 2016; Uc et al., 2007; Albani et al., 2015; Diederich et al., 2009

Complex visual hallucinations (VH) in PD

Decreased activation in posterior visual cortex (extrastriate cortex) and higher Lewy body load in PD patients with VH versus PD patients without VH





PET study (no task)
-weaker extrastriatal (PPC and TPJ) activation in PD patients with VH versus PD patients without VH
(however, patient groups differend in disease duration; longer in PD-VH)

Boecker et al., 2007

Pathology (Lewy bodies)
-more Lewy body pathology in PD patients with VH versus PD patients without VH (includes DLB, PDD, PD)
-in all tested brain regions
-especially when hallucinations start early (= DLB)

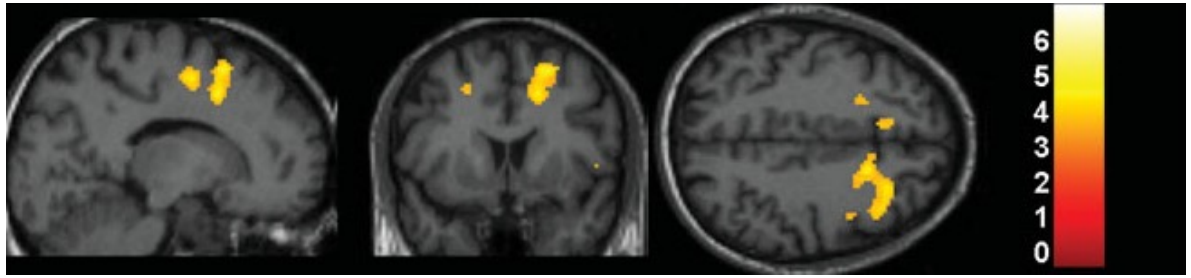
Harding et al., 2002, Papapetropoulos et al., 2006

Complex visual hallucinations (VH) in PD

Enhanced brain activations in frontal cortex during the perception of visual stimuli when comparing PD patients with VH versus PD patients without VH

Face perception study (fMRI)

Stronger frontal activation in PD patients with VH versus PD patients without VH (Ramirez-Ruiz et al., 2008)



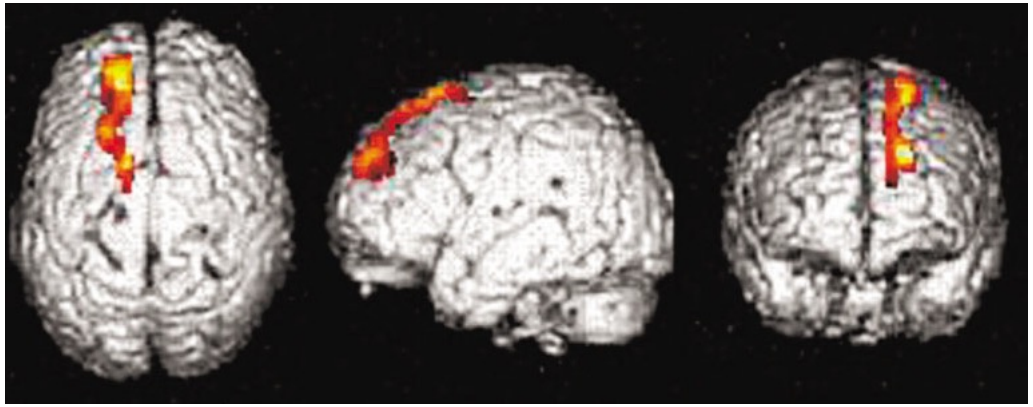
Motion perception study (fMRI)

-Stronger frontal as well as striatal activation in PD patients with VH versus PD patients without VH

-Deactivation in extrastriate visual areas and posterior parietal cortex in PD patients with VH versus PD patients without VH

(Stebbins et al., 2004, data not shown)

PET study also reveals stronger frontal activation in PD patients with VH versus PD patients without VH (Nagano-Saito et al., 2004)

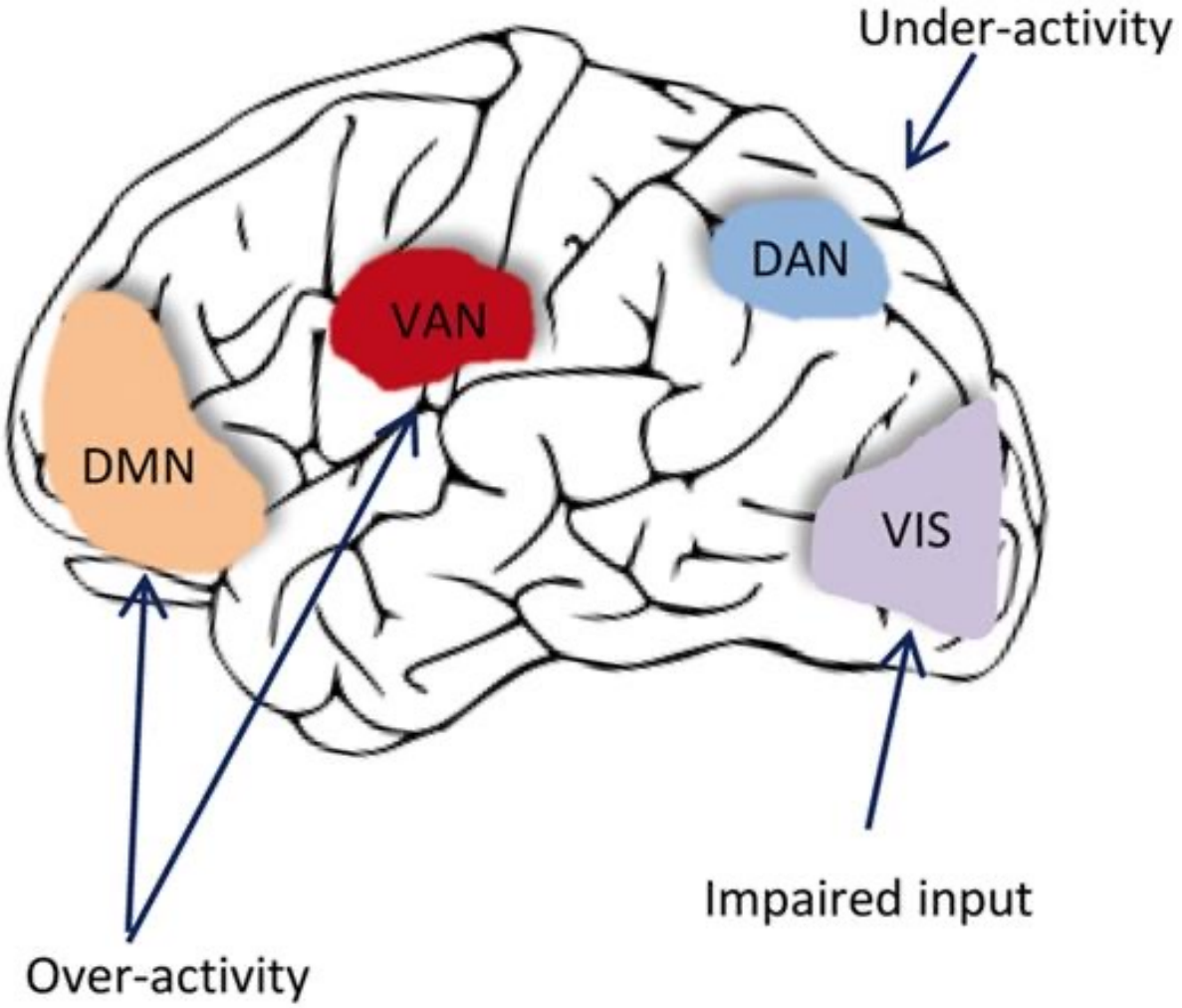


Data compatible with an imbalance of cortical activity – an increase of frontal (parietal) networks (involved in attentional, executive, inhibitory processes) to compensate for a decreased visual input in extrastriate and striate visual cortex.

Stebbins et al., 2004; Ramirez-Ruiz et al., 2008; Nagano-Saito et al., 2004

Complex visual hallucinations (VH) in PD

... a network disorder with impaired-decreased visual input-related activations and an overactivation of frontal executive and attentional networks



Weil et al., 2016; Shine et al., 2015

Minor hallucinations in PD

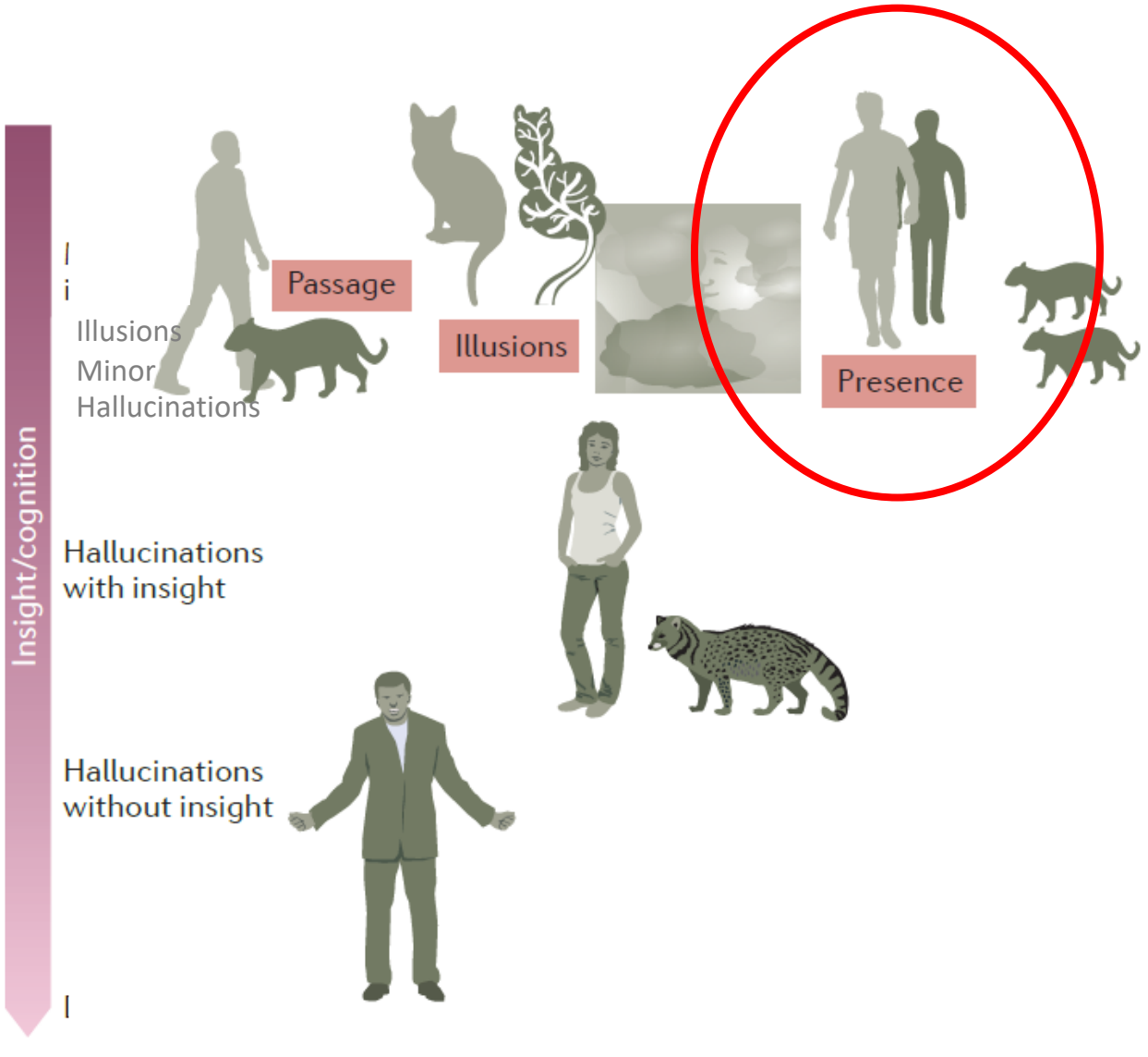
Presence hallucinations

(passage hallucinations)

