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REVIEW ARTICLE

Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions

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Background

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that delivers low-intensity, direct current to cortical areas facilitating or inhibiting spontaneous neuronal activity. In the past 10 years, tDCS physiologic mechanisms of action have been intensively investigated giving support for the investigation of its applications in clinical neuropsychiatry and rehabilitation. However, new methodologic, ethical, and regulatory issues emerge when translating the findings of preclinical

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and phase I studies into phase II and III clinical studies. The aim of this comprehensive review is to discuss the key challenges of this process and possible methods to address them.

Methods
We convened a workgroup of researchers in the field to review, discuss, and provide updates and key challenges of tDCS use in clinical research.

Main Findings/Discussion
We reviewed several basic and clinical studies in the field and identified potential limitations, taking into account the particularities of the technique. We review and discuss the findings into four topics: (1) mechanisms of action of tDCS, parameters of use and computer-based human brain modeling investigating electric current fields and magnitude induced by tDCS; (2) methodologic aspects related to the clinical research of tDCS as divided according to study phase (ie, preclinical, phase I, phase II, and phase III studies); (3) ethical and regulatory concerns; and (4) future directions regarding novel approaches, novel devices, and future studies involving tDCS. Finally, we propose some alternative methods to facilitate clinical research on tDCS.
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The effects of uncontrolled electrical stimulation on the brain have been reported since the distant past. Scribonius Largus (the physician of the Roman Emperor Claudius), described how placing a live torpedo fish over the scalp to deliver a strong electric current could relieve a headache.[1] Galen of Pergamum, the great medical researcher of the ancients, and Pliny the Elder also described similar findings.[2] In the 11th century, Ibn-Sidah, a Muslim physician, suggested using a live electric catfish for the treatment of epilepsy.[2]

With the introduction of the electric battery in the 18th century, it became possible to evaluate the effect of direct transcranial stimulation systematically. Individuals such as Walsh (1773), Galvani (1791, 1797), and Volta (1792) all recognized that electrical stimulation of varying duration could evoke different physiological effects.[3] In fact, one of the first systematic reports of clinical applications of galvanic currents date back to this period, when Giovanni Aldini (Galvani's nephew) and others used transcranial electrical stimulation to treat melancholia.[4,5] Over the past two centuries, many other researchers (see Zago et al.[3] for further references) used galvanic current for the treatment of mental disorders with varying results. In more recent history, the use of electroconvulsive therapy and psychopharmacologic drugs and lack of reliable neurophysiologic markers have obscured direct current stimulation of the central nervous system (CNS) as a therapeutic and research tool particularly in the field of psychiatry. Nonetheless, galvanic current has been used without interruption for the treatment of musculoskeletal disorders and peripheral pain.

In fact, a reappraisal of transcranial direct current stimulation (tDCS) as a form of noninvasive brain stimulation took place at the turn of this century. The seminal studies of Priori and colleagues,[6] followed by Nitsche and Paulus[7] demonstrated that weak, direct electric currents could be delivered effectively transcranially as to induce bidirectional, polarity-dependent changes in cortical. Specifically, anodal direct current stimulation was shown to increase cortical excitability, whereas cathodal stimulation decreased it. In addition, animal and human studies have provided insight regarding the mechanisms underlying tDCS effects on neuroplasticity[8-11] and current distribution according to the brain area being stimulated.[12-15] In addition, several studies showed that tDCS could induce specific changes in neuropsychologic, psychophysiologic, and motor activity as a function of targeted brain areas.[16-19] Moreover, certain appealing characteristics of tDCS (such as the fact that it is noninvasive and has mostly well-tolerated, transient, and mild adverse effects) have sparked an increase in clinical studies particularly for neuropsychiatric disorders such as major depressive disorder, chronic and acute pain, stroke rehabilitation, drug addiction, and other neurologic and psychiatric conditions.[20-22] Although reported effects have been heterogeneous and warrant further clinical studies, studies have been generally promising.

As the field of noninvasive brain stimulation moves towards more clinical applications, there are new issues that emerge. One is methodologic; how to study tDCS in neuropsychiatry that historically has been heavily pharmacotherapy-based.[23] Specifically, what are the optimal approaches regarding study design (eg, two-arm, three-arm versus factorial), study methodology (blinding, use of placebo, concomitant use of drugs), sample requirements (ie, sample size, eligibility criteria, sample recruitment), interventions (eg, electrode positioning, dosage, duration, and also comparison against pharmacotherapy), outcomes (eg, clinical versus surrogate outcomes), and safety. Another issue is ethical; who should apply tDCS in clinical settings (eg, physicians, neuropsychologists, specialized staff); the tolerable amount of risk for inducing maladaptive, long-term neuroplasticity, and whether tDCS could be used for

enhancing neuropsychologic performance in healthy subjects; finally, regulatory issues also need to be discussed. In contrast to transcranial magnetic stimulation (TMS), which is delivered through a sophisticated device, tDCS can be administered with devices already manufactured and used in pain and cosmetic medicine. These devices deliver direct current to the joints and/or the skin. Also, contrary to TMS, these devices are affordable and readily accessible and can be purchased by nontrained individuals, including patients.

The last question is why conducting clinical research on tDCS. Among others, we can identify three main reasons: (1) there is a theoretical clinical basis for tDCS as a *substitutive* treatment for pharmacotherapy, such as patients with poor drug tolerability or those with adverse pharmacologic interactions (eg, elderly people who use several drugs). For instance, one group that would potentially benefit from further investigation of tDCS safety is pregnant women with unipolar depression, as there is a lack of acceptable pharmacologic alternatives for this condition[24]; (2) using tDCS as an *augmentative* treatment—for example, tDCS and restraint therapy for stroke[25]; or tDCS and pharmacotherapy for chronic pain or major depression. Again, side effects and noninvasiveness make tDCS an appealing strategy to boost the effects of other treatments in addition to its neurophysiologic effects on membrane resting threshold that likely underlie its synergistic effects. And, (3) tDCS is inexpensive; being therefore attractive to areas lacking in resources. If proven effective, tDCS will be an interesting option for developing countries.

The purpose of this review is to assess the current stage of tDCS development and identify its potential limitations in current clinical studies as to provide a comprehensive framework for designing future clinical trials. This review is divided in four parts. The first part reviews the mechanisms of action of tDCS, parameters of use and computer-based human brain modeling investigating electric current fields and magnitude induced by tDCS. Given the conciseness of this section, the reader is invited to consult more recent reviews focusing exclusively on the mechanisms of action and technical development.[26,27] The second section covers methodologic aspects related to the clinical research application of tDCS. This section is divided according to study phase (ie, preclinical, phase I, phase II, and phase III studies). The third section focuses on ethical and regulatory concerns. The last section concludes with a presentation of what are expected in the near future regarding novel approaches, novel devices, and future studies involving tDCS.

The electrophysiology of tDCS

Mechanisms of action

TDCS differs from other noninvasive brain stimulation techniques such as transcranial electrical stimulation (TES) and TMS. TDCS does not induce neuronal firing by suprathreshold neuronal membrane depolarization but rather modulates spontaneous neuronal network activity.[27,28] At the neuronal level, the primary mechanism of action is a tDCS polarity-dependent shift (polarization) of resting membrane potential. Although anodal DCS generally enhances cortical activity and excitability, cathodal DCS has opposite effects.[7,29,30] Animal studies have shown that changes in excitability are reflected in both spontaneous firing rates[31,32]; and responsiveness to afferent synaptic inputs.[33,34] It is this primary polarization mechanism that underlies the acute effects of low-intensity DC currents on cortical excitability in humans.[6]

However, tDCS elicits after-effects lasting for up to 1 hour.[9,35] Therefore, its mechanisms of action cannot be solely attributed to changes of the electrical neuronal membrane potential. In fact, further research showed that tDCS also modifies the synaptic microenvironment, for instance, by modifying synaptic strength NMDA receptor-dependently or altering GABAergic activity.[36-38] TDCS also interferes with brain excitability through modulation of intracortical and corticospinal neurons.[10,39] The effects of tDCS might be similar to those observed in long-term potentiation (LTP), as shown by one recent animal study that applied anodal motor cortex stimulation and showed a lasting increase in postsynaptic excitatory potentials.[8] Experiments with peripheral nerve[39] and spinal cord[40] stimulation showed that DC effects are also nonsynaptic, possibly involving transient changes in the density of protein channels localized below the stimulating electrode.

