Transcranial Direct Current Stimulation (tDCS) in Anxiety Disorders

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21.1 Introduction

The interest in using transcranial direct current stimulation (tDCS) as a complementary or alternative tool for the treatment of neurological and psychiatric disorders has been significantly growing since the last decade, as shown by the exponential increase of scientific publications in the field (see [1], for an overview). One key factor for the interest in this noninvasive brain stimulation technique refers to its

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potential to modulate neural activity by acting on synaptic plasticity (e.g., [2]), which is supposed to be abnormal in several brain disorders [2–4]. tDCS has indeed been shown to induce long-term potentiation (LTP) and long-term depression (LTD)–like plasticity in humans (e.g., [5–8]). In line with these premises, therapeutic effects of tDCS have been shown in numerous clinical disorders of the central nervous system in both adult and pediatric populations. For recent reviews in the field, see [9–14].

In the current chapter, we provide an updated overview on the therapeutic effects of tDCS for the treatment of anxiety disorders in adult populations according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification of anxiety disorders [15]. In particular, we aim to examine the currently available literature on the effects of tDCS for the treatment of specific phobias (SP), social anxiety disorder (SAD), panic disorder (PD), agoraphobia, and generalized anxiety disorder (GAD).

According to recent suggestions (e.g., [16]), one important pathological mechanism in anxiety disorders is maladaptive neuroplasticity. Evidence for altered neuroplasticity is shown by studies documenting hypoactivation of the left dorsolateral prefrontal cortex (DLPFC) (e.g., [17, 18]) and hyperactivation of the right DLPFC in anxiety [19]. In line with these premises, tDCS might represent a useful tool to counteract respective patterns of maladaptive neuroplasticity by modulating pathological hypo/hyperactivation of the DLPFC in respective clinical populations. Moreover, the link between prefrontal regions and subcortical regions involved in threat and fear processing (e.g., amygdala) is another rationale for targeting anxiety through modulation of the DLPFC with tDCS [20]. In fact, functional abnormalities of the amygdala, the key neural region of the "fear circuit," have been documented in several anxiety disorders (see [21] for a review).

Since an extended overview of the neurophysiological foundation and mechanisms of action of tDCS is presented in this book, we are here only providing a brief introduction dedicated to this topic. For a more exhaustive/detailed overview, please see also the following recent reviews in the field (e.g., [8, 22–24]).

21.2 Mechanisms of Action of tDCS

tDCS is a well-established noninvasive brain stimulation tool that allows to stimulate the cerebral cortex via two or more electrodes with opposite polarities (i.e., anodal and cathodal) placed on the scalp and connected with a battery-driven constant current stimulator with a maximum output in the milliampere (mA) range [14]. A relatively weak electrical direct current (usually 1–2 mA) is applied via the electrodes, and a proportion of it enters the brain [6, 7, 25–28]. As a general principle, increases of cortical excitability have been documented during and after stimulation with the anode over the target area. On the other hand, a decreased cortical excitability was found to follow stimulation with the cathode over the respective region [8]. A single stimulation session of up to 15-minutes duration affects cortical excitability for up to 90 minutes [7, 26, 29], and this effect can be further extended by

repeated stimulation (i.e., cumulative effects) [5]. The prolonged effects of tDCS on cortical excitability are linked to mechanisms of synaptic modulation, as suggested by pharmacological studies in humans [30] and animal models [2, 3]. Evidence suggests that tDCS induces plasticity of glutamatergic synapses, which is calcium dependent. tDCS after-effects (both anodal and cathodal) are prevented by NMDA receptor block but enhanced by respective receptor agonists [6, 7, 31, 32]. Moreover, GABAergic activity is reduced by both anodal and cathodal tDCS [33], and this reduction might serve as a gating mechanism for tDCS-induced plasticity. Because of calcium dynamics involved in glutamatergic plasticity, nonlinear effects are observed if stimulation intensity and duration extend beyond specific limits. Low calcium enhancement of the postsynaptic neuron induces long-term depression (LTD), whereas high concentration is involved in long-term potentiation (LTP) [34]. Extending calcium concentration further activates counter-regulatory mechanisms antagonizing calcium influx, and reduces or converts plasticity induction [35]. This explains why enhancing the stimulation intensity of cathodal tDCS from 1 to 2 mA converts LTD- into LTP-like plasticity [36, 37, 38], and why extending stimulation duration of anodal tDCS from 13 to 26 minutes results in LTD-like plasticity [5].

