Transcranial Electrical Stimulation for Psychiatric Disorders in Adults: A Primer

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Transcranial electrical stimulation (tES) comprises noninvasive neuromodulation techniques that deliver low-amplitude electrical currents to targeted brain regions with the goal of modifying neural activities. Expanding evidence from the past decade, specifically using transcranial direct current simulation and transcranial alternating current stimulation, presents promising applications of tES as a treatment for psychiatric disorders. In this review, the authors discuss the basic technical aspects and mechanisms of action of tES in the context of clinical research and practice and review available evidence for its clinical use, efficacy, and safety. They also review recent advancements in use of tES for the treatment of depressive disorders, schizophrenia, substance use disorders, and obsessive-compulsive disorder. Findings largely support growing evidence for the safety and efficacy of tES in the treatment of patients with resistance to existing treatment options, particularly demonstrating promising treatment outcomes for depressive disorders. Future directions of tES research for optimal application in clinical settings are discussed, including the growing home-based, patient-friendly methods and the potential pairing with existing pharmacological or psychotherapeutic treatments for enhanced outcomes. Finally, neuroimaging advancements may provide more specific mapping of brain networks, aiming at more precise tES therapeutic targeting in the treatment of psychiatric disorders.

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Psychiatric disorders represent a public health concern, accounting for a significant portion of the general burden of disease—7.4% globally (1). Unfortunately, of those treated, only few patients respond to first-line pharmacological treatments (2). Also, both treatment resistance (3) and treatment-limiting adverse effects (4) are common, as well as high recurrence rates (5). Further, psychiatric disorders often occur comorbidly with other medical conditions, posing additional challenges for pharmacological treatments (6). Moreover, treatment challenges include overall access to providers and feasibility in treatment delivery, especially for psychotherapeutic options, and lack of treatment adherence (7). Together, these challenges underscore the critical need to identify alternative treatment approaches.

The current unmet need for treatment has led to increasing development and evaluation of noninvasive brain stimulation (NIBS), expanding the body of knowledge concerning the role of neural circuits that underlie psychiatric disorders (8), and highlighting the potential of NIBS as candidate interventions for these disorders (9, 10). Specifically, once a target neural circuitry has been identified as a related region of interest for a psychiatric disorder, NIBS could be used to selectively modify activities in the target region (11).

Among NIBS modalities, low-intensity transcranial electrical stimulation (tES) has been one of the most intensively investigated for both research and clinical applications, with particular promise for the treatment of psychiatric disorders (12). The most common tES technique is transcranial direct current stimulation (tDCS), in which a constant, low-amplitude current is delivered through electrodes placed on the scalp to the regions of interest. Related techniques in development include transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) (13). A strong record of safety and tolerability has been established for the use of tDCS, associated with only mild and transient side effects (e.g., tingling and redness at site of electrode, mild skin erythema [14]), and no serious adverse event has been reported across clinical trials to date. Skin lesions under the electrodes may occur but are rare and can be prevented by proper electrode preparation (14, 15).

Although each NIBS modality is uniquely advantageous over another, depending on the intended goal, tDCS presents some important advantages as treatment for psychiatric disorders. For example, compared with approaches that have shown high efficacy but that are in-clinic only, such as repetitive TMS (rTMS), tES devices can be portable

and are relatively inexpensive and therefore suitable for use in protocols where treatment is self-administered in the home setting (9, 16–18).

The potential uses of tES as a novel treatment approach for psychiatric disorders have been discussed elsewhere (12, 17, 19, 20). Yet, because tES is an area of recent and rapid scientific and technological development, knowledge of and familiarity with its use in clinical settings remain limited among mental health professionals (21). Thus, in this review, recent research examining the use of tES and its implications for the treatment of common psychiatric disorders in adults are discussed, primarily focusing on clinical findings of relevant controlled trials and meta-analyses (Table 1) (22–26).

BASIC TECHNICAL ASPECTS

A tES device is generally composed of the following items (27): a microprocessor-controlled current source, a battery compartment with single-use batteries or a power outlet electrical cable for recharging the device, connection cables most commonly leading to an anode (red cable) and a cathode (blue cable) electrode, conductive rubber pads for the electrodes (which are sites of electrochemical reactions and should not be in direct contact with the skin), saline-saturated sponges to cover the rubber pads (alternatively, the sponges or rubber or silicon pads can be coated in gel or conductive cream), and nonconductive headgear, such as

straps (28), to fix the electrodes over desired cranial locations (13) (Figure 1). The number, size, and positions of the electrodes are called montage (29). Typically, the term "electrode" refers to the rubber electrodes and the sponge together (29).

The anode is the electrode where positive current enters the body, and the cathode is the electrode where positive current exits the body (29, 30). In tDCS, the anode electrode and cathode electrode are fixed and defined, and these terms are used to describe the placement of each respective electrode. In tACS, because current regularly changes direction (with a timing defined by the stimulation frequency), the anode and cathode are not well defined—and so these terms are not used in tACS. In tRNS, the amplitude and direction fluctuate rapidly and irregularly (29).

