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REVIEW ARTICLE

Transcranial Direct Current Stimulation for Treatment of ADHD: A Review of the Mechanisms of Action

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Abstract: ***Background and Objective*:** Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder. The current pharmaceutical treatments are associated with side effects and with low efficacy so that about one third of the adults do not respond to these treatments. Transcranial direct current stimulation (tDCS) is a non-invasive and safe brain modulation technique with promising therapeutic effects on ADHD symptoms. This paper aims to comprehensively review the clinical trials of tDCS conducted in humans for the treatment of ADHD. We aim to review the clinical efficacy and mechanisms of action of the technique in ADHD treatment.

***Method*:** The databases of PubMed (1990-2017), Web of Sciences (1990-2017), Google Scholar (1990-2017) and Scopus (1990-2017) were searched using the keywords "Attention deficit hyperactivity disorder" OR "ADHD" AND "Transcranial direct current stimulation" OR "tDCS" AND "treatment" AND "mechanism". The title and abstract of the papers were reviewed by at least two authors and the relevant papers were selected for in depth review. We selected the preclinical and clinical trials that studied the effects of tDCS on ADHD patients through measuring behavioral, hemodynamic, or neurophysiological features.

***Results*:** The current evidence supports the therapeutic efficacy of tDCS in the improvement of ADHD, but, the findings are controversial. Anodal tDCS seems to be more effective than cathodal in ADHD. In addition, the appropriate sites of stimulation are frontal cortex in particular left dorsolateral prefrontal cortex and right inferior frontal gyrus. The tDCS can improve inhibitory control and interference control in ADHD patients.

***Conclusion*:** tDCS has shown promising but limited clinical efficacy for ADHD treatment. However, the current evidence supports continuing the preclinical and clinical studies to determine physiological mechanisms and dose response of tDCS in ADHD to establish a clinical protocol.

Keywords: Transcranial direct current stimulation, ADHD, clinical trials, mechanism of action, efficacy, hyperactive-impulsive type.

1. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder among children and adults. According to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the core symptoms of ADHD are abnormal levels of impulsivity, inattention, and hyperactivity. The three main subgroups of the disorder are the predominantly inattentive type, predominantly hyperactive-impulsive type, and the combined type [1]. ADHD starts in childhood and usually persists in adolescence. Experimental researches through families clarified the heredity of ADHD; thus the possibility of disease appearing in further generations increases. The symptoms of ADHD in adults and children overlap with each other in most of the clinical features for example, cardinal symptoms of inattentiveness, impulsivity and over-activity [2]. The general rate of prevalence ranges 3% to 7% among school-aged children [3] and 4.1 to 5% among children and teenagers [4, 5] and in approximately 40-60% of all ADHD cases, the symptoms persist to adolescence and adulthood [6] so that the prevalence of the disorder among adults is about 4.4% worldwide [7].

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The first-line treatment options in children and adults with ADHD are stimulant medications. Clinical and experimental studies show that just 70 percent of the patients respond to the stimulants [8]. In addition, these medications are usually associated with severe side effects including appetite suppression, lethargy, cardiovascular problems, sleep disturbances, headaches, abdominal discomfort, fatigue, increased risk of tics, possible dependence due to long-term administration, and growth suppression [4, 6, 7]. The second group medications for ADHD treatment include non-stimulants like tricyclic and non-tricyclic antidepressants, and specific norepinephrine re-uptake inhibitors. These medications also have the same drawbacks of stimulant medications. The other standard treatment option for ADHD patients is psychotherapy which is usually administered along with medications and immediately after them [9, 10]. Despite using the psychotherapy in combination with medication, a relatively large portion of patients do not respond to the treatment [11, 12]. Therefore, researchers have long time sought for an alternative treatment option for ADHD.

During recent years, different brain stimulation and modulation techniques have been developed for different neuropsychiatric disorders [13-15]. Among the brain modulation techniques, transcranial direct current stimulation (tDCS) has shown interesting potentials as an alternative or adjunctive treatment for different psychiatric disorders including ADHD [12, 16-23]. TDCS is a noninvasive, low-cost, easy to use technique where a week direct current is delivered to the scalp through a pair of electrode, through which the flowing current changes the cortical excitability of the neurons and ultimately alters behavior [24]. Depending on the polarity of the electrode excitability of the exposed neurons, increased where anodal (positive electrode) tDCS increases and cathodal (negative electrode) tDCS decreases it [22]. tDCS induces different physiological, hemodynamic, modulatory, and cognitive effects, which can be used as a treatment option in different neuropsychiatric disorders [25].

