Principles and Applications of Neuromodulation

MDS-PAS 5th Annual Neuromodulation School for Movement Disorders
13-Aug-2026

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Disclosures

- **Grant support:** National Institutes of Health (NINDS K23 NS099380, NIMH P50 MH119467, NINDS U01 NS121616, NIDCD R01DC022949), American Academy of Neurology/American Brain Foundation, Bachmann Strauss Dystonia and Parkinson's Foundation, Collaborative Center for X-linked Dystonia Parkinsonism, Michael J Fox Foundation
- **Industry-sponsored clinical trials:** Medtronic, Asklepios Biopharmaceutical
- **Consulting:** Medtronic (scientific advisory board), MarvelBiome, BlueRock Therapeutics (data safety monitoring board), iota Biosciences/ Epia Neuro, Franklin Causality Insurance Company (expert testimony)

FDA approved or authorized neuromodulation

Non-invasive

ECT — Catatonia; severe MDD (MDD / bipolar)

TMS — MDD; OCD; smoking cessation; migraine; PTSD

TDCS — MDD; CES: insomnia/anxiety[1]

eTNS — Migraine; pediatric ADHD

nVNS — Migraine; cluster; HC / PH

Transcranial NS — PTSD symptoms (device-specific)

Tongue / bimodal — MS gait rehabilitation; tinnitus

FUTURE / IN DEVELOPMENT

- tACS / temporal-interference stimulation
- Low-intensity focused ultrasound

Implanted

DBS — Tremor; PD; dystonia OCD[2]; epilepsy

RNS — Drug-resistant epilepsy

VNS — Epilepsy; treatment-resistant depression; paired stroke rehabilitation

FUTURE / IN DEVELOPMENT

- Implantable BCI: communication and motor restoration

Functional ablation

MRgFUS VIM — Essential tremor; tremor-dominant PD

MRgFUS GPi — PD motor complications

MRgFUS PTT — PD motor complications

RF ablation — ET, PD, Dystonia

Radiosurgery — ET, PD, Dystonia

FUTURE / IN DEVELOPMENT

- Vo / Vop, STN, cZI, ALIC, and other targets

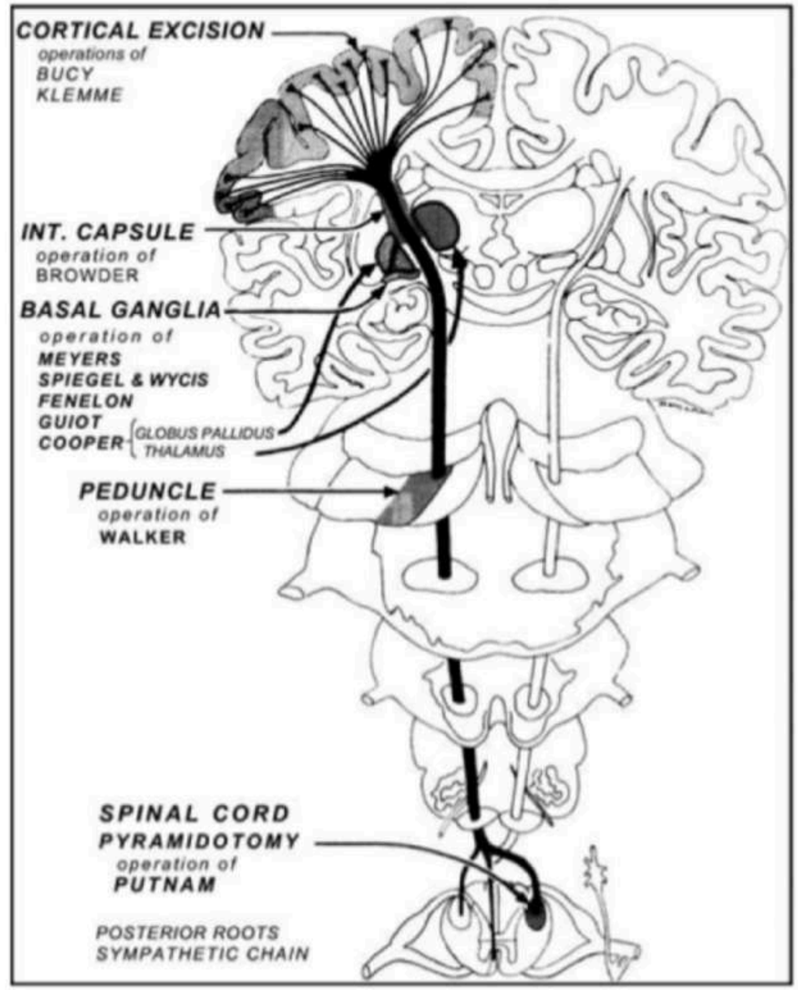
Outline

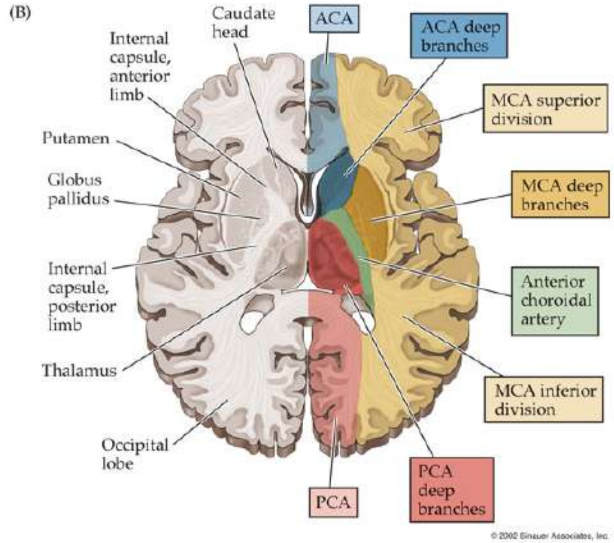
- A brief history of lesion therapy and deep brain stimulation
- Is DBS a “reversible lesion?”
- Effect of stimulation on neural tissue
- Mechanisms of DBS
- Expanding options for neuromodulation

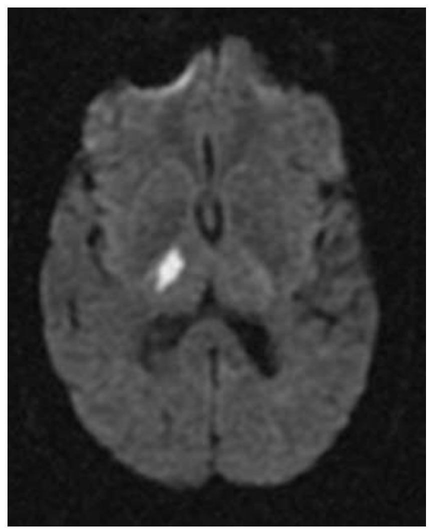
Early surgery for Parkinson’s disease

- **Surgical lesions of**
  - spinal cord
  - spinal nerve roots
  - motor cortex
  - cerebral peduncle

- **Limited benefit and high burden of side effects**







Anterior Choroidal Artery Ligation for Involuntary Movements

Irving S. Cooper

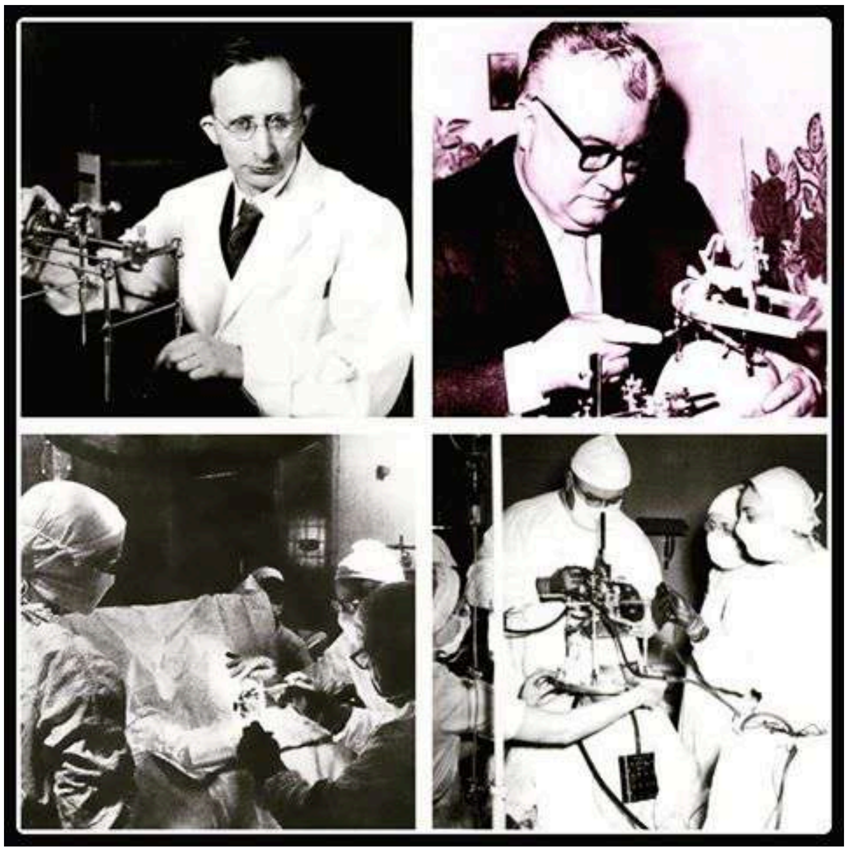
Department of Neurosurgery, New York University-Bellevue Medical Center, New York

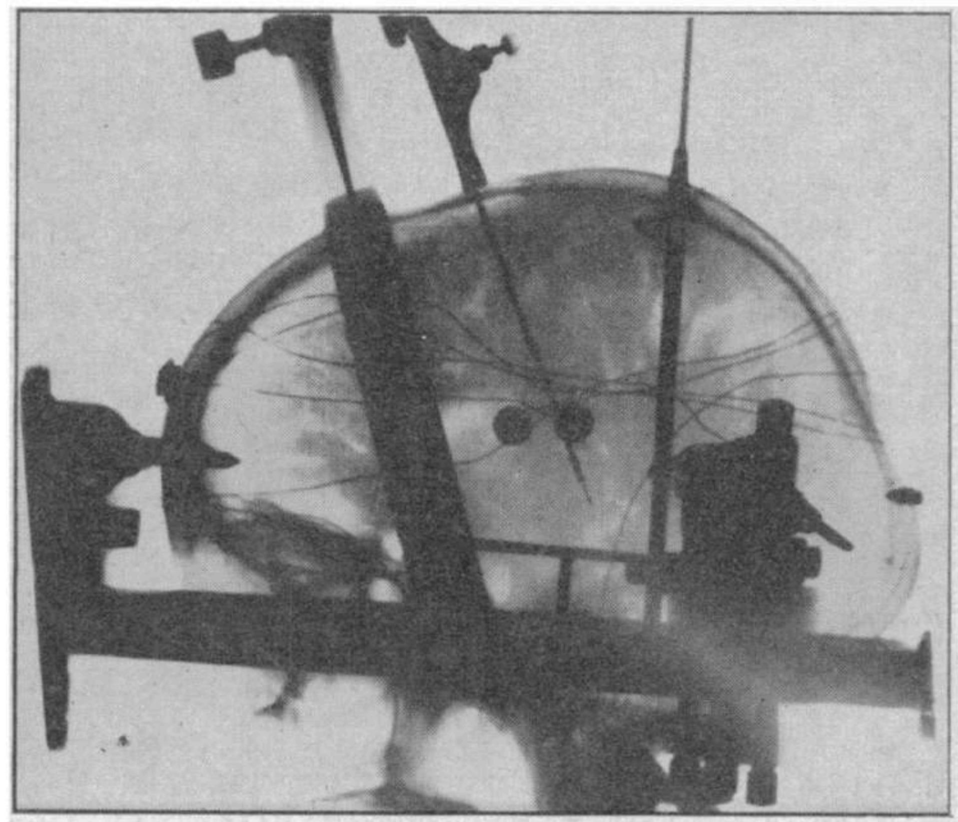
A new procedure for the investigative surgical treatment of involuntary movement disorders has been in use for the past 7 months. Certain significant clinical and physiological consequences of the operation appear to be worthy of note at this time. The procedure consists of an attempt to affect involuntary movement disorders and disorders of muscular tonus by ligation of the anterior choroidal artery. The rationale of this procedure lies in the fact that this blood vessel supplies most of the structures which have been attacked surgically in the attempt to relieve intractable involuntary movements (*1–4*). Among the structures irrigated by this vessel are the globus pallidus, ansa lenticularies, red nucleus, retrolenticular portion of the internal capsule, corpus luysii, substantia nigra, optic tract, and cerebral peduncle (*5*).

We should like to point out that the anterior choroidal artery has been ligated 8 times in 6 patients; the ligations were performed bilaterally in 2 of the cases. In our early studies, we have noted striking alleviations of Parkinsonian tremor at rest in the contralateral extremities. The procedure has been invariably followed by disappearance of most of the rigidity and cogwheelism from the contralateral extremities. There has been no instance of contralateral hemiplegia or hemianesthesia which was previously reported to be invariable following occlusion of this vessel (*6*). Tremor at rest has been relieved in the first patient of this series, since the operation was performed 7 months ago. This technique is

