EPFL

Neuro X Institute


# Non-invasive deep brain stimulation

**Nx-436**

***'Advanced methods for human neuromodulation'***

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Ecole Federale Polytechnique de Lausanne (EPFL)

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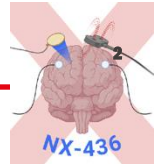
# Overview



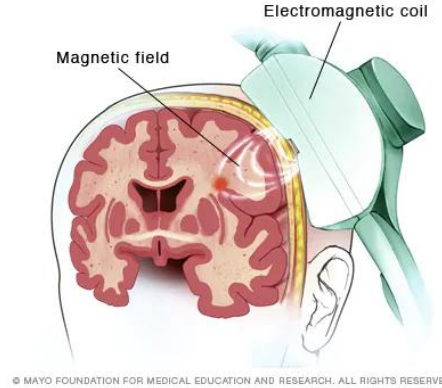

Non-invasive deep brain stimulation

- 2 methods that will be discussed
  - Deep TMS
  - transcranial Temporal Interference Stimulation (tTIS)
- Concepts and Mechanisms of these methods

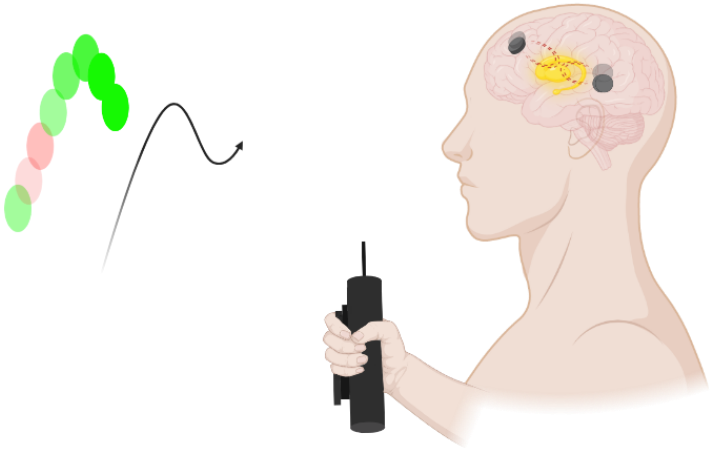
Applications

Challenges/Limitations

Optimization





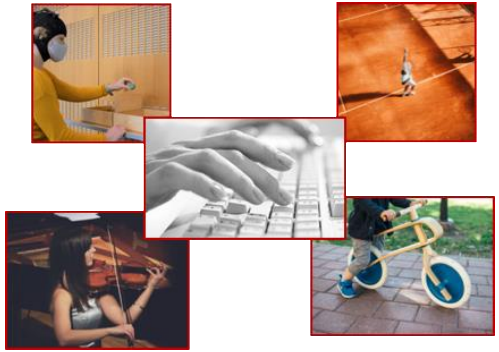


# Non-invasive deep brain stimulation

## deep TMS

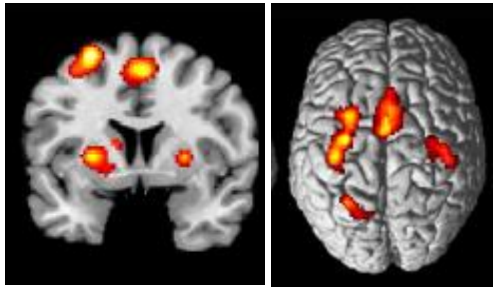
## transcranial Temporal Interference Stimulation (tTIS)

# Neuromodulation of deep brain structures

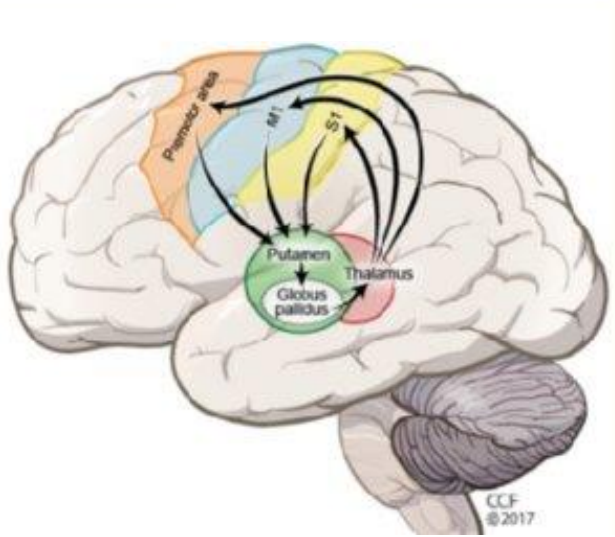


Motor Learning

Memory



# Motor, cognitive functions – cortico-subcortical processing



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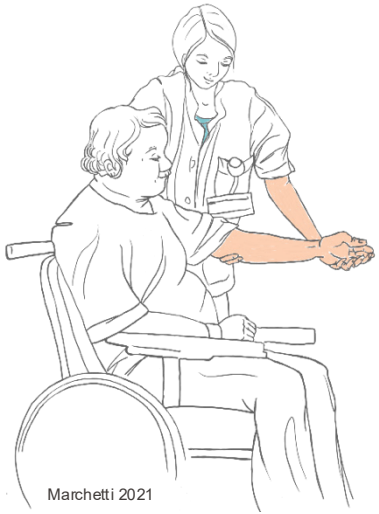
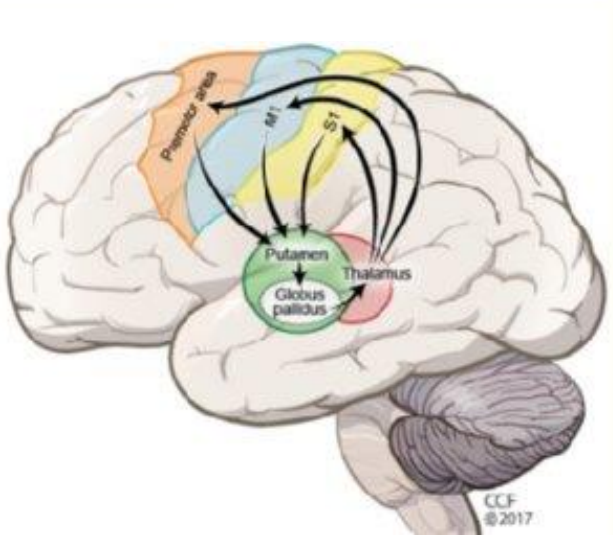


Marchetti 2021

Stroke

Parkinson's



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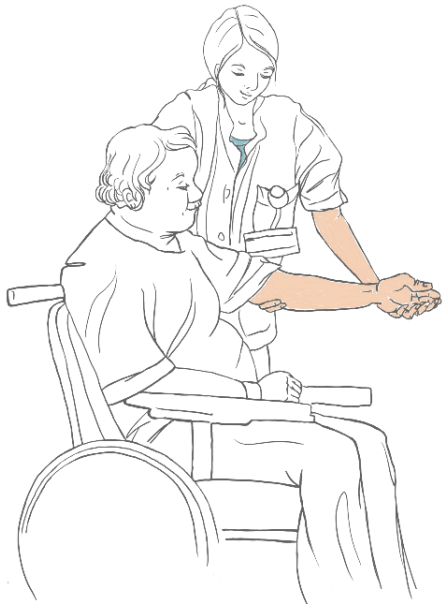
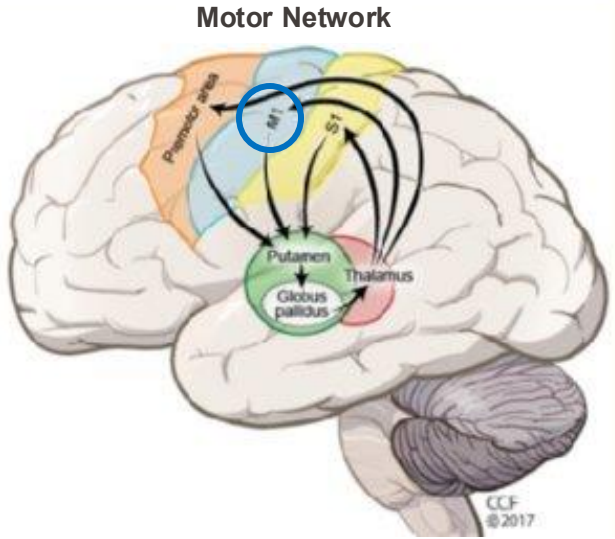


## Non-invasive brain stimulation




e.g., Maceira-Elvira *et al*. 2022 Sci Adv, Nat Nsc; Zimerman *et al*. 2013 Ann Neurol; Zimerman *et al*. 2014 Cerebral Cortex; Nitsche *et al*. 2000 J Physiol

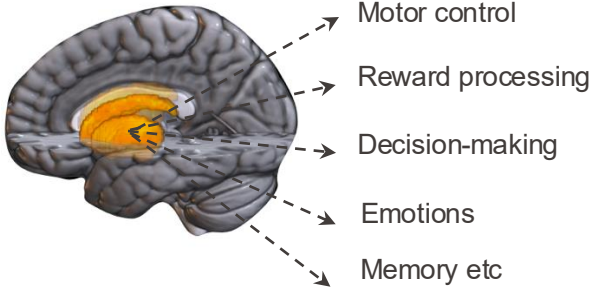
Stroke recovery: Hummel et al. 2005 Brain; Hummel & Cohen 2006 Lancet Neurology

# Neuromodulation of deep brain structures

Deep brain regions are altered in many **neuro-psychiatric disorders**:

*e.g.,* **striatum, hippocampus, thalamus, DLPFC**

- Stroke
- Apathy
- Parkinsons' disease
- Epilepsy
- Dementia…



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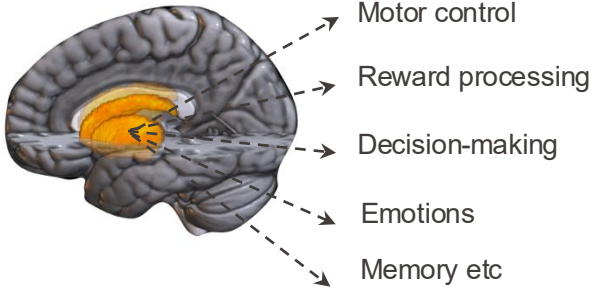
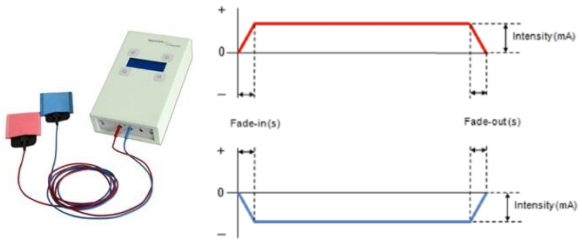
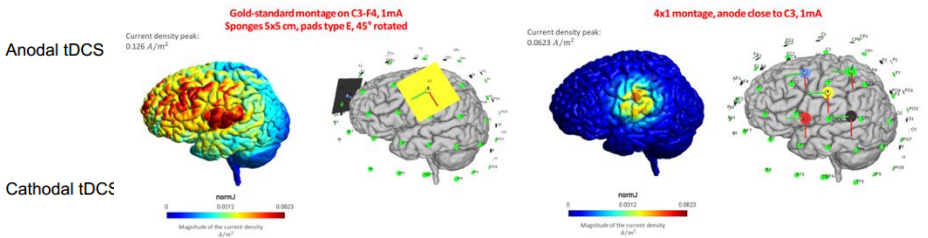



Challenge: focal, non-invasive deep brain stimulation is not possible with conventional approaches due to steep depth-focality trade-off

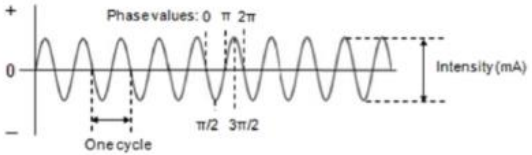
# Neuromodulation by NIBS

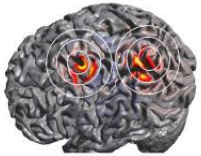
**transcranial Direct Current Stimulation (tDCS)**



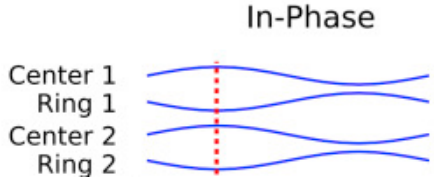




**transcranial Alternating Stimulation (tACS)**

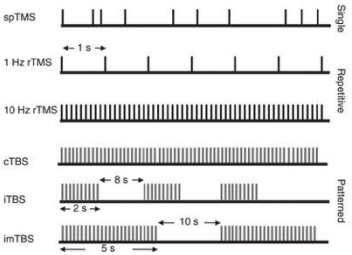


tACS




**transcranial Magnetic Stimulation (TMS)**




For review see e.g., Hummel & Cohen 2006; Wessel *et al.* 2015; Saturnino *et al.* 2017

# Neuromodulation by NIBS

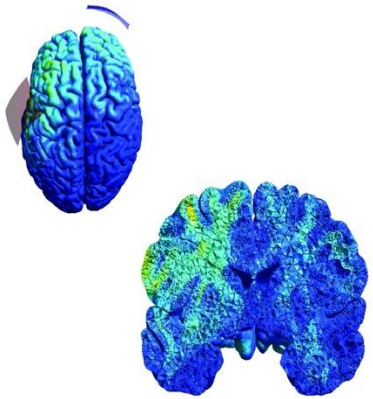
transcranial Direct Current Stimulation (tDCS)

transcranial Alternating Stimulation (tACS)

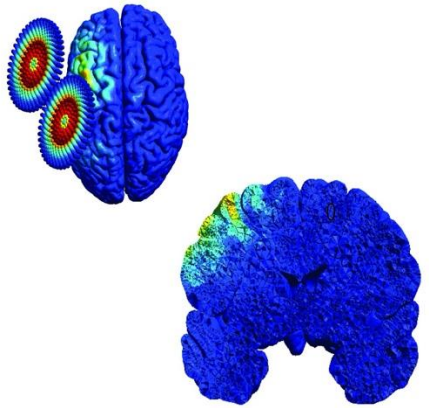
transcranial Magnetic Stimulation (TMS)

## Depth-focality trade-off

### Conventional tES




### TMS

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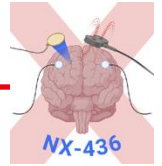
# Neuromodulation of deep brain structures

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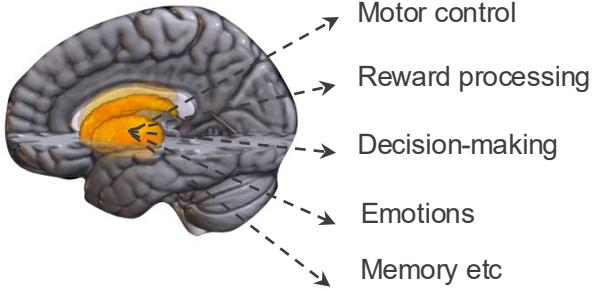
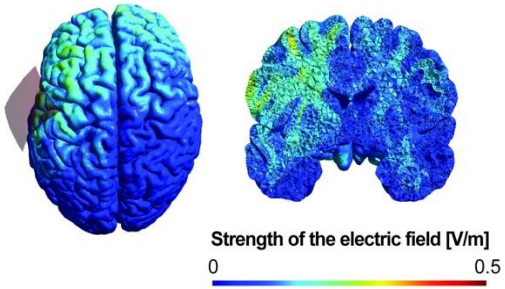
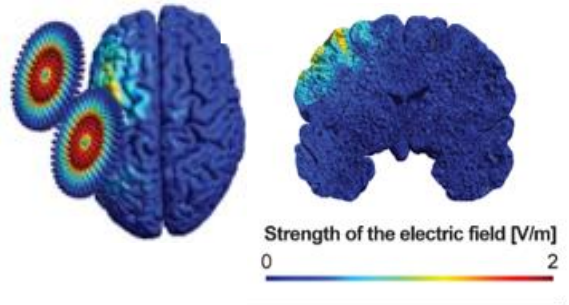



Challenge: focal, non-invasive deep brain stimulation is not possible with conventional approaches

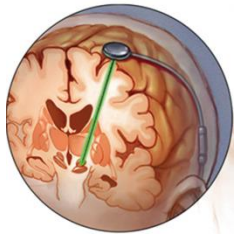
## Conventional tES



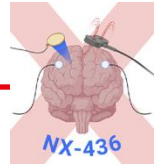

## TMS



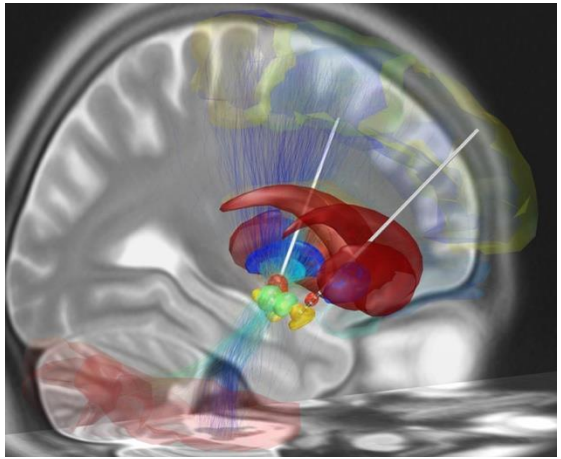

Deep brain stimulation is so far **limited to invasive methods**

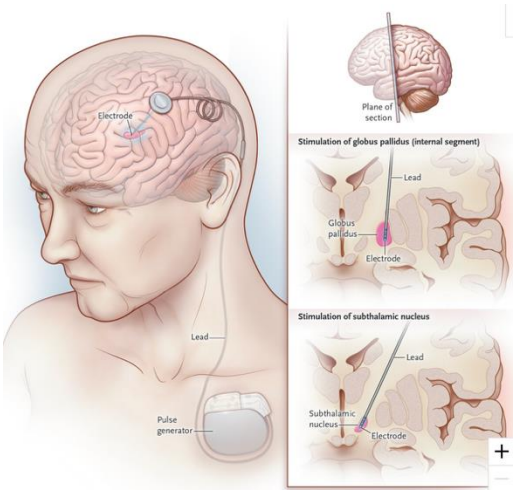


# Invasive CNS stimulation




## (Adaptive) invasive Deep Brain Stimulation

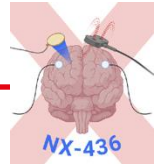




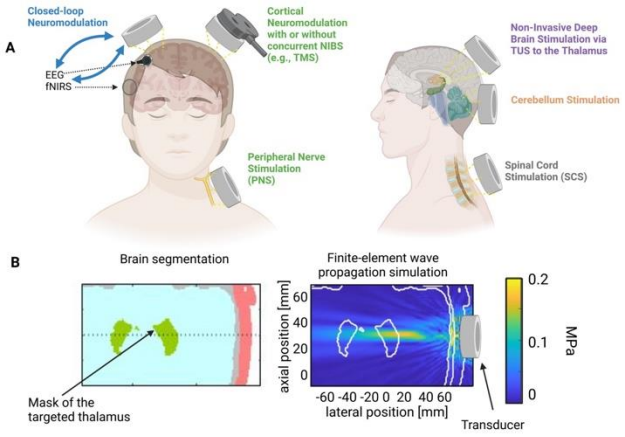

For review e.g., Marcegli *et al.* (2024) JNE

- Effective, excellent for 24/7 use
- Invasive with respective side effects
- Costly
- Not accessible for a large part of patients (e.g., only 2-4% of PD patients have DBS treatment)
- Not for responder, non-responder testing (personalization)

# Non-invasive Deep brain stimulation – novel technology

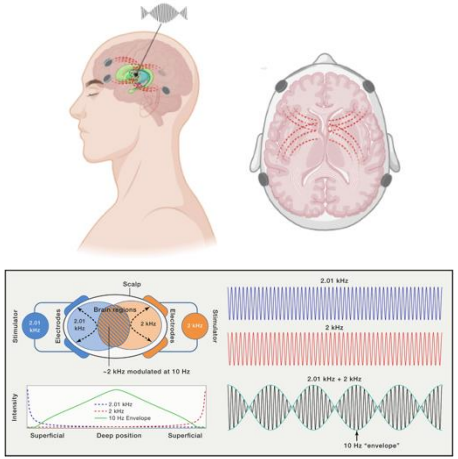



## transcranial focused Ultrasound (tUS)



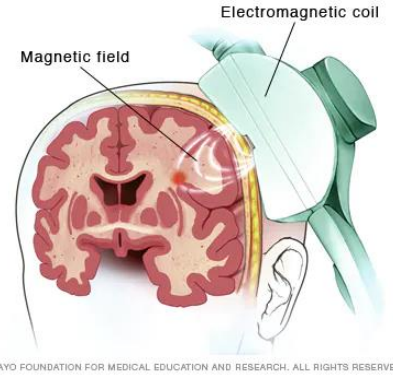

For review e.g., Yüksel et al. *IEEE EMBS* 2024

## transcranial Temporal Interference electrical Stimulation (tTIS)

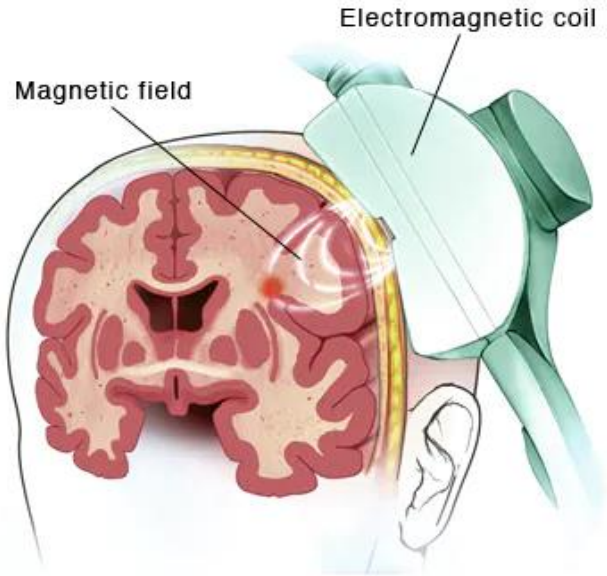



Vassiliadis et al. *Nature Biomed Eng* (in press)
Hummel & Wessel *Nature Review Neurology* 2024
Vassiliadis et al. *Nature Human Behavior* 2024
Beanato et al. *Science Advances*, 2024
Wessel, Beanato et al. *Nature Neuroscience* 2023
Violante et al. *Nature Neuroscience* 2023
Grossman et al. *Cell* 2017

