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Training in the practice of noninvasive brain stimulation: Recommendations from an IFCN committee

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Appendix A. Supplementary material

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Abstract

As the field of noninvasive brain stimulation (NIBS) expands, there is a growing need for comprehensive guidelines on training practitioners in the safe and effective administration of NIBS techniques in their various research and clinical applications. This article provides recommendations on the structure and content of this training. Three different types of practitioners are considered (Technicians, Clinicians, and Scientists), to attempt to cover the range of education and responsibilities of practitioners in NIBS from the laboratory to the

clinic. Basic or core competencies and more advanced knowledge and skills are discussed, and recommendations offered regarding didactic and practical curricular components. We encourage individual licensing and governing bodies to implement these guidelines.

Keywords

Training; Guidelines; Noninvasive brain stimulation; Transcranial magnetic stimulation; Transcranial electric stimulation

1. Introduction

1.1. The purpose of these guidelines

Noninvasive brain stimulation (NIBS) refers to a collection of techniques for stimulation of the central nervous system *in vivo* without the need for surgery or anesthesia. NIBS is safe if appropriate guidelines are followed (Rossi et al. 2009, 2011; Antal et al. 2017). NIBS covers a wide range of techniques, with the most widely used being transcranial magnetic stimulation (TMS) and low intensity transcranial electrical stimulation (tES; encompassing direct current, alternating current, and random noise stimulation). Adoption of TMS and tES approaches in basic and translational research and clinical medicine has grown tremendously over the past decades. In response to the growing use of these techniques, the International Federation of Clinical Neurophysiology (IFCN) has published and updated consensus guidelines for the proper use of TMS and tES (Rossini et al. 1994, 2015), issued recommendations for its safe and ethical applications (Rossi et al. 2009, 2011; Bikson et al. 2016; Antal et al. 2017), and addressed methodological (Groppa et al. 2012; Woods et al. 2016; Bikson et al. 2018) and clinical considerations (Chen et al. 2008; Lefaucheur et al. 2014, 2017). The present consensus paper complements these previous reports and fills an important gap by providing the first comprehensive set of recommended guidelines for education, training, and assessment of competency in all aspects (safety, methodology, and practice) of TMS and tES applications.

1.2. The importance of these guidelines

The use of NIBS is expanding beyond a few specialized centers into small and large research laboratories and clinics, as well as into the private sector. At the same time, the applications of NIBS are expanding and growing more diverse, both in terms of the protocols that are implemented and populations that are studied. The latter include children and elderly, pregnant women, as well as various patient cohorts with variable degrees of vulnerability. All these are a manifestation of the broadening acceptance of NIBS after decades of carefully conducted peer-reviewed published research and educational outreach.

Educational outreach remains essential, and there are a growing number of annual or semi-annual conferences focused on NIBS and different types of more formal educational opportunities and courses in NIBS being taught worldwide. However, with the expanded use of NIBS comes the risk of declining quality control, both, because of less effective use (with inconclusive outcomes) or more unsafe use (with risk of side-effects). If left unaddressed, this has the potential of harming the reputation of NIBS for example by

(1) improper application of techniques leading to lack of utility and increased risk of side-effects; (2) growing number of seizures and other serious adverse effects; (3) dilution of the literature with poorly conducted, inadequately powered, or experimentally-noisy studies, with the consequent appearance of decrease in efficacy of NIBS for treatment of appropriate conditions (e.g. medication-resistant depression); (4) decrease of therapeutic efficacy because of clinical application of NIBS to patients for indications or with protocols inadequately supported by the standard of knowledge; and (5) poor rationales for the application of NIBS in basic and translational research, and the resultant delay in the accumulation of knowledge and the wastefulness of resources.

To date, while the rate of reported adverse effects remains quite low, there is an increased focus on the degree of inter- and intra-individual variability of NIBS measures (Farzan et al. 2010; Hamada et al. 2013; López-Alonso et al. 2014; Vernet et al. 2014; Wiethoff et al. 2014; Chew et al. 2015; Vallence et al. 2015; Nakamura et al. 2016; Ammann et al. 2017; Brown et al. 2017; Fried et al. 2017; Hordacre et al. 2017; Jannati et al. 2017; Kerwin et al., 2018; Sasaki et al., 2018; Schilberg et al. 2017). One take-home message from these studies is that while certain NIBS protocols, such as the TMS resting motor threshold (RMT) demonstrate excellent test-retest reliability under normal conditions, variability remains high for many common protocols (including e.g. paired-pulse TMS protocols). Similarly, inter- and intra-individual variability of neuromodulatory after effects of tES or rTMS protocols has come under growing scrutiny (Cheeran et al. 2008; Chang et al. 2014; Wiethoff et al. 2014; Hordacre et al. 2017), and little is known about the reliability of these protocols outside the motor domain. An important challenge for the field of NIBS in addressing the problem of test-retest reliability is to separate which part of this variability is caused by state- or trait-dependent NIBS-brain interactions, and which part is the consequence of inconsistencies in NIBS administration and/or in the assessment of NIBS outcome measures such as the motor evoked potential (MEP) (Wassermann 2002; Zrenner et al. 2018). This critical goal, the detailed characterization of the variability of the effects of NIBS, simply cannot be accomplished without a concerted effort to establish uniform training guidelines.

Training guidelines are also critical when one considers specifically the growing clinical applications of NIBS. The resulting growing clinical use of NIBS requires careful definition of training requirements and competencies in both prescribing physicians and NIBS technicians, to ensure capable, proficient, and safe application of these techniques to patients. In the United States (US), the Food and Drug Administration (FDA) has, at the time of this article, cleared seven devices for therapeutic TMS in patients of treatment-resistant depression, one device for pre-surgical motor and language cortical mapping, and one device for abortive treatment of migraines. The number of cleared devices and thus approved diagnostic and therapeutic applications is likely to continue to expand. In Europe, a number of TMS and tES devices have gained CE mark, including some for home use. Around the world, health care services and regulatory agencies are similarly endorsing the clinical use of NIBS. Given the varying regulatory landscape, it is crucial to be aware of how NIBS devices are considered in one’s own country. In the US, most health insurance companies now cover the cost of repetitive TMS (rTMS) for treatment-resistant depression. Several countries in Europe also have developed policies for coverage of NIBS costs by national health systems and private health insurances. For example, in the Netherlands, the

national health advisory board has recommended TMS as a treatment for treatment-resistant major depression, and major Dutch health insurances have announced they will cover the associated costs within the basic public health insurance. Similarly, governmental insurances in Japan will now at least partially cover rTMS treatment of patients with drug resistant major depression. Similar developments are taking place around the world and in any case, the number of private, out-of-pocket pay practices is rapidly expanding.

1.3. The potential impact of these guidelines

Definition of training guidelines and competencies for clinicians prescribing NIBS to patients, scientists overseeing research protocols employing NIBS, and technicians applying NIBS to research participants or patients, will lead to reduced risk, improved quality, and higher cross-study comparability of NIBS. Such guidelines will put NIBS in line with other established neurophysiological methods. These guidelines are based on the consensus of a committee appointed by the IFCN, and should thus be considered as expert recommendations that might inform the development of formal accreditation and training criteria. However, it is up to individual governing, regulatory, and administrative bodies (including medical licensing Boards, hospital executive committees, residency training programs, Institutional Review Boards, higher education institutions, and professional societies) to adapt these training recommendations as needed and implement them in their own licensing, accreditation, and certification activities.

1.4. The development of these guidelines (Methods)

The IFCN Executive Committee identified the need of standardized recommendations for the training and practice of NIBS. In 2017 the IFCN Executive Committee asked Drs. Pascual-Leone and Hallett to take the lead in organizing training guidelines for TMS and tES. Drs. Pascual-Leone and Hallett, working with Drs. Fried and Santarnecchi, prepared an outline of the competencies required to ensure highest ethical and safety standards in the application of NIBS. They benefited from the training guidelines in place at the Berenson-Allen Center and from a training document that Bruce Luber had prepared and was using. A list of experts with documented mentoring and training track-records was generated with particular attention to ensure representation of different disciplines and fields of application of NIBS and diverse different geographical areas. Ensuring diversity was particularly important given the aim to generate guidelines that would be relevant for different roles, disciplines and regulatory frameworks. A rough outline that included the classes of trainees and the list of competencies, and the list of proposed members for the consensus committee, was approved by the IFCN Executive Committee. All proposed members accepted the invitation to participate in the IFCN committee and provided critical input for the outline and training aspects. Many shared written documents outlining training requirements are their institutions, laboratories and clinics. Following that input, Drs. Fried, Santarnecchi, Pascual-Leone and Hallett authored an initial draft of the guidelines, including a substantial literature search in PubMed to match each particular skill or knowledge article with the appropriate citation(s). Dr. Pascual-Leone shared this initial draft with all authors and collected feedback. Drs. Fried, Santarnecchi, and Pascual-Leone then incorporated this feedback into a final draft. Following detailed review and input from Dr. Hallett, Dr. Pascual-Leone circulated the final draft to all authors for final approval prior to submission.

2. The trainees

These guidelines envision three distinct classes of trainees: (1) Technician, (2) Clinician, and (3) Scientist. Each class has its own set of core competencies related to the role they play.

