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Review Article

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A Review of Transcranial Direct Current Stimulation for Attention Modulation in Healthy Subjects

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ABSTRACT

Attention is one of the highest cognitive functions among multitude processes including perception, memory, understanding, and learning. The first efforts for enhancement of attention are pharmacological methods whose side-effects sometimes dominate the beneficial effects. Then, the need for a noninvasive, low-cost, and efficient neuromodulation technique for improving attention method is necessary like transcranial direct current stimulation (tDCS). In this technique, a weak direct electrical current through anode or cathode electrodes, depolarizes or hyperpolarizes the cortical neurons and alters the excitability of them. This paper reviews the basic principles of tDCS, its procedures, and efficient protocols for improving attention in healthy subjects to the three network of attention: alerting, orienting, and executive control. Furthermore, the safety considerations of this technique as well as future clinical applications are discussed.

Keywords: Transcranial Direct Current Stimulation, Attention, Improvement

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INTRODUCTION

Attention defined as selecting information from the environment is one of the highest cognitive functions among multitude processes including perception (acquiring information), memory (retaining information), understanding (representing information), and learning (acquisition of knowledge or skills) (1, 2). This function plays a critical role in occupational and individual performance, especially in the occupations that require high level of attention and concentration. Enhancing the occupational and sport performance or improving the efficiency of armed force or police power or specialists in sensitive operations can be achieved through modulating the level of attention in the individuals. In addition, the enhancement of attention may be introduced with the aim of correcting a particular defect or pathology.

The first line efforts to enhance mental faculties have started in the past decade including conventional methods as martial arts, meditation, yoga and even school-based education and training as well as various pharmacological enhancement(1, 3-6). The use of pharmacological enhancements began from 1917 by observation of facilitating effects of strychnine in rats learning(7). Since then, we have witnessed the concomitant growth of pharmacological usages of stimulant drugs (8, 9).

Nowadays, drugs abuse like Ritalin, the trade name for methylphenidate, are used progressively as an attention improvement agent especially among college students (10). Ritalin is used mostly as a golden standard of treatment for attention deficit hyper activity disorder (ADHD) in which lack of attention is a critical factor of prevalence (11-

14). In DeSantis's study (2010), 34%(15), in the Babcock's study (2000), 16%(16), and additionally, 3% of the students in Teter study (2003)(17) at least had used the Ritalin one time in their life. In addition, Habibzadeh (2011) reported that 8.7% of the students in Tabriz University of medical sciences, Iran, had a history of Ritalin abuse(18).
During the recent years, non-medication techniques have been dramatically developed for the treatment of different disorders ranging musculoskeletal and soft tissue disorders to cognitive and behavioral disorders (19-24).

tDCS can modulate the attention to enhance its performance in different cognitive functions and can be used as an alternative to the conventional medications for modulation of attention and related higher order function for patients with attentional disorders like ADHD. Thus, we may witness getting rid of Ritalin abuse forever.

Introduction of a new cognitive modulating technique should be accompanied by enough knowledge on the potential side effects associated with this technique. The tDCS is a noninvasive, low-cost, and powerful neuromodulation method (25). In this technique a current generator delivers a weak, direct electrical current via electrodes placed on the scalp to the neuronal tissue to induce changes in cortical excitability, which consequently alters the cognitive functions.
Wilens et al in a meta-analytic review on the applications of tDCS for individual ADHD in specially for infants reported high therapeutic efficacy do not get addicted to their stimulant medications at treatment dosages (26), in approximately 4% to 10% of patients, more Severe side effects have been reported, such as jitteriness, stomach aches, decreased appetite, insomnia(12), cardiovascular, neurophysiological systems(27), etc. In addition, there are several known side effects that occur among 20–50% of individuals taking psychostimulant abuse, such as headaches, anxiety, irritability (28), inhibited growth, depression, and motor tics(29).

