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Programa de Doctorado Ciencia del Deporte

The ergogenic effect of transcranial direct current stimulation on cycling time to exhaustion task performance in physically active people.

Autora:
Shyamali Kaushalya Fernando

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Murcia, diciembre de 2020

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AUTORIZATION OF THE DIRECTORS OF THE THESIS

FOR SUBMISSION

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Sign to comply with the Royal Decrees 99/2011, in Murcia, 15th of December 2020.

Gonzalo Márquez Sánchez	Salvador Romero Arenas	Amador García Ramos
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"Challenges are what make life interesting and overcoming them is what makes life meaningful."

Joshua J. Marine

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INDEX

ABREVIATIONS

The abbreviations of the units from the International System Units and the abbreviations universally used in statistics are not included in the following list as there are internationally accepted standards for their use.

ANS	Autonomic Nervous system
a-tDCS	Anodal Transcranial Direct Current Stimulation
CG	Central governor
CGM	Central Governor Model
CNS	Central Nervous System
DLPFC	Dorsolateral Prefrontal Cortex
ETT	Endurance Time Trial
HR	Heart Rate
IC	Insular cortex
M1	Primary Motor Cortex
MU	Motor unit
MVC	Maximal Voluntary Contraction
NIBS	Non-invasive brain stimulation
PFC	Prefrontal cortex
PPO	Peak Power Output
RPE	Rating of Perceived Exertion
RPM	Revolutions Per Minute
s-tDCS	Sham Transcranial Direct Current Stimulation
TC	Temporal cortex
tDCS	Transcranial Direct Current Stimulation
TTE	Time to exhaustion
$\dot{V}O_{2max}$	Maximum Oxygen Uptake
W max	Maximum power

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ABSTRACT

Endurance exercise consisting of sustained whole-body dynamic exercise inevitably induces muscle fatigue, which leads to task failure. It is considered that the brain plays a key role during the regulation of endurance exercise performance. It is believed that exercise-induced muscle fatigue elicits a reduction in motor cortex excitability, spinal excitability, and the contractile capacity of the active muscle fibers. Therefore, an increased amount of descending drive from supraspinal regions is required to maintain task performance. Numerous investigations have conducted to identify the different method to decrease muscle fatigue during an endurance task. These studies have indicated that techniques that can increase motor cortex excitability could increase the time to task failure due to more efficient motor commands. Therefore, the main objective of this thesis was to investigate the ergogenic effect of transcranial direct current stimulation on endurance exercise performance in physically active people. In the first study, we performed a systematic review and meta-analysis to quantify the effect of a-tDCS on endurance (TTE and ETT) and sprint performance during cycling and running tasks. We found that the acute effect of a-tDCS increases TTE performance during endurance cycling and running (p = 0.04). The subgroup analysis revealed a positive effect of a-tDCS on TTE during cycling and running (p = 0.01), but not on ETT (p = 1.00) or sprint performance (p = 0.46). However, it should be noted that only four studies have investigated the ETT task, and two studies have investigated the sprint task. These results indicated that the task should be considered as it probably influences the results obtained by a-tDCS. Moreover, included studies results were inconsistent probably due to the influence of different tDCS parameters like stimulation duration, intensity, electrode montage, targeted brain area, and electrode size, which influence the excitability of the targeted brain area. In the second study, we conducted a crossover double-blind, randomized and placebo-controlled study design to investigate the effect of bilateral extracephalic tDCS applied over M1 during a constant-load cycling TTE task with 16 physically active people (3 women and 13 men). We found that bilateral extracephalic a-tDCS over M1 increases constant-load cycling TTE performance by 12% compared with

sham condition ($p = 0.04$), but without changes among two experimental conditions in HR response ($p = 0.12$), RPE ($p = 0.13$), and exercise-induced muscle pain ($p = 0.16$). Overall, this thesis shows that tDCS can influence active peoples' endurance TTE performance during cycling and running task. However, despite the influence of bilateral extracephalic tDCS over M1 on the increment in TTE, suggesting that no influence on variables including HR response, RPE, and exercise-induced muscle pain. Therefore, more studies are needed to understand the effect of tDCS on perceptual and physiological parameters during physical performance.

Keywords: tDCS, cycling performance, time to exhaustion, endurance, exercise-induced muscle pain, rating of perceived exertion, heart rate.

