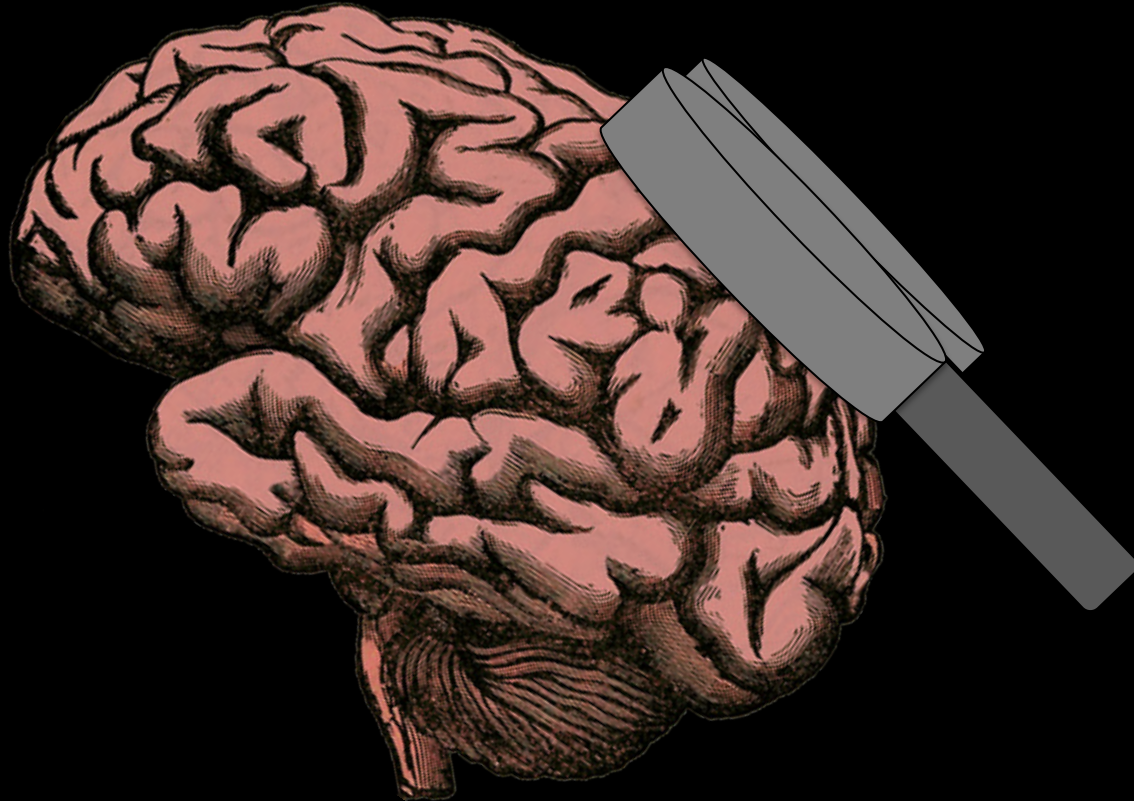


Transcranial Magnetic Stimulation: basic & advanced methodology (2 day)

Dr. Olga Lucía Gamboa Arana

Hong Kong, 30-11-2018

- 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



**"There are no new ideas.
There are only new ways
of making them felt"**

Audre Lorde

Session 4: “ TMS Methods”

Dr. Olga Lucía Gamboa Arana

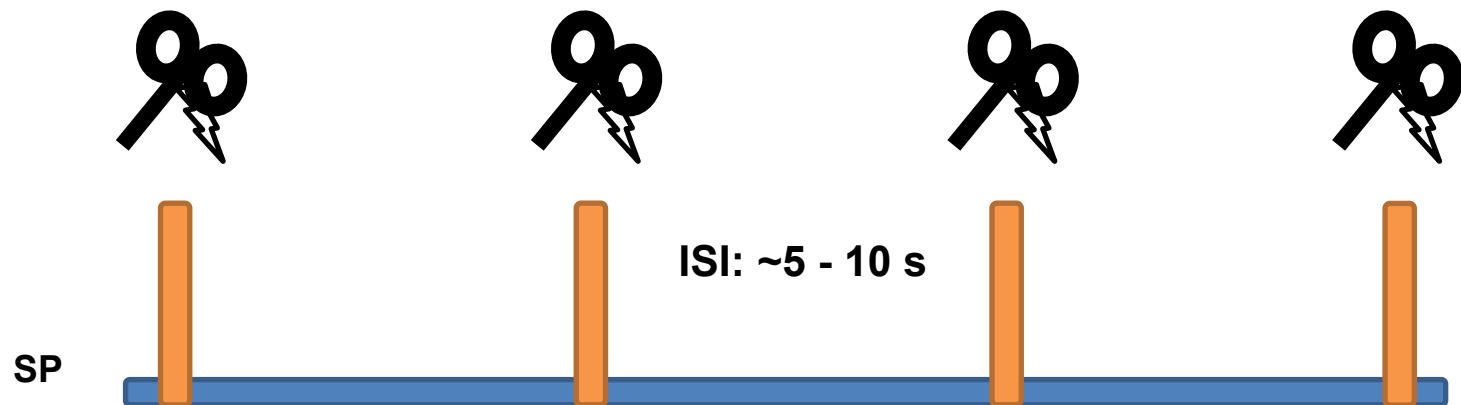
Hong Kong, 29-11-2018

Session 4 – Lecture “ TMS Methods”

- Single pulse protocols
- Paired pulse protocols
- rTMS protocols
- Sham and control conditions
- TMS –EEG
- TMS – MRI
- Summary: How to do a TMS experiment

Single pulse protocols

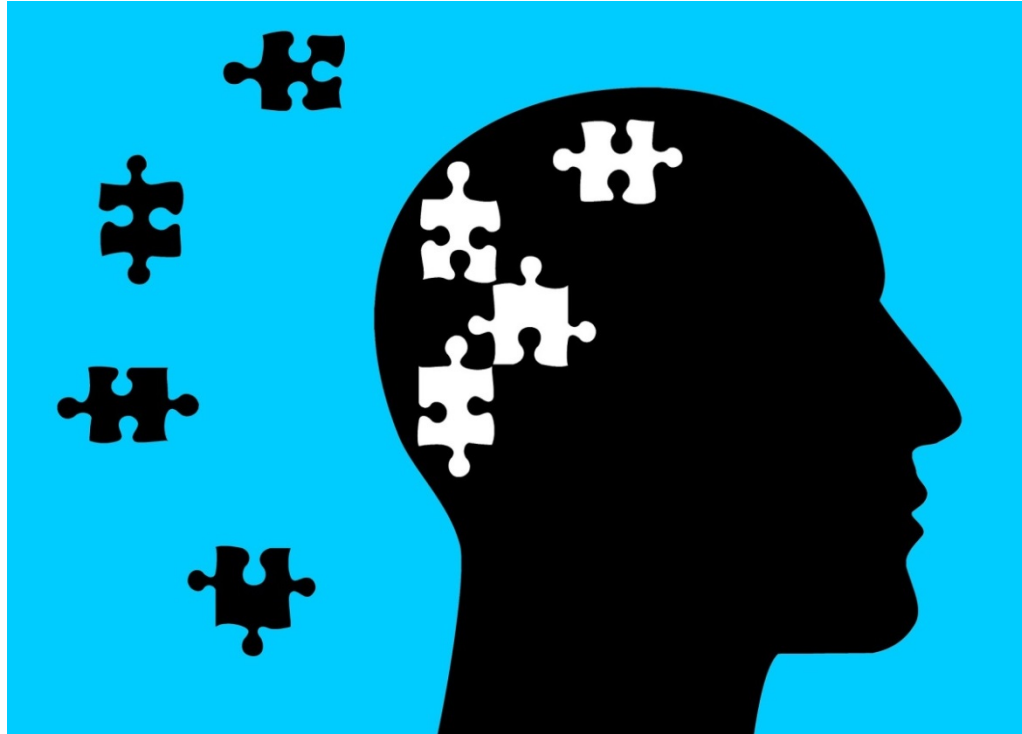
Single-pulse TMS protocols are paradigms using isolated pulses to study a particular cortical region. They are mainly used for evaluation of brain dynamics and diagnostic purposes.



Single Pulse protocols

OL Gamboa

Uses in research:



SP TMS and brain states: TMS can be used to interrupt the neural mechanisms of specific brain regions to help identify their roles in function and behavior.

Example: Evaluate the role of BA9 in memory.

Single Pulse protocols

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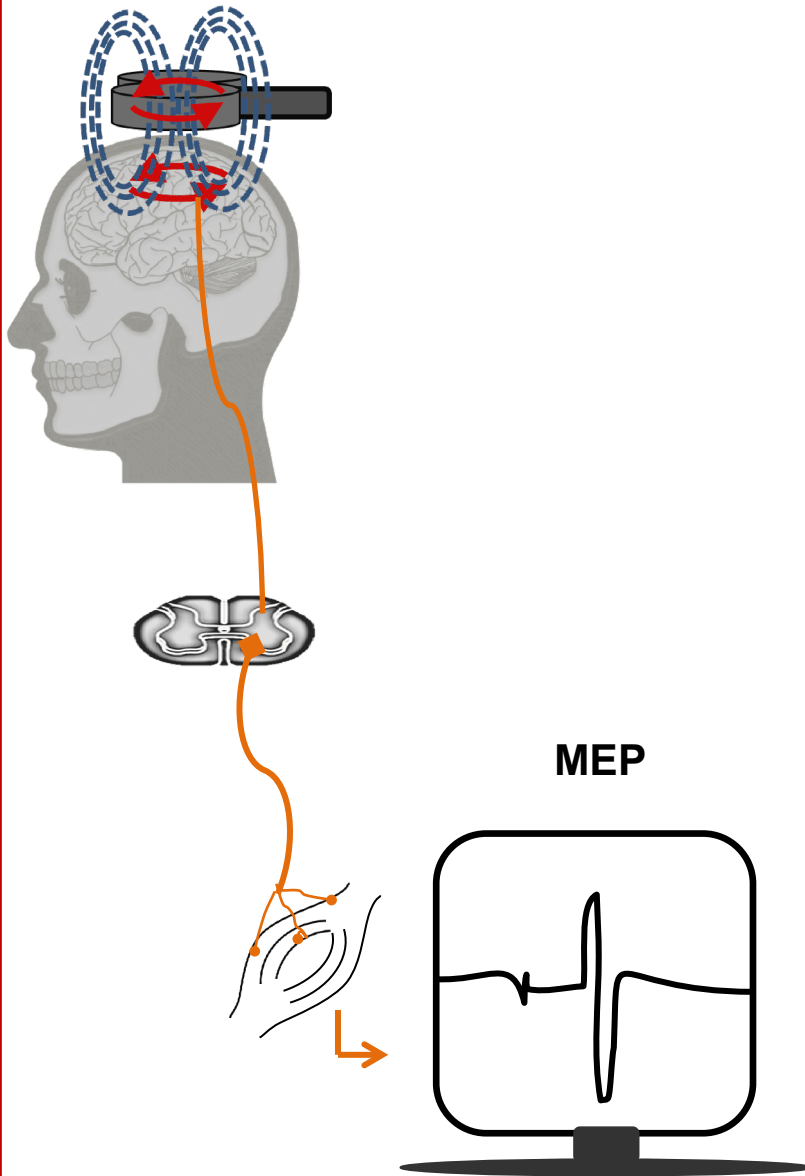
Uses in research:



Single pulse TMS and external interventions: TMS helps to assess the effect of an intervention in brain function.

Example: evaluation of cortical excitability using TMS to compare different stages of sleep and sleep deprivation

Let's remember ...

