Low-Intensity Transcranial Current Stimulation in Psychiatry

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Neurostimulation is rapidly emerging as an important treatment modality for psychiatric disorders. One of the fastest-growing and least-regulated approaches to noninvasive therapeutic stimulation involves the application of weak electrical currents. Widespread enthusiasm for low-intensity transcranial electrical current stimulation (tCS) is reflected by the recent surge in direct-to-consumer device marketing, do-it-yourself enthusiasm, and an escalating number of clinical trials. In the wake of this rapid growth, clinicians may lack sufficient information about tCS to inform their clinical practices. Interpretation of tCS clinical trial data is aided by familiarity with basic neurophysiological principles, potential mechanisms of action of tCS, and the complicated regulatory history governing tCS devices. A growing literature includes randomized controlled trials of tCS for major depression, schizophrenia, cognitive disorders, and substance use disorders. The relative ease of use and abundant access to tCS may represent a broad-reaching and important advance for future mental health care. Evidence supports application of one type of tCS, transcranial direct current stimulation (tDCS), for major depression. However, tDCS devices do not have regulatory approval for treating medical disorders, evidence is largely inconclusive for other therapeutic areas, and their use is associated with some physical and psychiatric risks. One unexpected finding to arise from this review is that the use of cranial electrotherapy stimulation devices—the only category of tCS devices cleared for use in psychiatric disorders—is supported by low-quality evidence.

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Neurostimulation can be defined as any intervention intended to alter nervous system function by using energy fields such as electricity, magnetism, or both. While the historical literature has described neurostimulation to treat physical maladies for over a thousand years (1), its use for psychiatric disorders became popular in the past century. Since the 1930s (2), electroconvulsive therapy (ECT) has been recognized as an effective treatment for severe depression, catatonia, and other mental health disorders. In addition to ECT, clinicians are expected to understand newer forms of neurostimulation, such as vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS) (3).

For a number of reasons, therapeutic neurostimulation has seen a recent surge of interest. First, neurostimulation targets electrical activity in brain networks, acting through mechanisms that are different from those of pharmacotherapy, thus offering the hope of treatment success where medications have failed. Identifying and targeting specific brain regions or circuits to reduce psychiatric symptoms may offer a level of focality beyond that offered by ECT or pharmacotherapy. Second, we are surrounded by technology that interfaces with the human body, such as smartphones, watches with sensors, and apps that monitor an individual's physical activity. As society accepts these devices, increased use of medical technology that interacts with the central nervous system may naturally follow. Third, since the side effects associated with neurostimulation are different from those of medications, neurostimulation may be perceived as having superior tolerability for use alone or in combination with pharmacotherapy (4) or psychotherapy (5). Finally, a growing body of evidence suggests neurostimulation might modify a broad spectrum of brain functions, giving rise to speculation about its potential to improve cognition or nonspecific symptoms in healthy individuals, thereby suggesting that similar gains might be achieved in psychiatrically ill patients.

In this article, we provide an overview of the devices and modalities that use low-energy electrical current for brain stimulation, described as transcranial current stimulation (tCS). Emerging technology has fueled rapid expansion of these devices in the last few years, without commensurate growth in accessible, clinician-directed information. To address this knowledge gap, here we provide a comprehensive review of the engineering and neurophysiology underlying tCS, relevant data from clinical trials, and potential safety considerations.

SECTION 1: ELECTRICAL ENGINEERING AND NEUROPHYSIOLOGY

Based on the principle that application of an electric current to the skin generates an electrical field, tCS devices differ

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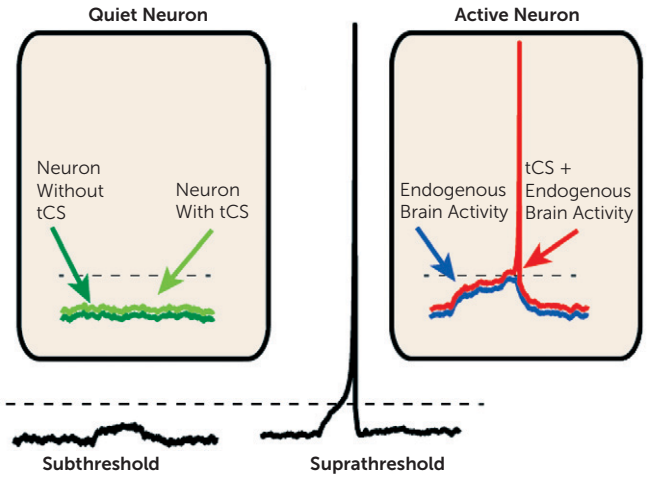
from one another based on the waveform of the electric current used. Perhaps the best-known type of tCS is transcranial direct current stimulation (tDCS), which delivers a constant, or "direct," waveform. Another type of tCS, called cranial electrical stimulation (CES), uses proprietary waveforms that may fluctuate over time. Other tCS approaches include use of sine waves, i.e., transcranial alternating current stimulation (tACS), or broadband noise, i.e., transcranial random noise stimulation (tRNS). Regardless of the waveform, the electrical resistance of the pathway through the patient's tissues determines how much voltage the device applies to achieve the level of current selected by the user.

Stimulation devices deliver a predefined amount of electric current (I), measured in milliamperes (mA). According to Ohm's law (V=IR), the amount of voltage (V) that is required to produce a specific current (I) depends on the resistance (R) between the two connectors on the device. Since the wires and electrodes have very low resistance, the main resistance in the system comes from the interface between the electrodes and the biological tissue located between the electrodes. Ohm's law dictates that a greater voltage will be needed to pass a current through tissue with higher resistance. During tCS, higher resistance (and hence higher voltage) can result in patient discomfort and may lead to skin burns under the electrodes (reviewed in Section 3) (6). Typical reasons for heightened resistance are poor electrode contact with skin or use of electrodes made from materials that do not conduct well. Devices that enforce a maximum upper limit of voltage mitigate this risk. Safe delivery of tCS requires low resistance for the duration of a stimulation session; this is achieved through steps taken to ensure 1) use of electrodes with good conductive properties, 2) good contact between electrodes and skin, and 3) integrity of connections between electrodes, lead wires, and the stimulator.

