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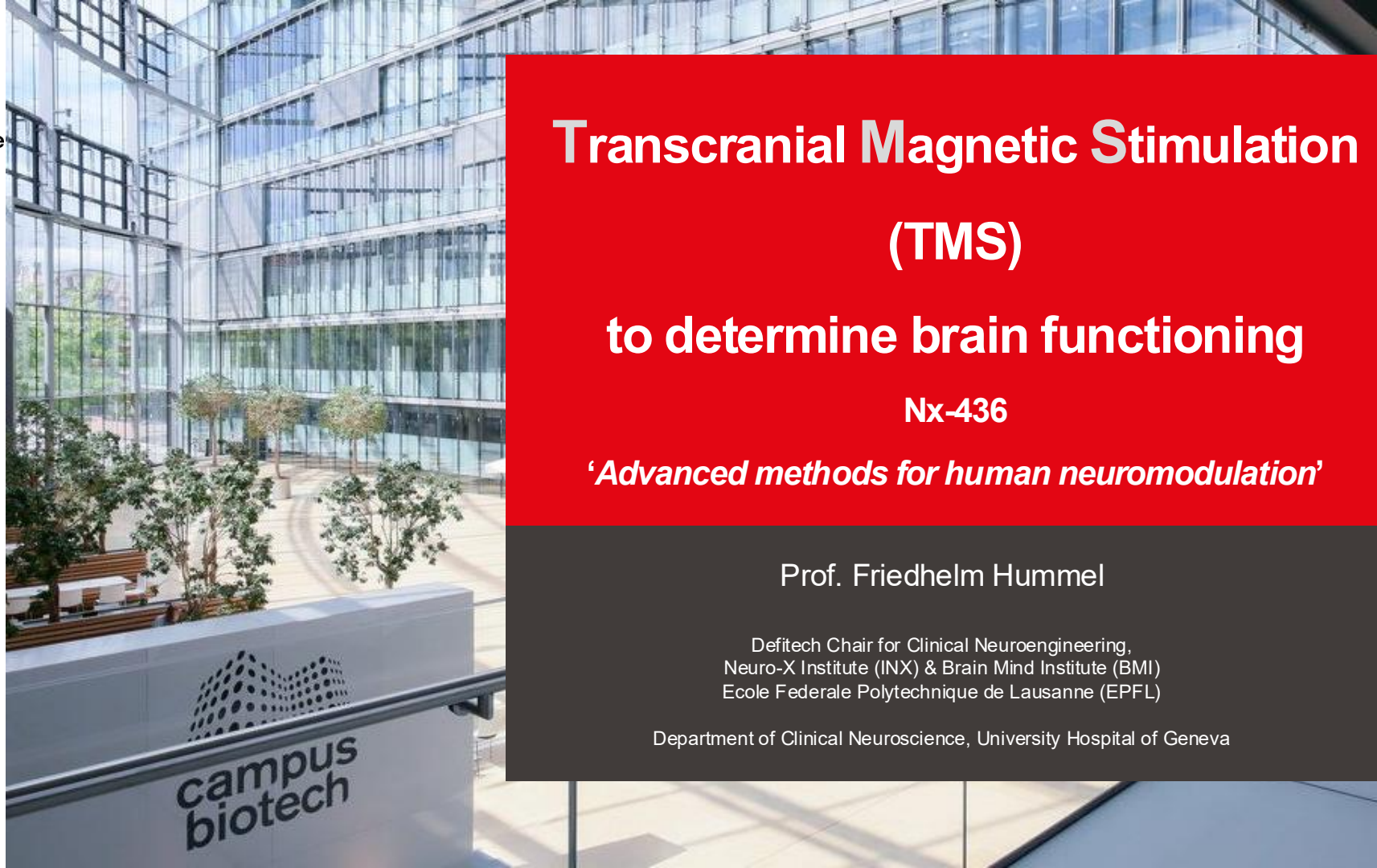

Transcranial Magnetic Stimulation (TMS) to determine brain functioning

Nx-436

'Advanced methods for human neuromodulation'

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Nx-436
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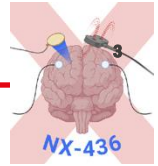
Learning goals

I. Understand the underlying concept of TMS

II. Understand how TMS can be used to determine brain functioning

Literature

(for review Lefaucheuer et al. 2020; Hummel & Cohen 2005, Siebner et al. 2003. Textbook: e.g. Transcranial Magnetic Stimulation by Rotenberg, Horvath, Pascual-Leone https://link.springer.com/book/10.1007/978-1-4939-0879-0)



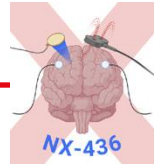
Three main areas of application for TMS:

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)

Developed in its current form 1985 by Baker *et al.*



Baker et al. suggested

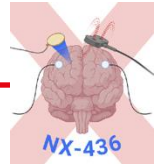
'…when the coil is placed on the scalp, over the appropriate region of the motor cortex, movements of the opposite hand or leg are easily obtained without causing distress or pain…."

Further,

"…each twitch, in response to a single stimulus, is accompanied by a muscle action potential just as with electrical stimulation through the scalp or at peripheral sites. Stimulation is assumed to be due to the current induced in the tissue by the rapid, time-varying magnetic field"

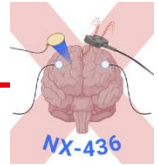
(Baker *et al.* 1985 Lancet).

Basics of TMS



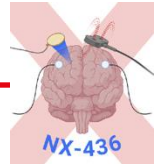
- Peak voltage up to 2800 V
- Peak coil currents up to several thousands of amperes
- Resulting maximum
  - magnetic fields reaching 2 T
  - electric fields reaching 200 V/m
- Requires magnetic field energy of 36 Joules to stimulate the brain (1000x higher than tES)
- energy inefficiency: poor electromagnetic coupling between the TMS coil and the human head.
- but much more tolerable than tES

Basics of TMS



- electric field induced by TMS is strongest on the surface of the head and attenuates rapidly in depth (zero in the center of the head)
- steep depth focality trade-off
  - computer simulations / field measurements suggest that the electric field decays to half of its maximum value in the brain at a depth of approximately 1.3–1.5 cm from the pial surface (figure-of-eight TMS coils
  - by enlarging the TMS coils, the half-maximum electric field penetration in
  - depth can be increased about 3.5 cm, but leads to a massive reduction of the coil focality up to 25 fold
- focality of TMS coils
  - spatial focality of TMS is approximately <1–2 cm^2
  - functionally: representation of an individual finger movement

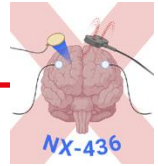
Basics of TMS



Neural Elements Directly Activated by TMS

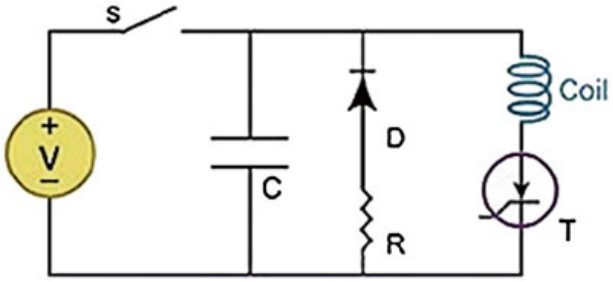
- brief electric field pulses, such as generated by TMS, depolarize and activate predominantly myelinated axons (as opposed to neuronal soma, dendrites, or unmyelinated axons).
- myelinated axons lower thresholds for activation by exogenous electric fields than unmyelinated axons
- large diameter of axons results in lower thresholds
- TMS activates the main axon or collaterals of excitatory large pyramidal cells, layer V and layer II/III and myelinated long-distance axons of inhibitory large basket cells.
- TES excites corticospinal axons *directly* within the subcortical white matter, compatible with the generation of a D (direct) wave seen in animal and humans experiments with
- epidural recordings from the spinal cord
- In contrast, TMS incapable of activating D waves, but preferentially excites corticospinal neurons transsynaptically, generating only I (indirect) waves

Basics of TMS



TMS is essentially electrical stimulation of the brain that is noninvasive, electromagnetically induced, and well-tolerated.

Overview - System



Charging system — generates the current used to generate the magnetic field essential to TMS (8,000 A within several 100 ms).

One or more energy storage capacitors — allow for multiple energetic pulses to be generated, stored, and discharged in quick succession (typical voltage rating of 7.5 kV).

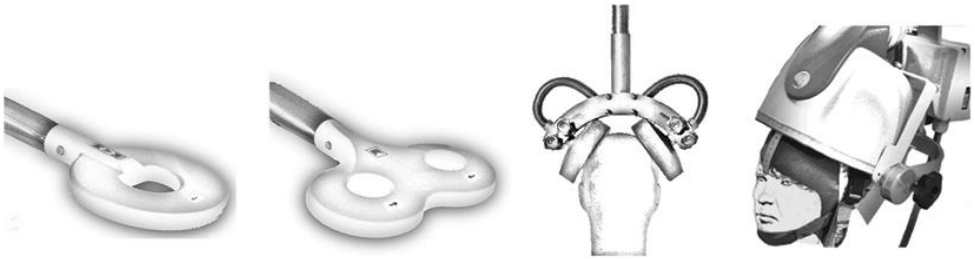
Energy recovery circuitry— allows for the main unit to recharge following discharge.

Thyristors — are electrical devices capable of switching large currents over a short period of time. Bridge between the capacitor and coil, transferring 500 J between the two in less than 100 ms.

Pulse-shape circuitry — can be used to generate either monophasic or biphasic pulses

Stimulating coils — one or more well-insulated coils of copper wire (frequently housed in a molded plastic cover).

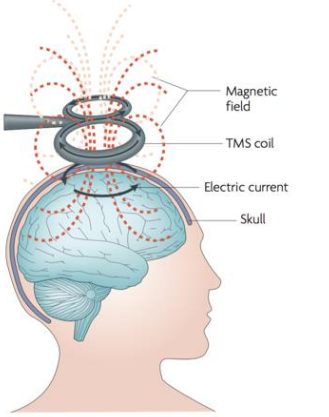
Overview - Coils



Circular or Round Coil— oldest and simplest TMS coil design. A single, centrally located coil generates a spherical magnetic fi eld perpendicular to the coil itself

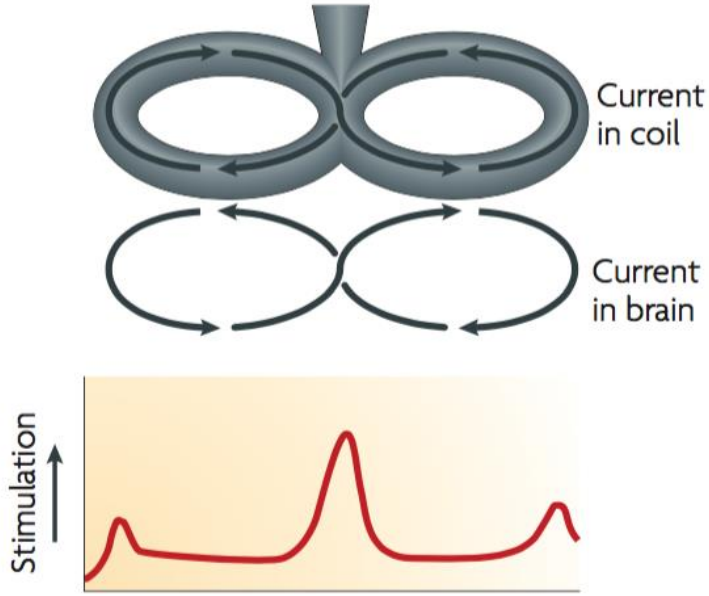
Figure-of-8 (Butterfly) Coil— Easily the most recognizable and utilized of coil designs, the figure-of-8-coil is formed by abutting two single, circular coils against one another. Although the pattern from each individual coil may be relatively non-focal, the combined magnetic field is stronger than in surrounding regions and is relatively easy to determine spatially

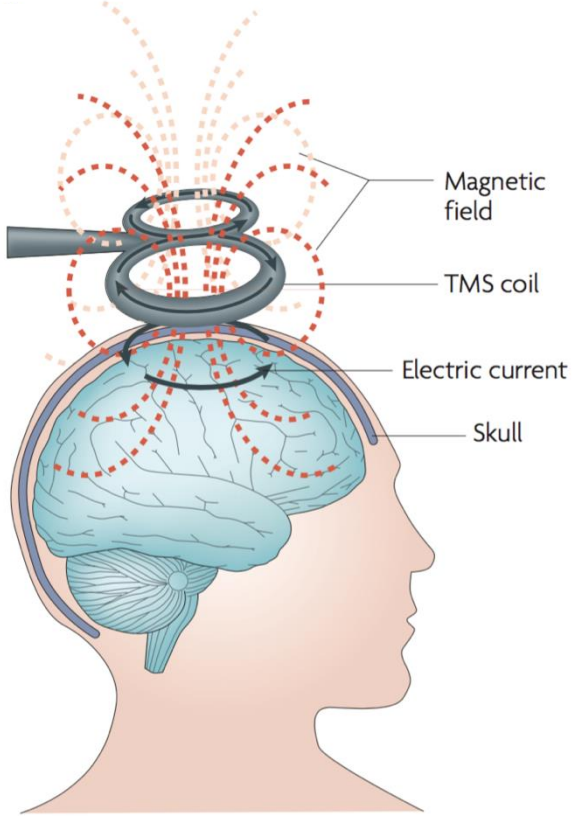
H-Coil— aims to stimulate deeper, non-superficial cortical layers. This is achieved by having a more complex coil design with several planes such that the decay function of the generated magnetic field is less steep and the current reaches deeper into the brain (although the superficial cortical layers still are exposed to the strongest field). H-Coil may be able to stimulate neural structures up to 6 cm below the cortical surface



Ridding & Rothwell, 2007

Overview - Coils

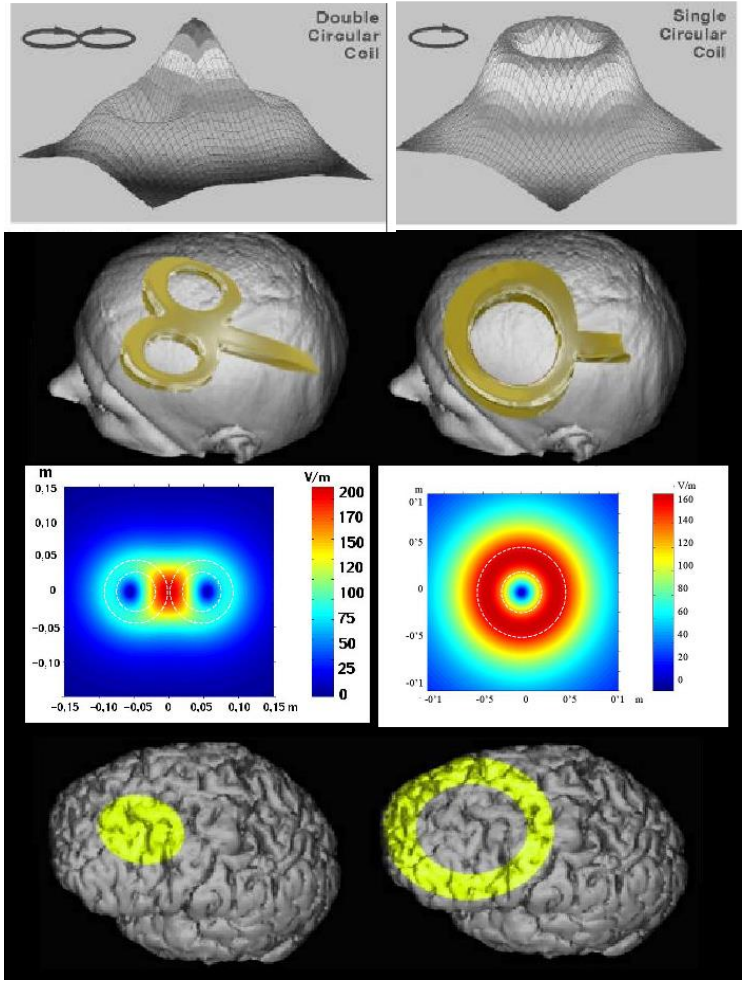




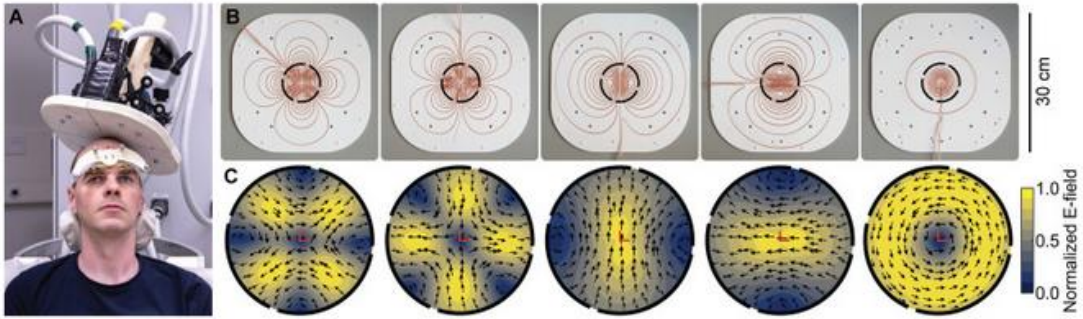
Ridding & Rothwell 2007 Nat Rev Neurosci

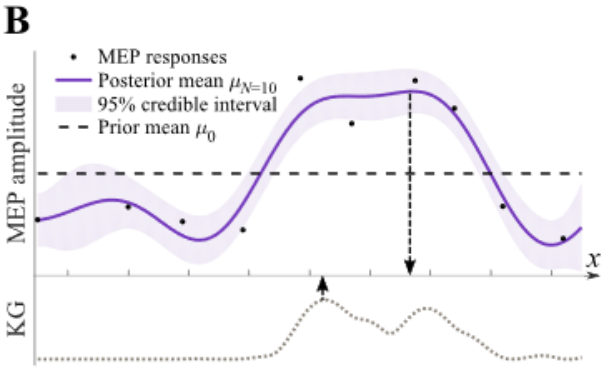
Overview - Coils

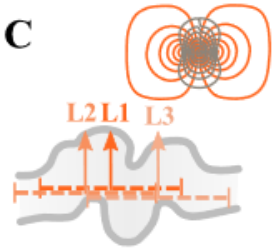
The geometry of the coil determines the focality of the magnetic field and of the induced current - hence also of the targeted brain area.