21.3 Overview of the Available tDCS Studies in Anxiety Disorders

Before reporting the effects of tDCS on anxiety disorders based on the DSM-5 classification, we start with a focus on the efficacy of this technique to modulate trait anxiety, which is a common aspect of all anxiety disorders [39, 40]. Ironside and coworkers [20] examined the effects of tDCS over the prefrontal cortex (PFC) on the behavioral response to a threatening stimulus (i.e., participants were required to perform an attentional task requiring them to ignore threatening face distractors) in individuals with trait anxiety. Additionally, threat-related activation of the amygdala, which is crucially involved in fear generation, was obtained by functional magnetic resonance imaging (fMRI). In this double-blind, within-subject, randomized clinical trial, eighteen women with high trait anxiety (age mean = 23.1; age range, 18–42 years) were included. High trait anxiety was defined as scoring higher than 45 on the Spielberger State-Trait Anxiety Inventory (STAI), which measures the severity of current symptoms of anxiety and a generalized propensity to be anxious [41]. Trait anxiety was further confirmed using the Structured Clinical Interview for DSM-IV disorders. Following a counterbalanced order, active vs. sham tDCS was applied over the left and right DLPFC (i.e., anodal left / cathodal right DLPFC; more details in Table 21.1), in two single sessions, separate by one month. Immediately after (roughly 7 minutes) the end of tDCS, participants began an fMRI emotional task with fearful or neutral facial expressions, in order to study amygdala activation during performance of attentional control over fearful stimuli. The results showed a reduced influence of threat distractors on task accuracy following tDCS. Active tDCS compared to sham improved performance accuracy under low

Table 21.1 A total of 83 participants were involved in all the examined studies

#	Article	Study type (blinding)	*N*	age (mean ± SD)	Target electrode site	Return electrode/ size	Intensity	Duration	Polarity	Control	Measure	Outcome
Specific phobia (SP)												
1	Palm et al. [53]	Open-label study	*N* = 8	45.6 ± 12.3	Left DLPFC (F3)	Right supraorbit/7 × 5 cm	2 mA	5 × 30 minutes	Anodal	No control	DHI, VSS, HADS	Reduction of DHI scores, no significant reduction of HADS
Social anxiety disorder (SAD)												
2	Heeren et al. [42]	RCT (double blind)	*N* = 19	24.16 ± 4.87	Left DLPFC (F3)	Ipsilateral arm/7 × 5 cm	2 mA	25 minutes (single session)	Anodal	Sham	Dot-probe task (online)	Decreased attention bias during anodal tDCS
Panic disorder (PD)												
3	Shiozawa et al. [43]	Case study (follow-up)	*N* = 1	44	Right DLPFC (F4)	Contralateral deltoid/5 × 5 cm	2 mA	10 × 30 minutes	Cathodal	No control	HAS/BAI	Decrease in HAS, BAI
Generalized anxiety disorder (GAD)												
4	Shiozawa et al. [44]	Case study (45-day follow-up)	*N* = 1	58	Right DLPFC (F4)	Contralateral deltoid/5 × 5 cm	2 mA	15 × 30 minutes	Cathodal	No control	HRS-A/BAI	Decrease in HRS-A, BAI
5	Movahed et al. [45]	RCT (single blind)	*N* = 18	28.73 ± 9.6	Right DLPFC (F4)	Contralateral deltoid/7 × 5 cm	2 mA	15 × 30 minutes	Cathodal	Sham	HARS, PSWQ	Decrease in HARS, PSWQ