Spatial Targeting: Electrode Montages

The spatial positioning of stimulation electrodes on the scalp can generate the misleading perception that only the brain underneath the electrodes, and no other area, is stimulated. This notion is mostly incorrect, since the human head exhibits heterogeneous electrical properties. For example, when the current is delivered through scalp electrodes, a large fraction of it is shunted away through the skin and does not penetrate the skull. Current may also travel through the orbits, foramen magnum, or cranial nerve foramina, as low-resistance interstitial fluid creates electrical shunts at these sites. Several tCS devices deliver stimulation through one or more electrodes placed on the ears, face, or elsewhere below the head and neck. It is possible that nonspecific cranial nerve stimulation plays an important part in the effects of tCS. Once the electrical field reaches the brain, tCS has a certain strength and direction; both are relevant for modulating the activity of individual neurons or networks of neurons. Similar to antennae, neurons must be positioned so they are aligned with the direction of an oncoming electrical field if the field is to influence them. When this happens, a series of events leads

FIGURE 1. Sub- and Suprathreshold Energy Input on Neuronal Action Potentials[a]



[a] Subthreshold membrane fluctuations are not sufficient to generate an action potential (left). However, if intrinsic fluctuations in a neuron's membrane voltage move it closer to its threshold, application of an inherently subthreshold input, such as low-intensity transcranial current stimulation (tCS), can trigger an action potential (right). Dashed line indicates threshold.

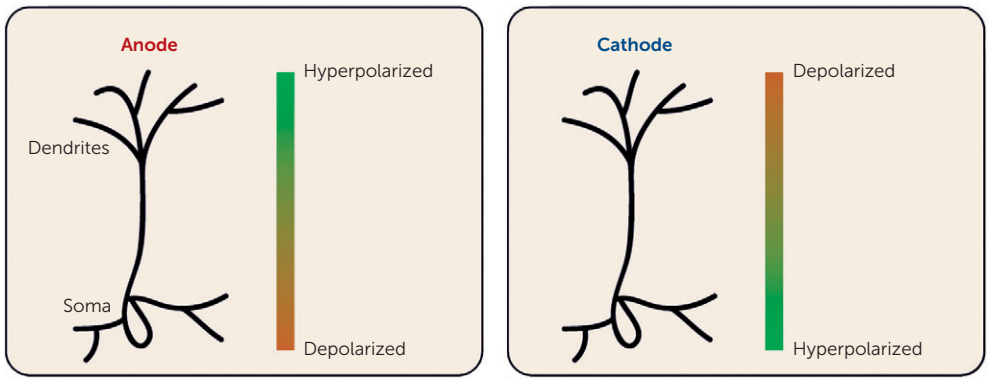
to a change in the voltage across the neuron's membrane (7); stronger electrical fields (i.e., those with greater amplitude) have greater effects on the neuronal membrane. Spatial targeting using computer simulations of the electrical field distribution, as a function of electrode number, size, and location, has been proposed (8) but lacks validation as an approach to guide clinical tCS. Moreover, given the distributed and complex deficits in neuronal networks associated with psychiatric disorders, identifying the correct target area(s) for therapeutic stimulation in a specific disorder or symptom remains an important challenge for the field.

Neurophysiological Effects of tCS

The electrical fields used in tDCS are generally considered a subthreshold perturbation, meaning that tDCS, by itself, is not thought to cause neuronal depolarization (Figure 1). However, the net effect of tDCS does not occur in isolation. Communication between individual neurons and neuronal networks is nonlinear and complex, with a large number of inputs influencing the activity of any individual neuron. Therefore, even a small change in the membrane voltage may impact neuronal firing.

Variation in the direction of current flow also impacts neuronal firing (Figure 2). As described above, when current travels in one direction, the effect is to depolarize or enhance the chance of firing. However, current traveling in the opposite direction causes hyperpolarization of the membrane, making the neuron less likely to fire relative to its resting state. Unfortunately, this neurophysiological principle is associated with the unproven model wherein "anodal tDCS" excites brain activity in the region under that electrode and "cathodal tDCS" inhibits brain activity in the region beneath that electrode. While application of this simplistic, and likely

FIGURE 2. Model of Anode Versus Cathode Stimulation[a]



[a] The schematic diagram represents effects of anode and cathode stimulation on neuron resting potentials. Placement of the anode over a brain region leads to a depolarization that increases the likelihood of neuronal firing in the cell body (left). In contrast, placement of the cathode leads to hyperpolarization, which decreases the likelihood of neuronal firing (right).

incorrect, model (9) has been used to support montages implemented in clinical trials (reviewed in Section 2), further research is needed to characterize the relationship between cellular physiology and clinical outcomes.

The potential therapeutic benefit of tCS arises because the neurophysiological effect of current applied during a single session is durable, to some extent, over time after the stimulation ceases. This phenomenon was demonstrated by a series of experiments wherein motor cortex neurons were stimulated with tDCS, and their excitability was measured after stimulation stopped (10). It is important to recognize that much of what we know about tDCS comes from studies of the motor cortex, and it remains unclear if the same principles apply to other brain regions, such as the prefrontal cortex. Furthermore, since neuronal organization may differ across the brain, it is possible that the same stimulation can result in varied effects when applied to different regions. Nevertheless, a number of experiments (e.g., 11–13) have now demonstrated enduring functional effects of tDCS on (nonmotor) cortical activity, persisting in the hour after stimulation ceases.