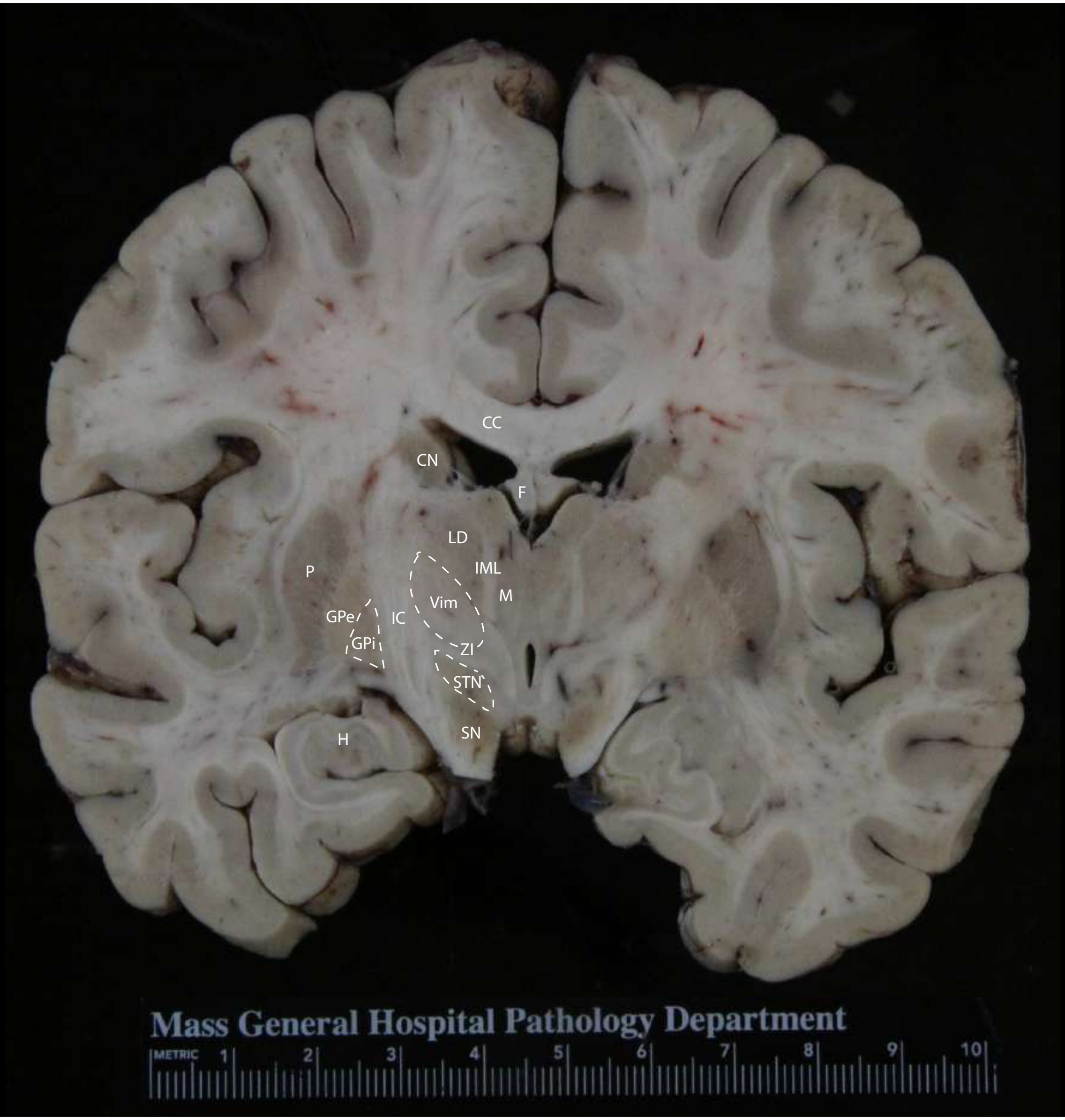
Invention of the stereotactic frame

New techniques enabled surgeons to place lesions precisely in deep structures





Ernest Spiegel and Henry Wycis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CN
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Mass General Hospital Pathology Department
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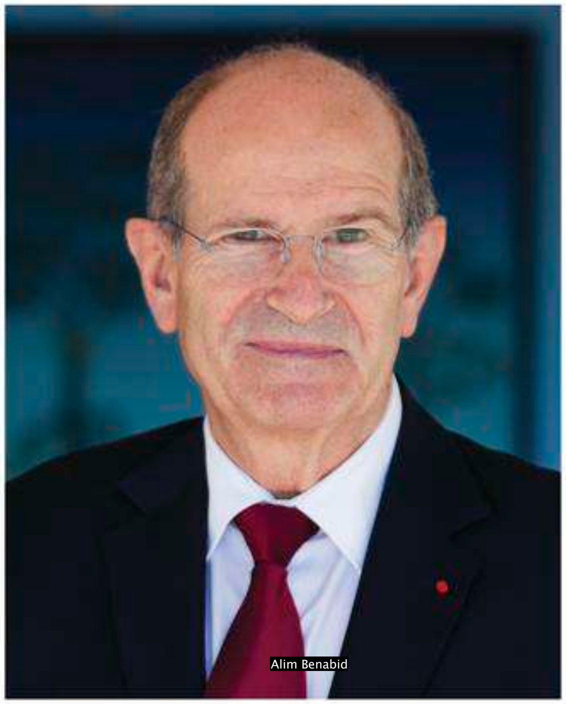
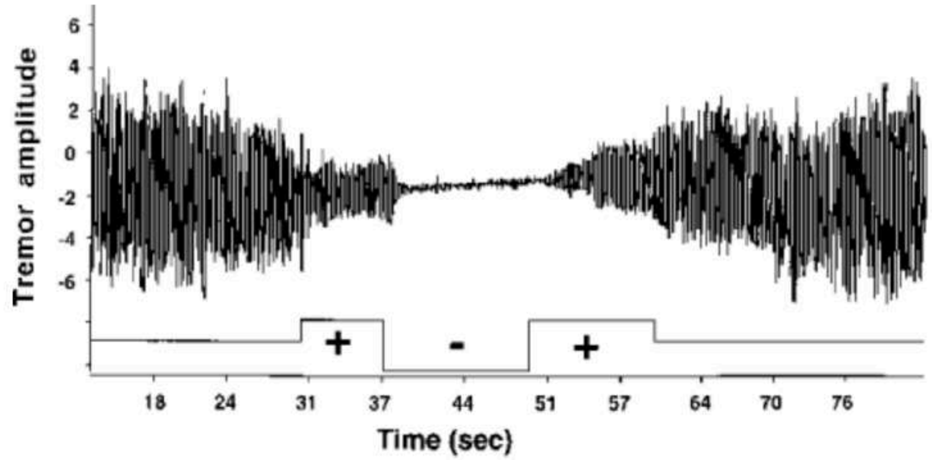
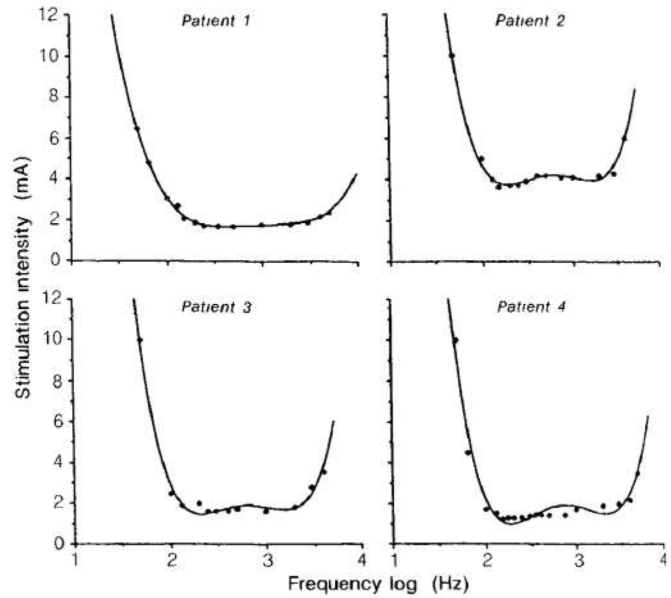
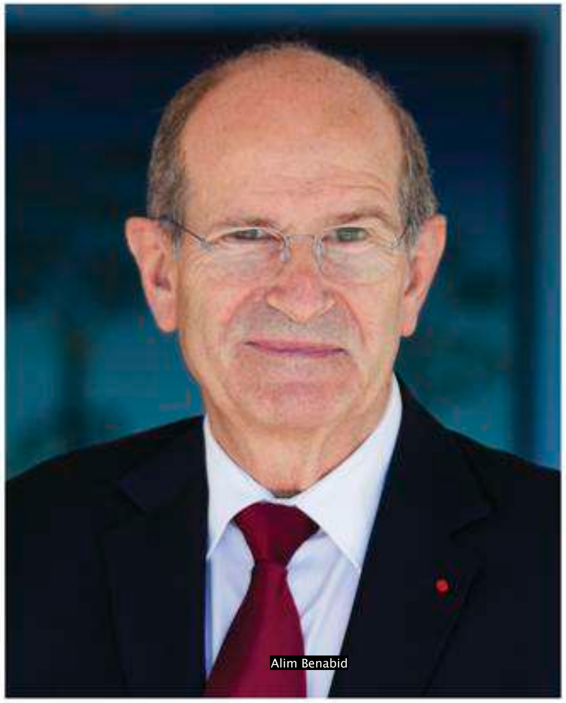


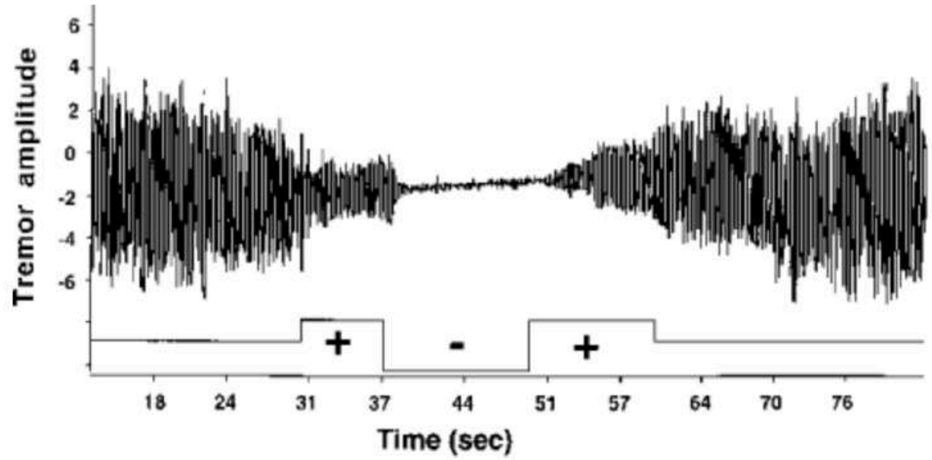




Relation between electrical stimulation frequency and intensity necessary to abolish tremor in four individual patients.

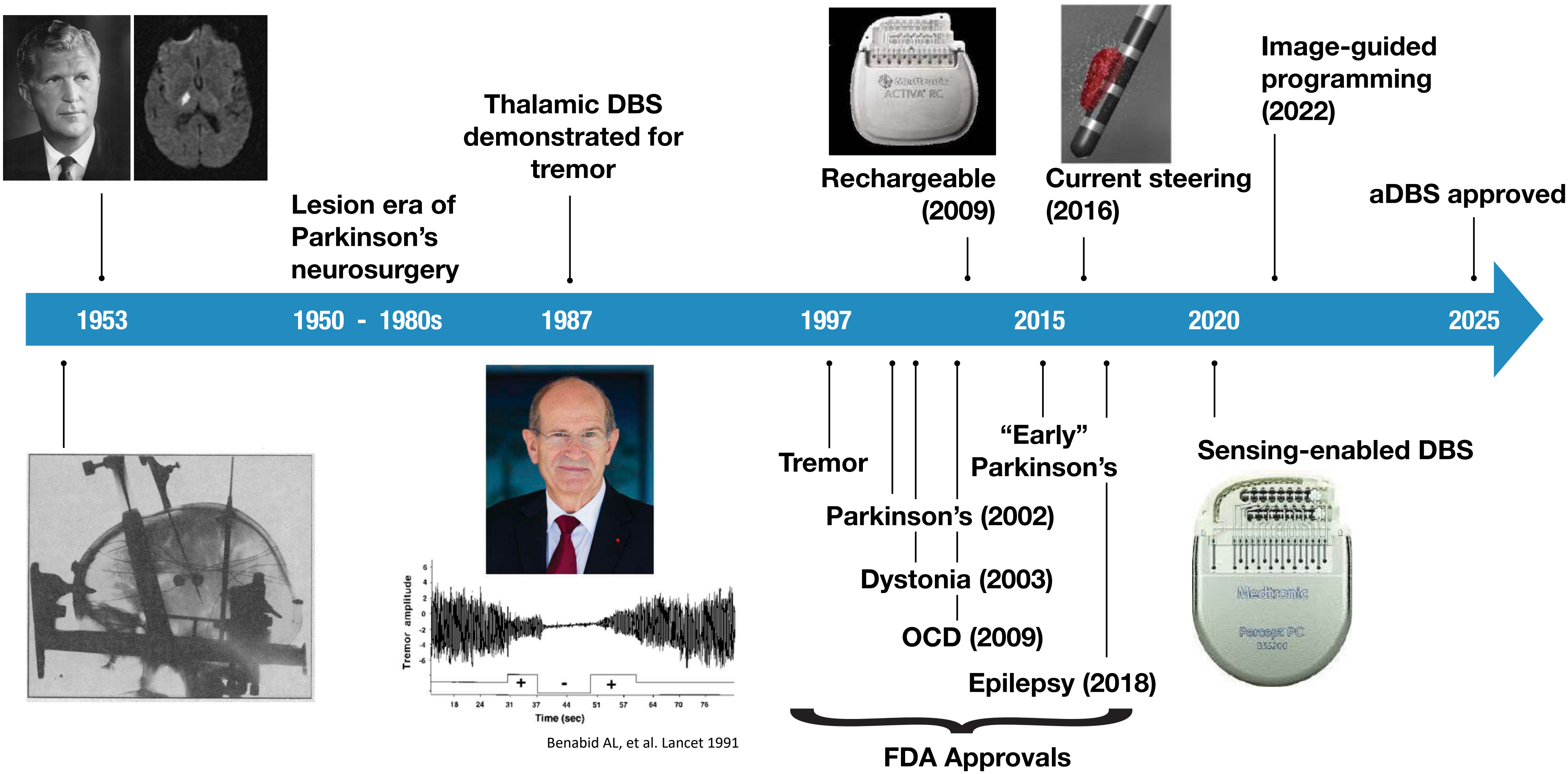
Benabid AL, et al. Lancet 1991


Alim Benabid

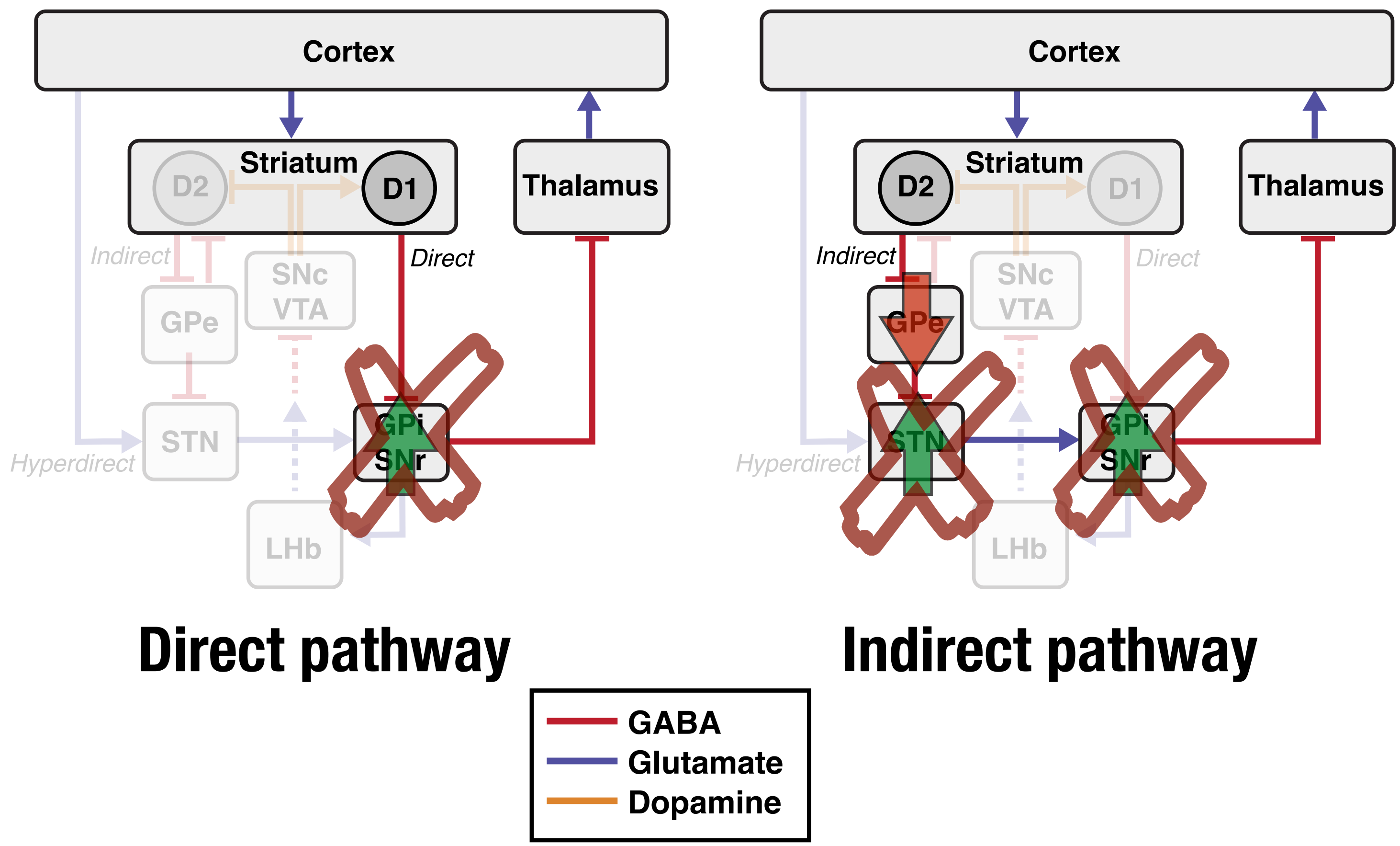

Tremor amplitude
6
4
2
0
-2
-4
-6
+
-
+
18
24
31
37
44
51
57
64
70
76
Time (sec)


A
B
C
D
E
6 CM

A brief history of deep brain stimulation



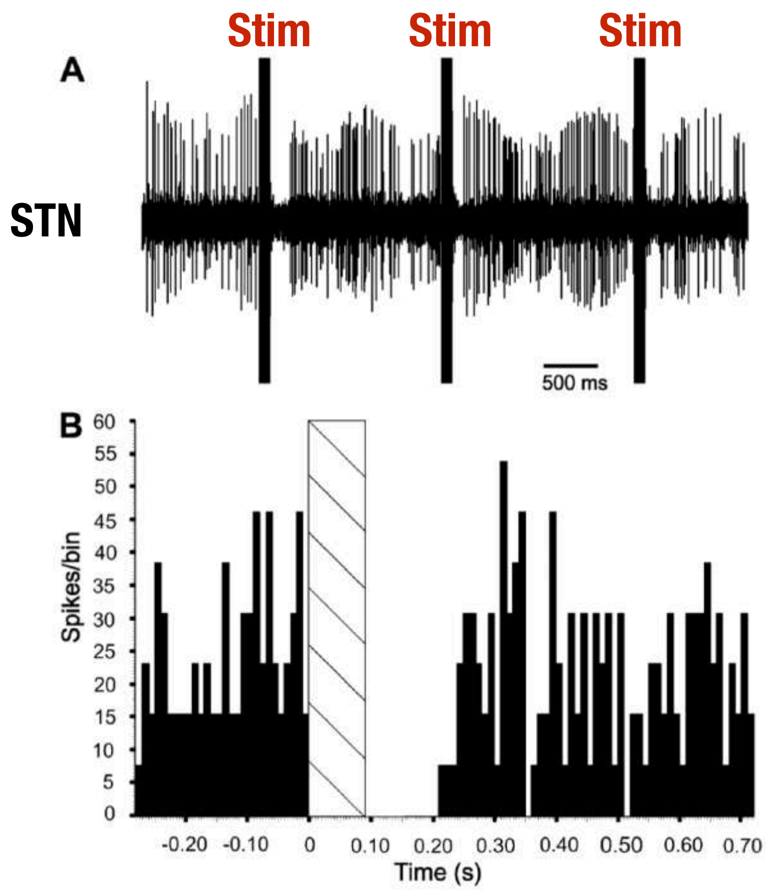
Rate model of Parkinson's disease



Soares et al. J Neurosci. 2004
Bergman et al., J Neurophysiol. 1994

Rate model of DBS

A reversible lesion?



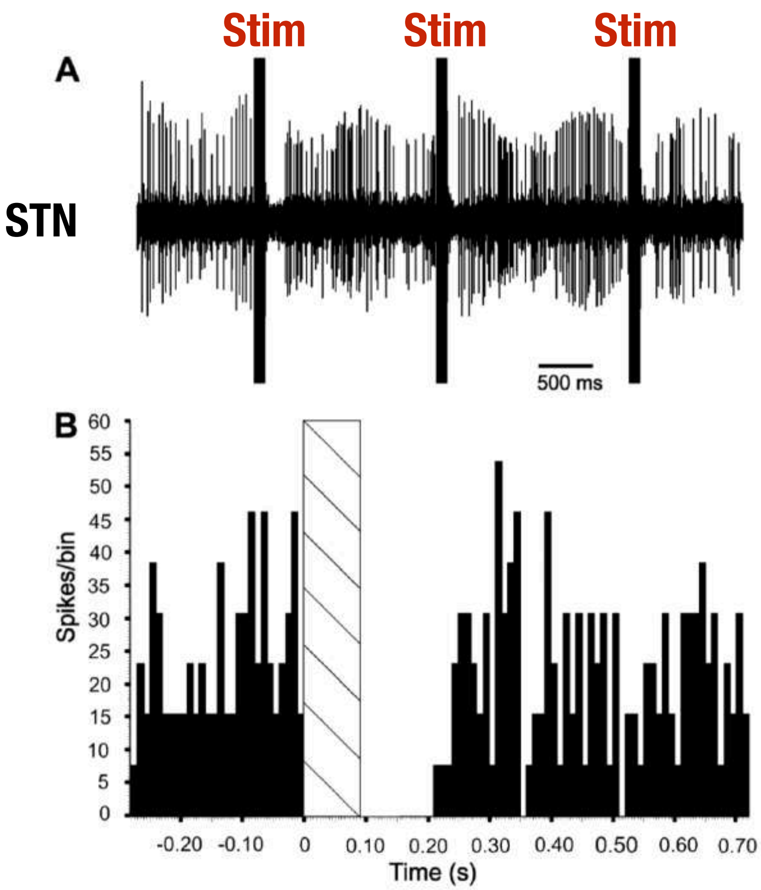
Filali et al., Experimental Brain Research 2004

<u>Mechanisms</u>

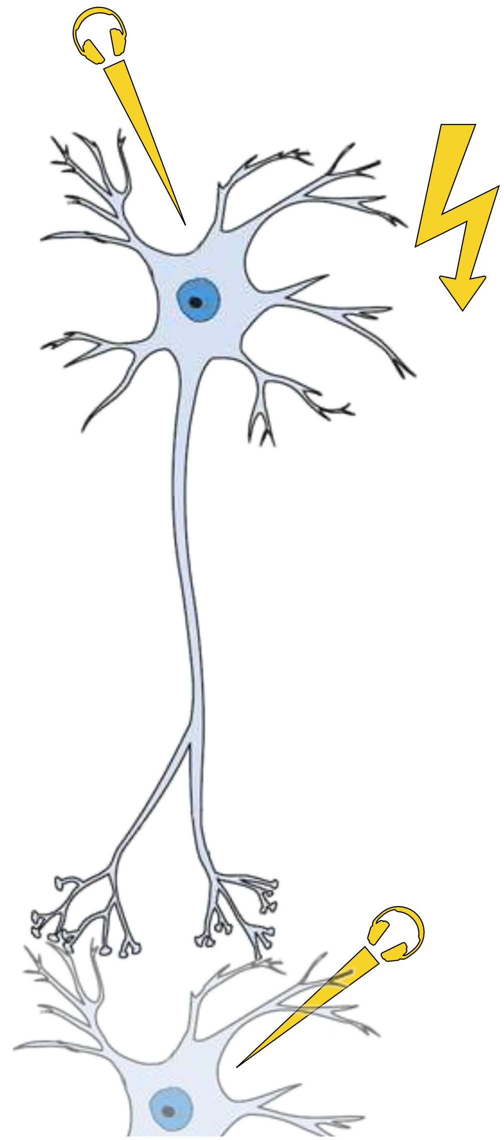
- **Incomplete recovery of voltage-gated Na channels**
- **Opening of voltage-gated K channels**
- **"Depolarization block"**
- **Local release of GABA (especially for prolonged effects)**

Rate model of DBS

A reversible lesion?



