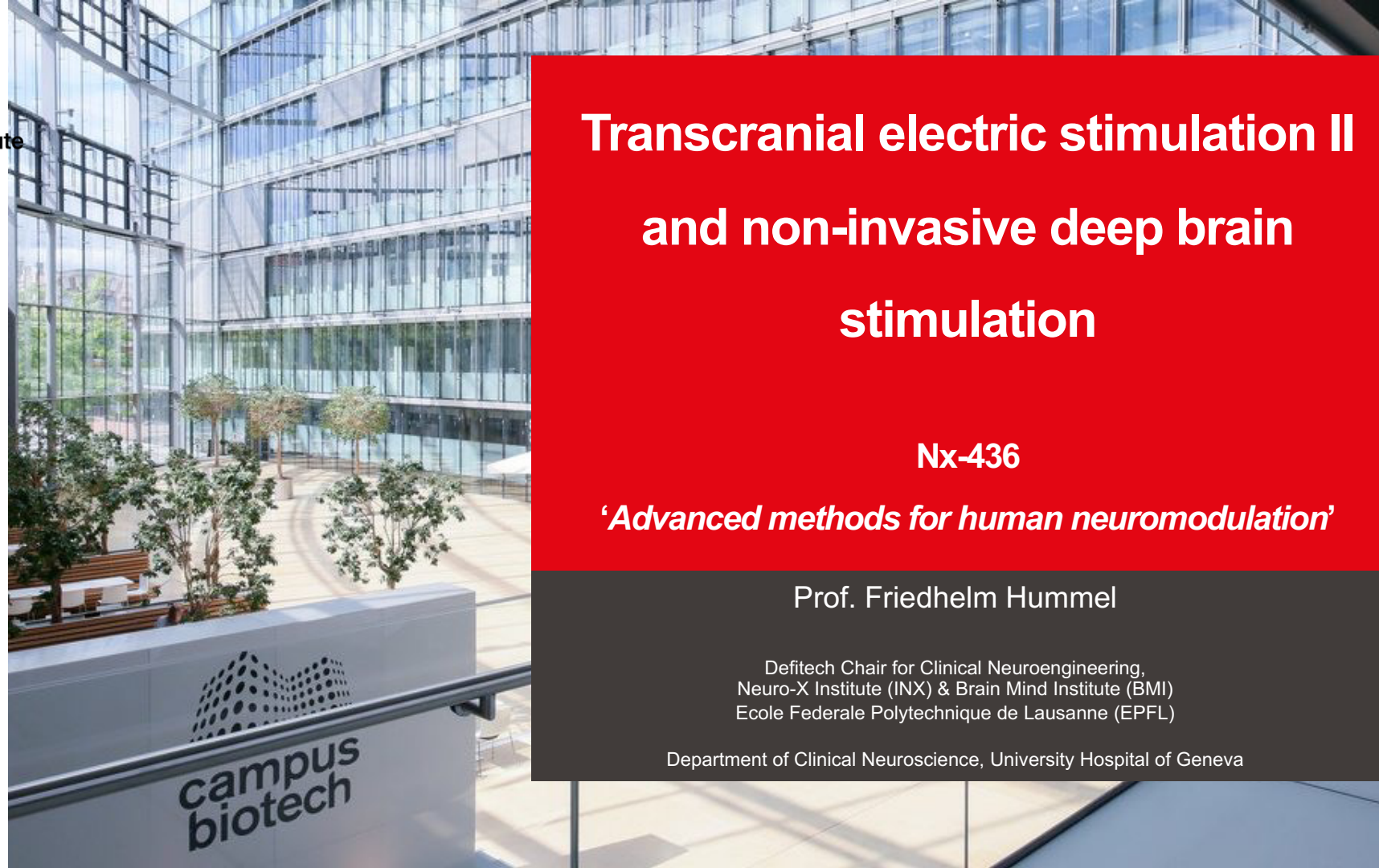
EPFL

Neuro X Institute



Transcranial electric stimulation II and non-invasive deep brain stimulation

Nx-436

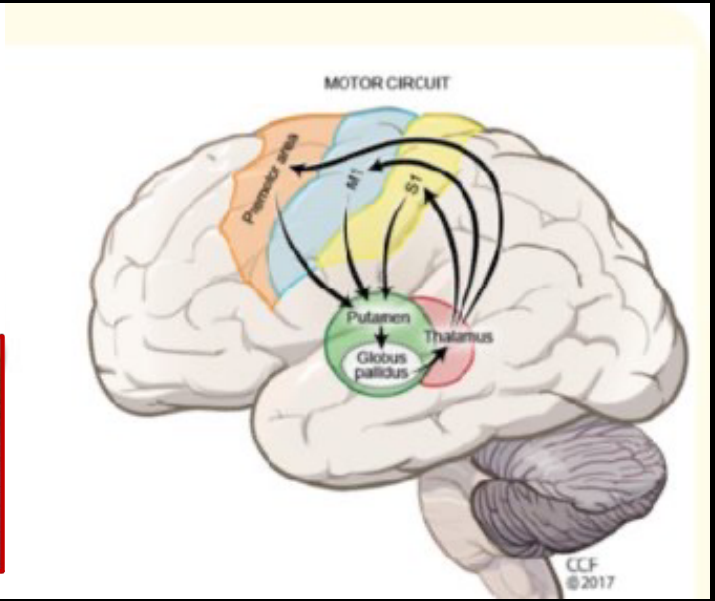
'Advanced methods for human neuromodulation'

Prof. Friedhelm Hummel

Defitech Chair for Clinical Neuroengineering,
Neuro-X Institute (INX) & Brain Mind Institute (BMI)
Ecole Federale Polytechnique de Lausanne (EPFL)

Department of Clinical Neuroscience, University Hospital of Geneva

Brain and Network



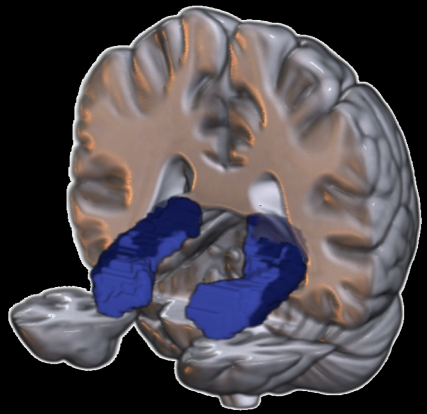
Impact

BG/Striatum alterations :

- Parkinson's, Huntington's disease
- Addiction
- Schizophrenia
- Stroke recovery
- ….

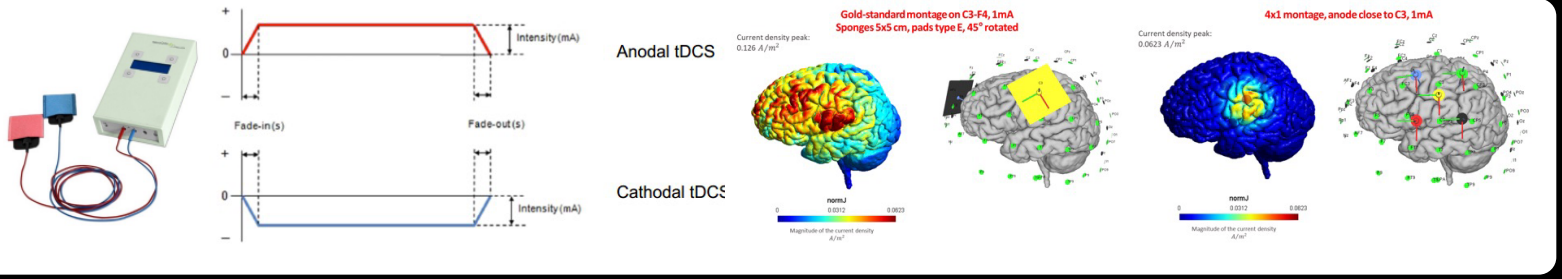
Hippocampus alterations :

- Epilepsy
- Traumatic Brain Injury (TBI)
- Alzheimer's disease
- ….

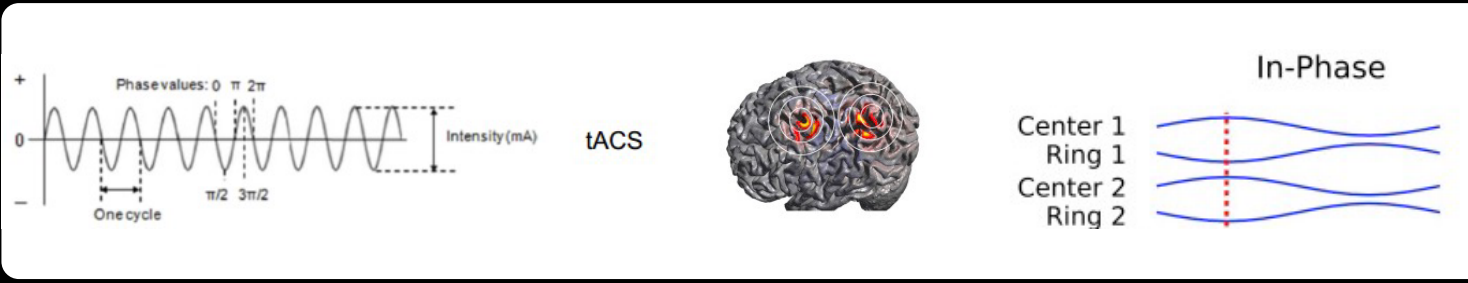


Neuromodulation by NIBS

transcranial Direct Current Stimulation (tDCS)



transcranial Alternating Stimulation (tACS)



transcranial Magnetic Stimulation (TMS)

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

Neuromodulation by NIBS

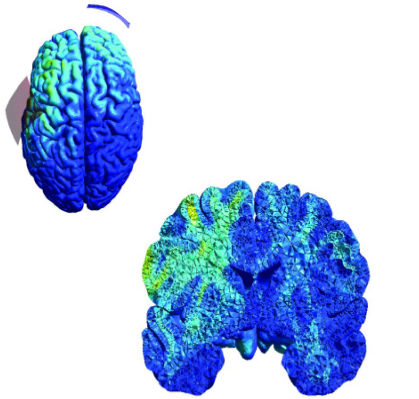
transcranial Direct Current Stimulation (tDCS)

transcranial Alternating Stimulation (tACS)

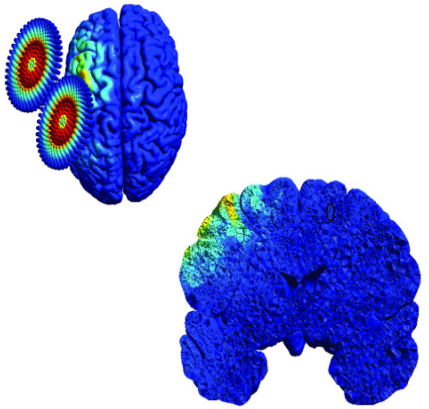
transcranial Magnetic Stimulation (TMS)

Depth-focality trade-off

Conventional tES



TMS

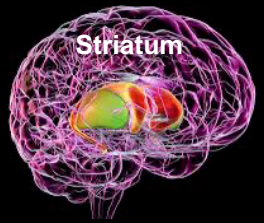


For review see e.g., Hummel & Cohen 2006,; Wessel et al. 2015; Saturnino et al. 2017)

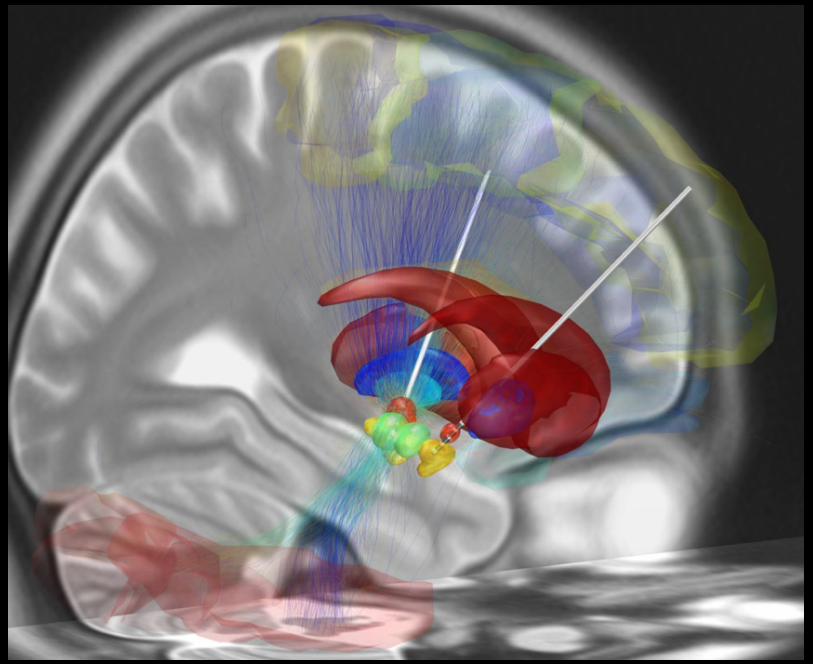
Deep Brain Stimulation (DBS)

DBS 1.0

lesioning



DBS 2.0

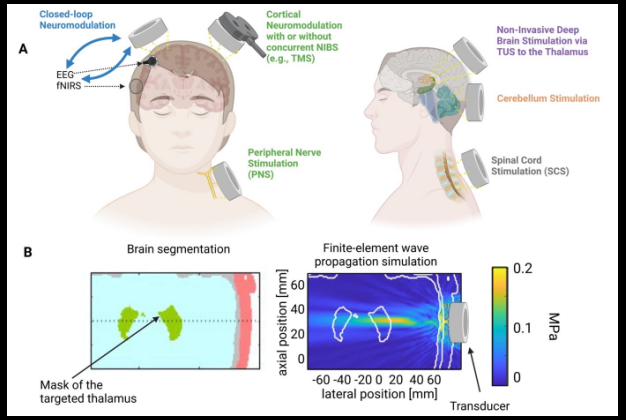


neuromodulation

...only invasive...!