The Technician applies NIBS to research participants or patients, monitors their wellbeing, and administers certain outcome assessments (e.g., depression severity indices). He or she generally has the most frequent direct contact with patients or study participants. Note that the Clinician or the Scientist – as defined below – might also be the Technician if they directly deliver the NIBS.

The Clinician establishes the indication, identifies and prescribes the optimum protocol for a given patient or indication, and supervises the Technician(s).

The Scientist might be the principal investigator (PI) or a key co-investigator responsible for the NIBS protocol in a given research study or clinical trial. He or she is responsible for designing the protocol of the NIBS intervention, including defining inclusion and exclusion criteria for the populations to be studied and the intervention and outcome measures being investigated. The Scientist either performs the study personally or supervises the Technician(s).

In addition, many studies conducting human subject's research using NIBS techniques engage a medically responsible investigator, especially as funding agencies and governing bodies such as the National Institutes of Health consider moving the field of NIBS towards a universal clinical-trial model of research. The role of the Scientist may be distinct from that of the medically responsible investigator, which may be more in line with a clinically trained person exerting a clinical supervisory role.

2.1. The Technician

The Technician could be someone with basic schooling requirements and some degree indicating advanced education pertinent to the role. For example, having a Bachelor of the Arts or Bachelor of Science degree (B.A/B.S.) might be sufficient, but for certain roles, applications or positions, more advanced training might be necessary or desirable, including a Masters of the Arts or Master of Science degree (M.A./M.S.), physician assistant, or nursing degree. Electroencephalography (EEG) or electromyography (EMG) technicians might also be appropriate. The Technician is employed by the Scientist or Clinician, or by a given Institution to perform TMS/tES experimental/clinical sessions. Training of the Technician requires attainment of both practical and theoretical competencies. Depending on the setting, the Technician may need to interact with healthy individuals, clinical patient populations, or both. This will necessitate different training (e.g., a Technician in an academic neuropsychology department applying tDCS in the setting of cognitive tasks will have to possess very different skills to a Technician in a private practice who primarily administers FDA-approved TMS protocols to patients with medication-resistant major depression). Because the role can vary, so will the educational background and the competencies required.

In addition, Technician may be someone specifically hired and trained to perform the work (i.e., hired and trained exclusively as NIBS technician), or refer to research fellows or Ph.D. (Doctor of Philosophy) students, or to physicians (e.g. residents or fellows in Neurology, Clinical Neurophysiology, or Psychiatry) who are beginning their training in NIBS, or deliver NIBS in a research setting under supervision (e.g. when double-blind delivery is required). Ultimately, these users may transition to the role of a Clinician or Scientist. The educational needs will thus also need to be tailored to the circumstances of the practice.

2.2. The Clinician

The Clinician refers to someone with a M.D. who has completed residency training in Neurology, Psychiatry, Neurosurgery, Rehabilitation Medicine, or other related specialties that may include Clinical Neurophysiology, Physical Medicine and Rehabilitation, Internal Medicine, Pediatrics, Pain Medicine, Gerontology, Neuroradiology, etc. In certain jurisdictions, it may be appropriate for the Clinician-type role to hold a clinical degree other than an M. D., including Doctor of Osteopathic Medicine (D.O.), clinical Ph.D. (e.g., Clinical Neuropsychology, Psy.D.), clinical therapist (Occupational, Physical, or Language), or Nurse Practitioner (N.P.). The Clinician maintains a clinical practice incorporating TMS/tES as a therapeutic treatment or diagnostic/prognostic tool. Training of a Clinician in TMS/tES should include substantial emphasis on theoretical, didactic competencies and, safety and ethics, in addition to practical skills.

2.3. The Scientist

The Scientist will often refer to someone with a M.D. or Ph.D. who has completed or is undergoing a post-doctoral fellowship in a field related to Neurology, Psychiatry, Clinical Neurophysiology, Neuroscience (including sub-disciplines such as Cognitive and Social Neuroscience, etc.), Neurological Rehabilitation, or Psychology, and related fields. However, with expanding indications and uses of NIBS, the background training is likely to continue to expand and include Pain Medicine, Nutrition and Metabolism, Anesthesiology, Neurosurgery, Physical or Occupational Therapy, Nursing, etc. The Scientist may be the PI of a study incorporating TMS/tES or serve as a Co-investigator or Medically Responsible Investigator (if distinct from PI or Co-Investigator) in such a research study. Training of a Scientist in TMS/tES will generally require a balance of didactic, theoretical, and practical competencies.

3. Guidelines for training courses and trainers

An important consideration should be given to the question of qualifications for those who offer and oversee the training. There are a growing number of training offerings in NIBS. One should generally distinguish between industry/company-dependent workshops (offered by the various industrial partners) versus academic and industry-independent courses (offered by independent researchers and clinicians, at a university or clinic, or organized by an official society, etc.). Industry/company-dependent workshops focus on training in the proper use on their specific systems. While this is important, the guidelines presented here aim to provide competencies beyond the correct utilization of a specific given device. Academic (industry-independent) courses are most relevant here, and they ought to

play a critical role in fulfilling the standards we define here. Academic courses provide a richer transfer of knowledge, that ideally should include hands-on training participants on various different systems to provide generalizable expertise. Training in the operation of a specific device can always be added following acquisition of competencies through academic training.

The trainers may be different for the different roles. As mentioned, many device manufacturers provide training in the operation of a specific device or system, and in many countries documentation of such training is mandatory for its operation. However, attainment of NIBS competencies should be unbiased and independent from the manufacturers and requires criteria and evaluation of the trainers themselves. Trainers should be Clinicians or Scientists with several years of experience and good command of the methods and required competencies, and key knowledge, as well as experience in training and mentoring.

In a clinical practice environment, the Clinician is ultimately also responsible for delegation of certain tasks, including training and supervision, often with some level of oversight from a medical executive board/committee. Non-clinical environments (including research centers, academic and clinical-research environments) are typically governed by the specific Institutional Review Board. For example, the PI, along with the medically responsible investigator (if distinct from the PI), may hold this responsibility. In certain circumstances, it may be appropriate for a highly-experienced Technician (who arguably may come to have more recent hands-on experience than the medically responsible physician or PI) to come into the role of a trainer for at least some of the roles (e.g., hands-on demonstration of a technique). On the other hand, the Clinician/Scientist ought to remain responsible for the didactic instruction on the fundamentals of NIBS and critical issues such as patient/subject safety.

Those providing didactic and practical instruction in TMS/tES should be highly experienced and possess a broad understanding of the relevant subject matter including the setup, assessment, and troubleshooting of neurophysiological tools and assessments used in conjunction with TMS/tES. For didactic instruction, it is common to have different individuals give lectures on a particular topic based on their background. For practical instruction, it is recommended that trainers have at least a year of experience working with a particular technique. It is recommended that the PI or medically responsible physician certify that the trainer is sufficiently knowledgeable about the subject matter.

4. Competencies

4.1. Overview and list of competencies

As described in detail in the following sections, we propose that any training regime be comprised of three core components: (1) theoretical and didactic knowledge; (2) hands-on training; (3) observation and supervised practice. Each NIBS technique (TMS, tES) has its own curricula (see Tables 1 and 2), which covers four general topics: *Core knowledge*; *Safety and ethical concerns*; *Basic skills*; and *Advanced skills*. Each area is further subdivided into competencies, each covering a specific aspect.

It is essential to understand that as the field of NIBS continues to expand new applications in research and new approved clinical indications continue to be added. In addition, new NIBS techniques are being developed and becoming increasingly adopted. Given this high level of innovation and rapid pace of development, we anticipate that new competencies will need to be added and others will need refining. Therefore, we offer a list of competencies as a framework rather than a prescriptive or closed curriculum.

As noted in Tables 1 and 2, different competencies apply to different potential trainees, that is, Technicians, Clinicians and Scientists are expected to have different expertise and thus required to achieve different competencies. Tables 1 and 2 note the minimum competencies required for a given trainee role.

Common across all types of trainees, training in TMS/tES should begin with a didactic curriculum in the fundamentals of brain stimulation. The main objective of the *Core knowledge* topic is to provide a systematic review and instruction in all major theoretical aspects of TMS/tES. The curriculum should cover topics that exemplify basic knowledge areas relevant to TMS/tES in which all specialists must gain competence regardless of their clinical or research background and specialization. The second topic, *Safety and ethical concerns*, covers all subject matter related to the safe and ethical practice of TMS/tES in the clinic or laboratory. The main objective of this portion of the curriculum is to provide trainees with the knowledge and resources to conduct human subjects research (or animal research, where appropriate) in accordance with all international, national, regional, and institutional regulations. Further, the curriculum should focus on issues that may be specific to TMS or tES administration, including, for example, screening for contraindications, assessing adverse effects, seizure, and syncope identification and management, and disease or condition-specific considerations. For the *Basic skills* topic, we propose that practical training in NIBS be comprised of a structured hands-on training in the core techniques, followed by observations of these techniques performed by a skilled technician, then practice of these techniques under the supervision of a skilled technician, and finally assessment of competency by some objective measure. Beyond the basics of device operation and the core skills outlined above, the *Advanced skills* topic should cover specialized TMS/tES protocols that may not be necessary for all trainees to learn. As such it may be up to the individual laboratory, clinic, or institution whether to explicitly design or require training of these skills.