RESUMEN

El ejercicio de resistencia que consiste en ejercicio dinámico sostenidas de todo el cuerpo inevitablemente induce la fatiga muscular, lo que conduce al fracaso de la tarea. Se considera que el cerebro juega un papel clave durante la regulación del rendimiento del ejercicio de resistencia. Se cree que la fatiga muscular inducida por el ejercicio provoca una reducción de la excitabilidad de la corteza motora, excitabilidad espinal y la capacidad de contráctil de las fibras musculares activas. Por lo tanto, se requiere una mayor cantidad de impulso descendente de las regiones supra espinales para mantener el rendimiento de la tarea. Se han realizado numerosas investigaciones para identificar los diferentes métodos para disminuir la fatiga durante el ejercicio de resistencia. Estos estudios han indicado que las técnicas que pueden aumentar la excitabilidad de la corteza motora podrían aumentar el tiempo hasta el fallo de la tarea debido a los comandos motores más eficientes. Por lo tanto, el objetivo principal de esta tesis fue investigar el efecto ergogénico de la estimulación transcraneal con corriente directa sobre el rendimiento del ejercicio de resistencia en personas físicamente activas. En el primer estudio, realizamos una revisión sistemática y un meta-análisis para cuantificar el efecto de la a-tDCS en la resistencia (TTE y ETT) y el sprint durante las tareas de ciclismo y carrera. Encontramos que el efecto agudo de a-tDCS aumenta el rendimiento de la TTE durante el ciclismo y carrera de resistencia (p = 0.04). El análisis de subgrupos reveló un efecto positivo de a-tDCS sobre el TTE durante el ciclismo y la carrera (p = 0.01), pero no sobre en el ETT (p = 1.00) o el rendimiento del sprint (p = 0.46). Sin embargo, se debe tener en cuenta que solo cuatro estudios han investigado la tarea ETT, y dos estudios han investigado la tarea sprint. Estos resultados indicaron que la tarea debe considerarse, ya que probablemente influye en los resultados obtenidos por a-tDCS. Además, los resultados de los estudios incluidos fueron inconsistentes, probablemente debido a la influencia de diferentes parámetros de tDCS, como la duración de la estimulación, la intensidad, el montaje de los electrodos, el área del cerebro, y el tamaño del electrodo, que influyen la excitabilidad del área de cerebro objetivo. En el segundo estudio, realizamos un diseño de estudio doble ciego, aleatorizado y

controlado con placebo para investigar el efecto de tDCS extracefálica bilaterales aplicado sobre M1 durante una tarea de carga-constante con 16 sujetos físicamente activas (3 mujeres y 13 hombres). Encontramos que la a-tDCS extracefálica bilateral sobre M1 aumenta el rendimiento de TTE de ciclo de carga-contante en un 12% en comparación con la condición sham (p = 0.04), pero sin cambios entre dos condiciones experimentales en la respuesta de la FC (p = 0.12), RPE (p = 0.13), y el ejercicio-induce dolor muscular (p = 0,16). En general, esta tesis muestra que tDCS puede influir en el rendimiento de TTE de personas activas durante la actividad de ciclismo y carrera. Sin embargo, a pesar de la influencia de la tDCS extracefálica bilateral sobre M1 en el incremento de la TTE, lo que sugiere que no hay influencia en las variables que incluyen la respuesta de FC, RPE, y el dolor muscular inducido por el ejercicio. Por lo tanto, se necesitan más estudios para comprender el efecto de tDCS sobre los parámetros perceptivos y fisiológicos durante el ejercicio físico.

Palabras clave: tDCS, rendimiento ciclismo, tiempo hasta el agotamiento, la resistencia, dolor muscular inducida por el ejercicio, esfuerzo percibido, la frecuencia cardíaca.

I – GENERAL INTRODUCTION

I – GENERAL INTRODUCTION

1.1. ENDURANCE EXERCISE PERFORMANCE

This section discusses endurance exercises and the physiological determinant of endurance performance. Sport events that require an individual to perform for a prolonged duration over a long distance are generally called endurance events. These kinds of endurance sports include the most popular road cycling, middle distance running, marathons and ultra-marathons, many swimming events, triathlons, rowing, and cross-country skiing. Particularly, endurance performance is defined as the prolonged maintenance of submaximal power or velocity (10), as well as "during the whole-body, dynamic exercise that involves continuous effort and lasts for 75 seconds or longer" (11). Moreover, this kind of endurance performance is often referred to as cardiorespiratory or aerobic endurance. However, endurance performance is determined by several physiological factors.