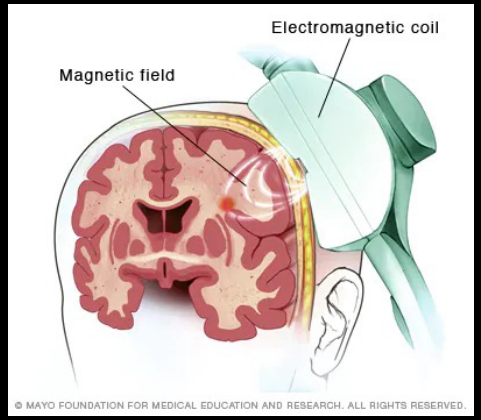
Non-invasive Deep Brain Stimulation (DBS)?

transcranial focused ultrasound (tUS)



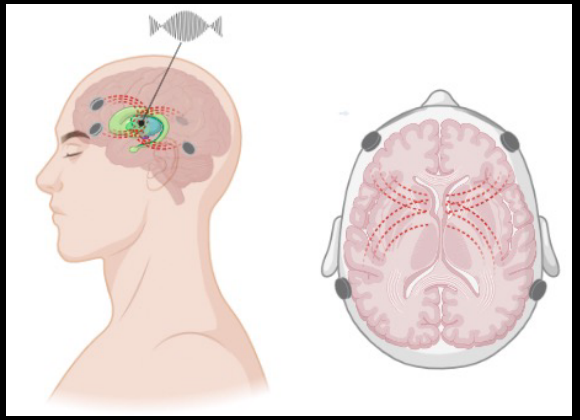
For review e.g., Yüksel *et al.* (2024) IEEE EMBS

Deep TMS

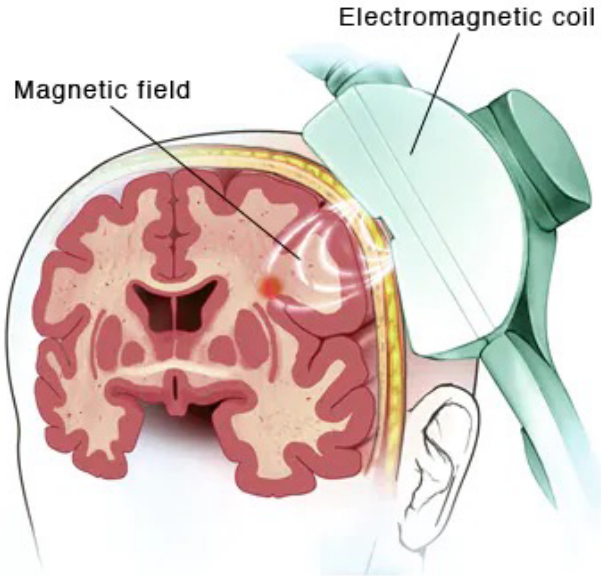


Zibma *et al.*, 2021, Pell *et al.*, 2023

transcranial temporal interference stimulation (tTIS)



Wessel *et al.* (2023) Nature Neuroscience
Violante *et al.* (2023) Nature Neuroscience

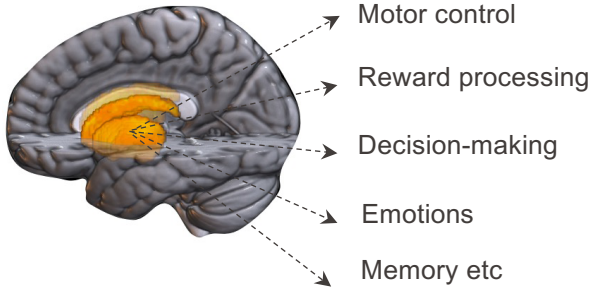


deep TMS

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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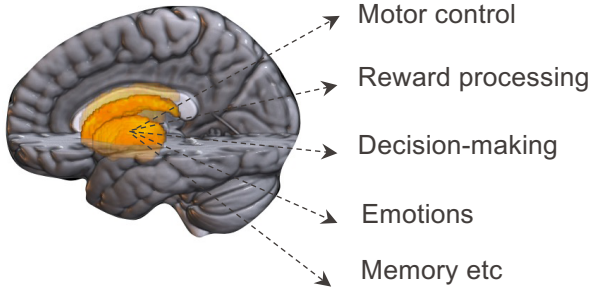


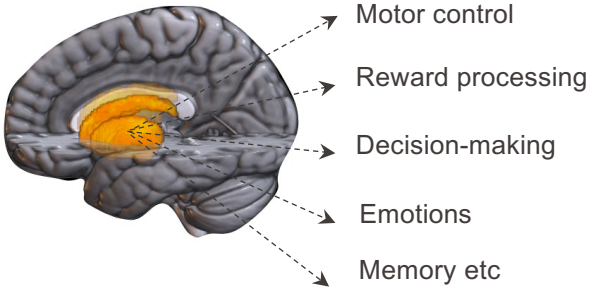
Challenge: focal, non-invasive deep brain stimulation is not possible with conventional approaches due to steep depth-focality trade-off

Neuromodulation of deep brain structures

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

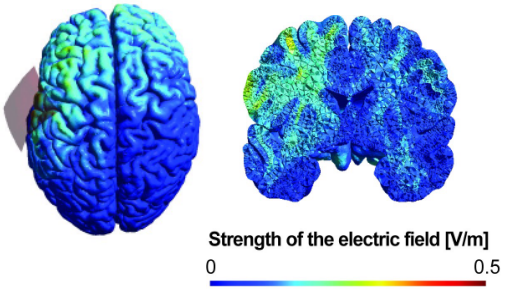
e.g., **striatum, hippocampus, thalamus, DLPFC**

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

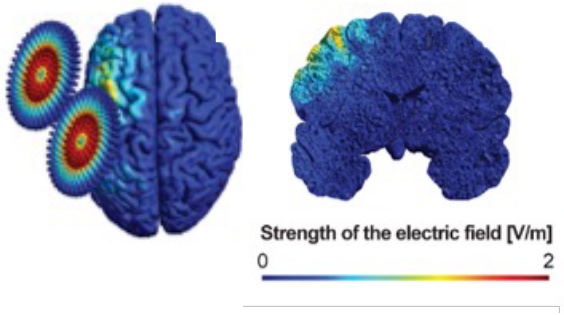


Challenge: focal, non-invasive deep brain stimulation is not possible with conventional approaches

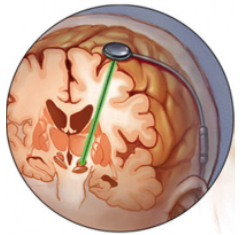
Conventional tES



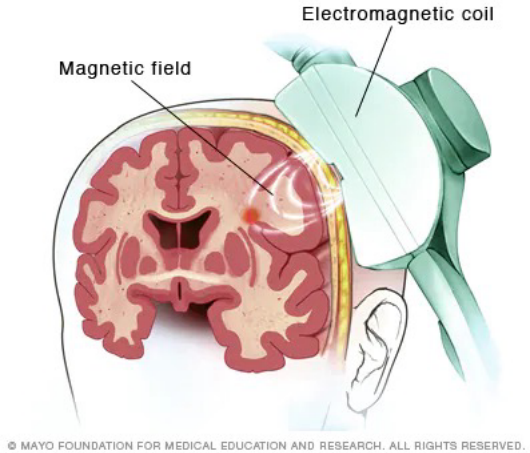
TMS

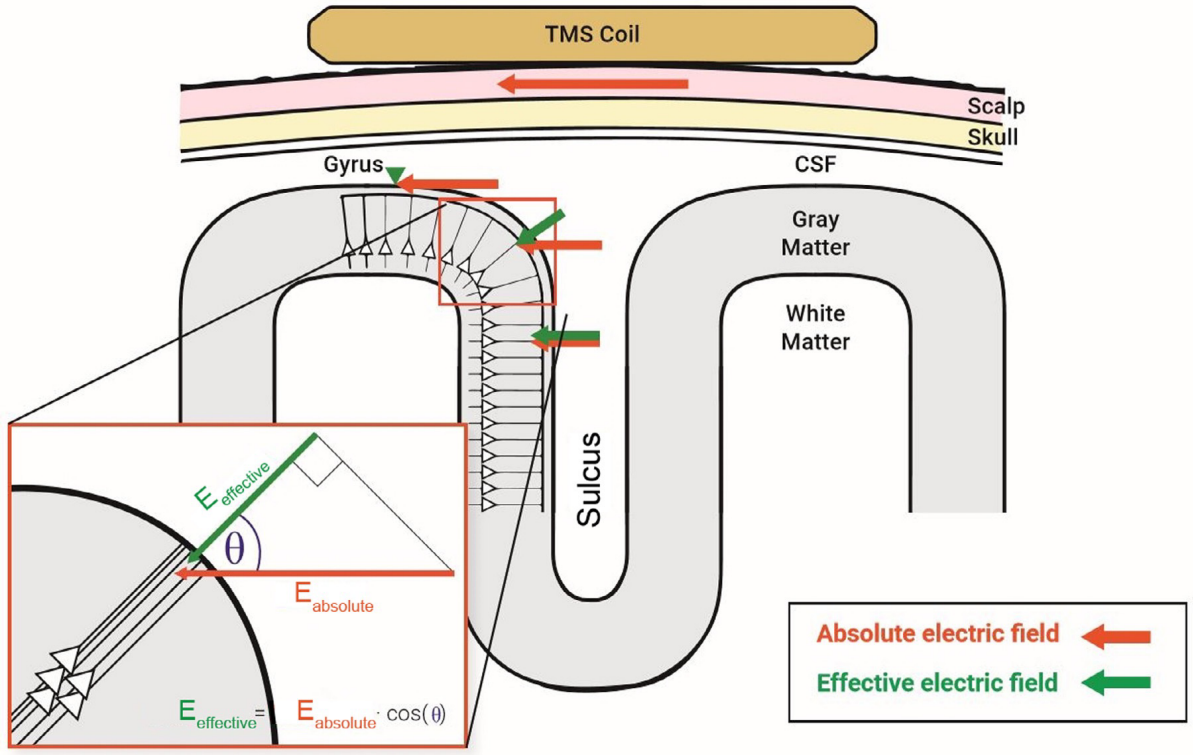


Deep brain stimulation is so far **limited to invasive methods**



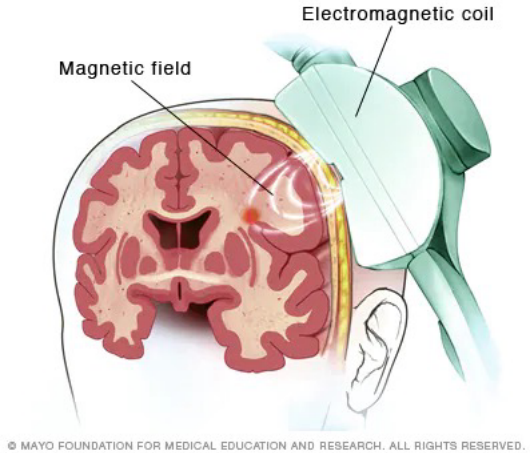
Deep TMS

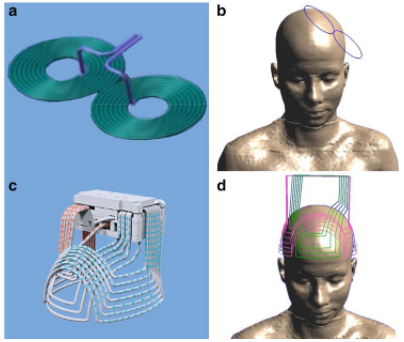


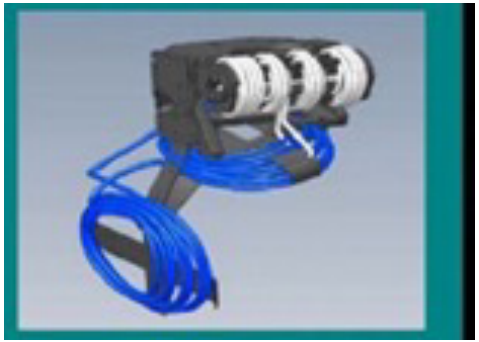


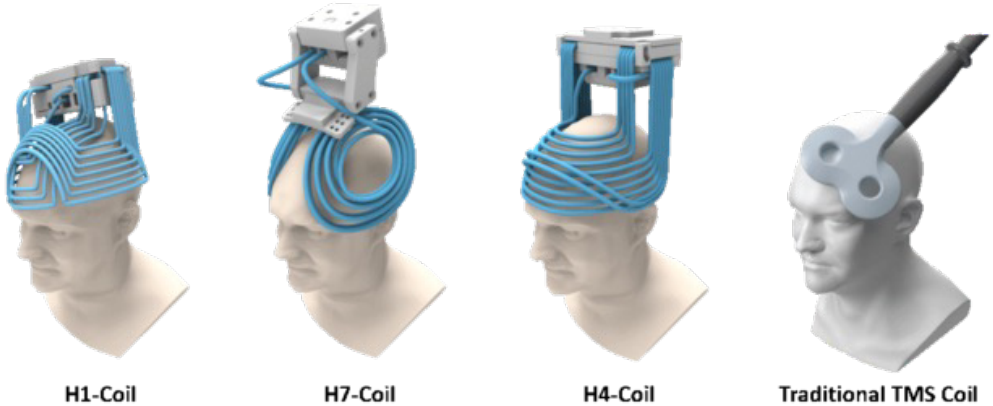
Zibma *et al*., 2021, Pell *et al*., 2023,