Historical advances of tDCS

The history of therapeutic electricity goes back to antiquity (In 43 AD), where Scribonius Largus, a physician of the Roman Emperor Claudius, described a detailed account of the use of the (electric) torpedo fish to alleviate gout and headache(30, 31). Since that time, several scientists experimented with electrical stimulation in hopes of treating various cognitive disorders and even bringing people back from the death(31). In the mid-1700’s, French physician Charles Le Roy, wrapped wires around the head of a blind man in hopes of restoring his eyesight(32) and Dutch, scientists in the South American colonies, utilized electric eels to relieve headaches and treat neuralgia(33). In addition, some practitioners began using Leyden jars to treat neuralgia, contractions, and paralysis(30). It was the invention of the battery by Alessandro Volta that made DC stimulation or faradization possible. He invented the Voltaic pile according to the electrical organs of the eel and torpedo fish in 1800(34). The studies of Luigi Galvani on “animal electricity” and invention of voltaic pile, emerged considerable interest in therapeutic effects of galvanism and utilizing electrical current to treat a wide range of disorders(30). The first documented use of a procedure similar to modern tDCS was in 1868, when Duchenne de Boulogne (1806–1875) improved electrotherapy procedures with Volta and Magnetofaradaic apparatuses and it was suggested as a potential therapeutic intervention for neuralgia, convulsions, and paralysis(35).

During the last few decades, tDCS has shown promising outcomes as a neuromodulating technique for different disorders (36-39). This technique can modulate different cerebral cortical functions through inducing focal and prolonged shifts of cortical excitability These studies marked the true beginnings of tDCS, whereas the first study to utilize the modern standard of current and electrode parameters was published just over a decade ago(37).

This field has experienced significant growth as evidenced by the number of publications in the past 15 years and this exponential growth reflects the ease of use of this method in addition to its so far favorable profile combined with its ability to produce significant effects on human neural plasticity(40).

Mechanism of Action

It is believed that, early childhood, is the critical periods of development of the brain which may undergo important changes(41). Changes to the brain were only possible in very specific areas of the brain such as the cerebellum and hippocampus by environmental changes or some stimulation. This principle of the brain is now beyond doubt and has become known as neuroplasticity or brain plasticity(27). However, tDCS has been reintroduced as a noninvasive tool to guide neuroplasticity and modulate cortical function by tonic stimulation with weak direct currents (42). It was recently re-evaluated and optimized as a powerful tool to induce prolonged neuroplastic cortical excitability changes (37, 38, 43).

The tDCS technique is most commonly delivered via 2 electrodes - 1 anode and 1 cathode - affixed to the scalp overlying cortical regions relevant to the outcome measure of interest(37). In primarily studies in animals, established in the 1950s and 1960s; it was shown that The short-term effects of tDCS are drown through alteration of the resting membrane potential so that, anodal (positive electrode) stimulation increases spontaneous neuronal activity through depolarization, while cathodal (negative electrode) stimulation decreases excitability through hyperpolarization(44, 45) and results in reduced activity(46-48).

TDCS, in contrast to other stimulation techniques (e.g., transcranial magnetic stimulation, intracranial electrical cortical stimulation, electroconvulsive therapy), is not thought to induce neuronal firing (action potentials). Rather, by acting at the level of the membrane potential, tDCS modulates the spontaneous firing rate of neurons via two mechanisms of actions(49). The first occurs during stimulation (online protocols), and involves ionic concentration shifts within the extracellular fluid which serve to modulate neuronal resting membrane potentials thereby hypo- and hyper-polarizing neurons underlying the anode and cathode, respectively(50). The second occurs following long duration (>7min) stimulation, i.e. measuring the outcome following stimulation (offline protocols); and involves long-term potentiation and depression-like mechanisms at the synaptic level thereby effecting hyper- and hypo-communicative activity in neurons underlying the anode and cathode, respectively(50). It is worth noting that while enhancement studies generally focus on the depolarization effects of anodal stimulation, the possibility of hyperpolarization has implications for unlearning phobias and addiction, as some pharmacological agents are used(51, 52) rather than enhancing learning and memory via increased neural activation. Typical current strengths are 1 - 2 mA delivered for up to 30 minutes(53).

