



# Transcranial Direct Current Stimulation of the Dorsolateral Prefrontal Cortex for Treatment of Neuropsychiatric Disorders

Qing Li<sup>1,2</sup>, Yu Fu<sup>1</sup>, Chang Liu<sup>3,4,5\*</sup> and Zhiqiang Meng<sup>2,4,5\*</sup>

<sup>1</sup> Medical School, Kunming University of Science and Technology, Kunming, China, <sup>2</sup> Shenzhen Key Laboratory of Drug Addiction, Brain Cognition and Brain Disease Institute, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China, <sup>3</sup> Shenzhen Key Laboratory of Viral Vectors for Biomedicine, Brain Cognition and Brain Disease Institute, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China, <sup>4</sup> Shenzhen-Hong Kong Institute of Brain Science, Shenzhen Fundamental Research Institutions, Shenzhen, China, <sup>5</sup> CAS Key Laboratory of Brain Connectome and Manipulation, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

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### \*Correspondence:

Chang Liu  
chang.liu3@siat.ac.cn  
Zhiqiang Meng  
zhiqiang-meng@163.com

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**Background:** The dorsolateral prefrontal cortex (DLPFC) is a key node of the frontal cognitive circuit. It is involved in executive control and many cognitive processes. Abnormal activities of DLPFC are likely associated with many psychiatric diseases. Modulation of DLPFC may have potential beneficial effects in many neural and psychiatric diseases. One of the widely used non-invasive neuromodulation technique is called transcranial direct current stimulation (or tDCS), which is a portable and affordable brain stimulation approach that uses direct electrical currents to modulate brain functions.

**Objective:** This review aims to discuss the results from the past two decades which have shown that tDCS can relieve clinical symptoms in various neurological and psychiatric diseases.

**Methods:** Here, we performed searches on PubMed to collect clinical and preclinical studies that using tDCS as neuromodulation technique, DLPFC as the stimulation target in treating neuropsychiatric disorders. We summarized the stimulation sites, stimulation parameters, and the overall effects in these studies.

**Results:** Overall, tDCS stimulation of DLPFC could alleviate the clinical symptoms of schizophrenia, depression, drug addiction, attention deficit hyperactivity disorder and other mental disorders.

**Conclusion:** The stimulation parameters used in these studies were different from each other. The lasting effect of stimulation was also not consistent. Nevertheless, DLPFC is a promising target for non-invasive stimulation in many psychiatric disorders. TDCS is a safe and affordable neuromodulation approach that has potential clinical uses. Larger clinical studies will be needed to determine the optimal stimulation parameters in each condition.

**Keywords:** non-invasive neuromodulation, dorsolateral prefrontal cortex (DLPFC), schizophrenia, addiction, depression, psychiatric disease

## INTRODUCTION

Neuropsychiatric disorders are combinations of psychiatric and neurologic malfunction that deal with mental disorders, including degenerative diseases, addictions, mood disorders, neurotic disorders, etc. Current treatments of neuropsychiatric diseases mainly include drug therapy, physical therapy and psychotherapy. Common physical therapies included electroconvulsive treatment (ECT), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), etc. Among these techniques, tDCS becomes an increasingly employed clinically due to its economical, convenient, non-invasive and mild side effects. However, current dilemma in using tDCS as a option of clinical treatment is that there is no common standard, and the therapeutic effects vary from case to case.

In this review, we discussed: (1) the mechanism of tDCS and the application of tDCS technique in clinical research, focusing on five types of psychiatric disorders; (2) and the potential therapeutic brain target DLPFC.

## AN OVERVIEW OF TRANSCRANIAL DIRECT CURRENT STIMULATION TECHNIQUE

Accumulating knowledge has supported that transcranial direct current stimulation (tDCS) can relieve symptoms of various diseases, including pain (Wrigley et al., 2013), depression (Sharafi et al., 2019), schizophrenia (Brunelin et al., 2012a), attention deficit disorder (Cosmo et al., 2015), drug addiction (da Silva et al., 2013), and anxiety disorder (Heeren et al., 2017). In recent years, tDCS has been widely used in clinical research due to the advantages mentioned above. tDCS is a non-invasive brain stimulation technique that uses low-intensity direct current (1–2 mA) to modulate cortical activity (Woods et al., 2016). A common tDCS stimulator consists of a controller to generate a constant current, and at least one pair of stimulation electrodes to attach to the surface of the scalp. Although there is no uniform standard for stimulation parameters in clinical studies, electrodes of 20–35 cm<sup>2</sup>, with application of 1–2 mA currents, 20- or 30-min stimulation duration for one session with one or multiple sessions through a certain period have been employed in a large body of studies.

