Non-invasive Electrical Stimulation for the Central and Peripheral Nervous System

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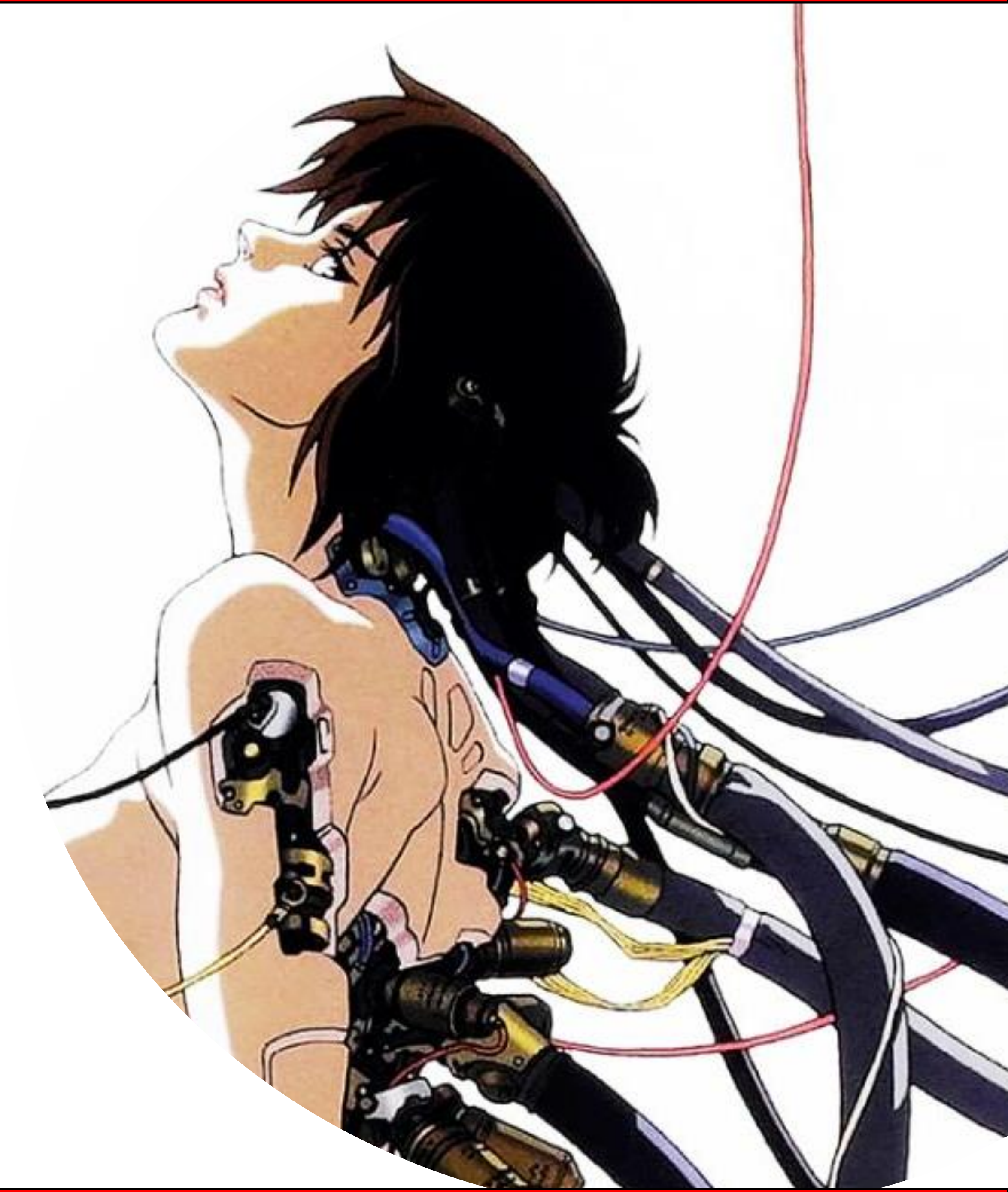
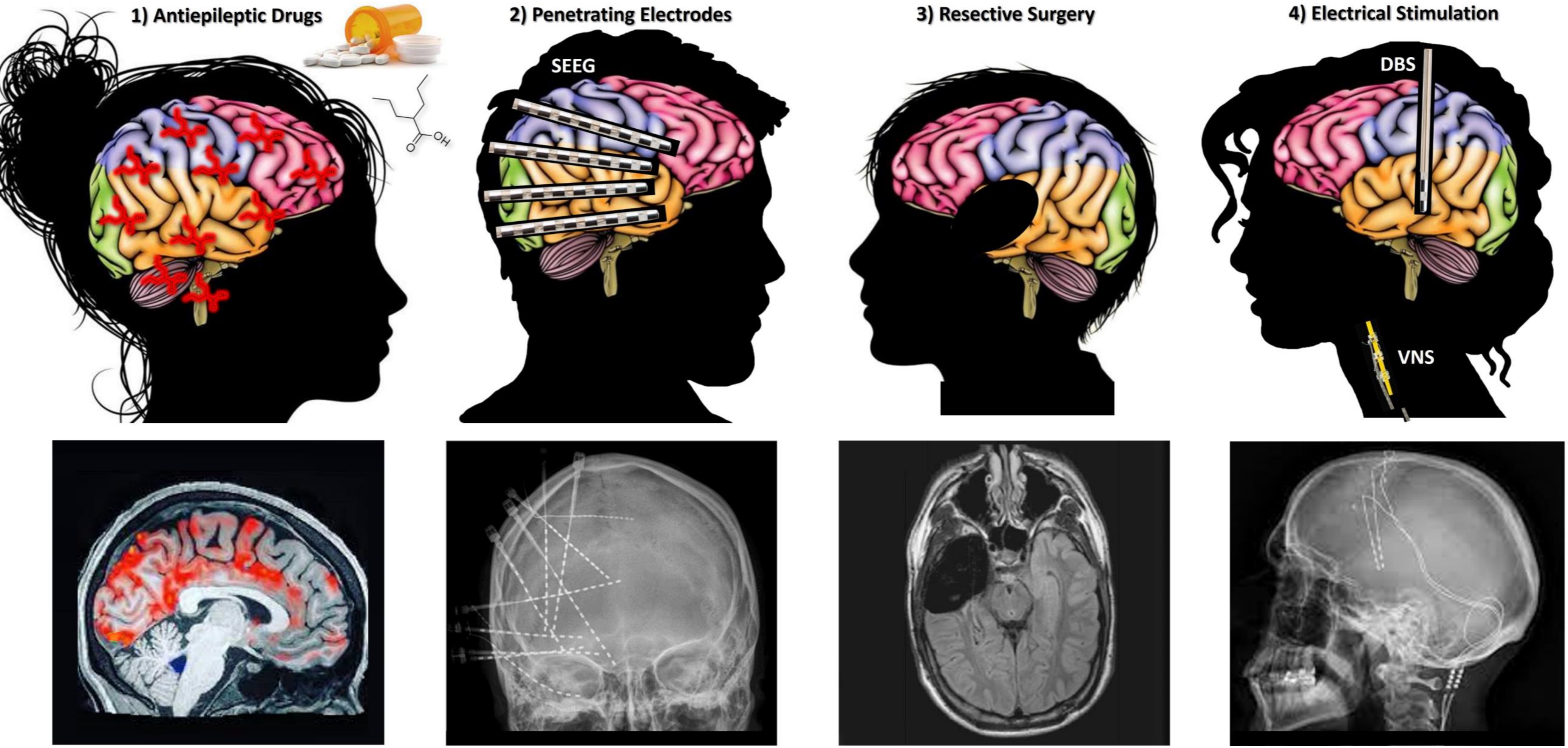


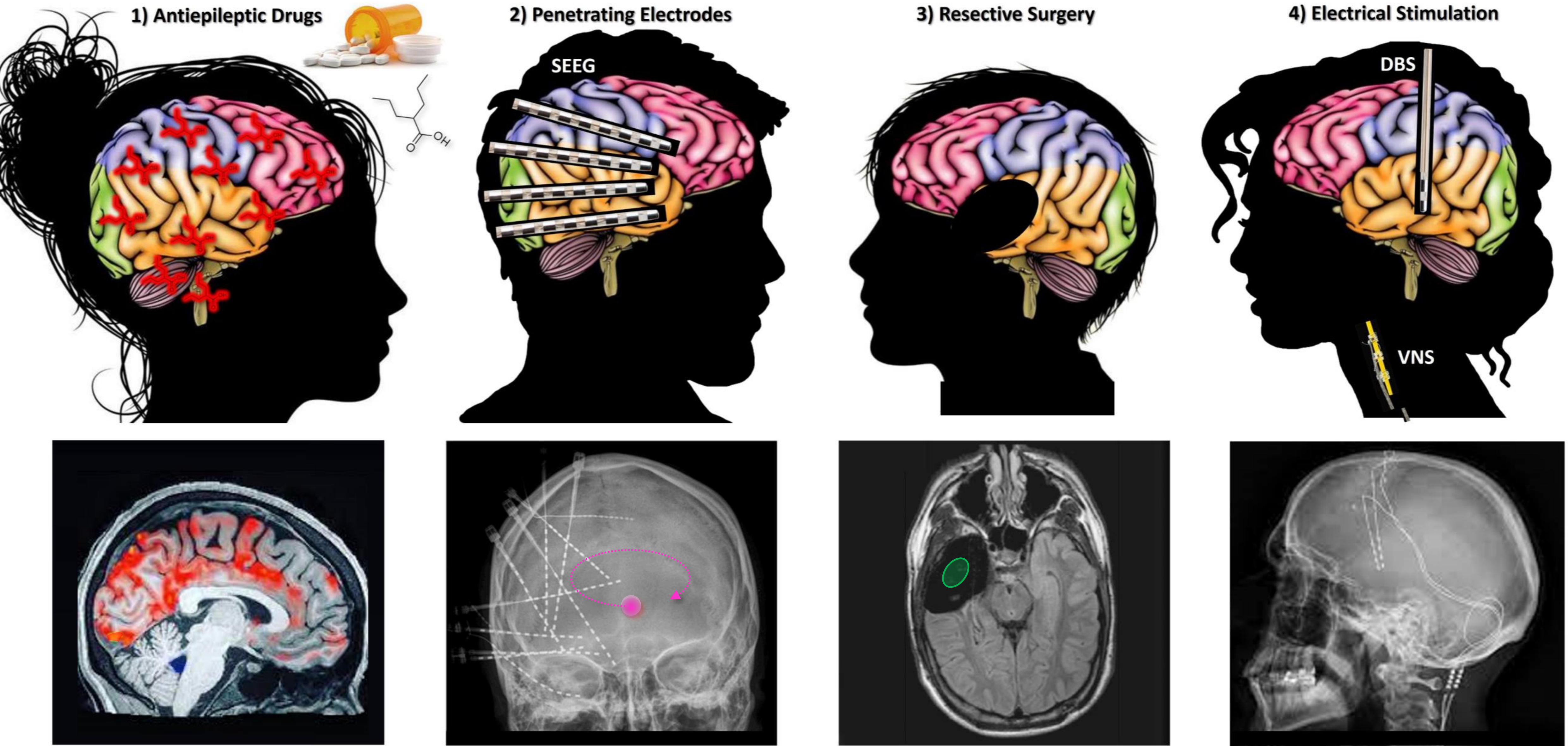
Outline

- Temporal Interference (TI): Epilepsy as a model
    - Preliminary work in rodents and scaling TI to humans
    - Clinical Temporal Interference
- Tremor and Parkinson’s disease
- Clinical TI of Peripheral nerves
    - Hypoglossal nerve
    - Vagus Nerve
- Conclusions

The Problem


1) Antiepileptic Drugs
OH
2) Penetrating Electrodes
SEEG
3) Resective Surgery
4) Electrical Stimulation
DBS
VNS

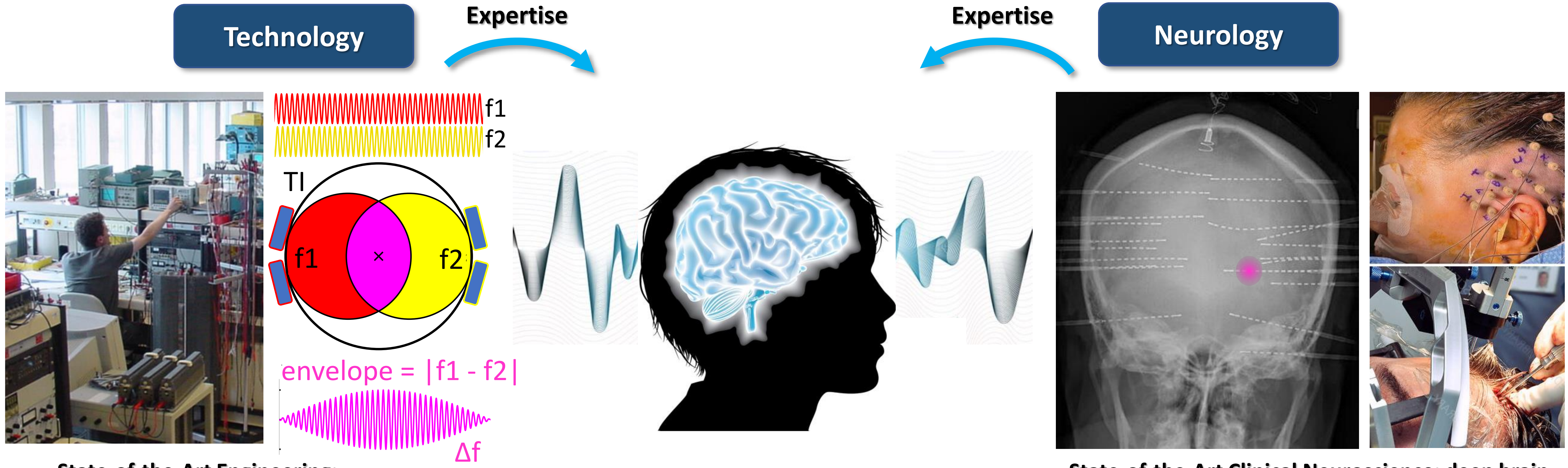
The Problem



increase explorable tissue

decrease resected tissue

The Solution



State-of-the-Art Engineering: non-invasive interferential electric fields

State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control

The Solution

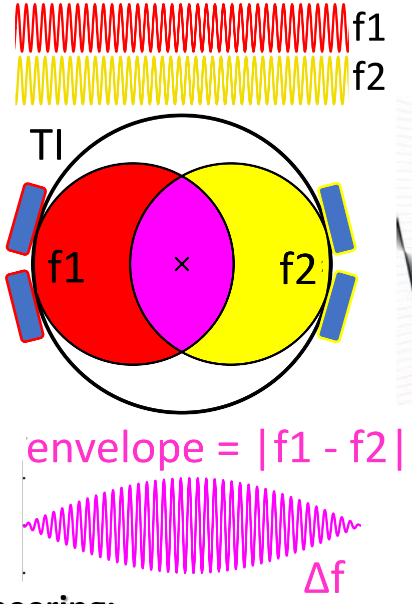
Technology

Expertise

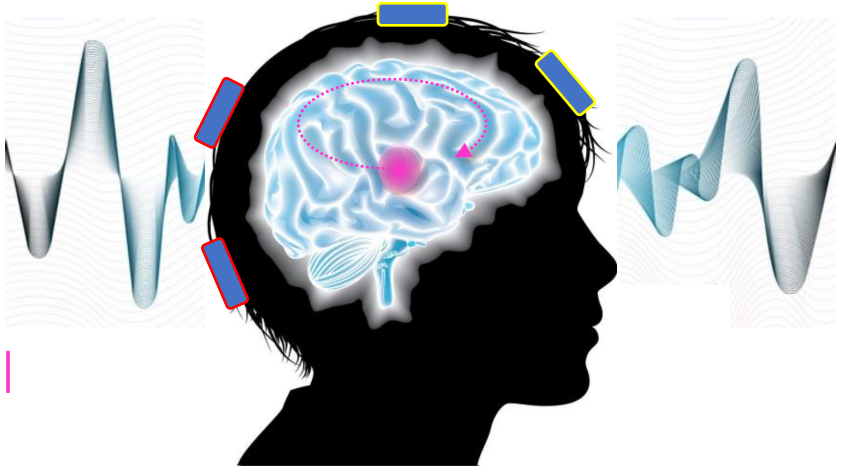
mTI

Expertise

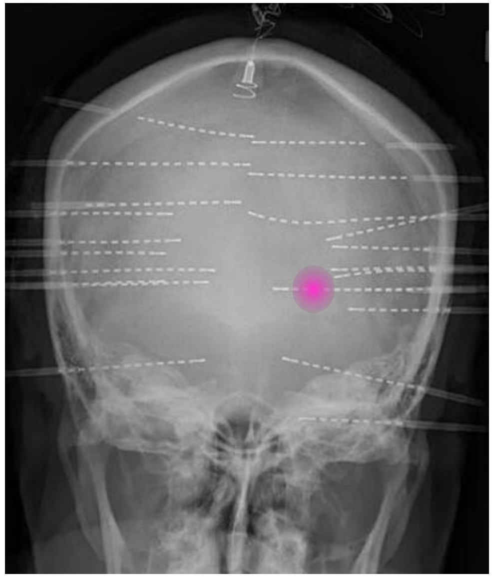
Neurology

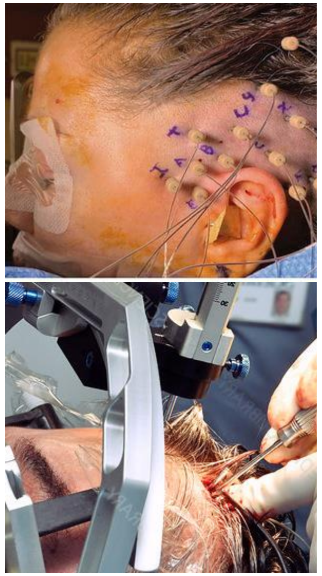


State-of-the-Art Engineering:
non-invasive interferential electric fields



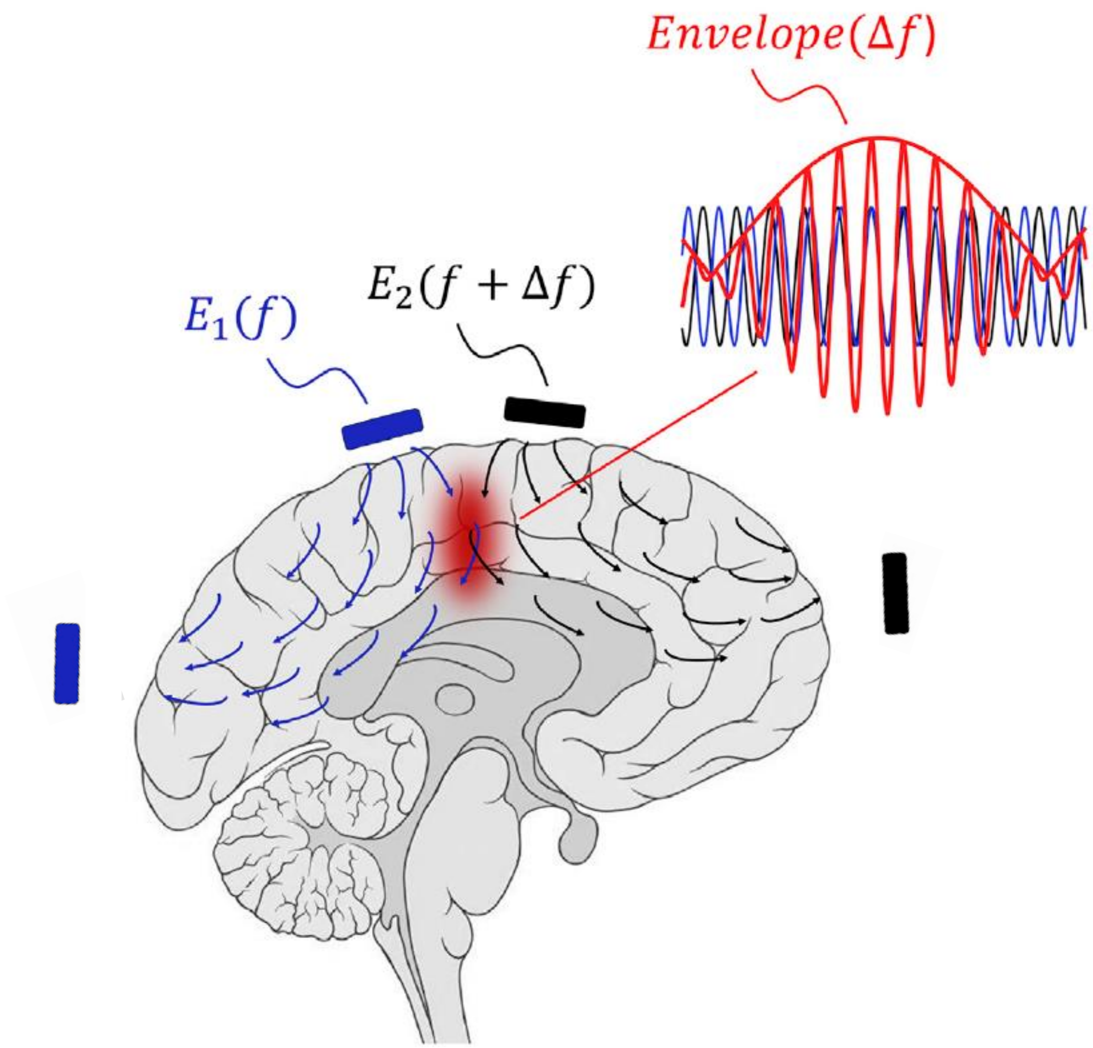
complete focal/position control

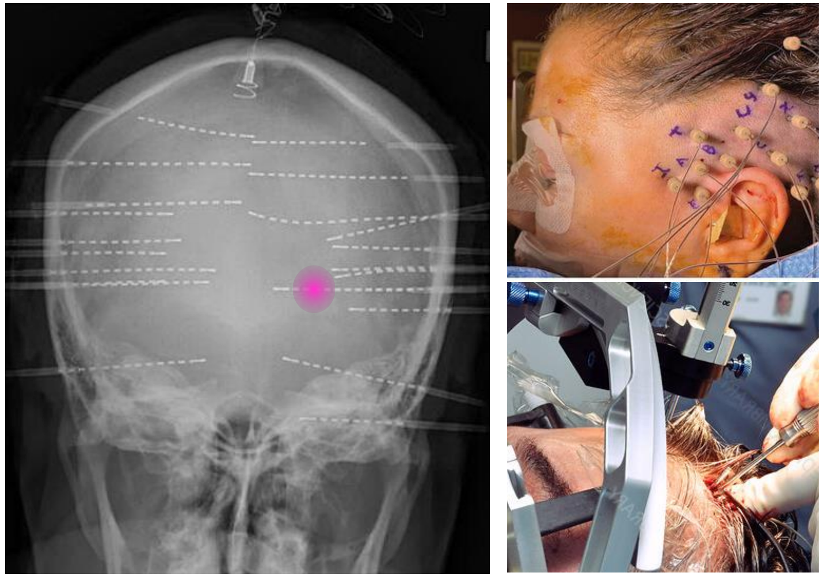




State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control

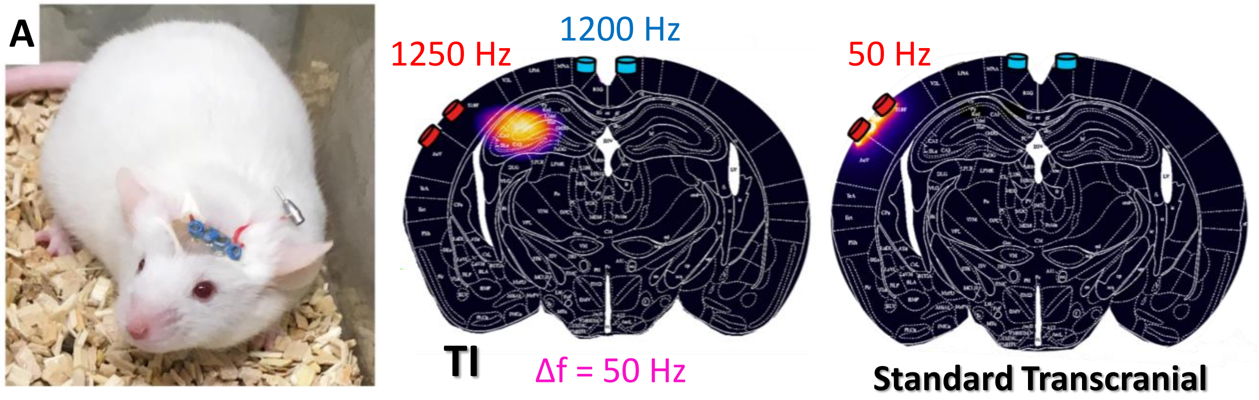
Complete Non-invasive Deep Brain Stimulation in Epilepsy





<u>T</u>emporal <u>I</u>nterference (TI) Stimulation

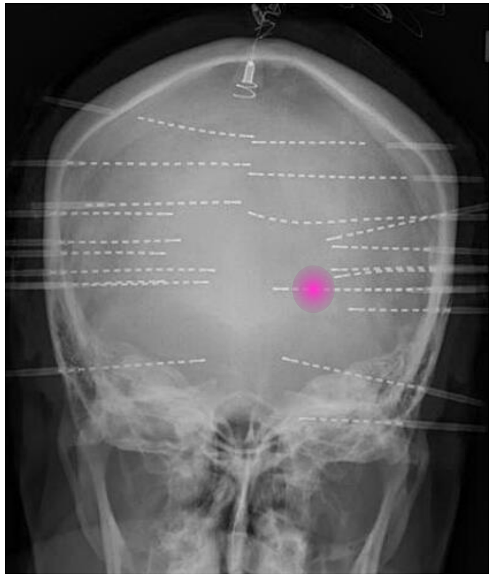
Preliminary Results: **Efficacy**



B **Excitatory Stimulation**

Classic Intracranial

f = 50 Hz



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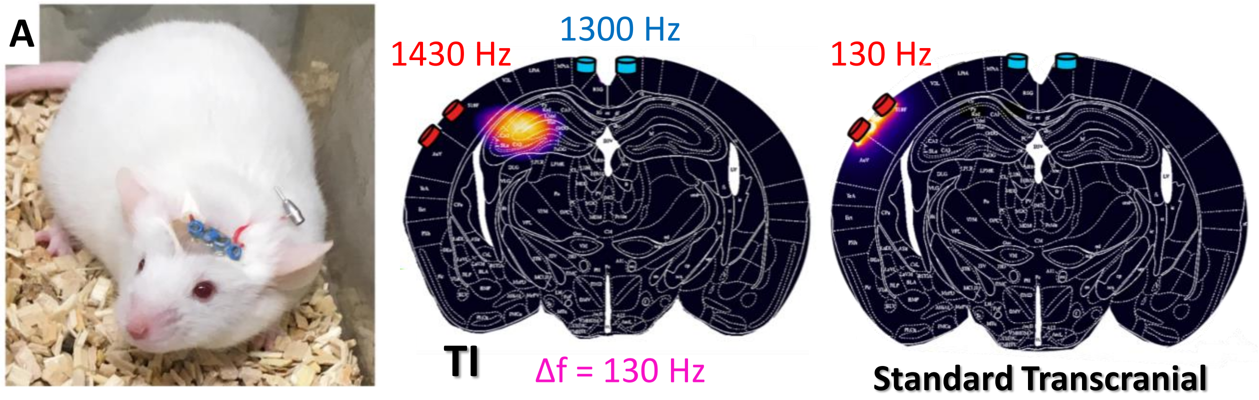
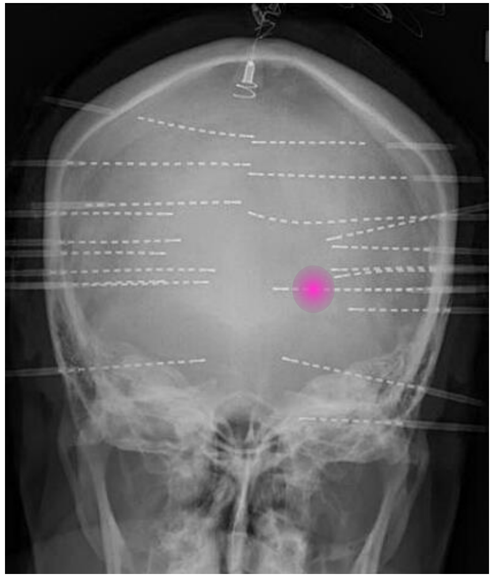


