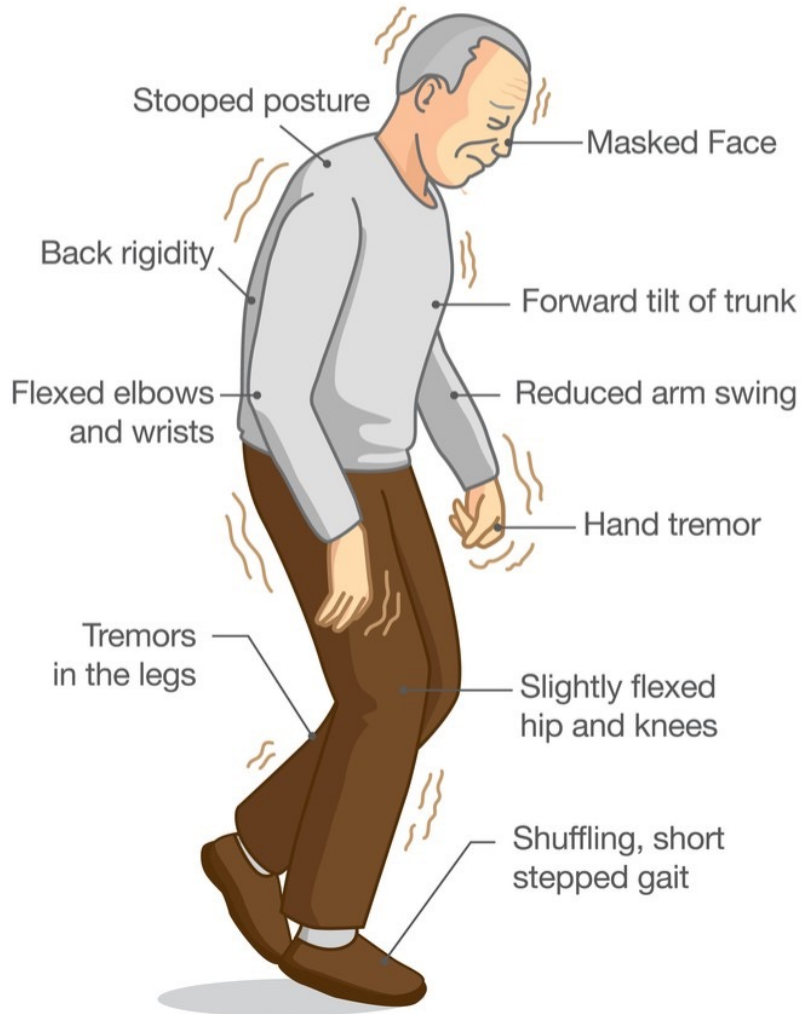
Neuro-X

Translational Neuroengineering

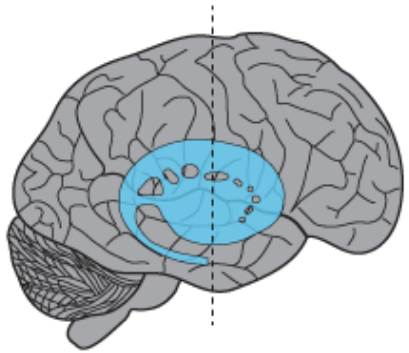
Parkinson’s disease II

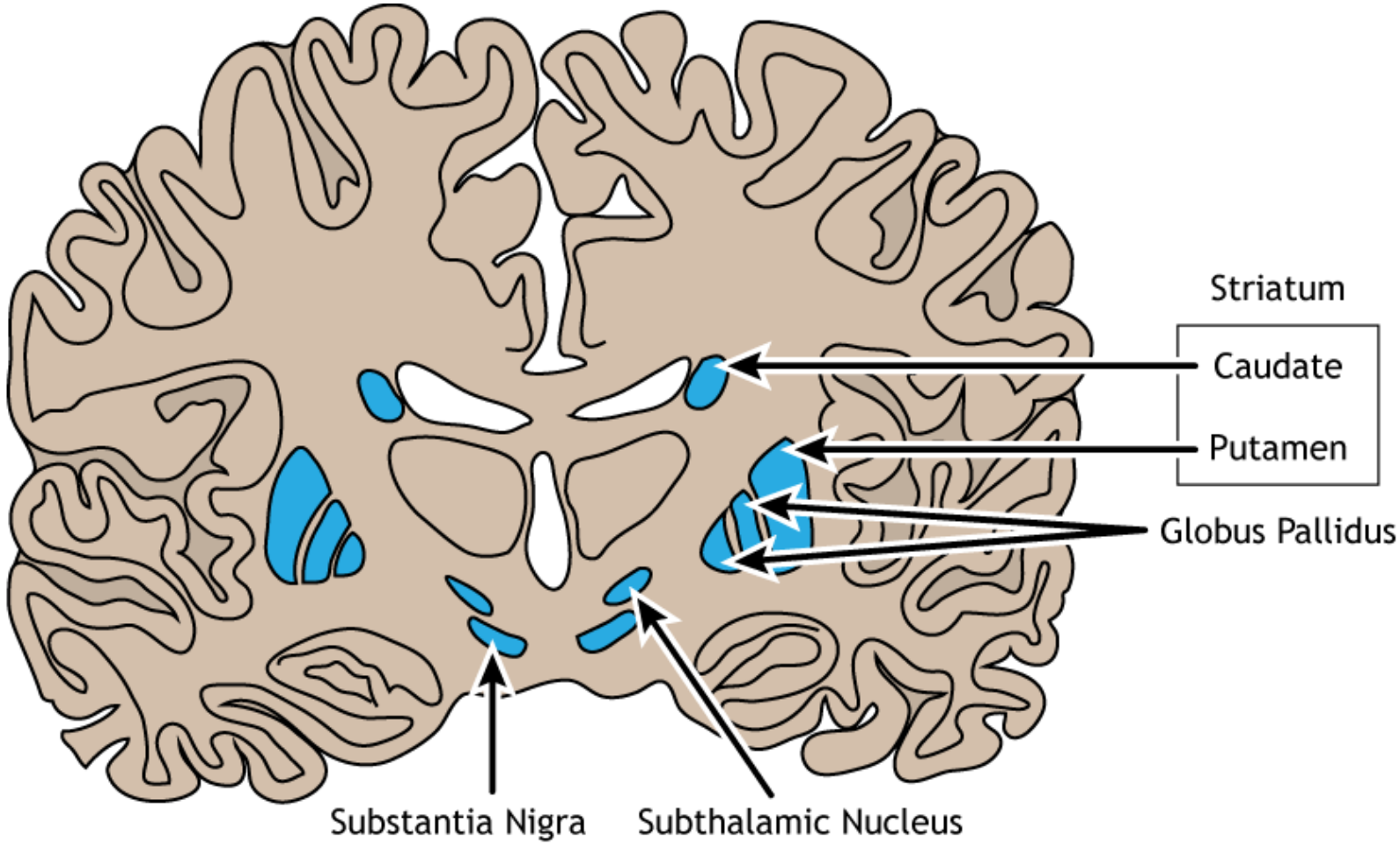
April 8, 2025

Olaf Blanke & Fosco Bernasconi


Stooped posture
Masked Face
Back rigidity
Forward tilt of trunk
Flexed elbows and wrists
Reduced arm swing
Hand tremor
Tremors in the legs
Slightly flexed hip and knees
Shuffling, short stepped gait

Basal ganglia

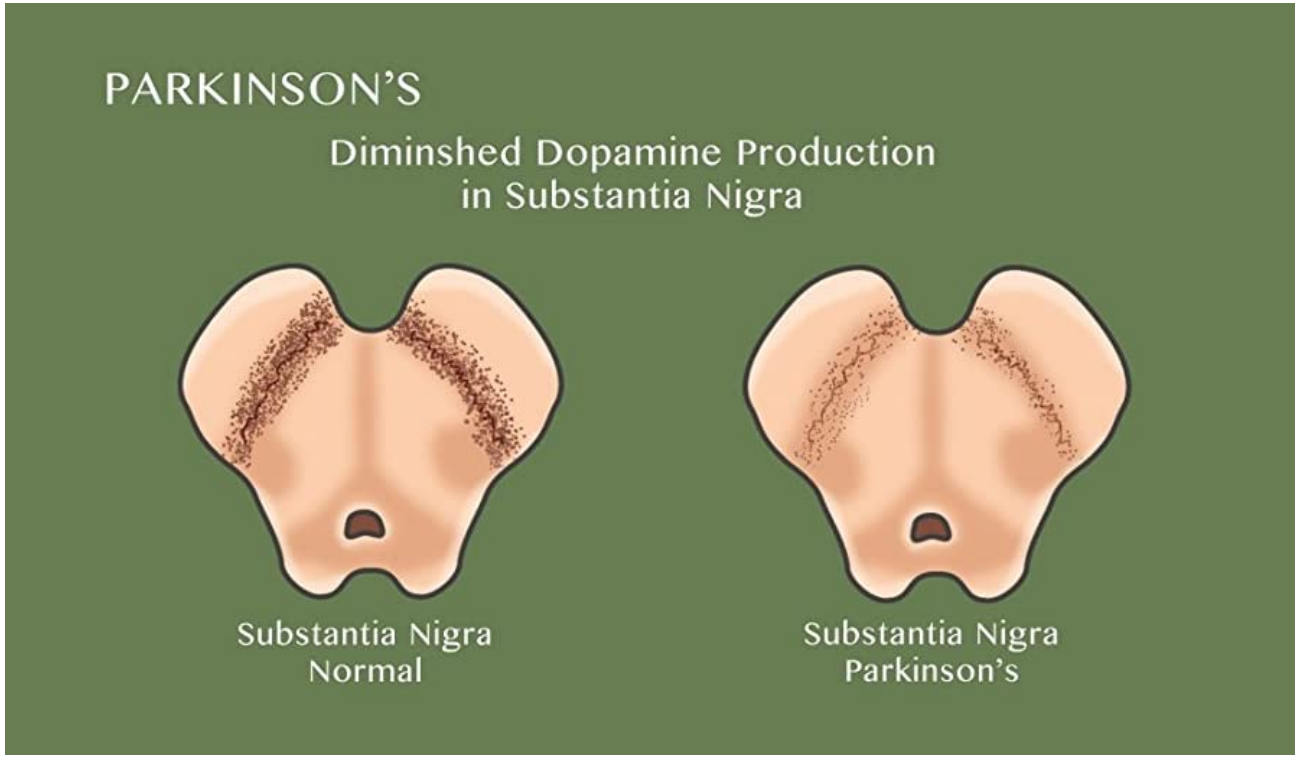


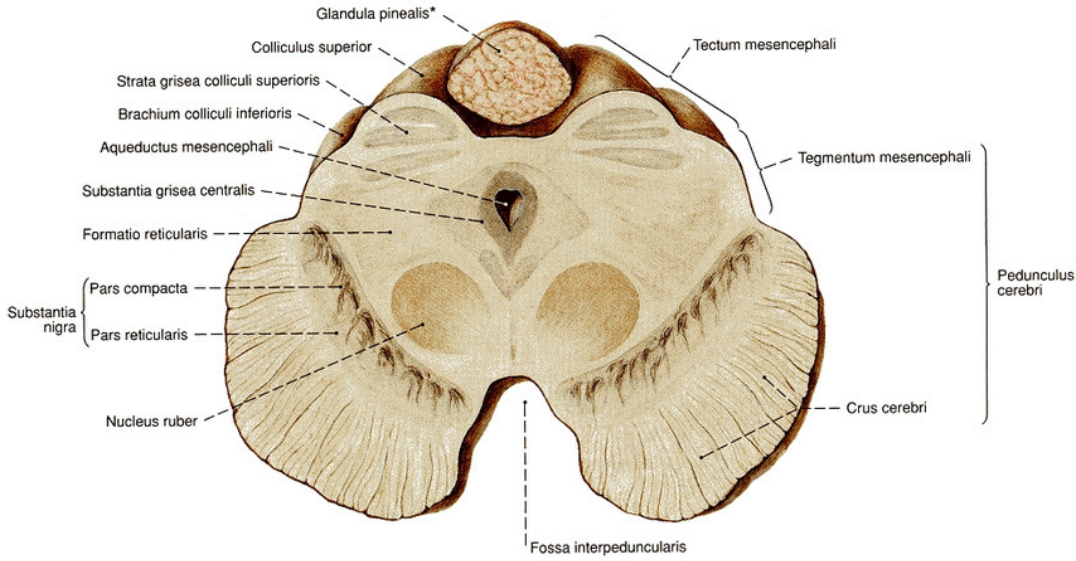


Coronal section/view

Parkinson's disease

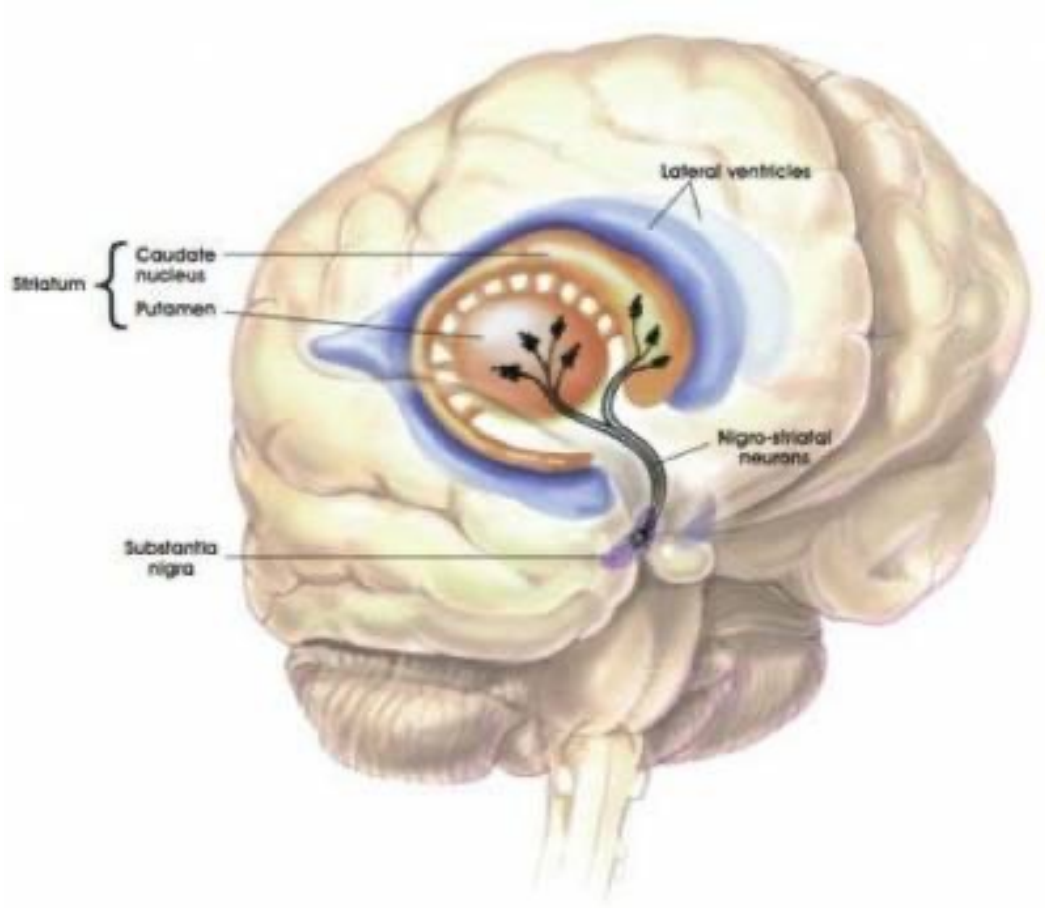
Cell loss in the substantia nigra pars compacta





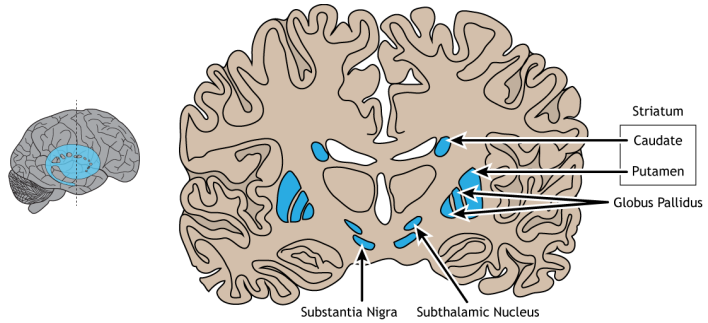
Loss of dopamine neurons affects the Pars compacta of the substantia nigra (not the Pars reticulata of the substantia nigra).

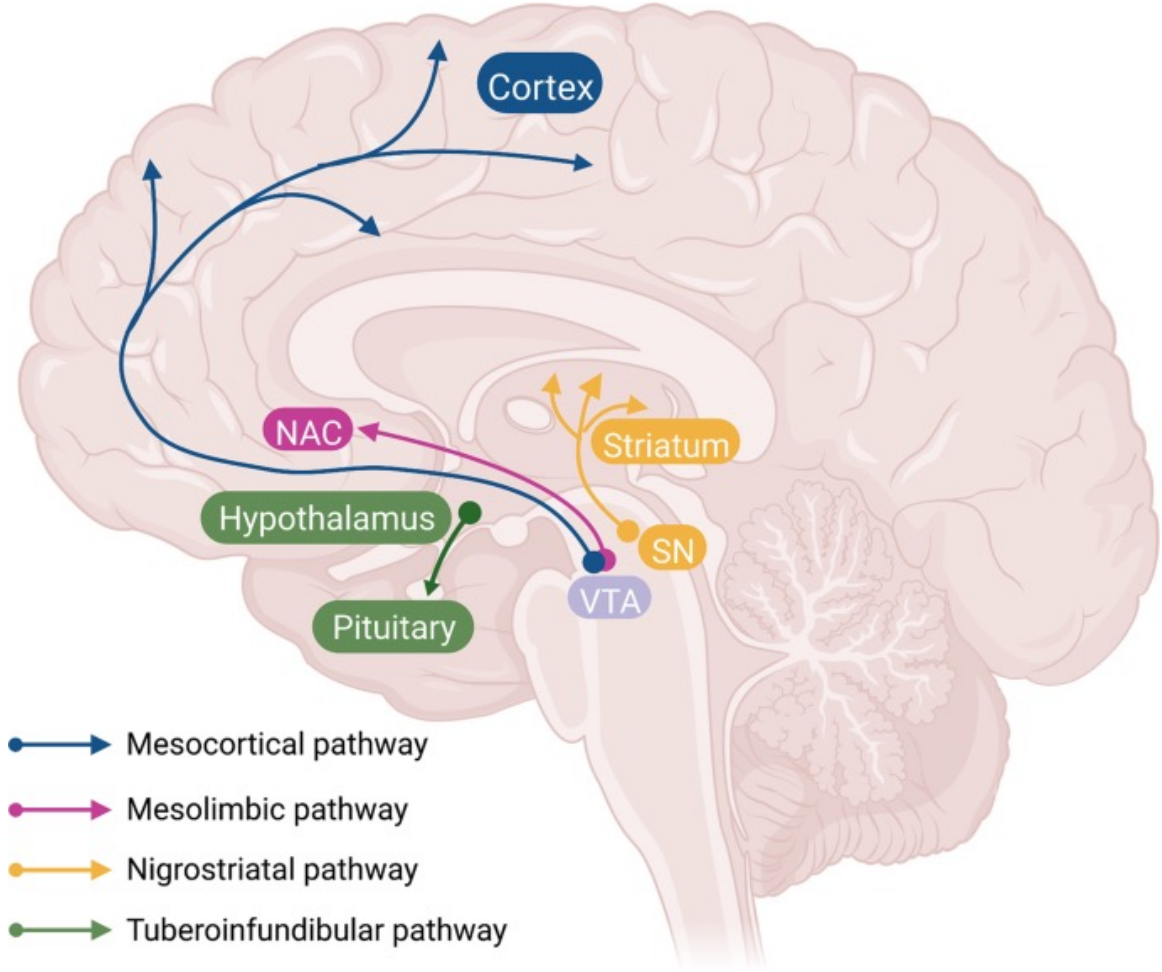
Degeneration of the nigro-striatal pathway



Dopamine & Parkinson's disease

Dopamine pathway in PD





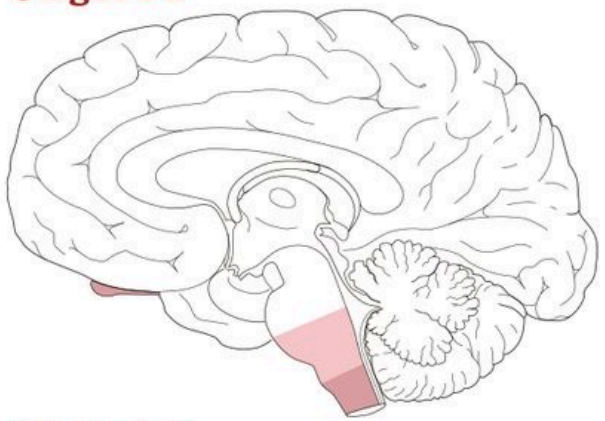
The nigrostriatal pathway between substantia nigra and striatum is affected in PD and is the key neuropathological hallmark of PD.

But there are several dopamine pathways.

