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Review

REVIEW

Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders

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Abstract

Background: Transcranial direct current stimulation has shown promising clinical results, leading to increased demand for an evidence-based review on its clinical effects.
Objective: We convened a team of transcranial direct current stimulation experts to conduct a systematic review of clinical trials with more than 1 session of stimulation testing: pain, Parkinson's disease motor function and cognition, stroke motor function and language, epilepsy, major depressive disorder, obsessive compulsive disorder, Tourette syndrome, schizophrenia, and drug addiction.
Methods: Experts were asked to conduct this systematic review according to the search methodology from PRISMA guidelines. Recommendations on efficacy were categorized into Levels A (definitely effective), B (probably effective), C (possibly effective), or no recommendation. We assessed risk of bias for all included studies to confirm whether results were driven by potentially biased studies.
Results: Although most of the clinical trials have been designed as proof-of-concept trials, some of the indications analyzed in this review can be considered as definitely effective (Level A), such as depression, and probably effective (Level B), such as neuropathic pain, fibromyalgia, migraine, post-operative patient-controlled analgesia and pain, Parkinson's disease (motor and cognition), stroke (motor), epilepsy, schizophrenia, and alcohol addiction. Assessment of bias showed that most of the studies had low risk of biases, and sensitivity analysis for bias did not change these results. Effect sizes vary from 0.01 to 0.70 and were significant in about 8 conditions, with the largest effect size being in postoperative acute pain and smaller in stroke motor recovery (nonsignificant when combined with robotic therapy).
Conclusion: All recommendations listed here are based on current published PubMed-indexed data. Despite high levels of evidence in some conditions, it must be underscored that effect sizes and duration of effects are often limited; thus, real clinical impact needs to be further determined with different study designs.

Key Words: tDCS, clinical evidence, evidence-based medicine, neurological disorders, psychiatric disorders

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique (Woods et al., 2016) that may help treat various neurological and psychiatric disorders, even when medically refractory, for example, intractable chronic pain (Moreno-Duarte et al., 2014; Brietzke et al., 2016; Mendonca et al., 2016). tDCS trials carry a "nonsignificant risk" designation; typical side effects are transient and minor, for example, skin irritation, itching, tingling, and erythema (Brunoni et al., 2011; Bikson et al., 2019). As it is low risk, well tolerated (Aparício et al., 2016; Bikson et al., 2016), easy to use, portable (Charvet et al., 2015; Dobbs et al., 2018; Im et al., 2019), and low cost, clinicians should consider if and how to make tDCS treatment available, particularly in patients with limited options (Bikson et al., 2016).

tDCS' official regulatory status is in development in many countries (Fregni et al., 2015; Antal et al., 2017), with early EU clearances for depression and pain, and many centers worldwide use tDCS as an investigational or off-label therapy (Fregni et al., 2015). Despite hundreds of published human trials led by independent researchers free of proprietary incentives, tDCS' non-linear development path challenges its advancement as a clinical tool. In drug trials, a single company validates a proprietary compound using an organized stepwise strategy, beginning with preclinical testing and progressing through phase I, phase II, and then phase III trials if results are confirmed. Clear Go/No-Go criteria in phase I/II randomized controlled trials (RCTs) and "success" milestones in phase III drug trials (typically developed in consultation with regulatory agencies) facilitate clinical benefit assessments. Conversely, no single corporation leads tDCS development, and studies are so diverse that clinicians might struggle to assess its potential benefits or decide on therapeutic approaches.

We therefore convened an expert panel to perform an evidence-based review of tDCS' therapeutic efficacy. We emphasize that the trials are heterogeneous, utilizing varying doses, montages, adjunct treatments, and inclusion/exclusion criteria (Brunoni et al., 2012; Woods et al., 2016; Bikson et al., 2016; Ekhtiari et al., 2019). Clinicians should always refer to the original publications as any claims, limitations, or lacking or mixed evidence must be interpreted in the context of different protocols. We explain how that might work below.

tDCS Clinical Application and Mechanisms of Action

Neuromodulation by tDCS is thought to follow Hebbian Theory ("neurons that fire together, wire together") (Hebb, 1950). If presynaptic and postsynaptic neurons are both active, the result is synaptic strengthening; if one or both are inactive, either no change occurs (co-occurrence rule) or, conversely, synaptic weakening occurs if one is active while the other is inactive ("neurons out of sync delink"), but no change occurs if both are

inactive (correlation rule, anti-Hebbian) (Földiák, 1990; Artola and Singer, 1993; Pulvermüller, 2018). Neural network excitation/inhibition exists in a finely tuned balance; any abnormalities can lead to pathology (Ziemann et al., 2015). Neuroplasticity involves long-term potentiation and long-term depression, which depend on post-synaptic calcium levels, with the involvement of *N*-methyl-D-aspartate (NMDA) (Bliss and Gardner-Medwin, 1973; Rioult-Pedotti et al., 1998, 2000) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Bashir et al., 1991; Beattie et al., 2000; Malinow and Malenka, 2002), metabotropic glutamate receptors, as well as gamma-aminobutyric acid (GABA)-A and GABA-B receptors (Wigström and Gustafsson, 1983; Davies et al., 1991).

tDCS occurs via a constant electric current produced by a battery-operated current generator connected to at least 2 electrodes (anode and cathode) applied to specific head locations (or extracephalic regions in the case of the return electrodes). Most of the electric current is shunted through scalp, skull, and cerebrospinal fluid, but the remainder alters neuronal resting membrane potentials, increasing the likelihood of depolarization or hyperpolarization without inducing action potentials (El-Hagrassy et al., 2018). Polarization directionality depends on axonal/dendritic orientations within the electric field. While some literature has questioned tDCS efficacy and placebo effects given the weak current (Schambra et al., 2014) and its exact mechanisms are unclear, the abundance of adequately blinded positive sham-control RCTs speaks to tDCS' therapeutic effects.

Multiple factors can alter tDCS after-effects, including the polarity, duration, and frequency of stimulation; current density (i.e., current intensity/electrode surface area); stimulation/return electrode locations; neuroanatomy; underlying pathology/state; and co-administered drugs/treatments (Nitsche et al., 2003). Traditionally, anodal stimulation increases cortical excitability and cathodal stimulation decreases it, but the net effects depend on alterations in the overall network balance; for example, longer durations and more frequent stimulation often lead to prolonged after-effects (Nitsche and Paulus, 2001) up to a limit, after which excitation may switch to inhibition or after-effects may be shorter (Monte-Silva et al., 2010, 2013). Additionally, although tDCS' effects are maximal under the electrodes, they do influence distant neural networks directly or indirectly (Marshall et al., 2004; Ardolino et al., 2005; Lang et al., 2005; Boros et al., 2008; Kwon et al., 2008; Vines et al., 2008). To ensure maximal effectiveness (and for safety), it is important to avoid factors increasing resistance (e.g., certain hair or skin products) or leading to shunting across the scalp. For example, we would recommend careful preparation of the scalp and hair and keeping a distance of at least 7 cm between the electrodes to avoid shunting; however, most people do not have 7 cm in distance between their motor cortices or between their dorsolateral prefrontal cortices, adding an extra challenge to bilateral montages. We recommend moving the electrodes further apart—even if that moves the electrode center away from the exact target so long as it still covers the desired region; this will likely prevent shunting and overall improve current delivery. However, studies do not typically report on the distances between electrodes, and those that do sometimes allow for as little as 1 cm between electrodes.

Thus, it is critical to carefully select participants and montage/stimulation parameters considering the various possibilities influencing tDCS outcomes in clinical trials.

Methodology

Review Criteria—Our team consists of international experts on tDCS trials in specific neurological, rehabilitation, and psychiatric conditions. We followed PRISMA guidelines (Liberati et al., 2009) in conducting a systematic review on interventional human tDCS studies (see supplementary Table 1). In summary, for each of the selected conditions, the inclusion criteria were PubMed-indexed English-language Class I–III (Table 1) tDCS adult RCTs with a sham control up to July 5, 2019. Obsessive compulsive disorder (OCD) and Tourette syndrome (TS) were exceptions: we allowed Class IV studies due to their intractability and limited evidence; additionally, we did not exclude studies on pediatric patients in epilepsy, OCD, and TS due to the limited adult data. We only addressed major clinical outcomes and did not include neurophysiologic outcomes such as motor evoked potentials or electroencephalography (EEG).

We did not search databases other than PubMed; however, we included a few additional papers identified by our authors that had not shown up in search results but that fit the above criteria (including the July deadline); these papers are detailed in each section.

Table 1. Evidence-Based Guidelines (Brainin et al., 2004; Lefaucheur et al., 2014) (adapted from (Brainin et al., 2004))

Class I	Level A: Definitely effective or ineffective
Representative population—n ⩾ 25 of patients receiving active treatment; Data-supported, prospective, randomized, placebo-controlled clinical trials; It should include all of these listed criteria: Randomization concealment; clearly defined primary outcomes; clearly defined exclusion/inclusion criteria; adequate accounting for dropouts and crossovers w/ numbers sufficiently low to have minimal potential for bias; relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences.	At least 2 convincing Class I studies or 1 convincing Class I study and at least 2 consistent, convincing Class II studies
	Level B: Probably effective or ineffective
	At least 2 convincing Class II studies or 1 convincing Class II study and at least 2 consistent, convincing Class III studies
Class II Smaller sample size, n < 25	Level C: Possibly effective or ineffective 1 convincing Class II study or at least 2 convincing Class III studies
Randomized, placebo-controlled trials Or Lacks at least 1 of above-listed criteria (1–5)	No evidence Absence of at least 2 convincing Class III studies w/ similar results on the same type of clinical features w/ similar stimulation method
Class III All other controlled trials	
Class IV Uncontrolled studies; Case series; Case reports	

Abbreviations: w/, with.

Search terms and main criteria for each condition:

Pain: "tDCS AND <the name of each pain condition>", which were neuropathic, fibromyalgia, migraine, post-operative, myofascial, and low back pain, respectively. We included only spontaneous pain outcomes.

Parkinson's disease (PD): "transcranial direct current stimulation" and "Parkinson Disease." We included only motor and cognitive functions. In studies with motor outcomes (PD and stroke), we did not include scores primarily on activities of daily living due to the difficulty of associating changes with a specific montage.

Stroke: "tDCS and Stroke." Briefly, stroke studies were classified as chronic (>6 months) or subacute (24 hours to 6 months), using 3 montages (ipsilesional anodal bilateral M1 tDCS, contralesional cathodal M1 tDCS, and bilateral M2 tDCS). We included motor outcomes in chronic and subacute stroke, and aphasia in chronic stroke only. Hemorrhagic strokes were also included.

Epilepsy: "transcranial direct current stimulation" OR "tDCS" OR "brain polarization" OR "galvanic stimulation" AND "epilepsy." We included seizure frequency.

Major depressive disorder: "transcranial direct current stimulation" and "major depressive disorder." We included depression scores.

OCD and TS: "tDCS" and "OCD"; "tDCS" and "Gilles de la Tourette syndrome."

Schizophrenia: "tDCS AND schizophrenia." We included auditory hallucinations/positive or negative symptoms in schizophrenia (schizoaffective disorder mixes were also allowed).

Addiction: "alcohol AND tDCS," "cocaine AND tDCS", and "methamphetamine AND tDCS." Addiction in each disorder was assessed separately, assessing relapses and cravings.

Qualitative Analysis

We used the same methodology of a recent evidence-based review on transcranial magnetic stimulation (TMS) (Brainin et al., 2004; Lefaucheur et al., 2014). Each study was classified based on population, sample size, randomization, placebo-control, allocation concealment, outcomes, inclusion/exclusion criteria, withdrawals/dropouts, and baseline characteristics. Class I, II, III, and IV studies have low, moderate, moderately high, and high risk of bias, respectively. See Table 1 for our classification criteria and how these classes were used for evidence level assessments and recommendations.

Please note that Lefaucheur and colleagues (Lefaucheur et al., 2017) published an evidence-based review on tDCS in 2017, employing somewhat different search terms than ours but using a classification system derived from the same source (Brainin et al., 2004). An important difference is that they classified Class II studies as having at least 10 patients in the active group receiving "active" tDCS (Lefaucheur et al., 2017). Also, their search period was up to 2015, although some of the studies included in their review were published in 2016. While we excluded case series/case reports (except in OCD/TS), we did include RCTs with smaller samples in the active group as (1) we have no evidence that a strict but arbitrary cutoff of active n = 10 will better estimate true effects; (2) this cutoff is not in the original criteria (Brainin et al., 2004; Lefaucheur et al., 2014); (3) pilot and especially device trials in emerging fields (particularly non-proprietary devices as tDCS) often have smaller samples, so excluding RCTs with smaller samples would likely exclude a large number of existing RCTs and bias the results; (4) power is a function of both the sample size and the effect size, thus even small RCTs might be adequately powered and show significant changes if the treatment is optimized and has a large effect (conversely, larger trials with weak effects might not show significant changes); and (5) given the same intervention with the same effect size, a small sample may increase the risk of false negatives (type II error) but would reduce the risk of false positives (type I error)—for this reason we prioritize positive results as they are less likely to be spurious.

Therefore, while our primary recommendations (the ones described in the tables) did not restrict by sample size, in conditions that included studies with $n < 10$, we performed a "sensitivity" analysis and described any changes in recommendations if those studies were removed.

Also, we included single-session studies in our descriptive data (table rows shaded in dark gray) and discussions as they are important to understand the literature. However, we only used studies with repeated tDCS sessions as well as comparable protocols to determine levels of evidence and recommendations (similar to Lefaucheur et al., 2017), as most therapeutic uses require multiple sessions. We would like to highlight that most repeated-session studies do not measure outcomes after the first tDCS session, making it harder to distinguish between acute and cumulative within-study effects—although some did take repeated measures at later points in the study (e.g., weekly for 4 weeks).

Another important difference from Lefaucheur and colleagues' work (Lefaucheur et al., 2017) is that we performed a risk of bias assessment, which we describe further under "Risk of Bias" below. We also summarize the pooled effect sizes of the included disorders and performed meta-analyses to better showcase existing data (see "Quantitative Analysis" section).

We use conventional nomenclature as applied across modern tDCS publications (Bikson et al., 2019). "Anodal" and "cathodal" tDCS indicate if a specific electrode (polarity) is hypothesized to drive the outcome of interest and is thus near the intended target region (e.g., anodal M1), even while computational models suggest more nuanced brain current flow patterns (Datta et al., 2009; Bikson et al., 2010). Similarly, "return" electrode indicates an electrode not necessarily implicated in the outcome of interest. "Bilateral" indicates that both electrodes are hypothesized to be active for the outcome of interest.

Outcomes

We classified relevant clinical outcomes as positive (significant improvement from baseline in active vs sham tDCS) or negative (no significant improvement compared with sham). For instance, if a motor outcome was significantly improved from baseline in the active tDCS group compared with sham, we considered the trial to be positive for motor function (i.e., tDCS improved efficacy), irrespective of whether this outcome was the primary endpoint of the trial or an exploratory outcome and irrespective of whether there were statistical corrections for multiple outcome measurements. This was necessary as many papers do not clearly state the primary outcomes.

We also listed related negative outcomes within the same trial but did not consider them to invalidate positive results as many "negative" outcomes were simply underpowered for efficacy (e.g., both active and sham groups improved from baseline, or the active group improved more but without significant differences between groups). Therefore, if a study was positive for 1 motor outcome but negative for several, we considered the trial positive and made recommendations accordingly. We did not include scales on activities of daily living in other outcomes we

considered too vague or nonspecific or where the score included unrelated categories.

Study Classification

Class I or II studies require concurrent controls; crossover studies are considered Class III as participants are used as their own controls. This is central for Level B and C recommendations. Second, sample size per active arm (with a cutoff n = 25) is used to classify studies as Class I vs all other classes (Table 1). Therefore, while we allowed for small samples, we did consider their representativeness of the target population and their potential influences on systematic error (i.e., bias).

A study's systematic error must first be assessed classify it, and there should be a clear strategy to account for conflicting evidence. An uncontrolled Class IV study is considered to be more prone to bias than Class I–III studies; therefore, only Class I–III studies are used to determine level of evidence. After that, the studies selected for the recommendation are assessed to see if they have conflicting results. Higher quality studies with less bias and random error are prioritized; for example, if a particular outcome such as motor function has a positive Class I study but a negative Class II and negative Class III study, the results of the Class I study would supersede the other 2 studies and the determination would be Level B rather than Level A. Therefore, by providing the best level of available evidence, a Class I study is enough to recommend a Level B of evidence (i.e., probable effect).

Risk of Bias

We also assessed for risk of bias using the Jadad Scale (Jadad et al., 1996), which is scored from 0 to 5 with questions relating to adequacy of randomization and blinding, and the description of withdrawals and dropouts. We conducted this bias risk assessment for all repeated-sessions trials; then a sensitivity analysis was conducted by excluding papers with a high risk of bias, defined as having less than 3 points in the Jadad Scale.

In each section, studies were divided differently according to tDCS mechanisms and available data; for example, chronic pain was divided by the main pain syndrome (i.e., neuropathic pain, fibromyalgia, etc.). Only epilepsy and OCD/TS included pediatric patients due to limited adult studies.

Panel Recommendations

Based on the qualitative review, the panel reached an agreement on the recommendations for each clinical indication. In the first step, each expert assessed studies published in his/her own field, summarizing the studies in a table and then discussing recommendations with the entire group. On the next step, M.M.E. read and assessed all papers in this review for comprehensiveness and discussed with F.F. to maintain consistency with our methodology across different sections in tables and text. In summary, we have 4 categories of recommendations: Level A (definitely effective or ineffective), Level B (probably effective or ineffective), Level C (possibly effective or ineffective), or no recommendation. All panelists approved the final recommendations of the manuscript.

Table Display

We prioritized ease of recognizing stimulation parameters such as montage, current density, duration, number of sessions, concomitant therapies/tasks, and the main outcomes that we would use to make recommendations for those sections. For this reason, we displayed studies with multiple montages (whether parallel or crossover) more than once in the tables; we did not add extra rows for sham groups/conditions, irrespective of montage, but did add extra rows for active control groups to better display their montages. Crossover studies are marked with a "+" followed by the conditions; for example, "+as" indicates crossover with anodal and sham tDCS conditions.

The sample size (n) column describes the total sample analyzed in both parallel and crossover studies. For example, if 130 patients were randomized but only 120 analyzed, we listed an n of 120 irrespective of how many groups this sample was divided into. If a parallel RCT on stroke with an n of 120 has 2 table entries, 1 in the ipsilesional and 1 in the contralesional sections, that means 120 patients were analyzed for the whole study, including both montages as well the sham group. For crossover studies, number of sessions describes the number for each condition; for example, 10 would mean they received 10 sessions for each of the active and sham conditions. Washout periods were variable, and we commented on them in the discussions only when strictly necessary. If anode and cathode electrode sizes were different (which usually meant the study had used a large reference electrode to reduce its biological activity), current densities for anodal conditions/groups were displayed unless the stimulation was specifically intended to be cathodal. All sessions were consecutive unless stated otherwise.

We aimed to standardize the montage description as much as possible by using 10–20 or 10–10 International EEG system nomenclatures to describe active electrode positions (as they were often described in this way, even when researchers used other measurement methods such as TMS or neuronavigation). We typically described reference electrodes as supraorbital (SO) as that may be more intuitive for readers compared with "FP1/FP2" (right and left frontopolar, the same location as supraorbital or anterior prefrontal). However, in some cases, the supraorbital cathode was active, and for consistency we kept the same nomenclature (i.e., left SO instead of FP1). We used the descriptions we thought most representative of where the electrodes had actually been placed, but papers sometimes described different locations for the same cortical regions. The most commonly used locations were C3/C4 for left/right primary motor cortex (M1), respectively; F3/F4 for left/right dorsolateral prefrontal cortex (DLPFC), respectively; and SO; see Abbreviations for further descriptions.

As mentioned above, single-session studies were shaded, and our levels of evidence or recommendations included only studies with repeated tDCS sessions. When useful, we subdivided tables by the studies we used for recommendations and those studies that we did not use for recommendations (e.g., because the protocol was too different to interpret them together).

In summary, we aimed to organize the tables in a way that would help provide a "recipe" for designing tDCS clinical trials. However, it is important to consider the variability between studies and how it might change sample size calculations or therapeutic plans in a target population.

Quantitative Analysis

To provide additional quantitative data, we extracted baseline and post-intervention values on each outcome of interest from each study/montage used for EBM classification using a structured form. We used WebPlotDigitizer v.3.11 to extract data from relevant graphs. The extracted data were tabulated, coded, and

then imported into a dataset for analysis. We selected only studies with n = 10 or more participants.

We performed an exploratory meta-analysis on our prioritized outcomes per condition, that is, the ones used for classification in Tables 2–11. We decided to conduct an exploratory synthesis to compare across the spectrum of available tDCS approaches in each condition despite the variability of those parameters. We did this because homogenizing would result in too small a sample of studies to perform a valid meta-analysis per disorder; additionally, pooled effect sizes are expected to account for some variability, and clinicians can best make their decisions when able to view the nuances of the existing literature in both the qualitative tables and the pooled quantitative data. Where possible, we used pre- and post-tDCS scores to calculate the mean difference between groups; this difference was then converted to an effect size (ES). Given that Cohen d_s has a slight bias to overestimate in small sample sizes ($n<20$ [Lakens et al., 2013] or $n<50$ [Higgins et al., 2011]), we adjusted Cohen d_s to Hedge's g_s by applying a correction factor (Lakens et al., 2013). We assessed publication bias visually by funnel plot, and also using Egger and Begg testing for meta-analyses with at least 10 included studies (Higgins et al., 2011).

In addition, we assessed heterogeneity using I^2 statistic considering low heterogeneity when $I^2<40\%$. We consider the random-effects models appropriate for use due to the overall heterogeneity in populations and interventions. The data were processed using Stata v15.0 software (StataCorp LLC).

Where pooled results were available and significant, they were listed under the qualitative recommendations for each disorder. Otherwise, pooled results available for each disorder are listed in Table 12; please note that they are often from a smaller study sample than those used for the qualitative recommendations. Additionally, we restricted the outcomes of interest to those that were in multiple studies and could thus be pooled. We pooled both positive and negative outcomes in the quantitative analysis but highlight that as many of these outcomes were exploratory (as opposed to primary outcomes), many of the negative results are likely underpowered and do not affect our qualitative recommendations. In fact, some of the positive results in the qualitative tables were positive only on adjusted analysis or modeling, and so their pooled effects may have been nonsignificant for the purposes of our quantitative analysis. The qualitative and quantitative analyses should thus be viewed as separate but complementary methods to understand the data.

TDCS in Neurological Disorders

Pain—Chronic pain is a prevalent, disabling syndrome with few evidence-based treatments, particularly in severe cases. Recurrent pain leads to maladaptive neuroplasticity (El-Hagrassy et al., 2018), perpetuating the sensation of chronic pain in the presence of central sensitization; neuromodulating maladaptive networks by tDCS is thus appealing (Naro et al., 2016). A recent Cochrane review on chronic pain (O'Connell et al., 2018) found a difference for pain intensity between active and sham groups (0.82 points of control group outcome), but the evidence was very low quality and clinically nonsignificant, with heterogeneity and small study bias and it is unclear whether experimental pain was included. While we cannot control for study size and heterogeneity due to the nature of the field, we evaluated spontaneous pain ratings and not experimental pain, as the former is more clinically informative.

Aiming to understand the effects of different prevalent pain conditions separately, we conducted a PubMed search using the keywords "tDCS AND <the name of each pain condition>" that yielded 12, 8, 2, 5, 2, and 3 results that fit our criteria for neuropathic, fibromyalgia, migraine, post-operative, myofascial, and low back pain, respectively (Table 2).

tDCS in Neuropathic Pain—Regarding studies with repeated tDCS sessions, all but 1 of the Class II studies showed significant pain improvements following anodal tDCS of M1 on the side opposite to pain. The 1 negative trial (Lewis et al., 2018) was on neuropathic upper limb pain and used one-half the current intensity (1 mA) of the others; the crossover studies were negative. We describe single- and repeated-session studies below.

