Imaging and stimulation for the mild Parkinson's disease.

Beatrice Campo
Sofiia Yeremeieva
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Parkinson’s disease (PD) is a complex progressive neurodegenerative disease characterized by **tremor, rigidity, and bradykinesia**, with postural instability appearing in some patients as the disease progresses [1].

Stages of PD by Hoehn and Yahr

Stage 1: Symptoms are present on **one side** only (unilateral);

Stage 2: Symptoms are present on **both sides** but no impairment of balance;

Stage 3: **Balance impairment** and mild to moderate disease progression;

Stage 4: Severe disability, but **still able to walk** or stand unassisted;

Stage 5: **Needing a wheelchair** or bedridden unless assisted [2].

https://www.verywellhealth.com/facts-about-parkinsons-disease-5200700

PD statistics

- PD is the second most common neurodegenerative disease after Alzheimer's disease;
- Nearly 90,000 people in the U.S. are diagnosed with PD each year. More than 10 million people worldwide are living with PD.
- Approximately 0.5–1% patients are in the age of 65–69 , rising to 1–3% among persons 80 years of age and older;
- Men are 1.5 times more likely to have Parkinson's disease than women.
- With an aging population, both the prevalence and incidence of PD are expected to increase by more than 30% by 2030 [1].

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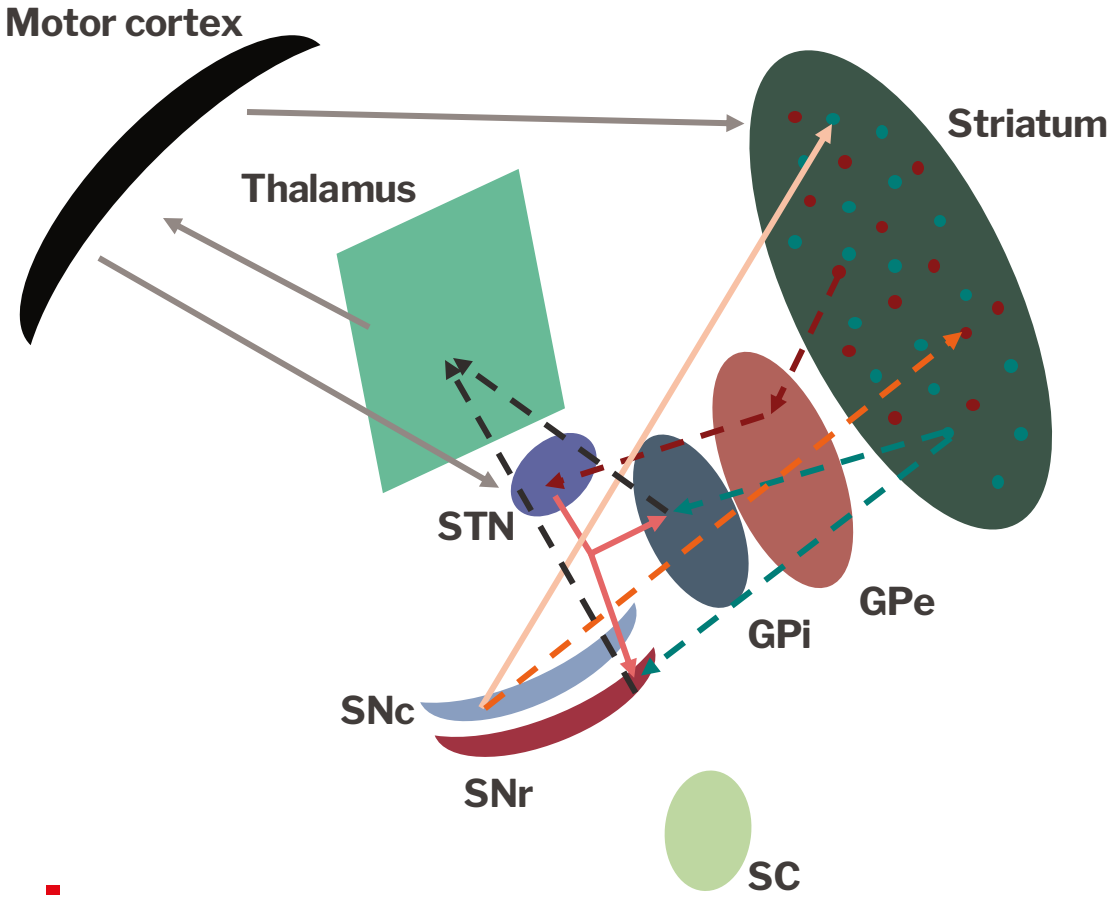
Basal ganglia circuit



Schema is based on the classical model of basal ganglia [3].

——— – excitation
- - - - - - - - - - – inhibition
STN – subthalamic nucleus
SNc – substantia nigra pars compacta
SNr – substantia nigra pars reticulata
GPe – globus pallidus pars externa
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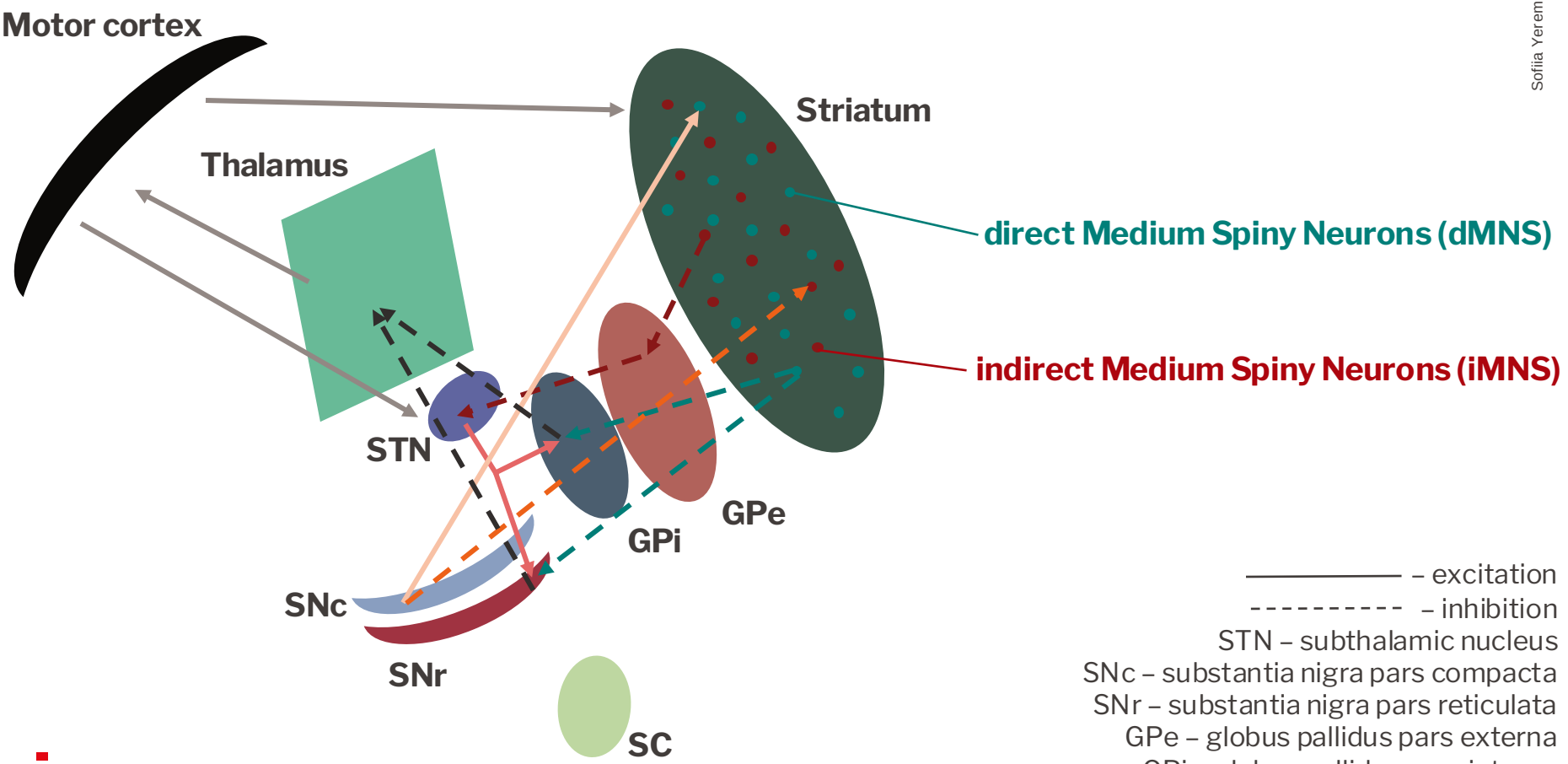

