Safety of TMS and Ethical Concerns

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Plan

1. What are potential concerns?
2. Ethics.
3. Overview of adverse TMS effects.
4. Risk of seizure.
5. Safety parameters and guidelines
6. Other adverse effects (known & theoretical)
7. Contraindications
8. Management of the risks

Ethical considerations

6 principles of medical (research) ethics

- **Beneficence:** the investigator should act in the best interest of the patient
- **Non-maleficence:** “first, do not harm”
- **Autonomy:** the subject has the right to refuse or choose the intervention
- **Justice:** concerns the distribution of resources and equality in deciding who participates
- **Dignity:** the subject has the right to dignity
- **Truthfulness and honesty:** the subject should not be lied to, and deserves to know the truth about his/her treatment

Ethical considerations

- Potential benefit **>** risk of the intervention
- Informed consent:

  -who will participate in the study

  -what will happen during the study

  -why this study is being done

  -**possible risks, side effects and discomforts**

  -benefits / alternatives

  -confidentiality / personal and health information

  -disclosure of special interest of the hospital or the investigator
- Informed consent does not substitute an ethical practice

Potential adverse effects of rTMS

Known risks

- seizure
- pseudoseizure and syncope
- headache and neck pain
- effects on cognition
- effects on mood
- endocrine effects
- auditory effects
- burns from scalp electrodes
- psychiatric symptoms
- nausea

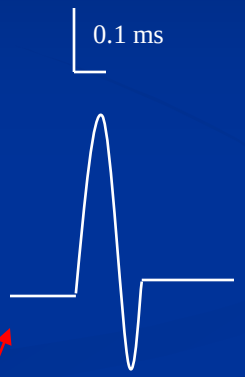
Theoretical risks

- histotoxicity
- kindling
- long-term potentiation
- long-term depression
- unknown

Wassermann 1998; Machii et al. 2005

Important parameters for safety

- **Frequency of stimulation** *(Hz)*
- **Intensity** *(% threshold/output)*
- **Duration: train/total** *(seconds)*
- **Intertrain interval** *(seconds)*
- **Number of pulses: train/total**



E.g. depression protocol (20Hz)

Potential adverse effects of rTMS

Known risks

- **seizure**
- pseudoseizure and syncope
- headache and neck pain
- effects on cognition
- effects on mood
- transient effects on hormones
- transient auditory effects
- burns from scalp electrodes
- psychiatric symptoms
- nausea

Theoretical risks

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Wassermann 1998; Machii et al. 2005

TMS-induced seizures

When applied in sufficiently high doses, high-frequency rTMS has proconvulsive potential in animals and humans.