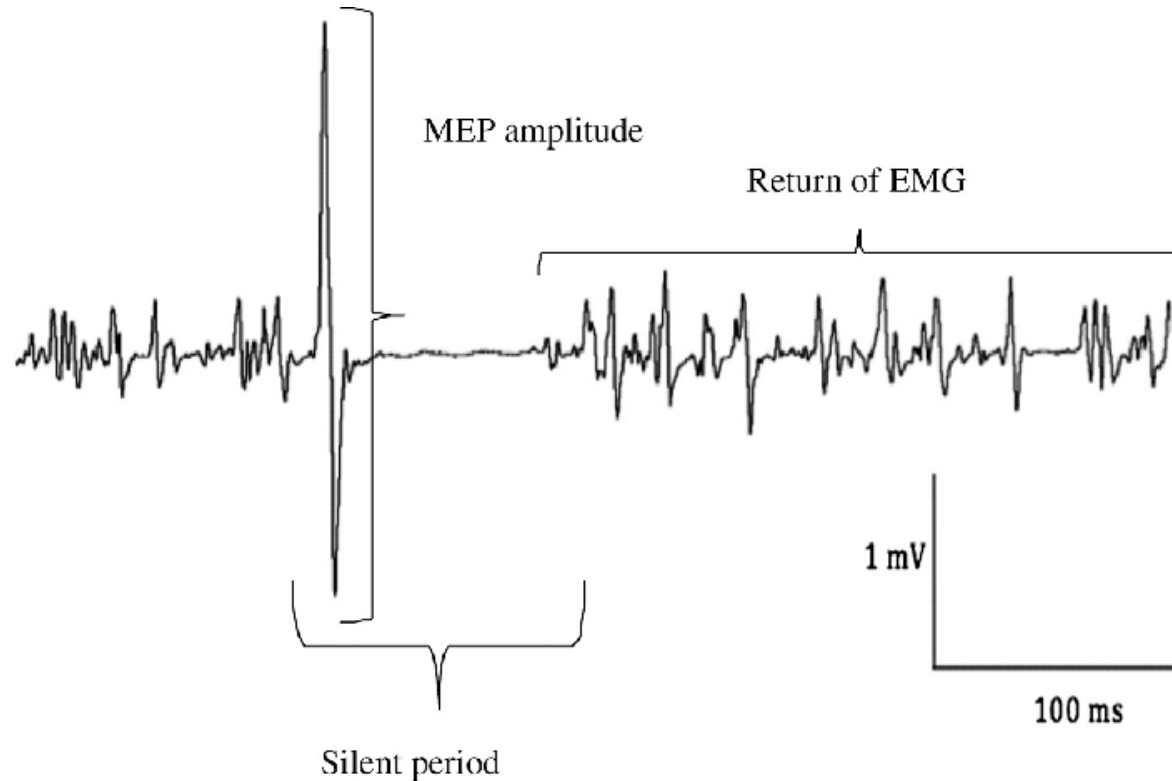


Motor Evoked Potential (MEP)

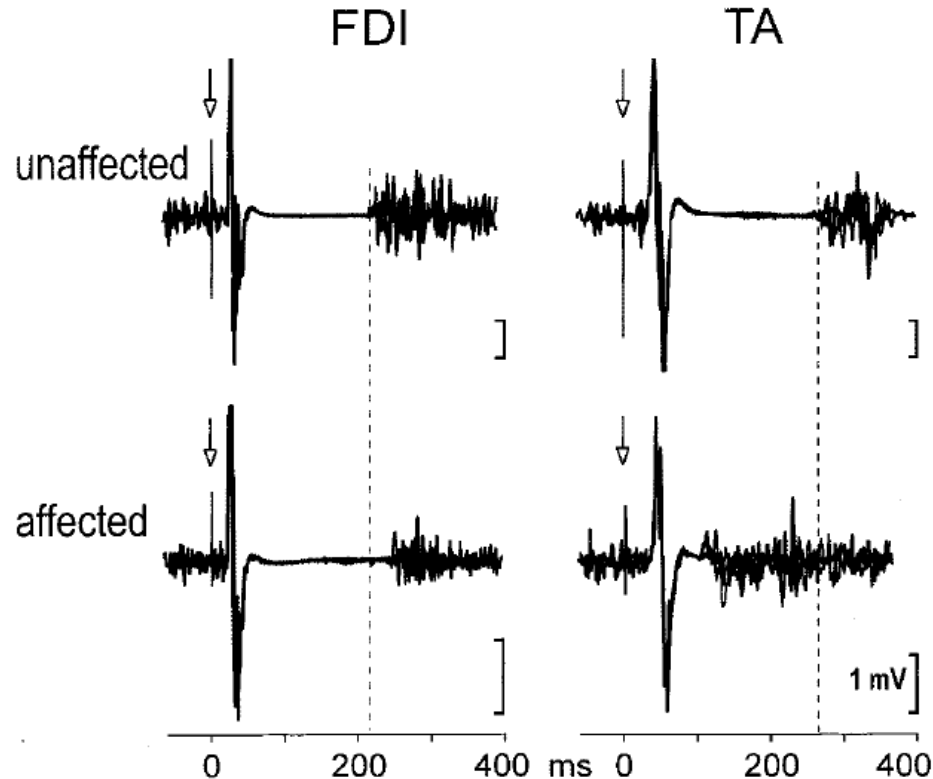
- MEPs are the muscle responses induced after activation of central motor pathways.
- Recording of MEPs induced by TMS can be achieved using surface electromyography.

Motor 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.



CSP is a temporary interruption of voluntary muscle contraction induced by TMS on of the contralateral motor cortex. The duration of cSP is used as a measure of inhibition in the stimulated cortical circuits.

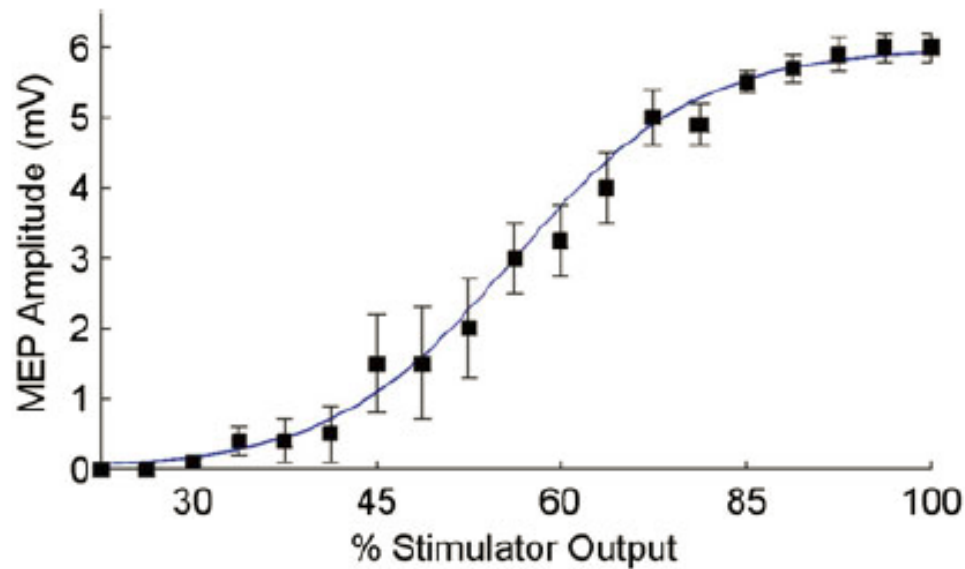


Surface EMG from one representative patient shows muscle activity from 50 ms before to 400 ms following the magnetic stimulus (open arrows). The dotted line indicates the end of the silent period (SP) in the unaffected limb. A marked shortening of the SP is seen in the affected TA of this patient. Vertical scaling bars indicate 1 mV.

Neurological measurements in various neurological disorders

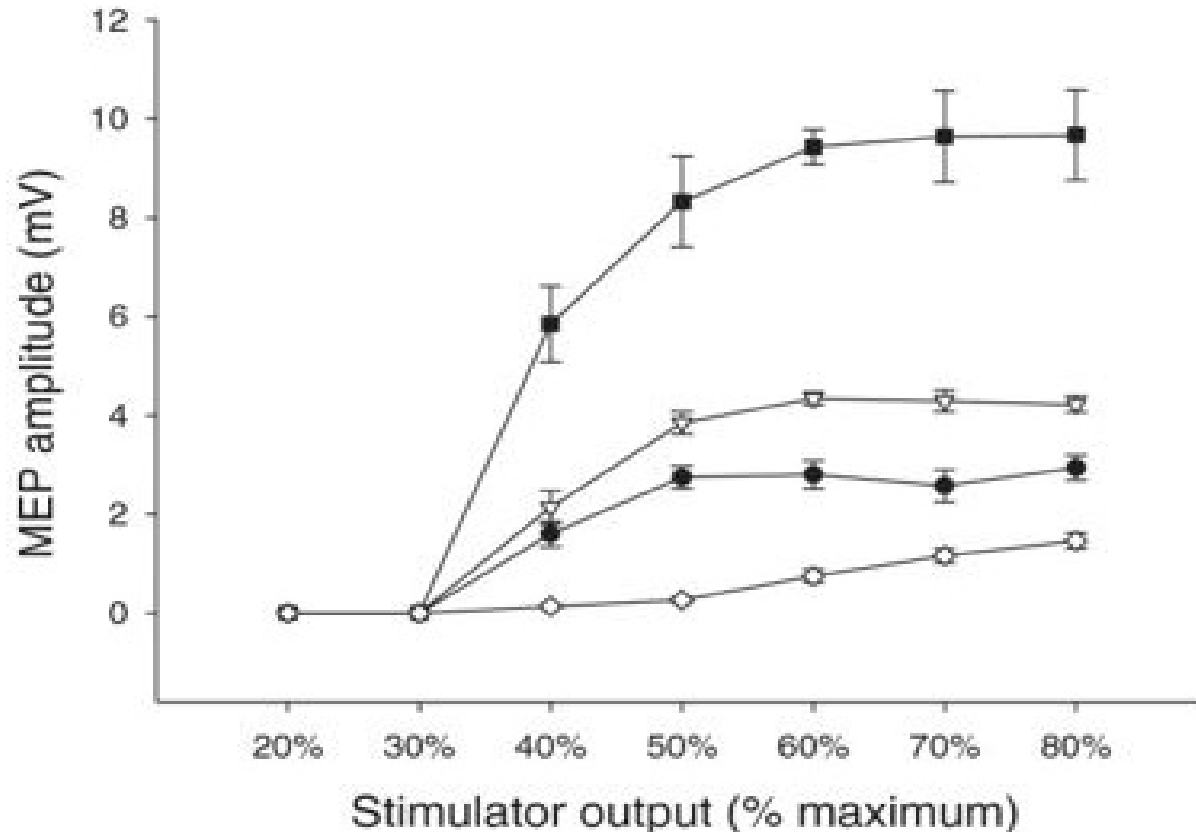
Neurological disorder	MEP amplitude	MT	CSP
Multiple sclerosis	Reduced	Increased	Prolonged
Stroke	Reduced	Increased or reduced	Shortened or prolonged*
Cervical myelopathy	Reduced	Increased	Shortened
Amyotrophic lateral sclerosis	Reduced	Increased (late) reduced (early)	Normal or shortened
Parkinson's disease	Facilitated (r)	Normal	Shortened
Dystonia	Normal (r) facilitated (a)	Normal	Shortened
Cerebellar ataxias	Normal or reduced	Increased	Prolonged
Epilepsies	Normal or reduced	Normal, reduced or increased	Normal, shortened or prolonged

Input/Output curves (IO curves)



These are response curves acquired by measuring MEP amplitudes at different intensities of the stimulator output. MEPs' size are then fitted to a sigmoid curve to the data

- Can be obtained with the muscle at rest or active.
- I/O TMS curve seems to be modulated by cortical mechanisms associated to both the GABAergic and the glutamatergic systems

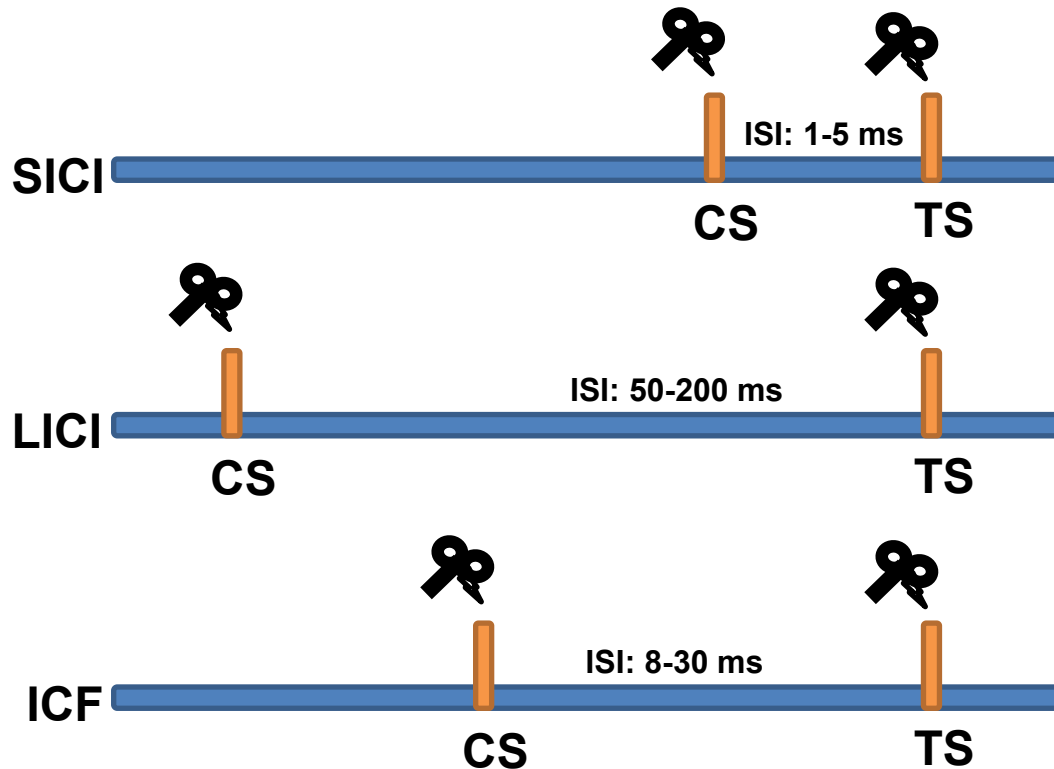


Sample stimulus–response curves. Stimulus–response curves at 50% maximal voluntary force for one subject for *vastus lateralis* (●), *rectus femoris* (▽), *vastus medialis* (■) and *biceps femoris* (◇). All values are presented as means \pm standard deviation .