The first tDCS human pain study was on pain due to spinal cord injury (Fregni et al., 2006f) and showed that anodal M1 tDCS improved pain cumulatively from the 2nd to 5th sessions, though the effect was no longer significant at follow-up. Spinal cord injury trials that followed had mixed results but were overall consistent with cumulative analgesic effects (Jensen et al., 2013; Wrigley et al., 2013; Thibaut et al., 2017). Meanwhile, tDCS combined with a visual illusion encouraging participants to "see" themselves walking reduced overall pain intensity as well as continuous and paroxysmal pain (Soler et al., 2010); the combined group had a shorter pain duration compared with the others. One study found benefits for breathing-controlled electrical stimulation, but the single session was insufficient in long-standing pain patients.

Meanwhile, home-based tDCS had no pain benefits in patients with unilateral drug-resistant central/peripheral neuropathic pain who previously received rTMS (O'Neill et al., 2018); they did not reach the minimal clinically important difference (MCID) despite an adequate sample size and placing the anode over the previous TMS-mapped M1 hotspot. Notably, there was no relationship between previous rTMS responders and tDCS responders, potentially highlighting mechanistic differences between the 2 techniques. Similarly, 1 RCT on radiculopathic pain found that 10-Hz rTMS improved pain significantly more than tDCS, which was no different than sham (Attal et al., 2016); tDCS duration was 10 minutes longer than usual, raising the question of altered after-effects.

Finally, tDCS reduced post-stroke pain (Bae et al., 2014), and a single session RCT found that participants with neurogenic arm pain had over twice the pain reduction (36.5% vs 15.5%) following 1 session of tDCS and transcutaneous electrical nerve stimulation compared with tDCS alone (Boggio et al., 2009).

Recommendation: anodal M1 tDCS is probably effective in reducing neuropathic pain (Level B) (Table 2). On excluding the 1 study (Class II) with $n<10$, the recommendation does not change.

tDCS in Fibromyalgia—Anodal M1 tDCS reduced pain in all Class II repeated-session RCTs; other montages had mixed effects. Five consecutive M1 tDCS sessions caused minor but significant pain reduction in the first fibromyalgia study (Fregni et al., 2006e) and a larger one where benefits lasted 30 days (Fagerlund et al., 2015); meanwhile, 10 sessions at higher current density reduced pain by 40% to 49% over 2 weeks (Khedr et al., 2017a). Later trials found benefits to combining M1 tDCS with rehabilitation or aerobic exercise (Riberto, 2011; Mendonca et al., 2016).

Computer modeling shows the importance of stimulation parameters and current flow: 1 single-session RCT using a higher current density and cervicothoracic junction return electrode found that M1 tDCS (temporoparietal current flow) was ineffective, but pain significantly decreased following both anodal and cathodal stimulation of the right prefrontal cortex (anterior prefrontal

Table 2. tDCS Studies in Chronic Pain

Pain								
Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/tasks	Results	Class
Neuropathic pain								
Boggio et al. (2009)	8	C3/C4 on side opposite to max pain	Contralateral SO	0.571, 30 min	$1^{+aaT,asT,ssT}$	TENS (active/sham)	Positive (VAS)	III
Jensen et al. (2013)	30	C3/C4 on side opposite to max pain	Contralateral SO	0.571, 20 min	$1^{+as,h,m,n}$	No	Negative (NRS pain—current, least, worst, average)	III
Li et al. (2018)	12	C3	Contralateral SO	0.571, 20 min	1^{+as}	Breathing-controlled electrical stimulation (BreEStim) to median nerve on dominant side	Negative (VAS)	III
O'Neill et al. (2018)	21	Contralateral SO	C3/C4 on side opposite pain	0.560, 20 min	5^{+acs}	No	Negative (NRS daily pain)	III
O'Neill et al. (2018)	21	C3/C4 on side opposite pain	Contralateral SO	0.560, 20 min	5^{+acs}	No	Negative (NRS daily pain)	III
Wrigley et al. (2013)	10	C3/C4 based on dominant hemisphere	Contralateral SO	0.571, 20 min	5^{+as}	No	Negative (NPS)	III
Attal et al. (2016)	35	C3/C4 on side opposite max pain	Contralateral SO	0.571, 30 min	3^{+as} (nested parallel trial, tDCS, rTMS)	No	Negative (BPI)	III
Fregni et al. (2006f)	17	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	No	Positive (VAS)	II
Soler et al. (2010)	39	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	10	Visual illusion/control illusion	Positive (combined group: NRS overall, continuous, paroxysmal; tDCS group: NRS paroxysmal)	II
Bae et al. (2014)	14	C3/C4 opposite to hemiplegic side	Contralateral SO	0.571, 20 min	9 (3/wk × 3 wk)	No	Positive (VAS)	II
Thibaut et al. (2017)/ Phase I	33	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	No	Positive (VAS average, VAS least), Negative (VAS present, VAS worst)	II
Thibaut et al. (2017)/ Phase 2	9	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	No	Positive (VAS average), Negative (VAS least, VAS present, VAS worst)	II
Lewis et al., (2018)	30	C3/C4 on side opposite affected upper limb	Contralateral SO	0.286, 20 min	5	No	Negative (BPI, SF-MPQ2)	II
Recommendation: anodal M1 tDCS probably effective in reducing neuropathic pain (Level B)								
Fibromyalgia								
Villamar et al. (2013)	18	C3	Cz, F3, T7, P3	1.000, 20 min	1^{+acs}	No	Positive (VNS)	III

Table 2. Continued

Pain								
Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/tasks	Results	Class
Mendonca et al. (2011)[a]	30	C3	Cervicothoracic	1. 250, 20 min	1	No	Negative (VNS)	II
Mendonca et al. (2011) [a]	30	Cervicothoracic	C3	1. 250, 20 min	1	No	Negative (VNS)	II
Mendonca et al. (2011) [a]	30	Right SO	Cervicothoracic	1. 250, 20 min	1	No	Positive (VNS)	II
Mendonca et al. (2011) [a]	30	Cervicothoracic	Right SO	1. 250, 20 min	1	No	Positive (VNS)	II
Fregni et al. (2006e) [a]	32	F3	Contralateral SO	0.571, 20 min	5	No	Negative (VAS)	II
To et al. (2017) [a]	42	Left occipital (nerve)	Right occipital (nerve)	0.429, 20 min	8 (2/wk × 4 wk)	No	Positive (NRS)	II
To et al. (2017) [a]	42	F3	F4	0.429, 20 min	8 (2/wk × 4 wk)	No	Positive (NRS)	II
Fregni et al. (2006e)[a]	32	C3	Contralateral SO	0.571, 20 min	5	No	Positive (VAS)	II
Riberto et al. (2011)	23	C3	Contralateral SO	0.571, 20 min	10 (1/wk × 10 wk)	Pain rehab program	Positive (SF-36 pain), Negative (VAS)	II
Fagerlund et al. (2015)	48	C3	Contralateral SO	0.571, 20 min	5	No	Positive (NRS)	II
Mendonca et al. (2016)	45	C3	Contralateral SO	0.571, 20 min	5	Aerobic exercise	Positive (VNS)	II
Khedr et al. (2017a)	36	C3	Contralateral arm	0.833, 20 min	10	No	Positive (VAS)	II
Recommendation: anodal M1 tDCS probably effective in reducing fibromyalgia pain (Level B); no recommendation for other montages								
Migraine								
Andrade et al. (2017)/Group C	13	F3	Contralateral SO	0.800, 20 min	12 (3/wk × 4 wk)	No	Positive (VAS)	II
DaSilva et al. (2012)	13	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	10 (every other d × 4 wk)	No	Positive (VAS, migraine attack duration)	II
Andrade et al. (2017)/Group B	13	C3	Contralateral SO	0.800, 20 min	12 (3/wk × 4 wk)	No	Positive (VAS)	II
Recommendation: anodal M1 tDCS probably effective in reducing migraine pain (Level B)								
Myofascial Pain Syndrome (MPS)								
Choi et al. (2014) [a]	21	F3	Contralateral SO	0.571, 20 min	5	Trigger point injections	Negative (VAS)	II
Sakrajai et al. (2014)	31	C3/C4 on side opposite max pain	Contralateral SO	0.286, 20 min	5	Standard MPS therapy	Positive (NRS)	II
Choi et al. (2014) [a]	21	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	Trigger point injections	Negative (VAS)	II

Table 2. Continued

Pain								
Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/tasks	Results	Class
No recommendation								
Postoperative acute pain after chronic pain-related surgery								
Dubois et al. (2013)[a]	59	F3	Above right ear	0.286, 20 min	1 (postop)	No	Negative (PCA use, VAS Dynamic pain)	II
Dubois et al. (2013) [a]	59	Above right ear	F3	0.286, 20 min	1 (postop)	No	Negative (PCA use, VAS Dynamic pain)	II
Borckardt et al. (2013)	39	C1h or C2h based on target knee	F4	1.250, 20 min	4 (2/d × 2 postop d)	No	Positive (PCA use), Negative (VAS)	II
Glaser et al. (2016)	27	Cz	F4	Unclear electrode size (2 mA), 20 min	4 (2/d × 2 postop d)	No	Positive (PCA use, NRS pain at its least), Negative (other pain measures)	II
Ribeiro et al. (2017)	40	C3	Contralateral SO	0.571, 20 min	4 (2/preop d × 2 d)	No	Positive (Analgesic use, VAS cumulative worst daily pain, VAS during rest), Negative (VAS worst pain when walking)	II
Khedr et al. (2017b)	50	C1/C2 on side opposite max knee pain	Ipsilateral arm	0.833, 20 min	2 (2/postop d)	No	Positive (PCA use, LANSS), Negative (VAS)	I
Recommendation: postoperative anodal M1 tDCS probably effective in reducing patient-controlled analgesia and pain (Level B)								
Low back pain								
Mariano et al. (2019)	21	Right mastoid	FC1	0.571, 20 min	10	No	Negative (DVPRS)	II
Straudi et al., (2018)	35	C3/C4 on side opposite max pain, or dominant C3/C4 in case of central or bilateral pain	Contralateral SO	0.571, 20 min	5	Group exercise	Positive (VAS)	II
Luedtke et al. (2015)	122	C3	Contralateral SO	0.571, 20 min	5	CBT	Negative (VAS)	I
No recommendation								

Abbreviations: +as, crossover with anodal/sham tDCS conditions; +aaT,asT,ssT, crossover with anodal tDCS/active TENS, anodal tDCS/sham TENS, sham tDCS/sham TENS conditions; +as,h,m,n, crossover with anodal/sham tDCS—hypnosis, meditation, neurofeedback conditions; +as, (nested parallel trial—tDCS, rTMS) with active/active or sham/sham groups, crossover within those groups to 10Hz rTMS/anodal tDCS or sham rTMS/sham tDCS; +acs, crossover with anodal/cathodal/sham tDCS conditions; max, maximal; MPS, Myofascial Pain Syndrome; postop, postoperative; preop, preoperative; rehab, rehabilitation.

a Multiple montages within different arms of the same study/experiment.

current flow) (Mendonca et al., 2011). Meanwhile, a single session of high-definition tDCS (HD-tDCS) using a 4×1 ring configuration led to better pain relief (effect size 0.36 vs 0.30) with anode center stimulation (inward current) compared with cathode center stimulation (outward current), but the latter had more immediate effects (Villamar et al., 2013). Finally, twice-weekly bi-occipital tDCS significantly improved pain but not fatigue (unlike invasive occipital nerve stimulation), while DLPFC tDCS improved pain and fatigue, perhaps providing top-down regulation to midbrain-thalamic-cingulate pathways (To et al., 2017).

Recommendation: anodal M1 tDCS is probably effective in reducing fibromyalgia pain (Level B) (Table 2). Quantitative analysis of 5 studies shows a barely significant ES of –0.62 (95% confidence interval [CI] = –1.23, –0.01) in favor of tDCS, primarily influenced by the favorable results of 1 study (Khedr et al., 2017a); there is significant and substantial heterogeneity (I^2 = 68.2%, P = .013) (Table 12; supplemental Figure 1a).

tDCS in Migraine—Anodal M1 tDCS reduced pain intensity in 2 Class II trials using nonconsecutive sessions (da Silva et al., 2013; Andrade et al., 2017), although the pain reduction was not significant until the fourth week of follow-up in 1 of them; this same study also showed shortened migraine attacks (da Silva et al., 2013). Using different parameters, pain reduction was greater following left DLPFC than M1 tDCS in the other study (Andrade et al., 2017).

Recommendation: anodal M1 tDCS is probably effective in reducing migraine pain (Level B) (Table 2).

tDCS in Myofascial Pain Syndrome (MPS)—Anodal M1 tDCS Class II studies had mixed results and used different concomitant therapies. Combining standard MPS therapy with anodal M1 tDCS accelerated pain reduction (1st week effect), but MPS therapy led to a ceiling effect at weeks 2–4 (Sakrajai et al., 2014). Trigger point injections (Choi et al., 2014) resulted in reduced pre-post session pain on days 2–5 in the left DLPFC tDCS group, but after the last session the DLPFC, M1, and sham groups had similar improvements.

Recommendation: none (Table 2).

tDCS in Postoperative Acute Pain After Chronic Pain-Related Surgery—M1 anodal tDCS reduced patient-controlled analgesia (PCA) in all Class II and 1 Class I repeated-session studies; pain was reduced in 2 Class II studies and 1 Class I study. M1 electrode location varied by type of surgery, and only 1 study gave tDCS pre- rather than post-operatively (Ribeiro et al., 2017). This novel RCT found a decrease in post-hallux valgus surgery PCA use (72.3%) and pain (Ribeiro et al., 2017).

Two studies on total knee arthroplasty (Borckardt et al., 2013; Khedr et al., 2017b) investigated reduced PCA use at higher current densities. In one (Borckardt et al., 2013), the active group used 46% less hydromorphone and found pain less unpleasant. The same group found 23% less hydromorphone use and a 31% decrease in "pain-at-its-least ratings" by discharge following lumbar spine surgery (Glaser et al., 2016). In both cases, researchers concluded that tDCS activation at the anode (motor cortex intended to represent the knee or lower back/trunk) and deactivation at the cathode (right DLPFC) might have reduced pain perception. However, single-session anodal/cathodal left DLPFC tDCS had no benefits. Due to the varying study parameters, we cannot give a "definitely effective" recommendation.

Recommendation: postoperative anodal M1 tDCS is probably effective in reducing PCA and pain (Level B) (Table 2). Quantitative analysis of 3 studies shows a significant ES of –0.70 (95% CI = –1.09, –0.30) in favor of tDCS effects on pain due to favorable results in 2 of 3 studies (Borckardt et al., 2013; Ribeiro et al., 2017) (Table 12; supplemental Figure 1a).

tDCS in Low Back Pain—Single Class I and Class II M1 anodal tDCS study results were mixed. M1 anodal tDCS plus offline cognitive behavioral therapy (CBT) showed no significant pain reduction at 2 primary endpoints measured after 1 week of tDCS and 4 weeks of CBT, respectively (Luedtke et al., 2015); however, the RCT design was based on their negative single-session crossover pilot on experimental pain (Luedtke et al., 2012) Additionally, if tDCS's maximum effect occurred during the 4 weeks of CBT, it would go unmeasured; following CBT, both groups improved to similar levels. In another study, 10 group exercise sessions followed 1 week of tDCS, and pain significantly improved up to the 1-month follow-up; exercise plus sham tDCS led to no improvements at any timepoint (Straudi et al., 2018).

Meanwhile, cathodal frontocentral tDCS targeting the left dorsal anterior cingulate cortex (ACC) may have improved affective dimensions but not pain intensity (Mariano et al., 2019).

Recommendation: none (Table 2).

Summary and Literature Synthesis—Anodal M1 tDCS probably improves neuropathic, fibromyalgia, migraine, and post-operative pain as well as reduces PCA post-operatively. Quantitative analysis of 18 studies in neuropathic, fibromyalgia, migraine, and post-operative pain showed a significant and moderate ES of –0.47 (95% CI = –0.71, –0.23) favoring tDCS effects on pain (Table 12; supplemental Figure 1a) with significant but low heterogeneity (I^2 = 39.7%, P = .043). No publication bias was found (symmetrical funnel plot and non-significant Egger and Begg tests; supplemental Figure 1b).

Consistent with the 2018 Cochrane review, studies often used heterogeneous therapeutic strategies, and there is a clear need for RCTs with larger samples and clinically meaningful long-term outcomes. Careful outcome selection is critical as different stimulation parameters can lead to changes in onset of pain relief (or pain threshold), intensity, duration, and location and may have different effects on clinical vs experimental pain. One tool to utilize is the IMMPACT consensus statement, which classifies a decrease in pain of <15% as no important change, ≥15% as a minimally important change, ≥30% as a moderately important change, and ≥50% as a substantially important change (Dworkin et al., 2008; O'Connell et al., 2018). It is important to carefully select the time period of pain measurement (e.g., average of previous 24 hours, previous week) and to include this consideration in the design and reporting of clinical trials. Mobile apps may help avoid the problem of pain recall accuracy if designed for clinical trial use as opposed to unvalidated commercial apps (Salazar et al., 2018; Zhao et al., 2019).

On comparing our results with other qualitative/quantitative studies, Lefaucheur et al. (2017) gave a similar recommendation (Level B) in fibromyalgia for anodal left M1 tDCS, although we had only 3 overlapping studies. Meanwhile, similar to our results, the most recent meta-analysis on tDCS in fibromyalgia (Lloyd et al., 2020) found active tDCS to be beneficial, but barely so (standardized mean difference (SMD) of –0.50 with 95% CI = –0.87, –0.14) with statistically significant but weak clinical relevance (17% pain improvement) and high heterogeneity. When only anodal M1 tDCS was considered, the effect size remained the same. Their results were also driven by Khedr et al. (2017a), and they plausibly suggested that the extra-cephalic reference may have better influenced pain processing in deep brain and midbrain structures.

As to migraines, a meta-analysis (Feng et al., 2019) found that excitatory M1 non-invasive brain stimulation (NIBS) (tDCS and rTMS studies pooled together) had a large effect size in reducing migraine headache intensity (5 studies: Hedges' g of –0.94, 95% CI = –1.28, –0.59) and frequency (4 studies: Hedges' g of –0.88, 95% CI = –1.38, –0.38). Meanwhile, our pooled effects of 2 studies were null; however, we did not include TMS, did not have their positive anodal tDCS studies (Feng et al., 2019), they did not have 1 of ours, and the 1 study we had in common was null at that timepoint (the effects of da Silva et al., 2013 were positive only on follow-up). Lefaucheur et al. (2017) made no recommendations.

A recent integrative review and meta-analysis on tDCS in chronic non-cancer pain (Zortea et al., 2019) found that active tDCS compared with sham improved pain with a pooled standardized mean difference of –0.66 (95% CI = –0.91, -0.41) and that results appeared better for M1 anodal tDCS (0.68, 95% CI = –1.00, –0.35) rather than anodal DLPFC tDCS (–0.54, 95% CI = –0.91, –0.16), although there were less than a handful of studies for DLPFC. Both measures are greater than the pooled effects for our pooled analysis on neuropathic pain, which had an effect size of –0.47, though the confidence limits overlapped (CI 95% = –0.71, –0.23). The literature seems consistent that active tDCS can reduce pain, typically with a moderate effect size, and particularly with M1 anodal tDCS. However, optimal strategies for each pain disorder require further investigation.

Parkinson's Disease

PD is a chronic progressive neurodegenerative disorder affecting 315/100 000 people aged 40 years and older (Pringsheim et al., 2014). Dopaminergic cell degeneration leads to dopamine depletion (Dauer and Przedborski, 2003) and downstream changes in basal ganglia circuitry (Niethammer and Eidelberg, 2012) with motor cortico-striato-pallido-thalamocortical circuit abnormalities (DeLong and Wichmann, 2007). Evidence suggests that contralateral M1 and bilateral cerebellar hemispheres are hyperactive in PD and that the supplementary motor area (SMA), pre-SMA, and putamen are hypoactive (Yu et al., 2007).

PD is characterized by resting tremor, bradykinesia, rigidity, asymmetric onset, postural instability, and responsiveness to dopaminergic agents (Gelb et al., 1999), although these medications can lead to serious side effects (Ray Chaudhuri et al., 2018). Patients often also have cognitive symptoms relating to executive functioning (Kehagia et al., 2010; Santangelo et al., 2015). While deep brain stimulation (DBS) has long been used for PD motor symptoms, it is associated with serious adverse events (Buhmann et al., 2017), including cognitive deterioration (Gruber et al., 2019). Therefore, we aimed to see if tDCS could non-invasively improve motor and cognitive functions.

A PubMed search using the keywords "transcranial direct current stimulation" and "Parkinson Disease" yielded 23 results for motor and cognitive function, respectively, that fit our criteria (Table 3).

***tDCS for PD Motor Symptoms*—**Regarding motor improvement in studies with repeated sessions, 1 Class III and 2/4 Class II studies on anodal motor/premotor/SMA tDCS were positive; regarding DLPFC tDCS, 3/4 Class II studies—1 repeated twice (Doruk et al., 2014)—were negative, but the montage was largely intended for comparison or cognitive functions.

***Motor/Premotor/SMA tDCS*—**Most motor studies aimed to target premotor and SMA regions, while others used M1 (the electrodes likely overlapped with premotor regions in either case). Bradykinesia, gait, and other motor functions were addressed using tDCS on typically alternating days, and in all cases motor function in the tDCS group improved beyond baseline; negative results meant sham tDCS improved similarly.

Two negative RCTs combined tDCS with physical therapy (Yotnuengnit et al., 2018) or gait training with visual cues (Costa-Ribeiro et al., 2017), yet the cued gait-training study used similar interventions to the group's earlier RCT (Costa-Ribeiro et al., 2016, 2017) where the active tDCS group improved more quickly and maintained the benefit 1 month later. Meanwhile, 1 RCT combining thrice-weekly M1 tDCS with dual task gait training found significant cognitive—not motor—improvements during motor testing (Schabrun et al., 2016).

Two trials of tDCS without concomitant motor therapy were positive: 1 RCT alternated anode positions between premotor and anterior prefrontal (SO) areas while likely inhibiting the posterior quadrant bilaterally (Benninger et al., 2010); multiple outcomes were positive but the trial was terminated early. One crossover RCT targeted the leg initiating movement after freezing of gait (FOG) with 5 consecutive sessions and found persistent benefits for 4 weeks (Valentino et al., 2014).

As to single-session crossover RCTs, protocols and results were quite mixed, although they give mechanistic insight. One ran 3 experiments (OFF state) and found that anodal M1 but not cathodal M1 (Experiments 1a and 1b) nor anodal DLPFC tDCS (as a control) (Fregni, et al., 2006d) significantly improved motor outcomes. Importantly, motor evoked potentials significantly increased and decreased following anodal and cathodal M1 tDCS, respectively, highlighting tDCS' neurophysiologic effects. Conversely, 1 trial (ON) found a significant decline in walking (Verheyden et al., 2013), and anodal M1 tDCS with treadmill training led to ceiling effects (Fernández-Lago et al., 2017). Meanwhile, HD-tDCS significantly improved freezing and other gait parameters compared with "active" sham (Dagan et al., 2018); the multi-target approach may have enhanced dopaminergic circuitry or executive effects on motor control or improved communication between DLPFC, M1, and subcortical regions (highlighting functional decoupling between the cognitive control network and basal ganglia in PD patients with freezing) (Shine et al., 2013). Yet a neuronavigated crossover RCT on FOG (OFF state) found no improvement in self-initiated anticipatory postural adjustments and execution despite substantial cue-induced improvements in gait initiation prior to baseline (Lu et al., 2018). This may have been due to having greater current densities anterior to SMA leg regions, or due to the lack of dopaminergic activity (OFF). Finally, a nested trial with a posterior current direction (small cathode at inion) showed significant improvements in gait and stability only with combined physical training plus tDCS (Kaski et al., 2014), perhaps by modulating cortico-cerebellar and cortico-striatal circuits involved in motor learning (Duchesne et al., 2016) and internal regulation of movement.

***DLPFC tDCS*—**Both active/sham group patients with mild cognitive impairment (Manenti et al., 2016) improved significantly in static and dynamic balance for up to 3 months and had a less lasting improvement of trunk flexibility. In a dual NIBS study, patients with FOG (ON) safely received left DLPFC anodal tDCS combined with excitatory M1 rTMS (Chang et al., 2017); rTMS led to motor (and motor evoked potential) ceiling effects except on post-5th session timed up-and-go test. Finally, targeting cognition with repeated DLPFC stimulation had no motor benefits (Doruk et al., 2014).

