"Safety brings first aid to the uninjured."

F.S. Hughes

Session 2: “ TMS Safety aspects”

Dr. Olga Lucía Gamboa Arana

Hong Kong, 29-11-2018

Outline Session 2

Session 2 – Lecture " TMS Safety aspects"

- Terminology
- Safety concerns
- Risks
- Participant selection
- Dosing
- Ethics and regulations

Terminology

TMS Safety: terminology

1. Single pulse
2. Paired pulse: two pulses separated by a certain interval
3. 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

Safety concerns

Safety Concerns

1. Tissue heating
2. Forces and magnetisation
3. Induced voltages
4. Magnetic field exposure
5. TMS and implanted – stimulating/recording electrodes

Safety Concerns: Tissue heating

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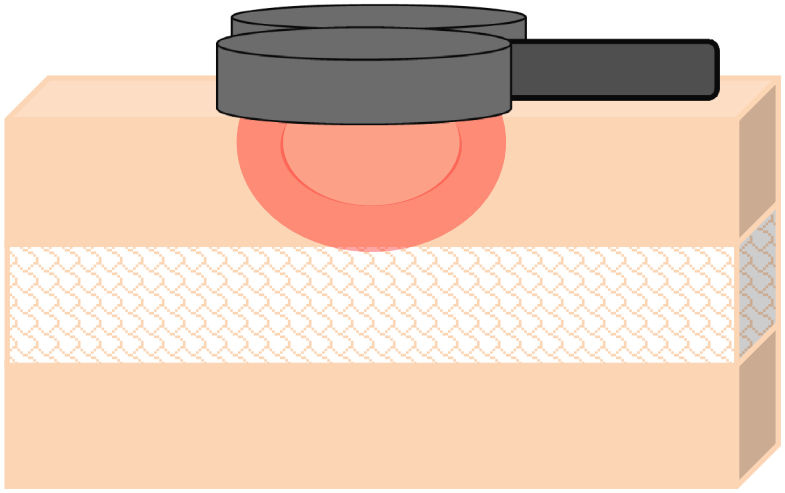
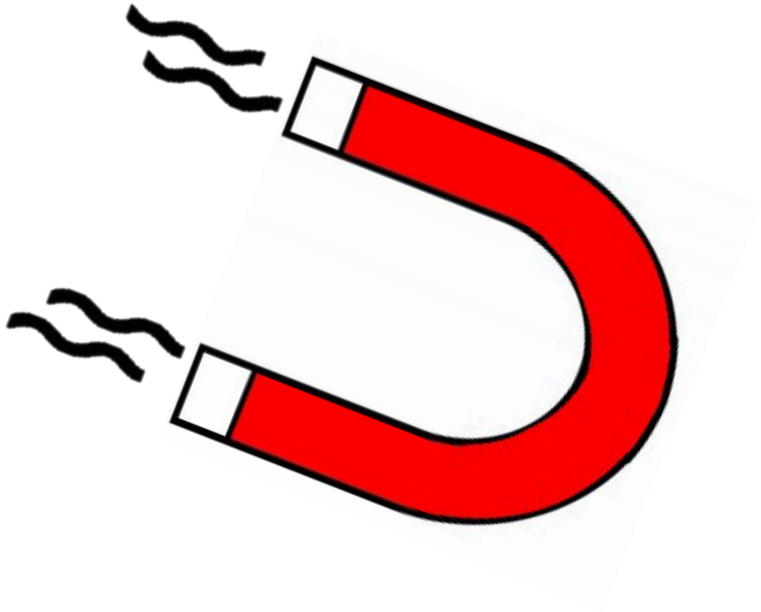
- Tissue heating due to single pulse TMS < 0.1 °C
- For implanted electrodes, eddy currents will induced a temperature increase
- Low conductivity plastic electrodes could be used in this cases.
- Before applying TMS near implants it is suggested to test the heating ex-vivo with the exact parameters of the desire protocol.
- Report the results of such testing



