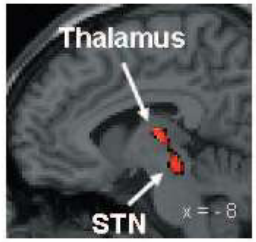
Deep brain stimulation

STN-DBS interferes with brain activity in a large network **(Brain activation caused by DBS measured with positron emission tomography, PET data)**

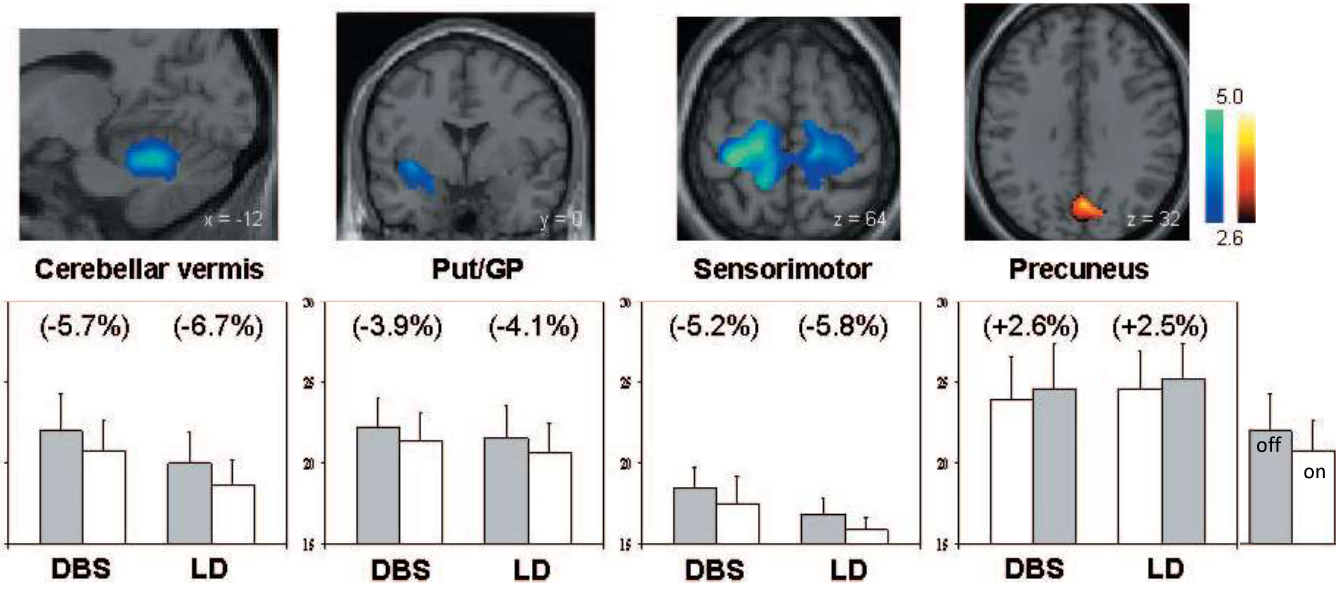
STN DBS enhances activity in STN/Thalamus



Thalamus

STN DBS decreases activity in cerebellum, putamen, GP

STN DBS decreases activity in bilateral S1, M1, and premotor cortex and enhances activity in posterior parietal cortex (precuneus)



Similar effects observed with i.v. dopamine therapy (LD)

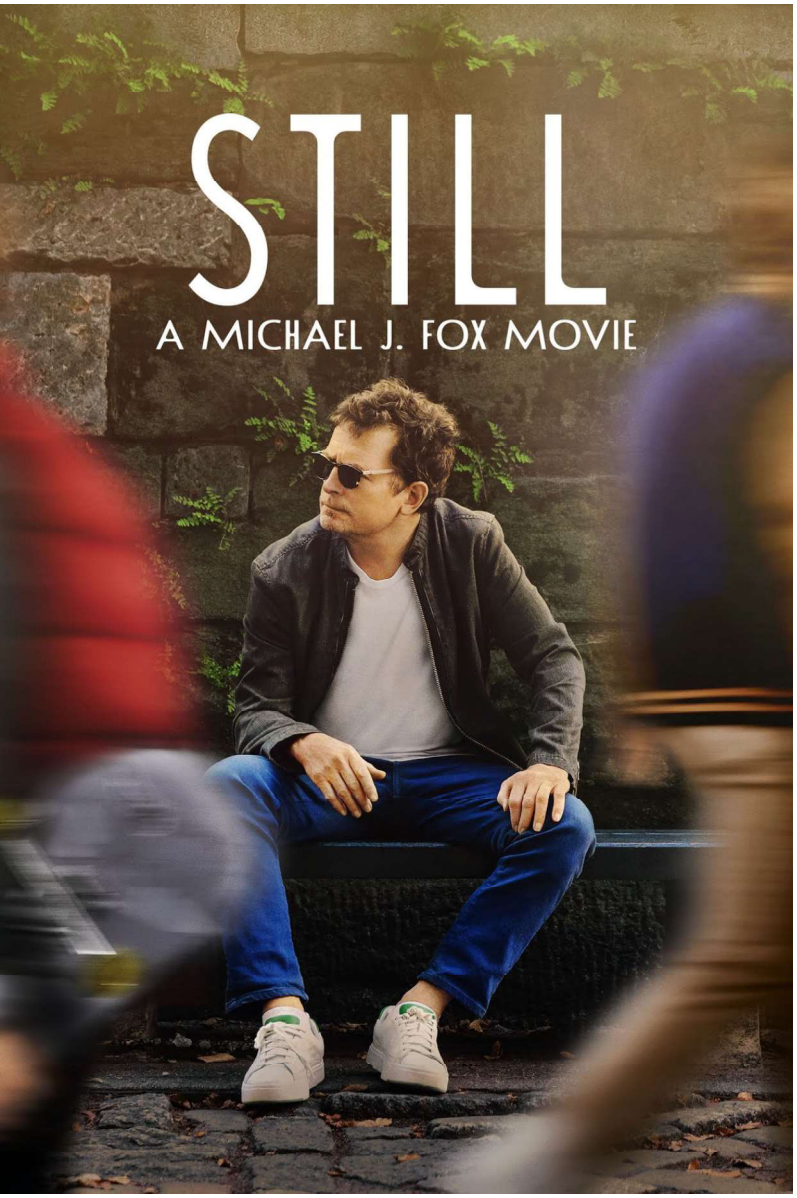
Asanuma et al., 2007 (PET study)

Neuro-X

Translational Neuroengineering

Parkinson's disease III

May 7, 2024 // Olaf Blanke

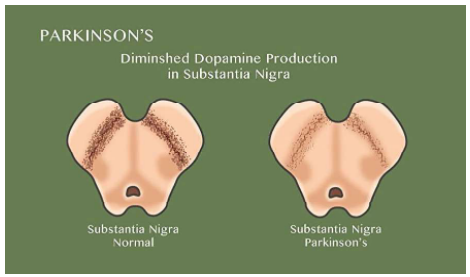


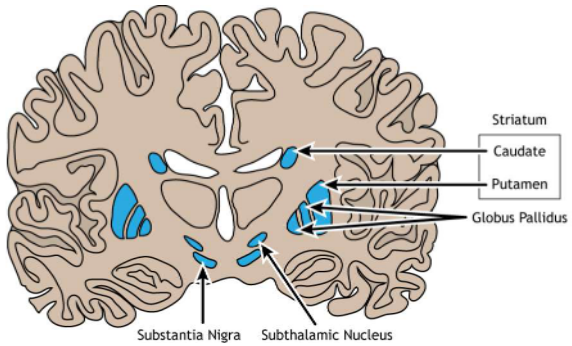
https://www.youtube.com/watch?v=lpz6QpJOkZE
(recent interview with Fox)

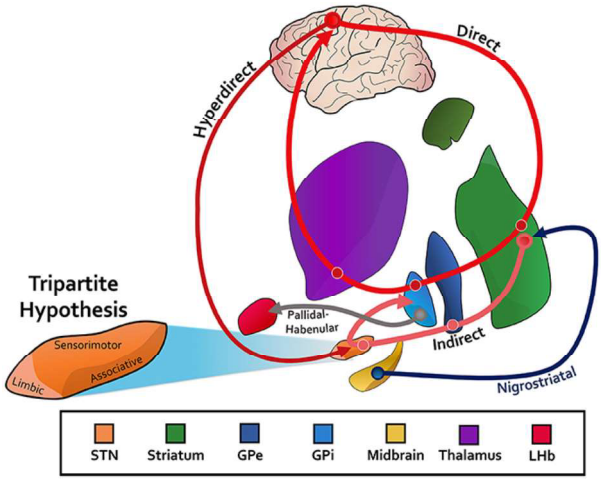
Documentary about Fox's life
Fox was diagnosied with PD at age 31 and
started the world's largest Parkinson foundation

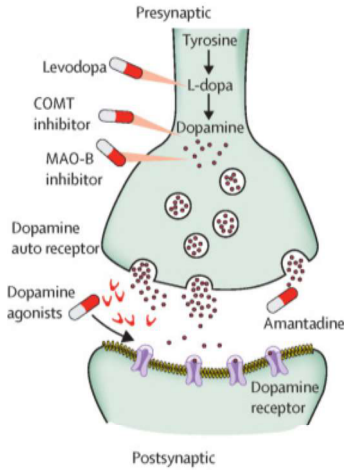
Parkinson's disease is a disorder of the basal ganglia …

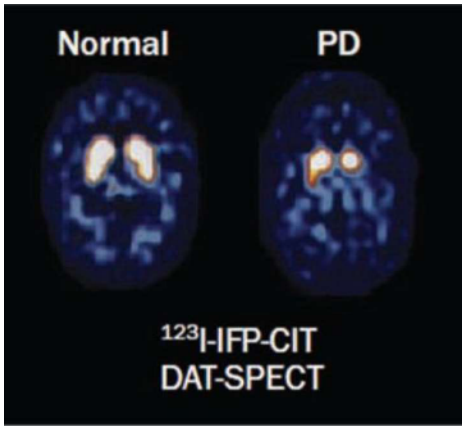
… is a movement disorder, caused by the loss of dopaminergic neurons in the substantia nigra, degeneration of the nigro-striatal pathway, and characterized by dopamine depletion in the striatum, leading to basal ganglia abnormality







