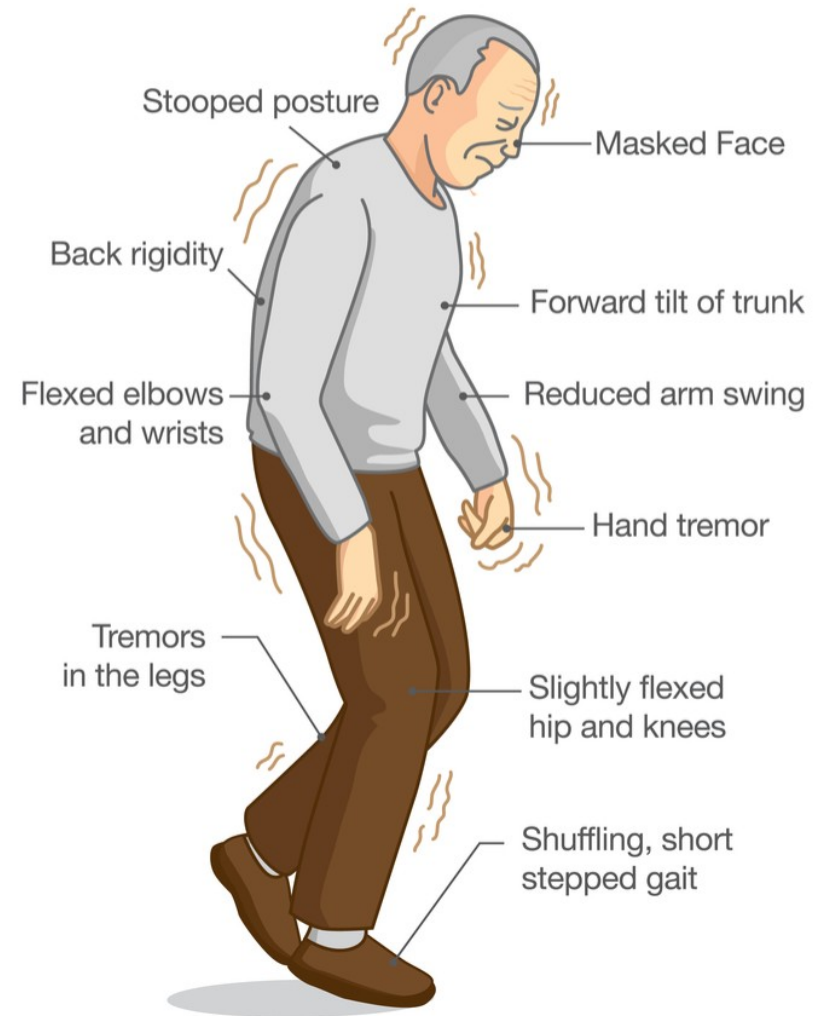


Neuro-X

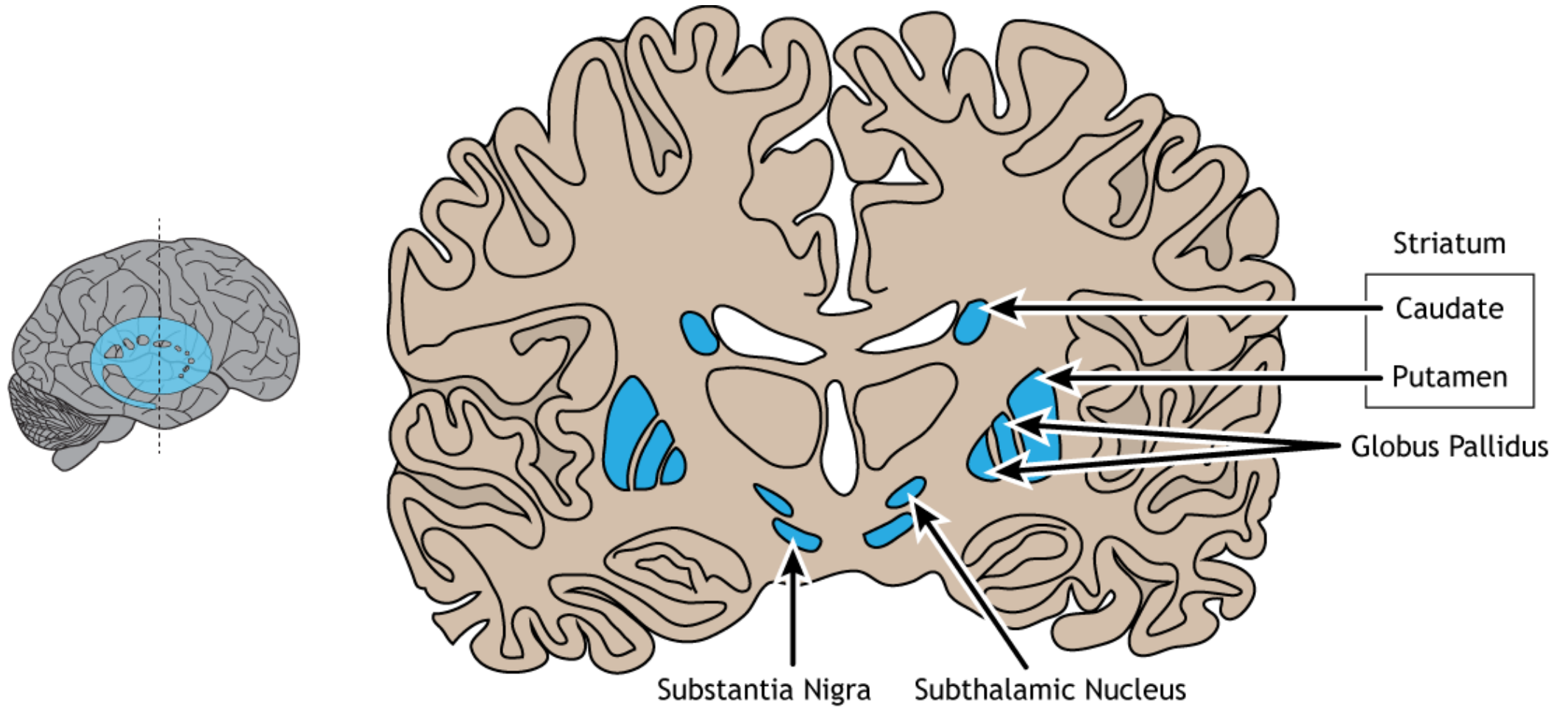
Translational Neuroengineering

Parkinson's disease II

April 30, 2024 // Olaf Blanke



Basal ganglia

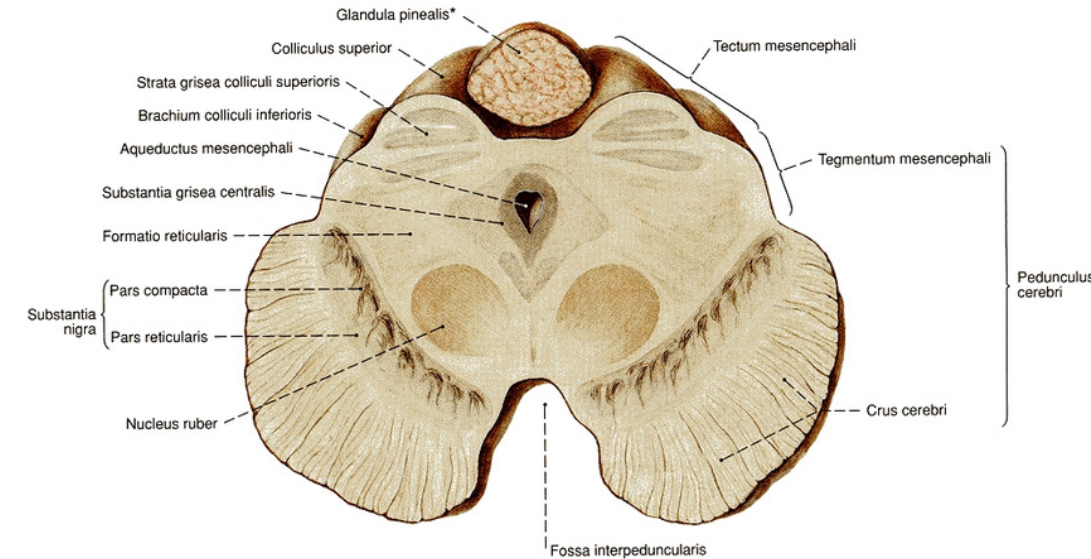
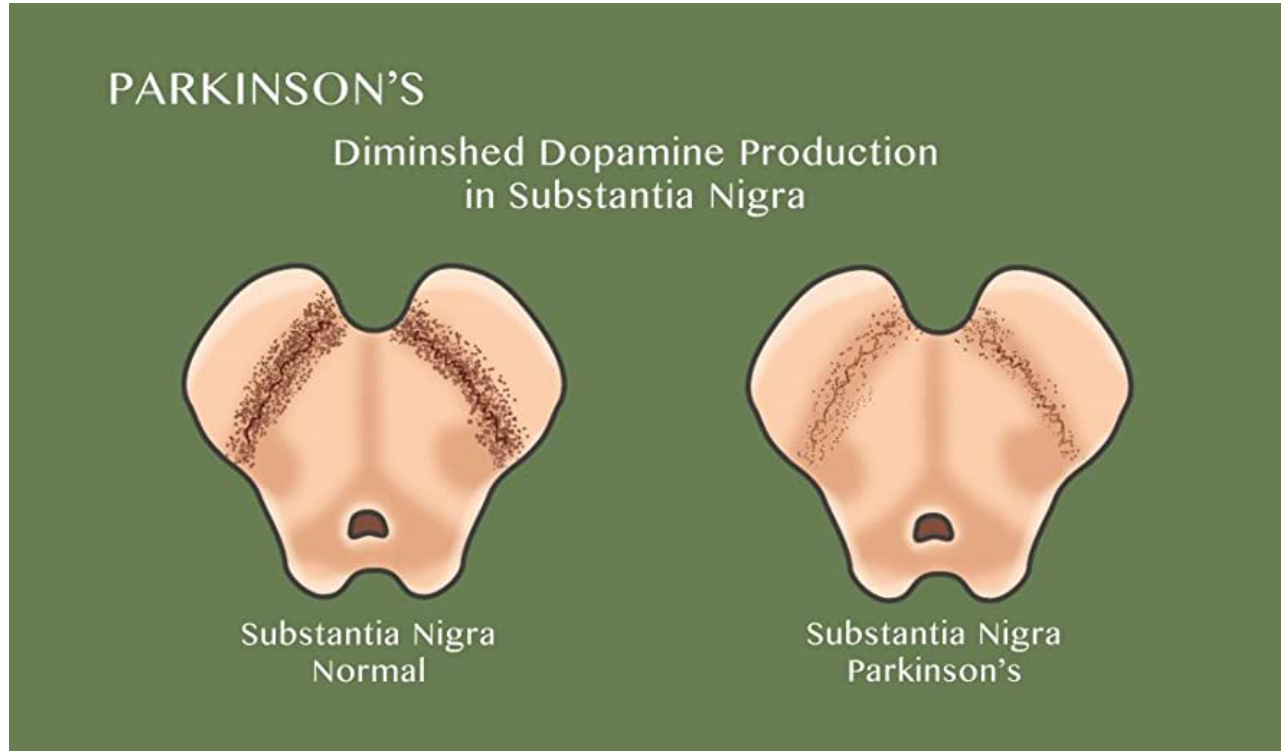


Parkinson's disease

Most characteristically affected brain region ?

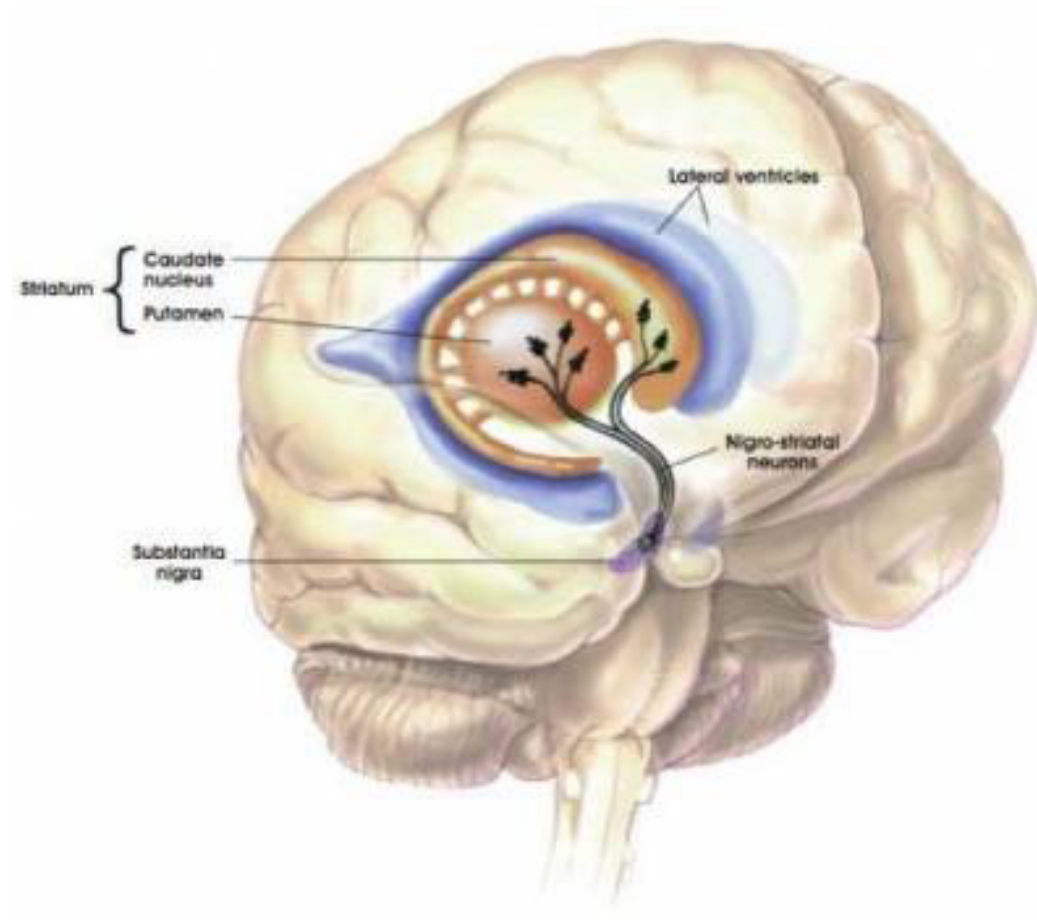
Parkinson's disease

Cell loss in the substantia nigra pars compacta



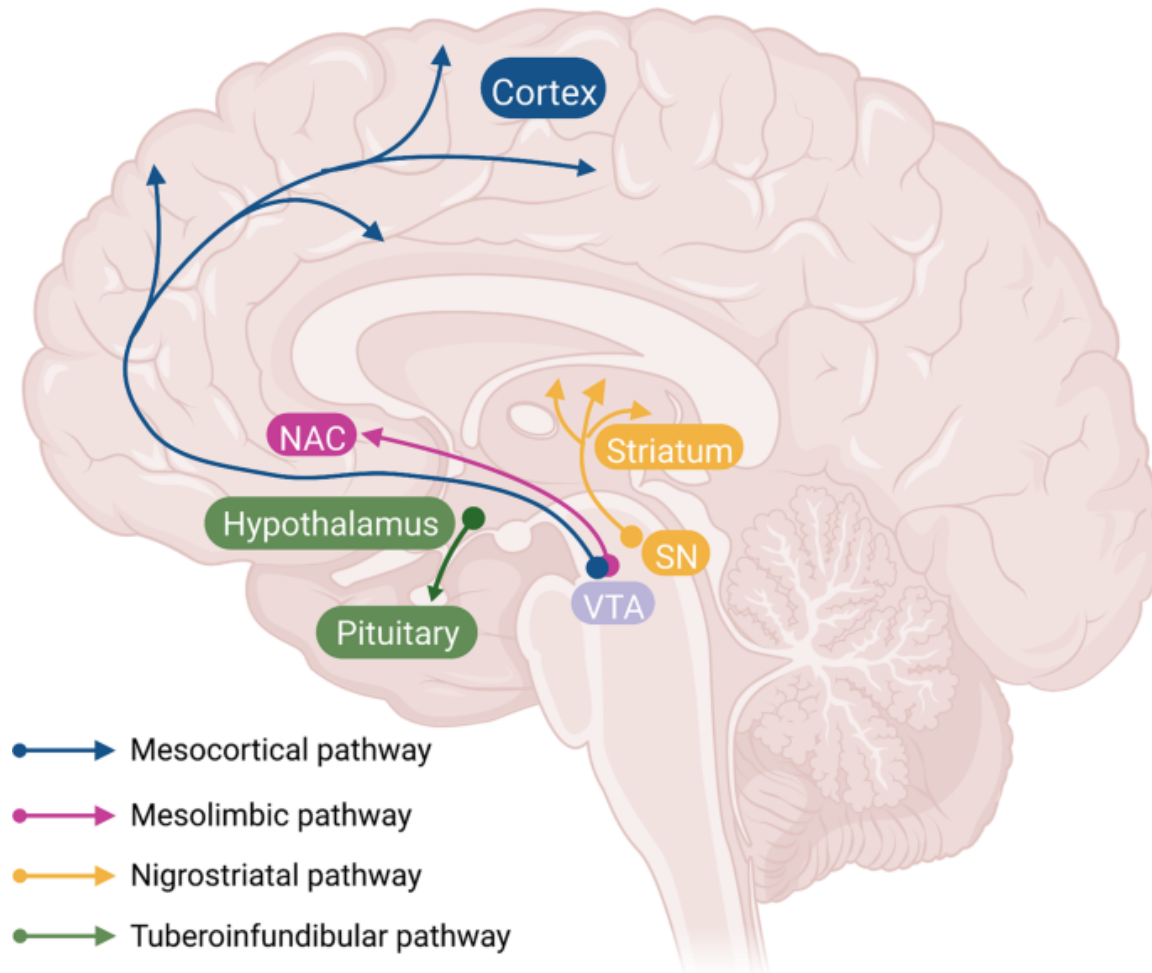
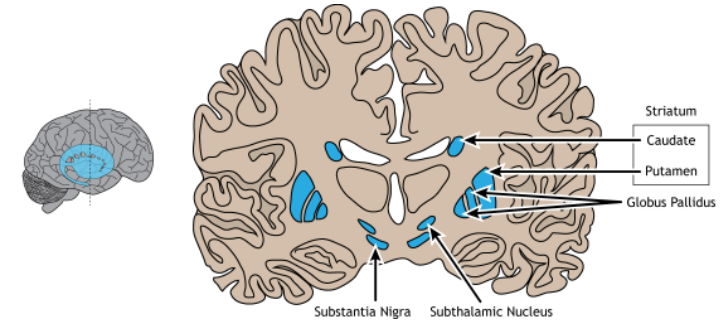
Loss of dopamine neurons affects the Pars compacta of the substantia nigra (not the Pars reticulata of the substantia nigra).

Degeneration of the nigro-striatal pathway



Dopamine & Parkinson's disease

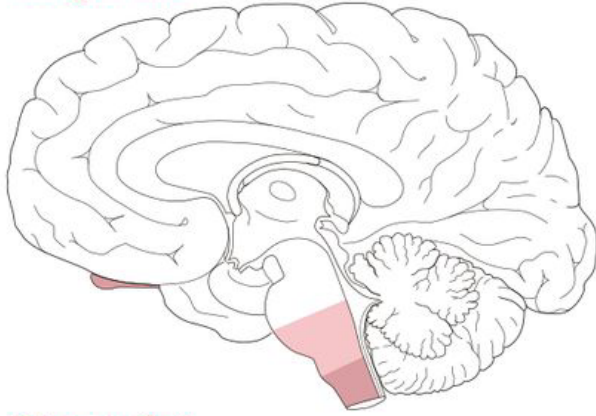
Dopamine pathway in PD



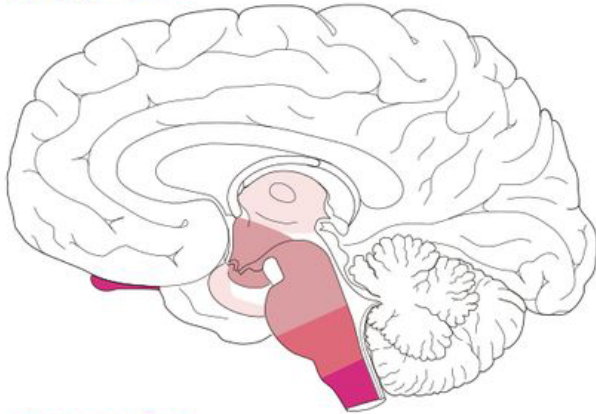
The **nigrostriatal pathway** between substantia nigra and striatum is affected in PD and is the key neuropathological hallmark of PD.

But there are several dopamine pathways.