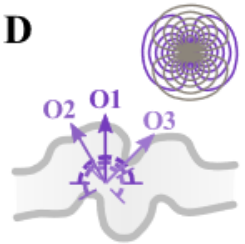


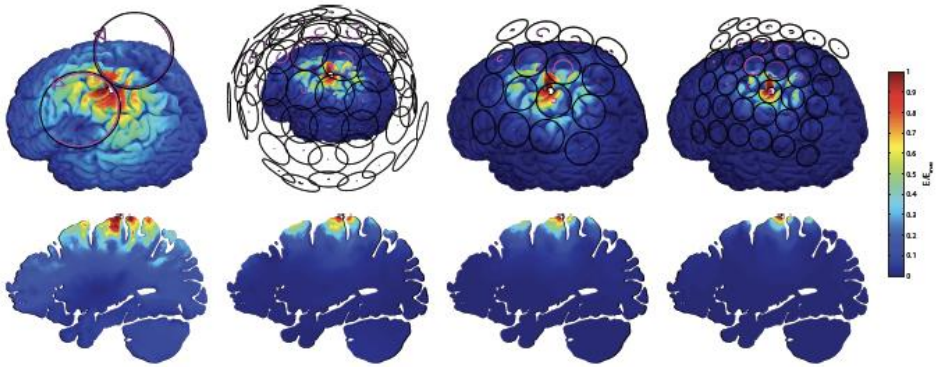
Next generation coil setups





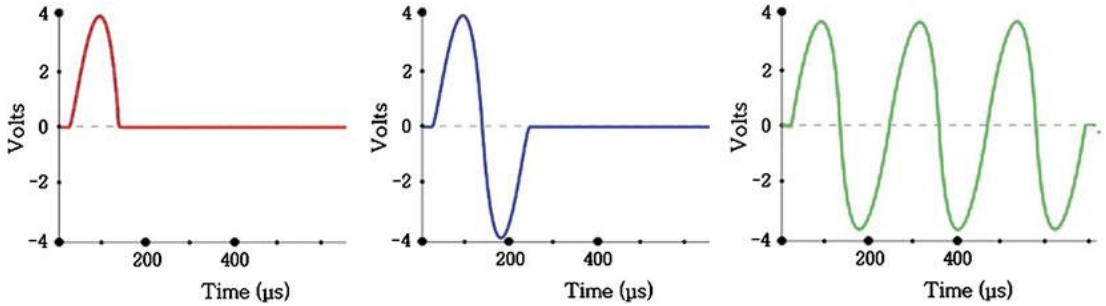






Tervo et al., NeuroImage, 2020 ; Nieminen et al., *Brain stim.*, 2022

Overview – Pulse Waveforms, Pulse Strength

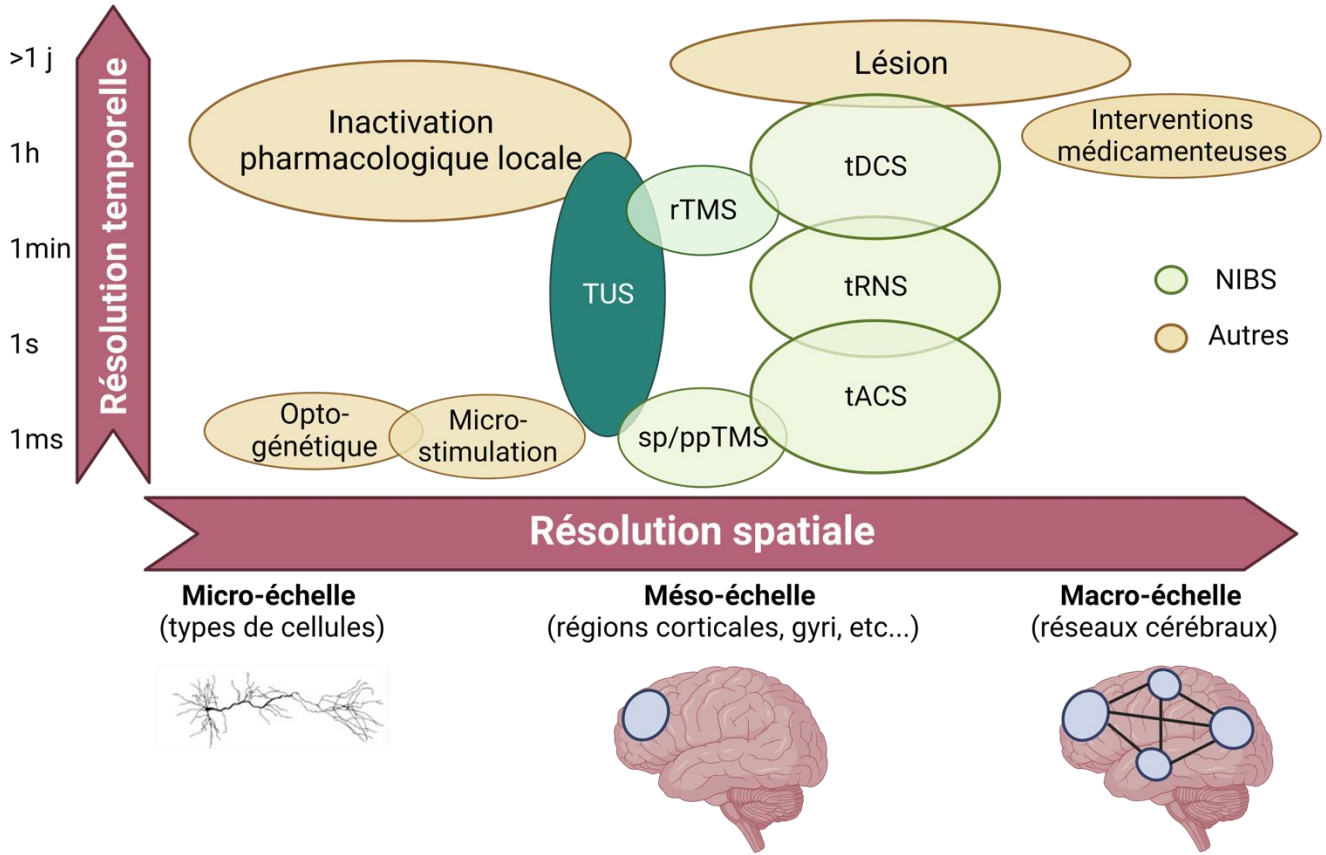


Monophasic pulses - generate only unidirectional voltage. As the initial course of voltage (positive) through a coil would induce an opposing (negative) oscillation, in order to generate a monophasic pulse a shunting diode and power resistor must be used to dampen this natural cycle. Due to this pulse-shaping, monophasic pulses can only be delivered singularly (unless multiple energy sources are utilized).

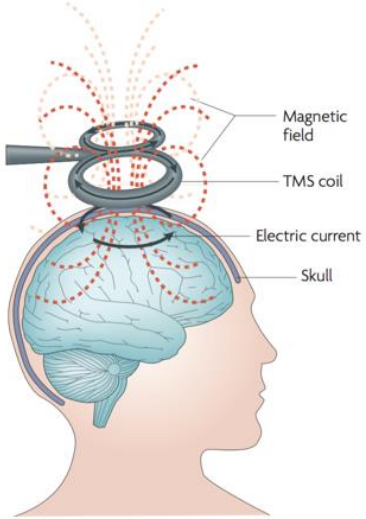
Biphasic (Polyphasic) pulses - generate full positive/negative voltage oscillations. This oscillation, in turn, causes a rapid directional shift of the initial and induced currents. This type of pulse can be terminated after a single cycle (biphasic) or after several oscillatory cycles (polyphasic pulses)

Pulse Strength - The amount of voltage passed through the stimulating coil can be adjusted. The strength of this initial current contributes to the strength of the induced current. Devices often express output current as percent of maximal output, rather than as absolute current values as these are different depending on the coils used. Frequently the applied stimulation strength will be referenced in terms of a subject's motor threshold at a specified baseline.

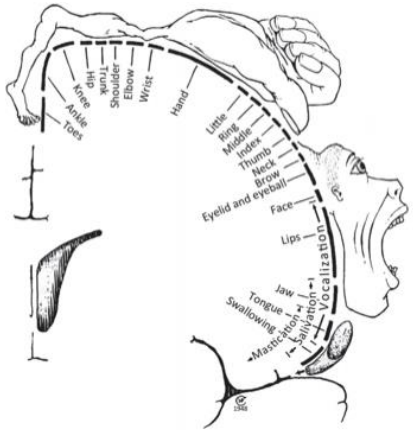
Topographic resolution



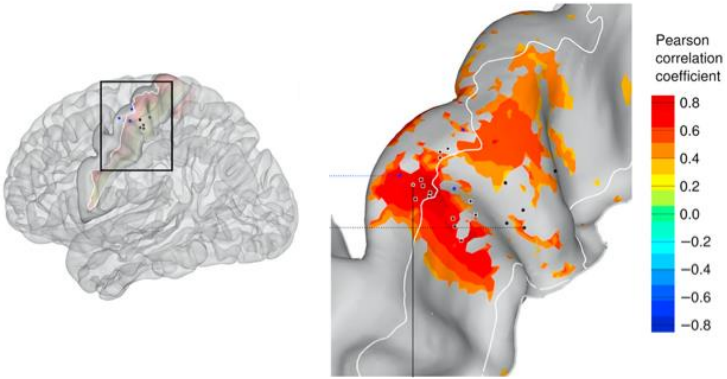
Topographic resolution



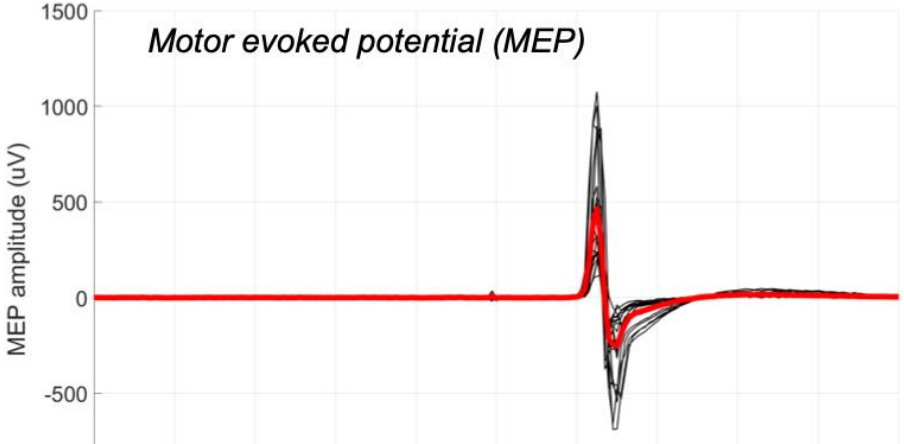
Ridding & Rothwell, 2007



Penfield & Rasmussen, 1950, Adapted from Graziano, 2016

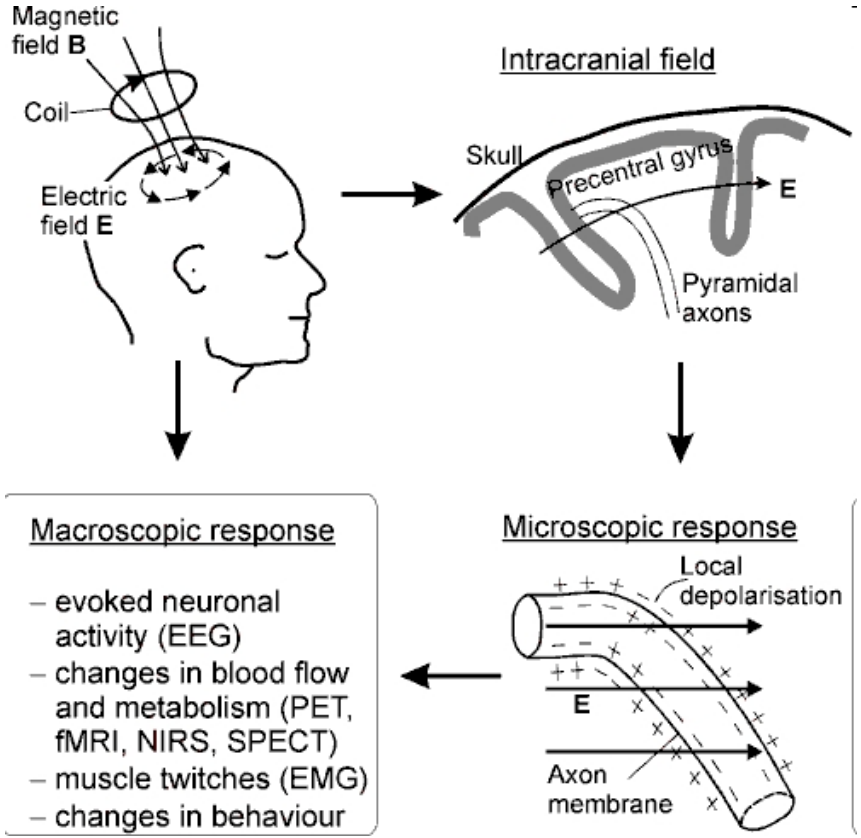


Adapted from Laakso et al., 2017

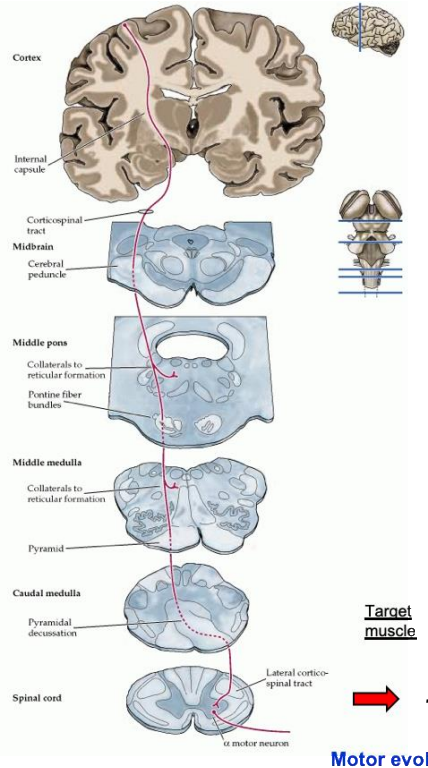


EMG

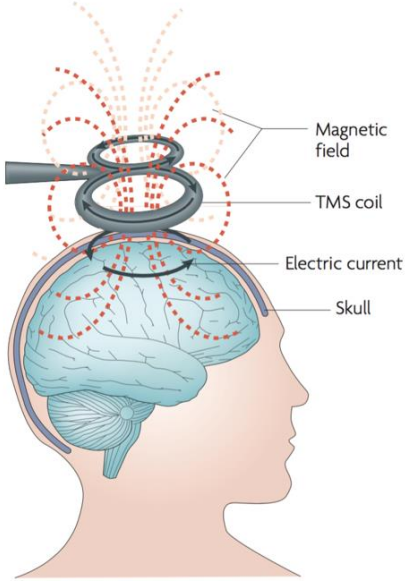
- Single pulse TMS (cortico-spinal excitability)
- Double Pulse TMS (Kujirai et al, 1993)
- Neurotransmitter systems, e.g. GABA-A-ergic, Glumatergic (Ziemann et al., 1998)
- Resting State, Event-related (Hummel et al. 2009, Heise et al. 2010, 2013, 2014)
- Interregional Interactions (Murase et al. 2004, Duque et al. 2005, Liuzzi et al. 2009, 2010)



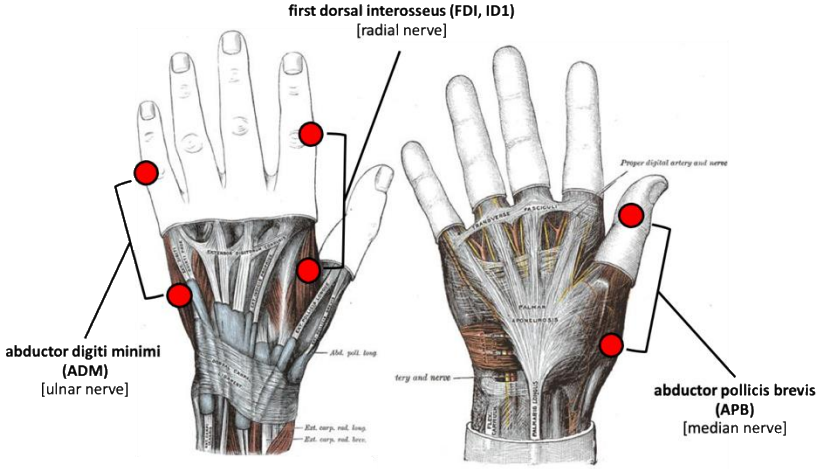
Depolarisation at the Axon. Induced electric field in direction of the axon, lowest magnetic field strength necessary to induce depolarisation



Motor evoked potential (MEP)



Ridding & Rothwell 2007 Nat Rev Neurosci



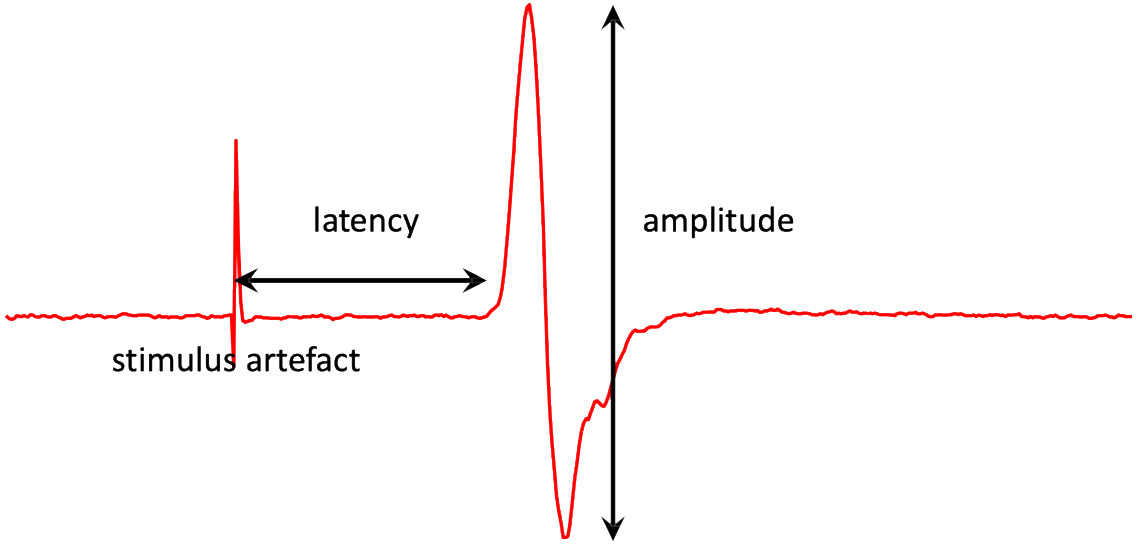
electrodes are placed in a bipolar belly-tendon montage

motor evoked potential (MEP)

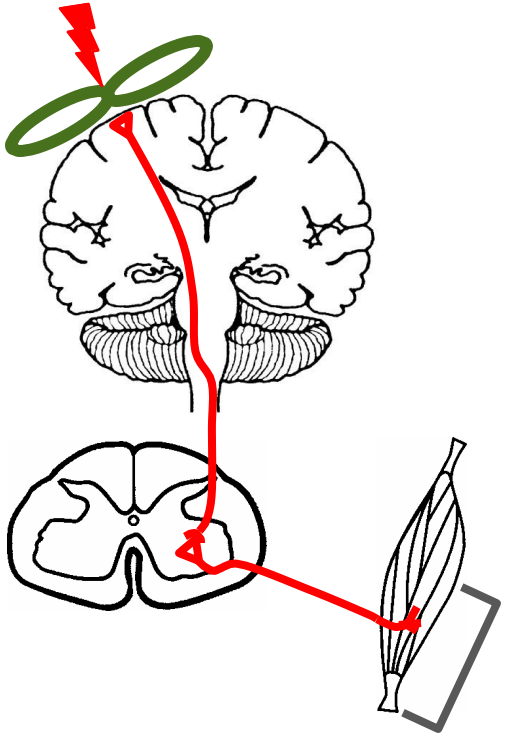
Barker, 1984

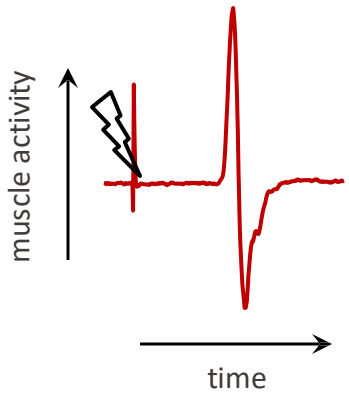
Physiological measures

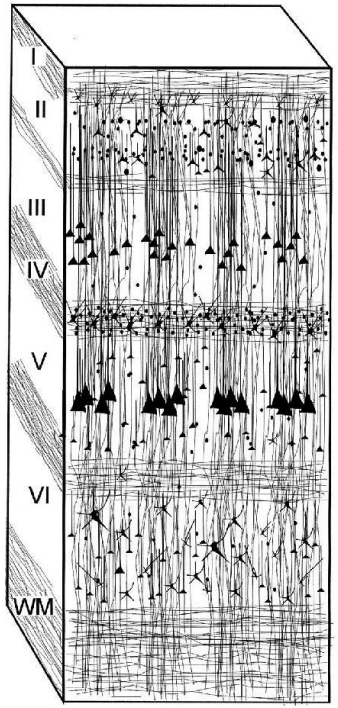
motor evoked potential (MEP)

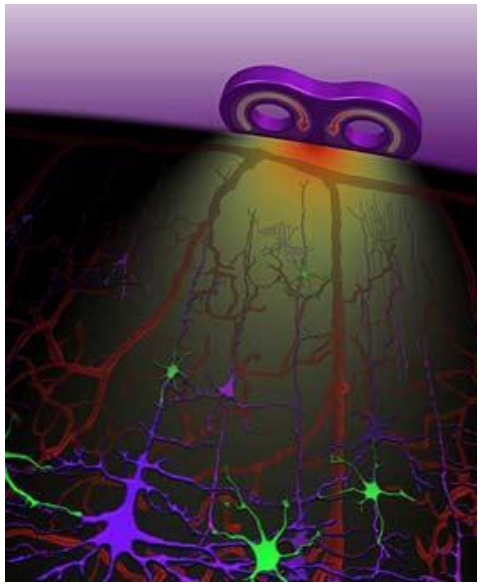


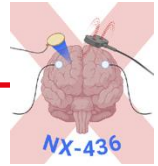
cortico-spinal system





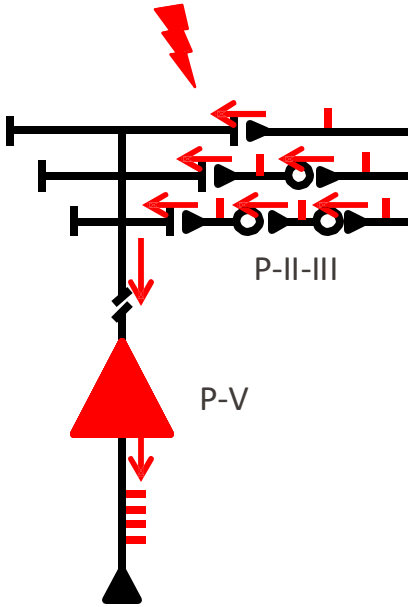






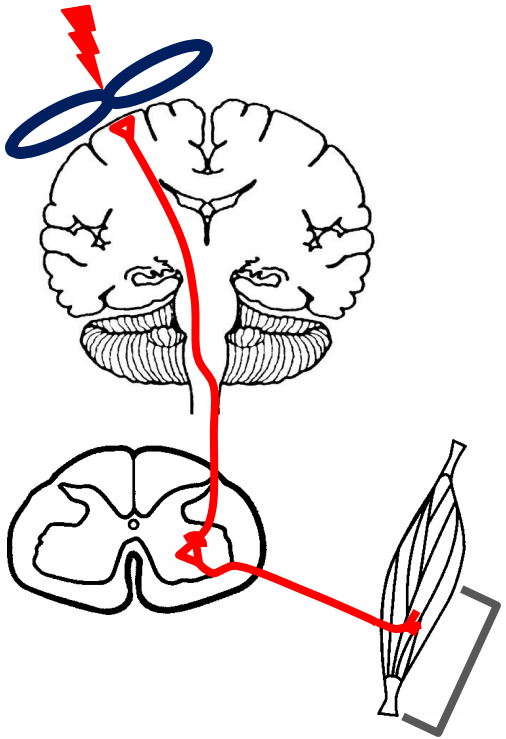
quantify: single pulse

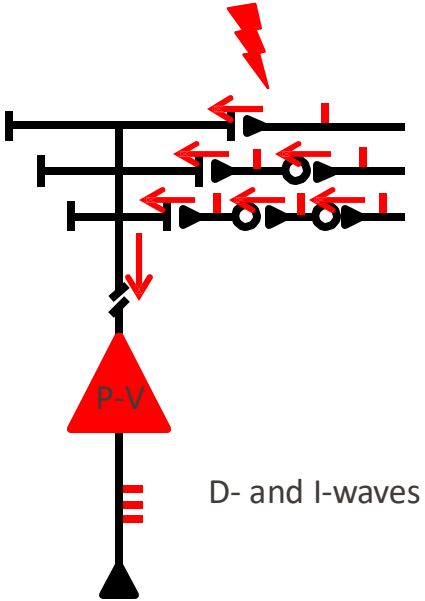
a single pulse?