1.1.1 Physiological determinant of endurance performance

There has been extensive research into determining the main determinants of endurance performance, including maximal oxygen uptake, lactate threshold and running economy. These physiological factors are determined by physiological variables such as muscle capillary density, maximum heart rate (HR) stroke volume, haemoglobin content, aerobic enzyme activity, muscle fibre type, and anthropometry and elasticity (12). The maximum Oxygen Uptake ($\dot{V}O_{2max)}$ has a predominant role in determining endurance performance. Previous researchers in exercise physiology have recognized that the ability to sustain repetitive muscle contractions was dependent on oxidative phosphorylation and the rate of oxygen delivery needed to meet the ATP demands of the muscles involved in the task (13). Recent studies provide considerable support for the hypothesis that performance in endurance events is limited by oxygen delivery, which is set by the subject $\dot{V}O_{2max}$ and percent of $\dot{V}O_{2max}$ that can be maintained (13). $\dot{V}O_{2max}$ is directly linked

to the rate of ATP generation that can be maintained during a distance race, even though distance races are not run at 100% $\dot{V}O_{2max}$ (14).

$\dot{V}O_{2max}$ is extensively recognized as an indicative measure of aerobic fitness and is used to prescribe the intensity during training sessions (15). However, due to its major role in endurance performance, it has been a long-term interest to understand the factors and mechanisms that limit $\dot{V}O_{2max}$. The $\dot{V}O_{2max}$ firstly introduced by Hill (16) suggests that the $\dot{V}O_{2max}$ is limited by the ability of the cardiorespiratory system to deliver O_2 to the working skeletal muscles. According to Hill's model, there is a physiological upper limit to maximal oxygen uptake, beyond which the oxygen uptake does not continue to rise (17). Consequently, endurance performance may be limited as a result of either a low oxygen uptake, a reduced maximum limit of oxygen uptake, or increased oxygen requirement (14) and this would be explained by the central governor model (18) and Psychobiological model (19-21). Previous investigations have demonstrated important physiological factors that could limit $\dot{V}O_{2max}$ (14, 22) including the pulmonary diffusing capacity, maximal cardiac output, the oxygen-carrying capacity of the blood, and skeletal muscle characteristics. The first three factors can be classified as "central" factors; the fourth is termed a "peripheral" factor (14). However, according to the previous evidence, $\dot{V}O_{2max}$ set the upper limit for energy production in the endurance event.

Another determinant of endurance performance is the lactate threshold. According to research, the percentage of $\dot{V}O_{2max}$ that can be maintained during an endurance event is dependent on the amount of lactate accumulation (23). Lactate threshold is a measure of the level of power output, $\dot{V}O_2$ or energy expenditure, where tissue hypoxia activates an imbalance between the formation and the clearance of lactate, leading to an increase in its concentration in the blood. Consequently, lactate during low-intensity exercise rarely exceeds baseline levels, whilst additional lactate provides evidence of anaerobic metabolism (24). Initially, it was understood that lactate was a waste product resulting from glycolysis, which converts glycogen into pyruvate, before being converted into Acetyl CoA and subsequently entering the Krebs cycle to release energy (17, 24). However, during intense exercise, lactate accumulates due to lactic acid production being greater than removals (24). When exercise intensity increases, blood lactate concentration

becomes higher due to several factors, including the extra demand for ATP not being met aerobically by mitochondria; and an increased reliance on fast-twitch fibres with fewer mitochondria and produce more lactate (24, 25).

Another important physiological determinant of endurance performance is the running economy or the ability to move economically. Studies have examined the effect of physiological factors on running economy. A growing body of literature studying the multiple factors involved in endurance events success has postulated that the performance is determined by maximal sustained power output and the energy cost of maintaining speed (14, 23). Analysis of research indicates that positive running economy changes reflect a lower oxygen consumption when exercises at the same submaximal exercise intensity. And they are likely to be accompanied by an increased long-term endurance, brought about by delaying fatigue, and enhanced anaerobic capacity and maximal speed (23). From this theoretical perspective, VO_{2max}, the lactate threshold, and economy of movement interact to determine the highest velocity or power that an endurance athlete can sustain during an event. This velocity or power is a strong predictor of endurance performance (26).

