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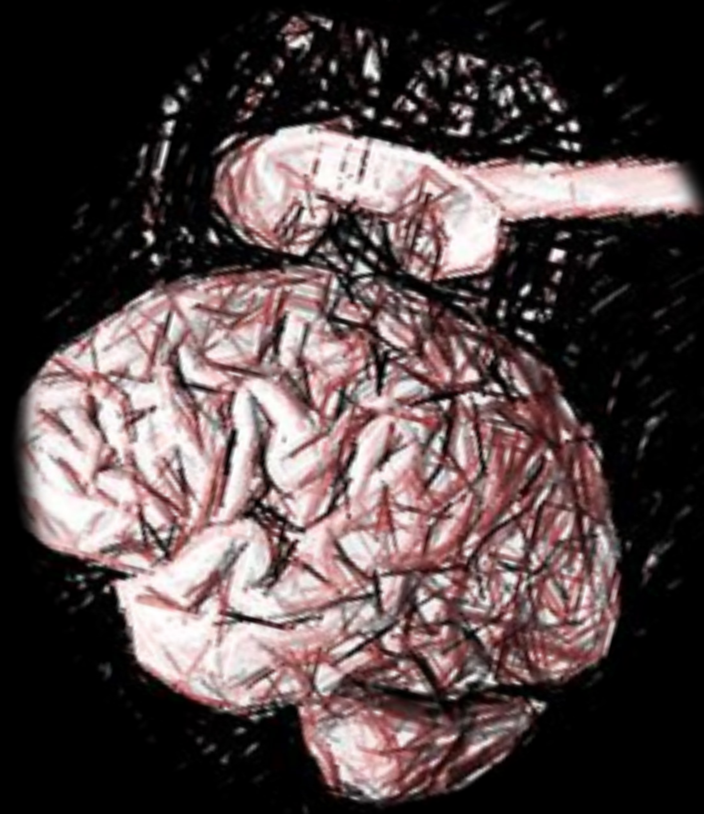

“But still try, **for who knows what is possible**?”

– *Michael Faraday*

Transcranial Magnetic Stimulation: basic & advanced methodology

(2 days workshop)

Dr. Olga Lucía Gamboa Arana

Hong Kong, 23-08-2018

Outline

- Session 1 – Lecture “TMS Principles”
- Session 2 – Lecture “ TMS Safety aspects”
- Session 3 – hands on: “The TMS technique I”
- End Session 1: final remarks, conclusions and questions

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- Session 4 – Lecture “TMS methods I”
- Session 5 – Lecture: “TMS methods II”
- Session 6 – hands on: “The TMS technique II”
- End Session 2: final remarks, conclusions and questions

Session 1: “ TMS Principles”

Dr. Olga Lucía Gamboa Arana

Hong Kong, 29-11-2018

Outline Session 1

Session 1 – Lecture “ TMS Principles”

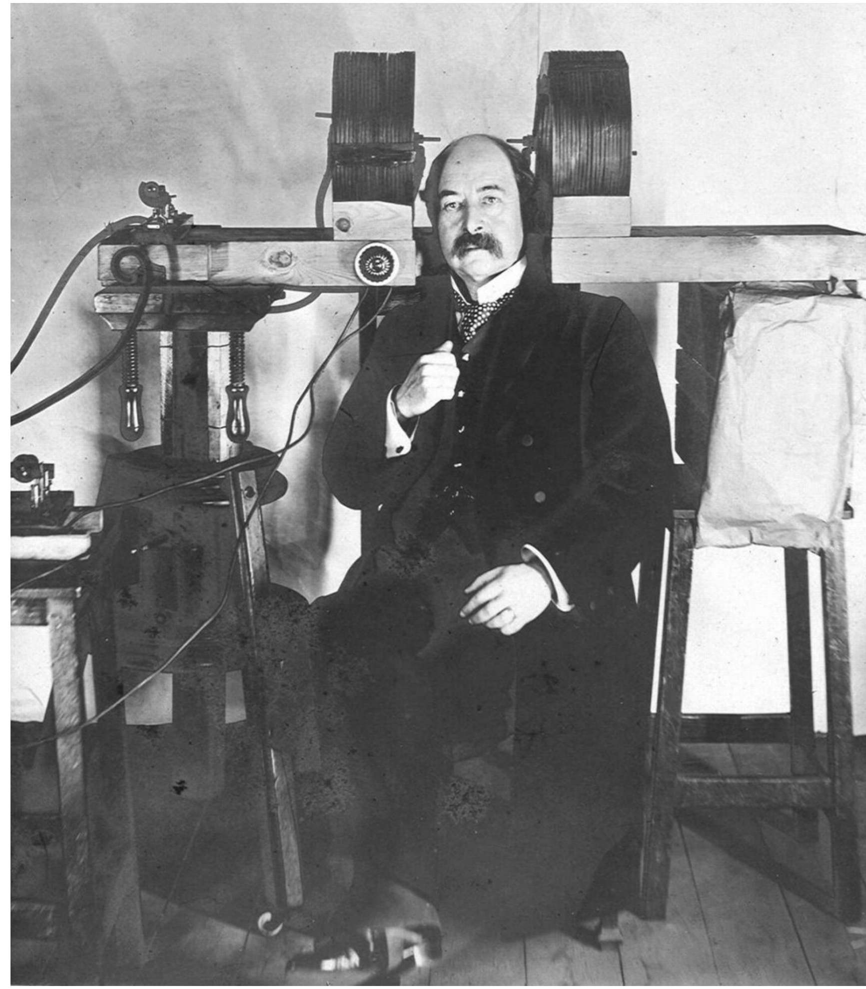
- TMS origin: history
- TMS definition and principle
- TMS neurophysiology
- Quantifying the TMS response: MEPs, Thresholds, hot-spot
- TMS equipment
- Stimulation site

TMS origins: history

Althaus 1881

Fig. 126.—General Faradisation.

Thompson 1910



TMS origins: breakthrough

Stimulation of the cerebral cortex in the intact human subject

P. A. Merton & H. B. Morton

The National Hospital, Queen Square, London WC1N 3BG, UK

Nature Vol. 285 22 May 1980

One of the most fertile methods of investigating the brain is to stimulate a part of it electrically and observe the results...

Recently, it was found that, on stimulating muscles in the human hand without any special preparation of the skin, the effective resistance fell to low values if brief but very high voltage shocks were used. Applying the same technique to the head, it has now proved possible at the first attempt to stimulate two areas of the human cortex, without undue discomlort.

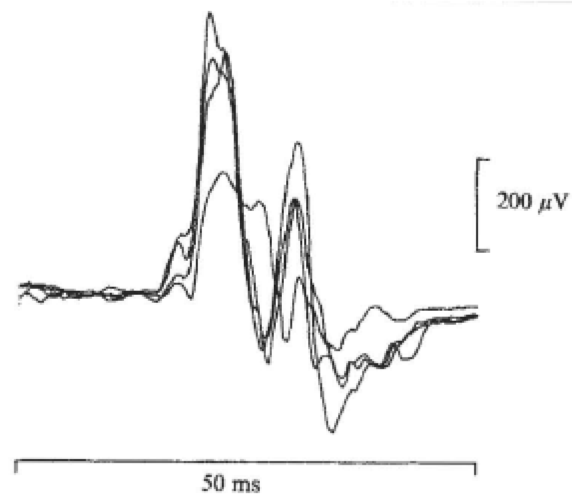
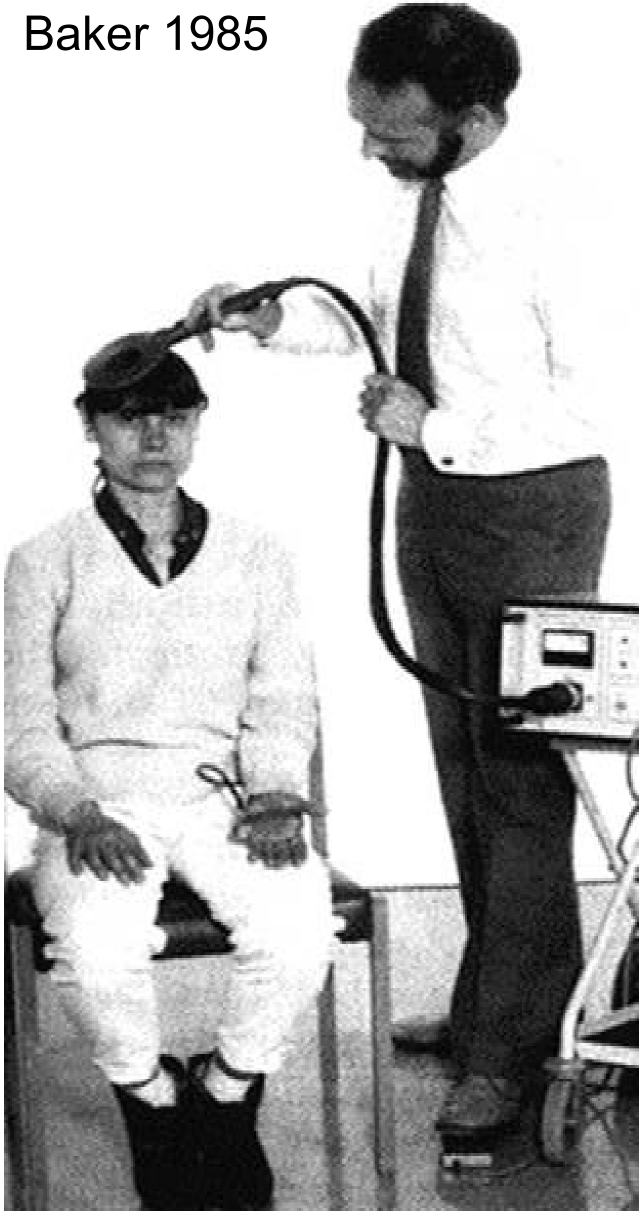


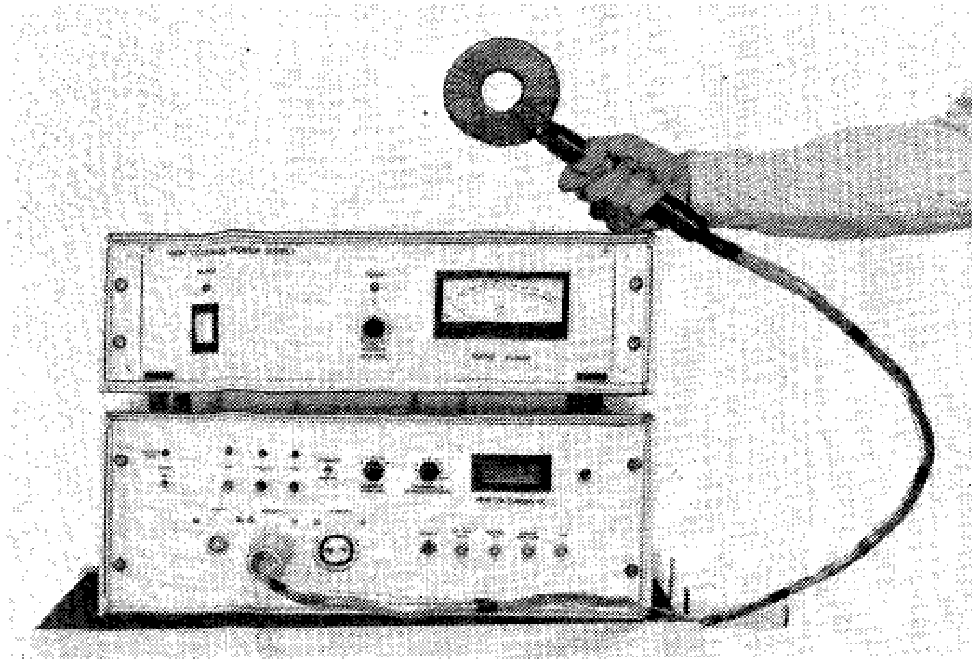
Fig. 1 Stimulation of the arm area of the motor cortex. The records shown are of action potentials from the contracting muscles in the forearm. Stimulation is at the start of the sweep. Four records are superimposed. The latency of responses was 16 ms. (Subject P.A.M.)

Photo: Hallett & Rothwell, (2011) Mov Disord, 26(6): 958–967.

TMS origins: the beginning of modern TMS times OL Gamboa

Baker 1985





fmi:Abductor digiti minimi – latency of response 23 ms

TMS definition

Transcranial magnetic stimulation is a non-invasive, “painless” technique used for assessing and modulating cortical excitability.

TMS principle

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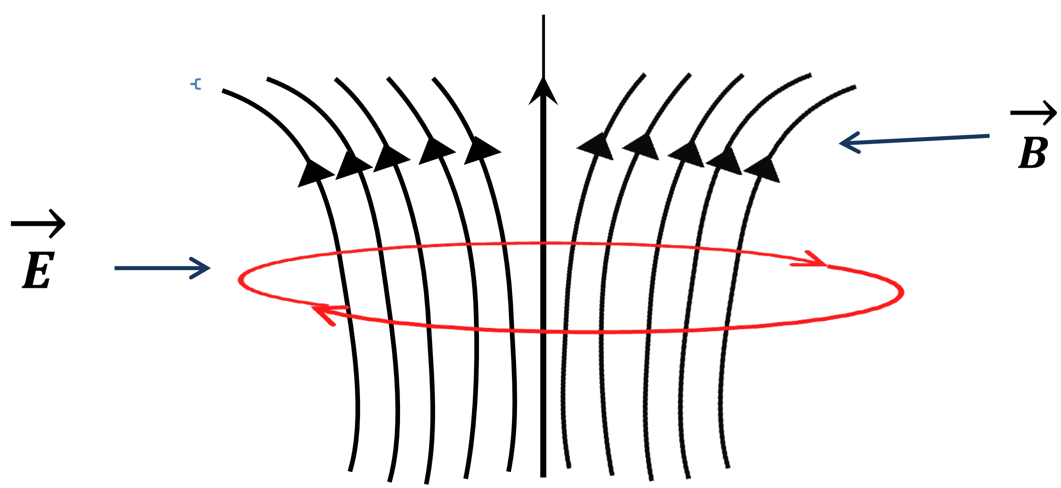
Transcranial magnetic stimulation is a method based on Faraday's law of electromagnetic induction

$$\nabla \times \boldsymbol{E} = -\frac{\partial \boldsymbol{B}}{\partial \boldsymbol{t}}$$

A variable magnetic field **(B)** induces an electric field (**E**)



The TMS principle and the brain

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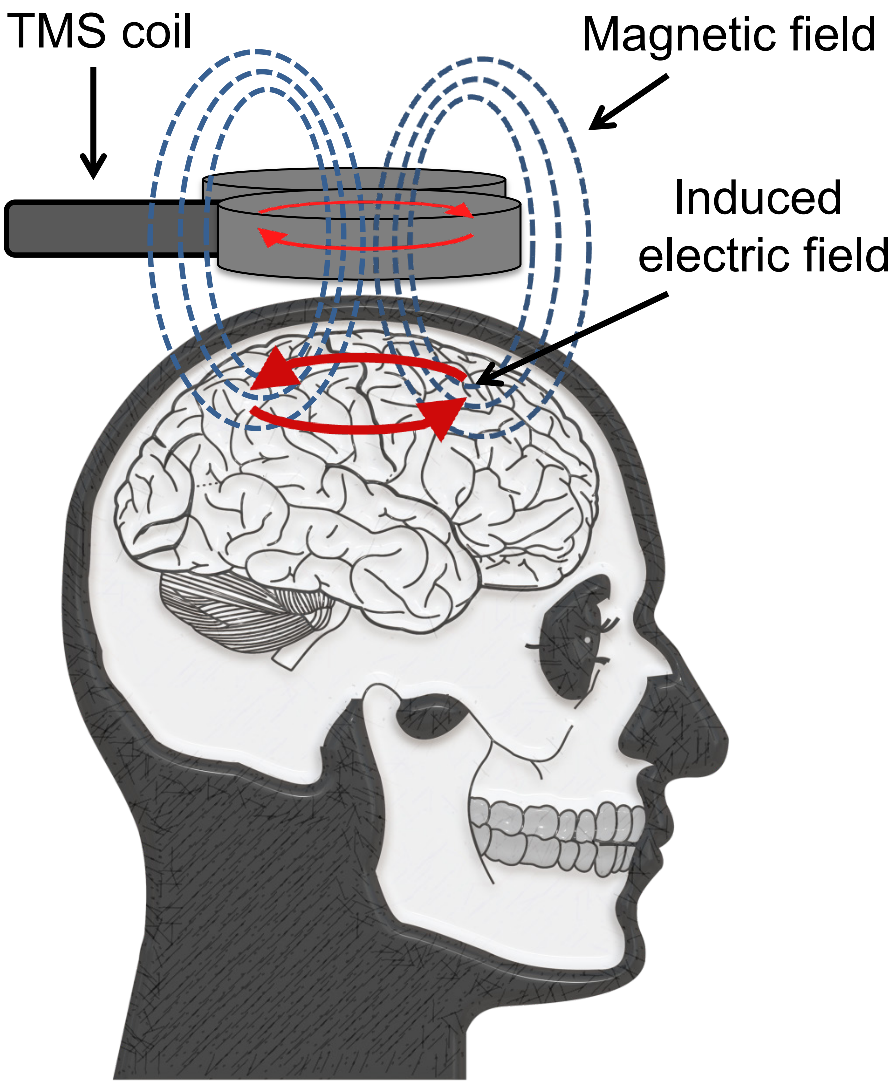

TMS Sequence of events

1. An electrical current (8 kA) is delivered to the coil.
2. A short but strong magnetic pulse (~2T) is produced and delivered on the scalp.
3. The magnetic field changes rapidly inducing an electric field.