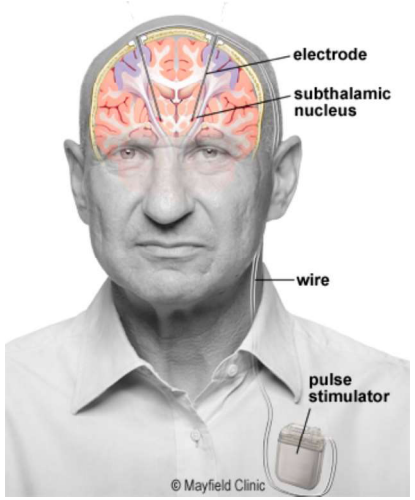


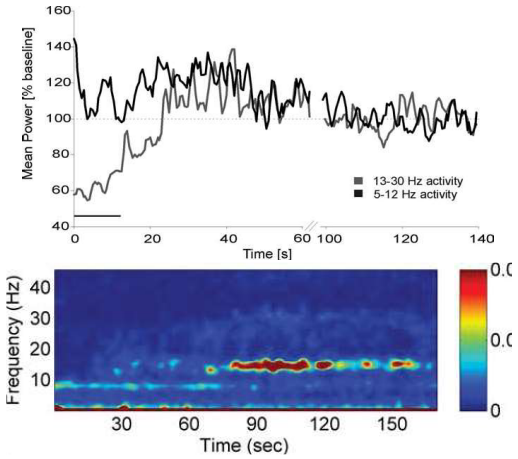


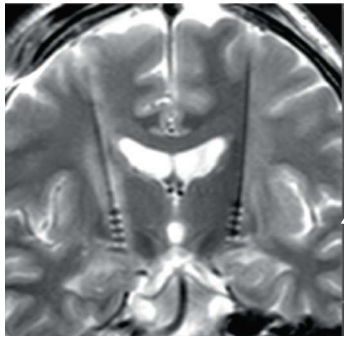
Neuropathology
Neuroanatomy
Chemical Neurotransmission
Clinical Neurology

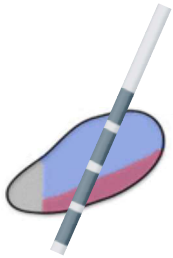
Parkinson's disease is not only a disorder of the basal ganglia, but also of the cortex …

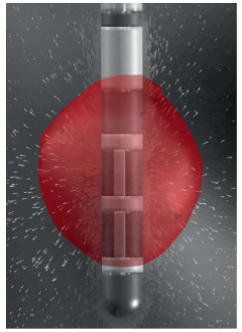
… brain oscilations (beta and gamma band) involve all parts of the basal ganglia and also involve many cortical systems in motor, premotor, supplementary motor cortex, as well as posterior cortical regions; DBS (and dopamine replacement therapy) normalize these distributed pathological oscillations

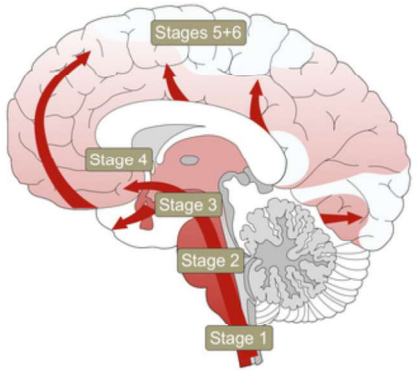


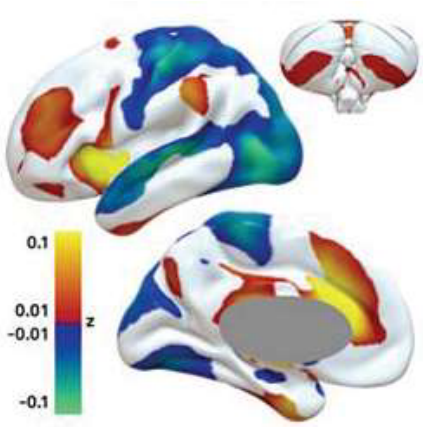








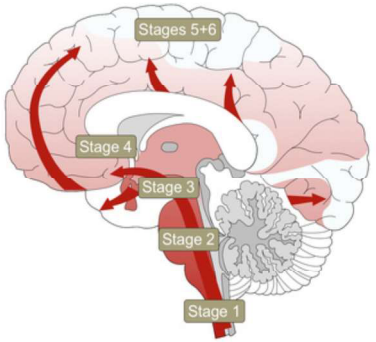


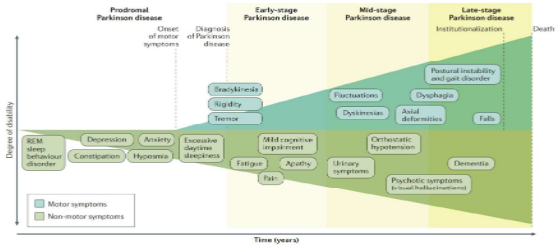


PD as a distributed disease

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)





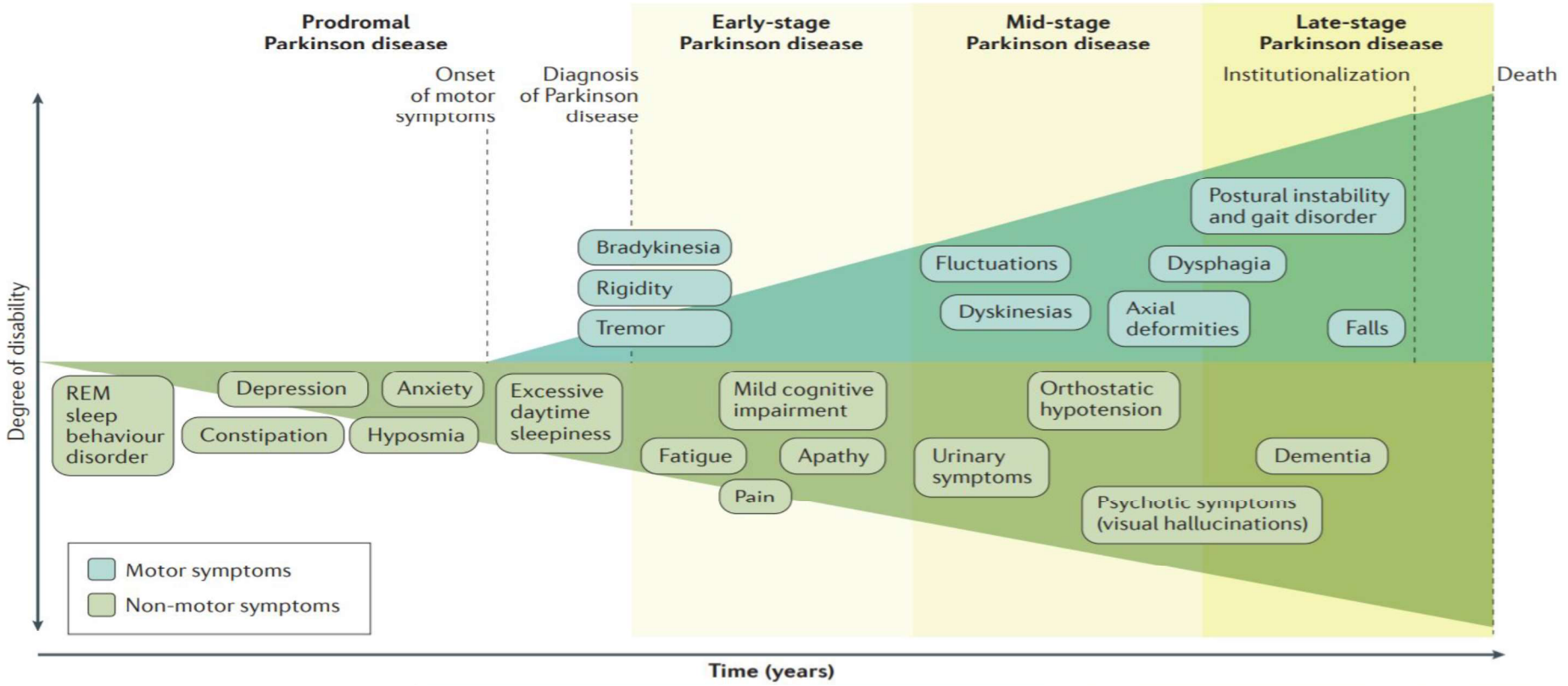
Many of the non-motor symptoms of PD are also compatible with PD as a disease that affects more then the nigro-striatal pathway and basal ganglia