Given that a constant electric field displaces all polar molecules and most of the neurotransmitters and receptors in the brain have electrical properties, tDCS might also influence neuronal function by inducing prolonged neurochemical changes.[38,40] For instance, magnetic resonance spectroscopy showed that after anodal tDCS brain myoinositol significantly increased, whereas n-acetyl-aspartate failed to change.[41]

In addition to the *"direct"* tDCS effects described previously, *"indirect"* effects are also observed. This is seen in connectivity-driven alterations of distant cortical and subcortical areas.[42,43] Interestingly, tDCS modulates not only single neuron activity and evoked neuronal activity, but also spontaneous neuronal oscillations. Ardolino et al.[39] found that below the cathodal electrode, the slow EEG activity in the theta and delta band increases. Animal and modeling studies suggest that a network of tightly coupled active neurons (eg, oscillations) may be more sensitivity to applied weak current than neurons in isolation.[44-46]

Although most early tDCS studies have been performed in the motor cortex, it should be noticed that tDCS does not only induce long-lasting alterations of motor-evoked potentials, but also affects somatosensory and visual-evoked potentials. This activity is dependent on the area stimulated.[47-49] Ferrucci et al.[50] and Galea et al.[51] provided evidence that tDCS can influence the human cerebellum.

Cogiamanian et al.[40] and Winkler et al.[52] demonstrated that transcutaneous DC stimulation modulates conduction along the spinal cord and the segmental reflex pathways.

An important aspect when discussing the mechanisms of tDCS is the magnitude and location of the current induced in cortical tissues. Several modeling studies have been conducted to address this issue and will be discussed in a later section.

Finally, constant electrical fields influence several different tissues (vessels, connective tissue) and pathophysiologic mechanisms (inflammation, cell migration, vascular motility); in addition, their effects are observed on multiple cellular structures (cytoskeleton, mithocondria, membrane). With that said, tDCS may also influence nonneuronal components of the CNS. Support for this theory is observed below anodal tDCS electrode as it can induce prolonged brain vasodilatation.[53]

In conclusion, the mechanisms of action of DCS remain to be completely elucidated, an issue that can have important repercussions for future clinical applications. These mechanisms likely involve different synaptic and nonsynaptic effects on neurons and effects on nonneuronal cells and tissues within the CNS.

Pharmacologic investigation of tDCS

In tDCS research, pharmacologic studies use diverse drugs to block and/or enhance the activity of neurotransmitters and its receptors to observe how and whether tDCS-induced cortical excitability is modified. Therefore, such studies aim to enhance our knowledge about the mechanisms of action of tDCS with regard to neuromodulation and neuroplasticity.

Evidence suggests that blocking voltage-gated sodium and calcium channels decreases the excitability enhancing effect of anodal tDCS. In contrast, cathodal tDCS-generated excitability reductions are not affected.[36,37] These findings are in line with the assumption that tDCS induces shifts in membrane resting threshold of cortical neurons.

Regarding neurotransmitters, it has been shown that NMDA-glutamatergic receptors are involved in inhibitory and facilitatory plasticity induced by tDCS. Blocking NMDA receptors abolishes the after-effects of stimulation, whereas enhancement of NMDA receptor efficacy by d-cycloserine enhances selectively facilitatory plasticity.[9,54] In contrast, GABAergic modulation with lorazepam results in a delayed then enhanced and prolonged anodal tDCS-induced excitability elevation[55] (Table 1).

Regarding the monoaminergic neurotransmitters, amphetamines (that increase monoaminergic activity) seem to enhance tDCS-induced facilitatory plasticity.[56] For the dopaminergic system, tDCS-generated plasticity is modulated in a complex dosage- and subreceptor-dependent manner. Application of the dopamine precursor l-dopa converts facilitatory plasticity into inhibition, and prolongs inhibitory plasticity,[57] whereas blocking D2 receptors seems to abolish tDCS-induced plasticity,[58] D2 agonists, applied at high or low dosages, decrease plasticity. Furthermore, plasticity is restituted by medium dosage D2 agonists.[59] Interestingly, the acetylcholine reuptake-inhibitor rivastigmine affects tDCS-induced plasticity in a similar fashion as l-dopa.[11] For the serotoninergic system, the 5-HT reuptake-inhibitor citalopram enhances facilitatory plasticity and also converts inhibitory plasticity into facilitation.[60]

From a clinical point of view, these results show that pharmacotherapy and tDCS interact, which might be an issue when studying clinical samples receiving both

Table 1 Pharmacologic agents that interact with tDCS effects on cortical excitability

Drug	Class	Effect
Amine metabolism		
Citalopram	SERT blocker	Enhancement of the duration of facilitatory anodal effects; Facilitation of cathodal tDCS effects[59]
Amphetamine	NET/DAT competitive inhibitor	Enhancment of the duration of facilitatory anodal effects.[55]
L-Dopa	Dopamine precursor	For anodal: excitability turns into inhibition; For cathodal: effects are enhanced[12]
Sulpiride	D2-receptor blocker	Abolishment of tDCS-induced plasticity[57]
Pergolide	Dopamine agonist agent	Enhancement of the duration of cathodal tDCS effects[57,58]
Amino acid metabolism		
Lorazepam	GABA allosteric modulator	Anodal effects are delayed, but then enhanced and prolonged.[100]
Rivastigmine	Cholinesterase inhibitor	Abolishment of anodal tDCS effects; stabilization of cathodal tDCS effects[11]
Dextromethorpan	NMDA antagonist agent	Abolishment of the after-effects of anodal and cathodal tDCS.[36,37]
D-cycloserine	NMDA agonist agent	Enhancement of the duration of anodal effects; no effects during cathodal stimulation.[54]
Voltage-sensitive channel blockers		
Carbamazepine	Voltage-sensitive sodium channel blocker	Abolishment of the depolarizing effects of anodal tDCS.[36,37]
Flunarizine	Voltage-sensitive calcium channel blocker	Similar effects of Carbamazepine.

tDCS = transcranial direct current stimulation; NET = norepinephrine transporter; DAT = dopamine transporter; GABA = gamma-aminobutyric acid; NMDA = n-methyl-d-aspartic acid; SERT = serotonin transporter.

interventions. In fact, the complex nonlinear interaction makes it difficult to foresee the specific effects of pathophysiologic alterations or drug application on the amount and direction of tDCS-induced plasticity; thus demanding further empirical research on this topic.

Parameters of stimulation

TDCS parameters can vary widely and several factors need to be defined. These factors include electrode size and positioning, intensity, duration of stimulation, number of sessions per day, and interval between sessions. By varying these parameters, different amounts of electric current can be delivered, thus inducing diverse physiologic and adverse effects. Another potential concern is that tDCS devices are not worldwide standardized. These devices can be easily constructed using standard equipment and technology in engineering laboratories of colleges and universities. In fact, more than a dozen different tDCS devices can be found throughout neuromodulation laboratories worldwide.

Electrode positioning

Although tDCS electrical fields are relatively nonfocal, electrode positioning is critical. For instance, a previous study showed that changing the electrode reference from DLPFC to M1 eliminated tDCS effects on working memory.[16] Other studies have shown that phosphene-thresholds are modulated only during occipital (visual cortex) DCS and not other areas.[49,61] Likewise, a tDCS trial for major depression showed that only DLPFC stimulation (and not occipital stimulation) ameliorated symptoms.[62] Although current evidence suggests site-dependent effects, other issues have yet to be explored—for instance, one open question is whether and how brain stimulation in one area influences adjacent and more distant areas.

TDCS studies usually use one anode and one cathode electrode placed over the scalp to modulate a particular area of the CNS. Electrode positioning is usually determined according to the International EEG 10-20 System. Given the focality of tDCS, this appears appropriate. For instance, studies exploring the motor cortex place electrodes over C3 or C4; for the visual system, electrodes are typically placed over O1 or O2 (for a review of tDCS studies exploring different brain areas see Utz et al.[63]).

In this study, some terms used to describe tDCS montages should be discussed: when one electrode is placed bellow the neck, the entire montage is usually described as "unipolar." In contrast, montages with two electrodes on the head are termed usually "bipolar." However, this nomenclature might be inaccurate as technically the DC stimulation is always generated via two poles (electrodes) generating an electric dipole between the electrodes. Therefore, an alternative nomenclature of "mono-cephalic" and "bi-cephalic" is proposed to differentiate between "unipolar" and "bipolar" setups, respectively. Researchers in the field also use the terms "reference" and "stimulating" electrode to refer to the "neutral" and "active" electrode, respectively. However, the term "reference" electrode may also be problematic, especially for bicephalic montages because the "reference" electrode is not physiologically inert and can contribute to activity modulation as well. This could be a potential confounder depending on the main study question. Nonetheless, researchers use these terms to highlight that (in their study) they are under the assumption that in their particular montage one electrode is being explored as the "stimulating," whereas the other is the "reference."