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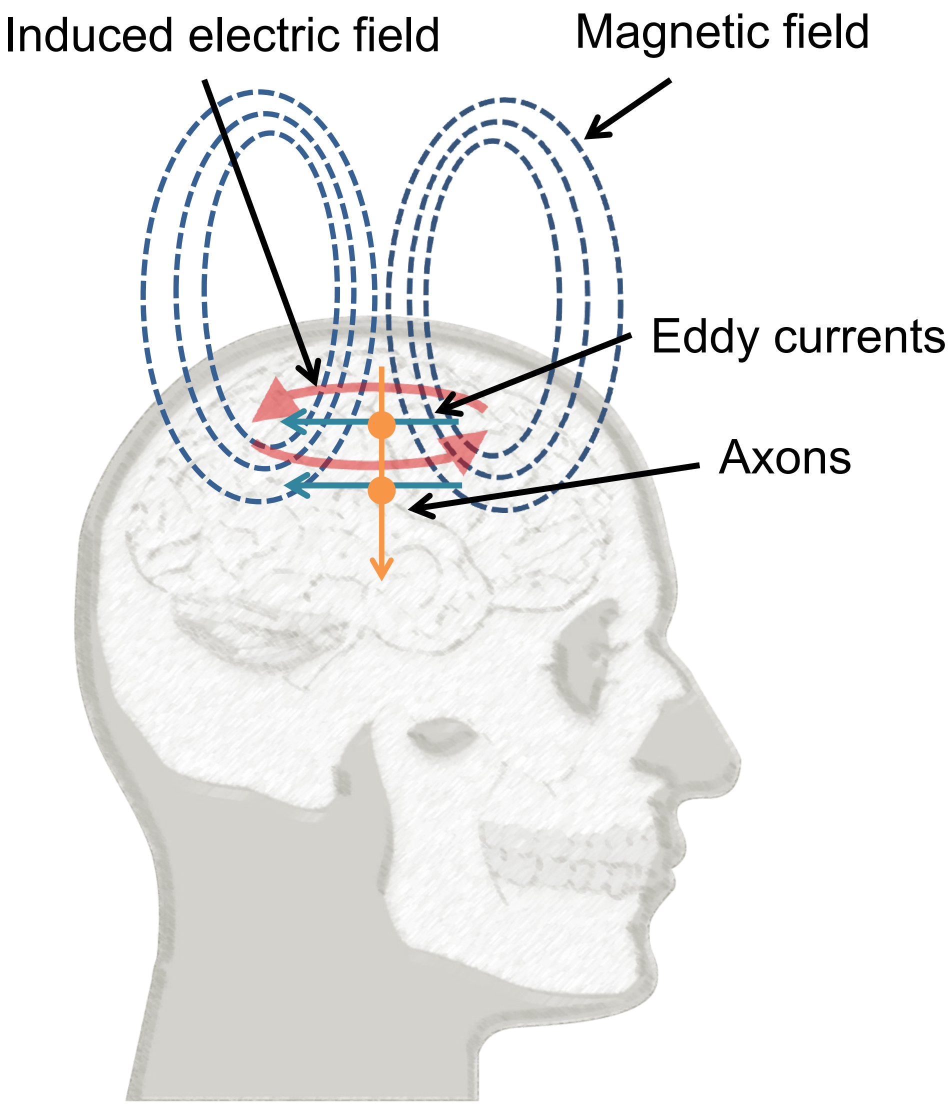

TMS Sequence of events

6. The electric field in turn generates a current.
7. This current produces changes in neural activity.

Activation mechanism in the brain due to TMS

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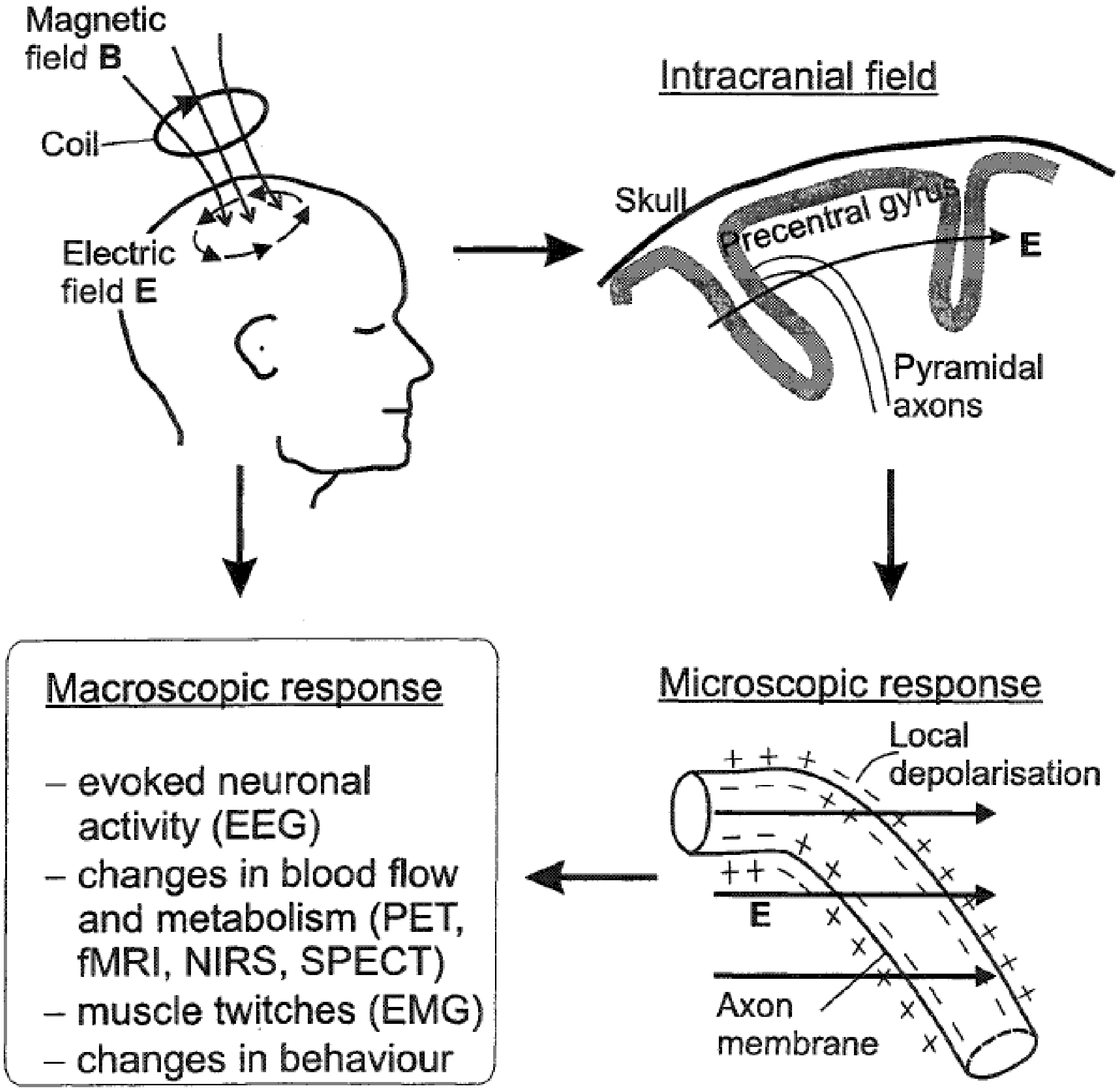

Ilmoniemi et al.,(1999) . Crit Rev Biomed Eng.27(3-5):241-84.

Activation mechanism in the brain due to TMS

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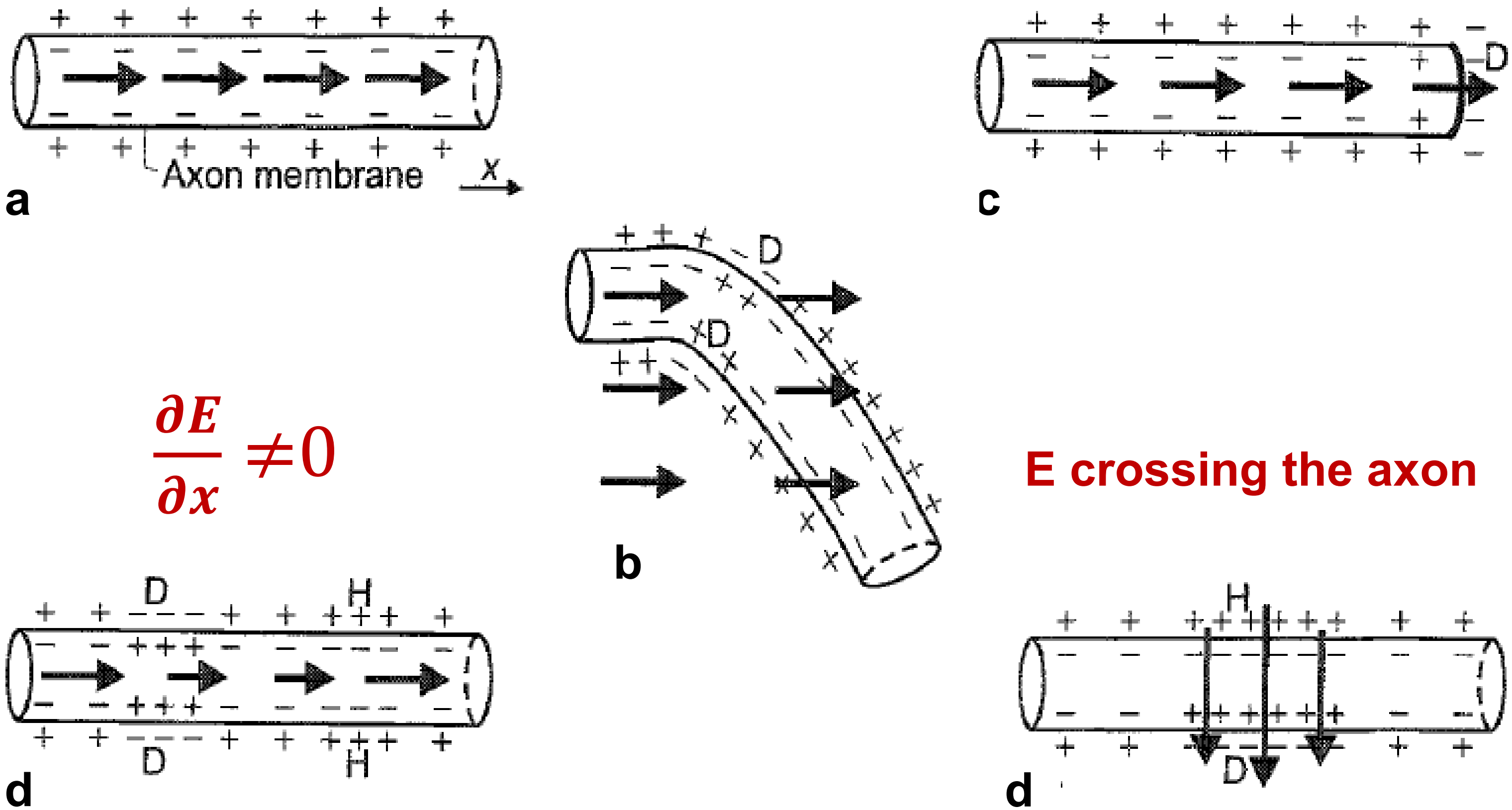
Uniform E



$$\frac{\partial E}{\partial x} \neq 0$$

E crossing the axon

Depolarization (D) or hiperpolarization (H) of an axon caused by the exposure to different electric field patterns applied externally.

Ilmoniemi et al.,(1999) . Crit Rev Biomed Eng.27(3-5):241-84.