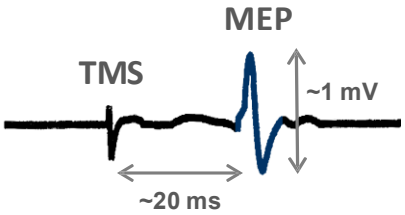
indirect (I) waves

direct (D) wave

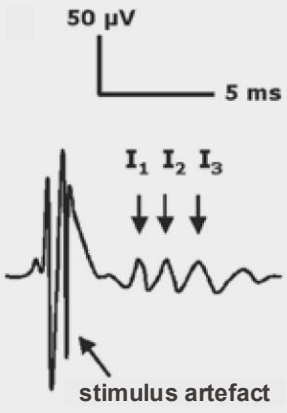


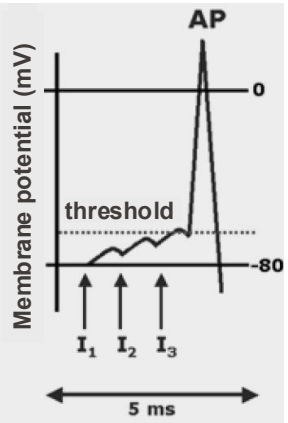


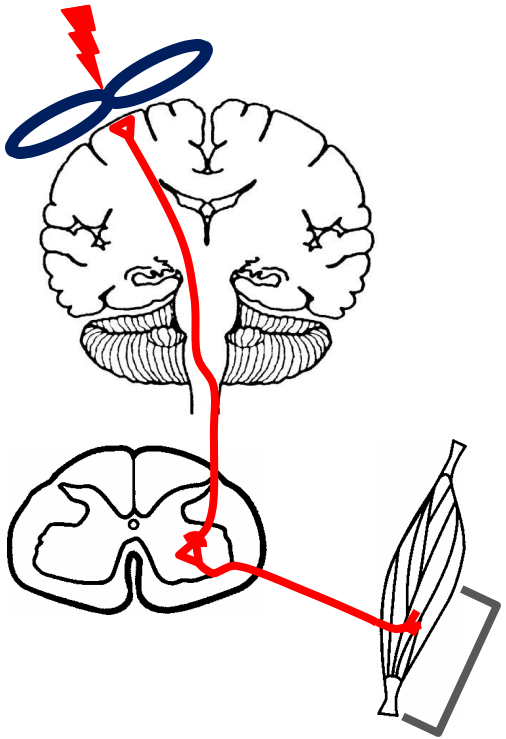
D- and I-waves

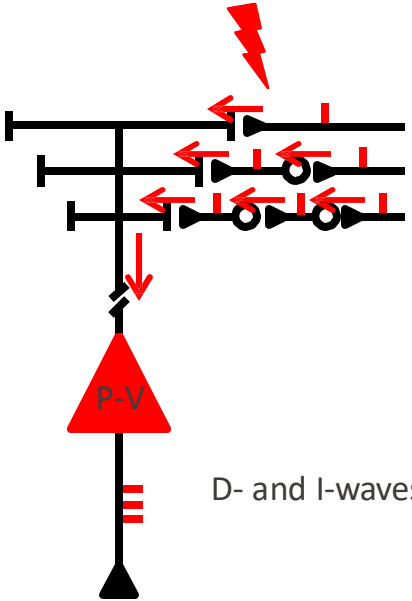


Siebner & Ziemann (2007) *Das TMS-Buch*

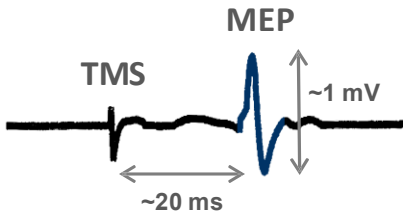








D- and I-waves



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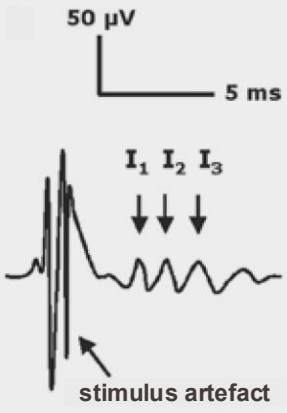
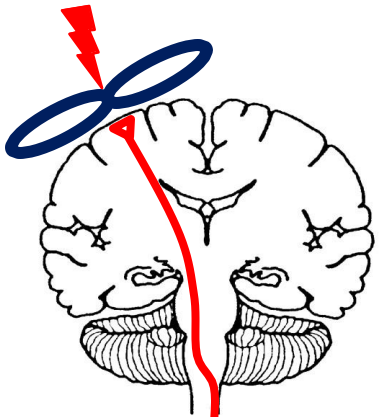
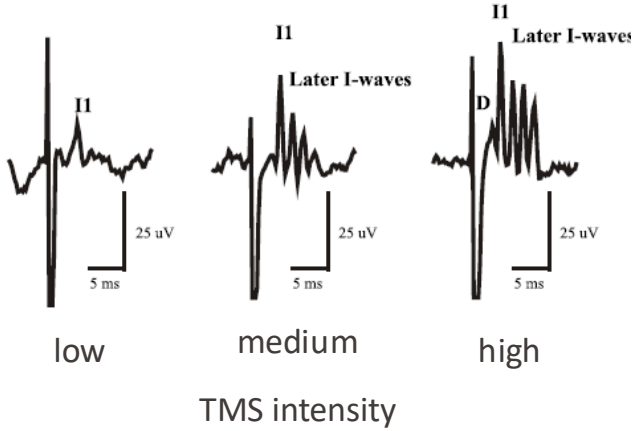
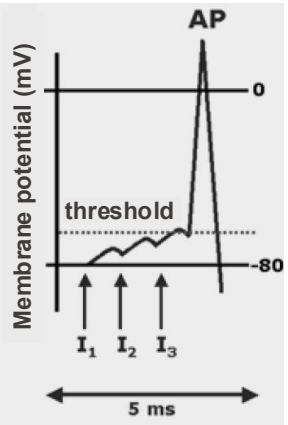
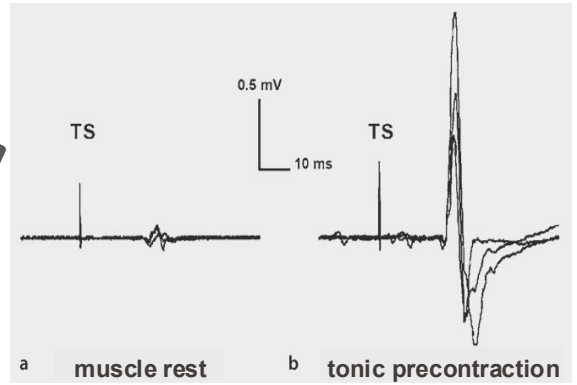




