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Review article

Basic and functional effects of transcranial Electrical Stimulation (tES)—An introduction

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ABSTRACT

Non-invasive brain stimulation (NIBS) has been gaining increased popularity in human neuroscience research during the last years. Among the emerging NIBS tools is transcranial electrical stimulation (tES), whose main modalities are transcranial direct, and alternating current stimulation (tDCS, tACS). In tES, a small current (usually less than 3 mA) is delivered through the scalp. Depending on its shape, density, and duration, the applied current induces acute or long-lasting effects on excitability and activity of cerebral regions, and brain networks. tES is increasingly applied in different domains to (a) explore human brain physiology with regard to plasticity, and brain oscillations, (b) explore the impact of brain physiology on cognitive processes, and (c) treat clinical symptoms in neurological and psychiatric diseases. In this review, we give a broad overview of the main mechanisms and applications of these brain stimulation tools.

1. Introduction

Over the past few decades, the introduction and development of non-invasive brain stimulation (NIBS) techniques have provided researchers and clinicians a valuable means to modulate activity of cerebral areas in humans and thereby contribute to the exploration of brain-behavior relations and develop treatment for various neurological and psychiatric disorders. NIBS has been shown to not only alter neural activity during application, but can also induce long-lasting alterations of cortical excitability and activity. Transcranial Electrical Stimulation (tES) and Magnetic Stimulation (TMS) are two of the most well-known forms of NIBS which influence neural activity based on different electromagnetic principles.

tES is a generic term that designates several techniques based on the modality of the applied electricity, which can be direct currents (transcranial direct current stimulation, tDCS), alternating currents (transcranial alternating current stimulation, tACS), or random noise currents (transcranial random noise stimulation, tRNS). tDCS, which is the most widely used form of tES, delivers weak direct currents to the scalp through two or more electrodes. tACS involves application of a balanced sinusoidal current across the scalp, and tRNS, a specific type of tACS, typically involves the application of a current which randomly fluctuates between a frequency range 0.1–640 Hz (Antal et al., 2008; Antal and Paulus, 2013; Deans et al., 2007; Helfrich et al., 2014b; Nitsche and Paulus, 2000; Nitsche and Paulus, 2001).

Acute effects of modern NIBS techniques distinguish tES from TMS, where the activation of neurons is pertinent. TMS induces high intensities of short-lasting electromagnetic currents in the cerebral cortex, which subsequently generate a supra-threshold activation of the neurons. In contrast, tES does not generate action potentials in neurons, but bi-directionally modulates their spontaneous firing activity via subthreshold alterations of resting membrane potentials (Barker et al., 1985; Nitsche and Paulus, 2000; Nitsche et al., 2003b; Purpura and McMurtry, 1965; Wagner et al., 2007). With regard to the after-effects, although the presumed induction procedure differs between respective stimulation protocols, which are theta-burst TMS, repetitive TMS (rTMS) and tDCS applied for some minutes, all are able to produce long-lasting facilitatory or inhibitory plastic changes in neural systems depending on the stimulation parameters (Dayan et al., 2013; George and Aston-Jones, 2010; Nitsche and Paulus, 2001; Rossini and Rossi, 2007; Rothwell, 1993). Concurrent application of stimulation with behavioral tasks is more difficult with rTMS compared to tES, as suprathreshold activations may inevitably disrupt task-relevant activity, whereas the subthreshold polarization induced by tDCS allows the online stimulation to enhance or reduce task-dependent neuronal activation. Whereas the spatial and temporal resolution of TMS is more superior, tES tools

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are generally more cost-effective, easier to operate, and easily adaptable for double-blind, sham-controlled studies. Both techniques are valuable adjunctive tools in neuroscience research and have the potential to overcome an inherent limitation of neuroimaging techniques: the difficulty to infer causal involvement of brain areas or functional networks in specific motor, perceptual, or cognitive processes.

In the following, we focus on tES as a re-introduced technique in the NIBS field. We first describe the main physiological mechanisms of excitability alterations and neuroplasticity induced by tES, which affect both regional and network levels. We then show some examples of how tES may be applied in healthy humans to alter cognitive and behavioral effects, or in patients to treat neurological or psychiatric disorders. In the last part of this introductory review, we discuss critical open questions and future directions of research.

