EPFL

Neuro X Institute

Transcranial magnetic stimulation (TMS) II - (neuromodulation)- (Nx-436)

Prof. Dr. med. Friedhelm Hummel

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

Department of Clinical Neuroscience, University Hospital of Geneva

Nx-436
20/10/2025

Overview

Three main areas of application for TMS:

I. Electrophysiological evaluation (Heise et al. 2010, 2014 Hummel et al. 2009, Liuzzi et al. 2010, 2014, for review Siebner et al. 2003)

II. Virtual lesion approaches (Lotze et al. 2006, Renzi et al. 2013, for review Siebner et al. 2003, Hummel&Cohen 2005, Hallett 2010)

III. Neuromodulation (Nitsche et al. 2000, Huang et al. 2004, Hummel et al. 2005, for review Hummel & Cohen 2006, Nitsche et al. 2008, Dayan et al. 2013, Rektorova et al. 2025; Koch et al. 2024)

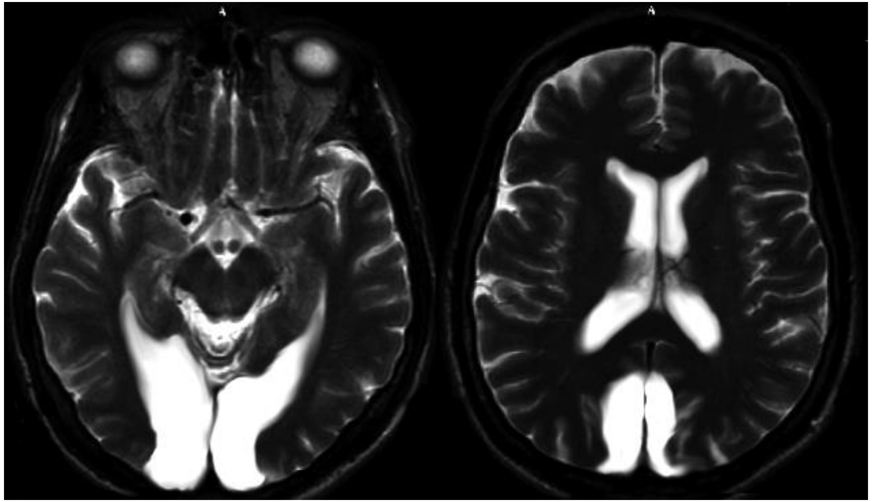
Virtual Lesioning

By deactivating/virtual lesioning of parts of the brain, and testing the behavioral /cognitive subsequent deficits, it is possible to gain causal insights into the functional role of the underlying cortex for behavior.

General concept

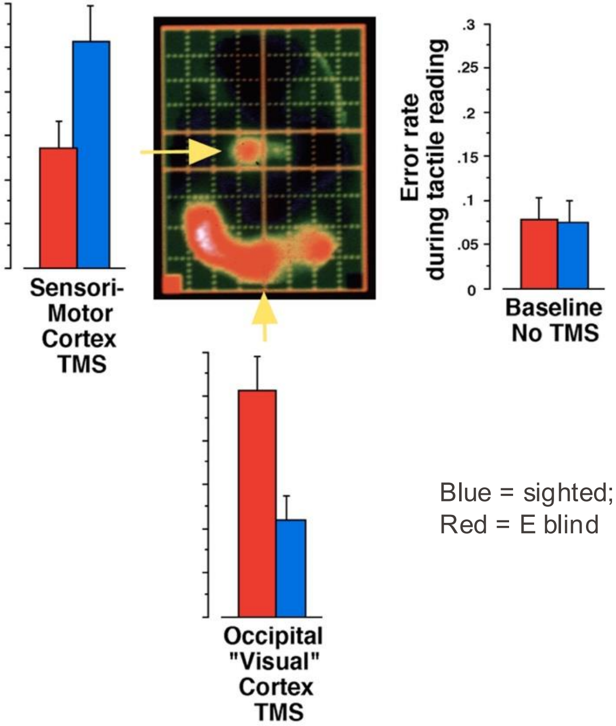
Virtual Lesions – example cross-modal plasticity

Real lesion



Reported case of blind woman who lost ability to read braille following bilateral occipital lesions (Hamilton et al., 2000)

TMS lesion



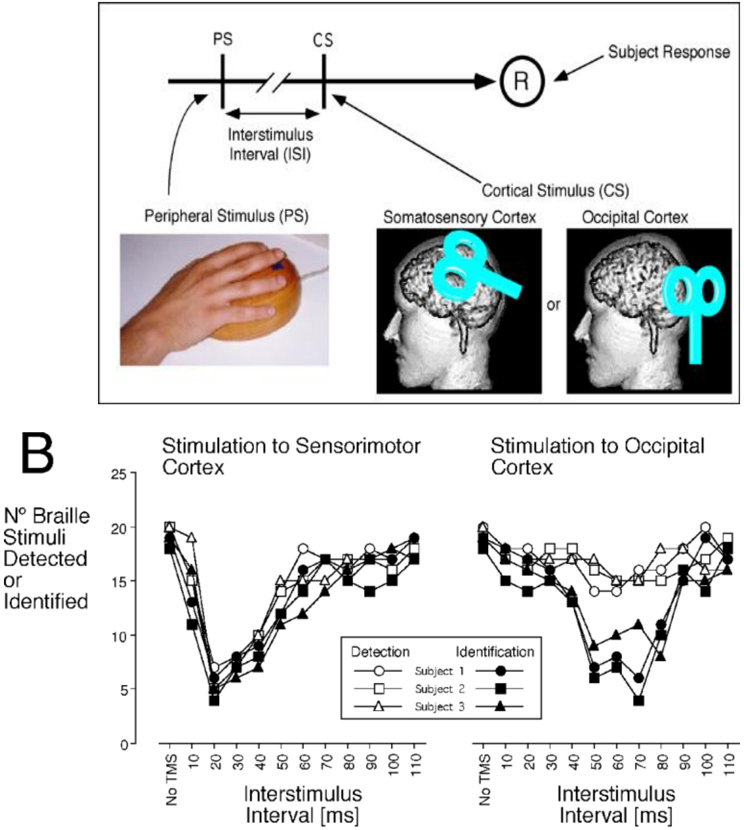
Blue = sighted;
Red = E blind

Occipital TMS disrupts braille reading in early blind, but not control subjects (Cohen et al., 1997).

Virtual Lesions

"Chronometry": timing the contribution of focal brain activity to behavior

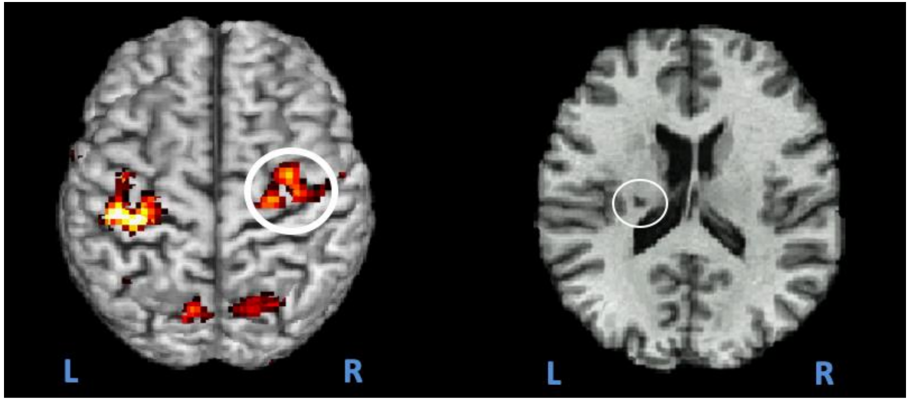
Role of "visual" cortex in tactile information processing in early blind subjects

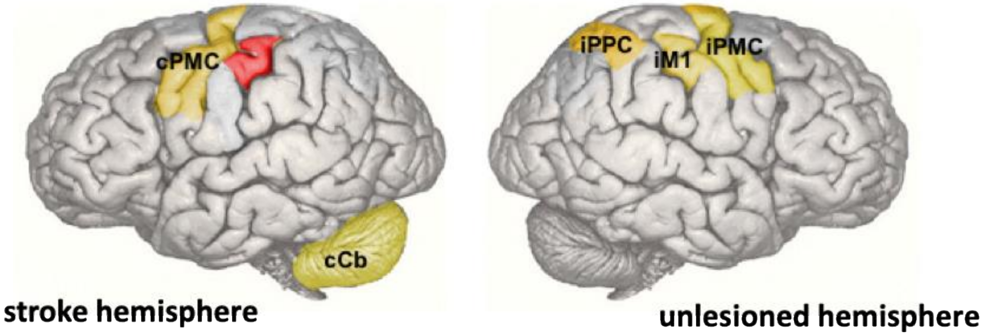


Hamilton and Pascual-Leone, 1998

Virtual Lesions – stroke recovery

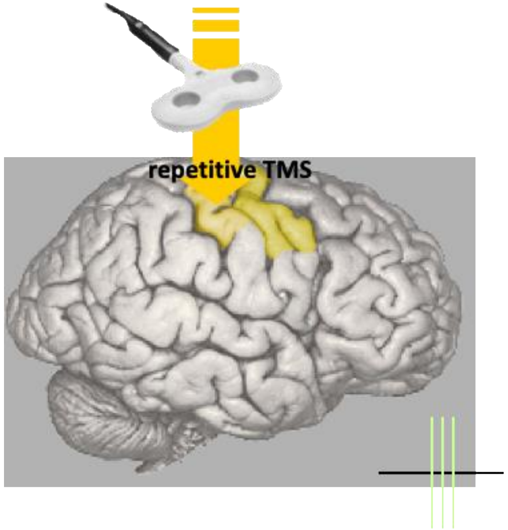
Stroke: movement with the paretic hand leads to bilateral motor cortical activity.





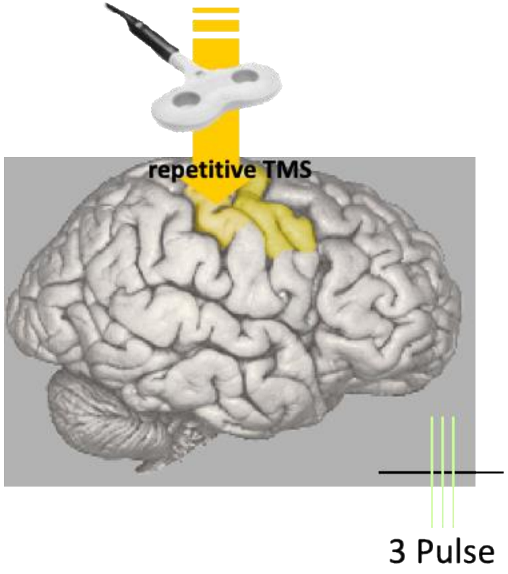
Are cortical areas active during functional neuroimaging have a causal link to a certain function?

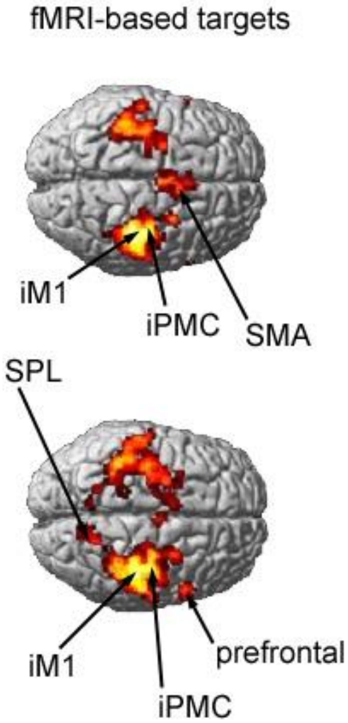
- "jamming": (virtual lesion) of motor areas
  - single pulses (silent period)
  - short high frequency trains (e.g., 20Hz triple pulses)

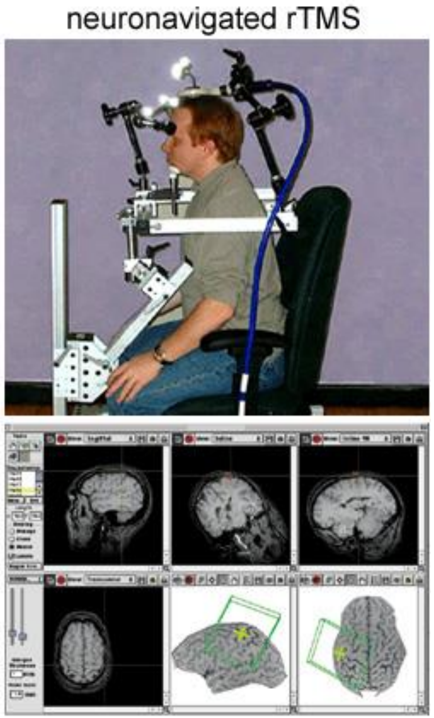


Virtual Lesions

- “jamming”: (virtual lesion) of motor areas
  - single pulses (silent period)
  - short high frequency trains (e.g., 20Hz triple pulses)

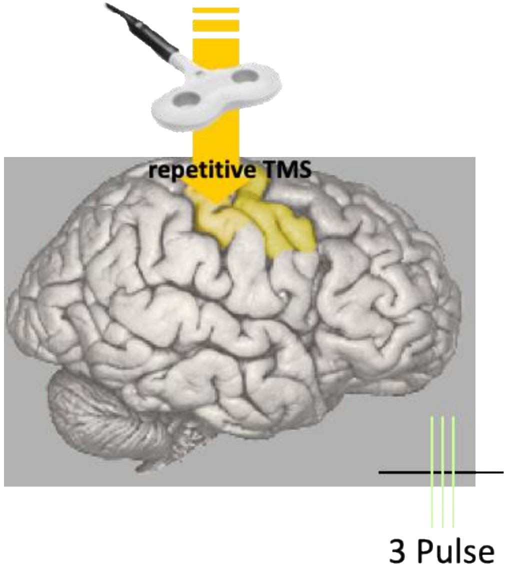


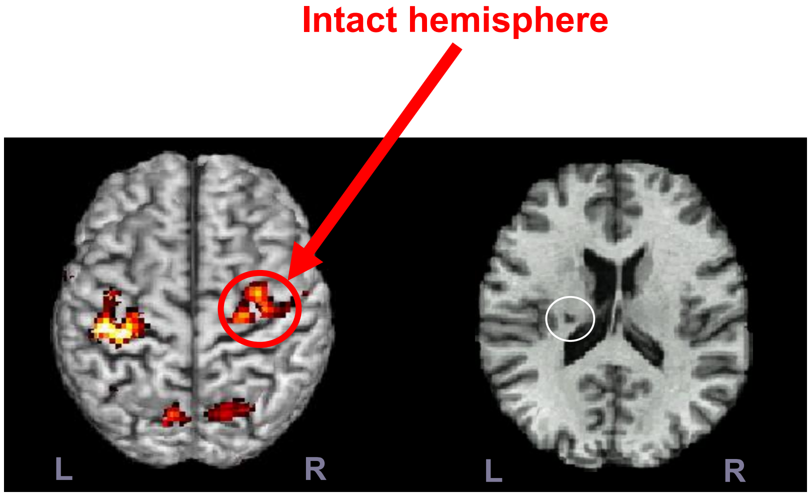




Virtual Lesions

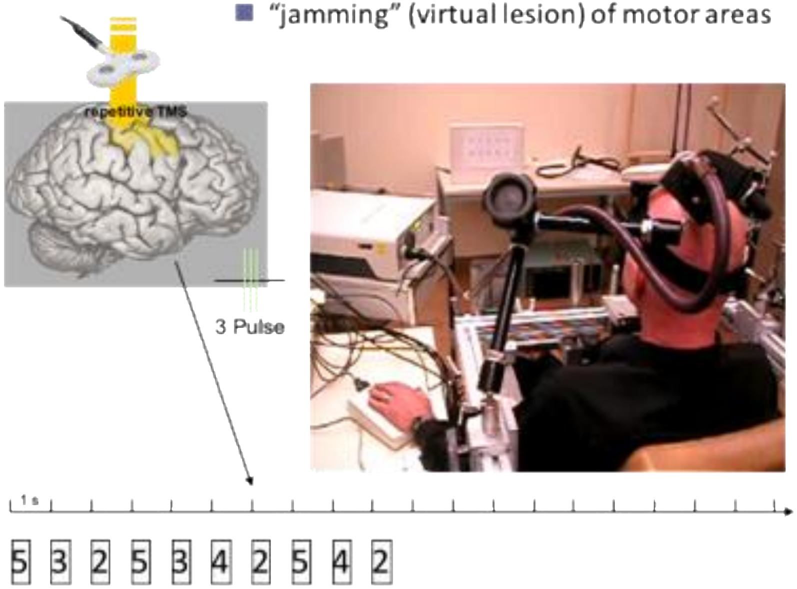
- “jamming”: (virtual lesion) of motor areas
  - single pulses (silent period)
  - short high frequency trains (e.g., 20Hz triple pulses)

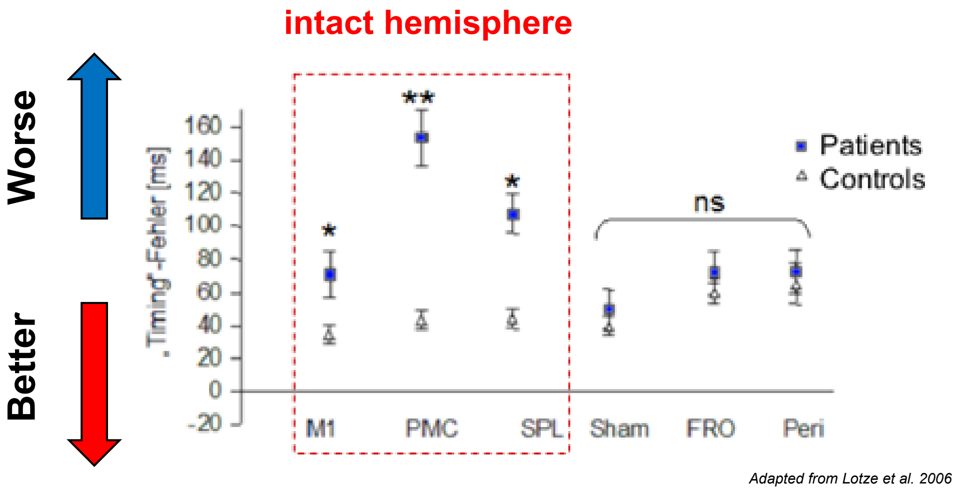




Stroke:
Movement with the paretic hand leads to bilateral motor cortical activity.

