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Transcranial direct current stimulation and emotion processing deficits in psychosis and depression

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Abstract

Emotional processing deficits (EPDs) are commonly observed among individuals diagnosed with (1) psychotic disorders (2) and depression. Given that EPDs can impact overall functioning and quality of life, the need to identify effective interventions is critical. To date, our current understanding of treatments for these impairments is limited. However, there is increasing interest in investigating the efficacy of transcranial direct current stimulation (tDCS). This neuromodulation technique releases a weak electrical current through the brain. Given research suggesting promise for using tDCS to improve symptoms and cognition across psychopathology, this approach may be useful for improving EPDs and related symptoms in psychosis and depression. In the current review, we provide an overview of the literature determining the effects of tDCS for EPDs and related symptoms in these groups. Furthermore, we highlight methodological advances and pinpoint potential future directions.

Keywords

Psychosis; Depression; tDCS; Emotional processing; Neuromodulation

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Declarations

Conflicts of Interests

None

Introduction

Impairments in emotional processing are commonly observed across psychopathology [1–5]. Emotional processing is a broader term that includes many domains such as experience (e.g., how an individual feels) [6, 7], outward expression (e.g., movements of the face, hands and body, and voice tone) [8–10], recognition (e.g., identifying what emotions others may be displaying such as happy, sad, anger) [11, 12], and regulation (e.g., managing and changing the way one feels to cope with different situations) [1, 13]. Emotional processing deficits (EPDs) are commonly evidenced among individuals with (1) psychotic disorders such as schizophrenia [2, 5, 14] as well as (2) affective disorders such as major depression (MDD) [4, 15]. Furthermore, EPDs have been found to relate to declines in social and occupational functioning [16, 17]. It is also important to note that there are several symptoms that relate to emotions (e.g., mood, negative symptoms). Given that abnormalities in emotional processing and related symptoms can vastly contribute to an individual's quality of life and well-being, identifying ways to ameliorate these symptoms is imperative.

Efforts to identify suitable treatments for EPDs and related symptoms is an area of investigation that remains ongoing. For example, while medication and psychotherapy treatment approaches have promise for reducing symptoms [18], they also are limited by side-effects, costs, required effort [19] and, availability (specialized treatments in these domains are only available in large wealthy urban centers despite the fact that these disorders have a high prevalence worldwide). One promising intervention technique that may help address some of these limitations is transcranial direct current stimulation (tDCS) [20,21]. The use of this neuromodulation approach involves releasing a weak electrical current through the brain. This technique has several benefits including minimal side effects, is easily accessible, and cost-effective [21, 22]. There have been several studies examining the use of tDCS for EPDs and related symptoms in psychotic disorders such as schizophrenia [23–27] and depressive disorders like MDD [28–30]. However, to our knowledge, there is currently only one review paper examining the efficacy of tDCS for schizophrenia and MDD [31] and there is no review to date that has examined the impacts of tDCS on EPDs among either of these psychiatric disorders.

A qualitative review, highlighting new developments as well as a few available foundational older studies, is critically important for providing an overview of the current efficacy and most promising prescriptions and targets of tDCS for EPDs and related symptoms as well as for highlighting both clinical priorities and a research agenda for years to come. The current qualitative review seeks to discuss literature investigating the effects of tDCS on EPDs and related symptoms in both psychosis and depression. To date, there are a growing number of studies suggesting promise for applying tDCS to improve EPDs and related symptoms, however, work in this area is still limited. The goal of this qualitative review is to pinpoint the limitations of the existing literature and discuss ongoing efforts to remedy arising issues in this area. It is important to note that a review as such cannot provide definitive conclusions (in contrast to a systematic review) about the nature of tDCS for EPDs and related impairments. However, the hope is that this manuscript may provide discussion and inform methodological questions that currently remain within the literature.

We begin by discussing EPDs and related symptoms in psychosis and depression literature, more generally, identifying commonly observed impairments. We then explain tDCS, providing detail on methodology. Furthermore, and of particular relevance to target optimization, this review highlights complexities among psychosis and depression, exploring how similar outward phenotypes of EPDs and related symptoms are but may in fact exhibit differing underlying neural circuitry. The final sections focus on the efficacy of tDCS for EPDs and related symptoms in psychotic and depressive disorders and suggestions for future research.

EPDs and related symptoms in psychosis and depression

Psychotic disorders such as schizophrenia are heterogenous [32] and are often characterized by positive (e.g., hallucinations and delusions), negative (e.g., reductions in functions including pleasure, motivation, and expressivity), disorganized (e.g., declines in hygiene, bizarre behaviors), cognitive (e.g., declines in processing), and social (e.g., impaired relations) symptoms [33–35]. EPDs have long been held to play a central role in reflecting the etiology of psychosis [33] and deficits are observed across the psychosis spectrum [36–39]. Within the construct of psychosis, EPDs occur across several of these domains and are particularly represented in negative symptoms (e.g., anhedonia, avolition) [2], Similarly, factor analytic studies have revealed particular dimensions among this category of symptoms; the experience (e.g., anhedonia) and outward expression (e.g., blunted affect) of emotion [40]. In addition to the presence of negative symptoms, there is also evidence that this group shows impairments in other aspects of emotional functioning including increases in the experience of negative emotions such as fear [41–43], emotion recognition [40, 44], and regulation [1, 45]. Together, many of these emotion-related symptoms tend to be resistant to antipsychotic medication [18], highlighting the need for more efficacious treatment approaches.

