TMS SAFETY

MOUHSIN SHAFI, MD/PHD
BERENSON-ALLEN CENTER FOR NONINVASIVE BRAIN STIMULATION
BETH ISRAEL DEACONESS MEDICAL CENTER
HARVARD MEDICAL SCHOOL
OVERVIEW

TMS is generally a safe and well-tolerated procedure

• Seizures, often considered the most serious risk, are very rare!
• Side effects are generally quite manageable
• BUT investigators should be prepared to manage the common and uncommon side effects
• Safety considerations in special populations and with devices
Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

Simone Rossi a,n, Andrea Antal b,c, Sven Bestmann d, Marom Bikson e, Carmen Brewer f, Jürgen Brockmüller g, Linda L. Carpenter h, Massimo Cincotta i, Robert Chen j, Jeff D. Daskalakis k, Vincenzo Di Lazzaro l, Michael D. Fox m,n,o, Mark S. George p, Donald Gilbert q, Vasilios K. Kimiskidis r, Giacomo Koch s, Risto J. Ilmoniemi t, Jean Pascal Lefaucheur u,v, Letizia Lecan u, Sarah H. Lisanby x,y,z, Carlo Miniussi z, Frank Padberg aa, Alvaro Pascual-Leone ab,ac,ad, Walter Paulus b, Angel V. Peterchev ae, Angelo Quararone af, Alexander Rotenberg ag, John Rothwell ah, Paolo M. Rossini ah, Emiliano Santarone ci, Mouhsin M. Shafi m, Hartwig R. Siebner bi,ak, Yoshikazu Ugawa al, Eric M. Wassermann am,2, Abraham Zangen an, Ulf Ziemann ao, Mark Hallett ap,2,3,

The basis of this article began with a Consensus Statement from the IFCN Workshop on “Present, Future of TMS: Safety, Ethical Guidelines”, Siena, October 17-20, 2018, updating through April 2020.
# Contents

1. Introduction .......................................................... 271
2. New TMS devices and methods .......................................................... 272
   2.1. Risk analysis and management .......................................................... 272
   2.2. Technical safety .......................................................... 272
   2.3. Stimulation dose safety .......................................................... 273
   2.4. Experimental/animal models .......................................................... 273
   2.5. Manufacturer vs user responsibilities .......................................................... 274
       Manufacturer responsibilities .......................................................... 274
       User responsibilities .......................................................... 274
   2.6. Brief review of new devices and paradigms .......................................................... 275
       2.6.1. New pulse generators and stimulus waveforms .......................................................... 275
       2.6.2. New pulse sequences .......................................................... 276
       2.6.3. New coils .......................................................... 276
       2.6.4. Other paradigms of stimulation (Low field magnetic stimulation; transcranial static magnetic stimulation) .......................................................... 276
       2.6.5. Role of neuroimaging in improving TMS safety .......................................................... 277
       2.6.6. Image-guided frameless navigation and robots for improving TMS safety: an emerging issue .......................................................... 277
3. Safety in combination with other devices .......................................................... 278
   3.1. MRI environment .......................................................... 278
   3.2. Implanted or non-removable intracranial metal or devices .......................................................... 278
BUT THOSE TOO!

3.2.1. Heating ......................................................... 278
3.2.2. Forces and magnetization .................................... 279
3.2.3. Induced electrode current .................................... 279
3.2.4. Malfunction or damage of electronic implants .......... 280
3.2.5. TMS in patients with implanted stimulating/recordings electrodes ........................................ 280
3.2.6. Conclusions and recommendations ...................... 281
3.3. tDCS/AES/DBS ................................................... 281
3.4. Drugs ................................................................. 282

