EPFL

Neuro X Institute

defitech fondation

HUG Hôpitaux Universitaires Genève

Clinique romande de réadaptation

Neuromodulation: towards personalization

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Neuro-X Institute (INX)
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Department of Clinical Neuroscience, University Hospital of Geneva

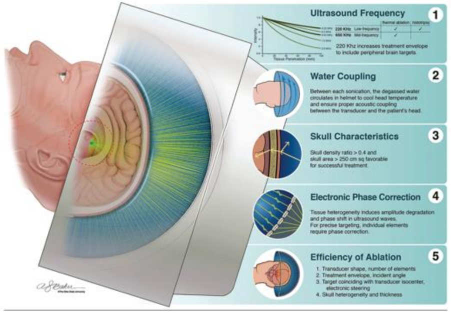
Overview

Neuromodulation – Towards personalization?

Invasive vs. Non-invasive	Method/Technique	Stimulation Protocol	Target Selection

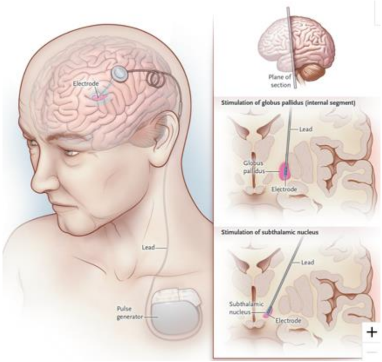
Invasive vs non-invasive

Lesioning



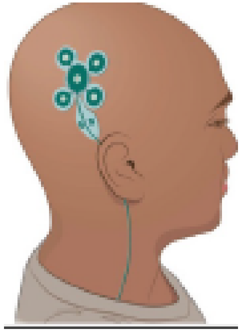
Elias *et al.* NEJM 2016

Invasive



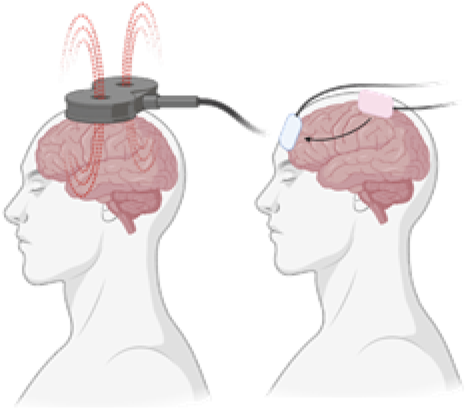
Volkmann J Clin Neurophysiol. 2004

Minimal Invasive



Schulz-Bonhage JAMA Neurol. 2023

Non Invasive



Raffin Neuroscientist. 2018

Neuromodulation – How to choose?

Invasive vs. Non-invasive	Method/Technique	Stimulation Protocol	Target Selection

Lesioning

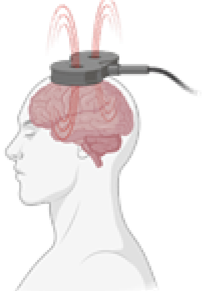
Invasive

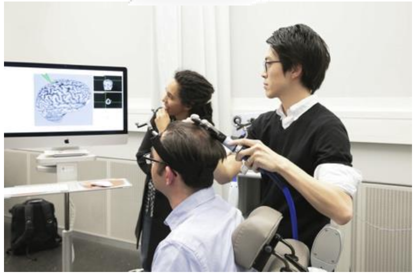
Minimal-invasive

Non-invasive

Non-invasive brain stimulation for neuromodulation

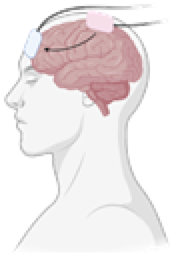
TMS

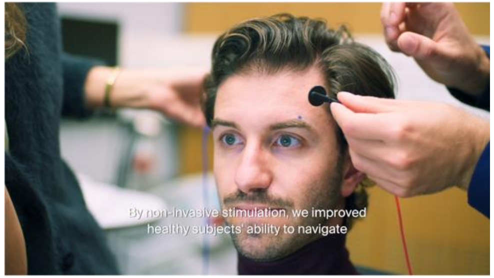




Lefaucheur *et al.* Clin Neurophys 2020

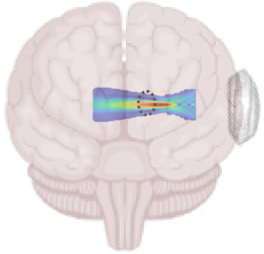
tES





Antal et al. Clin Neurophysiol. 2018

TUS



Murphy *et al.* Clin Neurophysiol. 2025

Overview

Neuromodulation – How to choose?

Invasive vs. Non-invasive	Method/Technique	Stimulation Protocol	Target Selection

Lesioning

Invasive

Minimal-invasive

Non-invasive

Invasive

- Lesioning (tUS)
- DBS
- Epidural
- Intracortical

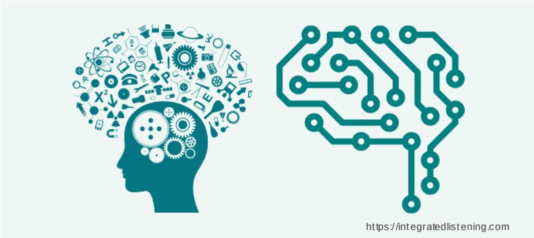
NIBS

- TMS
- tES
- TUS

EPFL

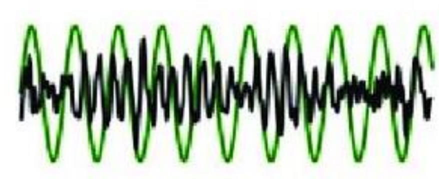
Protocols for neuromodulation

Neuroplasticity



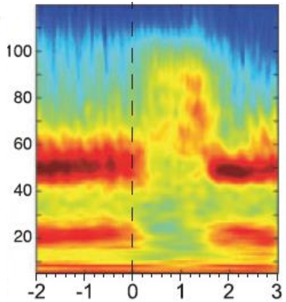
Bevilacqua *et al.* (2025) Brain
Beanato, Moon *et al. (2024)* Science Advances
Wessel, Beanato *et al.* (2023) Nature Neuroscience
Maceira-Elvira *et al.* (2022) Science Advances
Wessel *et al.* (2023) Cerebellum
Wessel *et al*. (2021) Sci Rep
Zimerman *et al*. (2014) Ann Neurol
Hummel *et al.* (2005) Brain

Neuronal entrainment



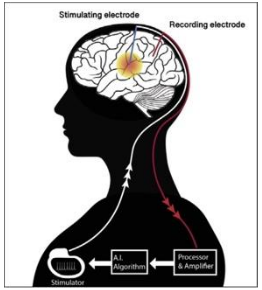
Raffin *et al.* under review
Bevilacqua *et al.* (2024) BrainStimulation
Draaisma *et al.* (2022) BrainStimulation
Salamanca *et al.* (2021) NeuroImage
Wessel *et al.* (2020) Sci Rep
Sauseng *et al.* (2009) Curr Biol
Plewnia *et al.* (2008) EJN

Interference



Vassiliadis *et al.* (2024) Nature Hum Beh
Renzi *et al.* (2013) J Cogn Neurosci
Liuzzi *et al*. (2010) Curr Biol
Fridman *et al.* (2004) Brain

Closed-Loop



Widge *et al.* (2024) Neuropsychopharm
Zrenner *et al.* (2018) Front
Neumann *et al.* (2023) Trends Neurosci.

Overview

Neuromodulation – How to choose?

Invasive vs. Non-invasive	Method/Technique	Stimulation Protocol	Target Selection

Lesioning

Invasive

Minimal-invasive

Non-invasive

Invasive
- Lesioning (tUS)
- DBS
- Epidural
- Intracortical

NIBS
- TMS
- tES
- TUS

Entrainment

Disruption - Desynchronization

Impact on plasticity

Enhance interregional interactions

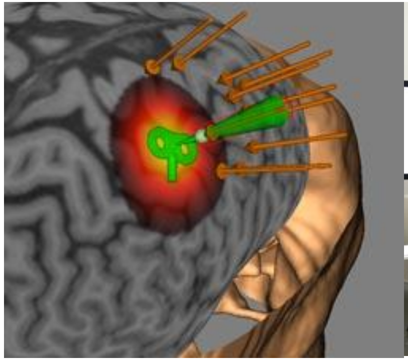
Adaptive

State-dependent/ Closed-loop

Target selection

Based on surface anatomy (10-20 system)

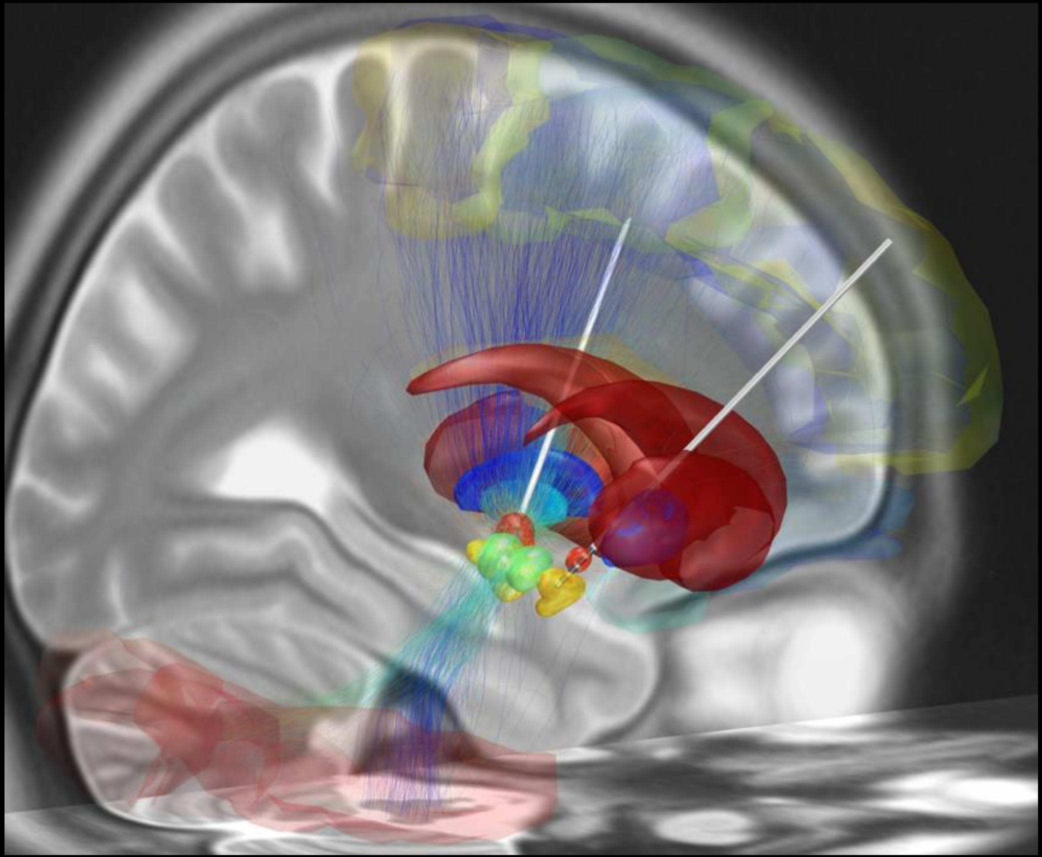
Neuronavigation



Prerequisite: the understanding that in **every** subject, in **every** patient the respective **brain region represents** the **same** (cognitive, motor) function

Structural / functional connectivity – predictors of response?

Deep Brain Stimulation (DBS)



Example: Obsessive-Compulsive Disorder (OCD)

Obsessive-Compulsive Disorder (OCD)

Obsessive-Compulsive Disorder (OCD) is a chronic mental health condition characterized by **obsessions**—intrusive, unwanted thoughts, images, or urges—and **compulsions**, which are repetitive behaviors or mental acts performed to reduce the anxiety caused by these obsessions.

Most Frequent Symptoms:

Obsession, e.g., :

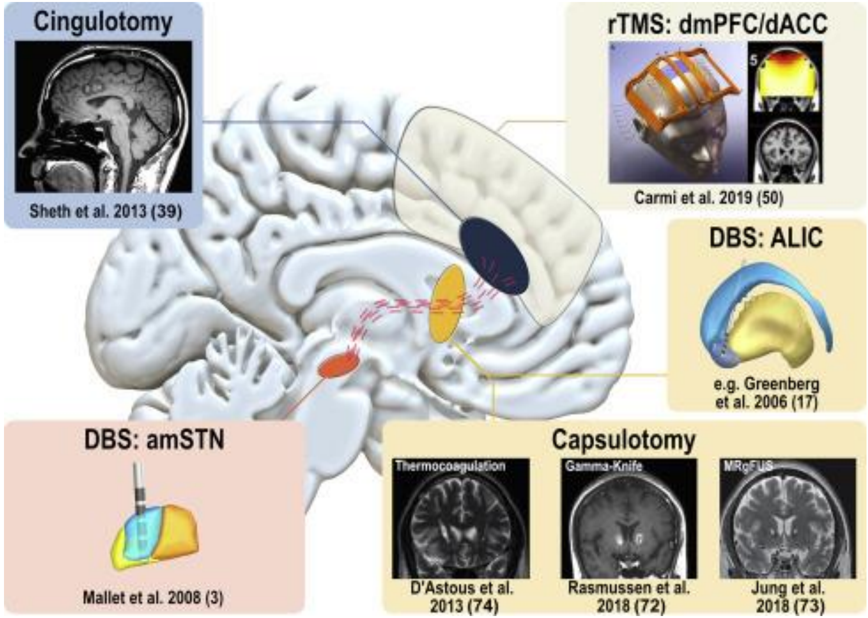
- Fear of contamination (e.g., germs, dirt)
- Doubts about having done something right (e.g., locking doors, turning off the stove)
- Intrusive thoughts about harm, taboo topics, or symmetry/order

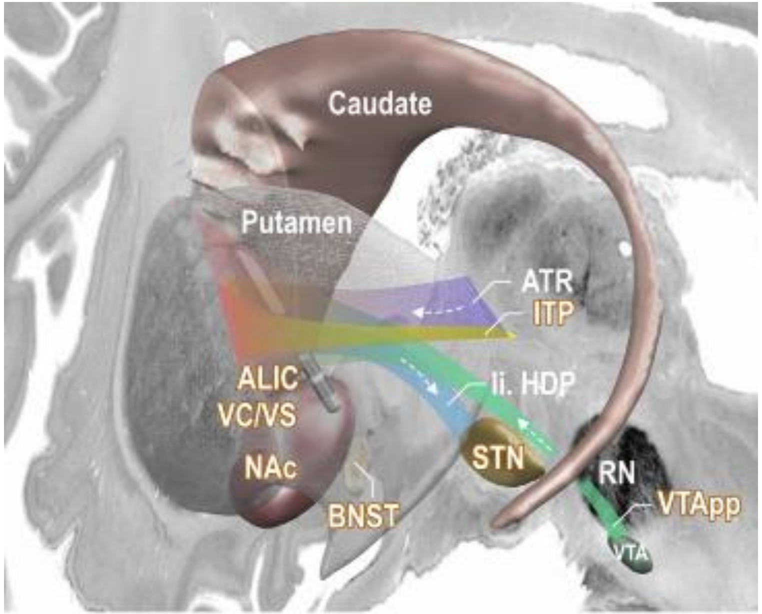
Compulsion, e.g.,:

- Excessive cleaning or handwashing
- Repeated checking (e.g., locks, appliances)
- Counting, repeating actions, or arranging items in a specific way

These symptoms can significantly interfere with daily functioning and quality of life.