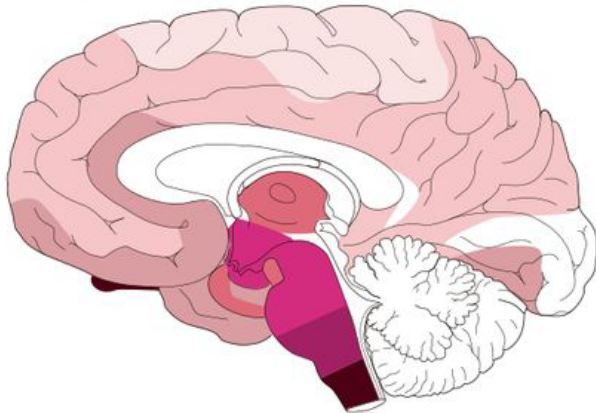
Stages 1-2



Stages 3-4



Stages 5-6



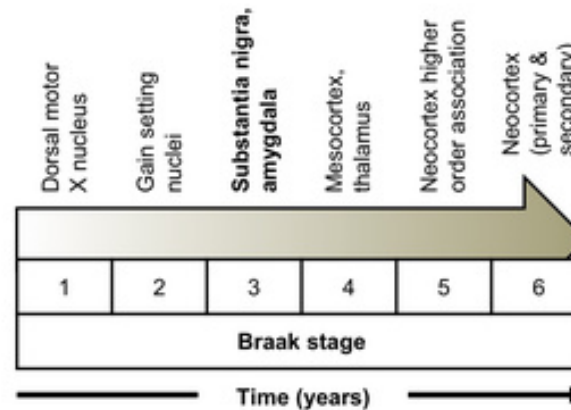
Parkinson's disease

Braak stages

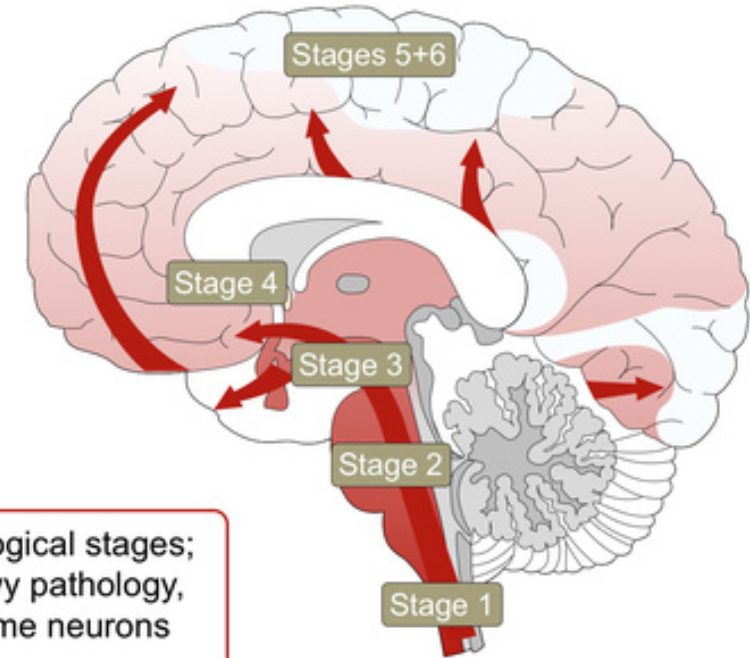
(based on presence of Lewy bodies across the brain)

Braak staging of Parkinson's disease

The ascending pathological process within the PD brain¹



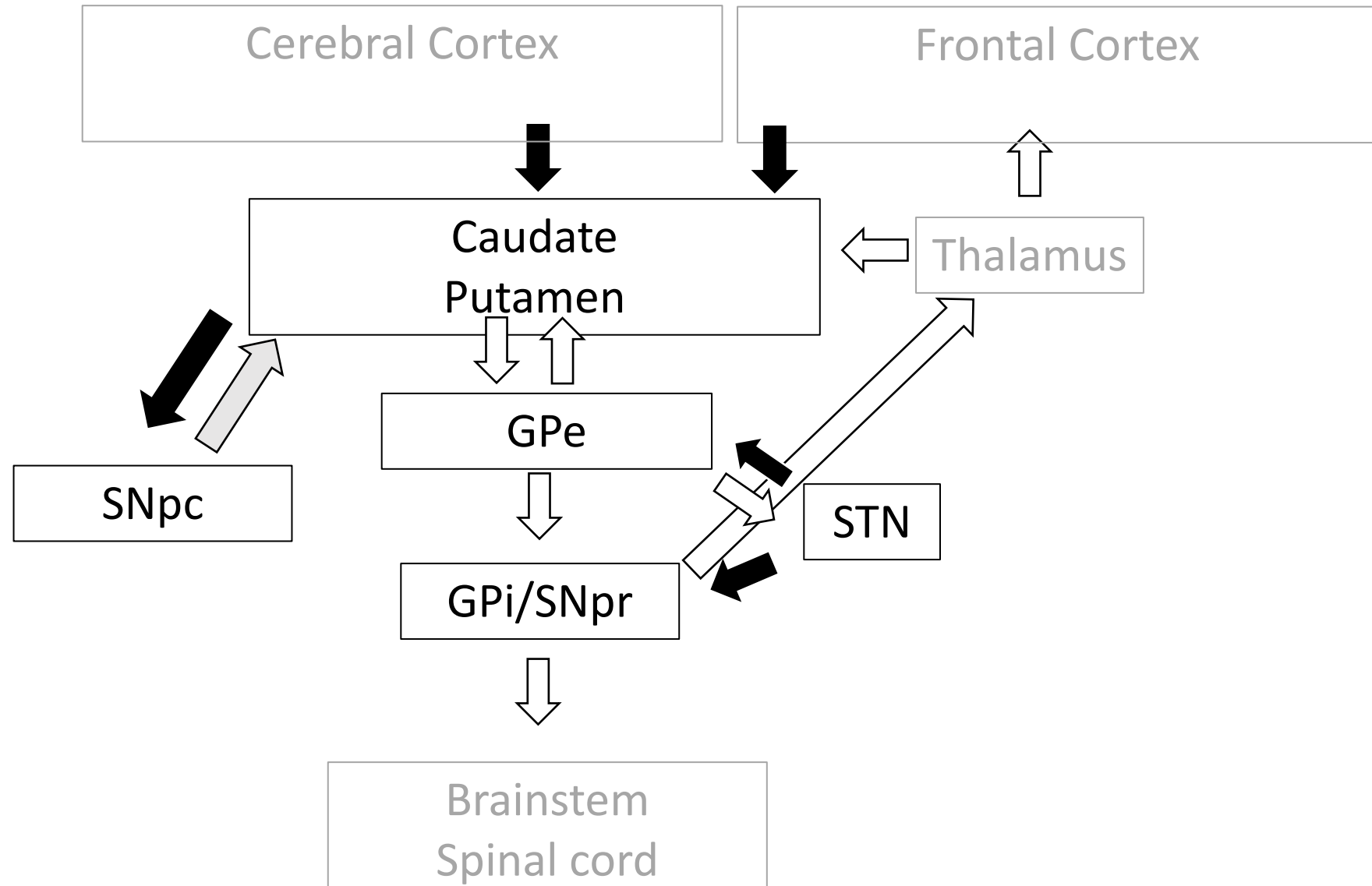
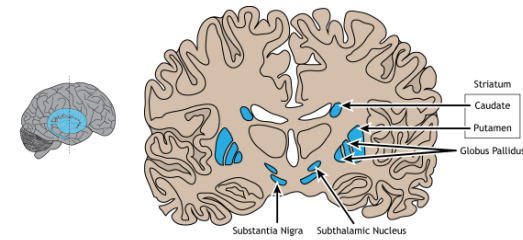
PD is hypothesised to progress in six neuropathological stages; all of the affected neurons eventually develop Lewy pathology, but, despite the presence of inclusion bodies, some neurons survive for a long period of time¹



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

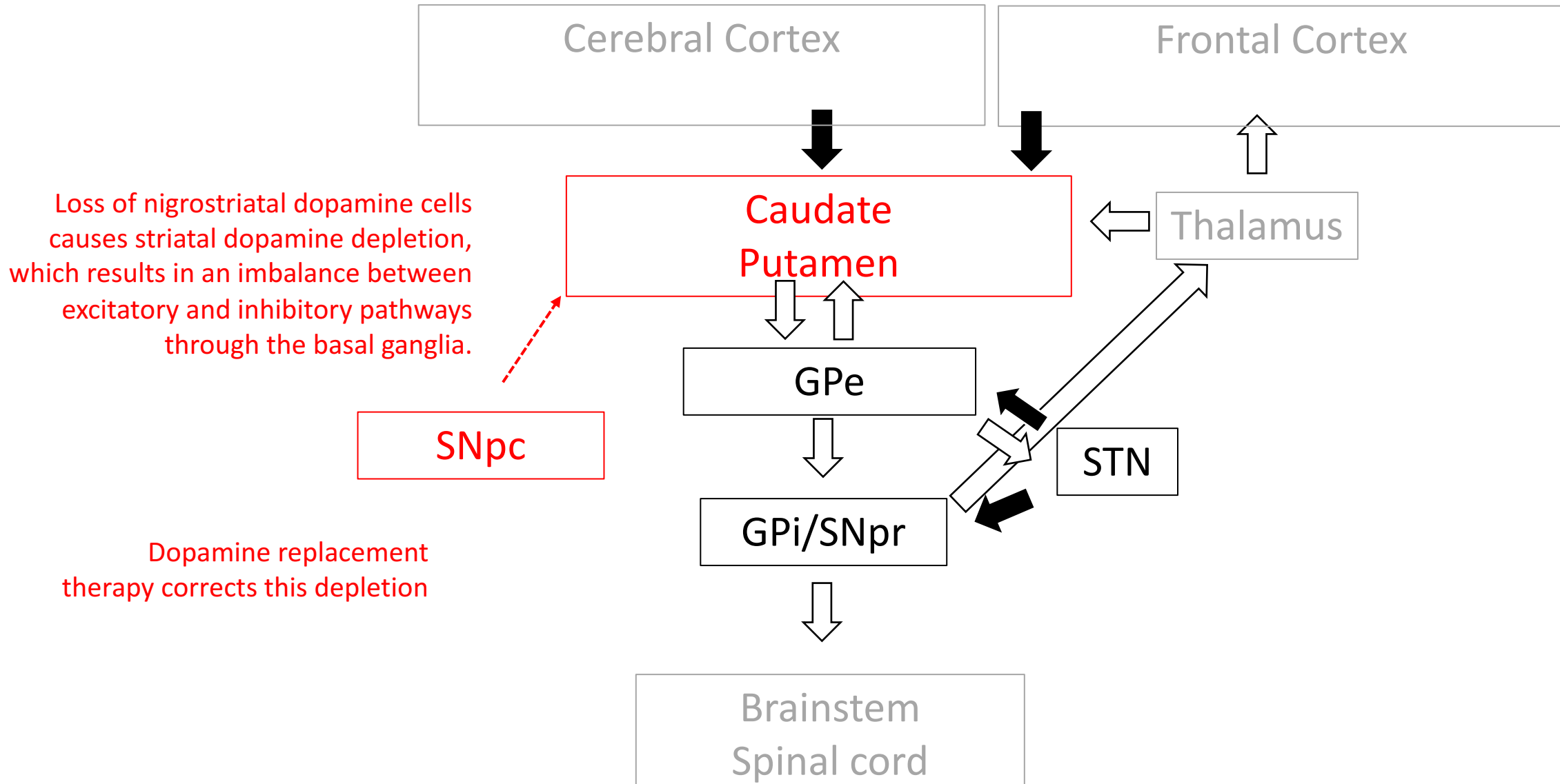
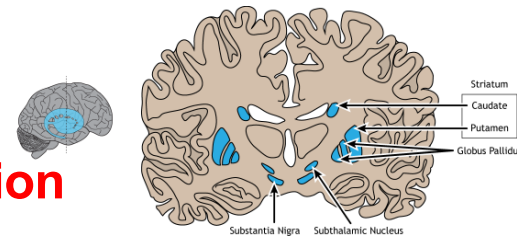
Basal ganglia

Functional circuits for movement control



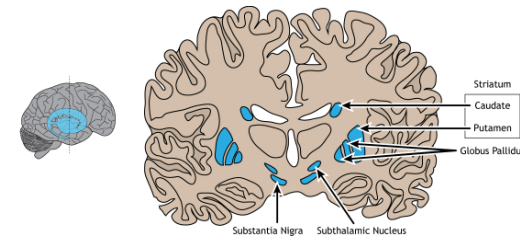
Basal ganglia

Loss of nigrostriatal neurons in PD leading to dopamine depletion in striatum

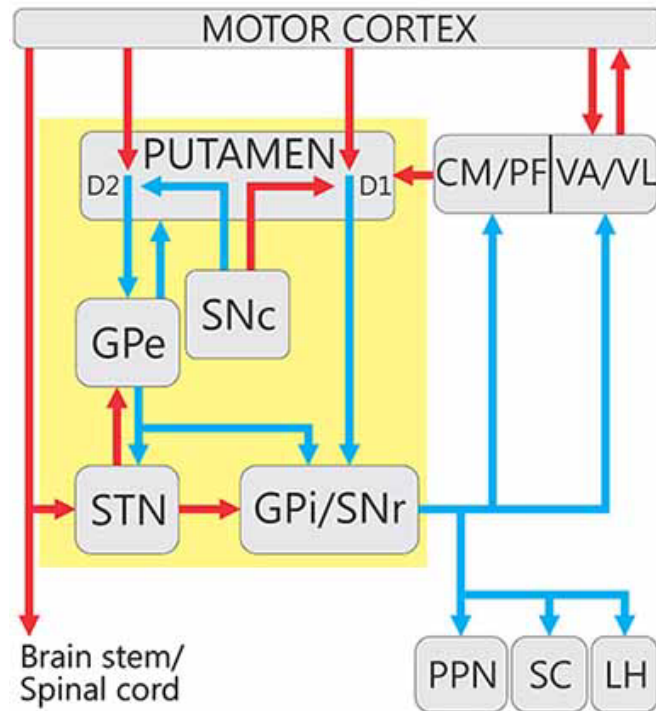


Basal ganglia

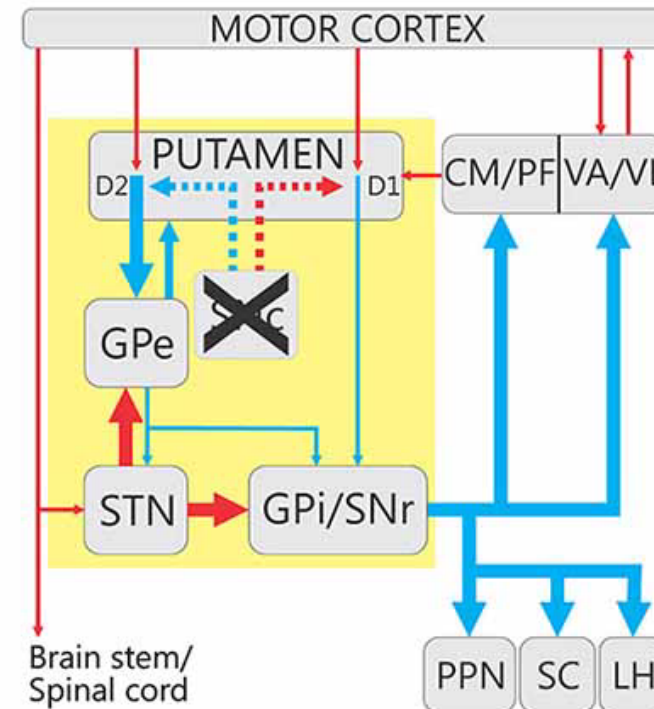
Loss of nigrostriatal dopamine leads to circuit changes beyond SN pars compacta and Putamen





Normal

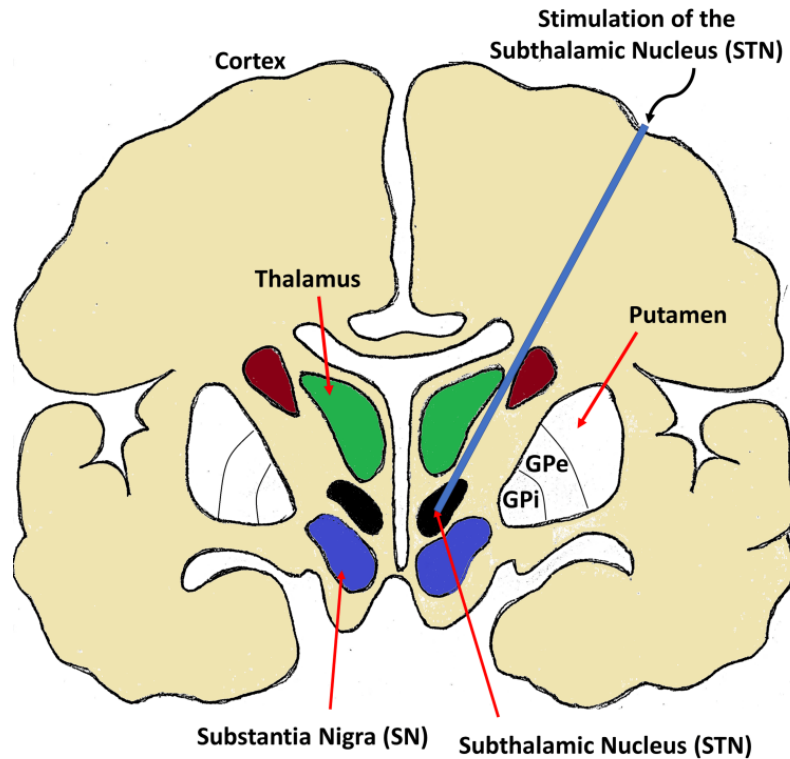


Parkinson's

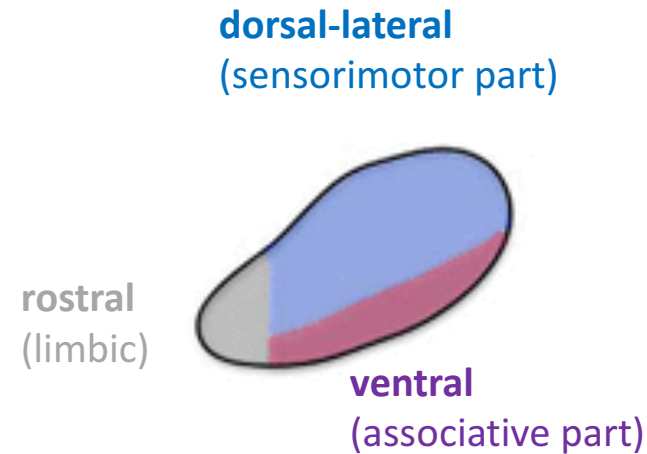


 excitatory
 inhibitory

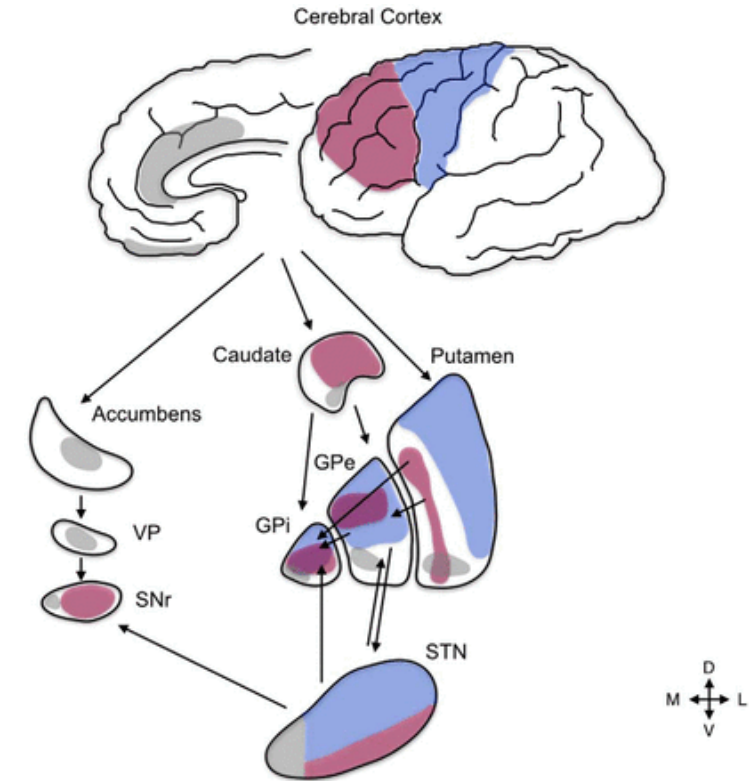
Subthalamic nucleus (STN) as THE target for deep brain stimulation (DBS) for Parkinson's

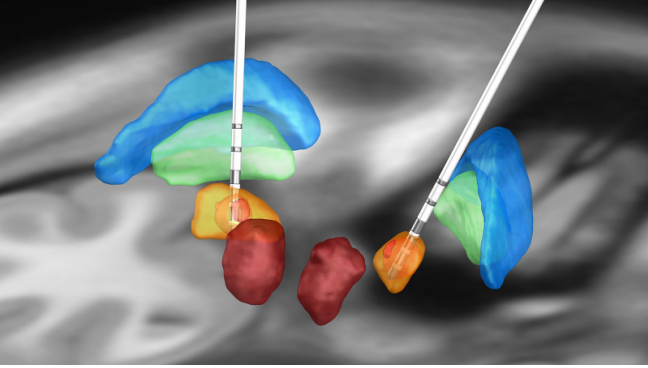


Key structure for deep brain stimulation (DBS) in PD



dorsal-lateral part of STN is targeted for DBS





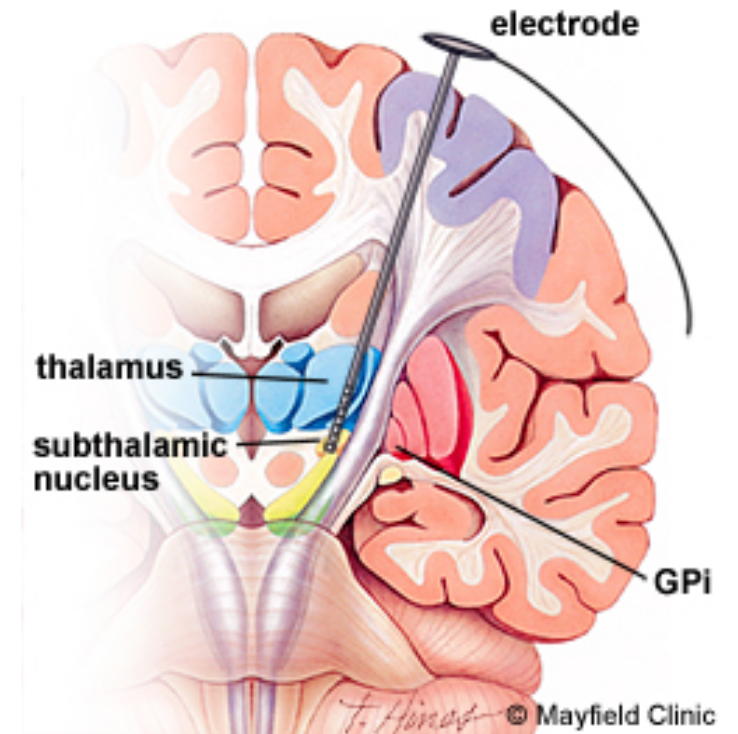
Neurosurgery and Parkinson's disease

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

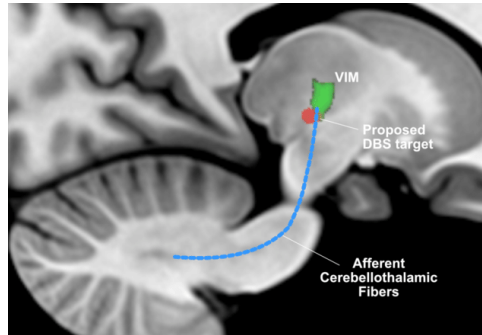
...low incidence of severe disability adverse side effects

DBS neurotechnology was developed ...

