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Application of Transcranial Direct Current Stimulation in Psychiatry

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Abstract
Transcranial direct current stimulation (tDCS) is a neuromodulation technique, which noninvasively alters cortical excitability via weak polarizing currents between two electrodes placed on the scalp. Since it is comparably easy to handle, cheap to use and relatively well tolerated, tDCS has gained increasing interest in recent years. Based on well-known behavioral effects, a number of clinical studies have been performed in populations including patients with major depressive disorder followed by schizophrenia and substance use disorders, in sum with heterogeneous results with respect to efficacy. Nevertheless, the potential of tDCS must not be underestimated since it could be further improved by systematically investigating the various stimulation parameters to eventually increase clinical efficacy. The present article briefly explains the underlying physiology of tDCS, summarizes typical stimulation protocols and then reviews clinical efficacy for various psychiatric disorders as well as prevalent adverse effects. Future developments include combined and more complex interactions of tDCS with pharmacological or psychotherapeutic interventions. In particular, using computational models to individualize stimulation protocols, considering state dependency and applying closed-loop technologies will pave the way for tDCS-based personalized interventions as well as the development of home treatment settings promoting the role of tDCS as an effective treatment option for patients with mental health problems.

Introduction

Noninvasive brain stimulation mainly comprises transcranial direct current stimulation (tDCS) as well as transcranial magnetic stimulation (TMS) and is rapidly emerging as a therapeutic strategy in various psychiatric disorders. tDCS is a neuromodulation technique which relies on the alteration of cortical excitability via weak polarizing currents between two electrodes placed on defined places of the scalp (Fig. 1). This neuromodulatory technique has gained increasing interest since it is comparably easy and cheap to use while being relatively well tolerated. With increasing evidence, tDCS has gained attention for implementation in national and international guidelines, especially in the field of affective disorders. However, recently published trials failed to demonstrate noninferiority to standard pharmacological treatments [1] and, thus, have increased skepticism against this noninvasive brain stimulation method and its clinical efficacy.

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Application	Anode	Cathode
MDD/BD	F3	F4 Fp2 F8 Right deltoid
Schizophrenia	F3	TP3 F4 Fp2
Substance use disorders	F3	F4 Fp2 Right deltoid
Social anxiety disorder	F3	Left arm
PTSD	F3	Right mastoid process

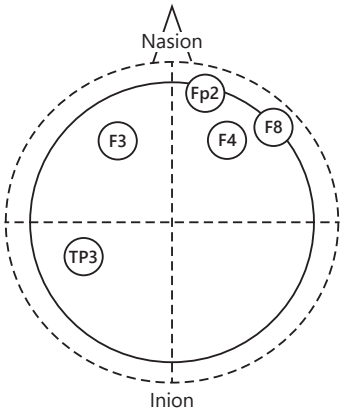

Fig. 1. Common tDCS montages using the 10-20 EEG system. MDD, major depressive disorder; BD, bipolar disorder; PTSD, post-traumatic stress disorder.

From our perspective, tDCS is currently at a crossroad and needs to prove its potential in the treatment of psychiatric disorders. We are convinced that this is possible since the existing broad knowledge about the physiology of tDCS (see the section "Physiological effects of tDCS") is a useful prerequisite to further improve the method by varying the various intervention parameters to positively influence stimulated cortical structures (see the section "Stimulation parameters and protocols"). This in consequence has the potential to further improve clinical effects, which have already been described for a number of psychiatric disorders (see the section "Direct current stimulation in clinical populations") with few side effects (see the section "Side effects"). Most importantly, the large body of clinical experience in combination with increasing knowledge about individually involved neuronal structures, complex interactions with pharmacological interventions and possibilities to remotely monitor stimulation devices might be the foundation for future developments of this method such as (to only name two prominent examples) personalized tDCS based on simulation techniques or closed-loop stimulation protocols as well as home treatment approaches (see the section "Outlook and future trends"). This in sum might lead to a more convenient, better tailored, neurobiologically informed and hopefully more effective usage of this easy-to-apply neuromodulation technique.

