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

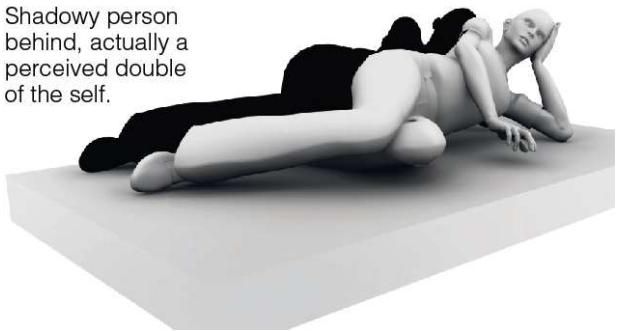
Presence hallucinations

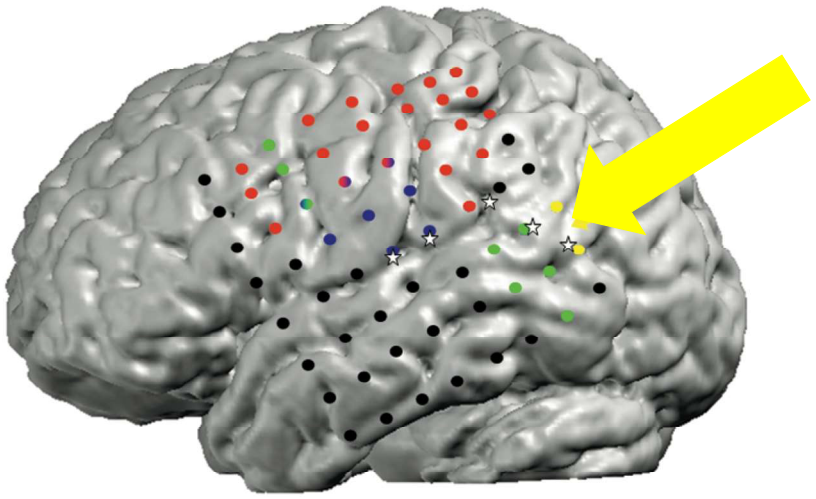
induced by stimulation of temporo-parietal cortex

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

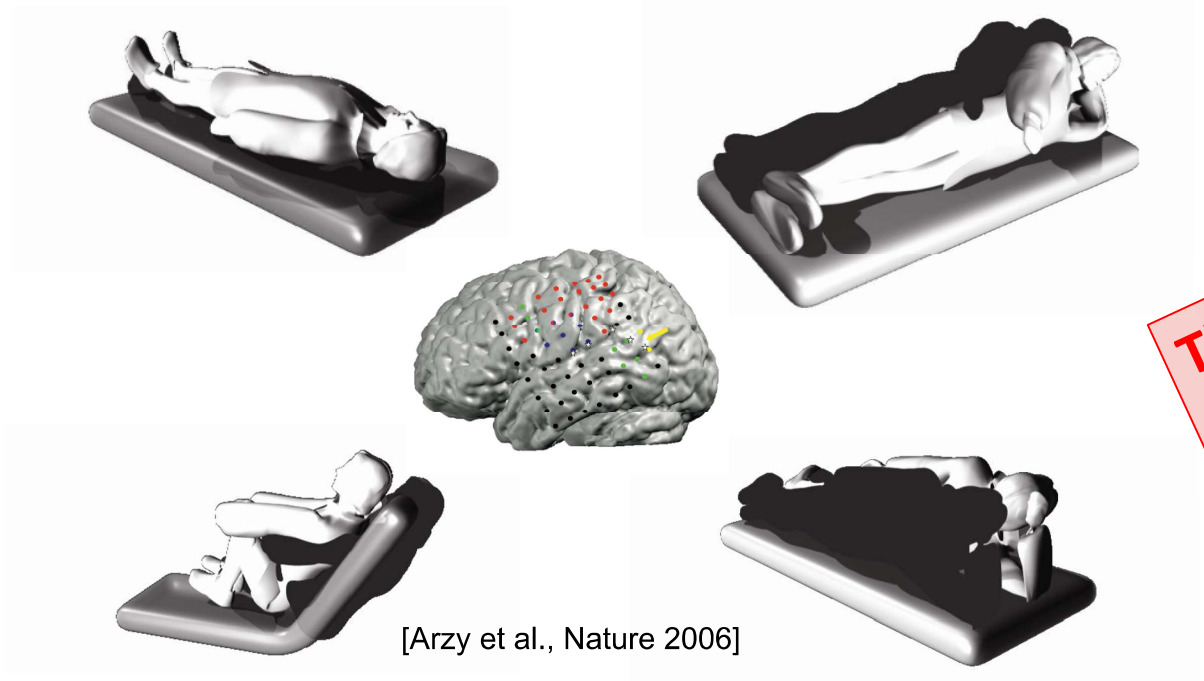
Focal brain stimulation (yellow arrow) in an epileptic patient induced repeatedly presence hallucinations

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





[Arzy et al., Nature 2006]



[Arzy et al., Nature 2006]

Presence hallucination

"He is behind me, almost at my body, but I do not feel to be (touched)."

"A young person" more male than female."

Shared position and posture: When patient was sitting, the "shadow" was sitting, when she was on her left side, presence also was on the left side, etc.

The state of PH investigated and induced, not just the trait

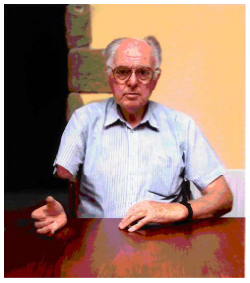
Experienced position and posture of the presence depends on the position and posture of the patient's body

→ own body perception (proprioception + touch) determines the felt presence's body

Sense of presence is a duplicated or second own body that is misperceived as another person (and not as a second self)

Sense of presence is an altered self representation and may be caused an by errors in sensorimotor perception

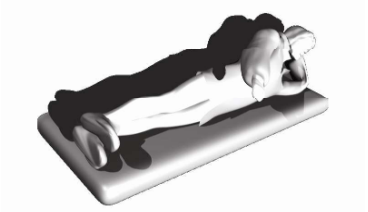
Presence hallucinations



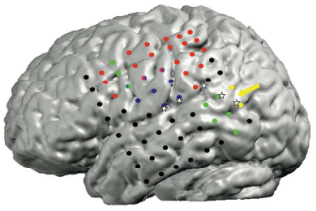
Presence hallucination is the misperception of a second own body as another person

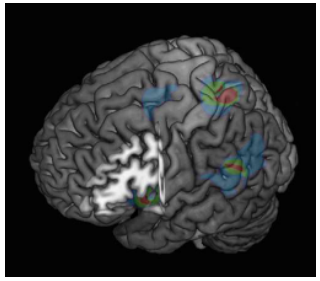
PH is an abnormal own body perception

(comparable to phantom limb sensations, but a misidentified phantom body)



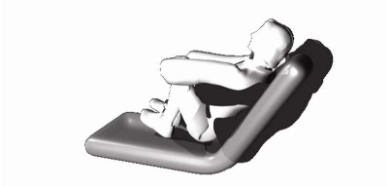
Multisensory own body signals (and potentially motor signals) are crucial (posture and position changes)





Temporo-parietal cortex, insula, frontal-partietal cortex are key brain region

But, these conclusions are only based on a unique single patient with epilepsy and the analysis of a very few neurological patients with focal brain damage (data not shown).



How can we study presence hallucinations experimentally, in healthy subjects?

How can we investigate its hypothetical sensory-motor origin linked to altered own-body perception?

What are the related brain mechanisms?

Are these brain mechanisms altered in PD patients with presence hallucinations?

Experimental induction of positive bodily phenomena (bodily illusions) by manipulating sensorimotor signals in healthy participants

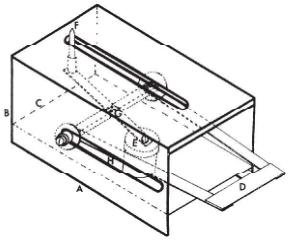

Larry Weiskrantz

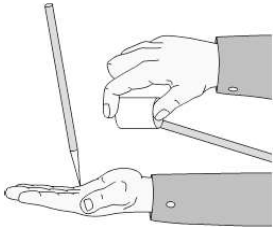

Sarah Jayne Blakemore

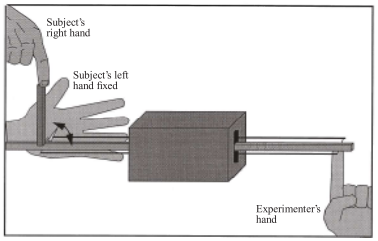

Chris Frith

"…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".
Charles Darwin (1872)

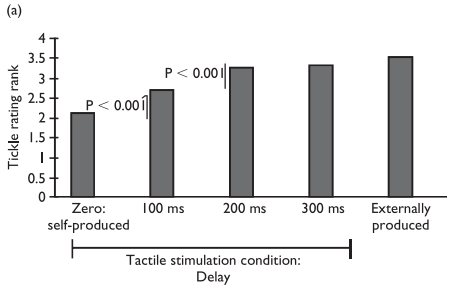
Ticklishness sensation (3 experimental setups)



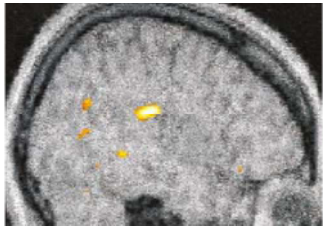


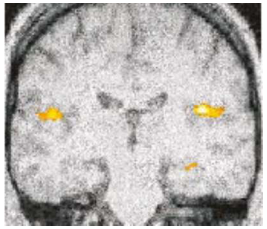


Ticklishness rating increases with increasing delay (increasing mismatch between CD and afferent sensory signal) or when produced by somebody else



Sensory (tactile) attenuation for self-generated, but not delayed stimuli





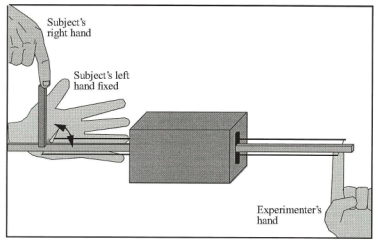
Somatosensory cortex (and cerebellum)

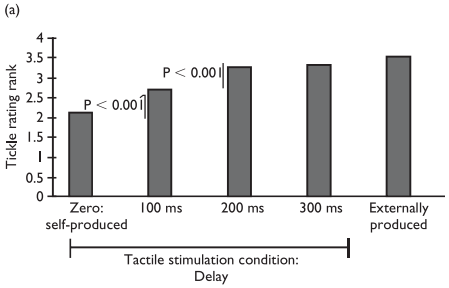
[Weiskrantz et al., Nature 1971; Blakemore et al., Nature Neurosci 1998; Blakemore et al., Neuroreport 2000]

