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Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.10.003.

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Abstract

This article is based on a consensus conference, promoted and supported by the International Federation of Clinical Neurophysiology (IFCN), which took place in Siena (Italy) in October 2018. The meeting intended to update the ten-year-old safety guidelines for the application of transcranial magnetic stimulation (TMS) in research and clinical settings (Rossi et al., 2009). Therefore, only emerging and new issues are covered in detail, leaving still valid the 2009 recommendations regarding the description of conventional or patterned TMS protocols, the screening of subjects/patients, the need of neurophysiological monitoring for new protocols, the utilization of reference thresholds of stimulation, the managing of seizures and the list of minor side effects.

New issues discussed in detail from the meeting up to April 2020 are safety issues of recently developed stimulation devices and pulse configurations; duties and responsibility of device makers; novel scenarios of TMS applications such as in the neuroimaging context or imaging-guided and robot-guided TMS; TMS interleaved with transcranial electrical stimulation; safety during paired associative stimulation interventions; and risks of using TMS to induce therapeutic seizures (magnetic seizure therapy).

An update on the possible induction of seizures, theoretically the most serious risk of TMS, is provided. It has become apparent that such a risk is low, even in patients taking drugs acting on the central nervous system, at least with the use of traditional stimulation parameters and focal coils for which large data sets are available. Finally, new operational guidelines are provided for safety in planning future trials based on traditional and patterned TMS protocols, as well as a summary of the minimal training requirements for operators, and a note on ethics of neuroenhancement.

Keywords

TMS; rTMS; TBS; QPS; Safety; Neuromodulation; Neurology; Psychiatry

1. Introduction

This is the third article on safety of use of repetitive Transcranial Magnetic Stimulation (rTMS) in clinical practice and research following by eleven years the last IFCN guidelines (Rossi et al., 2009), which itself followed the first guidelines by eleven years (Wassermann, 1998). To minimize redundancy, the current update (that began at the meeting in October 2018 and lasted up to April 2020) does not cover again some basic topics that have previously been fully discussed and approved on a consensus basis, nor will it discuss again certain guidelines and recommendations to prevent adverse effects which have proved useful in the interim: the need for neurophysiological monitoring for every new intervention protocol that exceeds, or is close to, the limits suggested in the original safety tables (Wassermann, 1998); pros and cons on resting motor threshold (RMT) or phosphene threshold as reference for “dosing” rTMS; minor side effects as local pain, headache or discomfort; description of conventional or patterned TMS protocols; and screening questionnaires for subjects/patients undergoing rTMS.

Rather, the update focuses on recent technological developments of stimulation devices and pulse configuration, including duties for device manufacturers, novel scenarios of application such as TMS in a neuroimaging context or imaging- and robot-guided TMS and TMS interleaved with other techniques of transcranial electrical stimulation (TES), as well as potential risks of new pharmacological interactions, especially in patient populations. Potential risks of paired associative stimulation (PAS) techniques are also covered.

We also address risks of magnetic-seizure therapy (MST), a topic that was not covered in previous guidelines. We provide an update on TMS-induced seizures, which remains the most serious risk of this technique, although by now it is certain that such a risk is very low. In this framework, we also remark on the need to distinguish at a clinical level between seizure and convulsive syncope. Finally, new operational guidelines will be provided for traditional and patterned TMS protocols whenever substantial data are available, as well as a summary of the minimal training requirements for operators.

When encountered in the text, the term “new” is intended to be in regard to previous 2009 safety guidelines, with the exception of “new” TMS devices which refers to the state of evidence for their safety.

Current guidelines reflect expert opinion based on the available evidence. The rating of the level of evidence is something that would have been very useful. Unfortunately, this is impossible, as virtually none of the studies were done with the specific purpose of assessing safety. In these studies, the safety information is just incidental.

In order to facilitate reading, in Table 1 we report the standardized classification of adverse events (AEs), with relative abbreviations. “Serious” adverse events (SAEs) are defined as those events which are life-threatening, result in death, require patient’s hospitalization or prolongation of their hospitalization.

2. New TMS devices and methods

This section addresses safety and risk management relevant to any new TMS device or method of use. For the purpose of this section, a TMS device or method of intervention is considered new when first introduced or functionally reconfigured (e.g., with new waveforms, coils, pulse train patterns, or intensity) by a device maker or user. A device will remain to be considered new until sufficiently strong evidence of safety is generated, regardless of absolute chronology. Devices and specific paradigms that have been subject of significant clinical testing, including as part of regulatory clearance [e.g., by the US Food and Drug Administration (FDA)], would not be considered new; guidelines for them will be discussed in subsequent sections of this document. Those recommendations for established TMS systems cannot automatically be applied directly to new TMS devices and paradigms, and new TMS devices generally require additional risk analysis and management.

2.1. Risk analysis and management

Risk analysis is warranted whenever there is a change in the TMS equipment or method of use, including hardware and software configuration, dose selection, environment, or subject population that result in potential new risks compared to TMS devices and methods with established safety records. Changes to complementary technologies and methods such as neuronavigation, coil holders, dosing algorithms, electroencephalography (EEG), electromyography (EMG) and magnetic resonance imaging (MRI) scanners may also affect risk. New instrumentation or methods do not necessarily imply increased risks; the risk level may possibly be lowered with more accurate targeting, optimized electric field (Efield) shaping, more sensitive and specific detection of responses, or more efficient threshold or dose determination algorithms. However, even if the risk analysis suggests unchanged or lower risks, when new technologies and methods of use are deployed, increased vigilance is warranted. The process (framework) of risk analysis for new TMS systems is already established through regulations such as those governing human trials [e.g., Institutional Review Board (IRB) approval] and medical device manufacturing (e.g., IEC/IEEE standards). Therefore, the following sections should not be understood as suggesting additional or new processes, but rather providing insight on how to apply relevant existing processes for new TMS devices and paradigms. Risk analysis and management is the overall principle guiding these processes. In deciding whether to proceed with a new TMS approach (either device or protocol), risk is also considered against benefit.

2.2. Technical safety

Technical safety of a TMS device refers to hazards to the subject or operator other than those related to the effects of the E-field induced in a body when the intended magnetic field is generated around the TMS coil. For example, technical aspects relevant to TMS safety include electrical insulation of high voltages; heating, vibration, fractures, acoustic clicking, biocompatibility and weight of the coil; reliability of generating the intended magnetic field; electromagnetic interference with other devices; neck pain due to head posture; headache or neck pain due to pressure on the scalp; and human factors (e.g., incorrect use or access by unqualified personnel) (Ruohonen and Ilmoniemi, 2005).

Technical safety is largely an issue of medical equipment design, manufacturing, maintenance, and proper use. Risk management for technical safety begins with compliance of the design and manufacturing with relevant medical device safety standards and guidelines, as well as consideration of novel contexts in which the device is intended to be used, such as in conjunction with another device such as an MRI scanner or EEG equipment. As applicable, national regulatory agencies (such as EU and Asian regulators and USA FDA) require compliance with a range of medical equipment standards; such standards indicate equipment-specific testing and cannot be based on “equivalence” when the hardware is unique (U.S. Department of Health and Human Services, 2011).

The risk management during the design, manufacture, delivery, maintenance, and use of medical devices as a formal process is the cornerstone for guaranteeing safety. It should be performed continuously throughout the device lifecycle. Formal risk management is defined as the application of engineering practices to analyze, evaluate, and control risk. As applicable, practices of risk management for medical devices can be informed by various national and international standards, including the ISO 14971 standard (International Organization for Standardization, 2007). The process involves identifying possible ways in which the device could bring harm to a user or patient. Then, the device maker determines the likelihood of occurrence of each potential risk and their gravity (e.g., the severity of the potential harm should the risk be realized, ranging from minor inconvenience to severe injury). Finally, the maker identifies and implements safety measures, called mitigators, that act to reduce each identified risk to an acceptable level. These can span warning labels (instructions) to features that automatically shut down the device when errant conditions are detected.

2.3. Stimulation dose safety

Stimulation dose safety refers to the effects of the TMS magnetic field with the intended dose induced in the body of anyone exposed to the field, including subject, operator, bystander, or fetus. The dose of TMS is defined as all device parameters that influence the generated magnetic field and the resultant induced E-field in the body (Peterchev et al., 2012). TMS accessories such as coil arms, neuronavigation, and software can affect the dose selection and delivery. The risks of stimulation can be subject-dependent. A stimulation dose that is safe for one subject may not be safe for another, e.g., because of a different seizure threshold or interaction with different drugs. Doses that are considered safe may depend on the cortical region that is targeted by stimulation and may differ depending on

the precise shape of the E-field that is generated by a specific coil. Moreover, the subject or operator may have implants or other objects attached to their body that introduce risk when exposed to the magnetic field and/or E-field (see Section 3.2). Further, because of different risk-benefit ratios, the criteria of what is an acceptable risk may vary when applied to a subject, pregnant woman, or patient who is the intended target of TMS versus an operator or fetus who are not targeted. Stimulation dose may be hard-limited by equipment design or guided by device instructions (indications for use), but given that most TMS devices allow for a wide range of waveforms, coil placements and off-label use, stimulation dose safety largely relies on risk management by the operator (see Section 2.5).

Risk analysis of the stimulation dose of new TMS devices or protocols begins with theoretical considerations related to the induced magnetic field, computational models or estimates of the resulting induced E-field, and theories or evidence of how pulse train parameters affect relevant neuronal activation. Given certain unknowns about the neurobiological mechanisms of TMS, comparison with the electromagnetic output and effects of other devices and protocols is useful, including documented AEs and approvals of instruments by regulatory agencies around the world. Risks to be evaluated include (but are not necessarily limited to) effects on the brain (e.g., seizures or thought processing), on implanted objects (e.g., cardiac pacemakers, brain implants, hearing aids, surgical clips), and on a fetus and operator. With the most significant established dose-related risk of TMS being induction of seizure, changes that may affect seizure threshold should be weighed, including alterations in the E-field distribution (e.g., more distributed field or field in new brain regions); temporal pulse repetition rates, patterns, or number of pulses; pulse waveforms; or intensity selection and individualization. For example, holding other parameters constant, one would generally expect higher risk for strong versus weak pulse intensities and more versus fewer pulses. When, based on such analysis, new potential risks are identified, then additional safety studies and careful safety monitoring during a research or clinical study are warranted.

Risk analysis can include evidence of one or more TMS predicates. This “biological effect equivalence” with predicates is based on stimulation dose safety. For stimulation dose safety (and efficacy), this is a model adopted by regulatory agencies such as the FDA when evaluating the safety and efficacy of TMS. Whereas, starting in 2008, the approval of the first rTMS system by the FDA involved substantial clinical trials with measures of efficacy and safety, new systems may be approved with little or no clinical trials if “the proposed device is sufficiently similar to the predicate device in terms of indications, device specifications, and energy output” (U.S. Department of Health and Human Services, 2011). When new TMS devices have equivalent output, i.e. can provide stimulation doses for the same indications as comparative (approved) predicate devices, FDA considers them to be capable of the same clinical performance demonstrated by the predicate. Note that when a device cleared by a regulatory body is used in an off-label manner (e.g., a waveform available through a research mode, a patient population not included in the original label, or a new coil), risk analysis is warranted and the sanctioning by the regulatory agency may or may not apply.

2.4. Experimental/animal models

An ongoing body of work on animal models has been steadily accumulating since the 2009 TMS safety guidelines. Most of the studies were performed in rodents or using in-vitro preparations, with the bulk of this work originating from a small number of specialized groups investigating mechanisms of action of TMS and the translational potential for clinical applications. In the following two paragraphs some emerging issues potentially relevant for safety are highlighted, as they raise two types of questions: (i) whether rTMS effects can act by eliciting action potentials or modulating axon membrane potentials only, or also by inducing intracellular changes in neuron architecture, axonal transport, or cytoskeleton; (ii) and therefore whether the magnetic field can influence cellular targets other than neurons, beyond the mechanisms affecting transmembrane potential (Rodger and Sherrard, 2015).

Key work in this sense has been carried out to understand the role of cortical inhibitory interneurons in plasticity induction. This work has highlighted the ability of protocols such as theta burst stimulation (TBS) to modulate fast spiking neurons (Funke and Benali, 2011; Trippe et al., 2009). At the cellular level, single-pulse TMS has been shown to induce GABA-mediated inhibition of cortical dendrites in layer V pyramidal neurons (Murphy et al., 2016), while very high intensity TMS in a rat model has been shown to transiently increase permeability across the blood brain barrier in a mechanism that is mediated by glutamate release (Vazana et al., 2016). An important technical achievement has been the development of a system in primates for focal TMS and single neuronal recording at the coil focus (Mueller et al., 2014). This work follows the fundamental work combining TMS with electrophysiological recordings undertaken in cat visual cortex (Allen et al., 2007; Moliadze et al., 2003). Using this setup, action potentials were recorded around 1 ms after the TMS pulses (Li et al., 2017).

It has been shown that low-intensity magnetic stimulation using small (<10 mm in diameter) circular coils with an iron core generating fields of less than 100mT at their surface modulate intracellular calcium release (Grehl et al., 2015), influence motor learning (Tang et al., 2018), increase levels of brain derived neurotrophic factor (BDNF) (Kim et al., 2016), induce topographical changes in visual cortex (Rodiger et al., 2012; Makowiecki et al., 2014) generate electrophysiological effects in in-vitro preparations that last beyond the stimulation period (Lenz et al., 2016; Tang et al., 2016a; Vlachos et al., 2012), and especially induce axon outgrowth and neural repair, possibly due to the presence of cryptochrome, a magnetoreceptor able to activate intracellular signaling cascades (Dufor et al., 2019; Sherrard et al., 2018).

Effects of repeated rTMS sessions have received attention with regard to mechanisms and safety. For example, following repeated sessions of 10 Hz rTMS over 5 days in rats, no changes were found in development of body and organ weights in female rats (Sato et al., 2017). However, high-intensity stimulation (150% of RMT) induced thinning of post-synaptic density, disordered synaptic structure, reduced the number of synapses, and downregulated BDNF–TrkB and synaptic proteins (Ma et al., 2014). Following 2000 pulses at 100% of RMT in a rat model, no evidence of DNA damage in brain cells was seen (de Sauvage et al., 2008). A study in which aged mice were exposed to 25 Hz rTMS over 14 days, showed a reversal of certain metabolic and behavioral markers of cognitive decline

(Wang et al., 2013); a study in a guinea pig model found that 10 daily sessions of 1 Hz low-intensity stimulation significantly reduced tinnitus without affecting BDNF levels or hyperactivity (Mulders et al., 2016), and a study in an animal model of depression found that 10 days of low- (1 Hz) or high-frequency (20 Hz) stimulation generated antidepressant effects (Hesselberg et al., 2016).

Finally, initial studies with regard to the pro- and anti-convulsant effects of TMS were examined in dedicated rat models (Chameh et al., 2015; Lin et al., 2014; Shojaei et al., 2014). The role of anesthesia in animal TMS studies on findings has been highlighted (Gersner et al., 2011) in which high-frequency rTMS in rats led alternatively to decreased and raised levels of neuroplasticity markers such as BDNF in anesthetized and awake animals, respectively. Diagnostic TMS in anesthetized rats showed that while long-interval cortical inhibition (LICI) was observed, its level was significantly reduced following injection of a convulsant agent, although single-pulse measures of excitability were unchanged (Vahabzadeh-Hagh et al., 2012). Metabolic effects of single sessions of high- versus low-frequency rTMS have been investigated using microPET in a rat model (Parthoens et al., 2014). Regional distribution of cerebral uptake of [18F]-PET was found to be largely similar between 1 Hz and 50 Hz sessions, (but the scale of uptake was larger for the high frequency), while high- (10 Hz) and low-frequency (1 Hz) stimulation differently affect regional cerebral blood flow, with more widespread or more pronounced effects, respectively (Wyckhuys et al., 2013).

Several issues need to be considered when translating the findings in rodent models to the safe use of TMS of the human brain (Vahabzadeh-Hagh et al., 2012). Many studies use electrical rather than inductive magnetic stimulation in small animal models (that moreover have to be anaesthetised) in order to better mimic the effects of TMS due to the impact of head size and coil-to-brain ratio on the distribution of induced fields (used for example by (Levy et al., 2007; Moshe et al., 2016), and the translational implications have been discussed. Finally, a significant body of work has addressed the issue of building practical and efficient TMS coils for small animals (for example, Rastogi et al., 2016; Tang et al., 2016b).

In summary, while TMS studies in small animals are by now not conclusive, mainly because focality of stimulation in these circumstances cannot be achieved, (thus, they do not directly mirror the actual stimulation conditions in humans), they still play an important role in investigating its basic mechanisms. Preclinical TMS studies are important for demonstrating safety at cellular and genetic levels, and they facilitate development of novel protocols and techniques.

2.5. Manufacturer vs user responsibilities

Technical and stimulation-dose safety should be analyzed and managed during both manufacturing and the use of TMS devices.

Manufacturer responsibilities—Risk management and quality assurance must be implemented by the entity that designed and constructed the TMS device, which is typically a commercial manufacturer but can be a maker based in an academic or medical center,

e.g., a research laboratory. The maker should identify and manage aspects of the device operation that present either technical or stimulation-dose risk. As applicable, technical safety is defined and regulated by medical device safety standards such as IEC/ UL60601–1(UL,2003)andIEC/EN62304(InternationalElectrotechnical Commission, 2006) as well as by environmental exposure standards such as those by the US Occupational Safety and Health Administration (OSHA) and International Commission on Non-Ionizing Radiation Protection (ICNIRP). The degree of relevant regulations may vary with the nature and scale of deployment including production for clinical use, investigational use, and custom device. The dose may be limited by the device maker to address risks including excessive coil heating or adverse neuromodulatory effects. The maker should also address human factors, e.g., by providing protections so that the device cannot be operated incorrectly in a way that increases risk. The maker provides instructions for safe operation and maintenance of the device, which users should respect in limiting how the device is used.

As applicable, a manufacturer's risk management may be audited by a regulatory agency. For example, in evaluating a device for approval, the FDA may require labeling materials, operator's manual, flammability and biocompatibility test report for the coil, software report, FDA-recognized standard electrical safety test report ('EN' reports are not acceptable, 'IEC' reports are), FDA-recognized standard electromagnetic compatibility test report, bench performance testing (magnetic field output, cooling system, acoustic output, etc.). Some of these tests may have to be certified by independent test laboratories. In Europe, the CE mark process follows largely comparable testing and certification plans. Audits are part of a manufacturer receiving government regulatory clearance (e.g., US FDA clearance, CE Mark per EU directive 93/42/EEC), but risk management should be applied in any case, including investigational devices. The appropriate degree and processes of risk management (and what regulation may apply for example to "custom" devices) is the responsibility of the maker to determine.

Quality assurance (or Quality System of Good Manufacturing Practice) comprises processes by device makers to ensure that their TMS systems perform safely and reliably. This includes delivering a magnetic field corresponding to the intended stimulation dose. If a device is provided without quality assurance in place, there are no comprehensive guarantees of what the device does. Even if the device appears to operate as expected initially, failures may emerge. One device may operate differently than others of the same serial and model number. For example, avoiding a production error that changes the coil inductance, resistance, or shape or the pulse generator capacitance in a way that changes the magnetic field is a quality issue. Another quality issue is that TMS coils and other system components may be subject to mechanical, electrical, or chemical stresses limiting the lifetime of the system. Quality is also in place to prevent technical hazards unrelated to the stimulation function such as electrical safety. Determining and implementing the appropriate degree and processes of quality control (including if and what regulations apply) is the responsibility of the maker. Medical device manufacturers are required to conform to ISO 13485 (Europe) or 21 CFR 820 (US) for their quality management system. If issues with the device quality are identified after the device has been cleared for use, regulatory agencies such as the FDA have mechanisms for postmarket reporting of AE, use errors, and product problems (U.S. FDA, 2018).

User responsibilities—The user should consider the provenance of any TMS device or accessory to ensure that the maker has implemented adequate risk management and quality assurance. Unless warranted, TMS devices should be operated according to the instructions, e.g., the user manual, in the frame of international guidelines (Rossini et al., 2015). The user can access information about device approvals as well as up-to-date safety communications from regulatory agencies (U.S. FDA, 2018). If operation beyond these instructions is attempted, risk analysis is necessary. Operating a device outside the maker's specified environments, configuration, or accessories, such as connecting a custom coil or measuring EEG simultaneously, can negate assurance of technical safety, and requires additional risk analysis and management. The user also has to be mindful of the lifetime of each device; for instance, the maker may define the maximum safe number of pulses for a coil or other components of the system. Adequate hearing protection should be used (see Section 4.2). Regardless of prior technical safety testing and even if the device is operated correctly, the user should be aware of faults that may occur over the course of a device lifetime, such as cracks in the coil or device enclosure, compromises in the insulation, altered sound, smoke, or unexpected smells. In case of such, use of the device should be discontinued immediately and it should be serviced by qualified personnel. The potential for interaction of TMS with other devices and associated risk should be considered too, for example when combining TMS with an MRI scanner, a PET scanner, or an EEG system.