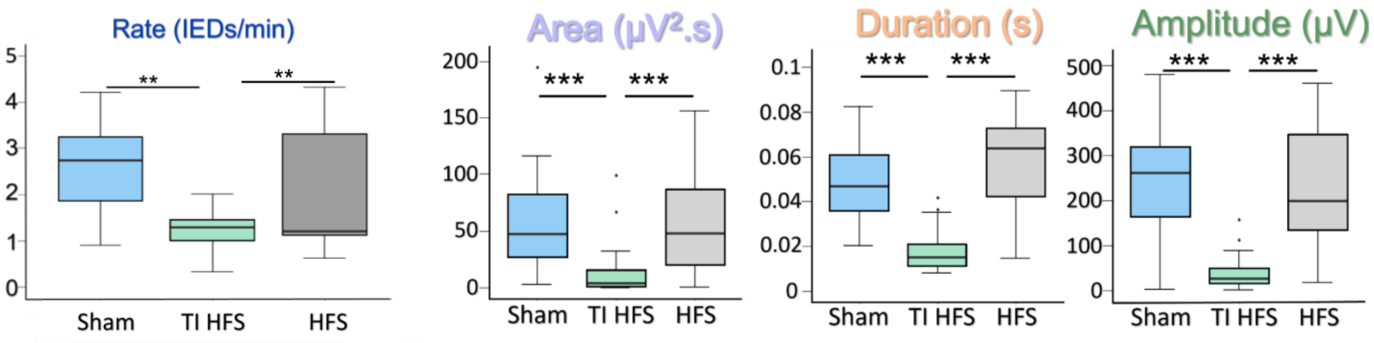
Classic Intracranial

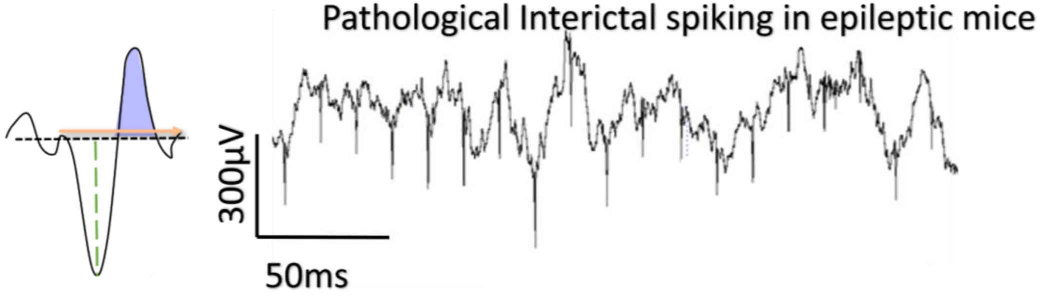
f = 130 Hz



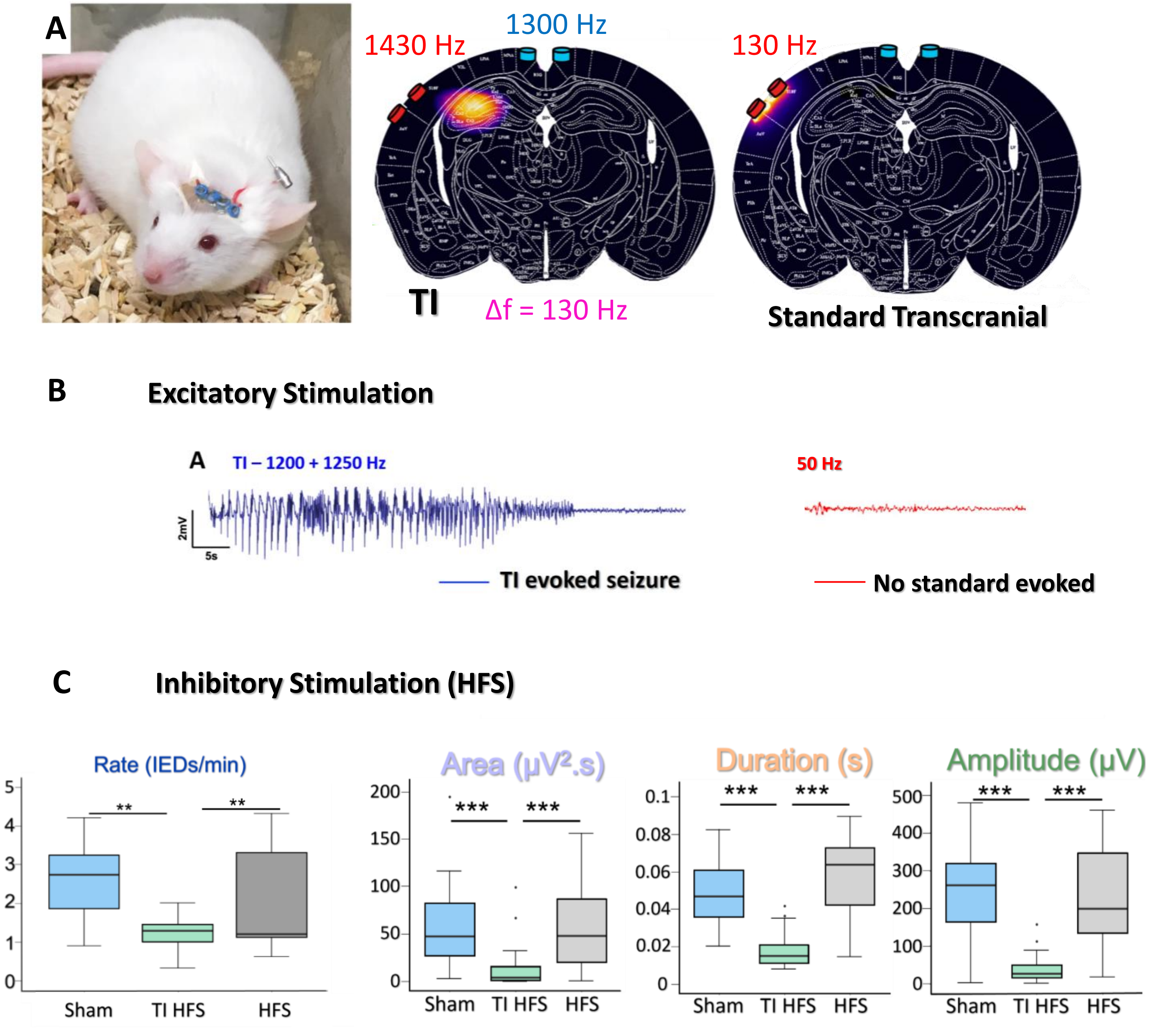
B **Excitatory Stimulation**

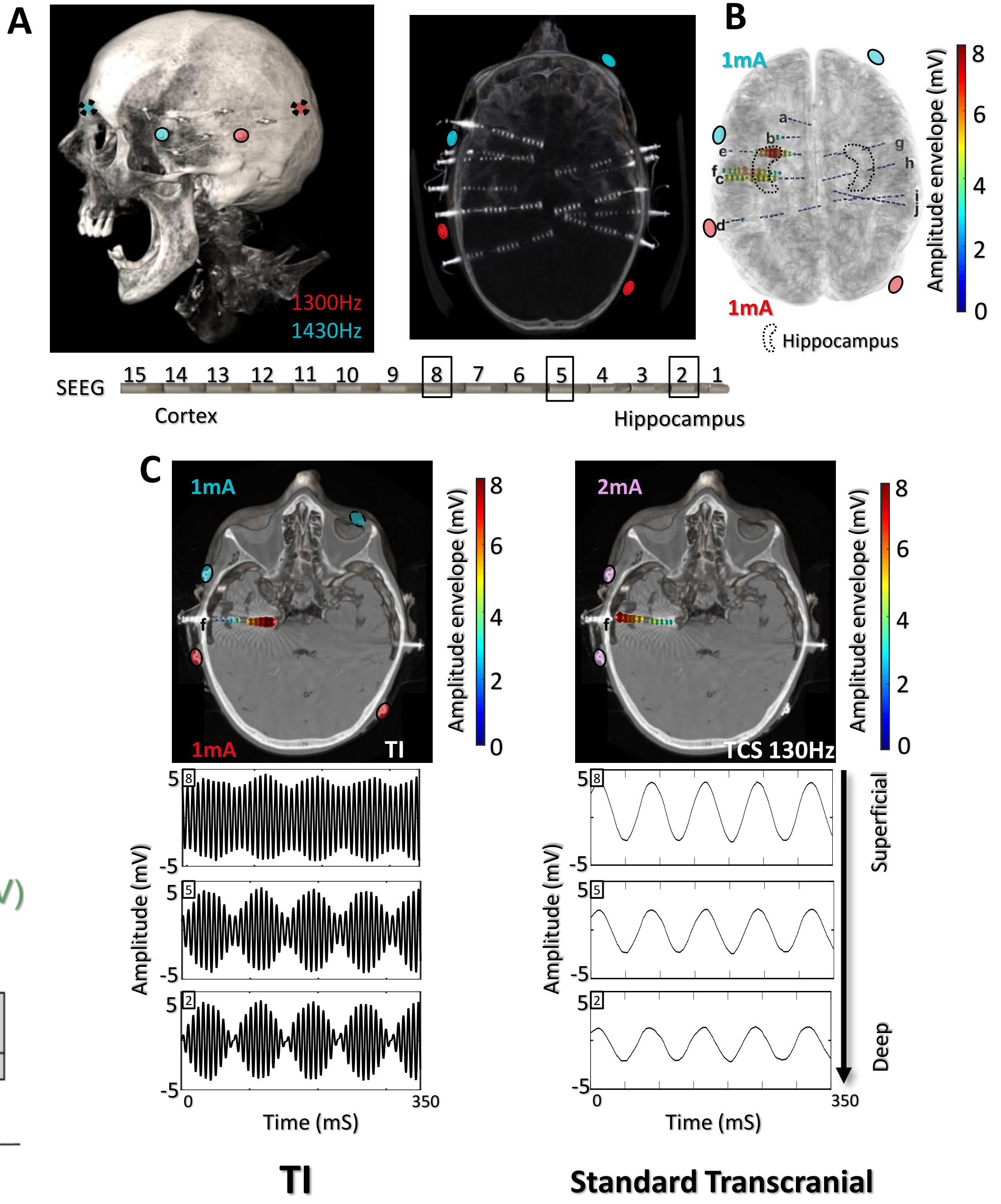
C **Inhibitory Stimulation (HFS)**

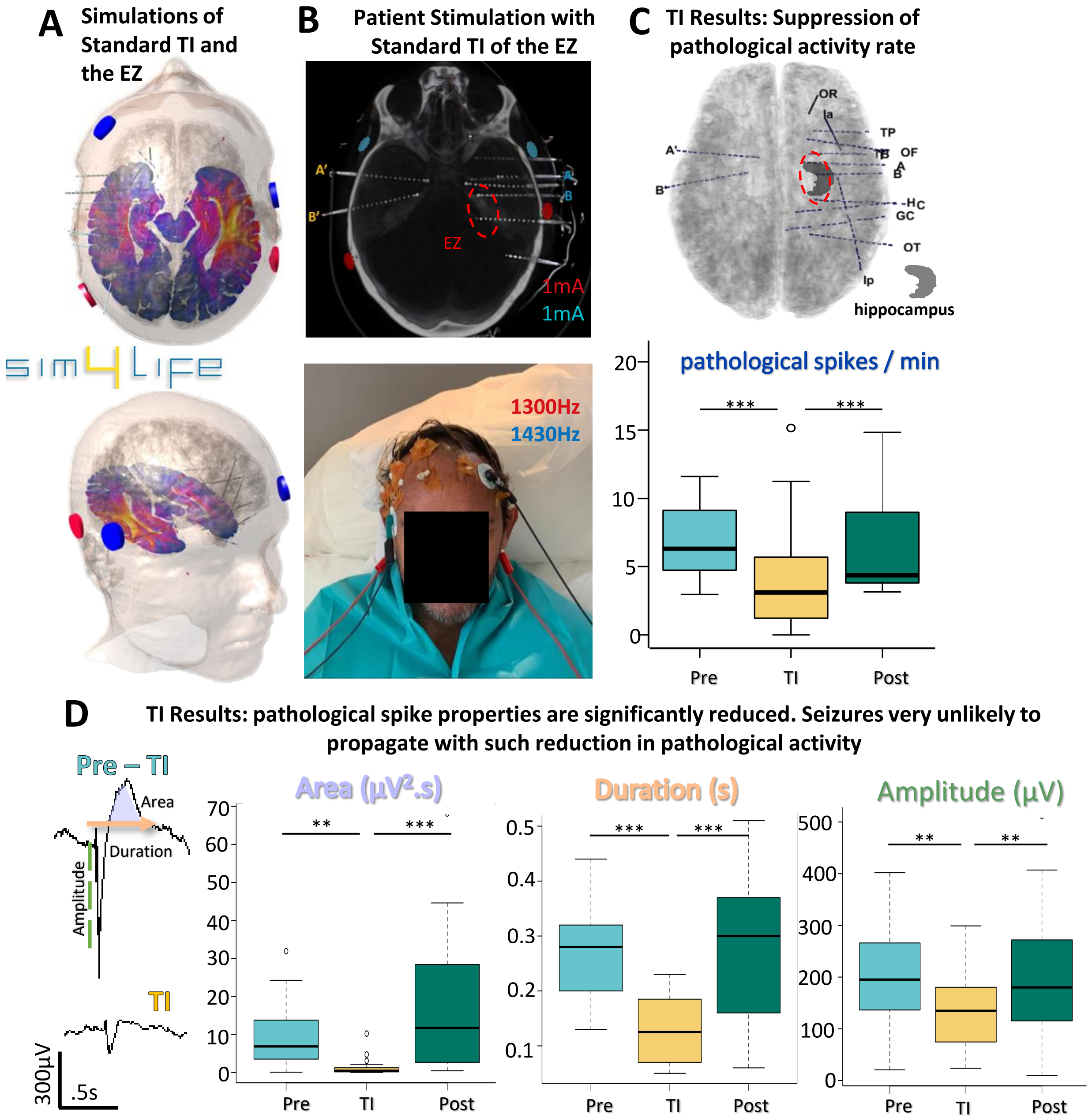


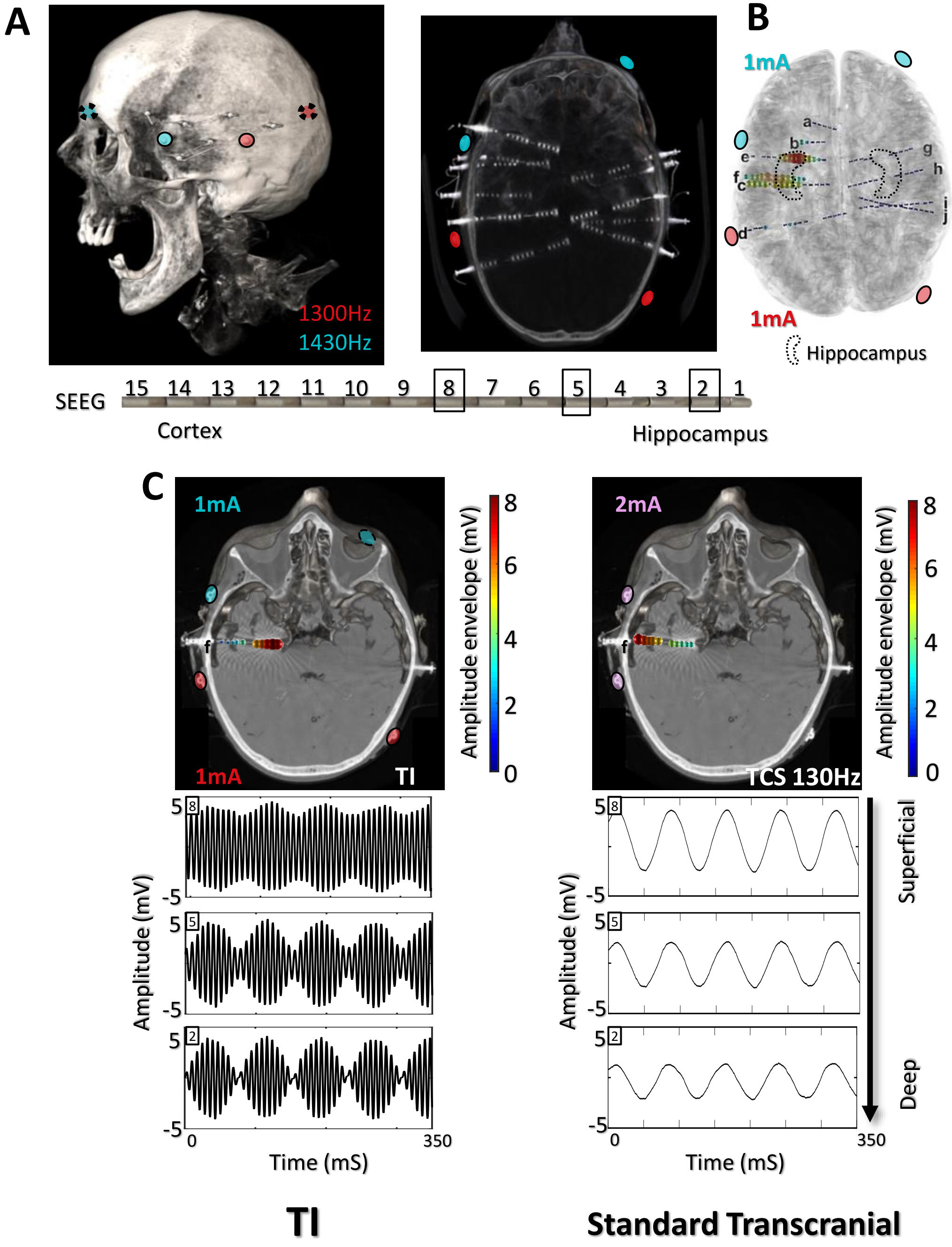


Preliminary Results: **Efficacy**






A
Simulations of Standard TI and the EZ
sim4life
B
Patient Stimulation with Standard TI of the EZ
A'
B'
EZ
1mA
1mA
1300Hz
1430Hz
C
TI Results: Suppression of pathological activity rate
OR
Ia
TP
OF
Hc
GC
OT
Ip
hippocampus
pathological spikes / min
***
***
Pre
TI
Post
D
TI Results: pathological spike properties are significantly reduced. Seizures very unlikely to propagate with such reduction in pathological activity
Pre – TI
Area
Duration
Amplitude
TI
300µV
.5s
Area (µV².s)
Duration (s)
Amplitude (µV)
**
***
Pre
TI
Post


A
1300Hz
1430Hz
SEEG
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
Cortex
Hippocampus
B
1mA
1mA
Hippocampus
Amplitude envelope (mV)
C
1mA
1mA
TI
2mA
TCS 130Hz
Amplitude (mV)
Time (mS)
Superficial
Deep
TI
Standard Transcranial

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- ❑ Temporal Interference (TI): Epilepsy as a model
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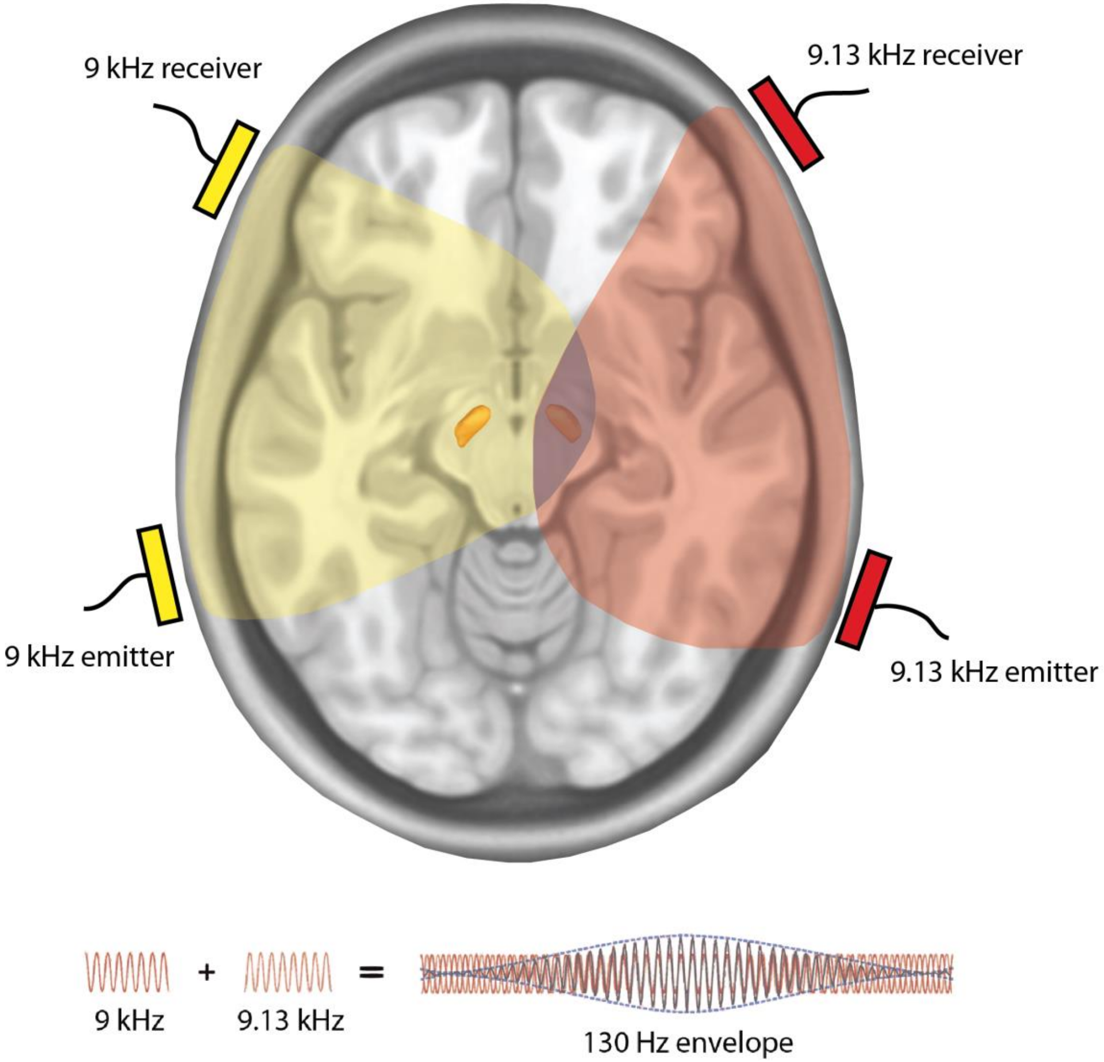
Temporal Interference Stimulation (TIS) - principle

- Subject specific modelling of e-fields and electrode positions



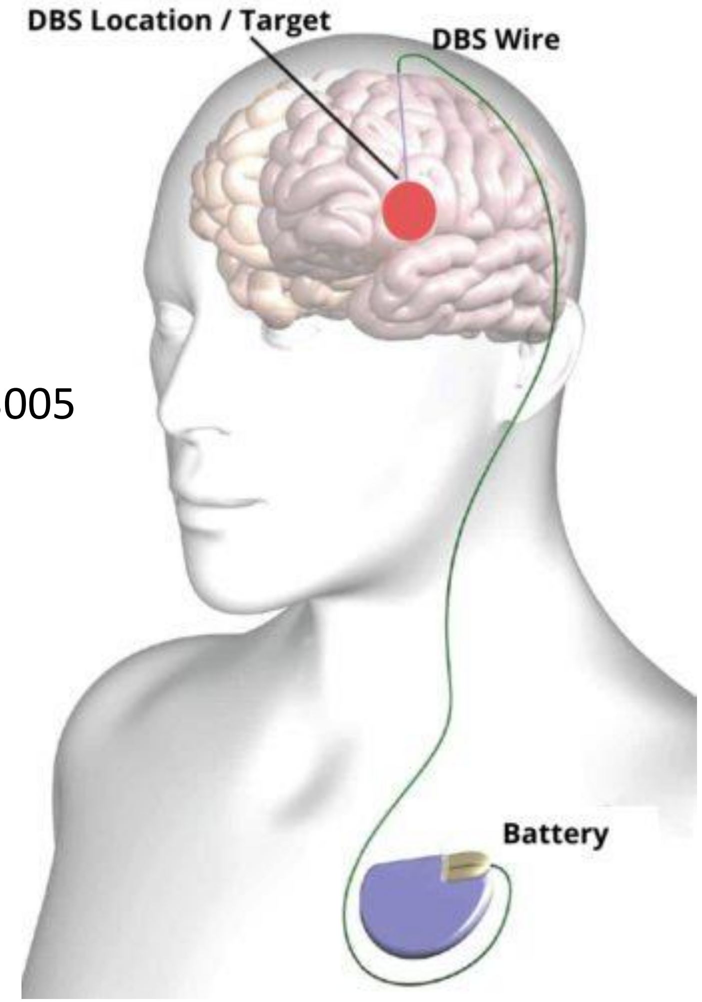
Temporal Interference Stimulation (TIS) of subthalamic nucleus (STN)

Pilot measurement – 1st patient

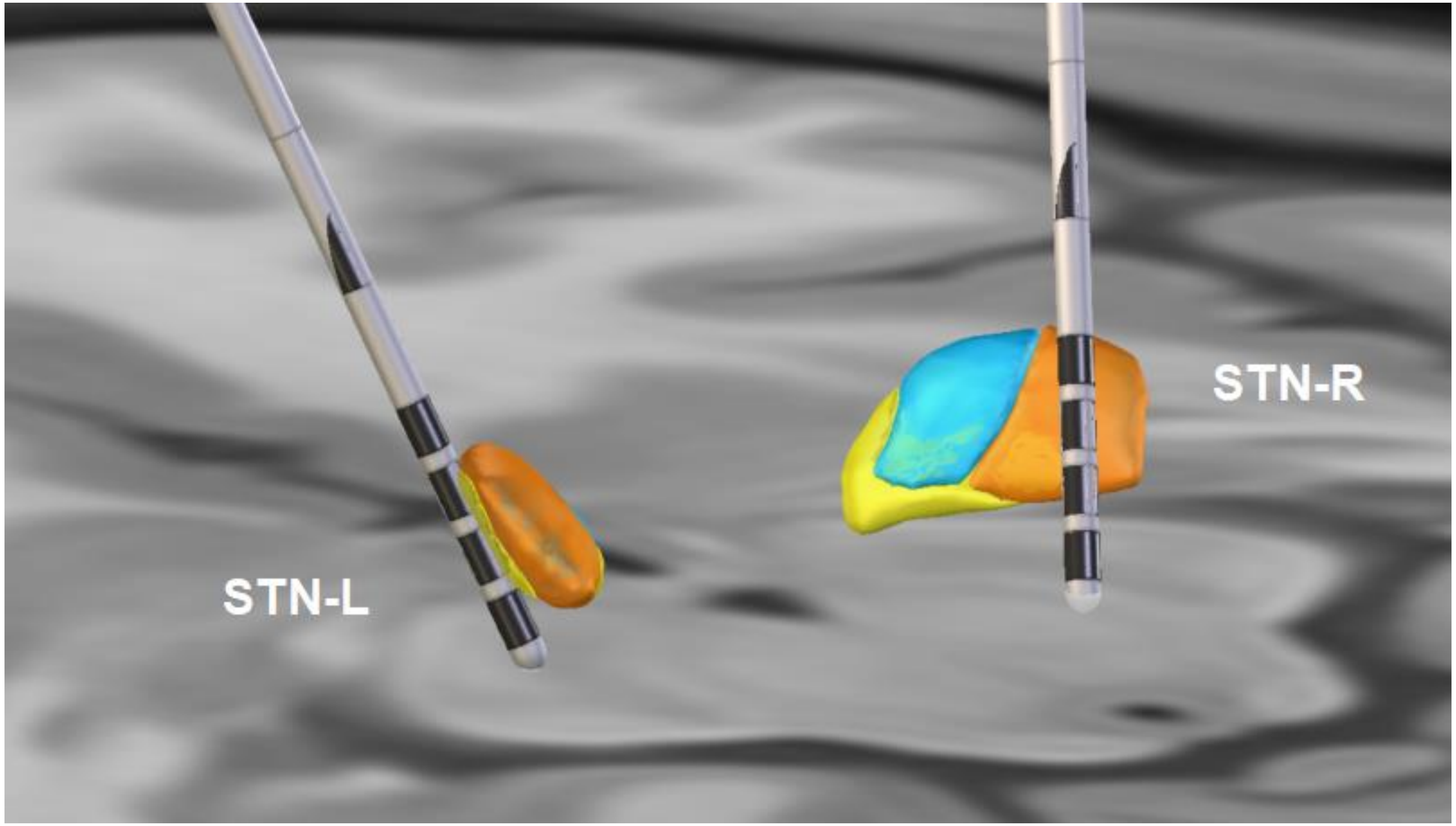
Parkinson‘s disease patient

- male, 64 years, right-handed
- Disease duration 14 years, dominant side - right
- With freezings, LED = 1385, UPDRS = 41
- Indicated to STN-DBS, Medtronic Percept IPG, Directional Leads B33005

- Externalized leads, LFP recording, medication OFF state



Lead localization

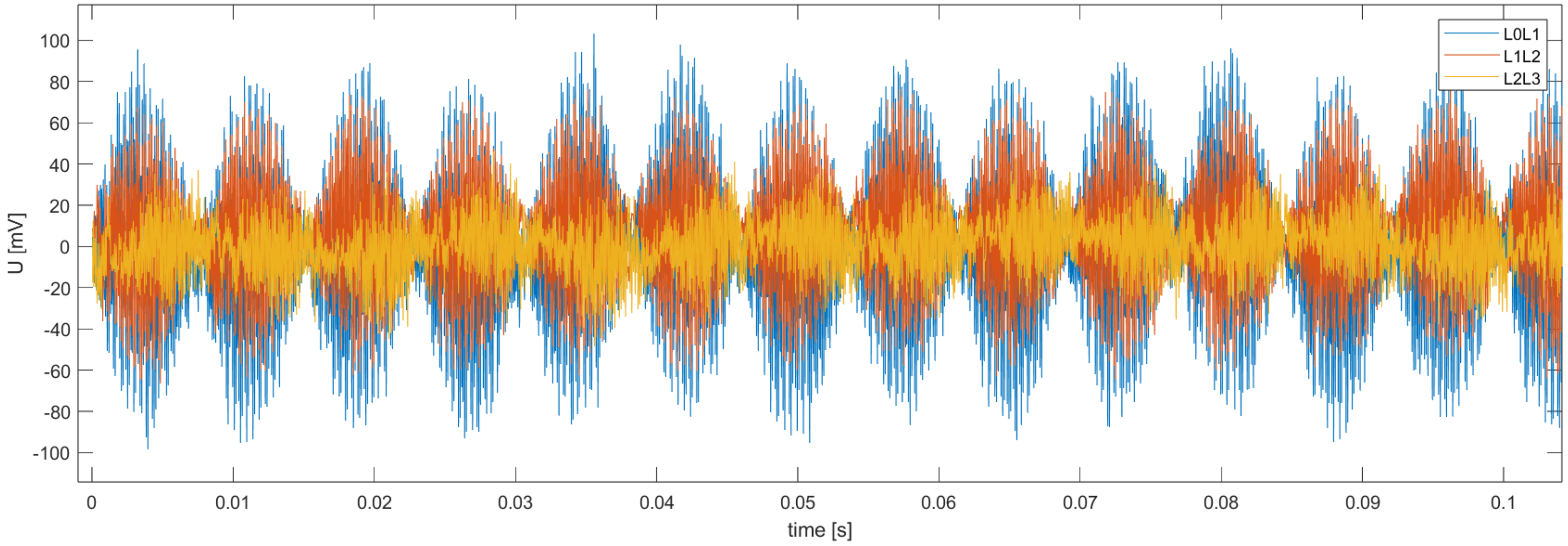


Orange – motor, blue – associative, yellow – limbic part of STN

Temporal Interference Stimulation (TIS)

- Two stimulation pairs on scalp, high frequency carriers
  - f1 = 9000 Hz, f2 = 9130 Hz, Δf = 130 Hz
  - Stimulation target: position of L1 contact

- LFP recording from externalized leads, fs = 25kHz, Cz scalp reference, recalculated to bipolar L0L1, L1L2, L2L3 (R0R1, R1R2, R2R3)



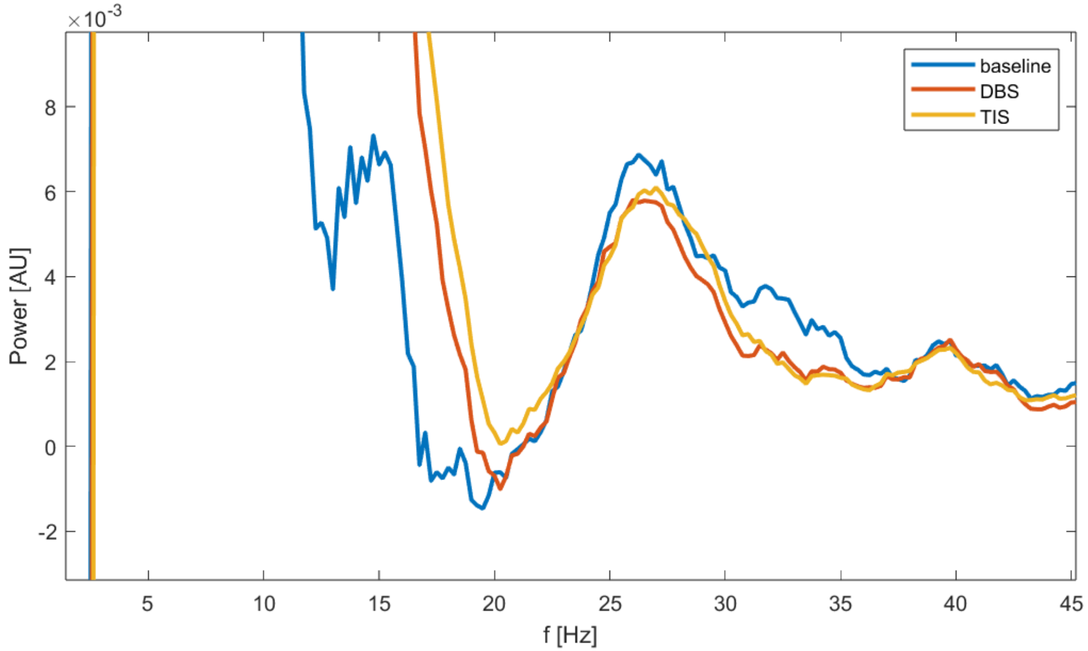
Note that magnitude of interference artifact differs across bipolar contacts on lead. It means we are able to focus the stimulation also in subcortical regions.

LFP recording, beta power analysis

- fs = 25kHz, Cz scalp reference, recalculated to bipolar
- analysis of L0L3 signal with focus on beta peak power

Comparison of oscillatory components of power spectrum between baseline, conventional DBS stimulation and non-invasive temporal interference stimulation

- Baseline resting state, 2 minutes, OFF medication
- Rest after DBS, 2 mins of recording immediately after 3 mins of stimulation of L1L2, 130Hz, 90us, 2V
- Rest after TIS, 2 mins of recording immediately after 3 mins of stimulation targeted L1, 130 Hz



Note that beta power peak at 26.5Hz is the highest in baseline condition and falls after DBS or TIS stimulation – evaluated after-effect of stimulation. Between DBS and TIS session was approx. 30 minutes pause.

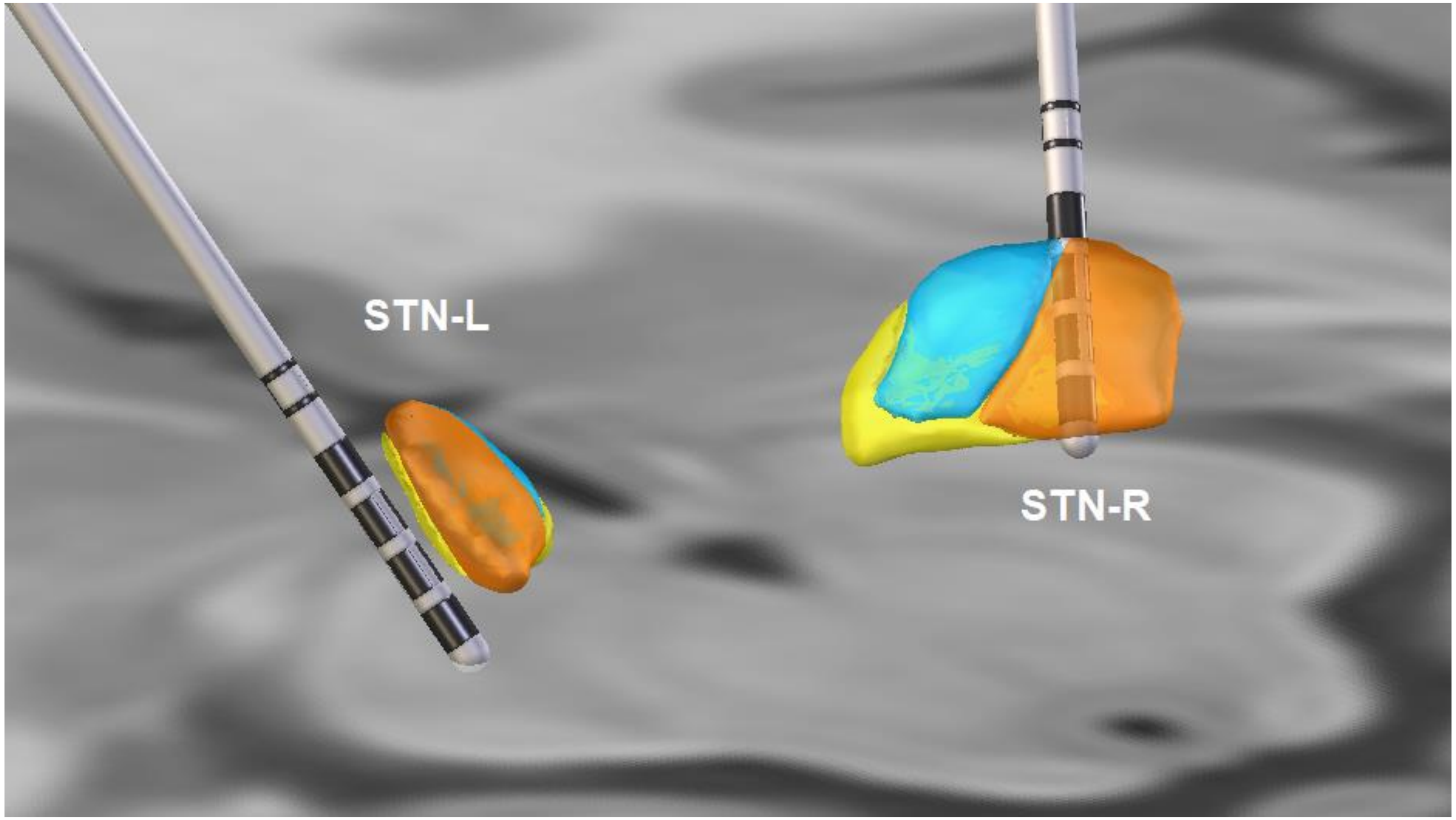
Temporal Interference Stimulation (TIS) of subthalamic nucleus (STN)

Pilot measurement – 2nd patient

- Parkinson‘s disease patient
- male, 53 years, right-handed
- Dominant side - left
- Indicated to STN-DBS, Abbott Infinity IPG, Directional Leads 6172

- Externalized leads, LFP recording, medication OFF state

Lead localization



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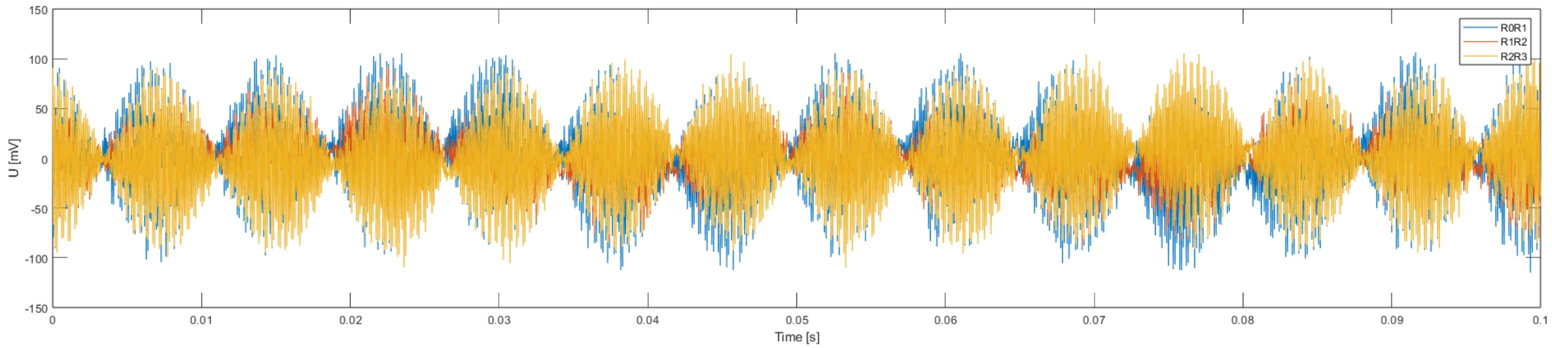