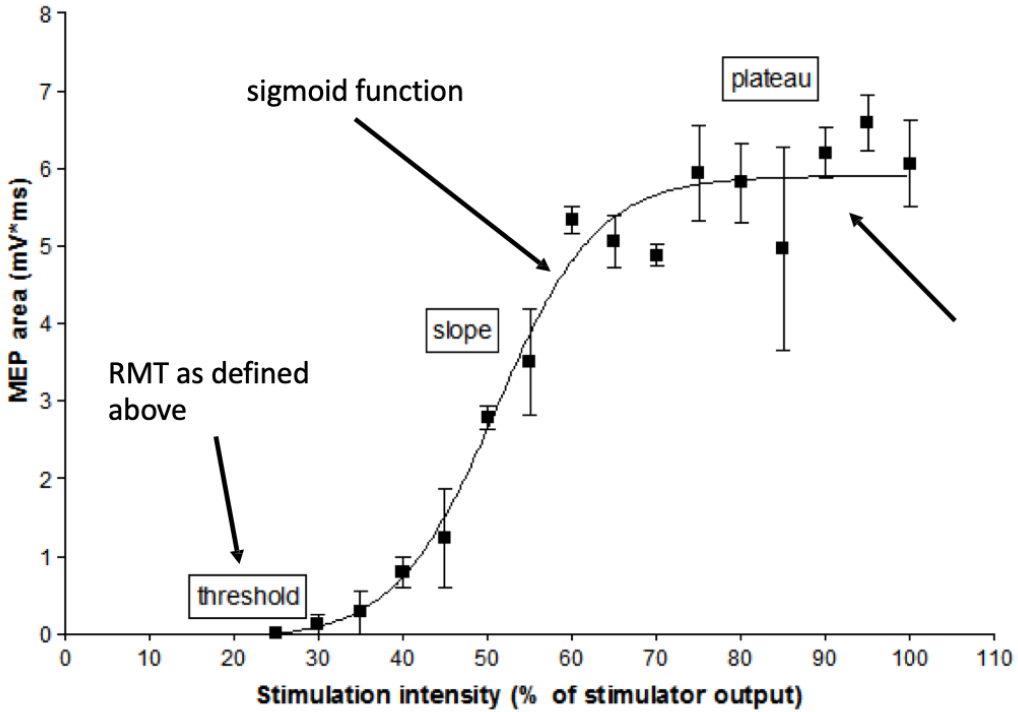






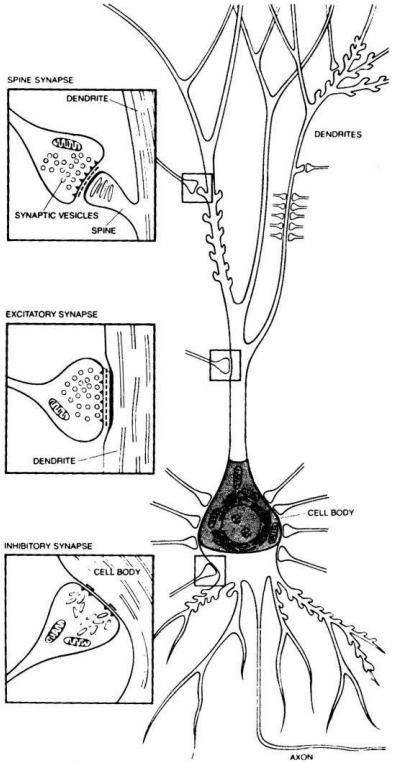
Siebner & Ziemann (2007) *Das TMS-Buch*

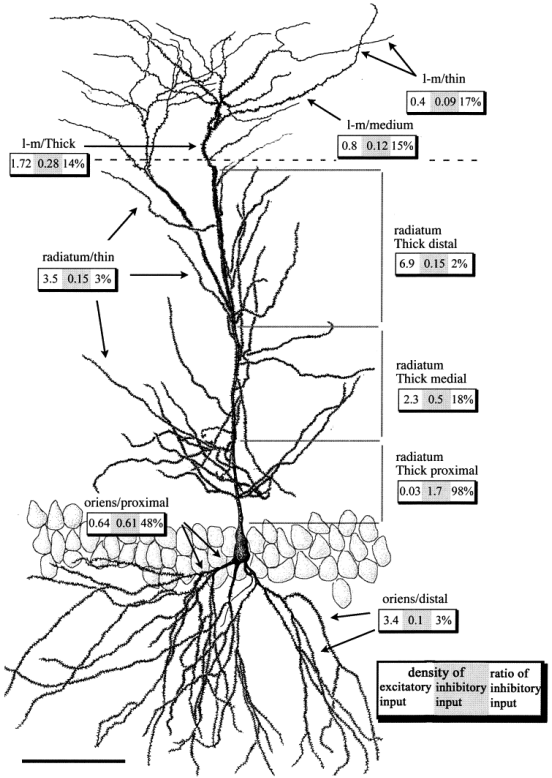
Intensity - response curve of the MEP



Siebner & Ziemann (2007) *Das TMS-buch*

pyramidal cells



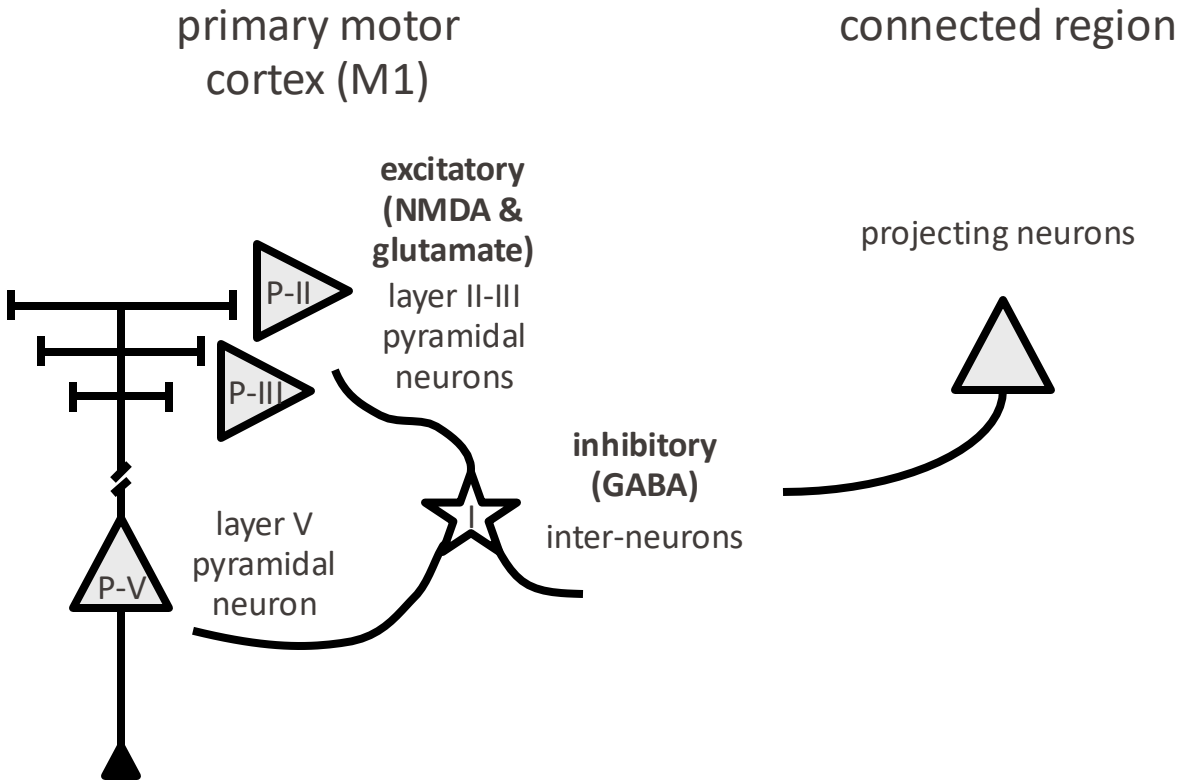


excitatory

inhibitory

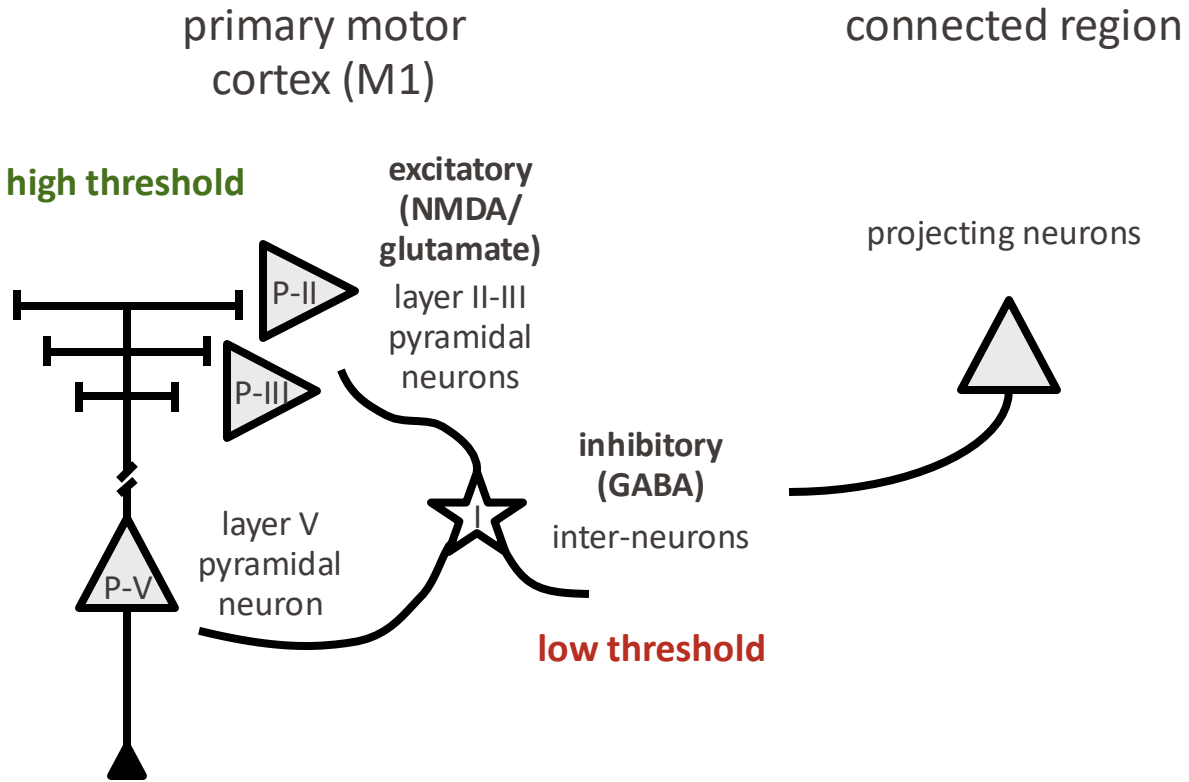
excitatory

pyramidal cells

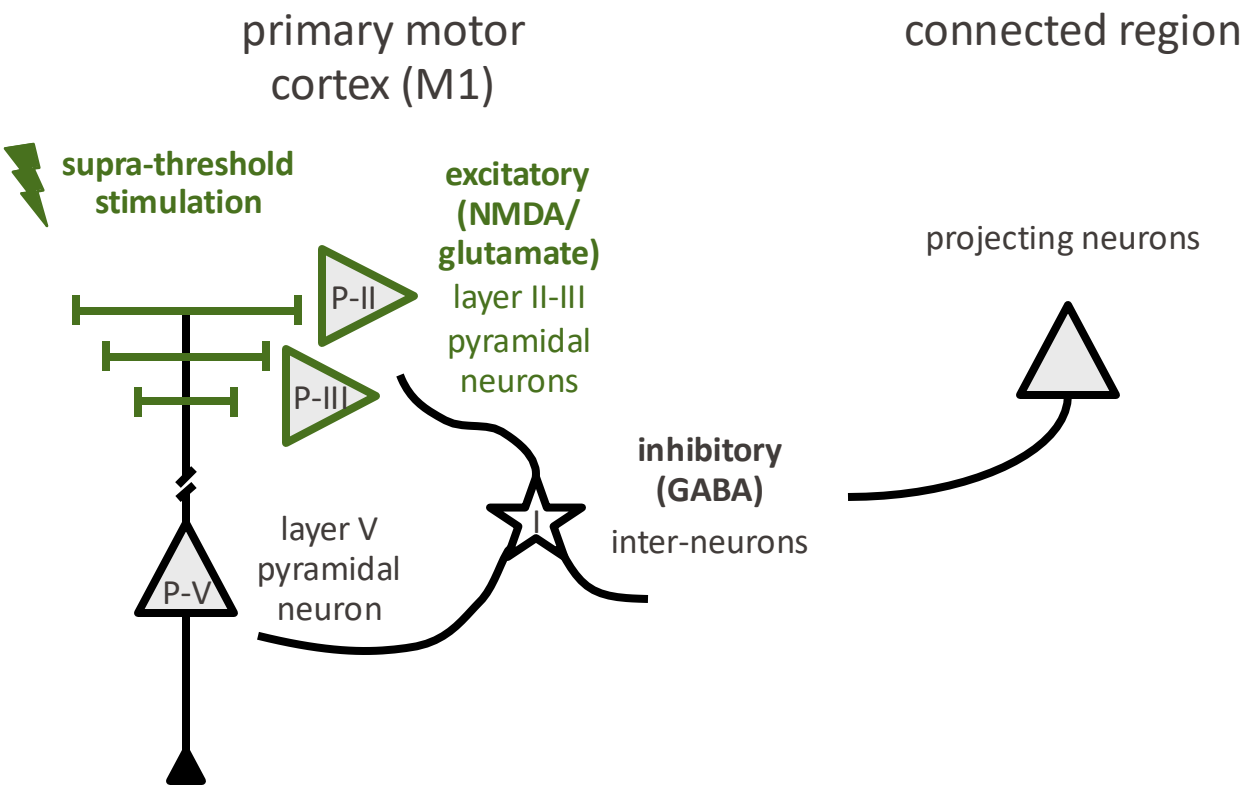


Determining intracortical neurotransmitter systems: paired pulse TMS

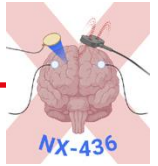
(intra-) cortical circuits



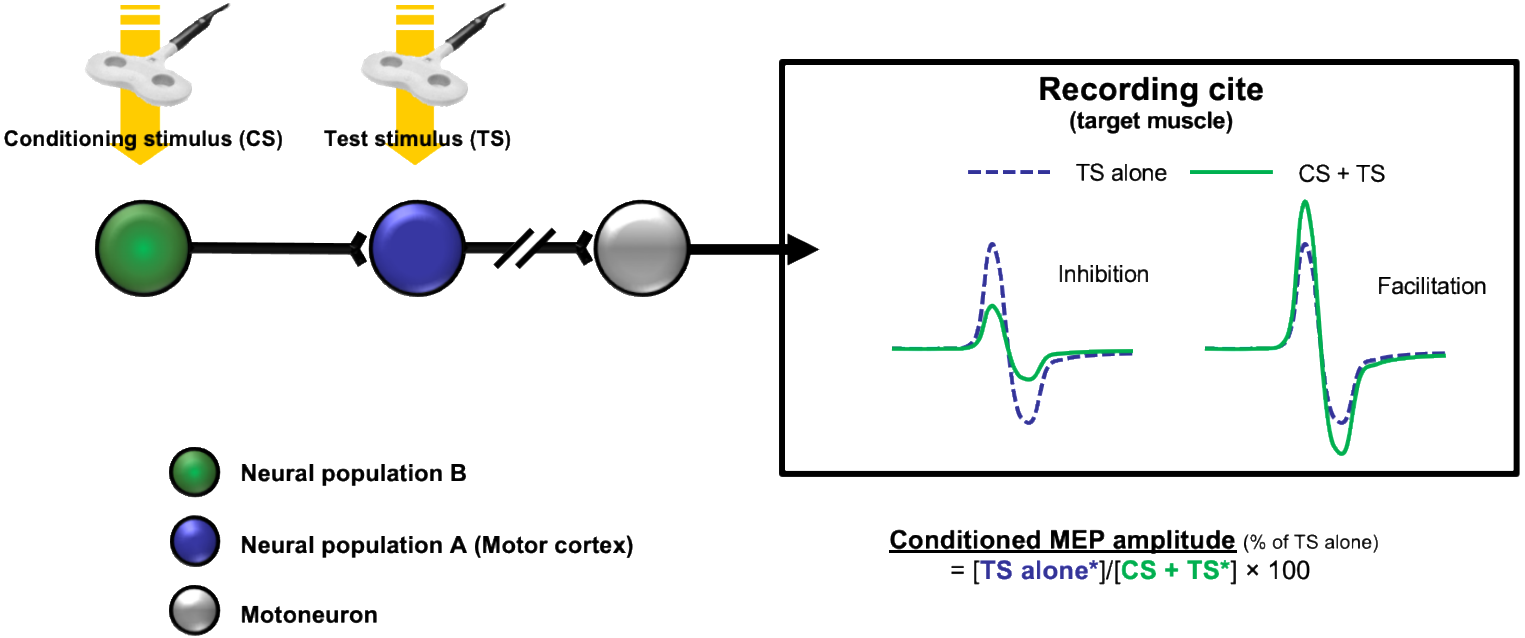
(intra-) cortical circuits



di Lazzaro & Ziemann (2013) *FrontNeurCirc*



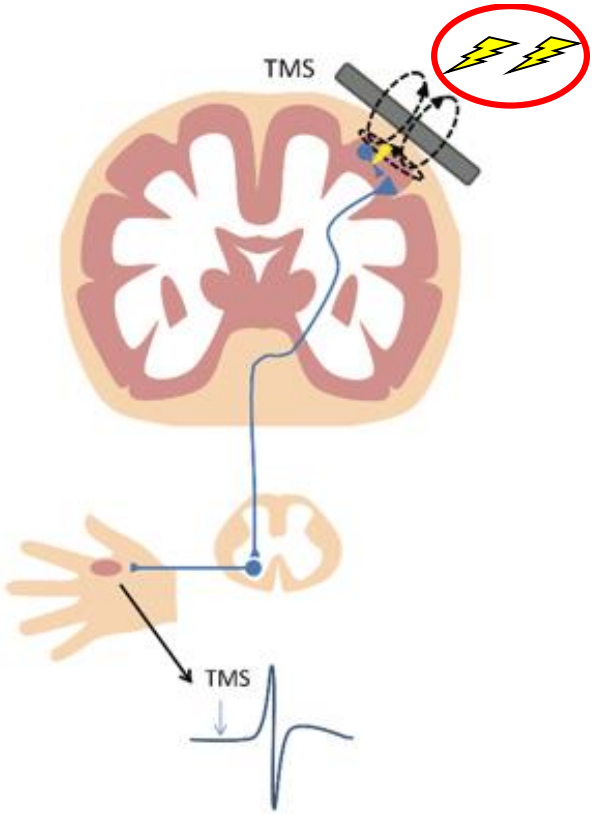
General principle paired-pulse TMS

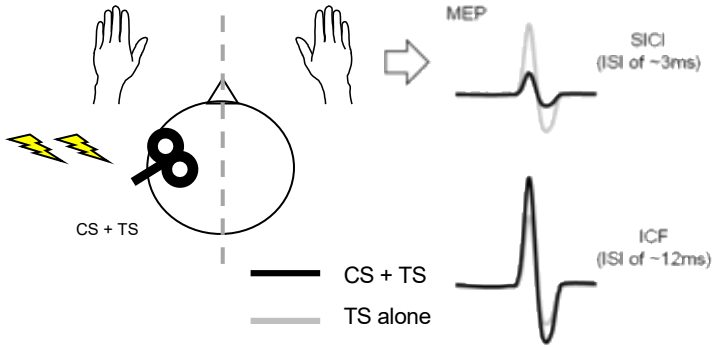


Conditioned MEP amplitude (% of TS alone)
= [TS alone*]/[CS + TS*] × 100

*Peak-to-peak amplitude is analyzed

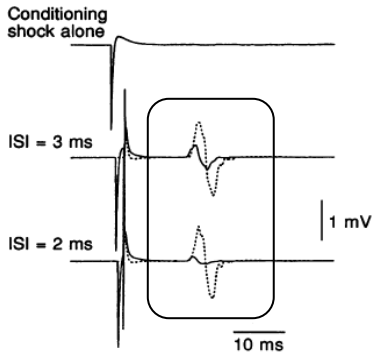
Physiology – neurotransmitter systems

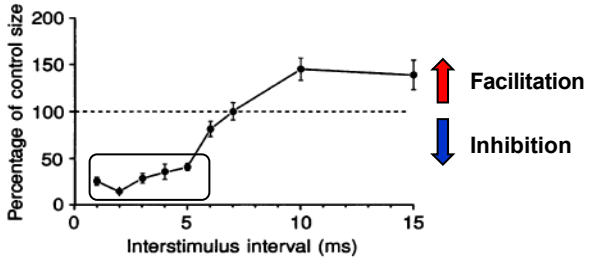




$GABA_A$ mediated

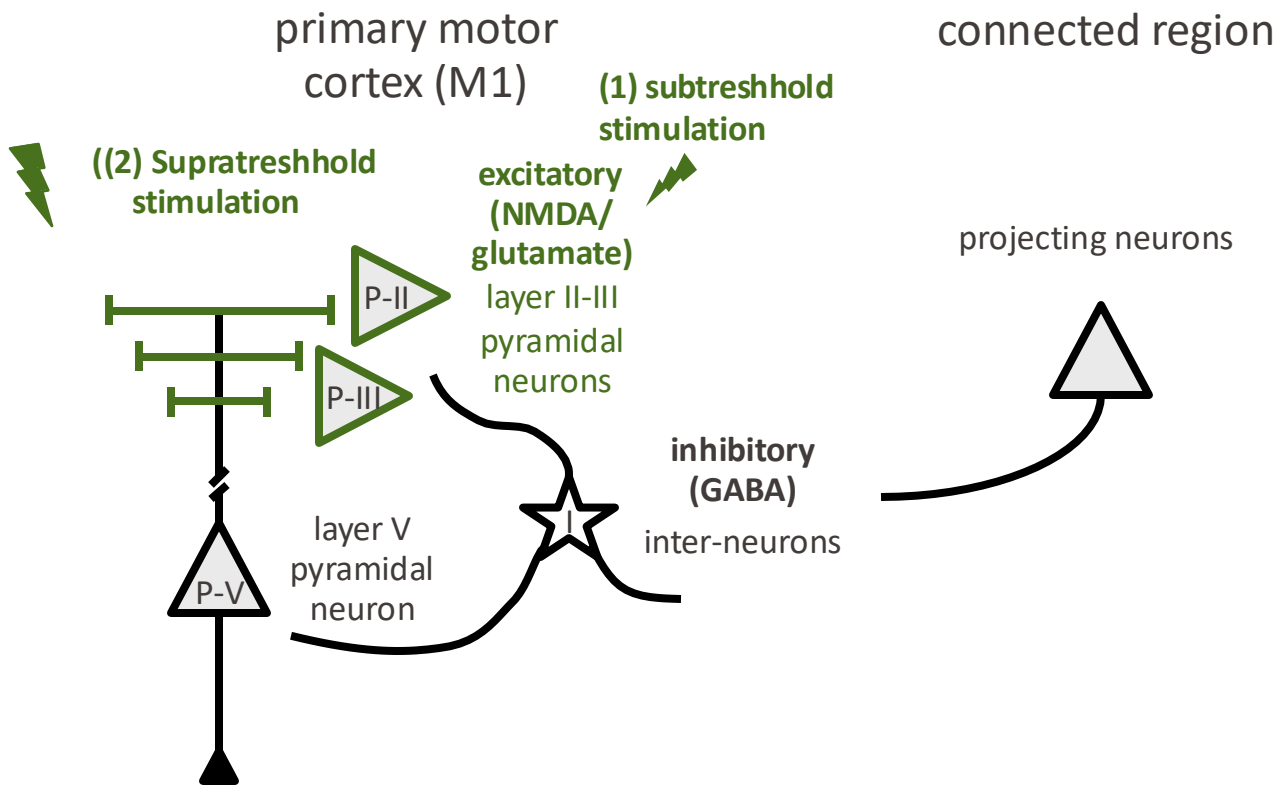
Glutamatergic mediated





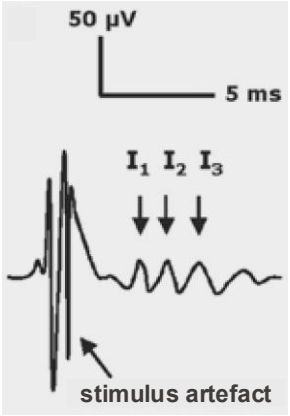
Adapted from Rogasch *et al.* (2013) *Schizopherenia Bulletin*; Kujirai *et al.* (1993) *Journal of Physiology*

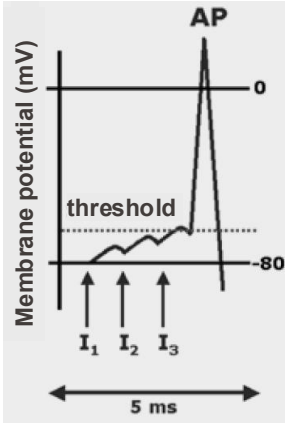
(intra-) cortical circuits



di Lazzaro & Ziemann (2013) *FrontNeurCirc*

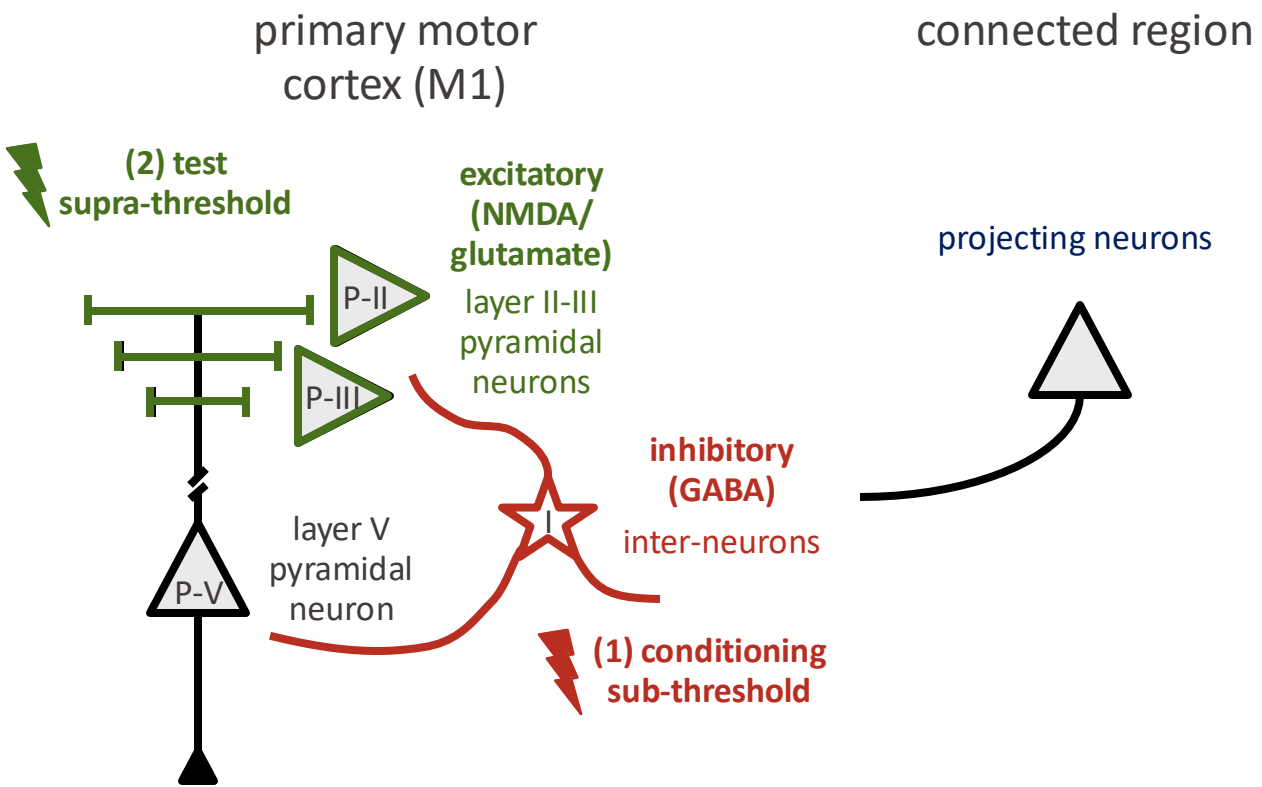
intra-cortical paired-pulse protocols



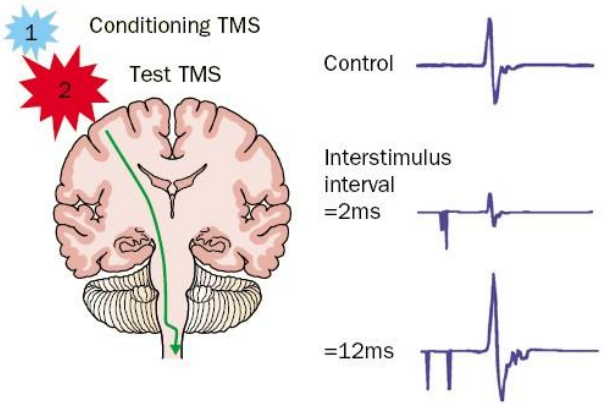


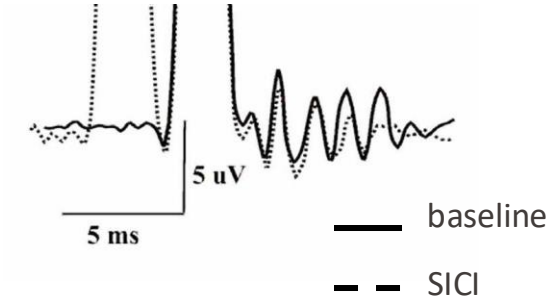
protocol	stim 1	stim 2	ISI	Mechanism
short-interval intracortical facilitation (SICF)	supra	sub	1.1-1.5 ms	I-waves

intra-cortical paired-pulse protocols



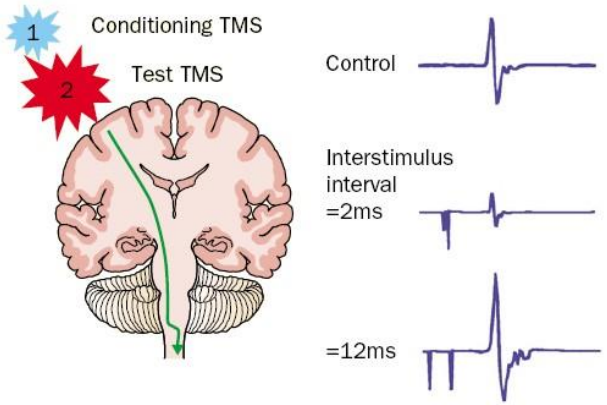
intra-cortical paired-pulse protocols

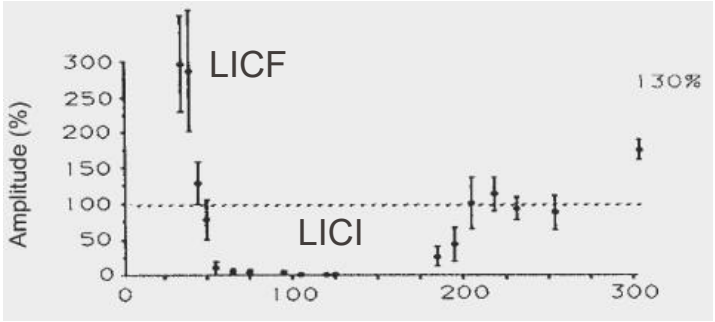




protocol	stim 1	stim 2	ISI	Mechanism
short-interval intracortical facilitation (SICF)	supra	sub	1.1-1.5 ms	I-waves
short-interval intracortical inhibition (SICI)	sub	supra	3ms	$GABA_A$-R
intracortical facilitation (ICF)	sub	supra	10-15 ms	NMDA-R