Filali et al., Experimental Brain Research 2004



Rate model of DBS

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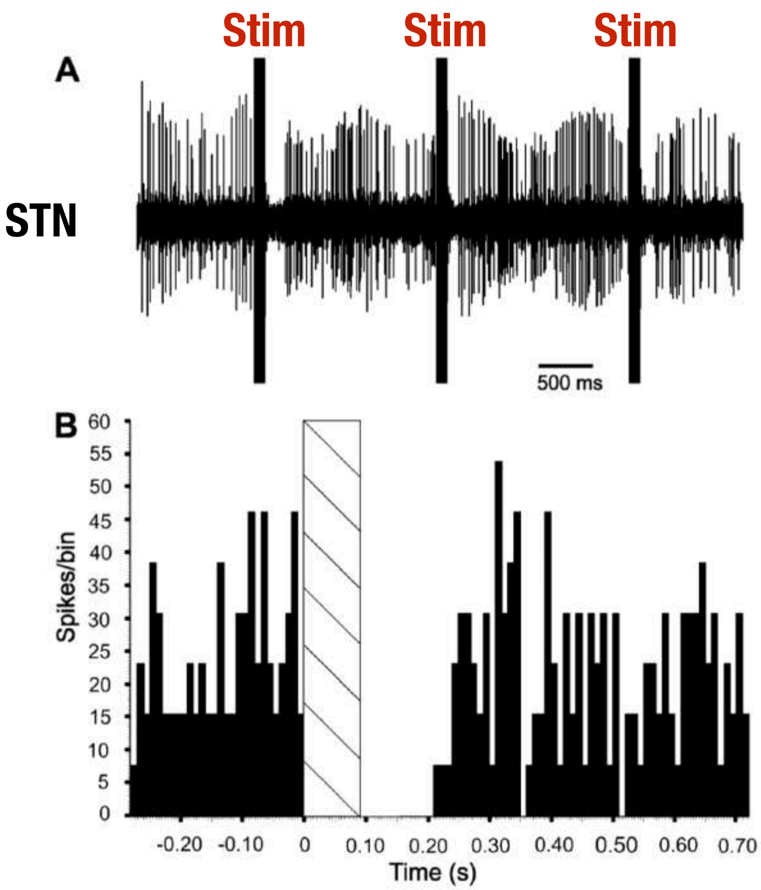
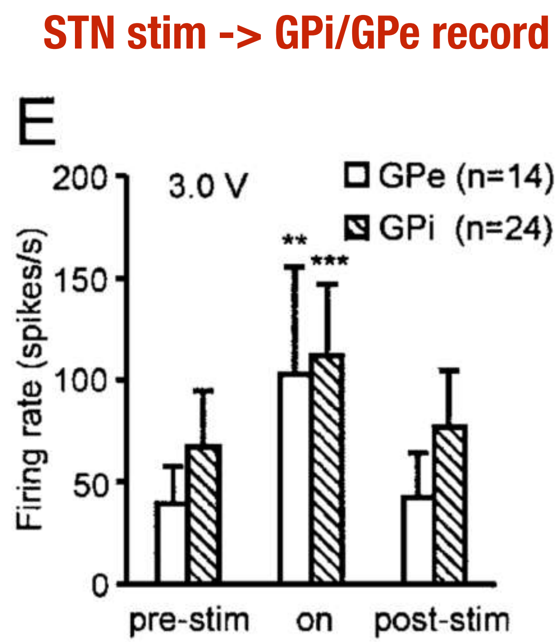


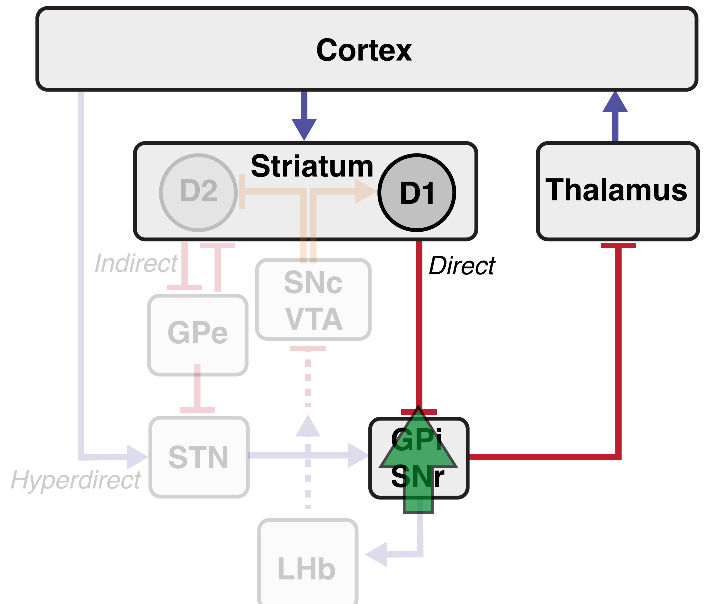
Filali et al., Experimental Brain Research 2004



