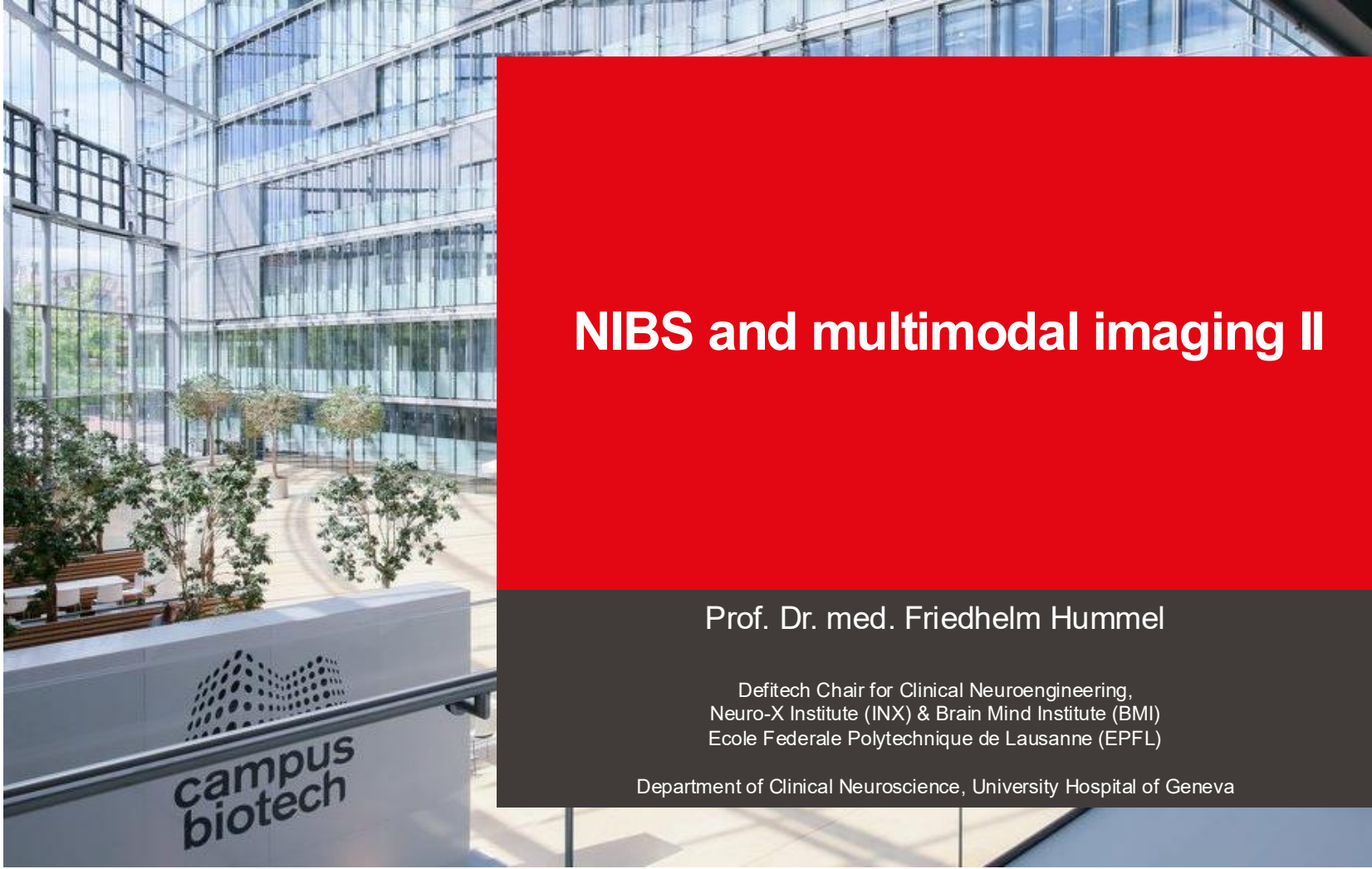
EPFL

Neuro X Institute



NIBS and multimodal imaging II

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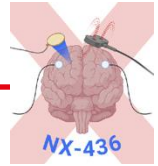
Nx-436
10/12/2025



Why combining neuroimaging with brain stimulation?

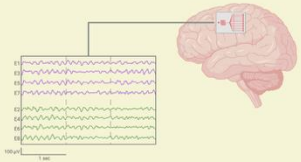
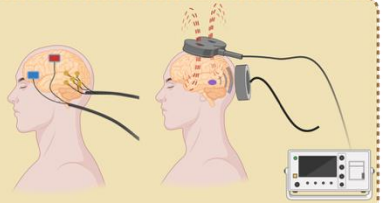
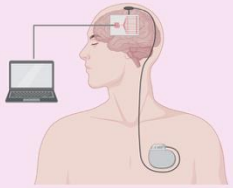
Why simultaneous NIBS and neuroimaging?

Challenges and Opportunities

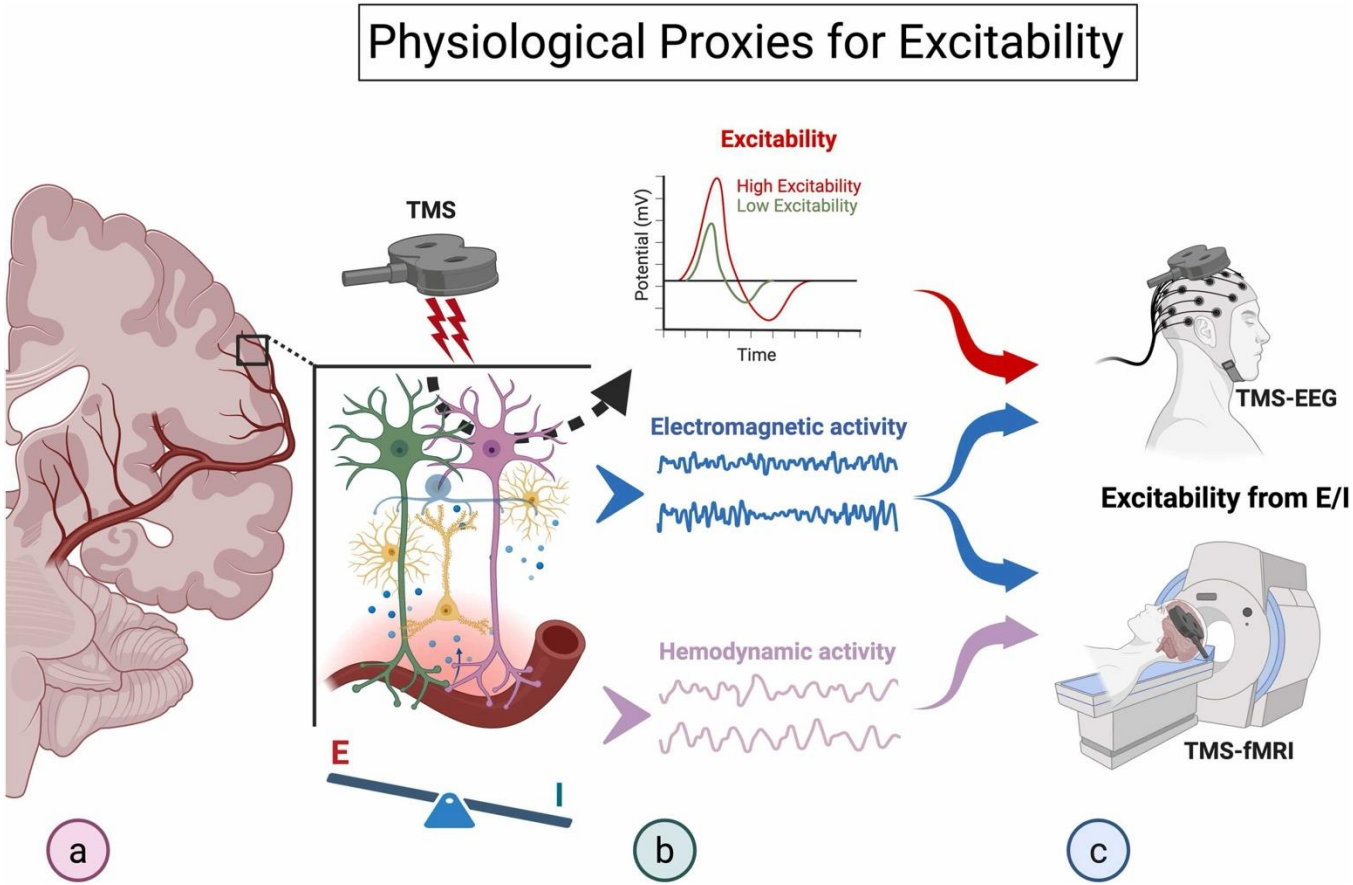
Safety

Examples of application

Introduction

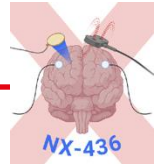
	INVASIVE	NON-INVASIVE
Neurosensing/ Neuro-monitoring "READ" Monitors electrical/BOLD activity in the central nervous system 	 eCoG, iEEG	 EEG, MEG, fMRI
Neuromodulation "WRITE" Targets and improves functions such as motor, attention, memory, decision-making, self-regulation either electrically, magnetically 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, ...

Introduction



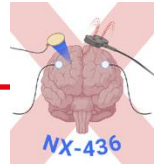
Schuler *et al*. 2025

Introduction



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

Introduction



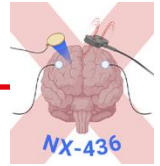
Recording of brain activity simultaneously
- target validation (especially relevant for nDBS)
- understanding of topographic specificity
- focally and at the network level
- adds to mechanistic understanding
- safety monitoring
- state dependent close-loop applications

Online interference with brain activity
- causal understanding
- network vs. local effects
- state dependent close-loop applications

Target selection for brain stimulation
- personalization

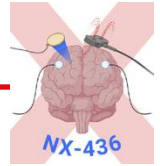
Parameter selection for brain stimulation
- personalization

Introduction



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

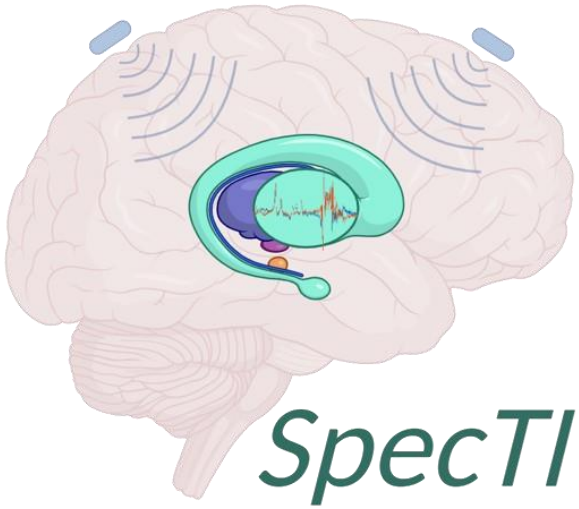
Introduction



Disadvantages and Challenges

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

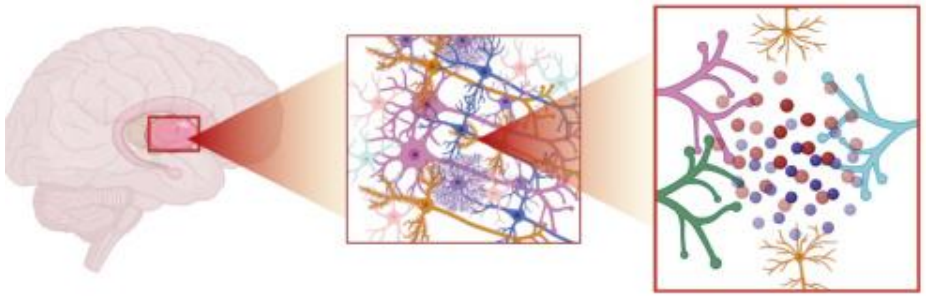
MR Spectroscopy (MRS)