In contrast, having the possibility to increase and decrease activity in different brain areas simultaneously may be advantageous. For instance, this could be useful in conditions involving an imbalanced interhemispheric activity (ie, in stroke).[64] In scenarios whether the reference electrode poses a confounding effect, an extracephalic reference electrode could theoretically aid in avoiding this issue. However, this might increase the risk of shunting the electric current through the skin (which would then not reach brain tissue) or displacing the current. Ultimately, the choice of montage will be application specific; for example, a recent study comparing different tDCS setups showed that, although bicephalic setups were effective, the monocephalic setup was no different than sham stimulation.[65] Finally, in a monocephalic setup, using very high currents there is the potential risk of influencing brain stem activity, including respiratory control (note that this risk is theoretical and was only observed in one historical report).[66] Nevertheless, in choosing the extracephalic position, the researcher must be confident that a significant electric field will be induced on the target brain area.

Moreover, because current flow direction/electrical field orientation relative to neuronal orientation might determine the effects of tDCS,[7] it might be that the effects of an extracephalic electrode differs relevantly from that of a bipolar electrode arrangement. Alternatively, enhancing the size of one electrode, thus reducing current density, might enable functional monocephalic stimulation also with a bicephalic electrode montage.[58]

Direct current stimulation can also be delivered over noncortical brain areas. Ferrucci et al.[50] stimulated the cerebellum showing changes in performance in a cognitive task for working memory. Galea et al.[51] explored the inhibitory effects of the cerebellum on motor-evoked potentials (MEPs) triggered by TMS over the motor cortex. This revealed that tDCS could modify MEPs in a polarity-specific manner. In addition, Cogiamanian et al.[40] observed that cathodal transcutaneous DC over the thoracic spinal cord suppressed tibial somatosensory-evoked potentials. Furthermore, Winkler et al.[52] observed that transcutaneous DCS over the spinal cord modulates the postactivation depression of the H-reflex. Preliminary data indicates spinal DCS also influences nociception[67] suggesting that the spinal cord as a target for transcutaneous DCS. Challenges for stimulation in this area must be considered such as location of induced electrical fields.

Modeling tDCS

During tDCS, current is generated across the brain; different montages result in distinct current flow through the brain and thus the ability to adjust montage allows customization and optimization of tDCS for specific applications (see above). Though tDCS montage design often follow basic assumptions (eg, "increased/decreased excitability under the anode/cathode"), computational models of brain current flow during tDCS (so called "forward" models) provide more accurate insight into detailed current flow patterns, and in some cases show that the basic assumptions are not valid. When interpreting the results of such simulations, it is important to recognize that the intensity of current flow in any specific brain region does not translate in any simple linear manner to the degree of brain modulation. However, it seems reasonable to predict that regions with more current flow are more likely to be affected by stimulation, whereas regions with little or no current flow will be spared the direct effects of stimulation.

Computational models of tDCS range in complexity from concentric sphere models to individualized high-resolution models based an individual's structural magnetic resonance imaging (MRI). The appropriate level of detail depends on the available computational resources and the clinical question being asked (see technical note below). Regardless of complexity, all models share the primary outcome of correctly predicting brain current flow during transcranial stimulation to guide clinical practice in a meaningful manner.

Most clinical studies use tDCS devices that apply direct electric currents via a constant current source, but even within this space there are infinite variations of dosage and montage that can be leveraged, with the help of models, to optimize outcomes. The current is sent through patch electrodes (surface areas typical range from 25 to 35 cm^2 but can vary by an order of magnitude) attached to the scalp surface. Total current injected ranges in magnitude are typically from 0.5 to 2 mA. Steps taken to improve tDCS specificity (including the use of larger "return" sponges and extracephalic electrodes) have been proposed but more analysis is required to determine the role of electrode-montage in neuromodulation and targeting. Modeling approaches are instrumental toward this goal. For example, modeling studies have recently predicted a profound role of the "return" electrode position in modulating overall current flow including under the "active" (or "stimulating") electrode.[68] Specifically, for a fixed active electrode position on the head, changing the position of the return electrode (including cephalic and extracephalic positions) influences current flow through the presumed target region directly under the active electrode. Therefore, in addition to considering the role of scalp shunting and action on deep brain structures (see above) when determining electrode distance, the complete design of electrode montage may subtly modulate cortical current flow.[69] Again, computer modeling can provide valuable insight into this process.

Recent modeling studies suggest that individual anatomical differences may affect current flow through the cortex. In comparison to TMS, which uses MEPs to index its potency, there is no similar rationale for titrating tDCS dosage. A related issue is the modification of tDCS dose montages for individuals with skull defects or stroke-related lesions. Such individuals may be candidates for tDCS therapy but defects/lesions are expected to distort current flow. For example, any defect/injury filled with cerebrospinal fluid (CSF), including those related to stroke of traumatic brain injury, is expected to preferentially "shunt" current flow.[15] Ideally, tDCS would be adjusted in a patient-specific (defect/lesion specific) manner to take advantage of such distortions in guiding current flow to targeted regions, while simultaneously avoiding any safety concerns (such as current hot spots).

Evidence from modeling studies suggests that for typical tDCS significant amounts of current can reach broad cortical areas especially between and under the electrode surface.[12,13] Modeling studies also show that electrode montage is critical to the amount of current shunted through the skin.

Electrode montage is critically associated to the amount of current being shunted through the skin, how much is delivered to the brain, and to what targets. The overall theme emerging from modeling efforts is that despite clinical success in applying simplifying rules in dose design, all the details and aspects of electrode montage design combine to influence current flow such that these simplifying rules are applicable but only within a limited parameter range. For example, average current density (total current/electrode area) at the "active" electrode may be a useful metric to normalize specific neurophysiologic outcomes (eg, TMS evoked MEPs), there is no universal relationship between current density and brain modulation when one considers the full spectrum of possible electrode montages.[13,70]

Recent modeling data taking into consideration gyri and sulci geometry have shown that electric current can concentrate on the edge of gyri.[71] Therefore, the effects might not be homogeneous throughout the stimulated area. Increased appreciation of the complexity of current flow through the head (reflecting the complexity of neuroanatomy), reinforces the use of applying computational models to assist in tDCS dose design[72] rather than simply relying on some heuristic rules (eg, "increased excitability under the anode").

In addition to predicting brain current flow, modeling studies also provide insight into electrode design by predicting current flow patterns through the skin. Modeling studies has reinforced that current is not passed uniformly through the skin but rather tends to concentrate near electrode edges or skin inhomogeneities.[13] Electrode design can be simple saline-soaked cotton or sponge pads or specifically designed patches with unique shapes and materials to maximize stimulation magnitude and focality.

Modeling confirms that decreasing the salinity of the pads reduces peak current concentration at the edges (even as the total current applied and average current density is fixed).[73]

In summary, modeling studies are expected to play a critical role in the development of next-generation tDCS technologies and approaches. Notably, tDCS devices have not drastically changed since the time when the battery was first discovered. Thus, conventional technology has certain limitations. These include focality (area stimulated), depth of penetration, and targeting-location control. To overcome these and other limitations, technologies using arrays of electrodes[74] such as "High Definition" tDCS (HD-tDCS)[71] and others (eg, simultaneous EEG monitoring during tDCS as to adjust dosage and parameters) have been recently proposed. Ultimately, as we begin integrating modern technology with transcranial stimulation techniques, clinical control and efficacy will undoubtedly improve.

On a final technical note: Though there has been a recent emphasize to develop increasingly accurate and complex models,[71,72,75] certain universal technical issues should be considered for high-precision models, beginning with: (1) high-resolution (eg, 1 mm) anatomic scans so that the entire model work flow should preserve precision. Any finite-element human head model is limited by the precision and accuracy of tissue dimensions (masks) and conductivity values incorporated (inhomogeneity and anisotropy). One hallmark of precision is the cortical surface used in the final finite-element mask solver should represent realistic sulci and gyri; (2) Simultaneously, a priori knowledge of tissue anatomy and factors known to shape current flow are applied to further refine segmentation. Particularly critical are discontinuities not present in nature that result from limited scan resolution; notably both unnatural perforations in planar tissues (eg, holes in cerebrospinal fluid where brain contacts skull) and microstructures (eg, incomplete or voxelized vessels) can produce significant aberrations in predicted current flow. Addition of complexity without proper parameterization can evidently decrease prediction accuracy. An improper balance between these factors can lead to distortions in brain current flow of an order of magnitude or more—uncontrolled additional complexity can in fact induce distortion. We thus emphasize that the most appropriate methodology (ranging from concentric spheres to individualized models) ultimately depends on the clinical question being addressed.