Similarly, EPDs are central to depressive disorders [46–50]. For example, MDD diagnoses are defined by low mood persisting for at least a 2-week period and/or loss of pleasure and interest in activities once enjoyed (i.e., anhedonia), in addition to other symptoms such as difficulties concentrating, appetite changes, and feelings of guilt and worthlessness [51]. Indeed, a preponderance of evidence suggests that there is an interaction between mood (e.g., states) and emotions (e.g., quick reactions typically present when there are meaningful stimuli) [50], suggesting these two constructs are highly intertwined. In terms of other emotion-related abnormalities observed among this group, there have been several studies indicating deficits in regulation [47, 52], and impairments in recognition [48, 53]. While antidepressant medications have been found to be efficacious in treating some symptoms, there still remains setbacks such as treatment resistance [54]. As a result, additional treatment intervention approaches are also sorely needed in this group.

Transcranial direct current stimulation

The interest in using neuromodulation as a means of treatment and intervention has been prevalent since the 1960s with recent, renewed attention in the last decade across psychiatric disorders [30, 55–57]. Application of tDCS releases a weak electrical current (low

amplitude, typically 1–3 mA) which travels between electrodes placed on the scalp [21]. The application of electrodes (cathode, anode) will vary depending on the predictions, exploratory goals, or treatment aims of a particular study [21,58]. For example, in a bilateral montage, one sensor (such as a surface-positive anode if the aim is to increase cortical excitability) is placed over the target area while another sensor (such as the surface-negative cathode) is placed over an intracephalic region irrelevant to the target behavior (e.g., contralateral area). Additionally, investigators might also elect to apply a unilateral montage and enhance or decrease the excitability of one target area, by placing an electrode over the region of interest, and the return electrode over another region that is intended to remain unaffected by direct stimulation. Another option is to place the return electrode over an extracephalic region (e.g., arm, shoulder) [59]. In addition, depending on the design, investigators also have the flexibility of employing "sham" stimulation that emits a brief current but then remains off during the remainder of the time. This is often used as a placebo condition. It should also be noted that technological advancements allow for new methods such as high-definition tDCS (HD-tDCS) [60, 61], which utilizes multiple electrodes (surrounding a target region). However, because of a dearth of current studies, the review is limited to investigations utilizing variants of the unilateral and bilateral electrode systems.

The underlying tDCS mechanism of action is not entirely clear. In contrast to methods such as transcranial magnetic stimulation (TMS) [62], tDCS may work more as a modulatory influence (raising or lowering the resting membrane potential and thereby increasing/decreasing the likelihood of neuronal firing) [21, 63]. Ongoing research is aimed at better explaining the precise mechanism of action but for the time being, and consistent with many pharmacological and psychotherapy treatments, there is clear evidence that the technique can influence emotion, cognition, and behavior [56, 57, 64].

Caveats

As noted, EPDs and related symptoms in psychotic disorders such as schizophrenia and depressive disorders such as MDD may share a common apparent symptom phenotype. For example, anhedonia (a lack of pleasure) and motivational issues (e.g., a volition) are central features of both disorders [65, 66]. However, the available evidence suggests that the aberrant underlying neural circuitry in each disorder is quite distinct [65]. Thus. it remains unclear if a particular target or montage for treating anhedonia, for example, in one population may be effective for the other. At the same time, it is also possible that because targets do not exist in isolation, are in fact just portions of a broader circuit or network of circuits, stimulating a given target may also have influence downstream. As such, when used as an exploratory tool, in isolation of follow-up experiments or other complementary strategies (e.g., functional imaging), it is difficult to definitively conclude mechanism. Conversely, it is also important to consider that although viable targets for placements may overlap in these populations (often sensors are placed over the dorsal lateral prefrontal cortex; DLPFC) [57, 67, 68], the pathophysiology of these disorders are different, and a shared tDCS prescription might affect different clinical populations in different ways. A final point to consider when reviewing these disorders is that schizophrenia can often occur along with affective illness (as in the case of schizoaffective disorder) and in addition, the depressive disorder may also co-occur with psychotic features [69–71]. As this review is the

first of its kind, we have elected to limit the focus primarily to studies focusing on psychosis and depression distinctly. This will be an important first step in coming to a consensus and forming a framework to inform future investigations in this area.

tDCS for EPDs and related symptoms in psychosis

Much of the literature examining tDCS for reducing symptomatology in psychosis has largely investigated effects on auditory hallucinations [22, 25, 72, 73], with increasing work determining impacts on other symptoms and characteristics such as impaired insight [74, 75]. Of particular relevance to the present review, there has been a growing interest in examining tDCS efficacy for EPDs and related symptoms [27, 76–78]. Specifically, as mentioned, EPDs are commonly observed in negative symptoms (experience and outward expression of emotion) [23, 26,79,80], but these impairments are not limited to these experiences. In fact, impairments in EPDs have also been identified in emotion recognition deficits often in the context of broader social cognition Studies in these groups [27, 81] and there may be potential for implementing tDCS to reduce abnormal experiences of negative emotions [82].