Regarding dose, conventional TMS devices and paradigms should be operated in accordance with the safety guidelines presented in this paper (Section 7) or a risk analysis should be conducted. Novel devices, paradigms, or subject populations require additional risk management steps, since the effects on the body may differ from those of conventional devices or paradigms (for examples see next section). When a trial involves novel aspects that could reasonably introduce new risks, there are established approaches to increase vigilance in monitoring for early indicators of risk [e.g., Motor Evoked Potential (MEP) after discharges indicative of excessive excitation that could result in a seizure] or management of an unexpected AE (e.g. protocol to contact clinical support staff). It is not possible to precisely identify and mitigate every possible risk, but reliance on predicates (e.g. prior tests of an investigational coil or comparable waveforms) with prudent considerations of those novel aspects of the protocol, can support rational risk analysis. Predicates may be weighted by the size of the trial (number of subjects) and rigor of their monitoring.

For TMS studies involving human subjects, risk analysis and management is an established process governed by the relevant IRB or Ethics Committee. In such studies, the investigator is required to identify and report risks, along with methods to mitigate them or manage AEs. In the US, an Investigational Device Exemption (IDE) is required for human studies with many medical devices; however, the FDA allows the local IRB to provide an IDE when specific conditions apply. IRBs may rely on approval by a regulatory body (e.g., FDA clearance or a CE mark) as evidence of risk management and quality control by the maker, but risk management is still needed if the method of device use (e.g., indication, environment) differs from that approved by the regulatory body. It is worth stressing that an

IRB approval is always an approval of a study, not of a device, and that IRB requirements will vary between institutions and countries.

2.6. Brief review of new devices and paradigms

Here we review the evidence for safety of recently introduced TMS devices and paradigms. It should be noted that the majority of studies using novel devices or stimulation paradigms have been conducted with relatively small numbers of subjects, so the absence of unexpected side effects should be interpreted with caution.

2.6.1. New pulse generators and stimulus waveforms—Over the past decade, devices have been developed that allow more extensive control over the waveform of the individual magnetic pulses than in conventional TMS devices. The latter produce damped sinusoidal pulses with fixed pulse width, whereas other devices such as those called cTMS (Peterchev et al., 2014, 2011, 2008) and FlexTMS (Gattinger et al., 2012) generate more rectangular E-field pulses with continuous control of parameters such as the pulse width and the positive/negative phase amplitude ratio of the pulse. These novel pulse shapes can be delivered at both low and high rTMS frequencies. TMS devices with even more flexibility of pulse shaping are under development (Goetz et al., 2015; Peterchev et al., 2015).

It is known that briefer pulses require larger E-field amplitudes to activate neurons (as described by the so-called strength–duration curve) (Barker et al., 1991; Rothkegel et al., 2010; Peterchev et al., 2012). FDA-approved rTMS devices have pulse widths that differ by a factor of up to two. There is no evidence that pulse-width differences on this order affect the risk for seizure when the stimulation intensity is adjusted relative to the RMT. There is some evidence from single-pulse studies that the pulse width may affect scalp sensation, but the effect is small and it is unclear how it translates to rTMS (Peterchev et al., 2017).

There is significant literature on the effects of pulse waveform and E-field direction on the neuromodulatory effect of rTMS (Sommer et al., 2013). Earlier data came from comparisons between conventional biphasic and monophasic pulses (Antal et al., 2002; Arai et al., 2007, 2005; Hosono et al., 2008; Sommer et al., 2002; Taylor and Loo, 2007; Tings et al., 2005), whereas more recent studies have used cTMS (Sommer et al., 2014; Peterchev et al., 2015; Goetz et al., 2016). Collectively, these results suggest that TMS pulses with asymmetric E-field phase amplitude —i.e., one phase having significantly larger amplitude than the other, such as in conventional monophasic pulses— confer stronger and direction-specific neuromodulatory effects in rTMS (Halawa et al., 2019). While at present complete mechanistic explanation of these effects is lacking, the most likely factor is differential recruitment of neural elements and neural populations by pulses of varying waveform shape, duration, and direction, as witnessed, for example, by different MEP latencies (D'Ostilio et al., 2016; Goetz et al., 2015; Hannah and Rothwell, 2017; Hannah et al., 2020; Sakai et al., 1997; Sommer et al., 2018, 2016), different corticospinal volley composition (Di Lazzaro and Rothwell, 2014) and evoked EEG potentials (Casula et al., 2018).

These studies with unconventional pulse shapes did not report unexpected AEs, with one qualified exception: Tings et al. (2005) found that trains of 80 pulses at 5 Hz over primary motor cortex (M1) with intensity adjusted to yield baseline MEP amplitudes of about 1

mV resulted in an alternating pattern of low and very high MEP amplitudes and spreading of excitation in 8 of the 18 participants. This occurred with the most excitatory pulse configuration, monophasic pulses with posterior–anterior direction (Prof. Martin Sommer, personal communication, December 20, 2018). It should be noted, however, that the pulse train parameters significantly exceeded the range (10 pulses at 5 Hz) of the original safety tables (Wassermann, 1998).

While instances of seizures have not been reported with waveforms other than conventional sinusoidal biphasic and sinusoidal polyphasic pulses used in early rTMS systems, the observations of stronger neuromodulation with asymmetric pulses should be flagged for appropriate risk management. For example, even if rTMS paradigms using alternative (especially asymmetrical) E-field pulses conform to the guidelines in Section 7, more extensive monitoring for potential seizure induction may be appropriate until there is adequate evidence that the risk is not significantly increased.

2.6.2. New pulse sequences—A protocol that combined features of TBS (200 ms interburst interval) and quadri-pulse TMS (four pulse bursts at 666 Hz or 200 Hz) applied at 90% of active motor threshold (AMT) with sinusoidal biphasic pulses has been shown to produce lasting neuromodulation in 16 healthy subjects, without AEs (Jung et al., 2016). This protocol did not only add a fourth pulse, but also chose an ultra-high pulse repetition rate within a single burst. The physiological impact of within-burst frequencies of 200 Hz or more remains to be explored. Regarding the number of pulses per burst in a TBS stimulation paradigm, modelling studies predict a fluctuating pattern of excitability increases and decreases with increasing number per burst rather than an increase in cortical excitability with the number of pulses per burst (Wilson et al., 2018).

No safety data are available yet for these new pulse sequences.

2.6.3. New coils—Coil characteristics relevant for TMS dose safety include shape, size, and number of winding turns. The shape and size of a coil as well as its placement and orientation determine the spatial pattern of the E-field induced in the body. The number of winding turns, in combination with the coil shape and size, affects the strength of the induced E-field as well as its pulse width (via the coil inductance). Pulse waveform effects are addressed above, and the strength of the E-field is adjustable by the coil current amplitude; therefore, here we focus on the effect of coil shape and size.

The simplest TMS coil type is circular (or round); it produces an annulus-shaped E-field pattern. A more focused E-field pattern is obtained with figure-8 coils, where the area of cortex significantly stimulated can be on the order of a square centimeter, depending on stimulation strength. For any coil shape, there is a fundamental trade-off between stimulation focality and depth, with larger coils having a deeper but less focal E-field (Deng et al., 2013; Gomez et al., 2018; Peterchev et al., 2015).

Likewise, increasing the coil current deepens and spreads out the stimulation. Double-cone (or angled butterfly/double) coils are a larger version of figure-8 coils where the two circular windings are angled toward the subject’s head to increase the magnetic field strength

in depth as well as the electrical efficiency. Consequently, the double-cone coil E-field penetrates deeper and is less focal than conventional figure-8 coils (Deng et al., 2014, 2013). Double-cone coils have been used to target various brain regions that may be difficult to reach with standard figure-8 coils, such as the leg motor area or medial prefrontal cortex, and were claimed to reach effectively the cingulate, insula, and cerebellum. In studies reviewed, no serious AEs such as seizures were reported (Ciampi de Andrade et al., 2012; Blumberger et al., 2018; Dunlop et al., 2015; Fernandez et al., 2018; Gerschlager et al., 2002; Grossheinrich et al., 2009; Huang et al., 2018; Kreuzer et al., 2015a; Kreuzer et al., 2015b; Modirrousta et al., 2015; Nauczyciel et al., 2014; Popa et al., 2010; Riehl, 2008; Ruohonen and Ilmoniemi, 2005; Sutter et al., 2015). Some double-cone coils have CE approval for use in Europe.

H-coils are designed to induce an E-field penetrating deeper in the brain than typical figure-8 coils at the expense of reduced focality (Deng et al., 2013; Guadagnin et al., 2016; Parazzini et al., 2017; Tendler et al., 2016). While the H1 and H7 coils that are part of FDA-cleared systems are discussed in Section 4.1.2, other H-coils are considered new by our definition. When other (non-FDA approved) H-coils were used, no serious AEs such as seizures were reported (Avirame et al., 2016; Carmi et al., 2018; Cervigni et al., 2018; Chieffo et al., 2014, 2014b; Cohen et al., 2016; Coppi et al., 2016; Dinur-Klein et al., 2014; Enticott et al., 2011; Gersner et al., 2016; Kranz et al., 2010; Onesti et al., 2013; Shahar et al., 2015; Shimizu et al., 2017; Spagnolo et al., 2014; Torres et al., 2015; Vazana et al., 2016). It should be noted that the winding configuration of some H-coils, including H3, H6, H7, and H10 somewhat resembles double-cone coils (Peterchev et al., 2015; Tendler et al., 2016). Therefore, after assessing similarity by comparing the induced E-fields, safety data from double-cone coil trials could potentially be used to inform the safety of comparable H-coils, and vice versa.

Other unconventional devices and paradigms include a pair of coils or coil arrays for multi-coil stimulation (Roth et al., 2014). In the latter case, one needs to analyze the safety issues that arise from the ability to stimulate two or more targets at the same time or with short time intervals. One such study used a pair of V-shaped coils activated synchronously at two sites in 43 patients to treat depression, without any reported seizures or other unexpected TMS-related AEs (Carpenter et al., 2017; Kavanaugh et al., 2018). A study of 16 subjects with four simultaneously activated V-shaped coils reported no serious AEs either (Tzabazis et al., 2013). Another study used a pair of H6 coils, activated synchronously at 10 Hz over the left PFC and 1 Hz over the right PFC, in 47 patients suffering from depression, with no reported seizures or other SAE (Harel et al., 2018). New types of TMS paradigms will be possible with multi-locus TMS devices (Koponen et al., 2018), which allow stimulation sequences with multiple arbitrarily located targets and arbitrary E-field directions, time differences, and intensities. At present, no significant data on safety for such multi-coil stimulation is available. Another recent technical advance is the computational design of coils that are more focal than figure-8 coils for a matched depth of stimulation (Gomez et al., 2018). This approach could potentially increase the precision of stimulation and reduce side effects; however, these designs have not been evaluated in human subjects yet.

2.6.4. Other paradigms of stimulation (Low field magnetic stimulation; transcranial static magnetic stimulation)

Low-field magnetic stimulation: Low-field magnetic stimulation refers to TMS paradigms that induce E-field pulses of very low amplitude, generally below 10% of the neural activation threshold (Deng and Lisanby, 2017; Wang et al., 2018). Some low-field paradigms, for which there is evidence of neuromodulatory effects, are derived from MRI gradient sequences (Cook et al., 2019; Dubin et al., 2017). Other approaches use even lower electromagnetically-induced E-field intensities and frequencies (Capone et al., 2009; Martiny et al., 2010). Finally, low-intensity E-fields have also been induced with rotating permanent magnets, with evidence for neuromodulatory effects as well (Cook et al., 2019). These studies reported no AEs resulting from the electromagnetic stimulation. This is consistent with the fact that both the magnetic fields and E-fields were lower than those in conventional TMS and would therefore be expected to carry less risk. Moreover, for the paradigms derived from MRI gradient sequences, the extensive experience with the safety of MRI supports a low-risk profile. The literature of transcranial alternating current stimulation and cranial electrotherapy stimulation (Antal and Paulus, 2013; Chaieb et al., 2014, 2011; Zaghi et al., 2010) may also be relevant in risk analysis of low-field magnetic stimulation, since these techniques share some E-field characteristics, especially its subthreshold and pulsed/alternating nature.

Transcranial static magnetic stimulation (tSMS): It has been reported that a sufficiently long exposure to static magnetic fields on the order of hundreds of millitesla can alter cortical excitability (Carrasco-Lopez et al., 2017; Dileone et al., 2018; Gonzalez-Rosa et al., 2015; Kirimoto et al., 2018, 2016, 2014; Lozano-Soto et al., 2018; Oliviero et al., 2011). These magnetic fields are approximately ten times lower than those in MRI scanners (Rivadulla et al., 2014; Tharayil et al., 2018), which are well-characterized in terms of safety (Schenck, 2000). No safety concerns related to the magnetic field exposure of tSMS have been reported (Oliviero et al., 2015). However, there are very strong forces exerted between the permanent magnets used for tSMS as well as between the magnets and other ferromagnetic objects. As a result of these forces, in one instance, a tSMS magnet operator sustained a clean break of two different phalanx bones in two fingers (Antonio Oliviero and Casto Rivadulla, personal communication, June 12, 2018); another one squeezing of two fingers that resulted in bleeding (Andrea Antal, personal communication, July, 2016). Therefore, permanent magnets for tSMS should be handled with extreme caution. As is the case for the static magnetic field of MRI scanners, the strong localized magnetic field of tSMS can also affect implants that contain magnets (such as cochlear implants) or ferromagnetic materials, or that are otherwise sensitive to magnetic fields. The use of tSMS nearby such devices must therefore follow strict safety precautions.

2.6.5. Role of neuroimaging in improving TMS safety—The combination of TMS with brain imaging has become common, if not standard, in research settings (Fox et al., 2012; Siebner et al., 2009) including large-scale clinical trials of rTMS for depression (Blumberger et al., 2018; George et al., 2010). Neuroimaging may help to improve patient selection (Drysdale et al., 2017), targeting (Fitzgerald et al., 2009; Fox et al., 2013; George et al., 2010; Opitz et al., 2016; Sack et al., 2009), and efficacy of TMS (Fitzgerald et al.,

2009; Sack et al., 2009; Weigand et al., 2018). Therefore, an important question is whether neuroimaging can improve TMS safety, although neuroimaging is currently still rarely used in clinical practice (McClintock et al., 2013).

The use of neuroimaging is not necessary for most patients undergoing TMS unless neuronavigation software will be used for precision targeting. However, it should be considered in patients with structural brain abnormalities such as stroke, tumor, or multiple sclerosis and when the stimulation targets a brain region outside the motor cortex. Although the absolute risk of seizure remains low (Gaede et al., 2018; Jorge et al., 2004; Tarapore et al., 2016), there are cases in which TMS delivered close to brain lesions has induced seizure (Cogné et al., 2017; Groiss et al., 2017; Haupts et al., 2004). Neuroimaging can help avoid these lesion locations, improving safety without sacrificing clinical benefit (Caulfield et al., 2017). Structural MRI can inform realistic modelling of the E-field distribution in the brain, which can help predict how stimulated tissue may change in the setting of structural abnormalities (Wagner et al., 2008, 2006). Finally, neuroimaging may allow for individual adjustment of stimulation intensity, accounting for factors such as scalp-to-cortex distance that vary across different stimulation sites (Kozel et al., 2000; McConnell et al., 2001; Nahas et al., 2001; Nathou et al., 2015; Stokes et al., 2013, 2007, 2005). Indeed, adjustment of the rTMS intensity based on the individual scalp-to-cortex distance at the target site has been deployed in clinical trials (Blumberger et al., 2016; Koch et al., 2018).

Neuroimaging and E-field modeling on an individual basis is recommended by the National Institute of Mental Health for any application of TMS as well as with TES to standardize coil placement and orientation, and to control for individual variation in delivered dose with the goal of improving the rigor and reproducibility of non invasive brain stimulation studies (Bikson et al., 2018; McMullen, 2018).

In theory, neuroimaging and increased neuroanatomical precision should lead to a reduction in off-target side effects and improved TMS safety, and therefore it should be recommended. The benefit of increased precision is evident comparing the side effects profile of TMS to non-focal electroconvulsive therapy (ECT), where AEs are due to the intense non-focal stimulation and generalzed seizure induction. However, improved neuroanatomical precision is only useful if one knows where one needs to stimulate to improve a target symptom and where one should avoid stimulating to avoid side effects. As these neuroanatomical targets become clearer (Fitzgerald et al., 2009; Fox et al., 2013; Weigand et al., 2018), neuroimaging is likely to take a stable place for therapeutic TMS applications.

2.6.6. Image-guided frameless navigation and robots for improving TMS safety: an emerging issue—Frameless navigation systems have been developed to integrate anatomical or functional brain imaging of subjects or patients to optimize the placement of the TMS coil on a defined target over their cortex (Ruohonen and Karhu, 2010). Navigation systems dedicated to MRI-based neuronavigated TMS (nTMS) practice have shown their reliability to determine cortical target location and to improve the reproducibility of coil placement throughout serial rTMS sessions (Lefaucheur, 2010). Only few comparative studies specifically addressed this issue, showing the beneficial impact of navigated (nTMS) versusnon-navigated rTMS protocols (Ayache et al., 2016; Bashir et al.,

2011; Fitzgerald et al., 2009; Sack et al., 2009). However, these systems need to be further evaluated both in terms of risk-benefit ratio and therapeutic effectiveness

One of the most important areas of development of nTMS, with an increasing clinical use, is the cortical mapping of language and motor functions in preoperative time, especially in patients with brain tumors (Lefaucheur and Picht, 2016). For motor mapping, single TMS pulses above the RMT are delivered over the rolandic region (Picht et al., 2011, 2009), while brief rTMS trains are used to induce speech arrest or errors for language mapping (Picht et al., 2013). The accuracy of these methods was demonstrated in comparison to intraoperative direct cortical stimulation, which is the gold standard in this domain (Picht et al., 2013, 2011). One study (Tarapore et al., 2016) addressed both tolerability and safety issues of motor and language mapping procedures performed in 733 patients with brain tumors, 50% of whom with a history of seizures due to the brain lesion. The nTMS mapping procedure was found to produce discomfort in 5.1% of the cases for motor mapping and 23.4% for language mapping, and pain in 0.4% of the cases for motor mapping and 69.5% for language mapping. However, although patients had a high risk for seizures, no seizures occurred during the procedures. In fact, in the rest of the literature, there is also no reported seizure with this practice. Therefore, it can be reasonably concluded that the nTMS approach allows motor or language mapping to be safely performed, at least according to the specific methods currently used in the studies mentioned above.

To further improve the reliability and repeatability of TMS coil positioning, the use of a robot to hold the coil, combined with image-guided navigation has been proposed. To our knowledge, only three robots are commercially distributed specifically for rTMS practice, which are the Smartmove™ (ANT, Enschede, Netherlands), the TMS-Cobot™ and the TMS-Robot™ (Axilum Robotics, Strasbourg, France), the last one being the only one robot specially developed for TMS use and not derived from an “industrial” environment (Ginhoux et al., 2013; Zorn et al., 2012). These robots used either a dedicated neuronavigation system (ANT) or are compatible with various commercial TMS navigation systems (Axilum Robotics). It is estimated that about 40 robotized nTMS systems are installed worldwide, of which more than 10 are used for therapeutic applications (data courtesy of Axilum Robotics).

To date, only a few studies have reported results obtained in patients who underwent repeated sessions of robotized nTMS (Lefaucheur et al., 2017; Pommier et al., 2016; Quesada et al., 2018, 2020). In fact, most studies aimed at describing the accuracy of more or less automated motor mapping procedures using robotized nTMS (Finke et al., 2008; Grab et al., 2018; Harquel et al., 2017; Kantelhardt et al., 2010; Matthäus et al., 2006; Meincke et al., 2016, 2018; Grab et al., 2018; Goetz et al., 2019; Giuffre et al., 2019). Thus, it has been shown that the use of a robot improves accuracy and repeatability of TMS targeting and motor mapping versus manual procedures (Ginhoux et al., 2013; Lancaster et al., 2004; Richter et al., 2013).

