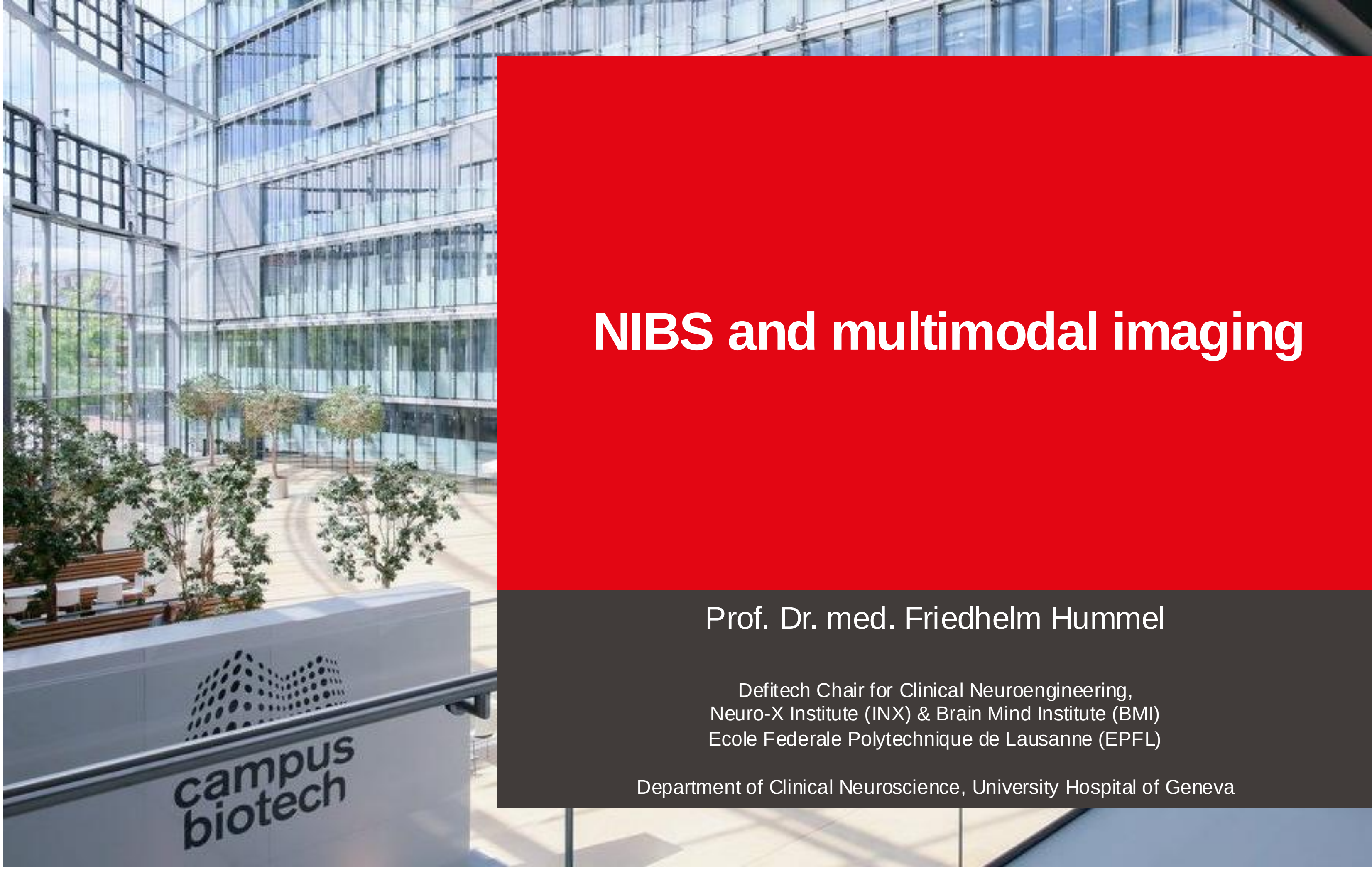
EPFL

Neuro X Institute



NIBS and multimodal imaging

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Nx-436
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What are the potential benefits of multimodal imaging combined with neuromodulation?

intro

Recording of brain activity simultaneously

- focally and at the network level
- adds to mechanistic understanding
- safety monitoring
- state dependent close-loop applications

Online interference with brain activity

- causal understanding
- network vs. local effects
- state dependent close-loop applications

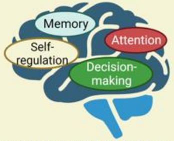
What are the disadvantages and challenges of multimodal imaging combined with neuromodulation?

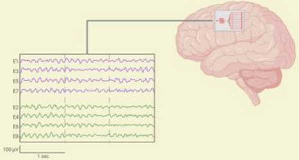
Challenges

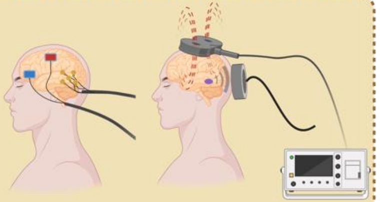
- temporal, spatial resolution
- safety
- artefacts
- feasibility
- accessibility, clinical translation
- cost

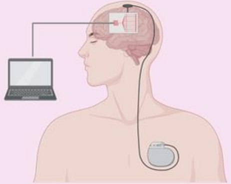
intro

	INVASIVE	NON-INVASIVE
Neurosensing/ Neuro-monitoring "READ" Monitors electrical/BOLD activity in the central nervous system	eCoG, iEEG	EEG, MEG, fMRI
Neuromodulation "WRITE" Targets and improves functions such as motor, attention, memory, decision-making, self-regulation either electrically, magnetically or via ultrasound	DBS	TMS, tES, TUS
Combinatory (bidirectional) "READ + WRITE" Monitors and reacts to brain states with prosthetics, robotics, brain stimulation	Closed-loop DBS	BCI, BBI, ...



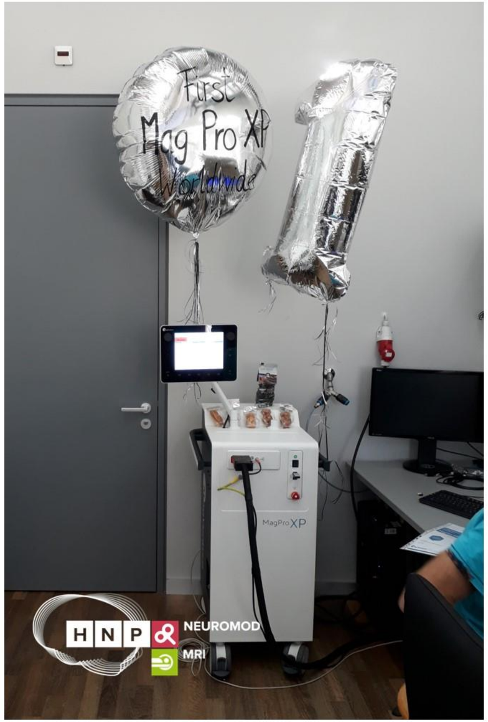


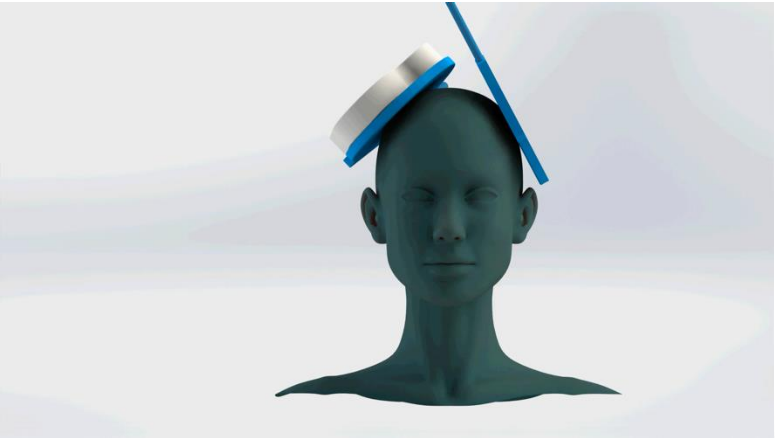




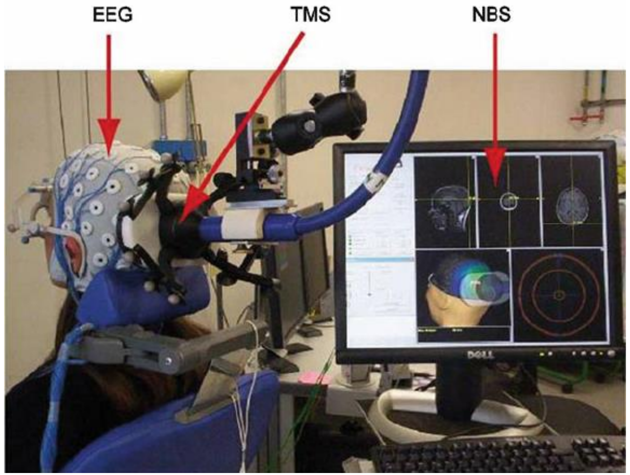
TMS-fMRI

WHITE: TMS coil (stimulation)



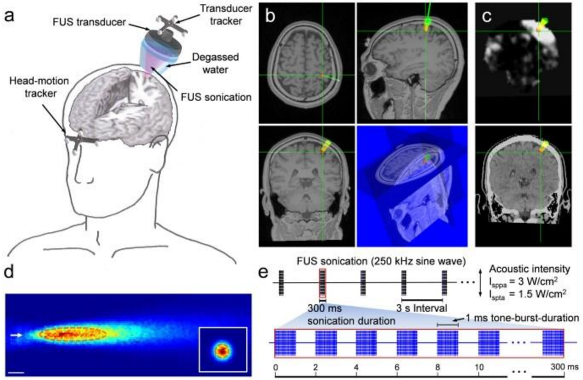


TMS-EEG

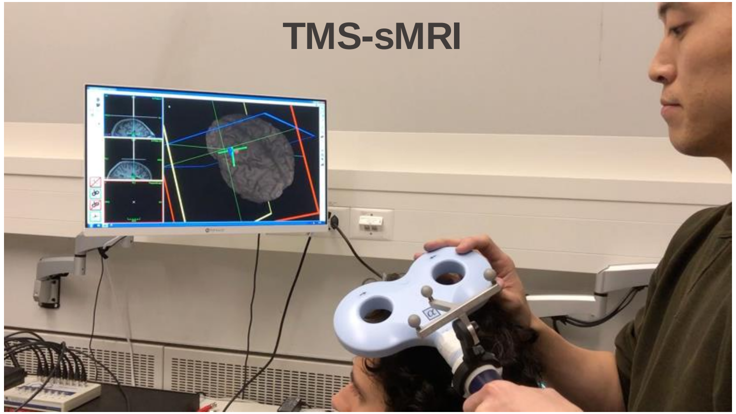


TMS-fMRI

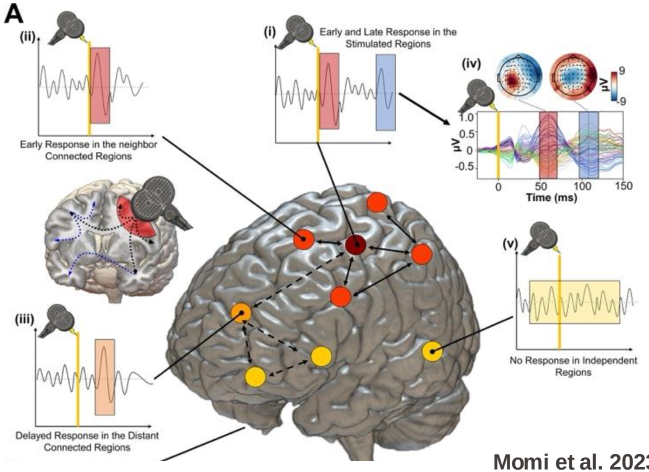
fUS-TMS/EEG/MRI



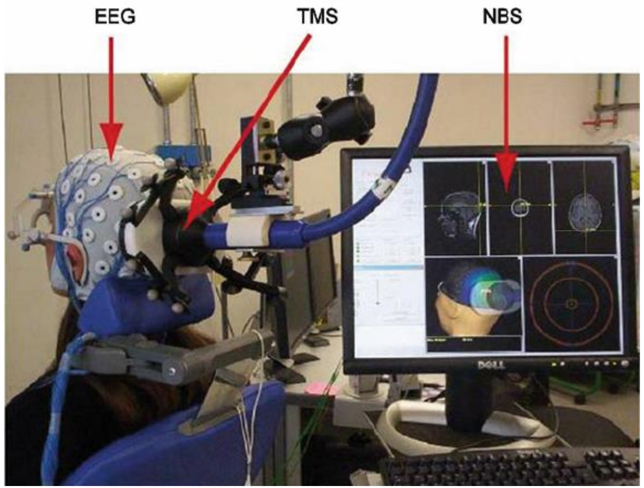
TMS-sMRI



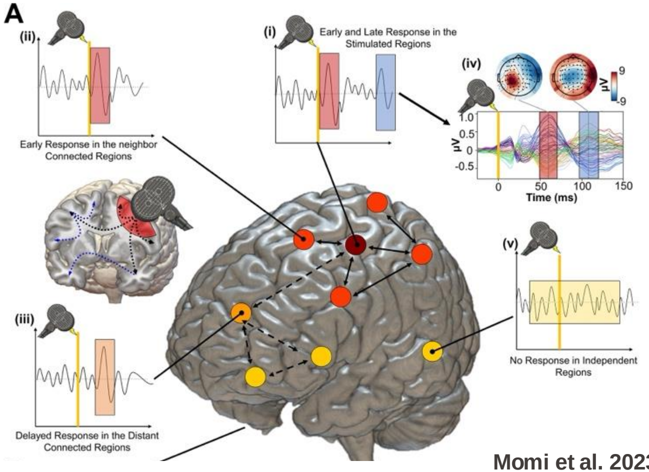
NIBS and Neuroimaging



Momi et al. 2023



NIBS and Neuroimaging



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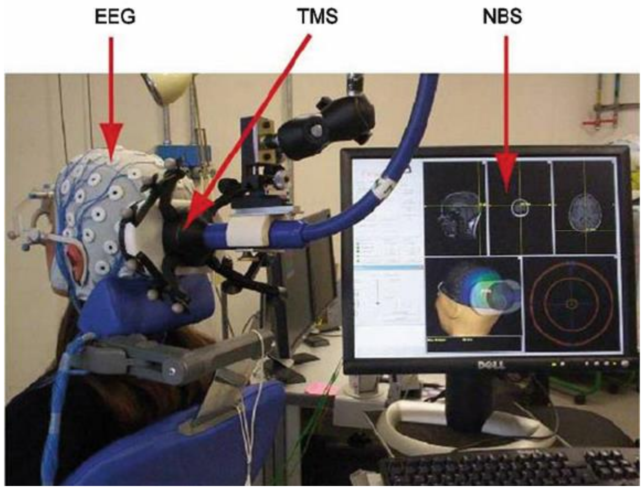
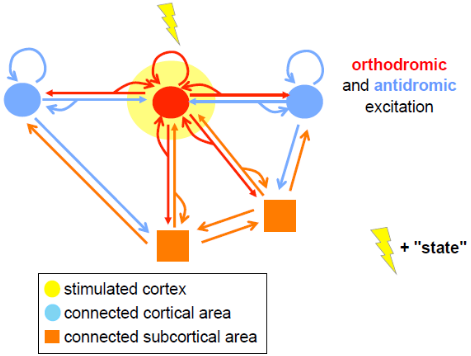


"Focal" TMS can induce systems effects

Applications
TMS-fMRI



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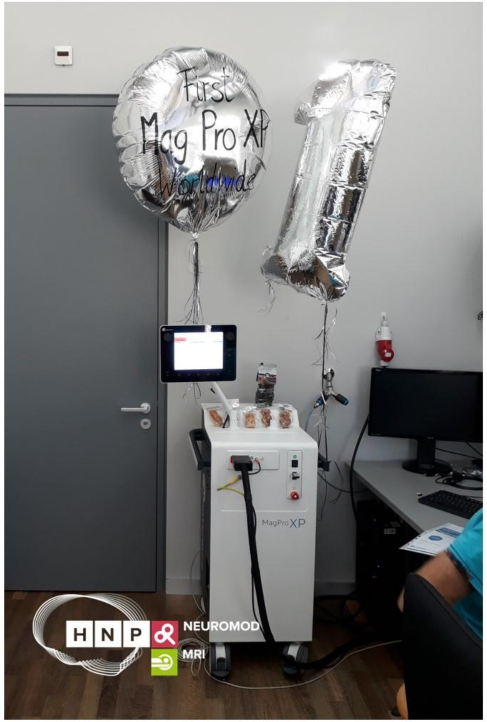
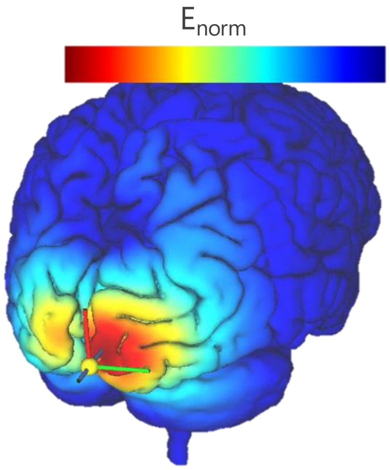
TMS - fMRI

