EPFL

Neuro X Institute

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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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)

Overview

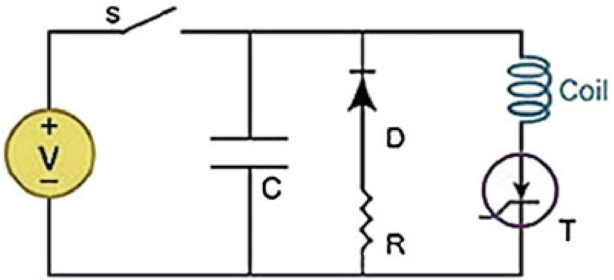
Three main areas of application for TMS:

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)

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).

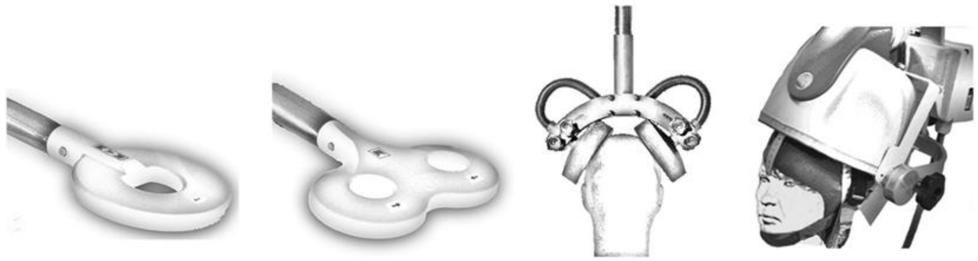
Energy recovery circuitry— allows for the main unit to recharge following discharge.

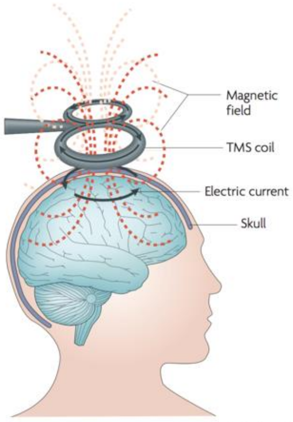
Thyristors — are electrical devices capable of switching large currents over a short period of time. Bridge between the capacitor and coil, transferring 500 J between the two in less than 100 ms.

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

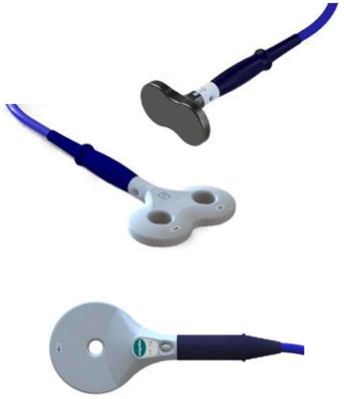
Stimulating coils — one or more well-insulated coils of copper wire (frequently housed in a molded plastic cover).

Overview - Coils





Ridding & Rothwell, 2007

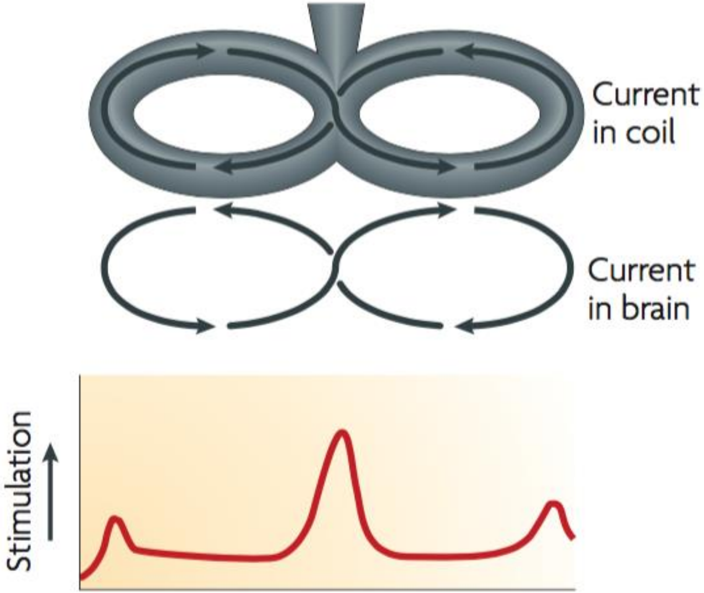


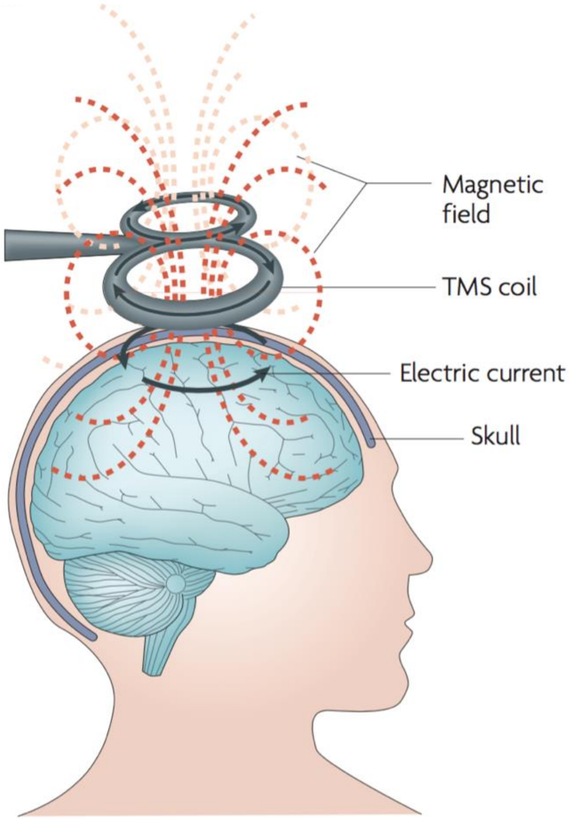
Circular or Round Coil— oldest and simplest TMS coil design. A single, centrally located coil generates a spherical magnetic fi eld perpendicular to the coil itself

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

Overview - Coils

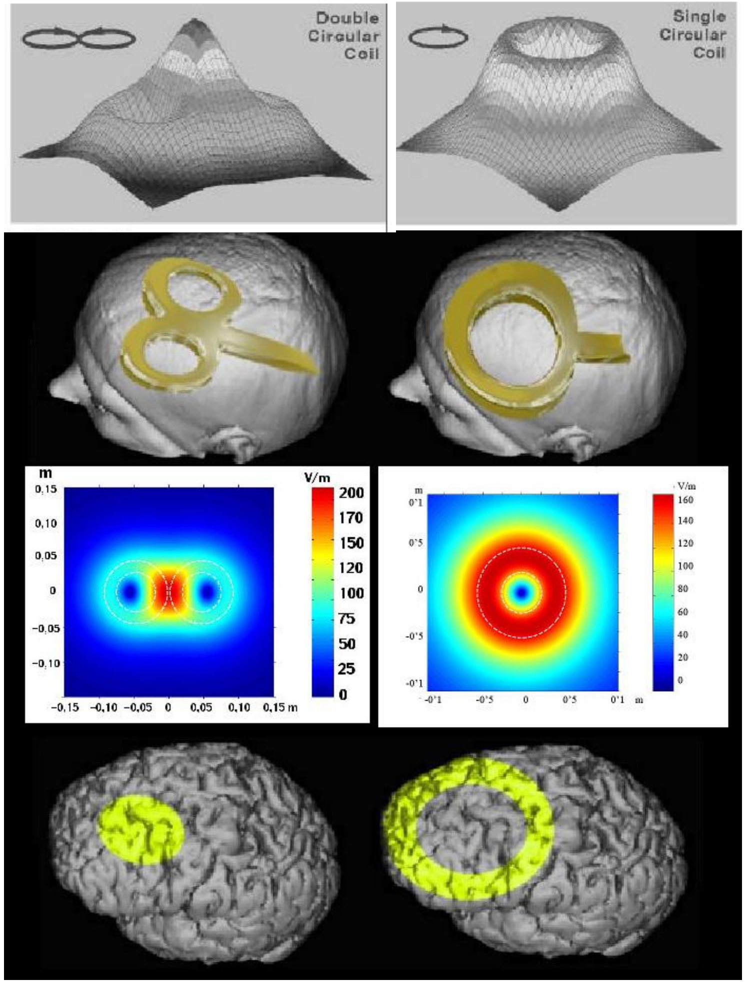




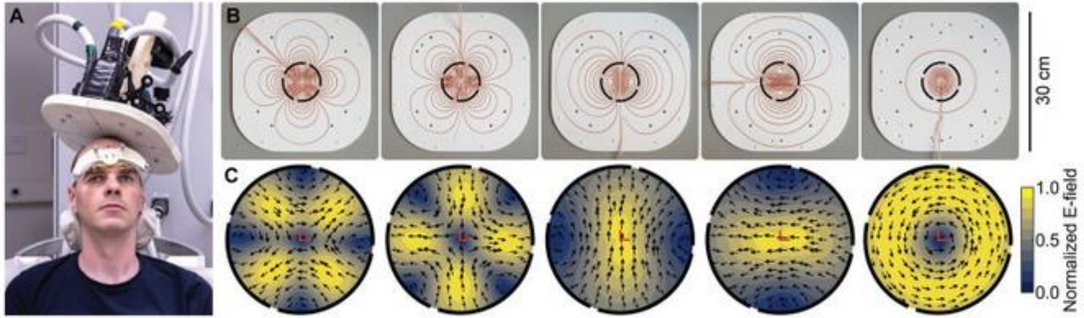
Ridding & Rothwell 2007 Nat Rev Neurosci

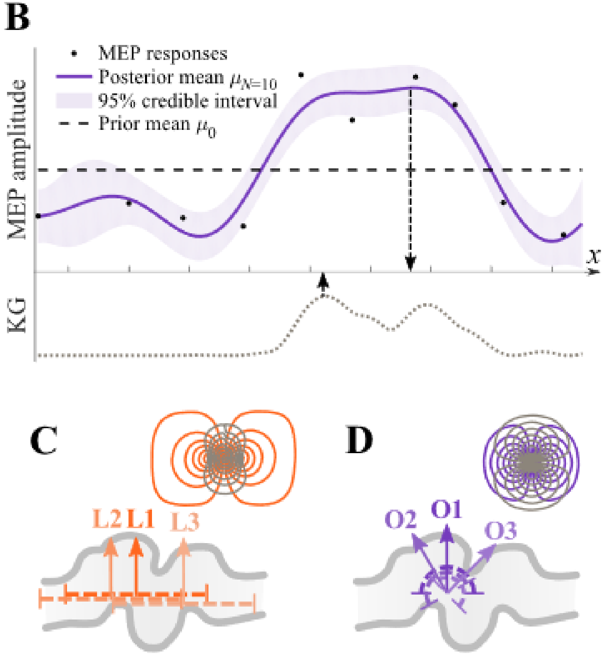
Overview - Coils

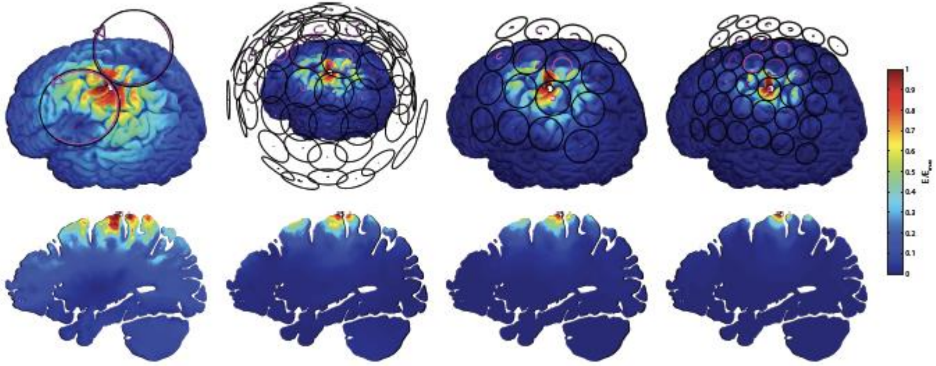
The geometry of the coil determines the focality of the magnetic field and of the induced current - hence also of the targeted brain area.



Next generation coil setups



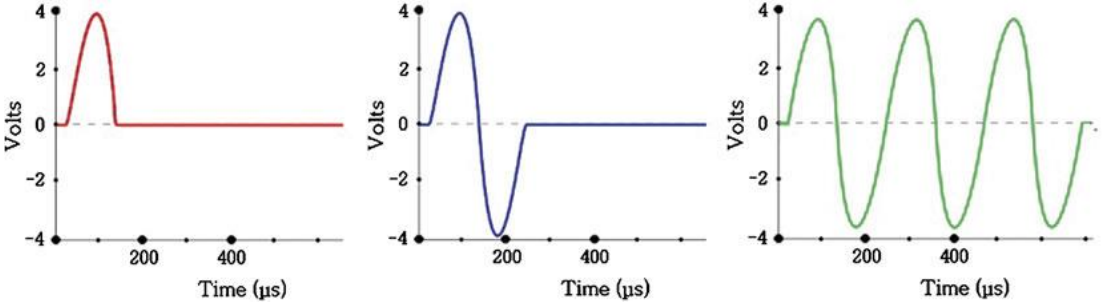




(a) Figure-8 (b) 64-channel (c) 16-channel (d) 36-channel

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

Overview – Pulse Waveforms, Pulse Strength

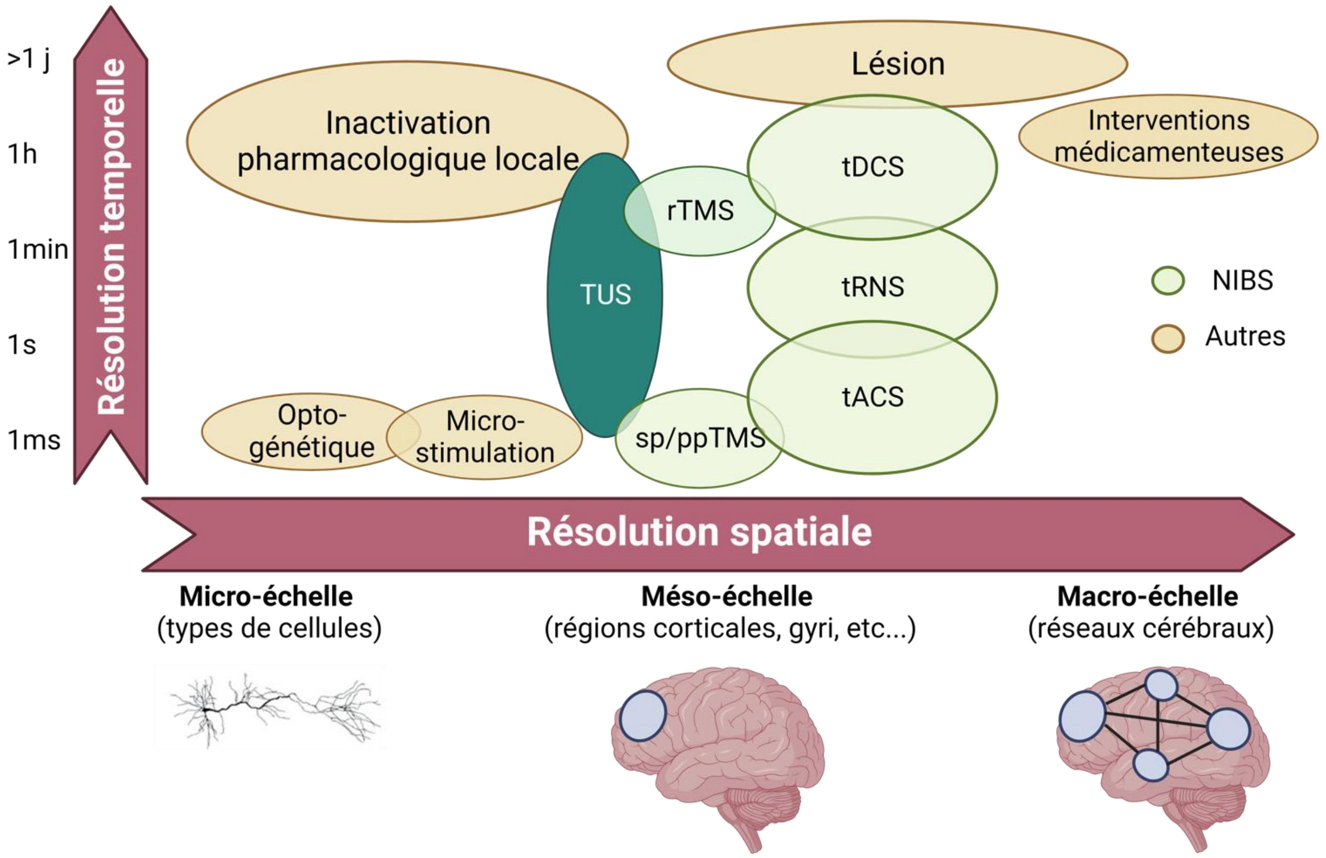


Monophasic pulses - generate only unidirectional voltage. As the initial course of voltage (positive) through a coil would induce an opposing (negative) oscillation, in order to generate a monophasic pulse a shunting diode and power resistor must be used to dampen this natural cycle. Due to this pulse-shaping,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

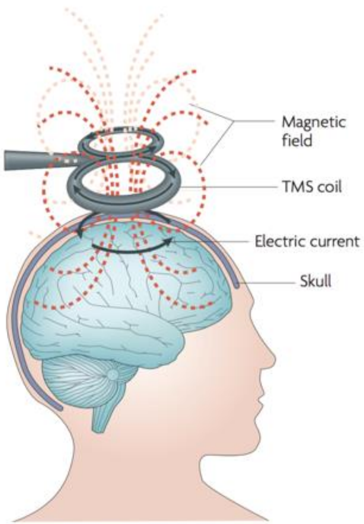
Biphasic (Polyphasic) pulses - generate full positive/negative voltage oscillations. This oscillation, in turn, causes a rapid directional shift of the initial and induced currents. This type of pulse can be terminated after a single cycle (biphasic) or after several oscillatory cycles (polyphasic pulses)

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.