Illusory self-other touch sensations

Combing ticklishness setup with somatic rubber hand illusion

Ticklishness experiment

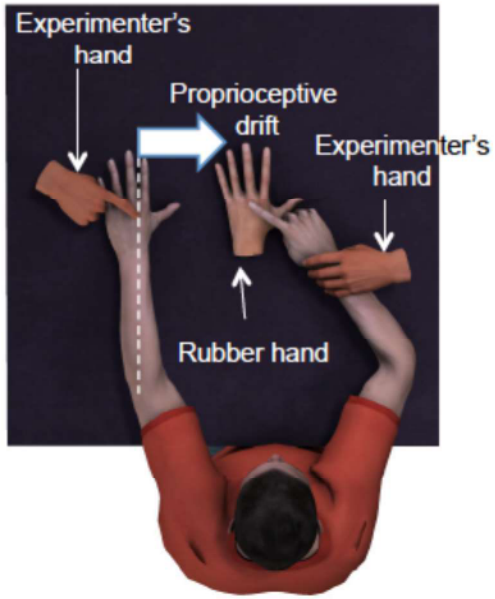




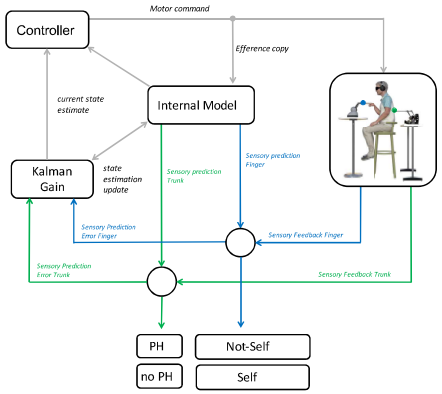
Active (=motor) non-visual rubber hand illusion

Mostly studied to investigate illusory self-touch (even though somebody else is touching you)

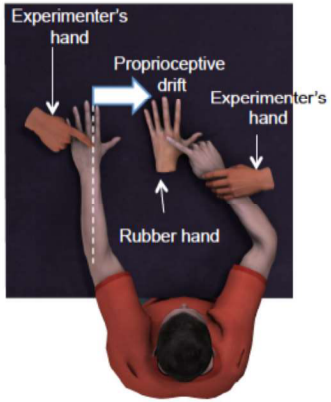
Can be adapted to induce the sensation that somebody else is touching you, although you are are applying the touch cues yourself



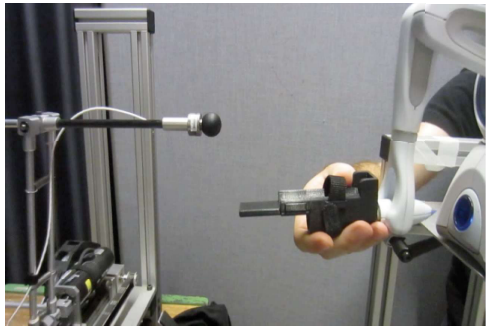
Self-touch illusion induced by sensorimotor stimulation

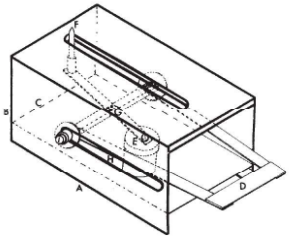


Illusory self-touch
(Somatic rubber hand illusion)

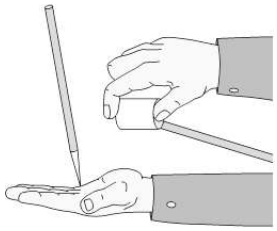


Robotic system used for <u>torso-trunk</u> feedback





Ticklishness sensation



Previous work has focussed on the upper extremity

[Weiskrantz et al., Nature 1971; Blakemore et al., Nature Neurosci 1998; Boulmore, Science 1951; Dieguez et al., Curr Biol 2009; Martuzzi et al., 2013]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LAB
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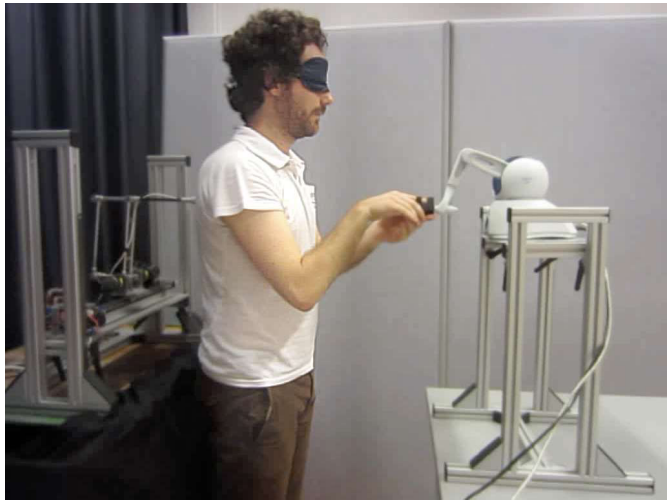
NEUROPROSTHETICS

Robot-induced bodily illusions

(as tested in the somatic rubber hand illusion)

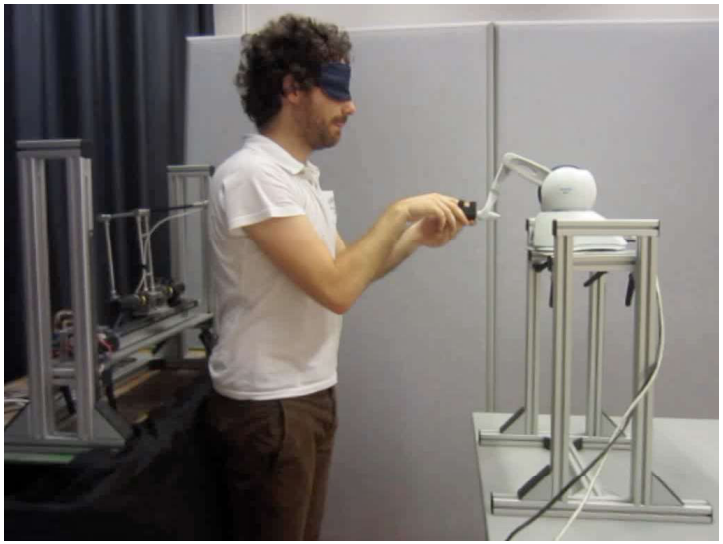


Spatially impossible self-touch does not prevent illusory self-touch

Extends previous (hand) illusions to full body (illusion and drift)

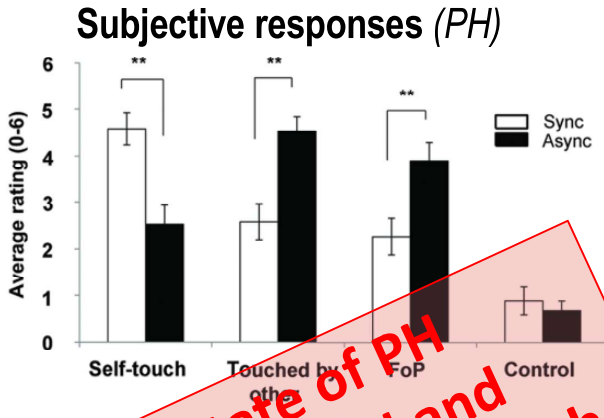
5 subjects spontaneously reported sense of presence; however, this was only the case in the asynchronous condition (with largest mismatch between finger and back)

Robot-controlled induction of the sense of presence



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

Accompanied by systematic behavioral changes in self-location and in social numerosity.



The state of PH investigated and induced, not just the trait

[Blanke et al., Current Biology 2014]


Brain mechanisms of
Presence hallucinations

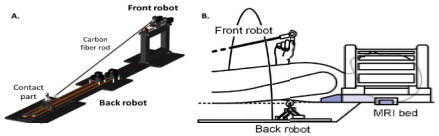
Hara et al., *IEEE/RSJ International Conference on Intelligent Robots and Systems,* **2011**
Hara et al., *J. Neurosci. Methods,* **2014**

Merging neuroimaging with robotics:

Brain imaging with fMRI compatible robot in the scanner

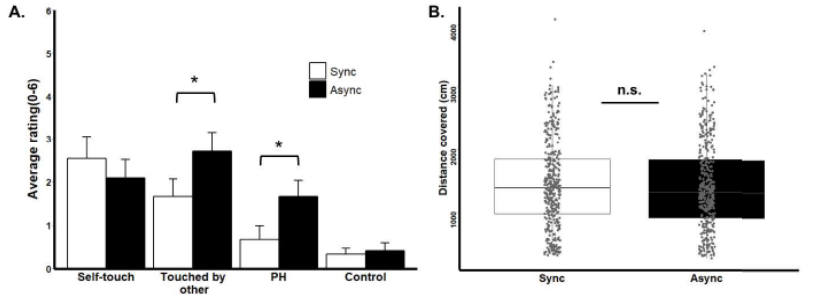
MRI-compatible robot

MRI-compatible robot



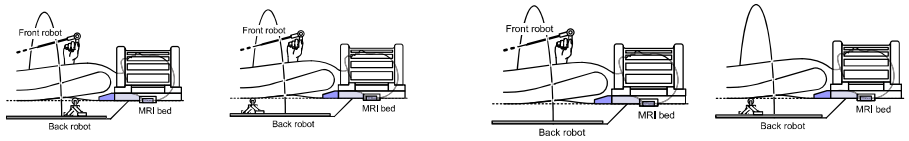
Robot-induced sense of presence

Movement (control)



Experimental conditions

Control conditions

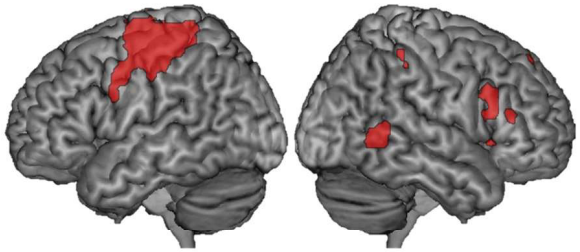


[Bernasconi, Blondiaux et al., Science Translational Medicine 2021]

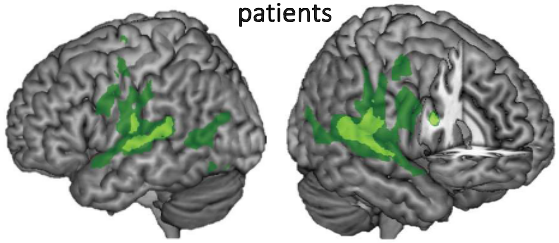
Common brain regions for presence hallucinations

Combining the regions found for symptomatic PH in neurological patients and robot-induced PH healthy people

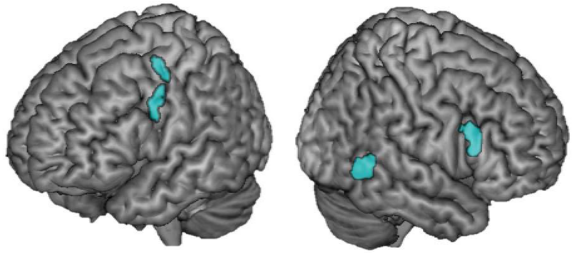
PH-network in healthy controls (N=25)
(both sensorimotor conflicts)



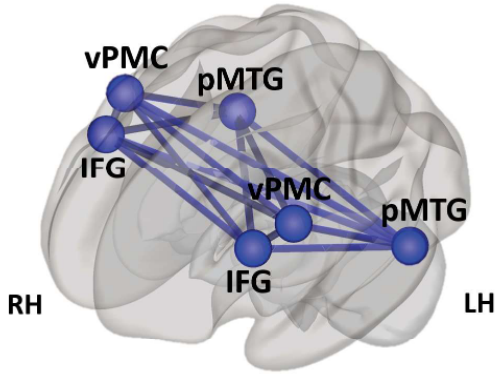
Symptomatic PH-network mapping in neurological non-parkinsonian patients



Common brain regions for robot-induced PH in healthy participants and symptomatic PH in neurological patients

