

Effects of peripheral and cerebral electrical stimulation on maximal isometric strength of knee extensors: a randomized clinical trial

Efeito da estimulação elétrica periférica e cerebral na força isométrica máxima dos extensores do joelho: ensaio clínico aleatorizado

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RESUMO | INTRODUÇÃO: Recentes evidências têm demonstrado resultados bastante promissores para o uso de estratégias não invasivas de neuromodulação na melhora de habilidades físicas ou esportivas. A estimulação elétrica periférica (EEP) e a estimulação transcraniana por corrente contínua (ETCC) são técnicas não invasivas e não farmacológicas bastante utilizadas para modular a excitabilidade neuronal de áreas cortico-motoras e estimular a recuperação funcional. No entanto, poucos estudos têm investigado o efeito dessas técnicas na melhora do desempenho muscular. **OBJETIVO:** Investigar o efeito da estimulação elétrica periférica sensorial (EEPs) seguida de estimulação elétrica periférica motora (EEPm) ou estimulação transcraniana por corrente contínua (ETCC) na força isométrica máxima dos extensores do joelho em indivíduos saudáveis. **MÉTODO:** 20 universitários saudáveis foram distribuídos aleatoriamente em dois blocos distintos de 10 participantes cada: Bloco n°1 EEPs real + EEPm real ou EEPs simulada + EEPm real e bloco n°2 EEPs real + ETCC real ou EEPs simulada + ETCC real em uma única sessão. A contração voluntária isométrica máxima (CVIM) dos extensores do joelho foi avaliada por meio da dinamometria manual antes, durante e 10 min pós-estimulação. **RESULTADOS:** A CVIM dos extensores do joelho aumentou significativamente 10 minutos pós-ETCC isolada (diferença média = 0,23 N/Kg; IC 95% = 0,01 a 0,44 N/Kg; p = 0,04). A ETCC isolada também apresentou maior proporção cumulativa de respondedores seguido de EEPs+ETCC. **CONCLUSÃO:** A estimulação transcraniana por corrente contínua induz a aumentos significativos na CVIM em indivíduos saudáveis. No entanto, a aplicação prévia de estimulação elétrica periférica sensorial não impulsiona os efeitos da estimulação elétrica periférica motora ou cerebral na CVIM.

PALAVRAS-CHAVE: Ativação muscular. Desempenho físico funcional. Estimulação elétrica. Neuromodulação.

ABSTRACT | INTRODUCTION: Recent evidence has shown very promising results for the use of noninvasive neuromodulation strategies in improving physical strength or sports skills. Peripheral electrical stimulation (PES) and transcranial direct current stimulation (tDCS) are non-invasive and non-pharmacological techniques widely used to modulate neuronal excitability of corticomotor areas and to induce functional improvements. However, few studies have investigated the effect of these techniques on improving muscle performance. **OBJECTIVE:** To investigate the effect of sensory peripheral electrical stimulation (PESs) followed by motor peripheral electrical stimulation (PESm) or transcranial direct current stimulation (tDCS) on the maximal isometric force production of the knee extensors in healthy individuals. **METHODS:** Twenty healthy university students were randomly assigned to two distinct blocks with 10 participants in each block: 1) block n°1 PESs + PESm or sham PESs + PESm, 2) block n°2 PESs + tDCS or sham PESs + tDCS (each in a single session). The maximum voluntary isometric contraction (MVIC) of the knee extensors was evaluated by manual dynamometry pre-, during and 10 min post-stimulation. **RESULTS:** MVIC of the knee extensors was significantly increased 10 min post-tDCS alone (mean difference = 0.23 N/kg, 95% CI = 0.01 to 0.44 N/kg, p = 0.04). Isolated tDCS also had a higher cumulative proportion of responders, followed by PESs + tDCS. **CONCLUSIONS:** Transcranial direct current stimulation induces a significant increase in MVIC in healthy subjects. However, prior application of peripheral electrical stimulation does not compound the effects of peripheral electrical motor or cerebral stimulation.