2. tDCS − from the "classical" protocols

Electrical brain stimulation has a long history, starting from the ancient Greeks, who were using electric fish to treat migraine (Kellaway, 1946). In the same line, in the 11th century, the physician Ibn-Sidah suggested to treat epilepsy with a living electric catfish (Kellaway, 1946). With the introduction of the electric battery in the 18th century, it became possible to systematically evaluate and report clinical applications of transcranial stimulation for treatment of neurological and psychiatric conditions. Aldini applied electrical stimulation in a patient with major depression, and described that galvanic currents improved his mood (Parent, 2004). Direct current (DC) stimulation was routinely applied for the treatment of mental disorders during the 19th century and the early part of the 20th century, but because of many unknowns about its mechanisms of action and a lack of reliable neurophysiological markers, which led to variable and/or inconsistent results, its use became disregarded for a while from the 1930s (Parent, 2004). In the 1950s, DC (mostly pulsed currents) reappeared as a therapeutic technique to induce a sleep-like state (Smith, 2008). Animal studies in 1960s showed the ability of low intensity DC currents to modulate the firing rate of neurons and cortical excitability (Bindman et al., 1964). Cathodal stimulation of the rat's medial cortex abolished retention (Albert, 1966b) and anodal stimulation improved memory consolidation (Albert, 1966a). In 1964, psychological effects of 50–500 μA DC currents over the forehead region of 32 healthy subjects were systematically investigated. It was reported that anodal current increased alertness, mood and motor activity, while cathodal current induced quietness and apathy (Lippold and Redfearn, 1964). However, subsequent double-blind studies failed to replicate these findings (Sheffield and Mowbray, 1968). Lack of significant effects of polarizing currents may have been due to either observer expectation bias in Lippold and Redfearn's work (Lippold and Redfearn, 1964), or a small sample size in Sheffield and Mowbray's study (Sheffield and Mowbray, 1968). In 1964, in a preliminary clinical study, anodal currents (20–250 μA) were applied over the forehead of 29 chronic depressed patients who had failed to respond satisfactorily to other forms of interventions. Most of these patients showed clinical improvements and felt better during current application, and the effect was usually sustained for one or two days (Redfearn et al., 1964). These findings were also confirmed by double-blind clinical trials (Costain et al., 1964).

Direct evidence for the generation of electric potential difference over the cortex by transcranially applied pulsed currents was provided by recordings from deep EEG (electroencephalography) electrodes in three patients with temporal lobe epilepsy. Anodal current of 0.1–1.5 mA was applied bilaterally over the frontal poles of patients (four small electrodes, two placed over the frontal poles and two over the mastoids) and about 50% of the transcranially applied direct current was shown to reach the brain through the skull (Dymond et al., 1975). Despite several promising reports from the 1960s and 1970s, this technique was once again almost abandoned, likely due to the lack of evidence of direct physiological effects in humans. In 1980, it was shown that application of a brief, high voltage capacitative discharge to the scalp over the primary motor cortex could elicit cortico-spinal activations, and result in cortically elicited muscle twitches (Merton and Morton, 1980). Although this technique, termed transcranial electric stimulation (TES), marked a paradigm shift in physiological assessments of brain stimulation, it was also associated with uncomfortable perceptions by the subject, likely due to the passage of high intensity currents through dermal pain receptors. In 1985, Barker et al. devised the novel concept of TMS. This technique marked a further breakthrough in the field, as it circumvented the involvement of pain receptors due to application of a strong, short-lasting electromagnetic current. Supra-threshold activation of neuronal populations within the motor cortex using single-pulse TMS could elicit an involuntary muscular contraction (motor evoked potential − MEP), whose amplitude could be recorded electromyographically. This important TMS measure of corticospinal excitability made it possible to monitor changes in cortical excitability following plasticity induction protocols (Rothwell, 1993). As such, application of low-intensity tDCS as a non-invasive, painless, and well-tolerated brain stimulation technique in the intact human brain was renewed at the turn of the 20th century by the seminal studies of Priori et al. (1998) followed by work of Nitsche and Paulus (Nitsche and Paulus, 2000). These studies investigated the impact of tDCS on cortical excitability using TMS and showed that tDCS could induce polarity-dependent, prolonged shifts in cortical excitability. Since then, tES applications have increased across various research and clinical areas over the past decade, with over 700 publications in the last year alone (Bikson et al., 2016). Subsets of the tDCS technique have also been introduced, such as transcranial micropolarization technique developed by Russian researchers, which employs smaller electrodes (100–600 mm^2) with currents of less than 1 mA (Guleyupoglu et al., 2013; Nitsche et al., 2003a; Sheliakin et al., 2005). In 2008, Antal and co-workers developed the concept of applying an alternating current − tACS (Antal et al., 2008)—which was shown to effectively entrain endogenous brain oscillatory activity (Antal and Paulus, 2013; Deans et al., 2007; Helfrich et al., 2014b). These techniques have proven to be valuable in clinical and research settings. In the next section, we discuss the underlying physiological mechanisms of these techniques.

3. Physiology of tES

Transcranial direct current stimulation can induce both acute and neuroplastic alterations of cortical excitability at the macroscopic level. Duration and direction of these effects are determined by stimulation parameters such as current density, polarity, stimulation duration and/or geometrical montage of electrodes (Nitsche et al., 2008; Woods et al., 2016). Stimulation in the order of a few seconds only induces excitability alterations during intervention (Nitsche and Paulus, 2000). If, however, tDCS is conducted for some minutes, both anodal and cathodal stimulation are able to induce neuroplastic after-effects. For instance, long-lasting changes of cortical excitability are induced by applying 13 min of anodal tDCS and 9 min of cathodal tDCS (Nitsche et al., 2003b; Nitsche and Paulus, 2001).

The primary effect of tDCS is a subthreshold modulation of resting membrane potentials (Nitsche and Paulus, 2000). Depending on the orientation of the neurons relative to the direction of current flow, neuronal compartments are de- or hyper-polarized (Bikson et al., 2004). Early animal studies demonstrated that anodal or cathodal tDCS increased or decreased spontaneous neuronal activity, likely caused by subthreshold changes in membrane polarization (Bindman et al., 1964; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). Studies in humans hint for comparable effects.

Acute effects of anodal tDCS appear to primarily depend on changes in membrane potential. Pharmacological studies demonstrated elimination or reduction of anodal tDCS online effects (increase in cortical excitability) after calcium and sodium channels blockade (Nitsche et al.,

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