Previous preclinical and clinical studies have shown that tDCS can improve the different cognitive functions in healthy individuals and patients with different neuropsychiatric disorders [17]. Some studies have demonstrated that anodal tDCS over prefrontal cortex increases the inhibitory control in healthy and neuropsychiatric patients and also improves cognitive performance in depression patients with major depression [26, 27]. Therefore, tDCS may have therapeutic efficacy in ADHD treatment. The initial studies have shown promising but controversial findings on the treatment efficacies of tDCS in ADHD. The studies are ongoing in developing efficient protocols of tDCS for the treatment of ADHD as well as to determine the mechanisms of action of this technique [22]. In the diagnosis and treatment of ADHD, one of the main steps is understanding the brain mechanisms and cortical activities in disease development and also following the therapeutic interventions [28]. This paper aims to comprehensively review the clinical trials of tDCS conducted in humans for the treatment of ADHD. We aim to comprehensively review the advancements in clinical applications of tDCS for the treatment of ADHD in clinical trials. The clinical efficacy and mechanisms of action of the tDCS technique in ADHD treatment are discussed.

2. METHODS

The databases of PubMed (1990-2017), Web of Sciences (1990-2017), Google Scholar (1990-2017) and Scopus (1990-2017) were searched using the keywords "Attention deficit hyperactivity disorder" OR "ADHD" AND "Transcranial direct current stimulation" OR "tDCS" SAND treatment. The title and abstract of the paper were reviewed by two authors and the relevant papers were selected for in-depth review. Those preclinical and clinical studies were selected for full review that investigated the effects of tDCS on ADHD patients through measuring behavioral, hemodynamic, or neurophysiological features.

3. RESULTS

A total of 23 studies were selected for detailed review. According to the electroencephalography data interpretation, the evidence of neurofeedback application to refine neurotransmitters imbalance is indicated. Besides, neuromodulation as a result of cortical stimulation can subsequently reduce or fully preclude the occurrence of further psychopathic events like depression and anxiety.

3.1. Treatment Efficacy of tDCS in ADHD

Different preclinical and clinical studies have investigated the therapeutic efficacy of tDCS in improving the symptoms of ADHD [19, 20, 23, 24] . Different sites of stimulation have been studied with different stimulation parameters including intensity, duration, and a number of sessions. Most of the conducted studies on tDCS for ADHD treatment have used anodal stimulation over frontal lobe to modulate neuronal activity. The next common site for ADHD treatment was right inferior frontal gyrus (rIFG) area that showed promising effects on improving cognitive functions. Dorsolateral prefrontal cortex (DLPFC) has been shown as an appropriate target site for improving neuropsychological and cognitive functions. Different studies on healthy individuals and also on neuropsychiatric disorders have shown that single or repeated sessions of tDCS over left DLPFC improved working memory and attention [27].

The configuration of anodal and cathodal electrodes respectively placed at left DLPFC and right DLPFC (F3 and F4 electrode locations has been demonstrated to be ideal for the tDCS electrode montage in cognitive and behavioral studies. Similarly, up to now, the most frequent electrode montage used in the studies investigating tDCS effects on ADHD patients used this configuration. There are two main study designs for investigating the tDCS effects on cognitive functions in ADHD: online and offline. In the online tDCS design, the outcome assessments through behavioral or EEG tests are performed concurrently with tDCS application. On the contrary, in the offline tDCS, the assessments are performed after the tDCS application.