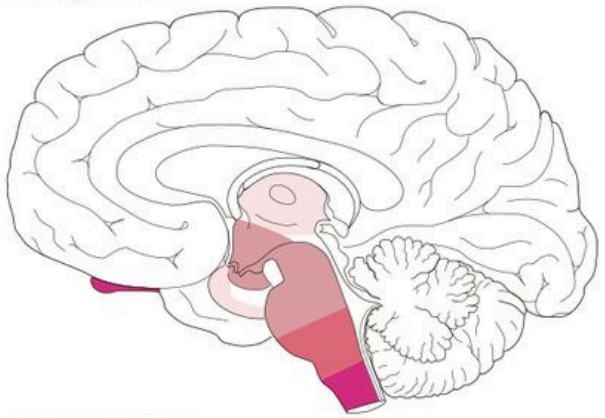
Parkinson's disease

Braak stages
(based on presence of Lewy bodies across the brain)

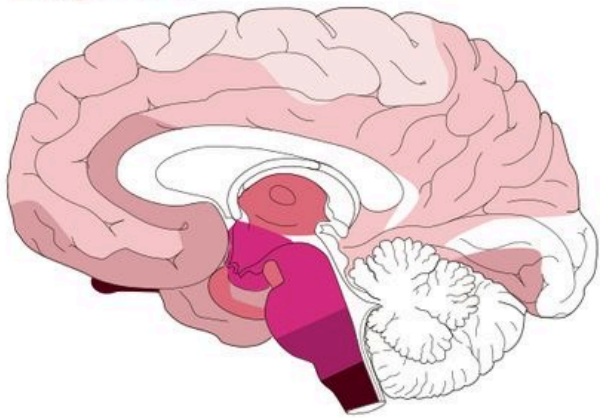
Stages 1-2



Stages 3-4

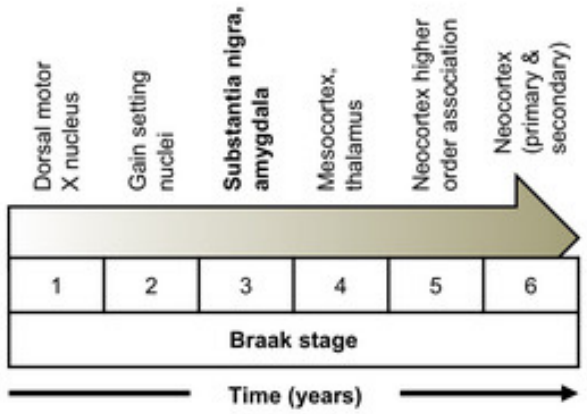


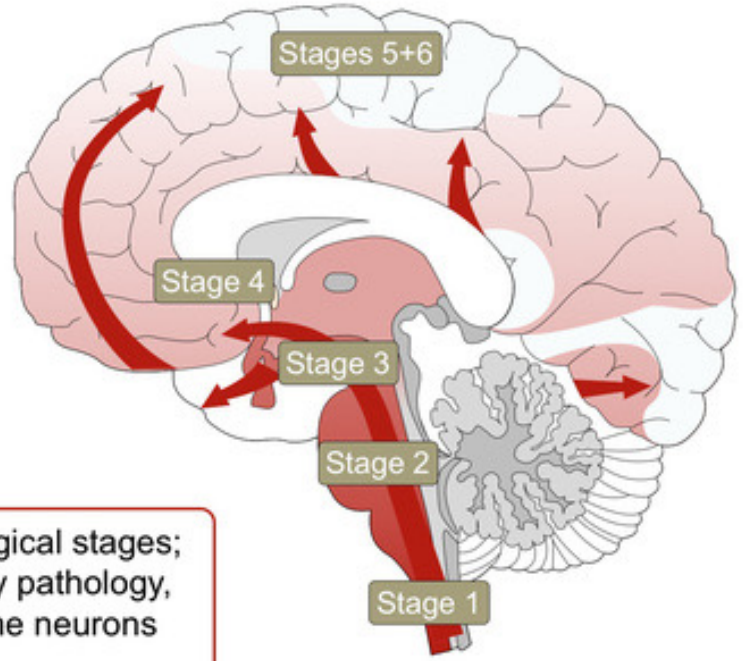
Stages 5-6



Braak staging of Parkinson's disease

The ascending pathological process within the PD brain[1]



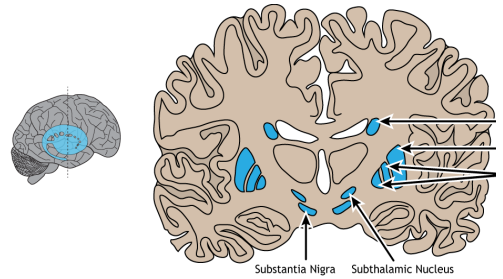


PD is hypothesised to progress in six neuropathological stages; all of the affected neurons eventually develop Lewy pathology, but, despite the presence of inclusion bodies, some neurons survive for a long period of time[1]

1. Braak et al. Cell Tissue Res 2004;318(1):121–134

Lundbeck Institute Campus

Two primary di-synaptic pathways from the cortex to basal ganglia output structures (Pgi/SNpr) and from there via thalamus back to cortex



Cerebral Cortex

Frontal Cortex

Caudate
Putamen

Thalamus

STN

GPi/SNpr

Broad excitation (via STN) and focussed inhibition (via striatum) of GPi/SNpr

Brainstem, Spinal cord

Direct pathway (from cortex to striatum to GPi)

- input from all cortical regions
- slow
- inhibitory
- focussed

Because GPi/SNr output is inhibitory → this leads to broad/surround inhibition of unintended movements and focussed dis-inhibition (facilitation) of intended movement
(via thalamus and brainstem)

Hyperdirect pathway (from frontal cortex to STN to GPi)

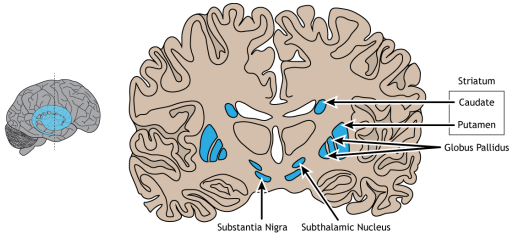
- only frontal input
- fast
- excitatory
- broad/divergent

inhibition

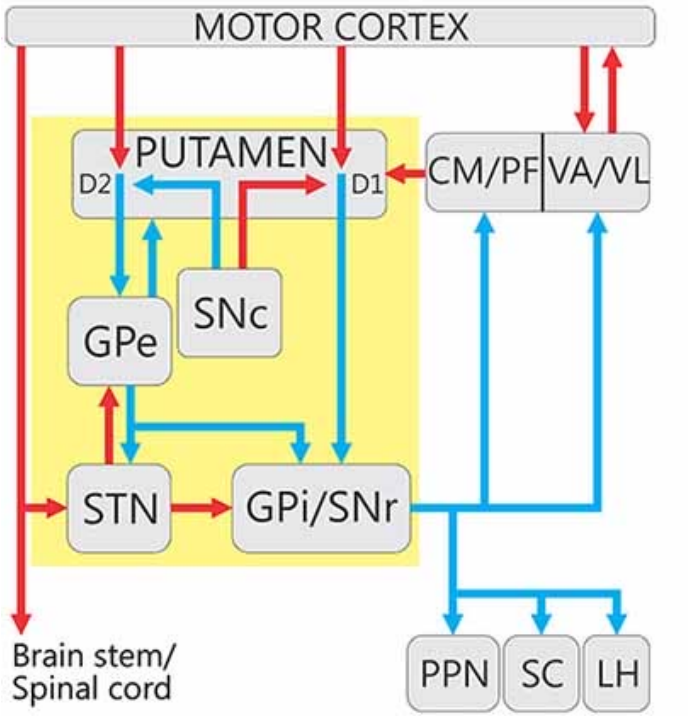
excitation

Basal ganglia

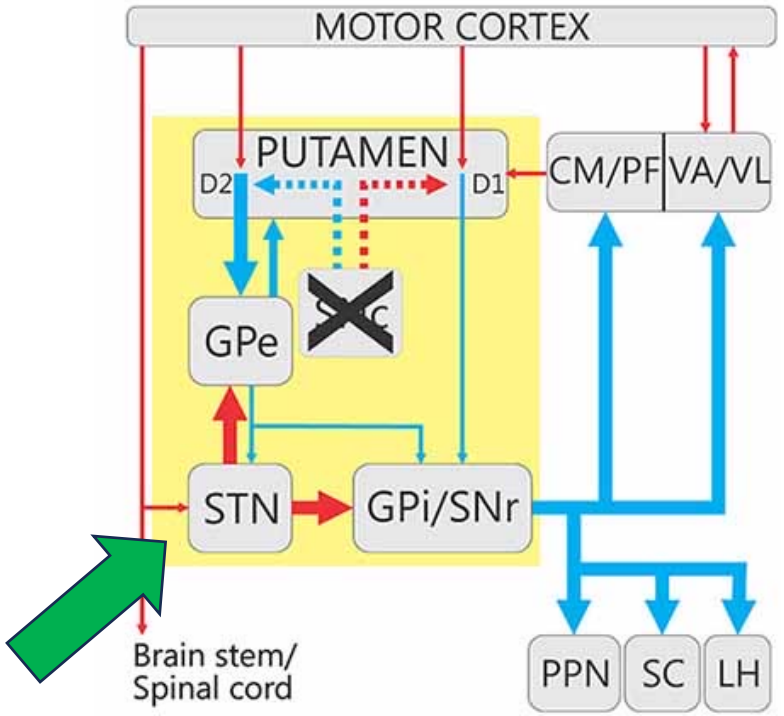
Loss of nigrostriatal dopamine leads to circuit changes beyond SN pars compacta and Putamen



Normal



Parkinson's

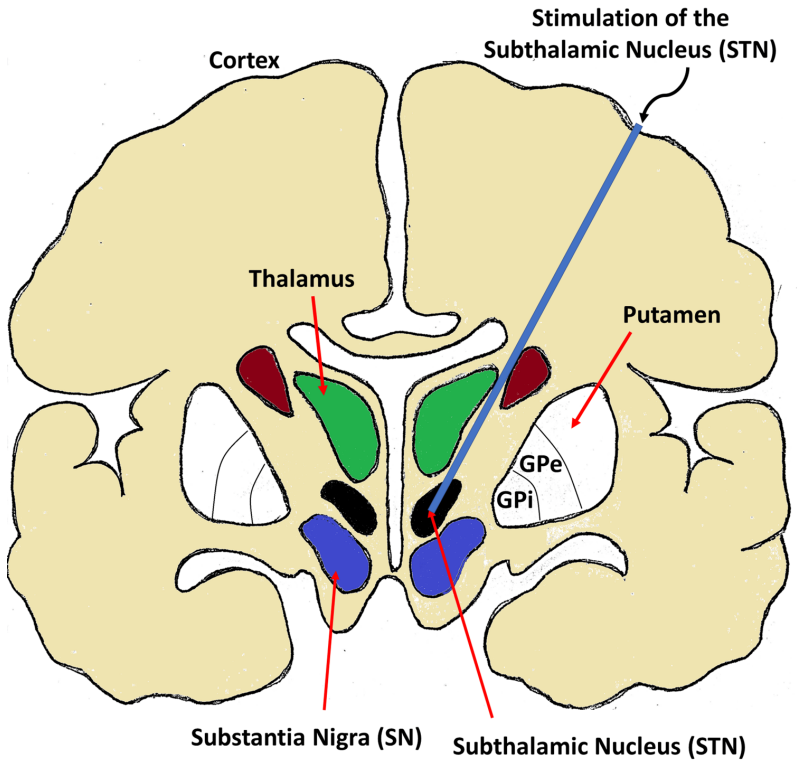


Deep brain stimulation also improves Parkinsonian motor symptoms

excitatory

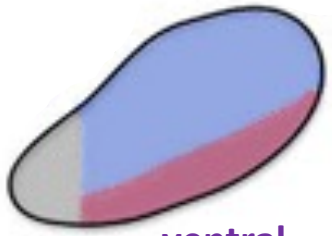
inhibitory

Subthalamic nucleus (STN) as the main target for deep brain stimulation (DBS) for Parkinson's



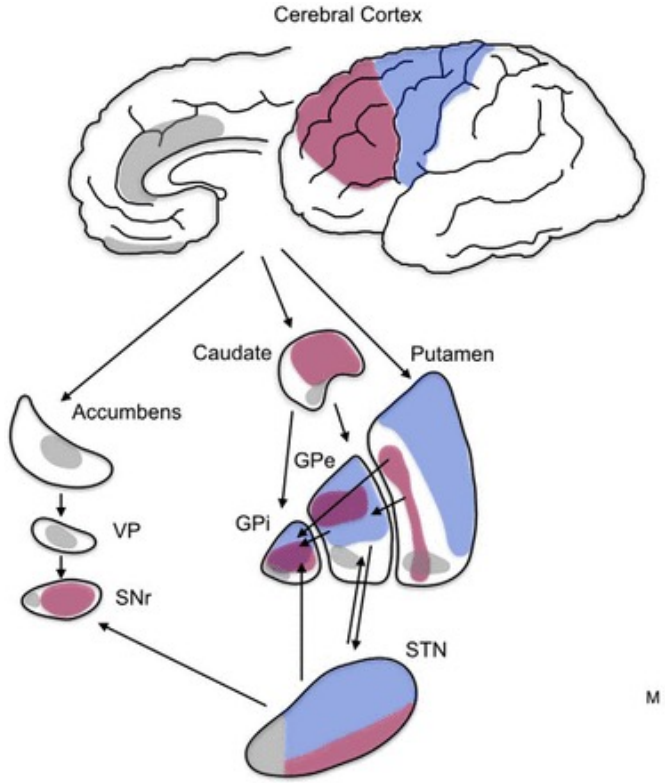
Key structure for deep brain stimulation (DBS) in PD

dorsal-lateral
(sensorimotor part)



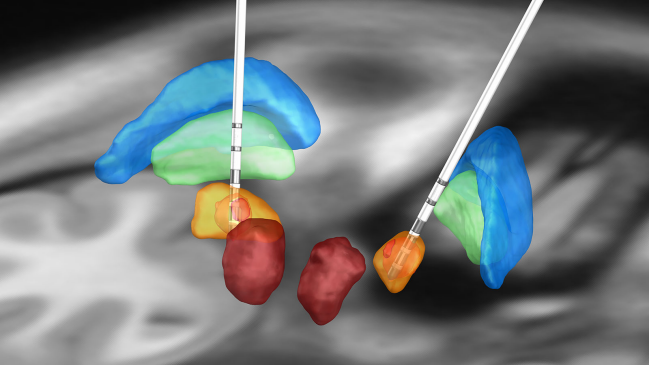
rostral
(limbic)

ventral
(associative part)



dorsal-lateral part of STN is targeted for DBS

Hamani et al., 2017



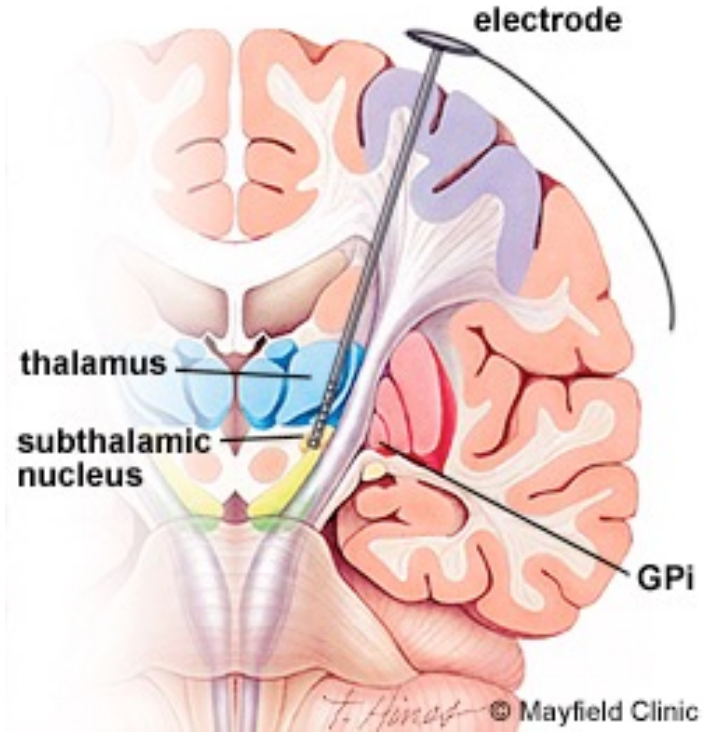
Neurosurgery and Parkinson's disease

Ablative surgery (chronic surgical lesion) (not covered)

Transplantation (not covered)

Focussed Ultrasound (reversible and chronic lesions) (not covered)

Deep brain stimulation



Deep brain stimulation (DBS)

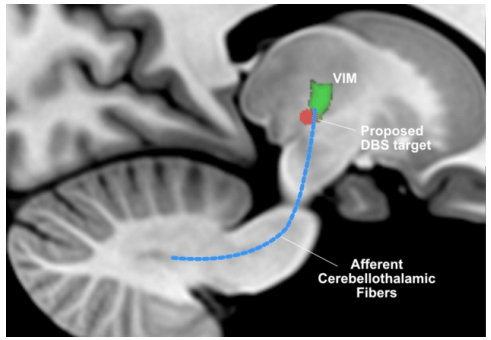
DBS has many medical indications
Parkinson's disease (over 200'000 patients have received DBS, worldwide)
Essential tremor (thalamic DBS: Vim)
Dystonia (DBS of STN)
Obsessive compulsive disorder (DBS of anterior limb of internal capsule)
Pain (DBS of thalamus or M1)
Epilepsy (DBS of anterior thalamic nucleus, centromedian thalamic nucleus)
Depression (DBS of subgenual cingulate cortex)
(memory deficits) (DBS of fornix or in temporal cortex)

DBS advantages are …
…high efficacy
…minimally invasive neurosurgery
…low incidence of severe disability adverse side effects

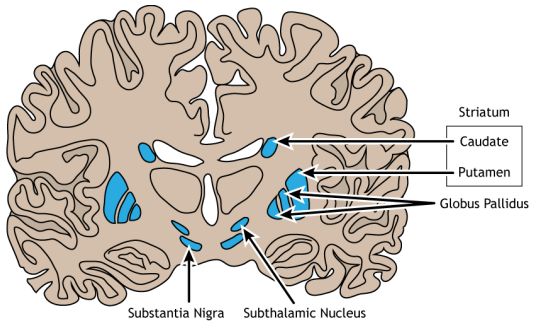
DBS neurotechnology was developed …
- following surgical approaches and lesions of the basal ganglia in a range of different diseases (mostly psychiatric diseases)
- Advanced understanding in basic animal neuroscience
- some adverse side effects of dopamine replacement therapy (after several years of pharmacotherapy, like dyskinesias, ON-OFF fluctuations) could not be treated otherwise (= urgent clinical need despite dopamine therapy)
- Technological advances in cardiac pacemakers

Deep brain stimulation (DBS)

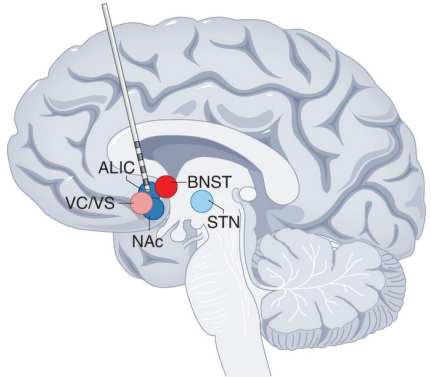
Essential tremor
Ventral intermediate thalamic nucleus (Vim)



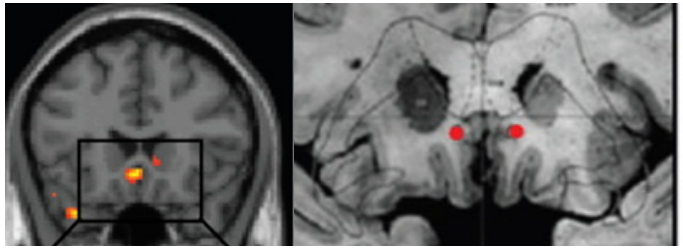
Dystonia
GPi, STN



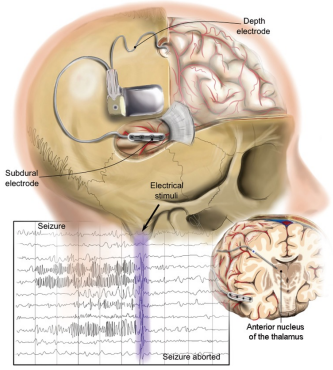
Obsessive compulsive disorder
Anterior limb of internal capsule



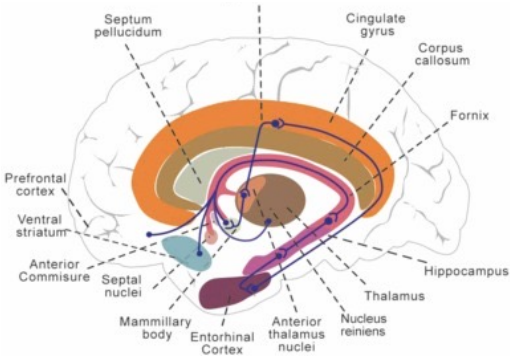
Depression
Subgenual cingulate cortex



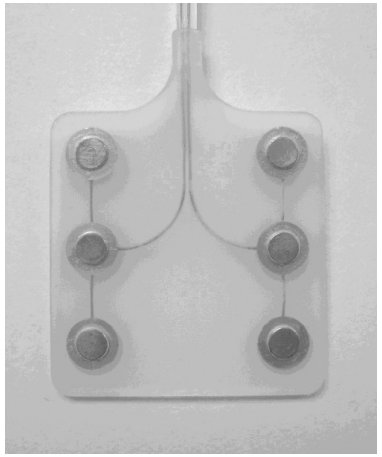
Epilepsy
Anterior thalamic nucleus,
Centromedian thalamic nucleus,
Responsive brain stimulation

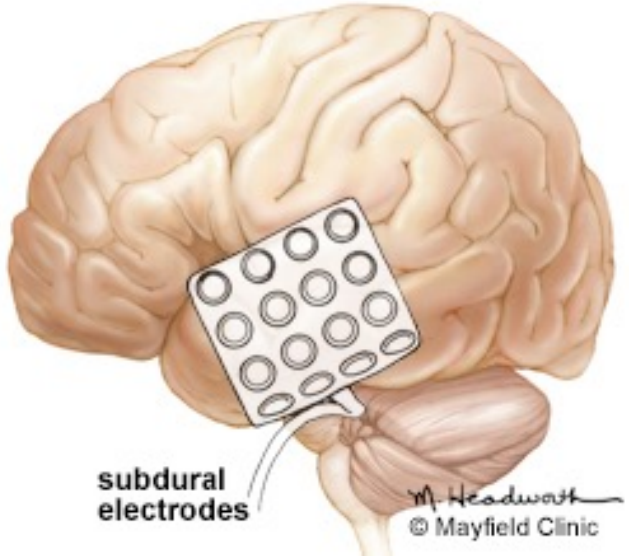


Amnesia/Memory
Fornix or in temporal cortex



Electroceuticals





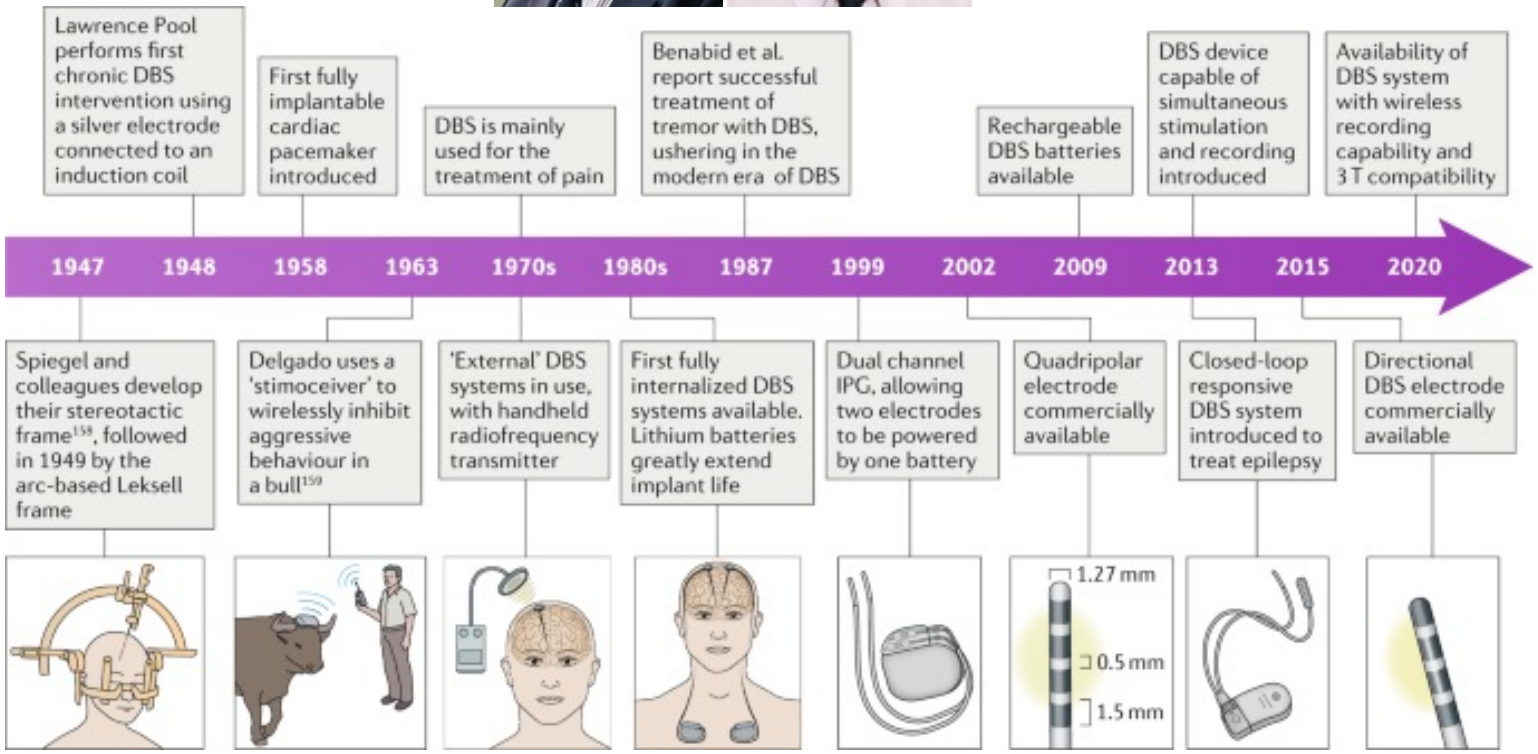
Pharmaceuticals
Digiceuticals

Parkinson’s disease & DBS

Deep brain stimulation

History - Medical research

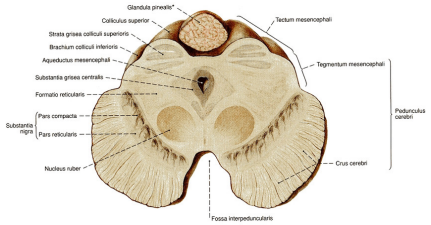
Modern era started in 1987 in Grenoble
Alim-Louis Benabid (neurosurgeon) & Pierre Pollak (neurologist)



