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REVIEW ARTICLE

Fundamentals of transcranial electric and magnetic stimulation dose: Definition, selection, and reporting practices

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Background
The growing use of transcranial electric and magnetic (EM) brain stimulation in basic research and in clinical applications necessitates a clear understanding of what constitutes the dose of EM stimulation and how it should be reported.

Methods
This paper provides fundamental definitions and principles for reporting of dose that encompass any transcranial EM brain stimulation protocol.

Results
The biologic effects of EM stimulation are mediated through an electromagnetic field injected (via electric stimulation) or induced (via magnetic stimulation) in the body. Therefore, transcranial EM stimulation dose ought to be defined by all parameters of the stimulation device that affect the electromagnetic field generated in the body, including the stimulation electrode or coil configuration parameters: shape, size, position, and electrical properties, as well as the electrode or coil current (or voltage) waveform parameters: pulse shape, amplitude, width, polarity, and repetition frequency; duration of and interval between bursts or trains of pulses; total number of pulses; and interval between stimulation sessions and total number of sessions. Knowledge of the electromagnetic field generated in the body may not be sufficient but is necessary to understand the biologic effects of EM stimulation.

Conclusions
We believe that reporting of EM stimulation dose should be guided by the principle of reproducibility: sufficient information about the stimulation parameters should be provided so that the dose can be replicated.

Keywords transcranial; stimulation; electric; magnetic; dose

The growing use of transcranial electric and magnetic (EM) brain stimulation in basic research and in clinical applications reflects its capabilities to modulate brain function in ways not feasible with other techniques. Transcranial EM stimulation techniques include, but are not limited to, transcranial electrical stimulation (TES), transcranial direct current stimulation (tDCS), high-definition transcranial direct current stimulation (HD-tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), cranial electrical stimulation (CES), electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), repetitive TMS (rTMS), low field magnetic stimulation (LFMS), and magnetic seizure therapy (MST). The proliferation of methods and applications of transcranial EM stimulation, coupled with the existence of dose-response relationships, invites a discussion of the principles of dosing in this field. Without precision in dosing, true progress in refining these technologies will ultimately be limited.

In pharmacology, the administered dose is defined by the chemical composition, amount, frequency, and route of administration of a drug. The drug dose affects the chemical concentration of the drug in the extracellular space of tissues, which, in turn, is a determinant of the biologic response. Therefore, the drug dose parameters have to be selected as part of the treatment decisions to effect the desired biologic changes. Clearly, the clinical action of a medication is also affected by individual factors affecting pharmacokinetics (e.g., weight, age, sex, volume of distribution, and metabolism), but these factors are not controllable by the clinician, and therefore do not constitute dose, even though they can be considered in deciding what dose to administer. Analogously, the biologic effects of EM stimulation are mediated through an electromagnetic field generated in the body. Hence, the characteristics of the field are determinants of the ultimate physiologic response to EM stimulation. Therefore, *transcranial EM stimulation dose ought to be defined by all parameters of the stimulation device that affect the electromagnetic field generated in the body.* Again, the electromagnetic field is also influenced by the individual anatomy (e.g., scalp and skull thickness and electrical impedance), and the physiologic response to these fields may depend on various individual and environmental factors (e.g., age, sex, cognitive and affective state, concomitant pharmacologic interventions, baseline hormone levels, neurotransmitter concentration and receptor expression, genetics, and circadian rhythm). However, these factors are not controllable by the brain stimulation device, and therefore do not constitute EM dose, even though they can be considered in the dose selection process.

A proper understanding of the parameters involved in the transcranial EM stimulation dose provides the basis for rational and reproducible dose selection and reporting. Indeed, this understanding is a prerequisite to the ability to develop transcranial EM stimulation techniques to their fullest clinical potential. Although techniques like rTMS have recently crossed the threshold for US Food and Drug Administration (FDA) approval, their therapeutic efficacy is limited, and means of optimizing that efficacy are not

completely clear. Even in the case of ECT—a gold standard treatment with a long track record of efficacy—progress in reducing its side effects has been slowed by a general failure to appreciate the contribution of individual dose parameters to clinical outcomes.

Practically, EM dose can be defined by (1) the parameters that affect the *spatial* distribution of the electromagnetic field, including the shape, size, position, and electrical properties of the stimulating electrodes or coil, and (2) the parameters of the voltage or current waveform applied to the electrodes or coil that affect the *temporal* characteristics of the electromagnetic field, including pulse shape, amplitude, width, polarity, and repetition frequency; duration of and interval between bursts or trains of pulses; total number of pulses; and interval between stimulation sessions and total number of sessions. Control and documentation of these stimulation parameters ensures *reproducibility* of the EM dose.

In current practice, the EM stimulation dose is often described relative to individual measures such as motor threshold, and/or in terms of summary metrics such as total stimulus charge, total stimulus energy, or electrode charge density. It should be recognized that using relative and summary metrics for selecting, individualizing, and characterizing the EM dose does not obviate the need to also specify the complete EM dose defined by all relevant device parameters. Such individual measures, summary metrics, as well as other relevant data (e.g., imaging or computational modeling) are integrated in the concept of "dose selection"—factors that can be used to help select the EM dose to be applied in an individual. Indeed, dose selection is integral to many protocols, often with the objective to normalize the stimulation outcome and the risk/benefit ratio across individuals. By analogy, in pharmacotherapy, dose selection incorporates rules such as the number of milligrams of the drug per kilogram of patient weight and/or incrementing the drug quantity until therapeutic action or side effects are observed, whereas the actual administered dose (which may be determined by a variety of distinct dose selection considerations) would be specified in milligrams. Both in EM stimulation and in pharmacotherapy, it is prudent to control and report both the dose selection rules and the final administered dose.

Because of inter- and intraindividual variability, neither the chemical nor the EM stimulation dose fully determines the biologic or therapeutic outcome. As with pharmacologic approaches, replication of the EM dose across subjects, or even within a given subject over time, does not guarantee that the outcomes of stimulation will be identical. Though individualized measures, summary metrics, or other aspects of dose selection can be useful in adjusting the EM dose on a subject-specific basis, such dose selection factors cannot fully determine every desired and undesired physiologic response. If dose selection considerations are reported without specifying the actual administered EM dose, it is impossible to reproduce the dose post hoc. In pharmacotherapy, the rationale for dose selection does not obviate monitoring and recording all aspects of drug dose, as this is fundamental to safe and effective clinical practice and research. Applying similar considerations, our definition of EM dose is response-independent and can be fully described and replicated. We define EM dose by what is externally applied (and therefore fully controlled) rather than by any physiologic or behavioral response to stimulation.

Theoretically, there is an infinitely large set of possible dose parameters for transcranial EM stimulation. Even within safety and technologic feasibility constraints, there is still a wide range of stimulus waveform parameters and electrode/coil designs and placements that are possible. This wide parameter space provides for exceptional flexibility of transcranial brain stimulation, but also presents a challenge to researchers and clinicians in determining optimal dose for specific applications. The multiple parameters of EM stimulation have also posed a challenge to properly controlling, documenting, and reporting EM dose. The need for a uniform and rational system for defining and reporting of EM dose, that allows interpretation, reproduction, and comparison of results across studies and laboratories, is apparent and pivotal for the advancement of EM stimulation techniques and their applications.

A number of publications have proposed guidelines for the description of dose in specific transcranial EM stimulation paradigms, including TMS,[1] tDCS,[2,3] and ECT.[4,5] Nevertheless, a general definition and reporting framework for transcranial EM stimulation dose that integrates these different techniques is still lacking. Likely because of uncertainty about all the parameters constituting dose, studies are often published with an incomplete description of the applied dose, hindering interpretation and replication of the findings. Generalizing and complementing previous discussions, in this paper we aim to provide fundamental definition and principles for reporting of dose that encompass any transcranial EM brain stimulation protocol, because all transcranial EM stimulation techniques share a set of generic features. We first overview the basic principles of transcranial EM stimulation, including device characteristics, interaction of the electromagnetic field with neural tissue, and inter- and intraindividual variability of the stimulation outcome. The parameters involved in EM stimulation dose are then described, and approaches to selecting those parameters as well as safety considerations are briefly reviewed. Finally, we recommend rules for reporting the dose of transcranial EM brain stimulation.