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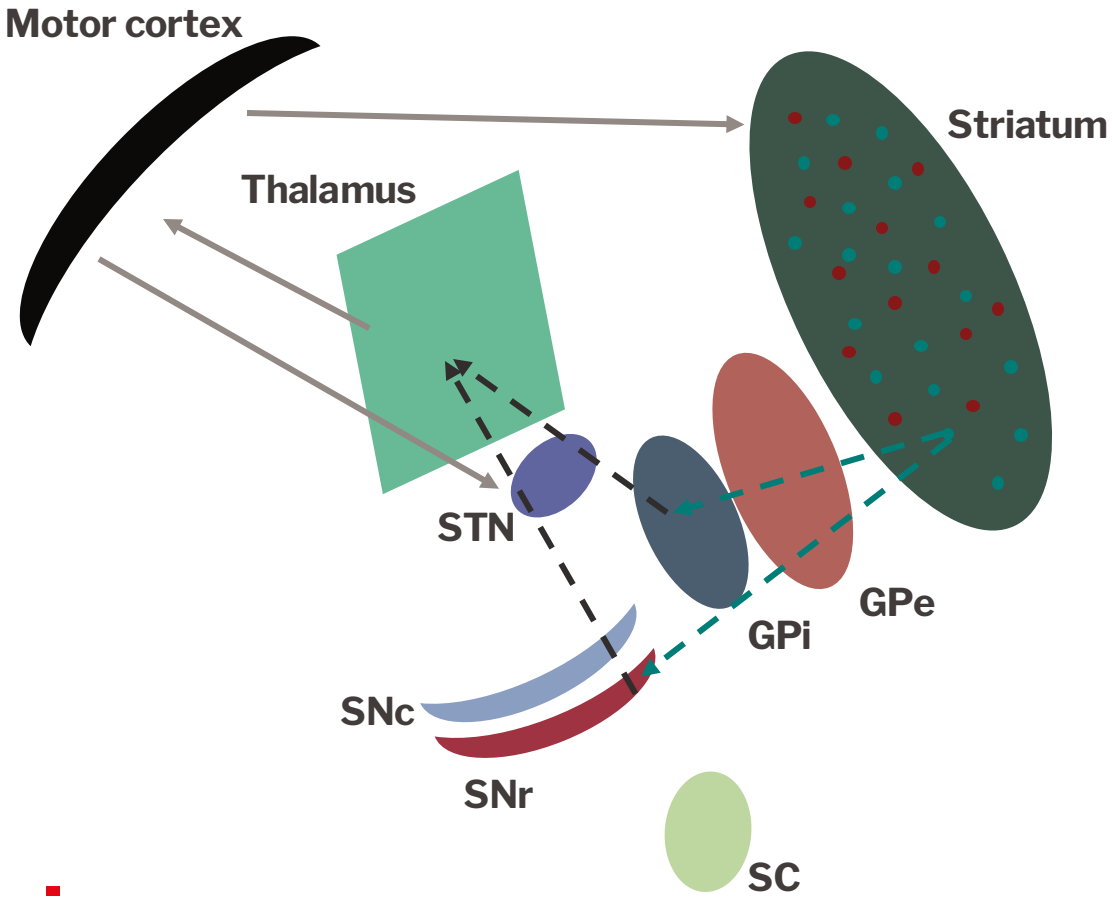

direct Medium Spiny Neurons (dMNS)

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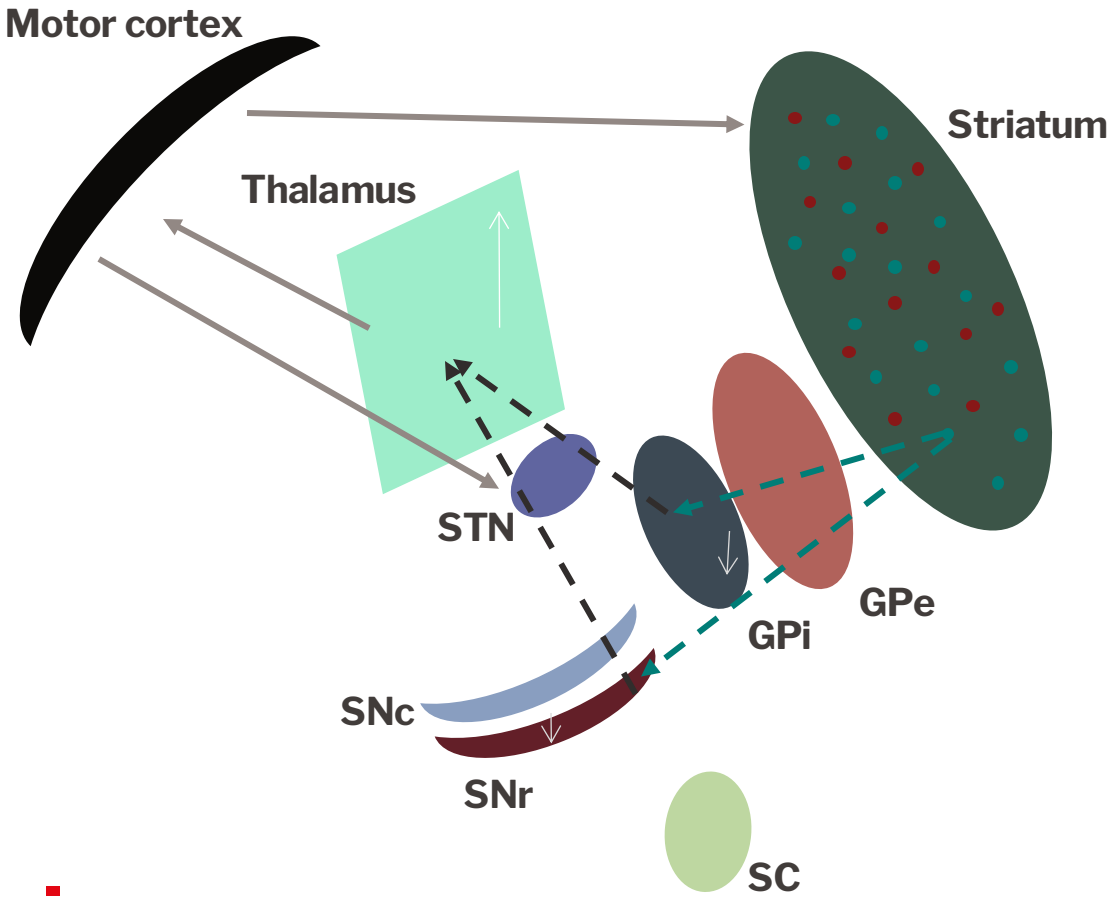

direct Medium Spiny Neurons (dMNS)