The activity of the brain is based on the electrical activity of neurons. It is believed that tDCS may modulate the brain activity at different scales. First, from a macro perspective, tDCS likely modulate the brain activity via changing the cortical excitability directly. In general, anodal stimulation depolarizes neurons, whereas cathodal stimulation hyperpolarizes neurons (Purpura and McMurtry, 1965; Bikson et al., 2004). In addition, tDCS may regulate the activity of neural networks by influencing other brain regions associated with the target brain region. It has been suggested that neuronal networks were more sensitive than single neuron in the weak electric field (Francis et al., 2003). By using resting-state functional magnetic resonance imaging (fMRI) technique, it has been found that anode tDCS intensified

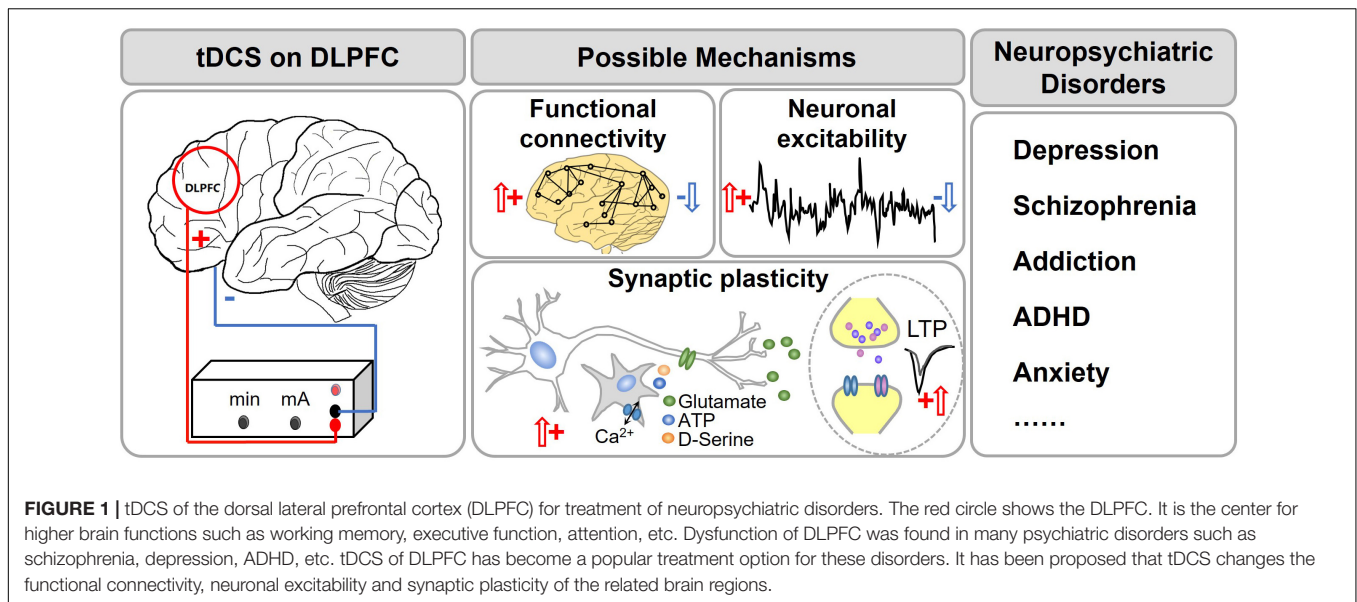
the functional connection among the thalamus, the temporal lobe and the left caudate nucleus (Dalong et al., 2020). At the neuronal levels, tDCS has been shown to modulate the neural oscillations. McDermott et al. (2019) reported that anode tDCS increased spontaneous activity in the theta (4–7 Hz) and alpha (9–14 Hz) bands in prefrontal and occipital cortices in a flanker task. Finally, from the molecular perspective, tDCS may modulate neurotransmitter release to regulate synaptic plasticity. For example, long-term potentiation (LTP) which was observed after anodal tDCS coupling with synaptic activation (Fritsch et al., 2010). Another study found that the effects of tDCS may be related to the polarity-specific changes in neurotransmitter concentrations. Anodal tDCS caused locally reduced GABA concentrations while cathodal stimulation caused reduced glutamatergic neuronal activity with a highly correlated increase in GABA concentration (Stagg et al., 2009). Liebetanz et al. (2002) showed that, dextromethorphan, an antagonist of N-Methyl-D-Aspartic Acid receptors (NMDAR, receptors that are involved in synaptic plasticity regulation), suppressed the post-stimulation effects of both anode and cathode stimulation.

In order to recommend this convenient technique as a powerful therapeutic strategy, a remarkable effort is still needed to further understand how tDCS modulate the brain activity.

## DORSOLATERAL PREFRONTAL CORTEX IS A TARGET FOR NON-INVASIVE STIMULATION IN NEUROPSYCHIATRIC DISEASES

One of the most common cortical targets for tDCS is the dorsolateral prefrontal cortex (DLPFC; **Figure 1**). DLPFC is a structurally and functionally heterogeneous region (Glasser et al., 2016), and is closely related with cognitive functions [attention (Vossel et al., 2014; Bidet-Caulet et al., 2015), decision-making (Philiastides et al., 2011; Rahnev et al., 2016), working memory (Barbey et al., 2013), and emotion regulation (Shahani and Russell, 1969; Buhle et al., 2014; Frank et al., 2014)]. The DLPFC is located in the middle frontal gyrus, and it is a part of the prefrontal cortex (PFC) which regulates the marginal reward area, and involves in higher executive function and impulsive behaviors (Fitzpatrick et al., 2013; Xu et al., 2017). The left DLPFC connects to the primary motor area, primary sensory area, etc. It mainly participates in pain perception and emotional cognitive processing through a top-down neural network (Koenigs and Grafman, 2009; Vaseghi et al., 2015). The right DLPFC is selectively involved in processing pessimistic, negative emotions and mediates vigilance and arousal (Hecht, 2010). DLPFC has become an important target in the treatment for mental disorders.