SECTION 2: REVIEW OF PUBLISHED RANDOMIZED CONTROLLED TRIALS

To describe the current evidence base for therapeutic effects of tCS in psychiatry, we performed a focused review of published clinical trial data, extracted from PubMed, recent review articles (14–16), and meta-analyses (17, 18). Because of the known limitations of open-label pilot studies (19), we included only treatment-based, randomized, controlled trials. Where there were no clinical randomized controlled trials, we included key proof-of-concept studies to illustrate the status of the field. The literature search was performed on March 24, 2016, and updated on Nov. 21, 2016. Search terms included tDCS, CES, tACS, tRNS, and several emerging tCS approaches, such as external trigeminal nerve stimulation (eTNS) and transcutaneous vagus nerve stimulation (tVNS). Each modality term was searched separately, with words spelled out and in abbreviated form, and searched in combination with each reviewed psychiatric disorder (major depressive disorder, bipolar disorder, schizophrenia, anxiety, obsessive-compulsive disorder, substance use, and dementia). Primary outcomes of the trials for major depression, schizophrenia, dementia/cognitive disorders, and substance use disorders appear below. Details of administration, such as anatomical target, stimulation strength, and stimulation duration, are included in the corresponding tables. Meta-analyses are also summarized below.

Consensus scores were generated to review the quality of the evidence base supporting tCS for several therapeutic areas by evaluating the scientific rigor of the published trials. We developed a list of 21 quality indicators (see the data supplement accompanying the online version of this article) based on the GRADE scoring guidelines (20), which reflect the elements required for a well-designed tDCS randomized controlled trial. These indicators incorporated standard elements of clinical trial design and those unique to studying clinical effects of tCS, such as standardization of the environment during stimulation. Furthermore, it was noted that while most pharmacotherapy randomized controlled trials use a double-blind design (i.e., patients and raters are blind to treatment assignment), tCS studies typically also need a blinded treatment administrator (i.e., triple-blind) to ensure that the nature of the investigational treatment remains concealed. In light of possible tCS interactions with psychotropic medications, we evaluated the extent to which investigators gathered and reported data on participants' concurrent medication use. A percentage score (0%−100%, rounded to the nearest whole number) was calculated for each trial, based on the number of indicators present, with 100% reflecting the highest quality rating. Each report was independently reviewed and scored by at least two coauthors; group discussion took place to resolve discrepancies and achieve consensus scoring.

Randomized Controlled Trials and Meta-Analyses of tCS for Major Depression

Efficacy studies for depression represent the largest group of available data for randomized controlled trials of tCS. tDCS is the dominant modality (Table 1), typically with the anode placed over the left dorsolateral prefrontal cortex (DLPFC). Some studies restricted enrollment to (unipolar) major depressive disorder, and others included participants with unipolar or bipolar major depressive episodes. Some of these

studies allowed participants to remain on stable regimens of psychotropic medications while others required medication-free participants.

Initial studies of tDCS generated mixed results regarding potential efficacy. Fregni et al. (25) performed the first clinical trial of tDCS for major depressive disorder (N=10) and found efficacy of active over sham treatment ($p<0.05$). This was followed by a larger study (N=40) by Boggio et al. (23) that also showed superiority of active stimulation. Subsequently, Loo and colleagues (26) found no difference between active and sham tDCS (N=40) ($p>0.1$). However, when they conducted a larger study (27) (N=64) with more treatment sessions, they found a significant advantage of active tDCS ($p<0.05$) but no difference in response rates; one bipolar patient receiving active tDCS became hypomanic. Palm et al. (28) (N=22) and Blumberger et al. (22) (N=24) also found no difference between active and sham tDCS. Bennabi et al. (21) (N=24) tested tDCS plus escitalopram (10–20 mg/day) and found no difference between active and sham tDCS.

In the largest study (N=120) of tDCS to date, Brunoni et al. (4) gave twelve 30-minute sessions of 2-mA tDCS (10 consecutive workday sessions followed by a single session delivered every other week) and/or a low dose of sertraline (50 mg/day) in a 2×2 factorial design; two of the groups (each N=30) were randomized to active tDCS. This approach enabled comparisons of active versus sham tDCS, placebo pill versus sertraline, and a drug-stimulation combination. The investigators observed greater reduction of depression in the group receiving combined sertraline plus active tDCS than in the groups receiving sertraline monotherapy (p=0.002), tDCS monotherapy (p=0.03), and both inactive treatments (placebo plus sham tDCS, $p<0.001$). Treatment with tDCS monotherapy was superior to placebo plus sham tDCS (p=0.01) but comparable to sertraline monotherapy (p=0.35). In comparisons of response rates, tDCS monotherapy (43.3%, $p<0.001$) and tDCS plus sertraline (63.3%, p=0.03) did better than placebo plus sham stimulation (16.7%). Remission followed a similar pattern, with worse outcomes for placebo plus sham stimulation (13.3%) compared with tDCS monotherapy (40.0%, p=0.02) and active tDCS plus sertraline (46.7%, p=0.007). Sertraline monotherapy did not statistically separate from placebo plus sham stimulation on any outcome measure. Seven episodes of treatment-emergent mania or hypomania were observed, with the majority (N=5, 17%) in the group receiving combined active tDCS plus sertraline.

Several research groups have evaluated the combined effect of tDCS plus psychotherapy for depression, an approach informed by data indicating that tDCS can facilitate neuronal firing in the context of appropriate environmental cues (10). Segrave et al. (5) (N=27) reported improved depressive symptoms when tDCS was combined with cognitive control therapy, although both Brunoni et al. (24) (N=37) and Vanderhasselt et al. (29) (N=33) found no difference between active and sham stimulation combined with therapy. Some have identified the timing of stimulation relative to therapy as a possible limitation of these studies, theorizing that "online" stimulation, occurring concurrent with therapy, might be superior to "offline" stimulation that precedes the session (35).