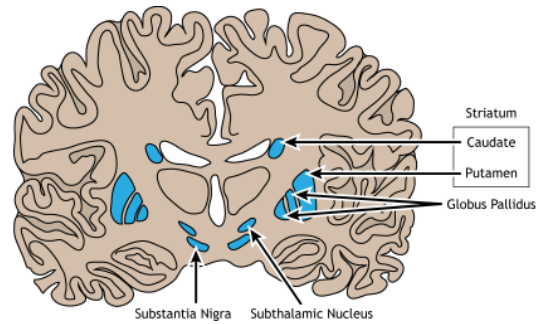
- following surgical approaches and lesions of the basal ganglia in a range of different diseases (mostly psychiatric diseases)
- Advanced understanding in basic animal neuroscience
- some adverse side effects of dopamine replacement therapy (after several years of pharmacotherapy, like dyskinesias,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

Deep brain stimulation (DBS)

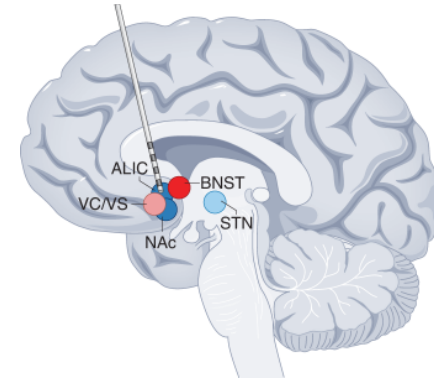
Essential tremor
Ventral intermediate thalamic
nucleus (Vim)



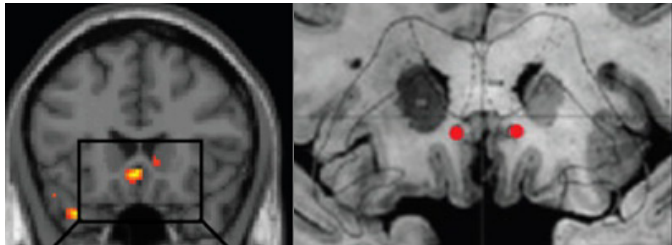
Dystonia
GPi, STN



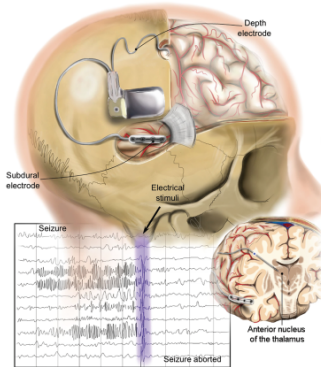
Obsessive compulsive disorder
Anterior limb of internal capsule



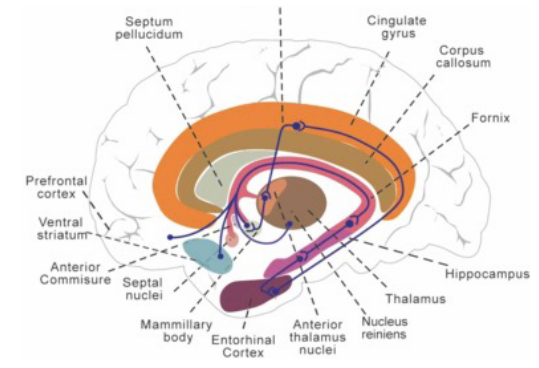
Depression
Subgenual cingulate cortex



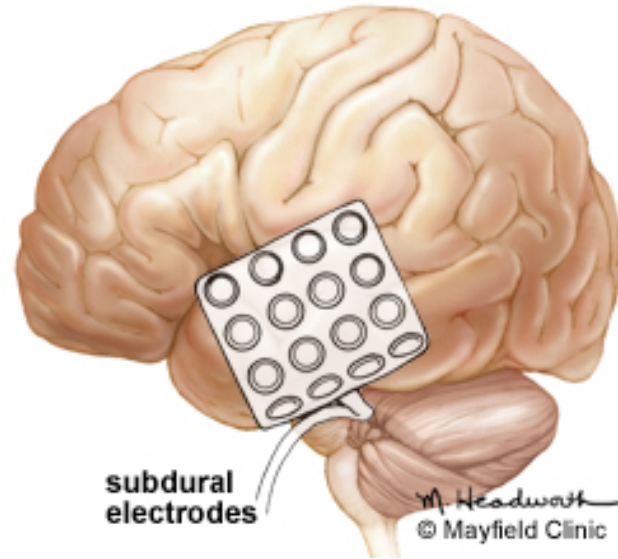
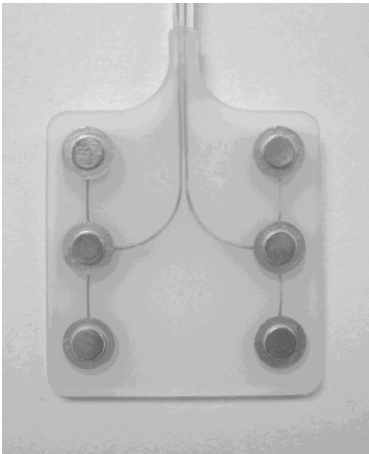
Epilepsy
Anterior thalamic nucleus,
Centromedian thalamic nucleus,
Responsive brain stimulation



Amnesia/Memory
Fornix or in temporal cortex



Electroceuticals



Pharmaceuticals
Digiceuticals

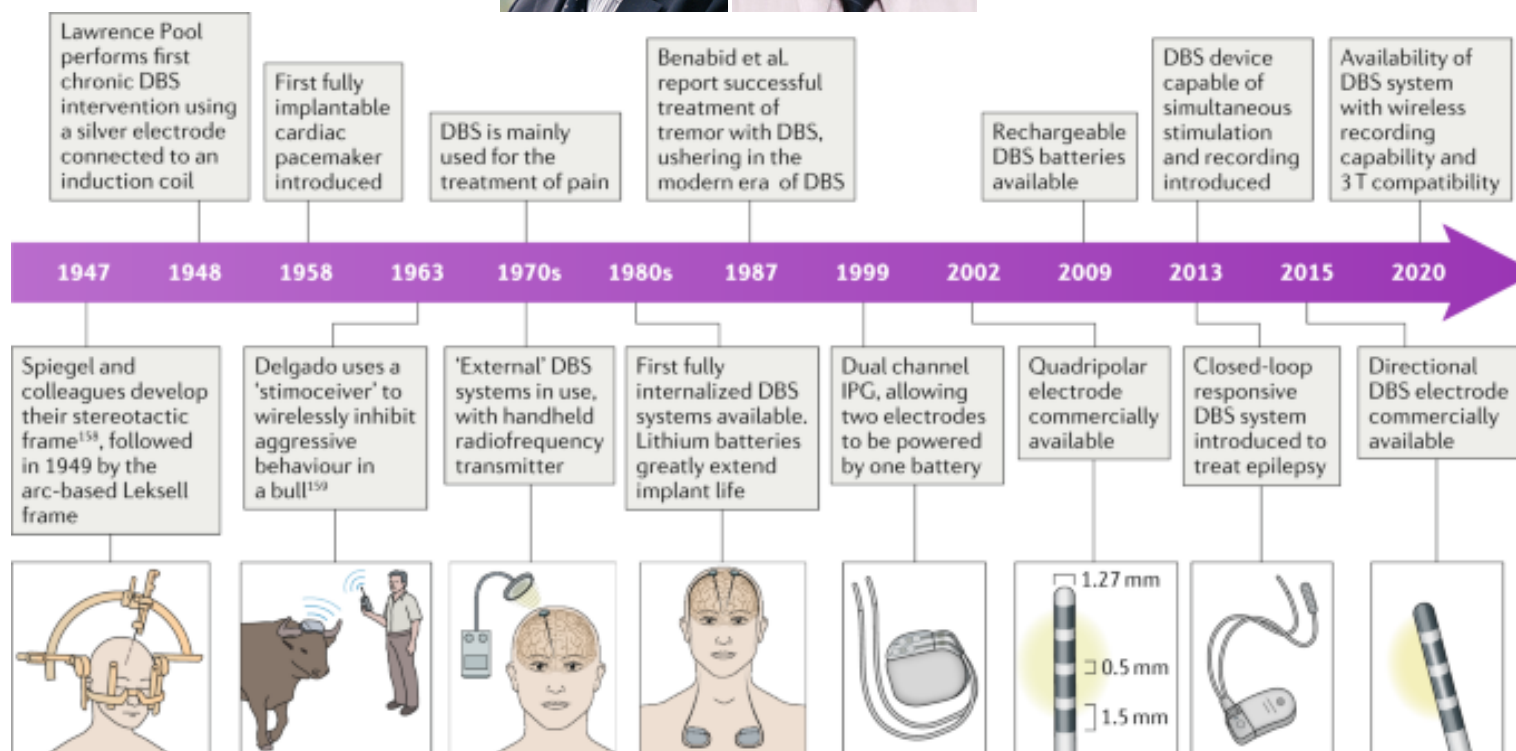
Parkinson's disease & DBS

Deep brain stimulation

History - Medical research



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



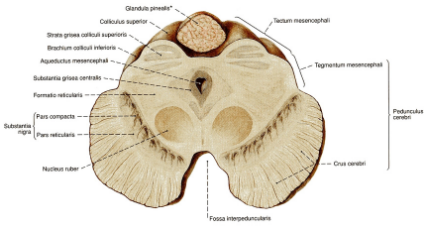
1950s Cardiac
Pacemaker

Modern-current
system since 2002

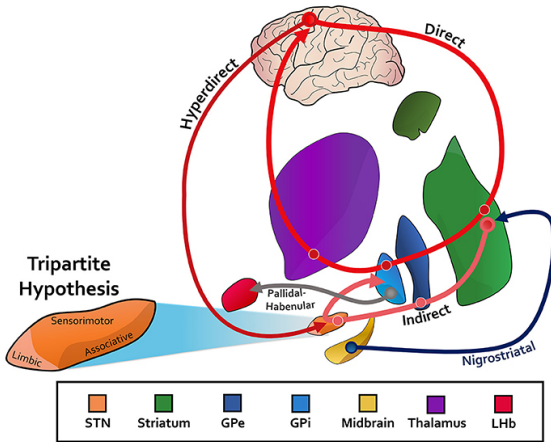
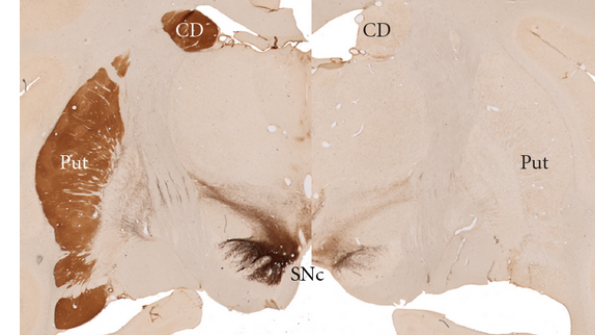
DBS + Recording, adaptive
DBS, since 2013

Deep brain stimulation

History – Animal preclinical research

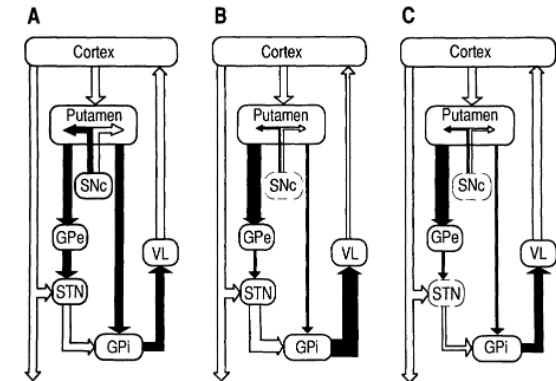


Main animal model of PD described in non-human primates: MPTP (specific neurotoxin) causes selective loss of dopaminergic neurons in SNpc (Burns et al., 1983; Langston et al., 1984).



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

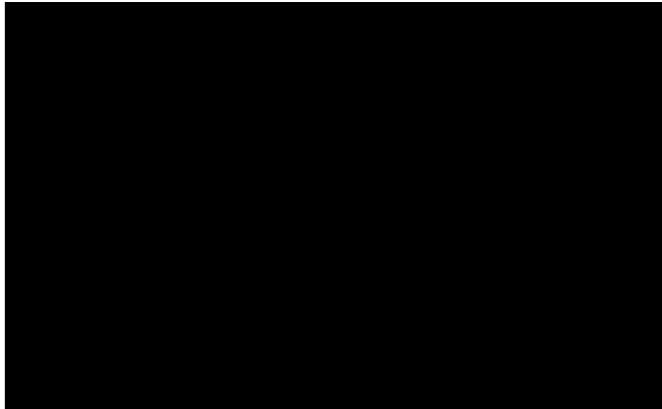


Malon DeLong

Deep brain stimulation

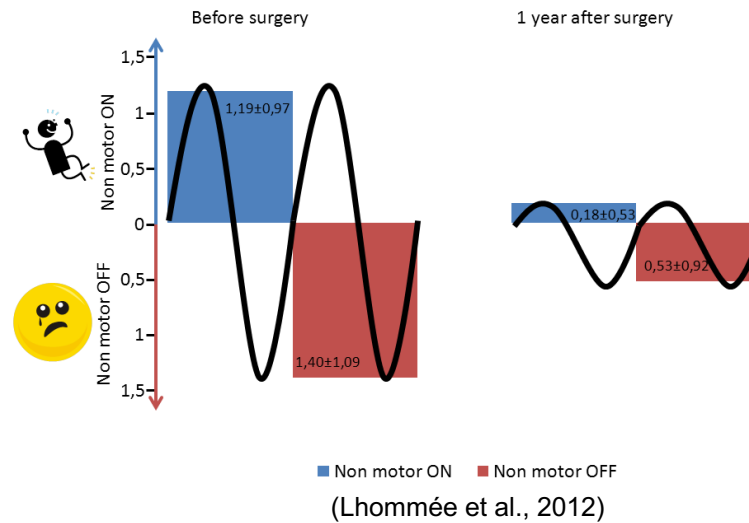
Origins

Levodopa-induced dyskinesias

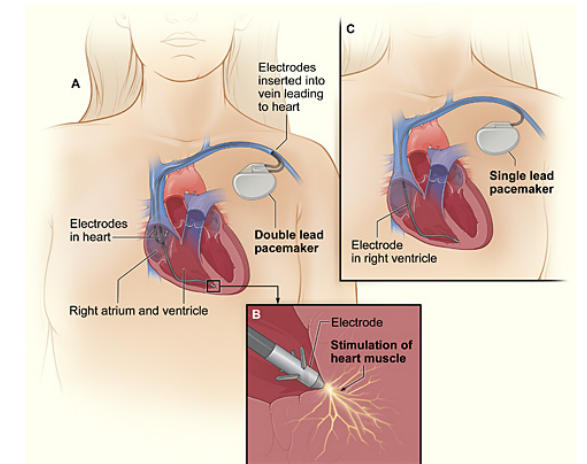


<https://youtu.be/CFhyigIHYKw>

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



Advances in cardiac pacemaker technology



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

Cardiac Pacemaker



- 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)

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

Cardiac Pacemaker

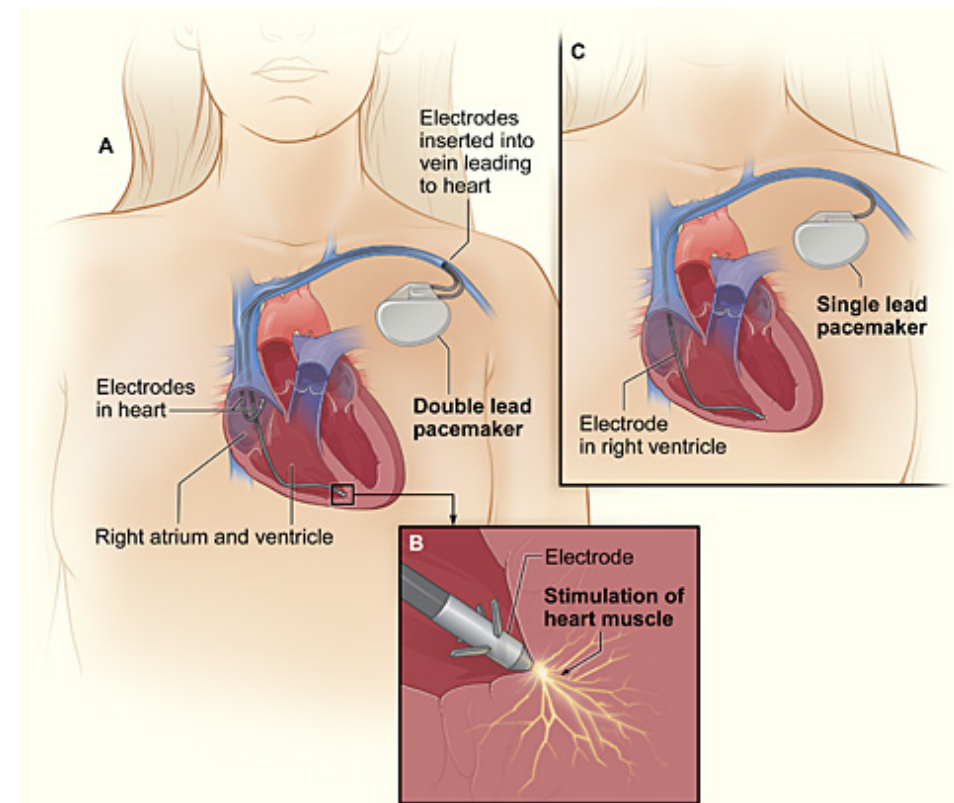
The pacemaker **leads** are thin, insulated wires that carry electrical signals to the heart (stimulation) and record electrical heart activity (monitoring).

Electrodes detect cardiac arrhythmias and the system can also stimulate if necessary (closed-loop system).

Different types of pacemakers may have one or several leads to the heart's atria and/or ventricle.

Tips hold the lead in the cardiac muscle cells (fixation “screws” into the heart muscle).

Pulse generators are relatively small. They contain computerized parts with a battery. Pulse generator “treats” the heart by sending very small amounts of electrical current to the heart through the leads.



EVOLUTION OF PACEMAKER TECHNOLOGY



1958
Weight: 73.4g
Size: 35cc



1981
Weight: 55g
Size: 25cc



1995
Weight: 14g
Size: 6cc

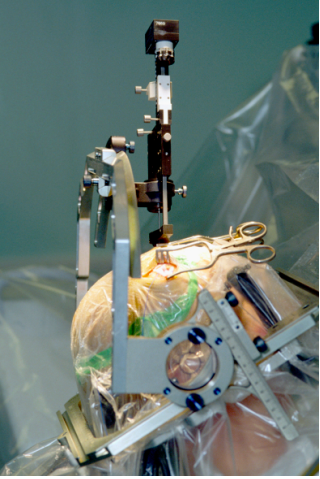


2009
Weight: 23g
Size: 12.8cc



2013
Weight: 2g
Size: 1cc





Deep brain stimulation

overview

Electrodes & Electrode configurations

Electrical pulse generator

Stimulation parameters

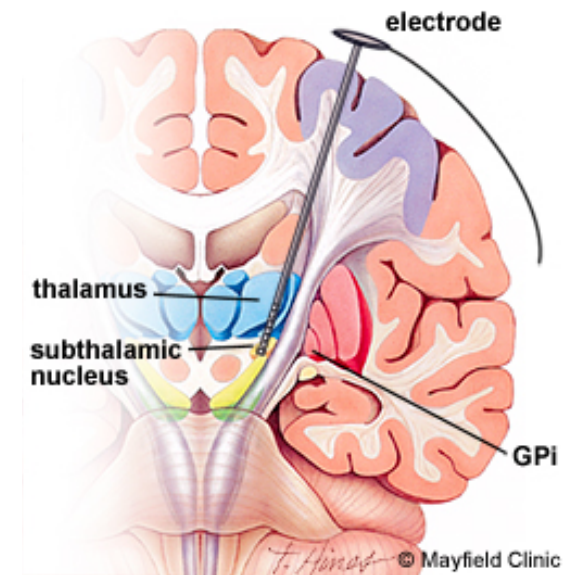
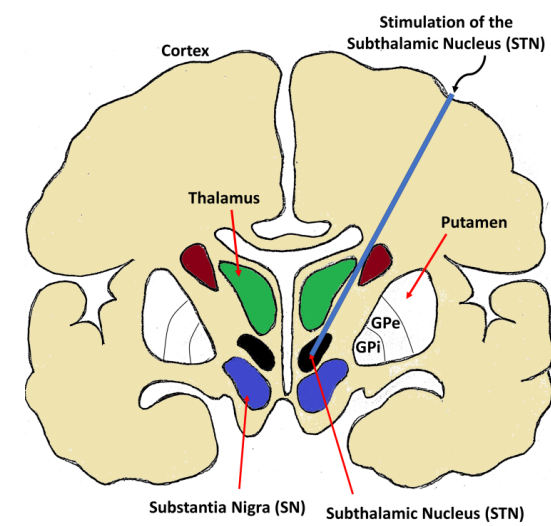
DBS of subthalamic nucleus (STN)

DBS target visualization in STN

STN implantation procedure

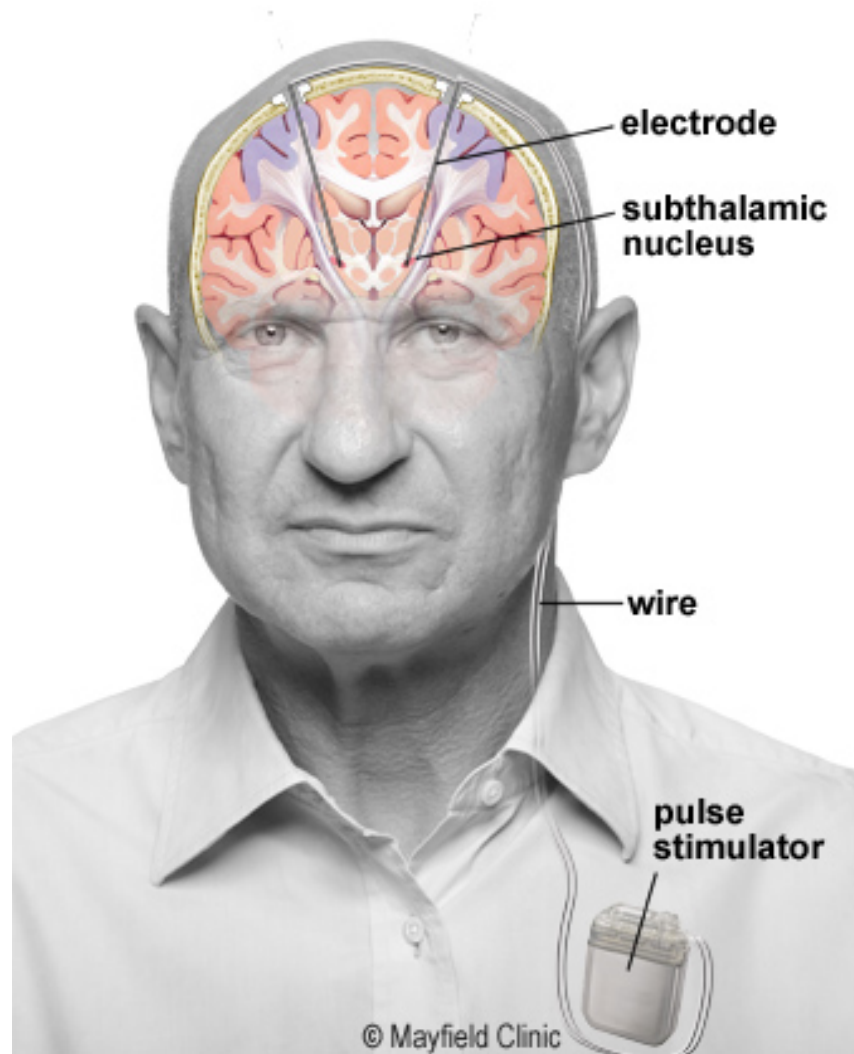
STN sweet spot determination

Volume of tissue activated (VTA)