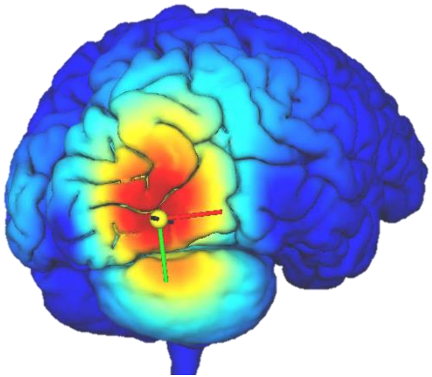

First
Mag Pro XP
Worldwide
MagPro XP
HNP
NEUROMOD
MRI


SIEMENS

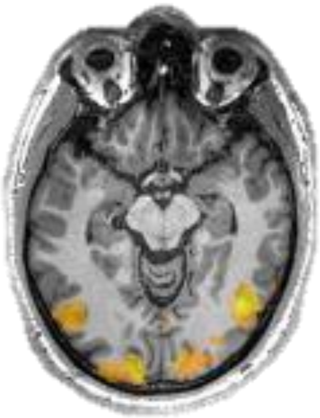
TMS - fMRI

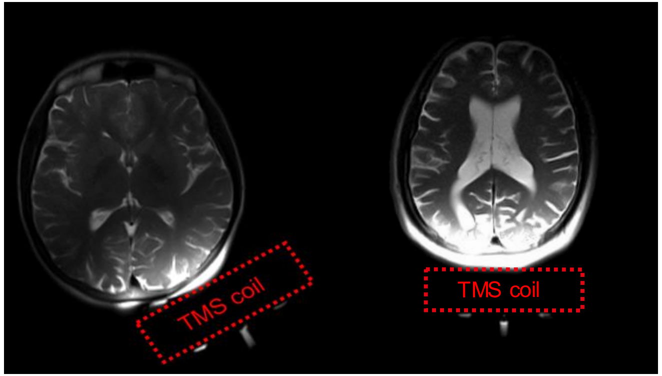


TMS$_{(V1)}$

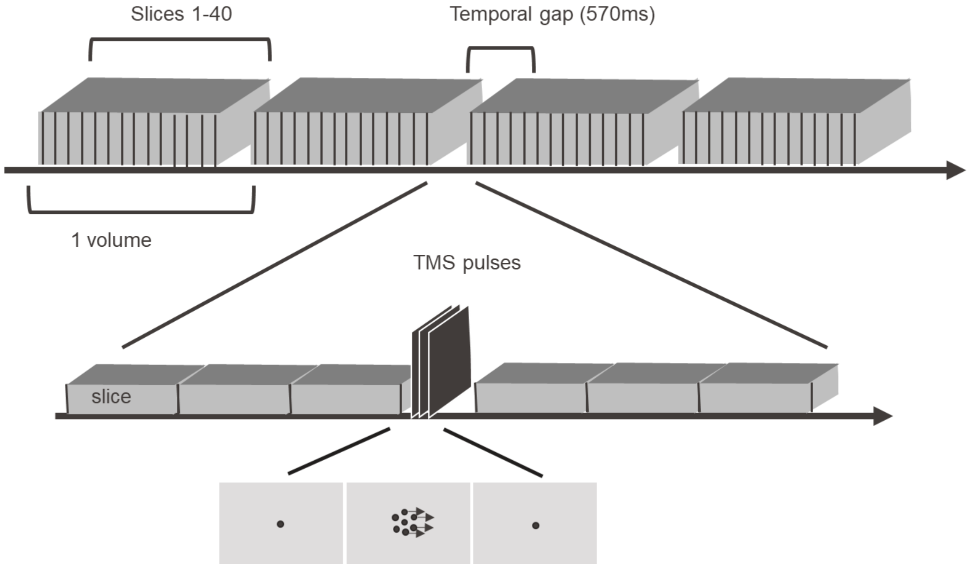


TMS$_{(MT)}$

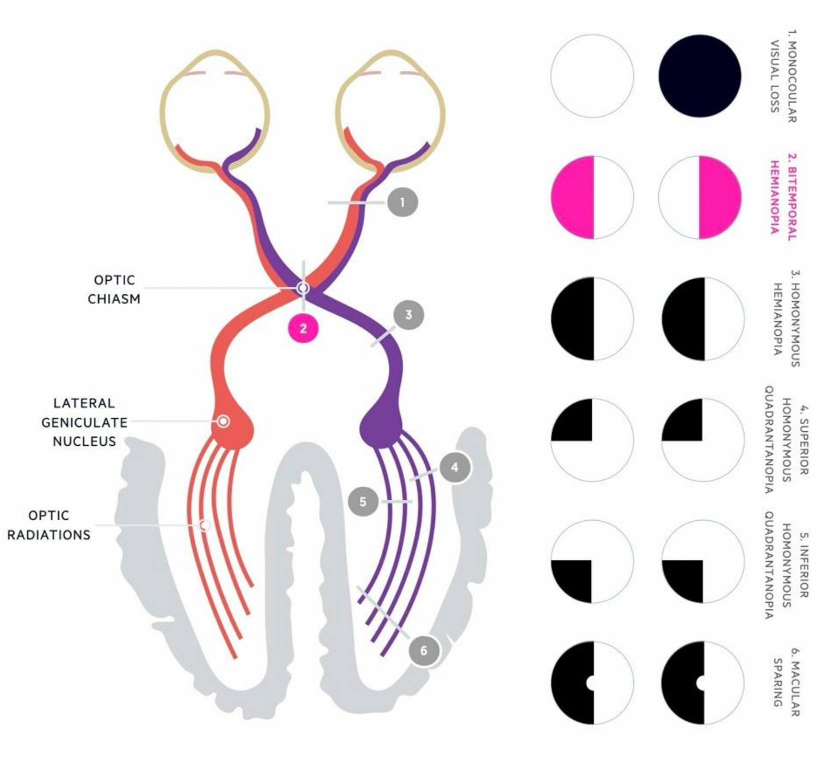




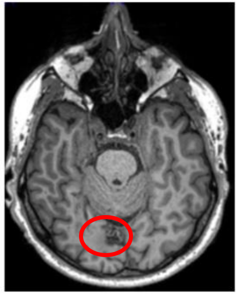
TMS - fMRI

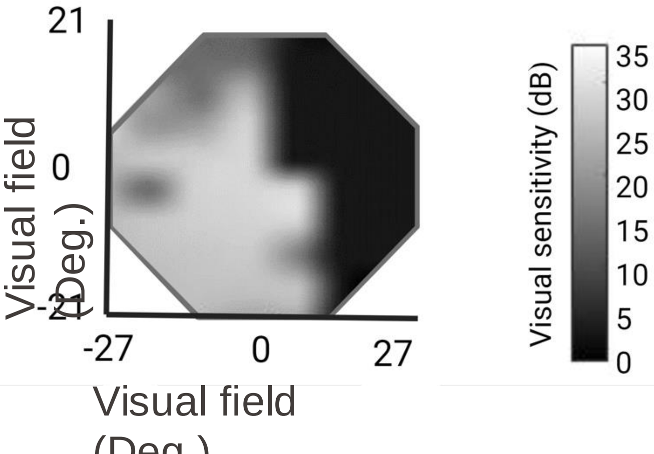


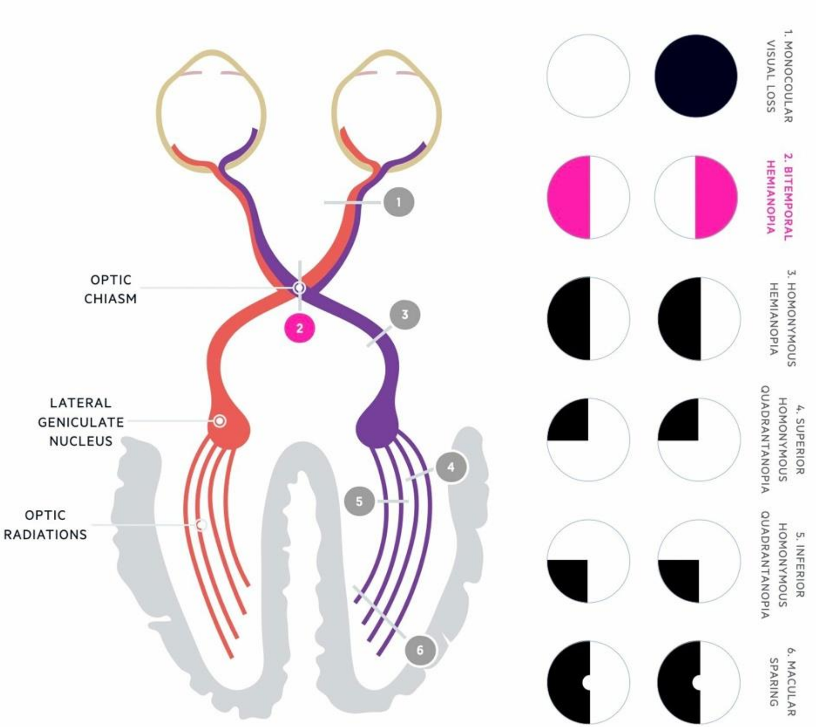
Visual field defects



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




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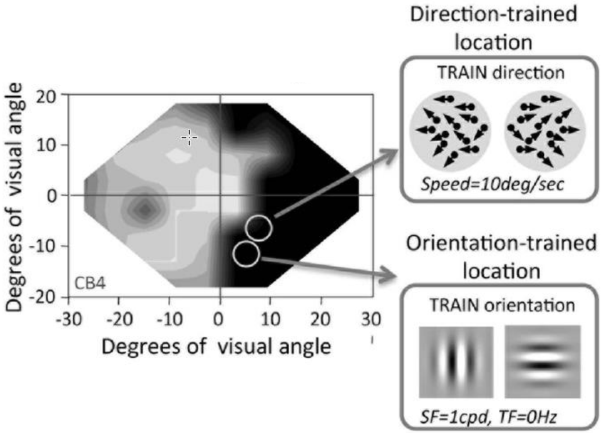
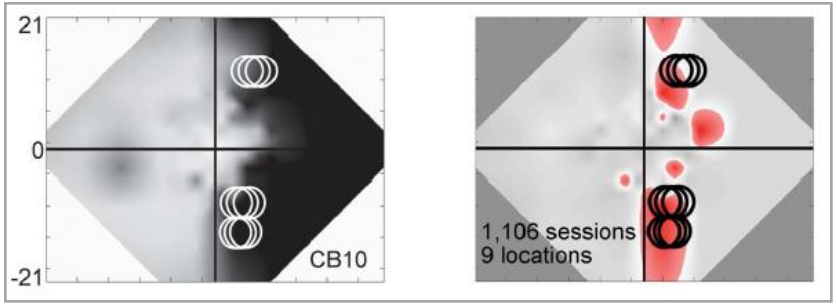
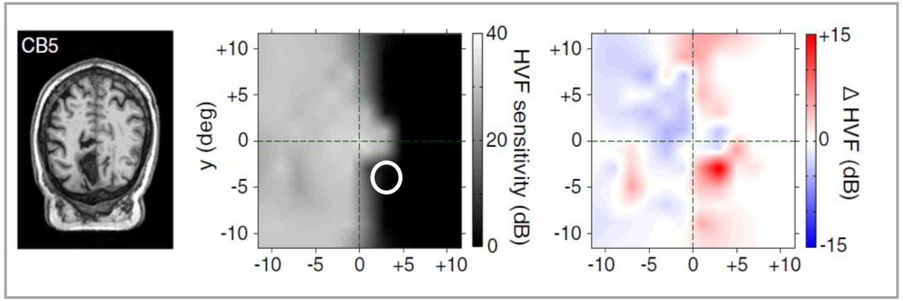
Visuo-attentional training



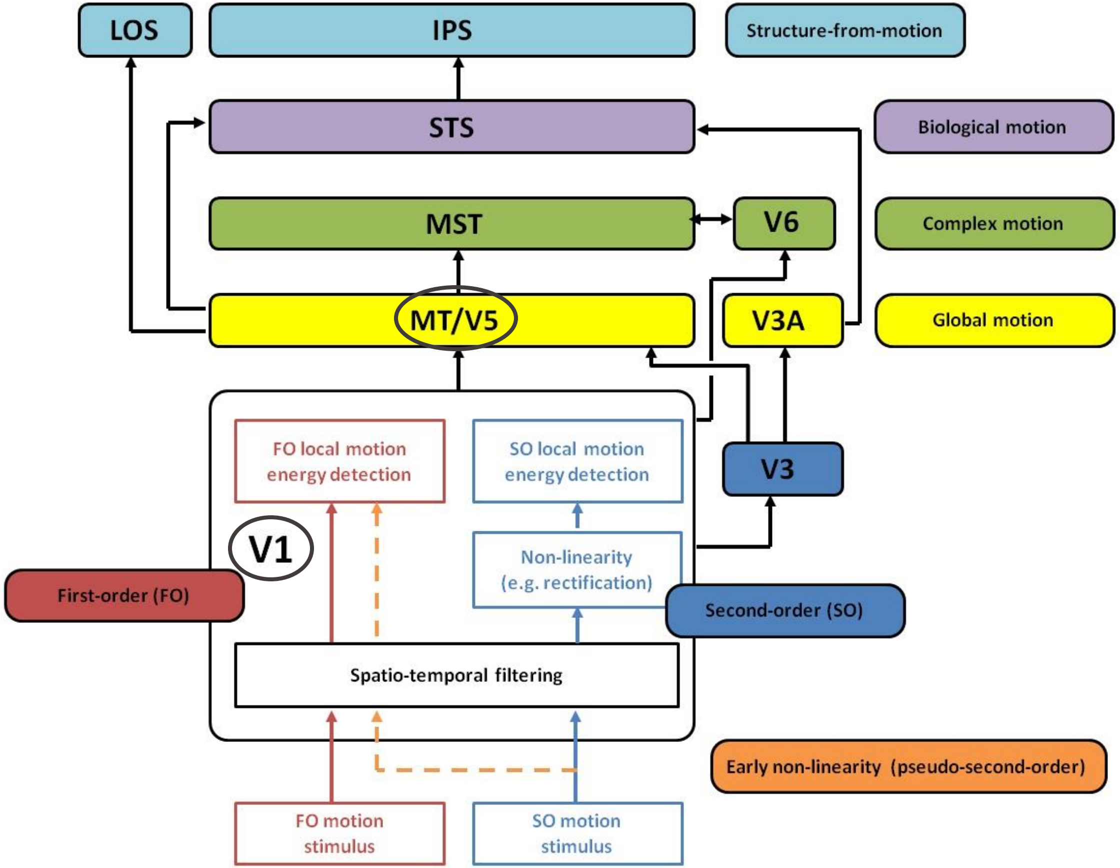


Cavaunaugh and Huxlin et al., 2017, Neurology



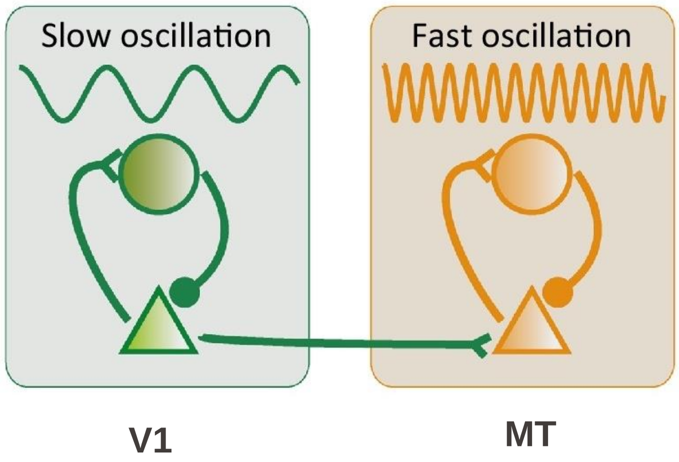
Barbot et al., 2021, J Neurosc.

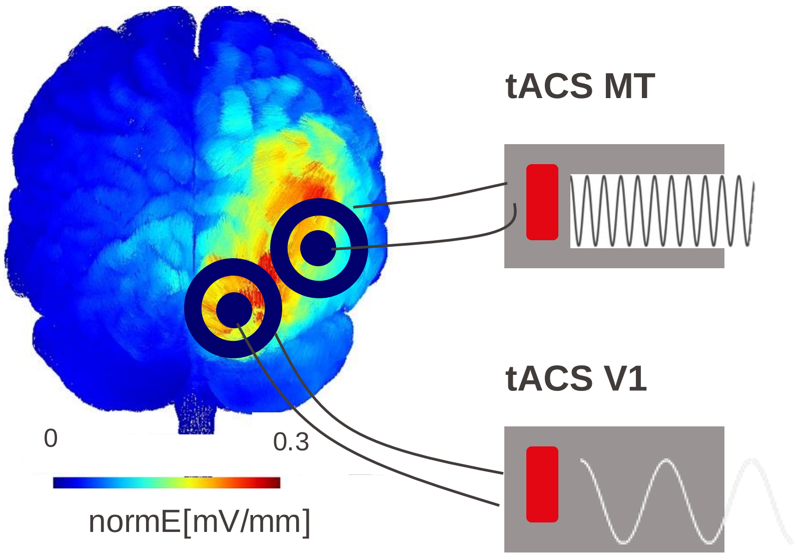
The motion processing hierarchy



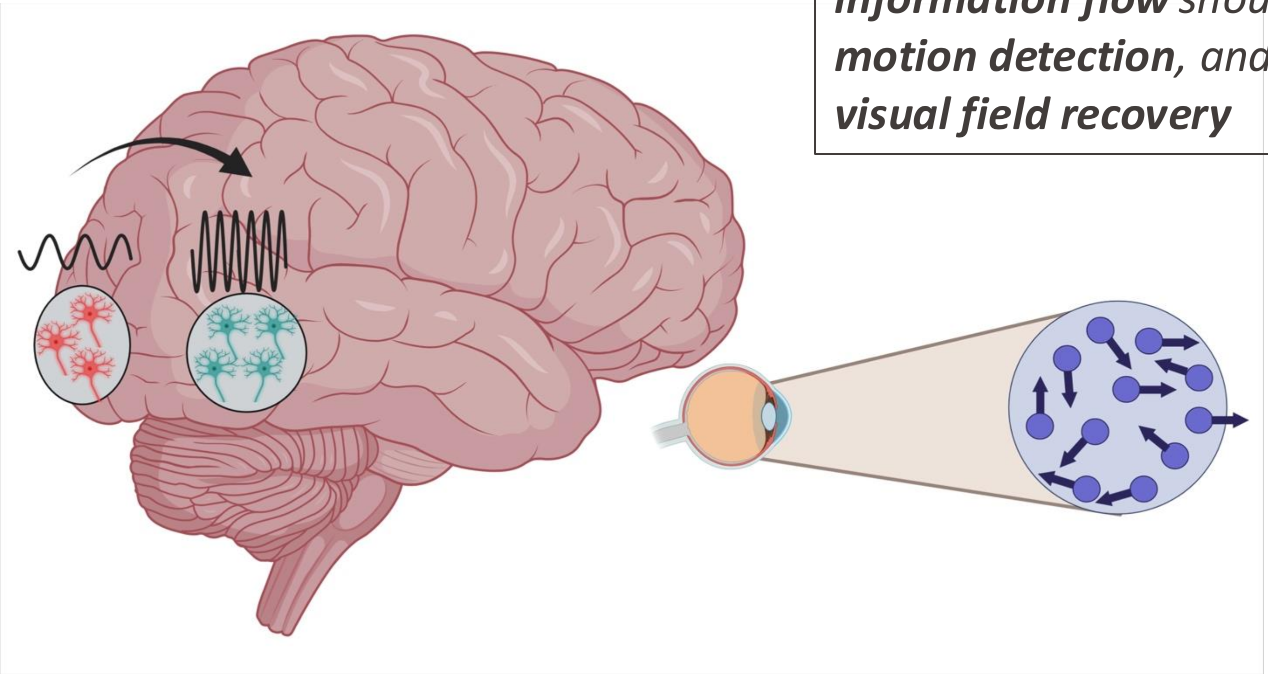
How to promote inter-areal communication?