intra-cortical paired-pulse protocols

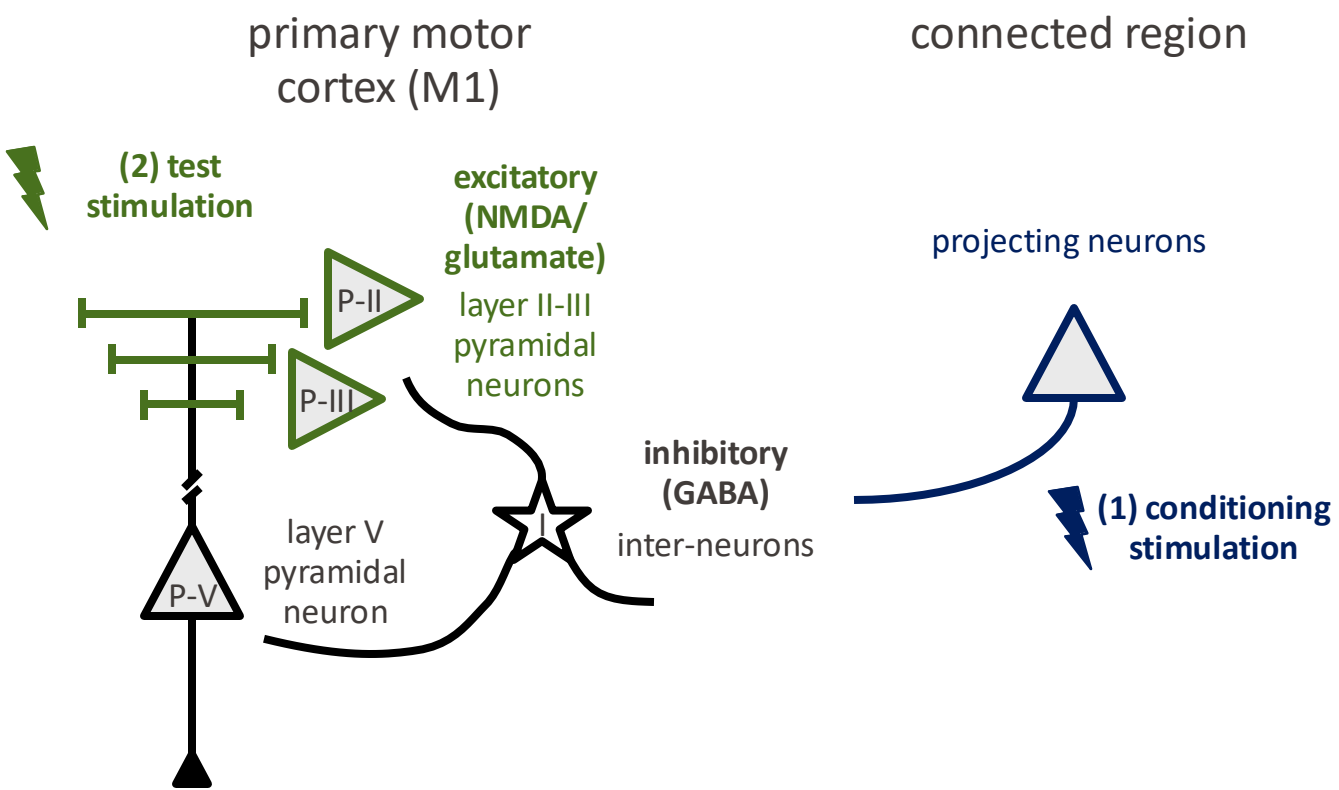




Siebner & Ziemann (2007) *Das TMS-Buch*

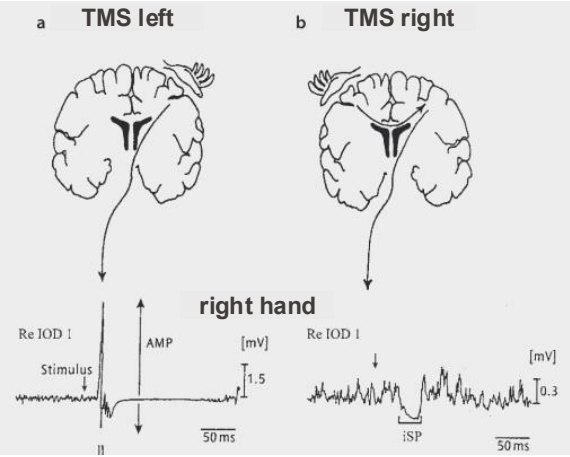
protocol	stim 1	stim 2	ISI	Mechanism
short-interval intracortical facilitation (SICF)	supra	sub	1.1-1.5 ms	I-waves
short-interval intracortical inhibition (SICI)	sub	supra	3 ms	$GABA_A$-R
intracortical facilitation (ICF)	sub	supra	10-15 ms	NMDA-R
long-interval intracortical facilitation (LICF)	supra	supra	10-30 ms	?
long-interval intracortical inhibition (LICI)	supra	supra	50-200 ms	$GABA_B$-R

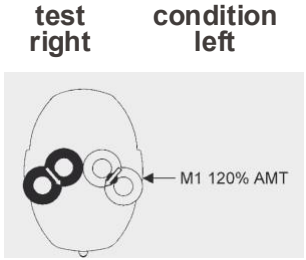
inter-cortical paired-pulse protocols



di Lazzaro & Ziemann (2013) *FrontNeurCirc*

inter-cortical paired-pulse protocols

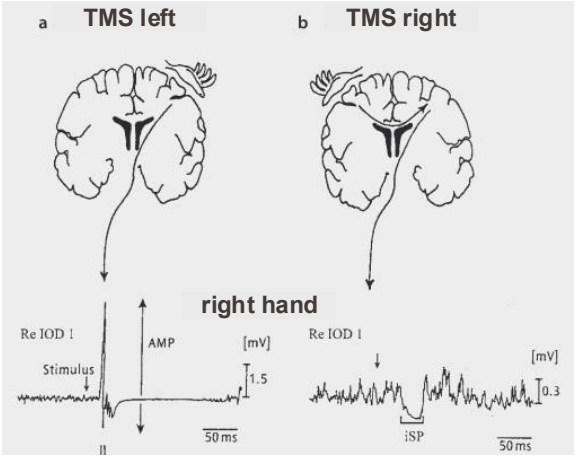




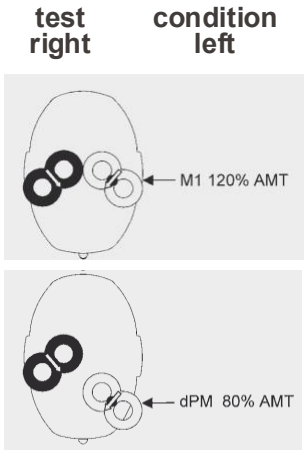
Siebner & Ziemann (2007) *Das TMS-Buch*

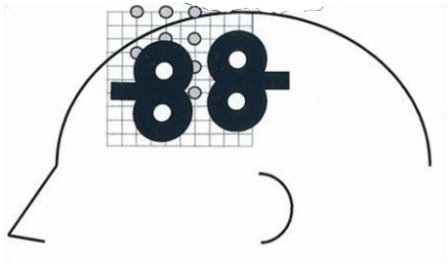
protocol	stim 1	stim 2	ISI	Mechanism
Interhemispheric inhibition (IHI)	supra	supra	6-12 ms	transcallosal projections
Interhemispheric facilitation (IHF)	supra	supra	4-5 ms	

inter-cortical paired-pulse protocols

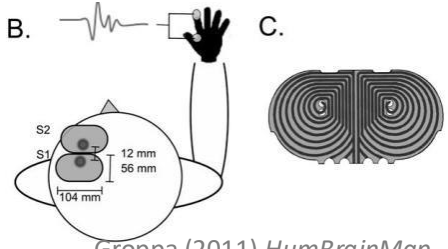


Siebner & Ziemann (2007) *Das TMS-Buch*



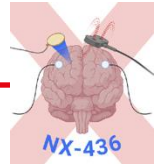


Civardi (2001) *NeuroImg*



Groppa (2011) *HumBrainMap*

protocol	stim 1	stim 2	ISI	Mechanism
Interhemispheric inhibition (IHI)	supra	supra	6-12 ms	transcallosal projections
Interhemispheric facilitation (IHF)	supra	supra	4-5 ms	
Interhemispheric dorsal premotor facilitation	sub	supra	8 ms	
Intrahemispheric dorsal premotor facilitation	sub	supra	2.4, 2.8, 4.4, 6	U-fibres



LETTER

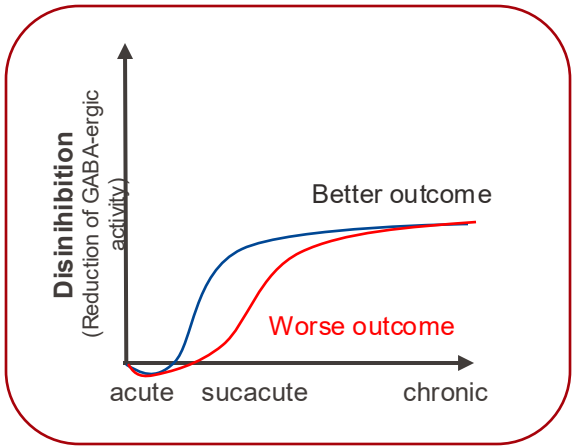
doi:10.1038/nature09511

Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke

Andrew N. Clarkson[1]*†, Ben S. Huang[1,2]*, Sarah E. MacIsaac[1], Istvan Mody[1,2,3] & S. Thomas Carmichael[1]

11 NOVEMBER 2010 | VOL 468 | NATURE | 305

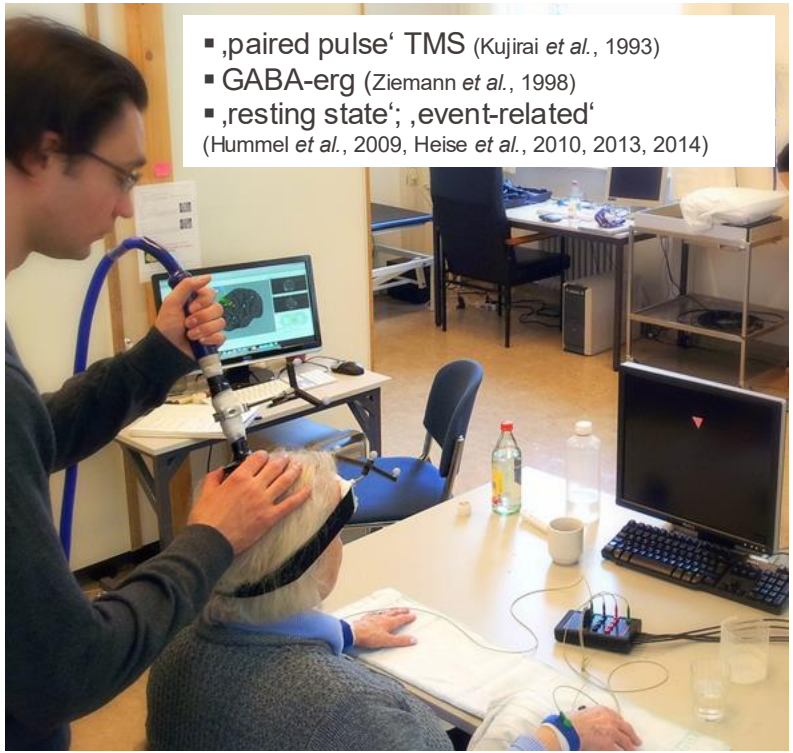
Animal model



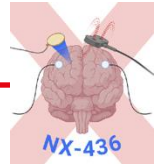
Transcranial magnetic stimulation (TMS)

- ‚paired pulse' TMS (Kujirai *et al.*, 1993)
- GABA-erg (Ziemann *et al.*, 1998)
- ‚resting state'; ‚event-related'

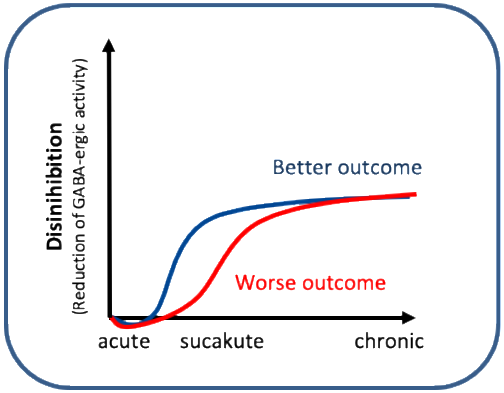
(Hummel *et al.*, 2009, Heise *et al.*, 2010, 2013, 2014)



Clinical examples

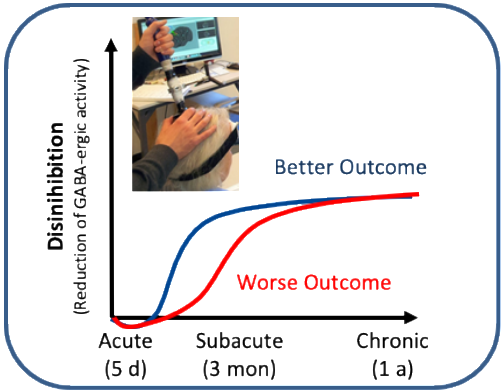


Animal model

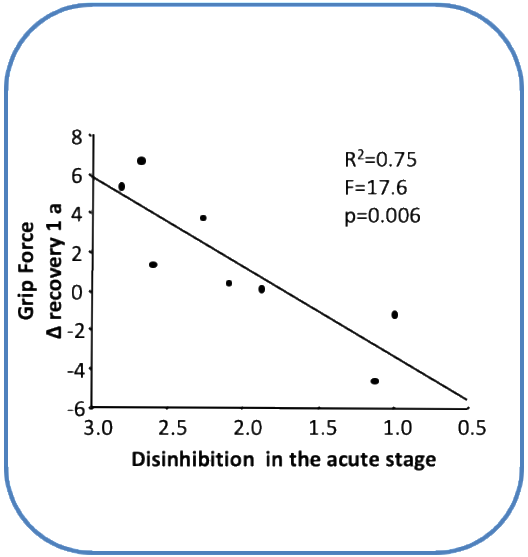


Model based on Clarkson *et al.* (2010) *Nature*

Model in stroke patients



Stroke Patients



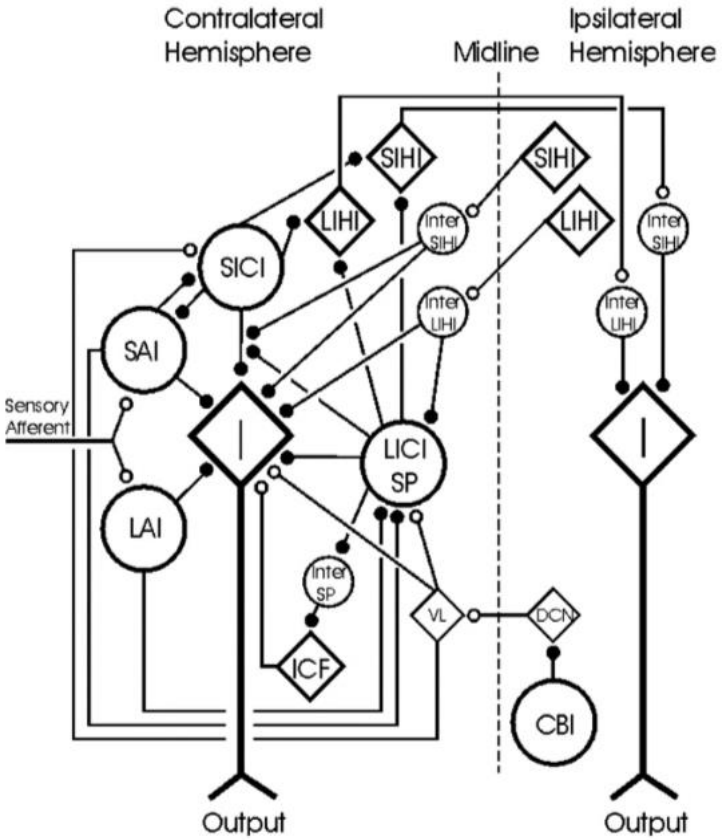
The earlier the reduction of GABA-ergic activity in the motor cortex (disinhibition),

the better the recovered function

(comparable to animal work, Clarkson *et al.*, 2010).

Adapted from Liuzzi *et al.* (2014) *Neurology*

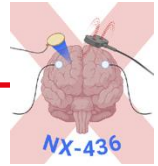
Neural circuits with TMS applications



TMS allows to probe specific neural circuits

Ni et al. 2011 Brain Stim

Summary



I. Important parameter for TMS are coil shape, pulse intensity, pulse form

II. TMS activates direct and indirect waves leading to activation of the CST

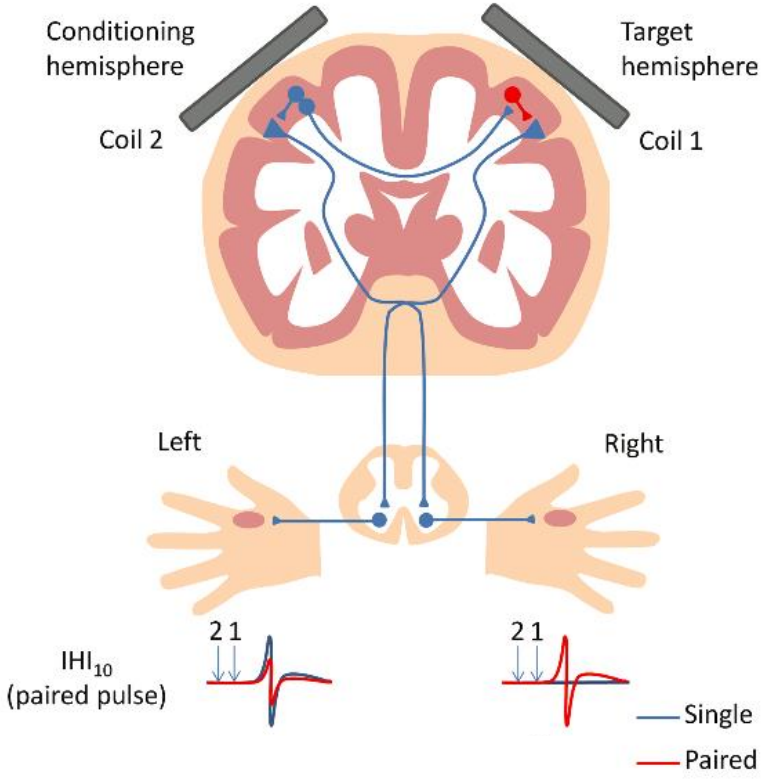
III. TMS allows to determine the recruitment patterns of the motor cortex

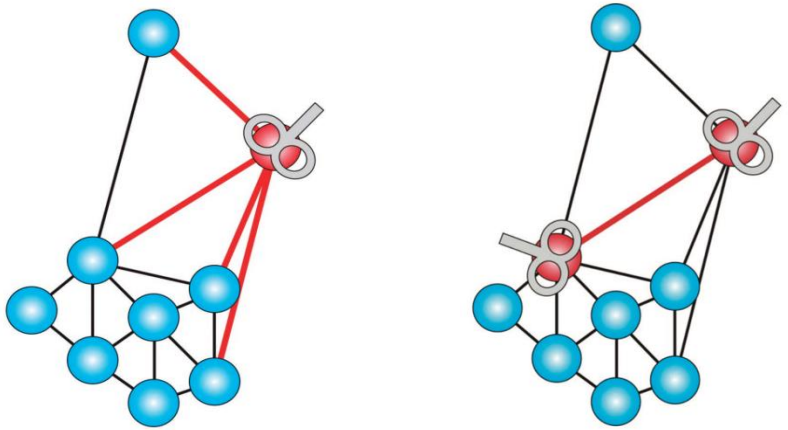
IV. TMS allows to evaluate differetn neurotransmitter systems (GABAergic, Glutamateergic) with paired pulse protocols