Presence Hallucinations

Visual illusions
Simple Visual Hallucinations
Pareidolia

Structured complex visual hallucinations
People
Animals



Minor hallucinations
Presence Hallucination
Passage Hallucination

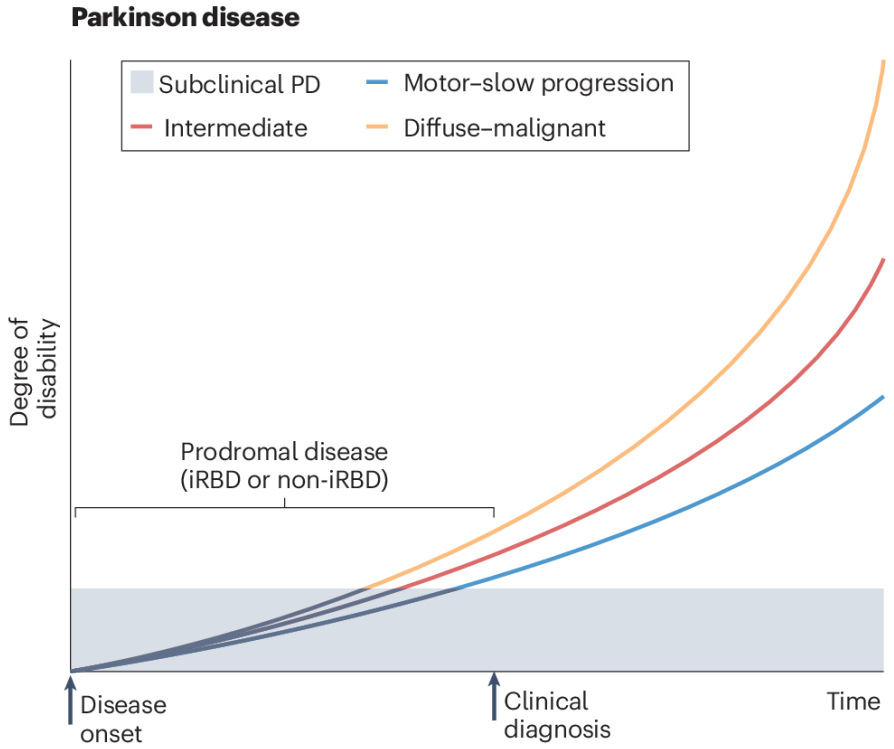
Presence Hallucinations in Parkinson's disease …

… are **frequent non-motor symptoms in PD** (**50-60%** of patients) and may occur weekly or daily.

… often with an **early onset** (in some PD patients even before the onset of motor symptoms).

… (like VH) PH are associated with **cognitive decline and dementia**, psychiatric complications, earlier home placement & higher mortality.

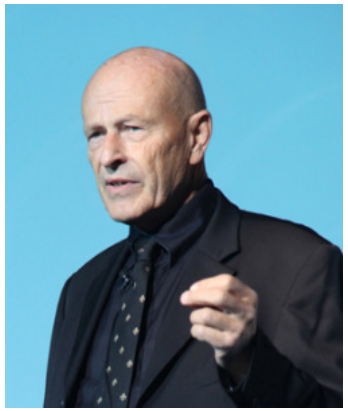
Hallucinations indicate a more severe and more rapidly advancing form of Parkinson's disease and presence hallucinations may indicate this early in the disease course.



[Wood et al., Front Neurol 2015; ffytche et al., Nat Neuro Rev 2017]

BLANKE LAB

CHAIR IN COGNITIVE NEUROPROSTHETICS



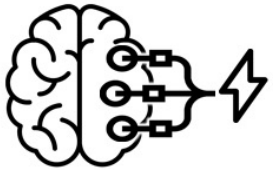

Thedi Landis & Peter Brugger
(1989, 1996, 1997, 1999)

-proposed that presences are linked to the self
- studied neurological patients with focal brain damage and presences
- linked presences to other autoscopic phenomena
- studied presences in extreme mountaineers

Gilles Fénelon
(2000, 2011)

-first to systematically describe presence hallucinations in Parkinson's disease
-first to discover that presence hallucinations are very frequent in early PD

<u>Sense of presence, Feeling of a presence, presence hallucination</u> is the hallucinatory perception that another person or being is in the space close by, mostly in the back (but person is not seen or heard or felt by touch)



Presence hallucination

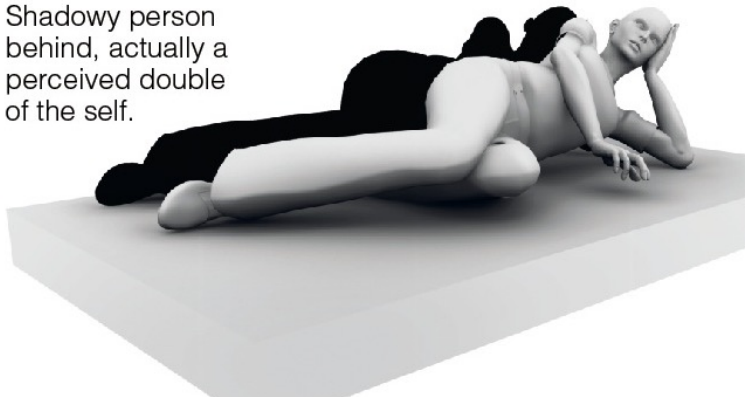
induced by stimulation of temporo-parietal cortex

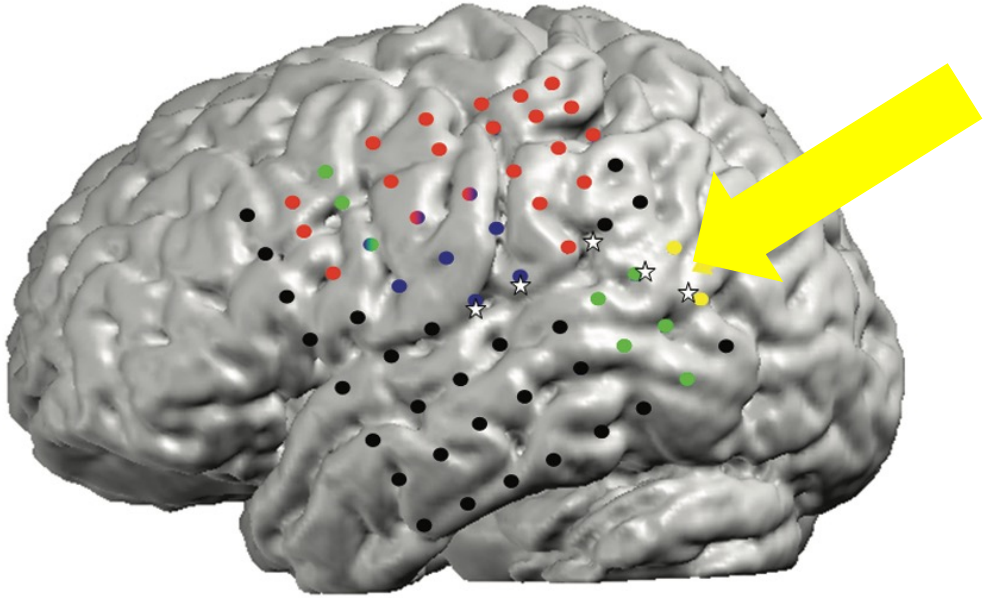
Shahar Arzy

23 year old female patient suffering from pharmacoresistant epilepsy (undergoing invasive presurgical epilepsy evaluation)