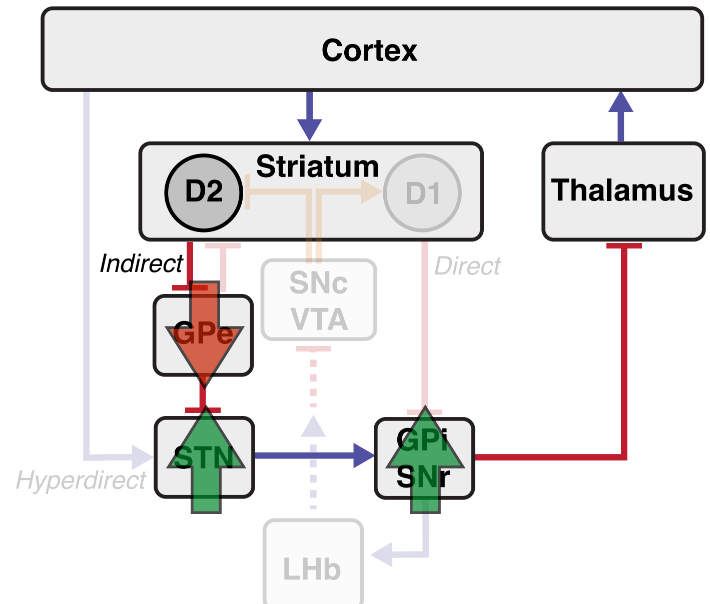
Hashimoto et al., J. Neurosci 2003

Rate model of Parkinson's disease

Not adequate to explain the effect of DBS



Direct pathway

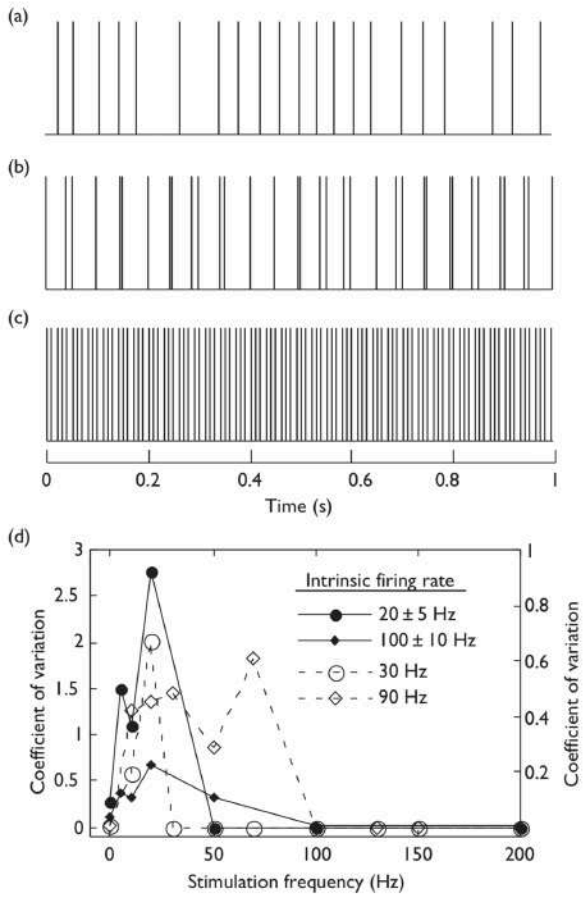


Indirect pathway

GABA
Glutamate
Dopamine

Soares et al. J Neurosci. 2004
Bergman et al., J Neurophysiol. 1994

DBS acts as an informational lesion



20 ± 5 Hz spiking

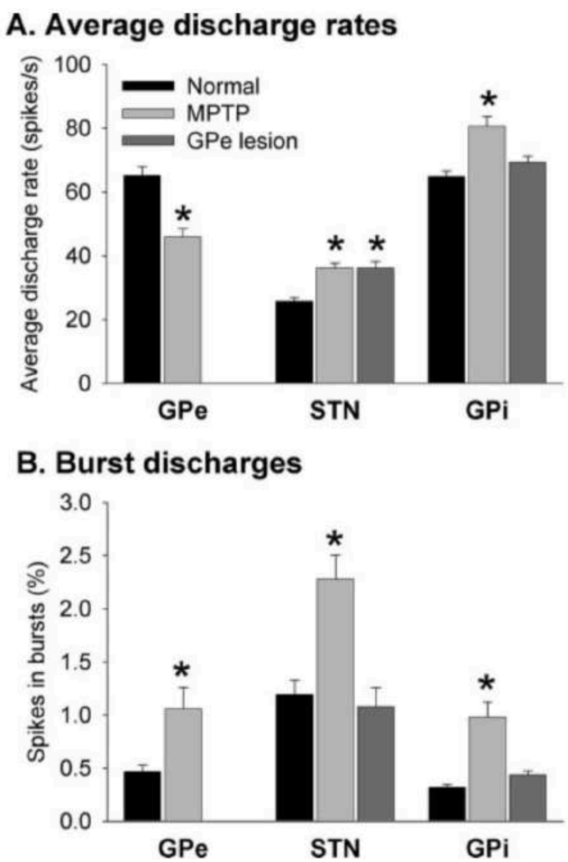
20 ± 5 Hz spiking +
20 Hz stimulation

20 ± 5 Hz spiking +
100 Hz stimulation

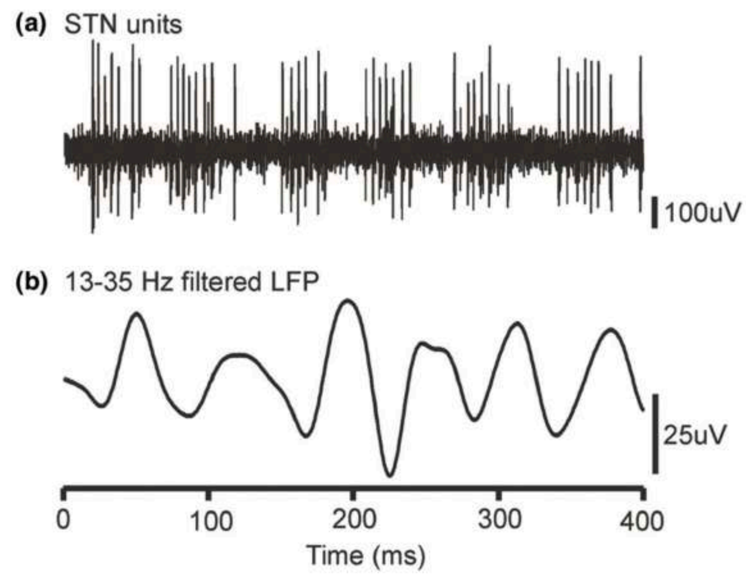
Grill et al., Neuroreport 2004

High-frequency stimulation overwrites the normal (or abnormal) neuronal activity

Basal ganglia bursting and beta oscillation

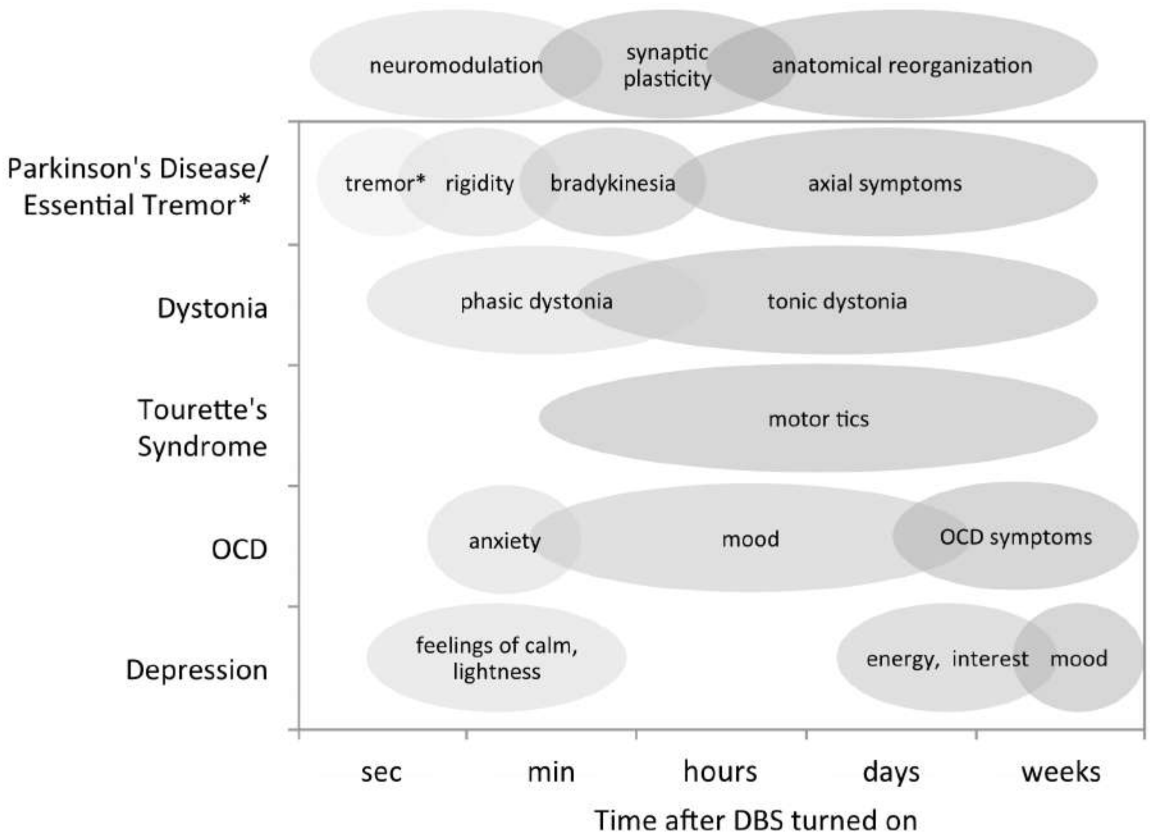


Soares et al. J Neurosci. 2004

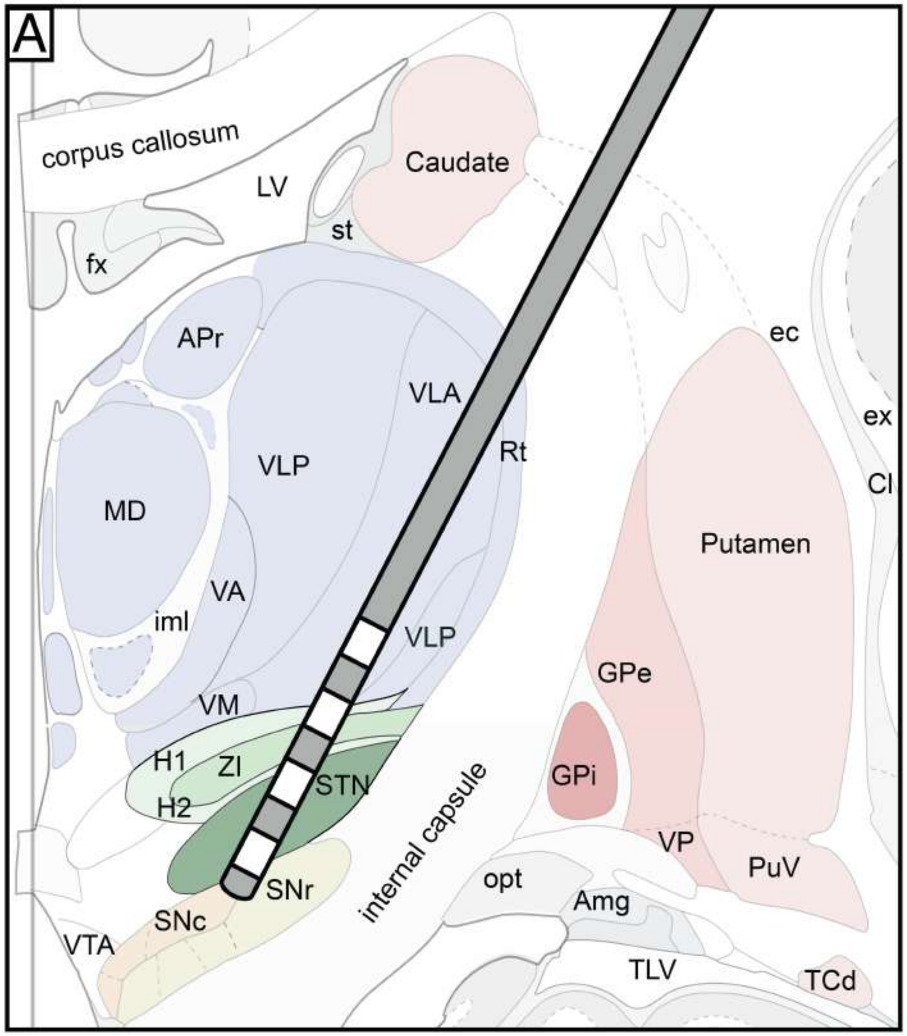


Little et al., Parkinsonism and Related Disorders 2014

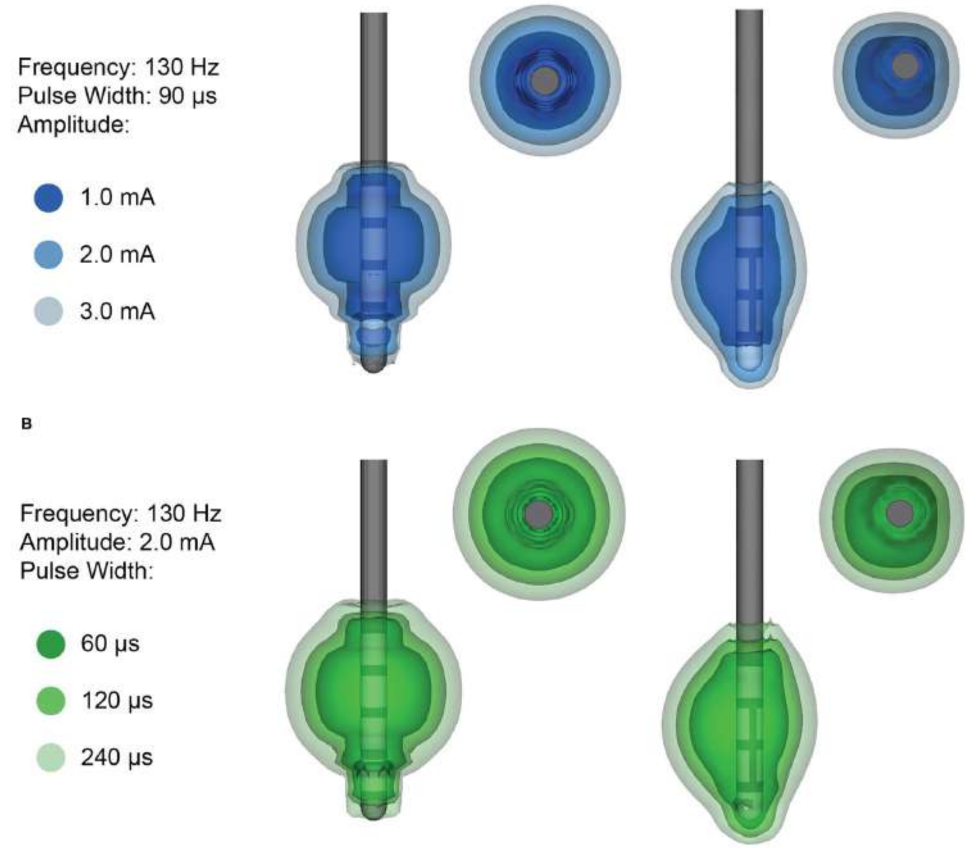
Different time scales of DBS effects suggests multiple mechanisms of action



Herrington, TM, et al. J Neurophysiology 2016



Herrington, Cheng & Eskandar. J. Neurophys. 2015

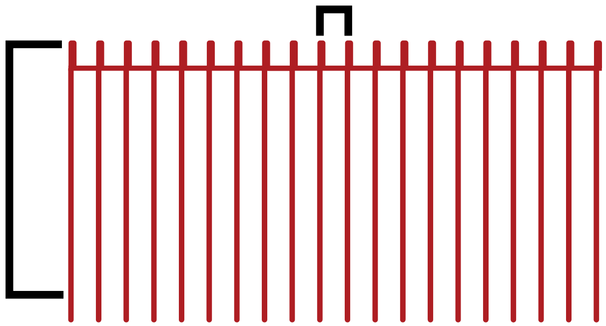


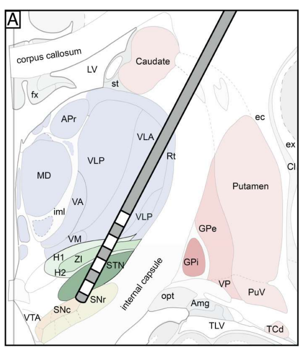
Frey et al., Frontiers in Neurology, 2022

DBS programming

3. Frequency
(100-185 Hz)

2. Current
(1-5 mA)





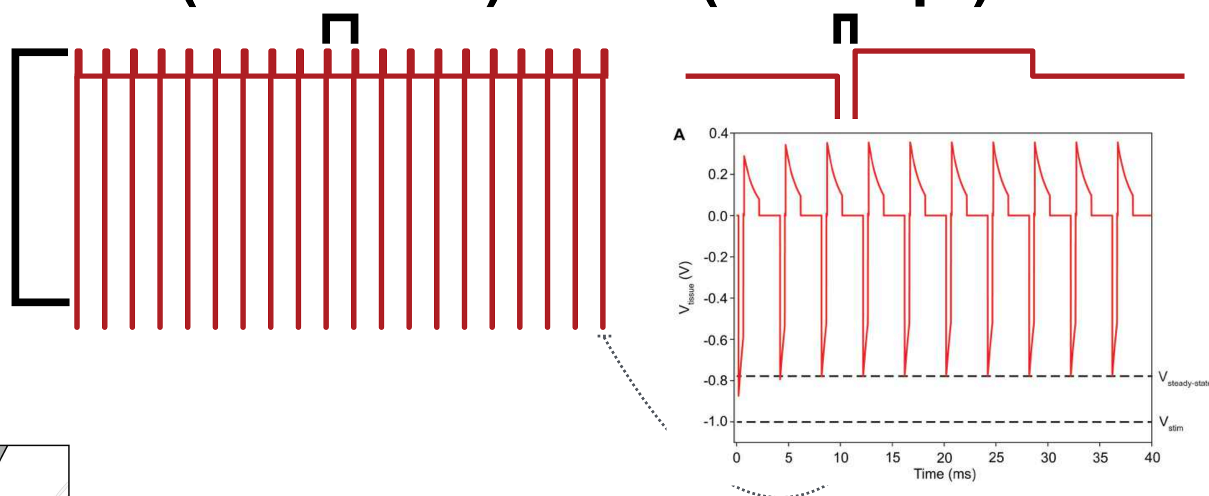
1. Configuration

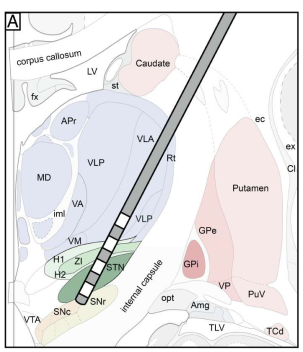
DBS programming

3. Frequency
(100-185 Hz)

4. Pulse width
(30-150 µs)

2. Current
(1-5 mA)



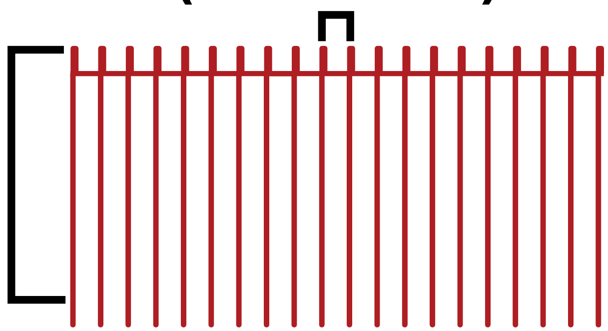


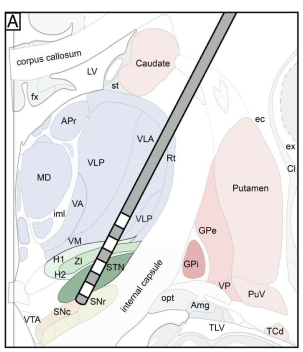
1. Configuration

DBS programming

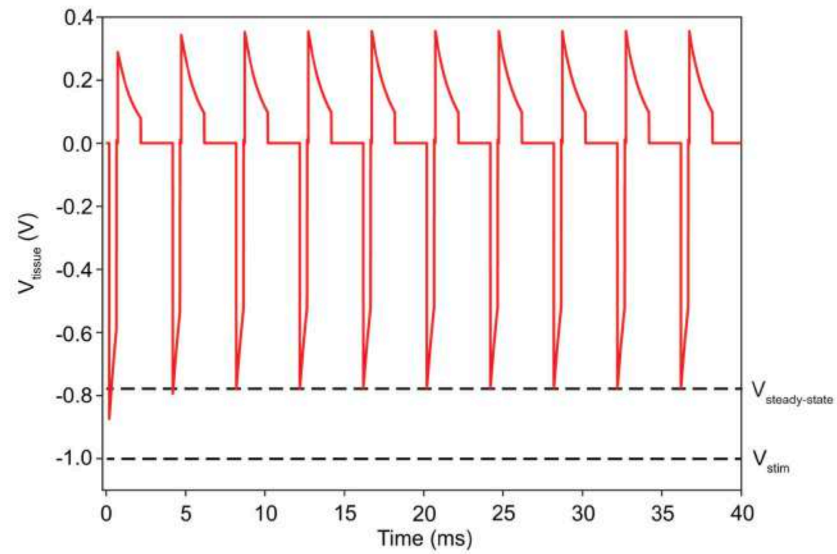
3. Frequency (100-185 Hz)

2. Current (1-5 mA)



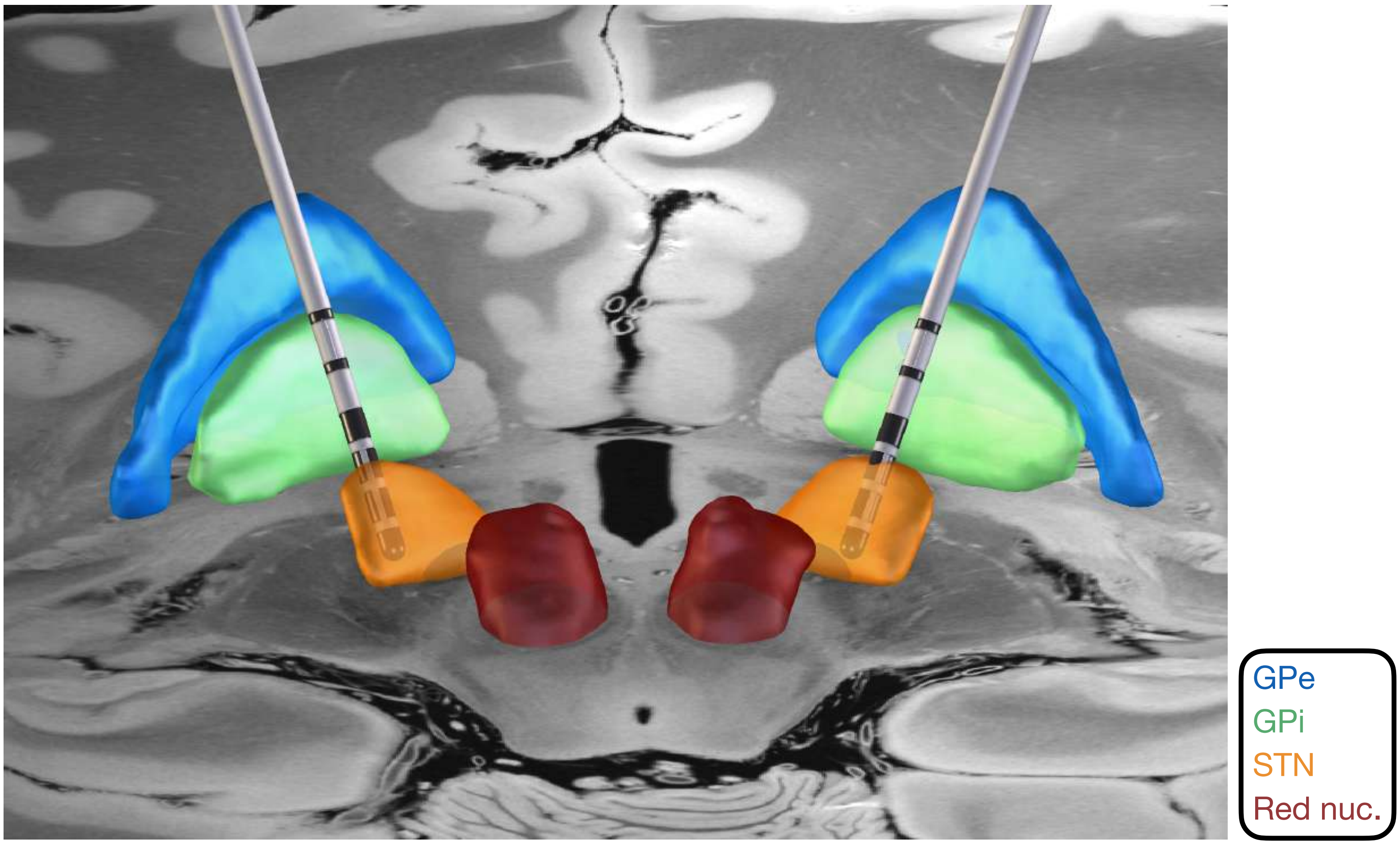


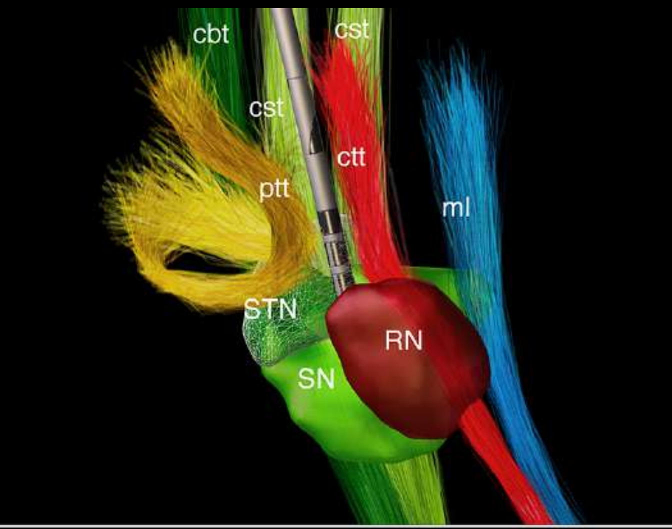
1. Configuration

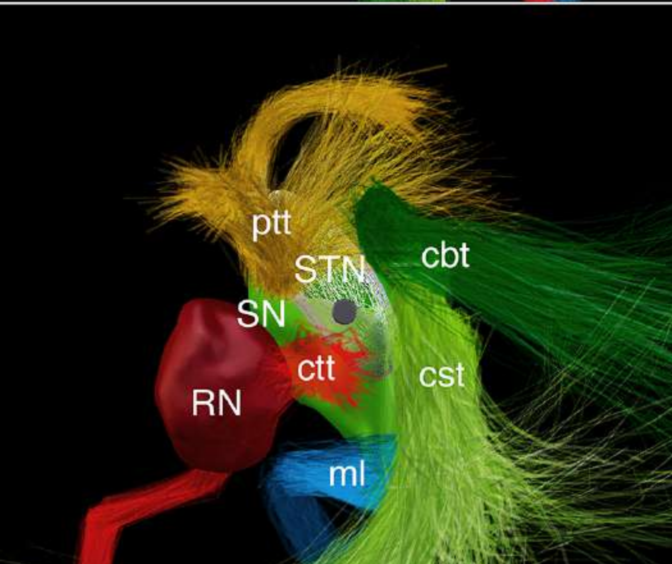


Lempka et al., Clin Neurophysiology 2018

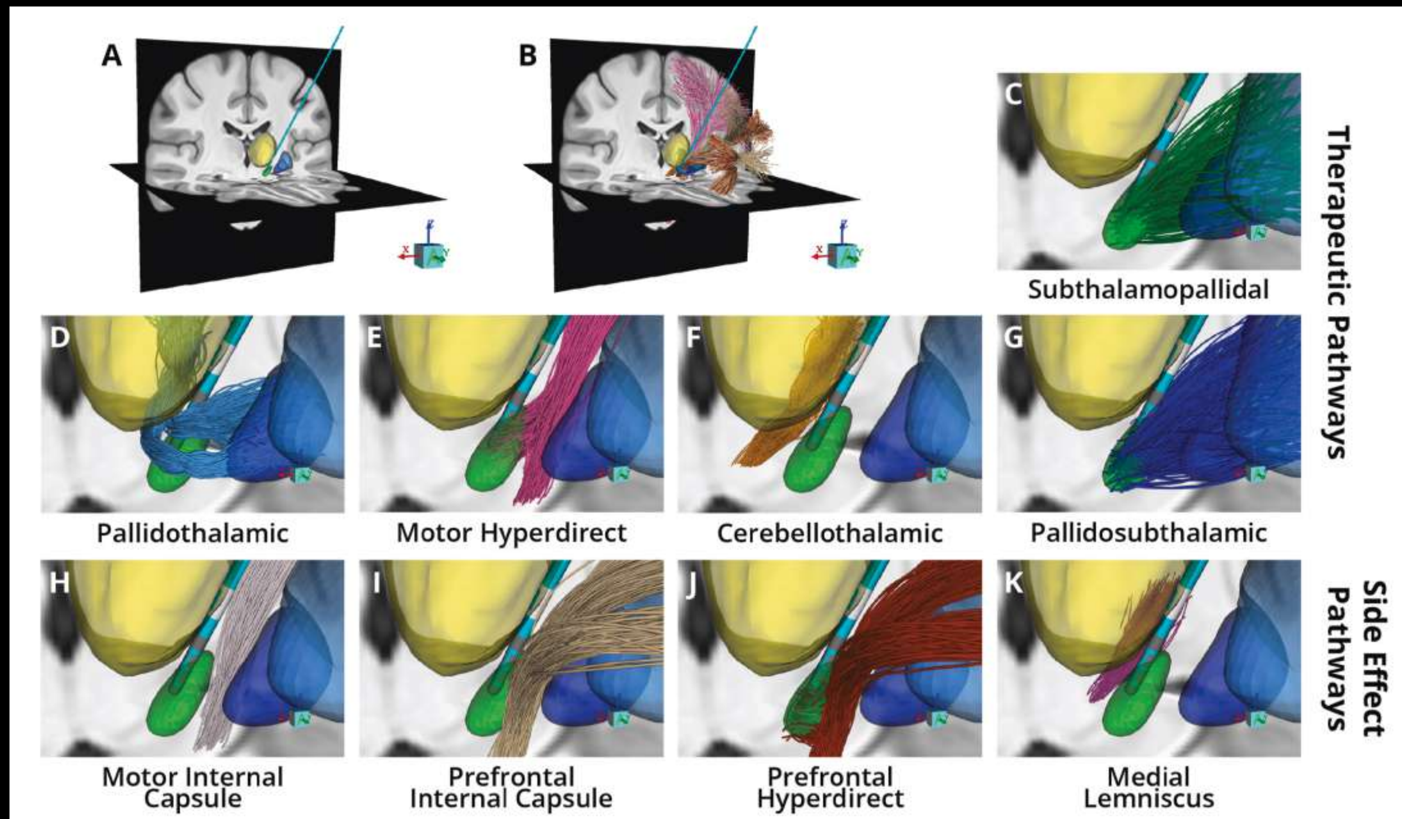
DBS “targets”