V. TMS allows to determine interregional interactions

Multifocal TMS: interregional interactions

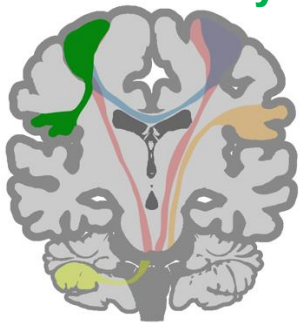
Overview - interregional interactions



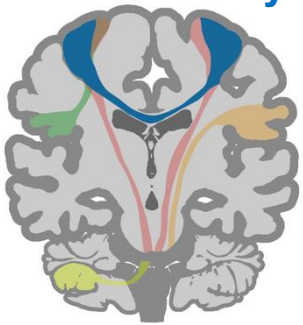


Dayan et al., 2013

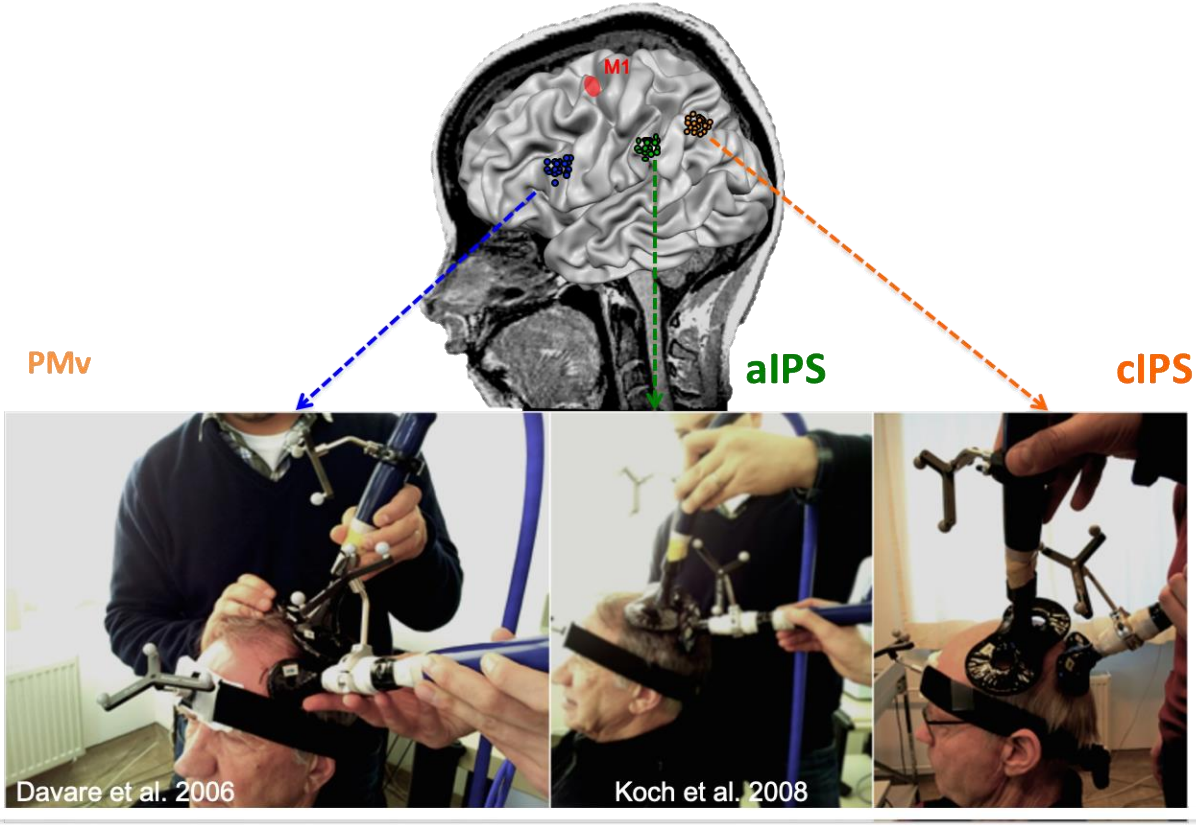
***Intra*-hemispheric connectivity**



***Inter*-hemispheric connectivity**



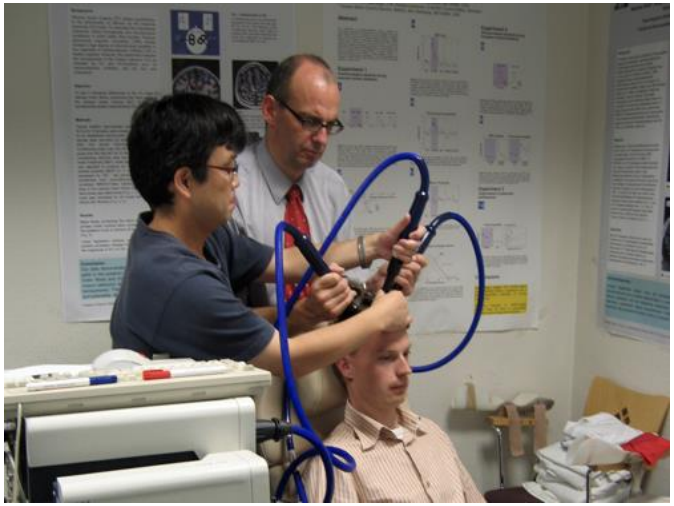
Multifocal TMS: interregional interactions

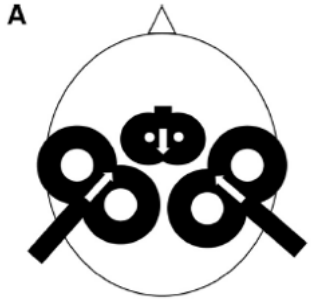


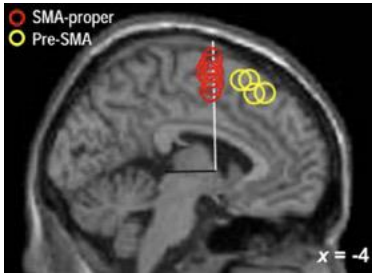
Multifocal TMS: interregional interactions

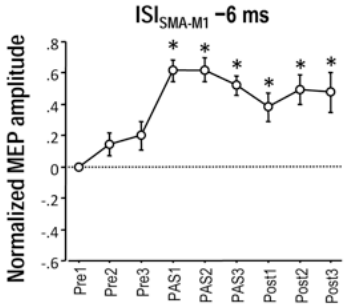
Multifocal TMS: interregional interactions

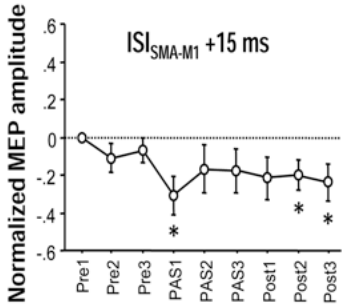
Multi-site stimulation of networks





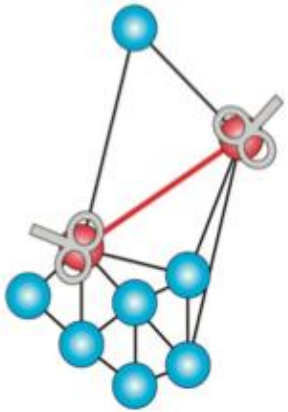




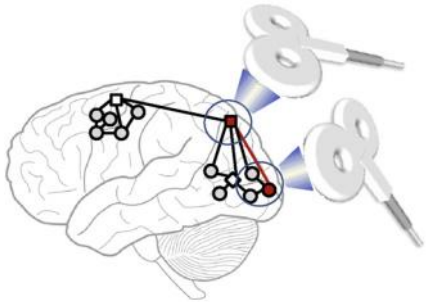


Arai et al. (2011) J Neurosci 31:15376-83

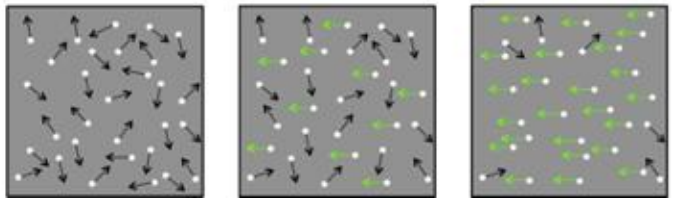
Multifocal TMS: interregional interactions



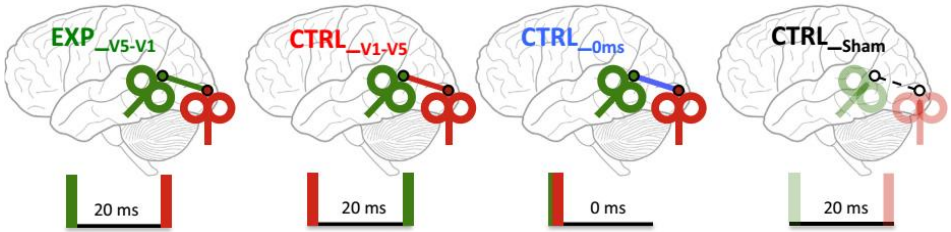
Dayan et al., 2013

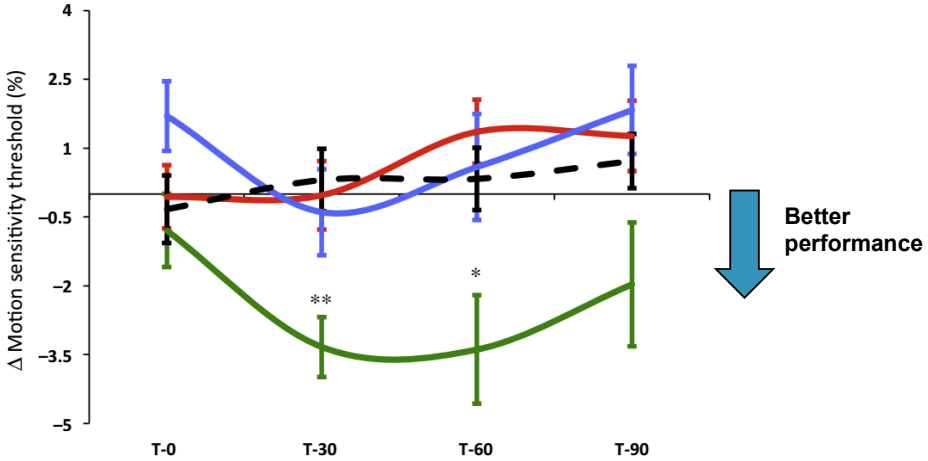


Romei et al., 2016



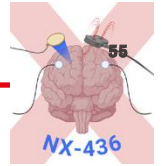
Motion detection visual task



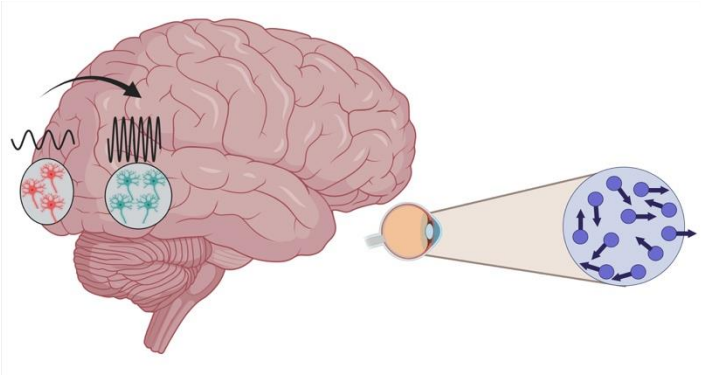


Adapted from Romei *et al.* (2016) *Current Biology*

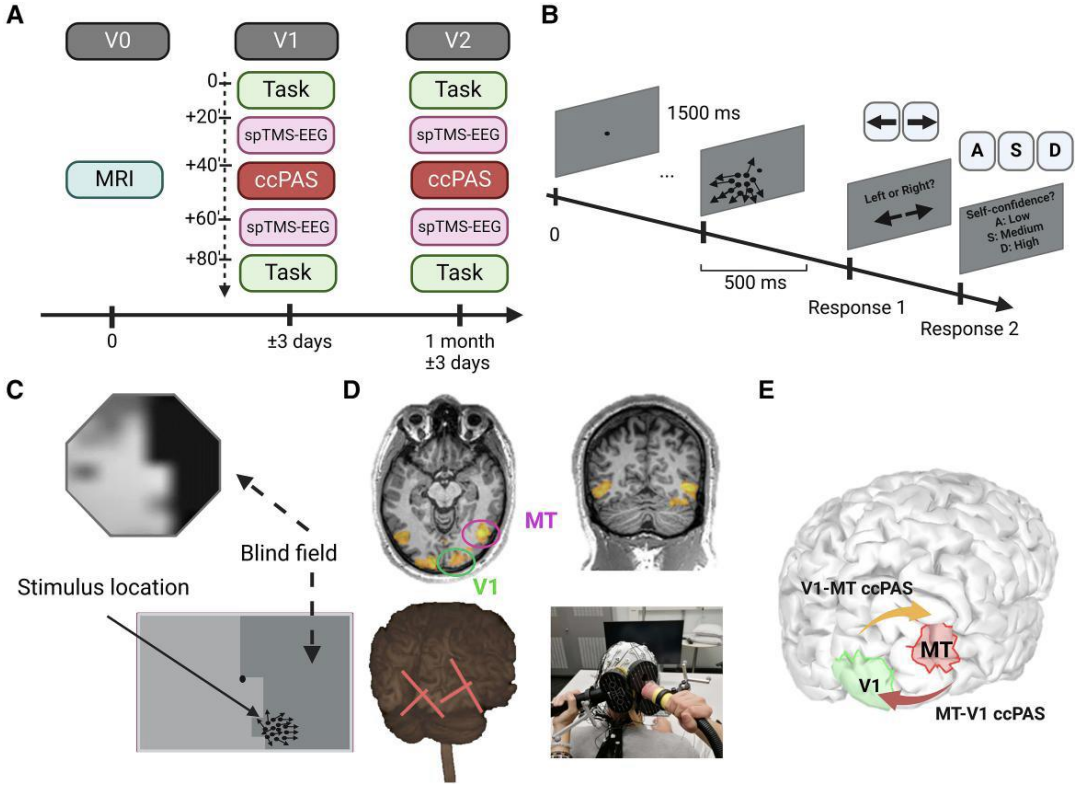
Multifocal TMS: interregional interactions



Motion processing

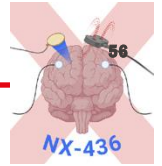


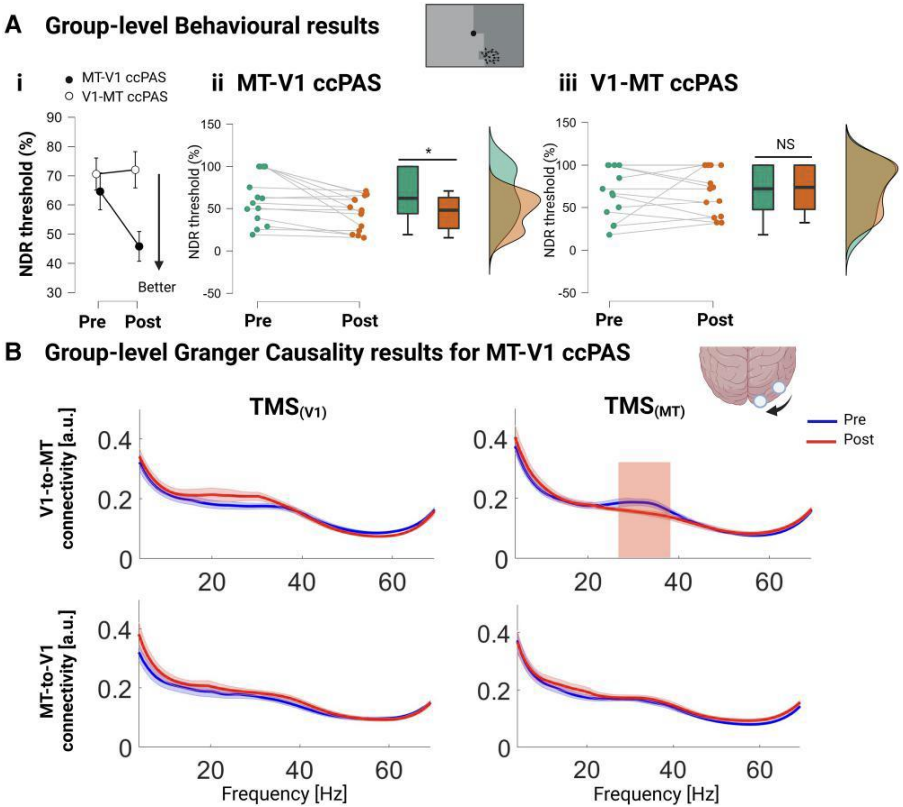
ccPAS:
- Hebbian-like spike-timing dependent plasticity
- 16 stroke patients
- Double-blind, cross-over



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

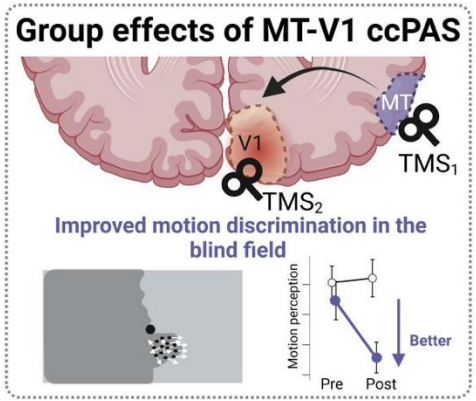
Multifocal TMS: interregional interactions

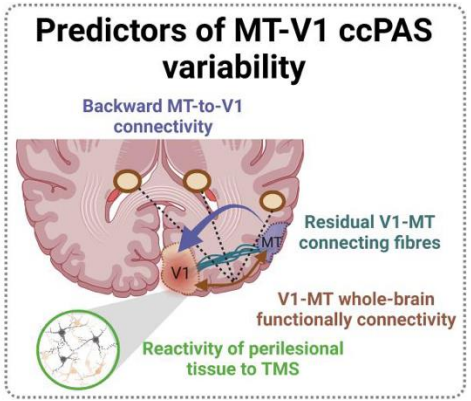




ccPAS intervention

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

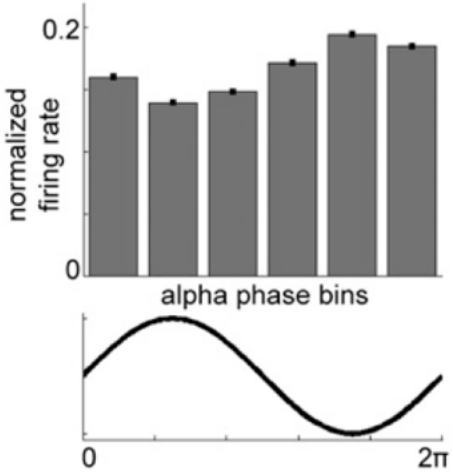




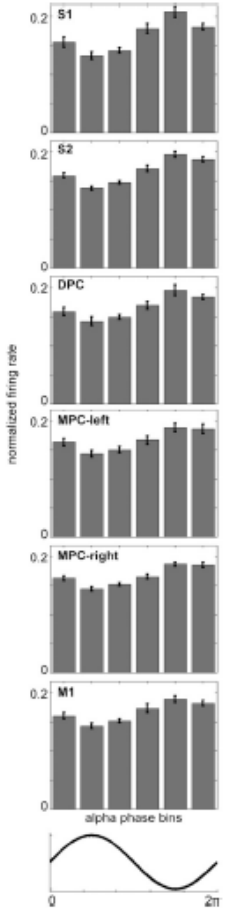
Bevilacqua, Raffin *et al.*, (**2025**) Brain