Safety Concerns: Forces and magnetisation

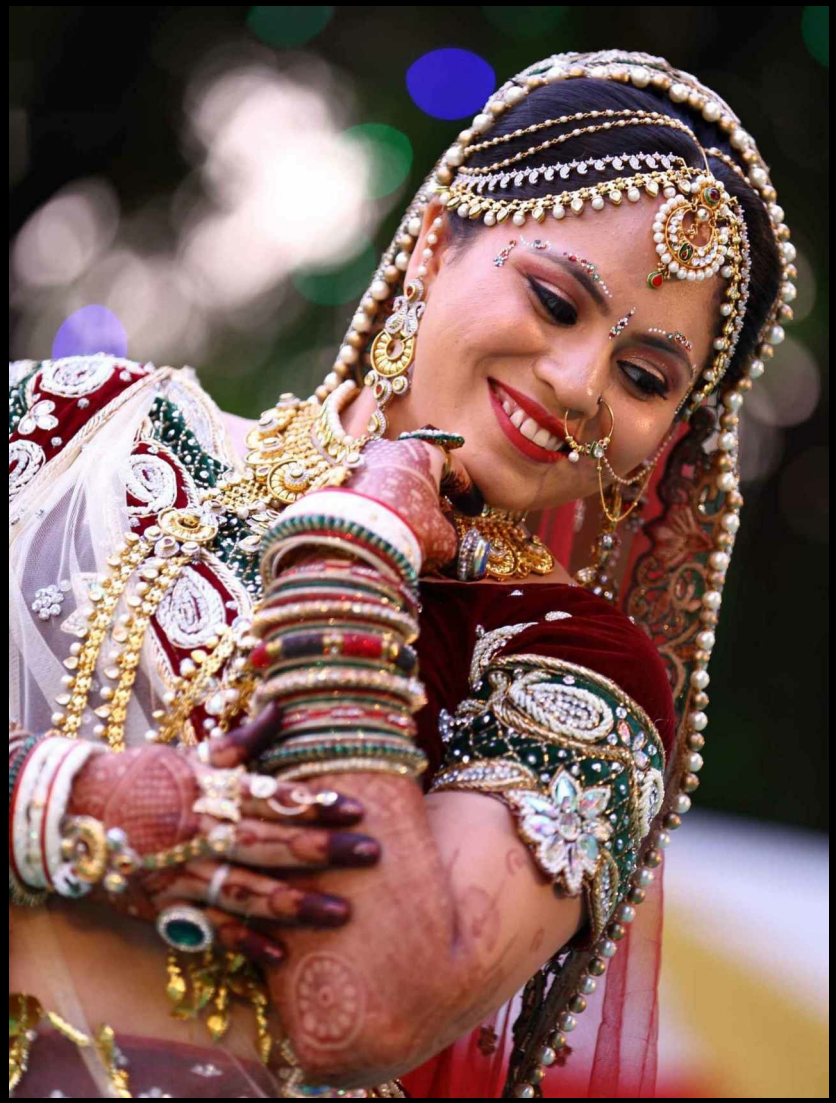
- Magnetic field pulses: attractive forces on ferromagnetic objects and repulsive forces on non-ferromagnetic conductors.
- TMS exerts forces over had implants, displacing them
- Some titanuium skull plates may be safe for TMS.
- Exvivo testing using the parameters of the tms protocol should be performed before applying it to people with implants.



Safety Concerns: Forces and magnetisation

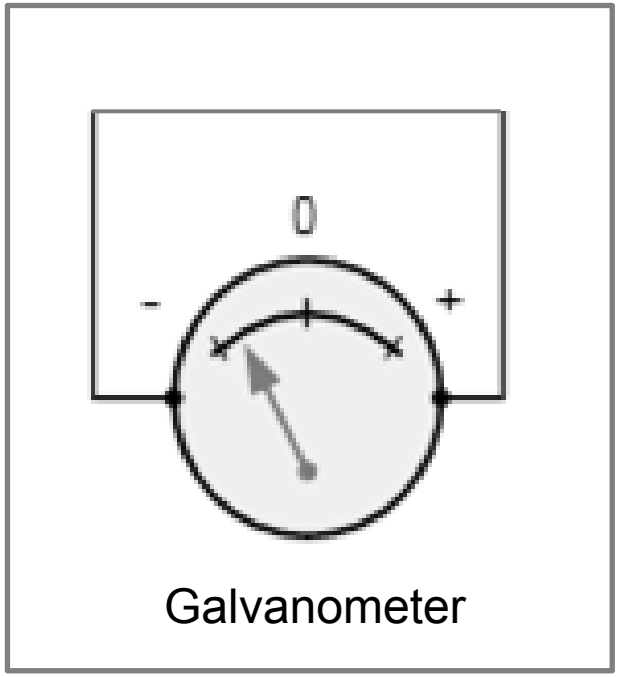
Important:

During TMS sessions: Jewelry, glasses, watches and other potential conducting or magnetic objects worn on the head should be removed.