Note: Unfortunately, no clear difference in envelope amplitude between bipolar contacts

LFP recording, beta power analysis

- fs = 25kHz, Cz scalp reference, recalculated to bipolar
- analysis of R1R2 signal with focus on beta peak power

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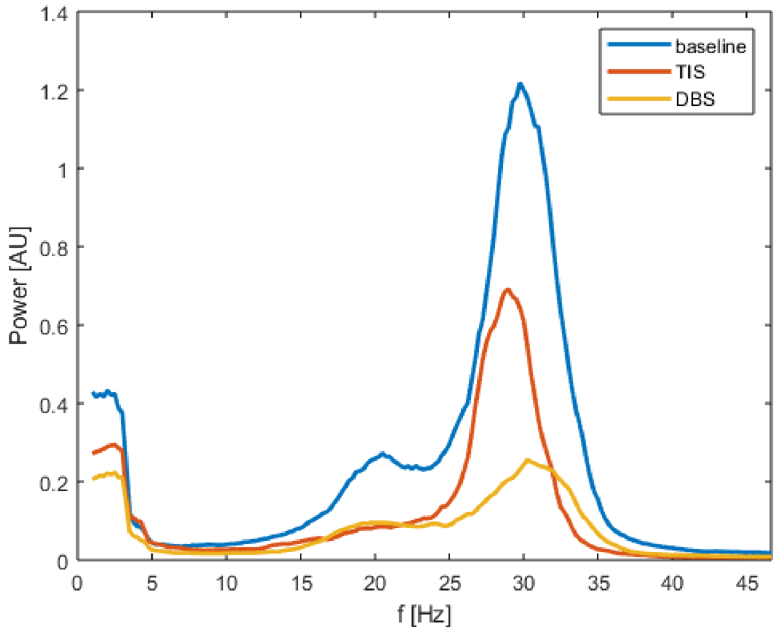
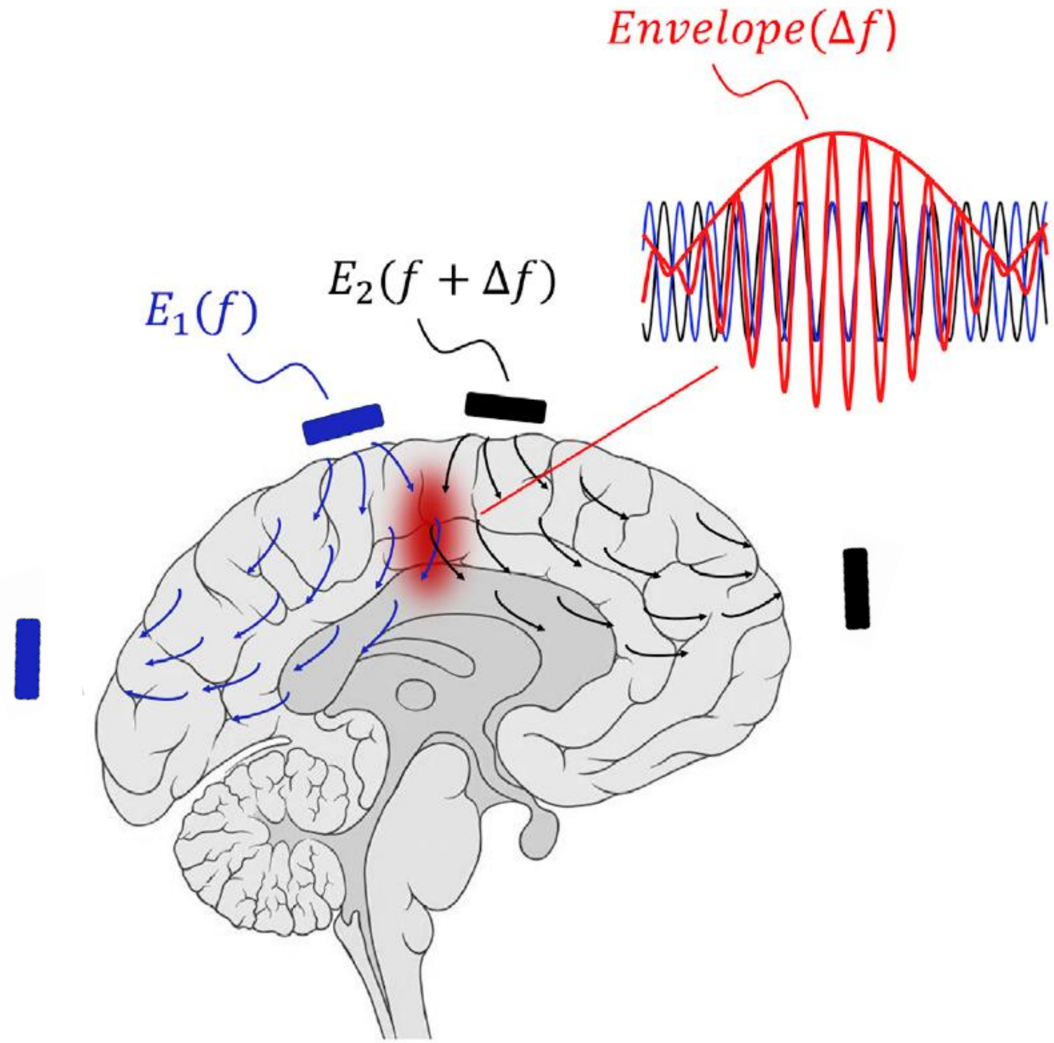
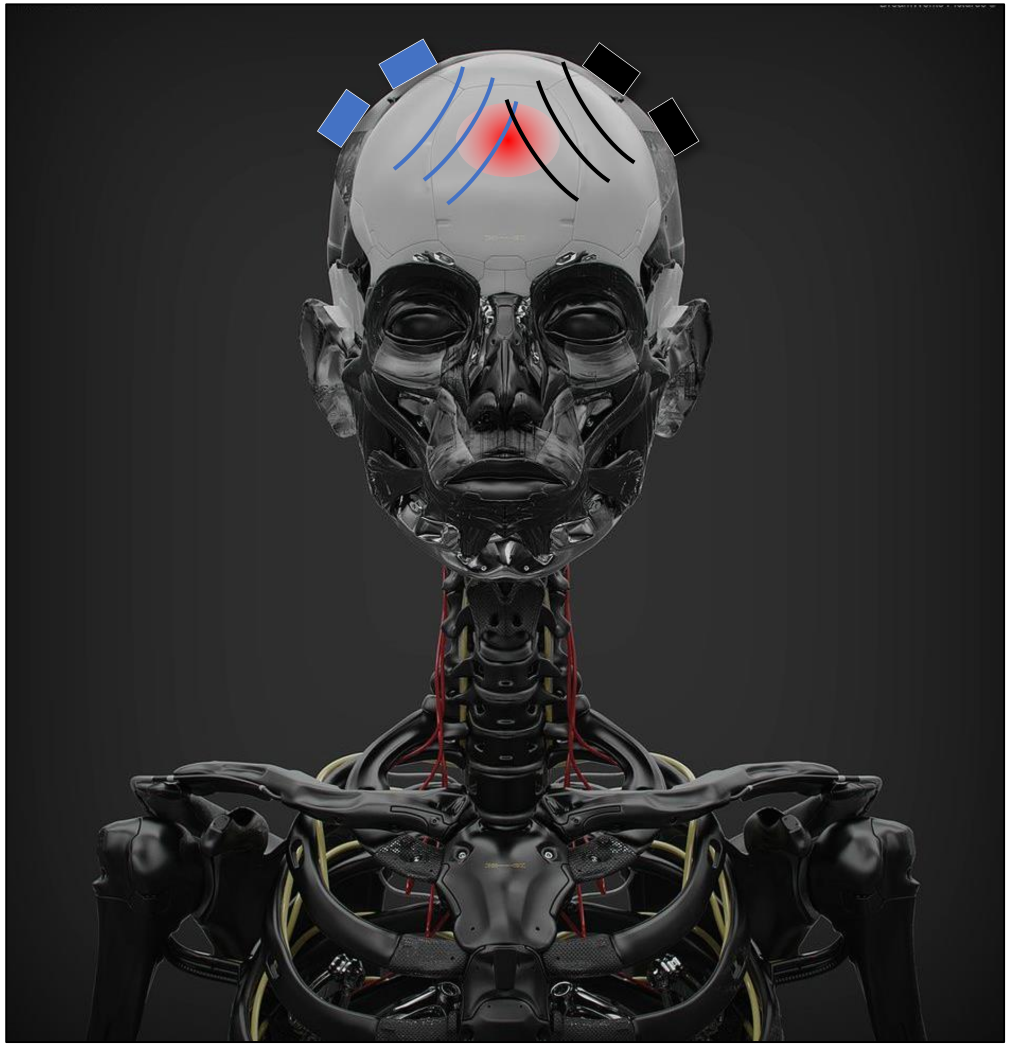
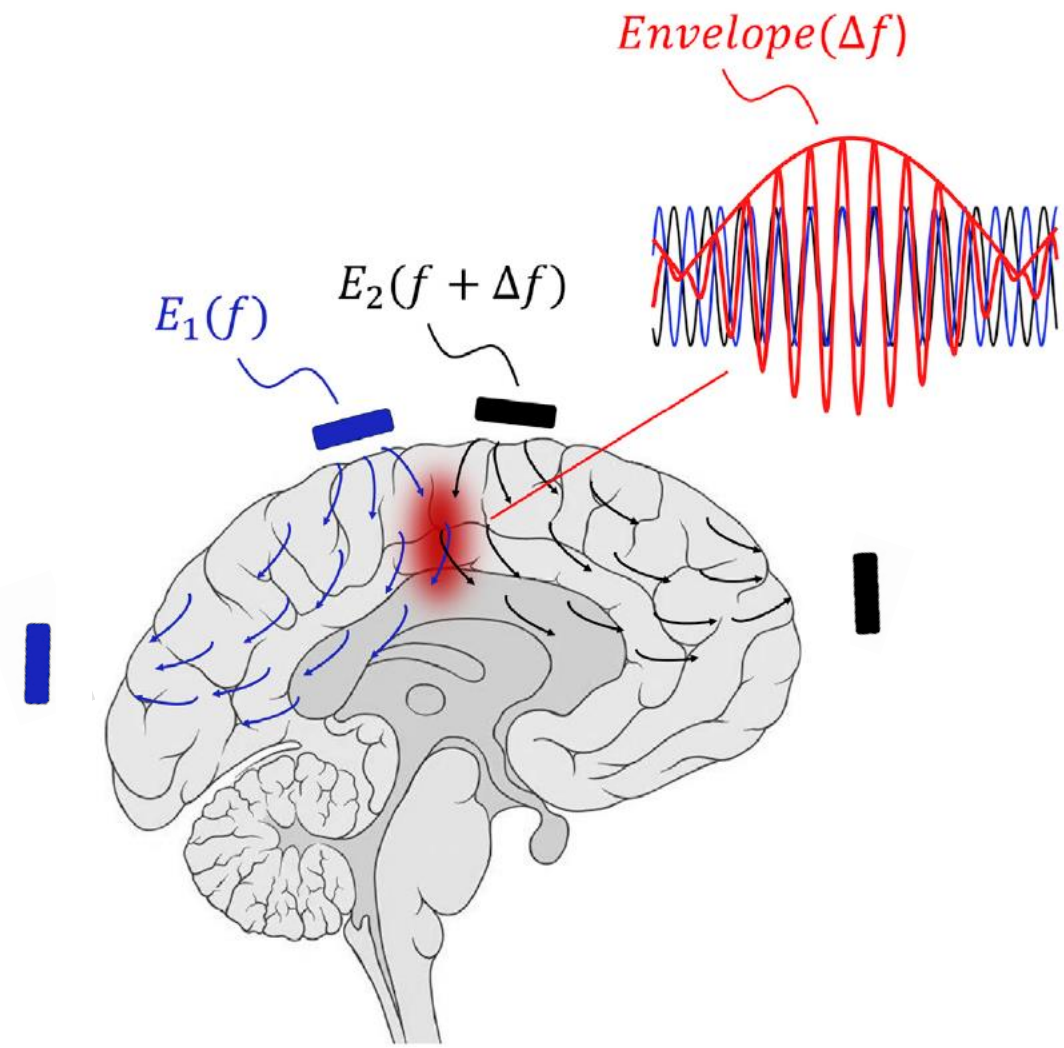
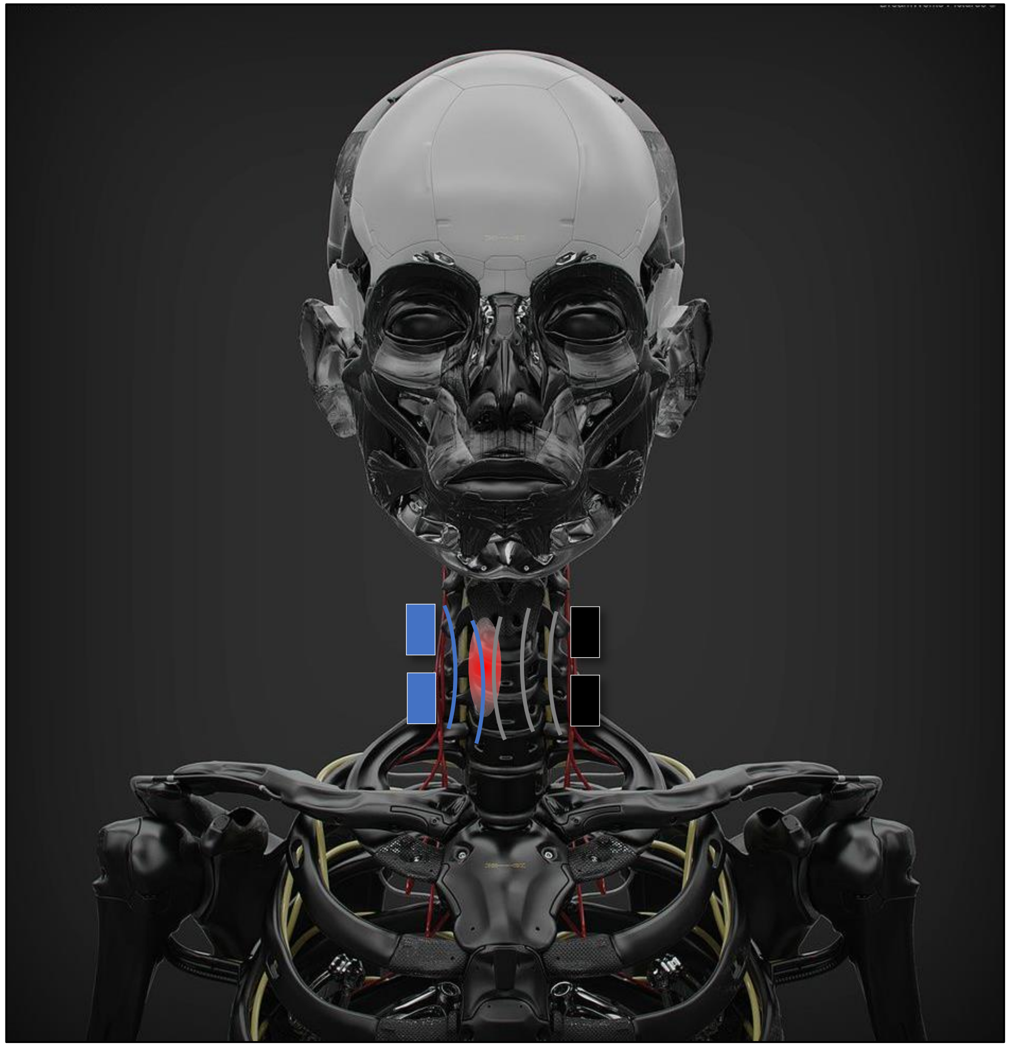


Note that beta power peak is the highest in baseline condition and falls after TIS and DBS stimulation – evaluated after-effect of stimulation. Between TIS and DBS session was approx. 20 minutes pause.


$Envelope(\Delta f)$
$E_2(f + \Delta f)$
$E_1(f)$




$Envelope(\Delta f)$
$E_2(f + \Delta f)$
$E_1(f)$



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  - ➢ Vagus Nerve
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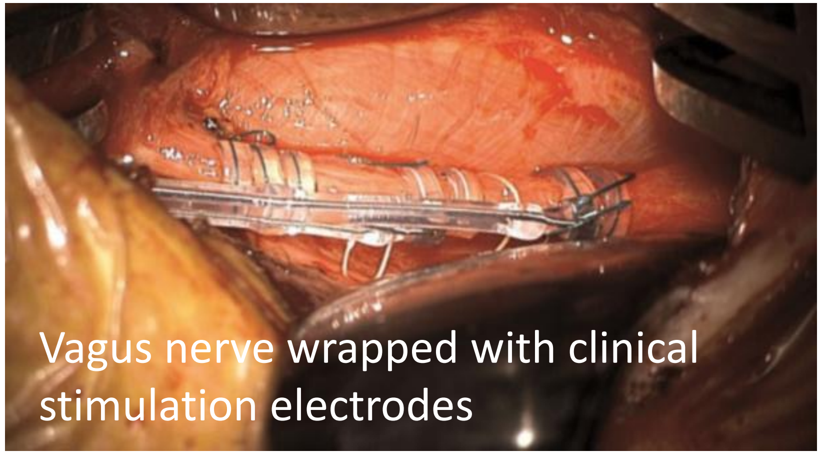
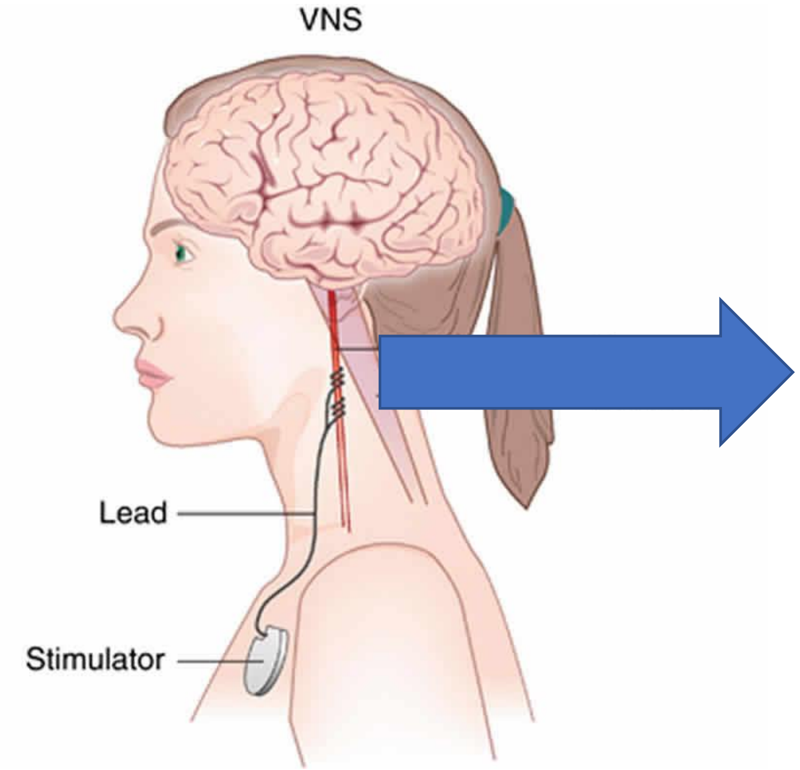
Clinical Temporal Interference



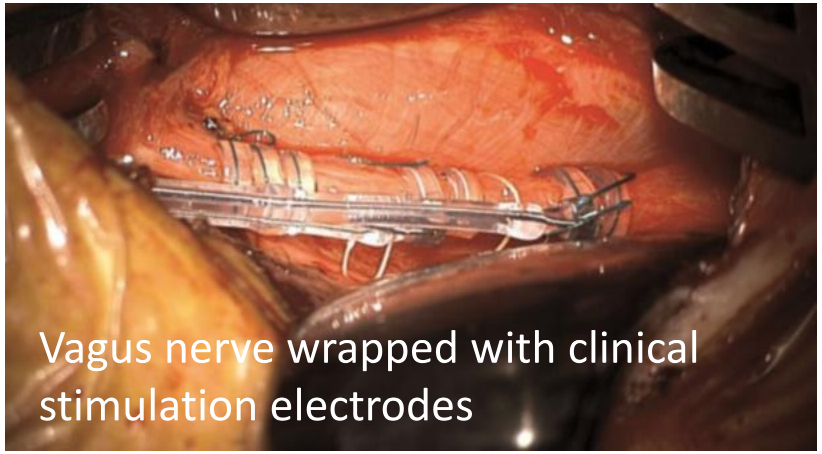
Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)



Vagus Nerve
Phrenic Nerve
Hypoglossal Nerve

implantable stimulator

Clinical Temporal Interference



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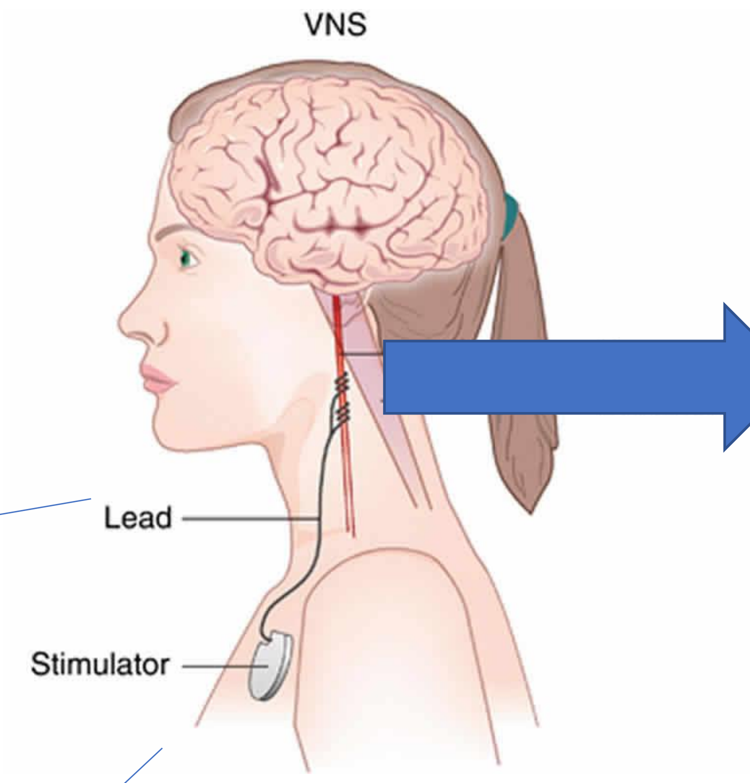

Vagus Nerve
Phrenic Nerve
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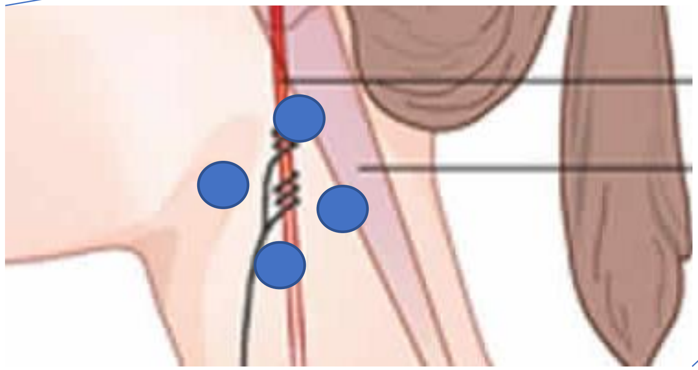
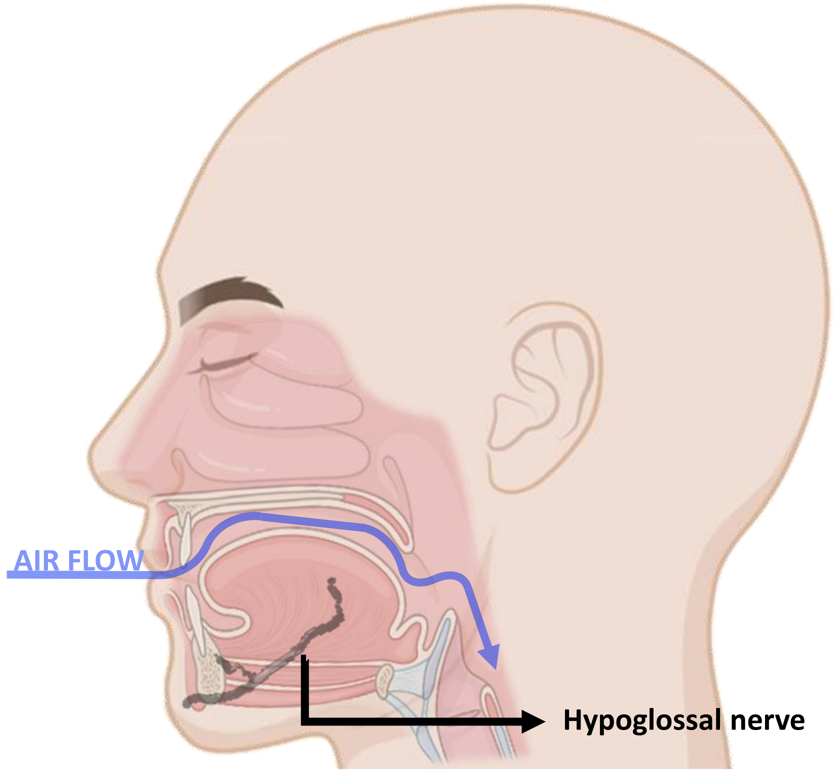
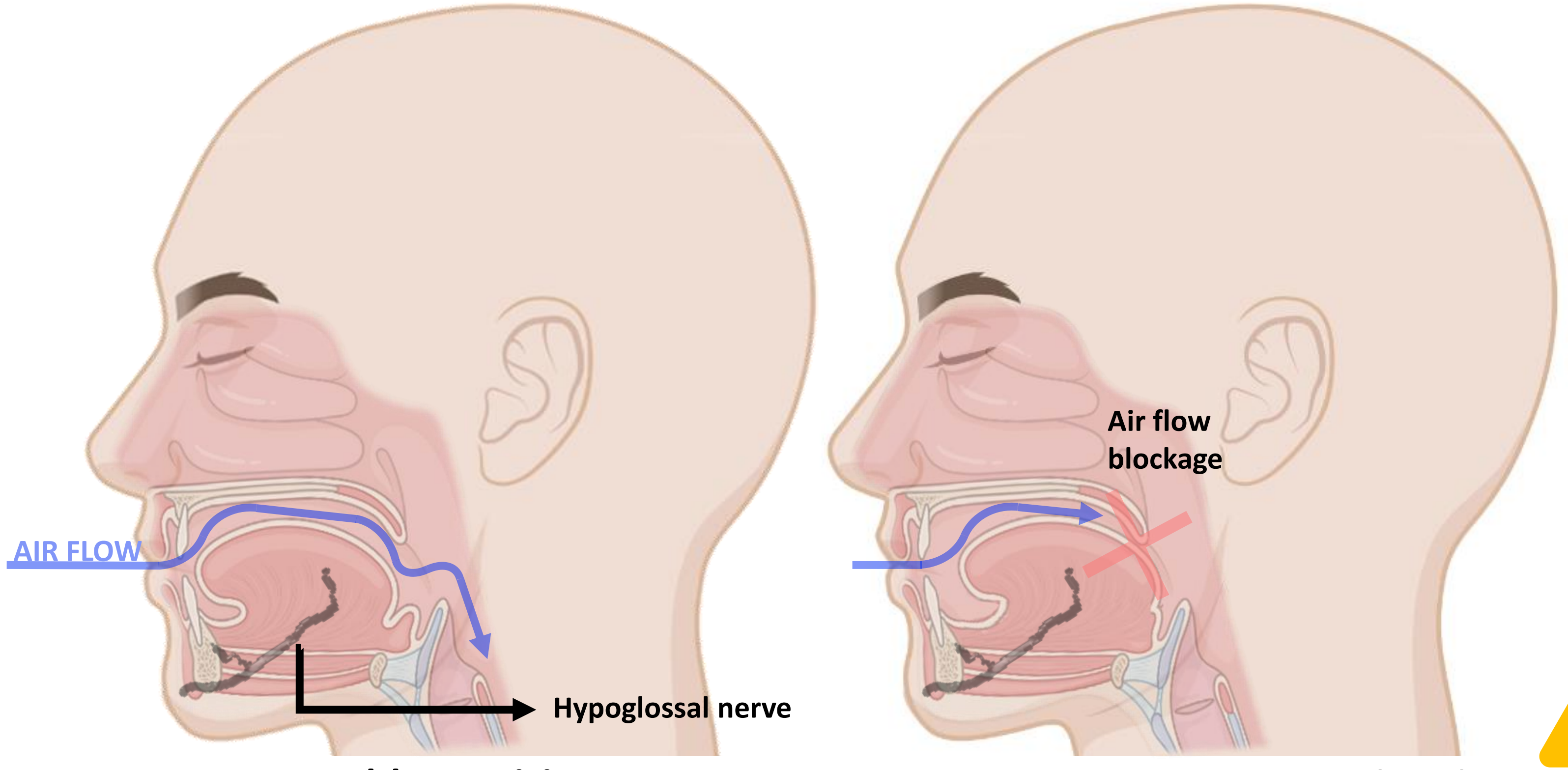


transcutaneous TI



Healthy participant

- **Normal airflow** with **no** pathological **obstruction** due to tongue collapse
- Hypoglossal nerve is responsible for tongue tonus



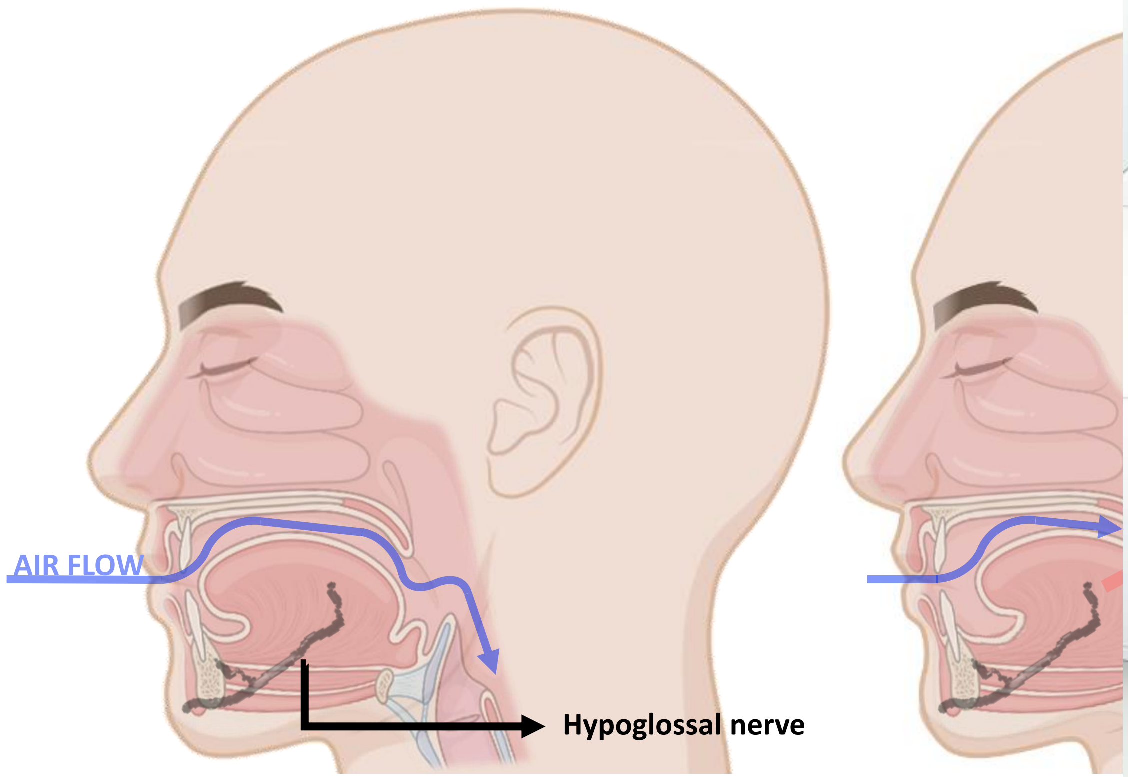
Healthy participant

Obstructive Sleep Apnea (OSA)

- For the **1 Billion people** with obstructive sleep apnea (OSA), CPAP is the standard of care