Deep TMS



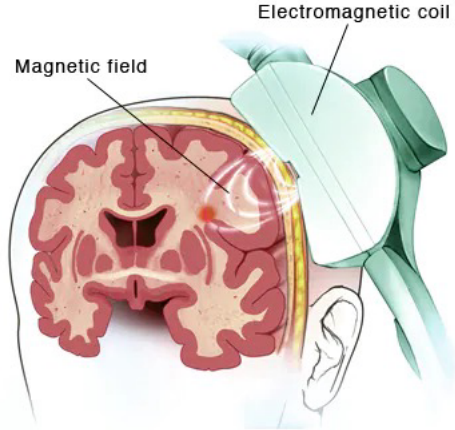


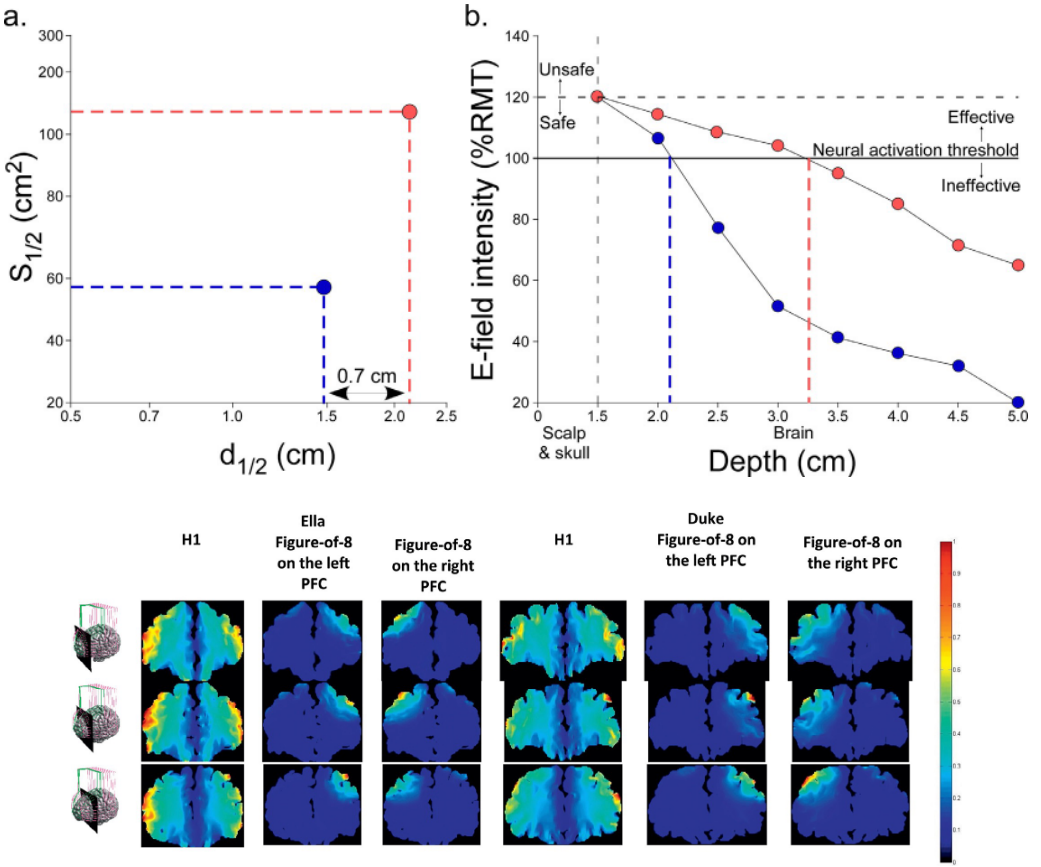




H1-Coil H7-Coil H4-Coil Traditional TMS Coil

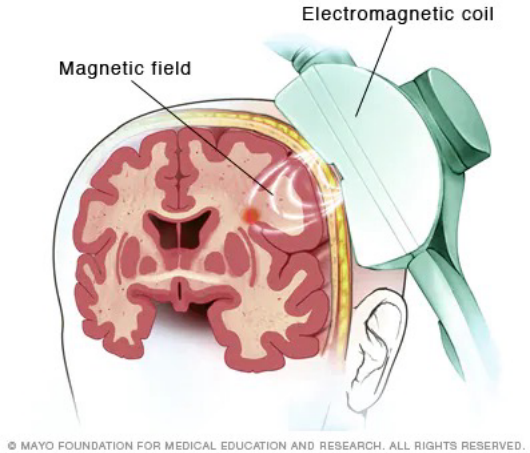
Zibma *et al*., 2021, Pell *et al*., 2023, https://www.brainsway.com





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

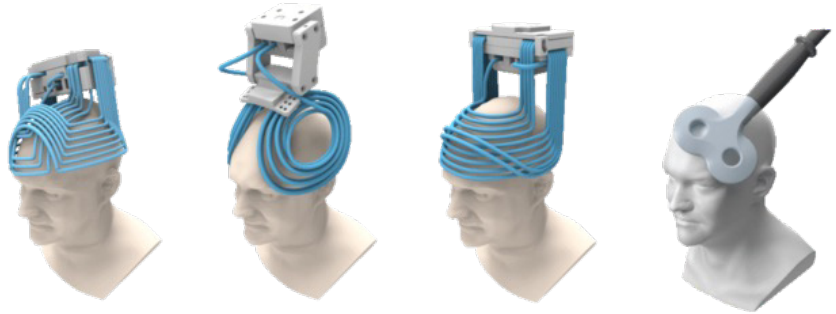
Deep TMS



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

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)

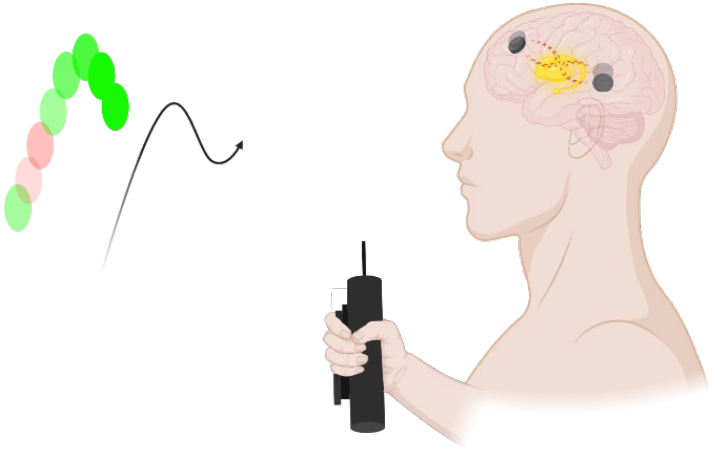
H7-Coil for Obsessive-Compulsive Disorder (OCD)

H4-Coil for Smoking Cessation

Traditional TMS Coil for Major Depressive Disorder (MDD)

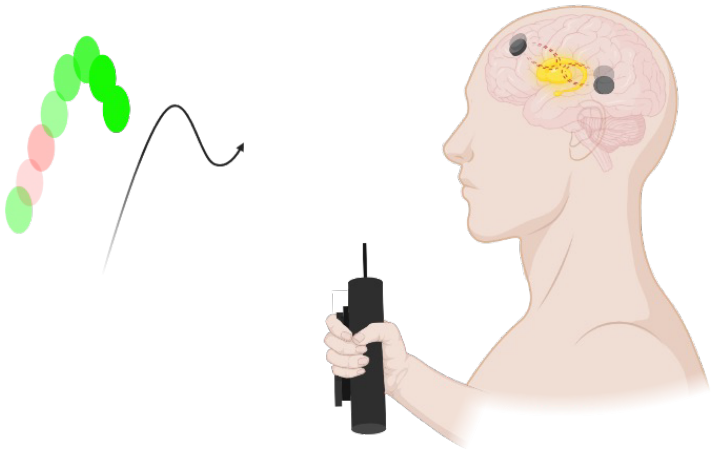
- **Deep TMS by means of H-Coils allows to reach deeper (cortical) structure**
- **Lower focality then classical Figure of 8 coils**
- **Based on special coil architecture**
- **Improves treatment effects**

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



tTIS

Transcranial temporal interference electrical stimulation (tTIS)

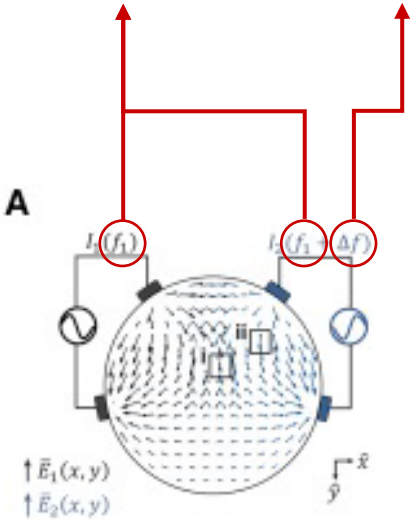


Wessel*, Beanato* *et al.,* 2023, *Nature Neuroscience;* Vassiliadis *et al.*, accepted *Nature Human Behaviour* (and bioRxiv); Violante *et al.* 2023 Nature Neuroscience; Grossman *et al.* 2017 Cell

Transcranial Temporal Interference Stimulation (tTIS)

High frequency outside neural operation

Frequency recruiting neurons



Grossman *et al.*, Cell 2017

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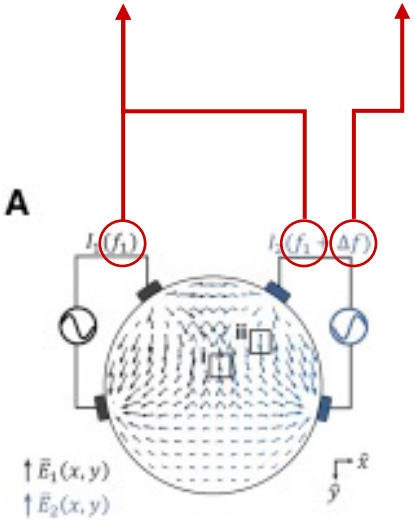
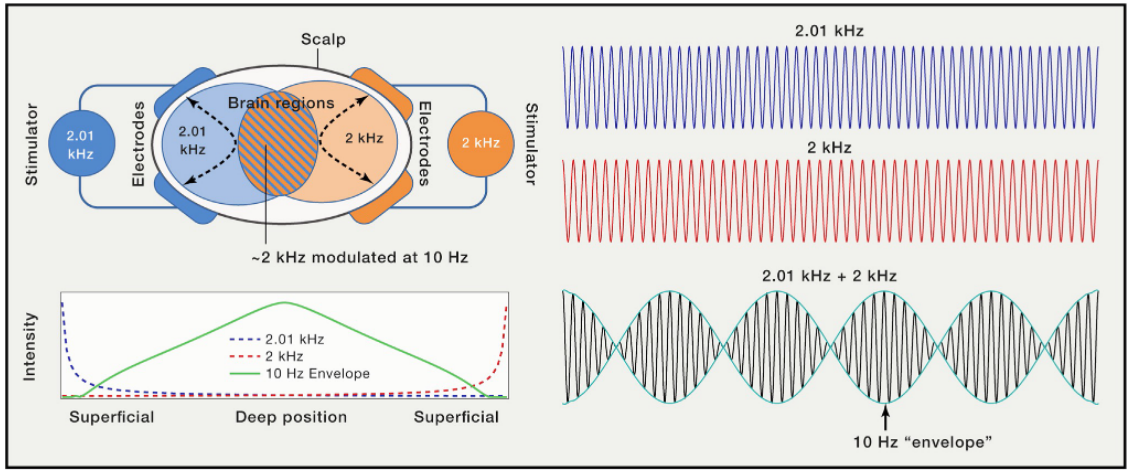
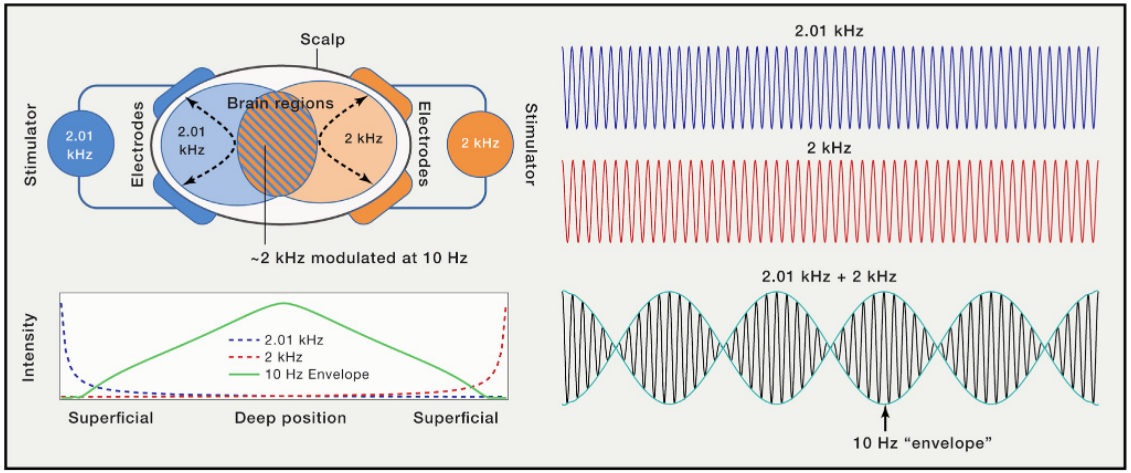
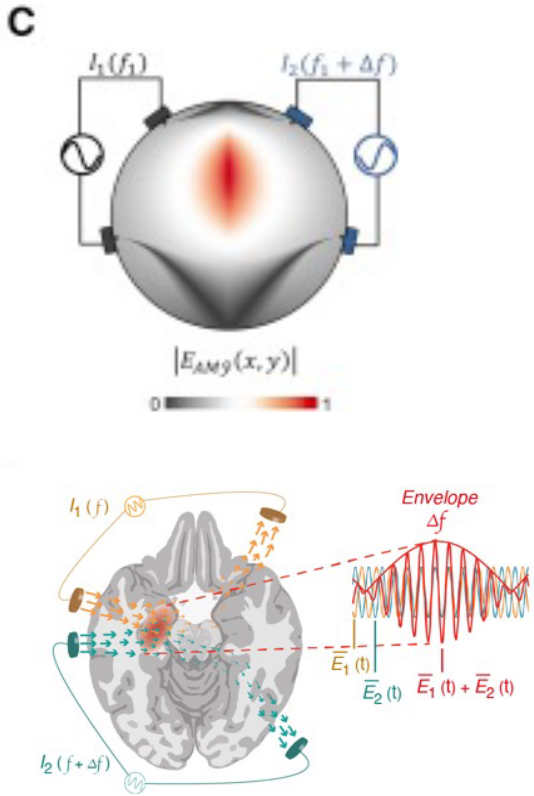