KEYWORDS: Muscle activation. Physical function performance. Electrical stimulation. Neuromodulation.

Introduction

The use of techniques with ergogenic potential to improve physical performance is of extreme interest to athletes, coaches and researchers¹. This is particularly true of techniques which adhere to ethical criteria and are not harmful to an athlete's health. Noninvasive brain modulation techniques, such as transcranial direct current stimulation (tDCS), have shown promising results in enhancing motor performance both in healthy individuals^{2,3} and under pathological conditions⁴. tDCS is a modulation technique of cortical neuronal activity⁵ in which a low intensity direct current (1 a 2 mA) is applied to a specific region of the cortex through electrodes with moistened sponges positioned and fixed on the scalp. These polarized currents penetrate the skull and are capable of inducing facilitatory or inhibitory changes in neuronal excitability⁵ beyond the stimulation period⁶. Although the mechanisms of action are not fully understood, tDCS has been associated with synaptic and non-synaptic effects. At the neuronal level, facilitation or inhibition of neuronal excitability depends on the polarity of the electrical current. An anodal pole generally increases cortical activity and excitability, whereas a cathodal pole generally induces the opposite effect. tDCS is also capable of changing the synaptic microenvironment both through stimulation of specific neurotransmitters and receptors, and by modifying the excitability of intracortical and corticospinal neurons. At the non-neuronal level, changes in brain excitability may occur through prolonged neurochemical changes⁷. When applied over the primary motor cortex (M1), anodal tDCS increases the excitability of the corticospinal pathway and the motor unit recruitment strategy is increased both in quantity and quality⁸. Taken together, these effects make tDCS a potentially efficacious tool for the improvement of muscle performance and physical ability¹.

Recent evidence has shown that peripheral electrical stimulation (PES) can also modulate corticomotor excitability, with potential effects on the neuromuscular system. Sensory-level PES (PESs) induces changes in the direction of neuronal inhibition^{9,10} whereas motor-level PES (PESm) induces changes in the direction of neuronal facilitation¹⁰. The modulation of the primary motor cortex (M1) has relative spatial accuracy due to the stimulation of a specific or partial muscle¹¹, which may have important clinical implications. For instance, this stimulation may be effective under conditions where an increase in corticomotor excitability is desired, such as after a central nervous system (CNS) injury (e.g. stroke). Under these conditions, increased excitability of M1 could increase the cortical representation of specific weakened muscles and facilitate recovery of impaired motricity. In contrast, in situations where there is a movement disorder (dystonias) associated with motor hyperexcitability, decreasing the excitability of M1 via high or low frequency sensory electrical stimulation¹⁰ could improve the overall clinical condition.

Given the potential ergogenic or facilitatory effects of both tDCS and PES, previous studies have investigated whether the combination of these techniques may result in a compounded effect on cortical excitability^{11,12} or therapeutic response¹³. The possibility of greater increases in cortical excitability utilizing the combination of the two neuromodulatory techniques can be attributed to the principle of homeostatic plasticity (or metaplasticity)¹⁴. Given that both tDCS and PES are capable of modulating neuronal activity in M1, the addition of a facilitative technique (anodal tDCS or motor PES) with an inhibitory technique (sensory PES) may result in increased corticomotor excitability. This may consequently result in an increase in physical performance and sports skills. However, few studies have investigated the application of an inhibition technique (PESs) on a subsequent cortical neuronal activity facilitation

technique (PESm or tDCS) in healthy individuals and the resultant effect this compounded intervention may have on muscle performance. The hypothesis of the present study is that the application of an inhibitory technique (PESs) followed by a facilitatory technique (tDCS or PESm) will increase maximal strength of the quadriceps when compared to the application of isolated facilitatory techniques alone.

