CHAPTER

Brain stimulation and physical performance

17

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Abstract

Non-invasive brain stimulation techniques have been used for decades to study brain function and for the treatment of various neurological disease. These techniques involve the passage of electrical current or magnetic field in a controlled manner to a targeted brain area. Recently, experimental studies explored the application of transcranial direct current stimulation (tDCS) for the improvement of physical performance in healthy individuals. In this chapter we reviewed and analyzed the current scientific literature, highlighted methodological limitations and also suggested possible neurophysiological mechanisms. The chapter also provides some technical and theoretical research-based principles for future research, to promote a better understanding of potential and caveats of this emerging field. Finally, ethical and regulatory issues related to performance enhancement via non-invasive brain stimulation are also discussed.

Keywords

Brain stimulation, Doping, Enhancement, Fatigue, Performance, Sport, Training, Transcranial direct current stimulation, tDCS

1 INTRODUCTION

Non-invasive brain stimulation (NIBS) has been widely used in neuroscience research to induce transient and controlled changes in the activity of a given brain region or network in order to study its role on a specific motor, cognitive or

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perceptual process. The two most common used techniques are transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). The basic principles and applications of TMS and tES have been previously covered in many excellent review articles (Hallett, 2007; Pascual-Leone and Tormos-Muñoz, 2008; Rossini et al., 2015; Stagg and Nitsche, 2011; Wagner et al., 2007a,b).

TMS delivers a rapid (approximatively 100–200 μs) and strong magnetic field via a coil placed over the targeted brain area. The magnetic field then penetrates the scalp and causes a rapid depolarization of the neuronal tissues (Hallett, 2007; Wagner et al., 2007a). In simple words TMS induces action potentials on the targeted neurons, making neurons fire. On the other hand, tES involves the application of weak electrical current through two or more electrodes placed over the scalp, for usually around 20 min period. Many types of tES have been developed, such as transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and transcranial direct current stimulation (tDCS) which represent the most widely used tES technique. Compared to TMS, tDCS induced electric field is too weak to generate action potentials but, by inducing a polarization of neurons, it is able to modulate resting membrane potential (Stagg and Nitsche, 2011; Wagner et al., 2007a,b). The result is an alteration (i.e., increase or decrease) of spontaneous firing rate of neurons affected by the electric field (Bikson et al., 2004; Rahman et al., 2013), leading to the notion of tDCS (and tES in general) being a "neuromodulatory" rather than a "neurostimulation" technique. The effect of tDCS is also polarity dependent, with an excitatory effect induced under the anodal electrode (a-tDCS) and an opposite effect under the cathodal (c-tDCS) as reflected by, respectively, an increase or decrease of corticospinal excitability as measured via motor evoked potentials (MEPs) elicited by single pulse TMS delivered on the primary motor cortex (Nitsche and Paulus, 2001, 2000). A placebo (sham) tDCS (s-tDCS) condition is typically applied as blinding procedure. Based on the same hardware setup, s-tDCS is delivered at the same stimulation intensity of real tDCS (usually between 1 and 2 mA) but only for the first 30–60 s of stimulation period. More recently, High-Definition transcranial direct current stimulation (HD-tDCS) has been introduced. Contrarily to tDCS which uses large sponge electrodes, HD-tDCS targets brain regions by using arrays of small gel-based electrodes over the scalp. tDCS is currently used for the treatment of various neurological (Fregni and Pascual-Leone, 2007) and psychiatric disorders (Kuo et al., 2014), to study brain function (Filmer et al., 2014; Polanía et al., 2018) and for cognitive enhancement in healthy individuals (Santarnecchi et al., 2015).

In recent years, researchers have begun investigating whether tDCS can be used to enhance physical performance in healthy individuals. To date, the number of studies is limited and the mechanisms by which tDCS might improve physical performance are largely unknown (Angius et al., 2017; Colzato et al., 2017). Nevertheless, several tDCS devices are available to the public and numerous professional athletes claim to have adopted tDCS during their training programs (Edwards et al., 2017; Reardon, 2016). Even more worrisome, a do-it-yourself (DYI) movement has

rapidly grown, with kits and instruction on how to build tES devices available on online forums and social media (Wexler, 2016). Some authors have already argued that tDCS may be considered a new form of doping (Davis, 2013; Edwards et al., 2017; Reardon, 2016), even though skepticism about the validity and reproducibility of tDCS effects have been also raised (Horvath et al., 2015a,b).

The main aim of this article is to review the existing literature on the ergogenic effects of tDCS. Potentially relevant articles were retrieved by performing a search on PubMed and Google Scholar databases without temporal restrictions. The following terms "performance," "physical exercise," "cycling," "effort," and "strength" were individually combined with "transcranial electrical stimulation", "transcranial direct current stimulation" and/or other acronyms. References from the retrieved material were examined for relevant publications. We included experimental studies that met the following criteria: (i) Single application of tDCS prior or during physical tasks; (ii) Physical tasks consisting of single-joint exercise or whole-body exercise; (iii) Physical performance was measured objectively, e.g., as endurance time, total work performed, and force production during a maximal voluntary contraction (MVC); (iv) Studies involving healthy individuals; (v) Original peer-reviewed articles written in English. We intentionally excluded (i) studies investigating the effects of tDCS on basic motor behavior (e.g., grip strength, small muscle groups, dexterity, etc.), as not indicative of physical performance in athletes, (ii) review articles, and (iii) single case studies. The final selection comprised 28 studies. For each study, the following details were retrieved: (i) number and participants details, (ii) tDCS montage and stimulation protocol, (iii) experimental design, (iv) exercise protocol, and (v) performance outcomes.