The clinical research of tDCS

Studies in nonhumans (Preclinical)

Previous animal studies have assessed safety limits of tDCS current intensity. In one study, 58 rats received tDCS with varying current densities for up to 270 minutes and histologic evaluation was conducted to assess neuronal lesion. Results suggest that brain lesions occurred when current density was at least two orders of magnitude higher than typically used in humans[88] and may reflect increase in brain temperature never observed using conventional tDCS protocols.[14] Another interesting insight from this study is that duration of tDCS only becomes a safety issue when the intensity of stimulation is near the threshold associated with neuronal lesion. Other animals studies conducted with different goals have also shown that tDCS used with charges similar to human studies do not induce histological lesions.[89]

Finally, animal studies are useful for test dosing and exploring physiologic aspects of tDCS mechanisms. In contrast, such studies are rare, and positioning of the electrodes as well as different cortical architecture, might be critical. Still, animal models might be important for answering specific questions not possible to be done in humans.

Studies on healthy volunteers (Phase I)

In drug-based trials, phase I studies are nonrandomized, noncontrolled clinical (human) trials designed to address safety and optimal dosage of drugs. This is performed by assessing the adverse effects/safety and dosage or the drugs. In this section, previous tDCS studies that address these questions and present issues that remain unsolved (dose parameters was above discussed) are reviewed (Table 2).

Safety/toxicity

Although tDCS differs in many aspects from other noninvasive neuromodulatory therapies in that it does not induce neuronal action potential and uses weak electric currents, there are safety concerns that must be addressed. If the electrochemical products generated by these currents contact the skin, skin irritation may occur; in addition, tissue heating associated with nonintact skin (therefore this is especially important in people with skin diseases and/or in protocols using daily tDCS applications and/or high electric currents) may induce skin burning[92]—although mild redness is more likely related to local, vasodilatation skin changes rather than skin damage.[93] In fact, considering there is no direct contact between the brain and the electrode and also the distance, electrochemical or heating lesions to the neuronal tissue is less likely. Moreover, experimental and modeling studies suggest no significant temperature increases for typical tDCS protocols.[7,71,73]

TDCS has been tested in thousands of subjects worldwide with no evidence of toxic effects to date. In addition to the hundreds of studies exploring tDCS effects in diverse contexts, some studies have focused specifically on safety. For instance, in a large retrospective study, Poreisz et al.[94] reviewed adverse effects in 77 healthy subjects and 25 patients who underwent a total of 567 1 mA stimulation sessions. Results show the most common effects were

Table 2 Main issues in the clinical research of tDCS and possible solutions to effectively handle them

	Current evidence	Key issues	Possible solutions
Phase I studies			
Safety/adverse effects	TDCS is not likely associated to long-term, deleterious effects. AEs are mild and transient at usual doses.	Safety has not been sufficiently investigated in people with skull defects and/or patients with neuropsychiatric disorders.	Further research should actively investigate adverse effects; long-term follow-up; modeling studies.
Dose-effect curve	Higher doses, higher current densities and higher periods of stimulation seem to be associated with effects of larger magnitude and duration.	Great between-subjects variability of effects; using higher doses is limited due to AEs; pharmacotherapy alters dose-effect curve; optimal parameters not yet defined.	Further research addressing pharmacological modification of tDCS effects; increasing duration span of tDCS to avoid skin damage; bayesian approaches and modeling studies to define optimal dose.
Phase II/III studies			
Subjects			
Recruitment	TDCS is still on its infancy, and few patients and physicians are aware of this novel technique.	Non-referral due to lack of knowledge/ suspiciousness of tDCS and time constraints in ambulatory settings; ethical issue of receiving placebo.	Using multiple referral sources; specific neuromodulation ambulatories; building trust with volunteers and physicians (lectures, web sites, explanatory videos).
Eligibility	Sample should be homogeneous, especially in phase II studies.	Sources of heterogeneity are: concomitant use of medications, incorrect diagnosis of neuropsychiatric condition, wide spectrum of severity and refractoriness.	Stratification during randomization; post-hoc analysis controlling for severity, refractoriness and medications; drug washout.
Attrition	High attrition rates might lead to negative findings; especially if intention-to-treat analyses are performed.	Daily visits to the research center and skin damage are specific issues related to dropout in tDCS trials.	Careful explanation of study objectives and possible side effects; covering of transportation costs; flexible schedules; using run-in period to identify noncommitters.
Methods			
Blinding	Blinding is the strongest approach to minimize bias. Sham TDCS involves applying an electrical current for less than 30 seconds, as to mimic intial side effects.	Several studies suggested that the sham method is reliable, at least in healthy volunteers, with intermediate-high doses and in one-session studies. TDCS device can be turned off manually (single-blinded, requiring another person to evaluate subjects) or automatically (double-blinded).	Further studies should explore whether this sham method is reliable in other contexts, e.g. daily stimulations for 5-10 days, higher doses and nonnaïve subjects. Staff blinding should also be more carefully evaluated.
Approach	To induce long-lasting (days to weeks) effects, tDCS must be delivered continuously (usually daily for 5 to 10 days).	Number of sessions and time period between stimulations are still undefined as well as the extent of such effects after the initial sessions.	Long follow-up of subjects (months to years); performing specific studies designed to evaluate cumulative changing in cortical excitability according to the number of stimulations (and time between them).
Control group	In tDCS research, the control group might be either a sham-group or an active group in which polarities are inverted.	The latter approach is an even more reliable blinding method than sham; although it can as well induce effects.	Studies exploring mechanisms of tDCS could have three groups; studies using tDCS as treatment should prefer using a sham group.

TDCS = transcranial direct current stimulation; AE = adverse effects.

mild tingling sensations (75%), light itching sensation (30%), moderate fatigue (35%), and headache (11.8%); and most of these effects did not differ from those of placebo stimulation. In another study, 164 sessions of stimulation were analyzed. Authors found only mild adverse effects with a low prevalence (0.11% in active and 0.08% in sham stimulation group).[95] Other initial studies[90,91,96-99] also reported only mild, benign, and transient side effects. In fact, the most severe adverse event reported is skin lesions on the site of electrode placement.[92]

Historically, the most severe adverse effect was observed in the first study of tDCS. During the 1960s Lippold and Redfearn[66] related a brief respiratory and motor paralysis in a bifrontal electrode montage with the current reference placed on the leg. No loss of consciousness was reported and respiration returned to normal when the current was stopped. This was attributed to the fact that the subject received 10 times the intended intensity, probably 3 mA.[27]

General exclusion criteria for noninvasive brain stimulation also apply for tDCS. Subjects must be free of unstable medical conditions, or conditions that may increase the risk of stimulation such as uncontrolled epilepsy; although epileptic seizures have not been observed in a pilot study with patients with active epilepsy.[100] Also, subjects must have no metallic implants near the electrodes.

Finally, it should be underscored that most of these observations were extracted from single stimulation studies in healthy subjects without medications. Less is known about the adverse effects of daily (or even twice daily) tDCS in patients with neuropsychiatric disorders who use pharmacotherapy. In such conditions, the adverse effects can be magnified and therefore they should be actively inquired during trials. For instance, some single-patient studies report that tDCS can induce mania/hypomania in patients with major depression.[101-103] Therefore, we suggest that a medical monitor should supervise tDCS treatment in such contexts of increased risk of significant adverse effects.

Dosage

TDCS dosage is defined by the following parameters: (1) current dosage (measured in amperes); (2) duration of stimulation; and (3) electrode montage (size and position of all electrodes). Current density (current dose divided by electrode size) is also an important parameter in considering dosage; especially for defining safety[58]; see the following review for additional information.[104] The most common electrode sizes are of 25-35 cm^2 with currents of 1-2 mA (generating densities ranging from 0.28-0.80 A/m^2) for up to 20-40 minutes. However, the current that *effectively* reaches neuronal tissue depends on other less controllable factors. These include skin resistance, skull resistance, resistance of intracranial structures (eg, blood vessels, cerebrospinal fluid, and meninges) and the resistance of brain tissue, which varies according to cell type and structure (eg, glial cells, pyramidal neurons, white matter, and so on). Moreover, patients with skull defects, brain lesions and other conditions will influence current amount and delivery. In addition, the baseline cortical excitability is different in people using pharmacotherapy (eg, benzodiazepines,[55] anticonvulsants,[105] antidepressants,[69] and others[106]) and/or presenting neuropsychiatric disorders (eg, major depression,[107] schizophrenia,[108] fibromyalgia,[109] migraine,[110] and others); an issue that is likely to interfere with the chosen dosage. Finally, other variables influence baseline cortical excitability such as gender,[111] age,[112] and smoking.[113] Hence, the same amount of current is likely to have nonuniform effects in subjects with different conditions. For instance, one study showed that low (25 mg) and high (200 mg) doses of l-dopa abolished tDCS-induced effects on cortical excitability, whereas an intermediate (100 mg) dosage increased inhibitory effects.[114] Notwithstanding, these studies should be regarded as exploratory and thus replicated in other contexts and samples, especially in clinical populations.