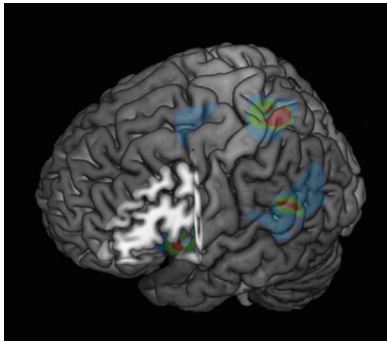


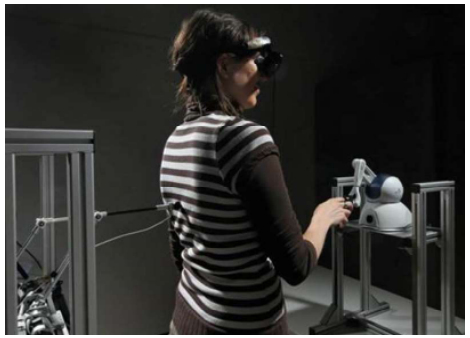
6 common brain regions (nodes) of PH
(used for network analysis in PD patients)



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

PH are sensorimotor hallucinations caused by errors in sensorimotor perception





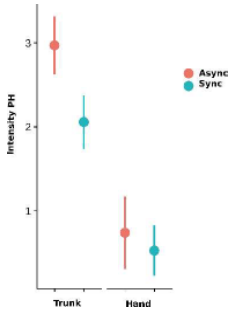
Robot-induced PHs in healthy participants are comparable to those reported by neurological patients (epilepsy, migraine, stroke, etc) and related to similar brain mechanisms

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

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

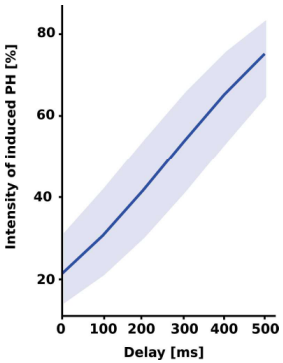
PH is **delay-dependent** and sensorimotor signals have to involve the **torso** (back or front), providing important input to computational models of sensorimotor control (forward model, sensory prediction)

Feedback location (torso-specificity)



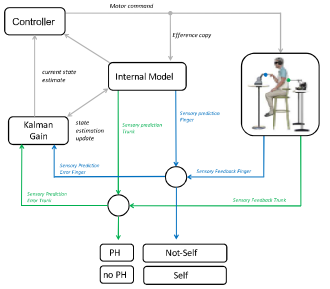
[Dhanis et al.]

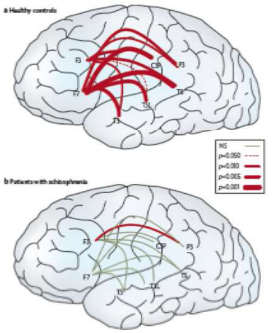
Delay-dependency



[Bernasconi et al., 2021]

Sensorimotor processing, Sensory predictions





How can we study presence hallucinations experimentally, in healthy subjects?

How can we investigate its hypothetical sensory-motor origin linked to altered own-body perception?

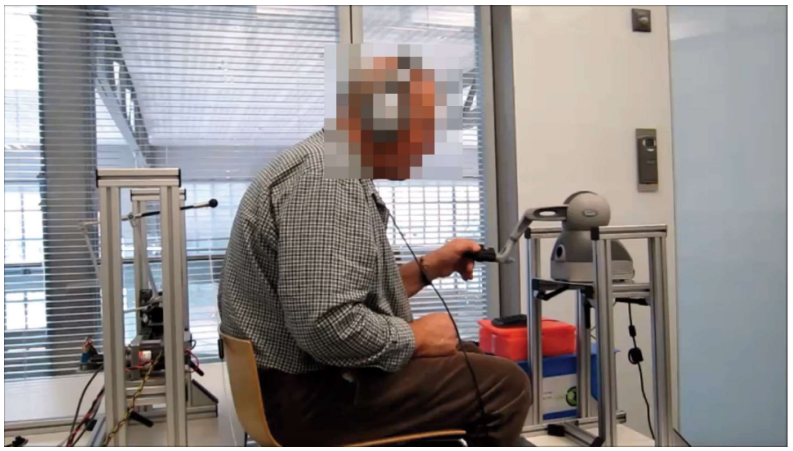
What are the related brain mechanisms?

Are these brain mechanisms altered in PD patients with presence hallucinations?

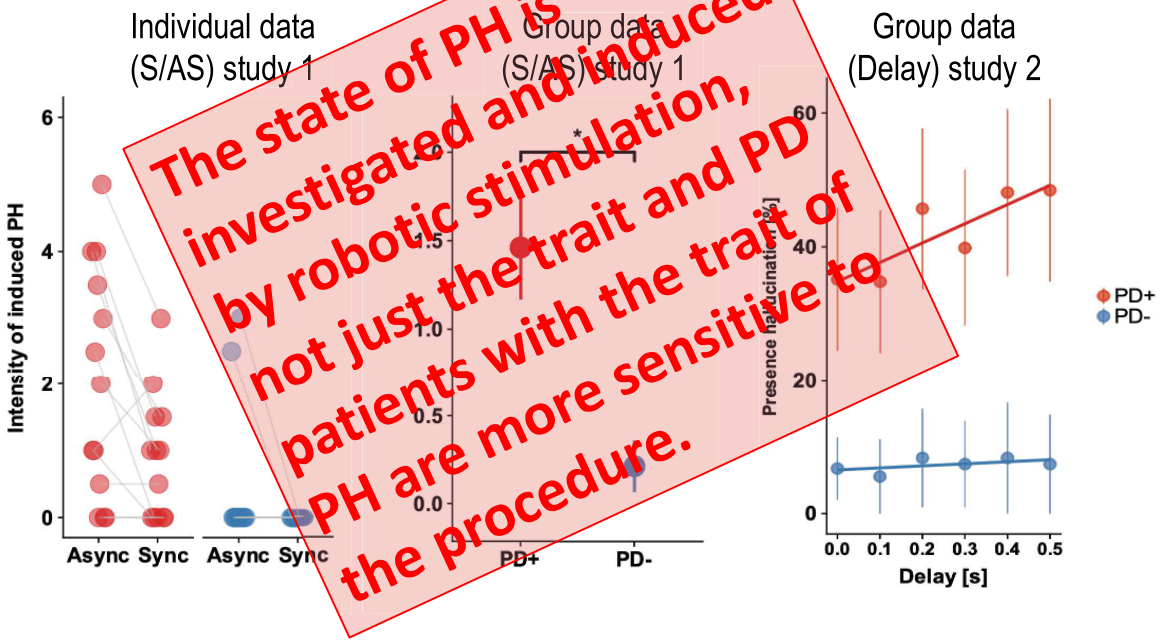
Presence hallucinations: the hallucinatory perception that another person or being is within the space close to the patient (but the person is not seen nor heard or felt by touch).

Presence hallucinations in PD are specific and stereotypical hallucinations, with regular occurence, for some patients weekly or daily, but linked to PD neurodegeneration

Patients with Parkinson's disease are highly sensitive to robotic stimulation and activate different brain regions



Patient performing robot procedure
(sitting position, adapted (shorter) sessions
Conditions: 6 delay conditions
2 AFC (PH yes-No)



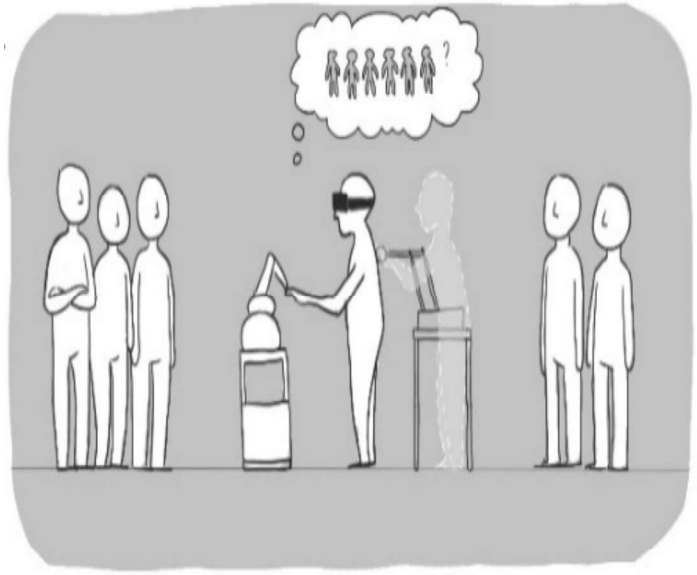
PD patients able to perform entire procedure

PD patients with symptomatic PHs (red) are 6x more sensitive (more vulnerable, different delay-dependency) to sensorimotor stimulation than controls and PD patients without PH

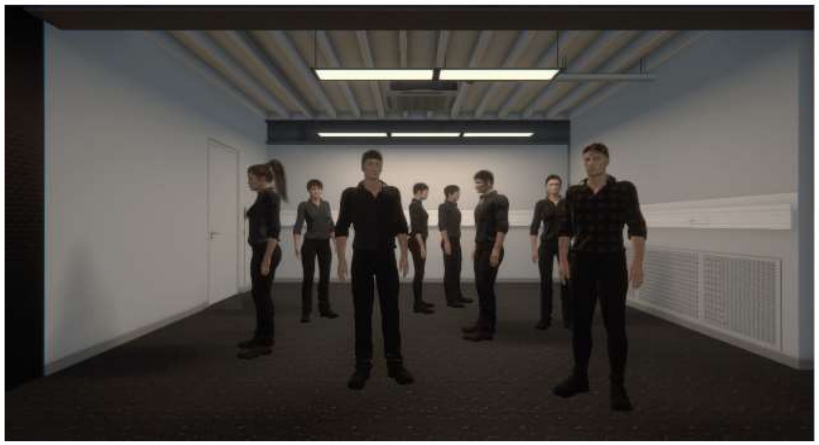
These differences are not related to the performed movements during the procedure

"Hallucination stress test"

Does the perception of an invisible person (presence hallucination) bias numerosity estimation of visual humans seen in a room ?

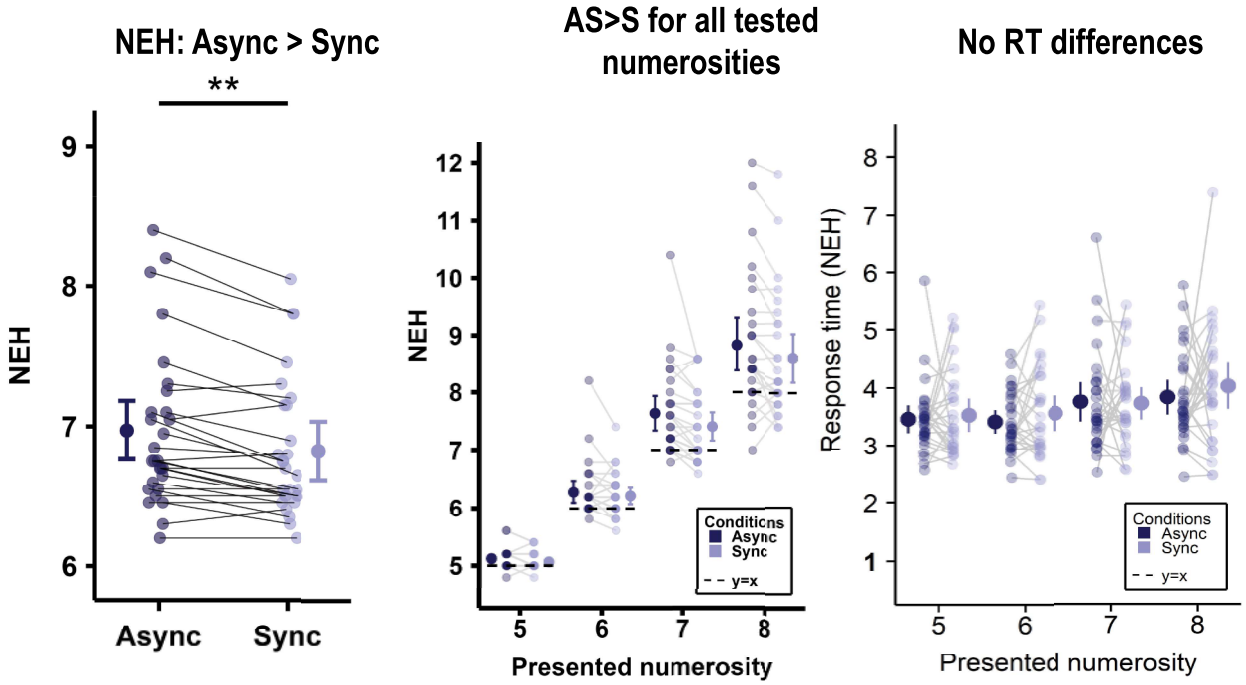


How many humans do you see in the room ?



