Clinical Neurophysiology 132 (2021) 214–215

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

Updated safety standards for TMS: A must-read in brain stimulation

See Article, pages 269–306

1. Introduction

The most recent contribution by Rossi et al. (2020) in this issue of *Clinical Neurophysiology* updates the previous guidelines from 2009 by largely the same group of international experts (Rossi et al., 2009). The article is the result of a consensus meeting in Siena, Italy, in 2018 and further research and discussion of this group of experts in the field of non-invasive brain stimulation, each with decades of experience. The now published expert guideline represents an update and extension of the existing 2009 guideline adding detailed statements on the most recent technological advancements in the field, such as new devices, pulse configurations, image- or robot-guided TMS, and TMS interleaved with transcranial electrical stimulation.

This current update is of considerable importance since it provides us with some clear positions of previously more vague recommendations, revises some of them and, therefore, helps considerably in daily routine when it comes to topics such as seizures, medications, navigation, pacemakers (and other implants), application in children or in women during pregnancy.

2. Perception

The international community will warmly welcome this guideline since the field experienced considerable changes and technical advances in the last decade and seeks for references to ease research and clinical applications of these new technologies. Especially, TMS guided by MRI and robot-guided TMS are practical advancements which could allow TMS a clinical breakthrough in other fields of neurosciences and neuro-associated specialties, such as neuroradiology, psychiatry, neurosurgery, pain medicine, spine surgery, etc. A broad width of applications and concepts emerged in the last decade. A comprehensive guideline, providing consensus from an international expert panel will ease the further development and application of TMS techniques for clinicians, researchers, institutional review boards (IRB), and ethics committees. The same applies to new coil designs, stimulation protocols, the combination of TMS with other devices (like electronic implants), or the use of TMS to induce therapeutic seizures as a diagnostic of even therapeutic application.

Worth mentioning that the existing recommendations on safe stimulation parameters, dosage, frequency and side effects from the 2009 guidelines have been confirmed by our all experience in the last decade and are therefore confirmed in their validity by the new guideline referring to the original 2009 version.

Concerning new parameters of stimulation, the article not only provides a thorough analysis but also a detailed overview on currently available stimulation setups of waveforms, sequences, coil design and intensity.

While TMS is still applied non-navigated by many groups and trials, the statement “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” in this new guideline deserves special attention. The advances in neuroimaging allow for better identification of stimulation targets in therapeutic applications but can also reduce variability and side effects of stimulation. This targeted stimulation was also reported for cortical mapping of 733 brain tumor patients with single-pulse and rTMS. While 50% of these patients had a history of epilepsy, no seizures were observed in this prospective database (Tarapore et al., 2016). Such data is crucial when it comes to the application of TMS in epilepsy patients since this subgroup of patients highly benefits from non-invasive mapping on the one hand and is subject of research for magnetic seizure therapy as a very new therapeutic option on the other hand. Thus, this detailed analysis in the current guidelines will facilitate enrolment of such patients into further research.

Seizures as the most severe adverse event during TMS consider special attention. This guideline also provides us with another remarkable statement. While, “previous TMS safety guidelines advised caution in the application of TMS in persons taking medications known to lower seizure threshold (, . . .) currently available data showing low seizure rate no longer support this recommendation”. Moreover, literature search of the expert panel only revealed 41 published cases of seizures; half of those during high-frequency TMS. Having the large number of patients and volunteers in mind receiving TMS over the last two decades, 41 seizures define this risk to be “certainly very low” (Rossi et al., 2020). A more accurate approximation is provided in the respective section for each stimulation type.

The update also provides us with very substantial guidance for TMS during pregnancy. At least with figure-of eight coils there seems to be minimal risk. The same statement is posed for TMS in pediatrics, even stating “that IRBs should be comfortable approving studies involving healthy children”, which is a strong and rather helpful statement for many TMS users worldwide.

https://doi.org/10.1016/j.clinph.2020.11.015

The guideline also covers application in patients with implants. In particular, we now receive a clear statement that "TMS with figure-8-coils is considered safe in individuals with cardiac pacemakers, vagus nerve stimulation systems, and spinal cord stimulators if the TMS coil is not activated close to (<10 cm) electronic components such as the implanted pulse generator located in the neck or torso." Having included such a strong statement considerably helps TMS users in their daily routine due to the increasing number of patients with active implants. Due to the steadily increasing applications of TMS, implant device manufacturers should have an eye on TMS compatibility of their products when it comes to specifications, official approval, or clearance of their products. Coming from the neurosurgical field, compatibility of ventriculoperitoneal shunting valves requires a short note. This issue is neither addressed in the current update nor the previous guidelines and according to our literature research only addressed in one study (Lefranc et al., 2010). Lefranc et al. clearly stated that TMS can actually interfere with valves for ventriculoperitoneal shunting and special care should be taken. While Rossi et al. were lacking sufficient data, this issue can serve as a perfect example that we all need to work together in order to create the best possible data on TMS safety. This, as does the current guideline, benefits all stakeholders: clinicians, researchers, patients, and healthy volunteers.

Altogether, the advancements made since 2009 and reported in this update are largely the result of ongoing innovation and studies in a controlled environment. New types of stimulation, coils, and guidance exerting current data and guidelines as described in this article are largely the result of off-label use under the surveillance of a research study granted by an IRB and an experienced principal investigator. Such are needed to further develop and broaden the whole field of non-invasive brain stimulation, and it is our all duty to further pursue this effort together.

3. Conclusions

This comprehensive update covers an impressive range of aspects relevant to the daily clinical and scientific use of TMS and may therefore further promote its application by overcoming insecurities, lack of knowledge, or limitations inflicted by the IRBs or legal authorities. Besides, this update should be read by anybody newly entering the field of non-invasive brain stimulation, as it gives, beyond safety information, an excellent overview on the currently used TMS-based approaches in clinical applications and research.

Declaration of Competing Interest

SK is consultant for Brainlab AG (Munich, Germany) and Ulrich Medical (Ulm, Germany) and received honoraria from Nexstim Plc (Helsinki, Finland), Spineart Deutschland GmbH (Frankfurt, Germany), Medtronic (Meerbusch, Germany) and Carl Zeiss Meditec (Oberkochen, Germany).

CG received (outside the submitted work) funding from German Research Council (DFG), European Union, Federal Ministery of Education and Research (BMBF), German Statutory Pension Insurance Scheme (RV Nord), National Innovation Fond, Wegener Foundation, and Schilling Foundation; CG received (outside the submitted work) honoraria as speaker or consultant from Abbott, Amgen, Bayer Vital, Bristol-Myers-Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Sanofi Aventis, and Prediction Biosciences.

References

Lefranc M, Ko JY, Peltier J, Fichten A, Desenclos C, Macron JM, et al. Effect of transcranial magnetic stimulation on four types of pressure-programmable valves. Acta Neurochir (Wien) 2010;152:689–97.

Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin Neurophysiol 2021;132:269–306. https://doi.org/10.1016/j.clinph.2020.10.003.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.

Tarapore PE, Picht T, Bulubas L, Shin Y, Kulchytska N, Meyer B, et al. Safety and tolerability of navigated TMS for preoperative mapping in neurosurgical patients. Clin Neurophysiol 2016;127:1895–900.

Sandro M. Krieg *
Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
* *Corresponding author at: Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, School of Medicine, Ismaninger Str. 22, 81675 Munich, Germany.*
E-mail address: Sandro.Krieg@tum.de

Christian Gerloff
Department of Neurology, Head and Neurocenter, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
E-mail addresses: gerloff@uke.de

Accepted 23 November 2020

Available online 2 December 2020