Grossman *et al.*, Cell 2017; Dmochowsk *et al.* 2017 Cell

Transcranial Temporal Interference Stimulation (tTIS)



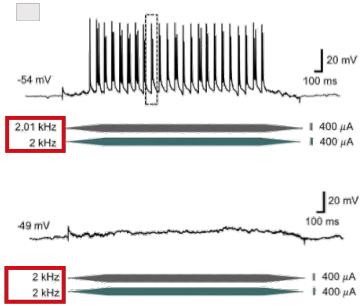


Grossman *et al.*, Cell 2017; Dmochowsk *et al.* 2017 Cell

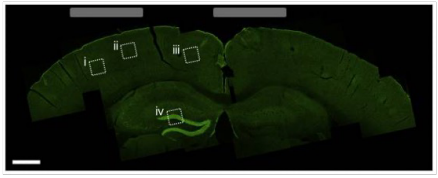
tTIS – animal /cadaver work

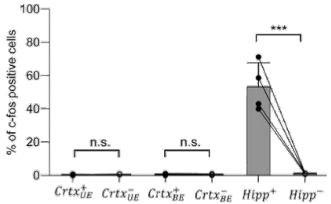
Rodents

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



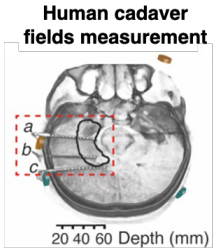
- Stimulation of deep structure does not engage overlying tissues

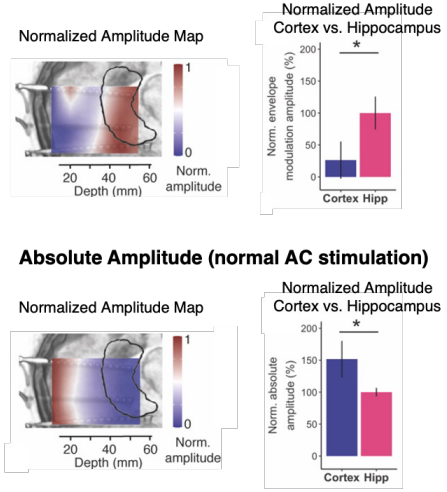




Grossman *et al.*, Cell 2017

Human cadaver



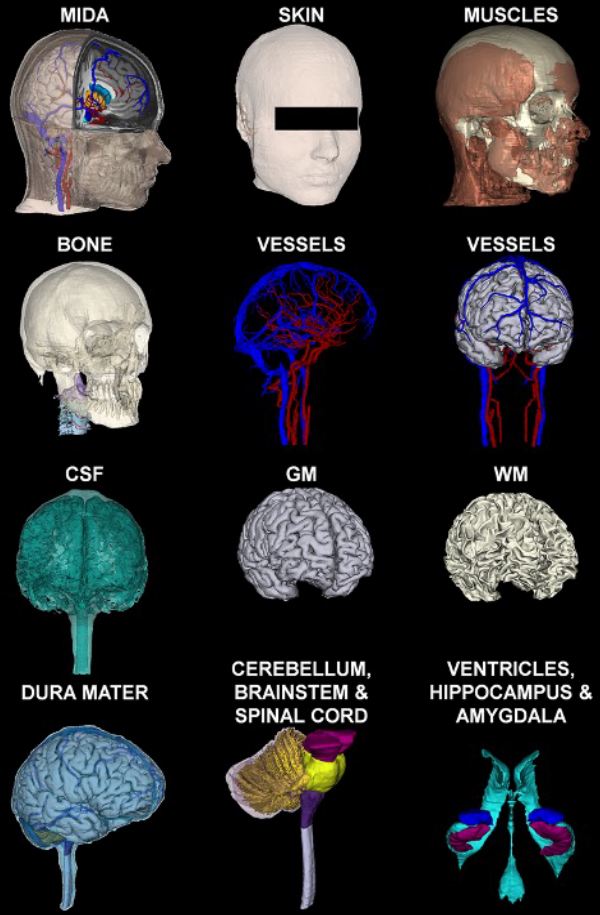


Violante *et al.*, Nat Neurosci 2023

Questions to solve

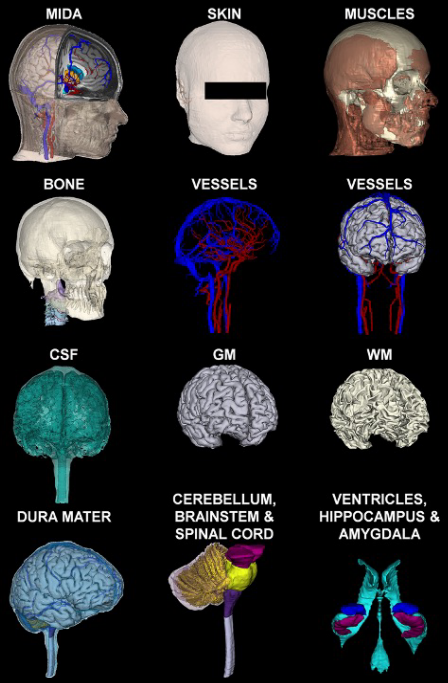
Localization
Stimulation parameters
Focality of stimulation effects
Validation of stimulation effects

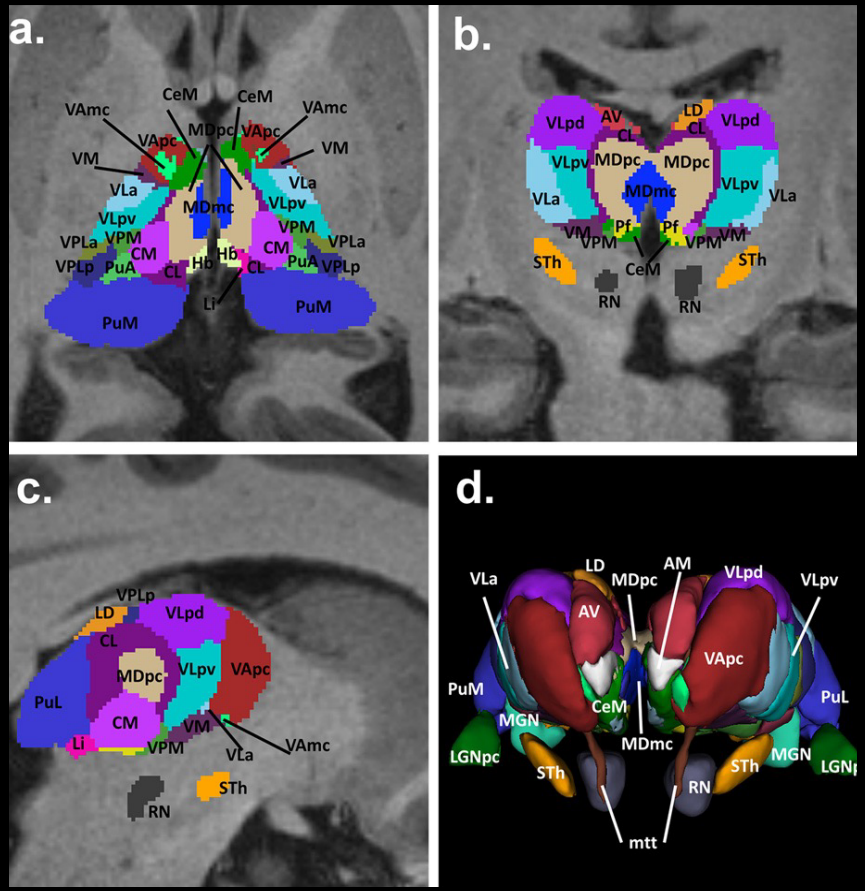
Simulations – anatomical modelx



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

Simulations – anatomical modelx





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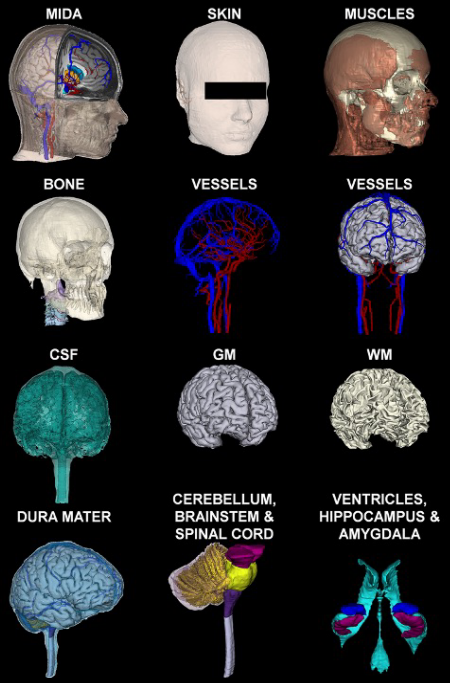
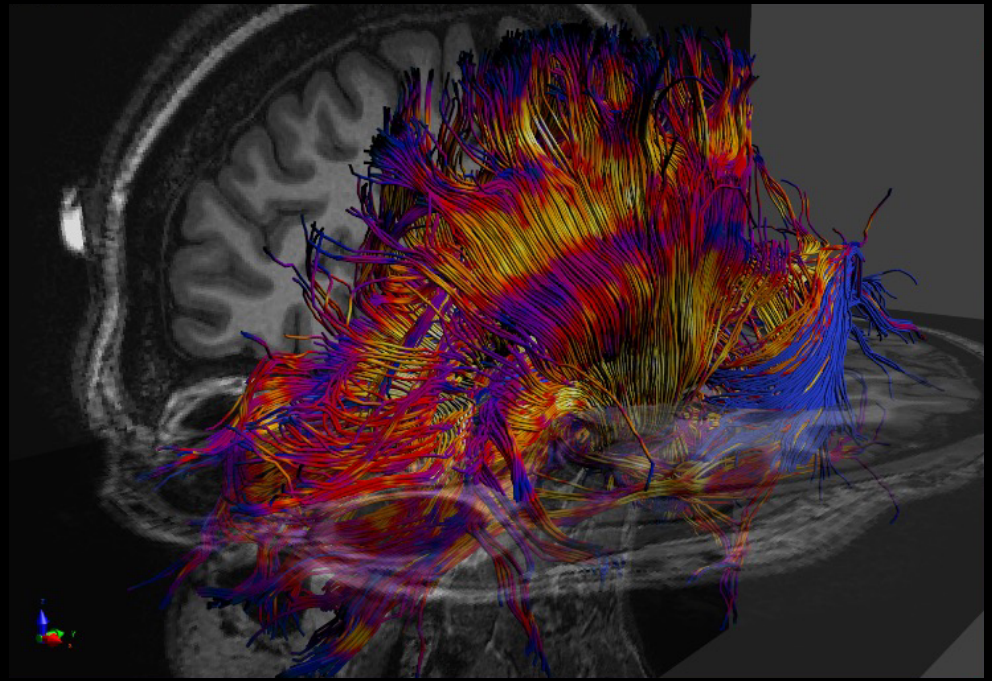
Simulations – anatomical modelx