To be clear, all trainees, Scientists, Clinicians, and Technicians, may not be expected to have a comprehensive command of all potential applications and protocols of NIBS. However, it is expected that Scientists and Clinicians, who serve as supervisors, will have competencies that go beyond those expected from Technicians.

There are many different protocols that utilize some form of NIBS in research or clinical practice. It is important to realize that each protocol has a core aspect. For many of the protocols, establishing the resting motor threshold (RMT) is a core expertise needed to apply TMS. However, correctly performing a TMS-based neurophysiological assessment requires different skills than administering an rTMS-based neuropsychological intervention. Thus, one should consider the training and assessment that is necessary for *each* TMS technique

separately. Similar arguments can be made for different forms of tES (e.g. tDCS versus tACS) or different protocols of a given tES modality (e.g. one channel versus multi-channel tES). Ultimately, it may not be feasible to provide training in every possible application of TMS or tES, particularly given the rapidly evolving nature of the field. Rather, training should focus on the core skills that underlie the vast majority of applications. We offer here a framework, anchored on core competencies, rather than an exhaustive list.

For TMS, core competencies include, for example, 1) basic device operation and setting parameters for subsequent stimulation, 2) proper coil handling, including placement (location, orientation, angulation) of the coil on the participant's scalp, returning to a chosen site, and maintaining chosen coil position and orientation over prolonged stimulation (with or without neuronavigation); 3) identification of the motor (and/or non-motor) hotspot; and 4) assessment of motor threshold (resting and active) using EMG and/or visible twitch—all of them according to the IFCN guidelines and procedures (Rossini et al. 1994, 2015; Rossi et al. 2009). With a few exceptions, e.g., stimulation of visual areas to elicit phosphenes, these core skills are currently common to most TMS protocols. Once a trainee has mastered these core skills, they can easily be adapted to other TMS protocols (i.e., paired-pulse TMS, repetitive/patterned TMS, etc.), which would mainly involve selecting/programming different stimulation parameters.

For tES, core skills include 1) identification of the positions for electrode placement (e.g. "International 10–20 System" or "10–10 Basic EEG Array"); 2) positioning of the electrodes and related head gear (e.g. sponges, gel-based electrodes, headband, cap) in a way that the position is comfortable for the participant and stable throughout the intervention (i.e., all electrodes have good contact with the scalp and that the contact area is limited to the electrodes); and 3) proper operation of the device for different stimulation protocols, including setting stimulation intensity, duration, ramp-up/down; 4) assessing participants perception during stimulation (e.g. tingling sensation, perception of phosphenes, scalp heating) and discomfort.

4.2. TMS: Core knowledge

Training in TMS should begin with a didactic curriculum in the fundamentals of TMS. The main objective of this curriculum is to provide a systematic review and instruction in all theoretical aspects of TMS. The curriculum should cover topics that exemplify basic knowledge areas relevant to TMS in which all trainees must gain competence regardless of their clinical or research background and specialization.

4.2.1. Basic mechanisms of TMS—This competency covers the fundamental principles and mechanisms of action of TMS, including the basics of electromagnetic induction, physics and physiology, and its physico-physiological interaction (e.g., the impact of orientation of induced current relative to the underlying neuroanatomy, the difference between monophasic and biphasic currents, the impact of head shape and skull defects, the impact of neuroactive drugs and substances, or the knowledge of the pharmacological mechanisms of TMS). This competency may be presented on its own or combined with *Fundamentals of clinical neurophysiology* (Section 4.2.4).

4.2.2. Fundamentals in design of TMS devices—This competency covers the design of a generic TMS device and describes the key components, including the charging circuit, capacitors to store charge, resistors to shape the current, diodes, an electric thyristor switch to allow delivery of a brief pulse. Similarly, this competency should confer knowledge of different coil designs (e.g., circular, figure-8, double-cone, or H-coils) and the impact of coil size and shape on the depth and focality of stimulation (and the trade-off between depth and focality). Furthermore, it is important to understand the implications of the fundamentals of the TMS devices regarding physics principles of electromagnetic induction (e.g. implications of pulse shape and duration on properties of the induced current).

4.2.3. Neuroanatomy and physiology—This competency provides a basic survey of neuroanatomy focusing on the common cortical targets for TMS, including, to name a few, the motor homunculus, early visual areas, Broca's area, dorsolateral and inferior prefrontal cortex, inferior parietal lobule, or the superior temporal gyrus (Wernicke's area). The use of scalp landmarks, such as the "International 10–20 system" or the standardized EEG electrode array of the IFCN for EEG electrode placement (Seeck et al. 2017), to target underlying cortical structures should be discussed both in terms of the approach and in regards to limitations. Additional topics should include the function of the corpus callosum and other connections, common cell types and basic circuitry of the cortical column, resting membrane potential and membrane depolarization/hyperpolarization. Anatomy and physiology, including neural conduction properties of descending pathways should be known as well as principles of cortical organization as they relate to TMS efficacy (e.g. column-based model of TMS cortical impact) (Fox et al. 2004).

4.2.4. Fundamentals of clinical neurophysiology—This competency covers the basic principles of clinical neurophysiology as pertinent to TMS. As such, it may be appropriate to combine this competency with that of *Basic mechanisms of TMS* (Section 4.2.1). This should start with coverage of fundamentals of nerve stimulation (e.g. which neural structures are more likely to be activated, which neurons are more likely activated, how synaptic transmission is involved, etc.) and should include discussion of electromagnetic induction and the up-to-date understanding of the how TMS activates neural tissue. Competencies should follow the polysynaptic path of elicited activity from the cortex to the peripheral musculature. This includes an understanding of direct (D) and indirect (I) waves, mechanisms of summation of descending cortico-spinal volleys at alpha moto-neurons in the spinal cord, and the resulting compound muscle action potential (CMAP) in the target muscle that can be recorded as a MEP using surface EMG. The physiological complexity of MEPs and their interpretational limitations should be appreciated (Bestmann and Krakauer, 2015). In addition, this competency should cover assessment of the M-wave and F-wave by peripheral electrical stimulation, and their use for calculation of MEP/CMAP ratio or central motor conduction time, the latter requiring additional knowledge on spinal stimulation techniques. Finally, the effects of posture (i.e., standing, sitting, lying), limb position, limb temperature, concomitant muscle activity, central nervous system (CNS)-active drugs, and the arousal or mental state of the subject (i.e. drowsiness, restlessness, anxiety, etc.) should be appreciated.

4.2.5. Regulatory landscape—The purpose of this competency is to cover issues surrounding regulation of devices as well as approval of protocols for specific indications. These regulations vary from country to country and instructions should focus on providing a framework and awareness of the applicable regulations and oversight agencies (e.g. FDA in the US). It also covers investigative device exemptions (IDEs) and off-label use of TMS. This competency is most relevant for Clinicians and Scientists and would only be required for Technicians if they also have a significant administrative role. However, Technicians should be trained on safety regulations for operators, which may also vary from country to country and have implications on the utilization procedures of each device (e.g. keeping a certain distance between coil and operator, use of coil holders or ear protection for the operator).

4.2.6. Knowledge of the literature—All trainees should have sufficient knowledge of the key literature. Given the rapidly expanding relevant literature, we can only offer here some examples. For example, this may include recent IFCN guidelines and consensus papers (Chen et al. 2008; Rossi et al. 2009, 2011; Groppa et al. 2012; Lefaucheur et al. 2014, 2017; Rossini et al. 2015; Antal et al. 2017) and top-cited papers in TMS (for a recent summary, see (Ziemann 2017). In addition, there are several textbooks and handbooks covering theory and practice of TMS that offer valuable resources (Pascual-Leone et al. 2002; Walsh et al. 2005; Epstein et al., 2008; Fitzgerald and Daskalakis 2013; Lozano and Hallett 2013; Holtzheimer and McDonald 2014; Rotenberg et al., 2014). A list of the suggested core literature can be found in Appendix 1.

4.3. TMS: Safety and ethical concerns

This curriculum covers all topics related to the safe and ethical practice of TMS in the clinic or laboratory. Its main objective is to provide trainees with the knowledge and resources to conduct human subject's research or clinical treatment in accordance with all international, federal, local, and institutional regulations. In addition to the general aspects of recruitment and consent (Section 4.3.1), the curriculum focuses on issues that may be specific to TMS administration, including screening for contraindications, discussion of potential adverse effects and benefits (if applicable) from TMS, and disease and/or condition-specific considerations.

This competency also covers the general safety issues concerning TMS, including seizures, syncope and other adverse effects, implanted metal and electronic devices, pregnancy (both participant and administrator), and drug interactions. It is important to realize that emphasis should be placed on training in the recognition and management of most common complications such as headaches, nausea, preventing tinnitus and hearing impairment (Section 4.3.2), in addition to the less frequent complications such as seizures or syncope (Section 4.3.3). Also important is proper training in correct documentation of adverse effects, including knowledge of applicable regulatory requirements. As in 4.2.5, all (Clinician, Scientist and Technician) should be trained on procedures to ensure operator safety (e.g. exposure to noise and to electro-magnetic fields) including knowledge of safety regulatory aspects that go beyond the application of operational instructions for a specific device.

4.3.1. Recruiting, screening, and consenting—This competency includes information on recruitment, pre-consent screening for eligibility, the informed consent process, and post-consent screening for TMS contraindications (Rossi et al. 2011). Most institutions have some mandatory training on “Protections of Human Subjects” and “Good Clinical Practice”; this theoretical knowledge should be supplemented with training in the process of obtaining written informed consent. General Data Protection Regulations (GDPR) should be followed, and consent needs to be done and handled with these in mind.