Inter-regional Phase-Amplitude Coupling (PAC)
reflects **unidirectional coupling**



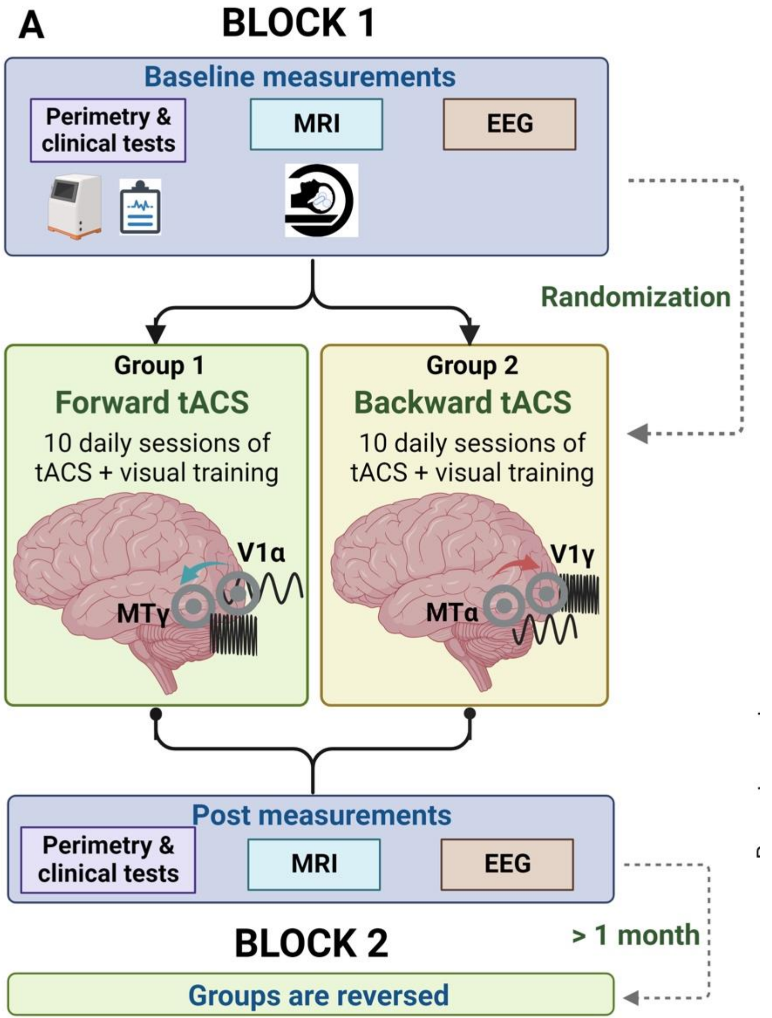


Hypothesis

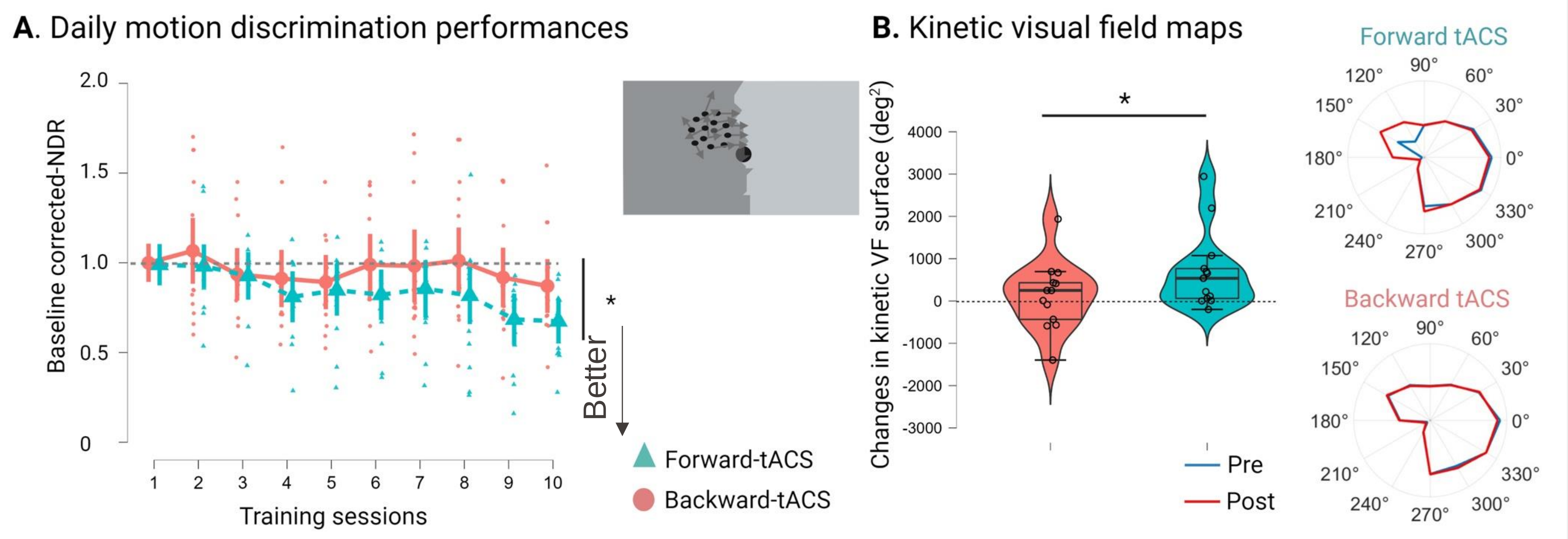


Promoting ***bottom-up direction of information flow*** *should facilitate* ***motion detection****, and in turn, boost* ***visual field recovery***

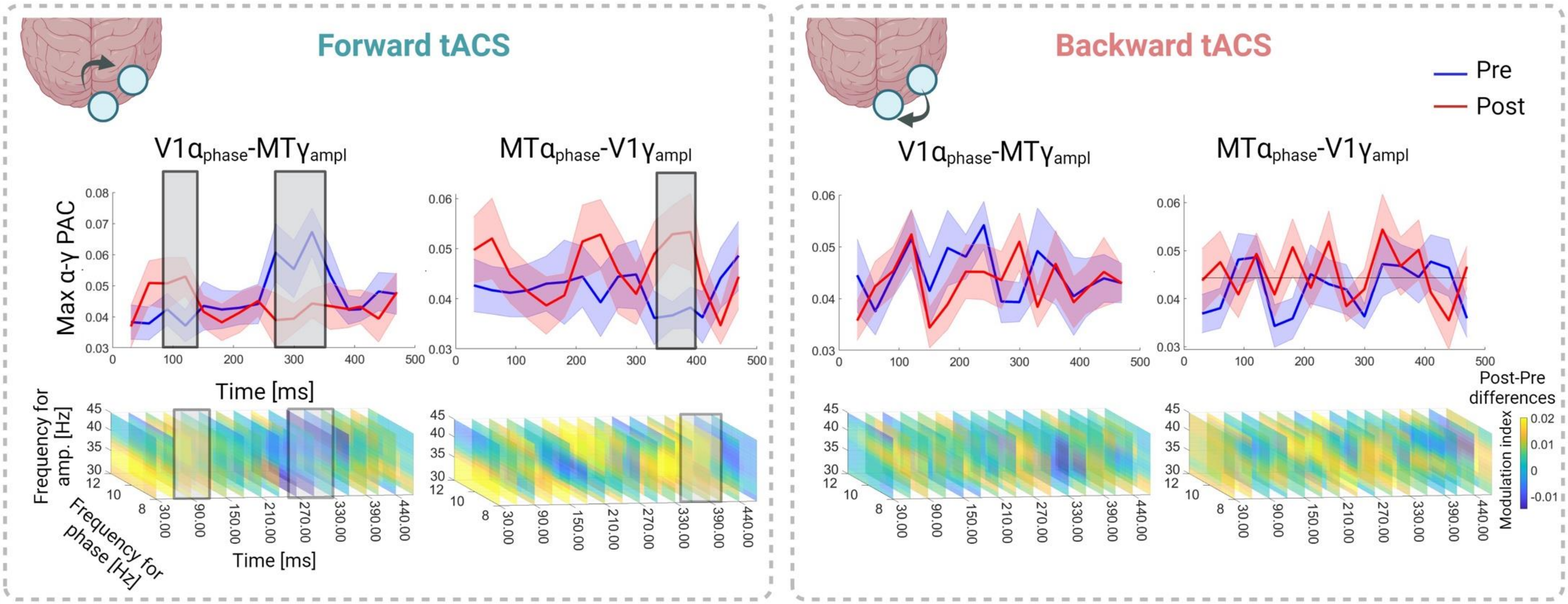
Experimental design



Results

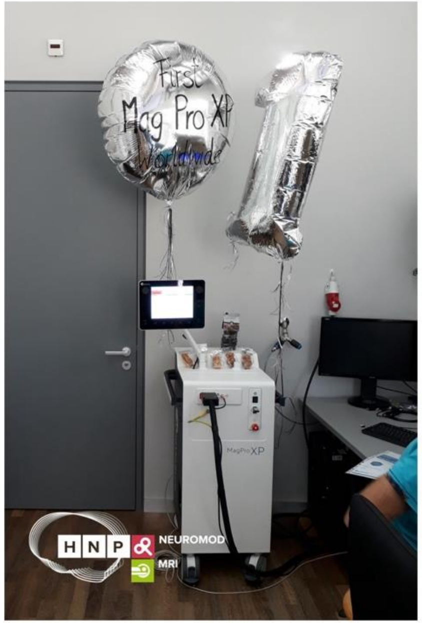

A. Daily motion discrimination performances
Baseline corrected-NDR
2.0
1.5
1.0
0.5
0
1
2
3
4
5
6
7
8
9
10
Training sessions
*
Better
Forward-tACS
Backward-tACS
B. Kinetic visual field maps
Changes in kinetic VF surface (deg²)
4000
3000
2000
1000
0
-1000
-2000
-3000
*
Pre
Post
Forward tACS
Backward tACS
90°
60°
30°
0°
330°
300°
270°
240°
210°
180°
150°
120°

V1-MT PAC



Forward tACS
Backward tACS
Pre
Post
V1αphase-MTγampl
MTαphase-V1γampl
Max α-γ PAC
Time [ms]
Frequency for amp. [Hz]
Frequency for phase [Hz]
Post-Pre differences
Modulation index

Does V1 reactivity predict recovery?



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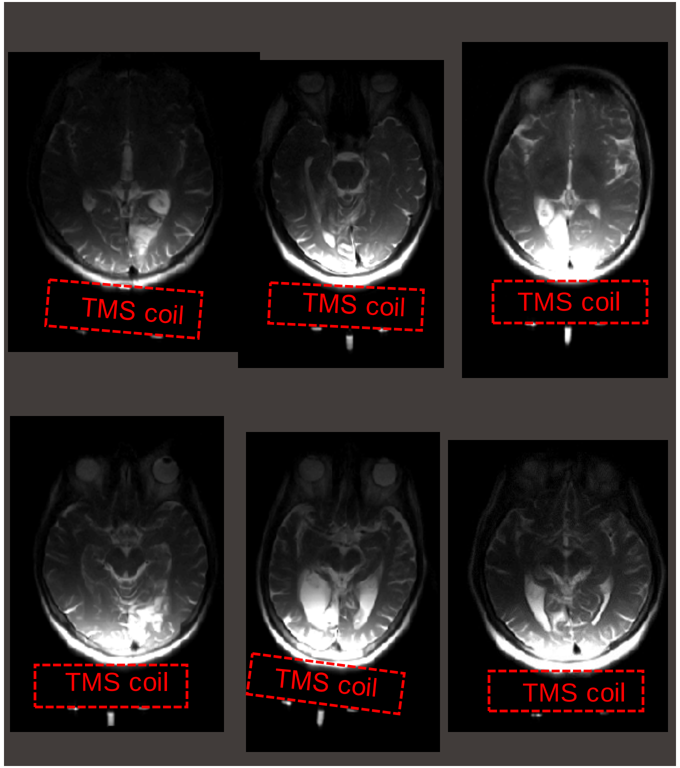

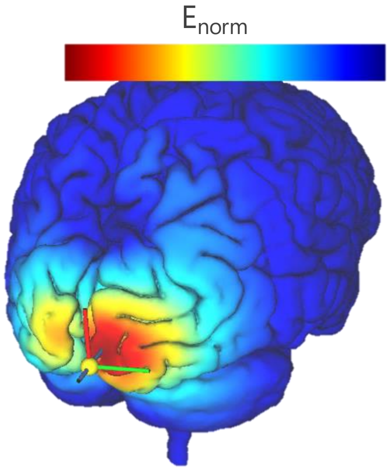

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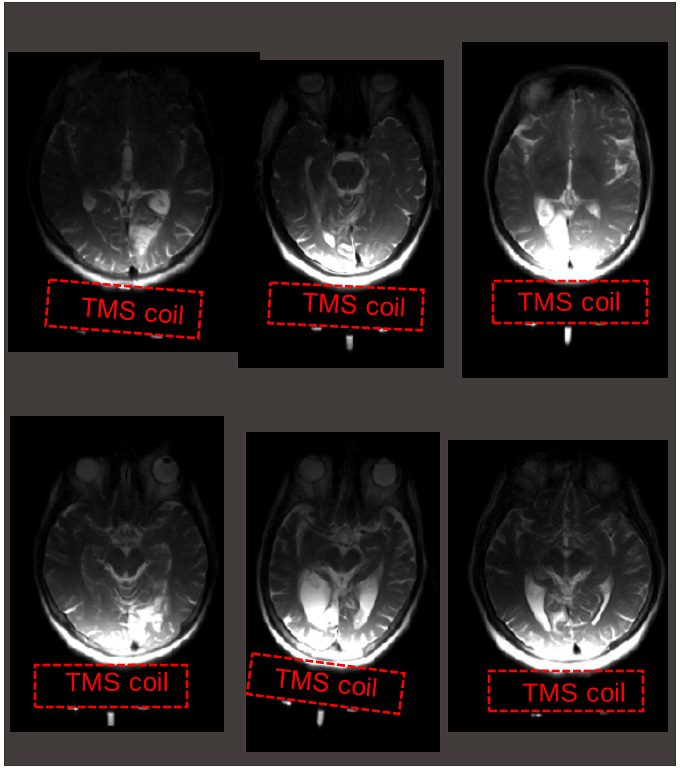
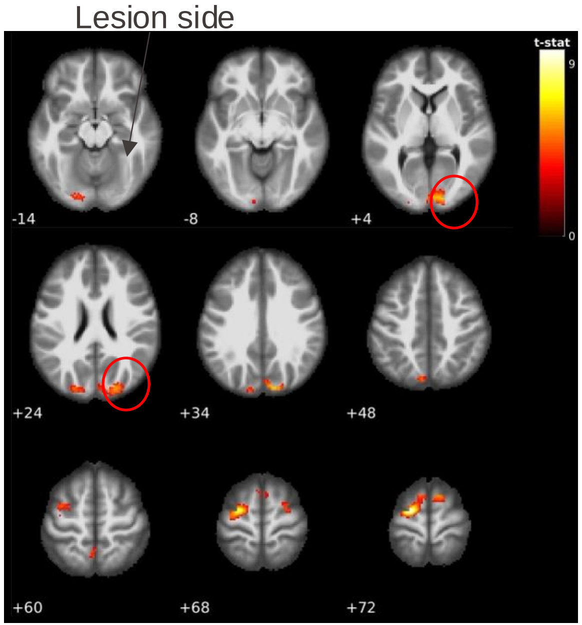


Group results
(HighTMS>LowTMS)



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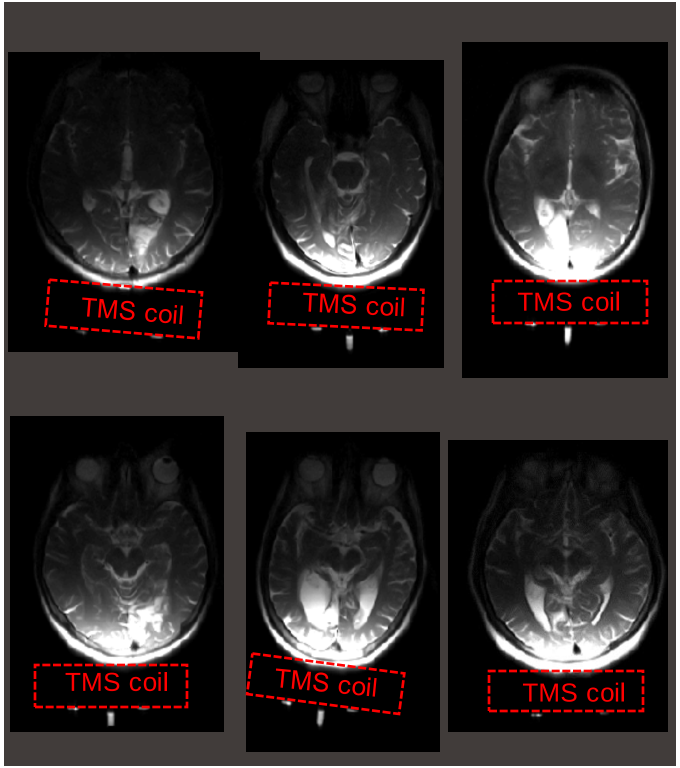

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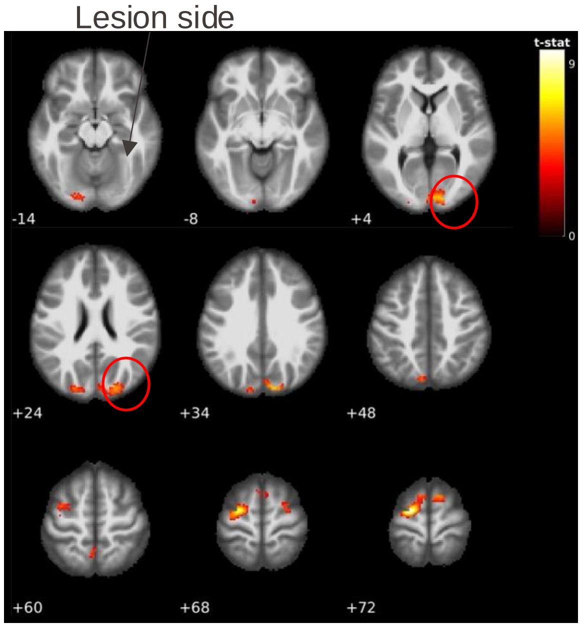
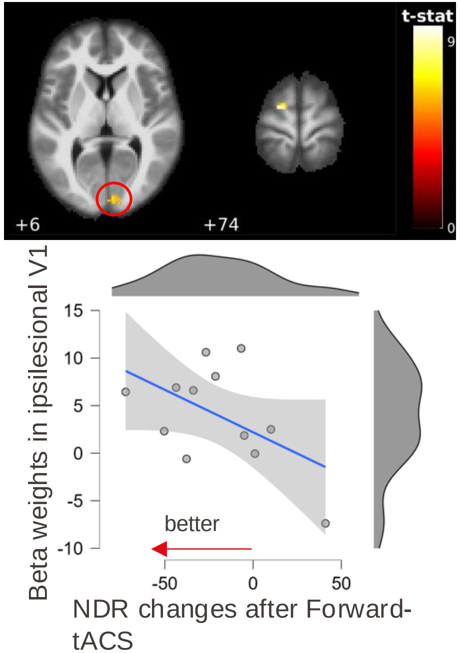
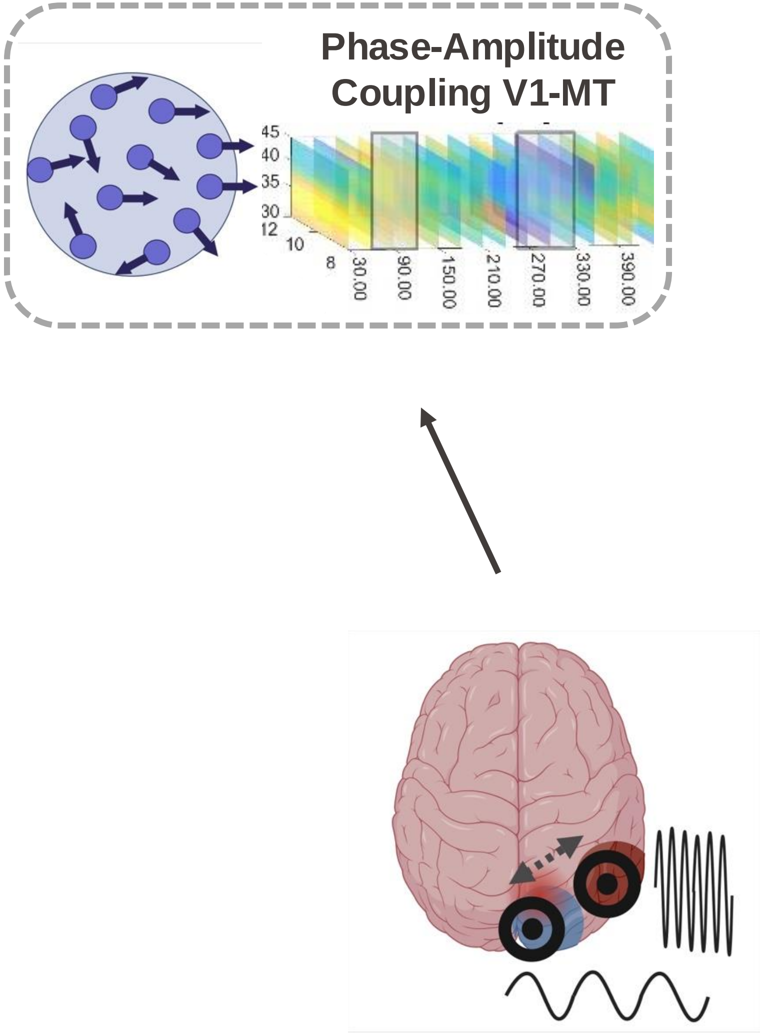