OCD: Brain stimulation based treatment

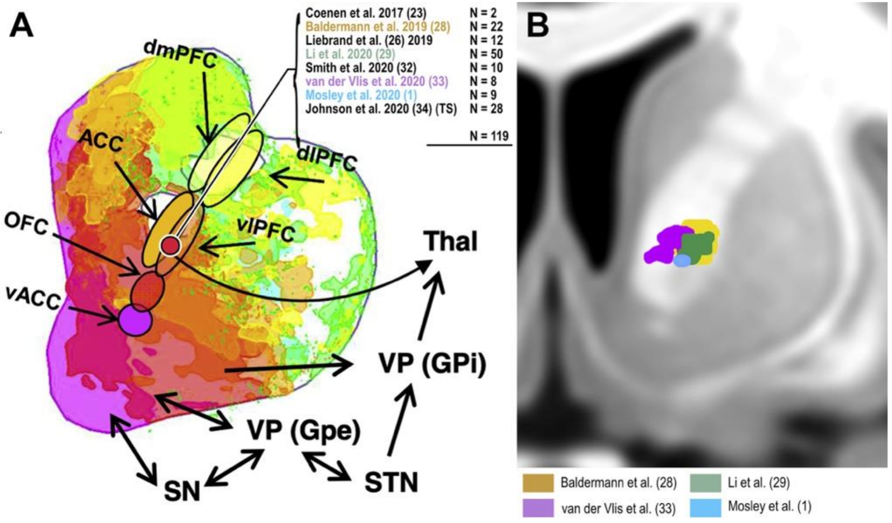




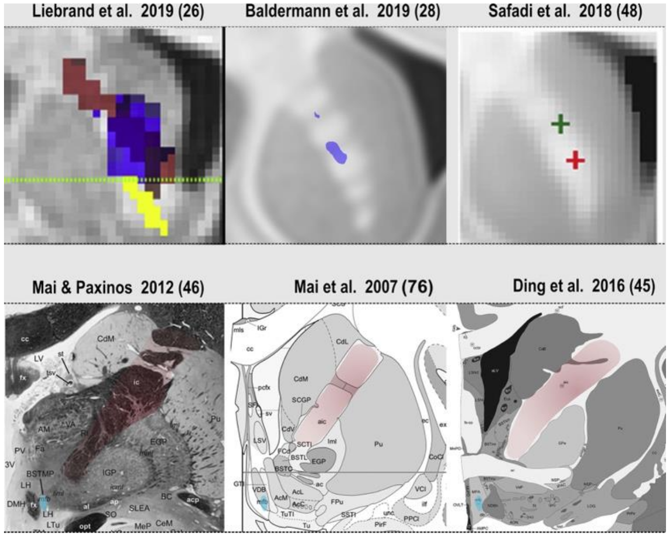
Baldermann et al. 2021 Biol Psych

OCD: Connectivity vs anatomy

anterior limb of the internal capsule (ALIC)



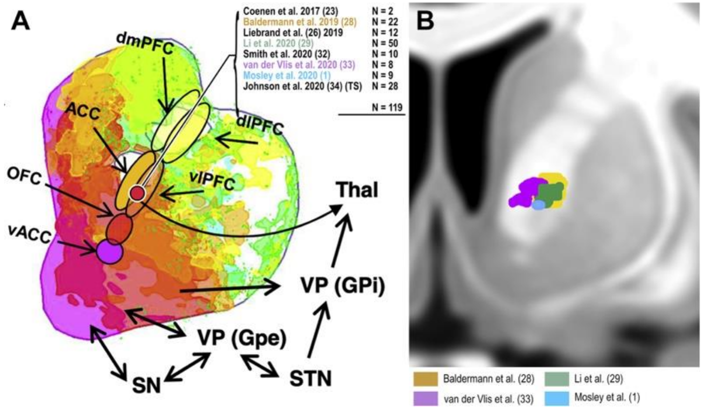
Incoherent anatomical definition



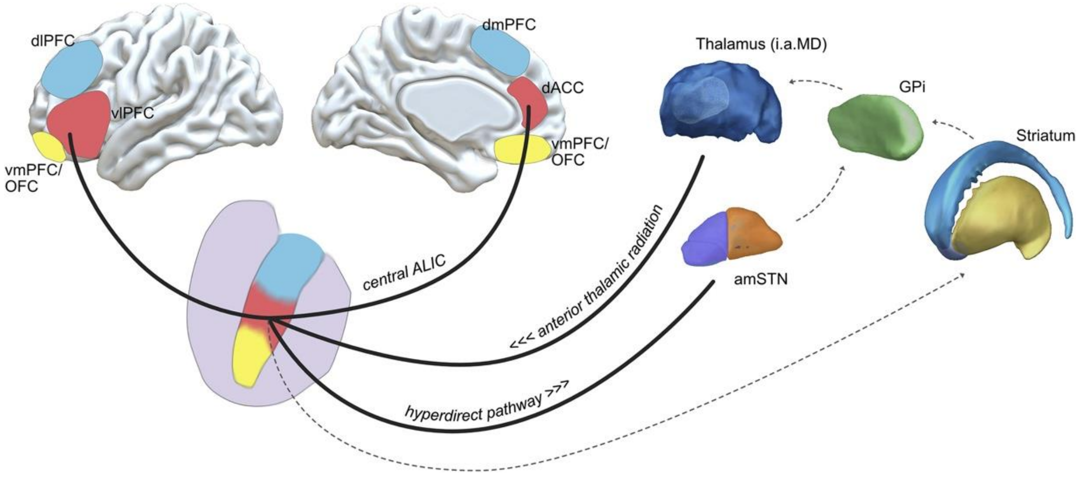
Baldermann et al. 2021 Biol Psych

OCD: Connectivity vs anatomy

anterior limb of the internal capsule (ALIC)

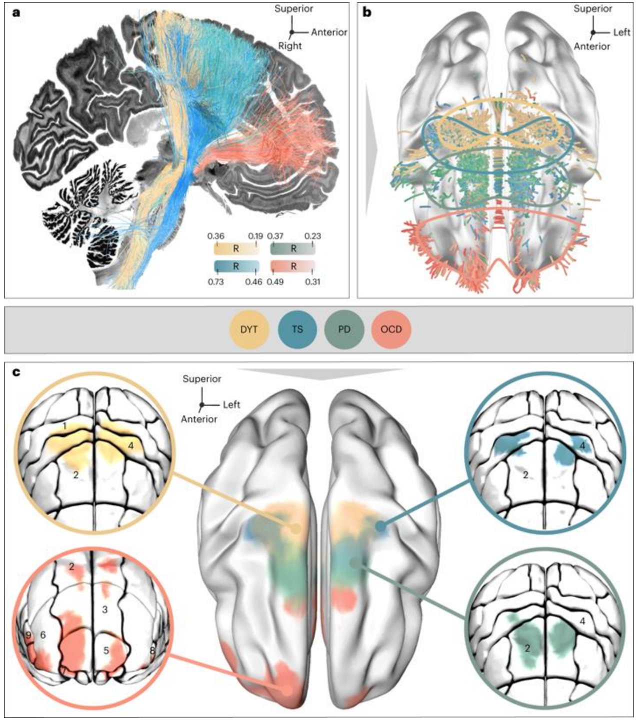


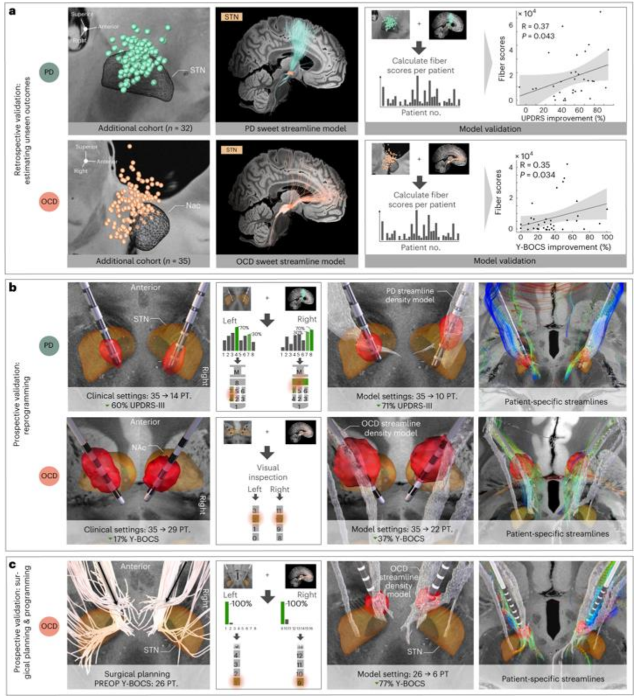
Connectivity of the ALIC



Baldermann et al. 2021 Biol Psych

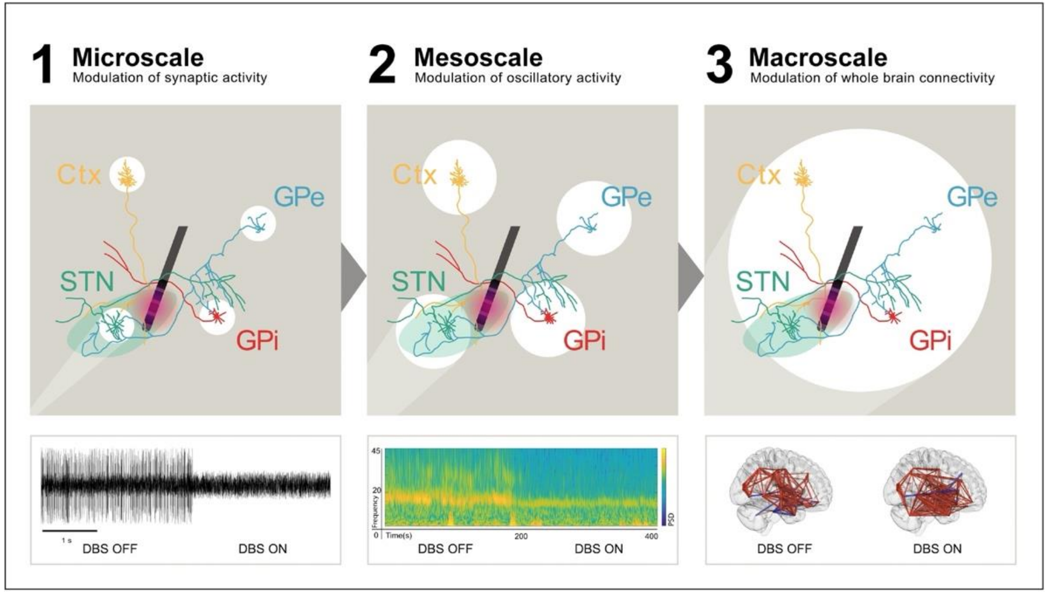
Structural connectivity – predictor of response?



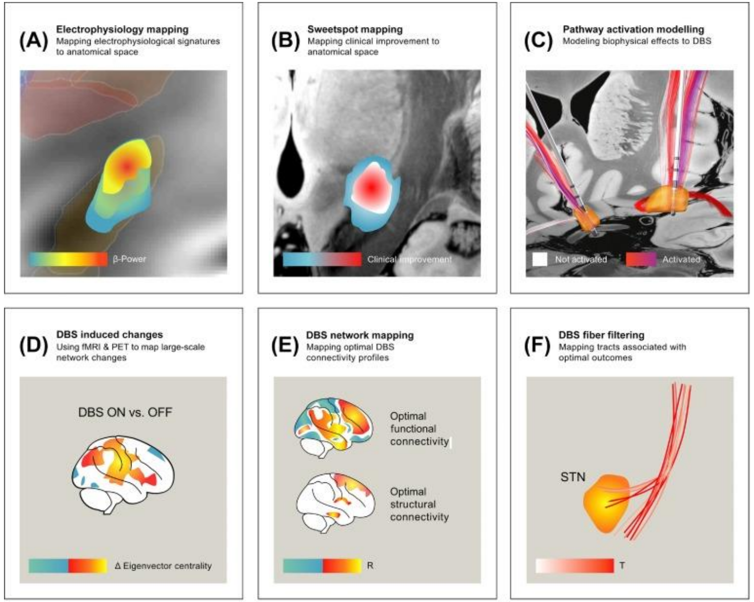


Hollunder et al. 2023 Nat Nsc

DBS – prediction of response?



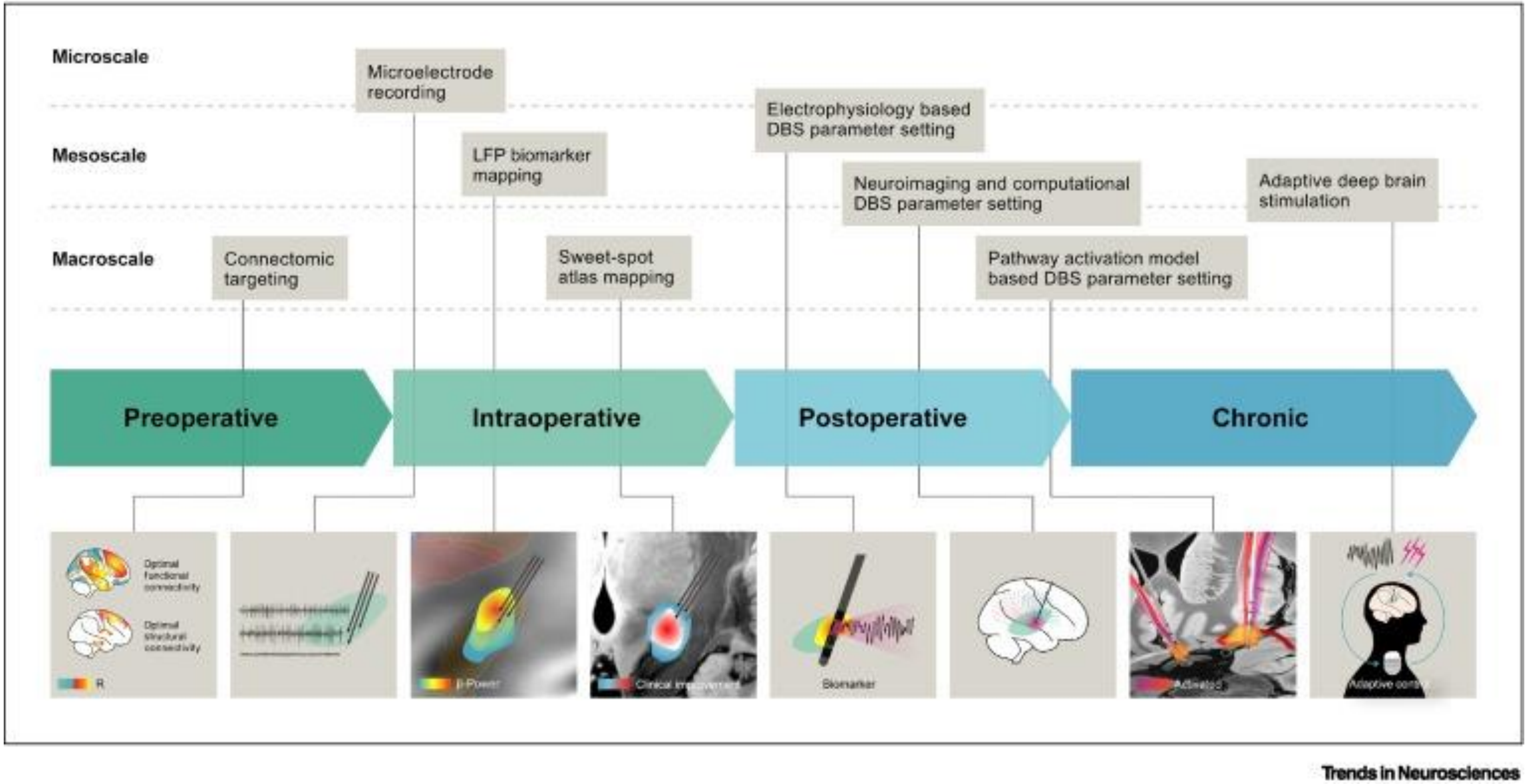
Trends in Neurosciences



Trends in Neurosciences

Neumann (2023) TINS

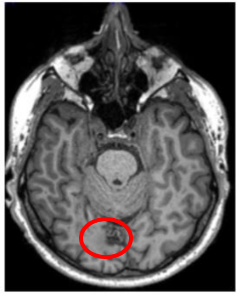
DBS – prediction of response?