The anxiolytic/antidepressant effects of other types of tCS have also been investigated. Over a dozen CES devices received Food and Drug Administration (FDA) clearance for treatment of "insomnia, depression, or anxiety" on the basis of technical features that were considered substantially equivalent to older CES devices already on the market before Congress introduced the Medical Device Regulation Act in 1976. While an older literature (36, 37) suggested clinical efficacy of CES, that body of evidence comprises trials that would not be considered rigorous by modern standards of clinical trial design. A 1995 meta-analysis of CES therapy raised questions regarding data reporting bias and adequacy of blinding (37). While the use of proprietary waveforms by most CES devices has created an obstacle for independent evaluation of efficacy and potential mechanisms of action, Barclay et al. (30) (N=115) conducted an investigation of CES efficacy using the Alpha-Stim device in patients with a primary anxiety disorder and some (unspecified) degree of comorbid depressive symptoms, and they reported significantly improved depression ($p<0.001$) and anxiety ($p<0.001$) after treatment. However, subsequent studies by Lyon et al. (31) (N=163) and Mischoulon et al. (32) (N=30) found no advantage of CES over sham stimulation in depressive symptoms (all $p>0.1$). One recent pilot study of bipolar II depression by McClure et al. (33) (N=16) indicated that 2 weeks of CES could reduce depressive symptoms ($p<0.003$).

Cranial nerve stimulation is another tCS approach under investigation. Shiozawa et al. (34) (N=40) reported the first randomized controlled trial evaluating the efficacy of eTNS and observed that active stimulation significantly reduced depressive symptoms ($p<0.01$). Rong et al. (38) (N=160) conducted a pseudo-randomized controlled trial of tVNS for major depressive disorder. While active tVNS was associated with greater reduction in depressive symptoms ($p<0.001$), no differences in response or remission were observed at endpoint.

To date there are four meta-analyses of tDCS for depression. Although earlier reports were negative (14, 38), recent analyses (incorporating larger studies) are positive. Shiozawa et al. (18) (N=259) found a significant advantage of active tDCS over sham (g=0.37, 95% confidence interval [CI] 0.04–0.7). Odds ratios (ORs) for response and remission were 1.63 (95% CI 1.26–2.12) and 2.50 (95% CI 1.26–2.50). Most recently, Brunoni et al. (39) (N=289) found similar results for response (OR=2.44, 95% CI 1.38–4.32) and remission (OR=2.38, 95% CI 1.22–4.64), and they also reported that treatment resistance predicted nonresponse, whereas higher tDCS dose (longer duration and higher current density) predicted response.

Questions remain about potential side effects or synergistic therapeutic effects when tCS is combined with psychotropic medications, since no large studies have investigated the use of tDCS concurrent with adequate doses of antidepressant medication. The currently available data do not support the

TABLE 1. Quality of Randomized Controlled Trials (N=16) of Low-Intensity Electrical Stimulation for Major Depressive Episodes[a]

Stimulation Type and Study	N per Group	Anatomical Target(s)	Stimulation Strength	Session Duration and Frequency (Total Sessions)	Main Findings[b]	Quality Score (%)[c]
Transcranial direct current stimulation (tDCS)						
Bennabi et al., 2015 (21)	Sham 12 Active 12 Total 24	L DLPFC	2 mA	30 min twice/day for 5 days (10)	No difference between active and sham tDCS in depression	68
Blumberger et al., 2012 (22)	Sham 11 Active 13 Total 24	L DLPFC	2 mA	20 min/day, 5 times/wk for 3 wk (15)	No difference in depression remission between active and sham tDCS	74
Boggio et al., 2008 (23)	Sham 10 Active control 9 Active 21 Total 40	L DLPFC	2 mA	20 min/day, 5 times/wk for 10 days (10)	Active stimulation reduced depressive symptoms	68
Brunoni et al., 2013 (4)	PBO/sham 30 Sert/sham 30 PBO/active 30 Sert/active 30 Total 120	L DLPFC	2 mA	30 min/day, 5 times per wk for 2 wk, then 2 sessions every other wk (12)	Sert/active tDCS superior to sert/sham, PBO/active, and PBO/sham groups	89
Brunoni et al., 2014 (24)	Therapy/sham 17 Therapy/active 20 Total 37	L DLPFC	2 mA	30 min/day for 10 days (10)	No difference between active and sham tDCS in depression	79
Fregni et al., 2006 (25)	Sham 5 Active 5 Total 10	L DLPFC	1 mA	20 min/day for 5 alternate days (5)	Active tDCS reduced depressive symptoms	32
Loo et al., 2010 (26)	Sham 20 Active 20 Total 40	L DLPFC	1 mA	20 min/day, 3 times per wk (M/W/F) for 5 sessions (5)	No difference between active and sham tDCS in depression	79
Loo et al., 2012 (27)	Sham 31 Active 33 Total 64	L DLPFC	2 mA	20 min/day, 5 days per wk for 3 wk (15)	Active tDCS reduced depressive symptoms	89
Palm et al., 2012 (28)	Sham 11 Active 11 Total 22	L DLPFC	1–2 mA	20 min/day, 5 days per wk for 4 wk (20)	No difference between active and sham tDCS in depression	74
Segrave et al., 2014 (5)	Therapy/active 9 Therapy/sham 9 Sham therapy/active 9 Total 27	L DLPFC	2 mA	24 min/day for 5 sessions (5)	Active tDCS reduced depressive symptoms	68
Vanderhasselt et al., 2015 (29)	Sham 14 Active 19 Total 33	L DLPFC	2 mA	30 min/day for 10 sessions (10)	No difference between active and sham tDCS in depression	53
Cranial electrical stimulation (CES)						
Barclay et al., 2014 (30)	Sham 55 Active 60 Total 115	Cortex	100 μA, 0.5 Hz	1 hr/day, 5 days/wk for 5 wk (25)	Active CES reduced anxiety and depressive symptoms	63
Lyon et al., 2015 (31)	Sham 81 Active 82 Total 163	Cortex	100 μA, 0.5 Hz	1 hr/day, 7 days/wk for 2 wk (14)	No difference between active and sham CES in depression	63
Mischoulon et al., 2015 (32)	Sham 13 Active 17 Total 30	DLPFC	1–4 μA	20 min/day, 5 days per wk for 3 wk (15)	No difference between active and sham CES in depression	84
McClure et al., 2015 (33)	Sham 9 Active 7 Total 16	Cortex	2 mA, 5 Hz, 500 Hz, 15,000 Hz	20 min/day, 5 days per wk for 2 wk (10)	Active CES reduced depressive symptoms	67