Physiological Effects of tDCS

tDCS applies a constant low-intensity current through two electrodes, which are superficially placed on the skull [2]. Its acute physiological mechanism lies in the modulation of the neuronal resting potential and thus in an alteration of the neurons' excitability [3]. This means that unlike TMS, tDCS applied at the conventional intensity (1–2 mA) does not directly elicit neuronal firing. After anodal stimulation, this alteration in membrane potential is done towards depolarization (hence called excitatory stimulation) and towards hyperpolarization after cathodal stimulation (inhibitory stimulation). This polarity-dependent activity may rely upon the spatial organization of the neurons. The cathodal stimulation elicits an outward current flow, which generates a somatic hyperpolarization and apical dendritic depolarization, while anodal stimulation creates an inward current with a resulting hyperpolarization of apical dendritic regions and depolarization of the soma [4].

The effects of tDCS seem to last beyond the acute alteration of the membrane potential [5]. Studies using TMS revealed that the application of a transcranial current induces a long-lasting excitability elevation shown by increased motor-evoked potential amplitudes [6]. After applying the direct current to the primary motor cortex, this effect can last from minutes to more than 24 h depending on the stimulation parameters [7].

Furthermore, pharmacological experiments performed on the primary motor cortex in humans revealed that the glutamatergic receptors, specifically N-methyl-D-aspartate (NMDA) receptors, are involved in plasticity-related processes induced by tDCS. In these studies, the administration of NMDA receptor agonists even enhanced the effects of anodal stimulation [8]. In accordance with these findings, it was shown that NMDA receptor antagonists blocked the excitatory as well as the inhibitory effects of direct current stimulation on motor cortical excitability [9]. The NMDA-mediated calcium

flux is a critical component of synaptic plasticity suggesting that intracellular calcium dynamics are involved in the aftereffects of direct current stimulation. These results support the idea that neuroplasticity induced by tDCS is both calcium and NMDA dependent and that its mechanism compares to that of long-term potentiation and long-term depression at glutamatergic synapses [10]. Additionally, studies using magnetic resonance spectroscopy found a reduction of GABA after excitatory and inhibitory stimulation in the motor cortex [11, 12]. tDCS may also influence the modulation of serotonergic and dopaminergic systems, which have traditionally been associated with the pathogenesis of affective disorders. One study found that long/long homozygotes for the serotonin transporter (SLC6A4) showed a significantly stronger improvement than short allele carriers after tDCS [13]. Additionally, genetic polymorphisms of the cathechol-*o*-methyltransferase, an enzyme involved in the catabolism of dopamine, seem to influence the effects of anodal stimulation on prefrontal functioning [14]. Taking advantage of these effects, different tDCS protocols have been developed to modulate neuronal processes that require long-term potentiation or long-term depression, such as learning and memory.

Stimulation Parameters and Protocols

With regard to tDCS efficacy, stimulation parameters such as current intensity and stimulation duration are crucial to consider [3]. The vast majority of behavioral studies and clinical trials apply current intensities of 1–2 mA with an electrode size of 25 (5 × 5) to 35 (5 × 7) cm^2 and a stimulation duration of 5–30 min, which is considered safe in humans [15]. As demonstrated by a recent study with 18 stroke patients, current intensities even up to 4 mA are safe and tolerable in humans [16]; however, more trials are needed to replicate these findings [17]. There still is a lack of studies systematically testing the efficacy of different intensities and durations using within-group designs [18]. Furthermore, it is not clear whether tDCS efficacy is subject to a linear or nonlinear dose-response relationship [19] and whether such a relationship might be specific for certain pathological or physiological conditions, specific brain regions or functions. For example, Hoy et al. [20] demonstrated that a 2-mA stimulation was superior to 1-mA and to sham stimulation in increasing cognitive performance in patients with schizophrenia. Chhatbar et al. [21] conclude in their meta-analysis that there is a dose-response relationship of tDCS when targeting upper extremity motor recovery in post-stroke patients. Other studies point to an interaction between current intensity and the status of the brain region being stimulated (e.g. gray matter volume/age, cerebral cytoarchitecture, baseline activity/excitability state) leading to a substantial outcome variability and a generally low replicability of findings across studies [22, 23]. Therefore, studies with a clinical focus now concentrate on combining tDCS with active tasks or interventions to take into account the hypothesis that tDCS efficacy may be activity dependent [24, 25]. Future researchers looking to decide on a suitable protocol fitting their hypothesis or therapeutic approach can consult a recent paper by Thair et al. [26] that thoroughly summarizes the current state of knowledge with regard to stimulation parameters.