Deep brain stimulation

3 main components of the DBS system

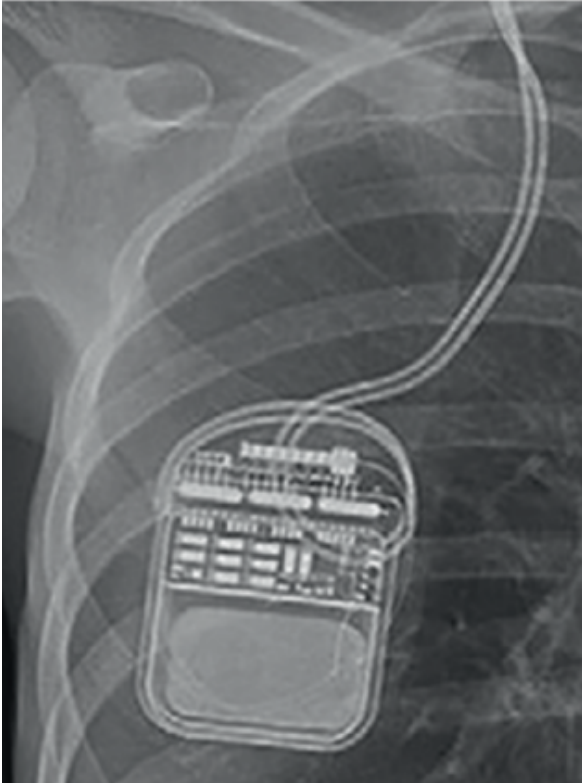


Electrode (with contacts in STN or GPi)

Pulse generator (implanted under the skin, chest area)

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

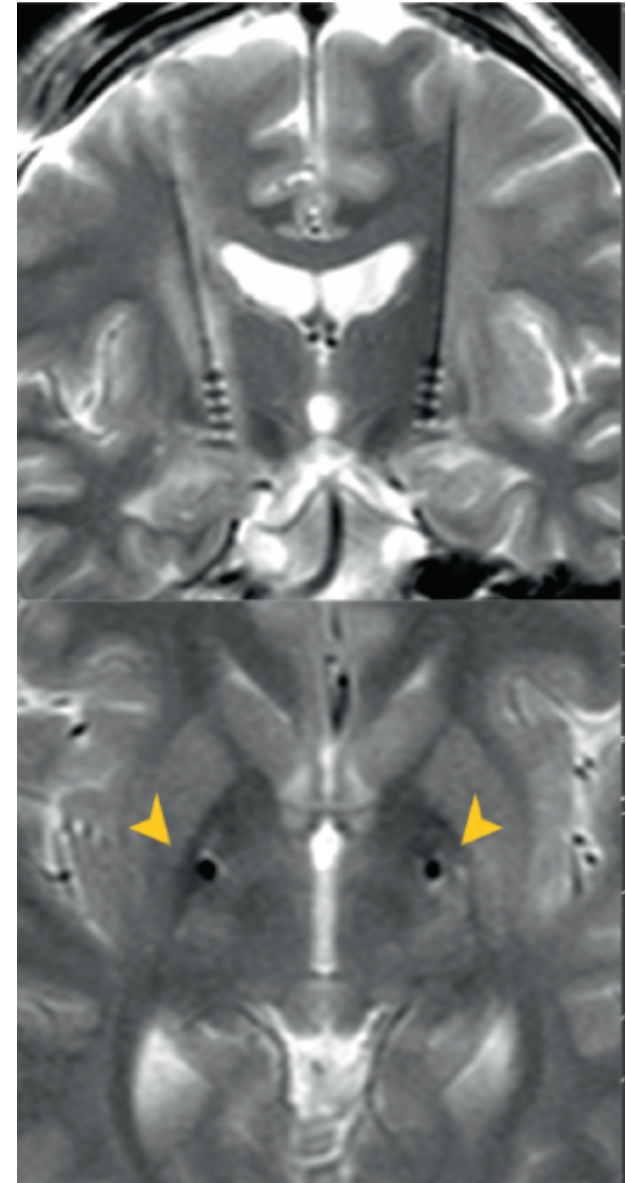
**Chest X-ray (pulse
generator, IPG)**



**Neck/head X-ray
(electrodes, wire)**

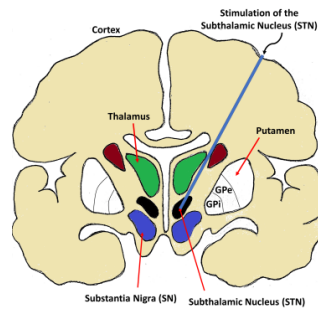


**MRI (electrode
contacts)**



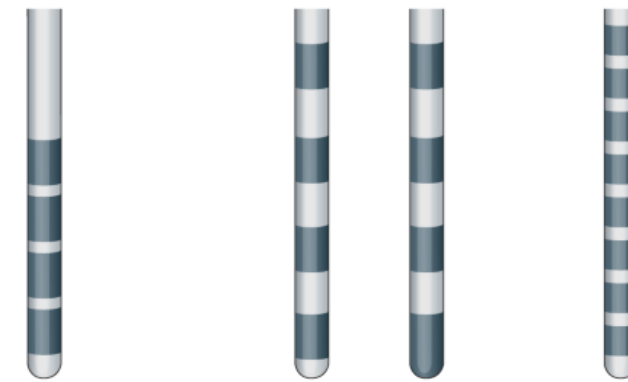
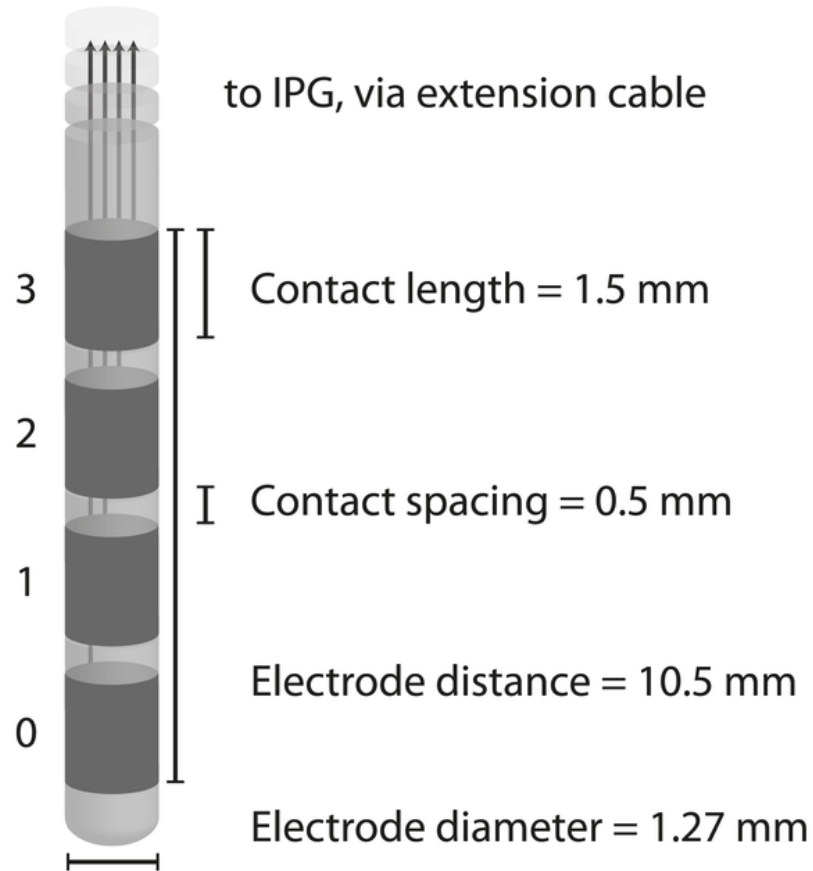
Deep brain stimulation

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



New electrodes with more contacts (experimental)

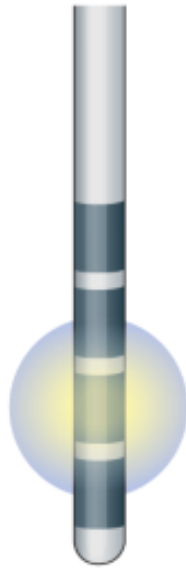
quadripolar electrodes in different configurations

Deep brain stimulation

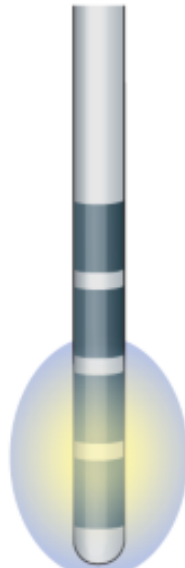
Electrode configurations & stimulation

b Types of stimulation

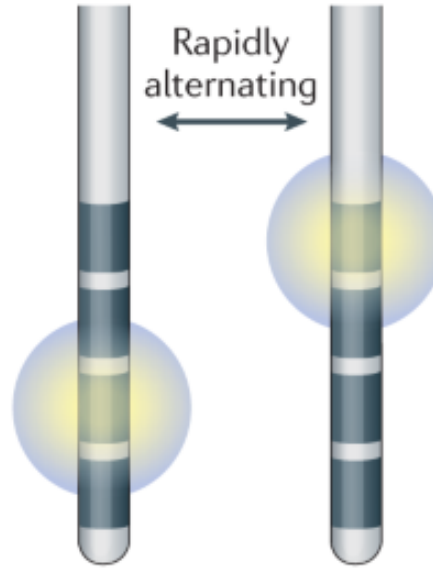
Unipolar



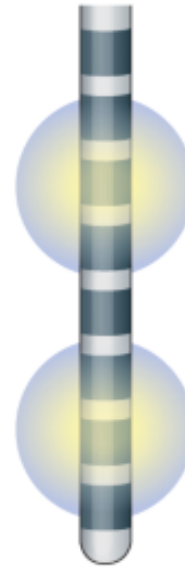
Bipolar



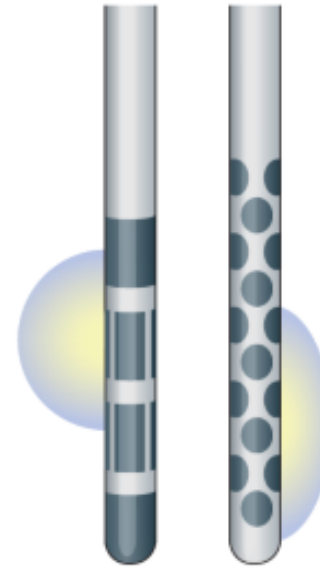
Interleaving



Multiple level

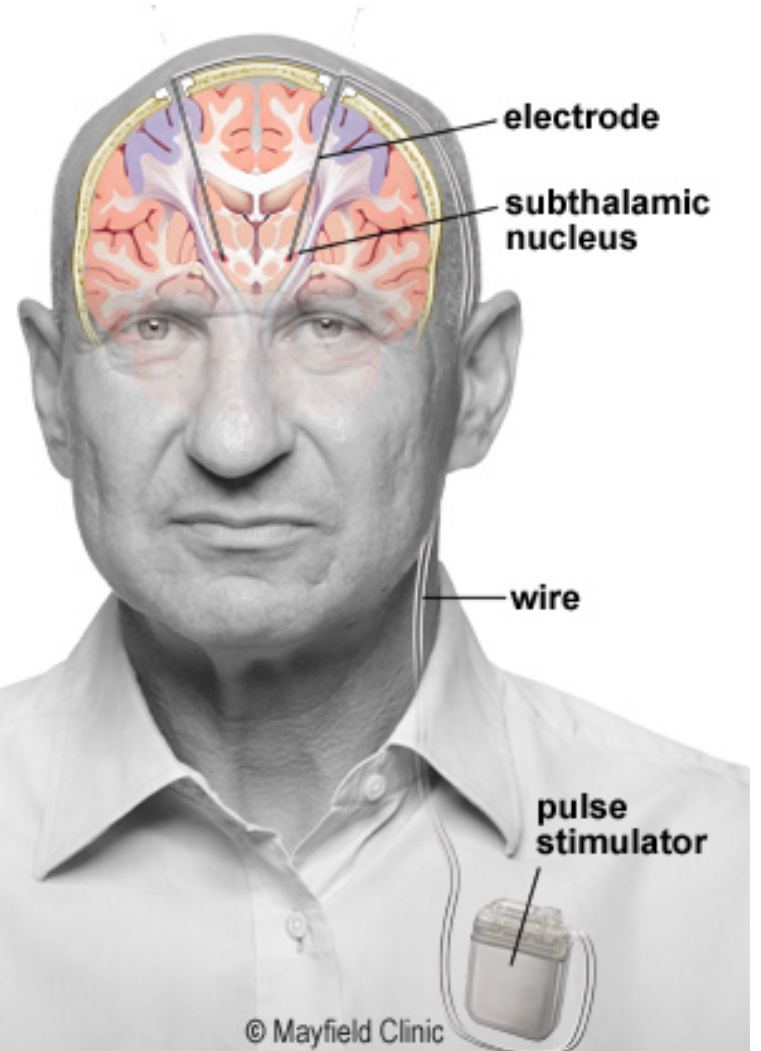


Directional



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

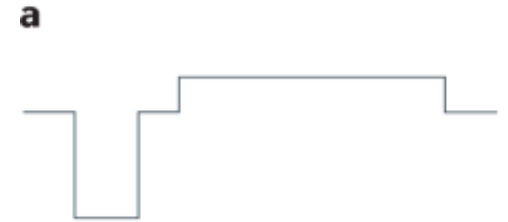
Stimulation parameters

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.

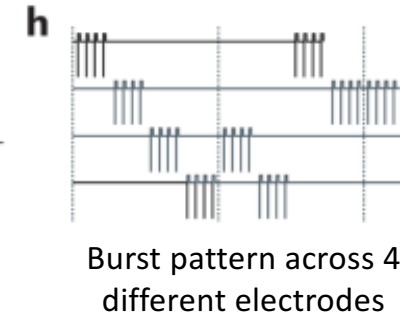
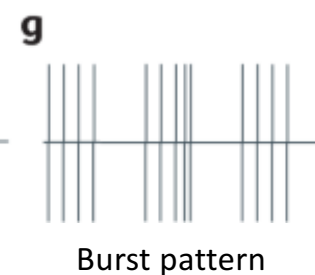
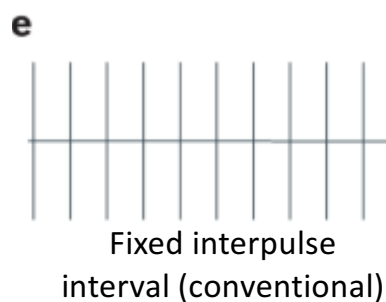
Conventional asymmetric waveform
(less battery drain)



Symmetric waveform
(potentially greater suppression of PD symptoms)



Different temporal patterns of DBS



Deep brain stimulation

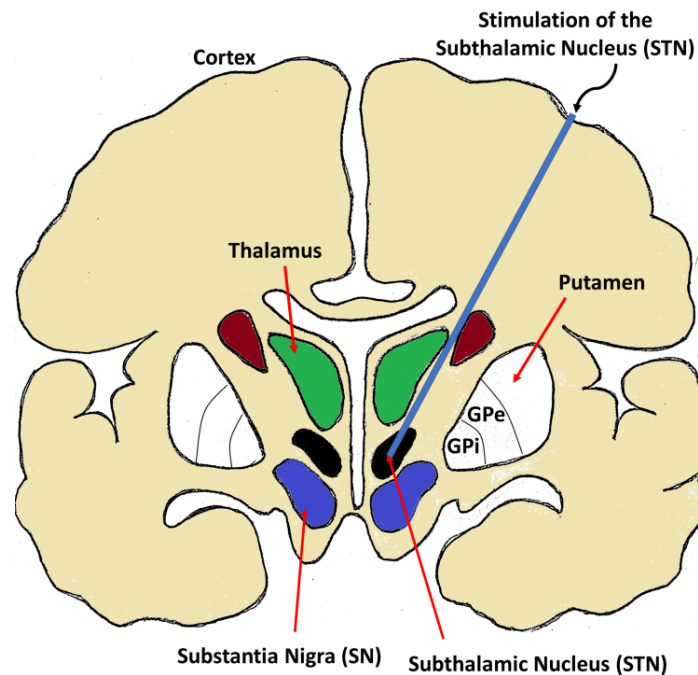
DBS of the subthalamic nucleus (STN-DBS)

STN

Today's class focusses on DBS-STN

Globus pallidus internus

GPe 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.
- 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 also a good candidate to profit from DBS.

Factors not impacting DBS success

Age, disease duration

GPe vs STN

GPe and STN have similar effects for bradykinesia, rigidity, tremor, axial symptoms

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

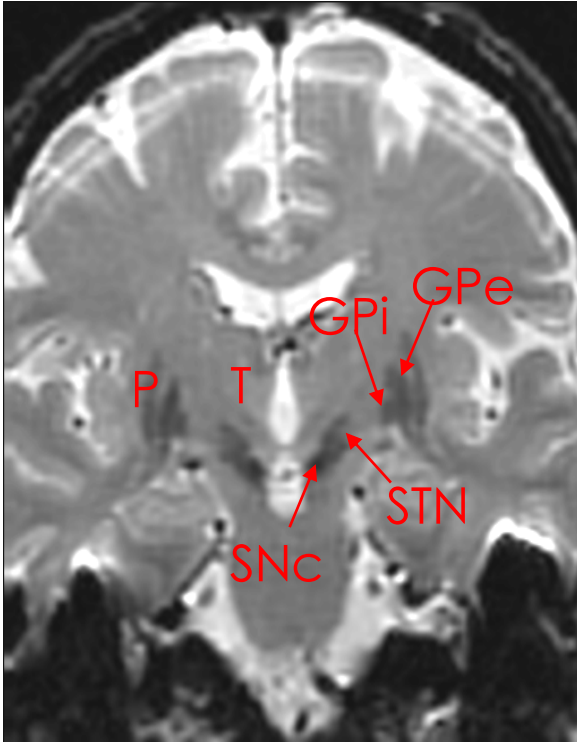
(DBS of ventrolateral thalamus also reduces tremor (essential tremor), but has no effects on bradykinesia or rigidity)

Deep brain stimulation

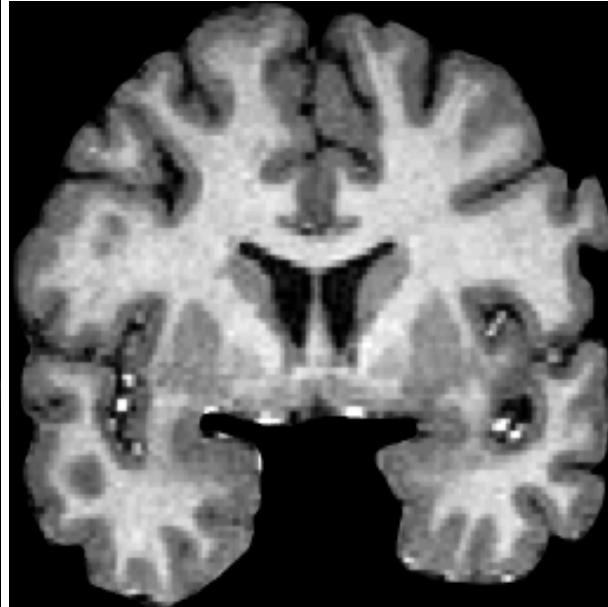
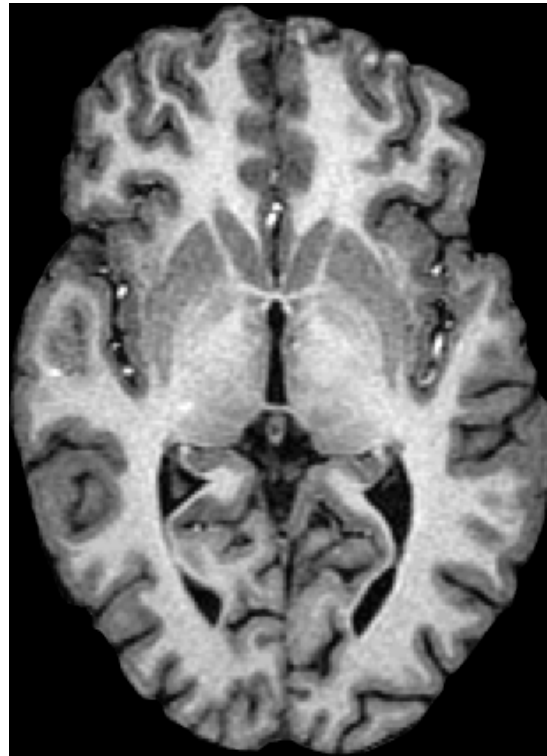
DBS target visualization (STN)

Lead location

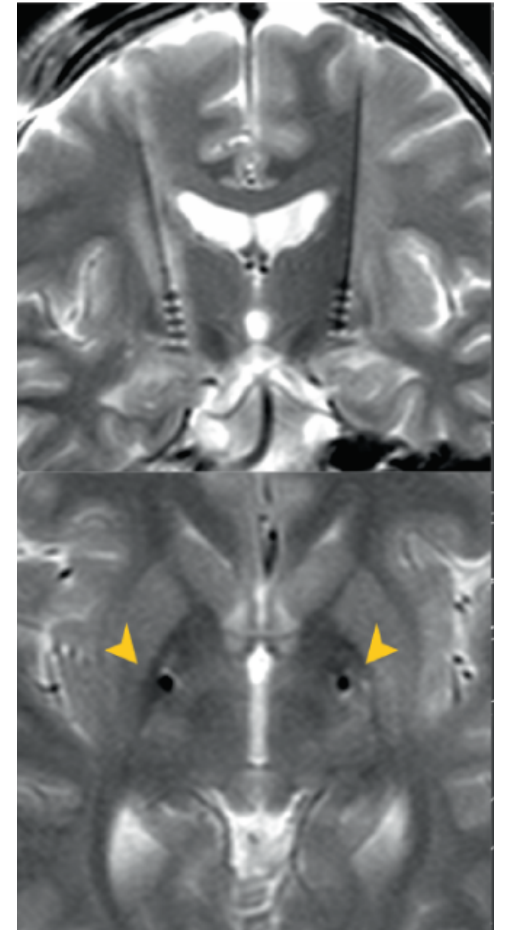
Preoperative MRI



special MRI sequences allow
for better visualization of STN



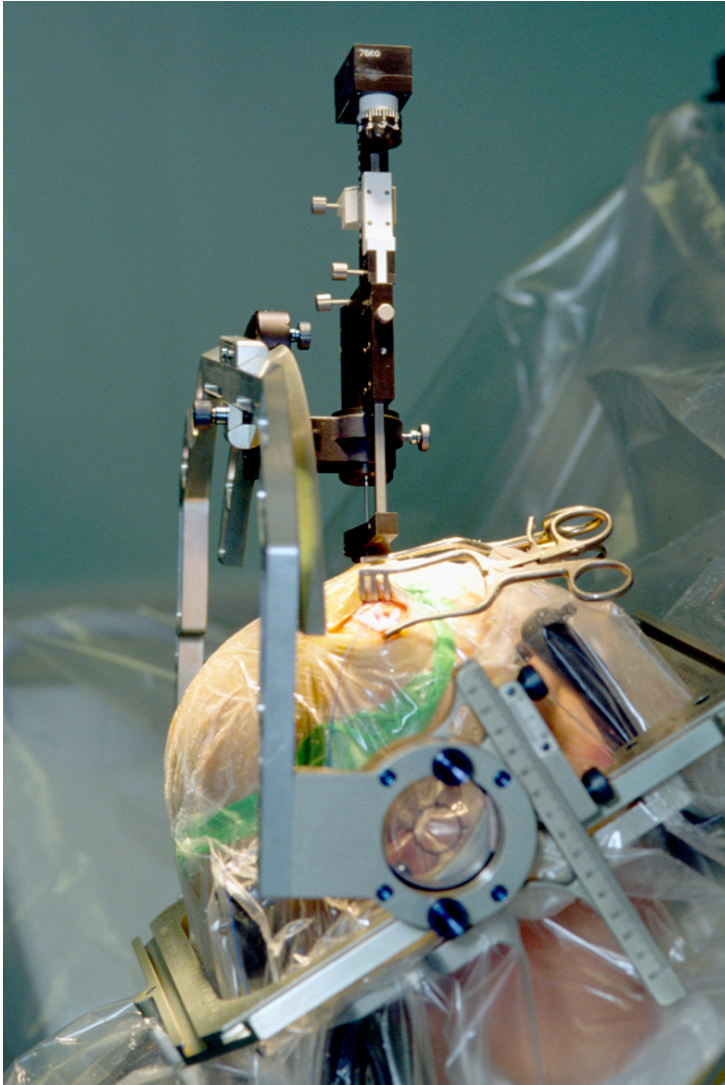
Electrode lead location
based on MRI artefact