Most safety issues for using robots in TMS practice are related to various regulatory, mechanical, electrical, and software aspects, as discussed in Sections 2.1–2.3, 2.5 for any new device. Mechanical safety aspects are managed by either limiting the motion of the

robot to an acceptable workspace, limiting motion speed or by adding force or torque sensors to detect a collision with the environment of the robot. Trajectory planning and execution remains challenging tasks, as motion must be restricted to avoid hitting the patient's head or the environment while the robot aligns the coil on the head. For TMS, a small workspace could be a limitation. To this regard, systems based on standard industrial-type robots are often more limited compared to dedicated architectures (Zorn et al., 2012).

The noise level emitted by the system, the pressure exerted by the coil handled by the robot on the head of the patient are also important features, as untimely movements of the patient or unpleasantness due to acoustic or musculoskeletal discomfort should not force the cessation of stimulation. Electronic safety is ensured by electrical isolation and emergency buttons, which are usually accessible to the patient or the operator to stop any ongoing robot motion. Specific safety issues must be considered if the robot system is connected to the TMS stimulator, automatically triggering the pulses when the target position is reached and contact with the head is confirmed. Finally, when used in combination with EEG or EMG, attention has to be paid to avoid any electromagnetic interference while acquiring the signals.

Robots are usually coupled with a navigation or 3D-targeting system to help the user to define a specific stimulation target. The usual precision of targeting is in the range of a few mm, taking into account the flexibility of the robot arm, the accuracy of the navigation system, and the method of manual registration, which needs an input from the operator (i.e. a possible source of human error). The risk of targeting and stimulating a wrong cortical region due to poor accuracy of the system itself is limited, as position feedback from the motors or by an external 3D sensor (usually a camera) ensures very low risk of positioning error. Some systems require the addition of optical markers on the coil or the robotic arm to adjust their position in real-time using a feedback control loop. This reduces any residual errors from the positioning system.

Thus, the main requirement for robot use in TMS practice is the need to maintain coil contact with the head at a given position and with a given orientation during a whole session of TMS pulse delivery. Systems may include a pressure or force sensor that measures if the coil is actually in close contact with head surface, so that the coil-to-head distance is maintained at the lowest value. The lack of pressure feedback is an acknowledged limitation of some robotic systems (Goetz et al., 2019). To conclude, a robotized nTMS procedure offers simplified positioning of the coil on the head, limits human bias and operator exposure to magnetic field, and allows for real-time compensation of head motion to increase targeting accuracy while the stimulation is executed.

A yet unexplored but timely and plausible advantage of robot-guided TMS can be the reduction of the risk of human-to-human transmission of infections.

3. Safety in combination with other devices

3.1. MRI environment

TMS can be combined with a wide range of brain mapping modalities based on MRI. The combined use of TMS with MRI or magnetic resonance spectroscopy (MRS) has great clinical and neuroscientific potential (Siebner et al., 2009; Bestmann and Feredoes, 2013; Hallett et al., 2017). For example, it can capture TMS-induced changes in tissue concentrations of relevant molecules such as glutamate or GABA in brain regions of interest. Diffusion weighted imaging (DWI) can help to link TMS-induced plasticity to regional changes in brain microstructure and to derive information about the structural connectivity of the targeted brain region. TMS can also be combined with functional MRI (fMRI) to delineate immediate and longer lasting effects of the TMS intervention on regional brain activity as well as functional connectivity within and among brain networks (Bestmann et al., 2008; Ruff et al., 2009). In addition, fMRI can be used as functional localizer to identify the optimal cortical target. DWI and fMRI can also reveal brain regions that are indirectly stimulated by TMS through spread of excitation along pre-existing neuronal connections.

In the majority of combined TMS-MRI or TMS-MRS studies, TMS and MR-based mapping are strictly separated in space and time. TMS is given “offline” outside the scanner environment before or after the MR session. In these instances, standard safety procedures for TMS and MR-based examinations apply without any additional safety concerns. This is different for TMS studies in which TMS is delivered in the MR scanner room to probe acute changes in human brain function during or shortly before and after TMS. In this case, specific safety concerns apply; we refer to our previous consensus paper on TMS safety for a comprehensive list of specific precautions (Rossi et al., 2009; Siebner et al., 2009). Importantly, only dedicated TMS coils whose use is approved inside the scanner must be used. The TMS coil must not contain ferromagnetic material and must be able to cope with the increased mechanical stress caused by the Lorentz forces, which the static magnetic field of the MR scanner creates on the coil windings during the discharge of the TMS pulses. The number of total pulses that can be applied by the MR-conditional TMS coil, which is currently commercially available, has been restricted by the vendor. Once this number is reached, the coil is blocked and needs to be returned to the vendor. This precaution has been implemented to secure that the integrity of the coil, including the wires and their insulation, is not endangered over time due to the increased mechanical stress levels. Finally, while MRI-comparible coils have a standard figure-8 configuration and magnetic field pattern, the intensity and focality of the field may be reduced compared to conventional coils due to thicker casing (Koponen et al., 2018; Nieminen et al., 2015). Therefore, the difference in absolute field strength and motor thresholds with different coils should be accounted for to maintain safety and efficacy

Recommendations: TMS coils dedicated for use in the MR scanner are currently only approved for MR systems with a magnet that produces a static field of 3T or less. They cannot be used in MR systems that have higher field strength than 3T. This also applies to a recently developed combined TMS-MR-coil design where the TMS coil is integrated into a multi-channel MR receiving coil (de Weijer et al., 2014; Lara et al., 2015).

3.2 Implanted or non-removable intracranial metal or devices

3.2.1 Heating—The heating produced by TMS in the brain is estimated to be very small (less than 0.1 °C) and this should not pose any safety issue (Brix et al., 2002; Ruohonen and Ilmoniemi, 2005). TMS can also induce currents in skin electrodes and implants that can heat them (Rotenberg et al., 2007; Roth et al., 1992). The heating depends on the structure, size, electrical conductivity, and placement of the electrode or implant, the geometrical and conductivity characteristics of the tissue it contacts, and the TMS coil configuration and pulse characteristics. Electrodes made of silver and gold have high conductivity and can heat up substantially, potentially leading to skin burns. Skin burns can be caused by temperature of 50 C for 100 s or 55 C for 10 s (Roth et al., 1992). Low-conductivity plastic electrodes are less prone to heating up. As well, radial slits that impede induced currents can reduce heating in electrodes and skull plates. Titanium skull plates tend to have low heating since this metal has low conductivity and the plates are either small in size or have radial slits (Rotenberg et al., 2007). Similarly, titanium rods for spinal implants showed no significant temperature change when exposed to magnetic stimulation (Petrosyan et al., 2015).

Metallic brain implants could heat up as well. Heating of brain tissue over 43°C can cause irreversible damage (Matsumi et al., 1994). Ex vivo studies with rTMS applied over implantable electrodes found no significant heating (Phielipp et al., 2017; Shimojima et al., 2010). Likewise, rTMS applied over vascular stents placed in gelled saline detected temperature increase below 1°C which is considered safe (Varnerin et al., 2017).

When there are electrodes or implants in the vicinity of the TMS coil, risk analysis should be conducted to assess the possibility of excessive heating (see Section 2.1). This analysis can be based on manufacturer data, results in the literature, theoretical calculations, simulations, and/or measurements. If measurements are conducted, ex vivo testing may be sufficient for the risk analysis. But sometimes it may be important to consider the electrical and thermal properties of the tissues in contact with the implant which would require modeling and/or in vivo testing. Sharing of the results of such safety analyses with the community via publications is encouraged.

3.2.2. Forces and magnetization—TMS pulses generate a magnetic field that exerts attractive forces on ferromagnetic objects as well as repulsive forces on non-ferromagnetic conducting objects. Thus, some head implants could experience forces and even be displaced by TMS. Ferromagnetic objects tend to experience larger electromagnetic forces than non-ferromagnetic conductors. Titanium skull plates, rods, and aneurysm clips do not appear to experience significant forces due to TMS (Petrosyan et al., 2015; Pridmore and Lawson, 2017; Rotenberg et al., 2007). This is because titanium is non-ferromagnetic and has relatively low electrical conductivity, and larger titanium plates tend to have slits. Similarly, it has been estimated that movement of a stainless steel aneurysm clip due to a TMS pulse is very small and unlikely to produce clinical complications (Barker, 1991). A modeling study suggested that mechanical movements induced by TMS in implanted electrodes, such as electrodes used for electrocorticography, are well below the limit for tissue damage (Golestanirad et al., 2012). This is consistent with the findings of ex-vivo studies that applied TMS over implantable cortical or deep electrodes and found

no significant displacement (Phielipp et al., 2017; Shimojima et al., 2010). Cochlear or other implants incorporating a magnet could move or demagnetize when exposed to a TMS pulse. Eye makeup containing ferromagnetic particles may contribute to facial pain during rTMS with frontal coil placements potentially due to local heating or electric current concentration near skin receptor/trigeminal fibers (Redolar-Ripoll et al., 2015). While no data have been reported on permanent makeup (e.g. for alopecia) or scalp tatoos, they may contain ferromagnetic and/or conductive particles such as iron oxide or metalcontaining ink which may interact with the TMS induced magnetic field, but with no risk to induce SAE.

Similar to risk analyses for heating, the possibility of significant forces and/or movement on implants should be assessed. In many cases, simple ex vivo ballistic pendulum measurements can indicate the presence of significant forces (Barker, 1991; Pridmore and Lawson, 2017). Potentially conducting or ferromagnetic objects, such as hearing devices, or materials worn on the head, including piercings, jewelry and glasses, should be removed if they can interact with the TMS magnetic field.

3.2.3. Induced electrode current—The TMS coil emits strong magnetic pulses that can induce high voltages and currents in adjacent wires and electronic devices. Wires connecting to surface electrodes, for example in EEG and TES, should be arranged to minimize loops that are coupled to the magnetic field and result in electromagnetically induced voltages and currents. Specifically, the wires should be arranged to be close or twisted together, without looping either between wires or of the whole wire bundle (Peterchev et al., 2012). Electronic implants, including systems for deep brain stimulation (DBS) or cochlear implants and subdural/epidural electrode arrays for cortical stimulation, contain intracranial electrodes connected to wires under the scalp. Spinal and cranial nerve stimulators, such as devices for vagus nerve stimulation (VNS), have subcutaneous wires too. Electrical currents can be induced in these electrode wires during the delivery of TMS, regardless of whether the implant is turned on or off; this can produce unintended stimulation in the central or peripheral nervous system (Hidding et al., 2006; Kühn et al., 2002). These induced currents may affect safety compared to TMS with no implant.

Several ex vivo studies have specifically addressed the safety of the voltages induced in DBS, cortical, and VNS electrodes by TMS. Generally, two types of measurements have been reported: (1) induced voltages or currents between a pair of electrode contacts or a pair of lead wire contacts that connect to the implanted pulse generator (IPG), and (2) induced voltages or currents between an electrode contact and the IPG case or the IPG-side connector of the lead. The first type of measurements in DBS and VNS devices have detected relatively low voltages of <2.8 V at 100% TMS device output (Kühn et al., 2004; Kühn and Huebl, 2011; Kumar et al., 1999; Schrader et al., 2005). The second type of measurements in deep as well as cortical electrodes have identified substantially higher voltages ranging from 15–100 V with 100% TMS device output, depending on the specific setup (Deng et al., 2010; Phielipp et al., 2017; Shimojima et al., 2010). The latter measurements are more relevant to safety, since they are orders of magnitude higher than the former. The physical reason for these differences in the induced voltage magnitudes is that the circuit formed by the electrodes, lead wires, IPG, and conductive tissue path back to the electrodes constitutes a loop with a significantly larger area than the circuit formed by the

wires connecting pairs of electrode contacts, which are very close to each other (Deng et al., 2010). Critical factors for the magnitude of the induced voltage are the TMS coil proximity to the lead as well as the number of lead loops. The highest voltages are induced when the center of the TMS coil is over the subcutaneous lead and the induced current orientation (e.g. axis between the two loops of a figure-8 coil) is aligned with the lead or when the TMS coil loops are centered over loops in the electrode lead (Deng et al., 2010; Shimojima et al., 2010). Depending on its size, each turn of a lead loop can contribute 16–28 V at 100% TMS intensity (Deng et al., 2010; Phielipp et al., 2017; Shimojima et al., 2010). The voltage induced in a lead loop can be calculated by the formula $V_{ind} = (\pi \cdot B \cdot A_{loop})/(2 \cdot t_r)$, where B is the magnetic field (flux density) penetrating a loop with area A_{loop}, and t_r is the rise time of the magnetic pulse (Mueller et al., 2014). Importantly, IPGs can conduct electrical current even if they are turned off, resulting in induced currents that are injected through the electrode contacts. Nevertheless, having the IPG off can offer some protection from induced currents, since the IPG may not conduct until the induced voltage reaches as high as 5 V, whereas it conducts for any induced voltage when on (Deng et al., 2010). The induced electrode current can be calculated by the formula $I_{elec} = (V_{ind} - V_{IPG})/ R_{elec}$, where V_{IPG} is the IPG voltage drop which is typically negligible in on state but can be a few volts in off state, and R_{elec} is the electrode impedance.

The voltages and currents induced by TMS in implanted stimulator electrodes can match and exceed the stimuli normally generated by the implant which are typically <10 V and <10 mA. Therefore, the safety of the induced currents should be assessed with respect to not only unintended neuromodulation, but also the potential for tissue damage. While strict limits have not been established, some implanted stimulator manufacturers specify a maximum allowable charge density of 30 $\mu C/cm^2$/phase (Shimojima et al., 2010). For conventional sinusoidal TMS pulses, charge per phase through the electrode is calculated as $Q_{elec} = 2 \cdot I_{elec} \cdot t_r/\pi$ for monophasic pulses and twice that amount for biphasic pulses, and charge density per phase is Q_{elec}/A_{elec}, where A_{elec} is the electrode surface area. A more sophisticated approach accounts for both charge per phase (in μC) as well as charge density per phase (in $\mu C/cm^2$) according to the formula $k = \log(Q_{elec}/A_{elec}) + \log(Q_{elec})$, with evidence for no histological damage for $k < 1.85$ and potentially higher (Phielipp et al., 2017). Both of these limits can be exceeded for certain configurations of the TMS device and the implanted stimulator, in particular when the TMS coil is close to the lead, there is looping in the electrode lead under the coil, and high TMS pulse intensities are used (Shimojima et al., 2010; Phielipp et al., 2017).

These considerations may apply in some cases when the electrode leads are externalized and connected to an external stimulator or an amplifier for electrophysiological recordings. While bioamplifiers typically have very high input impedance, if a large voltage is induced in the leads, the amplifier input impedance may drop essentially to zero due to clamping of the input protection diodes to the internal power supply rails. Moreover, loops through reference or ground leads connected to the patient may inject currents as well. As with any external wiring in the vicinity of the TMS coil, inductive loops should be minimized by bundling and twisting wires/leads together and placing them as far as possible from the TMS coil. Ideally the amplifier input or external stimulator output should be electrically isolated from earth ground.

Finally, it should be noted that burr holes or other openings in the skull do not affect significantly the E-field delivered to the brain by TMS. This is due to the fact that TMS induces an E-field that is primarily tangential to the scalp surface; therefore, openings in the skull generally do not result in additional current injected in the brain. This is in marked contrast to transcranial electrical stimulation which injects significant radial currents throught the skull and is therefore strongly affected by skull openings (Deng et al., 2010).

3.2.4. Malfunction or damage of electronic implants—The TMS electromagnetic pulse can also damage electronic implants near the coil. Ex vivo studies showed that TMS with the coil at a distance of 2–10 cm could cause malfunction of a DBS IPG, and distances of 2 cm or less could lead to permanent damage of the IPG (Kumar et al., 1999; Kühn et al., 2004). However, another study reported that VNS IPG was not damaged by TMS pulses (Schrader et al., 2005). TMS over a DBS electrode lead can shut off the IPG, presumably due to voltages induced across the IPG through the electrode lead, but no damage to the IPG was reported (Ni et al., 2018).

Cochlear implants involve an electrode implanted in the cochlea, a magnet, a loop antenna, and an electronic chip under the scalp. Although there are no reports on TMS being performed in people with cochlear implants, it may be unsafe based on physics considerations. TMS can damage the electronic chip, cause movement or demagnetize the permanent magnet or induce high voltages in the loop antenna. In addition, most cochlear implants are not compatible with MRI, although some newer models are. Therefore, unless additional safety evaluation showed that there are no AEs, TMS should be avoided in subjects with cochlear implants.

3.2.5. TMS in patients with implanted stimulating/recording electrodes—Many TMS studies have been performed in patients with implanted electrodes in the brain, spinal cord, or peripheral nerves for the treatment of migraine, chronic pain syndromes, movement disorders (Parkinson’s disease, tremor and dystonia), epilepsy, or psychiatric diseases (depression or obsessive- compulsive disorder). Most of them involved single or paired pulse TMS (ppTMS) and some used repetitive TMS (see Supplemental Material, Table S1). The main purposes of these studies were to:

- Determine the effects of TMS on the brain or spinal cord by recording TMS-evoked responses or changes in spontaneous electrophysiological signals induced by TMS using the implanted electrodes;
- Determine the effects of stimulation through the implanted electrodes on the central nervous system by measuring TMS-evoked responses;
- Evaluate the effects produced by paired stimulation combining TMS with DBS;

The first study of TMS in patients with implanted electrodes involved four patients with spinal cord stimulators. TMS was applied with the device turned on or off, and no AE was observed (Kofler et al., 1991). Subsequent studies involved patients implanted with five main types of electrodes: (1) epidural cortical or spinal cord electrodes; (2) subdural cortical electrodes; (3) DBS electrodes; (4) nerve stimulation electrodes over peripheral or cranial nerves (e.g., vagus nerve); or (5) cardiac pacemakers (Supplemental Material, Table S1).

Some studies were conducted when the leads of the electrode were externalized, usually within several days after electrode implantation and before the electrode was connected to the IPG. Other studies involved patients with chronic, implanted devices with the leads connected to IPGs. Two of these studies in patients with DBS electrodes showed that TMS can induce lead currents that led to motor responses (Kühn et al., 2002; Hidding et al., 2006). This is likely due to induced currents between the electrode contacts and the IPG case. In a study with 5 patients with dystonia and DBS electrodes in the globus pallidus internus, the authors suggested that TMS induced currents in the subcutaneous wire loops, which activated the corticospinal tract subcortically near the DBS site, eliciting motor responses in hand muscles (Kühn et al., 2002). Another study reported similar findings in 8 patients with Parkinson's disease who had subthalamic nucleus (STN) DBS electrodes with leads connected to an IPG (Hidding et al., 2006). After the implantation, the latencies of the MEP in the relaxed first dorsal interosseous muscle were shorter compared to latencies before the operation. This decreased corticomotor conduction time was likely due to inadvertent stimulation of the corticospinal tract near the STN from current induced in the scalp leads near the TMS coil, connecting the IPG with STN electrodes. Importantly, no AEs were reported in these studies (Kühn et al., 2002; Hidding et al., 2006). Another study found that the MEP latencies induced by TMS varied with current directions as expected and were longer than the latencies of motor responses evoked by increasing the intensities of STN DBS. There was no evidence of activation of the corticospinal fibers in the vicinity of the STN by TMS in that study (Kuriakose et al., 2010). Some of these differences could be related to the TMS coil position relative to the electrode leads and if there was coiling of the lead in the scalp (Shimojima et al., 2010; Phielipp et al., 2017). However, TMS over the electrode lead can shut off the IPG, although no AEs in patients or damage to pulse generators have been reported (Ni et al., 2018). A patient with intractable neuropathic pain and motor cortical subdural electrodes was safely treated with rTMS over the M1 following ex-vivo studies (Phielipp et al., 2017).

Philip et al. (2014) pooled information on the use of rTMS in 20 patients with VNS implants across 17 medical centers. All centers used TMS systems with focal figure-8 coils. None of the sites reported any unique AE in VNS patients undergoing rTMS therapy. This safety profile is supported theoretically by the significant distance between the TMS coil and the VNS implant.

There are two reports of TMS in patients with a cardiac pacemaker. One patient with depression was treated with rTMS to the left dorsolateral prefrontal cortex (DLPFC) (Hizli Sayar et al., 2016) and another patient with migraine was treated with single pulse TMS to the occipital cortex (Wei et al., 2018). No AE was reported.

TMS studies have been carried out safely in patients with implanted electrodes for epidural spinal cord stimulation or DBS during the period of externalization of the leads prior to their connection to the IPG (see Supplemental Material, Table S1).