1.1.2 Measuring endurance performance

Performance testing is one of the most common and important measures in sports science and physiology. There are various methods of measuring endurance performance in laboratory and field settings (27). The most commonly used protocols are the time to exhaustion (TTE) test and endurance time trial (ETT) (27, 28). The TTE tests measure the amount of time a subject can perform at a fixed power output or velocity (i.e., 80% of a person's peak power output) before they reach exhaustion. The ETT measures the amount of time it takes to complete a set distance or a fixed amount of work (i.e., time to cycle 10 km). Even though both methods were exposed to be valid and reliable (27). However, TTE tests do not investigate the self-regulation of speed/power output during the exercise (i.e., pacing). Additional measures include constant-duration tests and incremental tests. Constant-duration tests measure the distance or the amount of work that a person can complete in a set duration (i.e., distance ran in 30 min.), and incremental

tests measure the highest velocity or power-output a person can reach before exhaustion (29).

Some researchers have argued that a sizable error of measurement exists in constant-power tests (Coefficients of variation ~ 10-30%) (30, 31). Currell et al. (28) state that ETT is the most appropriate measure for investigating whether an intervention affects endurance performance. These authors demonstrated that ETT presents greater reliability compared to TTE. Further, they have mentioned that ETT is more valid than TTE tests because performance times in laboratory ETT positively correlate with performance times in competition time trials (32). However, according to Amann et al. (27), TTE and ETT have a similar sensitivity to hypoxia and hyperoxia and, presumably, affect other affecting endurance performance. The choice between the constant-power test and ETT should be based on other considerations. ETT is the obvious choice for studies in which the effect of self-selected pacing on performed is an issue, whereas constant-power tests provide better control of workload for studies aiming to assess the association between physiological variables and physical performance. In the experimental study of this thesis, we used the TTE test as a measure of endurance performance.

1.2. BRAIN FUNCTION AND ENDURANCE PERFORMANCE

This section will discuss some of the most common models proposed in the literature to explain fatigue during endurance exercise, focussing on the central nervous system (CNS), which centralises the brain's ability to regulate endurance exercise performance. Over the past 20 years, exercise physiologists have paid more attention to the brain because of its potential ability to handle endurance performance. Therefore, many researchers have included the brain as a centre of the models used to explain endurance exercise performance regulation. Since the mid-1990s, multiple models have attempted to explain how exercise is regulated (21, 33-35). These models can be classified as 1) afferent feedback model, 2) the central governor model, and 3) the psychobiological model. These models explain the physiological and psychological factors currently through to limit endurance performance in either short duration and high intensity or long duration and lower intensity.

1.2.1. Inhibitory afferent feedback model

During high-intensity endurance exercise, exhaustion occurs when the subject cannot produce the force or power required (36). Amann et al. (37) reveal that an inhibitory afferent feedback model explains performance during high-intensity endurance exercise. According to them, the brain regulates the force produced by the muscle responsible for movement to limit muscle fatigue. In this context, muscle fatigue is related to an increase in afferent feedback from these muscles to the CNS. Therefore, these authors showed that this afferent feedback has an inhibitory effect on the magnitude of the central motor drive (see Figure 1). The brain will reduce the force produced by the leg muscles as these muscles exhaust. Once muscle fatigue reaches the person-specific threshold, the performer will terminate the exercise (i.e., stop performing a TTE test). By regulating central motor drive, the CNS allows the performer to avoid intolerable levels of effort and pain, avoid severe muscle dysfunction, and preserve a functional muscle reserve after exhaustion (38).

However, to test this model, experiments involving spinal blocked of muscle afferents before exercise have been implemented (77, 78). By blocking the possible contribution of muscle afferents, subjects should have improved exercise performance and reduced the degree of central fatigue. But these investigations failed to find any changes in central fatigue or exercise performance. However, the blockade of muscle afferents has been demonstrated to impair cardiovascular response and negatively affect endurance performance. The lack of alteration in central fatigue might have been caused by a delay in assessing of the neuromuscular function following exercise. Whilst afferents as a single mechanism limiting the endurance exercise performance seem unlikely, their integration into a wider system has received significant attention. However, model has been challenged with caution regarding the interpretation of experimental results. In the next section, the central governor model (CGM) and the psychobiological model of endurance performance are explained. These models adopt general approaches to understanding endurance performance, and they explain how a wide range of

physiological and psychological factors interact to determine endurance performance.