Covariate analysis
(Changes in motion discrimination)



EPFL

- The pathway and direction-dependent tACS protocol **improves motion processing in the blind field**
  - Changes in bi-directional cross-frequency V1-MT interactions
  - More efficient pathway-dependent processing



EPFL

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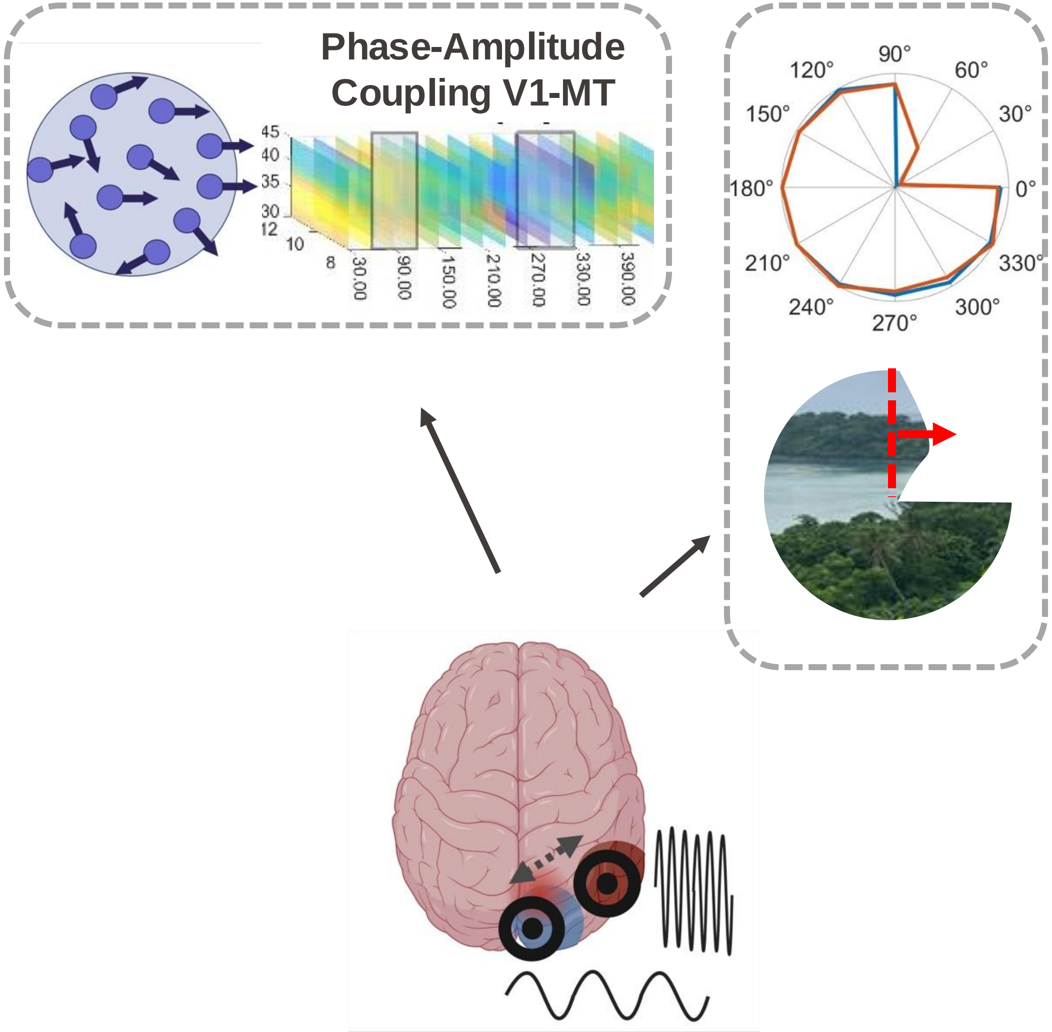
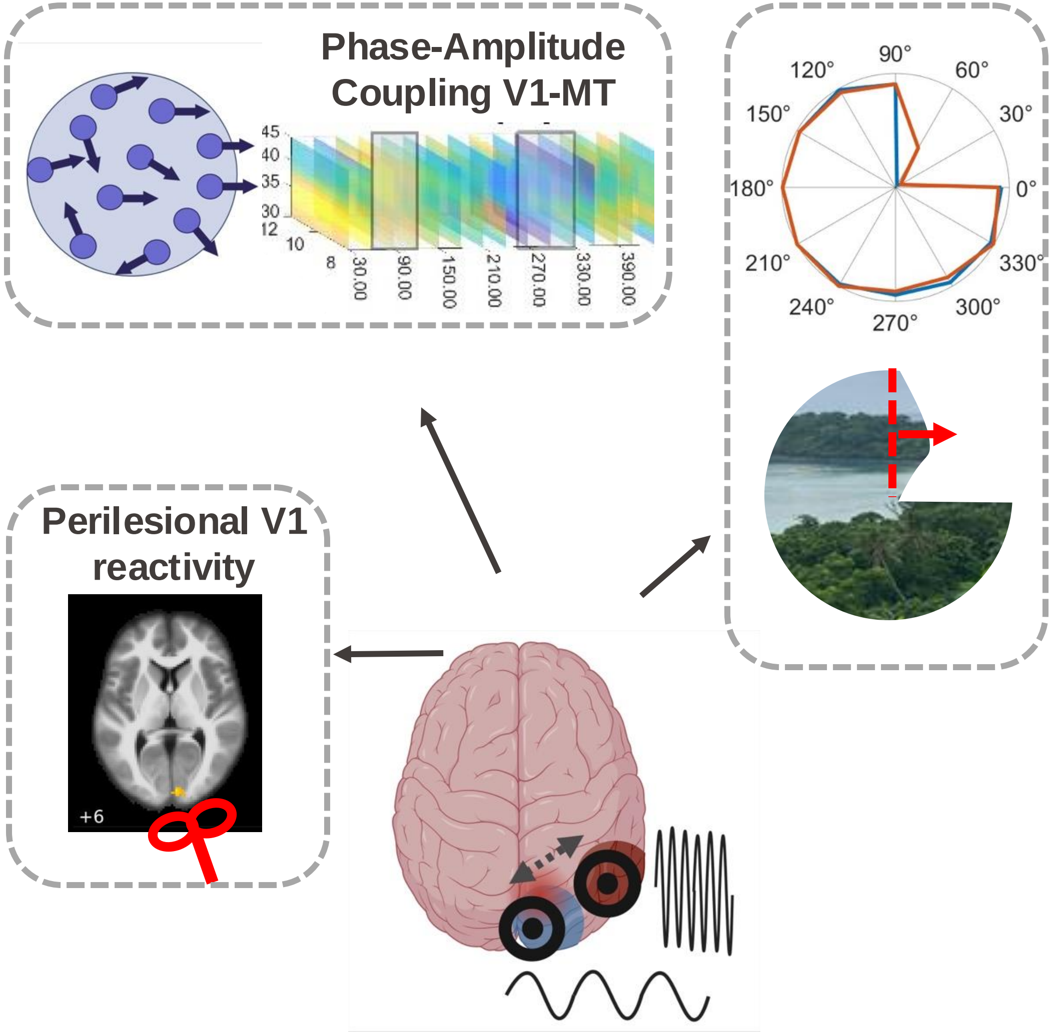
- and **enlarges visual field borders**

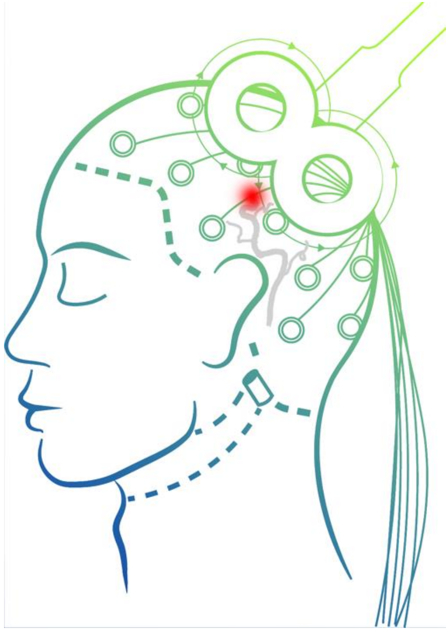


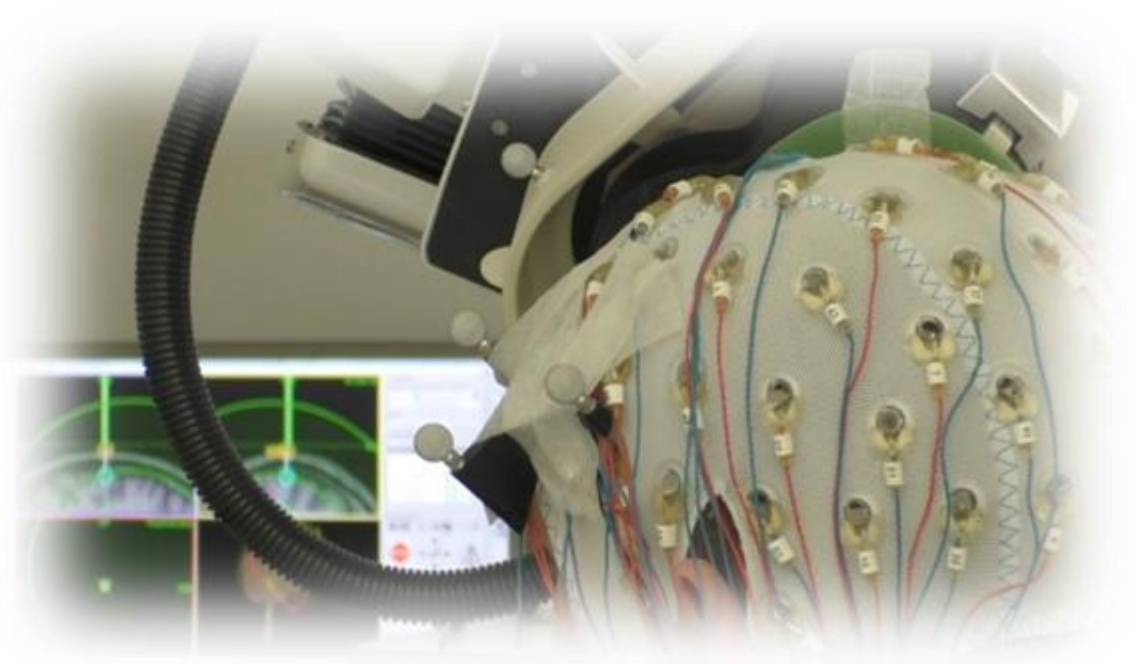
- The pathway and direction-dependent tACS protocol **improves motion processing in the blind field**
  - Changes in bi-directional cross-frequency V1-MT interactions
  - More efficient pathway-dependent processing

- and **enlarges visual field borders**
- was predicted by **more perilesional V1 activity** in response to TMS at baseline

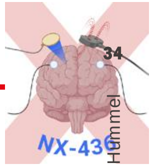


TMS-EEG





TMS-EEG



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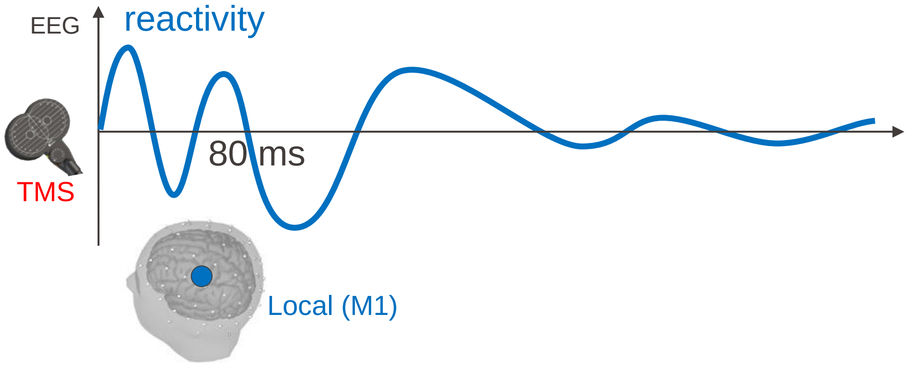
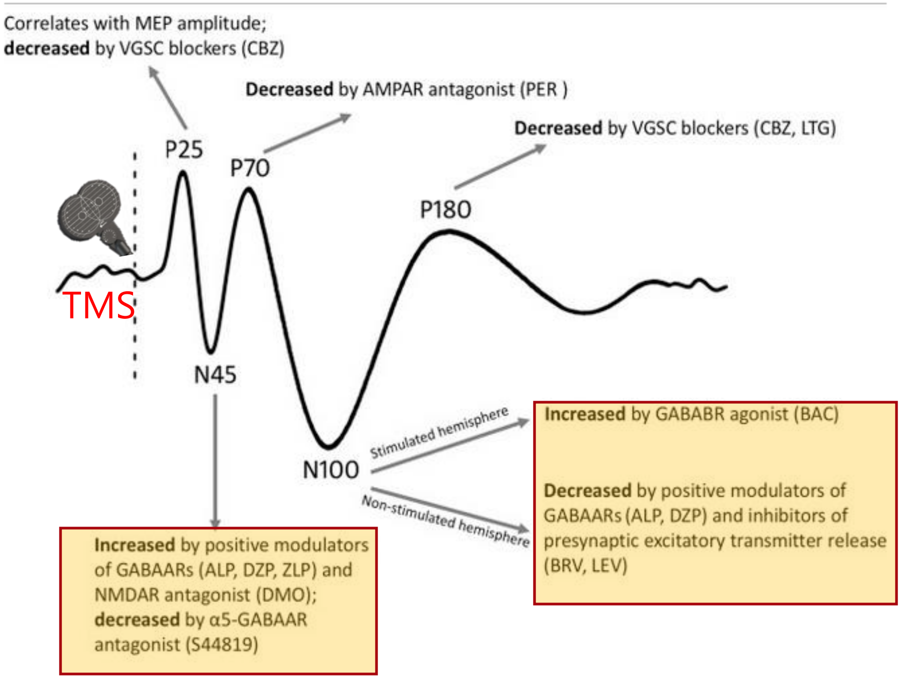
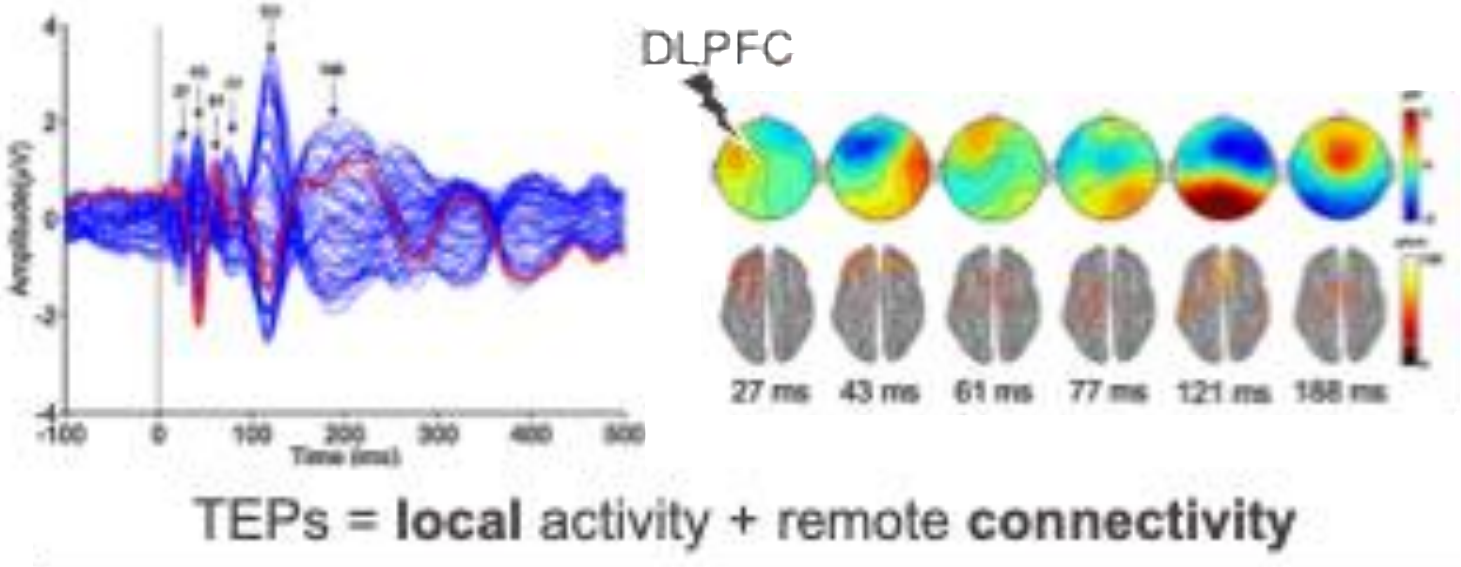
Early local TMS-**evoked** reactivity



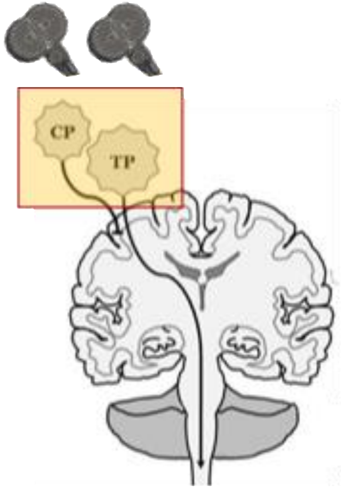


TMS-EEG

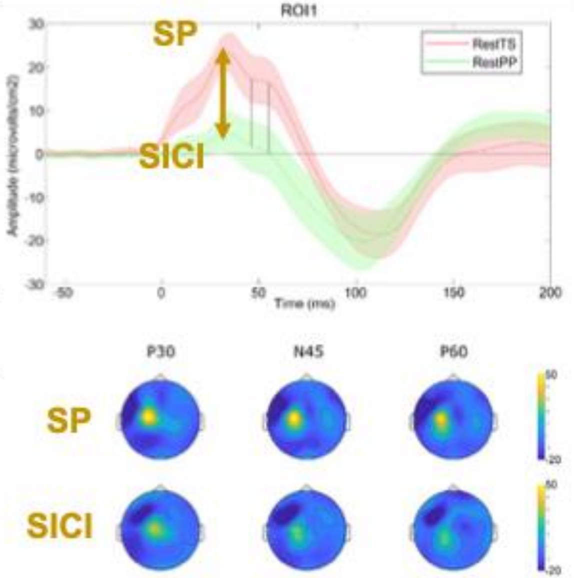


DLPFC
Amplitude (µV)
Time (ms)
-100
0
100
200
300
400
500
27 ms
43 ms
61 ms
77 ms
121 ms
188 ms
TEPs = **local** activity + remote **connectivity**

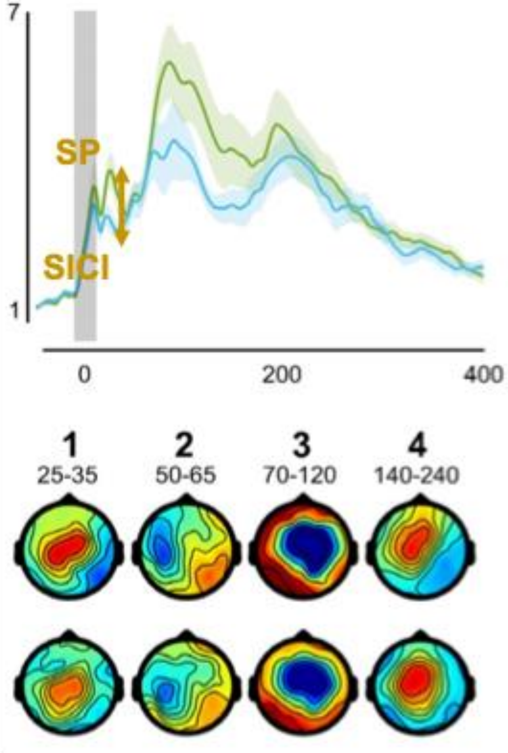
TMS-EEG



Short-Interval Cortical
inhibition (SICI)