--> promoting movement

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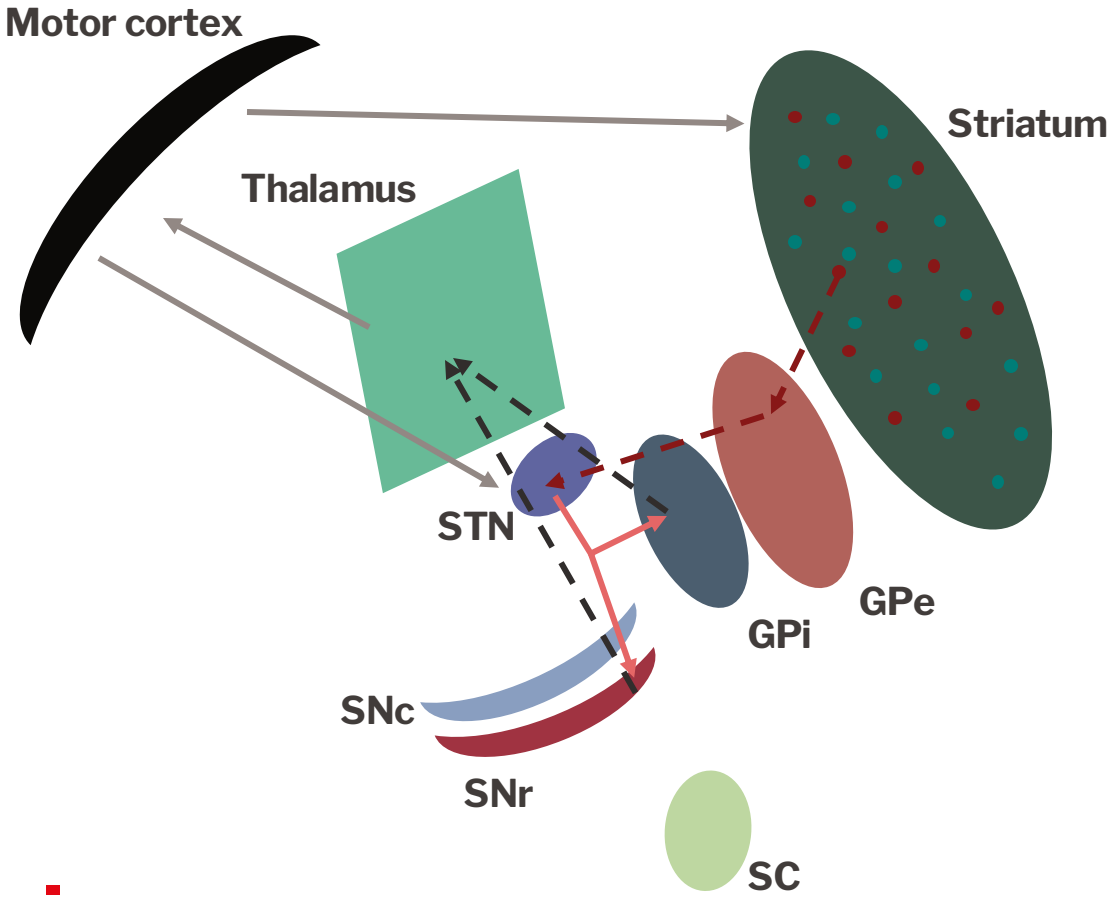

indirect Medium Spiny Neurons (iMNS)

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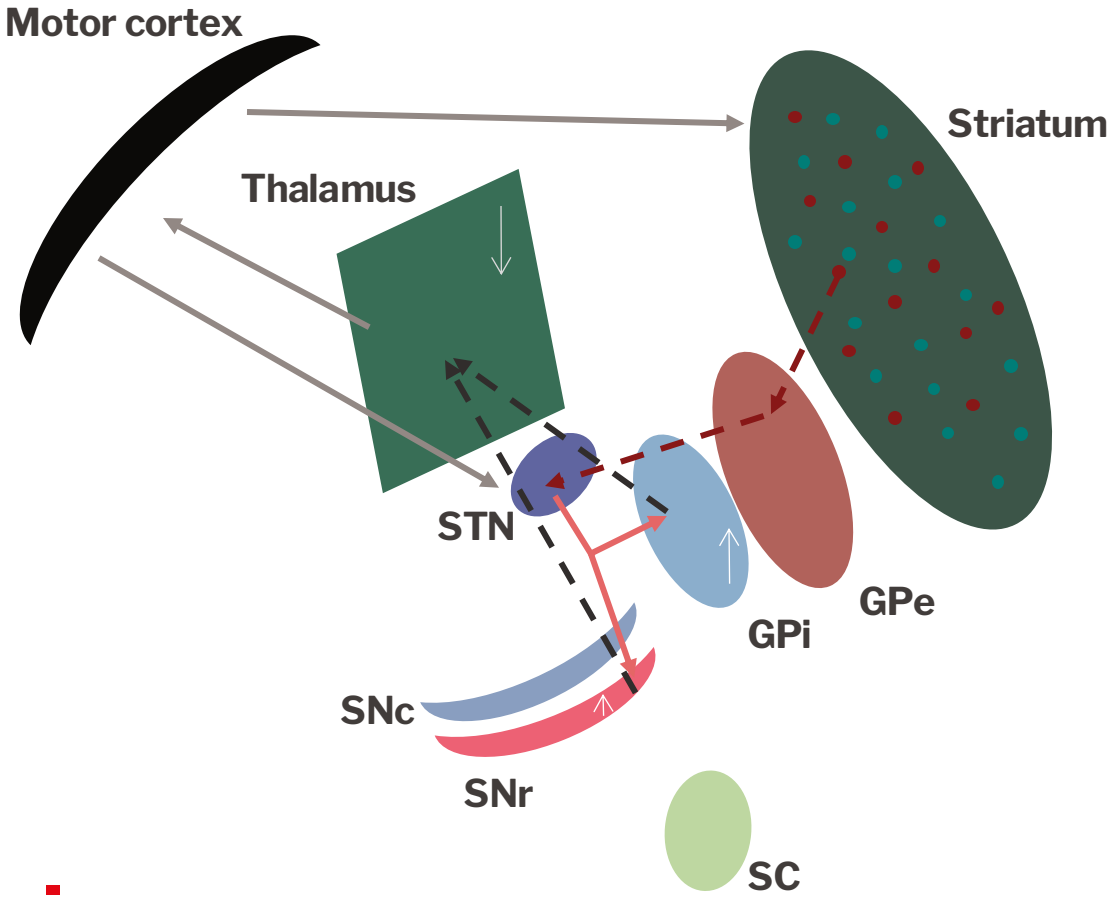

indirect Medium Spiny Neurons (iMNS)