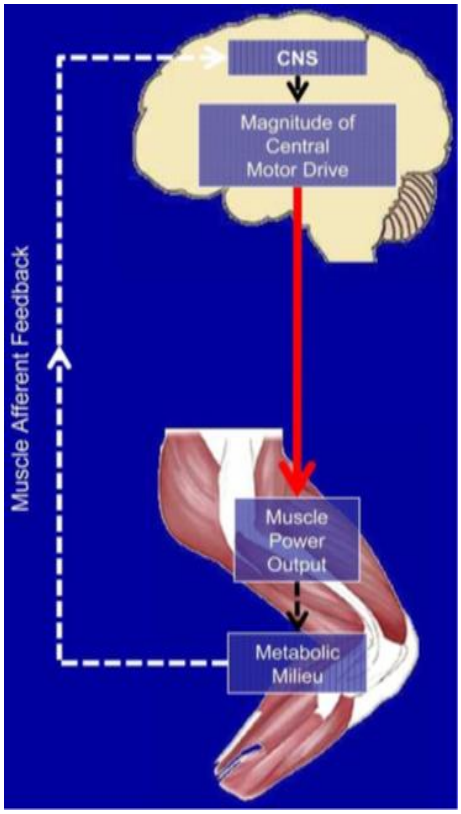

Figure 1. Schematic illustration of the afferent feedback model (5).

Note: The continuous line represents the central motor drive to the exercising muscles, while the dotted lines indicate the afferent feedback signal originating from group III/IV afferent fibres.

1.2.2. Central governor model (CGM)

In 1996, Ulmer (35) suggested that exercise performance might be controlled by a governor located somewhere in the CNS (35). Later, based on this model, Noakes introduced the current CGM (see Figure 2) (34, 39). This model proposes that a central governor (CG) located in the brain serves as an 'intelligent' regulator

of muscle recruitment with the primary role of protecting the body from a catastrophic failure of homeostasis (i.e., terminal loss of physiological system). According to the CGM, the CNS regulates the work rate that can be continued for an expected exercise duration and the moment at which exercise terminates, all to ensure that homothecies are maintained (34). Further, there are some important assumptions for exercise regulation. The brain does not recruit additional motor units during prolonged exercise because other recruitment would threaten the capacity to maintain homeostasis (34). Additionally, exhausting exercise's increasing perception of discomfort progressively reduces the conscious wish to over-ride this control mechanism (39). Another aspect of the CGM is that all changes in pace and termination of exercise occur as part of the regulatory strategy that is dynamic and continually altering and serves the teleological purpose of protecting the body from damage (34). The CGM proposes that perceived exertion (RPE) is playing a crucial role in preventing physical damage.

According to the anticipatory feedback model (40), based on the CGM, volitional exhaustion happens during endurance exercise when the RPE reaches intolerably high or uncomfortable levels. This intolerable level precedes potentially negative pressures to homeostasis. When the TTE test evaluates endurance performance, the anticipatory feedback model suggests that a "central controller" in the brain related to the CG subconsciously predicts the exercise duration that can be safely completed at the onset of exercise. And then, it uses this prediction to set an initial rate of increase in RPE**.** Therefore, during the exercise session, the central controller continuously uses afferent feedback from various physiological systems to regulate the pace of development in the perception of effort. Hence, the maximum sustainable RPE and consequent termination of exercise coincide with a duration that does not pass the body's safe physiological limit.

The CGM describes the effects of a wide range of physiological and psychological factors on endurance performance. However, the plausibility of this model has been challenged. For example, Noakes et al. (18) argued that a CG is essential to avoid myocardial ischemia development during exercise. Further, it has been documented that ultra-endurance athletes also develop myocardial ischemia (16). Moreover, the CGM proposes that RPE result from afferent signals representing the body's peripheral physiological changes during exercise. The

concept has been further challenged by some experiments, where, despite the spinal blockade of afferent signals from the exercising muscles, the RPE during exercise was not affected (38, 41). Together with previous investigations, this evidence further reveals that the RPE is independent of afferent feedback from the muscles and heart (20). Moreover, Marcora et al. (21) argued that the psychobiological model of endurance performance elucidates research observations equally well without relying on unproven assumptions, such as the existence of subconscious CG or RPE templates.

