Effect of transcranial direct current stimulation on exercise performance: a systematic review and meta-analysis

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been used to improve exercise performance, though the protocols used, and results found are mixed.

Objective: We aimed to analyze the effect of tDCS on improving exercise performance.

Methods: A systematic search was performed on the following databases, until December 2017: PubMed/MEDLINE, Embase, Web of Science, SCOPUS, and SportDiscus. Full-text articles that used tDCS for exercise performance improvement in adults were included. We compared the effect of anodal (anode near nominal target) and cathodal (cathode near nominal target) tDCS to a sham/control condition on the outcome measure (performance in isometric, isokinetic or dynamic strength exercise and whole-body exercise).

Results: 22 studies (393 participants) were included in the qualitative synthesis and 11 studies (236 participants) in the meta-analysis. The primary motor cortex (M1) was the main nominal tDCS target (n = 16; 72.5%). A significant effect favoring anodal tDCS (a-tDCS) applied before exercise over M1 was found on cycling time to exhaustion (mean difference = 93.41 s; 95%CI = 27.39 s to 159.43 s) but this result was strongly influenced by one study (weight = 84%), no effect was found for cathodal tDCS (c-tDCS). No significant effect was found for a-tDCS applied on M1 before or during exercise on isometric muscle strength of the upper or lower limbs. Studies regarding a-tDCS over M1 on isokinetic muscle strength presented mixed results. Individual results of studies using a-tDCS applied over the prefrontal and motor cortices either before or during dynamic muscle strength testing showed positive results, but performing meta-analysis was not possible.

Conclusion: For the protocols tested, a-tDCS but not c-tDCS vs. sham over M1 improved exercise performance in cycling only. However, this result was driven by a single study,

which when removed was no longer significant. Further well-controlled studies with larger sample sizes and broader exploration of the tDCS montages and doses are warranted.

Keywords: Athletic Performance; Exercise Performance; Meta-analysis; Non-Invasive Brain Stimulation; Systematic Review; Transcranial Direct Current Stimulation.

HIGHLIGHTS

- In this systematic review and meta-analysis, we assessed the effect of tDCS for improving exercise performance in healthy adults.
- We did find a weak evidence for an exercise performance enhancement effect favoring anodal tDCS during whole-body dynamic cyclic exercise, but this result was strongly influenced by one study.
- However, there is no evidence that tDCS improves measures of isometric, isokinetic and dynamic strength.

INTRODUCTION

Exercise performance is influenced by several physical, physiological, and psychological factors [1–3]. Particularly in the sports context, there has always been a search for ergogenic aids to boost performance [4], with some athletes even using illegal drugs to this end [5]. In recent years, the focus has changed to the brain and how it could limit/improve performance. Many studies have shown that the brain plays a key role in the establishment of fatigue and, therefore, exercise performance [6–9]. In this regard, several centrally-acting performance modifiers have been shown to influence exercise performance [6,10].

Transcranial direct current stimulation (tDCS) is a technique that has received increasing attention due to its potential impact on brain activity in healthy subjects as well as patient populations. tDCS is a non-invasive, portable, easy to use, safe [11,12], well-tolerated [13], and economical technique, in which a weak electric direct current (up to 2 mA for tens of minutes) is applied to the scalp with the intention to modulate cortical excitability [14,15]. Classically, placement of the anode electrode near the nominal target (anodal tDCS, a-tDCS) is presumed to increase neuronal excitability and plasticity, while placement of cathode near the nominal target (cathodal tDCS, c-tDCS) is assumed to have opposite effects [14,15]. Whilst ongoing studies have shown this polarity-dependent approach to be over-simplistic due to a non-linear dose-response (e.g. anodal inhibiting or cathodal exciting) [16–18] and the inevitable presence and interaction of both the active and reference electrodes [19,20], we adopt the conventional anodal and cathodal terminology for the purpose of our literature review.

Generally, the effects of tDCS outlast the time of stimulation for up to 120 min after tDCS has ended [14,15,21].

Given the complexity involved in exercise performance, there are multiple brain regions that may be involved in exercise regulation/limitation and, therefore, the rationale for using tDCS for performance enhancement may vary accordingly. However, most studies on sporting and exercise performance fail to provide a clear or stated hypothesis for why positioning the electrodes in a specific location targeted to excite/inhibit a given brain region could lead to an improved exercise performance. Although this is not an extensive list, some of these regions include the primary motor cortex (M1), prefrontal cortex (PFC), insular cortex (IC), and supplementary motor area (SMA).

M1 is the region most related to exercise performance due to its role in driving the exercising muscles. It has been consistently demonstrated that central fatigue (e.g. due to neural factors) can impact on the physical performance of single-joint exercises involving low muscle mass (e.g. elbow flexion) as well as multiple-joint or whole-body exercises (e.g. cycling). Specifically, spinal and supra-spinal factors such as the reduction in excitability of the motorneuron pool and the inability or limited capacity of the M1 and other supraspinal areas to increase the neural drive to compensate for this decreased spinal excitability leads to the decrease in muscle capacity to produce strength/power and thus cause fatigue [9,22,23]. Therefore, one reason for using tDCS over M1 would be to increase excitability of this region which could result in a sustained neural drive for the motor neuron, delay in the decrease of the neural drive to the active muscle and, therefore, improved performance. In addition, other possible reason for applying tDCS over M1 could be to modulate the pain perception. Although the exact mechanism is unclear, the reason for targeting M1 for pain modulation is due to its connections with the insula and

thalamus, as shown in studies with non-human animal models [24]. In fact, meta-analytical research has shown that anodal tDCS of M1 increases sensory and pain threshold in healthy individuals as well as pain level in patients with chronic pain [25]. In this regard, it has been suggested that exercise-induced pain plays a key role in the regulation of exercise performance, in which individuals with the better capacity to tolerate or overcome pain would be more successful [26]. Thus, targeting M1 could also improve performance via the attenuation of exercise-induced pain.

The PFC is another region of interest considering its role in the cognitive control of behavior. It has been suggested that the PFC plays an important role in the processing of internal and external cues related to the exercise being performed [27]. PFC exerts a top-down influence that may result in alteration of pace to complete the task, prolong the motor output delaying exercise end or derecruitment of motor units causing exercise termination [27]. In this regard, the psychobiological model proposes that task disengagement (i.e. exercise termination) is an effort-based decision-making process which depends on the potential motivation (e.g. the maximum effort a person is willing to exert), perception of effort, knowledge of the endpoint of exercise and distance/time remaining, and previous experience/memory of perception of effort during exercise of varying intensity and duration [28]. A systematic review confirmed that interventions aiming to decrease the ability of the PFC to exert control over the body signals during exercise, such as mental fatigue (e.g. performing a cognitively demanding task for a prolonged time) may reduce endurance performance [29]. In fact, it has been consistently demonstrated that there is a decrease in PFC oxygenation before fatigue occurs [30,31]. Therefore, applying tDCS over the PFC could strengthen the ability of this region to

disregard interoceptive cues (i.e. body signals), keeping the volitional drive to M1 and, thus, delaying task disengagement (i.e. exercise termination).

Another possible target for tDCS is the insular cortex (IC), which is involved in cardiac autonomic control. Non-human animal, experimental, and neuroimaging studies have demonstrated that the right IC is involved in sympathetic modulation while the left IC is involved in parasympathetic modulation [32–34]. The insula is a relatively deep brain structure and tDCS is thought to modulate, primarily, the excitability of cortical regions. However, considering the connections between the temporal cortex (TC) and IC, it has been shown by computational modeling and experimental studies that applying tDCS over the left TC probably modulates the activity of the IC resulting in an increased parasympathetic modulation at rest and during exercise [35,36]. At rest, the cardiac autonomic control is predominantly modulated by the parasympathetic branch and as exercise starts this modulation decreases progressively until its complete withdrawal. The point in which the parasympathetic withdrawal occurs can be measured using a marker termed heart rate variability threshold (HRV_{th}) and it has been demonstrated to coincide with the ventilatory threshold (VT), an important marker of transition of the exercise intensity domain [37,38]. Thus, delaying the HRV_{th} would increase the time exercising with a lower cardiovascular load, which in turn could postpone fatigue resulting in an increased time to exhaustion (TTE) [35].

The supplementary motor area (SMA) has also been implicated in exercise performance. It was recently demonstrated that decreasing neuronal excitability of SMA using repetitive transcranial magnetic stimulation (rTMS), to apply theta-burst stimulation, resulted in a decreased in perceived exertion during exercise and willingness to reproduce the effort [39]. It is important to note that perceived exertion directly

influences exercise performance being determinant in the establishment of fatigue [6,7,28]. So far, however, no study tested whether tDCS applied to SMA could induce the same result as rTMS.