State dependent TMS

State-dependent

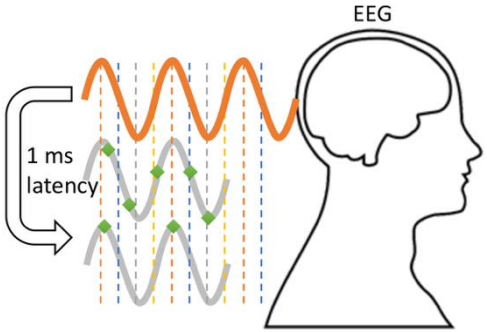


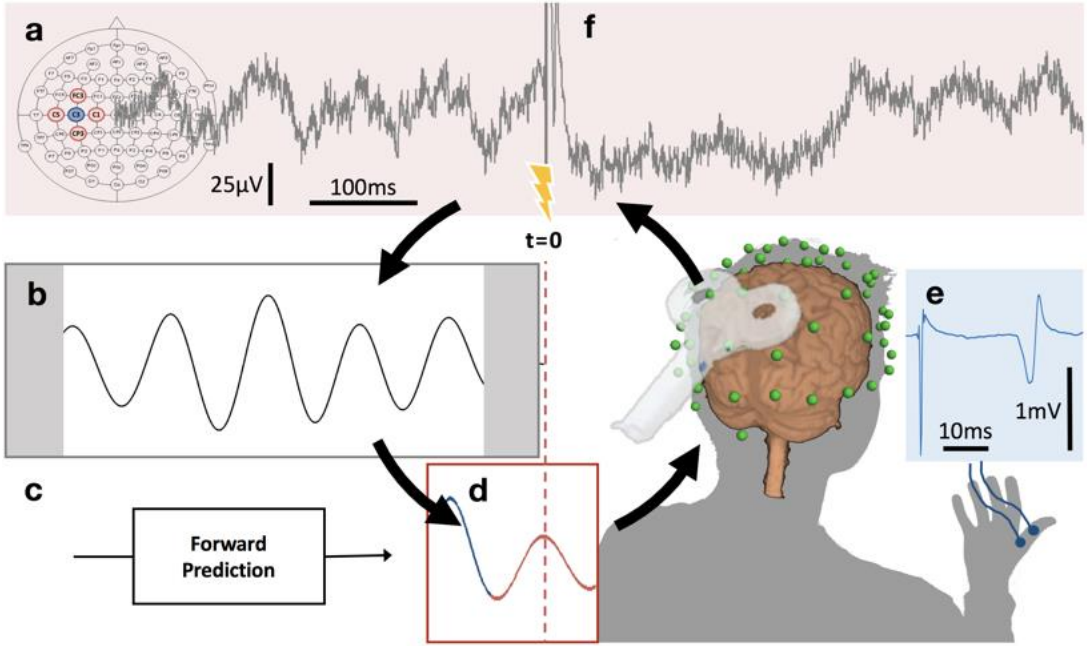
Local field potentials
in monkey cortex



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

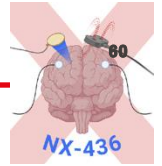
EEG-TMS: Dependence of corticospinal excitability on μ-rhythm phase

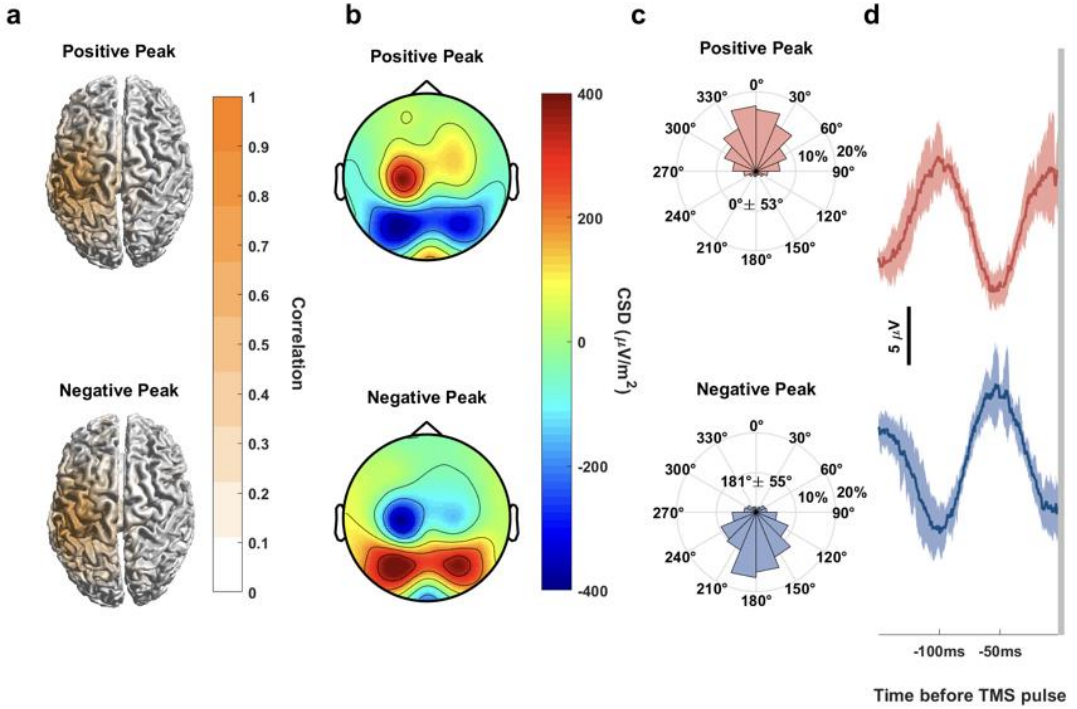


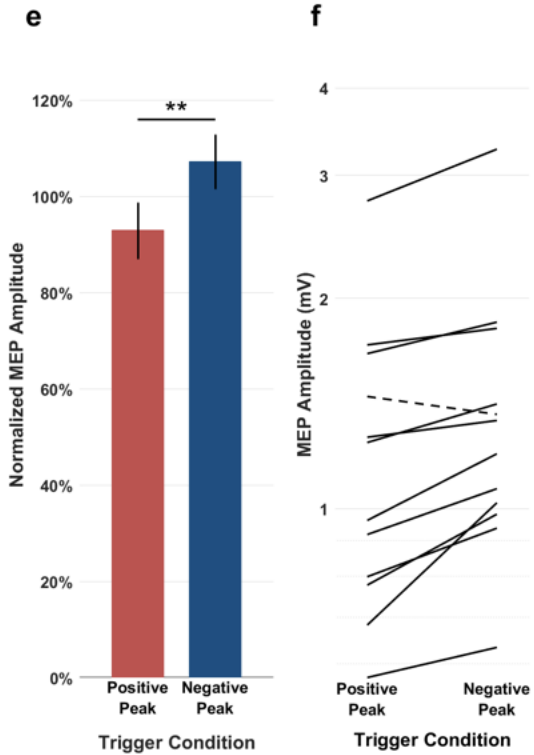


Zrenner et al. 2018

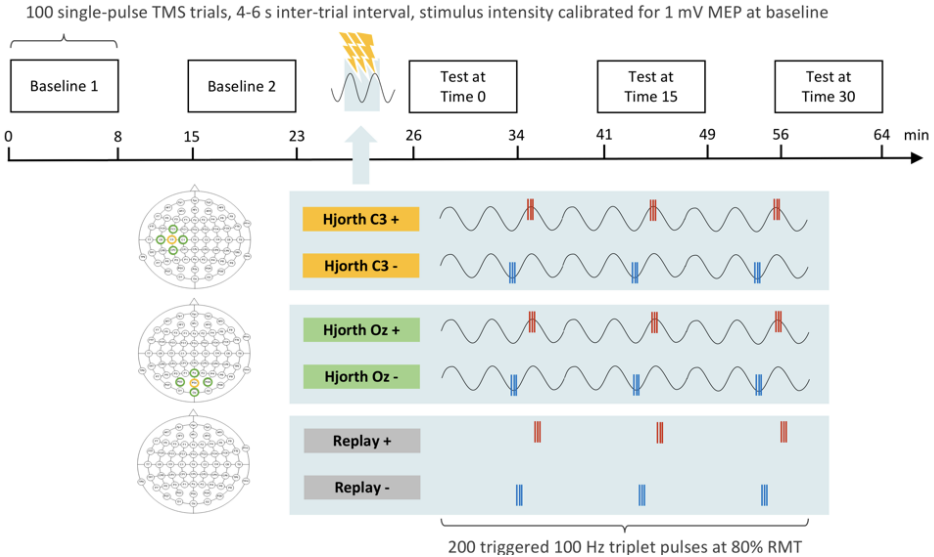
State-dependent



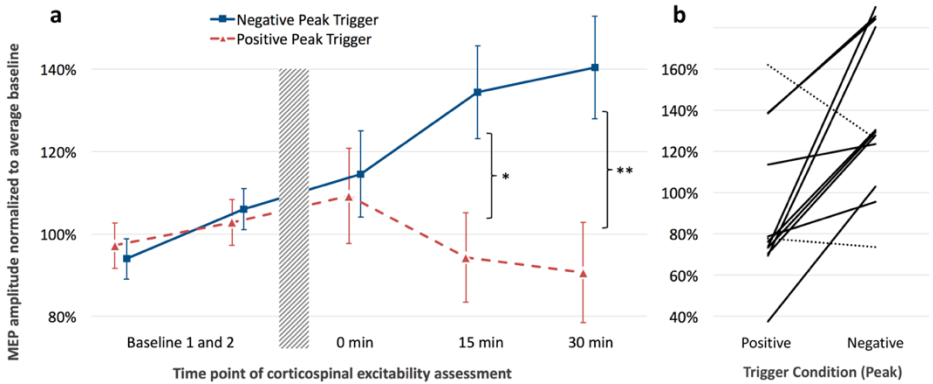


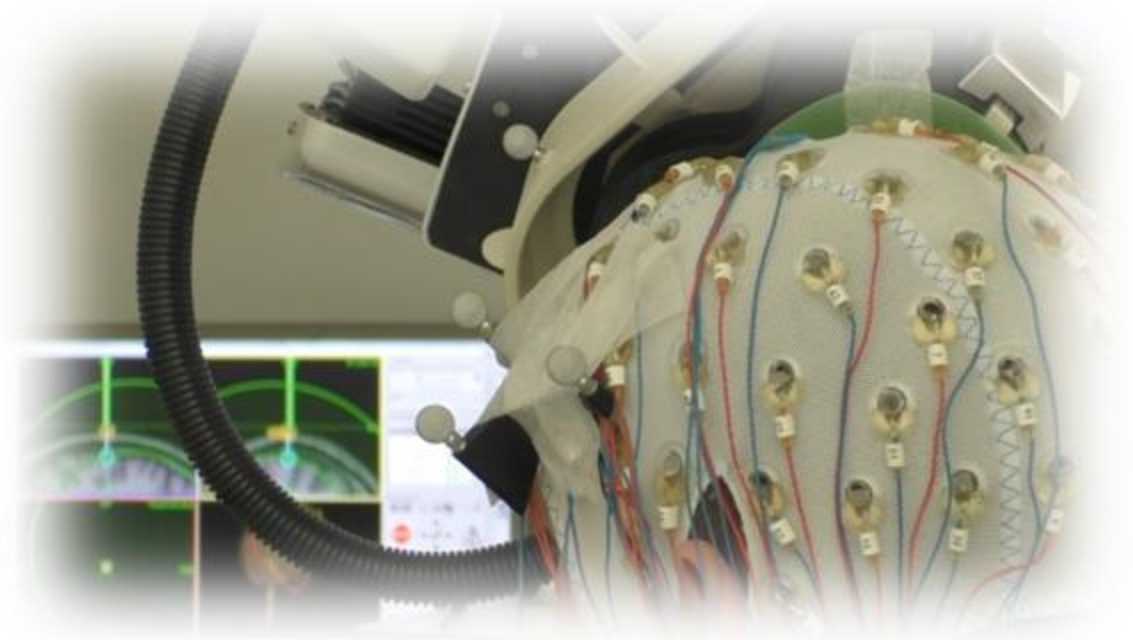


State-dependent



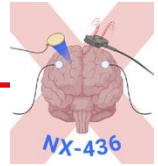
Effects of a TMS pulse depend on the phase of the ongoing brain activity when the pulse was applied.

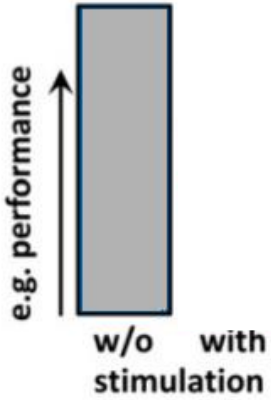


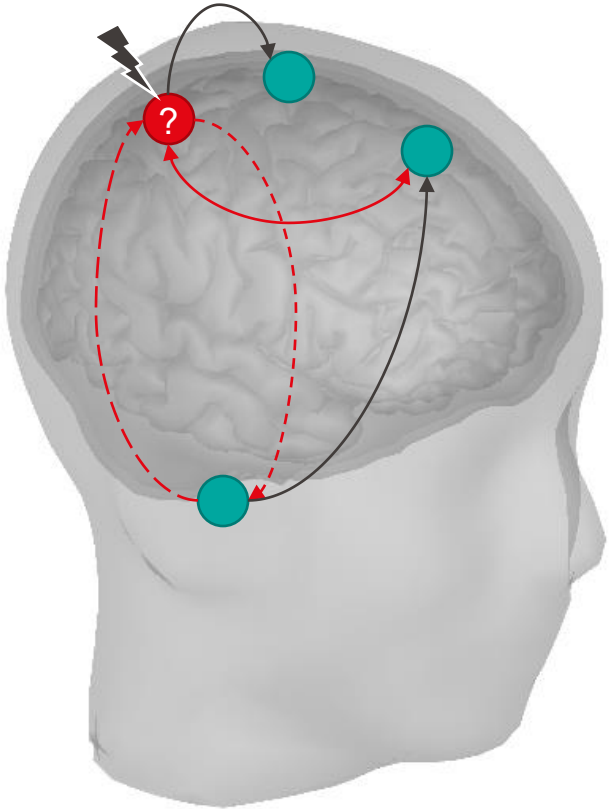


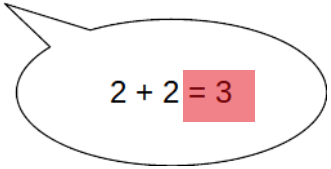
Cortical brain mapping using TMS (neuronavigated and robotized)

Location-function mapping





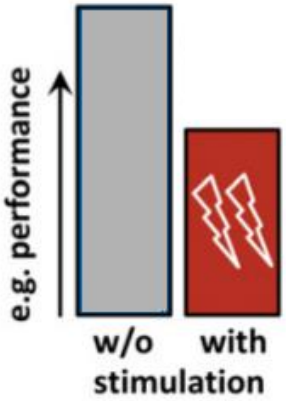


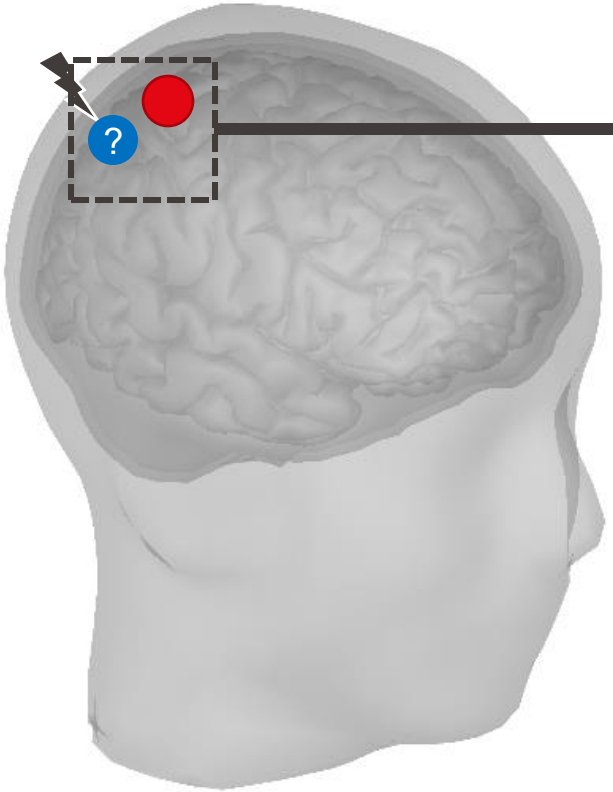


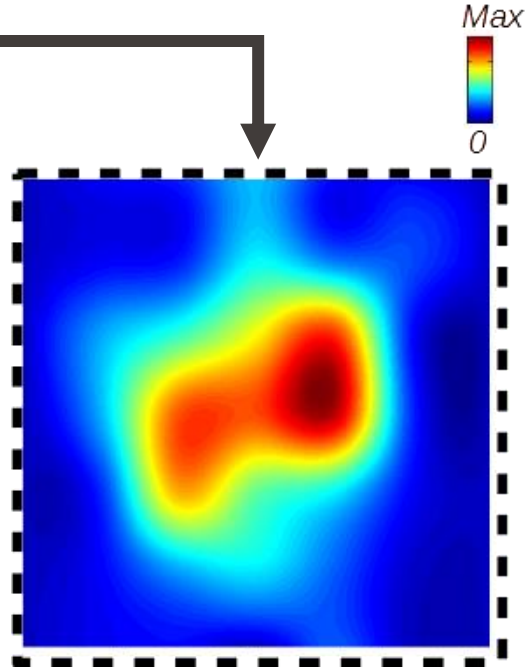
Cognitive process

Sensorimotor process

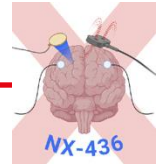
Location-function mapping

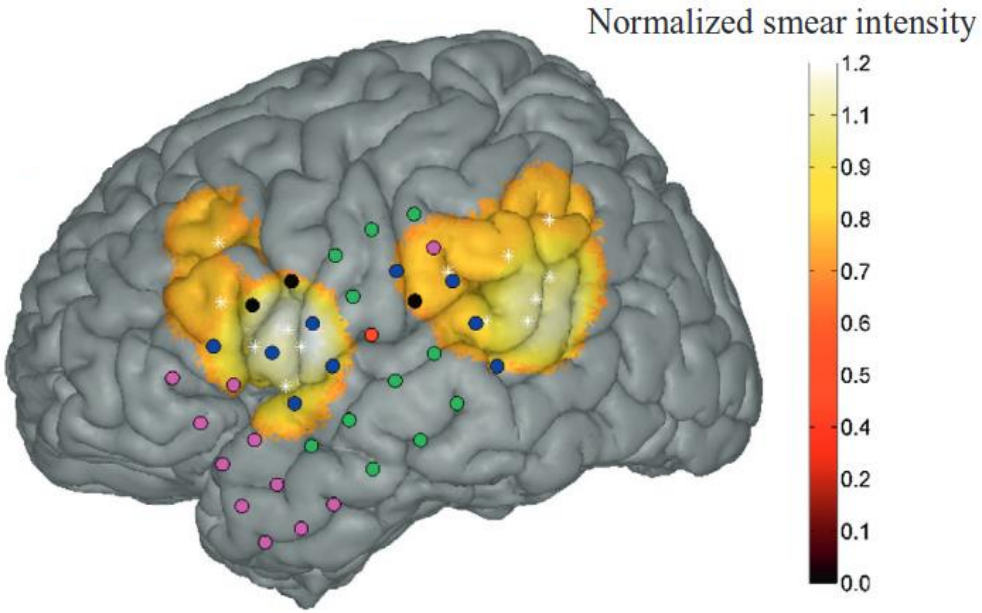






Location-function mapping

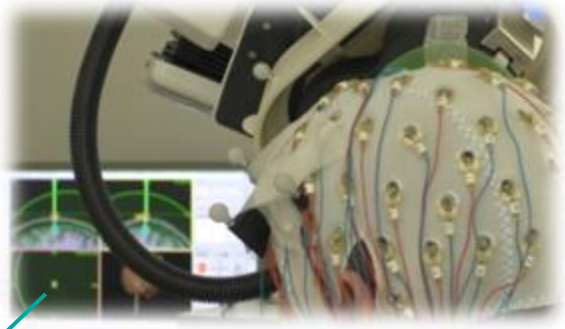




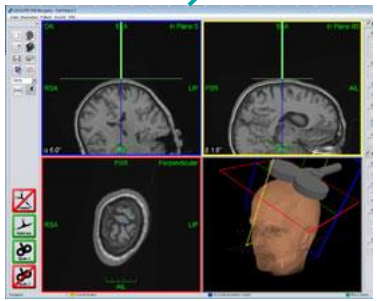
Language mapping

Technological evolution

Figure- Barker demonstrating TMS [1].