Table 3. tDCS Studies in PD Targeting Motor and Cognitive Functions

Function, author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy/ tasks	Results	Class
Motor function								
Fregni et al. (2006d)/ Exp1a	9	C3	Contralateral SO	0.286, 20 min	1^{+as}	No	Positive (UPDRS III, simple RT), Negative (PPT)	III
Fregni et al. (2006d)/ Exp1b	8	Contralateral SO	C3	0.286, 20 min	1^{+cs}	No	Negative (UPDRS III, simple RT, PPT)	III
Verheyden et al. (2013)	20	C3	Contralateral SO	Unclear electrode size (1 mA), 15 min	1^{+as}	Online motor assessments	Negative (10MWT, STS, FR, SS180 steps, SS180 seconds, TUG)	III
Kaski et al. (2014)	16	Anterior to Cz	Iz	0.500, 15 min	1^{+as} (nested parallel trial, PT/no PT)	Gait and balance training in PT group	Positive only in PT group (gait velocity, pull test, stride length, TUG, 6MWT)	III
Fernández-Lago et al. (2017)	18	C1/C2 opposite to most affected side of body	Contralateral SO	0.571, 20 min	1^{+as}	Treadmill walking (with/without active/ sham tDCS)	Negative (gait parameters: speed, stride length/frequency and coefficient of variation)	III
Lu et al. (2018)	10	Neuronavigated or anterior to Cz	SO	1.235, 10 min	1^{+as}	None	Negative w/ self-initiated gait (APA phase force amplitudes and CoP)	III
Dagan et al. (2018)[a]	20	Cz	AF4, FC1, CP1	1.5-mA max current at any electrode w/ max total injected current 4 mA, 20 min	$1^{+as\ Cz\ F3,\ Cz}$	None	Negative (Modified FOG, TUG, gait speed)	III
Dagan et al. (2018)[a]	20	Cz and F3	AF4, FC1, FC5, CP1	1.5-mA max current at any electrode w/ max total injected current 4 mA, 20 min	$1^{+as\ Cz\ F3,\ Cz}$	None	Positive (Modified FOG, TUG, gait speed)	III
Fregni et al. (2006d)/ Exp1c[a,b]	9	F3	Contralateral SO	0.286, 20 min	1^{+as}	No	Negative (UPDRS III, simple RT, PPT)	III
Swank et al. (2016)	10	F3	F4	0.571, 20 min	1^{+as}	No	Negative (single and dual task TUG)	III
Lattari et al. (2017)	17	F3	Contralateral SO	0.571, 20 min	1^{+as}	No	Positive (BBS, DGI, TUG)	III
Doruk et al. (2014)[a]	18	F4	Contralateral SO	0.571, 20 min	10	No	Negative (UPDRS III, simple RT, 4-CRT, PPT, finger tapping, walking time, buttoning-up, supination-pronation)	II
Doruk et al. (2014)[a]	18	F3	Contralateral SO	0.571, 20 min	10	No	Negative (UPDRS III, simple RT, 4-CRT, PPT, finger tapping, walking time, buttoning-up, supination-pronation)	II

Table 3. Continued

Function, author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy/ tasks	Results	Class
Manenti et al. (2016)	20	Midway between F3-F7 or F4-F8 (opposite to most affected side of body)	Contralateral SO	0.571, 25 min	10	PT	Negative (UPDRS III, Hoehn-Yahr Stage, SST, FSST, SRT, TUG)	II
Chang et al. (2017)	32	F3	Contralateral SO	0.400, 20 min	5	10-Hz rTMS at M1 of LL	Positive (TUG), negative (FOG-Q, turning steps, turn time, UPDRS III)	II
Valentino et al. (2014)	10	C3/C4 of leg initiating after FOG episode	Contralateral SO	Unclear electrode size (2 mA), 20 min	5^{+as}	No	Positive (SWS, MDS-UPDRS total and part III, FOG-Q, Gait and Falls Questionnaire)	III
Benninger et al. (2010)	25	Anterior to Cz, alternating w/ SO	Two over mastoids	0.205, 20 min	8 (3 sessions/wk ×2.5 wk; alternating anode positions)	No	Positive (10MWT, bradykinesia, UPDRS bradykinesia), Negative (UPDRS total and III, serial RT)	II
Schabrun et al. (2016)	16	C3	Contralateral SO	0.571, 20 min	9 (3/wk × 3 wk)	Dual task gait training	Negative (gait velocity during cognitive task, cadence, step length, double support time, TUG, bradykinesia, serial RT)	II
Costa-Ribeiro et al. (2016)	24	Anterior to Cz	SO contralateral to most affected side of body	0.571, 13 min	10 (3/wk ×4 wk)	Gait training w/ visual cues	Positive (TUG, ON and OFF), Negative (UL-MT)	II
Costa-Ribeiro et al. (2017)	22	Anterior to Cz	SO contralateral to most affected side of body	0.571, 13 min	10 (3/wk ×4 wk)	Gait training w/ visual cues	Negative (10MWT, TUG, cadence, stride length, UPDRS III affected side, UPDRS-Bradykinesia, UL-MT, BBS)	II
Yotnuengnit et al. (2018)	53	Cz	SO	0.571, 30 min	6 (3/wk × 2 wk)	PT	Negative (walking speed, step length, step width, cadence, UPDRS II and III)	II
Recommendation: anodal motor/premotor/SMA tDCS possibly effective for motor function in PD (Level C); anodal prefrontal tDCS probably not effective for motor function in PD (Level B)								
Cognitive function								
Boggio et al. (2006)/ Exp1	9	F3	Contralateral SO	0.286, 20 min	$1^{+as\ F3,\ C3}$	No	Negative (working memory accuracy and RT)	III
Boggio et al. (2006)/ Exp2	9	F3	Contralateral SO	0.571, 20 min	$1^{+as\ F3,\ C3}$	No	Positive (working memory accuracy), Negative (RT)	III
Boggio et al. (2006)/ Exp1	9	C3	Contralateral SO	0.286, 20 min	$1^{+as\ F3,\ C3}$	No	Negative (working memory accuracy and RT)	III
Boggio et al. (2006)/ Exp2	9	C3	Contralateral SO	0.571, 20 min	$1^{+as\ F3,\ C3}$	No	Negative (working memory accuracy and RT)	III

Table 3. Continued

Function, author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy/ tasks	Results	Class
Dagan et al. (2018)[a]	20	Cz and F3	AF4, FC1, FC5, CP1	1.5 mA max current at any electrode w/ max total injected current 4mA, 20 min	1[+as Cz F3, Cz]	None	Positive (Stroop)	III
Dagan et al. (2018)[a]	20	Cz	AF4, FC1, CP1	1.5 mA max current at any electrode w/ max total injected current 4 mA, 20 min	1[+as Cz F3, Cz]	None	Negative (Stroop)	III
Schabrun et al. (2016)	16	C3	Contralateral SO	0.571, 20 min	9 (3/wk × 3 wk)	Dual task gait training	Positive (TUG count, TUG words)	II
Doruk et al. (2014)[a]	18	F4	Contralateral SO	0.571, 20 min	10	No	Positive (TMT B maintenance of learning), negative (other cognitive tests[b])	II
Doruk et al. (2014)[a]	18	F3	Contralateral SO	0.571, 20 min	10	No	Positive (TMT B maintenance of learning), negative (other cognitive tests[b])	II
Manenti et al. (2016)	20	Midway between F3-F7 or F4-F8 (opposite to most affected side of body)	Contralateral SO	0.571, 25 min	10	PT	Positive (PD-CRS frontal-subcortical and total scales, semantic fluency), Negative (other cognitive assessments[b] on memory, attention, executive function, MMSE)	II
Chang et al. (2017)	32	F3	Contralateral SO	0.400, 20 min	5	10-Hz rTMS at M1 of LL	Positive (TMT B), Negative (DS-forward, DS-backward, Montreal Cognitive Assessment-Korean)	II
Manenti et al. (2018)	22	F3	Right SO	0.571, 25 min	10	Computerized cognitive training	Positive (phonemic verbal fluency), Negative (other cognitive assessments[b] on global abilities, memory, language, attention and executive functions)	II
Recommendation: anodal DLPFC tDCS probably effective for cognitive function in PD (Level B)								

Abbreviations: +as: crossover—anodal/sham tDCS; +cs: crossover—cathodal/sham tDCS; +as (nested parallel trial—PT/no PT): tDCS with/without PT groups, crossover within those groups to anodal/sham tDCS; +as F3, C3: crossover—anodal/sham tDCS over left DLPFC and M1; +as Cz F3, Cz: crossover—anodal left M1 and left DLPFC (multi-target), anodal left M1, and "active" sham; max, maximal; PD, Parkinson's Disease; w/, with.

a Multiple montages within the same study/experiment.

b This experiment was considered a control for M1 anodal tDCS in Experiment 1a and used the same participants.

*b*Please see the papers for full lists of cognitive tests.

Single-session RCT results were mixed (Fregni et al., 2006d; Lattari et al., 2017), though 1 negative trial suggested less dual task cost with active tDCS (Swank et al., 2016).

Overall, motor/premotor/SMA tDCS shows promise despite varying parameters and outcomes, while prefrontal tDCS is largely noneffective.

Recommendation: anodal motor/premotor/SMA tDCS is possibly effective for motor function in PD (Level C); anodal prefrontal tDCS is probably not effective for motor function in PD (Level B) (Table 3).

Quantitative analysis of motor function in the ON state (Unified Parkinson's Disease Rating Scale [UPDRS] III: 4 studies/montages, motor velocity: 4 studies/montages) irrespective of location of stimulation showed a significant ES of −0.38 (95% CI = −0.68, −0.09) in favor of tDCS despite none of the studies' effect sizes reaching statistical significance (Table 12; supplemental Figure 2a).

tDCS for PD Cognitive Symptoms—All Class II repeated-session DLPFC tDCS studies were positive for improved cognition, and the 1 M1 tDCS study found more accurate responses on word lists and counting during timed up-and-go test, as described above (Schabrun et al., 2016).

One sham-control RCT with parallel anodal tDCS groups (left DLPFC, right DLPFC, and either right or left DLPFC) (Doruk et al., 2014) found that only the active tDCS groups maintained improvements in Trail-Making Test B; no other cognitive measures were significant. Similarly, dual left DLPFC tDCS and excitatory rTMS of lower limb M1 led to improvements in TMT-B beyond rTMS effects alone (Chang et al., 2017), and using DLPFC/frontotemporal tDCS with physical therapy improved PD with mild cognitive impairment to the point that patients had normal scores after active treatment (Manenti et al., 2016). Meanwhile, left DLPFC tDCS with online computerized cognitive control training focused on executive function (Manenti et al., 2018) significantly improved phonemic fluency in the active group (independent of decreased depression); other cognitive measures improved over time in both groups, but PD-CRS reached MCID in the active group only.

Regarding single-session crossover RCTs, Boggio and colleagues' Experiments 1 and 2 found improved cognition (working memory) only following 2-mA anodal left DLPFC tDCS, while 1-mA and M1 tDCS had no benefits (Boggio et al., 2006). Multi-target left DLPFC and M1 tDCS—but not M1 tDCS alone—significantly improved the correct number of words on the Stroop test.

Recommendation: anodal DLPFC tDCS is probably effective for cognitive function in PD (Level B) (Table 3).

Summary and Literature Synthesis—Most studies were good-quality RCTs on idiopathic PD. While anodal motor/premotor/SMA tDCS may benefit motor function and while DLPFC tDCS likely improves cognition, there does seem to be a feedback loop between motor and cognitive function. The quantitative analyses measures grouped by motor UPDRS and velocity (for bradykinesia) in ON periods were each nonsignificant, as were the cognitive measures grouped by Trail-Making Test B; meanwhile, there were significant pooled motor (but not cognitive) effects. These were the most commonly measured quantifiable outcomes across studies. Meanwhile, Lefaucheur et al. (2017) gave no recommendations for either motor or nonmotor/cognitive benefits of tDCS in PD due to the variability of outcome measures and targets, although they thought that combining tDCS with rehabilitation or priming may improve efficacy.

As to quantitative analyses in other studies, a recent meta-analysis on PD locomotion (Lee et al., 2019) found that short-term but not long-term benefits were significant with an effect size of 0.36 ($P = .001$) and that multiregional targets improved outcomes compared with single brain targets. A meta-analysis (Kim et al., 2019) on freezing of gait combining both rTMS and tDCS studies found better results in the PD subset than in parkinsonism overall; the FOG-Q effect size in PD was moderate with an SMD of 0.57 (95% CI = 0.15, 0.98), and UPDRS III also improved by a SMD of 0.43 (95% CI = 0.01, 0.86). As to cognition, another pooled analysis (Goodwill et al., 2017) of 3 studies found no significant benefit to tDCS, although they had combined many more cognitive outcomes together.

Outcome selection is still challenging for motor and cognitive function. Clinical scales used often combine multiple aspects of motor function, for example, UPDRS part III rates speech, facial expression, tremor, rigidity, various movements of the hands and legs, bradykinesia, posture/stability, and gait. Varying stimulation targets and parameters (and whether patients were in OFF/ON states) could affect those motor subcomponents in different ways. Outcome measurements and study protocols varied for cognition as well. Larger PD motor/cognitive RCTs are necessary to identify best practices, different outcome MCIDs, and duration of effects.

Stroke

Stroke is the top cause of disability in the United States, with 3% prevalence and high morbidity and mortality rates (Ovbiagele and Nguyen-Huynh, 2011). There is tremendous need for effective therapies to help stroke survivors recover motor, language, and other functions. Rehabilitation typically follows recruitment of intact nearby tissues and reorganization of the brain to compensate for the damaged area, but despite high-quality rehabilitation patients often still have mild to severe residual deficits. We aimed to evaluate the efficacy of tDCS as a tool for stroke motor and language rehabilitation due to their impact on disability and caregiver burden.

tDCS Effects on Motor Function in Stroke—Strokes can lead to unilateral weakness in the face, arm, and leg as well as other symptoms relating to impaired sensation, visual, and balance problems, all of which may exacerbate motor disability. It may be easier to enhance the magnitude of plasticity with tDCS in acute/subacute vs chronic stroke due to the major plastic changes in this phase, although those changes can make it difficult to distinguish spontaneous recovery and therapeutic effects (thus necessitating sham control, where recovery is likely to be of similar magnitude). Spontaneous recovery is minimal in chronic stroke; thus, methods promoting adaptive neuroplasticity are desirable.

A PubMed search using the keywords "tDCS and Stroke" yielded 63 results that fit our review criteria. We then selected the categories we believe most critical to tDCS effects on motor function and excluded the few studies that did not fit those categories, as we discuss below. We were unable to categorize for other relevant criteria such as patient characteristics (e.g., side, volume of stroke, cortical vs subcortical stroke, anterior vs posterior circulation, ischemic vs hemorrhagic stroke, severity of impairment, age of patient, dominant side, concomitant treatments) and specific tDCS parameters (e.g., active/reference electrode sizes/presumed current distribution, stimulation duration, interval, and number of sessions) due to the scope of this paper and as the above information was not always available. Nor were

we able to categorize for outcome measures, although we list measured motor outcomes in Tables 4 and 5. However, the type of outcome is important for the research question, for example, the Jebsen Taylor Hand Function Test is considered appropriate for mild to moderate stroke due to a lack of ceiling effects, while the Fugl Meyer Test may reach both ceiling and floor effects (Lin et al., 2009; Thompson-Butel et al., 2015; Santisteban et al., 2016).

Classification of Studies—The first major category was time since stroke: "subacute" (24 hours to 6 months) or "chronic" (>6 months). It is important to note that some trials used different cutoffs for "acute" vs "subacute" designations, and while most strokes were infarcts, hemorrhagic "strokes" were also included.

The second major category was side and polarity of stimulation; patients received either (1) ipsilesional anodal M1 tDCS (anode over M1 on same side as stroke), (2) contralesional cathodal M1 tDCS (cathode over M1 on opposite side of stroke), or (3) bilateral M1 tDCS (ipsilesional M1 anode, contralesional M1 cathode). Therefore, we created 6 subcategories (see Tables 4–5). In the chronic stroke category, we also subdivided by repeated-session studies using tDCS to enhance robotic training and studies without it. Some trials enrolled both subacute and chronic stroke patients. The few papers with 1 to 2 subacute stroke patients among many chronic patients were included in the chronic stroke table (Lindenberg et al., 2010, 2012; Tanaka et al., 2011). Meanwhile, papers with a larger mix of subacute and chronic patients were marked ([b]) and added to both tables (Tables 4–5); one showed no significant effect of time since stroke (Fleming et al., 2017), mean time since stroke was 4.9 ± 3 months in another (Wu et al., 2013), and the third (Triccas et al., 2015) had a near even mix of subacute and chronic patients.

Chronic Stroke—All repeated-session Class II and III studies using ipsilesional anodal M1 tDCS were positive for motor improvement; however, when tDCS was used to enhance motor effects of robotic therapy/training, only 2/5 Class II studies showed tDCS benefits. As to contralesional cathodal M1 tDCS, 1/2 Class II and both Class III studies were positive; 4/6 Class II and 1 Class III study on bilateral tDCS were also positive. These studies had comparable montages, and thus the recommendation is that tDCS is probably effective in all 3 categories (Table 4), although ipsilesional anodal tDCS has no benefits over robotic training. Single-session studies were also mostly positive in all but bilateral tDCS.

Most studies trained participants in motor tasks to reach asymptotic levels prior to testing except when the intended outcome was related to skill acquisition (e.g., Zimerman et al., 2012). All but 1 of the ipsilesional repeat-session studies without robotics used additional training, including constraint-induced movement therapy, virtual reality, etc., yet tDCS benefits went beyond those therapies. Conversely, robotic training was more prone toward a ceiling effect, including the largest study (n = 77 ischemic stroke), which used intensive robotic therapy after each of 36 tDCS sessions (Edwards et al., 2019); improvements in Fugl Myer (by 5 points) and Wolf Motor Function Tests were not significantly different between groups. Most other tDCS montages were also combined with other therapies, again with mostly positive results, although there was great heterogeneity in tDCS protocols and concomitant therapies (descriptions of which are beyond the scope of this review).

An important question is whether one montage is superior to another in a particular population or whether it could lead to deleterious results. One single-session trial showed impaired motor function after contralesional anodal tDCS (i.e., facilitation of the intact hemisphere) and improved function with ipsilesional anodal tDCS (Madhavan et al., 2011). The above results may have related to the severity of corticospinal tract damage, which we discuss further below. One single-session study using robotics found a detrimental effect to cathodal contralesional M1 tDCS (Yao et al., 2015), showcasing the possibility that concomitant training/treatments may change or even reverse expected tDCS effects.

Recommendations: anodal ipsilesional, cathodal contralesional, and bilateral tDCS of M1 montages are probably effective for motor rehabilitation in chronic stroke (Level B). Anodal ipsilesional M1 tDCS to enhance robotic therapy is probably not effective in chronic stroke (Level B) (Table 4).

On excluding studies with n < 10, in anodal ipsilesional tDCS the exclusion of 2 studies—one without (Class III) and one with robotics (Class II)—does not change recommendations; in cathodal contralesional tDCS, the exclusion of 1 study (Class II) changes the recommendation from Level B to Level C (possibly effective).

For motor function in chronic stroke without robotics, quantitative analysis of 7 ipsilesional, 2 contralesional, and 5 bilateral tDCS studies showed a significant ES of 0.44 (95% CI = 0.10, 0.79) in favor of bilateral tDCS effects, and the 3 montages pooled together have a significant effect of 0.51 (95% CI = 0.19, 0.84) in favor of tDCS effects overall on chronic stroke, although there is also significant and high heterogeneity ($I^2 = 62.8\%$, $P = .001$) (Table 12; Supplemental Figure 3.1.1).

Acute/Subacute Stroke—Regarding repeated-session tDCS studies, 4/6 Class II studies showed benefits to anodal ipsilesional M1 tDCS; however, when used to enhance motor effects of robotic therapy/training, the 3 Class II studies and 1 Class I study showed no tDCS benefits. As to contralesional cathodal M1 tDCS, 4/6 Class II studies were positive, but the same Class I robotics study was negative. Finally, in bilateral tDCS, the largest Class II study and a Class III study were positive, while 2 Class II studies (with fewer sessions) were negative. Therefore, tDCS may be effective in all 3 categories (Table 4), although it has no benefits over robotic training. Almost all single-session studies were also positive.

Similar to chronic stroke, intensive robotic therapy improved clinical and sometimes kinematic (Triccas et al., 2015; Mazzoleni et al., 2017) outcomes in both active and sham groups comparably. Almost all non-robotic studies combined tDCS with other therapies, but active tDCS tended to enhance the effects of those therapies. We also highlight a single-session exploratory crossover RCT in subacute subcortical stroke showing that dual anodal tDCS of ipsilesional M1 and DLPFC significantly improved continuous time-based outcomes (reaction/response time (RT) and 9-hole peg test (9HPT)) compared with both sham and anodal M1 tDCS (Achacheluee et al., 2018). Dual tDCS benefits may have related to high current density and distribution with sensorimotor-cognitive integration.

Recommendations: anodal ipsilesional and cathodal contralesional M1 tDCS montages are probably effective for motor rehabilitation in subacute stroke (Level B). Bilateral M1 tDCS is possibly effective for motor rehabilitation in subacute stroke (Level C). Anodal ipsilesional and cathodal contralesional M1 tDCS to enhance robotic therapy are probably not effective for motor rehabilitation in subacute stroke (Level B) (Table 5).