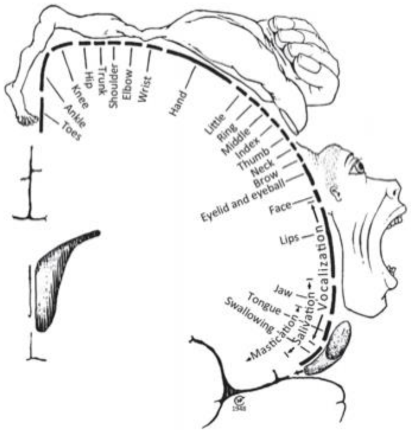
Topographic resolution



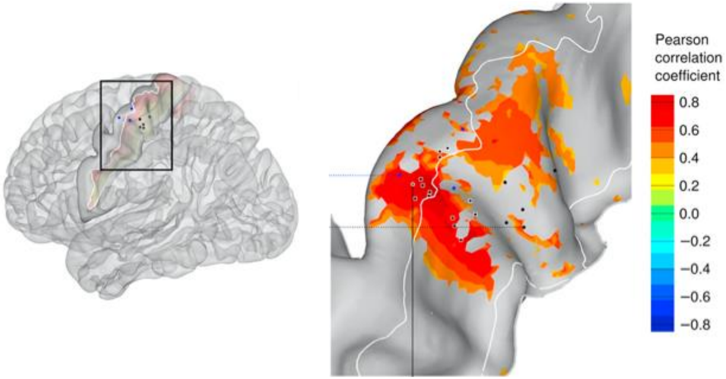
Topographic resolution



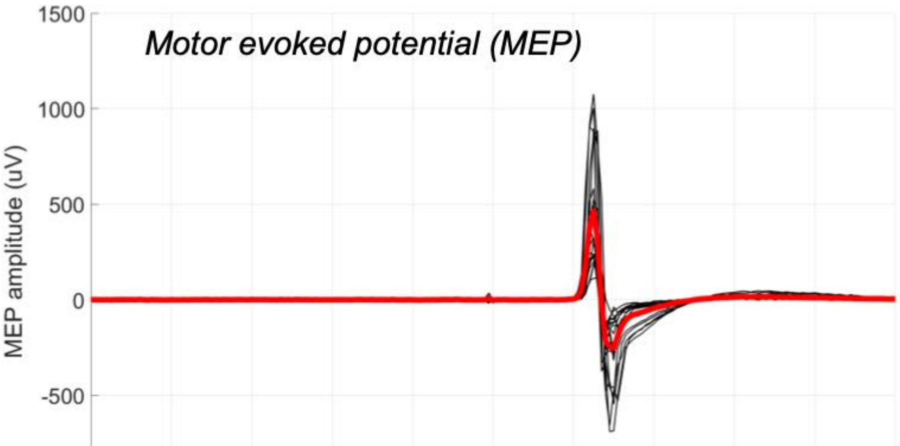
Ridding & Rothwell, 2007



Penfield & Rasmussen, 1950, Adapted from Graziano, 2016



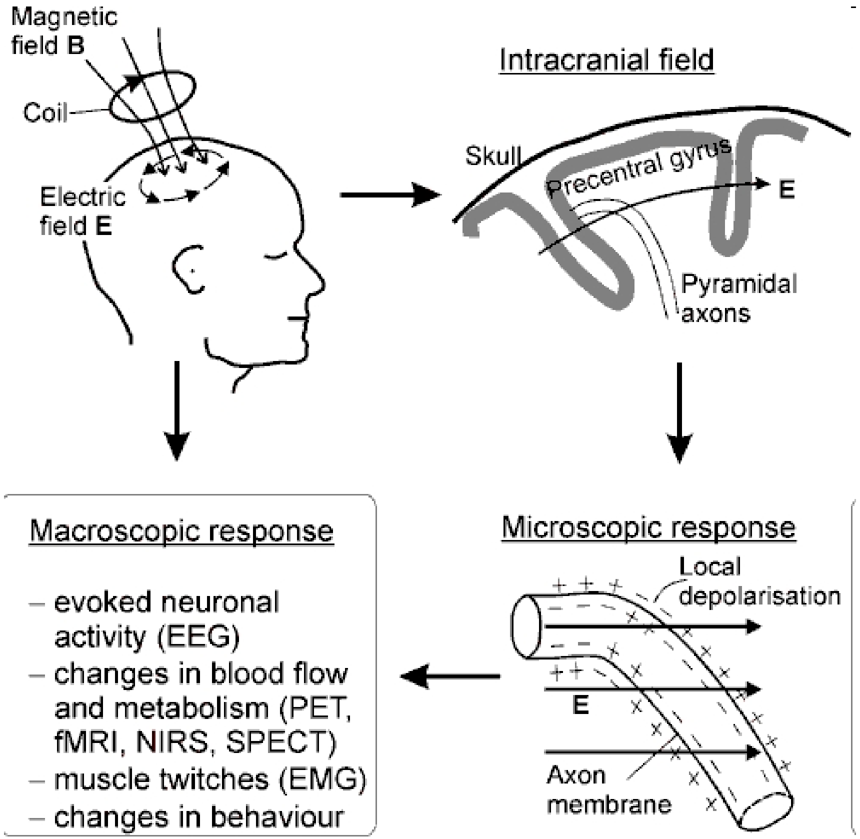
Adapted from Laakso et al., 2017



EMG

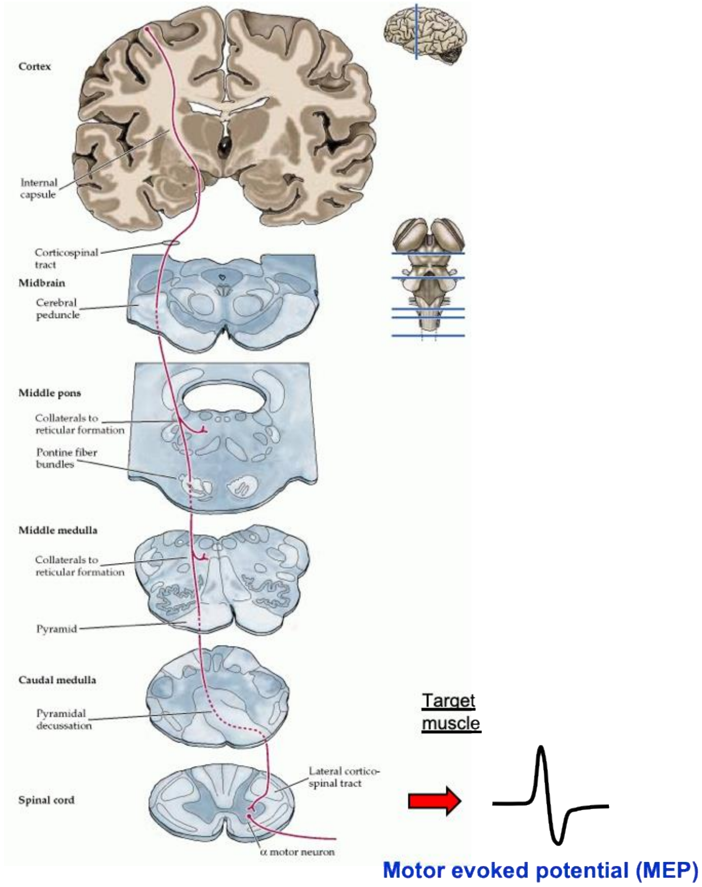
- ❑ Single pulse TMS (cortico-spinal excitability)
- ❑ Double Pulse TMS (Kujirai et al, 1993)
- ❑ Neurotransmitter systems, e.g. GABA-A-ergic, Glumatergic (Ziemann et al., 1998)
- ❑ Resting State, Event-related (Hummel et al. 2009, Heise et al. 2010, 2013, 2014)
- ❑ Interregional Interactions (Murase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

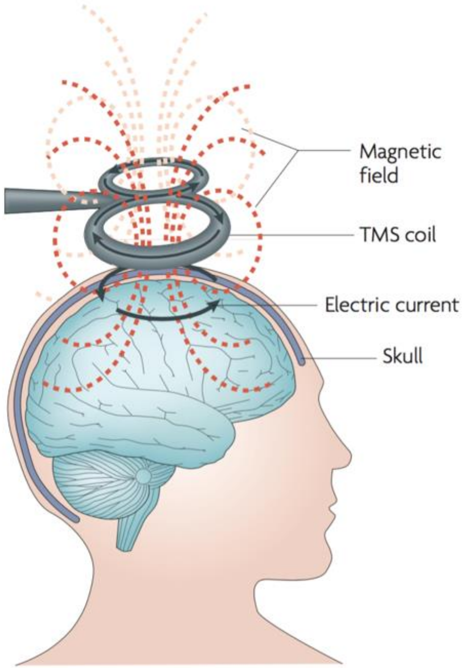
Physiology



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

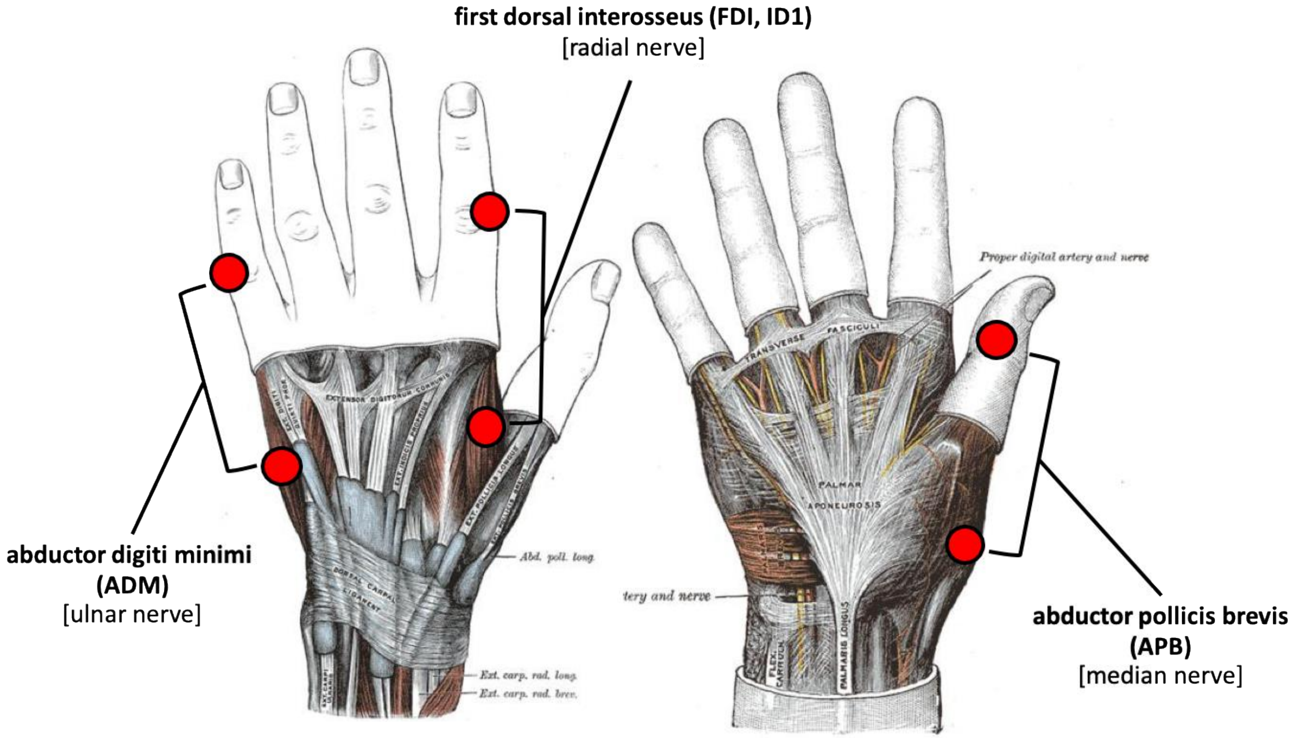
Physiology





Ridding & Rothwell 2007 Nat Rev Neurosci

electromyogram (EMG) of the hand

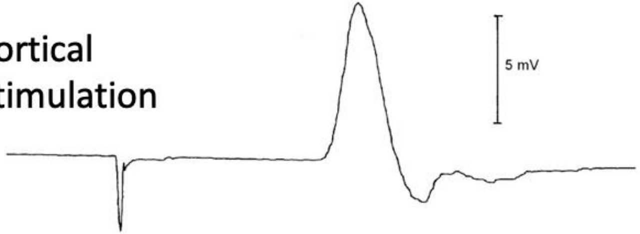


electrodes are placed in a bipolar belly-tendon montage

motor evoked potential (MEP)

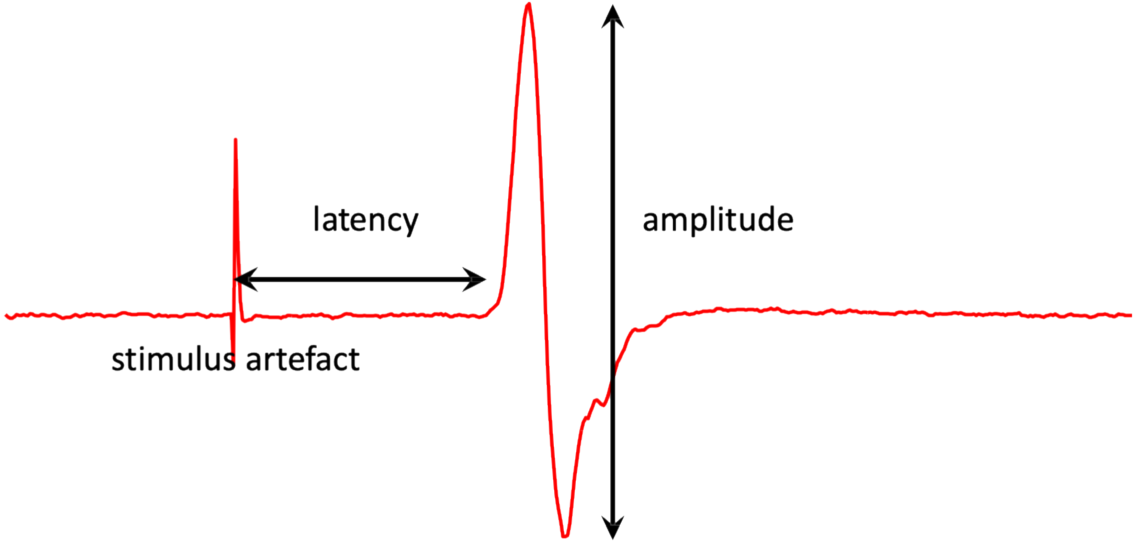
Barker, 1984

cortical
stimulation



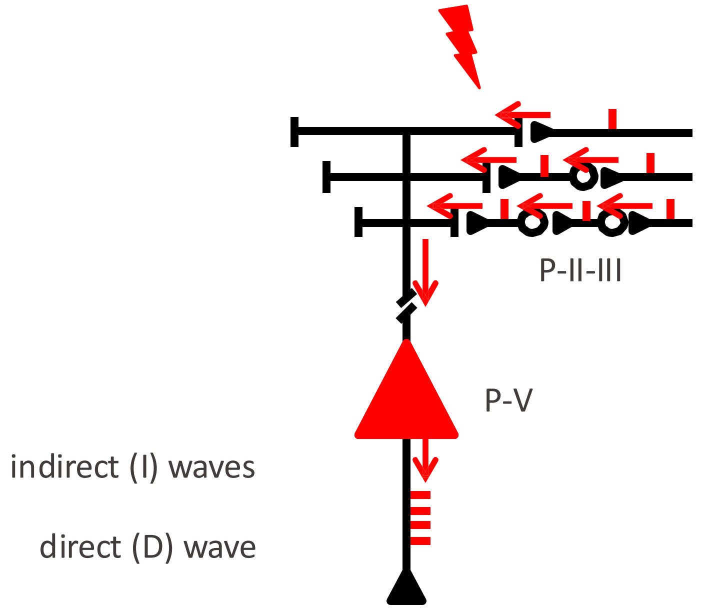
Physiological measures

motor evoked potential (MEP)

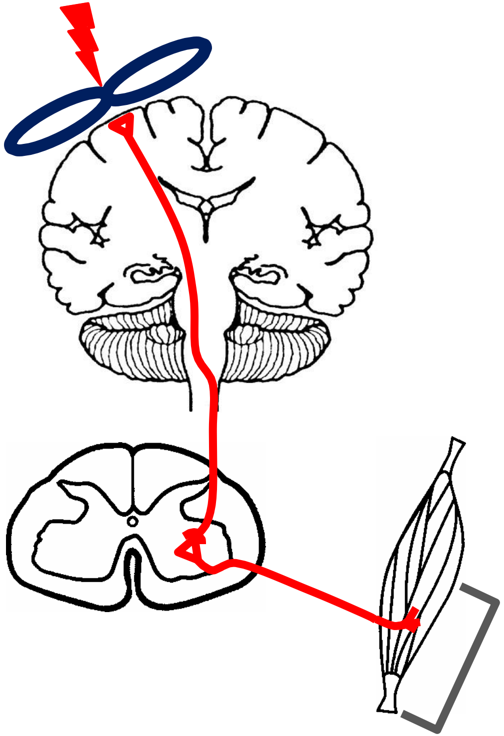


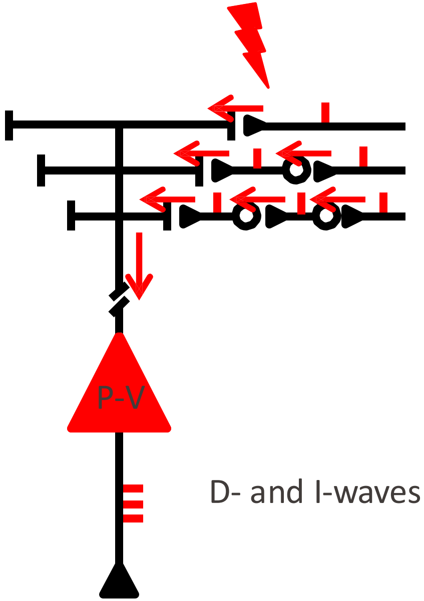
quantify: single pulse

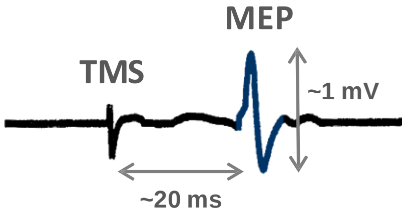
a single pulse?