Mechanism of TMS over M1

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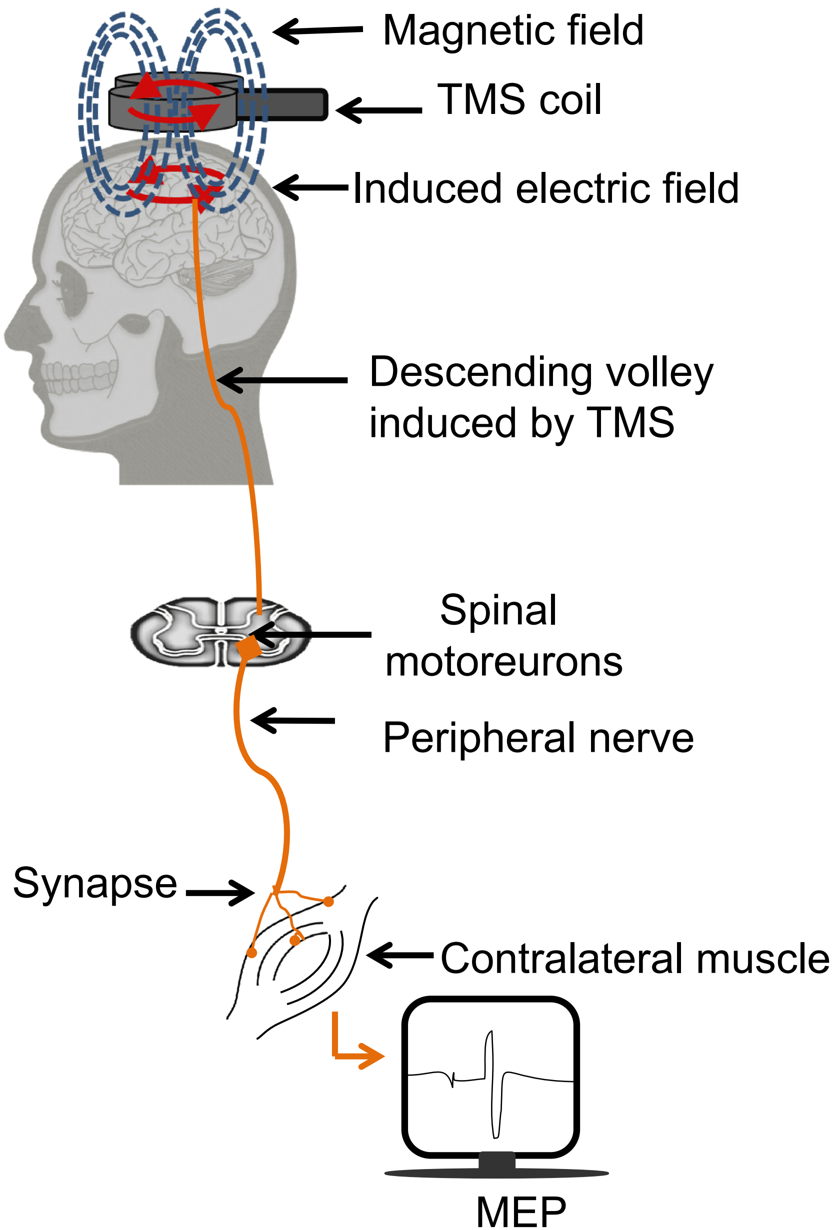
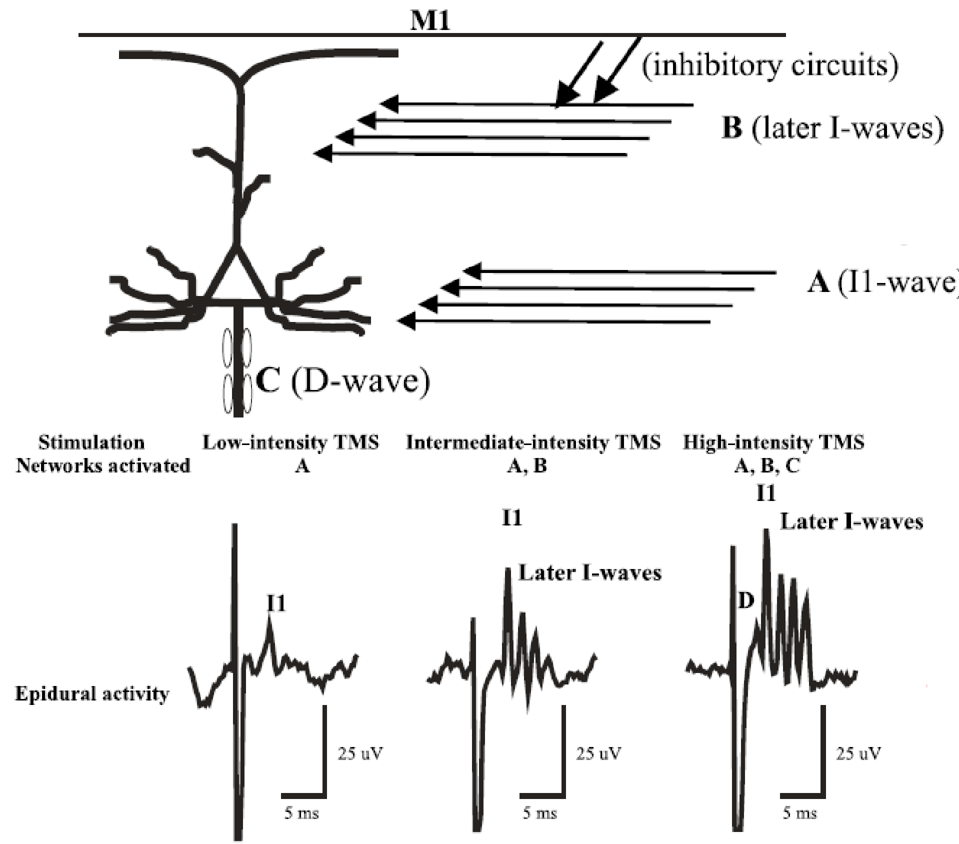


Excitatory circuits activated by TMS



Di Lazzaro et al., 2010. Clinical Neurophysiology 121 464–473

Models explaining mechanism of TMS over M1

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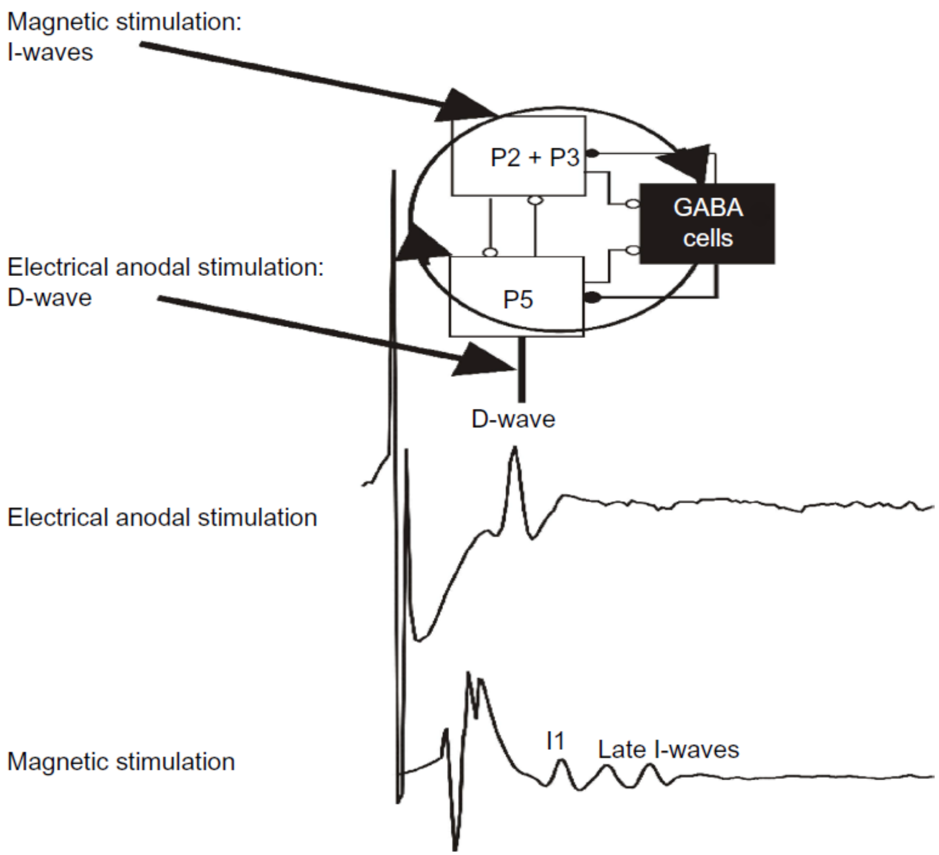

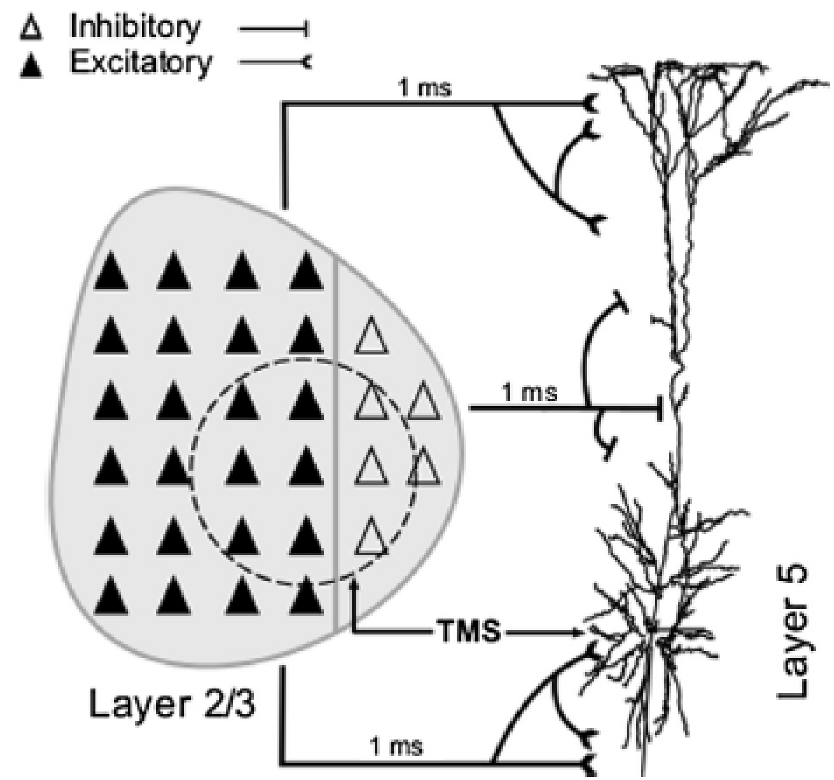

Caponte, et al., 2016. Neuroscience and Neuroeconomics, 6 April

Rusu, et al., 2014. Brain Stimulation 7: 401-414

To remember

- A strong and brief magnetic pulse induces an electric field.
- The electric field causes neural polarization.
- The magnetic component has no effect on the neural activation.
- Nerve activation will occur in spatially varying field or in homogeneous field crossing nerve bends.
- TMS induces descending volleys, I waves at low intensities and D waves at higher intensities.

Quantifying the TMS response

- Motor Evoked Potential
- Thresholds
- Hot spot
- Cortical silent period

Motor Evoked Potential & Motor Thresholds

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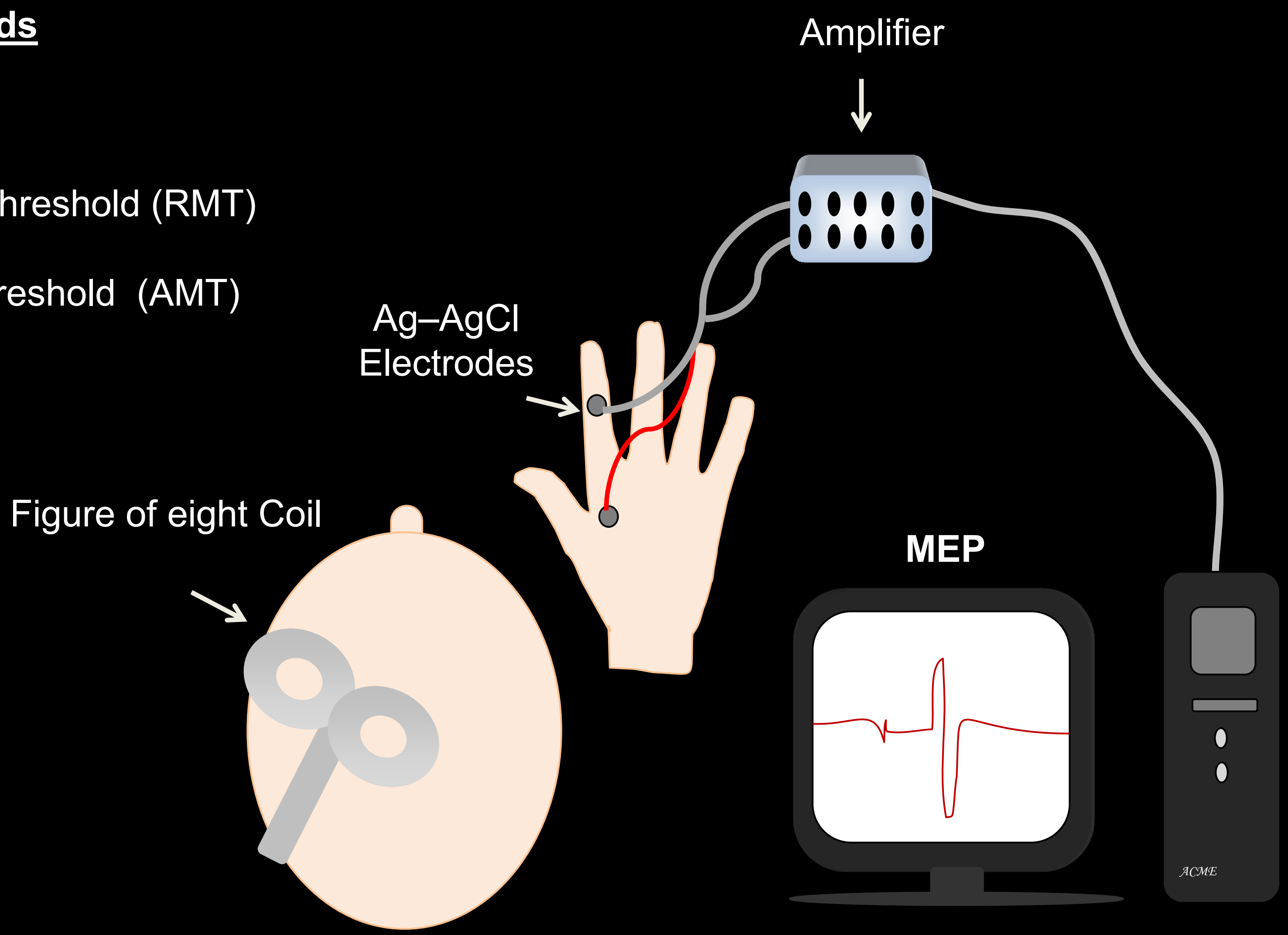
<u>Motor thresholds</u>

Baseline: 1mV

Resting Motor Threshold (RMT)

Active Motor Threshold (AMT)



Motor Evoked Potential (MEP)