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
Apathy
Urinary symptoms
…

3 major non-motor symptoms

Mental-psychiatric: Hallucinations & Psychosis

Cognitive: Mild cognitive decline & Dementia

Sleep-wake cycle: REM sleep behavior disorder

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
Apathy
Urinary symptoms
…

~~3~~ 2 major non-motor symptoms

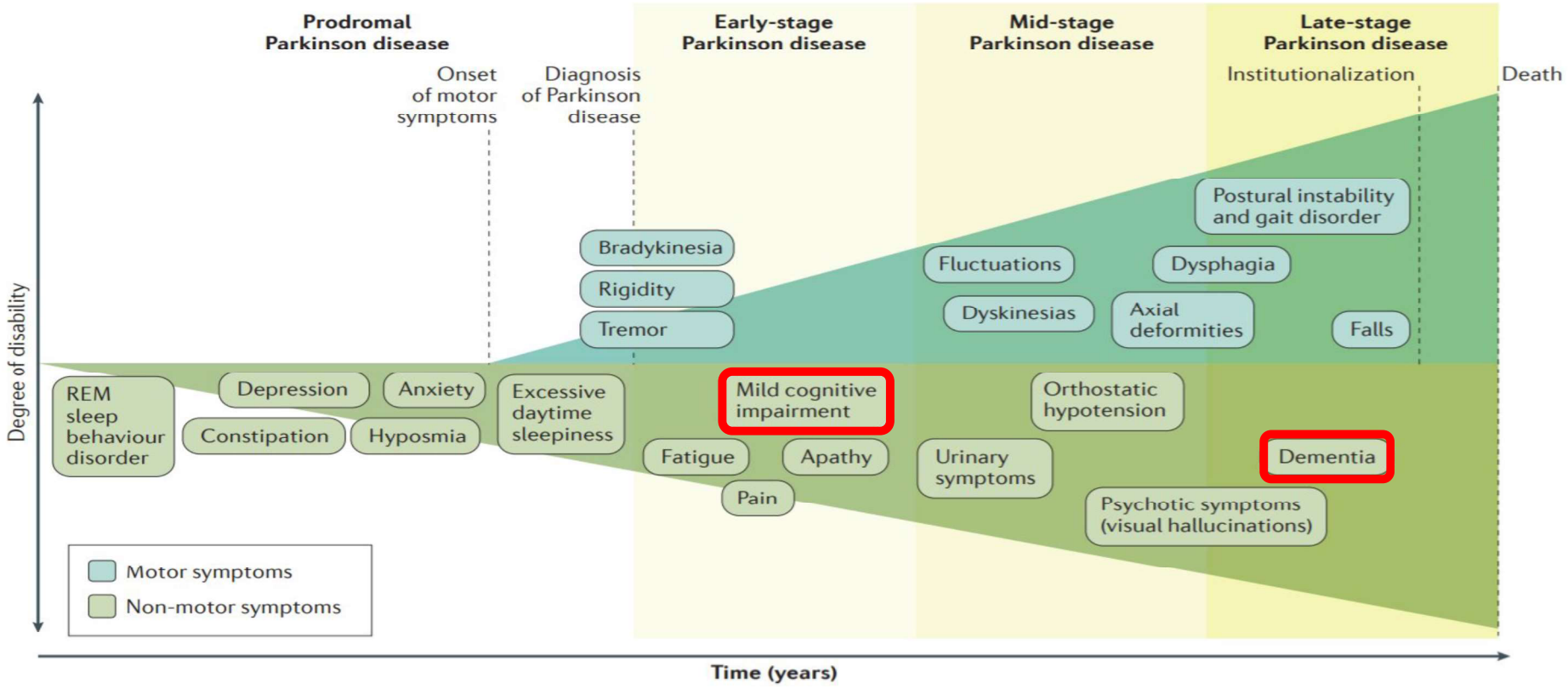
Mental-psychiatric: Hallucinations & Psychosis

Cognitive: Mild cognitive decline & Dementia

~~**Sleep-wake cycle: REM sleep behavior disorder**~~

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)

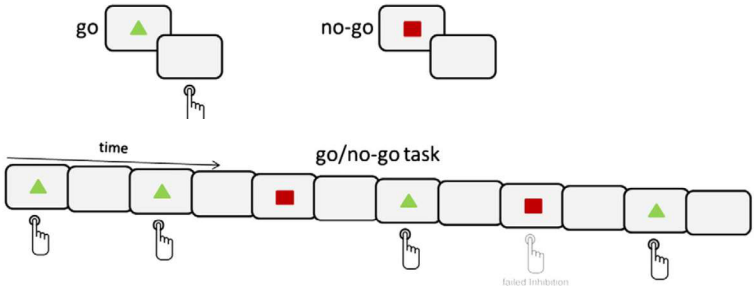
- 6x more frequent than in healthy aged matched people

-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

Cognitive impairment in PD

… language and memory are generally not impaired

Important:
Other major cognitive 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

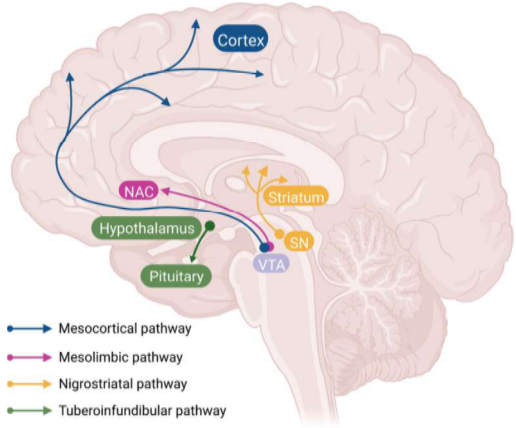
Cognitive impairment in PD has been linked to nigro-striatal-frontal pathology (impairment and slowness in fluency for example has been described as **bradyphrenia** (slowness of the mind), a slowness of initiation, alternation, and learning in cognition)**.**

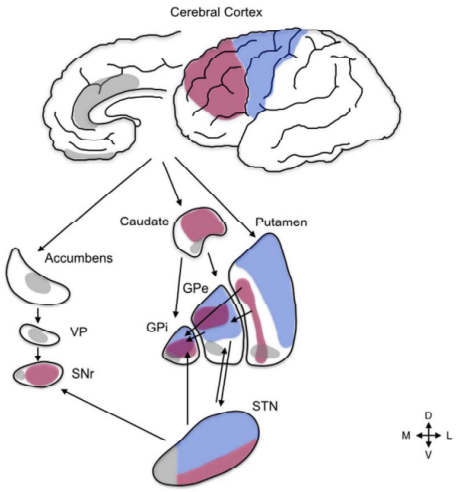
-Striatal dopamine depletion linked to the nigro-striatal projections to the striatum and to premotor and frontal cortex is involved in cognitive deficits in PD. This was shown by ...

... **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)

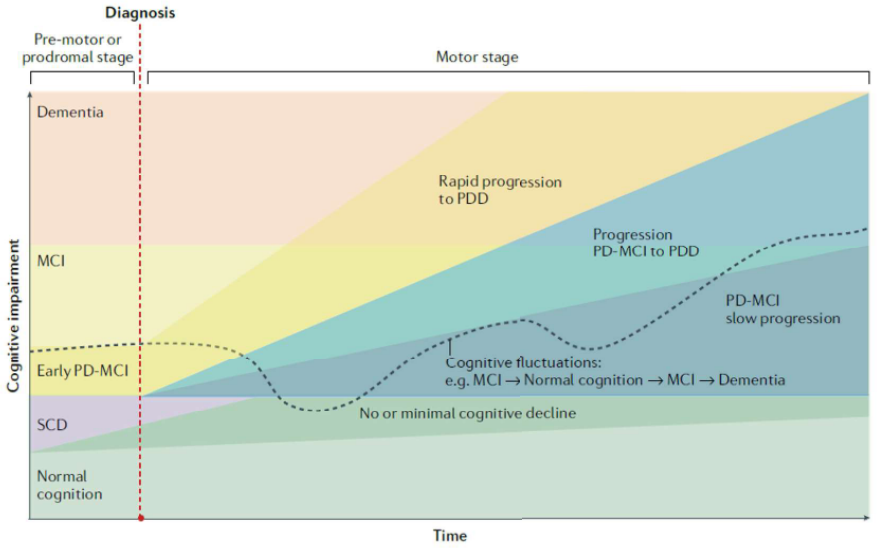
MCI (PD-MCI; 80%)
Mild cognitive impairment
-1 significant cognitive deficit detected by specific neuropsychological test
-Impairment does not impact daily life and functioning of patient

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

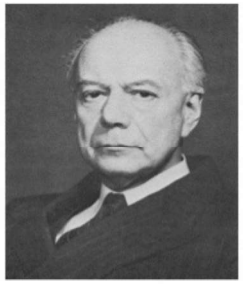
PD patients advancing from MCI to dementia (PDD) show significant disturbances in additional cognitive functions other than frontal-subcortical functions, involving parietal and temporal cortex:
-perceptual tasks
-visuo-spatial tasks
-memory

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



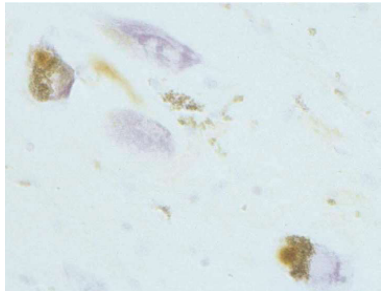
Aarsland et al., 2021; Heinzel et al., 2019; Kulisevsky et al., 2013



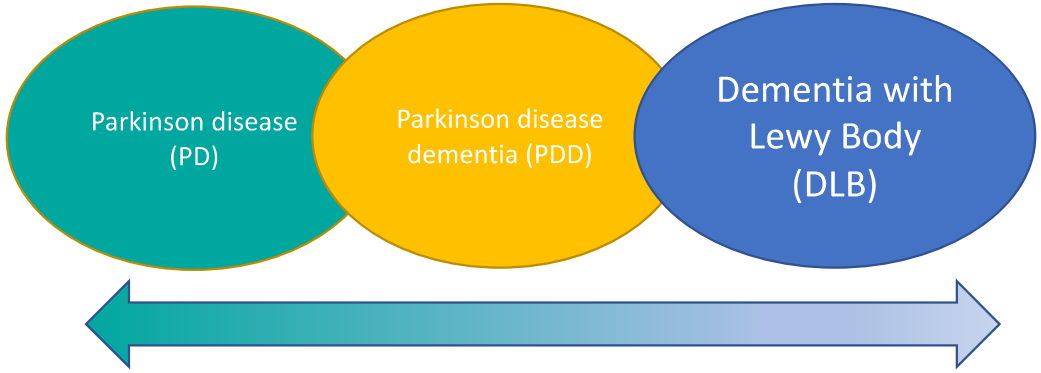
Fritz Lewy
(1885-1950)

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

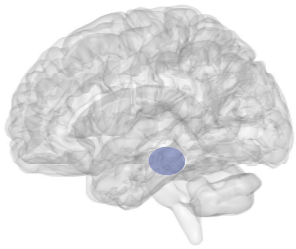
Three diseases on the Lewy body spectrum



Godaert, Science 2015

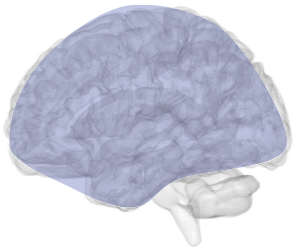


Basal ganglia



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

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)

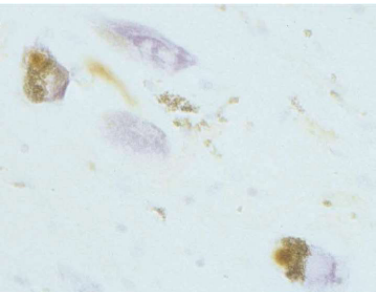
Core clinical PDD feature:
-**Dementia develops more quickly** than in PD, but **never earlier than 1 year** after diagnosis of PD (motor symptoms)
-frontal loby dysfunction (see previous slides) and progressively other posterior functions