Physiology

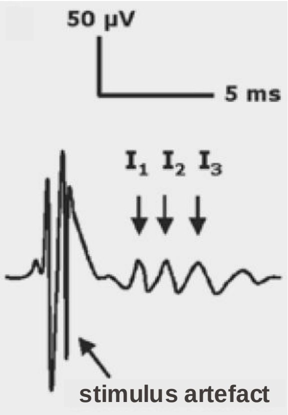


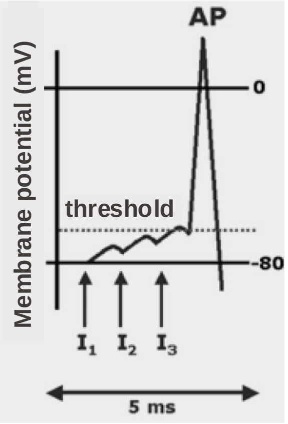


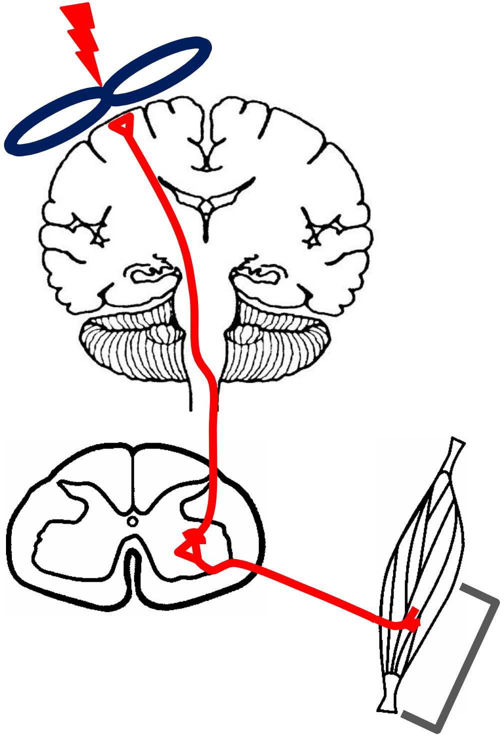


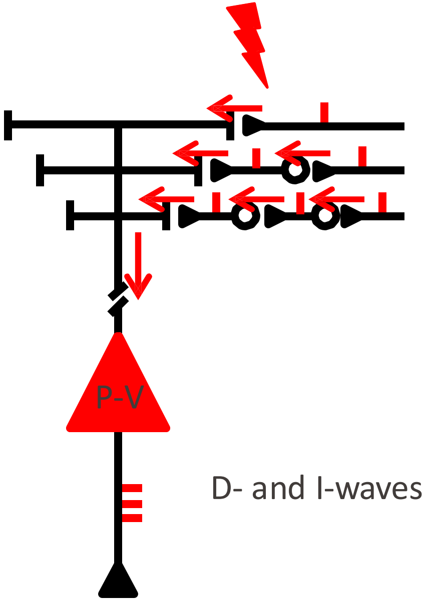
Siebner & Ziemann (2007) *Das TMS-Buch*

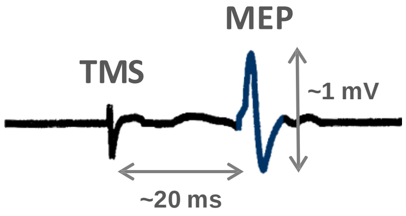
Physiology











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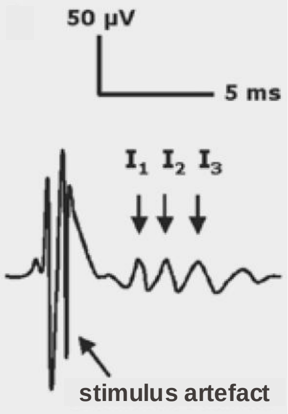
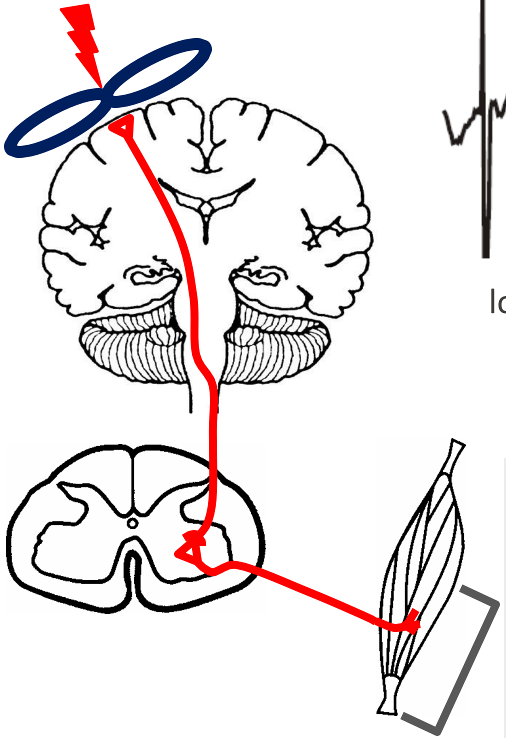
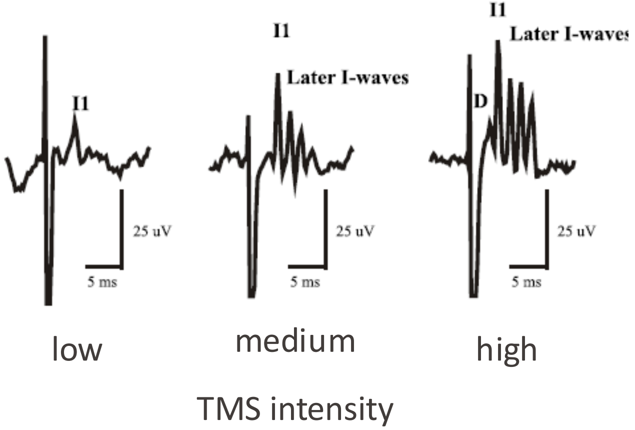
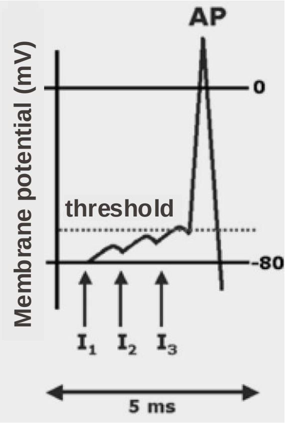
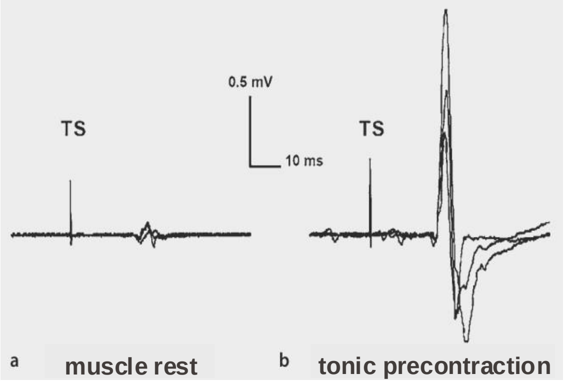
Physiology











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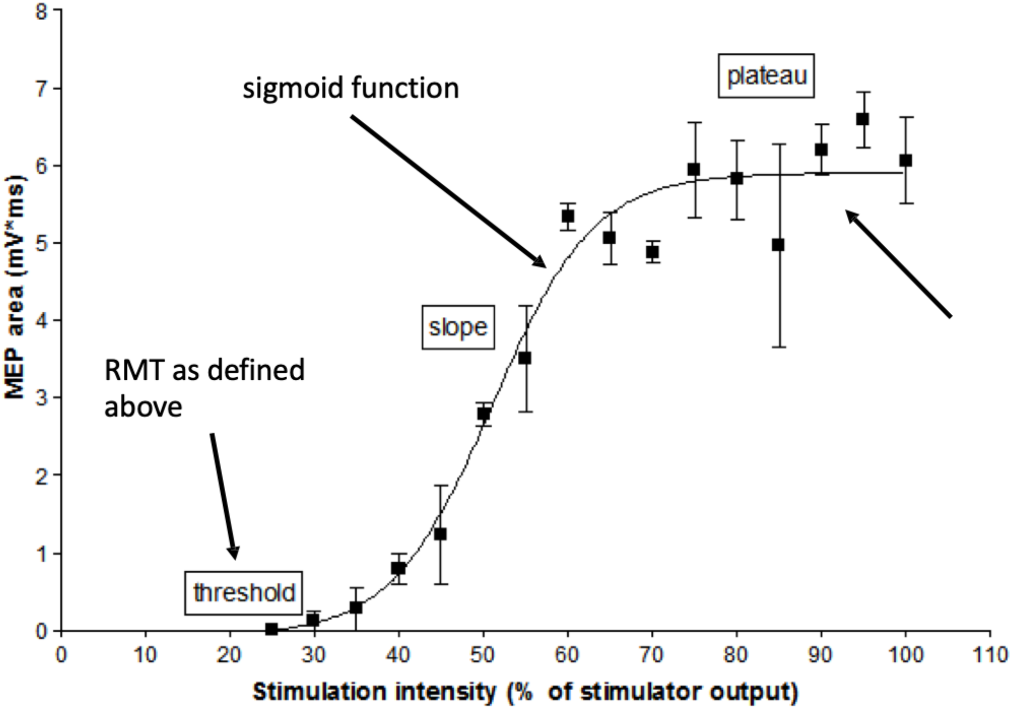
Intensity - response curve of the MEP



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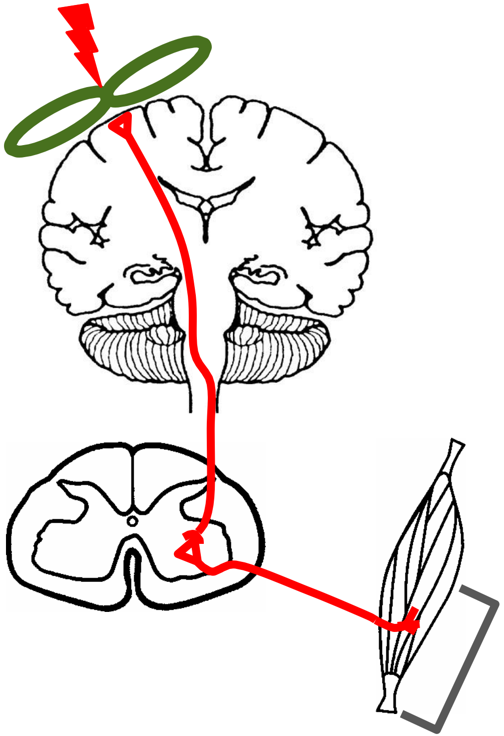
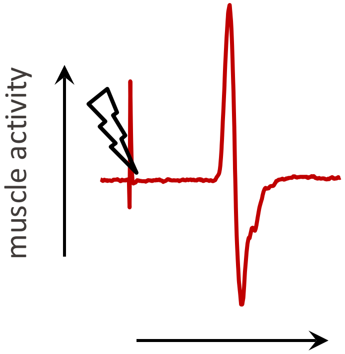
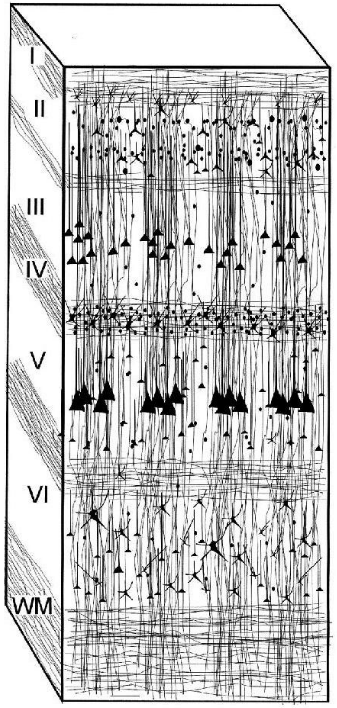
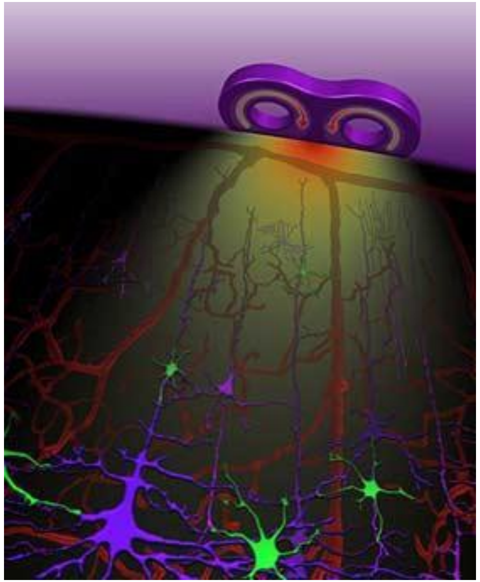
cortico-spinal system