The interest in the potential role of tDCS for improving performance has increased in the past few years. Cogiamanian et al. [40] were the first to demonstrate that tDCS could postpone fatigue. They showed that tDCS significantly decreased the fatiguing effects of prior exercise in healthy individuals, with an apparent 50% longer TTE in an isometric contraction of the elbow flexors after a-tDCS over M1 compared to no stimulation. Later, Okano et al. [35] also showed that a-tDCS over the TC (targeting the left IC) improved cycling performance by 4% (i.e. maximal power output and TTE) in national-level road cyclists. These results were further supported, albeit with different electrode montages and measures of performance [41–43]. Although some studies showed positive performance enhancements using tDCS [35,40–42], others have failed to reproduce the positive findings [44–47]. The mixed findings could be due to variations in the protocols; for instance, in electrode placement, current intensity, and density, the type of exercise test used, participant's level of physical /activity fitness and sample size. Likewise, the timing of tDCS use is not consistent, as studies have used tDCS before and during testing as well as during training sessions.

These early studies with positive results [35-36] motivated commercial and consumer interest in tDCS for sports performance, including at elite levels [48]. Despite encouraging results of a few controlled experiments, there is apprehension that adoption of tDCS for performance enhancement in the naturalistic setting such as commercial gymnasiums has outpaced research [49,50]. In addition, several opinion articles and literature reviews have implicated tDCS as an effective technique for improving

performance [51–54], including the discussion regarding the fairness and ethics of its use in sport (e.g. as a "neurodoping" technique [51–53,55]), with some authors debating ethical modes of the use of tDCS in sports [49,54], and others suggesting anti-doping regulation agencies to include tDCS as an illegal strategy to enhance performance in sports [50,54]. Consequently, there has been a call for researchers to identify biomarkers of the use of tDCS in order to be able to test for its use in/out of competition (e.g. anti-doping testing) [54]. However, the practical debate around the fairness of tDCS in sports, as well as its practical use, presumes meaningful effectiveness of the technique, which has yet to fully reach a consensus in the research to date.

So far, however, it is not clear in the light of the current evidence whether tDCS improves exercise/sporting performance, in what sort of exercise it is effective, and in which electrode set-up. Hence, the purpose of this systematic review and meta-analysis was to analyze the effect of tDCS for improving performance in muscle strength (isometric, isokinetic and dynamic) exercise as well as during whole-body dynamic cyclic exercise (e.g. cycling) in healthy adults. Our findings will consolidate extant knowledge in the application of tDCS for sports and help to guide future investigations.

METHODS

Protocol and registration

A systematic review and meta-analysis was performed according to the recommendations of the Cochrane group [56], which involves the procedure of review, selection of eligible articles according to inclusion/exclusion criteria, quality assessment

of included studies, data extraction of outcomes and relevant variables, and quantitative synthesis (meta-analysis) of the results. This report follows PRISMA guidelines [57]. Two reviewers independently selected articles and extracted the data according to an a priori elaborated data extraction checklist. Discrepancies we resolved by consensus and, if necessary, the inclusion of a third reviewer.

The protocol of the present review was registered into the International Prospective Register of Systematic Reviews – PROSPERO - (https://www.crd.york.ac.uk/prospero/) under the register number CRD42017076546 and is publicly available (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=76546).

Literature review

The review was performed in the following databases: PubMed/MEDLINE, Embase, Web of Science, SCOPUS, and SportDiscus. We searched for articles from the first data available in each database until 5 December 2017. The following keywords (MeSh) and Boolean terms were used: “exercise tolerance” OR "exercise" OR "fatigue" OR "physical exertion" OR "physical endurance" OR "athletic performance" AND "transcranial direct current stimulation" OR "tDCS" OR "HD-tDCS". In addition, further searches were performed in the reference list of the included articles and literature reviews on the subject in order to retrieve articles that were not covered by the database searches.

Eligibility criteria

We searched for full-text articles without language restrictions (only articles in English were found). Included articles had to: (a) enroll healthy adults; (b) perform transcranial direct current stimulation; (c) have a sham/control condition; (d) perform maximal physical testing (isometric, isokinetic or dynamic strength exercise and whole-body dynamic cyclic exercise); (e) provide data of at least one of the outcome measures (on the manuscript or upon request). The inter-reviewer agreement for the article selection was assessed using Kappa statistic (K) and the results show an "excellent" agreement between reviewers ($k = 0.85$; $p < 0.0001$).

Quality assessment

The assessment of study quality (risk of bias) was performed following the criteria proposed by Cochrane guidelines [56] that can negatively impact study: (a) assessments for sequence generation (randomization), (b) allocation sequence concealment, (c) blinding of participants and researchers, (d) incomplete outcome data, (e) selective outcome reporting and (f) 'other issues'. Each of these items were deemed as "low risk of bias" ("+"), "high risk of bias" ("-") or "unclear risk of bias" ("**?**") in a table available in the Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre), in which a description of what was reported to have happened in the study was included.

Data extraction

For each included article, we extracted data regarding sample size and characteristics (age, sex, level of physical activity, fitness or training, and type of exercise training), number and reasons for dropout, intervention characteristics (electrode location, current intensity density, and duration), side and adverse effects. For the outcome, we extracted the following data (absolute values): (a) TTE in whole-body dynamic exercise and isometric exercise for major muscle groups and (b) maximal isometric, isokinetic, and dynamic muscle strength.

Quantitative analysis

A separate meta-analysis was performed considering the type of exercise test used (isometric, isokinetic or dynamic strength exercise and whole-body dynamic cyclic exercise) as well as the brain region stimulated in each study.

To measure the intervention effect on continuous outcomes, we calculated the mean difference (MD) and 95% confidence interval (95%CI). The MD and 95%CI weighted by the inverse variance method was measured using a random-effects model. Heterogeneity was assessed using Chi^2 ($p < 0.1$ considered as significant) and I^2 (>75%), as well as the visual inspection of the forest plot. All analyses were performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre). When it was not possible to perform a meta-analysis of the studies, MD and 95%CI was reported if sufficient data was provided in the article or upon request.

RESULTS

Overview

A total of 1588 unique records were screened, and 27 full texts were assessed for eligibility. The most common reason for exclusion at the screening phase was studies involving exercise related performance with patients (e.g. multiple sclerosis, stroke, Parkinson's disease, Alzheimer's disease), as well as elderly and adolescents. Twenty-two studies were included enrolling 393 participants in the qualitative synthesis and 11 studies enrolling 236 participants in the quantitative synthesis (meta-analysis). The low number of studies included in the meta-analysis were, primarily, due to variations of stimulated area (i.e. PFC, M1, TC) and outcomes (e.g. isometric, isokinetic, dynamic muscle strength or TTE, sprint, time trial, peak power output in cycling), which did not allow quantitative synthesis. Only one study was included from the references of the included articles, which represents that our search strategy was sensitive to cover the literature regarding tDCS and exercise performance. This systematic review covered the period from 1966 to December 2017. Figure 1 summarizes the flow of the study.

*****INSERT FIGURE 1 AROUND HERE*****

Study characteristics

A comprehensive summary of the characteristics of the included studies examining the effects of tDCS on improving exercise performance can be found in Table 1. All included studies were randomized, 20 (90.9%) were crossover and 2 (9.1%) were parallel. Nineteen studies (86.4%) had a sham condition/group as a comparator, two (9.1%) had both sham and control (no stimulation), and one study (4.5%) had only a control group as a comparator. Seventeen studies (77.3%) performed only a-tDCS, while five (22.7%) studies applied both a-tDCS and c-tDCS. The current intensity applied was 1.5 or 2 mA, with a current density of (mean ± SD) 0.104 ± 0.110 mA/cm² (from 0.043 to 0.44 mA/cm²), and duration of 15.1 ± 4.8 min (ranging from 10 to 20 min).

Studies assessed both men and women, with mean ± SD sample size per study was 14.4 ± 5.7 (from 6 to 24 participants) with a median of 12, aged from 17 to 42 years and different levels of physical activity/fitness (ranging from low active individuals to athletes). Regarding tDCS timing, 16 studies (72.7%) applied tDCS before exercise, three studies (13.6%) applied tDCS during exercise, one study (4.5%) applied tDCS both before and during exercise, one study (4.5%) applied tDCS over repeated sessions, and one (4.5%) during exercise training [58]. The effect of tDCS for improving exercise performance was assessed for muscle strength in 15 studies (68.2%), from which 10 (45.5%) used isometric, three (13.6%) used isokinetic, and two (9.1%) used dynamic strength exercise. Seven studies (31.8%) assessed the effect of tDCS on improving whole-body cycling exercise performance. The most stimulated area was M1 (n = 16;

72.5%), but there were also studies stimulating dorsolateral PFC (n= 2; 9.1%), left TC (n = 3; 13.6%), and both M1 and lateral PFC (n = 1; 4.5%). Figure 2 presents electrode montage for the tDCS protocols used in the included studies.