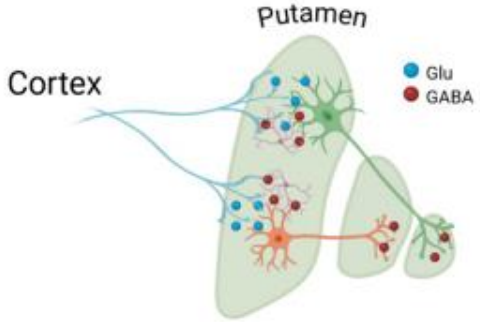
- Provides information about neurotransmitter levels, e.g. GABA, Glutamate
- Predefined volume, whole brain analyses not possible
- Temporal resolution low (minutes)
- Usually performed in resting state
- Task-related evaluation challenging due to low temporal resolution
- Accessibility limited
- Costly

For review Paparella *et al.* 2025 J Phys; Stagg 2014 Neuroimage

MR Spectroscopy (MRS)



- Measure the concentrations of neurotransmitters in a given region

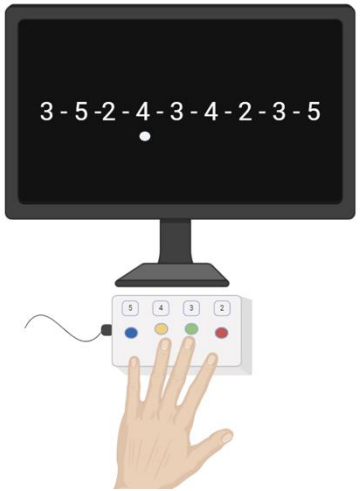


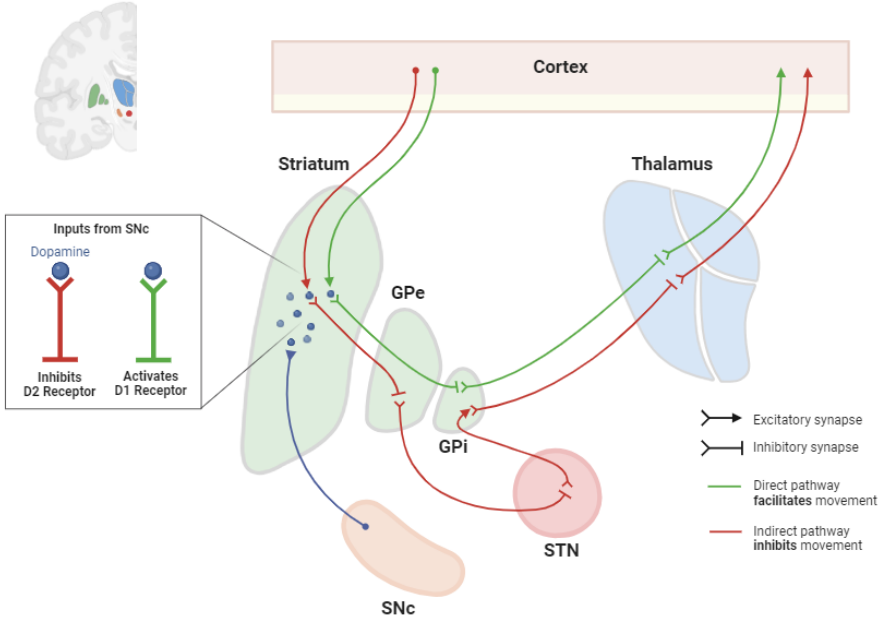
- Striatal circuits are largely GABAergic with cortical Glutamatergic inputs

How does striatal tTIS modulate these circuits to enhance motor learning?

MR Spectroscopy (MRS) - tTIS

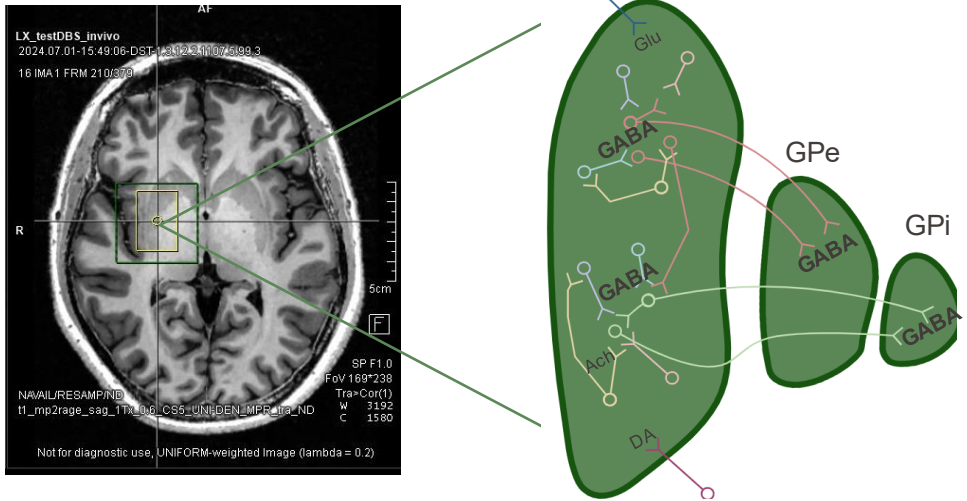
- How does striatal tTIS modulate neuromodulator levels in the putamen?
- How does this differ when performing a motor learning task?





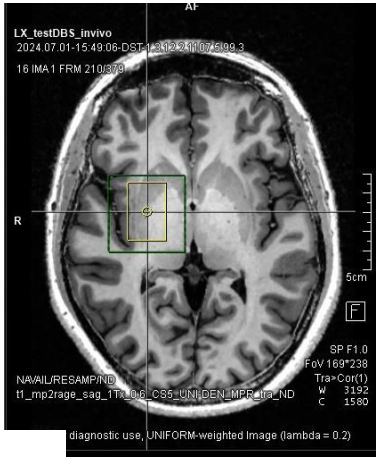
MR Spectroscopy (MRS) - tTIS

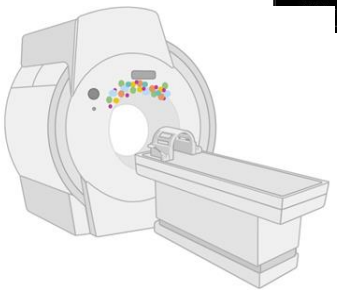
- Majority of neurons in Putamen are GABAergic
  - Medium spiny projection neurons
  - GABAergic Interneurons
  - Glutamate-ergic cortical inputs

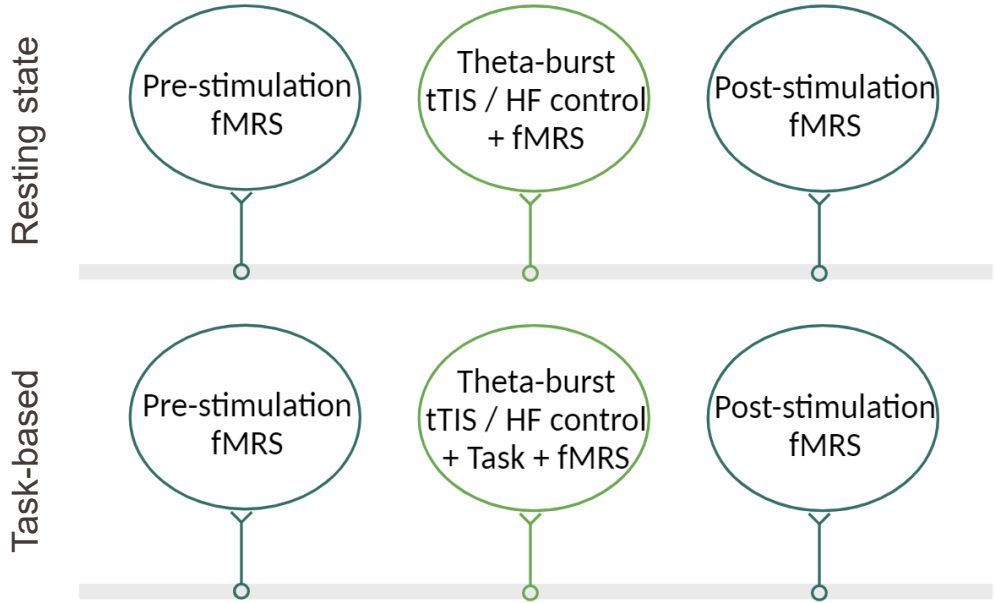


MR Spectroscopy (MRS) - tTIS

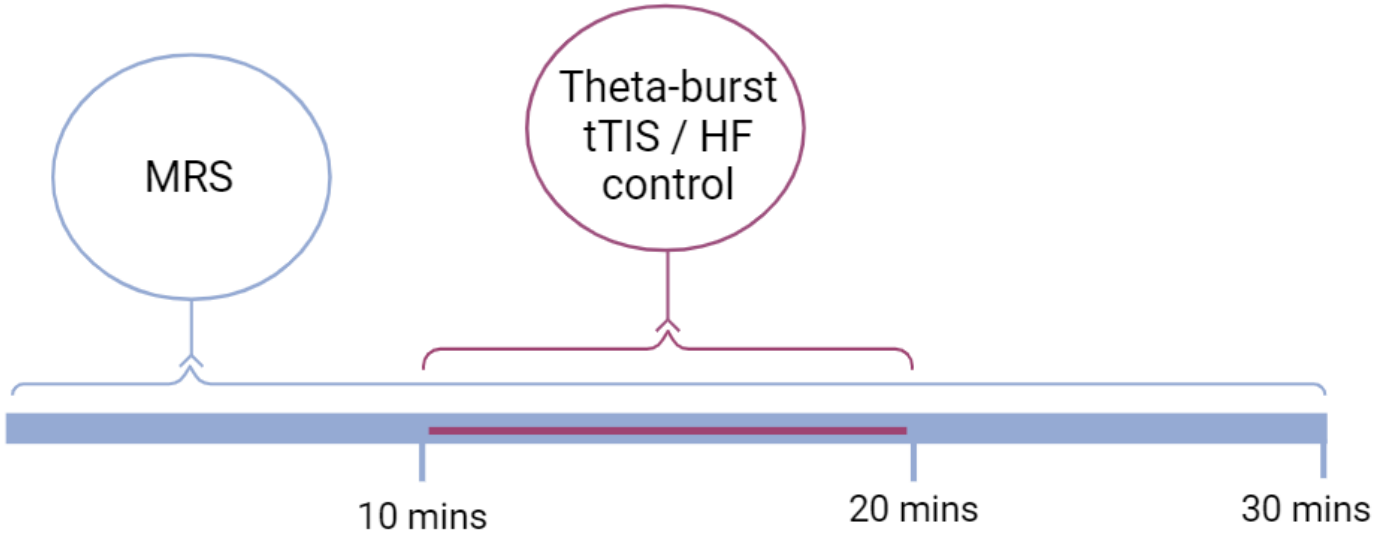
- Record functional MR spectroscopy of the Putamen at 7T