DLB

Central clinical feature:
Dementia is always present; already at moment of diagnosis (if parkinsonian symptoms also present dementia is already present or starts before 1 year after the motor symptoms)
-frontal lobe dysfunction (similar but more severe/advanced then PDD, memory not impaired in early phase)

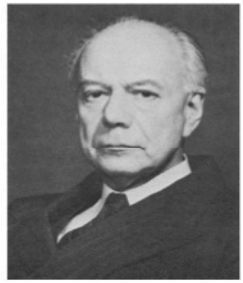
Core clinical DLB features:
-**Hallucinations** (more frequent than in PD or PDD; Aarsland et al., 2001)
-**Parkinsonian motor symptoms** (bradykinesia, rigidity, tremor), but they can also be absent in DLB (not needed for diagnosis)
-**Fluctuating cognition** and alertness (more prominent than in PDD)

Londos, 2013

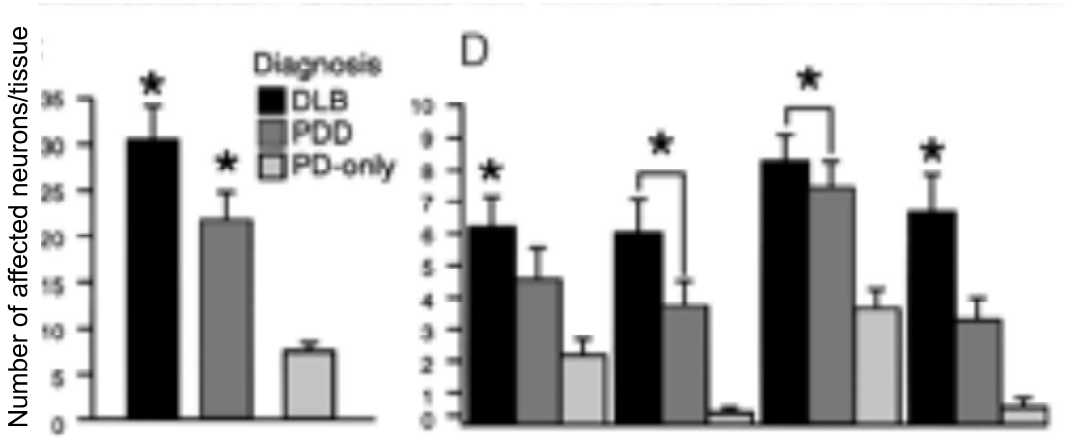


Godaert, Science 2015

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)

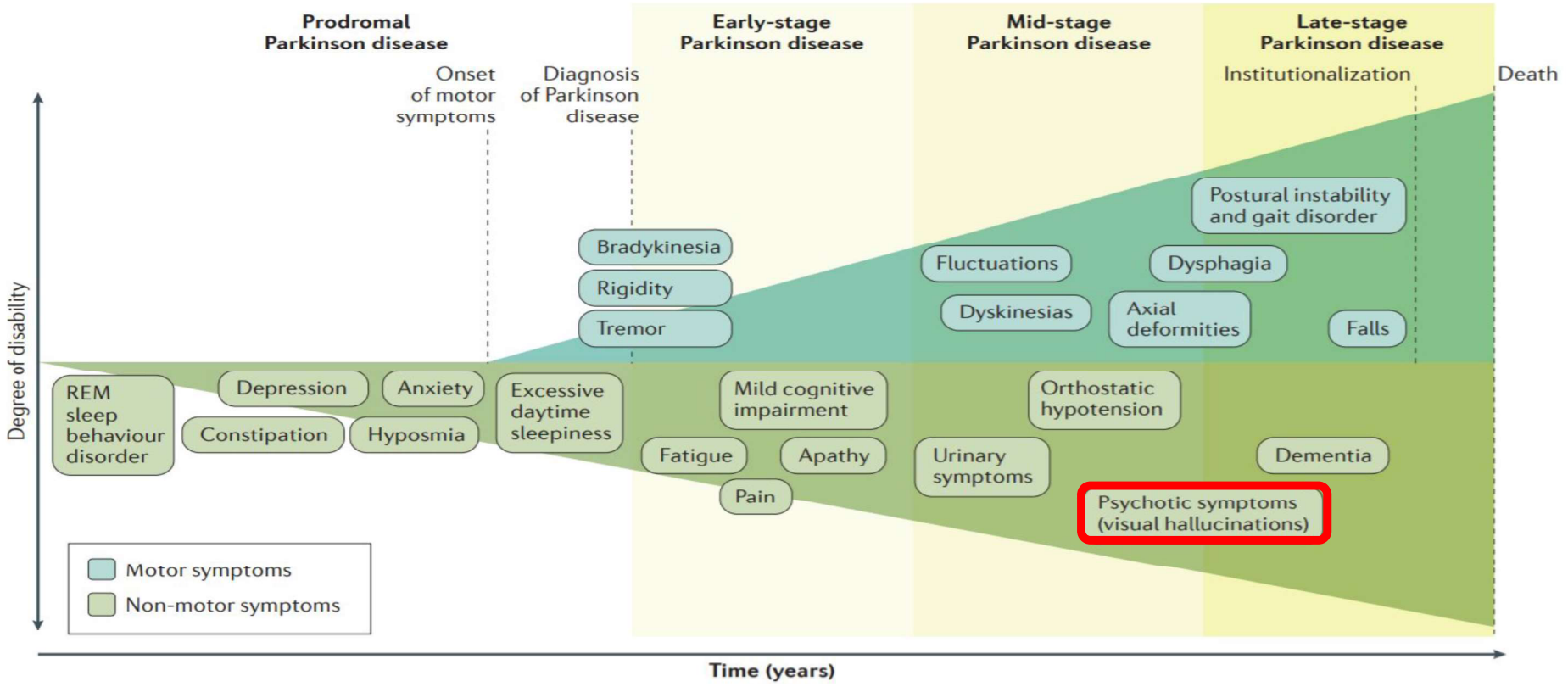
Saint-Cyr et al., 2002; Pal et al., 2022

Another major non-motor symptom in PD

Hallucinations (& illusions)

Hallucinations in PD

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

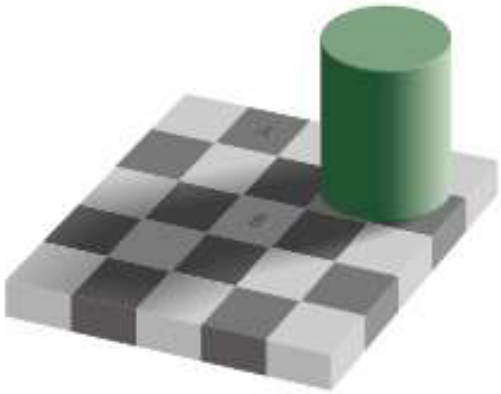


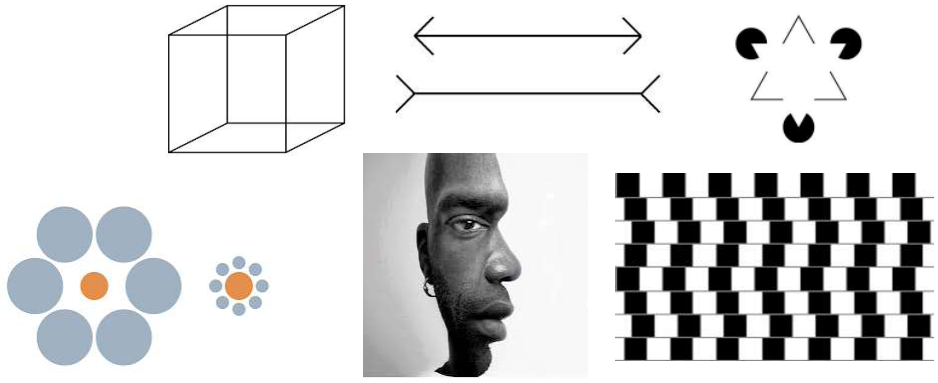
Poewe et al., 2017

Hallucinations & Illusions

Definitions, two types of false perception

Visual Illusions
(= errors in perception)





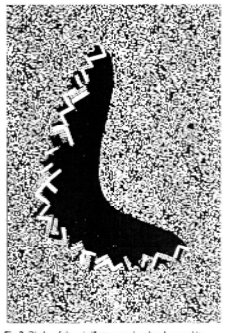
Hallucinations

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)

