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Transcranial Direct Current Stimulation (tDCS) Enhances the Excitability of Trigemino-Facial Reflex Circuits

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) causes a tiny burning sensation through activation of local cutaneous trigeminal afferents.
Hypothesis: Trigeminal sensory inputs from tDCS may generate excitability changes in the trigemino-facial reflex circuits.
Objectives and Methods: Sixteen healthy volunteers were submitted to 20 minutes tDCS sessions with two types of electrode-montage conditions: 1. Real vs Sham 'bi-hemispheric' tDCS (cathode/anode: C4/C3), for blinded assessment of effects, and 2. 'uni-hemispheric' tDCS (cathode/anode: Fp3/C3), for assessment of laterality of the effects. Supraorbital nerve stimuli were used to obtain blink reflexes before, during (10 minutes from onset) and after (30 minutes from onset) the tDCS session. Outcome measures were R2 habituation (R2H) to repeated stimuli, the blink reflex excitability recovery (BRER) to paired stimuli and the blink reflex inhibition by a prepulse (BRIP).
Results: Real but not sham bi-hemispheric tDCS caused a significant decrease of R2H and leftward shift of BRER curve ($p < 0.05$ for all measures). The effects of uni-hemispheric tDCS on BRER and BRIP were larger on ipsilateral than on contralateral blink reflexes ($p < 0.05$). Excitability changes were still present 10 minutes after the end of stimulation in a lesser extent.
Conclusions: This study shows that 20 minute tDCS enhances the excitability of trigemino-facial reflex circuits. The finding of larger ipsilateral than contralateral effects suggests that sensitization through cutaneous trigeminal afferents adds on other possible mechanisms such as activation of cortico-nuclear or cortico-reticular connections.

Introduction

A large amount of scientific literature shows neuromodulatory effects of transcranial direct current stimulation (tDCS) on cortical excitability [1,2]. tDCS modifies the resting membrane potential of cortical neurons [3–5] and, consequently, the susceptibility of neurons to respond to timed excitatory or inhibitory synaptic inputs. Although low-intensity static field potentials generated by tDCS are considered not strong enough to depolarize cortical neurons to the extent necessary to produce action potentials in human axons [6], they certainly activate cutaneous fibers at the stimulation site to generate the burning sensation usually felt at the beginning of a tDCS session. In fact, the injection of depolarizing currents into single neurons may change the membrane potential to reach above threshold and generate propagated action potentials [7]. In rats and cats, surface polarization of the cortex modified the firing rate in deeper layers of cortical neurons [8–10].

Even if very mild, the sensation produced by tDCS indicates that activity is generated in cutaneous receptors and trigeminal axons, and that those inputs reach the central nervous system. The fact that the sensation diminishes after a few minutes may result from activation of central mechanisms of control over sensory inputs leading to adaptation or habituation, but action potentials are likely to continue reaching the central nervous system via the trigeminal nerve while the current is flowing. We hypothesized that the constant input

Abbreviations: tDCS, transcranial direct current stimulation; R2H, habituation of R2 response; BRER, blink reflex excitability recovery; BRIP, blink reflex inhibition by a prepulse; T0, baseline; T1, during; T2, after; NIBS, non-invasive brain stimulation; rTMS, repetitive transcranial magnetic stimulation; DBS, deep brain stimulation; PET, positron-emission tomography; rCBF, regional cerebral blood flow.

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of tDCS to trigeminal nuclei may have a sensitizing effect and lead to transient changes in excitability of reflexes mediated by the trigeminal nerve [11–13]. Alternatively, we should consider the possible descending modulation of brainstem reflex excitability through cortico-nuclear or cortico-reticular inputs [14], as shown in electrophysiological and neuroimaging studies performed in both animals [15,16] and humans [17,18].

In the study reported here, we examined the effects of tDCS on excitability of the trigeminal system through the study of trigemino-facial reflexes. We first ran a double-blind placebo-controlled experiment to study the effects of 'bi-hemispheric' tDCS on blink reflex excitability. Then, we reasoned that if excitability changes were due to direct afferent-mediated sensitization of the trigeminal nuclei, the effect would be more marked in the side ipsilateral to the stimulation, whereas if they occurred because of changes in the supranuclear control of brainstem excitability, the effects would be bilateral or predominate in the side contralateral to brain stimulation. Consequently, we studied the effects of 'uni-hemispheric' tDCS on the excitability of trigemino-facial reflex circuits of the two sides, to sort out which one of the two mechanisms was more likely.

Methods

Subjects

Sixteen healthy volunteers (aged 31.3 ± 4.4 yo, 26–39 yo, all subjects right-handed, 8 women) were recruited for this study to participate in two experiments. None of them had a history of neurological or systemic disease, or had been prescribed medication for at least three months prior to inclusion. They were instructed to remain calm and relaxed during the experiments. All participants signed a written informed consent which was approved by the Ethics Committee of the Hospital Clinic in line with the principles laid down in the Declaration of Helsinki.