According to the ability of modulating cortical excitability, as a fundamental effect of this stimulation(37, 54-56), tDCS has been examined as a potential therapeutic intervention in multiple clinical disorders(57) such as chronic pain(58), major depressive disorder(59), stroke rehabilitation, Parkinson’s disease(60), etc.

Furthermore, this intervention can applied in healthy individuals with the aim of improving an already "healthy" cognitive system rather than targeting a specific defect e.g. facilitate cognition(61), working memory(62, 63), motor learning(64), motor function(65), simple somatosensory and visual motion perception learning(66), and memory for word lists(67). Quantifying the effects of tDCS on brain function is essential to understand and implement treatment and experimentation in this vigorous, growing field(1).

tDCS and Attention

Attentional networks

In recent years three attentional networks have been defined in both functional and anatomical terms(68) and Imaging data have supported the presence of these networks related to different aspects of attention. These networks carry out the functions of alerting, orienting, and executive control(69, 70).

The alerting network has been functionally defined as a network that facilitates achievement and maintenance of an alert state(68). The alerting system has been associated with the frontal and parietal regions of the right hemisphere(71). A particularly effective way to vary alertness has been to use warning signals prior to targets. The influence of warning signals on the level of alertness is thought to be due to modulation of neural activity by the norepinephrine (NE) system(72).

The orienting network is responsible for allowing attending to sensory events through movement of attention through space or selection of information from sensory input(71). Orienting involves aligning attention with a source of sensory signals. This may be overt, as in eye movements, or may occur covertly without any movement. The orienting system for visual events has been associated with posterior brain areas including the superior parietal lobe and temporal parietal junction and, in addition, the frontal eye fields. The superior parietal lobe in humans is closely related to the lateral intraparietal area in monkeys, which is known to produce eye movements(73).

The executive control network has been defined as a network that resolves conflict between expectation, stimulus, and response(71). Resolving conflict (e.g. in the Stroop task) activates midline frontal areas (anterior cingulate) and lateral prefrontal cortex(74, 75). The executive network is thought to involve the anterior cingulate and lateral frontal cortex modulated by a dopamine (DA) system with cell bodies arising in the ventral tegmental region(76, 77). A popular theory of cognitive control suggests that the dorsal anterior cingulate is part of a network involved in handling conflict between neural areas(74, 78).

The efficiencies of these networks have been shown to lack significant correlation, and have been deemed functionally orthogonal constructs(71).

TDCS protocols

The current distribution in the brain changes with the arrangement of the electrodes, such that specific areas of the brain can be targeted for delivery of anodal currents that increase the excitability of the underlying cortex, or cathodal stimulation that decreases excitability(53, 79). Brain activity (as measured with FMRI or PET) under the anode is enhanced by roughly 20% to 40% when the current density (concentration of amperage under the electrode) exceeds 40 µa/cm^2. The cathode reduces brain function under the electrode site by 10% to 30% at the fore-mentioned current density(31). Some recent studies, and in particular a study by Nitsche, et al., (2007), show that it is better to have a small stimulating electrode and large reference electrode(80). This way, the current density is high under the treatment electrode and low under the reference electrode(31). However, some models demonstrate that roughly 45% of applied current passes through the brain(81, 82) others estimate (using 2.0mA of scalp stimulation) that only about 10 percent of the applied current reaches the cortex(83). However, it is suggested that significant current density is only exhibited by areas relatively local to the stimulated cortex(83, 84).

The physiological effects of anodal tDCS are thought to include increased excitability in the neocortex(85). Then, as mentioned above; anodal stimulation modulate neuronal activity and applying anodal tDCS to improving attentional network is recommended. In addition, to the activity areas of attentional networks in view; prefrontal cortex as anode stimulating place, nearly; has the best position and is one of the vast area participating in any networks of attention. Siever in a review of tDCS (2013) concluded that to improving attention, The anode should be placed on FP1 or FP2 (in the international 10-20 system), with a contralateral shoulder cathode or a large anode electrode could also be placed across FP1 and FP2 at 2 mA, with a neck-placed cathode(31).

