Regulation and ethics of transcranial electric stimulation: A general view

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Transcranial application of low-intensity electrical stimuli is a non-invasive brain stimulation procedure, which allows one to alter the excitability of cortical cells in both humans and animals. There is a broad consensus regarding the safety of this approach in humans, and different versions and protocols of this technique have been used in basic research and clinical studies for years. In this review, we aim to provide updated information on regulatory and ethical issues concerning the use of different versions of transcranial electrical stimulation (tES). This information may be critical due to its implications on the welfare and health of patients. Although tES is a safe and effective method with potential clinical and research utilities, the legal regulation criteria concerning the use different versions of tES are of critical relevance due to implications of brain stimulation for human health and well-being. Recent publications that review and describe all regulatory and safety aspects regarding the use of tES offer a practical vision about the most up-to-date information in this field and more relevant ethical implications.

Keywords: ethics, health, legal regulation, non-invasive brain stimulation, safety, transcranial electric stimulation.

INTRODUCTION

In humans, the use of electrical stimulation applied transcranially at low intensities is a non-invasive and safe procedure to induce changes in cortical excitability [1–5]. The capability of this technique to alter the state of excitability of cortical neurons has been used for research and clinical purposes for some years. Hospitals, medical and clinical centers, universities, and research centers around the world have been using different versions of the transcranial electric stimulation (tES) procedure (see Table 1), such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), transcranial random noise stimulation (tRNS), or even transcutaneous spinal direct current stimulation (tsSDCS), and this use has been increasing in an exceptional way.

TABLE 1 APPROXIMATELY HERE, PLEASE

The simplicity of the device in inducing alterations of cortical excitability, the reduced cost compared to other stimulation techniques, and the portability and easy handling of the tES devices have ensured that this procedure is widely used all over the world and that its application is increasingly extended. Recently, even magnetic resonance imaging (MRI)-derived computational models have been designed, most of them based on the finite element method, to calculate the brain current flow induced by specific electrode configurations [6,7]. These models allow to simulate the intensity and density of the induced electric field, as well as the electric potential (see Fig. 1 for an example of computational modeling of current flow calculated for a typical tDCS electrode configuration). Using the finite element method to calculate the current flow, differences between conventional (2 carbon electrodes -one anodal and another cathodal- covered by saline-soaked pads, with a usual size of 5 × 5 cm) and HD (highdefinition stimulation using a ring electrode configuration, with 4 small cathodal electrodes around an anodal electrode in the center and over the target area, or vice versa) tES procedures have been revealed, as well as different parameters of the induced electric field according to the anatomical location of the specific target area and the characteristics of the biological tissue involved [6,8–12]. These calculation procedures provide relevant information on the effectiveness of non-invasive brain stimulation, and therefore, computational modeling is a useful tool for conducting research using tES in a more precise way and for increasing accuracy in clinical contexts.

FIGURE 1 APPROXIMATELY HERE, PLEASE

In spite of the safety and efficacy characteristics of tES, particularly tDCS, the regulation criteria regarding the use of these non-invasive stimulation methods are an issue that should be carefully addressed due to the importance of their implications [13]. Although tES is considered a non-invasive electrical brain stimulation procedure, and there is a consensus on the safety and effectiveness of its application under international stablished criteria [13,14], the overuse and misuse of tES should be prevented by clear regulatory restrictions.

METHODS

The main objective of this review is to resume the current state of affairs in terms of the regulated usage of different versions of tES. The information provided here could help in understanding the tendencies over time and future perspectives in terms of the legal regulation of these tools. For this purpose, a review of relevant articles about this topic was conducted in the PubMed database, using the “transcranial electric stimulation/non-invasive brain stimulation/legal regulation/safety/public health/regulatory laws/ethic" descriptors.

RESULTS AND DISCUSSION

Unlike other legally regulated and approved non-invasive stimulation procedures whose safety is supported by solid scientific evidence, such as repetitive, single or double-pulse transcranial magnetic stimulation (TMS) [15–19], there is not yet well-stablished international regulation on the clinical or research use of tES techniques [20,21]. As consequence of the above mentioned, there is a lack of an adequate number of publications on the international regulations concerning the use of the diverse versions of tES. In the United States of America (USA), there are several legal regulations for consumers of medical devices, not only from the Food and Drug Administration (FDA) but also from other American authorities including the Federal Food, Drug and Cosmetic Act [22]. These regulations are now oriented toward the intended use of each specific device rather than its action mechanism. Thus, the FDA considers three different classifications for medical devices (Class I, Class II and Class III) according to different safety and efficacy standards [13]. Although tES is not regulated by these American administrations, the characteristics of the tES devices could fall, in theory, into this area of regulation [13,23]. Two recent publications have described the legal regulatory guidelines for the use of tES in detail. Extensive and meticulous descriptions of all devices being considered by the FDA for therapeutic use is available in one of these publications [24], in which some considerations are made on the role of government and non-government agencies in public health standards with respect to the application of tES. In the aforementioned review, international regulatory criteria and laws applicable to tACS, tDCS and tPCS protocols are clearly presented and analyzed. In relation to the European Union (EU), important information is also provided here; for example, a description of the procedures for regulating the use of tES devices and information on the fact that a CE mark for marketing and distribution is the minimum requirement for the legal use of this tool [24].