Basic principles of EM stimulation

Though there remain many questions about the mechanisms of neuromodulation by transcranial EM stimulation, fundamentally, stimulation affects neural activity and ultimately behavior through the generation of an electric field and associated electrical currents (current density field) in the head.[6,7] There is evidence that neural activity may also be affected by static magnetic fields.[8] Therefore, in our general

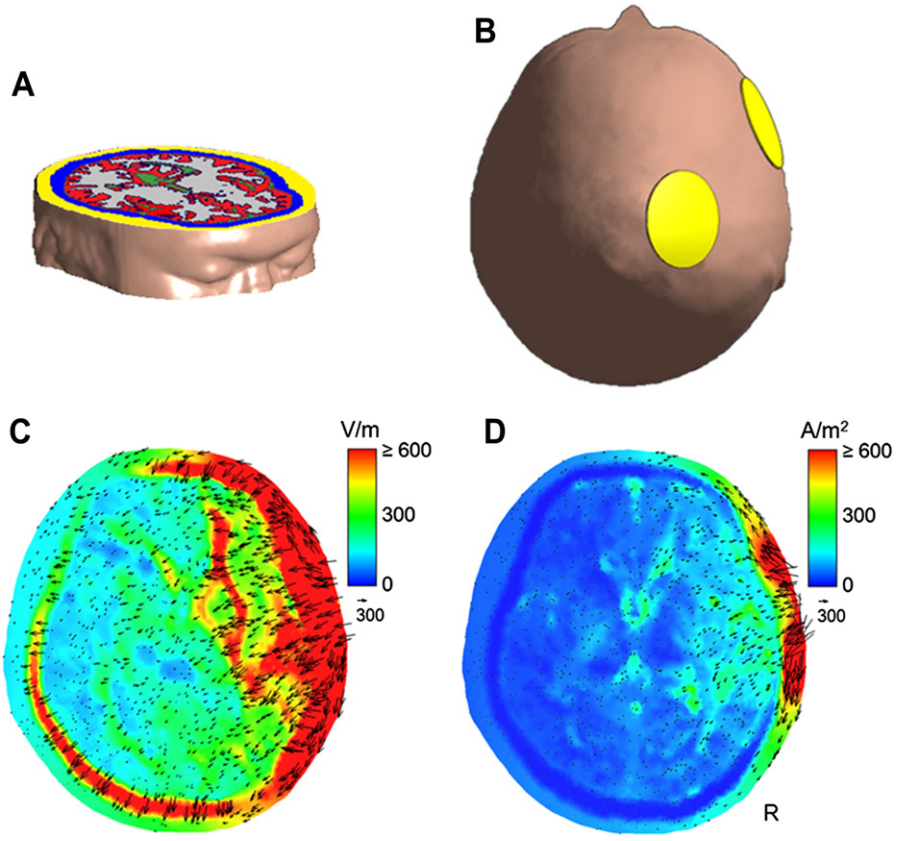

Figure 1 Simulation of the electric (**C**) and current density (**D**) fields injected by transcranial electric stimulation in a realistic head model (**A**) for right unilateral electrode configuration (**B**) commonly used in ECT. The cathode is centered 2.5 cm to the right of the vertex and the anode is centered 2.5 cm above the midpoint of the line connecting the external canthus and tragus on the right. The electrode current is 800 mA. Further details of the model are given in ref. 26. In (**C**) and (**D**) the color scale gives the magnitude of the field and the arrows indicate the magnitude and direction of the field.

discussion we refer to an electromagnetic field which subsumes the electric, current density, and magnetic fields. The biologic effects of all transcranial EM stimulation techniques are mediated by this exogenously generated electromagnetic field—what distinguishes each stimulation modality are the spatial and temporal field characteristics. To conceptually simplify the process, the problem of how transcranial EM stimulation affects brain function is generally parsed into consideration of (1) the characteristics of the electromagnetic field generated in the head during stimulation and (2) how this field modulates the brain function to ultimately effect cognitive/behavioral changes.

Electromagnetic field generation

All transcranial EM stimulation devices consist of two main components: (1) a waveform generator and (2) electrodes or an electromagnet coil positioned on the head. The waveform generator delivers electrical current to the electrodes or coil. In transcranial electric stimulation, scalp surface electrodes inject currents through the head, whereas in magnetic stimulation, currents are induced within the head by the coil. In both cases the result is an electric field (measured in volt/meter or related units) and a current density field (measured in ampere/meter^2 or related units) generated in the head. In magnetic stimulation, there is also a prominent magnetic field (measured in tesla or related units) generated by the coil. Neuromodulation results from the interaction of the electromagnetic field with the brain tissue (and its ongoing activity).

The electric field and the current density field are proportionally related through the tissue impedance. Importantly, the electric field and current density field direction and magnitude vary throughout the head as a function of tissue geometry and impedance—they are not described by a single value but rather by a spatial distribution of vectors, as illustrated by the computational model in Figure 1. Furthermore, the electric and current density fields also vary over time as a function of the current outputted by the waveform generator and the dispersive properties of the tissues. The magnetic field generated by the stimulation coil also varies as a function of space and time, but is virtually unaffected by the presence of biologic tissue. Thus, each of these fields and the electromagnetic field they comprise can be characterized by a temporal waveform and a spatial