For motor function in subacute stroke without robotics, quantitative analysis of 8 ipsilesional, 5 contralesional, and 3 bilateral tDCS studies shows a significant ES of 0.47 (95% CI = 0.10,

Table 4. tDCS Studies in Chronic Stroke Motor Function

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Ipsilesional								
Fregni et al. (2005)	6	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	1^{+ics}	No	Positive (JTHFT)	III
Hummel et al. (2005)	6	Ipsilesional C3/C4	Contralesional SO	0.400, 20 min	1^{+is}	No	Positive (JTHFT)	III
Hummel et al. (2006)	11	Ipsilesional C3/C4	Contralesional SO	0.400, 20 min	1^{+is}	Simple reaction time, pinch force tasks	Positive (simple reaction time, pinch force)	III
Celnik et al. (2009)	9	Ipsilesional C3/C4	Contralesional SO	0.172, 20 min	$1^{+is,\ isPNS}$	Motor training (all groups), PNS of paretic hand (in active tDCS+PNS and sham tDCS+PNS groups)	Positive (finger motor sequence)	III
Giacobbe et al. (2013)	12	Ipsilesional C3/C4	Contralesional SO	Unclear electrode size (2mA), 20 min	1^{+is}	InMotion3 wrist robot movements	Positive for pre-training tDCS (movement smoothness), Negative for tDCS during (worse aim) and post-training (slower)	III
Mahmoudi et al. (2011)	10	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	1^{+iibcs}	No	Positive (JTHFT)	III
Mahmoudi et al. (2011)	10	Ipsilesional C3/C4	Contralesional deltoid	0.286, 20 min	1^{+iibcs}	No	Negative (JTHFT)	III
Stagg et al. (2012)/Exp1[a]	13[b]	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	1^{+ics}	Motor simple reaction time and grip force tasks	Positive (simple reaction time), Negative (grip force)	III
Stagg et al. (2012)/Exp2	11[b]	Ipsilesional C3/C4	Contralesional SO	0.286, 10 min	1^{+ics}	Motor simple and choice reaction time tasks	Positive (simple reaction time), Negative (choice reaction time)	III
Madhavan et al. (2011)	9	Ipsilesional $C1/C2^{LL}$	Contralesional SO	0.625, 15 min	$1^{+ia,ca,s}$	Tracking sinusoidal waveform using ankle movements	Positive (accuracy index)[c]	III
Tanaka et al. (2011)	8	Ipsilesional $C1/C2^{LL}$	Contralesional SO	0.571, 10 min	1^{+is}	Knee extension and hand grip tasks	Positive (maximum force of knee extension), Negative (maximum force of hand grip)	III
Au-Yeung et al. (2014)	10	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	1^{+ics}	No	Negative (Purdue pegboard unimanual test, pinch strength)	III
Yao et al. (2015)	9	Ipsilesional C3/C4	SO	0.500, 15 min	$1^{+ia,cc,ca,s}$	Reaching task (ACT3 Drobot)	Negative (reaching distance w/ shoulder abduction loads)	III
van Asseldonk and Boonstra (2016)	10	Ipsilesional $C1/C2^{LL}$	Contralesional SO	0.571, 10 min	1^{+ibs}	Treadmill Walking	Negative (paretic leg positive work, propulsion, step length, cycle time), Positive (positive work in nonparetic leg)	III
Marquez et al. (2017)	25	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	1^{+ics}	No	Negative (JTHFT, pinch force, grip force)	III
Fleming et al. (2017)[e]	24	Ipsilesional C3/C4	Contralesional SO	0.400, 20 min	1^{+icbs}	Motor sequence learning task	Positive (JTHFT)	III

Table 4. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Ojardias et al. (2018)	18	Ipsilesional M1 C1/C2[LL]	Contralesional SO	0.800, 20 min	1[+as]	None	Positive (6MWT), Negative (Wade test, step length/symmetry, balance measures)	III
With robotic concomitant therapy								
Danzl et al. (2013)	8	Ipsilesional C1/C2[LL]	SO	0.800, 20 min	12	Locomotor training w/ a robotic gait orthosis (LT-RGO)	Positive (FAC), Negative (10MWT, TUG, BBS)	II
Geroin et al. (2011)	30	Ipsilesional C1/C2[LL]	Contralesional SO	0.429, 7 min	10	Robot-assisted gait training (Gait Trainer GT1)	Negative(6minWT, 10MWT, spatiotemporal gait, FAC, MI leg)	II
Triccas et al. (2015)[e]	22	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	18 (about 2-3/wk × 8 wk)	Robot Therapy	Negative (FM UE, ARAT, MAL, robotic Hand Path Ratio)	II
Seo et al. (2017)	21	Ipsilesional C1/C2[LL]	Contralesional SO	0.571, 20 min	10	Robot-assisted gait training	Positive (FAC, 6MWT), Negative (10MWT, FM LE, BBS, MRC)	II
Edwards et al. (2019)	77	Ipsilesional C3/C4	Contralesional SO	0.571, 20 min	36 (3/wk × 12 wk)	Robot-assisted arm training	Negative (FM, WMFT)	II
Without robotic concomitant therapy								
Wu et al. (2013)[e]	90	Contralesional shoulder	Ipsilesional C3/C4	0.283, 20 min	20	Physical therapy	Positive (MAS elbow, MAS wrist, FM UE)	I
Boggio et al. (2007)/Exp1	4	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	4 (one per wk × 4 wk) [+ics]	No	Positive (JTHFT)	III
Cha et al. (2014)	20	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	20	Functional training (PT)	Positive (BBT, FM UE, FM LE)	III
Kasashima-Shindo et al. (2015)	18	Ipsilesional C3/C4	Contralesional SO	0.286, 10 min	10	BCI training + OT	Positive (FM UE)	III
Viana et al. (2014)	20	Ipsilesional C3/C4	Contralesional SO	0.571, 13 min	15	VR	Positive (MAS), Negative (FM UE, WMFT)	II
Mortensen et al. (2016)	15	Ipsilesional C3/C4	Contralesional SO	0.429, 20 min	5	Home-based OT	Positive (grip strength), Negative (JTHFT)	II
Rocha et al. (2016)	21	Ipsilesional C3/C4	SO	0.286, 13 min	12 (3/wk × 4 wk)	mCIMT	Positive (FM UE, FM total), Negative (MAL, handgrip strength)	II
Ilic et al. (2016)	26	Ipsilesional C3/C4	Contralesional SO	0.800, 20 min	10	OT/control	Positive (JTHFT), Negative (handgrip strength, FM UE)	II
Recommendation: anodal tDCS of ipsilesional M1 probably effective (Level B) for motor rehab in chronic stroke Recommendation: anodal tDCS of ipsilesional M1 to enhance robotic therapy probably not effective (Level B) for motor rehab in chronic stroke								
Contralesional								
Fregni et al. (2005)	6	Ipsilesional SO	Contralesional C3/C4	0.286, 20 min	1[+ics]	No	Positive (JTHFT)	III
Mahmoudi et al. (2011)	10	Ipsilesional SO	Contralesional C3/C4	0.286, 20 min	1[+iicbs]	No	Positive (JTHFT)	III

Table 4. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Stagg et al. (2012)/Exp1[a]	13[b]	Ipsilesional SO	Contralesional C3/C4	0.286, 20 min	1^{+ics}	Motor simple reaction time and grip force tasks	Positive (simple reaction time), Negative (grip force)	III
Stagg et al. (2012)/Exp2	11 [b]	Ipsilesional SO	Contralesional C3/C4	0.286, 10 min	1^{+ics}	Motor simple and choice reaction time tasks	Positive (simple reaction time), Negative (choice reaction time)	III
Zimerman et al. (2012)	12	Ipsilesional SO	Contralesional C3/C4	0.400, 20 min	1^{+cs}	Motor Task	Positive (finger movement task)	III
Au-Yeung et al. (2014)	10	Ipsilesional SO	Contralesional C3/C4	0.286, 20 min	1^{+ics}	No	Positive (Purdue pegboard unimanual test), Negative (pinch strength)	III
Yao et al. (2015)	9	SO	Contralesional C3/C4	0.500, 15 min	$1^{+ia,cc,ca,s}$	Reaching task (ACT3D robot)	Negative (reaching distance w/ shoulder abduction loads)	III
Kwon et al. (2016)	20	Ipsilesional SO	Contralesional C3/C4	0.800, 20 min	$1^{+ca,cc,s/rTMS}$	10Hz rTMS (ipsilesional C3/C4), sequential hand motor training	Positive (motor training, movement accuracy)	III
Marquez et al. (2017)	25	Ipsilesional SO	Contralesional C3/C4	0.286, 20 min	1^{+ics}	No	Negative (JTHF, pinch force, grip force)	III
Fleming et al. (2017)[e]	24	Ipsilesional SO	Contralesional C3/C4	0.400, 20 min	1^{+icbs}	Motor sequence learning task	Positive (JTHFT)	III
Boggio et al. (2007)/Exp1	4	Ipsilesional SO	Contralesional C3/C4	0.286, 20 min	4 (one per wk × 4 wk)$^{+ics}$	No	Positive (JTHFT)	III
Del Felice et al. (2016)	10	Ipsilesional SO	Contralesional C3/C4	0.400, 20 min	5^{+cbs}	No	Positive (MRC hand, elbow flexion, Ashworth score)	III
Nair et al. (2011)	14	Ipsilesional SO	Contralesional C3/C4	Unclear electrode size (1 mA intensity), 30 min	5	Occupational therapy	Positive (ROM, FM UE)	II
Rocha et al. (2016)	21	SO	Contralesional C3/C4	0.286, 9 min	12 (3/wk × 4 wk)	mCIMT	Negative (FM UE, FM total, MAL, handgrip strength)	II
Recommendation: cathodal tDCS of contralesional M1 probably effective (Level B) for motor rehab in chronic stroke								
Bilateral								
Mahmoudi et al. (2011)	10	Ipsilesional C3/C4	Contralesional C3/C4	0.286, 20 min	1^{+iicbs}	No	Positive (JTHFT)	III
Lefebvre et al. (2013)	18	Ipsilesional C3/C4	Contralesional C3/C4	0.286, 30 min	1^{+bs}	Motor skill learning task	Positive (motor skill learning index, PPT, max hand grip force)	III
Lefebvre et al. (2014)	19	Ipsilesional C3/C4	Contralesional C3/C4	0.286, 20 min	1^{+bs}	Grip-lifts, PPT	Positive (precision grip measures, PPT)	III

Table 4. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
O'Shea et al. (2014)/Exp2[a]	13	Ipsilesional C3/C4	Contralesional C3/C4	0.286, 20 min	1[+icbs]	Motor reaction time and grip force tasks	Negative (reaction time)	III
van Asseldonk and Boonstra (2016)	10	Ipsilesional C1/C2[LL]	Contralesional SO	0.571, 10 min	1[+ibs]	Treadmill Walking	Negative (paretic leg positive work, propulsion, step length, cycle time), Positive (positive work in nonparetic leg)	III
Fleming et al. (2017)[e]	24	Ipsilesional C3/C4	Contralesional C3/C4	0.400, 20 min	1[+icbs]	Motor sequence learning task	Negative (JTHFT)	III
Doost et al. (2019)	21	Ipsilesional C3/C4	Contralesional C3/C4	0.286, 30 min	1[+bs]	Bimanual cooperative skill program (CIRCUIT)	Negative (bimanual speed/accuracy tradeoff, bimanual coordination factor, BBT)	III
Pavlova et al. (2020)	11	Ipsilesional and contralesional C3/C4 (bipolar anodal)	Contralesional SO	0.333, 20 min	40 (2/d × 4 wk)	Visuo-motor power grip force-tracking task	Positive (FM UE shoulder-elbow subscore, ramp error), Negative (FM UE and other subscores, WMFT-FAS, WMFT-time, BBT, grip maximum voluntary contraction, other movement parameters)	II
Del Felice et al. (2016)	10	Ipsilesional C3/C4	Contralesional C3/C4	0.400, 20 min	5[+cbs]	No	Positive (MRC hand, elbow flexion, Ashworth score)	III
Bolognini et al. (2011)	14	Ipsilesional C3/C4	Contralesional C3/C4	0.571, 40 min	10	CIMT	Positive (JTHFT, grip strength, FM UE)	II
Lindenberg et al. (2010)[d]	20	Ipsilesional C3/C4	Contralesional C3/C4	0.920, 30 min	5	PT + OT	Positive (FM UE, WMFT)	II
Lindenberg et al. (2012)[d]	10	Ipsilesional C3/C4	Contralesional C3/C4	0.920, 30 min	10 (2x5-d sessions separated by 2-29 d)	PT + OT	Positive (FM UE, WMFT)	II
Koh et al. (2017)	25	Ipsilesional C3/C4	Contralesional C3/C4	0.600, 30 min	24 (3/wk × 8 wk)	Sensory modulation on both hands + passive repetitive wrist/finger movements + cutaneous anesthesia of both upper extremities	Negative (FM UE, MAS, ARAT)	II

Table 4. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Beaulieu et al. (2018)	14	Ipsilesional C3/C4	Contralesional C3/C4	0.571, 20 min	12 (3/wk × 4 wk)	Progressive resistance training program	Negative (FM, WMFT, BBT, grip strength, MAS)	II
Salazar et al. (2019)	30	Ipsilesional C3/C4	Contralesional C3/C4	0.800, 30 min	10	Functional electrical stimulation	Positive (movement cycle time, mean reaching phase velocity, handgrip force), Negative (FM UL, other motor measures)	II
Recommendation: bilateral tDCS of M1 probably effective (Level B) for motor rehab in chronic stroke								

Abbreviations: max, maximal. LL– Target was the motor cortex corresponding to the left or right lower limbs, placed mesial to the upper limbs/just lateral to the sagittal plane, roughly corresponding with C1/C2 in the 10/10 International EEG system; +is—crossover with ipsilesional anodal and sham tDCS conditions; +ics—crossover with ispilesional anodal, contralesional cathodal and sham tDCS conditions (note—for Boggio et al., 2007/Experiment 1, each condition lasted for 4 weeks, so the experiment lasted 16 weeks); +is, isPNS—crossover with ispilesional anodal and sham tDCS conditions, and peripheral nerve stimulation; +iibcs—crossover with ipsilesional anodal (cathode over contralesional SO or deltoid), contralesional cathodal, bilateral, and sham tDCS conditions; + icbs—crossover with ipsilesional anodal, contralesional cathodal, bilateral and sham tDCS conditions; +ia,ca,s—crossover with ipsilesional anodal, contralesional anodal and sham tDCS conditions; +cs—crossover with contralesional cathodal and sham tDCS conditions; +bs—crossover with bilateral and sham tDCS conditions; +ia,cc,ca,s—crossover with ipsilesional anodal, contralesional cathodal, contralesional anodal and sham tDCS conditions (note—contralesional anode was no different than sham while contralesional cathode significantly worsened reaching distance at high load); +ca,cc,s/rTMS—crossover with 5 conditions for dual-mode bihemispheric stimulation: contralesional cathodal tDCS or contralesional anodal tDCS plus online ipsilesional 10 Hz rTMS (Conditions 1 and 2 respectively), contralesional cathodal tDCS or contralesional anodal tDCS followed by ipsilesional 10 Hz rTMS (Conditions 3 and 4), and contralesional sham tDCS plus online ipsilesional 10 Hz rTMS (Condition 5)—Condition 3 had significantly improved movement time compared with all other conditions; rehab, rehabilitation.

*a*Stagg et al., 2012 had included the same sample with ipsilesional, contralesional and sham tDCS conditions (pilot study) to which the sample in O'Shea et al., 2014, was later compared in a bilateral tDCS montage.

*b*2 participants dropped out between Stagg et al., 2012 Experiments 1 and 2.

*c*Positive results for ipsilesional motor anodal with contralesional SO cathodal tDCS condition, negative for contralesional motor anodal with ipsilesional SO cathodal condition.

*d*4/10 participants in Lindenberg et al., 2012 were from Lindenberg el al., 2010.

*e*Paper had a large or unclear mix of subacute and chronic stroke patients and was included in both subacute and chronic stroke tables.

Table 5. tDCS Studies in Subacute Stroke Motor Function

Author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy or motor tasks	Results	Class
Ipsilesional								
Sohn et al. (2013)	11	Ipsilesional C1/C2[LL]	Contralesional SO	0.800, 10 min	1[+is]	No	Positive (isometric peak torque for knee extensor, stability indices)	III
Fusco et al. (2013)	9	Ipsilesional C3/C4	Contralesional SO	0.429, 15 min	1[+icbs]	No		III
Fusco et al. (2014b)	16	Ipsilesional C3/C4	Contralesional SO	0.429, 15 min	1[+is]	Upper limb rehab	Positive (9HPT), negative (pinch force, grip force) positive (9HPT), negative (pinch and grip force)	III
Fleming et al. (2017)[b]	24	Ipsilesional C3/C4	Contralesional SO	0.400, 20 min	1[+icbs]	Motor sequence learning task	Positive (JTHFT)	III
Achacheluee et al. (2018)—A	15	Ipsilesional C3/C4 and F3/F4	Contralesional SO	0.16 per electrode × 2 electrodes at each site, 20 min	1[+asCF,C]	None	Positive (RT, 9HPT), negative (FM)	III
Achacheluee et al. (2018)—B	15	Ipsilesional C3/C4	Contralesional SO	0.16 (one electrode), 20 min	1[+asCF,C]	None	Negative (RT, 9HPT, FM)	III
With robotic concomitant therapy								
Triccas et al. (2015)[b]	22	Ipsilesional C3/C4	Contralesional SO	0.286, 20 min	18 (about 2-3/wk × 8 wk)	Robot Therapy	Negative (FM UE, ARAT, MAL, robotic hand path ratio)	II
Mazzoleni et al. (2017)	24	Ipsilesional C3/C4	Contralesional SO	0.571, 20 min	30	Wrist robot-assisted training	Negative (FM UE, FM wrist, MI, BBT, MAS wrist, kinematic parameters)	II
Mazzoleni et al. (2019)	39	Ipsilesional C3/C4	Contralesional SO	0.571, 20 min	30	Wrist robot-assisted rehab (InMotion WRIST)	Negative (FM UE, FM wrist, FM LE, MAS wrist, MI, BBT, wrist kinematic parameters)	II
Hesse et al. (2011)	96	Ipsilesional C3/C4	Contralesional SO	0.571, 20 min	30	Robot-assisted arm training (Bi-Manu Track)	Negative (FM UE, BBT, MRC, MAS)	I
Without robotic concomitant therapy								
Manji et al. (2018)	30	3.5 cm anterior to Cz	Inion	0.400, 20 min	5[+is]	BWSTT	Positive (10MWT, TUG), negative (FM LL, TCT, POMA)	III
Koo et al. (2018)	24	Ipsilesional CP3/CP4	Contralesional SO	0.400, 20 min	10	None	Negative (MFT, MBC, FAC)	II
Wu et al. (2013)[b]	90	Contralesional shoulder	Ipsilesional C3/C4	0.283, 20 min	20	Physical therapy	Positive (MAS elbow, MAS wrist, FM UE)	I
Kim et al. (2010)	18	Ipsilesional C3/C4	Contralesional SO	0.800, 20 min	10	OT	Negative (FM UE)	II
Rossi et al. (2013)	50	Ipsilesional C3/C4	Contralesional SO	0.571, 20 min	5	No	Negative (FM UE, NIHSS)	II
Khedr et al. (2013)	40	Ipsilesional C3/C4	Contralesional SO	0.571, 25 min	6	Conventional rehab therapy	Positive (OMCASS), negative (NIHSS, MAC)	II
Sattler et al. (2015)	20	Ipsilesional C3/C4	Contralesional SO	0.343, 13 min	5	rPNS, conventional rehab therapy	Positive (JTHFT), negative (FM UE, hand grip, 9HPT, hand tapping test)	II

Table 5. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy or motor tasks	Results	Class
Figlewski et al. (2017)	44	Ipsilesional C3/C4	Contralesional SO	0.429, 30 min	10	CIMIT	Positive (WMFT FAS), negative (WMFT time, grip strength, arm strength)	II
Andrade et al. (2017)	60	Ipsilesional C3/C4	Contralesional SO	0.571, 20 min	10	PT	Positive (falls, FSST, OSI, FES-I, BBS, 6MWT, STS)	II
Recommendation: anodal tDCS of ipsilesional M1 probably effective (Level B) for motor rehab in subacute stroke Recommendation: anodal tDCS of ipsilesional M1 to enhance robotic therapy definitely not effective (Level A) for motor rehab in subacute stroke								
Contralesional								
Fusco et al. (2013)	9	Ipsilesional SO	Contralesional C3/C4	0.429, 15 min	1^{+icbs}	No	Positive (9HPT, pinch force), Negative (grip force)	III
Fleming et al. (2017)[b]	24	Ipsilesional SO	Contralesional C3/C4	0.400, 20 min	1^{+icbs}	Motor sequence learning task	Positive (JTHFT)	III
With Robotic concomitant therapy								
Hesse et al. (2011)	96	Ipsilesional SO	Contralesional C3/C4	0.571, 20 min	30	Robot-assisted arm training (Bi-Manu Track)	Negative (FM UE, BBT, MRC, MAS)	I
Without robotic concomitant therapy								
Kim et al. (2010)	18	Ipsilesional SO	Contralesional C3/C4	0.800, 20 min	10	OT	Positive (FM UE)	II
Khedr et al. (2013)	40	Ipsilesional SO	Contralesional C3/C4	0.571, 25 min	6	Conventional therapy	Positive (OMCASS), negative (NIHSS, MAC)	II
Lee and Chun (2014)	59	Ipsilesional SO	Contralesional C3/C4	0.800, 20 min	15	OT but no VR (Group A) or VR (Group C)	Positive (MFT and FM UE in Group C), negative (MAS, MMT, BBT)	II
Fusco et al. (2014a)	11	Extracephalic (above right shoulder)	Contralesional C3/C4	0.429, 10 min	10	Traditional rehab	Negative (CNS, 9HPT, pinch force, grasp force, FM UE, TUG, 6MWT, 10MWT, FAC)	II
Andrade et al. (2017)	60	Ipsilesional SO	Contralesional C3/C4	0.571, 20 min	10	PT	Positive (falls, FSST, OSI, FES-I, BBS, 6MWT, STS)	II
Rabadi and Aston et al. (2017)	16	Ipsilesional SO	Contralesional C3/C4	0.286, 30 min	10	OT	Negative (ARAT)	II
Recommendation: cathodal tDCS of contralesional M1 probably effective (Level B) for motor rehab in subacute stroke Recommendation: cathodal tDCS of contralesional M1 to enhance robotic therapy probably not effective (Level B) for motor rehab in subacute stroke								
Bilateral								
Fusco et al. (2013)	9	Ipsilesional C3/C4	Contralesional C3/C4	0.429, 15 min	1^{+icbs}	No	Positive (9HPT), Negative (pinch force, grip force)	III
Fleming et al. (2017)[b]	24	Ipsilesional C3/C4	Contralesional C3/C4	0.400, 20 min	1^{+icbs}	Motor sequence learning task	Negative (JTHFT)	III
Klomjai et al. (2018)	19	Ipsilesional C3/C4	Contralesional C3/C4	0.571, 20 min	1^{+bs}	PT	Positive (FTSST), Negative (TUG, knee extensor MVC)	III
Wang et al. (2014)	9	Ipsilesional C3/C4	Contralesional C3/C4	0.286, 20 min	1	Methylphenidate	Positive (PPT)	II

Table 5. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy or motor tasks	Results	Class
Oveisgharan et al. (2017)	20	Ipsilesional C3/C4*, then F3	Contralesional C3/C4, then right SO	1.250, 30 min (C3/C4) then 60 min (F3)	10	No	Positive (FM UE, ARAT)	II
Saeys et al. (2015)	31	Ipsilesional C3/C4	Contralesional C3/C4	0.429, 20 min	16 (4/wk × 4 wk)+bs	PT + OT	Positive (Tinetti test total, RMA leg-trunk), Negative (TIS, Tinetti test and other RMA subscores)	III
Di Lazzaro et al. (2014)/Exp1	14	Ipsilesional C3/C4	Contralesional C3/C4	0.571, 40 min	5	Standardized PT	Negative (ARAT, 9HPT, hand grip, NIHSS)	II
Di Lazzaro et al. (2014)/Exp2	20	Ipsilesional C3/C4	Contralesional C3/C4	0.571, 40 min	5	CIMT	Negative (ARAT, 9HPT, hand grip, NIHSS)	II
Andrade et al. (2017)	60	Ipsilesional C3/C4	Contralesional C3/C4	0.571, 20 min	10	PT	Positive (falls, FSST, OSI, FES-I, BBS, 6MWT, STS)	II
Recommendation: bilateral tDCS of M1 possibly effective (Level C) for motor rehab in subacute stroke								

Abbreviations: +is, crossover with ipsilesional anodal and sham tDCS conditions; +icbs, crossover with ipsilesional anodal, contralesional cathodal, bilateral, and sham tDCS conditions; +asCF,C, crossover with ipsilesional anodal/sham M1 and DLPFC or M1 alone tDCS conditions; +bs, crossover with bilateral and sham tDCS conditions; LL, target was the motor cortex corresponding to the left or right lower limbs, placed mesial to the upper limbs/just lateral to the sagittal plane, roughly corresponding with C1/C2 in the 10/10 International EEG system; rehab, rehabilitation.

a M1 tDCS was active in all while left DLPFC tDCS was active/sham.

b paper had a large or unclear mix of subacute and chronic stroke patients and was included in both subacute and chronic stroke tables.

0.84) in favor of contralesional tDCS effects, and the 3 montages pooled together had a significant ES of 0.45 (95% CI = 0.18, 0.72) in favor of tDCS effects overall on subacute stroke, although there was also significant and high heterogeneity (I^2 = 64.8%, $P < .001$) (Table 12; Supplemental Figure 3.2.1.).

Other Relevant Parameters and Summary of Motor Function in Stroke—As previously mentioned, we focused on modifiable factors we think are most important to treatment; we were unable to categorize for several non-modifiable factors that may affect tDCS efficacy, for example, age, area of stroke, degree of impairment, etc. (Marquez et al., 2015). The most critical parameters appear to be montage, current density, number of sessions, duration of stimulation, and concomitant treatments. Higher current density and more frequent and longer sessions tend to cause improved and more durable clinical effects; however, a change in any of these factors can change outcomes, and we do not have a systematic measurement of how these factors interact.