A large number of studies have shown that tDCS targeting at DLPFC can alleviate a variety of neuronal and psychiatric diseases symptoms. For example, anode tDCS (2 mA) can reduce the pain caused by multiple sclerosis (Ayache et al., 2016). Anode stimulation of the right DLPFC, and cathode at the left DLPFC improved the risk preference of the subjects



(Yang et al., 2017). Studies have shown that anodal tDCS stimulation of left DLPFC could decrease negative emotions and improve cognitive control (Pena-Gomez et al., 2011). Here, we summarize and discuss perspectives of the parameters and effects of tDCS targeting DLPFC in the treatment of different types of neuropsychiatric disorders.

## Depression

Depression (also known as depressive disorder) is a mental disease that causes a persistent feeling of sadness and loss of interests, with high recurrence rate, disability rate and suicide rate. In general, it can be classified into major depression, bipolar disorder or treatment-resistant depression. Bipolar disorder, causing extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). Treatment-resistant depression refers to no response to at least two different antidepressant treatments.

Twenty studies collected from PubMed were shown in **Table 1**. Majority of these studies have shown that tDCS targeting at DLPFC (mostly the left DLPFC) can significantly improve depression symptoms for a month or longer. All studies placed the anode electrodes on the left DLPFC and the cathode electrodes on the opposite side (right DLPFC or orbitofrontal region). 17 out of 20 studies reported improvement of depressive symptoms. Besides, tDCS also improved working memory and attention (Loo et al., 2012). Importantly, tDCS in combination with other treatments, such as an antidepressant drug (Brunoni et al., 2013b) or with computerized cognitive behavioral therapy (Welch et al., 2019), can reduce depressive symptoms even better than tDCS alone (Brunoni et al., 2013a). It is important to note that tDCS on DLPFC may have some side effects, such as mania, although this is not common (Loo et al., 2012). For the stimulation parameters, most studies have used a current of 2 mA, electrode sizes of 25–35 cm<sup>2</sup>, and a total of more than five sessions (see details in **Table 1**). Though various parameters have shown

different effects on depression symptoms, most stimulation protocols with longer stimulation duration for one session and repeated sessions were shown to have therapeutic effects.

## Schizophrenia

Schizophrenia is a chronic mental disorder. The most typical symptoms of schizophrenia include hallucinations and delusions, which are often referred to as positive symptoms. Schizophrenia may also experience negative symptoms, such as social withdrawal, anhedonia, hyperboulia, affective blunting and alolia (Carpenter et al., 2016). In recent years, clinical studies have shown that tDCS may be effective in reducing auditory hallucination symptoms in patients with schizophrenia. For example, a study reported that anode tDCS showed a significant increase in short- interval intracortical inhibition in the left motor cortex, but no change in intra-cortical facilitation (ICF) compared to sham stimulation (Gordon et al., 2019). Yoon et al. (2019) found that decreased functional network connectivity was negatively correlated with the increase of hallucinogenic behavior at baseline and was significantly enhanced after anode 2 mA tDCS. This may suggest that fronto-temporal tDCS may regulate abnormal hallucination-related functional network connectivity in patients with schizophrenia. Decline in insight is also one of the main symptoms of schizophrenia. Patients with insight deficits often fail to recognize that they are ill and may refuse treatment. Bose et al. (2014) found that 2 mA anode tDCS stimulation over left DLPFC and cathode over the left temporo-parietal junction, could improve the insight and decrease auditory hallucination symptoms in patients. However, no such effect was observed after 1 mA stimulation, which indicates that the current intensity of tDCS is a key factor (Hill et al., 2016). A combination of medication, physical therapy, and psychotherapy usually have a synergic effect. Non-invasive brain stimulation combined with physical therapy has been shown to improve motor performance and language function