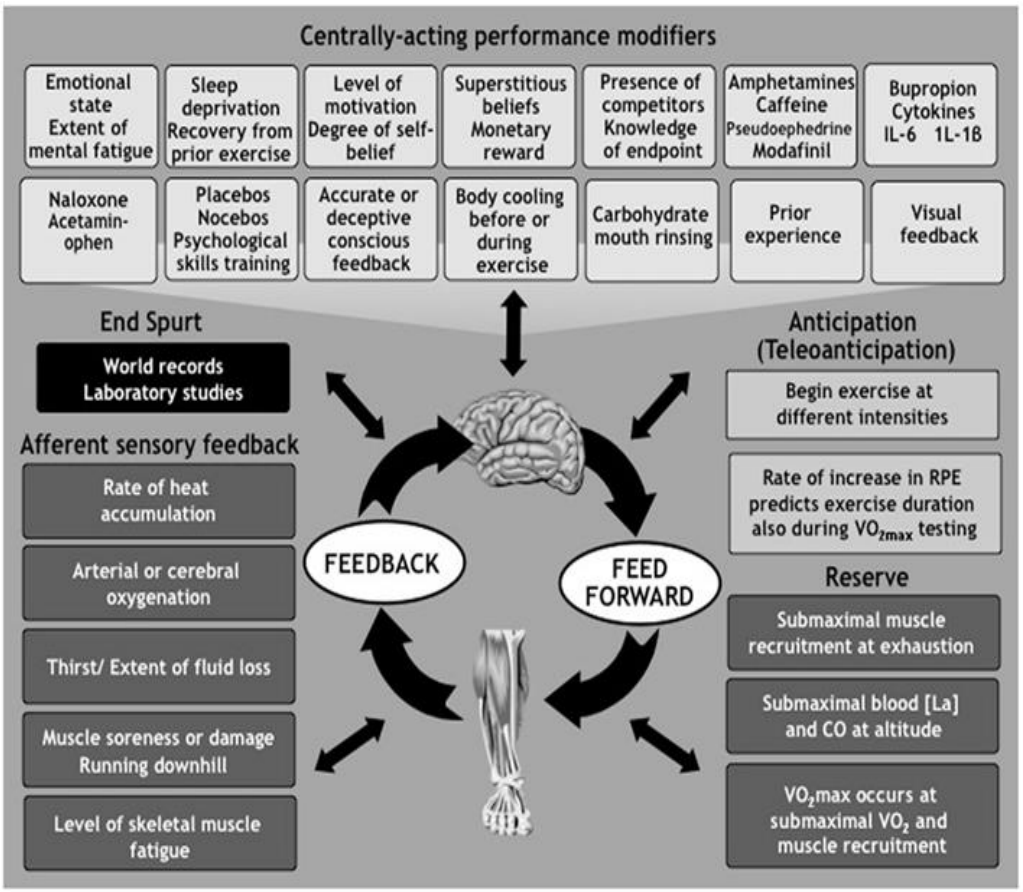

Figure 2. Update representation of the central governor model (3).

1.2.3. Psychobiological model

The psychobiological model is a model of endurance exercise performance based on a psychological theory proposed by Marcora et al. (19, 42) and it is based on the Brehm's motivational intensity theory (43, 44). It has been described through two main concepts: potential motivation and effort. The possible motivation refers to the maximum effort that the subject is willing to achieve in the task (43). In contrast, effort is the conscious sensation of how effortful heavy, and strenuous the exercise feels (19). It reflects a person's conscious awareness of the central motor commands sent to the locomotor and respiratory (20). According to the model, each subject is disposed to achieve the task, while effort can be expressed as the subject's effort. In other words, each subject will continue their task until the level of effort exerted reaches the maximal level.

An individuals' RPE and potential motivation also explain their endurance performance during time trials. In this case, the exerciser knows the total performance time or distance that they need to complete and has previous experience with the different exercise of varying intensities and durations (19). During TTE, the RPE increases over time (39, 45) and high values determine exercise disengagement. This phenomenon occurred when the exerciser did not prepare to invert the required effort or believe the task is possible (42). For example, during a TTE test, RPE gradually increases until a maximal level that coincides with the point of exhaustion.