Virtual Lesions





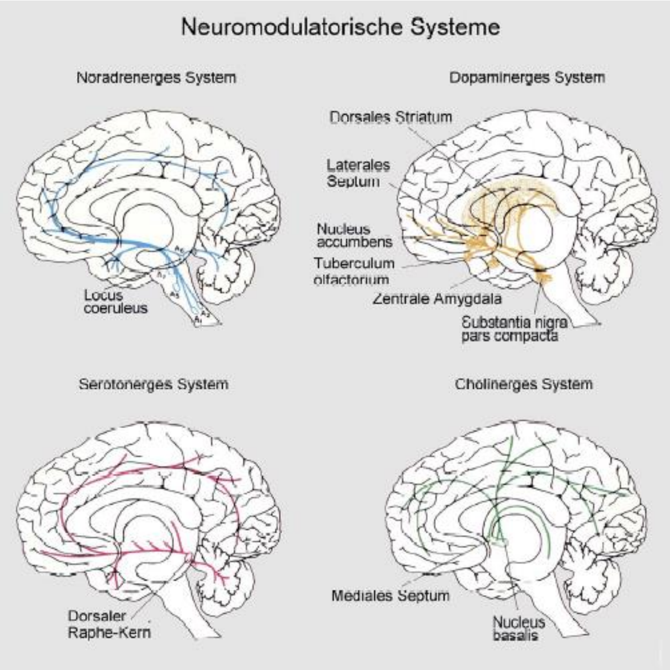
The intact hemisphere supports motor performance

Lotze et al. 2006 J. Neuroscience

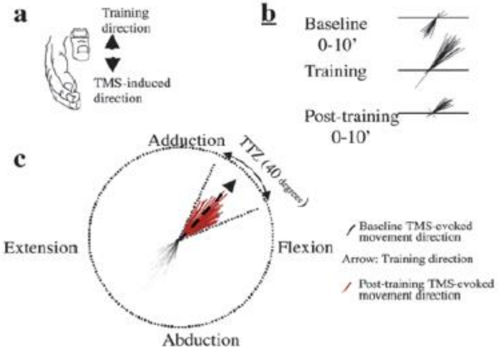
Use-dependent plasticity (UDP) – testing the impact of pharmacological interventions on plasticity using TMS

A simple **UDP** paradigm allows to determine the **effects** of different **neuroactive drugs** on neuroplasticity. UDP is easy to induce, **objective measurable** and **transient**.

UDP – Pharmacological intervention



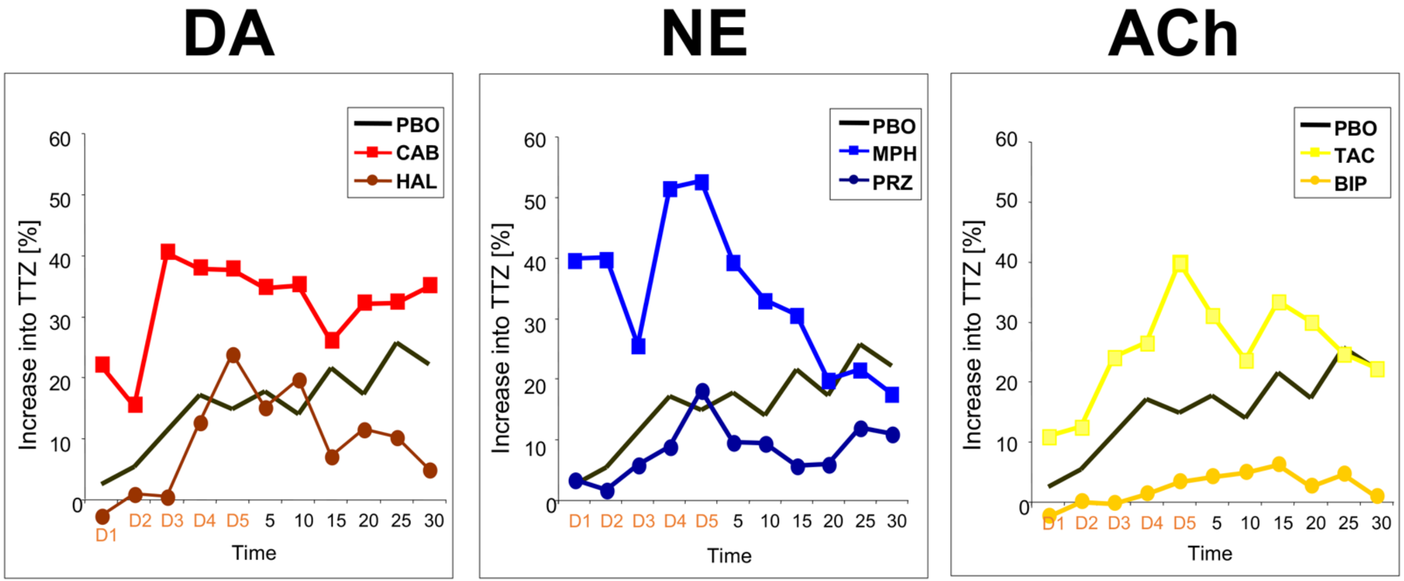
Meintzschel & Ziemann (2006) Cereb Cortex 16: 1106-15



Classen et al. 1998, J Neurophysiol 79:1117-23

Cabergoline DA+ 2 mg
Haloperidol DA- 2,5 mg
Methylphenidate NA+ 40 mg
Prazosin NA- 1 mg
Tacrine ACh+ 40 mg
Biperiden Ach- 8 mg
Placebo

UDP – Pharmacological intervention



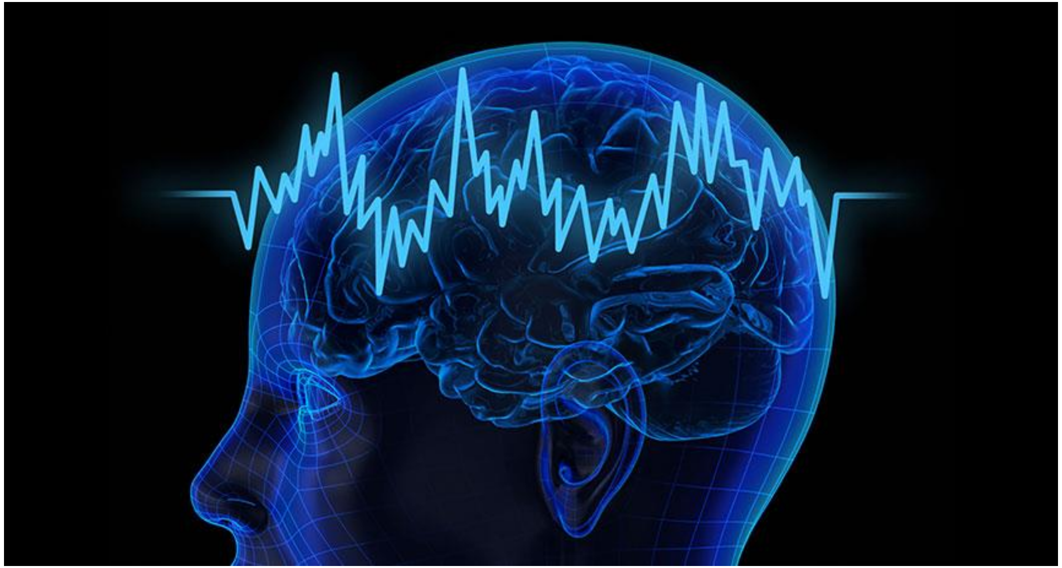
Meintzschel & Ziemann (2006) *Cereb Cortex* 16: 1106-15

Neuromodulating neurotransmitters enhance (DA+, NE+, ACh+) or reduce (DA-, NE-, ACh-) use-dependent plasticity

State-dependent/Closed-loop TMS

The brain is never ‘silent’. **Ongoing** brain activity while applying TMS might **influence** the **response to TMS**. **Reading out ongoing** brain activity in **real-time** will allow to apply **TMS** at **specific states** of this ongoing activity leading to specific and more homogenous responses.

TMS – Brain State dependent

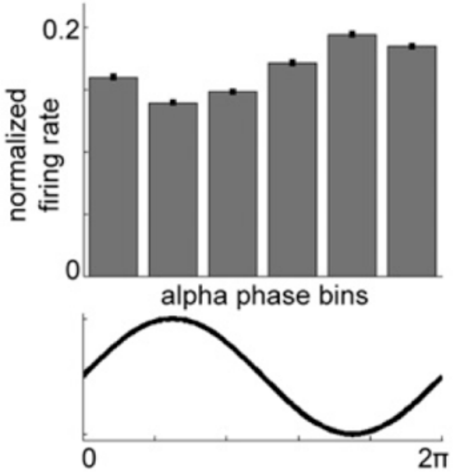


Why might this be important?

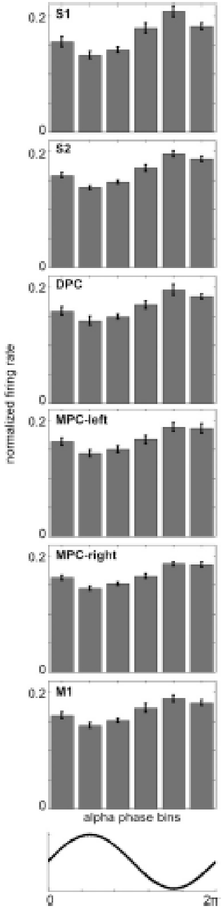
How to determine the brain state?

Technical challenges?

State dependent



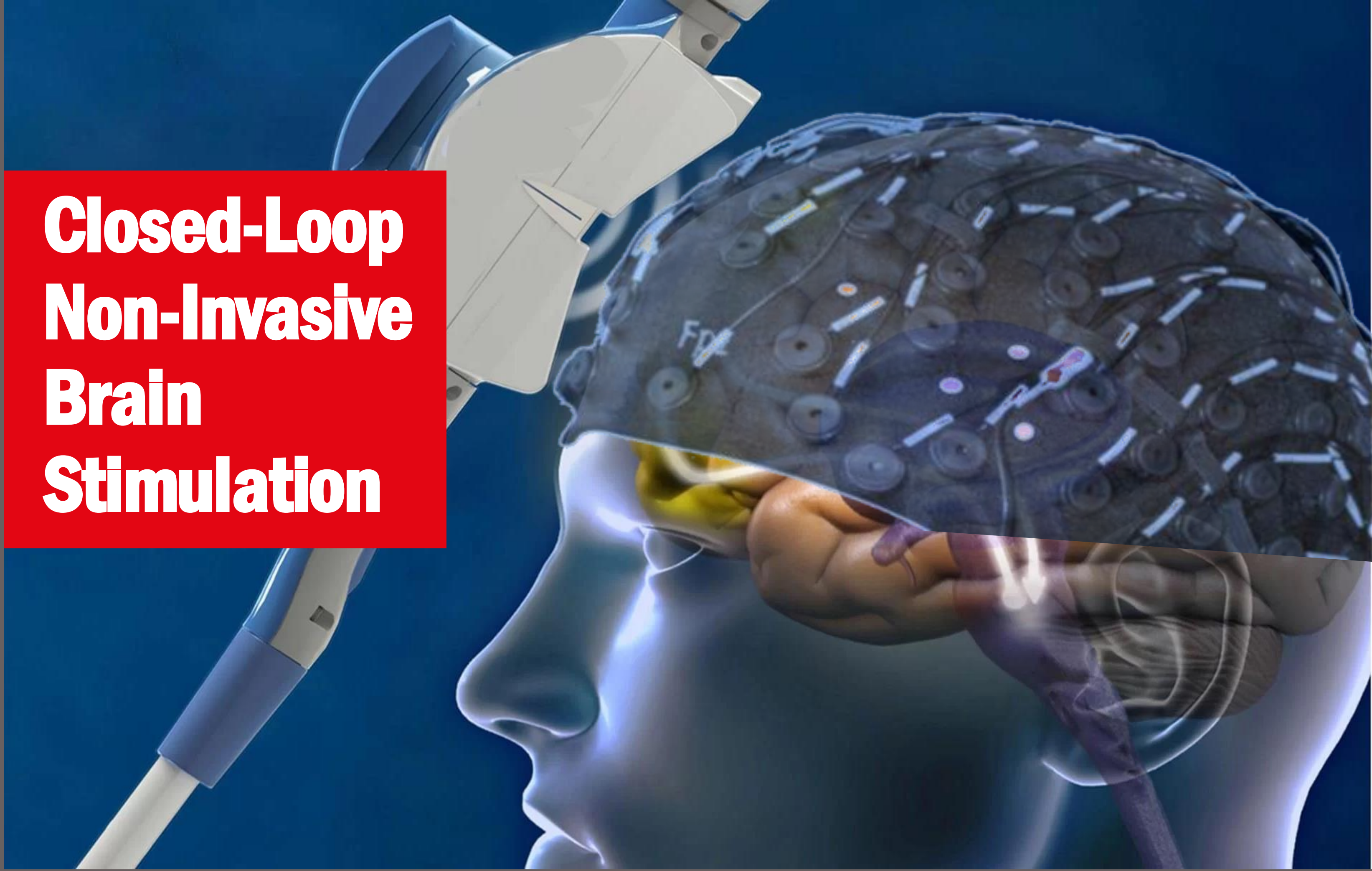
Local field potentials
in monkey cortex



Haegens et al. (2011) PNAS 108:19377-19382

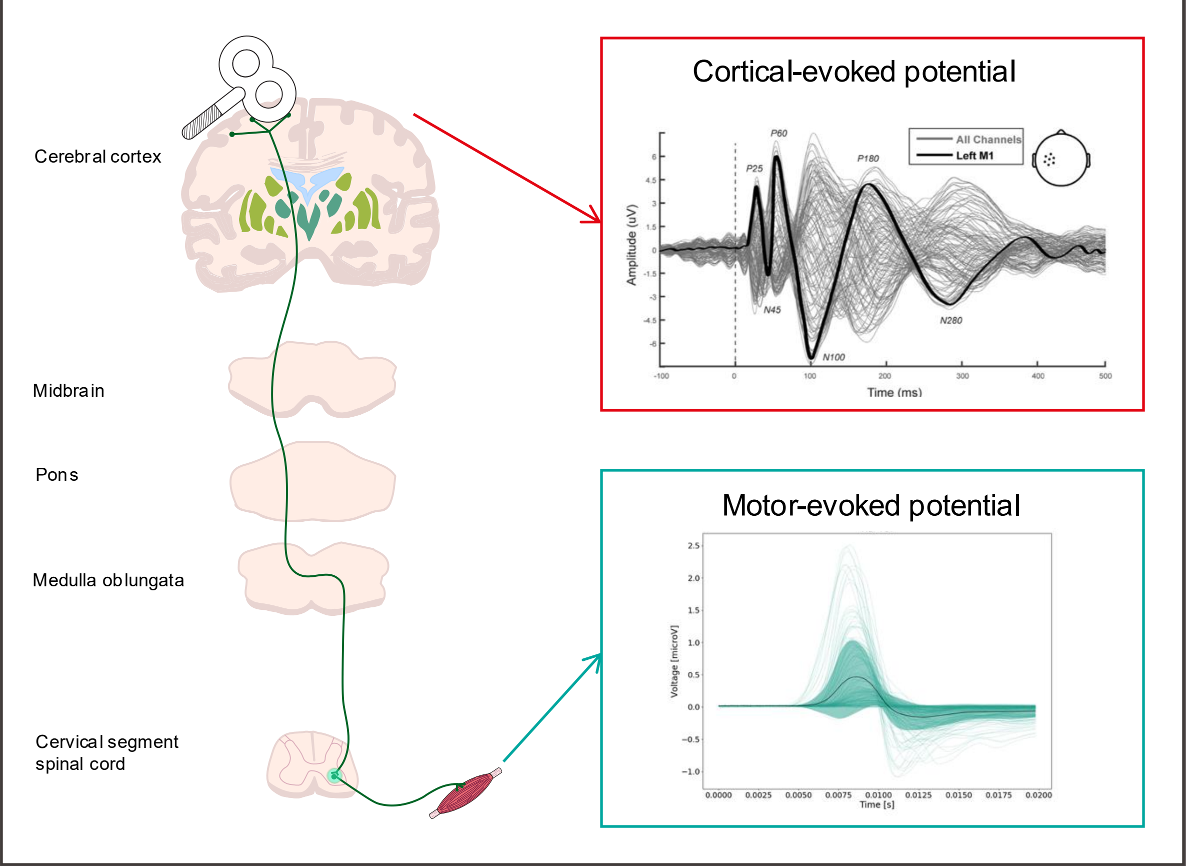
EPFL

Closed-Loop Non-Invasive Brain Stimulation



École
polytechnique
fédérale
de Lausanne

Transcranial Magnetic Stimulation (TMS)



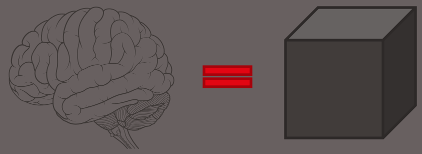
Mechanisms:

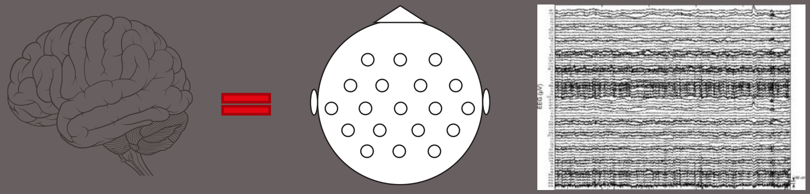
- Neuromodulation by current induction from magnetic impulse

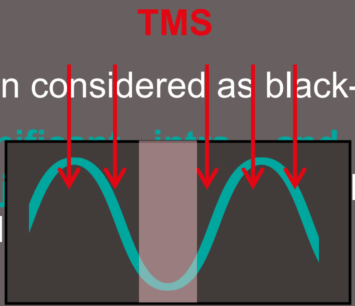
Clinical Applications:

- Diagnostic help
- Innovative therapeutics

From *black-box* to informed and personalized neuromodulation



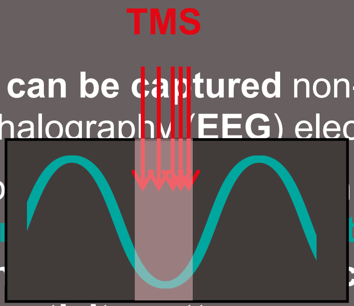




Brain considered as black-box.