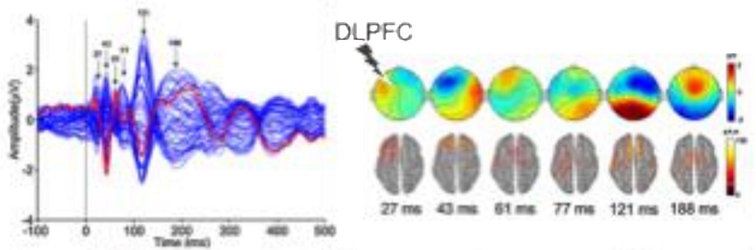


Leodori *et al.*, 2019



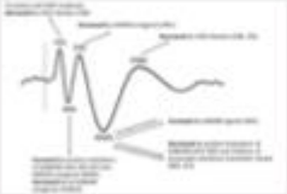
Raffin & Harquel *et al.*, 2020

TMS-EEG - Example



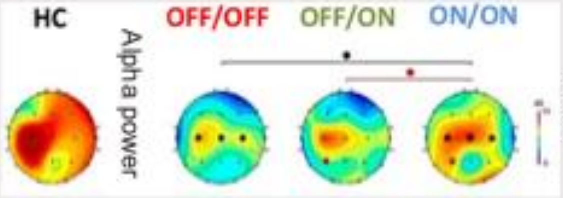
TEPs = **local** activity + remote **connectivity**

Neurotransmiters



Pharmaco TMS-EEG

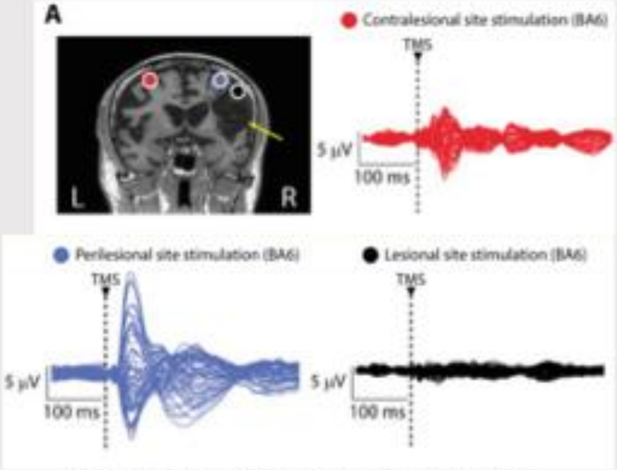
Darmani et al.
Brain stim., 2019



Casula et al., 2017

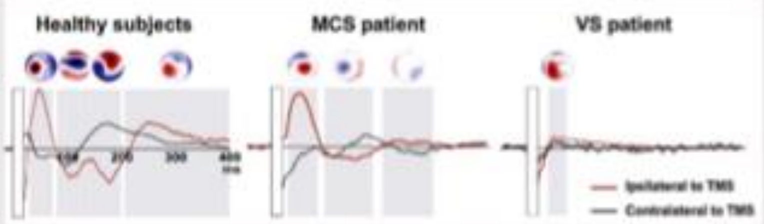
DBS and **levodopa** in **PD** patients

Clinical



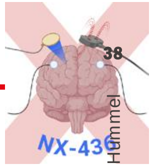
Cortical **reactivity** after **focal injury**

Sarasso et al., Brain, 2020



Impariment of **reactivity** and **connectivity** in **vegetative** state patients

Ragazzoni et al., PLOS One, 2013

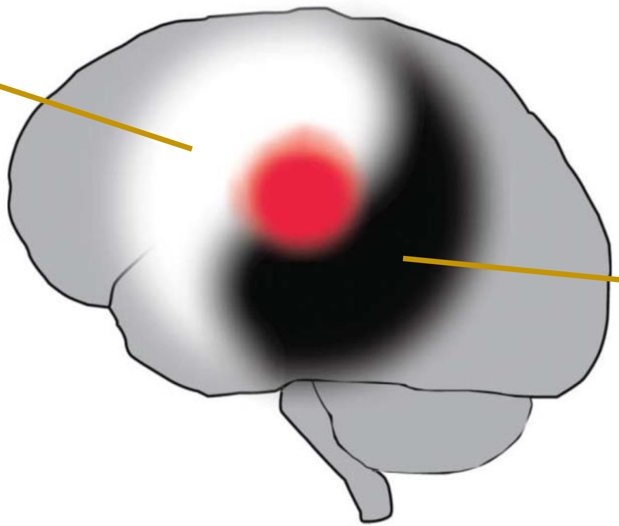


Friedhelm C. Hummel

Animal Models

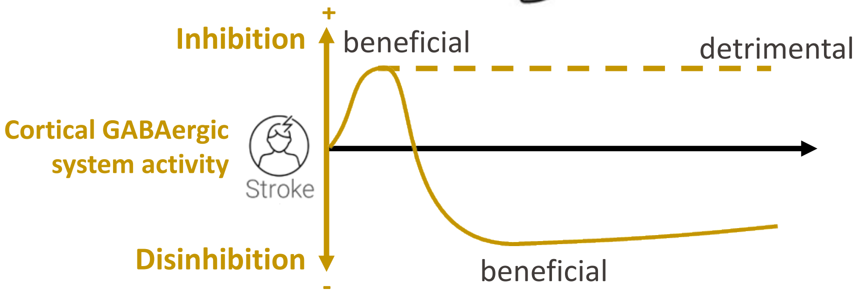
- Tonic Hyperinhibition
- Low excitability

-> **Beneficial** for preventing **excitotoxicity**



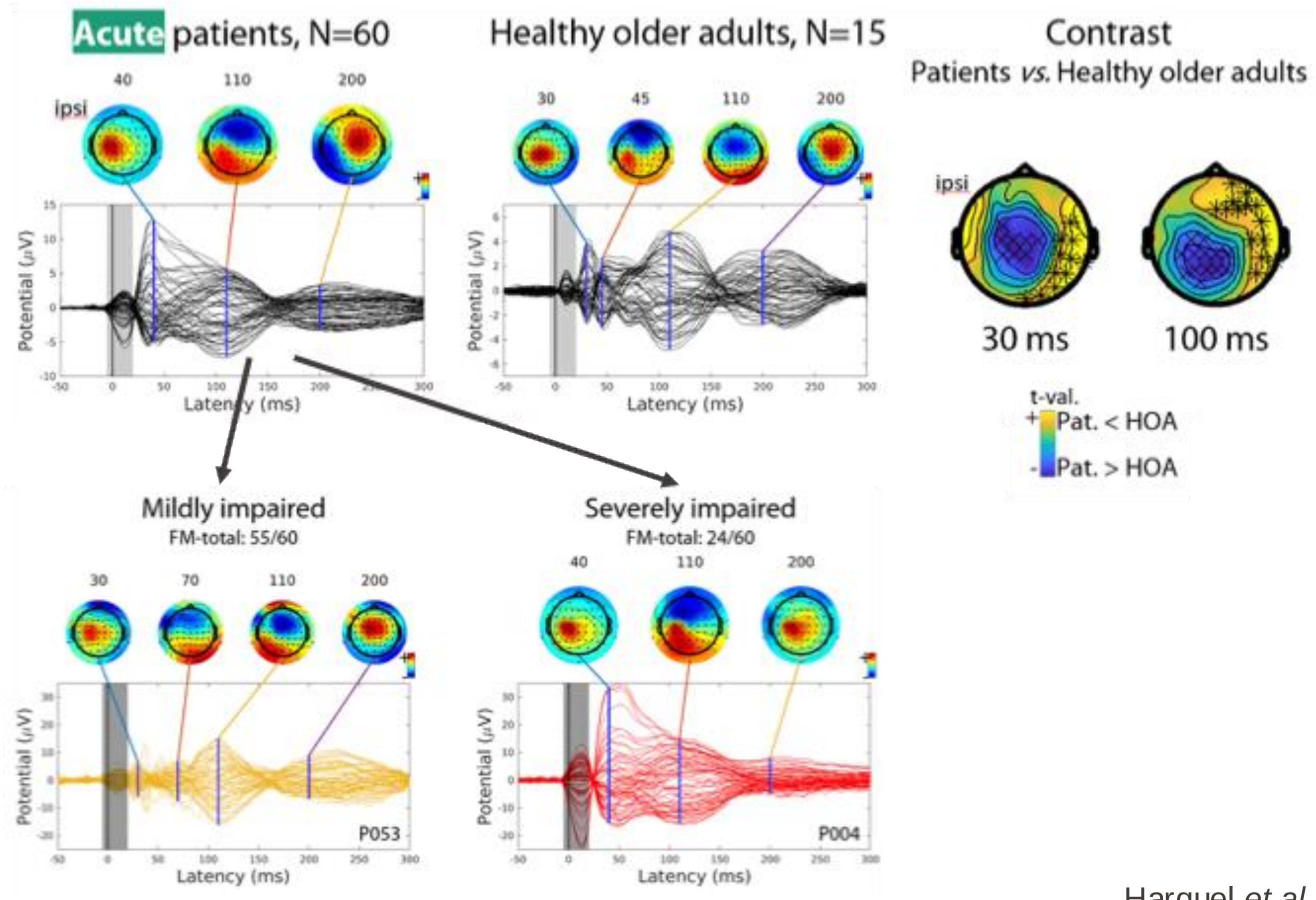
- Hyperexcitability
- Decrease of tonic inhibition

-> **Beneficial** for **plasticity**



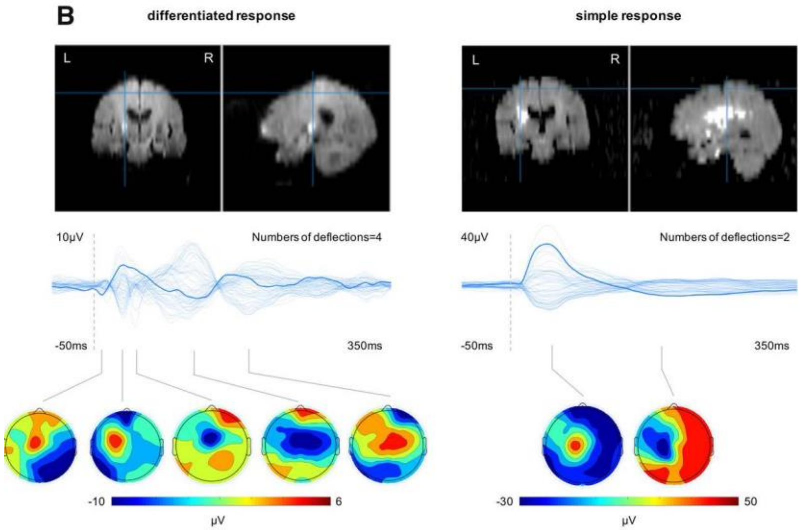
Carmichael, 2012

TMS-EEG



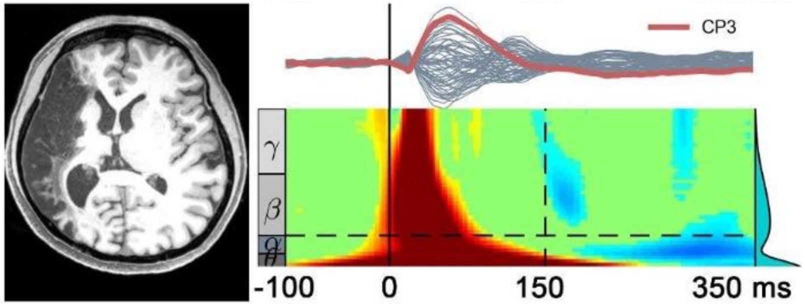
Harquel *et al.* 2024 Stroke

Stroke Patients



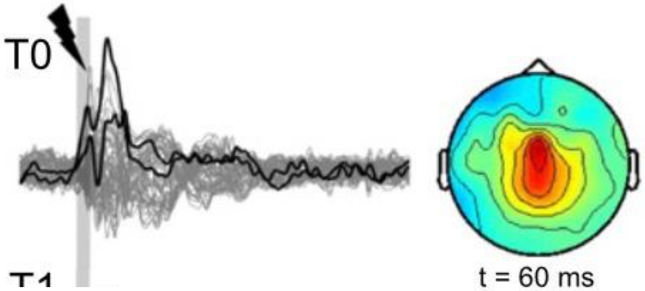
Tscherpel *et al.*, 2020

Acute stroke



Chronic stroke

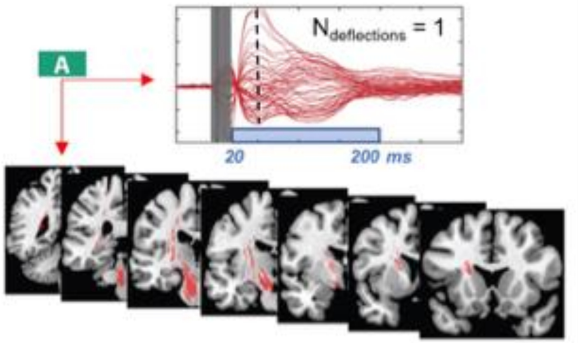
Bai *et al.*, 2023



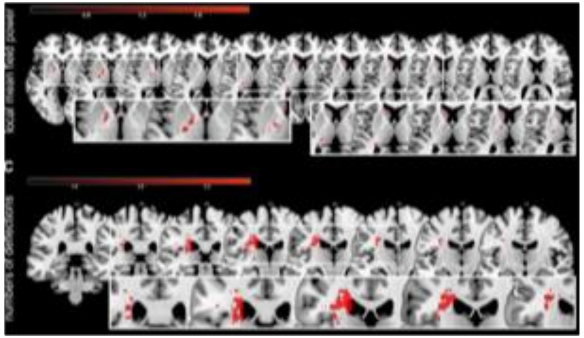
Chronic stroke

Bigoni *et al.*, 2023

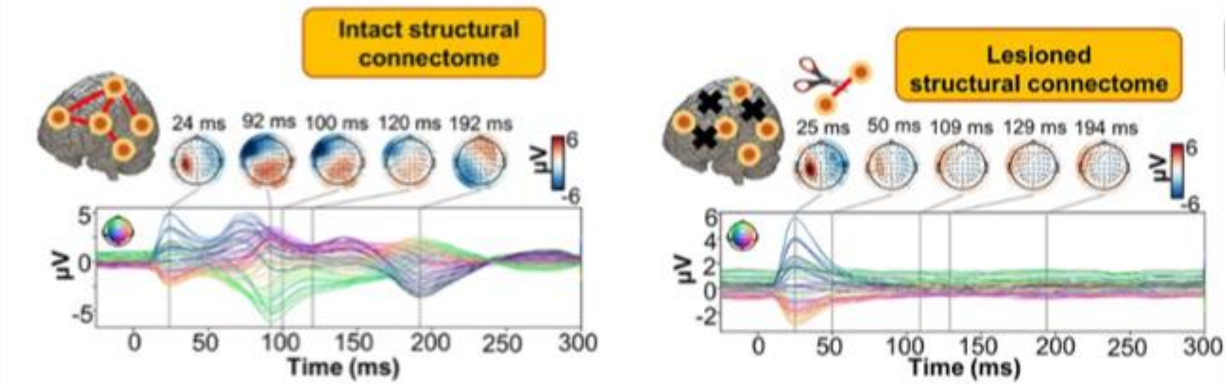
TMS-EEG - Stroke



Internal capsule (TiMeS)

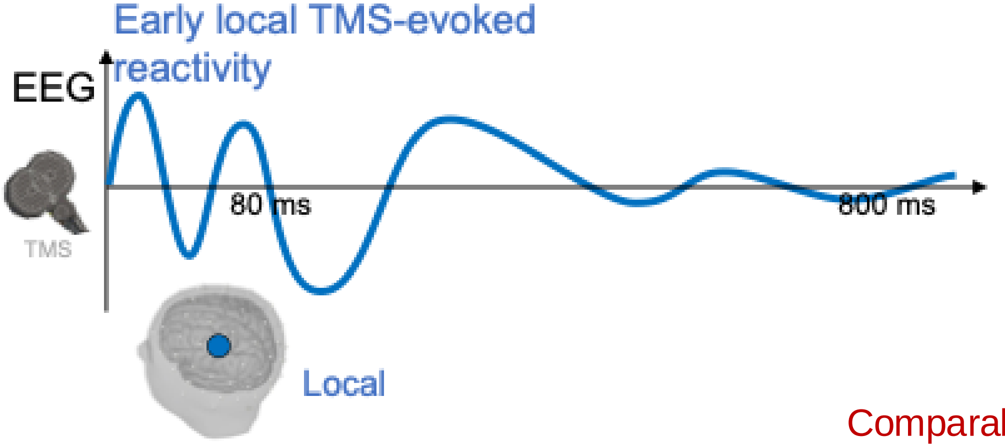


Internal capsule, caudate nucleus
(Tscherpel *et al.*, 2020)

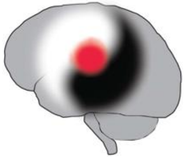


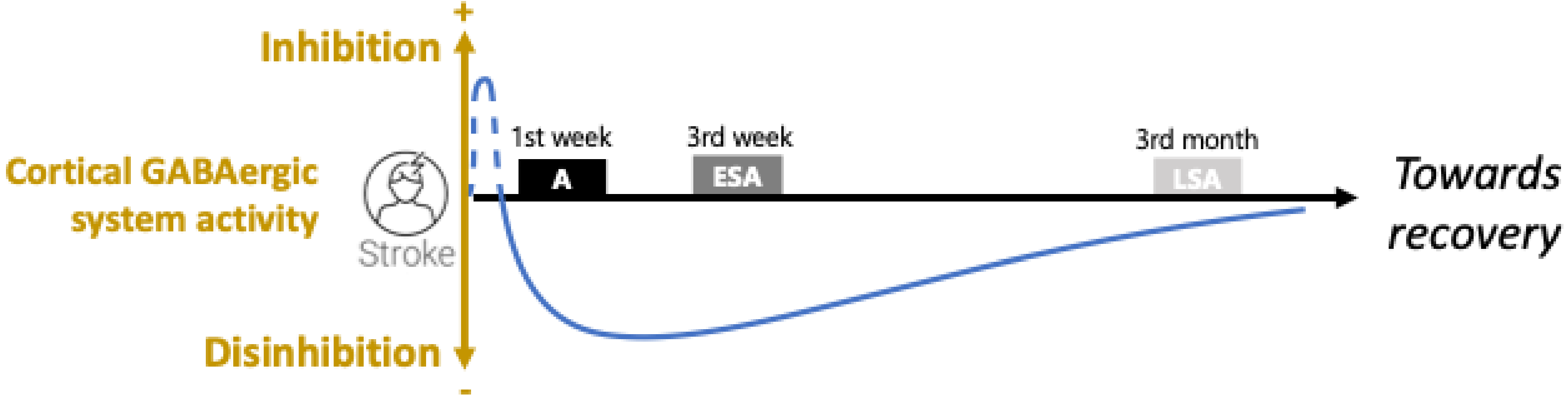
Computational modelling (Momi *et al.*, 2023)