Nonfocal brain current flow is an attribute of a larger electrode surface area, which in the most traditional montages, ranges from 25 cm^2 to 35 cm^2 per electrode (31), although the effects on the brain suggest electrode position-specific outcomes (32, 33). The alternate technique of high-definition tDCS or tACS (HD-tDCS, HD-tACS, respectively) uses electrodes with a smaller surface area (<1 cm in diameter) arranged in an array. For example, the 4×1 ring array increases the focality of the brain current, allowing noninvasive targeting of cortical regions (31, 34), whereas other HD-tDCS and HD-tACS configurations can target deeper regions simultaneously (35).

TABLE 1. Summary of recent meta-analyses and a randomized controlled trial of studies of transcranial direct current stimulation as a treatment for psychiatric disorders

Study, disorder, and measure	GRADE[a]	N of articles	N of participants	Test[b]	95% CI
Meta-analysis					
Razza et al., 2020 (22)	Low	25	1,092	Hedges' g=0.46	0.22, 0.7
Depression					
Depression improvement					
Response rate	Low	18	942	OR=2.28	1.52, 3.42
Remission rate	Low	18	942	OR=2.12	1.42, 3.16
Cheng et al., 2020 (23)					
Schizophrenia					
Positive symptoms	Low	14	566	SMD=0.17	0.001, 0.33
Negative symptoms	Low	14	566	SMD=0.43	0.11, 0.75
Kim et al., 2021 (24)					
Alcohol use disorder					
Alcohol craving	Low	17	820	Hedges' g=0.33	0.08, 0.58
Alcohol consumption	Low	5	321	Hedges' g=0.19	0.01, 0.37
Kang et al., 2019 (25)					
Nicotine use disorder					
Cue-provoked craving	Low	7	173	SMD=0.42	0.13, 0.71
Smoking intake	Low	8	287	SMD=0.56	0.17, 0.94
Randomized controlled trial[c]					
Silva et al., 2021 (26)					
Obsessive-compulsive disorder (OCD)					
OCD symptoms	—	—	43	Cohen's d=0.62	0.06, 1.18
Depression symptoms	—	—	43	Cohen's d=0.43	−0.06, 0.92
Anxiety symptoms	—	—	43	Cohen's d=0.48	−0.02, 0.97

[a] GRADE, Grading of Recommendations, Assessment, Development and Evaluation. A system for grading evidence and recommendations.
[b] OR, odds ratio; SMD, standardized mean difference.
[c] GRADE does not apply to the randomized controlled trial.

Current intensity is measured in amperes, which quantifies the rate of electric charge that passes through a specific point every second. In conventional tDCS, where two electrodes are used, the direction of current in the anode is the opposite of the current in the cathode, and the intensity is the same as both electrodes. If multiple electrodes are used, such as in HD-tDCS, the intensity is calculated by the sum of the current in all anodes, in opposition to all cathodes (14). Furthermore, electrode current density is calculated by dividing current intensity by the area of the electrode (e.g., 2 mA divided by 25 cm^2 yields an electrode current density of 0.08 mA/cm^2). The electrode montage, current, and duration of a tES session are the most important parameters that define stimulation dose (13, 36).

tES generally uses very weak electrical currents (in the order of a few milliamperes [mA]). Furthermore, only a small fraction of the current reaches the brain, with its greater part being deflected across the skin, connective tissue, muscles, skull, meninges, and cerebrospinal fluid, which all can divert current before it reaches the brain. The aggregate of all the resistance to current flow presented by the head is referred to as impedance or resistance (27, 37). Importantly, impedance (measured in ohms) then reflects the properties not only of the head but also of the electrodes in contact with the skin. In this way, when contact between the device and the head is poor at the electrodes, a high impedance may be detected by the tES device. High impedance levels are often associated with poor conductivity, reflecting a suboptimal electrode setup or humidification (38). To avoid high impedances, the sponges should always be properly humidified but never in excess, for if the solution spreads over the scalp, the current will likewise spread over a large superficial area and will not flow properly across the desired brain regions (13). The certified tES devices measure not only current intensity but also impedance and, for safety, warn the applicator or stop the current flow if too much impedance in the circuit is detected (13).

Definitive and optimal tDCS parameters for psychiatric research and clinical practice are still in development, as these parameters may depend on patient characteristics (39). Preliminary evidence suggests that increasing frequency of sessions, session duration, or current intensity might be associated with better clinical response (39), especially with concurrent and directed mental activity (i.e., "target engagement" [40]). Importantly, higher levels of total tDCS exposure (i.e., cumulative charge) have not been associated with greater adverse events (41).

Basic knowledge of these parameters is a prerequisite to operate a tES device. Although tES devices (especially for tDCS sessions) are typically straightforward and safe (14), it is important that certified equipment is used and that established protocols are followed by trained staff (13, 15). Some devices are designed to be especially portable and simple to use (42) and thus potentially adaptable for home use, provided there is proper patient training and remote supervision by clinical or research staff (18, 43).

FIGURE 1. A transcranial direct current stimulation (tDCS) device applied to a phantom head model, with the anode over F3 and the cathode over the right supraorbital area[a]


[a] Source: Soterix Medical Inc.