tDCS and negative symptoms

Negative symptoms have emotional components to them, such as anhedonia which is the lack of capacity towards experiencing pleasure [83], and targeting these symptoms may improve EPDs. To date, tDCS holds promise for improving negative symptoms, particularly stimulation of the prefrontal cortex [24, 84]. For example, Gomes and colleagues (2018) conducted a double-blind, randomized sham-controlled clinical trial to determine if tDCS could improve working memory performance (primary outcome) assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery [85] and negative symptoms (secondary outcome) assessed with the Positive and Negative Syndrome Scale (PANSS) [86]. A total of 10 sessions across 2 weeks (lasting 20 minutes each) of tDCS (2 mA) was administered to a sample of 24 individuals diagnosed with schizophrenia. The anode was placed over the left DLPFC and the cathode of the contralateral area. While this group did not find improvements in working memory deficits after receiving tDCS, there was a small effect ($d = .23$) for reduced negative symptomatology after anodal stimulation. In line with this study, many researchers have sought to utilize tDCS to effect multiple symptoms (e.g., working memory and negative symptoms) which, together, are providing insights regarding potential shared underlying neural circuitry and symptoms. Additionally, as seen in this study, negative symptoms tend to be a secondary outcome. Another example is a study conducted by Kantrowitz and colleagues (2019). In this study, a double-blind, randomized, sham-controlled design was employed [87]. Further, tDCS was applied twice daily for 20 minutes across 5 consecutive days. The anode was placed over the left DLPFC while the cathode over the left TPJ. Auditory hallucinations were the primary outcome of this study in which reductions in severity were observed. Of relevance, negative symptoms were a secondary outcome, however, no reductions in symptom scores were found.

In the last few years, strides have been made towards examining negative symptoms as a primary outcome and doing so utilizing larger samples, honing in on electrode placement, and including follow-up visits. For example, in a recent study, tDCS was applied to reduce negative symptoms, which was the primary outcome of the investigation [88]. Specifically, in this study, the group administered a double-blind, placebo-controlled randomized control trial (RCT) to determine whether tDCS can improve negative symptoms in a sample of individuals diagnosed with schizophrenia (N=100) [88]. The anode was placed over the left prefrontal cortex (PFC) and the cathode over the left temporoparietal junction (TPJ). Furthermore, tDCS was applied 2 times a day, over 5 days, for 20 minutes. The main outcome variable was the PANSS. This group found improvements in the PANSS total score (i.e. reductions in negative symptom severity) compared to individuals in the sham condition, with effects present even at 6-week follow-up (d = .57). Additionally, when investigating PANSS negative subscale scores, improvement in individual items was present in most negative symptom domains. While this study assessed negative symptoms as a primary outcome, future work would benefit from continuing to focus on study goals around these impairments. Doing so may help to optimize tDCS parameters for these symptoms specifically which is sorely needed within the literature. One consideration of negative findings in this area may be the role of antipsychotic medications as medications may be a source that can complicate the potential for tDCS enhancements [22, 23, 77]. Additional research is needed to better understand medication effects on this neuromodulation technique.

There is also a potential for the implementation of tDCS in conjunction with other treatment approaches (e.g., medication, psychotherapy) for reducing negative symptoms [89]. Palm and colleagues (2016) [80], in a proof of concept study, applied tDCS over the prefrontal cortex as an add-on to antipsychotic medication in efforts to investigate whether this approach improved negative symptoms. Specifically, patients with schizophrenia were randomized to receive 10 sessions of active or sham tDCS (2 mA for 20 minutes). The anode was placed over the left DLPFC and the cathode over the right supraorbital. Furthermore, participants underwent a magnetic resonance imaging (MRT) scan to investigate underlying functional connectivity at 4 timepoints. Results revealed a large effect (d = .96) for improved negative symptom ratings after receiving tDCS with antipsychotic medication. Furthermore, changes in seed-based connectivity after receiving tDCS was observed in frontal-thalamictemporoparietal networks. Together, these data provide evidence of using tDCS with other treatments that have found to be efficacious and furthermore, highlight the potential of using imaging techniques to inform mechanistic questions. In another example of a study implementing tDCS in conjunction with other treatments is shown in a case study conducted by Jacks and colleagues (2014) [89]. This group applied tDCS to a 53-year-old man diagnosed with schizoaffective disorder, with persisting auditory hallucinations. He was receiving weekly electroconvulsive therapy (ECT) and was taking clozapine (700 mg) daily. Furthermore, he was given tDCS for 20 minutes, 2 times a day, for 5 consecutive days, with the anode placed over the left DLPFC and the cathode over the left temporoparietal cortex. This technique with regular ECT and antipsychotic medication was found to improve negative symptoms, and in particular, blunted affect decreased by 20% and emotional withdrawal decreased by 40%, pre-to-post assessment. Together, these data highlight the

utility in applying a personalized treatment regimen. One benefit of this multi-dimensional approach is that it may help address some of the limitations observed in prevention and intervention research among these groups including clinical heterogeneity [32]. Given that schizophrenia is comprised of many symptoms, each individual may have a unique presentation of experiences and thus, one set of tDCS parameters may not be as useful or tDCS alone may not be sufficient. Heterogeneity in symptoms may be present within the negative symptom domain [40]. For example, some individuals may exhibit more deficits related to motivation or blunted effect [40, 90]. Thus, the use of tDCS with other treatment approaches may have the ability to combat these challenges.