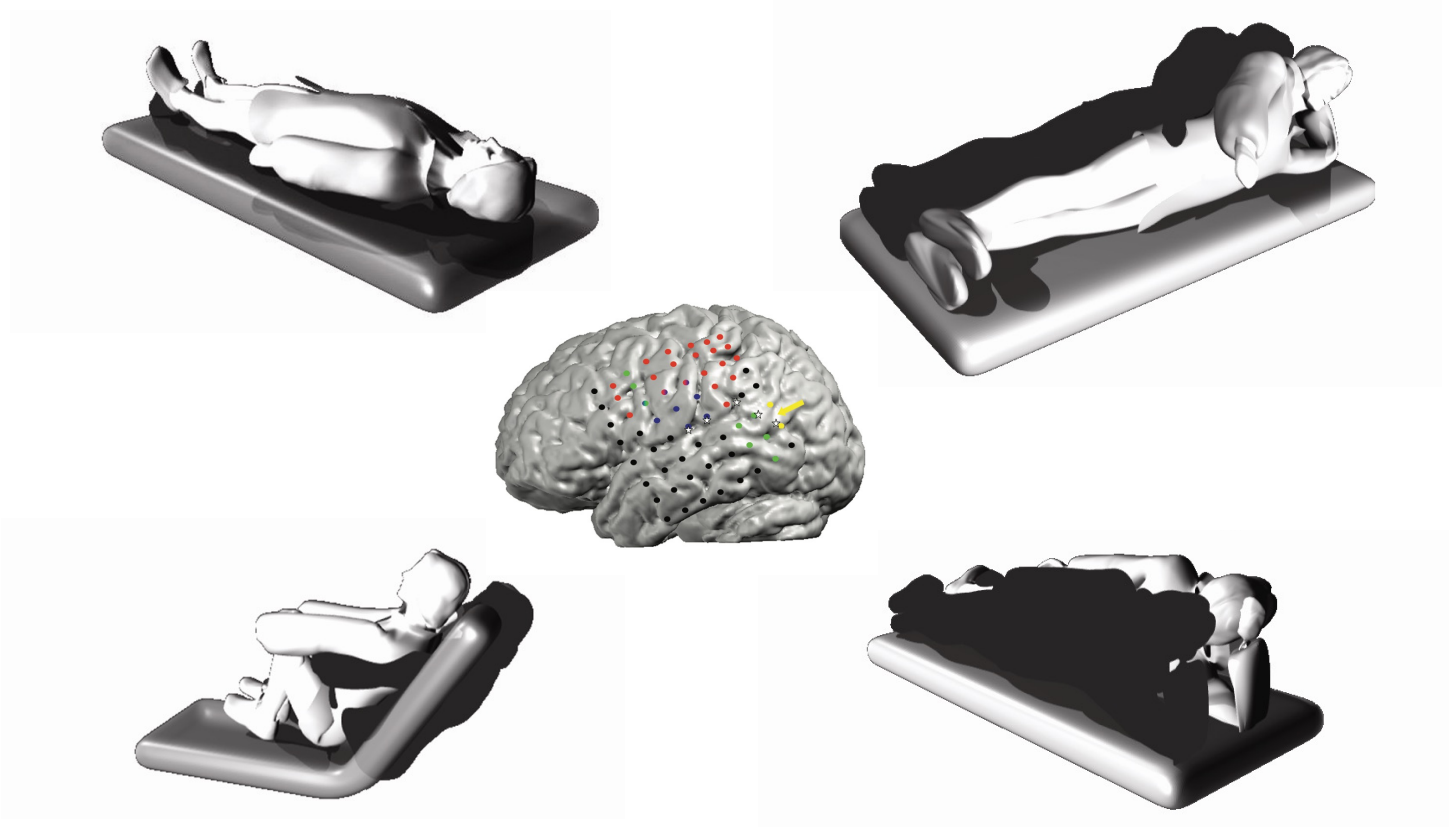
Focal brain stimulation in an epileptic patient induced repeated presence hallucinations (PH)

PH induction was site and current specific and lasted for the 2 seconds of current application





[Arzy et al., **Nature** 2006]



Presence hallucination is not seen or heard, but is 'felt' as another person who is close to patient's body; and has same posture and position as the patient (but is not perceived as self).

Experienced position and posture of the 'presence' depends on the position and posture of the patient's body: reveals the relevance of patient's own body perception (proprioception & touch) in generating a presence hallucination.

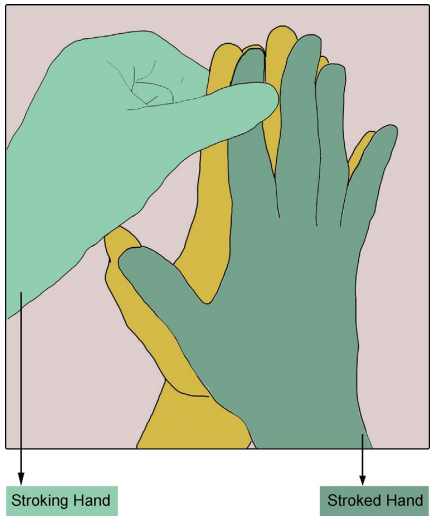
PH is a duplicated or second own body (a double, a 'Doppelgänger') that is misperceived as another person (not as a second self).

PH results from an altered self representation and is likely caused by errors in somato-motor perception.

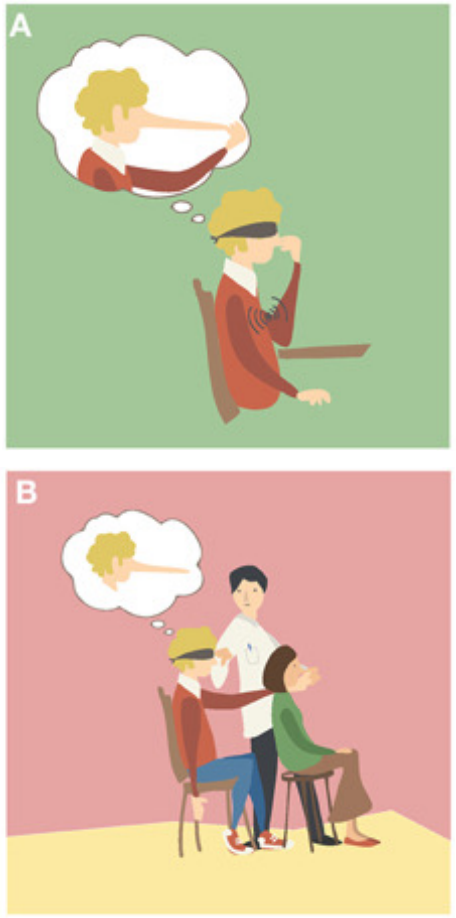
[Arzy et al., **Nature** 2006]

Classical illusions, false bodily perceptions & altered sense of self
--- induced by somato-motor stimulation ---

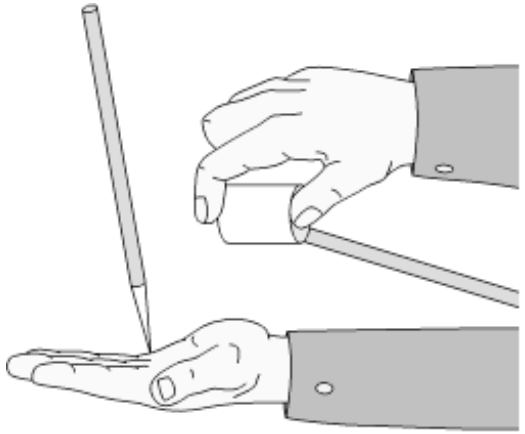
Numbness illusion



Pinocchio illusion

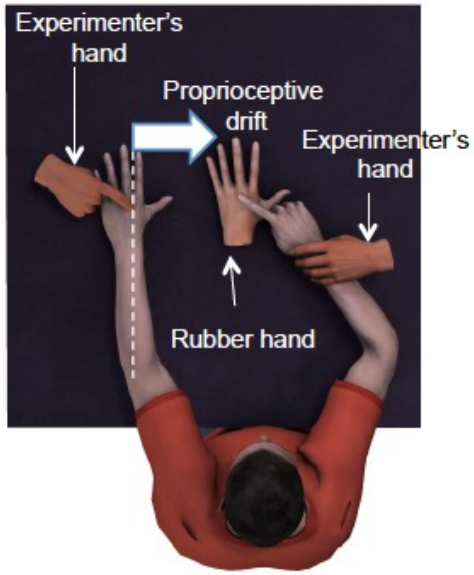


Ticklishness illusion



Ticklishness sensation
(sensory prediction signals)

Somatosensory rubber hand illusion

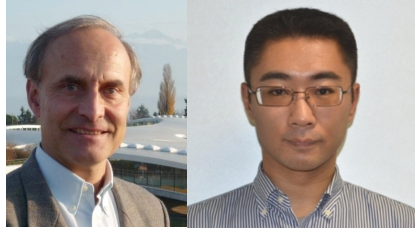


Illusory self-touch
Integration of tactile-proprioceptive signals

"…from the fact that a child can hardly tickle itself, or in a much lesser degree than when tickled by another person, it seems that the precise point to be touched must not be known" (sensory prediction). **Charles Darwin (1872)**

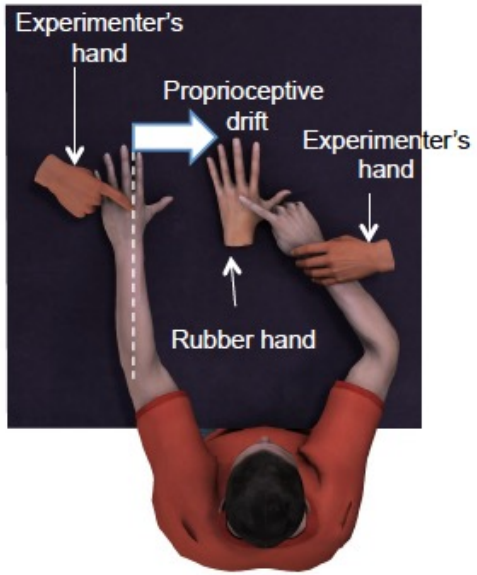
[**Weiskrantz et al., Nature 1971; Blakemore et al., Nature Neurosci 1998**; Boulmore, Science 1951; Ehrsson et al., JN 2006; Dieguez et al., Curr Biol 2009; Martuzzi et al., 2013]

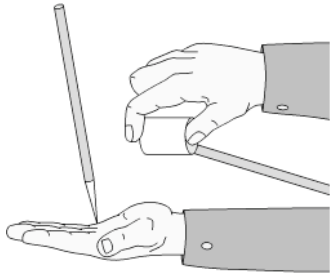
Extending body-part centered experimental setups to sensorimotor stimulation involving the global body representation (torso)

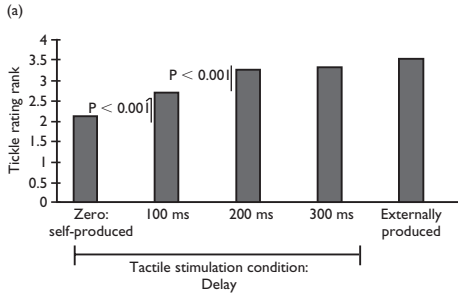


Hannes Bleuler
Masayuki Hara

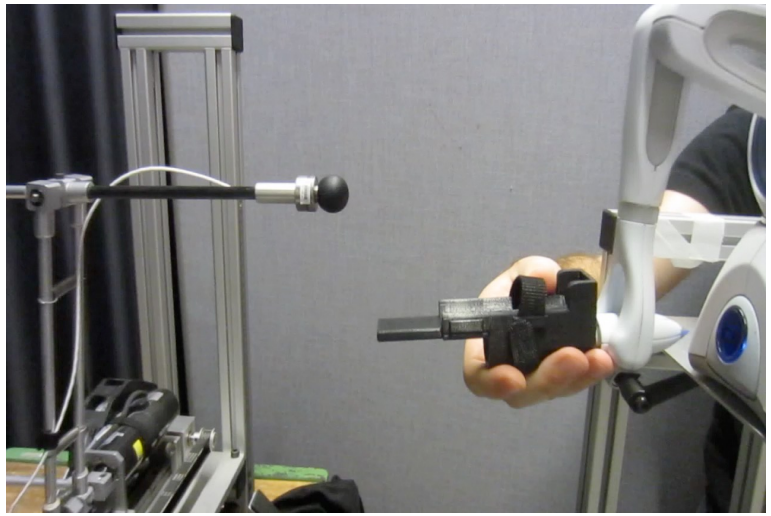
Somatosensory-motor stimulation
(sensorimotor prediction signals)



