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Anodal transcranial pulsed current stimulation: A novel technique to enhance corticospinal excitability

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HIGHLIGHTS

- Transcranial pulsed current stimulation (tPCS) is a novel non-invasive neuromodulatory paradigm with less side effects compared to the conventional transcranial direct current stimulation (tDCS).
- Despite tDCS which modifies neuronal excitability by tonic depolarization of the resting membrane potential, tPCS modifies neuronal excitability by a combination of tonic and phasic effects.
- tPCS appears to be a promising tool for clinical neuroplasticity research as a new method of delivering transcranial stimulation for modulation of corticospinal excitability.

ABSTRACT

Objective: We aimed to compare the effects of anodal-transcranial pulsed current stimulation (a-tPCS) with conventional anodal transcranial direct current stimulation (a-tDCS) on corticospinal excitability (CSE) in healthy individuals.
Methods: CSE of the dominant primary motor cortex of the resting right extensor carpi radialis muscle was assessed before, immediately, 10, 20 and 30 min after application of four experimental conditions: (1) a-tDCS, (2) a-tPCS with short inter-pulse interval (a-$tPCS_{SIPI}$, 50 ms), (3) a-tPCS with long inter-pulse interval (a-$tPCS_{LIPI}$, 650 ms) and (4) sham a-tPCS. The total charges were kept constant in all experimental conditions except sham condition. The outcome measure in this study was motor evoked potentials.
Results: Only a-tDCS and a-$tPCS_{SIPI}$ ($P < 0.05$) induced significant increases in CSE, lasted for at least 30 min. Post-hoc tests indicated that this increase was larger in a-$tPCS_{SIPI}$ ($P < 0.05$). There were no significant changes following application of a-$tPCS_{LIPI}$ and sham a-tPCS. All participants tolerated the applied currents in all experimental conditions very well.
Conclusions: Compared to a-tDCS, a-$tPCS_{SIPI}$ is a better technique for enhancement of CSE. There were no sham effects for application of a-tPCS. However, unlike a-tDCS which modifies neuronal excitability by tonic depolarization of the resting membrane potential, a-tPCS modifies neuronal excitability by a combination of tonic and phasic effects.
Significance: a-tPCS could be considered as a promising neuromodulatory tool in basic neuroscience and as a therapeutic technique in neurorehabilitation.
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1. Introduction

Non-invasive induction of neuroplastic changes by transcranial stimulation techniques have been increasingly used in recent years. Apart from transcranial magnetic stimulation (TMS) and repetitive transcranial magnetic stimulation, which are neurostimulatory techniques, transcranial direct current stimulation (tDCS) is a well-known neuromodulatory technique. This technique has been involved in a number of important discoveries in the field of human cortical function and has become a well-established method for enhancing brain function in healthy participants (Antal et al., 2007; Boggio et al., 2006; Boros et al., 2008; Uy and Ridding, 2003) and patients with neurological conditions (Boggio et al.,

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2007; Fregni et al., 2005; Hummel et al., 2005; Benninger et al., 2010). The direction of corticospinal excitability (CSE) changes depends on the polarity of the active electrode. The application of anode over the target brain area is called anodal tDCS (a-tDCS) and it depolarizes the resting membrane potential and causes increased excitability. On the other hand, the application of cathode over the brain target area is termed cathodal tDCS (c-tDCS) and it hyperpolarizes the resting membrane potential and causes decreased excitability (Nitsche and Paulus, 2000). A recent systematic review and meta-analysis of the efficacy of a-tDCS in healthy individuals and people with stroke indicated a-tDCS effectively enhances CSE and motor performance (Bastani and Jaberzadeh, 2012). This review indicates that the induced CSE changes in both healthy participants and patients with stroke depend on current intensity and its duration of application (Nitsche and Paulus, 2000; Nitsche et al., 2003b; Nitsche and Paulus, 2001). Another parameter which may also affect the outcome of stimulation, and which is the focus of the current study, is current type.

The use of tDCS involves the employment of direct current, which is an uninterrupted flow of charged particles in one direction (Fig. 1a). Polarity, referring to two oppositely charged poles, one positive (+) and the other negative (−), determines the direction in which the current flows. Indeed, polarity in the context of electric current means "*charge imbalance*". If direct current is applied to the body via skin-mounted electrodes, there will be a build-up of ions under the electrodes. Under the cathode, due to the excess of positive ions such as sodium ions and its combination with water, acidic reactions may happen. Under the anode, there will be a corresponding accumulation of negatively charged ions such as chloride ions (Cameron, 2012; Michlovitz et al., 2005). Combination of these ions with water may produce a basic (alkaline) reaction under the anode. These acidic and basic reactions are called electrochemical effects of direct current (Ledger, 1992). The body's response to changes in pH of the skin is to increase blood flow to the area in an attempt to restore normal pH. Blistering or chemical burns may occur if normal pH cannot be maintained. These chemical reactions could be a source of sensory side effects of tDCS such as burning sensation, itching and tingling.