According to the psychobiological model, an individual stops exercising with different physiological bodily stress, other environmental conditions, or under various external manipulations. For example, cycling with pre-fatigue locomotor muscles results in earlier exercise termination (42). This can be explained by the reducing the muscular apparatus responsiveness and the consequent increase in central motor command and RPE to maintain the same absolute power output compared to the non-fatigue state (42). Consequently, the exerciser disengages earlier from TTE exercise when mentally fatigue (20). This is explained by the higher RPE levels once mentally exhausted, as cardiorespiratory and muscular/energetic parameters did not differ between conditions (20). However, exhaustion can be postponed if the exerciser's potential motivation is higher once the critical level of RPE will be reached later in the same task. This model postulates

that an athlete decides to stop or give up the endurance exercise (or slow down, disengage from the task) when sustaining the required or desired velocity/power is perceived as impossible or excessively difficult to what they are willing to offer to achieve the particular outcome.

1.3. PHYSIOLOGY OF EXERCISE-INDUCED FATIGUE

1.3.1. Exercise-induced muscle fatigue

Exercise-induced muscle fatigue is a multidimensional concept comprising physiological and psychological aspects, and accordingly, definitions of fatigue vary between disciplines (46). In exercise physiology, the purposes of fatigue typically focus on the time-related loss of power during physical exercise (46) and any exercise-induced reduction in muscle ability to generate force or energy (47). This gradual decline in maximum muscle force capacity relative to pre-fatigue values can be viewed as developing activity-dependent weakness that resolves with rest (48, 49). It includes an acute impairment of exercise performance that leads to increased RPE and eventual inability to produce high quality and high amounts of muscular power (50). The neuromuscular fatigue mechanism is related to changes in both the central and peripheral nervous systems, which may lead the active muscle to fatigue, involving central fatigue. Fatigue in the neuromuscular junction and exhaustion occurring in the muscle is described as peripheral fatigue (51). It has been shown that the nervous system's failure to maintain sufficient activation of the muscle during exercise significant contributes to task failure in sustained submaximal contractions (47-49, 52) (see Figure 3).

Skeletal muscle tissue is related to voluntary control. Further, skeletal muscle tissue is composed of relatively large cells known as the muscle fibre, which can be categorised depending on the contractile twitch speed. When muscle tissue contracts the muscle, cells depolarise. When a motor neuron depolarises, an electrical current (the action potential) is passed down the nerve fibre. A motor unit is consisting of a single motor neuron located in the spinal cord and all of the muscle fibres that it innervates. The nerve and muscle communication area known as the neuromuscular junction or the motor endplate. After the electrical impulse

is transmitted across the neuromuscular junction, it is provoked in all of the particular motor unit's innervated muscle fibres.

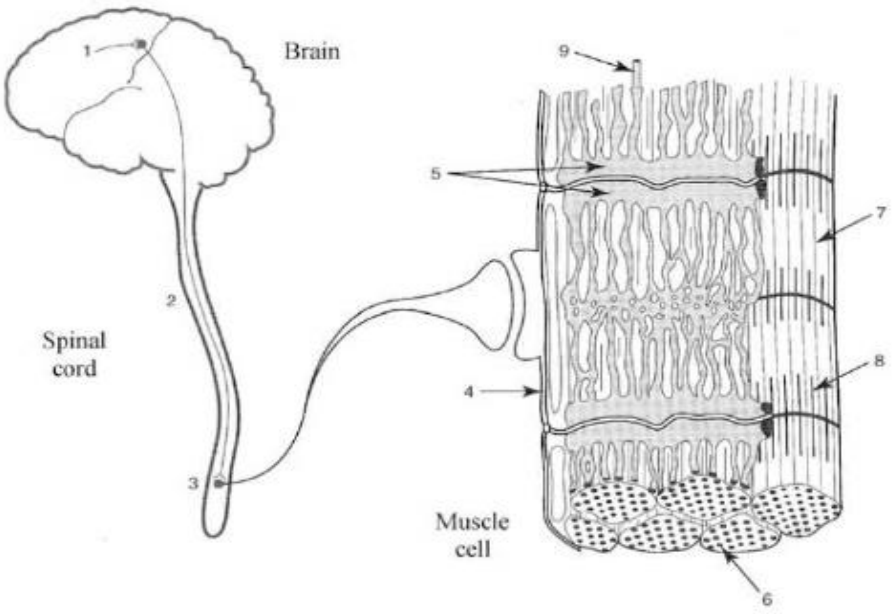

Figure 3. Site contribution to muscle fatigue (4).