tDCS and emotion recognition

There are a few studies determining the efficacy of tDCS for improving emotion recognition [27]. As noted, EPDs are observed in the context of social cognition, such as impairments in managing emotions and deficits in recognizing others' emotions. While the use of tDCS for enhancing social cognitive performance is currently limited, there are some studies that are setting the foundation for additional work in this area [81]. For example, in one study [27], a total of 36 individuals diagnosed with schizophrenia completed baseline social cognitive tests using the Mayer-Salovey-Caruso Emotion Intelligence Test (MSCEIT). Social cognitive tests included the assessment of managing emotions, emotion recognition/identification, social perception, and theory of mind. Approximately 1 –2 weeks later, participants were randomized to receive anodal, cathodal, or sham tDCS. The application of tDCS included placing the anode and cathode bilaterally over the DLPFC. Following 20 minutes of stimulation, participants completed these tasks again. Of all the tasks administered, there was a moderate effect ($d = .47$) for improved emotion recognition/identification performance after anodal stimulation.

Similarly, in more recent work by this group [81], tDCS was applied to a total of 37 participants with schizophrenia to investigate the effects of tDCS (2 mA) on social cognition (and other nonsocial functions) and electroencephalogram (EEG) measures. Specifically, participants underwent one of three conditions across three visits, separated by 1 week. Individuals were randomly assigned to tDCS conditions which included (1) anode over the left DLPFC and the cathode over the right supraorbital, (2) cathode over the left DLPFC and anode over the right supraorbital, or (3) sham stimulation. At each visit, participants were given 20-minute stimulation sessions, twice-daily. However, no findings were observed. Interestingly, the authors indicate that a single dose of tDCS over these areas may not be as efficacious. Another noteworthy potential limitation and future direction the authors highlight is that the task was not occurring at the same time as tDCS, also known as task-concurrent tDCS (individuals participate in tasks while completing cognitive training, for example). Task-concurrent tDCS may be a future direction for this work in psychosis populations.

Another potential consideration in work investigating the effects of tDCS on emotion recognition is electrode placements and brain targets. In particular, methodological decisions as such may vary depending on the type of emotion an individual is asked to identify through these tasks (e.g., recognition of anger vs. happy). While the DLPFC is a common

tDCS target for improving emotion recognition performance in schizophrenia samples [27, 81], there are studies from the general population applying tDCS to target areas potentially relevant for emotion recognition in schizophrenia. For example, there is some evidence of moderate effects when applying tDCS to the cerebellum to improve facial emotion recognition of negative expressions [92]. The cerebellum was used as a tDCS target for emotion recognition in a study in which a sample of 21 healthy controls was recruited [92]. Participants completed an emotion recognition task before and after cerebellar tDCS or prefrontal tDCS. In terms of the montages, the active electrode was placed over the cerebellum or prefrontal cortex (depending on the condition) and the reference was placed over the right deltoid muscle. Anodal or cathodal tDCS current was at 2 mA intensity for 20 minutes. Furthermore, there were three conditions which included anodal stimulation, cathodal stimulation, and sham, and each condition was separated by 1 week. Findings indicated that both anodal and cathodal tDCS to the cerebellum specifically improved negative facial emotion identification (anger and sadness, in particular). These data provide evidence that the cerebellum may be involved in the processing of emotional facial expressions, and it may be that mirror mechanisms in particular may be facilitating facial emotional signals [93]. However, additional work in this area is needed to better understand these relationships. Similarly, there may be key underlying differences in the identification of negative and positive facial expressions that may inform the use of this technique.

tDCS and increased negative emotions

While there is evidence for the efficacy of tDCS to improve EPDs and related symptoms, reduce negative symptoms, [76, 77], and enhance emotion recognition performance [81, 82], there are still many un-tested EPDs and related symptoms that tDCS could be beneficial for. In particular, individuals diagnosed with schizophrenia report increased negative emotions [42]. To date, interventions for these EPDs are few, and there has yet to be a study, to our knowledge, applying tDCS to improve negative emotional experience. However, there are increasing studies in the general population providing evidence for the utility of tDCS to enhance these experiences of emotion [83, 93]. One study in the general population that is relevant to negative emotional experience in psychosis was conducted by Vergallito and colleagues (2018). This group applied tDCS over the right ventrolateral prefrontal cortex (rVLPFC) to investigate whether tDCS could modulate the experience of emotions in healthy individuals (N=96). In this double-blind, sham-controlled study, participants were asked to watch video clips intended to evoke different emotional responses. Furthermore, after each video clip, they were instructed to fill out the Positive and Negative Affect Scales (PANAS) [95] asking about the experience of different emotions. Findings revealed, in contrast to the sham condition, tDCS over the rVLPFC reduced the experience of negative emotions (e.g., fear, $d = .12$; anxiety, $d = .12$; sadness, $d = .11$), although the magnitude of findings was small. These data provide a foundation for research that may choose to apply tDCS to reduce negative emotional experience in clinical samples, which is a critical future direction in this area.