*****INSERT TABLE 1 AROUND HERE*****

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tDCS for improving performance in whole-body cycling exercise

We found an increased TTE with constant load cycling exercise after a-tDCS (Figure 3A). Although a significant effect in favor of a-tDCS was found without a significant heterogeneity ($Chi^2 = 0.45$, $P = 0.80$ and $I^2 = 0\%$) the study of Vitor-Costa et al. [42] presented a disproportionate weight in the analysis (84.8%). After excluding that study from the analysis, the result was non-significant [MD = 114.96 s, 95%CI = -23.07 s to 312.99 s; $Z = 1.69$; $P = 0.09$] (Figure 3B). Similarly, there was no effect of c-tDCS on the time to exhaustion in constant load cycling exercise (Figure 3C). Although no significant heterogeneity was found ($Chi^2 = 0.03$, $P = 0.87$ and $I^2 = 0\%$) the study of Vitor-Costa et al. [42] also had a disproportionate weight (94.9%).

*****INSERT FIGURE 3 AROUND HERE*****

Four other studies that used tDCS to improve whole-body cycling exercise were found. However, they could not be quantitatively synthesized due to differences in brain areas and/or type of exercise testing performed. Okano et al. [35] and Barwood et al. [44] applied a-tDCS (2 mA for 20 min) over the left TC (T3) before exercise, but while the former used maximal incremental exercise, the latter used a 20-km time trial and a TTE test at 75% of peak power. Okano et al. [35] reported a significant increase the MD did not confirmed this significant improvement in peak power (MD = 12.20 W; 95%CI = -10.03 W to 34.43 W) and TTE (MD = 27.70 s; 95%CI = -24.66 s to 80.06 s). Barwood et al. [44] found no difference in either time trial completion time (MD = 0.00 s; 95%CI = -83.46 s to 83.46 s) or TTE (MD = -77.00 s; 95%CI = -418.31 s to 264.31 s).

On the other hand, Latarri et al. [59] applied a-tDCS over the dorsolateral PFC before exercise in physically active women and reported a significantly longer TTE at 100% of peak power but the MD did not confirm these positive result (MD = 62.40 s; 95%CI = -9.47 s to 134.27 s). Sasada et al. [60] applied a-tDCS and c-tDCS over M1 before a maximal 30 s sprint on a cycle ergometer in a sample of athletes from various modalities and found a significantly higher mean power output after a-tDCS compared to c-tDCS, but this was not different from the sham condition.

tDCS for improving muscle strength in isometric exercise

There was no effect of a-tDCS applied before exercise compared to sham on isometric muscle strength of either the upper limbs or the lower limbs (Figure 4).

Particularly for the upper limbs a significant heterogeneity was found ($Chi^2 = 11.51$, $P = 0.009$ and $I^2 = 74\%$; Figure 3A). Likewise, no significant effect of a-tDCS applied during exercise compared to sham on isometric muscle strength was found (Figure 4C).

Two studies were not included in the quantitative synthesis due to the assessment of different muscles or the use of repeated tDCS sessions. Hazime et al. [61] applied a-tDCS over the M1 of handball athletes and found an unchanged maximal isometric voluntary contraction (MIVC) of the external and internal rotators of the shoulder during tDCS (MD = 0.10 N/Kg; 95%CI = -0.05 N/Kg to 0.25 N/Kg and MD = 0.10 N/Kg; 95%CI = 0.00 N/Kg to 0.20 N/Kg, respectively), but it increased 30 min (MD = 0.20 N/Kg; 95%CI = 0.05 N/Kg to 0.35 N/Kg, for both) and 60 min (MD = 0.20 N/Kg; 95%CI = 0.05 N/Kg to 0.35 N/Kg, for both) after stimulation. Frazer et al. [62] assessed the effect of a-tDCS applied over M1 on four consecutive days and reported a significant improvement in the MIVC of the wrist flexors by 8% compared to 3% by sham.

*****INSERT FIGURE 4 AROUND HERE*****

tDCS for improving muscle strength in isokinetic exercise

Only three studies that analyzed the effect of tDCS on isokinetic muscle strength were found [58,63,64]. However, they could not be quantitatively synthesized due to the different brain areas stimulated. Two of these studies used similar tDCS parameters (2 mA for 20 min, 0.057 mA/cm²), isokinetic assessment (2-3 sets of 5 and 10 repetitions of knee extensors at $60^{o}.s^{-1}$), and sample (physically active men). Montenegro et al. [63] applied a-tDCS over M1, while Sales et al. [64] applied a-tDCS over TC. The former reported no

significant effect of tDCS on torque, total work or work fatigue, while the latter found a significant effect on the total work at both $60^{o}.s^{-1}$ (MD = 117.47 J; 95%CI = 0.05 J to 234.89 J) and $180^{o}.s^{-1}$ (MD = 77.40 J; 95%CI = 0.32 J to 154.48 J) movement speeds. Maeda et al. [58] applied a-tDCS over non-dominant M1 during the execution of isokinetic eccentric knee extension and flexion training over seven sessions and found no difference between a-tDCS and sham in knee extension (MD = -3.70 Nm; 95%CI = -66.74 Nm to 59.34 Nm) and knee flexion (MD = 7.50 Nm; 95%CI = -18.23 Nm to 33.23 Nm).

tDCS for improving muscle strength in dynamic exercise

Only two studies that assessed the effect of tDCS on dynamic muscle strength were found. Lattari et al. [65] applied a-tDCS and c-tDCS (2 mA, 0.057 mA/cm², for 20 min) before performing a second 10-repetition maximum test (i.e. workload needed to allow the execution of up to 10 repetitions) of elbow flexors in trained men and found a significant higher number of repetitions after a-tDCS compared to sham tDCS (MD = 4.28; 95%CI = 2.56 to 6.00). Interestingly, c-tDCS decreased the number of repetitions compared to sham tDCS (MD = -2.52; 95%CI = -3.75 to -1.28). Hendy and Kidgel [66] applied a-tDCS alone and a-tDCS/sham over M1 of the non-dominant hand while performing resistance exercise with the dominant hand. The authors reported that a single a-tDCS session, when associated with resistance exercise, could improve the maximum voluntary dynamic strength of the wrist extensors of the untrained limb more than sham + resistance exercise and a-tDCS alone, but the 95%CI of the MD did not confirm the positive effect (MD = 0.46 kg; 95%CI = -2.00 kg to 2.92 kg and MD = 0.56 kg; 95%CI = -2.01 kg to 3.13 kg, respectively) [66].

Risk of bias

The risk of bias regarding tDCS for improving exercise performance was deemed low for the majority of the studies. However, approximately 25% of the studies presented a high risk of bias regarding the blinding of the outcome assessment. The risk-of-bias graphs and summary are presented in Figure 5.

*****INSERT FIGURE 5 AROUND HERE*****

DISCUSSION

This systematic review with meta-analysis included 22 studies with 393 participants examining the effects of tDCS on exercise performance. For the protocols tested, we found weak evidence of a significant effect favoring a-tDCS applied before testing over the M1 on TTE in cycling, but this result was strongly influenced by a single study, with no significant effect for c-tDCS for the same outcome. In addition, for the protocols tested, no significant effect was found for a-tDCS applied either before or during exercise on isometric muscle strength of the upper or lower limbs. Although it was not possible to synthesize the evidence quantitatively, the studies present mixed results related to the application of a-tDCS on isokinetic muscle strength. The only two studies using a-tDCS applied over PFC and M1 either before or during dynamic muscle

strength testing also showed mixed results, although a quantitative synthesis was not possible due to different areas of stimulation.

The quantitative synthesis showed a significant effect of a-tDCS over the M1 improving TTE in cycling by approximately 93 seconds, suggesting that a-tDCS could, in fact, enhance performance and be used for this purpose before training sessions and/or competition. However, caution should be taken when interpreting this result, given that a single study [42] had a disproportionate weight in the analysis (84.5%), and when removed from the analysis this result became non-significant (Figure 3B). Considering that in a meta-analysis each study is weighted by the inverse of its variance plus the variance between-studies (if using random-effects model), the greater weight can be explained by the lower variance presented by the study [42].