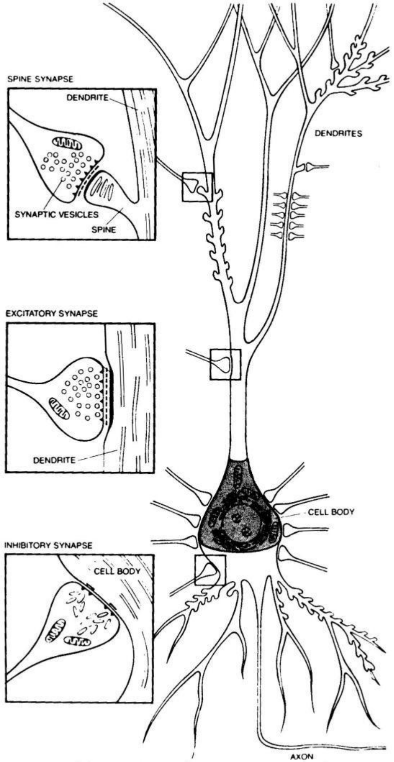


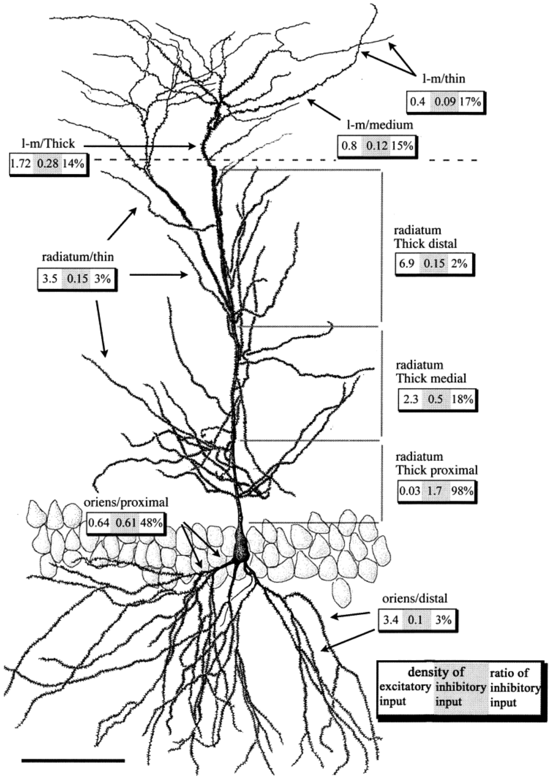






pyramidal cells



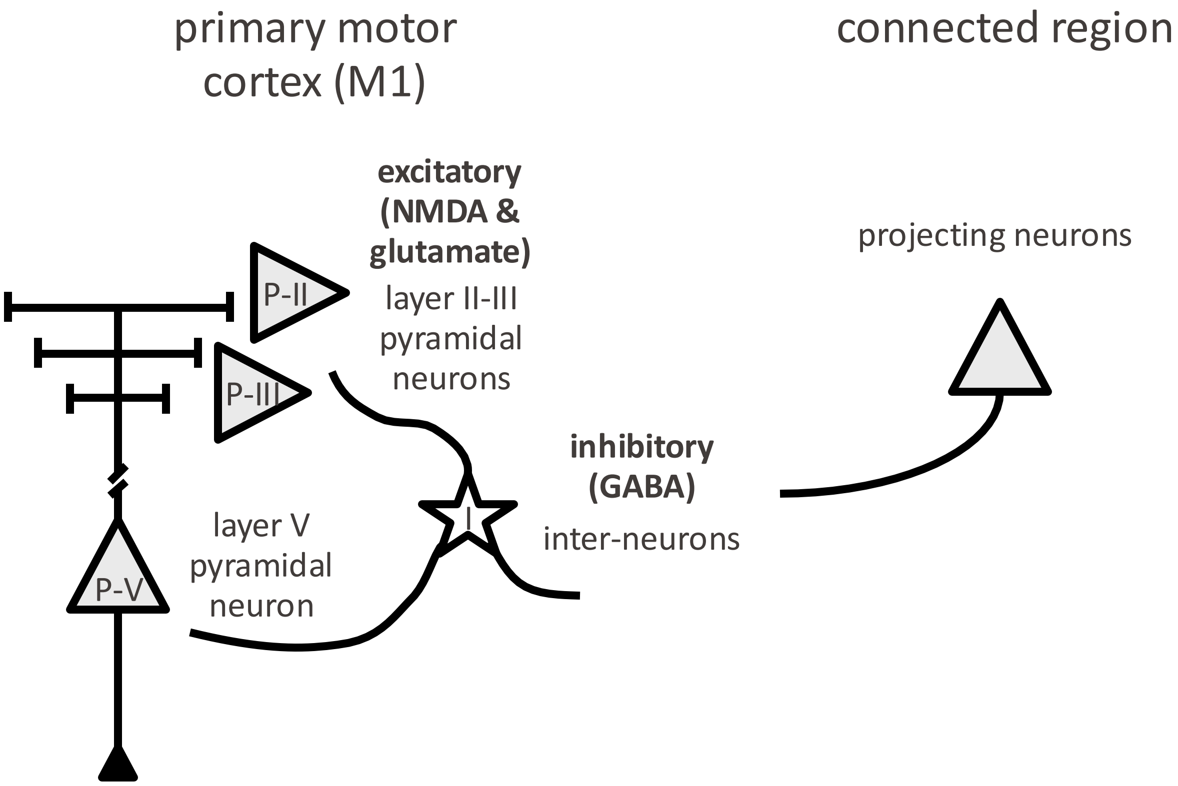


excitatory

inhibitory

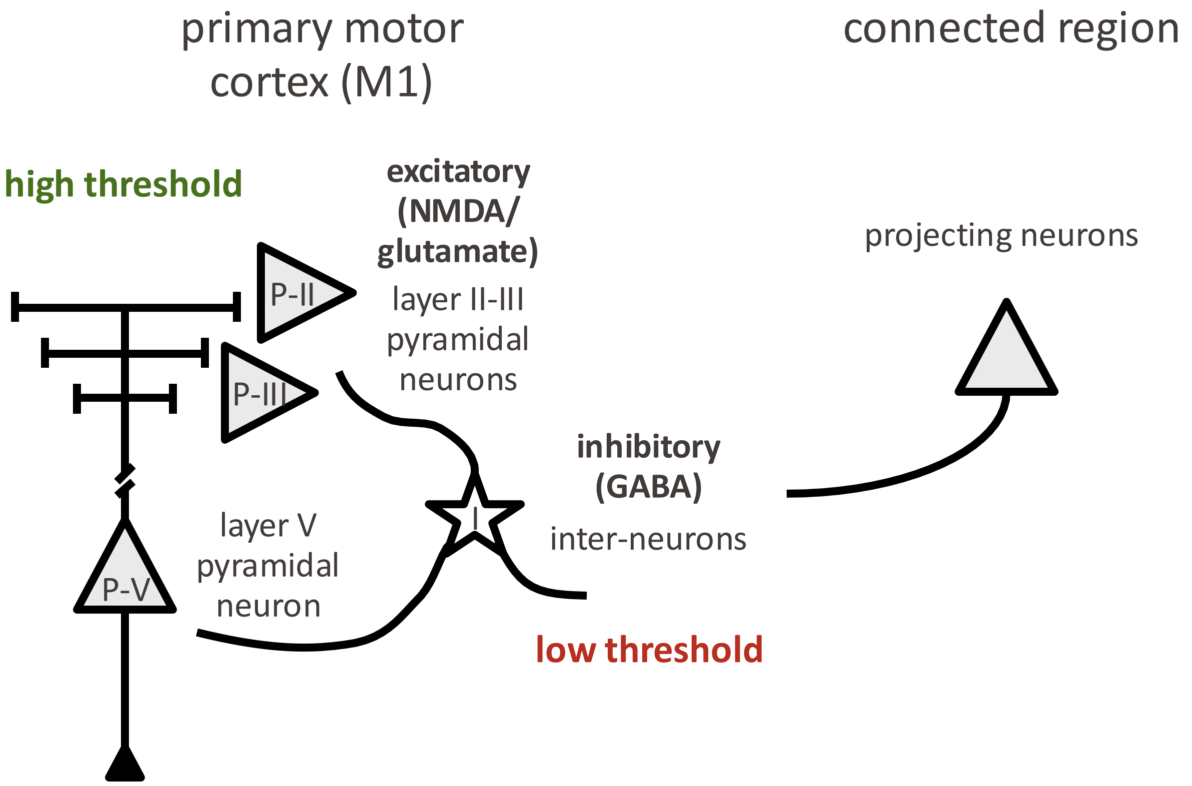
excitatory

pyramidal cells

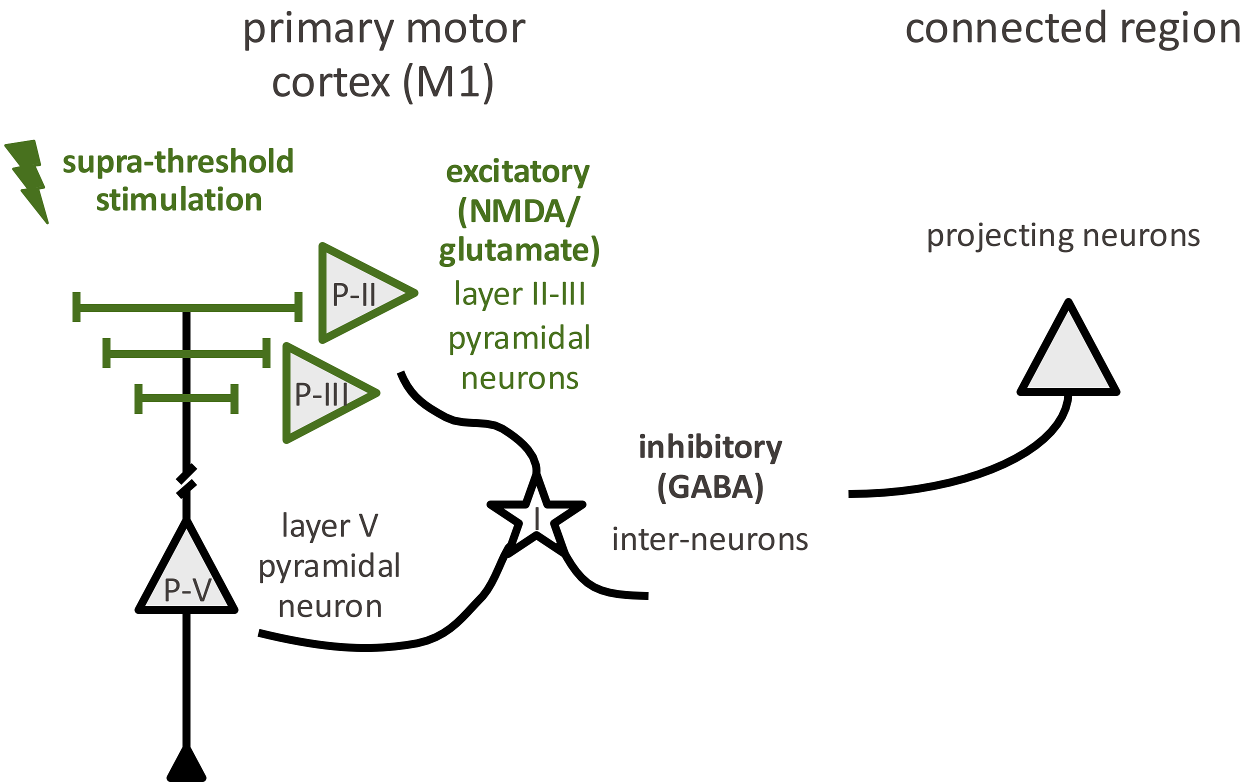


Determining intracortical neurotransmitter systems: paired pulse TMS

(intra-) cortical circuits

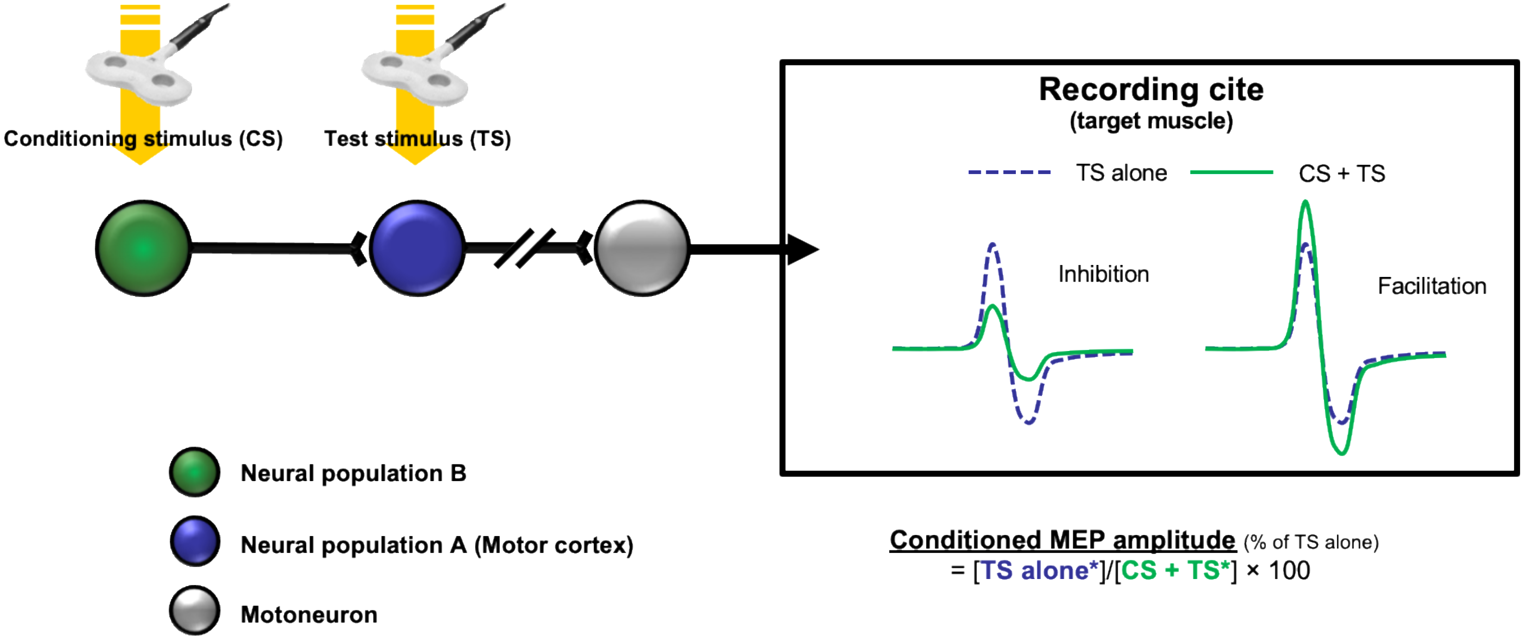


(intra-) cortical circuits



di Lazzaro & Ziemann (2013) *FrontNeurCirc*

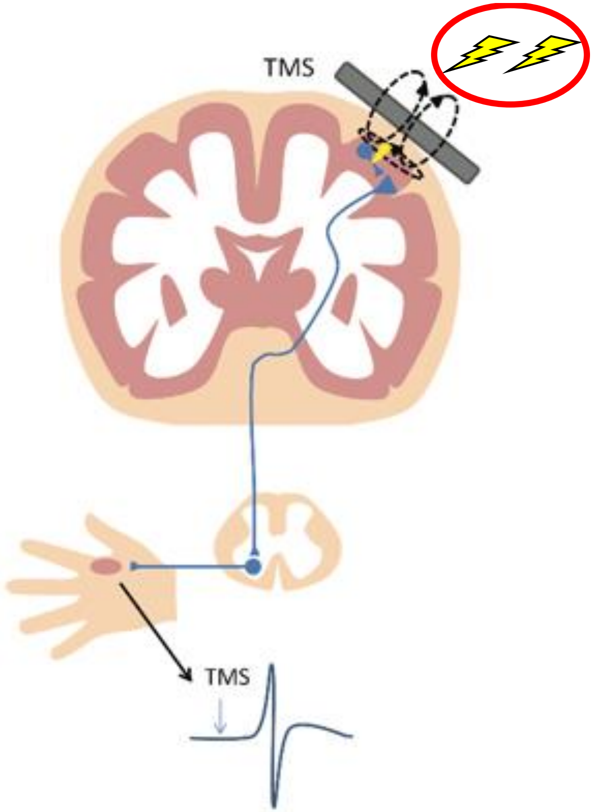
General principle paired-pulse TMS

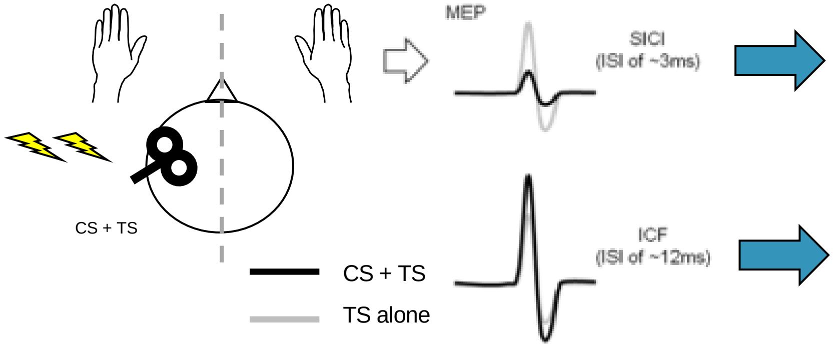


Conditioned MEP amplitude (% of TS alone)
= [TS alone*]/[CS + TS*] × 100

*Peak-to-peak amplitude is analyzed

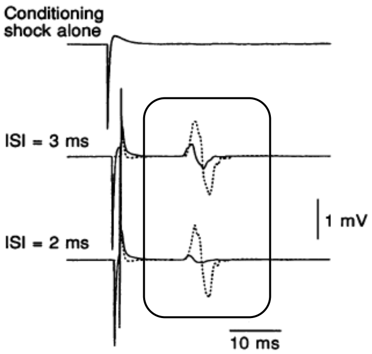
Physiology – neurotransmitter systems

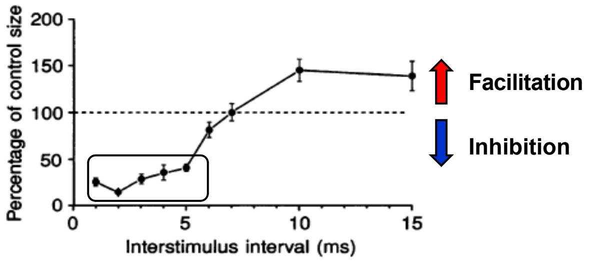




GABA$_A$ mediated

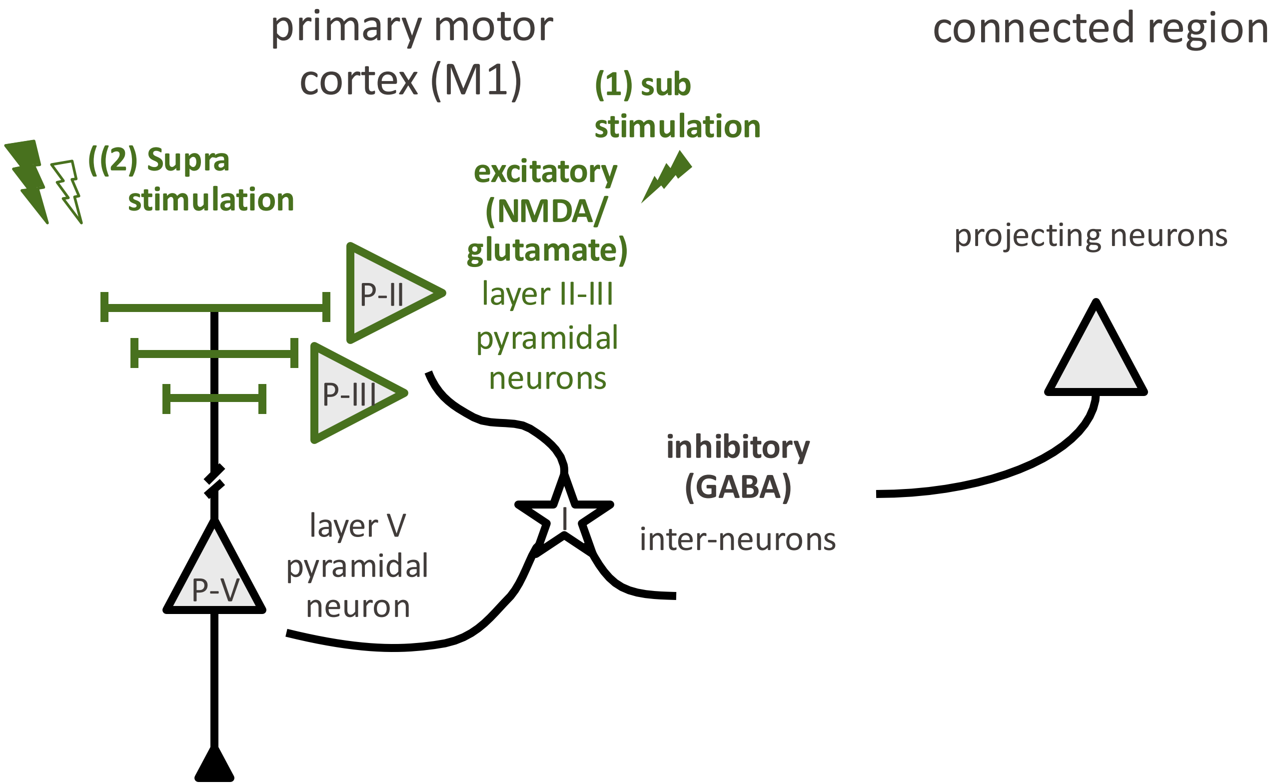
Glutamatergic mediated





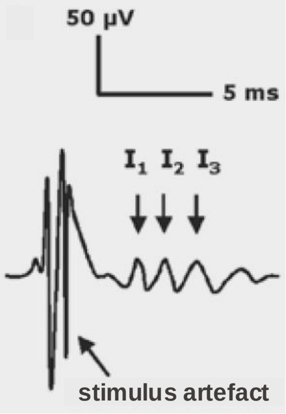
Adapted from Rogasch *et al*. (2013) *Schizopherenia Bulletin*; Kujirai *et al*. (1993) *Journal of Physiology*

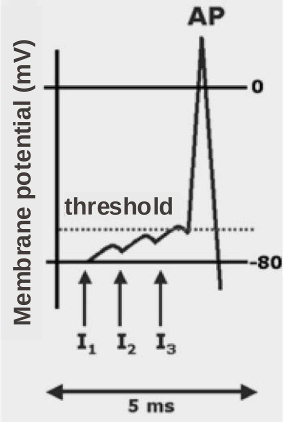
(intra-) cortical circuits



di Lazzaro & Ziemann (2013) *FrontNeurCirc*

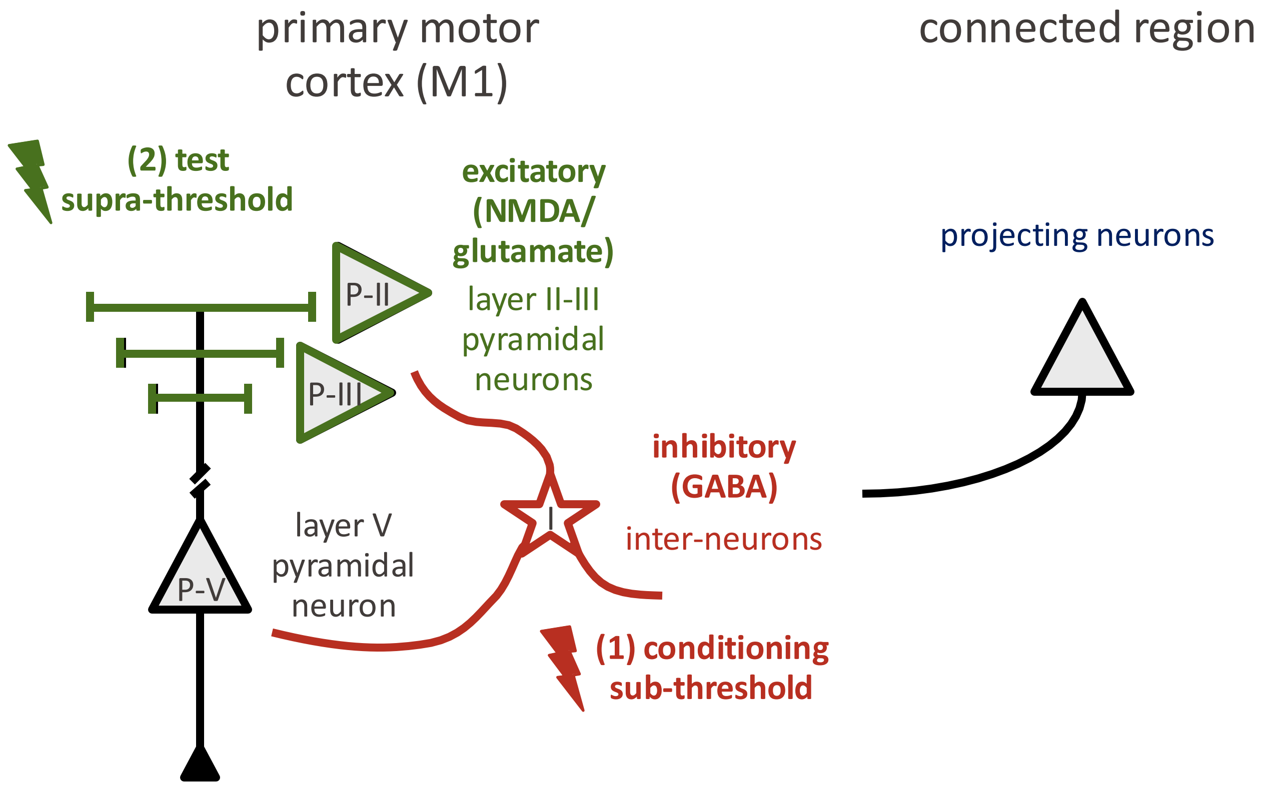
intra-cortical paired-pulse protocols



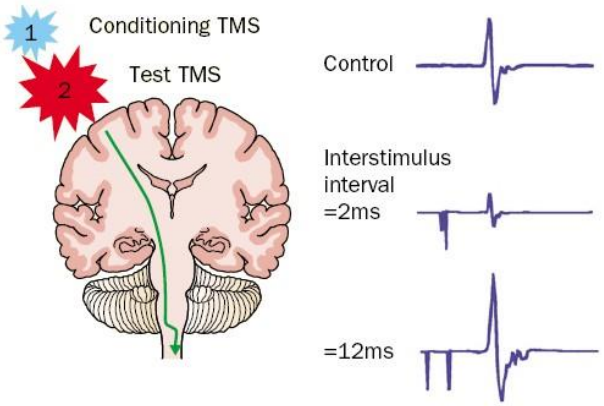


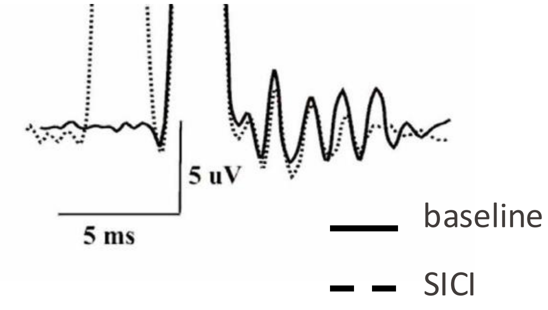
protocol	stim 1	stim 2	ISI	Mechanism
short-interval intracortical facilitation (SICF)	supra	sub	1.1-1.5 ms	I-waves