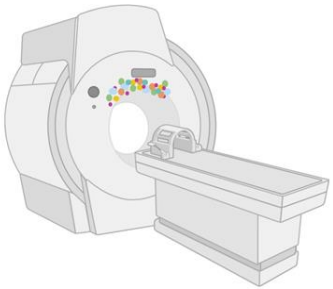






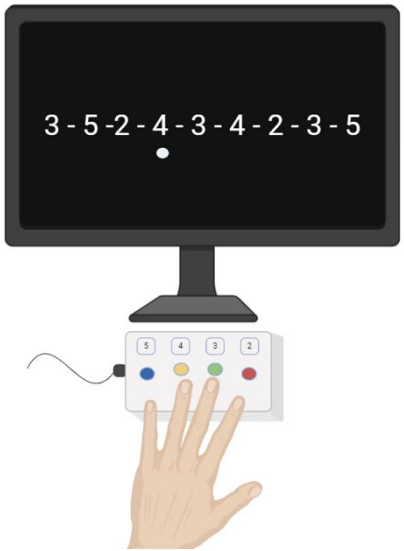
MR Spectroscopy (MRS) - tTIS

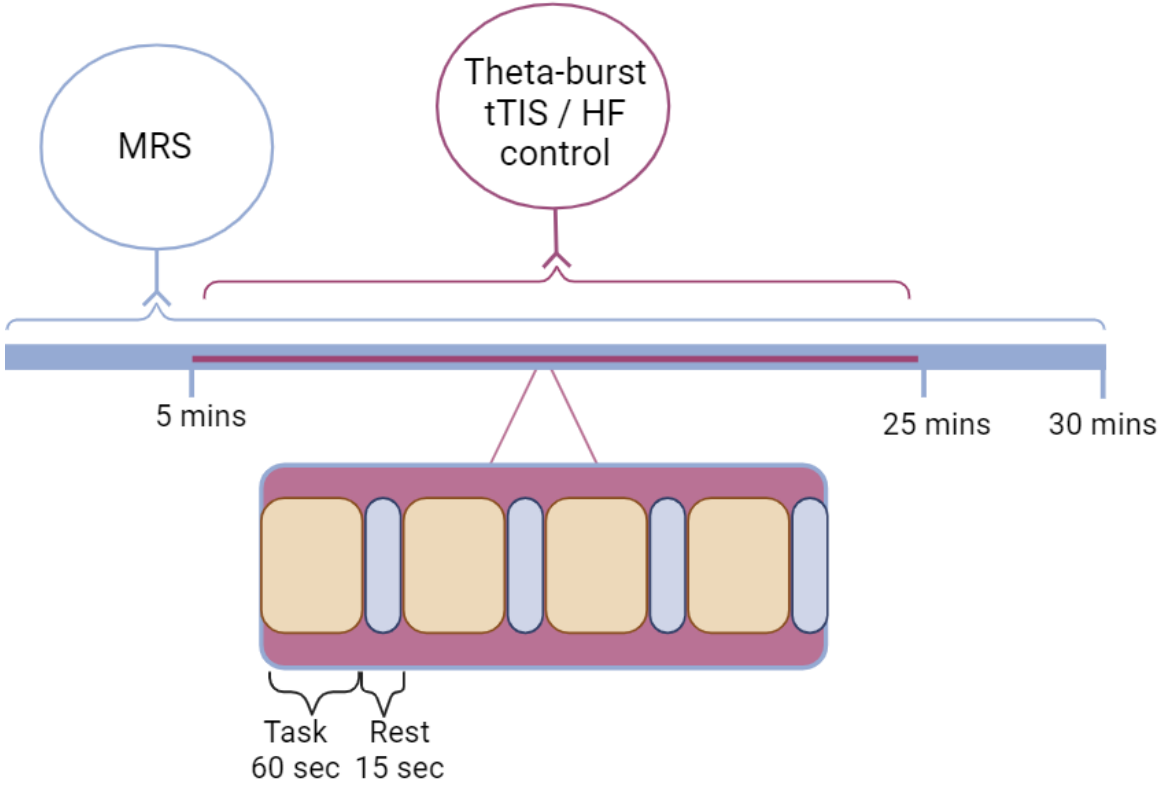




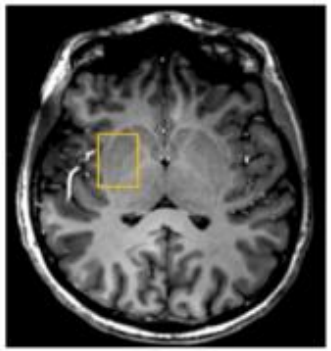
MR Spectroscopy (MRS) - tTIS

- Sequential finger tapping task to motor learning



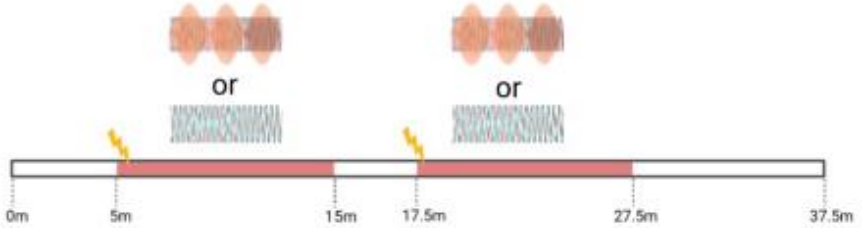


MR Spectroscopy (MRS) - tTIS



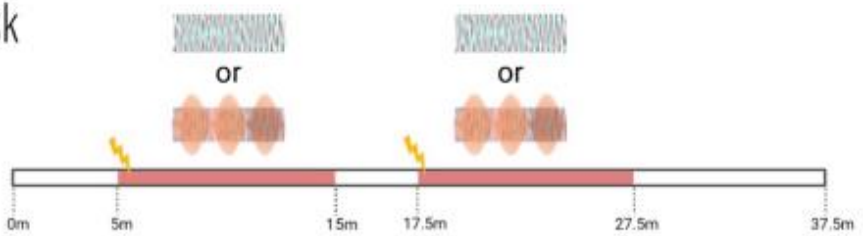
Resting state

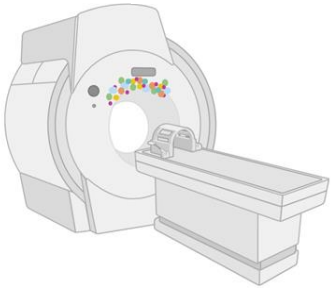
x2



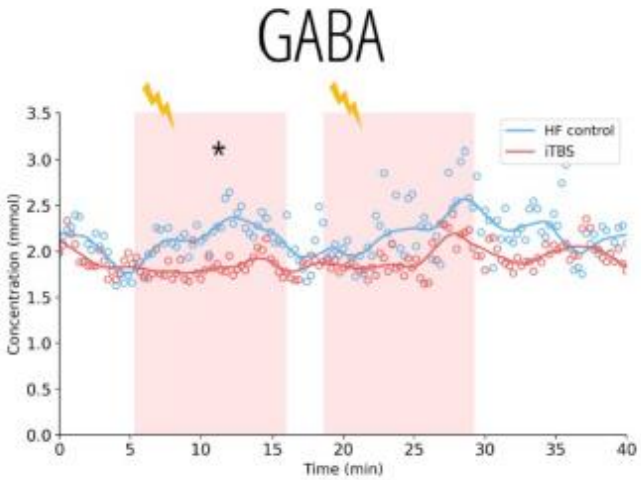
Motor learning task

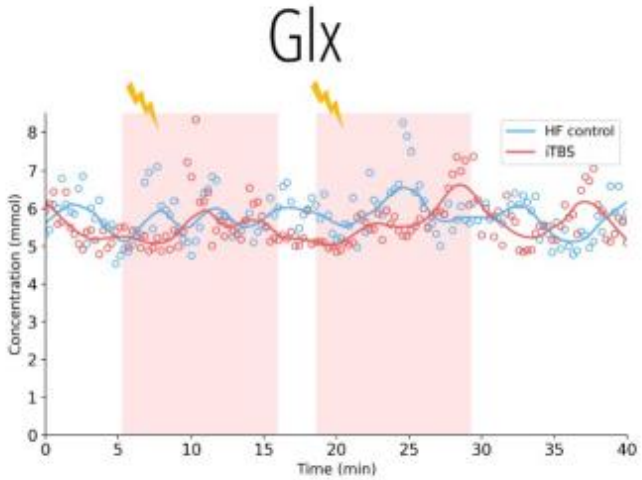
x2

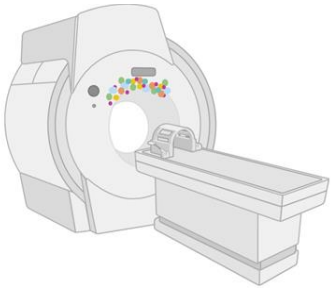




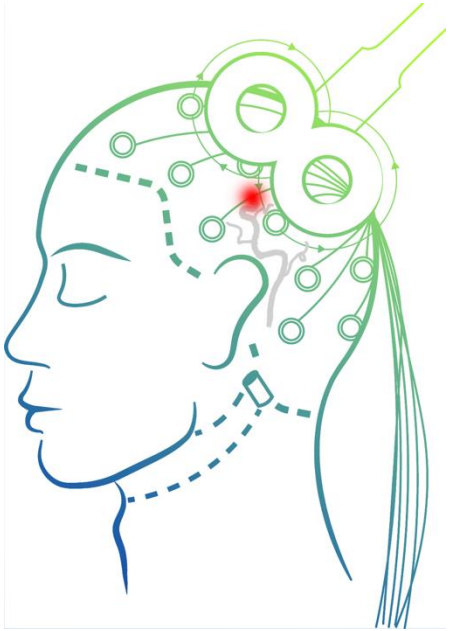
MR Spectroscopy (MRS) - tTIS

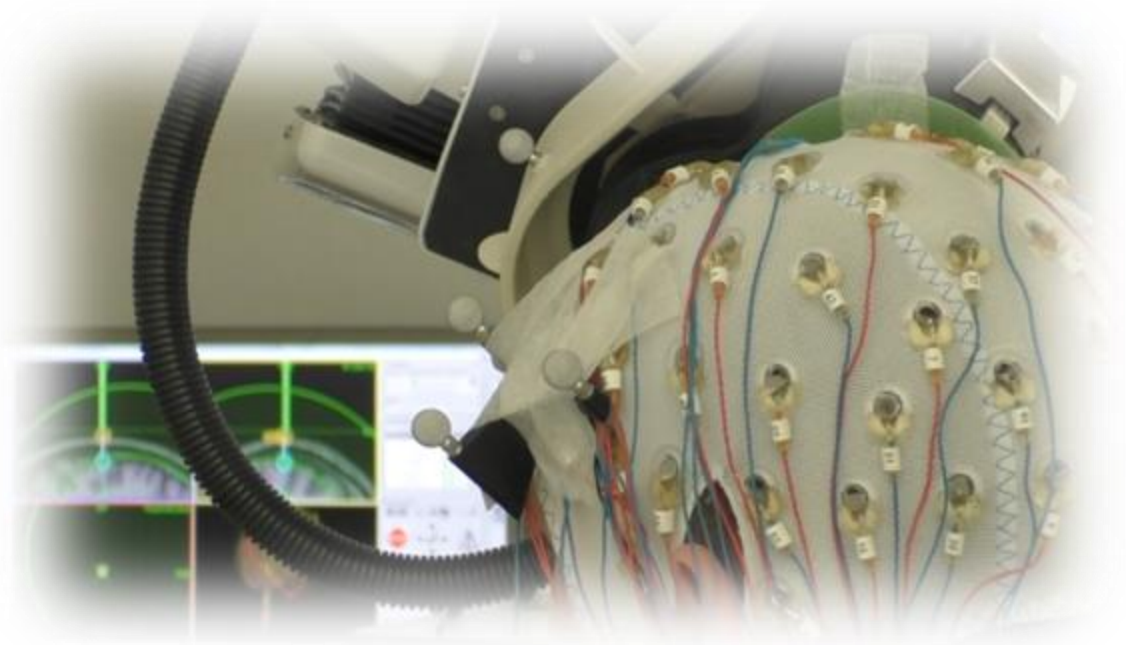






TMS-EEG





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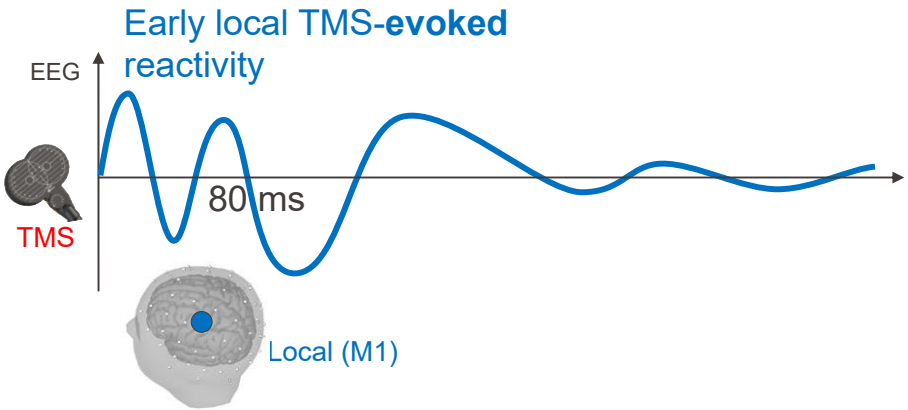
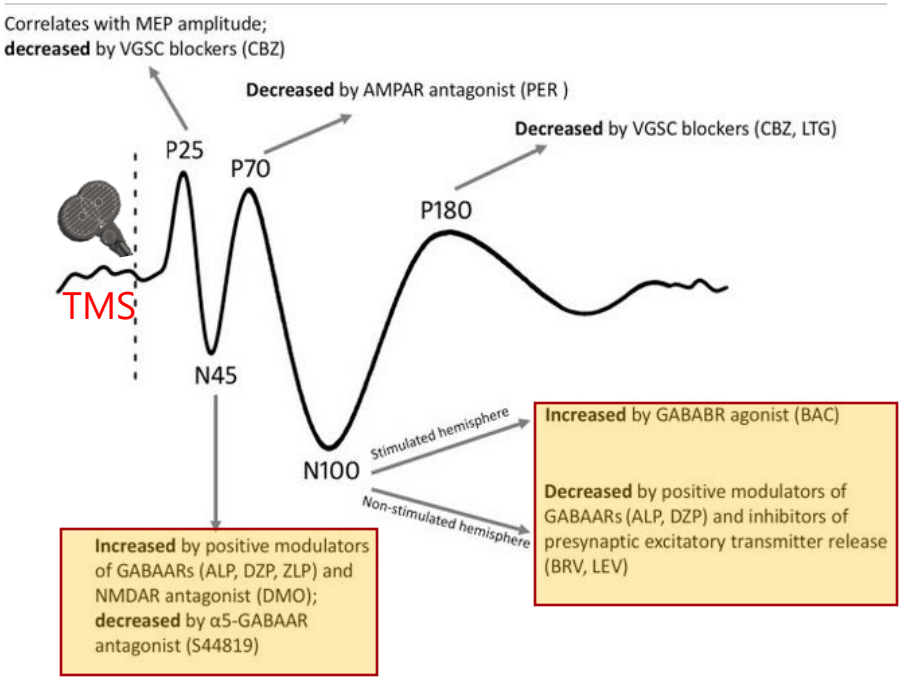
Review

Clinical utility and prospective of TMS–EEG

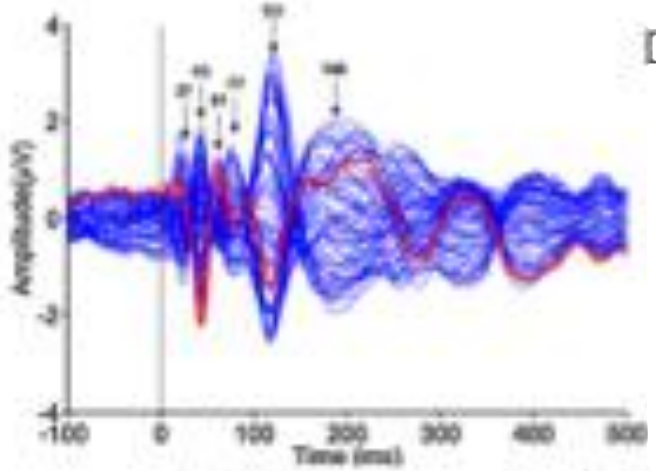