6	Lin et al. [46]	RCT (single blind) (8 weeks follow-up)	*N* = 20	44.5 ± 10.2	Right DLPFC (F4)	Left mastoid/7 × 5 cm	2 mA	10 × 20 minutes	Cathodal	Sham	HAMA, HAMD	Decrease in HAMA, HAMD
Trait anxiety												
7	Ironside et al. [20]	RCT (double blind)	*N* = 16	23.1 ± 3.7	Bilateral DLPFC	Right DLPFC/5 × 5 cm	2 mA	20 minutes (single session)	Right cathodal, left anodal	Sham	Attentional load task (offline in the scanner)	Improved attentional control and changes in the amygdala activity

BAI Beck Anxiety Inventory; *DLPFC* dorsolateral prefrontal cortex, *DHI* Dizziness Handicap Inventory, *HADS* Hospital Anxiety and Depression Scale, *HAMD* Hamilton rating scale for depression, *HAMA – HARS –HAS – HRS-A* Hamilton rating scale for anxiety, *PSWQ* Penn State worry questionnaire, *RCT* randomized controlled trial, *SD* standard deviation, *tDCS* transcranial direct current stimulation, *VSS* Vertigo Symptom Scale

attentional load by reducing vigilance to threat. Importantly, this behavioral improvement was accompanied by reduced amygdala activation and increased cortical activation (of the frontal and parietal regions) in response to fearful face distractors under tDCS. This study is an excellent example for the exploration of neurocognitive mechanisms of tDCS on fear processing. It delivers not only information about the alteration of psychological processes via this intervention, but it also suggests moreover respective physiological mechanisms, including activity reduction of the amygdala, which is relevant for fear induction, by altered dorsolateral prefrontal activity generated by tDCS.

21.3.1 tDCS for the Treatment of Panic Disorder (PD)

PD is classified as an anxiety disorder characterized by recurrent panic attacks with several symptoms such as palpitation, sweating, shaking, nausea, dizziness, derealization, and depersonalization [15]. This disorder is characterized by an alteration of the activity of key frontal and limbic areas, such as the medial prefrontal cortex and the amygdala [48]. Recent imaging studies have documented alterations of an even more extended brain network (e.g., [49]), including sensory regions of the occipital, parietal, and temporal cortices and the insula [48].

For the treatment of PD with tDCS, to date, only a case study performed by Shiozawa et al. [43] is available. In this study, a middle-aged woman was treated with ten stimulation sessions (once daily, five sessions per week, for 2 weeks) of cathodal (2 mA) stimulation over the right DLPFC (for more details, refer to Table 21.1). The Hamilton Anxiety Scale (HAS) showed a significant reduction of anxiety symptoms, as compared to baseline scores. Moreover, this pattern remained stable at the 30 days' follow-up. Although promising, the results shown in this single case report are too preliminary to make any firm conclusion about the therapeutic effectiveness of tDCS for the treatment of PD. Further investigations adopting a double-blind/sham-controlled design are recommended.

21.3.2 tDCS for the Treatment of Social Anxiety Disorder (SAD)

SAD is characterized by marked fear, anxiety, or avoidance of social interactions, including situations in which one is scrutinized, or situations in which one is the focus of the attention [15]. Functional and structural alterations of several neural regions, including the fusiform gyrus, thalamus, amygdala, insula, anterior cingulate cortex (ACC), as well as the striatum and DLPFC [50] have been identified to be involved in this disorder. This indicates that SAD, beyond the involvement of core regions relevant for fear and anxiety, is characterized by pathological alterations in a number of additional regions involved in sensory processing and attentional control [50].

Heeren et al. [42] performed a double-blind within-subject protocol in young female individuals with a DSM-5 diagnosis of SAD. Participants received a single

session of anodal (2 mA) or sham tDCS over the left DLPFC (more details are reported in Table 21.1) during conduction of a probe discrimination task assessing Attentional Bias (AB). This task was chosen due to evidence that SAD is associated with and maintained by AB for social threat [42]. The results document a significant decrease in AB for threat during anodal tDCS over the left DLPFC as compared to the respective sham stimulation condition. As for PD, the extremely limited literature in the field does not allow to derive clear conclusions about the therapeutic effectiveness of tDCS for the treatment of SAD. Moreover, the only currently available study [42] provides only indirect evidence for some potential of tDCS for the treatment of SAD, as the authors did not include standard clinical measures aiming to compare SAD symptom severity before and after treatment, but used a surrogate marker. Also here, further investigations adopting a double-blind/sham-controlled design are recommended.