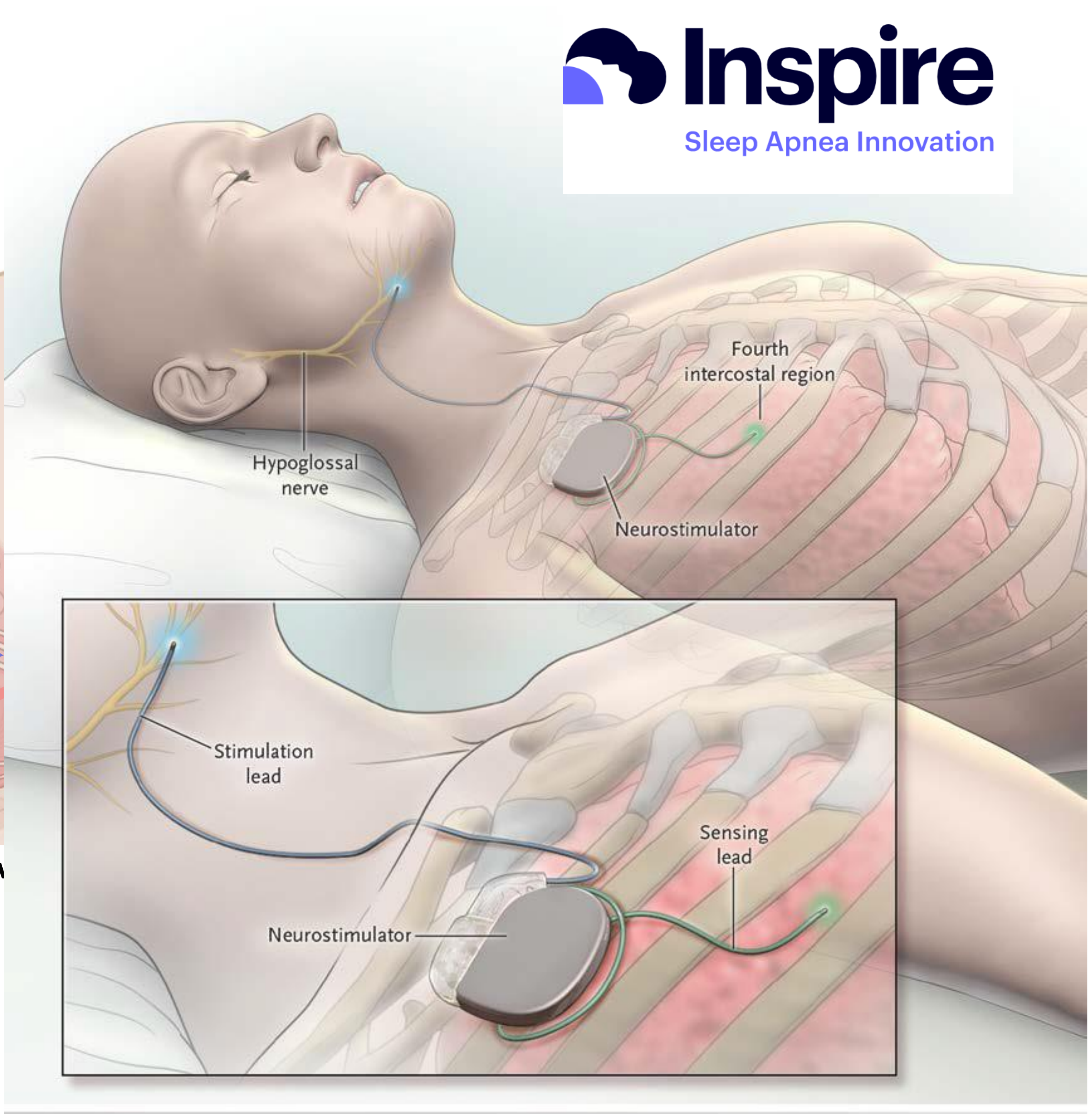
Loud, Uncomfortable,
Infection Risk,
Massive Recalls,
Poor Compliance

Inspire
Sleep Apnea Innovation

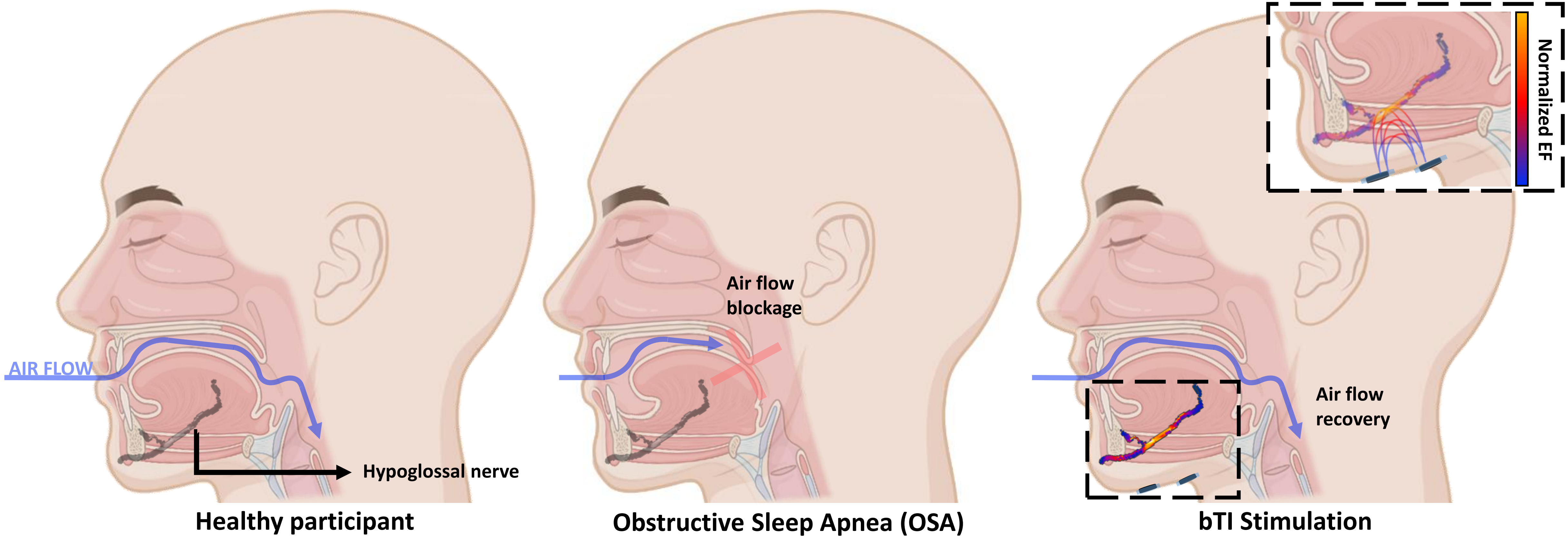


Healthy participant

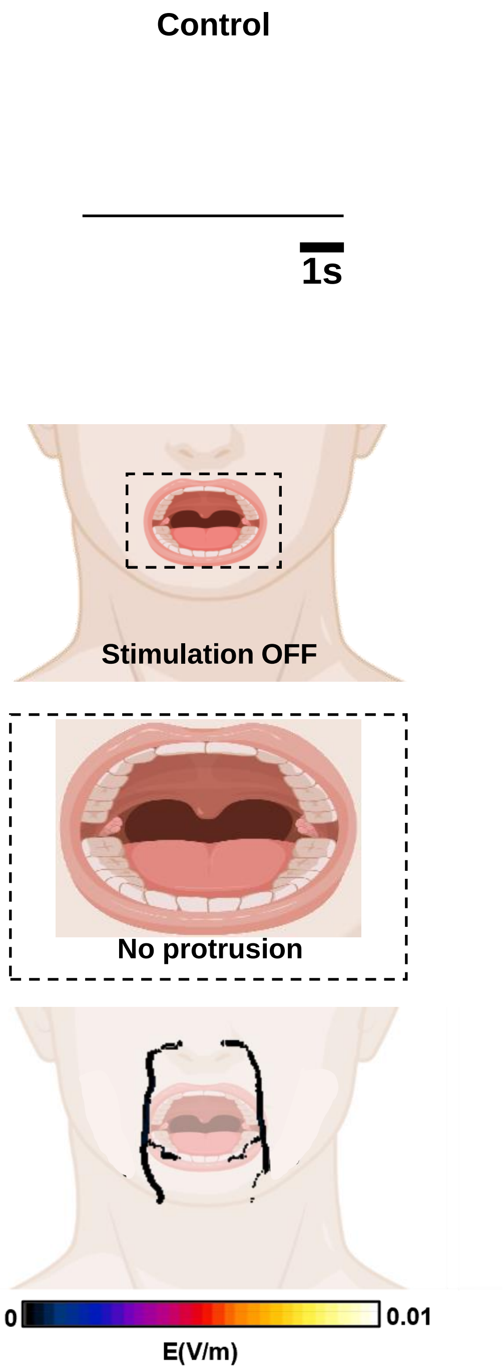
Obstructiv



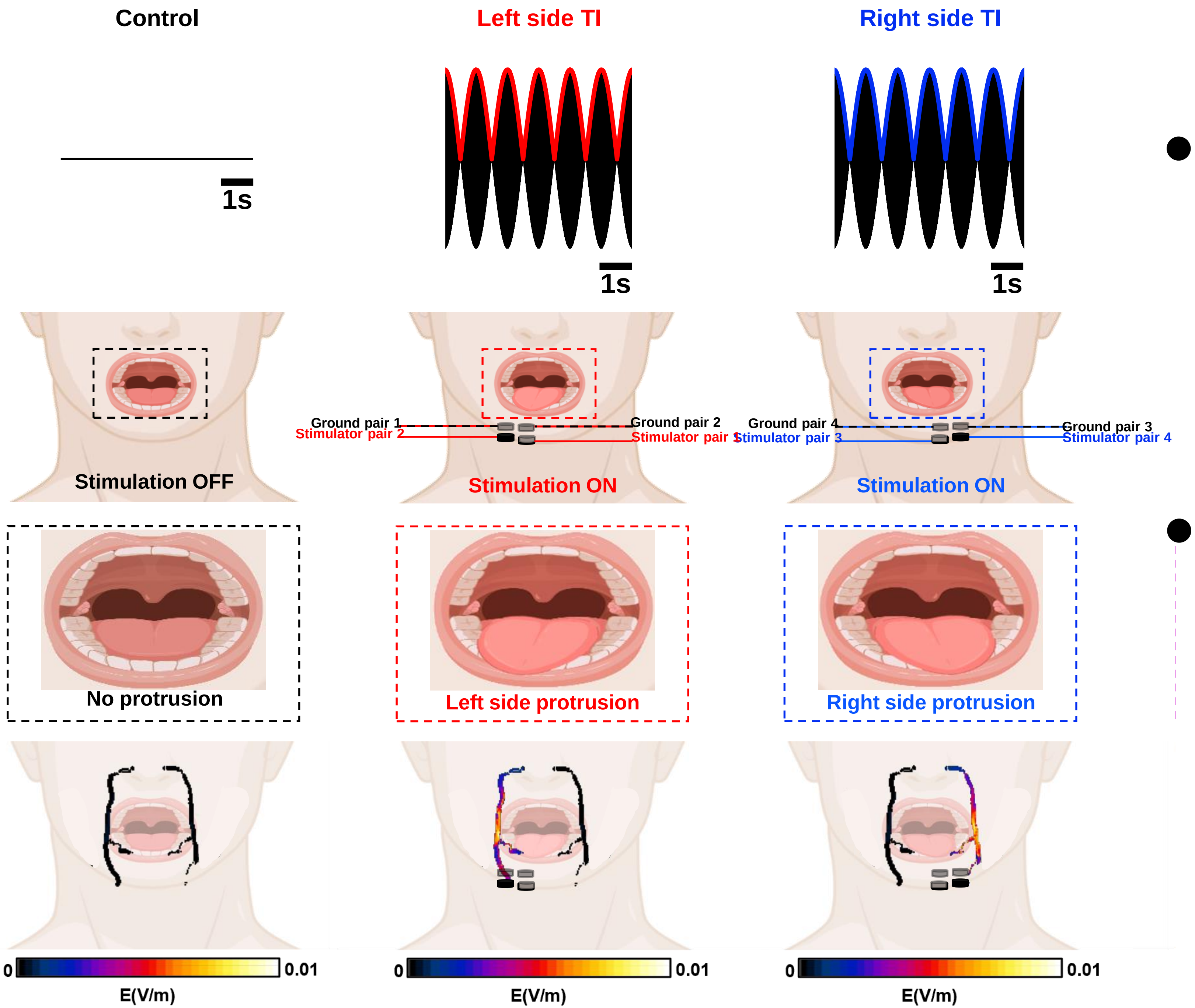
- **Hypoglossal nerve stimulation** is the standard surgical treatment for OSA



- Non-invasive stimulation is challenging but would avoid surgical procedure and tongue collapse during the night for OSA patients

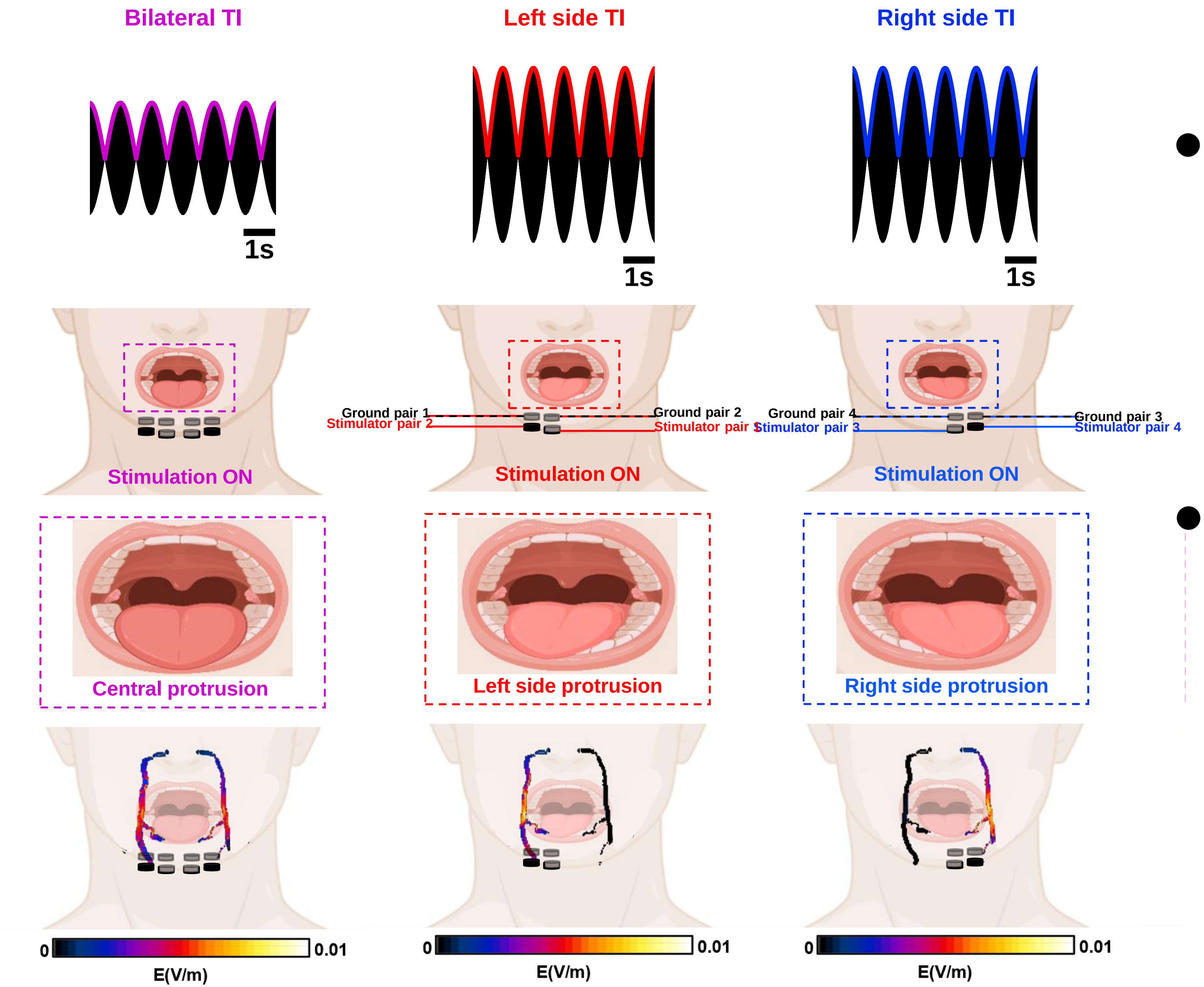


- With **no stimulation, no tongue tonus** and protrusion will be induced
- During an OSA event, the direct stimulation of the hypoglossal nerve will prevent tongue collapse



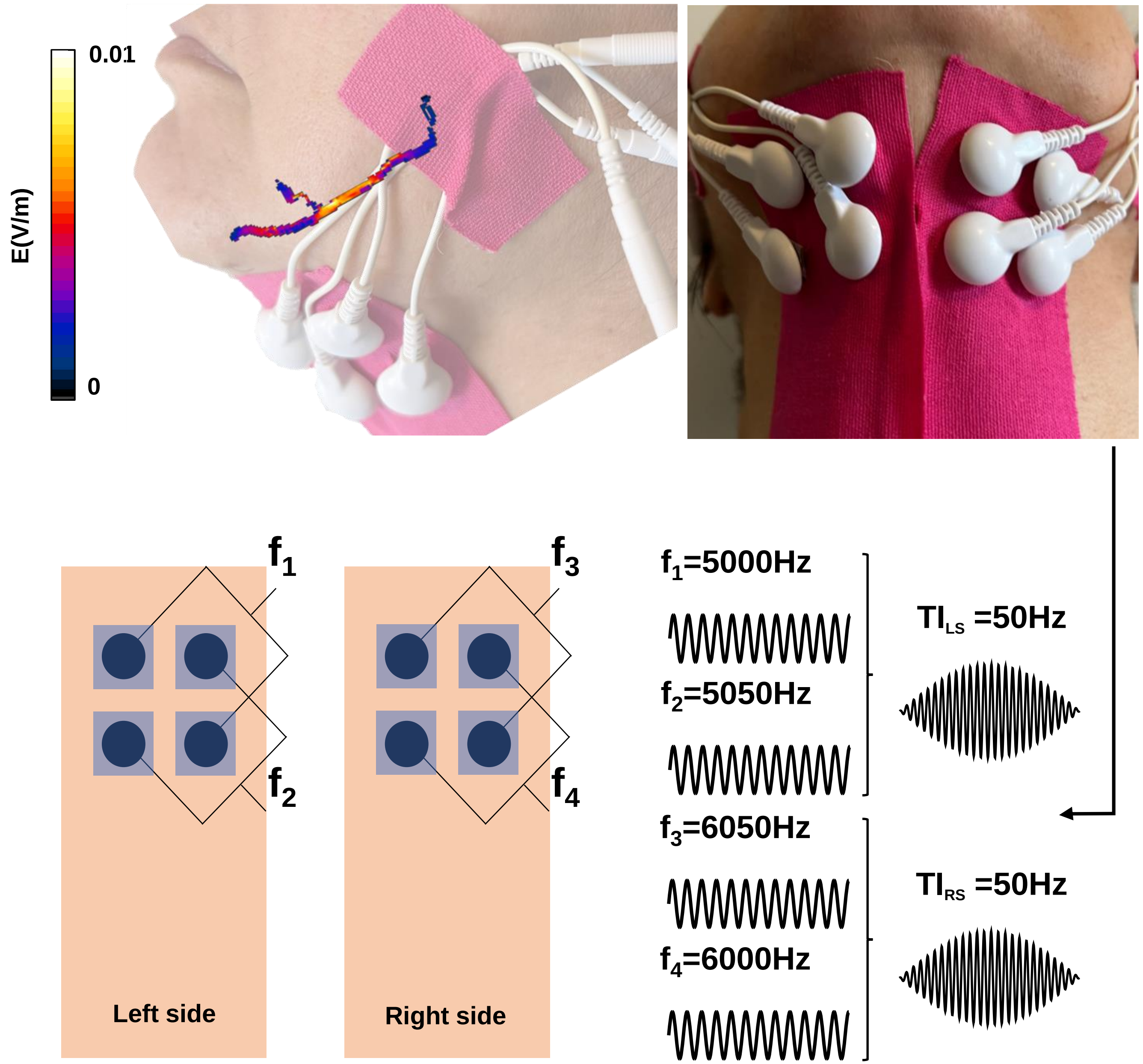
- **Unilateral** nerve stimulation only induces a **partial lateral** tongue protrusion

- The stimulation amplitude needed to induce a tongue tonus with unilateral TI is high and induce tingling on the skin



- **Bilateral** nerve stimulation induces a **complete central** tongue protrusion

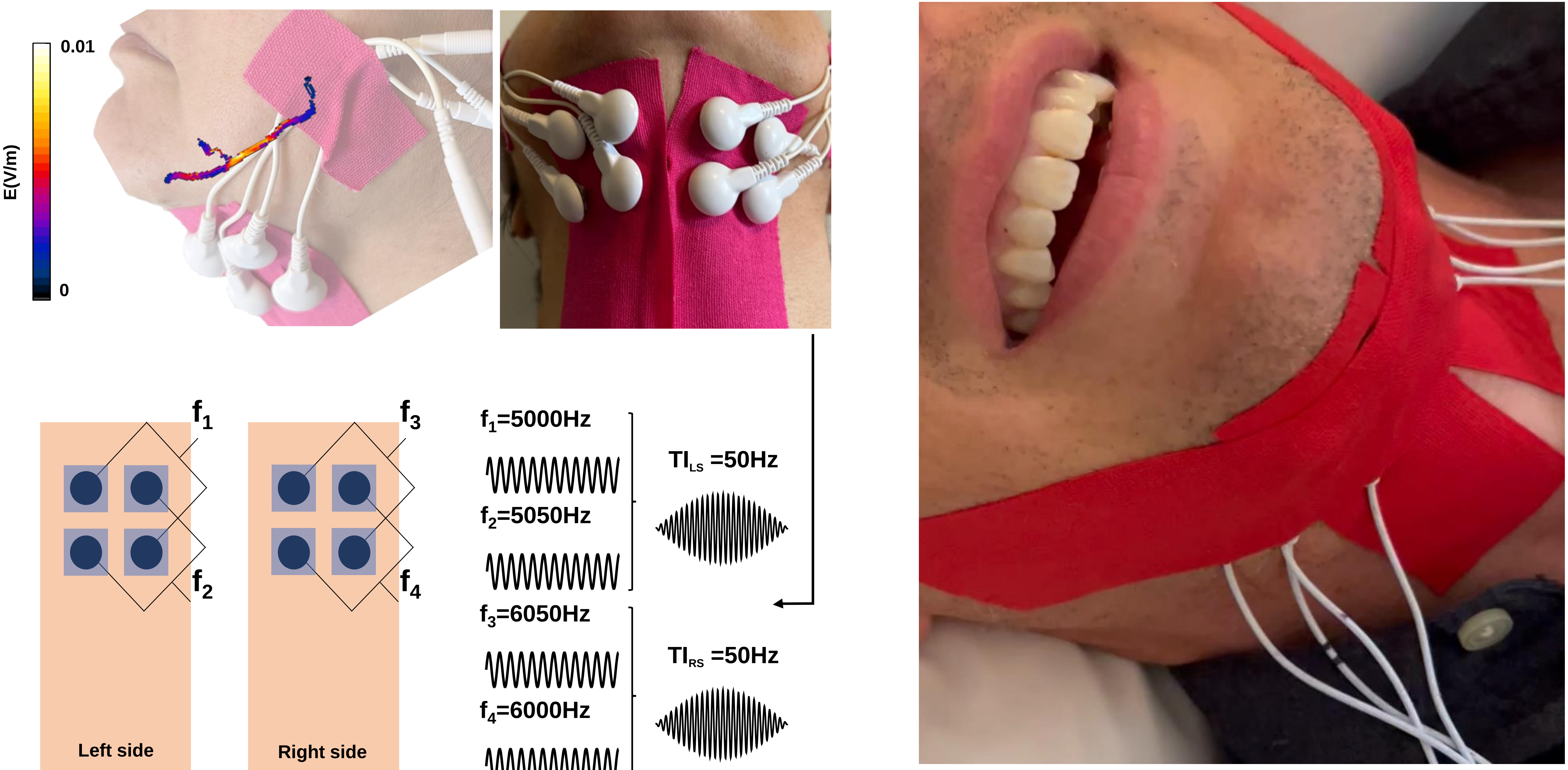
- **Diminution** of stimulation **amplitude** of about **40%,** reducing tingling sensation for a **same stimulation output**



- **Crossed TI design** for optimal hypoglossal nerve targeting

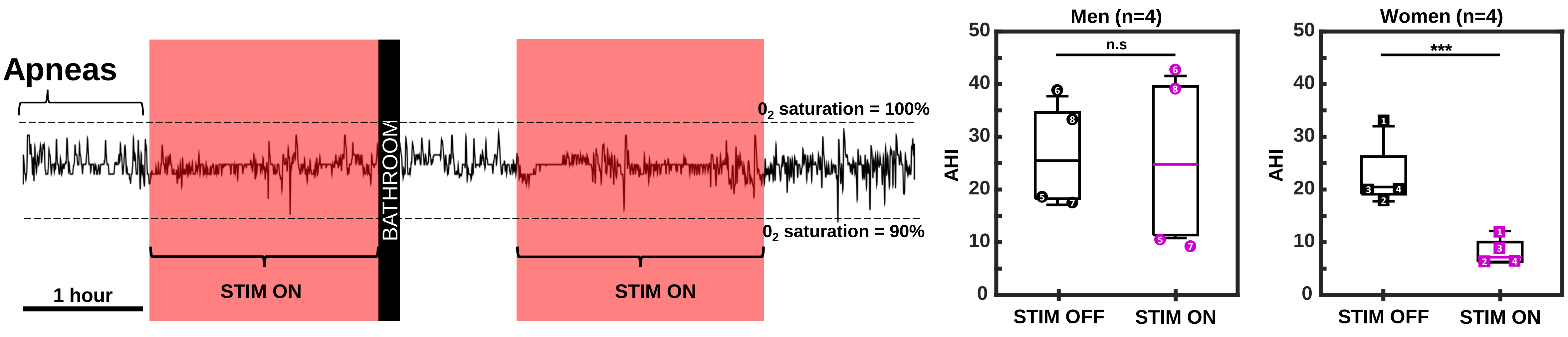
- **High-frequency carriers** to **reduce tingling sensation** on the skin when applying the bTI stimulation

- **Bilateral TI** with both hypoglossal nerve stimulation at Δf = 50Hz



bTI =50Hz, 0.5s ON / 2s OFF

- O_2 **saturation** is a direct readout of apneas and hypopneas
- **Apnea Hypopnea Index (AHI)** is calculated overnight and a low AHI is correlated with a good sleep



Overnight polysomnogram

- **bTI** stimulation efficiently **decreases** the number of **apneas** during the night and **reduces** overnight **AHI** (~ 60% reduction in women)
- **High sex dependency**, men hypoglossal nerves are more difficult to depolarize using electrical stimulation

- **Device downsizing**

- **FDA designation “Breakthrough Device”**

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received the above submission requesting designation as a Breakthrough Device. The proposed indications for use includes "The treatment of adult patients with a BMI<35 with moderate to severe OSA (AHI 15-50) who fail or do not tolerate PAP/oral appliances.." We are pleased to inform you that your device and proposed indication for use meet the criteria and have been granted designation as a Breakthrough Device. Please refer to the FDA guidance document entitled "Breakthrough Devices Program", for more information regarding the program, available at https://www.fda.gov/media/108135/download.

We recommend you review the FDA guidance document for the Breakthrough Devices Program referenced above for the available mechanisms for obtaining feedback from the Agency on device development for designated breakthrough devices. When submitting any new requests, please reference Q230334. Any new submission should be provided as an eCopy, it should include the FDA reference number for this submission, and should be submitted to the following address:

- **Of the 760 devices given Breakthrough Designation since the program started in 2015, only 7 have been under the ENT category and 0 for Sleep.**

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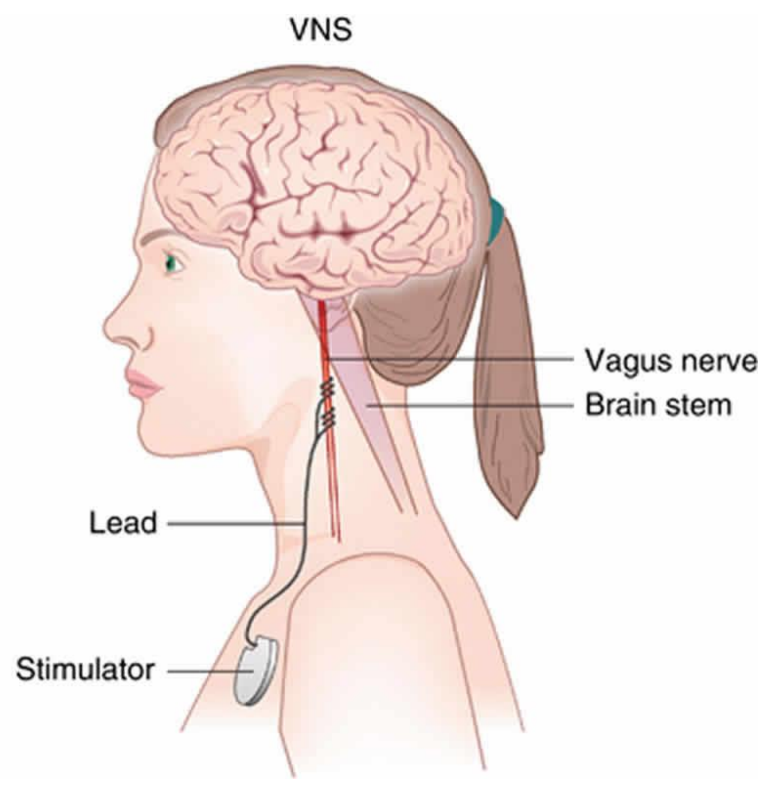
- **Vagus nerve**

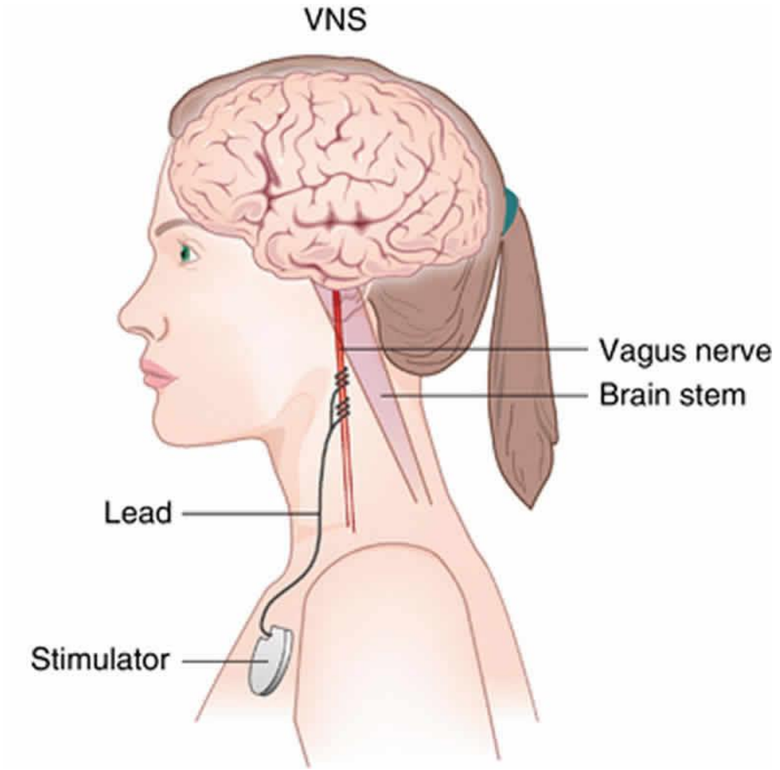
Vagus nerve stimulation (VNS) is an alternative treatment in pharmacoresistant epilepsy.



implantable VNS

- **Vagus nerve**

Vagus nerve stimulation (VNS) is an alternative treatment in pharmacoresistant epilepsy.

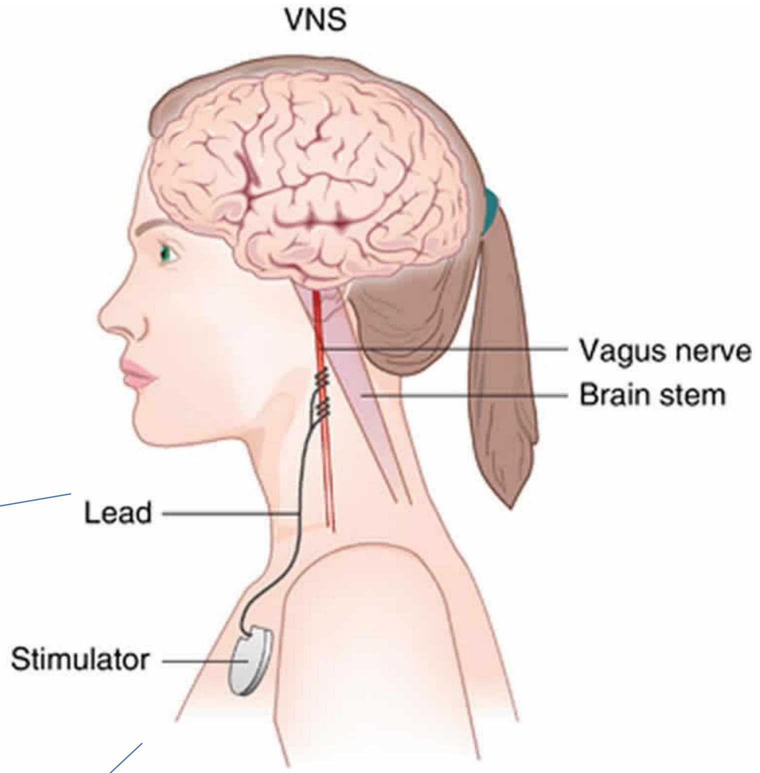


implantable VNS

transcutaneous VNS

- **Vagus nerve**

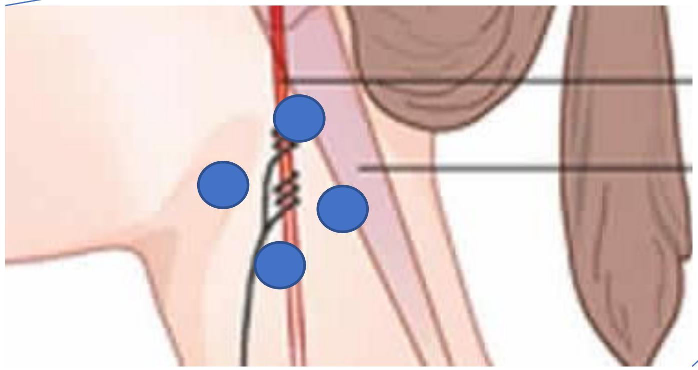
Vagus nerve stimulation (VNS) is an alternative treatment in pharmacoresistant epilepsy.