Sign... intra- and inter-subj... lted in the l...

HIGH variability in brain response



Brain signal can be captured non-invasively with electroencephalography (EEG) electrodes.

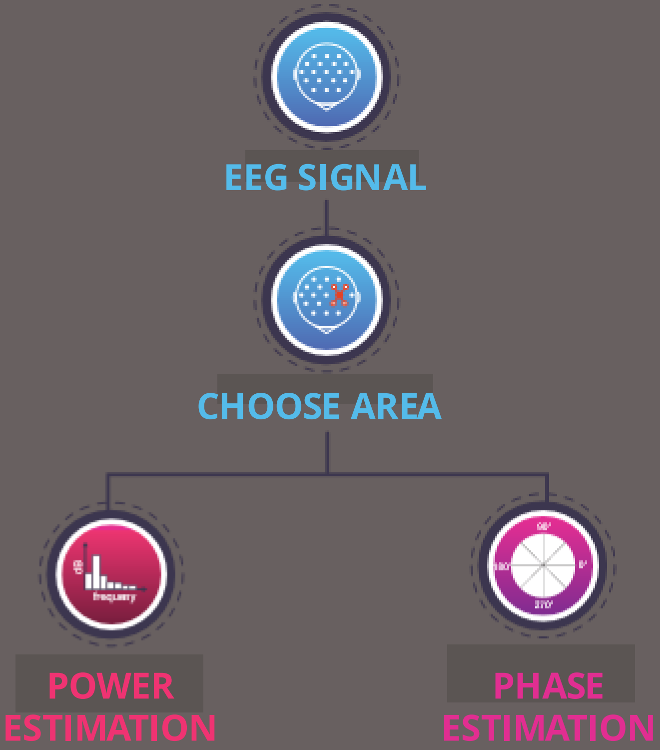
Signals can b... **ronous rhythmic activity of la... tions**. They depend on **ar... chitectonic**, **remote connectivity patterns**.

Heterogeneity could be reduced if stimulation provided at **specific brain states**.

LOW variability in brain response

EPFL

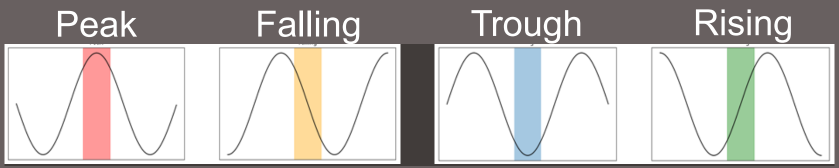
Understanding, predicting and stimulating the brain our approach



Sensorimotor rhythms fall within the **alpha band (8-12Hz).**

The two main characteristics of **oscillations** are:

- Power spectral density: ***how large*** *is the neural population that fires synchronously?*
- Phase angle - *what is the* ***current state*** *of the neural population activity?*



Working on the edge of science and technology

NEUROPHYSIOLOGY

Understand what influences responses to TMS

Understand which area to read from

Understand which area to target

Understand brain oscillation phases

ENGINEERING

Setup development
Connecting machines

Computational costs
Be as fast as possible

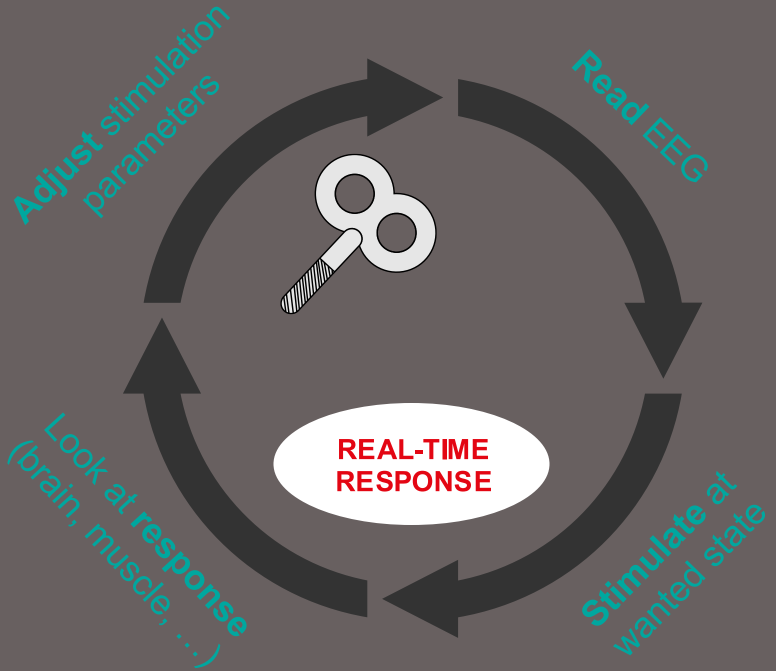
Real-time feedback of stimulation effects

Signal processing

EPFL

Applications and future perspective of a closed-loop system

- **Neurophysiology**
  - Brain networks interaction
- **Rehabilitation**
  - Stroke motor and visual
  - Parkinson
  - Depression
- **Assistance**

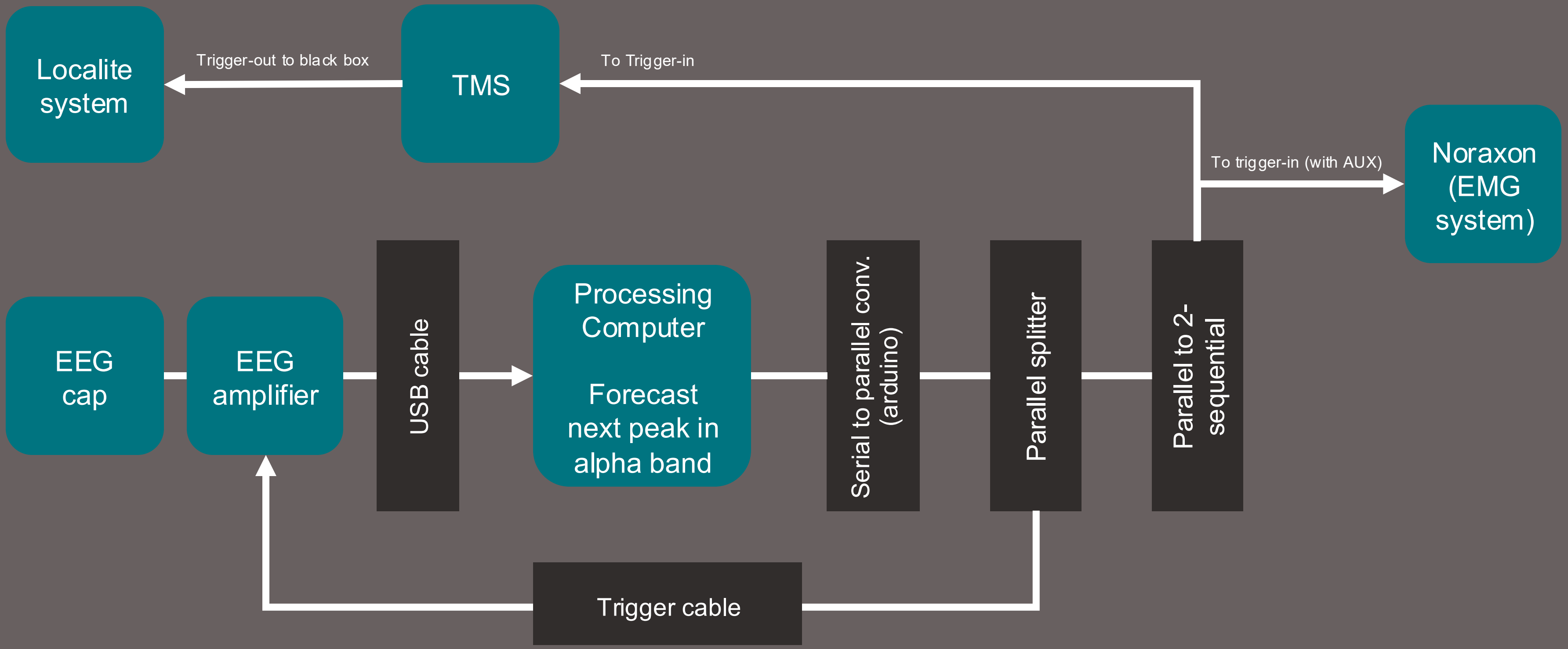


EPFL

SEE IT IN ACTION!

EPFL

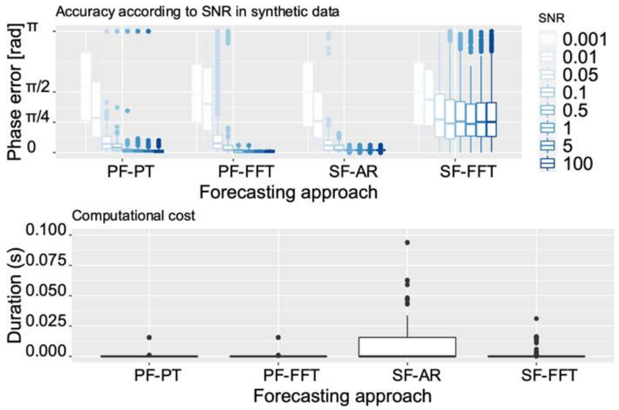
Setup

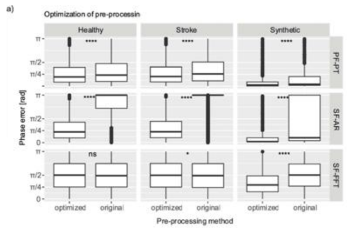


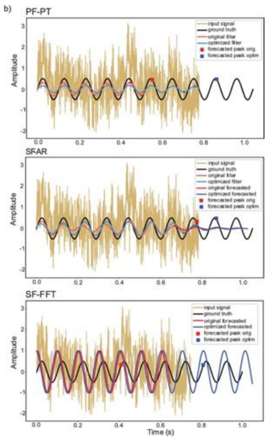
Localite system
Trigger-out to black box
TMS
To Trigger-in
To trigger-in (with AUX)
Noraxon (EMG system)
EEG cap
EEG amplifier
USB cable
Processing Computer
Forecast next peak in alpha band
Serial to parallel conv. (arduino)
Parallel splitter
Parallel to 2-sequential
Trigger cable

TMS – Brain State dependent

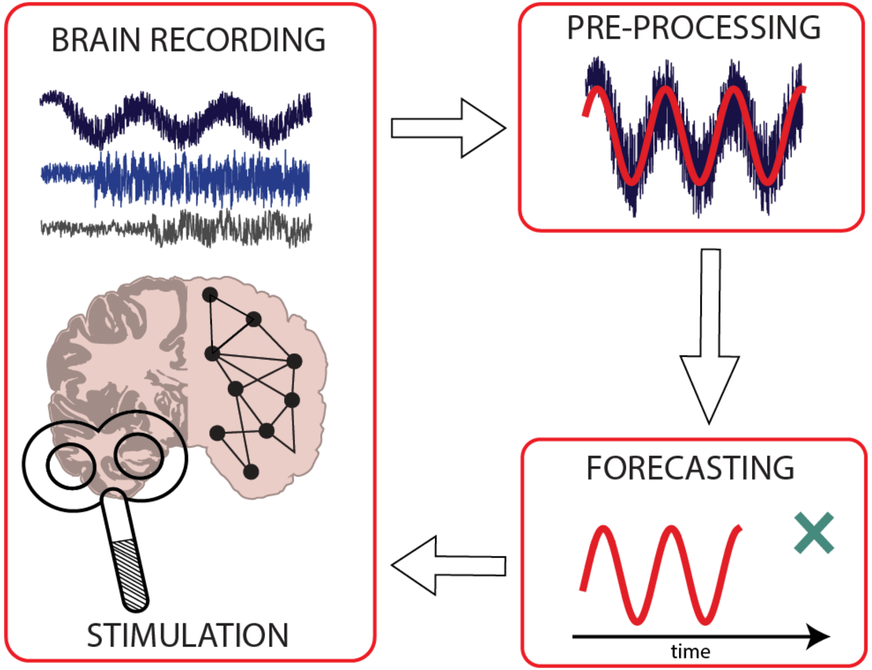
Challenges:Online recording - Online preprocessing - Forecasting



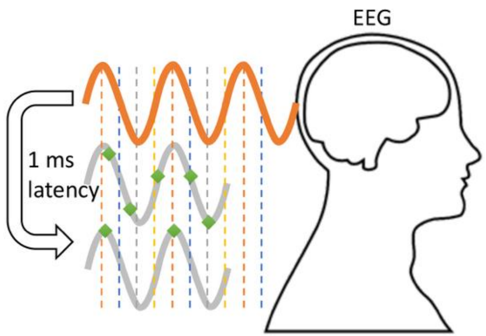




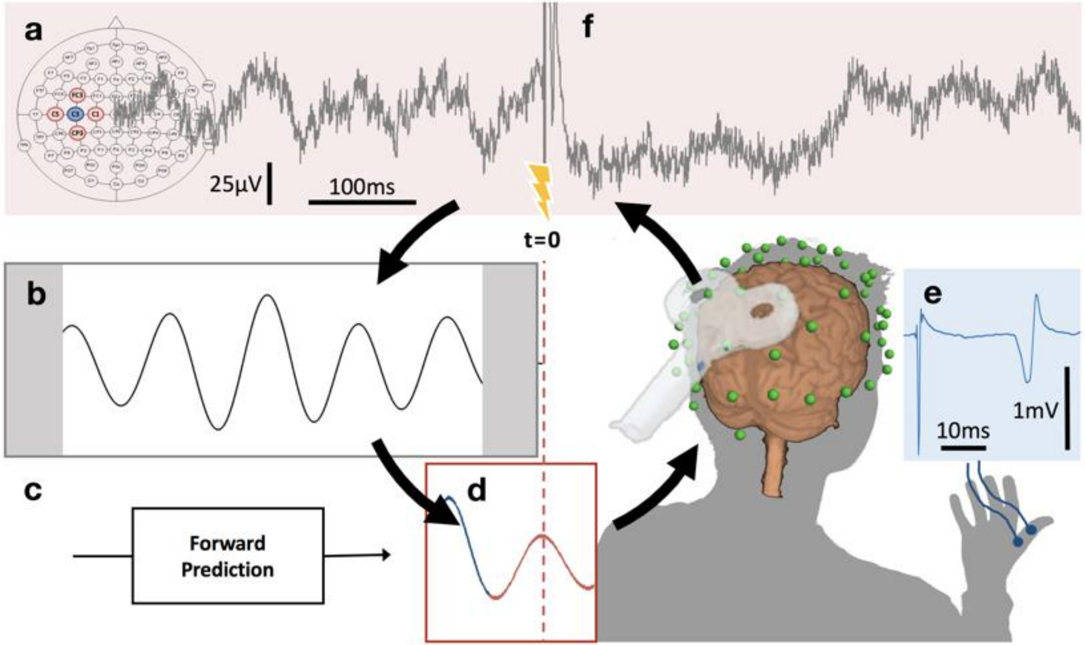
Bigoni et al. 2023



TMS – Brain State dependent

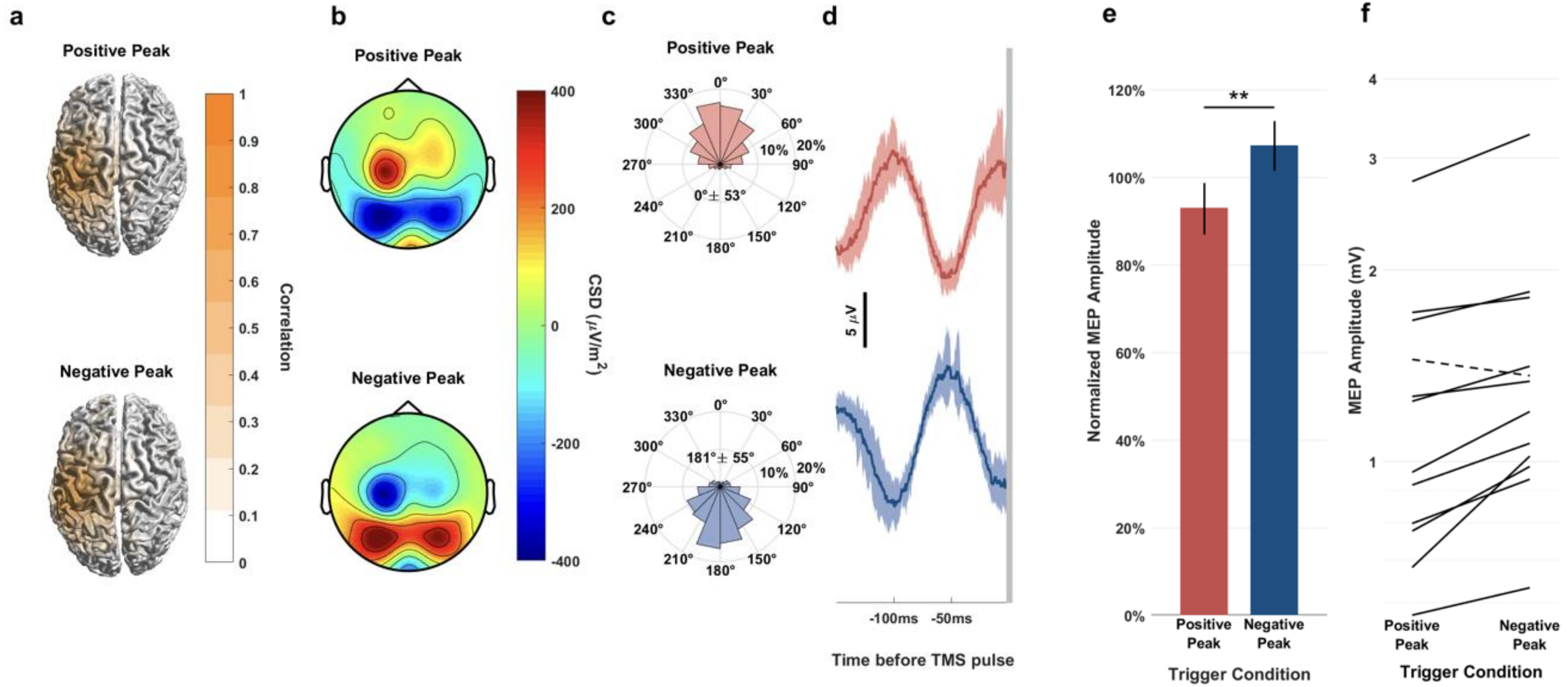


EEG-TMS: Dependence of corticospinal excitability on µ-rhythm phase



Zrenner et al. 2018

TMS – Brain State dependent



Zrenner et al. 2018

EPFL

Summary

I. TMS ‘virtual lesion‘ approach is an unique opportunity to determine causal relationships between brain areas and motor/cognitive functions in humans in vivo.