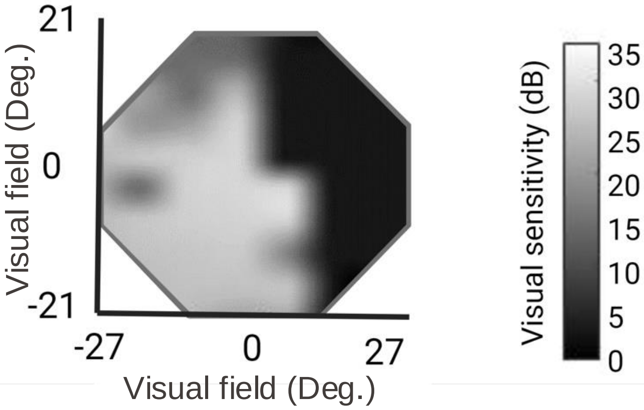


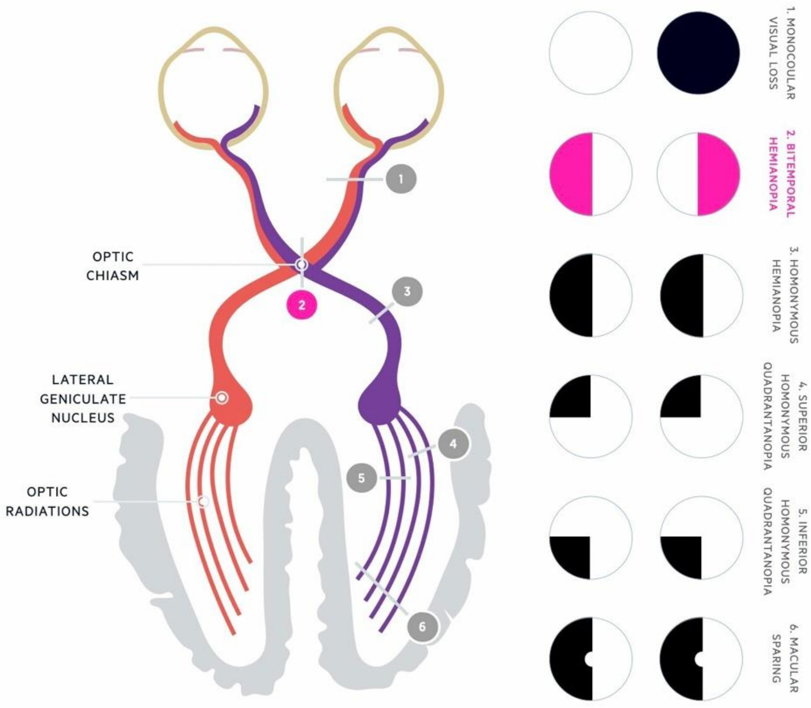
Neumann (2023) TINS

Non-invasive examples for the predictive role of connectivity for neuromodulation effects

Hemianopia

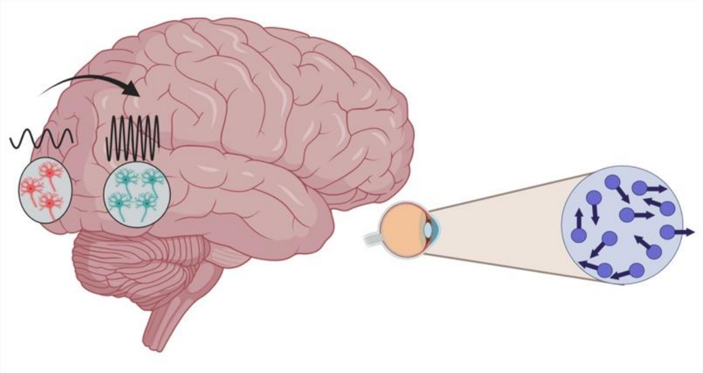


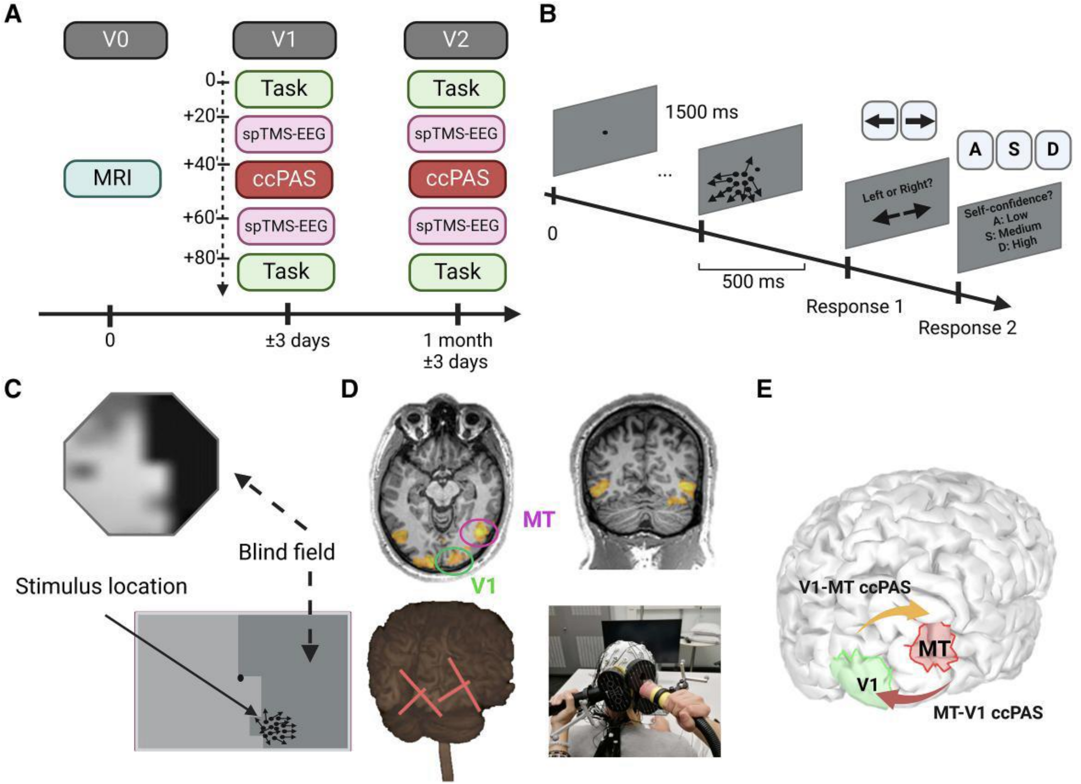

21
0
-21
-27
0
27
Visual field (Deg.)
Visual field (Deg.)
Visual sensitivity (dB)
35
30
25
20
15
10
5
0


OPTIC CHIASM
LATERAL GENICULATE NUCLEUS
OPTIC RADIATIONS
1
2
3
4
5
6
1. MONOCOULAR VISUAL LOSS
2. BITEMPORAL HEMIANOPIA
3. HOMONYMOUS HEMIANOPIA
4. SUPERIOR HOMONYMOUS QUADRANTANOPIA
5. INFERIOR HOMONYMOUS QUADRANTANOPIA
6. MACULAR SPARING

Orchestrated neuromodulation – ccPAS

Motion processing





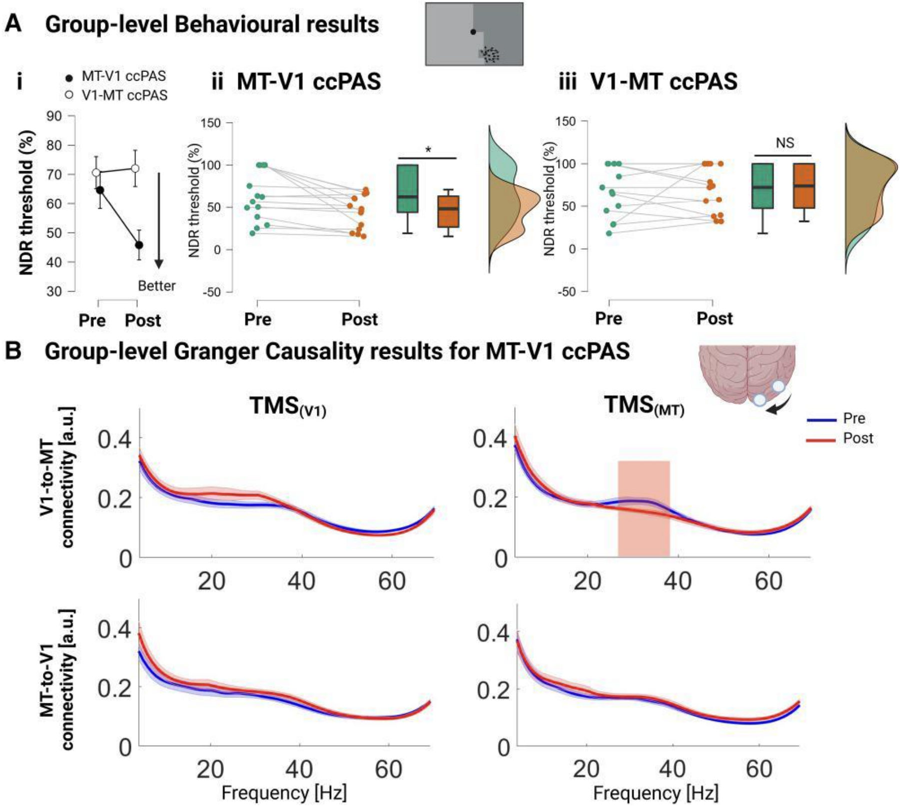
ccPAS:

- Hebbian-like spike-timing dependent plasticity
- 16 stroke patients
- Double-blind, cross-over

Bevilacqua, Raffin *et al*., (**2025**) Brain

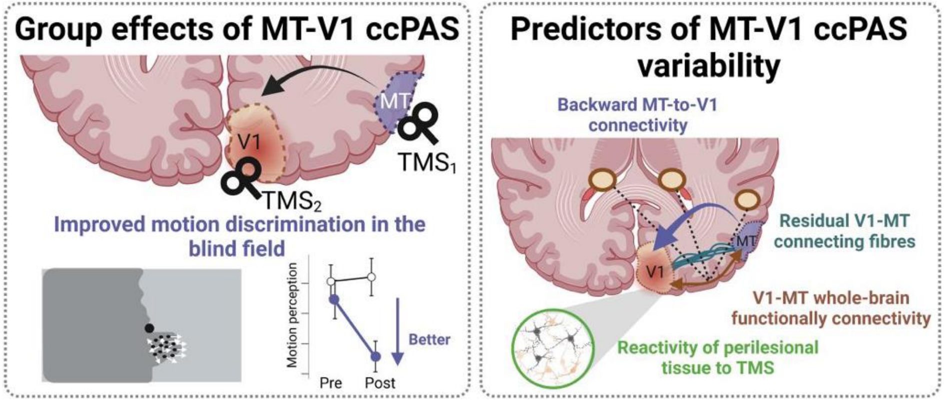
Orchestrated neuromodulation – ccPAS

EPFL



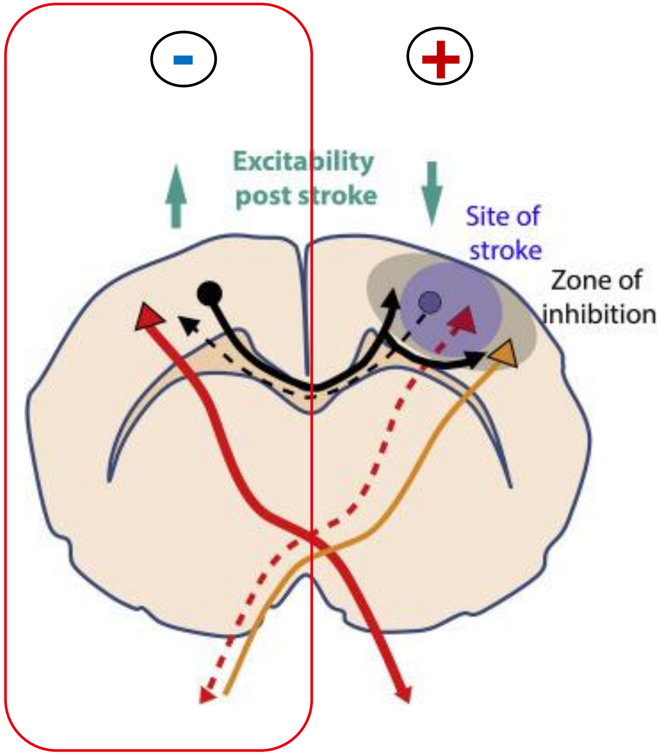
ccPAS intervention

- MT-to-V1 ccPAS enhanced motion direction discrimination
- changed top-down MT-to-V1 inputs only in patients with improvement in motion discrimination.
- Good responders demonstrated
  - improved functional coupling cortical motion pathway and other areas in the visual network,
  - more preserved ipsilesional V1-MT structural integrity



Bevilacqua, Raffin *et al.*, (**2025**) Brain

NIBS stroke recovery – conceptual Model



Boddington & Reynolds (2017) BrainStimulation
Murase *et al.* (2004) Brain

for review: Hummel & Cohen (2006) Lancet Neurol; Di Pino *et al.* (2014) Nat Rev Neurol; Micera *et al.* (2020) Neuron, Raffin & Hummel (2017) The Neuroscientist

Target non-lesioned hemisphere

NeuroImage: Clinical 21 (2019) 101620

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments

Juan Du[a,1], Fang Yang[a,1], Jianping Hu[b], Jingze Hu[a], Qiang Xu[b], Nathan Cong[a], Qirui Zhang[b], Ling Liu[a], Dante Mantini[c,d], Zhiqiang Zhang[b,e,*], Guangming Lu[b,e,*], Xinfeng Liu[a,*]

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur[a,b,*], André Aleman[c], Chris Baeken[d,e,f], David H. Benninger[g], Jérôme Brunelin[h], Vincenzo Di Lazzaro[i], Saša R. Filipović[j], Christian Grefkes[k,l], Alkomiet Hasan[m], Friedhelm C. Hummel[n,o,p], Satu K. Jääskeläinen[q], Berthold Langguth[r], Letizia Leocani[s], Alain Londero[t], Raffaele Nardone[u,v,w], Jean-Paul Nguyen[x,y], Thomas Nyffeler[z,aa,ab], Albino J. Oliveira-Maia[ac,ad,ae], Antonio Oliviero[af], Frank Padberg[m], Ulrich Palm[m,ag], Walter Paulus[ah], Emmanuel Poulet[h,ai], Angelo Quartarone[aj], Fady Rachid[ak], Irena Rektorová[al,am], Simone Rossi[an], Hanna Sahlsten[ao], Martin Schecklmann[r], David Szekely[ap], Ulf Ziemann[aq]

Stroke

Volume 49, Issue 9, September 2018, Pages 2138-2146

https://doi.org/10.1161/STROKEAHA.117.020607

American Heart Association.