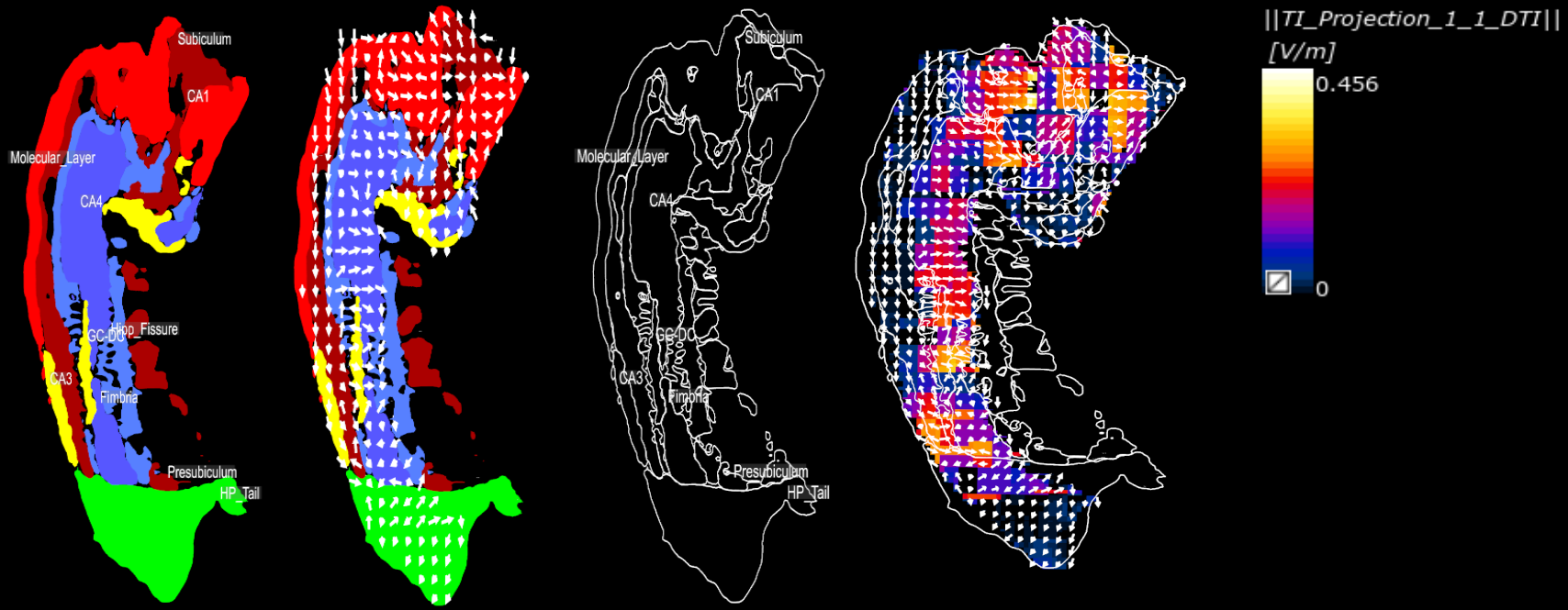
Further informing the model



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

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

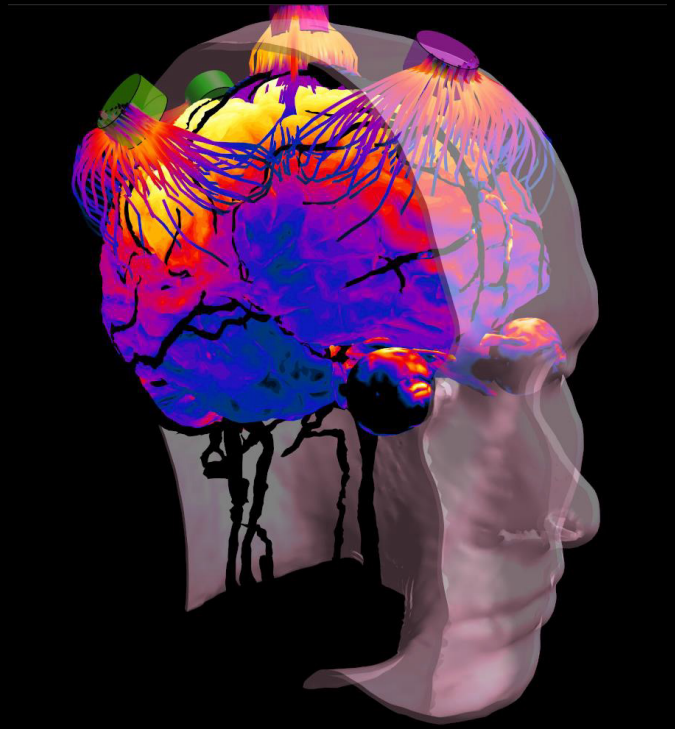
Hippocampus simulations (MIDA model)



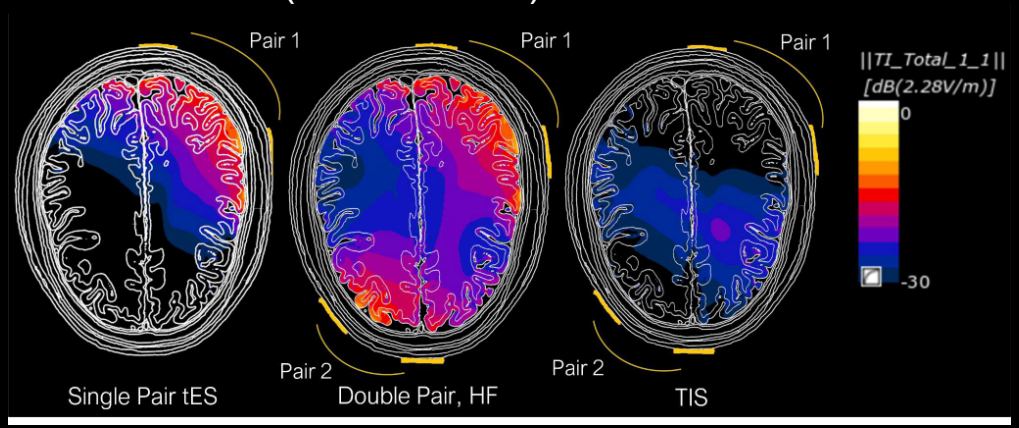
Labels DTI Directions Contours TI stimulation

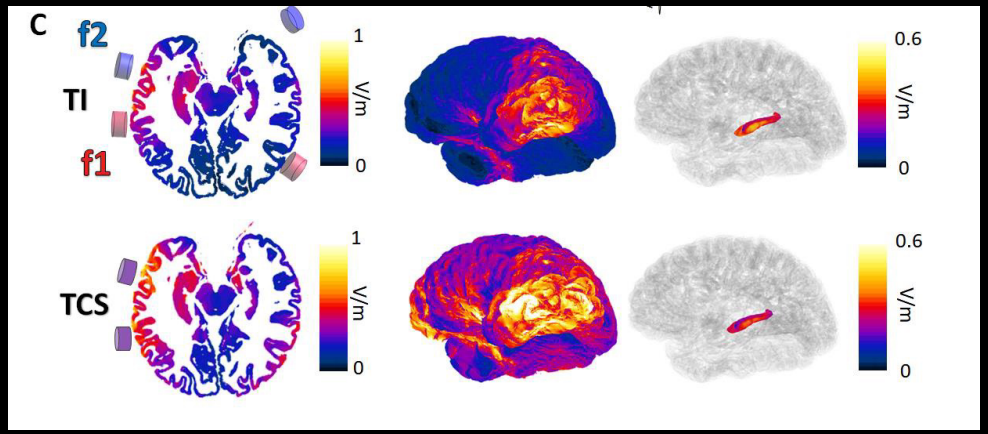
Courtesy E. Neufeld

Whole brain simulations (MIDA model)



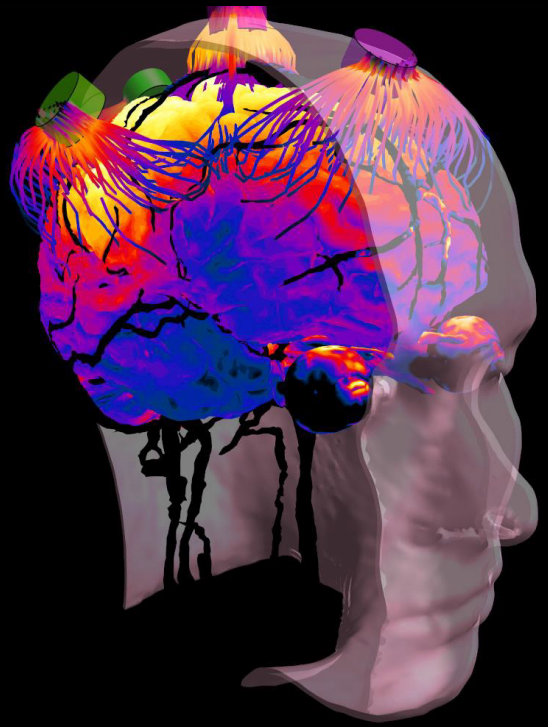
High resolution head model (MIDA, SIM-4-Life) in cooperation with E. Neufeld (IT'IS, ETH Zürich)





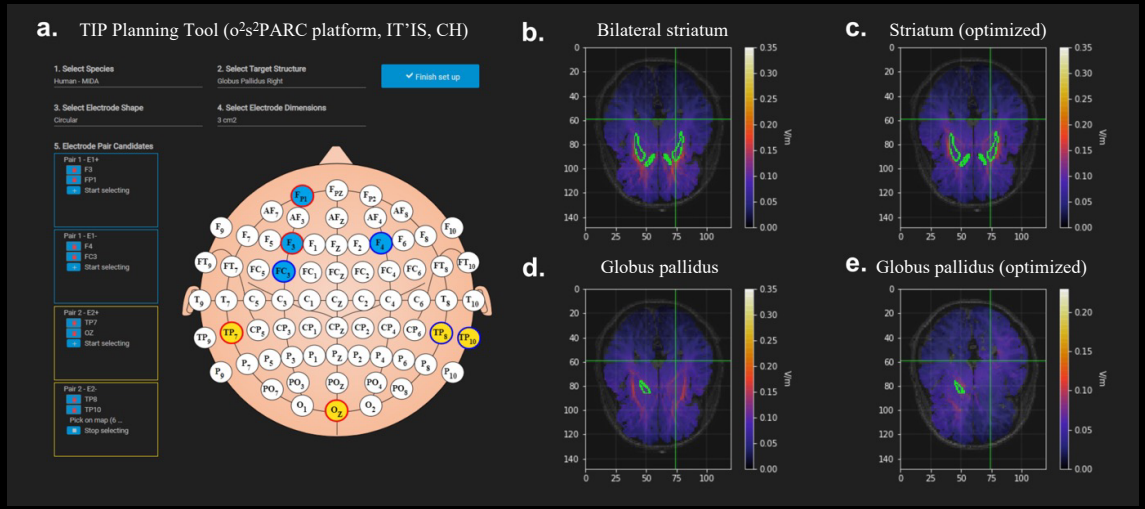
Courtesy E. Neufeld

tTIS - modeling



High resolution head model
(MIDA, SIM-4-Life; IT'IS, ETH Zürich)