Sara Tremblay [a,b,*], Nigel C. Rogasch [c], Isabella Premoli [d], Daniel M. Blumberger [a], Silvia Casarotto [e], Robert Chen [f], Vincenzo Di Lazzaro [g], Faranak Farzan [h], Fabio Ferrarelli [i], Paul B. Fitzgerald [j,k], Jeanette Hui [a], Risto J. Ilmoniemi [l], Vasilios K. Kimiskidis [m], Dimitris 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]

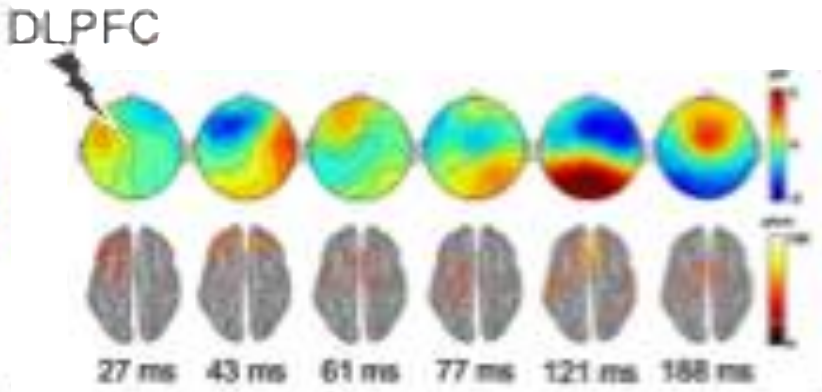
TMS-EEG


Early local TMS-evoked reactivity
EEG
80 ms
TMS
Local (M1)


Correlates with MEP amplitude;
decreased by VGSC blockers (CBZ)
Decreased by AMPAR antagonist (PER)
Decreased by VGSC blockers (CBZ, LTG)
P25
P70
P180
TMS
N45
N100
Stimulated hemisphere
Non-stimulated hemisphere
Increased by GABABR agonist (BAC)
Decreased by positive modulators of GABAARs (ALP, DZP) and inhibitors of presynaptic excitatory transmitter release (BRV, LEV)
Increased by positive modulators of GABAARs (ALP, DZP, ZLP) and NMDAR antagonist (DMO);
decreased by α5-GABAAR antagonist (S44819)