--> suppressing movement

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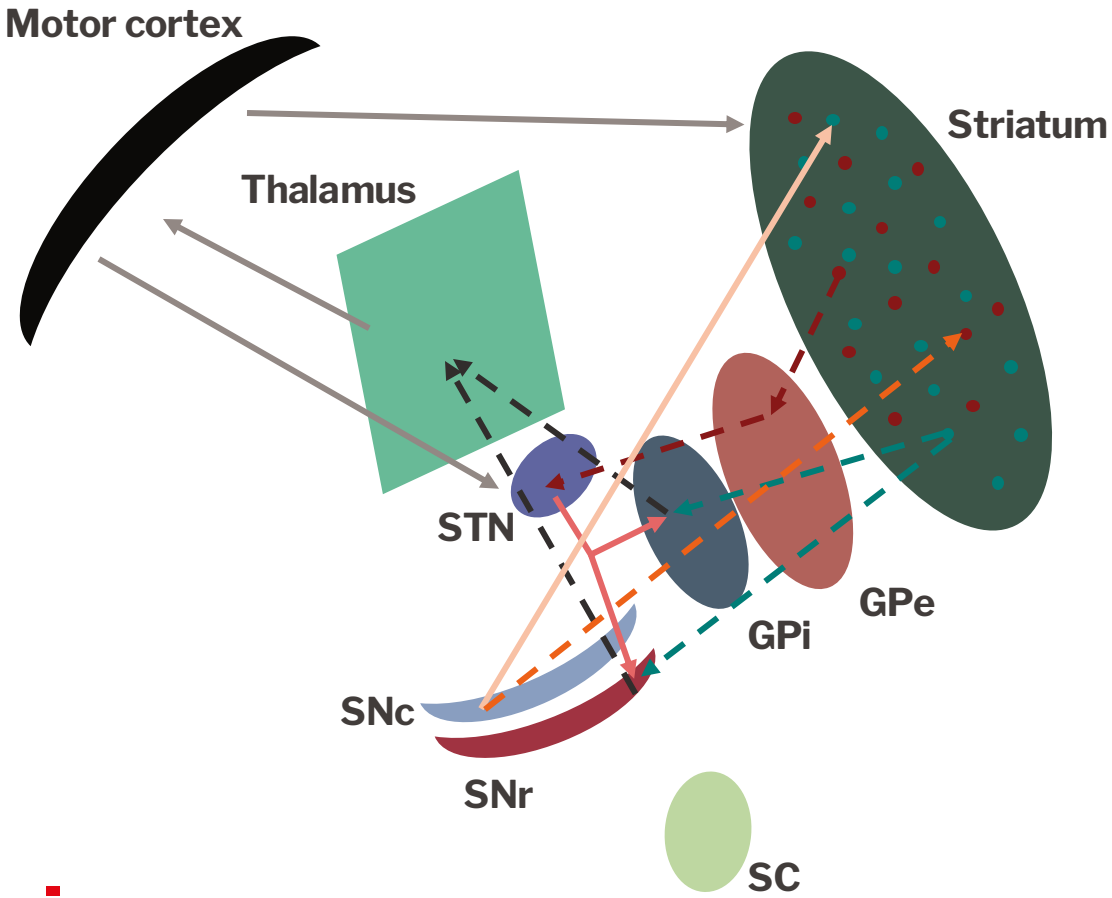

direct Medium Spiny Neurons (dMNS)

--> promoting movement
--> increasing

indirect Medium Spiny Neurons (iMNS)

--> suppressing movement
--> suppressing

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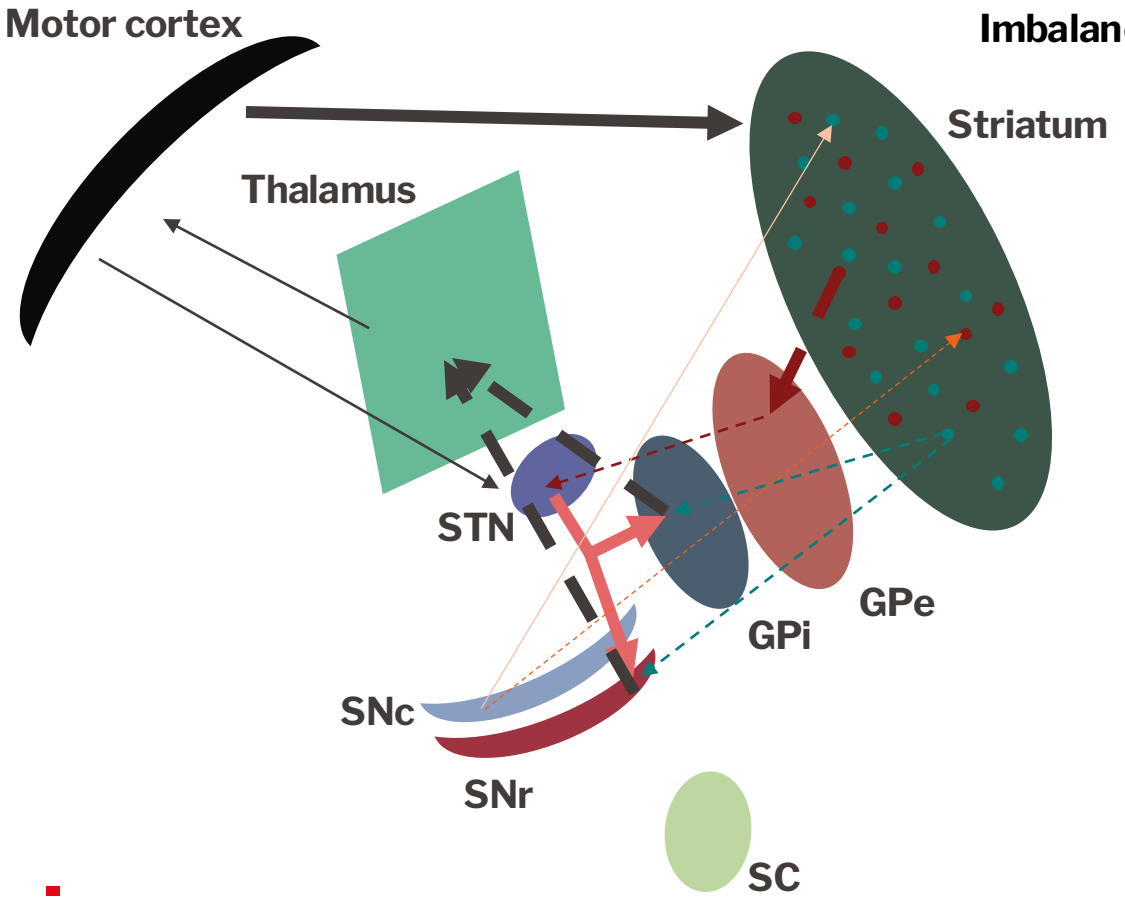
Imbalanced activity between the two pathways



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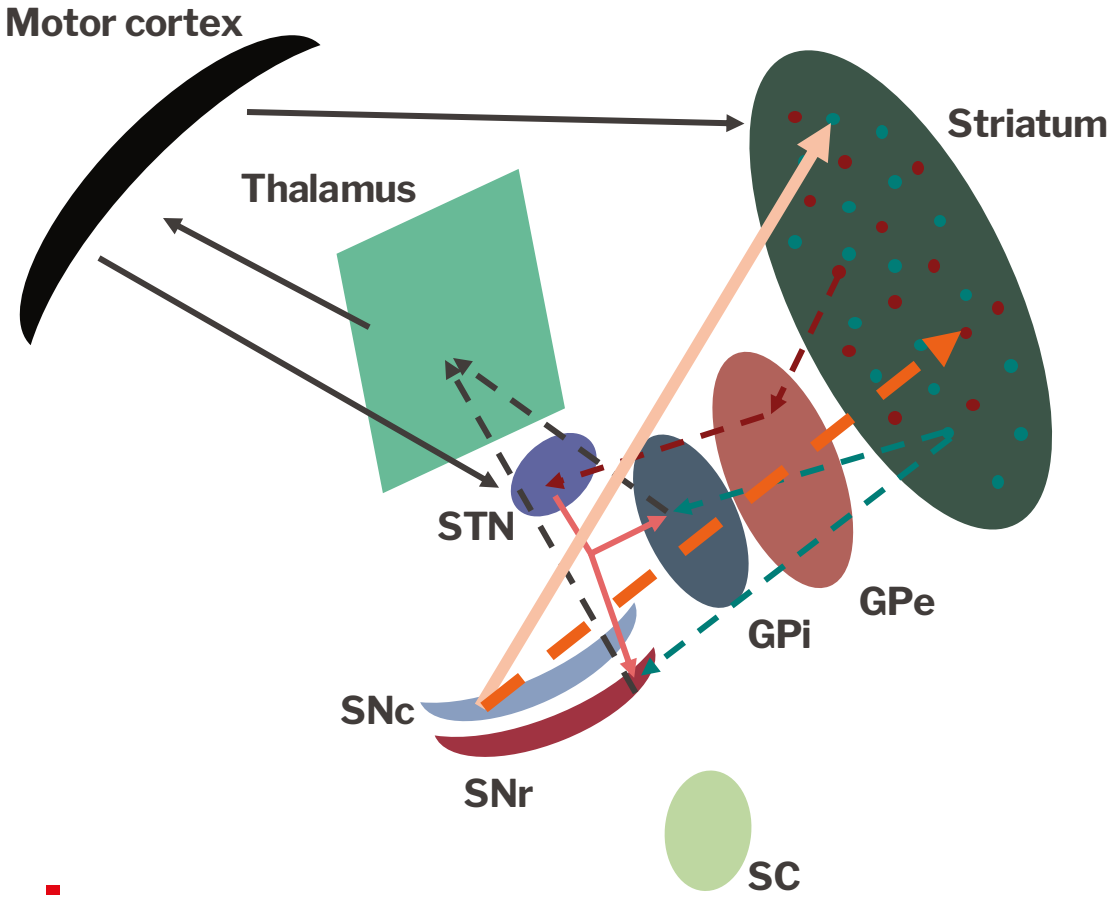
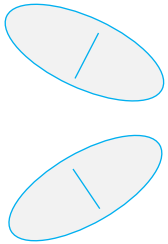
L-DOPA