The improvement in cycling performance is of particular interest as in top-level competitions an improvement even by seemingly trivial percentage (i.e. 1%) might have an impact on the sporting outcome such as changing positions in the podium in intense Olympic events [67]. Nevertheless, it should be noted that only three studies (13.6%) assessed actual athletes [35,60,61], the other studies included samples with different levels of physical activity and fitness (ranging from low active to active individuals), which may have influenced the variation in the results. Furthermore, even though most studies were conducted with small sample sizes and individual data were almost always unavailable, it is worth noting that the cost-effectiveness of tDCS may seem favorable, particularly when considering that no detrimental effect in exercise performance has been reported on the assessed tasks. However, it is possible that a negative impact on other tasks could occur as it has been shown, for instance, that tDCS may present improvements in some cognitive functions at the expense of other cognitive abilities

[68,69]. Furthermore, the use of tDCS outside the lab by the wider community may produce uncertain results due to inadequate electrode positioning, contact, impedance, and current flow. It should be noted that only two studies (9.1%) used tDCS for performance improvement over repeated sessions, with four [62] or seven sessions [58], and the safety for daily use of tDCS such as before/during training sessions is still to be evaluated. Therefore, the widespread application of tDCS outside the lab, such as with commercial devices, should be treated with significant caution until clear scientific evidence supports its safety and efficacy.

The meta-analysis of studies involving isometric muscle strength exercise showed no significant differences between a-tDCS and sham for the upper and lower limbs, for a-tDCS applied both before and during exercise (Figure 4). In addition, for fatiguing isometric contraction of elbow flexors, a significant heterogeneity in the results of the included studies was detected. Importantly, the studies that used isometric muscle strength as the outcome used surprisingly low percentages of MIVC ranging from 20% to 35%. The transferability of performance from this type of task to both exercise practice and sports performance is very limited. Future studies should consider using higher intensities that are more representative of the sporting context, for example, in combat sports that involves isometric actions such as Judo or Brazilian Jiu-Jitsu. So far, the available evidence does not support using a-tDCS to improve isometric muscle strength performance.

Regarding isokinetic muscle strength performance, the available studies stimulated different brain regions and found opposing results. Sales et al. [64] found improved isokinetic muscle strength of the knee extensors after a-tDCS applied to the left TC, while Montenegro et al. [63] found no difference after a-tDCS applied to M1.

In addition, Maeda et al. [58] applied a-tDCS over M1 during isokinetic training and found no effect of eccentric knee extension and flexion. Interestingly, the only two studies involving dynamic strength exercise showed contrasting results, where a single session of a-tDCS before exercise improved the number of maximum repetitions in elbow flexion exercise [65] and a single-session of strength training associated with a-tDCS did not change the maximal strength of the contralateral wrist extensors more than strength training or a-tDCS alone [66]. However, the effect size of these improvements ranged from very small to very large, which suggest heterogeneity in the findings. Therefore, the current evidence does not support the efficacy of tDCS for improving performance in isometric, isokinetic of dynamic muscle strength.

Interestingly, although commercial companies are selling tDCS devices for exercise performance enhancement to the wider community (for an overview see Edwards et al. [49]), in this systematic review, no published peer-reviewed study testing the effects and validity of these commercial devices on exercise performance were found. It is worth noting that only laboratory studies in a controlled environment used tDCS for performance enhancement and, therefore, the widespread use of tDCS outside this environment (e.g. commercial, home-based, do-it-yourself) must be taken with caution. This issue has raised concerns in the research community, particularly considering the safety of uncontrolled, prolonged, and repeated use of tDCS [49,70,71].

It should be noted that methodological aspects of tDCS may have an impact on the stimulation effects, and this must be considered in future studies using tDCS for performance enhancement. In recent years, the adoption of computational forward models of brain current flow has increased [72] as it provides more insight into brain current flow patterns and, in some cases, can even challenge simplified electrode-

placement based on the "classical" polarity-dependent assumption [20,73]. Of the 22 studies included, only three (13.6%) used computational modeling to predict the electrical field generated by tDCS in the target area. Generally, the application of tDCS using large electrode pads (termed as "conventional" tDCS) leads to diffuse brain current flow, therefore, presenting low focality, with peak intensity often not located at the nominal target, as is usually suggested [21,74,75]. To overcome this limitation, "High-Definition" tDCS (HD-tDCS) uses arrays of smaller electrodes arranged in various configurations including the 4x1-ring HD-tDCS montage [74,76–79]. The 4x1 HD-tDCS has shown improved focality compared to conventional tDCS with a gyri precise stimulation [21,74,78] having a potentially greater magnitude and duration of its aftereffects [21]. So far, only two studies (9.1%) have tested the effect of HD-tDCS for performance enhancement, but they found no significant change on the TTE an isometric contraction of the elbow flexors and knee extensors [80,81]. Moreover, studies on tDCS for sporting performance are mostly underpowered with a median of 12 (from 6 to 24 participants), which present a reduced chance of detecting a true effect and increasing the possibility of a false negative. Only five (22.7%) of the included studies performed *a priori* sample size estimation or *a posteriori* achieved power analysis. Underpowered studies are not specific to this field and have been criticized broadly in the brain sciences [82].

Regarding tDCS mechanisms, the positive charge imposed by a-tDCS is hypothesized to cause sub-threshold depolarization and c-tDCS hyperpolarization due to its negative charge. This assumption generated the "classical" polarity-dependent effect of tDCS (i.e. a-tDCS excite and c-tDCS inhibit), inferring that the effect of tDCS would be mediated by changes in neuronal excitability. Studies with non-human animals have shown that tDCS-induced changes in neuronal excitability may result from

phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and its translocation from the cytosol to the synapse [83]. In humans, the most common way to assess tDCS-induced changes in neuronal excitability (i.e. corticospinal excitability) is by using transcranial magnetic stimulation (TMS) to elicit motor-evoked potential (MEP). Increased MEP amplitude for the same TMS pulse intensity compared to baseline represent increased excitability and vice-versa. Previous studies using MEP have reinforced the "classical" polarity-dependent effect of tDCS and suggested that a-tDCS increases neuronal excitability and c-tDCS causes the opposite effect [14,15]. However, recent studies have shown large inter-individual variability in response to tDCS [84–86]. For instance, Wiethoff et al. [86] showed that 50% of the participants had minor or no change in MEP amplitude after 2 mA of either a-tDCS or c-tDCS over M1. The sub-group who responded to the stimulation, 36% presented the "classical" polarity-dependent response in cortical excitability (i.e. anode-excite and cathodal-inhibit), while 21% of participants displayed the inverted "classical" response to tDCS (i.e. anode-inhibit and cathode-excite), 38% and 5% showed an excitatory and inhibitory response for both polarities, respectively. The results of these studies have questioned the "classical" polarity-dependent effect of tDCS as previously stated [14,15].

In the context of exercise, researchers have used tDCS with their hypothesis based on the "classical" polarity-dependent assumption. However, only one study has actually found significant performance decrease after c-tDCS with dynamic strength exercise [65] with the rest of studies showing no change in performance [40,42,43]. In addition, this meta-analysis showed that c-tDCS had no detrimental effect on cycling performance, rather showing a non-significant trend toward increasing performance (MD = 35.20 s; 95%CI = -5.02, 75.43 s; p = 0.09; Figure 4C). This result is in-line with

a previous experimental investigation by Batsikadze et al. [18] who showed that 2 mA of c-tDCS for 20 min over M1 increased cortical excitability, instead of decreasing it. The measurement of MEP, however, is restricted to the motor cortex and measures of change in excitability by tDCS in other areas are difficult. Recent studies have used magnetic resonance spectroscopy [87] or electroencephalography [88,89] to assess the changes in cortico-cortical excitability of non-motor areas. However, only a handful of studies in the sporting field have directly measured changes in neuronal excitability as expressed by MEP amplitude [40,41,43,62,66,90]. Therefore, future research needs to identify that the hypothesized change to the brain area has actually occurred. Ideally, the effect of the proposed tDCS montages should be tested in terms of change in excitability before testing its effect on exercise performance. Interestingly, although studies have confirmed that changes in MEP are associated with performance improvement [40], others have shown that change in performance may occur without alterations in MEP [41,62,90]. Thus, multimodal measures of corticospinal, cortico-cortical, cortico-thalamic and cortico-sub-cortical excitability, depending on the area of stimulation, are highly recommended to help to clarify whether there is an effect of tDCS and through which mechanisms it could impact on performance. Monitoring tDCS neuromodulatory effects can be measured using electroencephalography (EEG) in conjunction with near-infrared spectroscopy (NIRS) [91]. Simultaneous use of one or two neuroimaging modalities can reveal bi-directional or uni-directional information flow patterns between the SMC, PMC and DLPFC brain regions, the three core regions of the cortical sensorimotor network for movement control. Recently, by combining fNIRS, EEG and fMRI neuroimaging methods, the effective connectivity of the same cortico-cortical sensorimotor networks (SMC, PMC, and DLPFC) during different

finger movement tasks has been assessed [92]. The dynamics of the significant connections for the cortical sensorimotor network during tDCS is not well known.