Summary

Overall, there is a promise for the use of tDCS to improve EPDs such as emotion recognition and related symptoms such as negative symptom, and findings from studies in

the healthy literature provide possibilities to use tDCS for impairments in the experience of negative emotions [76, 77, 81, 89, 92, 96]. Currently, many studies target the DLPFC, use 1–2 mA of intensity lasting for 20–30 minutes across multiple sessions (e.g., 10) [76], and include follow-up visits [76, 77, 81]. While studies in the last few years have made strides towards precision around methodology (e.g., longer tDCS application times, multiple sessions) additional work is still needed. Furthermore, there is promise in employing different tDCS designs, including use with other treatments such as medication and psychotherapy [89], which may be useful for those with unique clinical presentations. Similarly, there is a need to better understand underlying pathophysiology to enhance electrode placements, and differences in the experience and recognition of positive and negative emotions. Additionally, there is a general trend in assessing broad symptom scores, however, future work could benefit from honing in on individual domains (e.g., anhedonia).

tDCS for EPDs and related symptoms in depression

tDCS for improving mood

The literature investigating the efficacy of tDCS among individuals diagnosed with depressive disorders is ongoing [97]. In the current work, many of the main targets focus on depressive symptoms, utilizing sum scores on commonly collected measures such as the Hamilton Rating Scale for Depression (HRSD) and the Beck Depression Inventory (BDI) [98, 99]. As mentioned, mood and emotion are related in depression, yet distinct experiences [50]. Given the interconnected relationship between these constructs, understanding the impacts of tDCS on mood-related symptoms have the potential to inform our understanding of EPDs, more broadly.

The use of tDCS for the treatment of depression has been long-standing since foundational work from Fregni and colleagues (2006) [67]. In this hallmark study, 10 patients were randomized to either active tDCS (1 mA) or a sham condition. In this double-blind, randomized-controlled design, the anode was placed over the left DLPFC and the cathode over the contralateral supraorbital area. The neuromodulation technique was applied for 20 minutes across 5 days and was found to reduce MDD symptoms based on lower scores on the HRSD and BDI [67]. Since then, some studies are trying to enhance the likelihood of sustained effects from tDCS [100]. These data are critical for efforts to translate findings into clinical settings. For example, studies that implement tDCS for longer sessions, even outside of acute episodes, may encounter issues with relapse rates. To date, there is evidence of relapse rates with biweekly sessions with some evidence that weekly sessions instead may be optimal [101, 102]. Additionally, treatment-resistance may be a predictor of relapse [102]. Given the episodic nature of depression, there are complications to consider such as the benefits of tDCS during an acute episode and how to sustain effects at follow-up. Along these lines, in a study conducted by Aparicio and colleagues (2019), tDCS was applied as continuation therapy to examine relapse rates. Specifically, a total of 24 patients with unipolar (n=16) and bipolar (n=8) depression received 2 mA intensity of tDCS up to 6-months or relapse (after already receiving 15 tDCS sessions). This technique was applied 2 times weekly for 30 minutes over 24 weeks. In this study, the anode was placed over the left

DLPFC and the cathode of the right DLPFC. From this, reduced relapse rates after 6-months were observed suggesting the potential to use tDCS as a means for maintaining recovery.

Another direction the tDCS and depression literature is taking involves implementing tDCS in conjunction with other treatments (e.g., medications, ECT, psychotherapy) [103, 104], similar to studies in psychosis [89]. Heterogeneity in symptoms are present also in depressive disorders [105] and using multiple treatment approaches may be promising for some individuals. For example, Pavlova and colleagues (2018) applied 10 consecutive sessions of tDCS to 69 individuals diagnosed endorsing mild to moderate levels of depression. For tDCS application, the anode was placed over the DFPFC and the cathode over the right forehead and was combined with medication (50 mg sertraline). All participants were randomized into three conditions (30 minutes of active tDCS, 20 minutes of active tDCS, or a sham). Both 30 and 20-minute active tDCS applications were used in efforts to determine the optimal duration of stimulation, shedding light on broader methodological questions in this field. Findings indicated large effect sizes (d = 4.11) for active tDCS improving depressed mood when compared to the sham condition. Furthermore, 30 minutes of tDCS combined with sertraline improved clinical outcomes such as reductions in depression scores when compared to 20 minutes of tDCS, suggesting a longer session may be more beneficial in this population. These data provide insights regarding questions related to optimal tDCS duration. Furthermore, these findings indicate that tDCS combined with medication may be useful for some individuals, particularly those with mild and moderate levels of depression. Furthermore, studies have sought to compare the use of medications and tDCS. For example, in a large study with adults diagnosed with depression (N=245) participating in a noninferiority trial, individuals were randomized to receive tDCS and oral placebo, sham tDCS and oral placebo, or sham tDCS and escitalopram (10 mg per day for 3 weeks and 20 mg daily after) [106]. The 2 mA tDCS was applied for 22 sessions, lasting 30-minutes each. The anode and cathode were placed over the right and left DLPFC. The main outcome variable was changed in scores from the HDRS. From this double-blind, randomized trial, tDCS did not prove to have noninferiority to escitalopram. It is also important to note that those in the tDCS condition demonstrated more adverse effects such as skin redness and nervousness compared to the other groups.