Banderia *et al.* (2016) investigated the effects of offline tDCS over the left DLPFC on visual attention, visual and verbal working memory, and inhibitory control in ADHD patients [23]. They used daily session (intensity 2 mA, duration 30 min, electrode size of 35 cm^2) for five consecutive

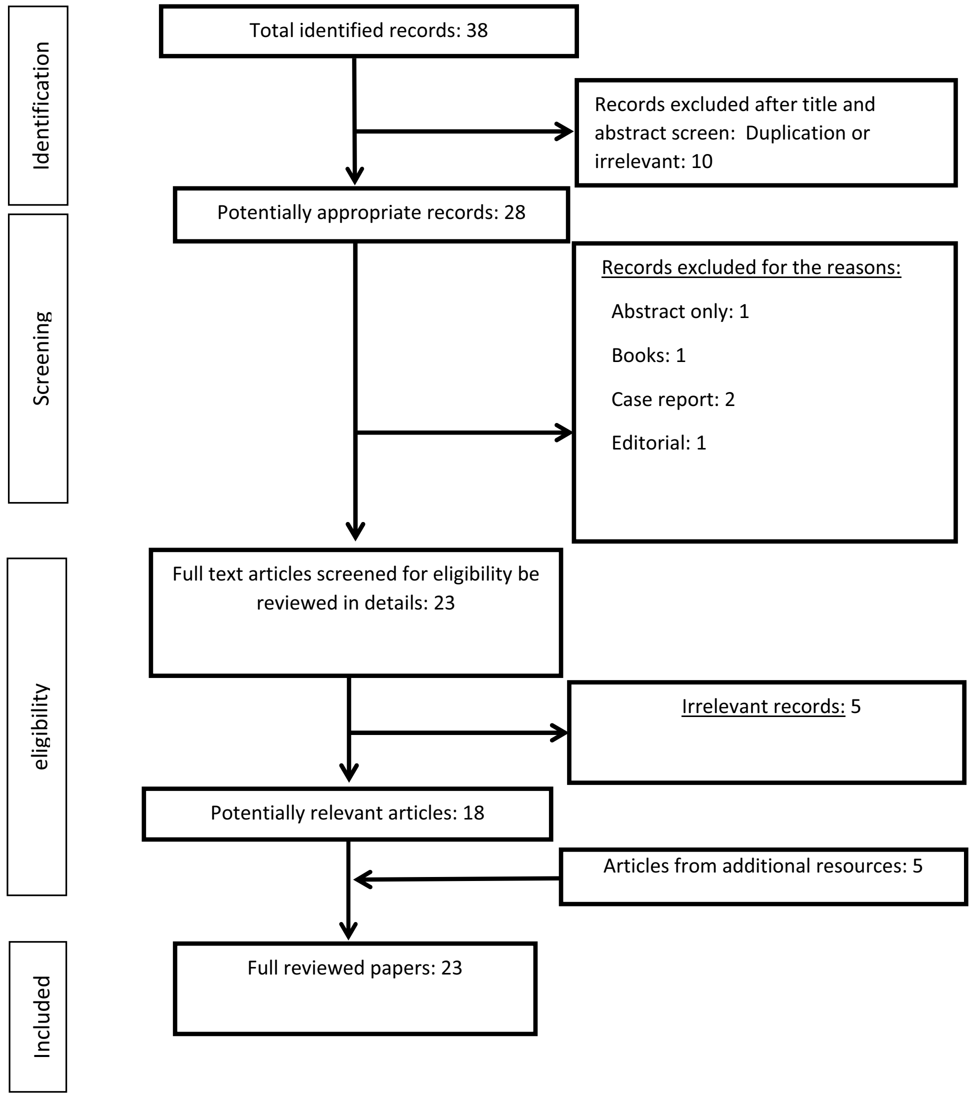

Fig. (1). The PRISMA flow chart of the study.

days. They reported that tDCS applied over the left DLPFC improved working memory and attention the anodal electrode was positioned over the left DLPFC (F3 of 10-20 EEG recording system) and the cathode over the right supraorbital area [23]. They concluded that anodal tDCS over LDLPFC can improve information processing, and the ability to switch between two different tasks [23].

Sotnikova *et al.* (2014) studied the effects of anodal online tDCS over left DLPFC on clinical symptoms and attention, executive functions, and working memory performance in ADHD patients (n=16). They applied daily 20-minanodal tDCS with a current intensity of 1 mA over left DLPFC for 5 consecutive days and assessed the changes in the neuropsychological parameters concurrent with the tDCS and at one week after the last tDCS session. They compared the effects between the treatment and placebo groups [29].

They reported that anodal tDCS significantly enhanced reaction time, working memory, and executive functions, compared to the sham stimulation [29]. The improvements can be attributed to the activation of attention/working memory network by the tDCS sessions. Their findings showed that anodal tDCS was effective in improving ADHD clinical symptoms that are associated with working memory, attention, and executive functions.