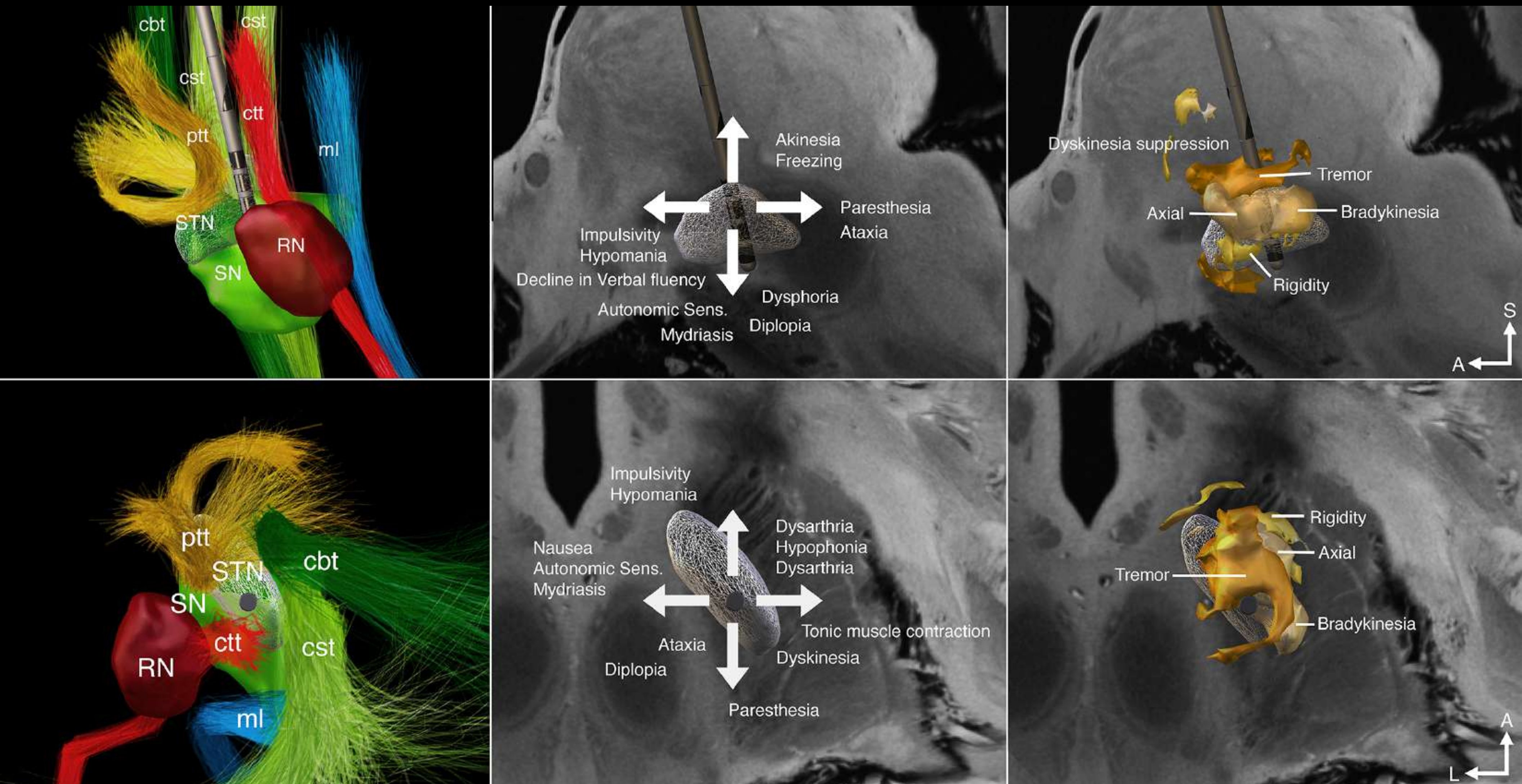




Neudorfer and Herrington, *in press*



Frankemolle-Gilbert et al, Brain Stimuilation 2026

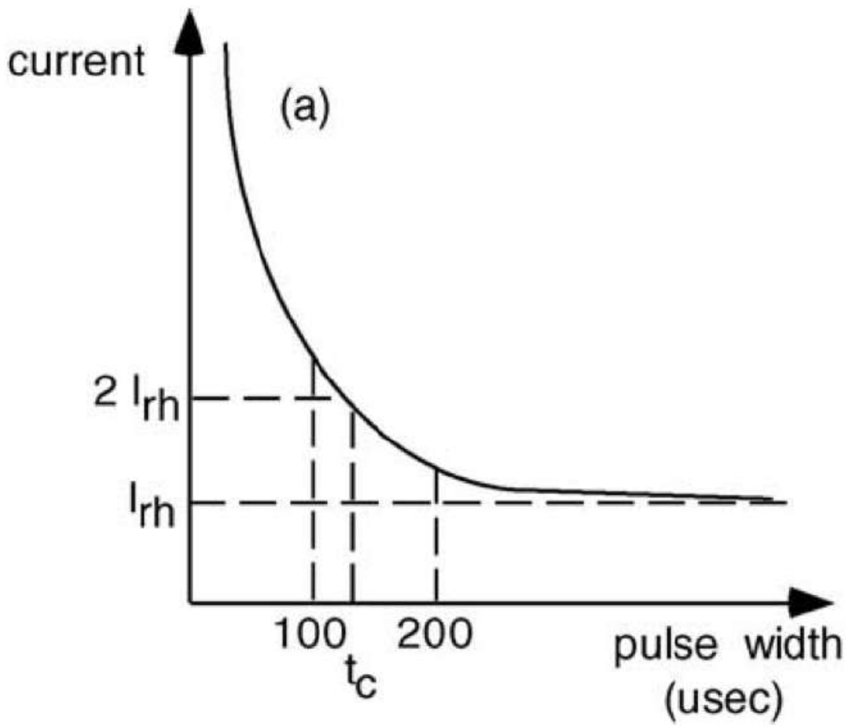


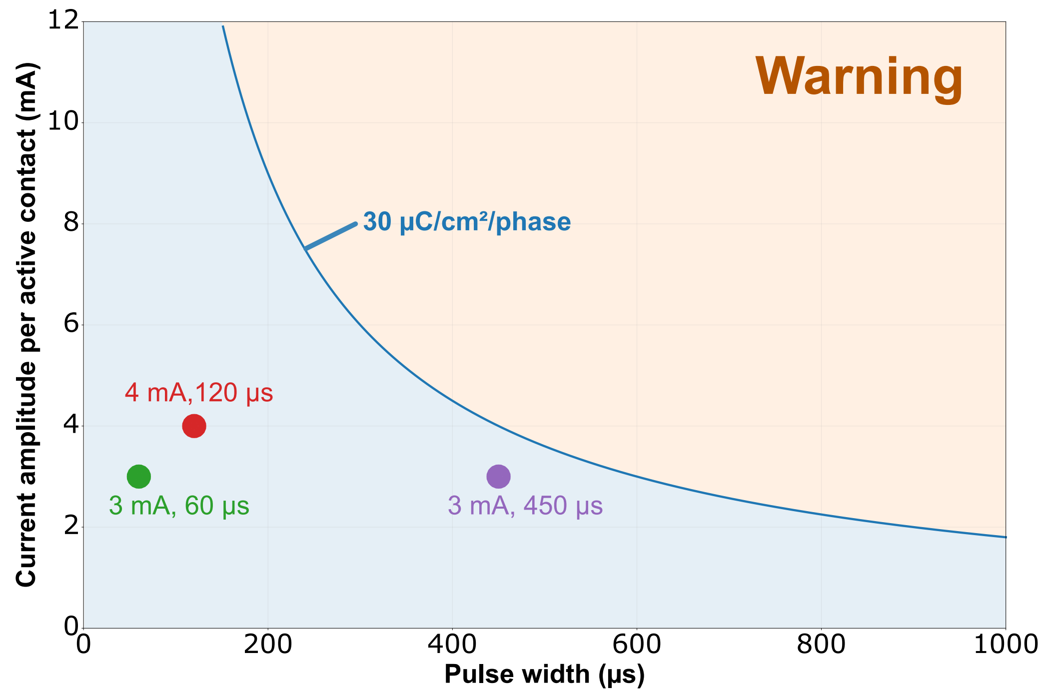
Neudorfer and Herrington, *in press*

adapted from Boutet A, et al. Brain Commun. 2021

Stimulation efficacy and safety

Membrane activation threshold



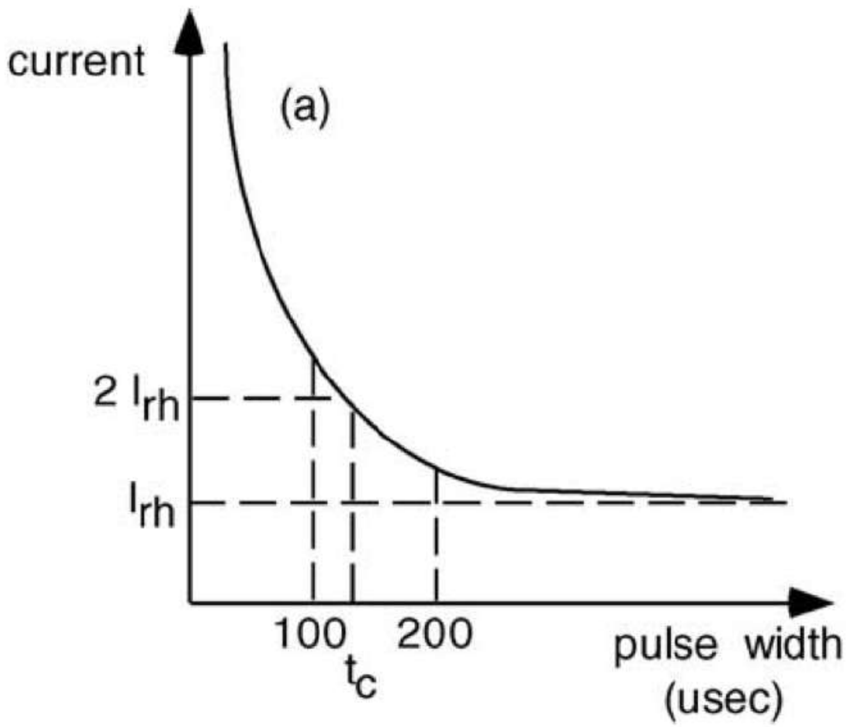


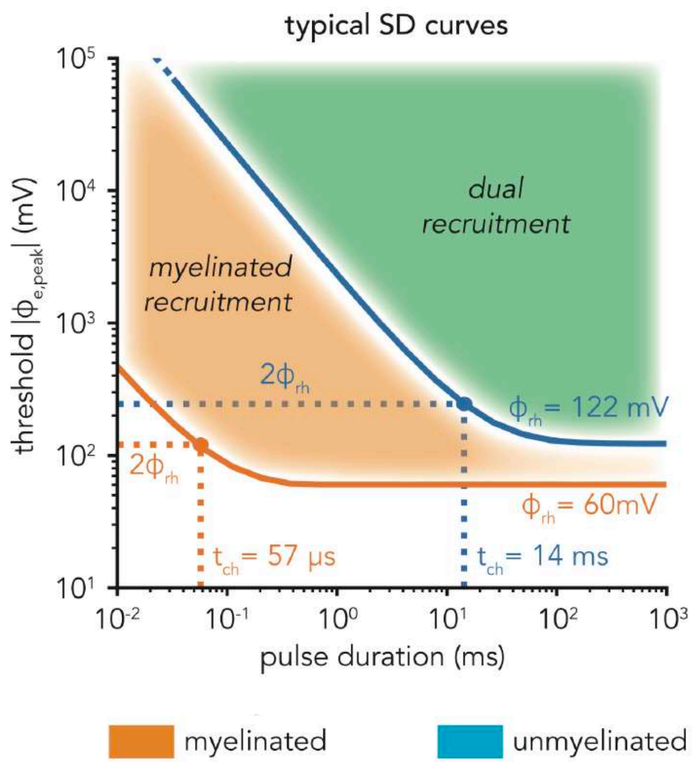
Merrill et al., J Neurosci Methods 2005

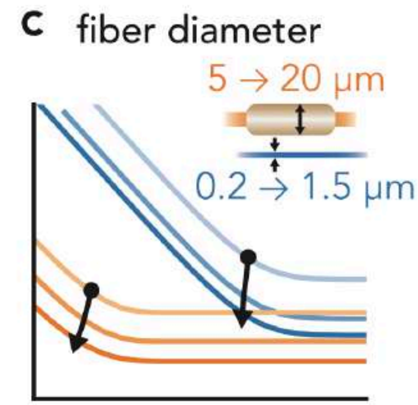
adapted from FDA PMA P150031 S048

Stimulation efficacy and safety

Membrane activation threshold



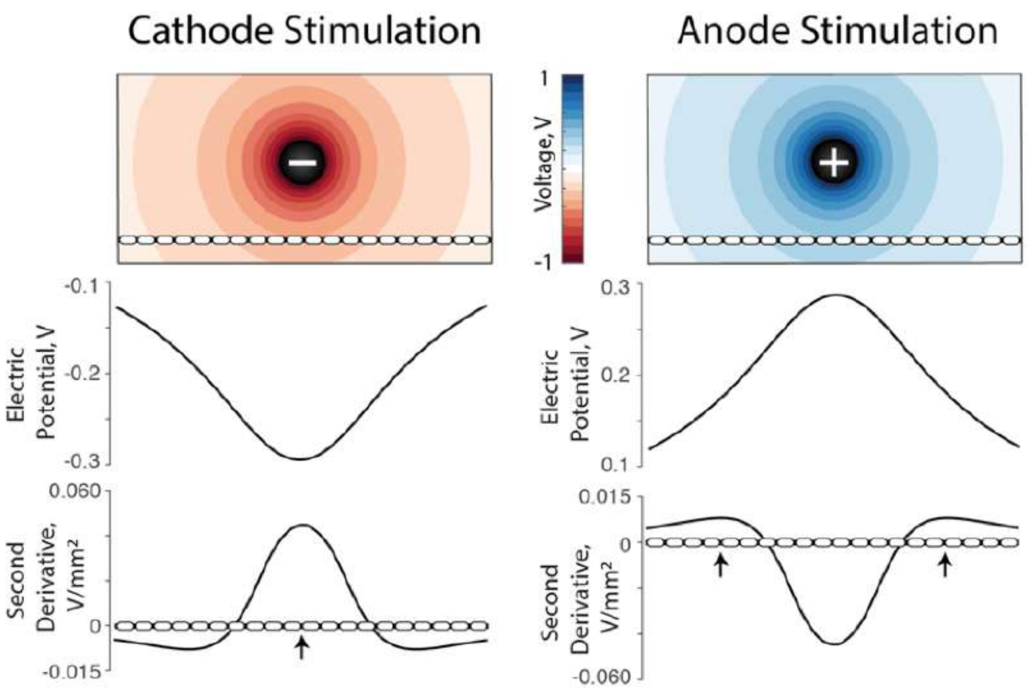


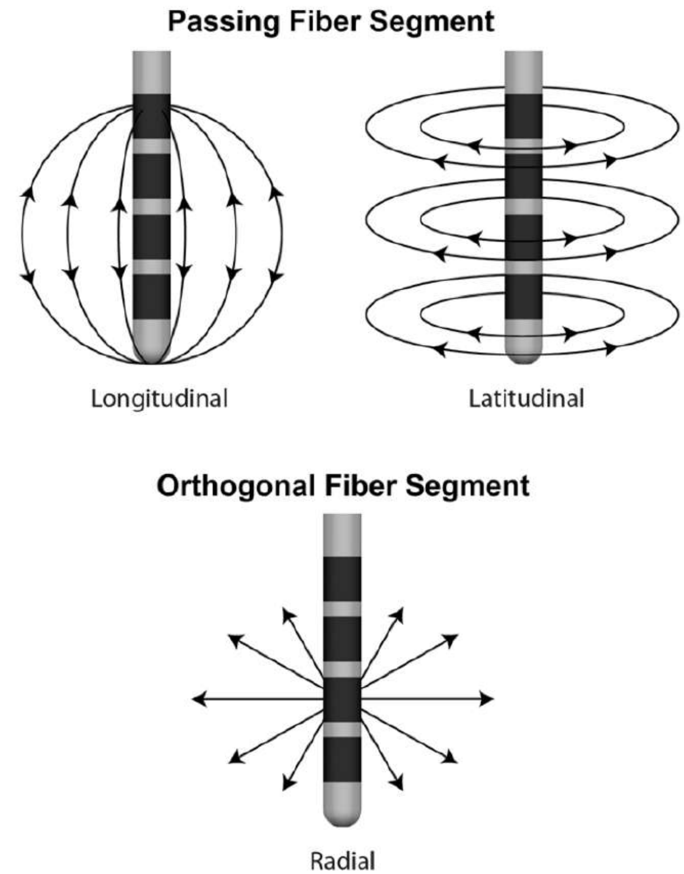


Merrill et al., J Neurosci Methods 2005

Lemaire et al, iScience 2021

Effect of cathodal (-) and anodal (+) stimulation