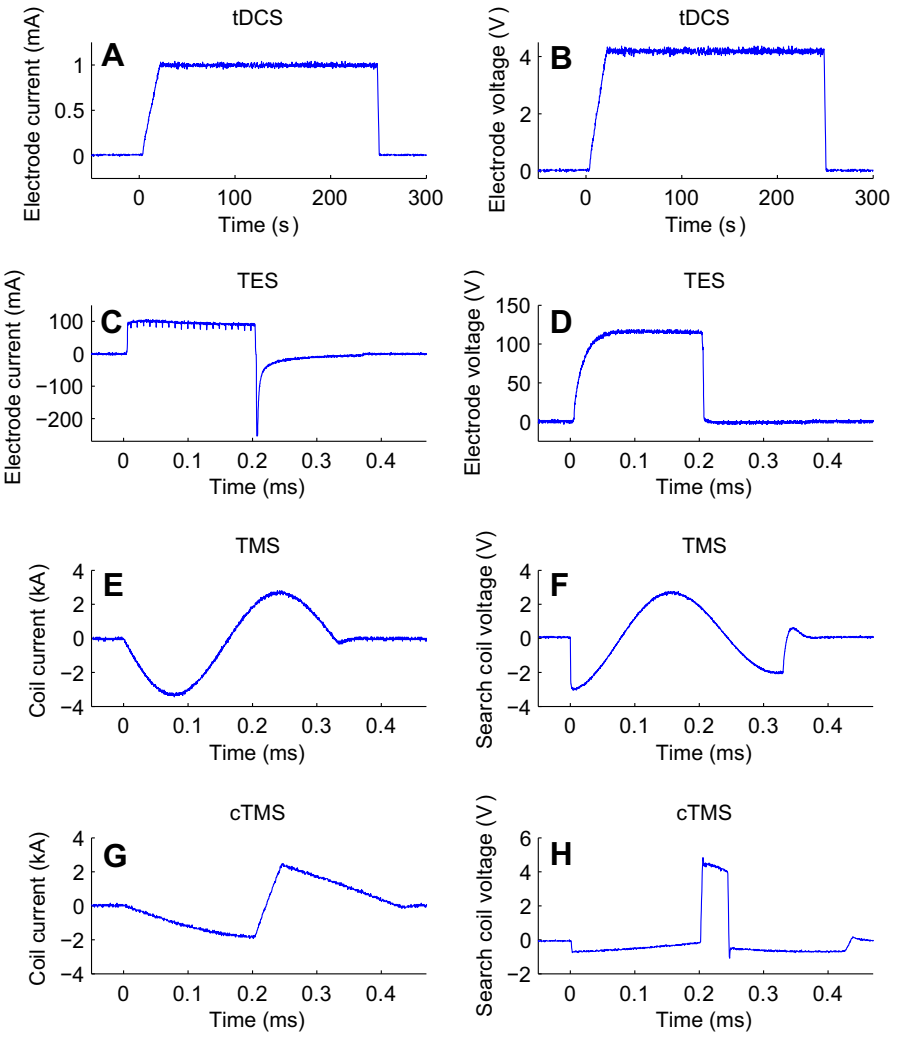

Figure 2 Example transcranial EM stimulation waveforms. Electrode current (**A**) and voltage (**B**) waveforms in tDCS delivered by Phoresor II Auto (Model No. PM850, IOMED, Inc., Salt Lake City, UT) with "dose" and "current" settings of 4 mA × min and 1 mA, respectively. Electrode current (**C**) and voltage (**D**) of a TES pulse delivered by Digitimer Model DS7AH (Digitimer Ltd., Hertfordshire, UK) with "pulse width" and "current" settings of 0.2 millisecond and 86 mA, respectively. Coil current (**E**) and search coil voltage (**F**) of a conventional TMS pulse generated by Magstim Rapid (Magstim Co., Whitland, UK) with "output" setting of 67% of the device maximum and a 70-mm figure-eight coil (P/N 9925-00). The search coil voltage is proportional to the TMS coil voltage and the induced electric field. The search coil was made of a single-turn rectangular winding with dimensions 1 cm × 30 cm, positioned perpendicular to the TMS coil plane, with one of the 1 cm sides standing 1 mm away from the TMS coil center, parallel to the electric field orientation.[16,102] Coil current (**G**) and search coil voltage (**H**) of a cTMS pulse produced by a custom-built waveform generator[16] connected to a Magstim figure-eight coil (P/N 9925-00).

distribution. From the stimulation device perspective, the temporal waveform is controlled chiefly by the waveform generator parameters, whereas the spatial distribution is controlled chiefly by the electrode/coil configuration. Therefore, the EM stimulation dose is defined by the stimulus waveform and the electrode/coil characteristics that govern the electromagnetic field generation.

Electric stimulation

Transcranial electric stimulation involves application of current/voltage to two or more surface electrodes, with at least one of them placed on the scalp. We use the term "electrode" to include the entire surface electrode assembly including any insulation, mechanical support, sponges, conductive solutions, and gels. The conductive elements of most surface electrodes are (1) a backing made of a solid conductor (metal or conductive rubber) attached with wires to the waveform generator, and (2) a conductive fluid or gel (electrolyte) that is placed between the skin and the solid conductor.[9] The fluid electrolyte may be suspended in a sponge (especially in relatively large electrodes), whereas the gel may be contained inside a hollow holder (for smaller electrodes, e.g., high-definition electrodes[10]). The current from the waveform generator passes through the solid conductor, the electrolyte, and the skin to enter or exit the body.

The electric and current density fields injected in the tissues are directly proportional to the current entering the body. Modern transcranial electric stimulators (e.g., for TES, tDCS, tACS, and ECT) typically have current-controlled output, meaning that the electrode current is controlled to follow the waveform characteristics programmed in the device (e.g., square current pulses with a set amplitude, pulse width, frequency). Figure 2A-D shows representative electrode current and voltage waveforms for tDCS and TES. The central reason for using current-controlled devices is that the electrode-skin interface has a complex, nonlinear, variable, and unknown impedance that depends on many factors including the skin conditions.[9,11] For current-controlled stimulators, the current entering the scalp is the same regardless of the value of the electrode-skin impedance. The tissue electric and current density field waveforms track the device-controlled current waveform and are therefore known and reproducible, independent of the electrode-skin impedance.

Some transcranial electric stimulation devices have outputs that are not current-controlled. There are devices (typically older ones) with voltage-controlled output, where the electrode voltage follows the waveform characteristics programmed in the device (e.g., square or sinusoidal voltage pulses). In the case of voltage-controlled devices, the current injected into the scalp and, hence, the electric/current density field in the body, depends on the impedance between the electrodes including the electrode-skin impedance.[9,12] As a result, the electric/current density field waveform in the body may not follow the device-controlled voltage waveform, and may vary widely over time and across subjects. For example, a square voltage waveform may be associated with an exponential current waveform, or the voltage may be zero even as current is passing through the tissue. Another family of devices (again, typically older ones) delivers a stimulus by discharging a capacitor through the electrodes. In this case, the electrode voltage and current waveforms have a decaying exponential shape; the exact parameters of the pulse depend on the device settings as well as on the impedance between the electrodes. Thus, for voltage-controlled or capacitor-discharge stimulators, the electrode current and the injected electric/current density field depend on the electrode-skin interface conditions, which may vary unpredictability during stimulation. Therefore, we recommend the use of current-controlled transcranial electric stimulation devices whenever practical.

Magnetic stimulation

TMS involves passing of current through one or more coils positioned on the head to generate a magnetic field that in turn induces an electric field and a current density field in the brain. The electric field induced by each coil is proportional to the rate of change of the coil current, which, in turn, is proportional to the coil voltage.[13,14] In conventional magnetic stimulation devices, the coil voltage pulse, and hence the electric field waveform, has a damped cosine shape,[13,15] whereas in controllable pulse parameter TMS devices (cTMS), the coil voltage can be near rectangular in shape.[14,16] Figure 2E-H shows representative coil current and induced electric field waveforms for a conventional TMS device and for a cTMS device. In both cases, the characteristics of the pulse voltage and current in the coil depend on the device and coil parameters, but not on the tissue properties of the subject, because the electrical impedance of biologic tissue is too high to significantly distort the TMS magnetic field. Thus, even though the head anatomy can affect the electromagnetic field induced in the head, the coil voltage and current are independent of the presence of the subject.

For both electric and magnetic stimulation, the distribution of the electromagnetic field in the head depends on both (1) the EM dose (i.e., the EM stimulation device parameters) and (2) the head tissue geometries and electrical properties. The EM dose can be controlled by the stimulator design and its operator-adjustable settings. However, unlike the waveform, electrode, and coil parameters, the individual anatomy and tissue properties are fixed and, at present, cannot be fully characterized, though some structural and tissue impedance data can be obtained with magnetic resonance imaging (MRI) methods. Interindividual variability in both gross anatomy (e.g., scalp and skull thickness, head diameter, skull-to-brain distance, and cortical folding[17-20]) and microscopic structure (e.g., tissue heterogeneity and anisotropy[21-26]) results in differences in the electromagnetic field exposure across subjects, even for identical EM dose.[27-32] The presence of any pathology (e.g., skull defect or implant, atrophy, tumor, infarction) can further alter the field in the vicinity of the pathology and throughout the head.[33-37] For these reasons, there is some level of uncertainty about the electromagnetic field distribution in the head during any stimulation protocol. Therefore, we restrict our definition of transcranial EM stimulation dose to the device parameters that control the electric field, which can be unambiguously specified (i.e., we define EM dose by the parameters of the field source, and not the parameters of the field itself).

Biologic effects of EM brain stimulation

The current state of knowledge of the physiologic mechanisms of transcranial EM brain stimulation remains limited. Recent reviews provide valuable summaries of current understanding.[38-49] We briefly discuss the fundamental aspects of the interaction between electromagnetic fields and neural tissue to establish a rational definition of EM stimulation dose.

At present, it is understood that the main mechanism by which electromagnetic field of the characteristics encountered in transcranial EM stimulation modulates brain function is neural membrane polarization shift. The membrane polarization change can, in turn, lead to diverse changes in single-neuron,[50] synaptic,[51] and network activity,[52] which

may ultimately be reflected in behavioral and cognitive changes. The electromagnetic field characteristics do not map in any trivial fashion to the nature or degree of neuromodulation, although one could distinguish between fields strong enough to depolarize neurons and weak fields that have subthreshold effects. Depending on the spatial distribution and temporal waveform of the electromagnetic field, and the regional brain (patho)physiology, a diverse range of changes could be triggered. Even though the mechanisms through which the generated electromagnetic field alters brain function are not fully understood, it is accepted that the spatial and temporal characteristics of the field are determinants of the physiologic responses. Thus, control of the field by EM dose manipulation enables a specific stimulation outcome to be effected.