A review by Li, Uehara, Hanakawa [85] summarized several factors associated with the inter-individual variability in response to tDCS, which includes anatomical variations [93], organization of local circuits, basal level of function, psychological state, level of neurotransmitters and receptor sensibility, baseline neurophysiological state, and genetic aspects [94]. Regarding the anatomical variations, there is evidence that individuals who displayed improvement in behavioral outcomes (i.e. working memory) presented greater current density at the nominal target of tDCS (i.e. dorsolateral PFC) as compared to those with no behavioral change [84]. This implies that tDCS montages should be individualized, aiming at increasing the likelihood of eliciting performance change [93]. No study, however, has tested the influence of anatomical variations on the effect of tDCS on motor performance. In addition, studies have shown that the baseline level of motor function influences the after-effects of tDCS. So that, individuals with lower baseline level of function show (greater) improvements after tDCS while those with higher levels of function display lower improvements or no change in performance [95,96]. However, those studies were performed with fine motor skills (i.e. playing an instrument), and the effect of tDCS on individuals with different performance levels in gross motor skills such as running, cycling, lifting or resisting weights is still to be tested. More widely, the inter-individual factors that determine responsiveness to tDCS, particularly in exercise, are not fully understood [86].

Regarding tDCS montages, most studies target the M1 (72.5%), with less attention being directed to other areas such as the dorsolateral PFC (9.1%), left TC

(13.6%), and lateral prefrontal cortex (4.5%). As already presented in the introduction, various brain areas are involved in exercise performance. Briefly, the rationale for stimulating M1 is aimed at increasing its excitability in order to extend the neural drive to the active muscles and delay central fatigue or changing exercise-induced pain processing via the connection between M1, thalamus and insular cortex (IC), thus increasing performance by decreasing pain sensation. PFC stimulation is aimed at improving the top-down control over M1 output due to an improved processing of the physiological and psychological states. TC stimulation, which is performed targeting the left insular cortex, is aimed at increasing parasympathetic control to postpone its withdrawal during exercise, which could result in delayed fatigue. Finally, inhibition of the SMA may reduce perceived exertion, a factor that contributes to task cessation and reductions in exercise intensity [6,7,28], which has been demonstrated with non-invasive brain stimulation during a handgrip exercise [39]. However, the aforementioned study was performed using theta-burst using rTMS, and this result has not been replicated with tDCS. These examples do not cover all areas related to exercise performance, and indeed multiple possibilities of different tDCS montages exist. In fact, it is estimated that when taking into account electrode location, size, number, density, polarities, and duration, there are between four million to eight trillion possibilities of tDCS montages (V.P. Clarck; Personal communication at the NIMH-sponsored tES workshop held on September 29th and 30th, 2016). Even if the anodal electrode is placed at the same anatomical location, variations in the position of the return electrode may induce changes in the current path, current density concentration and, thus, impact on the possible effect of tDCS [20]. For instance, a computational modeling study suggested that the non-cephalic montage (i.e. when the return electrode is not positioned on the head) showed the highest current density for two different montages under both

M1 and dorsolateral PFC, with a current density of 6-9 times greater compared to the HD-tDCS configuration and 2.5-4.4 times greater compared to the bi-cephalic configuration (i.e. when both active and return electrode are positioned on the head) [97].

So far, however, only one study in the exercise/sporting field has compared the bi-cephalic (anodal over left M1 and cathodal over dorsolateral PFC) to the non-cephalic (anodal over left M1 and cathodal over the shoulder) types of tDCS configuration and showed that the latter resulted in increased TTE of an isometric contraction of the knee extensor, while former resulted in no significant change [90]. In addition, the literature is scarce regarding the comparison of stimulation of different brain areas for the same outcome. Only a single study performed by Radel et al. [80] compared the effect of tDCS using HD-tDCS applied over the PFC and M1 on the TTE of an isometric contraction of the elbow flexors and found no changes in physical performance or perceived exertion. Therefore, there is still an open field for researchers to compare the efficacy and efficiency of different electrode montages, current intensity, and forms of application (e.g. comparison of bi-cephalic and non-cephalic montages to HD-tDCS). Unfortunately, the results of the present study do not allow us to suggest a specific montage, given that a meta-analysis was possible only for studies that applied tDCS over M1. In addition, individual results of the studies present mixed findings for stimulation of the TC (targeting the insular cortex) and the PFC, which also prevent us from recommending one of them.

The current study presents some limitations concerning individual studies and, thus, in the meta-analysis itself: (a) a considerably large variation in current intensity with a coefficient of variation of 105.8%; (b) different placement of the return electrode

(e.g. ipsilateral or contralateral shoulder, contralateral forehead or occipital protuberance); (c) different areas of stimulations (all of these can lead to variations in the amount of electrical current applied to the nominal target area and, therefore, impact on the outcomes); (d) lack of measures of reliability of the outcome variable; and (e) low sample size with mixed physical activity and fitness levels. On the one hand, existing studies exhibit protocol heterogeneity, while on the other hand, the theoretically optimal dose of tDCS remains largely unexplored (e.g. current above 2 mA [98]; weeks of session repetition as might be used in practical training) such that existing dose protocols should be considered as pilots rather than an optimized protocol.

CONCLUSION

The results of this systematic review and meta-analysis showed that for the protocols tested, anodal but not cathodal tDCS vs. sham over the motor cortex resulted in a longer TTE in cycling. However, this result was strongly driven by a single study and when removed the results were no longer significant. For the protocols tested, no significant improvement was found comparing a-tDCS vs. sham on isometric muscle strength of the upper and lower limbs. It was not possible to perform a quantitative synthesis of isokinetic and dynamic muscle strength performance, as studies are heterogeneous. In order to test the putative effects of tDCS on sporting performance, future studies should try to individualize tDCS protocols, such as using computational modeling with individual MRI data for defining the most efficient electrode placement (including the reference electrode) for achieving a given target. In addition, optimizing the timing of the application of tDCS (e.g. before training, during training, before

competing), for both acute and repeated days of stimulation, would help assess its efficacy and safety in relation to use in sport and exercise [99]. An assessment of a wider range of tDCS intensities, particularly those that go beyond the usual 2 mA, would also be helpful to identify whether there is a dose-response relationship [98]. Finally, a comparison of different tDCS montages for a given outcome, especially using newer techniques such as the HD-tDCS, should be explored [21].

Conflict of interests

CUNY has patents with M Bikson as an inventor. M Bikson is an advisor for and has equity in Soterix Medical Inc. AR Brunoni has received grants from São Paulo Research State Foundation and honorarium from Neuroacademy group and Delta Medical. DGS Machado, SM Andrade, G Unal, A Moreira, LR Altimari, S Perrey, AR Mauger, and AH Okano declare they have no conflict of interest with regard to the content of this manuscript.

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FIGURE LEGENDS

Figure 1 Study flow diagram.

Figure 2 Electrode placement, polarity, and size of the studies using transcranial direct current stimulation for performance enhancement in isometric (superior), isokinetic (middle left) and dynamic strength exercise (middle right), and cycling exercise (inferior). In all figures: anode = red; cathode = blue**.** Rationale for tDCS montages: ***primary motor cortex*** (M1) stimulation is aimed at increasing M1 excitability to extend its neural drive to the active muscles and delay central fatigue or changing the exercise-induced pain processing via the connection between M1, thalamus and insular cortex (IC) increasing performance by decreased pain sensation; ***prefrontal cortex*** (PFC) stimulation is aimed at improving the top-down control over motor output due to an improved processing of the physiological and psychological states; ***temporal cortex*** stimulation is performed targeting the left ***IC*** aimed at increasing parasympathetic control to postpone its withdrawal during exercise, which could result postpone fatigue.

Figure 3 Forest plot showing mean difference from the comparison between anodal vs. sham (A) and cathodal vs. sham (C) transcranial direct current stimulation applied before exercise in terms of time to exhaustion in whole-body cycling exercise. Note: given that the result of the anodal vs. sham analysis shown in panel A was driven by one single study (Vitor-Costa et al., 2015), it was removed from the analysis and the results were not significant (panel B).

Figure 4 Forest plot showing mean difference from the comparison between anodal vs. sham transcranial direct current stimulation applied before (A and B) and during (C) exercise in terms of time to exhaustion in isometric strength exercise of the upper (A and C) and lower (B) limbs.

Figure 5 Risk of bias graph (A): review authors' judgments about each risk of bias item presented as percentages across all included studies; and risk of bias summary (B): review authors' judgments about each risk of bias item for each included study.