**TABLE 1** | Effects of DLPFC tDCS on depression.

References	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
	Anode (+)	Cathode (-)						
Brunoni et al., 2017	DLPFC (F3)	DLPFC (F4)	/	2	30	1/day, 3 weeks + 1/week × 7 weeks	22	Have a significant effect, but it was inferior to escitalopram
Aparicio et al., 2019	DLPFC (F3)	DLPFC (F4)	25	2	30	1/day, 3 weeks, +1/week, 7 weeks	22	Reduced recurrence rate significantly
Moreno et al., 2020	DLPFC (F3)	DLPFC (F4)	/	2	30	1/day, 3 weeks, +1/week, 7 weeks	22	Reduced practice effects in processing speed, but no change in cognitive deficits
Palm et al., 2012	DLPFC (F3)	Orbitofrontal region	35	1/2	20	1/day, 4 weeks	20	No significant effect
Martin et al., 2013	DLPFC (F3)	Arm/opposite Side of track (F8) (two forms of tDCS)	35	2	20	1/week × 3 months + 1/2 weeks × 3 months	18	Reduced the recurrence rate for relapse significantly
Sampaio-Junior et al., 2018	DLPFC (F3)	DLPFC (F4)	25	2	30	1/day, 2 weeks + 2/other week, 6 weeks	16	Have a significant improvement
Brunoni et al., 2013b	DLPFC (F3)	DLPFC (F4)	25	2	30	1/day × 2 weeks + 1/2 weeks × 2	12	Improved mood significantly [tDCS + sertraline (50 mg/d)]
Welch et al., 2019	DLPFC (F3)	DLPFC (F4)	25	2	30	3/week × 4 weeks	12	Reduced depressive symptoms significantly (tDCS + computerized cognitive behavioral therapy)
Brunoni et al., 2014	DLPFC (F3)	DLPFC (F4)	25	2	30	1/day, 2 weeks	10	Reduced depressive symptoms significantly
Blumberger et al., 2012	DLPFC (F3)	DLPFC (F4)	35	2	20	1/day, 3 weeks	15	No significant effect
Loo et al., 2012	DLPFC (F3)	Orbitofrontal region (F8)	35	2	20	1/day, 3 weeks	15	Improved mood significantly
Loo et al., 2010	DLPFC (F3)	Orbitofrontal region	35	1	20	5 active + 5 active sessions	10	Improved overall depression significantly over 10 tDCS treatments, no between-group difference in the five-session, sham-controlled phase
					20	5 sham session + 5 active sessions	10	
Dell'Osso et al., 2012	DLPFC (F3)	Contralateral cortex	32	2	20	2/day × 5 days	10	Have a significant improvement
Sharafi et al., 2019	DLPFC (F3)	DLPFC (F4)	20	2	20	1/day, 2 weeks	10	Have a significant effect (lasted for 1 month after treatment)
Lin et al., 2021	DLPFC (F3)	DLPFC (F4)	35	2	20	2/day × 5 days	10	Improved unipolar and bipolar depression rapidly
Brunoni et al., 2011	DLPFC (F3)	DLPFC (F4)	35	2	20	2/day × 5 days	10	Improved depression for 1 week in MDD group and 1 month in BDD group
Rigonatti et al., 2008	DLPFC (F3)	Contralateral Superior orbital region	35	2	20	1/day × 10 days	10	Have a significant effect (similar to fluoxetine 20 mg/day for 6 weeks)
Boggio et al., 2008a	DLPFC (F3)	Contralateral Supraorbital area	35	2	20	1/day, 2 weeks	10	Reduced depression scores significantly (lasted for 1 month after treatment) after DLPFC tDCS compared to occipital and sham tDCS
Bennabi et al., 2015	DLPFC (F3)	Contralateral superior Orbital region	35	2	20	2/day × 5 days	10	No significant effect
Kumar et al., 2020	left DLPFC (F3) + right DLPFC (F4)	lz	25	1	30	1/day, 2 weeks	10	No significant effect

*MDD, major depressive disorder; BDD, bipolar depressive disorder.*

in stroke patients (Barros Galvao et al., 2014; Rubi-Fessen et al., 2015). Orlov et al. (2017) found that anode tDCS stimulation combined with cognitive behavioral training showed significant improvement in working memory and learning. However, Shiozawa et al. (2016) found that tDCS combined with cognitive training failed to produce a synergic effect in schizophrenia patients. This may be due to the small sample size and the use of antipsychotics in patients (Orlov et al., 2017).

We summarized 28 studies using tDCS as a treatment strategy for schizophrenia in **Table 2**. Overall, tDCS improved both positive syndromes and negative syndromes in patients with schizophrenia. Only two studies showed no significant improvement after tDCS. For the electrodes positions, in 26 out of 28 studies placed the anode in the left DLPFC (F3) or a point midway between F3 and FP1 and the cathode in the right hemisphere (left temporoparietal junction, FP2, or right contralateral superior orbital region). 20 out of 28 studies used 25–35 cm<sup>2</sup> electrodes. For stimulating current intensity, 26 studies used 2 mA current, only 1 study used 1 mA current, and 1 study used both 1 mA and 2 mA current. For stimulation duration, 26 studies used 20 min/session, 1 study used 30 min/session, and 1 study used 15 min/session. All studies adopted multiple stimulation sessions (from 5 to 20 sessions), only two studies used one single session of tDCS. Most multiple sessions of tDCS brought a better curative effect, pointing to a repeated application of tDCS as therapeutic strategy. In studies with one single session of tDCS, 2 mA but not 1 mA was shown to induce a positive effect. Taken together, 2 mA multi-session anodal tDCS of the left DLPFC or left temporoparietal junction area has the most potential to improve symptoms in patients with schizophrenia.

## Addiction

Addiction is a chronic brain disease characterized by compulsive use of drugs, with loss of self-control and a high relapse rate (Berke and Hyman, 2000; Preller et al., 2013). Patients may experience negative emotions during withdrawal, such as sadness, restlessness, subdued pleasure. The relapse tendency indicates that a solid memory of drugs, a pathological memory, also called drug memory formed in addiction patients (Boning, 2009; Nestler, 2013). Drug memory is signaled by dynamic neuronal activity patterns in the brain areas such as prefrontal cortex, hippocampus and the ventral tegmental area (VTA; Berke and Hyman, 2000). Drugs increase the activity of VTA dopaminergic neurons as well as the concentration of dopamine in the projection area (Hyman and Malenka, 2001; Pierce and Kumaresan, 2006). The downstream targets of VTA dopaminergic neurons mainly includes ventral striatum, which is responsible for processing reward information, and prefrontal cortex, which is responsible for higher brain functions such as decision making, executive function, etc. (Robbins and Everitt, 2002; Hyman et al., 2006). Reward related perception and executive function can be modulated by the release of dopamine in the frontal lobe (Goldstein and Volkow, 2002).