The review is structured by separating the literature in two main categories: (i) studies on the effects of tDCS on performance during single-joint exercise and (ii) studies on the effects of tDCS on performance during whole-body exercise. This distinction was necessary because these physical tasks differ in terms of cardiorespiratory, metabolic, and neuromuscular responses (Sidhu et al., 2013). Each category was further divided into submaximal physical tasks requiring endurance capacity, and physical tasks requiring maximal strength/power or anaerobic work capacity. After reviewing each study and summarizing the literature, we provide suggestions for future research based on the gaps in the existing literature, also briefly considering ethical and regulatory issues associated with the use of tDCS to enhance physical performance in athletes.

2 EFFECTS OF tDCS ON PHYSICAL PERFORMANCE

2.1 SINGLE-JOINT EXERCISE

A summary of the reviewed studies is shown in Table 1.

Table 1 List of Experimental Studies Involving Single-Joint Exercise

Study	Sample	Anode/ Cathode Location	Active Electrode Size (cm^2)	Stimulation Intensity (mA)	Stimulation Duration (min)	Blinding	Muscle Investigated	Online/ Offline	Exercise Protocol	Performance Outcome
Cogiamanian et al. (2007)	Study 1: EXP group (5♀, 4♂), CON group (9♀, 6♂). Study 2: 1♀, 5♂	Anode right M1/cathode right shoulder	35	1.5	10	Control	Left elbow flexors	Offline	Isometric TTF at 35% MVC	↑ Endurance time
Kan et al. (2013)	15♂	Anode right M1/cathode right shoulder	24	2	10	Sham	Elbow flexors	Offline	Isometric TTF at 30% MVC	No improvement
Muthalib et al. (2013)	15♂	Anode right M1/cathode right shoulder	24	2	10	Sham	Left elbow flexors at 90° flexion	Offline	Isometric TTF at 30% MVC	No improvement
Williams et al. (2013)	9♀, 9♂	Anode right M1/cathode left forehead	35	1.5	20	Sham	Left elbow flexors	Online	Isometric TTF at 20% MVC	↑ Endurance time
Hendy and Kidgell (2014)	5♀, 5♂	Anode left M1/cathode right supraorbital area	25	2	20	Sham	Wrist extensor muscles	Online	Four sets of six repetitions at 70% 1RM	↑ Strength of the untrained wrist extensor muscles
Montenegro et al. (2015)	14♂	Anode non-dominant M1/cathode Fp2	35	2	20	Sham	Lower limb	Offline	Concentric contraction of knee extensors and flexors muscles at 60° s^{-1} of dominant limb	No improvement

Abdelmoula et al. (2016)	3♀, 8♂	Anode left M1/cathode right shoulder	35	1.5	10	Sham	Left elbow flexors	Offline	Isometric TTF at 35% MVC	↑ Endurance time
Angius et al. (2016)	9♂	Active electrode both M1/ reference both ipsilateral shoulder	35	1.5	10	Sham and cathode	Lower limbs	Offline	Isometric TTE at 20% MVC	↑ Endurance time
Lattari et al. (2016)	10	Active F3/ reference Fp2	35	2	20	Sham and cathode	Lower limbs	Offline	10 Maximum repetition loads	↑ Number of repetitions
Oki et al. (2016)	8♀, 5♂	Anode right M1/cathode left forehead	35	1.5	20	Sham	Elbow flexors	Online	Isometric TTF at 20% MVC	↑ Endurance time
Sales et al. (2016)	19♂	Anode T3/ cathode Fp2	35	2	20	Sham	Knee extensor muscle	Offline	Two sets of five repetitions each, at 60° s^{-1} and 180° s^{-1}, 60 s rest between sets	↑ Total work
Washabaugh et al. (2016)	7♀, 15♂[a]	Anode contralateral M1/cathode right supraorbital area	35	2	12	Sham	Knee extensor muscle	Online	24 sets with Intermittent isometric 10 s contraction on 5% MVC with 20 s recovery	↑ Knee extension torque
Flood et al. (2017)	12♂	HD-tDCS[b]	—	2	20	Sham	Elbow flexors	Offline	Isometric TTF at 30% MVC	No improvement
Frazer et al. (2017)	5♀, 8♂	Right M1/left contralateral supraorbital area	25	2	20	Sham	Left biceps brachii	Offline	Four sets of six to eight reps at 80% 1RM with 3 min recovery	↑ Strength of the untrained limb

Continued

Table 1 List of Experimental Studies Involving Single-Joint Exercise—cont'd

Study	Sample	Anode/ Cathode Location	Active Electrode Size (cm^2)	Stimulation Intensity (mA)	Stimulation Duration (min)	Blinding	Muscle Investigated	Online/ Offline	Exercise Protocol	Performance Outcome
Hazime et al. (2017)	8♀	Anode contralateral M1/cathode ipsilateral supraorbital area of exercising limb	35	2	20	Sham	Internal and external shoulder rotator muscles	Offline	MVC	↑ MVC
Oki et al. (2017)	7♀, 4♂	Anode right M1/cathode left forehead	35	1.5	20	Sham	Elbow flexors	Online	MVC	No improvement
Radel et al. (2017)	9♀, 13♂	HD-tDCS[c]	—	2	≤20	Sham	Elbow flexors	Online	Isometric TTF at 35% MVC	No improvement
Vargas et al. (2018)	20♀	Anode M1 contralateral to exercising limb/cathode ipsilateral supraorbital region of the dominant limb	35	2	13	Sham	Knee extensor muscle	Online	Five knee extensor MVCs for both dominant and non-dominant limb	↑ MVC dominant limb
Ciccone et al. (2018)	10♀, 10♂	Anode T3/ cathode Fp2 Anode T4/ cathode Fp1	25	2	30	Sham	Knee extensor muscle	Online	50 repetitions at 90° knee extensor maximal contractions at 180° s^{-1}	No improvement
Lattari et al. (2018b)	15	Active F3/ reference Fp2	35	2	20	Sham and cathode	Knee extensor muscle	Online	10 Maximum repetition loads	↑ Volume load