Exhaustive regulatory information of the applications of tES in both the EU and USA is also provided in another recent review [20]. In this extensive review on tES practice, the international consensus established in the Göttingen meeting of 2016 regarding regulatory, practices, and ethical recommendations is widely described. Moreover, as a reference to understand the most up-to-date information on the regulatory aspects of the use of tES, specific points on ethical, legal, and regulatory issues are also included in the above mentioned review [20]. All these data are organized in several sub-sections that contain the latest information on ethics, regulatory aspects of tES in the USA and EU, as well as the safety of freely available brain stimulation devices. The publication also includes two very interesting sub-sections discussing where the tES procedures should and could be performed and by whom, as well as training proposals. Additionally, a questionnaire of sensations related to the effects of tES is provided in this complete review [20].

Other reviews have collected updated data on the regulation, efficacy and safety aspects of non-invasive brain stimulation but specifically in terms of tDCS [13,25] with special emphasis on international regulations [13]. For example, a recent review has reported interesting and useful details about the safety, ethical and legal aspects of the use of this tool [25]. In this publication, the regulatory and ethical status of the use of tDCS is widely described from an international and national perspective, and any reader interested in this field can find a rigorous and detailed explanation of the current state of this specific tES tool. Moreover, the description of the potential of this technique to induce improvements in cognitive performance is based on recent studies, and a relevant discussion on different methods, stimulation parameters, procedures, subject samples, variability of the effects, and combinatory therapies is also elaborated in the aforementioned review. The information provided in that work about the safety and ethical issues of the use of tDCS is particularly interesting. Here the authors clearly present the key differences between the professional and specialized use of tDCS by doctors and researchers and the so-called "do-it-yourself" tDCS use (DIY-tDCS) [26–29] through devices offered on the Internet. According to the authors, the possible uses reported in the latter case are aimed at achieving cognitive improvements, increased performance in video games, relaxation, sleep inducement, stress management, analgesic effects, and even improved athletic performance [25,30]. The last part of this review discusses the ethical procedures described in basic and clinical research using tDCS. These procedures include informed consent from each participant as well as medical inclusion and exclusion criteria. In addition, the ethic committees mentioned in the publications on tDCS are usually required to assure that the study is in accordance with the World Medical Association Declaration of Helsinki.

CONCLUSIONS

In summary, various rigorous works are available to obtain the relevant information on the regulatory and safety aspects of the use of tES [13,14,22–24]. From an international perspective, the current status on the use of one of the versions of tES, the tDCS technique, has been described in terms of several countries such as Australia, Brazil, France, Germany, India, Iran, Italy, Portugal, South Korea, Taiwan, and USA [13]. It can be concluded that a consensus on the regulation of the tES procedures and devices is necessary. Although the application of the different versions of tES is considered a non-invasive practice, a misuse or overuse, particularly of the tDCS procedure, should clearly be avoided through the implementation of legal regulations that take the scientific evidence into account [13,31].

ABBREVIATIONS

FDA, Food and Drug Administration

MRI, magnetic resonance imaging

tACS, transcranial alternating current stimulation

tDCS, transcranial direct current stimulation

tES, transcranial electric stimulation

tPCS, transcranial pulsed current stimulation

tRNS, transcranial random noise stimulation

tsSDCS, transcutaneous spinal direct current stimulation

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Figure legends

Fig. 1. Computational model of current flow induced by tDCS using the finite element method. This modeling was calculated for a typical electrode configuration, with anodal electrode (5 × 4 cm) positioned over C3 (according to the international 10-20 EEG system for electrode positioning). The cathodal electrode (5 × 7 cm) is positioned over Fp2 in the contralateral hemisphere, which is also a typical position for the return electrode. Current intensity was set to 1.5 mA (the most used intensities ranging from 1 to 2 mA). This electrode montage is assumed to involve the left primary motor cortex (C3 position), and computational modeling is useful to calculate the brain current flow induced by each specific electrode configuration. The three superior images of panel A show a dorsal, frontal and lateral (from left to right) view of the brain current flow, and the colors bar [online version] indicates the electric potential calculated in this model. The three inferior images and the colors bar of panel A show a brain modeling of the electric field intensity (V/m) induced by this tDCS electrode configuration. Numbers 1 and 2 indicate the position of the anodal and cathodal electrodes, respectively. COMETS v.2.0 toolbox was used for modeling the electric current flow. Panel B depicts the electric field intensity (V/m) induced by the same tDCS electrode configuration calculated by using a different software for modeling of the electric field (©2019 SimNIBS 3.1.2). Red and blue electrodes represent the anodal and cathodal electrodes positioning, respectively. Current flow and electric field intensities calculated are similar using both tools (with the higher electric filed intensity systematically over the primary motor cortex, i.e., the target area in this modeling, and with intensities ranging between 0.403 and 0.45 V/m).

Author contributions

Andrés Molero-Chamizo had the idea for the article. Andrés Molero-Chamizo, María Ángeles Salas Sánchez, Raquel Martín Riquel, Carolina Gutiérrez Lérida, and Guadalupe N. Rivera-Urbina performed the literature search and drafted the article.