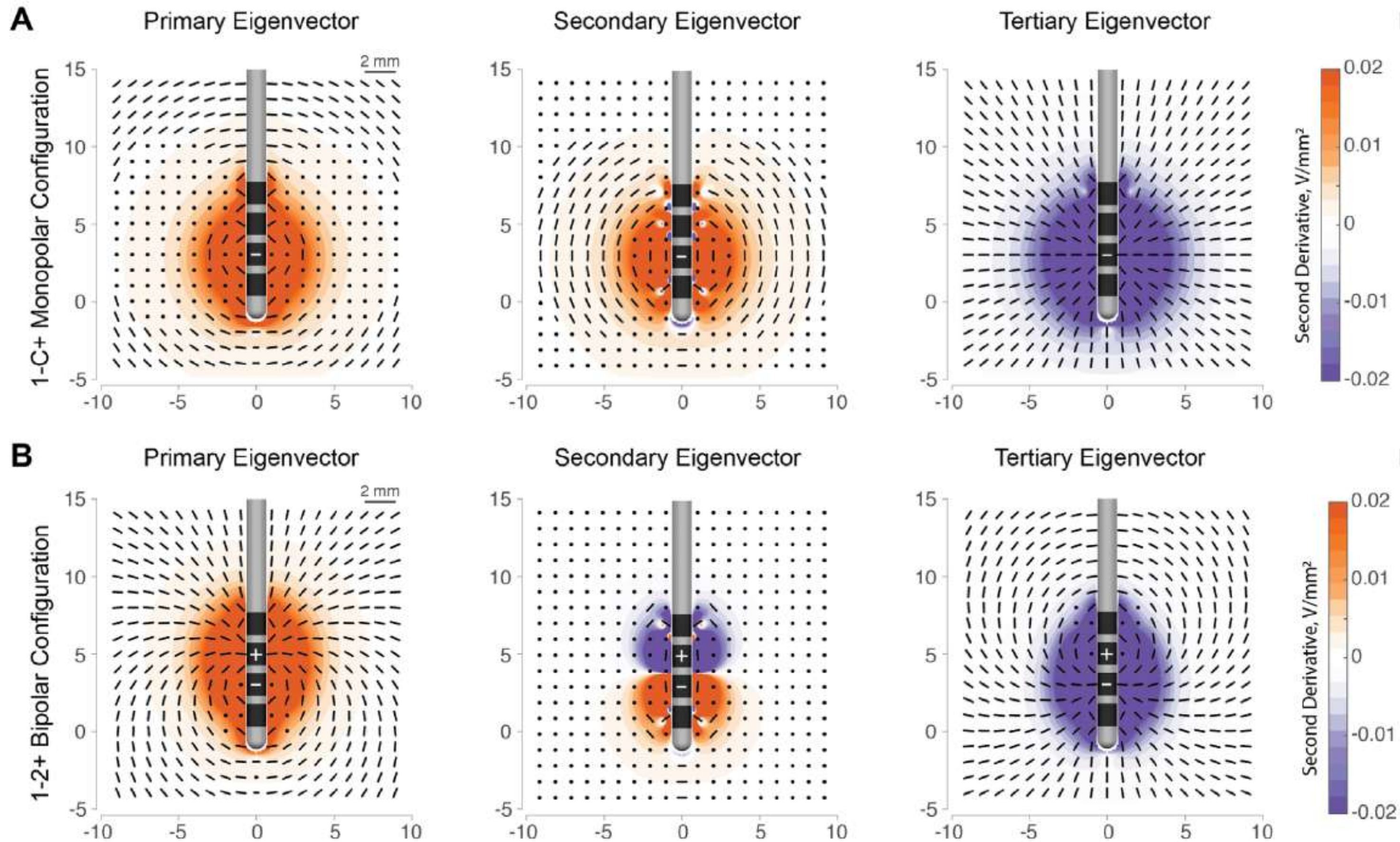


Anderson et al., J Neural Eng, 2019

Effect of cathodal (-) and anodal (+) stimulation

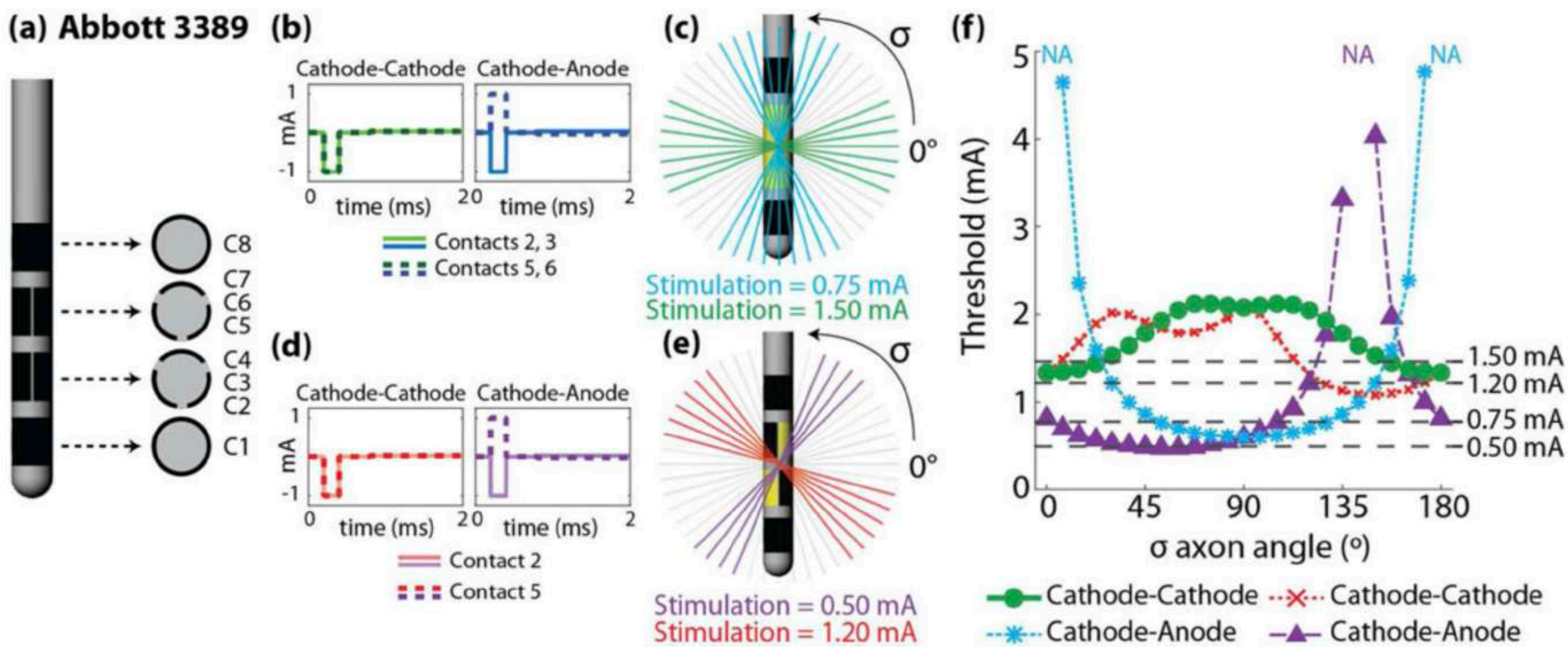
Cathodal

Bipolar



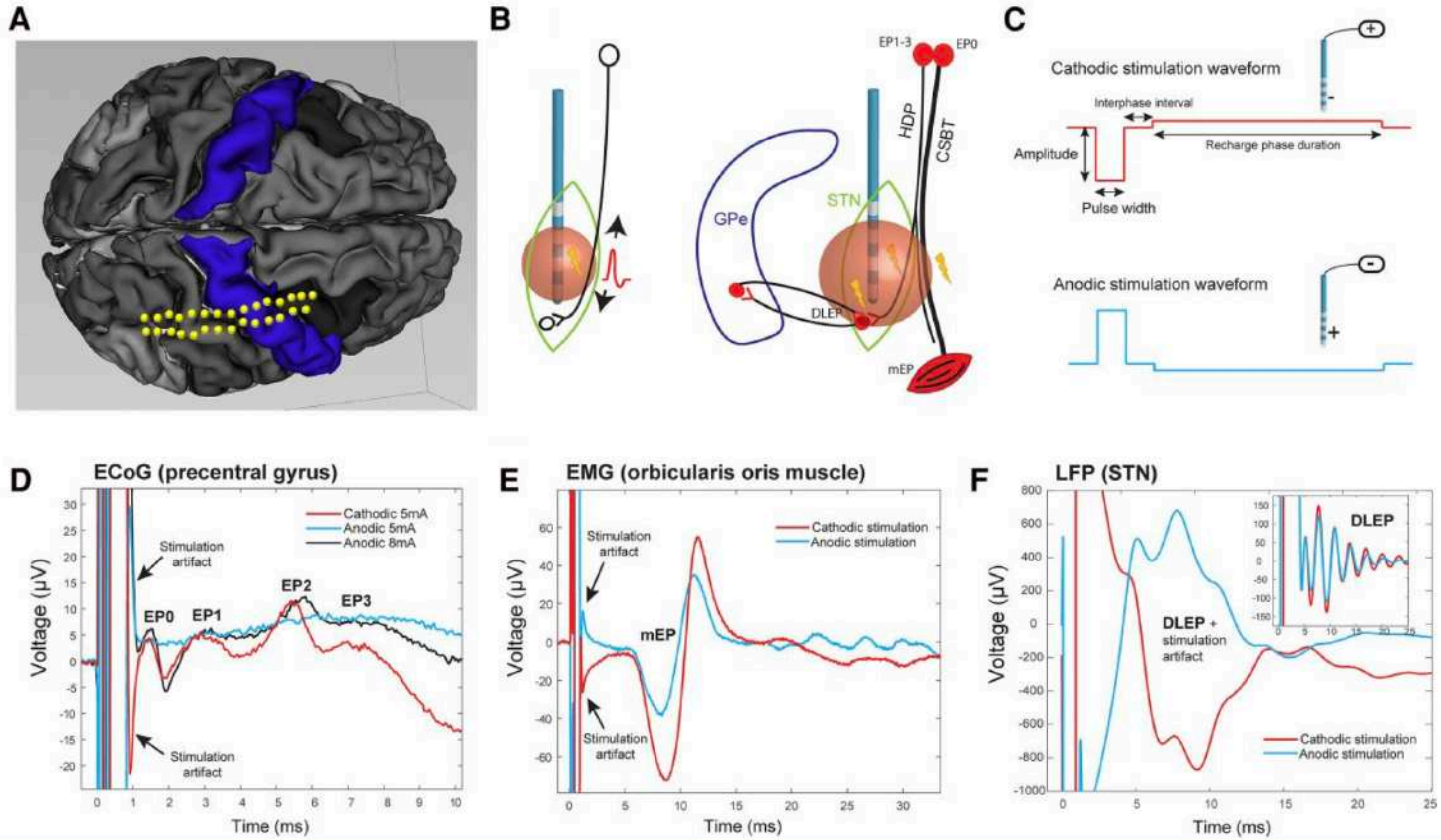
Anderson et al., J Neural Eng, 2019

Orientation-selective fiber activation



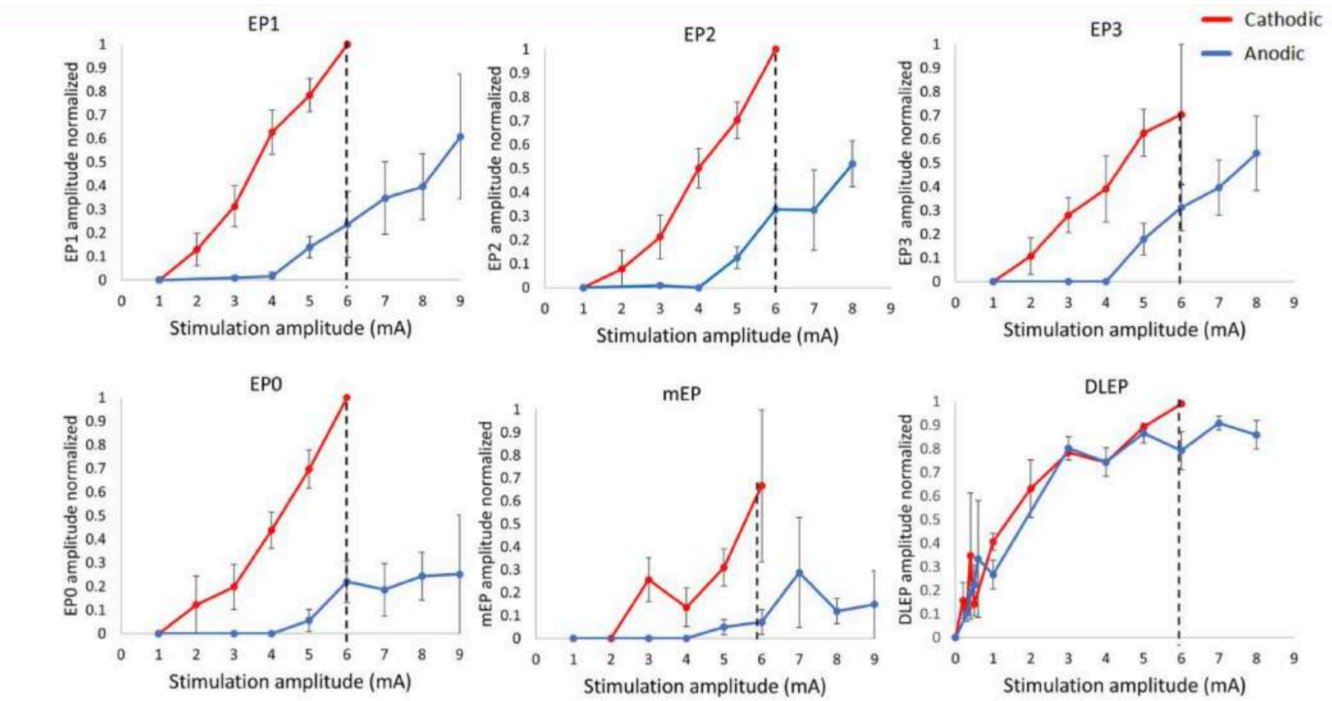
Slopsema et al., J Neural Eng, 2018

DBS activation of specific pathways correlates with clinical response



Borgheai et al, Brain Communications 2025

DBS activation of specific pathways correlates with clinical response

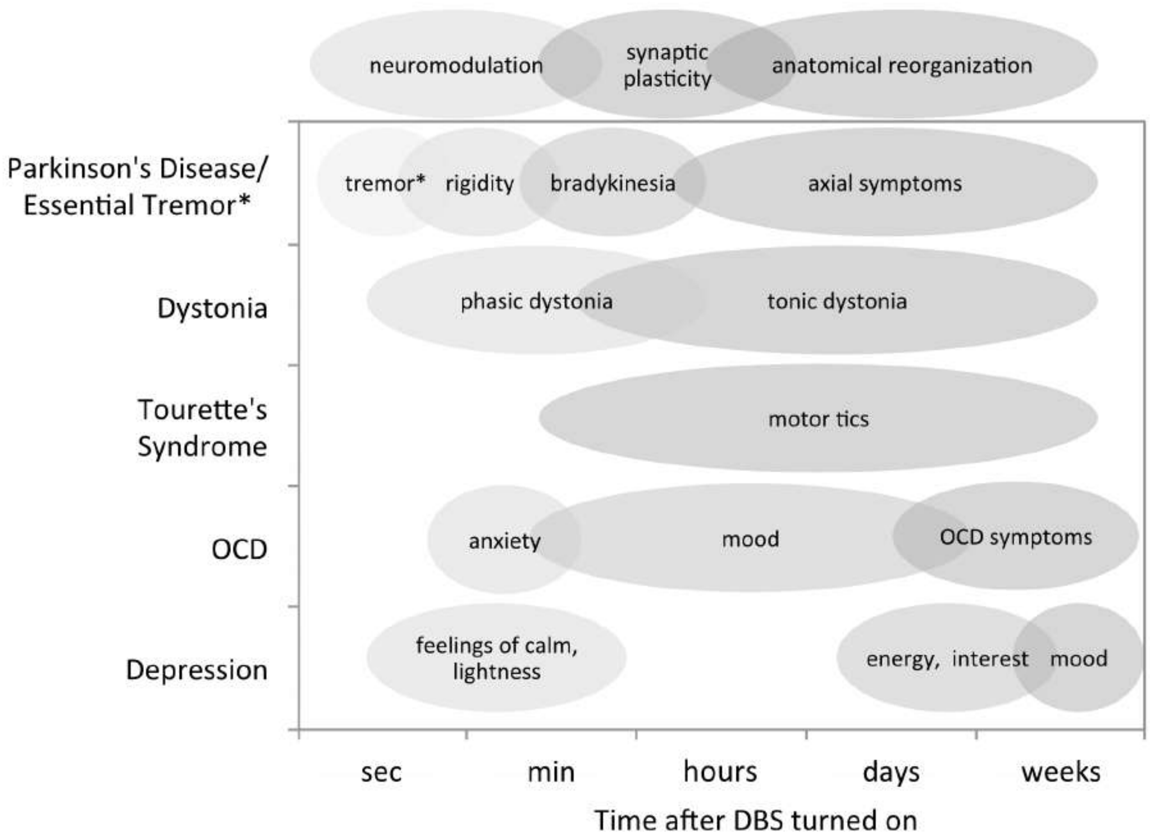


Borgheai et al, Brain Communications 2025

- Lowest threshold EP1 (proposed hyperdirect activation) predicted best clinical DBS contact in 5/7 patients (Miocinovic et al., J. Neuroscience 2018)

