Review

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Applications of transcranial direct current stimulation for understanding brain function

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In recent years there has been an exponential rise in the number of studies employing transcranial direct current stimulation (tDCS) as a means of gaining a systems-level understanding of the cortical substrates underlying behaviour. These advances have allowed inferences to be made regarding the neural operations that shape perception, cognition, and action. Here we summarise how tDCS works, and show how research using this technique is expanding our understanding of the neural basis of cognitive and motor training. We also explain how oscillatory tDCS can elucidate the role of fluctuations in neural activity, in both frequency and phase, in perception, learning, and memory. Finally, we highlight some key methodological issues for tDCS and suggest how these can be addressed.

Introduction to the use of tDCS in neuroscience

tDCS (see Glossary) offers a non-invasive means by which to establish causal relationships between circumscribed regions of the brain and their underlying perceptual, cognitive, and motor functions (Box 1). To date, tDCS has been used to alter performance across a range of cognitive tasks [1,2] (Table 1), and has been trialled as a treatment for a variety of psychiatric and neurological conditions [3,4], including depression [3,5], stroke [4], and altered states of consciousness [6]. Recently there has been debate in the popular media over the use of tDCS to enhance performance and augment gains from cognitive training [7–12]. We argue that tDCS is more than a tool for cognitive enhancement/treatment. Recent developments in our understanding of the neural basis of tDCS [5,13–15] have allowed researchers to make inferences regarding the neural processes underlying specific behaviours, including those tied to learning, memory, perception, and motor actions.

In this review, we provide a summary of the neurobiological effects of tDCS, highlighting polarity-specific modulations of neural excitability and synaptic processes. We discuss some of the important advances that have been made with tDCS in the fields of neural connectivity [16], neural oscillations [17], and cognitive training [18–20]. These advances are generating mechanistic insights into the neural bases of behaviour.

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Keywords: tDCS; neural oscillations; training; memory; prefrontal cortex; neural processes.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2014.08.003

Glossary

Anode: an electrode with a positive charge.
Anodal tDCS: stimulation applied via the anode, typically associated with increased cortical excitability and decreased levels of the neurotransmitter GABA.
Cathodal tDCS: stimulation applied via the cathode, typically associated with decreased cortical excitability and decreased levels of the neurotransmitter glutamate.
Cathode: an electrode with a negative charge.
Electroencephalography (EEG): measurement of electrical activity on the scalp, typically via multiple electrodes. Neural activity is reflected by small changes in electrical potential.
Magnetic resonance spectroscopy (MRS): type of magnetic resonance imaging that allows the non-invasive measurement of metabolites (including neurotransmitters). MRS provides the concentrations of detectable metabolites in the measured area of the brain.
Motor evoked potentials (MEPs): activity in a muscle induced, in this context, by a TMS pulse applied to the primary motor cortex. MEPs are measured via electrodes placed on the skin over the targeted muscle, and are used as a measure of cortico-spinal excitability.
Offline stimulation: stimulation applied at rest, before or after a task is undertaken.
Online stimulation: stimulation applied while a participant undertakes a task.
Oscillatory transcranial direct current stimulation (oscillatory tDCS): a form of tDCS in which the current oscillates at a given frequency.
Plasticity: changes in structural or functional pathways in the brain in response to experience.
Reference electrode: for a single target region in the brain, the second electrode is referred to as the reference. This electrode can be placed over a non-brain region (e.g., the cheek or mastoid) or a brain area thought not to be involved in the relevant process(es). The reference electrode is sometimes referred to as the 'return' electrode.
Region of interest (ROI): an area of the cortex targeted with tDCS.
Resting state fMRI (rsfMRI): measurement of the blood oxygen level-dependent (BOLD) signal while a participant is at rest. rsfMRI allows analysis of brain activity and networks in the absence of any specific task.
Sham stimulation: a form of stimulation in which the current duration or intensity are substantially smaller than in active stimulation. Sham stimulation can be thought of as a placebo condition.
Transcranial direct current stimulation (tDCS): non-invasive electrical stimulation of the brain via electrodes place on the scalp. Typically, a current is ramped up, held constant for a period of time (most commonly 8–15 min), and then ramped down.
Transcranial magnetic stimulation (TMS): non-invasive brain stimulation using a magnetic field to induce an electric current in underlying brain tissue.
TMS evoked potentials: a change in electric potentials measured with EEG in response to a TMS pulse.
Visual evoked potentials (VEPs): a change in electric potentials measured with EEG in response to a visual stimulus or a TMS pulse over visual cortex.

Box 1. Types and uses of transcranial electrical stimulation

There are several types of transcranial electrical stimulation (tES). All typically involve the application of a current via two electrodes, where one or both electrodes are placed on the scalp. The most widely used method of tES is transcranial direct current stimulation (tDCS), where a constant current is passed from one electrode (the anode) to the other (the cathode) over a period of time (usually 8–15 min). Stimulation typically leads to polarity-specific modulations in cortical excitability, and in neurotransmitter and neuromodulator systems in the stimulated cortex (see 'Neurobiological effects of tDCS'). tDCS has been used to examine the neural processes underlying a range of psychological processes, including working memory, language, mathematical cognition, spatial attention, and response selection (Table 1). Recently, tDCS has been shown to modulate high-level processes such as social norm compliance [115]. Clinical applications for several conditions exist, with evidence tDCS can aid the treatment of stroke [4], depression [3,5], and minimally conscious states [6].

