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Review

Neuroplasticity and learning: insights from transcranial direct current stimulation studies

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ABSTRACT

Transcranial direct current stimulation is a popular brain stimulation method that produces facilitative or inhibitory effects on various behaviors. Over time, it has become a widely used and safe non-invasive method to investigate cortical excitability in humans. This review briefly discusses the operation of the device, how it is used, post-application effects, and its impact on learning, working memory, aphasia, memory acquisition, and neuroplasticity.

Keywords: Learning, memory, transcranial direct current stimulation.

Transcranial direct current stimulation (tDCS) is a popular brain stimulation method used to modulate cortical excitability, with facilitative or inhibitory effects on various behaviors. Recently, it has emerged as a promising tool for modulating cognitive and motor skills. The technique has gained significant popularity in the past decade, with a notable increase in research studies. Transcranial direct current stimulation has been shown to not only treat mental disorders but also enhance cognitive performance in various tasks such as language and mathematical abilities, attention span, problem-solving, memory, and coordination. In this method, a weak current passes through the brain with two electrodes. The current enters the brain from the anode region, progresses through the tissue, and exits from the cathode region. Typically, a current of 1-2 milliamperes (mA) is applied. The electrodes remain fixed on the skull with the help of an elastic band. For a 3-minute application with an electrode area of 35 cm^2, a current of 1 mA is applied, and for a 5-minute application, the required current is 0.6 mA; these values are necessary for the onset of the effect. Increasing the current intensity and/or stimulation duration leads to post-application effects and an increase in the magnitude of effects. Depending on whether the anode or cathode is connected, the modulation of a specific brain region is referred to as "anodal tDCS" or "cathodal tDCS." The direction of current flow differentiates anodal and cathodal stimulation by modulating the resting membrane potential of stimulated neurons.[1] Anodal stimulation increases the probability of action potential generation by depolarizing neurons, whereas cathodal stimulation hyperpolarizes neurons, thereby decreasing the likelihood of action potential formation.[2] While tDCS protocols and electrical dosage often exhibit flexibility, determining the most effective design for a specific experiment can be challenging.[3]

Briefly, tDCS has significant potential to integrate into common interactive tasks to enhance various aspects of user experience through interactive applications.

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APPLICATION OF TRANSCRANIAL DIRECT CURRENT STIMULATION

First, the locations where the electrodes will be placed are determined. Before attaching the electrodes to the scalp, it is essential to ensure that the individual undergoing the experiment does not have any skin damage or skull fractures. If 'saline' is used as the conductive substance, electrodes can be placed in moistened sponge bags saturated enough not to drip. Using conductive paste or electroencephalography gel to adhere the electrodes to the scalp allows for more effective control of current distribution than saline. To ensure good contact between the electrodes and the scalp, the individual's hair must be parted. However, saline should not flow onto the scalp or come into contact with the hair. The electrodes are then connected to the stimulator via wires corresponding to the respective anodal/cathodal connection points. Once placed over the target region, the electrode should be secured using a cap or rubber bands. Subsequently, the reference electrode should be secured in the same manner. After the electrodes are attached, the stimulation duration, current density, and acceleration/deceleration times need to be programmed. Some stimulators allow the individual conducting the experiment to pre-program the stimulation parameters, while others require manual input before each session. Monitoring the individual undergoing the experiment during stimulation, including under sham conditions, is crucial to avoid any issues. For tDCS to be reliably and consistently applied, conductivity must be maintained throughout the circuit, and the electrodes must have good contact with the scalp. Checking the impedance levels displayed on the stimulator is important to ensure that stimulation is not unsuccessful. High impedance levels may indicate poor conductivity and can result from inadequate hair parting or insufficient contact between the scalp and the electrodes, indicating a lack of conductive substance between the electrode and the scalp. Monitoring these levels throughout the experiment is crucial as high impedance levels may suggest a lack of constant current, emphasizing the need for careful observation.[4]

Transcranial direct current stimulation is a non-invasive method that allows reversible modulation of activity in specific brain regions. It has provided a valuable opportunity to establish brain-behavior relationships in various cognitive, motor, social, and emotional domains. In healthy populations, it has been observed to temporarily alter behavior, accelerate learning, and enhance task performance.[5,6] For instance, while anodal stimulation has been shown to enhance facial expression recognition and inhibit aggressive responses, cathodal stimulation has been demonstrated to stimulate the dorsolateral prefrontal cortex by suppressing working memory activity and promoting implicit motor learning.[7,8]