Finally, TMS has been considered safe in patients with pressure-programmable valves to treat hydrocephalus; however, it is recommended to check the valve settings after a TMS session (Lefranc et al., 2010).

3.2.6. Conclusions and recommendations—Ex vivo studies and studies in patients showed that TMS can be safely applied in patients with implanted stimulators in the central or peripheral nervous system. In summary: TMS with figure-8coils is considered safe in individuals with cardiac pacemakers, VNS systems, and spinal cord stimulators if the TMS coil is not activated close to (<10 cm) electronic components such as the IPG located in the neck or torso. Caution should be taken to avoid accidental firing of the TMS coil near electronic implants.

1. TMS can also be conducted safely in patients with implanted electrodes in the central and peripheral nervous system that are not connected to an IPG; care should be taken to minimize the currents induced in any connections to external stimulators or amplifiers. Implants in the head that are MRI safe are more likely to be TMS safe than those that are not MRI safe.

2. In patients with DBS or cortical stimulation electrodes, TMS can induce currents in the electrode leads which could cause unintended stimulation: this may be a potential safety hazard. Therefore, when such systems are implanted, lead loops should be avoided if possible or wound with each turn circling in opposite direction (e.g. one turn clockwise and the next turn counterclockwise) in order to minimize electromagnetic induction.

If possible, TMS should be applied away from the electrode leads, particularly leads with loops. Specifically, it is desirable to minimize the magnetic coupling between the TMS coil and the electrode lead, i.e. minimize the magnetic flux encircled by the lead wire. For individual patients, this can be assessed by personnel with appropriate engineering or physics background based on information about the implant spatial configuration, e.g. from X-rays or detailed surgical records. While many studies have been conducted with the IPG on during TMS without AEs (Supplemental Material, Table S1), turning the IPG off during TMS confers some protection against induced electrode currents and should be considered in the overall risk/benefit analysis. TMS should start with low intensity and gradually increase to the desired intensity. If there is the potential of increased seizure risk due to expanded neural recruitment from induced currents through electrodes, for example during high-frequency rTMS and with cortical electrodes, EMG should be monitored for spread of excitation and afterdischarges. TMS in patients with DBS or cortical stimulators should only be done if there are justifiable scientific or medical reasons. There should be pre-specified protocols and oversight by IRB or Ethics Committee. Since TMS may be unsafe in subjects with cochlear implants, it should not be performed in these subjects unless thorough safety analysis is performed.

Finally, it is important to evaluate new implant devices as they become available since their behavior may differ from what was reviewed here. As both TMS and implants are becoming more common and approved for treating a wider range of disorders, implant device manufacturers should consider compatibility with TMS at the design or characterization stage.

3.3. tDCS/tACS/tRNS

Generally, the rationale for the combination of rTMS and transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) or transcranial random noise stimulation (tRNS) protocols is to utilize mechanisms of priming or meta-plasticity to enhance the effect size of either of the protocols (Karabanov et al., 2015; Müller-Dahlhaus and Ziemann, 2015). In these studies, low intensity TES is applied in combination with rTMS either concomitantly or sequentially. Theoretically, the concomitant application of TES and rTMS or priming with tDCS or tACS might intensify the AEs of subsequent rTMS (Rossi et al., 2009).

The number of studies using these kinds of combination in healthy subjects (e.g., applying stimulation over the primary motor or visual cortices: anodal and cathodal tDCS with 1 or 1.5 mA intensity for 10–15 min combined with 1 or 5 Hz rTMS 100–600 pulses 85–130% of RMT or 100% AMT or 90 % phosphene threshold) is limited (Moliadze et al., 2003, 2010; Siebner et al., 2004; Lang et al., 2004, 2007; Cosentino et al., 2012; Bocci et al., 2014). Even though “safety” or reporting AEs were not a primary outcome measure, there are few studies in which tolerability and AEs are mentioned. No AEs were reported in any of the available studies.

There are a few studies in which a combination of intermittent theta burst (iTBS) or continuous theta burst (cTBS) and tACS were used, applying both TBS and tACS concurrently over M1 in order to enhance the modulation of cortical plasticity induced by TBS (Doeltgen et al., 2012; Goldsworthy et al., 2016; Guerra et al., 2018). No AEs were reported in any of these studies, but the evidence is insufficient due to the small sample sizes and since none of the studies had been designed to specifically evaluate safety.

As for pathological conditions, the combination of tDCS with rTMS has been investigated in patients with migraine (Antal et al., 2008), depression (Loo et al., 2009) and writer’s cramp (Quartarone et al., 2005) (e.g. anodal and cathodal tDCS over M1 with 1 or 1.5 mA intensity for 10–15 min combined with 1 or 5 Hz rTMS 100–900 pulses 85–130% of RMT), also with the aim to explore abnormal meta-plasticity usually reported in these disorders. None of the reviewed studies observed AEs apart from one pilot study that combined priming-tDCS with 10 Hz rTMS of DLPFC in patients with major depression (Loo et al., 2009). Here, patients experienced stronger scalp pain while receiving rTMS after tDCS, possibly due to increase scalp sensitivity, but no serious AE were reported.

As for the combination of single pulse TMS and tDCS/tACS/tRNS, a few investigations are available when considering either concurrent (e.g. Bergmann et al., 2009; Feurra et al., 2013, 2011; Groppa et al., 2010; Raco et al., 2017; Santarnecchi et al., 2014) or sequential application (e.g. (Antal et al., 2008; Moliadze et al., 2012; Romero Lauro et al., 2014; Terney et al., 2008; Varoli et al., 2018). As in the case of rTMS, no AE were reported, although safety-specific assessments were not carried out. Moreover, a recent study has investigated the effect of multifocal versus bifocal tDCS over M1, assessed via corticospinal excitability (i.e. single pulse TMS) at various time points before and after tDCS. A slightly lower rate of scalp itching, redness and burning sensation was reported during multifocal tDCS, possibly due to the higher number of scalp electrodes and resulting lower current

density per electrode. Regardless, no differences in the perception of single pulse TMS were reported (Neri et al., 2020)

Recommendations: the available evidence suggests that the combination of tDCS/tACS/tRNS and TMS/rTMS used up to now is safe, if technical risks from heating or magnetically induced currents through the TES electrodes are ruled out (see Section y.2).

3.4. Drugs

Many hundreds of thousands of patients have been treated with rTMS to prefrontal cortex for depression, or other cortical targets for many other neuropsychiatric diseases, since 2008. It is estimated that the majority of these were concurrently taking one or more psychotropic medications from multiple pharmacological classes. Systematic data are not available regarding the specific medications and adverse outcomes of patients treated with rTMS for depression in clinical settings. Nevertheless, despite the large numbers exposed to TMS in the past decade, no specific toxicities arising from the combination of rTMS with such medications have been identified. Moreover, the actual risk for induction of seizures may depend on additional, not yet specifically explored, factors; these are drug dose, speed of dose change (increase or decrease), combination with other CNS active drugs or other factors potentially contributing to lower the seizure threshold (i.e., sleep deprivation, alcohol consumption, marijuana therapeutic and recreational use).

A number of medications have been reported to increase risk of seizure in clinical populations (Bhatti et al., 2017; Hitchings, 2016), and it was previously assumed that their use in combination with rTMS may confer heightened risk for seizure induction (Rossi et al., 2009). However, empirical evidence for this risk is lacking, and the observed seizure rate in rTMS patients is extremely low overall despite that the majority of them were on CNS-active medications. In a survey of researchers and clinicians performing sp/ppTMS or rTMS (Lerner et al., 2019), 19 seizures were reported in individuals at increased risk of seizure from all causes according to the previous guidelines (Rossi et al., 2009). These individuals underwent a collective total of 57185 rTMS sessions delivered within the previously published guidelines (Rossi et al., 2009). Among them, only three - all psychiatric patients free from anatomical lesions - were taking medications suspected of lowering the seizure threshold. Two seizures were reported in depressed individuals and one in a healthy individual on no medications. One seizure was reported in a healthy individual on an oral contraceptive.

Recommendation: The previous TMS Safety guidelines advised caution in the application of TMS in persons taking medications known to lower seizure threshold. However, the currently available data showing low seizure rate no longer support this recommendation. However, documentation of concurrent intake of drugs and other potentially seizure threshold lowering factors (such as sleep deprivation, infection, alcohol consumption) during TMS application and systematic capture/reporting of side effect data are recommended to further inform the field.

4. Adverse effects

4.1. Seizures

Induction of seizures is the most severe acute AE of TMS. Several cases of accidental seizures induced by TMS or rTMS have been reported to date; most of them occurred prior to the definition of safety limits. However, considering the large number of subjects and patients who received have TMS since 1998 and the small number of seizures, we can assert that the risk of TMS/rTMS to induce seizures is certainly very low.

Seizures depend by hypersynchronized discharges of groups of neurons in the gray matter as a consequence of an imbalance between inhibitory and excitatory synaptic activity in favor of the latter. Seizures have been described acutely during TMS with single-pulse, ppTMS and rTMS protocols. rTMS might theoretically induce seizures (1) during or immediately (seconds) after trains of rTMS and, (2) after rTMS with a temporal delay (i.e., during the after-effects) due to the modulation of cortical excitability (i.e., kindling effect, see (Wassermann, 1998). While the first has been observed, no evidence exists that the latter has ever occurred. Indeed, there is no solid evidence for kindling in humans in any situation.

The published literature up to February 2020 was searched for reports of seizures and 41 were identified (Chou et al., 2020). Although the numbers are difficult to interpret without denominator, the data have some value. There were 13 in healthy persons and 28 in patients with neurological or psychiatric conditions; 19 had high frequency repetitive rTMS, 1 had low frequency, 8 with single pulse, 9 with deep TMS of various patterns, 2 with iTBS, 1 with cTBS, and 1 unknown. It appears that any type of person with any pattern of stimulation might have a seizure.

It is most important to consider a convulsive syncope when associating TMS with seizures (see Rossi et al., 2009). Some observers may misinterpret myoclonic jerks in the context of a syncope as a seizure (Lempert et al., 1994), but return to conscious state after syncope is usually not characterized by the level of confusion and disorientation produced in a post-ictal state. Furthermore, tongue-biting, incontinence, oral frothing, and vomiting are rarely seen with syncope. Syncope is caused by global cerebral hypoperfusion and can result from functional hypotension in association with vagus-nerve mediated vasodilation during emotional stress or pain, dehydration, bradycardia and use of medications which cause orthostatic hypotension or reduce cardiac ouput. Hyperventilation can also lead to syncope, as falling carbon dioxide levels trigger cerebral vasoconstriction. Steps to manage syncope in the context of TMS include lowering the head of the subject/patient to facilitate cerebral perfusion, restoring fluid volume/hydration, cooling the skin (to reduce vasodilation), and providing reassurance to mitigate fear and stressful emotional states.

4.1.1. Risk factors for TMS-provoked seizures—Here we begin by reviewing risk factors for TMS-provoked seizures. We then briefly assess the potential utility of TMS coupled with simultaneous EEG to assess for TMS-induced epileptiform discharges that might indicate a high risk for seizures. Finally, we review a recent survey assessing the incidence of TMS-evoked seizures across the general TMS community.

Seizures in the setting of TMS are generally considered to be TMS-provoked, which implies a minimal risk of recurrent seizures in the absence of such a provocation (except in subjects with known epilepsy in whom the seizure may be coincidental and unrelated). A number of medical conditions and pharmacologic substances (see Section 3.4 for the latter) that lower the seizure threshold may increase the probability of provoking a seizure during TMS. As noted above, however, in regard to most drugs, while there is a theoretical risk, increased risk has not been seen in clinical practice. Also, first-degree relatives of persons with epilepsy have an increased risk compared to the general population (Peljto et al., 2014), but no TMS-related seizures have been described so far in these individuals.

While the presence of one or more of these factors does not represent a contraindication to TMS, additional precautions are certainly warranted when planning TMS in these subjects. In particular, the clinical indication for TMS, and the particular TMS protocol should be carefully considered when multiple factors that potentially lower seizure threshold are present. Furthermore, if multiple transient factors are present, postponement of the TMS session could be considered. In the next sections, we delineate some conditions and drugs that potentially lower seizure threshold.

Neuropsychiatric disease.: Besides the obvious case of epilepsy, patients with a broad range of neuropsychiatric disease are at elevated risk for seizures. Essentially all neurologic conditions with structural cerebral damage (e.g. stroke, multiple sclerosis, traumatic brain injury, Alzheimer's and other neurodegenerative diseases, meningoencephalitis or intracerebral abscess, parenchymal or leptomeningeal cancers) are associated with an elevated risk for seizures. More intriguingly, a broad array of studies has shown that patients with psychiatric disease are also at increased risk for developing seizures. Specifically, elevated risk for developing epilepsy has been reported in patients with major depression (Hesdorffer et al., 2000, 2006, 2012), with incidence rates approximately 19-fold higher than those typically reported in the general population seen in one study evaluating the rate of seizures in the placebo (and treatment separately) arm of antidepressant drug studies (Alper et al., 2007). Notably, some studies have suggested that in patients with depression, the risk of developing seizures is particularly increased in those with dementia or a recent stroke. Other significant predictors of incident seizures in depression include being underweight, a current smoker, having alcoholism or drug abuse, and concurrent use of cephalosporins and antiarrhythmics (particularly propranolol) (Bloechliger et al., 2016). An elevated risk of developing seizures has also been reported in other neuropsychiatric diseases such as schizophrenia or autism (Deykin and MacMahon, 1979; Bolton et al., 2011), bipolar disorder (Wotton and Goldacre, 2014; Sucksdorff et al., 2015) and alcohol abuse (Samokhvalov et al., 2010).

Section 6 describes in detail TMS risks in neurological and psychiatric patient populations.

General factors relevant to TMS-provoked seizure.: Numerous studies have explored precipitants for seizures in patients with epilepsy, which may also have implications for susceptibility to TMS-provoked seizures. Common provoking factors that might be relevant to subjects receiving TMS include sleep deprivation, stress, depression/anxiety, increased alcohol consumption, and menses (Balamurugan et al., 2013; Haut et al., 2007; Wassenaar

et al., 2014), with at least one study demonstrating that the degree of stress/anxiety or sleep deprivation significantly increased the risk of seizures (Haut et al., 2007). Sleep deprivation is of particular relevance, as studies using TMS in combination with EEG have reported increases in cortical excitability measures with sleep deprivation even in normal healthy subjects (Huber et al., 2013; Kuhn et al., 2016), although sleep deprivation was also associated with a decreased long-term potentiation (LTP)-like plasticity in response to a paired-associative stimulation protocol (Kuhn et al., 2016).

Medical factors relevant to TMS-provoked seizure.: Many medical conditions can lower seizure threshold and contribute to the risk of seizures. The list is vast, but includes in particular metabolic abnormalities (hyponatremia, hypocalcemia, hypomagnesemia, hypoglycemia, hyperglycemia, renal failure/uremia, liver failure); raised blood concentrations of proconvulsant medications due to reduced clearance (e.g. secondary to initiation of antibiotics for treatment of infections); alcohol withdrawal; use of stimulants such as cocaine or MDMA; use of immunosuppressive therapy with cyclosporine, tacrolimus and other agents that can cause the posterior reversible leukoencephalopathy syndrome; dialysis; systemic infection, and fever itself (Delanty et al., 1998).

4.1.2. The rate of seizures caused by TMS—While safety guidelines established first by Wassermann (Wassermann, 1998), augmented by Chen et al. (1997), and later on further improved (Rossi et al., 2009), have greatly reduced the incidence of seizures, they continue to occur even in individuals without identifiable risk factors and with stimulation within the “safe” parameter space. Since the literature was reviewed by Rossi et al. (2009), at least six additional clear TMS-induced seizures have been reported (Bagati et al., 2012; Chiramberro et al., 2013; Boes et al., 2016; Cullen et al., 2016; Cogne et al., 2017; Groiss et al., 2017). In addition, we have to mention a spontaneous seizure most likely not causally related to ppTMS (Vernet et al., 2012) and one other event, which may have been a convulsive syncope (Alonso-Alonso et al., 2011; Kratz, 2011; Kratz et al., 2011). However, as the use of TMS has spread and seizures are recognized as an “expected” potential AE, seizures are likely being newly reported only when the circumstances are remarkable in some way. The US FDA’s online database for mandatory post-market reporting contains only five seizure reports for approved devices, one from 2009, two from 2011, one from 2012, and one from 2015.

While the risk of seizure from TMS was described by Rossi et al. (2009) as “very low,” it has never been quantified and common assumptions, such as that single-pulse or low-frequency stimulation is less risky than rTMS within the recommended limits, have not been tested. To address this knowledge gap, Lerner et al. (2019) sent questionnaires to 2510 authors of papers using TMS and members of clinical TMS associations, requesting information on numbers of TMS sessions conducted and numbers of seizures for the five-year period, 2012–2016. 174 groups using a variety of coils (including figure-8, double cone and H-coils) and protocols responded, reporting over 300,000 TMS sessions and 24 seizures (standardized risk: 7/100,000 sessions). The data from the Lerner et al., study cannot be considered more than approximate and might have some reporting biases. Nineteen of these occurred in subjects with elevated risk, such as medications,

brain lesions, or epilepsy (standardized risk: 33/100,000 sessions). Respondents reported 19,308 TMS sessions delivered with a combination of parameter values outside the 2009 recommendations, of which 6749 were done in individuals with elevated risk. One seizure occurred in these sessions, in an individual with elevated risk (Table 1 of Lerner et al., 2019).

Together, single, paired (13), and low-frequency (3) stimulation (≤1 Hz) accounted for 16 seizures apparently caused by TMS in over 200,000 sessions for a standardized risk of 8/100,000 sessions across high and low-risk subjects. However, 13 of these occurred in high-risk subjects (standardized risk: 27/100,000 sessions). The other three had none of the risk factors listed by Rossi et al. (2009) (standardized risk: 2/100,000 sessions). All of these seizures occurred with single or paired stimulation. Eight seizures were reported with rTMS at a frequency >1 Hz, including one with iTBS (standardized risk: 7/100,000 sessions). Of these, 7 occurred in individuals with risk factors (standardized risk: 67/100,000 sessions) and one in an individual without identifiable risks (standardized risk: 1/100.000 sessions). While the numbers of seizures, especially in low-risk individuals, are too small for valid statistical comparison, an implication of these data is that high-frequency rTMS delivered within the 2009 guidelines is no more likely to cause seizures than sp/ppTMS, contrary to current assumptions and to the theoretical risk, which increases in proportion to the increase in the stimulation frequency. Finally, the likelihood of low frequency rTMS in inducing seizures seems even lower (possibily due to its inhibitory effects).

A new risk factor identified by this survey was lack of previous exposure to TMS. Over 62% of seizures occurred on the first exposure to TMS, and 75% occurred within the first three exposures. These data show that subjects who have undergone TMS safely are at less risk than first-time participants, even in the presence of risk factors. This suggests that precautions should be higher for early TMS exposures than for later sessions. This also may indicate the role of an individual risk and not of an accumulation of magnetic stimulation doses.

Regarding the new generation of deep H-coils, active monitoring by the manufacturer reported 48252 patients who were treated with H-coils until June 2019 (almost all with the FDA-approved H1-coil system): 46 experienced seizures (or convulsive syncope) and 5 pseudo-seizures, corresponding to a seizure per subject frequency of 85/100,000 and to a standardized risk of 4/100,000 sessions (Zibman et al., 2019b), thus similar to what previously reported (Tendler et al., 2018). However, only 11 of those reported seizures occurred in cases of low-risk subjects in which the protocol was administered according to instructions for use (Zibman et al., 2019). The survey by Lerner et al. (2019) included 6924 sessions with H-coil and reported three seizures (i.e., 43/100,000; all high-frequency rTMS). To conclude, although the H-coil appears to have a higher seizure rate, we do not have quantitative data from other manufacturers to make a proper comparison of seizure rate among the different coils.

The recent advent and expanding use of TMS-EEG for research and diagnostic purposes provides the opportunity to assess the potential of various TMS paradigms for inducing subclinical EEG abnormalities and epileptiform discharges in particular (Hui et al., 2019;

Noda, 2020; Tremblay et al., 2019). A literature search for relevant articles published between 2008 and March 2018 identified 173 studies containing EEG recordings concurrent with or immediately following a TMS session.