Methods

Sample

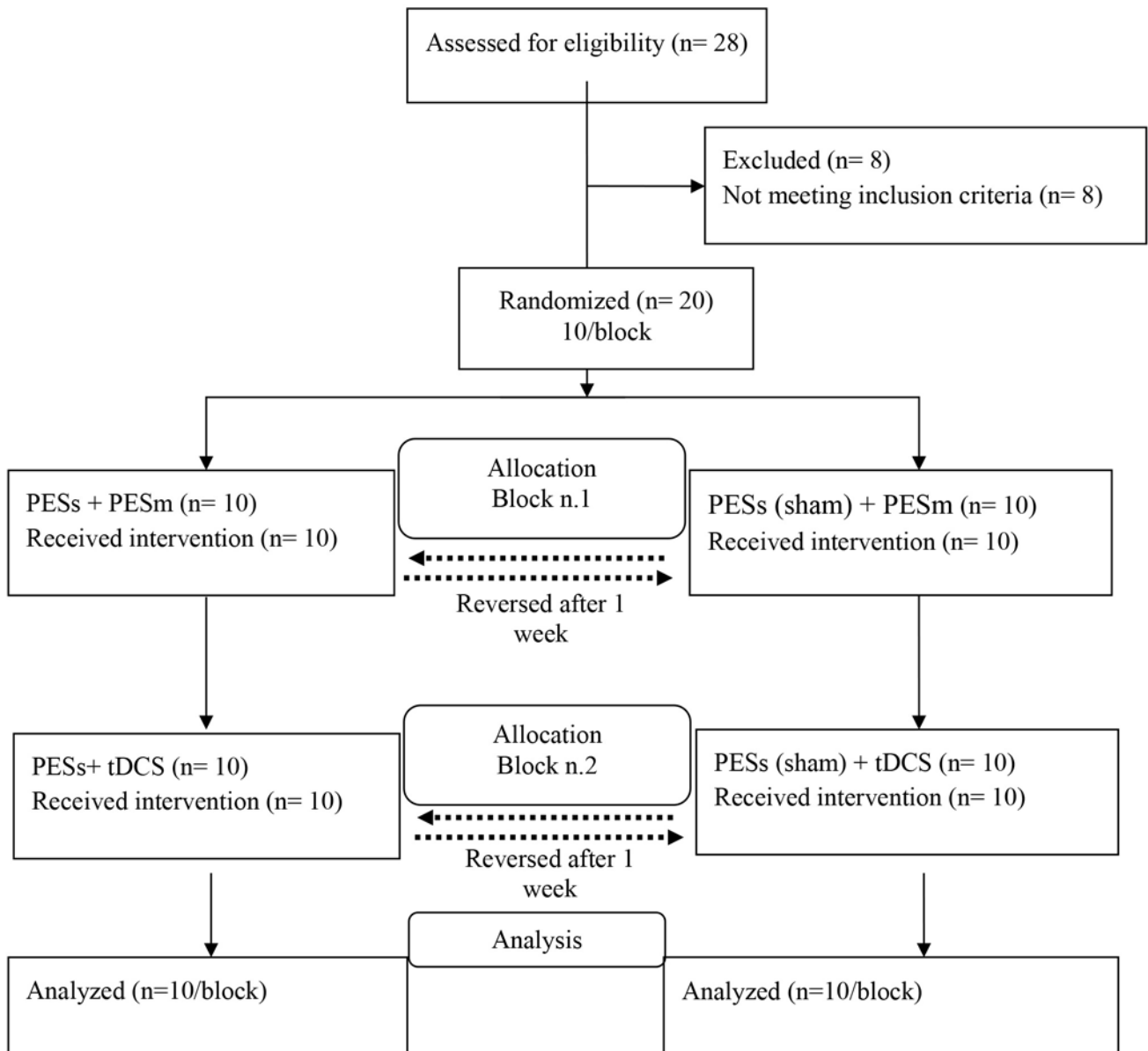
This study included 28 healthy university students of both sexes, aged between 18 and 34 years. Eight participants were excluded according to the following criteria: complaint of lower limb pain ≥ 3 according to the Numerical Pain Rating Scale (NRS 0-10), a medical diagnosis of musculoskeletal, neurological or psychiatric disorders, or epilepsy, a history of seizures, or seizures in the last 12 months. Twenty participants met the criteria and were included in the study. Sample size was estimated by power analysis¹⁵ based on previous studies that evaluated the immediate effect of tDCS on muscle performance in healthy individuals ($\alpha = 0.05$; $1 - \beta = 0.8$)¹⁶. According to the sample calculation data, a minimum value of 10 subjects per block was required, for a total of 20 participants ($n=10$ block #1 and $n=10$ block #2).