1950s Cardiac Pacemaker

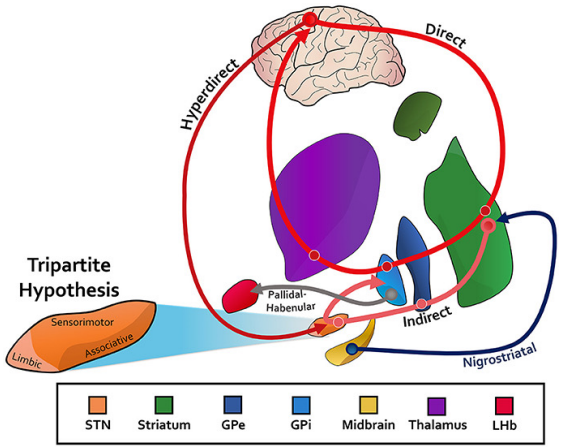
Modern-current system since 2002

DBS + Recording, adaptive DBS, since 2013



Deep brain stimulation

History – Animal preclinical research

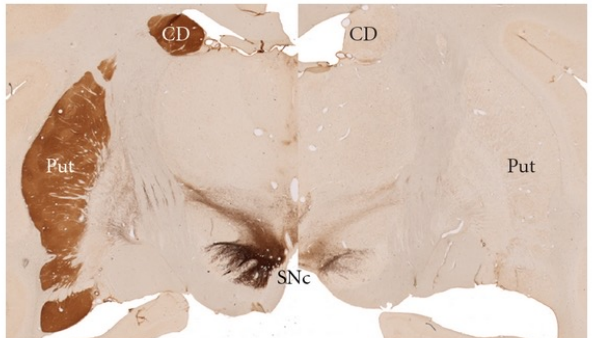


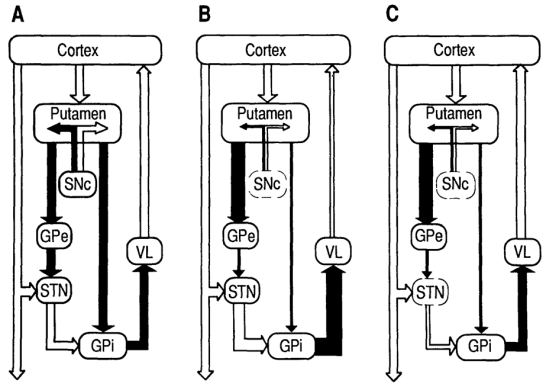
Main animal model of PD described in non-human primates: MPTP (specific neurotoxin) causes selective loss of dopaminergic neurons in SNpc (Burns et al., 1983; Langston et al., 1984).

In 1980s and 1990s indirect and direct pathways were discovered.

Bergman, Wichmann, Delong (1990) discovered that STN lesion (surgical lesion) and later that DBS of STN could reverse/treat Parkinsonism induced by MPTP

Together with the human work this led to DBS as carried out still today.





Hagai Bergman

Malon Delong

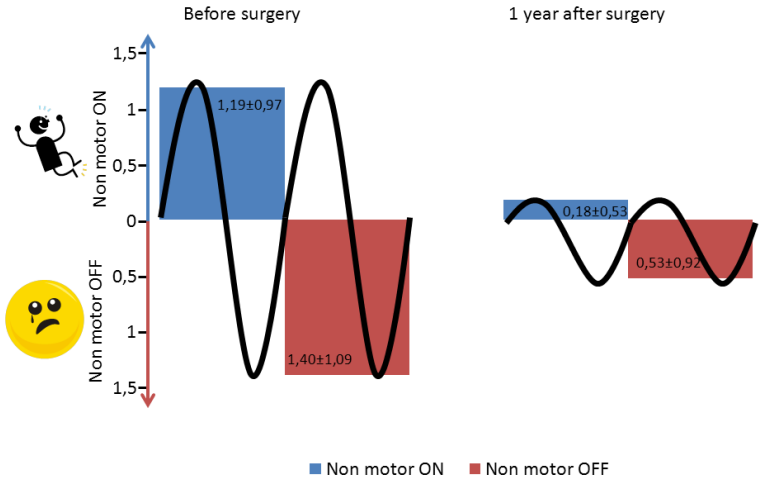
Deep brain stimulation

Origins

Levodopa-induced dyskinesias

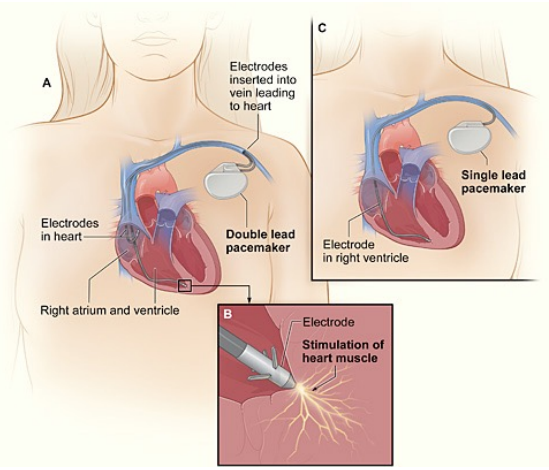
https://youtu.be/CFhyigIHYKw

Levodopa-induced dyskinesias often disappear with DBS (also because levodopa dose is decreased)



(Lhommée et al., 2012)

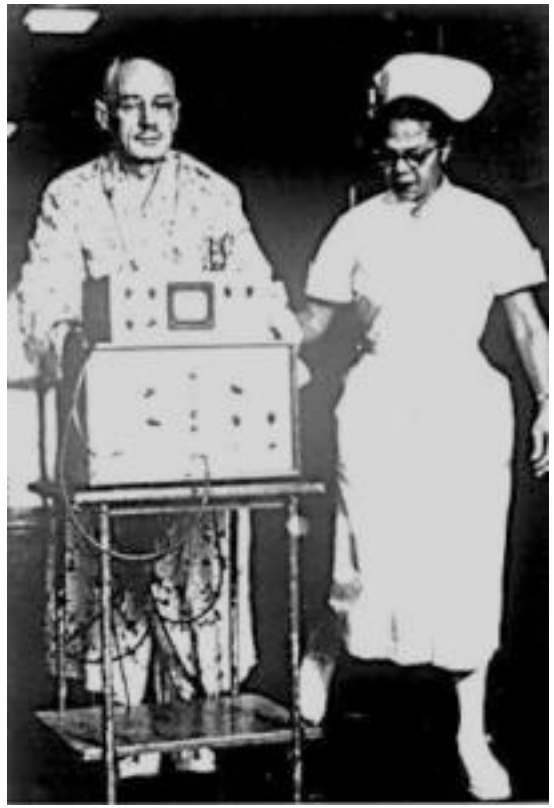
Advances in cardiac pacemaker technology



https://www.youtube.com/watch?v=hYJ9XOZA6a0

Cardiac Pacemaker

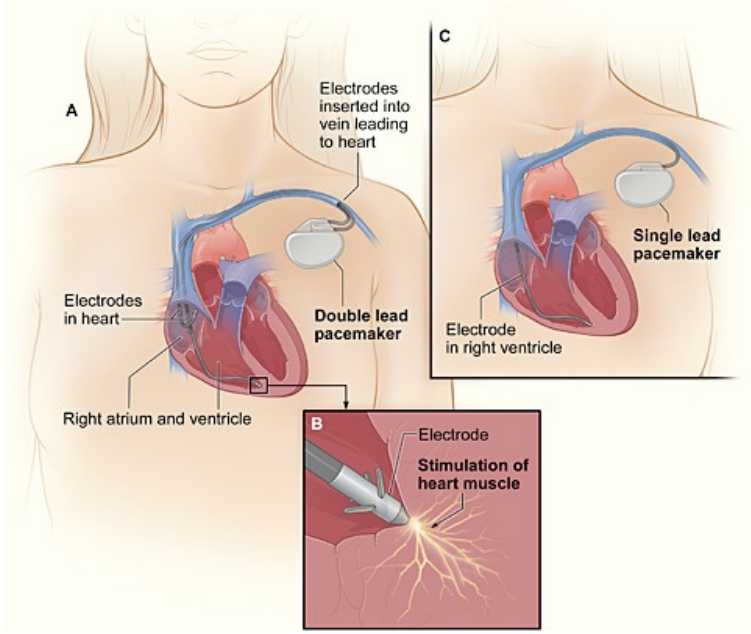
1952



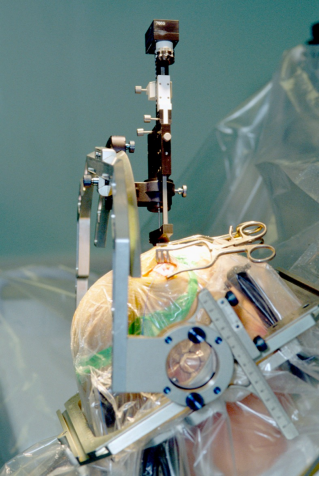
- External pacemaker (1952)
- stimulated the heart through the chest wall
- The electrodes were 5 cm diameter metal discs placed on the right and left sides of the chest (held by a rubber strap and making contact via a conductive electrode gel)
- This pacemaker revolutionized the concept of resuscitation of heart patients
- Stimulation of an adult required approximately 100 volt (very painful and required sedation, local skin burns).
- 1956: internal stimulation electrodes (myocardial wires placed during surgery)

(image: External “pacemaker” with cart)

Today



→ now over 5 million patients worldwide (about 600’000 new implants each year)



Deep brain stimulation

overview

Electrodes & Electrode configurations

Electrical pulse generator

Stimulation parameters

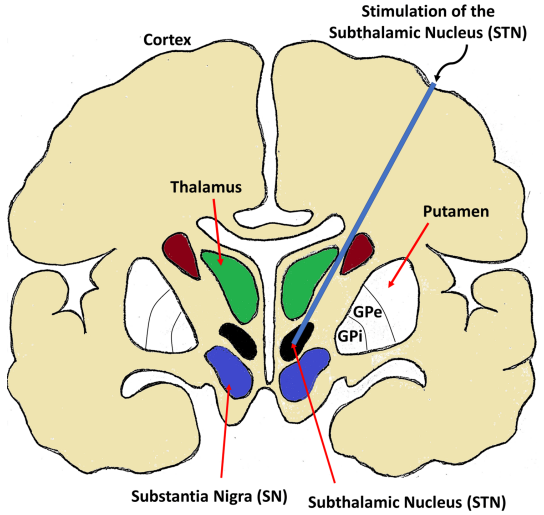
DBS of subthalamic nucleus (STN)

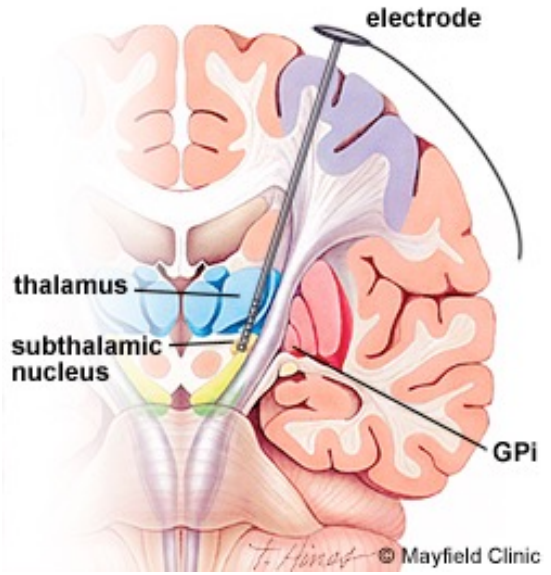
DBS target visualization in STN

STN implantation procedure

STN sweet spot determination

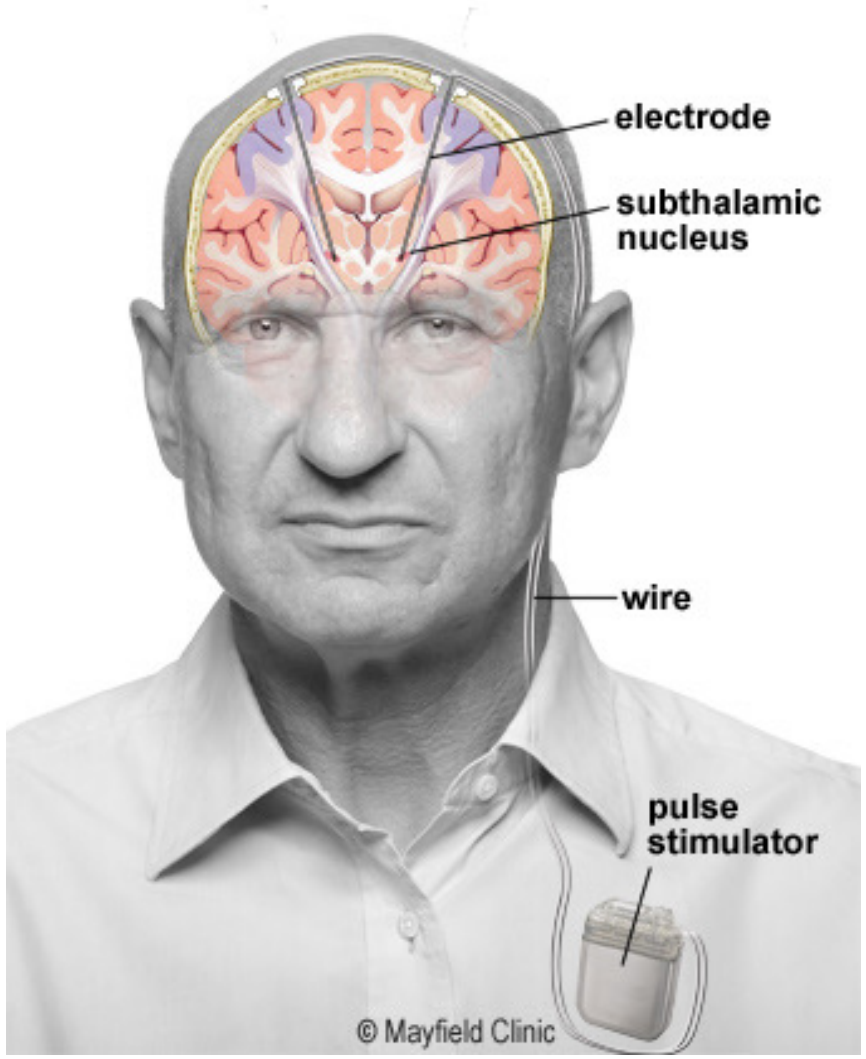
Volume of tissue activated (VTA)





Deep brain stimulation

3 main components of the DBS system

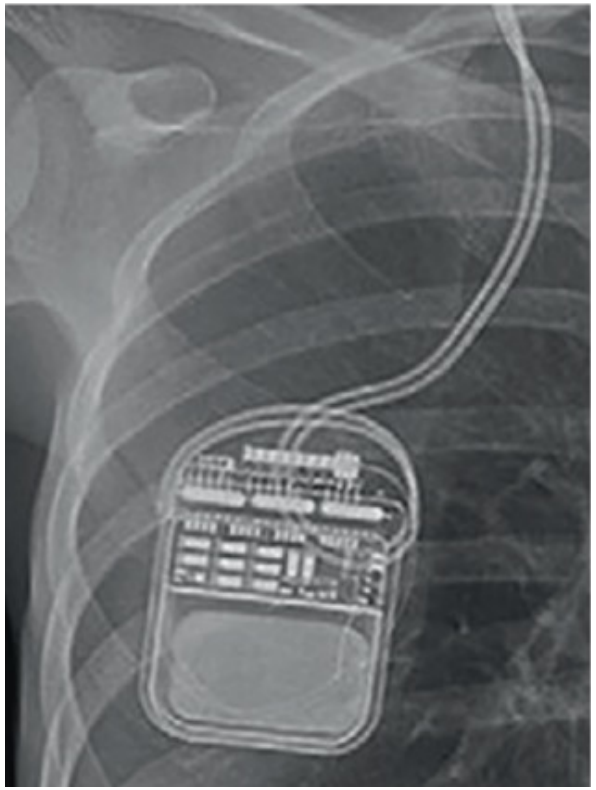


Electrode with contacts in STN (or GPi, not much covered in class)

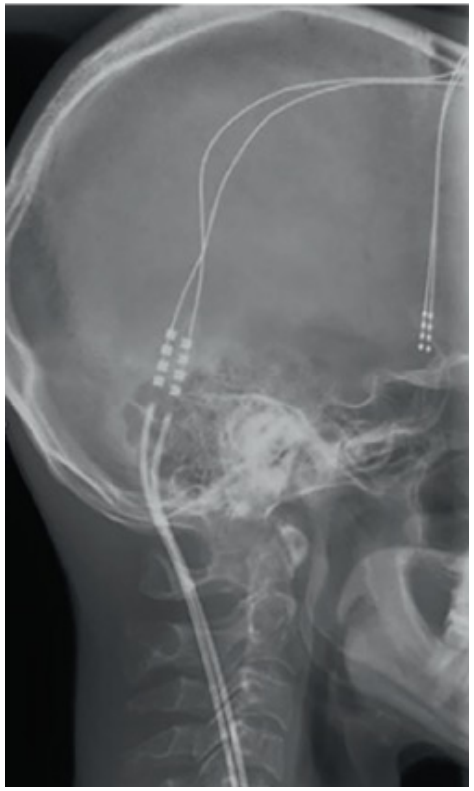
Pulse generator (implanted under the skin, chest area)

Wire/cables (connecting the electrode with the pulse generator)

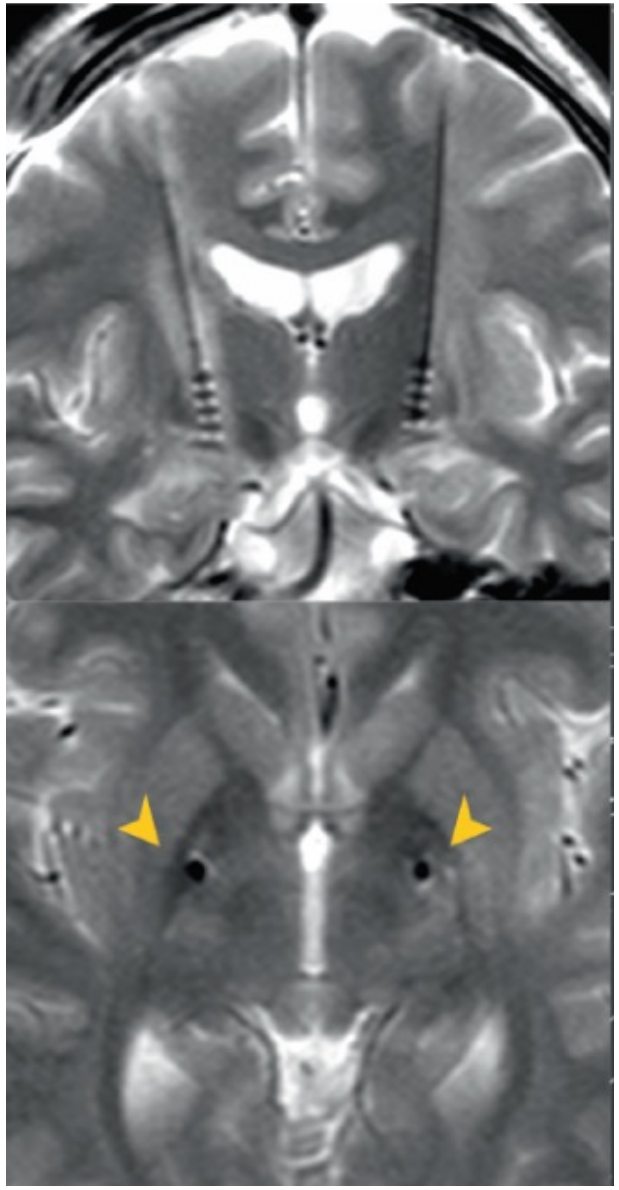
Chest X-ray (pulse generator, IPG)



Neck/head X-ray (electrodes, wire)

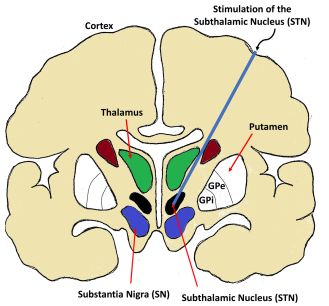


MRI (electrode contacts)