## Deep TMS




Bersani et al. *Eur Psychiatry* 2013
Di Passa et al. *J Psychiatr Res.*2024



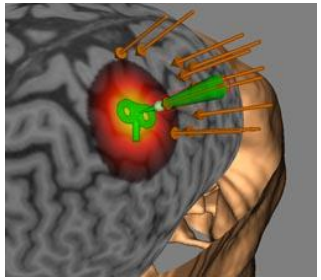


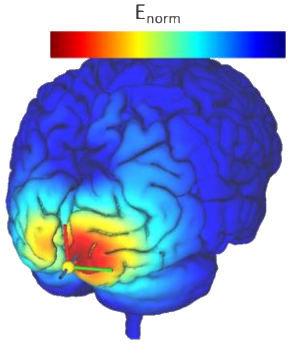

# deep TMS

# TMS

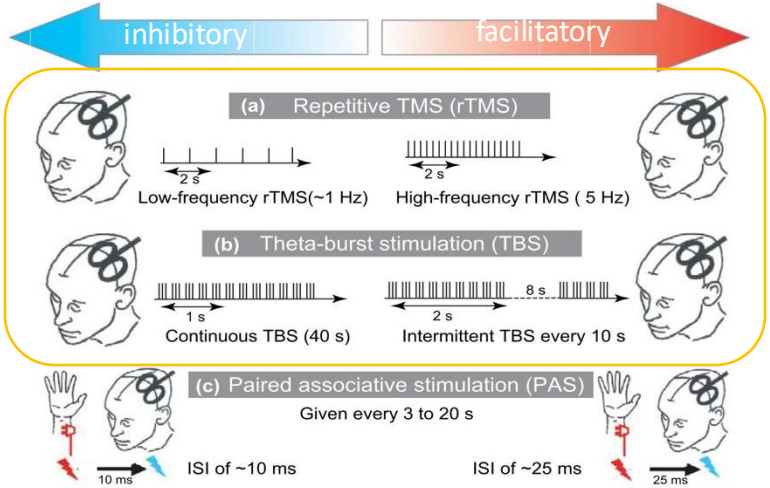


## Transcranial Magnetic Stimulaton (TMS)






$TMS_{(V1)}$



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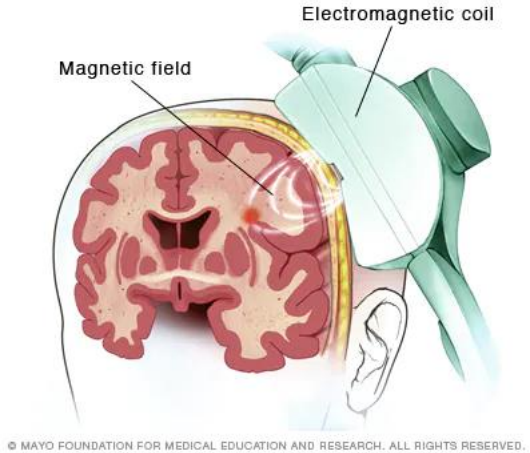



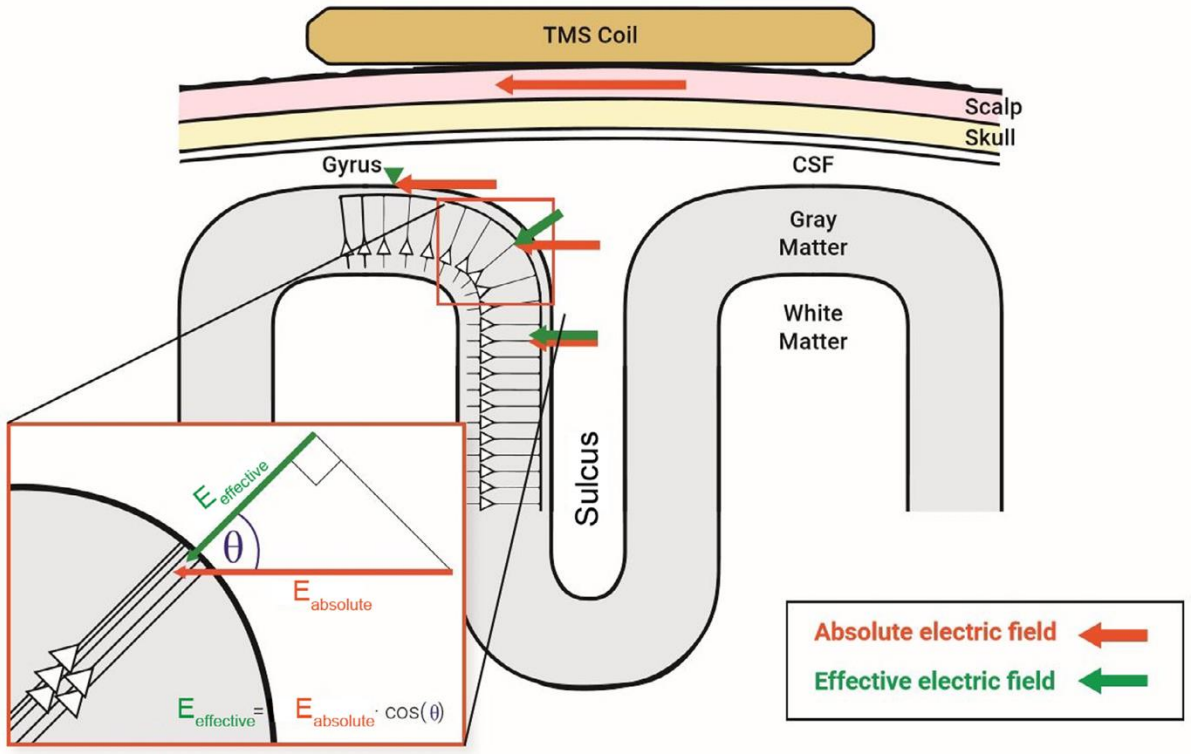


Zibma *et al*., 2021, Pell *et al*., 2023,

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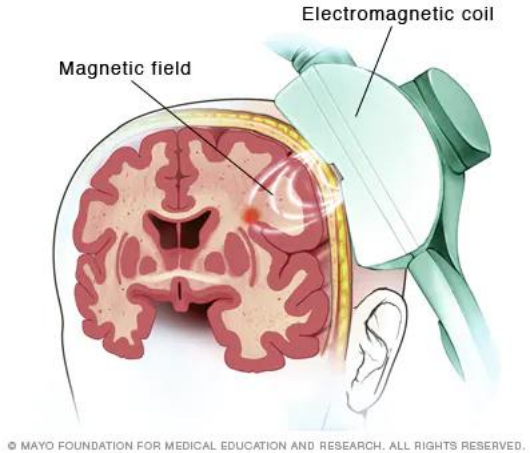



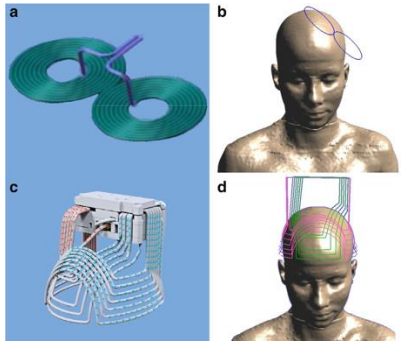


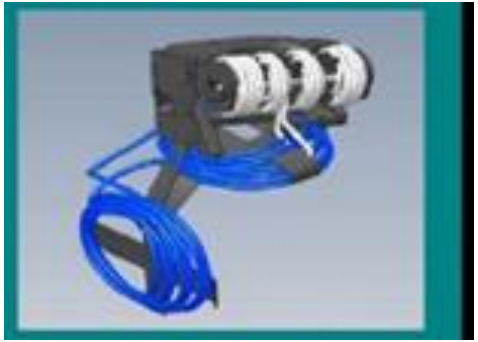

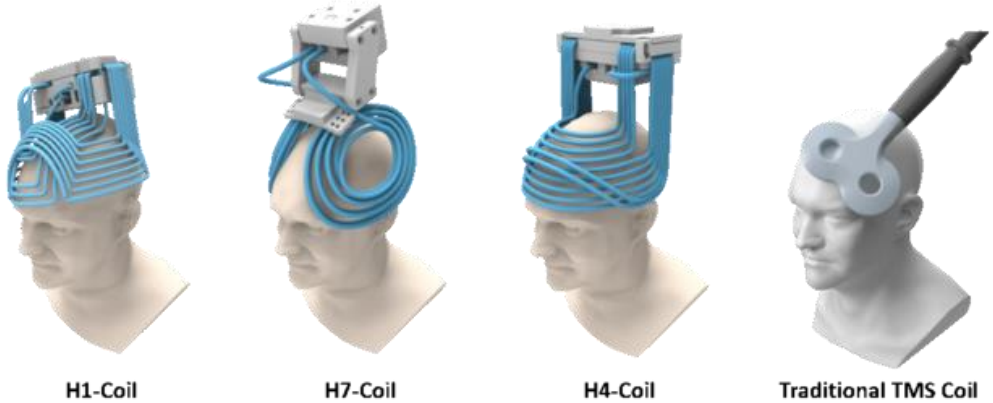


Zibma *et al*., 2021, Pell *et al*., 2023, https://www.brainsway.com

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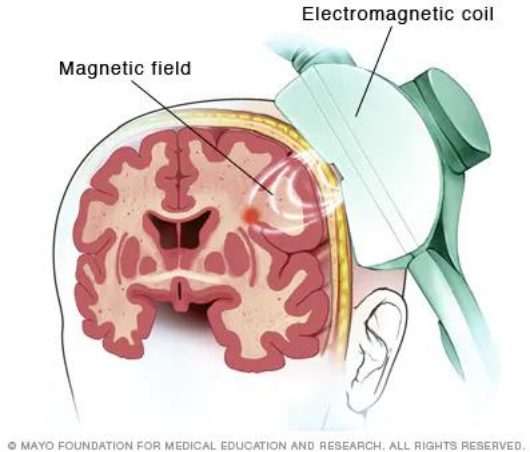




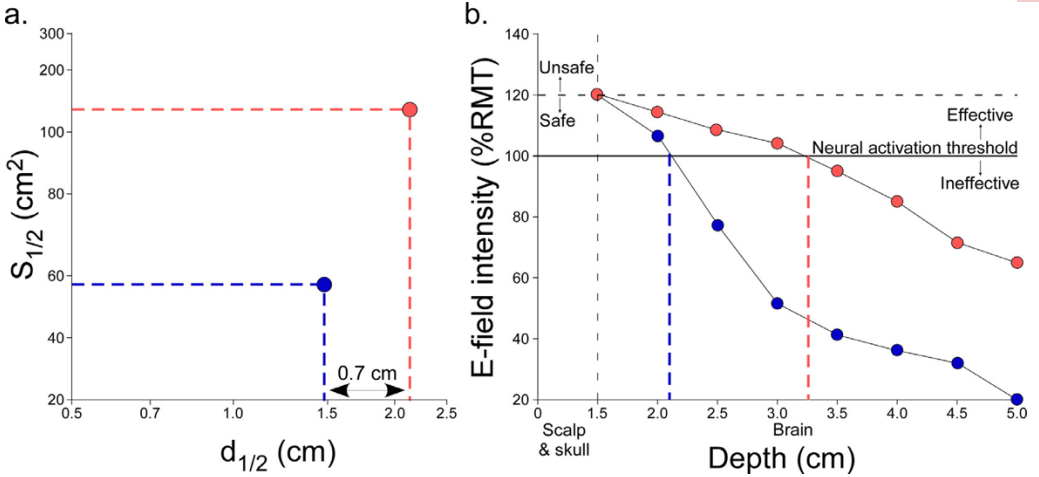


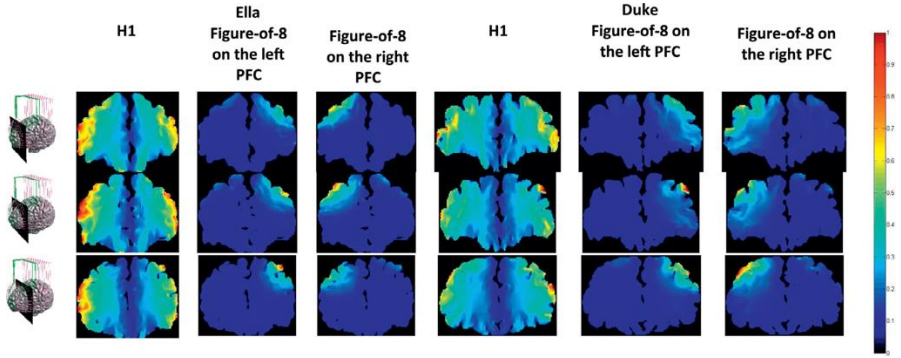


Zibma *et al*., 2021, Pell *et al*., 2023

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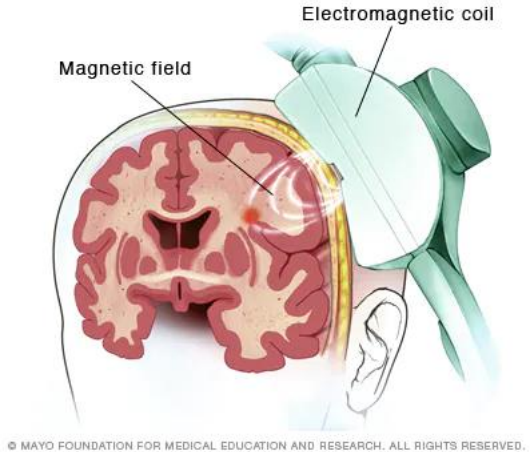



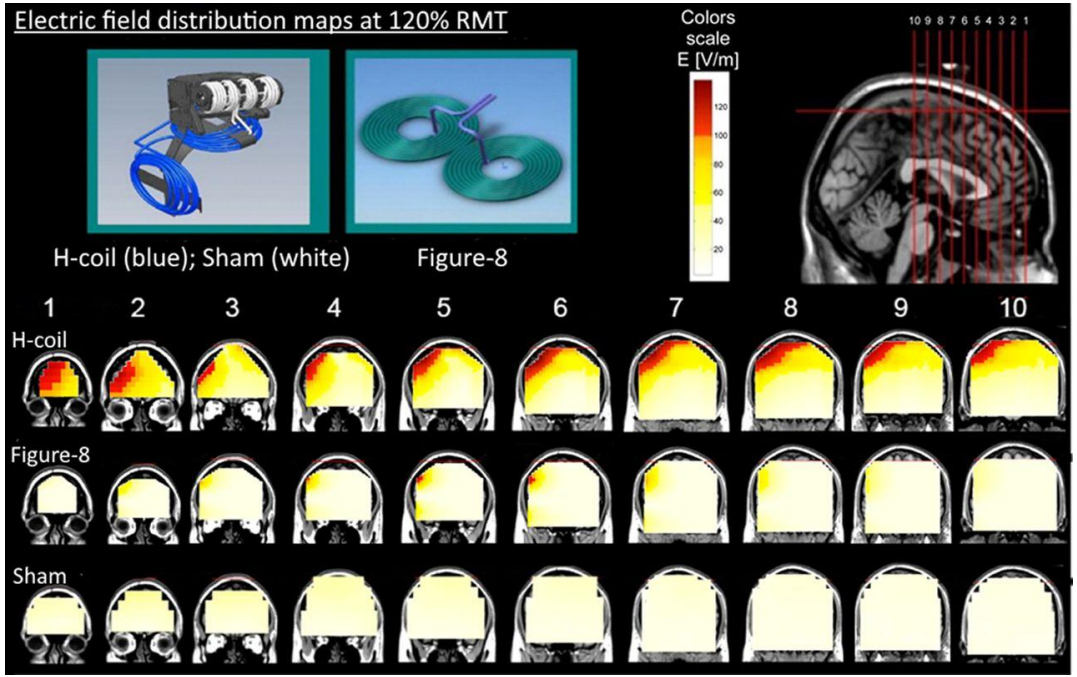


Zibma *et al*., 2021, Pell *et al*., 2023

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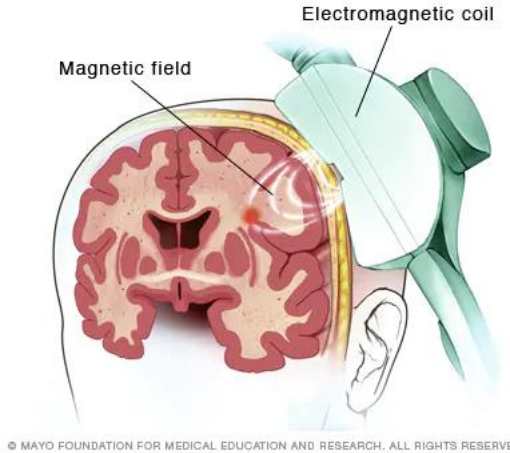


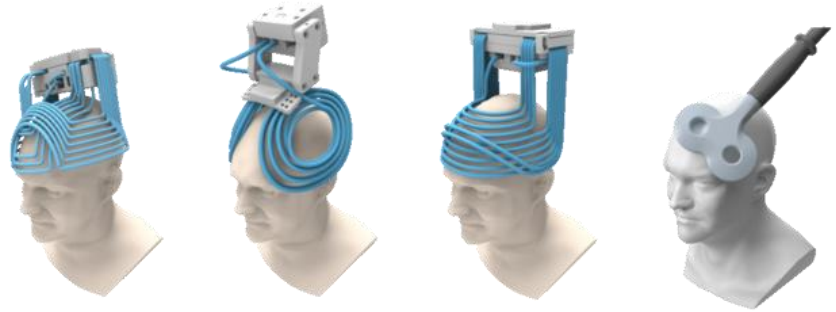


Zibma *et al*., 2021, Pell *et al*., 2023, https://www.brainsway.com

# Deep TMS

**Deep TMS has been CE-marked to treat:**

Patients diagnosed with major depressive disorder.
Patients diagnosed with obsessive-compulsive disorder.
Patients diagnosed with smoking addiction.
Patients diagnosed with Alzheimer's disease.
Patients diagnosed with autism.
Patients diagnosed with bipolar disorder.
Patients diagnosed with chronic pain.
Patients diagnosed with multiple sclerosis (MS).
Patients diagnosed with Parkinson's disease.
Patients diagnosed with post-stroke rehabilitation.
Patients diagnosed with post-traumatic stress disorder (PTSD).
Patients diagnosed with negative symptoms of schizophrenia



**H1-Coil** for Major Depressive Disorder (MDD)

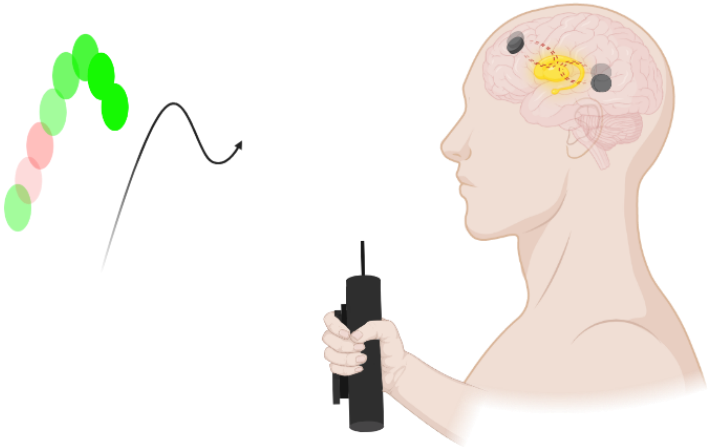
**H7-Coil** for Obsessive-Compulsive Disorder (OCD)

**H4-Coil** for Smoking Cessation

**Traditional TMS Coil** for Major Depressive Disorder (MDD)

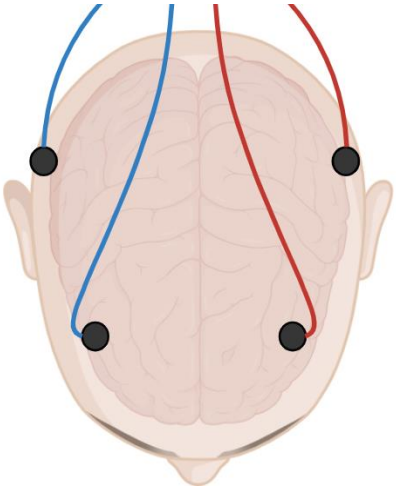
- **Deep TMS by means of H-Coils allows to reach deeper (cortical) structure**
- **Lower focality then classical Figure of 8 coils**
- **Based on special coil architecture**
- **Improves treatment effects**