21.3.3 tDCS for the Treatment of Generalized Anxiety Disorder (GAD)

Patients affected by GAD are characterized by persistent and excessive worries about a number of different things such as work, family, or money [15]. In terms of pathologically altered neural activation patterns/-rostral anterior cingulate cortex (sg/rACC) and medial prefrontal cortex (mPFC) has been described consistently, while activity alterations of the amygdala and the hippocampus seem to be more variable in GAD [50].

Shiozawa et al. [44] performed the first tDCS single case study in a middle-aged woman affected by GAD. The authors performed 15 consecutive once-daily cathodal tDCS sessions (except for the weekends) over the right DLPFC (more details are reported in Table 21.1); the anode was placed extracephalically over the contralateral deltoid muscle. Stimulation intensity was 2.0 mA. Anxiety symptoms measured via the HAS and Beck Anxiety Inventory (BAI) significantly improved after 15 days of treatment. This improvement remained stable at follow-ups after 30 and 45 days.

More recently [45], a total of 18 patients affected by GAD (46% females and 64% males) were randomly assigned either to (2 mA) cathodal tDCS ($n = 6$) over the right DLPFC (more details are reported in Table 21.1), pharmacotherapy ($n = 6$), or sham stimulation ($n = 6$) in a sham-controlled, double-blind parallel-group study. Symptoms were measured via the HAS. The intervention resulted in significant improvements of the anxiety index in the tDCS and pharmacotherapy groups, as compared to the sham group. The difference between the active intervention methods was not significant.

Finally, Lin et al. [46] conducted a randomized, placebo-controlled, single-blind study in which the effect of cathodal tDCS over the right DLPFC (with the reference electrode over the contralateral mastoid) was investigated in 20 patients diagnosed with GAD. The patients of the real stimulation group ($n = 10$) received 10 days of stimulation with a current intensity of 2 mA, for 20 min per day. The Hamilton Rating

Scales for Anxiety (HAMA) and depression (HAMD) were evaluated at baseline, 2 weeks, 4 weeks, and 8 weeks after the beginning of treatment. They found a significant improvement of the HAMA scores in the real stimulation group 2, 4, and 8 weeks after the start of the treatment, while no symptom improvement was reported in the group that received sham tDCS. In summary, the available study results suggest the right DLPFC as a potential target for the treatment of GAD via cathodal tDCS. The currently available literature in the field is however limited and does not allow to make exhaustive conclusions about the therapeutic efficacy of this stimulation protocol for the treatment of GAD. Nevertheless, compared to tDCS treatment of PD and SAD, the results provided by Movahed et al. [45] and Lin et al. [46] deliver more definite support for the therapeutic effectiveness of right DLPFC tDCS for the treatment of anxiety disorders, as the authors tested two relatively medium-sized samples ($N = 18$, $N = 20$ respectively), and the respective study designs were blinded. Further investigation adopting double-blind/sham-controlled designs is recommended in this regard. Reasonable next steps to enhance the efficacy of the intervention will also include the implementation of mechanistic studies that focus on optimizing approaches (additional stimulation areas, network stimulation, optimization of duration/intensity), and to embrace a larger multicenter perspective.

21.3.4 tDCS for the Treatment of Agoraphobia

Agoraphobia is an anxiety disorder characterized by marked fear or anxiety of situations such as public transportation, open or enclosed spaces [15]. Neuroimaging research [51] has pointed out an increased activation of the insula and the ventral striatum in patients affected by agoraphobia, compared with healthy controls, during anticipation of agoraphobia-specific stimuli. No studies testing the effects of tDCS for the treatment of agoraphobic patients have been performed so far.