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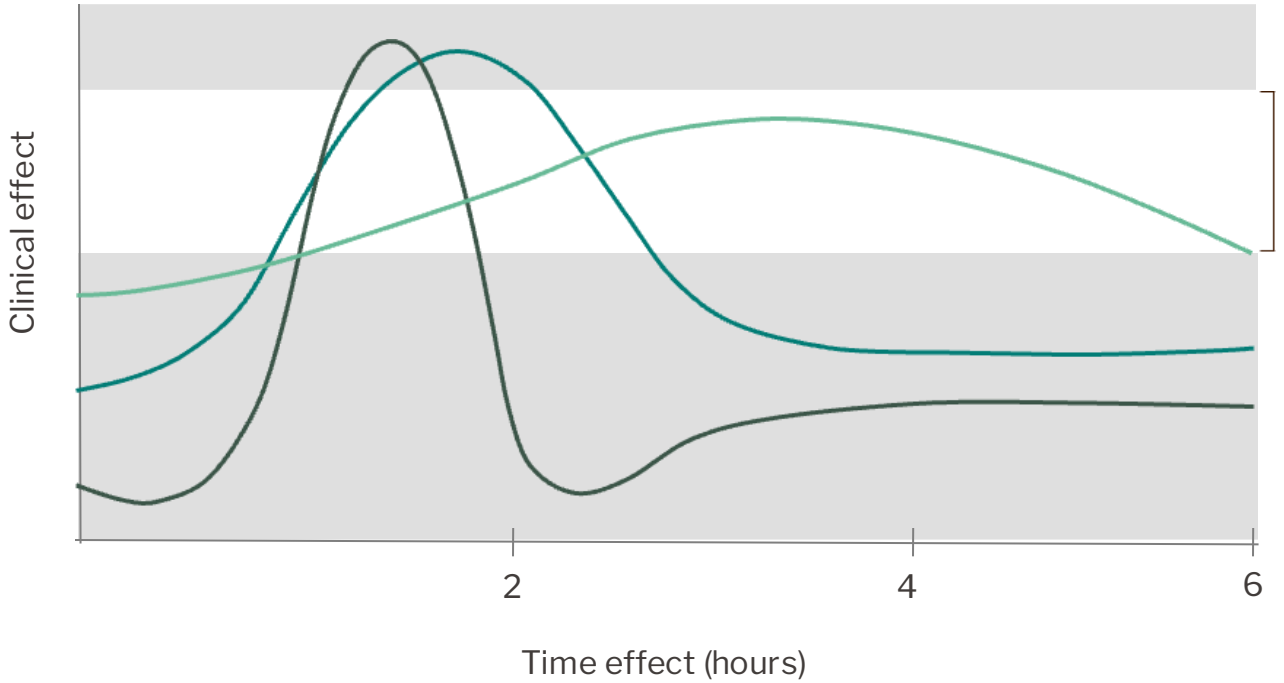
L-DOPA limitations



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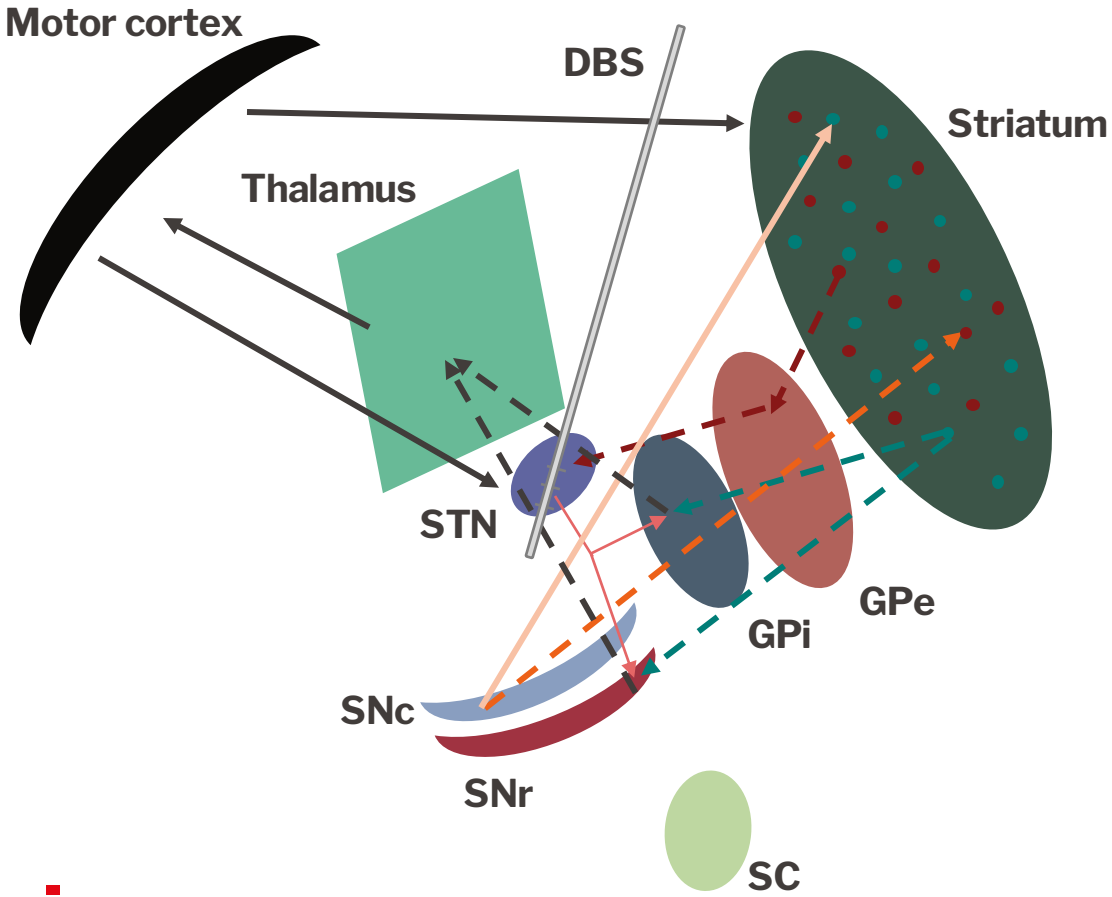
Deep Brain Stimulation



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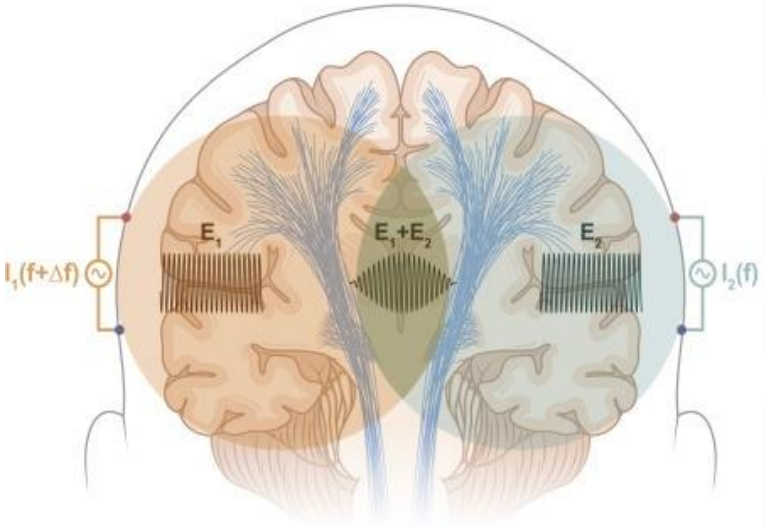
Deep Brain Stimulation limitations

- Higher chance of confusing a Parkinsonian disorder (such as multiple system atrophy) within the first 5 years of diagnosis [5];
- Inability to place the DBS electrode properly due to the brain anatomy;
- Possibility of an infection, hemorrhage, and even mortality during the surgery [6];
- Post-operative side effects such as confusion, delirium, and cognitive decline can be found. Any of these conditions may lead to hospitalization following DBS [6];
- High workload of hospitals and surgeons and growing number of patients.