Meanwhile, when planning the montage (electrode positions), it is important to consider stroke severity and whether the M1/corticospinal tracts are damaged beyond the point of effective neuroplasticity. In such cases, anodal stimulation of ipsilesional M1 may be ineffective, and cathodal stimulation of contralesional M1 may be detrimental due to the need for intact corticospinal tracts from the intact hemisphere to take over some motor functions of the lesioned hemisphere. We may speculate that studies using reversed polarity (e.g., anodal stimulation of contralesional M1 or reversed bilateral stimulation) could produce better results in some such cases; however, this must be formally studied as the outcome measure, and other factors will likely have an effect. For example, online anodal stimulation (with somewhat unusual parameters) of ipsilesional leg M1 in mostly subcortical strokes improved an ankle-tracking task, while anodal contralesional leg M1 stimulation had a detrimental effect on learning (Madhavan et al., 2011). In a negative trial on contralesional cathodal stimulation within a month of stroke, one-half of the participants' corticospinal tracts may have been too damaged to modulate, and using a right shoulder reference may have reduced current flow to the left M1 that was damaged in one-half of the patients (Fusco et al., 2014).

Computational models show that electrode positions (including "reference" electrodes) could dramatically change current flow directions (Brunoni et al., 2012). Standard tDCS is non-focal, and electrodes can overlap with and stimulate contiguous regions responsible for different functions. Cha and colleagues (Cha et al., 2014) showed improved upper and lower limb Fugl Meyer Test scores with an upper limb montage. Also, cortical anatomy changes post-injury and target areas are measured in variable ways, including tape measurements, TMS, and neuronavigation.

Most stroke studies included infarcts (predominantly) and hemorrhages; however, Mortensen et al. (2016) included only intracranial hemorrhages, mainly in the basal ganglia. One may speculate if this affected the positive results for handgrip strength (benefiting from intact M1) and negative results for the Jebsen Taylor Hand Function Test (as basal ganglia dysfunction can impair speed). Functional recovery may vary between ischemic and hemorrhagic strokes (Schepers et al., 2008); thus an imbalance may be important, especially in acute/subacute stroke and with longer treatment durations potentially confounding recovery.

Regarding trial duration, washout periods in crossovers are important to avoid carryover effects. As placebo effects tend to

drop during follow-ups, parallel arm RCTs with longer follow-ups may help identify whether tDCS alone is beneficial or whether it prolongs the benefits of concomitant therapies, especially acutely effective therapies such as robotics.

Most trials were performed with concomitant treatments or motor tasks that were online, offline, or both (sometimes depending on treatment duration and feasibility). In some studies, these associated therapies seemed to lead to improved outcomes in tDCS groups, while in others they caused a ceiling effect. The temporal relationship of concomitant treatments might enhance, counteract, or cancel out tDCS effects, depending on networks activated and desired outcomes. For example, Giacobbe and colleagues (Giacobbe et al., 2013) showed that tDCS applied prior to robotic training led to improvement, but tDCS during or after training worsened outcomes. A careful evaluation of the literature with power/sample size calculations and strategies to optimize neuroplasticity is thus particularly important for combined therapies. This is especially important for tDCS to enhance robotic therapy, since the negative results might be related to type II error. It is relevant to note that the pooled effects of robotic therapy (with anodal ipsilesional tDCS) on motor function were non-significant in both chronic and subacute stroke; however, the pooled effects of 3 tDCS montages without robotics were significantly favorable in both chronic and subacute stroke despite high heterogeneity.

Therefore, more high-quality RCTs are needed to better understand the effect of many parameters that can have a major impact on motor function in different stroke populations.

Summary and Literature Synthesis—TDCS improves motor rehabilitation in chronic and subacute stroke except when used to enhance robotic therapy. The overall moderate effect size of active tDCS does not seem to enhance the benefits of robotic therapy on any motor outcome using the study protocols tested in our sample, with the exception of 2 studies in chronic stroke. The quantitative analysis is consistent with these findings, although it is important to note that pooling multiple motor outcomes—and the occasional alternative montage—for each study may have affected the results. For example, while anodal ipsilesional tDCS is probably effective in chronic and subacute stroke in the qualitative assessment, the pooled motor results miss significance for ipsilesional tDCS (mostly anodal). Contalesional tDCS is probably effective in chronic stroke (possibly effective on excluding a smaller study) and in subacute stroke, and although its limited pooled sample missed significance in chronic stroke, the larger pooled sample is significant in subacute stroke. Bilateral tDCS is effective in chronic stroke by quantitative and qualitative measures. Overall, the pooled results of all montages in acute and chronic stroke consistently show that tDCS is beneficial, and there is substantial overlap of confidence intervals in favor of tDCS. Additionally, while there is significantly high heterogeneity among studies, there is no evidence of publication bias (Table 12; supplemental Figure 3.1–3.2).

Lefaucheur et al. (2017) also noted the heterogeneity between studies, giving no recommendations for tDCS in motor stroke recovery/rehabilitation (with a much more limited sample than ours), although they too suggested that tDCS seemed to trend toward synergistic effects when combined with other therapies. Meanwhile, a meta-analysis by Bai et al. (2019) analyzed tDCS effects on patients with limb dysfunction following a first unilateral stroke by various factors that are worth mentioning. They found that tDCS significantly improved post-stroke motor function in the upper limbs (SMD = 0.26, 95% CI = 0.09, 0.42) and lower limbs (SMD = 0.47, 95% CI = 0.17, 0.77). In the case of upper limb dysfunction, tDCS showed significant effects only in chronic stroke, but not subacute or acute stroke, and even then the effects were modest (SMD = 0.25, 95% CI = 0.04, 0.39); the pooled effects of acute through chronic stroke were also modest but significant (SMD = 0.22, 95% CI = 0.04, 0.39). Furthermore, anodal (SMD = 0.25, 95% CI = 0.66, 0.43) and especially cathodal (SMD = 0.41, 95% CI = 0.15, 0.67) but not bilateral tDCS significantly improved upper limb function. Interestingly, more tDCS sessions were not necessarily better; significant upper limb improvements were found following 10 or fewer sessions of anodal (SMD = 0.40, 95% CI = 0.16, 0.65) and cathodal (SMD = 0.79, 95% CI = 0.43, 1.16) tDCS at a current density greater than 0.29 A/m^2, but no improvements followed more than 10 tDCS sessions (in 4 anodal studies and 1 cathodal study). Our qualitative review also showed no clear benefit to more than 10 tDCS sessions, although this is confounded by the concomitant treatments. Bai et al. (2019) also reported in a smaller sample of lower limb dysfunction that tDCS had a significant moderate effect on subacute stroke (SMD = 0.56, 95% CI = 0.22, 0.90) as well as subacute plus chronic stroke pooled together (SMD = 0.47, 95% CI = 0.17, 0.77), but not chronic stroke alone (only 2 studies). Furthermore, bilateral tDCS (3 pooled studies) had a moderate effect size on subacute stroke lower limb dysfunction (SMD = 0.59, 95% CI = 0.14, 1.03). It is worth noting that this meta-analysis used only 1 motor outcome for each study and that their selected studies overlapped with ours but included other studies as well, perhaps as they had searched more databases than PubMed. They concluded that the optimal parameters and their timing for upper and lower limb post-stroke dysfunction were different.

Other meta-analyses addressed other aspects of tDCS for post-stroke motor function. For example, one found that rTMS but not tDCS improved postural control and functional balance (Kang et al., 2020); one found that tDCS improved fine motor function with a moderate effect size of 0.31 (95% CI = 0.08, 0.55) and had a large effect size of 1.25 (95% CI = 0.09, 2.41) on function of the non-dominant hand when applied to the contralesional non-dominant hemisphere (O'Brien et al., 2018); one found that paretic limb force production (grip force, pinch force, knee extension torque, etc.) benefited from tDCS and rTMS in acute to chronic stroke (Kang et al., 2016). Yet, despite multiple studies and meta-analyses, there is a great need for larger RCT samples and careful optimization of tDCS parameters.

tDCS Effects on Language Function in Stroke—One-third of strokes, particularly left-sided strokes involving language networks, lead to aphasia (Franzén-Dahlin et al., 2010; Basso et al., 2013; Rohde et al., 2013), an acquired language expression and/or comprehension disorder. Aphasia is one of the most socially disabling post-stroke deficits; symptoms often persist after therapy (Lazar et al., 2010), so new rehabilitation techniques are needed, particularly low-risk therapies such as tDCS. Generally, tDCS treatment aims to address interhemispheric competition between residual language areas in the damaged left hemisphere and the intact right hemisphere (Kiran, 2012). Thus, similar to stroke motor function parameters, tDCS strategies often aim to excite and thus enhance perilesional left hemispheric output or inhibit the intact right hemisphere and counteract its inhibitory effect on the ipsilesional hemisphere.

A PubMed search on "tDCS and aphasia" resulted in 25 studies on chronic aphasia that fulfilled our criteria, excluding the few variable publications on acute/subacute aphasia.

tDCS in Chronic Aphasia—Our results were divided into anodal (predominantly left-sided), cathodal (predominantly right-

sided), and bilateral stimulation groups. We mostly classified aphasia into nonfluent (expressive) and fluent (receptive), giving more detail when relevant as this broad categorization does not distinguish between different forms of nonfluent aphasia (e.g., Broca's aphasia, transcortical motor aphasia), fluent aphasia (e.g., Wernicke's aphasia, transcortical sensory aphasia), and so on. For example, repetition is impaired in perisylvian aphasias, including Broca's, Wernicke's, conduction, and global (expressive and receptive) aphasias, but relatively preserved in transcortical aphasias. Broca's aphasia is typically thought to follow damage to the inferior frontal gyrus (posterior aspect of the operculum), while Wernicke's aphasia follows damage to the posterior superior temporal gyrus. However, the exact areas can vary, subcortical regions may be involved, and injuries to other areas may lead to similar or overlapping deficits (Naeser et al., 1987; Alexander et al., 1990; Kreisler et al., 2000; Hillis et al., 2008).

We included aphasia types in the sample size column (Table 6). As areas targeted and their descriptions varied, sometimes guided by imaging, we mostly avoided EEG nomenclature (which was variable and less intuitive than with motor areas) and used what we thought was the clearest description of the target region.

Anodal tDCS—Regarding repeated-session RCTs, 1 Class I study was positive for non-futility, 2 Class II studies had different parameters and results, and 15/18 Class III studies/montages were positive (Table 6).

In line with approximate estimations of language regions, the studies in this review mostly targeted anodal tDCS at left inferior frontal regions for nonfluent aphasias and left posterior/temporal regions for fluent aphasias. However, this was not always consistent, and studies often included a mix of different types of aphasia. The vast majority were crossover RCTs, and all included study-specific language training or treatment (ranging from anomia treatment, to repetition tasks, melodic intonation therapy, conversational therapy, speech therapy, etc.) except for 1 crossover RCT where inpatients were undergoing speech therapy that was not intended as a concomitant treatment for tDCS (Volpato et al., 2013a). This RCT found no effect on object and action naming, perhaps because the inpatient logopedic therapy was separated from tDCS by 90 minutes (to avoid interaction) or perhaps because 6/8 patients had fluent aphasia but they targeted Broca's area (Volpato et al., 2013a). Nevertheless, patients reported subjective everyday language improvement. Likewise, 2 other studies were negative on providing anodal tDCS to the left superior temporal gyrus but in patients with nonfluent (including global) aphasia (You et al., 2011; Marangolo et al., 2014a).

All other studies were positive for anodal tDCS, although 1 Class I study used a nonfutility design and was not powered for efficacy (Fridriksson et al., 2018). Most crossover studies showed significant improvements compared with sham, predominantly in naming (for nouns and/or verbs) as well as reaction times, response accuracy, repetition, and also production of (conversational) content units. Multiple crossover studies (Fiori et al., 2013; Marangolo et al., 2013a) showed improvements in noun-naming accuracy after left temporal anodal tDCS and in verb-naming accuracy after left frontal anodal tDCS, highlighting the different functions of those regions. Anodal tDCS with conversational therapy led to significant improvements only when targeting left inferior frontal areas (Marangolo et al., 2014a, 2014b).

Meanwhile, a study tested anodal stimulation over Broca's homologue at the right inferior frontal gyrus (Cipollari et al., 2015; Keser et al., 2017) in patients with nonfluent aphasia. It combined tDCS (enhancing the unaffected hemisphere) with melodic intonation therapy and found improvements in word and sentence repetition (Cipollari et al., 2015); additionally, while cortical modulation occurred on TMS-EEG in active and sham conditions, cortical excitability was maximized by anodal tDCS. A smaller study that found improved verb fluency also combined melodic intonation therapy with anodal right inferior frontal tDCS, but more posteriorly and with only 3 (vs 15) tDCS sessions at a higher current density (Vines et al., 2011). Another study that combined right temporoparietal cortex anodal tDCS with online anomia training found improved picture naming for trained objects (Flöel et al., 2011).

One trial gave twice daily anodal left M1 tDCS with computer-assisted naming therapy, and yet this unusual montage improved aphasia (Meinzer et al., 2016).

The single-session crossover RCTs had unusual designs. One targeted the left DLPFC and found improvements in phonemic verbal fluency and in picture-naming RT, but only for very high-frequency words (Pestalozzi et al., 2018). The other was a small crossover RCT within a nested parallel study design (patients in the anodal left and cathodal right frontotemporal groups were randomized to active and sham tDCS conditions) (Monti et al., 2008); only cathodal tDCS right frontotemporal region led to positive results (in picture-naming accuracy but not response time), but there were errors in polarity applications.

Recommendation: anodal tDCS of Broca's area, its homologue, or Wernicke's area is possibly effective (Level C) in chronic post-stroke aphasia (Table 6). On excluding 13 studies/montages with $n<10$ (all Class III), the recommendation changes to anodal tDCS of Broca's area is possibly effective (Level C) in chronic post-stroke aphasia.

Quantitative analysis of 4 studies on ipsilesional anodal tDCS over Broca's area in aphasia (naming accuracy, production of correct content, object and naming accuracy) showed a significant ES of 0.65 (95% CI = 0.29, 1.01) in favor of tDCS (Table 12; supplemental Figure 3.3.).

Cathodal tDCS—Two Class II and 2 Class III repeated-session RCTs were positive. In the Class II study mentioned above, cathodal tDCS of the right superior temporal gyrus led to significant improvements (in auditory verbal comprehension), while anodal tDCS of the left superior temporal gyrus did not—perhaps because of the left infarcts (You et al., 2011). This may be consistent with the interhemispheric competition theory mentioned previously. Right temporoparietal cathodal (and anodal, as mentioned above) tDCS conditions improved trained picture naming (Flöel et al., 2011). The Class II and III studies on cathodal tDCS of Broca's homologue were both positive.

As to single-session studies, Monti and colleagues' (Monti et al., 2008) Experiment 1 was positive as mentioned above for cathodal tDCS of the left frontotemporal region, but Experiment 2 was unsurprisingly negative for occipital tDCS (Monti et al., 2008). Another crossover study shows the importance of tDCS target relating to lesion location as it was positive for patients with Broca's area lesions and also correlated with arcuate fasciculus integrity (Rosso et al., 2014).

Recommendation: cathodal right frontotemporal tDCS is possibly effective (Level C) in chronic post-stroke aphasia recovery (Table 6).

Bilateral tDCS—Four Class III studies repeatedly targeting the left inferior frontal gyrus with anodal tDCS and its homologue with cathodal tDCS in combination with language or speech therapy

Table 6. tDCS Studies in Chronic Post-Stroke Aphasia

Author	Sample (n) (aphasia type)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Anodal								
Monti et al. (2008)/Exp1	4 (nonfluent—Broca's, global)	Left frontotemporal area	Right shoulder	0.571, 10 min	$1^{+as,cs}$	No	Negative (picture naming accuracy, RT)	III
Pestalozzi et al. (2018)	14 (4 nonfluent, 10 fluent—Broca, global, anomic, conduction)	F3	Right SO	0.400, 20 min	1^{+as}	Picture naming, phonemic (verbal) fluency, repetition, Flanker tasks	Positive (verbal fluency, RT of picture naming very high frequency words), Negative (picture naming, repetition)	III
Baker et al. (2010)	10 (4 nonfluent, 6 fluent)	Left frontal area	Right shoulder	0.400, 20 min	5^{+as}	Computerized anomia treatment (online picture-word matching task)	Positive (naming accuracy for treated nouns and untreated nouns)	III
Fridriksson et al. (2011)	8 (fluent)	Left posterior cortex	Contralesional SO	0.400, 20 min	5^{+as}	Computerized anomia treatment (word-picture matching task)	Positive (RT during correct naming of trained nouns), Negative (for untrained nouns)	III
Vines et al. (2011)	6 (nonfluent)	Right posterior inferior frontal gyrus	Contralesional SO	0.736, 20 min	3^{+as}	Melodic intonation therapy	Positive (verbal fluency)	III
Marangolo et al. (2011)	3 (nonfluent apraxia of speech)	Left inferior frontal gyrus (Broca's area)	Contralesional SO	0.286, 20 min	5^{+as}	Language training (repetition tasks)	Positive (articulated response accuracy, various transfer of treatment effects)	III
Fiori et al. (2013)	7 (nonfluent)	Left frontal (Broca's) area	Contralesional SO	0.286, 20 min	5^{+aFaTs}	Language training (noun and verb training, separated by a month)	Positive (naming accuracy for verbs)	III
Marangolo et al. (2013b)	12 (nonfluent)	Left inferior frontal (Broca's) area	Contralesional SO	0.286, 20 min	10^{+aFaTs}	Conversational therapy (discourse skills)	Positive (production of correct Content Units, verbs, sentences, treatment generalization)	III
Marangolo et al. (2013a)	7 (nonfluent)	Left frontal (Broca's) area	Contralesional SO	0.286, 20 min	5^{+aFaTs}	Language training (verb naming)	Positive (verb naming accuracy)	III
Volpato et al. (2013a)	8 (6 fluent, 2 nonfluent)	Left inferior frontal (Broca's) area	Contralesional SO	0.571, 20 min	10^{+as}	No[a]	Negative (object and action naming)	III

Table 6. Continued

Author	Sample (n) (aphasia type)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Anodal								
Marangolo et al. (2014a)	8 (nonfluent)	Left inferior frontal (Broca's) area	Contralesional SO	0.286, 20 min	10+aFaTs	Conversational therapy	Positive (number of endophoric references, treatment generalization)	III
Vestito et al. (2014)	3 (2 nonfluent, 1 fluent anomic)	Left inferior frontal area	Contralesional SO	0.600, 20 min	10+as	Naming training	Positive (picture naming)	III
Campana et al. (2015)	20 (nonfluent)	Left inferior frontal gyrus	Contralesional SO	0.571, 20 min	10+as	Conversational therapy	Positive (picture description, noun and verb naming)	III
Cipollari et al. (2015)	6 (nonfluent)	Right inferior frontal gyrus (F8)	Left SO	0.571, 20 min	15+as	Melodic intonation therapy	Positive (improved words and sentences repetition)	III
Floel et al. (2011)	12 (nonfluent and fluent)	Right temporoparietal cortex	Contralesional SO	Unclear electrode size (1mA), 20 min	3+acs	Computerized anomia training	Positive (picture naming accuracy for trained objects)	III
Fiori et al. (2011)/Exp2	3 (nonfluent)	Left Wernicke's area	Contralesional SO	0.286, 20 min	5+as	Language training (anomic treatment paradigm—lists of different words)	Positive (picture naming accuracy, decreased vocal RT)	III
Fiori et al. (2013)	7 (nonfluent)	Left temporal (Wernicke's) area	Contralesional SO	0.286, 20 min	5+aFaTs	Language training (noun and verb training, separated by a month)	Positive (naming accuracy for nouns)	III
Marangolo et al. (2013b)	12 (nonfluent)	Left posterior superior temporal (Wernicke's) area	Contralesional SO	0.286, 20 min	10+aFaTs	Conversational therapy (discourse skills)	Negative (production of correct Content Units, verbs, sentences, treatment generalization)	III
Marangolo et al. (2013a)	7 (nonfluent)	Left temporal (Wernicke's) area	Contralesional SO	0.286, 20 min	5+aFaTs	Language training (verb naming)	Positive (noun naming accuracy)	III
Marangolo et al. (2014b)	8 (nonfluent)	Left posterior superior temporal (Wernicke's) area	Contralesional SO	0.286, 20 min	10+aFaTs	Conversational therapy	Negative (number of endophoric references, treatment generalization)	III
You et al. (2011)	21 (nonfluent global)	Left superior temporal gyrus	Contralesional SO	0.571, 30 min	10	Conventional speech and language therapy	Negative (auditory verbal comprehension, spontaneous speech, repetition, naming)	II

Table 6. Continued

Author	Sample (n) (aphasia type)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Anodal								
Meinzer et al. (2016)	26 (nonfluent and fluent—Broca's, global, amnestic Wernicke's)	C3	Contralesional SO	0.286, 20 min	16 (2/d × 8 d)	Computer-assisted naming treatment	Positive (naming trained items maintenance, transfer to untrained items, functional communication)	II
Fridikson et al. (2018)	74 (nonfluent and fluent)	Temporal lobe region w/ highest naming activation on fMRI	Right SO	0.400, 20 min	15	Speech therapy (computerized behavioral treatment of anomia)	Positive for non-futility (naming 80 trained items)	I
Recommendation: anodal tDCS of Broca's area, its homologue, or Wernicke's area possibly effective (Level C) in chronic post-stroke aphasia rehab								
Cathodal								
Monti et al. (2008)/Exp1	4 (nonfluent—Broca's, global)	Contralesional (right) shoulder	Ipsilesional (left) frontotemporal	0.571, 10 min	$1^{+as,cs}$	No	Positive (picture naming accuracy), Negative (RT)	III
Monti et al. (2008)/Exp2	8 (nonfluent—Broca's, global)	Contralesional (right) shoulder	Occipital	0.571, 10 min	1^{+cs}	No	Negative (picture naming accuracy, RT)	III
Rosso et al. (2014)	25 (nonfluent)	Left SO	Right inferior cortex	0.286, 15 min	1^{+cs}	No	Positive for group w/ Broca's area lesions and correlating w/ integrity of arcuate fasciculus (picture naming accuracy), Negative for group w/ no Broca's area lesions (picture naming accuracy)	III
Floel et al. (2011)	12 (9 nonfluent, 3 fluent)	Contralesional SO	Right temporoparietal cortex	Unclear electrode size (1mA), 20 min	3^{+acs}	Computerized anomia training	Positive (picture naming accuracy for trained objects)	III
Fiori B et al. (2019)—1[b]	10 (nonfluent)	Ring (4 electrodes around cathode at radius of 3.5 cm)	F6 (Broca's homologue)	Unclear electrode size (1 mA), 20 min	5^{+cs}	Verb retrieval task	Negative (verb recovery)	III
Fiori et al. (2019)—2[b]	10 (nonfluent)	Ring (4 electrodes around cathode at radius of 3.5 cm)	F6 (Broca's homologue)	Unclear electrode size (2 mA), 20 min	5^{+cs}	Verb retrieval task	Positive (verb recovery)	III

Table 6. Continued

Author	Sample (n) (aphasia type)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/task	Results	Class
Anodal								
Kang et al. (2011)	10 (8 nonfluent, 2 fluent)	Ipsilesional SO	Right inferior frontal (Broca's homologue) area	0.800, 20 min	5[+cs]	Conventional word retrieval training	Positive (picture naming accuracy), Negative (reaction times, cued responses)	III
You et al. (2011)	21 (nonfluent—global)	Ipsilesional SO	Right superior temporal gyrus	0.571, 30 min	10	Conventional speech and language therapy	Positive (auditory verbal comprehension), Negative (spontaneous speech, repetition, naming)	II
Silva et al. (2018)	14 (nonfluent)	Left SO	Right Broca's area homologue (F8)	Unclear electrode size (2mA), 20 min	5	No	Positive (Boston test mean time for correct responses w/ strategy), Negative (number of hits with/without strategies, mean time of hits)	II
Recommendation: cathodal right frontotemporal tDCS possibly effective (Level C) in chronic post-stroke aphasia rehab								
Bilateral								
dos Santos et al. (2017)	13 (fluent and nonfluent)	Left inferior frontal (Broca's) area	Right inferior frontal (Broca's homologue) area	0.200 (anode), 0.571 (cathode), 20 min	1[+bs]	No	Negative (picture naming/strategy, response time/strategy, total response time)	III
Marangolo et al. (2013c)	8 (nonfluent)	Left inferior frontal gyrus	Contralesional inferior frontal gyrus	0.571, 20 min	10[+bs]	Language therapy (for speech apraxia)	Positive (accuracy data for syllables, words, sentences; vocal reaction times data for words, sentences)	III
Marangolo et al. (2014b)	7 (nonfluent)	Left inferior frontal gyrus	Contralesional inferior frontal gyrus	0.571, 20 min	10[+bs]	Speech therapy	Positive (correct picture description and verb and noun naming)	III
Marangolo et al. (2016)	9 (nonfluent)	Left inferior frontal gyrus	Contralesional inferior frontal gyrus	0.571,20 min	10[+bs]	Language therapy (for speech apraxia)	Positive (accuracy data for syllables, words, sentences; vocal reaction times data for words, sentences)	III
Recommendation: bilateral tDCS w/ anodal stimulation of Broca's area and cathodal stimulation of its homologue is possibly effective (Level C) in chronic post-stroke aphasia rehab								

Abbreviations: +acs, crossover with anodal, cathodal and sham tDCS conditions; +aFaTs, crossover with anodal frontal, anodal temporal, and sham conditions; +as, crossover with anodal and sham tDCS conditions; +bs, crossover with bilateral and sham tDCS conditions; +cs, crossover with cathodal and sham tDCS conditions; rehab, rehabilitation; w/, with.

a Participants were undergoing inpatient rehabilitation, including speech therapy, but logopedic training was intentionally separated by 90 minutes from tDCS to avoid its physiologic effects.

b 2 separate groups of participants were crossed over to either 2 mA or 1 mA of cathodal tDCS vs sham; +as,cs, 2 groups of 4 participants each, and within each group participants were crossed over to anodal and sham or cathodal and sham tDCS conditions—note that all 8 participants were in Experiment 2, months later.

were positive (Marangolo et al., 2013c, 2014b, 2016). The single-session study was also positive (dos Santos et al., 2017).