21.3.5 tDCS for the Treatment of Specific Phobias (SP)

SP refers to a clinical condition characterized by marked fear, anxiety or avoidance of specific circumstances/situations, such as animals, environments, and others [15]. Results from neuroimaging studies suggest that SP is characterized by an enhanced activation in the insula, DLPFC ACC, amygdala, and prefrontal/orbitofrontal cortices during the processing of phobia-related situations compared to controls [52].

Palm et al. [53] have recently performed the first open-label pilot tDCS study on 8 adult patients affected by phobic postural vertigo (PPV) to modulate disease-related symptoms (vertigo/dizziness). A 2 mA anodal tDCS was applied over the left DLPFC (more details are reported in Table 21.1), once per day for 5 consecutive days. For the assessment of symptoms, the authors used the Vertigo Symptom Scale (VSS) [54], Dizziness Handicap Inventory (DHI) [55], and the Hospital Anxiety and Depression Scale (HADS) [56]. Overall, the results showed a significant

reduction of DHI scores. Moreover, anxiety and depression ratings were reported to be moderately improved, however, not significantly. In summary, as the previous anxiety disorders examined in this chapter, the limited literature in the field does not allow to derive firm conclusions about the therapeutic effectiveness of tDCS for the treatment of SP. Further investigations adopting a double-blind/sham-controlled design, as well as extended stimulation protocols, as conducted for other anxiety disorders (see earlier), are recommended.

21.4 Discussion and Future Directions

In this chapter, we provided an overview of all published studies ($N = 6$) investigating the therapeutic effectiveness of tDCS for the treatment of anxiety disorders. Moreover, we have included a recent study testing the effects of tDCS on trait anxiety [20], which is relevant for all anxiety disorders. Overall, the research examined in this chapter provides preliminary evidence in support of the hypothesis that tDCS is a promising therapeutic approach for the treatment of anxiety disorders. However, the extremely limited number of investigations (a total of seven studies, with no research in agoraphobia performed so far), the absence of double-blind/sham-controlled protocols in 4 out of 6 studies performed in anxiety disorders, and the low number of patients in several studies (3 of 7 studies are single case studies) show serious limitations of the current state of research in the field. DLPFC is the major cortical target in the treatment of anxiety disorders via noninvasive brain stimulation, although other cortical targets might represent valid alternatives according to the available physiological literature in the field (see [14] for a review). For instance, in the 57% of the examined studies (4 on 7), the authors chose the right DLPFC as a target with cathodal tDCS to treat anxiety disorders, while 28% of the studies (2 on 7) conducted anodal tDCS over the left DLPFC ($n = 2$); bilateral stimulation over the DLPFC (i.e., anodal left / cathodal right DLPFC) was conducted in one study. Since benefits were reported in response to all types of protocols, it might be concluded that all of these approaches are effective. This pattern of results is in line with a model proposed in a recent systematic review of our group [14], where we suggested that the stimulation of both the left and right DLPFC with anodal and cathodal tDCS, respectively, might counteract maladaptive plasticity of the cortico-meso-limbic network [57] in anxiety disorders, by acting on the up/downregulation mechanisms subserved by these regions for emotional outcomes [14]. In particular, according to this model, benefits from excitatory stimulation of the left DLPFC would be due to the relevance of this region for downregulation of negative emotion (e.g., [58]), and upregulation of positive emotion (e.g., [4, 59]). On the other hand, benefits from inhibitory stimulation over the right DLPFC would be determined from the relevance of this region for downregulation of reactions to negative emotional stimuli/outcomes, in line with evidence that this region is involved in the upregulation of reactions to negative emotional outcomes [60].

The relevance of prefrontal regions, especially the DLPFC, in anxiety disorders can be discussed at least from two perspectives. The first perspective includes the involvement of the DLPFC in cognitive control of behavior and emotion [61].

"Attentional control" and "cognitive change" are two major types of cognitive regulation of emotions that depend on PFC activity [61]. These regulatory strategies modulate both bottom-up and top-down responses to emotional stimuli, which construct expectations for, select alternative interpretations of, and/or make different judgments about emotional stimuli, including fearful objects and threats. This has been the rationale behind recent tDCS studies that aimed to improve emotion regulation through enhancing cognitive control functions in emotional disorders (e.g., [62, 63]).