Paired pulse protocols

Paired Pulse protocol

It is a powerful TMS technique to examine different intracortical inhibitory and excitatory circuits.



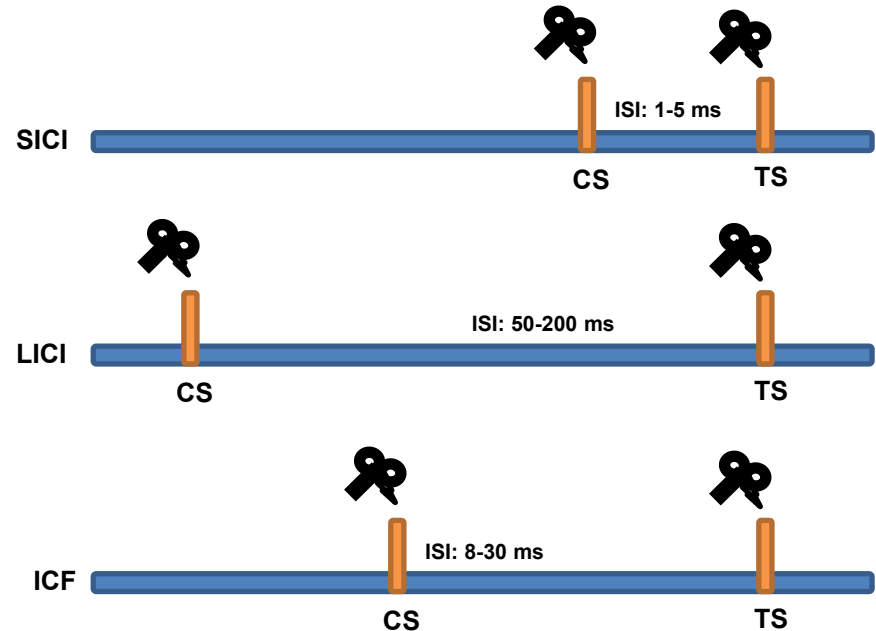
CS: Conditioning stimulus
TS: Test stimulus
ISI: Interstimulus interval

Here, a conditioning stimulus (CS) is followed by a test stimulus (TS). The effects induced will depend on the Intensity and interstimulus interval (ISI) between the two stimuli.

Paired Pulse protocol

Things to consider when using paired pulse paradigms:

- Stimulation site
- Intensities for conditioning and test pulse
- Interval between pulses



CS: Conditioning stimulus
TS: Test stimulus
ISI: Interstimulus interval

Paired Pulse protocol

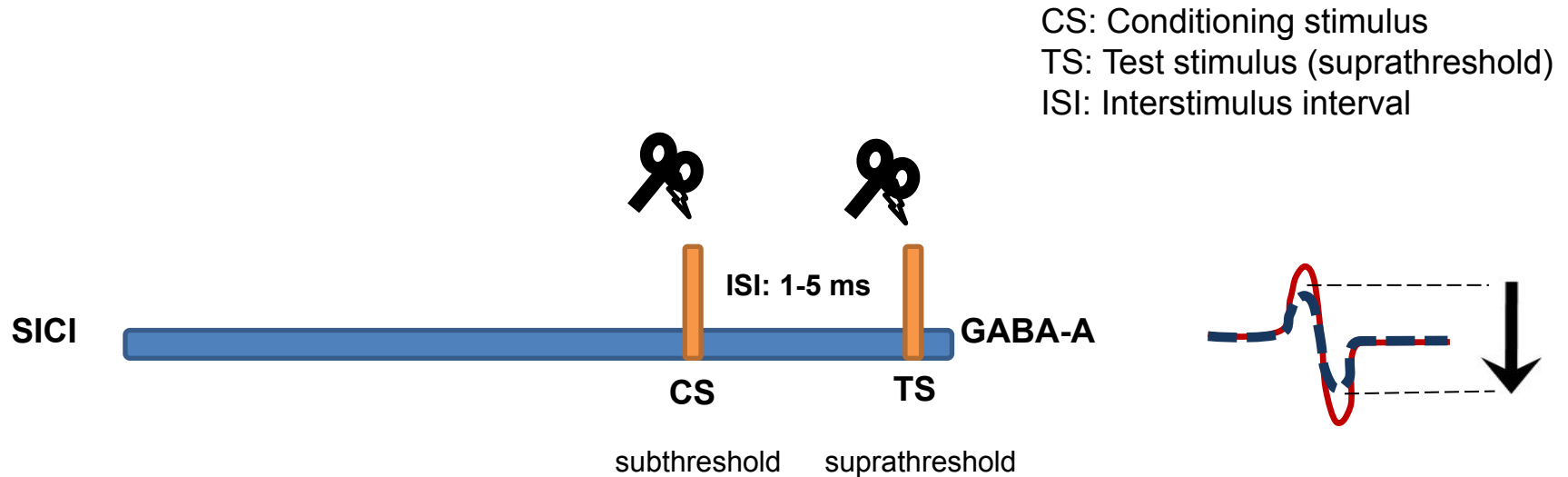
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	Circuit	ISI (ms)	CS	TS
Inhibitory	SICI	1–6	50–90 % RMT <100 % AMT	TS 1 mV >100 % RMT 120 % RMT
	LICI	50–200+	TS 1 mV 100–130 % RMT	TS 1 mV 120 % RMT
Excitatory	ICF	8–30	90+ % RMT >80 % AMT	TS 0.5–1.5 mV
	SICF	1.0–1.5 2.3–3.0 4.1–5.0	>RMT TS 1 mV 100–130 % RMT	<RMT 90 % RMT

Things to consider when using paired pulse paradigms:

- Stimulation site
- Intensities for conditioning and test pulse
- Interval between pulses

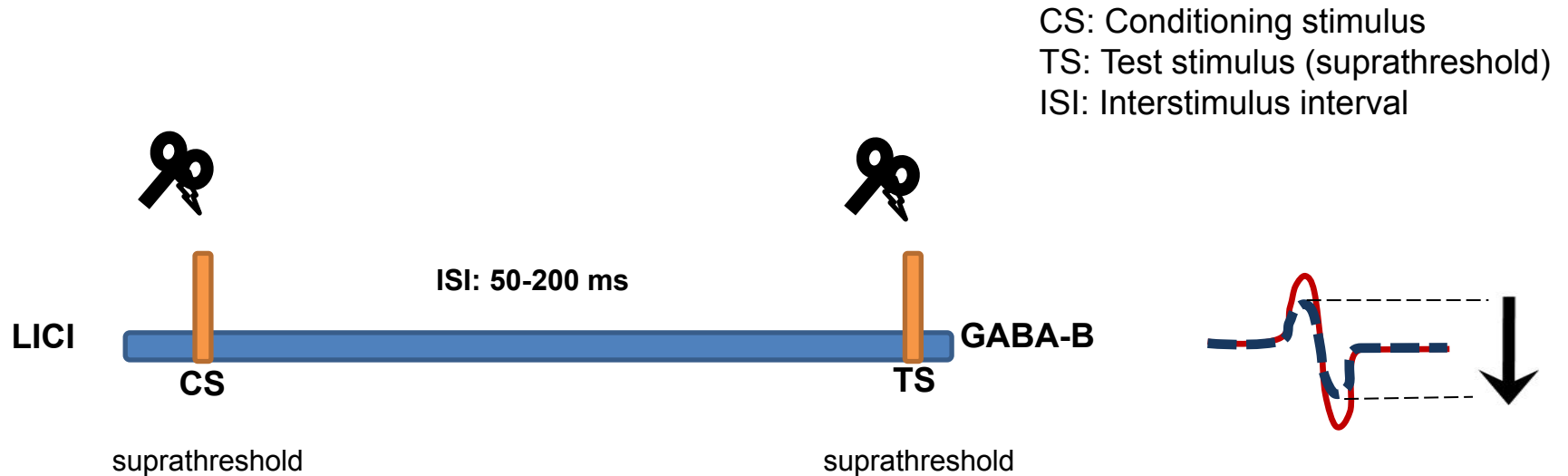
Short Interval Intracortical Inhibition



- In SICI a suprathreshold TS will be inhibited by a subthreshold CS at ISIs of 1-5 ms.
- Pharmacological studies support the view that SICI reflects GABAAR mediated inhibition.

SICI is reduced in patients with Parkinson's disease, dystonia, Huntington's disease, Alzheimer's disease, and schizophrenia among others.

Long Interval Intracortical Inhibition



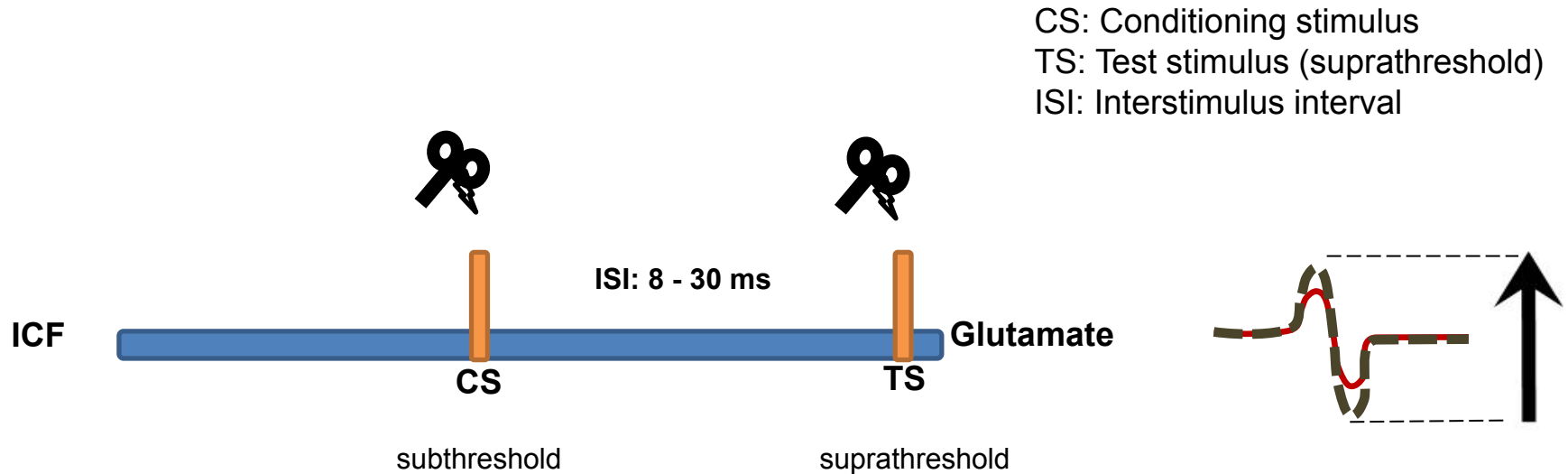
- In LICI inhibition is achieved by delivering both Conditioning and test suprathreshold stimuli at ISIs of 50-200 ms.
- Pharmacological studies support the view that LICI reflects GABABR mediated inhibition.

Paired Pulse protocols: LICI

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Patients with Parkinson's disease and cerebellar degeneration have shown enhanced LICI.

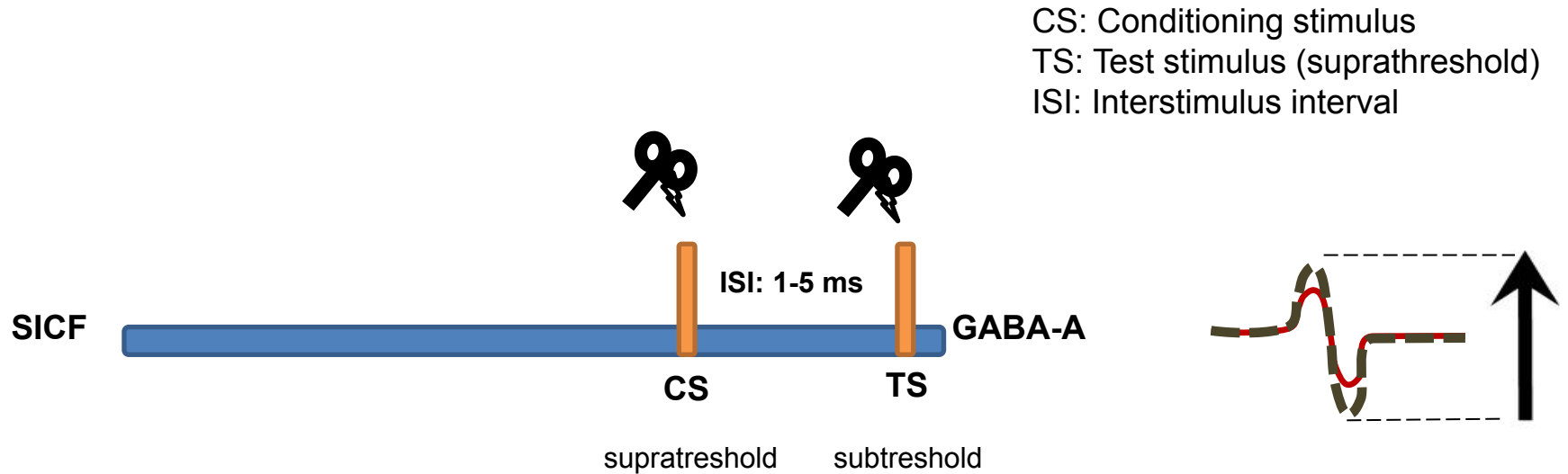
Intracortical Facilitation



- In IFC a suprathreshold TS will be facilitated by a subthreshold CS at ISIs of 8-30 ms.
- Pharmacological studies support the view that facilitation in ICF is mediated by glutamatergic NMDA receptors.

