4 Repetitive Magnetic and Low-Intensity Electric Transcranial Stimulation in the Interventional Psychiatry: Summary of Safety Issues

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4.1 Introduction

The aim of this review is to give a short but informative summary of the safety of repetitive transcranial magnetic stimulation (rTMS) and low-intensity transcranial electric stimulation (TES) based on available published research and clinical data in the interventional psychiatry, including animal models and human studies.

The current approach in the clinical field is to estimate the potential of a stimulation protocol becoming a hazard that could result in safety problems. Hazard and risks should be considered separately: hazard is a potential for an Adverse Event (AE) (e.g., using too high stimulations intensities). Risk is a measure of the combination of the hazard, the likelihood of occurrence of the AE and the severity [1, 2] (See also: http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf).

Risk is not the same as burden: a stimulation procedure may be burdensome, e.g., resulting in much discomfort (e.g., face muscle twitching during rTMS), but nevertheless safe, without relevant risk for permanent damage.

In brain stimulation research and related clinical applications, safety can only be considered in relative terms [3]. According to the definition of the European Medical Device Directive (MDD), "safe" is a condition where all risks are accepted risks

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(MDD; Annex I; § I. General Requirements). We have to keep in mind that all stimulation protocols could carry a certain degree of risk and could cause problems in specific circumstances, e.g., when medicated patients or children are treated with stimulation.

Generally, the assumption that a stimulation protocol is safe is based on a full and unprejudiced documentation of all AEs that may occur during application of a given protocol. However, it should be underlined here that the prevalence of published AEs in the brain stimulation studies is higher in studies specifically assessing AEs, compared to those not assessing them. Furthermore, in these studies AEs are frequently reported by subjects receiving placebo stimulation.

AEs are undesirable or harmful effects that are observed after a medical intervention that may or may not be causally related to it (https://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_5x7_Locked.pdf). A mild AE (grade 1) is defined as involving mild symptoms, for which no medical treatment is necessary (i.e., transient local discomfort during rTMS or skin redness after tDCS), while a moderate AE (grade 2) indicates the need of noninvasive treatment (e.g., transient but persistent pain after rTMS needing an analgesic, or in the case of tDCS local application of a cream after a skin burn). Serious AEs (SAE) (grade 3) are medically significant but not immediately life-threatening events: they include the requirement for inpatient hospitalization (or prolongation of it). *Life-threatening SAEs* include events that are life threatening (grade 4) or death (grade 5).

Special stimulation conditions that have been increasingly used during the last few years, e.g., combination of rTMS and TES with other methods, such as stimulating patients with intracranial implants or combination of TES with functional magnetic resonance imaging (fMRI) or EEG, or other types of noninvasive stimulation (magnetic seizure therapy, trans-spinal and transorbital stimulation) should require different and many times deeper and individually tailored safety considerations, and therefore will not be mentioned and discussed in this paper (but see [3]).

4.2 Transcranial Magnetic Stimulation

An impressive growing of scientific publications has appeared in the last 20 years concerning the use of rTMS, including theta burst (TBS) stimulation, in the psychiatric field. New coils for stimulation have been presented, able to stimulate deeper than conventional ones, and new protocols—as "high-density rTMS"—have been introduced. Meanwhile, the use of rTMS has been cleared by regulatory agencies in many countries for treatment of depression and obsessive-compulsive disorder. So, constant updating of safety issues remains a crucial point, and this is why the International Federation of Clinical Neurophysiology (IFCN) supported a further consensus meeting 10 years later the last available safety guidelines [4, 5]. The meeting has been held again in Siena during October 2018, and a new release of the safety guideline was scheduled for the end of 2019, as a result of that meeting.

4.2.1 A General Short Summary Related to the Safety Aspects of rTMS, and Basic Procedures to Limit AEs

If safety recommendations in terms of intensity, frequency, and timing of stimulation are adhered to, rTMS and TBS stimulation can be considered overall safe. Currently available safety limits are reported in [5]. These limits are not mandatory, but just reflect proven safety limits in healthy subjects. In fact, they are meant not to prevent the development of new protocols of stimulation, as indeed it has been done since their publication.

Therefore, in case of new protocols, it is advisable to use all precautions that might alert the treating physician on the occurrence of an incoming seizure, the most SAE that might take place during an rTMS intervention. These include: (1) adjustment of the parameters of the stimulation according to the resting motor threshold (RMT); (2) the neurophysiological monitoring during the rTMS application.

Regarding the RMT, it is traditionally considered as the minimum intensity required to elicit an electromyographic (EMG) response (motor evoked potential, MEP) of at least 50 μV with a probability of 50% in a hand muscle at rest [6]. RMT can also be determined by observing the clinical motor responses (finger or arm movement) rather than recording the MEP by surface EMG. Such a visual method, which is often used in private clinics to save time, overestimates the minimum intensity required to activate the motor cortex; therefore, it potentially increases the danger of TMS. During a treatment course, the RMT has to be searched every day of stimulation, as it may change from day to day and due to the intervention itself [7].