Robot-induced 'invisible' presence makes participants «see more people in the room» (implicit proxy for presence hallucination)

Number estimation of humans (NEH)

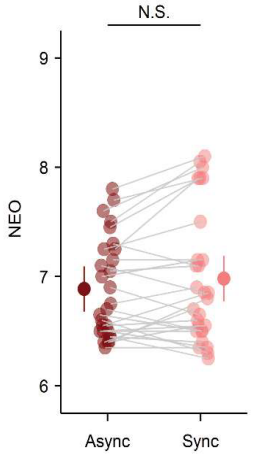


[Albert et al., **Nature Communications** 2024]

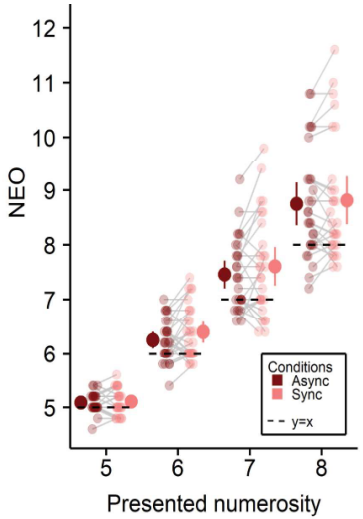
This is not the case for non-human control objects presented in the same room during induction of robot-induced PH

Number estimation of control objects (NEO)

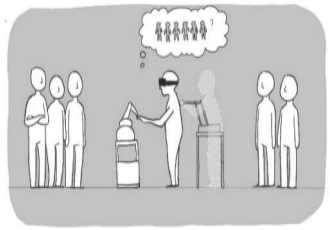
NEO:
Async = Sync



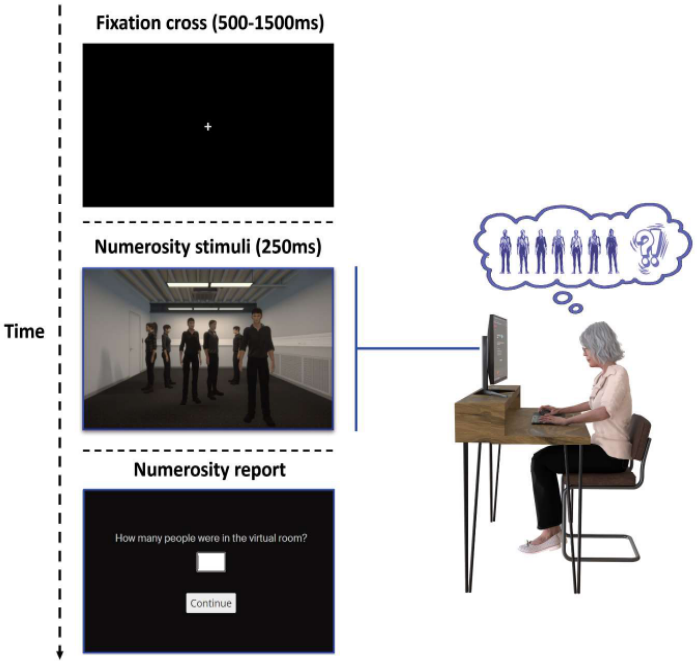
AS=S for all tested numerosities



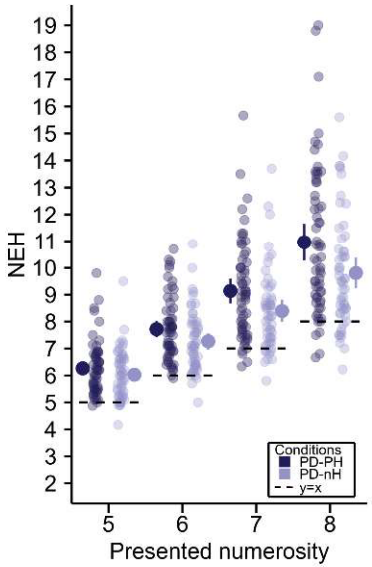
[Albert et al., **Nature Communications** 2024]

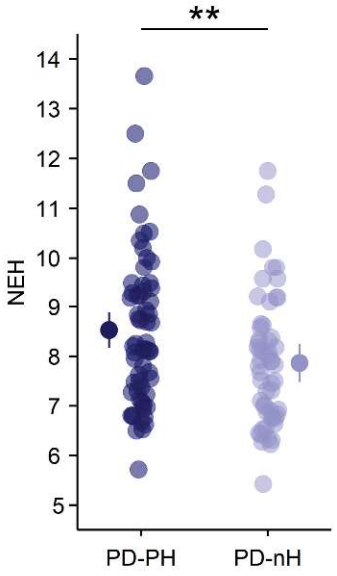


Online web-based study of human numerosity estimation at the home of Parkinson's patients also reveals overestimation

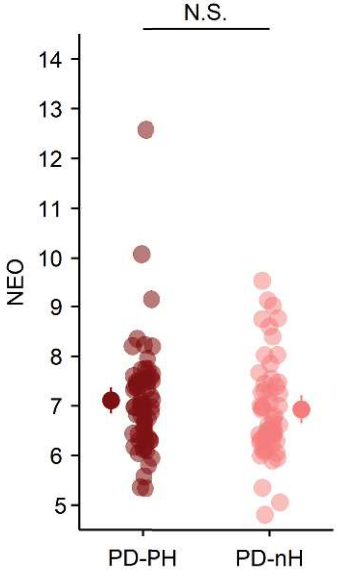


Number estimation of humans
NEH: PD-PH > PD-nH





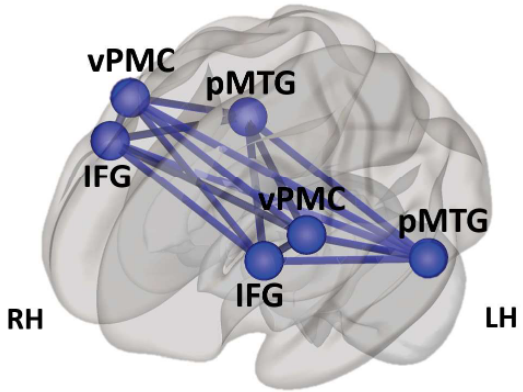
Number estimation of control objects; NEO: PD-PH=PDnH



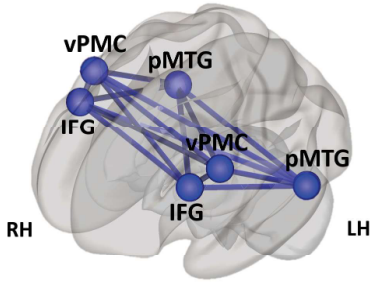
[Albert et al., **Nature Communications** 2024]

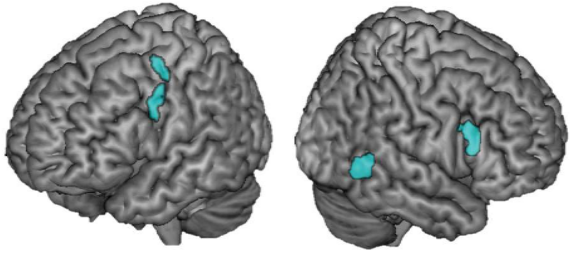
Patients with Parkinson's disease patients with presence hallucinations have stronger overestimation bias for humans, but not for control objects

Disrupted PH brain mechanisms in patients with Parkinson's disease



Patients with Parkinson's disease show disruption of presence hallucination cortical network and this disruption correlates with their degree of cognitive decline





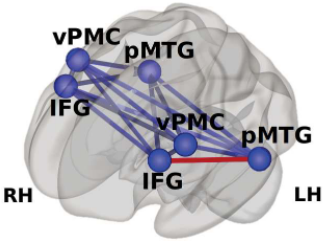
N = 15

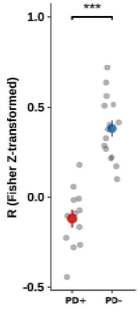
PD patients with PH

N = 15

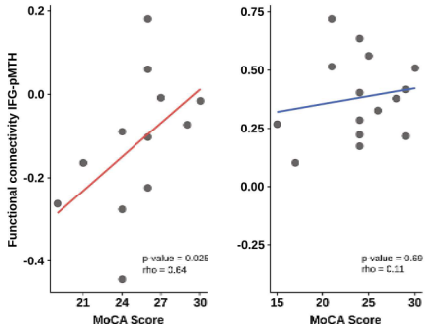
PD patients without hallucinations

Disrupted Hallucination network (Parkinson's disease patients)





Disruption correlates with cognitive decline (PD patients)