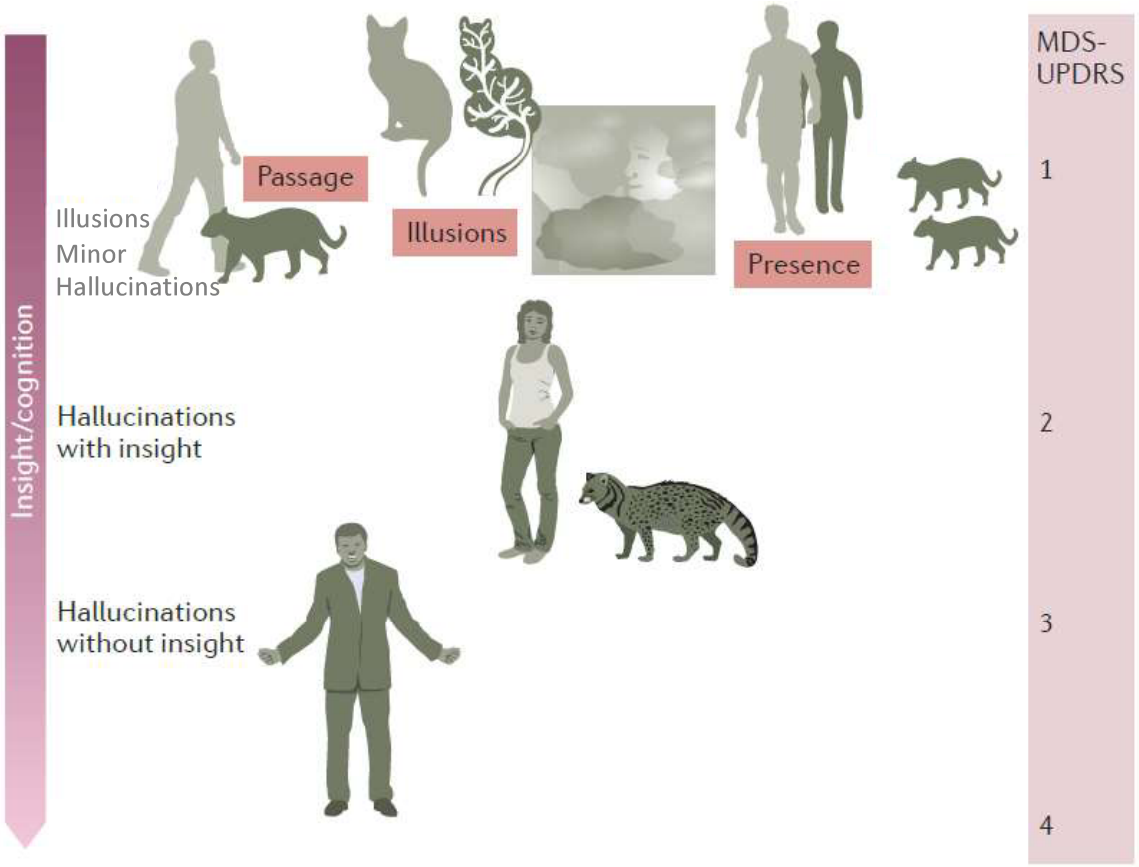


Hallucinations in PD

Illusions & minor hallucinations

Minor hallucinations
Presence Hallucination
Passage Hallucination

Complex visual hallucinations
People
Animals



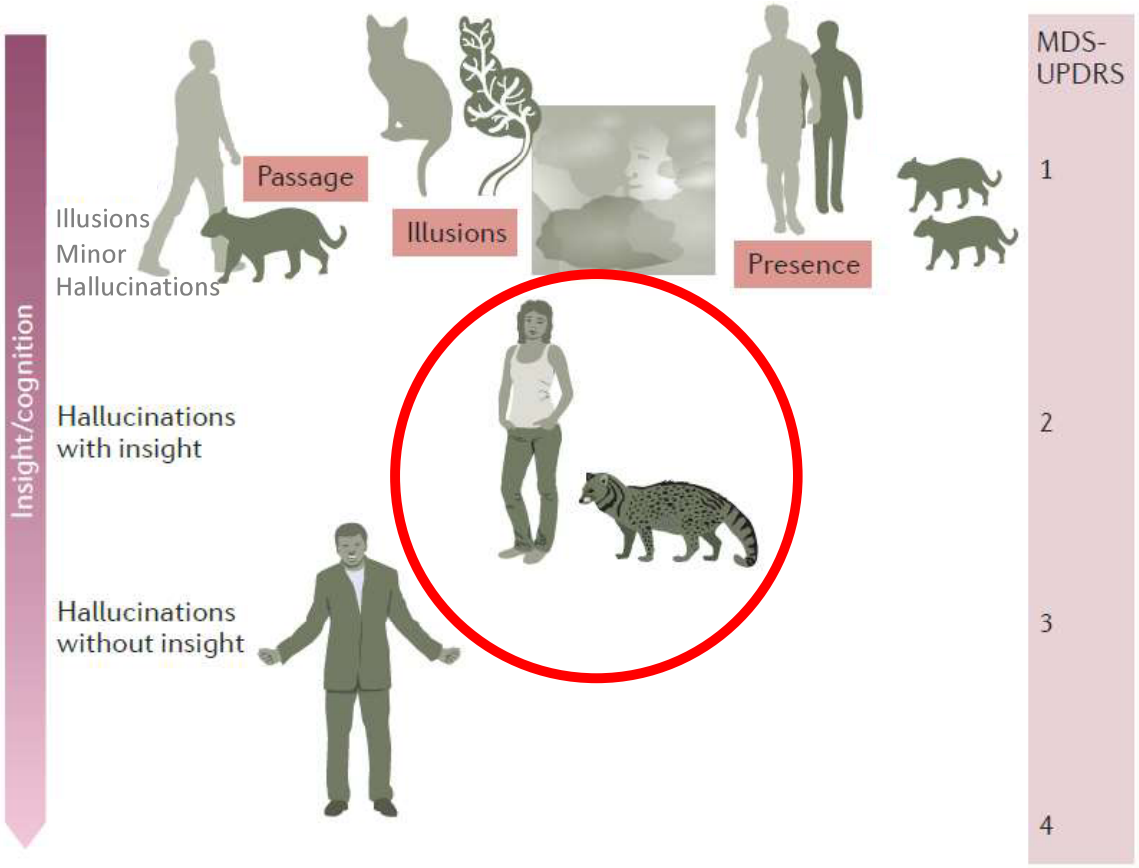
Visual Illusions
Pareidolia

Hallucinations in PD

Illusions & minor hallucinations

Minor hallucinations
Presence Hallucination
Passage Hallucination

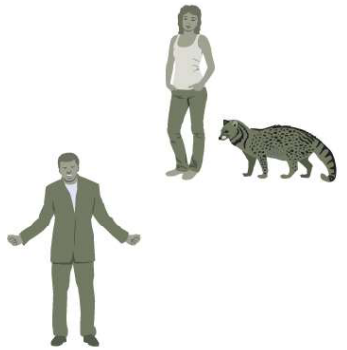
Complex visual hallucinations
People
Animals



Visual Illusions
Pareidolia

Complex visual hallucinations (VH) in PD

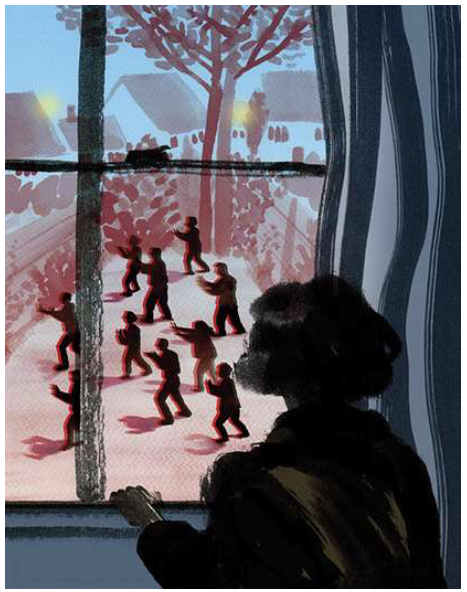
Illusions & minor hallucinations



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

Typical evolution from visual illusions to VH in PD

“Visual illusions are especially frequent. Familiar objects may be mistaken for something else. The patient may mention seeing worms on the floor, whereas actually there is a design in the flooring which is misinterpreted because the pattern seems to move. Spectral illusions generally of a benign if not pleasant character are experienced. There may be (visual) hallucinations of people or animals roaming around the house. … Complex scenes with a group of people wandering around, having a party … [who] seem to go about their business without disturbing the patient. Patients may experience these visions for long periods of time but are afraid to mention them to anyone for fear of being thought ‘crazy’… Finally, however, the patient reacts, angrily ordering the strangers out of the house, accusing them of stealing.”

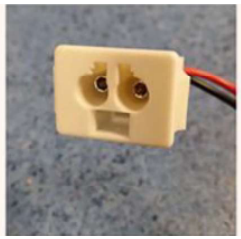
Duvoisin (1991)

Visual illusions in PD

Visual illusions & Pareidolias

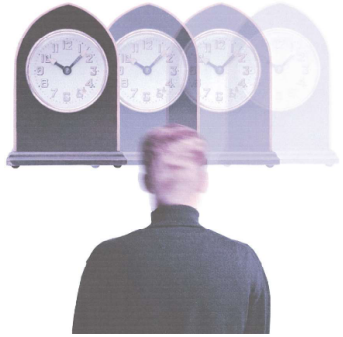
Visual illusions
-misperception of visual objects that are physically present
-need to be discriminated from VH
-precede VH in the course of PD
-examples: visual perseverations, inanimate objects are perceived as living beings or parts of living beings (show some examples)

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

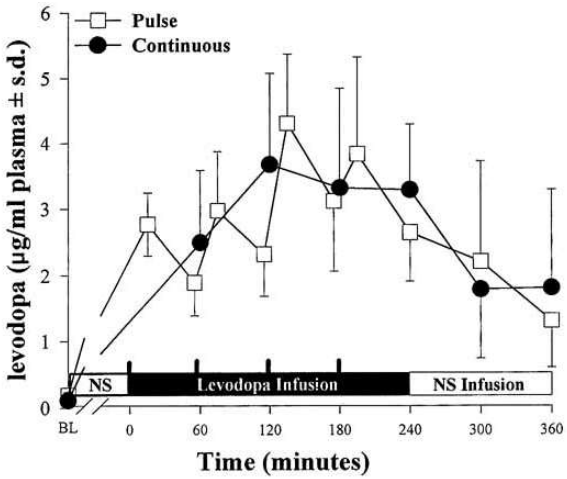
Dopamine
-PD leads to presynaptic striatal dopamine depletion caused by degeneration of the nigro-striatal pathway, which has been shown to lead to hypersensitive/upregulated postsynaptic dopamine receptors: →
Excess dopamine from medications could lead to VH

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

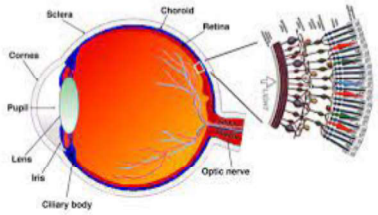


No habitual hallucinations were induced in any of the 5 tested patients (but 2 had their habitual dopamine side effects (dyskinesias)

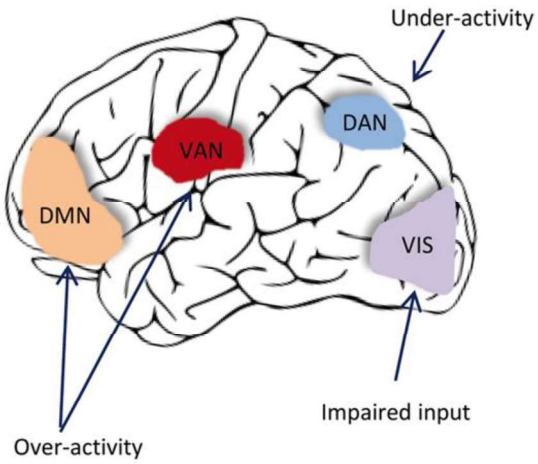
Goetz et al., 1998; Diederich et al., 2009

Many potential causes for Complex visual hallucinations (VH) in PD

Visual deficits are reflected in structural changes at many levels

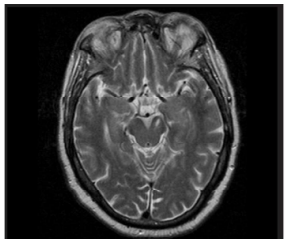


Retina
-retinal deficit (not covered in this class)

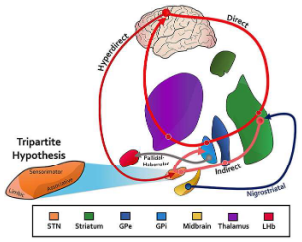


Cortex
-reductions in grey matter volume (MRI) in lingual gyrus (area 18), but also in extrastriate regions
-confirmed in pathological work (post-mortem)
-ventral pathway and the dorsal pathway of the visual system are impaired
-but also frontal cortex !