CLINICAL SCIENCES

Randomized Sham-Controlled Trial of Navigated Repetitive Transcranial Magnetic Stimulation for Motor Recovery in Stroke

The NICHE Trial

Richard L. Harvey, MD, Dylan Edwards, PhD, PT, Kari Dunning, PT, PhD, Felipe Fregni, MD, PhD, Joel Stein, MD, Jarmo Laine, MD, Lynn M. Rogers, PhD, Ford Vox, MD, Ana Durand-Sanchez, MD, Marcia Bockbrader, MD, PhD, Larry B. Goldstein, MD, Gerard E. Francisco, MD, Carolyn L. Kinney, MD, Charles Y. Liu, PhD, MD, and on behalf of the NICHE Trial Investigators*

ASNR AMERICAN SOCIETY OF NEUROREHABILITATION

Original Research Article

Neurorehabilitation and Neural Repair
2020, Vol. 34(9) 856–867
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DOI: 10.1177/1545968320948610
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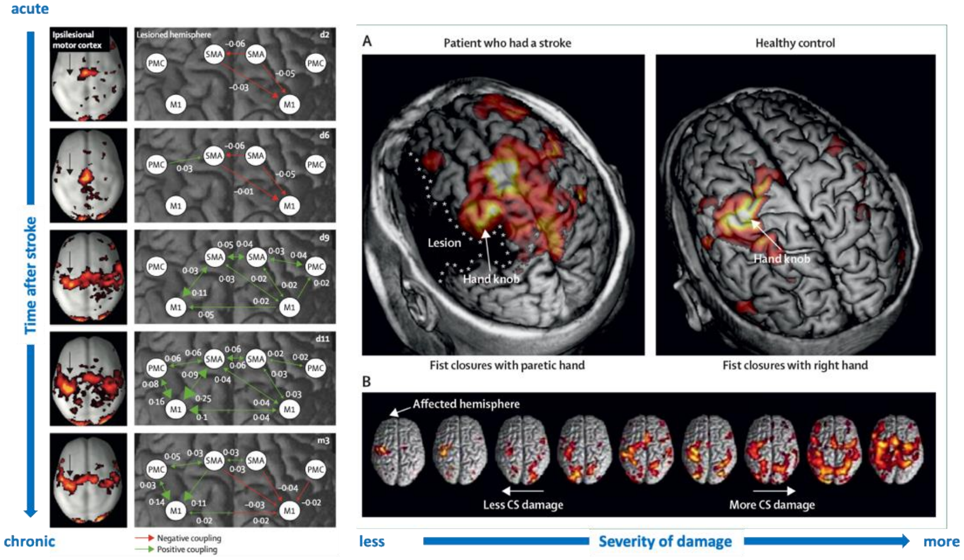
SAGE

Low-Frequency Repetitive Transcranial Magnetic Stimulation Over Contralesional Motor Cortex for Motor Recovery in Subacute Ischemic Stroke: A Randomized Sham-Controlled Trial

Won-Seok Kim, MD, PhD[1], Bum Sun Kwon, MD, PhD[2], Han Gil Seo, MD, PhD[3], Jihong Park, MD[1], and Nam-Jong Paik, MD, PhD[1]

Rastgoo *et al.* (2016) Disabil Rehabil; Forogh *et al.* (2017) Basic Clin Neurosci; Harvey *et al.* (2018) Stroke; LeFaucheur *et al.* (2020) Clin Neurophys

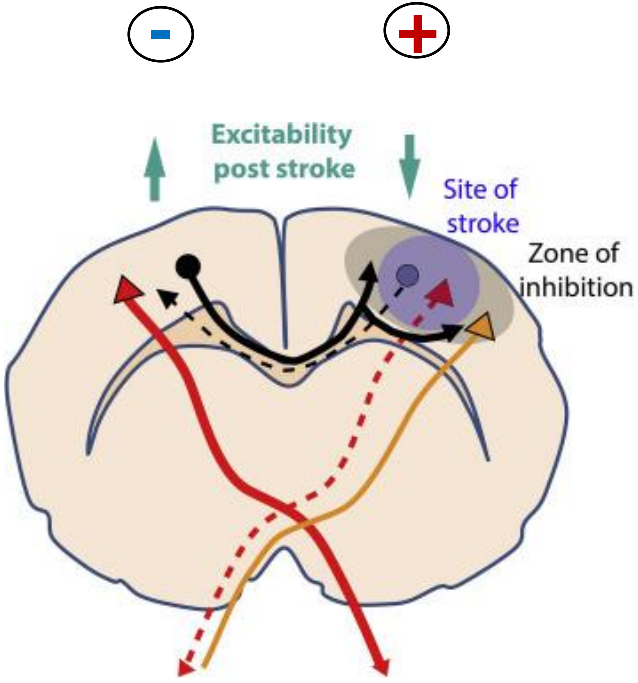
Role of non-lesioned hemisphere



For review Grefkes & Fink (2014) Lancet Neurology; Guggisberg *et al.* (2019) Clin Neurophys

Rastgoo *et al.* (2016) Disabil Rehabil; Forogh *et al.* (2017) Basic Clin Neurosci; Harvey *et al.* (2018) Stroke; LeFaucheur *et al.* (2020) Clin Neurophys

NIBS stroke recovery – Simplified Model



Boddington & Reynolds (2017) BrainStimulation
Murase *et al.* (2004) Brain

Enhance cortical **excitability** and **neuroplasticity** in the **lesioned** hemisphere

- Applying directly **excitatory** NIBS to the **lesioned** hemisphere
- Applying **inhibitory** NIBS to the **intact** hemisphere

Reduce maladaptive influence of the **intact** to the lesioned hemisphere

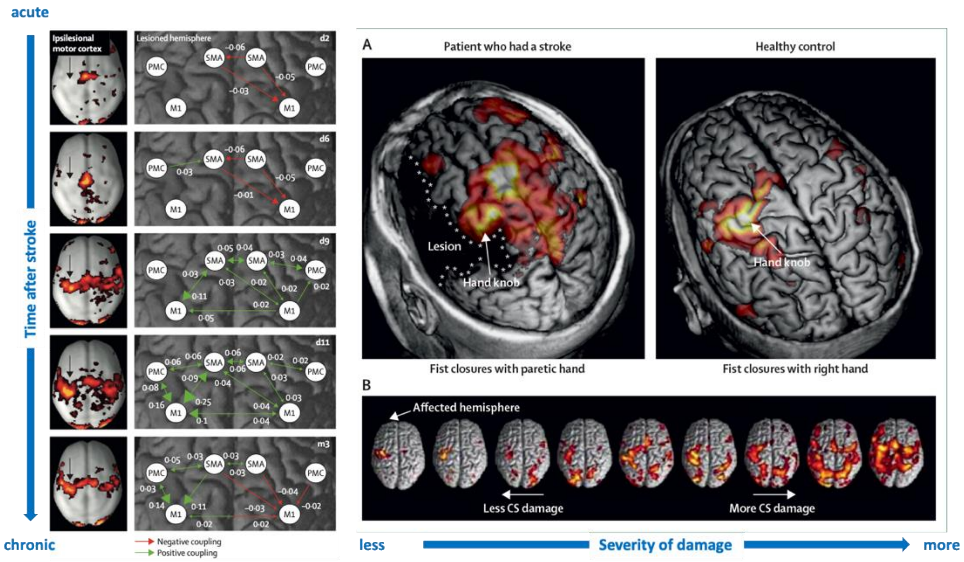
- However this concept has been challenged
- Might hold true only in a subgroup of patients

(for review Hummel *et al.* 2008)

Non-personalized 'one suits all' approaches

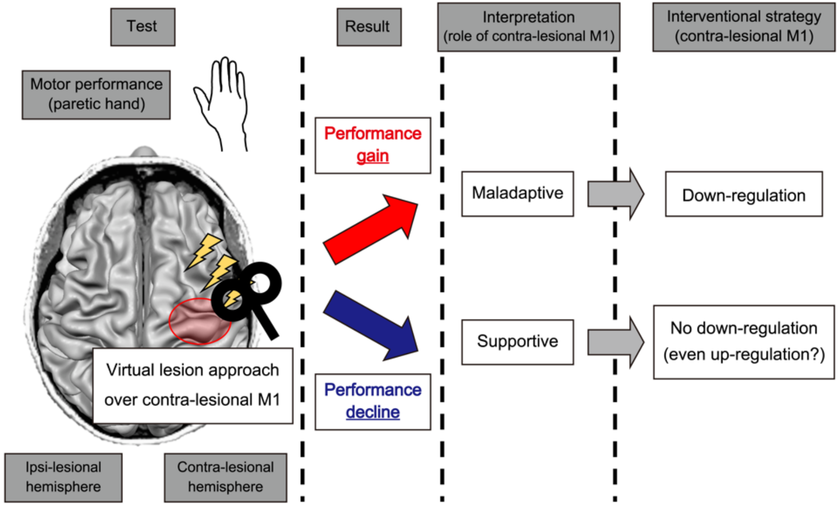
for review: Hummel & Cohen (2006) Lancet Neurol; Di Pino *et al.* (2014) Nat Rev Neurol; Micera *et al.* (2020) Neuron, Raffin & Hummel (2017) The Neuroscientist

Role of non-lesioned hemisphere – Treatment strategy



For review Grefkes & Fink (2014) Lancet Neurology; Guggisberg *et al.* (2019) Clin Neurophys

Personalized treatment strategy



For review Morishita & Hummel (2017) CBNR; Coscia *et al.* (2019) Brain, Micera *et al.* (2020) Neuron

Rastgoo *et al.* (2016) Disabil Rehabil; Forogh *et al.* (2017) Basic Clin Neurosci; Harvey *et al.* (2018) Stroke; LeFaucheur *et al.* (2020) Clin Neurophys

Role of non-lesioned hemisphere

Can we test this to predict response of individual patients?

CM1 is ***maladaptive***

CM1 is ***adaptive***

Non-lesioned hemisphere might have opposite function in different patients

Fleury *et al. in* prep

Role of non-lesioned hemisphere – Interference/virtual lesioning

Can we test this to predict response of individual patients? YES

Lower *mean error in Verum than Sham*

↓

VL ***increased*** *performance*

↓

CM1 is ***maladaptive***

Higher *mean error in Verum than Sham*

↓

VL ***decreased*** *performance*

↓

CM1 is ***adaptive***

Non-lesioned hemisphere might have opposite function in different patients, which can be determined by TMS virtual lesion approach.

Fleury *et al. in* prep

Role of non-lesioned hemisphere – Interference/virtual lesioning

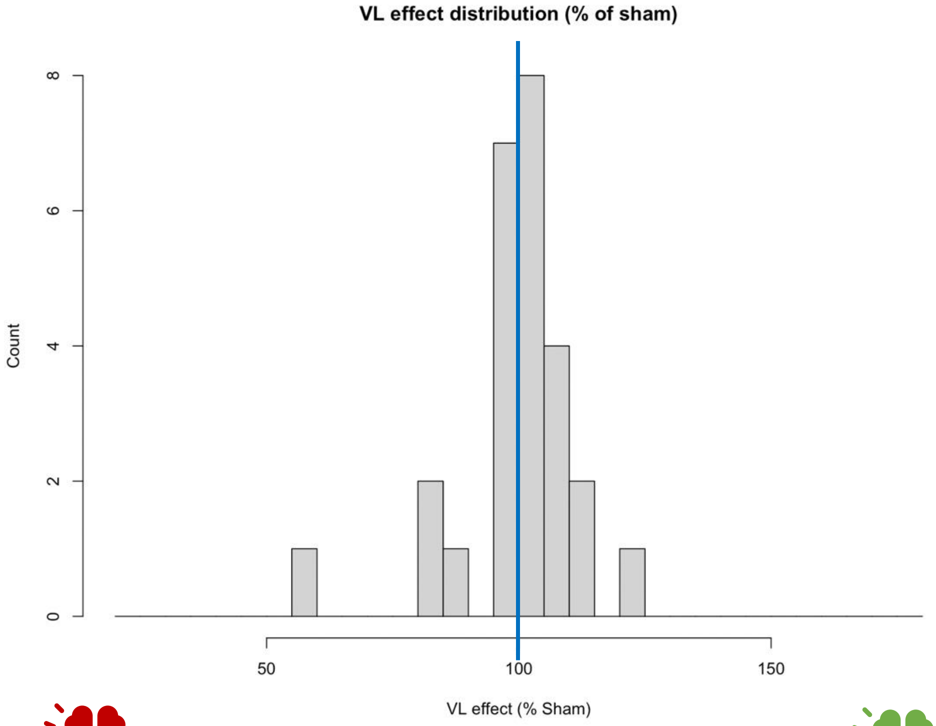
Lower *mean error in Verum than Sham*

↓

VL ***increased*** *performance*

↓

CM1 is ***maladaptive***



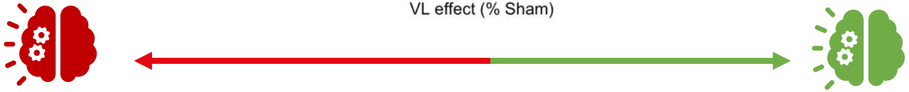
Higher *mean error in Verum than Sham*

↓

VL ***decreased*** *performance*

↓

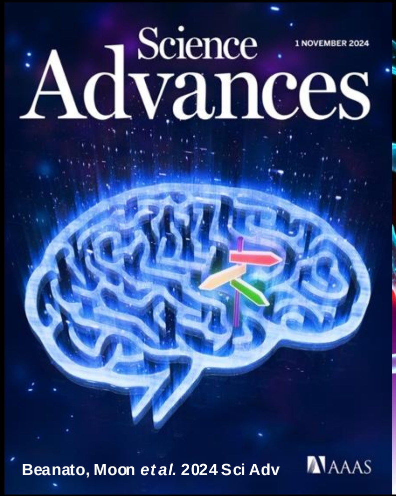
CM1 is ***adaptive***



Non-lesioned hemisphere might have opposite function in different patients, which can be determined by TMS virtual lesion approach.

