5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Hands-on Course 3/7

Transcranial magnetic stimulation(Level 1)

Letizia Leocani
Milan, Italy

Email: letizia.leocani@hsr.it

Oslo, June 29, 2019

Hands-on Course – Level 1

Hands-on course

Transcranial Magnetic Stimulation – TMS

Letizia Leocani

Neurology Dep.t University Hospital San Raffaele
Milan - Italy

DISCLOSURES (alphabetical order):

Letizia Leocani:

- Advisory board: Abbvie, Biogen, Merck Serono, Novartis
- Travel support: Almirall, Biogen, Genzyme, Merck Serono, Novartis, Teva
- Research support: Almirall, Biogen, Merck Serono, Novartis
- Speakers bureau: Almirall, Biogen, Excemed, Merck Serono, Novartis, Teva

key learning objectives

- how to:
  - Screen for safety limitations
  - record motor evoked potentials
  - measure motor threshold
  - measure central motor conduction time
  - measure silent period (research)

Suggested reading – IFCN guidelines

Clinical Neurophysiology 126 (2015) 1071–1107

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

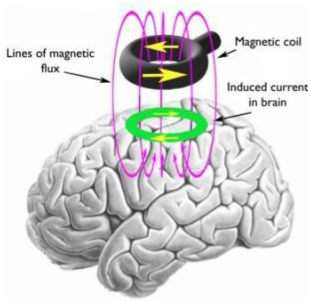
Reviews and Guidelines

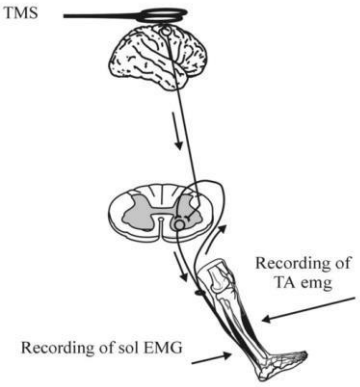
Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee

P.M. Rossini [a], D. Burke [b], R. Chen [c], L.G. Cohen [d], Z. Daskalakis [e], R. Di Iorio [a,*], V. Di Lazzaro [f], F. Ferreri [f,g], P.B. Fitzgerald [h], M.S. George [i], M. Hallett [j], J.P. Lefaucheur [k,l], B. Langguth [m], H. Matsumoto [n], C. Miniussi [o,p], M.A. Nitsche [q], A. Pascual-Leone [r], W. Paulus [s], S. Rossi [t], J.C. Rothwell [u], H.R. Siebner [v,w], Y. Ugawa [x], V. Walsh [y], U. Ziemann [z]

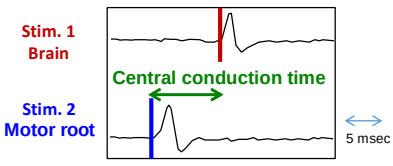
Rossini et al 2015

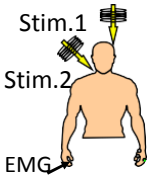
TECHNICAL PRINCIPLES OF TMS





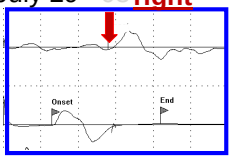
Motor Evoked Potentials - MEPs

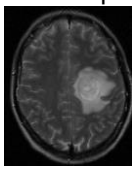


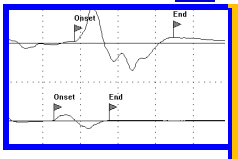


A.B. , female, 27 yrs Multiple Sclerosis relapse upper limbs MEPs

July 29th 03 **right** Acute paresis (1st week) **left**

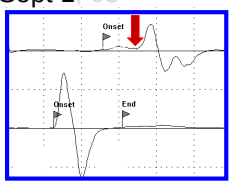


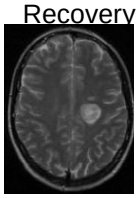


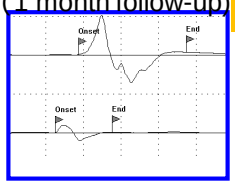


- MEPs amplitudes can be unreliable for axonal loss in the first 1-3months after Mutiple Sclerosis relapse
- MEPs latency useful to detect demyelination (>>delay)

Sept 1 03 Recovery (1 month follow-up)