Neurophysiological monitoring is strongly recommended either for all those studies that are based on new TMS protocols that are not fully tested yet by a safety point of view, or for all those protocols based on a combination of parameters of stimulation (including new coils or multiple-site intervention) that are close to upper safety limits of the published tables. This applies to both healthy subjects for research use and, even more, for patients' populations.

In studies where rTMS is not expected to generate MEPs (as during motor cortex stimulation below motor threshold or stimulation outside the motor cortex), the session can be monitored by recording MEPs in a hand muscle contralateral to the stimulated hemisphere: hand muscles are generally used to these purposes as they have the lowest threshold of excitation. The occurrence of TMS-evoked EMG activity during the rTMS application reflects an increase in cortical excitability, taking place at the motor cortex. The appearance of MEPs under these circumstances may indicate a lowering of the threshold in the subthreshold stimulated motor cortex, or the spread of excitation from neighboring areas to the motor cortex itself.

In studies where the stimulus is supposed to produce hand MEPs, EMG monitoring can be performed on a more proximal arm muscle, like the deltoid or the biceps muscle. If EMG recording is not available, a visual monitoring of the patients by a qualified person is mandatory, although it is less sensitive and objective [8].

Theoretically, the most appropriate method to detect an emerging seizure during rTMS could be represented by electroencephalographic (EEG) recordings. Indeed, EEG post-discharge after the cessation of cortical stimulation is classically considered to be the first indicator of an occurring seizure [9], as demonstrated for a variety of cortical targets [10–12] and for variable periods after the intervention [13, 14]. However, EEG monitoring is not feasible in the routine practice of rTMS, mostly because of the need for expensive specialized equipment to enable EEG recording during rTMS without artifacts due to magnetic pulses.

4.2.2 Illness-Therapy-Stimulation Interactions in Psychiatry

In a recent survey of the 5-year period 2012–2016, over 300,000 TMS sessions were applied with various frequencies and 21 seizures were reported (standardized risk 7/100,000): 14 of these occurred in subjects considered to have an elevated risk, such as taking medications, having brain lesions, or epilepsy (standardized risk: 24/100,000 sessions) [15]. However, the same survey reported that the concurrent use of psychotropic medications did not modify so much the risk of seizure occurrence (less than 0.02% of all treatment sessions; 8/45,000 sessions) [15]. Of these, only three—all psychiatric patients—were free from anatomical lesions and on medications suspected of lowering the seizure threshold. Two seizures were reported in depressed individuals without concurrent pharmacological treatment.

Regarding deep-coils, a recent review reported 31 seizures on 35,443 treated patients (seizure frequency of 0.00087) [16]. Of these, 29 occurred in depressed patients, one seizure in a schizophrenic patient and one in a post-traumatic stress disorder patient. In most cases, patients took one or more psychopharmacological agent(s) (amitriptyline, aripiprazole, bupropion, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, lithium, lurasidone, mianserin, mirtazapine, olanzapine, sertraline, trazodone, venlafaxine, vortioxetine). It remains difficult to answer whether these drugs have had a causal role or not, as seizures occurred either with high-risk drugs (e.g., clomipramine) or during treatment with drugs whose favoring seizure role is negligible [17].

Another AE potentially relevant in psychiatric patients undergoing TMS interventions is treatment-emergent mania, which has been reported after stimulation of the left prefrontal cortex, either with low- or high-frequency rTMS in patients with unipolar and bipolar depression [18]. However, the overall rate of 0.84% for active rTMS versus 0.73% for sham rTMS is even lower than the natural switch rate in bipolar patients under mood stabilizers treatment (2.3–3.45%) [18].

Suicidal ideation has never been described in healthy subjects during or after rTMS, and there is even evidence for an anti-suicidal effect of rTMS in depression [19, 20]. Psychotic symptoms, or anxiety, agitation, and insomnia have been occasionally reported: they were transient and resolved spontaneously or with light pharmacological treatment [21, 22], but it is unknown whether their frequency is higher during rTMS interventions than during the natural course of the disease.

Even if these AEs are minor and transient, it is advisable that psychiatric patients undergoing rTMS are clearly informed about the risk of psychiatric side effects, as they are not uncommon.

4.2.3 Conclusions and Recommendations

Patients undergoing rTMS intervention should be screened for suitability, as with magnetic resonance procedures [23]. When reviewing rTMS and TBS applications in human applications and clinical trials, no reports of an SAE or irreversible injury attributable to these interventions were found, despite the thousands of patients treated. Epileptic seizures induced by rTMS are a rare, but possible phenomenon: the most recent estimate shows a standardized risk of 7/100,000, which seems however not increased in psychiatric patient populations [15].