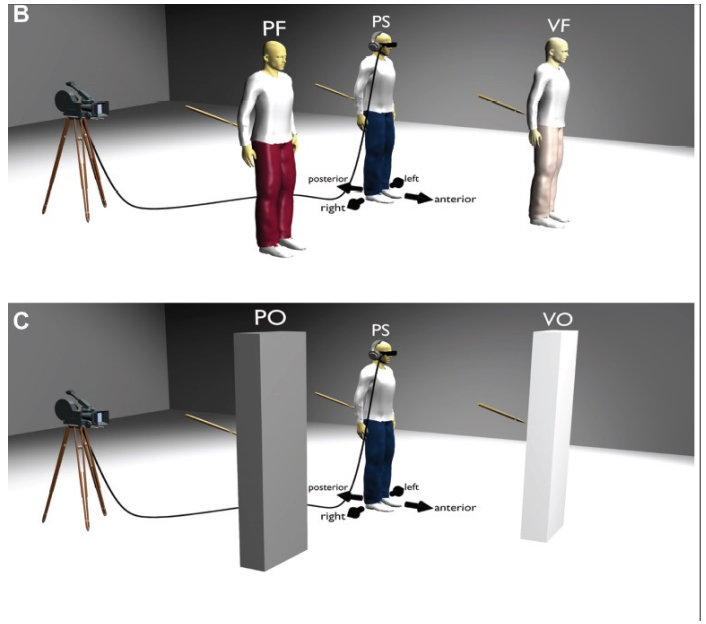




Robotic system designed for hand-torso feedback



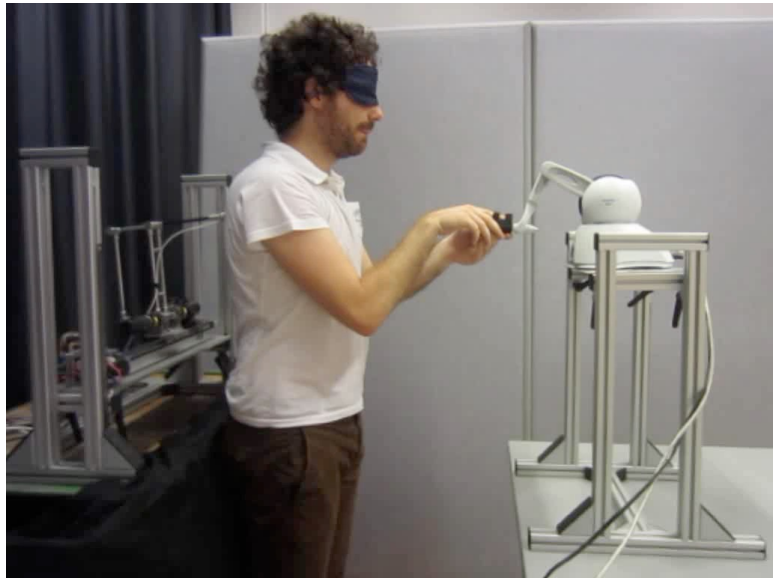
Global body representation
Self-consciousness



[**Weiskrantz et al., Nature 1971; Blakemore et al., Nature Neurosci 1998**; Boulmore, Science 1951; Blanke et al., Neuron 2015]

Technology and Neuroscience feasibility studies (robot-controlled induction of presence hallucinations)

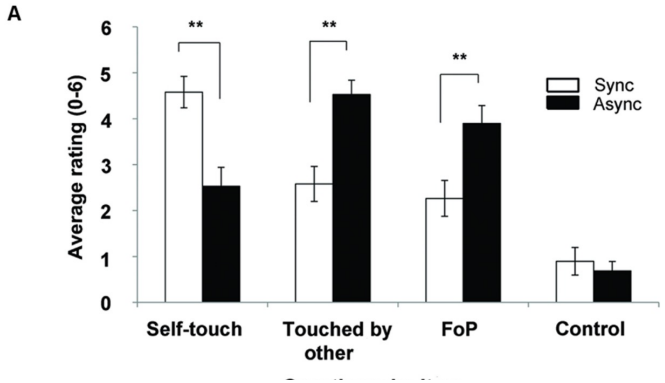
Technodelics in healthy participants (> 300 participants tested)



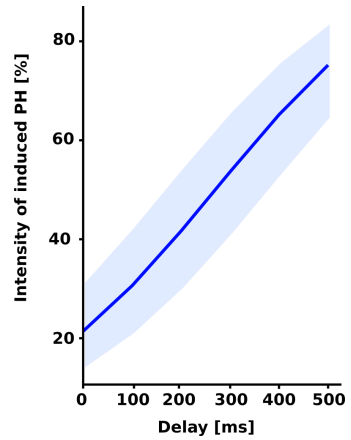
Robot-controlled sensorimotor conflict between forward extended arm (motor, touch, proprioception) and back (touch) is sufficient to induce presence hallucinations.

Quantified by changes in subjective experiences and behavioral changes in self-location and in social numerosity.

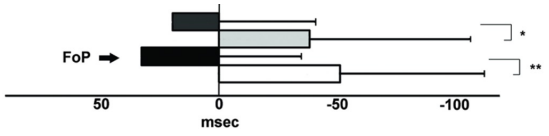
Hallucination Ratings



Delay-dependency



Behavioral Marker



Over 300 participants tested.

Faivre et al., **Cortex** 2020

Salomon et al., **Schizophrenia Bulletin** 2020

Stripeikyte et al., **J Neuroscience** 2021

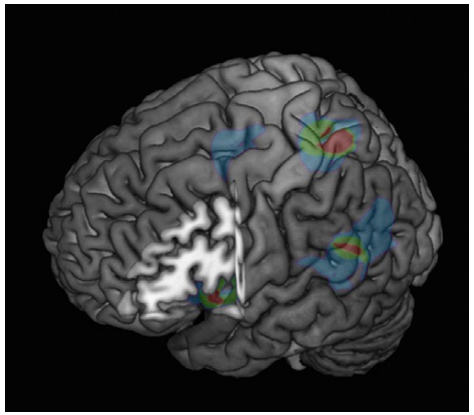
Stripeikyte et al., **Schizophrenia Bulletin** 2021

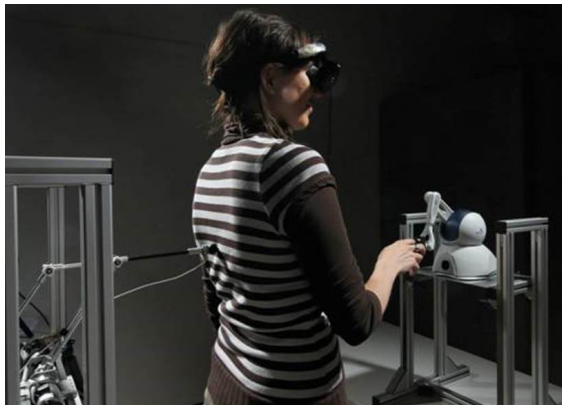
Salomon et al., **Schizophrenia Bulletin** 2022

Orepic et al., **Psychological Medicine** 2023

(auditory-verbal hallucinations, psychosis, thought insertion)

PH are somato-motor hallucinations caused by errors in sensorimotor perception





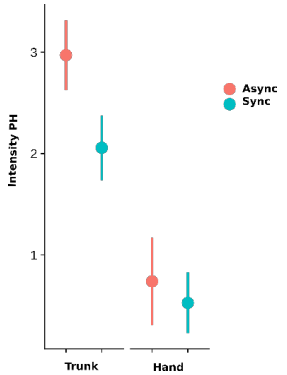
Robot-induced PHs in healthy participants are comparable to those reported by neurological patients (epilepsy, migraine, stroke, etc) and related to similar brain mechanisms

PHs are abnormal perceptions of a person's own body (comparable to phantom limbs (phanom body), but they are a misidentified supernumerary body)

Conflicting sensorimotor signals (motor, touch, proprioception) are sufficient: a moving forward extended arm (motor, touch, proprioception) combined with torso feedback (touch)

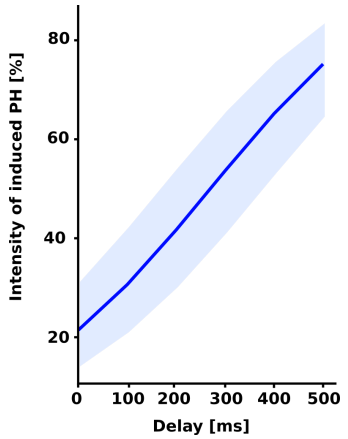
PH is **delay-dependent** and sensorimotor signals have to involve the **torso** (back or front), informing models of sensorimotor perception (forward model, sensory prediction)

Feedback location (torso-specificity)



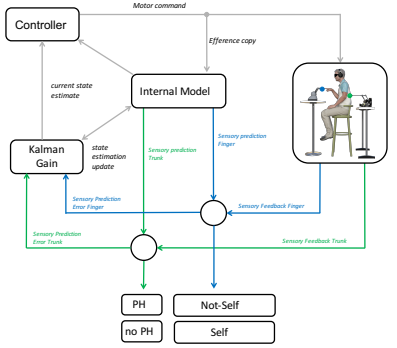
[Dhanis et al.,]

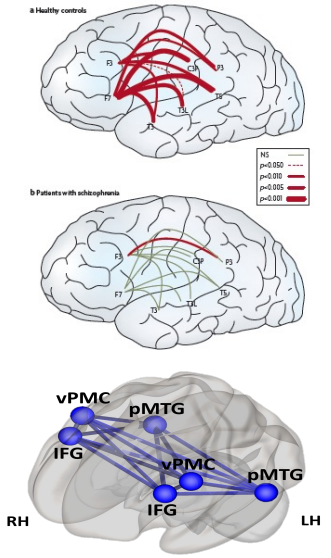
Delay-dependency



[Bernasconi et al.]