Study Design

This study was conducted at the pain neuromodulation and sensorimotor performance laboratory of the Federal University of Piau , Parna ba Campus, from March to May 2019. This is a randomized, double-blind, crossover, and placebo controlled clinical trial divided into two isolated experiments (Blocks 1 and 2).

The experiments were divided into two distinct blocks of 10 participants per block. Block 1: Participants were randomly assigned to two experimental groups: (1) Peripheral sensory electrical stimulation (PESs) associated with motor peripheral electrical stimulation (PESm), PESs + PESm, or (2) sham PESs + PESm. In the second block, 10 participants were also randomly assigned to two experimental groups: Block 2: (1) Peripheral sensory electrical stimulations (PESs) associated with transcranial direct current stimulation (tDCS), PESs + tDCS, or (2) sham PESs + tDCS (Figure 1). For each experimental block, an external collaborator utilized an online random number generator program (www.randomization.com) for randomization and individual opaque envelopes for allocation concealment. Initially, personal data, anthropometric characteristics, and general health data were collected through interviews using unstructured questionnaires. Subsequently, the maximal isometric voluntary contraction (MVIC) of the dominant quadriceps muscle was assessed by manual dynamometry¹⁷. Then the participants underwent peripheral electrical (sensory and/or motor) and cortical electrical stimulation. PESs (real and sham) were previously applied to PESm or tDCS. All electrical stimulation was applied only once in each block. Muscle strength was assessed at three different times: (1) pre-stimulation, (2) during stimulation, and (3) 10 min post-stimulation. The assessment of MVIC during tDCS and PES was performed after 13 and 10 min of stimulation, respectively. After a minimum interval of seven days, the stimulation between participants in each block was reversed. All evaluations were performed by a single evaluator who, like the participants, was unaware of which stimulation group they were participating in. This study was approved by the Research Ethics Committee of the Federal University of Piau  (n. 56009416.0.0000.5214) e registered on Clinicaltrials.gov (NCT03870139).

Figure 1. The flow diagram for study design. Participants from each block performed the interventions according to their allocations. After a minimum interval of seven days, the interventions were reversed in each allocation block, totaling 20 participants for each intervention (10/block)



Muscle strength evaluation

To assess muscle strength, three attempts at maximal voluntary isometric contraction (MVIC) of the dominant knee extensor muscles were assessed. All participants made two unrecorded attempts to familiarize themselves with the muscle strength assessment methods. To minimize the risk of muscle fatigue during MVIC, a 30 s rest interval was allowed for all participants. A manual dynamometer (Lafayette, USA) was placed on the tibia, on the anterior face of the leg, 5 cm above the lateral malleolus¹⁷. The participant remained seated on a stretcher and was instructed to perform a maximum knee extension contraction against the dynamometer for 5 s.

Interventions

Peripheral electrical stimulation

Sensory and motor PES was applied by means of a rectangular, biphasic, and asymmetric electric current equipment (Neurodyn III Ibramed, Brazil) using two self-adhesive electrodes (VALUTRODE 5 x 9 cm). The electrodes were positioned parallel to the quadriceps muscle, proximally to the rectus femoris muscle, and distally to the vastus medialis muscle of the dominant lower limb¹⁸. Sensory PES was applied for 30 min with the current intensity determined by the participant, considered strong but comfortable (maximum painless tingling), at a 10 Hz pulse rate and a 100 μ s pulse duration¹⁰. Motor PES was applied for 15 min with sufficient intensity to induce mild muscle contraction, with a frequency of 30 Hz, a pulse duration of 100 μ s, an on time of 4s, and an off time of 6 s¹⁰. The last 5 min were used for evaluation of quadriceps MVIC. The up and down ramps were maintained at 2 s. During the application, participants were asked about the intensity of the PESs and PESm (for real and sham stimulation) every 5 min. In all cases of sensory or motor habituation, the intensity was increased.