Temporal Interference (TI)

- Non-invasive brain stimulation technique ;
- Target deep brain regions;
- Uses two high-frequency alternating currents with a slight difference to create an envelop amplitude that oscillates in the low-frequency;
- Provide subthreshold neuromodulation rather than direct activation of neurons [8-9];



General schema of the TI frequencies overlap [7]

Temporal Interference (TI)

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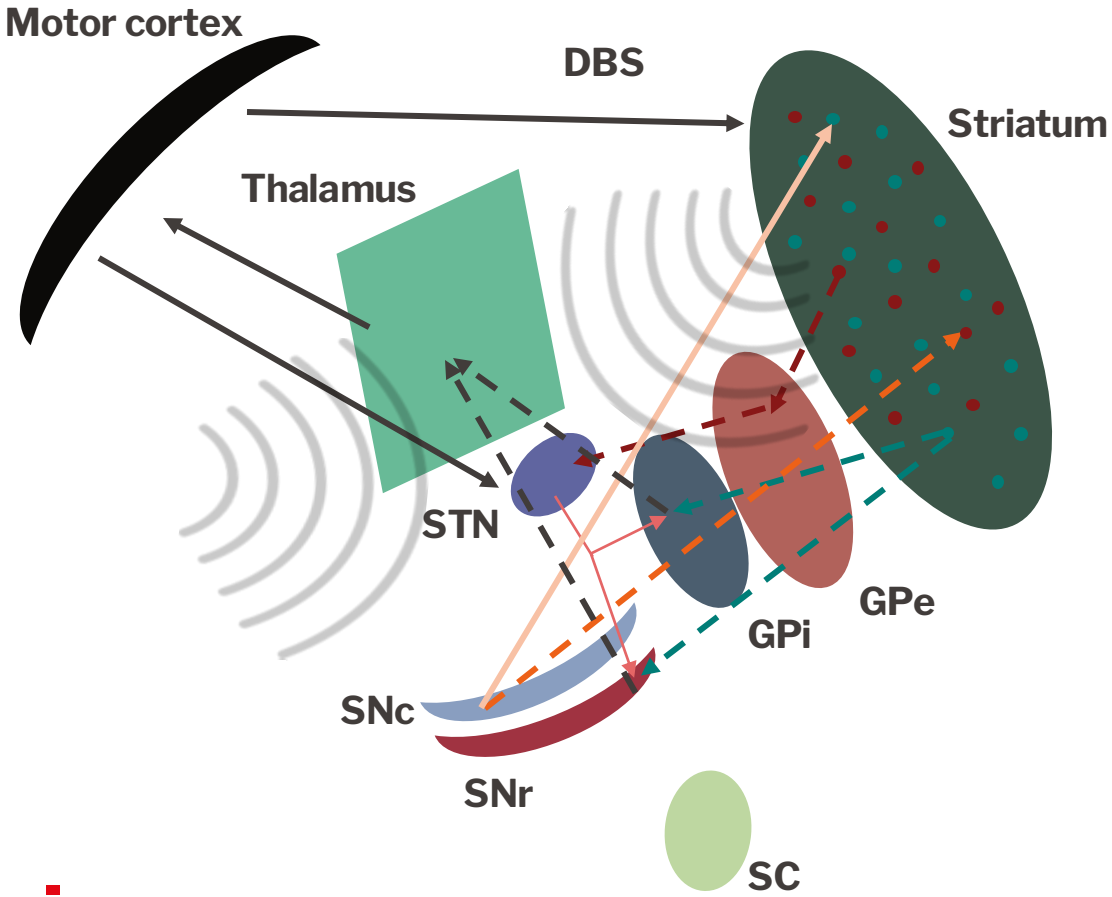

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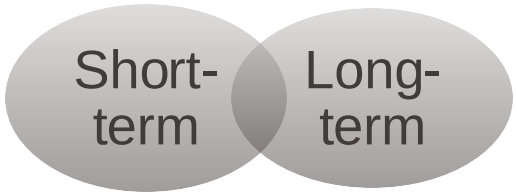
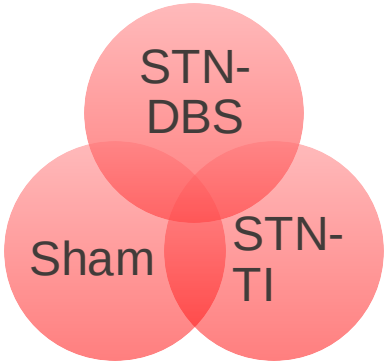
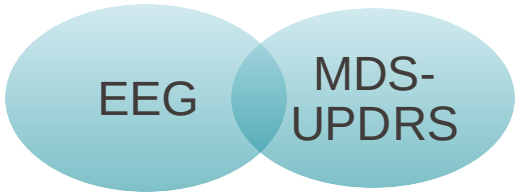
Aim of the study

- Investigate TI mechanism of action
  - Comparing EEG biomarkers of STN stimulation via means of TI and DBS
- Investigate the long term effects of TI
- Investigate feasibility of TI to treat early stage PD
  - We do not expect long term improvements, we would like not to see a fast decline in benefit from stimulation







Hypothesis

- TI is able to disrupt pathological frequencies even being a subthreshold stimulation [10][12]
- STN stimulation via TI results in measurable EEG activity [11][12][13]

[10] C. Yang et al (2024)
[11] J. Dale et al (2020)
[12] Vieira P.G., Krause M.R. (2024)
[13] Ying et al 2022

Group Design

DBS group of early PD patients

Sham group

tTI stimulation group

30s ramp up and 30s ramp down

High frequency tACs

Our Experimental Paradigm

Double-blinded, randomized, sham-controlled protocol, conducted by the World Medical Association's Declaration of Helsinki.

Daily 30-min sessions over 6 weeks

Three groups of 25 patients each

MDS-UPDRS before and after each session

EEG recording during the sessions

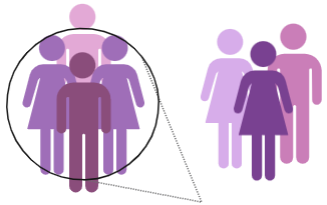
Self report of effects during the day

Methodology

- Head model FEM simulation of electrode placement and current injected
  - Target of 0.65 V/m interfering electric field in STN [10,12,18]
- Resting state stimulation with 1.3kHz and 1.43kHz to generate an envelope of 130Hz [10,13]
  - Similar parameters of current DBS STN stimulation protocols
  - During "medication ON" phase, one hour after ingestion
- EEG recording concurrent with stimulation, to gain insights on mechanism of action and possible ways to optimise parameter space

[12] Vieira P.G., Krause (2024) M.R.
[10] Yang C. (2024)
[13] Ying et al 2022
[18] Francis et al 2003

Participants selection



Inclusion Criteria [10]:

- Diagnosed with idiopathic PD with onset at age 40 or later.
- Responsive to levodopa medication, showing at least a 30% reduction in MDS-UPDRS-III scores after medication.
- Total MDS-UPDRS-III score ≥20.
- Hoehn and Yahr (H&Y) stages between 1.5 and 2.5.
- Regular intake of PD medication for at least 4 weeks before the study.