Recommendation: bilateral tDCS with anodal stimulation of Broca's area and cathodal stimulation of its homologue is possibly effective (Level C) in chronic post-stroke aphasia recovery (Table 6).

All 3 studies (Class III) had n < 10, so excluding them changed the recommendation to none.

Summary and Literature Synthesis—The research on tDCS in chronic post-stroke aphasia appears promising, though it is still in early stages. While there were many more trials in the anodal group than the others, they did not quite fulfill criteria for probable effectiveness. However, limited quantitative analysis of the only 4 studies we could extract showed that ipsilesional anodal tDCS significantly improves aphasia, and all studies had good overlap of their 95% confidence limits.

Conversely, Lefaucheur et al. (2017) gave no recommendation on anodal left Broca's area tDCS in post-stroke nonfluent aphasia. However, a previous meta-analysis (Bucur et al., 2019) found that tDCS moderately improved post-stroke naming with an effect size of 0.33 (95% CI = 0.03, 0.62), noting that effects were greater at follow-up (ES = 0.54, 95% CI = 0.21, 0.86) than immediately after tDCS treatment (ES = 0.34, 95% CI = 0.02, 0.65); benefits were in chronic stroke (there were only 2 subacute studies). Meanwhile, an individual patient data meta-analysis (Rosso et al., 2018) on repeated tDCS sessions in chronic post-stroke aphasia found a much higher improvement in naming (SMD = 0.80, 95% CI = 0.27, 1.33); furthermore, a dose-dependent relationship was found (more than 5 tDCS sessions), and naming improved irrespective of aphasia severity, disorders of comprehension, or time between stroke occurrence and tDCS application.

The literature is therefore encouraging of further investigation into different tDCS protocols and language outcomes; we recommend that methods of localization (by MRI as in much of our sample) and aphasia subtypes should guide eligibility criteria. We also recommend that future studies report primary language outcomes in a way that can be calculated for future meta-analyses.

Epilepsy

Epilepsy, a serious and prevalent chronic neurological disorder affecting nearly 70 million people (Ngugi et al., 2010), is "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition…." (Theodore et al., 2006; Fisher et al., 2014). About 25% to 30% of epilepsy patients do not reach the treatment goal of "no seizures and no side-effects" even on 2 appropriate antiepileptic drugs; these patients often require surgical evaluation (Kwan et al., 2010; Brodie et al., 2012). However, surgery is not always possible, so various adjunctive neuromodulation techniques have been used, predominantly vagal nerve stimulation, and to a lesser extent more invasive techniques such as cortical stimulation, responsive neurostimulation and DBS (Theodore and Fisher, 2004, 2007; Groves and Brown, 2005; Boon et al., 2007; Löscher et al., 2009; Salanova et al., 2015; Thomas and Jobst, 2015) and noninvasive techniques such as rTMS and tDCS. The underlying principle is that extrinsic stimulation can reduce hyperexcitability, suppress seizures, and interfere with epileptiform discharges (EDs) seen on EEGs (Löscher et al., 2009; San-Juan et al., 2015). We therefore evaluated the literature for safety and efficacy of tDCS in epilepsy regarding seizure frequency.

A PubMed search using the keywords "transcranial direct current stimulation" OR "tDCS" OR "brain polarization" OR "galvanic stimulation" AND "epilepsy" yielded 7 results that fit our criteria, and we added 2 more papers identified by our authors (Auvichayapat et al., 2016; Assenza et al., 2017). As mentioned previously, this disorder was 1 of the exceptions where we included trials with pediatric and/or adult patients.

tDCS in Epilepsy—Of repeated-sessions RCTs, 3/4 Class II and 1 Class III trial were positive for decreased seizure frequency. One Class II trial showed safety but not efficacy. All trials were well-tolerated.

A recent trial randomized patients with refractory mesial temporal lobe epilepsy with hippocampal sclerosis into 3 groups: 2 cathodal (3 vs 5 daily sessions) and 1 sham tDCS over the epileptic focus (San-Juan et al., 2017). Despite a prominent placebo effect with all groups improving, the 3- and 5-day active groups each did significantly better than sham at the 2-month follow-up (seizure frequency decreased respectively by 43.4%, 54.6% and 6.25%). Response was achieved by 50%, 62.5%, and 25% of those groups, respectively. The 2 active groups had no significant differences in efficacy, and active tDCS did not impact EDs. Meanwhile, a crossover RCT gave patients with refractory mesial temporal lobe epilepsy with hippocampal sclerosis modulated cathodal tDCS to decrease excitability and also modulated the cortex with its natural rhythm (using 12-Hz frequency based on EEG-neurofeedback studies). Three sessions significantly reduced seizure frequency up to 1 month later. About 83% of the active group (mostly male) achieved response (Tekturk et al., 2016). Another trial on TLE, this time well-controlled, gave left DLPFC anodal tDCS aiming to improve depression and working memory; indeed, depression improved, with no change in seizure frequency or EDs, thereby suggesting safety of even anodal tDCS in well-controlled epilepsy (Liu et al., 2016).

The last repeated-session RCT targeted children with Lennox-Gastaut Syndrome, a severe childhood epilepsy with highly frequent and different types of seizures, most with motor components. This study (Auvichayapat et al., 2016) found that cathodal left M1 tDCS significantly reduced seizure frequency compared with sham on each of the 5 days of tDCS, plus immediately and at 1-, 2-, 3-, and 4-week follow-ups. In fact, the baseline mean seizure frequency (nearly 81 seizures/day) of the active group dropped 99.84% by day 5 and 55.96% by 4 weeks later. The active group had significantly decreased frequency of tonic, atonic, and absence seizures (not myoclonic or partial seizures) compared with sham. Epileptiform discharges also decreased significantly up to 3 weeks later. Both groups tolerated the treatment well with no differences in vital signs or oxygen saturation during and after treatment.

As to single-session studies, the first aimed to investigate safety (Fregni et al., 2006c) due to concerns about increasing excitability under the (reference) anode. Patients with malformations of cortical development had a trend towards seizure reduction (by 56% 1 month later) and marginally significant ED reduction following cathodal tDCS (Fregni et al., 2006f). In pediatric patients with severely intractable focal epilepsy (Auvichayapat et al., 2013), 1 tDCS session led to a minor but significant drop in clinical seizure frequency and a significant decrease of EDs up to 57.6% by 48 hours later (Auvichayapat et al., 2013). Intractable TLE also had improved seizures after 1 session (Assenza et al., 2017).

Table 7. tDCS Studies in Epilepsy

Author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy/tasks	Results	Class
Assenza et al. (2017)	10	Contralateral homologue	Epileptic focus	0.286, 20 min	1[+cs]	No	Positive (seizure frequency decreased)	III
Fregni et al. (2006c)	19	Silent area	Epileptic focus	0.286, 20 min	1	No	Negative (seizure frequency not increased or decreased)	II
Auvichayapat et al. (2013)	36	Contralateral shoulder	Epileptic focus	0.286, 20 min	1	No	Positive (seizure frequency decreased)	II
Tekturk et al. (2016)	12	Contralateral SO	Epileptic focus—HS side (T7 or T8)	0.571[b], 30 min	3[+cs]	No	Positive (seizure frequency decreased)	III
Liu et al. (2016)	33	F3	Contralateral SO	0.571, 20 min	5	No	Negative (seizure frequency not increased or decreased)	II
Auvichayapat et al. (2016)	22	Right shoulder	C3	0.571, 30 min	5	No	Positive (seizure frequency decreased)	II
San-Juan et al. (2017)[a]	28	Contralateral (silent) SO	Epileptic focus	0.571, 30 min	3	No	Positive (seizure frequency decreased)	II
San-Juan et al. (2017)[a]	28	Contralateral (silent) SO	Epileptic focus	0.571, 30 min	5	No	Positive (seizure frequency decreased)	II
Recommendation: cathodal tDCS probably safe (no increase in seizures) and effective (decrease in seizures) in epilepsy (Level B)								

Abbreviations: +cs, crossover study with cathodal and sham conditions.
a One trial with 3 arms (3 sessions, 5 sessions and sham).
b modulated tDCS peak sinusoidal direct current, 12-Hz frequency.

Recommendation: cathodal tDCS is probably safe (no increase in seizures) and effective (decreased seizures) in epilepsy (Level B) (Table 7).

Quantitative analysis of 4 studies/montages shows a significant ES of –0.70 (95% CI = –1.38, –0.02) in favor of cathodal tDCS effects on seizure frequency in epilepsy (Table 12; supplemental Figure 4).

Summary and Literature Synthesis—While Lefaucheur et al. (2017) gave no recommendations for tDCS in epilepsy, in our review all cathodal tDCS studies/montages showed statistically significant, clinically relevant, and long-lasting reductions in seizure frequency in patients with intractable epilepsy with as few as 3 to 5 sessions. This was confirmed on quantitative analysis of pooled effects despite the small sample, and there was overlap of confidence limits in all studies included. Additionally, anodal tDCS to treat comorbid neuropsychiatric symptoms may be safe in well-controlled epilepsy. However, larger RCTs are needed to investigate different stimulation parameters and forms of tDCS on seizure control, EEG findings, long-term effects, and mechanisms of action. AED use should also be considered in epilepsy trials. While anodal tDCS might be inhibited by sodium-channel blockers such as carbamazepine, they may not influence cathodal tDCS. This is important as many antiepileptic drugs are sodium-channel blockers, and thus cathodal tDCS is a promising adjunctive treatment, even in women on lamotrigine who are pregnant or of child-bearing age. TDCS also theoretically poses no risk to the fetus (Vigod et al., 2014), and early results from a trial on depressed pregnant women show tolerability (Palm et al., 2017a).

tDCS in Psychiatric Disorders

Major Depressive Disorder (MDD)—MDD is a disabling chronic condition affecting 4.4% of the global population in 2015 and severely impairing millions (Murray and Lopez, 1997; Hedden et al., 2016; Anon, 2017). MDD symptoms include persistent low mood, anhedonia (diminished pleasure in previously enjoyable activities), negative thoughts, sleep impairments, and psychomotor retardation. Depression has an estimated all-cause mortality risk of 1.6 and suicide risk of 19.7 (Chesney et al., 2014). Additionally, nearly 30% of patients have refractory depression despite receiving appropriate psychological and pharmaceutical therapy (Rush et al., 2006) and thus need other treatment options.

Such options include electroconvulsive therapy (ECT) and NIBS techniques, for example, rTMS, which is now FDA approved for MDD even in refractory depression (Burt et al., 2002; Horvath et al., 2014), and deep-TMS (Yip et al., 2017). tDCS is safer than both techniques and has had positive results on multiple meta-analyses (Kalu et al., 2012; Berlim et al., 2013; Shiozawa et al., 2014). We therefore aimed to investigate the effects of tDCS on depression in MDD.

Lefaucheur and colleagues (Lefaucheur et al., 2017) gave a Level B recommendation (probable efficacy) for left DLPFC anodal/right DLPFC cathodal tDCS in non-resistant major depressive episodes. Electrode placement and polarity are important for network modulation in different populations, and MDD brains have structural and functional alterations, for example, in fronto-cingulo-striato-pallido-thalamic circuits (Bora et al., 2012a, 2012b) and other areas relating to emotional and cognitive regulation. These differences can relate to the severity, chronicity, and treatment responsiveness of the disease (Chen et al., 2007; Sacher et al., 2012; Fu et al., 2013; Sämann et al.,

2013; Chi et al., 2015; Dichter et al., 2015). For example, patients with more gray matter in the pregenual ACC had faster and longer lasting improvement with fluoxetine (Chen et al., 2007). Additionally, resting-state hyperconnectivity in the default mode network and hypoconnectivity in the cognitive control network (which includes DLPFC and ACC) are greater in treatment-resistant MDD compared with treatment-sensitive MDD; the latter occurs with higher fronto-limbic connectivity (Dichter et al., 2015). When designing NIBS protocols such as TMS or tDCS, it is important to consider the specific cortical and subcortical imbalances in MDD pathophysiology, the efficacy of modulating chosen targets, and the likely downstream effects of this modulation.

A PubMed search using the keywords "transcranial direct current stimulation" and "major depressive disorder" yielded 15 results that fit our criteria. It is relevant to note that while most papers excluded bipolar disorder, 2 studies included unipolar depression (primarily) and bipolar disorder patients (Palm et al., 2012; Loo et al., 2018). We did not restrict our recommendations to response and remission, influenced by a meta-analysis (Shiozawa et al., 2014) that showed efficacy with continuous outcomes (i.e., depression improvement) but not categorical outcomes (response or remission); most trials had small samples (Table 8), so we consider them underpowered for categorical/binary outcomes.

tDCS in MDD—All studies had at least 5 tDCS sessions, and the overwhelming majority placed the anode over the left DLPFC (F3) or just anterior to the left DLPFC ("pF3"). Seven studies placed the cathode over the right DLPFC (F4), while the rest placed the cathode over the right supraorbital area (frontopolar/orbitofrontal stimulation) or more laterally at F8 (frontotemporal), except for 1 RCT using an extracephalic reference. Due to evidence of hypofunction in the left DLPFC and hyperfunction in the right DLPFC in MDD (Mayberg et al., 2000), multiple recent studies targeted those sites for excitation and inhibition respectively (Table 8).

Left DLPFC Anode, Right DLPFC Cathode—Two Class I and 1/4 Class II studies were positive for this montage (a study on pregnancy was analyzed separately).

The negative studies included 1 on treatment-resistant MDD patients (many resistant to ECT) where both active and sham tDCS groups improved after 15 sessions (Blumberger et al., 2012); 1 combined active/sham tDCS with online cognitive control therapy (CCT); again, both groups improved but with no differences between them, suggesting that CCT had a ceiling effect (Brunoni et al., 2014) despite the higher current density and longer tDCS session (Table 8). Meanwhile, a pilot trial on severely depressed inpatients provided right unilateral ultrabrief ECT following bilateral DLPFC active/sham tDCS. Again, depression improved in the active tDCS group by the end of the second week, but it was not significant, perhaps overshadowed by stronger ECT effects (Mayur et al., 2018). Aside from demonstrating safety and feasibility of the combined intervention, it is interesting to note that the active tDCS group required a significantly higher stimulus dose at 6 times the seizure threshold (from the second to the sixth and last ECT session) compared with the sham tDCS group. It suggests that either the right cathodal DLPFC tDCS or the combination of left anodal and right cathodal tDCS raised the seizure threshold significantly, which might have implications for how to combine the 2 treatments in the future and also for patients at risk of seizures outside of ECT.

Of the positive studies, 1 found improved depression (and cognitive tasks including attention and working memory) in antidepressant-free patients with moderate to severe depression; there was an association between cognitive control and depression improvement (Salehinejad et al., 2017). The other positive studies were Class I RCTs comparing tDCS with selective serotonin reuptake inhibitors.

SELECT-tDCS (n = 120), a 2 × 2 factorial trial on sertraline vs tDCS (Brunoni et al., 2013), found significant and clinically relevant additive sertraline and tDCS effects; additionally, the combined tDCS+sertraline group and tDCS alone had significantly improved response (63.3% and 43.3%) and remission rates (46.7% and 40%), respectively. Driven initially by tDCS, only the combined group improved significantly at 2 weeks.

ELECT-TDCS (n = 245) compared tDCS with escitalopram in moderately to severely depressed but antidepressant-free patients. While they did not find tDCS to be noninferior to escitalopram (escitalopram had better results though this cannot be confirmed with a noninferiority design), tDCS was better than placebo and the difference was clinically relevant though delayed (by week 10 but not week 3); previous trials also showed delayed tDCS effects (Brunoni et al., 2017). By week 10, response (not remission) rates were significantly improved in each of the tDCS and escitalopram groups. Despite using 22 tDCS sessions, clinical improvements were similar to prior studies.

It is important to note that the combined group in SELECT-tDCS and tDCS group in ELECT-tDCS had more treatment-emergent mania/hypomania; however, patients had been antidepressant-free prior to enrollment.

Finally, a pilot study on pregnant women who declined antidepressants to avoid fetal effects showed nonsignificant improvements after active/sham treatment; nevertheless, the 4-point change on Montgomery–Åsberg Depression Rating Scale (MADRS) was greater than the MCID of 1.6 to 1.9 (Vigod et al., 2019). Significantly, 75% vs 15% of active vs sham tDCS patients were in remission 1 month postpartum. Safety outcomes for mother and child were similar between groups, showing that tDCS may be a good option for pregnancy, although larger studies are needed in this vulnerable population.

Left DLPFC Anode, Right Frontotemporal Cathode—For this montage, 1/2 Class I and 1/2 Class II studies were positive; all included moderately to severely depressed patients who were not necessarily antidepressant free.

One RCT combined active/sham CCT with active/sham tDCS (Segrave et al., 2014) and found significantly improved depression (and 44% response rates) in the tDCS+CCT group 3 weeks later but not immediately after the 5 sessions (the half-sham groups had the opposite effect). This montage may have better targeted the ACC (including the pregenual area) compared with the bilateral DLPFC montage used with CCT above, perhaps explaining the significant but delayed improvement in the combined group here, which correlated with improved working memory.

Meanwhile, Loo and colleagues (Loo et al., 2010) gave moderately treatment-resistant patients 5 active/sham tDCS sessions followed by 5 active tDCS sessions for both groups; both groups had similarly improved (and clinically relevant) depression, response, and remission rates. In Loo and colleagues' (Loo et al., 2012) later study, patients (n = 64) received double the current density over 15 sessions, and tDCS significantly improved MADRS with an effect size of 0.49. The patients then entered into an open-label phase, with better results; 27 patients became responders from both groups, though the active group had a longer duration of response. But then Loo and colleagues'

Table 8. tDCS Studies in Major Depressive Disorder

Author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy	Results	Class
Depressive symptoms								
Boggio et al. (2008a)[a]	40	Occipital (2 cm above Iz)	Right SO	0.286, 20 min	10	No	Negative (HDRS, BDI)	II
Nord et al. (2019)	39	F3	Extracephalic (ipsilateral deltoid)	0.286, 20 min	7–8 sessions (1/wk × 7–8 wk)	n-back working memory task, CBT	Negative (HDRS)	II
Vigod et al. (2019)	17 (pregnant)	F3	F4	0.571, 30 min	15	No	Positive (MADRS remission 4 wk postpartum), Negative (MADRS immediately post-treatment and 12 wk postpartum)	II
Blumberger et al. (2012)	24	F3	F4	0.571, 20 min	15	No	Negative (HDRS, MADRS, BDI-II)	II
Brunoni et al. (2014)	40	F3	F4	0.800, 30 min	10	CCT	Negative (HDRS, BDI)	II
Salehinejad et al. (2017)	24	F3	F4	0.571, 30 min	10	No	Positive (BDI, HDRS)	II
Mayur et al. (2018)	16	F3	F4	0.800, 30 min	10	Ultrabrief Electroconvulsive Therapy (right unilateral)	Negative (MADRS)	II
Brunoni et al. (2013)	120	F3	F4	0.800, 30 min	12 (10 daily sessions, then 1 session every 2 wk × 4 wk)	Sertraline/placebo	Positive (MADRS)	I
Brunoni et al. (2017)	245	F3	F4	0.571, 30 min	22 (5/wk × 3 wk, then 1/wk × 7 wk)	Escitalopram/placebo	Positive to placebo (HDRS, MADRS), Negative to placebo (BDI), Not significant for noninferiority to escitalopram (HDRS)	I
Loo et al. (2010)	40	pF3	F8	0.286, 20 min	10 (on alternate days; sessions 1–5 active/sham, sessions 6–10 all active)	No	Negative (HDRS, MADRS, CGI, BDI)	II
Segrave et al. (2014)	27	F3	F8	0.571, 24 min	5	CCT/sham CCT	Positive (MADRS, BDI-II)	II
Loo et al. (2012)	64	pF3	F8	0.571, 20 min	15	No	Positive (MADRS), Negative (IDS, QIDS-C, CGI)	I
Loo et al. (2018)	120	F3	F8	0.714, 30 min	20	No	Negative (MADRS, CGI)	I

Table 8. Continued

Author	Sample (n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy	Results	Class
Palm et al. (2012)	22	F3	Contralateral SO	0.286 and 0.571, 20 min	10+as	No	Negative (HDRS, BDI, CGI)	III
Fregni et al. (2006b)	10	F3	Contralateral SO	0.286, 20 min	5 (on alternate days)	No	Positive (HDRS, BDI)	II
Fregni et al. (2006a)	18	F3	Contralateral SO	0.286, 20 min	5 (on alternate days)	No	Positive (HDRS)	II
Boggio et al. (2008a)[a]	40	F3	Contralateral SO	0.286, 20 min	10	No	Positive (HDRS, BDI)	II
Bennabi et al. (2015)	24	F3	Contralateral SO	0.571, 30 min	10 (2x/d × 1 wk)	Escitalopram	Negative (HDRS, MADRS)	II
Recommendation: anodal left DLPFC tDCS definitely effective (Level A) for treatment of depression in MDD								

Abbreviations: +as: crossover study with anodal and sham conditions.
a Multiple montages in 1 study.

(Loo et al., 2018) largest study on stable patients using greater current density, stimulation duration, and frequency showed only modest improvement in the sample (n = 120) in both unipolar (n = 84) and bipolar (n = 36) depression, and it was negative for differences between active/sham groups. That said, the authors later found that their sham technique (giving 0.034 mA throughout) was biologically active. This suggests that 20 sessions of "sham" current density of 0.010 A/m² led to MADRS results similar to a current density of 0.714 A/m² and that perhaps the higher current intensity of 2.5 mA was not optimal—in fact, in unipolar depression the "sham" group had higher remission than the active group.

Left DLPFC Anode, Right Frontopolar Cathode—Class II studies (3/4) were mostly positive, and the 1 Class III study was negative for this montage. The first 2 MDD studies successfully used this montage on 5 alternate days (Fregni et al., 2006a). Another early study found that this montage improved depression, response, and remission compared with sham and active control groups, which did not differ (Boggio et al., 2008a); the effects persisted 1 month later in the DLPFC group. The purpose of the active control (with occipital anode) was to investigate right supraorbital cathodal effects, but it was the left DLPFC anode that improved depression. It is worth noting that while occipital bending is more common among MDD patients than healthy controls (Maller et al., 2014), any impact on occipital stimulation is unclear.

Patients were off antidepressants in the early studies above. However, combining twice-daily tDCS sessions with escitalopram in treatment-resistant MDD found no benefits for tDCS beyond those of the drug (Bennabi et al., 2015). Meanwhile, the 1 crossover study (Palm et al., 2012) evaluated treatment-resistant depression (including 2 bipolar patients) and found that tDCS improved depression minimally better than placebo and also improved positive emotions. They initially used 1 mA (for safety) and then 2 mA, but these changes did not affect the results, although notably they had no washout period.