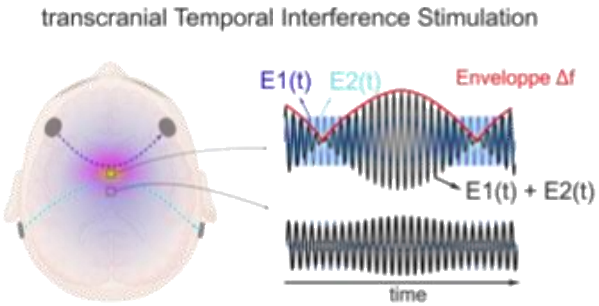
- **However, still limited to the Cortex!**

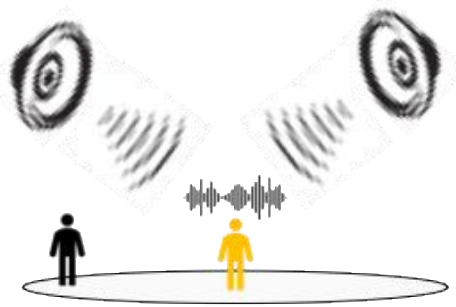


# Transcranial temporal interference stimulation (tTIS)

# transcranial Temporal Interference Stimulation (tTIS)



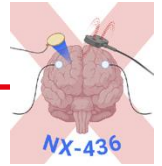


Wessel*, Beanato* *et al.,* 2023, *Nature Neuroscience;* Vassiliadis *et al.*, 2024 *Nature Human Behaviour,* Beanato, Moon *et al.* 2024 *Science Advances*; Vassiliadis et al. 2024 *JNE*; Yang et al. 2024 *MDS*; Lamos et al. 2025 MDS, Violante *et al.* 2023 *Nature Neuroscience*

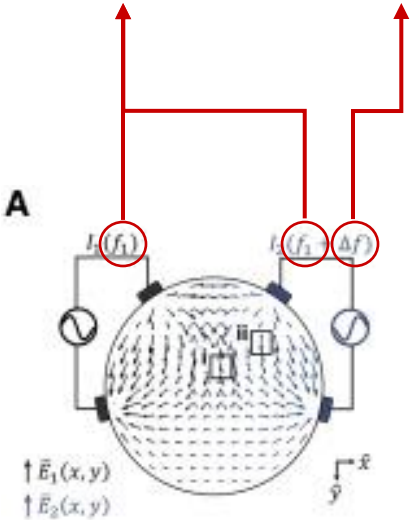
For review Rektorova *et al.* 2025 Nature Rev Neurol; Hummel & Wessel 2024 Nature Rev Neurol; Proulx & Hummel 2025 *Neural Reg Res*,

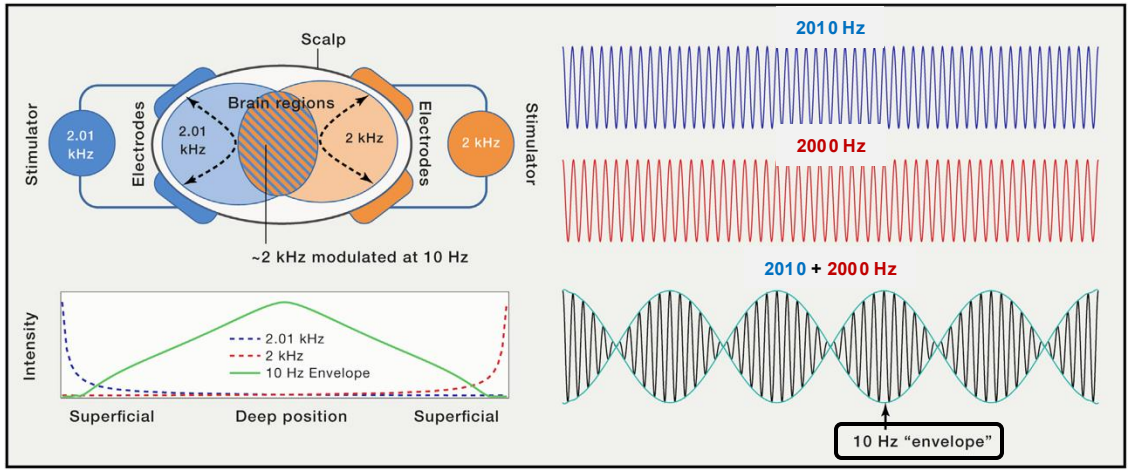
# transcranial Temporal Interference Stimulation (tTIS)




High frequency outside neural operation

Frequency recruiting neurons



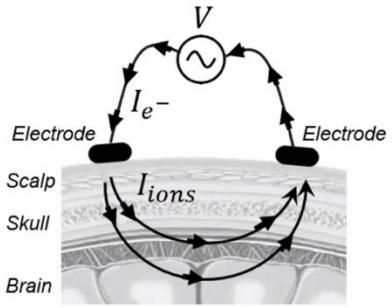




Grossman *et al.*, Cell 2017; Dmochowsk *et al*. 2017 Cell

# tTIS – Current source

**Problem**: Variable load resistance → Variable stimulation current

## Transcranial Electrical Stimulation




**Ohm's law**

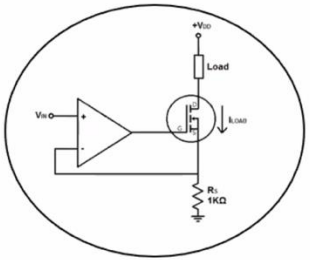
$$I_{e^-} = I_{ions} = \frac{V}{R_{Electrodes} + R_{Head}}$$

Variables

*Example*

*1 V drive* → *1 kΩ load → 1 mA*; *10 kΩ load → 0.1 mA*

## Solution: Current (not Voltage) Source




Voltage (V) is adapted automatically (via feedback) to yield the target current (I) value.

**Compliance Voltage**

Maximal voltage (V max) that the current source can output.

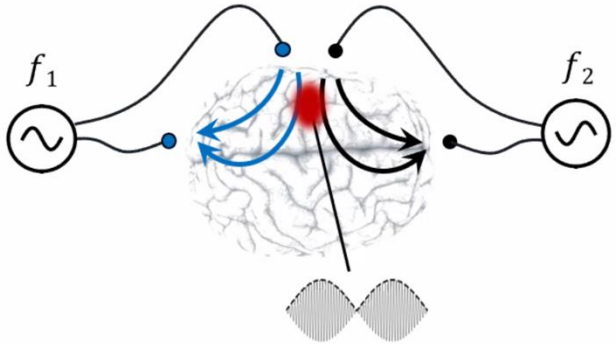
Example

1 mA drive, V max = ±24 V → 10 kΩ → 10 V → 1 mA; 48 kΩ → 24 V → 0.5 mA + Truncated waveform

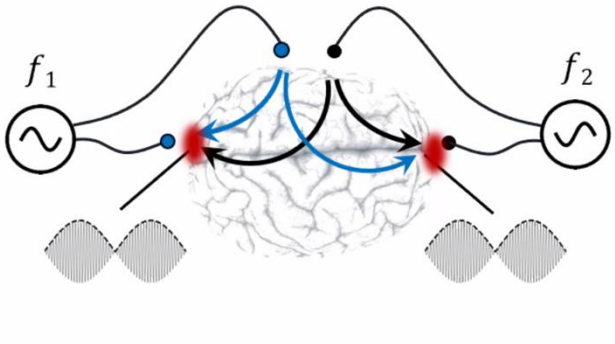
# tTIS – Current source

**Problem**: Cross-talk between currents → No TI stimulation focality

Channel Isolation




Channel Cross-Talk

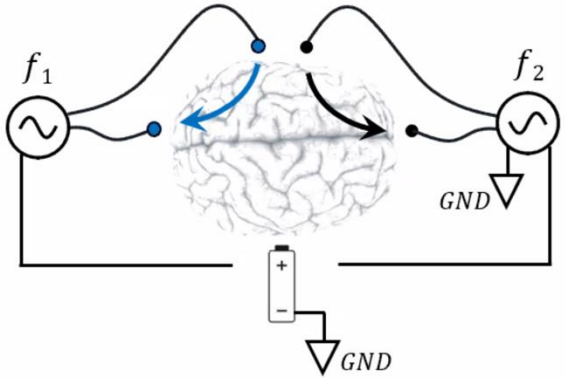



**Requirement**: Channel isolation (between current sources).

# tTIS – Current source

**Origin: Low cross impedance**

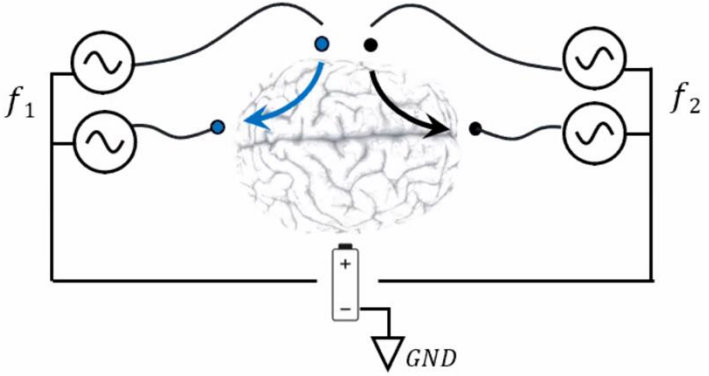
*Due to shared GND and/or voltage bias*




Solution

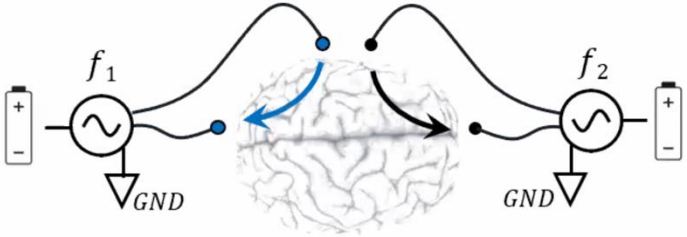
**1. Differential Drive**

*Each current is both injected and sinked.*



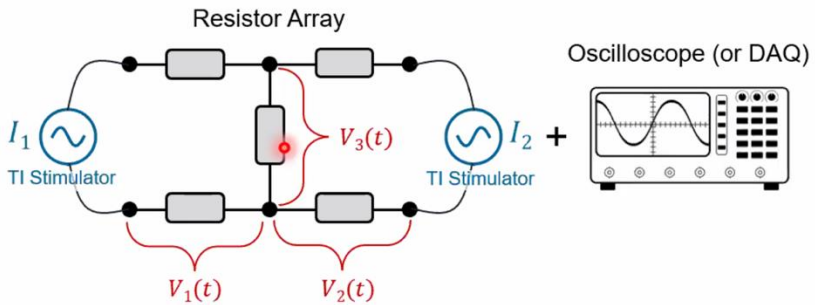

**2. Floating Drive**

*Each current is driven with a separated battery.*



# tTIS – Current source

## Setup

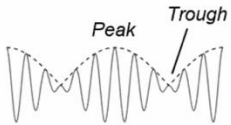



*Parameters: Resistors 1 kΩ , Current 2 mA*

## Analysis

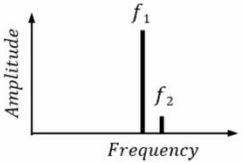
Amplitude Modulation (AM) Depth

Time domain




$$AM_{depth} = \frac{Envelope\ Peak - Envelope\ Trough}{Envelope\ Peak}$$

Frequency domain




$$AM_{depth} = \frac{A(f_2)}{A(f_1)}$$

## Procedure

Measurement of the amplitude modulation (AM) depth $AM_{depth}$ in $V_1(t)$, $V_2(t)$ and $V_3(t)$ waveforms.

## Performance target

$V_1(t)$, $V_2(t)$ $AM_{depth} < 0.01$ and $V_3(t)$ $AM_{depth} > 0.99$.

# tTIS – Stimulators

## Integrated TI stimulator

Examples

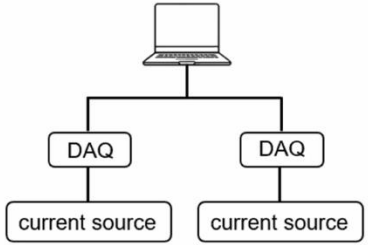
TI Solutions (Switzerland)

NeuroDome (China)

Soterix (USA)

Neuroconn (Germany)

## Assembled TI stimulator




DAQ requirements:

- Sampling rate: >100 kS/s
- Sampling depth: > 12 bits
- Isolated channels

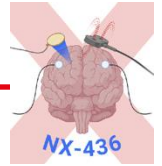
DAQ example:

- Handyscope HS5, TiePie
- USB-6216, National Instruments

Current source examples:

- Linear Current Isolator (LCI), Soterix
- DS5 Isolated Current Stimulator, Digitimer
- Model 2200 Analog Stimulus Isolator, A-M Systems

# tTIS – Stimulators




## Study Start

- Test (do not trust) equipment

  Frequency response, Cross-talk, EEG intermodulation distortion (IMD)

## Session Start

- Measure stimulation voltage output

  If V output ≥ Stimulator V compliance → Stimulation is truncated.

  Troubleshooting: Check electrode-scalp contacts.

- Compute impedance

  If impedance > 5 kΩ → Higher risk of scalp sensation an/or EEG IMD. $\text{Impedance} = \frac{\text{Measured voltage}}{\text{Set current}}$

  Troubleshooting: Check electrode-scalp contacts.

- Measure sensation threshold

  If high sensation → High risk of side-effects and/or sensory confound.

  Troubleshooting: Check electrode-scalp contacts → If persists, operate at lower current values → If persists across participants, test equipment (including waveform inspection)

## Session End

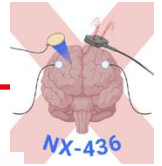
- Repeat stimulation voltage measurement and resistance computation

  To validate that the stimulation was not compromised during the session.

- Test participant blindness

  Perception of stimulation Yes/No & Confidence (e.g., 1-5).

# tTIS – Stimulators




## Study Report

### TI stimulation parameters

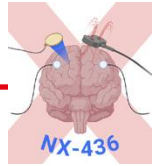
- TI type: standard TI, pulse-TI via frequency shift keying (FSK), pulse-TI via phase shift keying (PSK), pulse width modulation (PWM) TI
- TI sham approach (e.g., ramp up and shortly down)
- TI stimulator (model, manufacturer)
- Current frequencies (Hz, or kHz)
- Current amplitudes (mA; peak-to-zero or peak-to-peak), including ratio.
- Current timing: Duration (s or min), ramping-up (s), ramping-down (s)
- Electrode scalp configuration (using 10-20 or 10-10 system)
- Electrode dimensions* and material (including shape, including electrolyte material)
- Impedance (mean ± std kΩ)
- TI field modelling

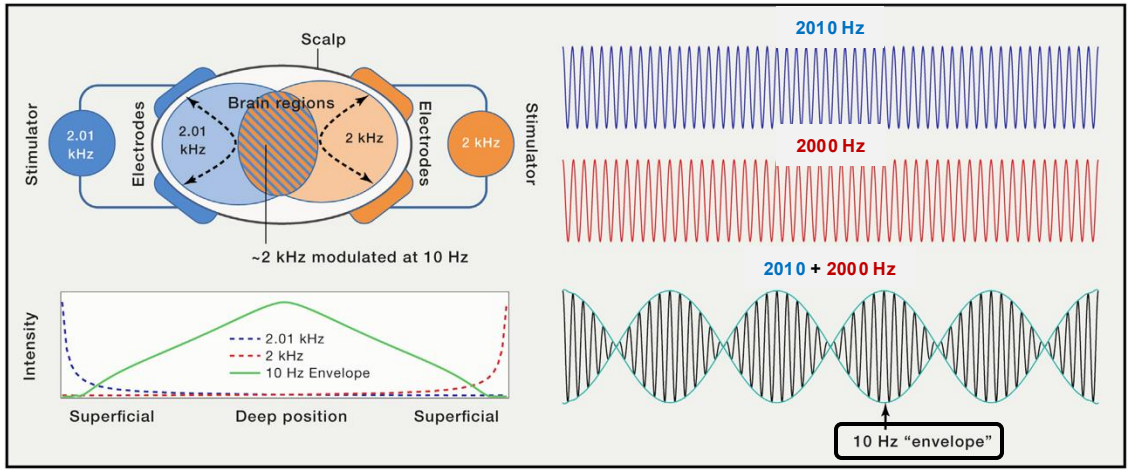
* Critical for scalp electrode current density calculation.

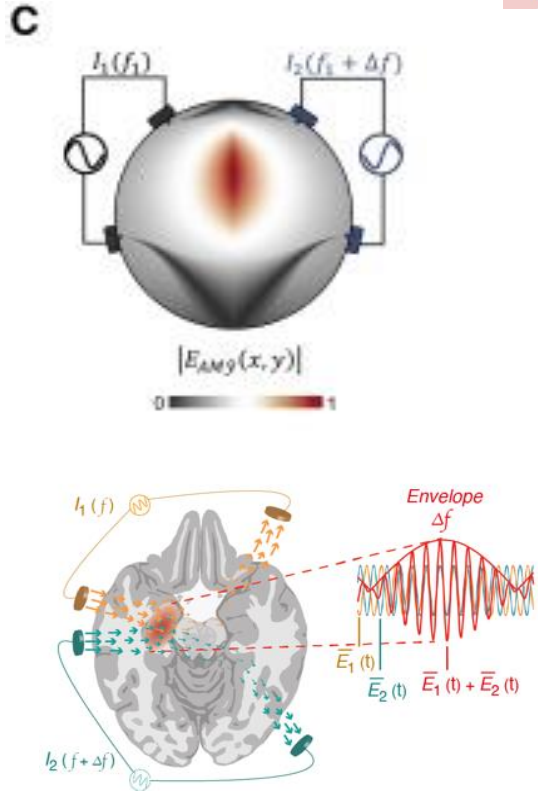
### Participant stimulation perception

- Sensation threshold (mean ± std mA)
- Blindness
- Side-effects

# transcranial Temporal Interference Stimulation (tTIS)



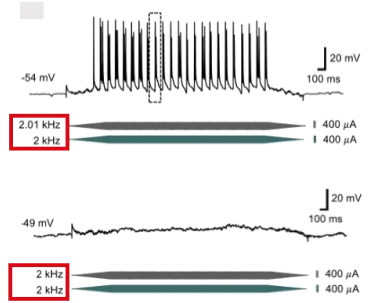




Grossman *et al.*, Cell 2017; Dmochowsk *et al*. 2017 Cell

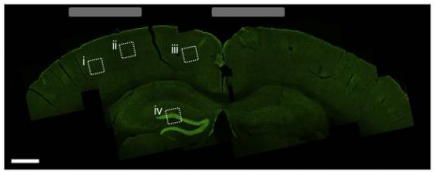
# tTIS – animal /cadaver work

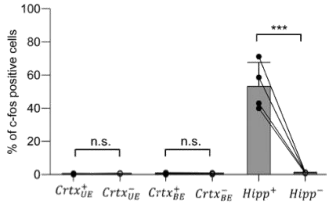
## Rodents

- Envelope modulated fields → synchronized neural firing
- Pure high frequency stimulation → no firing