↑ (increased); central midline (Cz); left temporal cortex (T3); maximal dynamic strength (1RM); maximal voluntary contraction (MVC); peak power output (PPO); prefrontal cortex (PFC); premotor cortex (PMC); primary motor cortex (M1); right frontopolar (Fp2).

[a]*Subjects were randomly assigned to: tDCS-Matching (n = 10), with stimulation while performing low-level force matching task or tDCS-Resting (n = 12), with stimulation administered at rest.*

[b]*HD-tDCS: electrodes were placed in a 4 × 1 ring configuration. Anode over non-dominant M1/cathodes 5 cm around anode.*

[c]*HD-tDCS: electrodes were placed in a 4 × 1 ring configuration. Anode over AF4 for PFC/cathodes 3.5 cm around anode. Anode over C2 for the PMC/cathode 3.5 cm around anode.*

2.1.1 Endurance

To the best of our knowledge, Cogiamanian et al. (2007) performed the very first study investigating the acute effect of tDCS on physical performance. This study involved a parallel group design and comprised two separate experiments. In the first experiment, participants were allocated to two different groups (experimental and control) with both performing two isometric endurance tests of the elbow flexors at 35% of the MVC force interspaced by 60 min of recovery. Prior to the second endurance test, the experimental group received either a-tDCS or c-tDCS over the ipsilateral primary motor cortex (M1) for 10 min at 1.5 mA, while the control group did not receive any tDCS. The second experiment involved a different group of participants and was performed to monitor the corticospinal responses following a-tDCS. Endurance time after a-tDCS was significantly longer (~15%) compared to the endurance time after c-tDCS and the endurance time of the control group. No differences in the electromyographic (EMG) activity during the endurance test and in muscle fatigue after the endurance test were found between conditions and groups. In the second experiment, corticospinal excitability was increased compared to baseline after a-tDCS, as documented by the higher amplitude of MEPs.

Other similar experimental studies (Abdelmoula et al., 2016; Flood et al., 2017; Kan et al., 2013; Muthalib et al., 2013) were performed using the study protocol originally designed by Cogiamanian et al. (2007). These involved a crossover design including a-tDCS and s-tDCS. Abdelmoula et al. (2016) reported an improvement in endurance time (~8%) following a-tDCS, with no changes in torque variability, EMG activity and corticospinal excitability of the elbow flexor/extensor muscles. On the other hand, other authors did not report any significant improvement in endurance time following a-tDCS (Flood et al., 2017; Kan et al., 2013; Muthalib et al., 2013).

In another crossover experiment, Williams et al. (2013) investigated the effect of a-tDCS on performance during an isometric endurance test of the elbow flexors muscles at 20% of the MVC force. No improvement in endurance time was initially found compared to s-tDCS. Subsequently, the researchers divided participants into two sub-groups: one group where the endurance test exceeded the tDCS stimulation period (part-time stimulation group) and a second group where the endurance test was shorter than the tDCS stimulation period (full-time stimulation group). Full-time stimulation group performed for longer during the endurance test (31%) and exhibited a greater increase in muscle fatigue (6%) immediately after the endurance test (5%) compared to s-tDCS. Moreover, no significant changes in corticospinal excitability were observed between conditions and groups, while a significant decrease in ratings of perceived exertion (RPE) in the full-time stimulation group was found compared to s-tDCS.

In a placebo controlled crossover experiment, Angius et al. (2016) were the first to examine the effect of a-tDCS on performance during an isometric endurance test of the knee extensor muscles at 20% of the MVC force. This study also sought to monitor the neuromuscular responses following a-tDCS and to compare the effects of two tDCS montages on endurance performance. In both montages the anodal

electrode was placed over the left M1 (contralateral to the exercising limb), while the cathode was placed either in one montage over the ipsilateral shoulder (extracephalic montage) or the right dorsolateral prefrontal cortex (cephalic montage). Longer endurance time was reported only when an extracephalic montage was applied. No significant changes in corticospinal excitability, voluntary activation level, and MVC force following a-tDCS and after the endurance test were found. During the endurance test, no changes in heart rate (HR), muscle pain and EMG activity were found. However, RPE was significantly lower when the extracephalic montage was applied.

The effect of a-tDCS has been also investigated in older healthy adults by Oki et al. (2016). Participants were asked to perform an isometric endurance test of the elbow flexor muscles at 20% of MVC force during 20 min of a-tDCS over the ipsilateral M1 at 1.5 mA. A significant improvement (15%) in endurance time was found compared to s-tDCS. Interestingly, the rate of increase in RPE was lower during a-tDCS. These authors found an association between the magnitude of treatment effect and baseline level of maximal strength ($r = -0.55$; $P = 0.05$), suggesting that tDCS may be more beneficial in weaker participants.