[10] Yang et al, 2024

Participants selection

Exclusion Criteria [10]**:**

- Presence of other neurologic diseases affecting the study (e.g., epilepsy).
- Orthopedic conditions affecting motor symptoms.
- History of taking antipsychotic drugs, antidepressants, or other drugs affecting dopamine levels.
- Severe psychiatric disorders, such as depression or psychosis.
- History of electroconvulsive therapy.
- Doctor-diagnosed cardiovascular risk factors

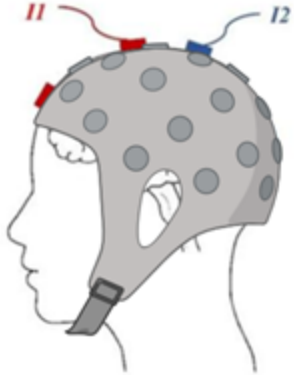
[10] Yang et al, 2024

Why? How many? 25 per group

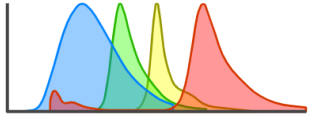
G*power

- It ensures appropriate power to detect medium effects
- It accounts for **drop-outs**
- It allows comparison across groups at different time points
- Accounts for within group **variability**
- Effect size measured with **Cohen's d** set to 0.5 (medium size)
- Alpha level set at 0.05
- Power level set at 0.8

TI-EEG



They work at different frequency ranges in the cortical level



Why?

- Better understanding of the mechanism underlying STN-TI
- Comparing DBS and TI cortical activity

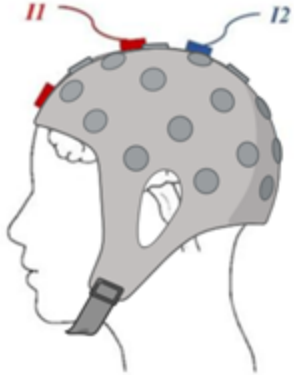
Problem:

- Nonlinear artefacts in the stimulation and recording hardware at beat frequency and its harmonics [11]

Custom-made front-end filters in the current source output and EEG input

[14] Alania et al, 2023

TI-EEG



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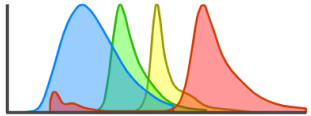

Set up configuration:

- Passive HPF after TI stimulator
- Active LPF before EEG

This ensures the nonlinear artefact at the modulation frequency is below EEG noise level

Problem:

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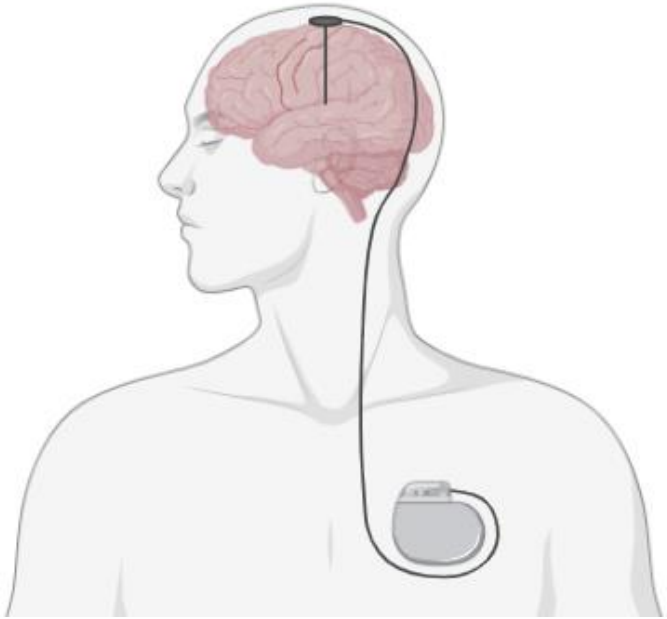
Custom-made front-end filters in the current source output and EEG input

[14] Alania et al, 2023

Beatrice Campo

DBS-EEG

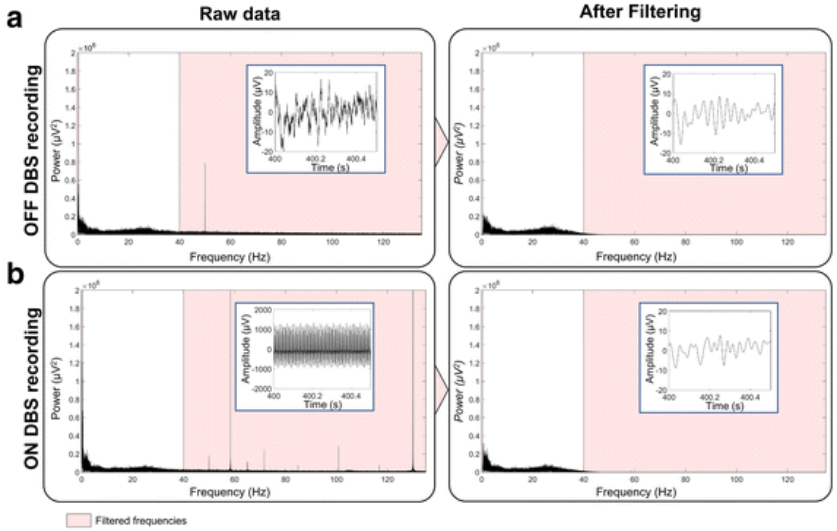


DBS-EEG

DBS-EEG

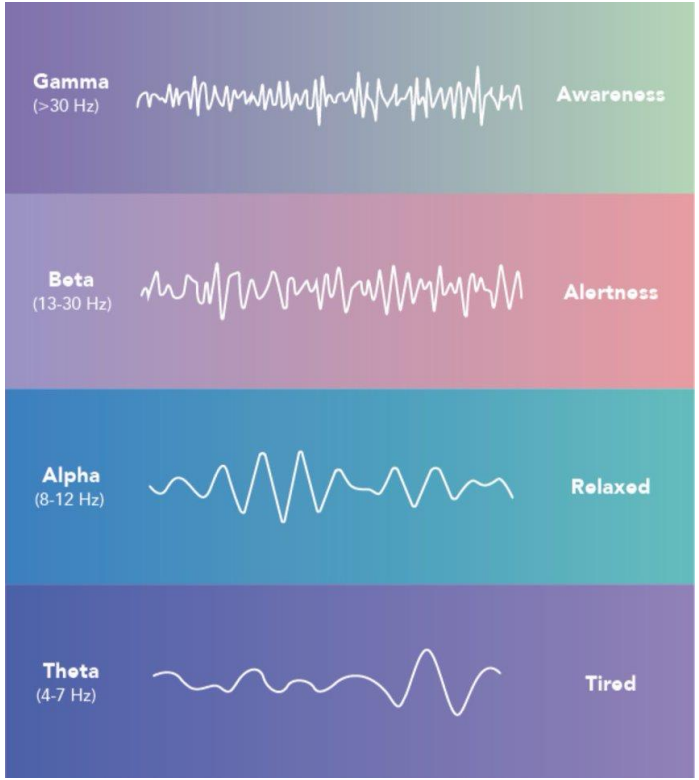
- DBS pulses usually induce high amplitude artefacts on EEG recordings, monopolar stimulation that induces artefacts up to 30 ms. [12]

- Low-pass filtering (e.g. with a 50 Hz cutoff) is usually sufficient to remove the DBS artefact and its harmonics when DBS is applied at high frequency, e.g. 130 Hz.