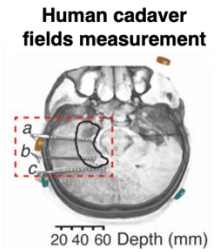

- Stimulation of deep structure does not engage overlying tissues

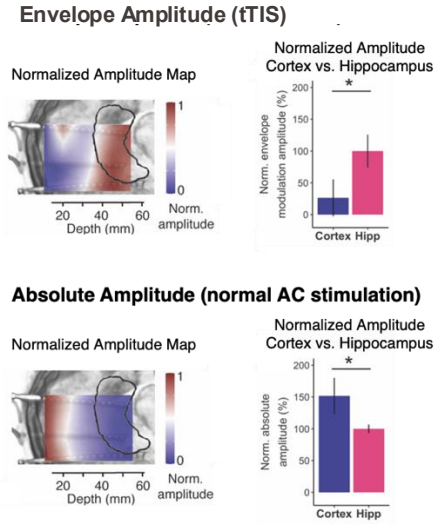



Grossman *et al.*, **Cell** 2017

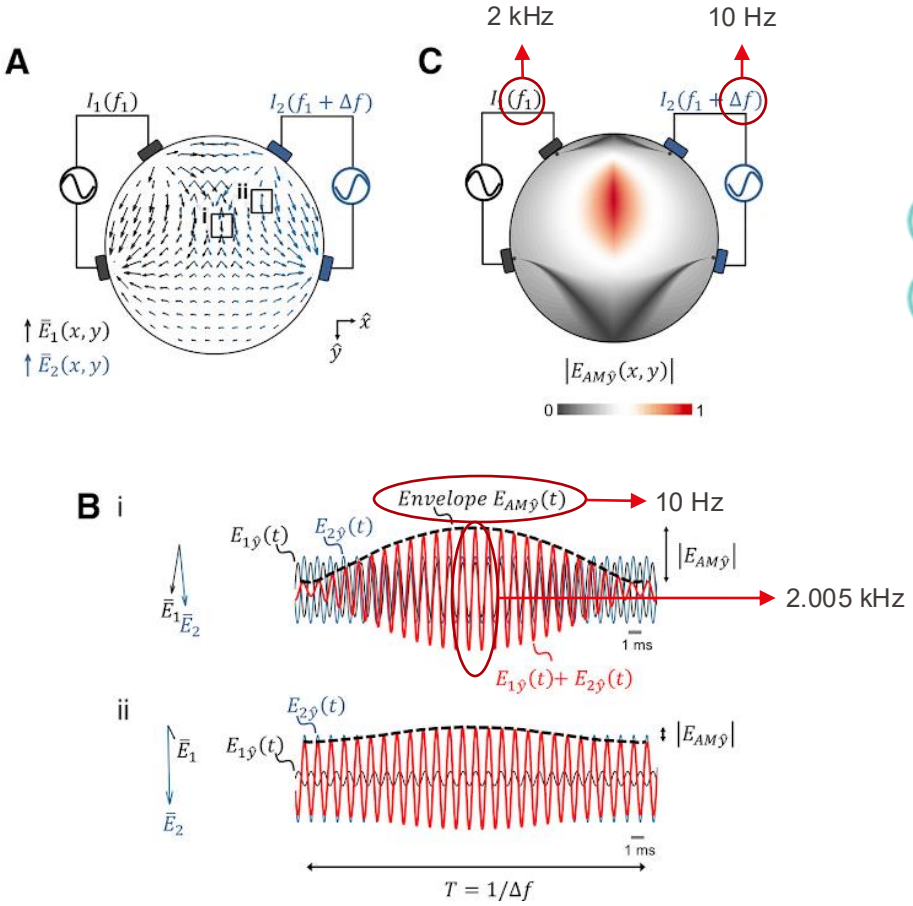
## Human cadaver



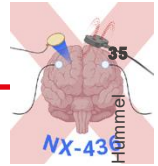

Violante *et al.*, **Nat Neurosci** 2023

# Transcranial Temporal Interference Stimulation (tTIS)

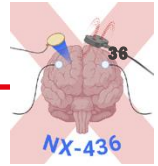



- Good **spatial** resolution
- Able to **reach deep brain structures**

Grossman et al., Cell 2017



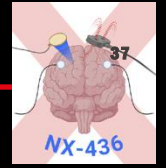

Friedhelm C. Hummel

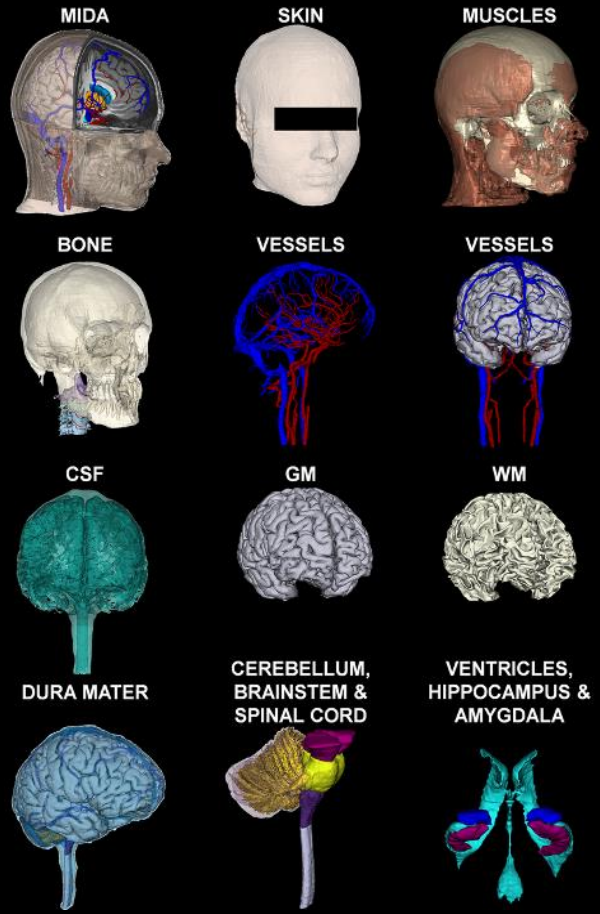



## Questions to solve

Localization
Stimulation parameters
Focality of stimulation effects
Validation of stimulation effects

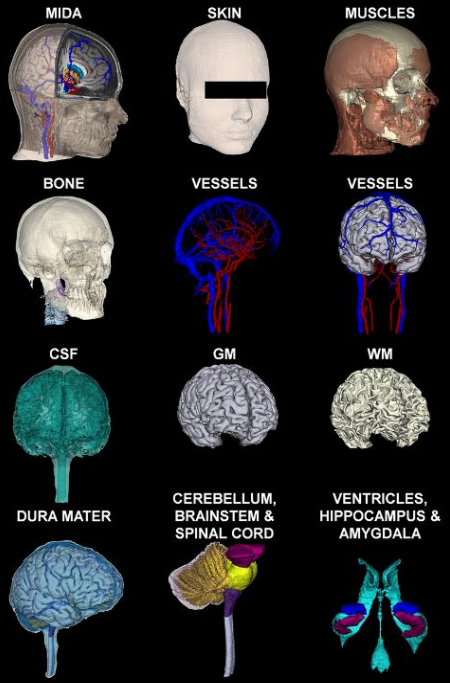
# Simulations – anatomical model

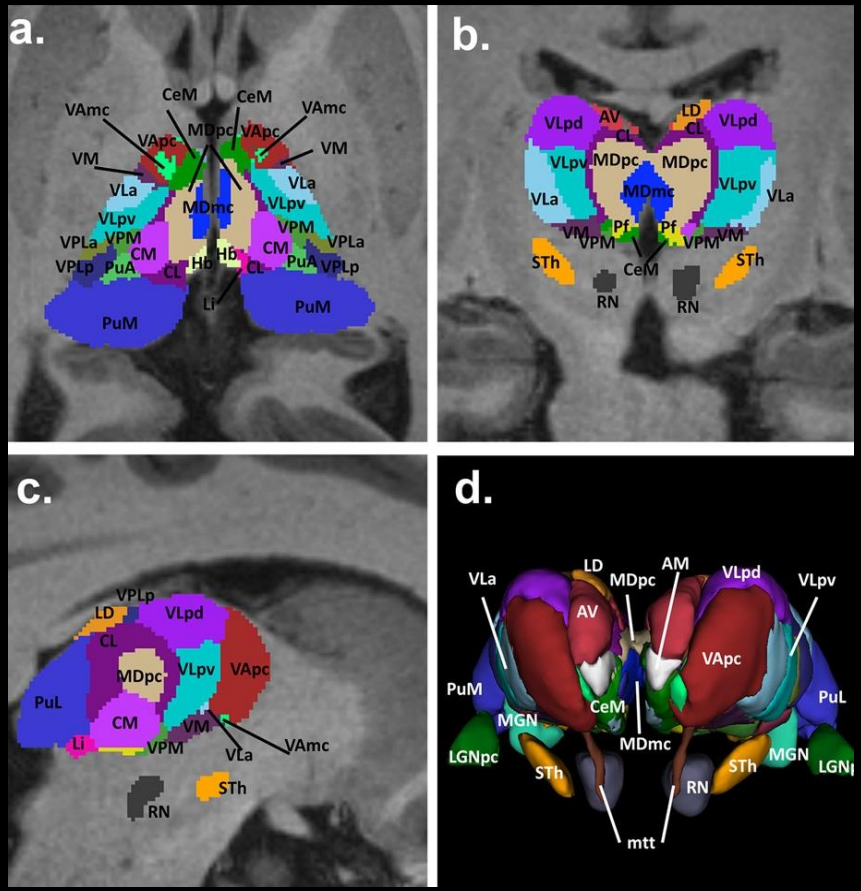


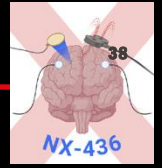




Iacono MI *et al.* (2015).: PLoS one **10**(4): e0124126

# Simulations – anatomical model

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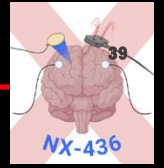
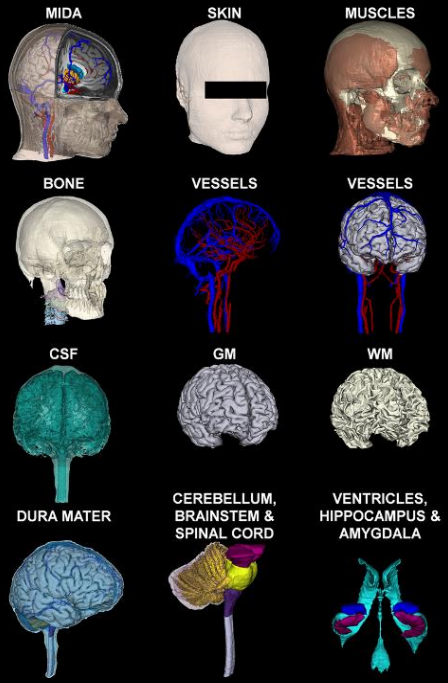
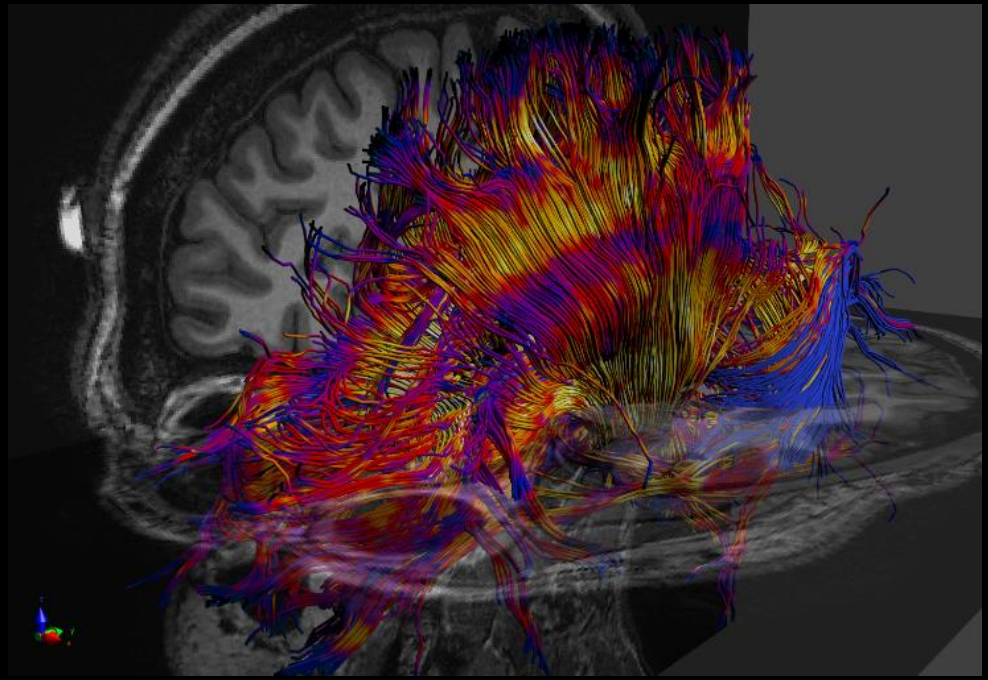
# Simulations – anatomical model



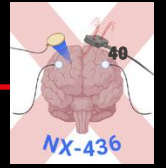

Further informing the model



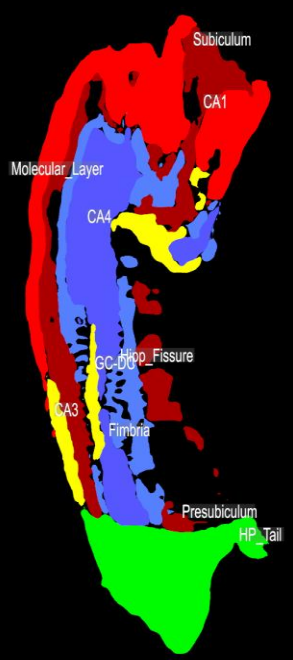
Diffusion tensor imaging (DTI) to obtain information on tissue anisotropy and fiber orientation

Iacono MI *et al.* (2015).: PLoS one **10**(4): e0124126

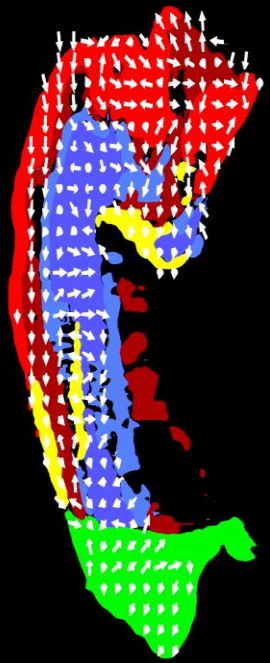
# Simulations – anatomical model



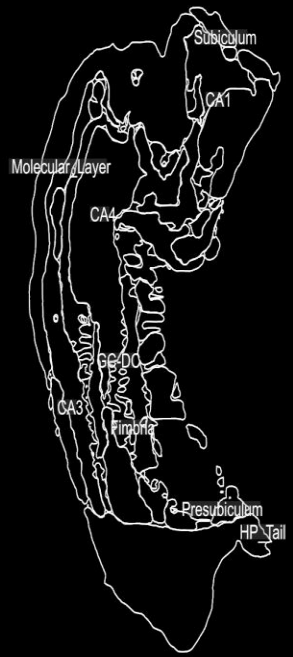

## Hippocampus simulations (MIDA model)



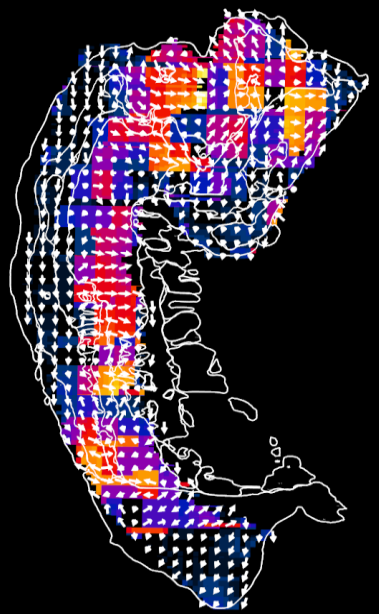

Labels

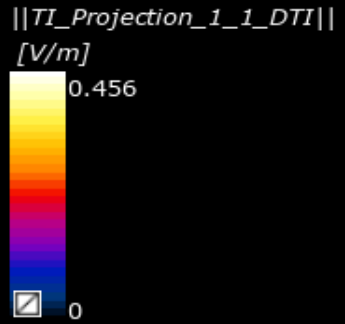


DTI Directions




Contours



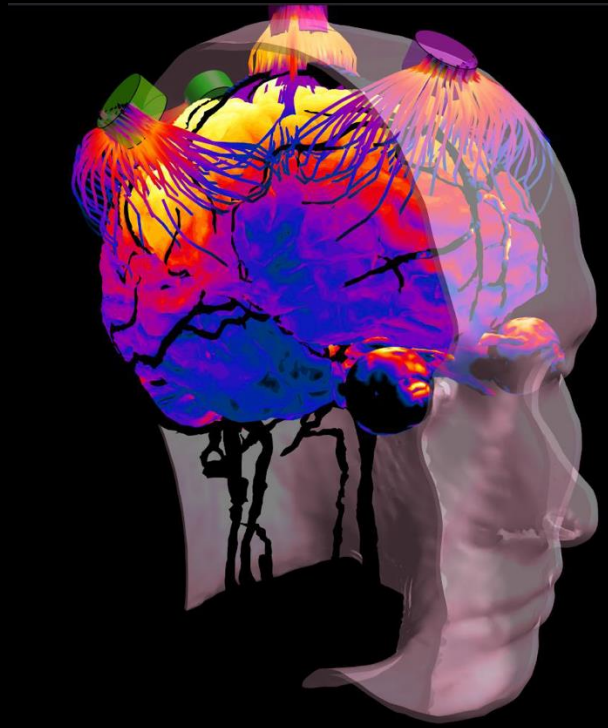



TI stimulation

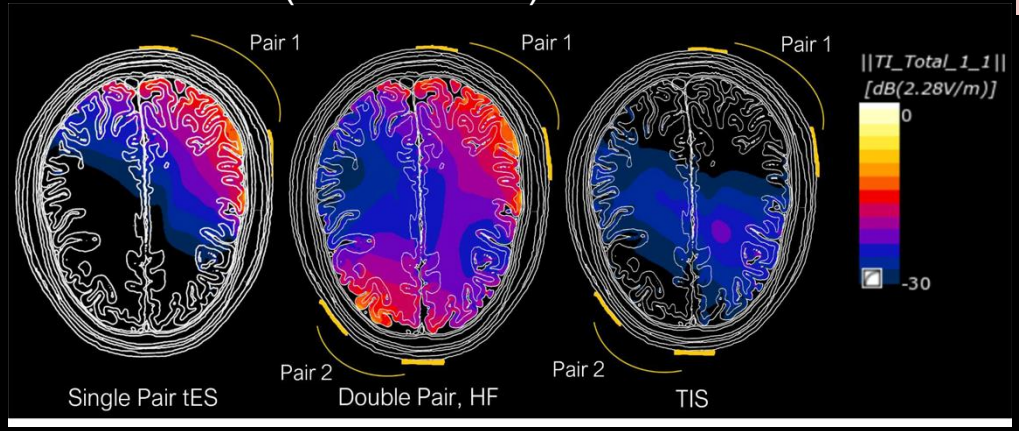
Courtesy E. Neufeld

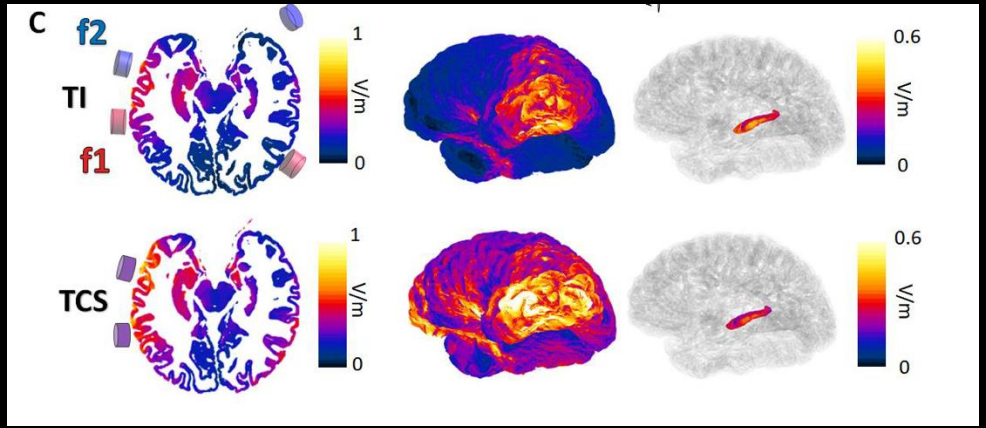
# Simulations – anatomical model

## Whole brain simulations (MIDA model)



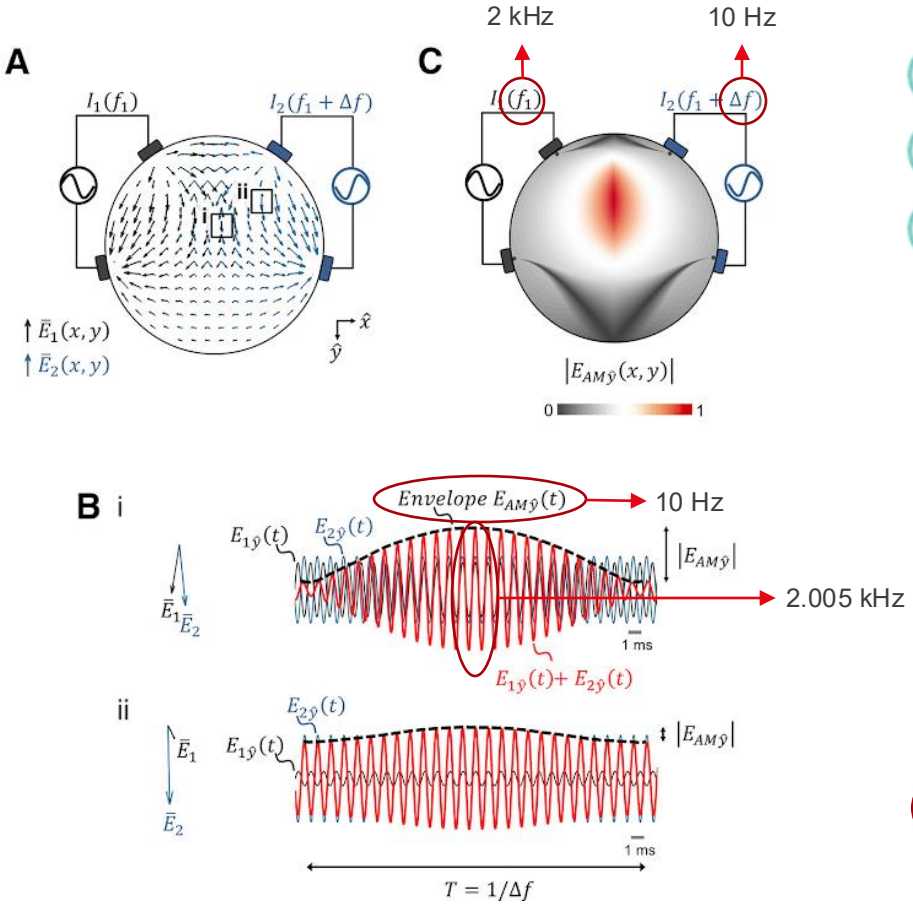
High resolution head model (MIDA, SIM-4-Life) in cooperation with E. Neufeld (IT'IS, ETH Zürich)



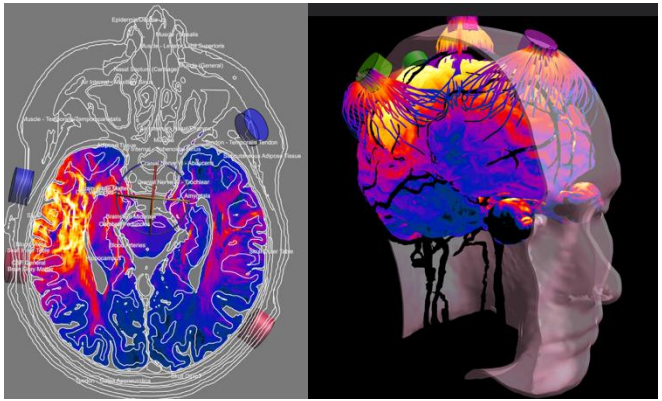

Courtesy E. Neufeld

# tTIS – human translation?



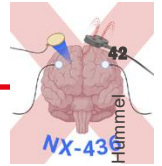

Grossman *et al.*, Cell 2017

- Good **spatial** resolution
- Able to **reach deep brain structures**
- **Simulations** crucially important for targeting



Courtesy E. Neufeld

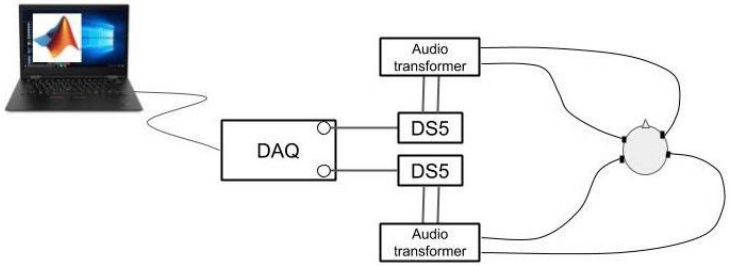
? **Feasible, effective** in humans




Friedhelm C. Hummel

# tTIS - equipment

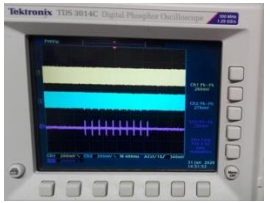




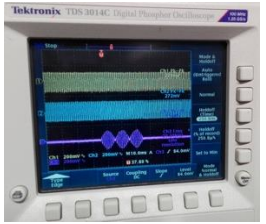

**Details component parts:**

- DS5: Digitimer DS5 Isolated Bipolar Current Stimulator
- DAQ: National Instruments DAQ model USB-6216 (16-Bit, 400 kS/s, BNC, Bus-Powered)
- Audio transformer: Hammond Manufacturing 1140-LN-B.