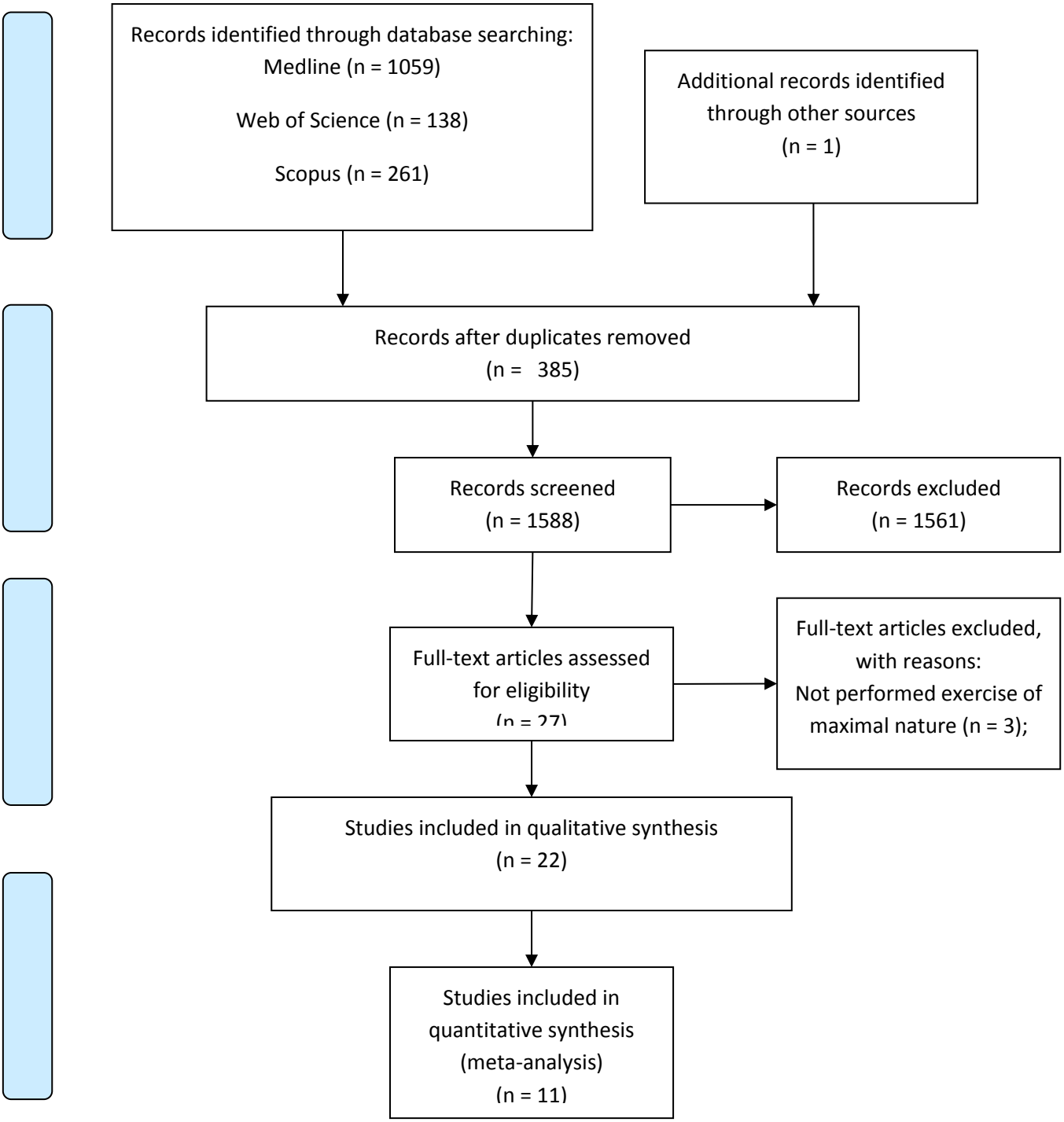
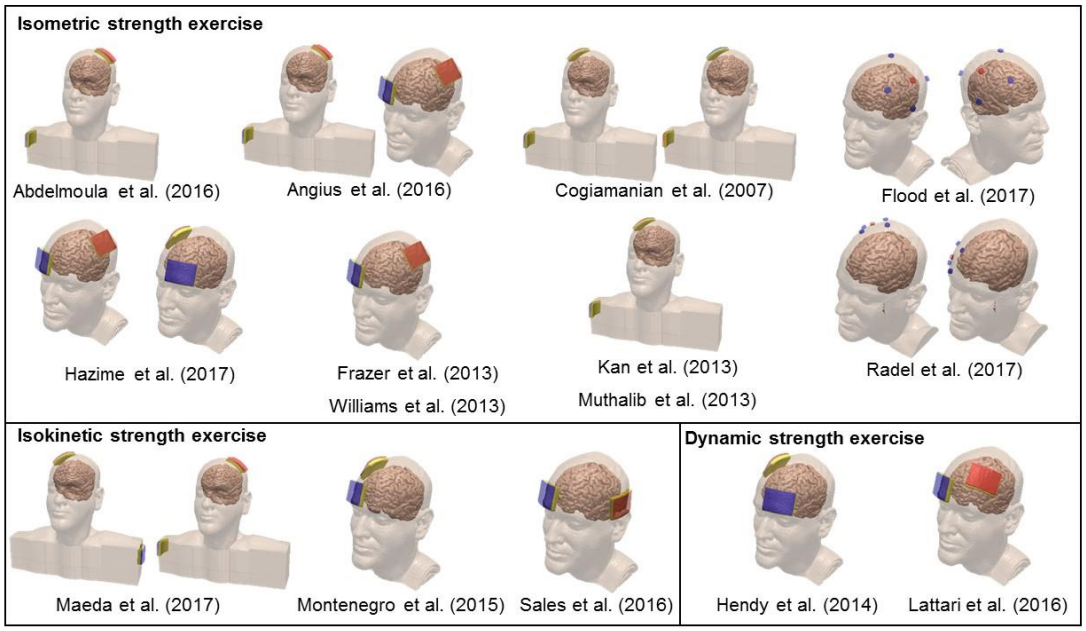


Fig. 1 Study flow diagram.


Isometric strength exercise
Abdelmoula et al. (2016)
Angius et al. (2016)
Cogiamanian et al. (2007)
Flood et al. (2017)
Hazime et al. (2017)
Frazer et al. (2013)
Williams et al. (2013)
Kan et al. (2013)
Muthalib et al. (2013)
Radel et al. (2017)
Isokinetic strength exercise
Maeda et al. (2017)
Montenegro et al. (2015)
Sales et al. (2016)
Dynamic strength exercise
Hendy et al. (2014)
Lattari et al. (2016)

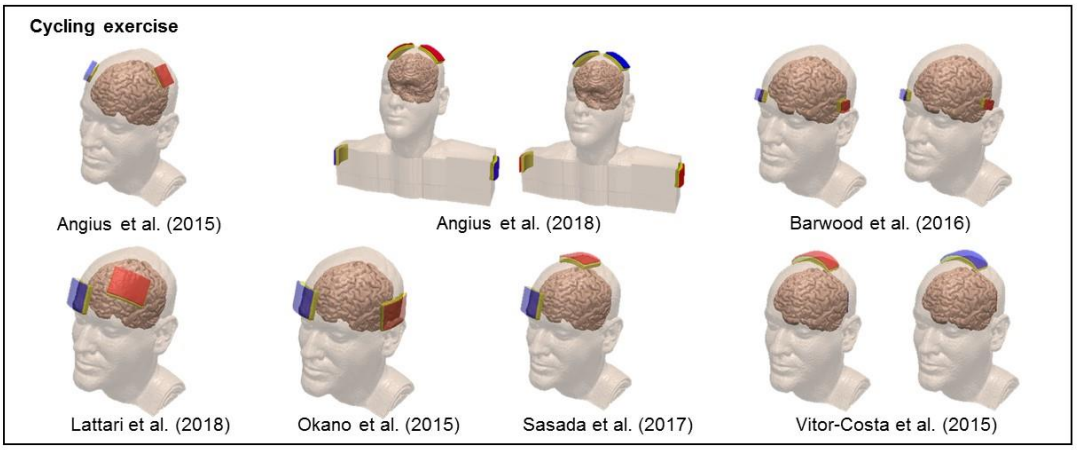

Cycling exercise
Angius et al. (2015)
Angius et al. (2018)
Barwood et al. (2016)
Lattari et al. (2018)
Okano et al. (2015)
Sasada et al. (2017)
Vitor-Costa et al. (2015)

Fig 2.