continued

TABLE 1, *continued*

Stimulation Type and Study	N per Group	Anatomical Target(s)	Stimulation Strength	Session Duration and Frequency (Total Sessions)	Main Findings[b]	Quality Score (%)[c]
Trigeminal nerve stimulation (TNS)						
Shiozawa et al., 2015 (34)	Sham 20 Active 20 Total 40	Trigeminal nerve	120 Hz, 250 μs	30 min/day for 10 days (10)	Active TNS reduced depressive symptoms	74

[a] PBO, placebo; sert, sertraline; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; mA, milliamperes; s, second(s); hr, hour(s); wk, week(s).
[b] Some studies included unblinded components; only double-blind outcomes are reported here.
[c] The 21-item quality checklist was developed (see the online data supplement) on the basis of GRADE scoring guidelines (20). The same criteria were applied to all clinical trials reviewed. The quality score is a summary score (0%–100%, rounded to the nearest whole number) calculated for each trial, based on the number of quality indicators that were present, with 100% reflecting the highest quality rating. Each published report was independently reviewed and scored by at least two coauthors; group discussion took place to resolve discrepancies and achieve consensus scoring for all indicators on all studies.

use of tDCS as a method to accelerate or enhance the short-term effects of psychotherapy. While risk of adverse events appears modest, the incidence of (hypo)manic induction in larger trials is noteworthy and deserves greater study.

Taken together, the available evidence from randomized controlled trials generally supports the use of tDCS to relieve symptoms of depression, with other stimulation modalities yielding mixed results. To date there is no defined regulatory pathway for tDCS devices, and none is approved or cleared for treating psychiatric disorders. On the other hand, despite having an FDA indication for depression, CES devices have not consistently demonstrated clinical efficacy.

Randomized Controlled Trials of tCS for Schizophrenia

tCS has been investigated as a treatment approach for schizophrenia (Table 2), mostly utilizing tDCS. Montages have typically utilized placement of the anode over the left DLPFC, with the cathode over the temporoparietal junction or over the supraorbital area. Brunelin et al (40) (N=30) conducted the first randomized controlled trial and observed that active tDCS reduced auditory hallucinations acutely ($p<0.001$) and over 3 months ($p<0.001$) and reduced negative symptoms (p=0.01). This was followed by a study by Smith et al. (45) (N=33) that found active stimulation improved cognition (p=0.008) but had no effect on positive or negative symptoms (all $p>0.1$), whereas Palm et al. (44) found that tDCS reduced negative symptoms (p=0.016) and Mondino et al. (43) found that tDCS reduced hallucinations ($p<0.001$). Several studies using tDCS (Fitzgerald et al. [41], N=24, and Frohlich et al. [42], N=26) and tVNS (Hasan et al. [46], (N=20) found no difference between active and sham stimulation.

The currently available data do not support use of tCS for schizophrenia. The evidence base comprises a small number of randomized controlled trials with conflicting results. More work is clearly needed to develop tCS for treatment of patients with schizophrenia.

Randomized Controlled Trials of tCS for Dementia or Cognitive Deficits

Dementia and cognitive deficits are other therapeutic areas of investigation (Table 3), inspired by the potential for tDCS to enhance attention, learning, and memory in healthy adults (reviewed in reference 50). While meta-analyses of single-session tCS (51, 52) indicate benefit in patient samples, the results of most clinical randomized controlled trials have been negative (47, 49), although Manenti et al. (48) (N=20) found that tDCS improved cognition in patients with Parkinson's disease. On the basis of these results, the available data do not support the use of tDCS for patients with dementia or cognitive deficits.

Randomized Controlled Trials of tCS for Substance Use Disorders

A number of studies have evaluated tCS for substance use disorders (Table 4). Da Silva et al. (57) (N=13) investigated tDCS for alcohol dependence, and they reported significant reductions in depressive symptoms ($p<0.001$) and craving (p=0.015), although they also reported a statistical trend toward a higher relapse rate (p=0.053). Klauss et al. (58) (N=33) found active tDCS improved alcohol abstinence (p=0.02). Regarding nicotine, two studies, by Boggio et al. (55) (N=27) and Fecteau et al. (56) (N=12), found that tDCS reduced nicotine craving and cigarette consumption ($p<0.05$). Findings in cocaine use are mixed; Conti et al. (54) (N=13) found no effect of tDCS on cocaine use ($p>0.1$), whereas Batista et al. (53) (N=36) found that tDCS reduced cocaine craving (p=0.028). There are some proof-of-concept studies of tDCS for other substances, with potentially concerning results. Boggio et al. (59) (N=25) found that tDCS increased risk-taking behaviors in chronic cannabis users ($p<0.001$), and Shahbabaie et al. (60) (N=22) found that tDCS increased cue-induced methamphetamine craving (p=0.012).