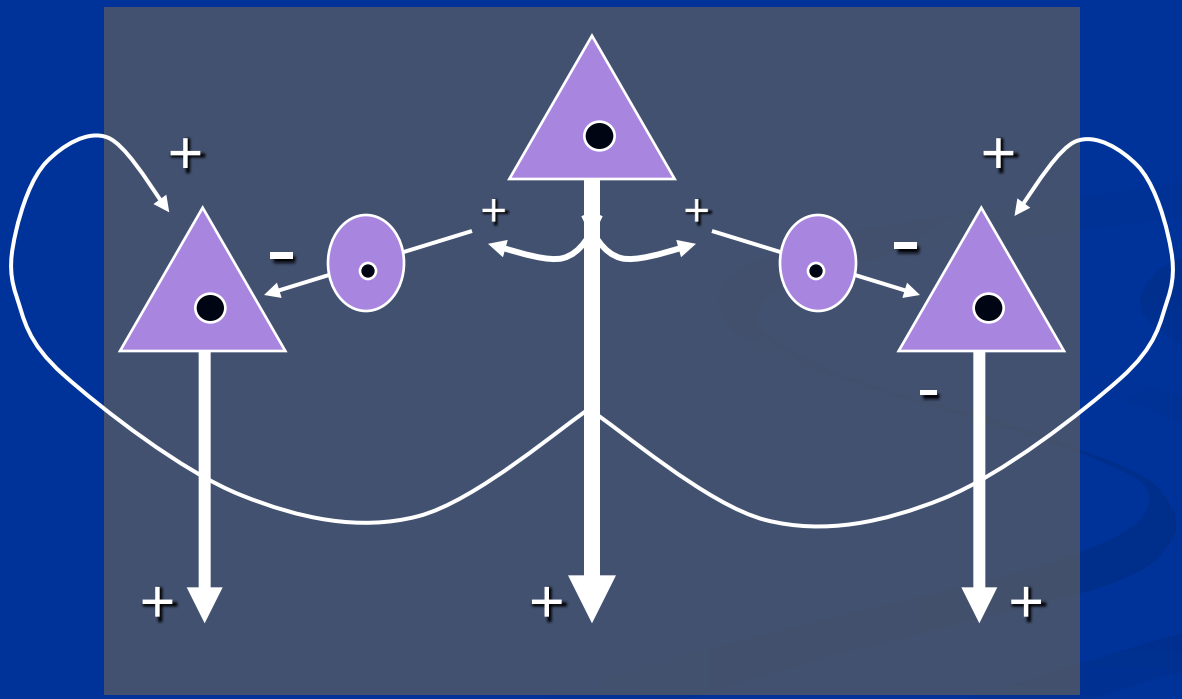
(Wassermann and Lisanby 2001, Jennum and Klitgaard 1996 Pascual-Leone et al., 1993; Wassermann et al., 1996; Lisanby et al., 2001).

TMS-induced seizures: mechanisms

EXCESSIVE ACTIVATION OF PYRAMIDAL CELLS

SPREAD OF EXCITATION TO NEIGHBORING NEURONS

OVERWHELMING OF INHIBITORY MECHANISMS



Daskalakis and Chen 2005

TMS-induced seizures in animals

In general, it is extremely difficult to induce seizures with TMS in animals

Examples of proconvulsive effects:

Rodents

Chronic stimulation: 1 and 5 sec trains, stimulus intensity of 1.8 x Tm, every day for 30 days reduces latency of onset of PTZ-induced seizure (Jennum and Klitgaard 1996)

Primates: 40Hz 400% MT 4-5s; local anesthesia; only with custom device (induced voltage equal to that of electroconvulsive shock). (Lisanby et al 2001)

TMS-induced seizures in humans

- Seizure induction w/ single pulse TMS

Healthy subjects: No cases reported to date.

- Seizure induction w/ single pulse TMS

Patients: Approximately 20 cases reported.

- Seizure induction w/ repetitive TMS

Healthy subjects: Approximately 6 cases when parameters are outside of safety guidelines. 1 case when parameters are within safety guidelines.

- Seizure induction w/ repetitive TMS

Patients: At least 3 cases.

Safety guidelines

Pascual-Leone et al. (1993), Safety of transcranial magnetic stimulation in normal volunteers. *Electroencephalogr Clin Neurophysiol*, 89(2):120-130

Chen et al. (1997), Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe rages of stimulation parameters. *Electroencephalogr Clin Neurophysiol* 105(6):415-421

Wassermann. (1998), Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. June-5-7, 1996. *Electroencephalogr Clin Neurophysiol* 108(1):1-16

Machii, et al. (2006). Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clinical Neurophysiology*. 117, 455-471.