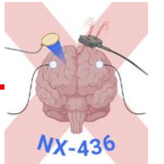
TMS-EEG - Stroke



Comparable to animal work







Contents lists available at ScienceDirect

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Review

Clinical utility and prospective of TMS–EEG

Check for updates

Sara Tremblay [a,b,*], Nigel C. Rogasch [c], Isabella Premoli [d], Daniel M. Blumberger [a], Silvia Casarotto [e], Robert Chen [f], Vincenzo Di Lazzaro [g], Faranak Farzan [h], Fabio Ferrarelli [i], Paul B. Fitzgerald [j,k], Jeanette Hui [a], Risto J. Ilmoniemi [l], Vasilios K. Kimiskidis [m], Dimitris Kugiumtzis [n], Pantelis Lioumis [a], Alvaro Pascual-Leone [o], Maria Concetta Pellicciari [p], Tarek Rajji [a], Gregor Thut [q], Reza Zomorrodi [a], Ulf Ziemann [r], Zafiris J. Daskalakis [a]

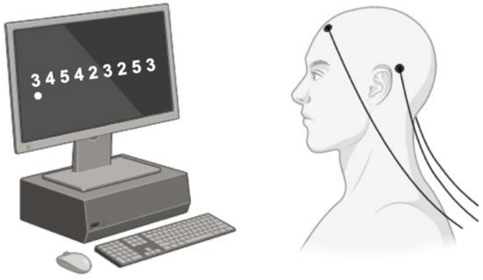
tTIS-fMRI

nature neuroscience

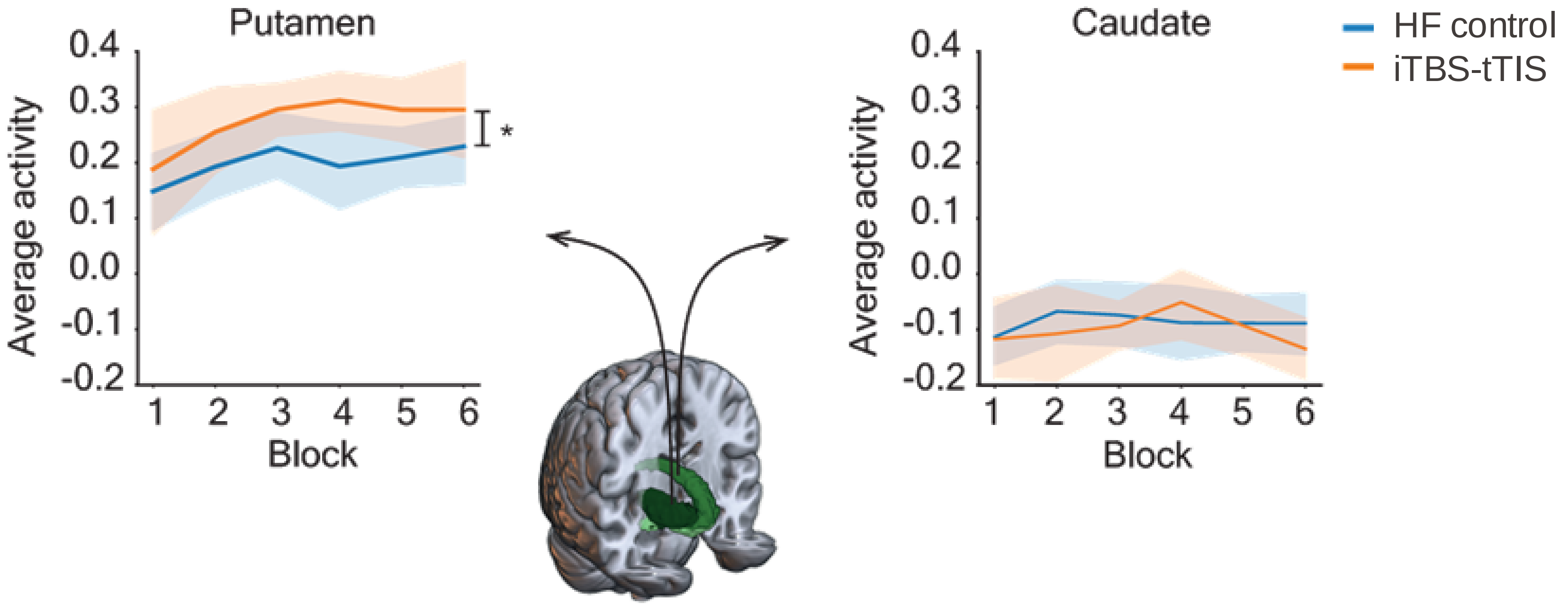
Article https://doi.org/10.1038/s41593-023-01457-7

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

Wessel, Beanato *et al.* 2023



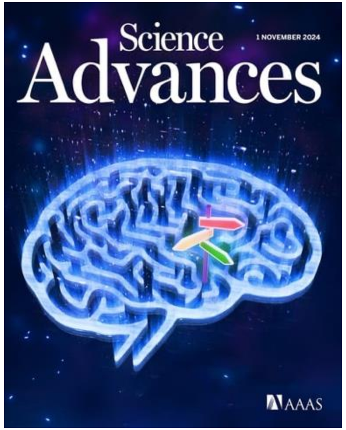
tTIS-fMRI

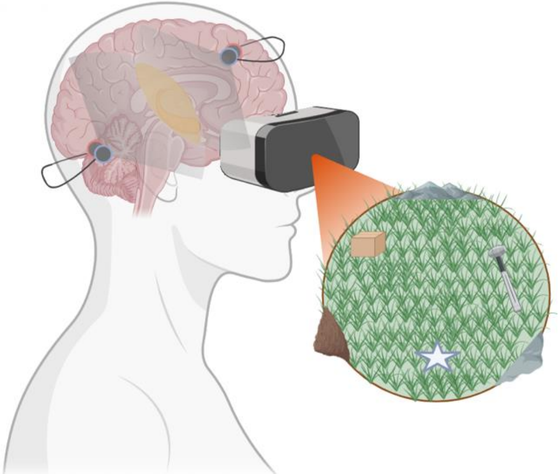


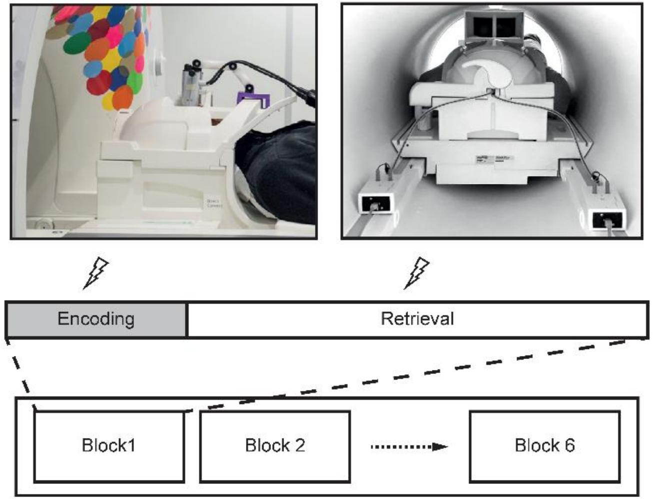
Stimulation effects are specific to the subregion already involved in the task

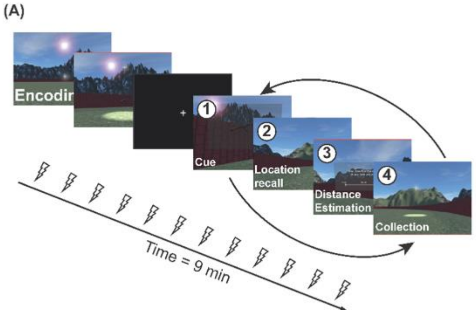
Wessel, Beanato *et al.* *Nature Neuroscience* (2023)

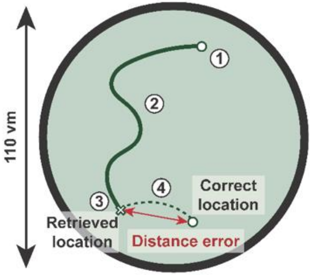
tTIS-fMRI





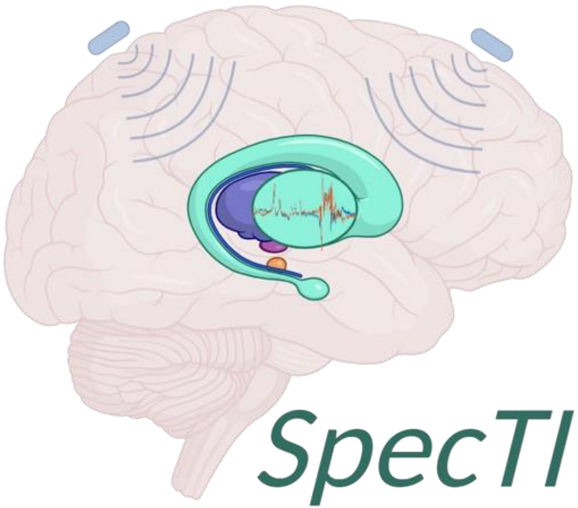




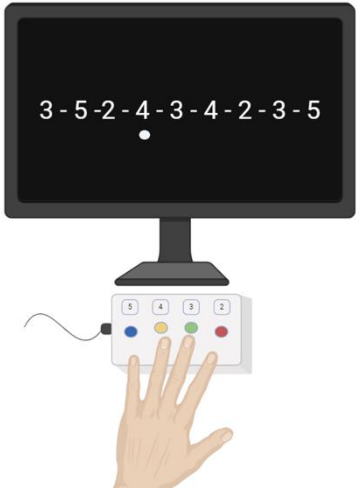


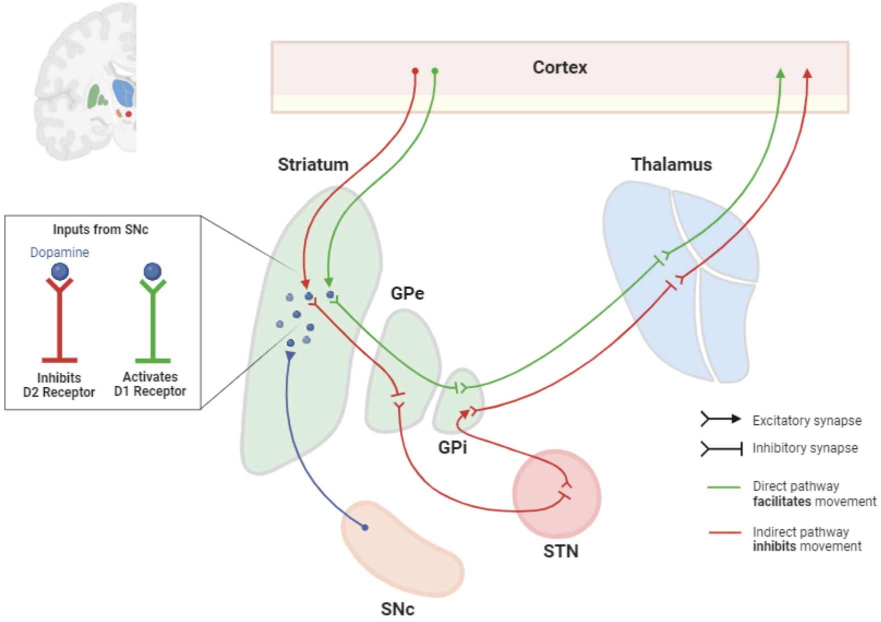
Beanato, Moon *et al.* 2024. *Science Advances*

tTIS-MR Spectroscopy



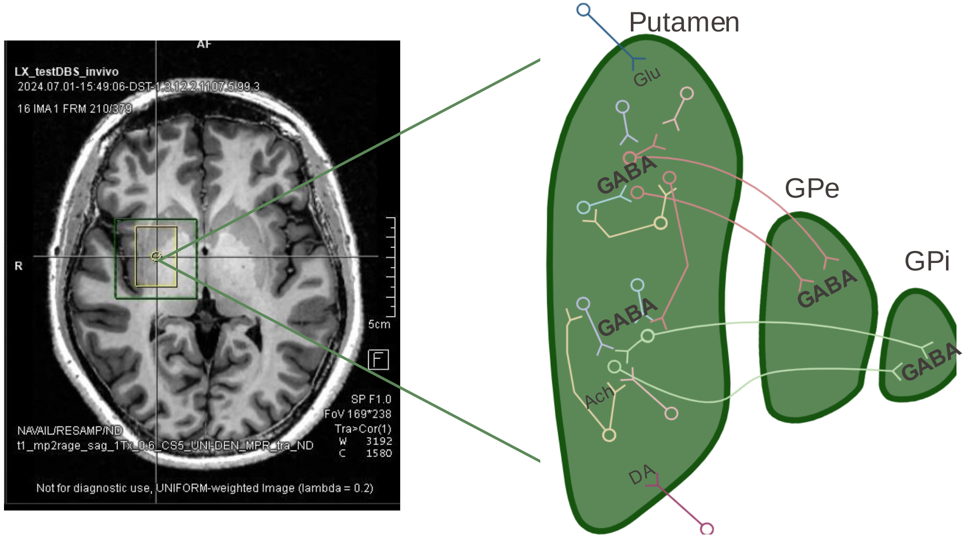
- How does striatal tTIS modulate neuromodulator levels in the putamen?
- How does this differ when performing a motor learning task?





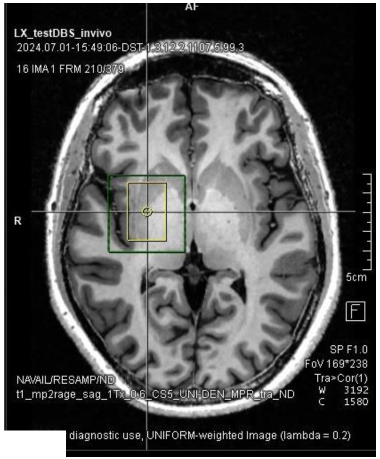
tTIS-MR Spectroscopy

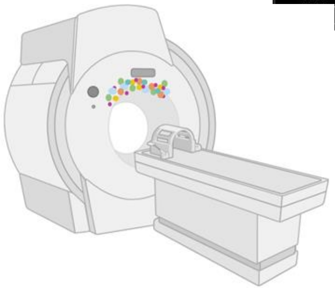
- Majority of neurons in Putamen are GABAergic
  - Medium spiny projection neurons
  - GABAergic Interneurons

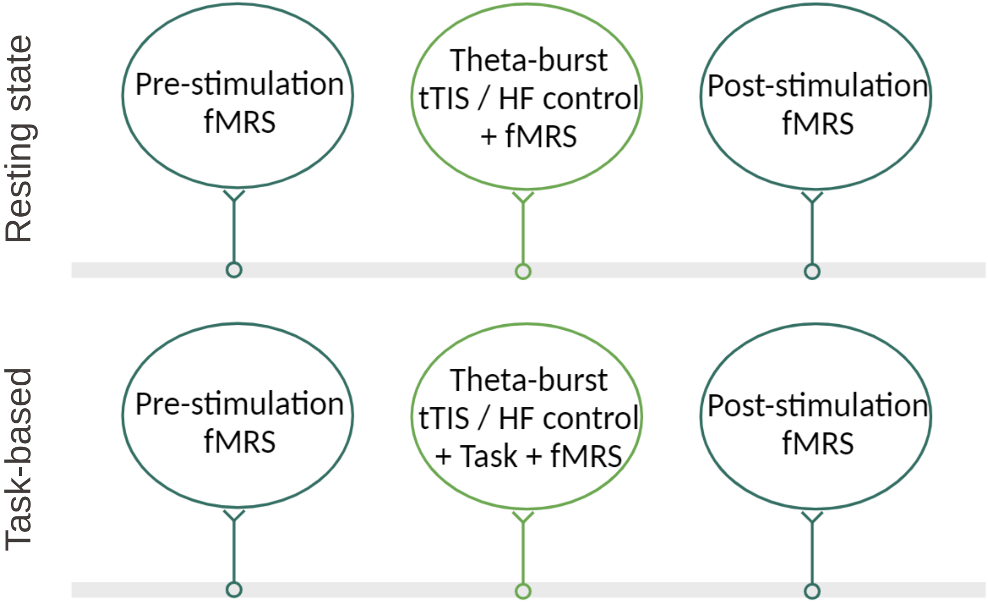


tTIS-MR Spectroscopy

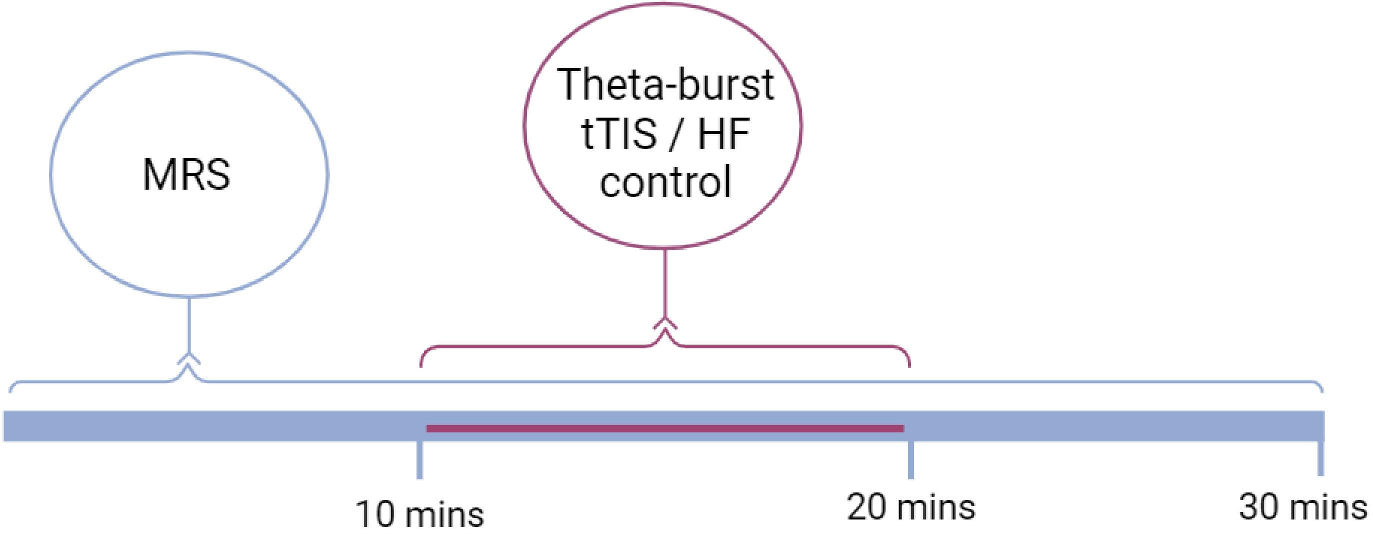
- Record functional MR spectroscopy of the Putamen at 7T