A critical aspect involves being able to explain TMS to potential research participants or prospective patients in a manner that is understandable to them. To this end, recruitment brochures, written in laymen’s terms, can be a potentially valuable resource (for an example of brochures developed by Harvard Catalyst, see Appendix 2). Issues related to screening and consent of special populations can be included in this module or discussed in a stand-alone topic (see Section 4.3.4).

4.3.2. Adverse effects of TMS—This competency covers potential adverse effects of TMS including those that are most frequently encountered (e.g. headache), less common (e.g. seizure), and possibly specific to certain TMS applications or cortical targets (e.g. mood changes). It is important to emphasize that different TMS protocols are associated with different risks of side effects. It is also important to be familiar of the distinction between adverse effects (referring specifically to the complications or side effects of a given intervention) and adverse events (referring to complications that occur in the setting of a research study or in the context of an intervention).

Moreover, potential interference with medical devices should always be considered whenever appropriate. Practical consideration of how to minimize the occurrence of adverse effects (e.g., mandatory hearing protection, loosening swim caps or tracker headbands, proper coil handling, using compatible EEG electrodes, etc.) and potential damage to magnetically-sensitive medical (pacemaker, spinal stimulators, etc.) and non-medical devices (i.e. credit cards, mechanical watches, etc.) and assessment of their severity should be covered along with the proper process of reporting serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR). A key component of this training is true familiarity with the published IFCN-endorsed guidelines and recommendations on safety of TMS (Wassermann 1998; Machii et al. 2006; Rossi et al. 2009) and other relevant safety literature (Pascual-Leone et al. 1993; Keel et al. 2001; Oberman et al. 2011; Rossi et al. 2011; Westin et al. 2014).

4.3.3. Identifying and managing seizures and syncopal episodes—Most institutions already require some sort of training in basic life support (BLS) including cardiopulmonary resuscitation (CPR). In addition, as seizure is the most serious, albeit rare, adverse effect associated with TMS, it is necessary for trainees to be able to identify the earliest signs of a seizure as well as those of syncope (which can often resemble a seizure). It may be helpful to have trainees observe (in person or by video) different types of seizures. If epilepsy is at high-risk, simultaneous recording from distal and proximal upper limb muscles might help in intercepting progressively higher excitability of the motor cortex to successive stimuli by the distal-to-proximal muscle recruitment. In

addition, all trainees should be practiced in the proper seizure management and response protocol: 1) remaining calm, 2) calling for help, 3) protecting the individual from harm (e.g., by assisting them to the floor and removing any nearby equipment), 4) timing the seizure, 5) remaining with the individual until help arrives, 6) loosening restrictive clothing (when appropriate), and 7) preventing aspiration from vomiting (e.g., by rolling the individual to their side). In addition, common misconceptions should be reviewed to avoid attempts to restrain the individual or place something in his or her mouth. A committee of the American Academy of Neurology and the American Epilepsy Society have published recommendations of the management of a seizure in adults. (Krumholz et al. 2015). Similar guidelines are available for other populations. A practical and useful factsheet on the recognition of seizure and appropriate first aid can be obtained, for example, from the Epilepsy Foundation at (https://www.epilepsy.com/sites/core/files/atoms/files/First%20Aid%20for%20Seizures.pdf). Ultimately the goal of the training is to enable the development of clinic or laboratory specific protocols that minimize risks and maximize protection of study participants or patients undergoing NIBS.

4.3.4. Recognizing and addressing needs of special populations—This competency covers issues pertaining to administering TMS to pregnant women, children and adolescents, the elderly, persons with diminished intellectual abilities, persons with dementia, non-autonomous persons (prisoners, wards of the state). Recruitment and consent of these individuals should be discussed if not already covered under a general “Protection of Human Subjects” training (see Section 4.3.1).

4.3.5. Recognizing and addressing disease-specific conditions and complications—Application of TMS in specific patient populations needs to consider potential disease-specific complications or patient characteristics. This requires awareness about the clinical phenotypes and manifestations in order to optimize study protocols, prevent complications, and avoid misinterpretation of findings. Ultimately, involvement of a clinician with expertise in the specific patient population is desirable for research studies and imperative for clinical trials and applications. A comprehensive list of the types of factors to consider is outside the scope of these guidelines and beyond the required competencies, but an awareness of such disease-specific conditions and complications is important as it might include, for example sensory hypersensitivity challenging the application of TMS with its associated loud click and sensory tapping sensation; cortical hyper-excitability that may increase the potential risk of seizures; tremor limiting the reliability of EMG outcome measures; or risk of modification of the expected stimulation effects in the presence of CNS-active medications or substances (e.g. coffee or alcohol). Furthermore, exacerbation or even provocation of symptoms of existing neuropsychiatric disorders—including pain (fibromyalgia, complex regional pain syndromes), acute mania (bipolar disorder), suicidal ideation (major depression), craving (substance-related and addictive disorders), or hallucinations (psychotic disorders)—may occur in the context of TMS-based therapies or assessments whether or not a definitive causal relationship can be established.

Psychiatric complications seem particularly important and warrant special mention. The vast majority of applications of TMS in therapeutic and diagnostic research studies and

in clinical practice to date, have been in patients with psychiatric disorders. This may be a reason for the relatively large number of the psychiatric side-effects reported following or in the context of TMS. Thus, it seems particularly timely to emphasize the importance of training in the appropriate monitoring and first aid for psychiatric complications and emergencies. A comprehensive list of potential complications and the steps to prevent, identify and treat are outside the scope of this manuscript and is addressed in the latest IFCN safety consensus report. Cases of TMS induced psychotic symptoms, anxiety, agitation, suicidal ideation and insomnia have been reported, but it is unknown whether these occur at higher rates compared to the natural course of disease being treated or associated with other interventions. Psychotic symptoms and suicidal ideation have never been described in normal subjects during or after TMS. In all cases the psychiatric side effects induced by TMS were transient, with a spontaneous resolution after TMS cessation or promptly controlled by pharmacological treatment. In the case of psychiatric patients, as indeed in the case of any other specific patient population, access to an appropriately trained clinician is essential and that may not necessarily be the same person as the Clinician or the Scientist as discussed in these recommendations.

4.4. TMS: Basic skills

With many different TMS protocols covering prognostic, diagnostic, interventional, and scientific applications in both clinical and research settings, it is not possible to design a completely comprehensive training curriculum covering all TMS practical skills, nor is such an endeavor necessary as many trainees will focus only on a selection of protocols (i.e., rTMS treatment for depression, neurophysiological assessments, etc.). Rather, this curriculum focuses on those techniques that serve as the foundation for nearly all TMS applications.

4.4.1. Device operation—This competency covers the basic operation of the TMS device. This includes turning the machine on/off, plugging/unplugging coils, arming/disarming the system, safety check (including, e.g. checking whether the coil is intact), setting stimulation parameters (intensity, timing, pulse shape, current direction), and troubleshooting. As many of these skills are device-specific, training should be completed on the device (and coil) that the trainee will use most often and repeated for any additional devices (and coils) they are likely to use. Manufacturer-sponsored training and demonstration may form a component of this competency, but it should not be the sole source of training.

4.4.2. Basic neurophysiology methods—This competency includes identifying the muscle belly and tendon of the target muscle, proper placement of surface electrodes using a bipolar (belly-negative/tendon-positive) montage, and placement of the ground electrode on an electrically-neutral site between TMS site and EMG recording site. Most commonly, the target will be an intrinsic hand muscle contralateral to the cortical site of stimulation, such as the first dorsal interosseous (FDI) or abductor pollicis brevis (APB) muscles, for which the ground may be placed at the ulnar styloid process of the wrist. Beyond these preparatory steps, relevant aspects of this competency include development of awareness of techniques for reducing impedance, measuring resting and active EMG activity, and understanding of

the relationship between a MEP and a visible twitch. This competency may be abbreviated or tailored for clinics or other settings that do not use EMG to assess RMT or AMT. If a trainee is not expected to use EMG, the focus of this competency should be on identifying a visible twitch and understanding its relationship to EMG activity.

This competency is important in regard to the safety of TMS interventions, as the motor cortex has a low threshold for *afterdischarge* and seizure induction, and thus the RMT or AMT provide a reliable reference for a safe intensity of further TMS. In this context, it is also worth mentioning that the use of EMG to assess motor thresholds is preferred, given that the safe ranges of TMS parameters were established based on using EMG and given the fact that visual observation tends to overestimate RMT (Westin et al. 2014). However, it should be noted that some clinical practitioners of TMS use visual observation to define stimulation intensity, and that whether this leads to an increased risk of complications (including seizures, syncopal episodes, or psychiatric complications) is not known.

In any case, it is important to note that EMG monitoring may also be valuable or required for other safety reasons, for example, to monitor the spread of cortical excitation during rTMS (especially when the risk of seizure is elevated), or for any novel stimulation protocol, for which safety guidelines have not yet been established (see Rossi et al. 2009).