Therefore, in the context of clinical research, such individual factors are a source of variability and, if important enough, may result in negative findings. To avoid this, one alternative is to standardize the source of error in the sample. For instance, using saline-soaked sponges to minimize skin resistance (which can also be measured by an ohmmeter adapted in the tDCS device—some devices do give the resistance), excluding patients under pharmacotherapy, or controlling when it is not feasible (eg, benzodiazepines), avoiding sample heterogeneity using specific diagnostic criteria, particularly when working with a small, neuropsychiatric subject pool. Future studies addressing the interaction of tDCS and drugs in psychopharmacology will continue to explore and identify which drugs do not interfere with tDCS effects and which ones could block or enhance tDCS-excitability effects.[10,27]

Initial studies measuring brain excitability demonstrate that currents as low as 0.28 A/m^2 present depolarizing and hyperpolarizing effects.[6,7] In addition, phase I/II studies addressed the effects of varying dose and/or time of stimulation on cortical excitability and/or neuropsychologic tasks. Ohn et al.[115] tested the effects on working memory during 30 minutes of stimulation, showing that performance increased in a time-dependent fashion. Other studies showed the cognitive effects induced by tDCS are dependent on the current intensity; demonstrating effects such as enhanced verbal fluency improvement at 2 mA (versus lower improvement at 1 mA)[18]; and working memory improvement at 2 mA (versus no improvement at 1 mA) (See Box 1 for other tDCS studies on cognition).[116] Nevertheless, it remains unclear whether there is a linear (dose versus effect) curve associated with direct current stimulation and the influence of each parameter (dose, current density, stimulation duration) on these effects. It is known that increasing current densities will increase the depth of the electrical field, thus affecting different populations of neurons. However, at greater intensity tDCS might be painful to the subjects. For these reasons, a more effective approach designed to prolong tDCS effects is to increase

Box 1 Insight from tDCS studies on cognition

TDCS has been increasingly used to transiently modify cognitive functions in the healthy human brain. This field presents an exciting opportunity to extend the application of tDCS from a neuroscience research tool to the potential treatment of cognitive impairments. Indeed, the understanding of how to successfully manipulate cortical excitability for the formation of new memories or the acquisition of new skills could fill an important gap between phase I and II clinical studies. TDCS studies have shown that anodal tDCS delivered over the dorsolateral prefrontal cortex facilitate visual working memory.[16] Conversely, cathodal stimulation had a detrimental effect on short-term auditory memory performance.[76] Regardless of polarity, tDCS over the cerebellum disrupts practice-dependent improvement during a modified Sternberg verbal working-memory task,[50] whereas intermittent bifrontal tDCS impairs response selection and preparation in the same task.[77] Moreover, anodal tDCS to the anterior temporal lobes delivered before the encoding and retrieval phase was effective in reducing false memories, whereas maintaining veridical memories.[78] Finally, the application of anodal tDCS during slow-wave sleep improved declarative memory consolidation.[79] Further effects of tDCS on cognitive functions in healthy individuals have been shown for decision-making,[80,81] probabilistic classification learning,[82] attention,[83-85] and language.[86,87] Overall, these studies focused on the short-term improvements in performance induced by a single session of stimulation, typically delivered online during the task or immediately before it. The main limitations are the lack of control conditions over different cortical areas and the lack of a systematic monitoring of the duration of the effects. The effects of repeated applications of tDCS, their interaction with specific learning stages and tasks and the extent to which these performance improvements are retained in the long-term remain to be addressed. Hypothesis-driven behavioral paradigms or stimulation strategies are also necessary to further explore the functional role of different cortical areas in human learning.

the stimulation duration as opposed to the current density.[7,27,35,37]

Short applications (ie, seconds to a few minutes) of anodal/cathodal tDCS result in excitability shifts during stimulation but no after-effects. However, no long-term effects are seen. In contrast, 10 minutes or more of stimulation can elicit prolonged after-effects, which can be sustained for over an hour.[7,27,39] The exact duration of effects depends on the targeted cortical area and on the type of variable assessed.

For clinical purposes, longer-lasting effects are crucial. Single-dose tDCS interventions have relatively short-lived after-effects. Multiple stimulation sessions are required to induce a significant manipulation in synaptic efficacy.[117,118] In fact, repeated sessions of tDCS may have cumulative effects associated with greater magnitude and duration of behavioral effects. For example, cathodal tDCS applied over 5 consecutive days is associated with cumulative motor function improvement lasting up to 2 weeks after the end of stimulation. This is an effect which is not observed when sessions are applied weekly (as opposed to daily).[98] Whether this approach is appropriate to maximize and stabilize the electrophysiologic effects of tDCS remains under investigation. The optimal repetition rate and duration to promote tDCS-induced plasticity also remains to be determined. In animal experiments, repetition of tDCS during the after-effects of a first stimulation session has been shown to enhance efficacy.[32] However, repeated plasticity induction may result in homeostatically driven antagonistic effects.[119] Recently, Monte-Silva and coworkers[118] directly compared the effects induced by single sessions of cathodal tDCS over the motor cortex to the effects of repetitive stimulation during or after the after-effects of the first stimulation. The results showed that increasing cathodal tDCS duration (1 mA, with no interstimulation interval) resulted in longer-lasting after-effects, typically over 1 hour (tDCS duration from 9 to 18 min prolonged the after-effects from 60 to 90 minutes). Interestingly, when the second stimulation was performed during the after-effects of the first, a prolongation and enhancement of tDCS-induced effects for up to 120 minutes after stimulation was observed. In contrast, when the second session was performed 3 or 24 hours after the first, tDCS effects on cortical excitability were mixed. This was shown with a primary reduction or abolishment of the initial effects of cathodal tDCS, followed by a later reoccurrence of tDCS-induced cortical inhibition. Such neurophysiologic evidence is indicative of a stimulation timing-dependent plasticity regulation in the human motor cortex. Understanding the interaction of the consecutive stimulation protocols appears crucial to effectively target spontaneous changes of cortical activity and excitability (See Box 2 for a discussion on "offline" vs. "online" stimulation). Hence, implementing more effective procedures of plasticity induction procedures in clinical settings is crucial—in fact these results need to be replicated in clinical populations.

Studies on patients with neuropsychiatric conditions (Phase II/III)

Phases II and III studies relate to using an intervention in clinical samples. Phase II studies are typically small and use targeted samples to obtain additional information regarding optimal parameters of stimulation. Phase III are pivotal

Box 2 Two types of study design in tDCS: "Online" versus "Offline"

Clinical researchers usually apply tDCS in two main modalities regarding the time point in which the primary outcome variable is collected. When tDCS and the main outcome are coincident in time (ie, when the variable is collected during tDCS application) the experiment is said to test the "online" effects of tDCS. The concept is also used when another intervention (usually having a similar time span than tDCS such as physical therapy) and tDCS are applied simultaneously. The rationale for an "online" approach is to take advantage of the putative property of tDCS to induce excitability modifications of the brain (which is analogous to TMS) to test neuromodulatory effects on the study hypothesis, such as alterations of brain functions during tDCS. For instance, an area of investigation that uses this approach is transient modulation of moral judgment and decision making during tDCS (see Discussion on ethics in this manuscript).

On the other hand, when tDCS and the variable being measured can be distinguished in time, it is said that the experiment is applying tDCS in an "offline" protocol. An "offline" tDCS protocol applies, for instance, when one surrogate outcome (or clinical parameter) is used before and after stimulation to index tDCS effects (see Discussion on surrogate outcomes). An "offline" approach is also used in phase II/III tDCS studies. In such cases, tDCS is an experimental intervention and its long-term, neuroplastic effects are indexed with one or more surrogate and/or clinical outcomes.

studies, involving larger samples. In the United States, two positive phase III trials are required for approving a drug or device by the Food and Drug Agency (FDA) (See Box 3 for phase II/III studies in major depression).

As mentioned previously, several studies have explored the therapeutic application of tDCS in several neuropsychiatric disorders. The results of these studies reveal long-lasting tDCS effects and have promoted its use in clinical settings. Because clinical development of tDCS is being conducted mainly in academia, studies are not widely standardized regarding variables and population samples, therefore limiting conclusions. These findings are also limited by small sample sizes and experimental design. In fact, a similar scenario has been observed for TMS 5 to 10 years ago.[120] This section aims to comprehensively review the main issues of the later phases of clinical trial development for tDCS.