Deep brain stimulation

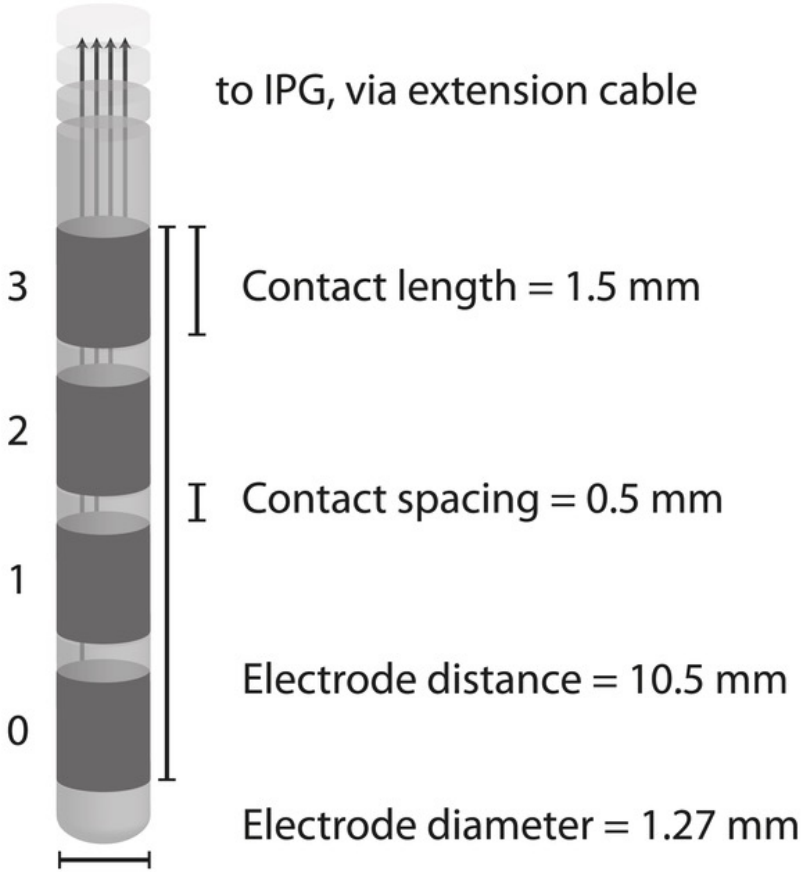
Electrodes



Characteristics of standard electrodes

-Platinum-iridium wires
-Nickel alloy connectors
-Polyurethane sheath

-Quadripolar electrode (4 stimulating electrode contacts at the tip of the probe)
-Probe has 1.27 mm diameter
-Cylindrical electrodes: 1.5 mm in length
-Electrodes are spaced either 0.5 or 1.5 mm



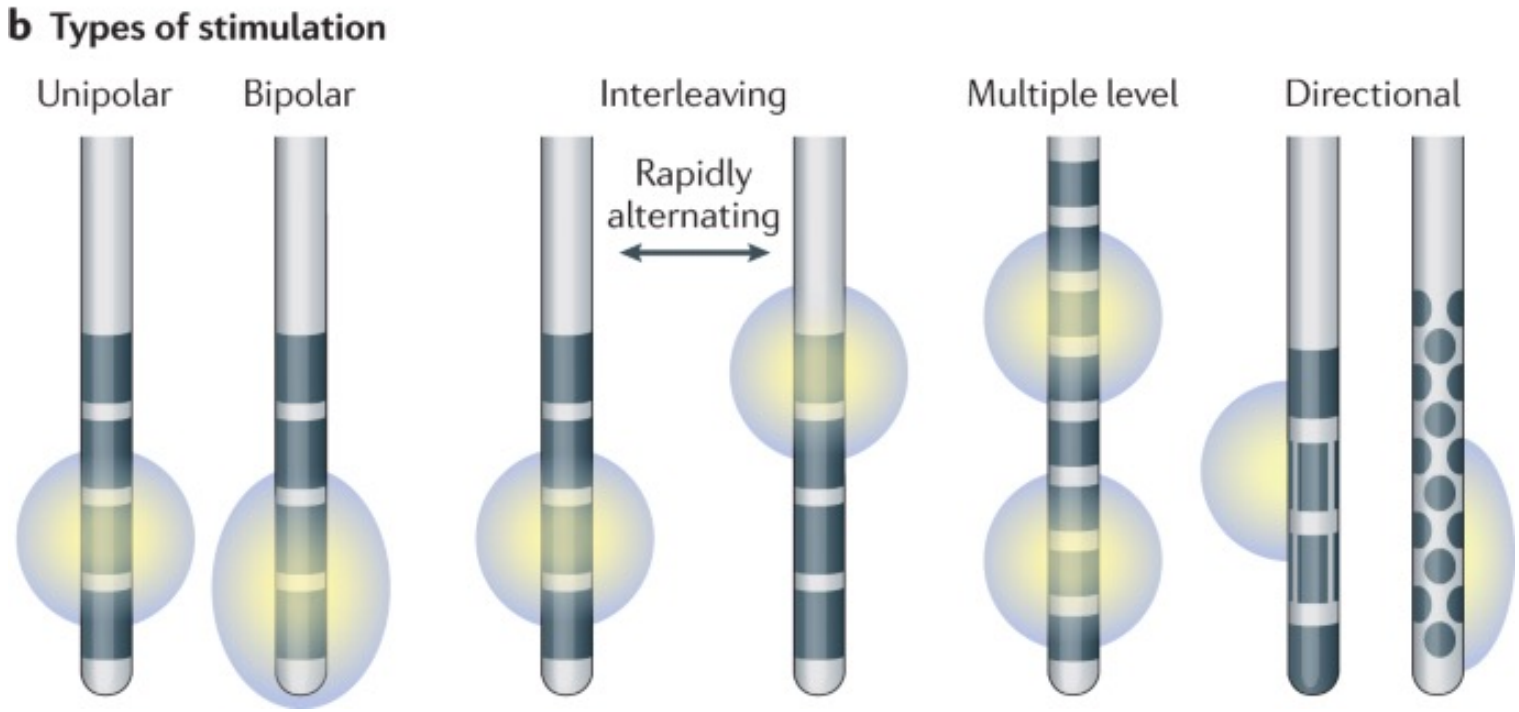
quadripolar electrodes in different configurations

New electrodes with more contacts (experimental)

Krauss et al., 2021

Deep brain stimulation

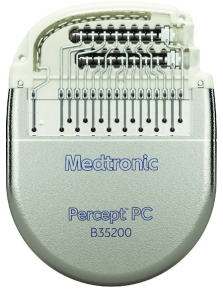
Electrode configurations & stimulation



Krauss et al., 2021

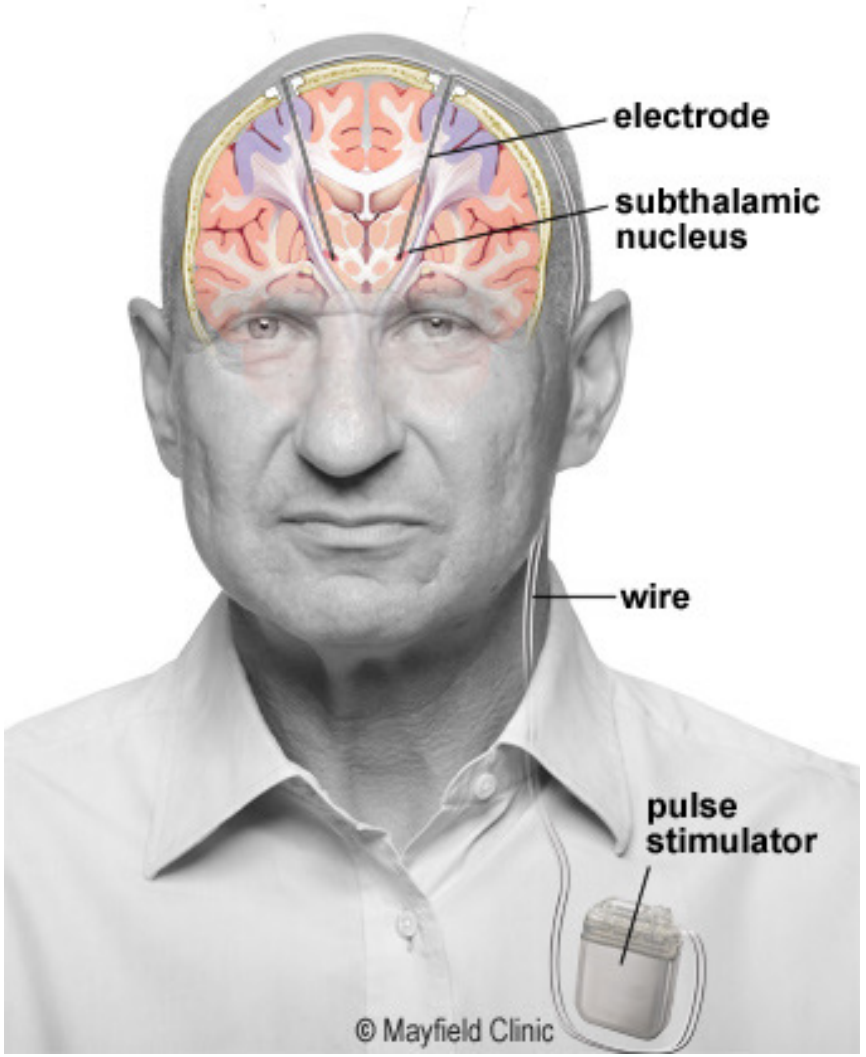
Deep brain stimulation

Pulse generator



Implantable impulse generator
Current systems weigh 40-70 grams

Current research in development…
-pairing of individual electrode contacts with different currents
-larger range of waveforms (very high frequency, bursts, etc)
-improve battery and recharging procedure
-miniaturization (decreases risk of wire damage and infection, MRI heating, etc)



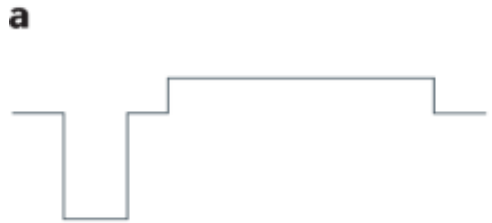
Deep brain stimulation

Stimulation parameters

Stimulation parameters
-High frequency stimulation of **130 Hz**
-Different waveforms possible, repeated at fixed interpulse intervals (conventional DBS applies asymmetric biphasic pulses)
-Interpulse interval of 7.7ms for 130 Hz

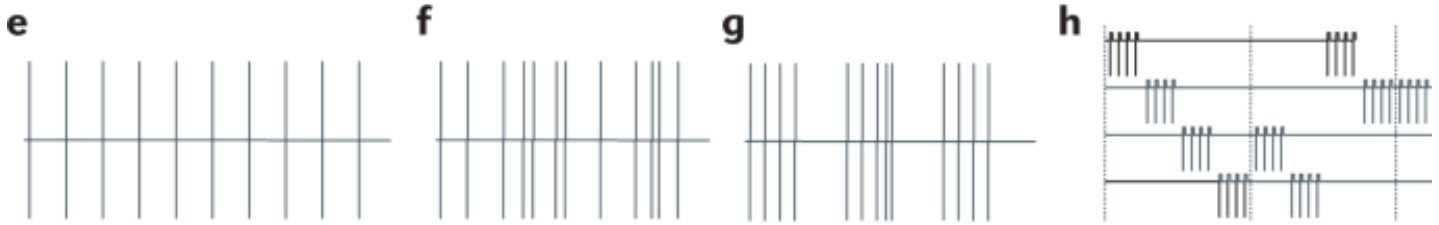
Choosing optimal pattern remains challenging, because requires evaluation of therapeutic effects during implantation surgery in awake patients (tremor, bradykinesia, dystonia), expertise, is time consuming, no automatized procedures.

Conventional asymmetric waveform
(less battery drain)



Symmetric waveform
(potentially greater suppression of PD symptoms)

Different temporal patterns of DBS



Fixed interpulse interval (conventional)

Burst pattern

Burst pattern across 4 different electrodes

Krauss et al., 2021

Deep brain stimulation

DBS of the subthalamic nucleus (STN-DBS)

Paul Krack

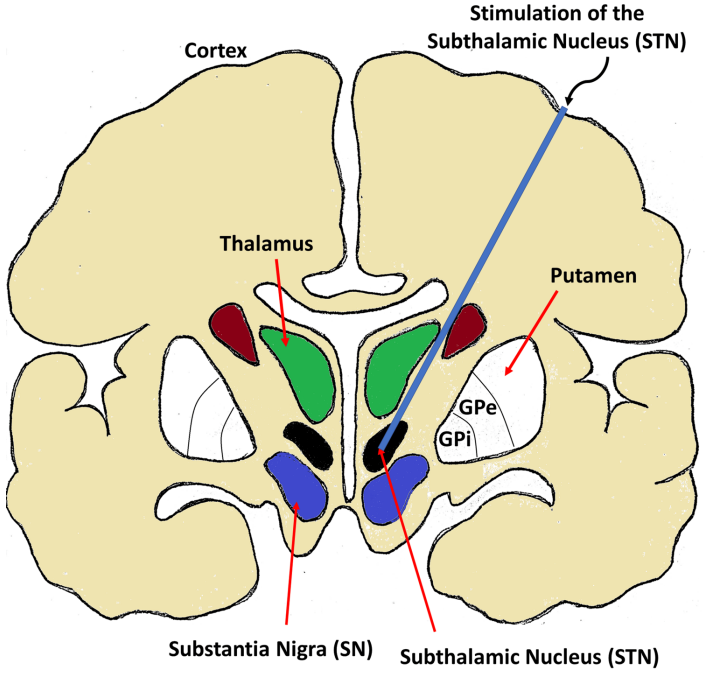
STN

Today's class focusses on DBS-STN

Globus pallidus internus

GPi DBS not covered

(Similar effects as DBS-STN)



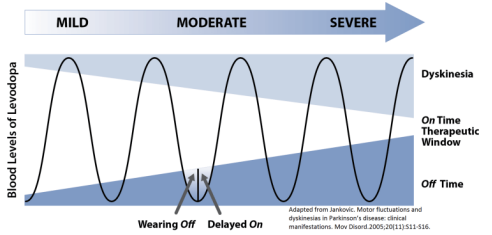
Patient selection for DBS of STN

DBS is medically indicated …

1…if dopamine replacement therapy loses efficiency (decreased ON effects).

2…if there are dopamine-induced side effects (dyskinesias) and/or severe ON-OFF symptom fluctuations.

3…if patient had initially responded well to dopamine, they are in general also a good candidate to profit from DBS.



Factors not impacting DBS success

Age, disease duration

GPi vs STN

GPi and STN have similar effects for bradykinesia, rigidity, tremor, axial symptoms (Paul Krack et al., 1998)

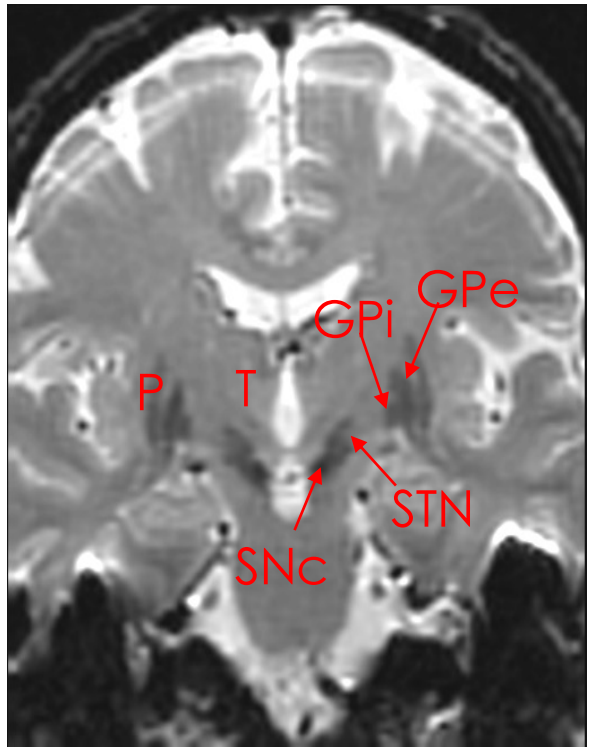
STN reported as better for bradykinesia (Paul Krack et al., 1998); GPi seems to have less adverse effects on cognitive function

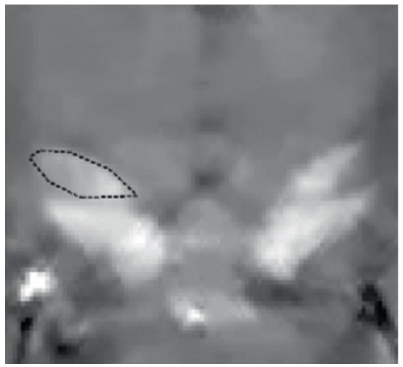
(DBS of ventrolateral thalamus also reduces tremor (essential tremor), but has no effects on bradykinesia or rigidity)

Deep brain stimulation

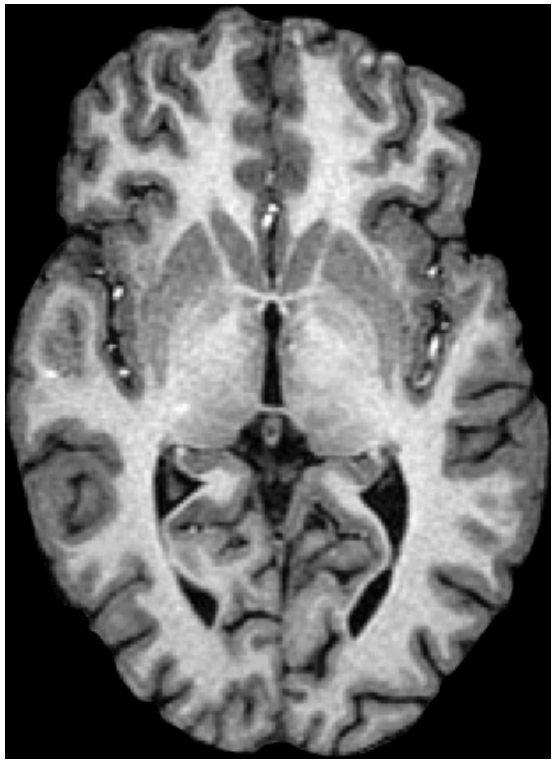
DBS target visualization (STN)
Lead location

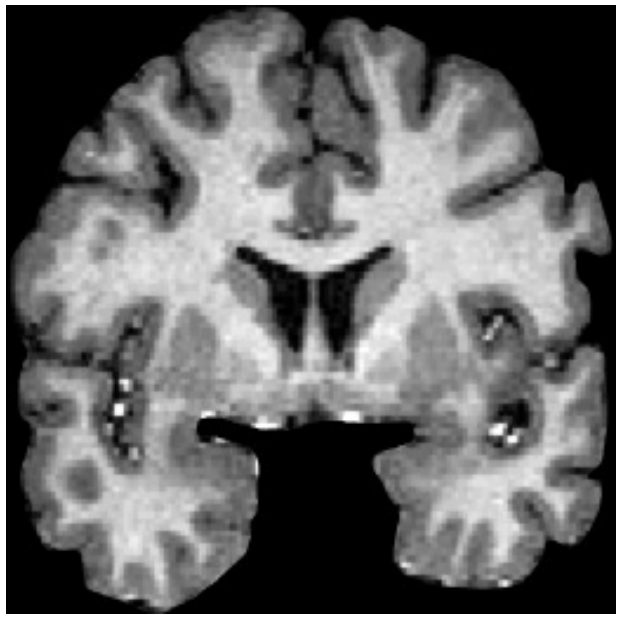
Preoperative MRI



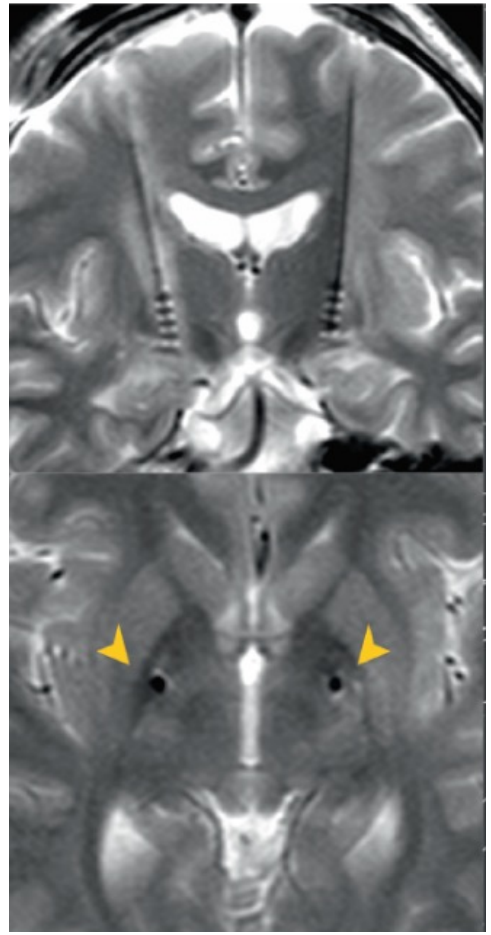


special MRI sequences allow
for better visualization of STN





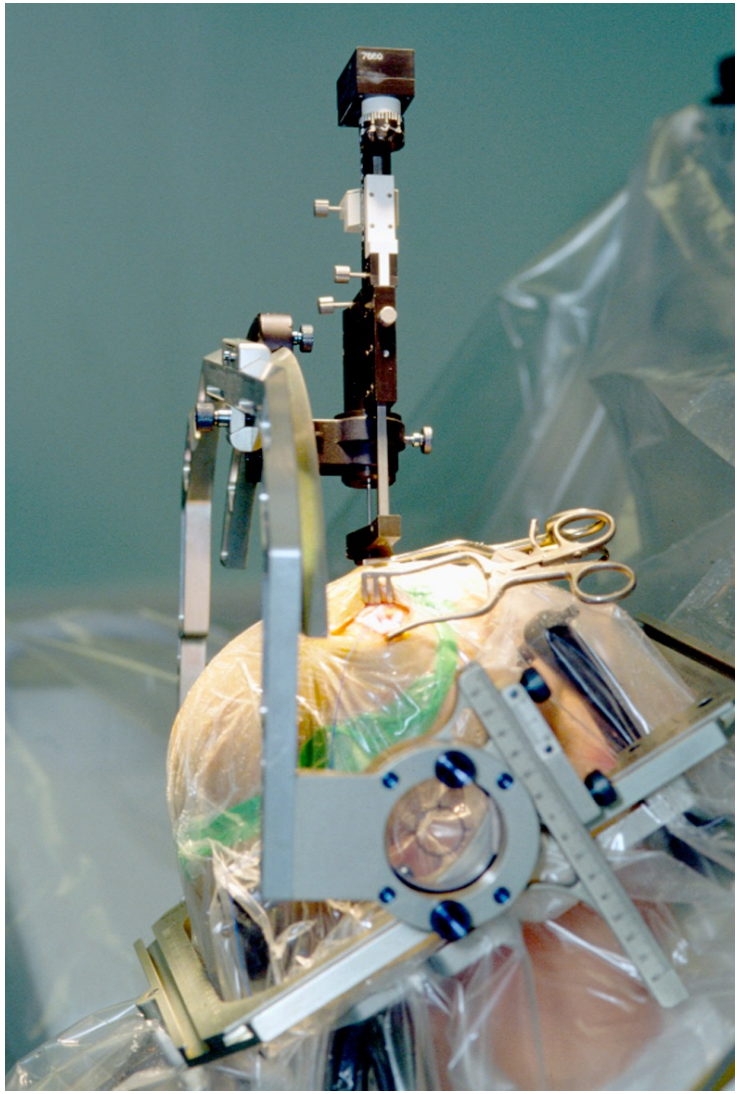
Electrode lead location
based on MRI artefact