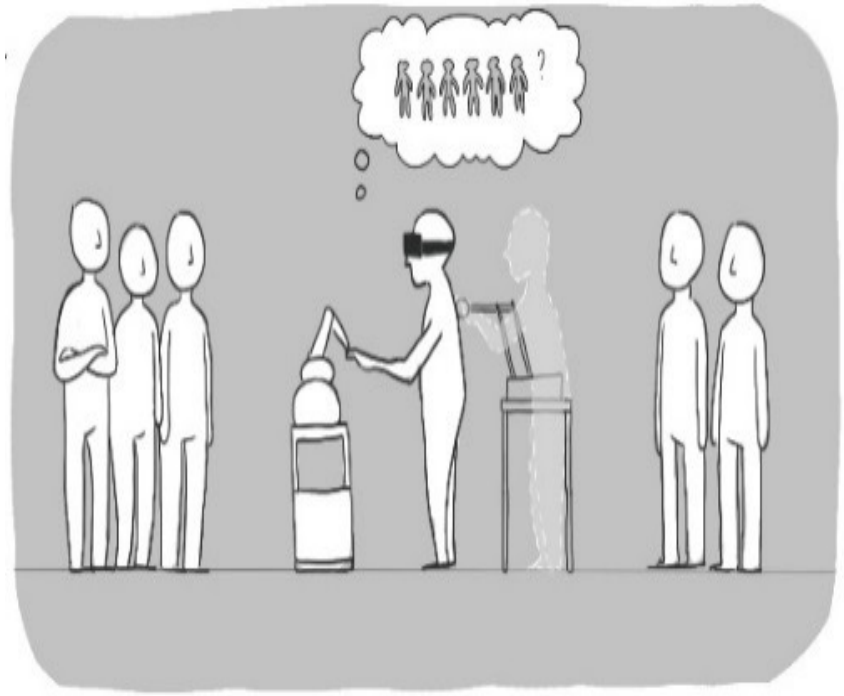
Sensorimotor processing, Sensory predictions





Measuring robotically-induced hallucinations

Integrating robotics with digital technology & cognitive neuroscience



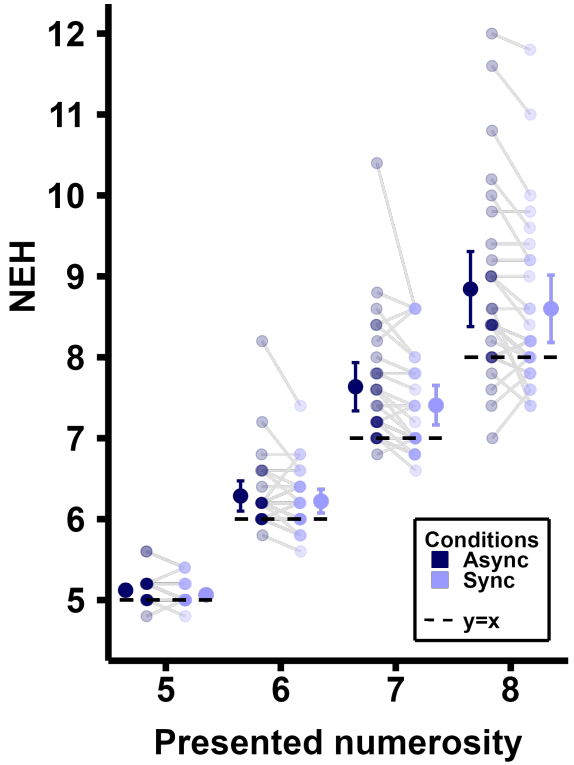
Does the perception of an invisible presence (i.e., a presence hallucination) change the estimation of how many humans are seen in a room ?

How many humans do you see in the room ?

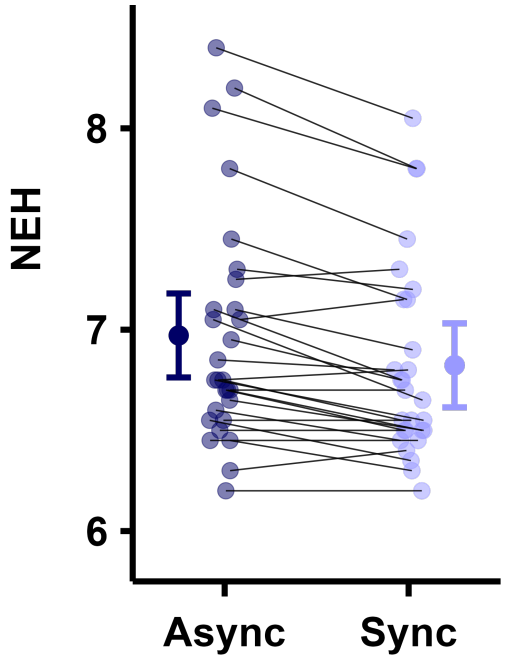
Technology+Neuroscience feasibility studies II

When asked to estimation the number of humans in a visual display (in VR), participants with robot-induced hallucination overestimate the number of humans

Strong tendency to over-estimate number of humans



Over-estimations larger in the condition in which participants reported a Presence Hallucination



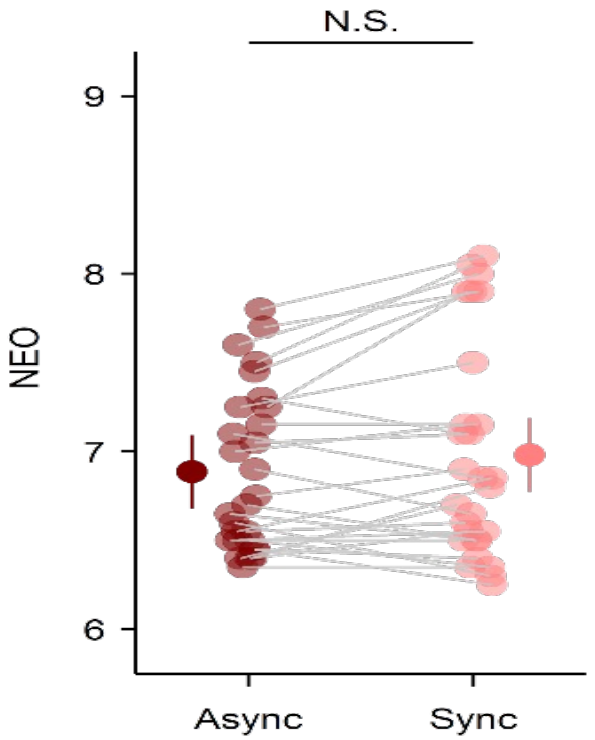
[Albert et al., **Nature Communications** 2024]

This is not the case for non-human control objects presented in the same room during induction of robot-induced PH

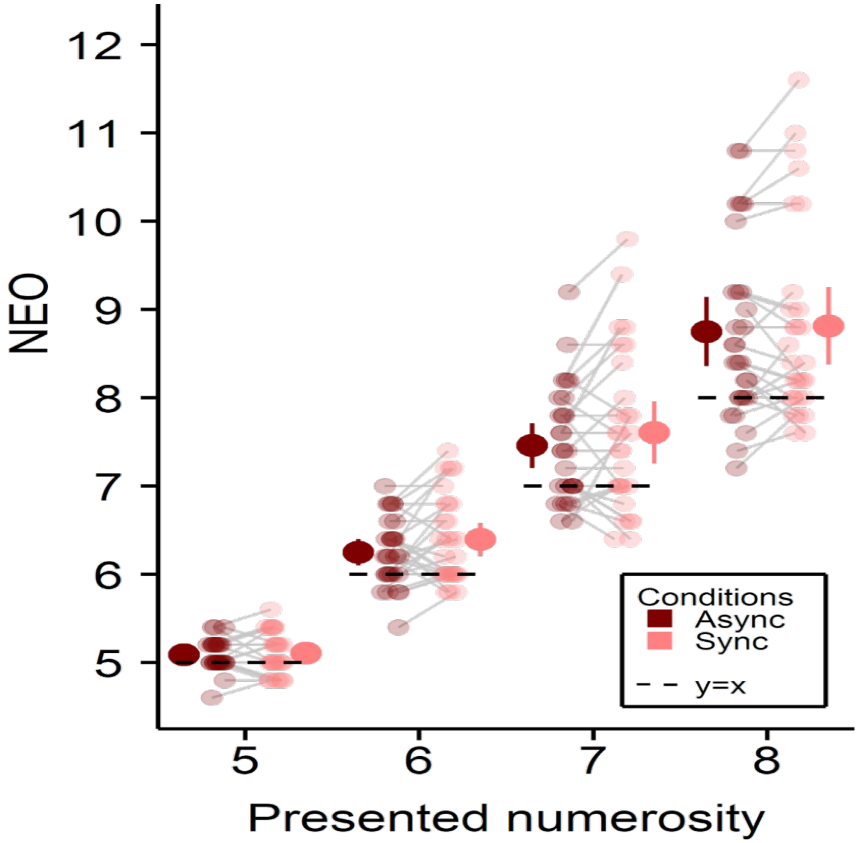
Number estimation of control objects

Boxes

Numerosity estimation for control objects
Async = Sync



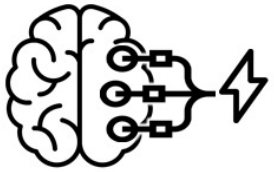
AS=S for all tested numerosities



Hallucination engineering

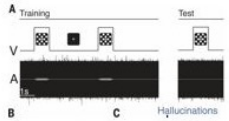
Methods and procedures using robotics, virtual reality & neurotechnology, enabling the repeated, safe, controlled and **real-time induction and quantification** of well-defined and clinically relevant hallucinations in healthy and clinical populations.