II. TMS ‘virtual lesion‘ approaches allow to determine exact timings of the involvement of a certain brain area in a task with a temporal resolution in the milliseconds range.

III. Closed-loop/state-dependent TMS offers to better understand underlying mechanisms of TMS, will lead to more homogenous responses to TMS and to better responses to TMS as a treatment

IV. Main challenge: real-time estimation of ongoing brain activity (power, phase)

Break

Neuromodulation with TMS

TMS offers the opportunity to **neuromodulate** the brain in **specific** ways, e.g. **enhance/reduce** cortical **excitability**, **enhance/reduce plastic properties** of cortical areas or **influence interregional** interactions and **network** activity.

General concept

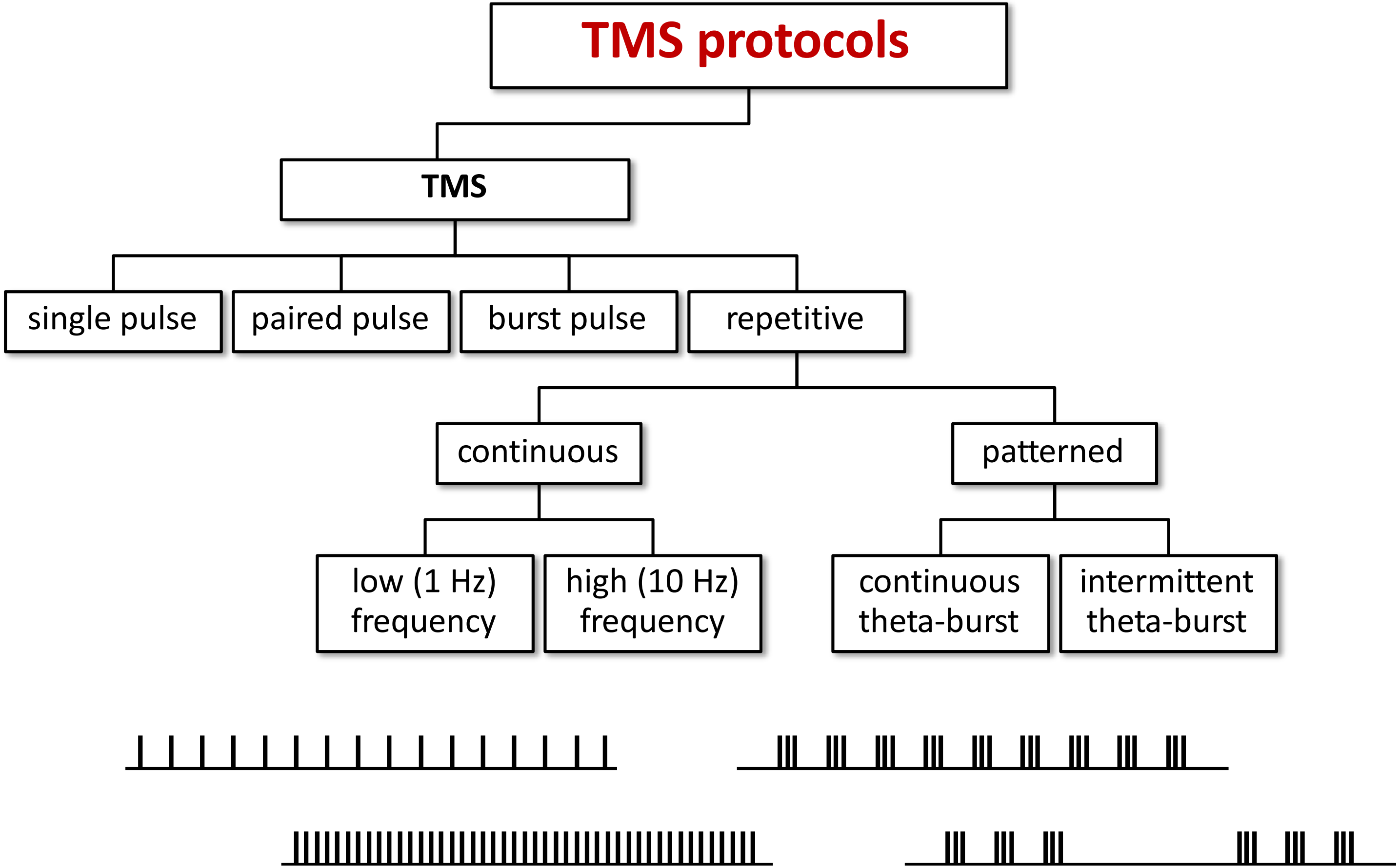
To modulate focal brain activity

To modulate plastic properties

To modulate interregional interactions

To modulate respective behavior

To do it in a safe and reproducible way


TMS protocols
TMS
single pulse
paired pulse
burst pulse
repetitive
continuous
patterned
low (1 Hz) frequency
high (10 Hz) frequency
continuous theta-burst
intermittent theta-burst

repetitive stimulation

- continuous repetitive stimulation
  - fixed inter-pulse interval commonly between 1 and 10 Hz
    - but faster (30Hz) and slower (0.1Hz) protocols exist
  - train of stimulation lasts between seconds to 30 minutes
  - known as “rTMS”

- patterned stimulation
  - fixed inter-burst interval commonly between 1 and 10 Hz
  - very fast intra-burst interval commonly between 30 and 50 Hz
  - best-known example: continuous theta-burst stimulation (cTBS)
  - higher-order pattern protocols exist, for example: intermittent TBS (iTBS)

Mechanisms of Action of rTMS

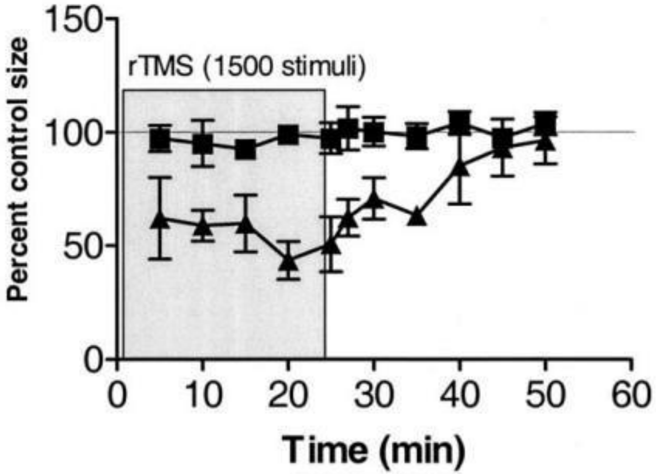
High-Frequency rTMS (≥ 5 Hz or iTBS – excitatory)

- Depolarizes neuronal membranes, increasing spontaneous firing rates.
- Enhances synaptic efficacy through LTP-like plasticity (NMDA-dependent).
- Increases intracortical facilitation and reduces GABAergic inhibition.
- Strengthens network connectivity (particularly fronto-hippocampal and parietal circuits).
- Upregulates neurotrophic factors such as BDNF, promoting synaptic growth and plasticity.

Low-Frequency rTMS (≤ 1 Hz – inhibitory)

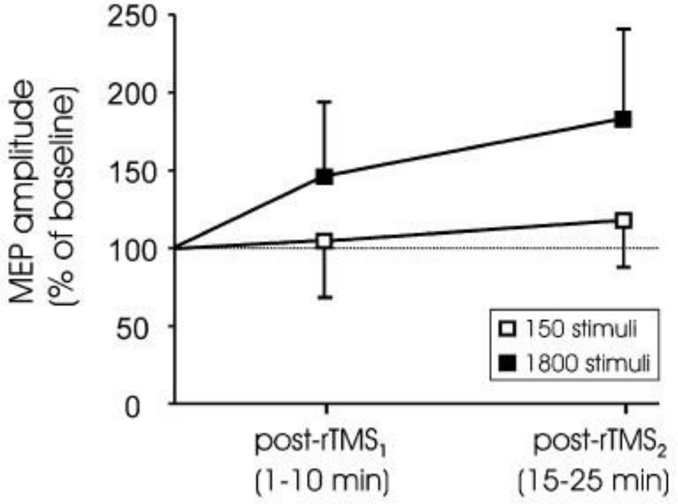
- Induces LTD-like synaptic depression via prolonged hyperpolarization and reduced glutamatergic transmission.
- Decreases cortical excitability by enhancing GABAergic interneuron activity.
- Suppresses overactive networks, restoring excitation–inhibition balance.

low frequency -inhibitory
~1Hz



Touge (2001) *ClinNeuroPhys*

high frequency – facilitatory
5-20Hz



Peinemann (2004) *ClinNeuroPhys*

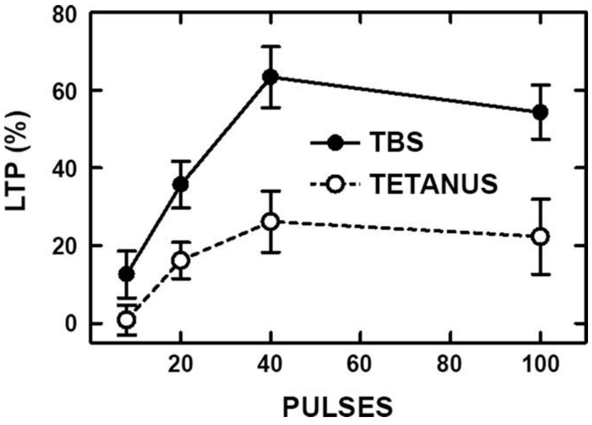
Example protocols (large variations in the literature!):

- 1 Hz: >900 pulses (e.g. 1500) in a continuous train at ~110% RMT
- 5 HZ: >900 pulses (e.g. 1500) in trains of 30s with 30s breaks at ~90% RMT

for reviews: Ziemann (2008) *BrainStim*; Fitzgerald (2006) *ClinNeuroPhys*

‘patterned’ rTMS

Hippocampal field CA1



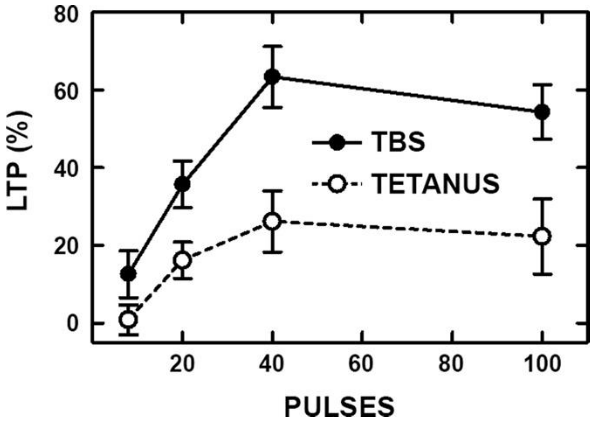
Larson& Munkasy 2015; Andersen 1991

iTBS = LTP-like Stimulation - facilitatory

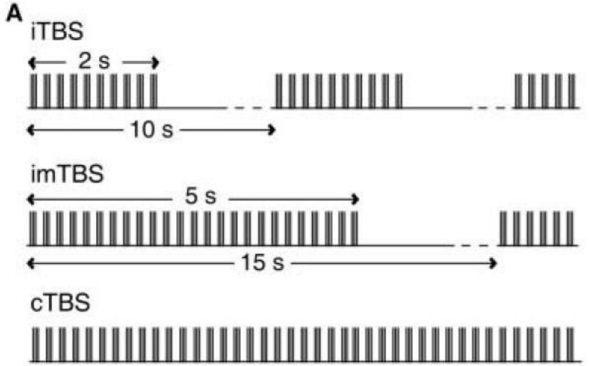
cTBS = LTD-like Stimulation - inhibitory

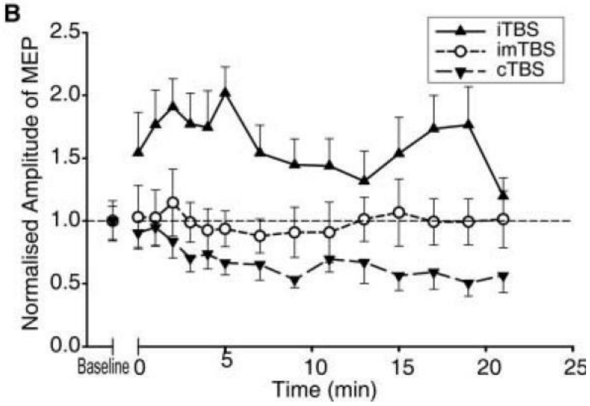
‘patterned’ rTMS

Hippocampal field CA1



Larson& Munkasy 2015; Andersen 1991



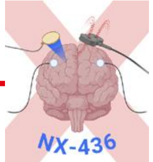


iTBS = LTP-like Stimulation - facilitatory

cTBS = LTD-like Stimulation - inhibitory

Huang (2005) *Neuron*

Mechanisms of Action of Theta-Burst rTMS (TBS)



Intermittent TBS (iTBS – excitatory)

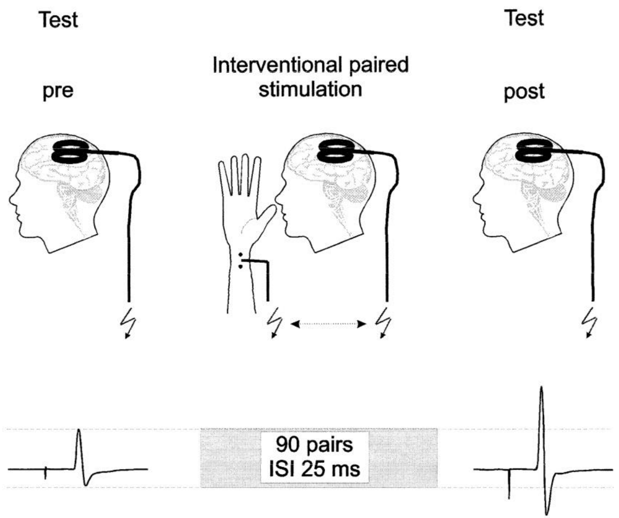
- Pattern: 2 s trains of 50 Hz bursts repeated every 10 s (typically 600 pulses).
- Mimics endogenous theta–gamma coupling, resembling hippocampal LTP induction patterns.
- Mechanism:
    - Induces LTP-like synaptic potentiation through NMDA receptor activation and calcium influx.
    - Enhances glutamatergic transmission and intracortical facilitation.
    - Increases BDNF expression and synaptic efficacy.
- Network effects:
    - Promotes functional connectivity within cognitive and motor networks (e.g., precuneus–hippocampus).
    - Leads to increased cortical excitability lasting 30–60 min or more post-stimulation.