While the available data appear to provide some support for the use of tDCS for some substance use disorders, there have been very few clinical trials, and several suggest potential harms, such as increased relapse (57), greater risk taking (59, 61), and heightened craving (60).

Proof-of-Concept Studies of tCS for Other Neuropsychiatric Disorders

Data describing tCS for therapeutic areas beyond those reviewed here are quite limited. For example, one study (62) (N=60) did not find efficacy of a single tDCS session for

TABLE 2. Quality of Randomized Controlled Trials (N=7) of Low-Intensity Electrical Stimulation for Schizophrenia[a]

Stimulation Type and Study	N per Group	Anatomical Target(s)	Stimulation Strength	Session Duration and Frequency (Total Sessions)	Main Findings[b]	Quality Score (%)[c]
Transcranial direct current stimulation (tDCS)						
Brunelin et al., 2012 (40)	Sham 15 Active 15 Total 30	L DLPFC, L TPJ	2 mA	20 min, twice a day for 5 days (10)	Active tDCS reduced auditory and verbal hallucinations	63
Fitzgerald et al., 2014[d] (41)	Sham 12 Active 12 Total 24	Bilateral (N=11): L+R DLPFC (both anodal), L+R TPJ (both cathodal); unilateral (N=13): L DLPFC, L TPJ	2 mA	20 min/day, 5 days/wk for 3 wk (15)	No difference between active and sham tDCS in hallucinations or negative symptoms	37
Frohlich et al., 2016 (42)	Sham 13 Active 13 Total 26	L DLPFC, L TPJ	2 mA	20 min/day for 5 days (5)	No difference between active and sham tDCS in auditory hallucinations	74
Mondino et al., 2016[e] (43)	Sham 12 Active 11 Total 23	L DLPFC, L TPJ	2 mA	20 min, twice a day for 5 days (10)	Active tDCS reduced auditory and verbal hallucinations	42
Palm et al., 2016 (44)	Sham 10 Active 10 Total 20	L DLPFC	2 mA	10 min/day for 5 days (10)	Active tDCS reduced negative symptoms	81
Smith et al., 2015 (45)	Sham 16 Active 17 Total 33	L DLPFC	2 mA	20 min/day for 5 days (5)	Active tDCS improved cognition; no effects on psychiatric symptoms or smoking	84
Transcutaneous vagus nerve stimulation (tVNS)						
Hasan et al., 2015 (46)	Sham 10 Active 10 Total 20	Vagus nerve	25 Hz, 250 μs pulse width, 0.1–10 mA	Morning to bedtime, daily for 12 weeks (84)	No difference between active and sham tVNS in schizophrenia symptoms	84

[a] L, left; R, right; DLPFC, dorsolateral prefrontal cortex; TPJ, temporoparietal junction; mA, milliamperes; s, second(s); min, minutes; wk, week(s).
[b] Some studies included unblinded components; only double-blind outcomes are reported here.
[c] The 21-item quality checklist was developed (see the online data supplement) on the basis of GRADE scoring guidelines (20). The same criteria were applied to all clinical trials reviewed. The quality score is a summary score (0%–100%, rounded to the nearest whole number) calculated for each trial, based on the number of quality indicators that were present, with 100% reflecting the highest quality rating. Each published report was independently reviewed and scored by at least two coauthors; group discussion took place to resolve discrepancies and achieve consensus scoring for all indicators on all studies.
[d] This study describes two pilot studies, reported together; the first used unilateral and the second utilized bilateral stimulation, in both cases with goals of inhibition of the TPJ and stimulation of the DLPFC.
[e] This study included participants (8 active, 7 sham) previously described in the 2012 clinical trial report by Brunelin et al. (40).

attention deficit hyperactivity disorder, and several case series or open-label studies suggested potential efficacy of tCS for working memory in posttraumatic stress disorder (PTSD) (63) and symptoms of comorbid PTSD and major depressive disorder (64). There are also a growing number of studies for nonpsychiatric conditions that may be of interest to psychiatrists, described elsewhere (14, 65).

SECTION 3: POTENTIAL RISKS OF tCS

The majority of tCS devices used in the trials we reviewed are not FDA-cleared for psychiatric disorders. The exceptions are CES devices that are FDA-cleared for insomnia, depression, and anxiety. Purchase of CES devices requires a written authorization from a licensed health care practitioner (who may be an acupuncturist, chiropractor, or pharmacist). CES devices should be safe when used according to the manufacturer's instructions, although CES device instructions may lack detail regarding aspects of use. Regarding tDCS risks, a recent review found no evidence of brain injury when applied using conventional parameters (≤40 min, ≤4 mA, ≤7.2 C) (66). However, this review included only data from published tDCS clinical research trials and therefore excludes information from unsupervised use outside of research protocols.