There is converging evidence regarding whether tDCS efficacy and sustainability increase with the number of sessions [27], and there are currently no specific guidelines addressing this issue. The majority of clinical trials do apply multiple sessions of tDCS (around 5–30 sessions) [28]. Furthermore, a study with 120 depressed patients showed that there is no significant impact on efficacy when, for example, 1 or 2 sessions from a series of 10 are missed [29]. However, no study so far has systematically investigated how many sessions can be missed without having a negative impact on tDCS efficacy. The authors thus recommend the use of flexible treatment schedules that adapt to patients' needs.

Furthermore, the majority of trials do not provide further information about how the issue of missing sessions was dealt with in the final analysis [30]. To overcome the problem of dropouts with increasing numbers of consecutive tDCS sessions, potential and limitations of a remotely supervised tDCS treatment ("home treatment") are currently under debate [31].

Direct Current Stimulation in Clinical Populations

As pointed out in a recent study reviewing clinical effects of tDCS [32], unipolar depression has been the most extensively studied psychiatric condition so far followed by schizophrenia and substance use disorders. Preliminary evidence exists for the use of tDCS in the treatment of anxiety disorders such as post-traumatic stress disorder. For treatment-resistant obsessive-compulsive disorder [33], generalized anxiety disorder [34] as well as anorexia nervosa [35], only case reports have been published so far.

Major Depressive Disorder

When used for the treatment of unipolar depression, the anode is positioned over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right DLPFC, supraorbital or extracephalic [36]. The rationale behind this montage comes from studies that developed the prefrontal asymmetry theory of depression, which states that right prefrontal activity is higher than left in depressed patients [37] and from clinical trials with rTMS using facilitatory stimulation over the left DLPFC and inhibitory stimulation over the right DLPFC [38].

The majority of stimulation protocols for major depression are performed with the same time and position parameters (20 min, bifrontal montage). Some investigations explored further the possible parameters that can be used. For example, a study found that combining sertraline with stimulation for 30 min was associated with a better response than a combined stimulation for 20 min [39]. Another study by Martin et al. [40] found that an extracephalic electrode position in a group of patients who did not respond adequately to bifrontal stimulation resulted in a better antidepressant effect. They also showed that performing weekly or second-weekly maintenance sessions induces remission rates of 80% after 3 months and 50% after 6 months [41].

In a number of clinical trials (Table 1), tDCS turned out to efficiently reduce clinical symptoms of major depression. Fregni et al. [42] were the first to perform a double-blind placebo-controlled study with 1-mA anodal stimulation for 20 min over the left DLPFC for 5 days, resulting in significant symptom improvement. Several randomized clinical trials followed, exploring different stimulation protocols and patient subpopulations with mixed results [24, 43–51]. Meta-analyses of randomized clinical trials showed a significantly stronger improvement in depression scores [52, 53] as well as higher response and remission rates [53] in the active tDCS group as compared to sham tDCS. In contrast, 1 meta-analysis found no difference when taking into account only response or remission rates between active and sham stimulation groups [54]. These mixed results highlight the problem of analyzing diverse stimulation protocols and small sample sizes, emphasizing the need for larger multicenter collaboration trials.

Further studies investigated the interplay between tDCS and pharmacological interventions. tDCS has been found to elicit similar antidepressant effects to 20 mg of fluoxetine; however, a significant response to tDCS occurred faster than a significant response to medication [55]. In 2013, Brunoni et al. [48] published a study comparing the effect of tDCS, sertraline and a combination of both in a clinical trial of 120 patients with major depression. Treatment with tDCS or sertraline alone improved depressive symptomatology [48]. Nonetheless, the combination of both treatments showed a greater effect. The same research group also performed the largest clinical tDCS trial so far. This trial consisted of a noninferiority study with 245 patients receiving either escitalopram, tDCS or placebo. Here, tDCS failed to show noninferiority to escitalopram [1].

The findings that depressed patients show an improvement in working memory and affective processing after one session of direct current stimulation over the left DLPFC [56, 57] led to the development of protocols that combine tDCS with cognitive tasks to improve cognitive performance and clinical symptoms [24]. An exploratory trial investigated whether tDCS could improve the efficacy of cognitive control therapy [24]. They found that both cognitive control therapy alone and tDCS improved the depressive symptoms and that only elderly patients benefited from the combination of both therapies, suggesting that this combination may be more beneficial for patients with cognitive decline. Vanderhasselt et al. [58] explored whether tDCS was able to improve the influence of neurocognitive training on rumination, a key feature of depression. Their results showed that tDCS did not enhance the results of the training. In line with these studies, a currently ongoing randomized clinical trial examines whether tDCS can augment cognitive behavioral therapy in depression [25].