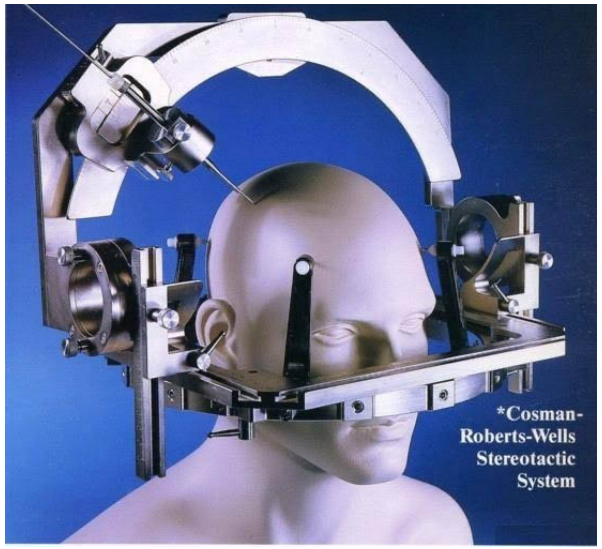
Postoperative MRI

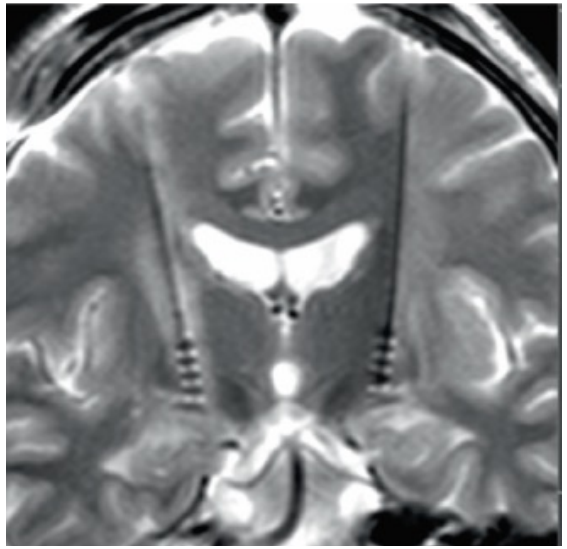
Deep brain stimulation

Implantation surgery for DBS, Anatomy



Standard procedure for implantation
-preoperative MRI (previous slide)
-**preoperative simulation** of electrode trajectory
-OP with electrode insertion with **patient awake**
-targeted location is in sensorimotor subregion of STN
-**clinical-functional mapping** to optimize electrode contact location by testing the effects of DBS for each electrode contact (determine “sweet” spot for best DBS effects)
-effects are tested on **tremor and on bradykinesia**, also by electrophysiological mapping



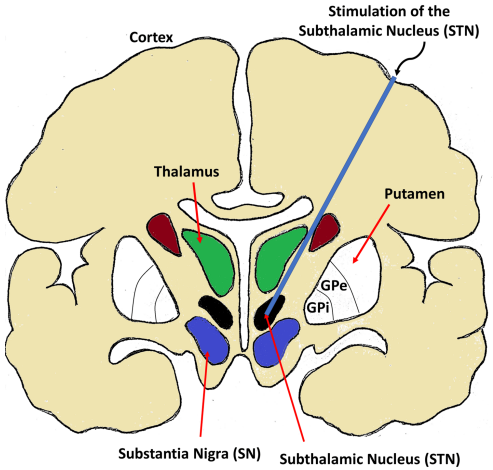


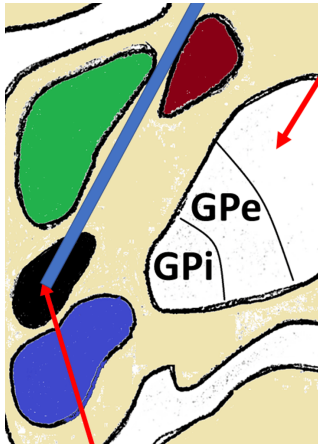
Deep brain stimulation

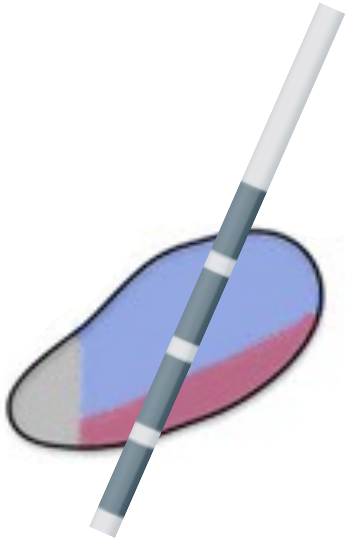
Implantation surgery for DBS, Anatomy

Anatomy, Function & Physiology

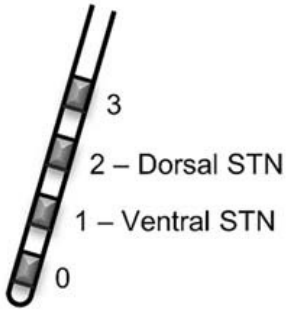
Target is the **sensorimotor part of STN** (shown in black) (see also image on the right)

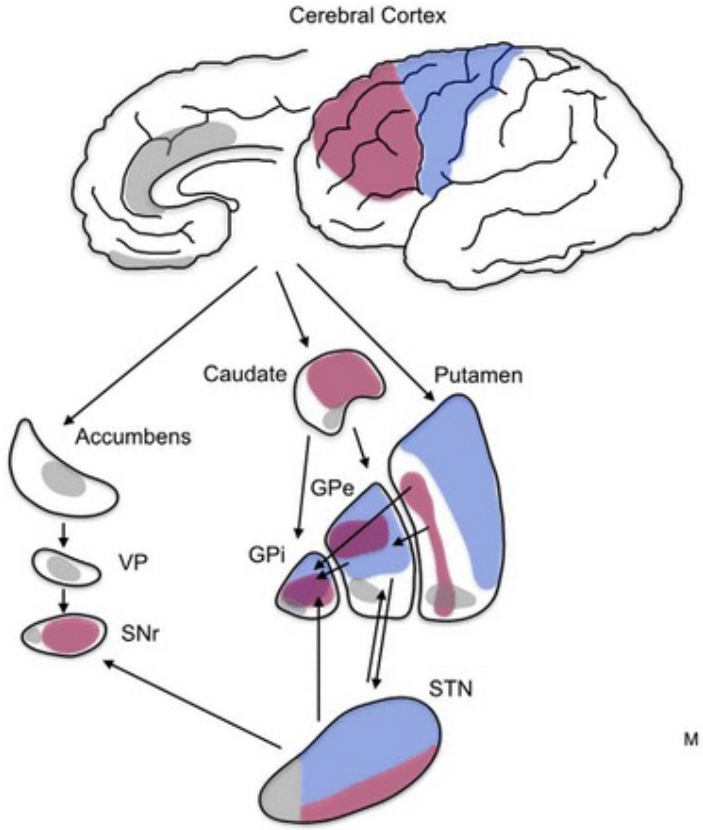






Target location is in the sensorimotor part of the STN (dorsal part)





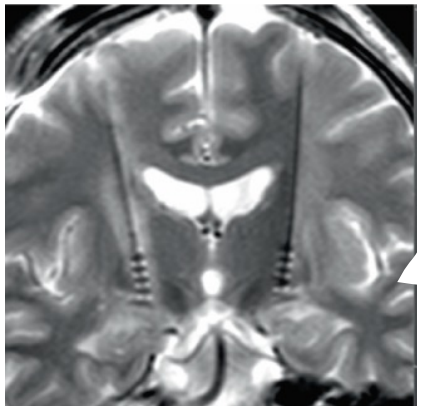
Depending on location of stimulation, different regions of BG and different networks are modulated by DBS

Sweet spot = DBS site that leads to highest efficacy on akinesia ands tremor symptoms

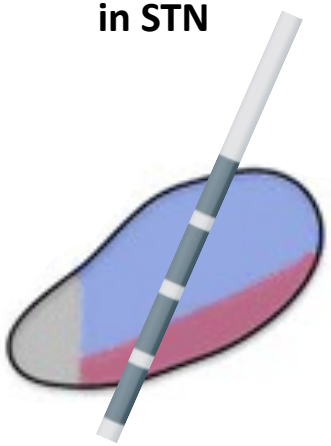
Deep brain stimulation

Brain imaging of basal ganglia circuits, pathways, and the
volume of tissue activated (VTA)

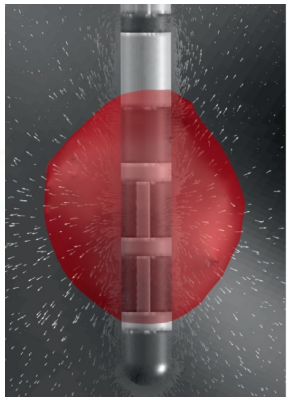
MRI



Location in STN



VTA



VTA is estimation of the electrical field of stimulation, within and beyond STN

VTA helps define the "sweet" spot (based on direct STN effects and many indirect effects beyond STN)

STN-DBS has direct STN effects and indirect effects beyond STN nerve cells because …

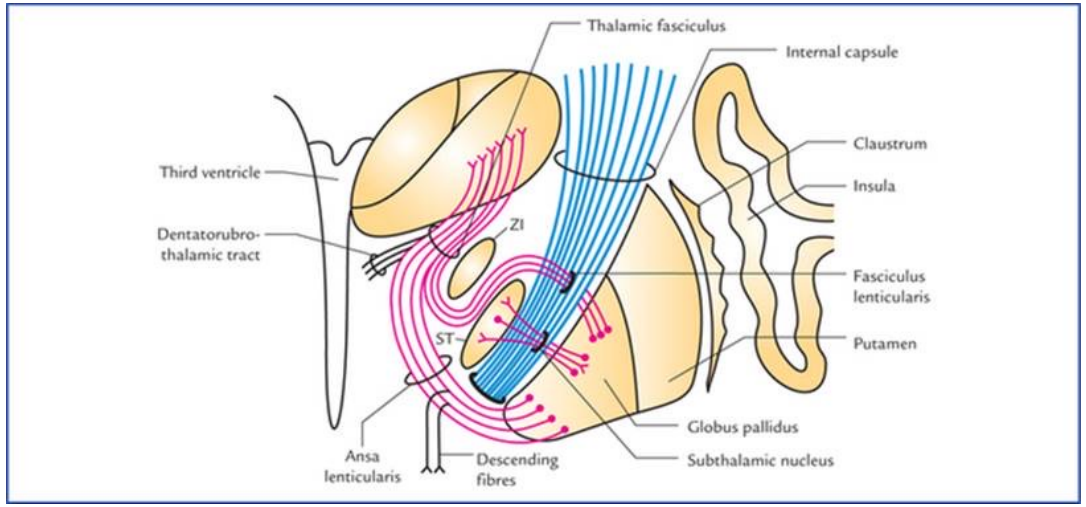
DBS stimulates passing white matter fibers

… in the IC (internal capsule)

… in the ML (medial lemniscal pathway)

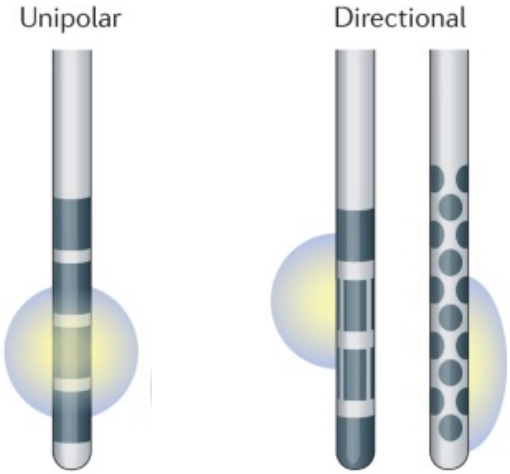
… in other basal ganglia pathways

VTA allows to estimate which structures are stimulated.



Deep brain stimulation

Volume of tissue activated (VTA) can be better oriented/directed with directional DBS systems



New directional electrodes (> 2015) allow for steering of the electrical field

-radially segmented electrodes (some current systems have replaced the 2 middle cylindrical electrodes by 3 segmental electrodes)

-**More versatile shaping of the electrical stimulation field**

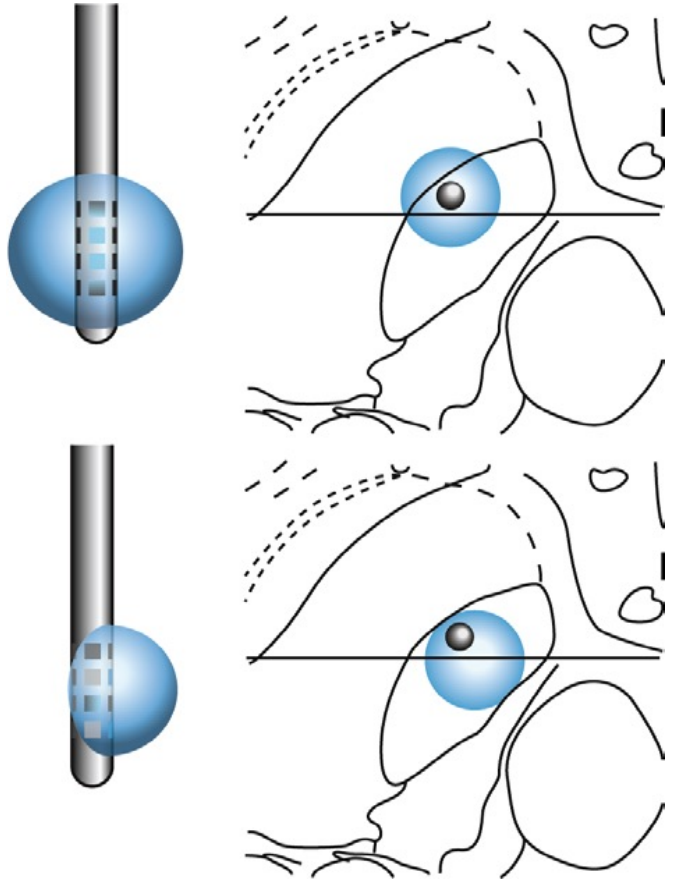
-potential to enhance therapeutic effects and minimize adverse side affects

But …

…add complexity to implantation surgery

…production is more complex

…automated support tools and neural biomarkers still missing

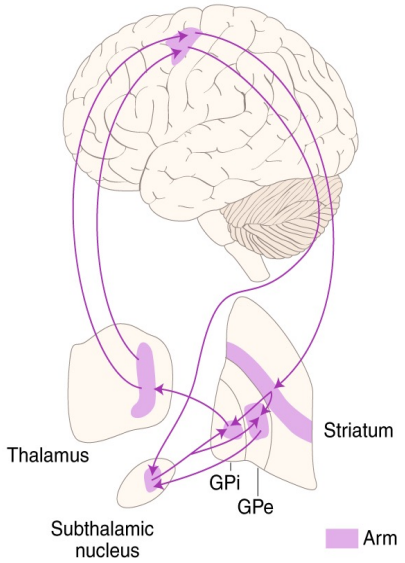


Conventional DBS: VTA outside STN

Directional DBS: VTA inside STN

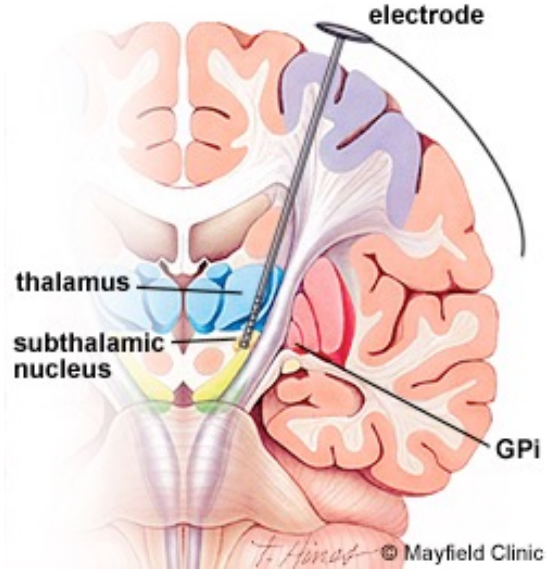
Cagnan et al., 2019

Questions ?



Deep brain stimulation

Overview



Therapeutic effects of DBS

DBS effects on neural activity

Network effects beyond basal ganglia

Imaging of networks and tracts stimulated/activated by DBS

Side effects

Beta oscillations

Open-loop DBS, Closed-loop DBS, adaptive DBS

Deep brain stimulation

Therapeutic effects (symptoms)

Tremor & Gait

Tremor & Bradykinesia

https://www.youtube.com/shorts/wZZ4Vf3HinA

Deep brain stimulation

Therapeutic effects of STN-DBS and their neural mechanisms

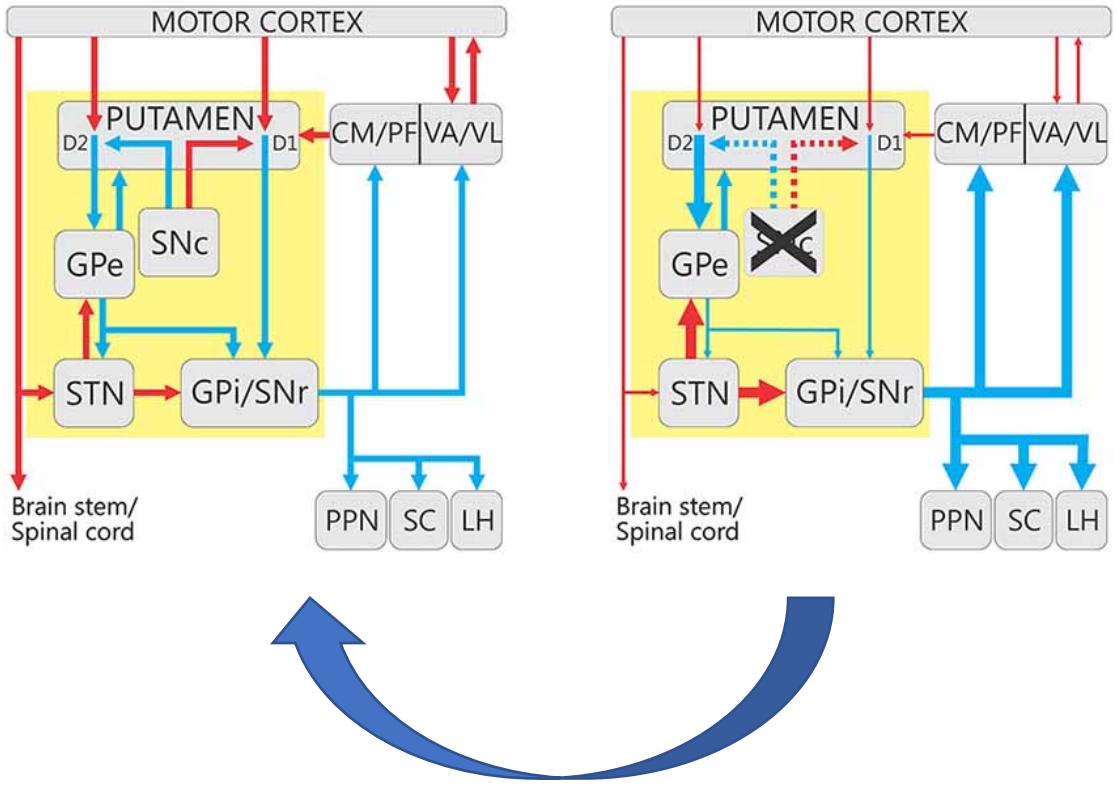
Long-term therapeutic outcomes & effects
UPDR scale (main PD scale in clinical studies)
Overall scores of 50-75% of patients are improved

Tremor 60-90% improved
Rigidity 50-70% improved
Bradykinesia 50-70% improved

(Axial symptoms 40-60%)

Other effects…
…Reduction of symptom fluctuations
…Shorter OFF periods
…Less dopamine-induced dyskinesias
…Quality of life improved
…Dopamine dosage reduction (of up to 40-80%)
…No negative effects on cognition

DBS changes activity in basal ganglia circuits (and basal ganglia-thalamic-cortical networks) towards a more normal oscillatory pattern (next slide)



Deep brain stimulation

Changes in pathological activity in basal ganglia circuitry by therapeutic DBS

Effects of STN DBS on neural activity

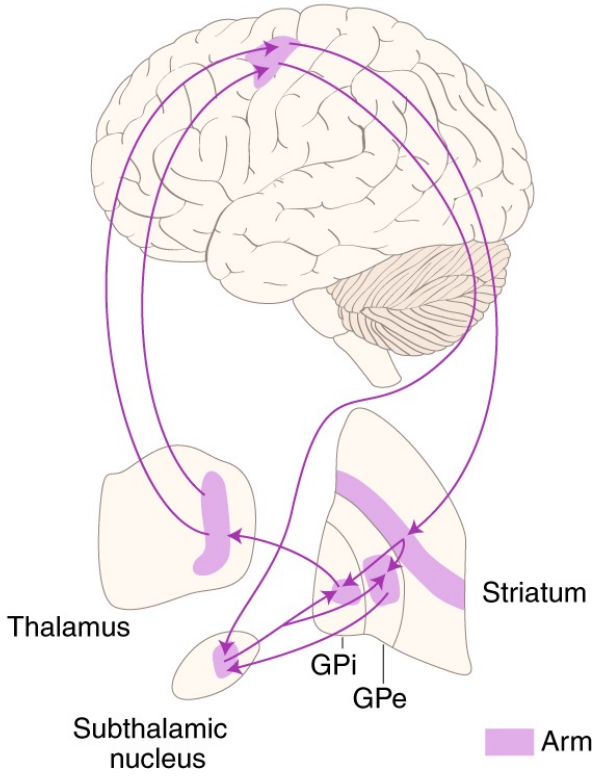
Initially, DBS was assumed to (only) inhibit activity of the STN, because DBS effects on PD symptoms are similar to those of a surgical ablation of the STN (also in animal models of PD).

Recent evidence shows a more complex picture involving many more structures beyond STN:
STN-DBS increased downstream activity of GPi; other evidence showed either up- or down-regulation of basal ganglia structures and this also included up-stream regions of the STN (by antidromic modulation).