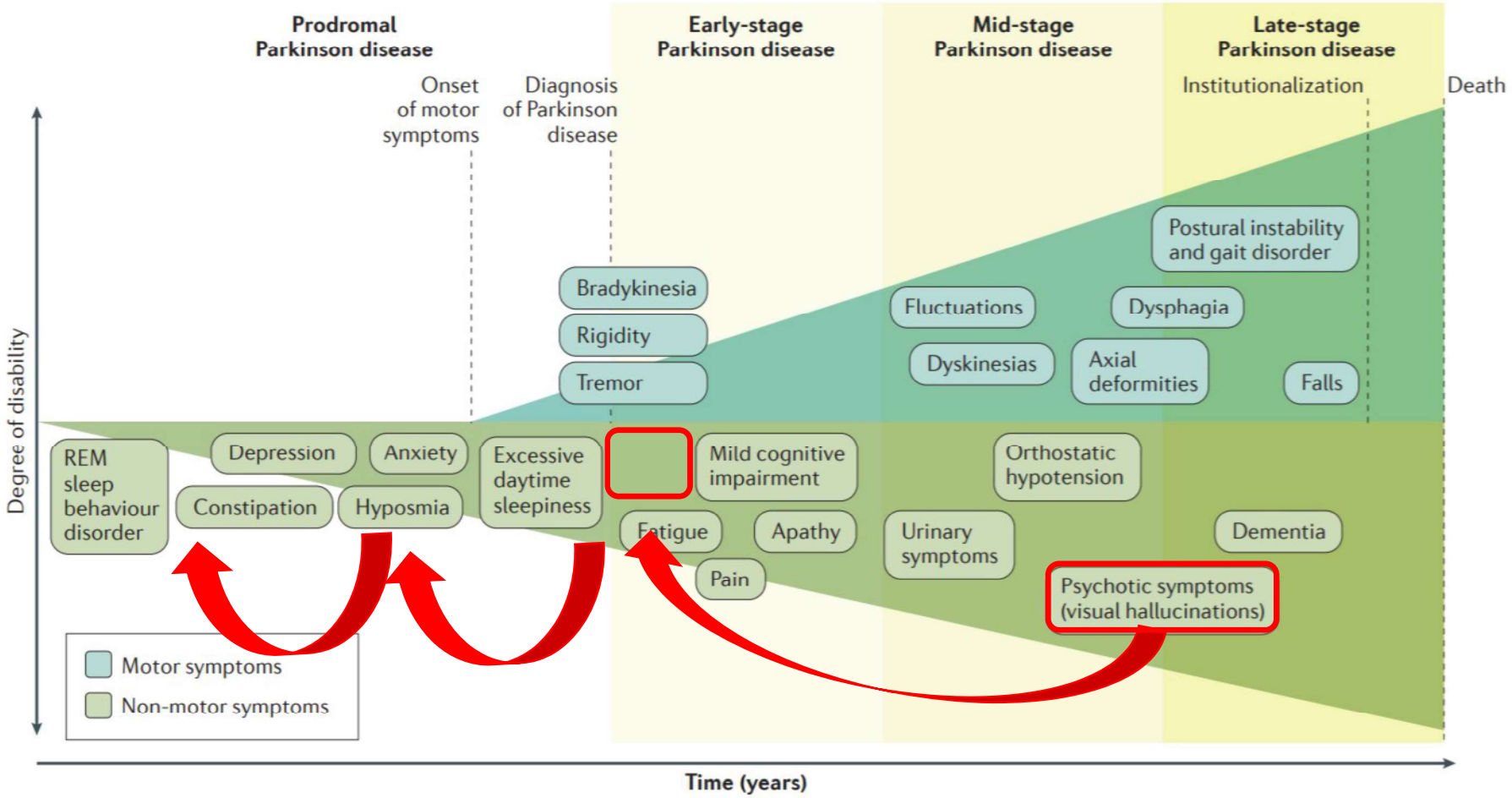


Neural marker Functional hypoconnection in 30 PD patients with symptomatic PD-related PHs in a specific network defined by robot-induced PHs in healthy subjects (Barcelona data)

Model Data show that sensorimotor processing and sensory prediction are crucial mechanisms in PH; compatible with fronto-temporal dysconnection model of hallucinations

Diagnostics Neural and behavioral robot-based marker for diagnostics (prediction of more severe and rapidly advancing form of PD; prediction of dementia in PD,…)

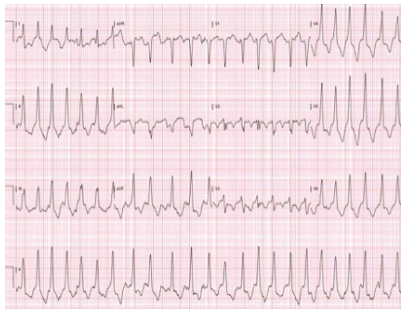
[Bernasconi, Blondiaux et al., Science Translational Medicine 2021]


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

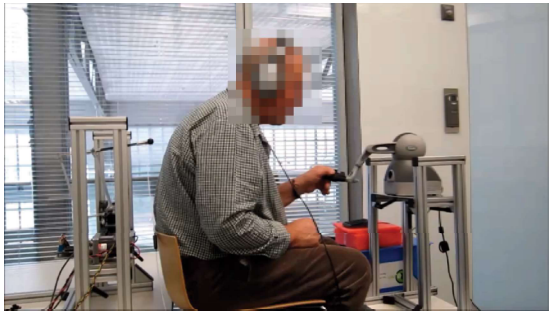
Diagnosis of PD psychosis and dementia based on hallucination stress test

Cardiac stress test

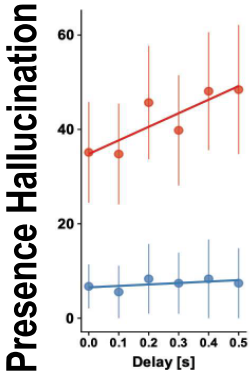
Electrocardiogram



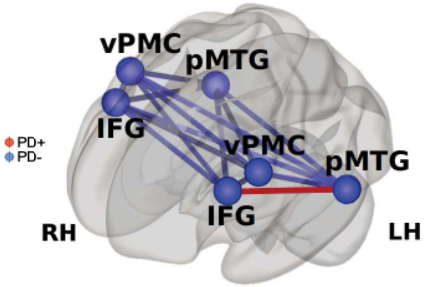
Hallucination stress test



Behavior



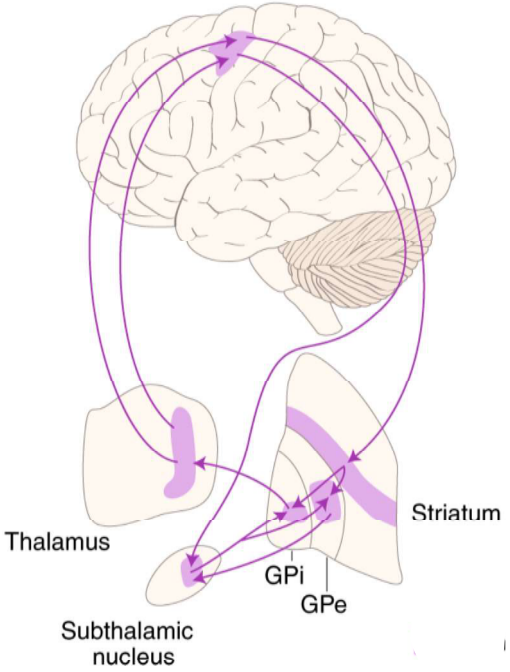
fMRI/EEG

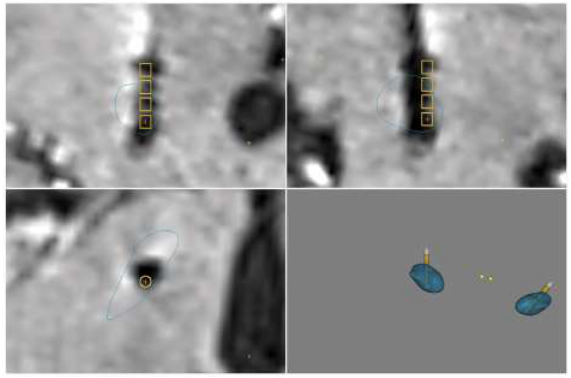


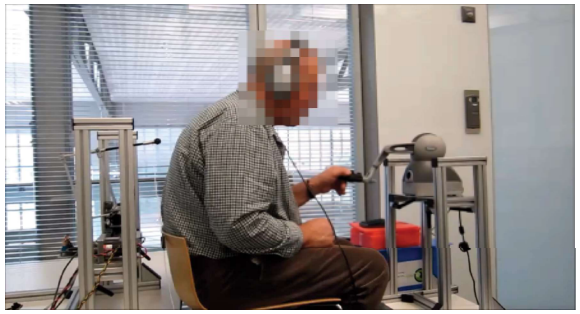
Ongoing project with EPFL & Rockefeller Neuroscience Institute (WVU)

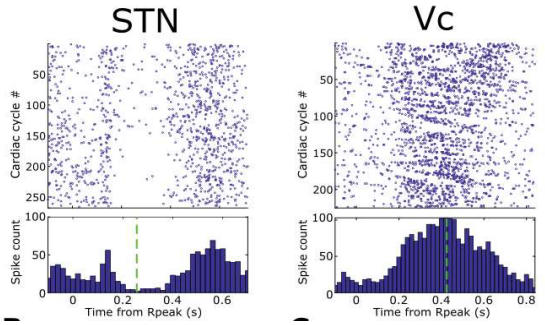
Presence hallucinations and oscillations in subthalamic nucleus

Goal is to develop neuroprosthetic therapy for mental & cognitive deficits in PD using closed-loop DBS





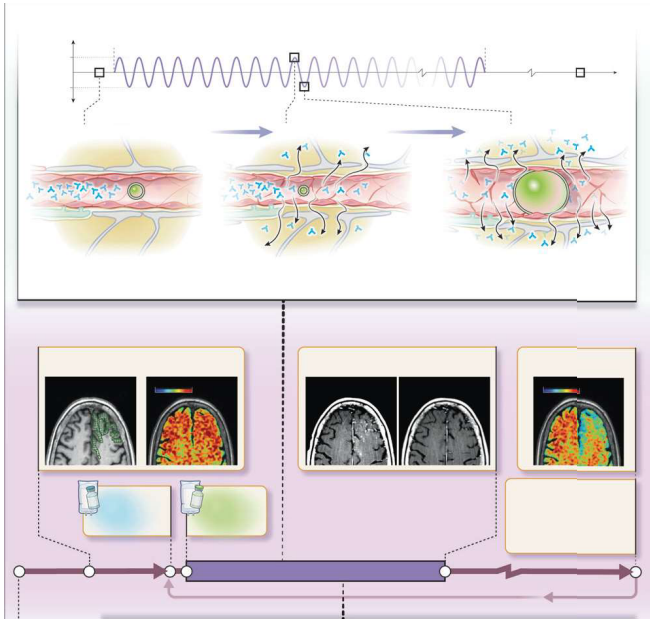




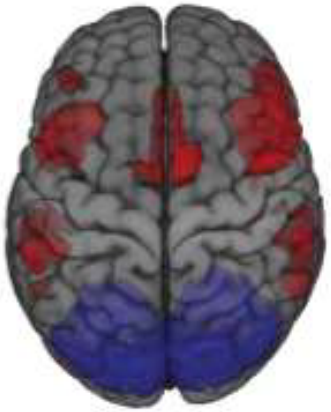
Pereira et al., **Nature Communications** 2021
Serino et al., **Nature Human Behavior** 2022
De Falco et al., **PNAS** 2024
Pereira et al., **eLIFE** 2023

Novel treatments for mental & cognitive decline in patients with Parkinson's disease

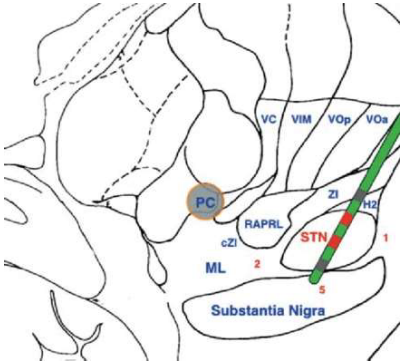
Focussed ultrasound & BBB opening

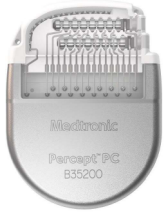


fMRI/EEG Neurofeedback



Deep brain stimulation

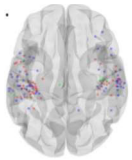




Hallucination engineering & Technodelics

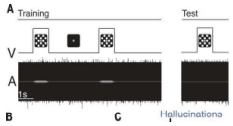
> Methods and procedures from robotics and related technology such as VR, allow the repeated, safe, controlled and real-time induction of well-defined and clinically relevant hallucinations in healthy and clinical populations