Increased ICF has been observed in patients with Huntington's disease and amyotrophic lateral sclerosis.

Short Interval Intracortical Facilitation



- In SICF facilitation occurs delivering a suprathreshold CS followed by a subthreshold TS (or both near to threshold intensity) at ISIs of 1-5 ms.
- Although is believed to have an intracortical origin. The utility of SICF is not clear.

Note:

- The inhibitory and excitatory effects of each PP protocol are believed to be a function of the conditioning stimulus intensity and the inter-stimulus interval.
- The test stimulus intensity is typically used suprathreshold. The reasons behind this are unknown.

Note:

- Having SICI and LICI associated to different pharmacological profiles makes possible to noninvasively assess different GABAergic inhibitory circuits in human brain.
- It has been reported that SICI is reduced in the presence of LICI, most likely through presynaptic GABAB receptors mediated inhibition of those inhibitory interneuron involved in SICI.

Repetitive TMS protocols

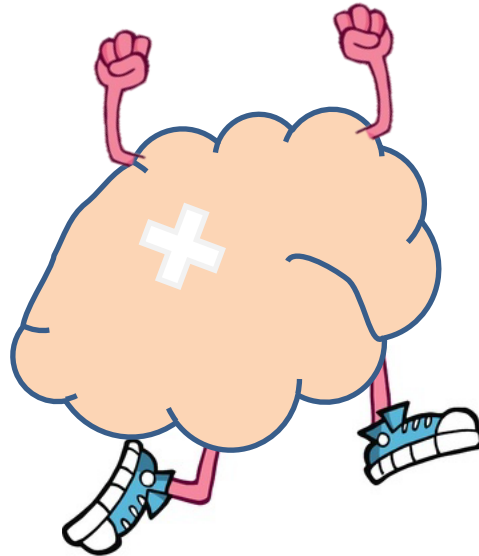
Terminology

TMS methods: terminology

Brain plasticity:

Is the capacity of the brain to change and adapt to new environmental demands.

It refers to processes of learning, memory formation and neural repair.



TMS methods: terminology

Synaptic plasticity:

Is an essential mechanism for correct learning and memory formation



Here, reorganization and adaptation in response to new information occurs via changes in synaptic strength among previously established synaptic patterns. Two of these mechanisms which commonly affect the efficacy of a synapse are Long Term Potentiation (LTP) and Long Term Depression (LTD).

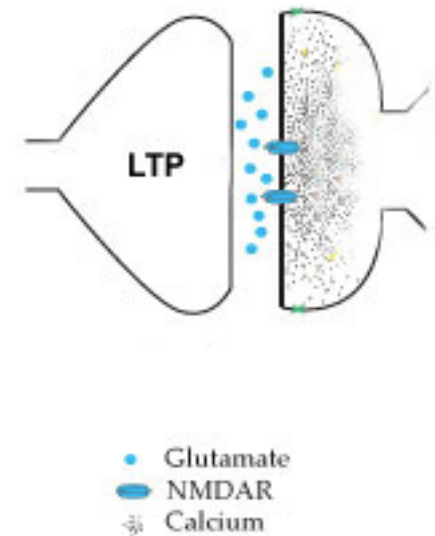
TMS methods: terminology

- It is believed that plasticity is usually dependent on glutamatergic synapses.
- The efficacy of a synapse can be modified by:
 - ❖ Increasing or decreasing the amount of neurotransmitter pre-synaptically released across the synapse or by increasing.
 - ❖ Decreasing the amount of AMPA receptors present post-synaptically (the synapse become more sensitive).
 - ❖ Changes taking place at one synapse affects the entire network of neurons to which that synapse is connected.

TMS methods: terminology

Long Term Potentiation (LTP):

Defined as an increase in synaptic strength, occurs when stimulating first the presynaptic neuron and then the postsynaptic neuron (pre-post) within an interval of tens of milliseconds.



Long Term Depression (LTD):

Reflects a decrease in synaptic strength. LTD is induced when stimulation is done in the reverse order first postsynaptic and then presynaptic (post-pre).



In practical TMS terms:

- An average increase in MEP amplitudes is interpreted as LTP- like plasticity and a decrease in MEP amplitudes as the induction of LTD-like plasticity.
- LTP is induced by short stimulation trains delivered at high frequencies.
- LTD is induced by low-frequency stimulations delivered for long periods of time.

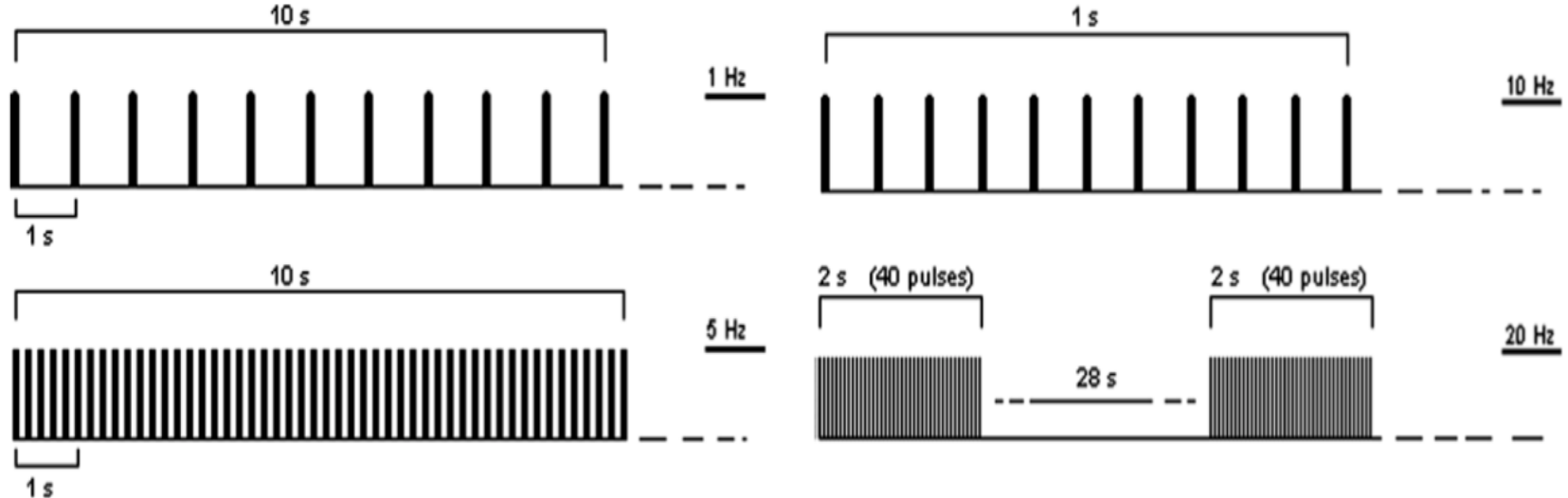
Let's remember ...

Repetitive TMS (rTMS): multiple TMS pulses delivered in trains

- Conventional: regularly repeated single TMS pulses
 - low frequency (≤ 1 Hz)
 - high-frequency (>1 Hz)
- Patterned: refers to repetitive application of short high frequency rTMS bursts interleaved by short pauses of no stimulation

Repetitive TMS (rTMS) protocols

OL Gamboa



Repetitive TMS has shown to induce changes in brain excitability that outlast the stimulation period.

These long term effects can be either inhibitory or excitatory and may last several minutes (1 session) or days/weeks (consecutive sessions)

The long duration of the after-effects makes rTMS an interesting method for the potential treatment of neurological and psychiatric disorders.

The after-effects are thought to be associated with changes in the strength of the synaptic connections between cortical neurons resembling long-term potentiation (LTP) and long-term depression (LTD) mechanisms.

rTMS after effects depend on:

- Frequency of stimulation: interpulse interval
- Structure of the train:
 - ❖ Number of pulses in one train
 - ❖ Number of trains
 - ❖ Length of intertrain interval.
 - ❖ Stimulation duration

Note:

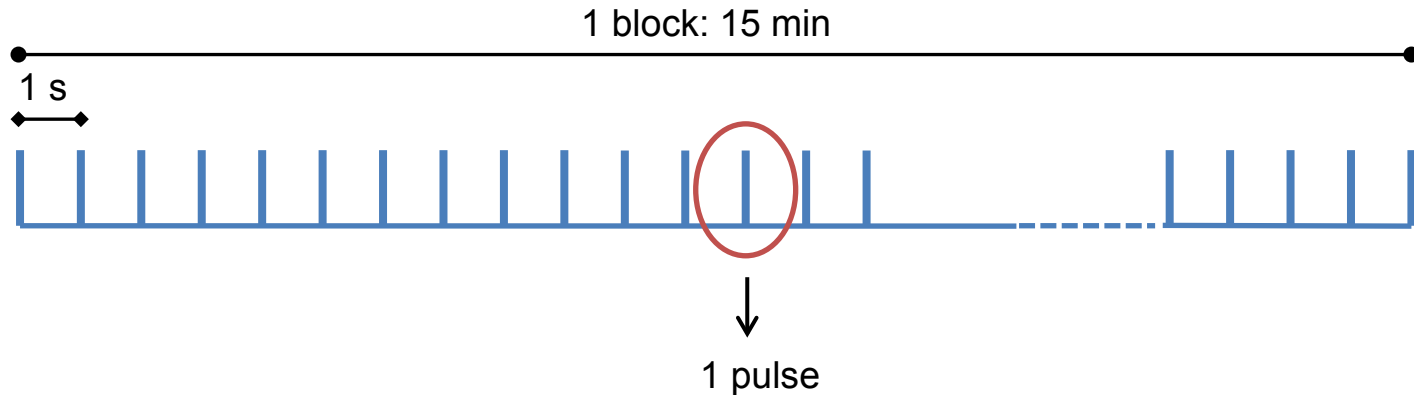
The effects seem to last according to stimulation length: Larger stimulation protocols seem to induce longer after-effects

In general:

- Low frequency stimulation is applied continuously
- High frequency protocols (5–25 Hz) are applied in a block fashion – stimulation delivered during 1- 2 s, with relatively long non- stimulation inter-train intervals in between lasting from 20–30 s

Low frequency rTMS: < 1 Hz (0.2 -1 Hz)

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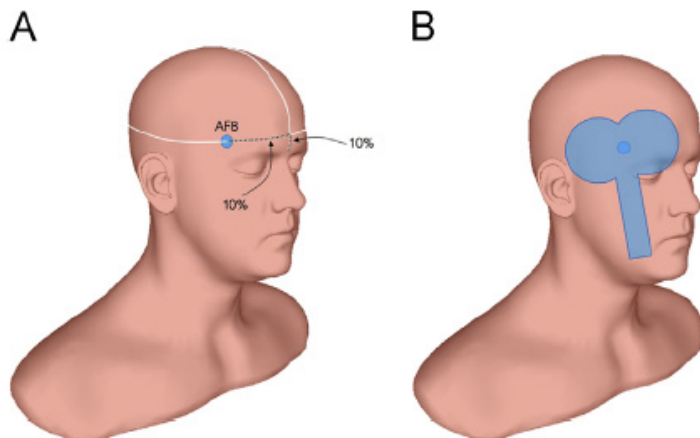


Low frequency rTMS protocols < 1 Hz

- Are typically inhibitory.
- At subthreshold do not show effects.
- Variability of response to 1 Hz is related to muscle excitability.
- 1Hz suppresses only when muscle is at rest.