From a practical perspective, the equipment is reusable, relatively inexpensive, and easily replaceable when worn or damaged. This contributes to its therapeutic potential in clinical sciences. Home application of tDCS is convenient for researchers or patients and can be used alongside or in lieu of drug treatments to accelerate recovery and enhance motor and cognitive performance after a short period.[9]

In addition to all these, tDCS has also yielded successful results when applied to reduce symptoms of depression. However, further expansion of the field is needed to support its use for this purpose. Small-scale studies have demonstrated its ability to reduce hallucinations in schizophrenia patients and improve delays in syntax acquisition in autism spectrum disorder.[10,11]

Anodal and cathodal stimulation

Despite the commonly held consensus on the excitatory effects of anodal stimulation, a recent examination has proposed limited inhibitory effects of cathodal stimulation in tDCS experiments stimulating non-motor regions.[12] In the same study, it was revealed that there is a 16% probability of researchers finding polarity-specific effects. An alternative review article also demonstrated that cathodal stimulation did not significantly alter cognitive function.[13] Alongside these uncertainties, it has been suggested that a single tDCS session has no impact on performance (without the influence of the stimulation type).[14]

In general, these differences may arise from a lack of standardized methodology and the failure of all studies to manage both anodal and cathodal polarity conditions, as well as a lack of genuine comparison. Indeed, a recent report suggested that approximately 90% of studies using tDCS to stimulate the motor cortex did not employ a sham-controlled design.[15,16] Collectively, these reviews emphasize the importance of incorporating three types of stimulation conditions into an experimental design to test different and unpredictable outcomes. The varying results of stimulation polarity raise questions about how precisely stimulation affects the target region.[17] Studies that delve into the effects of stimulation duration and intensity in more detail have provided some answers, suggesting that the relationship between polarity and enhancement is largely task-dependent. For instance, Antal et al.[18] reported a decrease in contrast sensitivity after cathodal stimulation but no change after anodal stimulation, indicating an area that may already be at its optimum level and therefore not further improvable. Polarity effects are also contingent upon the state of cortical activity for each individual upon arrival for testing and can be influenced by various factors (e.g., alertness, caffeine intake). This may lead to some participants showing facilitatory anodal effects, while others exhibit inhibitory effects.[19]

Scheduling sessions at the same time each week may help ensure that a participant's routine does not interfere with polar effects. Although these differences may be lost in the data after averaging, they still underscore the uncertain nature of how tDCS affects underlying cortices.

Effects of transcranial direct current stimulation

In the majority of studies, behavioral effects have been investigated in healthy individuals rather than patients. Positive results have been reported in the treatment of conditions such as pain, migraine, fibromyalgia, depression, and epilepsy. However, large-scale studies have not been conducted. Transcranial direct current stimulation has been proven to enhance motor functions and control in most studies conducted on healthy individuals. Therefore, it has been applied to stroke patients who have experienced a loss of motor control. The potential benefit of tDCS is not limited to the stimulation of damaged tissue alone. Silencing the unaffected part of the brain in conditions like stroke, for example, slowing down the motor cortex responsible for controlling the unaffected arm, may accelerate recovery in stroke patients, forcing them to use the affected arm. The anode placed on the damaged cortex stimulates this area, while the cathode placed on the intact part inhibits it. Despite the existence of positive results, well-designed, sham-controlled studies have not been conducted.[20]

Side effects

Any serious side effects have not been reported with the use of 1-2 mA tDCS.[21] However, mild and transient side effects such as headache, skin sensitivity in stimulated areas, moderate fatigue, redness in the skin under the electrode, difficulty concentrating, acute mood changes, and nausea may be observed.[22,23] These effects are reported in approximately 17% of healthy individuals. Cutaneous sensation is the most commonly reported side effect, and it tends to decrease when the current is stabilized.[22] Turning tDCS on and off, using smaller electrode sizes, applying a moderately saline solution to the sponge, and employing an up-and-down procedure on the holding bag can also reduce this sensation.[24,25] Additionally, using smaller electrodes may be cost-effective for current density, as applying lower current may be necessary if the current density becomes too high.