The second perspective regards, more specifically, the functional connectivity between prefrontal cortical regions and subcortical areas, which allows modulation of threat-related structures (e.g., the amygdala) [20]. While direct modulation of the activity of subcortical regions is not as feasible as modulation of cortical regions by noninvasive brain stimulation techniques, due to effects of regional stimulation on cerebral networks, including subcortical structures [64], it is possible to target subcortical areas indirectly by cortical stimulation. Indeed, evidence from stimulation of the DLPFC and motor areas suggests that tDCS can alter activation and connectivity in regions distant from the electrodes [64, 65].

In the context of research exploring the relevance of the prefrontal cortex as a neural target for the treatment of anxiety disorders via tDCS, it might be relevant to extend respective investigation to the ventro-medial PFC (vmPFC), whose relevance for the treatment of anxiety disorders has been explored only with transcranial magnetic stimulation (rTMS) so far [66]. The vmPFC is reciprocally connected with the amygdala, which is known to be dysfunctional in anxiety disorders [50, 67]. It has moreover been shown to be directly involved in downregulation of negative affective responses [68], and upregulation of positive (rewarding) outcomes [69], which makes it an interesting target for anxiety modulation. In the same line, stimulation of additional areas, which have been shown to be involved in specific syndromes, might be of interest in future studies. This might also include network stimulation approaches.

Lastly, while in this chapter we only included the application of tDCS in anxiety disorders according to the DSM 5 diagnostic criteria, some tDCS studies are available for effects in post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD). The results from these parallel research fields further enrich the picture on the effects of tDCS in the treatment of anxiety and anxiety-related disorders (e.g., [70–72]). For example, van't Wout-Frank et al. [72] observed a significant reduction of arousal (i.e., reduced skin conductance response) and a clinically meaningful reduction of symptom severity in PTSD in response to tDCS over the vmPFC.

21.4.1 Maximizing Clinical Efficacy

The research discussed here so far refers to pilot studies that were primarily designed to examine the principal efficacy of tDCS in anxiety disorders, aimed to determine whether conducting further research in the field would be promising. Most of the studies were not designed to optimize tDCS efficacy and draw definite conclusions

about the implementation of tDCS for clinical treatment of anxiety disorders. Based on the principally promising results of these pilot studies, the next step would be to design studies for optimizing the stimulation protocols in order to maximize clinical efficacy. In this prospective, future studies are recommended to consider optimization approaches, which we will briefly discuss here. These approaches include: [15] optimizing stimulation parameters (i.e., stimulation area, polarity, intensity, duration, repetition, etc.) and [47] combining tDCS with other techniques.

Parameters of respective stimulation protocols play an important role in the efficacy of tDCS and these should be considered and systematically investigated in future studies. The first important parameter is the stimulation target area, which was already briefly discussed in the previous section. Right DLPFC (4 of 7 studies) and left DLPFC (3 of 7 studies) were the only targeted regions in the discussed studies, which are in line with the suggested up/downregulation model of anxiety disorders [14]. Yet, further studies are required to systematically investigate the effects of unilateral / bilateral stimulation of both right and DLPFC regions, which might enhance efficacy of interventions. Furthermore, other target areas might be attractive candidates. The medial PFC, including the VMPFC, is a potentially important region in regulating emotions and anxiety, but also other areas, as discussed earlier, might be relevant. Another important stimulation parameter is stimulation polarity, which is closely associated with the intended LTP- or LTD-like effects of the target area [6, 7, 26]. In the studies conducted so far, the right DLPFC received cathodal stimulation to reduce excitability, and the left DLPFC anodal stimulation to enhance excitability. The underlying rationale is to counteract respective pathological activity reductions of the left, and enhancements of the right DLPFC, which have been identified in anxiety disorders, and share similarities with respective alterations in depression [73].