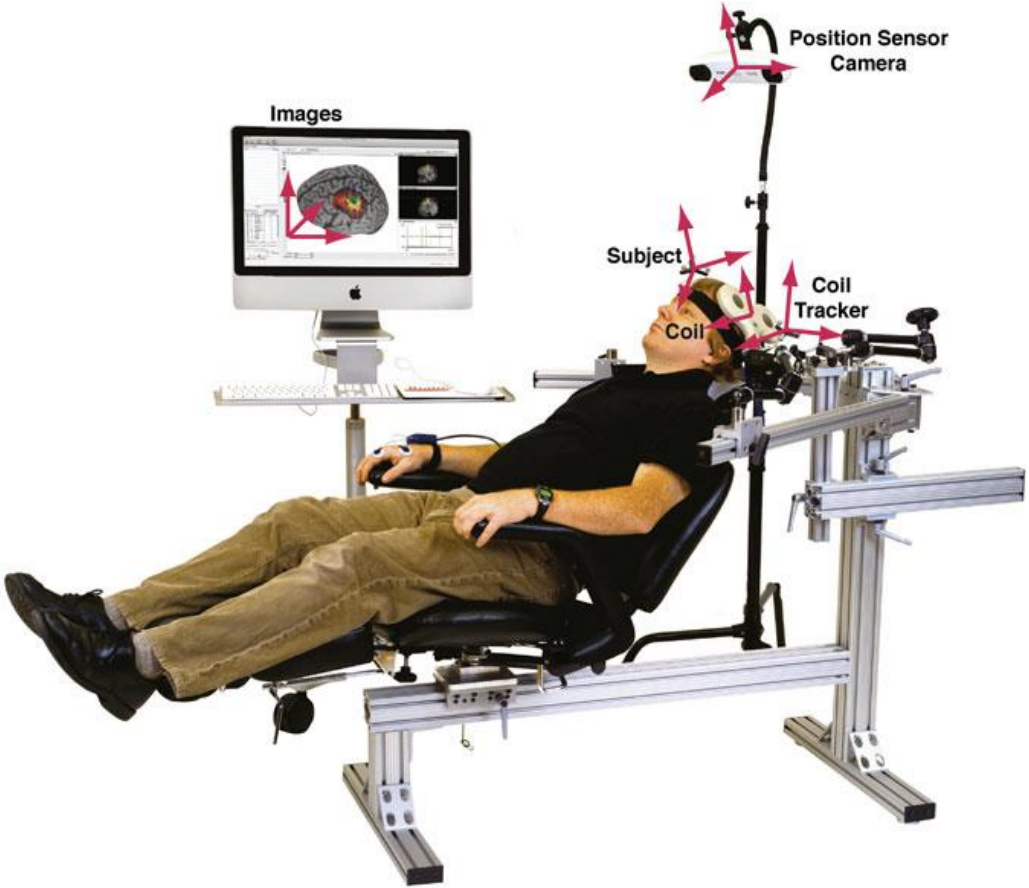


Neuronavigation systems

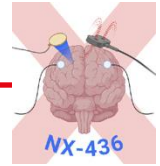


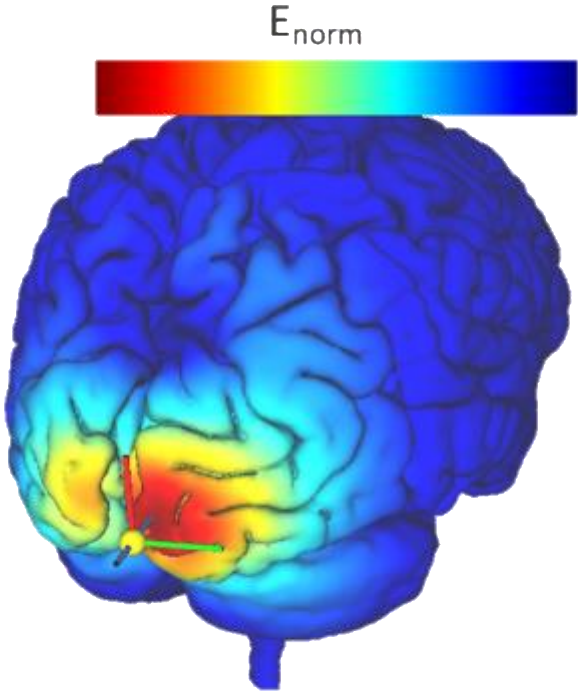
Robotized systems

Neuronavigation

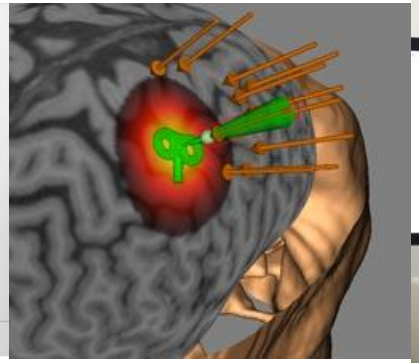


Neuronavigation

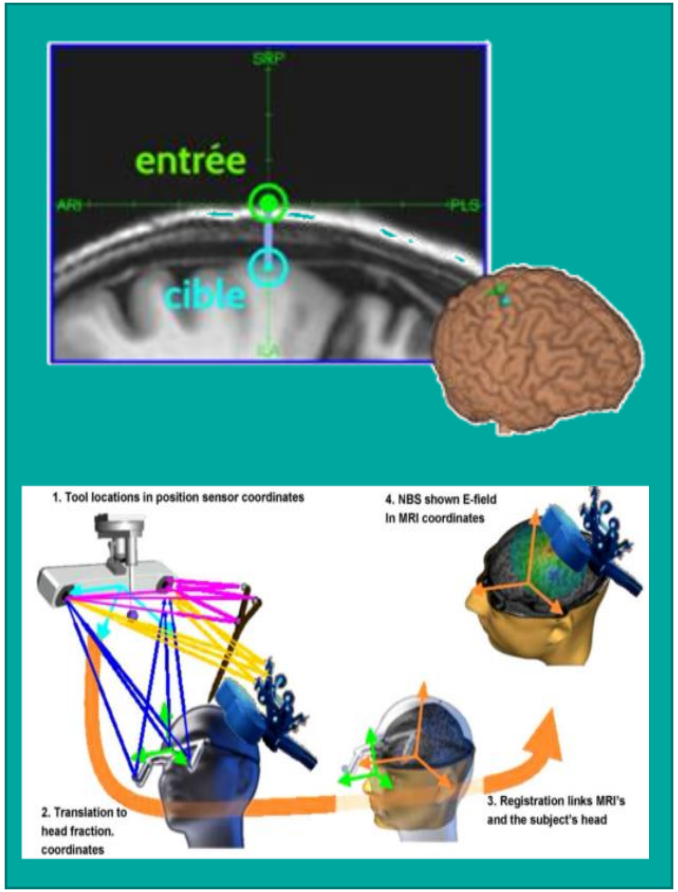




Neuronavigation

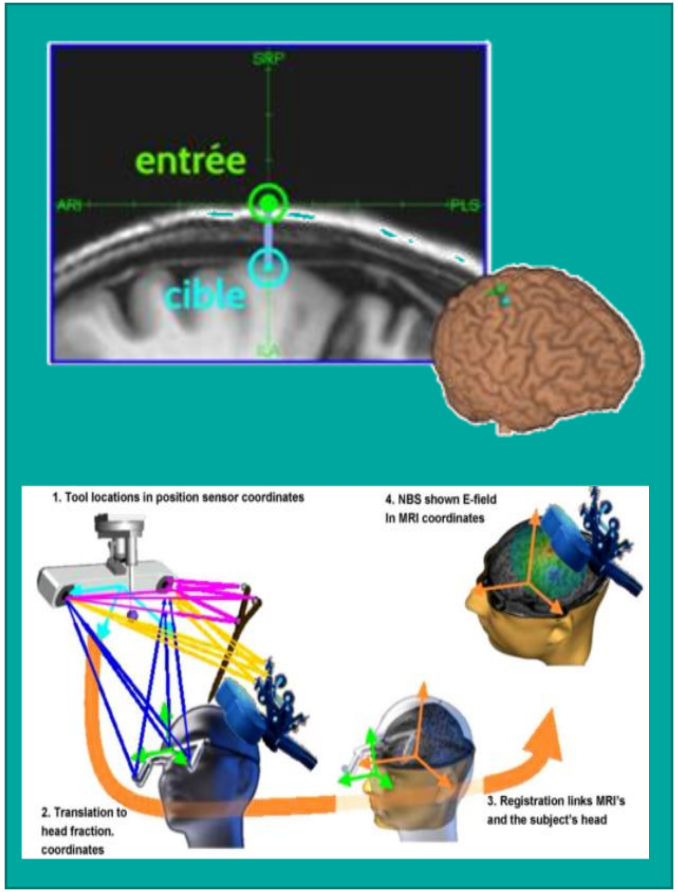


Neuronavigation

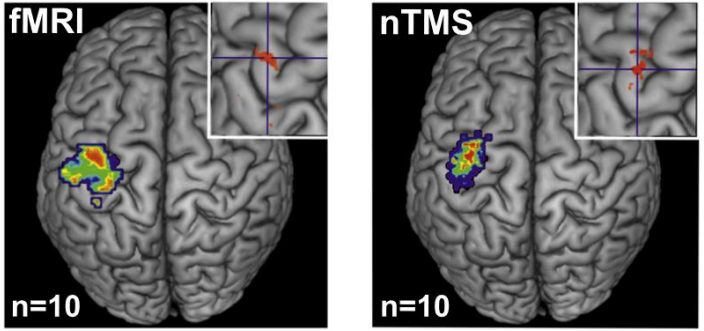


Bashir et al., Brain topo., 2011

Neuronavigation

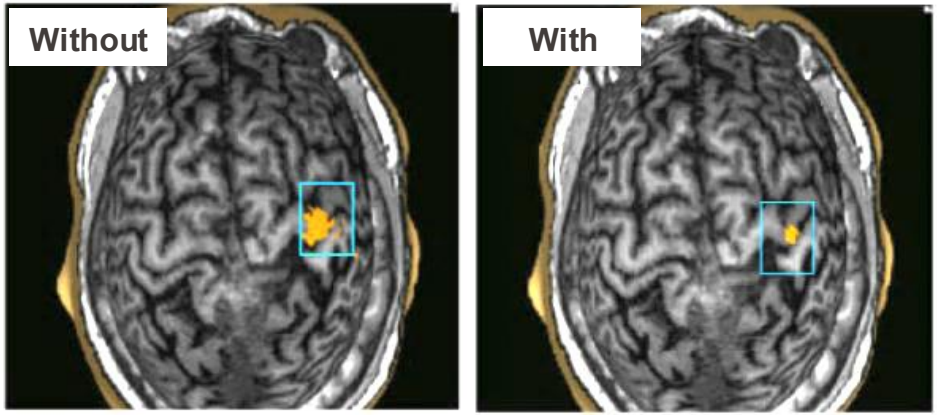


THUMB (APB)



✓ Increased **spatial precision**

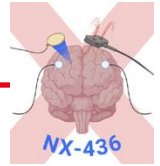
Weiss et al., NeuroImage, 2013

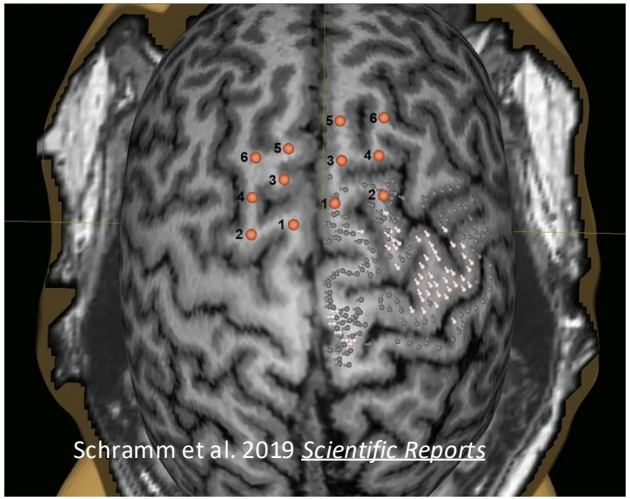


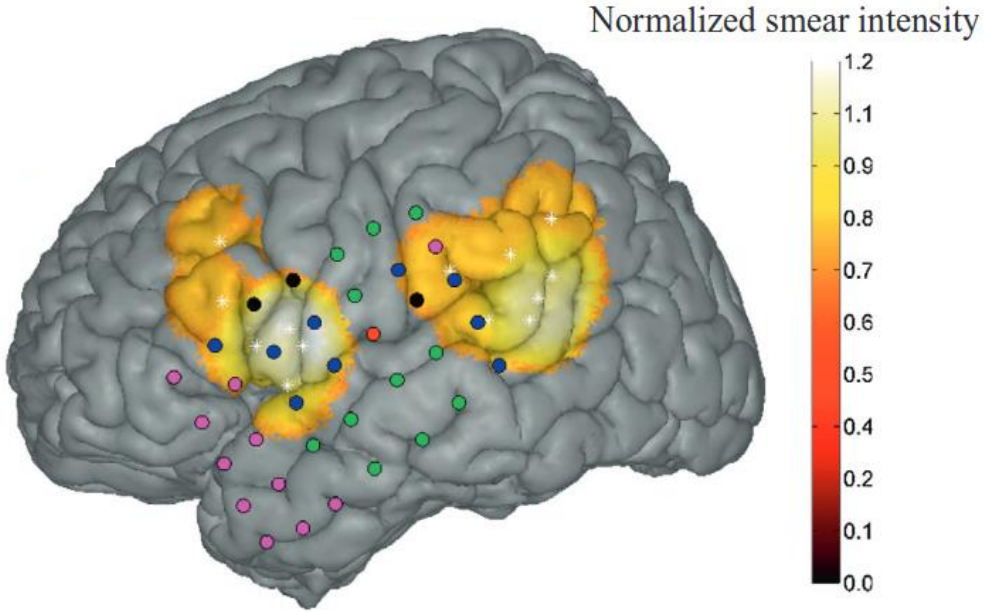
✓ Increased **reproducibility**

Bashir et al., Brain topo., 2011

Neuronavigation

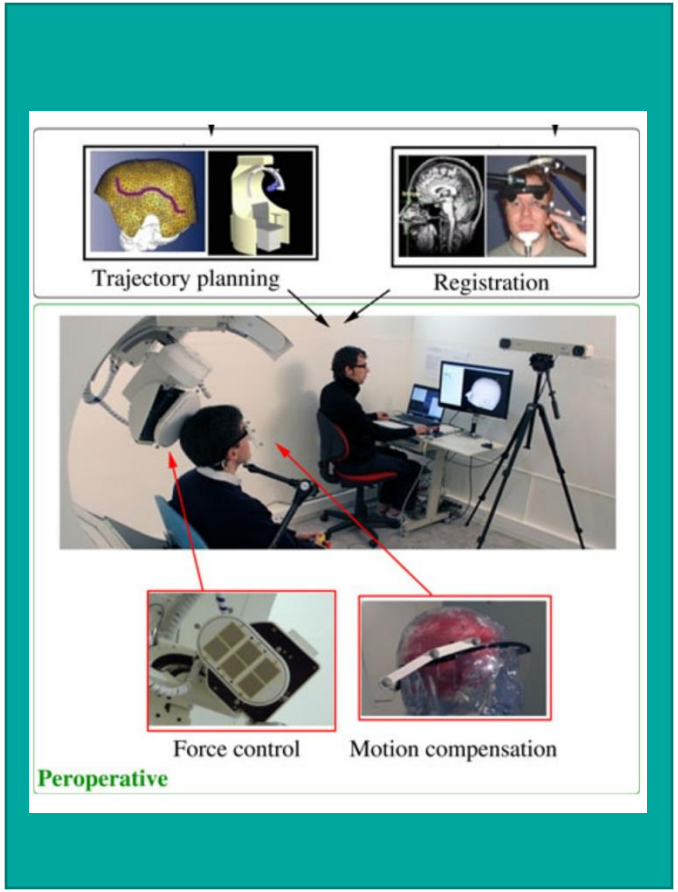






Tumor function mapping

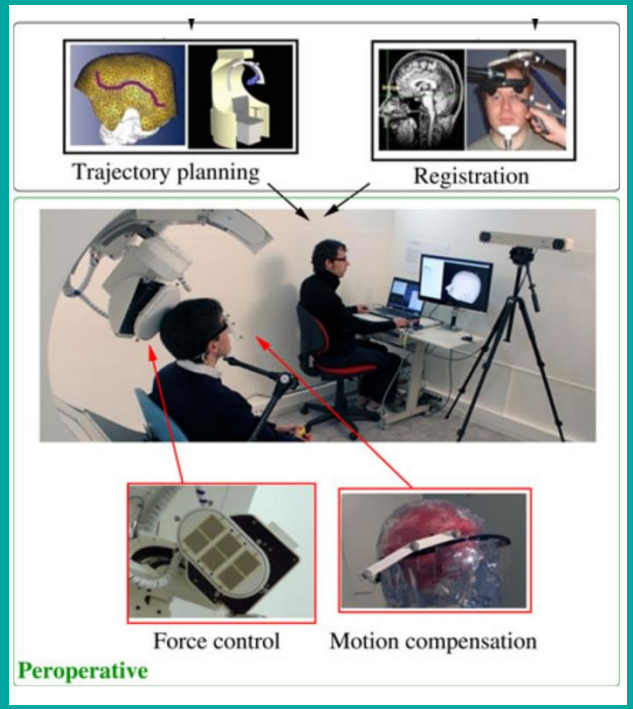
Robotized TMS

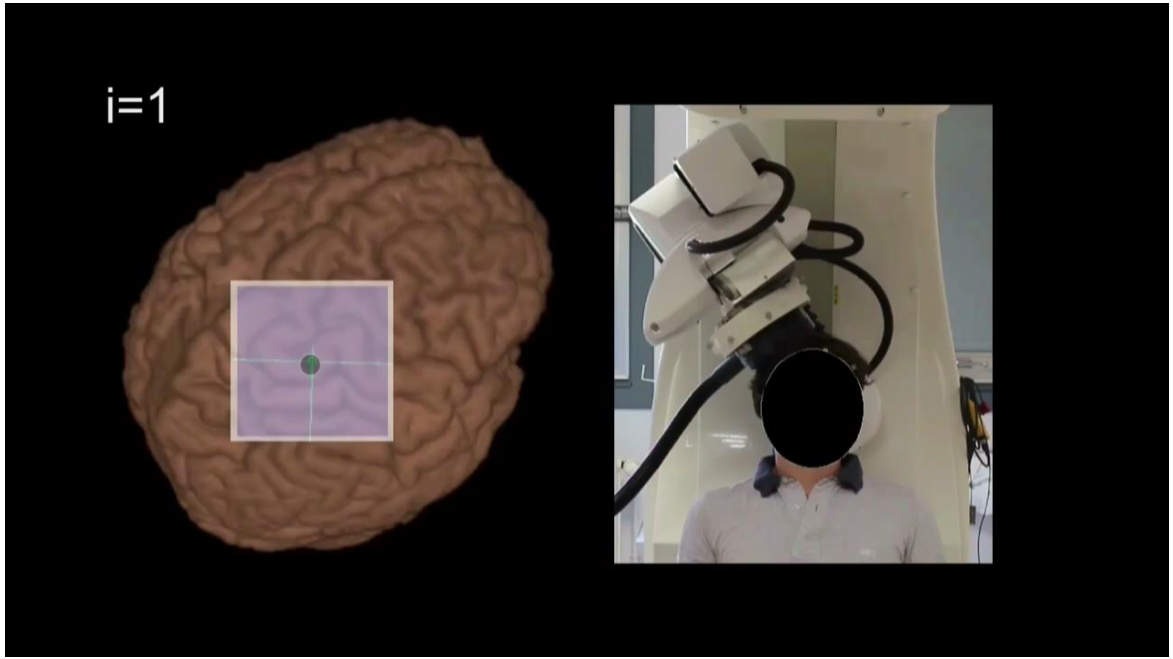


[redacted]

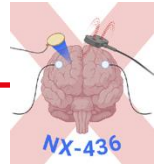
[redacted]

Robotized TMS





Summary



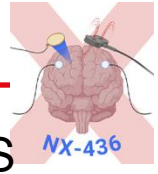
I. TMS effects change in relation to the ongoing activity

II. TMS allows mapping of functions

III. Precision of TMS is enhanced by the use of neuronavigation

IV. Robotic application of TMS is feasible

Safety



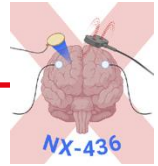
Seizure induction - Caused by spread of excitation. Single-pulse TMS has produced seizures in patients, but not in normal subjects. rTMS has caused seizures in patients and in normal volunteers. Visual and/or EMG monitoring for afterdischarges as well as spreading excitation may reduce risk.

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.

Heating of the brain - Theoretical power dissipation from TMS is few milliwatts at 1 Hz, while the brain's metabolic power is 13 W

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.

Safety

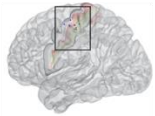


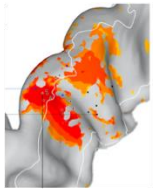
Scalp burns from EEG electrodes - Mild scalp burns in subjects with scalp electrodes can be easily avoided using, e.g., small low-conductivity Ag/AgCl-pellet electrodes.

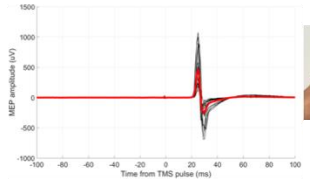
Effect on cognition - Slight trend toward better verbal memory, improved delayed recall and better motor reaction time

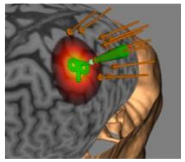
Local neck pain and headaches - Related to stimulation of local muscles and nerves, site and intensity dependant. Particularly uncomfortable over fronto-temporal regions.

Effect on Mood in normals - Subtle changes in mood are site and frequency dependant. High frequency rTMS of left frontal cortex worsens mood. High frequency rTMS of right frontal cortex may improve mood.









Thank you for your attention!