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

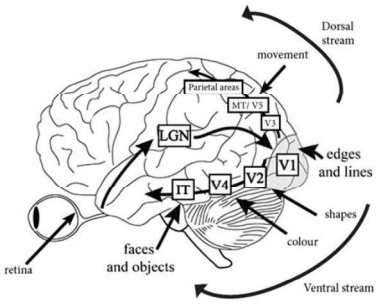


Basal ganglia and thalamus
(not covered in this class)



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

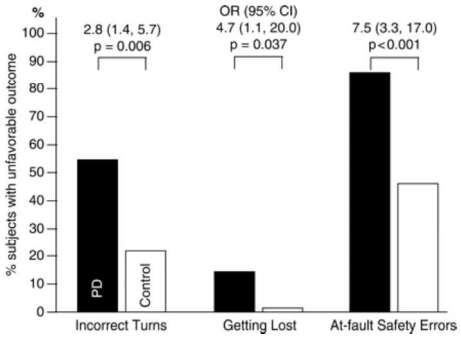
... bistable visual perception

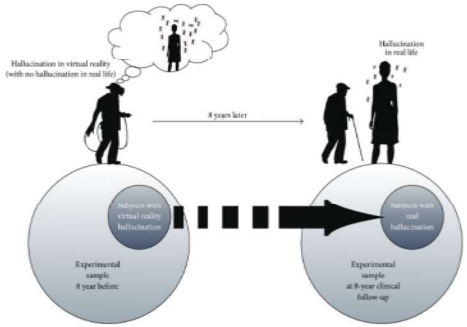
... visual acuity

... contrast sensitivity

(Gallagher et al., 2011)

Deficit in visual search (while driving)





Virtual Reality 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)

In the study by Uc et al., (2007)

-Patients were asked to play a game where they had to drive a car in a city to a specific location.

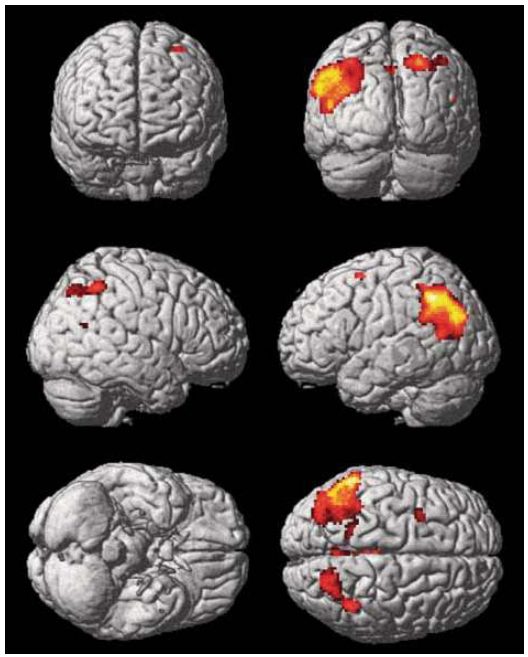
-Driving errors were compared between PD patients versus age matched controls

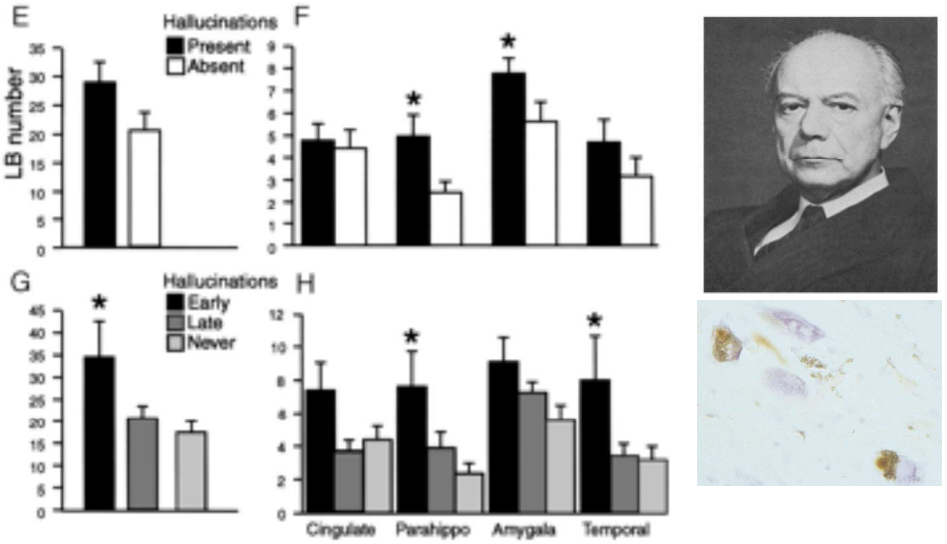
PD Patients with VH made more incorrect turns and safety errors

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 regions) 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)

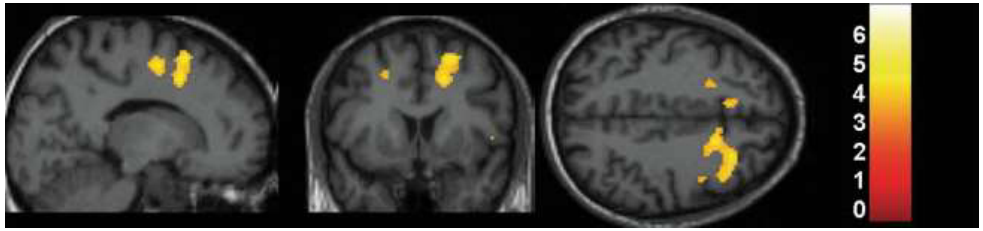
Harding et al., 2002, Papapetropoulos et al., 2006

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)



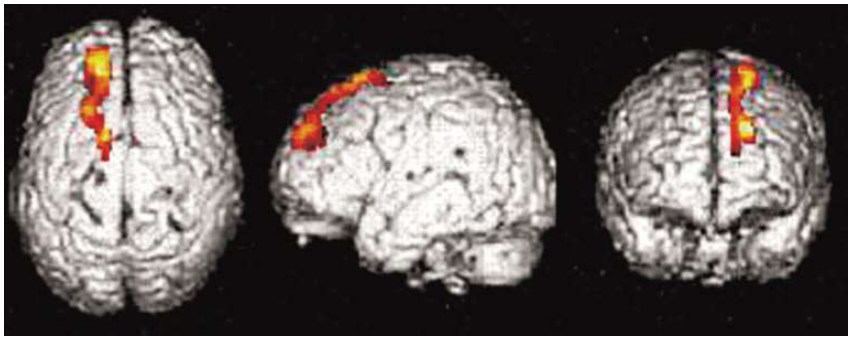
Motion perception study (fMRI)

-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)

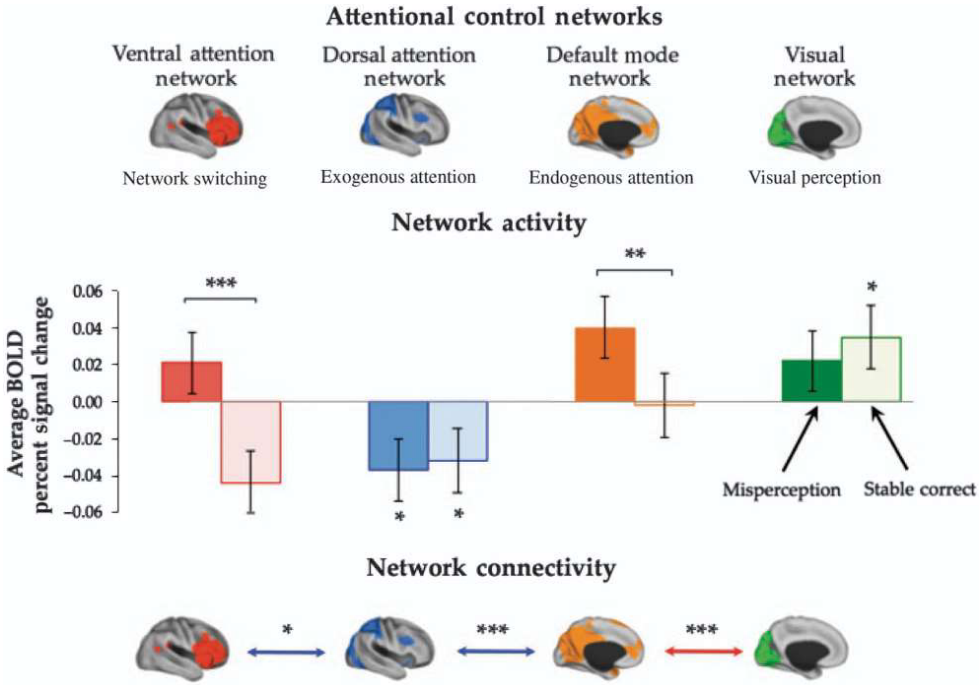


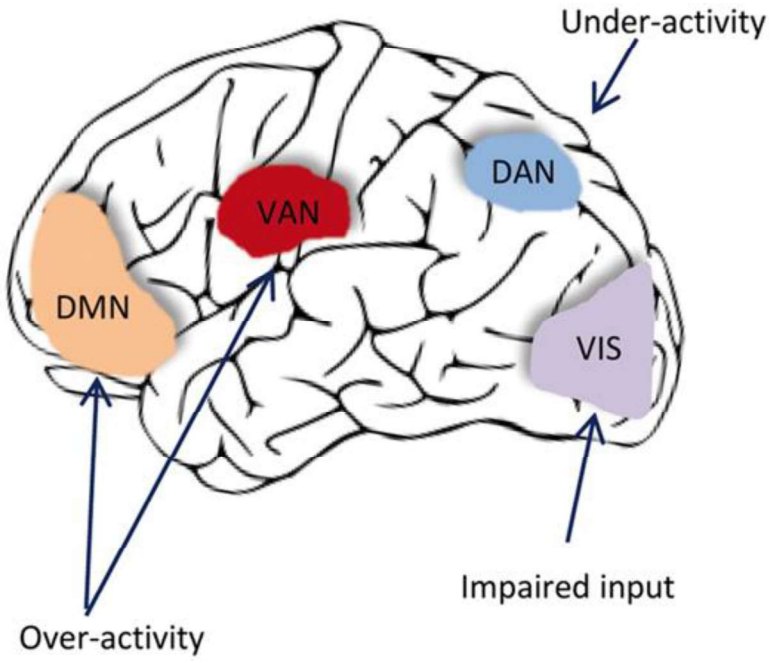
Data compatible with an imbalance of cortical activity – an increase of frontal (parietal) networks (involved in attentional, executive, inhibitory processes) to compensate for a decreased visual input in extrastriate and striate visual cortex.