In addition to tDCS montage (e.g., stimulation area and polarity, and also electrode size), stimulation intensity, duration, and repetition rate contribute to the efficacy of stimulation protocols. Findings from stimulation studies in other clinical fields (e.g., tinnitus [74], cognitive functions in Parkinson's disease [75], schizophrenia [76]) show that higher intensities of stimulation can result in more effective symptom improvement. However, the relationship between increased intensity and magnitude of the respective effects is not necessarily linear. It was recently shown that different intensities of anodal stimulation have similar effects on motor cortex plasticity at the group level [29], whereas the intensity-dependent effect of cathodal tDCS includes nonlinearities [36, 37, 77]. However, all of the above-mentionend studies were conducted with healthy adults. That said, the transferability of such nonlinear effects on clinical symptoms and cognitive/behavioral performance is not yet clear and needs further investigation. Due to pathologically altered cerebral activity in clinical syndromes, a one-to-one transferability might not be given, and thus titration studies in clinical populations are required to identify the optimal stimulation intensity in anxiety disorders .

Extension of the duration of stimulation sessions and repetitive stimulation are other factors to consider in order to improve the clinical efficacy of tDCS. tDCS studies on motor cortex excitability show that a longer duration of tDCS within a

specific time frame is able to prolong induced plasticity in the human motor cortex [6, 7, 26, 78], and that repetition within specific intervals enhances efficacy [5]. However, similarly to what has been observed in terms of stimulation intensity, a nonlinear relation between stimulation duration, repetitive stimulation, and observed effects on cortical excitability should be taken into consideration [5, 36, 37]. Finally, repetition rate is another important parameter to consider in order to enhance clinical efficacy of tDCS. Previous tDCS studies in clinical populations have shown that the efficacy of tDCS over motor and prefrontal regions is boosted by repeated sessions of stimulation [79, 80]. Optimizing stimulation protocols in anxiety disorders by adapting these parameters might improve tDCS efficacy and provide a more realistic picture of its clinical potential. Considering that daily stimulation over 4–6 weeks is required in order to achieve a clinically significant effects of rTMS in depression [81, 82], it might well be that most of the clinical tDCS studies conducted so far are relevantly underpowered.

In addition to the stimulation parameters discussed here, it is important to discuss the combination of tDCS with other standard interventions in anxiety disorders as an additional optimizing strategy. Behavioral, cognitive, and psychological interventions are major treatment approaches in anxiety disorders, which can be combined with tDCS to increase clinical efficacy. Previous studies showed sustained and longer symptom improvement following tDCS combined with cognitive training or psychological interventions in some neuropsychiatric disorders, including depression [47, 83, 84]. The respective sustained improvement of symptoms achieved by such combined therapies can be explained by fostering the formation of new memories induced by therapeutic approaches, which include relearning, enhancement of cognitive control [47], and other processes via tDCS-induced plasticity enhancement. Moreover, the combination of tDCS with pharmacological interventions further boosts the neuroplastic effects of tDCS (for an overview, see [4, 30]), which might have clinical relevance [85, 86].

21.5 Conclusion

In summary, the current state of research suggests that tDCS might be an efficient tool for the treatment of anxiety disorders. However, the low number of high-quality investigations in this field does not allow to make definite conclusions. Future investigations should not only enhance the number of available studies but also take into account approaches that might qualitatively improve the field. These includes (1) double-blind, sham-controlled protocols with a relatively high number of participants; (2) systematic titration of stimulation parameters such as intensity, duration, repetition rate/intervals, and cortical targets for optimization; (3) combination of tDCS with standard therapies such as cognitive-behavioral therapy and/or pharmacotherapy; (4) combination of tDCS with physiological measures, such as functional imaging, including fMRI, EEG, and vegetative parameters (e.g., heart rate and skin conductance), which provide important neurophysiological indices, in addition to the behavioral changes induced via tDCS [22]. Moreover, as suggested

in our recent work [14], to specifically test the up/downregulation model mentioned earlier, the exposure to positive/negative emotional stimuli should be systematically included in future investigations in the field.

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