Safety guidelines: Tables

Safe train durations / number of pulses for single trains of rTMS in healthy subjects

Frequency (Hz)	rTMS intensity (% of motor threshold)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>270/270[a]	>270/270[a]	180/180[b]	50/50[c]	50/50[c]	50/50[c]	50/50[c]	20/20	8/8	8/8	6/6	5/5	4/4
5	10/50[c]	10/50[c]	10/50[c]	10/50[c]	5.7/28	3.9/19	2.7/13	1.95/9	1.8/9	1.2/6	1.1/5	1.2/6	0.9/4
10	5/50[c]	5/50[c]	3.2/32	2.2/22	1.0/10	0.6/6	0.7/7	0.6/6	0.4/4	0.5/5	0.3/3	0.2/2	0.2/2
20	1.5/30	1.2/24	0.8/16	0.4/8	0.3/6	0.2/4	0.2/4	0.1/2	0.2/4	0.2/4	0.2/4	0.1/2	0.1/2
25	1.0/25	0.7/17	0.3/7	0.2/5	0.2/5	0.2/5	0.2/5	0.1/2	0.1/2	0.1/2	0.1/2	0.1/2	0.1/2

The maximum safe train duration (s) is shown followed by the number of pulses. See also [Wassermann (1997)].

[a]Based on [Chen et al. (1997a)].

[b]Based on [Wassermann et al. (1996b)].

[c]No spread of excitation or post-TMS EMG activity was observed at these train durations. Based on [Pascual-Leone et al. (1993)].

Safety guidelines: Tables

Safety recommendation for inter-train intervals for 10 trains of rTMS at less than 20Hz

Inter-train interval (s)	Stimulus intensity (% of MT)			
	100%	105%	110%	120%
5	Safe	Safe	Safe	Insufficient data
1	Unsafe (3)	Unsafe[a]	Unsafe (2)	Unsafe (2)
0.25	Unsafe[a]	Unsafe[a]	Unsafe (2)	Unsafe (3)

The minimum number of trains that caused spread of excitation or post-TMS EMG activity are indicated in the parentheses. The maximum duration/number of pulses for individual rTMS trains at each stimulus intensity should not exceed that listed in . Stimulus parameters produced by reducing a set of parameters that is considered safe (reduction in stimulus intensity, train duration, or increase in inter-train interval) is also considered safe. rTMS at 25 Hz, 120% of MT (0.4 s duration) is unsafe at inter-train intervals of 1 s or less. The safety of longer inter-train intervals at 25 Hz has not been determined.

[a]These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter-train interval, but no adverse event was observed with these parameters.

TMS-induced seizures : Summary

- **Within safety guidelines, in healthy subjects, risk of seizure is very low but still present. (<1 / 1,000 overall estimate; Machii et al 2006)**

- **Risk of seizure increases when rTMS is outside of safety parameters.**

- **Risk of seizure may be higher for patients, due to interaction of disease (e.g. stroke, Epilepsy) and TMS.**