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

Complex visual hallucinations (VH) in PD

Anti-psychotic (anti-dopaminergic) treatments are complex

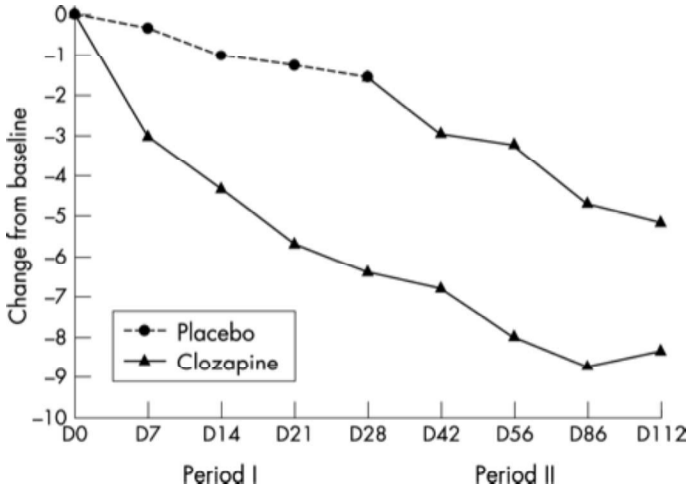
Dopamine
-reduce dopamine intake in case of over medication
-search for underlying non-PD illness (i.e., infection)

Neuroleptics/anti-psychotics

Typical neuroleptics (i.e., thioridazine)
-avoid
-initially used in low dosage, but lead to worsening of PD motor function (strong anti-dopaminergic effects)

Atypical neuroleptics (clozapine)
-most often prescribed and decrease VH (Parkinson study group, 1999; Pollak et al., 2004)
-are anti-psychotic in PD and do not worsen motor function (weaker anti-dopaminergic effect, additional anti-seritonergic effect)
-clinically efficient in > 80% of patients
-Problem: serious adverse effects (sedation, orthostatic hypotension, agranulocytosis); require regular blood control tests
-if antipsychotic medication is stopped VH re-occur (Pollak et al., 2004)

(New treatment: Pimavanserin; serotonin antagonist)



Complex visual hallucinations (VH) in PD

Limitations

1

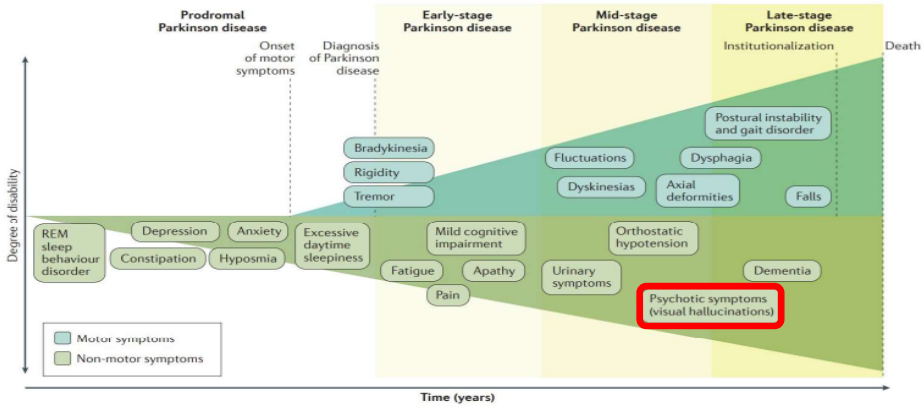
... Most studies have compared the brain structure, connectivity, or functional activity differences between PD patients with VH and without VH **(trait of VH)** (VH could have occurred a month before !)

This is not enough because ...

... no study has investigated brain activity **during an ongoing VH** of PD patients (state of VH)
... no study has **induced VH experimentally** and investigated the cortical brain mechanisms

Full understanding of VH in PD **requires explaining the state of VH** and **requires the experimental induction of VH in PD**.

→ **Project proposal (Virtual Reality ?)**



2

VH occur late in PD, just like dementia = once VH occur there are also moderate to severe cognitive deficits (dementia)

Biomarkers are needed that detect PD and PDD as early as possible (do not exist)

Identifying prodromal PD (or PDD) with a biomarker allows selecting appropriate patients for inclusion in trials of experimental disease-modifying interventions; ideally in the prodromal, pre-symptomatic, premotor phase of PD, before neurodegeneration is too advance to delay or prevent the disease.

Disease-modifying therapies

(not covered in class)

Transplantation of dopamine-producing cells, derived from human embryonic stem cells or from induced pluripotent stem cells, into the putamen could selectively restore dopamine loss. Most work focused on transplantation of human fetal ventral mesencephalic tissue.

The success of future trials will crucially depend on **reliable biomarkers for early detection.**

Bloem et al. (2021)

Target	Therapy	
	Preclinical studies	Clinical studies
SNCA	Beta-2 adrenergic receptor, siRNA, non-steroidal anti-inflammatory drugs, antistreptolysin O	Thiazolidinedione (glitazones)
Misfolded α-synuclein fibrils	Anti-LAG3 antibody, small molecule inhibitors, CLR01, KYP	Active or passive immunotherapy (eg, BIIB065), nilotinib, deferiprone
Autophagy lysosomal pathway	LTI-291, AT3375	Ambroxol, glucosylceramide synthase inhibitors
Calcium ion homoeostasis	Calcium ion channel blockers	Calcium ion channel blockers (eg, isradipine)
Mitochondria dysfunction Parkin pathway	Ursocholanic acid, mitochondrial division inhibitor 1, MIRO reduction, sirolimus	11-dehydrosinularoiolide, MitoQ, exenatide, LRRK2 small molecule kinase inhibitors
Neurotrophic factors	Brain-derived neurotrophic factors, vascular endothelial growth factor	Cerebral dopamine neurotropic factor, glial cell line-derived neurotrophic factor, neurturin
Inflammation	Anti-inflammatory (eg, non-steroidal anti-inflammatory drugs)	Sargramostim, exenatide, liraglutide, lixisenatide, AZD3241
Oxidative stress	DJ-1 chaperones	Deferiprone, inosine, coenzyme Q10, caffeine, nicotine, creatine
Therapies under investigation		
⏭ Vaccines, neuroinflammatory therapies, diets and microbiome, cannabinoids, novel druggable targets, gene therapy, and next generation adaptive deep brain stimulation **Emerging future therapies**		