Transcranial direct current stimulation (tDCS)

Subjects were seated on a comfortable chair in a dimly lit room. They were put on a suitable tDCS cap (StarStim, Neurolectrics, Barcelona, Spain). This cap has conveniently marked recording sites following the 10–20 EEG electrode position system where the stimulating electrodes are attached. Electrodes were enclosed in perforated sponge pockets (5 cm diameter) soaked with saline solution. The round sponges were attached to the inside of the cap in close contact with the scalp. A battery-driven constant current stimulator provided direct current at the pre-determined intensity and with the pre-determined composition: For 'real' stimulation, the intensity was set at 2 mA for a total stimulation time of 20 minutes, being increased at onset in a ramp-like manner [19,20] to 100% of output in 30 s. For 'sham' stimulation, the same parameters of slope and current output were used at the onset during 1 minute, while the offset was also configured in a ramp-like manner to achieve a good level of blinding between sessions [21].

Blink reflexes

Blink reflexes were recorded with a KeyPoint Net Electromyograph (Alpine Medical Instruments, USA). Surface silver/silver chloride 9-mm diameter recording electrodes were attached over both orbicularis oculi muscles with active electrode on mid inferior orbital rim and reference on the outer cantus of the eye. Surface electromyographic activity from orbicularis oculi was filtered at 20–2000 Hz. Stimulating electrodes were attached bilaterally over the supraorbital nerve to elicit the trigeminal blink reflex, with the cathode on the supraorbital notch and the anode 3 cm away, slightly lateral to the cathode on the frontal surface. The stimulus intensity was set to elicit a stable R2 response, usually about 4–6 times the sensory perception threshold, while the stimulus duration was set at 0.2 ms. Responses were recorded from both orbicularis oculi to unilateral supraorbital nerve stimuli.

We used three techniques to evaluate blink reflex excitability. First, we examined the habituation of the R2 response (R2H) by applying 7 consecutive single stimuli at a frequency of 0.2 Hz. The first sweep was excluded from further analysis to avoid contamination with a startle response [22]. Second, we examined the blink reflex excitability recovery (BRER) by applying pairs of conditioning and test supraorbital nerve stimuli at interstimuli intervals of 100, 200, 300, 400, 500, 600, 700, 800 and 900 ms, using the same stimulus intensity in both stimuli. We tested each interval twice for consistency of the results. Finally, we examined the blink reflex inhibition by a prepulse (BRIP). We applied electrical prepulses to the index finger 100 ms before the supraorbital nerve electrical stimuli of the ipsilateral side [23,24]. Prepulse was a low intensity somatosensory stimulus, usually less than 2 times the sensory perception threshold, which was noticed but unable to generate reflex responses on its own. Prepulses were randomly applied in 3 out of 6 trials.

Protocol setup

We divided the study in two experiments performed in different days. Each experiment was separated in two sessions randomly assigned. All sessions were performed at least 7 days apart to avoid possible interference from long-lasting after-effects of tDCS.

Experiment 1 was devised to test whether tDCS would exert a significant effect on blink reflex excitability and the duration of such effect. Stimulating electrodes were positioned over the scalp in a 'bi-hemispheric' montage with the anode placed on C3 and the cathode on C4. Blink reflexes were obtained from the right orbicularis oculi muscle to stimulation of the ipsilateral supraorbital nerve. R2H and BRER were examined in three time periods: (1) 'baseline' (T0), in which no direct current was applied; (2) 'during' (T1), in which examination began 10 minutes after the onset of stimulation; and (3) 'after' (T2), 10 minutes after the end of stimulation. Subjects were tested for either 'real' or 'sham' stimulation in separated sessions. An assistant selected the type of tDCS (condition real vs sham) in such a way that neither the investigator who performed the experiment nor the tested subject was aware of the tDCS condition.

Experiment 2 was devised to test whether the site of stimulation would play a significant role in the hypothesized change of excitability. We used a 'uni-hemispheric' tDCS montage with the anode placed on C3 and the cathode on Fp3 (i.e. at the left hemisphere). Blink reflexes were studied to both 'ipsilateral' (left) and 'contralateral' (right) supraorbital nerve stimulation. We studied BRER and BRIP at T0, T1 and T2, the latter being examined in a subset of 12 subjects.

Data analysis and reduction

Data were analyzed off-line blindly by the same person (CC), who did not have reference to the subject, date or condition of the exam. For the blink reflex, we measured off-line the area of the ipsilateral R2 response in $\mu V \times s$, using the automated system of the electromyograph. Then we calculated the R2H percentage by dividing the mean area resulting from averaging the three last responses by the area resulting from averaging the responses obtained in trials 2, 3 and 4, multiplied by 100. For BRER, we measured the area of the R2 response obtained to both, conditioning and test stimuli, and averaged off-line the values obtained in the two