Unlike correlational methods such as functional magnetic resonance imaging (fMRI) (where the BOLD signal is the dependent variable), tDCS can provide causal evidence that a brain region is involved in a behaviour of interest. tDCS offers a perspective that is unique with respect to other brain stimulation methods, such as transcranial magnetic stimulation (TMS). For example, tDCS influences a larger region of the cortex than TMS; it acts as a neural modulator without causing action potentials; it can produce opposing effects through anodal and cathodal stimulation, but with similar peripheral sensations (scalp tingling); it produces fewer physiological artefacts than TMS (e.g., muscle twitches and auditory noise); and it is cheaper, more portable, and easier to apply than TMS. Many of these advantages have led to the increased use of tDCS in clinical and research settings. In particular, the ability of tDCS to provide polarity-specific modulations (without causing action potentials) has provided a unique perspective on the relationship between brain and behaviour.

Two other types of tES are oscillatory tDCS and transcranial alternating current stimulation (tACS). Both oscillatory tDCS and tACS involve the application of a current in which intensity fluctuates at a given frequency. For oscillatory tDCS, these fluctuations remain polarity specific at each electrode. For tACS the current oscillates such that each electrode does not remain polarity-specific [116]. Both tACS and oscillatory tDCS allow the specific modulation of neural oscillations, giving causal insights into neural communication.

A final type of tES is transcranial random noise stimulation (tRNS). tRNS involves random fluctuations in current intensity, essentially adding neural 'noise' to the targeted region(s). This stimulation type has provided promise in the field of cognitive enhancement [117,118] and as a clinical treatment [119]. The idea of adding neural noise to a system, and finding resulting improvement, may seem counter-intuitive. However, the enhancement of a signal through the addition of noise can be explained via stochastic resonance [120], whereby a weak signal is boosted by an increase in background noise [120].

Neurobiological effects of tDCS

Excitability changes induced by tDCS

Animal studies have shown that anodal stimulation applied directly to the cortex causes the resting membrane potential to become more positive, whereas cathodal stimulation causes hyperpolarisation [21,22]. If stimulation is of sufficient duration, these effects are comparable during and immediately after application [21,22]. Conceptually, one can think of the effects of depolarisation and hyperpolarisation caused by anodal and cathodal tDCS as modulations that make it more or less likely, respectively, that a stimulated neuron will produce an action potential.

When tDCS is applied to the primary motor cortex in humans, anodal stimulation causes increased neural excitability, whereas cathodal stimulation results in decreased excitability (Figure 1), as reflected in motor evoked potentials (MEPs) [23–26] and transcranial magnetic stimulation (TMS) evoked potentials [26]. Comparable modulations by anodal and cathodal tDCS have been reported in the visual cortex, as measured by TMS-induced phosphenes [27] and visual evoked potentials (VEPs) [28]. These modulations are also reflected in changes in the blood oxygen level-dependent (BOLD) signal measured using fMRI [29–31]. Anodal stimulation tends to increase the BOLD signal, whereas cathodal stimulation decreases it [32,33]. It is noteworthy, however, that some researchers have found no change in BOLD within regions of targeted cortex, either during a relevant task (e.g., motor movements following motor cortex stimulation) or at rest [34]. Functionally connected regions distant from the electrode site can also be influenced by tDCS [15,33], including subcortical structures [16,33], and this modulation can be in the same [35] or opposite [34] direction to that predicted from the polarity of stimulation over the target region. Together these findings reveal that the effects of tDCS on brain function are complex, and that stimulation over relatively focal areas of cortex can yield widespread changes across the brain (see 'Using tDCS to examine connectivity and network communications').

Factors influencing tDCS-induced excitability changes

tDCS effects on excitability can be modulated by several factors. First, the intensity of stimulation affects excitability. Whereas low-intensity (1 mA) stimulation causes conventional polarity-specific modulation of neural excitability, higher-intensity (2 mA) stimulation can lead to increased excitability from both stimulation polarities [36]. Second, pairing a task with stimulation can modulate motor cortex excitability [37] relative to stimulation delivered at rest. For example, a cognitive task can reverse the typical relationship between polarity of current flow and excitability, whereas a motor task can reduce excitability following both anodal and cathodal stimulation [38]. Third, the reliability of the induced excitability changes can vary both from session to session within individuals, and across participants [37]. Some variability is undoubtedly due to differences in current flow between individuals (Box 2), in addition to potential differences in neurotransmitter efficiencies (see [5]).

Explanations for within-participant variability include individual modulating factors such as intake of neuroaffective substances (e.g., nicotine [39]), and fluctuations that occur over time. For example, time of day is known to influence motor cortex plasticity, as measured with TMS [40]. State-dependent variations in the effect of stimulation have been studied using the combined application of tDCS and TMS. For example, TMS can be used repetitively (rTMS) to induce prolonged changes that cause increased excitability (e.g., with 5 Hz stimulation [41]) or decreased excitability (e.g., with 1 Hz stimulation [42]). If the motor cortex is preconditioned with cathodal stimulation, however, a normally inhibitory rTMS protocol will increase excitability [43], and this interaction can modulate pain thresholds in healthy participants [44]. Similarly, for