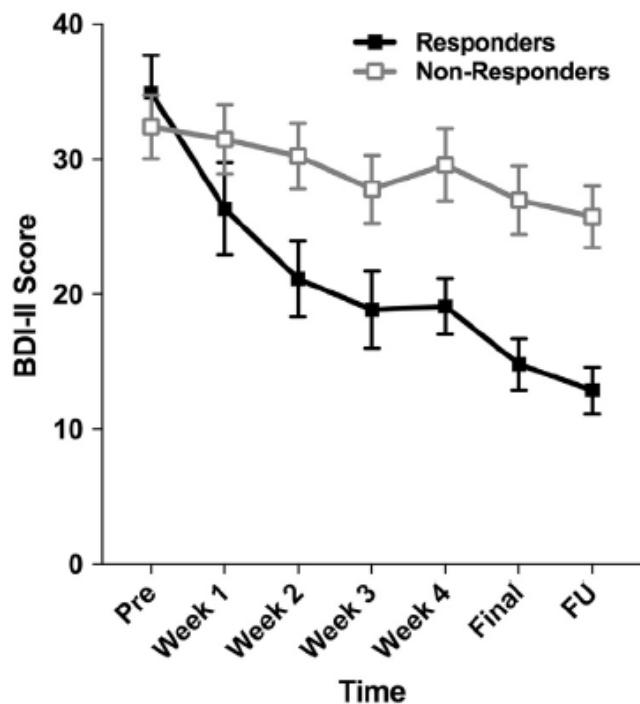
Low frequency rTMS: 1 Hz and depression

OL Gamboa



Protocol:

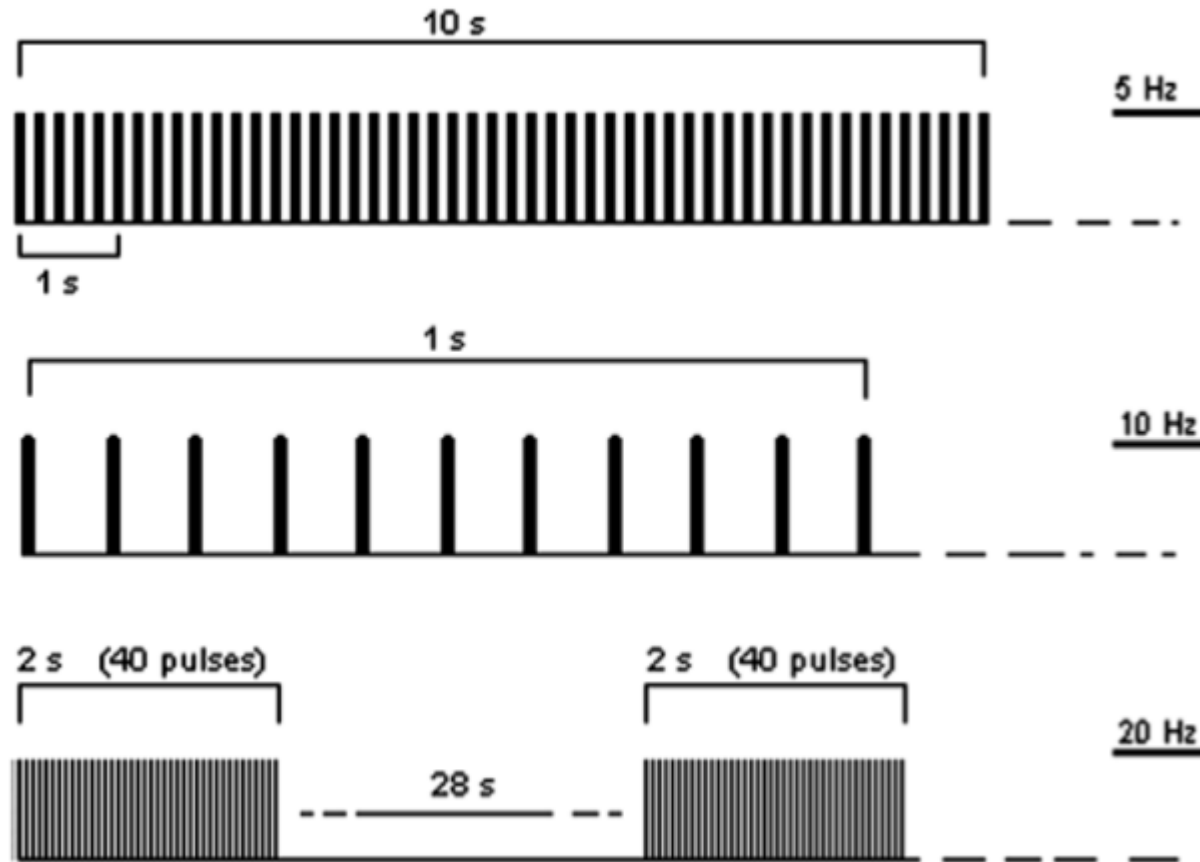
6 trains of 60 pulses at 1 Hz with 30 s inter-train interval for a total of 360 pulses in 8 min and 30 s, applied over OFC (AF8 EEG site). 120% RMT



Finding: 1 Hz right OFC-rTMS can be performed safely and tolerably in patients with major depressive disorder. Achieving around 25% remission rates even among patients who have previously failed to respond to DMPFC-rTMS.

High frequency rTMS > 5Hz (5-25 Hz)

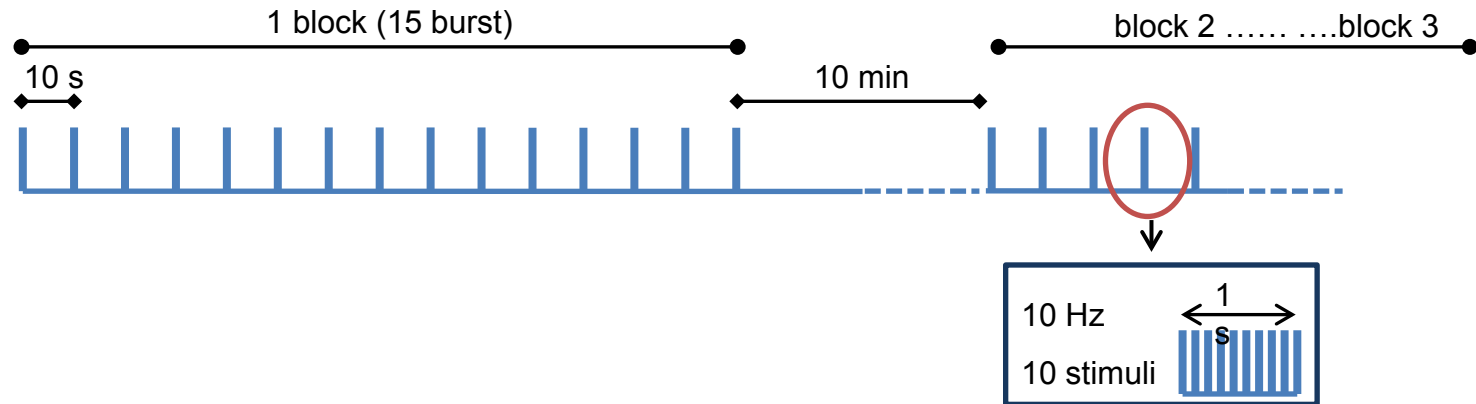
OL Gamboa



high-frequency rTMS protocols (5-25 Hz) are believed to increase cortical excitability

High frequency rTMS > 5Hz (5-25 Hz)

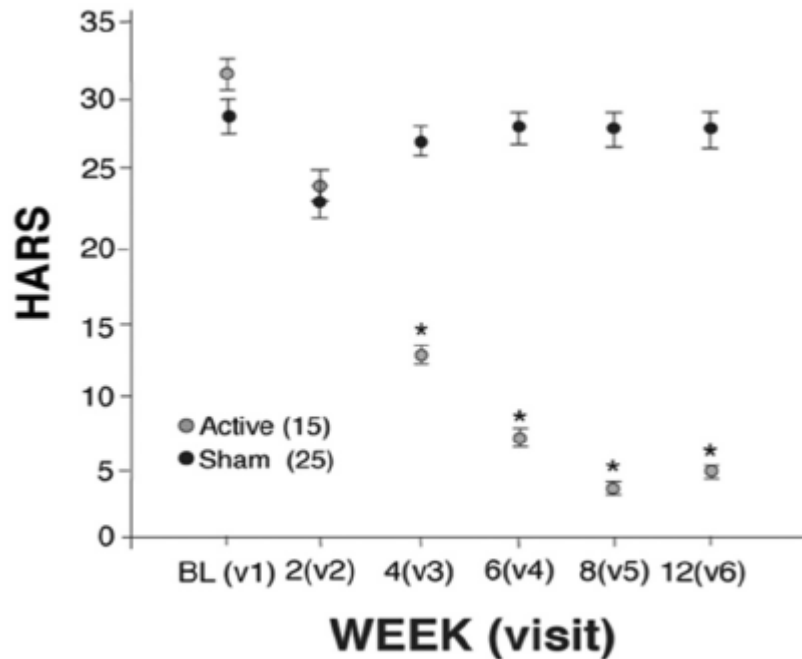
TMS protocol: 10 hz rTMS



- Duration of after-effects have been reported to last up to 90'.
- They depend on pulse number, stimulation intensity and stimulation duration.
- Effects can be reversed due to stimulation intensity.
- Stimulation intensities lower than subthreshold level decreases cortical excitability
- Stimulation intensities higher than subthreshold level increases cortical excitability

High frequency rTMS: 20 Hz and anxiety

OL Gamboa



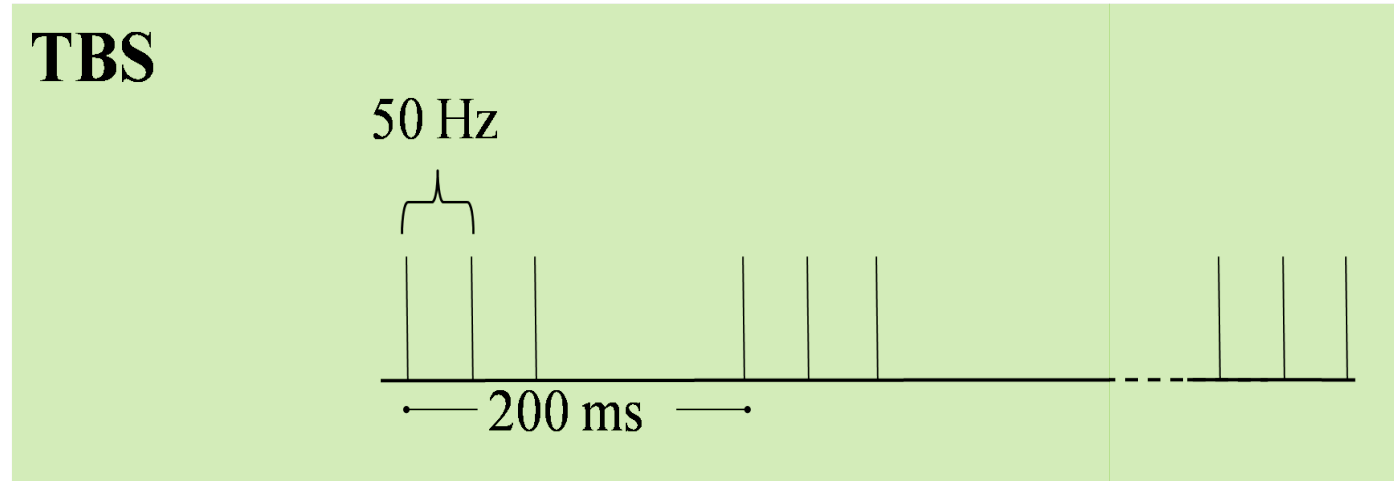
HARS: Hamilton Anxiety Rating Scale

Protocol:

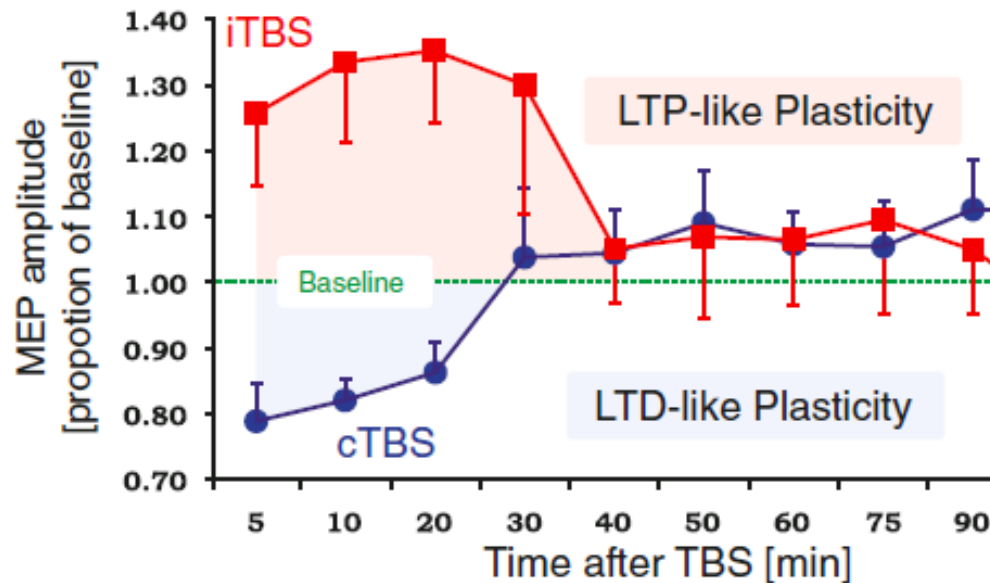
20 trains of 180 pulses at 20 Hz with 51 s inter-train interval for a total of 3600 pulses applied over RDLPFC (5 cm method).