In summary, despite the fact that major depressive disorder is the most studied disease within the tDCS literature, the results of its efficacy are mixed due to the heterogeneity of patient samples, depression severity and small sample sizes. Furthermore, a promising approach to increase efficacy currently under investigation is the combination of the stimulation with cognitive tasks.

Bipolar Disorder

In a clinical trial by Sampaio-Junior et al. [59], patients with bipolar depression received left prefrontal anodal stimulation as an add-on treatment to their pharmacological therapy. Patients receiving active stimulation had a more significant symptom reduction as compared to those treated with sham tDCS. A meta-analysis showed that tDCS could improve depressive symptoms in patients with bipolar depression, particularly after 1 week of treatment [60]. There is one published case report on the combination of tDCS with pharmacological treatment in a male patient with an acute episode of mania [61]. The

Table 1. Randomized clinical trials in patients with depression

Author	*n*	Diagnosis	Conditions	Montage: anode, cathode	Current strength, duration, number of sessions	Rating scales	Symptom improvement
Fregni et al. [42], 2006	10	MDD	(a) tDCS (b) Sham tDCS	F3, FP2	1 mA, 20 min, 5 sessions	HAMD, BDI	Improvement in depressive symptoms on active group versus sham
Boggio et al. [43], 2008	40	MDD	(a) tDCS on DLPFC (b) tDCS on occipital cortex (active control) (c) sham tDCS	F3, FP2	2 mA, 20 min, 10 sessions	HAMD, BDI	Improvement in depressive symptoms on DLPFC active group versus sham and occipital tDCS
Loo et al. [44], 2010	40	MDD	(a) tDCS (b) Sham tDCS	F3, FP2	1 mA, 20 min, 5 sessions	MADRS	No difference on symptom improvement on active group versus sham
Loo et al. [45], 2012	58	MDD, BD	(a) tDCS (b) Sham tDCS	F3, F8	2 mA, 20 min, 15 sessions	MADRS, HAMD, BDI, CGI	Improvement in depressive symptoms (MADRS) on active group versus sham but same response rate in both groups
Blumberger et al. [46], 2012	24	MDD	(a) tDCS (b) Sham tDCS	F3, F4	2 mA, 20 min, 15 sessions	HAMD, MADRS, BPRS, BDI	No difference on symptom improvement on active group versus sham
Palm et al. [47], 2012	22	MDD, BD	(a) tDCS (b) Sham tDCS	F3, FP2	1 or 2 mA, 20 min, 10 sessions	HAMD, PANAS, BDI	No improvement in depressive symptoms on active group versus sham
Brunoni et al. [48], 2013	103	MDD	(a) tDCS + placebo pill (b) Sham tDCS + sertraline (c) tDCS + sertraline (d) Sham tDCS + placebo pill	F3, F4	2 mA, 30 min, 12 sessions	HAMD, MADRS, CGI, BDI	Improvement in depressive symptoms on active group versus sham; greater effects on tDCS + sertraline group
Brunoni et al. [49], 2014	37	MDD	(a) tDCS + CCT (b) Sham tDCS + CCT	F3, F4	2 mA, 30 min, 10 sessions	HAMD, BDI	No difference on symptom improvement on active group versus sham
Segrave et al. [24], 2014	27	MDD	(a) tDCS + CCT (b) Sham tDCS + CCT (c) tDCS + sham CCT	F3, F8	2 mA, 24 min, 5 sessions	MADRS, BDI	Improvement in depressive symptoms on active group versus sham; greater but delayed effects on tDCS + CCT group
Bennabi et al. [50], 2015	24	MDD	(a) tDCS (b) Sham tDCS	F3, FP2	2 mA, 30 min, 10 sessions	HAMD, MADRS, BDI	No difference on symptom improvement on active group versus sham
Brunoni et al. [1], 2017	245	MDD	(a) tDCS + oral placebo (b) Sham tDCS + escitalopram (c) Sham tDCS + oral placebo	F3, F4	2 mA, 30 min, 15 sessions	HAMD	tDCS failed to show noninferiority to escitalopram
Loo et al. [51], 2018	130	MDD, BD	(a) tDCS (b) Sham tDCS	F3, F4	2.5 mA, 30 min, 20 sessions	MADRS	No difference on symptom improvement on active group versus sham; BDNF genotype unrelated to antidepressant outcome

tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; CCT, cognitive control therapy; BDNF, brain-derived neurotrophic factor; BDI, Beck Depression Inventory; BD, bipolar disorder; BPRS, brief psychiatric rating scale; CGI, clinical global impression; HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; PANAS, positive and negative affect schedule.