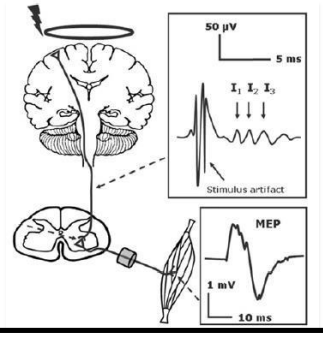






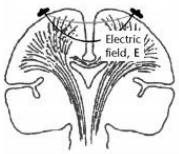
PHYSIOLOGICAL BASIS OF TMS

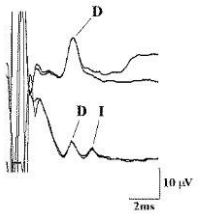
- **A single suprathreshold TMS pulse** with a large round coil produces a **series of descending volleys** (multiple I-waves and possibly a D-wave), indicating strong repetitive activation of the corticospinal neurons
- **Each descending volley** induces **glutamate release** in cortico-MN synapses leading to a depolarization at the postsynaptic cell membrane
- The glutamate release triggered by each volley sums up temporally and spatially; if the volleys are strong enough to exceed the firing threshold, they **trigger an action potential** (AP) in the spinal MN
- These APs propagate along the peripheral motor axons inducing a motor response that can be recorded as the MEP

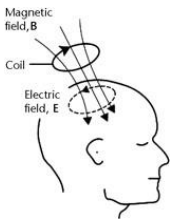


TECHNICAL PRINCIPLES OF TMS

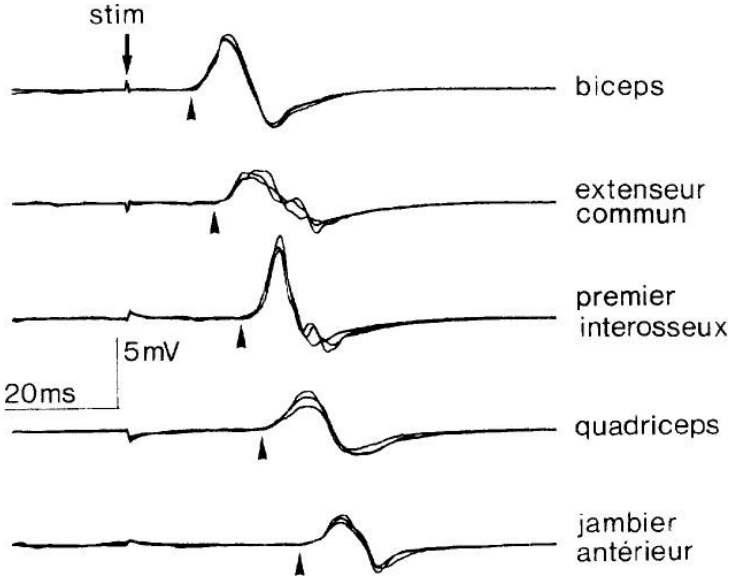
	TES	TMS
Direction of E	Parallel & perpendicular	Parallel
Sensitive to skull conductivity	Yes	No
Neuronal activation	Direct (D waves)	Indirect (I waves)
Resistance to anaesthetics	High	Low
Painful	Yes	No





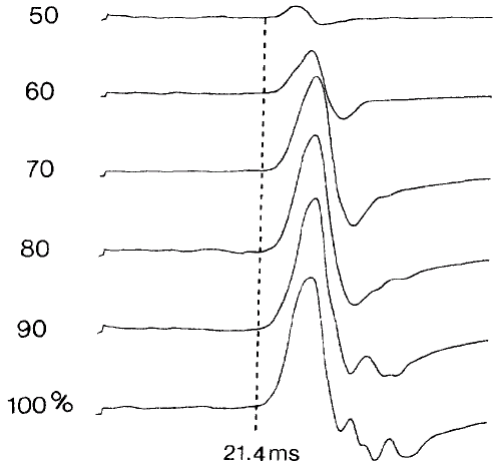


MEP latency > distal muscles



Maertens de Noordhout, 1998

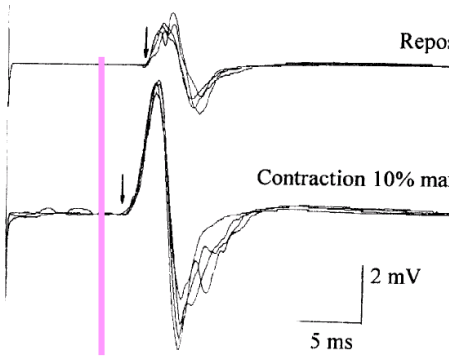
MEP amplitude > higher stimulusintensities



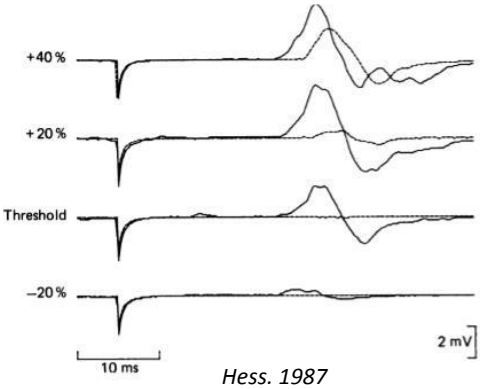
Maertens de Noordhout, 1998

MEP amplitudes > stimulus intensity & voluntary pre-activation *(I & II motoneuron facilitation)*