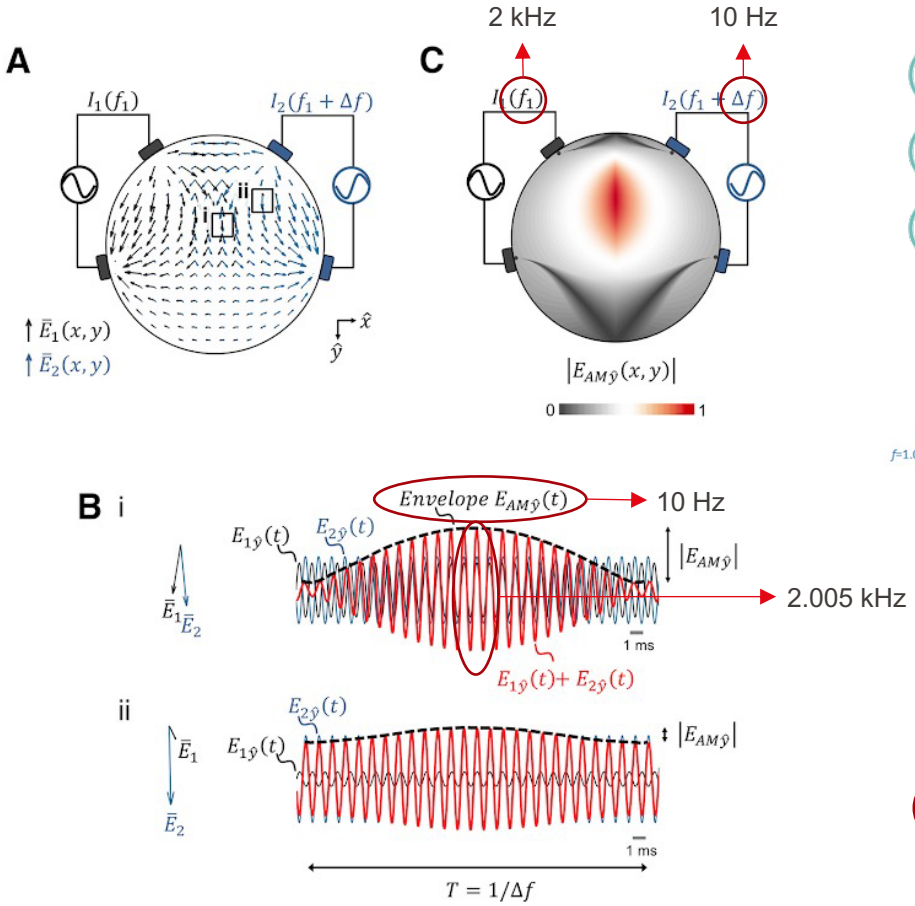
Planning electrode placement



Courtesy M. Wessel

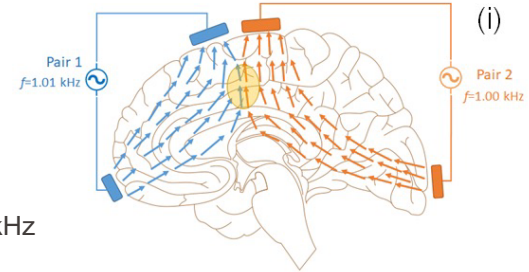
See also Lee *et al.* 2020; 2022

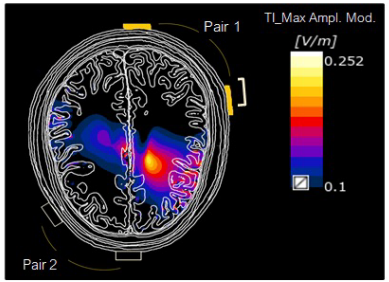
tTIS – human translation?



Grossman *et al.*, Cell 2017

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





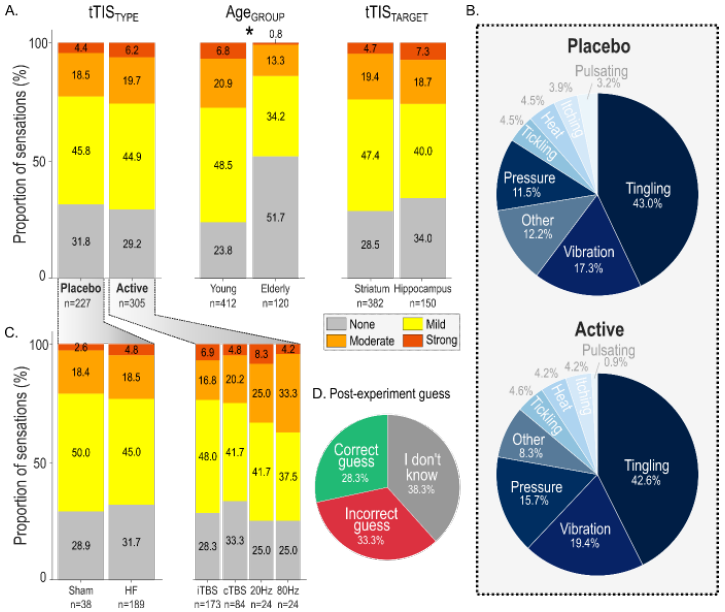
Cassara et al. 2022 bioRxiv

- **Feasible, effective** in humans

Blinding, perceived sensations, safety

Blinding, perceived sensations, safety

Deep tTIS
n=119 subjects, n=257 sessions



Cortical tTIS
n=38 subjects

Measurements (Range or Unit)	Active Group (Mean ± SD) Pre	Active Group (Mean ± SD) Post	Sham Group (Mean ± SD) Pre	Sham Group (Mean ± SD) Post	Statistical Results *F*	Statistical Results *p*
MoCA (0–30)	27.95 ± 1.47	27.68 ± 1.46	27.63 ± 1.17	27.89 ± 1.49	0.973	0.331
PPT (times [1])						
Right Hand	16.44 ± 1.56	17.21 ± 1.91	16.35 ± 1.60	17.65 ± 0.97	1.985	0.167
Left Hand	15.25 ± 1.86	16.10 ± 2.06	14.93 ± 1.29	15.91 ± 1.42	0.298	0.588
Both Hands	12.72 ± 1.68	13.35 ± 1.68	12.51 ± 1.60	13.30 ± 1.62	0.307	0.583
Assembly	41.30 ± 5.88	45.84 ± 6.68	40.23 ± 7.75	44.14 ± 6.40	0.340	0.564
A-CalCAP (ms [2])						
SRT	363.79 ± 82.52	357.17 ± 60.90	357.64 ± 50.01	367.96 ± 54.43	0.620	0.436
CRT	428.42 ± 33.54	441.08 ± 41.93	415.76 ± 35.18	422.66 ± 32.58	0.349	0.558
SPM1	501.01 ± 69.28	513.59 ± 83.14	487.74 ± 61.24	481.20 ± 65.78	1.589	0.216
SPM2	593.20 ± 94.59	540.83 ± 78.03	554.99 ± 67.63	535.68 ± 68.15	2.886	0.098
NSE (ng/mL)	14.09 ± 3.21	16.01 ± 2.94	13.40 ± 3.27	14.32 ± 3.72	0.460	0.503
VAMS-R (0–100)						
Sad	1.74 ± 2.16	8.63 ± 24.43	6.26 ± 9.15	9.21 ± 15.51	0.418	0.522
Confused	9.00 ± 19.06	8.16 ± 22.60	15.74 ± 18.47	11.00 ± 17.02	0.462	0.638
Afraid	7.05 ± 22.69	6.32 ± 21.76	4.53 ± 9.06	5.68 ± 11.33	0.060	0.808
Happy	47.00 ± 34.39	43.89 ± 34.41	49.26 ± 31.58	49.37 ± 27.95	0.098	0.756
Tired	31.21 ± 32.54	35.16 ± 30.03	35.47 ± 34.30	31.47 ± 29.62	0.928	0.342
Angry	7.05 ± 22.41	9.68 ± 25.74	2.53 ± 4.61	5.42 ± 10.60	0.006	0.941
Tense	16.68 ± 30.35	8.05 ± 22.31	5.74 ± 8.85	8.89 ± 20.32	2.361	0.133
Energetic	49.21 ± 28.49	47.84 ± 28.75	60.00 ± 30.01	49.16 ± 30.87	1.692	0.202
SAS (1–5)						
Concentration	3.74 ± 0.73	3.26 ± 0.81	3.32 ± 0.48	3.21 ± 0.63	3.196	0.082
Calmness	4.11 ± 0.74	3.79 ± 0.92	3.68 ± 0.75	3.58 ± 0.84	0.475	0.495
Fatigue	2.58 ± 0.84	3.05 ± 1.03	2.37 ± 0.96	3.16 ± 0.96	1.317	0.259
Visual perception	3.68 ± 0.67	3.37 ± 0.60	3.37 ± 0.90	3.32 ± 1.00	1.573	0.218

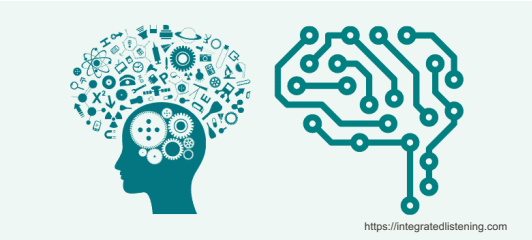
Vassiliadis *et al.* (2024) J Neural Eng

Piao *et al.* (2022) Brain Sciences

Stimulation protocol

NX-436

Neuroplasticity

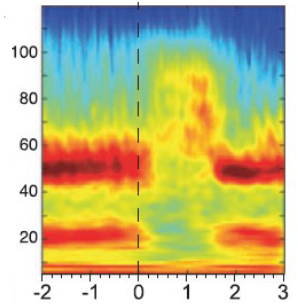


Wessel, Beanato *et al.* (2023) Nature Neuroscience
Popa, Beanato *et al.* (2023) bioRxiv
Beanato, Moon *et al.* (under review)

Neuronal entrainment

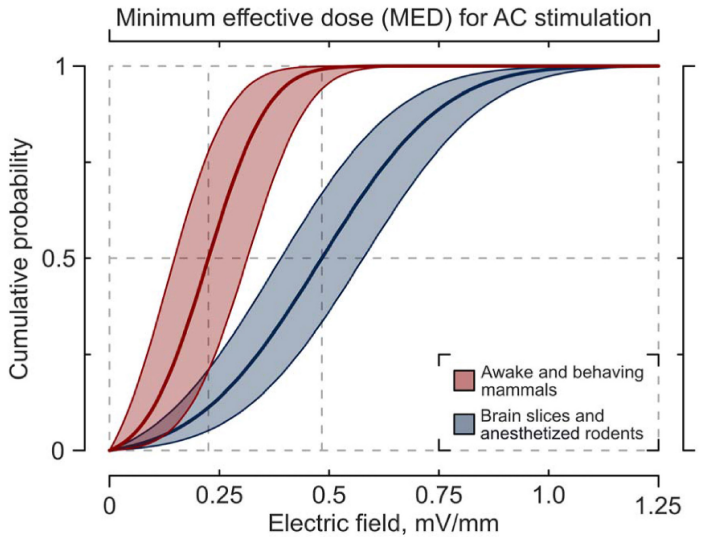
Violante *et al.* (2023) Nature Neuroscience

Interference



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

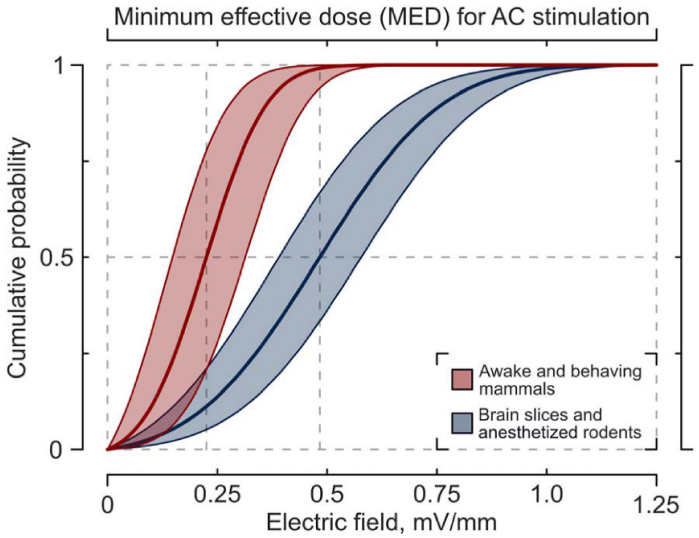
Co-activation



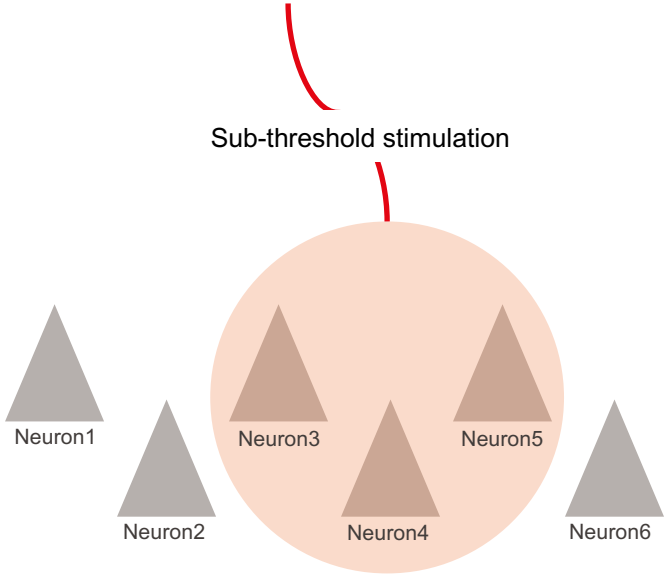
Alekseichuk, 2022

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

Co-activation



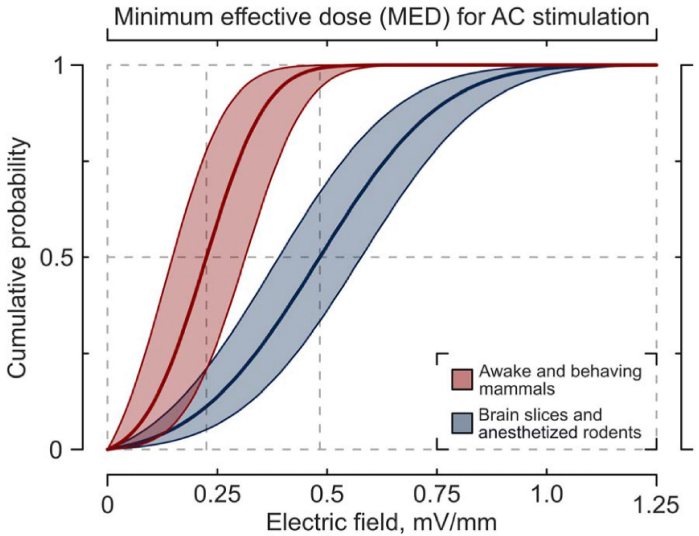
Alekseichuk, 2022



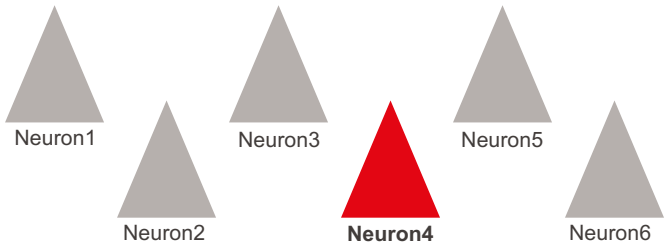
Subthreshold stimulation requires co-activation (Fritsch et al. 2010)