Table 2. Randomized control trials in patients with schizophrenia

Author	*n*	Conditions	Montage: anode, cathode	Current strength, duration, number of sessions	Rating scales	Symptom improvement
Brunelin et al. [62], 2012	30	(a) tDCS (b) Sham tDCS	F3–FP1, TP3	2 mA, 20 min, 10 sessions	AHRS, PANSS	Significant improvement in negative symptoms and reduction of AVH in active tDCS versus sham
Fitzgerald et al. [75], 2014	24	(a) Unilateral tDCS (b) Bilateral tDCS	F3/F4, TP3/TP4	2 mA, 20 min, 15 sessions	PANSS	No difference in reduction of AH severity or change in PANSS scores between active and sham stimulation for the group as a whole, for bilateral or unilateral tDCS
Mondino et al. [66], 2015	28	(a) tDCS (b) Sham tDCS	F3, TP3	2 mA, 20 min, 10 sessions	AH frequency	Reduction of AVH frequency after active versus sham tDCS
Smith et al. [73], 2015	33	(a) tDCS (b) Sham tDCS	F3, FP2	2 mA, 20 min, 10 sessions	PANSS, PSYRATS	No differences in PANSS or AVH scores between active and sham
Gomes et al. [76], 2015	15	(a) tDCS (b) Sham tDCS	F3, F4	2 mA, 20 min, 10 sessions	PANSS	Reduction in PANSS negative after active stimulation. No reduction of positive symptoms
Fröhlich et al. [77], 2016	26	(a) tDCS (b) Sham tDCS	F3–FP1, TP3	2 mA, 20 min, 5 sessions		No differences in AVH reduction on active versus sham
Shiozawa et al. [78], 2016	9	(a) tDCS + CCT (b) Sham tDCS + CCT	F3, F4	2 mA, 20 min, 5 sessions	PANSS	No improvement in clinical outcomes after tDCS plus cognitive training
Bose et al. [65], 2014	25	(a) tDCS (b) Sham tDCS	F3–FP1, TP3	2 mA, 20 min, 10 sessions	AHRS	Significant improvement in AVH in active stimulation compared to sham

AVH, auditory verbal hallucinations; AH, auditory hallucination; AHRS, Auditory Hallucination Rating Scale; PANSS, Positive and Negative Symptom Scale; PSYRATS, Psychotic Symptom Rating Scales; tDCS, transcranial direct current stimulation.

authors performed anodal tDCS over the right DLPFC combined with a pharmacological intervention and reported an improvement of manic symptoms that lasted until 72 h after stimulation.

In brief, tDCS potentially improves depressive symptoms in patients with bipolar depression. Nonetheless, larger randomized controlled trials are needed to define the efficacy and appropriate tDCS-modality in this patient population. Further investigations should also address the frequency of tDCS-emergent hypomania/mania.

Schizophrenia

The tDCS montage in patients with schizophrenia is designed to modulate the activity and connectivity between different brain areas in order to target the diverse symptomatology of this disease [62, 63]. In a sham-controlled clinical trial with 20 patients with schizophrenia, Brunelin et al. [64] were able to demonstrate a significant reduction of auditory hallucinations after anodal tDCS over the left DLPFC and cathodal stimulation over the left temporoparietal region (2 mA, 20 min, 5 consecutive days) as compared to sham. This montage was used to inhibit an area related to positive symptoms (temporoparietal) and to activate the prefrontal cortex, an area that has been described as hypoactive in schizophrenia and a promising target to treat negative symptoms. This result could be replicated by further studies [65, 66]. Underlying mechanisms behind improvement of positive symptoms may relate to a tDCS-induced increase in sensory gating as measured by the P50 event-related potential [67, 68], since patients with schizophrenia are supposed to show abnormal patterns of P50 suppression associated with an impaired ability to filter out redundant or unnecessary stimuli. One study pointed out that smoking might interfere with these processes and reduce tDCS efficacy in the treatment of hallucinations [69]. Glutamate levels in tDCS target areas might also play a role with regard to efficacy [70]. Moreover, negative symptoms can be reduced successfully as shown by one case study [71] and a small proof-of-concept trial with 9 patients [72]; however, randomized and sham-controlled trials with bigger samples are still lacking (Table 2). There is cumulating evidence

that tDCS increases cognitive performance in schizophrenia, particularly with regard to working memory and attention [73], and that a higher dose (2 mA) seems to be more effective than smaller doses (1 mA) or sham stimulation [20]. Along the line of tDCS studies in nonclinical populations, tDCS efficacy can be increased in patients with schizophrenia when considering state-dependent effects by combining stimulation with working memory training [74].