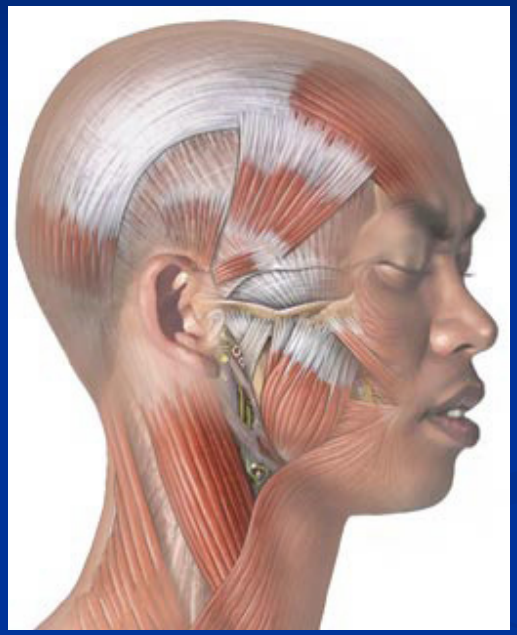
- **TMS-induced seizure ≠ Epilepsy**

- **<u>Balance of risk/benefit</u>**

Other adverse effects

Headache & Neck Pain

- most common adverse effects reported
  - headache ≈ 23%
  - neck pain ≈ 12%

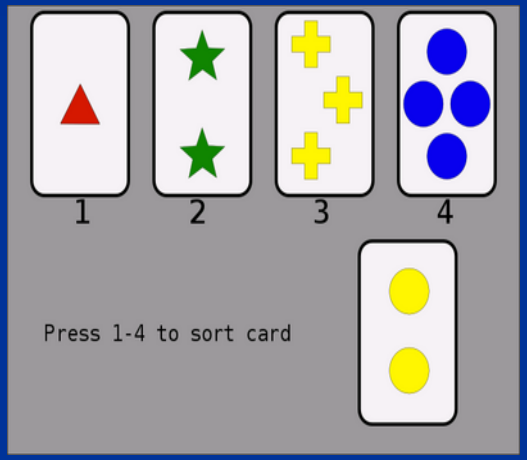


- responds well to analgesics
- contraindication for subjects susceptible to headaches
- shorter blocks; breaks ~ every 5 min

Machii et al., 2006

Neuropsychological & motor effects

- overall no evidence of long term adverse effect on cognitive, perceptual or motor functions (but not sufficiently studied)



Digit Span

3825
94318
596382
7918546
86951372
163874952
7154856193

- some studies observed a trend towards improved working memory and motor reaction time

Pascual-Leone et al. 1993; Wassermann et al. 1996; Jahanshahi et al. 1997; Loo et al.1999, 2001; Speer et al. 2001; Jenkins et al. 2002; Micheal et al. 2003; Wagner et al. 2005; Anderson et al. 2006, Martis, eta al, 2003

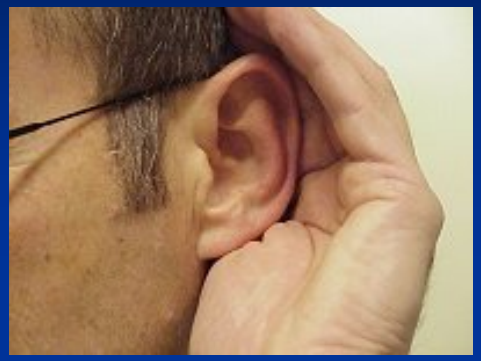
Effects on mood in healthy subjects

- not common in healthy participants - but observed for RPFC & LPFC
- healthy participants (10Hz, 110% MT, 25 - 5sec trains) changes in self-rating
  - L PFC: ↓ happiness, ↑ sadness
- depressed patients: high frequency rTMS to LPFC might improve mood

Pascual-Leone et al. 1996; George et al. 1996

Effects on hearing

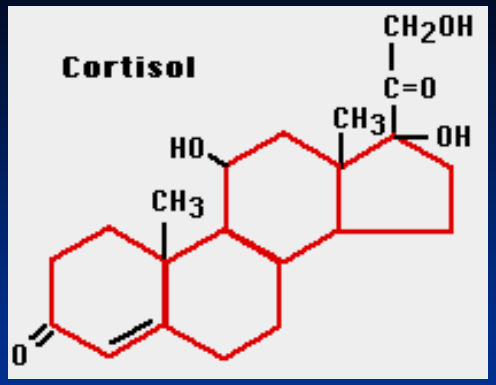
- no permanent hearing loss reported in humans



- rare, but reported:
  - transient rise in auditory threshold
  - tinnitus
  - mild high-frequency hearing loss after several weeks of rTMS
    - ✓ ear plugs recommended

Pascual-Leone et al. 1992; 1993; Loo et al. 2001; Boutros et al. 2002; Anderson et al. 2006

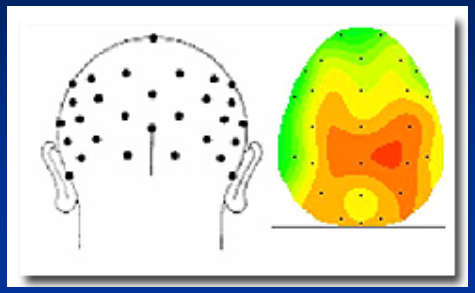
Endocrine effects



- no changes in:
  - prolactin
  - adrenocorticotropic (ACTH)
  - lutenizing- (LH)
  - follicle-stimulating hormones (FSH)
- change reported in:
  - increase in thyroid-stimulating hormone (TSH)
  - acute increase in cortisol (stress?)
- reported effects on neurotransmitters:
  - release of dopamine (caudate nucleus)
  - increase in glutamate/glutamine