Postoperative MRI

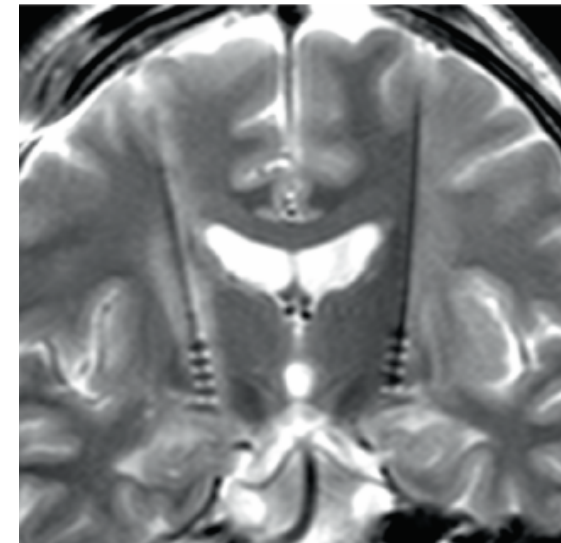
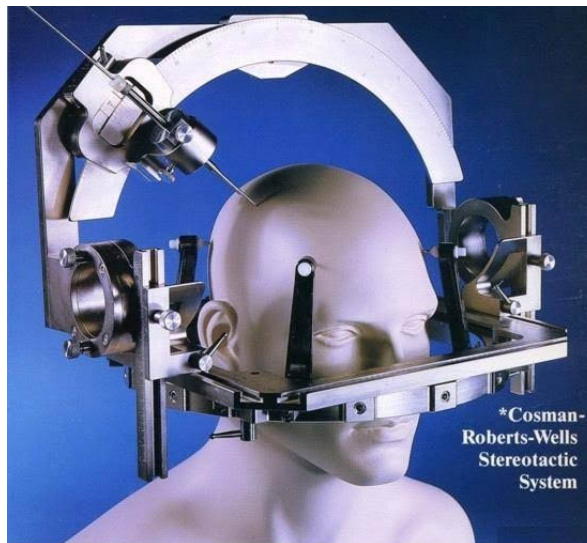
Deep brain stimulation

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 (“sweet spot”)
- effects are tested on tremor and on bradykinesia, also by electrophysiological mapping

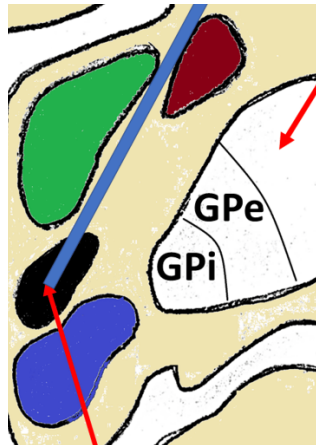
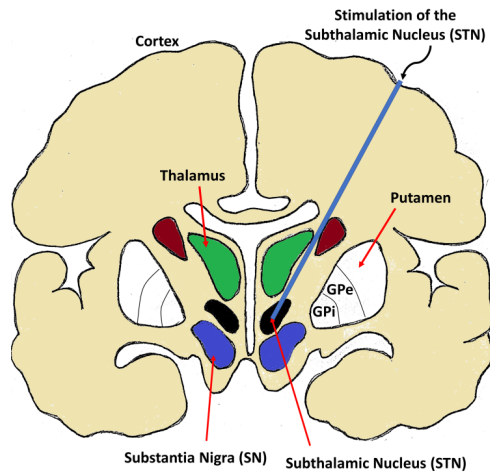


Deep brain stimulation

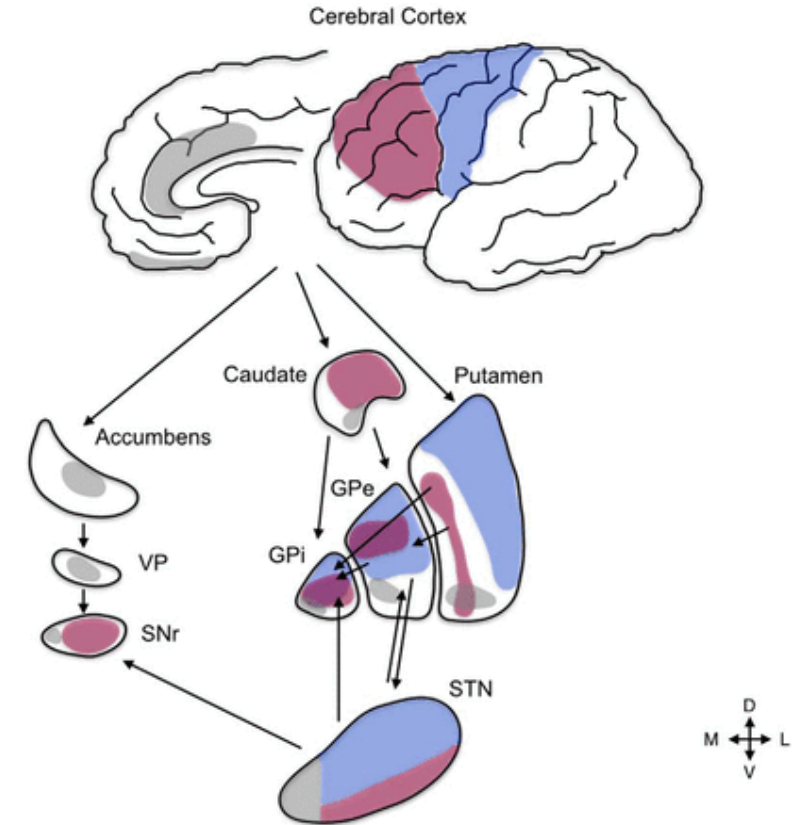
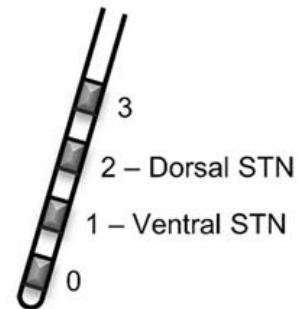
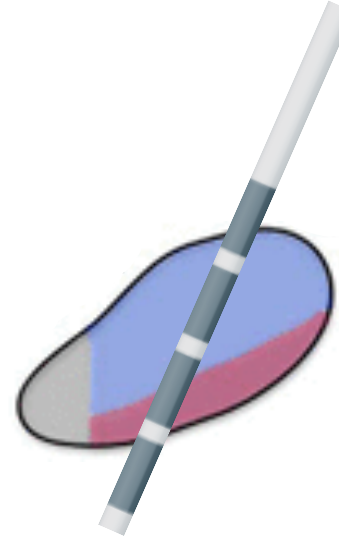
Implantation surgery for DBS, Anatomy

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)



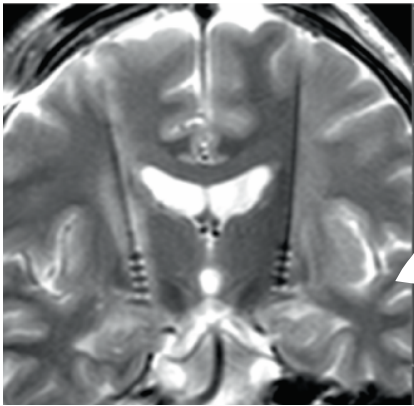
Depending on location of stimulation, different regions of BG and different networks are modulated by DBS

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

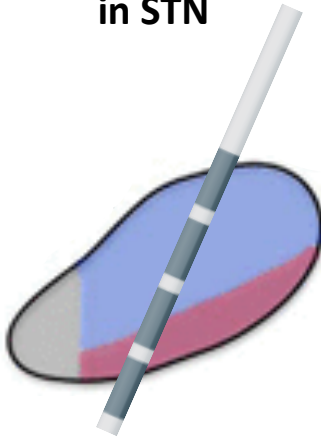
Deep brain stimulation

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

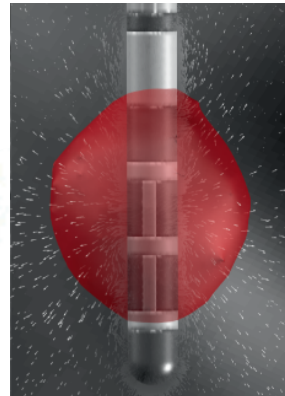
MRI



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 ...

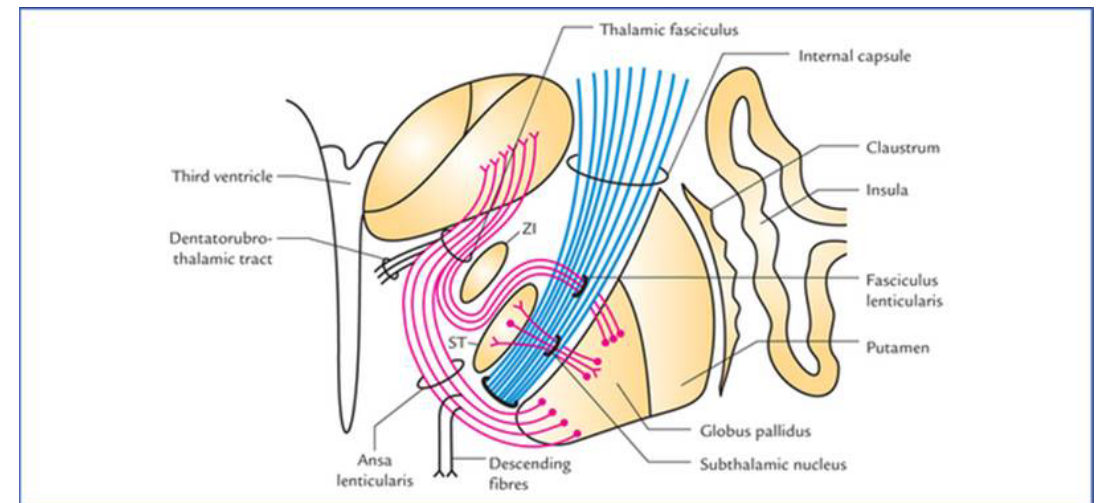
DBS stimulates passing white matter fibers

... in the IC (internal capsule)

... in the ML (medial lemniscal pathway)

... in other basal ganglia pathways

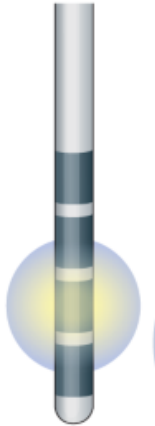
VTA allows to estimate which structures are stimulated.



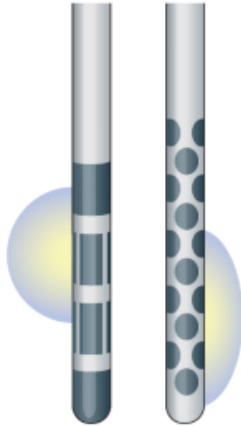
Deep brain stimulation

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

Unipolar



Directional

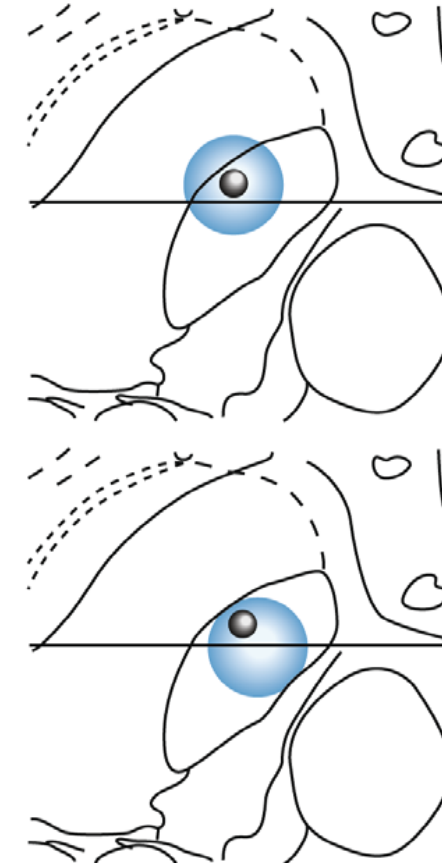
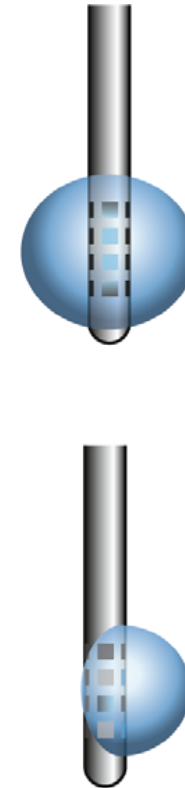


New directional electrodes (> 2015) allow for steering of the electrical field

- 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 effects

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

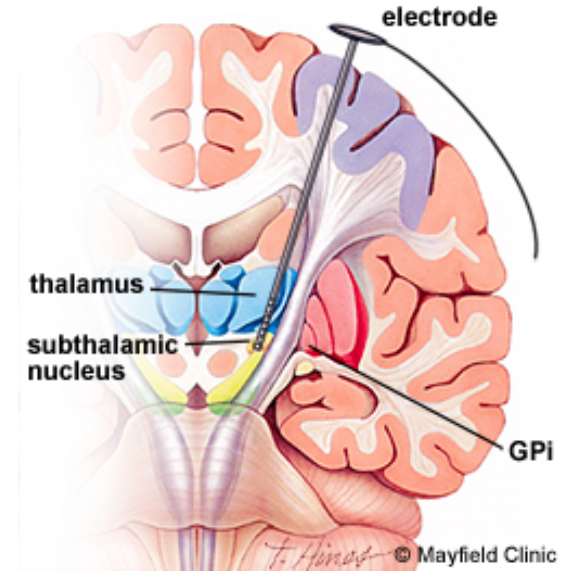
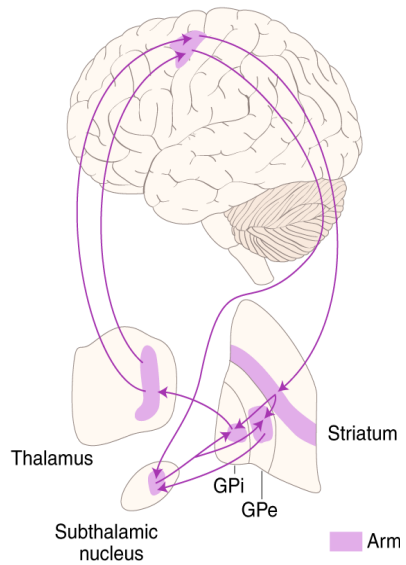
Cagnan et al., 2019

Questions

2

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

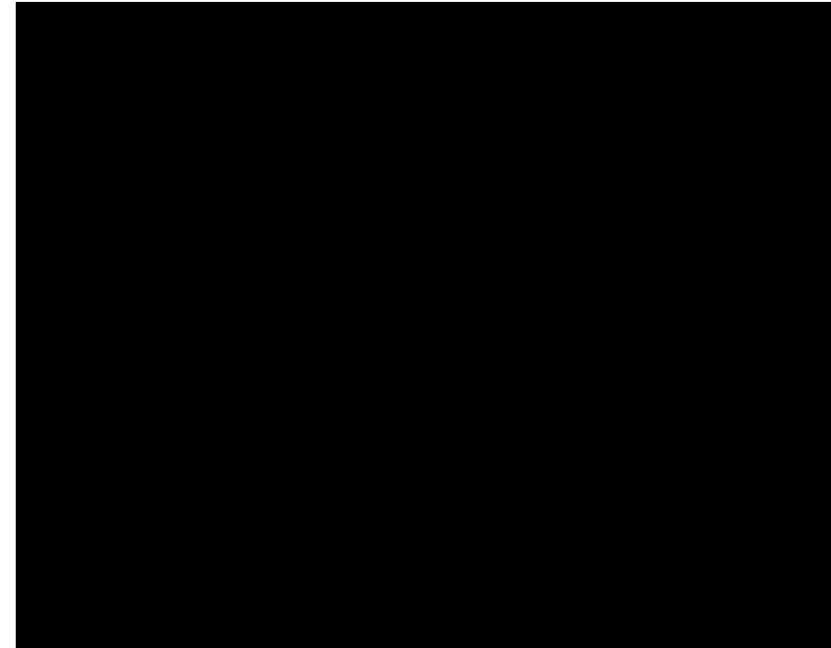
Deep brain stimulation

Therapeutic effects (symptoms)

Tremor & Gait



Tremor & Bradykinesia



<https://www.froedtert.com/videos/deep-brain-stimulation>

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

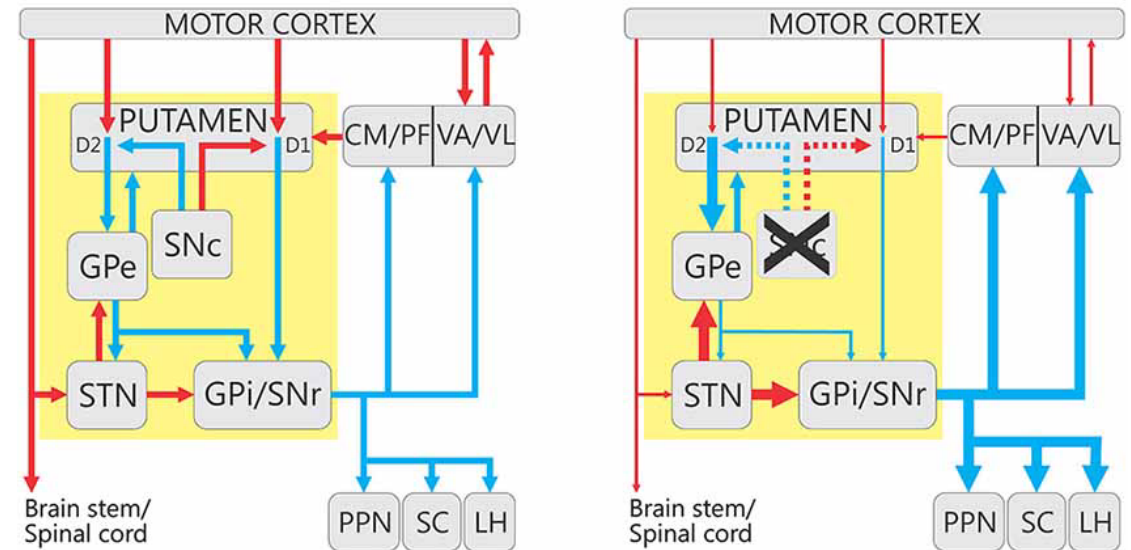
...Less dopamine-induced dyskinesias

...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

DBS is assumed to 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).

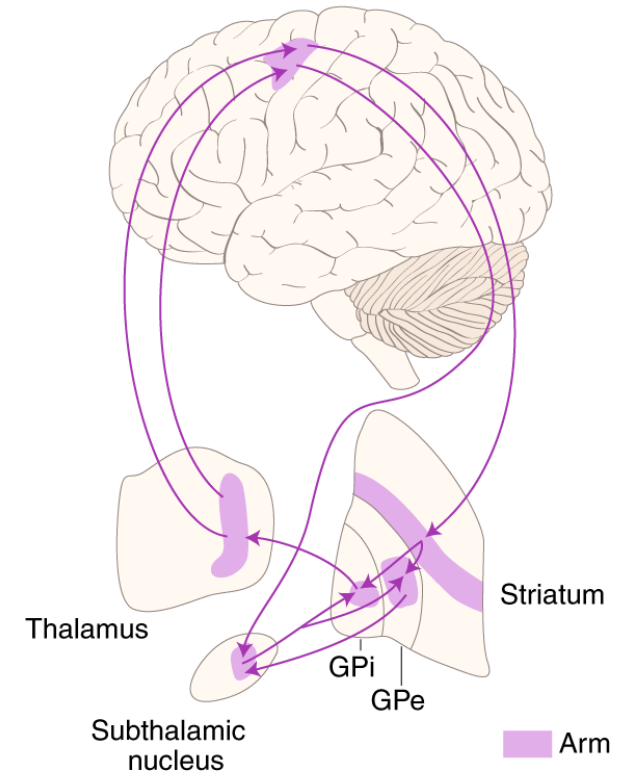
Recent evidence shows a more complex picture involving many more structures beyond STN:

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).

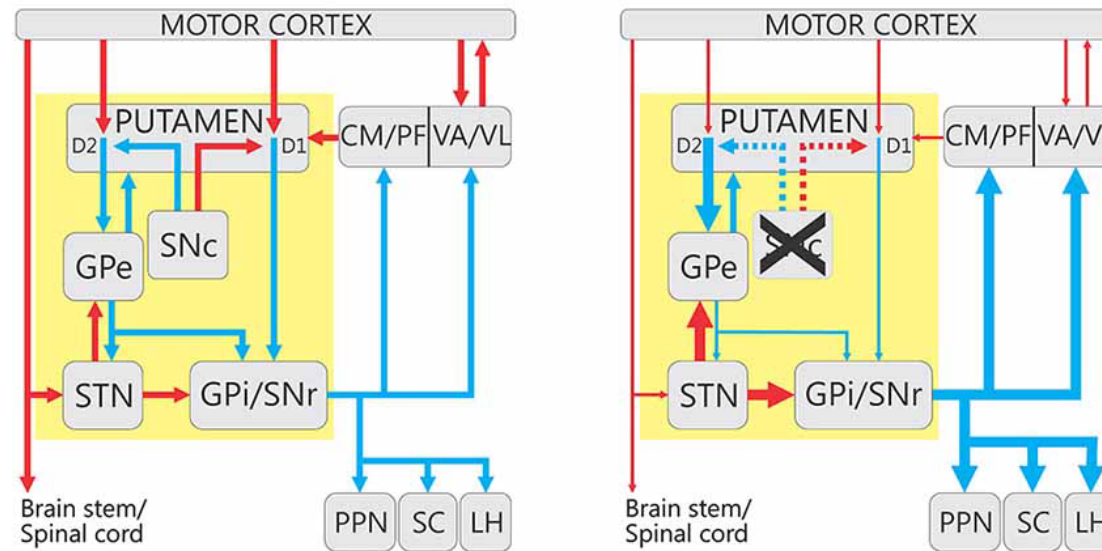
→ STN-DBS modulates activity at efferent and afferent brain regions to restore physiological activity and function.