MIND MODULATION

The learning boost

One of the first and most interesting studies conducted on the effects of tDCS on memory integrity and retrieval has leveraged the advantages of tDCS, such as its easy application and non-invasiveness. In this study, tDCS was applied bilaterally to the frontocortical region every 30 minutes during periods of slow-wave activity in sleep, using anodal stimulation, and improvements in memory were reported in tests conducted after the application.[26]

The impact of tDCS applied to the prefrontal cortex on implicit learning has also been tested in the setting of the probabilistic classification learning (PCL) protocol. It was observed that 10 minutes of anodal tDCS applied to the left prefrontal cortex in 22 healthy subjects improved implicit learning in the PCL task. Conversely, no effects were observed with cathodal tDCS applied to either the left prefrontal or primary visual cortex.[27]

To investigate the role of the primary motor cortex (M1), especially in the formation of motor memories, Galea and Celnik[28] applied anodal tDCS to the M1 of nine healthy subjects during motor training. As a result, it was found that anodal tDCS increased the size and duration of motor memories.

In another learning paradigm involving the implicit learning of an artificial language, de Vries et al.[29] applied tDCS for 20 minutes during the learning of an artificial grammar. Following the tDCS application, subjects were more successful in detecting grammar errors compared to control groups receiving tDCS to unrelated brain regions or sham stimulation during the learning of the artificial language.

The posterior parietal cortex (PPC), another cortical area, has been investigated during various visual orientation tasks under anodal tDCS. It was observed that tDCS applied to the right PPC improved visual search skills when applied alone or in addition to training, while anodal tDCS applied to the left PPC did not show such an effect.[30]

Memory acquisition

The role of the temporal lobes in the formation of false memories has been investigated by Boggio et al.[31] Thirty normal subjects were subjected to one of three stimulation conditions during the acquisition and retrieval phases: anodal tDCS to the left temporal lobe, cathodal tDCS to the right temporal lobe, and anodal tDCS to the left anterior temporal lobe. Both active stimulation forms reduced the formation of false memories by 73% without affecting true memories.

Reports indicating compensation of deficits in the left brain by the right brain in individuals with autism and the consequent enhancement of visual memory have formed the basis for a study. This study applied left cathodal anterior frontal tDCS together with right anodal anterior frontal tDCS, demonstrating an increase in visual memory in individuals similar to those with autism.[32]

Transcranial direct current stimulation applied to the frontotemporal lobes has been used to investigate the specific role of each cerebral hemisphere in the development of memories with different emotional values. It was found that right anodal/left cathodal tDCS particularly increased the recall of pleasant images compared to both unpleasant and neutral images. Conversely, left anodal/right cathodal tDCS led to the recall of unpleasant images compared to pleasant or neutral ones.[33] These results were interpreted in support of the specific valence hypothesis, which suggests a role for the right hemisphere in processing unpleasant memories and the left hemisphere in processing pleasant memories. Additionally, it is surprising to observe such results since, in most tDCS paradigms, anodal stimulation, which was the stimulant here, is known to enhance functional development.[34] However, in this case, to avoid contradicting the specific valence hypothesis, its effect should be interpreted as detrimental to the stimulated cortical region.

Therefore, scientists hypothesize that excessive stimulation of the underlying frontotemporal cortex could lead to impairment in processing unpleasant memories in the right hemisphere or pleasant memories in the left hemisphere.[33]

Neuroplasticity

Neuroplastic changes are the essence of learning, memory, higher cognitive functions, and recovery after central nervous system injuries. These can be modulated by tDCS and repetitive transcranial magnetic stimulation (rTMS) and partially investigated with single-pulse TMS. Transcranial direct current stimulation is a non-invasive stimulation technique that offers the possibility of inducing long-term excitability changes in different cortical areas. Animal experiments have shown that cathodal tDCS reduces the spontaneous firing rates of cortical cells, likely by hyperpolarizing the cell body, depending on the direction of the current in the targeted brain region. Transcranial direct current stimulation has become a widely used and safe method to non-invasively investigate cortical excitability in humans.[35,36]