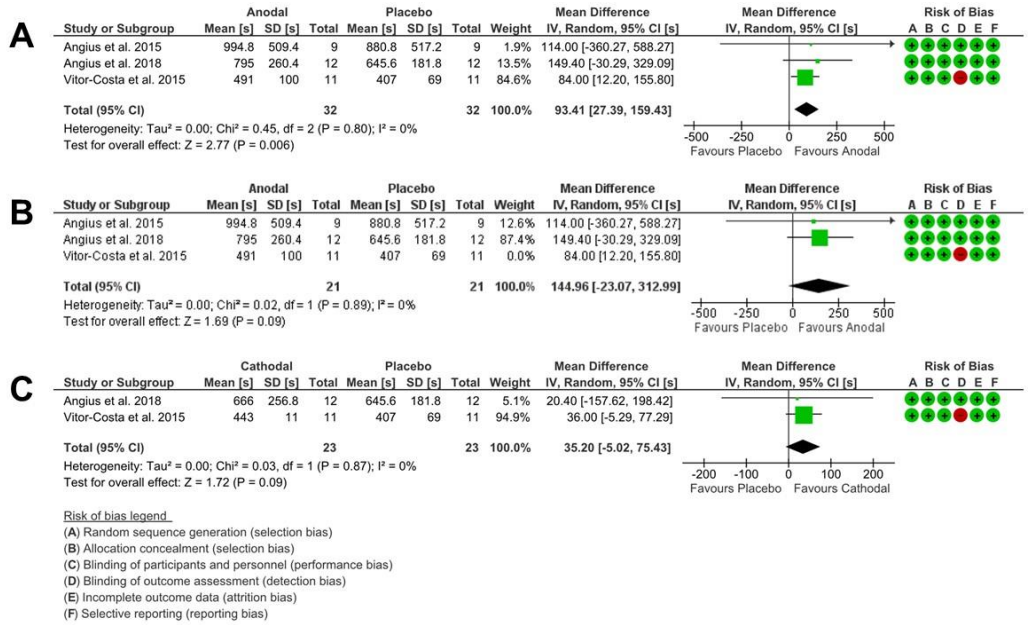

A
Anodal
Placebo
Mean Difference
Mean Difference
Risk of Bias
Study or Subgroup Mean [s] SD [s] Total Mean [s] SD [s] Total Weight IV, Random, 95% CI [s]
IV, Random, 95% CI [s]
A B C D E F
Angius et al. 2015 994.8 509.4 9 880.8 517.2 9 1.9% 114.00 [-360.27, 588.27]
Angius et al. 2018 795 260.4 12 645.6 181.8 12 13.5% 149.40 [-30.29, 329.09]
Vitor-Costa et al. 2015 491 100 11 407 69 11 84.6% 84.00 [12.20, 155.80]
Total (95% CI) 32 32 100.0% 93.41 [27.39, 159.43]
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.77 (P = 0.006)
-500 -250 0 250 500
Favours Placebo Favours Anodal
B
Anodal
Placebo
Mean Difference
Mean Difference
Risk of Bias
Study or Subgroup Mean [s] SD [s] Total Mean [s] SD [s] Total Weight IV, Random, 95% CI [s]
IV, Random, 95% CI [s]
A B C D E F
Angius et al. 2015 994.8 509.4 9 880.8 517.2 9 12.6% 114.00 [-360.27, 588.27]
Angius et al. 2018 795 260.4 12 645.6 181.8 12 87.4% 149.40 [-30.29, 329.09]
Vitor-Costa et al. 2015 491 100 11 407 69 11 0.0% 84.00 [12.20, 155.80]
Total (95% CI) 21 21 100.0% 144.96 [-23.07, 312.99]
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)
-500 -250 0 250 500
Favours Placebo Favours Anodal
C
Cathodal
Placebo
Mean Difference
Mean Difference
Risk of Bias
Study or Subgroup Mean [s] SD [s] Total Mean [s] SD [s] Total Weight IV, Random, 95% CI [s]
IV, Random, 95% CI [s]
A B C D E F
Angius et al. 2018 666 256.8 12 645.6 181.8 12 5.1% 20.40 [-157.62, 198.42]
Vitor-Costa et al. 2015 443 11 11 407 69 11 94.9% 36.00 [-5.29, 77.29]
Total (95% CI) 23 23 100.0% 35.20 [-5.02, 75.43]
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)
-200 -100 0 100 200
Favours Placebo Favours Cathodal
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Fig 3.

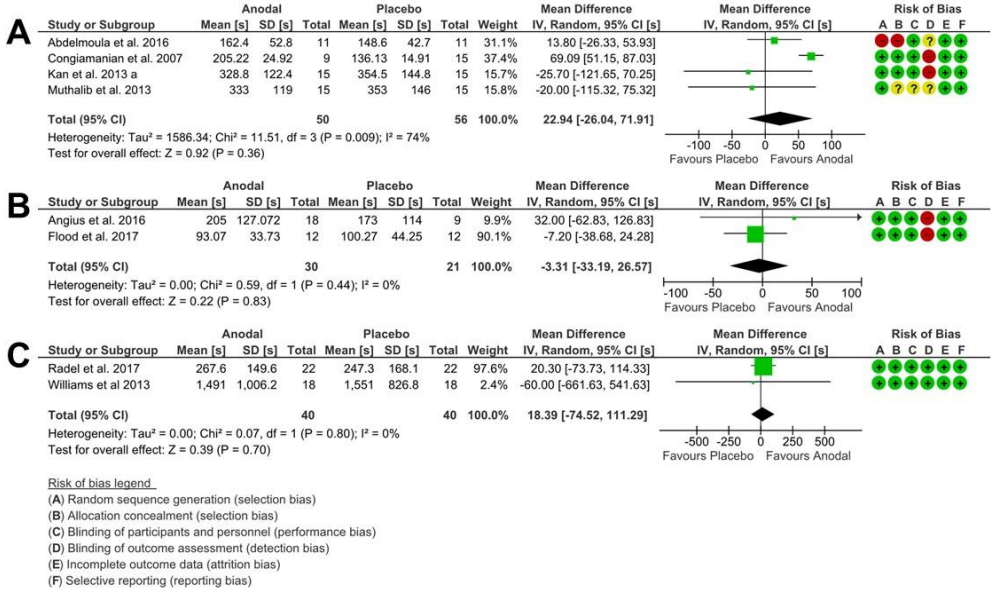

A
Anodal
Placebo
Mean Difference
Mean Difference
Risk of Bias
Study or Subgroup Mean [s] SD [s] Total Mean [s] SD [s] Total Weight IV, Random, 95% CI [s]
IV, Random, 95% CI [s]
A B C D E F
Abdelmoula et al. 2016 162.4 52.8 11 148.6 42.7 11 31.1% 13.80 [-26.33, 53.93]
Congiamanian et al. 2007 205.22 24.92 9 136.13 14.91 15 37.4% 69.09 [51.15, 87.03]
Kan et al. 2013 a 328.8 122.4 15 354.5 144.8 15 15.7% -25.70 [-121.65, 70.25]
Muthalib et al. 2013 333 119 15 353 146 15 15.8% -20.00 [-115.32, 75.32]
Total (95% CI) 50 56 100.0% 22.94 [-26.04, 71.91]
Heterogeneity: Tau² = 1586.34; Chi² = 11.51, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 0.92 (P = 0.36)
-100 -50 0 50 100
Favours Placebo Favours Anodal
B
Anodal
Placebo
Mean Difference
Mean Difference
Risk of Bias
Study or Subgroup Mean [s] SD [s] Total Mean [s] SD [s] Total Weight IV, Random, 95% CI [s]
IV, Random, 95% CI [s]
A B C D E F
Angius et al. 2016 205 127.072 18 173 114 9 9.9% 32.00 [-62.83, 126.83]
Flood et al. 2017 93.07 33.73 12 100.27 44.25 12 90.1% -7.20 [-38.68, 24.28]
Total (95% CI) 30 21 100.0% -3.31 [-33.19, 26.57]
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
-100 -50 0 50 100
Favours Placebo Favours Anodal
C
Anodal
Placebo
Mean Difference
Mean Difference
Risk of Bias
Study or Subgroup Mean [s] SD [s] Total Mean [s] SD [s] Total Weight IV, Random, 95% CI [s]
IV, Random, 95% CI [s]
A B C D E F
Radel et al. 2017 267.6 149.6 22 247.3 168.1 22 97.6% 20.30 [-73.73, 114.33]
Williams et al 2013 1,491 1,006.2 18 1,551 826.8 18 2.4% -60.00 [-661.63, 541.63]
Total (95% CI) 40 40 100.0% 18.39 [-74.52, 111.29]
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)
-500 -250 0 250 500
Favours Placebo Favours Anodal
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Fig 4.