Finally, an RCT on moderate-to-severe depression combined a working memory task with tDCS followed by CBT and found nonsignificantly greater improvements in depression scores (and response and remission) following active tDCS compared with sham (Nord et al., 2019). This may be because they used 7 to 8 weekly sessions at low current density as well as a left DLPFC anode with left deltoid reference. However, functional MRI (fMRI) did find that greater left DLPFC activation at baseline was associated with greater improvements in depression only in the active tDCS group, thereby demonstrating a potential biomarker.

Recommendation: anodal left DLPFC tDCS is definitely effective in improving depression in MDD (Level A) (Table 8).

Quantitative analysis of 13 studies on left DLPFC anodal tDCS effects on depression (HDRS, BDI, MADRS) showed a significant ES of −0.36 (95% CI = −0.66, −0.06) in favor of tDCS effects but with significant and moderately high heterogeneity ($I^2 = 44.7\%$, $P = .041$) (Table 12; supplemental Figure 5).

Summary and Literature Synthesis—Left DLPFC tDCS is effective in treating depression in MDD according to the qualitative review and quantitative analysis, with significant heterogeneity between different studies but no sign of publication bias (supplemental Figure 5b). Lefaucheur et al. (2017) reported that anodal left DLPFC tDCS with right orbitofrontal (defined as FP2 or F8) cathode is probably effective (Level B) in depression without drug-resistant major depressive episodes, but probably ineffective (Level B) in those with such episodes. They gave

no recommendation for bilateral DLPFC tDCS (left anode, right cathode). For our purposes, the study protocols using bilateral DLPFC tDCS tended to differ from those using a right supraorbital (FP2) or frontotemporal (F8) cathode, so we do not make that distinction.

A number of meta-analyses took different approaches assessing tDCS effects in depression. A 2018 systematic meta-review of previous-decade meta-analyses (McGirr et al., 2018) reported that active tDCS as well as rTMS in major depression have shown small to moderate effect sizes. One study compared various non-surgical brain stimulation techniques in a network meta-analysis: Mutz et al. (2019) found that, compared with sham, the summary odds ratio of improving MDD or bipolar depression response rose across the following techniques: tDCS showing the least improvement (odds ratio = 2.65, 95% CI = 1.55, 4.55) followed by high-frequency left rTMS, intermittent theta burst stimulation, low-frequency right rTMS, bilateral theta burst stimulation, bilateral rTMS, magnetic seizure therapy, priming TMS, and high-dose right unilateral ECT; the greatest improvement was in bitemporal ECT (odds ratio = 8.91, 95% CI = 2.57, 30.91). That is, although tDCS was not as effective as bitemporal ECT, it was still quite effective and showed much a much tighter 95% confidence interval; furthermore, tDCS is much safer.

Meanwhile, an individual patient data (rather than aggregate data) meta-analysis (Moffa et al., 2020) showed that compared with sham, active tDCS significantly improved depression (effect size: B of 0.31, 95% CI = 0.15, 0.47), as well as response (odds ratio = 1.96, 95% CI = 1.30, 2.95; number needed to treat [NNT]: 9) and remission (odds ratio = 1.94, 95% CI = 1.19, 3.16; NNT: 13). Finally, the most recent meta-analysis on depressive episodes (Razza et al., 2020) had similar findings for active tDCS vs sham: improved depression scores (effect size g: 0.46, 95% CI = 0.22, 0.70), response (odds ratio = 2.28, 95% CI = 1.52, 3.42; NNT: 6), and remission (odds ratio = 2.12, 95% CI = 1.42, 3.16; NNR: 10.7).

Therefore, both the qualitative and quantitative literature shows efficacy of active tDCS in depression; however, there is much room to enhance tDCS parameters and strengthen its benefits. We suggest giving more than 10 sessions of anodal left DLPFC tDCS lasting 20 to 30 minutes at a current density of at least 0.571 A/m^2. Whether to place the cathode over the right DLPFC to improve the imbalance or over the right supraorbital or frontotemporal regions to better target the ACC and subcortical regions is less clear and may depend on the severity and treatment-resistance of the population. CCT and pharmaceuticals such as sertraline and escitalopram may improve tDCS effects on depressive symptoms, but future studies should be carefully powered and adverse events such as treatment-onset mania/hypomania should be carefully monitored (particularly in populations with low treatment resistance).

OCD and TS

OCD and TS are disabling neuropsychiatric disorders; OCD is characterized by the presence of obsessions and/or compulsions, and TS by rapid, stereotyped movements and vocalizations (i.e., motor and vocal tics). Neuroimaging studies suggest that cortico-striato-thalamo-cortical loop alterations are implicated in the pathophysiology of OCD (Gonçalves et al., 2011, 2015) and TS (Wang et al., 2011), with the SMAs and pre-SMAS showing deficient response inhibition (Maltby et al., 2005; Nachev et al., 2008; Hsu et al., 2011; de Wit et al., 2012). Both conditions are often resistant to drugs and CBT, but early rTMS and tDCS studies show some promising effects (Mantovani et al., 2006; Kwon et al., 2011; Saba et al., 2015) in targeting dysfunctional circuits.

PubMed searches on "tDCS" and "OCD," and on "tDCS" and "Gilles de la Tourette syndrome" yielded 8 and 3 results, respectively, that fulfilled our criteria. As mentioned previously, we allowed for uncontrolled trials due to the limited literature. All OCD and TS results were Class IV studies except for 2 OCD Class III crossover RCTs; we identified additional PubMed-indexed papers through our authors, including a case study (Carvalho et al., 2015) and a recent Class II study (Gowda et al., 2019). All were on treatment-resistant patients receiving tDCS as an add-on to pharmacological treatment (Table 9).

***OCD*—**Based on a Class II, a Class III, and multiple Class IV studies, pre-SMA/SMA tDCS showed potential, but polarity impact (vs. individual variability) is unclear. The 1 Class II study (Gowda et al., 2019) gave anodal tDCS over the pre-SMA and found significant improvement; furthermore, active group participants who did not achieve response during the RCT were enrolled in the open-label extension and their scores improved significantly, although they still did not achieve response. A case series aimed to target the pre-SMA and SMA via an Fz anode (with right supraorbital cathode) based on the hypothesis that striatal hyperactivity in OCD results from deficient pre-SMA inhibition (Narayanaswamy et al., 2015). Yale Brown Obsessive Compulsive Scale (YBOCS) scores (40% and 46.7%) as well as depression and anxiety improved, and clinical results were sustained for 1 to 2 months; 1 patient had an fMRI confirming increased left SMA activity. Conversely, SMA cathodal tDCS in 2 cases led to a minor and delayed response in one while the other improved by 20 sessions and had 45% improvement 6 months later (da Silva et al., 2016). One case from another group had worsening of YBOCS with 10 sessions of anodal pre-SMA tDCS, so she was switched over to 10 sessions of cathodal tDCS, and YBOCS improved (D'Urso et al., 2016a). This was followed by a partial crossover study (D'Urso et al., 2016b) that placed the active anode/cathode anterior to Cz (closer to Fz) with a right deltoid reference (to better target the hyperactive pre-SMAs based on their computational model). The researchers found that only cathodal stimulation led to significant improvements, and 2 patients worsened with anodal tDCS, improving after being crossed over to cathodal tDCS.

An early case report used active/sham monopolar cathodal tDCS and low-frequency (inhibitory) rTMS over the left DLPFC, as fMRI had shown baseline hyperactivation and hypoactivation of the left and right anterior circuits, respectively (Volpato et al., 2013b). However, none of the conditions improved YBOCS (Volpato et al., 2013b). Meanwhile, another patient received left orbitofrontal cortex cathodal tDCS (Mondino et al., 2015a)—with a large right occipital reference—and YBOCS decreased by 26% only 1 month later. Likewise, an open-label study aimed to modulate the orbitofronto-striato-pallido-thalamic loop by inhibiting the hyperactive left orbitofrontal cortex and increasing excitability in the right hypoactive cerebellum (Bation et al., 2016) and found significant improvements on YBOC (26.4% decrease) and OCD-VAS (45.6% decrease) lasting 3 months. Finally, 1 case improved following bilateral DLPFC tDCS combined with sertraline (Palm et al., 2017b).

Our recommendation is based on 1 convincing Class II study and its open-label extension. Individual variability and expectations may have impacted the other cases.

Recommendation: anodal pre-SMA tDCS is possibly effective in improving OCD (Level C) (Table 9).

Table 9. tDCS Studies in OCD and TS

Author	Sample(n)	Anode	Cathode	Current density (A/m²)	Number of sessions	Concomitant therapy	Results	Class
OCD								
Volpato et al. (2013b)	1	Posterior neck-base	F3	0.571, 20 min	10[+cs,rTMSas]	No	Negative (YBOCS)	IV
Mondino et al. (2015a)	1	Above O2	Left SO	0.571, 20 min	10 (2/d × 1 wk)	No	Positive (YBOCS)	IV
Bation et al. (2016)	8	Right cerebellum	Left SO	0.571, 20 min	10 (2/d × 1 wk)	No	Positive (YBOCS, OCD VAS)	IV
Palm et al. (2017b)	1	F3	F4	0.571, 30 min	20 (2/d × 2 wk)	Sertraline	Positive (YBOCS total, obsessions and compulsions subscales)	IV
D'Urso et al. (2016b)[a]	12	Anterior to Cz	Right deltoid	0.800, 20 min	10 (10/phase × 2 phases)[+ac]	No	Negative (YBOCS)	III
D'Urso et al. (2016b)[a]	12	Right deltoid	Anterior to Cz	0.800, 20 min	10 (10/phase × 2 phases)[+ac]	No	Positive (YBOCS)	III
D'Urso et al. (2016b)[b]	1	Anterior to Cz	Right deltoid	0.800, 20 min	10	No	Negative (YBOCS)	IV
D'Urso et al. (2016b)[b]	1	Right deltoid	Anterior to Cz	0.800, 20 min	10	No	Negative (YBOCS)	IV
Da Silva et al. (2016)	2	Left deltoid	Bilateral SMA	0.800, 30 min	20	No	Positive (YBOCS)	IV
Narayanaswamy et al. (2015)	2	Fz	Right SO	0.571, 20 min	20 (2/d × 2 wk)	No	Positive (YBOCS)	IV
Gowda et al. (2019)	25	Fz	Right SO	0.571, 20 min	10 (2/d × 1 wk)	No	Positive (YBOCS total, compulsion and insight subscores)	II
Recommendation: anodal pre-SMA tDCS possibly effective (Level C) in improving OCD symptoms								
TS								
Mrakic-Sposta et al. (2008)	2	Right deltoid	Left motor-premotor areas	0.952, 15 min	5[+cs]	No	Positive (YGTSS)	IV
Carvalho et al. (2015)	1	Right deltoid	Bilateral pre-SMAs	0.570, 30 min	10	No	Positive (tic severity, YGTSS)	IV
Behler et al. 2018	3	Extracephalic (left and right sternocleidmastoid muscles)	C3 and C4 (longitudinally to cover pre-SMAs)	0.571, 30 min	10 (2/d × 1 wk)	No	YGTSS positive in 1/3, negative in 2/3; tic severity positive in 1/3, negative in 2/3, tic frequency worse in 3/3	IV
No recommendation								

Abbreviations: +ac: crossover study with anodal and cathodal tDCS condition; +cs crossover with cathodal and sham tDCS conditions; +cs,rTMSas: crossover with cathodal and sham conditions of tDCS, and active and sham conditions of rTMS; OCD, obsessive compulsive disorder; TS, Tourette syndrome.

a Multiple montages in 1 study.

b Multiple montages in another study.

On excluding 8 studies/montages with n < 10 (all Class IV), the recommendation does not change.

TS—All cases used variable parameters. Cathodal tDCS over the left motor-premotor areas of 2 TS patients decreased their motor and vocal tics compared with sham and dramatically increased their feelings of general well-being (Mrakic-Sposta et al., 2008). A severely refractory 16-year old received pre-SMA cathodal tDCS as compassionate treatment and had decreases of 41% and 46% in tic severity and global score, respectively (verbal tics improving before motor tics), by the end of 10 sessions; the benefits lasted at least 6 months (Carvalho et al., 2015). Additionally, fMRI showed decreased left precentral sensorimotor resting state network and cerebellar activity after cathodal tDCS (Carvalho et al., 2015). However, twice-daily sessions over 1 week using a different montage led to worsened tic counts in 3/3 other cases despite decreased tic severity and YGTSS in 1 patient (who had TS onset during childhood) (Behler et al., 2018).

Recommendation: no recommendation for TS (Table 9).

All 3 studies (Class IV) had n < 10, so excluding them did not change the recommendation.

Summary and Literature Synthesis—Overall, the studies showed promising but very preliminary results for tDCS in OCD and TS. Anodal pre-SMA tDCS was positive in a convincing Class II OCD study, but the cases showed variable results. It seems the bilateral pre/SMAs, left DLPFC, and orbitofrontal regions might be the most targets to study in future RCTs. Lefaucheur et al. (2017) adds no recommendations and there are no meta-analyses on these topics; our own limited quantitative analysis showed no significant results (Table 12; supplemental Figure 6). However, considering that DBS was FDA approved in severely intractable OCD under a humanitarian exemption (Bernad 2009), a systematic investigation of non-invasive measures is important, and off-label tDCS is an option for compassionate care.

Schizophrenia

Schizophrenia is a debilitating chronic neuropsychiatric disorder characterized by delusions (typically verbal auditory), hallucinations, disorganized speech/behavior, and decreased emotional expression. It might be the "most disabling" disease globally (Salomon et al., 2012). About 20% of patients are treatment resistant but may respond to ECT (Kennedy et al., 2014), so NIBS techniques including rTMS and tDCS have been investigated to treat resistant symptoms (Agarwal et al., 2013; Kubera et al., 2015; Mondino et al., 2015a). The typical tDCS montage is based on neuroimaging findings: cathodal stimulation of the hyperactive left temporoparietal region targeting auditory hallucinations (Jardri et al., 2011) and anodal stimulation of the hypoactive frontal areas (mainly left DLPFC and ACC) targeting negative symptoms (Molina Rodríguez et al., 1997; Sanfilipo et al., 2000; Brunelin et al., 2012).

A PubMed search on "tDCS AND schizophrenia" yielded 11 results that fit our criteria, including auditory hallucinations/positive or negative symptoms in schizophrenia (we also allowed studies that included schizoaffective disorder). We also added another paper identified by an author that fit our criteria (Bose et al., 2018).

tDCS Effects on Auditory Hallucinations, Negative and Positive Symptoms in Schizophrenia—Almost all montages placed the anode on the left DLPFC (F3) or midway between it and frontopolar/supraorbital region (FP1 in Table 10, left SO in other tables) than at a more anterior and mesial prefrontal location; cathode was typically on the left temporoparietal region (between midtemporal T7 and parietocentral P3), although some montage variations were used.

Left Prefrontal Anode, Left Temporoparietal Cathode—All were Class II RCTs using twice-daily tDCS with similar parameters, and 6/7 studies showed improvements in auditory hallucinations using Auditory Hallucinations Rating Scale scores (AHRS).

In the first RCT (Brunelin et al., 2012), after 1 week of twice-daily tDCS, the active group had a significant 31% drop in AHRS scores and a 38% improvement 3 months later. Two other studies (most of whose patients had participated in the one above; Brunelin et al., 2012) also found significant auditory verbal hallucination (AVH) improvements (Mondino et al., 2015b, 2016). After active tDCS, patients had fewer misattributions of covert and overt speech, which correlated with a (46%) drop in AVH frequency, supporting the hypothesis that hallucinations related to internal events were wrongly perceived as occurring in external space (Mondino et al., 2015b). The third study also showed decreased auditory hallucination severity following active tDCS, which correlated with decreased left temporoparietal junction resting state functional connectivity (rs-FC) with the left anterior insula; additionally, tDCS significantly reduced left temporoparietal rs-FC with the right inferior frontal gyrus (which is active during AVHs) but increased this rs-FC with the left DLPFC, left angular gyrus, and precuneus (Mondino et al., 2016).

Conversely, a study on patients with medication-resistant AVHs showed no difference in AHRS between active and sham tDCS groups despite being adequately powered and controlling for confounders, nor was it significant for positive/negative symptoms (Chang et al., 2018). However, the study had unclear eligibility criteria and included patients with schizoaffective disorder (n = 9/60) with schizophrenia, and they were on low doses of medications relative to the group's pilot study. Yet, the active tDCS group demonstrated significantly improved insight into their symptoms, particularly positive symptoms.

In a larger multicenter RCT (Kantrowitz et al., 2019) using similar stimulation parameters, AHRS improved in active vs sham groups only when chlorpromazine equivalents (which correlated with higher baseline AHRS) was added as a covariate. The authors suggested covariation for baseline medication doses when analyzing future AVH studies and that participants with putative high cognitive symptoms were less responsive. There were no differences between schizophrenic and schizoaffective (n = 17/53) patients, nor among sites, but outpatients receiving active tDCS had significantly improved remission and hallucination scores; conversely, inpatients on active tDCS had significantly less improvement than both active outpatients and sham inpatients.

In another study on inpatients with treatment-resistant schizophrenia or schizoaffective disorder (n = 9/28) that was also clozapine-resistant, an increased number of sessions (40 vs 10) was possibly helpful, as AHRS total scores decreased significantly by 21.9% with active tDCS and the decrease at week 4 was greater than week 2. Subscores on hallucination frequency and length and number of voices also decreased. While clinical significance is preliminary, the results are encouraging in this "ultra-treatment-resistant" inpatient sample (Lindenmayer et al., 2019). However, another 10-session study (Bose et al., 2018) found significant AHRS improvement with an effect size of 1.98

Table 10. tDCS Studies in Schizophrenia (and Schizoaffective Disorder)

Author	Sample (n)	Anode[a]	Cathode	Current density (A/m^2), session duration	Number of sessions	Con-comitant therapy	Results[b]	Class
Auditory hallucinations/negative and positive symptoms								
Brunelin et al. (2012)	30	Midway between F3-FP1	Midway between T7-P3	0.571, 20 min	10 (2/d × 1 wk)	No	Improvement (AHRS, PANSS total and negative), no improvement (PANSS positive)	II
Mondino et al. (2015b)	28	Midway between F3-FP1	Midway between T7-P3	0.571, 20 min	10 (2/d × 1 wk)	No	Improvement (AVH frequency, covert/overt speech misattribution)	II
Mondino et al. (2016)	23	Midway between F3-FP1	Midway between T7-P3	0.571, 20 min	10 (2/d × 1 wk)	No	Improvement (AHRS)	II
Chang et al. (2018)	60	Midway between F3-FP1	Midway between T7-P3	0.571, 20 min	10 (2/d × 1 wk)	No	No improvement (AHRS, PANSS total and subscores)	II
Kantrowitz et al. (2019)	89	Midway between F3-FP1	Midway between T7-P3	0.515, 20 min	10 (2/d × 1 wk)	No	Improvement (AHRS[c], AHRS Loudness, PANSS Hallucinatory behavior), no improvement (other AHRS items, PANSS total and subscores)	II
Bose et al. (2018)	25	Midway between F3-FP1	Midway between T7-P3	0.571, 20 min	10 (2/d × 1 wk)	No	Improvement (AHRS)	II
Lindenmayer et al. (2019)	28	Midway between F3-FP1	Midway between T7-P3	0.571, 20 min	40 (2/d × 4 wk)	No	Improvement (AHRS and frequency, no. of voices, and length of AH subscores, PANSS total), no improvement (other AHRS and PANSS subscores, PANSS Hallucinatory behavior)	II
Shiozawa et al. (2016)	9	F3	F4	0.571, 20 min	10 (2/d × 1 wk)	Cognitive training	No improvement (PANSS)	II
Jeon et al. (2018)	39	F3	F4	0.800, 30 min	10	No	No improvement (PANSS total and subscores, CGI positive and negative symptoms)	II
Fitzgerald et al. (2014)[d]	11	F3	Midway between T7-P3	0.571, 20 min	15	No	No improvement (PANSS, SANS)	II
Fitzgerald et al. (2014)[d]	13	F3 and F4	Midway between T7-P3 and T8-P4	0.571, 20 min	15	No	No improvement (PANSS, SANS)	II
Palm et al. (2016)	20	F3	Contralateral SO	0.571, 20 min	10	No	Improvement (SANS, PANSS total and negative)	II
Recommendation: anodal left prefrontal w/ cathodal left temporoparietal tDCS probably effective (Level B) for reducing auditory hallucinations in schizophrenia								

Abbreviations: +a1,a2,s: crossover anodal 1 mA, anodal 2 mA, sham; note, F3-FP1 targeted left prefrontal regions, T7-P3 targeted left temporoparietal regions; w/, with.
a FP1 is the left SO region.
b To avoid confusion with positive/negative symptoms in schizophrenia, we used the terminology "improvement" for studies showing significant improvement compared with sham, and "no improvement" for nonsignificant changes.
c AHRS showed improvement only when chlorpromazine equivalents (which had correlated significantly with higher baseline AHRS and PANSS Hallucinations scores) was added as a covariate.
d In the same paper.

(>1.58 in the study they were replicating; Brunelin et al., 2012); furthermore, the sham tDCS patients improved significantly more in the open-label phase than during the RCT.

Left DLPFC Anode, Right DLPFC Cathode—Both Class II studies were nonsignificant for positive/negative symptom changes with this bilateral DLPFC montage. Ten sessions of active bilateral tDCS did not improve these symptoms whether at a higher current density and duration (with daily sessions) in clinically stable multicenter schizophrenia patients (Jeon et al., 2018), or at the typical twice-daily dose combined with cognitive training (Shiozawa et al., 2016).

Other Montages—Only 1/3 of the remaining Class II trials showed apparent improvement in positive and negative symptoms. In this proof-of-concept RCT on severe paranoid/disorganized schizophrenia, left DLPFC anodal-right orbitofrontal cathodal tDCS (both electrodes considered active) improved the Positive and Negative Symptom Scale (PANSS) total and negative subscales and the Scale for Assessment of Negative Symptoms. Functional connectivity MRI data showed significant tDCS effects in the bilateral DLPFC and subgenual regions, but the relationship to symptoms was unclear (Palm et al., 2016).

Meanwhile, Fitzgerald and colleagues (Fitzgerald et al., 2014) conducted 2 pilot studies comparing left unilateral and bilateral tDCS (DLPFC anode, temporoparietal cathode) over 15 daily sessions but found no significant improvements in auditory hallucinations or positive or negative symptoms for unilateral or bilateral tDCS or for the whole sample (schizoaffective disorder n = 7/24).

Therefore, while there are clear benefits to tDCS in auditory hallucinations, effects on positive and negative symptoms are harder to determine. However, we did not include a Class I RCT (n = 100) by Valiengo and colleagues (Valiengo et al., 2019) that was published after our search date limits; this study showed significant and clinically relative benefits of anodal left prefrontal and cathodal left temporoparietal tDCS to negative symptoms, which would change our classification to probably effective (Level B) for negative symptoms in schizophrenia.

Recommendation: anodal left prefrontal with cathodal left temporoparietal tDCS is probably effective for reducing auditory hallucinations in schizophrenia (Level B) (Table 10).

On excluding the 1 study (Class II) with n < 10, the recommendation does not change.

Quantitative analysis of 7 studies/montages on auditory hallucinations (AHRS) showed a significant ES of −0.52 (95% CI = −0.86, −0.17) in favor of tDCS. Quantitative analysis of 6 studies/montages on positive and negative symptoms (PANSS) showed a significant ES of −0.45 (95% CI = −0.84, −0.06) in favor of tDCS, albeit with significantly high heterogeneity (I^2 = 57.4%, P = .029). Pooled analysis showed a significant ES of −0.47 (95% CI = −0.72, −0.22) favoring tDCS effects on AHRS and PANSS combined, although again with significant and high heterogeneity (I^2 = 50.2%, P = .020) (Table 12; supplemental Figure 7a).