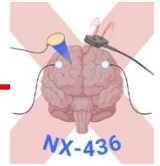
## Theta bursts waveforms








- 2kHz carrier frequency,
- 10 bursts at 5Hz,
- 3 pulses at 100Hz




www.nature.com/mp

Molecular Psychiatry

ARTICLE

Check for updates

# Placebo effects and neuromodulation for depression: a meta-analysis and evaluation of shared mechanisms

Matthew J. Burke[1,2,3,12]✉, Sara M. Romanella[3,4,12], Lucia Mencarelli[3,4], Rachel Greben[2], Michael D. Fox[3,5,6], Ted J. Kaptchuk[7], Alvaro Pascual-Leone[8,9,10] and Emiliano Santarnecchi[3,11]✉

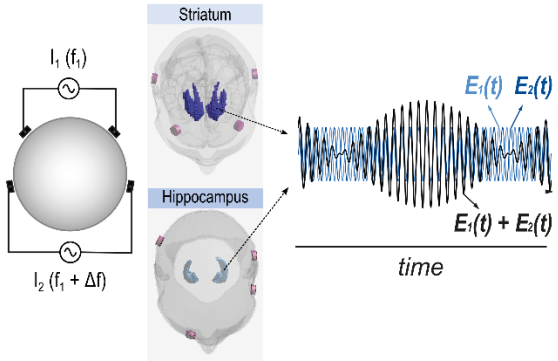
# Blinding – perceived sensations

A.

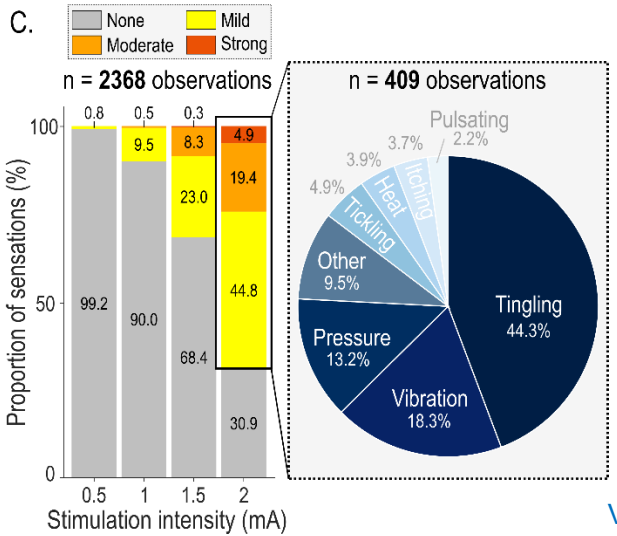
| Exp number | Subject number | Target | Population | tTIS Type | Session number/exp | Session number total | Sensation data points at 2mA |
|---|---|---|---|---|---|---|---|
| 1 | 15 | Striatum | Young | iTBS/HF | 4 | 59* | 118 |
| 2 | 15 | Striatum | Young | iTBS/HF | 2 | 30 | 60 |
| 3 | 8 | Striatum | Young | iTBS/cTBS/HF | 3 | 24 | 72 |
| 4 | 24 | Striatum | Young | 20Hz/80Hz/Sham | 1 | 24 | 72 |
| 5 | 15 | Striatum | Older | iTBS/HF | 2 | 30 | 60 |
| 6 | 30 | Hippocampus | Young | iTBS/cTBS/HF or Sham** | 1 | 30 | 90 |
| 7 | 15 | Hippocampus | Older | cTBS/HF | 2 | 30 | 60 |
| 8 | 15 | Hippocampus | TBI | iTBS/Sham | 2 | 30 | 60 |

Total:
- **119** participants
- **257** sessions
- **592** sensation data points at 2mA

B.

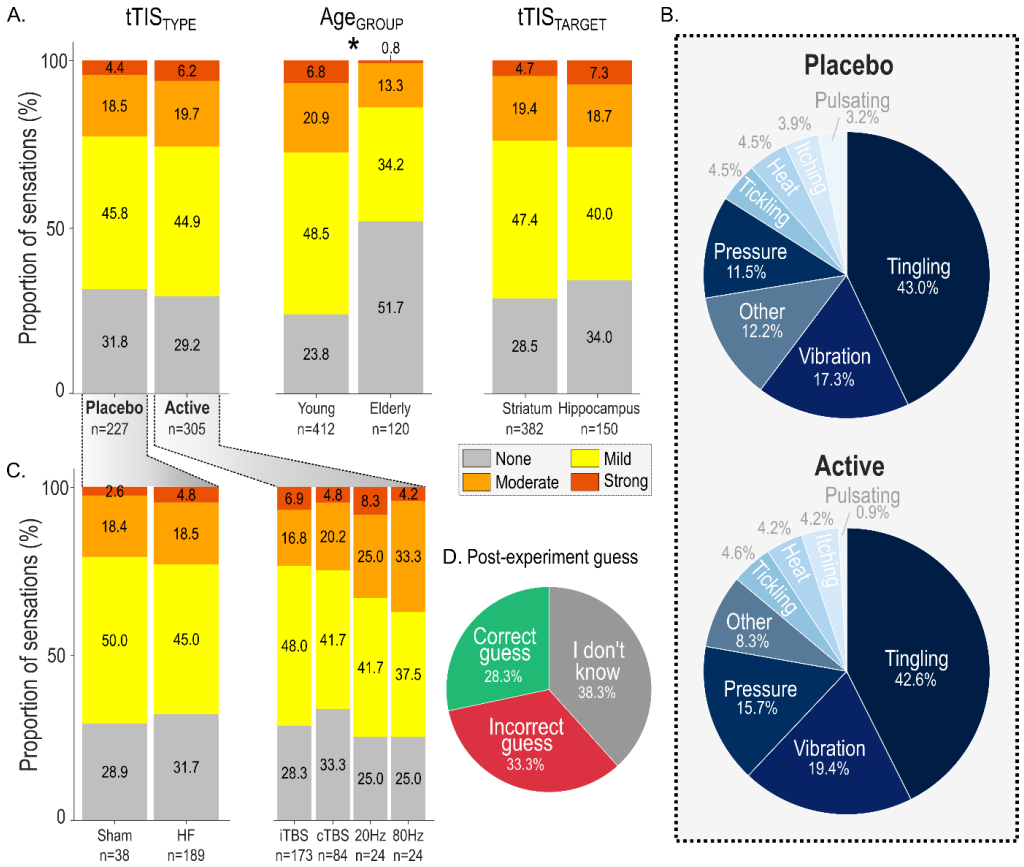



C.



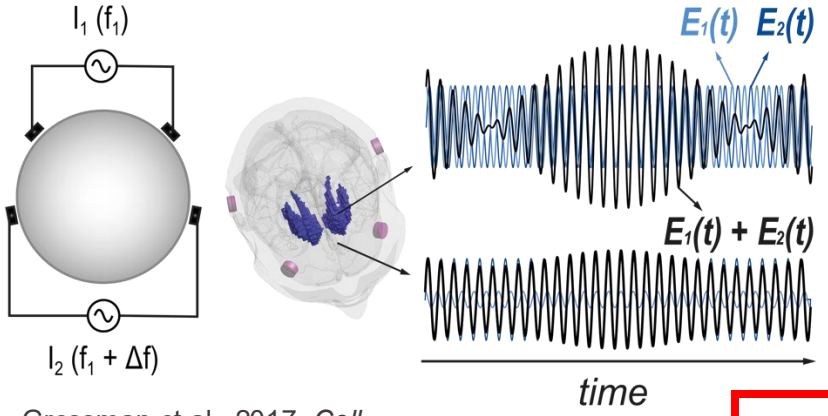

Vassiliadis *et al.*, JNE 2024

# Blinding – perceived sensations




Vassiliadis *et al.*, JNE 2024

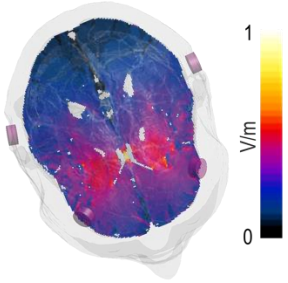
# transcranial Temporal Interference Stimulation (tTIS)

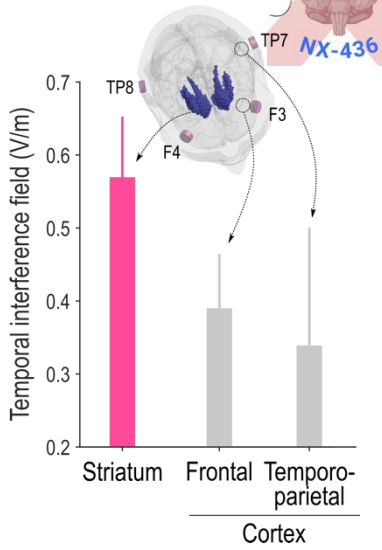



Grossman et al., 2017, *Cell*

First application of deep tTIS in humans

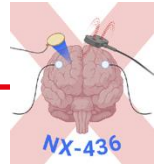
Simulations on high resolution head model (collab. Prof Neufeld)



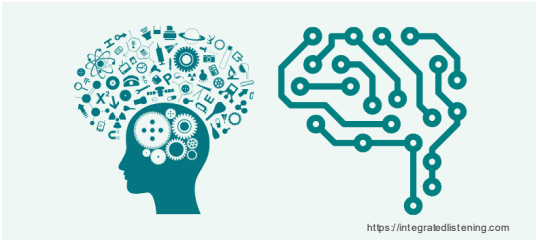




- Animal model validation (Grossman et al., 2017)
- Application on cortical structures in humans (Ma et al., 2021)
- Cadaver work (Violante et al., 2023)

# Stimulation protocols - tTIS

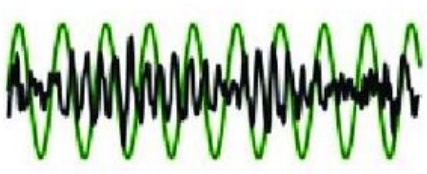



## Neuroplasticity



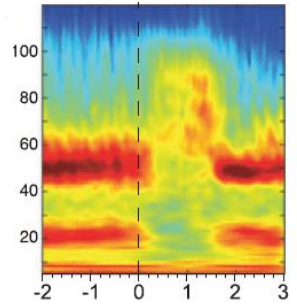

Wessel, Beanato *et al.* (2023) Nature Neuroscience
Beanato, Moon *et al.* (2024) Science Advances

## Neuronal entrainment



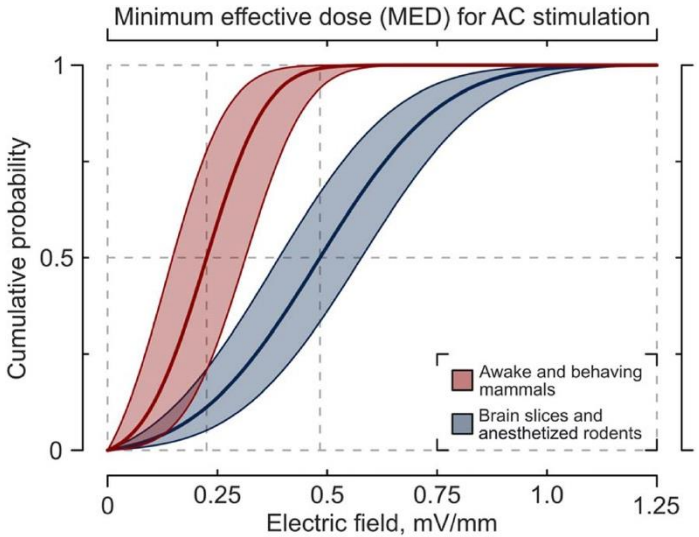
Violante *et al.* (2023) Nature Neuroscience

## Interference

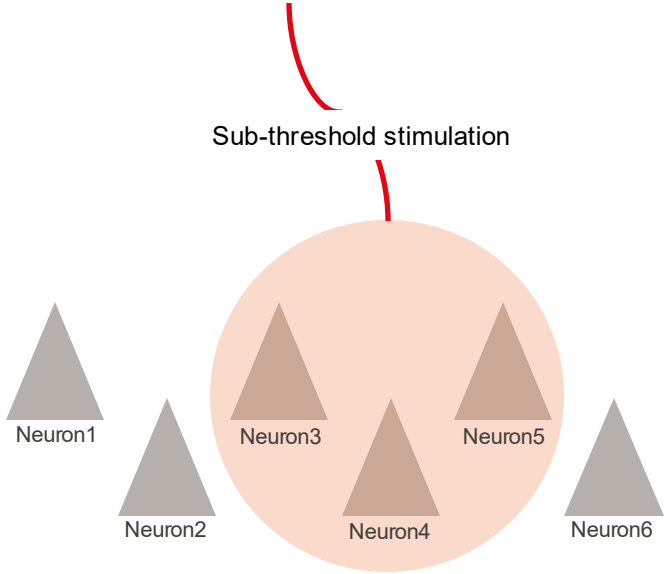



Vassiliadis *et al.* (2024) Nature Human Behavior

# Co-activation



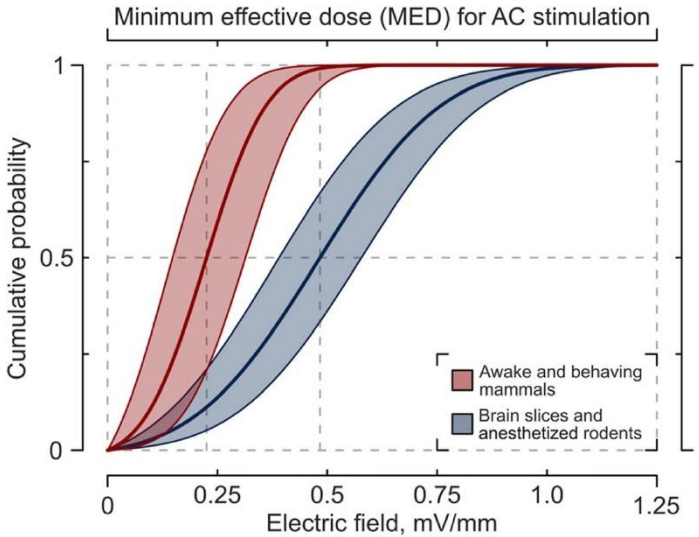

Alekseichuk, 2022



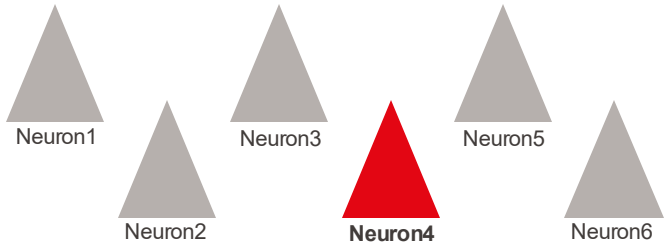

**No stimulation effect**

**Subthreshold** stimulation requires **co-activation** (Fritsch *et al*. 2010)

# Co-activation

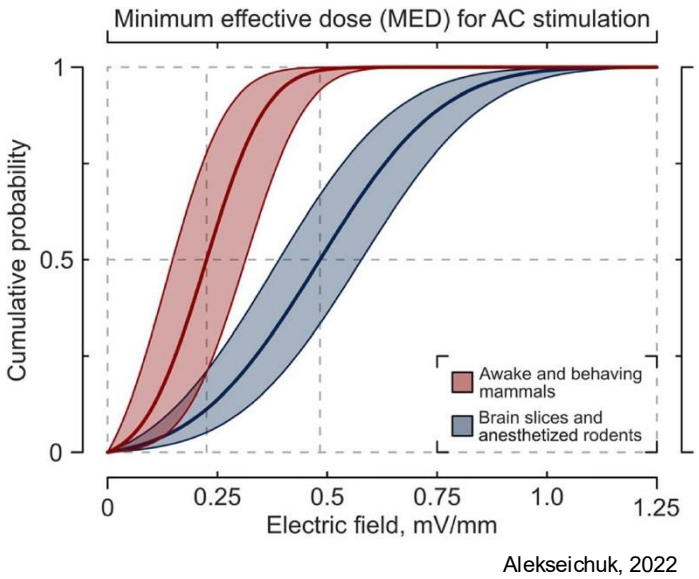



Alekseichuk, 2022

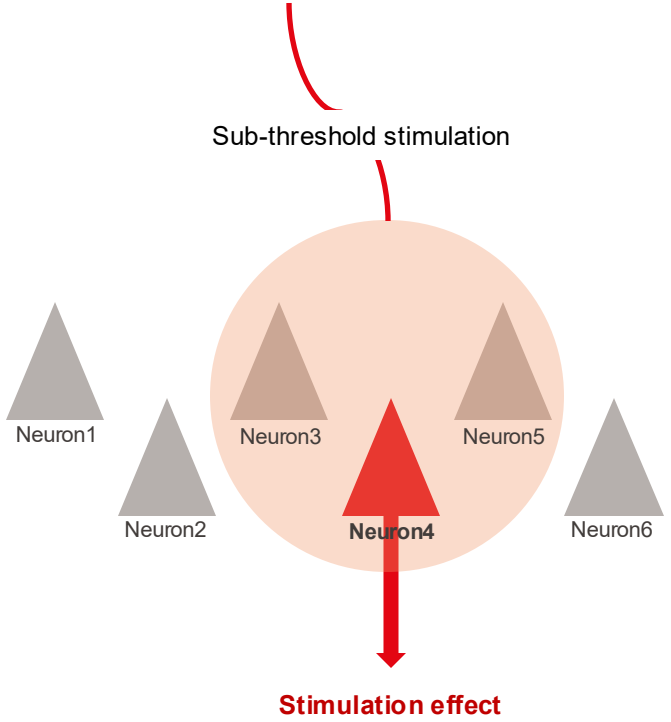



**Subthreshold** stimulation requires **co-activation** (Fritsch *et al.* 2010)

# Co-activation



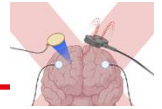

Alekseichuk, 2022



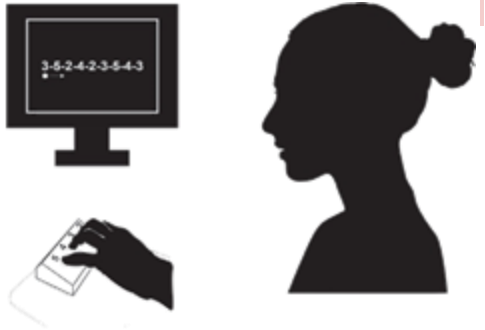

**Subthreshold** stimulation requires **co-activation** (Fritsch *et al.* 2010)

Co-activation **steers** the stimulation effects

# Theta burst stimulation (TBS)

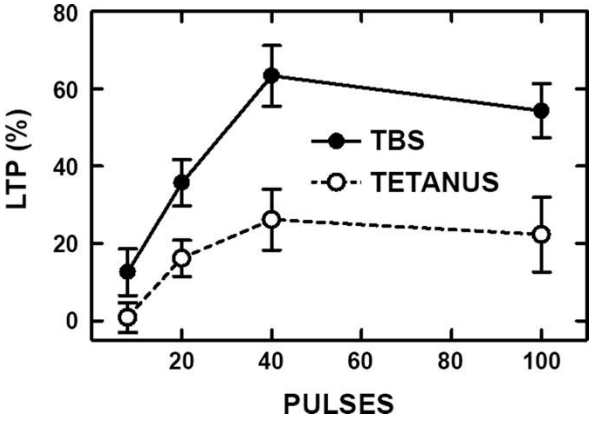


## Striatum

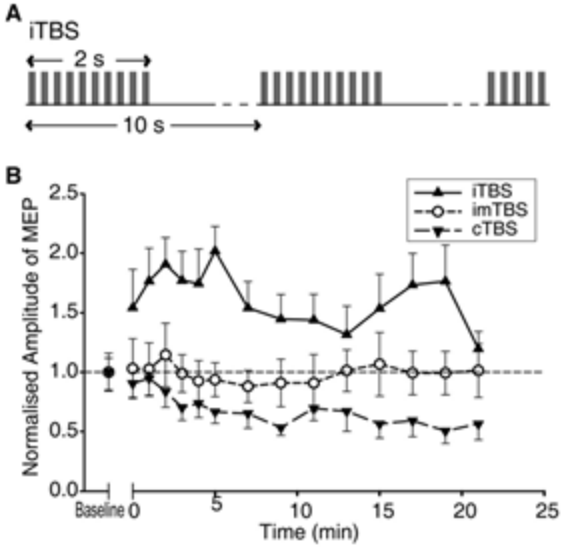


Zimerman *et al.* 2013, 2014; Draaisma *et al.* 2022, Maceida *et al.* 2022; Wessel *et al.* 2023