Sham PESs was applied with the same parameters as the PESs intervention, with the exception of the application time being only 30 s in duration. The sham PESs equipment had the same appearance as the real PESs equipment. After the initial 30 s of sham PESs, the current amplitude was gradually decreased over 15 s

until reaching zero, thus interrupting the emission of electric current. Participants were informed that the intervention could cause a slight tingling sensation or no sensation during the procedure¹³.

Transcranial direct current stimulation

Anodal tDCS was applied through a battery-powered (9 volt) direct current generator (Activados II, USA) using two electrodes measuring 5 x 7 cm (35 cm²) (Ibramed, Brazil) covered with a vegetable sponge, embedded with physiological saline solution, and fixed onto the head by means of velcro straps. The electrodes were mounted in accordance with the International 10-20 EEG System¹⁹ for more effective focalization of the primary motor cortex. The positively charged electrode (anode) was positioned at C3 or C4 (contralateral to the dominant limb) and the negatively charged electrode (cathode) was positioned at the ipsilateral supraorbital region of the dominant limb³. Active tDCS was applied with an electric current intensity of 2 mA, and an electric current density of 0.057 mA/cm², for 15 min. During the application of the tDCS, the participants remained at rest. After 13 min of stimulation, the MVIC evaluation was performed. This 13 min period of stimulation was chosen based on previous studies showing this was the minimum time necessary to achieve increased cortical excitability for up to 90 min⁶.

Statistical Analyses

Body mass (Kg) normalization of the means of the three peak force measurements was performed for each participant²⁰. Differences in MVIC of the knee extensor muscles (dominant limb) for each stimulation intervention (PESs + PESm or sham PESs + PES and PESs + tDCS or sham PESs + tDCS) and at each time sampled (pre-, during, and 10 min post-stimulation) were analyzed by two-way analysis of variance with repeated measures (2 x 3 ANOVA). The sphericity of the data was evaluated by the Mauchly test, being considered when the assumption values were above 0.05. In cases of non-compliance, the Greenhouse-Geisser correction was applied. Post hoc tests with Bonferroni corrections were used when necessary. Significance level was set at $p < 0.05$. The analysis of the cumulative proportion of responders with different cutoffs points was performed according to Farrar et al.²¹ The analyses were performed using the software program IBM SPSS v. 20 for Windows.

Results

The characteristics of the participants included in the study are described in Table 1. No adverse effects or reactions were reported during or after the application of the intervention protocols. Paired t-tests did not show any differences between MVIC means at pre-PESs ($t(9) = 0.21, p = 0.84$) or pre-tDCS intervals between the first and second week ($t(9) = -0.20, p = 0.85$).

Table 1. Participant characteristics

	PESs+PESm/PESm	PESs+tDCS/tDCS
Sex M n (%)	10 (100)	7 (70)
Age (years)	19.9 ± 1.4	23.8 ± 4.0
Weight (Kg)	70.3 ± 11.9	78.2 ± 22.9
Height (m)	1.8 ± 0.1	1.7 ± 0.1
BDI (Kg/m ²)	22.8 ± 3.4	25.8 ± 7.4
Physical activity n (%)	9 (90)	6 (60)

M: Male sex. PESs: Sensory peripheral electrical stimulation; PESm: Motor peripheral electrical stimulation; tDCS: Transcranial direct current stimulation; BDI: Body mass index. Continuous variables expressed as mean and standard deviation (SD).