Radel et al. (2017) investigated the effect of high definition (HD) a-tDCS on the right premotor cortex (PMC) and right prefrontal cortex (PFC) on an isometric endurance test of the elbow flexors at 35% of MVC force. Peripheral fatigue, central activation ratio, EMG activity, brain oxygenation as measured by near infrared spectroscopy (NIRS), heart rate variability and RPE were also monitored. No differences in endurance performance were found between conditions. Similarly, no effects of HD a-tDCS were found on central activation ratio, EMG and heart rate variability. However, oxyhemoglobin decreased significantly during the endurance test when the PFC was stimulated.

2.1.2 Maximal strength and anaerobic work capacity

Experimental evidences suggested that the modulation of corticospinal excitability following a-tDCS should induce transient improvement in muscular strength (Hummel et al., 2005; Tanaka et al., 2009). In this regards, Hendy and Kidgell (2014) examined the effect of a-tDCS applied during a single resistance exercise session on the corticospinal response untrained right extensor carpi radialis and maximal voluntary isometric strength of the wrist muscles. a-tDCS was applied ipsilaterally over the primary motor cortex of the trained limb. Participants were required to perform four sets of six wrist extensions at 70% of 1 repetition maximum (1RM) with a 3 min recovery period between each set. A significant increase in muscular strength (5%) was found only when resistance exercise was combined with a-tDCS, while no improvements were obtained with s-tDCS or with a-tDCS alone. Together with a significant increase in muscular strength, an increase in cross-activation (15%), a decrease in short-interval intracortical inhibition (−13%) were also found. No significant changes in corticospinal excitability were found between a-tDCS combined with strength session (17%) and a-tDCS alone (15%).

In two separate studies, Frazer et al. (2017) examined the effect HD a-tDCS prior a single session of resistance exercise on the maximal voluntary isometric

strength, cross-transfer of strength, corticospinal excitability and inhibition of elbow flexor muscles. HD a-tDCS was applied ipsilaterally of the exercising limb. The resistance exercise consisted on four sets of six to eight repetitions at 80% of 1RM of the bicep brachii with 3 min recovery between each set. In the first study, peripheral muscle function, cross-transfer of strength, corticospinal excitability and dynamic strength of the left untrained biceps brachii muscle were monitored before and after receiving tDCS and resistance exercise. The second study examined the effects of HD a-tDCS alone on corticospinal response in the absence of resistance exercise. Results showed that HD a-tDCS increased maximum voluntary isometric strength of the untrained left biceps brachii (12%), corticospinal excitability (12–33%) and cross-transfer of strength (25%), compared to s-tDCS when ipsilateral HD a-tDCS was applied prior to a single resistance exercise session. The second study showed increased ipsilateral corticospinal excitability following a-tDCS without any changes in cortical silent period.

Oki et al. (2017) studied the potential benefits of a-tDCS on maximal isometric voluntary strength in a group of people aged between 80 and 85 years old. Isometric MVC force of the bicep brachii was measured before (baseline) receiving a-tDCS over the right M1 and during the last two and half minutes of stimulation. EMG activity was also measured. Contrary to their initial hypothesis, no improvement in MVC force or changes in EMG activity were found.

Hazime et al. (2017) evaluated the application of a-tDCS over M1 on maximal isometric strength of upper limbs (shoulder external and internal rotators) in handball players (Hazime et al., 2017). They found a significant increase in isometric MVC force of external rotator muscles during, 30 and 60 min post a-tDCS while for internal rotator muscles isometric MVC force increased significantly only during and 60 min post a-tDCS.

Montenegro et al. (2015) investigated for the first time whether a-tDCS was able to increase maximal dynamic strength of lower limbs. Participants were required to perform maximal isokinetic contractions of the knee extensor and flexors muscles only in concentric mode. The range of motion was set between 0° and 90° with execution speed at $60° \, s^{-1}$. The exercise involved 3 sets of 10 repetitions with 120 s intervals between each set. No significant benefits were found on either the total and average work performed, fatigue index, power produced or EMG response of the rectus femoris, biceps femoris, and semitendinosus muscles.

Similarly, Lattari et al. (2016) examined the effect of tDCS on the volume of repetitions and perceived exertion in a group of recreationally trained subjects. Contrarily to previous studies (Angius et al., 2016; Hendy and Kidgell, 2014; Montenegro et al., 2015), tDCS was applied over the left dorsolateral prefrontal cortex (DLPFC, F3 according to the 10–20 EEG system). Participants were required to perform a 10-repetition maximum (RM) test of elbow flexors. A significant higher total number of repetitions completed was found compared to c-tDCS and s-tDCS together with a decrease in RPE. Similar findings regarding the improvement in the total work performed were found in a subsequent study

in experienced weight-training individuals by the same group (Lattari et al., 2018b). However, RPE was unchanged after a-tDCS but significantly higher following c-tDCS.

Sales et al. (2016) investigated the effect a-tDCS applied over the left temporal cortex (T3 according to the 10–20 EEG system) on the isokinetic performance of the knee extensor muscles in young adults. The isokinetic protocol consisted on two sets of five repetitions at 60 and 180° s^{-1} angular velocity with 60 s of rest between each set. The protocol was performed either after a-tDCS or s-tDCS. a-tDCS increased the total amount of work performed by 10.4% at 60° s^{-1} angular velocity and 9.4% at 180° s^{-1} angular velocity. In addition, there were trends for a 9.5% improvement in peak force at 60° s^{-1} and 7.8% at 180° s^{-1} angular velocity.