## Hippocampal field CA1




Larson& Munkasy 2015
Andersen 1991

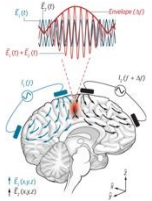



Huang *et al.* 2005

+

## Hippocampus

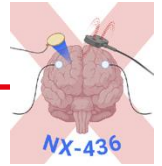
Moon *et al.* 2022

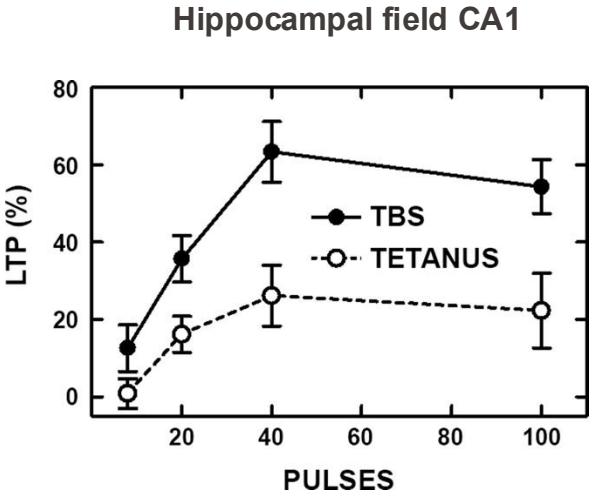


- **iTBS-TI**: 2 tACS channels @ 2kHz and 2.1kHz creating an interference wave with an envelope mimicking a theta-burst, with trains of 3 peaks @100Hz repeated every 200 ms applied for 2sec and followed by 8 sec of HF-control

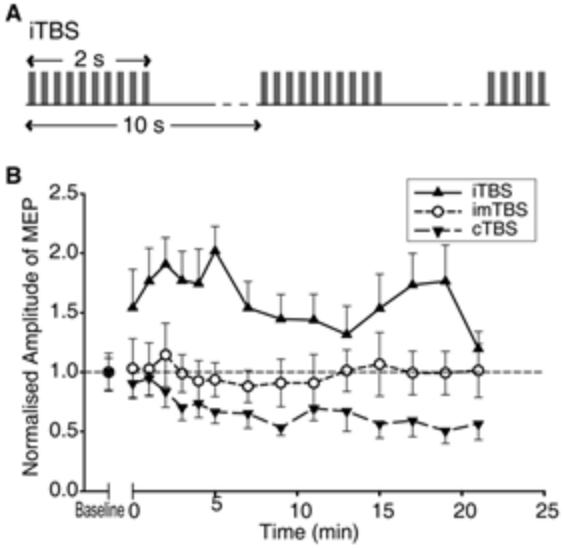
- **HF-control**: 2 tACS channels @ 2kHz without shift in frequencies

# Theta burst stimulation (TBS)




Larson& Munkasy 2015
Andersen 1991




Huang *et al.* 2005

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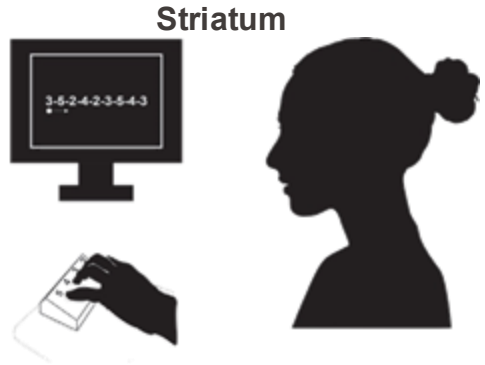
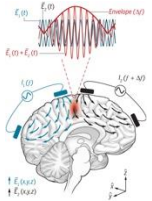



Zimerman *et al.* 2013, 2014; Draaisma *et al.* 2022, Maceida *et al.* 2022; Wessel *et al.* 2023



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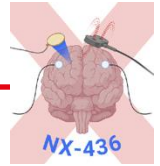
# Neuroplasticity – iTBS tTIS



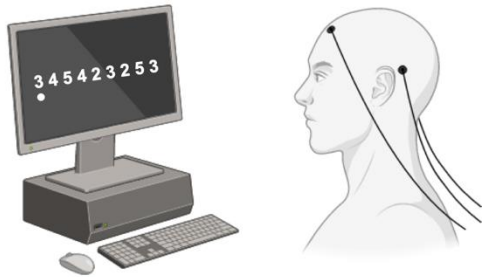

nature neuroscience

Article

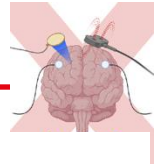
https://doi.org/10.1038/s41593-023-01457-7

## Noninvasive theta-burst stimulation of the human striatum enhances striatal activity and motor skill learning

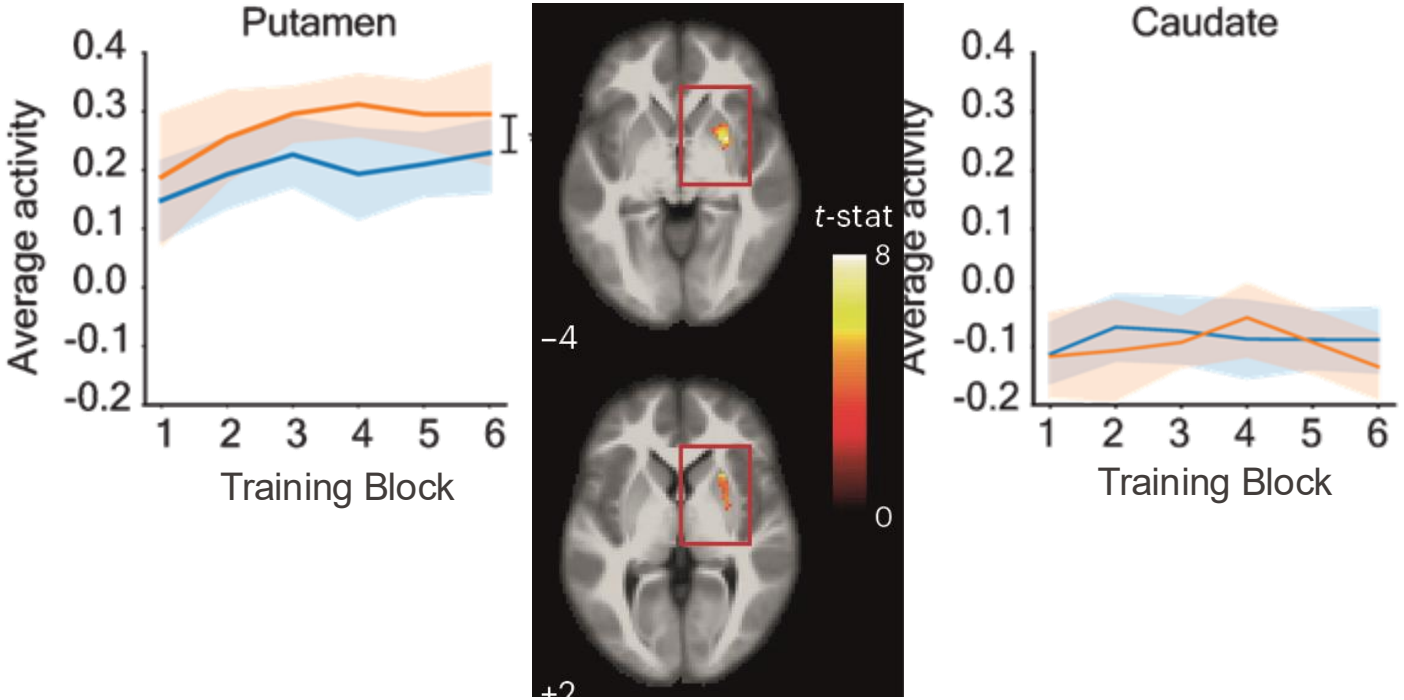
Wessel, Beanato *et al.* 2023




# Topographic specificity of the stimulation effects



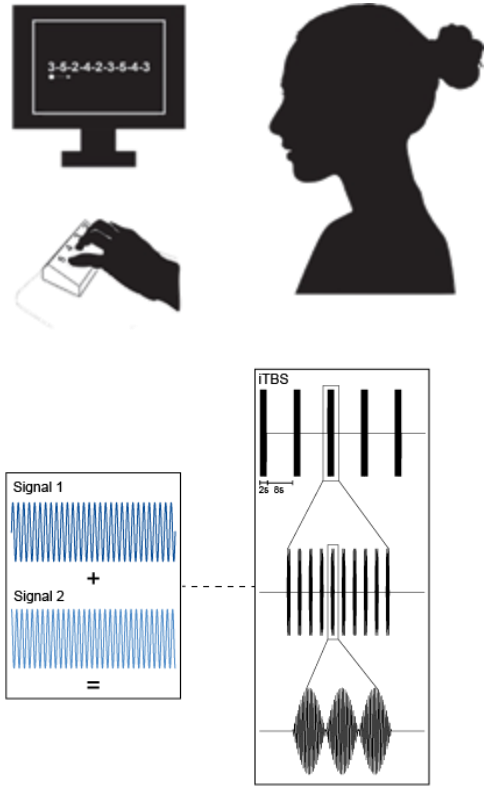
Associated with tTIS induced behavioral improvement

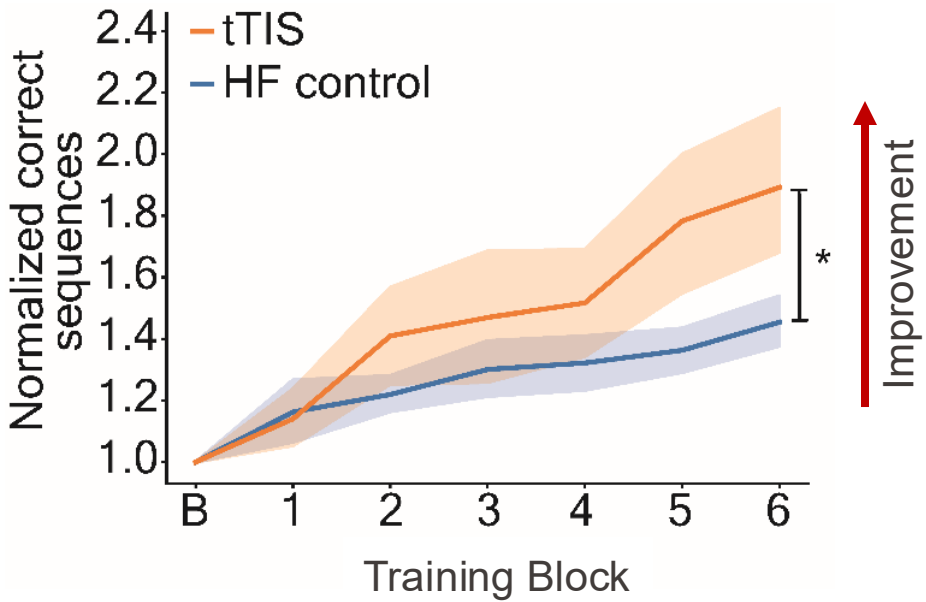



**Stimulation effects are specific to the subregion already involved in the task**

Wessel, Beanato *et al.* (2023) Nature Neuroscience

# Validation striatal tTIS - healthy older



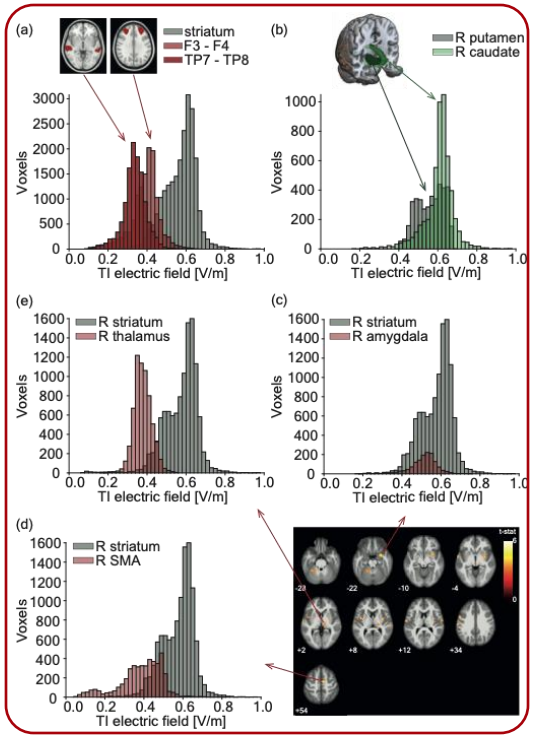




**Striatal TBS-tTIS can modulate striatal activity and improve motor sequence learning**

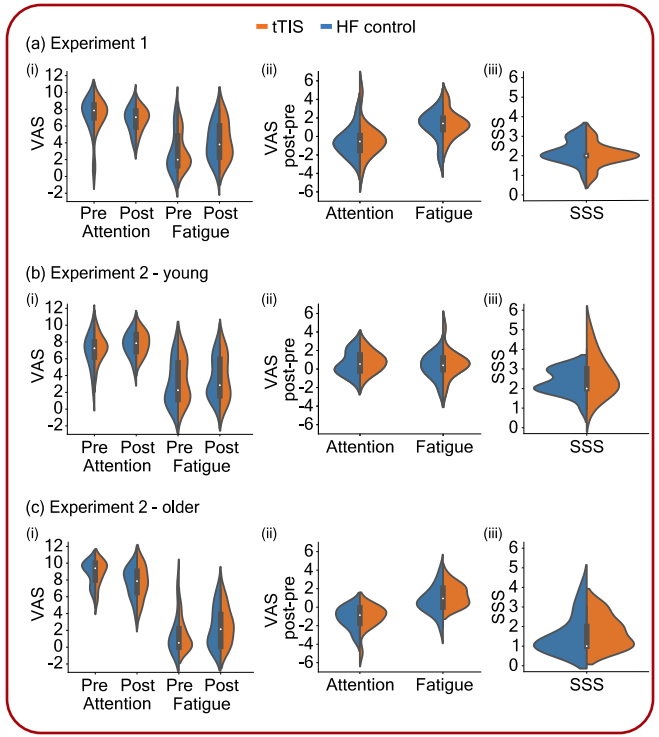
Wessel*, Beanato* et al., 2023, *Nature Neuroscience*

# Potential influential factors

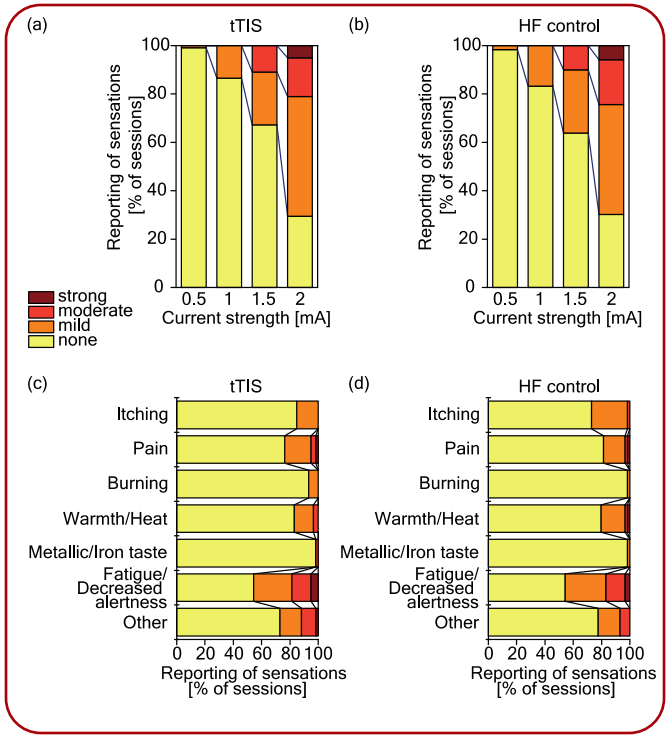
## Focality of field strength




## Attention, Fatigue

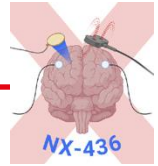


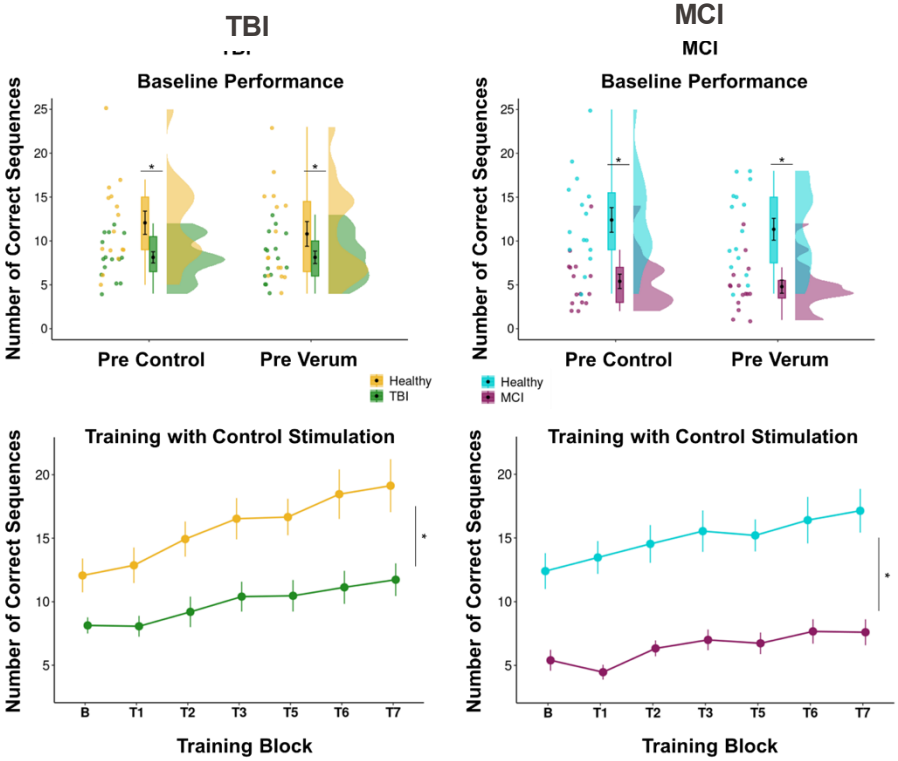

## Perceived sensations




Wessel*, Beanato* et al., 2023, *Nature Neuroscience*

# Transdiagnostic clinical translation



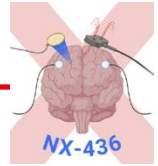




- Different neurological disorders show (motor) learning deficits (Stroke, TBI, MCI, PD)
- Despite the different underlying pathophysiological mechanisms
  - TBI: frontal-executive (e.g. Kozlowksi *et al.* 2013)
  - MCI: memory related (e.g. Koppelmans *et al.* 2022)
  - Stroke: motor control related (e.g. Koch *et al.* 2025)

  the striatum is a core part of the learning process and these networks

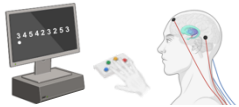
Ploumitsakou*, Beanato* *et al.*, in preparation

# Transdiagnostic approach - Enhancing Learning




TBI (n=15)

MCI (n=15)



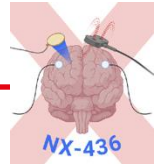
Striatal tTIS

Motor Learning
Striatal tTIS or Control
Cross-over design

- Training
- Post - assessment
- Follow-up 1 (90 min)
- Follow-up 2 (24h)