4. Adverse effects ..................................................... 282
4.1. Seizures .............................................................. 282
4.1.1. Risk factors for TMS-provoked seizures .................... 282
Neuropsychiatric disease ........................................ 283
General factors relevant to TMS-provoked seizure ............ 283
Medical factors relevant to TMS-provoked seizure........... 283
4.1.2. The rate of seizures caused by TMS ...................... 284
4.2. Hearing .............................................................. 284
4.3. TMS safety on cognition .......................................... 284
4.3.1. Cognitive TMS effects in experimental studies ........... 284
4.3.2. Cognitive TMS effects in clinical studies ............... 285
4.4. Special issues for children and pregnancy ................. 286
Hearing in pediatrics .............................................. 286
TMS in pregnancy ................................................... 287
5. Magnetic seizure therapy ........................................ 287
6. Side effects in specific patient populations ................ 288
6.1. Neurology and rehabilitation .................................. 289
6.2. Alzheimer’s disease and new multi-site stimulation paradigms .... 289
6.3. Psychiatry ......................................................... 289
7. Update of safety tables ............................................ 291
7.1. Conventional rTMS: low and high frequency .............. 291
7.2. Patterned rTMS: Quadrupulse stimulation (QPS) ......... 291
7.3. Patterned rTMS: theta burst stimulation (TBS) .......... 291
7.4. Paired associative stimulation (PAS) protocols .......... 291
8. Training of operators .............................................. 292
8.1. Requirements for TMS users (summary of IFCN training guidelines) .... 292
8.2. Safety for operators ............................................. 293
9. Regulatory issues and ethics (with a note on neuroenhancement) .... 294
9.1. TMS in research or clinical setting ........................... 294
9.1.1. Basic physiological, non-therapeutic research ........... 294
9.1.2. Therapeutic research ....................................... 294
9.1.3. Therapeutic clinical application ........................... 294
9.2. Steps to mitigate risk ......................................... 295
9.2.1. TMS in vulnerable populations ........................... 295
9.3. Recommendations on minimum safety precautions of different use and settings of TMS .......... 295
9.4. Limitations of current safety data ............................ 295
9.5. Registration, standardized documentation and reporting ...... 296
9.6. A note on neuroenhancement .................................. 296
Declaration of Competing Interest .................................. 297
Acknowledgments .................................................... 297
Appendix A. Supplementary material ........................... 297
References .............................................................. 297
ADVERSE EFFECTS OF TMS

Potential TMS adverse effects include

• Seizures
• Syncope & presyncope
• Hearing changes (Tinnitus, hearing loss)
• Headaches; neck, scalp and dental pain
• Cognitive changes
Seizures from transcranial magnetic stimulation 2012–2016: Results of a survey of active laboratories and clinics