The perceived safety of tCS has led to both direct-to-consumer sales and do-it-yourself (DIY) construction kits for tCS systems. Direct-to-consumer devices are commercial systems marketed and sold to consumers without a requirement for any involvement by a health professional, whereas

TABLE 3. Quality of Randomized Controlled Trials (N=3) of Transcranial Direct Current Stimulation (tDCS) for Dementia[a]

Study	N per Group	Anatomical Target(s)	Stimulation Strength	Session Duration and Frequency (Total Sessions))	Dementia Type	Main Findings[b]	Quality Score (%)[c]
Boggio et al., 2012 (47)	Total 15[d]	Temporal cortex	2 mA	30 min for 5 days (5)	AD	No difference on most measures; active tDCS improved visual recognition	52
Manenti et al., 2016 (48)	Sham 10 Active 10 Total 20	DLPFC[e]	2 mA	25 min/day, 5 days/wk for 2 wk (10)	PD	No difference between active and sham tDCS in motor ability or depressive symptoms	42
Suemoto et al., 2014 (49)	Sham 20 Active 20 Total 40	L DLPFC	2 mA	20 min/day, 3 days/wk for 2 wk (6)	AD	No difference between active and sham tDCS in apathy	68

[a] L, left; DLPFC, dorsolateral prefrontal cortex; mA, milliamperes; min, minutes; wk, week(s); PD, Parkinson's disease; AD, Alzheimer's disease.
[b] Some studies included unblinded components; only double-blind outcomes are reported here.
[c] The 21-item quality checklist was developed (see the online data supplement) on the basis of GRADE scoring guidelines (20). The same criteria were applied to all clinical trials reviewed. The quality score is a summary score (0%–100%, rounded to the nearest whole number) calculated for each trial, based on the number of quality indicators that were present, with 100% reflecting the highest quality rating. Each published report was independently reviewed and scored by at least two coauthors; group discussion took place to resolve discrepancies and achieve consensus scoring for all indicators on all studies.
[d] All participants received active and sham stimulation in a counterbalanced design.
[e] Stimulation was delivered contralaterally to the most affected side.

DIY devices are made by an individual for private use (i.e., with store-bought or homemade components), although where one category ends and the other begins is not clear (67). Because they have electronic components, direct-to-consumer devices for tCS must conform to certain regulatory standards regarding protections against shock and radiofrequency interference. However, the FDA regulates neither direct-to-consumer nor DIY devices, as these devices are not intended (at least explicitly) to provide specific medical benefits. Described in popular press as "jumper cables for the mind" and by companies as a way to "overclock your brain" (68), many direct-to-consumer tCS systems priced in the range of $100–$400 (U.S. dollars [USD]) are advertised as capable of promoting general "brain health" benefits. Discussed below are the three major risks associated with unsupervised tCS: device-related injury, cognitive effects, and treatment interference.

Device-Related Risks

The classic risk when stimulating the brain is seizure generation, although the energy used in tCS is orders of magnitude lower than in ECT (e.g., 800 mA) or rTMS (66). Therefore, seizures would be very unlikely in the absence of intracranial pathology. Additionally, the interaction between tCS and metal in the head or neck represents a major unknown risk. Most tCS studies excluded participants with head or neck metal, which could divert and adversely focus applied currents. While tCS in patients with head or neck metal may be safe in some cases, it should not routinely be considered outside of specialized research-based settings.

Perhaps the greatest device-related risk is skin burns from excess energy, although these are generally preceded by pain and redness as warning signs (6). Recent studies, with experienced investigators using devices with adequate safety features, have not resulted in skin burns, e.g., the study by Brunoni et al. (4). Self-administration of tCS by untrained individuals may present greater burn risk. A closely related risk is delivering more (or less) current than desired. Direct-to-consumer devices typically do not include instructions for the consumer to calibrate or otherwise assess the function of the device. Of concern, a growing community of DIY enthusiasts is building and using their own devices for noninvasive brain stimulation. For example, a 2015–2016 Internet search we did yielded five DIY device designs that could be constructed for $50–$100 USD and would likely be capable of delivering 1–2 mA. DIY interest is growing; a user support website with 2,700 registered users in 2013 (69) had grown to over 8,700 in 2016. Purported uses include improving mood and anxiety symptoms, enhancing exercise endurance, and gaining an edge in online gaming. Accessible plans for DIY devices did include multiple statements about safety precautions in building and using the device. Such disclaimers may protect DIY proponents from liability (69), but the information is likely insufficient for patients. Furthermore, since the FDA does not regulate direct-to-consumer devices or DIY device construction documents, serious adverse events may be occurring but are not reported: one DIY tCS website included subjective descriptions of migraines, photophobia, vivid dreams, increased anxiety, and possible mania. Such reports represent important safety information that is otherwise not recorded.

Risk of Adverse Cognitive Effects

Although claims that tCS improves brain function have been made (50–52), stimulation may also impair cognition (70). It may induce a functional trade-off, improving a single cognitive function at the cost of impairing another. For example,

TABLE 4. Quality of Randomized Controlled Trials (N=6) of Transcranial Direct Current Stimulation (tDCS) for Substance Use Disorders[a]

Substance and Study	N per Group	Anatomical Target(s)	Stimulation Strength	Session Duration and Frequency (Total Sessions)	Main Findings[b]	Quality Score (%)[c]
Cocaine						
Batista et al., 2015 (53)	Sham 19 Active 17 Total 36	L DLPFC	2 mA	20 min/day, every other day for 5 days (5)	Active tDCS reduced craving	62
Conti et al., 2014 (54)	Sham 6 Active 7 Total 13	Frontopolar cortex	2 mA	20 min/day, every other day (5)	No difference between active and sham tDCS on cocaine use	58
Smoking						
Boggio et al., 2009 (55)	Total 27[d]	L & R DLPFC	2 mA	20 min/day for 5 days (5)	Active tDCS reduced craving	42
Fecteau et al., 2014 (56)	Total 12[d]	R DLPFC	2 mA	30 min/day for 5 days (5)	Active tDCS reduced number of cigarettes smoked	58
Alcohol						
Da Silva et al., 2013 (57)	Sham 7 Active 6 Total 13	L DLPFC	2 mA	20 min, once a week for 5 wk (5)	Active tDCS reduced depressive symptoms and craving	58
Klauss et al., 2014 (58)	Sham 17 Active 16 Total 33	L & R DLPFC	2 mA	13 min, twice a day for 5 days (10)	Active tDCS reduced relapse	68