Mild AEs are instead quite frequent, but they are very mild, transitory, and do not require pharmacological treatment in most cases [5]: the most common are transient headache, local or neck pain, toothache, paresthesia, and transient hearing changes if earplugs are not properly positioned. Anxiety is possible, especially at the beginning of treatment, but it is likely an unspecific effect.

Although there is no evidence suggesting that AEs in psychiatric patients are significantly higher and different in magnitude in comparison to healthy subjects, care has to be taken to evaluate the concomitant treatment, as many of the drugs acting on the central nervous system may lower the excitability threshold. However, even in such a population of patients, the risk remains low [5].

For every new trial, stimulation parameters must always be chosen with safety considerations in mind, and be accepted by the Ethical Committee/IRB before initiation of a study.

4.3 Low-Intensity TES Methods

Low-intensity TES methods, which are used in psychiatry, are encompassing transcranial direct current (tDCS—most frequently), transcranial alternating current (tACS), and transcranial random noise (tRNS) stimulation or their combinations. “Low intensity” is defined as intensities <4 mA (at the case of tACS and tRNS peak-to-peak,) a total stimulation duration of up to 60 minutes per day, applied through at least 2 electrodes, using electrode sizes between 1 and 100 cm^2 (delivering ≤7.2 coulombs of charge) [3, 24]. With regard to tACS and tRNS, the applied frequency range is between 0.1 and 10,000 Hz.

4.3.1 A General Short Summary Related to the Safety Aspects of TES

The TES dose is defined by the parameters delivered by the stimulation device, generating an electric field (EF) in the body (in units of V/m or mV/mm) [25]. These

parameters can be well defined (intensity, duration of the stimulation, size of the electrodes); however, other parameters, including physiological factors such as individual anatomy, age, gender, baseline neurotransmitter concentrations, genetics, and dynamic state of the brain before and during stimulation are barely controllable (this, of course, applies to every brain stimulation protocol). Therefore, the current state of knowledge concerning the physiological mechanisms (and related safety aspects) of low-intensity TES still remains limited.

In most recent studies, the stimulation parameters are chosen based on previously published research and clinical data, computational modeling, and safety considerations based on human and animal experimental data. Finding the "optimal" dose for a given application still represents a challenge. With regard to the safe use of low-intensity TES for research and clinical purposes, it is recommended to consider the following issues.

1. EF modeling for targeting predefined areas for stimulation, including subject-specific current optimization can be helpful and results in increased safety. The current density is much higher in the skin than in the brain; therefore, the lack of skin injury indirectly supports the claim that the brain current flow is safe (assuming equal sensitivity to injury of skin and brain) [24–26]. It is suggested that the predicted EF strength is about 0.4–0.6 V/m in the cortex when the traditional stimulation protocols are used (up to 2 mA). The maximal value that was so far reported in a normal brain is 1.6 V/m [27]. Nevertheless, anatomical variations can lead to differences by a factor of ~2 for a fixed stimulation intensity [28–31]. The abovementioned data are very similar to those recorded in epilepsy patients with EF strengths of 0.6–1.6 V/m [32] and ≤ 0.5 V/m using 1 mA [33]. Of course, these small EFs are below the intensity required to elicit action potentials [34]; nevertheless, they can modify ongoing brain processes, inducing molecular or structural changes [35–38]. No irreversible electrochemical products are known to accumulate at the electrode with such low current densities. Conductive rubber electrodes are convenient for TES; they are not placed directly on the skin; an electrolyte that is saline or gel always separates the two [39]. Tap water is not recommended, and care should be taken, even when using a saline solution in longer-lasting experiments as increased contact resistance may also arise from the drying of the sponges [40]. Abrading the skin before electrode placement is not recommended [41].
2. Modeling studies can be just an estimation of the EF. However, the relation of this to time-integrated EF on the cortex is not simple [42, 43]. The other possibility is testing a given protocol in animal models; nevertheless, there are still many uncertainties in the translation of animal studies to human experiments. In humans, tDCS with 1 mA intensity using standard contact electrodes (16–35 cm^2) results in charge densities ranging from 170 to 480 C/m^2. In animal studies, at current densities between 14.3 and 28.7 mA/cm^2, corresponding to a charge density threshold below 52,400 C/m^2, no histologically detectable brain lesions were induced [44]. Threshold approximation obtained from rat experiments was estimated to be over one order of magnitude higher compared to current clinical protocols [24].