Adam J. Lerner a,*, Eric M. Wassermann b, Diana I. Tamir c,d

a Center for Bioethics, New York University, New York, NY 10003, USA
b Behavioral Neurology Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892, USA
c Department of Psychology, Princeton University, Princeton, NJ 08544, USA
d Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08544, USA
<table>
<thead>
<tr>
<th>Seizure description</th>
<th>Frequency</th>
<th>Target</th>
<th>Diagnosis</th>
<th>Medications</th>
<th>Previous TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &quot;Clinical seizure&quot;</td>
<td>Single/paired-pulse</td>
<td>Frontal cortex</td>
<td>Epilepsy</td>
<td>Valproate, zonisamide</td>
<td>None</td>
</tr>
<tr>
<td>2. Myoclonic</td>
<td>Single/paired-pulse</td>
<td>M1</td>
<td>Myoclonus epilepsy</td>
<td>Antiepileptic(s)</td>
<td>Some (unspecified)</td>
</tr>
<tr>
<td>3. Myoclonic</td>
<td>Single/paired-pulse</td>
<td>M1</td>
<td>Myoclonus epilepsy</td>
<td>Antiepileptic(s)</td>
<td>Some (unspecified)</td>
</tr>
<tr>
<td>4. Secondary generalized</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Epilepsy</td>
<td>Topiramate, valproate, clobazam</td>
<td>None</td>
</tr>
<tr>
<td>5. Partial</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Multiple sclerosis (possible)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Single-pulse</td>
<td>IPS</td>
<td>None</td>
<td>Oral contraceptives</td>
<td>None</td>
</tr>
<tr>
<td>6. Complex partial</td>
<td>Single-pulse</td>
<td>M1</td>
<td>None</td>
<td>None</td>
<td>1 session</td>
</tr>
<tr>
<td>7. Partial</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Tumor</td>
<td>Sertraline</td>
<td>2 sessions</td>
</tr>
<tr>
<td>8. Partial</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Tumor</td>
<td>Levetiracetam, lamotrigine</td>
<td>1 session</td>
</tr>
<tr>
<td>9. Partial</td>
<td>Single-pulse</td>
<td>M1</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>10. Secondary generalized</td>
<td>Single-pulse</td>
<td>IPS</td>
<td>None</td>
<td>Oral contraceptives</td>
<td>None</td>
</tr>
<tr>
<td>11. Generalized</td>
<td>Single-pulse</td>
<td>M1 (round coil at vertex)</td>
<td>Paraparesis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>12. Generalized</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Epilepsy</td>
<td>Clonazepam, pregabalin, zonisamide, levetiracetam, valproate, hydantoin</td>
<td>None</td>
</tr>
<tr>
<td>13. Not reported</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Stroke</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>14. Partial</td>
<td>Single-pulse</td>
<td>M1</td>
<td>Arteriovenous malformation</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>15. Myoclonic</td>
<td>0.3 Hz</td>
<td>M1 (round coil at vertex)</td>
<td>Myoclonus epilepsy</td>
<td>Valproate, zonisamide, levetiracetam, clobazam</td>
<td>None</td>
</tr>
<tr>
<td>16. Generalized</td>
<td>1 Hz</td>
<td>DLPFC</td>
<td>Stroke</td>
<td>Atorvastatin, warfarin</td>
<td>None</td>
</tr>
<tr>
<td>17. Partial</td>
<td>7 Hz</td>
<td>M1</td>
<td>Epilepsy</td>
<td>Valproate, eslicarbazepine, lacosamide, levetiracetam</td>
<td>None</td>
</tr>
<tr>
<td>18. Partial then generalized</td>
<td>10 Hz</td>
<td>M1</td>
<td>Stroke</td>
<td>Some (unspecified)</td>
<td>Some (Unspecified)</td>
</tr>
<tr>
<td>19. Secondary generalized</td>
<td>10 Hz</td>
<td>M1</td>
<td>Stroke</td>
<td>Trifluoperazine</td>
<td>None</td>
</tr>
<tr>
<td>20. Secondary generalized</td>
<td>15 Hz</td>
<td>DLPFC</td>
<td>Schizophrenia</td>
<td>Brexpandine</td>
<td>4 sessions</td>
</tr>
<tr>
<td>21. Secondary generalized</td>
<td>18 Hz</td>
<td>DLPFC</td>
<td>Depression</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>22. Secondary generalized</td>
<td>18 Hz</td>
<td>DLPFC</td>
<td>Depression</td>
<td>None</td>
<td>12 sessions</td>
</tr>
<tr>
<td>23. Generalized</td>
<td>18 Hz</td>
<td>DLPFC</td>
<td>Depression/rheumatoid arthritis</td>
<td>Methotrexate</td>
<td>Unreported</td>
</tr>
<tr>
<td>24. Secondary generalized</td>
<td>20 Hz</td>
<td>DLPFC</td>
<td>Depression</td>
<td>Mirtazapine</td>
<td>None</td>
</tr>
<tr>
<td>25. Secondary generalized</td>
<td>iTBS</td>
<td>M1</td>
<td>Stroke</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
**Table 1**
Seizures by TMS protocol and risk category.

<table>
<thead>
<tr>
<th>TMS Protocol</th>
<th>Total</th>
<th>Elevated subject risk</th>
<th>Elevated protocol risk</th>
<th>Elevated protocol &amp; subject risk</th>
<th>No elevated risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizures</td>
<td>Sessions</td>
<td>Risk</td>
<td>Total</td>
<td>Seizures</td>
</tr>
<tr>
<td>Single/Paired-pulse</td>
<td>13</td>
<td>112,897</td>
<td>.12/1000</td>
<td>10</td>
<td>12,201</td>
</tr>
<tr>
<td>Low-frequency (rTMS ≤ 1 Hz)</td>
<td>3</td>
<td>90,631</td>
<td>.03/1000</td>
<td>3</td>
<td>36,258</td>
</tr>
<tr>
<td>High-Frequency (rTMS &gt; 1 Hz)</td>
<td>4</td>
<td>82,588</td>
<td>.05/1000</td>
<td>3</td>
<td>5215</td>
</tr>
<tr>
<td>Intermittent Theta Burst</td>
<td>1</td>
<td>16,952</td>
<td>.06/1000</td>
<td>1</td>
<td>1813</td>
</tr>
<tr>
<td>Continuous Theta Burst</td>
<td>0</td>
<td>8568</td>
<td>.00/1000</td>
<td>0</td>
<td>826</td>
</tr>
<tr>
<td>H-coil high-frequency rTMS</td>
<td>3</td>
<td>6924</td>
<td>.43/1000</td>
<td>2</td>
<td>872</td>
</tr>
<tr>
<td>Totals</td>
<td>24</td>
<td>318,560</td>
<td>.07/1000</td>
<td>19</td>
<td>57,185</td>
</tr>
</tbody>
</table>