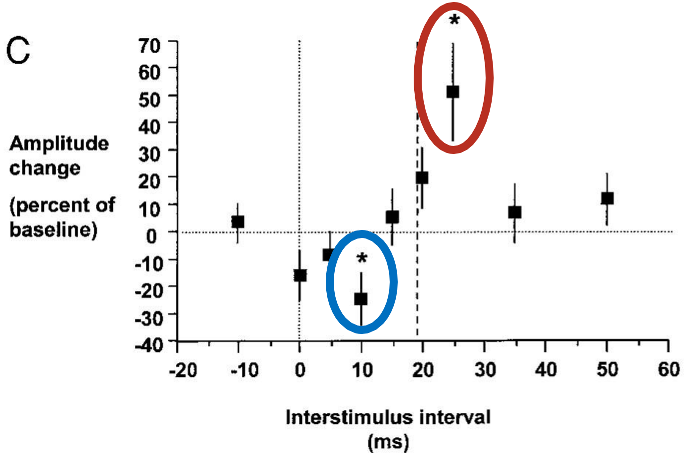
Mechanisms of Action of Theta-Burst rTMS (TBS)

Continuous TBS (cTBS – inhibitory)

- Pattern: Uninterrupted 40 s train of 50 Hz bursts at 5 Hz theta frequency (600 pulses).
- Mechanism:
  - Produces LTD-like synaptic depression by sustained intracellular calcium plateau and downstream inhibitory signaling.
  - Decreases neuronal firing and reduces glutamatergic transmission.
  - Enhances GABAergic tone and decreases cortical excitability.
- Network effects:
  - Temporarily suppresses activity in targeted circuits (e.g., motor or parietal cortex).
  - Facilitates rebalancing of hyperactive or maladaptive networks.

paired associative stimulation





facilitatory

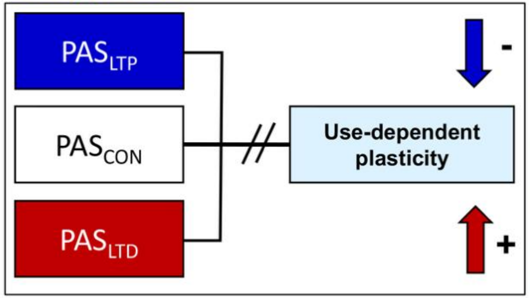
inhibitory

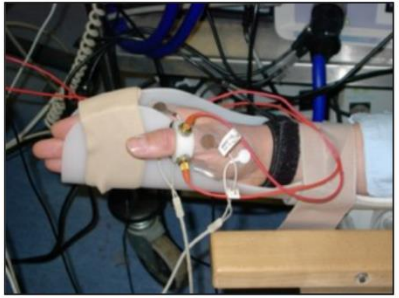
Standard protocol: 90 pairs at 10 or 25 ms ISI and at 0.05 Hz inter-pair interval with 1mV-MEP TMS intensity and 300% sensory threshold for median nerve stimulation

Stefan (2000) *Brain*; Wolters (2003) *JNeurophys*

TMS – PAS

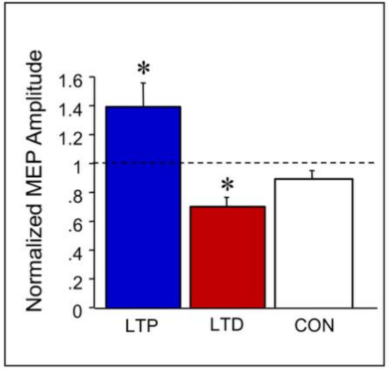
Study protocol



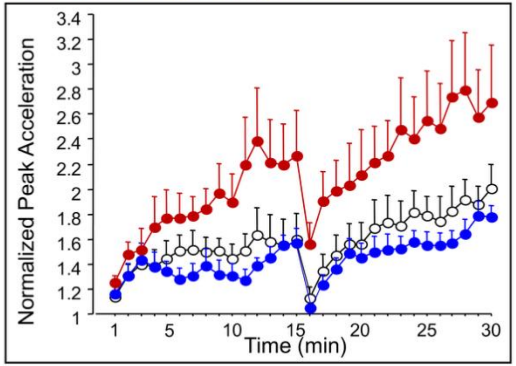


Jung & Ziemann 2009, *J Neurosci* 29, 5597-5604

PAS-induced plasticity

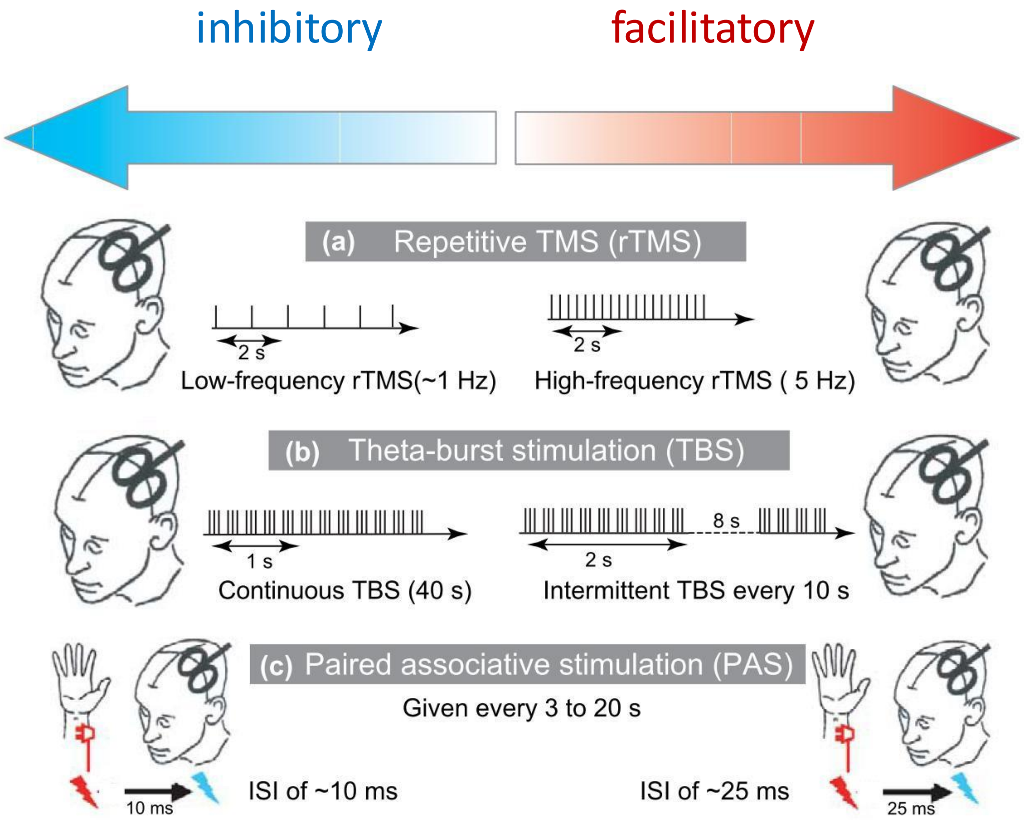


Use-dependent plasticity after PAS



Priming with PAS leads to homeostatic regulation of subsequent motor learning in healthy adults

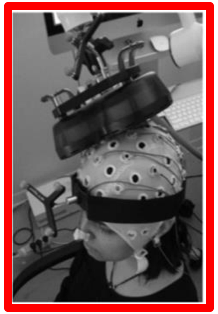
OVERVIEW: TMS - inhibitory and facilitatory neuromodulation effects

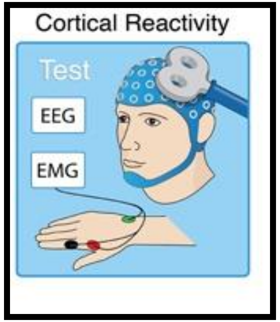


Quartarone (2006) *TINS*

Clinical Applications

TMS neuromodulation – clinical applications



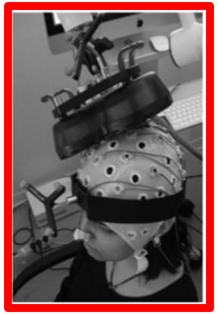


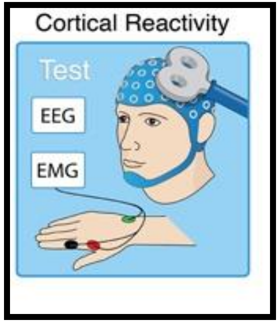
TMS/TES

BIOMARKER OF SYNAPTIC DYSFUNCTION

THERAPY

TMS neuromodulation – clinical applications



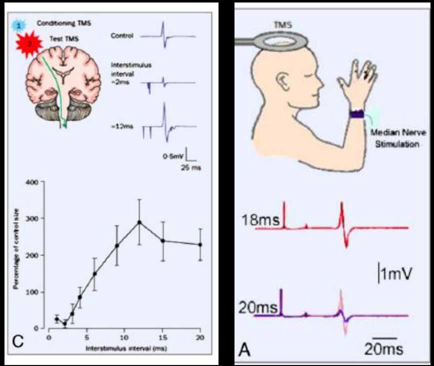


TMS/TES

BIOMARKER OF SYNAPTIC DYSFUNCTION

TMS neuromodulation – biomarking

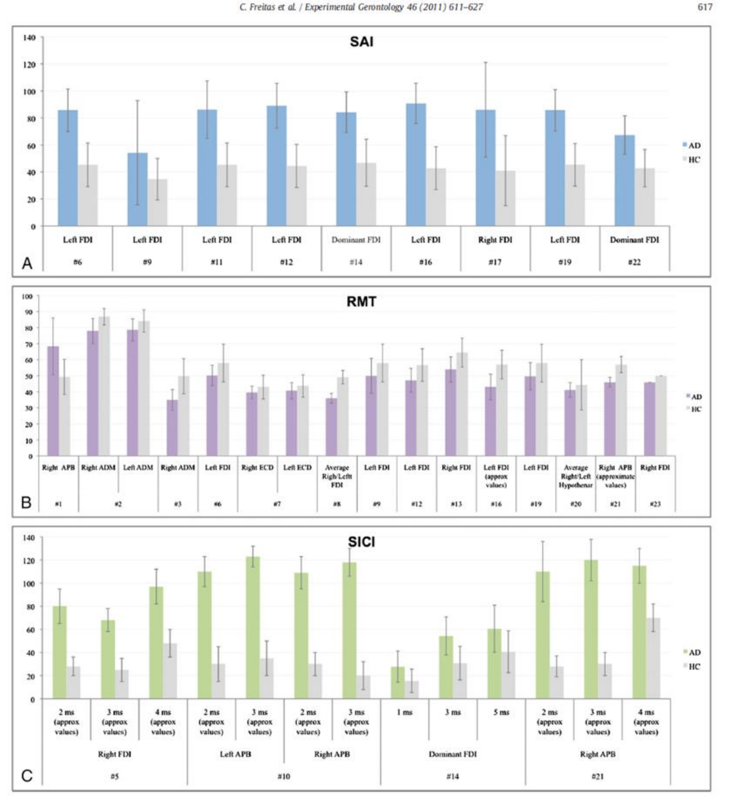
TMS in AD patients



To date, **several reports using TMS** have claimed the detection of **abnormalities in cortical reactivity, plasticity, and connectivity in AD patients.**

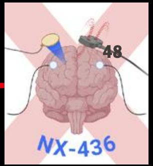
SAI and resting motor threshold are significantly reduced in AD patients as compared to healthy elders.

Results on other measures of cortical reactivity, e.g. intracortical inhibition (ICI), are more divergent.

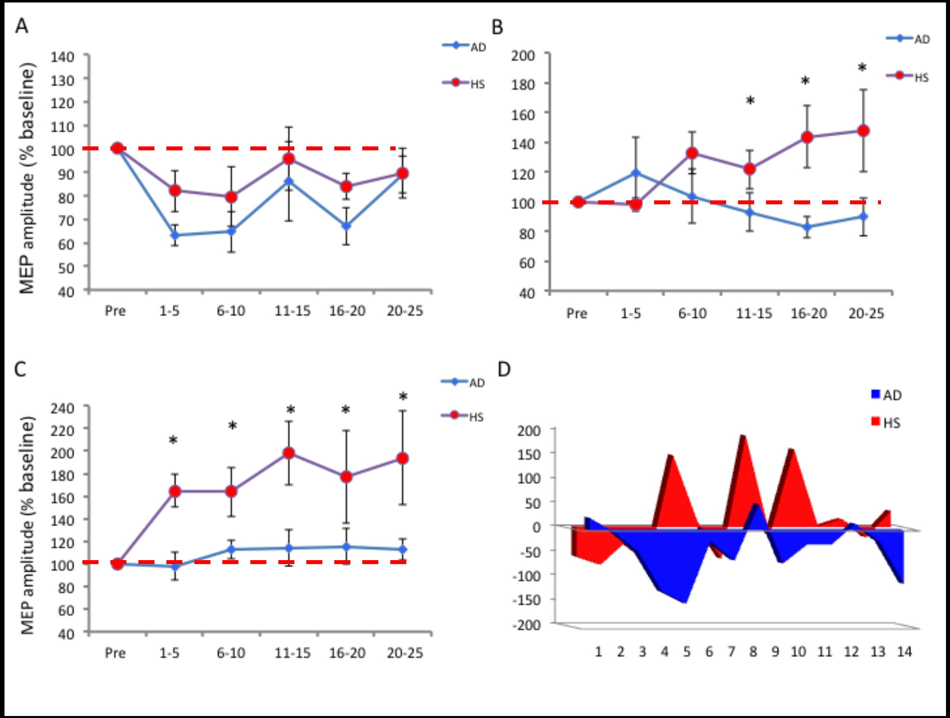


Freitas et al., 2011

TMS neuromodulation – biomarking



Impaired LTP-like cortical plasticiy in AD patients



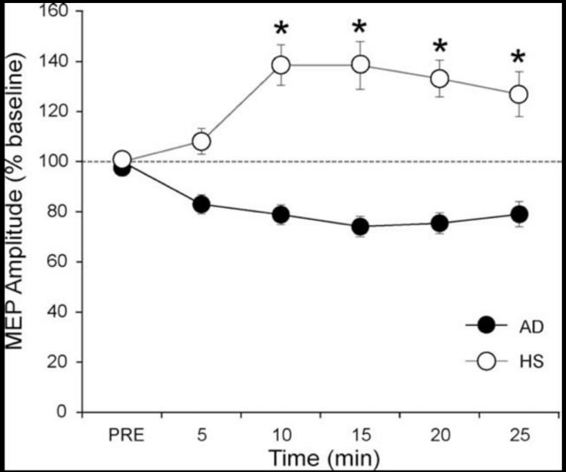
In a recent study Koch *et al.* applied theta burst stimulation (TBS) over the primary motor cortex in a sample of AD patients.

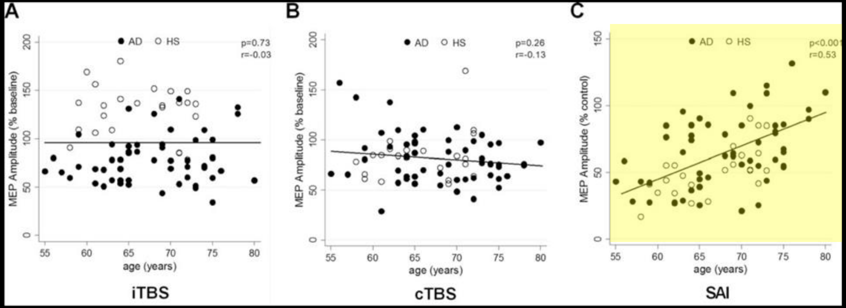
They found that LTP-like cortical plasticity is impaired in AD patients, while LTD seems to be preserved. These findings resemble the animal data.

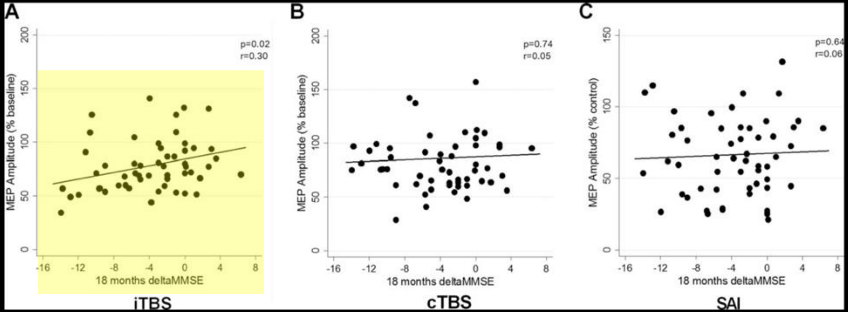
Koch et al., 2012

TMS neuromodulation – biomarking

Impaired LTP-like cortical plasticiy in AD patients indeendent of Age of onset





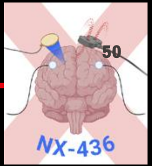


SAI correlates with **age**

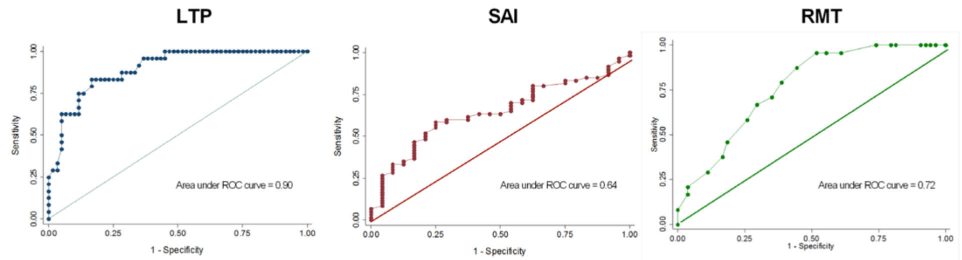
iTBS correlates with **cognitive decline**

Lorenzo et al., 2016

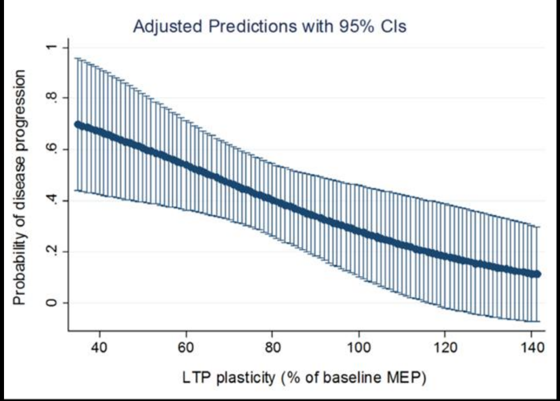
TMS neuromodulation – biomarking



LTP-like plasticity allows to discriminate AD from healthy and is a predictor for disease progression