intra-cortical paired-pulse protocols



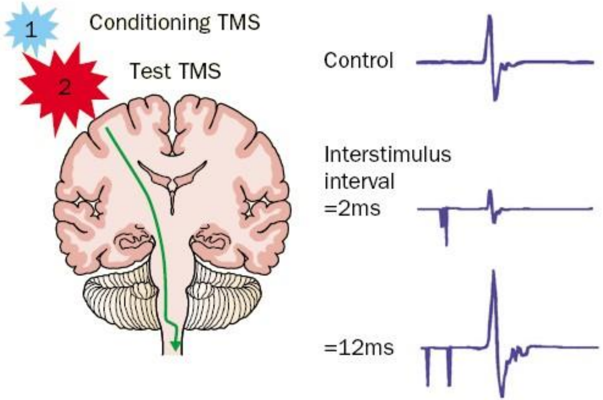
intra-cortical paired-pulse protocols

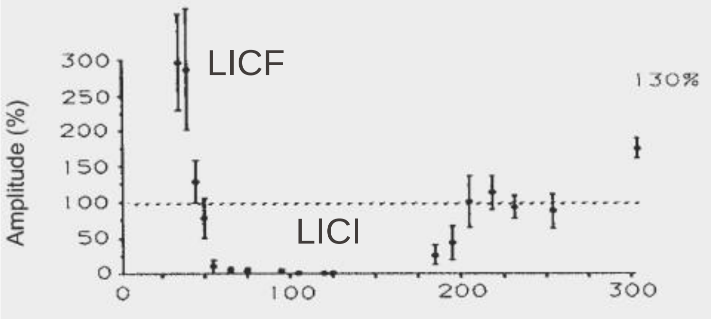




protocol	stim 1	stim 2	ISI	Mechanism
short-interval intracortical facilitation (SICF)	supra	sub	1.1-1.5 ms	I-waves
short-interval intracortical inhibition (SICI)	sub	supra	3ms	$GABA_A$-R
intracortical facilitation (ICF)	sub	supra	10-15 ms	NMDA-R

intra-cortical paired-pulse protocols

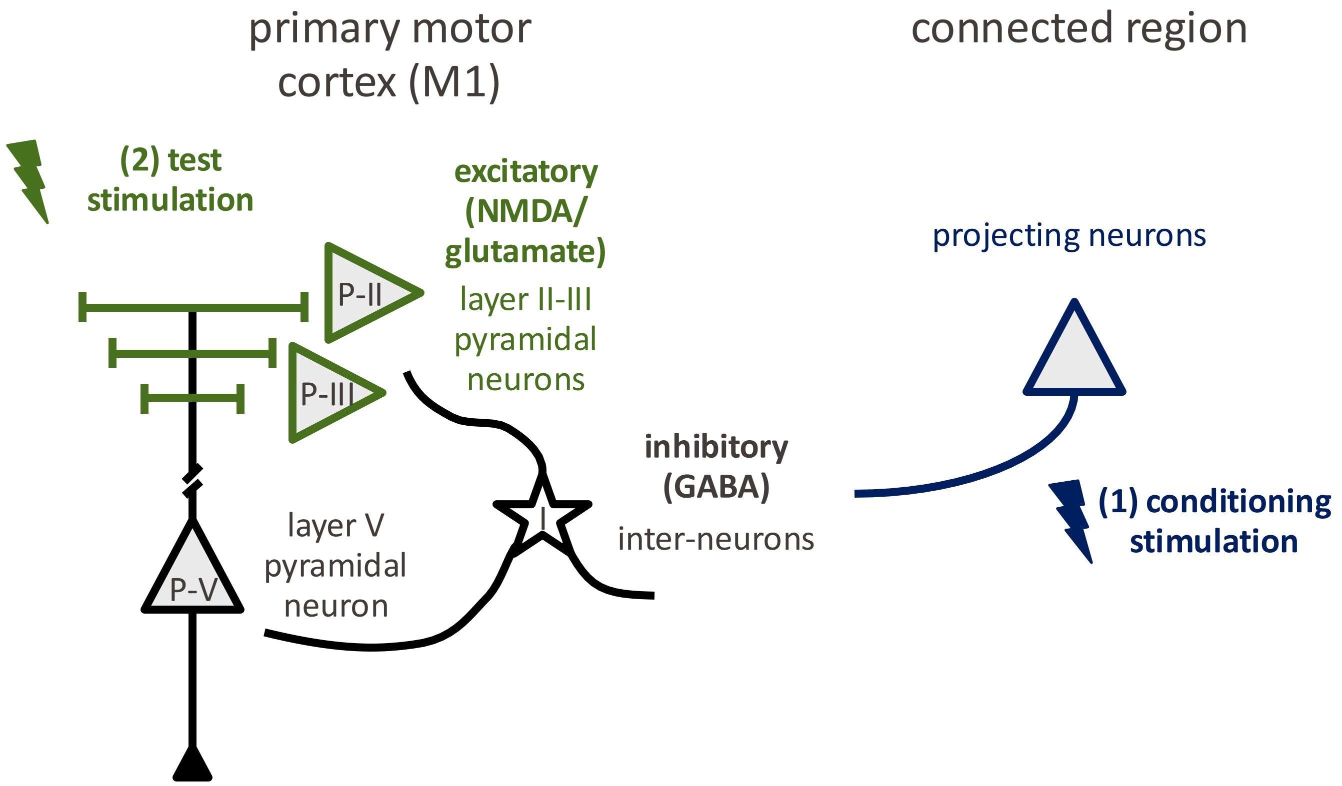




Siebner & Ziemann (2007) *Das TMS-Buch*

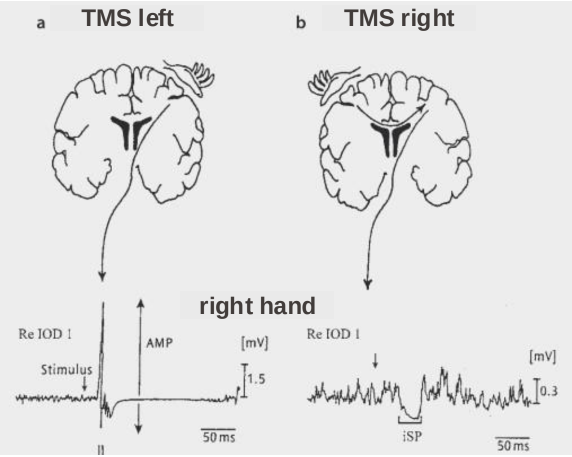
protocol	stim 1	stim 2	ISI	Mechanism
short-interval intracortical facilitation (SICF)	supra	sub	1.1-1.5 ms	I-waves
short-interval intracortical inhibition (SICI)	sub	supra	3 ms	$GABA_A$-R
intracortical facilitation (ICF)	sub	supra	10-15 ms	NMDA-R
long-interval intracortical facilitation (LICF)	supra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

inter-cortical paired-pulse protocols



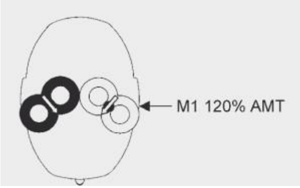
di Lazzaro & Ziemann (2013) *FrontNeurCirc*

inter-cortical paired-pulse protocols



test right

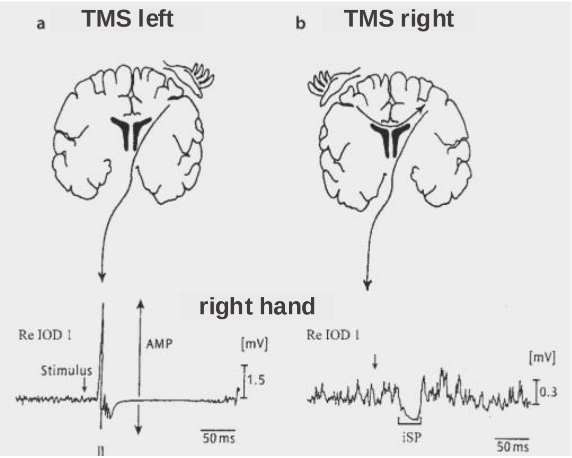
condition left



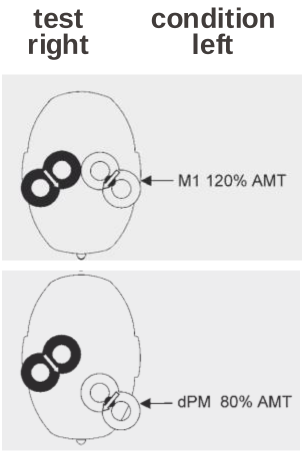
Siebner & Ziemann (2007) *Das TMS-Buch*

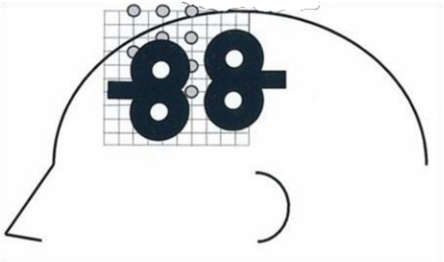
protocol	stim 1	stim 2	ISI	Mechanism
Interhemispheric inhibition (IHI)	supra	supra	6-12 ms	transcallosal projections
Interhemispheric facilitation (IHF)	supra	supra	4-5 ms	

inter-cortical paired-pulse protocols

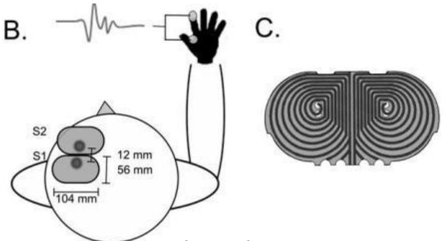


Siebner & Ziemann (2007) *Das TMS-Buch*





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

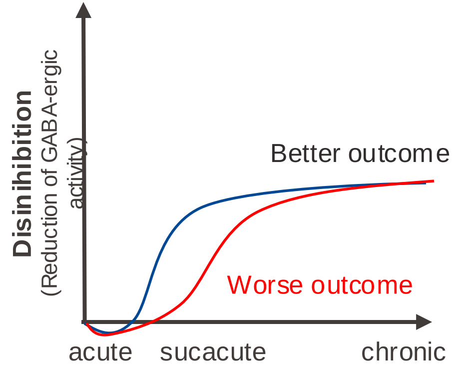
doi:10.1038/nature09511

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

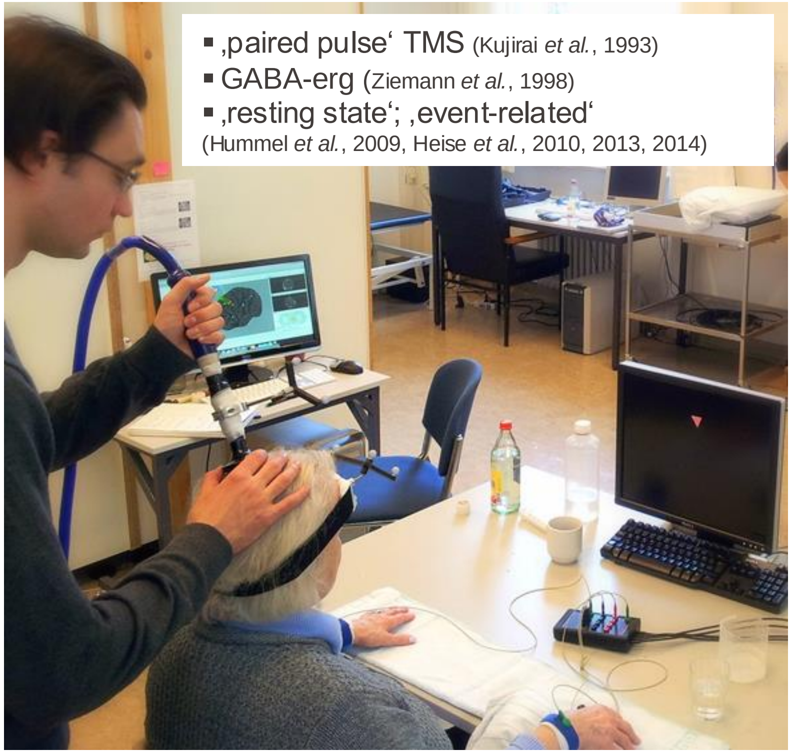
Animal model



Transcranial magnetic stimulation (TMS)

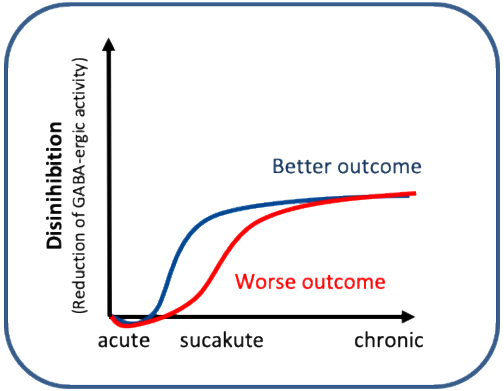
- ‚paired pulse' TMS (Kujirai *et al.*, 1993)
- GABA-erg (Ziemann *et al.*, 1998)
- ‚resting state'; ‚event-related'

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



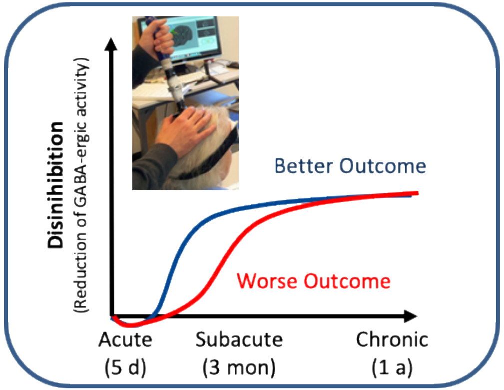
Clinical examples

Animal model

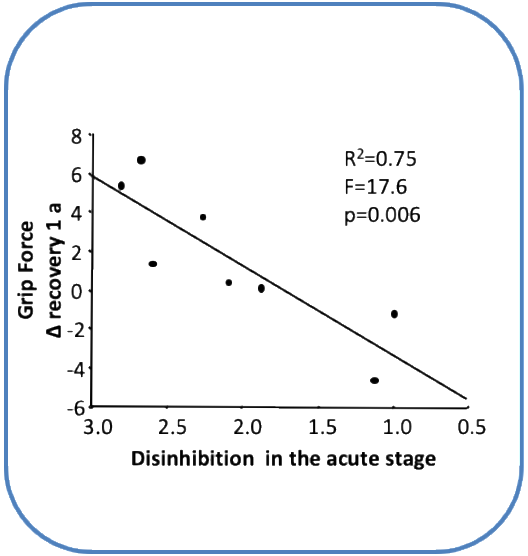


Model based on Clarkson *et al.* (2010) *Nature*

Model in stroke patients



Stroke Patients



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

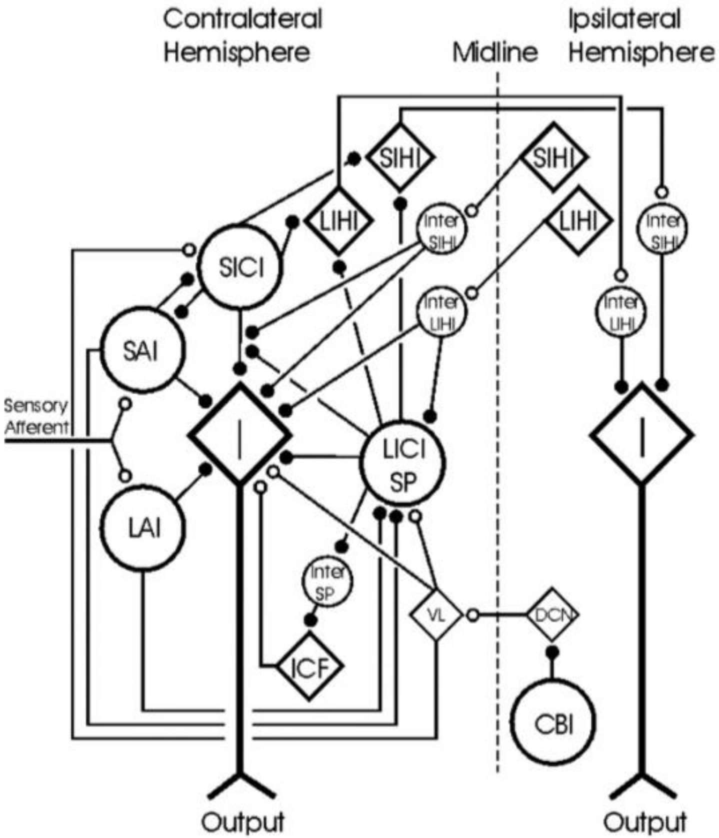
the better the recovered function

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

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

EPFL

Neural circuits with TMS applications



Ni et al. 2011 Brain Stim

TMS allows to probe specific neural circuits

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

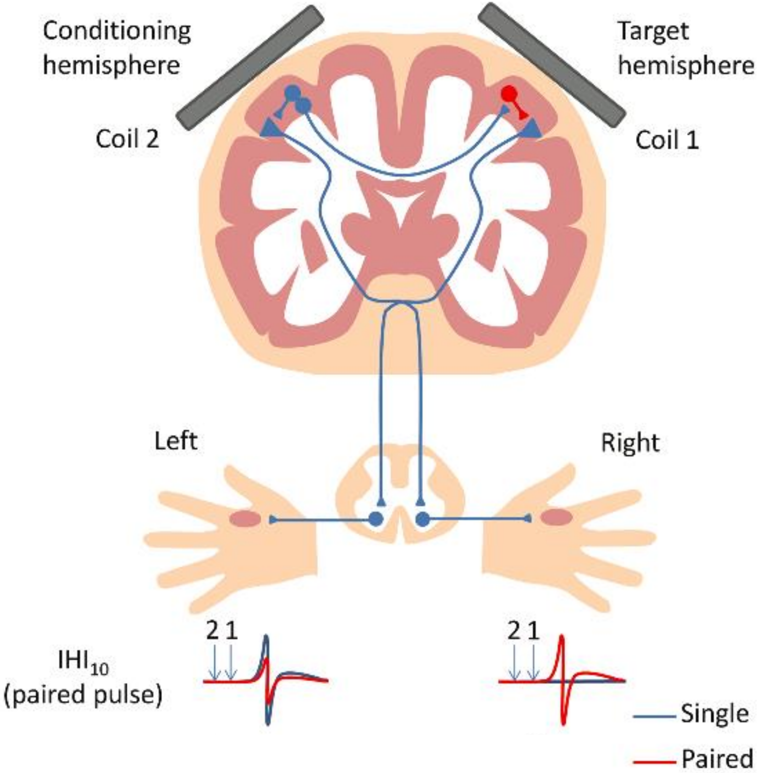
III. TMS allows to determine the recruitment patterns of the motor cortex