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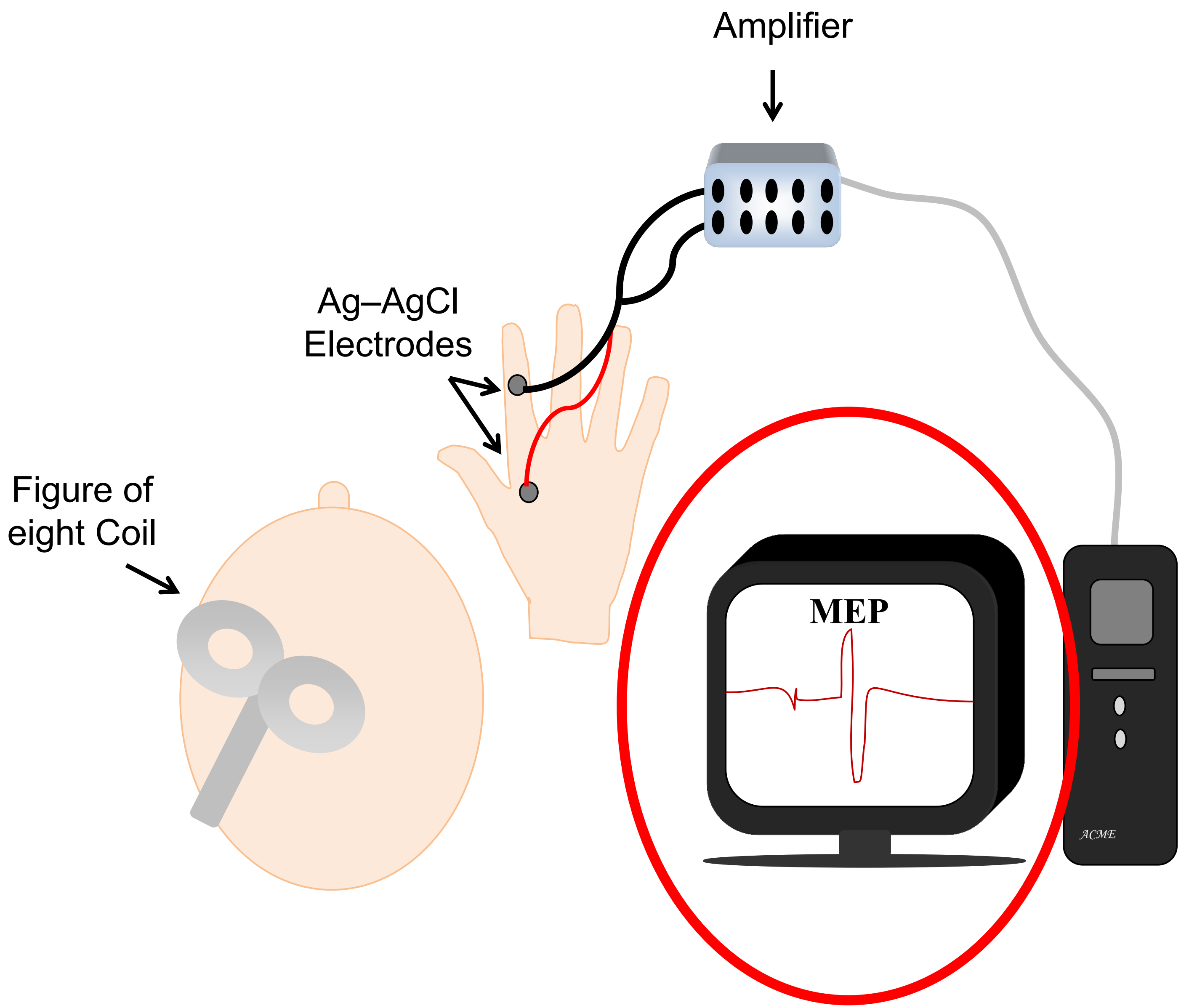
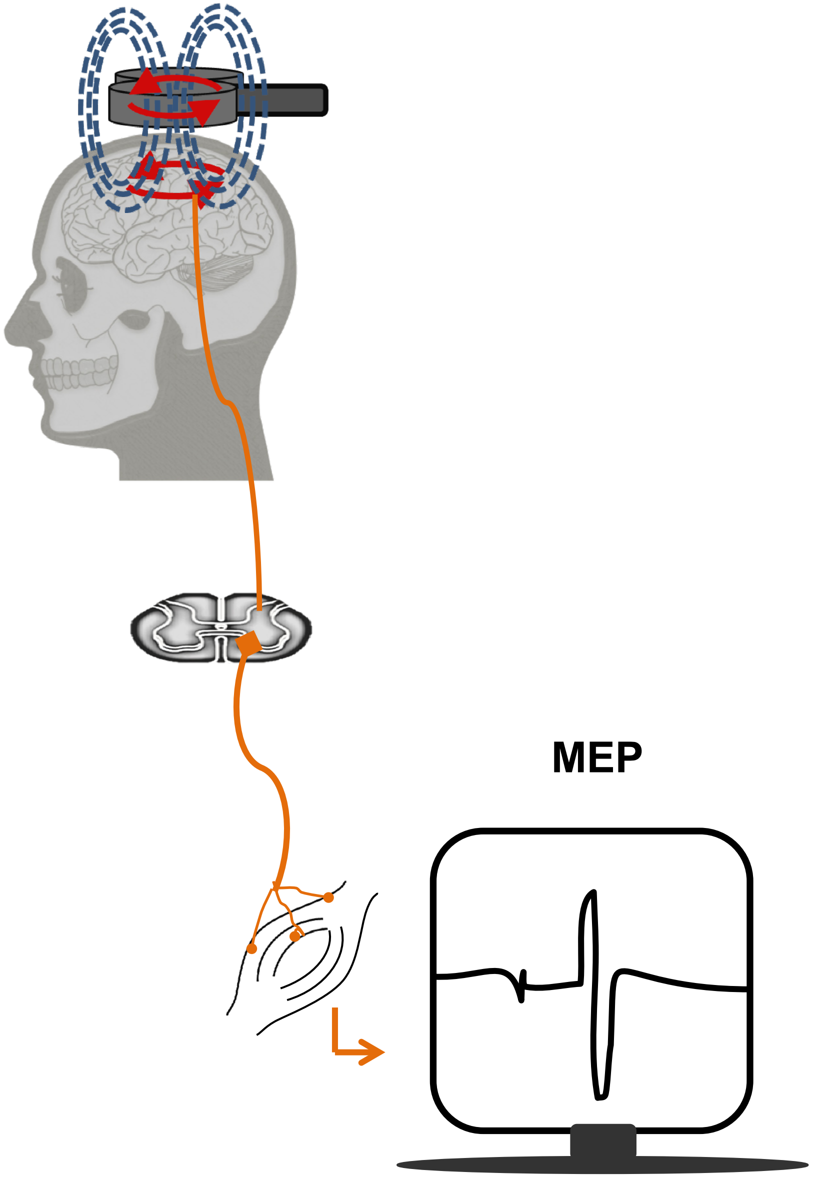


Motor Evoked Potential (MEP)

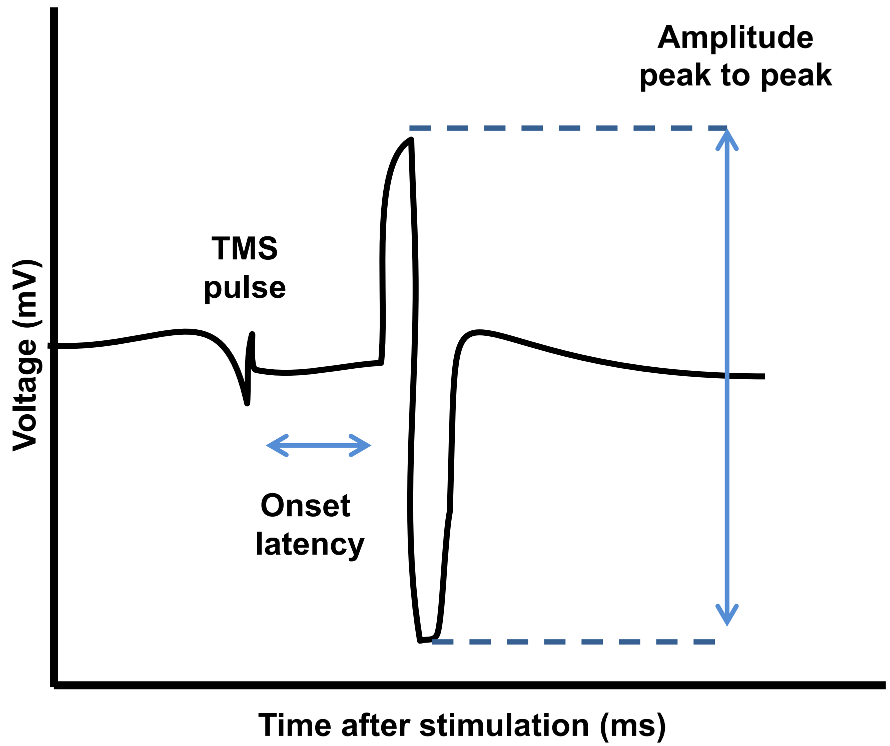
OL Gamboa



- MEPs are the muscle responses induced after activation of central motor pathways.
- Recording of MEPs induced by TMS can be achieved using surface electromyography.

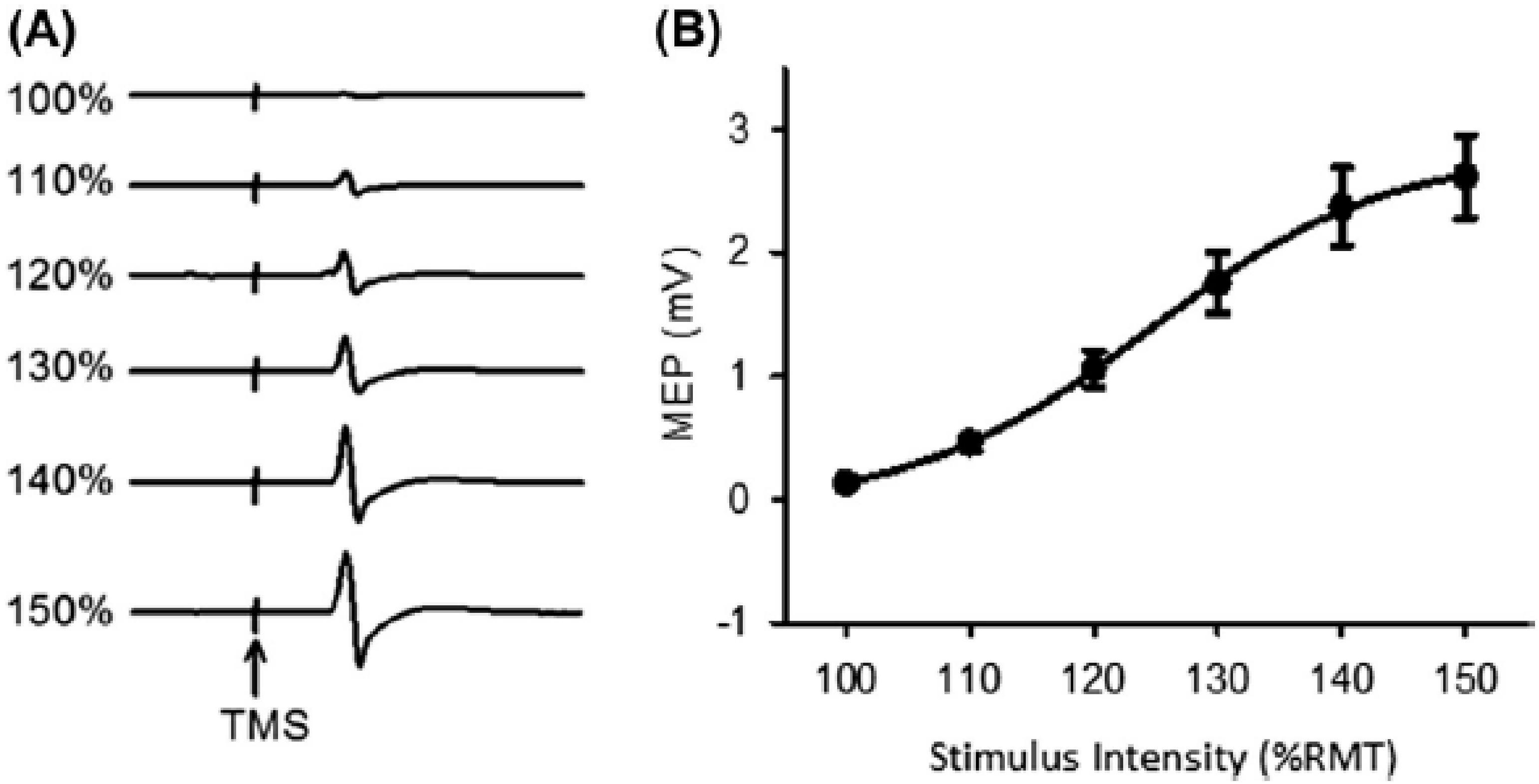
Motor Evoked Potential (MEP)

Three basic physiological mechanisms may influence MEP size:



1. Amount of motor neurons recruited in the spinal cord.
2. Amount of motor neurons discharging repeatedly.
3. Synchronization of the TMS-induced motor neuron discharges.

MEPs as a function of stimulus intensity



Zewdie & Kirton (2016). Pediatric Brain Stimulation

Motor Thresholds

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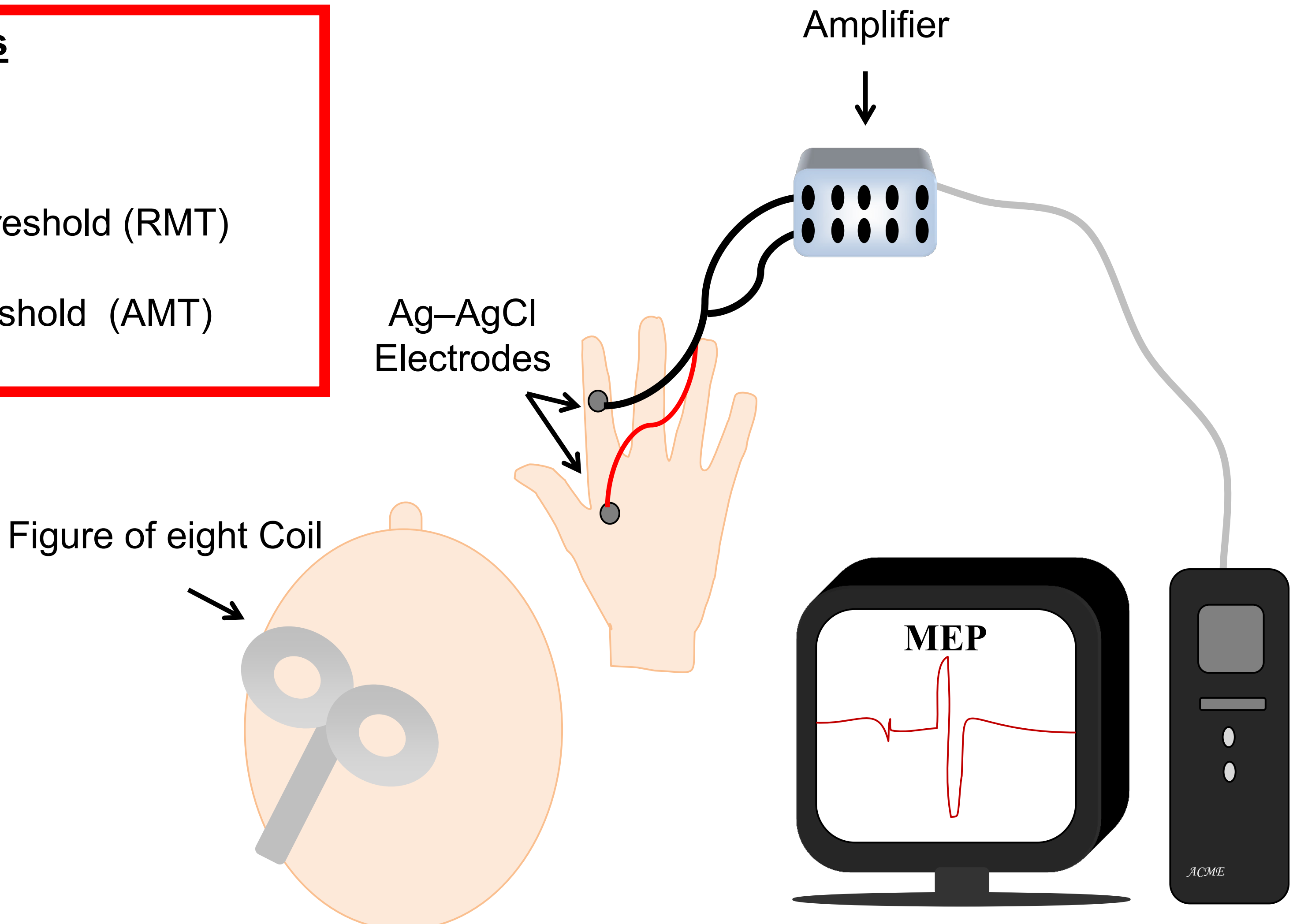
Motor thresholds

Baseline: 1mV

Resting Motor Threshold (RMT)

Active Motor Threshold (AMT)



Motor Threshold (MT)

MT is a parameter used to characterize the level of excitability in each individual. In the clinical setting as well as in research, MT gives information about the integrity of the corticospinal pathway. And it is typically used as a measure that helps guide the intensity to apply during the different TMS protocols.

Resting Motor Threshold (RMT)

The resting motor threshold (RMT) is typically defined as the lowest stimulus intensity able to evoke MEPs of an at least 50 μV peak-to-peak amplitude in 5 of 10 consecutive trials when the target muscle is relaxed or at rest.