Transcranial EM stimulation may act through various mechanisms besides directly shifting membrane potentials of cerebral neurons, although the involvement and role of such mechanisms has not been established. The electromagnetic field in the scalp is stronger than that in the brain and can stimulate scalp nerves and muscles. Furthermore, foramina may funnel current leading to low-threshold activation of cranial nerves, optic nerve, retina, or auditory nerve. Such afferent stimulation of the brain could produce neuromodulatory effects by itself or in conjunction with the electromagnetic field generated in the brain. For example, stimulation of cranial nerves could be a therapeutic intervention by itself, as exemplified by trigeminal nerve stimulation,[53] or can contribute to the outcome of techniques that target the brain directly, such as rTMS.[54]

Besides effecting changes in neuronal membrane polarization, additional putative mechanisms for the biologic effects of the electromagnetic field have been proposed, including activation of glial cells[55]; changes in blood-brain barrier permeability[56]; vasodilation[57,58]; electroporation[59]; joule heating[60]; electrophoresis[61]; effects on inorganic ion transport, second messengers, neurotransmitter activity, and/or neuronal metabolism[61,62]; protein signaling and transcription[61,63]; and effects on cell division.[64,65] Regardless of their relevance to any transcranial EM stimulation modality, these additional mechanisms are all based on the presence of the electromagnetic field. Therefore, the description of the EM dose is pertinent to these putative mechanisms as well. Indeed, proper documentation of the EM dose could allow post hoc analysis of studies to address the potential impact of such additional mechanisms.

EM stimulation devices may affect brain activity also via nonelectromagnetic interactions such as perception of device sound (e.g., TMS clicks), scalp pressure (e.g., from TMS coil vibration or elastic bands holding electrodes), and secondary afferent effects from direct muscle, cranial nerve, and peripheral nerve activation. Generally, any aspect of the environment during EM stimulation, including ambient lighting and sounds, subject comfort, and behavior of other individuals in the vicinity may influence the brain state and potentially the stimulation outcome. Indeed, even the knowledge that one is receiving EM stimulation, and the expectancy of specific outcomes of the stimulation, may, by itself, result in physiologic and behavioral changes, otherwise known as the placebo effect.[66,67]

The outcomes of transcranial EM brain stimulation are arguably as diverse and complex as the range of brain functions. It is becoming increasingly recognized that the response to EM stimulation is dependent on factors that affect the underlying brain state including age, sex, hormone levels, attention/cognitive state, chronic and acute physical exercise, pharmacologic interventions including medications and anesthesia, neurotransmitter concentration, genetics, time of day, and state of endogenous neural oscillations.[68-79] Thus, inter- and intraindividual variability also results from differences in the baseline brain state, which modulates responsiveness to EM stimulation. Therefore, it may be important to consider in the dose selection process the possible effects of the brain state on the EM stimulation outcome.

In summary, the electromagnetic field distribution in the head is controlled by both the EM dose (stimulation device parameters) and the tissue geometries and electrical properties. The effects on the brain are then determined by *both* the electromagnetic field in the head as well as the structure and the dynamic state of the neural circuits. Therefore, EM dose is necessary but not sufficient to explain the physiologic and behavioral effects of EM stimulation. Nevertheless, of all relevant factors, only the EM dose can be fully controlled and characterized in absolute terms.

Dose definition and dose selection

Figure 3 and Table 1 summarize the process of dosing transcranial EM stimulation. The researcher/clinician chooses an EM stimulation device and its settings based on subject-independent knowledge (e.g., scientific hypothesis, mechanisms of action, etiology of disorder, prior research/clinical experience, computational models) and subject-specific data (e.g., age, sex, structural and diffusion MRI, diagnosis, risk factors, treatment history, individual electromagnetic field model, prior EM stimulation response). The EM stimulation device consists of a waveform generator that is programmable through settings and is connected to electrodes (for electric stimulation) or an electromagnet coil (for magnetic stimulation). The structure and placement of the electrodes/coil and the current or voltage waveform applied to them constitutes the EM stimulation dose, because these are the device parameters that can be manipulated to control the electromagnetic field generated in the subject/patient's head. The EM dose can thus be defined by describing the physical device characteristics governing EM stimulation, or by indicating the specific commercial products and settings used, from which the physical device characteristics can be uniquely determined. The device output can be measured to verify that the EM stimulation dose is correct. Various summary metrics based on the

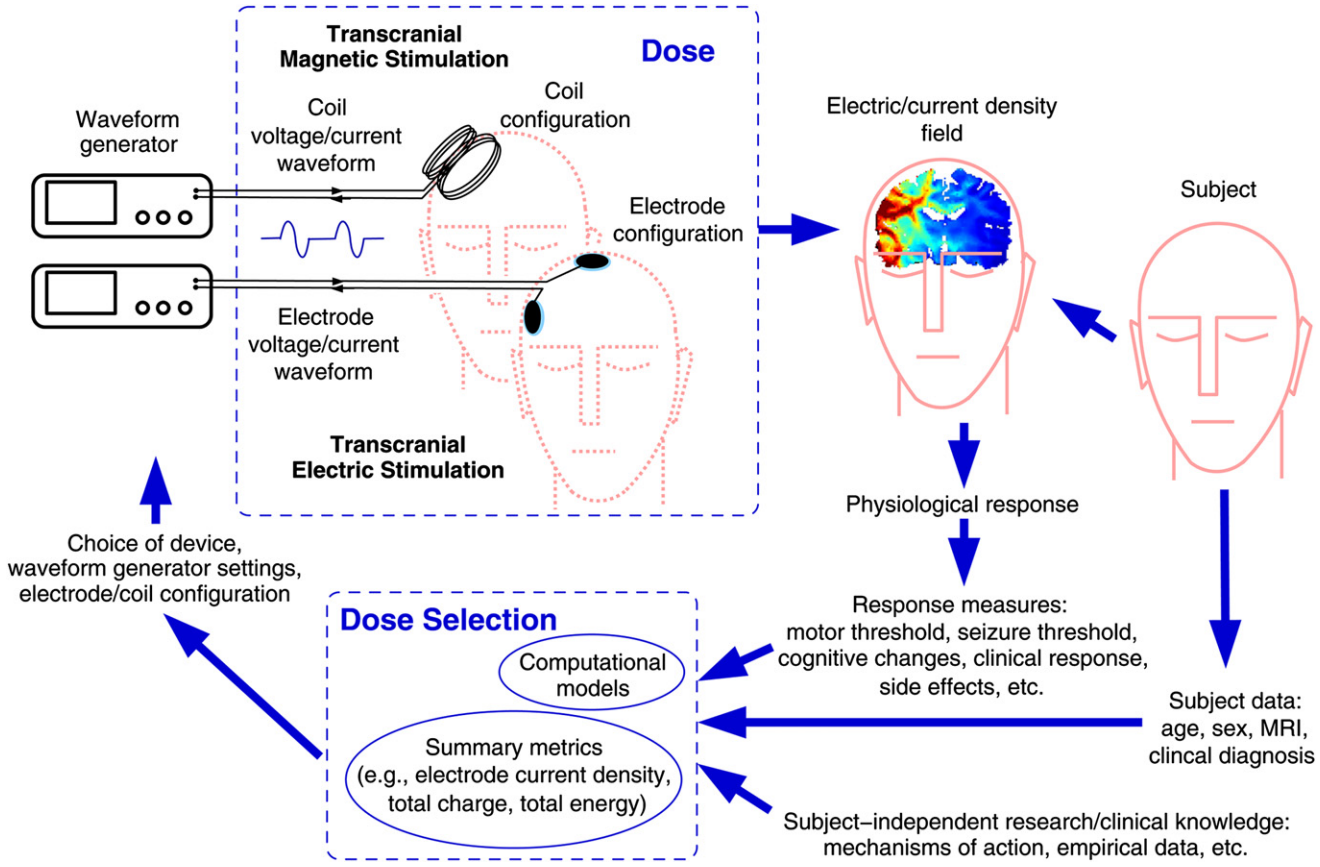

Figure 3 Summary diagram of transcranial EM stimulation dosing. The EM stimulation dose is described by the electrode/coil configuration parameters and the electrode/coil voltage or current waveform parameters. See "Dose definition and dose selection" for further discussion.

EM dose (e.g., electrode current density, total charge, total energy) could additionally be computed and used in the dose selection process. The EM dose is a determinant in the generation of an electromagnetic field in the head. The generated field produces acute and lasting physiologic changes that can be characterized by measures such as response thresholds, cognitive and behavioral changes, clinical improvement, side effects. The measured responses to the EM stimulation can be used in subsequent dose selection.