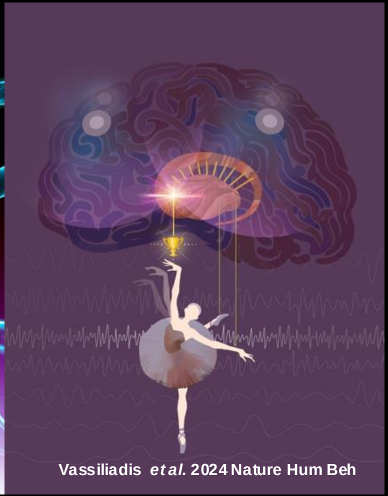
Fleury *et al. in* prep

Non-invasive deep brain stimulation by means of transcranial Temporal Interference Stimulation (tTIS) and transcranial focused ultrasound (TUS)



Beanato, Moon *et al.* 2024 Sci Adv

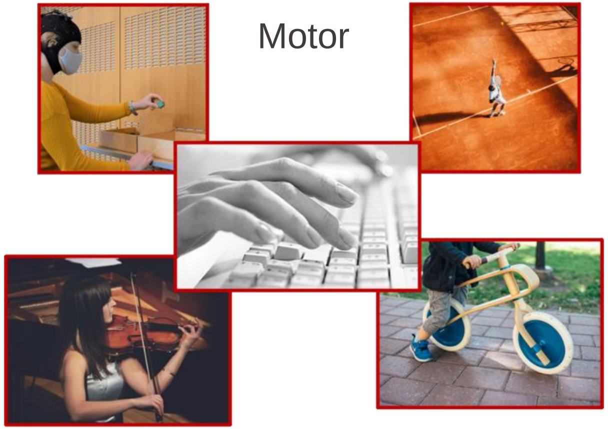
Wessel, Beanato *et al.* 2023 Nature Neurosci

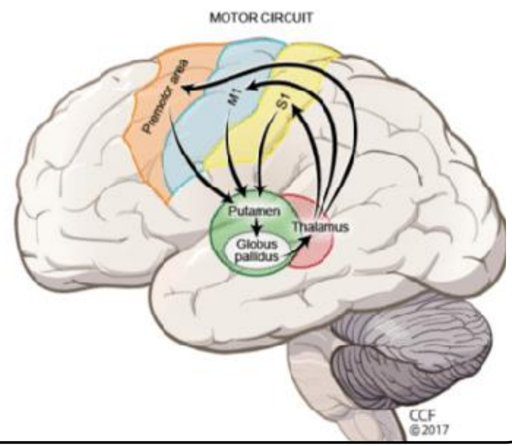


Vassiliadis *et al.* 2024 Nature Hum Beh

Motor, cognitive functions – network representation

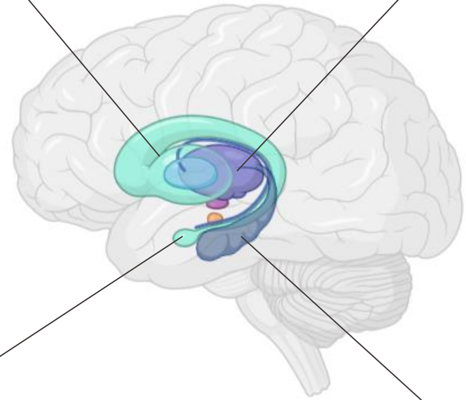
Motor





Striatum
Motor learning, memory, reinforcement, reward processing

Thalamus
Sensory processing, multisensory integration, inhibitory control, attention

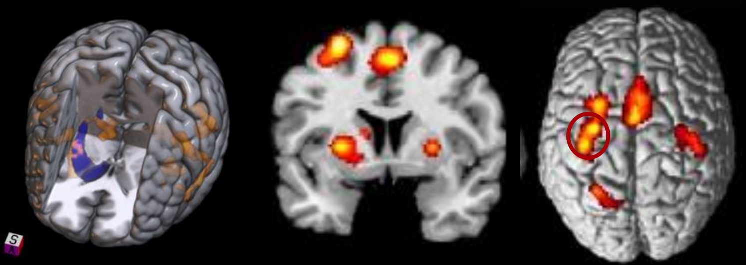


Amygdala
Emotion processing, impulse control, stress processing

Hippocampus
Declarative memory, spatial navigation

NIBS targets during motor (re-)learning

Motor cortex involved in motor behavior, primary target for NIBS



M1, PMd, PMv, SMA, **Basal ganglia**, Cerebellum, FPN

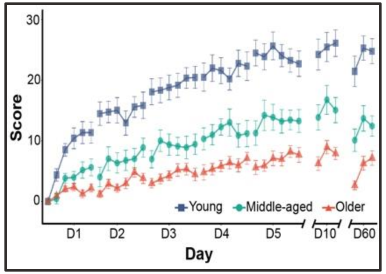
(for review Dyon *et al.* 2009; Diedrichsen & Kornysheva 2015; Krakauer *et al.* 2019)

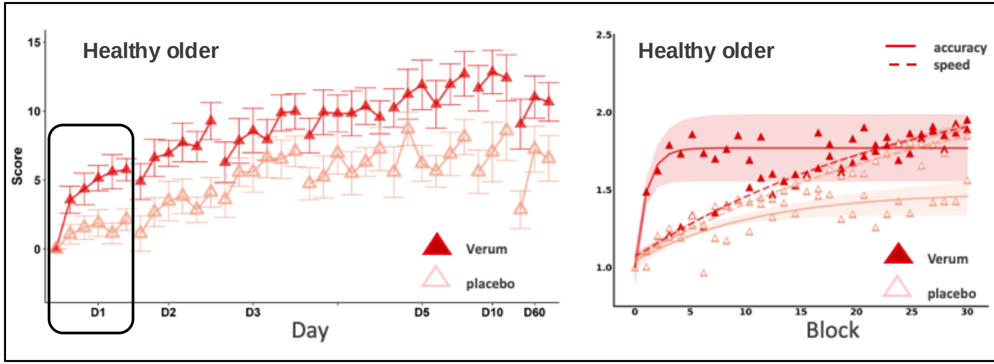
SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

Dissecting motor skill acquisition: Spatial coordinates take precedence

Pablo Maceira-Elvira[1,2]†, Jan E. Timmermann[3]†, Traian Popa[1,2]‡, Anne-Christine Schmid[1,2]‡, John W. Krakauer[4], Takuya Morishita[1,2], Maximilian J. Wessel[1,2,5], Friedhelm C. Hummel[1,2,6]*





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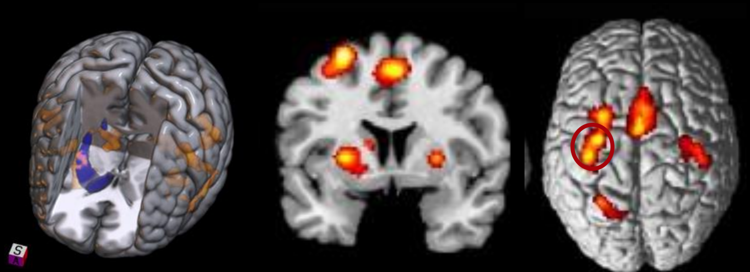


M1, PMd, PMv, SMA, **Basal ganglia**, Cerebellum, FPN

(for review Dyon *et al.* 2009; Diedrichsen & Kornysheva 2015; Krakauer *et al.* 2019)

…but probably only in an early phase of the (re-) learning process.

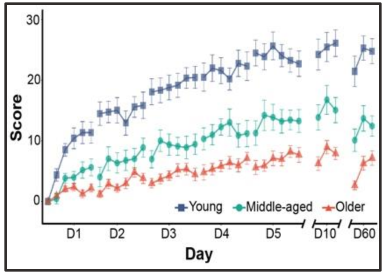
… other structures (e.g., striatum) longer involved in (re-) learning process.

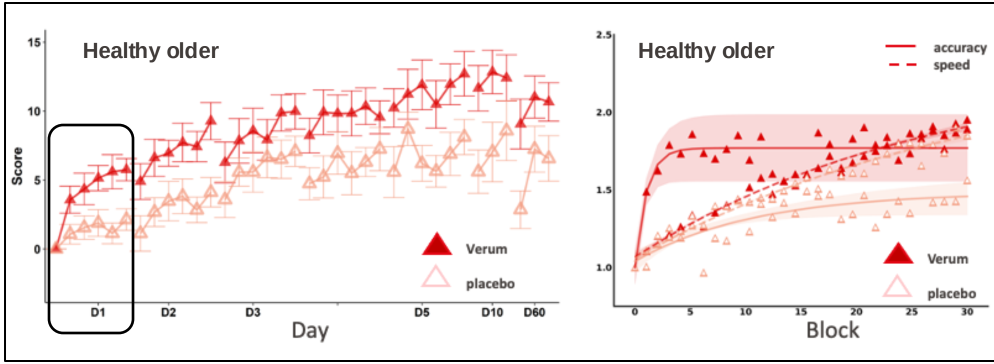
SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

Dissecting motor skill acquisition: Spatial coordinates take precedence

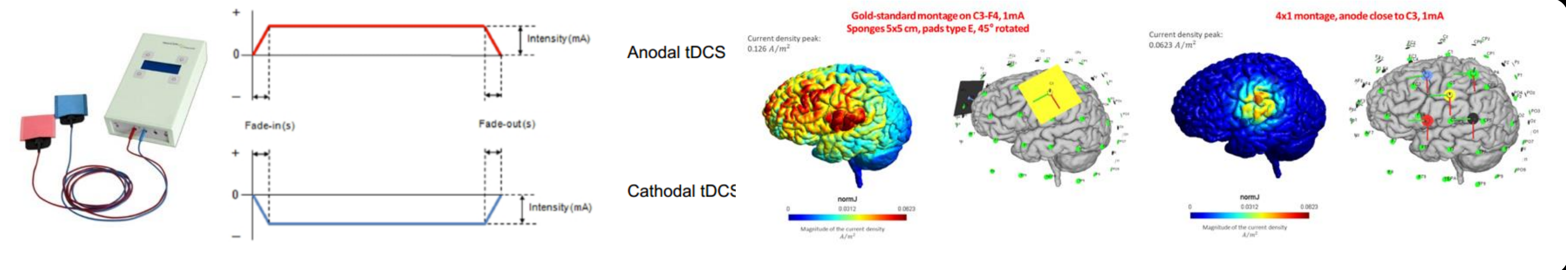
Pablo Maceira-Elvira[1,2]†, Jan E. Timmermann[3]†, Traian Popa[1,2]‡, Anne-Christine Schmid[1,2]‡, John W. Krakauer[4], Takuya Morishita[1,2], Maximilian J. Wessel[1,2,5], Friedhelm C. Hummel[1,2,6]*





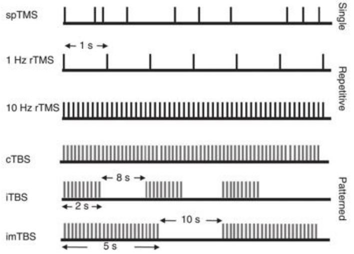
Neuromodulation by NIBS

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)

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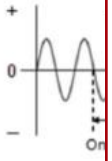
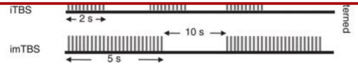
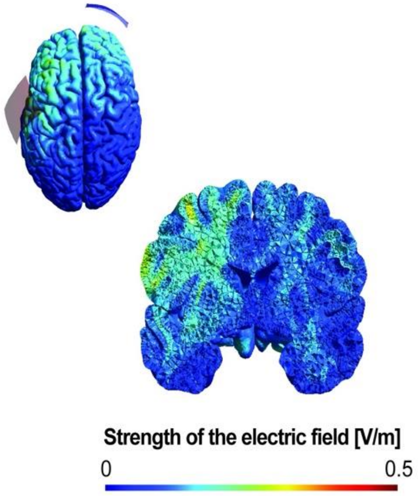


transcranial Magnetic Stimulation (TMS)

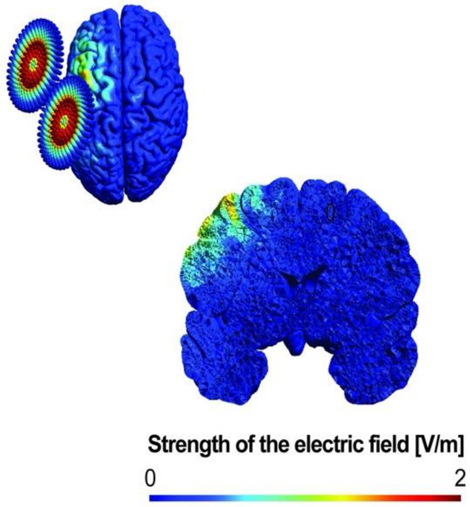


Depth-focality trade-off

Conventional tES



TMS



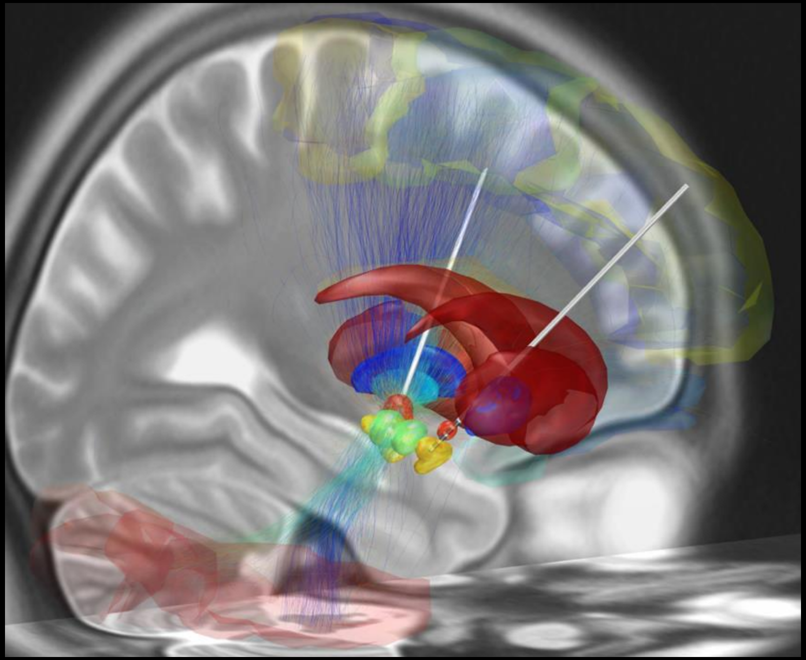
For review see e.g., Hummel & Cohen 2006,; Wessel et al. 2015; Saturnino et al. 2017)

Deep Brain Stimulation (DBS)

DBS 1.0

lesioning

DBS 2.0

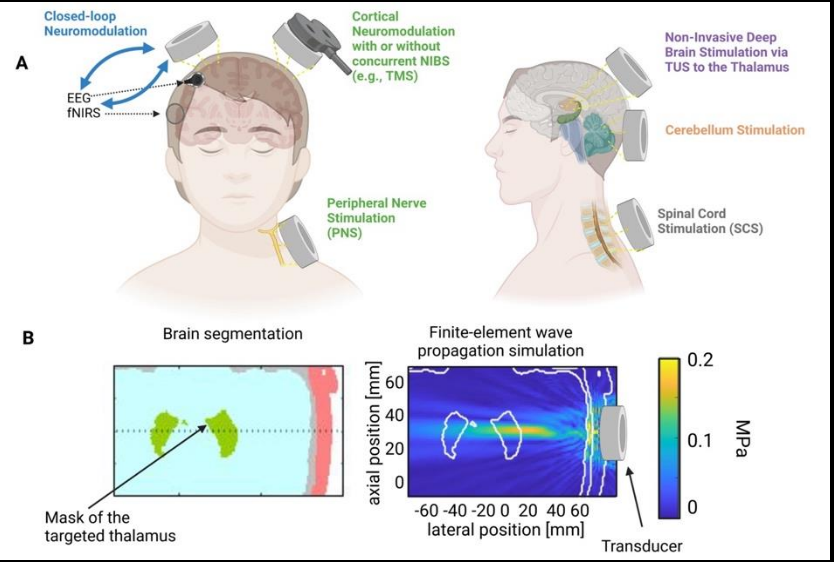


neuromodulation

...only invasive...!