Many studies have shown that tDCS can significantly relieve the symptoms of addictions (such as craving for cocaine, cigarette, alcohol, etc.). Bilateral DLPFC tDCS stimulation

reduced cocaine craving with a linear decrease within 4 weeks, and improved anxiety symptoms and overall quality of life in patients (Batista et al., 2015). In addition to cocaine, tDCS stimulation can also reduce cravings for alcohol and cigarettes. Klauss et al. (2018b) showed that bilateral DLPFC tDCS stimulation significantly reduced alcohol cravings and reduced recurrence rates. Fecteau et al. (2014) found that the number of cigarettes consumed decreased significantly after bilateral DLPFC stimulation, and the effect could last for 4 days after the stimulation. Besides, non-substance addiction, such as food addiction, gambling addiction and internet addiction, shows executive function (such as decision-making and risk-taking processes) and working memory deficits similar to those in drug addiction (Fernandez-Serrano et al., 2010; Marazziti et al., 2014; Potenza, 2014). Studies have shown that anode tDCS stimulation of the right DLPFC decreased craving and negative emotions in addicted internet gaming players (Wu et al., 2020). Fregni et al. (2008b) found that the bilateral tDCS stimulation, left anode/right cathode or right anode/left cathode, reduced the food craving as well.

In **Table 3**, we summarized 21 studies evaluated tDCS treatment in substance addiction. Four studies didn't observe any improvement after tDCS treatment. All other studies showed tDCS reduced craving, improved behavioral control and reduced likelihood of relapse. Most studies used 25–35 cm<sup>2</sup> electrodes. For stimulating current intensity, 14 studies used 2 mA current, and 7 studies used a lower current. For stimulation duration, 4 studies used 10~15 min/session, other studies used 20 min/session. There are 18 studies applied stimulation sessions from 1 to 4, and three of these studies showed no positive effects the rest studies used stimulation sessions from 5 to 20, which induced significant improvement of addiction symptoms except for one study. Roughly half of the studies placed anodal electrode on the right DLPFC, and the other half on the left. A couple of studies tried both montages. Together, tDCS of the DLPFC (left and/or right) has the potential to improve symptoms and reduce craving in substance addiction.

## Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a brain disorder that characterized with inattention, impulsivity, hyperactivity and learning disabilities. ADHD mainly occurs in primary and middle schools (6–17 years old), and the prevalence is as high as over 6% (Rowland et al., 2015). The prevalence of ADHD is higher in boys than girls, and the risk for premature infants is also higher (Polanczyk et al., 2015). Neuroimaging studies have shown that the symptoms in ADHD patients may be related to abnormalities in fronto-striato-cerebellar neural circuit, especially the prefrontal lobe (Cubillo et al., 2012; Christakou et al., 2013). Specifically, the activity of bilateral striato-thalamus, left DLPFC and superior parietal cortex was significantly reduced in ADHD patients, and the activity of precuneus was significantly increased (Hart et al., 2013). Adults with childhood ADHD showed reduced activation in bilateral inferior prefrontal cortex, caudate and thalamus compared to controls. Neuro-functional abnormalities in ADHD patients are likely to persist from childhood to

**TABLE 2 |** Effects of tDCS of DLPFC on schizophrenia.

References	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
	Anode (+)	Cathode (–)						
Weickert et al., 2019	Right DLPFC (F4)	Left Temporoparietal junction	35	2	20	1/day, 4 weeks	20	Improved language-based working memory after 2 weeks, and oral fluency after 2 and 4 weeks significantly
Bose et al., 2015	Right DLPFC (a point midway between F4 and FP2)	Right left temporoparietal junction	35	2	20	2/day × 9 days	18	Right DLPFC tDCS reduced auditory hallucinations, but no change after left DLPFC tDCS
	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction						
Fitzgerald et al., 2014	Left DLPFC (F3)	Left temporo-parietal junction (unilaterally F3/TP3 or bilaterally F3 + F4/TP3 + TP4)	35	2	20	1/day, 3 weeks	15	No significant effect
Brunelin et al., 2012a	Left DLPFC (F3)	Left temporo-parietal cortex	35	2	20	2/day × 5 days	10	Reduced AVH significantly (lasted for 3 months after treatment), improved negative symptoms
Brunelin et al., 2012b	Left DLPFC (F3)	Left temporo-parietal cortex	35	2	20	2/day × 5 days	10	Have a significant effect (lasted for 3 months after treatment)
Shiozawa et al., 2013	Left DLPFC (F3)	Cathode: right DLPFC (F4)	35	2	20	1/day × 10 days	10	Improved catatonic symptoms significantly (remained for 4 weeks after treatment)
Jacks et al., 2014	Left DLPFC (F3)	Left temporo-parietal cortex	/	2	20	2/day × 5 days	10	Improved mood, feelings of hope, and fewer AVH, but no change in PANSS score
Jeon et al., 2018	Left DLPFC (F3)	Right DLPFC (F4)	25	2	30	1/day, 2 weeks	10	Improved working memory over time
Valiengo et al., 2020	Left DLPFC (F3)	Left temporoparietal junction	35	2	20	2/day × 5 days	10	Improved PANSS score significantly
Narayanaswamy et al., 2014	Left DLPFC (F3)	Cathode: left temporo-parietal cortex	/	2	20	2/day × 5 days	10	Improved in negative symptoms and AVH significantly (lasted for 6 months after treatment)
Palm et al., 2016	Left DLPFC (F3)	Right contralateral superior orbital region	35	2	20	1/day, 2 weeks	10	Improved negative and positive symptoms significantly
Palm et al., 2013	Left DLPFC	Right contralateral superior orbital region	/	2	20	1/day × 10 days	10	Improved negative and positive symptoms significantly
Brunelin et al., 2015	Left DLPFC	Left temporoparietal junction	35	2	20	2/day × 5 days	10	Reduced AVH significantly
Bose et al., 2014	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	35	2	20	2/day × 5 days	10	Improved insight and reduced AVH
Mondino et al., 2015	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	35	2	20	2/day × 5 days	10	Reduced AVH significantly
Mondino et al., 2016	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	35	2	20	2/day × 5 days	10	Improved in negative symptoms and AVH significantly