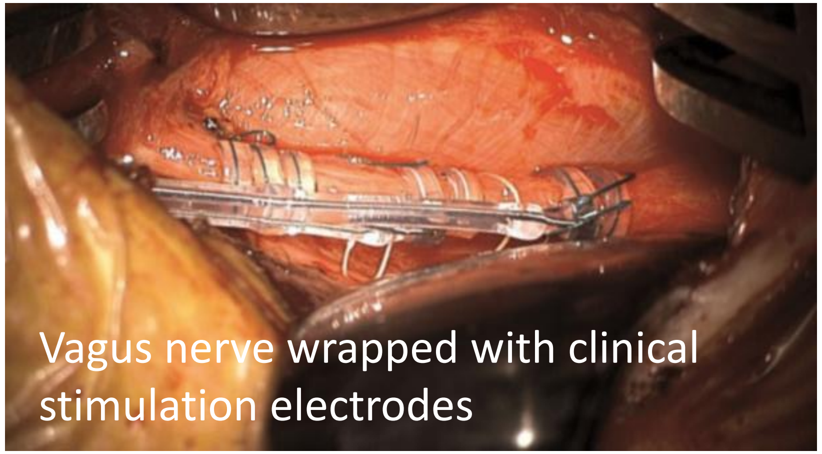
implantable VNS

gammaCore
Reset. Restore. Relieve.™

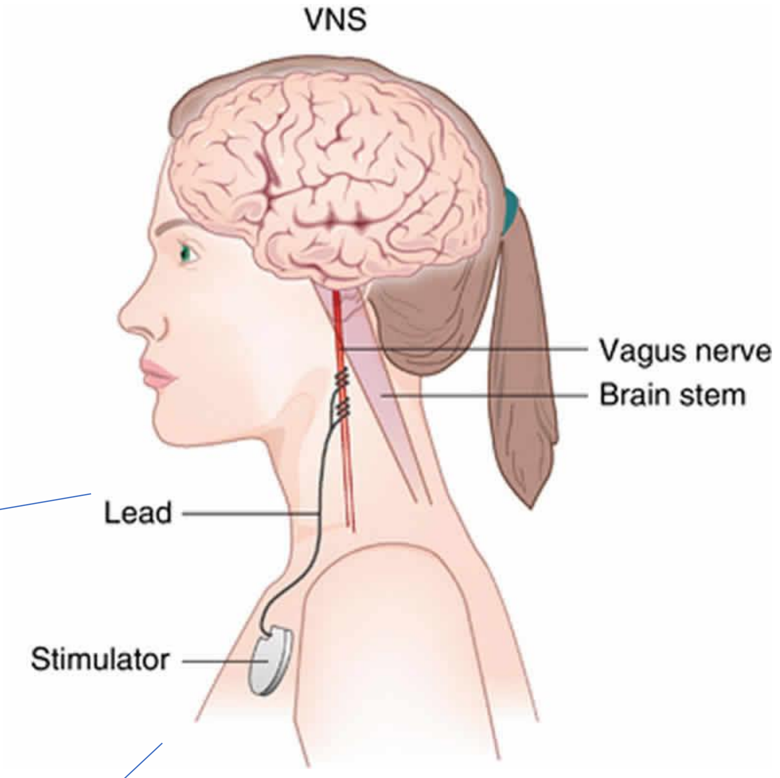
transcutaneous VNS



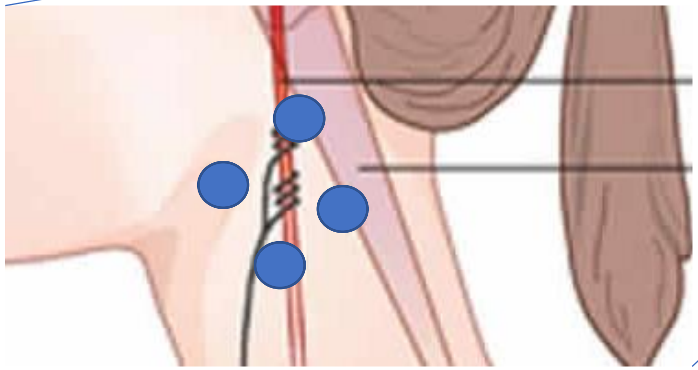
transcutaneous TI VNS



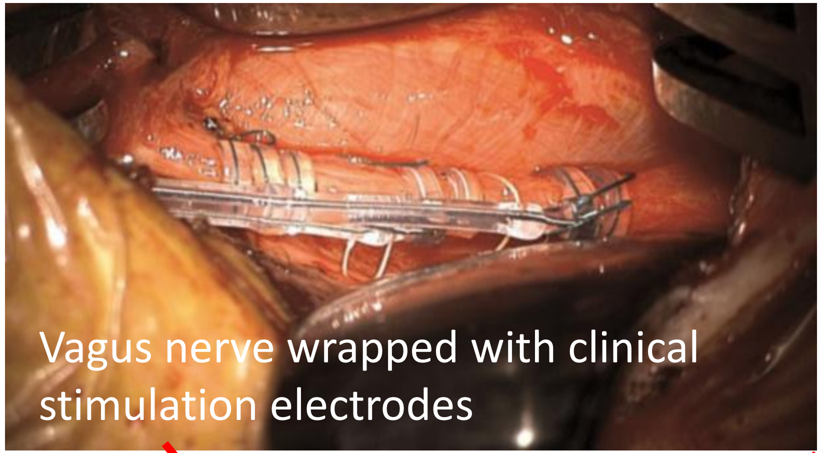
Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)



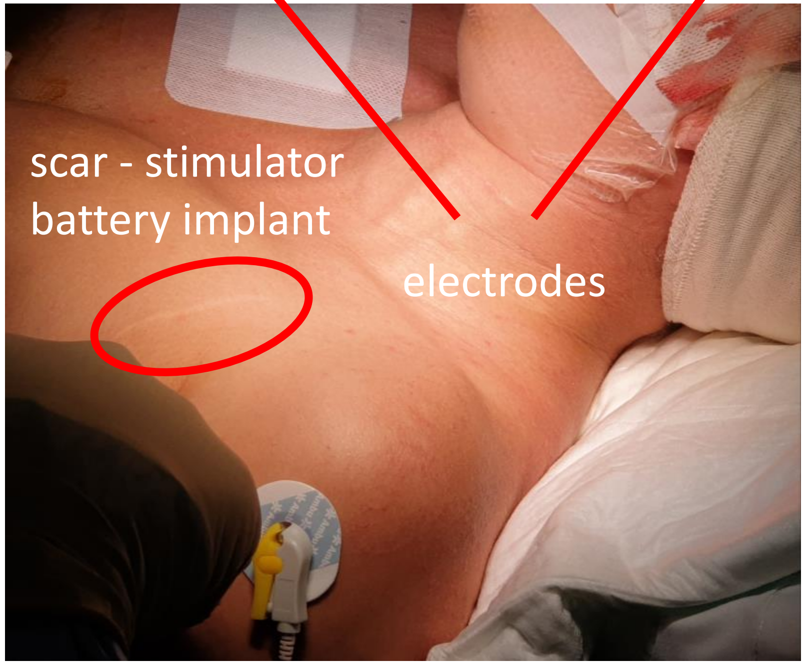
implantable VNS

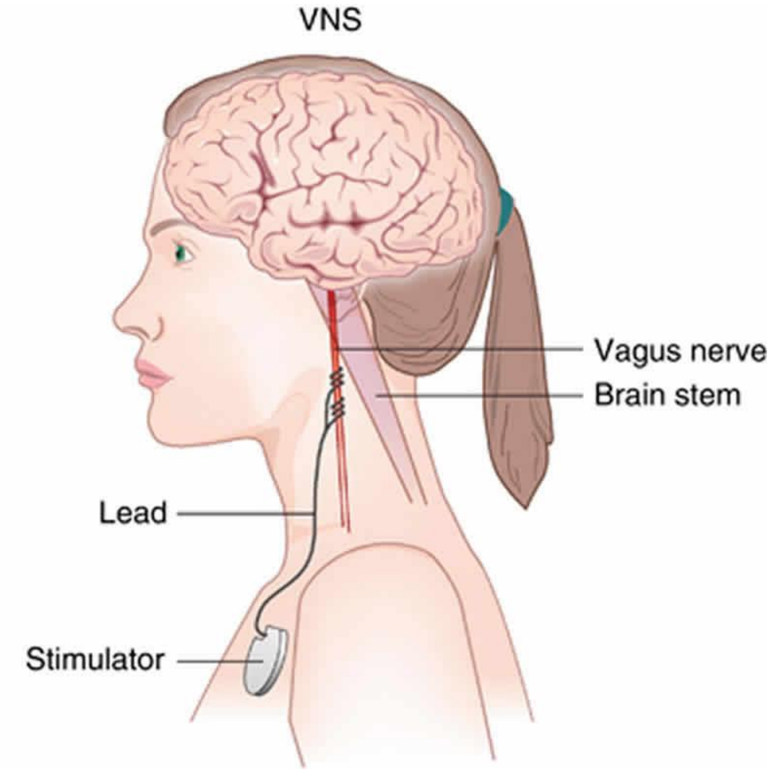


transcutaneous TI VNS

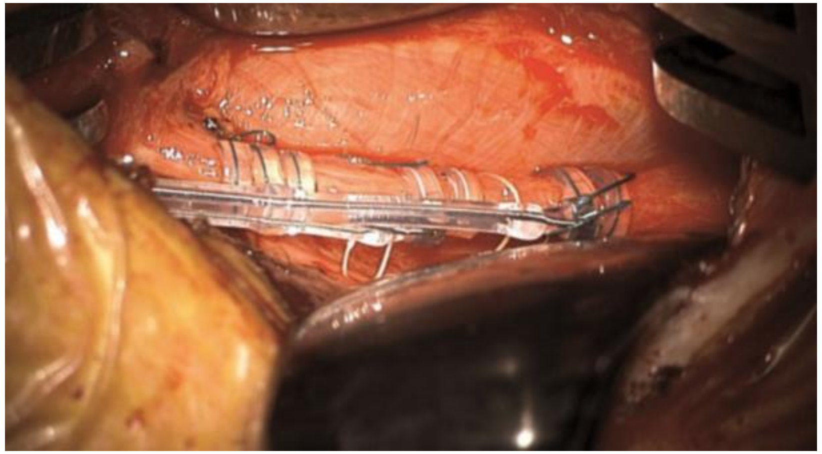


Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)

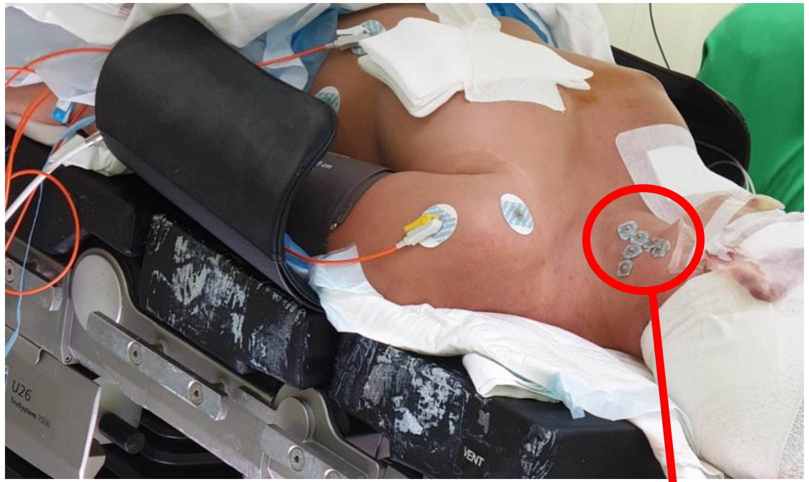




implantable VNS

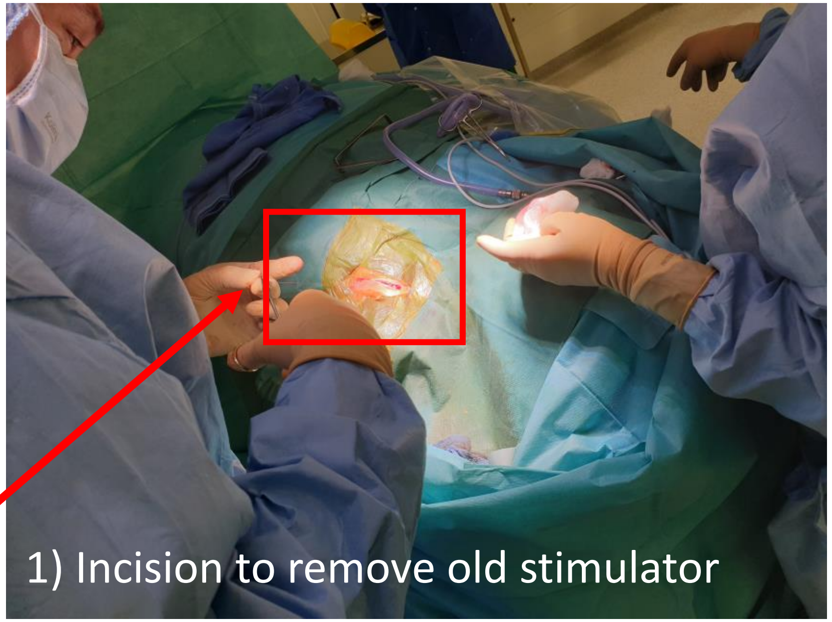


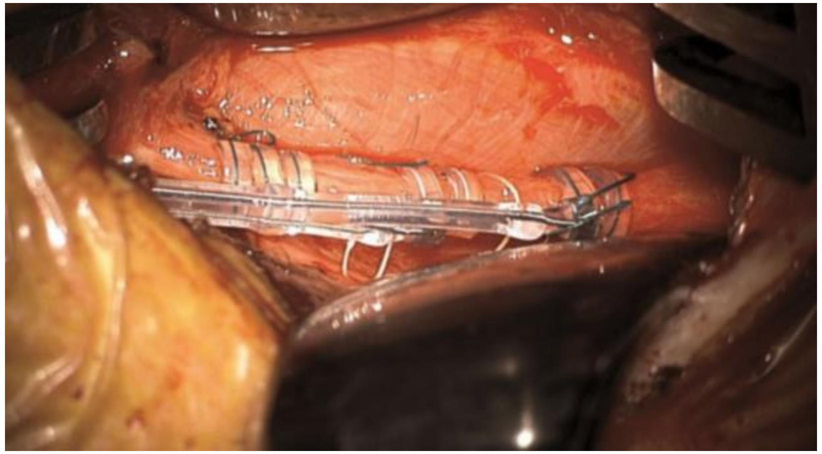
Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)



Arrangements of electrodes are placed on the skin above the vagus nerve and implant

Battery replacement





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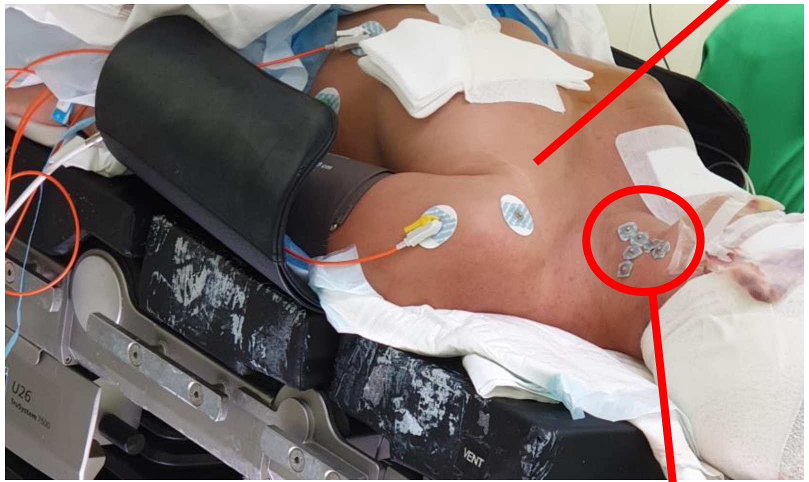
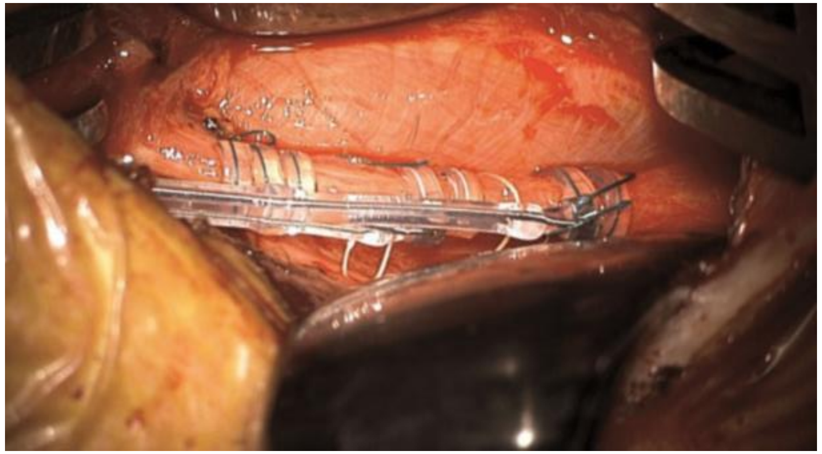


Arrangements of electrodes are placed on the skin above the vagus nerve and implant

Battery replacement



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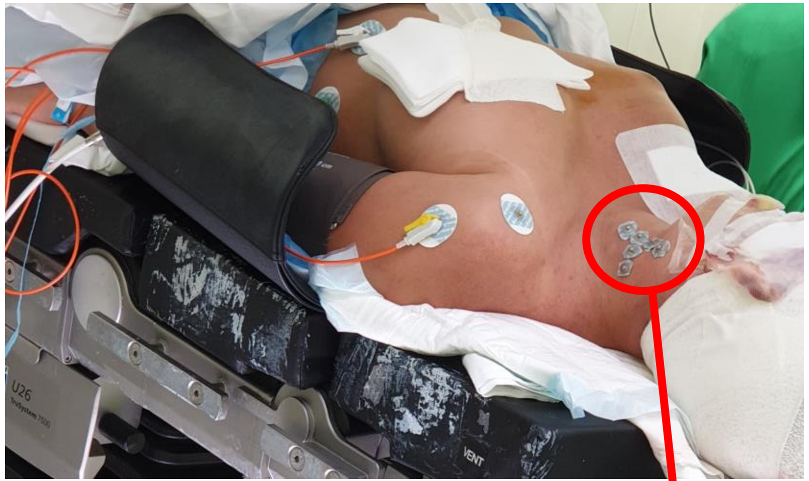
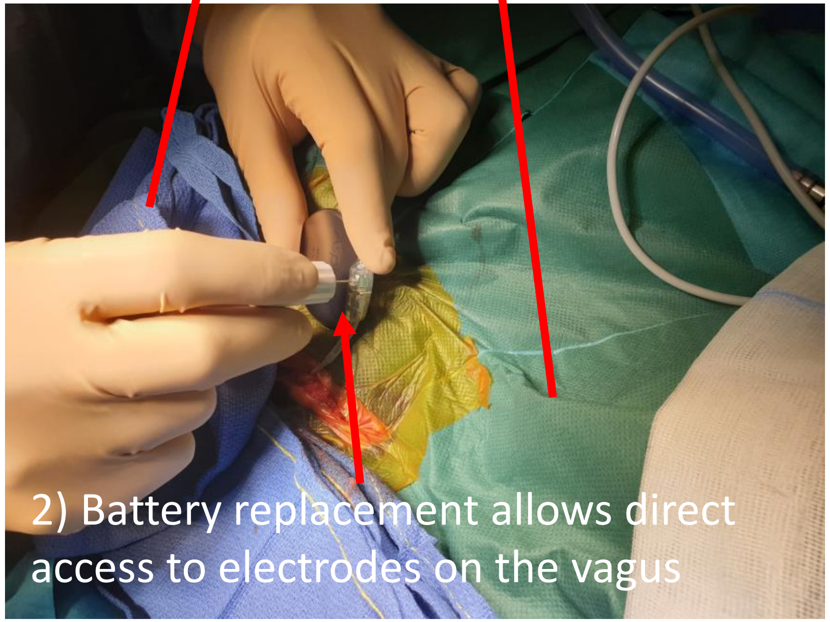
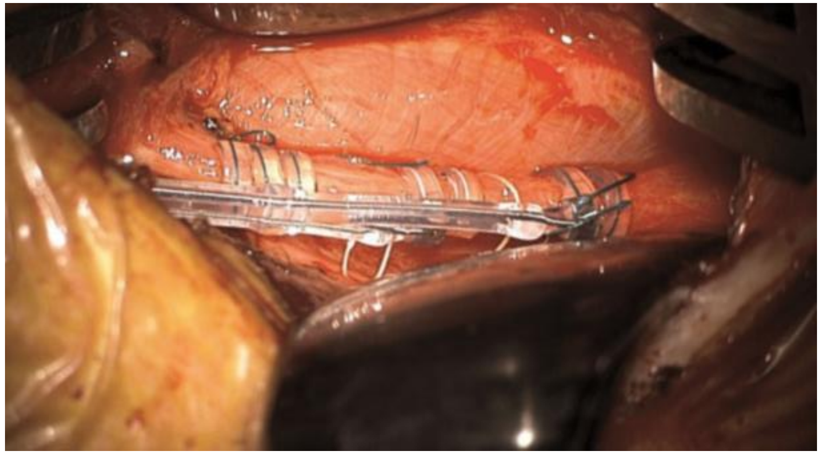


Arrangements of electrodes are placed on the skin above the vagus nerve and implant





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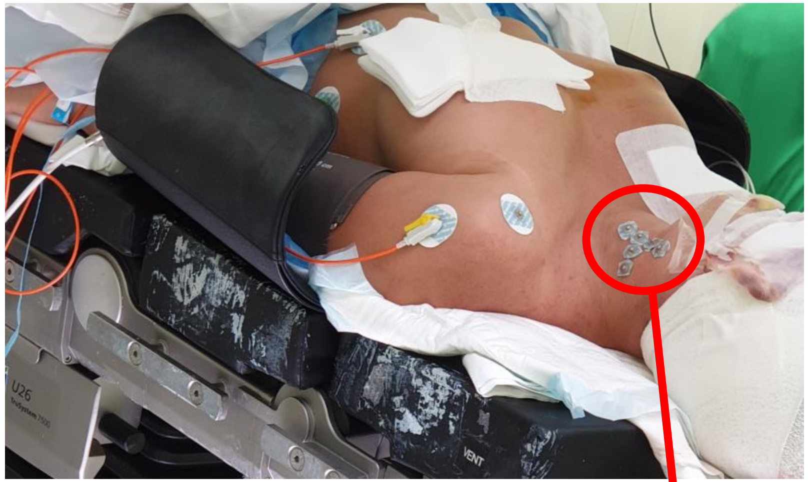
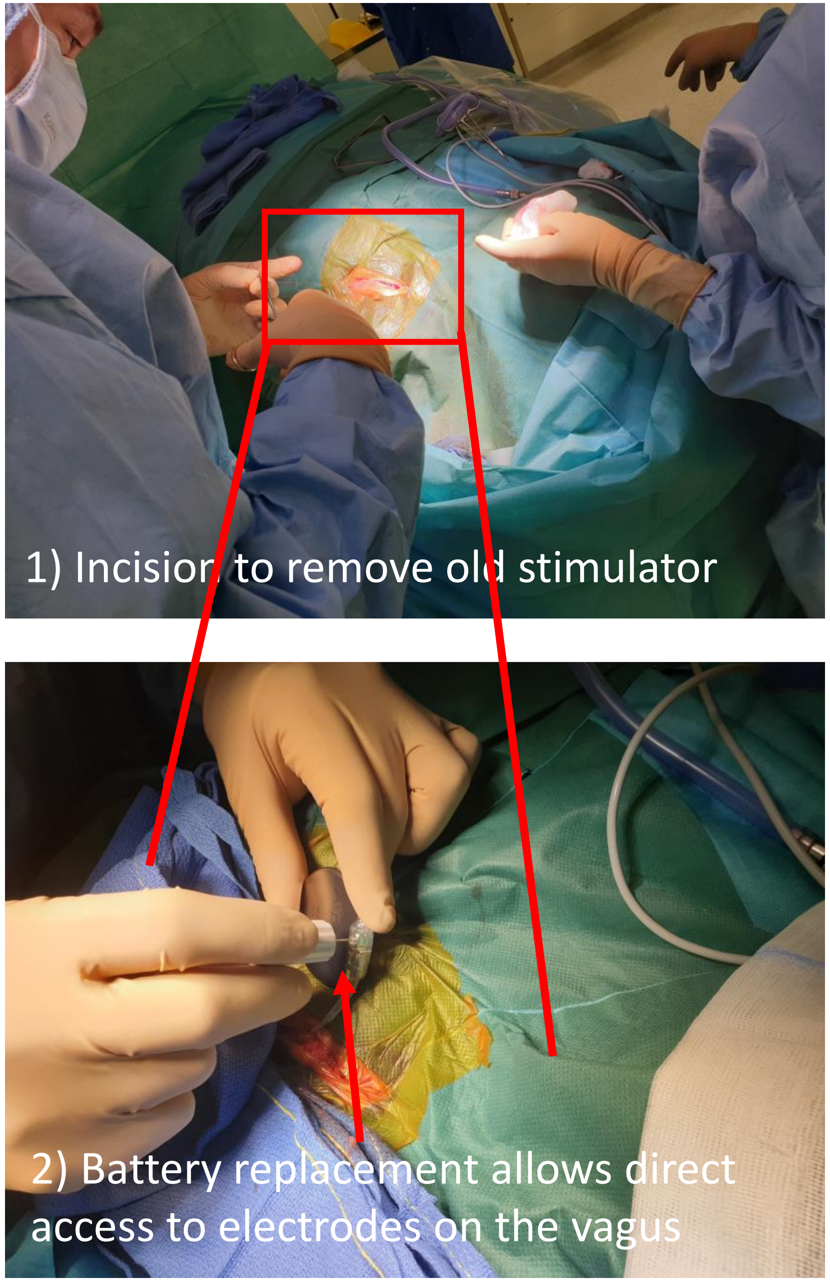
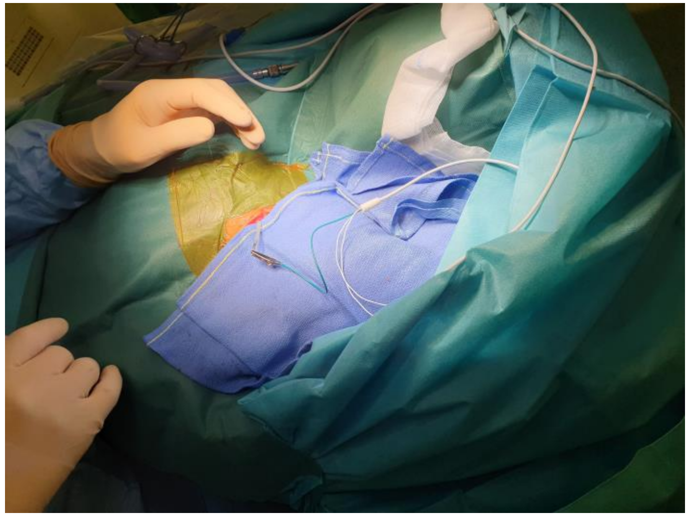


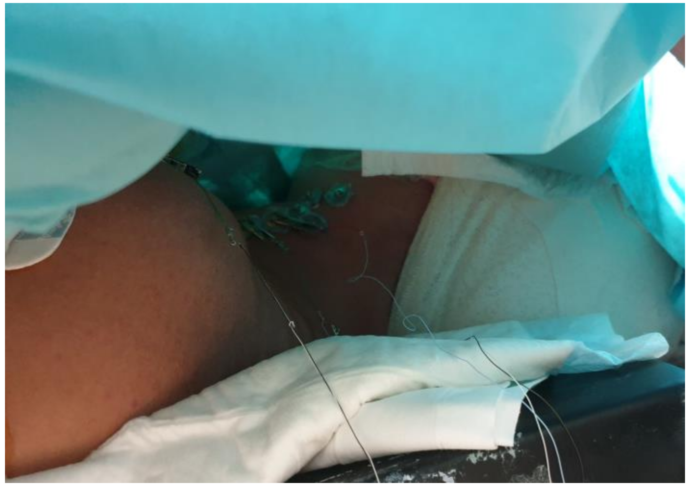
Arrangements of electrodes are placed on the skin above the vagus nerve and implant

Battery replacement



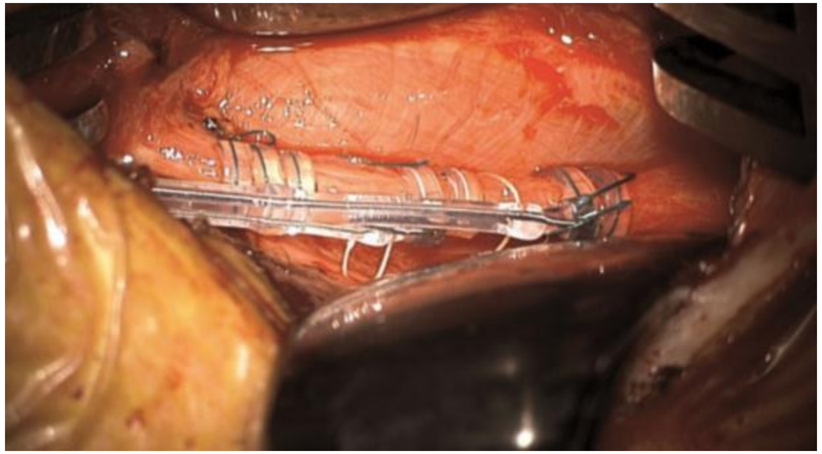
Connections from electrodes on the vagus to our recording equipment…





Connections from electrodes on the skin to our TI and transcutaneous stimulation…

Battery replacement



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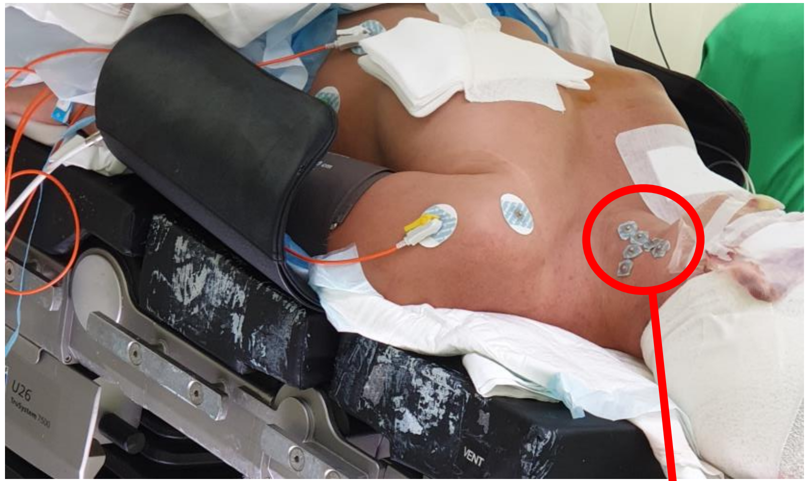
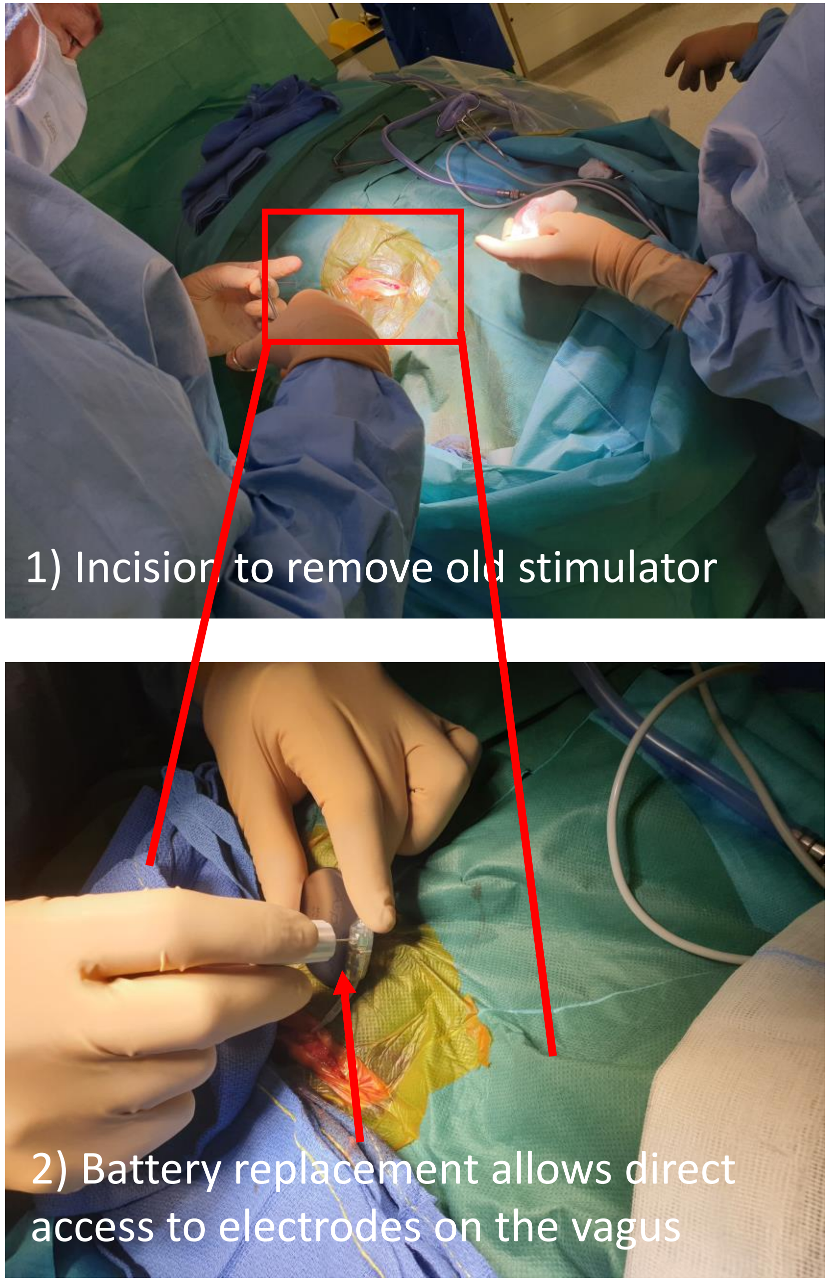
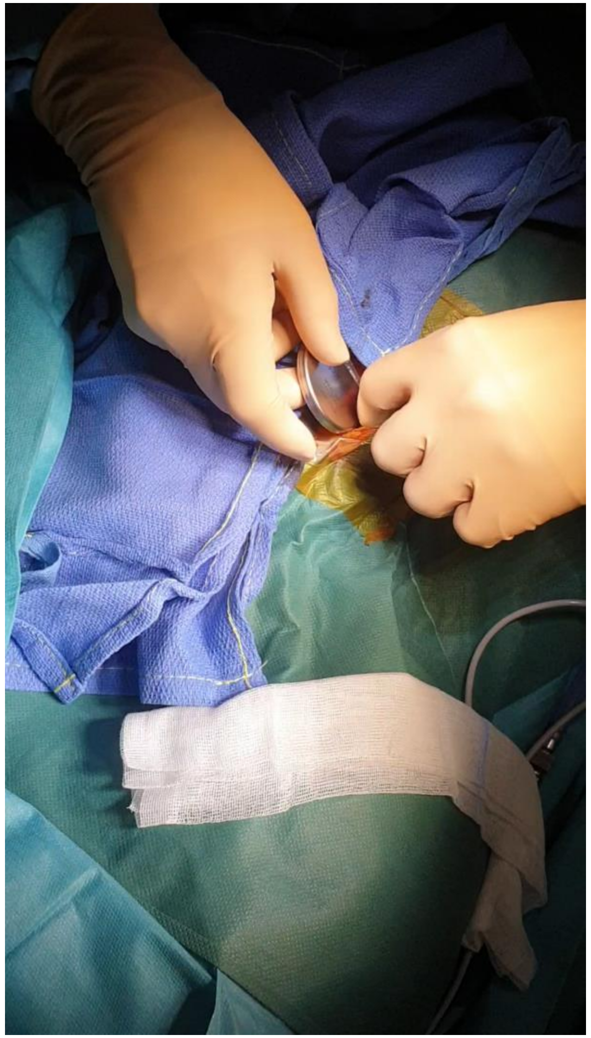
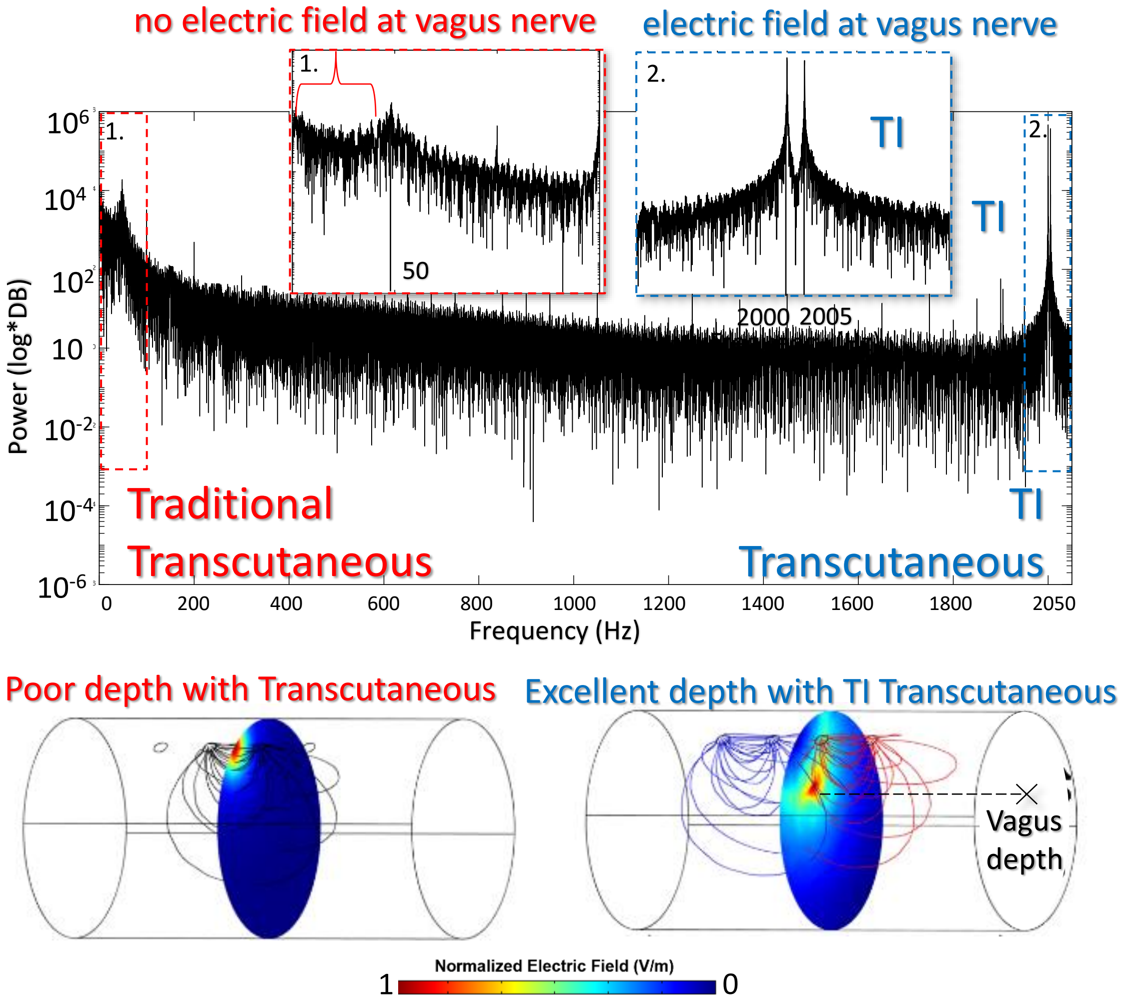