Maximal isometric strength of the knee extensor and flexor muscles was examined when exercise was performed with and without concurrent a-tDCS (Washabaugh et al., 2016). Two different groups were tested when stimulation was delivered while subjects performed a force matching task (tDCS-matching group) and when tDCS was delivered at rest (tDCS-resting group). Both groups performed an isometric MVC before (baseline) and every 5 min up to 25 min after the task. Authors found that the tDCS-matching group was able to generate higher torques only during knee extension compared to s-tDCS while for the tDCS-resting group no improvement in torque was found. Additionally, no improvement in knee flexion torque was found.

Anaerobic work capacity of knee extensor muscles has been also studied by Ciccone et al. (2018). In two different visits a-tDCS was applied over the left and right temporal cortex (T3 and T4, respectively) for 30 min before performing 50 maximal isokinetic contractions at 180° s^{-1} of the knee extensor muscles. Contrarily to what previously found (Lattari et al., 2016, 2018a; Sales, et al., 2016; Vargas et al., 2018) a-tDCS did not induce any improvement in maximal work capacity or change in fatigue index across all repetitions, EMG amplitude or mean fatigue index.

Maximal isometric strength of knee extensor muscles following tDCS has also been investigated in a group of female soccer players (Vargas et al., 2018). MVC force was evaluated in both lower limbs by a manual dynamometer at baseline, during tDCS, and 30 and 60 min after stimulation. MVC force was significantly higher from baseline measurement on the dominant limb during stimulation (5%), after 30 min (6%) and 60 min (9%) compared to s-tDCS. On the other hand, no significant improvements in maximal strength were found on the non-dominant limb.

The effect of tDCS on knee extensor muscle function has also been studied in two different experiments by Angius et al. (2016, 2018). In both experiments, subjects were required to produce an isometric MVC of the right knee extensor muscles at 90° flexion. The neuromuscular and corticospinal responses were also monitored to assess the effect of tDCS. No changes in MVC force were found after receiving a-tDCS over the contralateral M1. Moreover, no changes in EMG activity, voluntary activation level, and peripheral muscle function were found. Corticospinal response differed between the two experiments, with no changes in corticospinal excitability

and CSP in the first experiment (Angius et al., 2016) while an increase in corticospinal excitability after a-tDCS compared to both c-tDCS and s-tDCS in the second one was found (Angius et al., 2018).

2.2 WHOLE-BODY EXERCISE

A summary of the discussed studies is shown in Table 2.

2.2.1 Endurance

Okano et al. (2015) conducted the first study investigating the effect of tDCS during cycling exercise in a crossover, randomized experimental design. Unlikely previous studies that targeted M1, in this experiment participants received either a-tDCS or s-tDCS over T3. This electrode position has been chosen to target the insular cortex, which has been associated with autonomic nervous system control (Oppenheimer, 2007) and with the awareness of several subjective bodily sensations (Craig, 2009). Following a-tDCS, the peak power output (PPO) achieved during an incremental cycling test to exhaustion increased by ~4%. RPE and HR were significantly reduced in the first half of the test. The authors suggested that tDCS could have reduced RPE by affecting the activity of the insular cortex, and therefore increase exercise tolerance.

In a double blinded, randomized, placebo-controlled, crossover experimental design, Angius et al. (2015) investigated the effect of a-tDCS on muscle pain during cycling exercise in a group moderately trained individuals. This experiment included a second study investigating the effect of the same tDCS protocol on pain tolerance, as a manipulation check to demonstrate that the tDCS protocol used in the first study was able to elicit an analgesic effect. a-tDCS was applied unilaterally to the contralateral M1. In the first study, subjects were asked to cycle at 70% of PPO until exhaustion. No changes in endurance time, respiratory responses, blood lactate concentration, muscle pain and RPE were found following tDCS compared to s-tDCS. In the second study subjects were asked to performed a cold pressor test with their right hand immerged into a container filled with iced water. Contrarily to the first study which measured muscle pain during cycling exercise, a significant reduction in cold-induced pain was found. Therefore, like other analgesic manipulations (laser stimulation, electrical stimulation and mechanical stimulation), tDCS was not able to reduce exercise-induced muscle pain.

In the same year, Vitor-Costa et al. (2015) performed a similar single blinded, randomized, placebo-controlled, crossover study. However, contrarily to Angius et al. (2015), the active electrode was placed over the vertex (Cz, according to the 10–20 EEG system) to stimulate both left and right M1 simultaneously with a-tDCS, c-tDCS and s-tDCS delivered in different sessions. The authors reported a significant improvement in endurance time only after a-tDCS, despite no significant changes in self-reported mood, EMG activity of the vastus lateralis and rectus femoris, and RPE were reported. It should be noted, however, that a trend for a lower RPE following a-tDCS stimulation was reported ($P = 0.07$).