AUC: 0.90 AUC: 0.64 AUC: 0.72



AD=60
HC=30

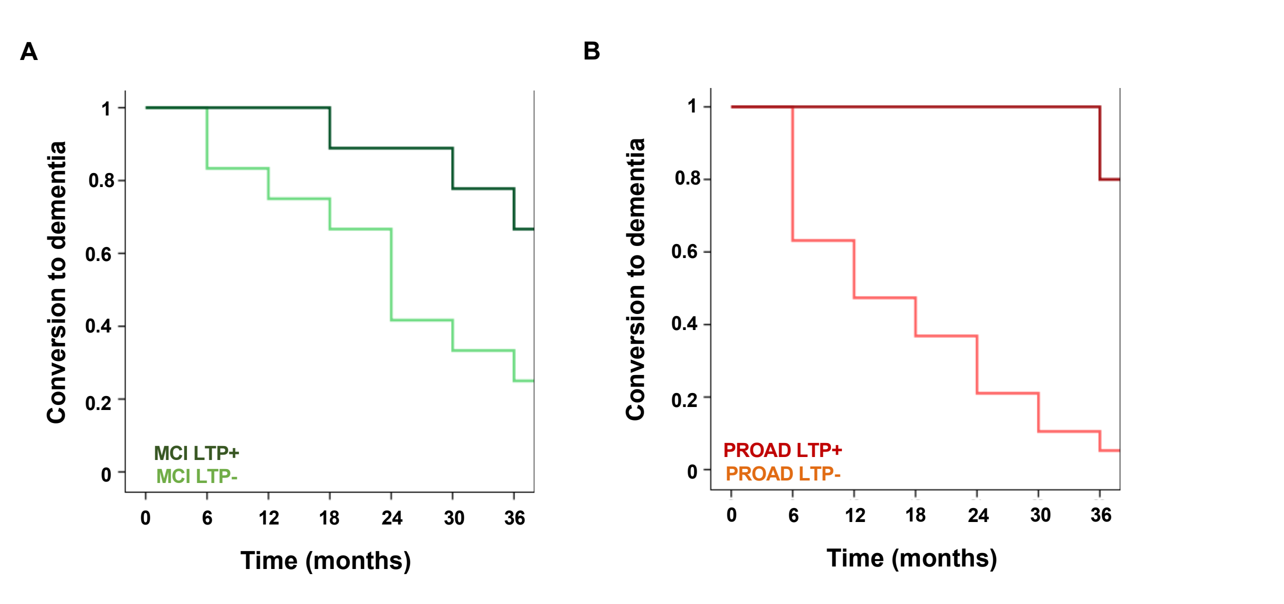
LTP-like plasticity discriminates patients with **AD** from **healthy controls**

LTP-like plasticity is the only predictor of disease progression at 18 months

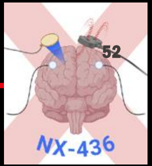
Motta et al., 2018

Cortical plasticity as a biomarker in MCI patients

LTP-like plasticity is a strong predictor of conversion to dementia in MCI patients

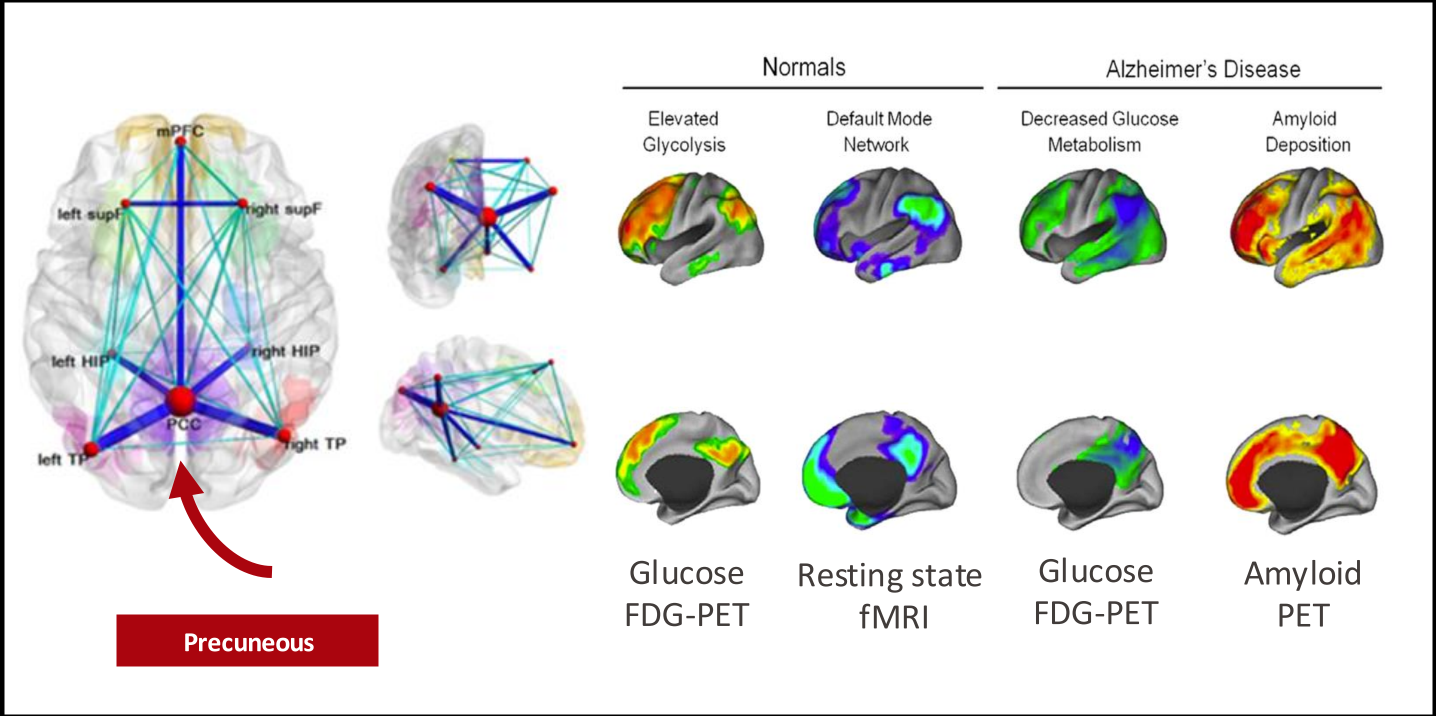


Di Lorenzo et al, *Brain Stimulation* 2020



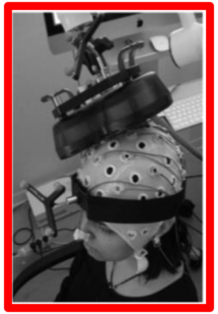
Aβ and Tau Accumulation And Dysfunction Across Brain Regions

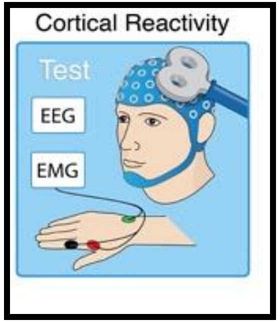
- There are eight functional networks in the brain and each network has a central hub
- The **Default Mode Network** (DMN) is responsible for memory and has preferential accoumulation of Aβ and Tau versus other regions
- The hub for the DMN is called the **Precuneous**



Yu M, et al. Nat Rev Neurol. 2021 Sep;17(9):545-563.
Sheline YI, Raichle ME. Biol Psychiatry. 2013

TMS neuromodulation – clinical applications





TMS/TES

THERAPY

TMS neuromodulation – Relevance of the Default Mode Network (DMN) in AD

1. Core concept

- The **DMN** is a large-scale intrinsic brain network active during **rest, memory retrieval, and self-referential thought**.
- It includes key hubs: **posterior cingulate cortex (PCC) / precuneus**, **medial prefrontal cortex (mPFC)**, **inferior parietal lobule**, and **hippocampus**.
- The DMN shows **task-negative** activity (deactivated during attention-demanding tasks) and **synchronizes during rest** for memory and introspective processes.

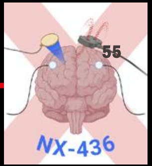
2. DMN dysfunction in Alzheimer's

- **Earliest functional alteration** in AD: disrupted **functional connectivity** within DMN hubs.
- **Precuneus/PCC** and **hippocampus** show **hypometabolism**, **atrophy**, and **reduced synchronization** even in prodromal stages (MCI).
- **Amyloid-β and tau deposition** preferentially occur along DMN hubs — correlating with **cognitive decline and disease progression**.
- DMN disintegration leads to **impaired episodic memory**, **attention switching**, and **default–executive network imbalance**.

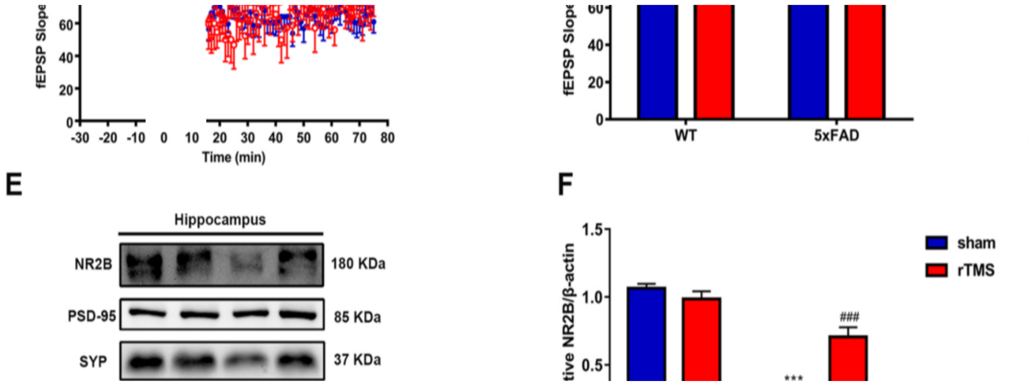
3. Relevance for neuromodulation

- The DMN represents a **therapeutic target network** for rTMS/TBS:
- **iTBS over the precuneus or DLPFC** can **reactivate hypoactive DMN nodes**.
- Enhances **precuneus–hippocampal connectivity**, improving **episodic memory** (Koch et al., *Brain* 2018, 2022).
- Modulating DMN hubs may **restore network integrity** and **compensate for pathological disconnection**.

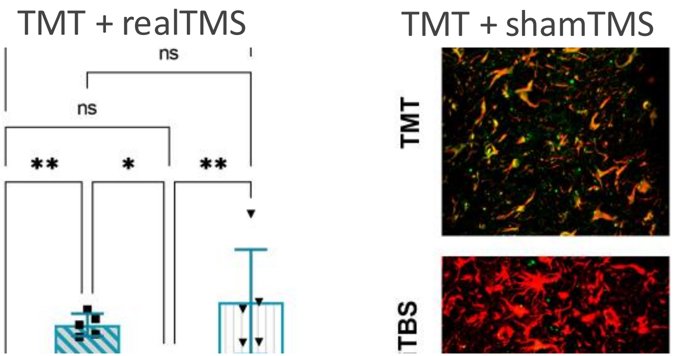
Interventional strategies – rTMS



rTMS improves synaptic plasticity and reduces neuronal death in AD animal models.

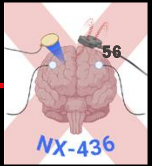


20Hz-rTMS increases the expression of dopamine DR4 gene and of neurogenic proteins (BDNF) in the cerebral cortex and the hippocampus (McNerney et al., 2022; Choung et al., 2021). Early intervention with rTMS attenuates synaptic plasticity impairment and neuroinflammation in 5xFAD mice (Li et al., 2020).



rTMS reduces TMT-induced inflammation and increases anti-inflammatory molecules in rats with hippocampal neurodegeneration (Stekic et al., 2022)

Adaikkan & Tsai 2020



rTMS improves synaptic plasticity and reduces neuronal death in AD animal models.

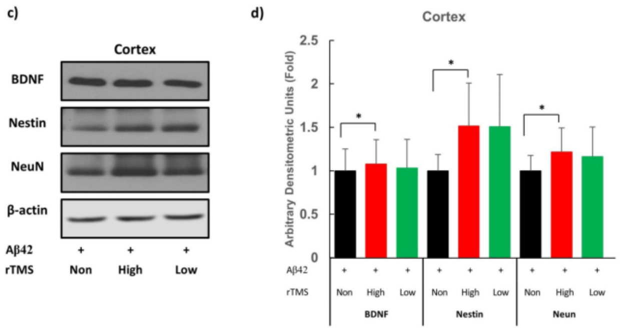
scientific reports

Check for updates

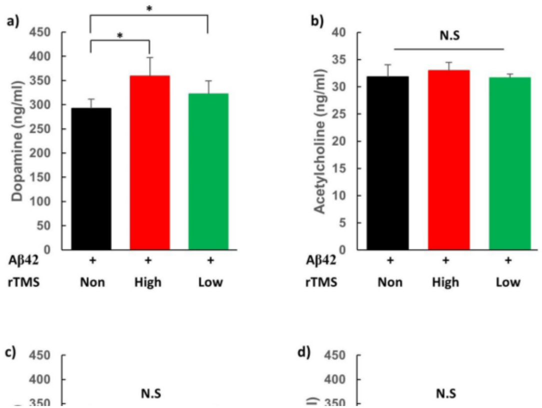
OPEN

Therapeutic efficacy of repetitive transcranial magnetic stimulation in an animal model of Alzheimer's disease

Jin Seung Choung[1,5], Jong Moon Kim[1,2,5], Myoung-Hwan Ko[3], Dong Sik Cho[4] & MinYoung Kim[1,2]

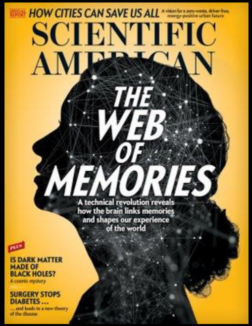


Repetitive TMS (rTMS) upregulates neurogenic factors expressions (BDNF) in an AD mouse model



rTMS elevates concentration of dopamine and gene expression of dopamine receptor DR4 in AD mouse model. **Dopamine** is the main regulator of **synaptic plasticity**

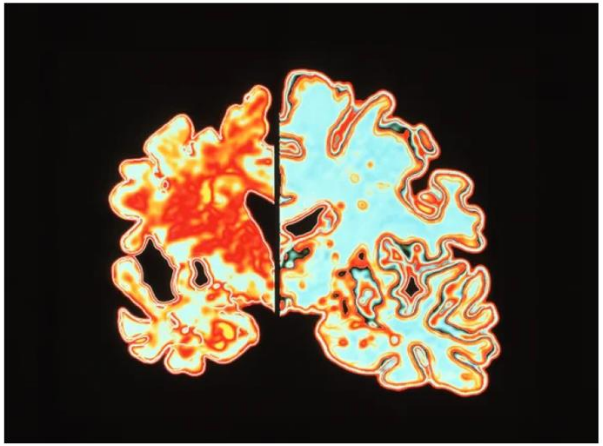
Interventional strategies – rTMS



Could Magnetic Brain Stimulation Help People with Alzheimer's?

A technology that uses magnetism to regulate neural activity shows a small benefit in patients with mild forms of the disease

By Esther Landhuis on May 18, 2017



[INVALID] Computer graphic of a vertical (coronal) slice through the brain of an Alzheimer patient (*at left*) compared with a normal brain (*at right*). Credit: PASIEKA *Getty Images*

://www.scientificamerican.com/article/could-magnetic-brain-stimulation-help-people-with-alzheimer-rsquo-s/

Interventional strategies – rTMS

eNeuro Review

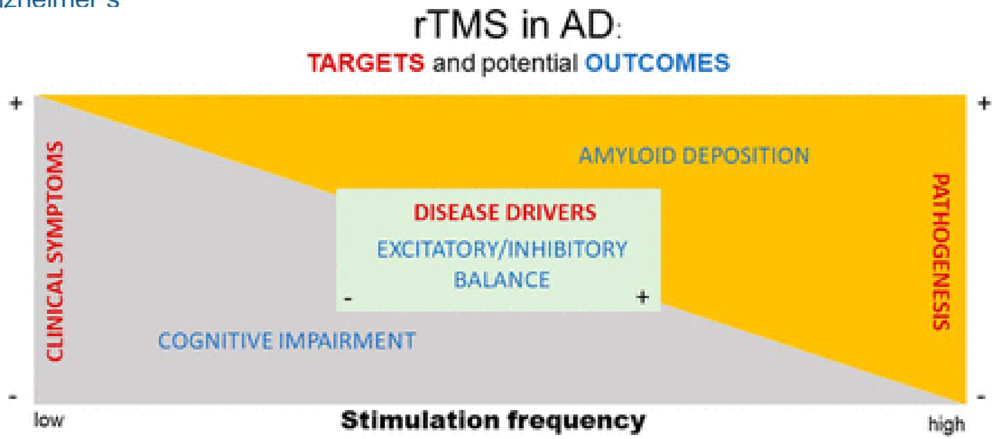
Disorders of the Nervous System

Transcranial Magnetic Stimulation in Alzheimer's Disease: Are We Ready?

Marina Weiler, Kevin C. Stieger, Jeffrey M. Long, and Peter R. Rapp

https://doi.org/10.1523/ENEURO.0235-19.2019

Repetitive TMS as therapeutic tool

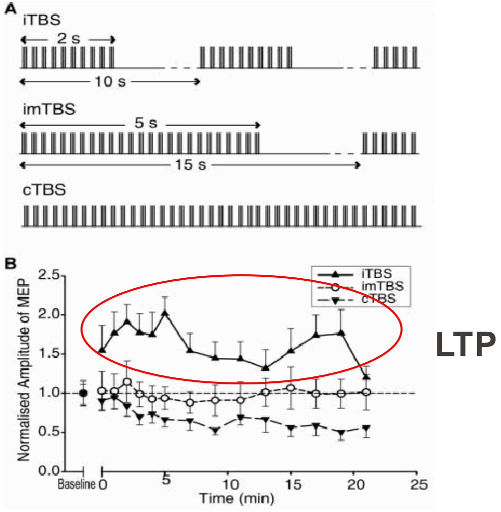


Significance Statement

There is an urgent need for the development of new, effective strategies in the battle against Alzheimer's disease (AD). Transcranial magnetic stimulation (TMS) has emerged as a promising possibility, but evidence regarding long-term efficacy and mechanism of action is limited. Among the major unresolved issues, findings linking the effects of TMS on excitatory/inhibitory balance with mechanisms of AD pathogenesis merit careful consideration. Our survey of clinical TMS studies in AD alongside basic research aims to move the area forward toward effective treatment development using noninvasive brain stimulation.