- Stimulate at 1.4-1.5 times corticomotor threshold with slight preactivation (~ 10 % of max force)
- Select the best of 5-6 repetitions



Maertens de Noordhout, 1998



Hess. 1987

MEP amplitude > eyes opening
facilitation I (and II?) motoneuron

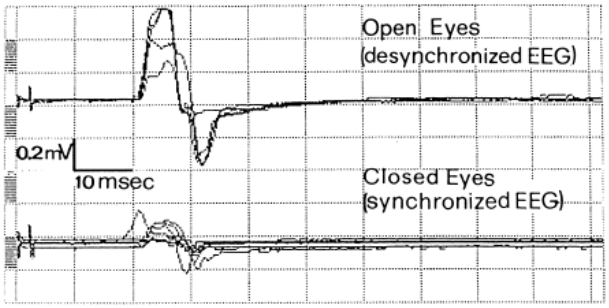
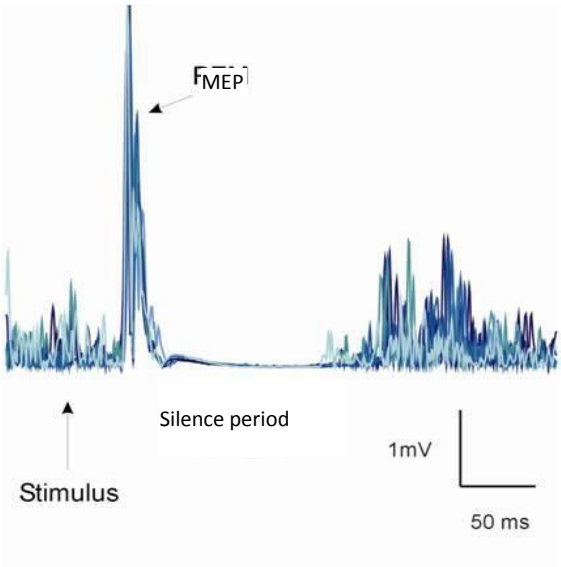


Fig. 1. The amplitude of relaxed-MEPs was evaluated during TCS with stable intensity; the subjects were randomly asked to close the eyes and maintain mental inactivity (lower traces) or to open the eyes and to perform mental calculations (upper traces). Spectral analysis of the on-going EEG demonstrated that the alpha band was much larger with eyes closed. This corresponded to small and unreproducible MEPs (partly modified from Rossini et al., 1991a).

Cortical silent period (CSP)

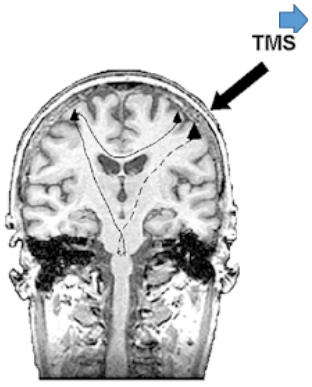


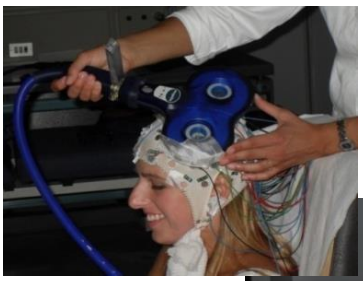
Suprathreshold stimulus during muscular contraction interrupts the voluntary EMG activity. The higher the stimulus intensity, the longer the silent period

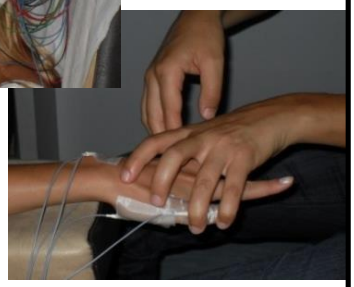
Trompetto et al 2001

Ipsilateral Silent Period

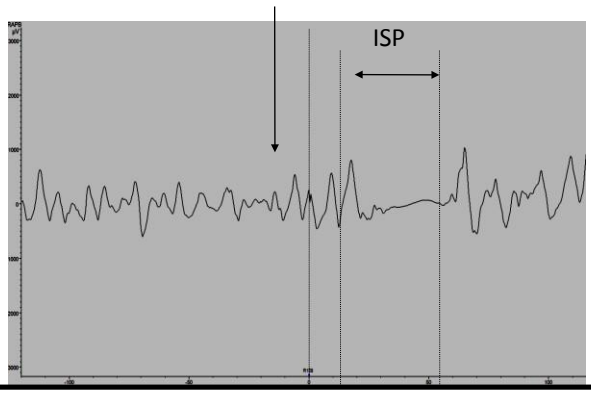
Allows to study inter-hemispheric interactions







TMS pulse



TECHNICAL PRINCIPLES OF TMS

STIMULUS WAVEFORM

Two different pulse waveforms are commonly used for clinical TMS:

- monophasic pulse
- biphasic pulse

The depth penetration of TMS depends upon:

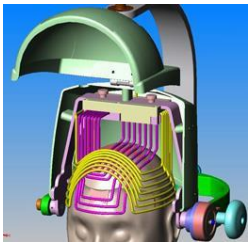
- distance coil - cortex
- stimulus intensity
- coil shape

Coils

Figure-of-eight

Circular

Double cone



H-coil

TECHNICAL PRINCIPLES OF TMS
COIL DESIGN

Round coil (or circular coil)

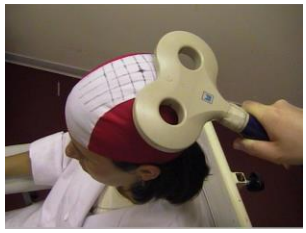
- outer diameter of ≥ 10 cm
- more powerful than figure-of-eight coil
- good depth penetration
- non-focal stimulation
- the induced electrical field attenuates towards the geometrical center of the coil, therefore the annulus of the coil and not the center has to be placed over the target to achieve effective stimulation

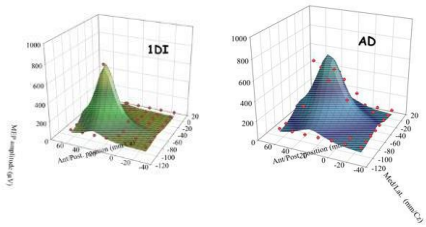
TECHNICAL PRINCIPLES OF TMS
COIL DESIGN

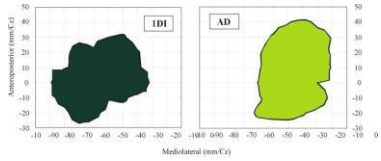
Figure-of-eight shaped coil (double or butterfly coil)

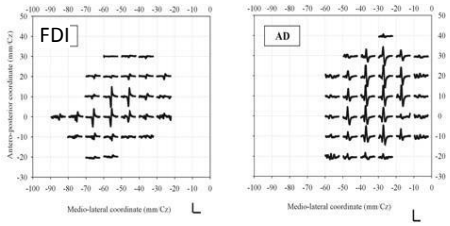
- two circular coils are wired in a way that the current in each circular coil has an opposite direction
- the largest current density in the tissue is under the intersection of the round components, oriented in parallel to the wires in the center of the coil. The center of the coil should be placed over the target region
- focal stimulation
- the focality of the figure-of-eight coil is more appropriate for research application or for specific clinical situations in which mapping is required

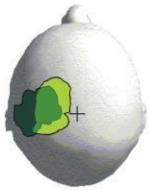
Cortical mapping











(From Devanne et al, Eur J Neurosci, 2006)

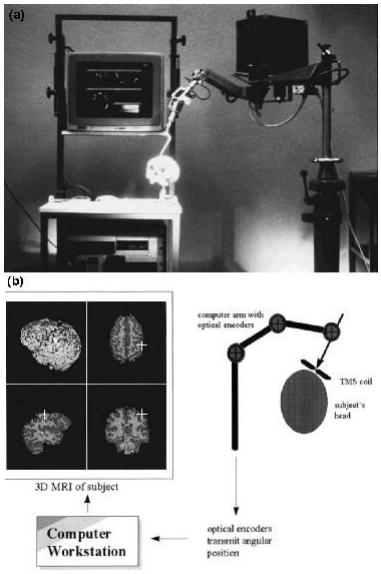
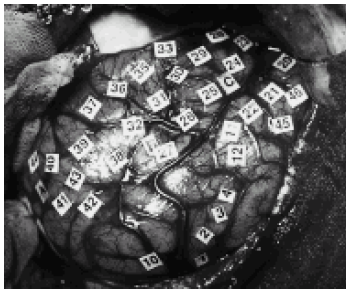


Fig. 1. (Frame a and b) Photograph and schematic drawing of the frameless stereotactic system. Optical encoders within the joints of the 3D digitizing arm transmit their angular position to the computer workstation where the spatial localization of the arm tip is computed in real-time and overlaid on the 3D MR data set of the subject.