Arrangements of electrodes are placed on the skin above the vagus nerve and implant



New stimulator is replaced when we finish





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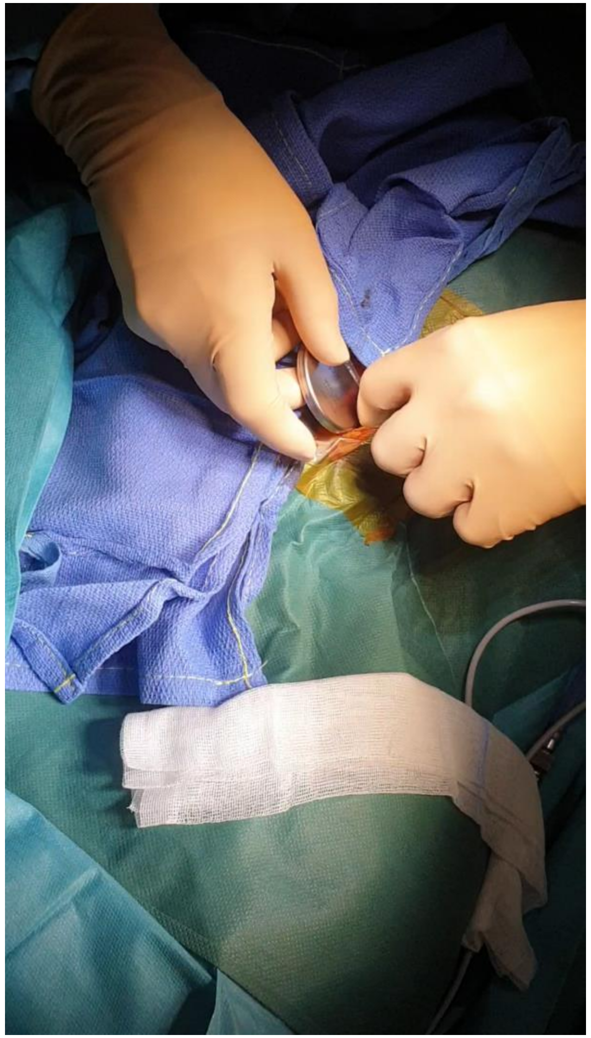
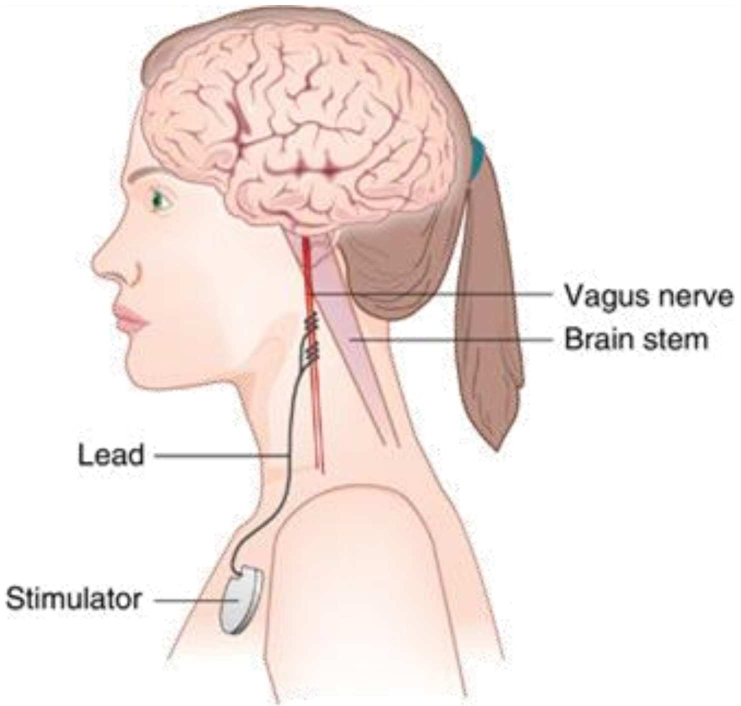
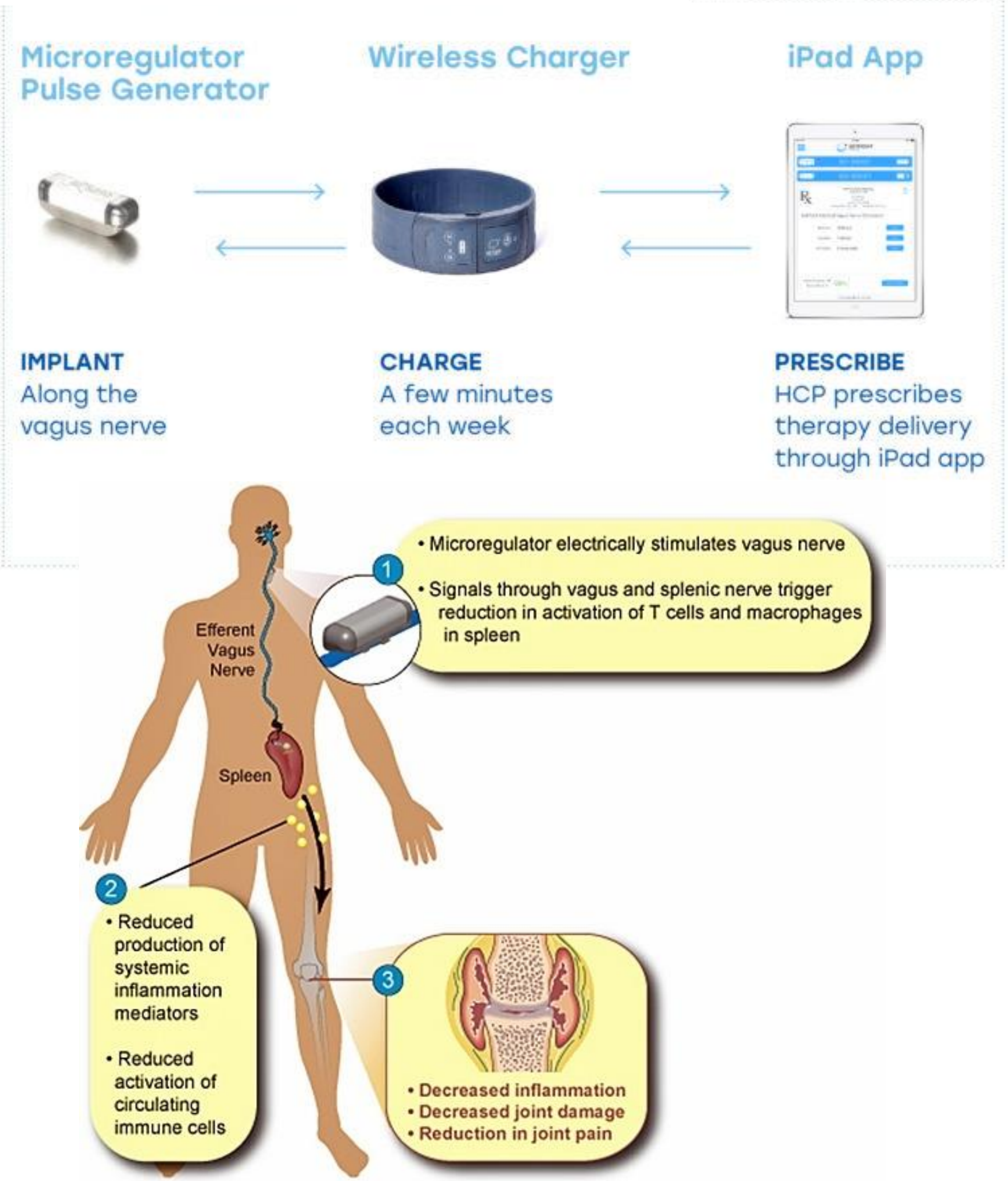


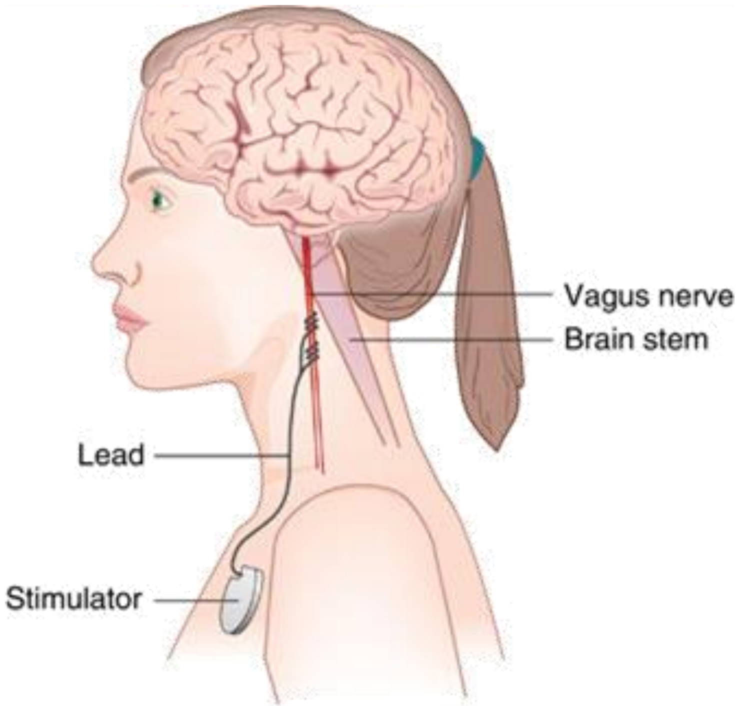
- **Vagus nerve**



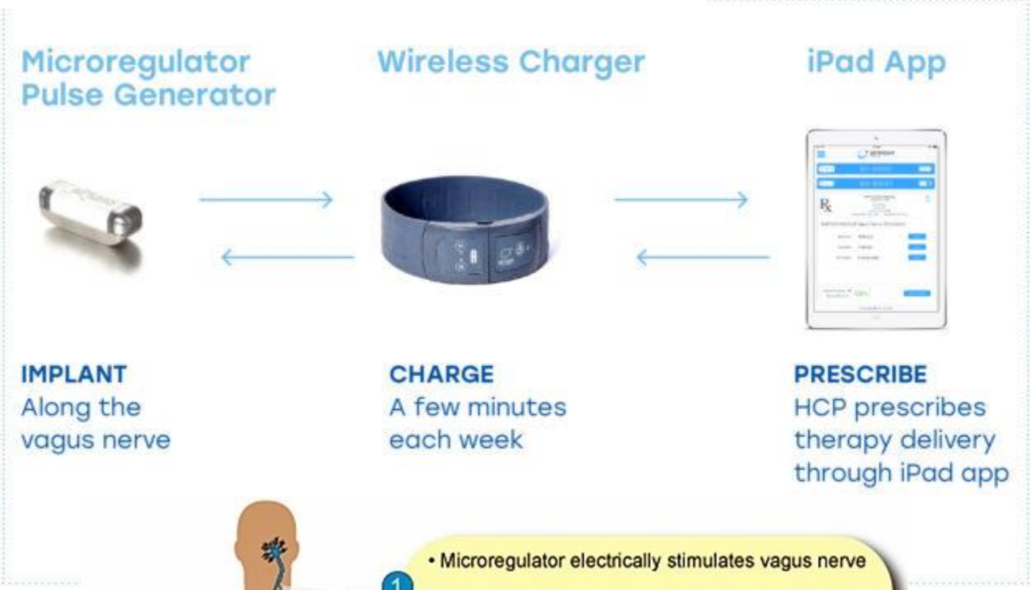
SETPOINT® MEDICAL

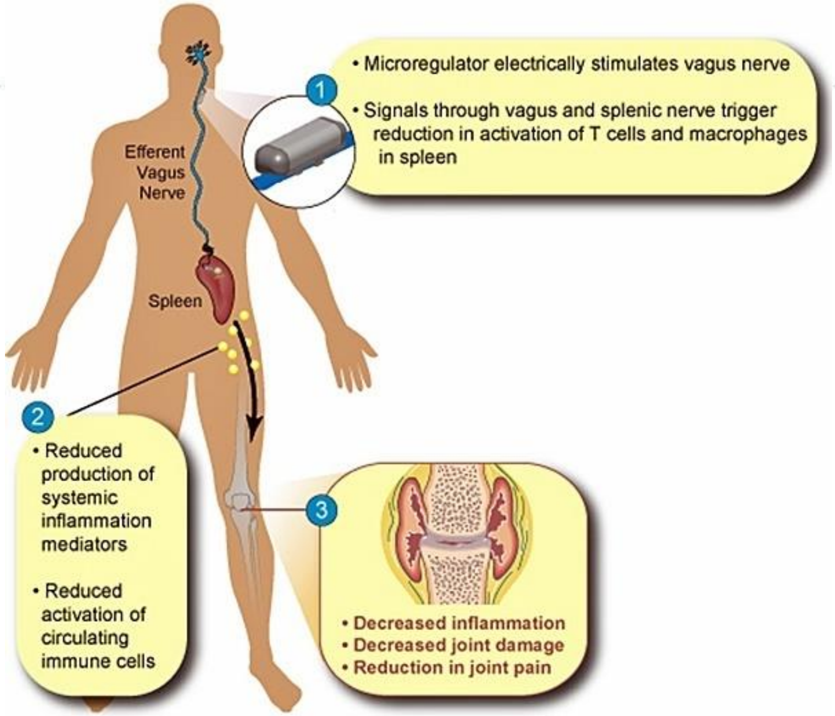


- **Vagus nerve**

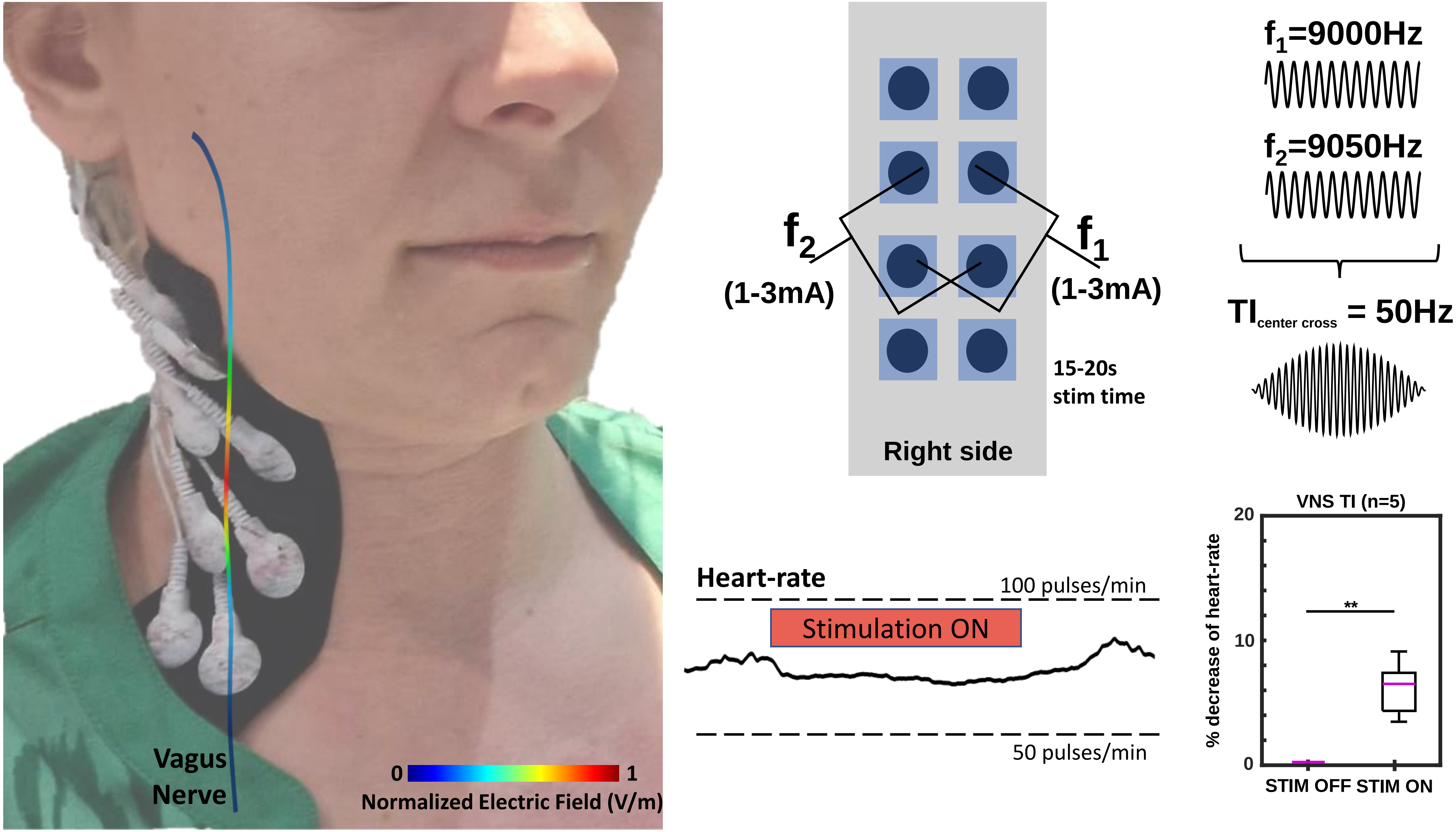


SETPOINT® MEDICAL





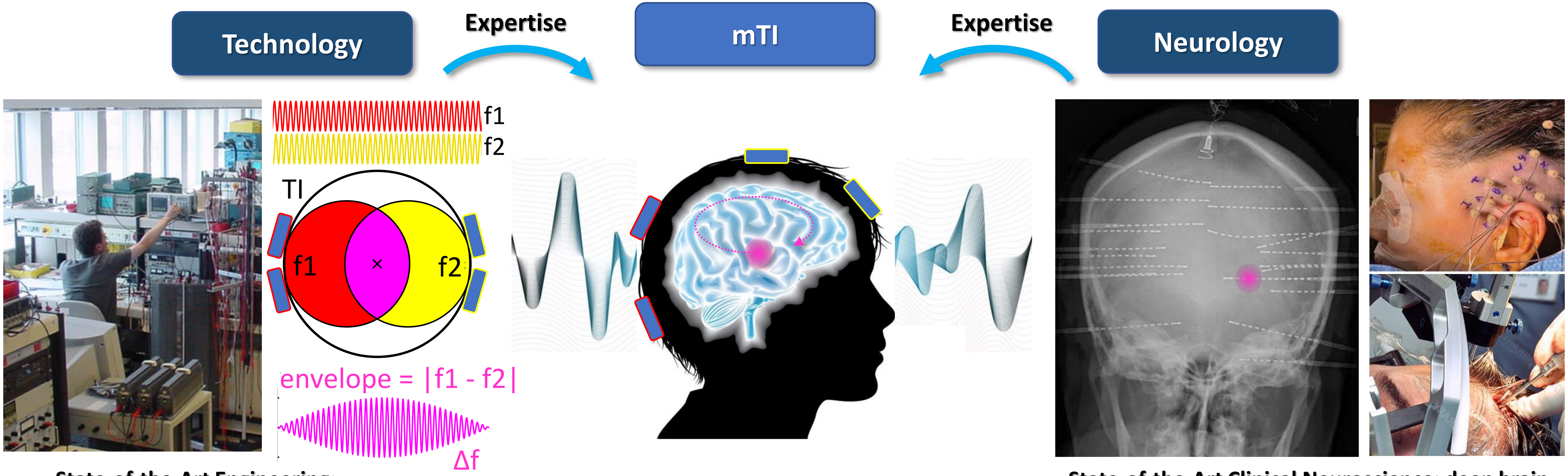
MicroRegulator



Vagus
Nerve
0
1
Normalized Electric Field (V/m)
f2
(1-3mA)
f1
(1-3mA)
Right side
15-20s
stim time
f1=9000Hz
f2=9050Hz
TIcenter cross = 50Hz
Heart-rate
100 pulses/min
Stimulation ON
50 pulses/min
VNS TI (n=5)
% decrease of heart-rate
20
10
0
**
STIM OFF
STIM ON

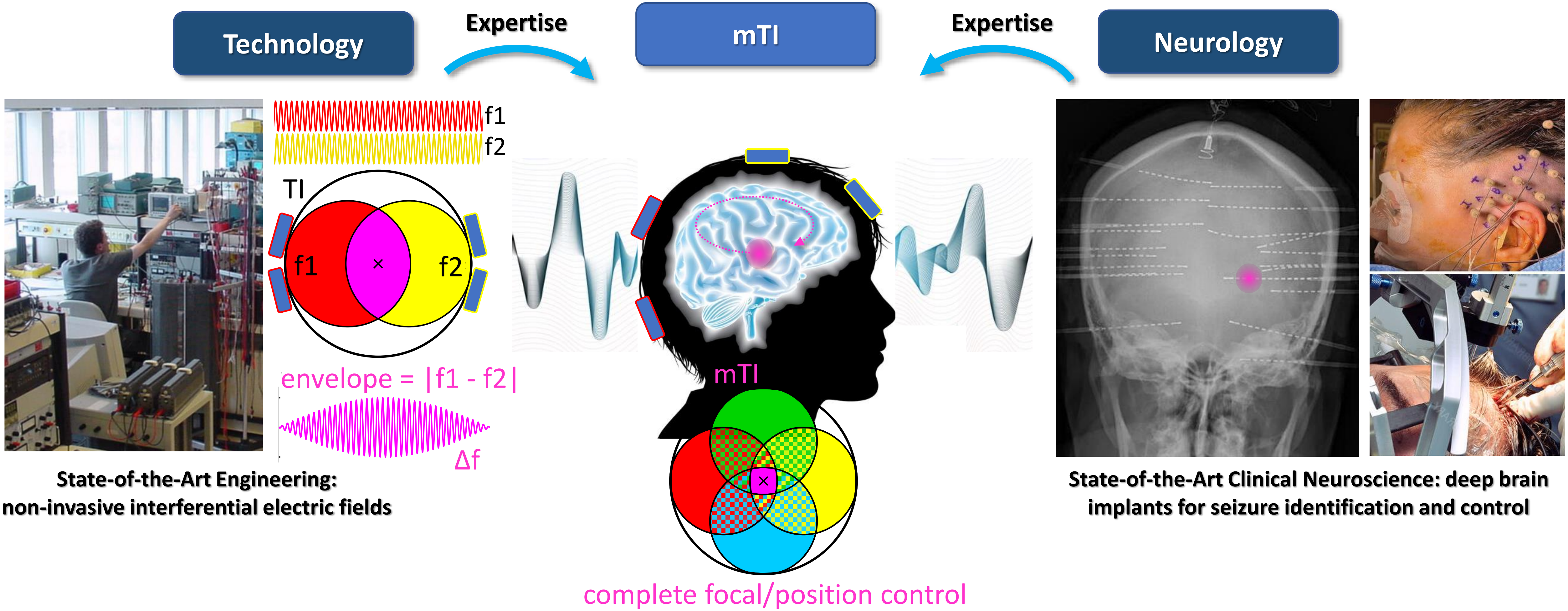
Outline

- ❑ Temporal Interference (TI): Epilepsy as a model
  - ➢ Preliminary work in rodents and scaling TI to humans
  - ➢ Clinical Temporal Interference
- ❑ Tremor and Parkinson’s disease
- ❑ Clinical TI of Peripheral nerves
  - ➢ Hypoglossal nerve
  - ➢ Vagus Nerve
- ❑ Conclusions



State-of-the-Art Engineering:
non-invasive interferential electric fields

State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control



Complete Non-invasive Deep Brain Stimulation in Epilepsy

Team

Adam WILLIAMSON

Funding

European Research Council (erc)

European Innovation Council

DARPA

Collaborators

University of Wisconsin Madison

Emory University

UC Davis University of California

IT'IS Foundation

Imperial College London

Karolinska Institutet

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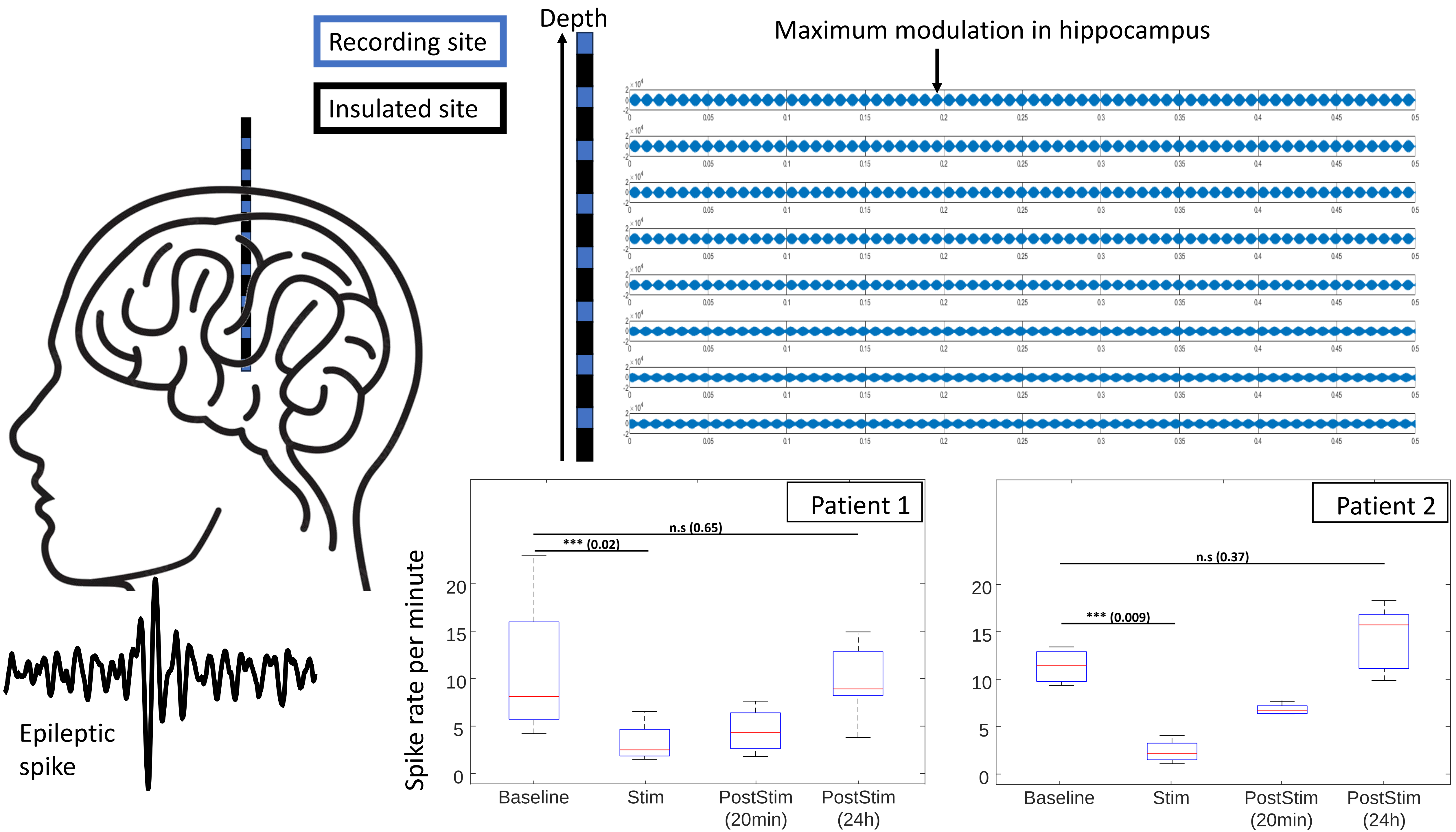
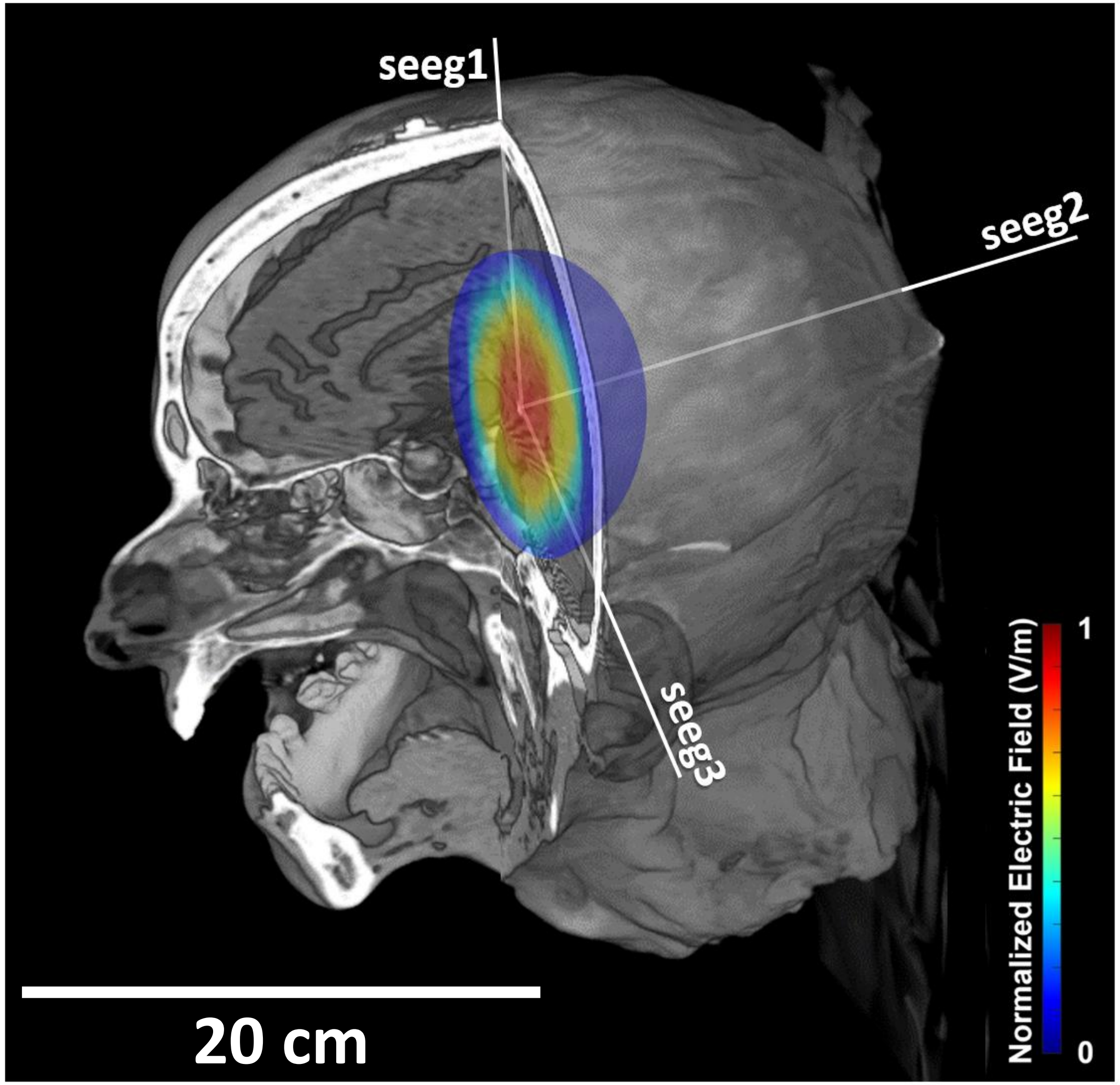
Mariane Silva