Number of sessions and seizures for different TMS protocols and subject and protocol risk categories. H-coil high-frequency stimulation data are listed separately from standard high-frequency (>1 Hz) data. With the exception of standard high-frequency (>1 Hz) data, other numbers include round, figure-8, "double cone," and H-Crps. Three likely spontaneous seizures (#8, #12, and #17 in Table 3) are included. Seizure #7 is not included because the number of sessions was not reported. No seizures reported; sample size < 1000 sessions.
SOME NOTABLE FACTS

• Majority of seizures (62%) occurred on first exposure to TMS
• With the exception of patients with epilepsy, risk of seizures is very low even in otherwise “high-risk populations”
  • 19 seizures in 57,185 sessions = 0.33/1000
  • At least 8 of these 19 seizures occurred in patients with known epilepsy
• Seizure risk in patients with epilepsy is higher
  • Between 1.4% (Bae et al, 2007) and 2.9% (Pereira et al, 2016)
• Seizure risk may be higher using H-coil device
WHAT ABOUT WITH CLINICAL RTMS?

Seizure risk with repetitive TMS: Survey results from over a half-million treatment sessions

Joseph J. Taylor a, b, *, Noam G. Newberger c, Adam P. Stern d, e, Angela Phillips f, g, David Feifel h, i, Rebecca A. Betensky j, Daniel Z. Press d, k

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation
consistencies. In total, 18 seizures were reported in 586,656 sessions and 25,526 patients across all device manufacturers. The overall seizure rate was 0.31 (95% CI: 0.18, 0.48) per 10,000 sessions, and 0.71 (95% CI: 0.42, 1.11) per 1000 patients. The Brainsway H-coil seizure rate of 5.56 per 1000 patients (95% CI: 2.77,9.95) was significantly higher (p < 0.001) than the three most widely used figure-8 coil devices' combined seizure rate of 0.14 per 1000 patients (95% CI: 0.01, 0.51).

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Per 10,000 Sessions</th>
<th>Per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated Seizure Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>All</td>
<td>0.25</td>
<td>(0.14, 0.42)</td>
</tr>
<tr>
<td>Brainsway</td>
<td>1.56</td>
<td>(0.78, 2.80)</td>
</tr>
<tr>
<td>Magstim</td>
<td>0.00</td>
<td>(0.00, 0.51)</td>
</tr>
<tr>
<td>MagVenture</td>
<td>0.24</td>
<td>(0.03, 0.88)</td>
</tr>
<tr>
<td>Neuronetics</td>
<td>0.03</td>
<td>(0.00, 0.17)</td>
</tr>
</tbody>
</table>
SO WHAT CAN WE CONCLUDE?

BUT you still need to be prepared!
WHAT ABOUT OTHER ADVERSE EFFECTS?

Syncope (Fainting) and presyncope

- True incidence is unknown, but several cases reported. Likely underreported as not as “serious” as seizure
- In study by Lerner et al, 29/174 responding facilities (17%) reported experiencing cases (often multiple) of syncope (much more than seizures)
- Risk factors can include orthostasis, prior history of syncope (including in response to blood draws), history of cardiac issues etc.
- Features suggesting syncopal origin included preceding presyncope / lightheadedness, diaphoresis, nausea; and very short post-event confusion
- Be aware of convulsive syncope as a differential for seizures!
HEARING CHANGES