Focal TMS mapping not only for research purposes (plasticity) but also for pre-operative M1 localization

Krings et al. 1998

TECHNICAL PRINCIPLES OF TMS

It is recommended to use a **large round coil for diagnostic TMS**:

- easier coil positioning over M1, because coil stimulates a larger cortical volume
- better depth penetration, which facilitate TMS of primary motor leg area
- stimulation of M1 is less susceptible to the minor changes in coil position

Author	Threshold determination	N.stimuli	Definition
Rossini/Rothwell 1994	relative frequency method	75	Lowest stimulus intensity (% MSO) inducing 5 MEP in 10 trials
Mills and Nithi, 1997	Two-threshold method	48	Mean of lower and upper threshold. LT: highest stimulus intensity at which no motor response is evoked in 10 trials. UT: lowest stimulus intensity at which MEP responses are evoked in all 10 trials
Awiszus, 2003	Adaptive method	14-7	Parameter Estimation by Sequential Testing (PEST) and Maximum Likelihood regression Motor Threshold Assessment Tool, version 2.0: http://www.clinicalresearcher.org/software
Qui, 2011	Bayesian adaptive method	3-7	Parameter Estimation by Sequential Testing (PEST) and Maximum Likelihood regression. 3 when using subject-specific priors

THRESHOLD FOR CORTICOMOTOR EXCITATION

RELATIVE FREQUENCY METHOD

- **Original method** (Rossini et al., 1994)

CMT is defined as the lowest stimulus intensity (given as % of MSO) that is required to induce a MEP in 5 out of 10 trials

- MEP ≥ 50 µV in relaxed muscle

- MEP ≥ 200 µV during tonic contraction of the target muscle

- **Slightly modified method**

CMT is defined as the lowest stimulus intensity (given as % of MSO) at which TMS evokes a MEP in at least 5 out of 10 trials

I. TMS should start with a subthreshold intensity of stimulation

II. Stimulus intensity is gradually increased in steps of 5% MSO until TMS consistently evokes MEPs with peak-to-peak amplitude > 50 µV in each trial

III. Then stimulus intensity is gradually lowered in steps of 1% MSO until less than 5 positive responses out of 10 trials are recorded

IV. This stimulus intensity plus 1 is then defined as CMT

THRESHOLD FOR CORTICOMOTOR EXCITATION

- Cortical motor threshold (CMT) for the target muscle **reflects the excitability of the whole corticomotor projections**, including **cortical and spinal level**
- Two methods for determining CMT in clinical practice:

1. Resting Motor Threshold (RMT)

determined with the target muscle being completely relaxed

method commonly employed in clinical practice

2. Active Motor Threshold (AMT)

obtained during a slight tonic contraction of the target muscle:

10-20% of the maximal strength

- CMT is not a static measure but is subject to state-dependent fluctuations which account for some intra-individual variations (individual posture, pharmacological influence, target muscle, sleep-wake cycle, age, CNS maturation, technical setup)
- The diagnostic use of the CMT is limited due to its **inter- and intra-individual variability**, even in healthy subjects

In spite of these limitations, it **is recommended to integrate CMT measurement** in the overall neurophysiological assessment, and the CMT value, together with the method used for its estimation, **should be listed in the final report**

SAFETY ASPECTS OF SINGLE-PULSE TMS
CONTRAINDICATIONS

Although single-pulse TMS is considered to have no significant risk, a **short safety check list should be used to screen patients before they undergo TMS** investigations, including:

- implanted biomedical devices (*absolute c.i.*)
  (brain stimulation systems, epidural/subdural electrode arrays for cortical stimulation, cochlear implants, infusion pumps, pace-makers)
- history of seizures or syncope (*relative c.i.*)
- brain diseases or medications associated with increase seizure risk (*relative c.i.*)
- pregnancy (avoid magnetic nerve root stimulation over the lumbar spine) (*relative c.i.*)
- age ≤ 18 months (mechanical injuries due to excessive coil pressure) (*relative c.i.*)

Metal implants outside the head: because of the rapid attenuation of the induced electromagnetic field with increasing distance from the discharging coil, **there are no safety hazards** in adults carrying metal implants (e.g., prostheses, pumps for drug injection or any other hardware device) at any place in their body outside the head

TMS safety – screening questionnaire

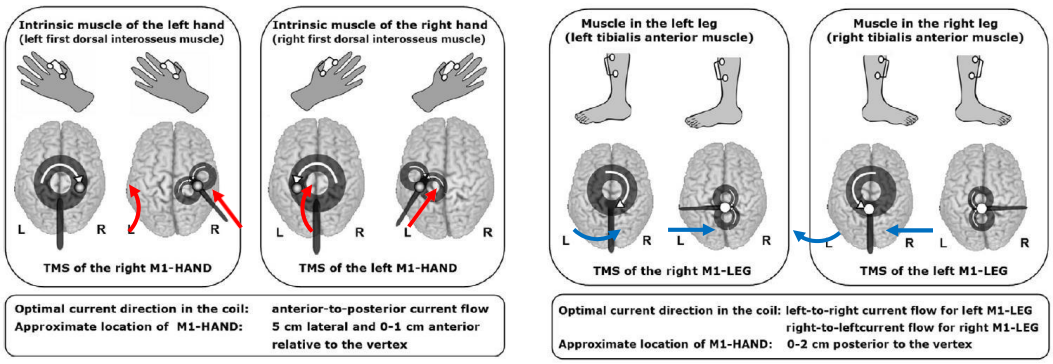
(1) Do you have epilepsy or have you ever had a convulsion or a seizure?
(2) Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
(3) Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
(4) Do you have any hearing problems or ringing in your ears?
(5) Do you have cochlear implants?
(6) Are you pregnant or is there any chance that you might be?
(7) Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.
(8) Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?
(9) Do you have a cardiac pacemaker or intracardiac lines?
(10) Do you have a medication infusion device?
(11) Are you taking any medications? (please list)
(12) Did you ever undergo TMS in the past? If so, were there any problems.
(13) Did you ever undergo MRI in the past? If so, were there any problems.