[15] Sun et al, 2014

Expected cortical activity



STN-DBS may enhance gamma oscillations, reflecting improved cortical synchronization and motor control

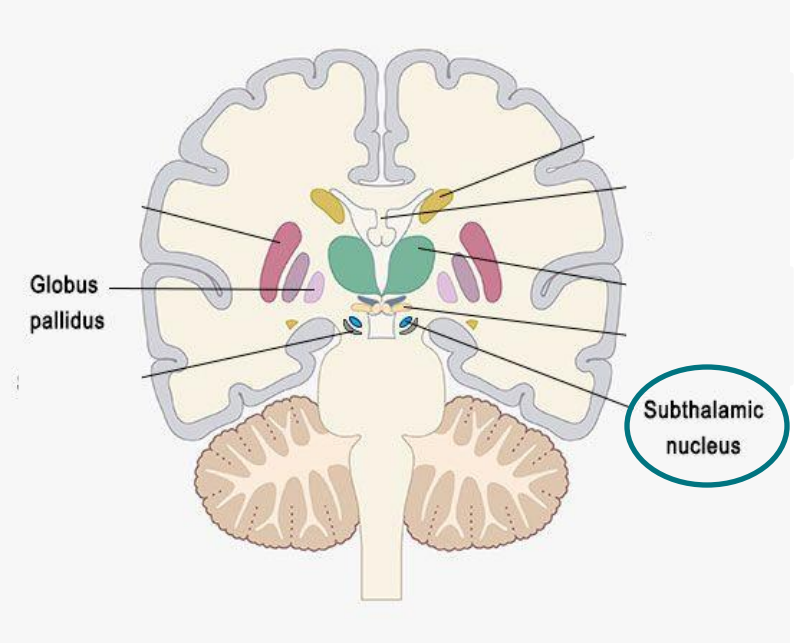
STN stimulation significantly reduces pathological beta power in both the STN and motor cortex.

PD patients typically show reduced resting-state alpha power, associated with disrupted cortical networks. STN-DBS might partially restore alpha rhythms in some cortical regions, reflecting improved baseline network stability and sensorimotor integration [13]

[16] Kibleur et al, 2018

Innovation

- One study published targetting **GPi**, while we target **STN**
- Not only behavioral data but also EEG (mechanisms, biomarkers)
- Comparison of DBS and TI EEGs to compare cortical oscillations
- Long term assessment of TI (online/offline effects)
- Assessing long-term complications via recording patient's diaries



STN-DBS is generally associated with greater reductions in motor symptoms as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) compared to GPi-DBS. [14]

[17] Wong et al, 2020

Limitations

- Only one set of parameters→ different envelope frequencies, amplitudes, and carrier frequencies
- Non-personalized solution

Possible variations

- TI stimulation with more couples of electrodes [19]
  - Robustness of filters will be assessed by a pilot study
  - In presence of unexpected artefacts, the experiment will be conducted with only two pairs of electrodes
- T1 MRI acquisition for personalized FEM simulation and accurate parameter tuning

[19] Acerbo et al, 2024

Open Questions & Developments

- Offline effects of TI?
- Will there be adverse effects on using TI every day for a long time?
- Basis for implementing TI home-based or subcutanoeus electrodes
- If any biomarkers have been found-> **closed loop applications**


Thanks for the attention!
Any questions?

References:

1. Kouli, A., Torsney, K. M., & Kuan, W. (2018). Parkinson's Disease: etiology, neuropathology, and pathogenesis. In *Codon Publications eBooks* (pp. 3–26).
2. Templeton, J. M., Poellabauer, C., & Schneider, S. (2022). Classification of Parkinson's disease and its stages using machine learning. *Scientific Reports*, *12*(1).
3. McGregor, M. M., & Nelson, A. B. (2019). Circuit mechanisms of Parkinson's disease. *Neuron*, *101*(6), 1042–1056
4. Halbig, T., & Koller, W. (2007). Levodopa. *Handbook of Clinical Neurology*, 31–72.
5. Okun, M. S., & Foote, K. D. (2010). Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. Expert Review of Neurotherapeutics, 10(12), 1847–1857.
6. Olson, M. C., Shill, H., Ponce, F., & Aslam, S. (2023). Deep brain stimulation in PD: risk of complications, morbidity, and hospitalizations: a systematic review. Frontiers in Aging Neuroscience, 15.
7. Mirzakhalili, E., Barra, B., Capogrosso, M., & Lempka, S. F. (2020). Biophysics of temporal interference stimulation. *Cell Systems*, *11*(6), 557-572.e5.
8. Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S. B., Rudenko, A., Suk, H., Cassara, A. M., Neufeld, E., Kuster, N., Tsai, L., Pascual-Leone, A., & Boyden, E. S. (2017). Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell*, *169*(6), 1029-1041.e16.
9. Wessel, M. J., Beanato, E., Popa, T., Windel, F., Vassiliadis, P., Menoud, P., Beliaeva, V., Violante, I. R., Abderrahmane, H., Dzialecka, P., Park, C., Maceira-Elvira, P., Morishita, T., Cassara, A. M., Steiner, M., Grossman, N., Neufeld, E., & Hummel, F. C. (2023). Noninvasive theta-burst stimulation of the human striatum enhances striatal activity and motor skill learning. *Nature Neuroscience*, *26*(11), 2005–2016.
10. Yang, C., Xu, Y., Feng, X., Wang, B., Du, Y., Wang, K., Lü, J., Huang, L., Qian, Z., & others. (2024). Transcranial temporal interference stimulation of the right globus pallidus in Parkinson's disease. Movement Disorders.
11. Dale et al, 2020, Evoked potentials generated by deep brain stimulation for Parkinson's disease
12. Vieira, P.G., Krause, M.R. & Pack, C.C. Temporal interference stimulation disrupts spike timing in the primate brain. *Nat Commun* **15**, 4558 (2024). https://doi.org/10.1038/s41467-024-48962-2

References:

13. Ying Yu ,Fang Han, Qingyun Wang,(2022)Exploring phase–amplitude coupling from primary motor cortex-basalganglia–thalamus network model
14. Alania, K., Rhodes, E., Bin Suhayl, I., Violante, I., & Grossman, N. (2023). Investigating the direct effect of temporal Interference (TI) stimulation on cortical activity with simultaneous EEG recording in humans. Movement Disorders, 16(1), 343
15. Sun, Y., Farzan, F., Garcia Dominguez, L., Barr, M. S., Giacobbe, P., Lozano, A. M., Wong, W., & Daskalakis, Z. J. (2014). A novel method for removal of deep brain stimulation artifact from electroencephalography. Journal of Neuroscience Methods, 237, 33–40.
16. Kibleur, A., & David, O. (2018). Electroencephalographic read-outs of the modulation of cortical network activity by deep brain stimulation. Bioelectronic Medicine, 4(2).
17. Wong, J. K., Viswanathan, V. T., Nozile-Firth, K. S., Eisinger, R. S., Leone, E. L., Desai, A. M., Foote, K. D., Ramirez-Zamora, A., Okun, M. S., & Wagle Shukla, A. (2020). STN versus GPi deep brain stimulation for action and rest tremor in Parkinson's disease. Frontiers in Human Neuroscience, 14, 578615.
18. Joseph T. Francis, Bruce J. Gluckman and Steven J. Schiff (2003), Sensitivity of Neurons to Weak Electric Fields Journal of Neuroscience 13 August 2003, 23 (19) 7255-7261; https://doi.org/10.1523/JNEUROSCI.23-19-07255.2003
19. Acerbo, E., Botzanowski, B., Dellavale, D., Stern, M. A., Cole, E. R., Gutekunst, C.-A., Gantt, M. L., Steiner, M., Missey, F., 19. Cassarà, A. M., Neufeld, E., Berglund, K., Jirsa, V. K., Gross, R. E., Drane, D. L., Głowacki, E. D., Pakhomov, A. G., & Williamson, A. (2024). Improved temporal and spatial focality of non-invasive deep-brain stimulation using multipolar single-pulse temporal interference with applications in epilepsy. bioRxiv