Similarly, the use of tDCS in conjunction with other treatments may be useful for individuals with medication-resistant depression. In a study by Monnart and colleagues (2019) [107], tDCS was combined with a mindfulness-based cognitive therapy (MBCT) (n=15) for individuals with drug-resistant depression compared to a control condition receiving tDCS with relaxation (n=16). To begin with, participants were randomly assigned to participate in a tDCS condition and then, instructed to complete an intensive block of MCBT or relaxation sessions for 8 days. Participants also came in 2 weeks after the treatment to complete clinical measures. In terms of electrode placements, the anode was placed over the left pre-frontal dorsolateral cortex (PFDLC) and the cathode over the right PFDLC. Stimulation was applied at an intensity of 2 mA for 20 minutes. Improvements were observed in both treatment conditions, but tDCS with mindfulness had a large effect (d = 1.57) in maintaining clinical improvements during follow-up 2 weeks later. Together, these data inform the potential for more multi-dimensional and comprehensive treatment approaches for individuals with depression. It is important to highlight the need to take into

account differences in symptoms (e.g., medication resistance). Additionally, there may be more long-lasting effects for some individuals by taking a combined approach as such. However, more work is needed in this area.

tDCS and emotion recognition

The use of tDCS for improving emotion recognition deficits is gaining attention in studies with MDD samples. For example, in one randomized, placebo-controlled study, tDCS was applied at 1.5 mA for a maximum of 30 minutes to a sample of individuals with depression (n=17) and controls (n=20) [108]. The anode was placed over the DLPFC and the cathode over the contralateral supraorbital area. In this study, participants completed an emotion recognition task (in addition to several other cognitive tests) in which faces with different emotional expression intensities were presented (ranging from 40% to 100%) while receiving anodal stimulation or sham. While the main finding of the study indicated that anodal stimulation led to the improvement of emotion identification in the control group (d = .36), there were findings in the clinical group as well. In particular, anodal stimulation was found to improve the recognition of anger expressions presented at 80% intensity among individuals with MDD. Participants in this group also improved in the ability to identify happiness at 40% intensity. These data are important in that they offer the potential for studies to implement tDCS for emotion recognition tasks.

Similar to studies investigating tDCS effects in schizophrenia, there is interest in employing tDCS concurrently with emotion recognition tasks. In a recent, open-label design, Martin and colleagues (2018) [103] implemented tDCS to 20 individuals with medication-resistant depression during Cognitive Emotional Training (Emotional Faces Memory Task), which has been previously found to have antidepressant effects [109]. Outcomes included cognition, emotion regulation, and symptoms. The tDCS montage involved placing the anode over the left DLPFC and cathode over the right upper arm and participants received 30–40 minutes of the neuromodulation 3 times a week, over 6 weeks. Furthermore, this group included follow-up visits to measure clinical and cognitive outcomes at 3 weeks and 6 weeks. This study found that participants exhibited improvements in depression scores (38% improvement over 6 weeks) and furthermore, enhanced emotion recognition (although no other findings with cognitive measures were observed) and findings were in the moderate to large effect size range (d = .65 – 1.89). The use of tDCS concurrent with tasks may be a promising future direction, and additional research is required. Furthermore, these individuals were resistant to the effects of medication, which sheds light on the relationship between tDCS, medication use, and emotion recognition performance, although additional research in this area is warranted.

tDCS and cognitive control

In addition to the application of tDCS in efforts to improve depressive symptoms that may be related to EPDs [67, 100, 104, 107] and to improve emotion recognition deficits [108], tDCS has also been applied to potential mediators, such as cognitive control [29]. Given that there are minimal studies investigating tDCS for EPDs in depression, it may also be useful to understand tDCS studies that employ this technique for targets related to foundational aspects of the disorder, that can underlie a range of functions, including emotions. Cognitive

control has been suggested to be associated with affect emotion regulation in depression [110]. Along these lines, this technique has been employed in efforts to ameliorate cognitive control deficits. This is relevant to EPDs given literature indicating that deficits in cognitive control may be central to MDD [108]. Specifically, there is evidence that individuals with MDD may exhibit attention and memory for negative emotional stimuli specifically, representing a broader attentional bias [111]. Along these lines, one study sought to target the DLPFC with tDCS (1 mA, 15 minutes) to ameliorate cognitive control deficits [29]. Specifically, in this double-blind, randomized, sham-controlled trial, a single session of tDCS was applied to individuals with MDD (n=22) and controls (n=22) during the completion of a delayed working memory (DWM) task. In this study, the anode was placed over the left DLPFC and the reference was placed on the deltoid muscle. Participants completed tDCS sessions during 2 visits that were separated by 1 week. In the DWM task, letters were presented on a computer screen. During the distraction phase of the task, pictures were displayed of either neutral, emotional, or blank content. After this portion, participants saw letters on the screen and were to respond as fast as possible as to whether the letter was previously presented. Findings revealed small effects (d = .23) for results suggesting that emotional pictures presented in the task contributed to lower performance in accuracy and time of responses. However, anodal tDCS was able to increase working memory performance in both groups, and in particular, those with MDD no longer exhibited attentional bias.