In Figure 3 and Table 1, we emphasize the distinction between EM dose and dose selection. Describing dose selection considerations and/or stimulation response measurements does not supersede reporting the complete EM dose. In the following sections we discuss in more detail the parameters that describe the EM brain stimulation dose (the next section) and overview approaches to selecting the EM dose ("Dose selection" section).

Dose parameters

Reporting of EM stimulation dose should be guided by the principle of *reproducibility*: *sufficient information about the stimulation parameters should be provided so that the stimulation dose can be independently replicated or modeled based on this description*. No aspect of the EM stimulation device configuration that affects the electromagnetic field should be omitted because the researcher/clinician considers it unimportant for outcome, as subsequent interpretations of the results could necessitate data on dose parameters that were not initially deemed significant. The parameters comprising transcranial EM stimulation dose can be segregated into (1) those describing the stimulus waveform and (2) those describing the electrode/coil configuration.

Stimulus waveform generator parameters

The stimulus waveform refers to the current and/or voltage waveform generated by the stimulation source and applied to the stimulating electrodes or coil (see Figure 2 for some examples). The stimulus waveform governs the temporal variation of the electromagnetic field during the stimulation session. For a particular EM stimulation device, some waveform parameters may be fixed, whereas others may be user-adjustable over a given range. The principle of reproducibility dictates that when documenting and reporting a procedure, sufficient information about the stimulation waveform should

Table 1 Summary of recommended transcranial EM stimulation dose parameters for reporting and reproducing research and clinical protocols. Factors relevant to the selection of EM stimulation dose are summarized separately and do not reduce the value of fully reporting the applied absolute dose

Transcranial EM stimulation dose[1]	
Electric stimulation	Magnetic stimulation
Stimulus waveform parameters • Complete characterization of electrode voltage (for voltage-controlled devices) or current (for current-controlled devices) waveform, e.g. • pulse shape, amplitude, width, and polarity; • pulse repetition frequency, duration of and interval between bursts or trains of pulses, total number of pulses; • for repeated sessions, interval between sessions and total number of sessions[2]	• Complete characterization of coil current waveform, e.g. • pulse shape, amplitude, width, and polarity; • pulse repetition frequency, duration of and interval between bursts or trains of pulses, total number of pulses; • for repeated sessions, interval between sessions and total number of sessions[2]
Electrode/coil configuration parameters • Electrode geometry and materials including the solid conductor, electrolyte, electrolyte supporting materials (e.g., sponge)[2] • Skin preparation techniques • Electrode position and orientation on the scalp relative to a reproducible reference frame	• Winding shape (e.g., circular, figure-eight) and diameter, number of turns in each winding, core dimensions and material, parameters of any auxiliary windings or cores[2] • Coil position and orientation on the scalp relative to a reproducible reference frame
Example factors for selection of transcranial EM stimulation dose	
• All available, relevant subject data (e.g., imaging data, pathology reports, relevant physiologic measures) • Experimental or clinical individual response measures (e.g., TMS motor threshold, ECT seizure threshold) • Summary metrics (e.g., average electrode current density, total charge, total energy) • Computational models (e.g., electric field or current density field model) • Prior clinical experience • Safety considerations (e.g., study exclusion criteria) • Methods to normalize functional/clinical responses across individuals	

[1] Parameters should be reported for each electrode or coil.

[2] Commercial manufacturer, electrode/coil product numbers, and waveform generator product number and settings may be provided in substitute. Even if the complete EM dose can be specified without reference to a commercial product, it is recommended that the make/model of all devices and accessories be indicated. Vice versa, when the commercial make/model is provided, a description of key features of the device is still valuable.

be provided so that the electrical output of the stimulator can be replicated accurately. It is important to report the parameters describing the entire waveform generated and applied to the subject. The waveform can typically be described using simple mathematical functions like direct current (dc) or a train of rectangular, sinusoidal, or exponential pulses, and their associated parameters such as amplitude, polarity, pulse width, frequency, and duration (Figure 4). In some cases, moderately more complicated waveforms are used such as damped sinusoidal pulses, amplitude modulated sinusoids, or types of noise. In most cases these waveforms can nevertheless be simply described by indicating just a few parameters. In many rTMS protocols, the stimulus involves intermittent trains and/or bursts of pulses.[80-82] In these cases the intervals between the distinct trains and/or bursts should be described. Protocols involving types of noise stimulation can be described by the spectral characteristics of the stimulus.[83] The description should include any "preconditioning" stimulation (e.g., ramping up of the pulse amplitude in the beginning of the stimulation session, as shown in Figure 2A and B). In some cases a figure accompanied by explanatory text is useful in describing the waveform. For example, a recording (e.g., an oscilloscope trace) of the actual generated waveform could be supplied, coupled with a description of the corresponding device settings and the measurement method (as in Figure 2). In some protocols, transcranial stimulation is applied during repeated stimulation sessions. The intervals between the sessions should be included in the dose description[84]; any variation in the spacing of the sessions or in the stimulus parameters within each session should be reported.

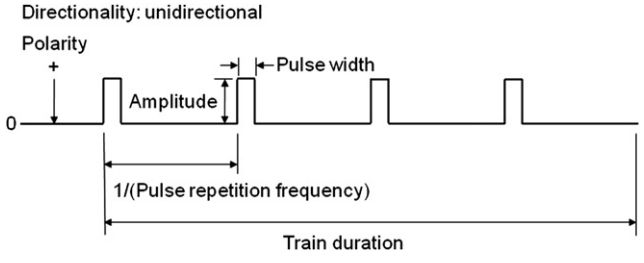

Figure 4 Definitions of typical transcranial EM stimulation waveform parameters.

A complete description of the EM dose parameters may not be practical when using commercial devices because,

for instance, some aspects of the dose are not transparent to the user (e.g., the coil current pulse shape and amplitude in a TMS device). In such cases, sufficient information should be provided so that the electrical output of the stimulator can be reproduced, including the device manufacturer, make, unique model number (often called product number, P/N), and device-specific settings. However, users should be aware of several ambiguities related to commercial stimulation devices discussed below.

Commercial stimulators, especially devices customized and restricted to a specific class of therapy, often do not make the generated waveform transparent to the user. Rather, the user is allowed to adjust a few settings—these settings may or may not correspond to a single waveform parameter and may be given in terms of a relative scale rather than an absolute quantity. For example, some ECT devices provide a single dial that adjusts the total charge of the stimulus train. Physically, the charge is adjusted by changing the pulse train duration, frequency, or pulse width. The schedule used by the device to convert the total charge setting to actual pulse train parameters is usually documented in the device manual (and may be programmable by the user). However, clinicians are frequently unaware of the specific schedule used. Because identical total charge delivered by different combinations of parameter values may have distinct physiologic effects that have been shown to alter clinical outcomes, the specific parameter values (pulse amplitude and width, and train frequency and durations) should be documented in addition to or in lieu of the total charge.[5] The total charge can always be calculated from the current waveform parameters, but not vice versa.

tDCS devices generally control and indicate the duration and peak strength of the applied current. Some devices used for tDCS, but not specifically designed for that application, may not allow independent programming of the current duration and strength, and may not make transparent the nature of the on/off ramp. Furthermore, such devices may not include sufficient information about the accuracy of the actual applied waveform.

The stimulus waveforms produced by CES devices often have complex characteristics that vary widely among manufacturers and brand names. In some cases, a single CES device can produce a variety of stimulus waveforms based on user-controlled settings. On other devices, only a single parameter (typically stimulus amplitude) can be adjusted.