Summary and Literature Synthesis—Our findings are overall consistent with and promising for twice-daily (3 hours apart) left prefrontal anodal and left temporoparietal cathodal tDCS modulation of the network producing and monitoring internal speech, thereby improving auditory verbal hallucinations. Our quantitative analysis shows that tDCS (all montages pooled) significantly improves AHRS and PANSS to a moderate degree, but with high heterogeneity and some evidence of publication bias (supplemental Figure 2a–b). Lefaucheur et al. (2017) gave no recommendations for tDCS in schizophrenia based on fewer studies.

Meanwhile, a prior meta-analysis (Yang et al., 2019) showed that active left DLPFC-left temporo-parietal tDCS significantly improved auditory hallucinations compared with sham with a standardized mean difference of −4.59 (95% CI = −7.91, −1.27); the results were nonsignificant when pooled with a study using a left DLPFC-right supraorbital tDCS montage (Smith et al., 2015) in a population of smokers with schizophrenia or schizoaffective disorder. Additionally, another meta-analysis (Kim et al., 2019) showed that while tDCS did not improve auditory hallucinations or positive or negative symptoms on the main analyses, there were more specific benefits on subgroup analyses that confirm our own results and add direction for stimulation protocols. Specifically, based on 3 to 7 pooled studies, there were significant improvements in auditory hallucination severity following twice-daily tDCS (SMD = 1.04, P = .02), while 10 or more stimulation sessions improved auditory hallucinations (SMD = 0.86, 95% CI = 0.22, 1.51) as well as severity of negative symptoms (SMD = 0.41, 95% CI = 0.01, 0.81). Upon meta-regression, mean age was negatively associated with auditory hallucinations (slope −0.15, 95% CI = −0.22, −0.09) and negative symptoms (slope −0.08, 95% CI = −0.16, −0.02); also, studies with greater severity of negative symptoms at baseline seemed to respond better to tDCS (Kim et al., 2019). These are all factors to consider in future RCT design.

Drug Addiction

Drug addiction or dependence is a chronic disease leading to severe medical, psychiatric, psychological, and social consequences (Healey et al., 1998; Daley et al., 2013). Alcoholism is an important risk factor for disease (Navarro et al., 2011), disability, and death (Suokas et al., 2005), yet medical treatments for alcohol dependence are often underutilized and have limiting contraindications or side effects (Goh and Morgan, 2017). Meanwhile, the psychoactive stimulant crack-cocaine (Fischer et al., 2015) establishes a rapid and severe dependence with powerful withdrawal effects and a poor prognosis (Hatsukami and Fischman, 1996; Moura et al., 2014). Methamphetamine or "crystal meth" is also a potent psychoactive stimulant with numerous healthcare consequences, including psychosis; dependent patients have few effective medical options (Härtel-Petri et al., 2017). Bio-psychosocial and pharmacological therapeutics often focus on managing acute or protracted abstinence (Siegal et al., 2002; McKay et al., 2005) but seldom focus on craving (the uncontrolled urge to use drugs) (Robinson and Berridge, 1993; Hormes et al., 2012) and/or relapses (resuming previous patterns of heavy drug use) (Wesson et al., 1986; Iruzubieta et al., 2013); they tend to have only modest efficacy (Assanangkornchai and Srisurapanont, 2007; Miller et al., 2011; Fischer et al., 2015).

Addiction results from progressive maladaptive neuroplasticity, beginning with an initial impulsive action (Koob and Volkow, 2016); later environmental cues can lead to cravings and trigger relapses. Addicted patients have impaired executive functions, likely due to decreased volume and disrupted activity in relevant areas such as the DLPFC and cingulate and orbitofrontal cortices (Moselhy et al., 2001; Di Sclafani et al., 2002; Duka et al., 2011; Koob and Volkow, 2016). The DLPFC is involved in "top-down" regulation of attention (Cummings, 1993; Arnsten and Rubia, 2012) and the ability to control drug intake (Duka et al., 2011). As such, modulating excitability in the DLPFC

and other regions by tDCS may help improve success in abstinence from drugs.

PubMed searches on "alcohol AND tDCS," "cocaine AND tDCS," and "methamphetamine AND tDCS" yielded 9, 2, and 1 studies, respectively, that fit our criteria. We focused on cravings and relapses.

Alcohol Dependence—Of repeated-session RCTs, 2/2 Class II studies on right DLPFC anode and left DLPFC cathode were positive, 2 Class II studies with reversed polarity and bias modification training were negative, and other montages were mixed.

Klaus and colleagues had 2 RCTs using right/left DLPFC anodal/cathodal tDCS. One study using twice daily tDCS for 1 week found 3 times less relapse in the active group at 6 months compared with sham even though both groups had similarly improved cravings (Klauss et al., 2014). Their next study (using alternating days) found that craving scores significantly decreased in a linear fashion over the weeks from baseline to 1 week after tDCS with a large effect size (1.1 Cohen *d*), a 3-fold drop in alcohol cravings, and an NNT of 3.5 patients (Klauss et al., 2018b). Additionally, 72.7% of the active group (vs 27.8% of sham) maintained alcohol abstinence over 3 months post-treatment. Our recommendations are thus based on these results.

Meanwhile, den Uyl et al. (2017) used left/right DLPFC anode/cathode tDCS for 4 sessions. The first combined tDCS with cognitive bias modification/its control but found no significant improvements in alcohol craving or relapse with either online or offline cognitive bias modification. This study listed a number of limitations such as missing data, change in primary outcome, and some baseline differences. Their next study on alcohol-dependent but abstinent patients combined the above tDCS montage with active/control attentional bias modification with active/sham tDCS (den Uyl et al., 2018), but tDCS did not help craving (which was very low at baseline), automatic biases, or relapse; however, the study was limited by the large number of dropouts in follow-up, and there was still 16% less relapse with active tDCS (similar magnitude to the previous study). The limitations of those studies led to them being Class II rather than Class I RCTs despite larger samples.

As to other tDCS montages, 1 RCT aimed to modulate the right inferior frontal gyrus with anodal tDCS while combining it with mindfulness-based relapse prevention to reduce drinking in alcohol use disorder but found no benefit to tDCS (Witkiewitz et al., 2019). Weekly left DLPFC tDCS in Lesch IV alcoholics improved depression and craving on one scale but unfortunately led to a trend toward more relapses and less abstinence in the anodal group (which drank twice as much at baseline) compared with sham (da Silva et al., 2013).

As to single-session RCTs, all DLPFC tDCS irrespective of polarity improved outcomes, but left inferior frontal gyrus tDCS did not help (Table 11).

Recommendation: right DLPFC anodal with left DLPFC cathodal tDCS is probably effective in decreasing relapses or craving in alcohol addiction (Level B) (Table 11).

Crack-Cocaine—Two Class II RCTs using right/left DLPFC anodal/cathodal tDCS had mixed results. TDCS for 5 alternate days significantly decreased craving and had other neuropsychological benefits in crack-cocaine addicts admitted to an addiction clinic (abstinent for 35 days) (Batista et al., 2015). This is consistent with the efficacy of the right/left DLPFC montage in addiction. In a second study on more severe crack-cocaine use, baseline craving scores were greater and the effect size after treatment was also larger (Hedge's g 0.97 vs 0.54)—however, there were no significant differences between groups in cravings or relapse 30 and 60 days later (Klauss et al., 2018a).

Recommendation: none (Table 11).

Methamphetamine Dependence—A single-session crossover RCT on abstinent methamphetamine users found that 1 session of right DLPFC anodal tDCS with an online computerized cue-induced craving task reduced immediate craving at rest but worsened craving on exposure to meth-related cues (Shahbabaie et al., 2014). This was possibly due to DLPFC effects on drug cue saliency and craving.

Recommendation: none (Table 11).

Summary and Literature Synthesis—While available evidence for tDCS use in drug addiction is somewhat promising, there is a need for larger studies. Lefaucheur et al. recommended that combined right DLPFC anodal with left DLPFC cathodal tDCS is probably effective (Level B) in addiction/craving reduction (of alcohol, crack-cocaine, and smoking combined). We found this montage to be probably effective for alcoholic cravings or relapses (Level B), although our limited quantitative analysis combining Pennsylvania Alcohol Craving Scale, Obsessive Compulsive Drinking Scale, and relapse missed significance (Table 12; supplemental Figure 8). We can give no recommendation for crack-cocaine or methamphetamine users.

Risk of Bias Assessment and Sensitivity Analysis

Mean Jadad scores for each condition in this review can be found in Table 13. We conducted a sensitivity analysis by excluding papers with high risk of bias. There were no changes in the recommendations for all clinical conditions.

Additionally, for the secondary meta-analyses, we included funnel plots and Egger and Begg tests to evaluate publication bias in disorders with 10 or more pooled studies (Supplemental Material); in each disorder we mentioned when there was evidence of publication bias.

Discussion

tDCS is a flexible, low-cost, and relatively benign tool. In this review, a panel of tDCS experts gave evidence-based recommendations on tDCS use in 9 neurological and psychiatric conditions: pain, PD (motor function and cognition), stroke (motor function and language), epilepsy, MDD, OCD, TS, schizophrenia, and drug addiction (Table 12). Although many tDCS studies appear promising, the heterogeneity in populations, outcomes, tDCS parameters, and concomitant therapies necessitate further research before its clinical benefits can be fully demonstrated. This review is therefore important to provide initial guidance to assess tDCS' potential clinical benefits.

Most clinical trials primarily aimed to investigate efficacy, and safety profiles typically came from secondary analyses (Brunoni et al., 2011; Poreisz et al., 2007), although no moderate or severe adverse events have been reported thus far. That said, clinicians should exert caution when using tDCS off-label before more conclusive reports are published; long-term effects have not been established, nor is it clear in what conditions tDCS can reach at least MCIDs. It is also important to note that electrode locations were measured in different ways while electrode sizes were almost always standardized across patients. Considering the varying measurements and head sizes and shapes, we cannot guarantee that the current distribution is comparable

Table 11. tDCS Studies in Addiction (Craving and Relapses For Alcohol, Crack-Cocaine, Methamphetamine)

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/ task	Results	Class
Alcohol: craving or relapses								
Boggio et al. (2008b)	13	F3	F4	0.571, 20 min	1[+F3a,F4a,s]	No	Positive (AUQ)	III
Boggio et al. (2008b)	13	F4	F3	0.571, 20 min	1[+F3a,F4a,s]	No	Positive (AUQ)	III
den Uyl et al. (2015)	41	F3	Contralateral SO	0.286, 10 min	1	No	Positive (AAAQ)	II
den Uyl et al. (2015)	41	Crossing of F7, Cz, Fz, T7[a]	Contralateral SO	0.286, 10 min	1	No	Negative (AAAQ)	II
Wietschorke et al. (2016)	30	F4	F3	0.286, 20 min	1	No	Positive (VAS desire to drink), negative (VAS other subscales)	II
Witkiewitz et al. (2019)	84	F10[a]	Left upper arm	1.330, 30 min	8 (1/wk × 8 wk)	Mindfulness-based relapse prevention	Negative (DDD, PHDD, PACS)	II
da Silva et al. (2013)	13	F3	Right supra-deltoid area	0.571, 20 min	5 (1/wk × 5 wk)	No	Positive (OCDS), negative (AUQ, relapse)	II
Den Uyl et al. (2017)	91	F3	F4	0.571, 20 min	4	Cognitive bias modification/control	Negative (PACS, relapse)	II
den Uyl et al. (2019)	83	F3	F4	0.571, 20 min	4	ABM/control ABM	Negative (PACS, ABM, IAAA, relapse)	II
Klauss et al. (2014)	33	F4	F3	0.571, 13 min	10 (2/d × 1 wk)	No	Positive (relapse), negative (OCDS)	II
Klauss et al. (2018b)	45	F4	F3	0.571, 20 min	10 (alt. days incl. wkends × 3 wk)	No	Positive (OCDS, relapse)	II
Recommendation: right DLPFC anodal w/ left DLPFC cathodal tDCS probably effective in decreasing relapses or craving in alcohol addiction (Level B)								
Crack-cocaine								
Batista et al. (2015)	36	F4	F3	0.571, 20 min	5 (alt. days)	No	Positive (OCDS)	II
Klauss et al. (2018a)	33	F4	F3	0.571, 20 min	10 (alt. days incl. wkends × 3 wk)	No	Negative (OCDS, relapses)	II
No recommendation								
Methamphetamine								
Shahbabaie et al. (2014)	30	F4	Contralateral SO	0.571, 20 min	1[+as]	CICT	Positive (VAS craving), negative (CICT)	III
No recommendation								

Abbreviations: alt, alternate; +as, crossover active and sham tDCS; +F3a,F4a,s, crossover bilateral tDCS with DLPFC anode/cathode (F3/F4), DLPFC anode/cathode (F4/F3), and sham tDCS; incl., including; w/, with.
a Authors of those papers were targeting the left inferior frontal gyrus (crossing of F7, Cz, Fz, T7) and right inferior frontal gyrus (F10).

Table 12. Summary of Recommendations on tDCS Efficacy According to Clinical Indications [a]

	Condition	Recommendation	Pooled effect sizes *
Pain	Neuropathic pain	Anodal M1 tDCS probably effective in reducing neuropathic pain (Level B)	−0.29 (−0.60, 0.02)
	Fibromyalgia	Anodal M1 tDCS probably effective in reducing fibromyalgia pain (Level B)	−0.62 (−1.23, −0.01)
	Migraine	Anodal M1 tDCS probably effective in reducing migraine pain (Level B)	−0.41 (−1.40, 0.59)[a]
	MPS	No recommendation	Not estimable
	Postoperative acute pain	Postoperative anodal M1 tDCS probably effective in reducing patient-controlled analgesia and pain (Level B)	−0.70 (−1.09, −0.30)
	Low back pain	No recommendation	Not estimable
PD	Motor function	Anodal motor/premotor/SMA tDCS possibly effective for motor function in PD (Level C); anodal prefrontal tDCS probably not effective for motor function in PD (Level B)	−0.38 (−0.68, −0.09)
	Cognitive function	Anodal DLPFC tDCS probably effective for cognitive function in PD (Level B)	−0.33 (−1.02, 0.35)
Chronic stroke	Motor function	Anodal tDCS of ipsilesional M1 probably effective for motor rehab in chronic stroke (Level B);	0.52 (−0.04, 1.09)
		Anodal tDCS of ipsilesional M1 to enhance robotic therapy probably not effective for motor rehab in chronic stroke (Level B);	0.23 (−0.31, 0.77)
		Cathodal tDCS of contralesional M1 probably effective for motor rehab in chronic stroke (Level B);	0.44 (−.18, 1.06)
		Bilateral tDCS of M1 probably effective for motor rehab in chronic stroke (Level B)	0.44 (0.10, 0.79)
	Aphasia	Anodal tDCS of Broca's area, its homologue, or Wernicke's area is possibly effective in chronic post–stroke aphasia rehab (Level C)	Broca's Area: 0.65 (0.29, 1.01)
			Not estimable
		Cathodal right frontotemporal tDCS is possibly effective in chronic post–stroke aphasia rehab (Level C)	Not estimable
		Bilateral tDCS w/ anodal stimulation of Broca's area and cathodal stimulation of its homologue is possibly effective in chronic post–stroke aphasia rehab (Level C)	
Subacute stroke	Motor function	Anodal tDCS of ipsilesional M1 probably effective for motor rehab in subacute stroke (Level B)	0.44 (−0.03, 0.91)
		Anodal tDCS of ipsilesional M1 to enhance robotic therapy is definitely not effective for motor rehab in subacute stroke (Level A)	0.01 (−0.33, 0.34)
		Cathodal tDCS of contralesional M1 probably effective for motor rehab in subacute stroke (Level B)	0.47 (0.10, 0.84)
		Cathodal tDCS of contralesional M1 to enhance robotic therapy probably not effective for motor rehab in subacute stroke (Level B)	Not estimable
		Bilateral tDCS of M1 is possibly effective for motor rehab in subacute stroke (Level C)	0.39 (−0.07, 0.86)
Epilepsy	Seizure frequency	Cathodal tDCS probably safe (no increase in seizures) and effective (decrease in seizures) in epilepsy (Level B)	−0.70 (−1.38, −0.02)
MDD	Depression	Anodal left DLPFC tDCS is definitely effective for treatment of depression in MDD (Level A)	−0.36 (−0.66, −0.06)
OCD and TS	OCD	Anodal pre–SMA tDCS is possibly effective in improving OCD symptoms (Level C)	−0.61 (−1.87, 0.64)
	TS	No recommendation	Not estimable
Schizophrenia	Auditory hallucinations and positive/negative symptoms	Anodal left prefrontal w/ cathodal left temporoparietal tDCS probably effective for reducing auditory hallucinations in schizophrenia (Level B)	−0.47 (−0.72, −0.22)
Addiction	Alcohol: craving or relapses	Right DLPFC anodal w/ left DLPFC cathodal tDCS probably effective in decreasing relapses or craving in alcohol addiction (Level B)	0.21 (−0.08, 0.49)
	Crack-cocaine	No recommendation	Not estimable
	Methamphetamine	No recommendation	Not estimable

Abbreviations: MDD, Major Depressive Disorder; MPS, Myofascial Pain Syndrome; OCD, obsessive compulsive disorder; PD, Parkinson's disease; rehab, rehabilitation; TS, Tourette syndrome.
a Effect sizes are based on a smaller number of studies due to data availability.

Table 13. Risk of Bias Assessment for Each Condition (Studies With Repeated tDCS Sessions)

Condition		Jadad score (SD)	% of low risk of bias (≥3 points)	Mean Jadad on exc. studies w/ score <3	SD of Jadad on exc. studies w/ score <3	Studies w/ Jadad score <3	Does removing studies w/ Jadad <3 change recommendation?
Pain	Neuropathic pain	4.40 (0.70)	100	4.38	0.70	None	N/A
	Fibromyalgia	5.00 (0.41)	100	4.83	0.00	None	N/A
	Migraine	4.50 (0.71)	100	4.50	0.71	None	N/A
	MPS	3.50 (2.12)	50	5.00	2.12	Choi et al., 2014	No
	Postoperative acute pain	4.25 (0.96)	100	4.25	0.96	None	N/A
	Low back pain	4.67 (0.58)	100	4.67	0.58	None	N/A
PD	Motor function	4.50 (0.73)	100	4.44	0.73	None	N/A
	Cognitive function	4.60 (0.55)	100	4.60	0.55	None	N/A
Chronic stroke	Motor function	4.32 (0.72)	100.00	4.45	0.72	None	N/A
	Aphasia	3.90 (0.62)	100.00	4.53	0.62	None	N/A
Subacute stroke	Motor function	4.45 (0.76)	100.00	3.95	0.76	None	N/A
Epilepsy	Seizure frequency	4.00 (0.00)	100.00	3.75	0.00	None	N/A
MDD	Depression	4.53 (0.74)	100.00	4.53	0.74	None	N/A
OCD and TS	OCD	1.56 (1.67)	25.00	3.67	1.67	Mondino, 2015; Narayanaswamy, 2015; Bation, 2016; Silva, 2016; Palm, 2017b	No
	TS	1.67 (1.15)	33.33	3.00	1.15	Carvalho, 2015; Behler 2018	No
Schizophrenia	Auditory hallucinations	4.00 (0.77)	90.91	4.20	0.77	Fitzgerald 2014	No
Addiction	Alcohol	4.33 (1.21)	83.33	4.80	1.21	da Silva, 2013	No
	Crack/cocaine	5.00 (-)	50	5.00	0.00	None	N/A

Abbreviations: exc., excluding; MDD, Major Depressive Disorder; MPS, Myofascial Pain Syndrome; OCD, obsessive compulsive disorder; PD, Parkinson's disease; TS, Tourette syndrome; w/, with.
Jadad scores are presented as mean and SD.

between different patients across studies. One potential solution is HD-tDCS (Villamar et al., 2013; Karvigh et al., 2017), which can account for head shape and size variations and perhaps lead to more comparable current distributions in tDCS. Most tDCS studies thus far are underpowered to show significance in categorical outcomes, and effect sizes should be evaluated in larger RCTs, which are necessary to find optimal parameters for stimulation across different populations and disorders.

Importantly, few RCTs in this review were Class I. As a result, most recommendations are either Level B or Level C (probably or possibly effective), and in a number of conditions no recommendations could be given. These levels of recommendation should only be used when no better treatments exist or when they have failed, in which case tDCS could be offered off-label as long as local regulatory policies are followed. Also, while we excluded single-session RCTs from our recommendations, we cannot guarantee that repeated-session tDCS changes were always due to cumulative as opposed to acute benefits, as many studies did not measure changes immediately after the first stimulation session; however, some did take repeated measurements over time showing cumulative neuroplastic benefits. We consider the inclusion of single-session studies important to demonstrate the history and mechanisms of the intervention.

Despite the above limitations, we believe that our work has certain strengths, such as our team of experts, our comprehensive review of repeated- and single-session studies, our assessment of methodological bias and sensitivity analyses excluding low-quality and smaller studies, and our easy-to-read tables showcasing the heterogeneity of parameters used in tDCS trial design. Furthermore, our secondary meta-analyses strengthen our claims for tDCS benefits in most disorders, including, neuropathic pain, PD (motor), epilepsy, depression, schizophrenia, chronic and subacute stroke (motor without robotics), and post-stroke aphasia. Additionally, the quantitative analyses also provide objective measures of heterogeneity and publication bias although sometimes with very limited samples.

While it may impact outcomes, we have no evidence that this heterogeneity in tDCS trials outweighs that of surgical or behavioral trials or even drug trials considering pharmacokinetic and pharmacodynamic variabilities. Finally, there are many recommendations but little consensus on how to investigate clinical heterogeneity (or "clinical diversity") in systematic reviews of RCTs, although we believe we covered many of the suggested methods, including using a team of clinical experts, careful covariate selection based on scientific rationales, and cautious interpretation of our findings (West et al., 2010; Gagnier et al., 2012).

Conclusions

According to this evidence-based review, we are able to recommend specific tDCS protocols for only some indications (e.g., MDD). These results were confirmed when studies with high risk of bias were excluded. Table 12 summarizes the recommendations on tDCS efficacy/safety according to clinical indication in 9 neurological and psychiatric disorders. A secondary meta-analysis provides even stronger evidence of tDCS benefits in multiple disorders, although sometimes with very limited samples. We summarize our results and synthesize them with the literature.

Supplementary Materials

Supplementary data are available at: International Journal of Neuropsychopharmacology (IJNPPY) online.

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Authors contributions: Felipe Fregni: study design, decisions on recommendations. Mirret M. El-Hagrassy: study design, literature search, study selection, comprehensive review of all papers included for intellectual content, drafting and revision of the entire manuscript and all tables, guidance and revision of all quantitative analyses, decisions on recommendations, risk of bias assessment, literature review, and synthesis. Kevin Pacheco-Barrios: literature search, study selection, comprehensive review of papers included for intellectual content, drafting of tables and recommendations, quantitative analyses, revision of the entire manuscript and all tables, decisions on recommendations, risk of bias assessment. Sandra Carvalho: literature search, study selection, drafting of tables and recommendations, revision of the entire manuscript and all tables, decisions on recommendations, risk of bias assessment. Jorge Leite: literature search, study selection, drafting of tables and recommendations, revision of the entire manuscript and all tables, decisions on recommendations, risk of bias assessment. Marcel Simis: study design, revision of the entire manuscript and all tables, decisions on recommendations. Jerome Brunelin: study design, revision of the entire manuscript and all tables, decisions on recommendations. Ester Miyuki Nakamura-Palacios: study design, revision of the entire manuscript and all tables, decisions on recommendations. Paola Marangolo: study design, revision of the entire manuscript and all tables, decisions on recommendations. Ganesan Venkatasubramanian: study design, revision of the entire manuscript and all tables, decisions on recommendations. Daniel San-Juan: study design, revision of the entire manuscript and all tables, decisions on recommendations. Wolnei Caumo: study design, revision of the entire manuscript and all tables, decisions on recommendations. André R. Brunoni: study design, revision of the entire manuscript and all tables, decisions on recommendations. Marom Bikson: study design, revision of the entire manuscript and all tables, decisions on recommendations. Neuromodulation Center Working Group: literature search, study selection, risk of bias assessment, and drafting of tables.

Statement of Interest

M.B. is affiliated with CUNY. CUNY has patents on brain stimulation with M.B. as inventor. The other authors report no conflicts of interest.

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