*(Continued)*

TABLE 2 | (Continued)

References	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
	Anode (+)	Cathode (-)						
Nawani et al., 2014a	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	/	2	20	2/day × 5 days	10	Have a significant reduction in AHRS score
Rakesh et al., 2013	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	/	2	20	2/day × 5 days	10	Reduced AVH significantly
Shenoy et al., 2015	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	/	2	20	2/day × 5 days	10	Reduced AVH significantly (lasted for 1 month after treatment)
Chang et al., 2019	Left DLPFC (a point midway between F3 and FP1)	Left temporo-parietal junction	35	2	20	2/day × 5 days	10	Improved overall symptoms
Chang et al., 2020	Left DLPFC (a point midway between F3 and FP1) + right DLPFC (a point midway between F4 and Fp2)	Forearms	35	2	20	2/day × 5 days	10	Reduced AVH significantly (lasted for 3 months after treatment)
Homan et al., 2011	Left temporo-parietal cortex	Right supraorbital area	35	1	15	1/day, 2 weeks	10	Reduced AVH significantly (lasted for 6 weeks after treatment)
Praharaj et al., 2015	Left DLPFC (F3)	Midway between T3 and P3	25	2	20	1/day × 5 days	5	Reduced AVH temporarily
Nawani et al., 2014b	Left prefrontal	Left temporoparietal	/	2	20	1/day × 5 days	5	Reduced AVH significantly
Smith et al., 2015	Left DLPFC (F3)	Right contralateral superior orbital region	5.08	2	20	1/day × 5 days	5	Improved memory, attention, and cognitive function significantly
Frohlich et al., 2016	Left DLPFC (a point midway between F3 and FP1)	Left temporoparietal junction	35	2	20	1/day × 5 days	5	Reduced AVH, but overall symptoms did not change significantly
Schilling et al., 2021	Left DLPFC (F3)	FP2	25	2	20	1/day	1	No enhancement in executive functions
Hoy et al., 2014	Left DLPFC (F3)	Right contralateral superior orbital region	35	1/2	20	1/day	1	Improved cognitive performance only after 2 mA tDCS

adulthood (Cubillo et al., 2010). fMRI studies also showed that striatum activation was abnormal in ADHD children (Durstun et al., 2003).

In recent years, tDCS has been considered to have an ameliorative effect on ADHD symptoms. Studies have shown that 1 mA anode tDCS of the left DLPFC improved the executive function in adolescent ADHD patients. After tDCS, they showed better inhibitory control, interference control, working memory and cognitive flexibility (Nejati et al., 2020). Blair's research showed that inhibitory control is the main executive problem

for adolescents with ADHD, and the problems with inhibitory control will lead to dysfunctions in memory, emotion regulation and other executive functions (Blair and Razza, 2007). tDCS improves the symptoms not only in adolescent patients, but also in adult ADHD patients. Left DLPFC tDCS in adult ADHD patients improved the impulsiveness symptoms (Allenby et al., 2018), and bilateral tDCS (anode over right DLPFC, cathode over left DLPFC) improved the inattention symptoms (Cachoeira et al., 2017). Only several studies were collected here which were shown in **Table 4**. All these studies targeted left DLPFC with

**TABLE 3** | Effects of DLPFC tDCS on addiction behaviors.

References	Substance	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
		Anode (+)	Cathode (–)						
Ghorbani Behnam et al., 2019	Smoking	Left DLPFC (F3)	Right DLPFC (F4)	35/100	2	20	1/day, 4 weeks	20	Reduced smoking addiction only in active group (20 sessions, 12 weeks). The effect was similar to 300 g bupropion
Mondino et al., 2018	Smoking	Right DLPFC (F4)	Left occipital region	35/100	2	20	2/day × 5 days	10	Reduced smoking cue related craving significantly and increased brain reactivity in the right posterior cingulate cortex
Klauss et al., 2018a	Cocaine	Right DLPFC (F4)	Left DLPFC (F3)	35	2	20	1/every other day	10	No significant effect
Klauss et al., 2018b	Alcohol	Right DLPFC (F4)	Left DLPFC (F3)	35	2	20	1/every other day	10	Reduced alcohol cravings and recurrence rates significantly
da Silva et al., 2013	Alcohol	Left DLPFC (F3)	Contralateral (right) supradeltoid area	35	2	20	1/day × 5 days	5	Improved depressive symptoms and reduced alcohol craving
Holla et al., 2020	Alcohol	Right DLPFC (F4)	Left DLPFC (F3)	35	2	20	1/day × 5 days	5	Increase the global efficiency of brain networks significantly with a concurrent significant reduction in global clustering
Batista et al., 2015	Cocaine	Left DLPFC (F3)	Right DLPFC (F4)	35	2	20	1/every other day	5	Decreased craving for crack-cocaine use, anxiety, and improved quality of life
Vitor de Souza Brangioni et al., 2018	Smoking	Left DLPFC (F3)	Right supra-orbital area	35	1	20	1/day × 5 days	5	Reduced cigarette consumption up to 4-weeks post-intervention coupled with high motivation to quit
Boggio et al., 2009	Smoking	Left DLPFC (F3)	Right DLPFC (F4)	35/100	2	20	1/day × 5 days	5	A significant cumulative effect on modifying smoking cue-provoked craving, with significant decrease in the number of cigarettes
Fecteau et al., 2014	Smoking	Right DLPFC (F4)	Left DLPFC (F3)	35	2	30	1/day × 4 days	4	Decreased the amount of smoking significantly (lasted for 4 days after stimulation)
den Uyl et al., 2017	Alcohol	Left DLPFC (F3)	Right DLPFC (F4)	35/100	2	20	1/day × 4 days	4	No significant effect
den Uyl et al., 2016	Alcohol	Contralateral supraorbital region	Left DLPFC (F3)	35	1	15	1/day × 3 days	3	Decreased cue-induced craving (but not overall craving) on post assessment, but no effects on cognitive bias modification (CBM)
Alghamdi et al., 2019	Smoking	Left DLPFC (F3)	Right DLPFC (F4)	25	1.5	20	1/day × 3 days	3	No significant effect