Safety Concerns: Induced voltages

- The TMS pulse can induce large voltages in nearby wires and electronic devices.
- TMS can damage the internal circuitry of electronic implants near the coil causing them malfunction.



Galvanometer

Safety Concerns: TMS & implanted electrodes

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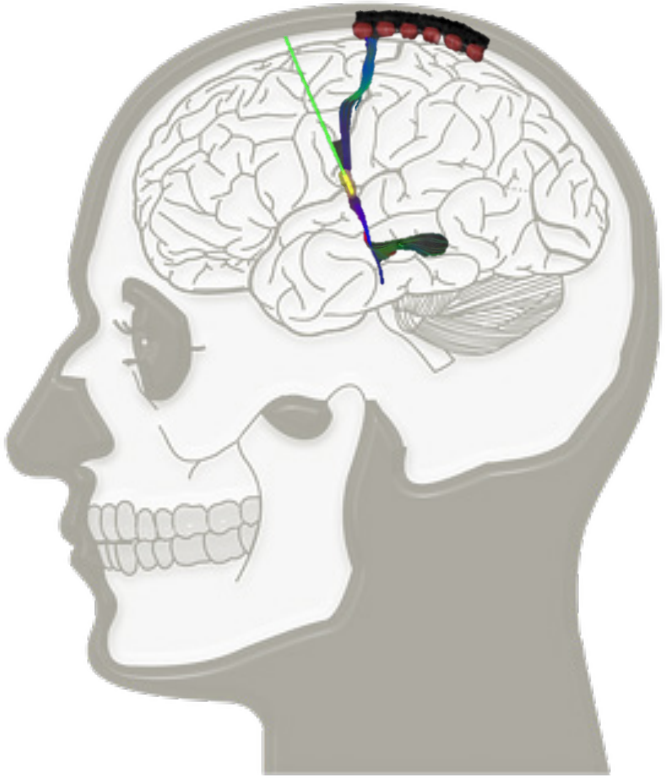
- TMS can be safely applied to patients with implanted stimulators (ex *ex vivo* and *in vivo* studies).

- But there is lack of detailed information to define safe guidelines for it to be performed: the safe distance between the TMS coil and the implanted stimulator, and how coil shape, coil angulation, etc.



Safety Concerns: TMS & implanted electrodes

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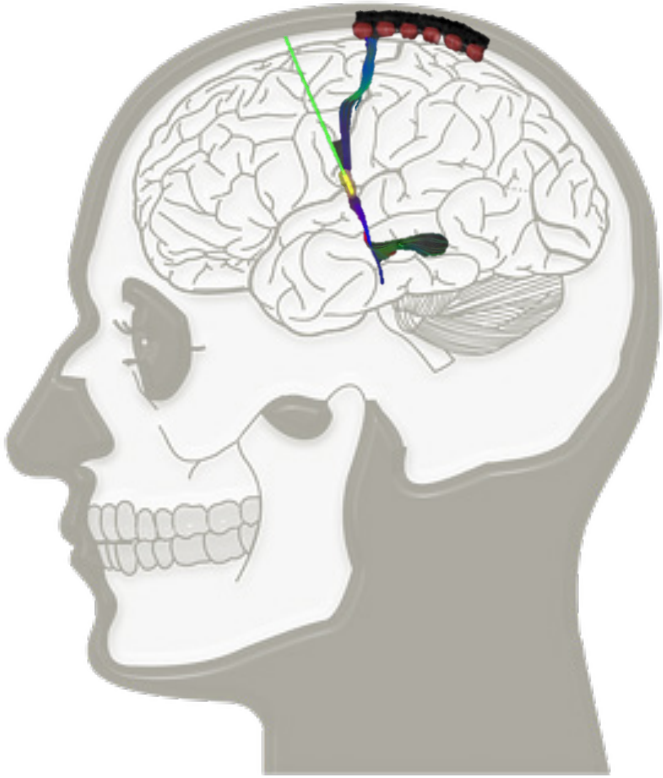
- TMS should only be done in patients with implanted stimulators if absolutely necessary

- following strict experimental protocols should be followed with rigour and must be regulated and followed closely by the institutional review board or ethic committee.