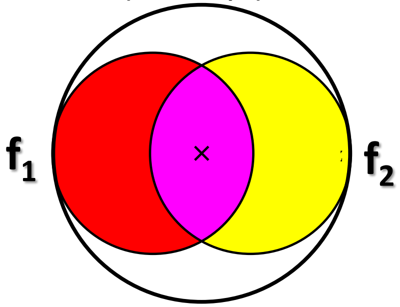

Děkuji za pozornost
FNUSA
ICRC


Recording site
Insulated site
Depth
Maximum modulation in hippocampus
Epileptic spike
Patient 1
Patient 2
Spike rate per minute
n.s (0.65)
*** (0.02)
n.s (0.37)
*** (0.009)
Baseline
Stim
PostStim (20min)
PostStim (24h)

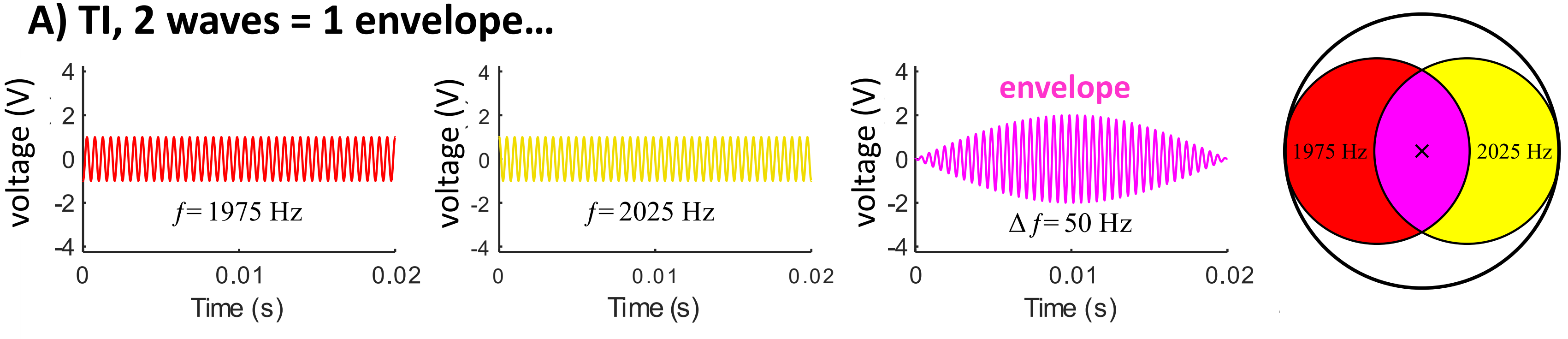
Preliminary Results: **Focality**

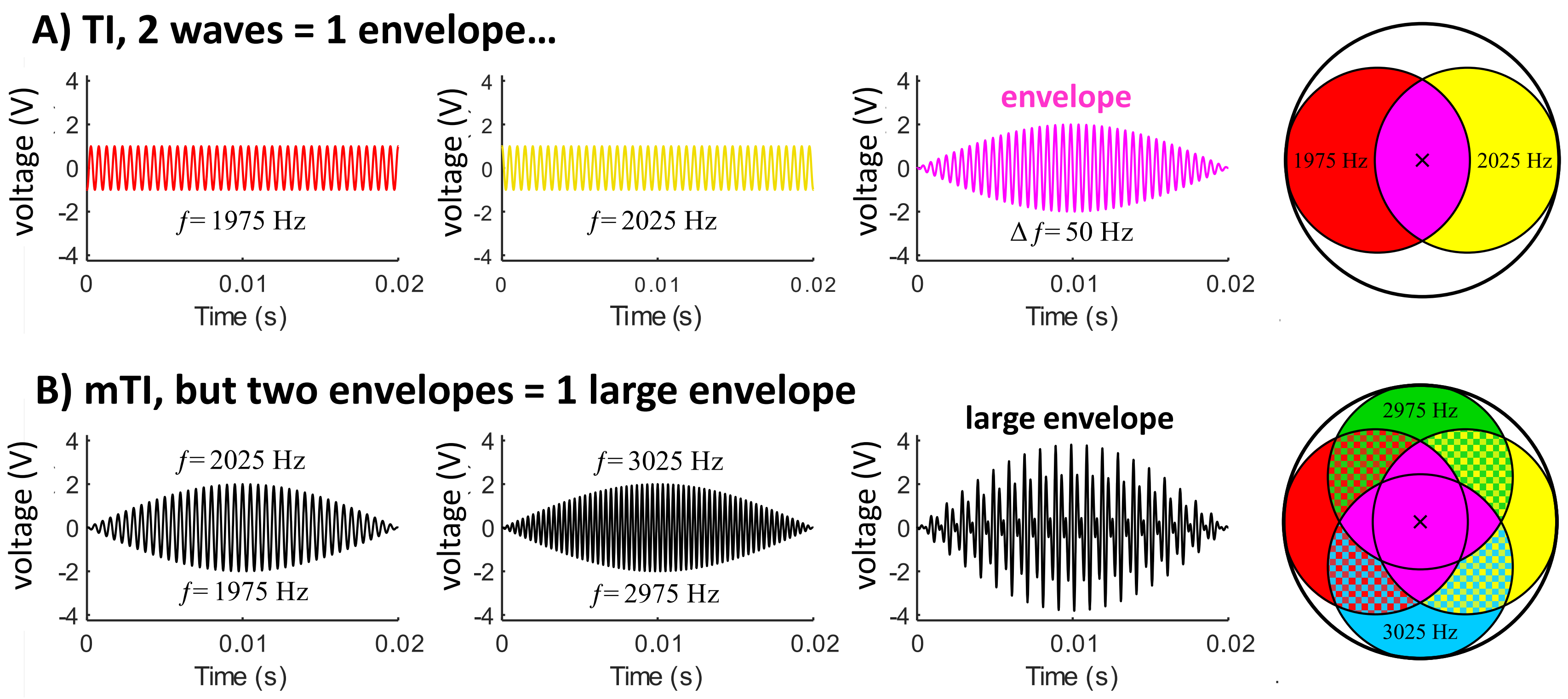


Standard TI

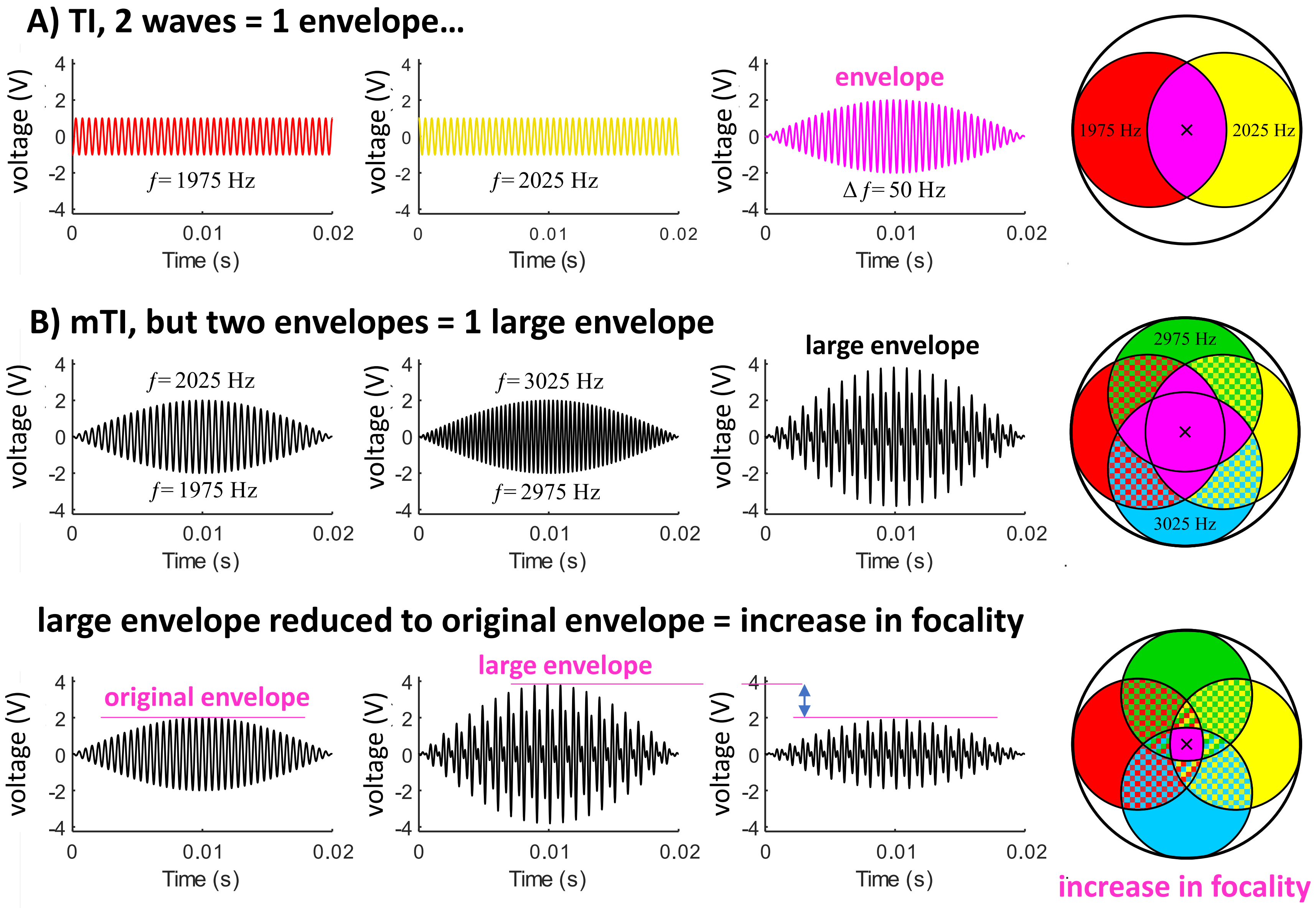


A) TI, 2 waves = 1 envelope…





A) TI, 2 waves = 1 envelope...
voltage (V)
f = 1975 Hz
f = 2025 Hz
envelope
Δ f = 50 Hz
Time (s)
1975 Hz
2025 Hz
B) mTI, but two envelopes = 1 large envelope
f = 2025 Hz
f = 1975 Hz
f = 3025 Hz
f = 2975 Hz
large envelope
2975 Hz
3025 Hz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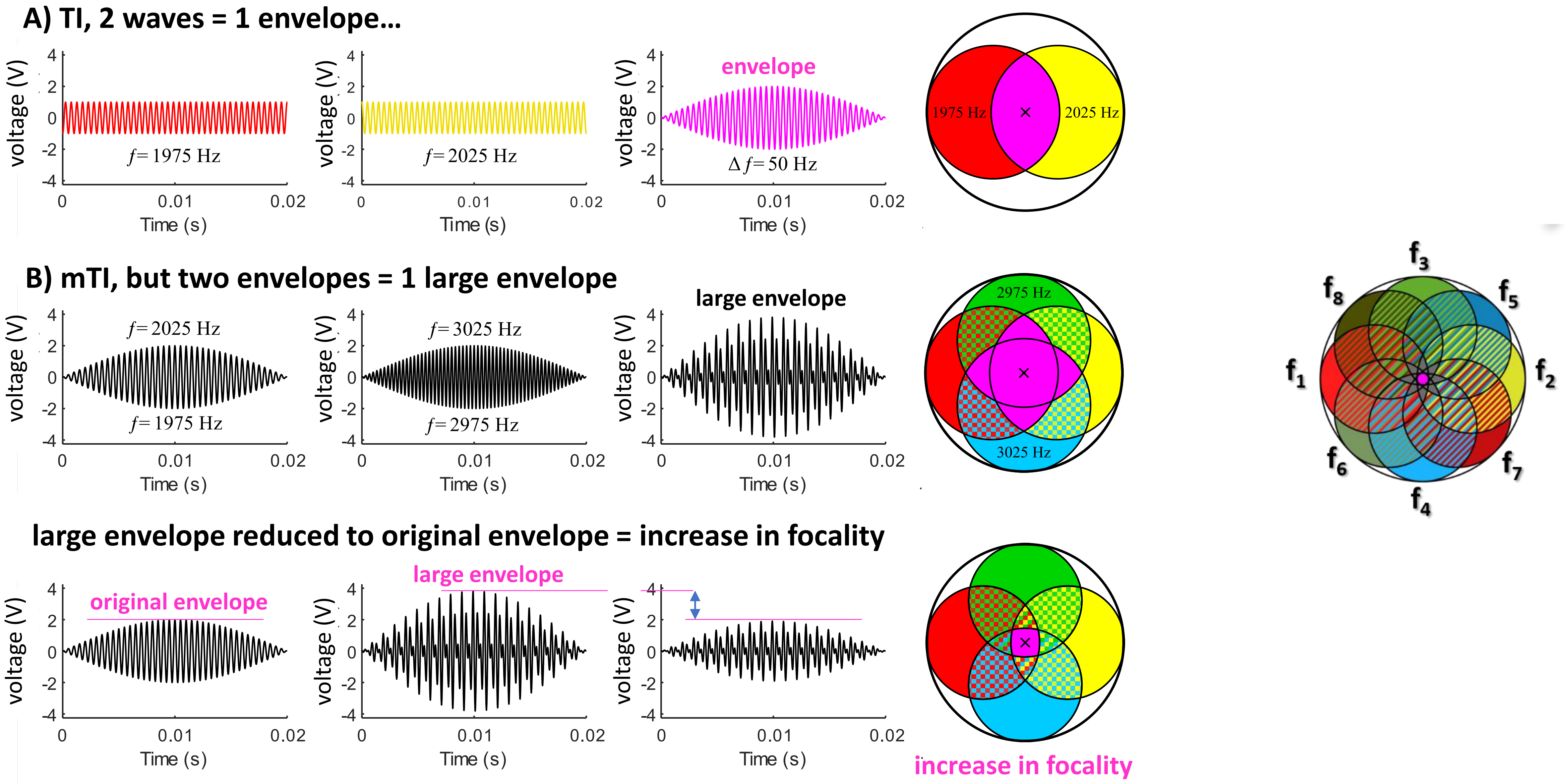
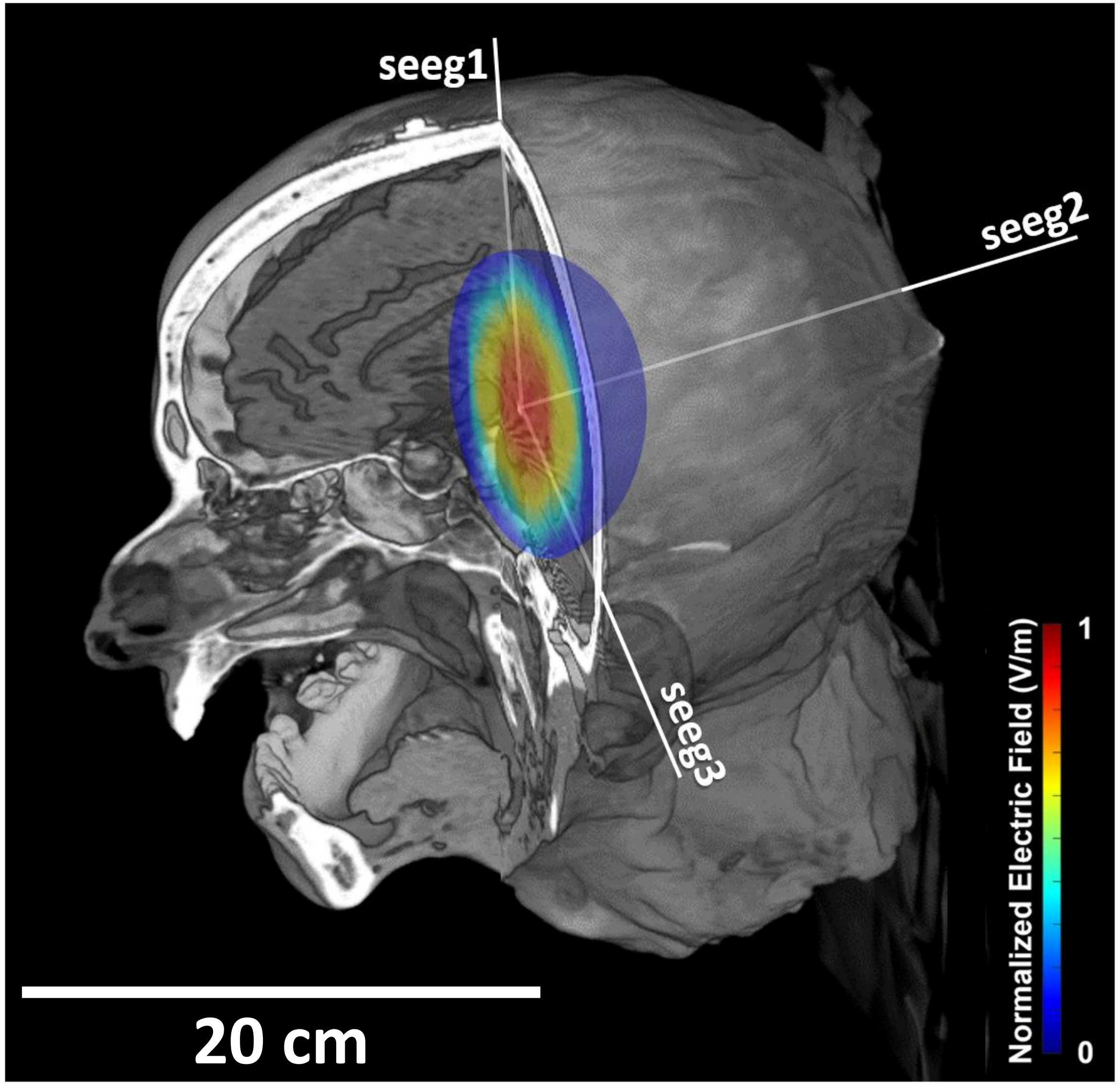
voltage (V)
Time (s)
f = 1975 Hz
f = 2025 Hz
envelope
Δ f = 50 Hz
1975 Hz
2025 Hz
B) mTI, but two envelopes = 1 large envelope
f = 2025 Hz
f = 1975 Hz
f = 3025 Hz
f = 2975 Hz
large envelope
2975 Hz
3025 Hz
large envelope reduced to original envelope = increase in focality
original envelope
large envelope
increase in focality

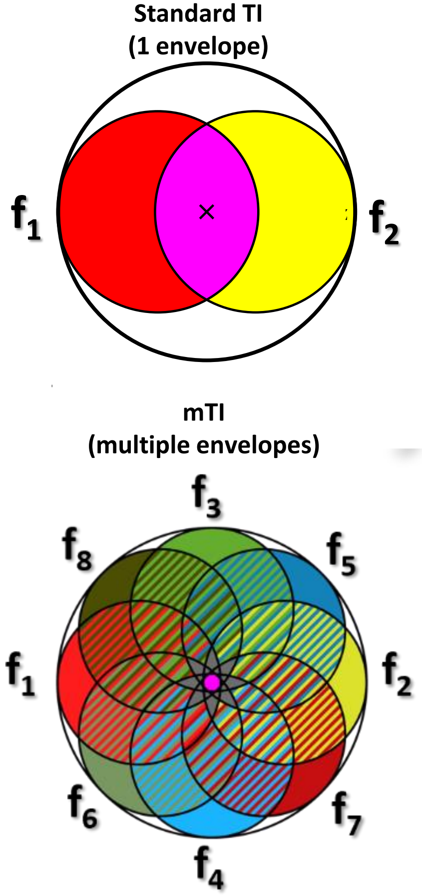


A) TI, 2 waves = 1 envelope...
voltage (V)
Time (s)
f = 1975 Hz
f = 2025 Hz
envelope
Δ f = 50 Hz
1975 Hz
2025 Hz
B) mTI, but two envelopes = 1 large envelope
f = 2025 Hz
f = 1975 Hz
f = 3025 Hz
f = 2975 Hz
large envelope
2975 Hz
3025 Hz
f_3
f_8
f_5
f_1
f_2
f_6
f_7
f_4
large envelope reduced to original envelope = increase in focality
original envelope
large envelope
increase in focality

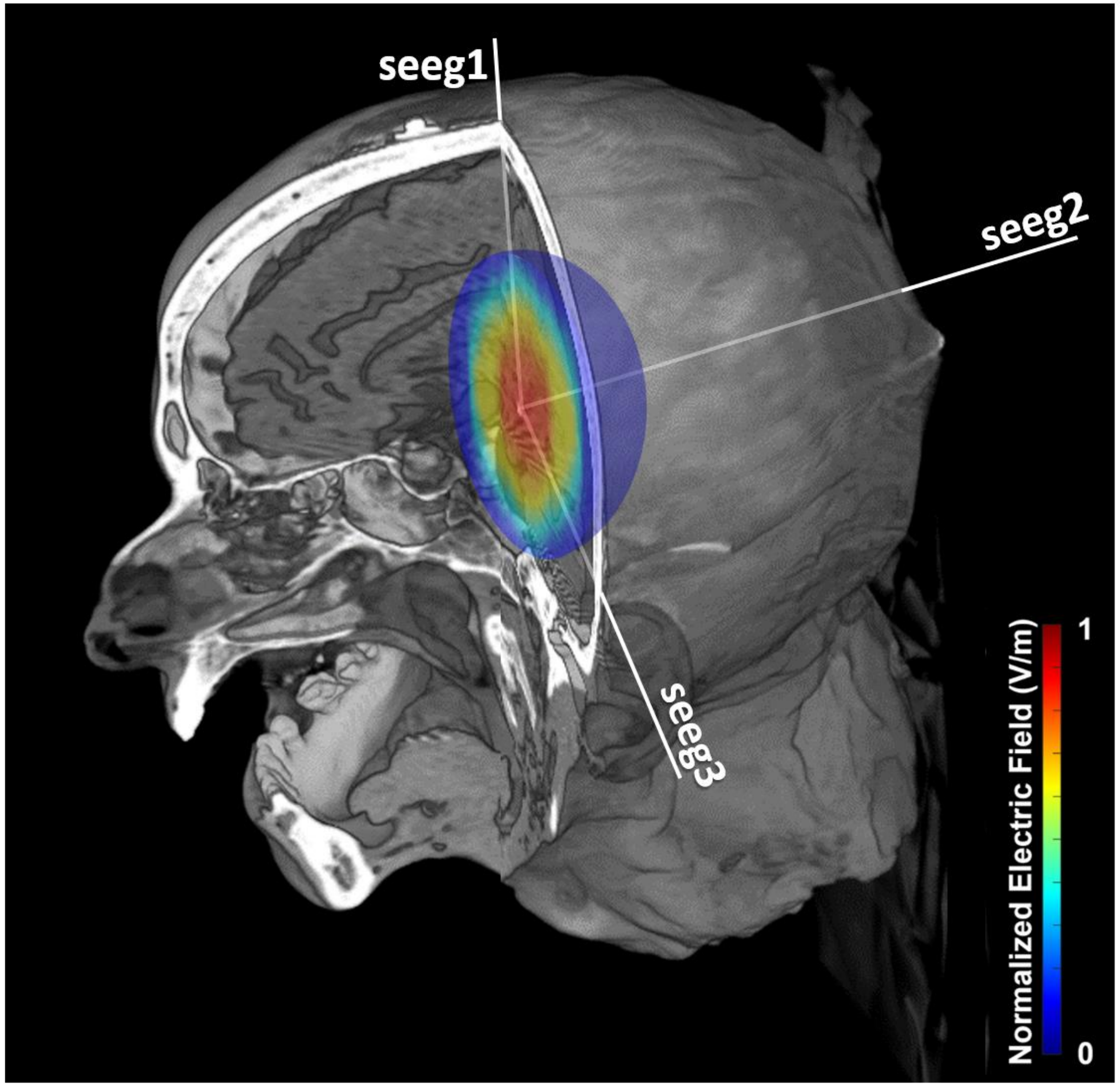
Preliminary Results: **Focality**



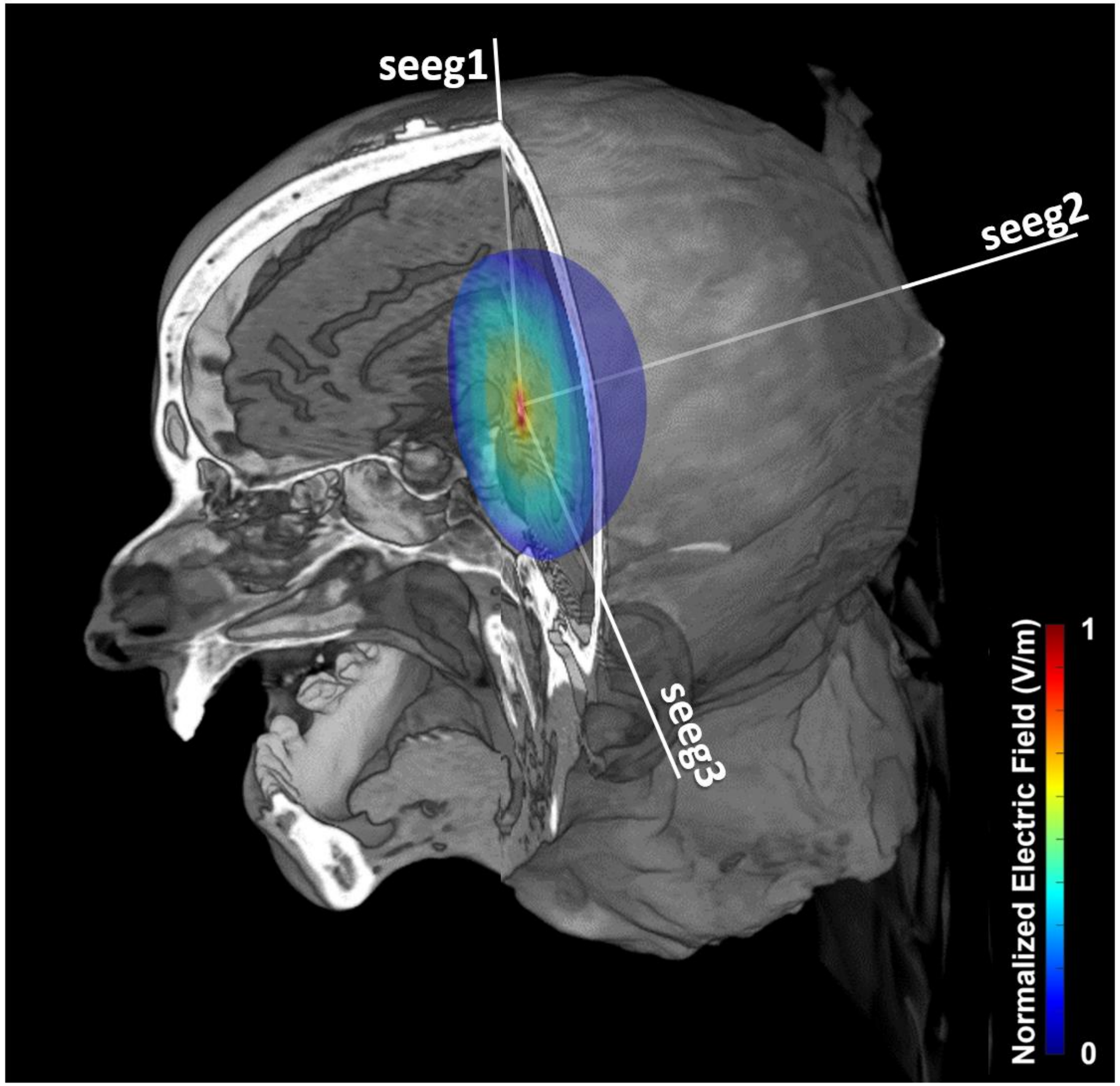
Standard TI



Preliminary Results: **Focality**



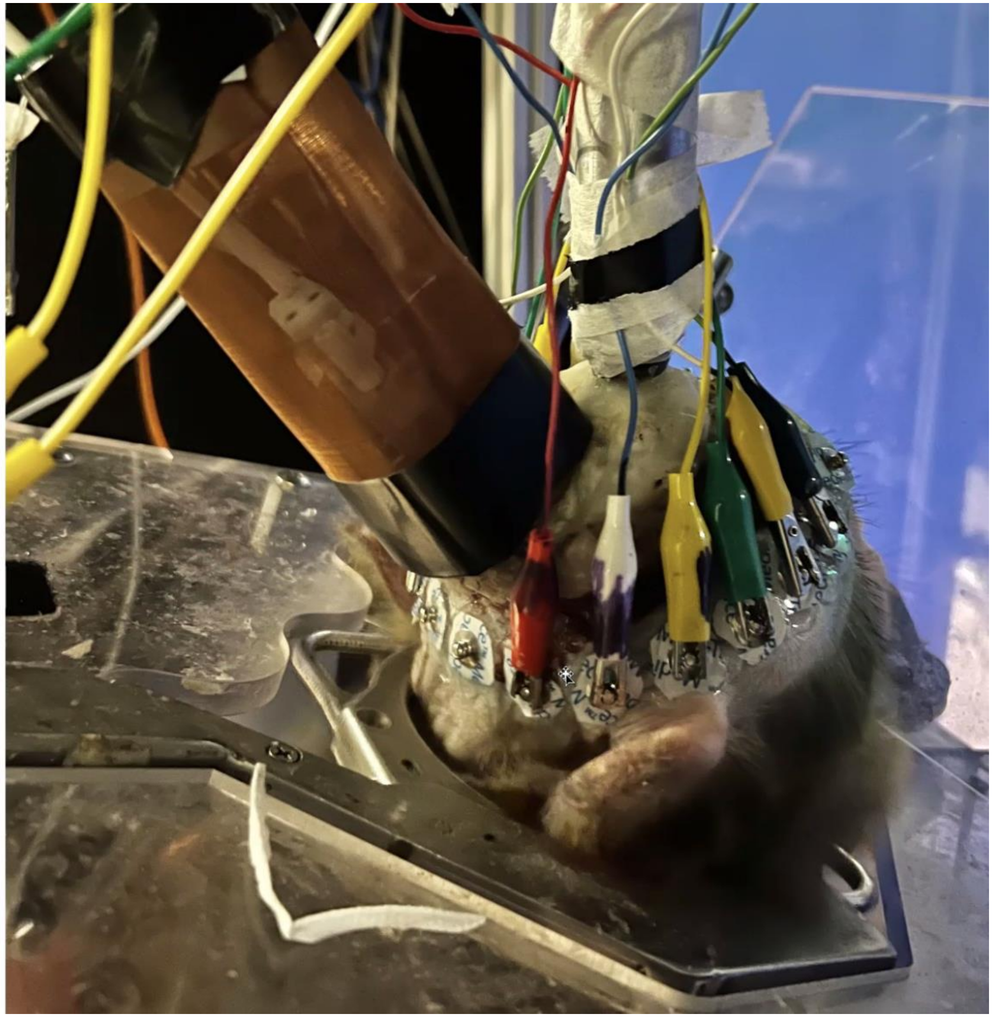
Standard TI

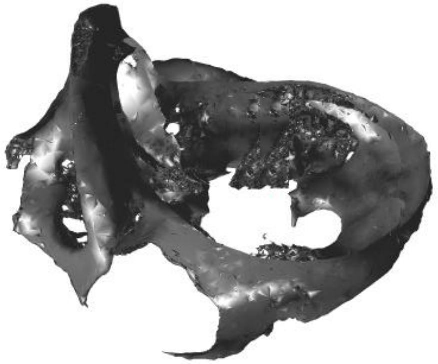


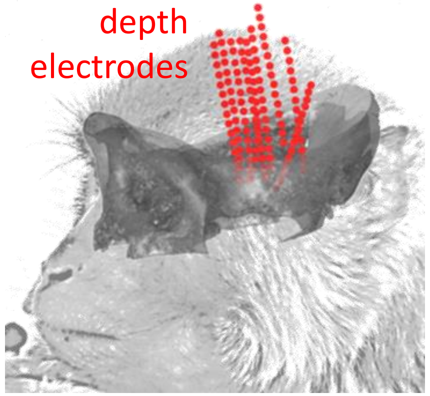
mTI

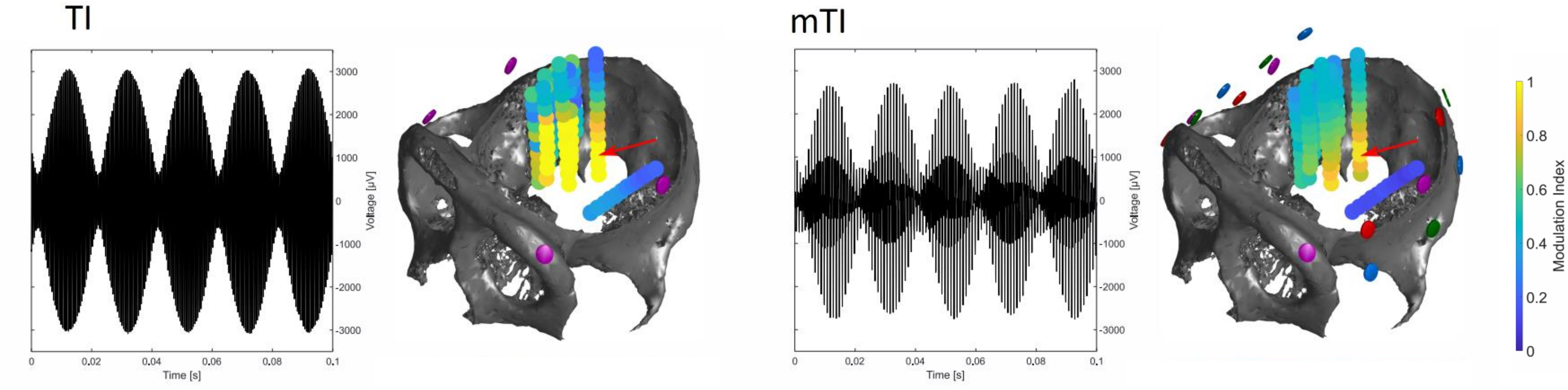
Patent EP 21306447 - DEEP BRAIN STIMULATION SYSTEM