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.

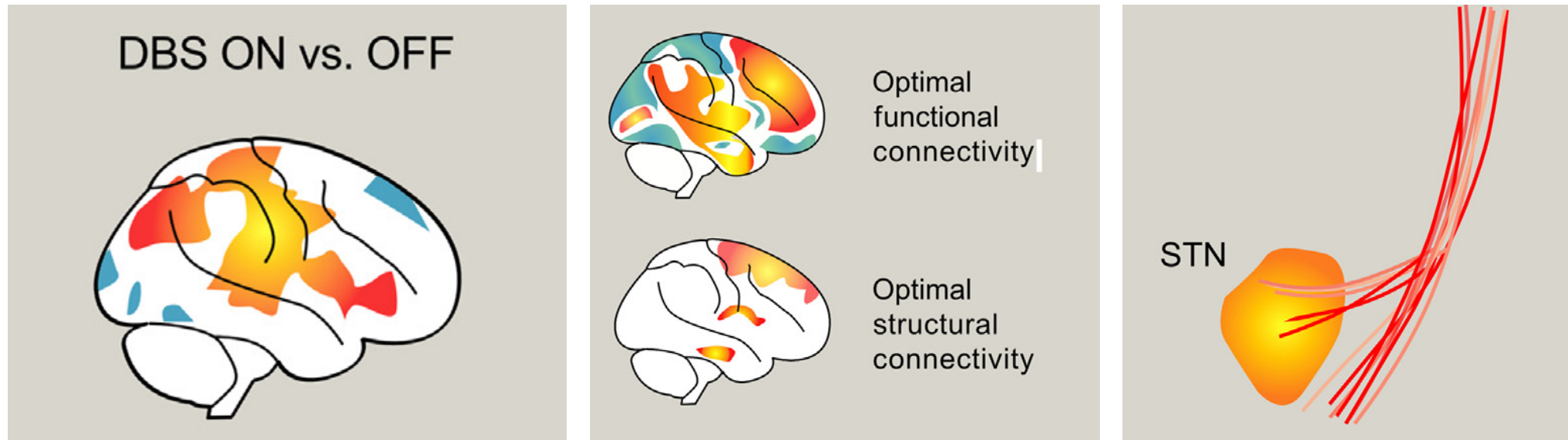


This likely involves hyperdirect, direct and indirect pathways
(difficult to directly study the pathways in humans mediating the STN DBS effects)

Deep brain stimulation

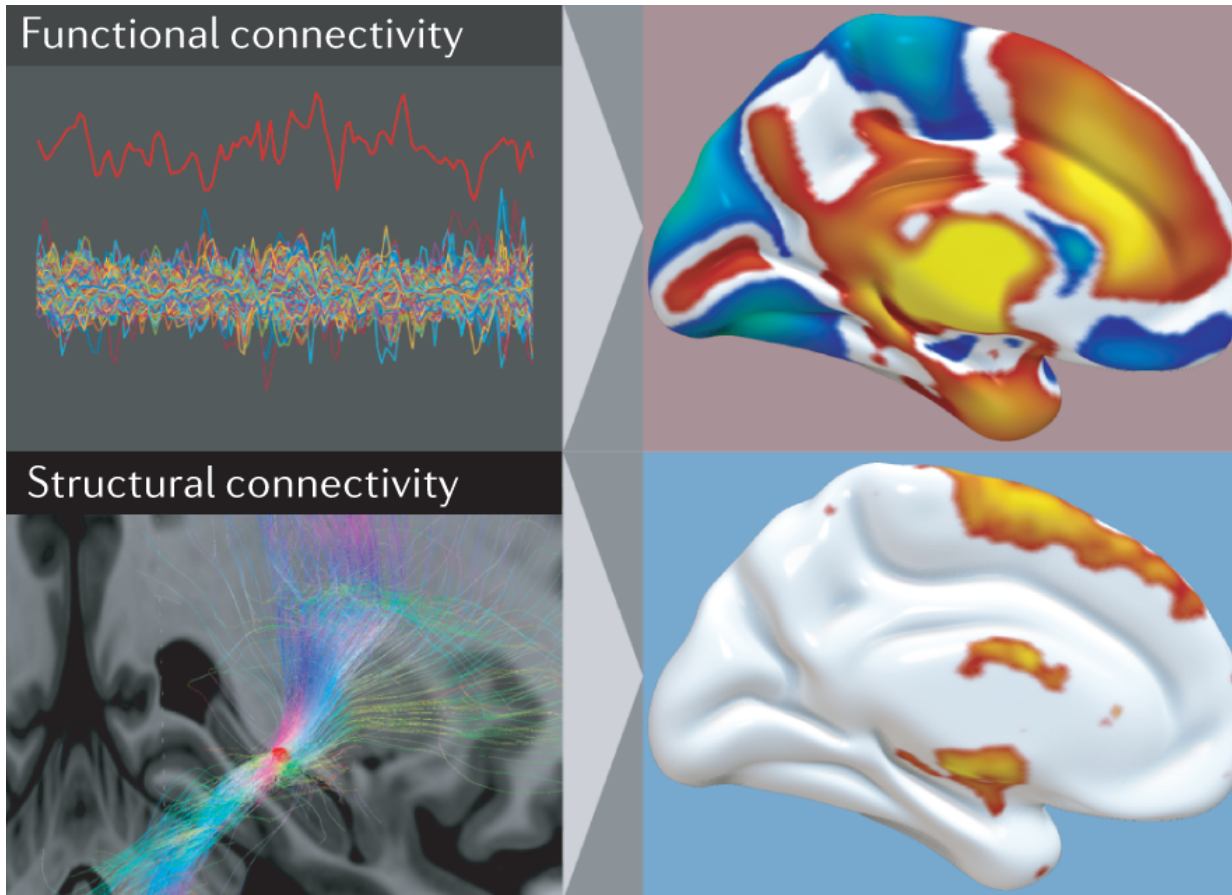
Network effects beyond basal ganglia

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 (but with system OFF).

Most DBS functional and structural connectivity studies use large data bases from healthy control subjects (n=1000) to perform connectivity analysis. Patient data about STN sites are normalized-transferred to these data bases.

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**.

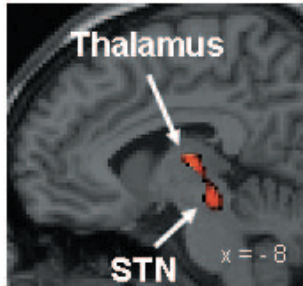
Alleviation of **tremor** was related to **functional connectivity between** active STN-DBS contact and **primary motor cortex (M1)**.

STN-DBS functional (and structural) connectivity may be even more relevant for **psychiatric disorders and psychiatric and cognitive symptoms** related to PD.

Deep brain stimulation

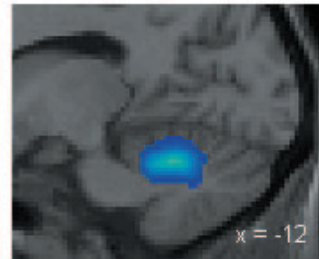
STN-DBS interferes with brain activity in a large network (Brain activation caused by DBS measured with positron emission tomography, PET data)

STN DBS enhances activity in STN/Thalamus

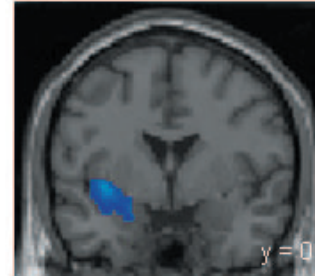


Thalamus

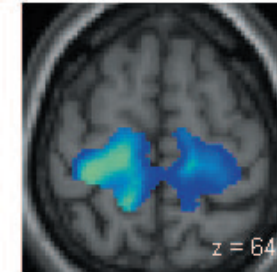
STN DBS decreases activity in cerebellum, putamen, GP



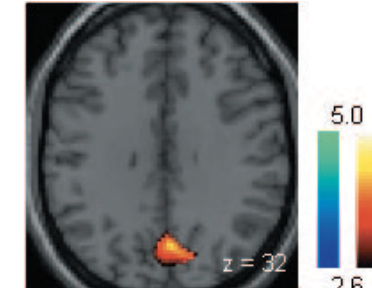
Cerebellar vermis



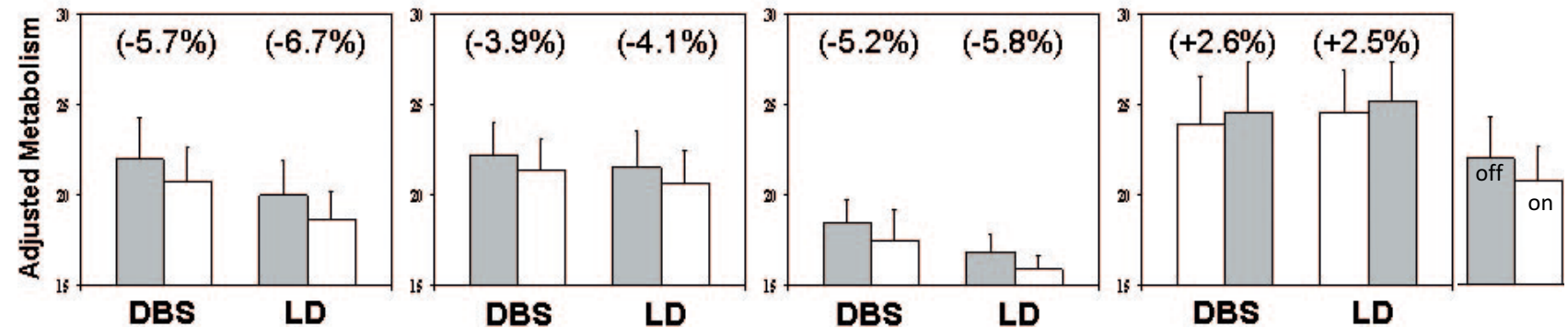
Put/GP



Sensorimotor

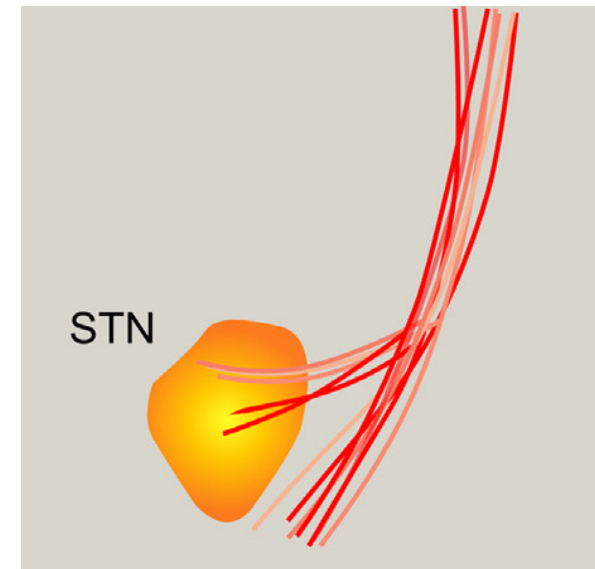


Precuneus



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

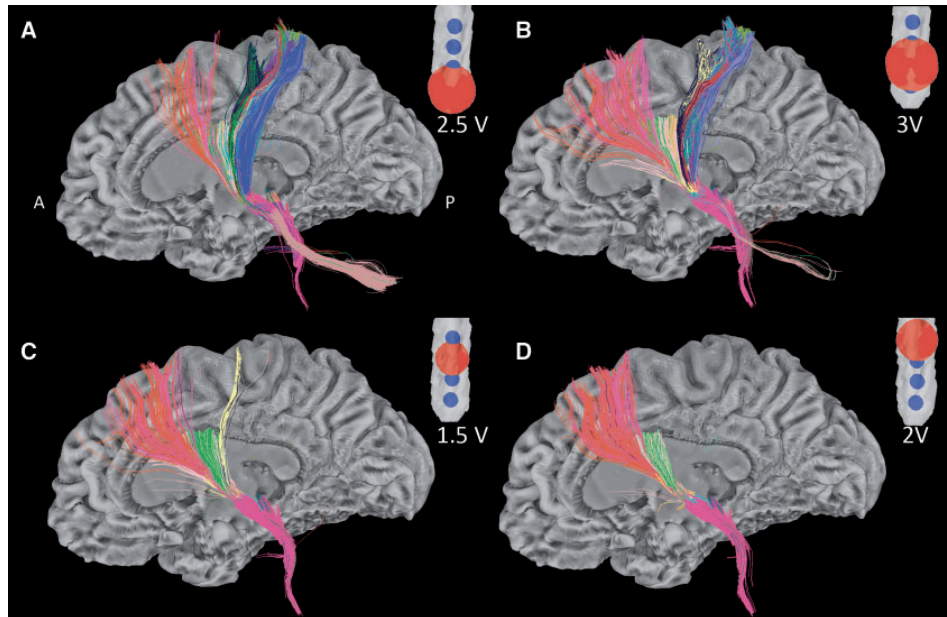
Mapping the tracts (or anatomical pathways) mediating DBS effects



Deep brain stimulation

MRI-based tractography (or structural connectivity)
reveals networks of STN DBS that are therapeutic

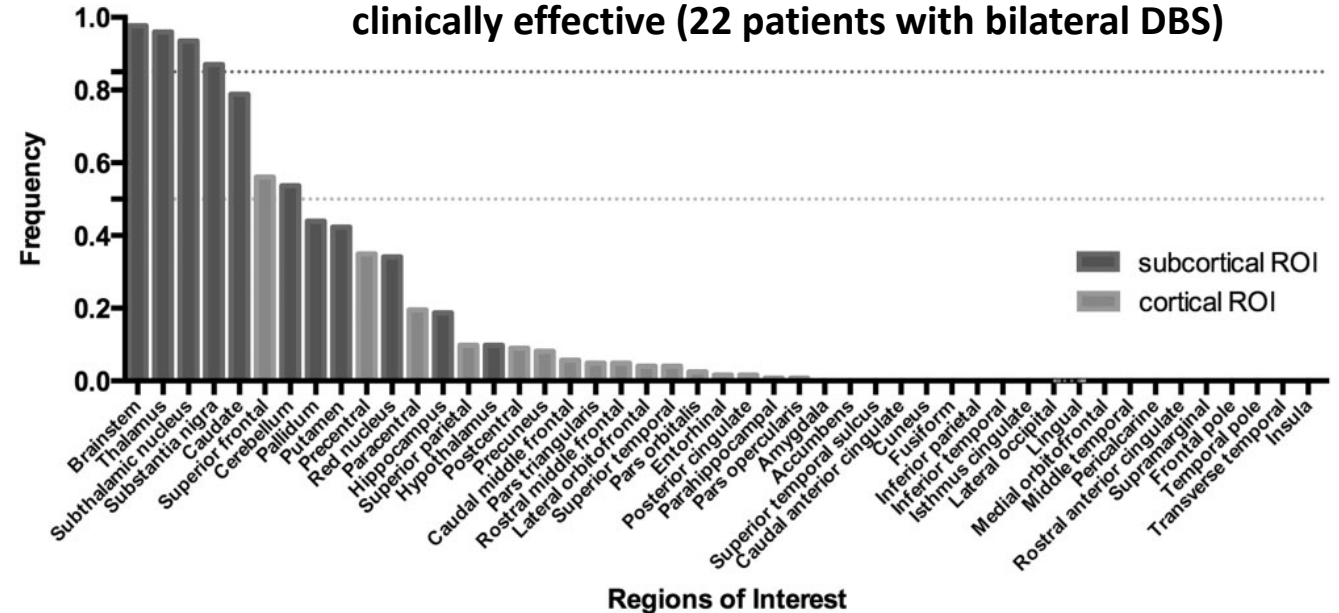
Divergence of structural connectivity depending on
STN lead location



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)

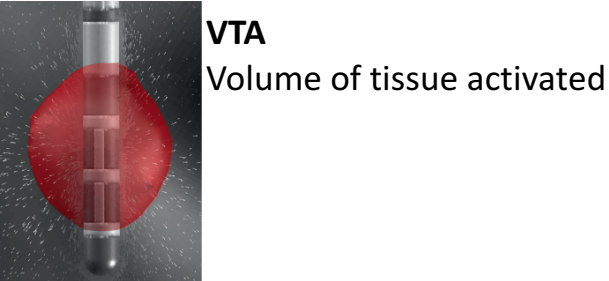


Main connected subcortical areas

Brainstem
Thalamus
STN
Substantia nigra
Caudate
Cerebellum

Main connected cortical areas

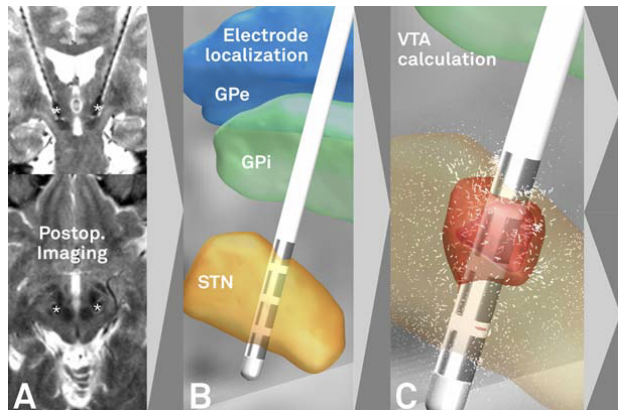
Superior frontal gyrus
(SMA and premotor cortex)
M1
S1



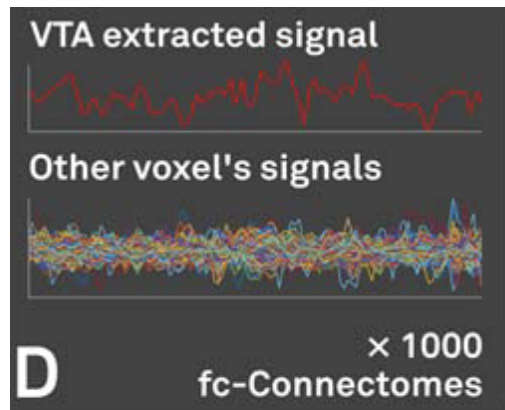
Deep brain stimulation

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)

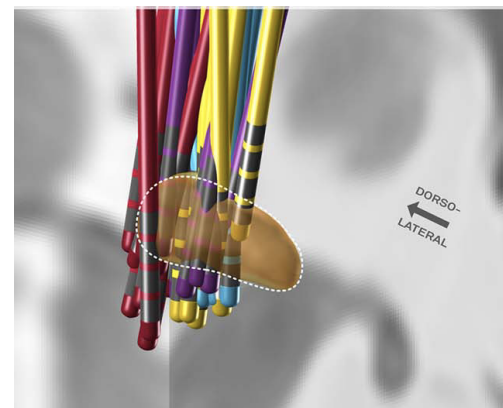


VTA functional connectivity with all other brain voxels tested (per patient)

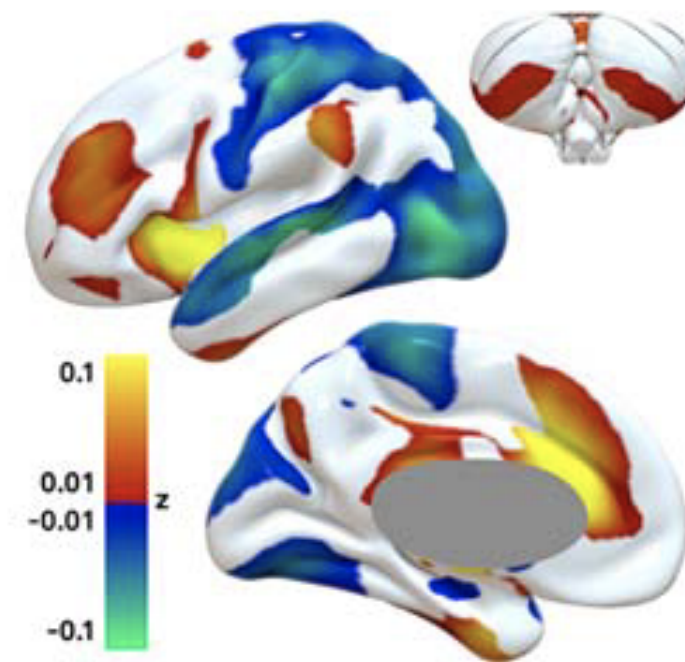


VTA connectivity in normalized data base (> 1000 healthy participants)

Electrode location for all included patients



Group functional connectivity



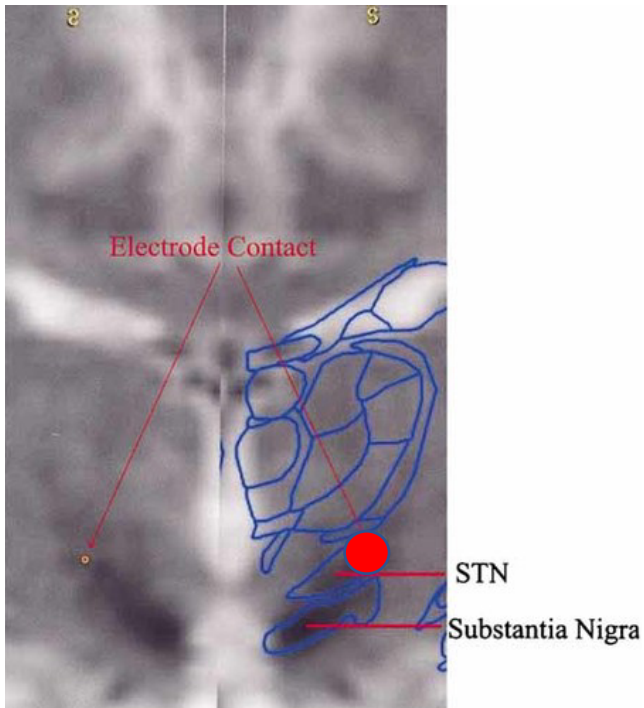
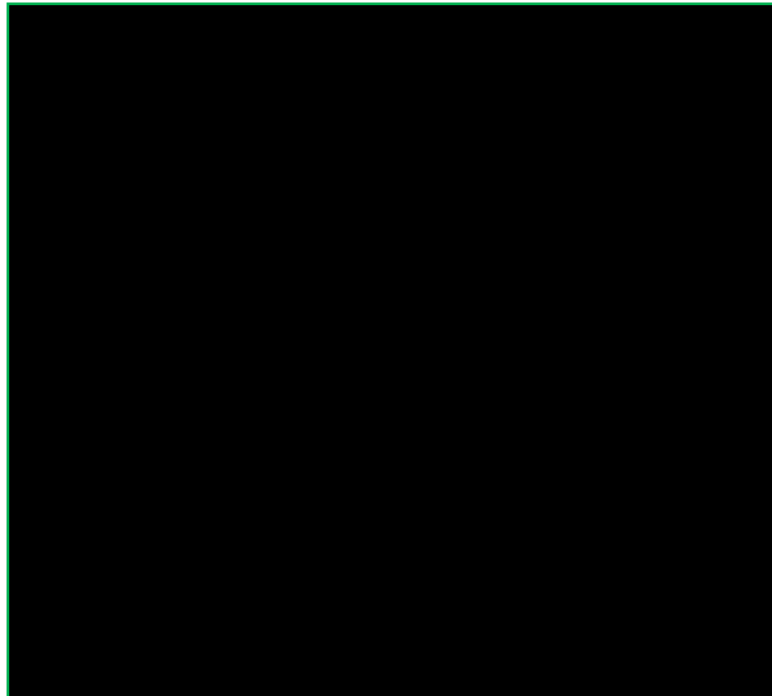
Functional connectivity with M1 (and posterior parietal cortex) is negatively connected with STN DBS (VTA), weighted by DBS efficacy (also other regions; experimental work, ongoing, not needed in detail for course)