Safety Concerns: TMS & implanted electrodes

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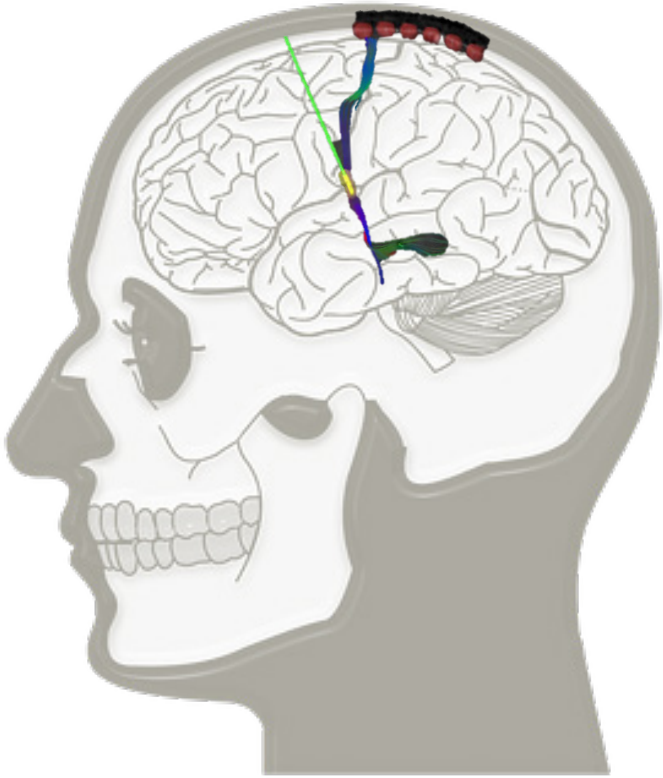
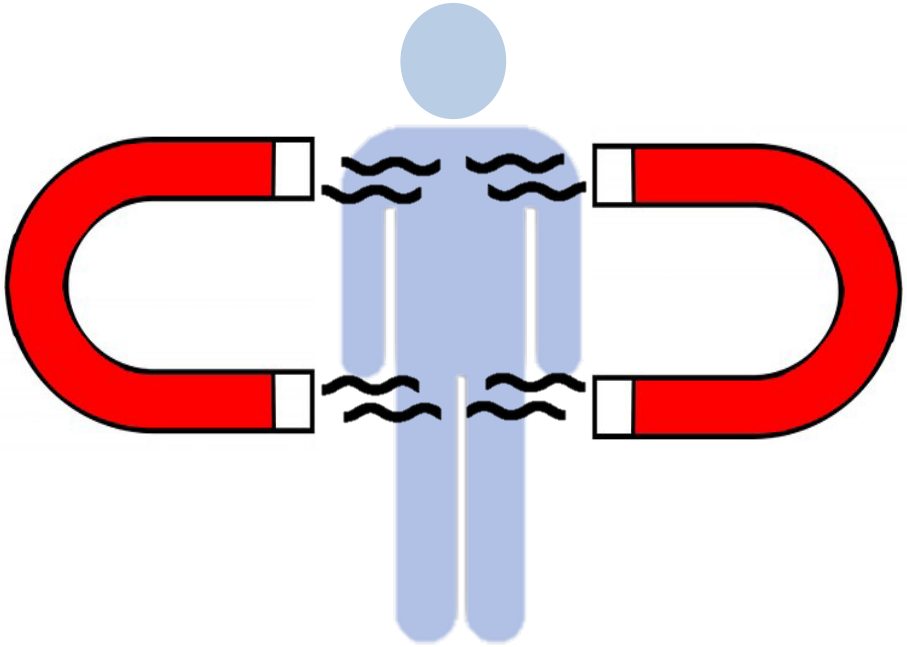
- Adequate steps to avoid accidental firing of the implanted stimulator due to TMS should be taken.

- As long as the TMS coil is not activated near the components located in the neck or chest TMS is considered safe in individuals with implants (VNS systems, cardiac pacemakers, and spinal cord stimulators).



Safety Concerns: Magnetic field exposure



- Based on one study performed by Karlström et al., 2006, it is suggested that operators must keep a distance of about 0.7 m from the surface of the coil.

- Long term effects for rTMS operators working daily with rTMS for years should be addressed in future research.

Risks

TMS Safety: Risks

1. Hearing
2. Headaches and local pain
3. Syncope
4. Seizures
5. Cognitive changes
6. Mood changes

TMS Risks – Hearing

- The acoustic TMS artifact → > 140 dB
- Some adults after TMS → increase auditory threshold
- A participant not using earplugs being stimulated with an H-coil → Permanent threshold shift

TMS Risks – Hearing

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Considerations before, during and after a TMS:

- Individuals with cochlear implants should not receive TMS due to multiple possibly unsafe interactions between the TMS pulse and the implant.

