Safety Review for Clinical Application of Repetitive Transcranial Magnetic Stimulation

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HIGHLIGHTS

- Repetitive transcranial magnetic stimulation (rTMS) conforming to the safety guideline is generally safe.
- Any precautions and risks for rTMS should be screened prior to starting rTMS.
- Risk-benefit ratios of rTMS should be carefully discussed in high-risk situations.
Studies using repetitive transcranial magnetic stimulation (rTMS) in healthy individuals and those with neuropsychiatric diseases have rapidly increased since the 1990s, due to the potential of rTMS to modulate cortical excitability in the brain depending on the stimulation parameters; therefore, the safety considerations for rTMS use are expected to become more important. Wassermann published the first safety guidelines for rTMS from the consensus conference held in 1996, and Rossi and colleague then published the second safety guidelines from the multidisciplinary consensus meeting held in Siena, Italy in 2008, on behalf of the International Federation of Clinical Neurophysiology. More than 10 years after the second guidelines, the updated third safety guidelines were recently published in 2021. The general safety guidelines for conventional rTMS have not substantially changed. Because the most frequently used rTMS protocol is conventional (low- and high-frequency) rTMS in research and clinical settings, we focus on reviewing safety issues when applying conventional rTMS with a focal cortical stimulation coil. The following issues will be covered: 1) possible adverse events induced by rTMS; 2) checklists to screen for any precautions and risks before rTMS; 3) safety considerations for dosing conventional rTMS; and 4) safety considerations for using rTMS in stroke and traumatic brain injury.

Keywords: Repetitive Transcranial Magnetic Stimulation; Safety; Seizures; Stroke; Traumatic brain injury

INTRODUCTION

Studies using repetitive transcranial magnetic stimulation (rTMS) in healthy individuals and those with neuropsychiatric diseases have rapidly increased since the 1990s [1,2], due to the potential of rTMS to modulate cortical excitability in the brain depending on the stimulation parameters [3]. Recent evidence-based guidelines have recommended the application of rTMS in various neurological and psychiatric diseases, with higher evidence of efficacy in depression, pain, and motor recovery after stroke [2]. Therefore, rTMS use in research and clinical settings is anticipated to become more common, and the safety considerations for rTMS use are expected to become more important.
Wassermann [4] published the first TMS safety guidelines from the consensus conference held in 1996, and Rossi et al. [1] then published the second safety guidelines from the multidisciplinary consensus meeting held in Siena, Italy in 2008, on behalf of the International Federation of Clinical Neurophysiology. More than 10 years after the second guidelines, the updated third safety guidelines were published in 2021 [5]. The general safety guidelines for conventional rTMS did not substantially change in the new safety guidelines. Because the most used rTMS protocol is conventional (low- and high-frequency) rTMS in research and clinical settings, we focus on reviewing the safety issues when applying conventional rTMS with a focal cortical stimulation coil (e.g., a figure-8 coil). The following issues will be covered: 1) possible adverse events induced by rTMS; 2) checklists to screen for any precautions and risks before rTMS; 3) safety considerations for dosing conventional rTMS; and 4) safety considerations for using rTMS in stroke and traumatic brain injury (TBI). Updated safety issues for new devices (e.g., new pulse generators or new coils), other stimulation paradigms including patterned rTMS and paired associated stimulation, as well as combinations with other devices, are comprehensively reviewed in the 2021 safety guidelines by Rossi et al. [5].

**ADVERSE EVENTS**

**Seizures**

Seizures induced by rTMS are the most concerning acute adverse event, and can occur during or immediately after rTMS or during the after-effects of rTMS due to the long-lasting modulation of cortical excitability. In a recent systematic review including 93 placebo-controlled clinical trials (n=1,854 in the placebo-treated group and n=2,290 in the TMS-treated group), the risk of seizures was extremely low (0.1% in the active TMS group and 0.2% in the placebo group) [6]. Lerner et al. [7] conducted a survey to investigate observed seizures between 2012 and 2016 in 714 active laboratories or clinics, which reported an estimated 318,560 TMS sessions. Overall, TMS induced rare cases of seizures (24 seizures, 8/100,000 sessions). Only 4 seizures (<2/100,000 sessions) occurred when TMS was delivered within the dosing parameters according to previously published guidelines in subjects without risk factors (e.g., brain lesions and epilepsy) [1,4]. The total risk of seizures was comparable between different rTMS protocols (low frequency: 3/1,000,000 sessions, high frequency: 5/1,000,000 sessions, intermittent theta burst: 6/1,000,000 sessions, continuous theta burst: 0/6,924 total sessions). No seizure cases were reported in either low- or high-frequency rTMS delivered within the specifications of the published guidelines to subjects with no risk factors for seizure. Therefore, the risk of seizures induced by rTMS is low if the stimulation parameters are within the previously published safety guidelines and focal coils [5]. However, since seizures can arise in any subject and using any rTMS protocol [8], medical readiness to deal with a seizure during rTMS and immediately after the rTMS session is necessary, especially when treating individuals with risk factors (Table 1).