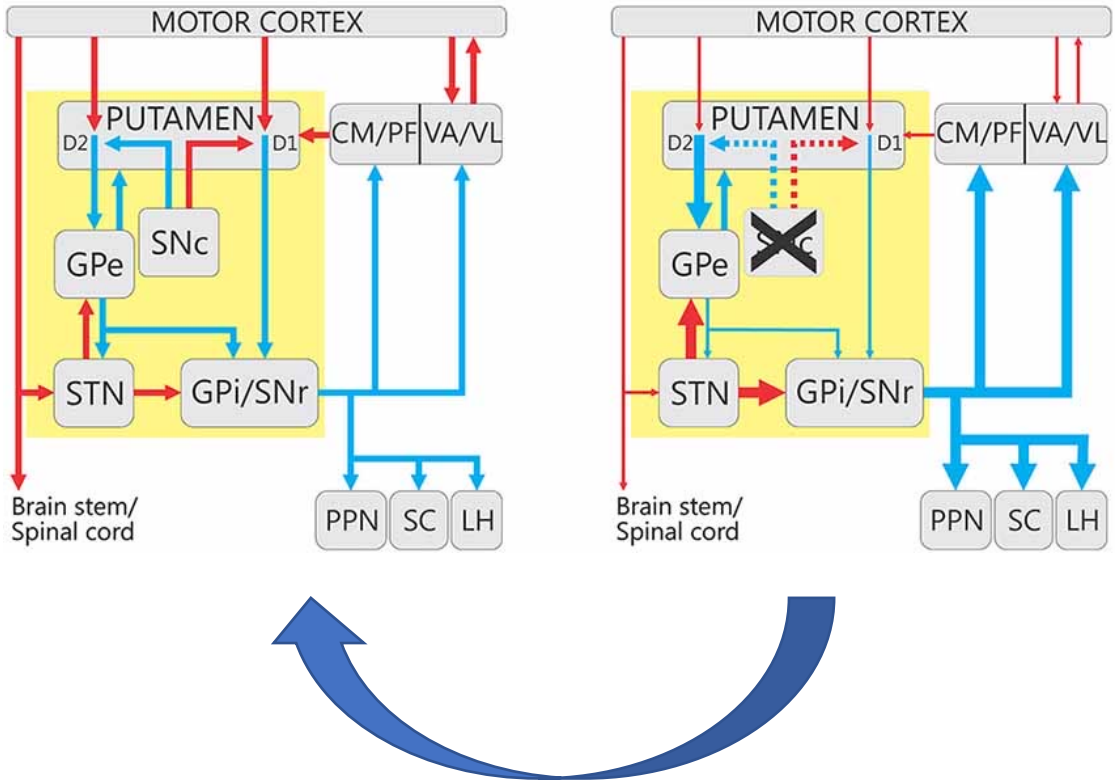
→ STN-DBS modulates activity at efferent and afferent brain regions to restore physiological activity and function.

In PD, excessive rhythmic activity/oscillations have been observed (i.e. beta, gamma and alpha/theta frequency range). STN-DBS suppresses this pathological activity, but if you stop DBS, these oscillations return (see next slides).

Several pathways and structures contribute to the therapeutic effects of STN DBS



Although STN DBS is applied locally, it changes activity in basal ganglia circuits (and basal ganglia-thalamic-cortical networks) towards a more normal oscillatory pattern.

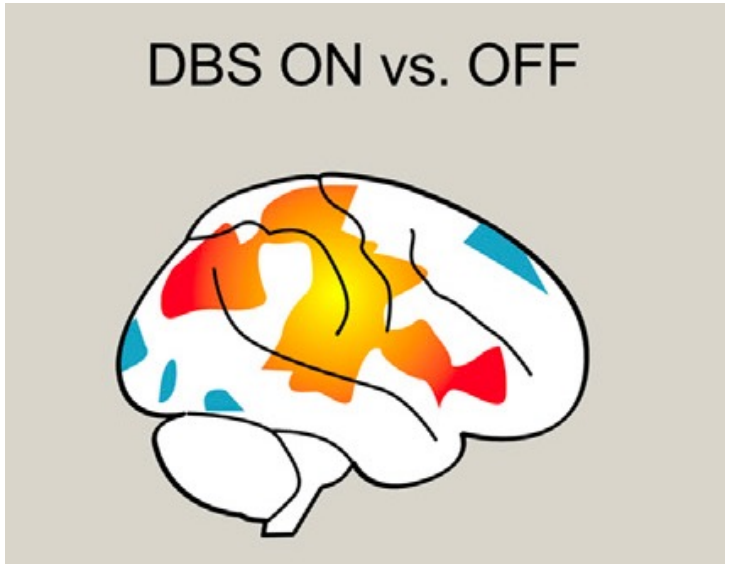


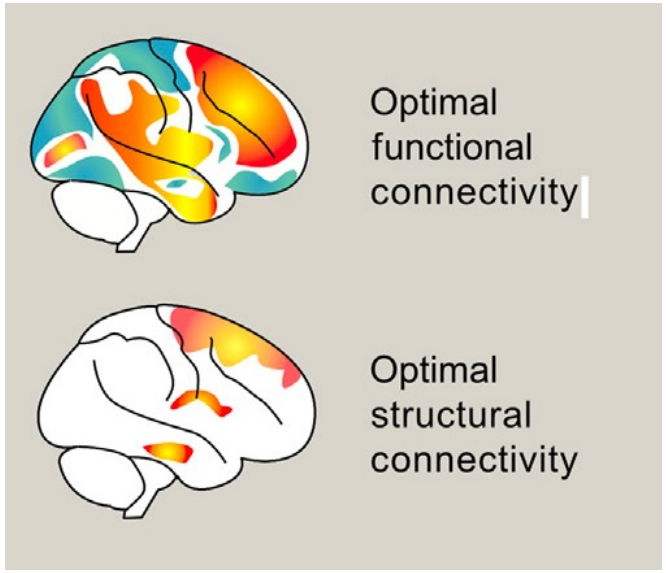
This likely involves hyperdirect, direct and indirect pathways
(difficult to directly study the pathways in humans mediating the STN DBS effects)

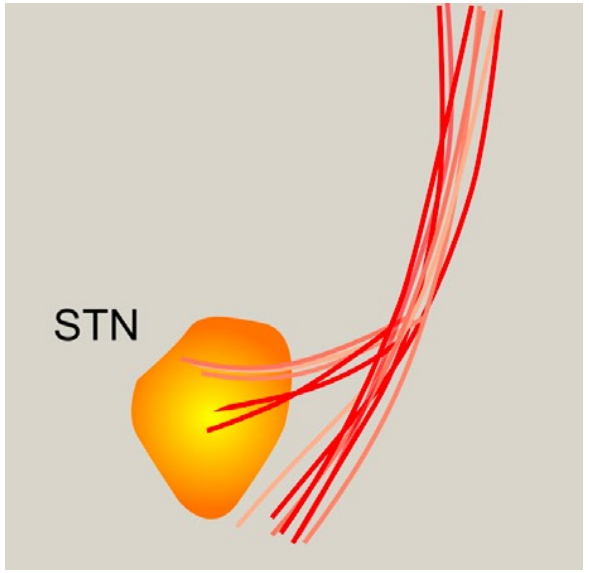
Deep brain stimulation

Network effects beyond basal ganglia

Imaging of networks and tracts stimulated/activated by DBS

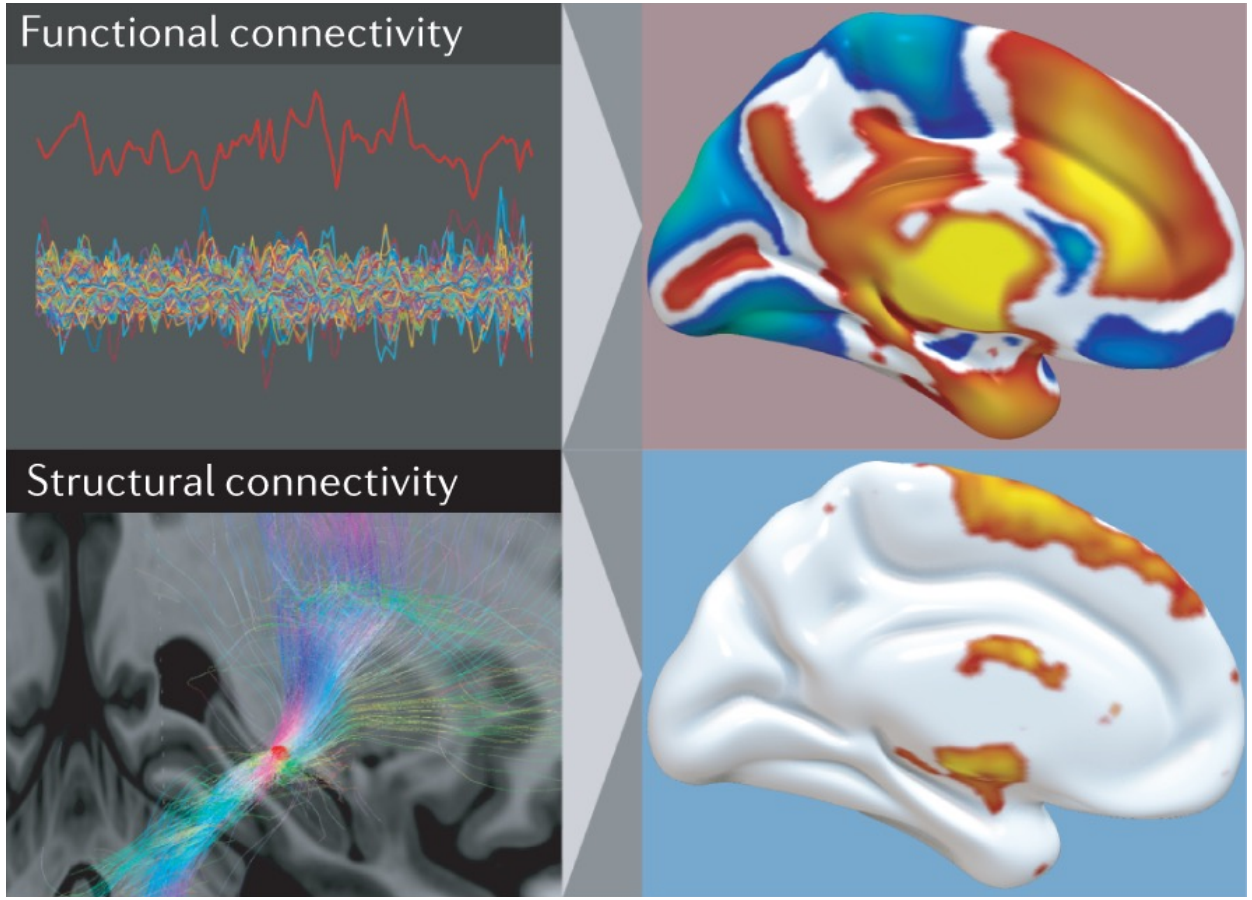






Deep brain stimulation

Revealing the regions, anatomical tracts and networks engaged in therapeutic DBS effects by brain imaging



Tractography or **structural connectivity** is based on preoperative DTI/DSI.

Functional connectivity is based on resting state fMRI measured before implantation.

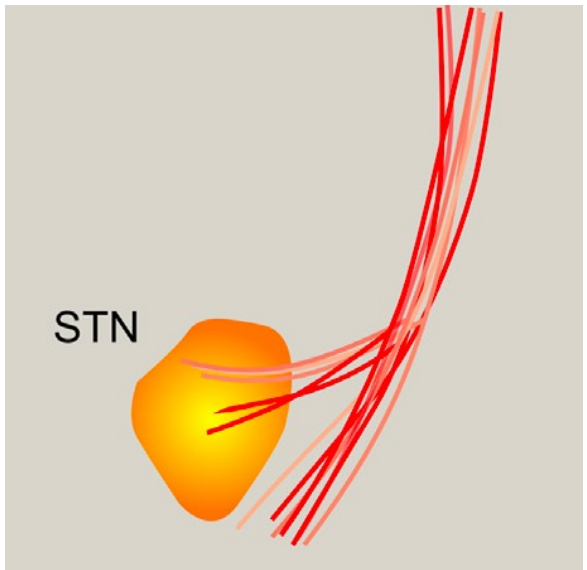
Most DBS functional and structural connectivity studies use large data bases from healthy control subjects (n=1000) to perform connectivity analysis. → Data from each patient about STN implantation sites (electrode locations) are normalized-transferred to these data bases (recorded in large samples of healthy subjects).

Functional connectivity from active STN-DBS connects **with M1, premotor cortex and supplementary motor area (SMA)** & has been associated with DBS-improvements on **rigidity and bradykinesia.**

Alleviation of **tremor** was related to **functional connectivity between** active STN-DBS contact and **primary motor cortex (M1).**

STN-DBS functional (and structural) connectivity may be even more relevant for psychiatric disorders and psychiatric and cognitive symptoms related to PD (cognition, depression, apathy, hallucinations).

Mapping the tracts (or anatomical pathways) mediating DBS effects

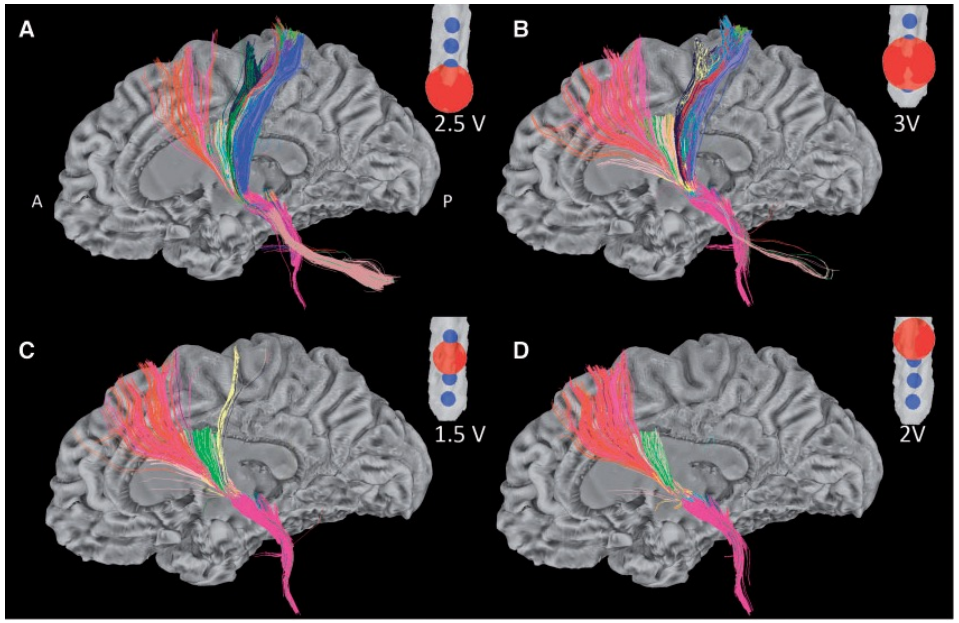


Deep brain stimulation

MRI-based tractography (or structural connectivity)

reveals networks of STN DBS that are therapeutic

Divergence of structural connectivity depending on STN lead location

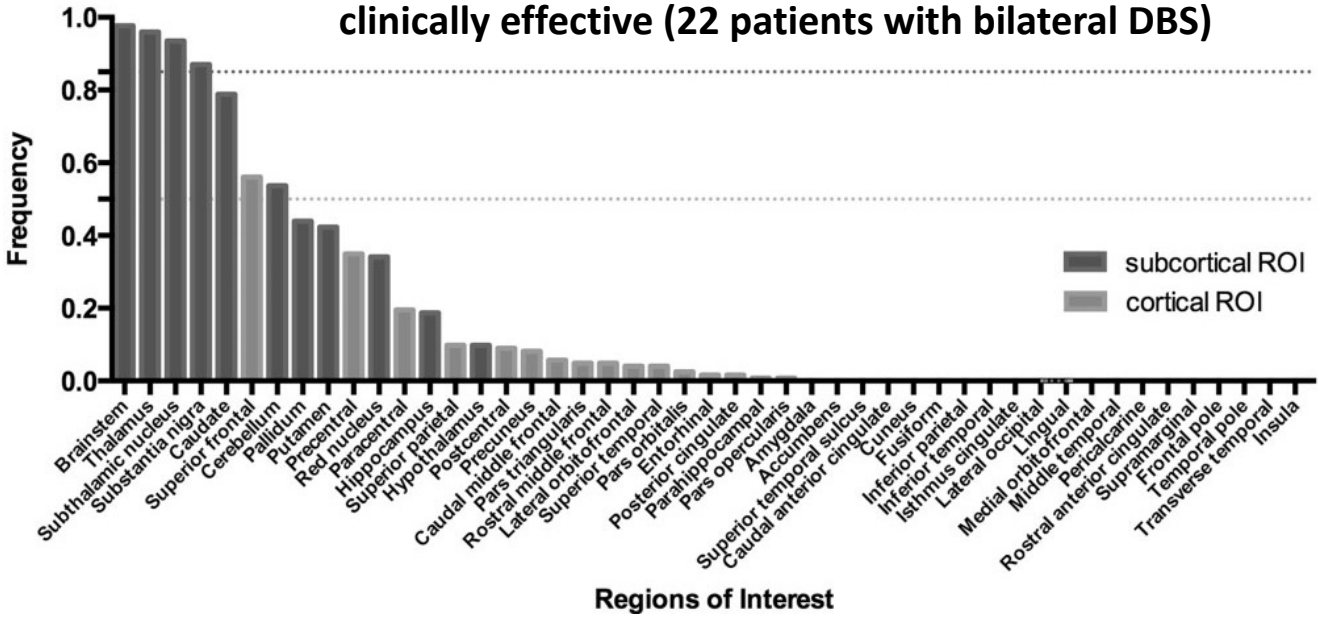


Single patient example

Bottom row (2 efficient STN-DBS sites):
Enhanced connections to SMA, PMC, M1

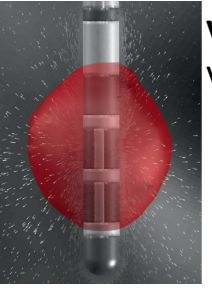
Top row (inefficient STN-DBS sites)
(color code of connections reflects anatomy)

Tested structural connectivity for 123 STN contacts that were clinically effective (22 patients with bilateral DBS)



Main connected subcortical areas	Main connected cortical areas
Brainstem	Superior frontal gyrus
Thalamus	(SMA and premotor cortex)
STN	M1
Substantia nigra	S1
Caudate	
Cerebellum	

Vanegas-Arroyave et al., 2017 (tractography study)

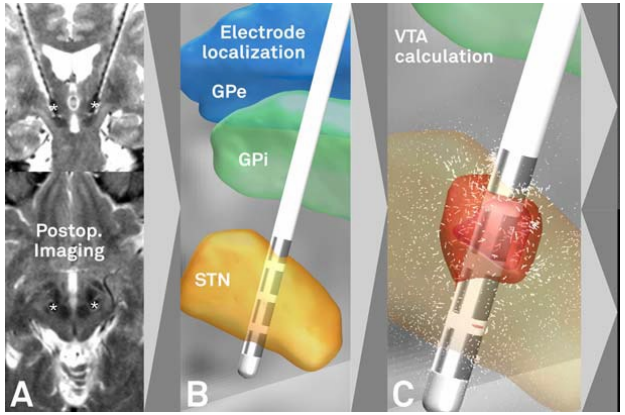


VTA
Volume of tissue activated

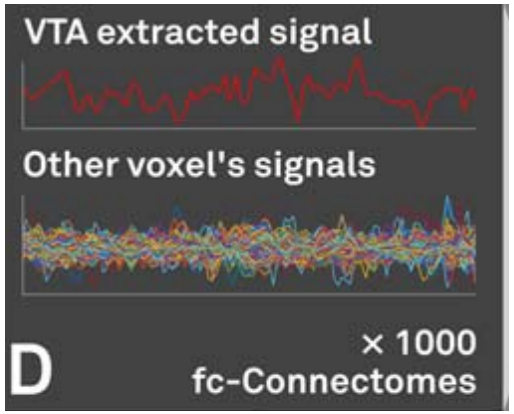
Deep brain stimulation

Functional MRI-based connectivity also used to reveal networks of STN DBS and its efficacy (still only in experimental use)

Electrode location and VTA determination (per patient)

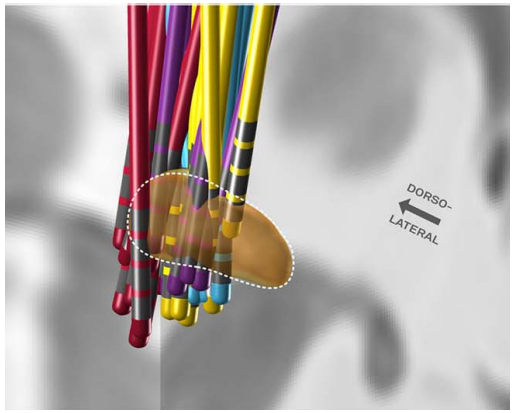


VTA functional connectivity with all other brain voxels tested (per patient)

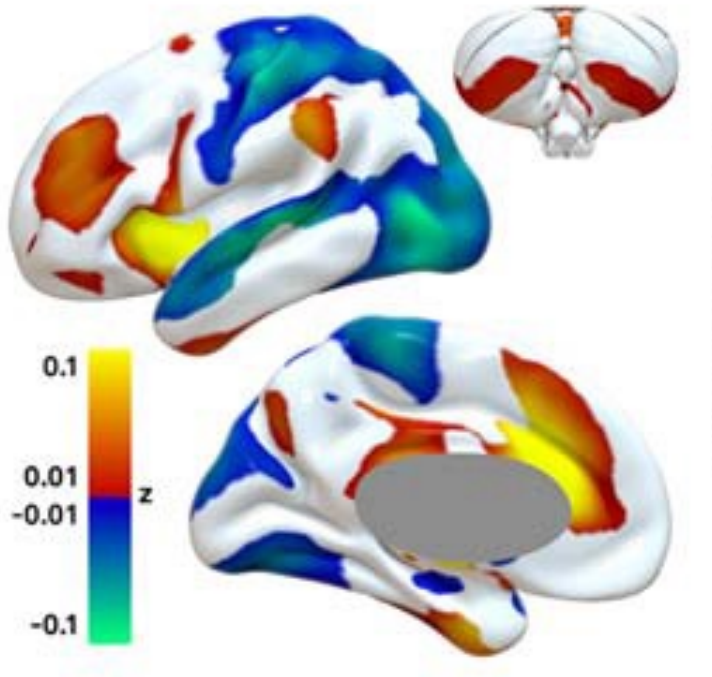


VTA connectivity in normalized data base (> 1000 healthy participants)

Electrode location for all included patients



Group functional connectivity



Functional connectivity with M1 (and posterior parietal cortex) is negatively connected with STN DBS (VTA), weighted by DBS efficacy (also other regions; experimental work, ongoing, not needed in detail for course)

(Horn et al., 2017)

Why is focal DBS of specific structures within STN clinically so important ?