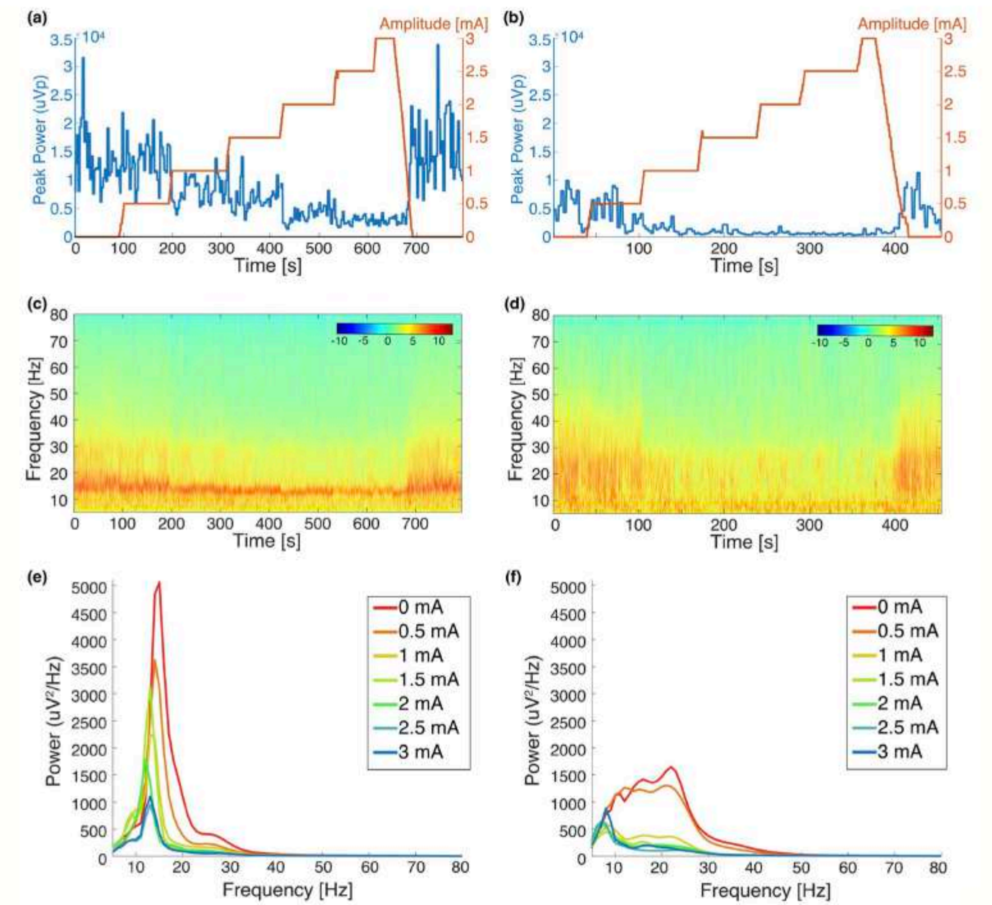
- mEP threshold predicted clinical side effect (tonic contraction or dysarthria) threshold (Testini et al., Clin Neurophysiology 2026)

Different time scales of DBS effects suggests multiple mechanisms of action

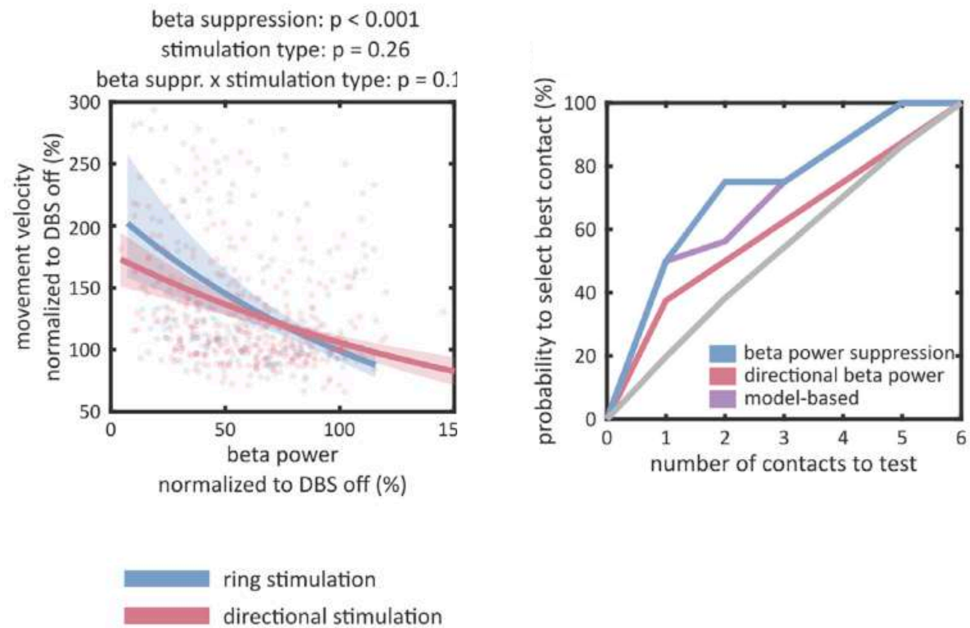


Herrington, TM, et al. J Neurophysiology 2016

DBS disrupts pathological oscillations - beta

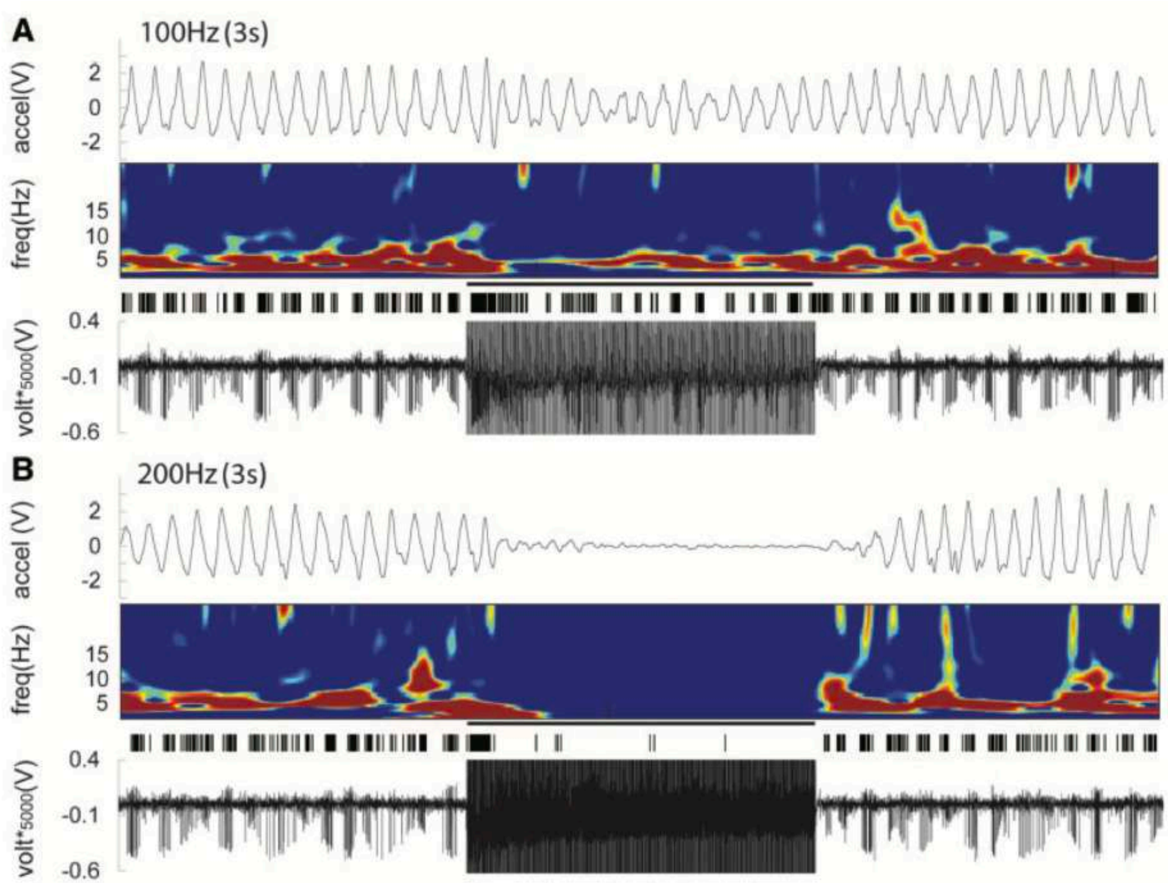


Feldmann JL, et al. Euroean J of Neurology, 2021



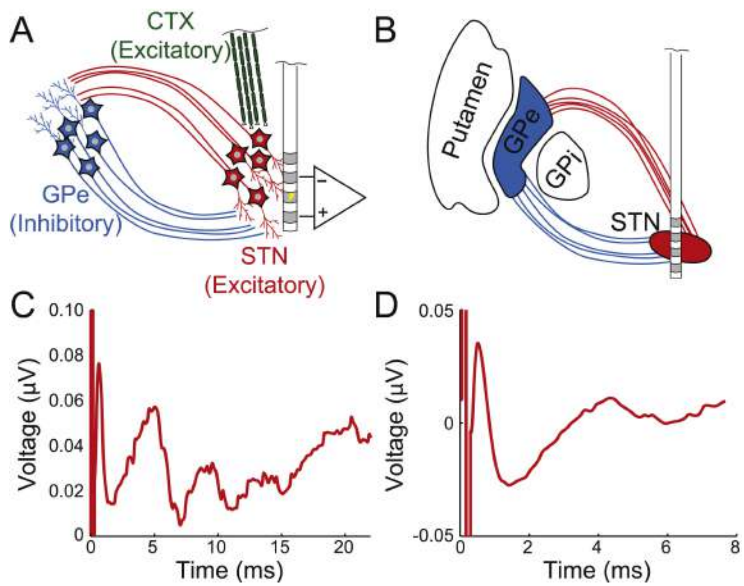
Busch JL, et al. Mov Disord 2023

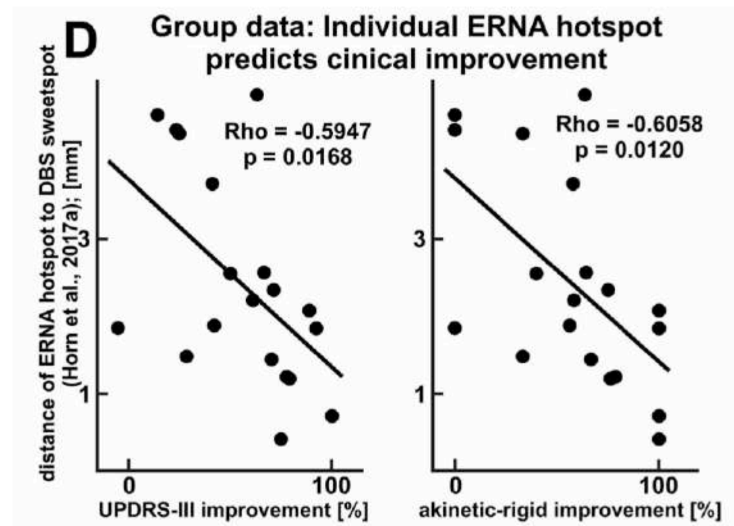
DBS disrupts pathological oscillations - tremor



Milosevic, et al. Brain 2018

DBS evokes resonant neural activity (ERNA)





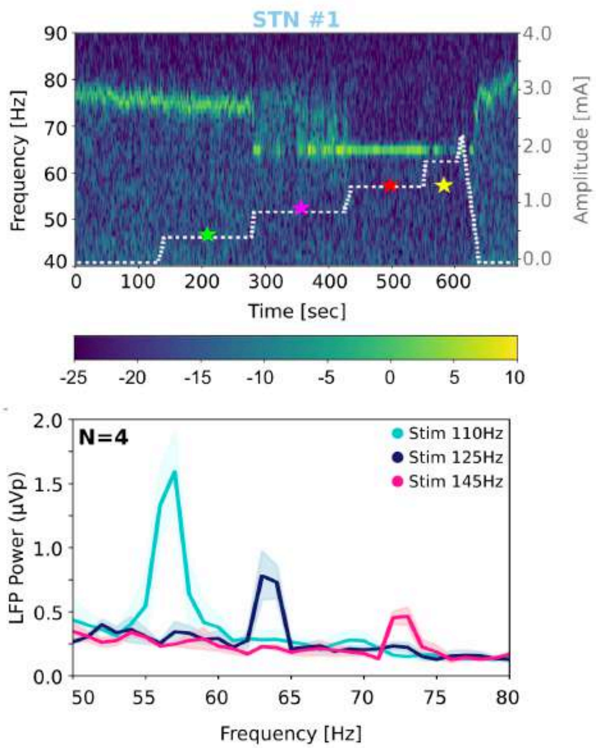
High-frequency DBS induces a 200-500 Hz oscillation that decays gradually after DBS cessation. Most likely an STN-GPe oscillator.

DBS contacts that more effectively engage this ERNA oscillations are associated with better clinical response

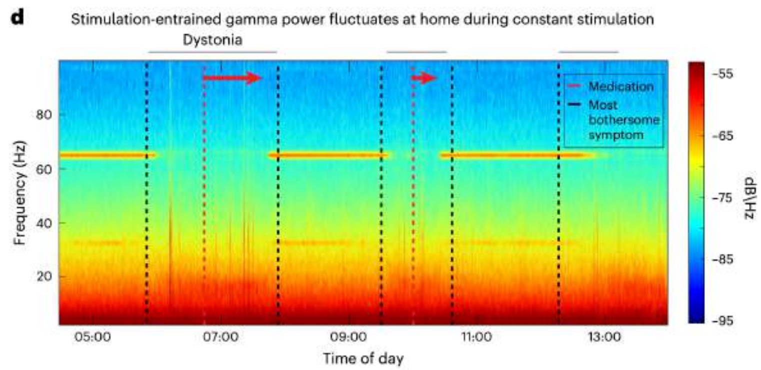
Steiner et al., Nat Communications 2024

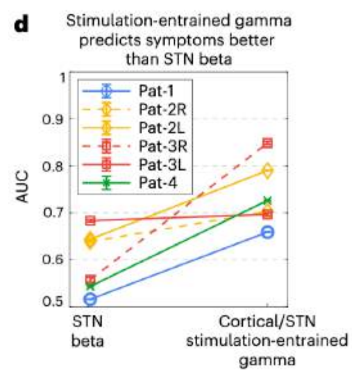
Schmidt et al., Brain Stimulation 2020

DBS entrains fine-tuned gamma (FTG)



Mathiopoulou, et al., Nat Communications 2025

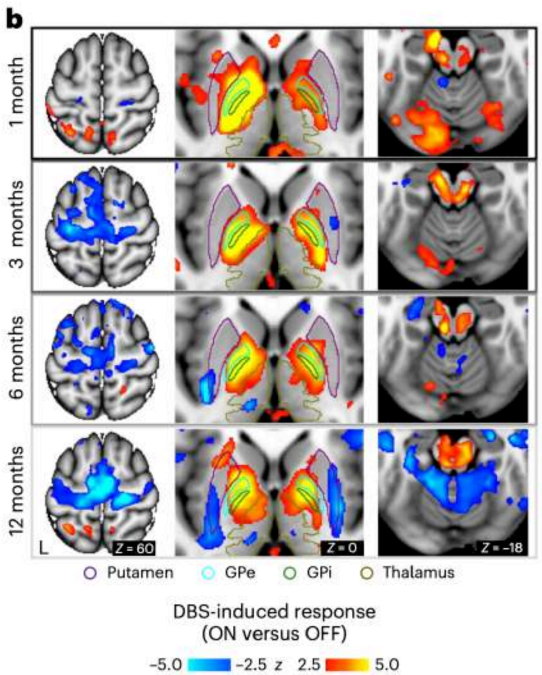


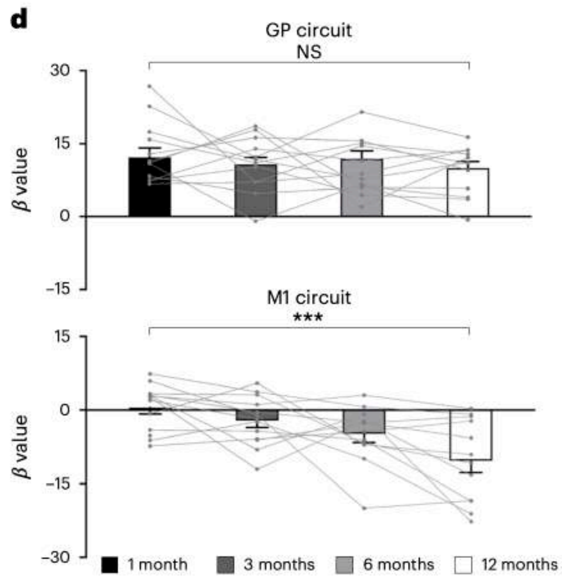


Oehrn, et al., Nature Medicine 2024

- High-frequency, narrow-band cortical and STN gamma occurs during the Parkinson's ON state
- This narrow-band gamma is entrained by DBS typically at 1:2 the stimulation frequency.
- DBS entrained gamma correlates with ON state.