Breitling *et al.* (2016) studied the effects of single session online anodal, cathodal, and sham tDCS (current density of 29 $\mu A/cm^2$, 20 min) over the right inferior frontal gyrus (rIFG) on interference control in ADHD patients and compared the results with the age matched healthy peers [20]. They reported no significant tDCS effect in either group. However, they observed that anodal tDCS improved the performance levels including commission errors and reaction time variability so that their performance was comparable to the healthy subjects. These findings indicated that anodal tDCS over the rIFG could improve interference control in ADHD patients. However, we should be careful on this conclusion as further clinical trials are needed to verify that improving specific functions such as interference control can improve the clinical symptoms such as general behavioral control or impulsivity in ADHD patients.

In another relatively well designed study, Soltaninejad *et al.* (2015) investigated the online tDCS (1.5 mA, 15 min) over the rIFG on inhibitory control in ADHD patients (n=20). The cathode was placed on the left supraorbital region(30). Inhibitory control is one of the main components of executive function. They used a double blinded, placebo-controlled design to compare the tDCS effects on between the real and placebo groups and used Stroop and Go/no-Go tests to measure inhibitory control. The Go/no Go test showed that anodal rIFG stimulation significantly improved correct responses (p=0.01). However, the other two dimensions did not show a significant difference between the real and placebo groups. The Stroop cognitive test also showed no significant difference between the anodal and sham stimulation [30].

3.2. Safety Profile of tDCS in ADHD Treatment

The studies conducted on the tDCS effects on ADHD patients showed that the tDCS sessions were well tolerated. The studies did not report severe adverse effects by tDCS. Only local sensations such as itching under the stimulation electrode were described by some patients that are reported in both real and sham tDCS conditions. Current density is the main parameter in assessing the safety of tDCS protocols and using big electrodes with big and wet surface reduces the adverse effects due to the smaller amount of current per area entered the scalp. The majority of the studies have applied low current density about 30 µA/cm2, which were associated with no severe adverse effects. The highest current density applied in human studies was 57.1 µA/cm2. In an animal study, Leffa *et al.* (2016) used a current density higher than 14290 µA/cm2 and reported brain lesions [31].

The most reported adverse effects of tDCS sessions are the experience of itching, tingling, and pinching and in some cases, mild levels of skin irritation, headache, and sense of burning that were not serious. In general, all of the conducted studies for the treatment of ADHD symptoms reported that the tDCS sessions were well tolerated and the patients showed a good level of tolerability.

3.3. Mechanism of Action of tDCS

3.3.1. EEG Based Assessments

Consistent with the recent studies, through neuropsychiatric abnormalities, the implication of an effective technique which can hopefully elucidate brain mechanisms; actuates the neuroscience to more investigation about non-invasive brain stimulation like tDCS to fortify the knowledge of cognitive and neurophysiological diseases [32].TDCS delivers a weak direct constant electrical current to the scalp through electrodes [33]. Consequently, neuronal membrane excitability changes in response to the electrical current. Thereby, the emergence of new variations in cortical activity is the ultimate outcome. Therefore, synchronous recording of electroencephalography (EEG) can help to get beneficial information which plays an important role in the diagnosis of electrophysiological and behavioral abnormalities [34, 35]. Conspicuously, the target of tDCS action is defined as neuronal activity and threshold, besides induction of spatial changes through synaptic activities *e.g.* sensitivity and neurotransmitter release probability [36]. The current source polarity and the distance between an individual neuron and the current source are the main factors influencing neuronal response upon the applied current. In comparison to the electrode polarity, the concept of distance has more prominence impression; as it can alter the exclusive polarity effects [12]. Data analysis according to the effects of tDCS on EEG waves by means of anodal and cathodal electrode positioning indicates the following contexts [37] (Fig. **2**):

- Bilateral increase of frontal delta and theta band
- Frontal and prefrontal delta band deceleration
- Decrease of delta band through all areas of the brain
- Anodal: Increase of the theta and alpha band locally
- Cathodal: Decrease in theta and alpha band locally
- Locally increased beta and decreased alpha band

It should be noted that all of the mentioned bands are in phase and synchronized.