Pascual-Leone et al. 1993; George et al. 1996; Wassermann et al. 1996; Cohrs et al. 2001; Evers et al. 2001; Strafella et al. 2001; Padberg et al. 2002; Micheal et al. 2003, Szuba, et al., 1999

Burns from scalp electrodes



risk of heating and skin burns with the use of rTMS near metal surface EEG electrodes

- ✓ the use of MRI compatible electrodes is recommended

Roth et al. 1992

Psychotic symptoms

• psychotic symptoms induced by rTMS to the dorsolateral prefrontal cortex in patients with depression (4 cases)

Garcia-Toro 1999; Dolberg et al. 2001; Zwanzger et al. 2002

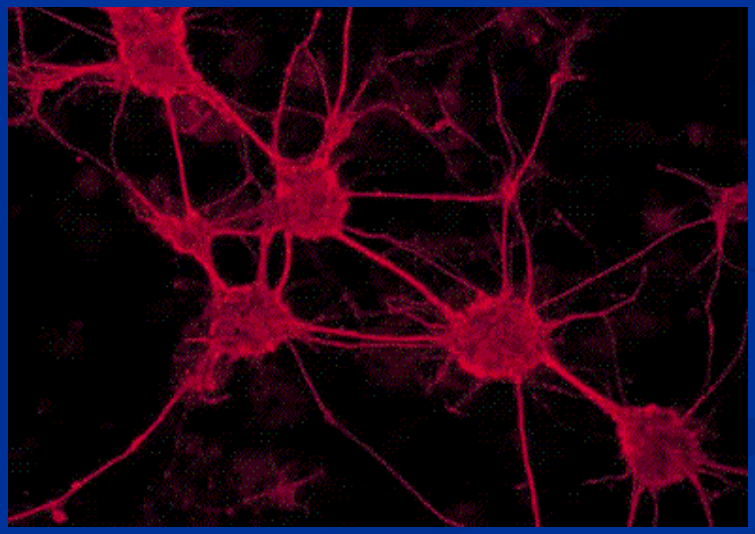
Theoretical risks

Effects that have never been reported in humans with TMS, but remain safety considerations.

- histotoxicity: tissue damage
- kindling
- long-term potentiation
- long-term depression
- effects of magnetic field

Theoretical risks: Histotoxcity

- Evidence from animals: surface electrode stimulation & TMS
- Evidence from TMS in humans



"The chance of excitotoxicity with rTMS in humans seems to be remote."
(Wassermann, 1998)

Theoretical risks: kindling & epileptogenisis

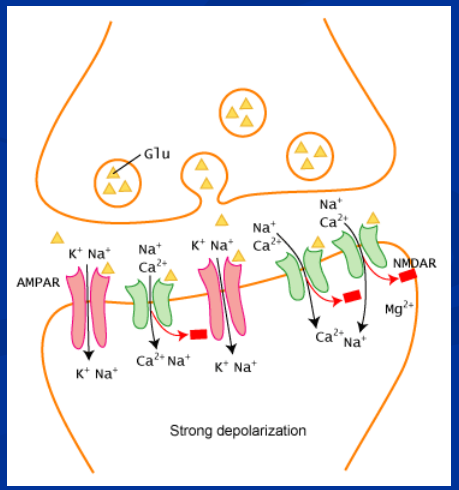
- electrical stimulation can induce kindling in animals
  - conditions necessary for kindling are not met by current TMS protocols
  - no kindling in humans receiving DCS or ECT

Devinky and Duchowny, 1983; Goldensohn, 1984

Theoretical risks: LTP or LTD

electrical stimulation can induce LTP or LTD of synaptic transmission in animals

Iriki et al. 1991; Artola et al. 1991, Ziemann (2004)