MECHANISMS OF ACTION

One main distinction that separates the tES modalities from one another is the waveform (temporal pattern) in which the electrical current is applied (Figure 2). In tDCS, a continuous, direct electrical current of low intensity (e.g., typically up to 1–3 mA) passes through at least two electrodes (i.e., anode and cathode) that are applied noninvasively over the scalp (14). tACS, unlike tDCS, delivers an oscillating, sinusoidal electrical current of low intensity (i.e., typically spanning 1–2 mA or less) to the brain via two electrodes applied on to the scalp, whose position and size are determined based on the target region of the brain (29, 44). The method in applying conventional tACS is largely similar to tDCS, with the electrical current delivered via electrodes and saline-saturated sponges.

tDCS modulates neuronal activity on the network level by producing current flow around neurons, which results in an incremental shift in neuronal membrane potentials (e.g., polarization [45]) and which, in turn, leads to a host of neuronal function changes, such as a change in firing rates (20, 29, 46). These modulation effects may last after the stimulation period, potentially up to 0.5–2 hours, depending on the intensity and duration of stimulation due to changes in synaptic neuroplasticity (i.e., via mechanisms that resemble either long-term potentiation or depression) (47, 48). In addition, the direction of current flow (i.e., parallel or perpendicular to the underlying pyramidal neurons of the stimulation sites [49, 50]) is one of the key determinants of the desired neuromodulatory effects, along with dosage (i.e., current density and duration of stimulation), polarity, size, and placement of the electrodes (19, 20).

tACS, in contrast, is considered to entrain neuronal oscillations to the stimulation frequency by producing an oscillating polarization of neurons (51–53). tACS may also

FIGURE 2. Current patterns of transcranial electrical stimulations
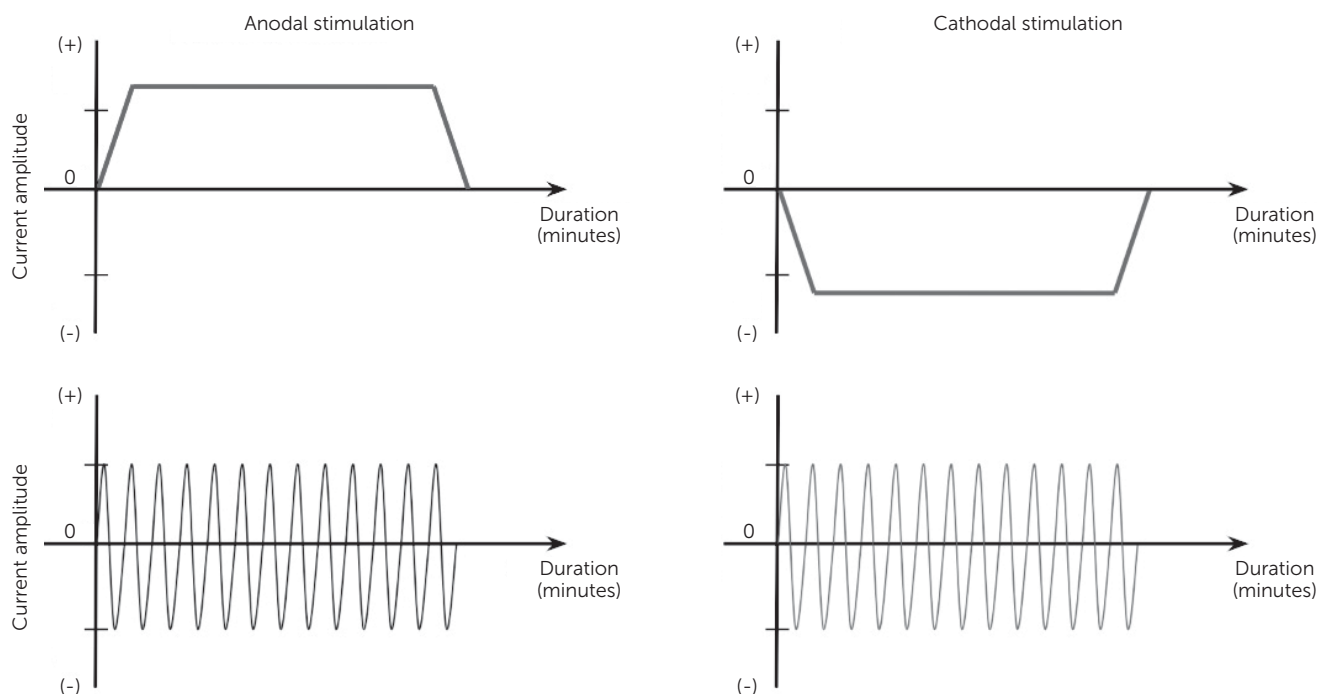
produce changes in brain function outlasting the stimulation duration (54–56). During the half cycle of an AC oscillation, one electrode acts as the anode while the other acts as the cathode, and vice-versa for the other half cycle (57).

Modulation achieved by tDCS and tACS is considered network based within the functionally connected regions beyond the superficial cortical regions, thus presenting more functionally specific stimulation, which can modulate task-relevant brain networks that may yield strong implications for clinical use (12, 17, 19, 20, 58).