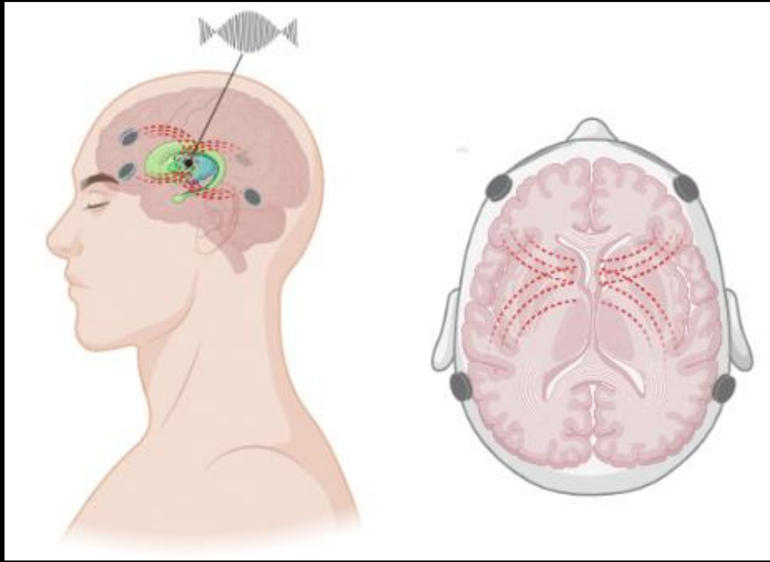
Non-invasive Deep Brain Stimulation (nDBS)?

transcranial focused ultrasound (tUS)



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

transcranial temporal interference stimulation (tTIS)

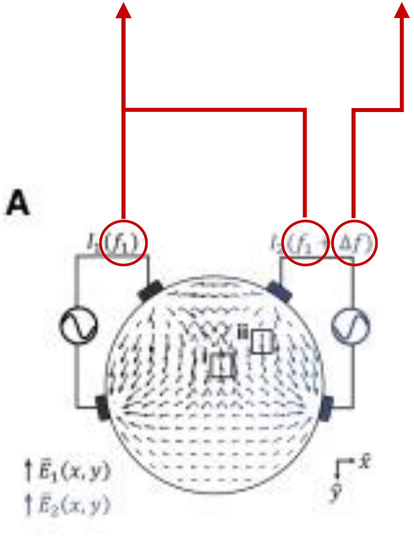


For review
Proulx & Hummel (2025) Neural Regen Research
Wang *et al.* (2025) The Innovation
Hummel & Wessel (2024) Nat Rev Neurol

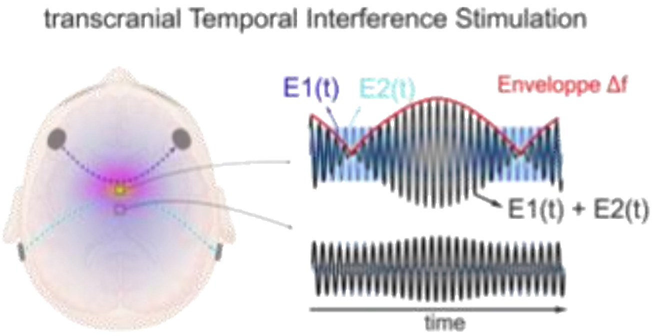
transcranial Temporal Interference Stimulation (tTIS)

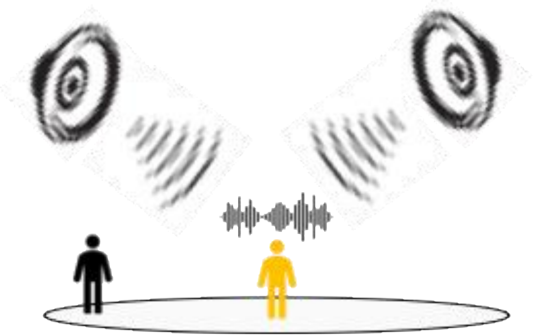
High frequency outside neural operation

Frequency recruiting neurons



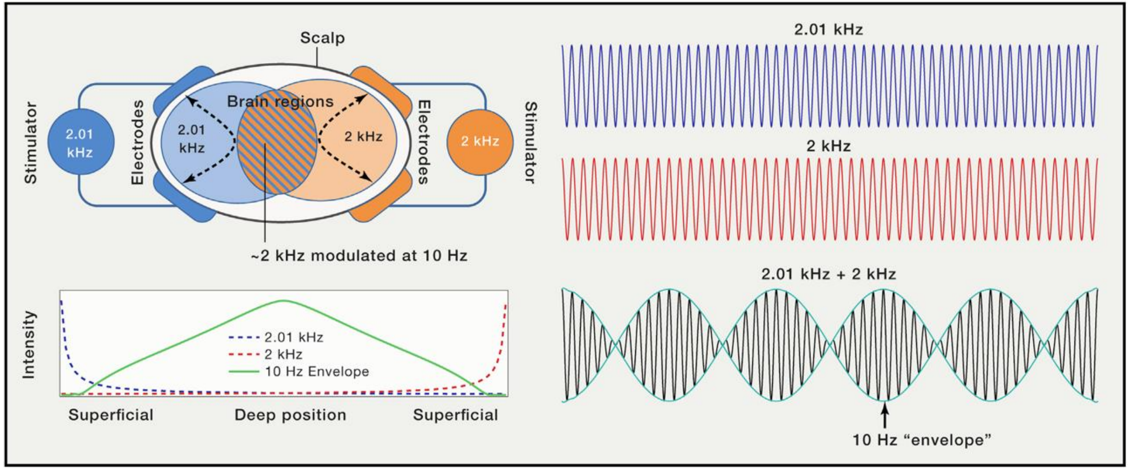
Based on a clever concept…2 waves that interfere….!

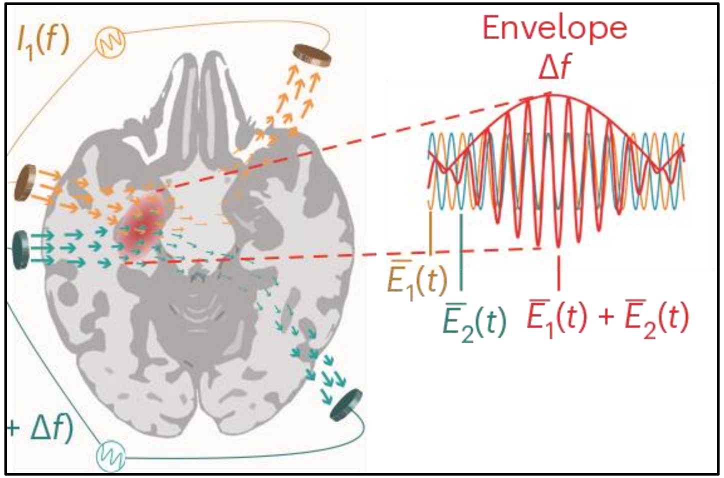




Grossman *et al.*, Cell 2017

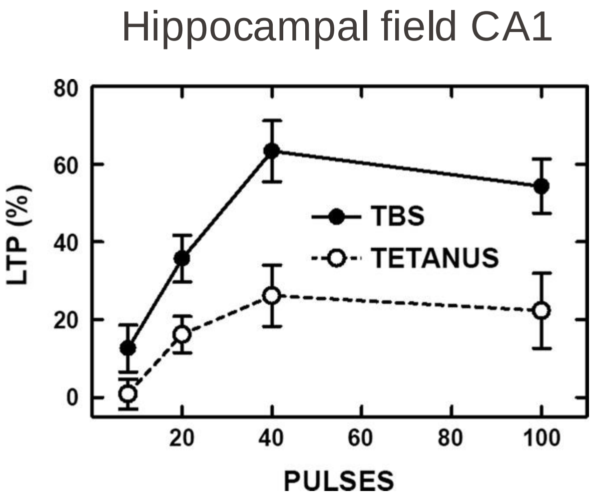
transcranial Temporal Interference Stimulation (tTIS)



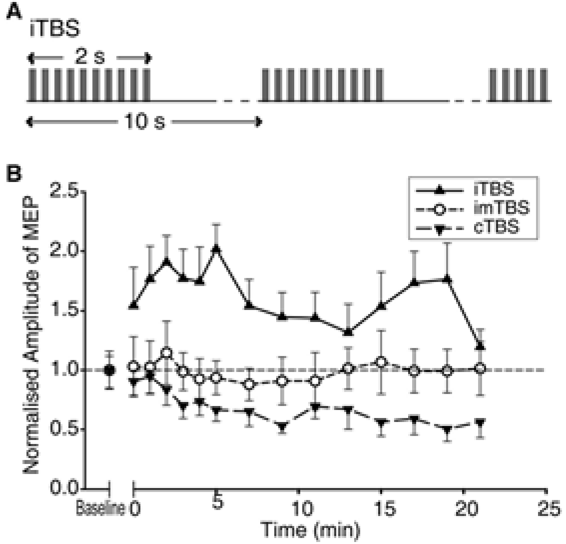


Grossman *et al.*, Cell 2017; Dmochowsk *et al*. 2017 Cell

Theta burst stimulation (TBS): LTP-/LTD-like



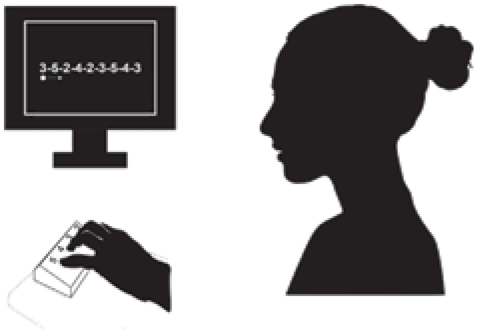
Larson& Munkasy 2015
Andersen 1991



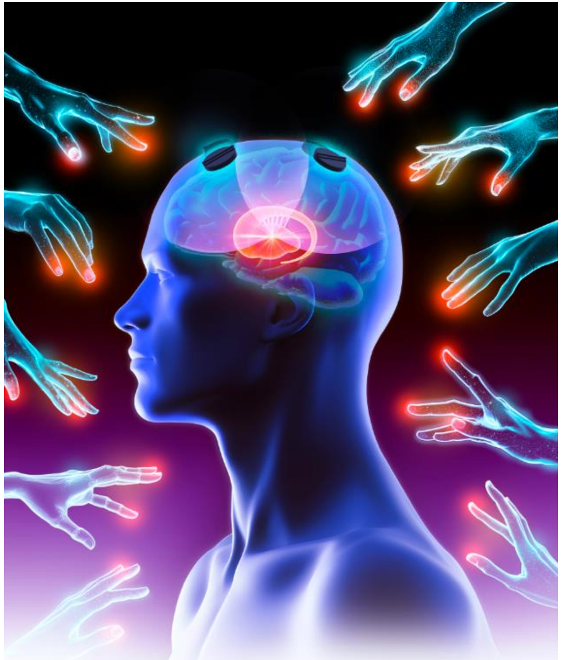
Huang *et al.* 2005

Moon *et al.* 2022

+



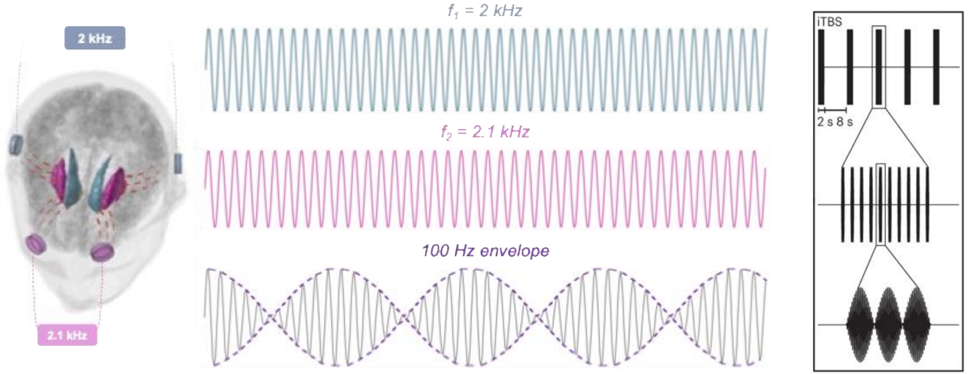
Zimerman *et al.* 2013, 2014; Draaisma *et al.* 2022, Maceida *et al.* 2022; Wessel *et al.* 2023



Neuromodulation of the striatum to enhance motor skill acquisition

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

Can striatal tTIS modulate striatal activity and improve motor learning?

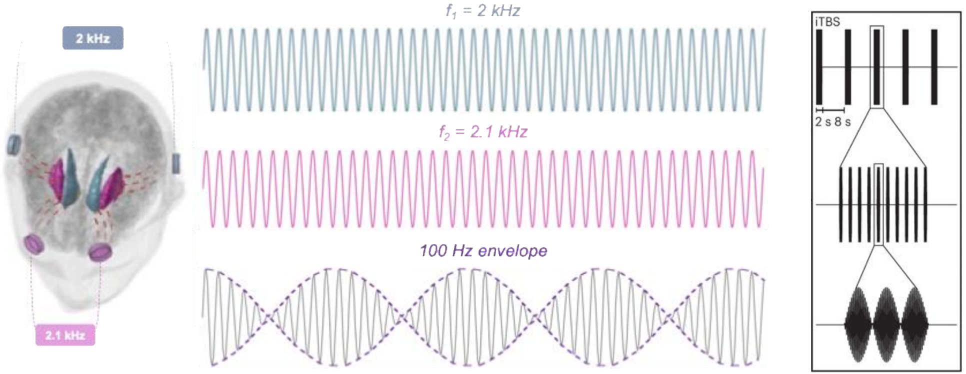


Intermittent theta bursts tTIS

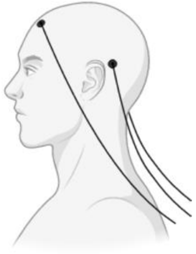
Wessel, Beanato *et al.* 2023 Nature Neuroscience

Neuroplasticity - Striatum

Can striatal tTIS modulate striatal activity and improve motor learning?