Table 2 List of Experimental Studies Involving Whole Body Exercise

Study	Sample	Anode/ Cathode Location	Active Electrode Size (cm^2)	Stimulation Intensity (mA)	Stimulation Duration (min)	Blinding	Muscle Investigated	Online/ Offline	Exercise Protocol	Performance Outcome
Angius et al. (2015)	Study 1: 9♂; Study 2: 7♂	Anode right M1/cathode Fp2	35	2	10	Sham and control	Lower limbs	Offline	Cycling TTE at 70% PPO	No improvement
Vitor-Costa et al. (2015)	11♂	Active Cz/ reference over occipital protuberance	36	2	13	Sham and cathode	Lower limbs	Offline	Cycling TTE at 80% PPO	↑ Endurance time
Okano et al. (2015)	10♂	Anode left T3/cathode Fp2	35	2	20	Sham	Lower limbs	Offline	Maximal incremental cycling test. From 15 W +25 W min^{-1}	↑ PPO
Barwood et al. (2016)	Study 1: 6♂; Study 2: 8♂	Anode left T3/cathode Fp2	35	2	20	Sham	Lower limbs	Offline	Study 1: 20 km TT; Study 2: TTE at 75% PPO	Study 1: TT; Study 2: TTE
Angius et al. (2018)	4♀, 8♂	Active electrode both M1/ reference over both ipsilateral shoulders	35	2	10	Sham and cathode	Lower limbs	Offline	Cycling TTF at 70% PPO	↑ Endurance time
Lattari et al. (2017)	10	Active F3/ reference Fp2	35	2	20	Sham and cathode	Lower limbs	Offline	Countermovement Jump	↑ Jump height, ↑ Flight time, ↑ power
Lattari et al. (2018a)	11♀	Anode F3/ cathode Fp2	35	2	20	Sham	Lower limbs	Offline	Cycling TTE at 100% PPO	↑ Endurance time
Sasada et al. (2017)[a]	6♀, 17♂	Active Cz/ reference right forehead	NS	2	15	Sham and cathode	Lower limbs	Offline	Cycling, 30 s sprint	No improvement

↑ (increased); = (no improvement); central midline or vertex (Cz); left temporal cortex (T3); maximal voluntary contraction (MVC); peak power output (PPO); primary motor cortex (M1); right frontopolar (Fp2); time to exhaustion (TTE); time trial (TT).

[a]*This reference includes only details related to tDCS.*

The effect of tDCS on endurance performance during cycling exercise has been also studied in hot environment (33 °C) (Barwood et al., 2016). This experiment consisted of two separate studies, both using the same tDCS montage previously used by Okano et al. (2015) (see also Table 2). In the first study, subjects performed a 20 km simulated time trial, while in the second study a different group of participants performed a cycling test consisting of 25 min at 55% of PPO immediately followed by cycling to exhaustion at 75% of PPO. In the first study, the pacing profile during the time trial showed a consistent pattern without any significant change in mean power and overall performance. The lack of effect of a-tDCS on performance was also found for endurance time in the second study. No changes in perceptual responses (RPE and thermal perception) or physiological responses (HR, blood lactate concentration, aural and skin temperature) were found in both studies.

Angius et al. (2018) investigated again the effect of tDCS on endurance performance during cycling exercise to exhaustion. Based on the results found in their previous study involving unilateral isometric exercise (Angius et al., 2016), they used an extracephalic montage (Angius et al., 2016) (see Table 2). This montage was applied bilaterally in order to stimulate both M1 and avoid potential negative effects caused by the reference electrode. In a double blind, randomized study, subjects received a-tDCS, c-tDCS or s-tDCS over both M1 prior performing a cycling TTE at 70% of PPO. To investigate the potential neurophysiological mechanisms, neuromuscular and corticospinal response was monitored before and after tDCS. An increase in corticospinal excitability of the knee extensor muscles was found after a-tDCS, while no changes were found regarding maximal strength. In line to what previously reported by Vitor-Costa et al. (2015), endurance time increased only following a-tDCS (∼23%). No changes in muscle pain and HR were found while a significant reduction in RPE was observed.

Further improvements on endurance performance in cycling exercise following tDCS have been also reported at higher exercise intensity by Lattari et al. (2018a). A group of 11 moderately active women cycled at 100% PPO until exhaustion after receiving a-tDCS over F3 for 20 min at 2 mA. No differences in HR and RPE were found between conditions. Most probably because the high intensity and short duration (∼200 s) of the task performed, it was difficult to detect any significant changes in both examined variables.

2.2.2 Maximal power and anaerobic work capacity

To the best of our knowledge, only two studies have measured performance during whole-body exercise that requires maximal power and anaerobic work capacity. In a randomized, double-blind, crossover study, Lattari et al. (2017) investigated the effect of tDCS over Cz for 20 min on subsequent countermovement jumps (CMJs). CMJ height, flight time and muscular peak power were significantly improved after receiving a-tDCS. Notably, the response after tDCS was different between conditions as all participants reported improvement after a-tDCS, 80% of the subjects reported a decrease in all measured variables after c-tDCS, while a less

homogeneous response was observed after receiving s-tDCS (increases 60%, decreases 30% and unaltered 10%).

Sasada et al. (2017) investigated whether tDCS can improve power output during an all-out sprint on the cycle ergometer. In a crossover design with randomized ordering of conditions, participants received either a-tDCS, c-tDCS or s-tDCS over Cz before performing a 30 s all-out sprint on cycle ergometer against a predetermined load based on participant's body weight. Authors reported an increase in mean power output after a-tDCS compared to c-tDCS, but no significant differences between s-tDCS and either a-tDCS or c-tDCS were found. In addition, no significant differences in peak power output were found between all conditions.