Sensory PES + motor PES

Analysis of variance with repeated measures showed no significant effect of stimulation factors ($F(1, 9) = 0.01; \eta^2_p = 0.001; p = 0.91$) or time ($F(2, 18) = 0.66; \eta^2_p = 0.069; p = 0.53$). There was also no significant stimulation x time interaction ($F(2, 18) = 0.45; \eta^2_p = 0.048, p = 0.64$). The graphical analysis of the cumulative proportion of responders showed no differences in the proportion of participants who achieved an increased MVIC during the PESs + PESm period compared to the isolated PESm (Figure 2). Ten minutes post-stimulation, isolated PESm presented low, but there was a higher proportion of responders at 5 and 10% cut-off points in relation to PESs + PESm (Figure 3).

Figure 2. Analysis of the cumulative proportion of responders. Increased maximal isometric voluntary contraction (MVIC) over the pre-stimulation interval, during transcranial direct current stimulation (tDCS), combined sensory peripheral electrical stimulation (PESs) with tDCS, PESs combined with peripheral motor electrical stimulation (PESm), and isolated PESm. Cutoff points at 5, 10, and 15% increases in MVIC

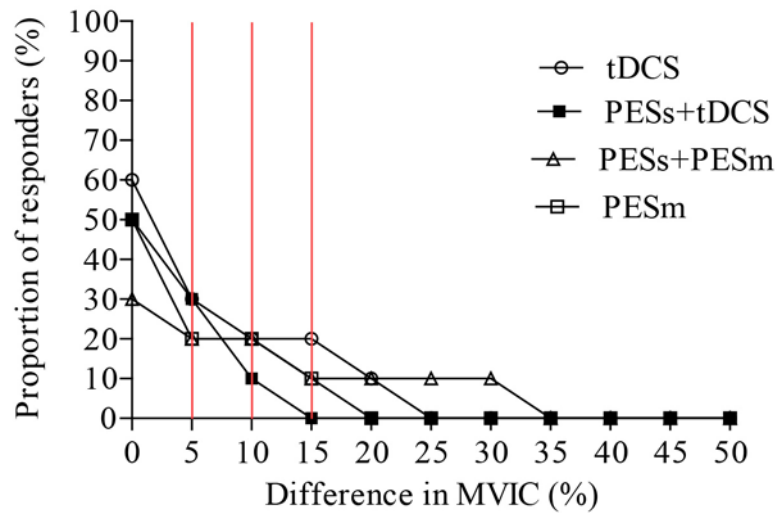
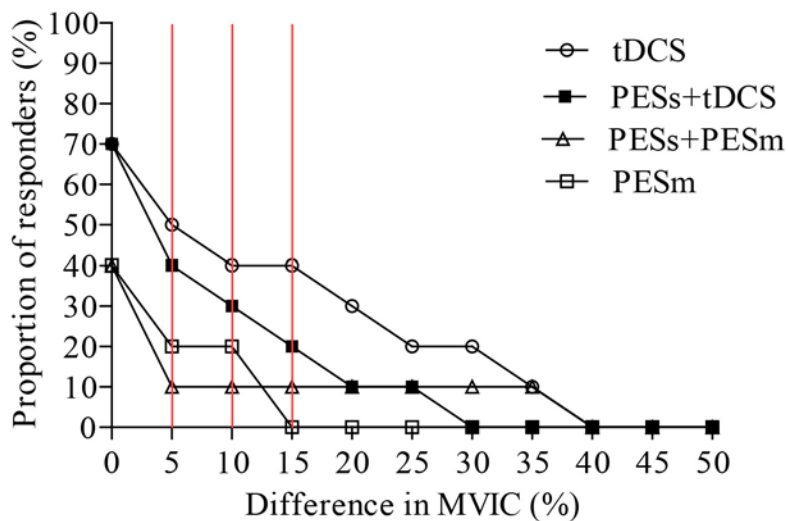