Resting Motor Threshold (RMT) and age

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Active Motor Threshold (AMT)

The active motor threshold (AMT) is typically defined as the lowest stimulus intensity able to evoke MEPs of an at least 250 μV peak-to-peak amplitude in 5 of 10 consecutive trials when the target muscle is tonically contracted.

To keep in mind about MEPs and MTs

- MEP and MT are different, they have different mechanisms

- For example MEP size is not affected by MT changes

Phosphene Threshold (PT)

Phosphene threshold (PT) can be defined as the minimum TMS intensity that elicits perception of illusory flashes of light termed phosphenes on a certain number of trials.

The PT is accepted as a valid parameter to determine the intensity used in TMS visual perception studies.

The hot - spot

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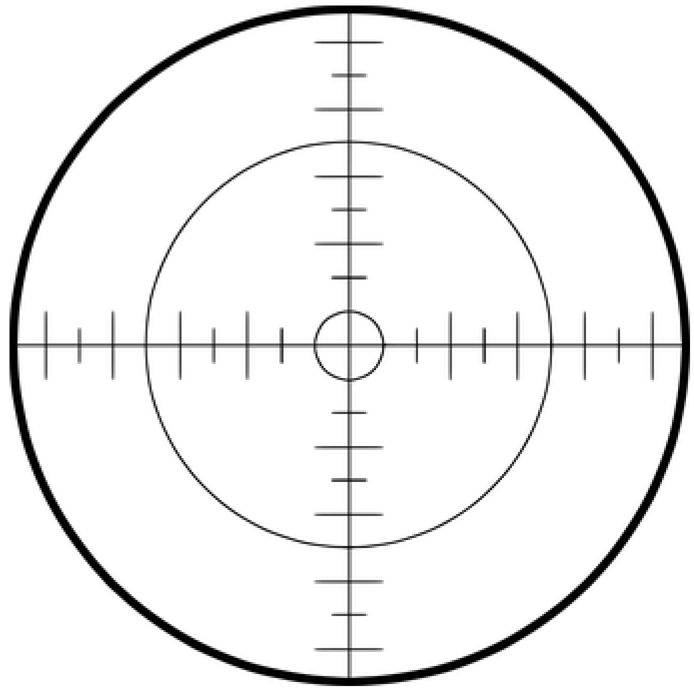

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Magnetic stimulation: motor evoked potentials

J.C. Rothwell* (UK), M. Hallett (USA), A. Berardelli (Italy), A. Eisen (Canada), P. Rossini (Italy) and W. Paulus (Germany)

the centre of the map and taper off to the edges. The site of the maximal amplitude can be called the 'optimal position'. For accurate mapping, it is

Magnetic stimulation: motor evoked potentials

J.C. Rothwell* (UK), M. Hallett (USA), A. Berardelli (Italy), A. Eisen (Canada), P. Rossini (Italy) and W. Paulus (Germany)

Measurement of motor threshold

In order to measure the threshold for evoking a response in target muscles, the coil must first be placed over the most effective point on the scalp for eliciting any response at all. When this point is found, the stimulus intensity must be progressively reduced in 2% or 5% steps until a level is reached below which reliable EMG responses disappear. The rate of stimulation is relevant and there should be more than 3 s between consecutive stimuli. If threshold is measured in relaxed muscle, then a reliable response can be defined as an MEP of 50–100 μV occurring in 50% of 10 to 20 consecutive trials. When responses are elicited in active muscle, the minimal response size may be around 200–300 μV because of the difficulty in distinguishing it from the background activity.

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Preconditioning Repetitive Transcranial Magnetic Stimulation of Premotor Cortex Can Reduce But Not Enhance Short-Term Facilitation of Primary Motor Cortex

A. Suppa,[1,2,3] M. Bologna,[2] F. Gilio,[2] C. Lorenzano,[2] J. C. Rothwell,[1] and A. Berardelli[2,3]
[1]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom;* [2]*Department of Neurological Sciences and* [3]*Neuromed Institute, University of Rome "La Sapienza," Rome, Italy*

Submitted 6 July 2007; accepted in final form 3 December 2007

Test-rTMS

Test-rTMS was delivered over the left M1 through a high-frequency magnetic stimulator (Magstim Super Rapid; Magstim, Whitland, South West Wales, UK) connected to a figure-of-eight coil with mean loop diameter of 9 cm. The magnetic stimulus had a biphasic waveform with a pulse width of about 300 μs. During the first phase of the stimulus, the current in the center of the coil flowed toward the handle. The coil was held tangentially to the scalp with the handle pointing back and away from the midline at 45°, inducing posteroanterior followed by anteroposterior (PA–AP) current in the brain. The coil was placed over the optimum scalp position (hot spot) to elicit motor responses (MEPs) in the contralateral first dorsal interosseus (FDI) muscle.

Accuracy of Transcranial Magnetic Stimulation (TMS) 'hotspot' for lower limb motor representation

Taiser Elsaeed, Sangeetha Madhavan, PT, PhD

Abstract

The purpose of this study was to determine the accuracy of mapping lower limb muscle position on the motor cortex during transcranial magnetic stimulation (TMS). TMS was directed on the primary motor cortex of the target muscle to measure and track cortical excitability by inducing motor evoked potentials (MEPs). These MEPs are detected by an electromyograph (EMG) placed on the surface of the skin for the muscle of interest. Once these MEPs are seen to be reproducible, consistent, and showing the greatest amount of activity this position on the scalp was recorded as the hotspot. Yielding precise and consistent hotspot coordinates is crucial for producing reliable data in regards to lower limb muscle excitability. A retrospective data analysis of fifteen healthy patients and fifteen stroke patients was used to look for patterns in hotspot locations for the tibialis anterior muscle. In patients that have suffered from a stroke, the cortical excitability of the brain is compromised and thus TMS can be used to study the effects of a stroke on muscle activity. This study aims to validate the accuracy of hotspot locations for the tibialis anterior muscle in both healthy patients and afflicted stroke patients. The study hypothesized that the stroke patients will have a larger hotspot location variance than the healthy patients.

Results of the data analysis revealed that there was a strong consistency of hotspot location in the healthy subjects. In addition, the stroke patients had similar hotspot location patterns. No differences could be concluded from the data. This study is relevant to the brain plasticity field because lower limb mapping is infrequently attempted and this accuracy analysis conveys any patterns that individuals may or may not share.

NeuroImage 103 (2014) 152–162

OL Gamboa

Contents lists available at ScienceDirect

NeuroImage

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

Full Length Articles

Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS–EEG

Isabella Premoli [a,b], Davide Rivolta [c], Svenja Espenhahn [a], Nazareth Castellanos [d], Paolo Belardinelli [e], Ulf Ziemann [a,*], Florian Müller-Dahlhaus [a]

2.3. Transcranial magnetic stimulation (TMS) and electromyography (EMG)

Focal TMS of the hand area of left primary motor cortex (M1) was performed with a figure-of-eight coil (external diameter of each wing, 90 mm) connected to a Magstim 200^2 magnetic stimulator (Magstim Company, Carmarthenshire, Wales, UK) with a monophasic current waveform. The optimal coil position over the hand area of left M1 for eliciting MEPs in the right abductor pollicis brevis muscle (APB) was determined as the site where TMS at a slightly suprathreshold intensity consistently produced the largest MEPs. MEP recordings were obtained by surface electromyography (EMG), using Ag–AgCl cup electrodes in a belly–tendon montage. The EMG raw signal was amplified and band-pass filtered (20 Hz to 2 kHz; D360 amplifier, Digitimer, Hertfordshire, UK) and digitized at an A/D rate of 10 kHz per channel (CED Micro 1401; Cambridge Electronic Design, Cambridge, UK). The coil was held tangential to the scalp with the handle pointing backwards and 45° away from the midline, thus activating the corticospinal system

The definition of the TMS ‘hotspot’:

TMS ‘hotspot’ and baseline (Göttingen, Germany) (Siebner –Ziemann: das TMS Buch, Mills: Magnetic stimulation oft he nervous system)

After adjusting the hand electrodes the ‘hotspot’ is determined. The ‘hotspot’ is defined as the coil position that produced the largest MEPs of the FDI/ADM. This spot is identified by TMS (the TMS is set to give 1 pulse every 4 seconds with an external trigger, connected to the software “Signal 3”). The coil is held in a 45 degrees angle tangential to the head. To find the ‘hotspot’ the coil is moved over the M1-region of the left hemisphere. The TMS intensity is increased until a muscle activity is observed –MEPs. The best possible position of the coil is found at the place, where the MEPs are the biggest and the most stable. This spot is marked with a permanent waterproof marker. Then the stimulation intensity (SI_{1mV}) is adjusted to elicit single pulse MEPs with peak to peak amplitudes of an AV of 1mV from 20-40 MEPs. That is stated as the individual threshold for each subject. After determining the threshold the baseline is recorded over the marked ‘hotspot’ using the previously found SI_{1mV}.

Some suggestions for correct hot spot localization:

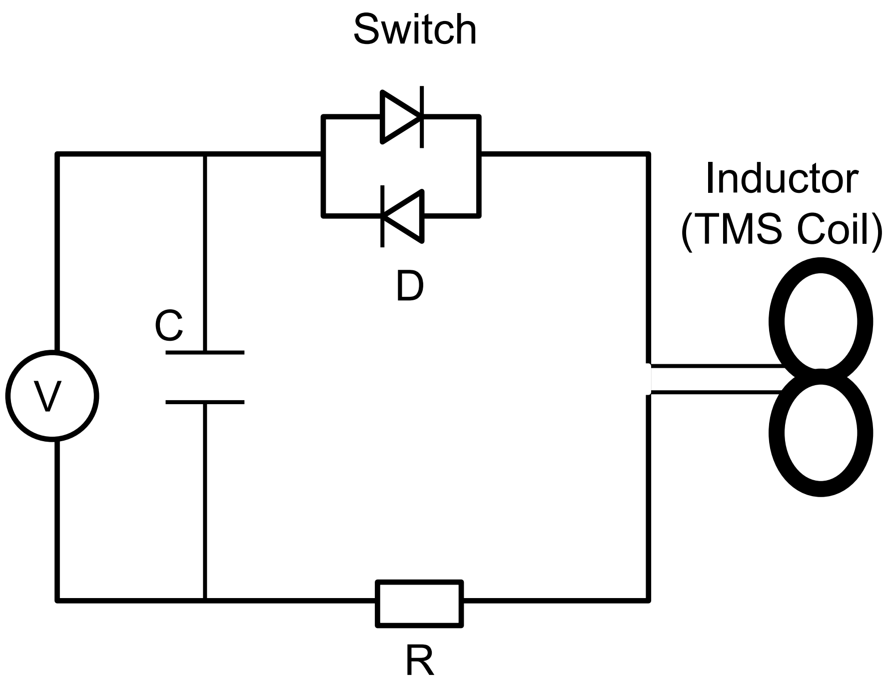
- Quiet environment during MEP recording.
- Avoid muscle pre-innervation.
- Take into account stability besides MEP amplitude:
  - ❖ Stay longer than one pulse on a selected spot.
  - ❖ Once a stable spot has been found: re-check that this is actually the spot by measuring again after a short brake. Ideally this should not take longer than 20 min.

The TMS equipment

- Machine
- Coils
- TMS Pulse

The TMS machine

Biphasic stimulator



TMS machine sequence of events

1. An electrical current (8 kA) is delivered.
2. A charge is stored in the capacitor.
3. The capacitor (C) is discharged through a stimulation coil.
4. A magnetic field pulse is generated in the coil.

TMS machine

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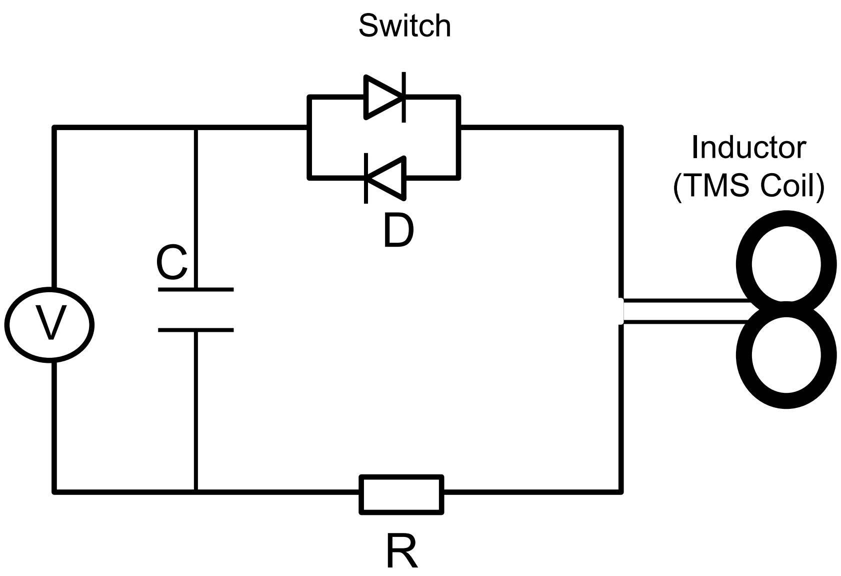
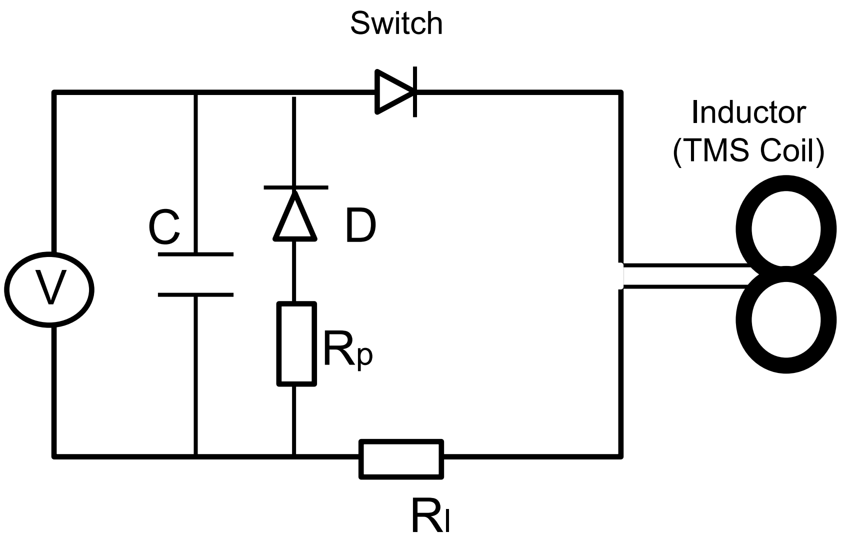
Biphasic stimulator



Monophasic stimulator



TMS Coils

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There are different types of coils.

Each of them has different capabilities.

TMS Coils

<u>Circular coils</u>:

- Has a diameter of 8–15 cm,
- Maximum induced current is at the outer edge of the coil
- Activates superficial cortical layers (Neurons located at a depth of 10.5 mm from the surface of the skull)
- recommended for large and superficial motor areas such as upper limb motor areas.

TMS Coils

Figure of eight coils:

- More focal than the circular.
- Maximal current at the intersection where both coils meet. Thus electric field is at max under its center (hot spot).
- Recommended for more accurate and defined areas
- Stimulates neurons located at a depth of 11.5 mm from the surface of the skull.