- Except cases → rTMS used as therapy for tinnitus: participants with known hearing issues should receive TMS only if the benefit is greater than the risk

TMS Risks – Hearing

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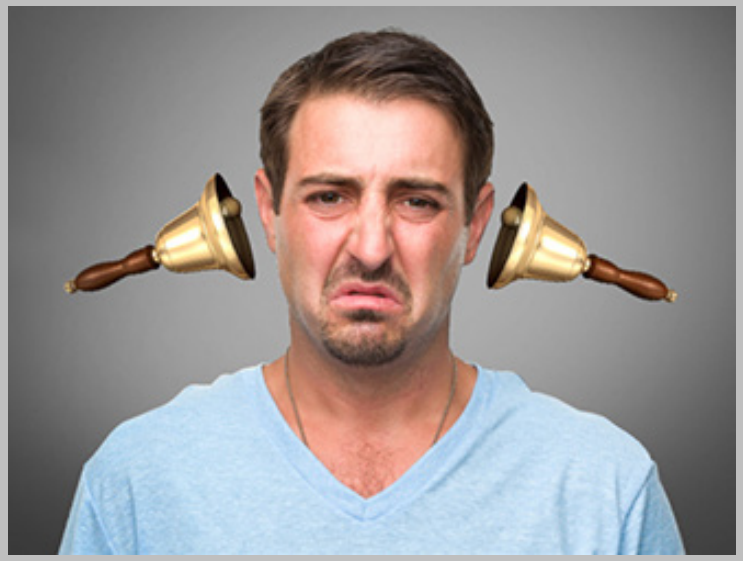
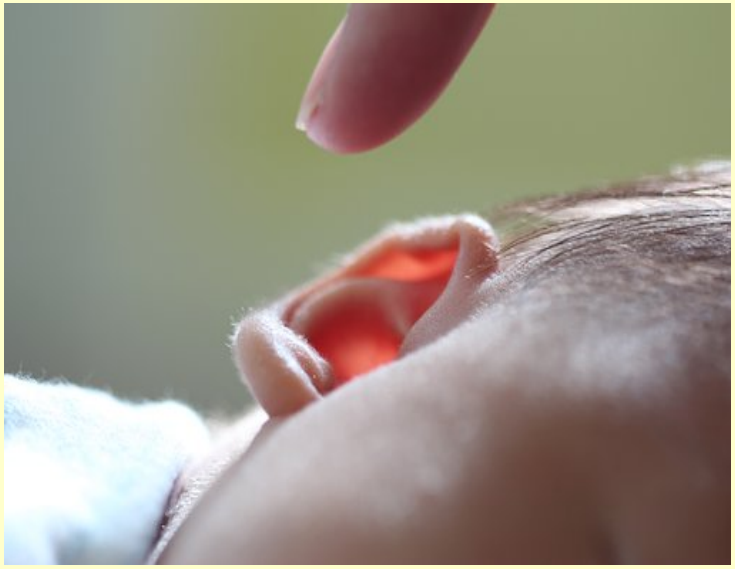


Considerations before, during and after a TMS:

- Participants should use earplugs or ear muffs during the TMS session.
- Participants complaining about hearing loss, aural fullness or tinnitus must be immediately referred to auditory assessment

TMS Risks – Hearing



Considerations before, during and after a TMS:

- Participation of healthy children in TMS studies is not recommended → more studies are needed
- rTMS in children only if the potential benefits are superior to the theoretical risks of hearing problems.

TMS Risks: headaches, migrains and other pain

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- Single pulse is generally well tolerated
- Sometimes rTMS can be painful
- Headache and neck pain are the most frequent rTMS side effects reported (~ 40% of the cases).
- Analgesic can be provided to ease persistent headache.
- Other types of pain reported are, toothache but it fades quickly
- No migraine attacks have been reported after rTMS neither in normal nor in migraine patients.

TMS Risks: headaches and migraines

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- During therapeutic rTMS local pain has been reported due to frontal rTMS.
- It declines after a few days of daily treatment.
- A commonly used option is to use a ramp up method during the first week of treatment

TMS Risks: Syncope

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- Syncope is a common experience in TMS and it is more often than seizures.
- Vasodepressor syncope is a common reaction to anxiety and psychophysical discomfort.