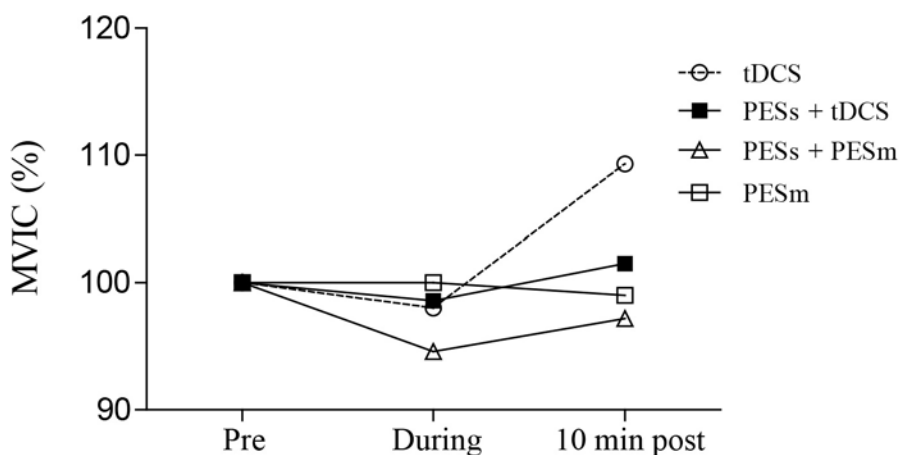
Figure 3. Analysis of the cumulative proportion of responders. Increased maximal isometric voluntary contraction (MVIC) over pre-stimulation interval, 10 min post transcranial direct current stimulation (tDCS), combined sensory peripheral electrical stimulation (PESs) with tDCS, PESs combined with peripheral motor electrical stimulation (PESm), and isolated PESm. Cutoff points at 5, 10, and 15% increase in MVIC



Sensory PES + tDCS

Analysis of variance with repeated measures showed no significant effect of the stimulation factor ($F(1, 9) = 1.28$; $\eta^2_p = 0.125$; $p = 0.28$). However there was a significant effect of the time factor ($F(2, 18) = 4.46$; $\eta^2_p = 0.331$; $p = 0.03$). There was also no significant stimulation x time interaction ($F(2, 18) = 0.66$; $\eta^2_p = 0.069$, $p = 0.52$). Bonferroni corrections for multiple comparisons showed no significant intragroup differences between the pre-, during, and 10 min post-stimulation intervals for PESs + tDCS or isolated tDCS. However, significant intergroup differences were identified within 10 min post-tDCS (mean difference = 0.23 N/Kg; IC 95% = 0.01 a 0.44 N/Kg; $p = 0.04$). tDCS alone presented with a 9.3% increase over the pre-stimulation interval. tDCS combined with peripheral sensory stimulation (PESs + tDCS) showed no significant increases (Figure 4).

Figure 4. The effect of sensory peripheral electrical stimulation (PESs) sequentially combined with motor peripheral electrical stimulation (PESm). Isolated PESm; sensory peripheral electrical stimulation (PESs) sequentially combined with transcranial direct current stimulation (tDCS) and isolated tDCS in maximal isometric voluntary quadriceps contraction. Values normalized by the pre-stimulation condition



Ten minutes after the end of the stimulation, the graphical analysis of the cumulative proportion of responders showed that a higher proportion of participants achieved an increase in MVIC during the tDCS, followed next by PESs + tDCS, PESs + PESm, and PESm (Figure 3).

Discussion

According to our review of the currently available literature, this is the first study to evaluate the effect of motor (PESm) and cerebral (tDCS) stimulation combined with prior application of sensory electrical stimulation (PESs) on the maximal isometric strength of the knee extensor muscles in healthy individuals. We analyzed quadriceps MVIC modulation during and after the application of sensory stimulation followed by motor stimulation (PESs + PESm), brain stimulation (PESs + tDCS), isolated motor stimulation (sham PESs + PESm), and isolated brain stimulation (sham PESs + tDCS). Analysis of the results did not reveal significant differences in the maximal isometric force of the dominant quadriceps during and 10 min after the application of the combined techniques, or when utilizing isolated PESm. However, the application of isolated anodal tDCS led to a 9.3% increase in MVIC of the dominant quadriceps after 10 min of stimulation, when compared to basal conditions (pre-stimulation). These results indicate that PESs previously applied to PESm or tDCS do not induce significant increases in MVIC in healthy individuals. The increase in isometric force via tDCS observed in our study and previous studies with healthy subjects^{2,3} or in pathological

conditions²² may be related to changes in motor unit recruitment strategy and/or the efficiency of neuromuscular responses^{8,23}.