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

Example complex motor behavior:
unsuppressable 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)

3

Pathological oscillations in PD



Brain oscillations

Brain oscillations reflect synchronized activity of large neuronal 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

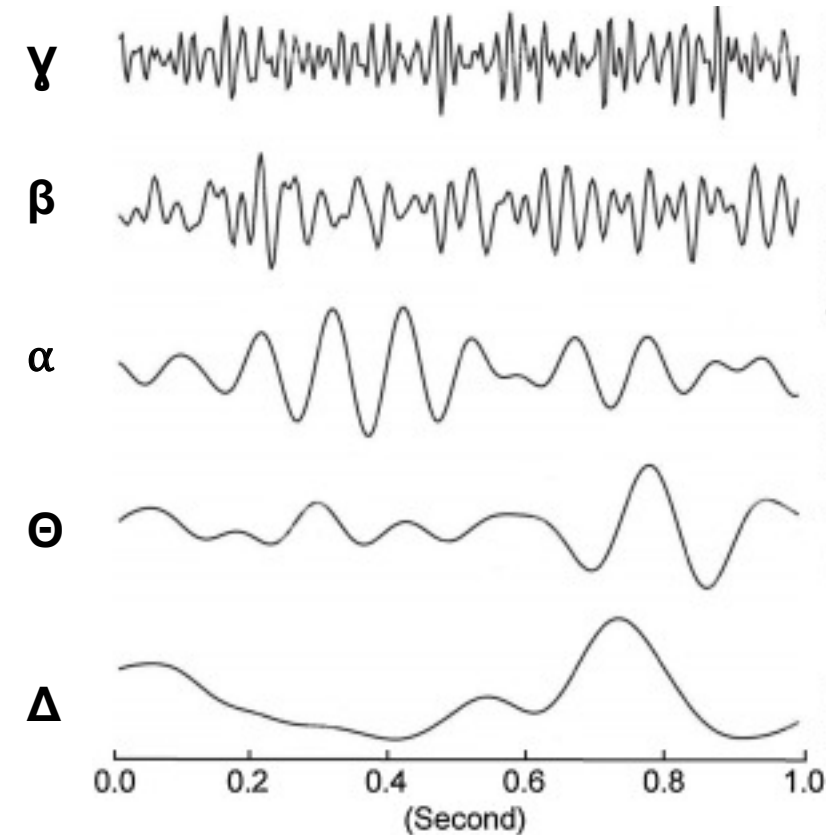
Gamma oscillations: 40-90 Hz

Theta oscillations: 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)

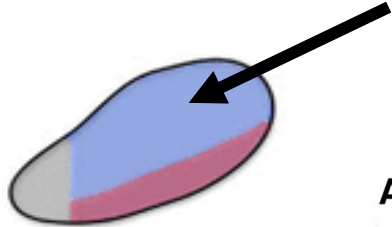
Pathological β oscillations in the basal ganglia in PD

Exaggerated beta oscillations in the STN in PD

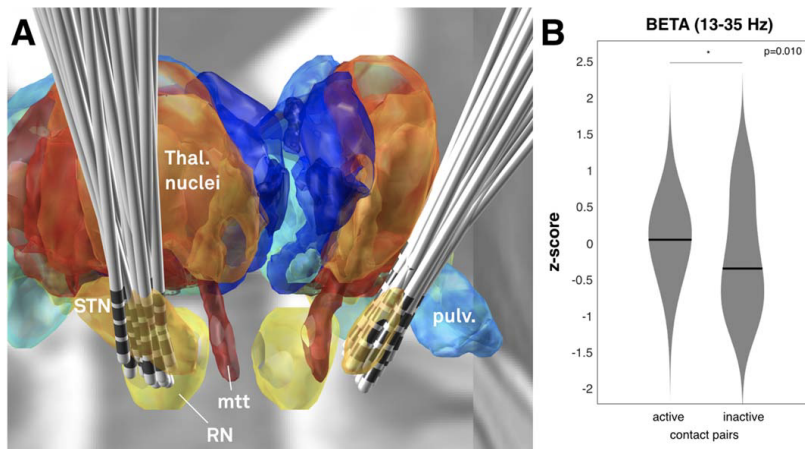
STN recordings of LFP allowed to study brain oscillations in the STN in PD patients, with high spatial resolution.

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 al., 2016).

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

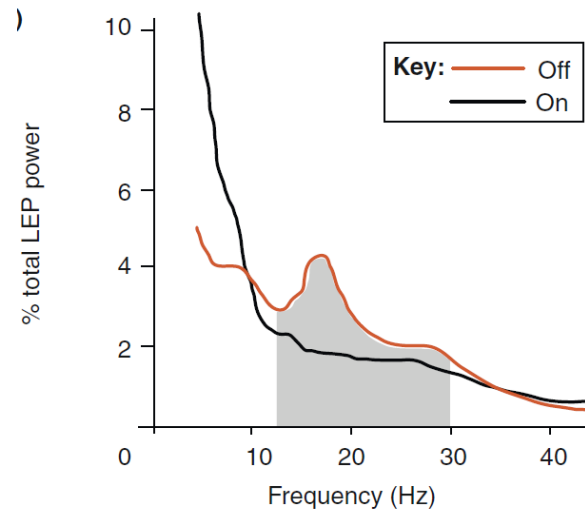
Suppression of exaggerated β oscillations in STN correlates with an improvement of motor symptoms (bradykinesia, rigidity; i.e. Kühn et al., 2006, 2008).

β oscillations predominate in sensorimotor part of the STN

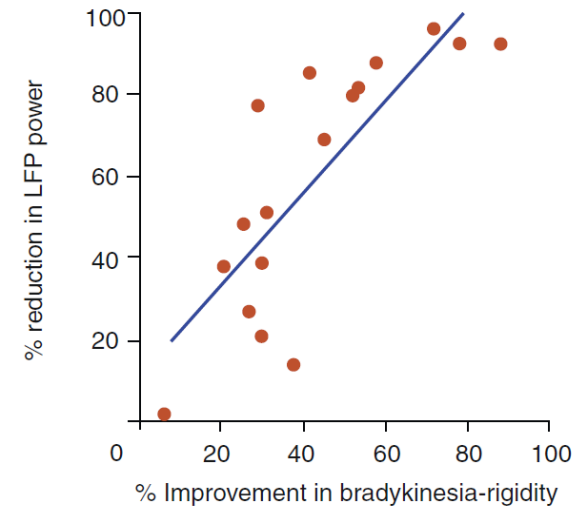
(These oscillatory changes are mostly carried by the low beta band activity (13-20 Hz) and not the high beta band (20-30 Hz)).

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

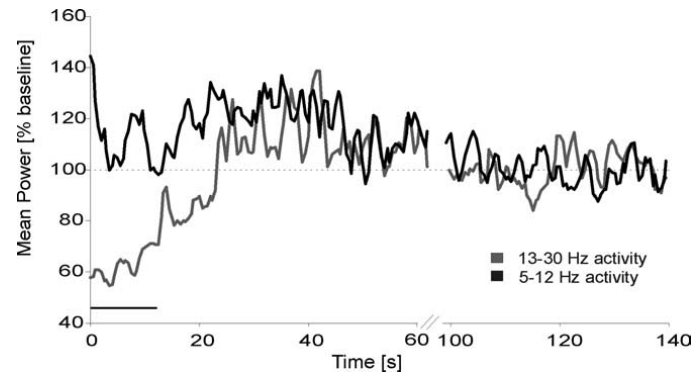


Beta oscillations are decreased by dopamine replacement therapy (ON) and increased when OFF medication, in PD patients

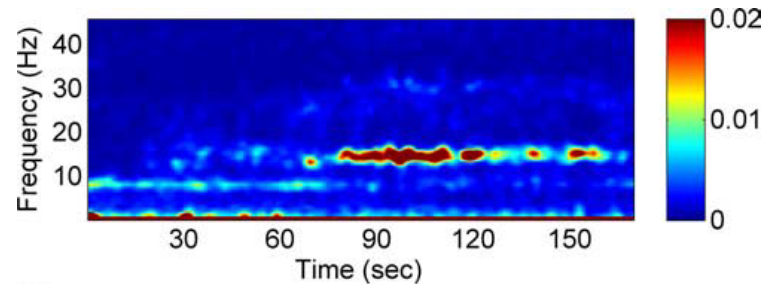


Improvement of motor symptoms correlates with the decrease of beta oscillations recorded in STN

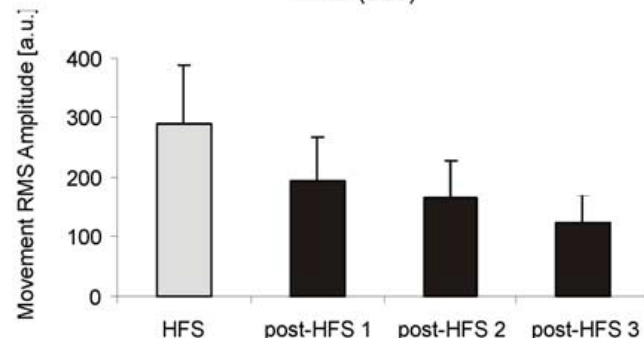
Beta oscillations in STN are suppressed by high-frequency STN DBS and improve bradykinesia



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

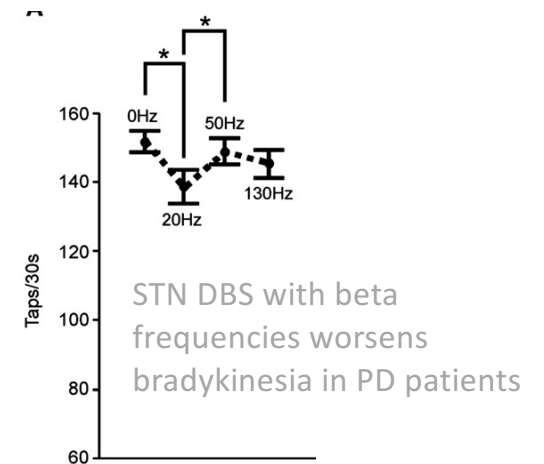


analysis for all recorded frequencies shows prominent changes in β band (preceded by alpha band changes)



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

STN DBS 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)

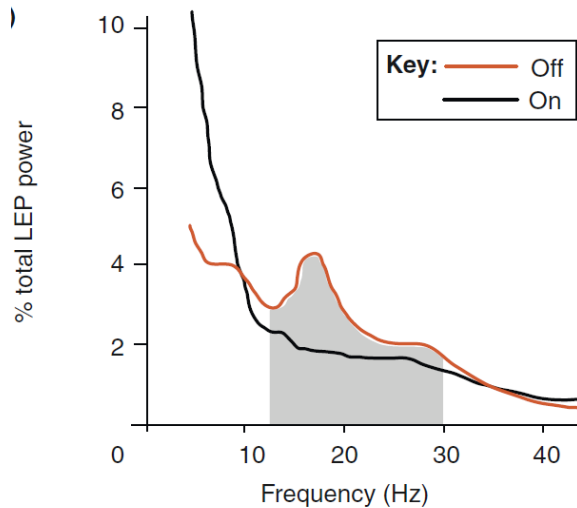


STN DBS with beta frequencies worsens bradykinesia in PD patients

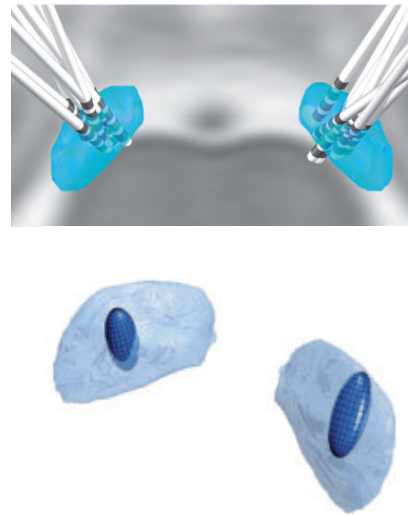
Deep brain stimulation

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

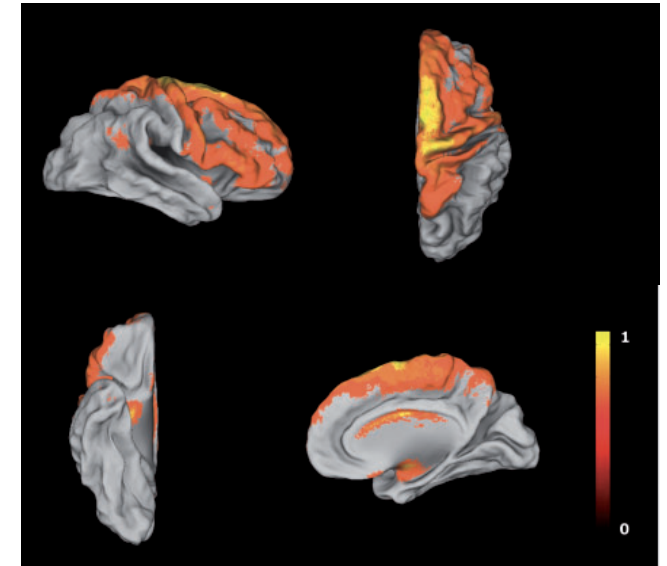
**Beta oscillations
(in STN)**



**STN contacts
with beta oscillations ...**



**... are connected premotor and
supplementary motor regions**



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



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)

More on Beta oscillations in STN

But ...

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).

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, γ) 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.**

Gamma γ

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

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

Gamma oscillations

Observed in STN, but currently mostly studied in motor cortex

γ oscillations are a physiological in nature, but have also been linked to specific symptoms related to PD.

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

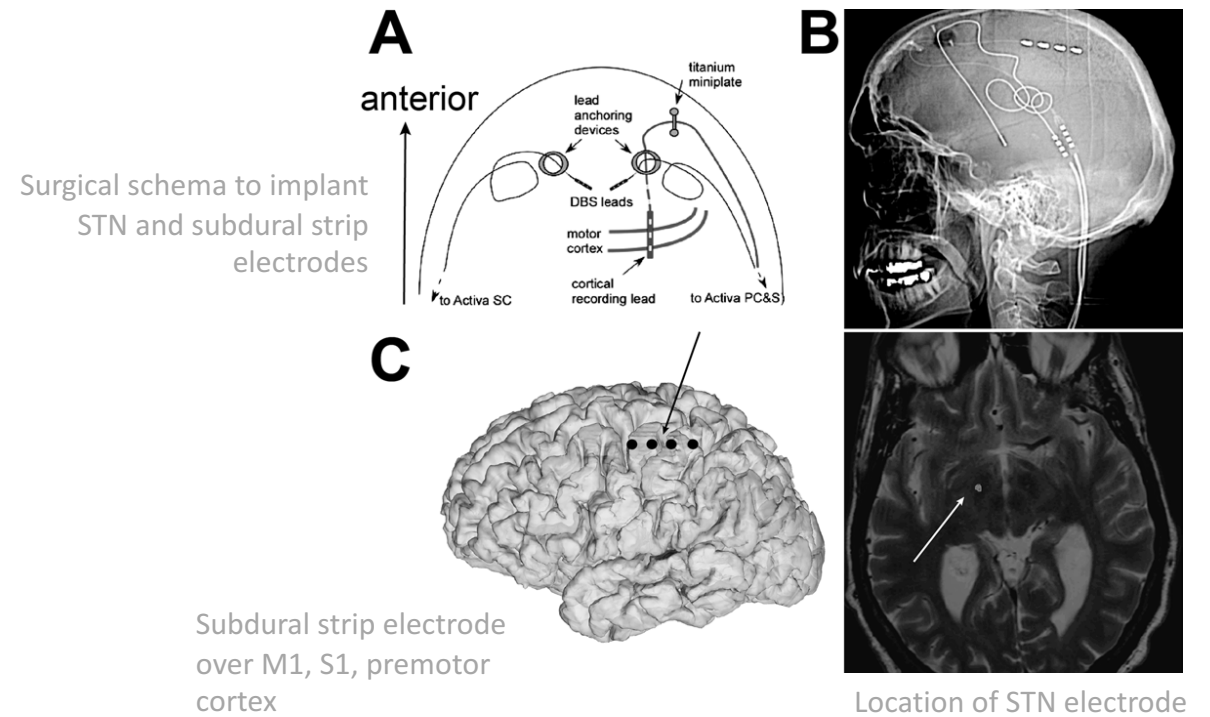
Dopamine medication increases γ oscillations (decreases beta oscillations).

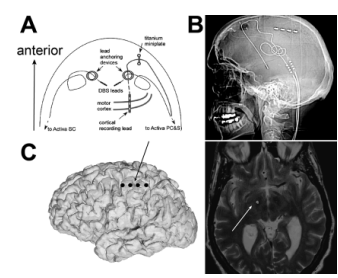
γ oscillations increase during voluntary movement and **in PD have been shown to characterize abnormal hyperkinetic states (dyskinesias, dystonia)**.

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

γ 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



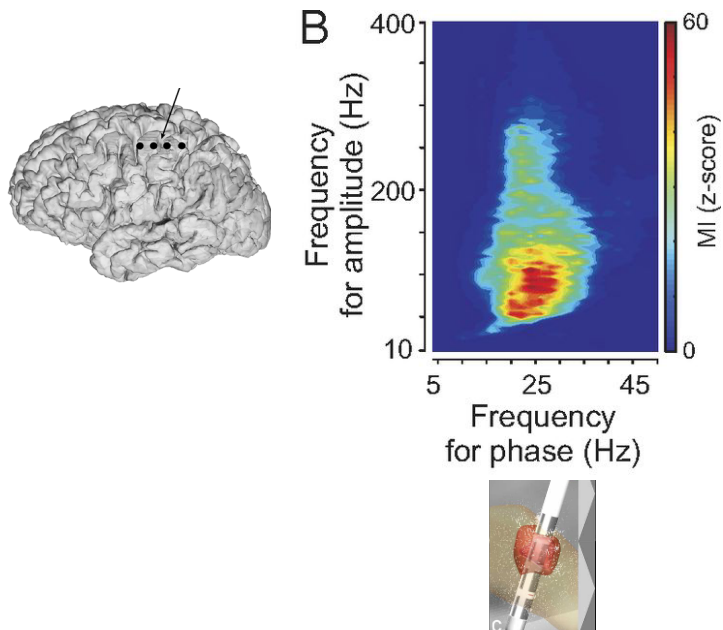


Power of gamma oscillations

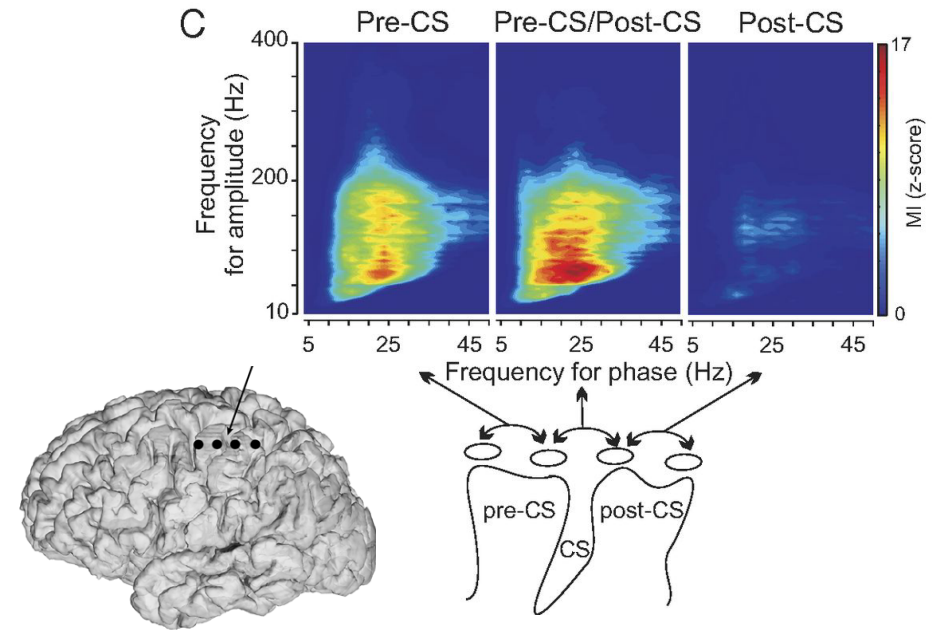
in motor cortex is coupled with phase of beta oscillations in STN

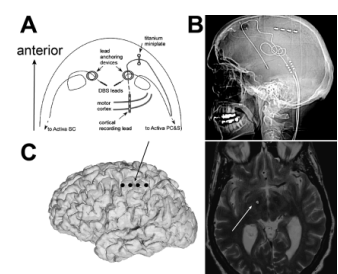
Coupling of oscillations by linking the amplitude of a high frequency oscillation (gamma) with the phase of a lower frequency rhythm (beta).