110% RMT

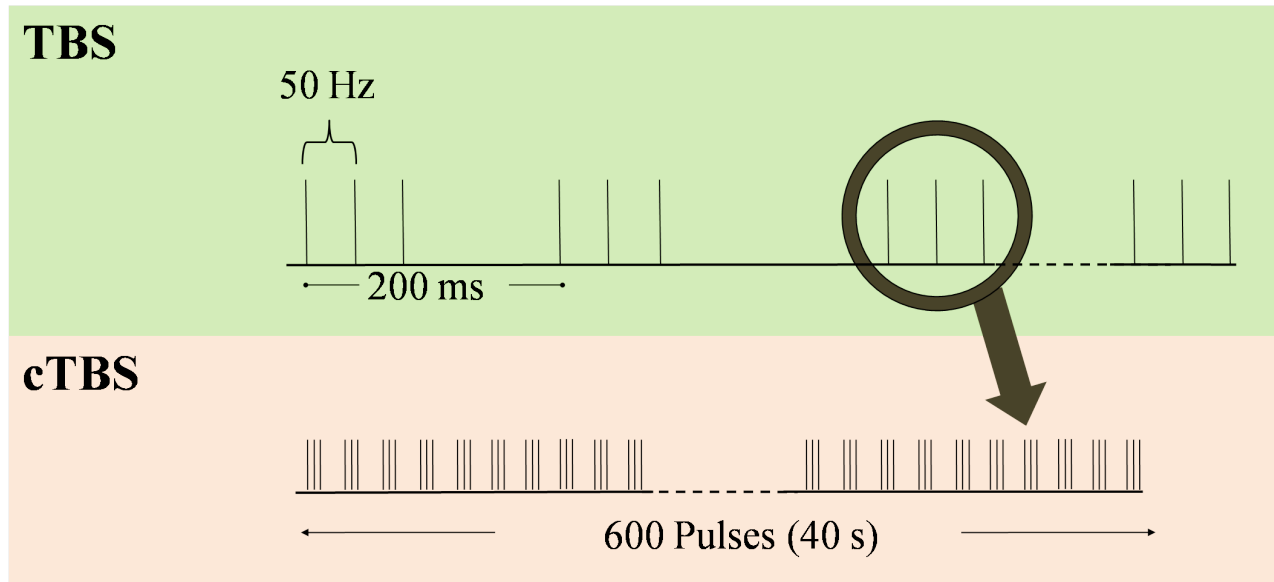
Finding: 25 rTMS sessions of 20 Hz rTMS over right DLPFC significantly improves clinical symptoms of Generalized anxiety disorder (HARS scores > 50%) in all treated participants. The effect was maintained for at least four weeks after treatment completion.



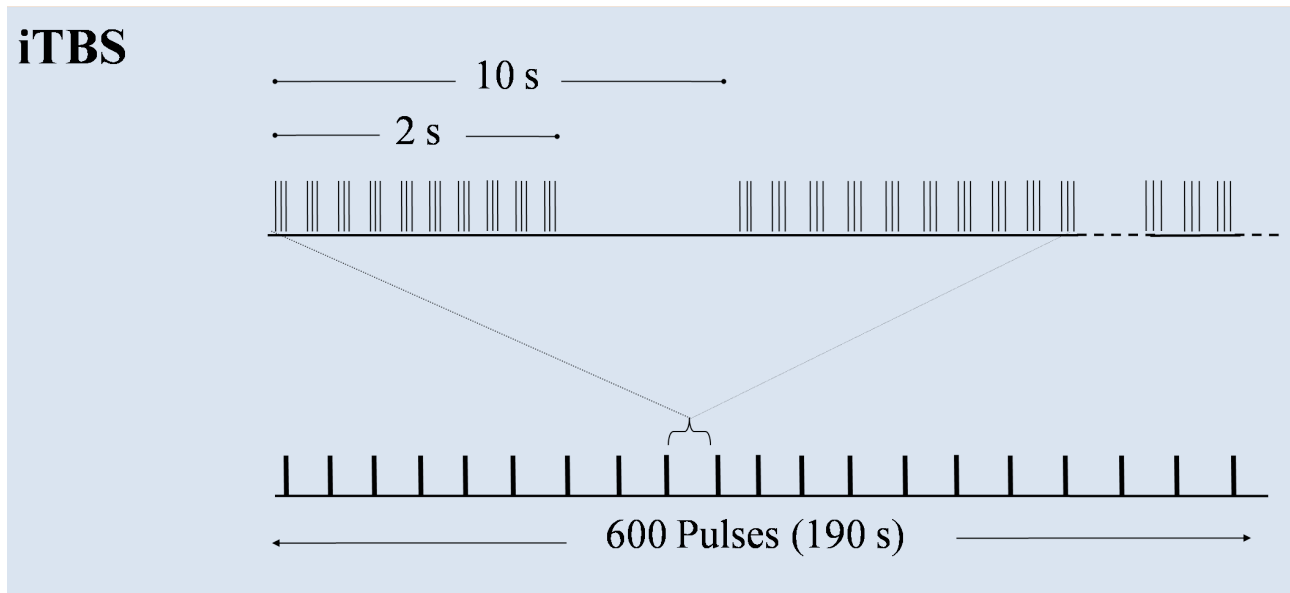
- TBS are rTMS protocols where pulses are delivered in bursts of three at 50 Hz with an inter-burst interval of 200 ms (5 Hz).
- TBS is based on animal models indicating that theta rhythms are related to LTP processes.
- The aim was to develop protocols that allow to assess the mechanisms of brain plasticity.



- TBS seems to induce synaptic plasticity
- TBS produces a mixture of facilitatory and inhibitory effects.
- There are two main TBS protocols: cTBS and iTBS
- The continuous form cTBS is mainly inhibitory
- The intermittent form iTBS is mainly excitatory
- Facilitation builds faster than inhibition

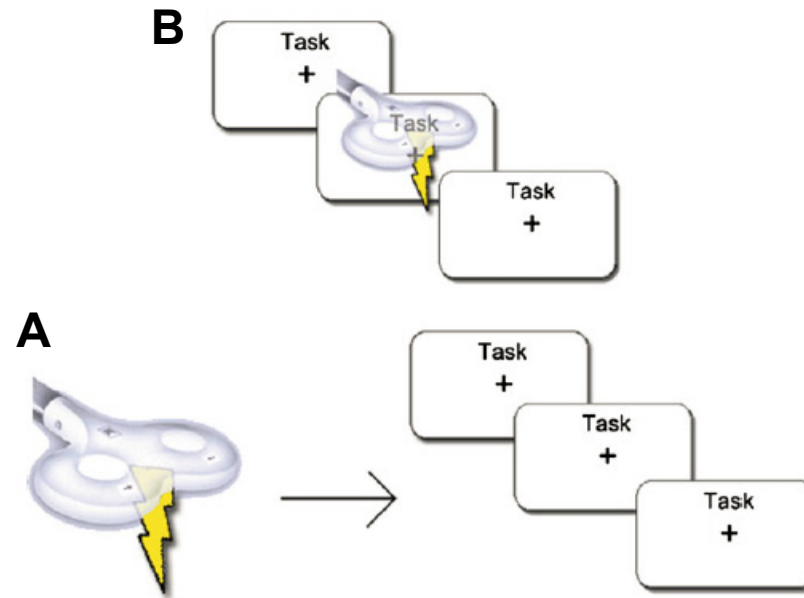


- cTBS induces sustained LTD-like effects
- Leads to a local GABA increase
- Has shown to be effective in improving visuospatial neglect and major depression and reducing tics in Tourette Syndrome



- iTBS induces sustained LTP-like plasticity
- Seems to modulate brain glutamate metabolism
- Seem to have potential in the treatment of depression, multiple sclerosis and schizophrenia

Off-Line Protocols are those protocols where TMS is applied before the behavioral task has been provided (A).



Online TMS protocols refer to TMS protocols applied during performance of the behavioural task. Interleaved short burst of stimulation are used for this type of methodology (B).

Off-line suppressive rTMS protocols: 1 Hz rTMS

OL Gamboa

- One of the most common TMS protocols used offline to induce suppression.
- Stimulation during 15-30 minutes causes an effect lasting several minutes.
- It is believed this protocol induces a LTD-like effect on cortical synapses.
- Cortical responses to 1 Hz rTMS are dependent on activity at both GABAA and NMDA receptor systems.

- A protocol growing in popularity.
- Stimulation during 40 seconds causes an effect lasting 30 - 40 minutes
- Stimulation is more comfortable than 1 Hz.
- It is believed this protocol induces a LTD-like effect on cortical synapses.
- Cortical responses are associated only to GABA mechanisms.

- Long high frequency protocols are mainly used.
- Many studies have found that high-frequency rTMS enhances left dorsal lateral prefrontal cortex activity when compared to sham stimulation
- As it has been found that that patients with depression have hypoactivity in the left prefrontal cortex, the most common application is the treatment of medication resistant depression.

- Based on study's results it has been suggested that high-frequency rTMS applied to the left dorsal lateral prefrontal cortex may be as effective as commercially available antidepressant medications.
- The exact protocol utilized differs between clinicians
- However a typical protocol used for this purpose is 10-Hz at suprathreshold stimulation (110–120 % RMT)

- Online protocols have been mainly used to induce disruption.
- Interestingly short bursts of high frequency stimulation (standard high frequency rTMS leads to excitation) have been applied to this end.
- Stimulation protocol can be 3/ 5/ 6...x number of pulses at 5/ 10/ 20/ 25 Hz
- In this case, stimulation is administered during task performance such that each TMS pulse briefly interferes with cortical activity in a time-controlled manner.
- Literature shows contrasting results: disruption, enhancement or no-effect.

TMS is able to disrupt brain function temporarily if the intervention is performed before the onset of a critical point of such brain function. This phenomenon is called “**virtual lesion**” because this transient interruption simulates the effects of a real cerebral lesion.

Virtual lesions give information about brain-behaviour relationships allowing the study of both unique cognitive processes and functional connectivity.

Possible explanations to cortical processing disruption:

- Introduction of external noise through TMS.
- Activation of GABAergic inhibitory interneurons

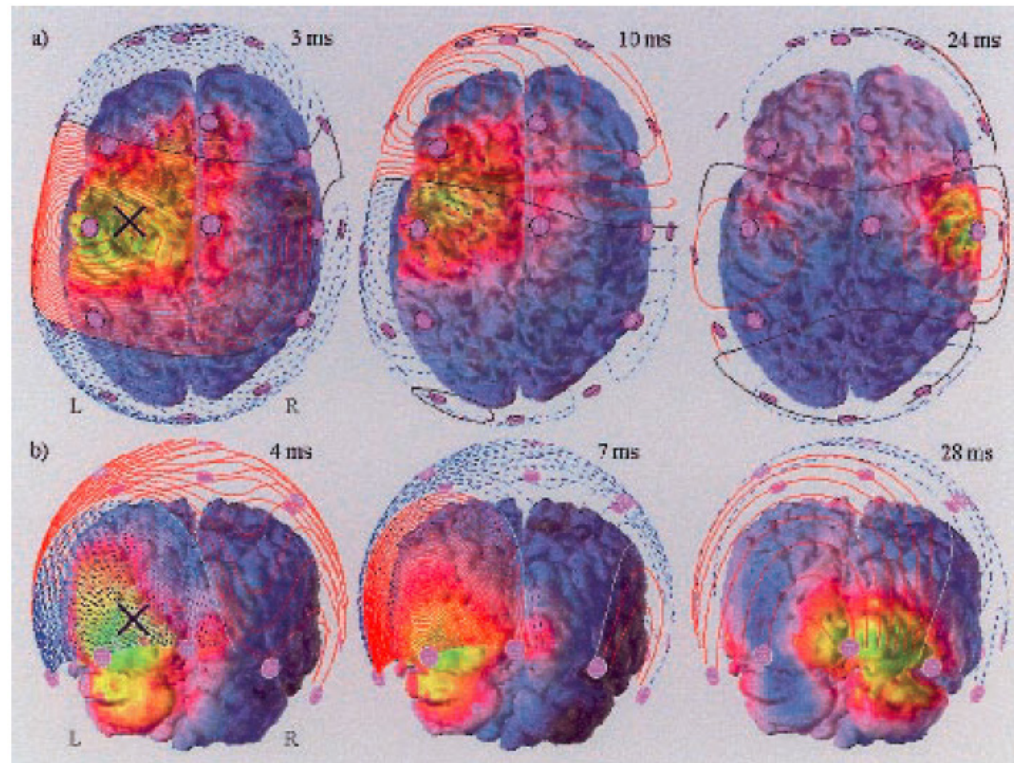
Virtual lesions can be caused using:

- Single pulses
- rTMS: conventional and patterned

They can be:

- Online
- Offline

TMS - neuroimaging → TMS effects reach brain regions distant from the stimulation site. Making possible functional connectivity TMS Studies



- **Keep in mind:** TMS after-effects **are Not region specific** but can be the result from combined responses coming from other regions also affected by that stimulation.