**Syncope**

Vasovagal syncope is common during noninvasive or minimally invasive medical procedures due to procedure-related anxiety or psychophysical discomfort, which can lead to fall-related injuries. In the survey by Lerner et al. the most common adverse events were syncope or presyncope (17% among 174 respondents) [7]. Distinguishing syncope from seizure is often difficult, but the following symptoms and signs may favor syncope over seizure: light-headedness, sweating, pallor, slow pulse, and low blood pressure [16].

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Hearing

rTMS can evoke a transient repetitive acoustic artifact with a maximum sound pressure level ranging from 96.5 to 110 dB [17,18], which exceeds the 80 dB safety threshold, for 3 seconds. Moreover, conventional sound measurements cannot quantify the bone conduction through skull during rTMS and can underestimate the acoustic artifact [18,19]. The effect of the acoustic artifact induced by rTMS on the subject’s ear can be influenced by the simulation intensity, frequency, coil type, stimulation site (proximity to the ear) and pre-existing auditory symptoms (e.g., tinnitus). The recent expert guidelines recommended well-fitted hearing protection (e.g., earplugs) for both subjects and rTMS operators, and careful screening for any hearing-related complaints after rTMS [5].

Other minor side effects

Headache or local pain around the stimulation site after TMS was found to be common (16% among respondents from active laboratories or clinics) [7]. In a systematic review on the safety of rTMS for depression including sham-controlled studies, headache (28%) and local pain or discomfort (39%) were also common [20]. The cause of pain during rTMS is not clear, but it is postulated that scalp or upper facial muscle contractions or trigeminal stimulation by rTMS may play a role [1]. The headache and local pain is usually transient and long-term continuation of pain after rTMS is rare. Acute psychiatric changes (e.g., mania, hypomania, anxiety, agitation, or psychotic symptoms) have been reported in several rTMS studies and the survey by Lerner et al., but the occurrence rate is low and these changes were usually transient [1,5,7,21-23]. Moreover, most studies reporting acute psychiatric changes after rTMS were conducted in patients with psychiatric disorders; therefore, it is unclear whether these psychiatric symptoms are induced by rTMS or occurred during the natural course of the underlying psychiatric disorders [5,21-23]. However, the recent safety guidelines by Rossi et al. [5] recommended that “patients with depression undergoing rTMS should be informed about the unlikely possibility of developing acute psychiatric side effects.”

CHECKLISTS FOR rTMS CANDIDATES

To reduce the potential risk of adverse events induced by rTMS, checklists to screen rTMS candidates must be considered (Table 2) [1].
SAFETY CONSIDERATIONS ON DOSING PARAMETERS FOR rTMS

The consensus-based safety table for conventional rTMS (low- or high-frequency) using a figure-8 coil was presented in the previous guidelines by Rossi et al. in 2009 (Tables 3-5) [1]. These safety tables were considered to be effective to prevent seizure in healthy subjects and patients, and no revisions were made in the 2021 safety guidelines [5]. In high-frequency rTMS, an inter-train interval of more than 5 seconds is usually considered to be safe (Tables 4 and 5). The maximal safe duration of a single rTMS train according to the frequency and stimulation intensity also must be considered. For example, the safe parameters for 10 Hz rTMS with a stimulation intensity of 110% of the resting motor threshold using a figure-8 coil according will be an inter-train interval of >5,000 ms, with up to 5 seconds (50 pulses) in a single rTMS train (Tables 3-5). A longer duration of the inter-train interval is considered

Table 2. Checklist for rTMS candidates [1]

| Checklist                                                                 |
|--------------------------------------------------------------------------|
| History of epilepsy, convulsion or seizure, syncope                       |
| History of a severe head trauma                                           |
| Presence of any hearing problems or tinnitus                              |
| Pregnancy or any chance of pregnancy                                      |
| Any metal in the brain/skull                                              |
| Cochlear implants, internal pulse generators                              |
| Any medications that lower the seizure threshold                          |
| Previous experiences of rTMS (e.g., any side effects induced by previous rTMS) |

Table 3. Maximum safe duration (seconds) of single trains of conventional rTMS using a figure-8 coil

| Frequency (Hz) | 90%         | 100%         | 110%         | 120%         | 130%         |
|----------------|-------------|-------------|-------------|-------------|-------------|
| 1              | >1,800      | >1,800      | >1,800      | >360        | >50         |
| 5              | >10         | >10         | >10         | >10         | >10         |
| 10             | >5          | >5          | >5          | 4.2         | 2.9         |
| 20             | 2.05        | 2.05        | 1.6         | 1.0         | 0.55        |
| 25             | 1.28        | 1.28        | 0.84        | 0.4         | 0.24        |

*" indicates the longest duration tested. This table is adapted from Rossi et al. [1] with permission for electronic reuse from the publisher.
rTMS, repetitive transcranial magnetic stimulation.

Table 4. Safety recommendations for inter-train intervals for 10 trains at <20 Hz

| Inter-train interval (ms) | Stimulation intensity (% of resting motor threshold) |
|--------------------------|-----------------------------------------------------|
|                          | 100%       | 105%      | 110%      | 120%      | Insufficient data |
| 5,000                    | Safe       | Safe      | Safe      |           |               |
| 1,000                    | Unsafe*    | Unsafe†   | Unsafe*   | Unsafe*   |               |
| 250                      | Unsafe†    | Unsafe†   | Unsafe†   | Unsafe*   |               |

*EMG spread after 2 or 3 trains; †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.