3 SUMMARY

The present review article aimed to discuss the current knowledge about possible ergogenic effects of tDCS. Overall, we reviewed the experimental findings from 28 articles investigating the effect of tDCS on physical performance (see Tables 1 and 2). Experimental studies on tDCS have produced contrasting results and high variability regarding the effects on physical performance. Some studies were mainly designed to investigate the neurophysiological mechanisms while others were investigating performance during physical tasks more relevant to sport applications. Among the 28 reviewed studies, ~60% of the studies reported improvement in physical performance when a-tDCS was administered. More specifically to the type of exercise performed, ~62% of the studies involving whole-body exercise reported an improvement in physical, with similar benefits for single-joint exercise (~60%). Additionally, 60% studies investigating endurance (both in whole body and single joint exercise) found improvement in performance, while ~57% of the studies have found improvement in strength, power or anaerobic work capacity.

As it is clear from the previous literature review, the effects of tDCS on physical performance are highly variable. López-Alonso et al. (2015) suggested that the high inter-individual variability (i.e., responders vs non-responders) to NIBS and more specifically to tDCS could explain the variance in experimental outcomes. In addition, the different electrode montages used and stimulation protocols (see Tables 1 and 2) could have surely contributed to mixed result. Likewise, due to differences in electrode size and position, as well as to the relatively low focality of induced electric field (Miranda et al., 2013), other brain areas beyond the targeted one could be affected by tDCS and deeply affect the experimental outcomes. Overall, tDCS seems to improve endurance, strength, power and anaerobic capacity. Taken together, the currently available literature provides interesting insights about the potential for tDCS to enhance physical performance.

Although many differences exist in terms of experimental design and physical task performed, some trends can be found: (i) the primary motor cortex (M1) has been the most targeted area (see Fig. 1); (ii) a-tDCS has been mainly delivered prior to the physical task; (iii) most of the studies involved 20 min stimulation at 2 mA with

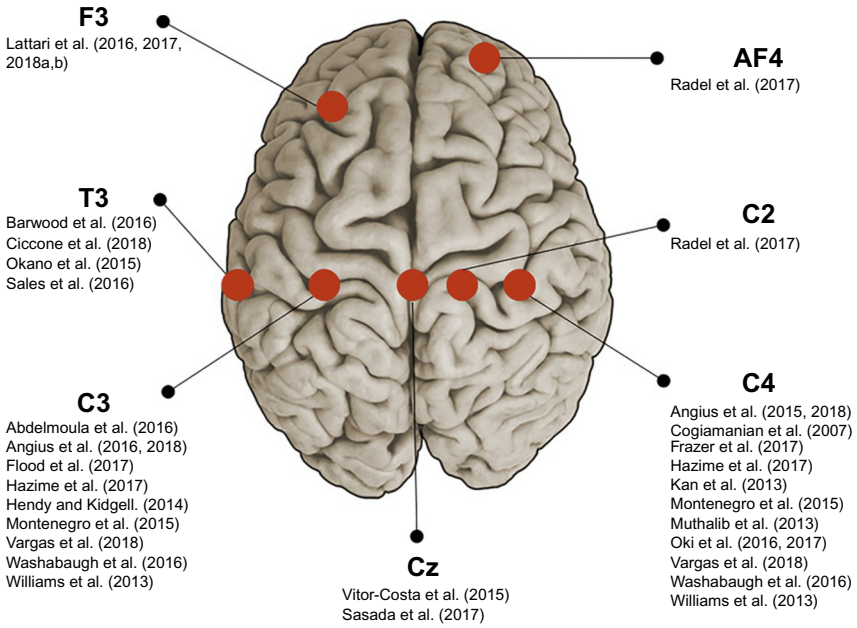

FIG. 1

tDCS and physical performance: a summary of the available literature. The list of studies targeting different brain regions of interest. Note: electrodes locations refer to the 10–20 EEG system.

an active electrode size of 35 cm^2. Regarding the neuromuscular parameters exanimated, a-tDCS generally increased corticospinal excitability (Angius et al., 2018; Cogiamanian et al., 2007; Frazer et al., 2017; Hendy and Kidgell, 2014; Williams et al., 2013) while the physiological responses during exercise did not show consistent changes following a-tDCS. Notably, when perceptual responses were measured, the improvement in physical performance induced by tDCS was often associated with a lower perception of effort (Angius et al., 2016, 2018; Lattari et al., 2018b; Okano et al., 2015; Oki et al., 2016; Williams et al., 2013) while muscle pain did not change.

The neurophysiological mechanisms supporting the effect of tDCS for the improvement on physical capacity are still unclear. However, several proposals have been made. With regards to endurance, Cogiamanian et al. (2007) suggested that a-tDCS could have improved subjects motivation, reduced muscle pain, modulated muscle synergy. However, none of the proposed mechanisms and corresponding parameters have been monitored. Other authors propose that the improvement in endurance performance following a-tDCS could be due to increased neural drive and to a reduction in supraspinal fatigue (Oki et al., 2016; Vitor-Costa et al., 2015; Williams et al., 2013). Other authors suggested that a-tDCS could influence sensorimotor integration and associated cognitive demand, without changing the motor command

(Abdelmoula et al., 2016). Angius et al. (2016, 2018) proposed that because of increased corticospinal excitability induced by a-tDCS, less excitatory inputs to M1 were required to produce the same submaximal force or power. Given that perception of effort seems to depend on excitatory inputs from supplementary motor area (SMA) and other brain regions (de Morree et al., 2012; Zénon et al., 2015), a reduction in such inputs would result in a lower perception of effort. It must be noted, however, that two studies have reported improvements in endurance performance without significant changes in corticospinal excitability (Abdelmoula et al., 2016; Angius et al., 2016). This is not surprising as previous studies demonstrated a considerable variability in corticospinal response after tDCS over the motor cortex (Madhavan et al., 2016; Wiethoff et al., 2014).