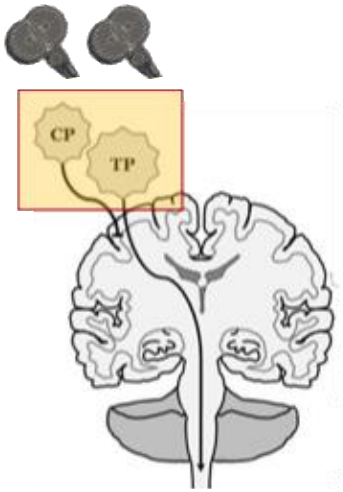
TMS-EEG



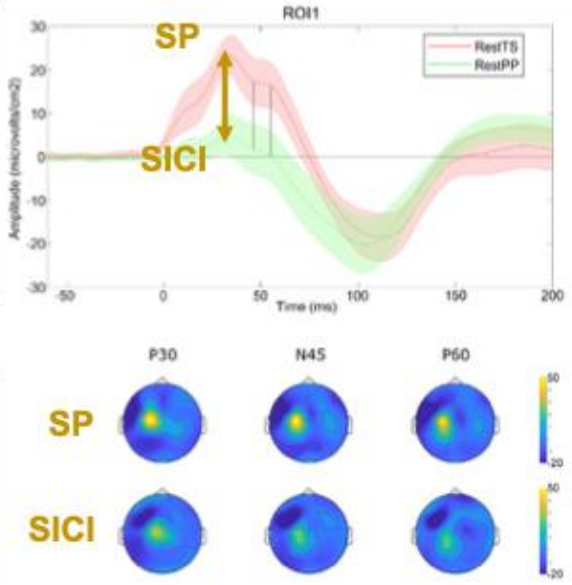


TEPs = **local** activity + remote **connectivity**

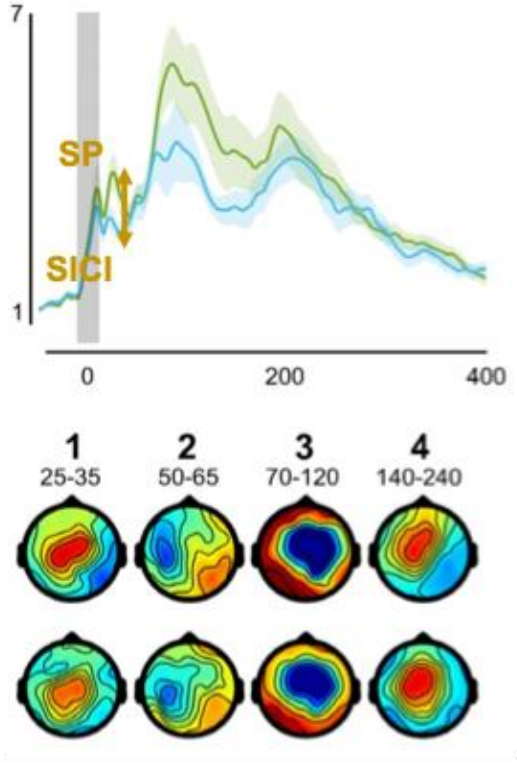
TMS-EEG



Short-Interval Cortical **inhibition (SICI)**



Leodori *et al.*, 2019



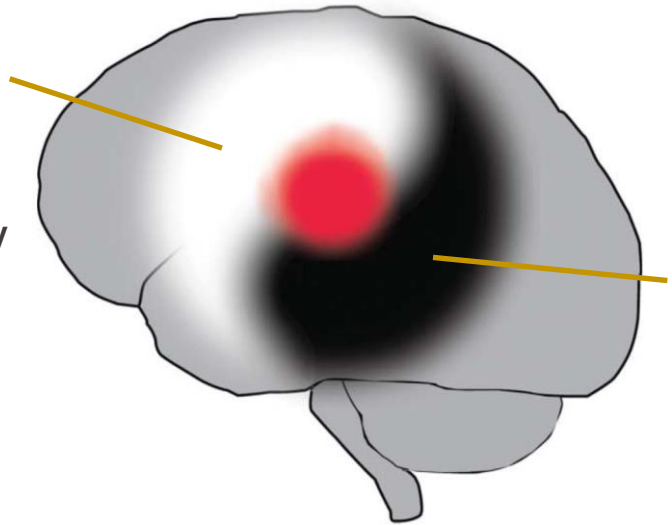
Raffin & Harquel *et al.*, 2020

TMS-EEG – Example of application Stroke

Animal Models

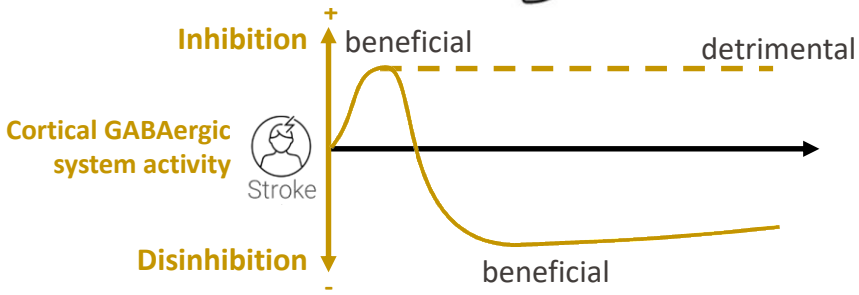
- Tonic Hyperinhibition
- Low excitability

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



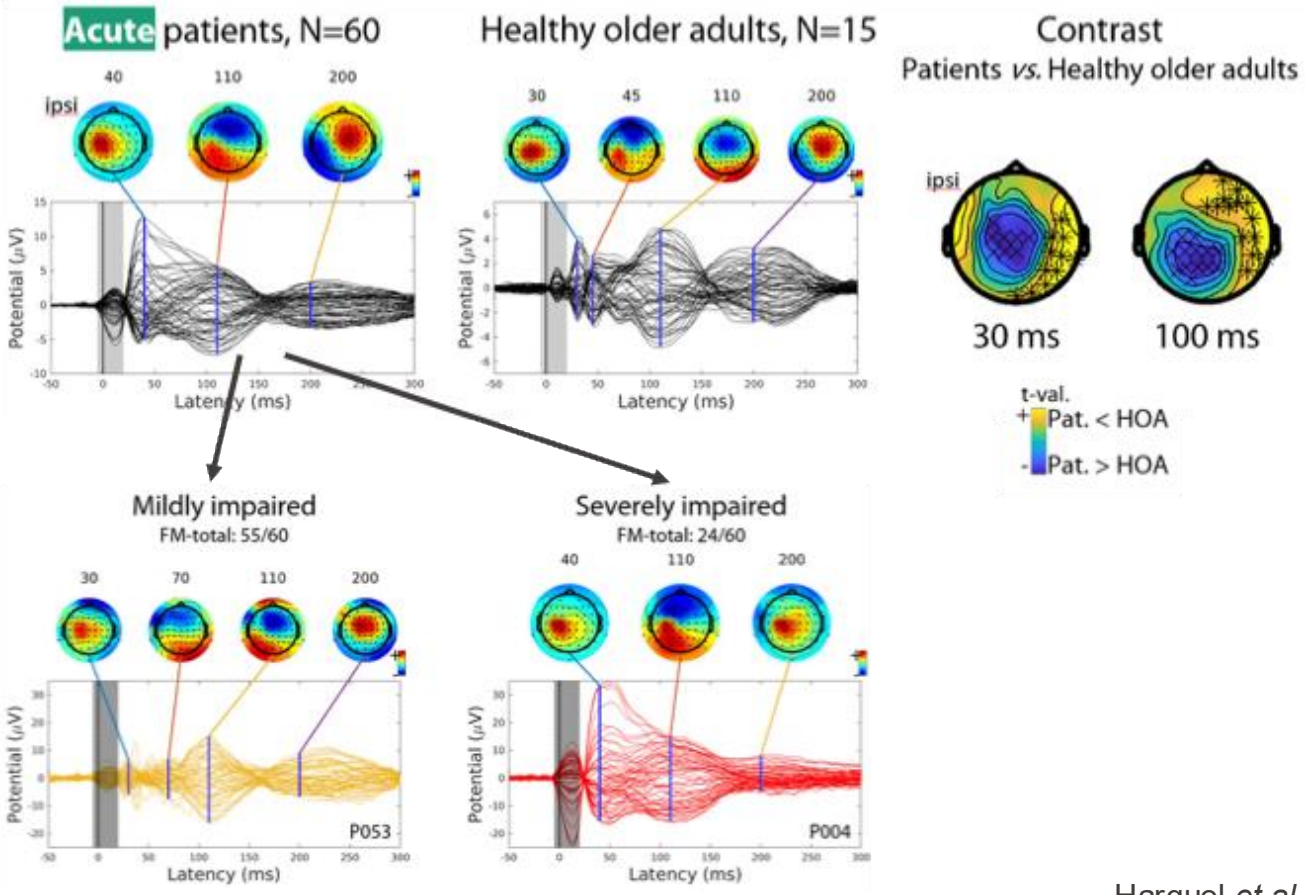
- Hyperexcitability
- Decrease of tonic inhibition