Co-activation steers the stimulation effects

Co-activation



Alekseichuk, 2022



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

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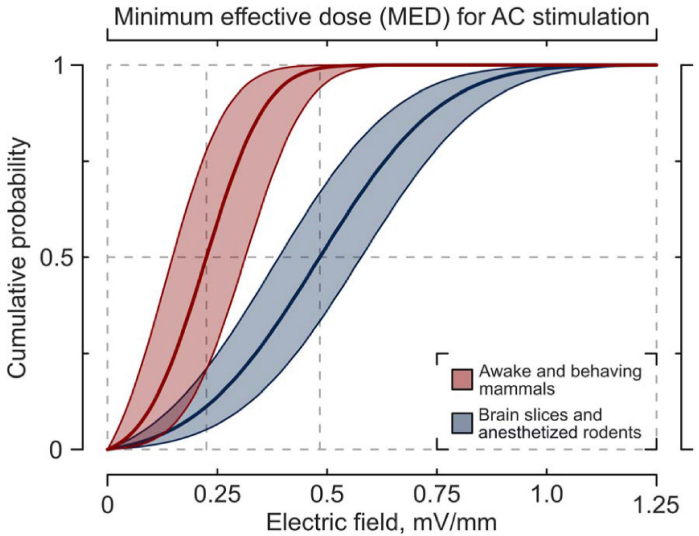
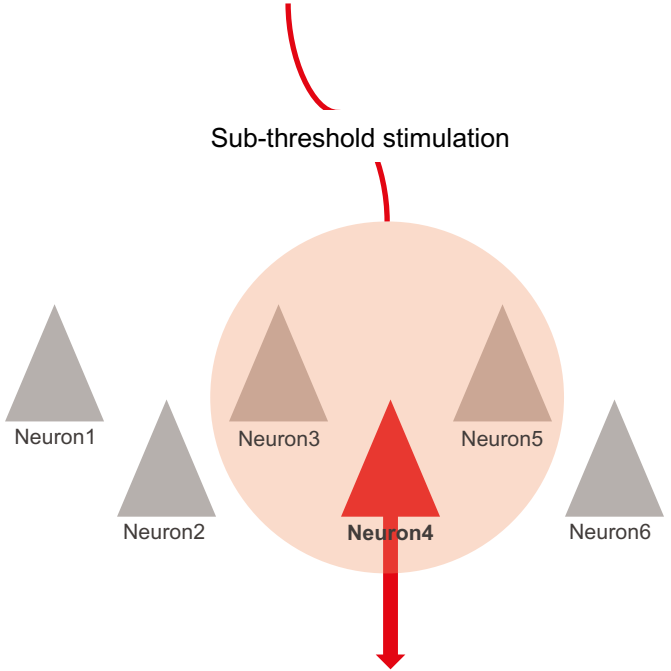
Co-activation



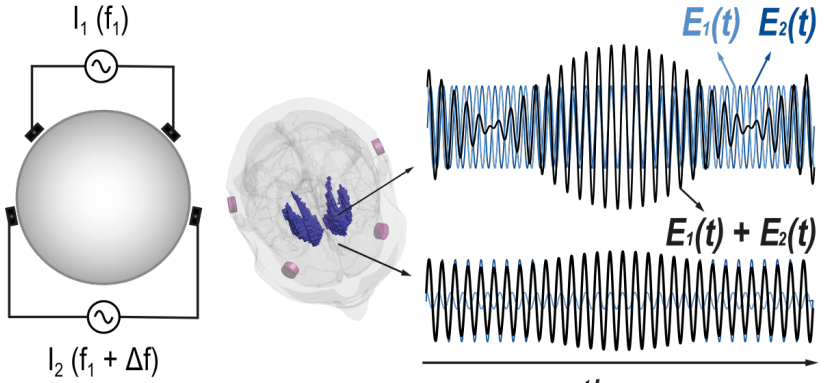
Alekseichuk, 2022



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

Co-activation steers the stimulation effects

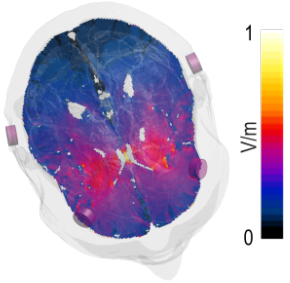
transcranial Temporal Interference Stimulation (tTIS)

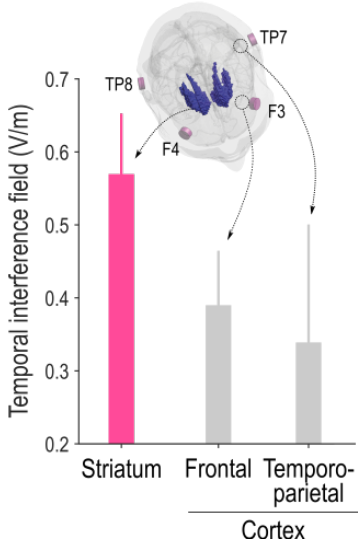


Grossman et al., 2017, *Cell*

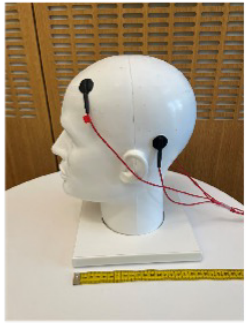
First application of deep tTIS in humans

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

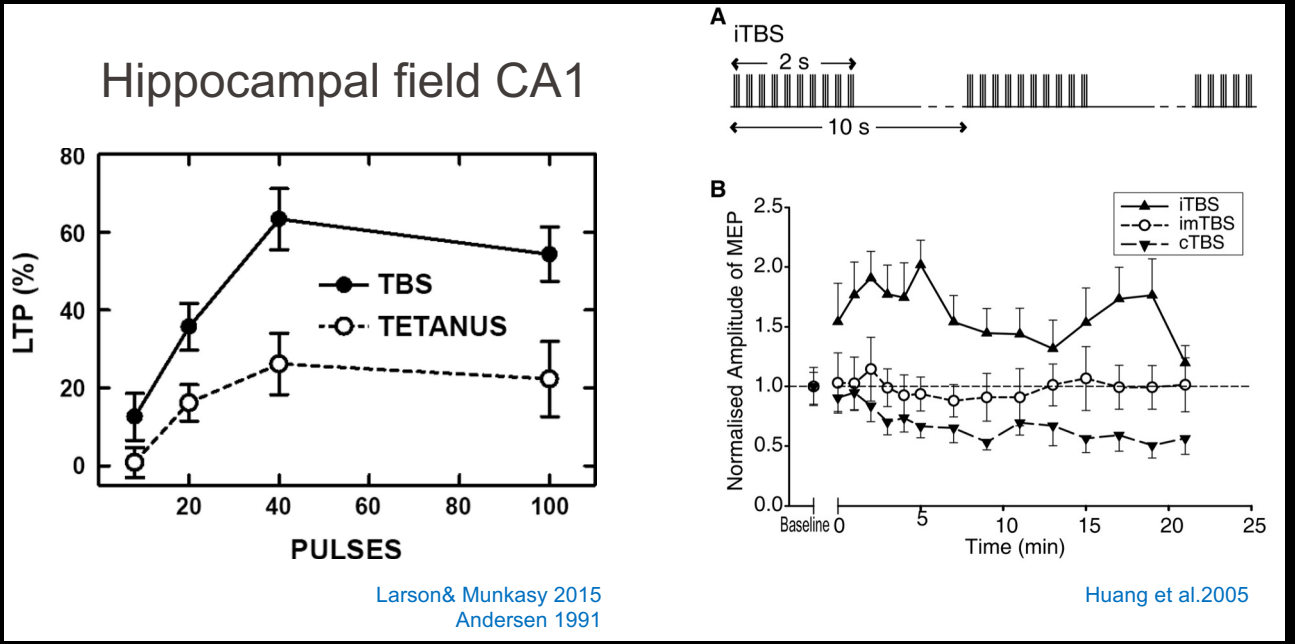




- Animal model validation (Grossman et al., 2017)
- Application on cortical structures in humans (Ma et al., 2021)
- Cadaver work (Violante et al., 2023)

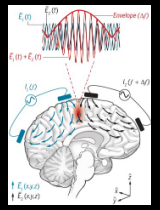


Plasticity enhancing-Theta burst stimulation



Larson& Munkasy 2015
Andersen 1991

Huang et al.2005

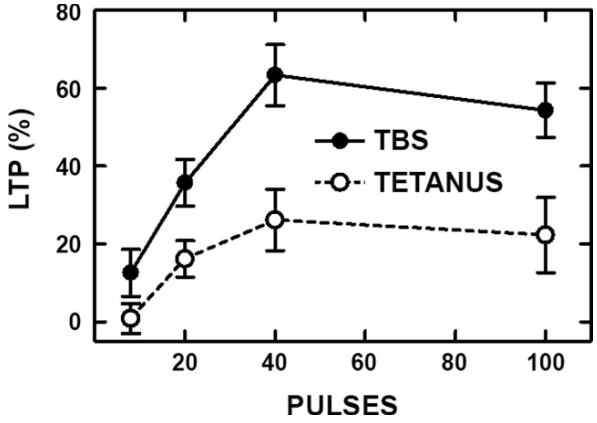


- **iTBS-TI**: 2 tACS channels @ 2kHz and 2.1kHz creating an interference wave with an envelope mimicking a theta-burst, with trains of 3 peaks @100Hz repeated every 200 ms applied for 2sec and followed by 8 sec of HF-control

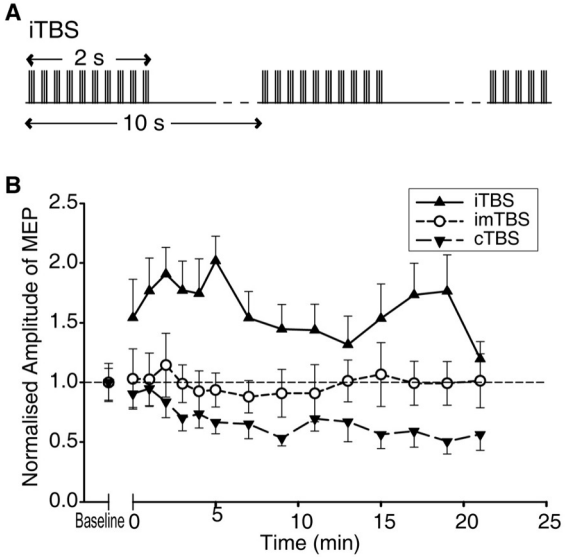
- **HF-control**: 2 tACS channels @ 2kHz without shift in frequencies