The application of single and paired-pulse TMS in healthy subjects as well as patients with various neurological disorders (including traumatic brain injury, stroke, mild cognitive impairment, Alzheimer's disease, myoclonus dystonia and disorders of consciousness) did not result in subclinical EEG abnormalities. In patients with epilepsy, however, a limited number of studies (Valentin et al., 2008; Kimiskidis et al., 2017, 2013) reported the induction of epileptiform abnormalities by single and paired-pulse TMS stimuli and delineated the stimulation characteristics that are associated with this excitatory effect (e.g. the spatial extent of the induced E-field and the employed stimulation intensity). Accordingly, for patients at particularly high risk of seizures (for instance, epileptic patients with uncontrolled seizures), continuous EEG monitoring during the TMS session and careful selection of stimulation parameters is advisable.

As for sp/ppTMS, the application of rTMS with low-frequency, high-frequency and TBS (at least cTBS) protocols in healthy subjects, neurological and psychiatric patients also did not result in subclinical EEG abnormalities (Hui et al., 2019; Noda, 2020; Tremblay et al., 2019). Specifically, for iTBS, the risk to induce seizures is very low (Oberman et al., 2011). This favorable outcome probably reflects the fact that these studies were generally performed in line with the 2009 safety Guidelines.

Recommendations: the risk of rTMS in inducing a seizure is definitely low, even in patient populations taking drugs acting on the central nervous system, at least with the use of traditional stimulation parameters and focal coils for which large data sets are available. While this is reassuring and helpful information for subjects, it remains necessary to be prepared to deal with a seizure that might arise in any experimental protocol.

4.2. Hearing

Rapid mechanical deformation of the TMS discharging coil produces a transient acoustic artifact originally reported as greater than 140 dB sound pressure level (SPL) (Counter and Borg, 1992) a level that exceeds the permissible noise exposure limit for impulsive noises (OSHA 2010, 2014; EU Directive 2003). More recent measurements have documented peak SPL below but near the 140 dB limit for single pulses: 139 dB (Z-weighted scale) and 136 dB (C-weighted) (Koponen et al., 2020) as well as 127.6 dB (C) (Kukke et al., 2017). The maximum SPL level during rTMS when the stimulator is set to 100% output is reported to be 96.5 dB (A-weighted scale, Dhamne et al., 2014) and 112 dB(A) (Koponen et al., 2020), which exceed safety thresholds of 80 dB(A) for 3 seconds and 85 dB(A) for 1 second (ACGIH, 2012; DOD, 2015).

Variations in measured output can be attributed to several factors including the weighting scale of the sound level meter, type of coil, type and rate of the TMS stimulus, and position and distance of the coil from the measurement microphone. The transient nature of the acoustic artifact makes accurate measurement with standard sound level meters difficult and is complicated by averaging response times that are much longer than the TMS artifact,

resulting in underestimation of the actual level of the peak by as much as 50 dB (Goetz et al., 2015). Moreover, since the TMS coil typically rests on the head, sound can be conducted through the skull bone and contribute risk which is not quantified with conventional sound measurements (Goetz et al., 2015; Koponen et al., 2020).

After exposure to the TMS stimulus, few adult subjects have experienced transient increases in auditory thresholds (PascualLeone et al., 1993; Loo et al., 2001). Permanent small threshold shift occurred in a single individual whose ear plug slipped out of one ear during stimulation with an H-coil (Zangen et al., 2005). When hearing protection was used, as in the majority of studies, no change in hearing sensitivity after TMS has been reported (Pascual-Leone et al., 1992; O'Reardon et al., 2007; Janicak et al., 2008). While pure tone hearing sensitivity remained unchanged in a group of adults immediately after TMS, small declines in otoacoustic emission (OAE) amplitudes were observed in the ear ipsilateral to the stimulus in the subset of participants for whom ear protection was less effective (Tringali et al., 2012). This OAE pattern resolved in the subsequent hour suggesting a temporary effect on the auditory system. While temporary threshold elevation or reduction of OAE amplitude appears reassuring, it has been shown long term degeneration of afferent auditory nerve fibers not detected by standard hearing measures (Kujawa and Liberman, 2009).

Factors affecting the amount of sound reaching a patient ear include the number and repetition frequency of TMS pulses, the type of coil (Dhamne et al., 2014; Koponen et al., 2020), proximity of coil to the ear, contact of the coil with the head, pulse amplitude setting of the device, the size of the ear canal and use of hearing protection. Furthermore, adequate fit of foam earplugs may be difficult for some patients or participants to achieve on their own. Of additional concern is the use of TMS for groups who may be at greater risk for noise-induced hearing loss. This includes persons who are being treated with ototoxic medications (aminoglygoside antibiotics and platinum-based compounds) and current exposure to solvents.

There is a risk of worsening hyperacusis by performing stimulations applied over the auditory cortex, near the ear, in patients with rTMS indicated for the treatment of tinnitus, especially when hyperacusis was already present before rTMS (Lefaucheur et al., 2012). More generally, pre-existing auditory symptoms were found to be possibly aggravated by rTMS applied over the auditory cortex in 1–2.2% of patients treated for tinnitus or auditory hallucinations (Muller et al., 2012). Given the relatively poor level of evidence of rTMS efficacy in these two applications (Lefaucheur et al., 2020), this particular use of rTMS should be approached with more caution.

Recommendations:

1. Hearing safety concerns for adults should be addressed by: (i) use of well-fitted and approved hearing protection (earplugs or ear muffs) by patients, subjects, and TMS operators (see Section 8.2); (ii) referral for auditory evaluation of any individual complaining of hearing loss, tinnitus, or aural fullness following TMS; (iii) individuals with pre-existing noise-induced hearing loss or concurrent treatment with ototoxic medications (aminoglycosides, cisplatin) should undergo TMS only after careful consideration of risk/benefit ratio. Temporary hearing

threshold shifts do not mean there has not been permanent damage to the auditory system, and the goal should be to avoid even temporary hearing changes.

2. The risk of increased auditory symptoms, although very low,should be considered in patients treated for tinnitus (or even auditory hallucinations) with hyperacusis present before rTMS application near the affected ear.

3. Individuals with cochlear implants should not undergo TMS(see also Section 3.2).

4. The evaluation of the acoustic output of newly developed coilsis needed, and hearing safety studies should be conducted as indicated by these measures. Because the actual sound level of the TMS pulse may be underestimated and sound conduction through the skull bone is not captured by standard sound level meters, it is recommended to consider TMS sound artifact levels as potentially hazardous to hearing without hearing protection devices.

5. Hearing safety concerns for children is dealt with in Section 4.4.

4.3. TMS safety on cognition

In this section, we will separately deal with cognitive effects described in experimental studies and those emerging in clinical studies.

4.3.1. Cognitive TMS effects in experimental studies—This section only concerns cognitive side/AEs, not the effects of TMS in cognitive studies. It should be underlined that is difficult to quantify all aspects of cognition during TMS: indeed, only the functions that are specifically measured as changes in performance on neurocognitive tests can be quantified.

In general, the overall impact of on-line TMS on cognition is disruptive, i.e., a decrease in performance during or immediately after stimulation, although there are some notable exceptions where TMS coupled with on-line working memory task performance enhanced working memory function (Luber et al., 2013, 2008, 2007; Luber and Lisanby, 2014). The overall effects of TMS on cognition are generally low to modest, in both health and disease. Within the protocols used in basic research in healthy participants, the effects of TMS on behavior are generally short-lived (in the order of minutes), and effect sizes generally low to modest as well. Both in absolute and relative terms are the effects of TMS on behavioral readouts such as reaction times and error rates, recall rates, and accuracy very short-lived, and rarely extend the time of stimulation for longer than tens of minutes when actually assessed.

Systematic assessment of the safety of TMS for cognition is complicated also by an enormous variance in study designs, small sample sizes and under-reporting of experimental and statistical details. Moreover, studies in healthy participants, generally do not assess long-term effects (over hours/days/weeks) of the TMS protocols used, which rarely involve the multiple sessions over repeated days that are delivered in patients. In light of this, the issues arising from neuroenhancement studies can be viewed similarly (at least for TMS),

where cognitive enhancement can be defined as *"any augmentation of core information processing systems in the brain, including the mechanisms underlying perception, attention, conceptualization, memory, reasoning and motor performance"* (see Luber and Lisanby, 2014). Given the small effect sizes, enhancement rarely occurs beyond the time immediately during or a short time after TMS, and we propose that the definition should be expanded by the duration over which this enhancement occurs (e.g., in our view a change in error rate over a few minutes of testing is not a concern). Repeated sessions of TMS coupled with on-line task performance can produce enhanced performance lasting up to 18 hours after the last stimulation, which the authors described as "extended" (Luber et al., 2013).

A comprehensive assessment of TMS studies showing performance improvements (with >60 studies up to that point) suggests that there is no systematic relationship between the type of enhancement (e.g., decrease in RT) and the stimulation protocol (single pulse, low/high frequency/TBS) (Luber and Lisanby, 2014). However, there is scant data to suggest how long substantial changes in cognition can last: Narayana et al. (Narayana et al., 2014) conducted a month of training combined with rTMS (6000 pulses, 5 Hz) spread over 4 sessions, that showed improved motor learning ability.

Lage et al. (2016) reviewed the effects of low-frequency TMS (max 1 Hz) in healthy participants, without evidence for lasting cognitive improvement nor deterioration. However, occasional "paradoxical improvement" following 1 Hz rTMS, which scaled with changes in effective connectivity in the stimulated network, has been described (Herz et al., 2014; Ward et al., 2010).

Non-specific effects on cognition might therefore also occur from auditory and somatosensory stimulation. For example, auditory threshold shifts (Tringali et al., 2012) or mild headaches due to sensory stimulation and/or coil-induced pain symptoms will likely impact on cognition (attention, memory) for the duration of these symptoms. Such effects can occur with any stimulation protocol (TMS/rTMS). However, they are unlikely to pose safety concerns.

4.3.2. Cognitive TMS effects in clinical studies—The issue is potentially different in clinical applications of rTMS. In this context, more extensive protocols (with regard to duration and intensity) are used, compared to any studies in healthy participants. Because these protocols can, in some cases, change the clinical appearance of patients over weeks if not longer, it is important to consider whether cognitive changes occur. In fact, given the clinical efficacy of these protocols, at least in some occasions such as major depression, one should a priori assume that concomitant changes in cognition will occur, and that these may not necessarily be beneficial. This notion is further emphasised by the fact that most clinical application target cortical areas (e.g., DLPFC) that have important roles in cognition.

The majority of data come from the use of TMS in depression. Serafini et al. (2015) included 22 studies in a systematic review of rTMS to DLPFC in major depression. An overall trend towards improvements in the neurocognitive profile was reported, but also negative findings were often present. This study acknowledged the problem of small samples and limited study designs. Importantly, in almost all cases, in this area of clinical research,

it remains unclear whether the cognitive changes are a consequence of the primary treatment effects (i.e., reduction in depressive symptoms), or directly caused by stimulation. Schulze et al. (2016) concluded that after 20 sessions of 10 Hz rTMS to dorsomedial PFC, no cognitive changes were observed in treatment resistant depression, apart from what are likely to be incidental changes out of a large battery of behavioural tests that were administered. A systematic review and meta-analysis of randomized controlled trials of rTMS to DLPFC (n = 30) concluded that active rTMS was not associated with generalization of gains across the majority of domains of examined cognitive functioning (McClintock et al., 2019). A subsequent systematic review by (Iimori et al., 2019) concluded that there was no reliable evidence for cognitive side effects across 31 randomized controlled studies administering rTMS to DLPFC in depression, schizophrenia, or Alzheimer's disease (albeit some pro-cognitive effects on executive function and attention in depression were found in six studies). Analysis of randomized or matched-groups, blind, sham-controlled studies (12 studies, 347 participants) on "excitatory" rTMS applied to left DLPFC in depression found no evidence of rTMS induced effects on executive functions as age advances.

Recommendations: Across clinical investigations of TMS, the heterogeneity in study design and patient samples is even larger than those in healthy participants. The paucity of evidence regarding cognitive side-effects of TMS in healthy subjects is exacerbated by an often untargeted "scanning" of cognitive changes, e.g., via questionnaires, without sufficient control for either type-1 or type-2 errors. It is strongly recommended that future studies that seek to systematically investigate the effects of TMS on cognition, including safety and cognitive enhancement, should consider the following:

Pre-registration of the precise methodology and expected outcomes. For patient studies in particular, large test batteries are often used, and the impact of rTMS on cognition is then generally assessed in exploratory analyses, but rarely with sufficient control for type-1 and type-2 errors. Consequently, there is little consistency across studies. However, it should be noted that concerns about safety are in light of overall small to modest effects on behaviour and cognition in the first place.

Studies should distinguish between (potentially) desired effects in which performance improves (enhancement), and undesired effects in which performance is impaired (impairment). Here, again, pre-registration should be employed.

Any improvement in a dependent variable (e.g. reaction time, error rate) should be interpreted with the distinction between genuine improvements, paradoxical improvements, and isolated improvements, as previously stated (Bestmann et al., 2015; see also Luber and Lisanby, 2014). Similar considerations apply to the assessment of any impairment or enhancement of cognitive function. Such assessment rarely provides sufficient demonstration of enhancement without quantifying multiple functions and dependent variables; for example, a decrease in RT cannot necessarily, *sine qua non*, be taken as evidence for enhancement or genuine improvement without demonstration that accuracy is not also affected. Genuine enhancement also requires demonstration of generalisability to qualify as genuine, and to distinguish it from an isolated improvement (i.e., the improvement

of a specific task that does not extend to tasks requiring the same or similar cognitive operations) (Bestmann et al., 2015).

Future studies should include follow-up assessments to quantify the longer-lasting impact of TMS on cognition, in particular in clinical applications in which stimulation is often delivered over days or weeks.

We conclude at present that TMS does not appear to cause apparent lasting perceptual or cognitive AEs in healthy subjects.

4.4. Special issues for children and pregnancy

TMS in pediatrics—Research in children poses special ethical as well as technical challenges (Hameed et al., 2017). From an ethical standpoint, children are considered a protected, special population because they cannot provide informed consent. Moreover, serious AEs, were they to occur, could affect a child's developing nervous system and result in life-long impairments. Finally, from a technical standpoint, performing research in young children, whose resting thresholds for cortical activation are higher, may exceed the stimulation intensity capacity of commercial TMS machines. Higher intensity stimulation could also be linked to increased discomfort and thus poorer cooperation and artifacts related to motion and muscle activation (Kaye and Rotenberg, 2017).

Despite these issues and challenges, since the last safety assessment in 2009 (Rossi et al., 2009), the use of TMS for a variety of physiological and treatment studies in children has continued to grow and has been recently reviewed (Allen et al., 2017). The published data from more than 100 studies since 2009 includes reports of TMS applied to approximately 2000 children under 18 years. These include not only case reports but clinical and biomarker studies involving larger groups of children (Allen et al., 2017; Gilbert et al., 2019; Oberman et al., 2014; Pedapati et al., 2019; Zewdie et al., 2020). Similarly, single-site safety reviews of repetitive TMS in 131 children (Zewdie et al., 2020) and TBS in 76 children (Hong et al., 2015) have been published. Indications have varied from severe motor disorders like hemiplegic cerebral palsy to neurodevelopmental disorders like autism spectrum disorder. Most studies reported no side effects. Those which did reported only mild, transient side effects such as headache. At present, many IRBs are comfortable with the risk benefit ratio for sp/ppTMS for biomarker or mapping studies and rTMS for biomarkers or clinical interventional trials in neurological disorders in children. However, IRB approval of the use of rTMS for assessments of biomarkers, such as of long-term-depression (LTD)-like and LTP-like cortical measures, in studies including healthy control children remains more variable.

The vast majority of TMS studies in children continue to be single and paired pulse studies. Serious AEs have not been reported in these studies, suggesting that these procedures pose minimal risk and that IRBs should be comfortable approving studies involving healthy children.

Hearing in pediatrics—A longstanding concern for TMS safety in children is whether special care for hearing protection would be needed, in part for anatomic reasons, in

children. Limited data have been published about changes in auditory acuity associated with TMS in children. One study reports no change in hearing in a group of 18 children (aged 2 months-16 years) that did not wear hearing protection (Collado-Corona et al., 2001). Another study of 16 children and young adults found no change in hearing thresholds after exposure to 1 to 2 sessions of TMS with up to 100% of maximum stimulator output. This study employed standard single and paired pulse techniques, up to 446 pulses, and children wore earplugs with a 29 dB noise reduction rating (Kukke et al., 2017).

To date, study sample sizes remain too small and TMS scenarios too limited to ensure hearing safety for pediatric cases. There is a particular concern in young children for which appropriately sized ear plugs are not available. Additional concerns are that their canal resonance is different from adults and their smaller head size results in the TMS coil being closer to the ear.

Recommendations: we cautiously conclude that when suitable hearing protection is used, single-pulse and paired-pulse TMS in pediatrics is safe for children two years and older. For children younger than two years, data about risk for acoustic injury are not available, and therefore specialized hearing protection may be required. Also, for children age one year and younger, safety data are not available, and will have to be obtained. The larger number of children, including healthy children, now reported to have undergone sp-ppTMS, or rTMS provides reassurance regarding safety of these techniques.

TMS in pregnancy—Pharmacologic interventions for neurologic and psychiatric disease in pregnancy are at times associated with risk to the fetus. This has prompted a growing interest in noninvasive brain stimulation as an alternative to pharmacotherapy during pregnancy. While studies specifically aimed to test TMS safety in pregnancy are absent, the physics of conventional clinical rTMS appear compatible with pregnancy. A finite element model indicates that the TMS-induced E-field, generated by a figure-of eight coil adjacent to the DLPFC, approximates 100 mV/m when the coil-uterus distance was ≥60 cm (Yanamalda et al., 2017). This value is far below the safety threshold to stimulate myelinated central and peripheral nerves (800 mV/m) stated in the International Commission on Non-Ionizing Radiation Protection Guidelines (McRobbie, 2010). Further studies of migraine patients during pregnancy assessed TMS-induced magnetic field safety, and concluded that single-pulse TMS applied to the occiput generates a magnetic field that decreases from 0.9 T at 1 cm away from the coil surface to ~11×10^{-6} T at 46 cm away from the coil surface—an approximate point where the uterus may reach at full term (Clarke, 2006; Dodick, 2010; Knoth et al., 2010).

While the E-field electric exposure is close to nil, the major source of risk to the fetus is a TMS-induced seizure in the mother. Seizures can be induced safely during pregnancy when using ECT, however in that case the mother is anesthetized, has received a paralytic agent to prevent movement of the body, and has her respiration supported. Without such safeguards, a seizure during pregnancy can be a source of complications. Further, it has been shown that reproductive hormones affect cortical excitability.

Of twelve published reports and trials applying rTMS for depression or other indications during pregnancy (n = 50 total patients) (Nahas, 1999; Klirova, 2008; Zhang et al., 2011; Kim, 2011, 2019; Gahr, 2012; Burton et al., 2014; Hizli Sayar, 2014; Guerrero Solano and Pacheco, 2017; Ferrao and Silva, 2018), the stimulation protocol for the majority of patients (n = 36, 72%) included high-frequency rTMS, targeting the left DLPFC. In addition, 12 patients (24%) underwent low frequency stimulation of the right DLPFC, and 2 patients (4%) underwent bilateral stimulation of the left and right DLPF cortices. Among all stimulation protocols, 58% (29/50) of patients showed significant improvement (≥50% reduction in symptom severity from baseline). In studies where the left DLPFC was the single stimulation target, researchers used 5–25 Hz rTMS, and the response rate was 50% (18/36). In studies where 1 Hz rTMS was delivered to the right DLPFC, 75% of patients (9/12) were considered treatment responders. Both of the two patients who received bilateral rTMS therapy responded to the treatment initially, before symptom relapse approximately two months following rTMS. The reported AEs in the published cases were transient, mild, and usually limited to scalp pain and mild headache. Singular instances of supine hypotension syndrome, concentration difficulty, and anxiety were reported, each of which resolved spontaneously. Adverse event prevalence for left, right, and bilateral DLPFC stimulation were 11% (4/36), 50% (6/12), and 0% (0/2), respectively.

With respect to long-term effects on the offspring, the data are also limited. However, encouragingly, 18–62 month-old children (N = 26) born to mothers treated with high-frequency rTMS for depression during pregnancy did not present with increased perinatal complications and were within normal limits in both cognitive and motor development comparable to those infants who were born to mothers with untreated depression (Kim et al., 2019).

Recommendations: from the reports cited above, a cautious conclusion can be made that rTMS is minimal risk for the mother and child. A logical extension is that spTMS and ppTMS are also minimal risk procedures in pregnancy. Notably, this assessment is based on data largely with a figure-of eight coil.