TMS Risks: Syncope

Clinically the main feature that differentiate syncope from seizure is rapid recovery of consciousness within seconds and NOT minutes.

TMS Risks: Syncope

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In a case of syncope the participant may report:

- Black out or visual field narrowing
- Dizziness
- Sensation of increase of heat
- Need of air
- Diaphoresis
- Nausea
- Pallor

TMS Risks: Induction of seizures

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- This is the most acute adverse effect of rTMS.
- Some cases of seizures caused by TMS have been reported when no safety guidelines were established.
- Currently the low number of reported seizures in proportion to the amount of studies performed.
- This means that following the safety guidelines the possibility of inducing a seizure is very low.
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TMS Risks: Induction of seizures

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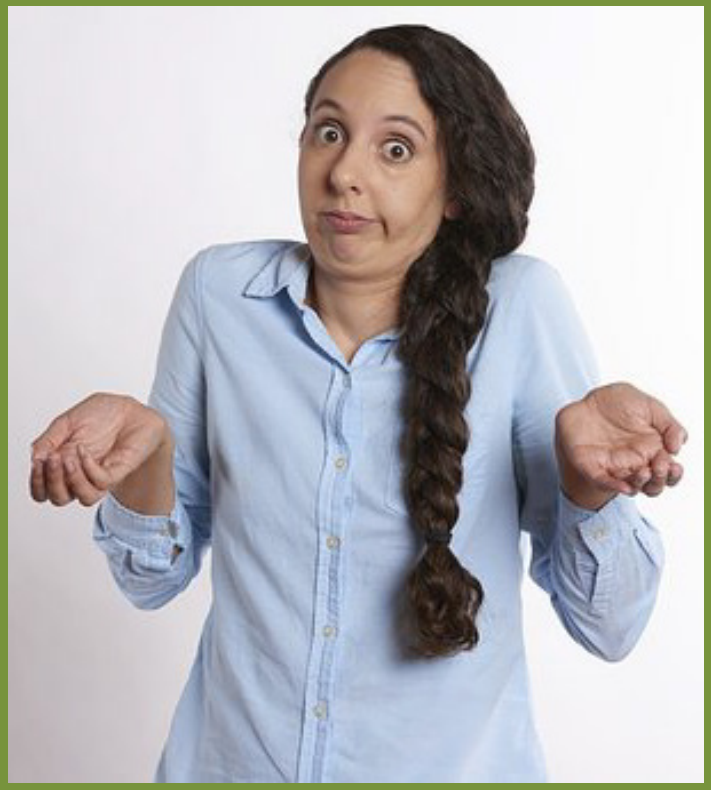
- Seizures can be induced by rTMS in protocols with high frequency and short inter-train interval periods.

- Seizures induced by rTMS can occur:

  1. During or immediately after the rTMS train (commonly seen)

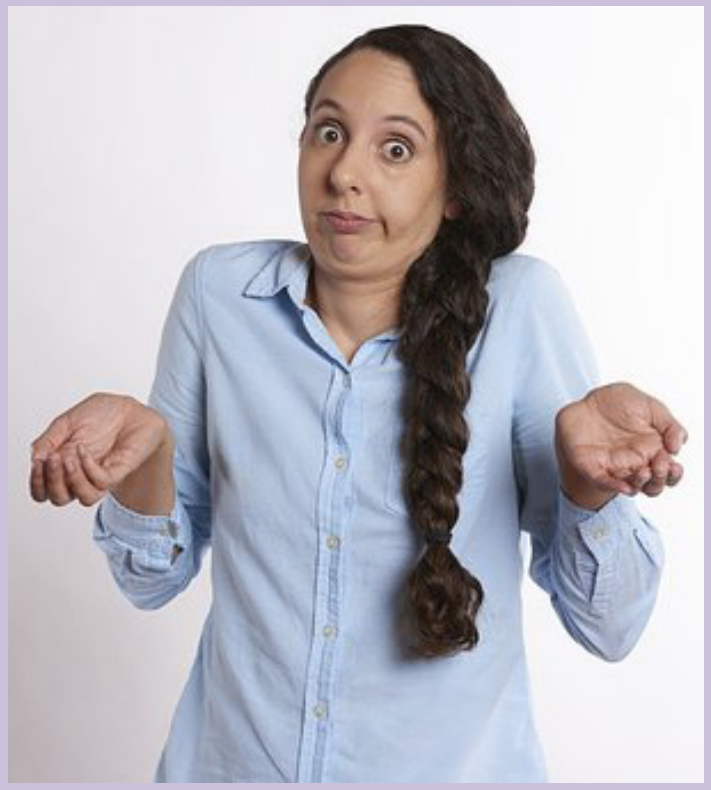
  2. During the after effects due to the modulation of cortical excitability (has not been reported)