3.4. TDCS and Neurotransmitters Modulation

Previous studies have shown therapeutic efficacies of tDCS in cognitive and clinical domain; the suitable circumstances to mend neurophysiological disorders are accommodated by the influence of weak electrical current in cortical activity and neurotransmitters imbalance. The findings of the controlled clinical trials have demonstrated that tDCS decreases the release of inhibitory neurotransmitters [39].

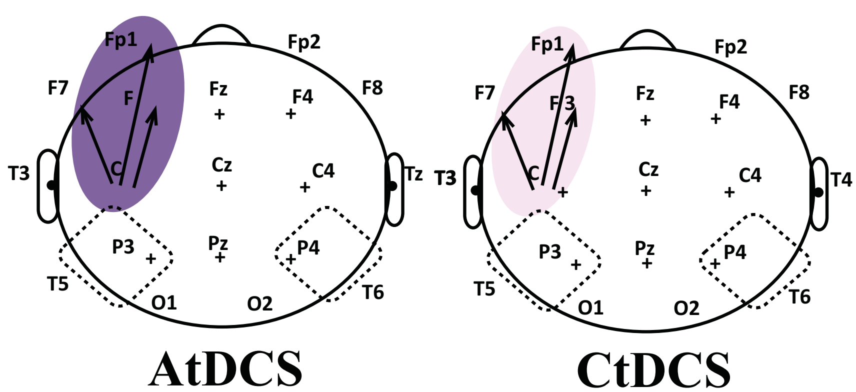

Fig. (2). The effects of anodal and cathodal tDCS on the EEG waves of the subjects [25]. Anodal stimulation increases cortical excitability, whereas cathodal stimulation has contrary effect [38].

Inhibitory transmitters are secreted from different parts of the central nervous system (CNS) including:

- GABA: Spinal cord, Cerebellum, Basal ganglions and several areas of the brain cortex [40].
- Glutamate: Several brain sensory and cortical domains [41].
- Dopamine (most inhibitory): Caudate and lentiform nuclei, substantia nigrosine [42].

In general, dysregulation of brain cortex excitability may result in the emergence of pathologic symptoms. In addition, the area through which neurotransmitters imbalances occur, diseases manifestations become deteriorated [28]. Gamma Amino Butyric acid (GABA) and glutamate imbalances are the most incredible issues for which psychoanalytical investigations are focused on. To make subtle diagnosis for the patients afflicted with Attention deficit Hyperactivity Disorder (ADHD), contemporary and accurate inquiry of GABA-Glutamate is crucial [43]. Different preclinical and clinical studies conducted on the GABA-Glutamate excitation/inhibition (E/I) ratio have demonstrated significant correlations between different types of psycho-physiological abnormalities with the E/I ratio. Actually, the spectrum of the ratio variations, leads to choose the best therapeutic choice as the more effective approaches are consulted. In cases with autism, E/I ratio is higher than normal individuals. On the other hand, an elevated level of glutamate besides the deceleration of GABA level, can give a brief story of what is going on through the brain mechanisms of ADHD patients [44]. Accordingly; the main purpose of ADHD treatment can be planned to decrease E/I ratio; so cathodal TDCS procure make it possible to yield this goal [18, 27, 45-47].

CONCLUSION

This study reviewed the current evidence on the efficacy of tDCS for the treatment of ADHD symptoms and also the reported mechanisms of action of the technique. The studies showed that the best stimulation site to improve cognitive function and treat patients with the attention disorders like ADHD, is the frontal cortex, in particular, the left hemisphere and the higher current densities result in higher improvement in ADHD.

It seems that online tDCS where the outcome assessments are performed concurrently with the tDCS may result in more beneficial outcomes than the offline tDCS protocols. In addition, our review showed that future trials should investigate the protocols with intensities more than 1 mA and online tDCS. The current evidence from preclinical and clinical trials demonstrates that tDCS could be effective in modulating cortical excitability and improving cognitive performance in healthy subjects and in different neuropsychiatric disorders. However, conducting more comprehensive clinical trials with placebo control in big sample size are necessary to reach a decisive conclusion on the clinical outcome and efficacy of the tDCS in ADHD treatment. In addition, conducting well designed cellular, physiological, and neurobiological assessments on the mechanisms of action of the tDCS can help researchers to determine reliable dose-response profile and develop clinical approved tDCS protocols for ADHD treatment.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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