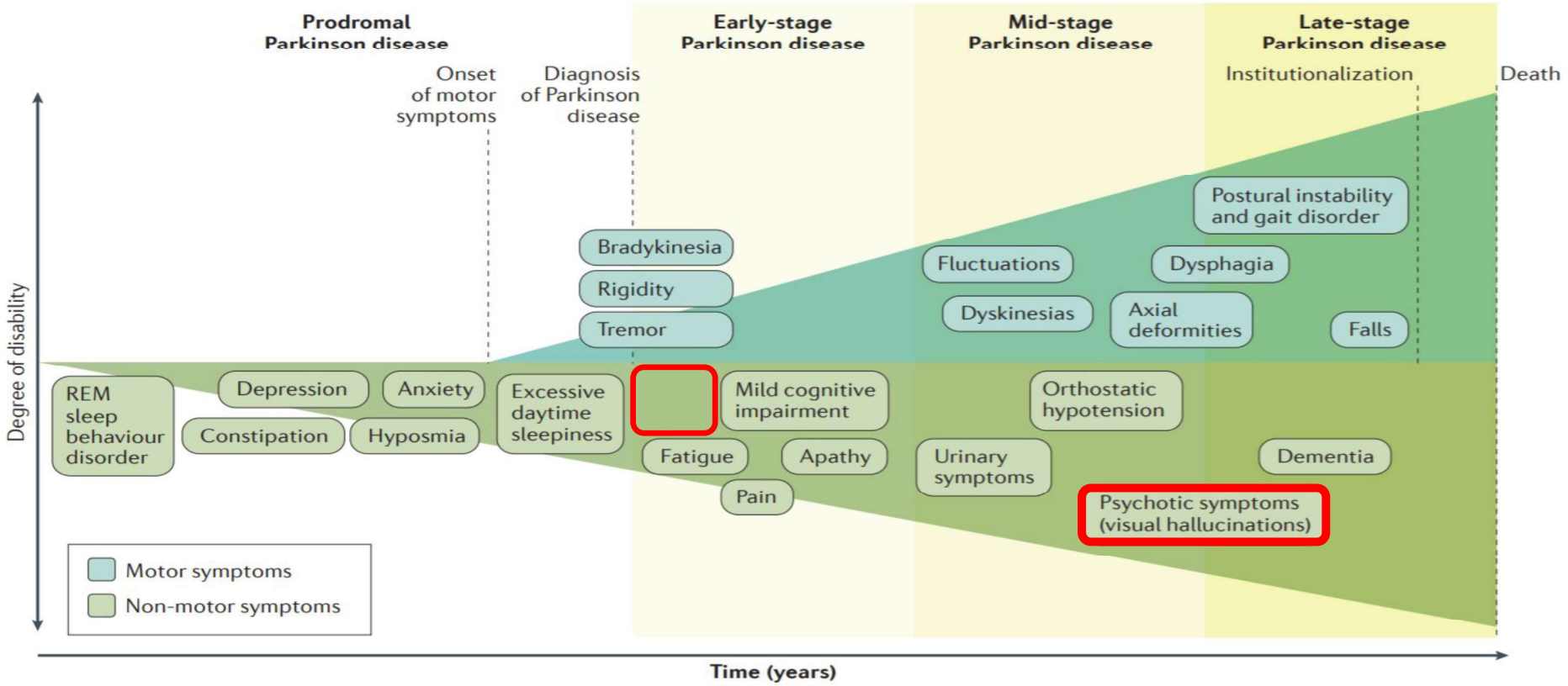
Minor hallucinations in PD

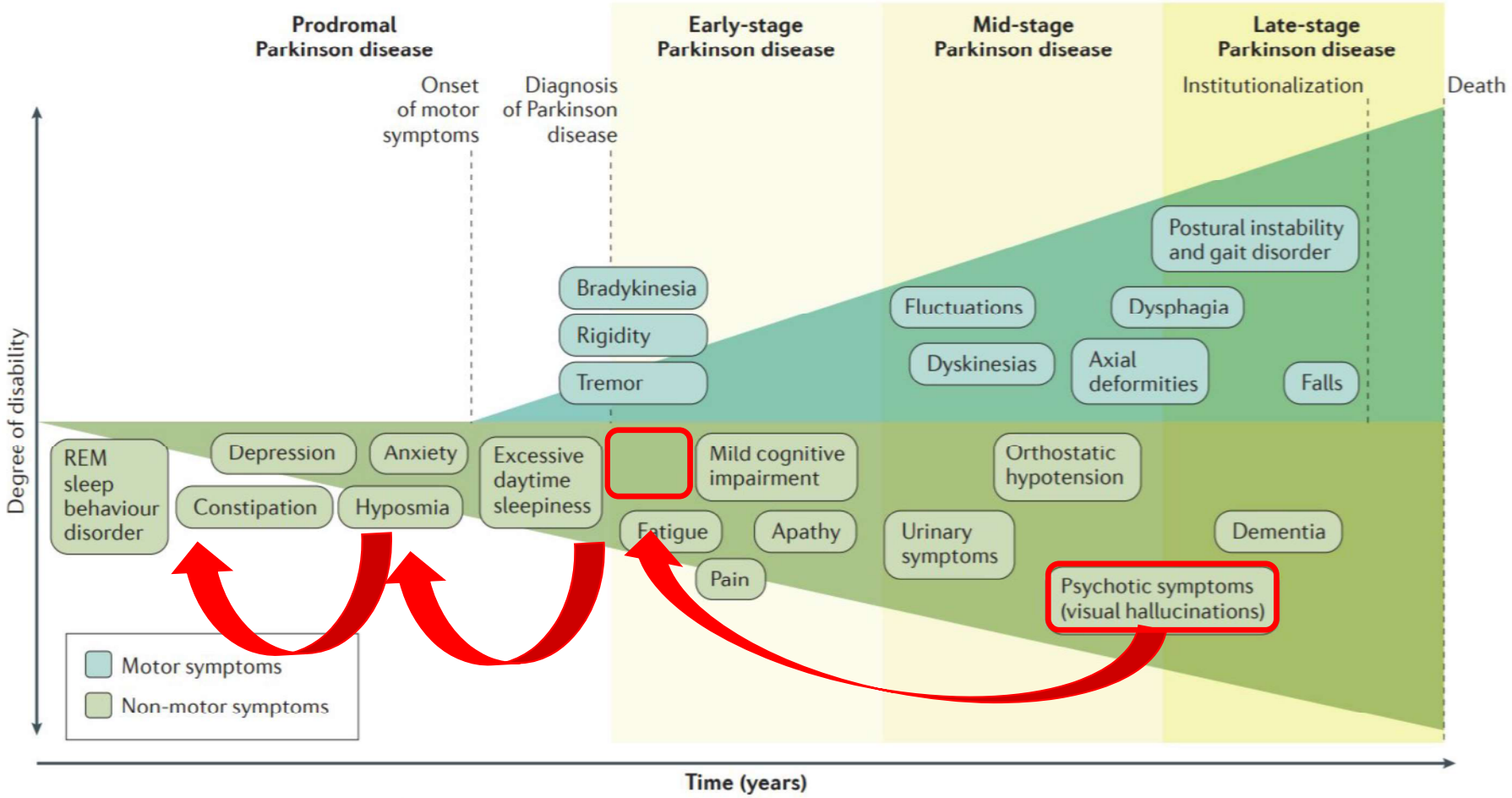
Presence hallucinations

(passage hallucinations)

Minor hallucinations

are another frequent non-motor symptom, affecting up to 40% of PD patients,
but already early in the disease, sometimes even before diagnosis of PD

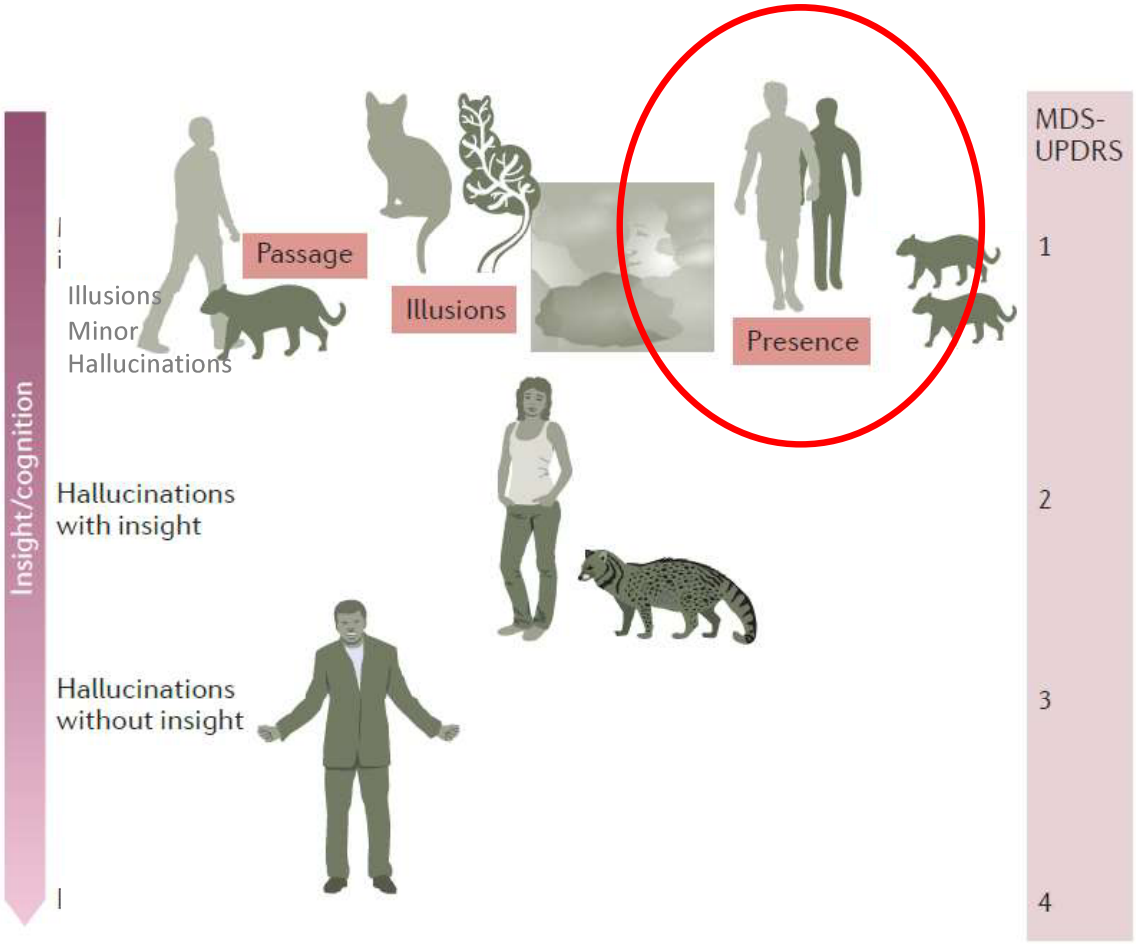



Prodromal Parkinson disease
Early-stage Parkinson disease
Mid-stage Parkinson disease
Late-stage Parkinson disease
Onset of motor symptoms
Diagnosis of Parkinson disease
Institutionalization
Death
Degree of disability
Time (years)
Bradykinesia
Rigidity
Tremor
Postural instability and gait disorder
Fluctuations
Dysphagia
Dyskinesias
Axial deformities
Falls
REM sleep behaviour disorder
Depression
Anxiety
Excessive daytime sleepiness
Constipation
Hyposmia
Fatigue
Apathy
Pain
Mild cognitive impairment
Orthostatic hypotension
Urinary symptoms
Dementia
Psychotic symptoms (visual hallucinations)
Motor symptoms
Non-motor symptoms

Presence Hallucinations

Visual illusions
Simple Visual Hallucinations
Pareidolia

Structured complex visual hallucinations
People
Animals



Minor hallucinations
Presence Hallucination
Passage Hallucination

What is a presence hallucination ? - History

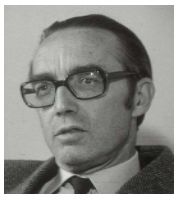
Psychiatry & Neurology

Karl Jaspers
(1913) Leibhafte Bewusstheit
Schizophrenia - Psychiatry

«There are patients who have a certain feeling (in the mental sense) or awareness that someone is close by, behind them or above them, someone that they can in no way perceive with the external senses (visual, auditory, or tactile), yet whose actual/concrete presence is clearly experienced. »

Erich Meninger-Lerchenthal
(1935) Neurology
Jean Lhermitte (1939)

Meninger-Lerchenthal and Lhermitte studied presences in psychiatric and neurological patients.



Henri Hécaen
Julien de Ajuriaguerra (1952)
Macdonald Critchley (1943, 1955)
Neurology

Hécean & Ajuriaguerra extended Menninger-Lerchenthal's proposal and added many detailed neurological case descriptions. Critchley gave a broader perspective, beyond clinical neurology and linked presences with sensory deprivation, social isolation, physical exhaustion, imaginary friend (children).

Brain stimulation induces presence hallucinations by interfering with brain processes **altering own-body representation**