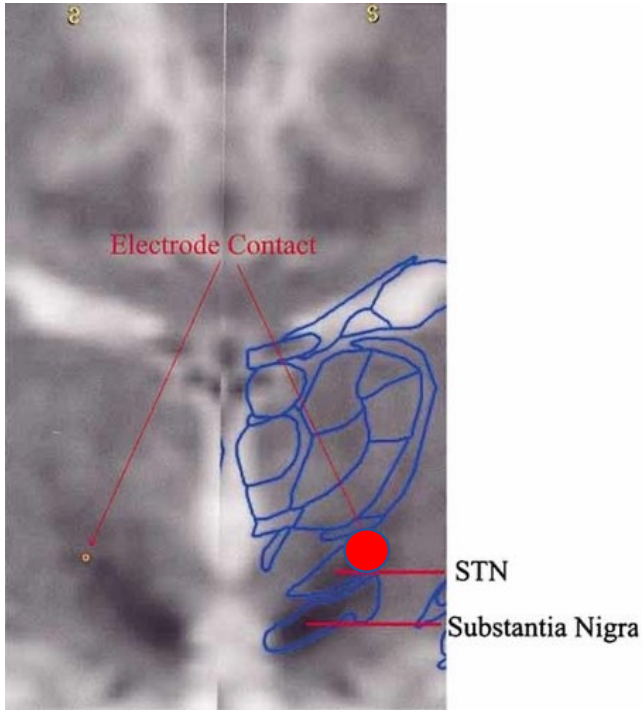
Adverse side effects

of DBS when non-targeted STN regions and adjacent structures are stimulated

Pierre Pollak

Paul Krack

Example complex motor behavior:
unsupressable laughter



Other adverse side effects of STN-DBS

Disinhibition
Gambling
Hypersocial
Euphoria
Hyperactivity
Hypomania
Mood changes

Speech changes

Careful STN implantation, target visualization, intraoperative testing, and connectivity mapping minimizes adverse side effects.

Main DBS complication are dyskinesias
(as dopamine replacement therapy)

Krack et al 2001

Pathological oscillations in PD

Brain oscillations & DBS

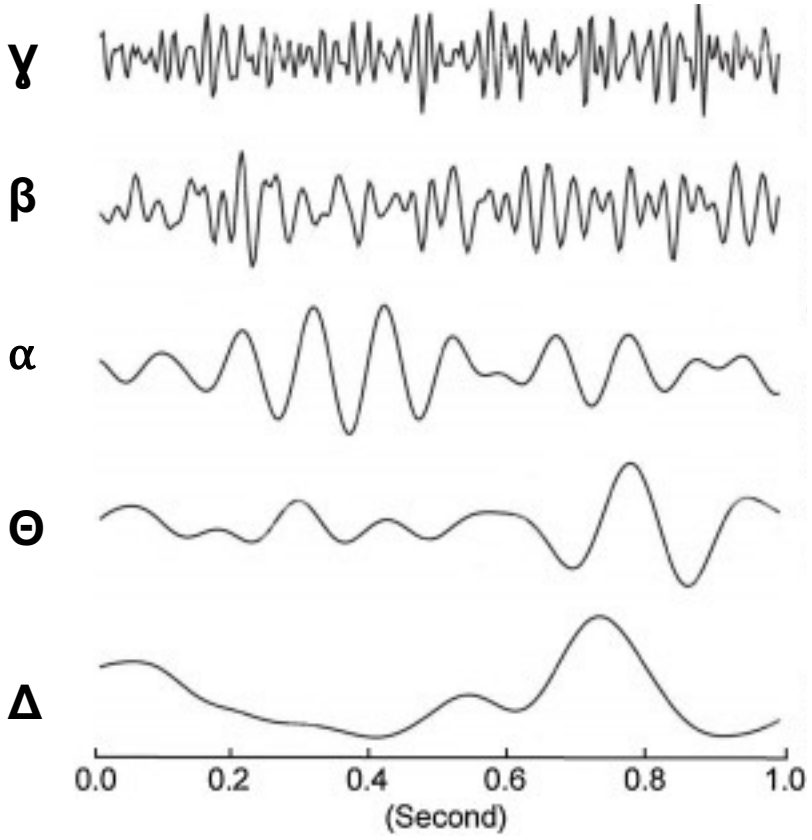
Brain oscillations reflect synchronized activity of large neuonal assemblies, if recorded intracranially, for example in STN, they are referred to as local field potentials (LFPs)

…LFPs can be also recorded outside the brain, but with much lower spatial resolution (EEG, MEG)

Alpha oscillations: 8-12 Hz
Beta oscillations: 13-35 Hz
Gamma oscillations: 40-90 Hz
Theta oscilations: 4-8 Hz
Delta oscillations: below 4 Hz

Have been linked to motor, sensory and cognitive functions, as well as physiological functions.

Alpha and beta oscillations (synchronization-desynchronization) have been linked to the motor system and movement (in this class we mainly cover STN beta-oscillations and their coupling with other brain structures).



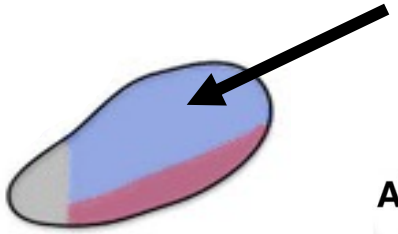
Pathological in the STN of PD patients
Beta oscillations: 13-35 Hz
Gamma oscillations: 40-90 Hz
Alpha-theta oscillations: 8-12 + 4-7 Hz
(Fosco Bernasconi)

Pathological β oscillations in the basal ganglia in PD

Exaggerated beta oscillations in the STN in PD

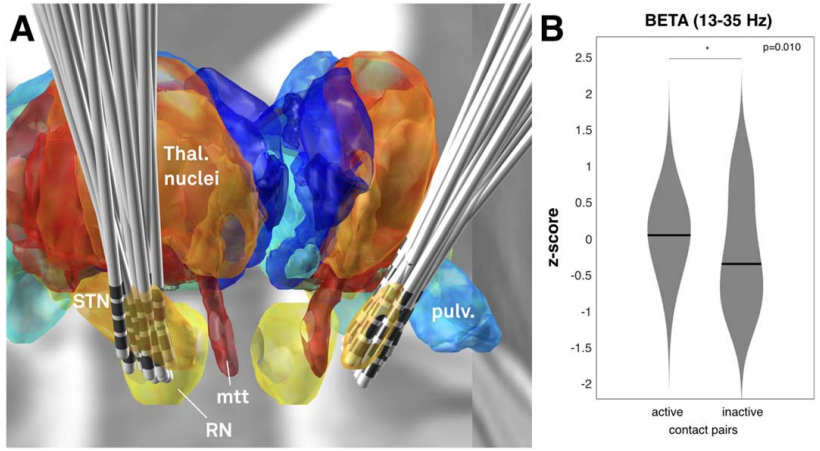
STN recordings of LFP allowed to study brain oscillations in the STN in PD patients, with high spatial resolution.

This had to be recorded in early DBS systems immediately after the implantation (but can now also be done by chronic and continuous recordings of new DBS systems (which have stimulation and recording capacity).



Main location of β activity in STN is in dorsal-lateral sensorimotor part (1-3 mm below dorsal border)

Therapeutic DBS sites have higher **β** power than non-therapeutic or inactive DBS sites, within the STN



Horn et al., 2017

β activity in STN is a brady-/hypo-kinetic signal (i.e., is a biomarker for the brady-/hypo-kinetic motor state)
PD patients show enhanced amplitude of beta β oscillations in STN

β oscillations correlate with PD motor symptoms (bradykinesia, rigidity; i.e. Neumann et l., 2016).

β oscillations are reduced by dopamine replacement therapy (Kühn et al., 2009).

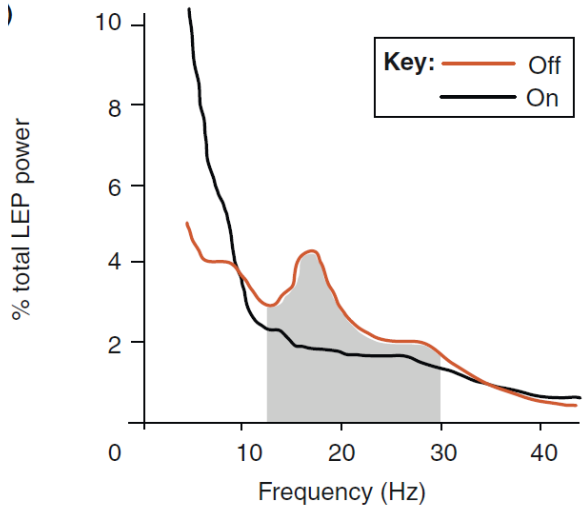
Supression of exaggerated β oscillations in STN correlates with an improvement of motor symptoms (bradykinesia, rigidity; i.e. Kühn et al., 2006, 2008).

β oscillations predominate in sensorimotor part of the STN

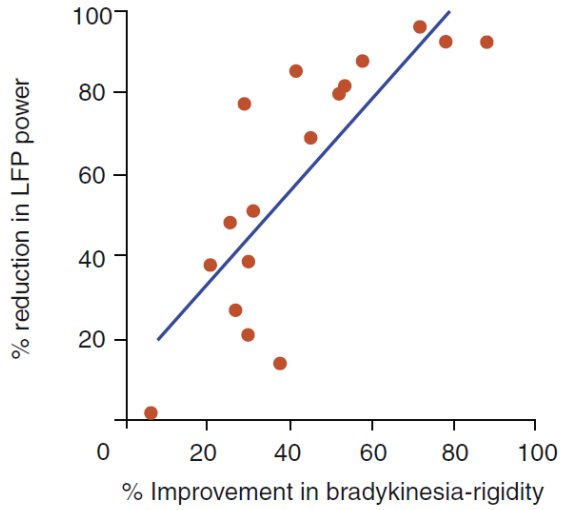
(These oscillatory changes are mostly carried by the low beta band activity (13-20 Hz) and not the high beta band (20-30 Hz)).

β oscillations, dopamine & motor symptoms in PD

STN recordings (local field potentials) reveal abnormal oscillations in the beta frequency (13-30 Hz, especially lower beta) in PD



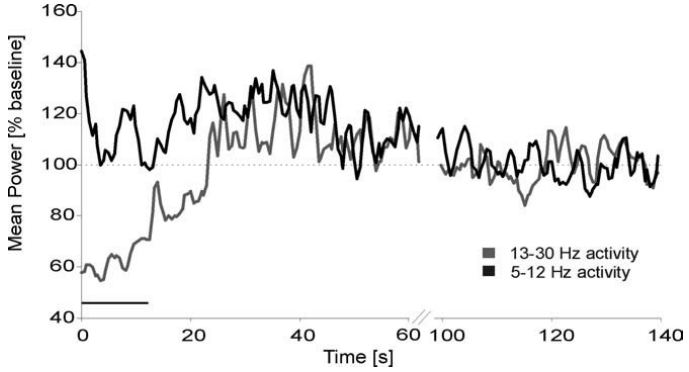
Beta oscillations are decreased by dopamine replacement therapy (ON) and increased when OFF medication, in PD patients



Improvement of motor symptoms correlates with the decrease of beta oscillations recorded in STN

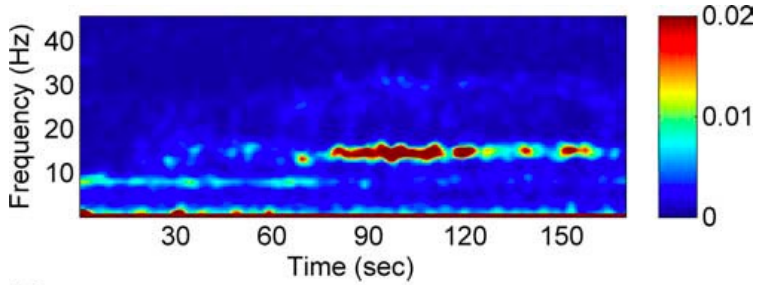
Jenkinson ... Brown (2011)

Beta oscillations in STN are suppressed by high-frequency STN DBS and improve bradykinesia

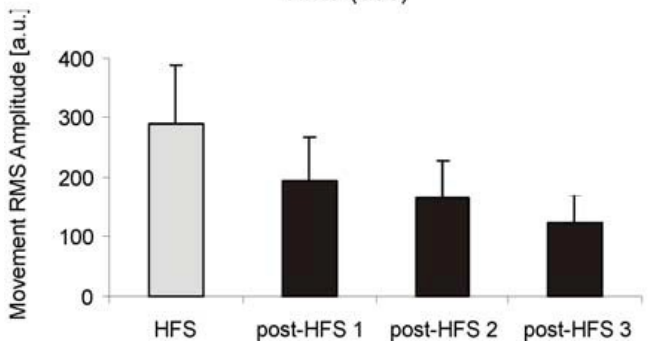


STN DBS supresses β oscillations: after stopping STN DBS (time 0 in figures on the left), β oscillations reappear continuously , reaching their non-DBS baseline after 30 seconds (in PD patients).

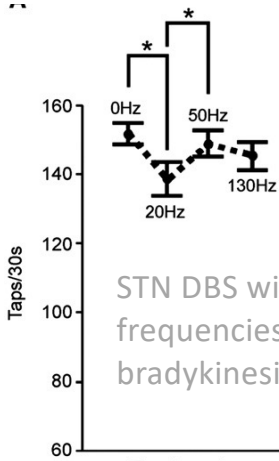
STN DBS induced reductions in beta-oscillations correlate with decreases in bradykinesia and rigidity (these findings make the monitoring of beta oscillations a key signals for closed-loop DBS)



analysis for all recorded frequencies shows prominent changes in β band (preceded by alpha band changes)



After DBS is stopped and beta oscillations reappear, **bradykinesia progressively reappears** (movement amplitude decreases in plot on the left)



STN DBS with beta frequencies worsens bradykinesia in PD patients

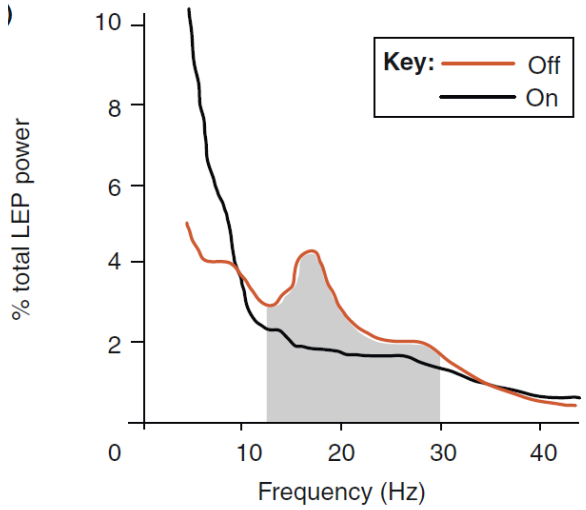
(Brown et al., 2001; Kühn et al., 2008, 2009; Ray et al., 2008)

(Chen et al., 2007; Eusebio et al., 2008)

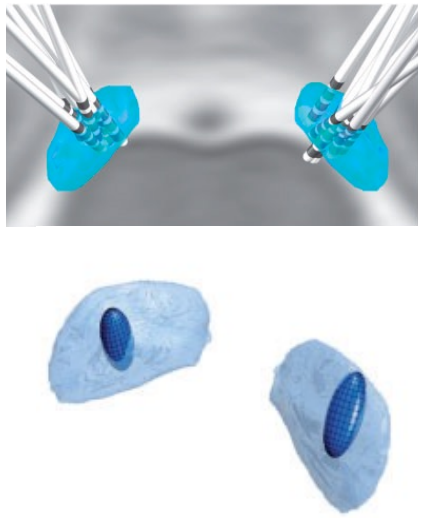
Deep brain stimulation

MRI-based tractography (and structural connectivity) reveals **motor network in frontal cortex connected to STN-regions driving beta oscillations**

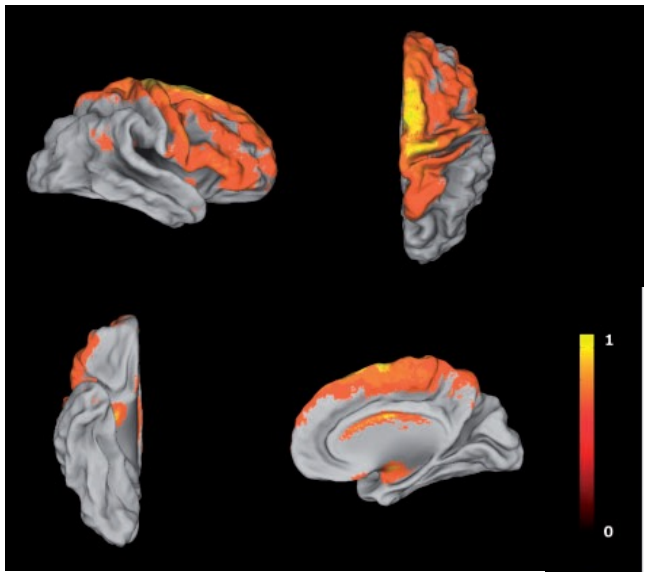
Beta oscillations (in STN)



STN contacts <u>with</u> beta oscillations …



… are connected premotor and supplementary motor regions



Contacts in dorso-lateral STN (sensorimotor part) had maximal beta oscillations and were connected anatomically with premotor cortex, SMA, M1 (some propose that this is the hyperdirect pathway between these structures and the STN)

Not found for neighboring more dorsal contacts outside STN and **without** beta oscillations (different structural connectivity)

(Accolla et al., 2016)

More on Beta oscillations in STN

Limitations/Shortcomings/Open questions …

Tremor in PD not well reflected by β oscillations (only bradykinesia and rigidity are).

Abnormal β oscillations are **not specific to PD**: also found in many other diseases and even in healthy subjects.

Abnormal β oscillations are **not specific to STN**: also found in striatum, pallidum, thalamus, and cortex (M1).

Coherence and phase-amplitude coupling across these basal ganglia regions and the cortex further links β oscillations across several brain regions = **extended network phenomenon.**
Within the cortex: STN beta coherence is found with lateral premotor and motor areas as well as medial premotor areas such as SMA).

But STN β oscillations are considered the most robust electrophysiological description of a PD patient's motor state (bradykinesia).

β activity also strongly depends on ongoing motor state (i.e., not just disease)**.** Body movements like reaching, walking, or cycling decrease and desynchronize β oscillations (also everyday life events).

"… the principal pathological alteration of exaggerated beta in PD … originate(s) from global cortico-subcortical network interactions instead of a single neural cell type or nucleus."

Neumann et al., 2023

Beyond beta

Theta/alpha oscillations and gamma oscillations in basal ganglia and cortex in PD

Theta/alpha band activity (3-12 Hz, Θ/α) and **gamma band activity** (40-90 Hz, ɣ) have also been linked to movement disorders and the basal ganglia.

Both frequency bands have been related to **hyperkinetic movement disorders** such as dystonia and Tourette's syndrome, but **also levodopa-induced dyskinesias in PD**.

Theta/alpha

Θ/α band activity (3-12 Hz) is observed during normal movement (as beta), can be identified in STN and other BG nuclei (as β), and is coupled across these regions (as β), not specific for a PD or other diseases or pathological states (as β), can be modulated by medication or DBS (as β). **Current focus in DBS research is on beta oscillations, because the signal is more robust, especially in STN.**

Alpha-theta oscillations: 8-12 + 4-7 Hz (Fosco Bernasconi)

Gamma ɣ

ɣ band activity (40-90 Hz) has been associated with levodopa-induced dyskinesias = abnormal hyperkinetic state (Jenkinsen et al., 2013; Swann et al., 2018).

This difers from beta oscillations, which are linked to the bradykinetic state.

(Neumann et al., 2023)

Gamma oscillations

Observed in STN, but currently mostly studied in motor cortex

ɣ oscillations are a physiological signals, but have also been linked to specific symptoms related to PD.

ɣ band activity has been found in **STN** (thalamus and GPi) as well as in **motor cortex** (M1 and premotor cortex).

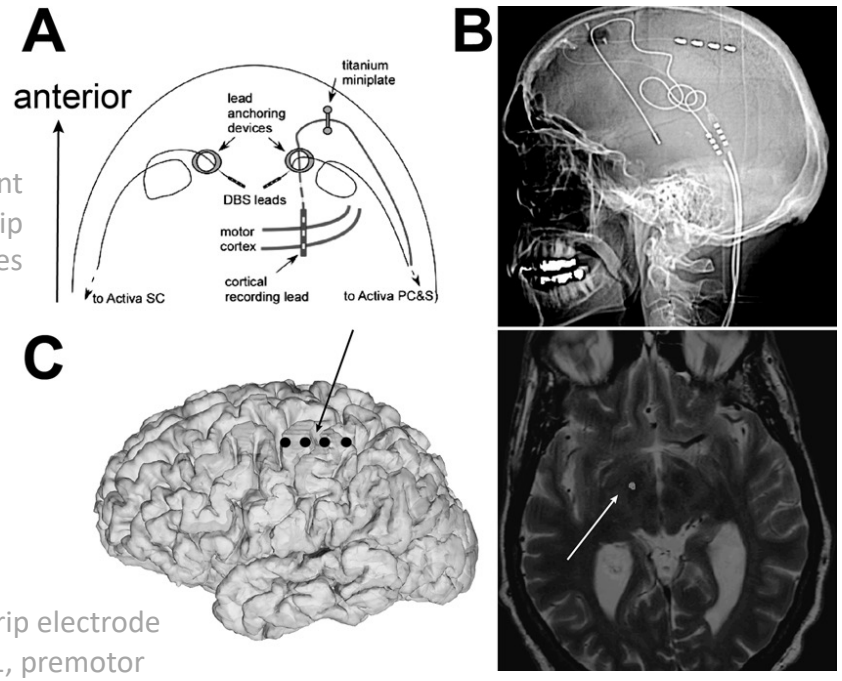
Dopamine medication increases ɣ oscillations (decreases beta oscillations).

ɣ oscillations increase during voluntary movement and **in PD have been shown to characterize abnormal hyperkinetic ststes (dyskinesias, dystonia).**

ɣ oscillations are not specific to PD (also found in essential tremor and dystonia)

ɣ oscillations also decrease during drowsiness and sleep (reappear during REM sleep) (= physiological responses).

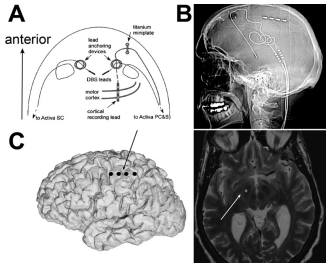
Recording standard STN DBS signals and signals from subdural electrodes implanted over motor cortex



Surgical schema to implant STN and subdural strip electrodes

Subdural strip electrode over M1, S1, premotor cortex

Location of STN electrode

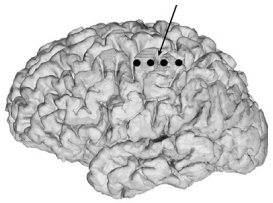


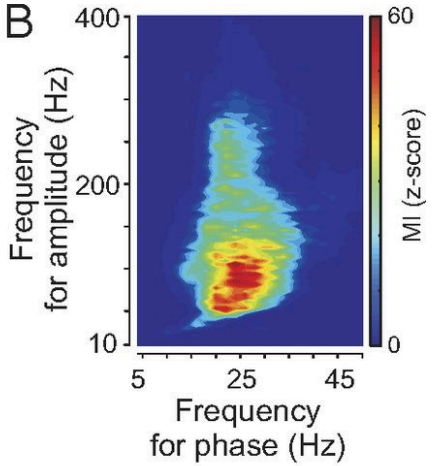
Power of gamma oscillations

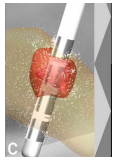
in motor cortex is coupled with phase of beta oscillations in STN

Coupling of oscillations by linking the amplitude of a high frequency oscillation (gamma) with the phase of a lower frequency rhythm (beta).