Issues related to recruitment and eligibility

Recruiting subjects for tDCS clinical trials presents a challenge. Proposing an intervention alternative to the mainstream pharmacotherapy might be seen by prospective patients and referring physicians in nonacademic settings as suspicious. This issue can be particularly important when a large sample size is required and/or if the eligibility criteria exclude refractory patients who are more prone to enroll in research protocols. Likewise, referral physicians, due to time constraints in the ambulatory setting, usually prefer to treat drug-naïve patients themselves. Indeed, daily visits for 1-to-2 weeks to research centers might sound unappealing and/or unaffordable even to refractory patients. In such contexts, it is advisable to have multiple referral sources and to use broad recruitment strategies. Building trust with potential volunteers is imperative. One cost-effectiveness approach could be using explanatory videos in lay language.[26]

Another issue is sample heterogeneity. In pivotal clinical trials comparing tDCS against pharmacotherapy, large samples are typically required and patient heterogeneity might be larger than for drug trials for the same condition. This is due to the fact that the severity of the condition ranges from drug-naïve to refractory subjects. Targeting only the former would create difficult enrollment (for the reasons mentioned previously), although targeting only the latter decreases overall generalizability. Possible solutions include stratification during randomization (refractory versus nonrefractory), post hoc analysis controlling for refractoriness, or increasing sample size to address some of the issues associated with heterogeneity.

Blinding issues

It appears easier to conduct sham-controlled trials using tDCS compared with TMS. TMS induces itching and pain sensations over the stimulation site, whereas tDCS induces a mild tingling sensation that usually rapidly fades. Therefore, sham protocols begin with active tDCS, which is switched off within a minute. In addition, the tingling sensation relates to the velocity in which the current is either increased or decreased. In fact, an increase of current delivery from 0.1 to 0.2 mA/s generates no discomfort for most subjects.[121] Interestingly, some subjects in the sham group continue feeling some tingling even after the current is discontinued.

These sensations are related to the total amount of charge delivered. Although this has yet to be systematically evaluated, this relationship can be a potential issue when delivering relatively high charges (>1.5-2 mA/s) and/or higher current densities. There is evidence that electrolyte solutions with lower NaCl concentrations (15 mM) are perceived as more comfortable during tDCS than those solutions with higher NaCl concentrations (220 mM).

Box 3 Insights from tDCS studies for major depression

In the past 10 years, several trials applied tDCS to subjects with major depressive disorder (MDD). Fregni et al.[124] performed a pilot randomized, sham-controlled, double-blind trial in which 10 patients were randomly assigned to receive either 5 days of active or sham stimulation. Boggio et al.[62] also enrolled 40 MDD subjects with different degrees of refractoriness (but medication-free) and randomized them to 10 sessions of active dorsolateral prefrontal cortex (DLPFC) tDCS, active occipital tDCS or sham tDCS. The findings suggested that the active DLPFC tDCS group presented a superior, significant improvement in HDRS scores compared with the other groups. Rigonatti et al.[90] demonstrated in an open-label study that Fluoxetine 20 mg/d and active tDCS (from patients of Boggio's study) presented similar scores after 6 weeks of treatment. Ferrucci et al.[91] stimulated 14 patients with severe MDD using 2 mA for 20 minutes for 5 days twice a day, showing a significant improvement in mood. Such effects seem to be more robust in more severe patients.[125] Loo et al.[99] enrolled 40 patients with severe MDD, in a double-blinded, sham-controlled study but failed to demonstrate significant difference between groups in this phase; tDCS was only more effective during the open-label phase in which patients received additional five sessions. However, this study has some limitations: the dose applied was relatively low (1 mA), and only five stimulations sessions were held, which were alternated (other studies used consecutive sessions). Moreover, patients with axis II disorders were not excluded. Finally, Brunoni et al.[126] compared patients with unipolar versus bipolar depression and found that tDCS might be a potential treatment for both conditions. However, as with phase II trials, these studies share common characteristics: relatively small sample sizes, heterogeneous sample (eg, refractoriness, medication use), blinding vulnerability (some studies were open-label), absence of primary hypothesis (most of them used several depression rating scales), and presence of "carryover" effects (in crossover studies). These initial trials likely incurred in some false-positive and false-negative results; nevertheless, they revealed the potential effectiveness of tDCS for major depressive disorder. Finally, a search made on clinicaltrials.gov in September 2010 revealed that there are at least seven trials exploring the antidepressive effects of tDCS worldwide; and the design and methods of one of them[127] has been recently published.

Because the ionic strength of deionized water is much less than that of all NaCl solutions, there is a significantly larger voltage required to carry current through the skin compared with NaCl solutions. Thus, it is recommended the use of solutions with relatively low NaCl concentration, in the range 15 mM to 140 mM, as tDCS at these concentrations is more likely to be perceived as comfortable, requires low voltage and still allows good conduction of current.[122] It has also been proposed to apply topical anesthetics to alleviate this issue.[27]

An additional blinding issue is the local vasodilatation after tDCS. This causes the skin to turn red that might not be acknowledged by the subject but might be seen by the staff and other patients. In clinical protocols, such redness can be evident after several days of stimulation. This can become a logistical issue, demanding stimulated patients to leave the setting immediately, avoiding contact with other people (patients and researchers) as to avoid blinding breaking. Another approach would be to interview patients before (and not after) being stimulated. If a rater notices evidence of redness on the scalp of a patient, another blinded rater should substitute him/her, although this matter is more important in sham-controlled studies as in studies using active groups differing only regarding polarity (and not scalp site of stimulation) cathodal and anodal stimulation cannot be distinguished between each other. Also, 30 seconds of active stimulation in the sham protocols might also lead to local redness.

Clinical protocols should assess post hoc the effectiveness of blinding; though investigators need to be aware that potential differences might occur because active tDCS is more effective than sham tDCS. It is not easy to detangle unblinding versus response because effectiveness. Other alternatives are (1) to avoid crossover trials, especially when the crossover happens in the same section, as to avoid subjects noticing the differences; (2) to apply active protocols but switching polarity so that adverse effects do not threaten blinding even if noticed, although the issue would be whether changing polarity would be an appropriate control condition, when the reference electrode is not physiologically inert.

Study design

Four approaches in tDCS clinical trials for neuropsychiatric disorders are possible: (1) to compare active versus tDCS sham in a superiority trial; (2) to compare tDCS versus another therapy (eg, acupuncture, pharmacotherapy) as a superiority or noninferiority trial; (3) to combine tDCS with another therapy (eg, physical therapy, pharmacotherapy) versus sham tDCS and another therapy as a superiority trial; and (4) combination of these approaches.

Two-arm designs are suitable when comparing active versus tDCS sham, an approach commonly used in pilot, "proof-of-concept" studies. This approach is effective in studies exploring the mechanisms of action of tDCS, for example, with neuroimaging or serum measurements.

Three-arm and "double-dummy" (ie, placebo pill + active tDCS versus pharmacotherapy + sham tDCS) designs are adequate for comparing tDCS against another therapy. The placebo arm is interesting for increasing assay sensitivity, although ethical concerns might impede using placebo groups when there are reasons to believe that treatment efficacy among study arms is imbalanced (principle of clinical equipoise).[123]

Another option is a factorial (2×2) design, which could be useful to test tDCS with and/or against another therapy of interest. For instance, in a trial testing tDCS for chronic pain, patients could be randomized to four groups: only tDCS, only pharmacotherapy, tDCS, and pharmacotherapy and sham plus placebo. In fact, such a design is the most robust as it tests two interventions simultaneously and also one intervention against another, making them optimal for pivotal studies. Although comprehensive, this approach is more demanding regarding resources, sample size, and logistics.

The n-of-one (n = 1) trial is a possible approach when the researcher is confident that tDCS effects are short-lasting (which is not usually the case for studies using multiple sessions of tDCS). In this design, one subject is randomized to receive repeated randomized allocations of the tDCS treatment. This is helpful especially to address different parameters of stimulation for single session protocols.

Attrition

Attrition (or "dropout") is the premature discontinuation of participation in a trial occurring either immediately after the baseline visit or at any time before endpoint. The specific reasons for attrition in tDCS trials should still be investigated. Although some might be the same for pharmacotherapy, one reason more specific for tDCS trials is the difficulty to comply with required daily visits to the research center (that usually occur during the first 2 weeks of the study). In intention-to-treat trials, this issue can be particularly perturbing as such subjects will maintain the same baseline scores at endpoint and thus diminish the effect size between groups. To avoid attrition in tDCS trials, some measures can be taken such as: (1) concede one or two nonconsecutive missing visits, which are replaced at the end of the daily stimulation phase and (2) using a "run-in" period, that is, a phase before trial onset in which subjects receive either active or placebo/sham treatment (usually for 1 week) as a method to preemptively screen and discard nonadherent subjects. Although the usefulness of run-in phases is controversial in pharmacotherapy given the potential for selection bias, the rationale for using tDCS is to select subjects that can commit to the stimulation protocol requirements.

Finally, although uncommon, another issue is skin burn. This would prevent further stimulations, breaking blinding, and also forcing the investigators to withdraw treatment, leading to a study dropout. Skin burning can be avoided by diminishing electric density (ie, increasing electrode size and/or diminish electric current) and electric resistance (by using rubber electrodes involved with saline-soaked sponges) over the stimulation site.

Statistical issues

Being that most tDCS trials are exploratory and using small samples, they are particularly vulnerable to type I and type II errors.