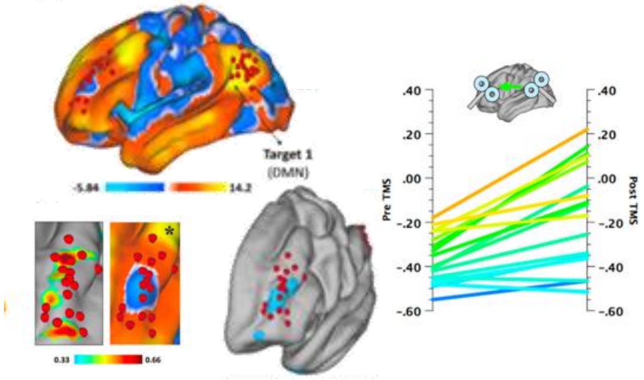
Interventional strategies – rTMS

- rTMS **promotes brain plasticity** by activating mechanisms of synaptic plasticity such as **long-term potentiation (LTP)**



Huang et al., Neuron 2005

- rTMS increases both local and distributed brain activity, **rewiring brain connections** and leading to **changes in network connectivity** with an **impact on cognition**



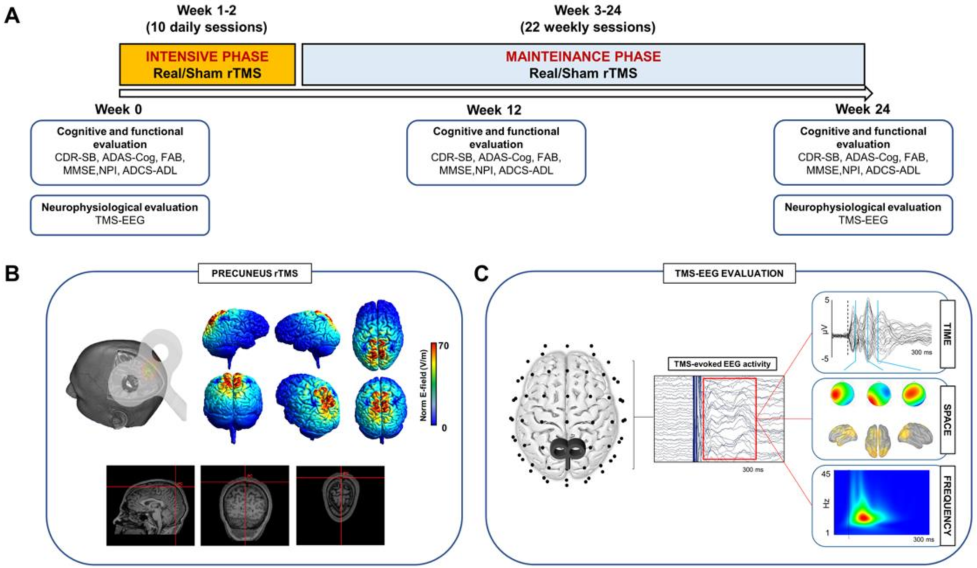
Santarnecchi et al.. Human Brain Mapping 2018

https://doi.org/10.1093/brain/awac285 BRAIN 2022: 00; 1–11 | 1

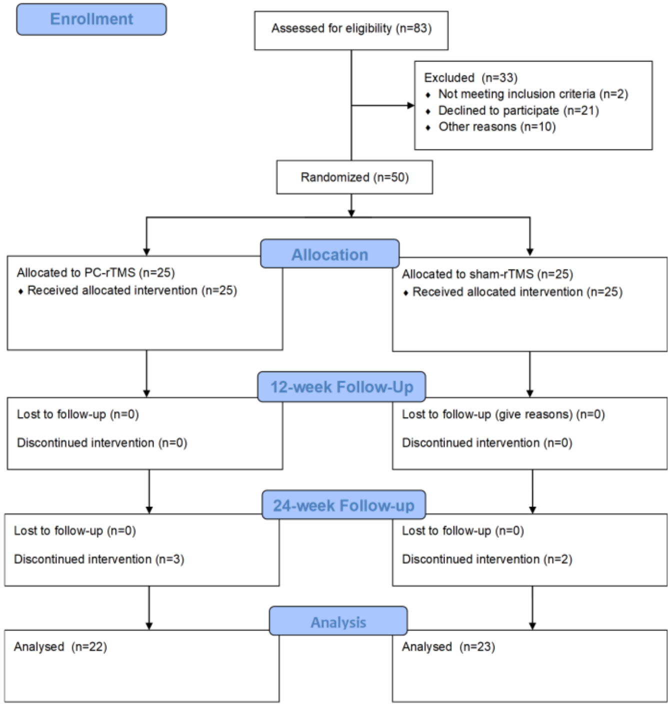
BRAIN
CLINICAL TRIAL

Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial

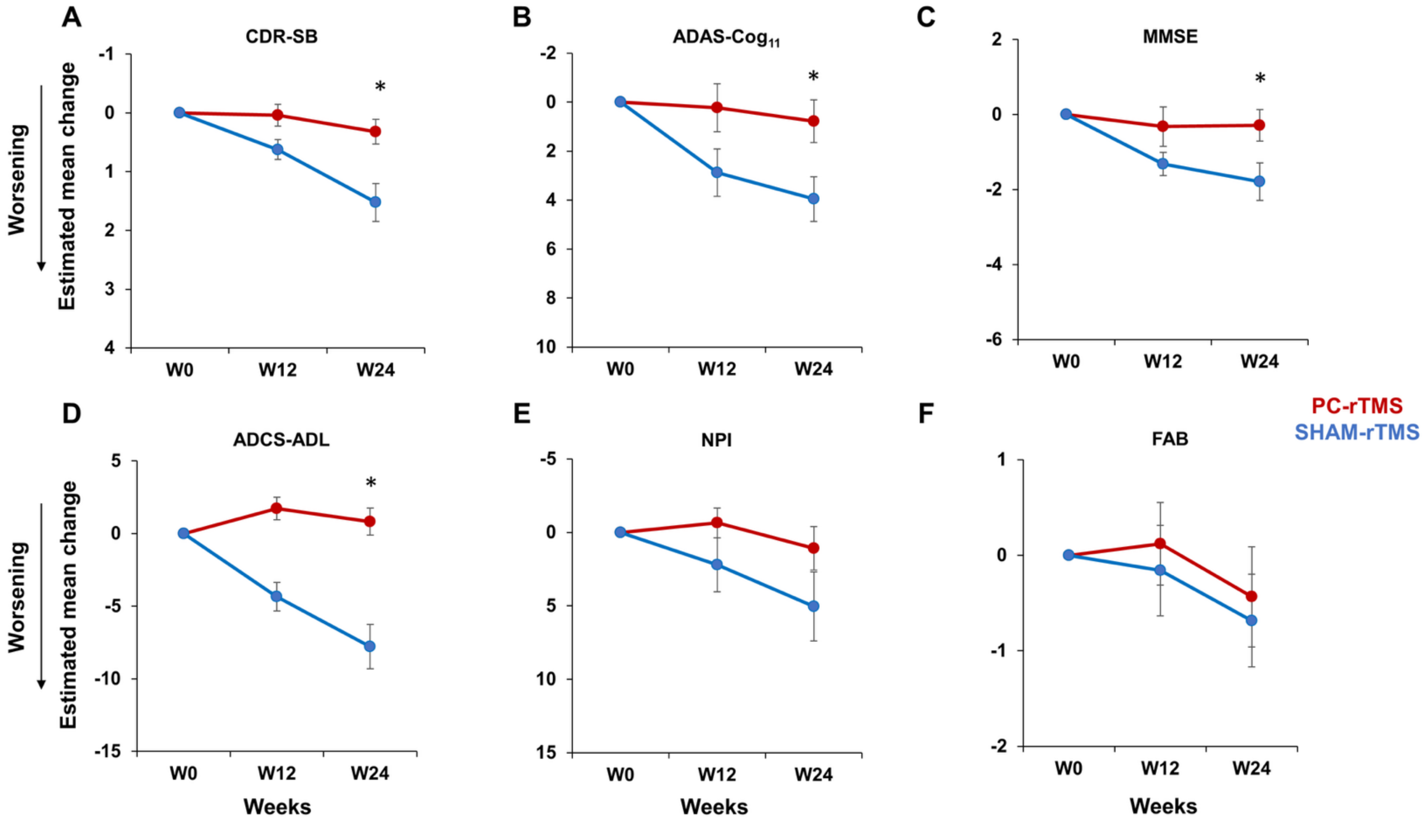
Giacomo Koch,[1,2] Elias Paolo Casula,[1] Sonia Bonnì,[1] Ilaria Borghi,[1] Martina Assogna,[1,3] Marilena Minei,[1] Maria Concetta Pellicciari,[1] Caterina Motta,[1] Alessia D'Acunto,[1] Francesco Porrazzini,[1] Michele Maiella,[1] Clarissa Ferrari,[4] Carlo Caltagirone,[1] Emiliano Santarnecchi,[5] Marco Bozzali[6,7] and Alessandro Martorana[1,3]



Flow diagram



Koch et al., *Brain 2022*

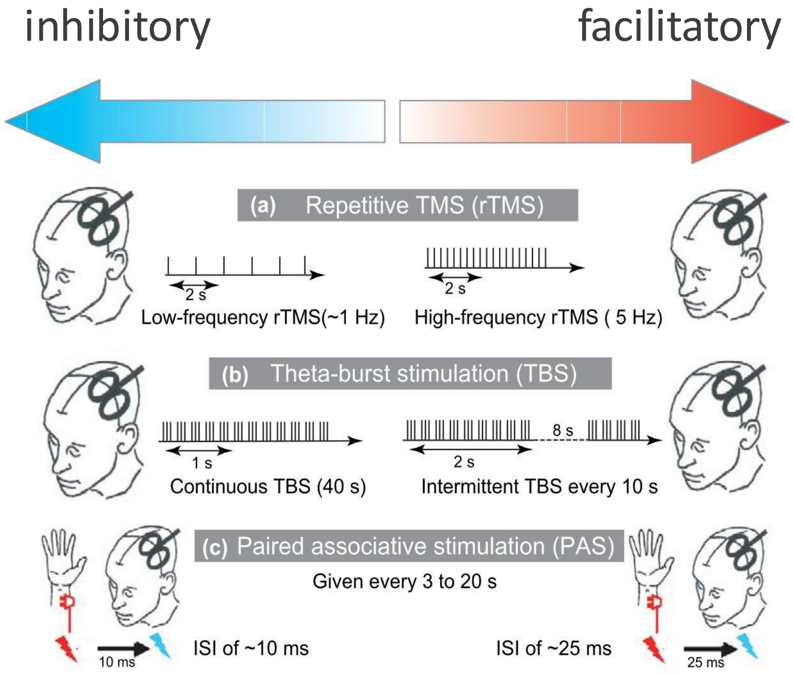


Koch et al., *Brain 2022*

Take home

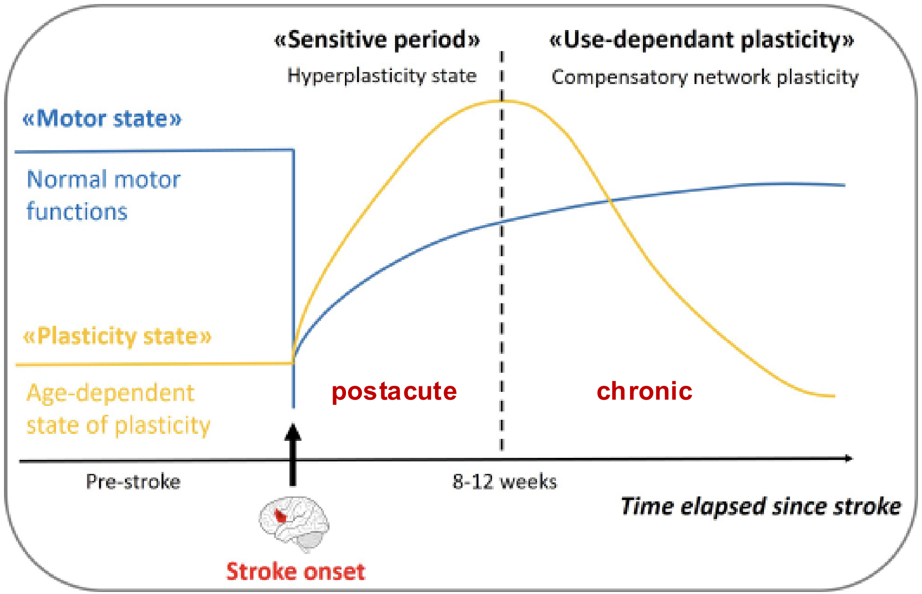
- TMS combined with EEG may be used as a novel biomarker of synaptic dysfunction to predict disease course and response to therapy in patients with Alzheimer’s disease.
- Cortical plasticity, hyperexcitability and gamma oscillatory activity are the most promising measures.
- Repetitive transcranial magnetic stimulation may slow down cognitive and functional decline in Alzheimer’s disease.
- Non-invasive brain stimulation of the default mode network could represent a novel therapeutic approach in Alzheimer’s disease patients.

Clinical applications – rTMS



Quartarone *et al.* 2006 TINS

Course of stroke-related changes



Raffin & Hummel *et al.* 2018 Neuroscientist

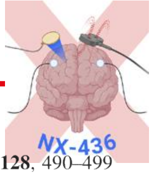
Quartarone *et al.* 2006 TINS, Ziemann (2008) BrainStim; Hummel & Cohen (2005) Curr Op Neurol; Grefkes & Fink (2014) Lancet Neurol

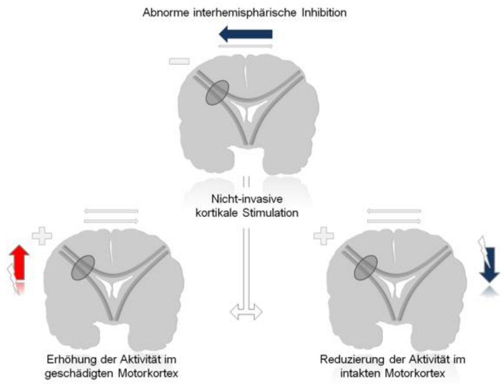
Stroke rehabilitation – "unsatisfactory"

- **2 Mio stroke patients in Europe suffer from long-term deficits**
- **20% of stroke survivors remain severely impaired**
- **Effects are so far not satisfactory (<20% back to work)**
- **No effective treatment strategy for (severe) upper-limb impairment**

EPFL

NIBS for stroke recovery – 20 years ago





For review Di Pino *et al.* Nat Nsc Reviews (2014); Hummel & Cohen Lancet Neurol(2006)

doi:10.1093/brain/awh369 *Brain* (2005), **128**, 490–499

Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke

Friedhelm Hummel,[1,2] Pablo Celnik,[1] Pascal Giraux,[1] Agnes Floel,[1] Wan-Hsun Wu,[1] Christian Gerloff[2] and Leonardo G. Cohen[1]

Neurology
August 09, 2005; 65 (3) BRIEF COMMUNICATIONS

Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke

Eman M. Khedr, Mohamed A. Ahmed, Nehal Fathy, John C. Rothwell

First published August 8, 2005, DOI: https://doi.org/10.1212/01.wnl.0000173067.84247.36

Transcranial direct current stimulation of the unaffected hemisphere in stroke patients

NeuroReport

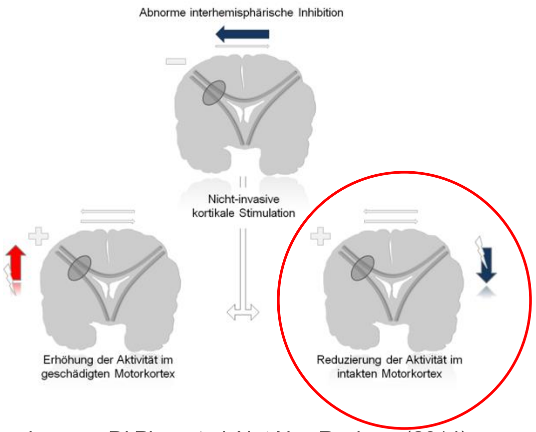
Fregni, Felipe[a] *; Boggio, Paulo S.[b c d] *; Mansur, Carlos G.[c]; Wagner, Tim[a]; Ferreira, Merari J. L.[d]; Lima, Moises C.[c]; Rigonatti, Sergio P.[c]; Marcolin, Marco A.[c]; Freedman, Steven D.[a]; Nitsche, Michael A.[e]; Pascual-Leone, Alvaro[a]

Author Information

s

NeuroReport 16(14):p 1551-1555, September 28, 2005. | ***DOI:*** 10.1097/01.wnr.0000177010.44602.5e

Functional heterogeneity – controversy intact hemisphere



For review Di Pino *et al.* Nat Nsc Reviews (2014); Hummel & Cohen Lancet Neurol(2006)

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*

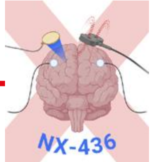
ASNR American Society of Neurorehabilitation
Original Research Article
Neurorehabilitation and Neural Repair
2020, Vol. 34(9) 856–867
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1545968320948610
journals.sagepub.com/home/nnr
SAGE

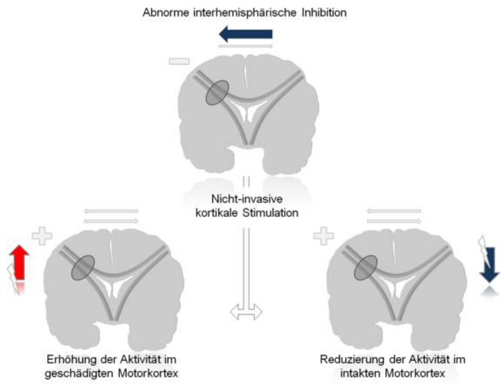
Low-Frequency Repetitive Transcranial Magnetic Stimulation Over Contralesional Motor Cortex for Motor Recovery in Subacute Ischemic Stroke: A Randomized Sham-Controlled Trial

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]

For review Lefaucheur (2020); Hummel *et al.* (2008)

Functional heterogeneity – controversy intact hemisphere





For review Di Pino *et al.* Nat Nsc Reviews (2014); Hummel & Cohen Lancet Neurol(2006)

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, Lyr d Vox, MD, Ana Durand-Sanchez, MD, Marcia Bockbrader, MD, PhD, La ierard E. Francisco, MD, Carolyn L. Kinney, MD, Charles Y. Liu, PhD, MD ICHE Trial Investigators*

?