Table 5. Safety recommendations for maximal duration of pulses for individual rTMS trains at each stimulus intensity

| Frequency (Hz) | 100% Durations (sec) | 100% Pulses (No.) | 110% Durations (sec) | 110% Pulses (No.) | 120% Durations (sec) | 120% Pulses (No.) | 130% Durations (sec) | 130% Pulses (No.) |
|----------------|----------------------|-------------------|----------------------|-------------------|----------------------|-------------------|----------------------|-------------------|
| 5              | 10                   | 50                | 10                   | 50                | 10                   | 50                | 10                   | 50                |
| 10             | 5                    | 50                | 5                    | 50                | 3.2                  | 32                | 2.2                  | 22                |
| 20             | 1.5                  | 30                | 1.2                  | 24                | 0.8                  | 16                | 0.4                  | 8                 |
| 25             | 1.0                  | 25                | 0.7                  | 17                | 0.3                  | 7                 | 0.2                  | 5                 |

This table is adapted from Rossi et al. [1] with permission for electronic reuse from the publisher.
rTMS, repetitive transcranial magnetic stimulation.
as the number of rTMS trains increases. However, an enormous variety of combinations of rTMS parameters, some of them exceeding the safety limits, have been applied in numerous rTMS papers. The 2021 safety guidelines recommend that “the principal investigator has to balance the overall risk/benefit ratio of the proposed intervention and use neurophysiological monitoring in case the combination of parameters of stimulation exceed the 2009 safety guidelines” [5]. Regarding the safety parameters of patterned rTMS (quadripulse stimulation, theta burst stimulation), supplementary tables S3 and S5 in the 2021 safety guidelines should be consulted [5].

SAFETY CONSIDERATIONS IN STROKE AND TBI

Stroke
rTMS to improve the recovery of motor and non-motor impairments has been actively investigated [24,25]. In recent large clinical trials of low-frequency rTMS using a figure-8 coil in subacute or chronic stroke, no seizure was reported and serious adverse device events were not statistically significantly different between real and sham rTMS [26,27]. In a recent systematic review of rTMS and upper limb motor recovery after stroke [28], only three studies reported adverse events among 28 studies monitoring adverse events, and these events were minor and transient (e.g., mild headache, nausea, neck pain, dizziness, tingling sensation, abnormal sleep) [29-31]. In addition, no serious adverse events were reported for high-frequency rTMS [28]. In a systematic review of high-frequency rTMS for post-stroke depression, minor adverse events including headache, loss of appetite, local pain, local discomfort, and anxiety were reported in 6 studies [32]. Among those reported adverse events, only headache was more common in the high-frequency rTMS group than in controls. Therefore, rTMS within the parameters of the safety guidelines is generally safe in patients with stroke, but the individual risk-benefit ratio for rTMS should be evaluated, especially for patients with an elevated risk of seizure or requiring precautions for rTMS, and when new devices or protocols are applied.

TBI
In a recent scoping review by Pink et al. [33], 30 empirical rTMS studies including case reports and randomized controlled trials in patients with traumatic brain injuries were fully reviewed. Although most studies reported no adverse events [34-36] or minor side effects such as headache, dizziness, and fatigue [37-39], Cavinato et al. [40] reported a partial and secondarily generalized tonic-clonic seizure after the fourth daily session of 20 Hz rTMS within the parameters in the safety guidelines. Pape et al. [41] also reported an electroencephalographic seizure without clinical accompaniment after the 21st excitatory rTMS session in a 32-year-old man with disordered consciousness after TBI. In an open-label study including seven patients with disordered consciousness after traumatic brain injuries, 75 nonserious adverse events and one seizure were reported during total 30 excitatory rTMS sessions (300 pulses/session) over the right or left dorsolateral prefrontal cortex [42]. One patient with a seizure event during the rTMS trial continued planned rTMS sessions with antiepileptic drugs and no seizure recurrence was observed. Therefore, rTMS protocols for TBI patients conforming to the safety guidelines [1] seem generally to be safe, but the potential for seizure induction and any precautions for rTMS should be thoroughly evaluated based on the clinical information before rTMS. Possible seizure events should also be closely monitored during and after rTMS sessions with an appropriate seizure management plan.
SUMMARY

rTMS conforming to the current safety guidelines (Tables 3-5) can be applied safely to both healthy volunteers and patients with acquired brain diseases such as stroke and TBI. However, the principal investigator and clinician should screen rTMS candidates with a checklist (Table 2) to identify any contraindications and precautions for rTMS, as well as risk factors for rTMS-induced major side effects such as seizures (Table 1). If rTMS candidates have higher risks for serious adverse events or rTMS protocols are not considered to be safe (e.g., parameters exceeding safety guidelines, a new stimulation paradigm, new stimulation devices), the risk-benefit ratio should be carefully evaluated, and an adequate management and monitoring plan should be established prior to rTMS.

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