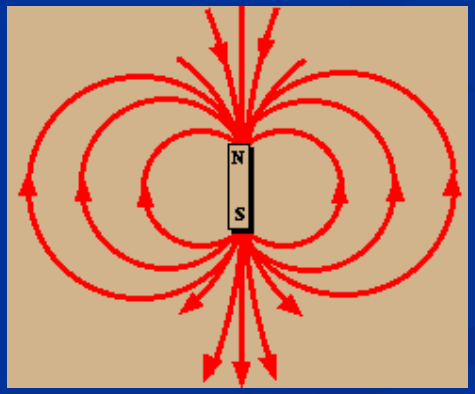


Theoretical risk: magnetic fields

Properties of magnetic field produced by TMS:

- strength in 1.5*T* to 2*T* range
- falls of rapidly with distance from the coil
- rapidly changing

No proven health risks of electromagnetic fields



Contraindications (1)

- intracranial metallic or magnetic pieces
  - transient magnetic field can displace or heat objects
- pacemakers and other implantible medical devices
  - induced pulse may disturb electronic circuitry
- history of seizures or epilepsy
  - including history in a first degree relative
- medications (e.g. TCAs, neuroleptic agents)
  - reduction in seizure threshold
- subjects who are pregnant
  - test those of childbearing potential

Contraindications (2)

- history of serious head trauma
- history of substance abuse
- stroke
- brain surgery
- other medical/neurologic conditions either associated with epilepsy or in whom a seizure would be particularly hazardous

TMS Adult Safety Screen

Have you ever:	Yes	No
-Had an adverse reaction to TMS?	❍	❍
-Had a seizure?	❍	❍
-Had an electroencephalogram ?	❍	❍
-Had a stroke?	❍	❍
-Had a serious head injury (include neurosurgery)?	❍	❍
-Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?	❍	❍
-Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines?	❍	❍
-Do you suffer from frequent or severe headaches?	❍	❍
-Have you ever had any other brain-related condition?	❍	❍
-Have you ever had any illness that caused brain injury?	❍	❍
-Are you taking any medications?	❍	❍
-If you are a woman of childbearing age, are you sexually active, and if so, are you not using a reliable method of birth control?	❍	❍
-Does anyone in your family have epilepsy?	❍	❍
-Do you need further explanation of TMS and its associated risks?	❍	❍

If you answered ***yes*** to any of the above, please provide details:

✓**Adapted from Keel et al. 2001**

Managing the risks

TMS should be administered:

- under the supervision of an appropriate trained and licensed physician
- by a trained *first responder* to render appropriate care in the event of seizure
- in a medical setting with appropriate emergency facilities

Belmaker et al. 2003

Monitoring: during TMS

Subjects should be monitored to:

- detect potential epileptogenic markers (after-discharges and spread of excitation)

- reconstruct the events preceding the seizure

✓ EEG
✓ EMG
✓ visual monitoring

Monitoring: after TMS

Neuropsychological monitoring to assess short and long-term effects on cognitive function

- ✓ Beck scores for patients with depression at different time period
- ✓ Cognitive Assessment

TMS acute side effects questionnaire

symptoms	severity	relationship	notes
headache			
neack pain			
seizure			
scalp burns			
hearing impairment			
impaired cognition			
trouble concentrating			
acute mood change			
other (specify)			

Severity ratings: 1- absent, 2- mild, 3- moderate, 4- severe

Relationship ratings: 1- none, 2- remote, 3- possible, 4- probable, 5- definite

Our lab policies

Staff

- specially trained in recognition and treatment of seizures
- a neurologist is on location during all TMS sessions

Equipment

- the TMS equipment is regularly checked
- a fully equipped “crash cart” with emergency medical equipment is in lab and regularly checked

Supplies

- include IV access equipment, oxygen, and emergency medications for treatment of a seizure
- ear plugs, acetaminophen