4.4.3. Coil handling and placement—This competency covers the proper technique for handling the coil. This includes holding the coil in an ergonomic fashion (i.e., standing with feet at shoulder's width, holding the coil close to one's center of gravity, supporting its weight with one hand and using the fingers of the opposite hand to steady the coil and guide its placement); placing the coil against the recipient's head and keeping it steady without applying undue pressure (which can lead to neck strain); angulating the coil so that its center rests tangentially over the desired target; and removing the coil and returning it to the same position.

For targeting of the primary motor cortex (M1), the cortical column cosine model suggests a current flow entering the cortex at 90° (relative to the central sulcus, which runs at approximately a 45° angle from the midline) should be most efficient. Therefore, this competency should cover rotating the coil handle so that the direction of induced current is approximately 45° relative to the midline (if neuronavigation is not used) or 90° to the central sulcus (if neuronavigation is used). When discussing the importance of coil orientation, it should be conveyed that the most efficient orientation depends on the particular cortical target and the influence of orientation has not been well studied outside of M1. So, in more general terms, the competency should emphasize that in regards to coil placement it is important to consider position, angulation (tangential), and orientation (pointing direction of handle), and to make sure these parameters are monitored and kept constant when removing and returning the coil to the same position. One approach to reinforce the importance of coil orientation—and guide trainees' development of an intuition about it in coil placement—is by demonstrating how MEP amplitude changes as one rotates the coil at the same spot over the motor cortex.

While coil-holding robots are being sold commercially, many laboratories and clinics rely on mechanical coil holders to assist in supporting the weight of the coil and maintaining a consistent position. Proficiency with these coil holders should be developed to reduce displacement of the coil from the targeted position while tightening or from movement of the recipient's head. The use of neuronavigation systems (see Section 4.5.1), with or without an individual MRI, can be valuable in this regard.

Specific coil placement competencies may need to be developed and taught for less widely used applications of TMS, including targeting other areas beyond M1 or other cortical representations besides the hand. For example, special coils (i.e. bat coils, double-cone coils), used to target deeper structures such as lower limb representations, cingulate cortex, or the cerebellum, necessitate additional training. This is fundamental to ensure proper stimulation of the desired target area at the correct intensity and prevent complication or cofounding effects, such as direct stimulation of the brachial plexus or brainstem (Celnik 2015).

4.4.4. Scalp-based targeting—This competency covers how to identify an initial search site for the motor cortex based on scalp landmarks: identifying the inion and nasion, and the tragi of the left and right ear; identifying the scalp vertex at the intersection of the mid-sagittal (nasion-inion) and interaural (tragus-tragus) lines; measuring a given distance in antero-posterior and latero-medial directions from the motor hotspot or a given scalp location. Furthermore, given the widespread use of rTMS for medication-resistant major depression, this competency should cover targeting the dorsolateral prefrontal cortex (DLPFC) with commonly used coil placement protocols. These include, the "5 cm rule" measured anterior from the motor hotspot (now commonly recommended as 5.5, 6 or 7 cm), as well as the "International 10–20 system" for EEG electrode placement, including abbreviated approaches such as the Beam-F3 method (Beam et al. 2009).

4.4.5. Mapping the motor hotspot—This competency covers mapping the motor hotspot without the use of neuronavigation. This should include the principle that proper search for the motor hotspot should involve systematically changing only one parameter (i.e., intensity, location/orientation, etc.) while holding the other(s) constant. For example, many approaches start with the coil in an initial starting location and orientation (see Section 4.4.4) and gradually increase intensity from a very low level (to minimize startle response) to one in which some motor response is observed. Then, once the intensity is high enough that some motor response is observed (and thus able to be compared), intensity should be kept constant and the location varied using a grid or similar system centered on the starting location. Finally, once a location is chosen, the rotation of the coil can be varied slightly to identify an optimal orientation. Other key points to emphasize include monitoring the targeted muscle for visible movement even if EMG is used, and sampling at least 3 pulses for any stimulation intensity or location since there are many factors that could result in a biased (larger or weaker) response (see Section 4.2.4).

4.4.6. Assessing motor cortex excitability during rest—This competency includes assessing RMT using visible twitch as well as with EMG (including monitoring the live EMG for background noise); and collecting a set of MEPs at suprathreshold

intensities (with sufficient inter-pulse interval and jitter to avoid inducing neuromodulatory effects). The number of protocols and techniques for determination of RMT (Rossini et al. 1994, 2015; Awiszus 2003; Groppa et al. 2012; Karabanov et al. 2015; Slotty et al. 2015) is expanding and basic competency should include familiarity with all the protocols and command of at least one of them.

Aside from learning the means to assess TMS dosage, this competency should include practice assessing RMT and collecting MEPs using the method of limits with an expert, using EMG (and neuronavigation if possible), to become aware of the impact of coil handling (i.e., how easily a slight, often unconscious, rotation or spatial displacement of the coil can dramatically change MEP/motor responses), as well as developing an appreciation for intrinsic MEP variability and an understanding of state-dependent factors such as arousal/drowsiness, pre-TMS muscle activity, and limb position. This practice will assist in the development of intra- and inter-operator reliability.

4.4.7. Assessing motor cortex excitability during voluntary contraction—This competency covers stimulation of the motor cortex with the targeted muscle during voluntary contraction. It includes: techniques for obtaining consistent voluntary EMG activity of 100–200 mV in the targeted muscle; assessing active motor threshold (AMT) using EMG; identification and assessment of the contralateral cortical silent period (cSP) and ipsilateral cortical silent period (iSP).

4.4.8. Conventional rTMS protocols in research and clinical practice—This competency covers setting up a TMS machine for a repetitive TMS (rTMS) protocol. It includes setting the appropriate parameters, including intensity (as a % of RMT), duration, and specific train pattern/frequency, for commonly used protocols. At a minimum, this competency should cover the 10 Hz (4 sec-on, 26 sec-off) and continuous 1 Hz protocols for major depression, as well as the recently-cleared 20 Hz protocol for obsessive–compulsive disorder (Carmi et al. 2019). This competency can be expanded for additional protocols and off-label indications used in the trainee's clinic and may include device-specific training.

4.4.9. Theta-burst repetitive stimulation paradigms—Theta-burst stimulation (TBS), which involves coupling 50 Hz (gamma) bursts at 5 Hz (theta), has been growing in popularity since its development in the mid-2000s (Huang and Rothwell 2004; Huang et al. 2005). This competency focuses on the two most common TBS protocols: continuous TBS (cTBS) and intermittent TBS (iTBS), and includes familiarity and experience with potential applications, requirements, challenges and limitations (including risks) of such protocols, and ongoing areas of debate, such as the intensity of stimulation and whether to base it on AMT or RMT see Sections 4.4.6 and 4.4.7). In particular, this competency should cover the iTBS protocol for major depression (Blumberger et al. 2018) that was recently cleared for use by the U.S. FDA and the E.U.

4.5. TMS: Advanced skills

4.5.1. Neuronavigation—This competency covers the use of MR-based frameless stereotaxic systems for targeted TMS delivery and consistent and reliable intra- and inter-

session coil positioning. Given the increasing number of commercially available systems, this competency can be customized to the particular system(s) available to the trainee. This competency covers the process of setting up a neuronavigation session; co-registering the participant to his or her individual brain anatomy (e.g. MRI), and/or the use of a template standard brain; offline planning of targets; selecting a target from prior stimulation; online navigation of the coil (with sufficient practice to develop motor learning); and offline analysis of available coordinate data. While neuronavigation can be a useful aid for other skills such as assessing motor cortex excitability (Section 4.4.6), it is recommended that core skills such as finding the motor hotspot (Section 4.4.5) be developed prior to and independent of this competency to avoid forming an overreliance on neuronavigation; and that proper discussion of potential sources of error in registration and troubleshooting be included.

4.5.2. Navigated mapping of the motor cortex—This competency covers mapping the motor responses of one or more muscles guided by the recipient's own MRI. This includes identification of the central sulcus (which can be unambiguously located on the medial surface immediately anterior to the marginal branch of the cingulate sulcus); orientation of the coil so that the induced current is perpendicular to the central sulcus (consistent with the cortical column cosine model), and strategies for efficient and complete mapping of the cortical area of interest. If applicable, this competency could include displaying the results of mapping as a "heat map" on the MRI volume or surface reconstruction.

4.5.3. Assessing non-motor cortical function—This competency covers cortical mapping of non-motor areas, specifically phosphenes elicited from stimulation of visual areas (Marg and Rudiak 1994; Kammer 1999; Kammer et al. 2005) and the induction of speech arrest from online repetitive stimulation of Broca's area (Pascual-Leone et al. 1991; Könönen et al. 2015). If neuronavigation is not available, training can focus on the use of fiducial targets based on the EEG coordinates (i.e., "International 10–20 system" or "10–10 Basic EEG array") or other scalp landmarks (Kim et al. 2007) (see Section 4.4.4).

4.5.4. Assessing the MEP input-output curve—This competency covers assessment of a MEP input-output curve (synonyms: stimulus-response curve, recruitment curve) (Ridding and Rothwell 1997). It includes the selection and pseudo-randomization of stimulus intensities (x-axis) and the choice of MEP amplitude and/or proportion of positive motor responses (y-axis).