TMS Coils

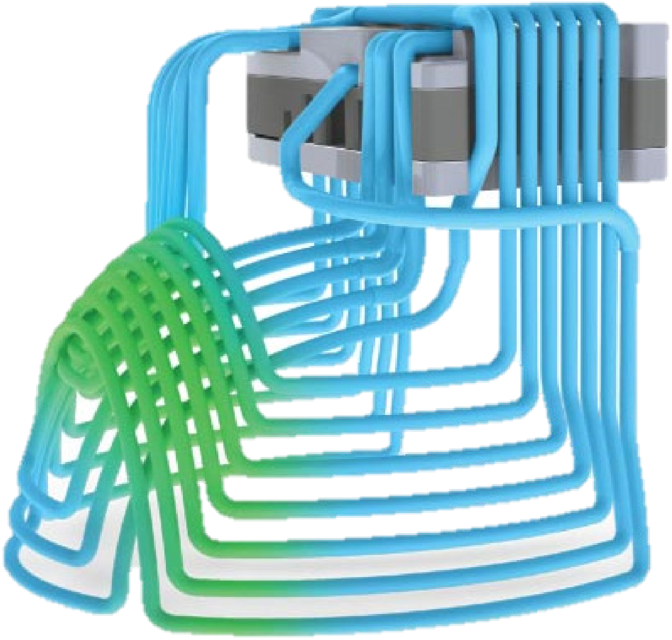
<u>Double cone coils</u>:

- Stimulation is not focal coil.
- Electric field reaches deep cortical layers.
- Recommended for deep cortical layers such as motor areas of lower limbs.
- Stimulation reaches broad M1 areas, activating bilateral lower and upper limbs as well as facial muscles (facial contraction).

TMS Coils

H coils:

- Stimulation has reduced focality.
- Are bigger than conventional coils and ave complex winding patterns.
- Have a slower electric field attenuation with depth.
- Recommended for deeper and broader prefrontal brain region.

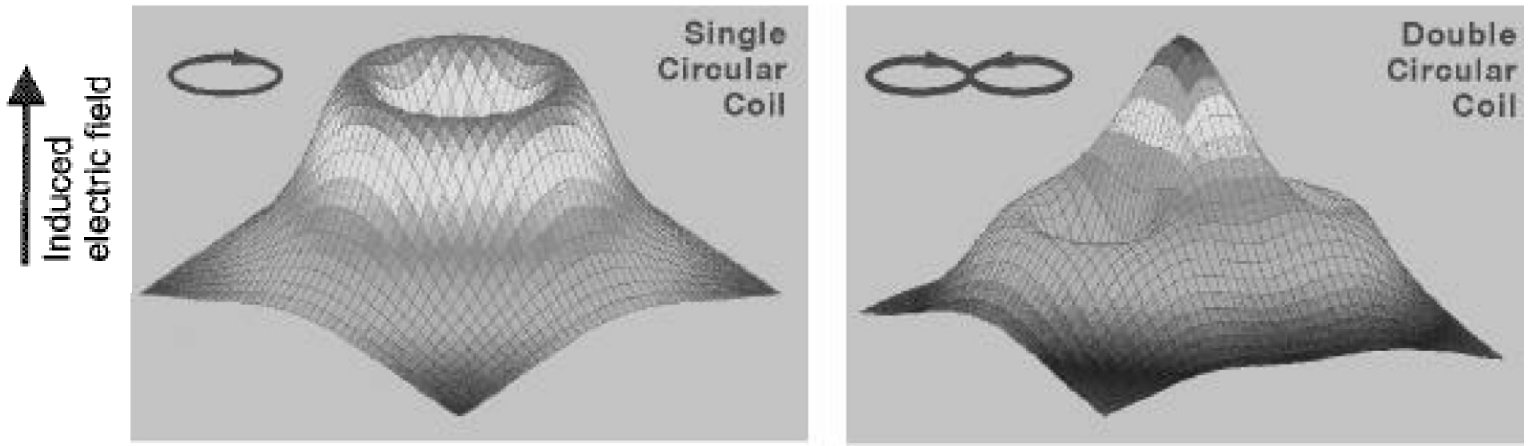


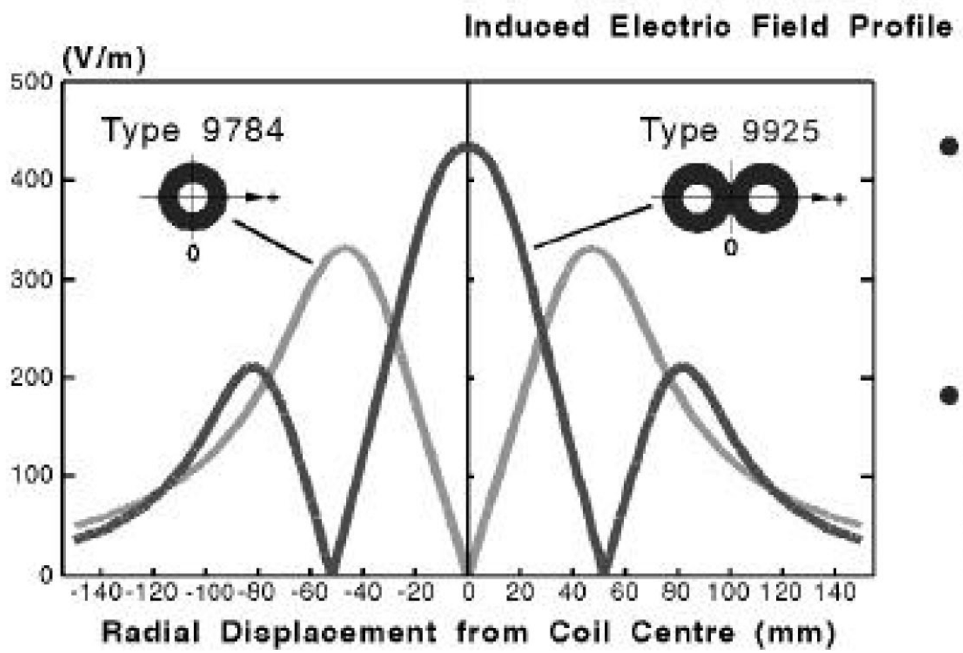
TMS Coils

<u>Cool coils</u>:

- Designed mainly to deliver repetitive TMS
- The cooling system aims to prevent coil over- heating

TMS Coils





- Double coils induce their highest eddy currents where the windings join improving stimulation accuracy.
- Circular coils induce their highest eddy currents under the winding and no current under their center.

Zewdie & Kirton (2016). Pediatric Brain Stimulation

TMS Coils

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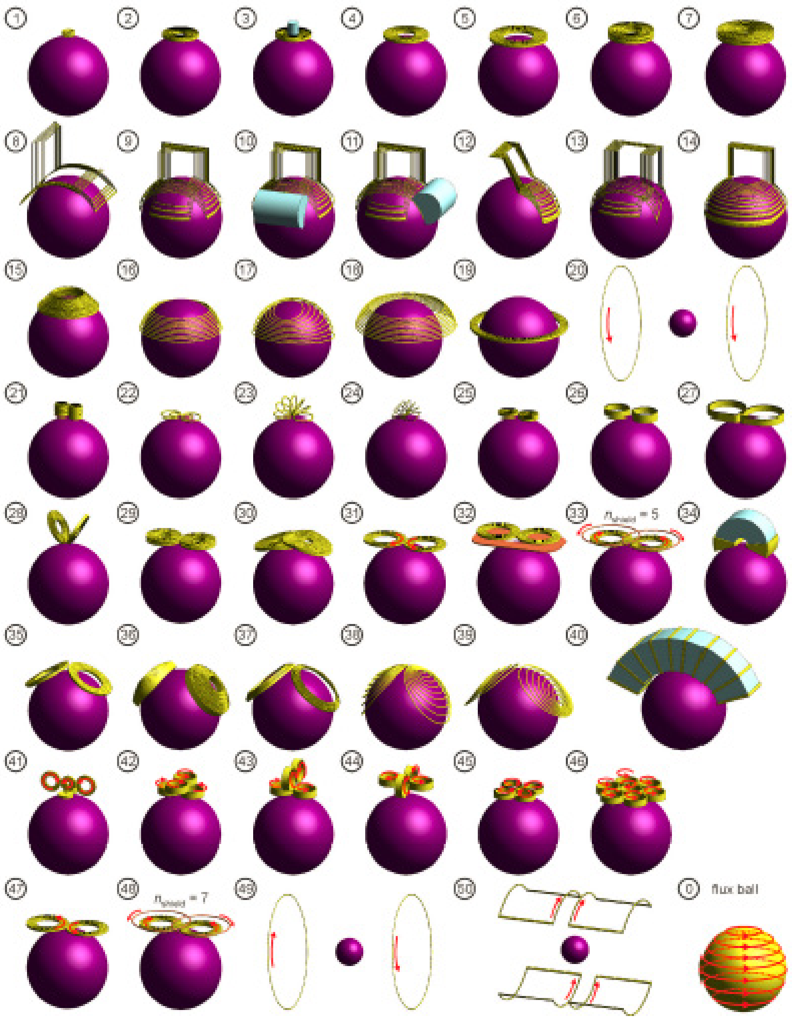
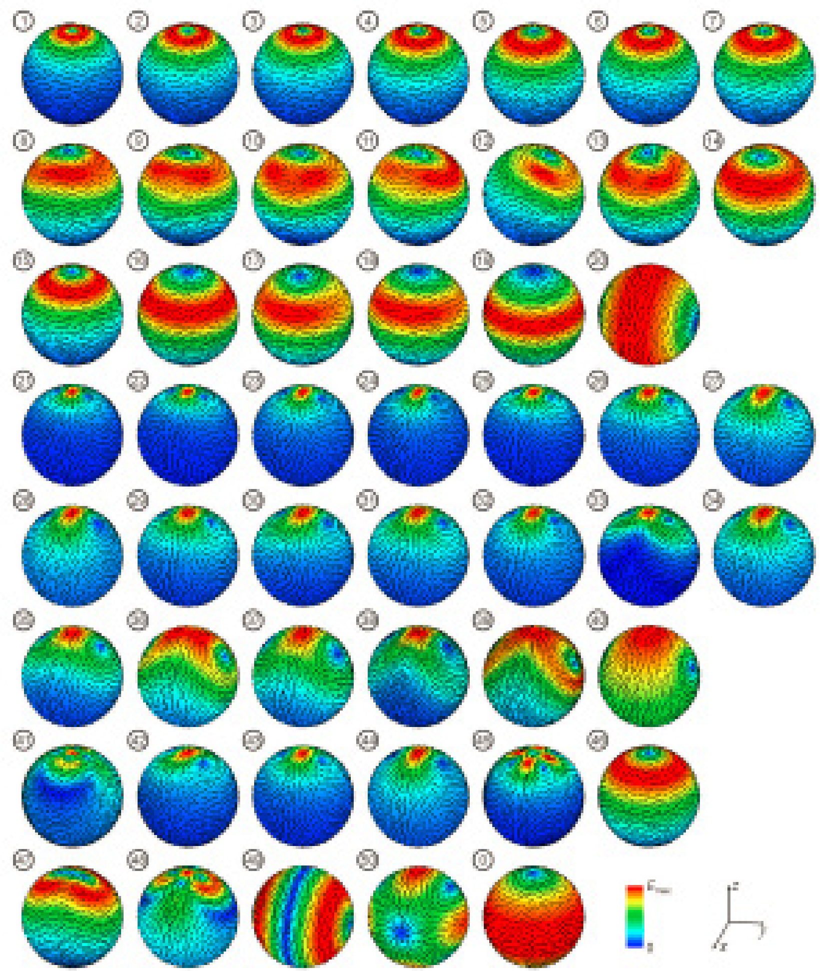
Coil types

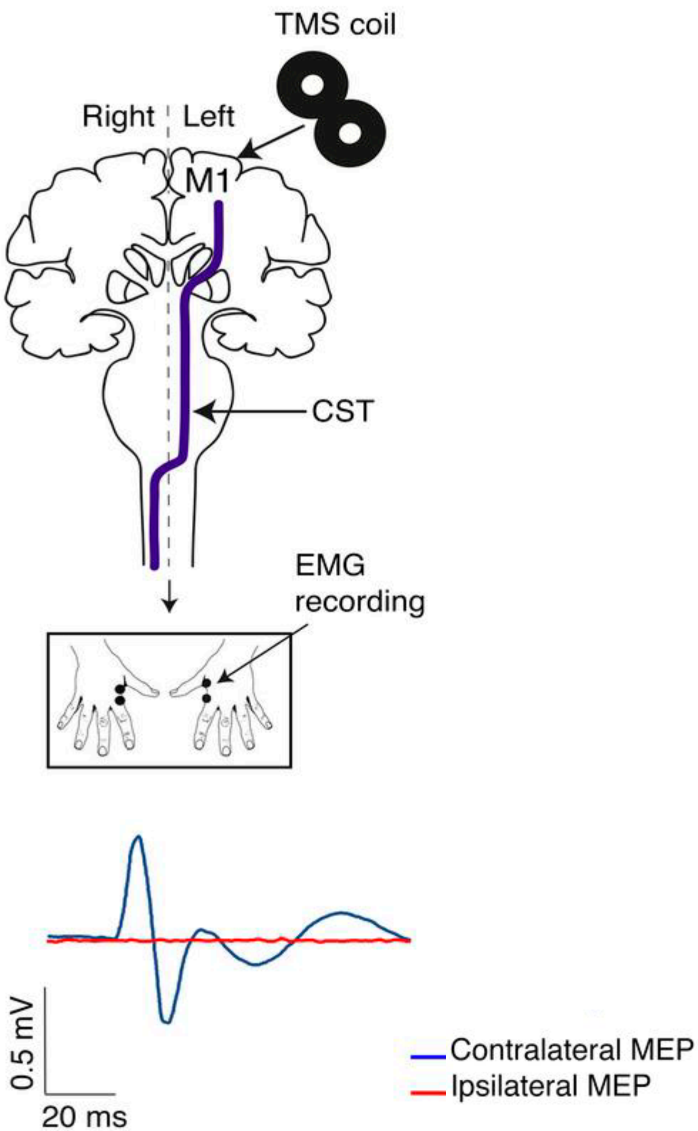


induced electric field in the brain



Deng. et al., (2013). Brain Stimul. January ; 6(1): 1–13

Single pulse TMS



- Available in all TMS devices
- Safe to use
- It is capable to depolarize neurons
- Effects are observable and measurable in different cortical areas
- It is most useful in assessing the descending motor pathways
- Based on the capacitor of the TMS device different types of pulses can be generated.