Original Research Article

ASNR AMERICAN SOCIETY OF NEUROREHABILITATION

Neurorehabilitation and Neural Repair
2020, Vol. 34(9) 856–867
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1545968320948610
journals.sagepub.com/home/nnr
SAGE

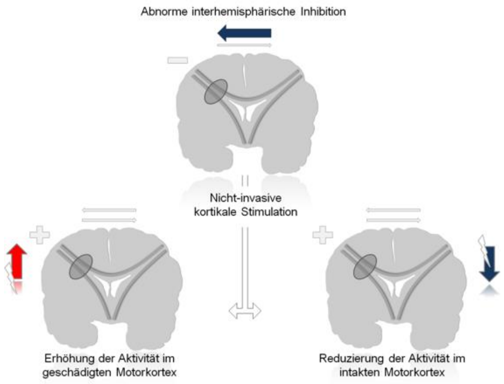
Low-Frequency Repet inial Magnetic Stimulation esional Motor Cortex for Motor Recovery in Subacute Ischemic Stroke: A Randomized Sham-Controlled Trial

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]

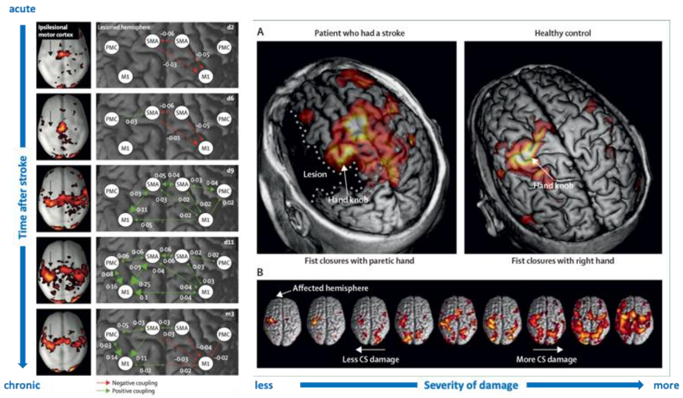
For review Lefaucheur (2020); Hummel *et al.* (2008)

EPFL

Functional heterogeneity – controversy intact hemisphere



For review Di Pino et al. (2014); Hummel & Cohen (2006)



For review Guggisberg *et al.* (2019); Koch et al. (2017); Grefkes & Fink (2014)

Intact hemisphere **supports** residual function/recovery
- by additional ‘computational’ power
- enhanced connectivity with the lesioned hemisphere
- by uncrossed projections

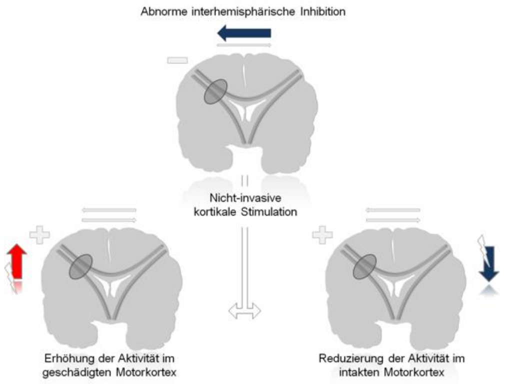
Intact hemisphere **impairs** residual function/recovery
- maladaptive changes
- enhanced inhibitory impact on the lesioned hemisphere

Impacts massively on the **NIBS strategy** (inhibitory vs. facilitatory)

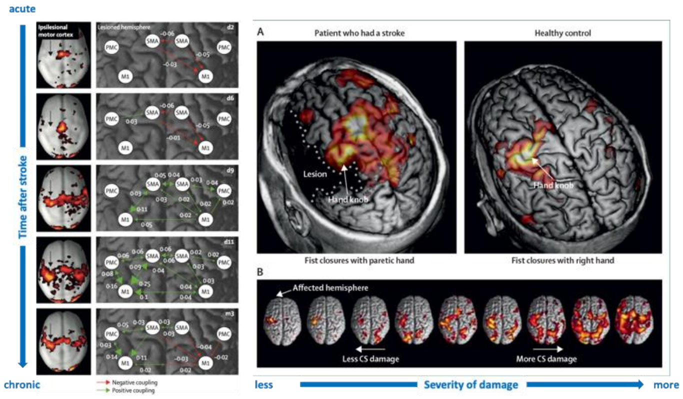
Knowledge of **individual** functional role will lead NIBS intervention, more homogenous and maximized effects of NIBS

For review Lefaucheur (2020); Hummel *et al.* (2008)

Functional heterogeneity – controversy intact hemisphere



For review Di Pino et al. (2014); Hummel & Cohen (2006)



For review Guggisberg *et al.* (2019); Koch et al. (2017); Grefkes & Fink (2014)

Intact hemisphere **supports** residual function/recovery
- by additional 'computational' power
- enhanced connectivity with the lesioned hemisphere
- by uncrossed projections

Intact he ...phere **impairs** residual function/recovery
- mal ...anges
- en ...y impact on the lesioned hemis...

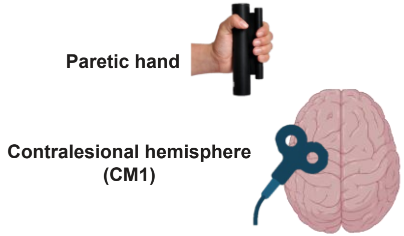
Impacts massively on the **NIBS** ...
(inhibitory vs. facilitatory)

Knowledge of **individual** functional role will lea.. NIBS intervention, more homogenous and maximized effects of NIBS

Functional role?

For review Lefaucheur (2020); Hummel *et al.* (2008)

Functional heterogeneity – controversy intact hemisphere



Virtual lesion (TMS) **cM1** during a motor task - transient disruption

Gain in performance - cM1 is **maladaptive**

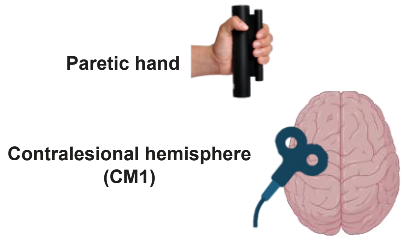
Decline in performance - cM1 is **adaptive**

Personalised group
Inhibitory NIBS

Personalised group
Excitatory NIBS

Fleury *et al.* (in preparation)

Functional heterogeneity – controversy intact hemisphere



Virtual lesion (TMS) **cM1** during a motor task - transient disruption

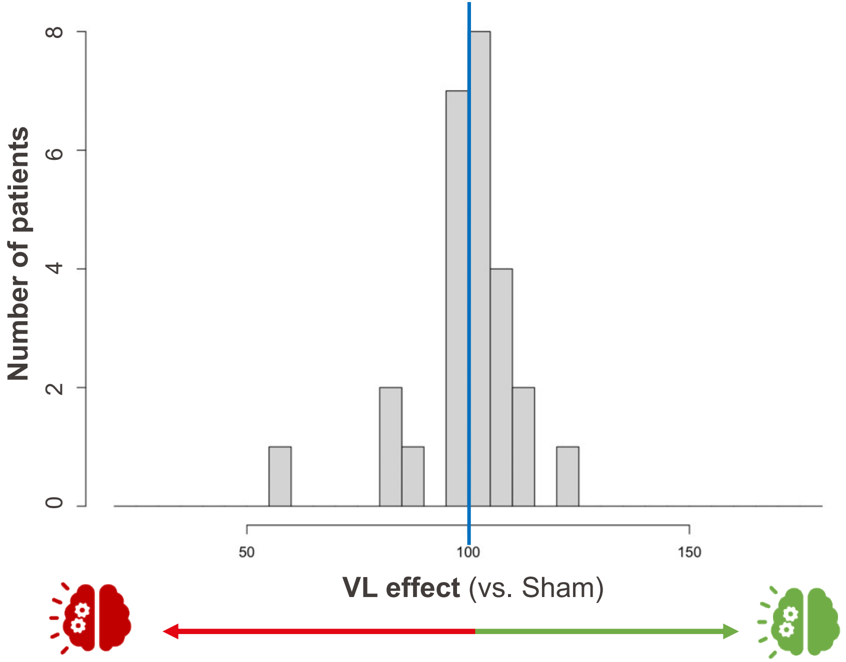
Gain in performance - cM1 is **maladaptive**

Decline in performance - cM1 is **adaptive**

Personalised group
Inhibitory NIBS

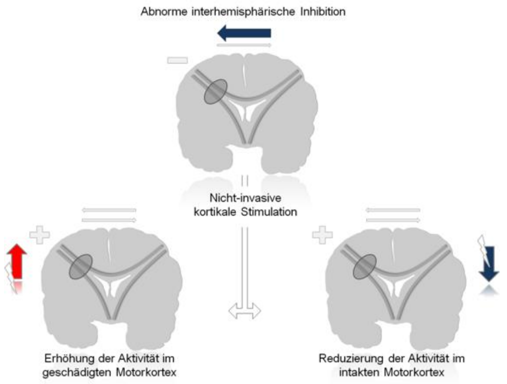
Personalised group
Excitatory NIBS

N=26 stroke patients

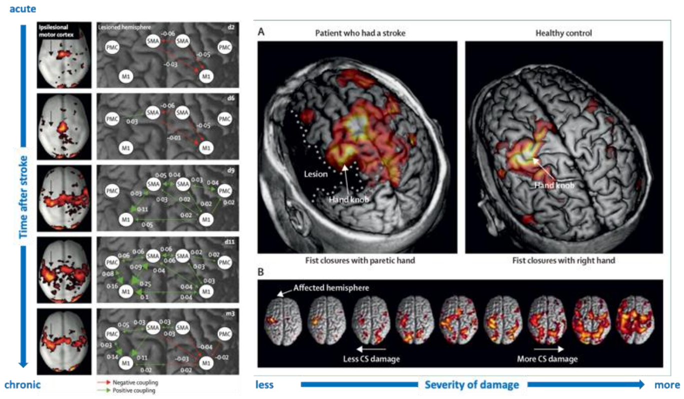


Fleury *et al.* (in preparation)

Functional heterogeneity – controversy intact hemisphere

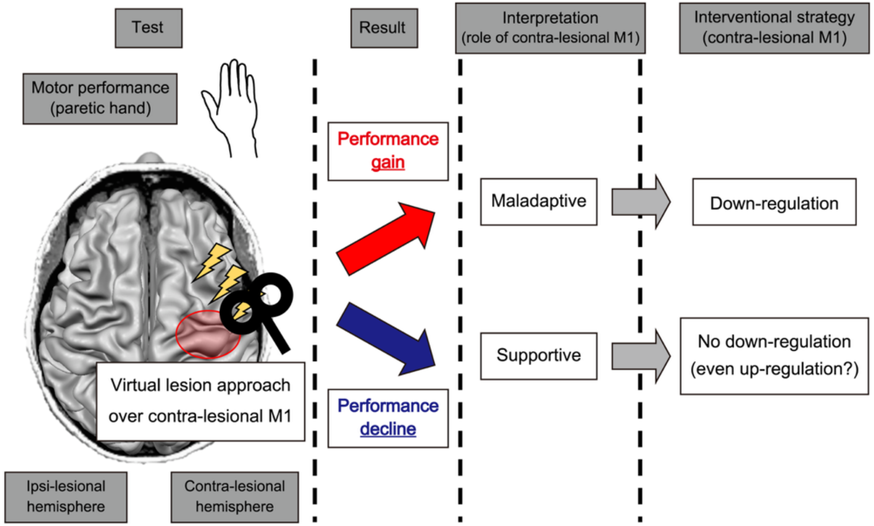


For review Di Pino et al. (2014); Hummel & Cohen (2006)



For review Grefkes & Fink (2014); Guggisberg *et al.* (2019)

Steering of NIBS by functional role of contralesional MC



For review Morishita *et al.* (2017); Raffin *et al.* (2018)

Accelerated rTMS protocols

www.nature.com/npp

American College *of* Neuropsychopharmacology

REVIEW ARTICLE OPEN

Check for updates

Accelerated TMS - moving quickly into the future of depression treatment

Sanne J. H. van Rooij[1], Amanda R. Arulpragasam[2,3], William M. McDonald[1] and Noah S. Philip[2,3]✉

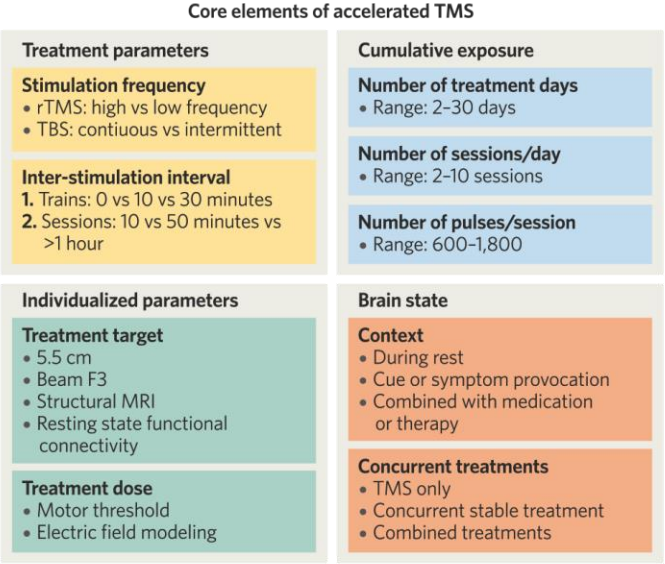


Fig. 1 Core elements of accelerated TMS. The nine core elements considered in this review for accelerated TMS. rTMS repetitive transcranial magnetic stimulation, TBS theta-burst stimulation, MRI magnetic resonance imaging.

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]

e.g., FDA approved treatment for Depression

Safety – TMS

Seizure induction - Caused by spread of excitation. Single-pulse TMS and rTMS has produced seizures (rarely, last 10 years less than 10 cases worldwide). Visual and/or EMG monitoring for after discharges as well as spreading excitation may reduce risk.

Hearing loss - TMS produces loud click (90-130 dB) in the most sensitive frequency range (2–7 kHz). rTMS = more sustained noise. Reduced considerably with earplugs.

Local neck pain and headaches - Related to stimulation of local muscles and nerves, site and intensity dependent. Particularly uncomfortable over fronto-temporal and cerebellar regions.

Engineering safety - TMS equipment operates at lethal voltages of up to 4 kV. The maximum energy in the capacitor is about 500 J, equal to dropping 100 kg from 50 cm on your feet. So don’t put your tea on it.

EPFL

Safety – TMS

Maximum safe duration of single rTMS train at 110% MT

Frequency (Hz)	Max. duration (s)
1	1800+
5	10
10	5
20	1.6
25	.84

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

ELSEVIER

Review

Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

Simone Rossi [a,*], Andrea Antal [b,c], Sven Bestmann [d], Marom Bikson [e], Carmen Brewer [f], Jürgen Brockmöller [g], Linda L. Carpenter [h], Massimo Cincotta [i], Robert Chen [j], Jeff D. Daskalakis [k], Vincenzo Di Lazzaro [l], Michael D. Fox [m,n,o], Mark S. George [p], Donald Gilbert [q], Vasilios K. Kimiskidis [r], Giacomo Koch [s], Risto J. Ilmoniemi [t], Jean Pascal Lefaucheur [u,v], Letizia Leocani [w], Sarah H. Lisanby [x,y,2], Carlo Miniussi [z], Frank Padberg [aa], Alvaro Pascual-Leone [ab,ac,ad], Walter Paulus [b], Angel V. Peterchev [ae], Angelo Quartarone [af], Alexander Rotenberg [ag], John Rothwell [d], Paolo M. Rossini [ah], Emiliano Santarnecchi [m], Mouhsin M. Shafi [m], Hartwig R. Siebner [ai,aj,ak], Yoshikatzu Ugawa [al], Eric M. Wassermann [am,2], Abraham Zangen [an], Ulf Ziemann [ao], Mark Hallett [ap,2,*],

The basis of this article began with a Consensus Statement from the IFCN Workshop on "Present, Future of TMS: Safety, Ethical Guidelines", Siena, October 17-20, 2018, updating through April 2020 [1]

Summary TMS

TMS provides an unique opportunity to determine :

I. Cortico-spinal, intra-cortical, inter-cortical physiological/ pathophysiological parameters and interactions in vivo in humans

II. Causal relationship between brain areas and behavioral functions in vivo in humans

with high topographic (mm) and temporal resolution (msec)

Summary TMS

TMS provides an unique opportunity to determine :

I. Cortico-spinal, intra-cortical, inter-cortical physiological/ pathophysiological parameters and interactions in vivo in humans

II. Causal relationship between brain areas and behavioral functions in vivo in humans

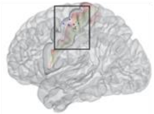
with high topographic (mm) and temporal resolution (msec)

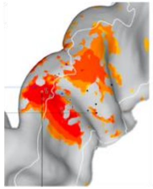
TMS provides an unique opportunity for neuromodulation :

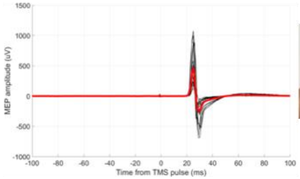
I. Study aspects of neuroplasticity in vivo in humans

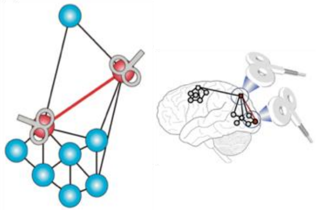
II. Modulate brain activity and respective behavior in vivo in humans

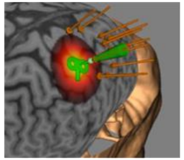
III. Use it as a therapeutic strategy for neurological and psychiatric disorders











Thank you for your attention!