Safety data in pregnancy with the use of the H-coil, or with other neuromodulation technologies are not yet available. Notably, no AEs related to the fetus or newborn child have been reported.

5. Magnetic seizure therapy

As it is the first time that Magnetic Seizure Therapy (MST) is addressed in the safety guidelines, and because it is offered as treatment in few labs around the world, we provide an introduction regarding definition and therapeutic settings of MST. In contrast to sub-convulsive rTMS, where the goal is to select parameters to minimize seizure risk, optimal MST dosing involves selecting parameters more efficient in inducing seizure.

Definition

MST refers to the use of TMS to induce seizures deliberately, under anesthesia, for the treatment of depression or other serious neuropsychiatric conditions (Lisanby et al.,

2003, 2001a, 2001b). The rationale behind MST is that the increased control over site of stimulation permits sparing of brain regions related to the AEs of ECT, thereby resulting in a safer way of administering seizure therapy (Lisanby, 2002).

Therapeutic setting and pre-procedure evaluation

MST is given under general anesthesia, therefore it is required that it be performed in a procedure room equipped with a crash cart and an anesthesia station by a multidisciplinary team including a psychiatrist (or other physician or nurse practitioner with experience in performing ECT), anesthesiologist, and nursing staff who monitor the patient during the procedure and during the immediate post-treatment recovery period until full orientation is regained. Anesthesia for seizure therapy involves intravenous sedation with a sedative/hypnotic (typically methohexital) followed by muscular paralysis with a depolarizing neuromuscular blocker (typically succinylcholine) to prevent musculoskeletal injury from the motor convulsion, and 100% oxygen given via facemask and manual ventilation during the period of muscular paralysis. Seizure induction and duration are assessed using two methods: (i) 2-channel frontomastoid scalp EEG, and (ii) motor seizure expression using a tourniquet on a leg applied prior to the infusion of the muscle relaxant. Pre-procedure medical evaluation entails the standard pre-ECT workup, including physical examination, blood and urine lab analysis, pregnancy test, drug screen, electrocardiogram, and pre-anesthesia evaluation with additional testing as indicated based on comorbid medical illnesses. Further information about the context and pre-treatment workup for ECT can be found in [APA Task Force Report on ECT] and at present, it is reasonable to require the same workup for MST.

Dosing

MST is usually given at 100% of maximal stimulator output, at a frequency of 25–100 Hz, in a single train lasting up to 10 s. Even at maximal stimulator output intensity, studies using realistic head modeling of the E-field induced in the brain with MST demonstrate that it is much lower and much more focal than ECT (Deng et al., 2013, 2011, 2009, Lee et al., 2017, 2014) which is thought to underlie its superior side effect profile. Studies have shown that the optimal frequency for inducing seizure with MST, and with ECT, is actually lower than the frequencies typically used with clinical ECT (specifically, 18–25 Hz) (Peterchev et al., 2015).

Optimal dosing of MST to maximize therapeutic benefit while minimizing side effects is not known. Dosage for ECT is typically personalized based on individually titrated seizure threshold to maximize the risk/benefit ratio of ECT, and this practice has been adopted in many MST studies as well. Seizure threshold titration entails administering stimuli at successively increasing dosage every 20 s in the same anesthesia session until a seizure is induced. Subsequent sessions are given at a specific percentage above seizure threshold, based upon the electrode placement, in the case of ECT. Optimal dosage above the seizure threshold for specific MST coils is not known at the time of this writing.

TMS coils differ in their efficiency of seizure induction. In general, less focal and larger coils are more efficient in inducing seizure (e.g. the twin-coil and double-cone coil) in

comparison with the more focal figure-8 coil (Lisanby et al., 2001a). Much of the work has utilized round or double-cone coils placed on the vertex, which is reported to have a lower seizure threshold than other placements, such as the midline prefrontal cortex.

Future research should determine the dose-response relationships among dosage relative to threshold, coil selection, and site of stimulation and risk of side effects with MST. Further research could also examine whether intensity should be individualized with MST, as it is with TMS (Peterchev et al., 2015).

Animal testing

Testing in nonhuman primates using modern neuropathological and stereological cell counting methodology demonstrated the safety of MST, as well as the safety of ECT. Both interventions lacked neuropathological evidence of tissue damage (Dwork et al., 2004), and both showed no reductions in the count of neuronal and glial cell (Dwork et al., 2009). Studies using a sensitive non-human primate model of the neurocognitive effects of ECT demonstrated MST was significantly safer than ECT and was no different from anesthesia alone sham (Moscrip et al., 2006; Spellman et al., 2008; McClintock et al., 2013). This is an important result because human studies have typically contrasted MST with ECT with no sham condition. Animal studies also substantiate that the seizures induced with MST are less robust and differ in their physiological expression than ECT induced seizures (Cycowicz et al., 2008, 2009, 2018).

MST in clinical trials

Cognition: To date, all work with MST in humans has been in patients with clinical conditions necessitating ECT, mostly major depressive disorder (Daskalakis et al., 2020; Fitzgerald et al., 2013; Kirov et al., 2008; Kosel et al., 2003; Lisanby et al., 2003; Sun et al., 2016), bipolar disorder (Cretaz et al., 2015; Kayser et al., 2009; Tang et al., 2020), and to a lesser extent, schizophrenia (Tang et al., 2018). Furthermore, the demographics of ECT demonstrate that a large proportion of patients receiving ECT are elderly. These diagnoses and age groups are associated with cognitive changes at baseline, highlighting the clinical significance of developing a safer alternative to ECT for such patients to spare cognitive function. Clinical trials with MST demonstrate an excellent safety profile with minimal to no detectable cognitive side effects (McClintock et al., 2011; Polster et al., 2015). Several of these studies have used randomized double-blinded controlled trials to compare the side effects of ECT versus MST (Fitzgerald et al., 2013; Kayser et al., 2011; Lisanby et al., 2003). These studies have consistently found superiority of MST over ECT in terms of cognitive side effects.

Experience with MST in schizophrenia is more limited than with mood disorders. Tang et al 2018 reported on a study of 8 patients with treatment resistant schizophrenia who receive up to 24 MST treatments. Cognitive side effects were evaluated using a neurocognitive test battery assessing multiple cognitive domains, including tests sensitive to the cognitive effects of schizophrenia, and most measures showed no change.

Cardiovascular effects and complications from anesthesia: Cardiovascular effects are among the leading causes of morbidity and mortality from ECT, which are rare. Studies suggest that these risks are even lower with MST than with ECT (White et al., 2006) and that MST induced seizures are less likely to require medications to control cardiovascular responses, which include bradycardia in response to the parasympathetic surge seen with subconvulsive stimuli, and tachycardia as well as hypertension in response to the sympathetic surge following convulsive stimuli (Rowny et al., 2009). Pre-treatment with an anticholinergic agent (typically atropine 0.4 mg iv) is given when subconvulsive stimuli are anticipated, such as during a seizure threshold titration procedure.

Serious complications from anesthesia are rare with ECT. Data indicate that given the more focal nature of MST, it typically requires lower dosages of the paralytic agent to effectively protect the body, which reduces the time during which respiration needs to be supported until the paralytic agent has worn off. Given that MST is associated with less amnesia and more rapid return of orientation, it is even more important that the sedative agent is dosed so that it lasts until the paralytic agent has worn off. Otherwise, the patient has a risk of regaining consciousness while still paralyzed, which is a distressing event. Other more common but less serious side effects of anesthesia include muscle soreness (due to depolarizing neuromuscular blockade), but the degree of muscle soreness as well as headache and other subjective side effects are reported to be lower with MST than ECT (Lisanby et al., 2003).

Psychiatric Complications: Mania has been reported as a psychiatric complication of ECT, which is a side effect shared with other effective antidepressant treatments. To date, there are 3 cases of mania reported with MST (Daskalakis et al., 2020), therefore, monitoring for symptoms of mania is recommended.

Other potential complications of ECT, not reported to date with MST: As described in [APA Task Force on ECT] there are other potential complications of ECT which have not to date been reported with MST. These include death (extremely rare with ECT and attributed to a rare complication of general anesthesia), cerebral herniation (attributed to a pre-existing condition associated with increased intracranial pressure, such as spaceoccupying lesion), prolonged seizure (aka status epilepticus), postictal agitation, and dental fracture (secondary to masseter contraction induced by ECT, mitigated through the use of a bite block to protect the teeth). Masseter contraction is not observed with MST, however use of bite block is considered an appropriate precaution to protect the teeth and the airway during MST.

The number of patients who have received MST to date is small compared to over 8 decades of clinical experience with ECT, therefore, low incidence side effects of MST may be as yet unknown. Given this, being prepared for side effects reported with ECT is medically appropriate.

Other potential complications specific to MST: Although the patient is under anesthesia at the time of the treatment, hearing protection via earplugs is required during MST just as it is during TMS. In fact, intensities used with MST (usually 100% of maximal

stimulator output) are typically higher than those used with subconvulsive dosages of TMS (which are typically based on individually titrated RMT). Like TMS, MST will induce electrical eddy currents in metal on or in the head. For this reason, intracranial metal implants, skull plates, or aneurysm clips are contraindicated. It is also important that the scalp EEG electrodes used to monitor the seizure must be TMS compatible to avoid scalp burns that have been reported when TMS is used over traditional EEG electrodes. Given the high intensities, frequencies, and long train durations used with MST, heating of the stimulating coil may represent a safety issue. Typically, MST coils are pre-cooled in a refrigerator prior to each use. While coil temperatures can rise above 40 C, the rate of temperature rise is slow, so as long as the coil is removed from the head immediately after the stimulation train is delivered, the risk of skin burn is low. To date there is one report of a superficial scalp burn due to a coil malfunction (Daskalakis et al., 2020).

Special Populations ——Most reported work to date with MST is in adults. There is one published case report of MST being used safely in an adolescent with depression (Noda et al., 2014). The safety of MST in children, adolescents, and in pregnancy has not been reported to date.

6. Side effects in specific patient populations

6.1. Neurology and rehabilitation

A systematic review of the literature through the database PubMed from March 2008 (last TMS Safety meeting) to October 2019 was conducted. The following keywords (repetitive TMS) OR (rTMS) OR (deep TMS) OR (dTMS) OR theta burst) AND (side effect OR AE OR safety[title] OR seizure[title]) initially identified 199 articles, which were reviewed, and finally 40 relevant papers were considered. They consisted of: (i) original articles reporting cases of AEs occurred during rTMS studies in healthy volunteers (n = 3); (ii) original articles reporting cases of AEs occurred during rTMS therapy trials for neurological (n = 4) or psychiatric (n = 7) indications; (iii) review papers on safety issues regarding rTMS application in neurology (n = 4), in psychiatry (n = 15) (mostly on depression, including TBS, dTMS, and accelerated protocols), in children or adolescents (n = 4), or concerning the use of TBS in general (n = 3).

In this section, we will only analyze the reported SAEs occurred in the context of the treatment of neurological diseases (including tinnitus) by means of rTMS (or TBS) protocols. In our previous work (up to 2008) (Rossi et al., 2009), 3 cases had been identified concerning rTMS use in patients with chronic pain (n = 1) (Rosa et al., 2006), tinnitus (n = 1) (Nowak et al., 2006), and epilepsy (n = 1) (Dhuna et al., 1991). In the current literature search, 5 patients were identified as case reports with migraine (n = 1) (Wang et al., 2018), motor stroke (n = 1) (Gómez et al., 2011), post-stroke pain (n = 1) (Cogné et al., 2017), post-stroke aphasia (n = 2) (Cogné et al., 2018). Two additional cases of patients with chronic pain (Picarelli et al., 2010; Lee et al., 2012) were found as cited in relevant review articles.

Among these 10 cases, 8 events were seizures and the remaining two cases were the occurrence of a sudden, uncontrollable and intense thirst during procedures of low-

frequency (1 Hz) rTMS delivered over the right inferior frontal gyrus in patients with post-stroke anomic aphasia (Cogné et al., 2018). The pathophysiology of this atypical AE is very obscure and will not be discussed further. In addition, this was not really a SAE, since thirst immediately disappeared in both patients just after drinking water, without requiring medical intervention and did not lead to any significant disability or incapacity.

Concerning the 8 cases of seizures, also no sequel and no reoccurrence was reported. However, predisposing factors were not found in 4 cases. Among the other patients, one had left temporal epilepsy (although motor seizure occurred after rTMS), one underwent a session of brain mapping using high-frequency rTMS at 100% RMT two days prior, one had stroke, and one had stroke and alcohol withdrawal syndrome. In terms of rTMS protocol, the "technical" factors possibly involved in the 6 seizures produced by 10 Hz-rTMS delivered over M1 (hand representation) were as follows: (i) a too high intensity of stimulation, i.e. 100–110% RMT (Rosa et al., 2006; Wang et al., 2018); (ii) a too short inter-train interval, i.e. 5–10 s. (Lee et al., 2012; Cogné et al., 2017); (iii) the use of an angulated figure-of-8 coil (B70, MagVenture, Farum, Denmark) (Rosa et al., 2006; Picarelli et al., 2010; Gómez et al., 2011). Indeed, the B70 coil is more powerful and activates brain deeper than the flat B65 figure-of-eight coil (Kammer et al., 2001), which is more widely used in rTMS practice. The B70 coil is really useful to target deeper cortical structures, such as the representation of the lower limb or the perineum within M1 and therefore valuable for the treatment of symptoms, such as pain, affecting these body regions (Hodaj et al., 2018). However, this type of coil may be less suitable to stimulate more superficial cortical areas, such as the motor cortical representation of the upper limb.

Regarding the two cases of seizures that occurred after temporal or parietal stimulation (Dhuna et al., 1991; Nowak et al., 2006), a procedure of 15/16 Hz-rTMS was performed at relatively high intensity (100% MSO or 100% RMT) and using a large (circular) or deep (B70) coil.

Finally, as recently reviewed (Pereira et al., 2016; Chen et al., 2016), the risk of AE in epileptic patients is low.

6.2. Alzhemer's disease and new multi-site stimulation paradigms

The traditional multi-session design targeting the DLPFC using high-frequency rTMS is showing promising results in reducing the behavioral and psychological symptoms in Alzheimer's Disease (AD) patients (Cotelli et al., 2011; Ahmed et al., 2012; Rutherford et al., 2015; Wu et al., 2015; Zhao et al., 2017; Dong et al., 2018; Cui et al., 2019).

Recently, the precuneus has been suggested as another cortical target with potential cognitive aftereffect because of its importance as an episodic memory hub as well as a major hub node of the Default Mode Network. Two weeks of precuneus rTMS led to improvements in long-term episodic memory (Koch et al., 2018). Each daily stimulation session consisted of forty trains of 2 sec delivered at 20 Hz spaced-out by 28 s of no stimulation (total number of stimuli: 1600). The entire session lasted approximately 20 min. Intensity of stimulation was set at 100% of the RMT. Notably, no significant AEs were reported in these studies, irrespective of the DLPFC or precuneus targets.

Another recent approach is based on multi-site, high-frequency rTMS protocols combining the stimulation with cognitive training. The intervention targets six different brain regions in the same stimulation session: left and right DLPFC; Broca's area; Wernicke's area; left and right inferior parietal lobule. Daily sessions are applied across three targeted regions, with a total of 1300 rTMS pulses at 10 Hz in short bursts of 20 pulses. rTMS intensity was set up to a maximum of 110% of each participant's RMT. 30 sessions have been shown to have possible beneficial immediate and long-lasting effects (more than six weeks) on overall cognitive improvement based on evidence from at least one class II study (Lee et al., 2016) and one class III study (Rabey et al., 2013). Another recent clinical trial evaluated the efficacy and safety of a 6-week course of daily neuroAD™ therapy with multi-site rTMS combined with cognitive training. Patients with milder form of AD (ADAS-Cog ≤30) showed a significant benefit favoring active over sham (Sabbagh et al., 2019). In all these multi-site studies, no major AEs were reported.

6.3. Psychiatry

In major depressive disorder (MDD), rTMS protocols have been approved as treatment option in many countries, and other psychiatric disorders are a focus of current research as well (Lefaucheur et al., 2020). The large body of evidence including thousands of patients in clinical trials led to (i) a more rapid development of new protocols seeking innovation, (ii) expanding the stimulation parameter matrix beyond previous limits and (iii) applying rTMS in conditions where depressive disorders occur as co-morbid entity.

In their recent meta-analysis of 81 studies with 4233 patients, Brunoni et al. (2017) included accelerated TMS; "deep" (H-coil) TMS; priming TMS, synchronized TMS and TBS in addition to classical low and high frequency protocols. The different categories do not comprise standardized protocols, but rather represent a heterogeneous group. Among innovative protocols there has been a tendency of increasing parameters (i.e., stimulation intensity) towards a putative higher efficacy. One example is TBS which was first applied at 80% AMT stimulation intensity according to Huang et al. (2005). For MDD, pilot application was performed with 80% RMT intensity in a safety study with healthy subjects (Grossheinrich et al., 2009), and in MDD at 80% RMT with two series of iTBS with 10 min interval or iTBS followed by cTBS corresponding to the higher number of stimuli of standard 10 Hz protocols (Holzer and Padberg, 2010; Plewnia et al., 2014). More recently, iTBS has been applied in an accelerated fashion with five sessions per day and 1620 pulses per session in 54 triplet bursts (2 s. on, 8 s. off) (Duprat et al., 2016) or with a marked higher stimulation intensity of 120% RMT (Blumberger et al., 2018). In this large randomized non-inferiority trial, rate and characteristics of AEs in 208 patients undergoing iTBS were not different from those in the 204 undergoing 10 Hz (Blumberger et al., 2018). Though these protocols appeared to be clinically effective, it cannot be concluded that higher intensity or stimuli numbers are superior to standard iTBS at 80% RMT or AMT in terms of its risk/benefit ratio, due to the lack of studies investigating dose response relationships in iTBS. Theoretically, lower intensity protocols may still have advantageous safety profiles and should also be further investigated.

In comparison with MDD, safety data for other psychiatric disorders are less comprehensive. However, there is no evidence of a clinically different AE or SAE profile in other disorders including conditions where rTMS is applied for co-morbid depressive syndromes, e.g. post-stroke depression where its application has been controversially discussed (Bucur and Papagno, 2018; Deng and Lisanby, 2017).

The expansion of protocols and putative indications in psychiatry converges with the problem that psychiatric side effects are difficult to follow across studies. Treatment-emergent mania and new onset psychotic symptoms (as mentioned in the 2009 guidelines) are still examples of such side effects occurring within acceptable safety limits for TMS dose. Treatment-emergent mania has been reported for both low and high frequency rTMS in patients with uni- and bipolar depression (Xia et al., 2008) after stimulation of the left prefrontal cortex. Although single cases suggest a causal relationship between rTMS and mania, the overall rate (13 cases) across 53 randomized controlled studies in depression appears to be low (0.84% mania for active rTMS vs. 0.73% for sham rTMS) and even below natural switch rates in patients with bipolar disorders receiving mood stabilizers (2.3 to 3.45%)" (Xia et al., 2008). A sub-manic activation syndrome, characterized by onset or worsening of insomnia, agitation, or anxiety, is not uncommon among depressed patients receiving daily high-frequency rTMS in naturalistic settings (Philip et al., 2015) and likely accounts for the majority of cases where concomitant benzodiazepines or hypnotic medications were initiated as allowed in large regulatory RCTs.

Similarly, cases of rTMS induced psychotic symptoms, agitation, anxiety, insomnia and suicidal ideation (Zwanzger et al., 2002; Janicak et al., 2008) have been reported; however, it is still unknown whether such AEs are more frequent during rTMS compared to the natural course of the underlying conditions. Psychotic symptoms and suicidal ideation have been never described in normal subjects during or after rTMS and there is even some evidence for an antisuicidal effect of rTMS in MDD (George et al., 2014; Weissman et al., 2018). However, when given as an accelerated schedule of TMS treatments (3 sessions per day for 3 days), active stimulation was associated with greater patient ratings of anxiety/ irritability over time than sham (George et al 2014).

In all the above cases, psychiatric AEs induced by rTMS were transient, with a rapid spontaneous resolution after TMS cessation or parameters change, or promptly controlled by pharmacological treatment. Identifying TMS-associated psychiatric AEs and SAEs in samples with neuropsychiatric disorders is intrinsically challenging and particularly complex when it comes to reporting suicidality, given controversy that may be generated surrounding reports of suicidal behavior associated with noninvasive transcranial brain stimulation (Weintraub et al., 2013).