TMS devices commonly provide pulse amplitude adjustment as percentage of the maximum amplitude for that device or in other relative units. In the literature, the term "percentage of maximum output" is often used to mean "percentage of maximum amplitude." We discourage this practice because various parameters characterize the device output, including amplitude, frequency, train duration, pulse width (in some devices). Therefore, the specific output parameter referred to should be indicated—in this case the pulse amplitude. Physically, the amplitude setting corresponds to the voltage of the TMS energy storage capacitor, which is the voltage applied to the TMS coil in the beginning of the magnetic pulse. However, the actual capacitor voltage range and capacitance are typically not provided to the user. Furthermore, the pulse width and damping vary among devices and coil models. Consequently, various TMS device models with identical user-adjustable settings may output substantially different waveforms. Therefore, the stimulation procedure has to be documented by specifying the device and coil model and manufacturer, in addition to the device settings. In some cases, unintuitive behavior of the device may be documented in the device manual, but may not be obvious in the device controls. For example, some rTMS and MST devices automatically reduce the pulse amplitude for pulse train frequencies above a certain limit. In that case, even though the operator sets the pulse amplitude to "100% of maximum," this maximum is different at low and at high frequencies.

Electrode and coil parameters

Another component of the transcranial EM stimulation dose refers to the dimensions, materials, and position of the electrodes or coil. Typically commercial electrodes or coils are used, in which case the manufacturer and part number should be provided in addition to basic information about the electrode/coil physical characteristics. Placement of the electrodes or coil is controlled by the researcher/clinician and should be carefully documented and reported, specifying how the placement was initially determined and maintained throughout the stimulation session.

Electrodes

The region where current enters or exits the body through the electrode is defined by the area of skin covered by the electrolyte. The area of electrolyte-skin interface, rather than the dimension of the solid-conductor in the electrode, defines the functional electrode position and perimeter. If, for example, the electrolyte is saline, it may wet the hair beyond the contours of the electrode, thus increasing the effective electrode area. Indeed, for this reason, limiting the amount of fluid while still ensuring adequate and even coverage, or using a relatively viscous conductive electrode gel or cream may be preferable. Conversely, if portions of the electrode surface are not in proper contact with the skin, the effectively reduced electrode area may lead to altered electric field distribution, tingling sensations that can affect blinding, and even skin lesions.[85]

The electrode current density is not spread evenly across the contact area, but tends to be concentrated near the electrode edges, with higher concentration along the edges closest to another electrode.[86-88] Higher current concentration can also occur near skin inhomogeneities. Thus, the distribution of the applied current across the electrode-skin surface will be affected by the properties of the electrodes and the skin. Though the uneven distribution of current along

the electrode-skin surface may not be reflected in the brain,[87] it may nonetheless profoundly affect sensation and/or skin safety. In some applications, the skin is prepared by cleaning with alcohol and an abrasive gel to reduce and stabilize the electrode-skin impedance.[12,89,90] Any skin preparation steps should be documented as part of the EM dose, in addition to the materials and dimensions of the solid-conductor and the electrolyte.

In the literature, one electrode is sometimes considered to be "active," presumably exerting the neuromodulatory effect on brain function, whereas the other electrode is considered to be a "return" or "reference" electrode, collecting the current from the active electrode presumably without effecting neuromodulation. For example, in tDCS the presumed "active" electrode is typically placed over the targeted brain area, whereas the "return/reference" electrode (often having the same design and dimensions as the active electrode) is placed elsewhere on the head or on the body. In this case, the physical properties of both the presumed "active" and "return/reference" electrodes should be documented. Even if the direct functionality of the return/reference electrode is mitigated by its position (e.g., extracephalic[91]) or size (e.g., significantly larger than the active electrode[92]), the return/reference electrode still determines the current path from the active electrode through the brain. Importantly, the region of brain modulation is not simply under the electrode of interest; rather, it is a function of the position and properties of both electrodes (as well as the stimulus waveform and tissue parameters).[18,93]

Diverse terminology to describe electrode configurations has been used in the literature, and in some cases the terminology is not accurate or does not fully characterize the EM stimulation dose. For example, it is not sufficient to report that an "extracephalic" electrode was used—the characteristics and placement of that electrode on the body should be specified. The term "unipolar" has been used to describe stimulation producing one dominant polarity in the cortex, even though technically tDCS must always be bipolar with an anode and a cathode. Guided by the principle of reproducibility, in defining EM dose any potentially ambiguous terms should be defined or avoided.

Coils

Coils are made of windings of conductive wire that are encased in an insulator. The coil core is either empty (air core) or is filled with a ferromagnetic material.[15,94,95] The relevant physical parameters of coils include the winding shape (e.g., circular, figure-eight), the diameter of the loops, the number of turns in each winding, the core dimensions and material, and any additional windings or cores (e.g., intended to reduce scalp sensation or to cancel the main coil magnetic field for placebo stimulation). When using commercial coils, it is possible to identify a unique make and model number that will allow determination of the physical properties relevant to EM dose (nevertheless, it is still preferable to also specify the basic coil characteristics like the winding shape and diameter).

Positioning

For both electrical and magnetic stimulation, the position and orientation of the electrode or coil on the body should be clearly defined to the precision possible. Reporting that the electrode/coil was placed over a certain brain region should be accompanied with a description of how the corresponding scalp location was determined, that is, what reference system was used for positioning the electrodes or coil. The orientation of the electrode or coil has to be specified whenever they are not centrally symmetric. We do not aim to recommend a particular reference system for all stimulation modalities and therapeutic objectives. Rather, as with other aspects of EM dose, the description of the electrode/coil position should be guided by the principle of reproducibility. A reproducible EM dose positioning description would allow accurate repositioning of the electrode/coil on the same subject, as well as matched positioning on a new subject. Positioning reference systems include those based on scalp landmarks (e.g., the EEG 10-20 system) or brain anatomic structures (e.g., specific gyri or sulci identified by an individual MRI scan and targeted with a stereotactic positioner). Tools used to assist positioning relative to a reference frame, ranging in sophistication from rubber bands to frameless stereotactic image-guided systems and robotic arms, are important for EM dose as they may affect the accuracy of the electrodes/coil position relative to the chosen reference frame, and the maintenance of that position over the course of the stimulation session and subsequent sessions.

Often the coil position in TMS is individualized based on functional measures (e.g., a "hot spot" defined as the optimal site of the coil for maximum measured response such as a finger twitch or phosphenes). We suggest that there is still value in noting the resulting location of the TMS coil relative to an anatomical reference frame. Documentation of the absolute coil position provides for better reproducibility. Furthermore, some aspects of the stimulation response may depend on the coil position relative to anatomic landmarks in addition to functional landmarks (see also discussion in "Dosing relative to individual measures").

Connectivity

For an electric stimulator with two electrodes or a magnetic stimulator with a single coil only the current direction needs to be indicated. In electric stimulation, the terms "anode" and "cathode" are used to refer to positive current entering and exiting the tissue, respectively. This is the convention in electric stimulation, regardless of how "anode" and cathode" are used in other technical fields. For a two electrode system, the anode and cathode always correspond to the positive and negative voltage terminals, respectively. For example, in tDCS, where the current flows generally only in one direction

during a stimulation session, it is convenient to refer to a given electrode as an anode or a cathode. For stimulation with symmetrical bidirectional waveforms, such as tACS and conventional bidirectional ECT, there is no consistent anode or cathode, because the direction of current flow is alternating. In such cases, the connection polarity is irrelevant. In cases where the waveform is not symmetrical around zero, such as in TES (Figure 2C and D), tACS superimposed on tDCS,[96] or unidirectional ECT,[97] the electrode connectivity relative to the waveform polarity should be reported.

For TMS coils, the direction of either the current flowing in the coil or the current induced in the head (which, by Lenz's law, runs opposite to the coil current) should be specified. It should further be specified which TMS pulse phase the current direction is referring to, e.g., "the direction of the initial phase of the induced current was posterior-anterior." Some TMS coils can be used with either side facing the head; in that case the TMS coil side has to be specified, because this determines the induced current direction.