Summary

Overall, there is promise in applying tDCS to reduce EPDs in samples with depression [28–30, 107]. In many tDCS studies using MDD samples specifically, the anode is typically placed over the left DLPFC and there is some variation in the placement of the cathode (e.g., upper arm) [21, 30]. Furthermore, there is a trend towards employing an intensity of tDCS current between 1–2 mA, with sessions lasting anywhere from 10–30 minutes for several weeks [28]. Recent studies have found that tDCS can improve mood impairments [67, 100, 104, 107] with increasing work investigating the impacts on EPDs such as emotion recognition [108] and mediators like cognitive control [29]. In the last decade, and in line with work in psychosis, advances have been made towards improving methods by increasing sample sizes, and testing duration and optimal current intensity [100, 103, 104]. One of the challenges, as seen in the psychosis literature, is the heterogeneous nature of clinical symptoms [112], Current studies may have the potential to inform this issue, as seen with studies utilizing combined tDCS and psychosocial treatment approaches for medication-resistant symptoms [103, 104). Furthermore, medication use may influence tDCS [113], and future work is needed to better understand this area.

Conclusion and future directions

Taken together, the research investigating tDCS for reducing EPDs and improving related symptoms in psychosis and depression is ongoing and there is promise in the efficacy of this technique. Strides have been made towards optimizing this approach in both groups, with increasing use of 2 mA current intensity, multiple tDCS sessions, and follow-up visits [77, 100, 103, 104]. It is also important to note that negative findings exist as well [28, 120]

highlighting the need to continue research efforts in this area. While there is still much to know about tDCS, such as questions around optimal electrode placements, the length at which effects remain, and the number of sessions needed, the current research suggests promise for use of this method in clinical settings [55–57]. This neuromodulation technique has several benefits (cost-effective, portable, easy to administer, minimal side effects) and as a result has the potential to be useful for many.

There are several potential future directions that may be beneficial for the broader tDCS literature, particularly in the efforts to apply this technique to improving EPDs and related symptoms. For example, additional research should continue to examine how tDCS compares to other interventions and treatment strategies. Findings from studies employing tDCS to improve EPDs and other related symptoms discussed in this review are in line with traditional interventions in both psychosis and depression. Specifically, effect sizes across many of the noted tDCS experiments and interventions in psychosis (ranging from small, d = . 11 to large, d = .96) are comparable and in some cases favorable to estimated effect sizes seen in commonly administered treatments including medication use (e.g., d = .48, d = .60) [114, 115], cognitive remediation (e.g., d = .30) [116], and psychotherapy (e.g., d =16) [117]. In depression, estimated effect sizes range from small (e.g., d = .23) to large (d = 4.11) as well in studies using tDCS which is also in line with traditional interventions such as medication (e.g., d = .20) [118] and behavioral therapies (e.g., d = .70) [119]. Given the favorable, low-cost, minimal side effects, and widely available nature of tDCS, observations that in several cases the method performs as well or better to alternatives are quite promising. However, future work should consider a systematic review, which can directly compare all studies, and allow for the ability to draw formal conclusions about the strength of one intervention over another.

Additionally, future research is needed to better understand underlying neurobiological underpinnings, which may inform tDCS parameters in this area of research. Currently, neurobiological pathways largely point towards involvement of frontal and limbic brain areas in emotional processing such as the DLPFC and striatum [2, 121–124]. As seen throughout this review, several studies applying tDCS to patients with psychosis and depression often target the DLPFC, despite these disorders generally exhibiting differing neurobiological pathways [49, 104, 125]. The reason this may be the case is that the DLPFC has been found to play a putative role in the pathophysiology of psychosis [126] and depression [127]. Similarly, in depression, cognitive biases (e.g., propensity towards negative information) are characteristic of the disorder and abnormalities in the DLPFC largely underlie these impairments [128]. DLPFC abnormalities are also observed among individuals with psychotic disorders, particularly in regards to integrating cognition and reward processes, which are critical for several emotion-related functions [129]. Along these lines, targeting the DLPFC may modulate mesocorticolimbic dopamine transmission [130], which in turn can potentially improve impairments characteristic of these disorders. It is also important to note that studies applying tDCS to these populations also provide insights on other brain regions that may be involved, but are largely understudied. For example, findings from Ferrucci and colleagues (2012) hint towards the possible role of the cerebellum in negative emotional processing [92]. A future direction of these data involves disentangling

the role of the cerebellum in emotion, given lines of research indicating the cerebellum may be involved in other processes beyond sensorimotor control [131, 132].

There are several additional promising future directions applying tDCS for EPDs to individuals with psychosis and depression. For example, there is a clinical utility in further understanding which individuals benefit from tDCS, drawing from precision medicine in particular. For example, an important area of investigation is determining brain biotypes [133] that are linked with tDCS responses. Given the heterogeneity of these disorders, it may be that tDCS is particularly advantageous for specific subgroups. Other areas of investigation include assessing the noted caveats and in particular, comparing how tDCS influences psychosis and depressive populations similarly and uniquely. Furthermore, combining tDCS with functioning magnetic resonance imaging (fMRI) or EEG can shed light on underlying mechanisms. Additionally, utilizing tDCS with other therapies may be a promising future direction as well.