4.5.5. Assessing central motor conduction time—This competency covers the assessment of central motor conduction time (Nakanishi et al. 2010). TMS can be used to elicit MEPs from transcranial stimulation, as well as to evoke CMAPs from radicular stimulation, and latencies can be calculated for both sites, and subtracted to calculate the latency of the central component. However, an alternate, and more accurate, method uses electrical stimulation of peripheral nerves to assess the latencies of M- and F-waves (based on the direction of current), which can be averaged to estimate the peripheral component, which in turn is subtracted from the latency of a transcranial MEP. Familiarity with the

various methods and awareness of their respective advantages and disadvantages should be achieved.

4.5.6. Paired-pulse to one brain region—This competency covers the most common paired-pulse TMS protocols, including short-interval intra-cortical inhibition (SICI), intra-cortical facilitation (ICF), and long-interval intra-cortical inhibition (LICI) (Valls-Solé et al. 1992; Kujirai et al. 1993), including parameters such as intensities (of conditioning and test pulses) and the inter-pulse latency. Additional training could involve assessing a full inhibition-excitation curve using a range of inter-stimulus intervals and variable conditioning pulse intensities.

4.5.7. Paired-pulse to two brain regions—This competency covers the two most common dual coil paired-pulse TMS protocols, including inter-hemispheric inhibition (IHI) (Ferbert et al. 1992) and cerebello-dentato-thalamo-motor cortex inhibition (CBI) (Ugawa et al. 1995; Pinto and Chen 2001).

4.5.8. Paired central-peripheral stimulation—This competency covers protocols that pair a central TMS pulse with a peripheral electrical stimulation. This includes short-afferent inhibition (SAI), paired associative stimulation (PAS), spinal associative stimulation (SAS), and triple-pulse stimulation (Tokimura et al. 2000; Cortes et al. 2011). At a minimum, this competency should cover placement of the peripheral electrode, approaches to setting the intensity of peripheral and central stimulation, and the inter-stimulus and inter-train (for PAS/SAS) intervals. Discussion of the potential and limitations of the use of somatosensory evoked potentials to aid in the optimization of inter-stimulus intervals between peripheral stimulus and TMS might be included.

4.5.9. Patterned repetitive stimulation paradigms—Various protocols for repetitive stimulation have been developed and are continuing to evolve building on conventional rTMS and theta-burst stimulation protocols (see Sections 4.4.8 and 4.4.9). This competency includes familiarity and experience with potential applications, requirements, challenges and limitations (including risks) of current such protocols, including quadripulse stimulation (QPS) as well as its various variations depending on inter-stimulus interval (e.g. QPS5 or QPS50), as well as novel protocols as they are developed.

4.5.10. Combined TMS and EEG—This competency covers the use of TMS with concurrent EEG. TMS-EEG is a powerful approach for characterizing and modulating brain networks across developmental, behavioral and disease states (Bonato et al. 2006; Thut and Pascual-Leone 2010a; Rogasch and Fitzgerald, 2013; Vernet et al. 2013; (Farzan et al., 2016). TMS-EEG offers translational biomarkers that can be applied in healthy and diseased subjects, across the lifespan, and bridge the gap between animal models and human subjects (Aydin-Abidin et al. 2006; Esser et al. 2006; Pascual-Leone et al. 2011; Canali et al. 2014). However, extracting full utility of TMS-EEG requires standardization of study protocols. This competency should cover principles of TMS-EEG methodological requirements and challenges in TMS-EEG data acquisition, as well as methods and approaches for TMS-EEG data processing and analysis (Thut and Pascual-Leone 2010b; Atluri et al. 2016; Mutanen et al. 2016; Rogasch et al. 2017).

4.5.11. Combined TMS and neuroimaging—This competency covers the combination of TMS with neuroimaging methods. Specific and different competencies will apply to the combination of TMS with different brain imaging methods, including e.g. PET, MRI, optical imaging. Brain imaging in general can offer significant advantages but poses technical challenges both in regards to equipment, experimental protocols, data acquisition, and data analysis (Bestmann et al. 2003). These competencies should thus be specific for the neuroimaging technique to be used and should cover principles of methodological requirements and challenges in data acquisition and processing (Baudewig et al., 2001; Bestmann et al., 2005; Fox et al., 2012; Bestmann and Feredoes, 2013).

4.5.12. Combining TMS with other interventions—This competency covers the integration of rTMS-therapies with other interventions. TMS may be used to augment existing pharmacologic interventions or combined with cognitive, behavioral, or psychotherapies to be administered during or immediately following rTMS. An example of an area that is actively being researched is in the treatment of Alzheimer's disease and related dementias (Gonsalvez et al. 2017; Buss et al. 2019; Sabbagh et al. 2020), wherein over the course of multiple daily sessions, 10 Hz rTMS is applied to different cortical regions and interleaved with short cognitive training activities designed to engage the targeted regions (Andrade et al. 2018). Another example is the use of behavioral interventions to induce a given brain state or provoke specific symptoms (Silvanto and Pascual-Leone 2008) following which TMS is administered. The recently FDA cleared application of the Brainsway H-coil targeting prefrontal cortex and anterior cingulate cortex for obsessive-compulsive disorder (OCD) is an apt example of this strategy (Carmi et al. 2019), where TMS is applied following symptom provocation. Given this FDA-cleared indication and protocol, such combination of TMS with behavioral interventions may well need to become a basic skill in short time. As emphasized up front, these recommendations will require ongoing adaptation and should be taken as providing a framework.

4.5.13. Approaches to sham/placebo TMS—This competency covers approaches to sham TMS including a discussion of different types of sham (e.g., turning coil on its end, using a sham coil with electrical stimulation, etc.) (Loo et al. 2000; Lisanby et al. 2001; Hoeft et al. 2008; Deng and Peterchev 2011) as well as the importance of assessing blinding to condition (Broadbent et al. 2011; Berlim et al. 2013). In place of, or in addition, to the placebo/sham condition, it should be recommended that an active control condition be utilized whenever appropriate. For example, an active control condition might involve stimulation of a brain area that is close to the targeted brain region, but predicted not to evoke the intended effect, thus enabling one to define effects that are not only stimulus-specific but also brain site-specific. This is particularly true for experiments in which non-motor areas are stimulated. Technicians should be trained on the importance of blinding in sham-controlled trials (of patient, assessor and operator if possible), and on the need for a separation between the personnel performing interventions and those assessing the effects.

4.6. tES: Core knowledge

The main objective of this curriculum is to provide a systematic review and instruction in all theoretical aspects of tES. The curriculum should cover topics that exemplify basic knowledge areas relevant to tES in which all trainees must gain competence regardless of their clinical or research background. This will include mechanisms of action, considerations on the impact of stimulation parameters, basic brain anatomy and physiology, as well as the safety of tES.

The fundamental structure of the curriculum and competencies for TMS and tES is the same. Therefore, the following sections applicable to tES are kept shorter, but readers are encouraged to refer also to the relevant paragraphs in the discussion of TMS above.

4.6.1. Basic mechanisms—This competency covers the fundamental principles and mechanisms of action of tES, including the history of tES and its physics principles; basic cortical anatomy and physiology, including description of basic circuitry of cortical column, cell types, neuroanatomy of common cortical targets (e.g. DLPFC, motor cortex, Broca); concepts of cortico-spinal excitability, resting membrane potential, depolarization and hyperpolarization; basic knowledge on brain oscillations and time frequency analysis using EEG/MEG; up-to-date knowledge on the mechanisms of action of tDCS, tACS and tRNS; the implications of stimulation intensity, phase, stimulation montage and current density; computational models of induced electric field and their interpretation; the impact of head shape and skull defects.

4.6.2. Fundamentals in design of tES devices—This competency covers the design of a generic tES device and describes the components, including battery, resistors, potentiometer, digital voltmeter and the circuitry for impedance check. This might be supplemented with device-specific instruction as needed.

4.6.3. Safety and risk—This competency covers the general safety issues concerning tES, including risk of skin burns, visual percepts due to retinal stimulation (i.e. phosphenes), required adaptation of stimulation intensity in participants with skull defects, and possible drug interactions.

4.6.4. Knowledge of the literature—All trainees should have sufficient knowledge of the literature. At a minimum, this should include recent IFCN guidelines, consensus papers and top-cited papers in tES. In addition, there are several textbooks and handbooks covering theory and practice of tES. A list of the suggested core literature can be found in Appendix 1.

4.6.5. Regulatory landscape—This competency is most relevant for Clinicians and Scientists and would only be required for Technicians if they also have a significant administrative role. The purpose of this competency is to cover issues surrounding regulation of devices as well as approval of protocols for specific indications. These regulations vary from country to country and instructions should focus on providing a framework and awareness of the applicable regulations and oversight agencies (e.g. Food and Drug

Administration in the US). It also covers investigative device exemptions (IDEs) and off-label use of tES.

4.6.6. tES: Safety and ethical concerns—This curriculum covers all topics related to the safe and ethical practice of tES in the clinic or research laboratory. Its main objective is to provide trainees with the knowledge and resources to incorporate tES into clinical practice or conduct human subjects research in accordance with all international, federal, local, and institutional regulations. Further, the curriculum focuses on issues that may be specific to tES administration, including screening for contraindications, assessing adverse effects, and disease and/or condition-specific considerations. A particular focus needs to address home-stimulation options, which are rapidly expanding and for which several devices have obtained CE mark in Europe. Moreover, following the recent surge in direct-to-consumer neurotechnologies and the rapidly growing "Do-It-Yourself" tES movement (Wexler and Reiner 2019), a distinction from licensed/approved medical devices needs to be made. This will ensure operators have a clear understanding of the regulatory landscape and of the device characteristics required for research/medical use. Importantly, the present training recommendations only apply (and refer) to licensed/approved medical devices.