Type I (false-positive) errors occur in exploratory studies performing several statistical tests, being the case of many phase II tDCS trials. In this scenario, investigators need to decide whether to claim findings as exploratory or to determine a priori the statistical method for the primary outcome, differentiating other statistical analyses as secondary.

Type II (false-negative) errors occur in small studies and are related to underpowered trials. Again, most phase II tDCS trials recruit small samples and are prone to this error. To avoid this, researchers must perform sample size calculations when designing the trial. Another approach is to use adaptive designs, which allow sample increasing during the study, although this method may be challenging for researchers and readers to interpret the data. In this context, given that most of tDCS trials are conducted with limited resources, the best choice of primary study outcome is a continuous outcome and two time points so as to increase statistical power (and consider other analyses as secondary). Although baseline differences are usually not significant in tDCS trials probably because trials have a relatively homogeneous population, one option is to calculate normalized differences from baseline. In this case a simple approach to calculate sample size is to use independent two-sample *t* test provided in most statistical software packages.

Pilot versus pivotal studies for tDCS

Most phase II studies are also referred as "proof-of-concept" or "pilot" studies. These studies typically use small, high-targeted samples that represent the more severe spectrum of a disease to address the efficacy of a given treatment in optimal conditions. They also use several surrogate endpoints and perform many exploratory analyses. Exploratory phase II studies are necessary as they provide data to be used in subsequent trials. Furthermore, data of small studies can be pooled together in metaanalyses. However, the validity of these analyses can be contested when approving clinical interventions.[128,129]

An additional challenge for pilot studies is the exploratory nature and thus an important degree of risk regarding outcomes that is normally not seen in animal models in neuromodulation research. This hinders the ability to test the clinical efficacy of tDCS for a particular condition for the first time. In such context, a negative finding might be due to tDCS parameters or a poor neurobiologic model (eg, a negative finding in a pain trial with anodal stimulation over the DLPFC area might represent, besides being a true-negative, either the use of incorrect tDCS parameters,

a misconception in the neurologic model; thus the DLPFC area being unrelated to pain pathophysiology). This issue poses an additional challenge in tDCS research.

Therefore, pivotal (phase III) studies are necessary to validate tDCS as an effective treatment when proof-of-concept trials showed encouraging results. Future phase III studies should include: (1) sample size estimation based on prior, pilot trials or metaanalyses; (2) robust blinding method (eg: using tDCS devices that can be automatically turned off as to keep both patients and appliers unaware of the intervention delivered) and (3) assessment of sample heterogeneity, either targeting particular samples (eg, medication-free patients) or identifying potential sources of heterogeneity (eg, degree of refractoriness, number of depressive episodes, depression severity, and others) and controlling for them during study design (stratified randomization approaches) or statistical analysis.

Surrogate outcomes

Although several definitions for surrogate (or substitutive) outcomes exist, they are typically understood as laboratory measurements that substitute clinically meaningful outcomes for being in a prior step in the pathophysiologic pathway of the disease.[130] In neuromodulation research, this also includes neuropsychologic tests and neuroimaging scans. The advantage of using surrogate outcomes is avoiding long-term, expensive research. This is achieved by substituting "hard" outcomes (death or serious events) for "soft" measurements that take place earlier. Furthermore, surrogate outcomes must have high accuracy and low variability; otherwise their utility is limited (Table 3).

One surrogate outcome that is often used is TMS-indexed cortical excitability, a neurophysiologic measurement. According to the protocol used, it indexes and detects changes in brain activity.[131] For instance, measurement of motor threshold—the lowest intensity to elicit motor-evoked potentials of more than 50 uV in at least 50% of trials—is used for studying whether different tDCS protocols change motor cortical excitability. Also, measurement of the silent period—the period of electromyographic suppression (or voluntary muscle activity) after one single suprathreshold TMS pulse—can be also used for addressing whether and how tDCS affects the inhibitory cortical interneurons that are recruited during this task. Moreover, paired-pulse TMS is also used for studying inhibitory or excitatory cortical mechanisms elicited after one suprathreshold pulse and is another method that can be coupled with tDCS for indexing cortical excitability. Nonetheless, all these methods are limited to the motor cortex and thus might not necessarily reflect net brain cortical excitability and/or cortical excitability of specific brain areas.

Neuropsychologic tests are able to measure brain activity in some areas, especially those that cannot be indexed through TMS. Moreover, cognitive deficits are a common consequence of brain injury, stroke, epilepsy, neurodegenerative, and other neurologic disorders. Hence, the rehabilitation of cognitive function, such as language, spatial perception, attention, memory, calculation, and praxis represents an expanding area of neurologic rehabilitation and has recently attracted growing attention within the scientific community. For instance, changes in the activity of the prefrontal cortex can be measured using tests of working memory and attention, whereas temporoparietal stimulation can be evaluated using working memory tests. A drawback of several neuropsychologic tests is the need of a control group to adjust for learning effects biases. Performance is also influenced by educational level and, therefore, the results of one study might not be valid for similar samples in different countries.

Neurophysiologic measurements are another possible approach to surrogate outcomes. Besides TMS, brain activity can be measured using electrodes, which can be interpreted using several methods. These include the qualitative EEG, which measures spontaneous neuronal firing; the event-related potentials (ERPs), which modifies according to the brain area provoked; the quantitative EEG (qEEG), which maps brain activity; and, finally, new approaches that provide a three dimensional brain imaging based on electromagnetic reconstruction of the brain (which in fact are not widely accepted due to the "inverse problem solution." For a review on this topic, see Pascual-Marqui et al.[132]). Such measurements lack specificity—simple psychological, cognitive, or motor task recruits several brain networks and thus the measured ERP can be an epiphenomenon of another brain region rather than a relevant finding (ie, a "noise" and not a "signal"). Another issue is that the devices measuring brain activity must be adapted to decrease the electrical noise generated by the tDCS device; or, alternatively, the measurement must be collected either before or after (but not throughout) tDCS delivery.

Neuroimaging methods are divided into two branches: the first uses radiotracers and is represented by the positron-emission tomography (PET) and the single-photon emission computed tomography (SPECT), which assess brain metabolism through the emission of gamma rays. The advantage of PET/SPECT in tDCS research is that the radiotracer can be injected during brain stimulation, thus providing "real-time" brain imaging. However, the spatial resolution of such methods is poor. Because they obligatory require using radiotracers, the radiation dose needs to be carefully controlled and monitored. The second branch of neuroimaging is the MRI. This technique presents high spatial resolution. There are several methodologic approaches for MRI, which allows evaluation of different aspects of brain activity. For example, functional MRI (fMRI) explores the paramagnetic properties of hemoglobin to infer brain metabolism (based on blood oxygen saturation), whereas magnetic resonance spectroscopy (MRS) analyzes the magnetic fields of relevant molecules (eg, glutamate, GABA) and provides a noninvasive "chemical biopsy" of the brain. Some of these techniques such as

Table 3 Substitutive outcomes used in tDCS research

Outcome	Definition	Pros	Cons
Neuropsychologic tests	Paper or computerized tests that explore cognitive performance.	Nonexpensive, relatively easy to apply, specific tests can be used according to the brain area under study.	Low signal-to-noise ratio, as performance depends on the rater, the subject's characteristics (age, educational level); learning effects, thus requiring a control group. Relatively nonspecific.
Neurophysiologic measurements	Techniques that record electrical brain activity (EEG, qEEG,ERP) as to examine changes in brain activity.	Strong temporal relationship (ie, very sensible to change), able to index subclinical changes.	Relatively nonspecific (measurement of several brain networks) and medium to low spatial relationship. Devices should be adapted to minimize electrical noise of tDCS.
Transcranial magnetic stimulation (TMS)	TMS used as a tool to index cortical excitability.	Relatively affordable and easy to apply, provide several measures of cortical excitability.	Measures obtained with TMS have considerable intra and inter-subject variability; usually applied over the motor cortex only.
Neuroimaging methods-radiotracers	Methods such as PET and SPECT that use radioactivity to assess brain metabolism.	Good temporal relationship, able to index subclinical changes, can be used during "online" tDCS.	Poor spatial resolution, invasive, PET is expensive and not always available (requires a cyclotron).
MRI-based neuroimaging methods	MRI-based analyses (e.g. functional, structural, spectroscopy, DTI) that provide static and dynamic neuroimages.	Not-invasive, excellent spatial and temporal resolution (according to the method), specific.	Analyses are difficult and can yield false-positive results, expensive, not always available, tDCS devices and MRI cannot be used simultaneously.
Blood chemistry	Blood measurement of substances expressed by the CNS that cross BBB.	Minimally invasive, easy to perform, samples can be frozen and analyzed later, gives a quantitative measurement, sensible to change.	Minimal spatial resolution (brain metabolites are usually not specific of a particular area), low temporal resolution (metabolites must cross the BBB), lack of important biologic blood markers in neuropsychiatry.