To summarize, the tDCS montage can be designed to target both negative and positive symptoms; nonetheless, little is known about optimally suited tDCS protocols for the treatment of schizophrenia [75–78]. *Few clinical studies have been conducted on this disease, but these conferred promising and positive results and encourage further investigation.*

Substance Use Disorders

tDCS over the DLPFC has been shown to be clinically useful in the treatment of drug addiction, with DLPFC being an important brain structure for the regulation of craving behavior [79]. As a randomized controlled trial with 33 patients with alcohol dependence demonstrated, prefrontal tDCS was associated with a reduction of relapse probability and an improved perception of quality of life [80]. A small sham-controlled study showed that active tDCS was able to inhibit the increase in neural activation triggered by alcohol-related cues in 13 alcohol-dependent subjects [81]. Also, food craving induced by visual stimuli in patients with abnormal eating behavior and food addiction could be decreased by tDCS [82]. A currently running clinical trial with 340 alcohol-dependent patients and a follow-up period of 24 weeks will certainly shed more light on the therapeutic potential of tDCS in addiction [83].

In sum, the therapeutic effect of tDCS could be due to a disruption of the reward networks between prefrontal regions. Despite these promising results, studies with reasonable sample sizes, consistent stimulation protocols and adequate study duration are still lacking so that a final assessment of tDCS efficacy in addiction seems to be difficult at the moment [84].

Anxiety Disorders

With the DLPFC being also involved in threat processing [85], tDCS over the DLPFC might be an effective treatment option for anxiety disorders. Empirical evidence, however, is still scarce [86]. In a small proof-of-concept study with 19 patients with social anxiety disorder, Heeren et al. [87] were able to show that a single session of anodal tDCS over the left DLPFC significantly decreased participants' attentional bias for social threat in a probe discrimination task as compared to sham stimulation. The authors conclude that tDCS may be an interesting tool to gain insight into underlying mechanisms of social anxiety disorders; however, drawing direct conclusions for tDCS-based interventions would have been premature. Since exposure-based psychotherapy is the gold standard in the treatment of anxiety disorders, it may also be useful to evaluate noninvasive brain stimulation techniques such as tDCS with regard to their ability to improve or augment extinction learning, which is an important process in exposure-based interventions. Here, the ventromedial prefrontal cortex has been chosen as a target due to its involvement extinction learning and subsequent retention of extinction memories [88]. In a recent study with 28 veterans with post-traumatic stress disorder, which was designed to test the optimal timing of tDCS augmented extinction learning, the authors found that tDCS over the ventromedial prefrontal cortex was more effective when applied during consolidation of fear extinction than during extinction learning itself [89]. However, in this study, fear extinction was not tested in the context of individual traumatic memories, but of a standardized experimental paradigm, so conclusions regarding tDCS in post-traumatic stress disorder treatment would be premature as well.

To summarize, tDCS is a promising therapy for anxiety disorders but results are still preliminary. Optimal dosing, treatment targets and mechanism of action are still open questions. The combination of tDCS with cognitive-behavioral techniques seems to be a particularly good fit in the management of anxiety disorders.

Side Effects

In general, tDCS is a safe technique and adverse effects after stimulation are usually mild in nature. Predominant adverse events reported in clinical trials are itching, tingling, headache, discomfort, fatigue and burning sensation on the application site [90]. Several predisposing factors increase the risk of local side effects like high skin impedance, small and dry electrodes, wrong electrode position and contact with the skin, as well as an allergic predisposition [91]. Repeated sessions do not increase the risk for a higher number of adverse events [28]. Cases of treatment-emergent mania and hypomania have also been reported in clinical trials for bipolar depression [92–95]. An important point is that the majority of patients in

clinical trials receives medication, and thus it may be difficult to deduct whether tDCS is solely responsible for the side effects. A recent meta-analysis was not able to confirm that the reported treatment-emergent mania was actually induced by the stimulation [96]. Under the conventional protocols for humans, there is currently no record of a serious adverse effect or irreversible tissue injury attributable to tDCS [97]. There is one report of a seizure in a pediatric patient with a history of idiopathic infantile spasm and spastic tetraparesis [98]. It is unclear, however, whether tDCS induced the seizure in this case. Further analyses of risk factors and clinical characteristics of patients who report side effects are essential for the improvement of participant selection, inclusion and safety in future trials.