Méneret et al., (2017). J Clin Invest. 127(11):3923-3936

The TMS pulse: current waveform and direction

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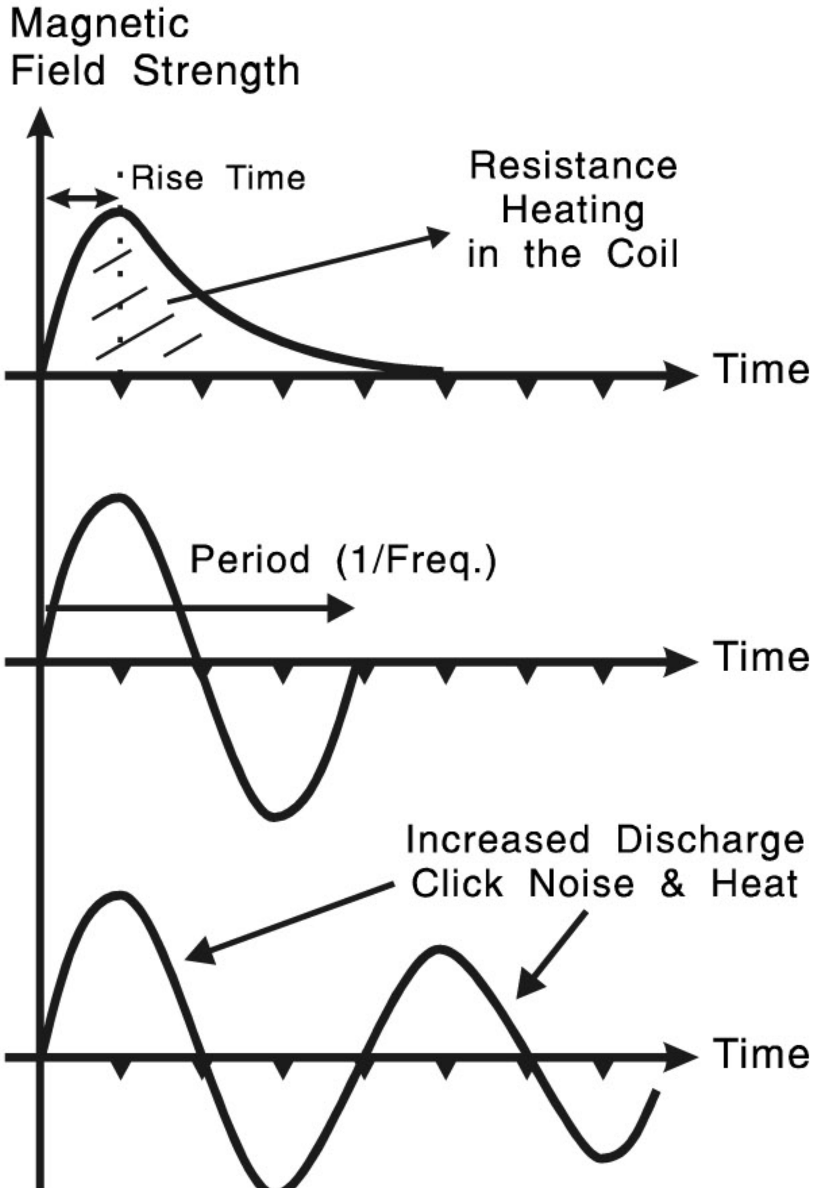
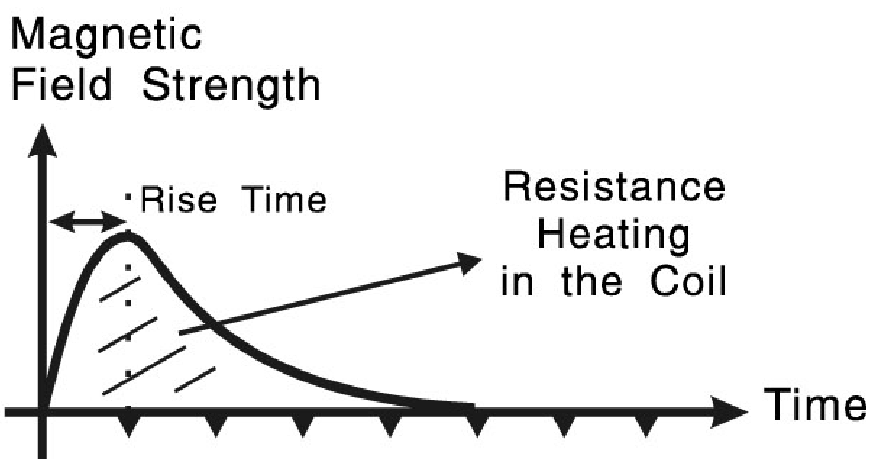


Monophasic

Biphasic

Polyphasic

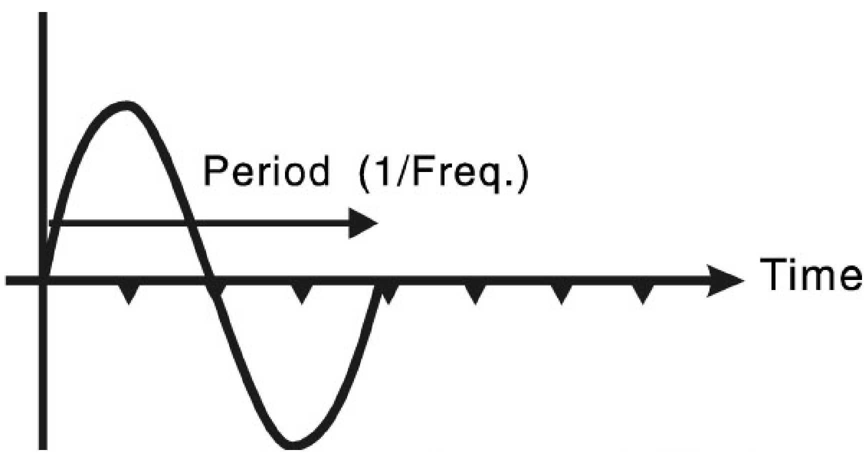
Intraoperative Neurophysiologic Monitoring, ch3



Monophasic

For: More accurate than biphasic, lower noise, lower heat

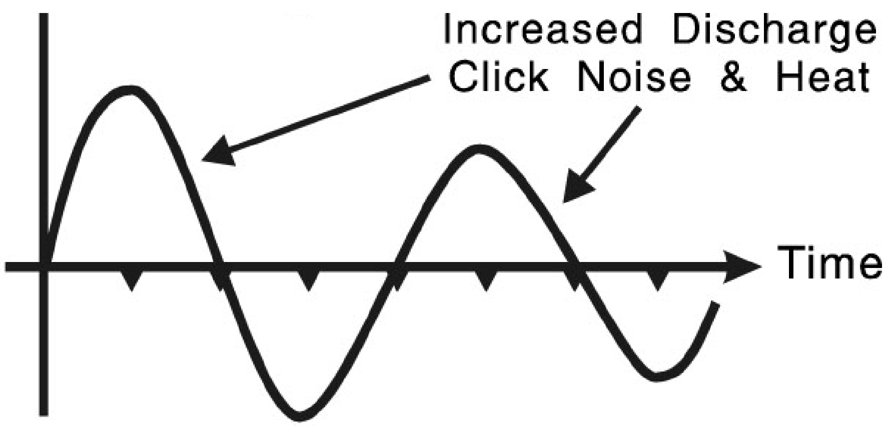
Against: Not easy to obtain bilateral cortical responses



Biphasic

For: Short efficient pulse, suited to bilateral cortical stimulation

Against: Higher noise, possibly less accurate than monophasic



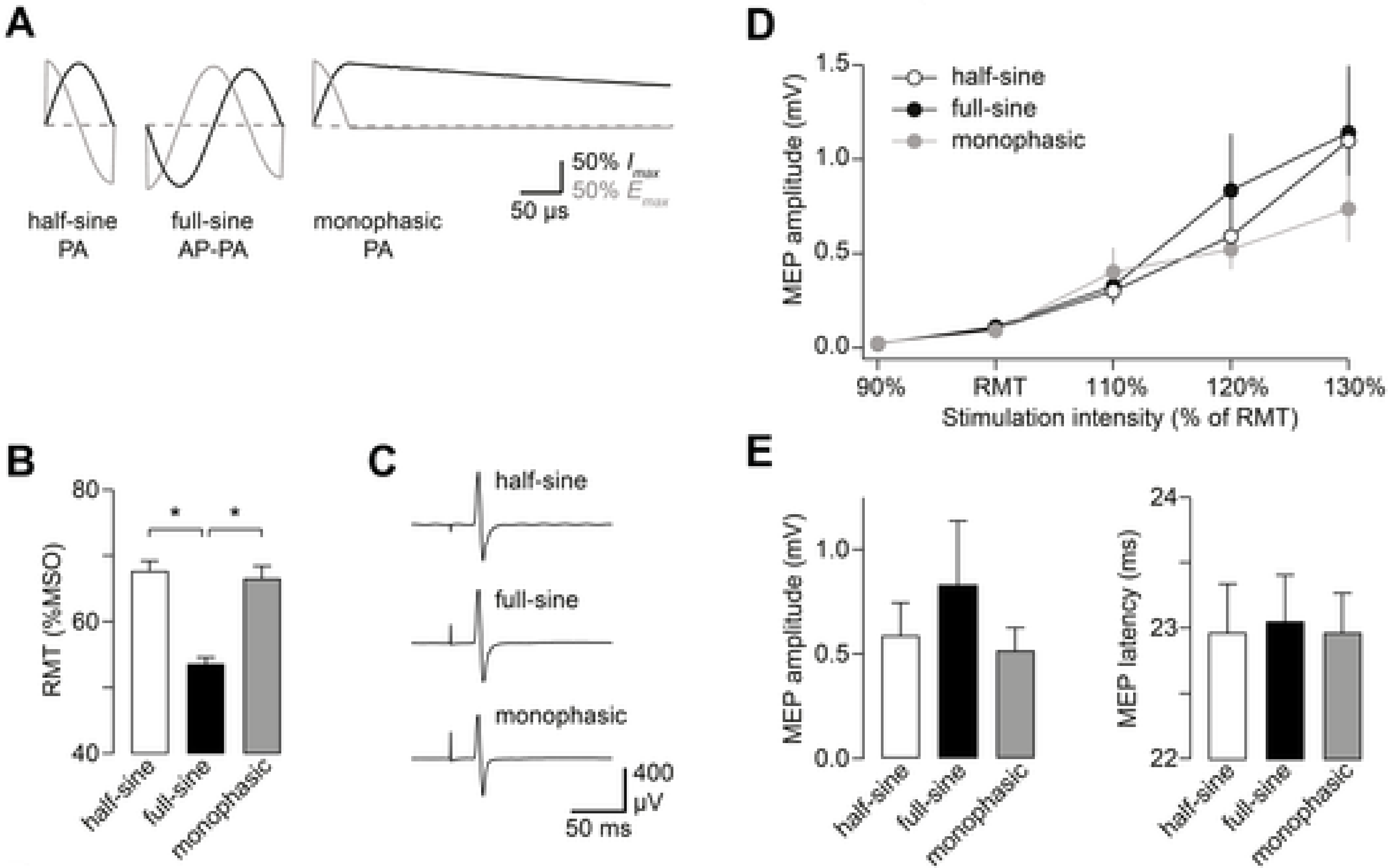
Polyphasic

For: Efficient, suited to bilateral cortical stimulation

Against: Highest noise and heat; less accurate than monophasic

Intraoperative Neurophysiologic Monitoring, ch3

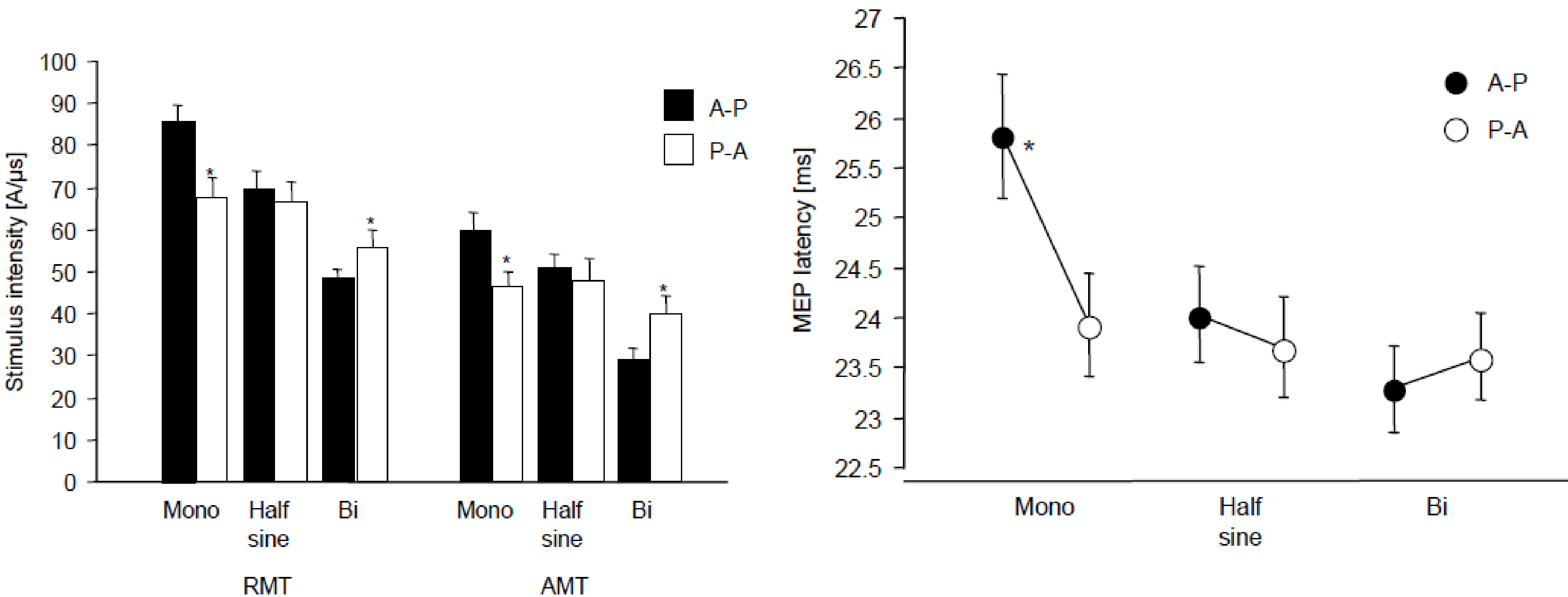
Effects of TMS pulse waveform



Delvendahl et al., (2014). . PLOS ONE 9(12): e115247.