Focality in NHPs

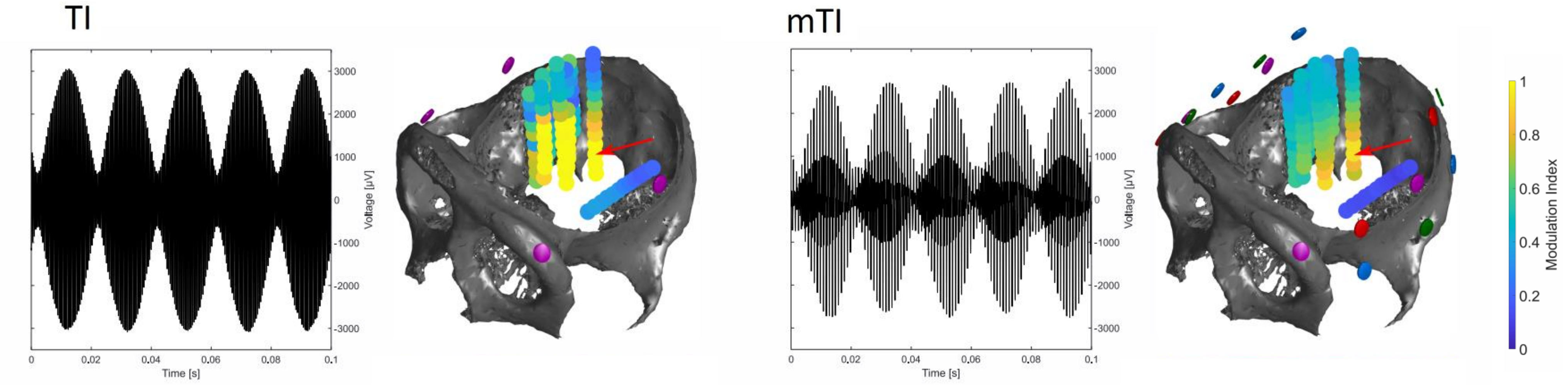




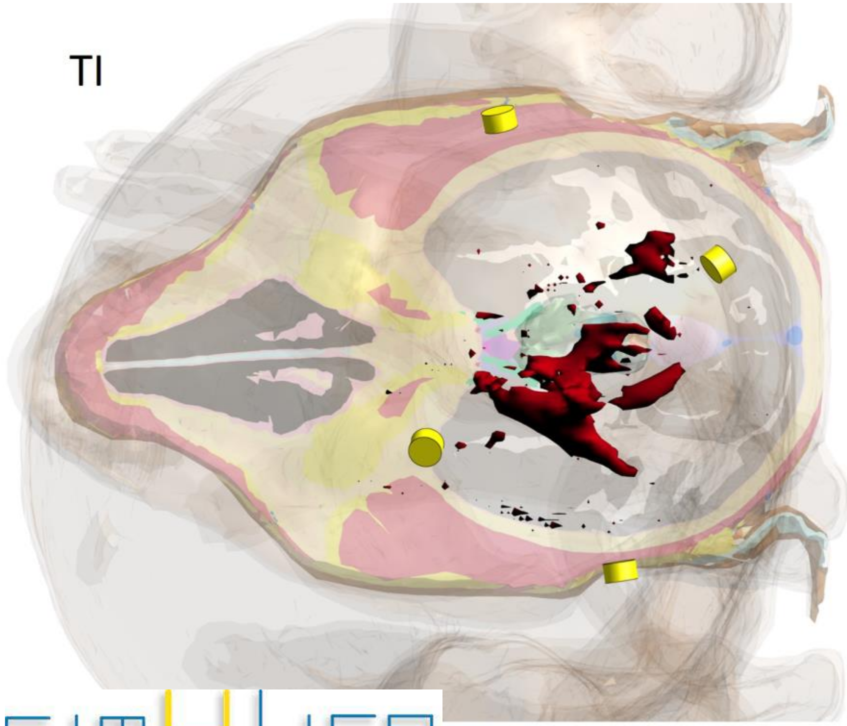


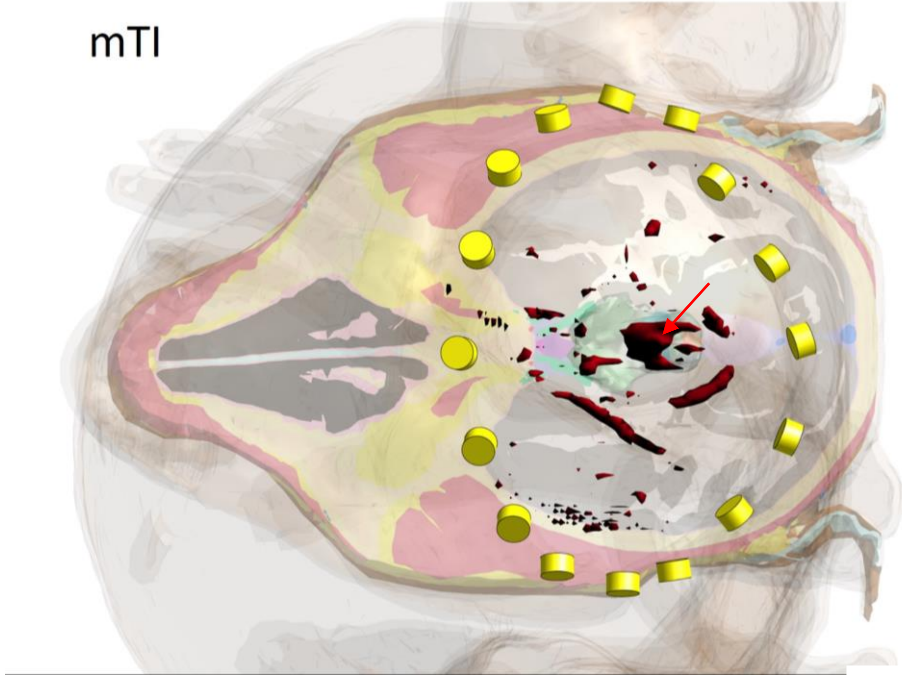


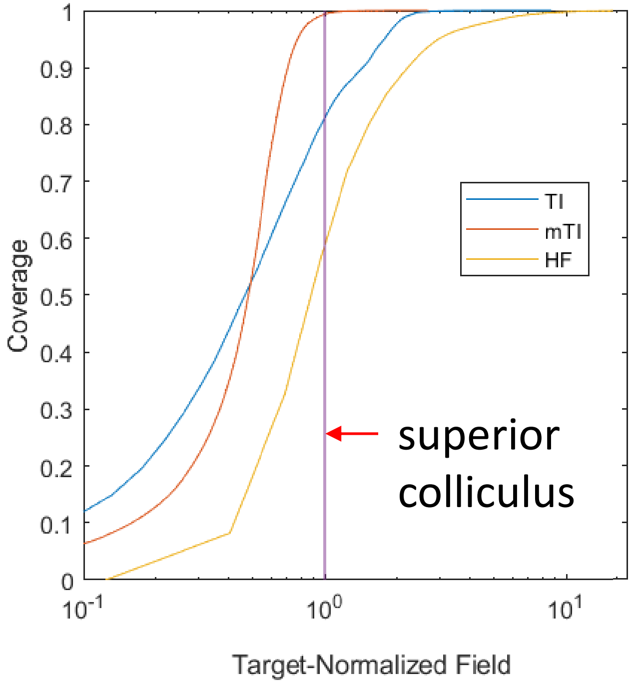
Target: superior colliculus

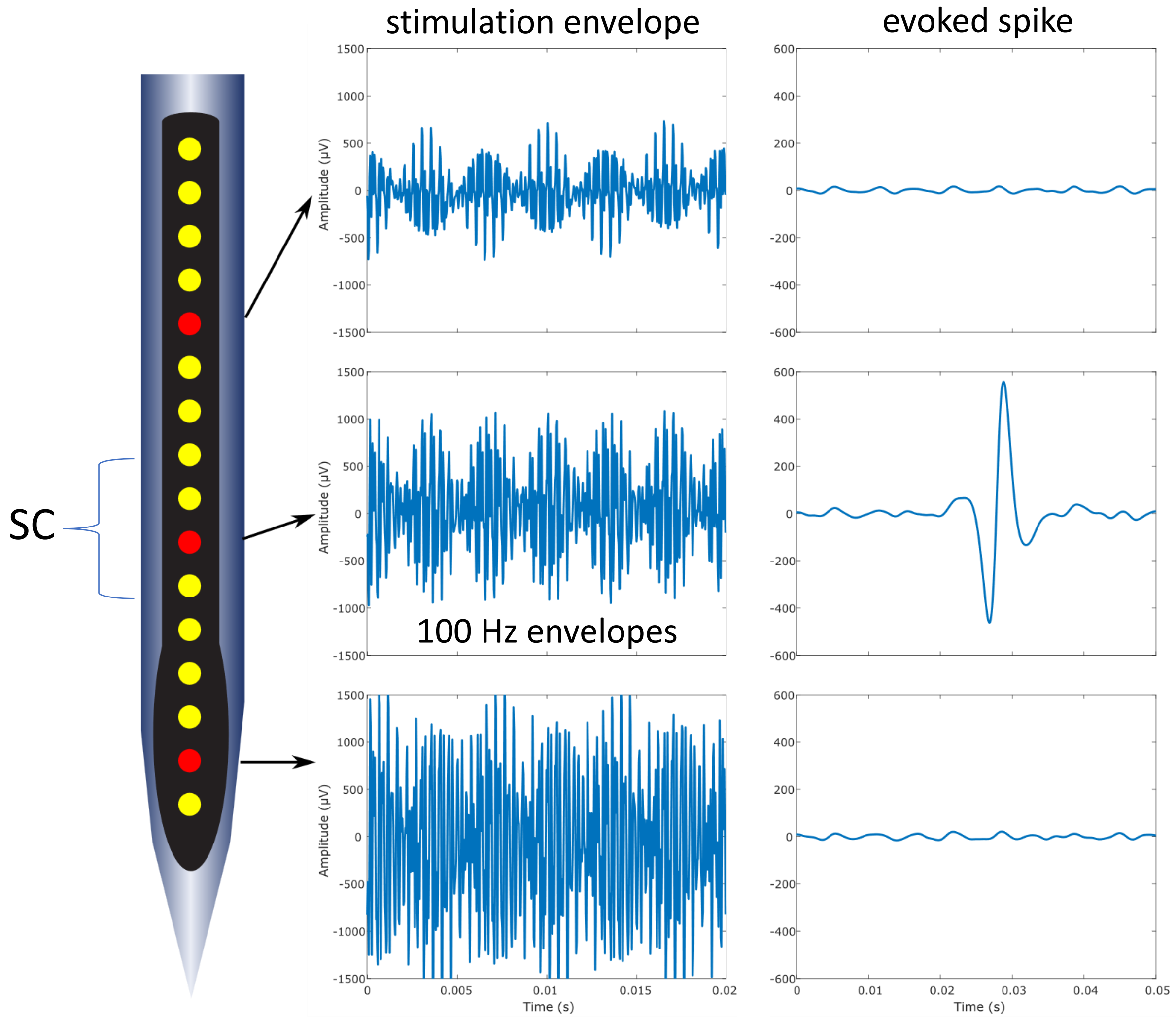


Target: superior colliculus

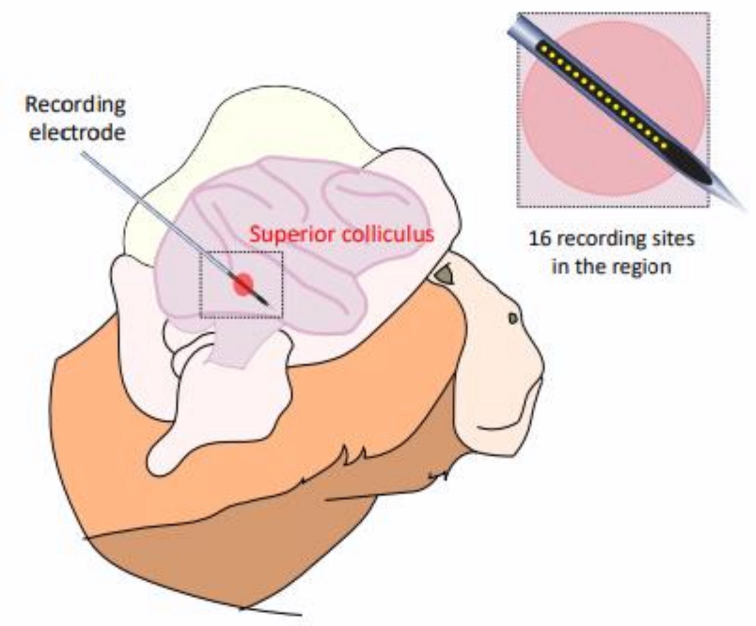


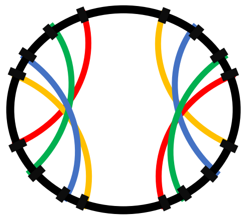


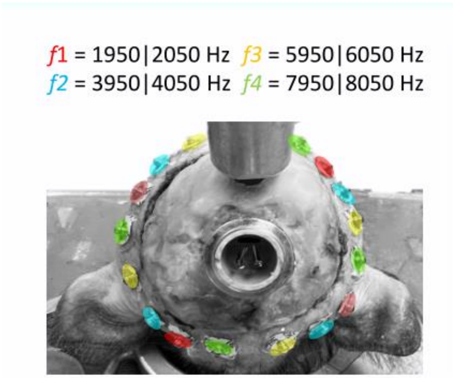


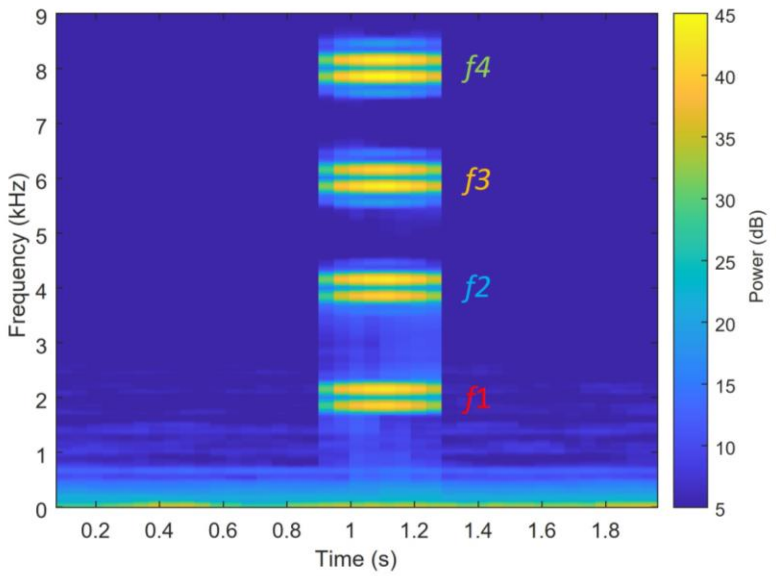

stimulation envelope
evoked spike
SC
100 Hz envelopes
Amplitude (μV)
Time (s)

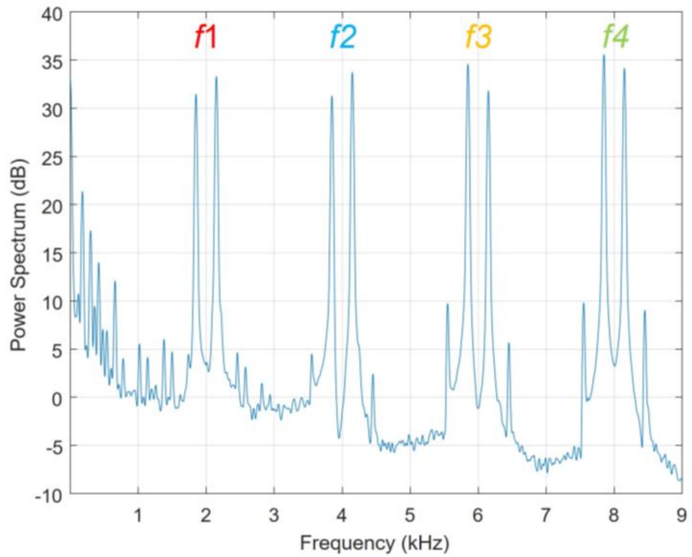

saccades


Recording electrode
Superior colliculus
16 recording sites in the region

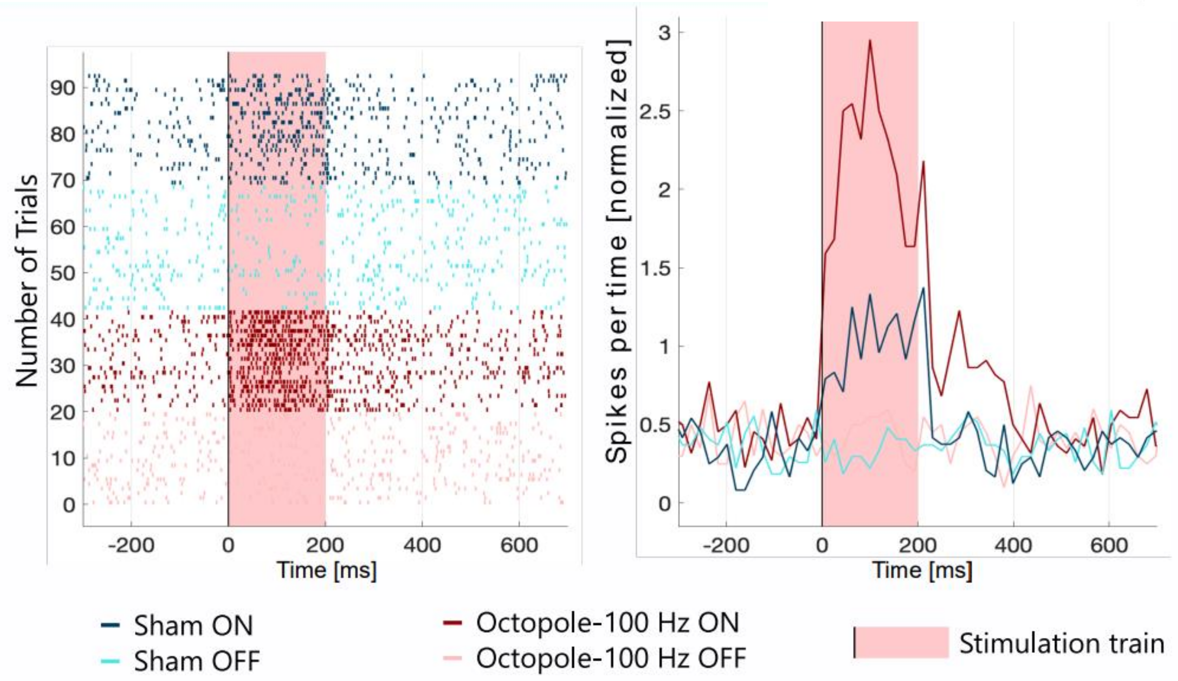


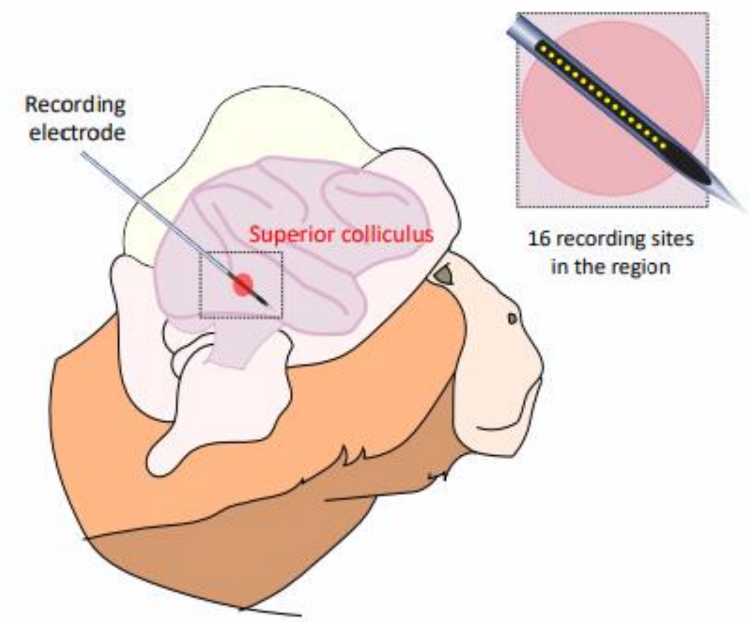


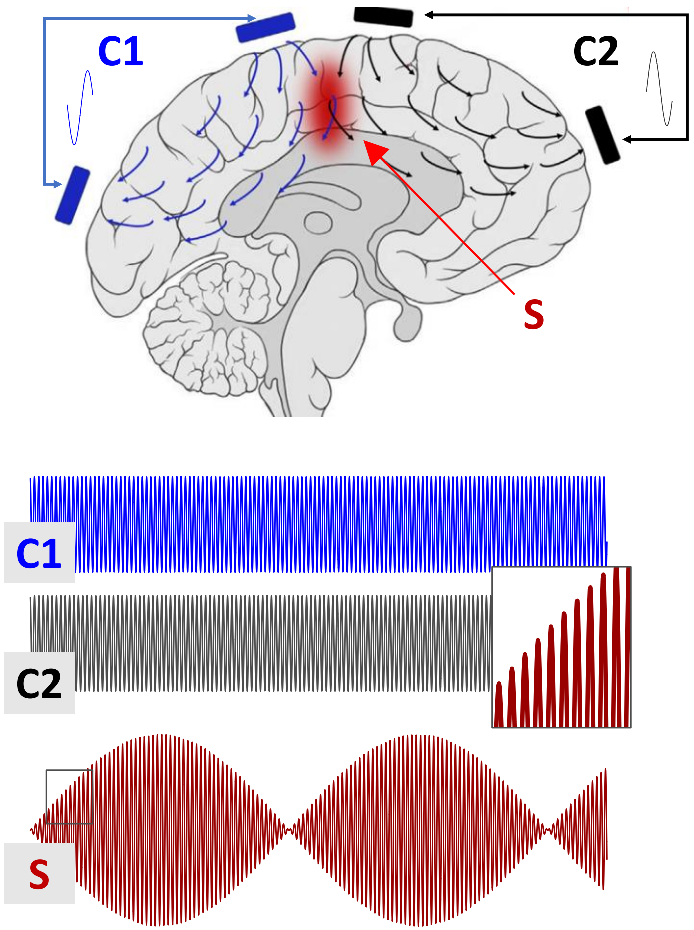


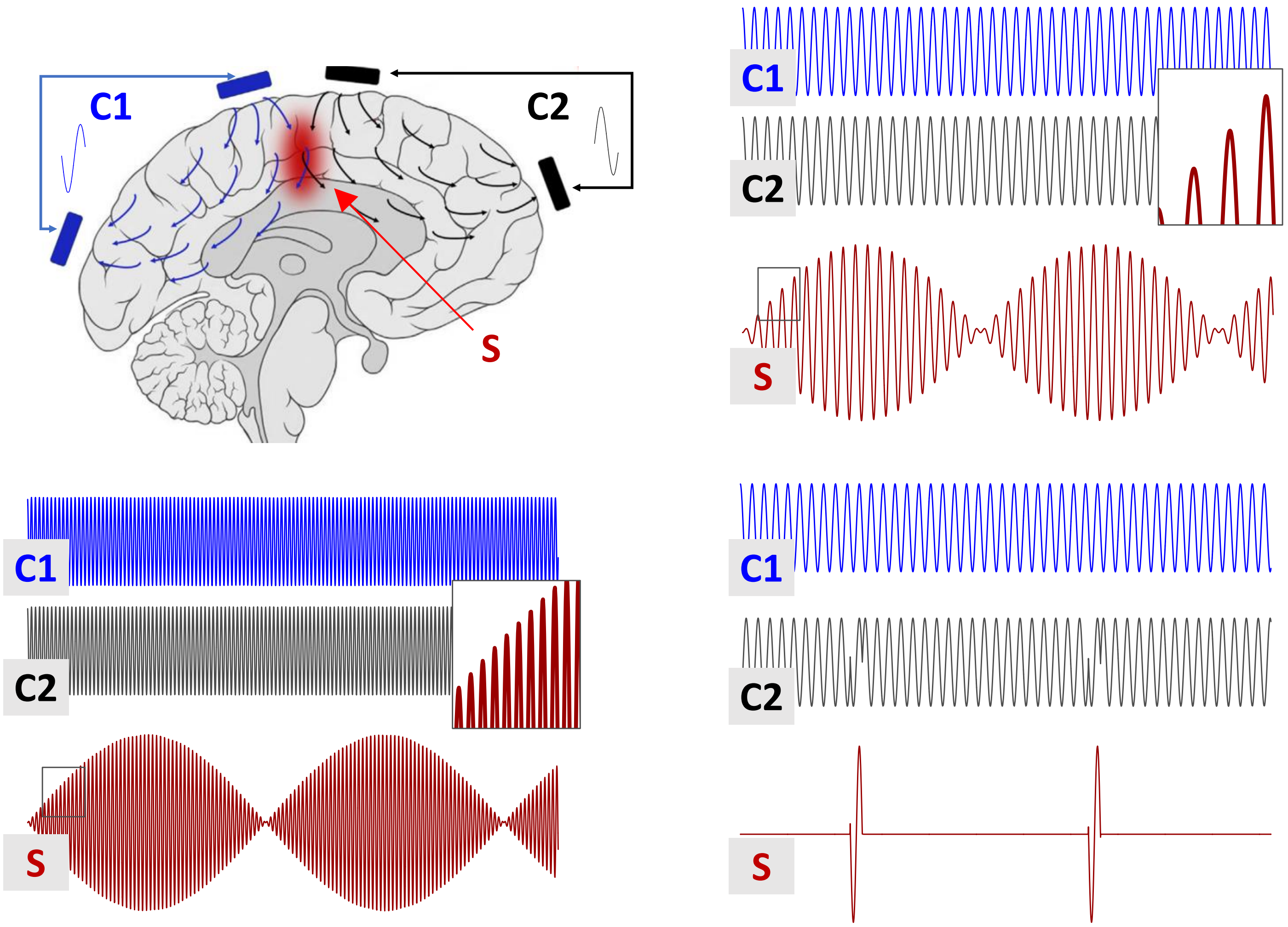


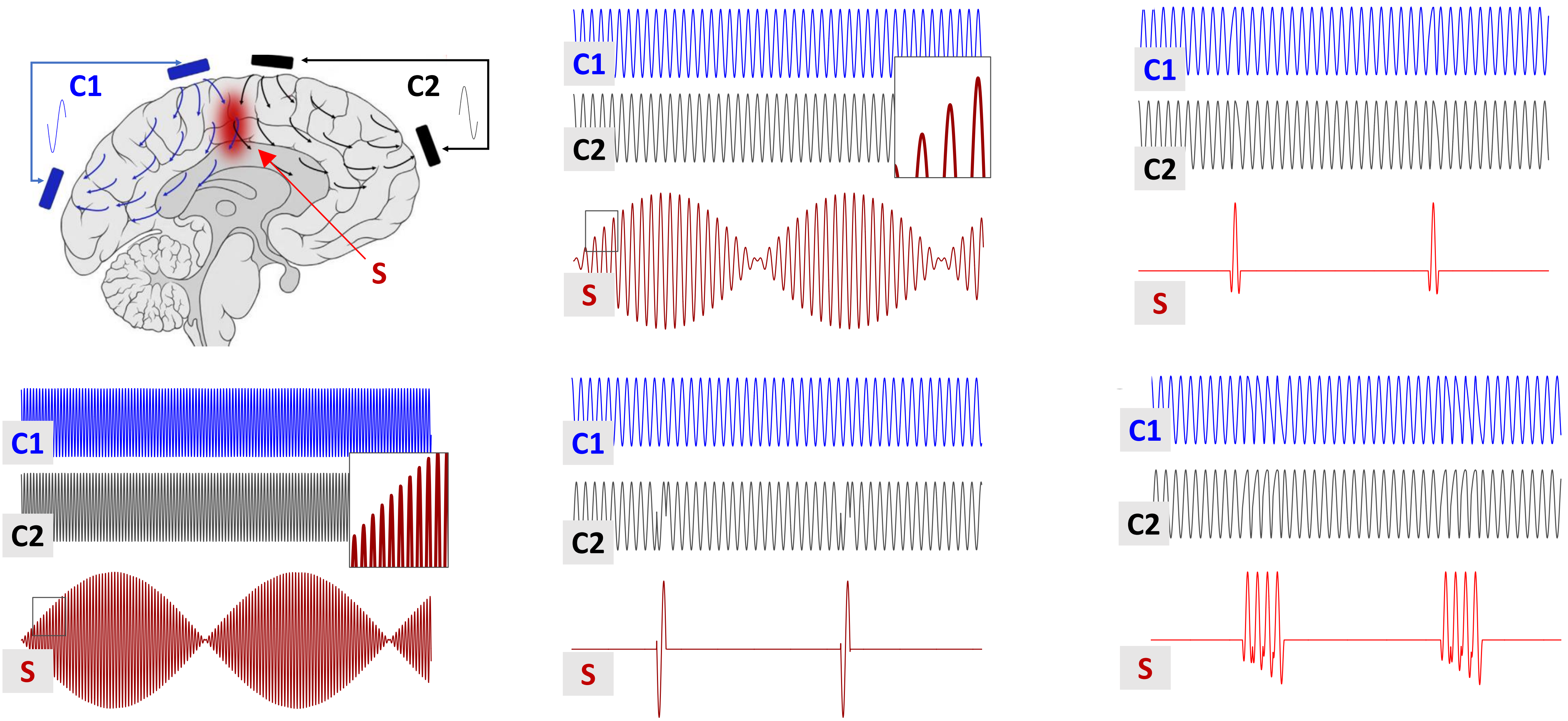
A "burst of envelopes"

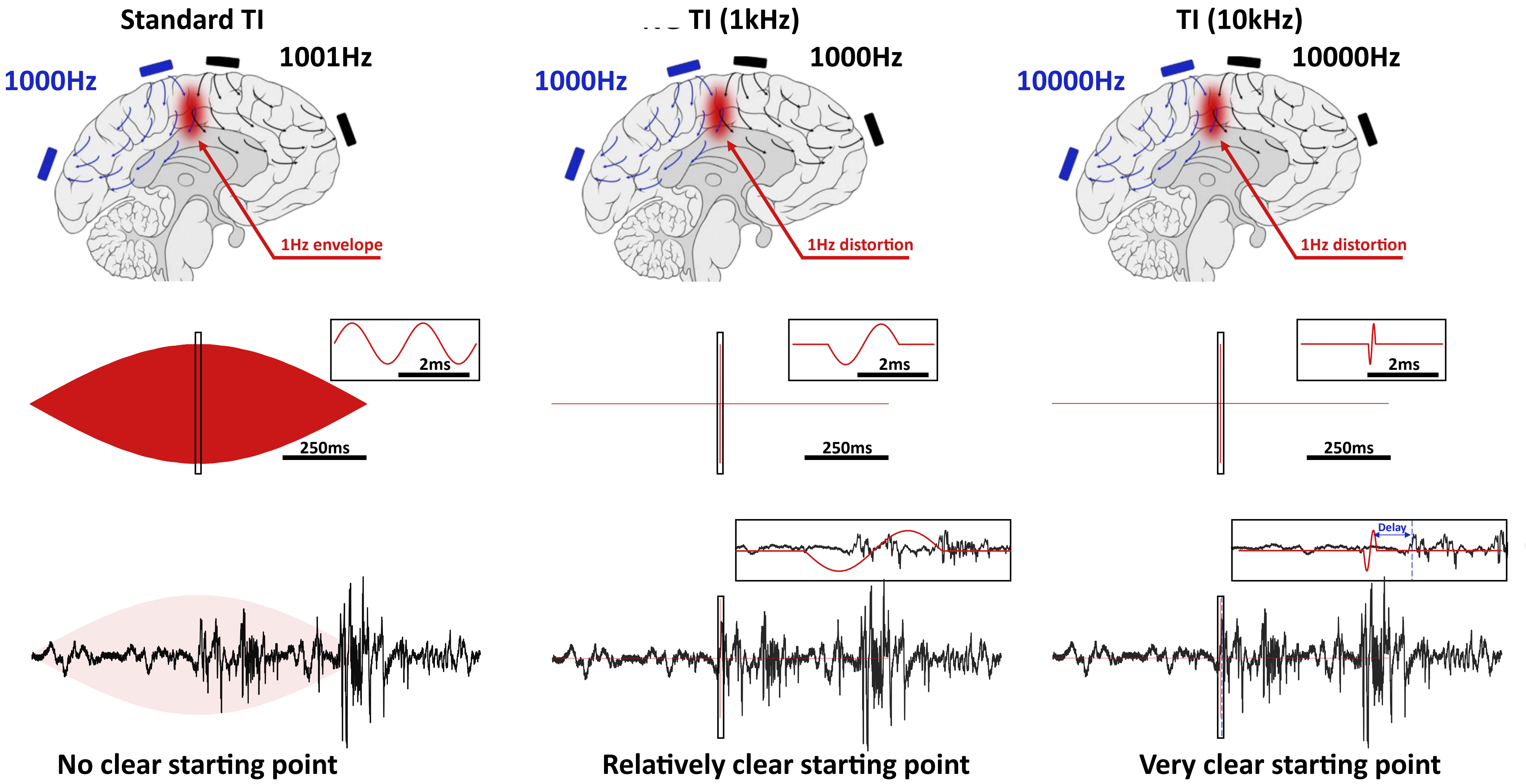





C1
C2
S
C1
C2
S


C1
C2
S
C1
C2
S
C1
C2
S
C1
C2
S


C1
C2
S
C1
C2
S
C1
C2
S
C1
C2
S
C1
C2
S
C1
C2
S


Standard TI
1000Hz
1001Hz
1Hz envelope
2ms
250ms
No clear starting point
TI (1kHz)
1000Hz
1000Hz
1Hz distortion
2ms
250ms
Relatively clear starting point
TI (10kHz)
10000Hz
10000Hz
1Hz distortion
2ms
250ms
Delay
Very clear starting point