Phase–amplitude coupling (PAC) between the amplitude of gamma oscillations in M1 and the phase of β oscillations in the STN (De Hemmtine 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

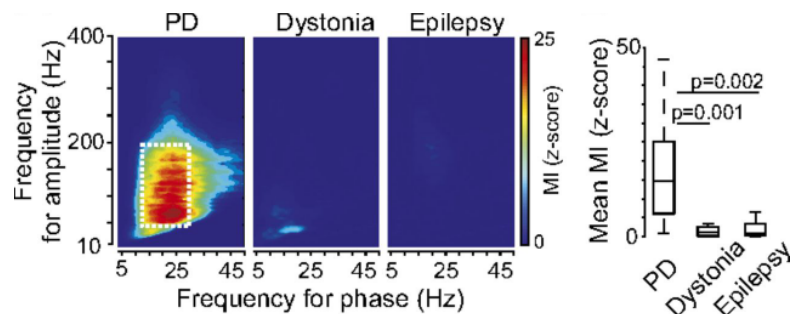




Gamma-beta phase amplitude coupling

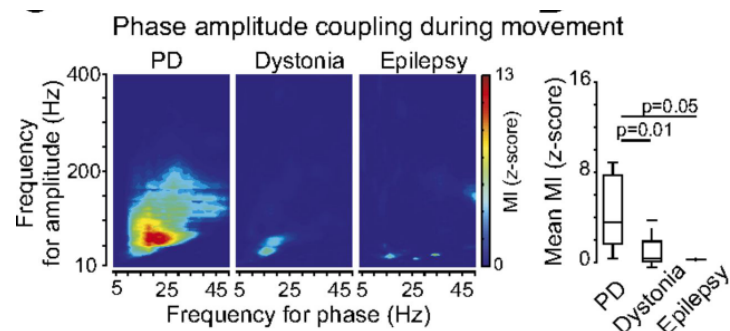
only observed in PD and persists during movement

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



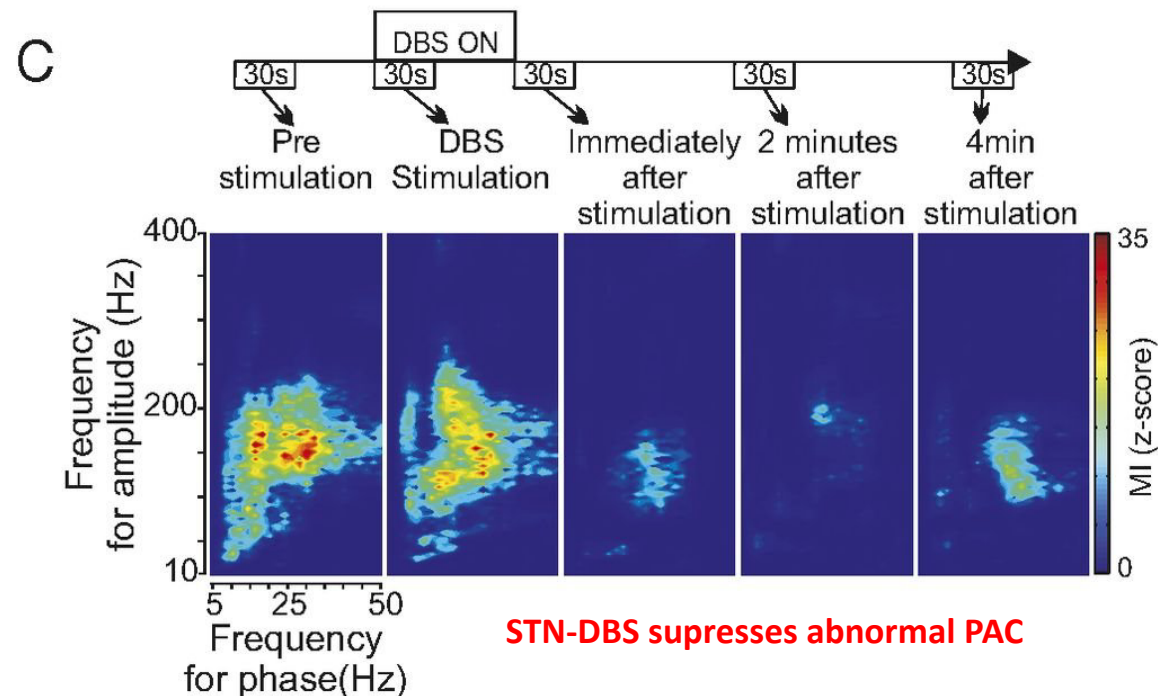
Abnormal gamma-beta PAC not observed in other medical conditions (dystonia, epilepsy)

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



Abnormal gamma-beta PAC persists during simple movement

Therapeutic effect of STN-DBS on Gamma-beta PAC



STN-DBS suppresses abnormal PAC

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

Theta/alpha oscillations

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

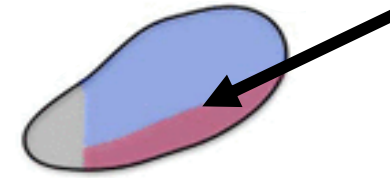
Θ/α band activity (3-12 Hz) has also been found in the STN

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

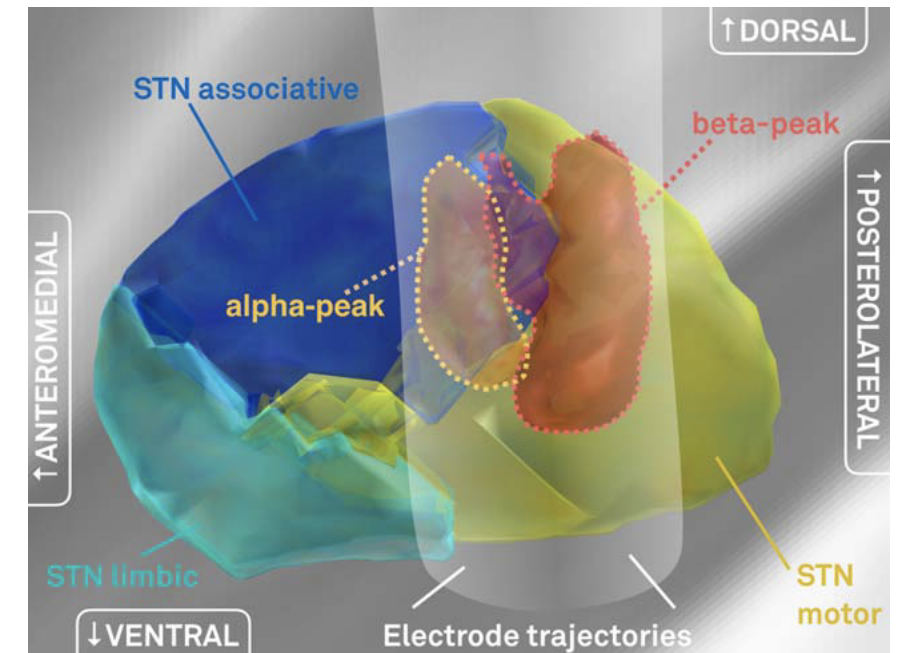
Main locus of **Θ/α band activity in STN** is below the peak for β oscillations (there is also overlap): locus is shifted towards the border with the associative/cognitive part of the STN.

Coherence between STN Θ/α oscillations with several cortical regions such as superior temporal 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).



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



Deep brain stimulation

Outlook

a Current DBS systems

Electrode

- Single or bilateral electrodes
- Continuous stimulation

Extension cables

Implantable pulse generator

- Lithium battery in titanium housing
- Adjusted with physician programmer
- 3–5-year battery life

b Future DBS systems

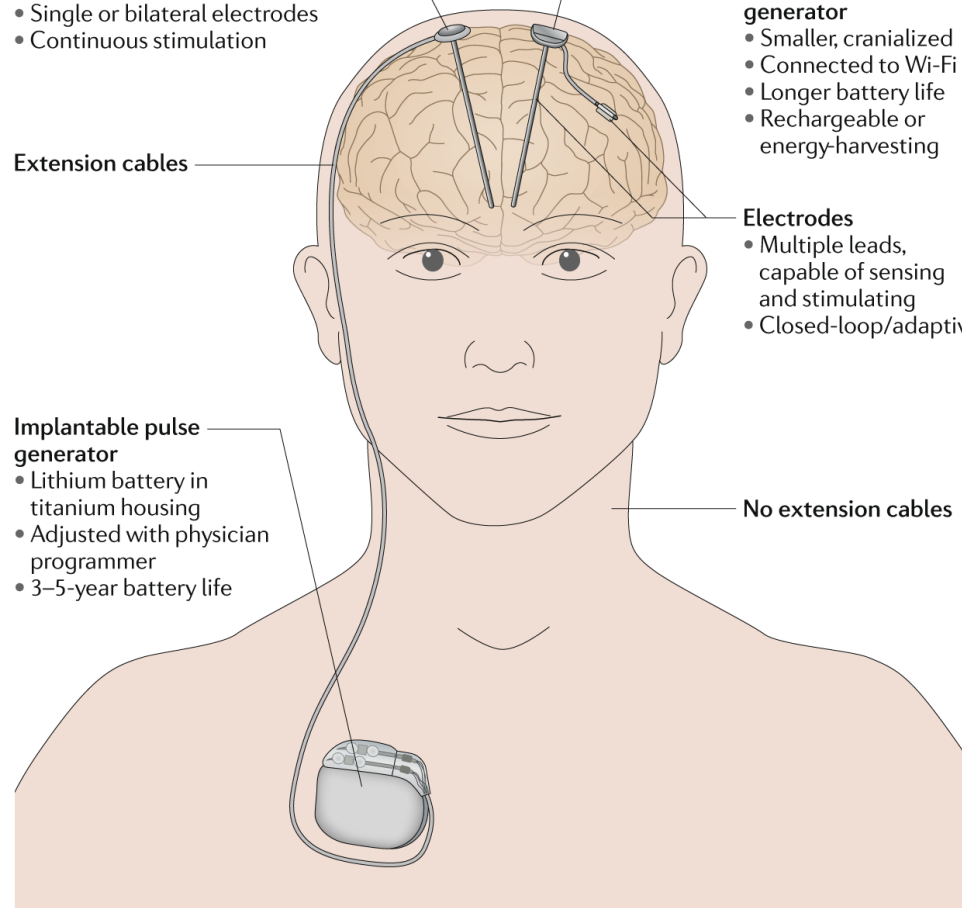
Implantable pulse generator

- Smaller, cranialized
- Connected to Wi-Fi
- Longer battery life
- Rechargeable or energy-harvesting

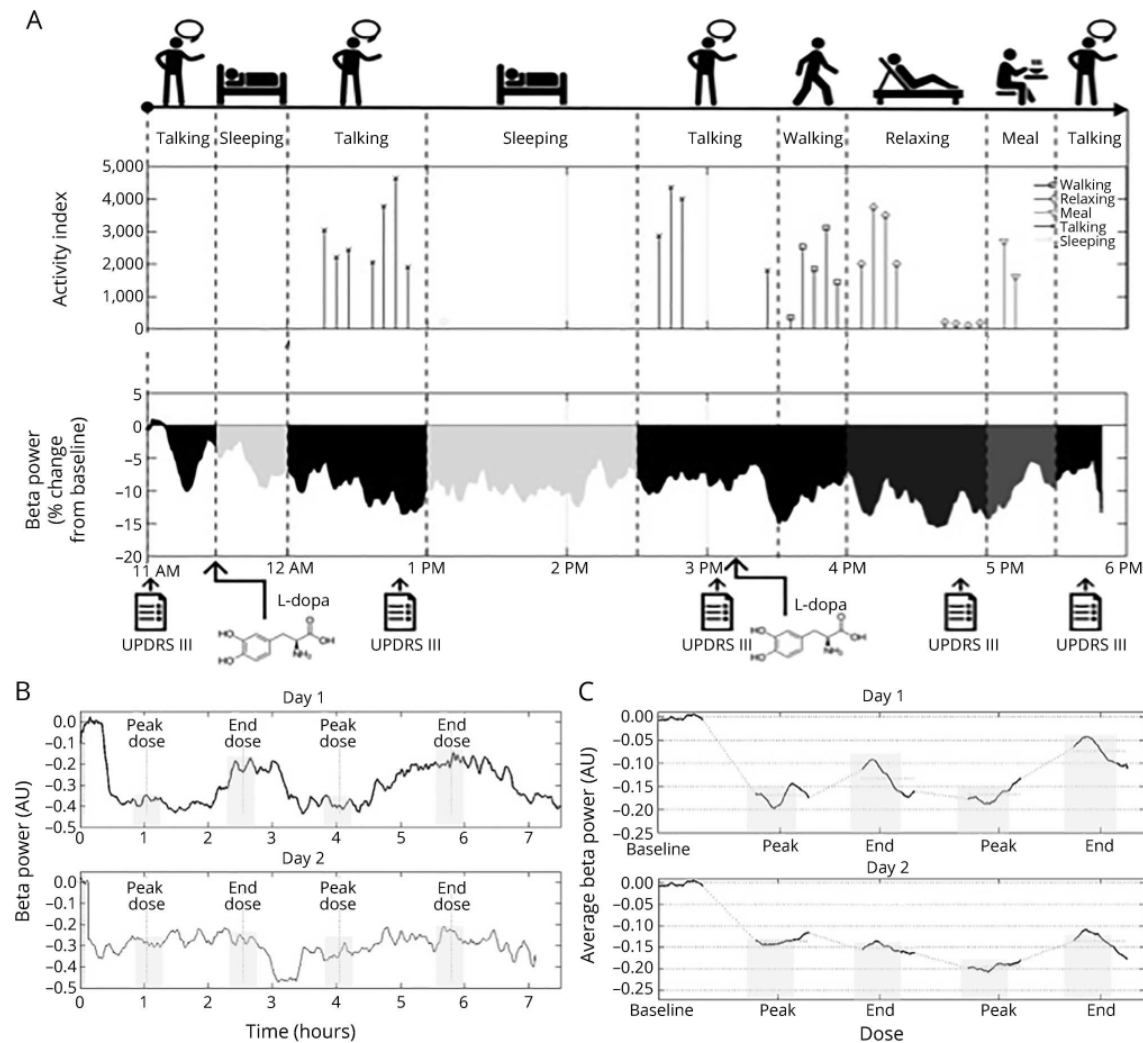
Electrodes

- Multiple leads, capable of sensing and stimulating
- Closed-loop/adaptive

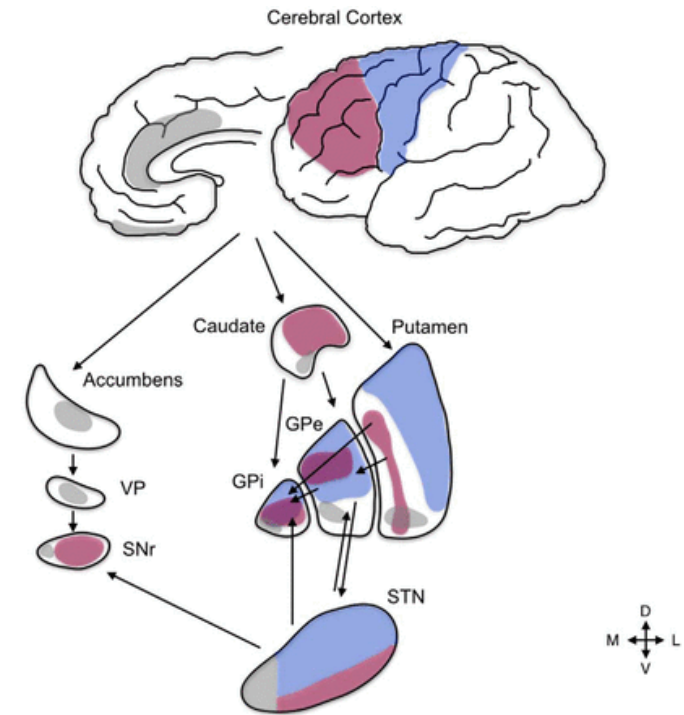
No extension cables



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.

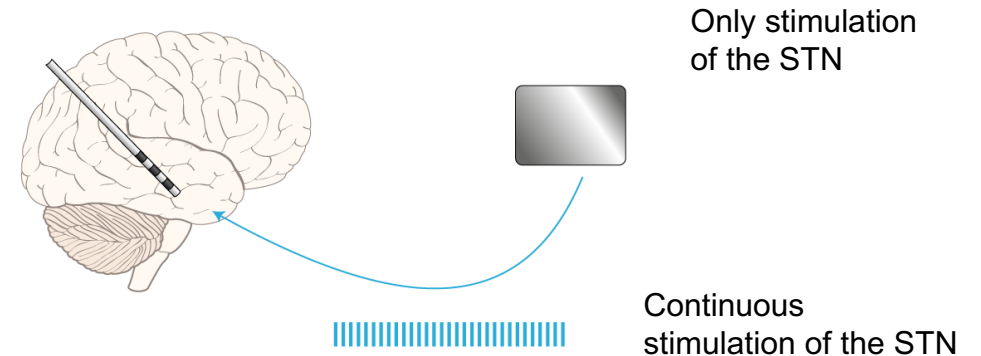
For some patients open-loop DBS does not lead to satisfying outcomes.

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

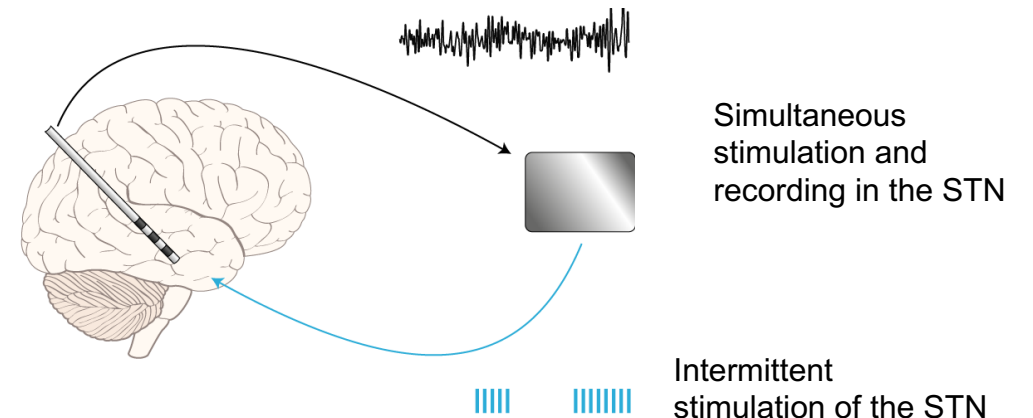
Continuous DBS may cause side effects (such as dyskinesias or dysarthria); closed-loop DBS may minimize these.

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)



Closed-loop DBS (STN)



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

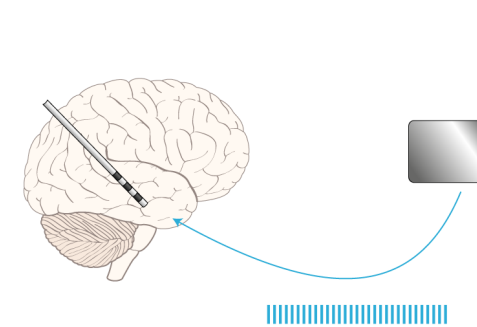
1-Beta oscillations (13-30 Hz) in STN (tremor, bradykinesia): when detected DBS is turned ON.

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

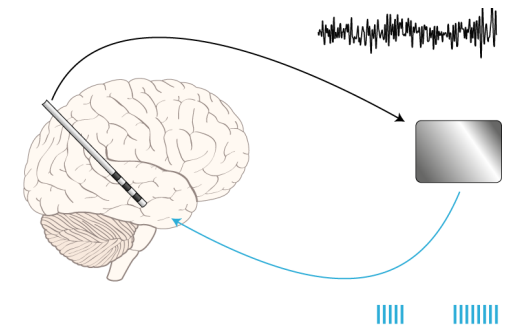
3-Peripheral wearable sensors to detect symptoms (tremor): when detected DBS is turned ON.

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.

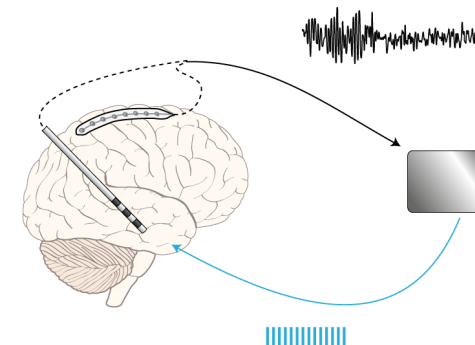
Open-loop DBS (STN)



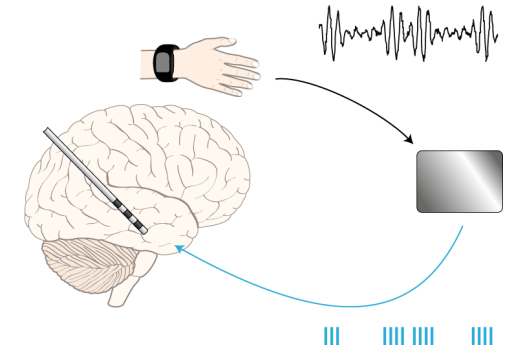
Closed-loop DBS (STN)



Closed-loop DBS (motor cortex & STN)

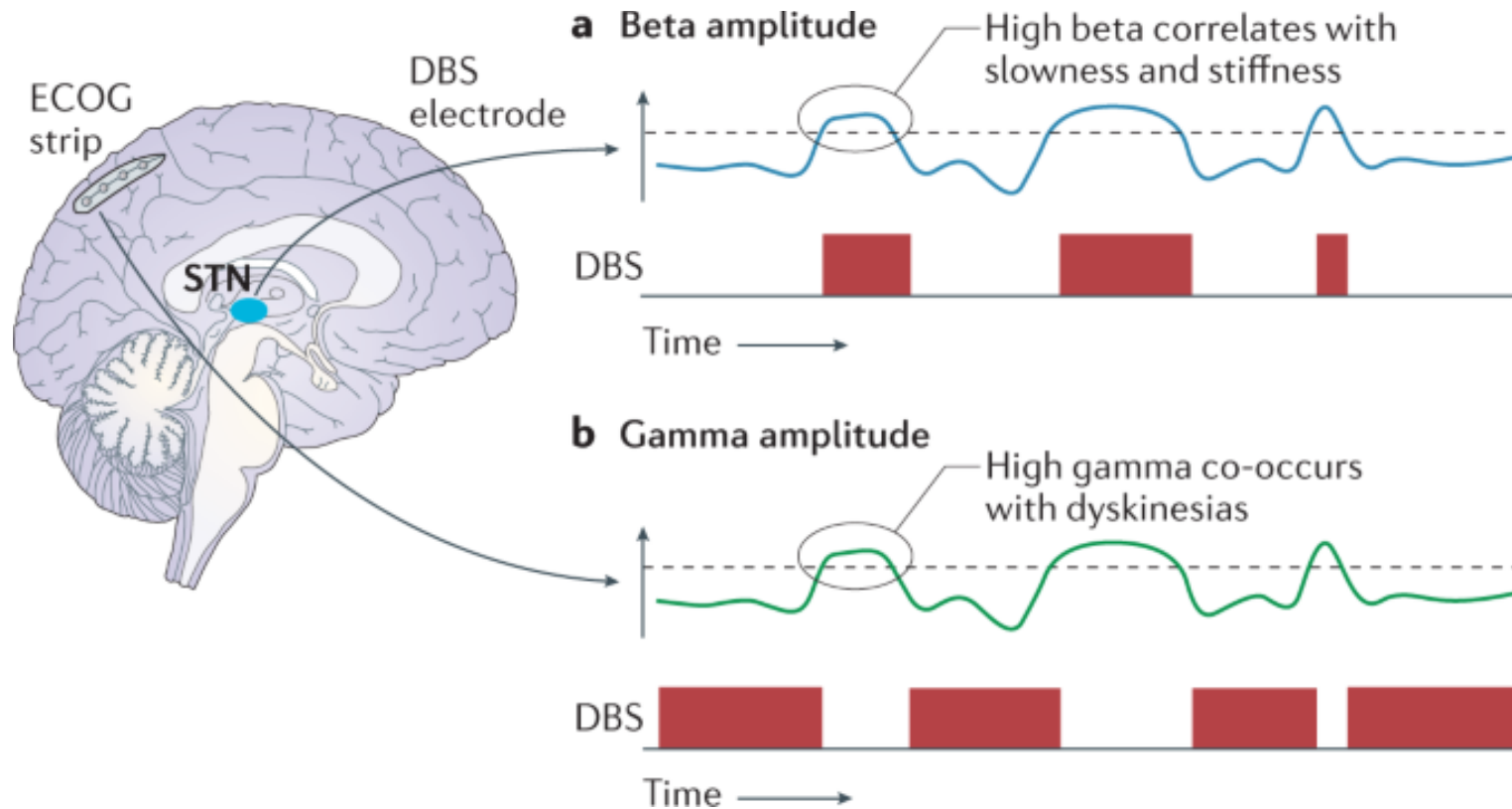


Closed-loop DBS (wearable sensor & STN)



Deep brain stimulation

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



Questions