The absence of any effect of PESm alone or combined with PESs was not expected in this study, and can likely be attributed to the methodological parameterization. Previous studies have shown that 30 min of PESm at a 30Hz frequency, a 100µs pulse duration, and a sufficient current amplitude to induce muscle contractions with joint movement can significantly increase excitability in M1¹⁰. Although we have used the same pulse frequency and duration parameters in this study, the magnitude of the amplitude used induced only minor muscle contractions. In addition, the short period of PESm, restricted in the present study to MVIC tests, may have been insufficient to induce changes in the excitability of M1²⁴. Taken together, the parameterization of the PESm used in this study may have been insufficient to increase cortical excitability²⁵ and induce significant changes in the muscle recruitment strategy.

When interpreting our data for clinical significance, graphical analysis of the cumulative proportion of responders showed very promising results for PESs combined with tDCS. Ten minutes after the different stimulation techniques, more participants increased their MVIC by 5, 10%, and 15% compared to the baseline condition via isolated tDCS, followed next by PESs + tDCS and then PESs + PESm and PESm (Figure 3). According to the principle of homeostatic plasticity (or metaplasticity) the addition of a neuronal excitability inhibition technique with another facilitation technique may result in greater

excitability in M1¹⁴. Both tDCS and peripheral electrical stimulation (PES) are able to modulate neuronal activity in M1, promoting transient or non-transient neuroplastic effects. Anodal tDCS increases neuronal excitability^{5,6}, whereas excitability in M1 via PES is dependent on stimulation parameters. High or low frequency sensory level stimulation (PESs) decreases neuronal excitability^{9,10}, and low-frequency motor-level stimulation (PESm) increases neuronal excitability¹⁰.

This concept detailed above relies on the principles of homeostatic plasticity with sequential neuromodulatory application²⁶, and, as in our study, can be applied using concomitant neuromodulatory techniques^{12,13}. Previous studies have also shown that the application of tDCS followed by PESs can induce increased excitability in M1, which is opposite of the sequence used in our study (PESs followed by tDCS)¹¹. In our experiment, the previous application of PESs followed by tDCS may have resulted in a higher excitability in M1 and, consequently, influenced the MVIC. This is supported by our observation that a higher proportion of responders were found in the PESs + PESm intervention than in PESm alone. However, these results should be interpreted with caution, since the parameterization of the PESm may have been insufficient to induce changes in corticomotor excitability and, consequently, in the task of maximal isometric contraction of the dominant knee extensor muscles.

Differences between the statistical significance and the clinical significance found in our result are likely attributed to several methodological limitations: 1) a low sample size, 2) a low current amplitude implemented during PESm, 3) the PESm stimulation time being restricted to the evaluation period of the MVIC, and 4) a high variability in tDCS. Specifically addressing the tDCS limitation, several factors have been pointed to as modifiers of cortical excitability. These include a sedentary lifestyle, age, level of attention, gender, use of centrally acting drugs, genetic factors, and time of day²⁷, in addition to electrode size and current density. Finally, although the hypothesis of this study is based on the assumption that we would be increasing or decreasing corticomotor excitability via peripheral and cerebral electrical stimulation, the present study did not directly evaluate neurophysiological measures of cerebral excitability.

Conclusion

Transcranial direct current stimulation induces a significant increase in MVIC in healthy subjects. However, prior application of peripheral electrical stimulation does not compound the effects of peripheral electrical motor or cerebral stimulation.

Authors contribution

All authors substantially contributed to the revision and its reporting, approved of the final version of the manuscript and agree to be accountable for all aspects of the work. Santos GAC, Souza TBS, Benício RVR, Araújo BJM, Dias FICR e Fontenele ARB contributed to data collection, literature search and writing. Cavalcante PGL e Hazime FA contributed to the overview methodological quality, study design and writing

Conflicts of interest

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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