For more complex multichannel stimulation ($>$ 2 electrodes and/or $>$ 1 coil), connectivity should be fully documented, and careful consideration should be given to the distribution of current among the electrodes and coils, and the integrity of the applied stimulus waveforms. For example, if TMS is applied to a subject simultaneously receiving some form of transcranial electric stimulation (e.g., tDCS), the TMS magnetic field could potentially induce unintended currents in the scalp electrodes and leads, thus confounding the experimental paradigm and potentially compromising safety. Studies on the interactions between TMS and transcranial electric stimulation devices are currently lacking, but caution is warranted as significant currents induced by TMS in the leads and electrodes of deep brain stimulation implants have been reported.[98,99]

Measuring/verifying dose

As defined previously, the EM stimulation dose is comprised of the device parameters that affect the electromagnetic field in the brain. Therefore, the EM dose corresponding to particular device configuration and settings can be calibrated and verified independent of the presence of a subject. As stimulation devices remain in use over periods of years and as faults can compromise safety and reproducibility, a basic level of verification and vigilance is warranted. The waveform generator, wiring, and electrode/coil physical condition should be checked by visual inspection before each stimulation session. Nevertheless, devices can malfunction without visible signs, producing, for example, the wrong pulse shape.[100] Manufacturer error or lack of proper labeling can also occur, resulting, for instance, in incorrect reporting of the stimulus current direction.[101] We recommend that the user or a technician verify the device output before initial deployment and subsequently at some regular interval. There is also a role for self-check and output monitoring features built into the stimulation device to automate this process wherever possible and, hence, to reduce user burden.

For electric stimulation, the simplest waveform verification technique is to monitor the voltage across a resistive load (typically 200 Ω to 10 kΩ, representative of the typical interelectrode impedance encountered when the electrodes are attached to a subject). The load voltage is directly proportional to the electrode current per Ohm's law. For magnetic stimulation, the simplest technique to verify key aspects of the EM dose is to use a calibrated search coil placed at a well-defined location relative to the TMS coil.[102] The search coil voltage is proportional to the induced electric field. The electric field is proportional to the TMS coil current rate of change, which, in turn, is proportional to the TMS coil voltage. By Lenz's law, the induced current flow in the search coil, like the induced current flow in the subject's head, is in direction opposite to the current in the TMS coil. Thus, the stimulus waveform parameters (pulse shape, amplitude, width, damping, and direction, and pulse train frequency and duration) can be measured with the search coil.

If the device manufacturer provides guidelines for safety checks or calibration of the device, they should be followed. Furthermore, in some institutional settings like hospitals, a basic safety check (test of leakage current of line-powered devices that are used on human subjects) is typically performed annually.

Summary metrics

Summary metrics (also known as "composite parameters"[4]) are defined as quantities that are a function of two or more EM stimulation dose parameters.[5] Examples include average electrode current density (defined as electrode current divided by electrode area), which is sometimes used in tDCS and tACS,[92] charge per pulse phase that is used to define safety limits,[103,104] and charge rate and total stimulus charge or energy that are used in ECT.[12,105] Summary metrics reduce the information content of the dosing system and are generally not sufficient to allow reproduction of the stimulation paradigm, because there are distinct EM stimulus parameter combinations that can result in an identical summary metric value.

For example, in ECT electrical dose is typically reported in terms of the total charge or energy delivered during the treatment. Charge is a summary metric that depends on several waveform parameters including pulse train amplitude, pulse width, frequency, and duration. Charge is insensitive to other potentially important parameters such as pulse train directionality and polarity. Energy depends on the same parameters as charge as well as on the interelectrode impedance. We recommend that the waveform parameters be reported explicitly because neither charge nor energy uniquely determine the stimulus waveform.[4,5] As an illustration of how the use of total charge as a summary dosing metric in ECT can be misleading, consider a typical tDCS

session where a current of 1 mA is applied for 20 minutes through scalp electrodes, resulting in total administered charge of 1200 mC. This amount of charge is more than 10 times the typical seizure threshold in ECT, yet, because of the low amplitude of the current, tDCS does not trigger a seizure and only produces minimal scalp sensation.[5] Similarly, in tDCS paradigms, reporting only the electrode current density or the electrode charge density, does not uniquely define the electrode dimensions, current, and stimulation time. The electric and current density fields in the brain are not simply related to the electrode current density, and hence this summary metric cannot be used to accurately account for the effect of changes in electrode area.[86,106]

The essential point is that given just the summary metric, one cannot recover the unique EM stimulation dose, whereas the summary metric can always be calculated from the complete dose description. Even when summary metrics are useful for the dose selection process or for analysis of the procedure outcome, reporting a summary metric does not obviate the need to fully describe the EM dose to ensure reproducibility of the procedure.

Dose selection

Dose selection includes all steps that inform the choice of transcranial EM stimulation dose to be delivered.

Individual anatomic and physiologic data

All relevant, available subject/patient data should be considered in determining the EM dose. These include any biologic factors that affect the stimulation outcome including subject anatomical data (affecting the electromagnetic field distribution; refer to "Electromagnetic field generation") and physiology (affecting responses to the electromagnetic field; refer to "Biologic effects of EM brain stimulation"). Relevant patient data may include disease cause and information on additional pharmacologic or EM treatments and their outcomes. Especially relevant are measurements conducted before, during, or after the EM stimulation that provide insight into the injection of electromagnetic field (e.g., electrode/body impedance for transcranial electric stimulation) or the physiologic response (e.g., evoked response thresholds or other excitability measures). Indeed, one advantage of noninvasive EM stimulation is the capability to readily customize EM dose based on relevant subject-specific data.

It is evident that no realistic description of a subject is complete, with most subject data unknown or not relevant to transcranial EM stimulation. Nevertheless, given that anatomic and physiologic differences among individuals influence the response to a given EM dose, documenting subject-specific information provides important information in interpreting the results. For example, data on individual anatomy may range in detail from sex/age to gross head dimensions to imaging data. If the EM stimulation subject has structural abnormalities or implants in the head, the characteristics of the pathology/implant should be considered (e.g., tissue pathology properties, pathology geometry and location, burr holes, and implant properties and location).[33-37,99,107] Study inclusion and exclusion criteria represent one component of dose selection.

Dosing relative to individual measures

Transcranial EM stimulation dose is often individualized based on physiologic, cognitive, or behavioral measures. For example, the EM dose may be adjusted relative to evoked physiologic responses and/or a clinical outcome. The motivation for the use of relative dosing is that the absolute EM dose does not fully determine outcome because of variability across individuals. Indeed, a functional measure may be perceived as more accurate than absolute measures because it reflects the net sum of administered dose, individual differences in responses to the dose, and final functional outcome. However, regardless of the perceived value of any given individual measure, the use of relative dosing does not reduce the need to also report the absolute applied EM dose, and may even be misleading when the relative measure used to select dosage was derived from a brain function unrelated to the ultimate desired clinical outcome.

The most common example of an individual measure applied in dosing is the TMS motor threshold that is routinely used to individualize the TMS pulse amplitude.[1] Other individual measures include phosphene TMS threshold and visual masking TMS threshold.[74,108] The current strength in tDCS is usually fixed, but it has been proposed that it should be individualized too based on measures of the change in motor cortex excitability induced by tDCS.[86] In ECT, the stimulus dose is commonly individualized based on the patient's seizure threshold[109] or age.[110] The position of the electrodes/coil may be chosen based on an individual "hot spot" corresponding to the optimal site for an evoked motor, sensory, or fMRI blood oxygenation level dependent response.

There are several advantages and disadvantages of dose selection based on individual measures.[111] The main advantage is that relative dosage may control for a number of device-specific (e.g., TMS pulse shape[112] and width[14,113,114]) and subject-specific (e.g., skull and scalp thickness[115]) variables. Dose individualization measures are also selected to be practical to obtain. One limitation of relative dosing is that the act of measuring a threshold response could, by itself, effect neuromodulation (e.g., change of excitability of the targeted circuit). For example, the subthreshold stimulus trains delivered during seizure threshold titration in ECT could affect the measured seizure threshold. Another disadvantage of many individual measures is that the process being probed and used to individualize the stimulus (e.g., single pulse TMS motor threshold) is often spatially and functionally distinct from the process being subsequently targeted

(e.g., repetitive TMS of the prefrontal cortex for depression treatment). Furthermore, whereas dosing relative to individual measures may help reduce the interindividual variability of the stimulation outcome, some aspects of the outcome may depend also on the absolute dose. For example, rTMS of the dorsolateral prefrontal cortex for the treatment of depression is conventionally applied with pulse amplitude adjusted relative to the patient's motor threshold and at a scalp location set to 5 cm anterior to the motor evoked response hot spot.[81,116-118] In this case both pulse amplitude and scalp location are determined in a relative fashion. However, there is evidence that the response thresholds of different brain areas are not correlated[74] and that the "5 cm rule" coil positioning strategy results is widely variable localization relative to brain anatomic landmarks[119] that may reduce the treatment effectiveness compared with anatomic-landmark-based positioning.[120] There is also debate on the most appropriate dosing strategy for ECT.[5,121-123]

Therefore, regardless of the value of relative dosing in the dose selection process, it is recommended that the resulting absolute EM dose be documented and reported in addition to the dose selection strategy. Applying this recommendation to the examples previously described, data on the absolute dose of the rTMS and ECT stimuli should be provided, e.g., "rTMS was applied at 120% of motor threshold, corresponding to 64 ± 12% (mean ± SD) of maximum pulse amplitude" and "ECT was delivered at 6× seizure threshold, corresponding to 785 ± 154 pulses" (if the ECT dose was adjusted by individualizing the number of pulses in the stimulus). Similarly, the position of the electrodes or coil should be reported relative to scalp or brain anatomic landmarks, in addition to the position relative to functional hot spots.