Invasive brain stimulation



Psychedelics

Pavlovian conditioning



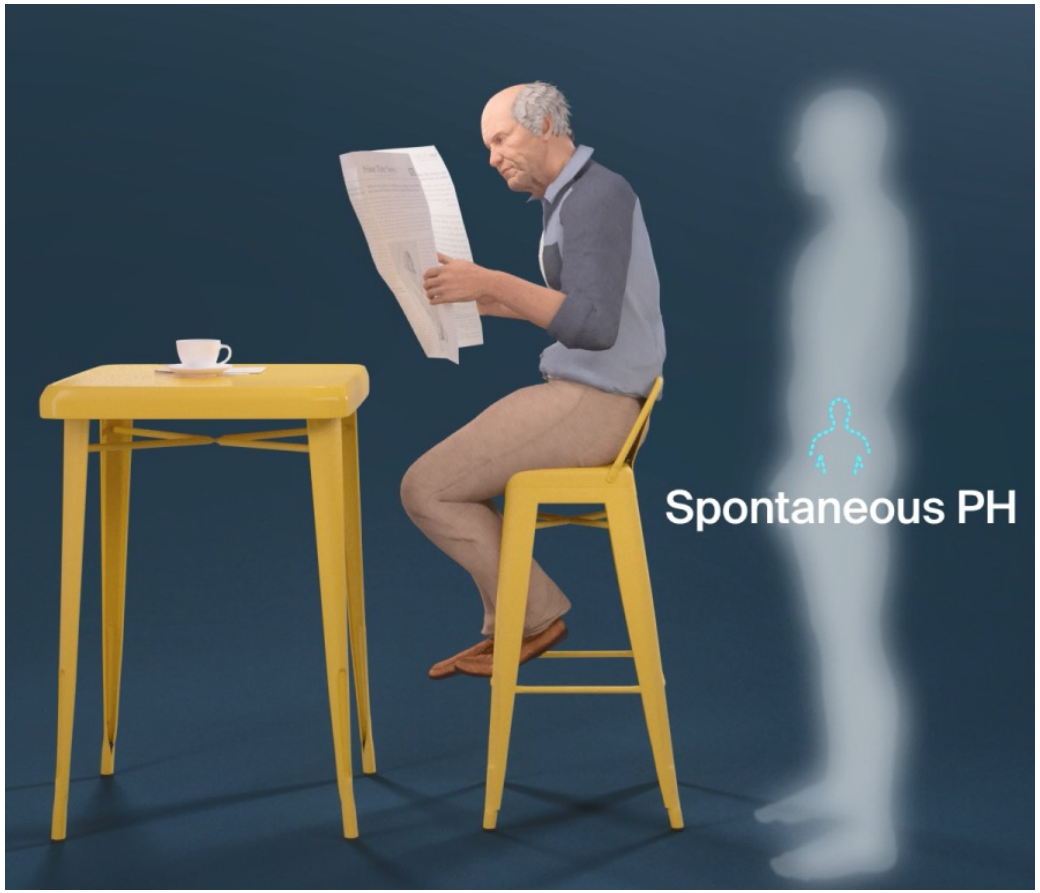
Flickering light

Ganzfeld effect

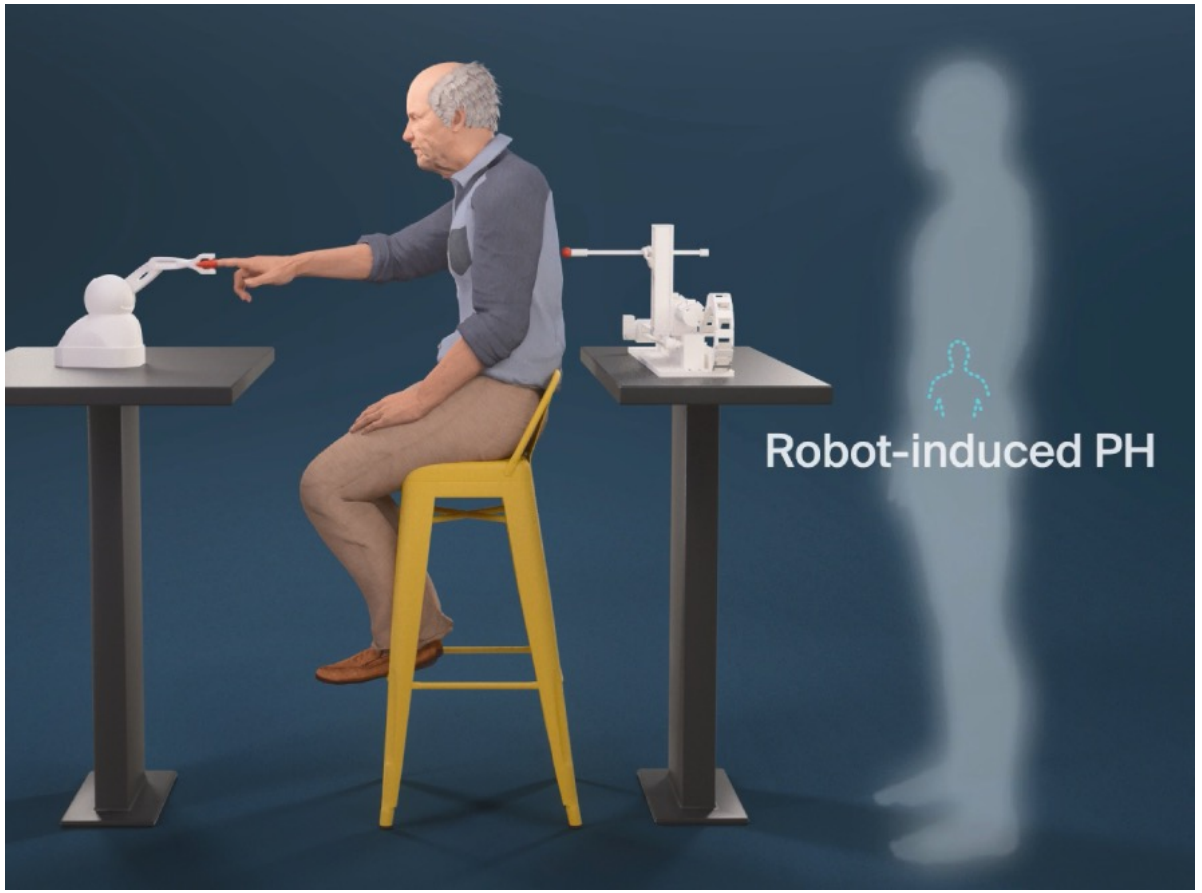
Sensory deprivation

Bernasconi et al., **Nature Protocols** 2022

Spontaneous presence hallucinations at home in Parkinson's Disease



Controlled induction of presence hallucinations in the Lab (Robotics)



Are patients with spontaneous presence hallucinations more sensitive to somato-motor stimulation?

Can we induce clinically-relevant presence hallucinations in patients with Parkinson's disease?

Clinical Network in Western Switzerland to study hallucinations & cognitive decline in patients with Parkinson's disease

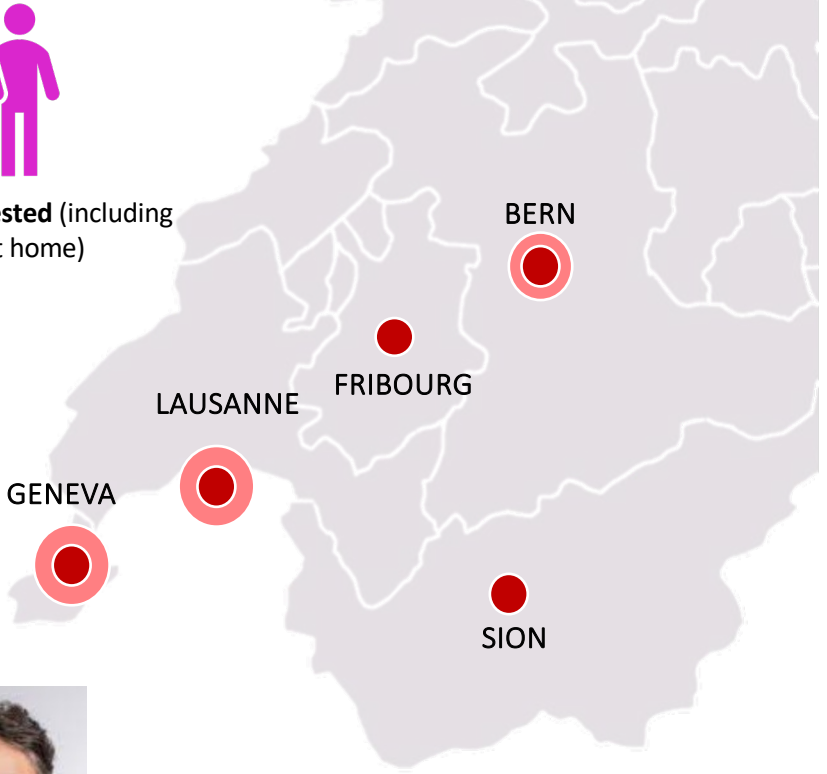
Dr. Jevita Potheegadoo

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Prof. Paul KRACK

Marie MARADAN

> 400 PD patients tested (including 170 online at home)



HUG

Prof. Pierre BURKHARD

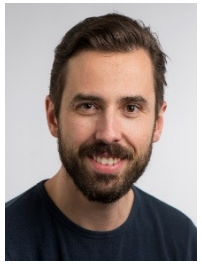
Dr. Vanessa FLEURY

Hôpital de La Tour

Dr. Judit HORVATH

Hôpital du Valais
Spital Wallis

Prof. Joseph-André GHIKA



Dr. Benoît WICKI

CHUV

Dr. Julien BALLY

Prof. Gilles ALLALI

Hopital San Pau, Barcelona, Spain

Charité, Berlin, Germany

Rockefeller Neuroscience, WVU, US

ICM, Paris, France

Fosco Bernasconi

Jevita Potheegadoo

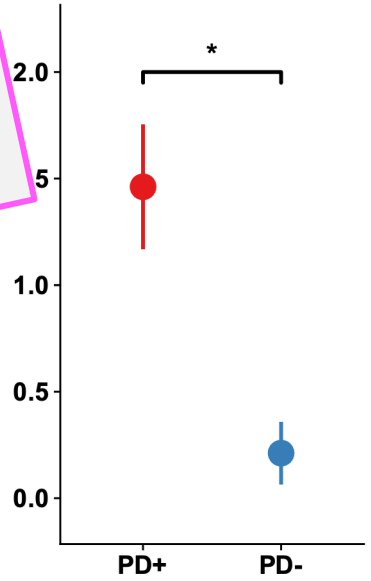
Patients with Parkinson's disease are highly sensitive to robotic stimulation and activate brain network differently

Patient performing rob

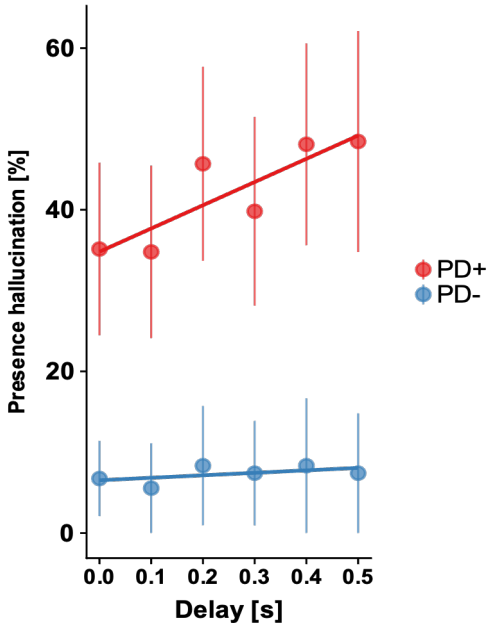
Replicated in ongoing trial
(> 100 new PD patients tested)