• TMS is louder than it sounds!
  • Noise level of a single pulse has been reported to be between 125-140 dB! (Koponen 2020, Kukke 2017), but hard to measure using standard sound meters because pulse is so short
  • rTMS may be 95-115 dB (Koponen 2020), well above OSHA safety limits
• Permanent hearing threshold changes reported in one participant whose ear plug slipped out of one ear (Zangen 2005)
• Hearing protection critical (e.g. using 32dB noise-reducing earplugs)
  • No changes in hearing sensitivity after TMS when used (Pascual-Leone 1992, O’Reardon 2007)
• TMS technicians should wear earplugs too!
• Individuals with cochlear implants should NOT undergo TMS
HEADACHES AND MUSCULOSKELETAL PAIN

• The most common TMS side effect
  • Studies in RCTs that systematically capture side effects have reported rates between 28% (Loo 2008) and 65% (Blumberger 2018), much higher than with sham stimulation (typically 10-20%)
• TMS stimulation itself can be painful, particularly to naïve patients
• Musculoskeletal and pain side effects vary greatly depending on location and orientation of stimulation (e.g. DLPFC >> M1)
  • With DLPFC, can get repetitive blinking, eye pain
  • In posterior regions, can get neck muscle and jaw activation
• Headaches typically respond well to OTC analgesics
• Local painfulness of prefrontal rTMS declines over first few days of treatment (Janicak 2008, Anderson 2009)
COGNITIVE CHANGES

• In patients undergoing experimental single-session studies, transient cognitive changes lasting only a few minutes typically reported.

• Following rTMS course for TRD, no clear cognitive gains or cognitive side effects in systematic reviews (McClintock 2019, Iimori 2019).

• Possible “trends toward improvement in the neurocognitive profile” in patients undergoing rTMS for TRD (Serafina 2015).
  • May have some improvement in performance with the Trail Making Test (Martin 2017).
  • Patients with baseline cognitive dysfunction may have improvements in verbal memory associated with improvements in affective symptoms (Gregory 2022).

• Some patients can report transient lightheadedness / “brain fog” immediately at the end of a session, which improves within minutes.
TASK PERFORMANCE CHANGES WITH RTMS
PREGNANCY

• No meaningful / physiologically relevant electric field at the level of the developing fetus (Yanamalda 2017)

• TMS has been used for treatment of depression during pregnancy, with no significant side effects

• Children born to mothers treated during pregnancy with rTMS for depression did not have increased perinatal complications or cognitive/motor developmental abnormalities (Kim 2019)

• Main risk is risk of maternal seizure (which is very low)
Zewdie 2020: Reviewed data from 384 children who received > 3.5 million stimulations at a single center (U of Calgary, Canada)
  - Included >500k stimulations with single- and paired-pulse TMS, and ~3 million stimulations with rTMS
  - No seizures (despite 221 participants having brain injuries or epilepsy)
  - Reported side effects to rTMS include HA (<17%), neck pain (<30%), tingling (<25%), presyncope / lightheadedness (<30%), and nausea (10%)

Hong 2015: No major adverse effects in 76 children receiving TBS
  - HA 6.6%, tingling 2.6%
  - Hearing protection again recommended, but no documented hearing changes
SEIZURES DURING TMS MAPPING

• TMS motor or language mapping carried out in 500 sessions (410 pediatric, 90 adult) in 429 patients. 399 sessions were in patients with dx of epilepsy.
• 29 seizures occurred, 28 of which were in patients with epilepsy. Remaining 1 seizure occurred in patient with brain tumor.
• Most common adverse event was transient pain at stimulation site.
“SAFETY TABLES”
Rossi 2009

Table 4
Maximun safe duration (expressed in seconds) of single trains of rTMS. Safety defined as absence of seizure, spread of excitation or afterdischarge of EMG activity. Numbers preceded by > are longest duration tested. Consensus has been reached for this table.

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Intensity (% of MT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>1</td>
<td>&gt;1800</td>
</tr>
<tr>
<td>5</td>
<td>&gt;10</td>
</tr>
<tr>
<td>10</td>
<td>&gt;5</td>
</tr>
<tr>
<td>20</td>
<td>2.05</td>
</tr>
<tr>
<td>25</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Table 5
Adapted from Table 4 (Part A) and Table 3 (part B) of Chen et al., 1997, with permission from the authors. Safety recommendations for inter-train intervals for 10 trains at <20 Hz. The maximum duration of pulses for individual rTMS trains at each stimulus intensity should not exceed those listed in the Part B of the table. A consensus has been reached in adopting this table at this point. However, there is a need to extend these investigations and provide more detailed guidelines that may apply also to non-motor areas.