TMS pulse waveform & current direction

OL Gamboa



Sommer et al. (2006). Clinical Neurophysiology 117: 838–844

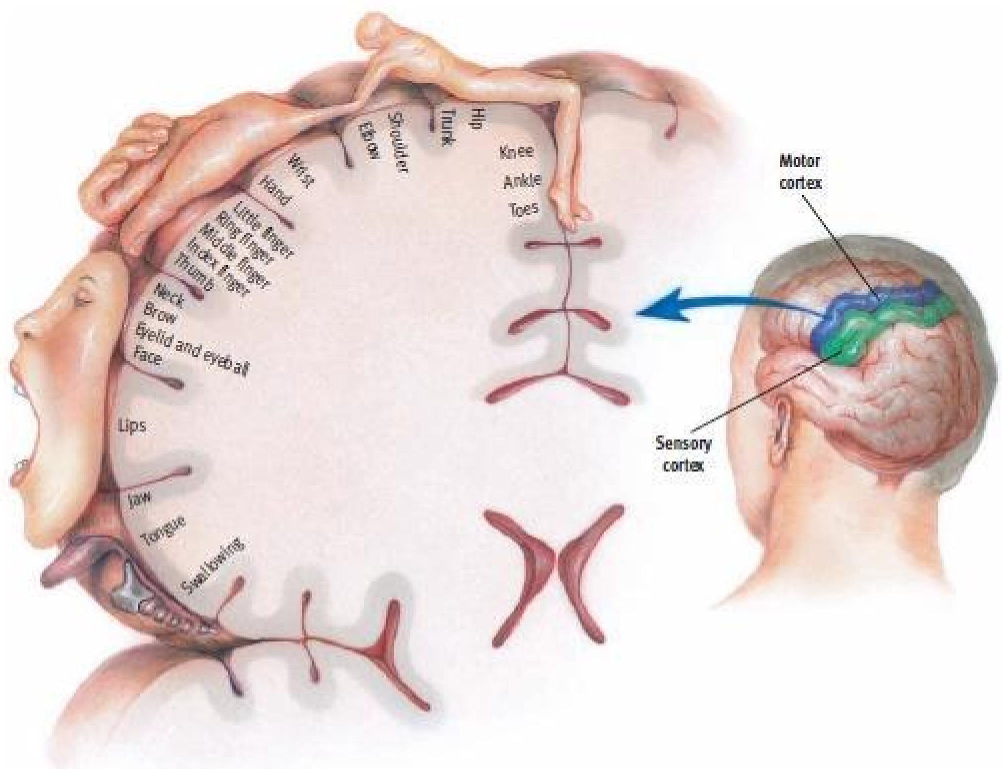
The stimulation site

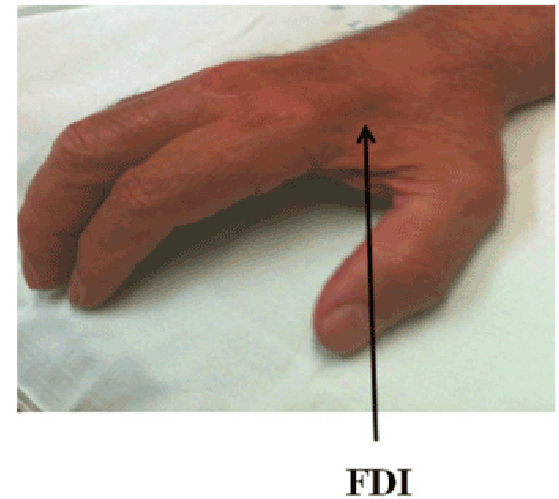
- Motor Cortex
- Outside Motor Cortex

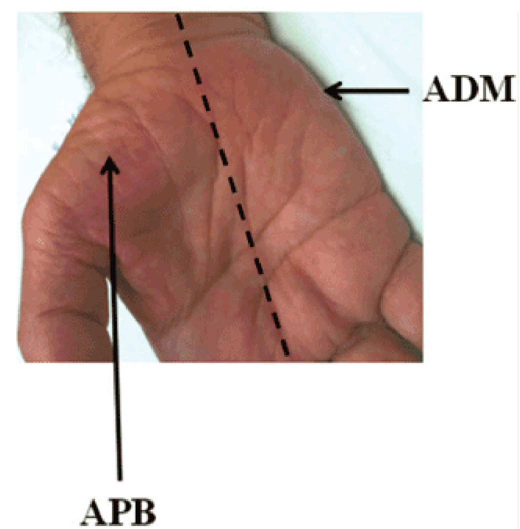
TMS stimulation sites

- Motor areas: hand, knee, mouth, legs
- Non-motor areas: DLPFC, Visual regions(V1, V5), others(somatosensory)

TMS stimulation site: Motor cortex



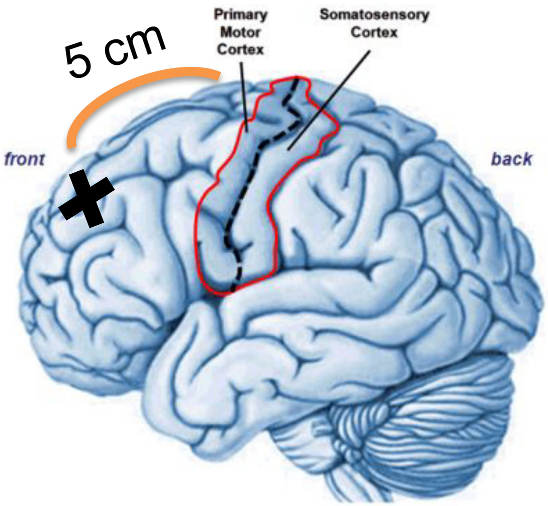




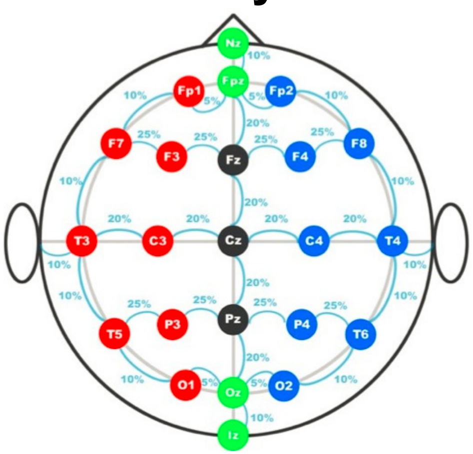
Motor regions of the brain with the performance of each region (Weiten, 2006, p 95) Check….

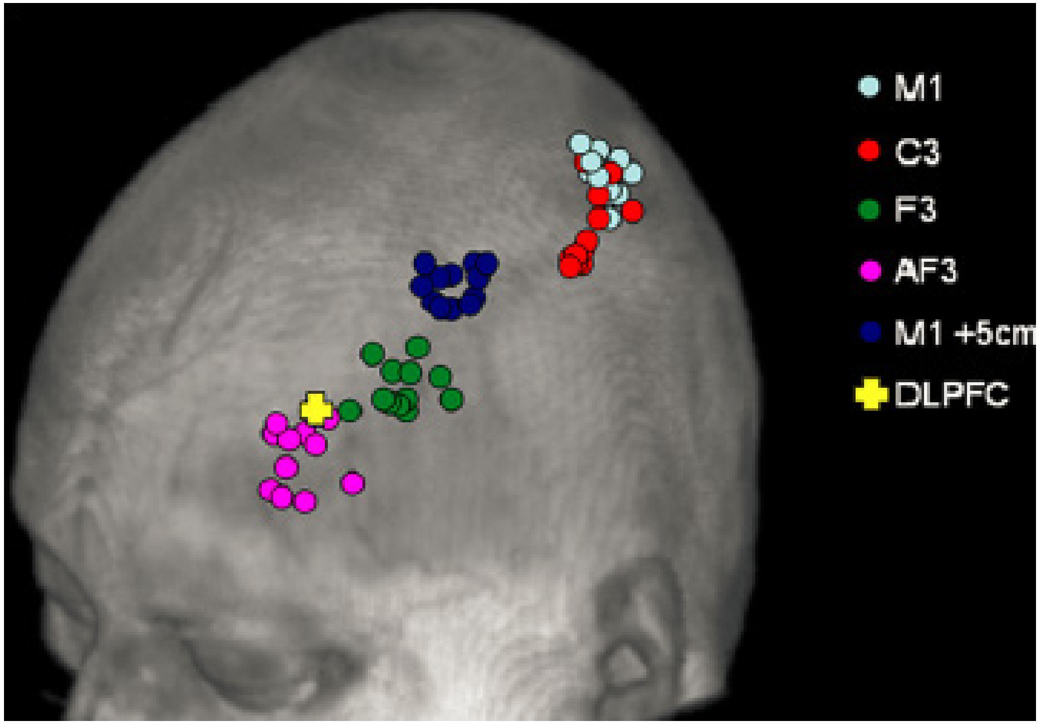
TMS stimulation site: Non motor areas

Locating dorsolateral prefrontal cortex (DLPFC)



10/20 system





DLPFC site located between F3 and AF3.

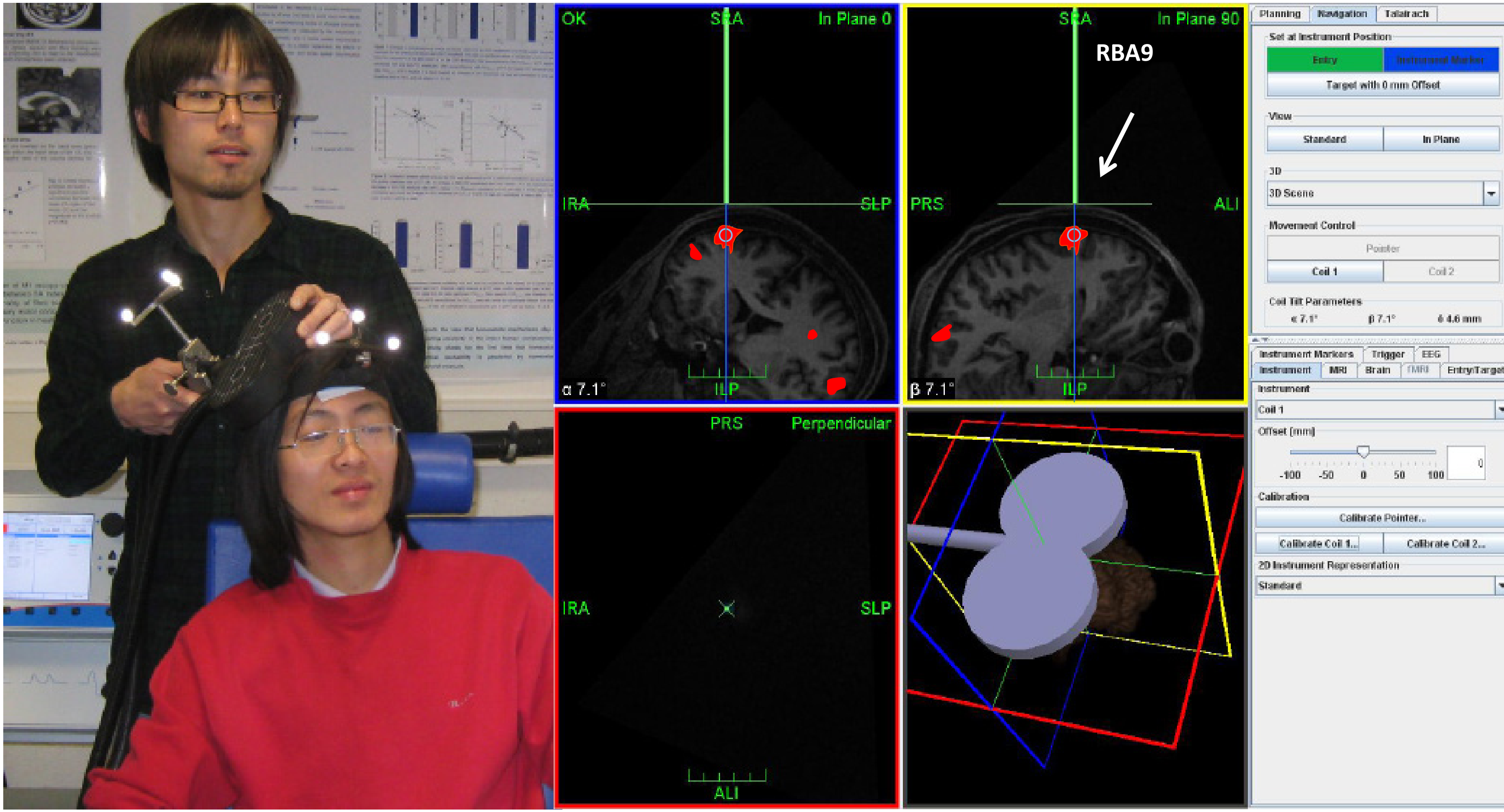
Fitzgerald et al., (2009). Brain Stimulation 2: 234–7

TMS stimulation site: Non motor areas

OL Gamboa

Locating dorsolateral prefrontal cortex (DLPFC)

fMRI-navigated TMS

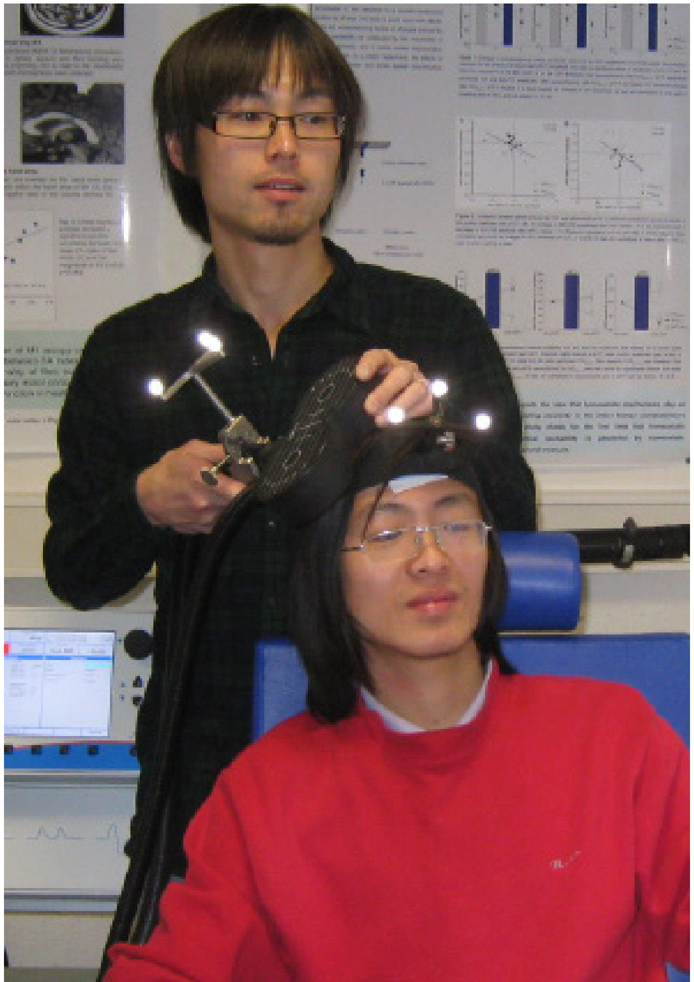


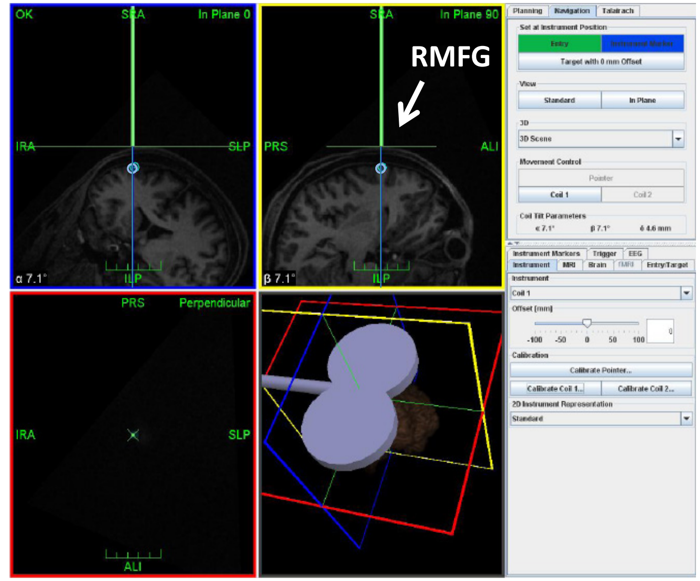
OL Gamboa

TMS stimulation site: Non motor areas

Locating dorsolateral prefrontal cortex (DLPFC)

fMRI-navigated TMS





on the cortical surface (SD) and related Brodmann and anatomical areas of each ROI.

ROI	Channel	MNI-space correspondence				Cortical areas	
		x	*y*	*z*	SD	BA	
1 APFC	46	23	72	8	4	10	SFG
	47	−8	73	6	5	10	MeFG
	48	−31	66	3	5	10	MFG
2 Left DLPFC	18	−51	23	41	5	9	MFG
	28	−47	39	28	6	46	MFG
	29	−61	11	28	6	9	IFG
3 Right DLPFC	13	48	31	42	5	9	MFG
	23	57	26	29	5	46	MFG
	24	45	62	29	5	46	MFG

BA, Brodmann area; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; MeFG, medial frontal gyrus.

To Remember

The TMS induced response depends on several factors:

- Stimulation site
- Coil type (figure of eight, H shape, circular)
- Coil orientation and tilt
- Magnetic pulse waveform (monophasic – biphasic, polyphasic)
- Pulse direction (a-p, p-a)
- Current intensity and dose
- Frequency and pattern of stimulation
- Tissue properties (conductivity and permittivity)
- Interaction coil – tissue: unique for each subject
- Brain state

“But still try, **for who knows what is possible**?”

– Michael Faraday