4.6.7. Adverse effects of tES—This competency covers potential adverse effects of tES including more common ones (e.g. headache and skin burns) as well as the rare and theoretical (mood or cognitive changes, seizure). Practical consideration of how to minimize the occurrence of adverse effects (e.g. loosening stimulation caps or headbands, insufficient electrode contact) and assess their severity should be covered along with the proper process of reporting unexpected or serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) (Questionnaires and forms in English and German: Antal et al, 2017). A key component of this training is true familiarity with the published IFCN-endorsed guidelines and recommendations on safety of NIBS and other relevant safety literature (Antal et al. 2017; Lefaucheur et al. 2017).

4.6.8. Recruiting, screening, and consenting—This competency includes information on recruitment, pre-consent screening for eligibility, informed consent process, and post-consent screening for tES contraindications. Most institutions have some mandatory training on "Protections of Human Subjects;" this knowledge should be supplemented with training specific to tES. A critical aspect involves being able to explain any tES intervention/modality to potential research participants or prospective patients in a manner that is understandable to them. Issues related to screening and consent of special populations can be included in this module or discussed in a stand-alone topic. An example of recruitment brochures written in laymen's terms is provided in Appendix 2.

4.6.9. Recognizing and addressing needs of special populations—This competency covers issues pertaining to administering tES to pregnant women, infants, children and adolescents, the elderly, persons with diminished intellectual abilities, persons with dementia, non-autonomous persons (prisoners, wards of the state), etc. Recruitment and consent of these individuals should be discussed if not already covered under a general "Protection of Human Subjects" training.

4.6.10. Recognizing and addressing disease-specific conditions and complications—Similar to the issues raised in Section 3.3.5 above in regard to TMS, application of tES in specific patient populations needs to consider potential disease-specific complications or patient characteristics. This may in fact be different for the various modalities of tES and requires familiarity with the clinical phenotypes and manifestations in order to optimize study protocols, prevent complications, and avoid misinterpretation of findings.

4.6.11. tES: Basic skills—Research-oriented tES applications are increasing exponentially, and new therapeutic options for neurological and psychiatric diseases are being explored in clinical trials all around the world. This curriculum focuses on those techniques that serve as the foundation for nearly all current tES applications, i.e. tDCS, tACS and tRNS protocols available with standard, commercially-available devices. Some of the more recent exploratory applications (e.g. multi-frequency tACS for the induction/modulation of cross-frequency coupling, temporal interference [TI] tACS) mentioned in the tES Core section of this manuscript will not be covered since their implementation is either not fully validated or requires custom-made devices.

4.6.12. Device operation—This competency covers the basic operation and procedures of tES devices. This includes turning the tES device on/off, plugging/unplugging electrodes, setting stimulation parameters (e.g. intensity, timing, ramping up/down), checking impedance, and troubleshooting. As many of these skills are device-specific, training should be completed on the device that the trainee will use most often and repeated for any additional devices they are likely to use.

4.6.13. Basic applications of tES—This competency covers more in-depth procedures for electrodes placement, including using the 10–20 or more recently IFCN recommended modified electrode system for placement of electrodes. This competency includes review of procedures for checking electrode impedance, troubleshooting of device operation, as well as procedures and tools (e.g. questionnaires) for assessing participants' perception during as well as after stimulation (e.g. phosphenes, itching, scalp heating and discomfort). Bi-cephalic and extra-cephalic montages, multichannel stimulation should be covered.

4.6.14. Transcranial direct current stimulation (tDCS)—This competency includes knowledge on the application of tDCS and the key differences with other tES techniques, including the positioning of anode and cathode electrodes.

4.6.15. Transcranial alternating current stimulation (tACS)—This competency includes knowledge on the application of tACS and key differences from other tES techniques. This includes setting the stimulation frequency and the stimulation phase across electrodes.

4.6.16. Transcranial random noise stimulation (tRNS)—This competency includes knowledge on the application of tRNS and key differences from other tES techniques. This includes setting the band-pass filter in order to deliver low- and high-frequency tRNS.

4.6.17. Approaches to sham/placebo tES—This competency covers approaches to sham tES including a discussion of different types of sham solutions (e.g. ramp up and ramp down, continuous low intensity stimulation), as well as the importance of assessing appropriate blinding and review of available tools (e.g. questionnaires) and approaches for doing so.

4.7. tES: Advanced skills

This competency will cover more advanced tES applications, including tDCS/tACS/tRNS montages involving multiple stimulation electrodes, and methods for concurrent tES-EEG recording as well as concurrent tES-MRI.

4.7.1. Theory and methods of multifocal/multisite tES—This competency covers stimulation montages involving more than 2 stimulation electrodes, e.g. high-definition tDCS (so called “4-by-1”), multichannel/multifocal tES, and montages for inducing synchronization/desynchronization via in-phase/antiphase tACS using 2 + electrodes.

4.7.2. Combined tES and EEG—This competency includes recommendations and practical considerations for setting up EEG recording during/before/after bifocal or multifocal tES, using commercial tES devices. Also, considerations about how to collect TMS-based neurophysiological measures (e.g. MEPs) during/after tES will be covered. See Section 4.5.10 for parallel competencies regarding TMS-EEG.

4.7.3. Combined tES and neuroimaging—This competency includes recommendations and practical considerations for setting up MRI acquisition during/before/after tES with two (bifocal) or multiple electrodes (multifocal). See Section 4.5.11 for parallel competencies regarding TMS-MRI.

5. Assessment and documentation of competencies

If the goal of a training program is to develop trainees who consistently administer NIBS with the highest level of care, its success should be felt throughout the day-to-day operations of the clinic, laboratory, or center. However, to gauge an individual trainee’s acquisition of the material and progress in mastering the various techniques, some amount of structured evaluation is necessary. Assessments may take the form of testing (e.g., multiple-choice quizzes) for didactic knowledge. However, for some skills assessment should be based on the principles of “see 5, do 5, test 1,” where at a minimum, trainees will observe 5 sessions in 5 different participants, administer 5 sessions with supervision, and then be tested on 1. Certain core skills such as the motor hotspot and motor threshold for TMS are so fundamental that they may require additional testing and evaluation sessions.

As with any education program, there is no one-size-fits-all approach and thus these guidelines should serve as a common framework around which to build a training and assessment program to suit the individual needs for each clinic or laboratory. It is important to recognize that documentation of competencies is important and should be kept with periodic updates in a personnel folder.

Finally, while some trainees learn within the expected time/session frame, others require a lot more. Therefore, any suggestions offered should be considered only a guide and a minimum level.

5.1. Assessment of didactic knowledge

1. Multiple-choice quizzes, written exams, oral evaluations, etc.
2. Certification in Protection of Human Subjects Training, Certification in Good Clinical Practice, Certification in First Aid and Cardio-Pulmonary Resuscitation, Documented training in seizure identification and response.
3. Mock or chaperoned informed consent, safety screening and side-effect questionnaires.

5.2. Assessments of practical skills

1. TMS (clinical): find motor hotspot, assess RMT locate DLPFC site (e.g. measure 5.5 cm anterior from the motor hot spot, or other method), deliver 30 pulses at 30% RMT to DLPFC site (to be conducted without EMG – i.e., visible twitch, and without neuronavigation available to trainee).
2. TMS (research): find motor hotspot, assess RMT, deliver 30 pulses at 120% RMT to motor hotspot (to be conducted with EMG, and without neuronavigation available to trainee).
3. tES (clinical): identify motor cortex and DLPFC according to 10–20 system (i.e., using tape measure), set up cap or sponges, set stimulation intensity, check impedance level before stimulation and monitor impedance level during stimulation, ramp up and ramp down current, monitor patient discomfort during stimulation.
4. tES (research): identify motor cortex and other relevant brain regions (e.g., DLPFC) according to 10–20 system (i.e. using tape measure), set up cap or sponges, set stimulation intensity, check impedance level before stimulation and monitor impedance level during stimulation, ramp up and ramp down current, monitor patient discomfort during stimulation, specify phase and frequency for tACS, specify intensity and band-pass filter for tRNS, assess phosphene threshold for tACS.