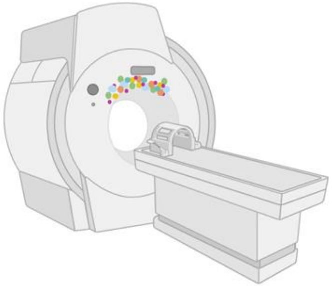




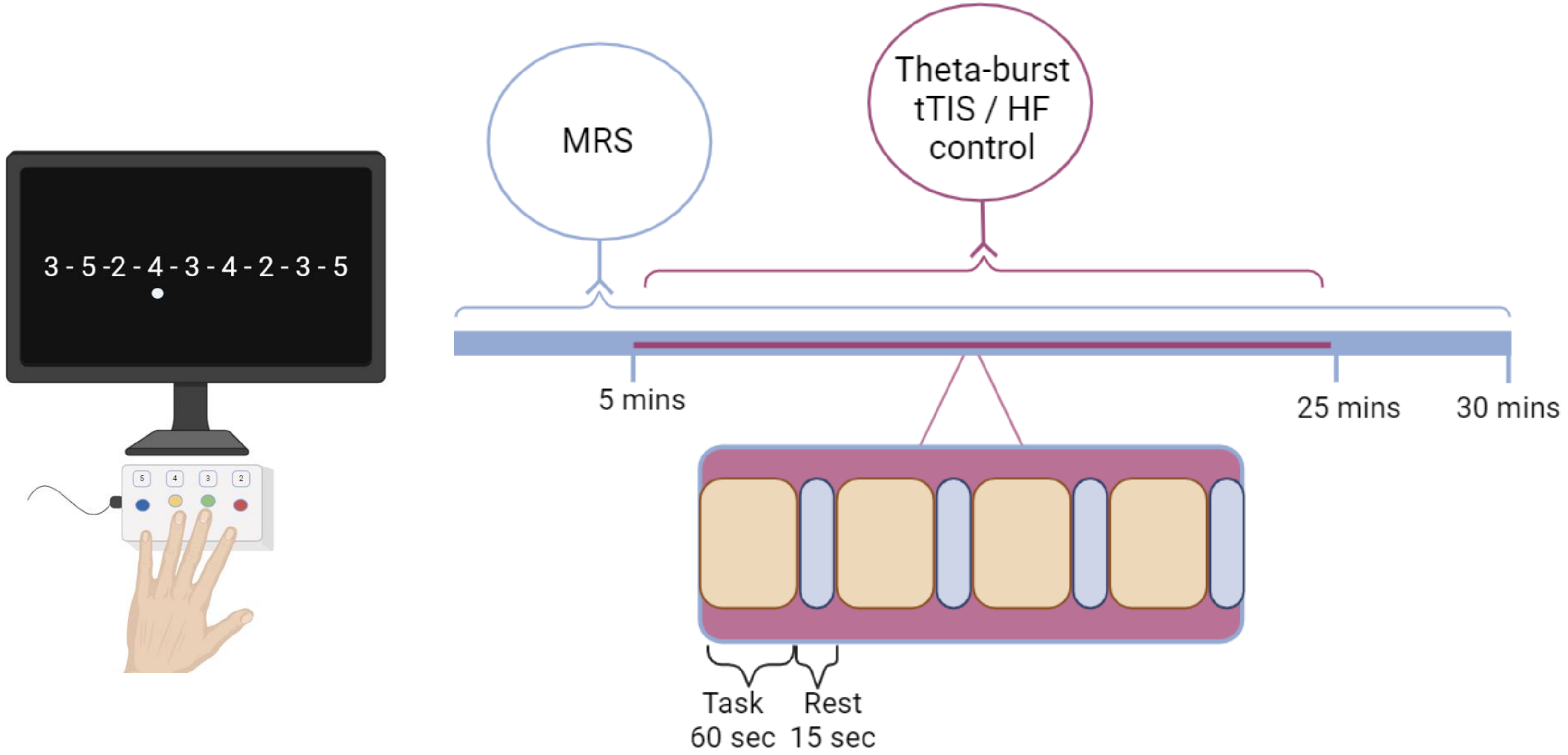


tTIS-MR Spectroscopy

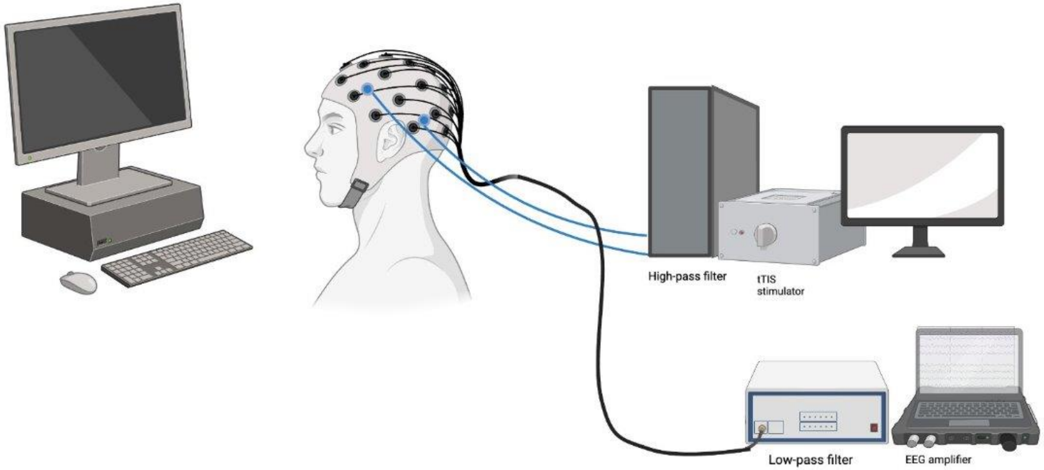




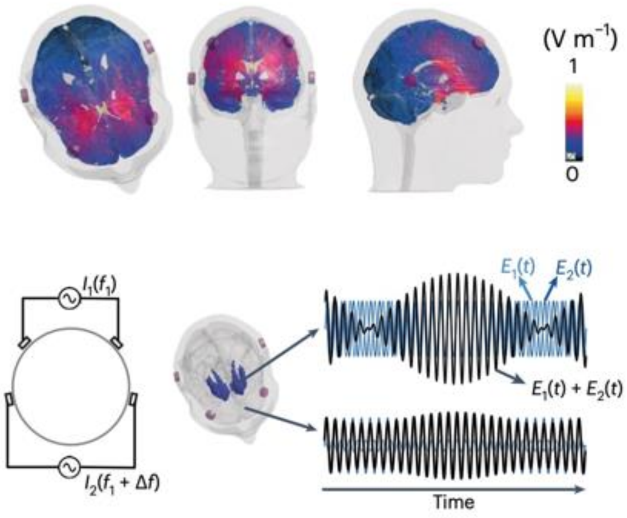
- Sequential finger tapping task to motor learning



tTIS-EEG


High-pass filter
tTIS stimulator
Low-pass filter
EEG amplifier

Transcranial Temporal Interference Stimulation (tTIS)



Electric field modeling with striatal montage
Maximilian J. Wessel, Elena Beanato et al. 2023

Temporal Interference (TI) Stimulation uses two electric fields at frequencies f1 and f2 to stimulate the brain at the difference frequency (|f1-f2|=∆f), which lies within the range of brain activity, non-invasively.

'Pulsed Temporal Interference' uses two electric fields at frequencies, f1 and f2, and periodically switch a particular field to f2+ ∆f in a timed, pulsed manner (i.e. in bursts).

Each electric field is generated by a constant current sources

EPFL

Transcranial Temporal Interference Stimulation (tTIS)

What is the current hypothesis of how tTIS modulates brain activity?

Subthreshold stimulation that requires behavioral co-activation of the brain area of focus (rs- fMRI vs. task-based fMRI)

(Wessel, Beanato et al. 2023, Violante et al. 2023)

Disruptive effect on the underlying network oscillation pattern when applied in a continuous and not in a pulsed-stimulation pattern (it is not phase locked to the underlying oscillatory rhythm or the continuous stimulation masks the underlying network activity

(Vassiliadis et al. 2024, Viera et al. 2024, Chenhao Yang et al. 2024)

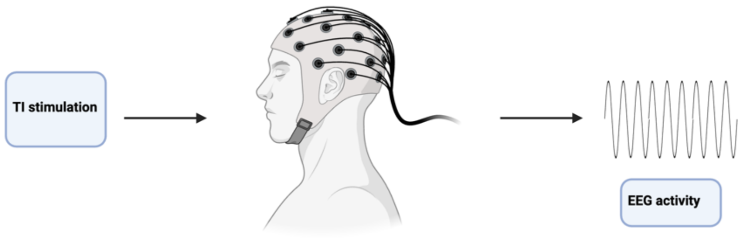
At a cellular level, neuron can mix the high carrier frequencies and produces non-linear mixed products – new frequencies -

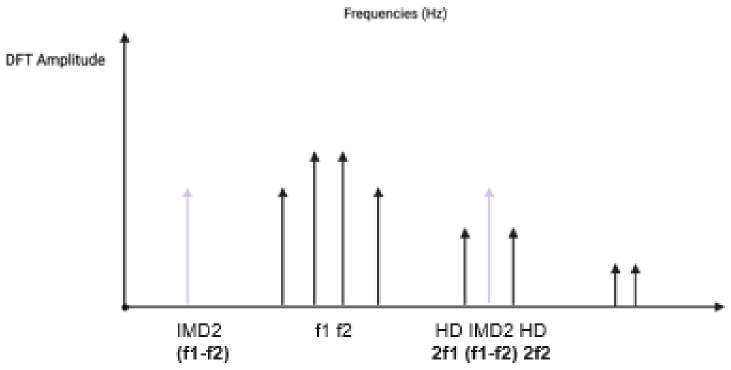
(Mirzakhalili et al. 2020)

Neuron is mixing exogenous and endogenous subthreshold membrane potential oscillations to create new oscillatory frequencies (Kinetics of voltage-gated sodium channels are non-linear)

(Luff et al. 2024)

tTIS - EEG concurrent recording





Concurrent TI-EEG recording:

Advantages

Continuous EEG recording during and after tTIS:

- Mechanistic understudying of tTIS effects on brain circuits with high temporal resolution
- Reveal sustained effects of tTIS during and after the experiment

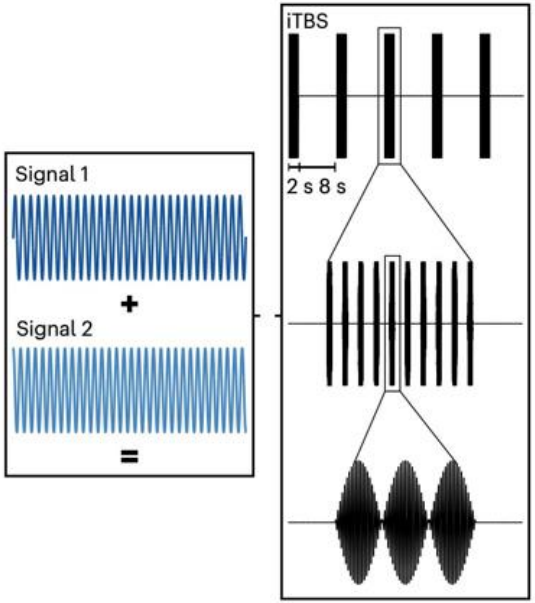
Technical challenges

tTIS creates voltage potential that is above the limits of commercially available EEG amplifiers: **non-linear system**

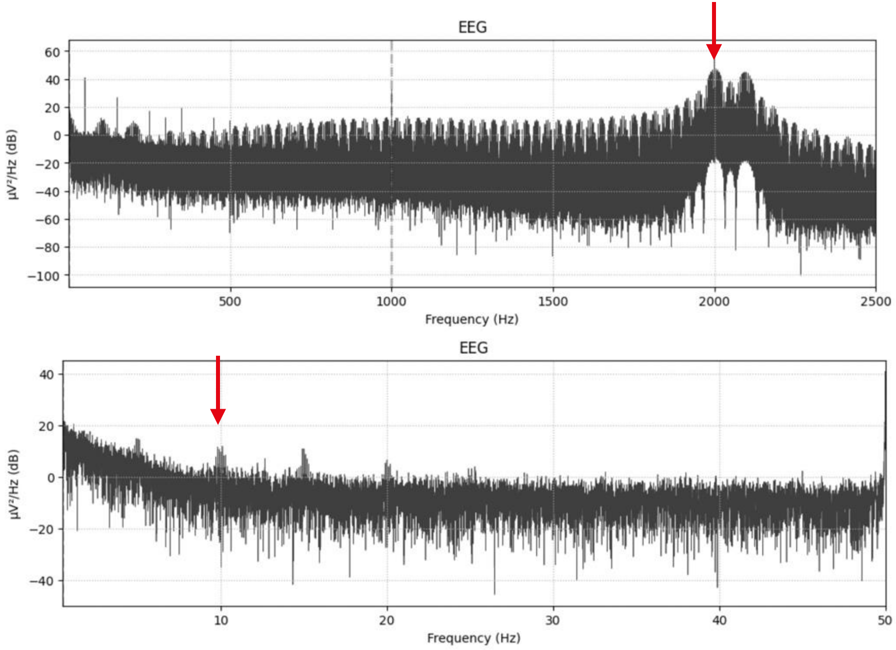
EEG recording will be distorted by non-linear artefacts, as a result of the tTIS

tTIS - EEG concurrent recording

Example of stimulation artefacts



Intermittent theta burst stimulation pattern
Maximilian J. Wessel, Elena Beanato et al. 2023



Red arrows: Carrier TI frequencies (2kHz, 2.1kHz), TI stimulation artefact at 5Hz (FFT)

Lack of Linearity

Stimulation artefacts can be approximated by Taylor expansion:

Is an infinite sum of terms which represent an approximation of a function around a specific point on the function.
It allows any function (including non-linear ones, as long as it is infinitely differentiable) to be represented as the sum of terms scaled by the function's derivatives at a specific point (with approximation accuracy reducing the further one gets from the specified point)

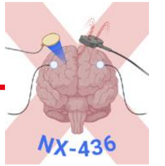
A Maclaurin Series is the same thing as a Taylor Series but with the specified point around which to approximate defined as zero:

$$f(0) + \underbrace{\frac{f'(0)}{1!}x}_{\text{Linear}} + \underbrace{\frac{f''(0)}{2!}x^2 + \frac{f'''(0)}{3!}x^3 + \cdots}_{\text{Non-Linear}} = \sum_{n=0}^{\infty} \frac{f^{(n)}(0)}{n!}x^n$$

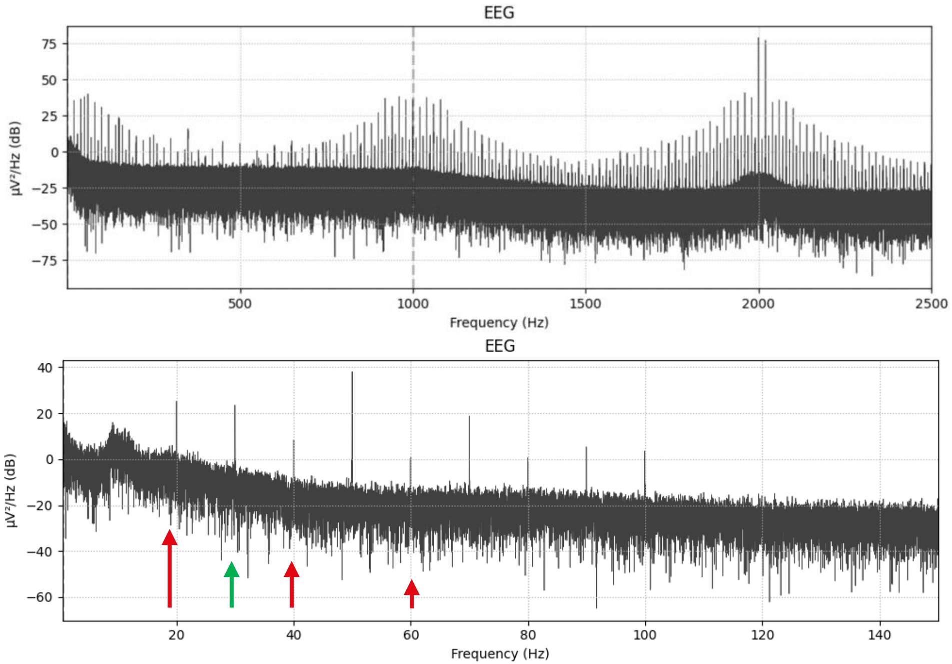
Linear

Non-Linear

tTIS - EEG concurrent recording



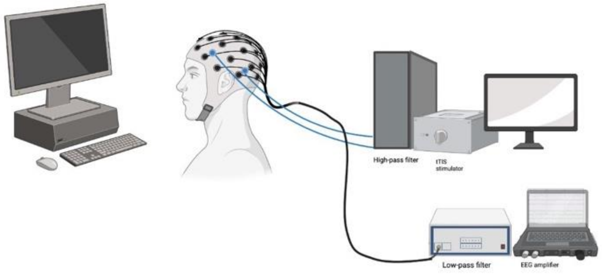
Example of stimulation artefacts with continuous TI stimulation, beat frequency at 20Hz

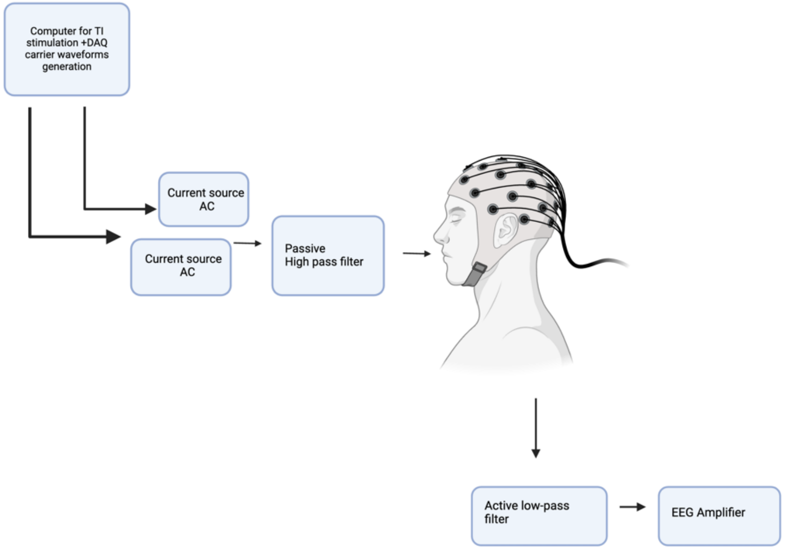


Carrier TI frequencies (2kHz, 2.02kHz)
Red arrows: TI stimulation artefact at 20Hz and its harmonics (FFT)
Green arrows: TI stimulation artefact at 30Hz (mixing with power line noise)

TI stimulation, beat frequency 20Hz (enveloppe graphical representation)

tTIS - EEG concurrent recording, Hardware filter solution



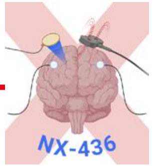


TI-EEG set up configuration:

Passive high-pass filter: allows only the high carrier frequencies to pass, after the TI stimulators

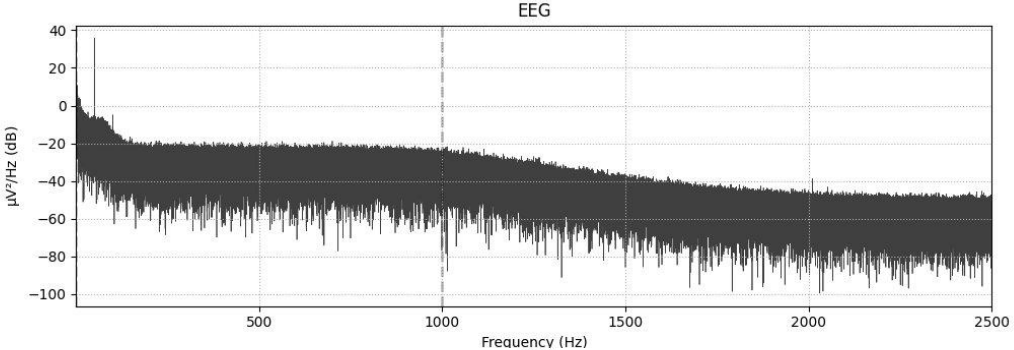
Active low-pass filter: allows only the frequencies below 100Hz to pass, eliminating the carrier frequencies before reaching the EEG amplifier