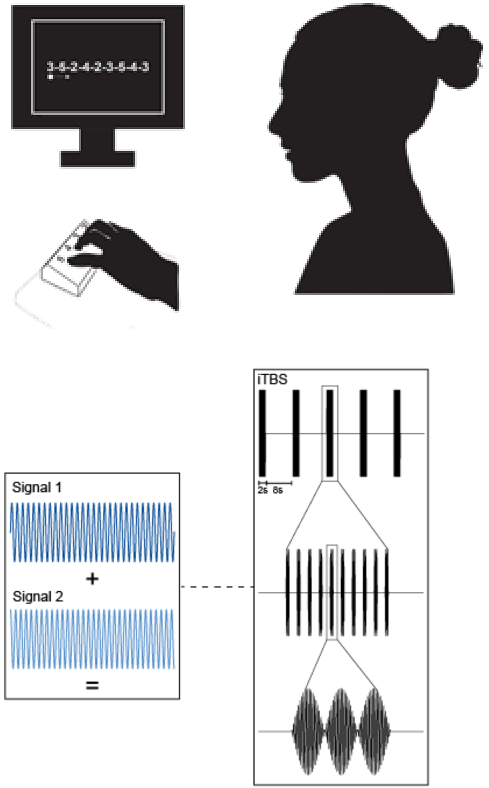


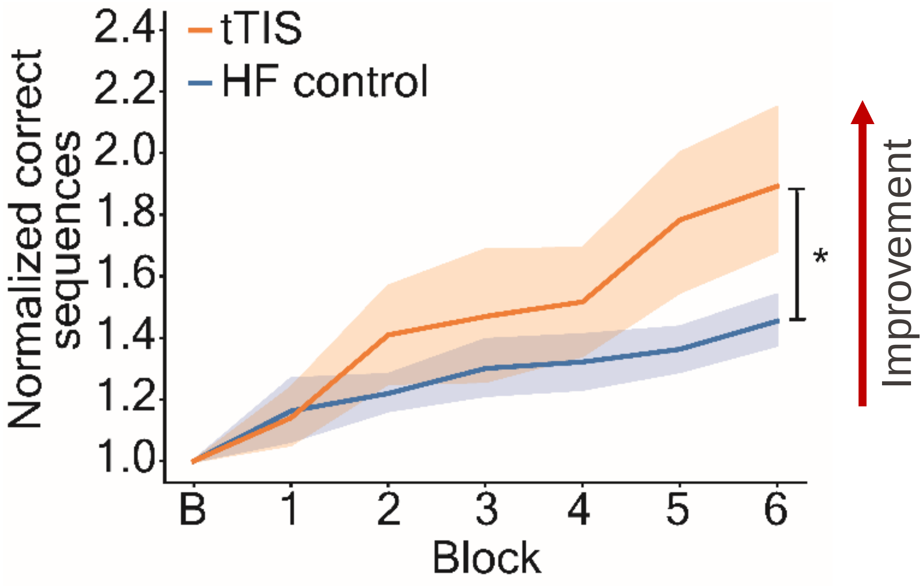
Intermittent theta bursts tTIS



Wessel, Beanato *et al.* 2023 Nature Neuroscience

Validation striatal tTIS - healthy older



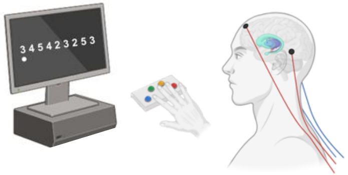


Striatal tTIS can modulate striatal activity and improve motor sequence learning

Wessel, Beanato *et al.* 2023 Nature Neuroscience

Enhancing Learning in TBI Patients

15 TBI patients
3 female, 12 male
age: 52.67 ± 13.6
double-blind
Cross-over



Motor Learning
tTIS or Control

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

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

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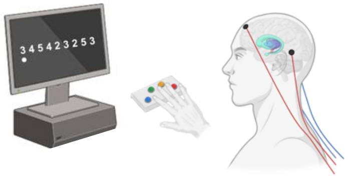
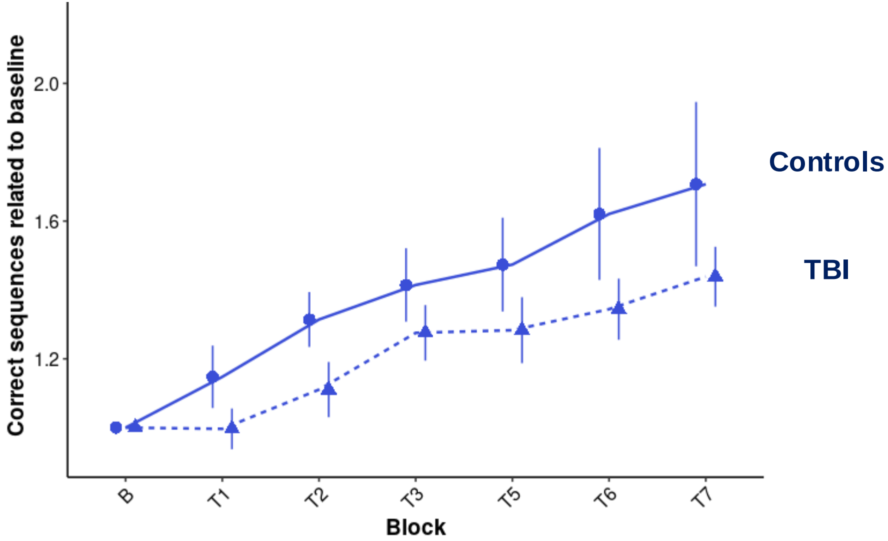


Motor Learning
tTIS or Control

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

TBI vs Age-matched controls - behavior



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

EPFL

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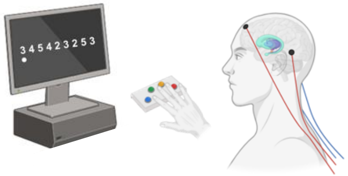

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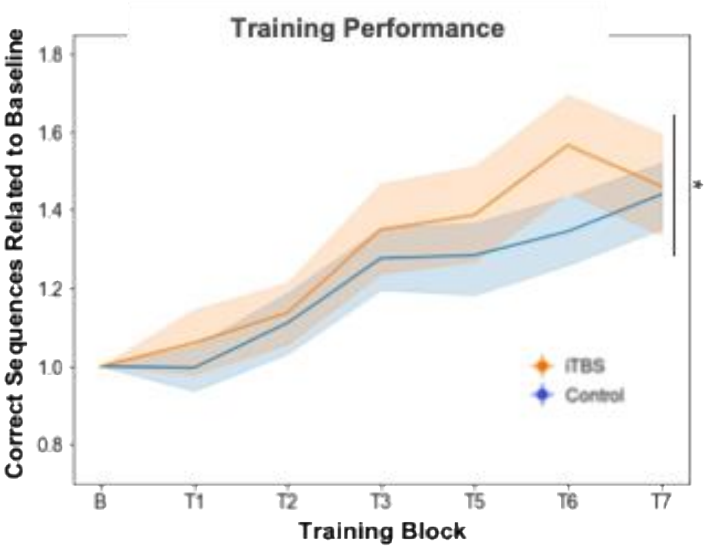
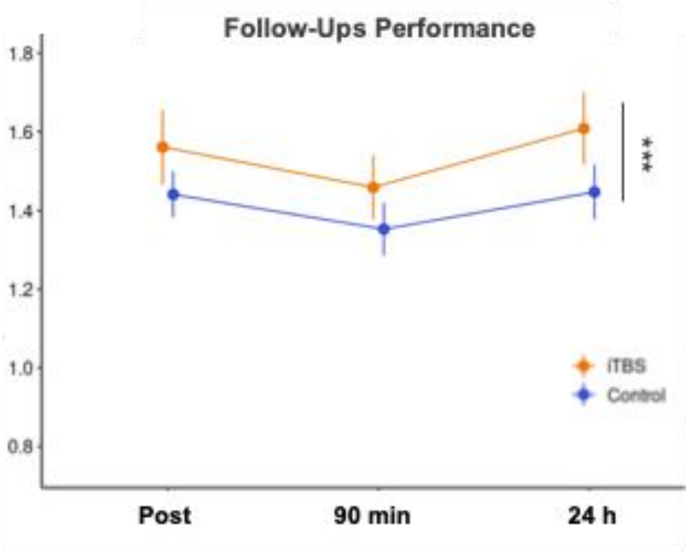
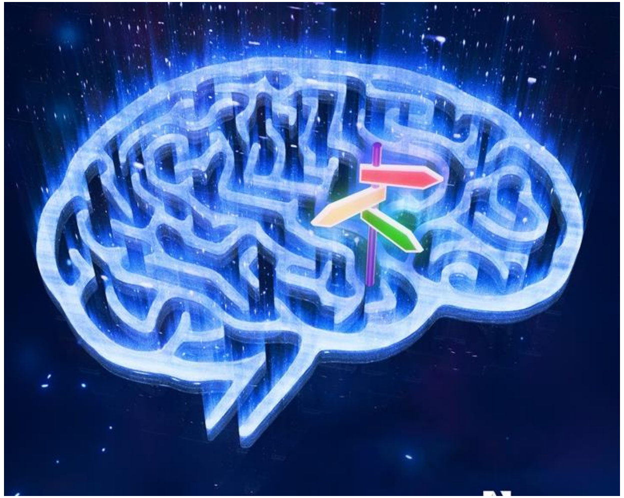




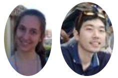
Ploumitsakou*, Beanato* *et al.*, in preparation

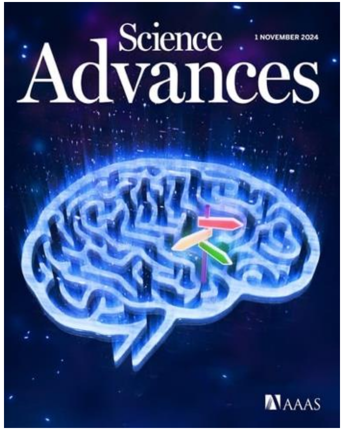


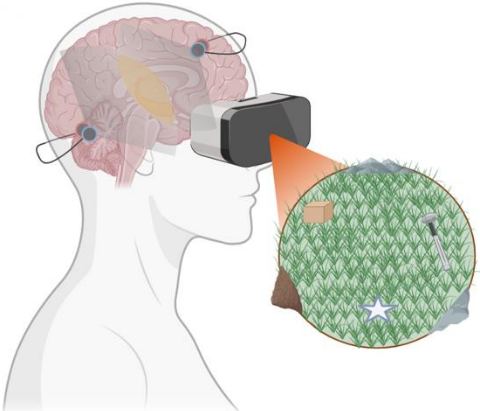
Functional role of neuromodulation of the hippocampal-entorhinal complex for spatial navigation

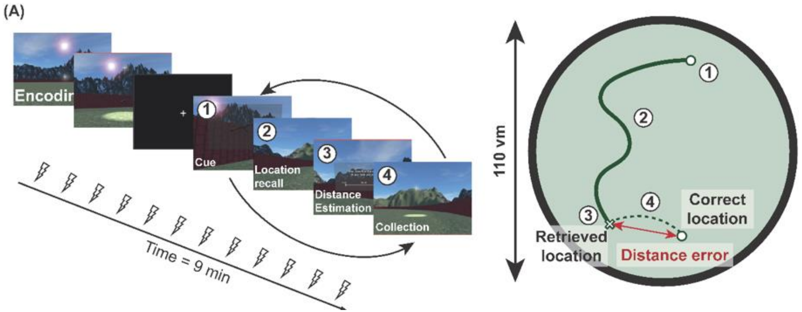
Beanato, Moon *et al.*, 2024 Science Advances