TMS Risks: Cognitive changes



- Side effects related to interaction with task performance have not been reported in studies using rTMS in healthy subjects.
- These studies have followed the established safety guidelines and the safety TMS questionnaire to eliminate contraindications.

TMS Risks: Cognitive changes



Safety parameters to consider when designing this type of experiments are:

- TMS-train duration
- Stimulation rate (in Hz),
- Inter-train interval
- Number of trials / session

For safety reasons, the combination of parameters is important, with short train durations and long inter-train intervals carrying less risk

TMS Risks: Psychological changes

- Transient psychiatric side effects induced by TMS such as:
  - ❖ psychotic symptoms
  - ❖ Anxiety
  - ❖ Agitation
  - ❖ suicidal ideation
- Remission has been observed once the stimulation has finished or by means of appropriate medication.

TMS Risks: Psychological changes

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- It is important to inform psychiatric patients about the (low) likelihood of presenting these side effects which could be related to type and severity of their pathology.

- The side effects of cumulative therapeutic stimulation are unknown.

TMS Risks: Psychological changes

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Studies in healthy participants have not reported mood or psychological changes related to TMS.

Participants selection

Participant selection

1. Patients and TMS
2. Children and TMS
3. Pregnancy and TMS
4. Other factors affecting TMS effectiveness

Patients and TMS

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- There is an interaction between TMS intervention and the neurological or psychiatric illness under treatment.
- The difference between clinical TMS and basic neuroscience research is that patients are being medicated with a range of CNS acting drugs.

Patients and TMS

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When selecting patient population for TMS studies:

- Neurological and psychiatric patients are expected to be under different forms of treatment: psychotherapy, neurorehabilitation and medication.
- Attention to: CNS medication (antidepressants, antipsychotic, anxiolytics, analgesics, anticonvulsants), as they may interact with TMS, increasing seizure risk.

Patients and TMS

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When selecting patient population for TMS studies:

- Different TMS effects are expected if the TMS intervention is performed in the acute phase of the illness or the relapse prevention after recovery

Patients and TMS

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When selecting patient population for TMS studies:

- Additionally, factors such:
  - ❖ drug dose,
  - ❖ speed of dose increase or decrease
  - ❖ combination with other CNS active drugs

  Increase the risk of seizure induction.

Patients and TMS

Note:

It is important to keep an eye on the list of drugs that interacts with TMS.

For more information on drugs and TMS interaction please refer to the more recent safety guidelines available and their equivalents in the area.

Children and TMS

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Single pulse and paired pulse TMS are minimal risk procedures for kids.

Children and TMS

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However, some concrete developmental processes may play a role in paediatric TMS:

- Maturation of cortical excitability
- Closure of fontanelle
- Growth of the external auditory canal (children no TMS)

Pregnancy and TMS

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- Magnetic fields attenuate rapidly with distance so it is unlikely that TMS affects he foetus.
- No side effects has so far been reported in pregnant women receiving TMS.

Pregnancy and TMS

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However a conservative approach must be used and the risk benefit ratio must be evaluated at the individual level. Several points to keep in mind:

- For clinical routine: TMS on the lumbar spine must be avoided unless absolutely necessary
- Pregnant operators should stay at least 0.7 m away from the discharging coil.

Other factors affecting TMS effectiveness

Other factors contributing alone or in combination to change the pre -TMS levels of neuronal activity and therefore changing the resulting TMS effects and risks are:

- Menstrual cycle
- Age
- Levels of anxiety of mood
- Sleep deprivation
- Alcohol or drug abuse
- Thickness of brain layers
- Brain atrophy
- Neurological and psychiatric illness
- Activity previous to the TMS study

Dosing

About the TMS dose:

There are 4 fundamental parameters that define rTMS:

1. Train intensity
2. Frequency
3. Train duration
4. Inter - train interval,

Other rTMS dosing parameters to account for the cumulative exposure to rTMS:

1. Total pulses /session
2. Sessions/day
3. Days/week
4. Weeks/acute course
5. Maintenance frequency

About TMS thresholds:

- For conventional rTMS over motor cortex (using a figure of eight coil) stimulation ranges from 10%-130% RMT

Note

When an individual MT cannot be determined the lower 95% of confidence interval of the average value of the MT in the remaining subject/population can be used for the specific coil - stimulator.