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



Carmichael, 2012

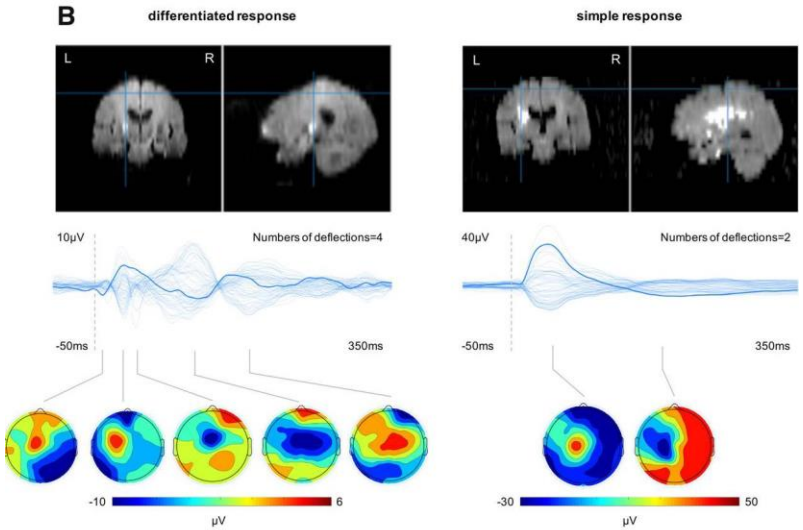
TMS-EEG – Example of application Stroke



Harquel *et al.* 2024 Stroke

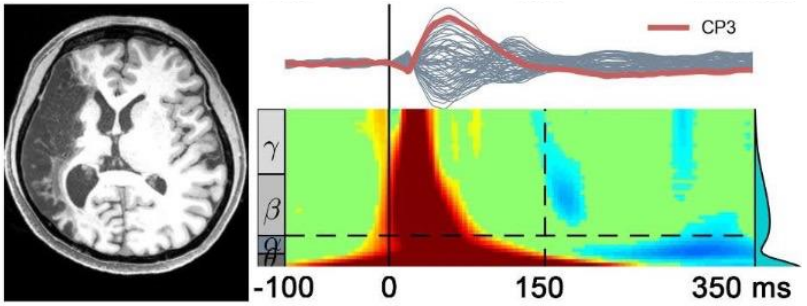
TMS-EEG – Example of application Stroke

Stroke Patients



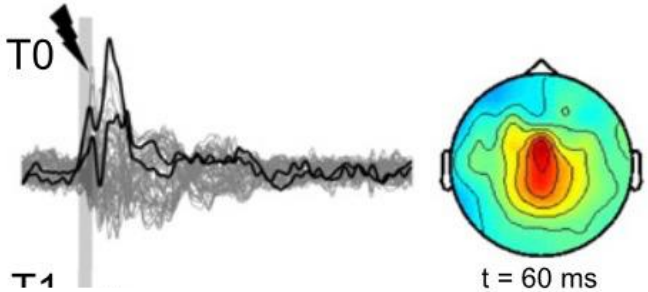
Tscherpel *et al.*, 2020

Acute stroke



Chronic stroke

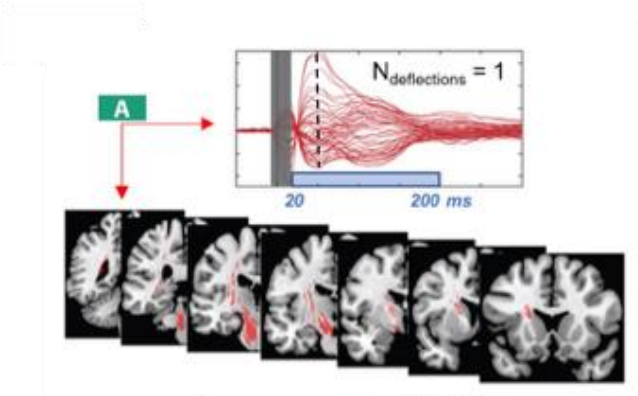
Bai *et al.*, 2023



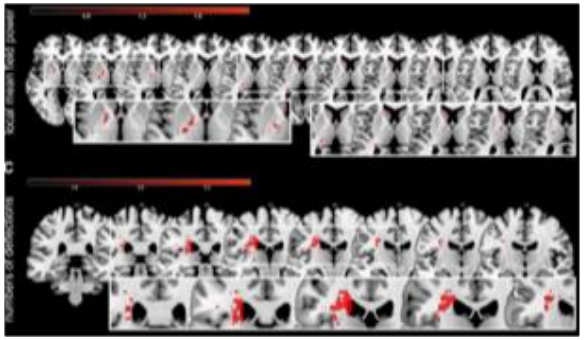
Chronic stroke

Bigoni *et al.*, 2023

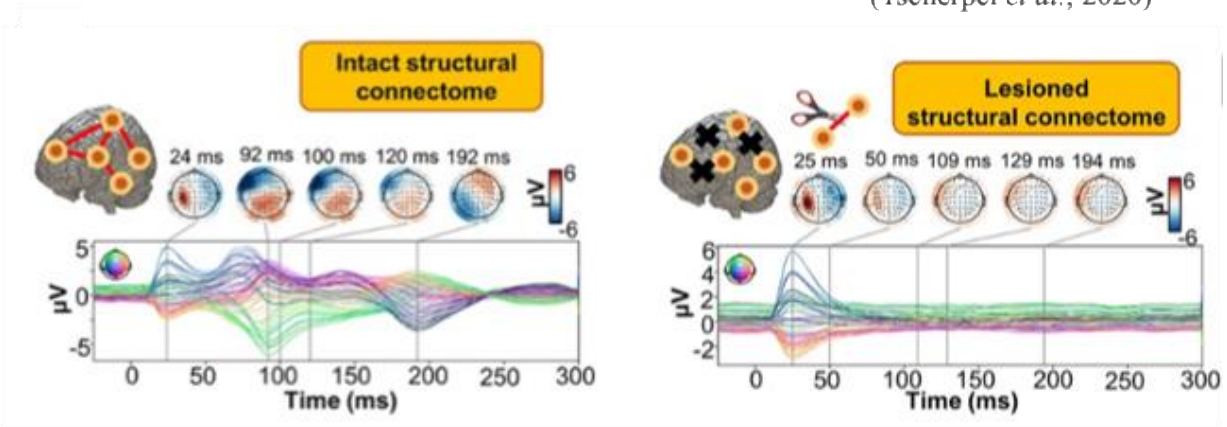
TMS-EEG – Example of application Stroke



Internal capsule (TiMeS)

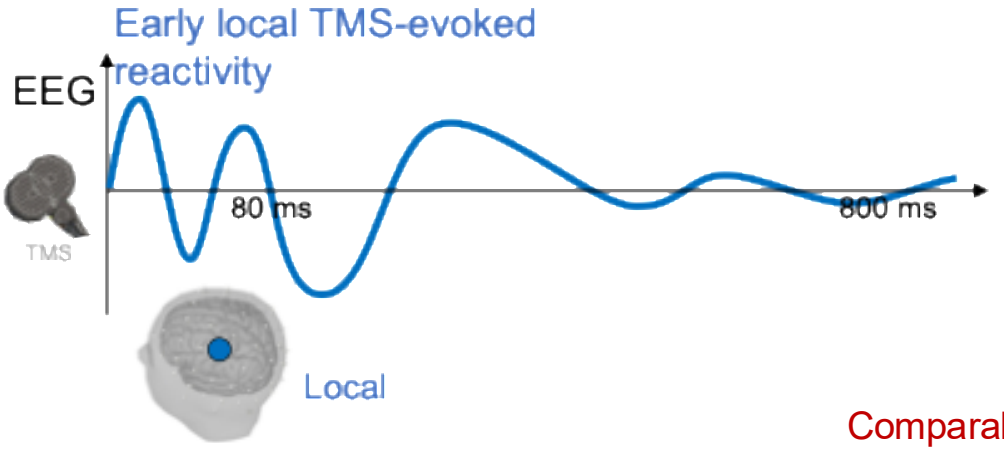


Internal capsule, caudate nucleus
(Tscherpel *et al.*, 2020)

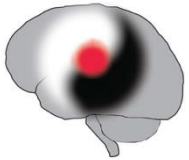


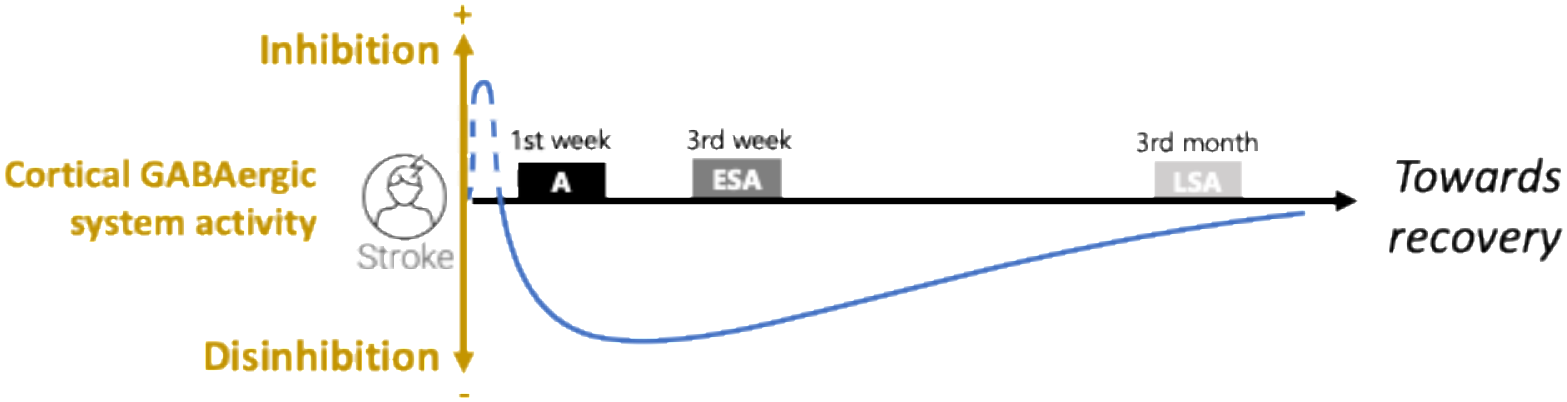
Computational modelling (Momi *et al.*, 2023)

TMS-EEG – Example of application Stroke

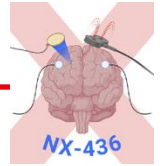


Comparable to animal work



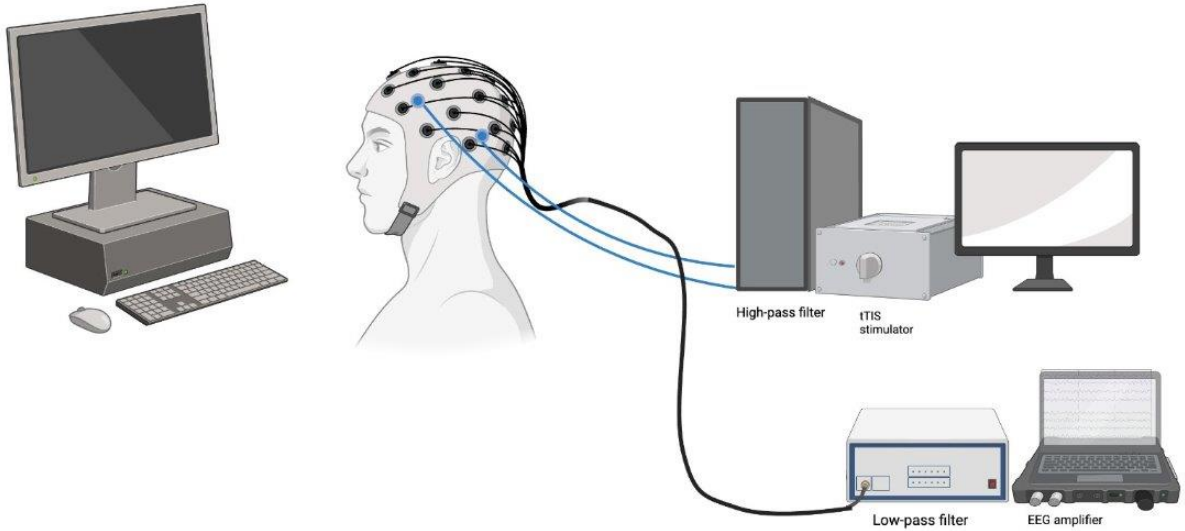


TMS-EEG

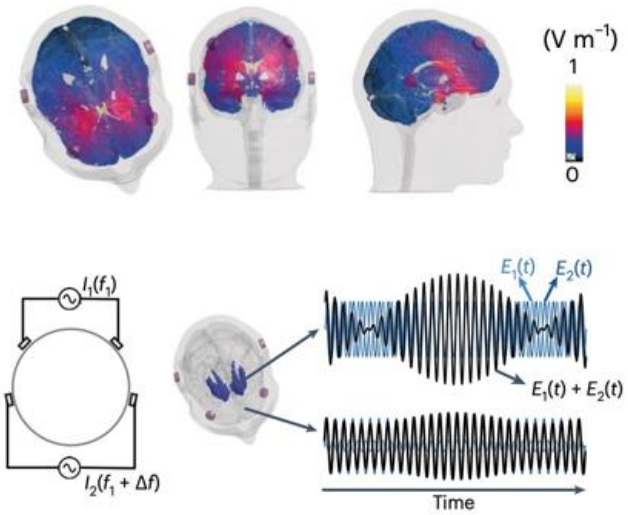


- whole brain activity
- with excellent temporal resolution
- sufficient topographic resolution
- provides information about the activated network by the TMS pulse
- activation can be well standardized and therefore comparable
- provides information about underlying transmitter systems
- well accessible and clinically translatable
- state dependent close-loop applications

tTIS - EEG concurrent recording



tTIS - EEG concurrent recording



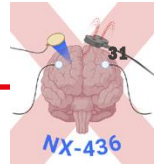
Electric field modeling with striatal montage
Maximilian J. Wessel, Elena Beanato et al. 2023

Temporal Interference (TI) Stimulation uses two electric fields at frequencies f1 and f2 to stimulate the brain at the difference frequency (|f1-f2|=Δf), 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+ Δf in a timed, pulsed manner (i.e. in bursts).