Thus, our recommendations are mainly based on data from large RCTs in psychiatric disorders (n > 100 patients) where rTMS and sham stimulation can be compared in terms of AEs and SAE. An overview on these studies is shown in Supplemental Material, Table S2. An exception from active vs sham comparability is the RCT by Blumberger et al. (2018), which compared iTBS to standard 10 Hz rTMS, but not sham TMS. However, we have included this study as the data recently led to approval of the iTBS protocol by the U.S.

Food and Drug Administration (FDA). The AE and SAE rates reported from RCTs indicate categories of side effects and provide an approximation to identifying TMS specific side effects. In sum, psychiatric SAE occurred at a rate between 1 and 5%, but their occurrence did not clearly differ between treatment groups. However, psychiatric patients undergoing rTMS should be clearly informed about the risk of psychiatric side effects which are not uncommon but relatively minor in severity.

A critical issue is the occurrence of seizures in psychiatric patients, as there are various predisposing factors, e.g. pharmacotherapy with effects on seizure thresholds, substance consumption (e.g. alcohol, caffeine), instable behavioral patterns (e.g. agitation, sleep deprivation). These circumstances may be more relevant when technical parameters are at upper limits based on protocols or coil designs.

Tendler et al. (2018) recently reported details in 31 seizures and two pseudo-seizures during H1 coil TMS. Twenty-nine seizures occurred in depressed patients, one in a case of schizophrenia, and one in a case of post-traumatic stress disorder (PTSD). In the majority of cases, patients received concomitant pharmacological treatment with psychopharmacological agents, mostly in combination (amitriptyline, aripiprazole, bupropione, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, lithium, lurasidone, mianserine, mirtazapine, olanzapine, sertraline, trazodone, venlafaxine, vortioxetine). The question whether these drugs had a causal role is difficult to answer, as substances with a comparably higher risk (e.g. clomipramine) were involved, but also substances whose seizure facilitating potential is usually regarded as negligible (Steinert and Fröscher, 2018).

We recommend that vigilance is warranted if rTMS is applied in patients receiving concomitant pharmacotherapy with medication that has pro-convulsant properties, although no additional risk has been documented to date (see Section 2.4). We note that in three large RCTs (O'Reardon et al., 2007; George et al., 2010; Levkovitz et al., 2015) rTMS was applied as monotherapy; however in numerous other large RCTs (e.g., Herwig et al., 2007; Carpenter et al 2017; Blumberger et al 2018), it was adjunctive to psychiatric medications and the observed rate of AEs was not substantially different. Tendler et al (2018) reported alcohol consumption in six and poor sleep in two patients who had a seizure during H1 coil rTMS. Patients treated with all TMS coils shapes should be informed and closely monitored regarding substance intake and behavioral habits, particularly sleep patterns. Finally, thorough evaluation and reporting of psychiatric AEs/SAEs in RCTs according to Good Clinical Practice (GCP) criteria by principal investigators of RCTs is essential, and similar systematic assessment of AE/SAE to benefit rations should be also introduced in clinical practice.

Data are still needed to characterize the potential adverse or beneficial effects of concurrent marijuana products (e.g., THC and CBD) during rTMS therapy.

Recommendations: available data indicate no additional risks of major AEs in specific patient populations so this is not a concern that needs to be taken into account, at least with the protocols of intervention considered.

7. Update of safety tables

7.1. Conventional rTMS: low and high frequency

As reviewed in other sections of these guidelines, the previous safety tables were overall effective in preventing seizure occurrence both in healthy volunteers and patient populations. This was the case despite the fact that they were determined in healthy young subjects, using only figure-8 coils. Such efficacy of those safety table in preventing seizures may be attributed to the use of M1 as target of stimulation, that is traditionally considered the most epileptogenic area of the neocortex after the mesial temporal area (that is deeper and not directly accessible to TMS). In the following years, no studies explored systematically further combinations of intensity/frequency/number of pulses and trains/intertrain intervals/ and coil types with the purpose to test their safety in healthy subjects. This probably happened because the previous tables concerned already the most used range of parameters in research and clinical settings.

In the last ten years the number of rTMS studies including clinical trials has grown impressively; a Medline search (October 2019) using “TMS” or “rTMS” or “Transcranial Magnetic Stimulation” as keywords identified 14,000 papers of which about 1400 included the term “clinical trial”. The imagination of researchers in designing new combinations of frequency, intensity, train duration, number of pulses per day, number of sessions day/week, duration of a standard course of therapy, type of coil, and number and location of brain stimulation sites has been enormous. For these reasons, it is unrealistic to categorize all these variables into new tables.

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 intensity/frequency/duration of conventional rTMS treatment (when seizure induction is not the goal) must remain well below this combination of parameters.

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 scientifc community through dedicated scientific Journals about the new possibly unsafe combinations of parameters.

We believe that this strategy should not preclude the development of new protocols, while respecting a scientific-based safety profile.

7.2. Patterned rTMS: Quadripulse stimulation (QPS)

The QPS was invented to induce robust LTP/LTD effects in human brain using monophasic magnetic/electric pulses (Hamada et al., 2009, 2008, 2007; Hamada and Ugawa, 2010). A recent review paper has summarized the details of this stimulation method (Matsumoto et al., 2020). All of those are summarized in Supplemental Material, Table S3. To our knowledge, more than 500 normal volunteers and 30 patients with dementia, 30 with Parkinson's disease, and 10 with epilepsy participated in some QPS experiments. The target stimulation area was mostly the M1, but the supplementary motor area, premotor cortex, DLPFC and sensory cortex have all been target areas in a few papers (Supplemental Material, Table S4). Most of them followed the original stimulation parameters reported by Hamada et al (2008); in others, some unprecedented stimulation parameters were used, such as the intensity of 1.3 times AMT for hand muscles (or 0.9 AMT for tibialis anterior muscle) with 2880 total TMS pulses given in one session, without noticing AEs.

In addition to the original study group, Simeoni et al. (2016) studied the inter-individual variability of QPS in normal subjects, and no AEs were noted. One group used QPS for the treatment of depression (Nakamura, 2017). They stimulated the left DLPFC with QPS5 which gave a beneficial effect on depression and no AEs.

Based on the above data, we propose the safety guideline for QPS in Supplemental Material, Table S3. We may conclude that QPS with a figure-8-coil is safe in normal subjects.

7.3. Patterned rTMS: theta burst stimulation (TBS)

The majority of TBS papers have used the parameters originally described by Huang et al (50 Hz bursts of 3 pulses repeated at 5 Hz; stimulus intensity of 80% AMT) (Huang et al., 2005). To the best of our knowledge, there has only been one seizure reported using these parameters (Lenoir et al., 2018). The other seizures reported using TBS have used parameters that exceed these levels.

The first seizure was reported by Oberman and Pascual-Leone (2009) in a healthy individual after cTBS to M1 delivered at an intensity of 100% RMT. Two more seizures (one definite generalised and one suspected partial) were reported (Lenoir et al., 2018) after cTBS over the right sylvian fissure using a double cone coil and an intensity of 80% RMT of the tibialis anterior muscle of healthy individuals. A recent survey of TBS in treatment of psychiatric disease reports no seizures (Rachid, 2017), as does a review of the use of TBS in 165 children aged 6–18 years (Hong et al., 2015b). Perhaps the most extreme parameters are those used by Hanlon et al. (2017) who used 6 trains of cTBS at 110% RMT (separated by 1 min intervals) applied to ventro-medial PFC in cocaine users or alcohol-dependent volunteers without incident].

As reported in Supplemental Material, Table S5, parameters of TBS are quite standard among studies, ranging between 80–100% of RMT, with the exception of two studies (Hanlon et al., 2017a, b) that used TBS applied over the left frontal pole or the medial prefrontal at 110% of RMT and one study targeting the left DLPFC at 120% of RMT (Blumberger et al., 2018). Based on these data, it can be concluded that TBS in this range is

safe. For future clinical trials exceeding the parameters of Supplemental Material, Table S5, the same recommendations suggested in the paragraph 6.1 should be followed.

7.4. Paired associative stimulation (PAS) protocols

PAS protocols are emerging as an experimental method to investigate principles of neural plasticity in humans based on spike-timing dependent plasticity (STDP) rules elaborated in animal models (Koch et al., 2013). PAS protocols were developed originally by applying a single electrical stimulus to a peripheral nerve few ms before a TMS pulse delivered to the contralateral M1 (Stefan et al., 2000). Depending on the interstimulus interval (ISI) "repeated pairing of the stimuli (i.e., association) over an extended period may increase or decrease the excitability of corticospinal projections from hand M1, thereby inducing LTP-like and LTD after effects" (Wolters et al., 2005). Other similar protocols have been developed in order to apply PAS by targeting the primary motor leg area. TMS was applied over the motor hot spot of the tibialis anterior muscle (120 pulses at intensity for eliciting MEPs of about 0.5 mV), paired with the electrical stimulation of the common peroneal nerve (Stinear and Hornby, 2005; Prior and Stinear, 2006). Some PAS protocols used nociceptive stimuli (intraepidermal electrical or laser stimulation) as conditioning peripheral stimuli applied at the limb (Suppa et al., 2013; Gavaret et al., 2018).

Recent PAS protocols introduced repeated paired-coil focal TMS over different cortical areas to modify the activity of corticocortical networks: this is called cortico-cortical PAS (ccPAS). Associative ccPAS of homologous areas of left and right M1 resulted in an ISI-specific long-term MEP increase in the conditioned M1 (Koganemaru et al., 2009; Rizzo et al., 2009). Following these initial observations, there have been several attempts to modulate cortico-cortical plasticity in a STDP manner using ccPAS. Novel cc-PAS protocols have been developed to investigate STDP within different interhemispheric cortical networks, being able to induce bidirectional modulation of cortical plasticity in the conditioned target area (Rizzo et al., 2009; Arai et al., 2011; Koch et al., 2013; Veniero et al., 2013; Momi et al., 2019; Nord, 2019; Romei et al., 2016; Santarnecchi et al., 2018; Zibman et al., 2019a).

Most studies used MEP elicited by TMS over the hand M1 as test stimulus modulated by applying the conditioning stimulus over a second cortical area. The paired conditioning stimulus usually precedes or follows the test stimulus by 5–20 ms (Koch et al., 2013). The intensity of conditioning stimulus is relatively weak, ranging from 90% RMT up to 120% RMT, while the intensity of the test pulse over M1 is set an intensity sufficient to elicit a 1 mV MEP following a single pulse TMS (spTMS) (~130% RMT). The number of paired stimuli is relatively low, ranging from 100 up to 200. The paired pulses are delivered at frequencies ranging from 0.05 Hz up to 1 Hz, with the entire inducing plasticity protocol lasting between 6 and 30 minutes. The conditioning pulses have been applied over the contralateral M1 (Koganemaru et al., 2009; Rizzo et al., 2009, 2011), the premotor cortex (Buch et al., 2011; Johnen et al., 2015; Fiori et al., 2018), the supplementary motor area (Arai et al., 2011), the posterior parietal cortex (Chao et al., 2013; Koch et al., 2013; Veniero et al., 2013; Ribolsi et al., 2017; Di Lorenzo et al., 2018). PAS protocols also tested the effects of afferent volleys to M1 driven by subcortical structures, by applying a conditioning TMS pulse over the cerebellum (Lu et al., 2012) or by coupling stimulation

of the subthalamic nucleus (Udupa et al., 2016) or internal globus pallidus (Ni et al., 2018) with DBS electrodes and TMS over hand M1. M1 PAS has also been coupled with peripheral laser stimulation (60 stimuli, intensity for 1 mV MEPs at 0.1 Hz) or associated with passive movements achieved by a robotic device, at 1 Hz (Edwards et al., 2014).

While most studies have adopted low-frequencies for cc-PAS stimulation, others developed rapid-rate cc-PAS of the primary motor and sensory hand area pairing TMS over M1 (600 stimuli at 90% AMT with electric median nerve stimuli at 5 Hz (2 min of stimulation) (Quartarone et al., 2006; Rizzo et al., 2008; Tsang et al., 2015). No major AE, including seizure occurrence were reported in these studies using high frequency PAS.

Other innovative approaches used TMS-EEG as read out in a “silent” cortical area after paired condition stimulus applied over a second interconnected brain region. For instance, conditioning stimulations in the posterior parietal cortex (PPC) as well as the contralateral DLPFC, have recently been paired with DLPFC showing LTPLTD after effects in the DLPFC (Casula et al., 2016; Ziebman et al., 2018). Alternatively, resting state fMRI can be used to monitor the network effects of cc-PAS in certain cognitive domains (Momi et al., 2019; Santarnecchi et al., 2018). Other studies explored the effects of cc-PAS in the context of the visual system by measuring changes in the primary visual cortex after repeated conditioning stimuli applied over the V5 (Chiappini et al., 2018; Romei et al., 2016) or testing visuo-motor integration by coupling peripheral visual stimulation with TMS applied over M1 (Suppa et al., 2013). cc-PAS has been also tested in the auditory system either by coupling paired TMS stimuli over the auditory cortex (Schecklmann et al., 2011) or paring TMS over M1 (200 stimuli, at 120% RMT) with auditory cues (Sowman et al., 2014) or transauricular electric stimulation of the auditory nerve (Naro et al., 2015).

PAS protocols have also been tested at the spinal cord level. Taylor and Martin (2009) introduced a new protocol “employing electric peripheral stimulation of the brachial plexus able to elicit antidromic motor axon activation timed to coincide at the alphamotor neuron with descending volleys induced by cervicomedullar stimulation (cervical MEPs – cMEPs, in the biceps brachii muscle)”. The authors applied TMS (50 stimuli adjusted in intensity for producing 1 mV MEPs) paired at 0.1 Hz with electric stimuli at various ISIs (about 8 min of stimulation). Cortes et al. (2011) designed a protocol “consisting of TMS given over the M1 hot spot for the soleus muscle (90 stimuli at 80% RMT) paired with electric stimulation of posterior tibial nerve able to elicit H-reflex from soleus muscle, at 0.1 Hz (15 min of stimulation)”. Leukel et al. (2012) applied TMS over M1 hot spot of the soleus muscle (360 stimuli at 100% RMT) paired with electric TN stimulation, at 0.2 Hz and 1 ms ISI (30 min of stimulation).

Only a couple of studies evaluated the effects of repeated sessions of PAS in clinical populations. Tarri et al. (2018) did not report any majorsideeffectsafter5 days of PAS-targeting the Extensor Carpi Radialis (ECR) muscle belly of the paretic limb. The intensity of the stimulation was adjusted to 1.5 times the RMT. Cortical magnetic stimulation was adjusted to obtain an ECR MEP with a peak-to-peak amplitude of about 1 mV. The ISI between the last pulse of the electrical train and the TMS was 25 ms. This paired stimulation was applied every 10 s (0.1 Hz) for 30 min. Tolmacheva et al. (2017) evaluated in a

sampleoffivepatientswithspinalcordinjurytheeffectsof16sessions of PAS (at 0.2 Hz) during 4 weeks (5 sessions/week during the initial two weeks and 3 sessions/week thereafter). The ISI between TMS and peripheral nerve stimulation was determined individually for each patient based on individual F-response and MEP latencies as described previously. After four weeks of stimulation and 1-month follow-up, each deficient muscle in the PAS-treated hand improved by 1 point on average on a 0–5 scale. There were no AEs on autonomic functions. Two patients reported some discomfort in sitting in the same position during the 2-h session; no seizures were reported.

Recommendations: In conclusion, with regards to safety, it has to be considered that all the studies mentioned above were planned to investigate physiological mechanisms of corticocortical plasticity in healthy subjects or in pathological conditions and thus did not require repeated sessions over several days in order to reach a clinical effect. Under these circumstances, no major AE, including seizure occurrence, was reported in both healthy subjects and pathological conditions. Thus, there should not be any special concern in studies of this type.

8. Training of operators

8.1. Requirements for TMS users (summary of IFCN training guidelines)

Over the past decades, adoption of TMS in basic and translational research and clinical medicine has grown tremendously and the use of TMS has expanded beyond a few specialized centers into research laboratories and clinics in the public and private sector. In parallel, the applications of TMS have continued to grow more diverse, both in terms of the protocols and populations being studied. This expanded use harbors the risk of declining quality control, less reliable or less effective application, and potentially unsafe practices. Training guidelines are critical to address testretest reliability and minimize the risk of less effective and unsafe use. Definition of training guidelines and of competencies for clinicians prescribing TMS, scientists overseeing research protocols employing TMS, and technicians applying TMS to research participants or patients, will lead to reduced risk, improved quality, and higher cross-study compatibility. To this end, the IFCN convened a committee that generated consensus training guidelines (Fried et al., 2021). These can be implemented at the individual laboratory or institution, but might also be valuable for governing bodies and professional societies to develop accreditation guidelines, for medical insurance agencies, health care systems, medical executive boards, investigational review boards and ethics committees, funding agencies, and journal editorial boards, to assess competencies and define minimal standards of quality.

The consensus training guidelines endorsed by the IFCN envision three distinct classes of trainees: (1) Technicians, (2) Clinicians, and (3) Scientists. The Technician applies TMS to research participants or patients, monitors their wellbeing, and administers certain outcome assessments (e.g., depression severity indices). The Clinician establishes the indication, identifies and prescribes the optimum protocol for a given patient or indication, and supervises the Technician(s). The Scientist might be the principal investigator (PI) or a key co-investigator responsible for the TMS protocol in a given research study or clinical trial. The Scientist either performs the study personally or supervises the Technician (s), and

may be distinct from the medically responsible investigator, who may be more in line with a clinically trained person exerting a clinical supervisory role. For each class of trainees there are specific sets of core competencies defined (see Fried et al., 2021).

Any training regimen should be comprised of three core components: (1) theoretical and didactic knowledge; (2) hands-on training; (3) observation and supervised practice. The curriculum should cover three domains: (1) Core knowledge; (2) Safety and ethical concerns; (3) Technical application and hands-on training, which can be separated into (a) Basic skills and (b) Advanced skills (Fried et al., 2021).

Common across all types of trainees, training in TMS should begin with a didactic curriculum in the fundamentals of brain stimulation. The main objective of the Core knowledge topic is to provide a systematic review and instruction in all major theoretical aspects of TMS. The second topic, Safety and ethical concerns, should cover all subject matter related to the safe and ethical practice of TMS in the clinic or laboratory. This provides trainees with the knowledge and resources to conduct human subjects research (or animal research, where appropriate) with the utmost protections and in accordance with all international, national, regional, and institutional regulations. For the Basic Skills competencies, training should be structured, hands-on instruction in the core TMS techniques, followed by observations of these techniques performed by a skilled technician, then practice of these techniques under the supervision of a skilled technician, and finally assessment of competency by some objective measure. Examples of Basic Skills competencies are: (1) basic device operation and setting parameters for subsequent stimulation; (2) proper coil handling, including placement (location, orientation, angulation) of the coil on the participant’s scalp, returning to a chosen site, and maintaining chosen coil position and orientation over a given stimulation session (with or without neuronavigation); (3) identification of the motor hotspot and definition of a non-motor target location; and (4) assessment of RMT and AMT) according to the IFCN guidelines and procedures. Once a trainee has mastered these core skills, they can easily be adapted to other TMS protocols (e.g., ppTMS, repetitive/patterned TMS, etc.). The Advanced skills topic should cover such more specialized TMS protocols that may not be necessary for all trainees to learn. Therefore, it may be up to individual laboratories, clinics, or institutions to design or require training of such skills.

Structured evaluation is important for the assessment and documentation that each individual trainee has acquired the material and mastered the various techniques. Assessments may take the form of testing (e.g., multiple-choice quizzes) for didactic knowledge, but for most practical skills assessment might be based on the principles of “see x, do y, and test z”. For instance, a trainee might observe 5 sessions, do 5 sessions with supervision, and then be tested in a final test session. Recently, a TMS phantom has been developed for both practice and then testing of these motor threshold finding skills (Finetto et al., 2019). As with any education program, there is no one-size-fits-all approach. The IFCN endorsed consensus training guidelines (Fried et al., 2021) should therefore serve as a common framework around which to build a training and assessment program to suit the individual needs for each clinic or laboratory.

A final important consideration should be given to the question of qualifications for those who offer and oversee the training. Industry/company-dependent workshops focus on training in the proper use on their specific systems. While this is important, training in TMS should provide competencies beyond the correct utilization of a specific given stimulation device. Attainment of competences should be unbiased and independent from the manufacturers or other financial interests and requires criteria and evaluation of the trainers themselves. Therefore, academic (industry-independent) training programs and courses are most relevant. Trainers should be Clinicians or Scientists with several years of experience and good command of the methods and required competencies, as well as experience in training and mentoring. In certain circumstances, it may be appropriate for a highly experienced Technician with extensive hands-on experience to come into the role of trainer (e.g., for hands-on demonstration of a technique).