In summary, tDCS and tACS present unique neuromodulation options whether the goal is a more functionally or spatially specific target. These techniques are capable of modulating or stimulating task-related neural networks, and as such, they may allow modulation or normalization of dys-regulated neural activity that is associated with specific psychiatric disorders. This review focuses on the use of tDCS in treatment of psychiatric disorders (Figure 3) (59).

CLINICAL USES OF tDCS FOR PSYCHIATRIC DISORDERS

Depressive Disorders

Major depressive disorder is one of the main causes of disability and morbidity worldwide, besides being one of the most prevalent psychiatric disorders (60). First-line treatments, such as psychotherapy and antidepressant drugs, are, respectively, time-consuming and can present several adverse events (6). In such a scenario, tDCS can

serve as an alternative treatment for major depressive disorder and could be provided as a first-line treatment for patients who do not wish to take medications or undergo psychotherapy.

The neurobiological rationale for using tDCS as the treatment for major depressive disorder is based on evidence of an interhemispheric functional asymmetry in depressive states that leads to a hypoactivation of the left dorsolateral prefrontal cortex (DLPFC) and hyperactivation of the right DLPFC (61). Therefore, the trials investigating the effects of tDCS for depression typically apply the anode over the left DLPFC (which corresponds to the F3 position of the 10–20 electroencephalogram [EEG] system), while the cathode is placed either over the right DLPFC (F4 in the 10–20 system) or the supraorbital area (22, 46).

In the first trial evaluating the clinical efficacy of tDCS for major depressive disorder, five sessions of tDCS over the left (anode) and right (cathode) DLPFC of 10 patients were conducted, and the study found significant symptom improvement in the active group (62). The initial positive results of tDCS for major depressive disorder subsequently led to several larger randomized controlled trials (RCTs) in unipolar and bipolar depression. A larger trial was conducted to investigate the safety and efficacy of tDCS alone and combined with sertraline 50 mg per day (SELECT-TDCS trial), in which tDCS was applied bilaterally (anode over F3 and cathode over F4) for 12 sessions (63). tDCS effects were similar to those of sertraline and superior to those of placebo or sham, whereas the combination of tDCS

and medication led to a significantly greater effect, compared with placebo or sham (63). The largest trial to date of tDCS for unipolar depression (ELECT-TDCS trial), a noninferiority study that included 245 patients, assessed the efficacy of tDCS with the maximally effective dose (20 mg per day) of escitalopram (64). The participants were randomly assigned to three groups: active tDCS plus placebo medication, sham tDCS plus real medication, or sham tDCS plus placebo medication. The superiority analyses showed that tDCS was inferior to escitalopram in reducing depressive symptoms, although superior to sham.

Further studies performing secondary analyses with data derived from the ELECT-TDCS trial increased the understanding of the clinical aspects of both tDCS and pharmacotherapy for major depressive disorder. Overall, these results suggest that both interventions produce distinct effects in depressive symptoms and point to important directions that can optimize tDCS response. Studies applying machine learning, symptom clustering, and distinct-trajectory approaches showed that tDCS response might be improved in specific subgroups of patients. For instance, patients presenting insomnia or sleep symptoms and negative affect may benefit more from tDCS treatment, and older and more anxious patients may respond faster to the treatment (65–67).

Moreover, the effects of tDCS for bipolar depression were also assessed. First, an RCT with 59 participants who were allocated to a sham or an active group showed a significant improvement of depressive symptoms and sustained response for the tDCS group, compared with sham (68). However, a recent multicentric trial with 130 patients with unipolar and bipolar depression did not show significant differences between active and sham groups regarding symptom improvement and response rates (69). Nevertheless, these results might be justified by the sham method, which was found to elicit biological effects by itself (41), in addition to improvement in depressive symptoms (Hedges' g=1.09, 95% confidence interval [CI]=0.8–1.38 [70]). Such effects are currently viewed as a possible hidden source of variability among tDCS studies (71). Although mixed effects were found in studies of tDCS for depression in past years, results of recent aggregate and individual patient data (IPD) meta-analyses corroborated tDCS as having a moderate effect for depression (22, 72). Both aggregate and IPD meta-analyses have found a medium effect size favoring active tDCS over sham for continuous