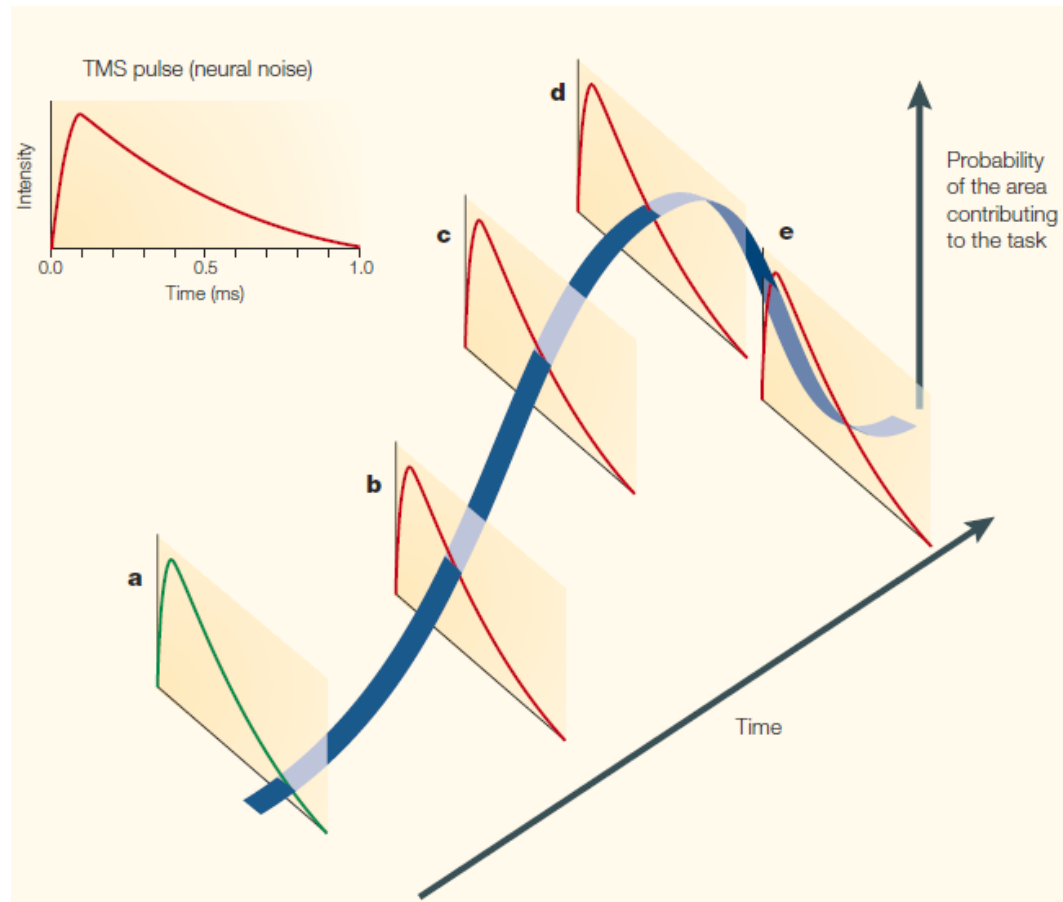
Is a method in which TMS pulses are delivered at different time points to learn the temporal pattern of information processing.

TMS chronometry allows inferences about:

- **When** a brain region executes a behaviour
- **What** is the role of the region in such behaviour.



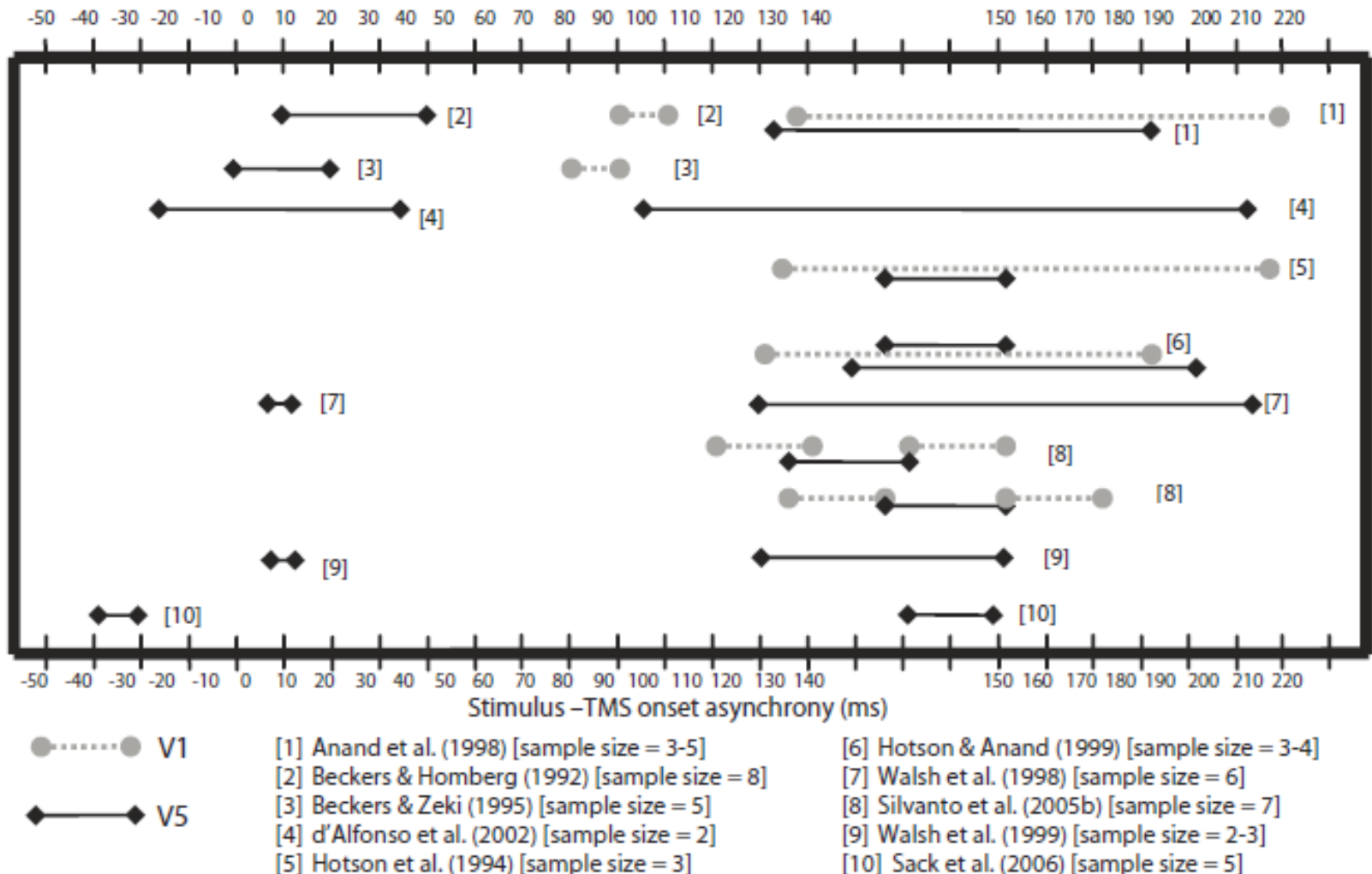
Temporal relationship between TMS & behaviour OL Gamboa



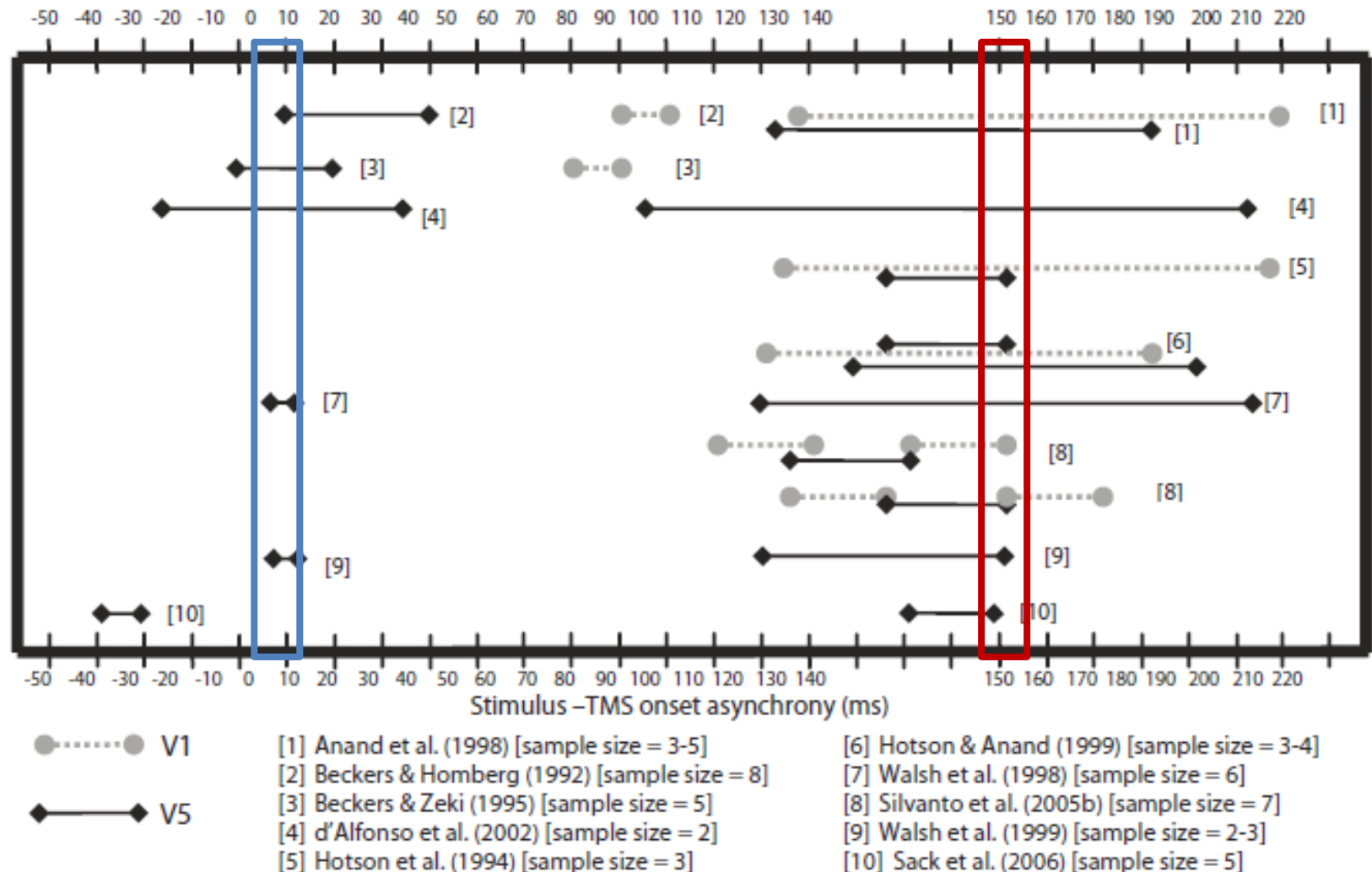
Temporal resolution of TMS is limited by two factors:

- Duration of TMS pulse effects
- Duration of an area's involvement in the task.

Critical time periods for inhibition of motion processing with TMS to visual cortex



Critical time periods for inhibition of motion processing with TMS to visual cortex



Knowing the concept of state-dependency in TMS is important as the quality of the ongoing brain activity will determine the outcome of TMS interventions.

The principle of state - dependency states that the response of a system to an external stimulus is affected

- by the properties of that stimulus
- by the internal state of the system

Understanding of the interaction brain state – TMS:

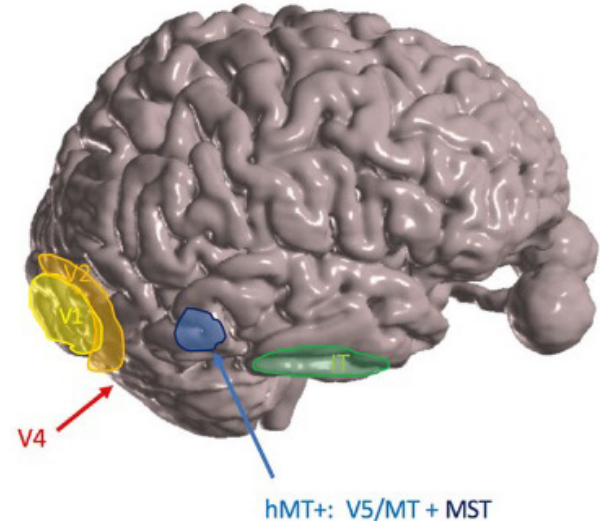
- Significantly enhances TMS efficacy
- Allows to investigate intrinsic properties in the stimulated region (neural specificity)
- Gives insights about basic aspects of brain function.