Invasive brain stimulation

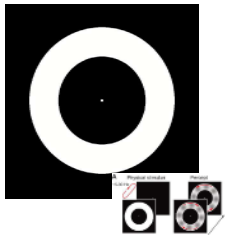


Pharmacology

Pavlovian conditioning

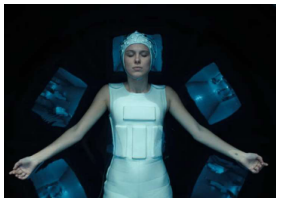


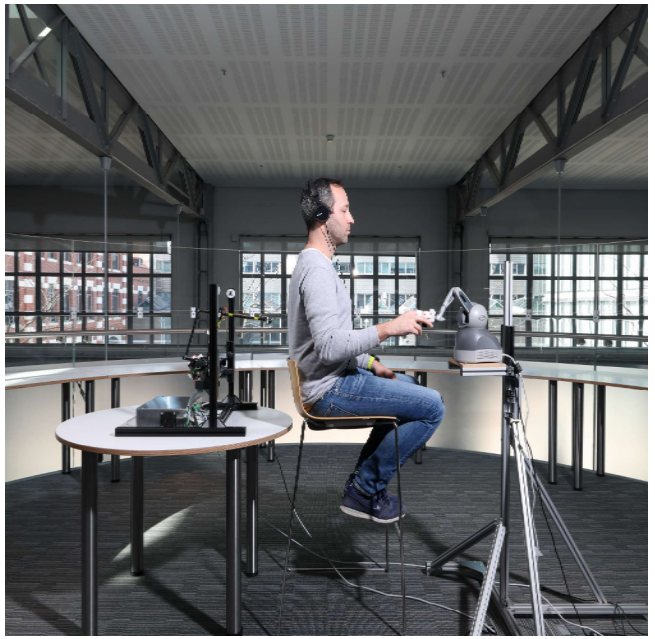
Flickering light



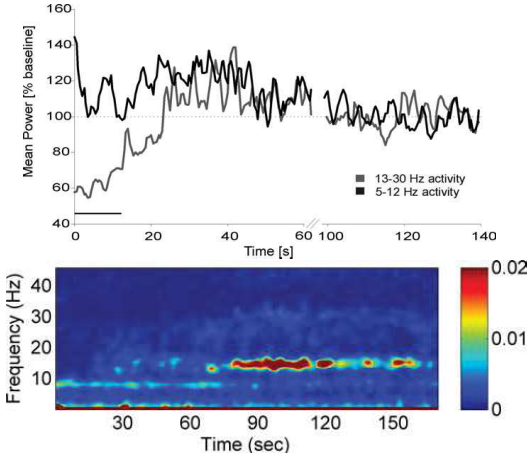
Ganzfeld effect

Sensory deprivation



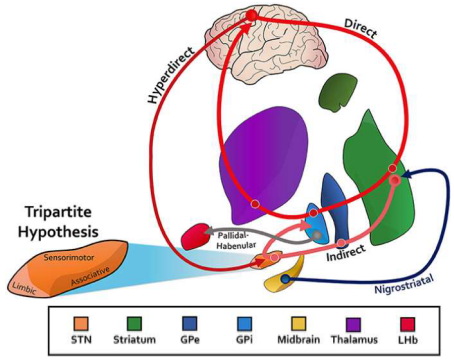


Bernasconi et al., **Nature Protocols** 2022

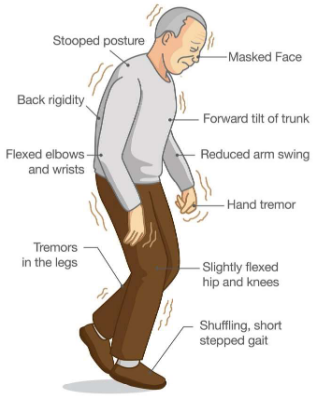


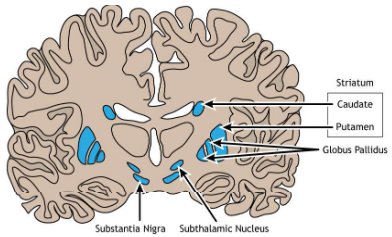
Are PH reflected by abnormal oscillations in patients with Parkinson's disease, like bradykinetic symptoms ?

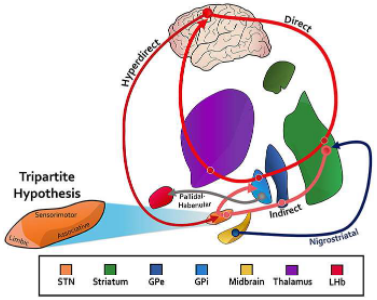
Are the basal ganglia involved in PH ?

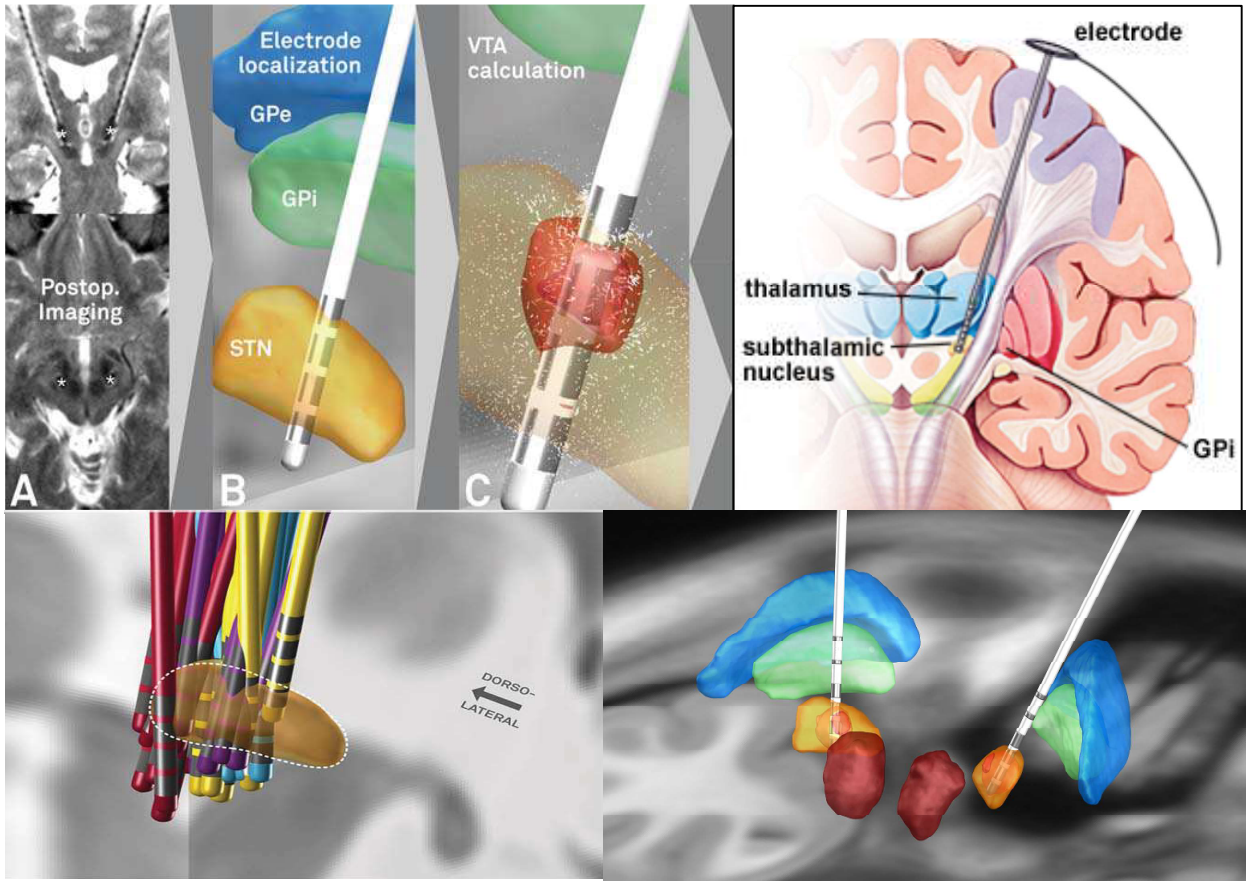


Parkinson’s disease / Deep brain stimulation

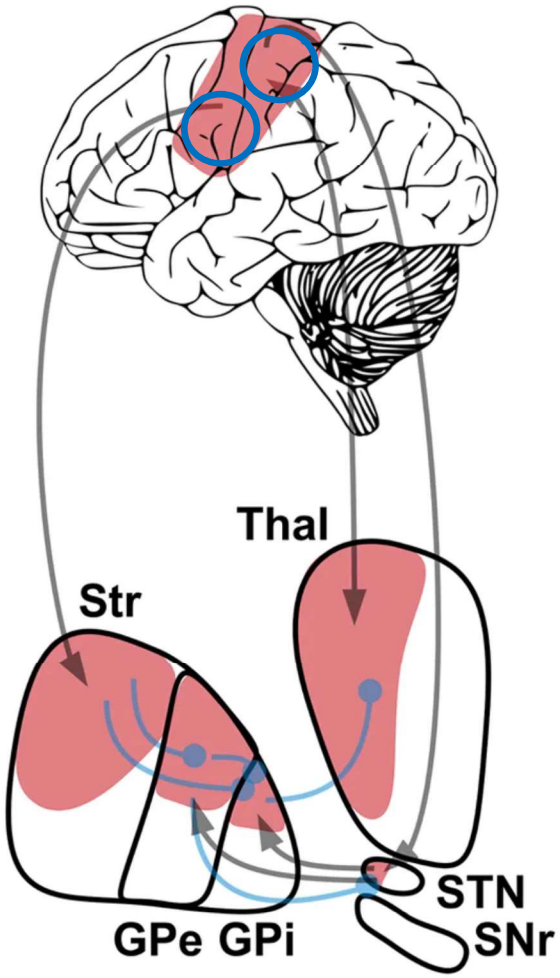


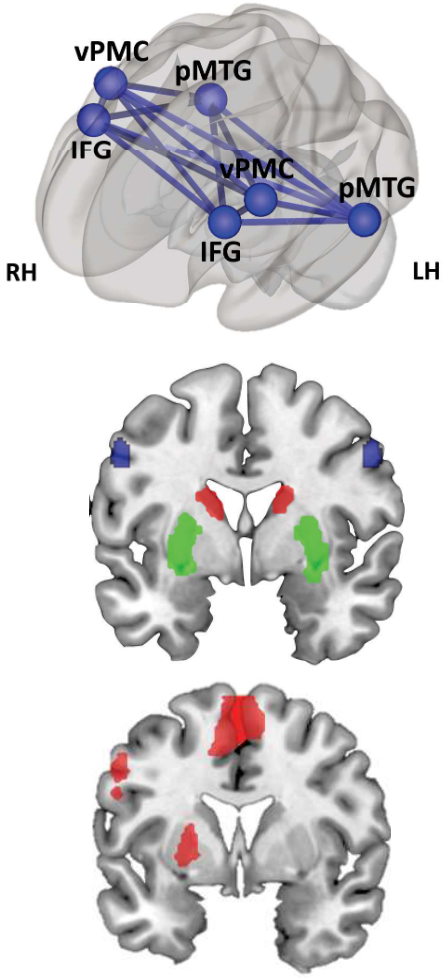




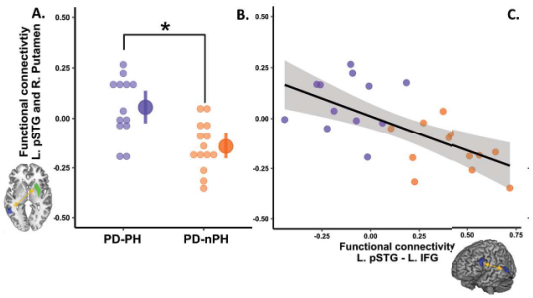


Presence hallucinations involve basal ganglia with dopamine depletion





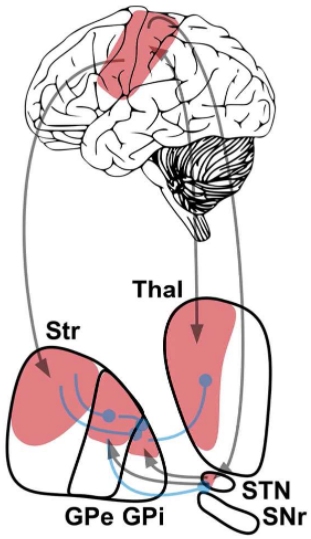
Involvement of basal ganglia (putamen) in presence hallucinations