FIGURE 3. Transcranial direct current stimulation electrodes position and the current flow direction for each psychiatric disorder[a]
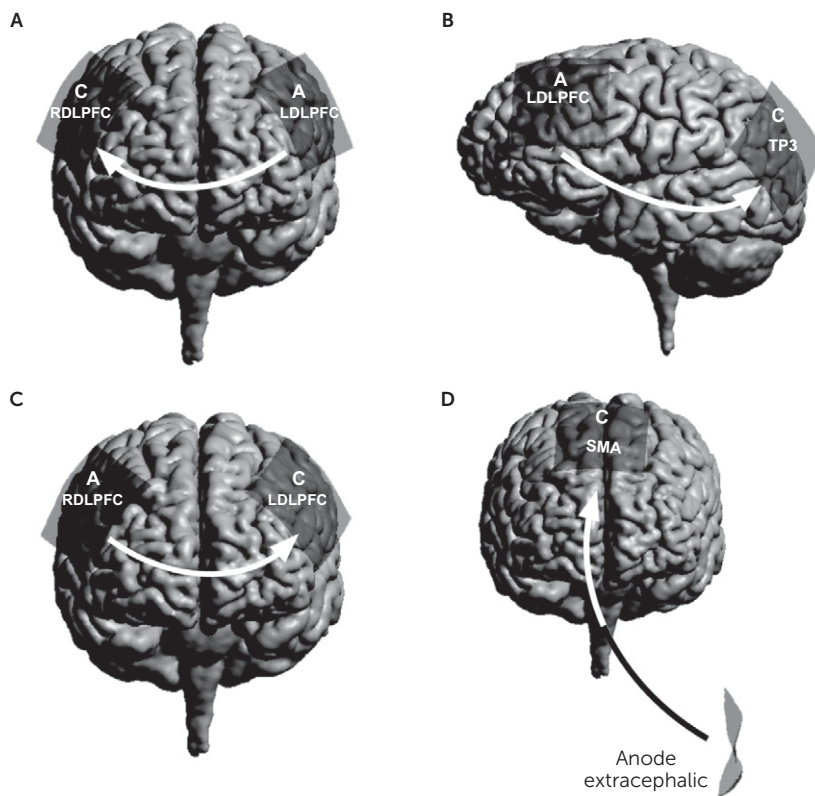
[a] A, anode; C, cathode; RDLPFC and LDLPFC, right and left dorsolateral prefrontal cortex, respectively; SMA, supplementary motor area; TP3, left temporoparietal junction. Panel A, depression; panel B, schizophrenia; panel C, substance use disorders (alcohol and cigarettes); panel D, obsessive-compulsive disorder.

outcomes after the acute treatment period (N=25, Hedges' g=0.46, 95% CI=0.22–0.70 and N=9, β=0.31, 95% CI=0.15–0.47) and both response and remission rates favoring the active group (72). Moreover, subgroup analyses showed that tDCS presented similar efficacy for both unipolar and bipolar depression (22, 73).

The follow-up effects of tDCS for depression were less investigated to date, with high design heterogeneity observed among the trials, which involved mixed follow-up duration and number of sessions (from nine to 48). A recent meta-analysis conducted to investigate the evidence of the tDCS follow-up effects for depression identified that interventional studies (with tDCS during the follow-up period) might lead to greater symptom improvement after the acute treatment (74), compared with observational follow-ups.

Although research evidence suggests feasibility and efficacy of clinical implementation of tDCS in treatment of depression, official recommendations for tDCS in clinical practice vary from country to country, and the field has been urged to create formal, uniform guidelines. Recently, a guideline focusing on the therapeutic use of tDCS for both neurological and psychiatric disorders considered anodal tDCS on the left DLPFC to be effective (level A) in

improving symptoms in major depressive disorder (17), without differentiating its efficacy for drug-resistant patients, as in a previous guideline (46). However, no specific recommendations were made regarding cathode position, which was either at F4 or right supraorbital in most studies. In this regard, and taking into consideration the favorable safety profile, the National Institute for Health and Care Excellence guidelines recommend tDCS for the treatment of major depressive disorder in the United Kingdom, with written consent by patients, and special arrangements for clinical governance and careful record of selected parameters.

Schizophrenia

Schizophrenia is a chronic neuropsychiatric disorder characterized by positive (e.g., hallucinations) and negative (e.g., anhedonia) symptoms (75). The first-line treatment consists of pharmacotherapy with antipsychotics. However, this class of drugs primarily targets positive symptoms, with modest effectiveness at best, and is limited in the management of negative and cognitive symptoms (76). Furthermore, poor adherence and intolerable side effects are common even with newer antipsychotics, often leading to discontinuation and poor clinical outcomes (77).

Functional neuroimaging studies in patients with schizophrenia demonstrate hyperactivity in the left temporoparietal junction (TP3), a cortical area relevant for language or speech perception that is related to auditory verbal hallucinations (78). Negative symptoms, however, have been linked to deficits in prefrontal activity and its connectivity to other cortical areas and also to subcortical structures (79). Thus most employed NIBS protocols are aimed at decreasing cortical activity in the left temporoparietal junction, increasing the activity of the left DLPFC, or both.

The first RCT investigating the effects of tDCS in schizophrenia recruited 30 subjects diagnosed as having auditory verbal hallucinations and applied 10 tDCS sessions (twice a day for 5 days), with the anode positioned at F3 and the cathode at TP3 (80, 81). At follow-up, clinical improvement both for positive and negative symptoms was superior in the active group, compared with sham. Subsequent studies with the same stimulation protocol further supported its efficacy (82, 83). On the other hand, RCTs that applied bilateral tDCS targeted at the frontal lobes, with anode at F3 and cathode either on F4 or Fp2, showed nonsignificant results for positive or negative symptoms (84, 85). Another trial that positioned the anode over the left DLPFC and the cathode over TP3 did not show reduction in the severity of positive symptoms (86). The delivery of a single daily session, contrary to two daily sessions in prior RCTs, might explain the null effects in that trial, because the other parameters of stimulation were similar. In a recent meta-analysis (10 RCTs, 338 participants), the superiority of active tDCS over sham regarding the reduction of auditory verbal hallucinations emerged only in a subgroup analysis that included studies that performed either twice daily sessions or 10 or more sessions overall, suggesting that the delivery of a higher number of sessions is associated with greater efficacy (standardized mean difference [SMD]=1.04, 95% CI=0.20–1.89, p=0.02 and SMD=0.86, 95% CI=0.22–1.51, p=0.009, respectively) (87).