*(Continued)*



TABLE 3 | (Continued)

References	Substance	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
		Anode (+)	Cathode (-)						
Boggio et al., 2008b	Alcohol	Right DLPFC (F4)	Left DLPFC (F3)	35	2	20	1/day	1	Reduced alcohol craving significantly in two active stimulation groups, and alcohol craving did not increase further after treatment
den Uyl et al., 2015	Alcohol	left DLPFC (F3)	Right DLPFC (F4)	35	1	10	1/day	1	Anodal tDCS over the DLPFC reduced alcohol craving significantly, stimulation of the IFG did not decrease craving
		Left DLPFC (F3)	Contralateral supraorbital region						
Wietschorke et al., 2016	Alcohol	Right inferior frontal gyrus (IFG)	Contralateral supraorbital region	35	1	20	1/day	1	Reduced alcohol craving
		Right DLPFC (F4)	Left DLPFC (F3)						
Fregni et al., 2008a	Smoking	Left DLPFC (F3)	Contralateral hemisphere	35/100	2	20	1/day	1	Both anodal and cathodal tDCS to left DLPFC significantly reduced craving
		Right DLPFC (F4)	Contralateral hemisphere						
Xu et al., 2013	Smoking	Left DLPFC (F3)	Right supra-orbital area	35	2	20	1/day	1	Reduced negative emotions, but no reduction in cigarette craving
Kroczyk et al., 2016	Smoking	Left DLPFC (F3)	Contralateral right supradeltoid area	35	2	15	1/day	1	No significant effect
Falcone et al., 2016	Smoking	Left DLPFC (F3)	Right supra-orbital area	25	1	20	1/day	1	Increased latency to smoke and decreased the total number of cigarettes smoked significantly
Gorini et al., 2014	Cocaine	Left DLPFC (F3)	Right DLPFC (F4)	32	1.5	20	1/day	1	Increased safe behavior after right DLPFC anodal stimulation, increased risk-taking behavior after left DLPFC anodal stimulation
		Right DLPFC (F4)	Left DLPFC (F3)						

anodal stimulation. One out of six studies (used a single session protocol) showed negative results, and all the rest found tDCS improved ADHD related symptoms. The stimulation current was 1 mA or 2 mA, 1 session to 5 sessions in total. While the potential of tDCS of the DLPFC to treat ADHD is promising, the published studies are relatively fewer compared to other diseases.

## Anxiety

Anxiety disorders are the most common form of emotional disorder characterized by nervousness, worry and fear. There

are several types of anxiety disorders, including generalized anxiety disorder (GAD), Social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), panic disorder (PD), obsessive compulsive disorder (OCD), agoraphobia and specific phobia. Studies have shown that OCD symptoms are related to the cortico-striato-thalamocortical circuitry, including DLPFC, orbital frontal lobe (OFC), medial prefrontal lobe (MPF), and anterior cingulate cortex (ACC; Del Casale et al., 2011; Fineberg et al., 2011). Striatal dysfunction may lead to hypothalamic gating problems and hyperactivity in the

**TABLE 4** | Effects of DLPFC tDCS on ADHD.

References	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
	Anode (+)	Cathode (–)						
Soff et al., 2017	DLPFC (F3)	Vertex	3.14/12.5	1	20	1/day × 5 days	5	Improved inattention and impulsivity, and the effect lasted for 7 days
Cachoeira et al., 2017	DLPFC (F3)	DLPFC (F4)	35	2	20	1/day × 5 days	5	Improved inattention
Allenby et al., 2018	DLPFC (F3)	Supra-orbital area	25	2	20	3/week	3	Improved impulsivity symptoms acutely (conners continuous performance task) but not the stop signal task
Dubreuil-Vall et al., 2021	DLPFC (F3)	Contralateral Supraorbital region (Fp1 or Fp2)	3.14	2	30	1/day	1	Modulated reaction time and P300 amplitude in the Eriksen flanker task, but not in the stop signal task
Cosmo et al., 2015	DLPFC (F3)	Right DLPFC (F4)	35	1	20	1/day	1	No significant differences in behavioral performance
Gogler et al., 2017	DLPFC (F3)	Right contralateral Superior orbital region	25	2	20	1/day	1	Improved inattention