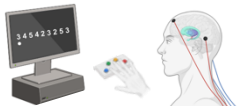
Ploumitsakou*, Beanato* *et al.*, in preparation

# Transdiagnostic approach - Enhancing Learning




TBI

MCI



Striatal tTIS

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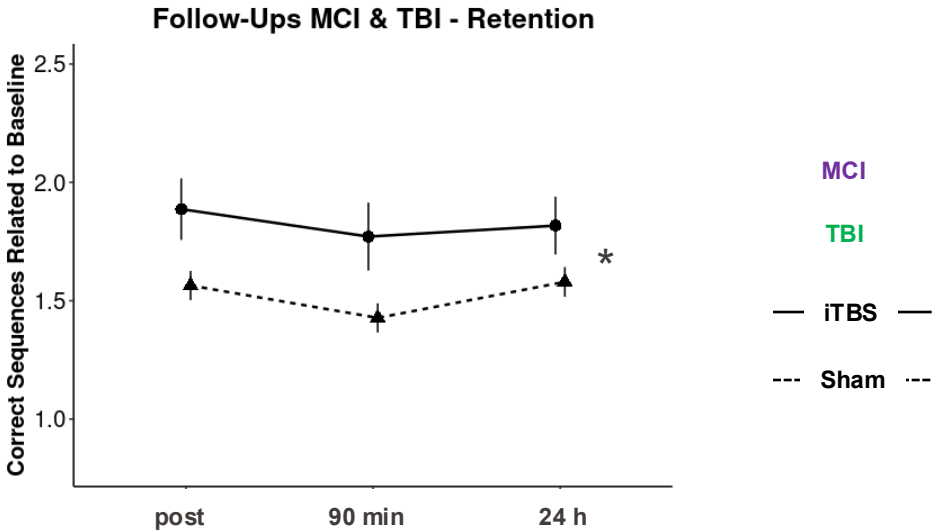
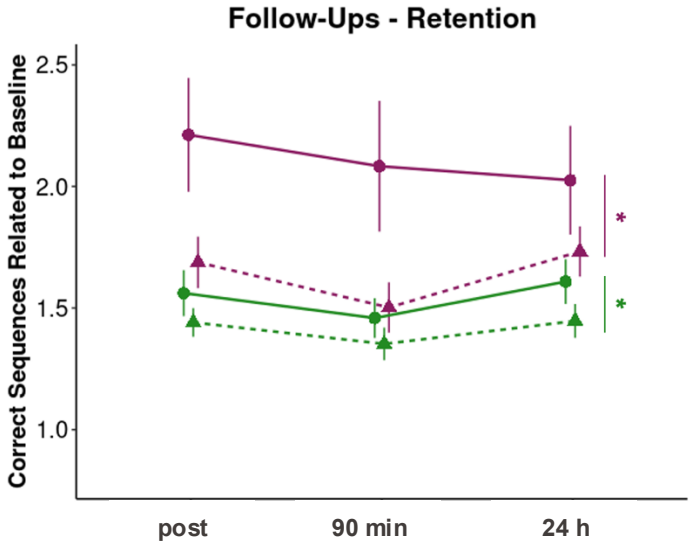
- Follow-up 2 (24h)

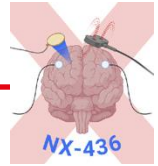



Striatal tTIS led to **improved** skill acquisition with effects that **persisted** for at least 24h

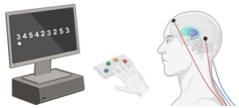
Ploumitsakou*, Beanato* *et al.*, in preparation

# Transdiagnostic approach - Enhancing Learning




TBI

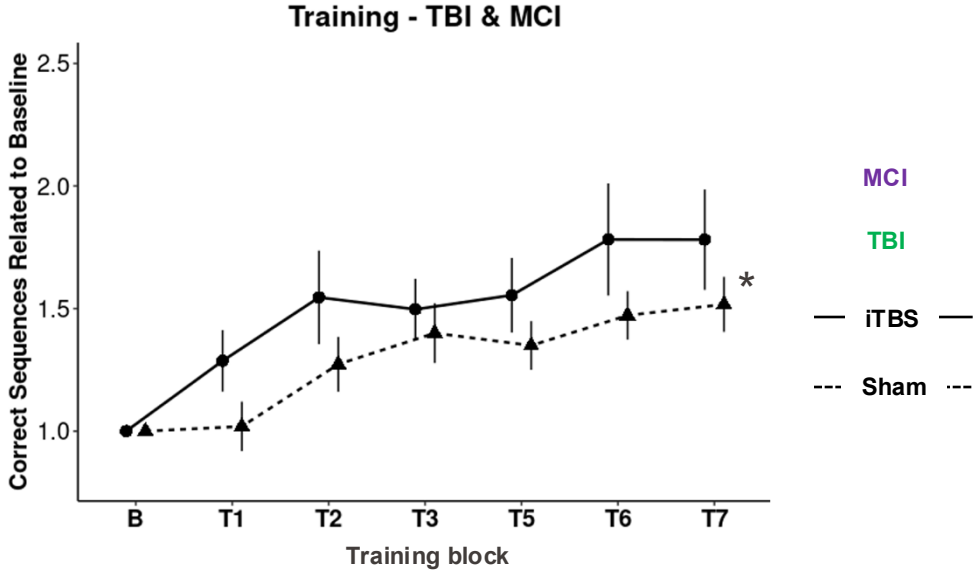
MCI

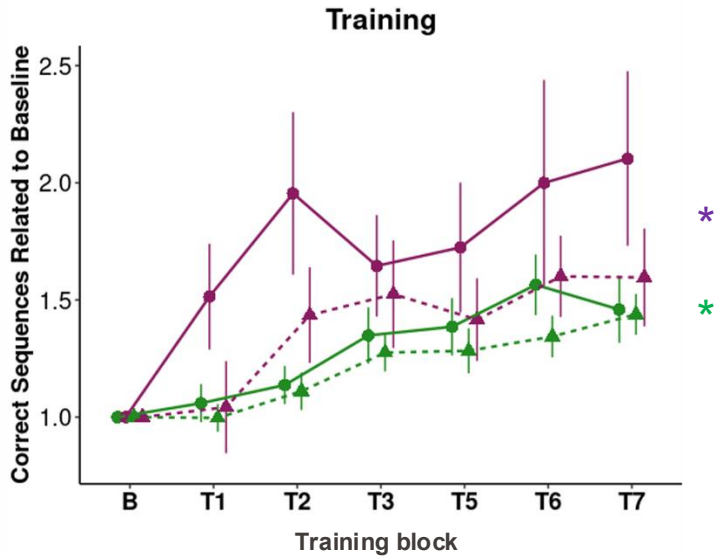


Striatal tTIS

Motor Learning
Striata ItTIS or Control
Cross-over design

- Training
- Post - assessment
- Follow-up 1 (90 min)
- Follow-up 2 (24h)

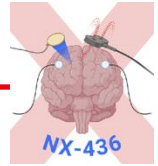



Striatal tTIS led to **improved** training effects

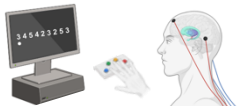
Ploumitsakou*, Beanato* *et al.*, in preparation

# Transdiagnostic approach - Enhancing Learning




TBI

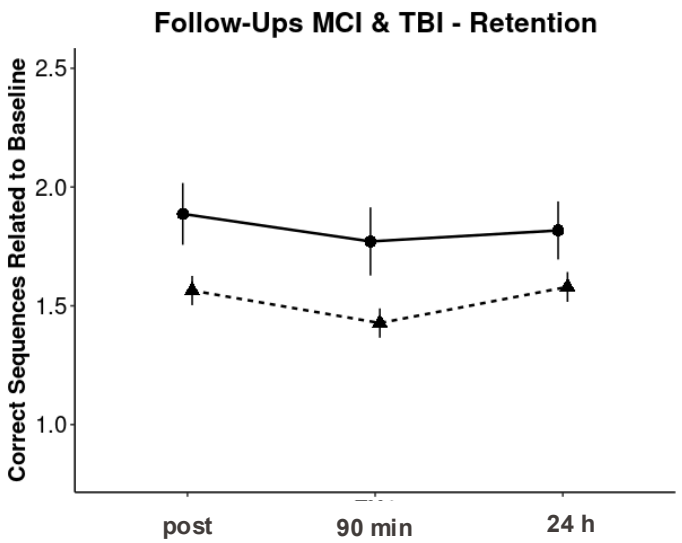
MCI

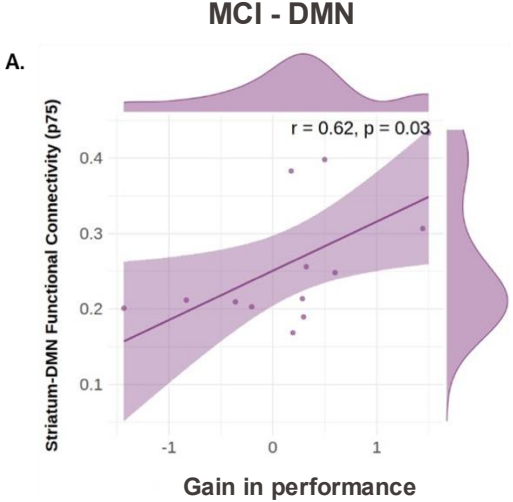


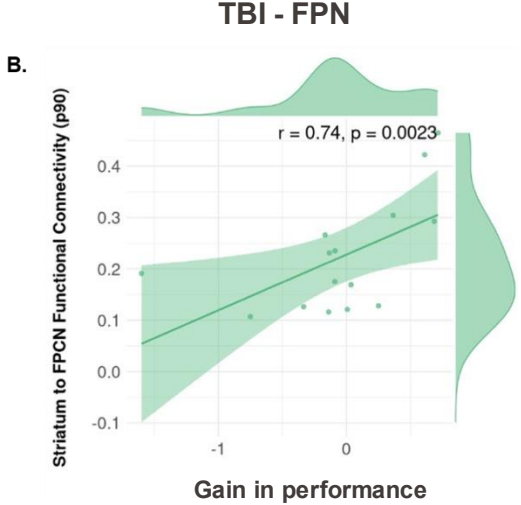
Striatal tTIS

**Motor Learning**
**Striata ltTIS or Control**
**Cross-over design**

- Training
- Post - assessment
- Follow-up 1 (90 min)
- Follow-up 2 (24h)



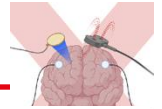



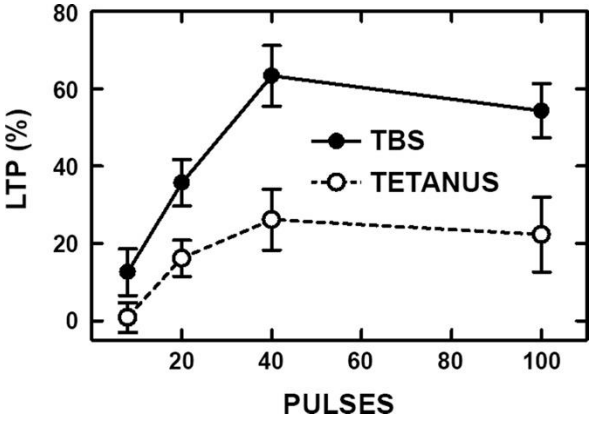

The effect of striatal tTIS was associated with the functional **connectivity** of **disease relevant** underlying **networks**

Ploumitsakou*, Beanato* *et al.*, in preparation

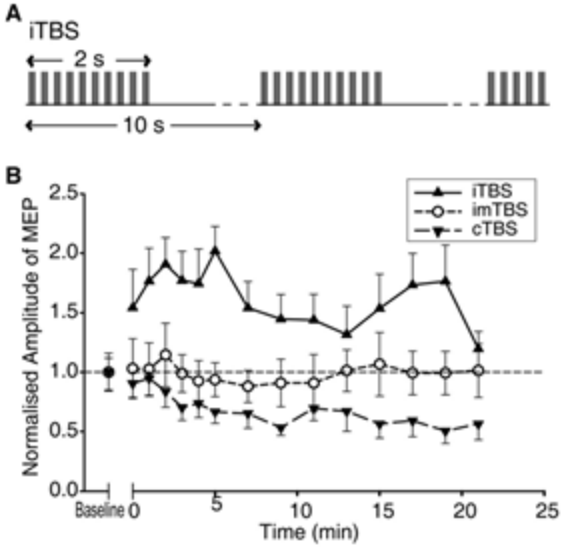
# Theta burst stimulation (TBS)



Hippocampal field CA1




Larson& Munkasy 2015
Andersen 1991

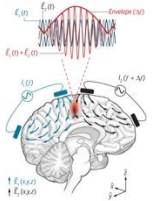



Huang *et al.* 2005

+

Hippocampus

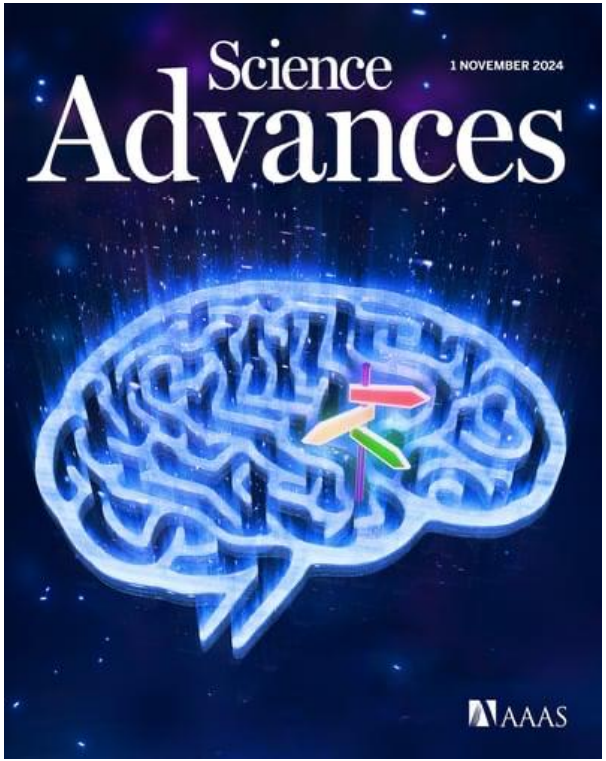
Moon *et al.* 2022

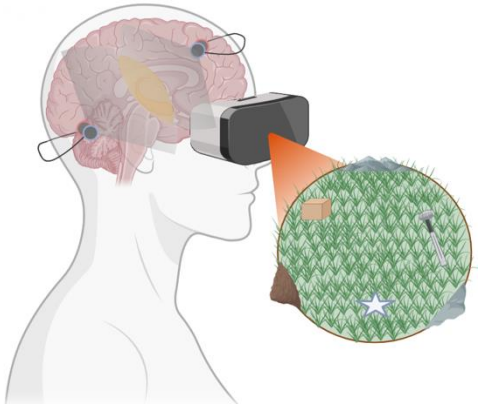


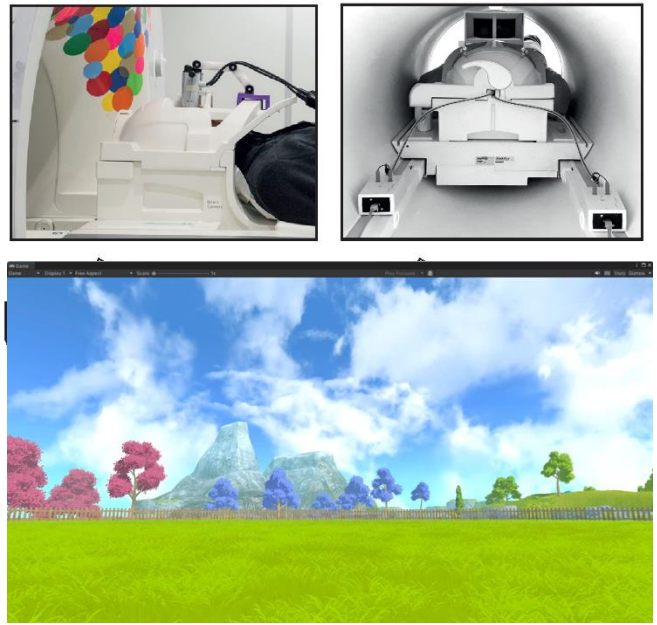
- **iTBS-TI**: 2 tACS channels @ 2kHz and 2.1kHz creating an interference wave with an envelope mimicking a theta-burst, with trains of 3 peaks @100Hz repeated every 200 ms applied for 2sec and followed by 8 sec of HF-control

- **HF-control**: 2 tACS channels @ 2kHz without shift in frequencies

# Non-invasive DBS - memory

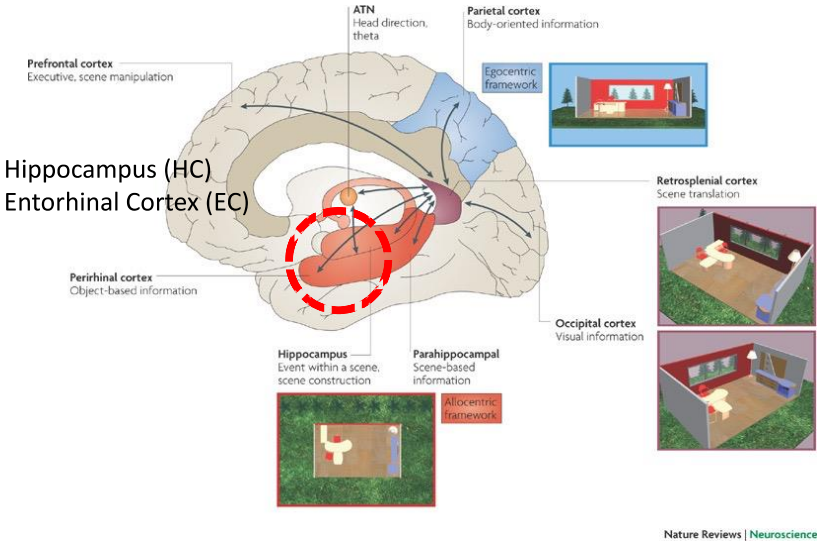


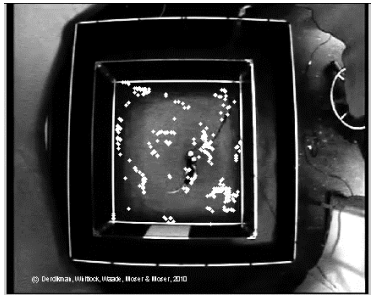


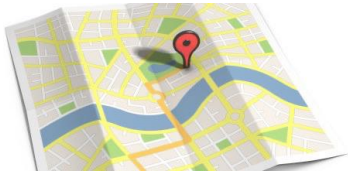
Beanato, Moon *et al. Science Advances* (2024)

# Plasticity-inducing tTIS during spatial memory




- Grid cells in Entorhinal cortex (EC)

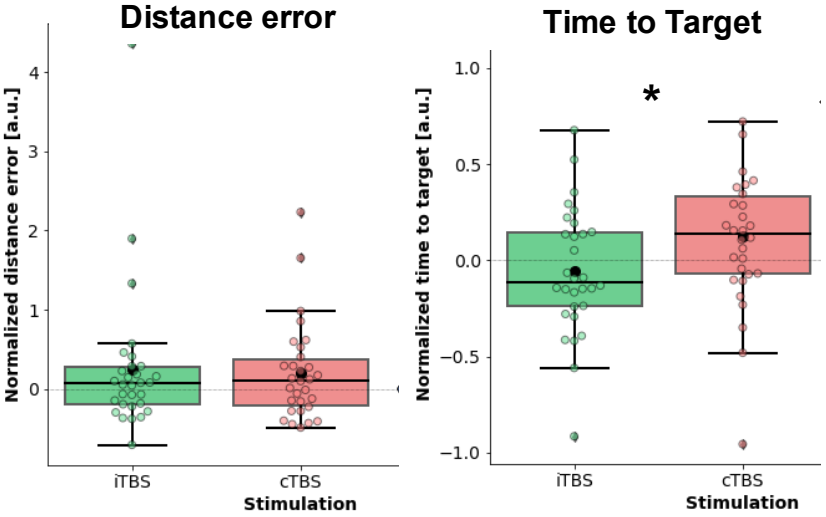


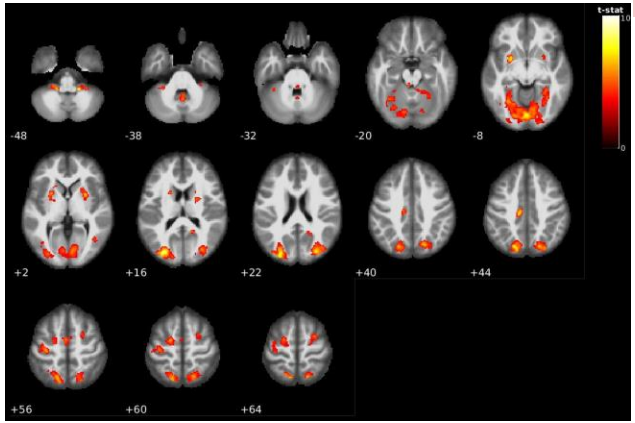


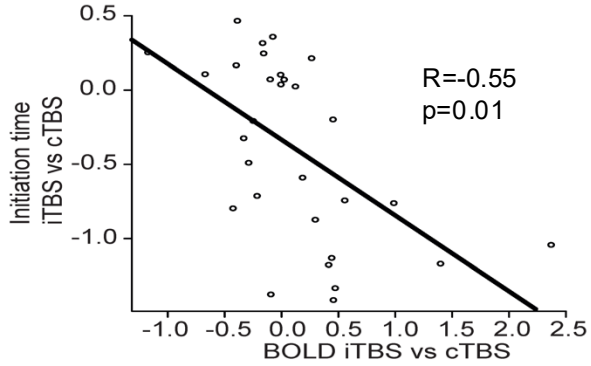
- allocentric spatial representation in the brain
- Spatial navigation
- Memory
- Alzheimer's disease (AD) /MCI