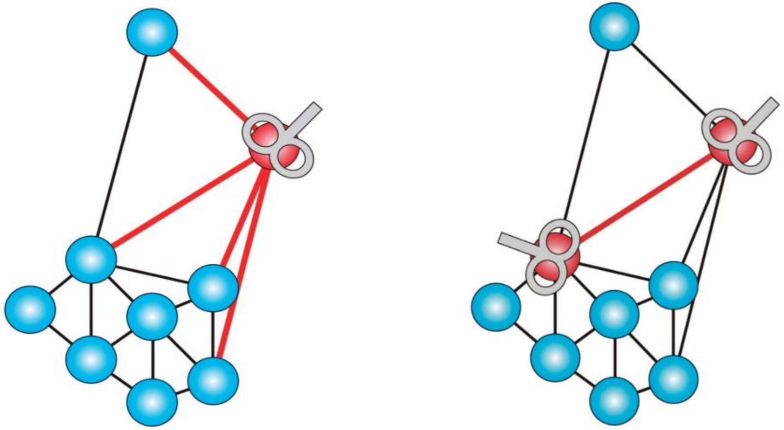
IV. TMS allows to evaluate differetn neurotransmitter systems (GABAergic, Glutamateergic) with paired pulse protocols

V. TMS allows to determine interregional interactions

Multifocal TMS: interregional interactions

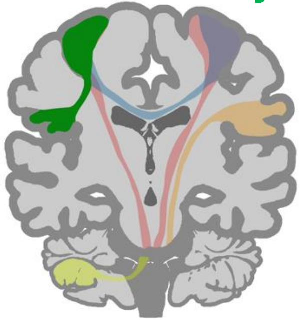
Overview - interregional interactions



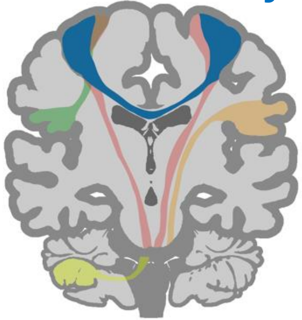


Dayan et al., 2013

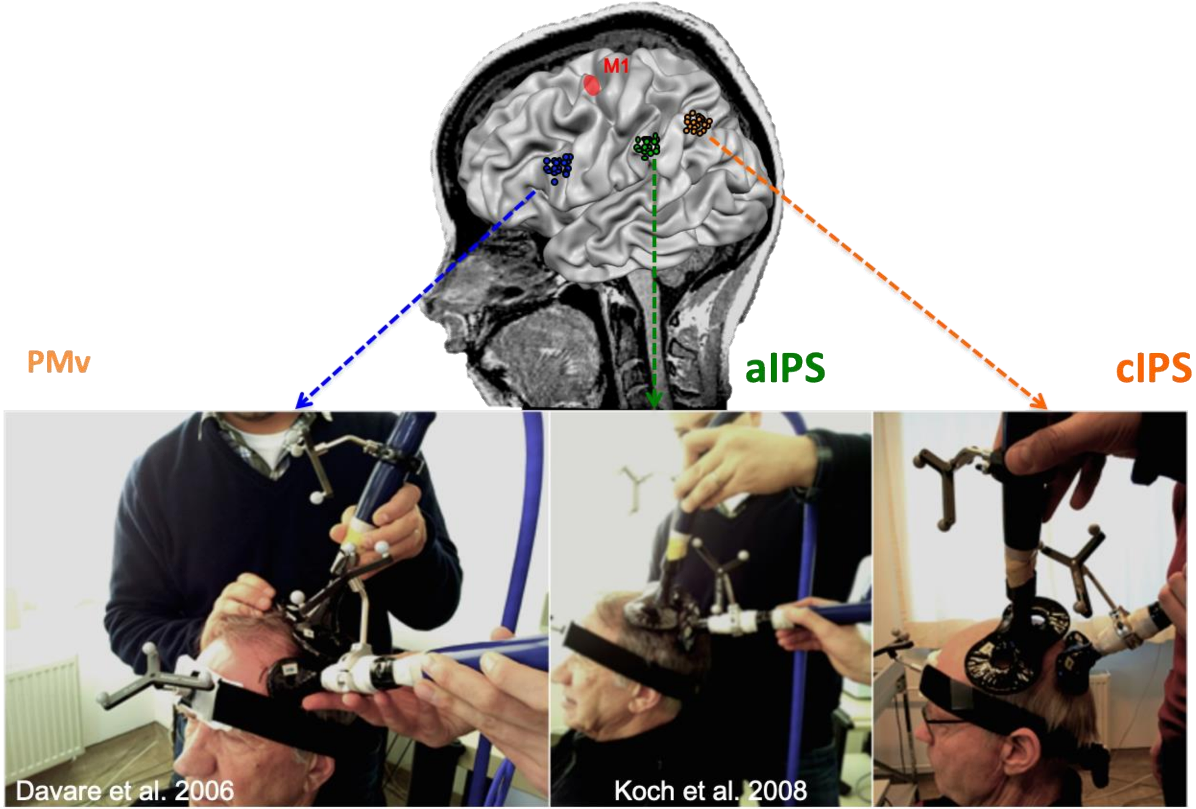
***Intra*-hemispheric connectivity**



***Inter*-hemispheric connectivity**



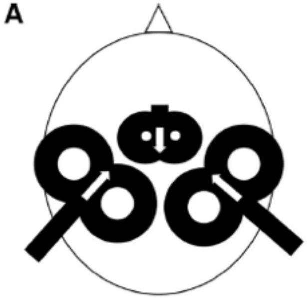
Multifocal TMS: interregional interactions

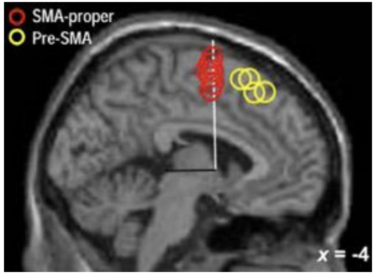


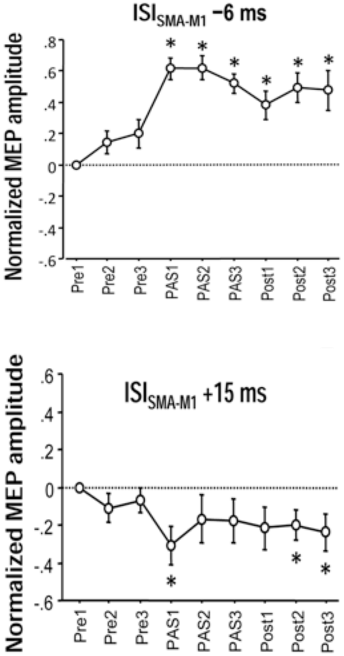
Multifocal TMS: interregional interactions

Multifocal TMS: interregional interactions

Multi-site stimulation of networks

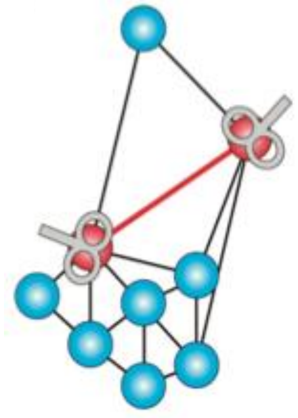




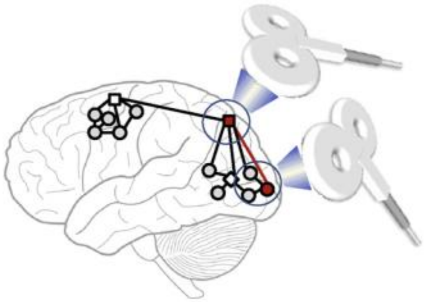


Arai et al. (2011) J Neurosci 31:15376-83

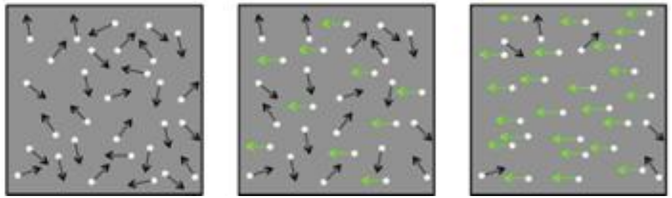
Multifocal TMS: interregional interactions



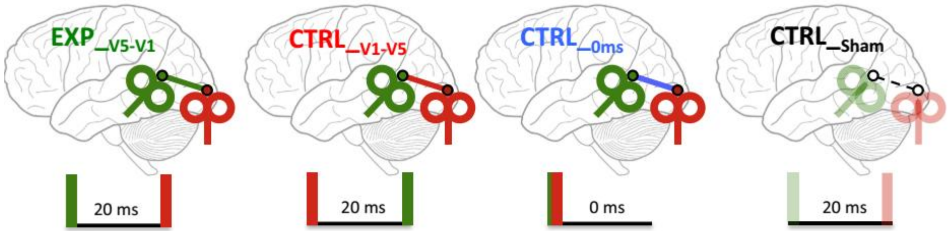
Dayan et al., 2013

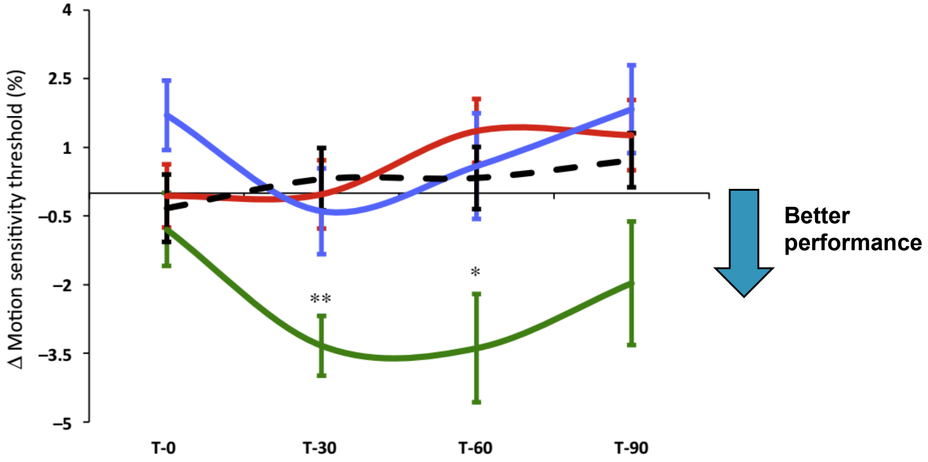


Romei et al., 2016



Motion detection visual task

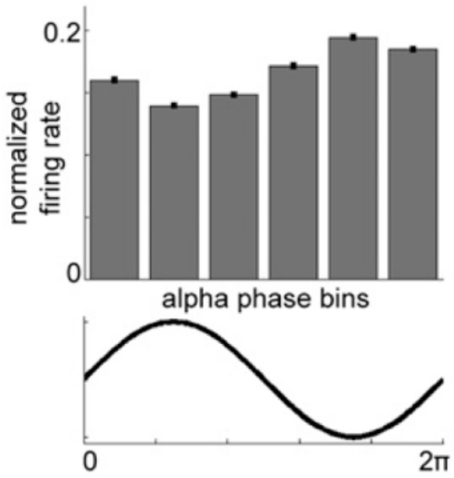




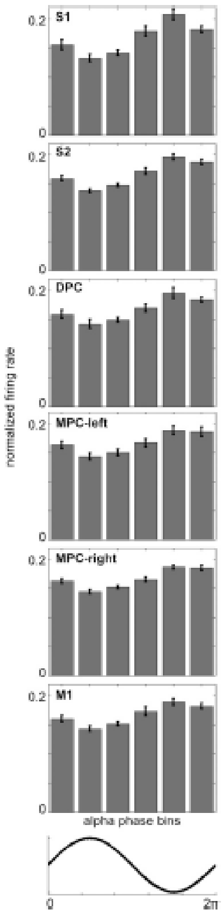
Adapted from Romei *et al.* (2016) *Current Biology*

State dependent TMS

State-dependent



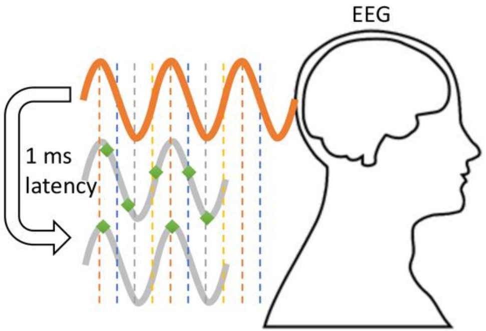
Local field potentials
in monkey cortex

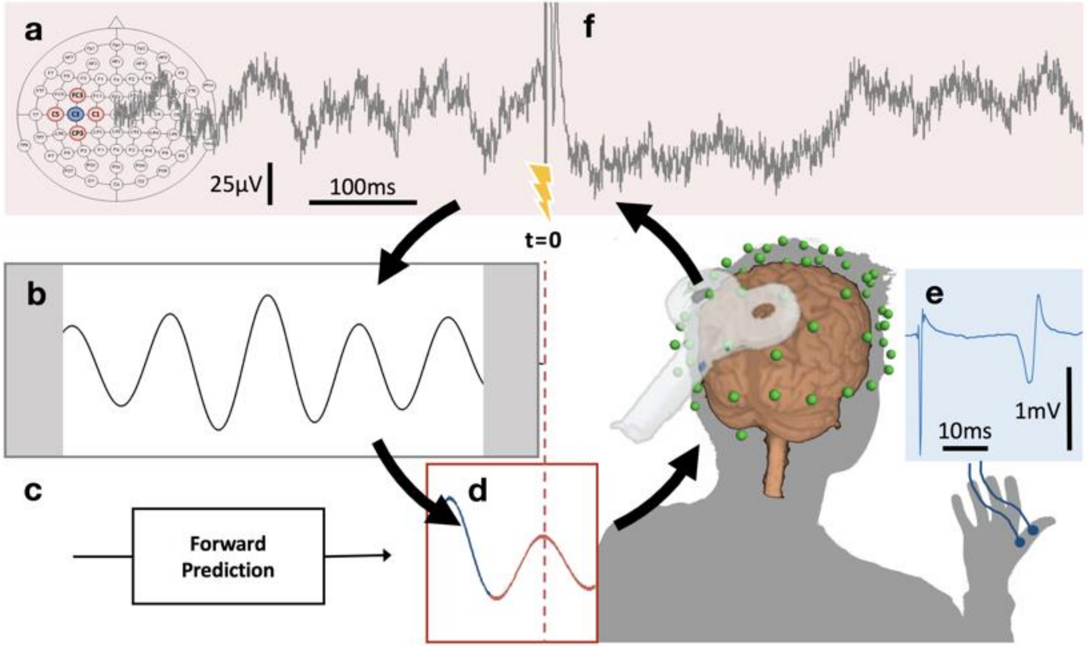


Haegens et al. (2011) PNAS 108:19377-19382

State-dependent

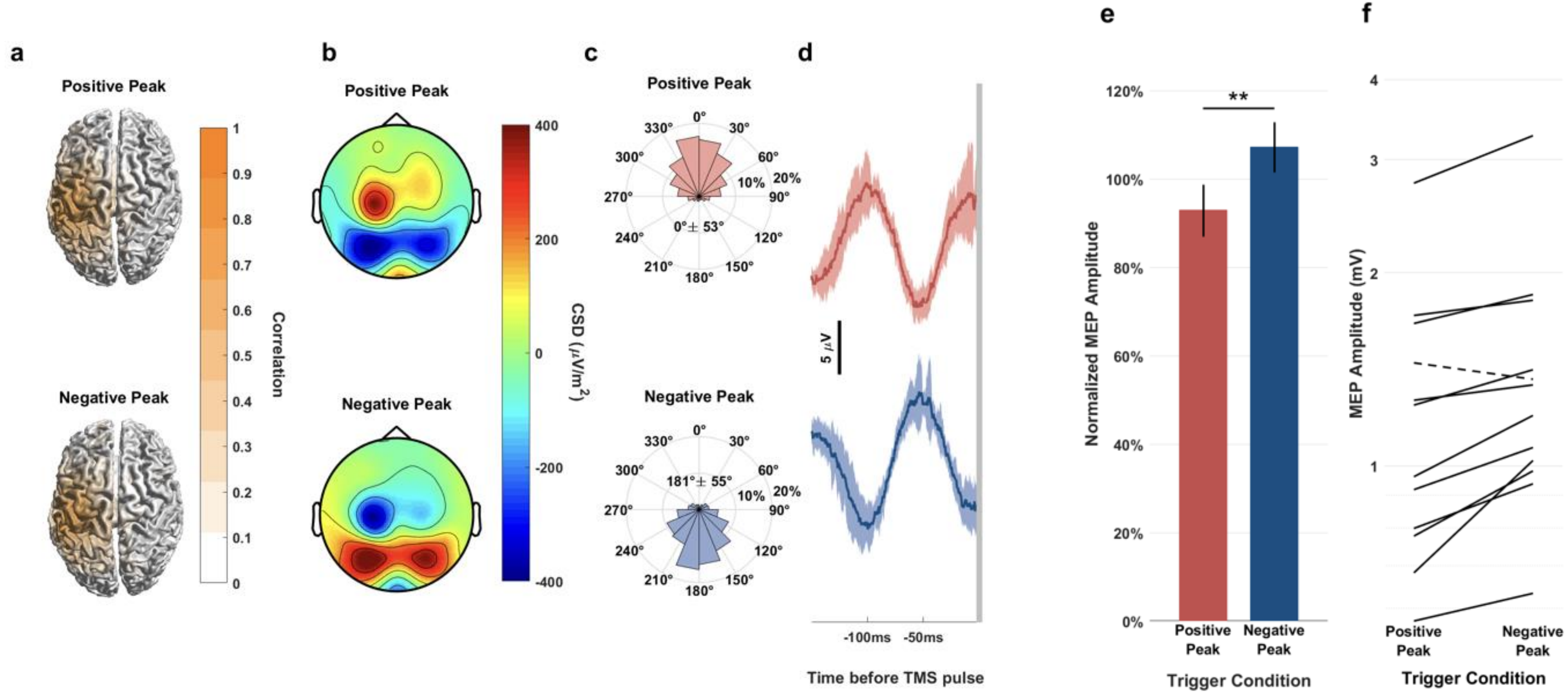
EEG-TMS: Dependence of corticospinal excitability on μ-rhythm phase