A later meta-analysis (14 RCTs, 566 participants), however, showed a marginal superiority of active tDCS, compared with sham, in positive symptoms (SMD=0.17, 95% CI=0.001–0.33), with a greater improvement of negative symptoms (SMD=0.43, 95% CI=0.11–0.75) (23). In the largest RCT to date, 100 patients were recruited with stable negative symptoms (83); the study replicated the tDCS study originally conducted by Brunelin and colleagues (80). The anode and cathode positions were F3 and TP3, respectively, and the primary outcome was clinical evaluation 6 weeks after the end of the study. The investigators observed a greater improvement in negative symptoms in the active group, compared with sham, for both continuous outcomes and response rates. Of interest, tDCS sessions were delivered twice for only 5 days, but the improvement was greatest at the 6-week follow-up assessment and persisted for 12 weeks.

Although a few other trials have suggested that prefrontal tDCS might improve cognition in patients with schizophrenia (85, 88), findings in this domain are still preliminary. Furthermore, a recent meta-analysis indicated that active tDCS was not superior to sham regarding working memory performance in this population (89). The most current guideline on the topic specified that tDCS with the anode over F3 and the cathode over TP3 was probably effective (level B of evidence) for reducing positive symptoms (17).

Substance Use Disorders

Substance use disorders have a chronic and relapsing course, characterized by compulsive behavior aimed at drug consumption, difficulty in limiting its intake, and anxious or dysphoric symptoms if access to it is prevented (90). Nicotine and alcohol dependence rank among the most prevalent substance use disorders. For instance, in the United States, the prevalence of nicotine dependence is estimated at 14% (91, 92), with an estimated global prevalence of 100 million cases of alcohol use disorder in 2016 (93).

Management of substance use disorders aims at ceasing intake and preventing relapse, usually with multimodal approaches that include psychotherapy and pharmacological and psychoeducational interventions. Specific pharmacological treatments are currently available only for substance use disorders related to a limited number of substances, such as alcohol, nicotine, and opioids. Nonetheless, pharmacotherapy targets mainly withdrawal symptoms, having limited efficacy in preventing relapse (94).

It has been suggested that specific symptoms of substance use disorders occur as a consequence of abnormal activity in several neural circuits, which include overactivation of ascending meso-cortico-striatal dopaminergic

projections that comprise the reward system and underactivation of multiple regions in the prefrontal cortex (90). Neuromodulatory strategies aim at improving executive function and top-down inhibitory control that the prefrontal cortex exerts at the overly hyperactive reward system (95). Alternatively, stimulation may be used to reduce the negative affect in the withdrawal phase and to diminish the craving intensity.

In the first published RCT to use tDCS to treat substance use disorders, 13 patients who were diagnosed with alcohol dependence received tDCS interventions (96). In this study, participants received three distinct tDCS montages, separated by a 48-hour interval (i.e., washout period). Active interventions (anode at F3 and cathode at F4 or anode at F4 and cathode at F3) led to a significant improvement in craving symptoms after cue provocation, compared with sham.

Subsequently, two larger RCTs were conducted to better investigate the effects of reversed polarities over the DLPFC in patients with alcohol dependence, applying anode and cathode over F4 and F3, respectively (97, 98). In the first trial, 31 patients received one session of 13-minute active or sham tDCS per day, during 5 consecutive days (97). The results showed three times less relapse in the active group, compared with sham, at the 6-month follow-up . In the second study, 49 participants were recruited and received tDCS once a day, every other day, in a total of 10 sessions, (98). After treatment, significant reduction in craving was observed only for the active group, and the relapse rate in the active group was almost three times lower (27.8%) than in the sham group (72.7%) in a 3-month follow-up assessment.

In turn, separate trials were conducted to compare different electrode positions (99). Among them, two larger RCTs investigated the effects of bilateral tDCS, having the anode over F3 and cathode over F4 (99). The first trial applied four sessions in 91 participants who were allocated to three groups: active tDCS during cognitive bias modification (CBM), sham tDCS during CBM, and active tDCS separate from CBM. The results showed no significant improvements in alcohol craving or relapse with either the online or the offline CBM at endpoint and subsequently in a 3-month and 1-year follow-up. Lastly, a recent meta-analysis also showed that bilateral tDCS over the DLPFC can improve symptoms of alcohol abuse disorder (N=11, Hedges' g=0.44, 95% CI=0.10–0.79) (24).

Although few studies to date have examined tDCS as a treatment approach for nicotine dependence, several prior studies document favorable effects of tDCS for reduction in nicotine intake. A crossover trial, in which 24 patients underwent sham or active anodal tDCS over either the left or the right DLPFC, showed that both active interventions reduced craving, compared with the sham group (100). Subsequent trials also showed that both polarities (anode over the right DLPFC plus cathode over the left DLPFC and anode over the left DLPFC plus cathode over the right DLPFC) were significantly beneficial for the reduction in nicotine intake (101, 102). However, more recent large trials presented mixed results applying anodal tDCS over the left DLPFC.