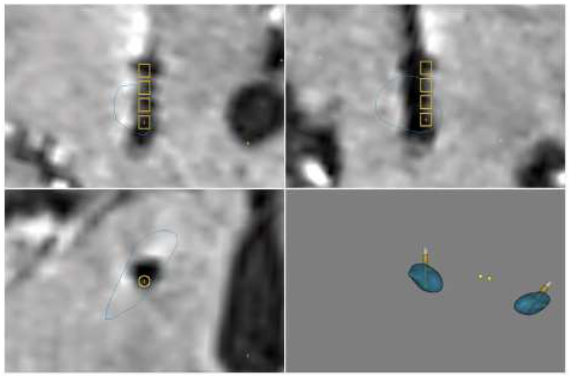
PD patients with PH vs. PD patients without PH have disrupted connectivity between striatum (putamen) and cortical hallucination PH-network

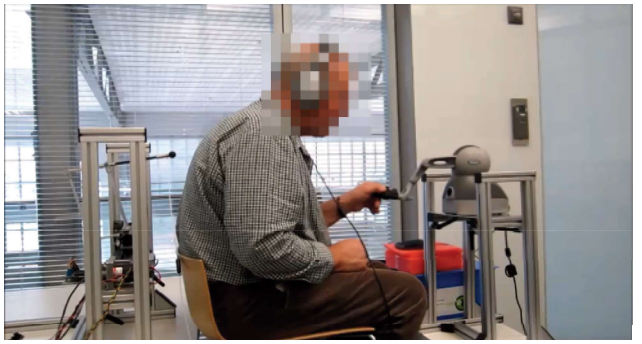
Ongoing project with EPFL & Rockefeller Neuroscience Institute

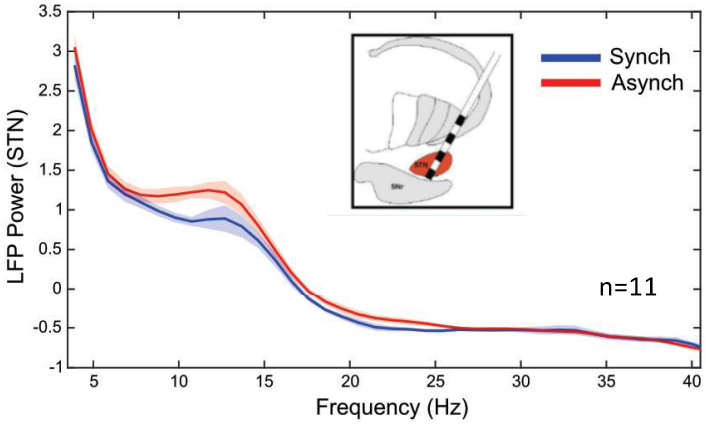
Presence hallucinations and oscillations in subthalamic nucleus



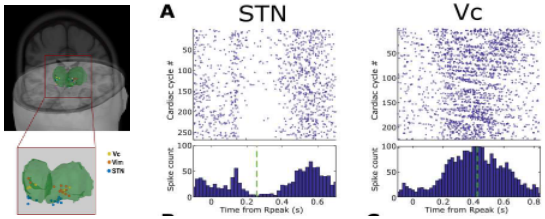
STN recordings
(LFP, single unit)







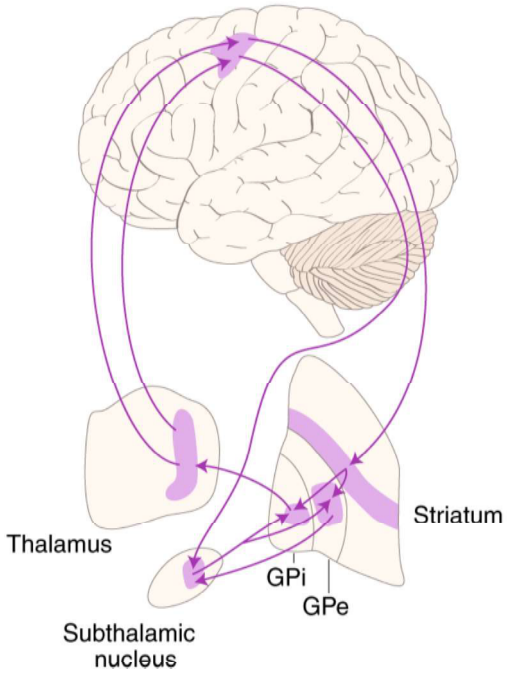
[De Falco et al., ongoing study]



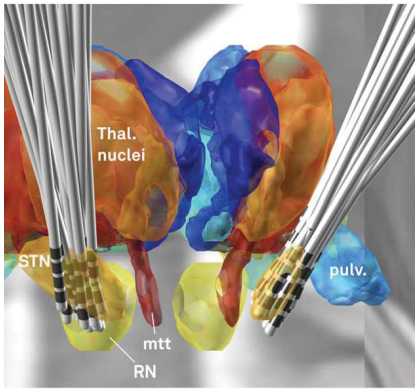
Pereira et al., **Nature Communications** 2021
Serino et al., **Nature Human Behavior** 2022
De Falco et al., **PNAS** 2024

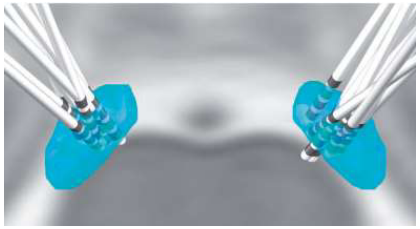
Deep brain stimulation & recordings

Beta oscillations & Motor neuroprosthetics

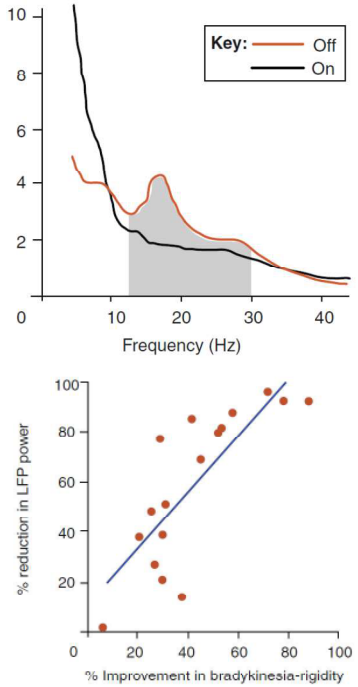


Targeting the STN

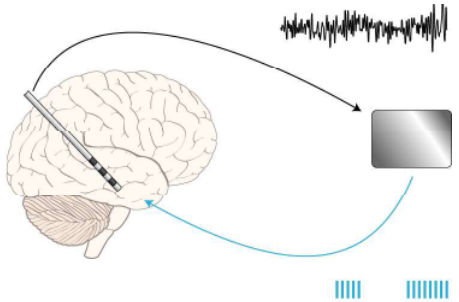




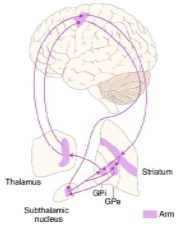
Beta oscillations

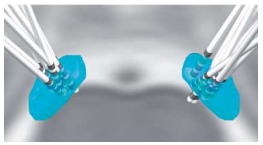


Closed-loop DBS



Horn et al., 2017; Jenkinson et al., 2011; Cagnan et al., 2019

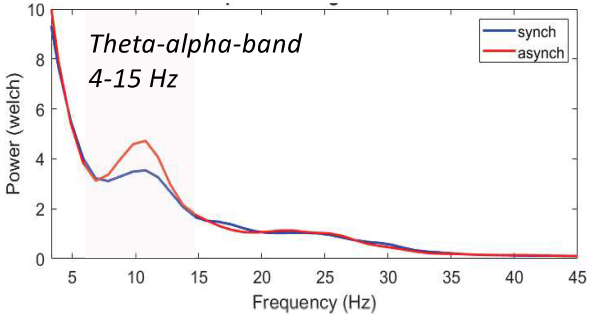


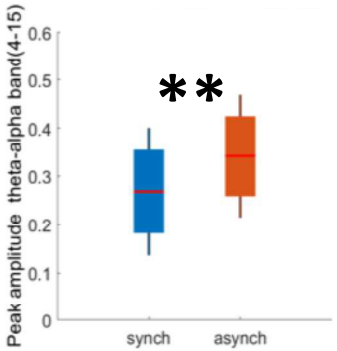


N = 15

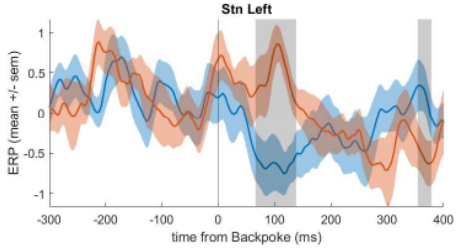
Theta-alpha oscillations in subthalamic nucleus reflect presence hallucinations

Alpha-theta oscillations
(STN: async > sync)

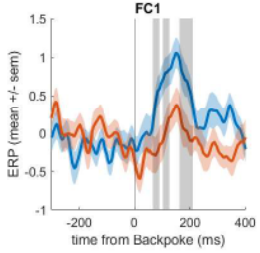




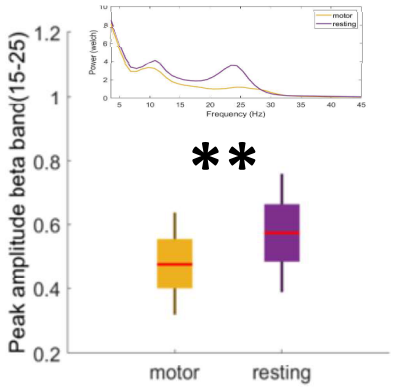
Robot-induced SEPs
(STN: asyn > sync)



Robot-induced SEPs
(EEG: asyn > sync)



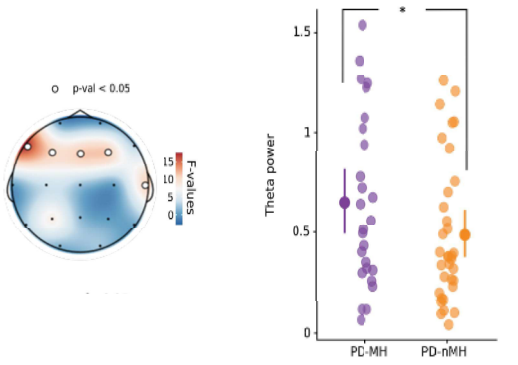
Beta suppression
(motor control)



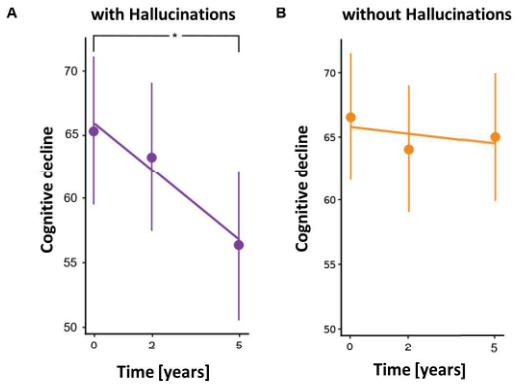
(De Falco et al.)