Plasticity enhancing-Theta burst stimulation

Hippocampal field CA1

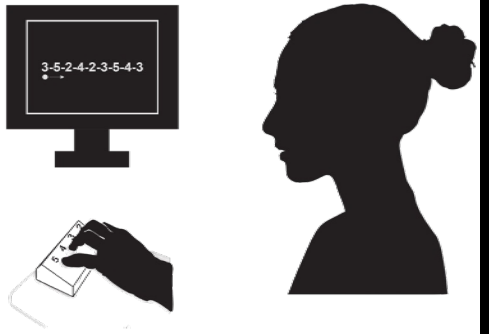


Larson& Munkasy 2015
Andersen 1991

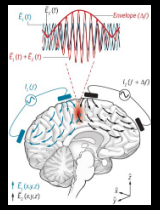


Huang et al.2005

+



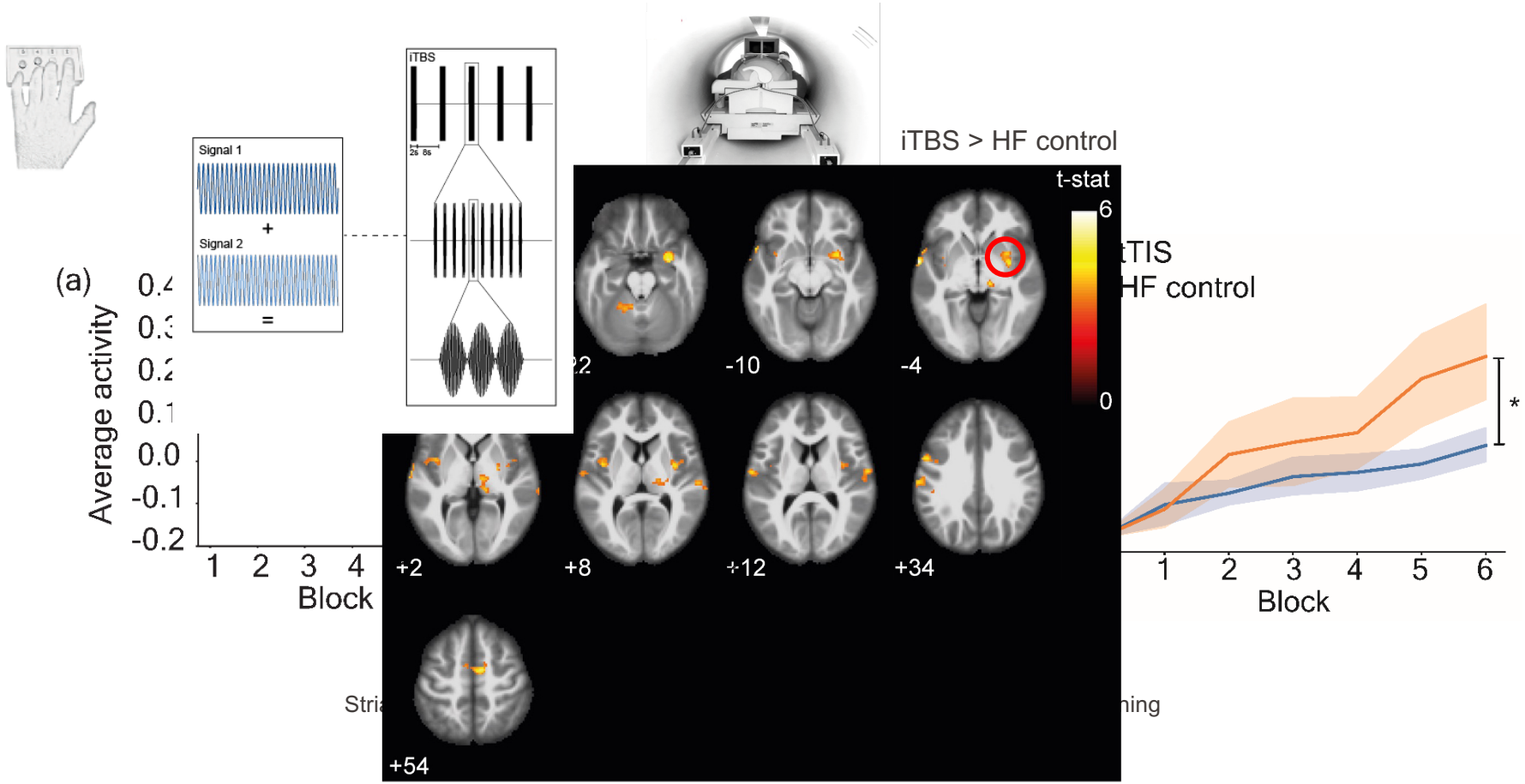
Zimerman et al.2013, 2014; Draaisma et al. 2022, Maceida et al. 2022; Wessel et al. 2022



- 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

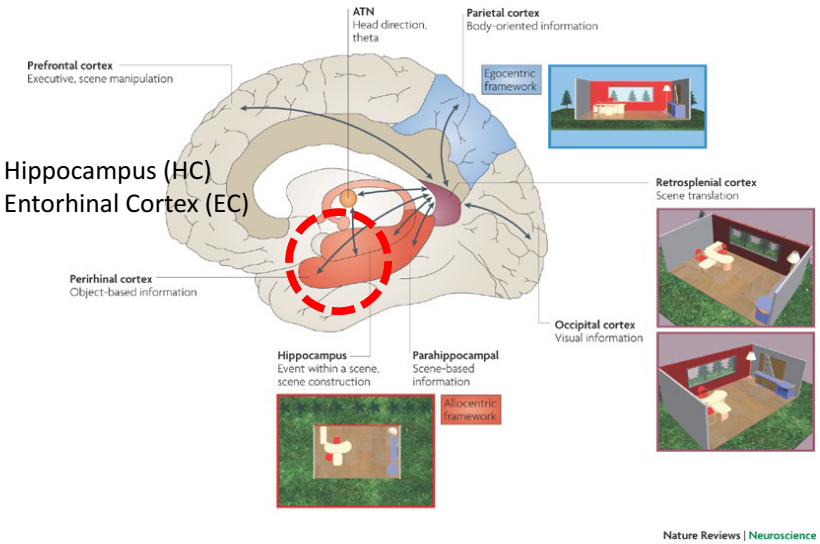
- HF-control: 2 tACS channels @ 2kHz without shift in frequencies

Plasticity-inducing tTIS during motor sequence learning

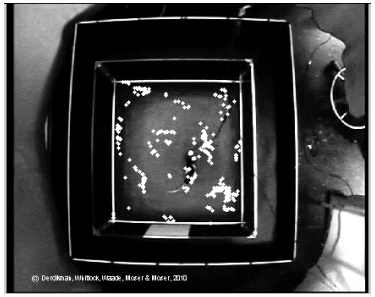


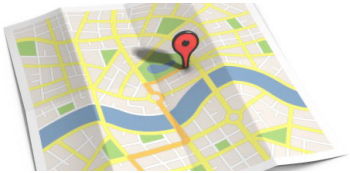
Wessel*, Beanato* et al., 2023, *Nature Neuroscience*

Plasticity-inducing tTIS during spatial memory



- Grid cells in Entorhinal cortex (**EC**)

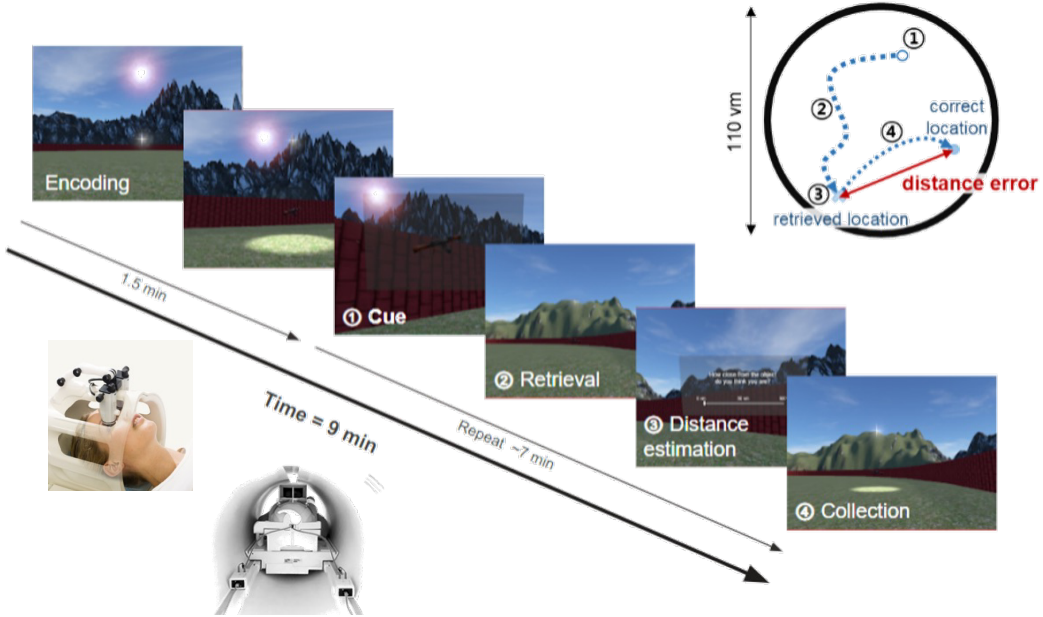




- allocentric spatial representation in the brain
- Spatial navigation
- Memory
- Alzheimer's disease (AD) /MCI

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

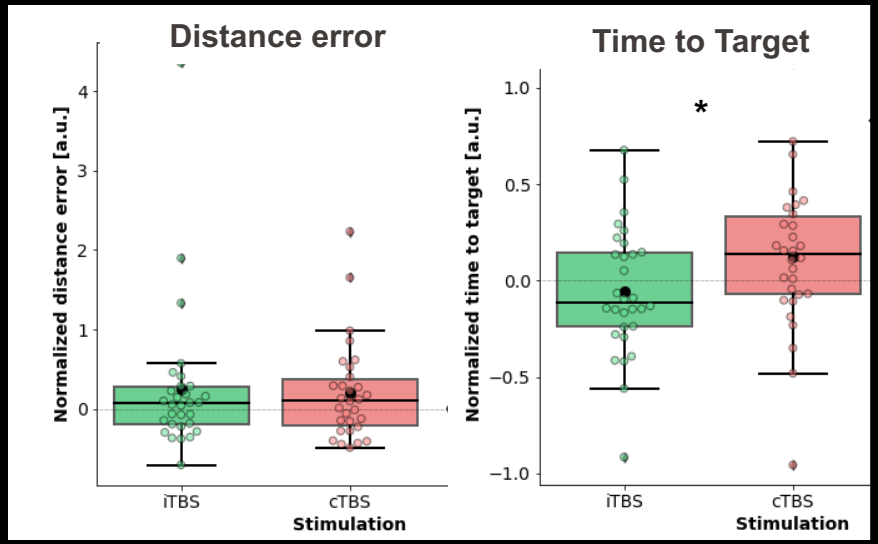
Plasticity-inducing tTIS during spatial memory



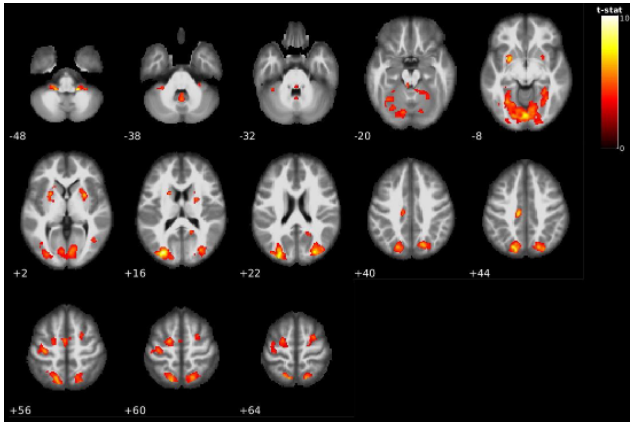
- N = 30 young healthy subjects
- Age 23.6 ± 4.07
- Randomized, double-blind design
- 6 blocks of ~ 9,5 min each
- A-B-C-C-B-A design
- Stimulation: **iTBS-TI** vs. **cTBS-TI** vs. **control** during encoding and retrieval phase
- Target: **right hippocampus**
- Instruction: “perform as **accurate** as possible”

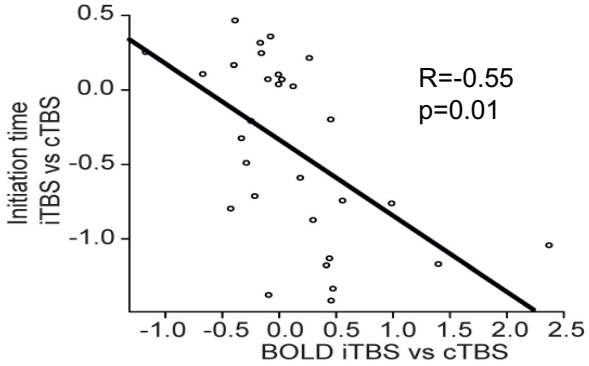
Beanato, Yoon *et al.* (in prep)

Plasticity-inducing tTIS during spatial memory



The bigger the hippocampal activity during iTBS vs cTBS the faster subjects retrieve the information about where to go





Beanato, Yoon *et al.* (in prep)

Non-invasive deep brain stimulation (DBS3.0)

- **Non-invasive** focal **deep** brain stimulation in humans is **possible** (Wessel, Beanato *et al.* 2023 Nature Neuroscience; Violante *et al.* 2023 Nature Neuroscience; Vassiliadis *et al.* acc Nature Hum Beh)
- **Good** safety profile (Vassiliadis *et al.* JNE 2024)
- Huge **potential** for **clinical** applications, as **deep brain structures** like the striatum (e.g., stroke recovery, addiction, apathy, movement disorders) or the hippocampus (e.g., dementia, epilepsy) play a **key role** in the **pathophysiology** of the disorder
- Allows to **extend** orchestrated neuromodulation to **subcortical-cortical** interactions

Summary

- Temporal Interference stimulation (**tTIS**) provides a **promising, disruptive** opportunity to neuromodulate **non-invasively deep** brain structures like the
  - striatum (e.g., Wessel, Beanato *et al.* 2023 Nature Neuroscience; Kwak et al. 2023 Brain Stimulation)
  - hippocampus (e.g., Violante *et al.* 2023 Nature Neuroscience; Grossman et al. 2017 Cell)

  with good focality-depth trade off in first proof-of-concepts

- Detailed simulations crucial for topographic specific application

- tTIS well perceived, good blinding, safe (Vassiliadis et al. submitted; Piao et al. 2022 Brain Sci)

- Open new **opportunities** to study **causal** relationships between deep brain structures and function in vivo in humans and to develop **novel non-invasive interventional strategies** for **neurological** and **psychiatric** disorders targeting deep brain structures causally involved in the pathophysiology

- Open questions, challenges
  - Personalized application
  - Higher topographic resolution
  - Understanding of underlying mechanisms
  - Closed-loop stimulation
  - Home-based self-application
  - Proof-of-concept in clinical populations

Questions?