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)

<table>
<thead>
<tr>
<th>Train 1</th>
<th>Intertrain Interval</th>
<th>Train 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 pulses</td>
<td>28 sec</td>
<td>40 pulses</td>
</tr>
<tr>
<td>2 sec</td>
<td></td>
<td>2 sec</td>
</tr>
</tbody>
</table>
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**
- histotoxicity
- kindling
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- unknown

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.

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


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

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>rTMS intensity (% of motor threshold)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>&gt;270/270(^{c})</td>
</tr>
<tr>
<td>5</td>
<td>10/50(^{c})</td>
</tr>
<tr>
<td>10</td>
<td>5/50(^{c})</td>
</tr>
<tr>
<td>20</td>
<td>1.5/30</td>
</tr>
<tr>
<td>25</td>
<td>1.0/25</td>
</tr>
</tbody>
</table>

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

\(^{c}\)Based on [Chen et al. (1997a)].

\(^{d}\)Based on [Wassermann et al. (1996b)].

\(^{e}\)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

<table>
<thead>
<tr>
<th>Inter-train interval (s)</th>
<th>Stimulus intensity (% of MT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Safe</td>
</tr>
<tr>
<td>5</td>
<td>Unsafe (3)</td>
</tr>
<tr>
<td>1</td>
<td>Unsafe(^a)</td>
</tr>
<tr>
<td>0.25</td>
<td>Unsafe(^a)</td>
</tr>
</tbody>
</table>

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 table. 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

  - Balance of risk/benefit
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)

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

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
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: Histotoxicity

- 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 & epileptogenesis
- 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

Theoretical risk: magnetic fields

Properties of magnetic field produced by TMS:
- strength in $1.5T$ to $2T$ 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 implantable 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**

<table>
<thead>
<tr>
<th>Have you ever:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Had an adverse reaction to TMS?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Had a seizure?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Had an electroencephalogram?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Had a stroke?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Had a serious head injury (include neurosurgery)?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Do you suffer from frequent or severe headaches?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Have you ever had any other brain-related condition?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Have you ever had any illness that caused brain injury?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Are you taking any medications?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- 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?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Does anyone in your family have epilepsy?</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>- Do you need further explanation of TMS and its associated risks?</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>symptoms</th>
<th>severity</th>
<th>relationship</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neck pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>seizure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scalp burns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hearing impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>impaired cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trouble concentrating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute mood change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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