Vann et al., 2009; Moser et al. 2008; Byrne et al. 2007; Kunz et al., 2015

# Enhancing spatial navigation



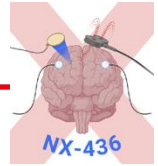




Non-invasive deep brain stimulation of the hippocampus enhances spatial memory

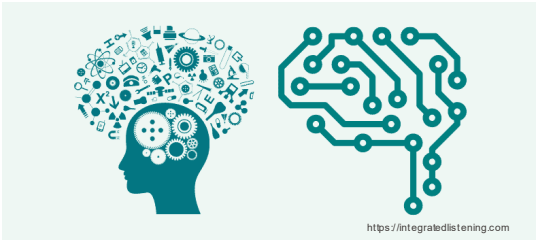
Opportunity to provide this treatment strategy to patients suffering from memory deficits

Beanato, Moon *et al.* 2024 **Science Advances**

# Stimulation protocol

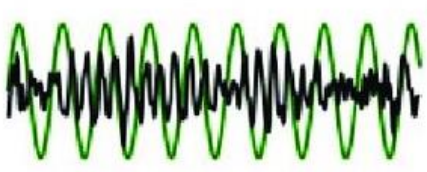



## Neuroplasticity



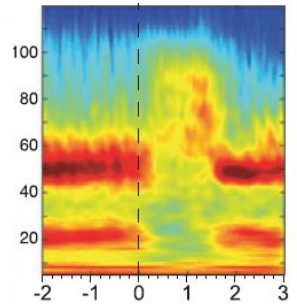

Wessel, Beanato *et al.* (2023) Nature Neuroscience
Popa, Beanato *et al.* (2023) bioRxiv
Beanato, Moon *et al.* (under review)

## Neuronal entrainment



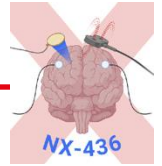
Violante *et al.* (2023) Nature Neuroscience

## Interference

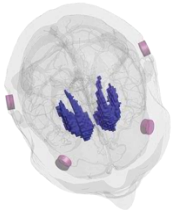



Vassiliadis *et al.* (2024) Nature Human Behavior

# Causal role of the striatum – reinforcement learning?



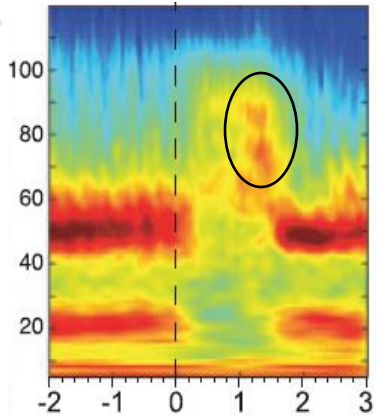

Striatum active in reinforcement learning (Bartra *et al.*, 2013) and motor learning (Hardwick *et al.*, 2013; Wessel, Beanato *et al.*, 2023)



Striatum suggested to be involved in the benefits of reinforcement on (motor) learning

Specific oscillations in the striatum associated to different functions:

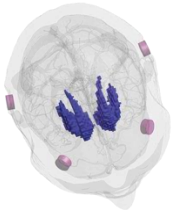
- **Beta** (~20Hz) ⟺ sensorimotor control (Jenkinson et al., 2013)
- **High gamma** (~80Hz) ⟺ reward processing (Berke, 2009)




Reward

# Causal role of the striatum – reinforcement learning?

Striatum active in reinforcement learning (Bartra *et al.*, 2013) and motor learning (Hardwick *et al.*, 2013; Wessel, Beanato *et al.*, 2023)



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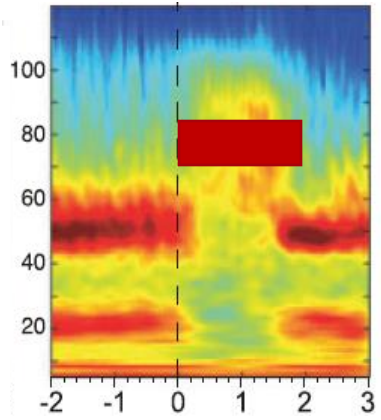



Reward will be disrupted

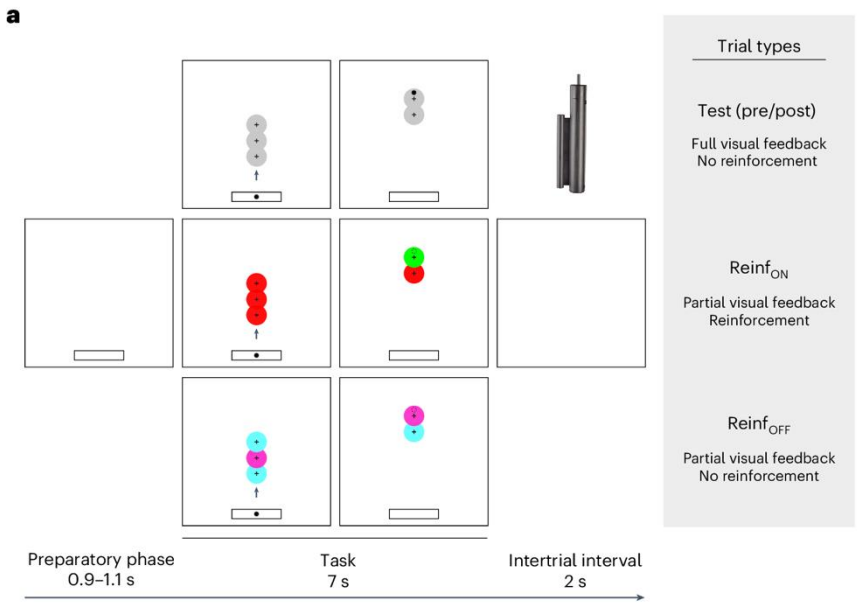
No Reward

**Hypothesis:**

Continuous, open-loop **striatal** stimulation at **80Hz** will **perturb** the **reinforcement-dependent** regulation of high gamma oscillations and **disrupt** the benefits of reinforcement on learning

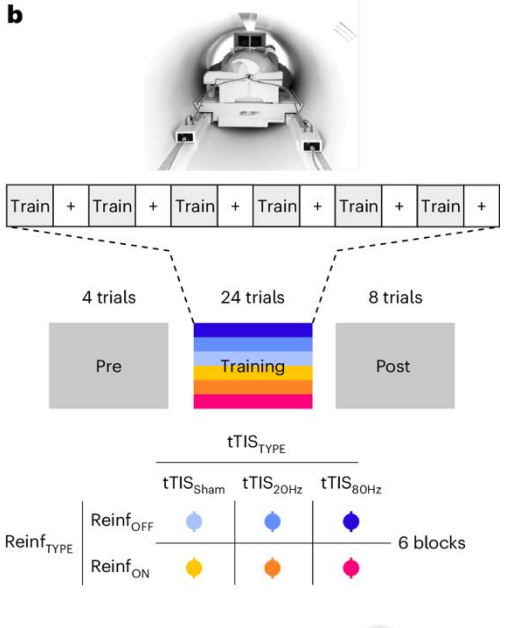
# Experimental set up

## Renforcement Learning



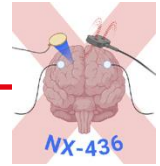

Vassiliadis *et al., 2021, 2022* iScience

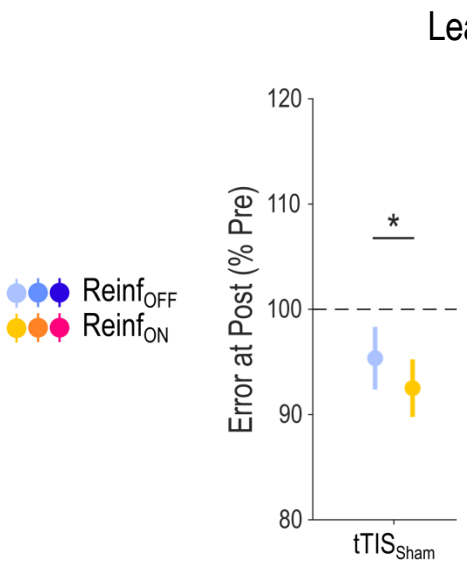
## tTIS + task concomitant with fMRI




Vassiliadis *et al., 2024* Nature Human Behavior

# Results - Behaviour

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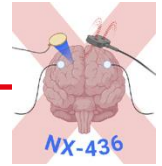
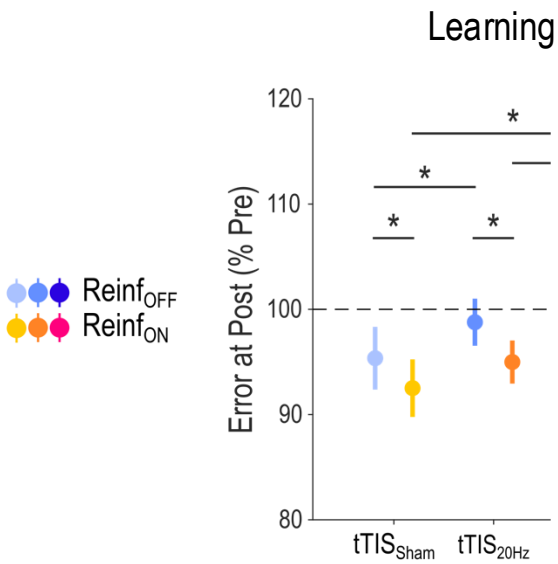
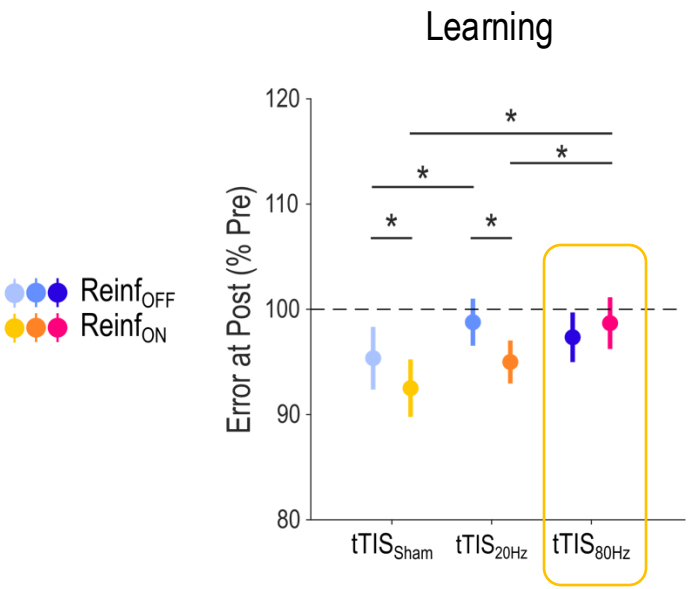
# Results - Behaviour




Vassiliadis *et al., 2024* Nature Human Behavior

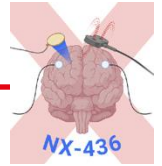
# Results - Behaviour

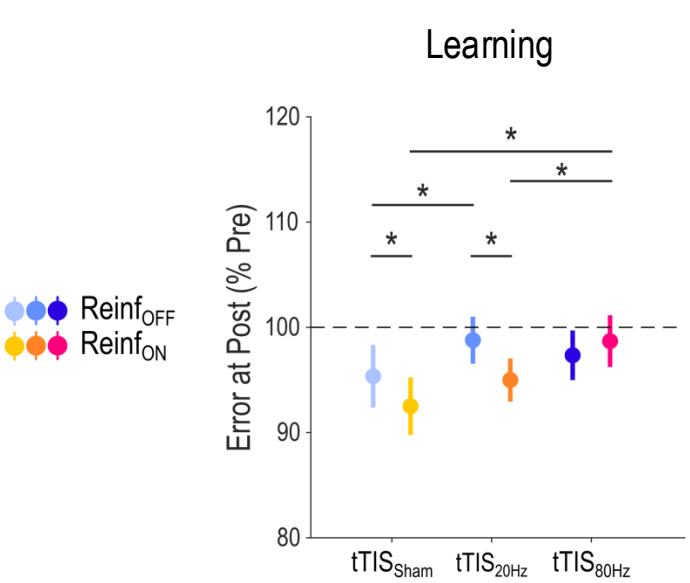



→ **tTIS$_{80Hz}$ disrupts** the benefits of **reinforcement** on motor learning, not motor learning in general

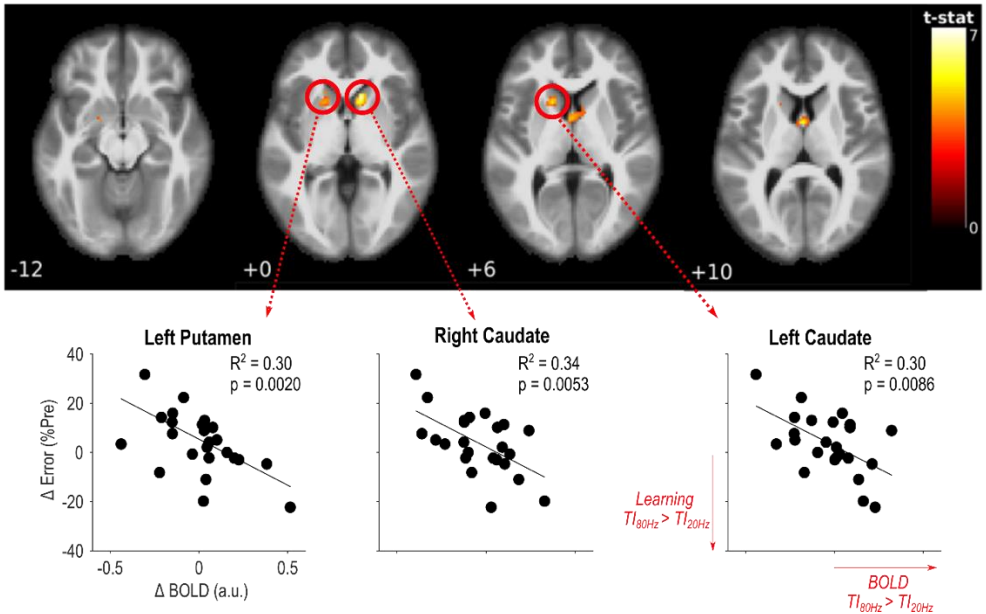
Vassiliadis *et al., 2024* Nature Human Behavior

# Results – Behaviour + fMRI




tTIS$_{80Hz}$ – tTIS$_{20Hz}$ contrast; Reinf$_{ON}$

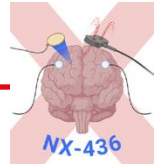



→ **tTIS$_{80Hz}$ disrupts** the benefits of **reinforcement** on motor learning, not motor learning in general

**Disruption** of reinforcement motor learning with tTIS$_{80Hz}$ **correlates with changes of neural activity in the striatum**

Vassiliadis *et al., 2024* Nature Human Behavior

# Clinical translation




nature human behaviour
Article
https://doi.org/10.1038/s41562-024-01901-z

**Non-invasive stimulation of the human striatum disrupts reinforcement learning of motor skills**

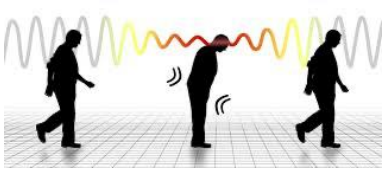
Vassiliadis *et al.* 2024

**OCD, Essential Tremor, Dystonia**

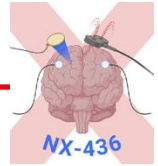
**Case evidence in ET**
Liu *et al.* 2024 NIMG

**Parkinson**
Yang *et al.* 2024 MDS
Lamos *et al.* 2025 MDS
Yang *et al.* 2025 BtainStimulation

**Parkinson**

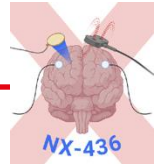


**Freezing of Gait (FoG)**




# Clinical translation – Parkinson's

# First clinical proof-of-concept

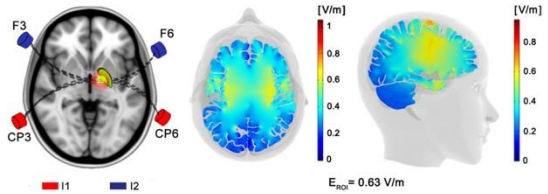


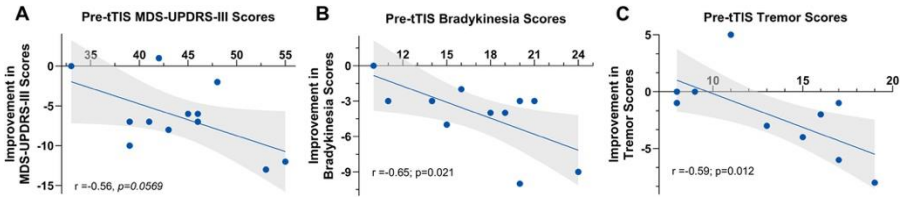

Movement Disorders — Official Journal of the International Parkinson and Movement Disorder Society

RESEARCH ARTICLE

## Transcranial Temporal Interference Stimulation of the Right Globus Pallidus in Parkinson's Disease

Chenhao Yang, PhD,[1] Yongxin Xu, PhD,[1] Xiaofan Feng, MPT,[1] Bowen Wang, MPT,[1] Yichao Du, MPT,[1] Kexin Wang, MPT,[1] Jiaojiao Lü, PhD,[1] Lingyan Huang, PhD,[1] Zhenyu Qian, PhD,[1] Zhen Wang, PhD,[2] Nan Chen, PhD, DPT,[3] Junhong Zhou, PhD,[4] Chencheng Zhang, MD, PhD,[5,6*] and Yu Liu, PhD[1*]




**Unilateral GPi 130Hz tTIS**

RESEARCH ARTICLE

## Noninvasive Temporal Interference Stimulation of the Subthalamic Nucleus in Parkinson's Disease Reduces Beta Activity

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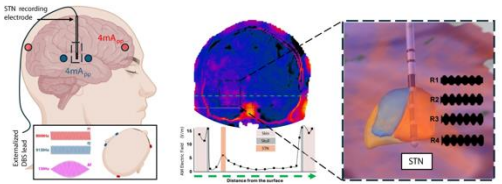
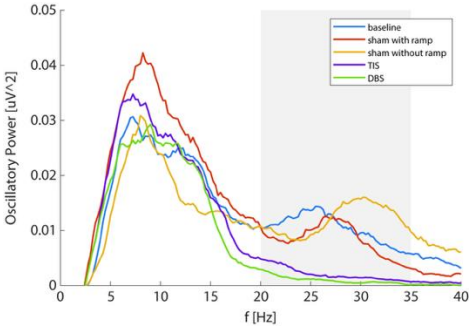



**Unilateral STN 130Hz tTIS**

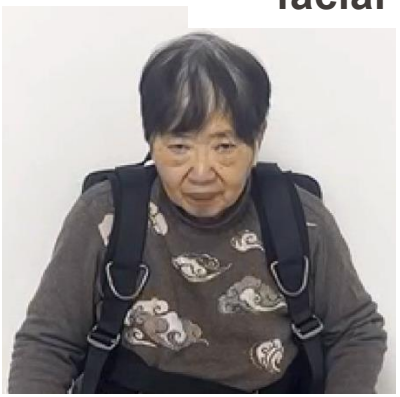
See also Yang *et al.* **2025 BrainStimulation**, Liiu *et al.* **NIMG** 2024; for review Hummel & Wessel 2024 **Nat Rev**

# Clinical translation – Parkinson's

## Unilateral STN 130Hz tTIS



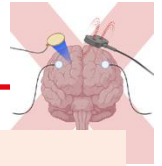
facial masking





Courtesy from Prof. Chencheng Zhang (Shanghai)

# Summary

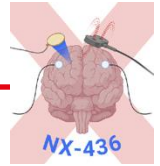


- Novel innovative neurotechnology extends the use of orchestrated non-invasive brain stimulation to deep brain structures (hippocampus, basal ganglia)

- Temporal Interference stimulation (**tTIS**) provides a **promising** opportunity to neuromodulate **non-invasively deep** brain structures like the
  - striatum
  - hippocampus
  - first applications in patients

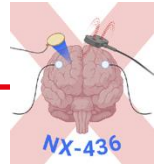
- Opens new promising **opportunities** for **novel non-invasive interventional strategies** for **neurological** and **psychiatric** disorders targeting deep brain structures involved in the pathophysiology or in the recovery process of the disorders
  - TBI or Stroke
  - Parkinson's
  - Dementia
  - Anxiety, Addiction
  - Apathy or Fatigue

- Next steps require further technological development and acquisition of strong clinical evidence




Open questions, challenges

- Parameter space (frequency)
- Higher topographic resolution
- Understanding of underlying mechanisms
- Personalized application
- Closed-loop stimulation
- Home-based self-application
- Proof-of-concept in clinical populations




# Questions?