Recently, a large RCT applying the anode over F3 and the cathode over the right supraorbital area in 106 participants failed to find significant differences in the daily nicotine intake rate or number of cigarettes smoked among two active tDCS groups (1 mA and 2 mA) and sham (103). Nevertheless, a recent meta-analysis (12 studies, 392 participants) investigating the effects of tDCS for nicotine dependence revealed that tDCS can decrease an individual's nicotine dependence symptoms for both cue-provoked craving (i.e., phasic increases in the urge for nicotine use induced by situational cues [104]) and nicotine intake, but positive effects on cue-provoked craving levels were driven by anodal tDCS on the right DLPFC (SMD=0.65, 95% CI=0.32–0.99; p<0.001) (25). Inconsistent findings across studies with opposite-polarity DLPFC stimulation suggest that samples might be heterogeneous regarding regional neural activity. Finally, a guideline (17) on the therapeutic use of tDCS has recommended that combining anodal tDCS of the right and cathodal tDCS of the left DLPFC is probably effective in alcohol addiction or craving symptoms (level B).

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by the presence of obsessions (intrusive and unwanted thoughts), often associated with anxiety, and compulsions (e.g., repetitive behaviors rigidly performed in response to obsessions) (105, 106). The lifetime prevalence of OCD is 2%−3%, and it is often underdiagnosed and undertreated, despite the significant impairment it causes in daily functioning (106).

First-line interventions include psychotherapy (cognitive-behavioral therapy with exposure and response prevention) and pharmacotherapy (mainly antidepressants). However, a significant proportion of patients (40%−60%) do not respond satisfactorily to initial management strategies, prompting the need of novel interventions (107). Regarding more established neuromodulatory approaches, high frequency rTMS targeted at the dorsomedial prefrontal cortex with symptom provocation has been recently approved by the U.S. Food and Drug Administration (108).

Disruptions in the functioning of neural circuits in patients with OCD include multiple cortical regions and their related cortico-striato-thalamo-cortical connections, each associated with a distinctive cluster of symptoms. Most studies of tES interventions in OCD patients target the supplementary motor area (SMA) and pre-SMA, which are important components of the sensorimotor and dorsal cognitive circuits, respectively. Abnormal neuronal hyperactivity at the SMA has been specifically linked to symptomatic behavior (i.e., compulsions), and the pre-SMA, together with other prefrontal areas, is related to disruptions in executive function and emotion regulation (106).

The first RCT to use tDCS for OCD was conducted by applying anodal or cathodal tDCS for 10 days (daily consecutive 2-mA, 20 minutes) over the pre-SMA/SMA area, with an extracephalic return electrode (commonly over the left or right deltoid) (109). In this crossover study, cathodal stimulation over SMA, but not anodal, significantly improved OCD symptoms. A subsequent parallel RCT investigated the effects of bicephalic tDCS (anode over pre-SMA and cathode over the right supraorbital area) in 25 patients with treatment-resistant OCD (110). The results showed symptom improvement in the active group, compared with the sham group. The largest clinical trial was performed with cathode over the SMA and anode over the left deltoid muscle in 43 patients over 4 consecutive weeks (20 sessions, 2-mA, 30 minutes per session) (26). There was a significant reduction in OCD symptoms for patients in the active group, which was not observed for anxiety and depression symptoms. This study, however, was not included in the most recent tDCS guideline for OCD, which indicated a level C evidence (possibly effective) recommendation for anodal stimulation of the SMA (17).

FUTURE DIRECTIONS

Home Use

Although testing clinical efficacy of tES in treating psychiatric disorders has grown exponentially in the past few years, research examining the efficacy and accessibility of patient self-administered, home-use tES is still in its infancy (9, 18, 111). tES treatments have a cumulative effect and require daily application for optimal benefit. Most studies examining the efficacy of tES in mental health have been performed primarily in clinical and research settings, where patients are required to make multiple visits to the facilities to complete the trial; this arrangement, however, poses significant financial and logistical burdens in a real-world scenario (72). The development of portable, user-friendly tES devices for home use is a highly desirable goal for increasing accessibility and reducing health disparities, particularly for patients who have limited mobility or are immunocompromised (111, 112).

Few studies to date have examined the feasibility of remotely controlled and supervised tES for home-use intervention for psychiatric disorders (9, 16, 39, 111, 113). In one open-label study, 34 patients with depression self-administered 20 or 28 tDCS sessions (2 mA, 30 minutes per session) for 4 weeks, followed by a taper phase of four sessions with 1 week apart (113). The study showed a significant reduction in depressive symptoms (114), with transient and mild side effects, similar to the lab-based applications (113). Another pilot trial of home-use tDCS, in combination with app-based psychological interventions for major depressive disorder, has also shown promising results (16). Thus, early evidence supports the feasibility and initial efficacy of self-administered, at-home use of tES, and such development could lead to a breakthrough in the use of tES in the context of clinical practice, offering scalability and wide availability. Finally, as an approach that could be easily adapted to be used at home, this modality can be an alternative to investigate the follow-up effects of tDCS for psychiatric disorders.