The idea is to selectively stimulate a specific population of neurons in a certain brain region

It is established that each cortical region is specialized.

For instance in the visual cortex:

- V5/MT → process motion perception.
- V4 → process colour perception.



Besides V5/MT neurons → selective for motion perception, there are subgroups specialized in the direction of motion and motion speed.

In order to investigate functional specialization within a specific brain area, one must select a technique that can selectively assess neuronal function independent of neighbouring neural regions.

For example in the visual cortex this can be done via priming or adaptation.

Sham and control conditions

Sham and control conditions

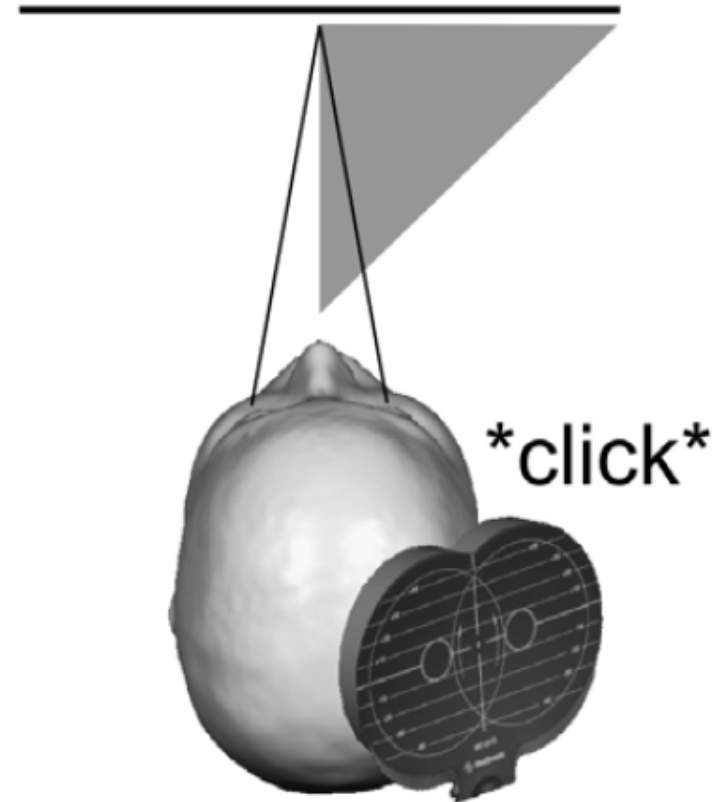
In order to confirm the integrity of TMS results there is need to have control conditions.



- Regardless of how TMS is applied, different psychological as well as sensory side effects come with it.
- They can either shadow TMS outcomes or cause false positives.
- Therefore it is important to make sure that the obtained effects are due to neural manipulation after or during TMS intervention

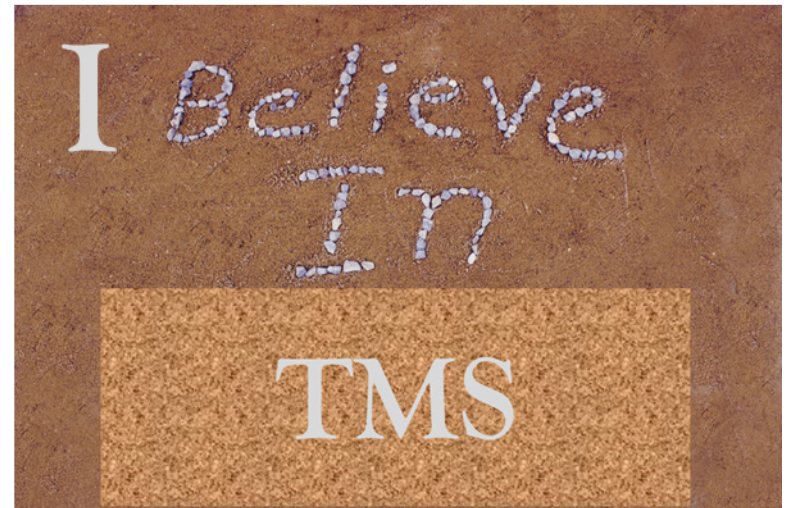
Some of the TMS side effects:

- Auditory effect: due to TMS clicking sound, difficult to fully attenuate with passive hearing protection
- Somato-sensory effects: due to TMS pulse also stimulating the scalp.
- Strong twitches of facial muscles due to peripheral nerve stimulation.



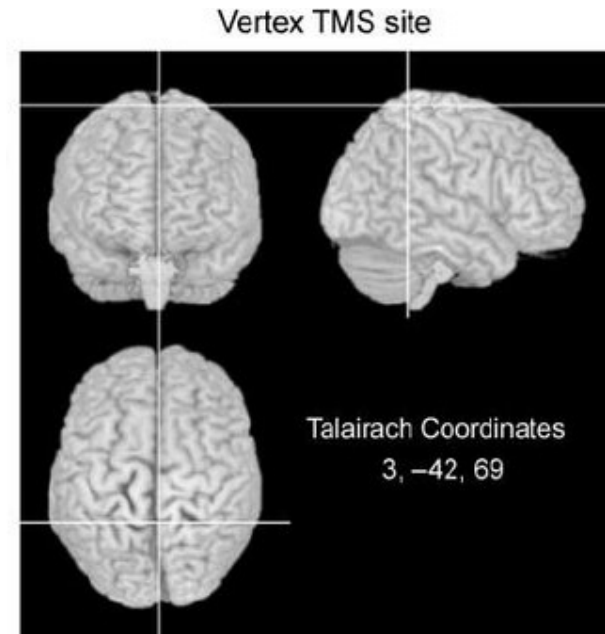
Two things to consider:

1. Sensory side effects of TMS (might interact with the task)
 - Attentional shifts due to auditory and somato-sensory perception during the TMS intervention
 - Change in alertness



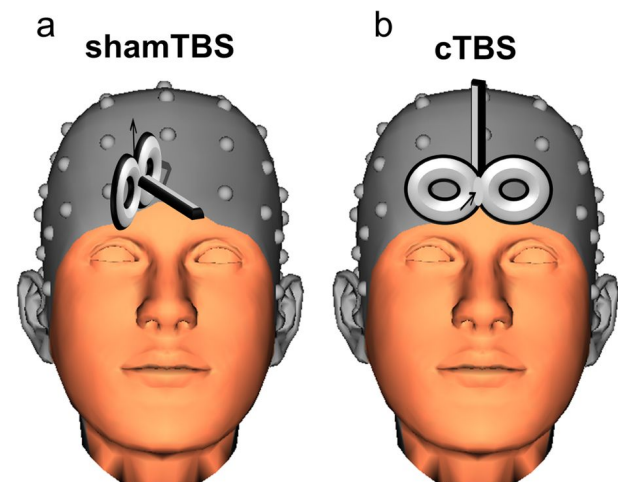
2. Placebo effects due to coil position: psychological and behavioral associated to the belief or expectations TMS effects. Might cause behavioural or cognitive changes unrelated to neural effects caused by TMS

- There is need to address these methodological issues towards lessening the interference of these side effects.



Harries et al., (2008), J Cogn Neurosci 20(5):916-26

- There are different ways to control during TMS experiments
 - ❖ Control task
 - ❖ Control sites
 - ❖ Sham stimulation



Gohil et al., (2016), Scientific Reports 6: 22317

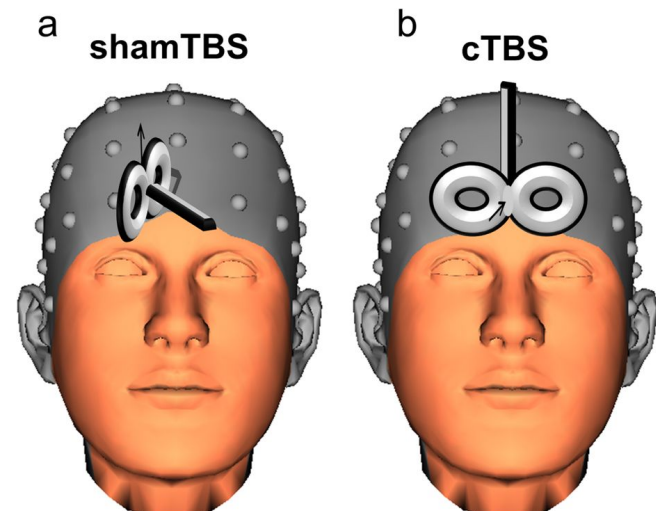
According to Walsh (1999) the choice of a control site can be determined in one of three ways:

- Dissociation: TMS applied to an area known to have different function than the one under study: to check for **specificity** of the effect
- Proximity: Select the site of interest and stimulating points around it (grid). This helps to state that site X is important for a certain function while neighbouring sites are not. This method is useful during the piloting sessions and when lacking participant's structural MRI images.
- Time: Stimulating after an intervention when the effect is not available.

What is sham TMS:

It is any approach that aims at imitating the auditory and/or somatosensory effects of active TMS without actual stimulation of the brain. Two approaches to sham:

- Tilted coil
- Sham coil



Gohil et al., (2016), Scientific Reports 6: 22317

Issue: Lack of somatosensory effects and peripheral nerve stimulation present during active TMS

Electrical stimulation as sham:

In order to counteract this limitation, surface electrodes can be used for electrical stimulation of the scalp time-locked to the TMS pulse, so that somatosensory effects of sham and active TMS are closer.



In practical matter the combination of a sham TMS coil in with electrical stimulation seems to be the best available sham approach.

It is good:

- To show site specificity of TMS effects

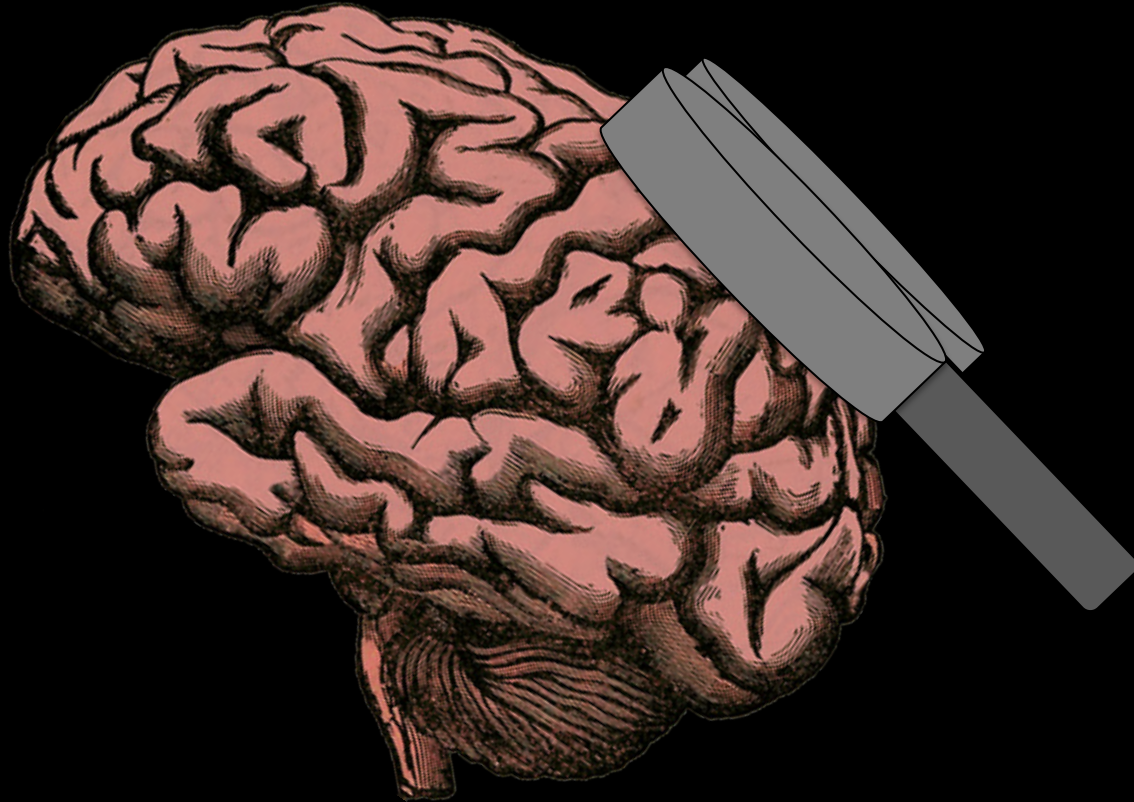
TMS control condition (vertex, other) + Sham stimulation

- To have sham for each active condition

But it is practical?

- Time requirements of the task
- Participant fatigue.

It may be needed to compromise in the experimental design



**"There are no new ideas.
There are only new ways
of making them felt"**

Audre Lorde