tDCS = transcranial direct current stimulation; EEG = electroencephalography; qEEG = quantitative EEG; ERP = evoked-related potentials; PET = positron-emission tomography; SPECT = single photon emission computed tomography; MRI = magnetic resonance imaging; DTI = diffusion tensor imaging; CNS = central nervous system; BBB = blood-brain barrier.

fMRI lack temporal resolution as it does not measure electrical activity changes directly (it does indirectly via changes in cerebral flow). Diffusion tensor imaging (DTI) focuses on the white matter fibers, revealing the neural connectivity between brain areas. Finally, voxel-based morphometry (VBM) is a computational analysis of morphologic images that makes inferences about brain activity based on the differences of brain tissue concentration among areas. For tDCS, these methods present the advantage of high spatial resolution; allowing to assess subtle changes in the stimulated area. For instance, one study used VBM to assess neuroplastic changes after 5 days of TMS over the superior temporal cortex; showing macroscopic gray matter changes in the region.[133] Even though, the reliability of some methods of MRI are currently under dispute.[134] Moreover, tDCS is not used concomitantly with MRI yet due to serious risks of overheating and thus an "online" visualization of the stimulated area is not possible although this technical difficulty might be resolved in the near future.

Finally, there is a wide range of blood measurements used in neuropsychiatry research for surrogate outcomes.[135] One biomarker under intensive investigation is the brain-derived neurotrophic factor (BDNF). This marker plays an important role in synaptogenesis and neuroplasticity and is thus believed to be linked with some neuropsychiatric disorders, for instance, BDNF serum levels are low in depressed patients and increase after antidepressant treatment.[136] A recent study showed BDNF expression also increases after tDCS.[8] Additional biomarkers used in neuropsychiatry include inflammatory proteins such as interleucin-1, interleucin-6, and TNF-alpha[137]; hypothalamic-pituitary-adrenal activity, which is measured by serum and salivary cortisol[138]; and oxidative stress proteins such as nitric oxide and other neuroinflammatory protein markers.[139,140] These biomarkers present two important drawbacks: first, because of the blood-brain barrier, serum levels might not reflect "real-time" brain activity (or even brain activity at all); second, serum levels can only express the net brain activity, and do not represent a specific area. Therefore, perhaps the most effective use in tDCS research is to index disease improvement in phase II/III studies (Also see Box 4 for a discussion on surrogate outcomes).

TDCS in children

As the brain is under intensive development during childhood and adolescence—particularly the prefrontal cortex,[141] intensive research is currently being made to explore how cognition, emotion, behavior, and other

Box 4 Challenges for outcome measures in tDCS clinical research

As neither the full spectrum of clinical efficacy nor the mechanism of action of tDCS are completely described, outcome measures for tDCS trials ideally will inform both about tDCS clinical potency and about the biology of tDCS. With respect to clinical data, the common accepted behavioral outcomes might be insensitive to subtle changes in neurologic function. This is particularly relevant for tDCS as it has a modest (perhaps subclinical) neuromodulatory and behavioral effect, particularly for single exposures. Thus in the present early stages of investigation, the field of study may benefit from clinical trial designs that incorporate secondary outcomes in addition to measures of the patient's chief symptom. Among these are changes in normal function that may be affected by tDCS. For example, an investigator testing tDCS effects on chronic pain might add a battery of motor tasks to see whether there is any subtle loss of normal function with treatment. Similarly, an investigator applying tDCS for treatment of epilepsy may add a questionnaire to assess mood.

Further, prospects for improving tDCS clinical efficacy improve if the tDCS mechanism of action is better understood. To date, the common feature in tDCS trials appears to be its capacity to produce a lasting change in regional cortical excitability. Given these data, outcome measures aimed to capture the extent to which tDCS induces synaptic plasticity may also be useful additions to ongoing trials. That is, one could ask whether tDCS improved the symptom in question, and in parallel ask whether an LTP-type or LTD-type change in regional cortical excitability has occurred. If so, then perhaps in future trials, the tDCS effect may be augmented by the addition of appropriate pharmacologic agents or behavioral tasks that facilitate synaptic plasticity. As an example, in future trials in which cathodal tDCS may be applied over an epileptic seizure focus, whether LTD-type suppression has occurred over the stimulated area can be determined within hours of tDCS. However to find out whether seizures are reduced in frequency may take days to weeks. Thus subjects can be stratified into groups that have or have not undergone regional LTD, and clinical outcomes can be evaluated separately for subjects that did and did not experience regional depotentiation. This subclassification of subjects in an epilepsy trial would potentially reduce confounding results from subjects where tDCS was not biologically effective at the time it was administered. In addition, investigators would be wise to bear in mind the potential pitfall of choosing outcome scales that are not sufficiently sensitive to capture a relatively modest clinical tDCS effect. Thus, if tDCS strongly changes a component of a larger clinical scale, further research can be stimulated, even if negative results were found initially.

functions evolve. Having neuromodulatory properties, tDCS would be an interesting tool to explore which brain areas are particularly important in each stage of development both in healthy and pathologic conditions, such as epilepsy, cerebral palsy, autism, and mental deficiency. However, because of its potential to induce neuroplastic changes, tDCS should be used carefully especially during important phases of brain development associated with intensive plasticity and also other processes such as synaptic pruning.

A further step would be using tDCS for treating neuropsychiatric disorders in children, but this has not been tested yet. In a review of TMS studies in children, no adverse effects were reported, but its use is still limited for some reasons, including lack of established safety guidelines.[142] Notwithstanding, tDCS is a promising tool for children neurology and psychiatry.

The ethics of tDCS

TDCS is a putative candidate for adjuvant therapy for a range of neuropsychiatric conditions. tDCS is a valuable tool in neuroscience research, as its focality can be used to explore several brain aspects. Studies regarding tDCS ethics reveals its ability to induce changes in behavior such as in moral judgment,[143] deception,[144,145] and decision-making.[146] For instance, one recent study showed tDCS affected utilitarian behavior. Similarly to other studies in tDCS, the polarity-dependent effects resulted in a selfish versus selfless behavior in women.[143] Although the effects were short-lasting (volunteers were not exposed to daily stimulation), the targeted area is similar than used in studies exploring the long-lasting tDCS effects. Therefore, the ethical concern is whether tDCS could induce maladaptive behavior changes, and if so, to what intensity and extent of time.

Diverse tDCS studies on healthy subjects have shown positive changes in attention and memory.[84,85,147] From the scope of neuroethics, the issue is whether tDCS enhances cognition in healthy subjects. Can tDCS be used to boost performance in specific situations (eg, before school tests)? Another issue is that the cognitive effects described (increased attention and memory) from tDCS are in some aspects similar to amphetamines. Despite therapeutic applications, amphetamines are sold illegally as a recreational and performance enhancer drug (with the suggestive name of "speed"). As a tDCS device is easily built and inexpensive (contrary to TMS), it could also be used for nonresearch and nontherapeutic objectives by lay people. In fact, there are online videos in popular web sites such as *Youtube* explaining how to build and use a tDCS device.[148] Although it should be underscored that all the enhancement effects were present for a short period, it is possible that prolonged daily stimulation could increase the time span of such effects, thus inducing maladaptive changes. In contrast, other legal substances such as caffeine are also frequently used as cognitive boosters.

In fact, because applications in these fields are currently in the research stage, fixed protocols and safety guidelines are yet to be defined. Research and development of any new devices provides an opportunity for brain science and clinical care to advance, and also challenges the medical and wider communities to address potential dangers and complications, ethical and moral quandaries, and issues of healthcare economics and distributive justice. For innovative neurotechnologies, these are major potential pitfalls to look out for. Intervening in the brain is always fraught with the potential for serious consequences. Despite these concerns, only by conducting carefully planned clinical and experimental studies can we provide the impetus to advance care for people with brain, emotional or psychologic, or neuropsychiatric disorders.

Conclusion

The current paper addresses the main aspects of the clinical research of tDCS. This technique has a wide range of potential applications and can be used to explore the basic aspects of neurosciences as well as for the treatment of neuropsychiatric disorders. TDCS has unique characteristics such as ability to induce antagonistic effects in cortical excitability according to the parameters of stimulation; concomitant ("online") use with neuropsychologic and psychophysiologic tests; noninvasiveness and thus absence of pharmacokinetics interactions, being a putative substitutive/augmentative agent in neuropsychiatry; and low-cost and portability, making it suitable for increasing access to novel therapies. However, such characteristics also bring challenges regarding clinical design, neuroethics and legal issues. In this paper, we aimed to provide an overview of tDCS in clinical research; thereby providing knowledge for conducting proper clinical trials using this promising approach.

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