Each electric field is generated by a constant current sources

tTIS - EEG concurrent recording



What are the current hypotheses 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)

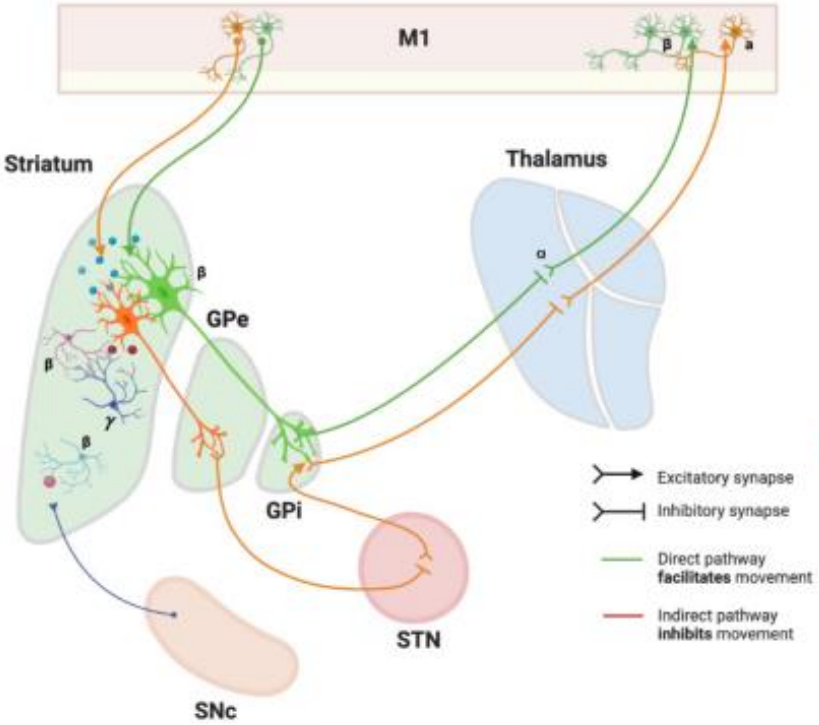
Neuron is mixing exogenous and endogenous subthreshold membrane potential oscillations to create new oscillatory frequencies (Kinetics of voltage-gated sodium channels are non-linear)

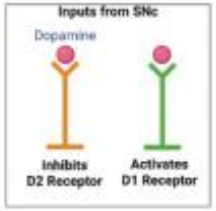
(Luff et al. 2024)

tTIS-EEG concurrent recording will allow to add to the mechanistic understanding

tTIS - EEG concurrent recording

Neuronal networks of cortico-striatal interactions



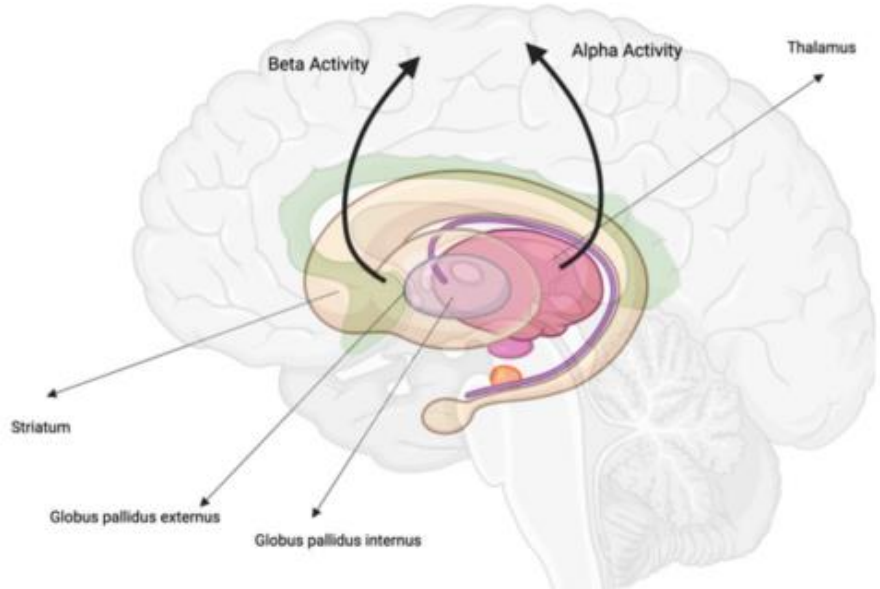


Beta and mu activity modulation in M1

(Min Yu et al. 2025, Dyck et al. 2024)

tTIS - EEG concurrent recording

Electrophysiological correlates of Motor Learning



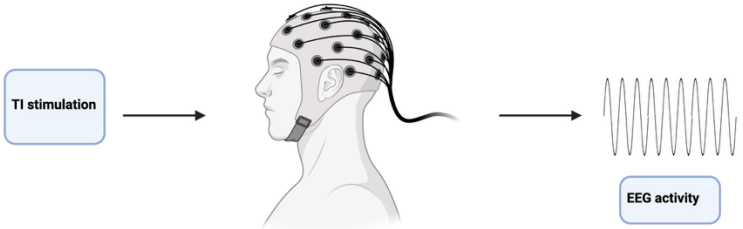
Sensorimotor oscillatory activity:

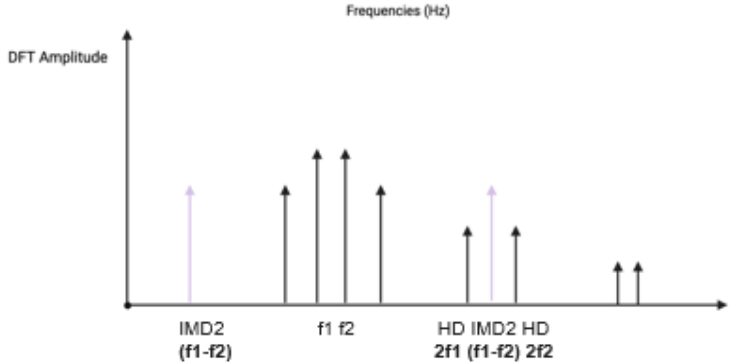
- Mu oscillations
  - **Thalamic nuclei** -> cortical cells
- Beta oscillations
  - **Striatal nuclei** -> cortical cells

- Modulation by motor activity during learning:
  Desynchronisation during movement ↓

(Min Yu et al. 2025, Dyck et al. 2024, Hummel et al. 2006, Gerloff et al. 1998, Hikosaka et al. 2002, Doyon et al. 2003, Neuper et al. 2005, Pfurtscheller et al. 2006)

tTIS - EEG concurrent recording





Concurrent TI-EEG recording:

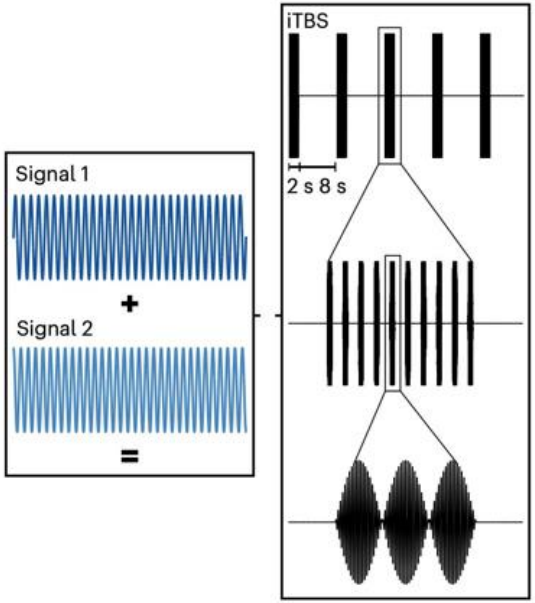
Advantages
Continuous EEG recording during and after tTIS:

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

Technical challenges

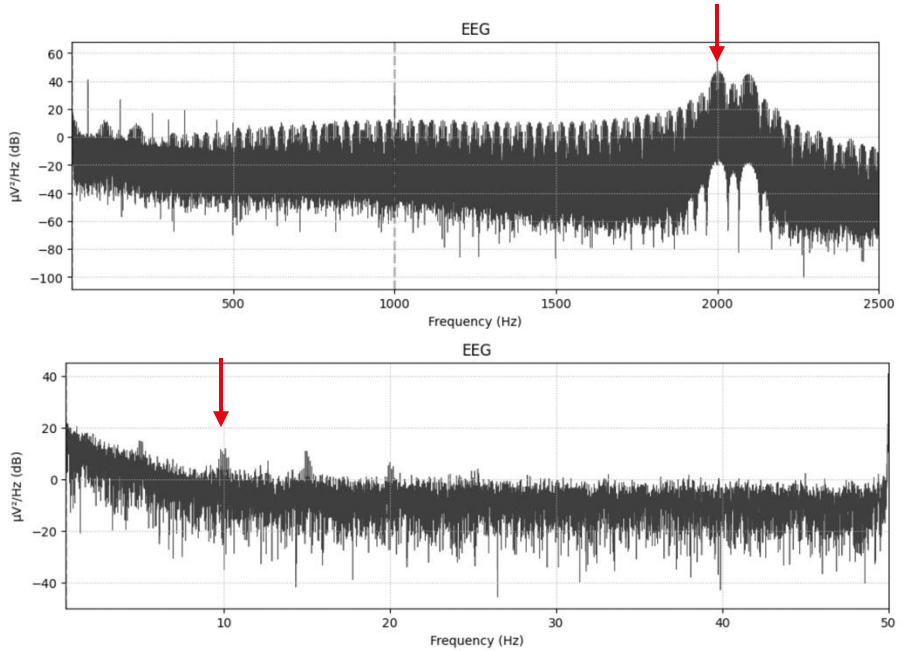
tTIS creates voltage potential that is above the limits of commercially available EEG amplifiers: **non-linear system**

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



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

Example of stimulation artefacts



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:

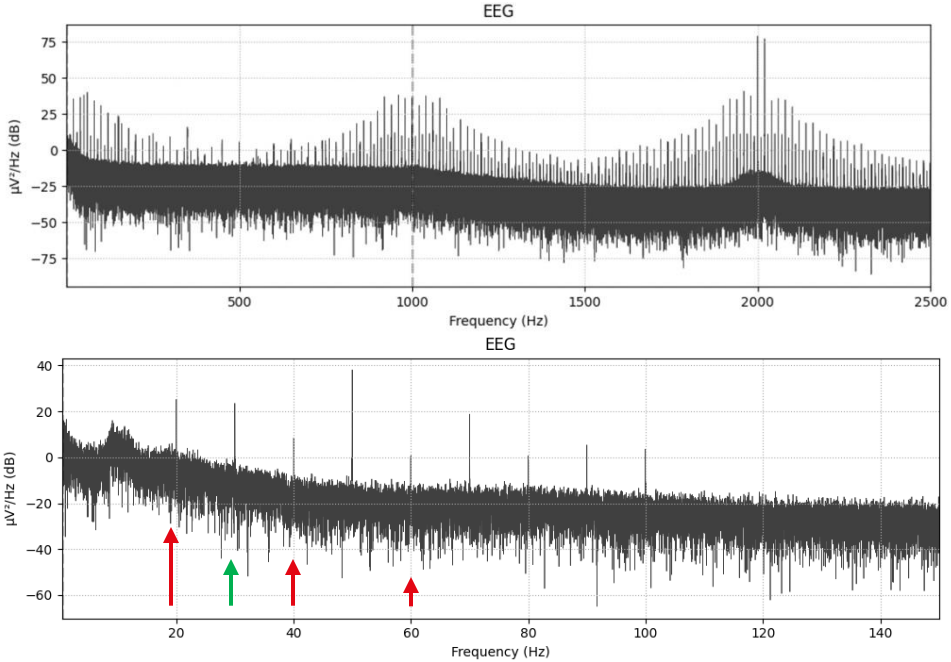
$$f(0) + \frac{f'(0)}{1!}x + \frac{f''(0)}{2!}x^2 + \frac{f'''(0)}{3!}x^3 + \cdots = \sum_{n=0}^{\infty} \frac{f^{(n)}(0)}{n!}x^n$$