Human applications - nDBS & memory







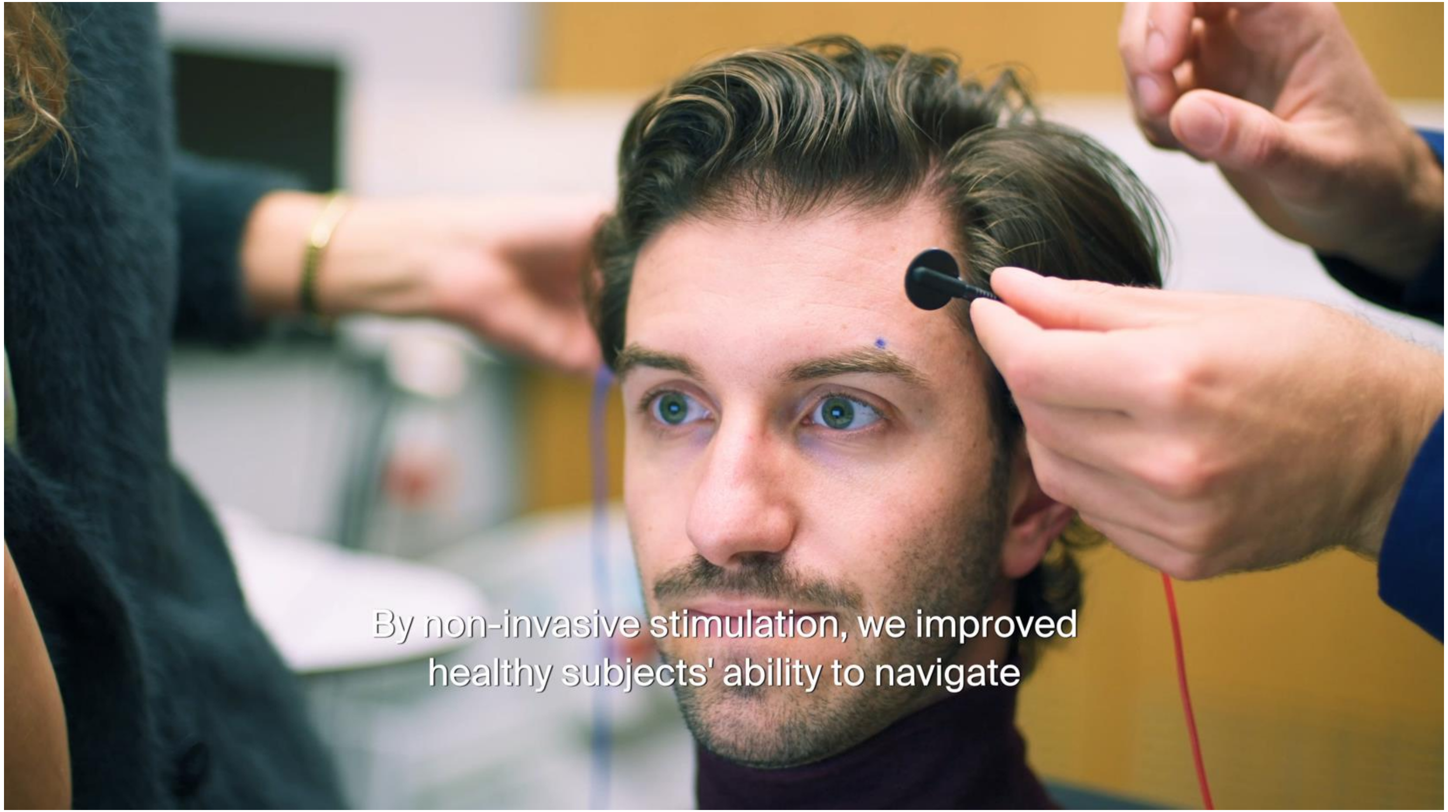


Can non-invasive deep brain stimulation of the hippocampus enhance memory

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

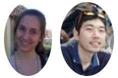
EPFL

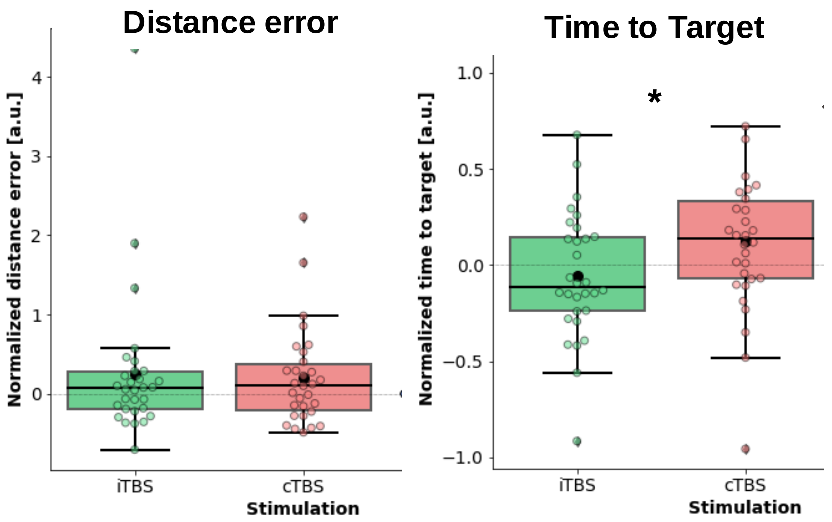
Human applications



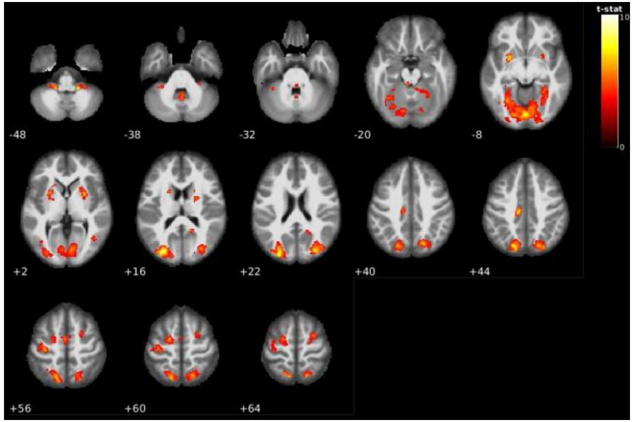
EPFL

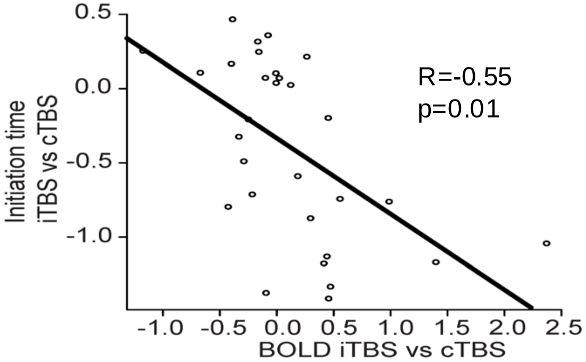
Enhancing spatial navigation





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





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

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

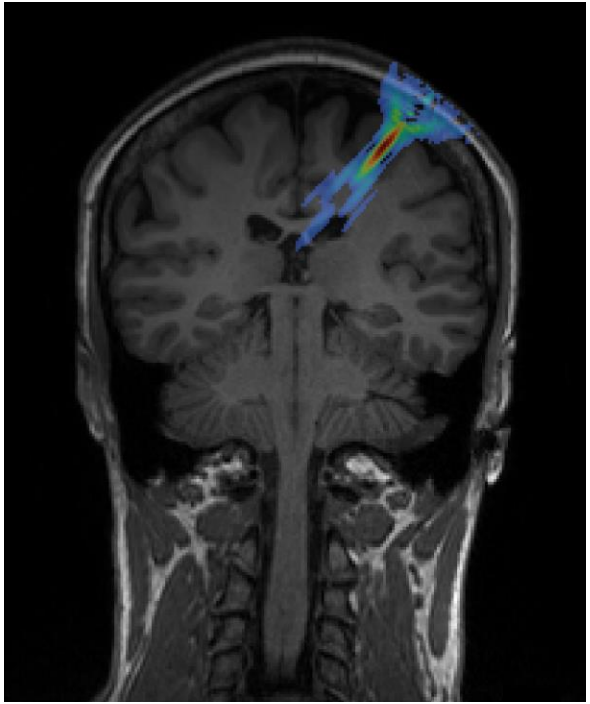
Vassiliadis *et al.* 2024

OCD, Essential Tremor, Dystonia

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

Parkinson

Parkinson
N=12 patients with clinical improvement
Yang *et al*. 2024 MDS
Lamos *et al*. in press MDS



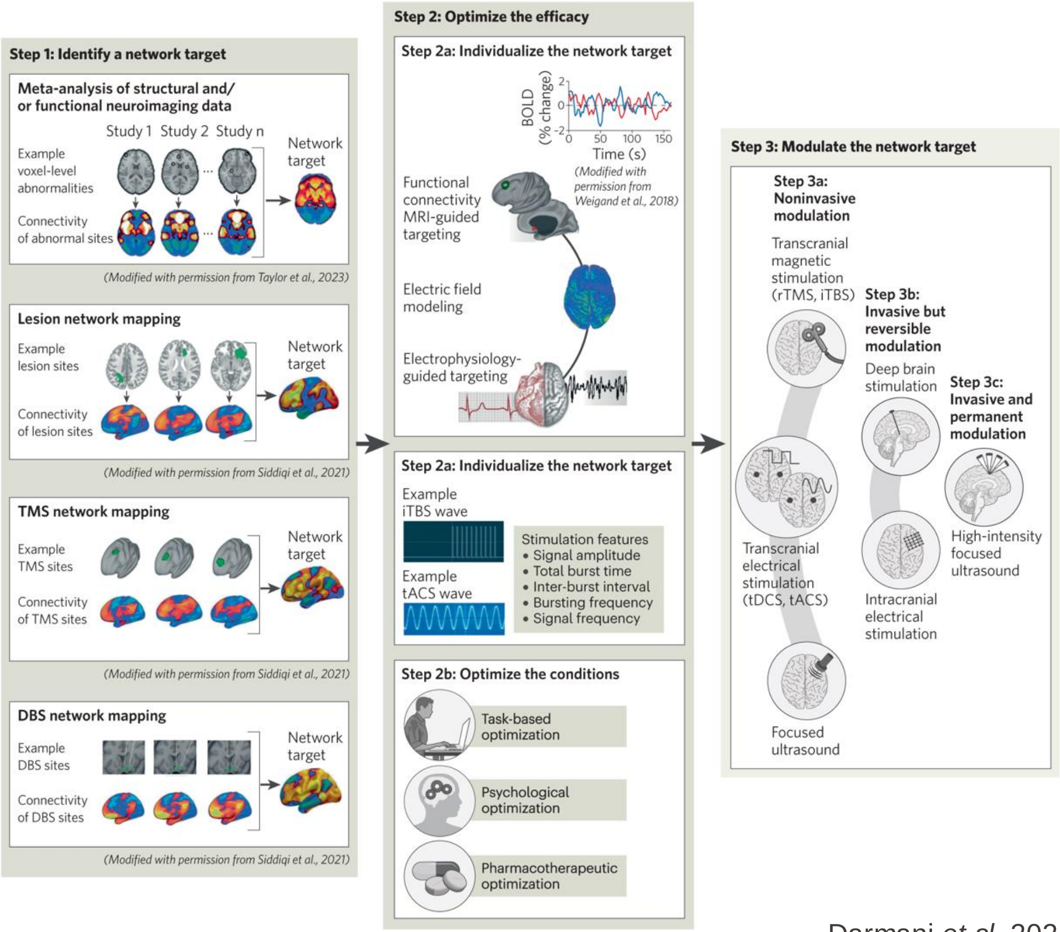
Individualized non-invasive deep brain stimulation of the basal ganglia using transcranial ultrasound stimulation

Damian *et al.* (2024) Nature Comms

Neuromodulation – How to choose?

Invasive vs. Non-invasive	Method/Technique	Stimulation Protocol	Target Selection
Lesioning **Invasive** **Minimal-invasive** **Non-invasive**	**Invasive** - Lesioning (tUS) - DBS - Epidural - Intracortical **NIBS** - TMS - tES - TUS	**Entrainment** **Disruption - Desynchronization** **Impact on plasticity** **Enhance interregional interactions** **Adaptive** **State-dependent/ Closed-loop**	**Anatomical** **Physiological** **Simulation-based** **Functional**

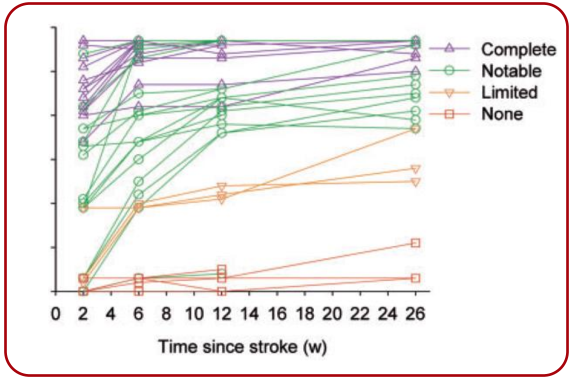
Overview



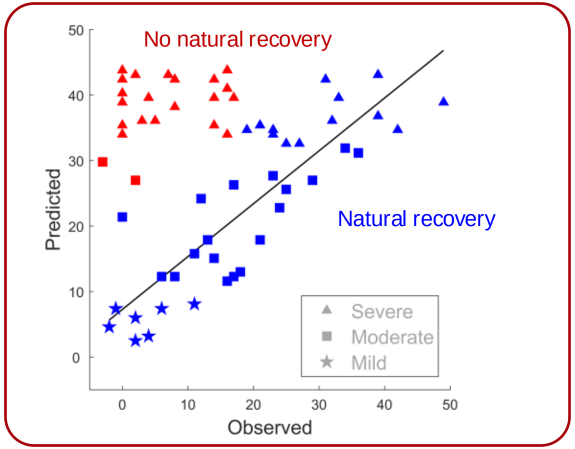
Darmani *et al*. 2024 Neuropsychopharmacology

Factors impacting/predicting neuromodulation response

Prediction of natural recovery

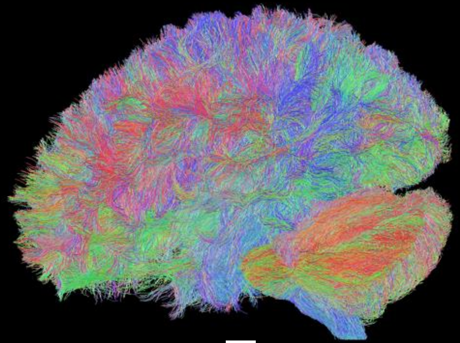


Stinear *et al.* 2011

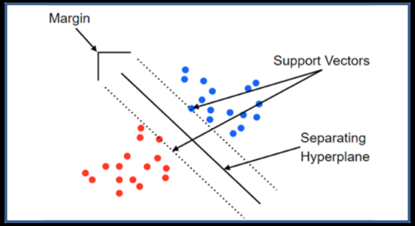


Koch *et al.* 2021

Structural connectome



Support Vector Machine (SVM) Classifiers (recovery-no recovery)



Connectome allows Classification /prediction

Subgroup	Accuracy	Precision
Severely impaired patients	0.92	0.93
2 weeks after stroke		

Subgroup	Accuracy	Precision
Severely impaired patients	0.92	0.93
2 weeks to 3 months		

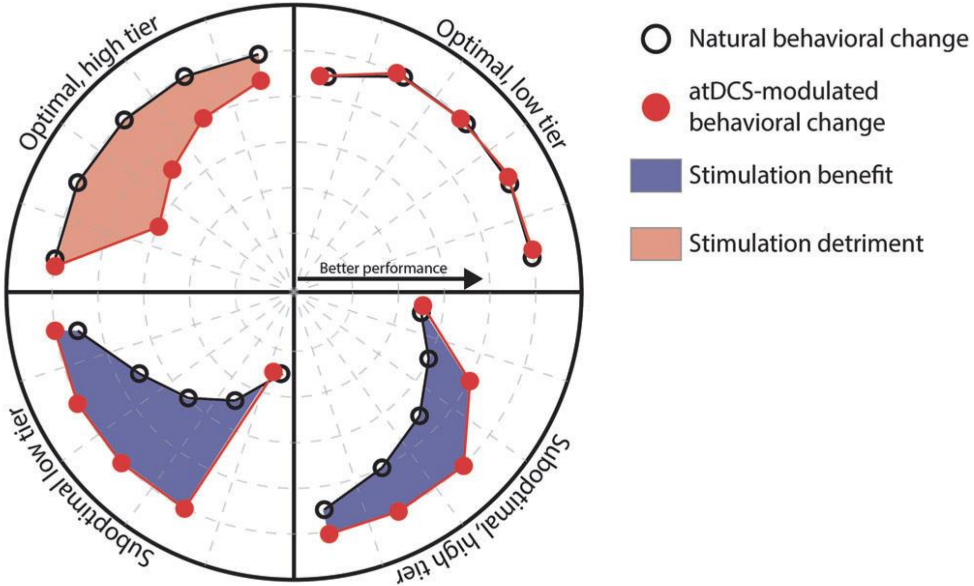
Koch *et al.* Brain 2021

Behavioural background

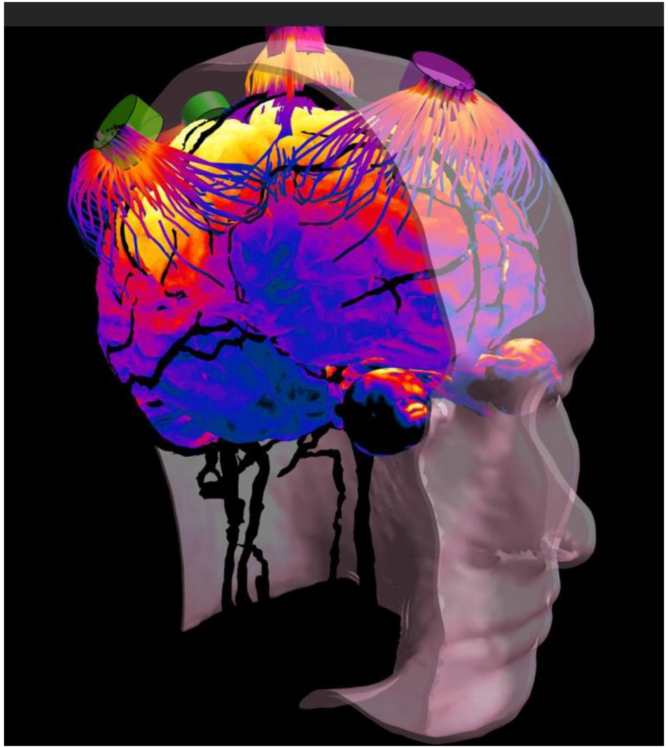
npj | science of learning
Article
Published in partnership with The University of Queensland
https://doi.org/10.1038/s41539-024-00278-y

Native learning ability and not age determines the effects of brain stimulation

Maceira-Elvira et al. 2024



Stimulation Strength



EPFL

Main Summary

- ‘Bouquet’ of methods and protocols for orchestrated personalized neuromodulation

- Orchestrated physiology-inspired neuromodulation allows to impact on brain processing and behavior
  - by modulating brain plastic properties (e.g., Wessel et al. 2023 Nature Neurosc; Darmian *et al.* 2025 Nat Comm)
  - by interfering with ongoing brain activity (e.g., Vassiliadis *et al.* 2024 Nature Human Behavior)
  - by entraining or re-instating brain activity (e.g. Bevilacqua *et al.* 2025 Brain)

- Orchestration is not anymore limited to cortical areas, but subcortical areas can also be targeted non-invasively and safe (Vassiliadis *et al.* 2014 JNE; Piao *et al.* 2022 Brain Sciences)
  - striatum (Wessel, Beanato *et al.* 2023 Nature Neuroscience; Vassiliadis *et al.* 2024 Nature Human Behavior; Darmian et al. 2025 Nat comms)
  - hippocampus (Beanato, Yoon *et al.* 2024 Science Advances, Violante *et al.* 2023 Nature Neuroscience;)

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

- Structural, functional information, e.g., connectivity informs the modality, target for neuromodulaton and potentially allows to predict response.

- To determine further factors that impact on neuromodulation response and implement them (course of disorders, individual dosing, personalized target selection)