Rossi et al 2011

SINGLE-PULSE TMS
ADVERSE EVENTS

- Seizures (very low risk with single-pulse TMS)
- Vasodepressor syncope (reaction to anxiety and physical discomfort)
- Local mild discomfort under the stimulating coil
- Slight tongue paraesthesias (during high-intensity TMS delivered on the midline for activation of lower limb corticospinal neurons)

TECHNICAL PRINCIPLES OF TMS
COIL ORIENTATION



For the clinical use of TMS, the **direction of the induced tissue current** is important because the **M1 is best stimulated by currents** penetrating it when **flowing in the brain in a posterior-to-anterior direction**

STANDARDS FOR CLINICAL PRACTICE
RECORDING

Recording Parameters	
Band-pass filter	1-2000 Hz
Sampling frequency	4000-5000 Hz
Notch filter (50-60 Hz)	No
Impedance	< 5 KΩ
Screen amplificator factor	50-100 µv/div for CMT 1-2 mV/div for MEPs
Screen temporal resolution	5 ms/div for UL 10 ms/div for LL
Pre-stimulus EMG recording	50 ms
Post-stimulus recording	100 ms (400 ms for CMT)

- For proper characterization of MEP amplitudes and latency several MEPs should be recorded from homonymous (right and left) target muscles
- Bipolar surface recording electrodes (e.g., Ag/AgCl cup electrodes) are applied on the distal muscles of the hand and leg

STANDARDS FOR CLINICAL PRACTICE
STIMULATION

- **Each hemisphere has to be investigated separately** and only the MEPs elicited in the controlateral target muscle should be analyzed
- There is no universal agreement on the preferred **state of the muscle** for clinical studies, but a **slight tonic contraction** is commonly used to increase efficacy of TMS
  - if tonic muscle contraction is employed, it is recommended that both contra and ipsilateral muscles are simultaneously contracted
  - those patients who cannot perform a contraction due to hemiparesis should not be asked to unilaterally preactivate the healthy side as this would artificially induce an asymmetric MEP result

- The **clinical report** must state **whether the MEPs were recorded** with the muscle at rest or during contraction, since the latter affects only the MEP but not CMAP

- **Every laboratory should establish a standard instruction and a monitoring method** (e.g., acoustic or visual online feedback of EMG activity) to ensure a standardized procedure across patients

STANDARDS FOR CLINICAL PRACTICE
STIMULATION

- **STEP 1: Coil position**
  - Identify the scalp location where TMS elicits the largest single-trial MEP
  - When using the large round coil with limited focality, it is feasible touse a standard positioning procedure based on external landmarks
  - Once the coil position for TMS has been defined, the rim of the coil should be marked with a pen on the scalp to maintain a constant position
- **STEP 2: CMT definition**
  - Individual CMT should be estimated at rest and expressed in % of the MSO
- **STEP 3: Stimulation**
  - Single-pulse stimulation at suprathreshold intensity (**140% of resting CMT**)
  - 5-6 MEPs recorded from target muscle during isometric tonic contraction
  - If the MEP amplitude appears to be reduced, it is advisable to apply 5-6 stimuli at higher stimulus intensity (**170% of resting CMT**)

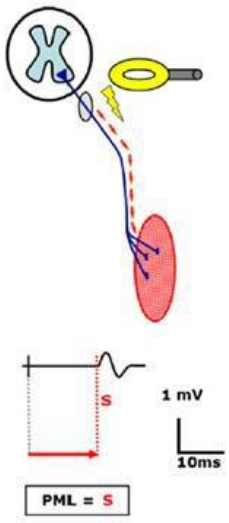
Optimal stimulation depends on **coil position** & **current direction** (different for right and left M1)

STANDARDS FOR CLINICAL PRACTICE
MEASUREMENT OF PERIPHERAL MOTOR CT

1) FORAMINAL ELECTROMAGNETIC STIMULATION

- The round coil is positioned over spinal roots: **C7/C8** and **L1/L2**
- The windings of the coil follows the orientation of target root
- The coil is placed flat on the skin and centered **over body midline** or **1-2 cm lateral to the spine** (to stimulate spinal nerve passing foramen)
- Foraminal magnetic stimulation should use a **low stimulus intensity** which is just suprathreshold