**TABLE 5** | Effects of tDCS on OCD and anxiety.

References	Disease	Electrode montage		Electrode size (cm <sup>2</sup> )	Current intensity (mA)	Stimulation duration (min)	Stimulation sessions	Total sessions	Key findings
		Anode (+)	Cathode (–)						
Narayanaswamy et al., 2015	OCD	Fz2	Right supra-orbital area	35	2	20	2/day × 10 days	20	Clinical improvement, enhanced pre-SMA/SMA activation
D'Urso et al., 2016a	OCD	Presupplementary motor area (pre-SMA)	Right deltoid	35	2	20	1/day × 20 days	20	Improved OCD symptoms
Shiozawa et al., 2014	OCD	Contralateral deltoid	Right DLPFC	25	2	20	1/day, 3 weeks	15	Improved anxiety symptoms
Volpato et al., 2013	OCD	Posterior neck-base	Left DLPFC (F3)	35	2	20	1/day, 10 days	10	Improved depression and anxiety, reduced interhemispheric imbalance
Ahmadzadeh et al., 2019	PTSD	DLPFC (F3)	Right DLPFC	35	2	20	1/day, 2 weeks	10	Reduced PTSD symptoms, hyper-arousal and negative alterations in cognition and mood sub-symptoms as well as depressive and anxiety symptoms
Jafari et al., 2021	SAD	DLPFC (F3)	Medial PFC (Fpz)	35	1/2	20	2/day × 5 days	10	Reduced fear/avoidance symptoms, worries and improved emotion regulation
de Lima et al., 2019	GAD	DLPFC (F3)	Contralateral supraorbital area (Fp2)	35	2	20	1/day, week	5	Improved in physical symptoms significantly, but no improvements in anxiety, mood symptoms of stress, affectivity, or depression
Heeren et al., 2017	SAD	DLPFC (F3)	Vertically at the ipsilateral arm	35	2	25	1/day	1	Decreased attentional bias

orbitofrontal cortex and anterior cingulate cortex in OCD patients (Milad and Rauch, 2012). Sakai et al. (2011) found that functional connections of the orbitofrontal cortex, medial prefrontal cortex, DLPFC and ventral striatum were significantly increased in patients with OCD, but there was no significant correlation between symptom severity and connection strength. D'Urso et al. (2016b) reported that patients received cathode stimulation over the left DLPFC showed significant improvement in OCD symptoms.

Generalized anxiety disorder is characterized by persistent unspecified nervousness, excessive anxiety and worry about everyday life events (Locke et al., 2015; Stein et al., 2017). Previous studies have shown that brain regions related to rumination and introspection in GAD patients were overactivated (Locke et al., 2015). Patients also showed autonomic nervous dysfunction, vagus-mediated decreased heart rate variability, and neurostructural abnormalities in the rostral ACC, left medial orbitofrontal cortex, and right isthmus cingulate gyrus (Etkin and Wager, 2007; Carnevali et al., 2019). Neuroplasticity in prefrontal and limbic regions is also altered in patients with a variety of subtypes of anxiety disorders (Ironsides et al., 2019). Vicario et al. (2019) reviewed the using of non-invasive brain stimulation techniques for the treatment of anxiety previously. A study showed that stimulation of the left DLPFC with 2 mA tDCS significantly improved physical stress symptoms in patients, however, there was no significant improvement in major psychological symptoms, such as anxiety, tension, emotion, or depression (de Lima et al., 2019). In another case report, a total of 15 sessions of 2 mA cathode tDCS stimulation improved anxiety symptoms in patients with GAD (Shiozawa et al., 2014).

Social anxiety disorder is an anxiety disorder characterized by extreme fear in getting involved in social interactions. Studies have shown that patients with SAD have attentional bias brought by social threats, and the attentional bias will increase the anxiety of patients with SAD (Klosowska et al., 2015). Anode tDCS of the left DLPFC significantly reduced attentional bias compared to the sham stimulation (Heeren et al., 2017). In addition, a single dose of 1 mA of tDCS reduced pain anxiety caused by burns (Hosseini Amiri et al., 2016), and improved anxiety symptoms caused by major depression (Nishida et al., 2019). Although there are only a few studies on the tDCS treatment of anxiety, these findings indicate that this technique can be an effective therapeutic option. We have summarized some of the published studies in **Table 5**.

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## SUMMARY AND OUTLOOK

In recent years, tDCS is increasingly being studied for the therapeutic potential in neurological and psychiatric disorders. DLPFC is involved in many higher brain functions such as working memory, decision making, impulsivity, attention, etc. DLPFC also plays an important role in cognition and emotion. These brain functions were often disrupted in neurological and psychiatric diseases. Thus, modulation of the activity of DLPFC is a major strategy in treatment of these diseases. Although the neural mechanisms of tDCS is still not quite clear. It is believed that anodal stimulation increases brain activity while cathodal stimulation inhibits brain activity. One of the major problems of tDCS treatment of neuropsychiatric diseases is that each study used slightly different stimulation parameters. For instance, the current intensities were from 1 to 2 mA, tDCS sessions were from one session to more than 20 sessions. The tDCS frequency varies from twice daily to once every other day. Thus, it's not appropriate to compare the current results directly side by side. Future studies will need to investigate the effects of tDCS using the different parameters in the same study or the same parameters in different studies. Nevertheless, this review demonstrates clearly that tDCS of DLPFC has a great potential to treat neuropsychiatric disorders.

## AUTHOR CONTRIBUTIONS

CL and ZM discussed and initiated the review topic and edited the manuscript substantially. QL drafted the manuscript. All authors interpreted the results together, revised the manuscript critically, and contributed to the article and approved the submitted version.

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