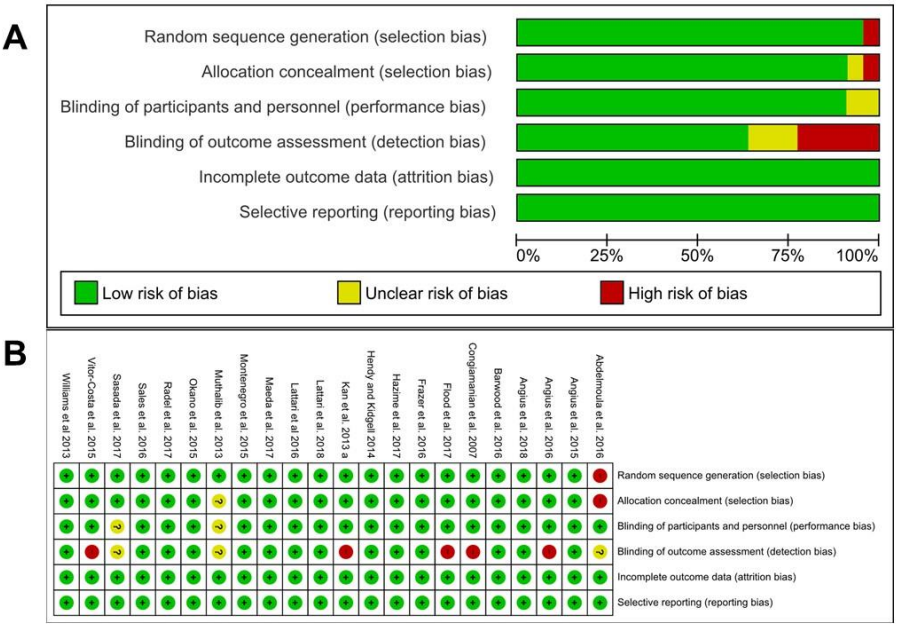

A
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias
B
Williams et al 2013
Vitor-Costa et al. 2015
Sasada et al. 2017
Sales et al. 2016
Radel et al. 2017
Okano et al. 2015
Muthalib et al. 2013
Montenegro et al. 2015
Maeda et al. 2017
Lattari et al 2016
Lattari et al. 2018
Kan et al. 2013 a
Hendy and Kidgell 2014
Hazime et al. 2017
Frazer et al. 2016
Flood et al. 2017
Conglemanian et al. 2007
Barwood et al. 2016
Angius et al. 2018
Angius et al. 2016
Angius et al. 2015
Abdelmoula et al. 2016
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)

Fig 5.

Table 1 Characteristics of the included studies.

Study information					Sample		tDCS set-up			
Authors	**Design**	**Exp**	**Exercise type**	**Exercise Protocol**	**n (M/W)**	**Training status**	**Anode or cathode Return electrode**	**Intensity (mA)**	**Density (mA/cm²)**	**Duration (Min)**
Abdelmoula et al. [41]	Cross	1	Isometric strength	35% of MIVC of elbow flexion	11 (8M/3W)	N/D	Left M1 Right shoulder	1.5	0.043	10
Cogiamanian et al. [40]	Parallel	1	Isometric strength	35% of MIVC of elbow flexion	24 (10M/14W)	N/D	***A*** Right M1 Right shoulder	1.5	0.043	10
	Parallel	2	Isometric strength	35% of MIVC of elbow flexion	24 (10M/14W)	N/D	***C*** Right M1 Right shoulder	1.5	0.043	10
Kan et al. [45]	Cross	1	Isometric strength	30% of MIVC of elbow flexion	15 (M)	N/D	Right M1/ Right shoulder	2.0	0.083	10
Muthalib et al. [46]	Cross	1	Isometric strength	30% of MIVC of elbow flexion	15 (M)	N/D	Right M1/ Right shoulder	2.0	0.083	10
Radel et al. [80][a]	Cross	1	Isometric strength	35% of MIVC of elbow flexion	22 (13M/9W)	N/D	***A*** C2 and ***C*** 4 cm around (HD-tDCS 4x1)	2.0	N/D	N/D
	Cross	2	Isometric strength	35% of MIVC of elbow flexion	22 (13M/9W)	N/D	HD-tDCS (***A)*** AF4 and (***C)*** 4 cm around	2.0	N/D	N/D
Williams et al. [100][a]	Cross	1	Isometric strength	20% of MIVC of elbow flexion	18 (9M/9W)	9 active / 9 low active	Right M1 Fp2	1.5	0.043	≤20

Note: [a] = tDCS applied during exercise; A/C = anode/cathode electrode; Cross = crossover design; Exp = experiment; HD-tDCS = high-definition transcranial direct current stimulation; M/W = men/women; M1 = primary motor cortex; MIVC = maximal isometric voluntary contraction; N/D = not described; tDCS = transcranial direct current stimulation

Table 1 Characteristics of the included studies (*continuation…)*

Study information					Sample		tDCS set-up			
Authors	**Design**	**Exp**	**Exercise type**	**Exercise Protocol**	**n (M/W)**	**Training status**	**Anode/Cathode Return electrode**	**Intensity (mA)**	**Density (mA/cm²)**	**Duration (Min)**
Angius et al. [90]	Cross	1	Isometric strength	20% MIVC of knee extension	9 M	Recreationally active	***A*** Left M1/Fp2	2.0	0.17	10
	Cross	2	Isometric strength	20% MIVC of knee extension	9 M	Recreationally active	***A*** Left M1 Shoulder	2.0	0.17	10
Flood et al. [81]	Cross	1	Isometric strength	30% MIVC of knee extension	12 (M)	Recreationally active	C3/C4 and 5 cm around (HD-tDCS 4x1)	2.0	0.057	20
Hazime et al. [61]	Cross	1	MIVC	Shoulder internal/external rotators	8 (W)	Handball athletes	C3/C4 Fp2/Fp1	2.0	0.057	20
Frazer et al. [62] [b]	Cross	1	MIVC	Wrist flexors	14 (6M/8W)	N/D	Left C3 Fp2	2.0	0.08	20
Maeda et al. [58] [a]	Parallel	1	Isokinetic strength	5 reps of eccentric knee extension/flexion	24 (12M/12W)	N/D	M1 Shoulder	2.0	0.08	10
Montenegro et al. [63]	Cross	1	Isokinetic strength	10 reps of knee extension/flexion	14 (M)	Trained in RT (≥6 months)	Left M1 Fp2	2.0	0.057	20
Sales et al. [64]	Cross	1	Isokinetic strength	5 reps of knee extension	19 (M)	Physically active	T3 Fp2	2.0	0.057	20
Hendy et al. [66] [a]	Cross	1	Dynamic strength	1RM wrist extension	10 (5M/5W)	N/D	Right M1 Fp1	2.0	0.08	20
Lattari et al. [65]	Cross	1	Dynamic strength	10RM elbow flexion	10 (M)	Trained in RT (≥6 months)	F3 Fp2	2.0	0.057	20

Note: [a] = tDCS applied during exercise; [b] = multiple tDCS sessions; A/C = anode/cathode electrode; Cross = crossover design; Exp = experiment; HD-tDCS = high-definition transcranial direct current stimulation; M/W = men/women; M1 = primary motor cortex; MIVC = maximal isometric voluntary contraction; N/D = not described; RM = repetition maximum; RT = resistance training; tDCS = transcranial direct current stimulation.

Table 1 Characteristics of the included studies (*continuation…)*

Study information					Sample		tDCS set-up			
Authors	**Design**	**Exp**	**Exercise type**	**Exercise Protocol**	**n (M/W)**	**Training status**	**Anode/Cathode Return electrode**	**Intensity (mA)**	**Density (mA/cm²)**	**Duration (Min)**
Angius et al. [43]	Cross	1	Cycling	TTE at 70% PP	12 (8M/4W)	Recreationally active	***A*** both M1/ shoulders	2.0	0.057	10
	Cross	2	Cycling	TTE at 70% PP	12 (8M/4W)	Recreationally active	***C*** both M1/ shoulders	2.0	0.057	10
Angius et al. [47]	Cross	1	Cycling	TTE at 70% PP	9 (M)	Recreationally active	Right M1/F4	2.0	0.17	10
Barwood et al. [44]	Cross	1	Cycling	20km time trial	6 (M)	Physically active	T3/Fp2	1.5	0.43	20
	Cross	2	Cycling	TTE at 75% PP	8 (M)	Physically active	T3/Fp2	2.0	0.44	20
Lattari at al. [59]	Cross	1	Cycling	TTE at 100% PP	11 (W)	Moderately active	F3/Fp2	2.0	0.057	20
Okano et al. [35]	Cross	1	Cycling	Incremental maximum	10 (M)	Athletes (cyclists)	T3/Fp2	2.0	0.057	20
Sasada et al. [60]	Cross	1	Cycling	Wingate test	23 (17M/6W)	Athletes (various)	Cz/Fp2	2.0	0.057	15
Vitor-Costa et al. [42]	Cross	1	Cycling	TTE at 80% PP	11 (M)	Physically active	***A*** both M1/ Inion	2.0	0.056	13
	Cross	2	Cycling	TTE at 80% PP	11 (M)	Physically active	***C*** both M1/ Inion	2.0	0.056	13

Note: A/C = anode/cathode electrode; Cross = crossover design; Exp = experiment; M/W = men/women; M1 = primary motor cortex; PP = peak power; tDCS = transcranial direct current stimulation; TTE = time to exhaustion.