[a] L, left; R, right; DLPFC, dorsolateral prefrontal cortex; mA, milliamperes; min, minutes; wk, week(s).
[b] Some studies included unblinded components; only double-blind outcomes are reported here.
[c] The 21-item quality checklist was developed (see the online data supplement) on the basis of GRADE scoring guidelines (20). The same criteria were applied to all clinical trials reviewed. The quality score is a summary score (0%–100%, rounded to the nearest whole number) calculated for each trial, based on the number of quality indicators that were present, with 100% reflecting the highest quality rating. Each published report was independently reviewed and scored by at least two coauthors; group discussion took place to resolve discrepancies and achieve consensus scoring for all indicators on all studies.
[d] All participants received active and sham stimulation in a crossover design.

one study of healthy individuals found tDCS improved the learning of new associations at the cost of worse performance of old ones (71). Another reported that tDCS increased mathematics performance but reduced executive function (72). These effects may be greater in psychiatric patients, whose cognitive reserve may be reduced as a consequence of illness. Specific electrode configurations may also be associated with adverse cognitive effects. Several studies described learning and working memory impairments when the tDCS cathode was applied over the parietal lobe or cerebellum (73, 74), and another found reduced cognitive performance when the tDCS anode was placed over the DLPFC (i.e., the configuration used by the vast majority of tDCS studies) (70). Worsened working memory has also been reported after use of a commercial tDCS device (75).

Risk of Interference With Psychiatric Treatment

The ostensibly benign profile of tCS could lead patients with mental illness to substitute stimulation for evidence-based care. In a large-scale survey of the DIY community, depressive symptoms were cited as a common reason for trying tCS. Less than half (44%) of those using tCS for a medical condition were seeing a physician for that same condition (69). As reviewed in Section 2, only a small handful of studies systematically evaluated the effects of stimulation concurrent with psychopharmacology or psychotherapy. Given that tCS effects are likely state-dependent, the field should expect to find significant, unexpected, and potentially harmful interactions between tCS and other interventions. As described above, Brunoni et al. (4) described an elevated rate of conversion from depression to hypomania in participants receiving tDCS and sertraline. As tCS becomes widely available to consumers, more patients with a bipolar diathesis may try it and switch into a (hypo)manic state. Clinicians might erroneously attribute the change in mood state to pharmacotherapy, thereby removing a potential treatment option. Several of the reviewed substance abuse studies showed an increase in cravings or related symptoms (57, 59–61), suggesting that occult tCS could attenuate the efficacy of substance abuse treatment. Therefore, unreported or unsupervised tCS may pose a significant risk to patients by interfering with evidence-based psychiatric treatments.

SUMMARY: EFFICACY AND SAFETY OF tCS IN PSYCHIATRIC DISORDERS

Our review of tCS randomized controlled trials pointed to many cases of inadequate blinding and lack of standardized environment. Only tDCS for major depressive disorder has consistently demonstrated positive therapeutic effects, with the caveats that risk of (hypo)mania needs to be studied further and that longer-term outcomes have yet to be

evaluated. It is important to note that positive tCS studies require replication, and the precise interactions among stimulation, antidepressant medication, and psychotherapy (or other cognitive states surrounding stimulation) are unknown. Data regarding tCS for other psychiatric disorders demonstrate negative or mixed results, with some evidence of harm in individuals with substance use disorders. One potential explanation for these outcomes is the overapplication of simplistic neurophysiologic principles. Expectations that a specific tCS electrode montage will be "excitatory" or "inhibitory" to a given brain region or cognitive function may not be appropriate for the more complicated neural pathology that characterizes psychiatric disorders.

The majority of tCS clinical trials in this review utilized tDCS, which, when delivered by experienced research teams to medically healthy patients, is associated with a relatively benign side effect profile. However, in a recently published letter, a group of researchers with extensive experience in noninvasive brain stimulation summarized concerns about unknown risks of tDCS, emphasizing 1) "Stimulation affects more of the brain than a user may think," 2) "Stimulation interacts with ongoing brain activity, so what a user does during tDCS changes tDCS effects," 3) "Enhancement of some cognitive abilities may come at the cost of others," 4) "Changes in brain activity (intended or not) may last longer than a user may think," 5) "Small differences in tDCS parameters can have a big effect," 6) "tDCS effects are highly variable across different people," and 7) "The risk/benefit ratio is different for treating diseases versus enhancing function" (76).

It is possible that future tCS modalities may demonstrate clinical efficacy (or greater potential for harm) for psychiatric disorders. A search of ClinicalTrials.gov found over 450 registered studies using tCS for psychiatric disorders, dwarfing the number of studies in this review. Burgeoning research activity demonstrates a significant interest in the therapeutic potential of tCS and the rapid development of this field. Research into mechanisms of action, findings generated in other types of clinical samples, and a variety of sources of clinical information will continue to shape the evidence base surrounding tCS.

At this time, enthusiasm for tCS in clinical practice settings should be mitigated by the fact that there are no tDCS devices with FDA clearance for treatment of psychiatric disorders. Devices cleared for other indications (e.g., iontophoresis) were utilized in some clinical tDCS studies, while other trials used devices that are only available for purchase and use in research protocols. Translating the tDCS literature into guidelines for tCS in clinical practice is thus complex. Further, tCS devices that do have FDA clearance (e.g., CES devices manufactured by Fisher-Wallace, Alpha-Stim) either have not shown efficacy in recent published trials or have only limited support arising from low-quality data. While conclusions from this review reflect the perspective of clinicians working and practicing in the United States, other considerations may exist for our international colleagues. If eventually proven safe and effective, with appropriate regulatory controls and guidelines for clinical monitoring, the relative ease of use and abundant access to devices could render tCS a broad-reaching and important advance in mental health care.

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