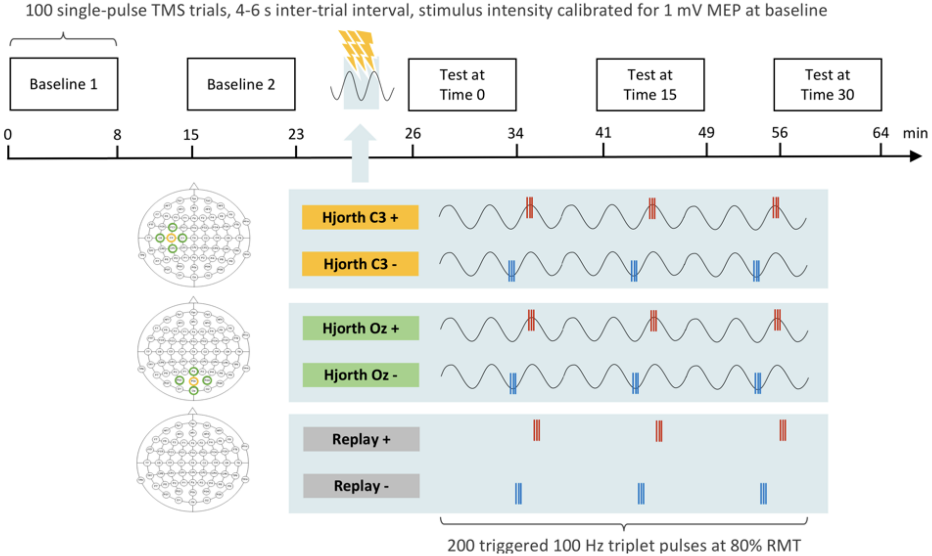


Zrenner et al. 2018

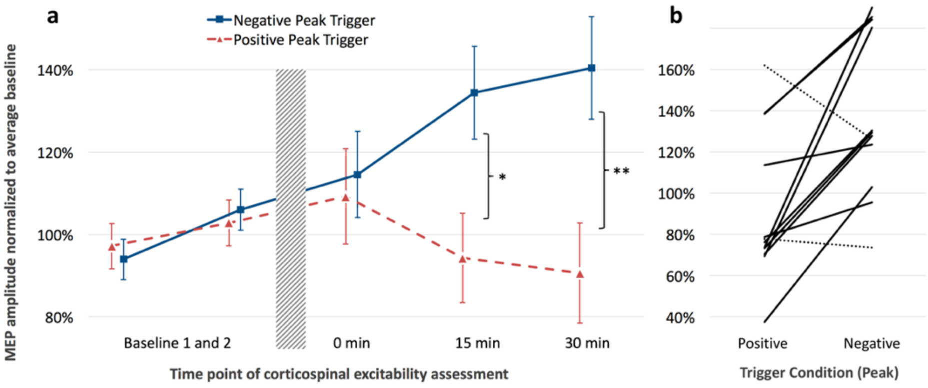
State-dependent

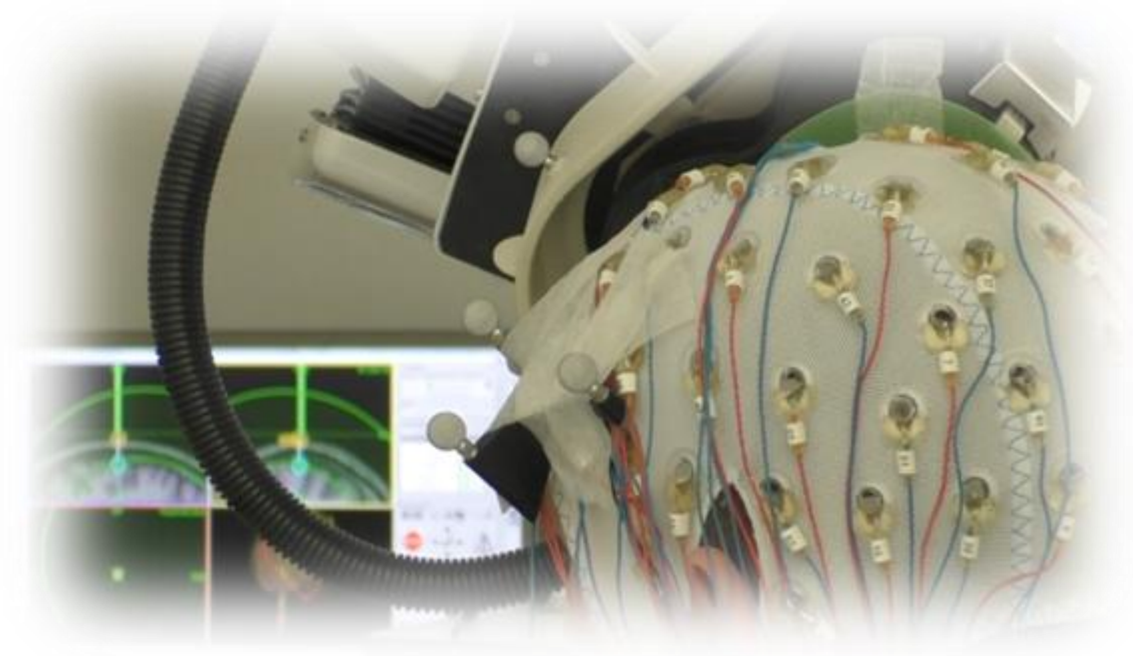


State-dependent



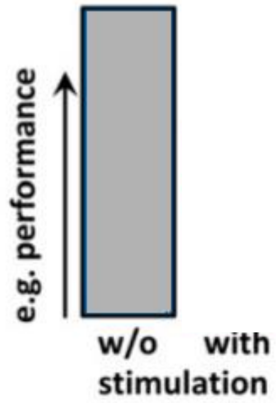
Effects of a TMS pulse depend on the phase of the ongoing brain activity when the pulse was applied.

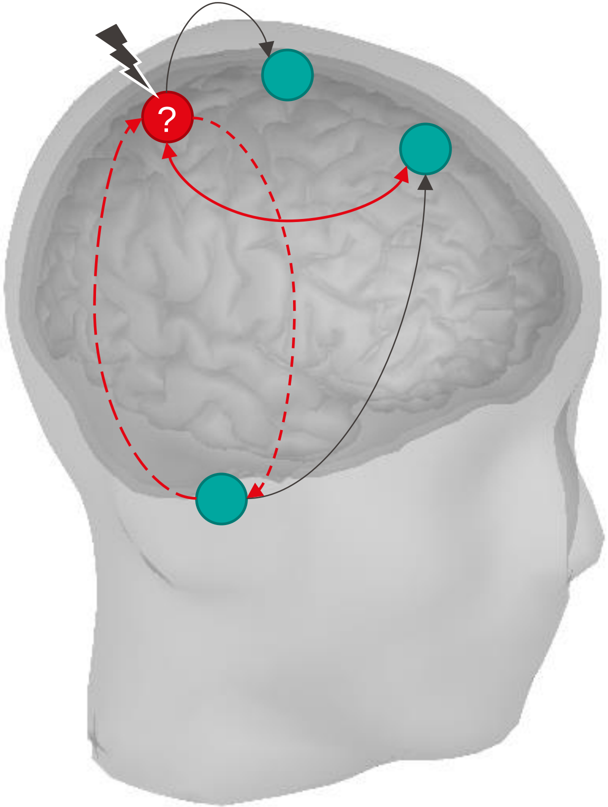


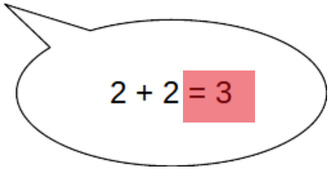


Cortical brain mapping using TMS (neuronavigated and robotized)