Individualization Approach for tES

The concept of precision medicine in psychiatry describes how personalized treatment and prevention efforts targeting individual differences and transdiagnostic mechanisms can refine and improve prevention and intervention efforts, consistent with the Research Domain Criteria (RDoC) approach proposed by the National Institute of Mental Health (9, 10). Although precision medicine is in its nascent stage, approaches derived from precision medicine have the potential to enhance treatment outcomes by identifying treatment-relevant subgroups among target clinical populations (9, 115). tES is one such candidate, which can be used independently or combined with more traditional cognitive, behavioral, or pharmacological interventions to target specific treatment mechanisms that are best suited for each individual (19, 22, 26, 46).

Ideally, tES treatments could be built on the existing neuroimaging evidence for neural circuitry associated with specific psychiatric disorders, making it a unique approach to develop personalized medicine (10). For example, in transdiagnostic approaches that characterize psychiatric disorders based on their neurobiological underpinnings, tES has the advantage of being able to target specific brain regions or neural network (10). However, due to a broad electrical current field produced by tES, which may often result in networkwide stimulations, and the complexity in identification of neurobiological underpinnings of various psychiatric disorders (e.g., comorbidity), this goal may be more difficult to achieve.

With the current state of research, optimization of tES as an individualized treatment can be accomplished by other personalized indices. More specifically, tES allows for variability in dosage and stimulation techniques (e.g., tDCS and tACS), which can then be used to identify optimal parameters and type of stimulation that are individualized to each patient (52). Further, based on individual variabilities in brain activity, closed-loop systems (e.g., tES coupled to EEG to detect brain waves) might be used to dynamically control stimulation parameters in the pursuit of improved and personalized outcomes (116).

In sum, the idea of precision medicine using tES in combination with other biomarkers that are unique to different subgroups could enhance treatment outcomes and may accelerate progress of adaptation of neuromodulation approaches as an intervention method.

Combining tES With Other Interventions for Psychiatric Disorders

Although tES has shown efficacy in monotherapy (117), when combined with other treatment methods, it may lead

to superior treatment outcomes (40, 63). In a study examining the efficacy of tDCS and pharmacological treatment for major depressive disorder, the combination of the two methods increased the efficacy of each treatment, compared with those treatments alone or sham (63). Further, several studies have demonstrated that a combination of cognitive therapy and tDCS yielded superior improvement in self-reported depressive symptoms (118, 119). Additionally, several studies that examined anxiety-related symptoms (e.g., attention bias to threat) showed that combination of tDCS and attention bias modification training reduced the attention bias to threat, compared with sham (120–122). Importantly, these multimodal therapies in psychiatry can maximize treatment outcomes when carried out carefully with the timing of delivery (e.g., simultaneous, sequential) (40). Thus, further investigation in the multimodal therapy approach is necessary for increasing treatment outcomes.

Beyond tDCS

Across clinical trials, tDCS has been more widely used for stand-alone or combined interventions. However, tACS has also been examined in recent RCTs. For major depressive disorder, 32 participants were randomly assigned to one of the three groups: tACS at 10 Hz (alpha range), tACS at 40 Hz (gamma range), or sham (123). Active electrodes were placed over the DLPFC bilaterally, with a return electrode at the vertex. Although the groups did not differ regarding depressive symptoms at 4-week follow-up (primary outcome), the group that underwent 10-Hz stimulation had a higher response rate at 2 weeks (77.8% versus 40% in 40-Hz tACS and 20% in sham). The 10-Hz stimulation protocol was also effective in engaging alpha oscillations (substitute outcome) in this feasibility study (123) and in the subsequent trial (124). In the first RCT to evaluate the effects of tACS in schizophrenia, 25 patients with medication-refractory auditory verbal hallucinations were randomly assigned to one out of three arms (tACS, tDCS, or sham) (125). Although the tACS group showed a higher symptom improvement for the primary outcome, the differences between groups were not significant, which may have been due to the small sample size of each subgroup.

With OCD, the only clinical study using tACS published to date was an open-label case series that included seven patients who received gamma stimulation (40 Hz) targeted at the DLPFC bilaterally, with improvement in all cases (126).

CONCLUSIONS

The goal of this review was to provide an overview of recent advancements in tES research, with an aim to identify its appropriate application in clinical settings as an intervention for psychiatric disorders. Research using tES in clinical samples has grown exponentially over the past decade. This body of evidence reflects substantial safety and modest efficacy of tES in clinical practice, along with its potential to help patients with resistance to existing treatment options, increasing its clinical relevance. This review suggests that most promising clinical outcomes have been documented in major depressive disorder research, along with growing evidence of its application to treat schizophrenia, OCD, and substance use disorders. Furthermore, the review has demonstrated promising technological and methodological improvements in tES that allow for greater specificity in treating specific psychiatric disorders. Future research, using a precision medicine framework, should leverage cutting-edge neuroimaging findings to improve the mapping of disruptions in specific brain networks associated with distinct psychiatric disorders to better personalize tES treatment protocols. In all, the clinical use of tES is particularly alluring for its mild side effects and its potential to be used as an independent or combined treatment method. With better understanding of its impact on and interaction with brain functions, future research can provide more standardized guidelines that are specific to each psychiatric disorder, leading to improved clinical outcomes.

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