  (*rule*: the amplitude of the foraminally *induced CMAP* should have a single-trial peak-to-peak amplitude *< 1 mV*. If higher intensities of stimulation are used, the point of nerve stimulation will move distally, inducing an error in the estimation of PMCT)
- The CMAP evoked by foraminal magnetic stimulation is used to calculate the peripheral motor latency (PML) which corresponds to the peripheral conduction time from the neuroforamen to the muscle

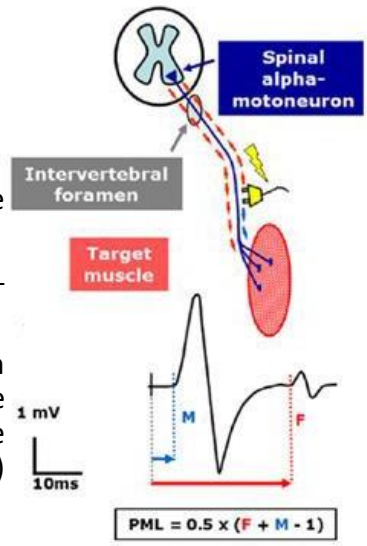


- This implies that the conduction time along the very proximal section within the spinal canal is assigned to the CMCT. The resulting error in CMCT estimation depends on the length of the nerve section in the spinal canal and amounts to **0.5-1.4 ms** for cervical and **3.0-4.1** ms for lumbar spine
- This method can falsely increase CMCT in patients with nerve root lesions

STANDARDS FOR CLINICAL PRACTICE
MEASUREMENT OF PERIPHERAL MOTOR CT

2) F-WAVES METHOD

- F-waves are elicited by supramaximal peripheral nerve stimulation with the cathode pointing proximally
- 10-20 consecutive F-waves need to be recorded and the F-wave with the shortest latency is used for calculation of PMCT
- This method gives a better approximation of the CMCT than intraforaminal magnetic stimulation, because the F-wave probes peripheral motor conduction along the entire peripheral motor axon, including the intraspinal (proximal) nerve segment



- This method can only be used to estimate PML in distal but not proximal muscles
- It only gives information on a relatively small sample of α-MN and related motor axons

STANDARDS FOR CLINICAL PRACTICE
SUPRAMAXIMAL DISTAL NERVE STIMULATION

- An electrical square stimulus is given to the distal peripheral nerve supplying the target muscle via bipolar surface electrodes with the cathode pointing distally
- The maximal CMAP is recorded by gradually increasing stimulus intensity until the CMAP amplitude shows no further increase
- The peal-to-peak amplitude of the maximal peripheral CMAP is measured to be able to calculate the **MEP/CMAP ratio**

STANDARDS FOR CLINICAL PRACTICE
ANALYSIS OF NEUROPHYSIOLOGICAL RECORDINGS

For clinical examination, every department using TMS should have a table of normative values for:

- **MEP/CMAP ratio**
- **CMCT**
- **Resting CMT**
- CSP (if needed)

in both absolute values and right-to-left differences

Normative values should be available for each muscle tested and should be divided for sex, height, decades of age

Abnormal value $\geq$ 2.5 (conservatively 3 SD) *vs* control mean

UPPER LIMB CORTICOMOTOR CONDUCTION

Normative data for the upper limb examination.

Target muscle	Method	CML	PML	CMCT	References
First dorsal interossus	Cervical MS	20.6–21.2 ± 1.8*	14.0–14.9 ± 1.4*	5.8–6.5 ± 1.1*	Kloten et al. (1992)
	Cervical MS	No data	13.2 ± 1.5	No data	Britton et al. (1990)
	F-wave method	No data	14.5 ± 1.4	No data	Britton et al. (1990)
Abductor digiti minimi	Cervical MS	18.8 ± 1.2 (f)	11.8 ± 1.0	7.0 ± 0.8	Chu (1989)
	Cervical MS	19.7 ± 1.0 (m)	12.7 ± 1.1	7.1 ± 1.1	Chu (1989))
	Cervical MS		14.0 ± 1.5	6.0 ± 0.9	Claus (1990)
	Cervical MS	20.5 ± 1.2		7.0 ± 0.9	Furby et al. (1992) (21–54 years)
	F-wave method			6.1 ± 1.0	Furby et al. (1992) (21–54 years)
	F-wave method			7.2 ± 1.2	Cicinelli et al. (1997a)
	F-wave method			5.8 ± 0.8	Claus (1990)
Abductor pollicis brevis	Cervical MS	21.8 ± 1.8	14.4 ± 1.4	7.2 ± 1.8	Tabaraud et al. (1989)
	Cervical MS	21.4 ± 1.5	14.8 ± 1.2	6.6 ± 1.4	Ludolph et al. (1989)
	Cervical MS	20.2 ± 1.6		7.9 ± 2.1	Eisen and Shtybel (1990)
	F-wave method			5.66 + 0.84	Rossini et al. (1992) (16–35 years)
	F-wave method			5.45 + 0.72	Rossini et al. (1992) (51–86 years)
Biceps brachii	Cervical MS	10.8–11.4 ± 1.3*	6.3–6.8 ± 1.1*	4.5–4.6 ± 1.0*	Kloten et al. (1992)
	Cervical MS	12.5 ± 1.2		7.1 ± 1.1	Furby et al. (1992) (21–54 years)
	Cervical MS	9.4 ± 1.7		6.0 ± 1.2	Eisen and Shtybel (1990)