About TMS thresholds:

- Motor threshold must be adjusted when used as a parameter to stimulate non-motor areas to compensate for increase coil-to cortex distance.

- This can be done by modelling or other TMS intensity adjustment methods

- Stokes Formula:

$$\mathrm{AdjMT\%} = \mathrm{MT} + 3 \times (\mathrm{D_{SiteX}} - \mathrm{D_{M1}})$$

About TMS thresholds:

Note

Protocols safe for M1 must be safe in non-motor regions since M1 is highly excitable.

Ethics and regulations

Ethics and regulations

1. Ethics and regulations basics
2. Managing emergencies
3. Credentials of the TMS operator
4. Contraindications
5. Recruitment and the TMS questionnaire

Ethics and regulations

Research and clinical application of TMS must follow the three basic ethical and legal requirements related to al studies on human subjects:

1. Informed consent
2. Risk benefit ratio
3. Fairness and equity in research participation

Ethics and regulations: Informed consent

People taking part of either TMS or clinical studies must be given all important information about TMS and the potential risks for them to be able to make an informed decision.

- Children and mentally disable persons require a legal representative in charge of making the decision
- Language should be non-scientific and clearly understandable for the general community. So that they can be addressed and discussed properly by the local ethic institution
- The form must list all the procedures, risks and discomfort of the study.

Ethics and regulations: Risk-Benefit ratio

Benefits must be greater than the risk in both research and clinical trials.

Fairness & equity in research participation

TMS should not only be conducted on vulnerable population (understanding vulnerable as population with less favourable social, economic or physical conditions

Managing emergencies

Syncope and seizures:

- Each TMS lab must have a program ready to deal with syncope and seizures.
- All members of the TMS team should be familiar with it
- Life support equipment should be available when doing rTMS procedures
- Efforts should be made to prevent complications during episodes of seizures and syncope.

Managing emergencies

Syncope and seizures:

Important Notes

People experiencing TMS induced seizures must be informed that their frequency of seizure episodes is not higher than before.

Medical and psychological support should be provided to patient and normal subjects who have experiended TMS induced seizures.

Credentials of the TMS operator

- Regardless of the type of study being either with research or clinical purposes, people performing TMS should be properly trained.
- Neurologist or clinical neurophysiologist should supervise clinical routine
- In research studies, the PI who should be trained is the person responsible for the study.

Credentials of the TMS operator

- Screening procedures should be checked by a licensed physician identified as a medically responsible clinician.

- All TMS operators must be trained in how to recognize and manage syncope and seizures and their potential acute complications.

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Contraindications

1. History of seizures
2. History of seizures in first-degree relatives
3. History of any illness involving the brain
4. Consumption of medications known to lower the seizure threshold
5. History of tinnitus
6. Presence of cardiac pacemaker or intracardiac lines of any sort
7. History of bipolar disorder
8. Presence of any metal in the head (except the mouth)

Contraindications

9. Traumatic brain injury with loss of consciousness for greater than 5 minutes
10. Pregnancy
11. History or presence of increased intracranial pressure
12. Presence of medication pumps or cochlear implants
13. Significant cardiac disease
14. Vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain

    (without history of seizure, and without anticonvulsant medication)
15. Sleep deprivation
16. Alcoholism

Recruitment and the TMS 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 in which occasion(s)
3. Have you ever had severe (i.e., followed by loss of consciousness) head trauma?
4. Do you have any hearing problems or ringing in your ears?
5. Are you pregnant or is there any chance that you might be?
6. Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.)
7. Do you have cochlear implants?
8. Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)
9. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
10. Do you have a medication infusion device?
11. Are you taking any medications? (Please list)
12. Did you ever have a surgical procedures to your spinal cord?
13. Do you have spinal or ventricular derivations?
14. Did you ever undergo TMS in the past?
15. Did you ever undergo MRI in the past?

Affirmative answers to one or more of questions 1–13 do not represent absolute contraindications to TMS, but the risk/benefit ratio should be carefully balanced by the Principal Investigator of the research project or by the responsible (treating) physician.

"Safety brings first aid to the uninjured."

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