Other directions of tDCS research may involve examining different aspects of emotional functioning (i.e., expression, recognition of others emotion). Similarly, future studies would benefit from teasing apart specific negative symptoms (schizophrenia) and mood (MDD) domains such as anhedonia that may share similar phenotypes to examine tDCS efficacy. Other areas of research that are already gaining interest include the effects of medication use on the technique and task-concurrent tDCS [97]. There is also some potential for tDCS administration in home-environments [134], which may optimize the portable and accessible nature of this technique, accessing communities that have geographic barriers to receiving psychiatric care. Furthermore, there may be potential in applying tDCS to high-risk populations, which have been found to exhibit a wide array of EPDs [26, 38, 135, 136]. However, it is important to consider adverse effects in applying tDCS to these populations. For example, it is possible that some processes improve, but there may be declines in others, highlighting the need to further examine the specificity of this approach.

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Table 1.

Summary of studies suggesting promise for the use of tDCS for improving emotional processing deficits in psychosis

Author	Population	N	Design	Montage/ sites	mA	Duration/ Frequency	Variables of interest	Emotion or related symptom	Relevant Findings
Negative Symptoms									
Gomes et al., 2018	Schizophrenia	24	Double-blind, randomized, sham-controlled	Anode over the left DLPFC and cathode over the contralateral area	2	10 sessions over 2 weeks, 20 minutes	MCCB working memory, PANSS negative symptoms	Related symptom	Reductions in PANSS negative symptom severity scores after anodal stimulation
Kantrowitz et al., 2019	Schizophrenia/ schizoaffective	89	Double-blind, randomized, sham-controlled	Anode over the left DLPFC and cathode over the left TPJ		2x a day for 5 days, 20 minutes	AHRS, PANSS	Related symptom	No reductions in negative symptoms
Valiengo et al., 2020	Schizophrenia	100	Double-blind, randomized, placebo-controlled	Anode over the left PFC and cathode over the left TPJ	2	2x a day for 5 days, 20 minutes	PANSS	Related symptom	Improvements in PANSS negative symptom scores after active tDCS with effects present at 6-week follow-up
Palm et al., 2016	Schizophrenia	20	Proof of concept, double-blind, sham-controlled	Anode over the left DLPFCand cathode of right supraorbital	2	10 sessions over 2 weeks, 20 minutes	SANS	Related symptom	Reduction in negative symptom severity scores after tDCS compared to baseline
Jacks et al., 2014	Schizoaffective	1	Case study, tDCS combined with ECT and medication	Anode over the left DLPFC and cathode over the left TP cortex	2	2x a day for 5 days, 20 minutes	PANSS	Related symptom	tDCS with ECT and antipsychotic medication reducec negative symptom severity
Emotion Recognition									
Rassovsky et al., 2015	Schizophrenia	36	Randomized, sham-controlled	Anode and cathode bilaterally placed over DLPFC	2	1x, 20 minutes	MCCB, MSCEIT, FEIT, PONS, TASIT	Emotion	Improvements in emotion identification performance in the active condition
Rassovsky et al., 2018	Schizophrenia	37	Randomized, sham-controlled	Anode over the left DLPFCand the cathode over the right superorbital or cathode over the left DLPFCand anode over	2	2x, 20 minutes	MCCB including MSCEIT, EEG measures	Emotion	No positive findings

Author	Population	N	Design	Montage/ sites	mA	Duration/ Frequency	Variables of interest	Emotion or related symptom	Relevant Findings
				the right supraorbital					
Ferrucci et al., 2012	Healthy *	21	Randomized, sham-controlled	Anodal or cathodal current over cerebellum or right PFC, reference electrode over the right deltoid muscle	2	1x, 20 minutes	Facial Emotion Recognition Task	Emotion	Faster reaction times for recognizing negative facial expressions after anodal and cathodal stimulation
Negative Emotions									
Vergallito et al., 2018	Healthy *	96	Double-blind, sham-controlled	Anode placed over the rVLPFC and the cathode over the contralateral supraorbital area	1.5	1x, 20 minutes	Ratings after viewing emotionally evocative film clips	Emotion	Reductions in emotion ratings after anodal stimulation

Note: Studies are organized in the order in which they are presented in the review. Please also note this is a qualitative review and the selected papers are not intended to be a representation of all published papers covering the topic, but rather key examples that serve as the basis for discussion; Emotion and related symptoms is intended to indicate whether targets were primarily emotion-specific or a broader symptom that entails emotional aspects (e.g., negative symptoms); Milliamps (mA); Prefrontal cortex (PFC); Dorsal lateral prefrontal cortex (DLPFC); Temporoparietal junction (TPJ); right ventral lateral prefrontal cortex (rVLPFC); Auditory Hallucination Rating Scale (AHRS); Scale for the Assessment of Negative Symptoms (SANS); The Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT); MATRICS Consensus Cognitive Battery (MCCB); Facial emotion identification task (FEIT); Profile of Nonverbal Sensitivity (PONS); The Awareness of Social Inference Test (TASIT); Positive and Negative Affect Scale (PANAS); Electroconvulsive therapy (ECT)

* notes studies in healthy populations that may be relevant to emotion targets in psychosis.