8.2. Safety for operators

As an important introduction, it is worth noting that there are no specific reports of AEs of TMS in operators. Safety issues are seldom addressed for operators, despite their being exposed to magnetic fields for several hours daily, even for years. Guidelines for occupational levels of exposure to electromagnetic fields have been proposed and updated by the International Commission on Non-Ionizing Radiation Protection (see ICNIRP, 2003, 2017) and by Directives from the European Parliament (directive 2004/40/ EC, directive 2013/35/EU). These directives “introduce Exposure Limit Values for workers and also Action Values (magnitude of electromagnetic field which is directly measurable)”. In contrast, long term effects have not been addressed because these are out of the scope of the directives. Occupational exposure to magnetic fields has been measured for MRI units (Riches et al., 2007). These exposure values are one hundred times below the recommended limits (Bradley et al., 2007), with the exception of interventional procedures (Hill et al., 2005; Riches et al., 2007). Regarding rapidly time varying magnetic fields, as those of TMS/rTMS, one study took into account the MagPro machine (Medtronic), MC-B70 figure-8 coil, 5 Hz frequency, and stimulus intensity of 60–80% of the maximal stimulator output (Karlström et al., 2006): exposure limit values for the magnetic field pulses were transgressed at a distance of about 0.7 m from the surface of the coil. Recently, using the same equipment (magnetic stimulator and coil), stimulation parameters, and methods of measurement, Møllerløkken et al (2017) reported that the distance needed from the coil to avoid magnetic field exposure exceeding these limit values is 40 cm. These observations warrant further research to characterize the limiting distance to the coil according to: (i) the type of TMS machine and coil; (ii) the frequency/intensity of stimulation and (iii) the total exposure time. Furthermore, the potential risk of long-term AEs for rTMS operators due to daily close exposure (even to weak electromagnetic fields), repeated for months or even years, is a still open issue that should be addressed in the future. In the absence of these data, the following recommendation can be put forward:

Using a finite element method full-body model, (Yanamadala et al., 2019) extended their observations on the fetal exposure to TMS-induced electric field to the case of a pregnant woman acting as operator. When the distance uterus-stimulating coil was 60 cm, the extimated induced current peak electric field throughout the fetal volume was far below

the value recommended by ICNIRP 2010 to avoid stimulation of both central and peripheral myelinated fibres.

The sound waveforms of seven different figure-of-eight coils with high bandwidth has been recorded (Koponen et al., 2020). The data showed that during high frequency (>1 Hz) rTMS, the sound can reach or even exceed the standard exposure limits at distances relevant for operators holding a coil, whereas the airborne sound from lower rate rTMS and spTMS was below these exposure limits. According to these findings, hearing protection (earplugs or earmuffs) is recommended not only for subjects undergoing TMS (Section 3.2), but also for operators who manually hold a coil during high-frequency rTMS.

An emerging potential risk for both the operator and the patient, when in close contact, is human-to-human Transmission of infectious diseases, particularly respiratory infections, and there would be an advantage for robot-guided TMS to minimize such contact. This issue was not discussed at the Consensus Conference but has emerged as important since; a detailed and timely discussion on this topic can be found in a recent review (Bikson et al., 2020).

Recommendation: the presence of the operators in proximity (i.e., less than 40 cm) of the magnetic coil during prolonged stimulation sessions should be minimized. The use of ear plugs or earmuffs is mandatory for operators.

9 Regulatory issues and ethics (with a note on neuroenhancement)

This section covers ethical aspects of performing TMS in healthy subjects and in patients. As in medical research in general, acceptable risks and burdens differ depending on the scenario. We differentiate between basic (nontherapeutic research), therapeutic research in patients, and therapeutic applications in medical care.

9.1. TMS in research or clinical setting

9.1.1. Basic, physiological, non-therapeutic research—Non-therapeutic applications cover everything which does not have potential medical benefits for the study participant, either because the study participant is healthy or, if performed on persons with neuropsychiatric or medical disorders, because the intervention is not intended to be of therapeutic or diagnostic value for the individual. Research on cognitive enhancement in healthy subjects may also be classified here. The risk for permanent harm should be minimal in nontherapeutic research in healthy humans. Participants usually get financial compensation for participation. Remuneration may also compensate for burden (e.g. discomfort, pain, time spent in research), but should not be intended to compensate for risks, although limited, of permanent health damage.

Nontherapeutic research may not be acceptable in vulnerable populations or may be acceptable in vulnerable populations only if the study is considered to have risk of minimal harm and/or minimal risk. There is no clear operational definition of minimal risk and minimal burden but looking at analogies from current literature on medical ethics usually facilitates classification. For instance, MRI scans are usually considered minimal risk and minimal burden but would not be thus classified when the scan procedure also requires

anesthesia. The risk and burden from venipuncture (with an existing but very low risk of SAE) may be classified as minimal in many but not all countries. Given the accumulated safety data from rTMS experience to date, some research protocols may qualify for minimal risk/minimal burden status based on local IRB or ethics board review, while others may not.

9.1.2. Therapeutic research—Therapeutic research includes studies on interventions aiming to prevent or cure a disease or to alleviate symptoms of a disease. This includes diagnostic research with potential benefits of the studied diagnostic procedures for the participants. Study participants have some chance for individual benefits. In placebo-controlled trials, some portion of participants have a chance to benefit from the active intervention, but empirical research has shown that those allocated to inactive treatment arms may also benefit to some extent, e.g. from the placebo effect and/or intensified monitoring and care. Acceptable risks and burdens in therapeutic neuromodulation research depend on the burden and the risk of the disease and on the anticipated benefits. New and experimental treatment interventions are typically conducted if approved therapies are inadequate or unacceptable, or if there are no approved therapies.

Review and approval of a proposed therapeutic research study by an IRB or ethics committee provides a mechanism to ensure that the safety and welfare of human subjects are adequately protected. Requirements for evidence of adequate training, reporting of AEs, and long-term follow-up assessments are examples of steps often required by IRBs or ethics committees who oversee research studies.

9.1.3 Therapeutic clinical application—This category includes interventions intended to cure a disease or to alleviate or prevent symptoms but not aiming to study the effects of the intervention in a scientific fashion. Data from standard-of-care therapeutic clinical rTMS application may later be analyzed retrospectively to generate findings and insights that contribute to generalizable knowledge. However, a prospective plan for nonstandard clinical care with a TMS device is considered therapeutic research, and as such must comply with various research regulations. Which rTMS procedures comprise standard of care may be defined by the medical device or product labeling, professional guild or expert consensus guidelines, or by other widely accepted authoritative sources. Depending on countryspecific regulations and on the quality and strength of published evidence for safety and efficacy, some off-label applications of rTMS may be acceptable. Acceptability of off-label, experimental, or nonstandard neuromodulation interventions is often evaluated through consideration of available treatment alternatives and by peer-reviewed data suggesting possible benefits and the associated safety profile.

Clinicians not performing research also have an ethical obligation to describe relevant risks and benefits of a nonstandard therapeutic procedure, and to obtain written informed consent from patients who will undergo a TMS procedure for therapeutic purposes. Disclosure to the patient of a plan to use a nonstandard rTMS protocol is a critical element of the informed consent process.

9.2. Steps to mitigate risk

In basic, nontherapeutic research with TMS, factors which may produce any additional risk should be avoided not only for safety reasons, but also for scientific reasons to reduce scatter and bias. A history of epilepsy or intracranial ferromagnetic metal implants are typically exclusionary but not absolutely contraindicated. Depending on the specific condition under scrutiny, one or more factors that heighten risks associated with rTMS may be acceptable if adequate precautions are taken.

In most therapeutic research studies and in therapeutic application of rTMS in clinical care settings, the presence of any condition resulting in a significantly increased risk should be allowed only if there are no acceptable therapeutic alternatives or when special precautions are in place to reduce known risks.

In early phases of new treatment development research, however, it may be necessary to include participants whose conditions confer heightened risk. Precautions to mitigate seizure risk may include heightened levels of participant screening, neurophysiological monitoring during the stimulation, use of a supportive medical setting for procedures, and/or the presence of medical professionals or other clinical experts.

9.2.1. TMS in vulnerable populations—Persons who are members of vulnerable subgroups should not be excluded from participation in research involving innovative therapies nor from receiving them in clinical care settings. However, for some subgroups (e.g. prisoners, minors, pregnant women, persons unable to give informed consent) country-specific legal regulations or medical device labeling may prohibit or otherwise limit participation in TMS research. The potential risks and benefits of treatment with rTMS should be weighed against the risks associated with alternative treatments and against the risks associated with lack of treatment in vulnerable populations. Special considerations are needed for research in pregnant women because AEs associated with treatments may in some instances cause harm not only to the mother but also to the unborn child, however, in certain cases (e.g., a pregnant woman with severe depression) the risks may be justified.

When nontherapeutic research is deemed acceptable in children, application of a rTMS protocol should be performed only after the method has been sufficiently studied in adults to establish safety. Nontherapeutic rTMS research in children may not be acceptable if administration of narcotic or sedative drugs is required to perform the procedure. Although the legal distinction for minors is defined as younger than or older than the legal age (e.g. 18 years, or in some cases 21 years), ethically the criteria for inclusion of children may differ if they have reached an age (typically about 12–14 years, if otherwise healthy with normal development) where they are able to understand the procedures and to express their own will.

Acceptability of research in samples with significant decisional impairment due the presence of neuropsychiatric disorders varies across countries and when acceptable these TMS studies may require additional steps to ensure proper informed consent. Consent “partners” are sometimes required for studies in patients selected on the basis of dementia or severe cognitive deficits, and consent “tools” (e.g., videos or single-page summary descriptions

of research procedures with a “teach-back” interview) may be used to facilitate participant understanding of the main risks and potential benefits.

As presented in another section, according to best current evidence, risk of seizures induced by TMS is about <0.03%. Even if a seizure occurs, in current TMS practice such a seizure has never been resulted in any permanent damage. Seizure, if induced by rTMS, occurs only during the application of stimulation. Beyond studies conducted specifically in patients with epilepsy, there has been no reported incidence of rTMS-associated seizure that had onset within hours or days after the stimulation procedure concluded. Therapeutic research involving application of rTMS to clinical samples where seizure risk is inherently heightened (e.g., alcohol or drug use disorders, stroke or traumatic brain injury, persons taking medications that lower seizure threshold) may carry relatively greater risk and thus require special evaluation of potential risks and benefits. The ethics in these studies must also consider the relative risks of requiring discontinuation of certain medications or alterations to ongoing treatments, which may on the one hand serve to diminish seizure risk but at the same time introduce other unacceptable risks (e.g., withdrawing antidepressants from depressed patients could be associated with increase in suicidality, administration of anticonvulsant agents may compromise cognitive function or confer other side effects). In summary, depending on the specific study protocol and the participant characteristics, the risk of TMS may or may not be considered minimal.

9.3. Recommendations on minimum safety precautions of different use and settings of TMS

Use and settings of different types of TMS in research and for clinical applications have been defined in Table 7 of Rossi et al. (2009) and are still operationally valid. The type of qualification required for doing TMS research or applying TMS in clinical settings is defined in Fried et al. (2021). In the two following paragraphs, we summarize basic requirements for research and clinical use of TMS:

Research Setting: Consistent with the protections for human subjects in research studies, TMS research should be conducted under a research protocol that is approved by an IRB or other relevant research ethics committee. Informed consent should be obtained by an individual listed on the research protocol who is authorized to obtain informed consent. The research protocol will specify the level of risk, the risk benefit ratio, and the roles of each member of the study team who will be involved in the delivery of TMS. It will also specify the degree of medical supervision required based on the anticipated risks of the specific protocol.

Clinical Setting: Consistent with the standards of the practice of medicine, decisions about prescribing the therapeutic use of TMS for the treatment of a clinical disorder outside of the research context should always be made by an adequately trained physician, and informed consent for the therapeutic use of TMS should be obtained by a physician. TMS may be delivered by the physician or by an appropriately trained individual operating under the supervision of the physician. TMS should be delivered in a context where anticipated side effects may be appropriately managed.

9.4. Limitations of current safety data

In research and therapeutic settings, participants and patients have always to be informed about all possible AEs, although the present review shows that generally TMS is safe with most of the currently applied protocols and that there are no demonstrated permanent AEs from TMS. However, lack of reported AEs does not mean that there are no AEs possible, given the rapidly developing nature of the field, so researchers and clinicians using TMS must remain vigilant for eventual unexpected and still unknown risks. Although investigators and TMS medical device industry sponsors have put extensive efforts into collecting safety data, our knowledge base remains limited to the relatively low number of large studies and paucity of long term follow up data. Use of TMS devices that do not conform to regulatory guidelines may confer more risk.

9.5. Registration, standardized documentation and reporting

As required by the declaration of Helsinki in its current version, every interventional TMS study should be registered (prior to enrolling the first participant) in a publicly available database. Negative outcomes should be reported in publicly available databases or published in regular scientific journals. Standardized reporting modalities and forms should be used by TMS researchers to allow a more valid summary of the observed worldwide safety. Standardized classifications (Table 1) should be used to record and report AEs.

Follow up of all SAEs with possible causality to the research procedures is typically required. A definitive assessment of causality is often not possible for AEs. In addition to seizures, other AEs such as cognitive change, syncope, and suicidality should trigger reporting, even when relationship of the events to TMS is not certain

9.6. A note on neuroenhancement

An emerging ethical aspect is neuroenhancement that refers to the possibility of inducing a supernormal “improvement” of brain activity with TMS. The term “neuroenhancement” refers to any augmentation of core information processing systems in the brain of healthy subjects, apart from natural training, including the neural mechanisms underlying attention, conceptualization, perception, reasoning, memory and motor performance.

Pharmacological neuroenhancement is well recognized in the scientific community, in terms of use of substances with the purpose of cognitive enhancement (e.g., of concentration, vigilance, mood or memory). Among devices, TMS has also been proposed as neuroenhancer, although it is obviously less exposed to an anarchic, unregulated use as compared to other non invasive brain stimulation (NIBS) techniques such as low-intensity TES, which can be performed at home without any medical supervision.

Below, we outline relevant considerations for the use of NIBS techniques [also indicated as NTBS (non-invasive transcranial brain stimulation)] for neuroenhancement, but point out that to this date, the overall cognitive impact of NIBS is at best weak to moderate, and generally short-lasting, thus providing a logical barrier to concerns about neuroenhancement.

Theories behind a potential for neuroenhancement include the following mechanisms:

1. Balance effect. These effects are based on the model of the inter-hemispheric rivalry that would take place between homologous areas. Inter-hemispheric balance effects have been hypothesized to account for the paradoxical enhancement of ipsilateral motor function, lateralized verbal memory and language abilities and ipsilateral visuospatial attention, when using brain stimulation to suppress activity in specific cortical regions.
2. Entrainment theory. This theory is based on the relationships between oscillatory activity in brain networks and specific functions. According to this notion, if this link is causal, then external rhythmic stimulation mimicking endogenous brain oscillations might have an effect by entraining the brain's natural state.
3. Stochastic resonance. This refers to the notion that injecting subthreshold noise into a system can serve to enhance signal detection.

Single or repetitive TMS studies targeting dicrete brain areas have suggested an improvement of various cognitive functions, even in healthy subjects: (i) DLPFC: planning and deceptive abilities, risk-taking/impulsivity, attention, logical reasoning (ii) inferior Frontal Cortex: deceptive abilities and attention; (iii) PPC: attention; (iv) M1: motor control; (v) temporoparietal junction: working memory. This kind of "brain doping" obviously raises numerous ethical and social concerns, that should be necessarily addressed in future research centered on safety considerations.

Ethical implications and compensatory trade-offs on applying these technologies for neuroenhancement requires careful scrutiny both for adults and children. For the latter, compensatory tradeoffs associated with NIBS posit a big challenge, insofar as these trade-offs have the effect of limiting the child's future options. The distinction between "treatment" and "enhancement" can be blurry, and making enhancement into a treatment requires a major change in thinking. The idea of neuroenhancement creates considerable uncertainty in weighing of the benefits, risks, and costs as well as the appropriateness of the parents as proxy decision makers. Given the limited evidence for a real long-lasting cognitive benefit of NIBS effects in normal individuals, the need to protect the child's (future) autonomy looms larger. NIBS for enhancement involving trade-offs should therefore be delayed, at least until the child reaches a state of maturity and can make an informed, personal decision. Expert-based opinions of specific Scientific Societies might play an important role in governing these issues worldwide, and dedicated research is needed. The IFCN has made a public statement (quoted in Wurzman et al., 2016) that, as a minimum, NIBS should not be undertaken as "do-it-yourself" but only under medical supervision.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interests (related to TMS devices) in the last three years

Andrea Antal has received speaker's and consultat's honoraria from NeurCare, Munich and Savir GmbH, Magdeburg.

Marom Bikson has equity in Soterix Medical, is inventor on patents on brain stimulation, and consults or receives grants from Boston Scientific, Mecta, Halo Neuroscience, X, and GSK.

Linda Carpenter has received grants or donated equipment for clinical research from Janssen, Affect Neuro, Neuronetics, Nexstim, and Neosync. She has been a paid consultant for Magstim, Neuronetics, Affect Neuo, Sage Therapeutics, and Neurolief.

Jeff Daskalakis has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc

Mark George has been Consultant (unpaid), received Research Grant or donated equipment for research trials by Brainsway, Magstim, Neuronetics, NeoSync

Michael Fox has intellectual property on using brain connectivity to guide TMS

Risto Ilmoniemi is founder, minority shareholder and advisor of Nexstim Plc.

Sarah Lisanby is co-inventor on a patent for TMS coil design, with no revenues. She has received equipment support from Magstim and Magventure.

Mark Hallett may accrue on US Patent #7407478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He is on the Medical Advisory Boards of CALA Health and Brainsway.

Frank Padberg is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and has received speaker's honoraria from Mag&More GmbH, Munich, and neuroCare, Munich. His lab has received support with equipment from Brainsway Inc., Mag&More GmbH and neuroCare.

Alvaro Pascual-Leone currently serves, or has served in the past three years, on the scientific advisory boards for Neosync, Neuronix, Starlab Neuroscience, Neuroelectrics, Magstim Inc., Axilum Robotics, and Nexstim; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

Walter Paulus Is member of the scientific advisory board of Precisis AG

Angel Peterchev is inventor on patents and patent applications related to TMS. In the past 3 years he has received travel support as well as patent royalties from Rogue Research related to controllable pulse parameter TMS; research and travel support, consulting fees, as well as equipment donation from Tal Medical / Neurex related to low-field magnetic stimulation; patent application and research support from Magstim related to TMS; TMS equipment loans and hardware donations from Magventure; and expert witness compensation from Neuronetics.

Simone Rossi Is holder of a patent for a sham coil (REMP coil) and consultant for EB-Neuro and Neurocare Group Italy.

Alexander Rotenberg has received research support by Brainsway and Nextim

Emiliano Santarnecchi is consultant for Neuroelectrics and Neurocare Group Italy

Hartwig Roman Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and Gyldendahl, Copenhagen, Denmark.

Abraham Zangen is one of the co-inventors of deep cortical TMS H-coils, serves as a scientific consultant for Brainsway and has financial interest in Brainsway.

Ulf Ziemann has the following patents: SMARTCOIL (EEGElectrodes and logic integrated with TMS Coil for EEG-triggered stimulation, PCT/EP2016/070499). He is a project leader in an ERC synergy grant "Connecting to the Networks of the Human Brain" (Acronym: ConnectToBrain, Grant Nr. 810377).

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HIGHLIGHTS

- This article updates the previous safety guidelines from 2009.
- Safety of new devices and techniques is considered.
- Operational guidelines for future protocols using TMS are provided.

Table 1

Standardized classification of adverse effects, according to EU regulation definitions.

Abbreviation	Definition	Hints for interpretation
AE	Adverse event	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device
SAE	Serious adverse event	Adverse event that: (a) led to a death, injury or permanent impairment to a body structure or a body function. (b) led to a serious deterioration in health of the subject, that either resulted in: - a life-threatening illness or injury, or - a permanent impairment of a body structure or a body function, or - in-patient hospitalization or prolongation of existing hospitalization, or - in medical or surgical intervention to prevent life threatening illness (c) led to foetal distress, foetal death or a congenital abnormality or birth defect.
ADR	Adverse device-related adverse reaction	Adverse event related to the use of an investigational medical device.
SADE	Serious adverse device-related adverse event	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE	Unexpected serious adverse device-related adverse event	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.