Cervical MS – cervical foraminal magnetic stimulation; CML – Corticomotor latency; PML – Peripheral motor latency; CMCT – Central motor conduction time.
* Increase with age (age range: 19–60 years; (f) females; (m) males).

LOWER LIMB CORTICOMOTOR CONDUCTION

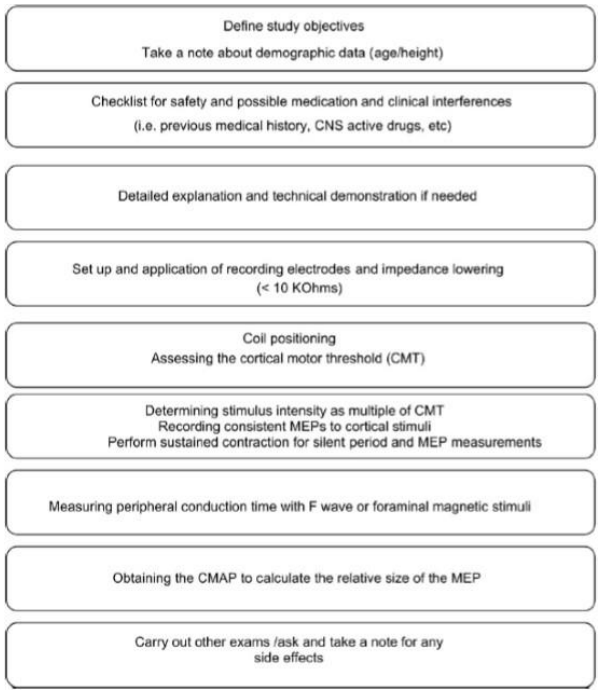
Normative data for the lower limb examination. Overview of published normative data on central motor conduction time (CMCT) for the lower limbs using M. tibialis anterior as target muscle. In all studies a standard circular coil and a monophasic pulse configuration was used for TMS of the M1-LEG. Data is given as mean ± SD: standard deviation.

Reference	Group description number (age range)	Central motor conduction time (lower limb)		
		Mean ± SD (ms)	Upper normal limit (ms)	Side-to-side difference (ms)
F-wave method				
Claus et al. (1991)	n = 45 (18–71 years)	9.7 ± 2.7	16.5	4.5
Furby et al. (1992)	n = 50 (21–54 years)	9.9 ± 1.8		1
Rossini et al. (1992)	n = 25 (16–35 years)	12.7 + 1.20		1
	n = 40 (51–86 years)	12.9 + 1.69		2
Lumbar (foraminal) electromagnetic stimulation				
Chu (1989)	n = 52 (17–35 years)	14.8 ± 1.1	17.6	No data
Kloten et al. (1992)	n = 18 (19–29 years)	13.4 ± 1.9	18.2	1.6
	n = 21 (30–59 years)	16.1 ± 1.9	18.5	2.2
	n = 18 (>60 years)	13.4 ± 1.9	20.9	2.0
Furby et al. (1992)	n = 50 (21–54 years)	13.8 ± 1.5		0.9
Electrical high-voltage stimulation				
Claus (1990)	n = 54 (19–59 years)	12.5 ± 1.7	16.7	3.6

CORTICAL SILENT PERIOD

- Time **from MEP onset to the resumption of sustained EMG**
- Measured **during tonic voluntary activation of the target muscle**
- Large number of trials (**20-30 trials**) **estimating CSP duration**
- Usually measured at a single intensity level, with insufficient information on the stimulus intensity / CSP duration relationship.
- Given these limitations, 2 strategies can be adopted to estimate the CSP duration using all CSP recordings: 5–6 trials per muscle:
  - Method I: mean CSP duration (or median) based on trial-by-trial measurements. The end of CSP is established when the EMG activity reaches or exceeds the pre-TMS baseline level for at least 50 ms. The reoccurring EMG activity marks the end of CSP.
  - Method II: rectify and average the collected 5–6 MEP/CSP traces. The end of the CSP defined as reoccurrence of voluntary EMG relative to baseline.
- Automatic algorithms based on pre-stimulus EMG *(Daskalakis et al, 2003; Garvey et al, 2001; King et al, 2006)* can be integrated in clinical practice and might help increasing CSP estimation reliability, on single trials or rectified/averaged multiple traces

Steps for diagnostic TMS



Groppa 2012