Some similar protocols are used in different study and meet interesting results; for instance, Kang et.al. (2009) meet significant improvement in attention of stroke patients with applying anodal tDCS to the left DLPFC and a cathode positioned over the contralateral supraorbital region(86); Wrightson et.al. (2015) to probe the role of the prefrontal cortex in the control of stride time variability (STV), trunk RoM and cognitive task performance during dual-task gait, applied anodal tDCS on the prefrontal cortex and concluded that Anodal tDCS reduced STV and the dual-task cost on STV, and improved cognitive task performance(87); and miler et al (2014), applying anodal tDCS over the left PFC and cathodal tDCS over the right PFC; reported greater executive control in 30 healthy volunteers(88).

Safety considerations

Contrast-enhanced MRI and EEG studies have found no pathological concerns associated with application of tDCS(89, 90). Of course, current density is the most important consideration when using tDCS, as even 1mA will cause significant discomfort and skin burns if the electrode used is small or a part of the sponge is dry(31). Then, to minimize chemical reactions at the electrode-skin-interface; tDCS should be performed with adequate large and water-soaked sponge electrodes(91). However it was reported recently that repeated daily tDCS with a current density of about 60 µA/cm2 caused clinically significant skin irritation under the electrodes in some patients(53); while Nitsche and Paulus (2000) found that a minimum current density of 17 µa/cm2 was needed to excite motor neurons(37). Studies involving other regions of the brain have suggested that 20 to 25µA/cm2 are needed to excite neurons under the electrode(31). Then, Painful stimulation, which might occur with significantly higher current densities than those in current use, should be avoided and personnel conducting tDCS should be appropriately trained before applying the technique(53).

TDCS neither causes epileptic seizures nor reduces the seizure threshold in animals(92). Although patients with history of seizures are routinely excluded from current tDCS studies, no instances of epileptic seizures caused by tDCS have been observed in humans(93) and tDCS has actually been used to treat seizure(94). The safety of tDCS use in pregnant women and children has not yet been investigated.

For tDCS studies with healthy subjects, general exclusion criteria available for electrical stimulation apply: Subjects should be free of neurologic diseases such as epilepsy or acute eczema under the electrodes. Furthermore, they should have no metallic implants near the electrodes. Subjects have to be informed about the possible side effects(53). However, currently applied tDCS protocols (typically 1– 2 mA intensity, electrode size between 25 and 35 cm2, stimulation for up to 20 min per session) should be regarded as safe(42). With the typical current levels and experimental protocols, the side-effects of tDCS are mild, benign, and short lived(95); so that, within these limits, no major adverse events had been reported so far for about 2000–3000 subjects in laboratories worldwide(42).

In a recent systematic review, Brunoni et al. reviewed the tDCS studies conducted during 1998 to 2010. Out of 172 articles, 56% mentioned adverse effects and 63% reported at least one adverse effect(91). In the subsample reporting adverse effects, the most common were, for active vs. sham tDCS group, itching (39.3% vs. 32.9%), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), burning sensation (8.7% vs. 10%) and discomfort (10.4% vs. 13.4%)(91).

Future Research

The immediate impact of tDCS on cognitive networks may be the most promising advantages of this technique over conventional drug treatments to improve attention as a cognitional function. Future studies should explore various aspects of this technique to reach an efficient clinical technique. In this regards, determining the brain regions responsible for attention performance, determining the possible side effects of different protocols of thetechnique, as well as determining the dose-response for a controlled attention modulation using tDCS are some of the main avenues be addressed.

According to the existing literature, with appropriate training, tDCS will become a common clinical approach to neurotherapy. Thus it might be assumed that the combination of this stimulation with other modulating neural activity like rTMS and specially neurofeedback causes the comparatively large effects of tDCS. Despite this, as this field moves forward, it will be important future studies include measures which directly replicate prior work, explore potential state dependent effects within and between studies, and report quantitative data for all explored outcome measures so that a more clear picture of the state of the field can be derived.

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