Linear

Non-Linear

tTIS - EEG concurrent recording, Hardware filter solution

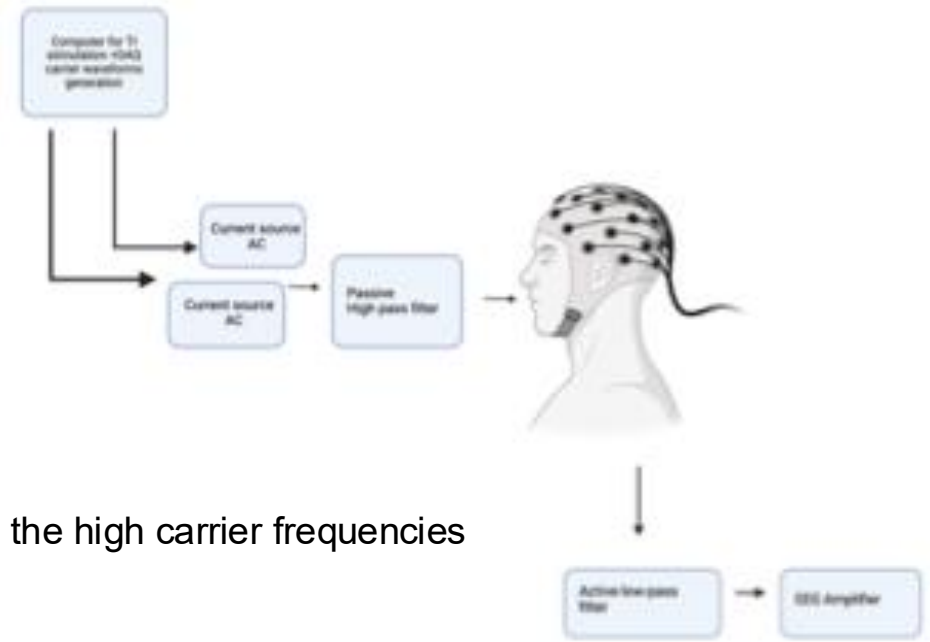
Example of stimulation artefacts with continuous TI stimulation, beat frequency at 20Hz



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

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)

tTIS - EEG concurrent recording, Hardware filter solution



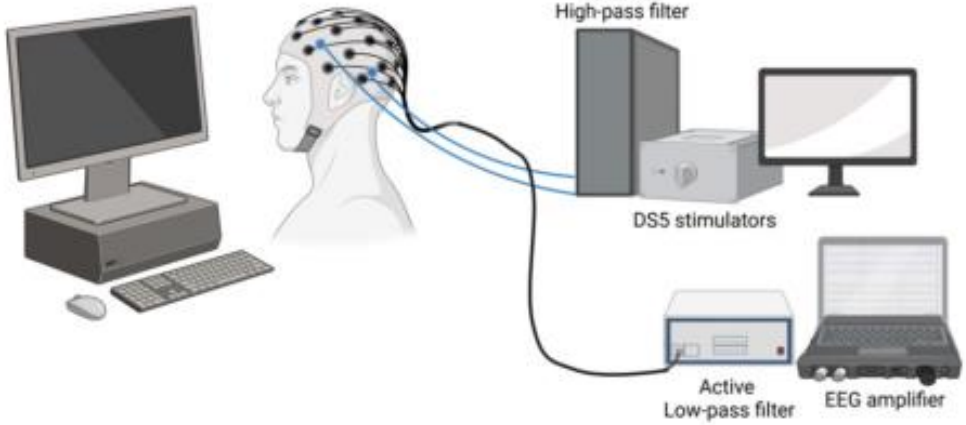
TI-EEG set up configuration:

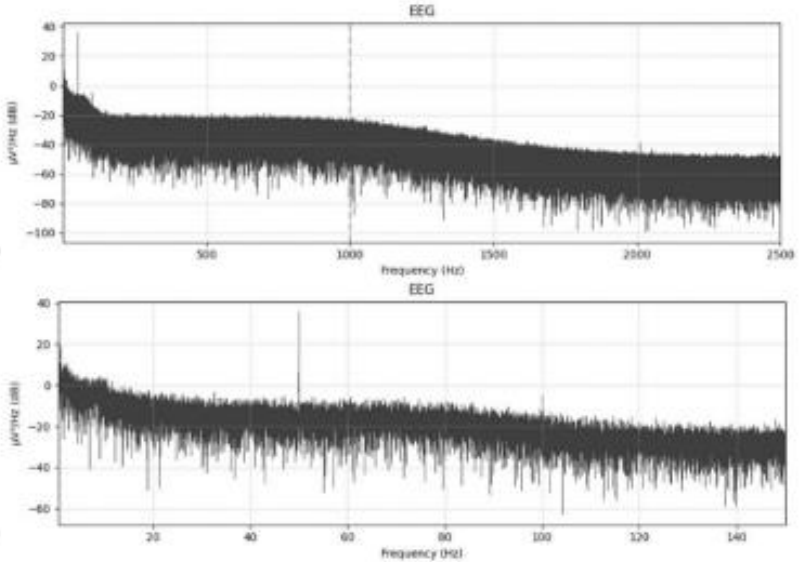
Passive high-pass filter: allows only the high carrier frequencies to pass, after the TI stimulators

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

Concurrent tTIS-EEG: Online Artefact-free EEG recording

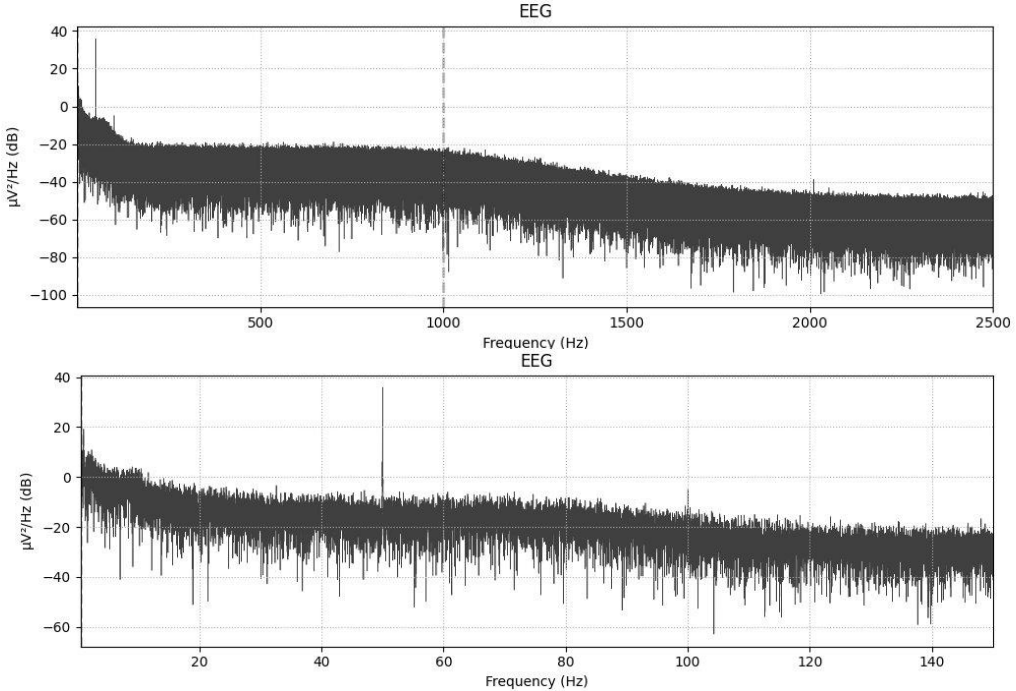




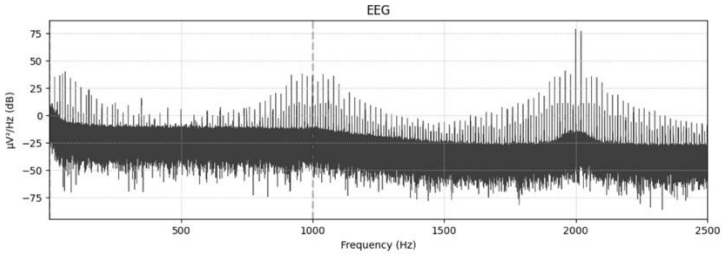
tTIS - EEG concurrent recording, Hardware filter solution

Hardware filters, tTIS 2kHz, Beat frequency 20Hz

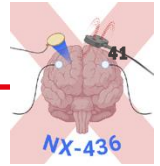
EEG recording with hardware filters, no artefacts for all the EEG channels



Without hardware filters:



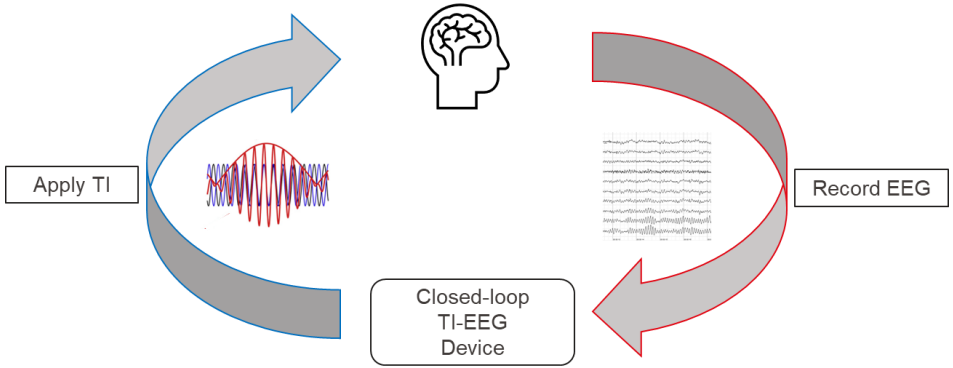
tTIS - EEG concurrent recording

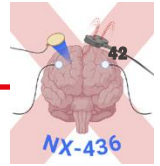


Applications with tTIS-EEG recording and possible technological developments:

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 tTIS and EEG cortical output:

Alzheimer's disease (AD):

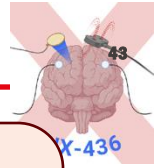
- Establish physiological rhythm patterns in DMN and FPN
- Cortical biomarkers of response to TI stimulation

Striatum tTIS 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

Take Home Messages



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

Target selection, target validation

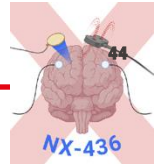
- personalization
- validation of approach

Challenges

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

Selection of method

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



Questions