DBS induces plastic changes over time





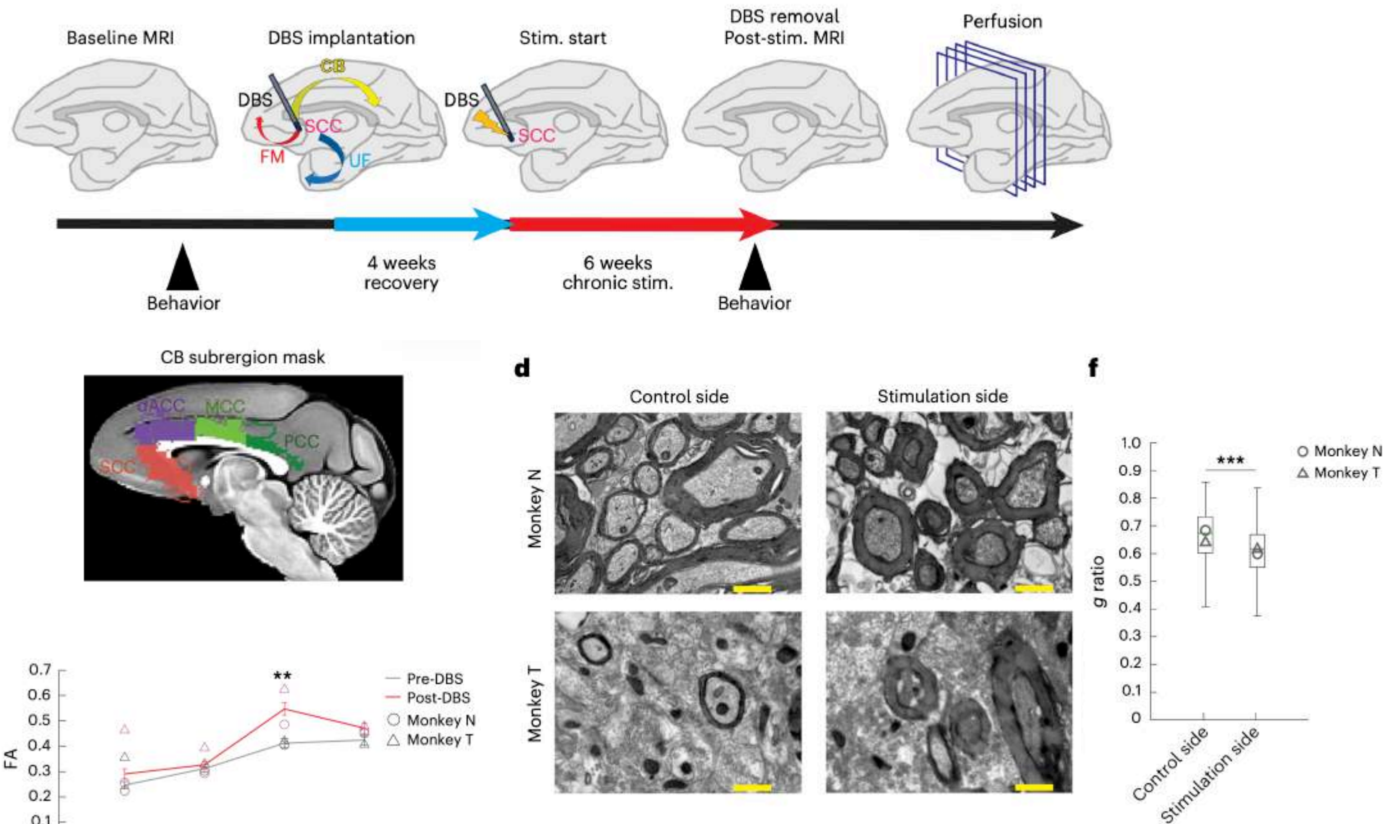
- After 12 months of continuous STN DBS, DBS ON vs. OFF showed:

- Stable activation of globus pallidus

- Progressively deactivation of the primary motor cortex

Ren, et al., Nat Neurosci 2026

DBS induces plastic changes over time



Fujimoto, et al., Nat Neurosci 2026

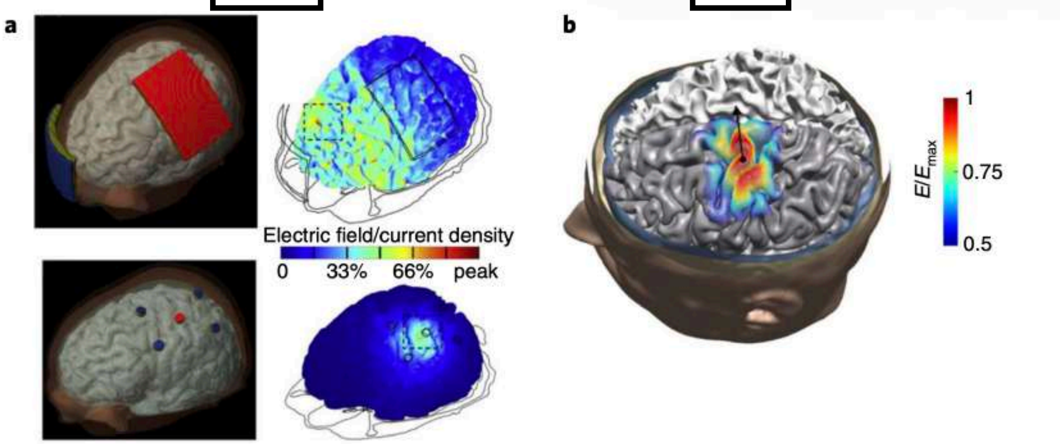
- 6 weeks of continuous subcallosals cingulate DBS:

- Increased fractional anisotropy in the cingulum bundle

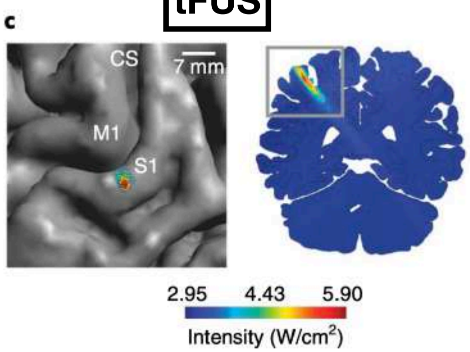
- Increased myelination histologically

Noninvasive stimulation

tDCS **TMS**

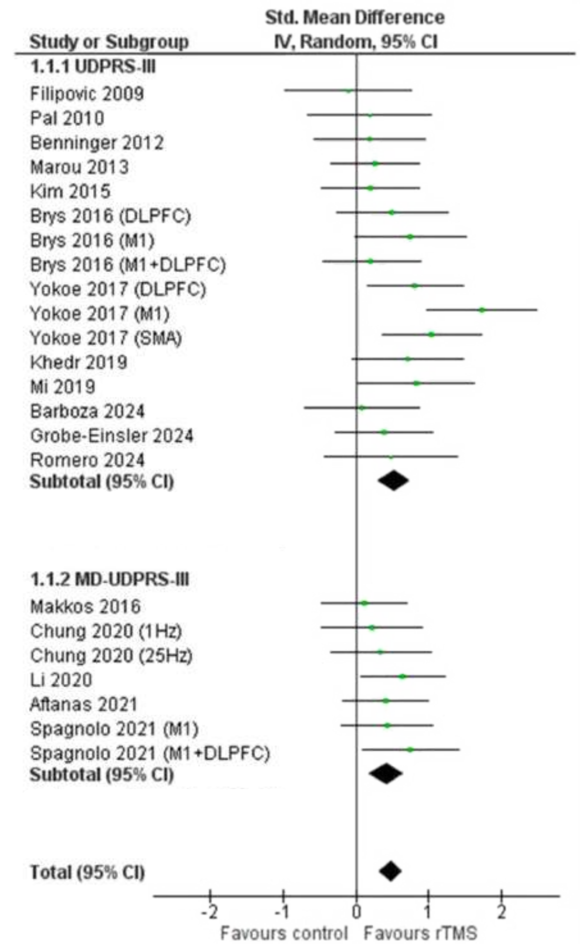


tFUS



There are no FDA-approved tDCS, tACS, TMS, or low-intensity tFUS treatments for movement disorders

Polanía R, et al. Nat Neurosci 2018

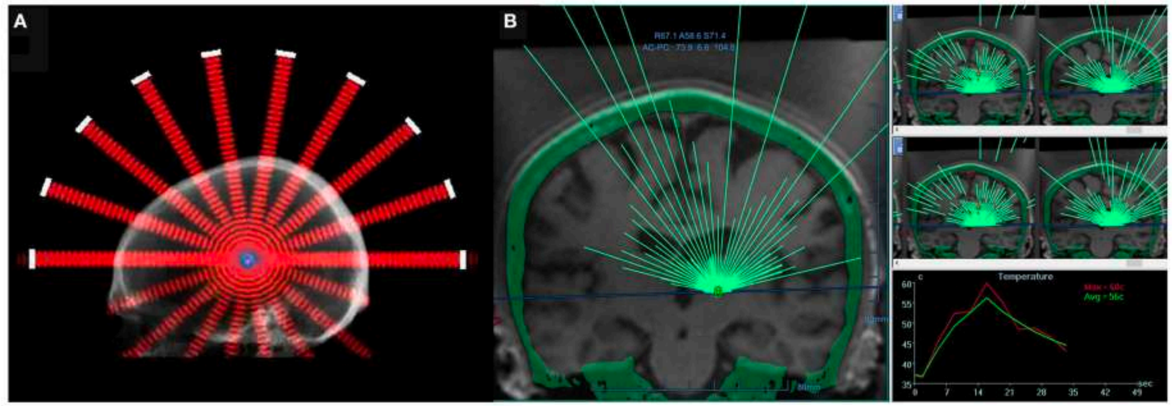


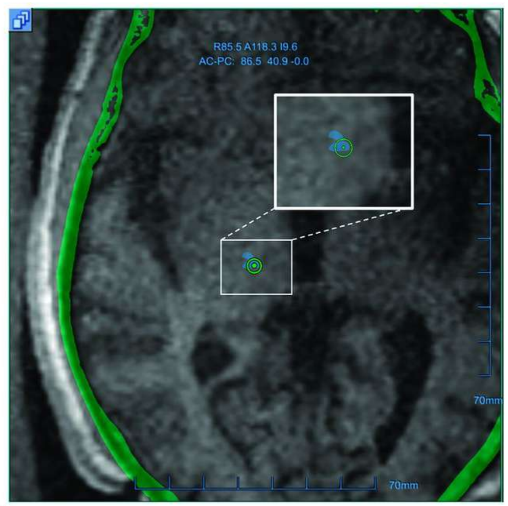
In Parkinson's disease: ~3 pt improvement in (MDS)UPDRS

Khattak M, et al. Annals of Medicine and Surgery 2025

Focused ultrasound

InSightec





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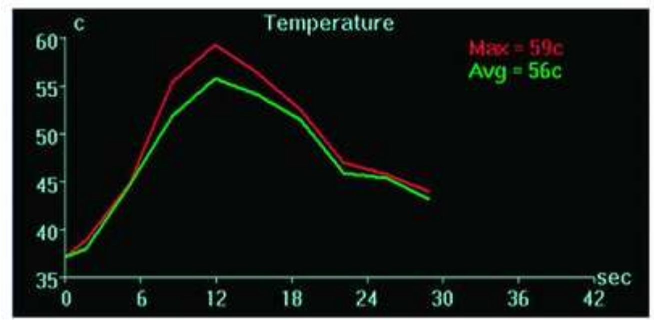
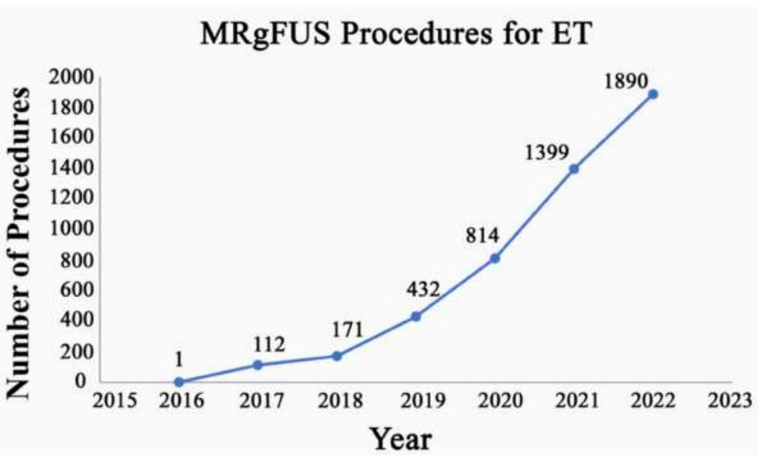


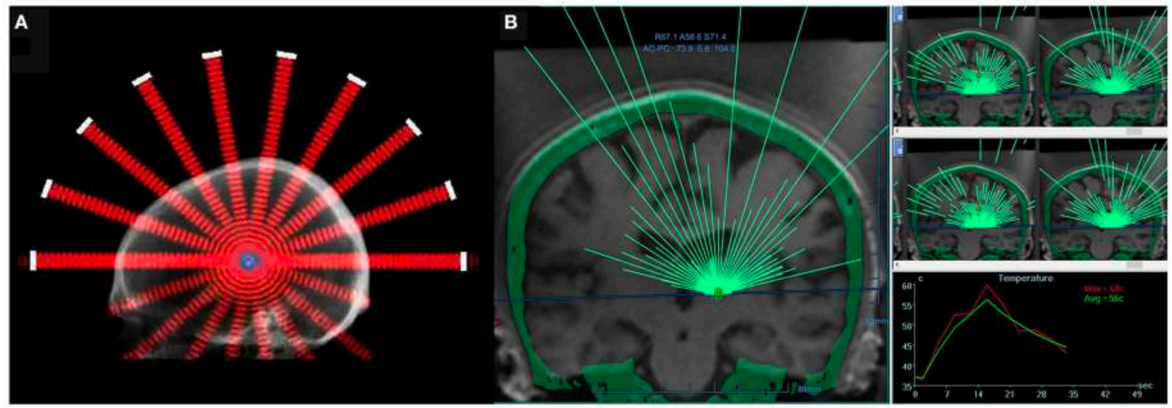
Meng et al., Stereotact Funct Neurosurg 2021
Baek et al., Frontiers Neurology, 2022
Mattay et al., Am J of Neuroradiology, 2024

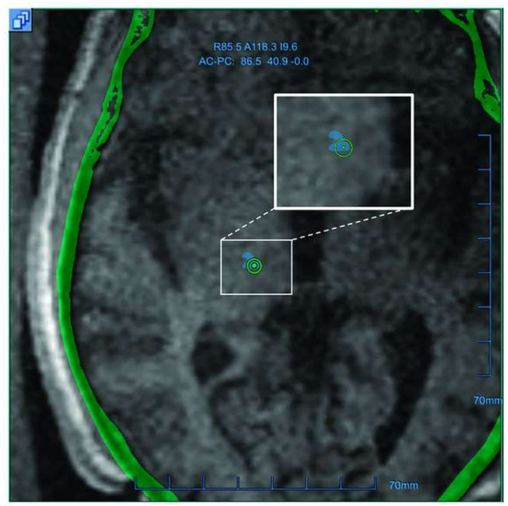
Focused ultrasound



For ET, MRgFUS procedural volume now (likely) exceeds DBS in the US

Gautam D, et al. BMJ Neurol Open 2024





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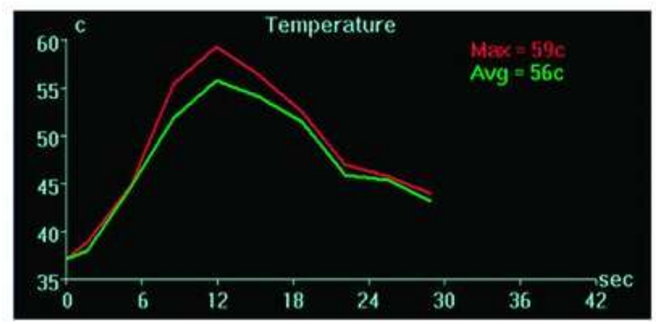
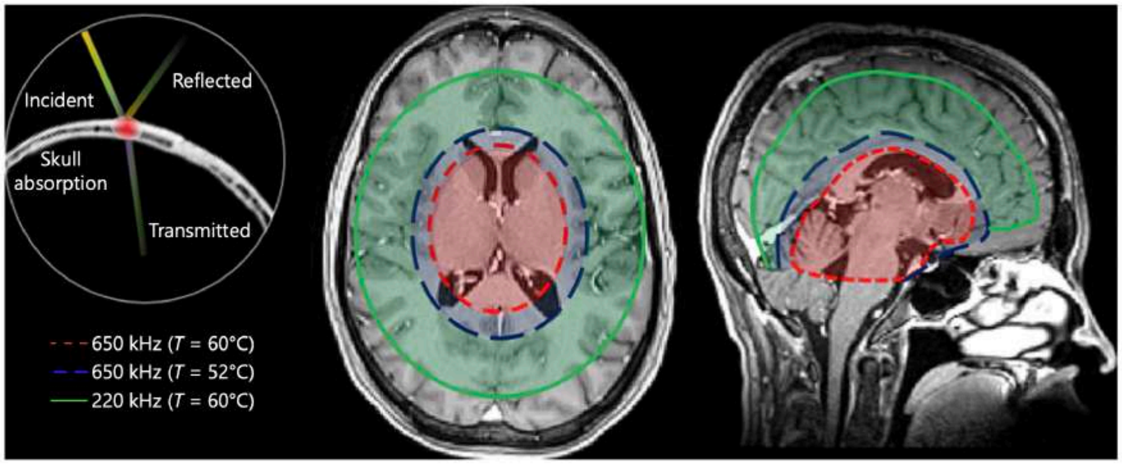
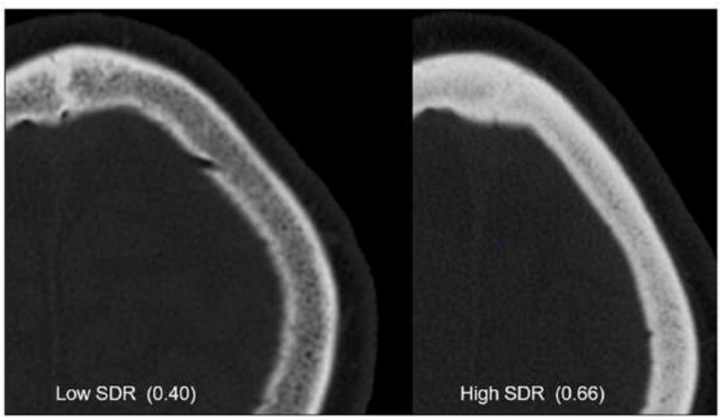


Meng et al., Stereotact Funct Neurosurg 2021
Baek et al., Frontiers Neurology, 2022
Mattay et al., Am J of Neuroradiology, 2024

Focused ultrasound technical constraints





Meng et al., Stereotact Funct Neurosurg 2021
Baek et al., Frontiers Neurology, 2022

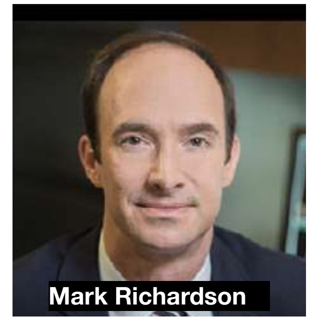
- Central structures are more accessible, especially for high-frequency sonication
- Sub-lesional heating temporarily disrupts neural tissue allowing for reversible clinical assessment, but may not perfectly reflect size/impact of the final lesion.
- Low skull density ratio reflects sound energy, resulting in inefficient deep heating and increased skull heating.
- Bilateral lesion therapy carries higher risk of side effects.

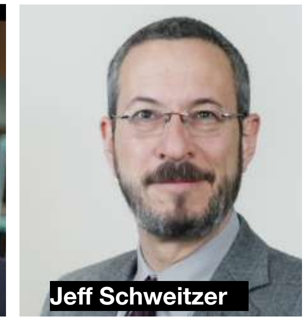
(core) DBS team at Massachusetts General Hospital

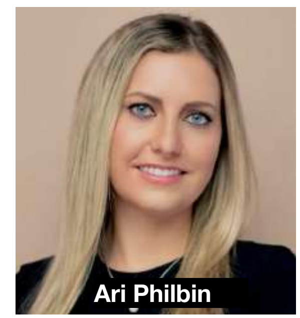
Neurology

Neuropsychology/Psychiatry

Neurosurgery








Thank you