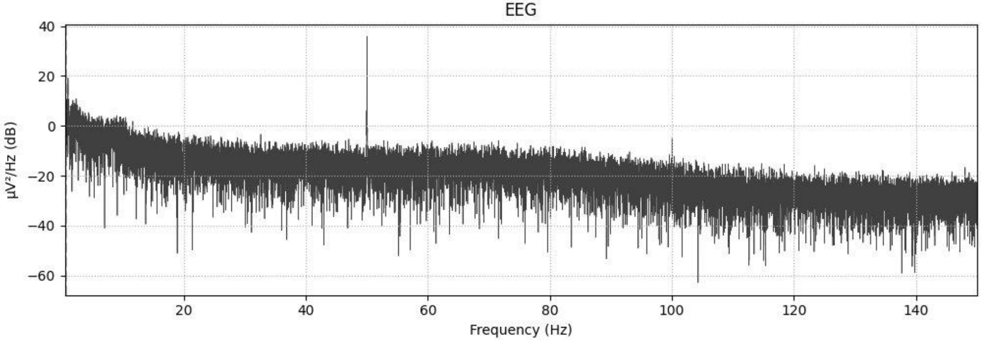
tTIS - EEG concurrent recording, Hardware filter solution



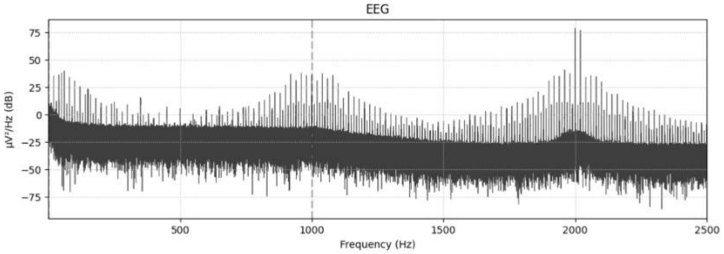
Hardware filters, tTIS 2kHz, Beat frequency 20Hz

EEG recording with hardware filters, no artefacts for all the EEG channels





Without hardware filters:

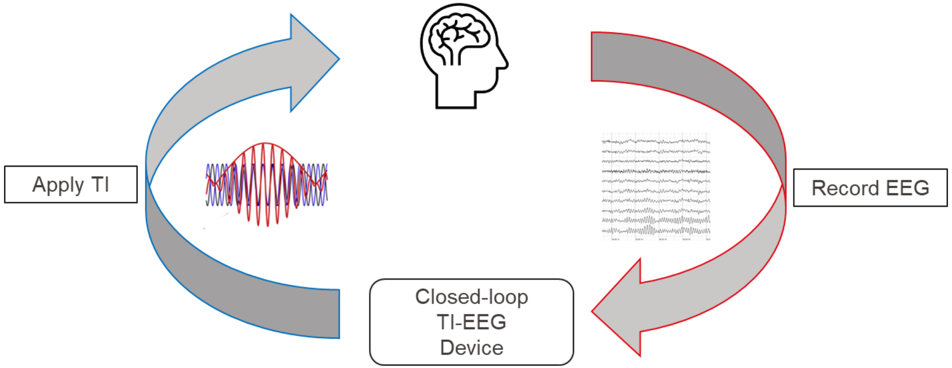


tTIS - EEG concurrent recording

Applications with tTIS-EEG recording and possible technological developments:

Closed-loop application based on neurofeedback and/or behavioral performance:

1. Optimize tTIS (beat frequency, pattern) based on cortical output EEG activity
2. Deliver pulsed-pattern stimulation, locked to endogenous cortical EEG activity
3. Enhance or disturb reinforcement learning, closed-loop with changes in cortical EEG recording
4. Modeling striatal sEEG activity in correlation with EEG cortical activity:
   adjust online envelope focus, beat frequency to endogenous rhythm, for example in Parkinson s disease
5. Phase-locking tTIS



Applications with tTIS-EEG recording:

Hippocampus TI stimulation and EEG cortical output:

Alzheimer's disease (AD):

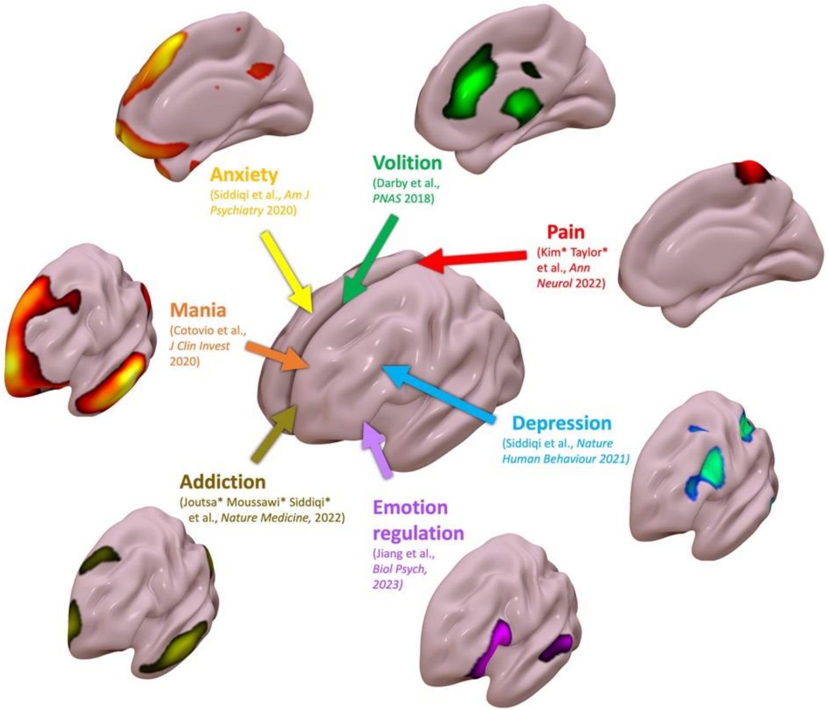
- Establish physiological rhythm patterns in DMN and FPN
- Cortical biomarkers of response to TI stimulation

Striatum TI stimulation and EEG cortical output:

Parkinson's disease (PD):

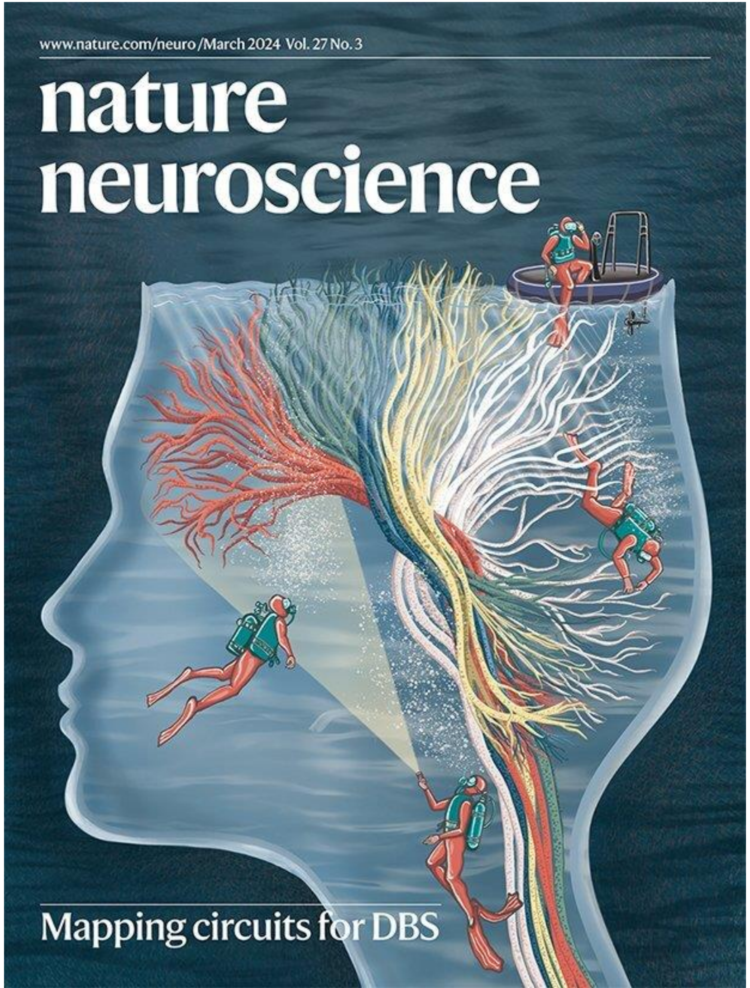
- Establish physiological rhythm patterns in cortico-basal ganglia loop, targeting pathological beta activity
- PD apathetic patients and targeting altered EEG alpha and theta oscillations

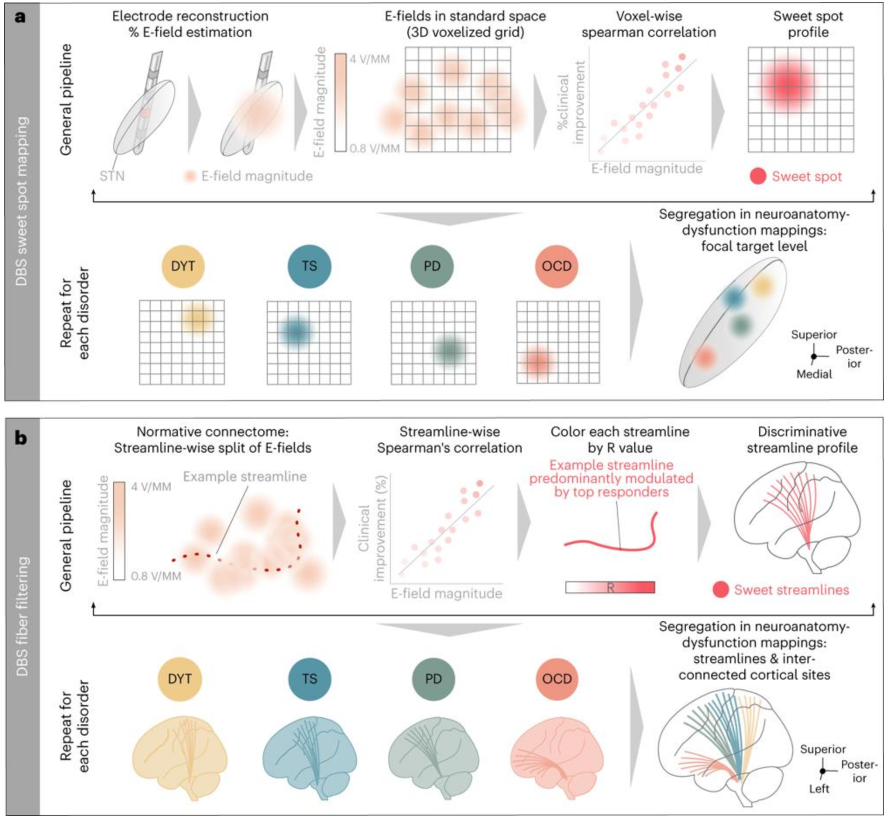
Lesion-Network Mapping and Brain Stimulation Therapy



Siddiqi & Fox 2023

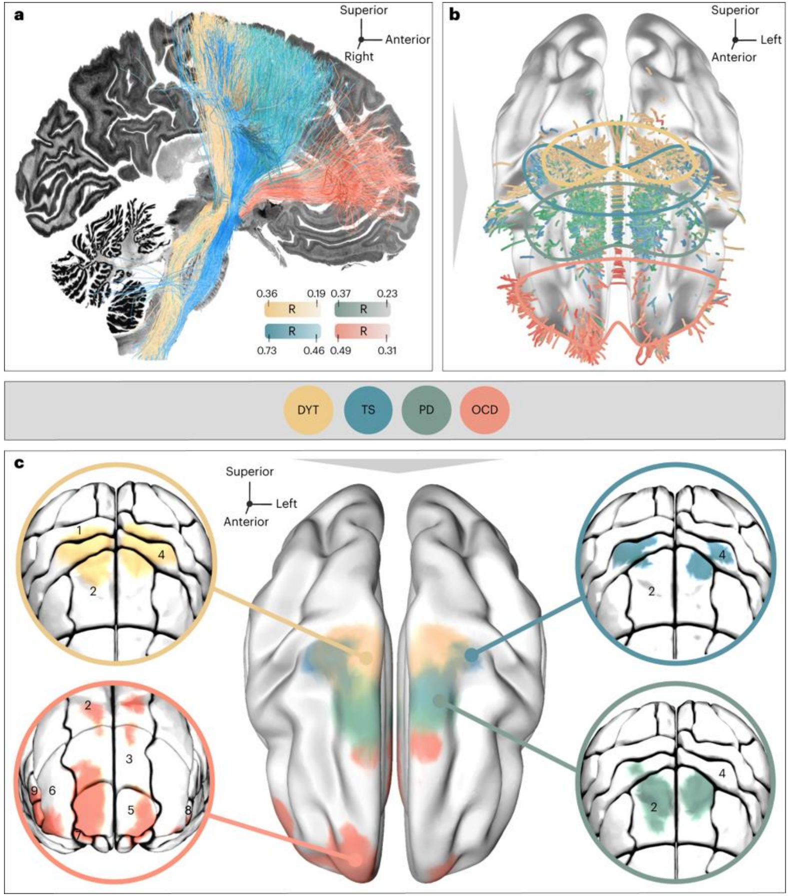
Lesion-Network Mapping and Brain Stimulation Therapy

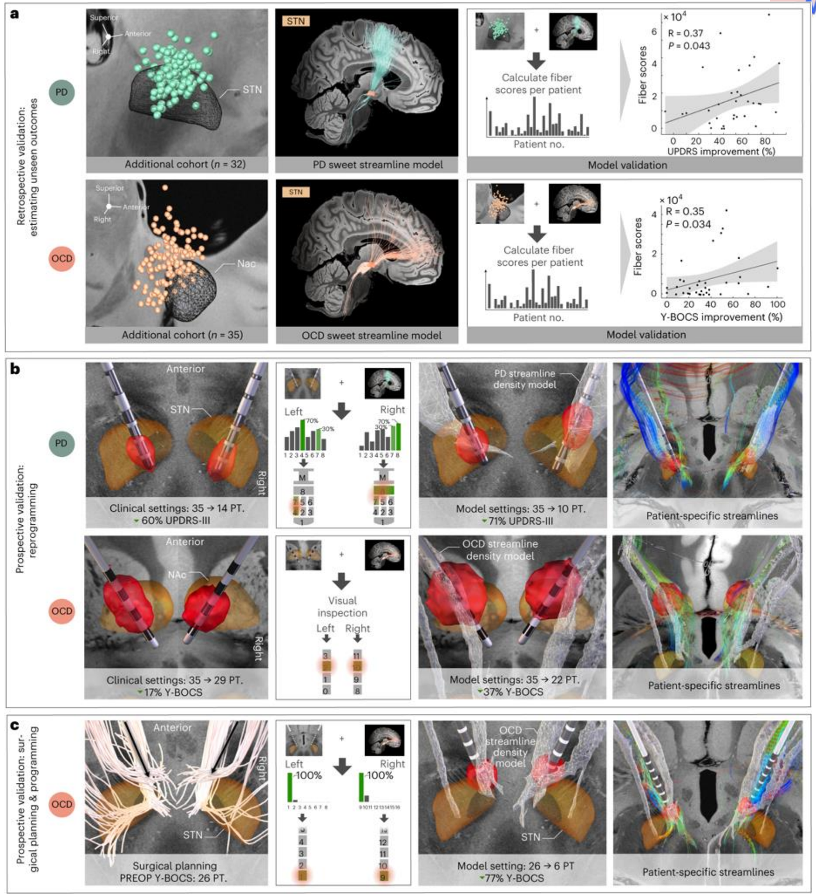




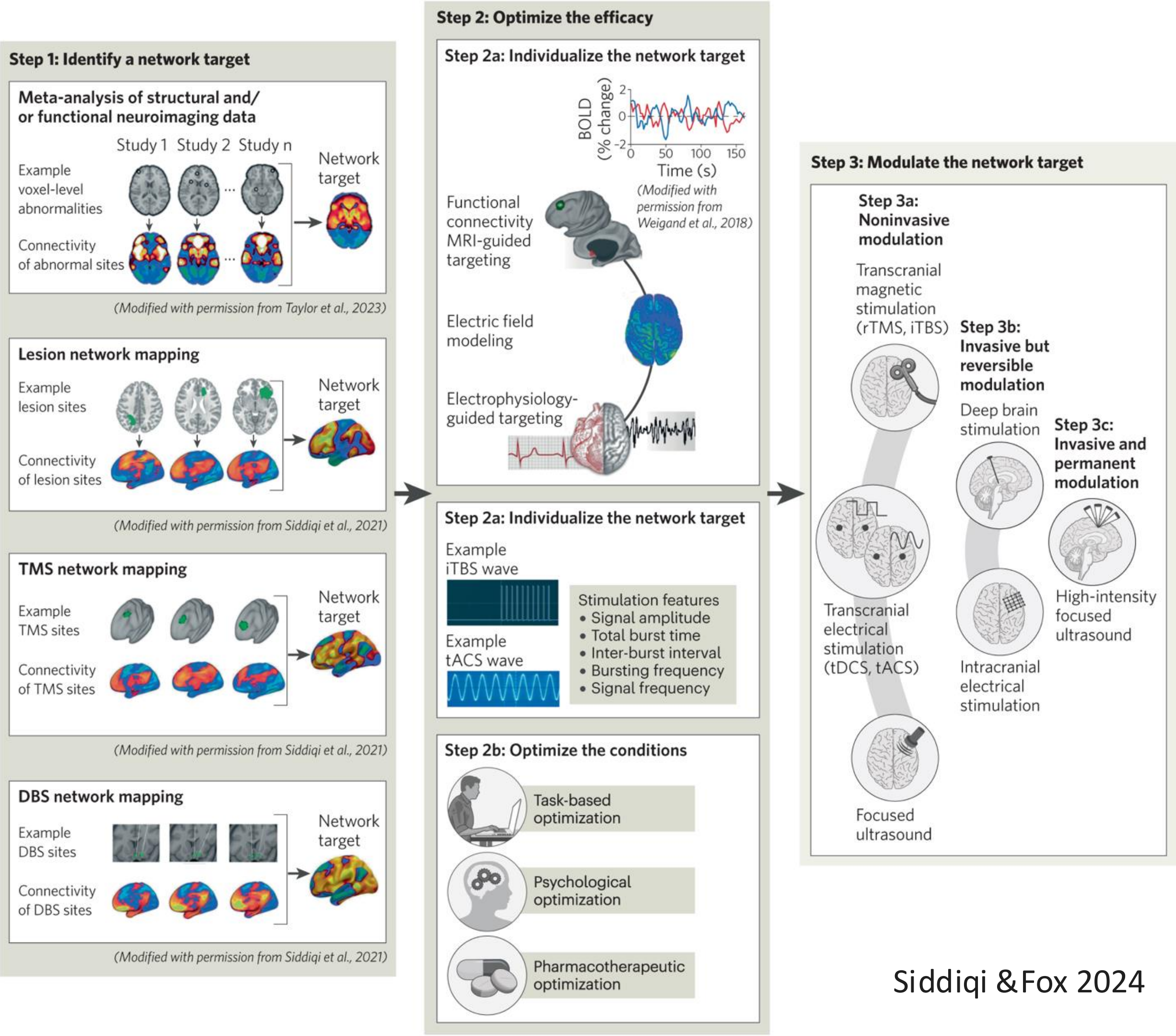
Hollunder et al. 2024

Lesion-Network Mapping and Brain Stimulation Therapy





Hollunder et al. 2024



Siddiqi & Fox 2024

Friedhelm C. Hummel

Recording of brain activity simultaneously

- focally and at the network level
- adds to mechanistic understanding
- safety monitoring
- state dependent close-loop applications

Challenges

- safety
- artefacts
- feasibility
- accessibility, clinical translation
- cost

Online interference with brain activity

- causal understanding
- network vs. local effects
- state dependent close-loop applications

Selection of method

- local vs network activity
- oscillatory vs. activation
- artefact profile