Some of the studies investigating the effect of tDCS on maximal strength or work capacity during resistance exercise suggested that the improvement was achieved by both increased corticospinal excitability, a reduction in short-interval intracortical inhibition and increase in cross-activation (Frazer et al., 2017; Hendy and Kidgell, 2014). Other authors suggested that the improvement in workload was achieved by a significant reduction in perception of effort (Lattari et al., 2016, 2018b). These proposals about the mechanisms behind the ergogenic effect of tDCS remain hypothetical and should be interpreted with caution, since none of the here mentioned studies have monitored brain activity during exercise following tDCS.

4 LIMITATION OF CURRENT LITERATURE AND FUTURE DIRECTIONS

The variability in experimental outcomes and other methodological constrains suggest caution when evaluating the effectiveness of tDCS as ergogenic aid. A crucial step forward can be achieved only by a systematic standardization of methodological variables, such as montage, stimulation duration and intensity, state-dependency (online and offline stimulation), coupled with comprehensive investigation of the neurophysiological underpinnings of tDCS effects. Nevertheless, the findings obtained by aforementioned experiments provided interesting insights about the potential for tDCS to enhance physical performance.

The number of experiments investigating the effect of tDCS on physical performance is rapidly increasing, with important methodological limitations to consider. First, the mechanism responsible for the improvement in physical performance is largely unknown. In this regard, experimental studies suggested that the transient improvement in physical performance seems to be the results of the modulation of corticospinal excitability or other targeted brain areas following tDCS. However, only a few studies have monitored corticospinal or brain activity following or during tDCS. Further studies should include electrophysiology and/or neuroimaging monitoring of brain activity, implementing, e.g., functional magnetic resonance imaging (fMRI) or EEG recording. Second, the spatial resolution of induced electric field in the brain is relatively low for tDCS compared to TMS

(Miranda et al., 2013; Wagner et al., 2007a,b) and therefore it can affect the function of brain areas beyond the regions of interest. In light of this, an accurate evaluation of the electrical field distribution should be carried out in order to optimize tDCS application to specifically target brain areas (or networks) of interest. Third, the vast majority of the studies are based on very small samples, which might increase the probability of false positive results (Button et al., 2013). Lastly, the absence of an effective blinding procedures in most of the studies (see Tables 1 and 2) should also be considered. An ineffective blinding procedure could have led to a number of unwanted confounding psychological effects which could have played an important role on the variability of results.

In our opinion, experimental studies addressing the points listed above will greatly improve the quality of the future experiments and will provide the knowledge necessary for understanding the mechanisms of tDCS on physical performance. Other neuromodulatory techniques such as tACS or tRNS have been show to induce transient changes in brain activity and improve motor and cognitive performance (Santarnecchi et al., 2017). Future research should also investigate the application of these techniques as potential alternative to tDCS.

5 ETHICAL ISSUES

Despite experimental research has recently started investigating the possibility for tDCS to enhance physical performance, its application has rapidly moved outside the laboratory. Companies have introduced portable off-the-shelves tDCS devices to the market, in light of the overall good safety profile of tDCS. Professional and non-professional athletes have started using tDCS during training (Edwards et al., 2017; Reardon, 2016). Although no serious adverse side effects have been reported in healthy participants (Bikson et al., 2016), many uncertainties exist regarding the prolonged administration of tDCS.

According to Davis (2013) brain stimulation can potentially improve sport performance in two ways, either by modulating brain and corticospinal activity right before a competition, or during training. As discussed in the previous sections, the number of studies investigating the effect of tDCS on whole-body exercise is limited and no studies have yet investigated the effect of chronic tDCS administration on physical performance. In addition, the improvements obtained in controlled laboratory settings cannot easily be translated in the real world.

Non-invasive brain stimulation has recently been subjected to extensive discussion on whether it should be considered a new form of doping (neuro-doping). The World Anti-Doping Agency (WADA) has consistently banned many substances or methods that might exert ergogenic effect when two of the following criteria are met: (i) It has the potential to enhance or enhances sport performance; (ii) It represents an actual or potential health risk to the athlete and (iii) It violates the spirit of sport. Albeit its early experimental phase, tDCS *seems* to meet only the first criteria while it must be established whether it represents a violation for the spirit of sport.

Even though tDCS would meet two or three criteria, WADA does not necessarily ban immediately. In addition, it is not possible to determine whether an athlete has or has not used tDCS prior a competition, which might open an unprecedented scenario for doping testing strategies.

Regulatory and ethical issues (Farah, 2015; Wexler, 2016) have been also raised about the DIY brain stimulation community which compromises individuals using tDCS with the purpose to enhance cognitive or physical abilities. As such, additional experimental studies and efforts should be made to understand and regulate the prolonged application of tDCS (Farah, 2015; Wexler, 2016; Wurzman et al., 2016).

6 CONCLUSION

Although its early experimental phase, tDCS *seems* to have the potential to enhance athletic performance. However, it must be acknowledged that more rigorous and extensive experimental research is needed. tDCS is still in its early experimental phase, with uncertainties regarding unexpected potential side effects from either regular use or abuse. More research on larger sample (ideally through a collective effort among investigators), with proper blinding procedures and techniques to explore the neurophysiological mechanisms of tDCS effects, is deeply needed, as much as a more informed debate about ethical implications of neuro-doping.

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