Enhanced theta-alpha (5-10 Hz) oscillations predict cognitive decline by 5 years (in PD patients with mild cognitive deficits)

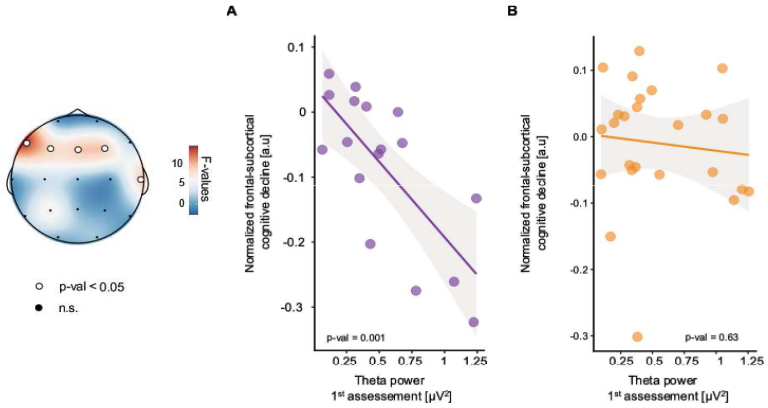
PD patients with PH: higher frontal theta power



PD patients with PH: stronger cognitive decline



Frontal theta power predicts the magnitude of cognitive decline by 5 years



Alpha-theta oscillations in STN/frontal cortex reflect hallucination-like state, linked to cognitive decline

Alpha-theta suppression by DBS (or non-invasive brain stimulation, tTIS, fUS) as neuroprosthetic therapy

N = 75

PD patients

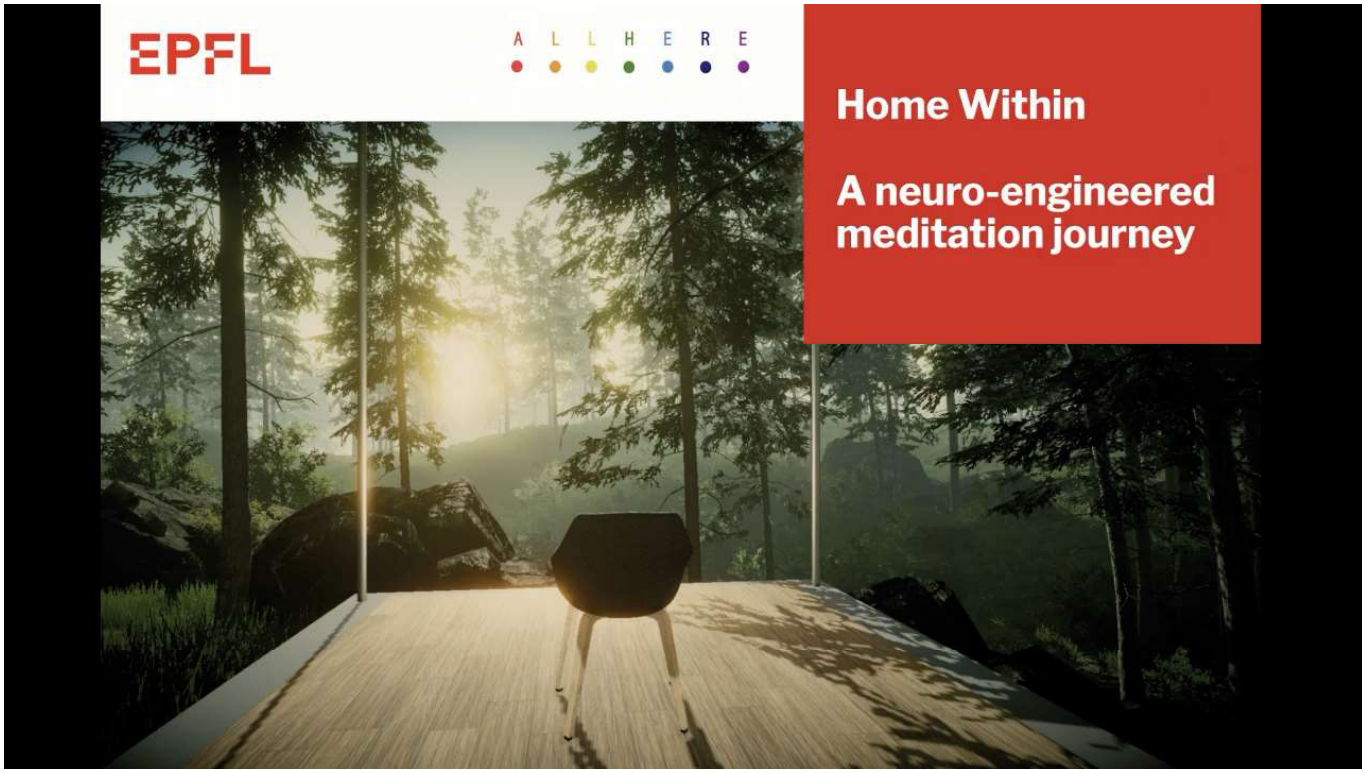
[Bernasconi, et al., **Nature Mental Health** 2023]

Engineering of complex conscious experiences (Meditation engineering)

Physical Lab

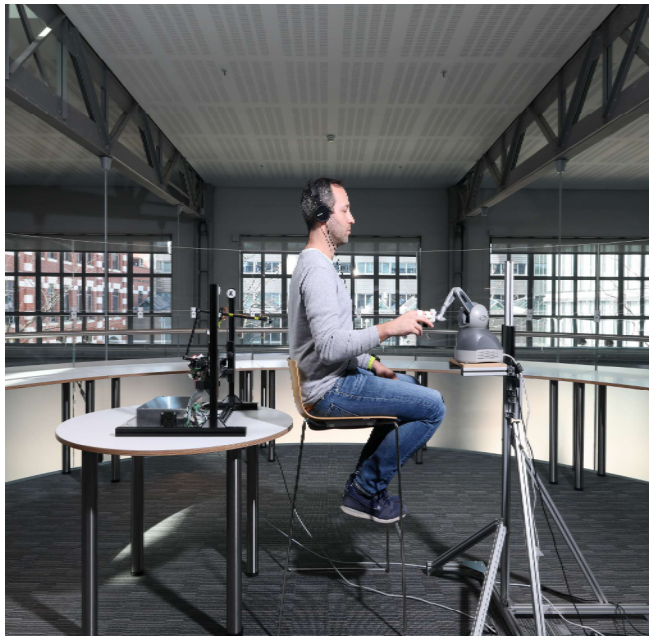
Virtual Lab

Virtual Forest



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.



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

Technodelics

We have a large ongoing project in translational neuroengineering and neuroscience for novel diagnostics and therapeutics for hallucinations and dementia in PD (STN recordings & DBS, real-time fMRI, high-density electrophysiology, robotics, and wearables).

Interested in translational neuroengineering or neuroscience project or in joining a technodelic startup on PD ?

Just send an email …

METAPHYSIKS

mindmaze

Open-loop DBS
Closed-loop DBS / Adaptive DBS

Closed-loop DBS

Motivated by shortcomings of open-loop DBS

Open-loop DBS has limitations

Current DBS is delivered in constant manner, without any real-time adjustments and thus not adapted to different needs depending on the current situation or patient state.

DBS needs **trained clinician**. It is still **time-consuming** to program and setup the optimal final open-loop DBS setting.

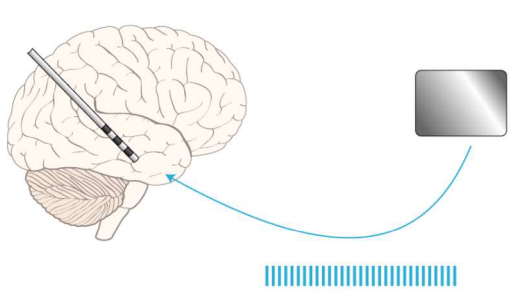
For some patients open-loop DBS does not lead to satisfying outcomes.

Continuous stimulation drains the battery, even when stimulation is not needed.

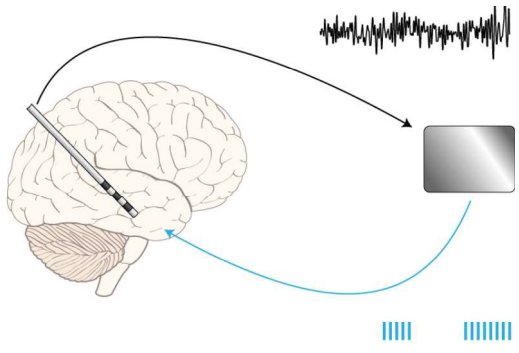
Continuous DBS may cause side effects (such as dyskinesias or dysarthria); closed-loop DBS may minimize these.

Closed-loop DBS may better preserve some basal ganglia function, as continuous stimulation may also lead to damage by chronic overstimulating.

Open-loop DBS (STN)



Closed-loop DBS (STN)



Cagnan et al., 2019

Closed-loop DBS

Different closed-loop DBS systems

Biomarkers for closed-loop DBS
Biomarkers indicate disease severity (i.e., bradykinesia) or side effects (i.e., dyskinesias) or track the response to the therapeutic intervention

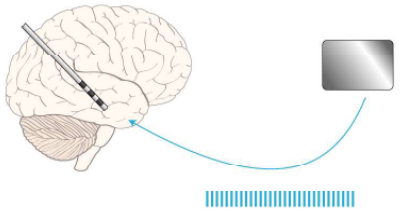
3 Closed-loop DBS systems
1-Beta oscillations (13-30 Hz) in STN (tremor, bradykinesia): when detected DBS is turned ON.

2-Gamma oscillations (50-75 Hz) in motor/premotor cortex (dyskinesias): when detected DBS is turned OFF.

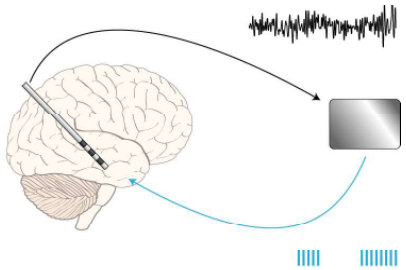
3-Peripheral wearable sensors to detect symptoms (tremor): when detected DBS is turned ON.

Closed-loop has increased over the last 10-15 years, but is still very far from being standard therapy and most current approaches are at the experimental-clinical stage.

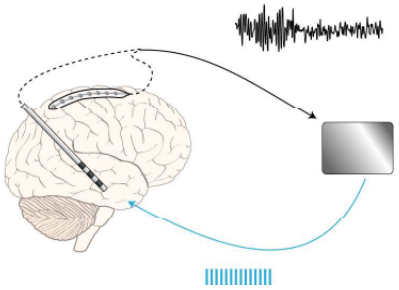
Open-loop DBS (STN)



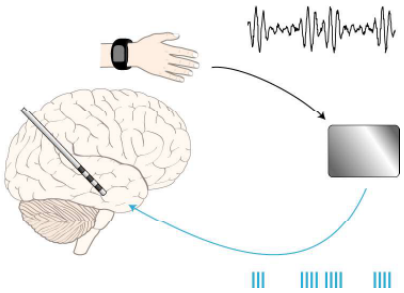
Closed-loop DBS (STN)



Closed-loop DBS (motor cortex & STN)



Closed-loop DBS (wearable sensor & STN)



Cagnan et al., 2019

Deep brain stimulation

Closed loop DBS tracks neural signals as biomarkers for PD symptoms and stimulates when symptom-related biomarkers are detected