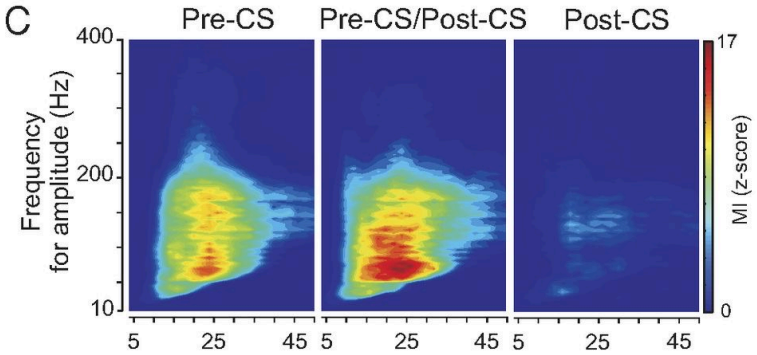
Phase–amplitude coupling (PAC) between the amplitude of gamma oscillations in M1 and the phase of β oscillations in the STN (De Hemptinne et al., 2013, 2015) **has been linked to PD.**

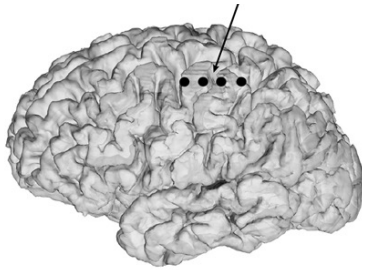


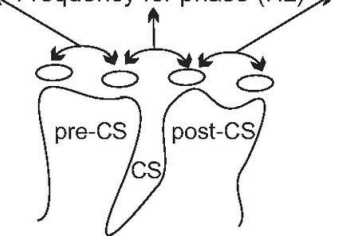


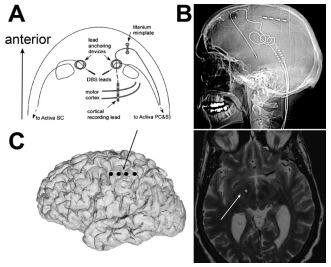


Gamma-beta PAC between cortex and STN is present in M1 and premotor cortex, but not in S1





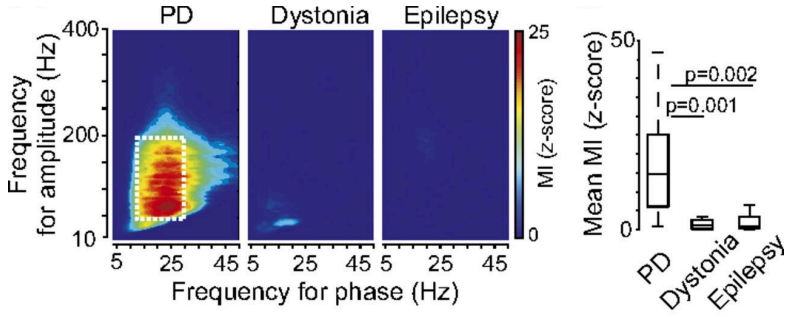




Gamma-beta phase amplitude coupling

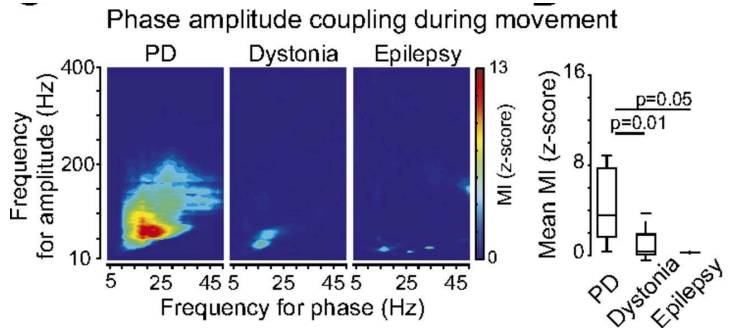
only observed in PD and persists during movement

Gamma-beta PAC at rest
(between M1 and STN)



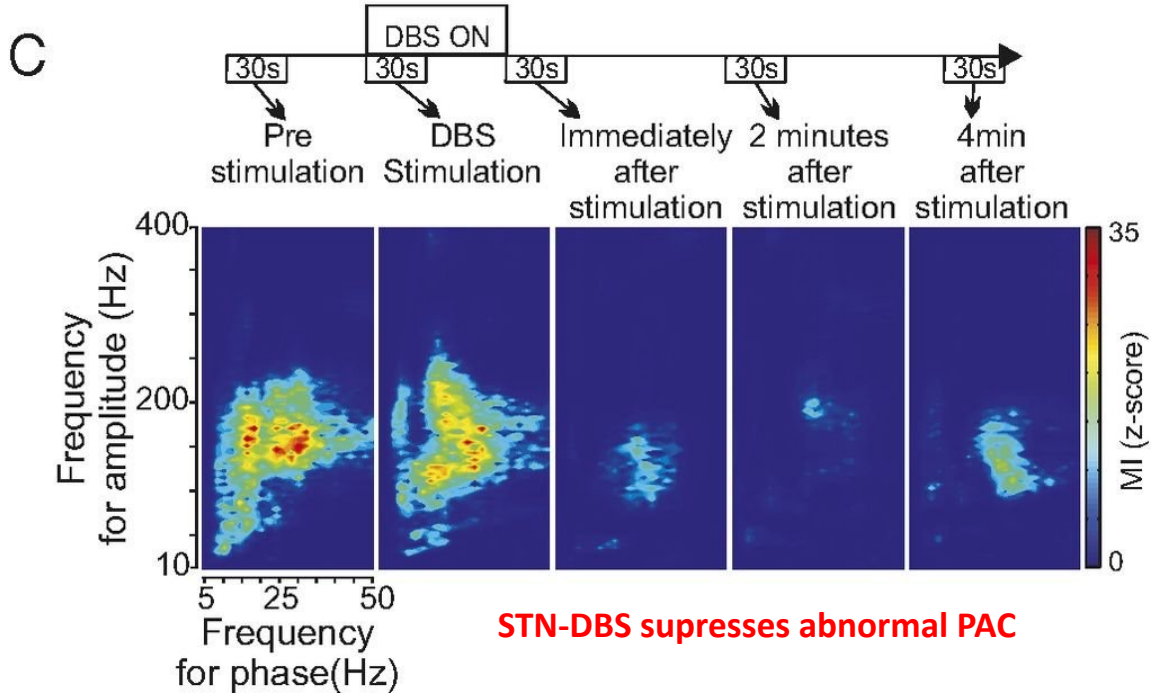
Abnormal gamma-beta PAC not observed in other medical conditions (dystonia, epilepsy)

Gamma-beta PAC during simple-repeated limb movement (between M1 and STN)



Abnormal gamma-beta PAC persists during simple movement

Theraputic effect of STN-DBS on Gamma-beta PAC



STN-DBS supresses abnormal PAC

Other work has shown that gamma oscillations in M1-premotor cortex (and PAC with STN) correlate <u>with dyskinesias</u> in PD patients (→ adaptive DBS)

De Hemmtine et al., 2013

Theta/alpha oscillations

Different STN location, different connections with frontal cortex, and associated with hyperkinetic motor states

Θ/α band activity (3-12 Hz) has also been found in the STN

Less work in STN than on β oscillations. Linked to **levodopa-induced dyskinesias in PD.**

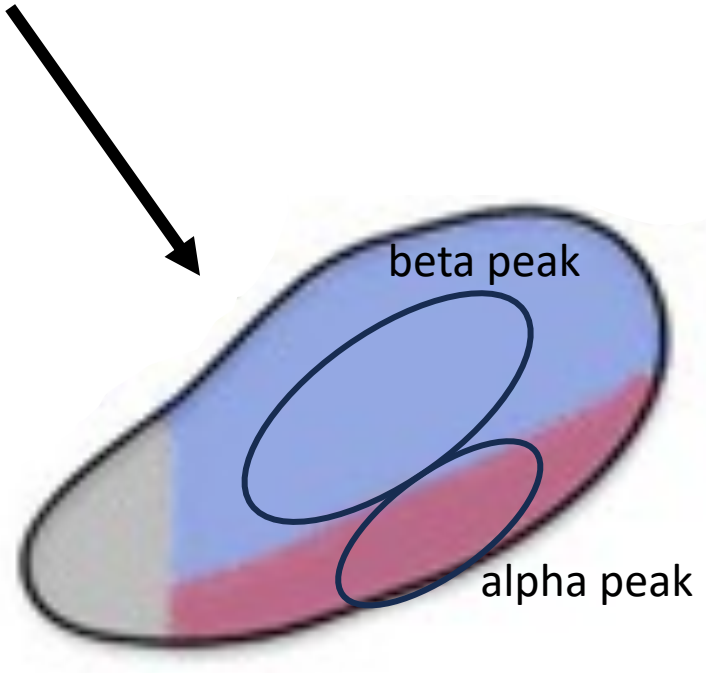
Main locus of **Θ/α band activity in STN** is below the peak for β oscillations (there is also overlap): locus is shifted towards the border with the associative/cognitive part of the STN.

Coherence between STN Θ/α oscillations with several cortical regions such as superior tempora gyrus (Hirschmann et al., 2011, Litvak et al., 2011) and inferior frontal gyrus/premotor cortex (van Wijk et al., 2022).

Cortico-Θ/α band coherence has also been observed between STN and midfrontal regions such as the SMA during tasks involving sensorimotor conflicts and response inhibition (Zavala et al., 2014, 2016).

Alpha-theta oscillations are correlated with a major non-motor symptom in Parkinson's disease: Hallucinations
→ Fosco Bernasconi: next class

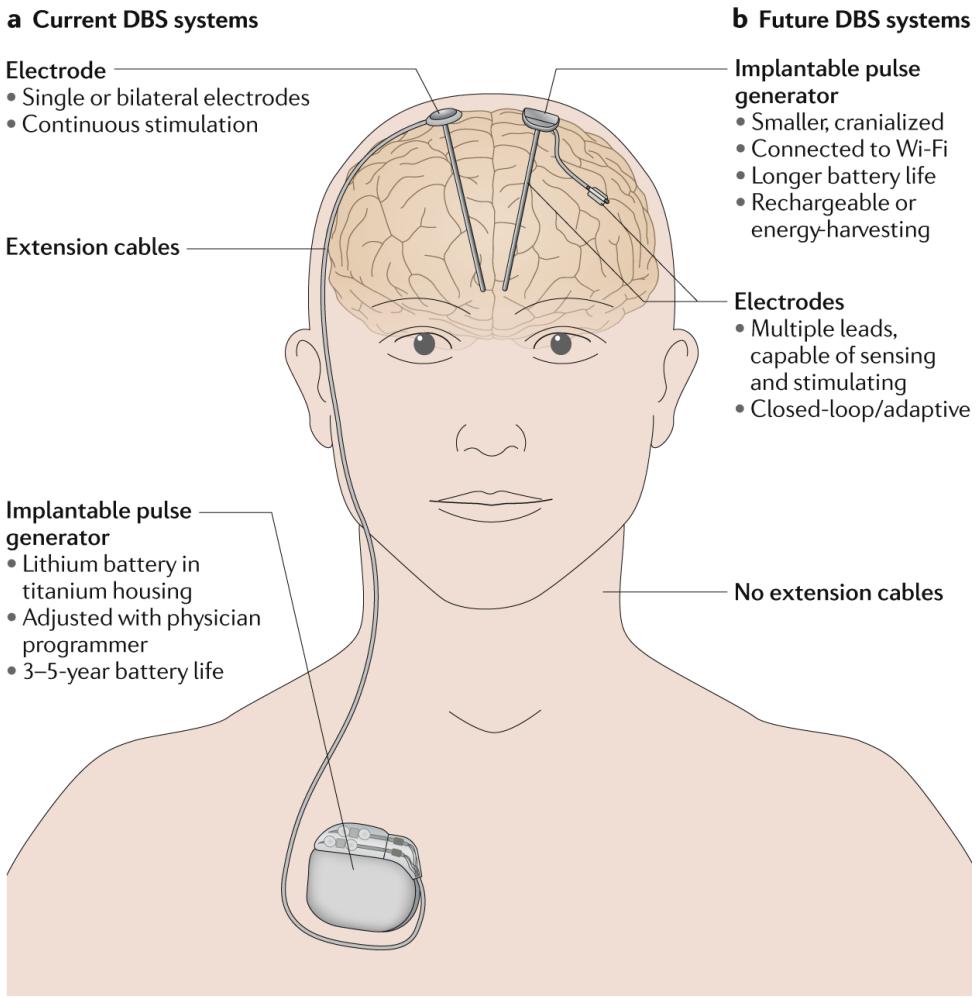
Main location of Θ/α activity in STN is at the border between sensorimotor part and associative/cognitive part) and thus inferior to the dominant β oscillation site



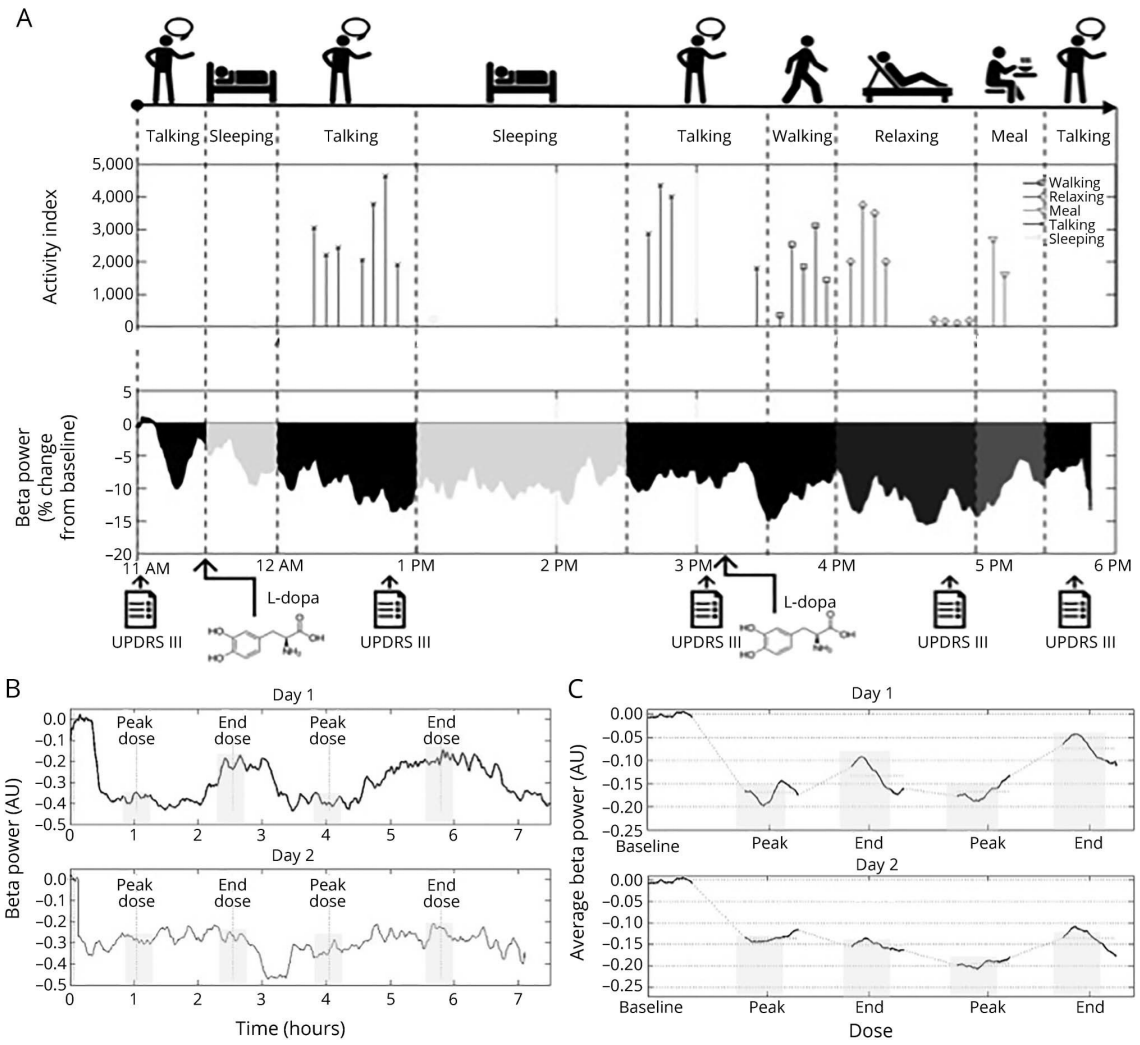
(Horn et al., 2017; Neumann et al., 2023; van Wijk et al., 2022)

Deep brain stimulation

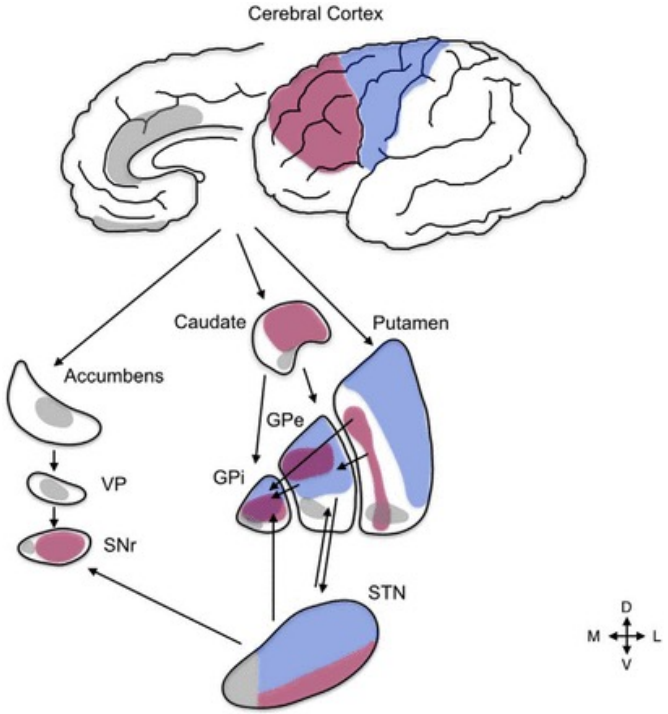
Outlook



NEW: Continuous STN recordings



Application to other diseases & brain systems



Essential tremor (not covered, thalamic DBS: Vim)
Dystonia (not covered, DBS of STN)
Obsessive compulsive disorder (not covered, DBS of anterior limb of internal capsule)
Pain (not covered, DBS of thalamus or M1)
Epilepsy (not covered, DBS of anterior thalamic nucleus, centromedian thalamic nucleus)
Depression (not covered, DBS of subgenual cingulate cortex)
(memory deficits) (not covered, DBS of fornix or in temporal cortex)

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.

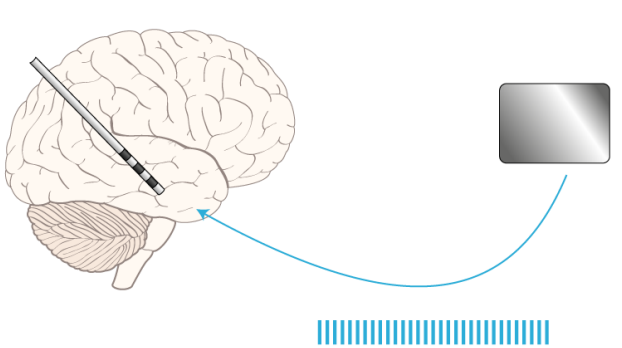
For some patients open-loop DBS does not lead to satisfying outcomes.

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.

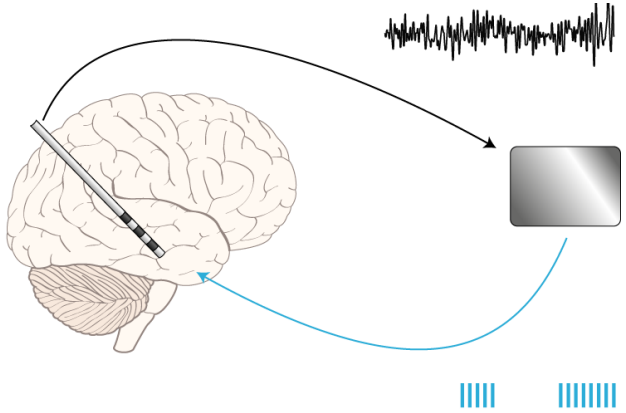
Open-loop DBS (STN)



Only stimulation of the STN

Continuous stimulation of the STN

Closed-loop DBS (STN)



Simultaneous stimulation and recording in the STN

Intermittent stimulation of the 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

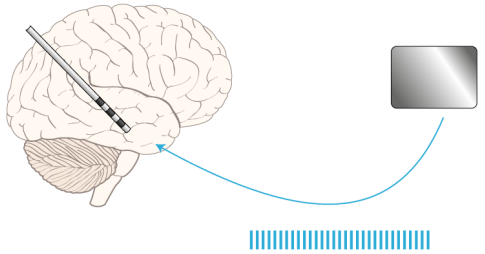
3 different types of closed-loop DBS systems for motor symptoms
1-Beta oscillations (13-30 Hz) in STN (tremor, bradykinesia): when detected DBS is turned ON.

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

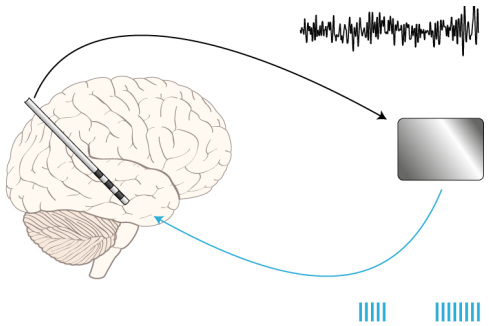
3-Peripheral wearable sensors to detect symptoms (tremor): when detected DBS is turned ON.

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.

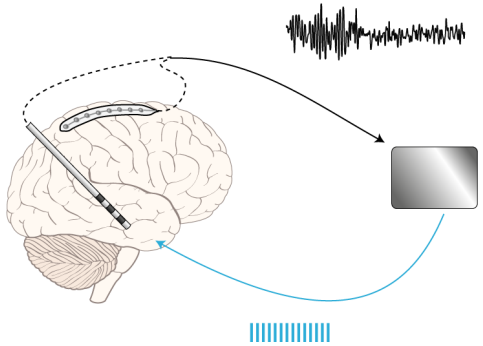
Open-loop DBS (STN)



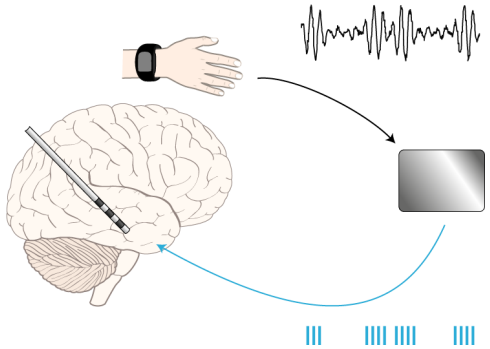
Closed-loop DBS (STN)



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