3. In clinical practice, safety of low-intensity TES (mainly tDCS) is mostly derived from an analysis assessing efficacy as the primary outcome; the number of trials targeting only "safety" is limited. In general, these human studies evaluated parameters of neuronal damage, such as neuron-specific enolase (NSE), magnetic resonance imaging (MRI) [45], electroencephalography (EEG), and neuropsychological tests [46, 47] and they all support the safety of TES.

Concerning human studies, the most typical events during stimulation are slight transient tingling sensations, very rarely local pain under the electrodes or light flashes when the stimulation was switched on or off abruptly, or when tACS is used in the EEG frequency range, with an intensity of 1–2 mA. Following the stimulation, light headache and erythema or contact dermatitis under the stimulation electrodes were reported [3]. It was repeatedly documented that the profile of AEs in terms of frequency, magnitude, and type is comparable in healthy and clinical populations, and this is also the case for more vulnerable populations, such as children, elderly persons, or pregnant women [3]. With regard to skin irritations, the contributing factors are pre-existing conditions, such as allergies to skin creams, high impedance (e.g., electrode dry or defect, inappropriate contact solution, nonuniform contact pressure of electrodes to skin), prolonged duration or repeated sessions, and too high current density (high current, small electrode) [3]. Therefore, irritation of the skin can be prevented by the best possible preparation of skin and stimulation electrode (without abrading the skin). The application of the stimulation over nonhomogenous (e.g., scars) or inflamed skin areas should be avoided. During and after treatment, participants should be instructed to report discomfort immediately.

4.3.2 Illness-Therapy-Stimulation Interactions

TES, similarly to rTMS, can be combined with basically any other therapeutic intervention, including motor or cognitive training, behavioral interventions or the application of medications [48–50]. Combinations of TES with motor or cognitive training or behavioral interventions appear to be safe (e.g., in the neurorehabilitation). However, some pharmacological interventions might increase the risk of AEs, e.g., when they amplify cortical excitability changes. On the other side, anticonvulsant medications can decrease or abolish anodal tDCS effects [51]. In the following section, we concentrate on reported AEs in one of the most frequently TES-treated patient groups in interventional psychiatry: major depressive disorder (MDD).

Generally, the burden associated with TES in MDD trials was basically the same as in all other trials with tDCS, i.e., cutaneous symptoms and sensations occurring with the same frequency [52]. Several RCTs [50, 53–55] described treatment-emergent mania/hypomania cases (generally, less than 15 patients until 2019). Only two occurred in patients with bipolar disorder. Five patients out of these cases started receiving tDCS and sertraline simultaneously. In a meta-analysis on the topic [56], it was found that the treatment-emergent hypomania/mania rates were not statistically different between active and sham stimulation, although they were higher in active (3.5%) vs. sham (0.5%) stimulation.

Treatment-emergent suicidal ideation or behavior is a risk in the treatment of any depressed patient. According to available data, one patient committed suicide during a clinical tDCS trial, but this was most likely unrelated to tDCS intervention [54].

In summary, patients should be carefully assessed for a history of bipolar disorder or of switching into mania with past antidepressant treatments, as these factors may indicate a higher risk of manic switch with tDCS; yet, a causal relationship is difficult to prove because of the low incidence rate and limited numbers of subjects in controlled trials. In these patients, concurrent treatment with mood stabilizer medications during the tDCS treatment course should be considered.

4.3.3 Conclusions and Recommendations

When reviewing only conventional bipolar tDCS in human applications and clinical trials, no reports of an SAE or irreversible injury attributable to low-intensity TES were found in over 33,200 sessions and 1000 subjects with repeated sessions [24]. About 400 publications using low-intensity TES between 2000 and 2019 reported mild AEs, mainly in the category of skin sensations; however, several studies were not placebo controlled and double blinded. At present, there is no direct evidence suggesting that the AEs in patients or in vulnerable populations are significantly higher and different in magnitude in comparison to healthy subjects. Generally, in a systematic review of 64 tDCS trials [52], it was found that the quality of AEs reporting in neuropsychiatry was quite low. Lack of adequate AEs reporting is a problem because this usually leads to an underestimation of the true rate of AEs.

Stimulation parameters should always be chosen with safety considerations in mind, and be accepted by the Ethical Committee/IRB before initiation of a study. Alterations during applications should always be documented. We suggest using standard questionnaires for screening and reporting [3] (http://www.neurologie.uni-goettingen.de/downloads.html). Additional questions and information can be inserted according to particular experimental or clinical demands. Furthermore, reporting each patient's guess for type of stimulation and reporting the researcher's assessment of the patient's propensity to complain [57, 58] should be required in future studies. As mentioned above, AEs have been rare and minor in the course of thousands of hours of TES in controlled settings, using CE certified stimulation devices around the world. There is little reliable data on the safety of direct-to-consumer brain stimulation devices. Therefore, we warn against the use of devices and methods unless they have shown both efficacy and safety in appropriately designed clinical trials.

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