About 40 years ago, it was demonstrated in rats that neuroplasticity could be induced with weak direct currents. The underlying mechanisms were attributed to changes in protein synthesis, intracellular cyclic adenosine monophosphate, and calcium levels. Pharmacological studies showed that the excitability-enhancing effect of anodal tDCS was disrupted when voltage-gated sodium channels were blocked with the antiepileptic drug carbamazepine or the calcium channel antagonist flunarizine. However, the cathodal effect remained unaffected. Since synaptic arrangements are not triggered by short-duration stimulation (e.g., four seconds), the effects after stimulation do not persist. The post-stimulation effects of tDCS are not solely dependent on electric current. The effects decrease when N-methyl-D-aspartate (NMDA) receptors are blocked by the NMDA receptor antagonist dextromethorphan. Conversely, the post-tDCS effect increases with the NMDA receptor agonist D-cycloserine. Animal experiments have shown that amphetamine enhances tDCS-induced excitability through a pathway that may be associated with beta-adrenergic effects. D2 agonists enhance the effects of cathodal tDCS.[37,38]

Modulation in working memory performance

The neurophysiological basis of modulation in working memory within the left dorsolateral prefrontal cortex has been investigated by recording electroencephalographic activity in the background.[39]

After anodal tDCS, an increase in oscillation power in theta and alpha bands was observed, leading to improved performance in working memory. Conversely, the application of cathodal tDCS resulted in a decrease in alpha and theta oscillation activity, negatively affecting working memory performance. The impact of transcranial random noise stimulation (tRNS) applied to the left dorsolateral prefrontal cortex on working memory performance was compared with the effects of tDCS applied to the same region. It was observed that tDCS increased the performance speed of two backward working memory tasks, while tRNS had no effect.[40]

In patients with parietal lobe damage, impairment in working memory can be observed in recognition tasks, while no impairment is seen in recall tasks. This finding formed the basis for a study where cathodal tDCS was applied to the right PPC of patients, and their working memory was assessed in terms of recall and recognition. It was observed that working memory is selectively impaired in patients with parietal lesions, a common occurrence in such cases.[41]

Studies on aphasia

Aphasia is a disorder that can occur in conjunction with speech disorders such as dysarthria or apraxia of speech due to brain damage. It disrupts language expression and comprehension, as well as reading and writing. Monti et al.[42] were the first researchers to attempt to clarify the effects of tDCS in aphasic patients. In individuals with non-fluent chronic aphasia, they applied tDCS to the damaged left frontotemporal regions and assessed the effects of anodal, cathodal, and sham stimulation. Patients were tested with a picture naming task before and immediately after tDCS. They found that naming abilities increased by 33.6% after cathodal stimulation. No contribution to naming abilities was observed with applied anodal and sham tDCS, and cathodal tDCS applied to the occipital region also had no effect on naming ability. Therefore, improvements in naming after cathodal tDCS applied to the left frontotemporal region vary according to polarity and region. The naming improvements following cathodal tDCS may indicate internetwork suppression triggered by tDCS-induced inhibition, as cathodal tDCS reduces the stimulation of cortical inhibitory circuits, leading to increased function in damaged language areas of the cerebral cortex when inhibition is relieved.[43]

In line with this hypothesis, Suzuki et al.[44] found that cathodal tDCS increased the excitability of damaged cortex in stroke patients. Regardless of the mechanism, this pioneering report paved the way for studies exploring how tDCS can be used to improve language in patients. Researchers suggested that daily applied tDCS could lead to even greater language development, proposing further studies to investigate how this technique could be used, particularly in conjunction with speech rehabilitation, to treat post-stroke aphasia.

In conclusion, daily, the utilization of tDCS is gaining prominence as a methodology for exploring the intricate interplay between the brain and behavior. It is a tool that can be used to transiently and/or reversibly modulate cognitive states and actions, but development and research are still ongoing. Current knowledge about tDCS is limited to published studies. Experiences derived from conducted studies have shown that tDCS does not cause any pain, and general side effects are tolerable. In the future, with a better understanding of the mechanisms of action, strategies can be devised to enhance cognitive and motor skills in both patients and subjects. To determine how long-lasting the effects are, experiments could be designed. If studies are conducted to improve learning and memory, and if the longevity of these effects can be ensured, the use of tDCS will become more meaningful. Transcranial direct current stimulation, a popular brain stimulation method used to modulate cortical excitability with facilitatory or inhibitory effects on various behaviors, is a reliable, accessible, and cost-effective treatment method that can be used to treat various disorders today. When regularly applied, it yields positive results. In tDCS, currents of typically 1 or 2 mA are delivered between two electrodes placed on the scalp, stimulating specific areas of the brain. This method contributes to the treatment of motor and cognitive disorders and can also assist in accelerating learning or enhancing task performance in healthy individuals.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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