6. Summary and future directions

In the present paper we acknowledge the rapidly expanding use of non-invasive magnetic and electrical stimulation in the modern era from around mid 1980s until today, and the transition from purely research settings to the clinic. While training has historically involved one-to-one research mentorship as with other specialized laboratory equipment and methods, the adoption of NIBS into diverse settings by users with diverse backgrounds, requires consideration of needed competencies and some assessment of practices for training. Here we define categories of users or practitioners and provide a basic framework to serve as a training model from which the NIBS community can build on. The goal has been to

offer guidelines that can be implemented at the individual laboratory and clinic level, but that might also be valuable for governing bodies and professional societies to develop and establish accreditation guidelines. Many institutions, including medical licensing boards, academic medical centers, and institutional review boards, but also funding agencies and journal editorial boards, should find these guidelines for training useful. It is ultimately up to individual governing and regulatory bodies to implement these guidelines to establish accreditation or training certification programs in NIBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and acronyms:

AMT	Active motor threshold
APB	Abductor pollicis brevis
B.A.	Bachelor of the Arts
B.S.	Bachelor of Science
BLS	Basic life support
CBI	Cerebellar inhibition
CMAP	Compound muscle action potential

CPR	Cardiopulmonary resuscitation
cSP	(Contralateral) cortical silent period
cTBS	Continuous theta-burst stimulation
D-wave	Direct wave
D.O.	Doctor of Osteopathic Medicine
EEG	Electroencephalography
EMG	Electromyography
FDA	(United States) Food and Drug Administration
FDI	First dorsal interosseous
I-wave	Indirect wave
ICF	Intra-cortical facilitation
IDE	Investigational device exemption
IFCN	International Federation of Clinical Neurophysiology
IHI	Inter-hemispheric inhibition
iSP	Ipsilateral cortical silent period
iTBS	Intermittent theta-burst stimulation
LICI	Long-interval intra-cortical inhibition
LTD	Long-term depression
LTP	Long-term potentiation
M.A.	Master of the Arts
M.D.	Doctor of Medicine
M.S.	Master of Science
MEG	Magnetoencephalography
MEP	Motor evoked potential
MRI	Magnetic resonance imaging
N.P.	Nurse Practitioner
NIBS	Noninvasive brain stimulation
PAS	Paired associative stimulation
PET	Positron emission tomography

QPS	Quadripulse stimulation
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SAE	Serious adverse event
SAI	Short-afferent inhibition
SAS	Spinal associative stimulation
SICI	Short-interval intra-cortical inhibition
SUSAR	Suspected unexpected serious adverse reaction
tACS	Transcranial alternating current stimulation
TBS	Theta-burst stimulation
tDCS	Transcranial direct current stimulation
tES	Transcranial electric stimulation
TMS	Transcranial magnetic stimulation
tRNS	Transcranial random noise stimulation
US	United States

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HIGHLIGHTS

- The field of NIBS is expanding and adequate training for all NIBS practitioners is needed.
- Training should be matched to the responsibilities of Technicians, Clinicians, and Scientists.
- We define competencies and propose curricula for TMS and tES organized in Core knowledge, Safety/ethics, Basic Skills, and Advanced Skills.

Table 1

Competency Table for Transcranial Magnetic Stimulation (TMS).

	Competency	Clinician	Scientist	Technician
CORE KNOWLEDGE	**1. Basic Mechanisms of TMS** *Including*: - Physics - Orientation - Electromagnetic Coupling - Head Shape - Skull Defects - Pharmacological Mechanisms	+	+	+
	2. Fundamentals in design of TMS devices	+	+	+
	3. Neuroanatomy and Physiology	+	+	+
	4. Fundamentals of Clinical Neurophysiology - Compound action potential - M Wave - 10–20 System - D Waves and I Waves	+	+	+
	5. Safety and Risk	+	+	+
	6. Regulatory Landscape	+	+	(+)
	7. Fundamentals of FDA Approved Conditions - Mood Disorders - Cortical Mapping - Migraine - Obsessive Compulsive Disorder	+	(+)	
	8. Knowledge of the Literature - IFCN Recommendations - Top Cited Papers	+	+	(+)
SAFETY AND ETHICS	**9. Adverse effects of TMS**	+	+	+
	10. Screening Risk and Stratification	+	+	(+)
	11. Diagnosis and Management of Seizure and Syncope	+	+	+
	12. Hearing Protection	+	+	+
	13. Recognizing and Addressing Needs of Special Populations - Pregnant Women - Children/Adolescents - Elderly - Non-autonomous persons (prisoners, wards of the state) - Patients with seizures	+	+	
	14. Recognizing and Addressing Disease-specific Conditions and Complications. *Conditions Include:* - Sensory Hypersensitivity - Cortical Hypo-/hyper-excitability *Complications include:* - Suicidality - Hypomania - Pain Exacerbation	+	(+)	(+)

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	Competency	Clinician	Scientist	Technician
TECHNICAL APPLICATIONS AND HANDS-ON TRAINING *	**15. Device Operation (including Troubleshooting)**	+	+	+
	16. Scalp Measurements	+	+	+
	17. Basic Neurophysiology Methods and Techniques - Recording surface EMG - EMG vs. visible twitch	+	+	+
	18. Setting up and Recording Concurrent TMS-EEG		(+)	
	19. Targeting TMS - Scalp based landmarks - Coil location, orientation, angulation - Neuronavigation	(+)	+	+
	20. Basic Applications of TMS - Finding motor hotspot - Assessing resting motor threshold - Assessing active motor threshold	+	+	+
	21. Assessing Non-motor Cortical Function - Phosphenes - Speech Arrest		+	
	22. Assessing the Input/Output (I/O) Curve		+	
	23. Assessing Central Motor Conduction Time (CMCT)		+	
	24. Paired-pulse TMS to One Brain Region - Short Interval Intracortical Inhibition (SICI) - Long interval Intracortical Inhibition (LICI) - Intracortical Facilitation		+	
	25. Paired-pulse TMS to Two Brain Regions - Inter-Hemispheric Inhibition - Cerebellar Inhibition		(+)	
	26. Paired Associative Stimulation (PAS) and Spinal Associative Stimulation (SAS)		(+)	
	27. Conventional rTMS	+	+	+
	28. Theta-burst Stimulation	(+)	+	(+)
	29. Quadripulse stimulation	(+)	(+)	
	30. Apply and Assess SHAM TMS	(+)	+	(+)

Required competencies are marked with "+". Suggested competencies (or those that may be required under certain circumstances) are marked with "(+)".

* Assessment of the technical application/hands-on training will be done using the see 5, do 5, and test 1 where trainees will observe 5 sessions on different subjects, do 5 sessions with supervision, and then be tested on 1. This assessment should be completed for each individual device a user will have access to.

Table 2

Competency Table for Transcranial Electric Stimulation (tES).

	Competency	Clinician	Scientist	Technician
CORE KNOWLEDGE	**1. Basic Mechanisms of tES***Including* A. **Physics** B. **Neuroanatomy and Physiology** a. Common cell types and basic circuitry of the cortical column b. Basic anatomy of common cortical targets (e.g. DLPFC, motor and visual cortex, Broca) c. Cortico-spinal excitability, resting membrane potential, depolarization, hyperpolarization d. Brain oscillations and time frequency EEG/MEG analysis C. **Concepts:** a. Anodal and Cathodal stimulation b. Current density (concept, calculation) c. Stimulation intensity (peak-to-peak vs 0-to-peak) d. In-Phase, Antiphase and phase-lag stimulation D. **Mechanisms:** a. Membrane polarization b. Frequency-specific modulation (e.g. entrainment) c. Stochastic Resonance d. Neuroplasticity E. **Stimulation montages** a. Impact of electrodes location, orientation, number and position b. Bifocal, multifocal/multielectrode and extracephalic montages c. Computational Modeling of induced electric field: theory and interpretation	+	+	+
	2. Fundamentals in Design of tES Devices	+	+	+
	3. Safety of tES	+	+	+
	4. Knowledge of the Literature - IFCN Recommendations - Most relevant papers	+	+	
	5. Regulatory Landscape (e.g. FDA approval)- Requirements and procedures for FDA approval- Direct-To-Consumer Devices- Do-It-Yourself (DYI) tES	+	(+)	
SAFETY AND ETHICS	**6. Adverse effects of tES**	+	+	+
	7. Screening Risk, Consent and Stratification	+	+	(+)
	8. Recognizing and Addressing Needs of Special Populations - Pregnant Women - Children/Adolescents - Elderly - Non-autonomous persons (prisoners, wards of the state) - Patients with implanted devices - Patients with seizures	+	+	
	9. Recognizing and Addressing Disease-specific Conditions and Complications.*Conditions Include:* - Sensory Hypersensitivity - Cortical Hypo-/hyper-excitability	+	(+)	(+)

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	Competency	Clinician	Scientist	Technician
TECHNICAL APPLICATION/ HANDS-ON TRAINING *	**10. Device Operation (including Troubleshooting)**	+	+	+
	11. Basic Applications of tES - Scalp measurement and scalp-based landmarks (10–20 EEG system) - Electrodes placement (e.g. sponges, gel-based electrodes, headband, cap) - Setting stimulation intensity, duration, ramp-up/down - Impedance check - Assessing participants perception during stimulation (e.g. tingling sensation, phosphenes perception, scalp heating) and discomfort	(+)	+	+
	12. Transcranial Direct Current Stimulation (tDCS) - Defining and positioning Anode and Cathode	+	+	+
	13. Transcranial Alternating Current Stimulation (tACS) - Setting stimulation frequency - Setting phase difference	(+)	+	(+)
	14. Transcranial Random Noise Stimulation (tRNS) - Setting band-pass filters	(+)	+	(+)
	15. Advanced tES Applications - Multifocal/multisite tES - Concurrent tES/EEG recording - Concurrent tES/fMRI recording		+	(+)
	15. Apply and Assess SHAM tES	(+)	+	(+)

Required competencies are marked with “+”. Suggested competencies (or those that may be required under certain circumstances) are marked with “(+)”.

*Assessment of the technical application/hands-on training will be done using the see 5, do 5, and test 1 where trainees will observe 5 sessions on different subjects, do 5 sessions with supervision, and then be tested on 1. This assessment should be completed for each individual device a user will have access to.