Patient performing robot procedure
sitting position, adapted (shorter) sessions

Study 1 (AS vs. S)



Study 2 (6 Delays)

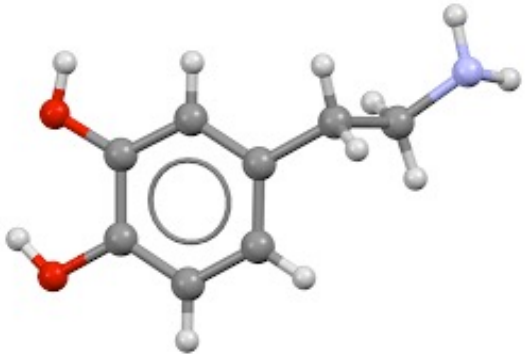


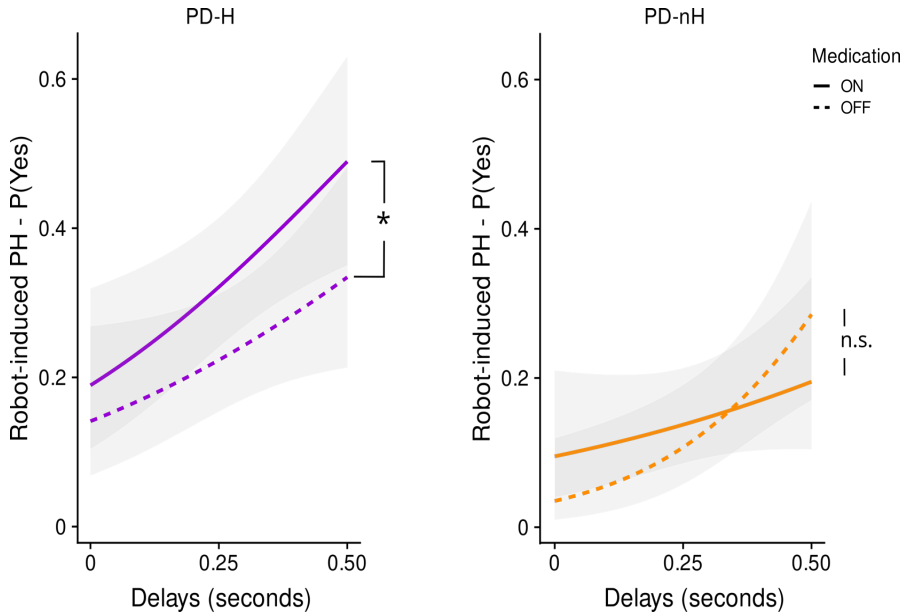
Parkinson's disease patients (PD+) are 6x more sensitive than **PD-patients**
Differences are not related to the performed movements during the procedure

[Bernasconi et al., **Science Translational Medicine** 2021]

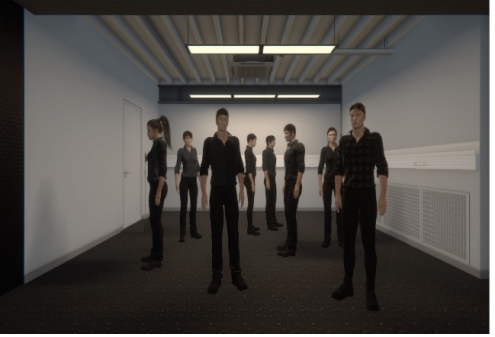
Combining Technodelics & Psychodelics (Pharmacology-Dopamine)

PD patients are more sensitive to robot-induced PH if they are ON dopamine





Quantifying presence hallucinations at the home of patients

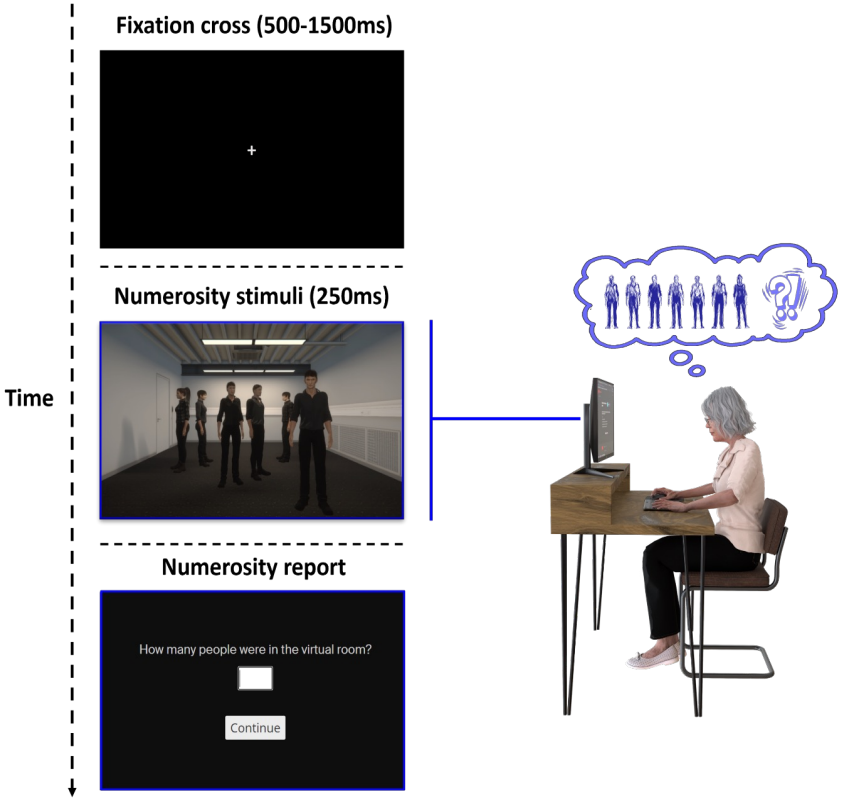


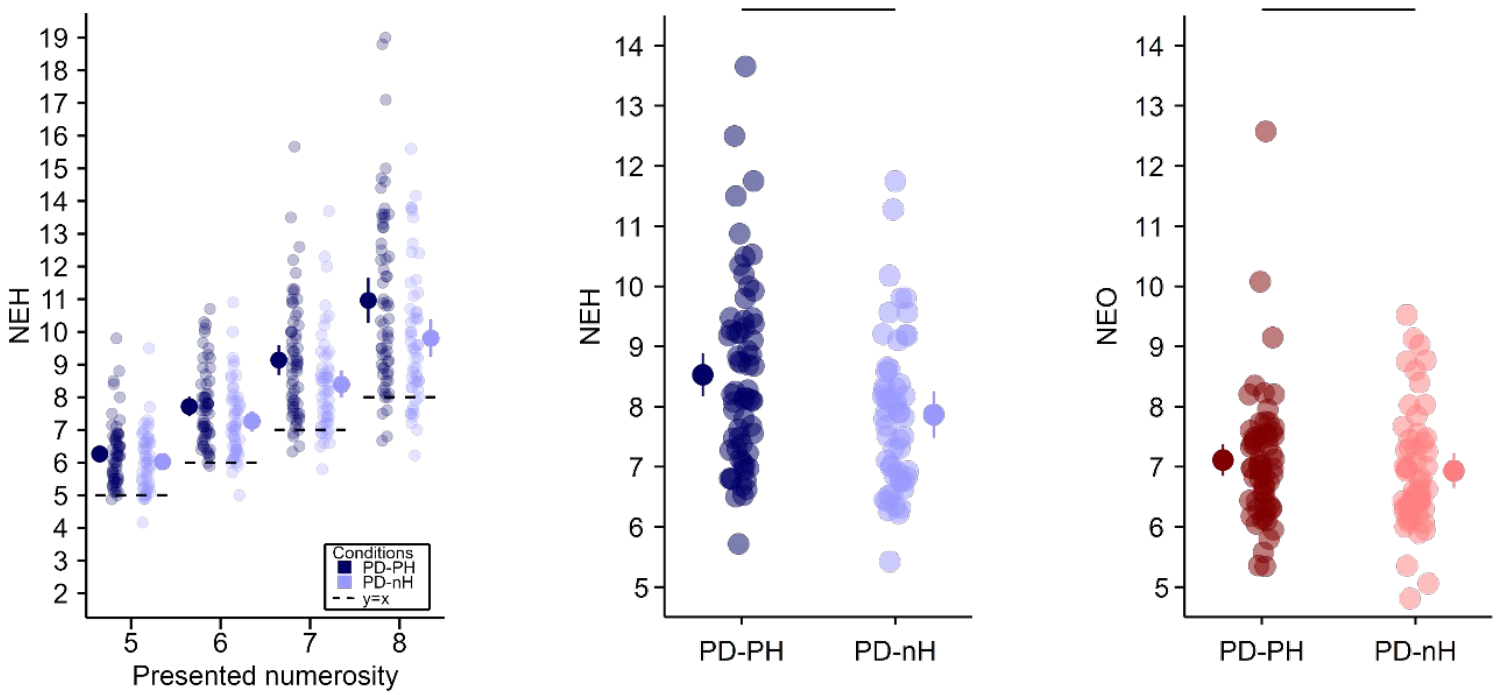
Quantifying presence hallucinations at the home of patients: Overestimation in numerosity perception in patients with Parkinson's disease & presence hallucinations

N = 170

PD patients

Over-estimations are larger in PD patients with Hallucinations (PD-PH), but not for control stimuli and less in PD patients without hallucinations





[Albert et al., **Nature Communications** 2024]
[Albert et al., **J Parkinson's Disease** 2025]

FRANCE PARKINSON

Parkinson schweiz suisse svizzera

PARKINSON'S UK
CHANGE ATTITUDES. FIND A CURE. JOIN US.

Hallucinations are difficult phenomena to quantify

- Hallucinations are **unpredictable, spontaneous & private experiences**, making their investigation (induction & assessment) highly challenging
- Hallucination measurements rely mostly on **subjective self-reports** and **subjective interpretations** by patients, family, clinicians, researchers
- Self-reports **not sufficient for quantifying hallucinations** → scientific-quantitative measurements are needed that detect the alteration **BEFORE the symptom arises**
- **Stigma** associated with hallucinations → hallucinations are often underreported

Hallucination Engineering // Technodelics

(1) Safe induction of hallucinations and (2) robotic-digital behavioral markers and (3) brain markers to quantify hallucinations in Parkinson's disease, but also in Dementia with Lewy Bodies, Psychiatry (schizophrenia) and other conditions. (4) AI and chatbot testing additionally boosts technodelics.