<table>
<thead>
<tr>
<th>Inter-train interval (ms)</th>
<th>Stimulus intensity (% of MT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>105%</td>
</tr>
<tr>
<td></td>
<td>110%</td>
</tr>
<tr>
<td></td>
<td>120%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part A</th>
<th>5000</th>
<th>1000</th>
<th>250</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safe</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>5000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>unsafe (EMG spread after 3 trains)</td>
<td>unsafe (EMG spread after 2 trains)</td>
<td>unsafe (EMG spread after 2 trains)</td>
</tr>
<tr>
<td>250</td>
<td>unsafe</td>
<td>unsafe</td>
<td>unsafe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Part B</th>
<th>100%</th>
<th>110%</th>
<th>120%</th>
<th>130%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&gt;270</td>
<td>&gt;270</td>
<td>&gt;270</td>
<td>&gt;180</td>
<td>&gt;180</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>50</td>
<td>5</td>
<td>3.2</td>
<td>32</td>
</tr>
<tr>
<td>20</td>
<td>1.5</td>
<td>30</td>
<td>1.2</td>
<td>0.8</td>
<td>16</td>
</tr>
<tr>
<td>25</td>
<td>1.0</td>
<td>25</td>
<td>0.7</td>
<td>0.3</td>
<td>7</td>
</tr>
</tbody>
</table>

* These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter-train interval, but no adverse effects were observed with these parameters.
Despite such variety, as reviewed for these guidelines, neither seizure occurrence nor other AEs emerged consistently, thus indicating that whatever the protocol of intervention, the technique can be considered basically safe. Therefore, we have decided not to provide a formal update of the previous safety tables, and that, instead, we propose “operational guidelines”. Clearly, the parameters of stimulation used for MST should not be exceeded. The usual lowest parameters of stimulation to induce seizures during MST are 100% of maximal stimulator output (at least for these commercially available devices), frequency of 25 Hz, delivered in a single train lasting up to 10 s. Therefore, every combination of inten-

**Recommendations:** we propose that in all clinical trials and scientific studies that use conventional rTMS protocols, the Principal Investigator (PI) has to: (i) balance the overall risk/benefit ratio of the proposed intervention, (ii) use neurophysiological monitoring (i.e., emergence of motor twitches during stimulation) as a warning for increased cortical excitation, in case the combination of parameters of stimulation exceeds the 2009 safety guidelines, (iii) reconsider the protocol of the trial if a seizure occurs under these circumstances, and iv) alert the scientific community through dedicated scientific journals about the new possibly unsafe combinations of parameters.
WHAT ABOUT OTHER DEVICES

MRI

• Conventional TMS coils and systems are NOT MRI-compatible

• Special MRI-compatible coils are available, restricted to 3T or less scanners
IMPLANTED DEVICES

• TMS pulses delivered >10 cm from implanted pulse generator (IPG) have minimal effective electric field
  • Kuhn 2004: TMS at 2-10 cm from IPG caused malfunction. TMS < 2cm caused permanent damage
  • Considered safe in patients with pacemakers, ICDs
  • We delivered rTMS in patient with ventricular assist device without any complications
• TMS is safe in patients with Vagal Nerve Stimulation (VNS) devices providing stimulation is not applied to the neck
INTRACRANIAL IMPLANTS

- TMS causes minimal heating / displacement of titanium plates / rods / clips
- TMS is NOT safe in patients with cochlear implants
- In patients with DBS, TMS may be not safe if
  - < 10 cm from IPG
  - OR TMS is close to lead, there are loops in the electrode wires under the coil, and high TMS pulses are used (Phielipp 2017)
- Recent work suggests that TMS may be safe in patients with implanted stereotactic EEG electrodes for epilepsy monitoring (Wang 2024 Molecular Psychiatry)
SUMMARY

- TMS is generally safe and very well-tolerated
- The most common side effects are musculoskeletal pain and headache
- Seizures are very rare outside of patients with epilepsy
- TMS can be performed in patients with implanted devices, provided safety guidelines are adhered to