Location-function mapping



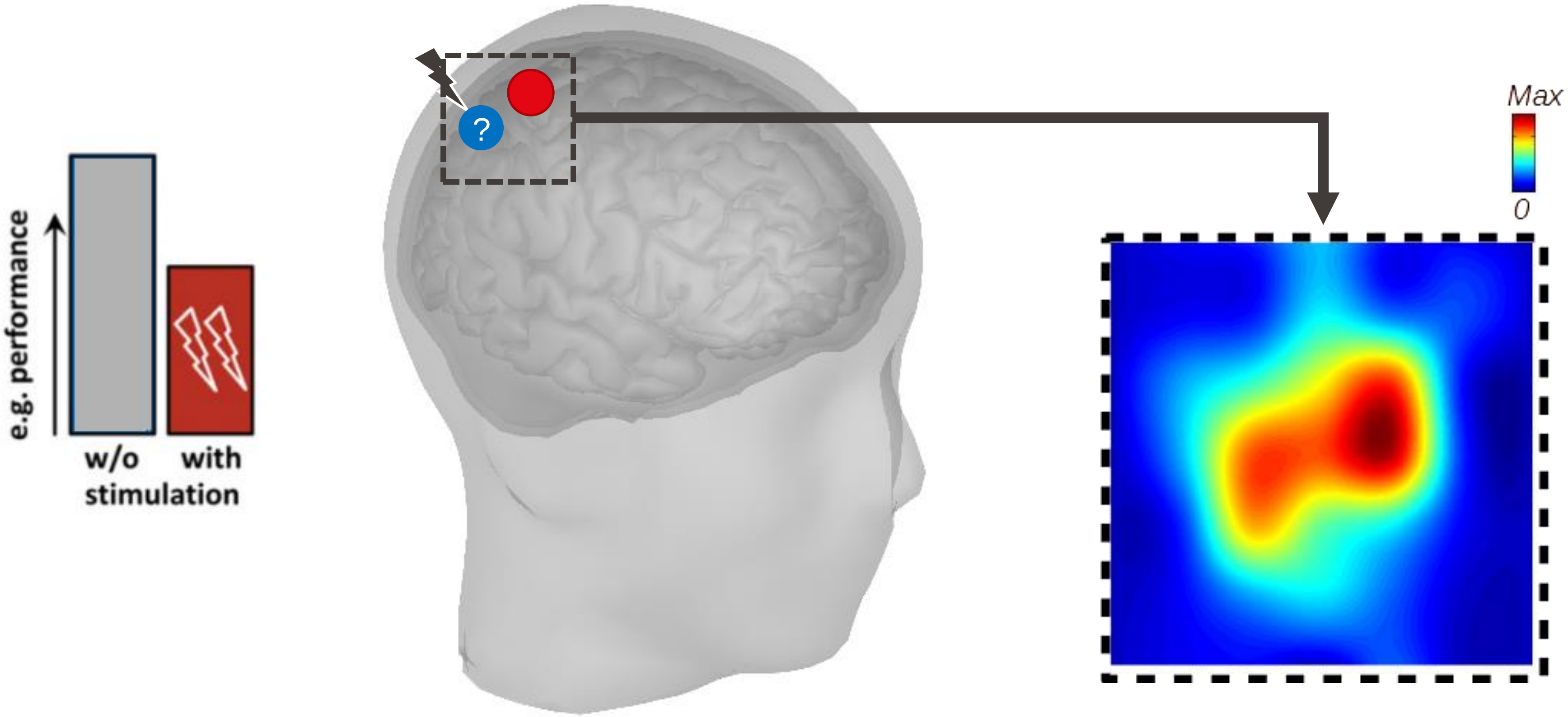




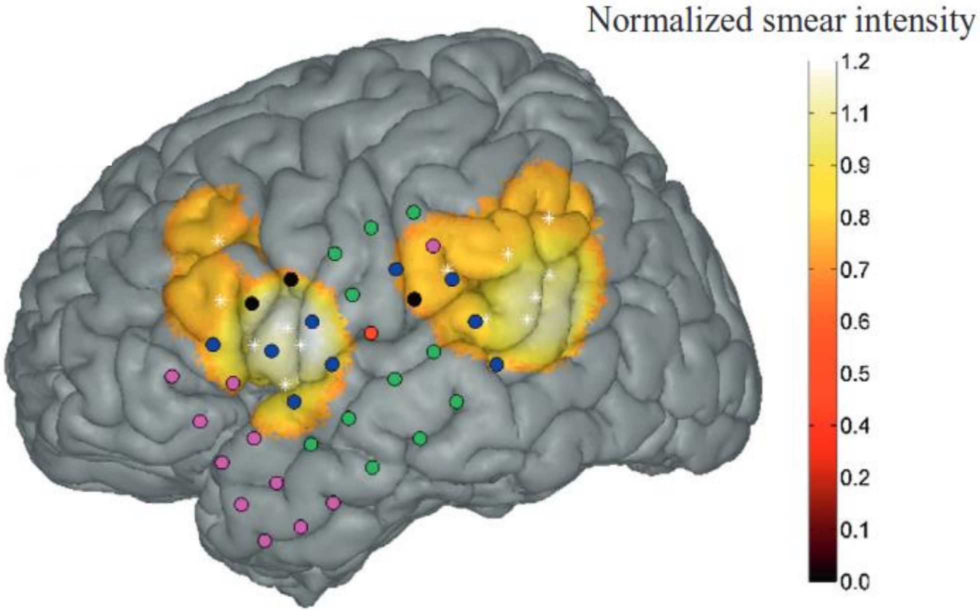
Cognitive process

Sensorimotor process

Location-function mapping

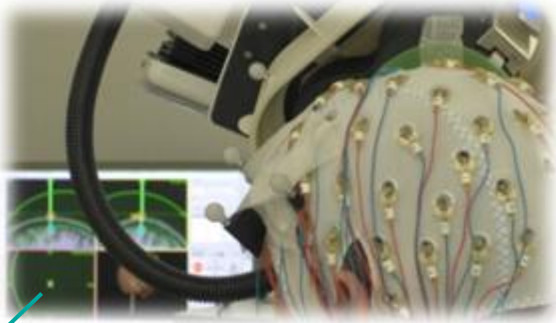


Location-function mapping

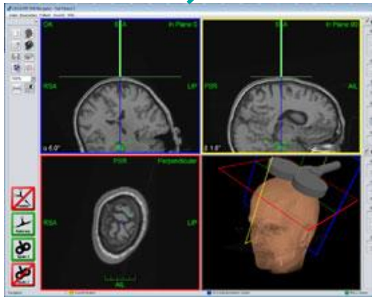


Language mapping

Technological evolution

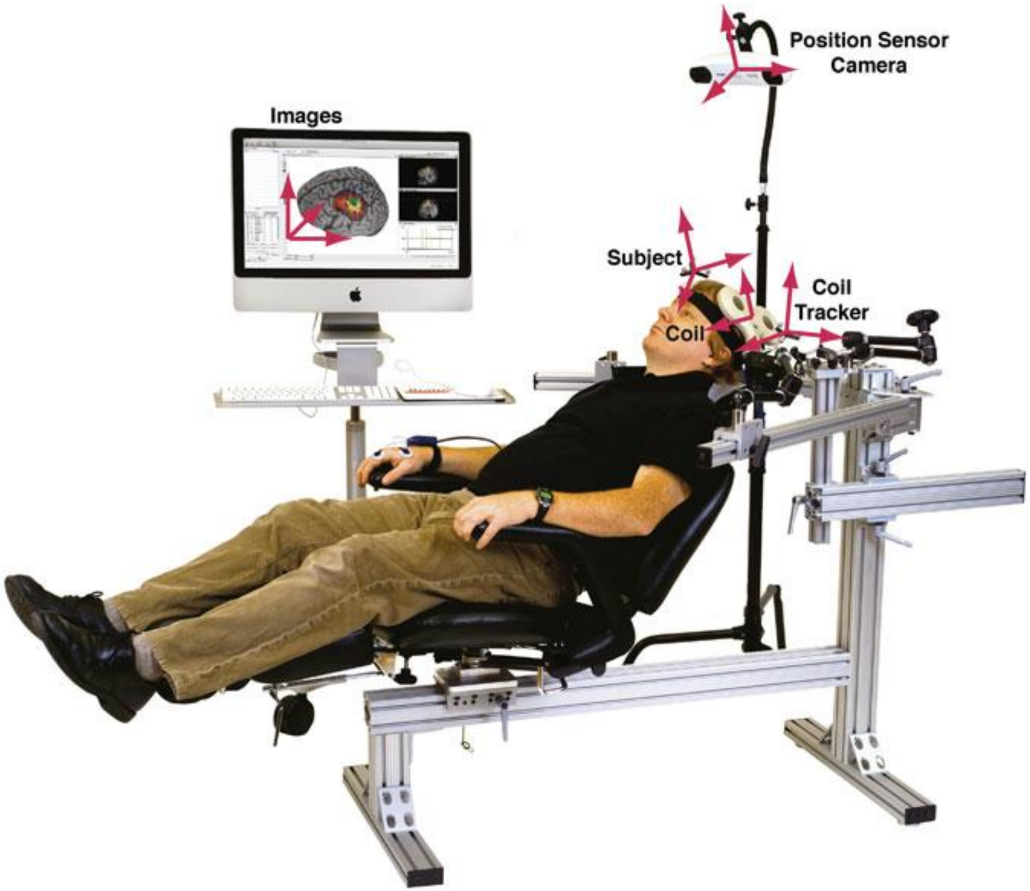


Neuronavigation systems

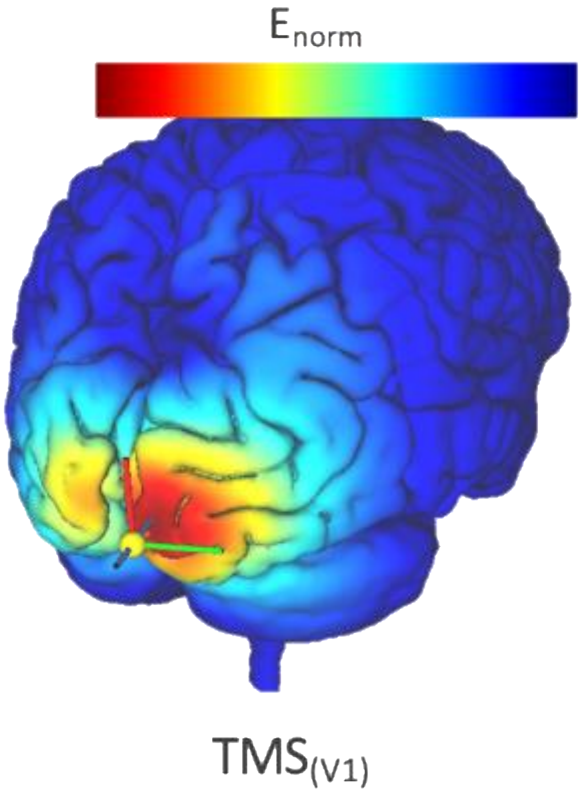


Robotized systems

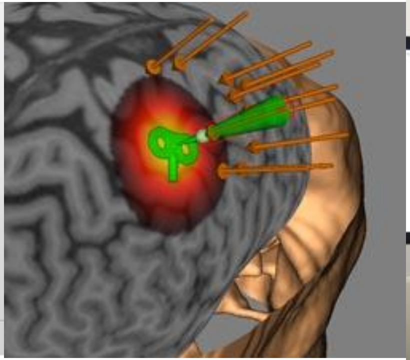
Neuronavigation



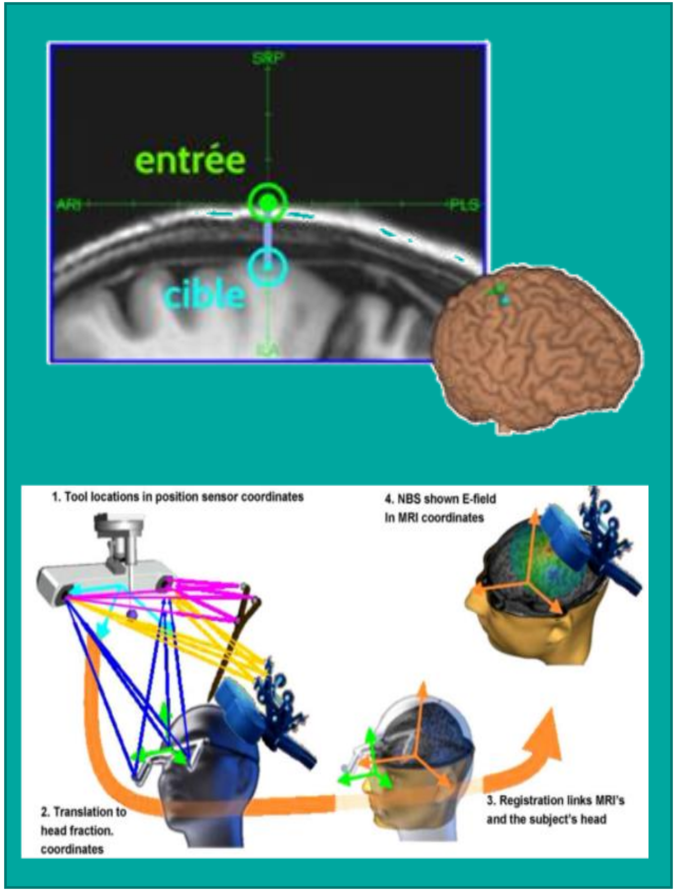
Neuronavigation



Neuronavigation

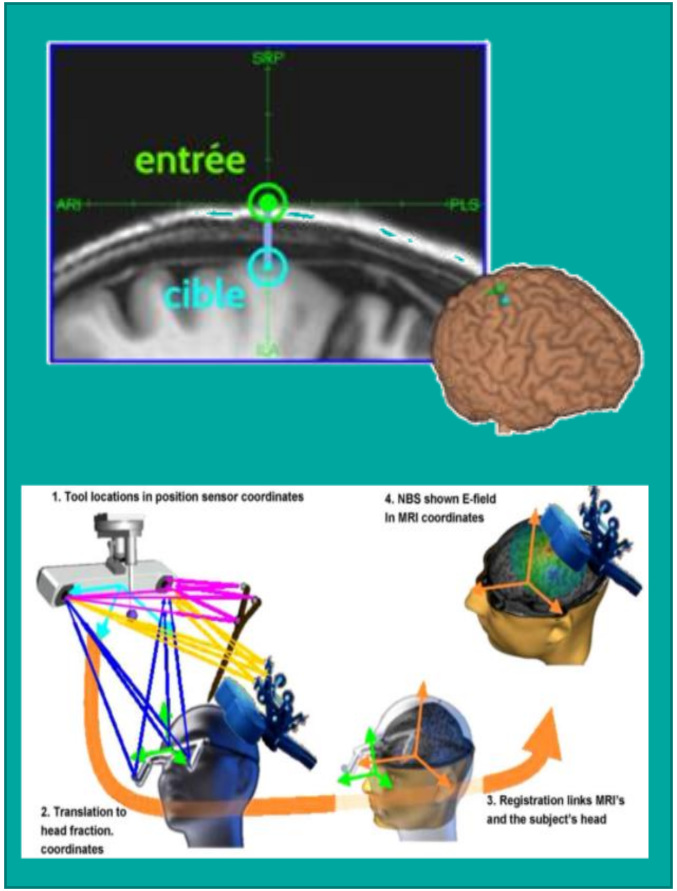


Neuronavigation

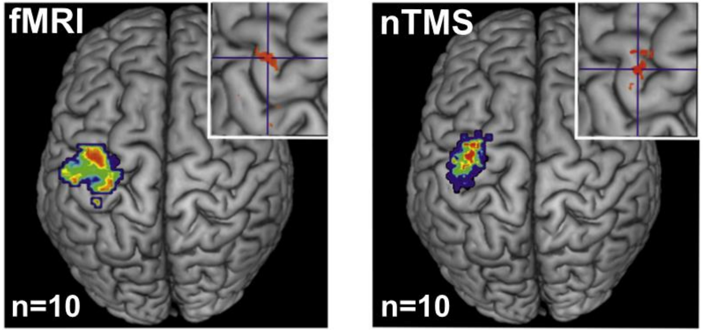


Bashir et al., Brain topo., 2011

Neuronavigation

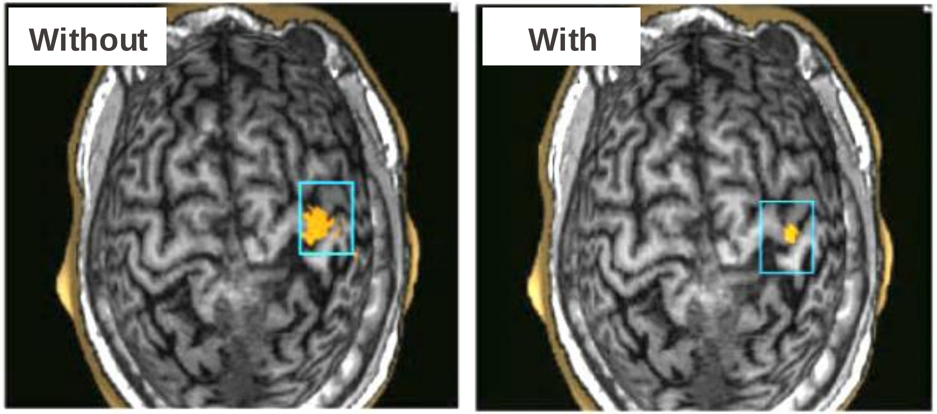


THUMB (APB)



✓ Increased **spatial precision**

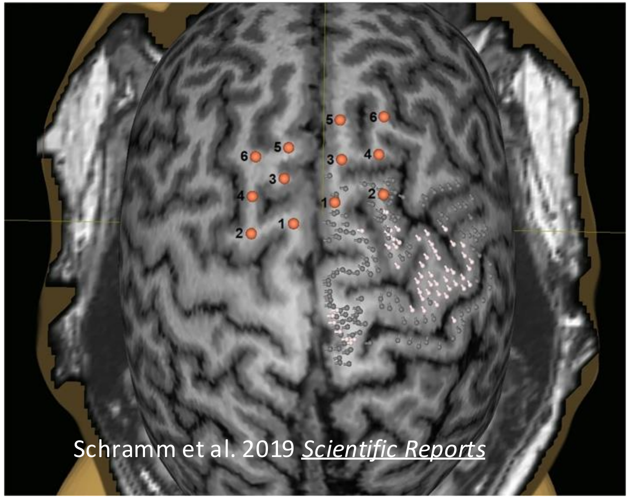
Weiss et al., NeuroImage, 2013

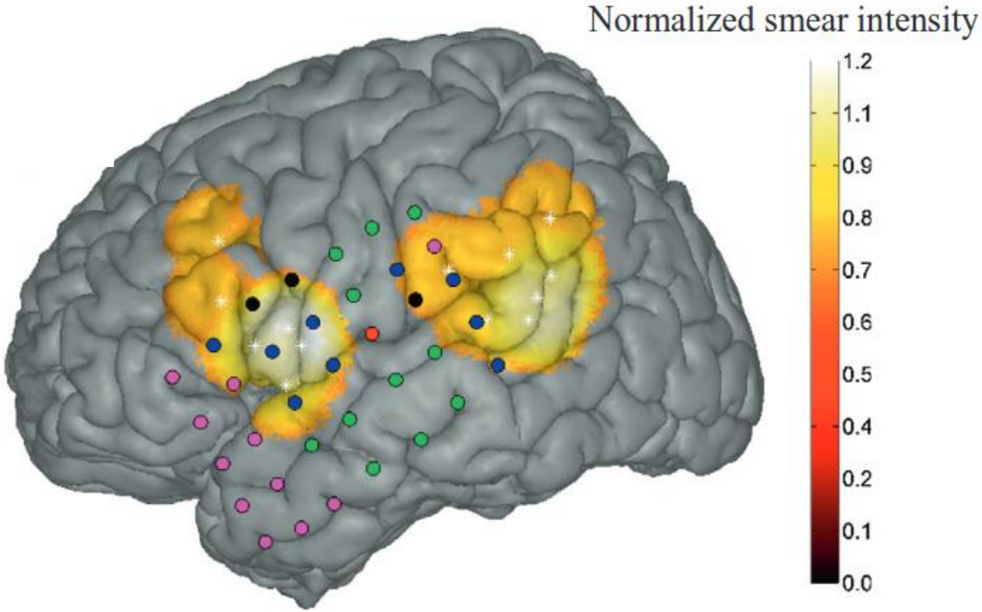


✓ Increased **reproducibility**

Bashir et al., Brain topo., 2011

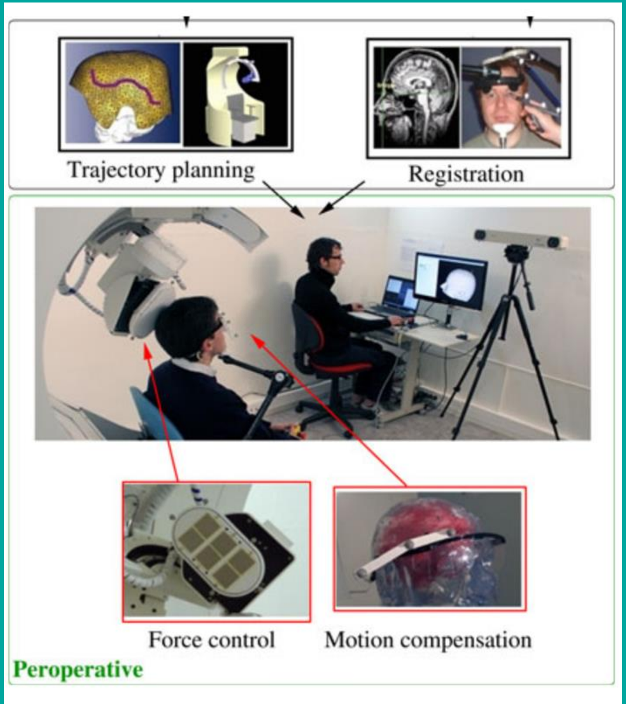
Neuronavigation



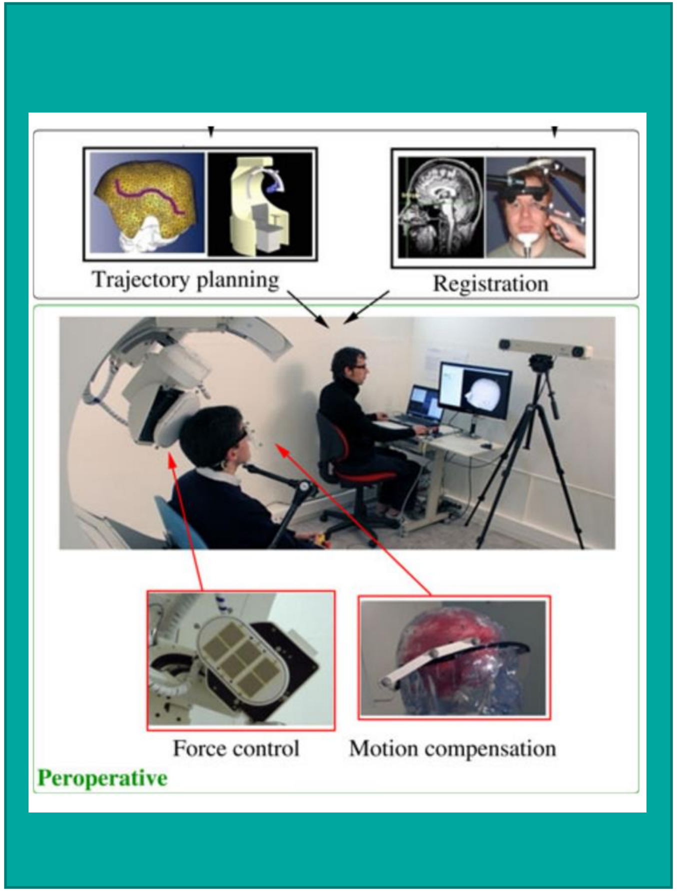


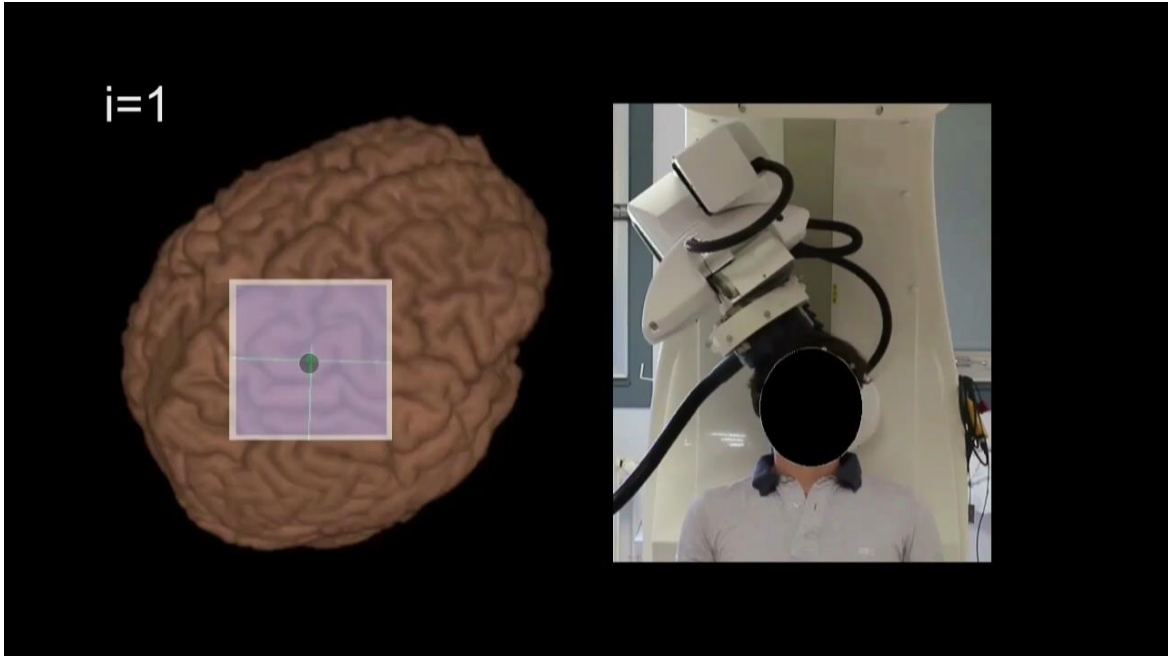
Tumor function mapping

Robotized TMS



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.

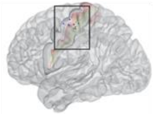
Safety

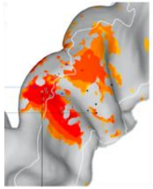
Scalp burns from EEG electrodes - Mild scalp burns in subjects with scalp electrodes can be easily avoided using, e.g., small low-conductivity Ag/AgCl-pellet electrodes.

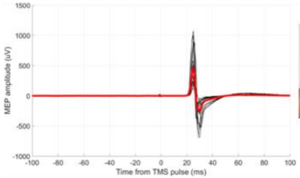
Effect on cognition - Slight trend toward better verbal memory, improved delayed recall and better motor reaction time

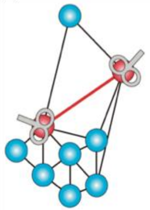
Local neck pain and headaches - Related to stimulation of local muscles and nerves, site and intensity dependant. Particularly uncomfortable over fronto-temporal regions.

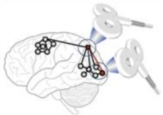
Effect on Mood in normals - Subtle changes in mood are site and frequency dependant. High frequency rTMS of left frontal cortex worsens mood. High frequency rTMS of right frontal cortex may improve mood.

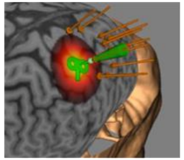












Thank you for your attention!