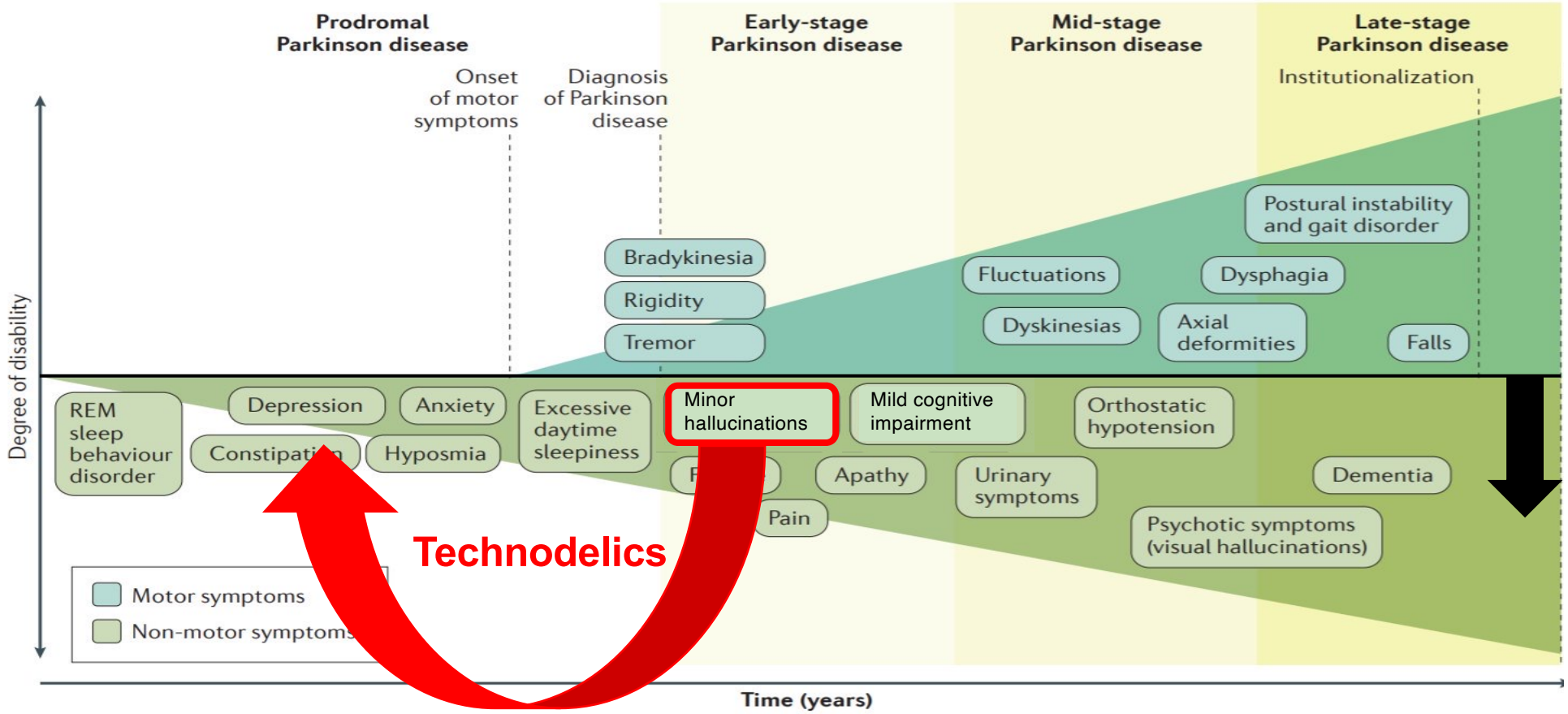
Bernasconi et al., **Nature Protocols** 2022
Rogers et al., **Philos Trans R Soc Lond B Biol Sci** 2021

Parkinson's disease

Parkinson's disease

Parkinson's disease is characterized by a large number of **non-motor symptoms**
Non-motor symptoms **appear 10-15 years before motor symptoms** (Prodromal Parkinson's disease)
Non-motor symptoms **do not respond to standard PD treatments** and massively **impact quality of life**

PD pathology extends beyond the basal ganglia
Disease-modifying therapies (DMTs) targeting alpha-synuclein with antibodies (i.e., Prasinezumab, PASADENA study; Pagano et al., 2024 Nature Medicine) require early disease markers (temporal window to stop disease progression)



(i.e. Poewe et al., 2017)

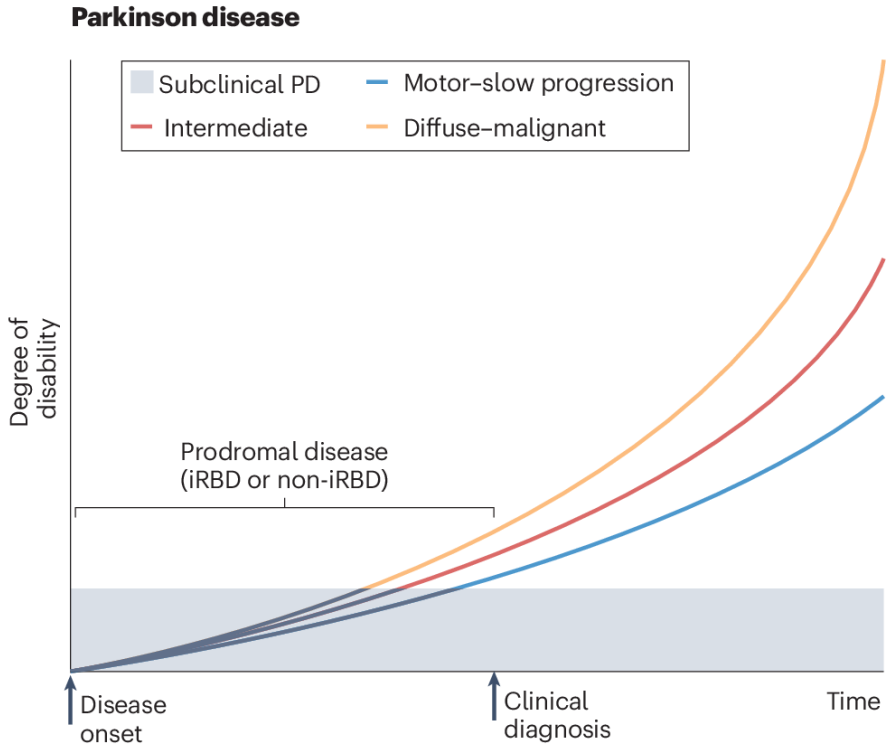
Presence Hallucinations in Parkinson's disease …

… are **frequent non-motor symptoms in PD** (**50-60%** of patients) and may occur weekly or daily.

… often with an **early onset** (in some PD patients even before the onset of motor symptoms).

… are associated with **cognitive decline and dementia**, psychiatric complications, earlier home placement & higher mortality.

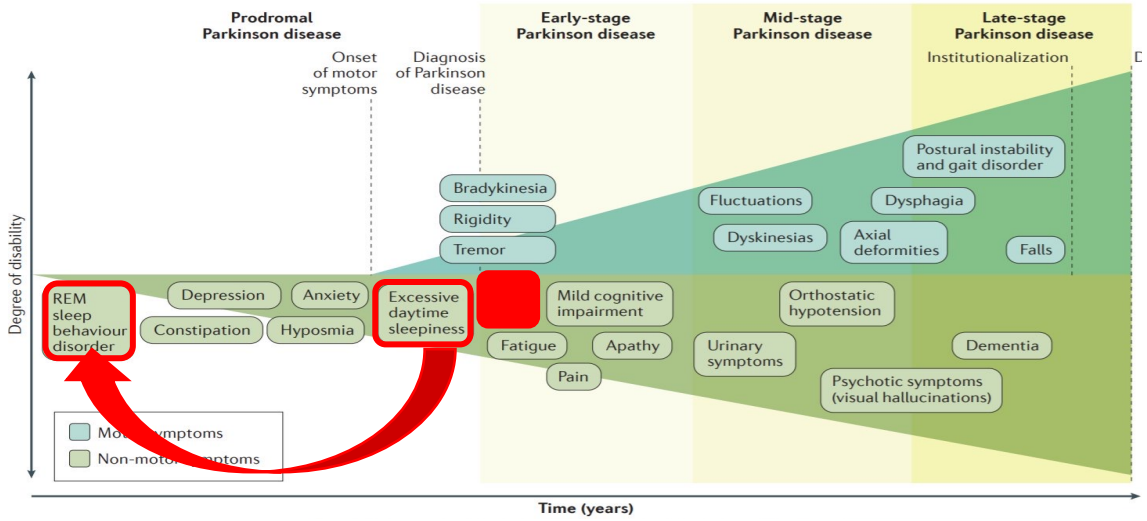
Hallucinations indicate a more severe and more rapidly advancing form of Parkinson's disease.

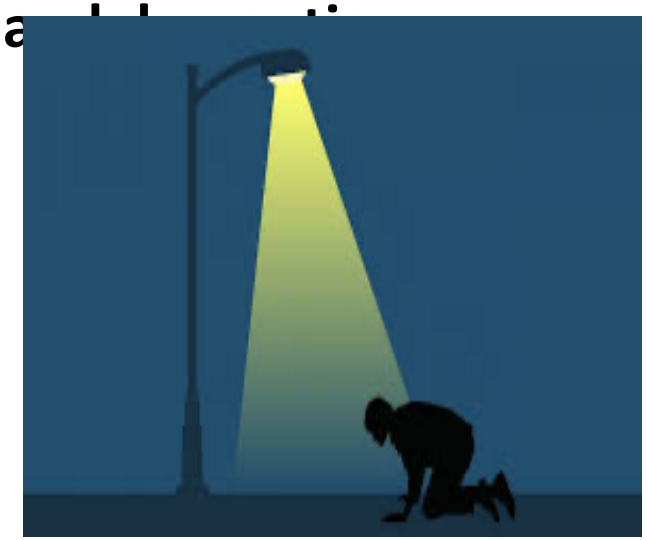


[Wood et al., Front Neurol 2015; ffytche et al., Nat Neuro Rev 2017]

Motor symptoms start too late in PD for early diagnosis based on movement analysis

Hallucination Engineering will enable early detection of a more severe and more rapidel





Current treatments are only symptomatic and non-efficient for hallucinations & dementia; there are currently no approved disease modifying treatments (DMTs); motor symptom tracking not sufficient.

DMTs (i.e., Prasinezumab, PASADENA study; Pagano et al., 2024 Nature Medicine) need to start as early as possible, in the prodromal phase, best decades before appearance of symptoms