Outlook and Future Trends

tDCS has clear effects on neuronal structures and has been applied – as described above – in various clinical populations. The current evidence, however, does not provide yet a level-A recommendation [99]. From our perspective, efficacy could be further improved by personalizing this method. tDCS is a good candidate for individualized approaches since its application is based on the modulation of clearly defined neuronal structures involved in the pathomechanism of depression [100, 101].

The need for personalized approaches is self-evident, taken into closer consideration the anatomical and functional heterogeneity of stimulated neuronal structures, the heterogeneity of concomitant medication patients usually take, as well as heterogeneity of defined psychiatric categories. Those multiple heterogeneities might be responsible for negative findings or studies, in which even negative synergies have been described [102, 103]. In order to tailor tDCS as a therapeutic method to the individual needs, there are currently three interweaved research lines all aiming at increasing tDCS effects by using computational models, considering state dependency and applying closed-loop technologies. First, there is increasing evidence that computational models can be used to modulate the intervention and adapt it to individual differences in tDCS responses [104] and individual differences in the distribution of electrical currents [105]. As a consequence, such models provide information, which are needed to individualize stimulation protocols allowing reducing of stimulation intensity [106] or modification of electrode montages [107]. Second, there is converging evidence that effects of noninvasive brain stimulation are tailored by the activity level of the stimulated cortical regions as demonstrated by studies investigating linguistic functions in parietal regions [108], cognitive functions in cerebellar regions [109] as well as cognitive domains in stimulated prefrontal regions [110]. Third, recent technological developments such as the development of suitable sensors [111] and algorithms laid the foundation of developing applications in which stimulation intensity and frequency are dynamically adapted to local brain activities, or in brief the foundation for closed-loop applications. As "second-generation" brain stimulators they are currently used and investigated mainly in the field of epilepsy [112] and deep brain stimulation [113], but also in the field of noninvasive brain stimulation with encouraging effects comprising improvement of memory [114] and motor functions [115].

Furthermore, the correct identification and understanding of the different sources of individual variability can be achieved if this is taken into consideration when designing a clinical trial. This variance identification would require a replication at the level where the differential response is thought to be present, in this case at the patient level. This could be achieved for example by implementing a repeated crossover design, where patients are treated by each treatment in randomized sequences [116] or with *n*-of-1 trials, which are multiple crossover trials conducted in a single patient [117].

Besides being a candidate for individualized approaches, tDCS has a second big advantage: whereas electroconvulsive therapy and deep brain stimulation usually require inpatient settings, tDCS can be successfully implemented outside the walls of psychiatric private practices and hospitals, i.e. it can easily be applied in an outpatient setting. This is important, since most of the neuromodulatory treatments require patients to come into hospitals repeatedly (e.g., in case of rTMS at least 20 times) [118], which is often difficult for patients suffering from affective disorders or for patients living in rural areas with usually long distances to mental health services. Such home treatment approaches using tDCS have been proven to be feasible in other indications such as Parkinson's disease [119]. In-home treatment requires structured supervision which may be achieved by domiciliary care models where technicians attend the patient's home or by guiding via videoconferencing technologies [120] or by using cloud-based technologies in order to monitor stimulation parameters such as electrode impedance [121]. Of importance, one needs to take into consideration that such approaches will not be feasible for all patients and exclude those who do not have the cognitive and/or technological

prerequisite to independently apply such forms of self-treatment.

Potential reductions of acceptance rates within the target patient population as well as substantial response differences in patients with various psychiatric disorders are among the main shortcomings when using tDCS. From our point of view, there are different auspicious avenues to overcome these shortcomings, mainly by personalizing treatment settings and/or by taking advantage of new technological development in order to promote home treatment settings. With these two approaches, tDCS may find its role as a safe, cost-effective treatment for patients with mental health problems.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.L.H.-M., M.B. and S.A. reviewed the literature, structured and wrote the article, provided critical feedback and approved the final version of the paper.

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