Transcranial alternating current stimulation (tACS) is another neuromudulatory paradigm which has been introduced to directly modulate human cortical excitability (Antal et al., 2008; Paulus, 2011; Zaghi et al., 2010; Kanai et al., 2010; Pell et al., 2011; Jung and Ziemann, 2009). It employs a continuous flow of charged particles in alternating directions, and the direction of flow cycles back and forth over time. This is a balanced current because alternating biphasic pulses have equal electric charges, therefore the net direct current component (NDCC), the average value of the voltage or current over application time, is zero. Compared to tDCS, tACS allows manipulation of CSE not only based on intensity, but also based on the frequency of the applied current. Unlike tDCS which its excitatory or inhibitory effects are polarity dependent, tACS effects are determined by the frequency of the current (Kanai et al., 2010; Zaghi et al., 2010) and are not polarity dependent. In addition, sinusoidal tDCS (tSDCS) (Antal et al., 2008) or slow oscillatory tDCS (so-tDCS) (Bergmann et al., 2009; Groppa et al., 2010) are modified protocols where the alternative currents are added to a DC offset. In tSDCS or so-tDCS, anodal or cathodal stimulation is sinusoidally modified at a given frequency. The tSDCS has a given single low or high frequency. However, so-tDCS is applied with a slow frequency range (Bergmann et al., 2009; Groppa et al., 2010; Kirov et al., 2009). A recent study by Antal et al. (2008) did not find any significant effects in CSE after application of both anodal or cathodal tSDCS to M1 of hand muscle (Antal et al., 2008).

Moreover, one known side effect for alternative, sinusoidal or oscillatory types of current is a very slight flashing of light in eyes. These light flashes – a phenomena characterized by the experience of seeing light without light actually entering the eye – are also known as phosphenes, or retinal phosphenes (Lakhanpal et al., 2003). Phosphenes can be directly induced by mechanical, electrical, or magnetic stimulation of the retina or visual cortex as well as by random firing of cells in the visual system (Kanai et al., 2008). It has been reported that phosphenes result from the normal activity of the visual system after being stimulated by other stimuli rather than light.

The current study was designed to investigate the effects of a new neuromodulatory paradigm which uses transcranial pulsed current stimulation (tPCS). In this paradigm, the tDCS was interrupted by a typical modern electrical stimulator to take advantage of two extra parameters, "pulse duration (PD)" and "inter-pulse interval (IPI)", which may dramatically affect the size of CSE. In this new neuromodulatory paradigm, the current flows in unidirectional pulses separated by an IPI instead of a continuous flow of direct current in tDCS. Even though the physiological mechanisms underpinning these effects are not understood yet, but it was assumed that the new paradigm induces its effects not only by polarity-dependent modulation of the baseline activity of the motor cortex, but also through the on–off nature of pulses on voltage gated carrier proteins (Bennett, 2000; Malenka and Bear, 2004; Rioult-Pedotti et al., 2000) in the membranes of M1 neurons.

The extent of activation within the cortex during tPCS may be influenced by a number of variables, including the size of the electrodes and their positions over the head; intensity and frequency of the pulses; the intervals between the pulses; output waveforms

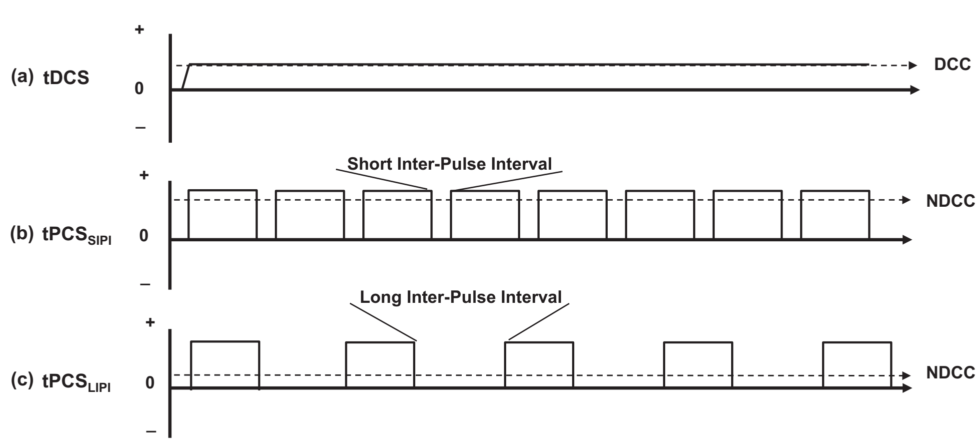

Fig. 1. (a) Transcranial direct current stimulation (tDCS), (b) tPCS$_{SIPI}$: transcranial pulsed current stimulation (short inter-pulse interval) and (c) tPCS$_{LIPI}$: transcranial pulsed current stimulation (long inter-pulse interval). DCC, direct current component; NDCC, net direct current component.

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