EM field models

Because the effects of transcranial EM stimulation are thought to result chiefly from the electric and current density fields generated in the head, knowledge of the electric/current density field characteristics can help to select the dose for and/or to interpret a study or a treatment using EM stimulation, and can be useful in optimizing stimulation techniques. There are presently no established techniques for noninvasively measuring in vivo the electric/current density field distribution in the head, although some MRI-based methods to image exogenously generated electric/current density fields in the body may be promising.[124] Invasive measurements in humans are limited to brain-surgery patients, and even in these cases are challenging to implement and provide very limited spatial information about the field distribution.[125] Measurement in conductive phantoms (e.g., spherical or head-shaped vessel filled with saline solution) can provide some information on the induced electric field in TMS. However, phantoms have simplified geometry and impedance profile, and, therefore, the measured electric field is only an approximation of the in vivo field. These limitations of phantoms make them inadequate for even approximate modeling of transcranial electric stimulation.

The electric and current density fields are, at present, best estimated using computational models, although these models rely on assumptions about tissue impedance, and model validation is challenging and indirect. The representation of the head in computational models can range in detail from concentric spheres[17,21,87,126-133] to more detailed, simplified geometric representations[35,107,134-138] to high resolution, individualized models incorporating complex tissue geometries and, in some instances, tissue conductivity anisotropy (dependence of impedance on orientation).[18-20,26,139-145] Figure 1 shows an example of a computational electric and current density field model based on anatomic and diffusion-tensor MRI scans.[143] Subject-specific anatomic information (e.g., individual MRI scans) enables individualization of the model.

The computational model can be used to simulate an already selected dose or to help select an appropriate dose. In the former case, the field models require a complete record of the EM dose used in the modeled transcranial stimulation paradigm. Failure to control or document the EM dose makes construction of an accurate computational model impossible. To use a computational model to inform dose selection, constraints on the desired electric or current density field distribution have to be specified first. Then an optimization algorithm is deployed to calculate the scalp electrode or coil currents that best meet the imposed constraints on the generated field.[146,147]

Safety considerations in EM dose determination

Risk/benefit considerations override other aspects of dose selection, and are in the realm of clinical decision making beyond the scope of this paper. After consideration of subject specific risk factors, controlling the EM dose is the primary method to address safety concerns. Conversely, without controlling and documenting the EM dose, it is impossible to ensure subject safety and to accumulate safety data that can inform the development of safety guidelines.

The ability to draw safety inference across clinical, normal-subject, animal, and ex vivo studies is often limited by the different EM doses used. For example, tissue damage studies using implanted electrodes in the brain[103] are not directly translatable to safety guidelines for transcranial stimulation using scalp electrodes or coils, and different waveforms. Any proposed clinical safety standards apply only to the limited parameter space indicated.[1,148] Changing a single EM dose parameter to values outside this parameter space (e.g., a new coil or pulse waveform) may diminish the relevance of the guideline. Furthermore, safe dose ranges may depend on individual factors such as age—take for example the fact that children have smaller heads, lower seizure thresholds, higher motor thresholds, and lower degrees of

myelination. The use of summary metrics (e.g., source current density, charge per phase, total charge, total energy) to inform EM dose safety may be applicable within a restricted stimulation parameter space, but evidently two stimulation protocols with distinct EM dose but an identical summary metric may have drastically different safety profiles. Thus, accurately controlling and documenting the complete EM dose is of paramount importance for developing more informative guidelines to improve the safety of EM stimulation.

Device artifacts and environmental factors

As discussed in the section on biologic effects of EM brain stimulation, besides effects on neural activity resulting from the intracerebral electromagnetic field, transcranial EM stimulation paradigms may affect brain function via direct extracranial nerve and muscle stimulation and non-electromagnetic interactions such as sound and scalp pressure. Direct activation of extracranial nerves and muscles is inherently encompassed by the EM dose description, since the EM dose parameters determine the electromagnetic field in all tissues in the head. Nonelectromagnetic effects of EM stimulation devices are not directly linked to the EM dose description, though in many cases they may be inferred and reproduced from the EM dose (e.g., the acoustic characteristics of the TMS coil click could be replicated based on the TMS coil model and current waveform parameters). In some cases, the impact of undesirable artifacts of the device operation could be intentionally mitigated for safety or study integrity reasons. For example, the effect of the TMS coil clicking sound could be attenuated with earplugs and/or auditory masking (e.g., playing white noise through earphones). Even though environmental factors and device nonelectromagnetic artifacts do not influence the electromagnetic field and are thus not part of the EM dose description, such indirect influences on the brain as well as measures to mitigate them should be considered, documented, and reported, because they may influence the EM stimulation outcome.

Conclusion

In 2011, there remains no standard for reporting transcranial EM brain stimulation protocols, and adequate information for study reproduction is often omitted. That is a surprising state given that this concept is not new to the literature. In 1988, Weiner and colleagues[4] reported that in ECT literature, dose "frequently is not adequately presented to allow the reader to understand the nature and intensity of stimulation delivered" and cited Ulett who, in 1952, complained that from the publications on electric stimulation therapies "it is not possible to know what stimulus was actually given and hence there is no way to duplicate, or in many cases even approximate, the experiment or treatment conditions."[149] Addressing this critical gap, we propose that EM dose should be defined by *all parameters of the EM stimulation device (including waveform generator and electrodes or coils) that affect the electromagnetic field induced in the head*, as summarized in Table 1. The basic guiding principle in EM dose reporting is that the parameters of stimulation should be reproducible. The research and clinical communities should allow no more ambiguity in documenting and reporting EM stimulation dose than they would allow in prescribing drug dose.

We recognize that the increasing complexity of EM stimulation devices and the ubiquitous reliance on commercial devices may result in lack of transparency of all the EM dose parameters to the operator. Especially in magnetic stimulation, the operator may have little knowledge about the EM dose parameters, beyond control of some aspects of the waveform, typically in relative units, and choice of coil. Similarly, in electrical stimulation the user may have incomplete understanding of the device parameters (e.g., voltage versus current control, parameters constituting a charge setting). Therefore, in Table 1, we provide practical accommodations for reporting aspects of EM dose by citing specific commercial products (e.g., manufacturer name and unique device model number) and their user-adjustable settings.

We distinguish the concept of EM dose selection from the concept of applied EM dose. Dose selection may involve considerations of risk/benefit, various subject-specific anatomic and physiologic data, response measures, and computational models. Regardless of their value in individualizing dose, reporting of dose selection considerations does not diminish the need to fully report the resulting applied EM dose.

Whereas the effect of the various EM stimulation dose parameters on brain activity is not fully understood, it is possible and critical to accurately describe the EM dose when reporting basic and clinical studies. The rational development of this field cannot proceed without clear description of EM dose in each published study. Implementing our recommendations on documenting and reporting EM dose requires in most cases minimal controls and effort, but would effect an immediate enhancement of safety and reproducibility. Our recommendations can mostly be implemented by controlling and reporting the EM stimulation procedure setup, product identification of the devices used, and information on the applied user-adjustable device settings. The impact of this minimal effort to report EM stimulation dose completely is of outstanding clinical importance if we are to advance the field and bring to the bedside device-based therapies with rationally designed and quantifiable action. Failing this effort, clinical progress may be slowed or in some cases never realized because of lack of reliable data on dose-response relationships.

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