Note: Fatigue may be due to alterations in 1) activation of the primary motor cortex (supraspinal fatigue); 2) propagation of the command from the central nervous system to the motoneurons (spinal fatigue); 3) activation of the motor units and muscles; 4) neuromuscular propagation (including propagation at the neuromuscular junction); 5) excitation-contraction coupling; 6) availability of metabolic substrates; 7) state of the intracellular medium; 8) performance of the contractile apparatus; 9) blood flow.

Traditionally, investigators have fundamentally focused on factors that result in dysfunction of the contraction process within the muscle itself (peripheral fatigue), with little consideration for CNS fatigue's important role. However, muscle fatigue contains both central and peripheral components, although their contribution to fatigue seems to be task-dependent (49). During sustained submaximal contractions, muscle fatigue will be present before task failure;

however, task performance will continue for some time without appreciable disruption (47, 48). When the task duration increases, muscle fatigue will progress to the degree. It interferes with the capacity to sustain the precise amount of submaximal force output required impeding accuracy of performance and eventually prohibiting effective task performance. However, task failure becomes the point when the force output required for successful task performance can no longer be sustained as demanded by the activity (53).

1.3.2. Central fatigue

Alteration within the CNS associated with the onset of fatigue is broadly classified as "central fatigue". Given the neuroanatomical and physiological link between the nervous system and the muscles, the complex interplay between these two systems provides various hypotheses regarding the causes and origin of fatigue within the CNS (47). A decrease in muscles' voluntary activation level during exercise has been defined as central fatigue (47). Central fatigue may occur at various levels and for several reasons, including i) loss of recruitment of high threshold motor units (54, 55); ii) reduced central drive (56); iii) blocked central conduction from motor neuron dropout (57); and iv) increased negative feedback from muscle afferent type III and IV sensory neuron (58).

Particularly, when fatigue occurs at a spinal level is defined as spinal fatigue, leading to a decrease in the motoneuronal pool's excitability (47). It has been hypothesized that a complex system resulting from muscle response at the spinal level might be the key contributor to the motoneuron's inhibition (47). Muscle spindles (group I a and II afferents) are well known to detect variations in muscles' mechanical tension during exercise. Their inputs at a spinal level have been suggested to contribute to the spinal fatigue (47). However, it should be considered that their inhibitory effect at a spinal level is still uncertain. This is likely because of difficulty isolating these structures and their variable and rapid discharge rates during muscle contraction (47). Another group of muscle afferent classified as group III and IV likely contributes to the spinal level's inhibitory effect due to their projection at the spinal cord's dorsal horn (59). These afferents have been demonstrated to be sensitive to exercise-induced metabolites (K^+, La^- , H^+, phosphates) and mechanical variations in the muscle (60). Numerous research

studies had exposed the motoneuronal pool's modification when group III and IV afferents were activated, thus supporting the hypothesis of an inhibitory effect at the spinal level (61). Supraspinal fatigue can be defined as a suboptimal output from the motor cortex to the muscles (47). Limiting supraspinal sites' influence in central fatigue progress has been facilitated by developing the transcranial magnetic stimulation technique. Moreover, recent studies propose that a decrease in oxygen availability to the brain might in part lead to supraspinal fatigue (62), which further increases during acute exposure to hypoxia (63). Furthermore, metabolic changes within the brain have also been demonstrated to increase supraspinal fatigue (64-66).

1.3.3. Peripheral fatigue

A variety of cellular mechanisms contributes to the generation of peripheral fatigue. The equilibrium of electrolytes inside and outside the cell is fundamental and consequently, any change in the electrochemical properties of muscle cells might compromise the force generated. Observed differences in the concentration of Na^+ inside the cell, with an increase of K^+ outside the cell (67), might in part explain the changed propagation of the action potential (67). Peripheral fatigue has also been associated with modification of Ca^{++} (68). It is known that Ca^{++} is fundamental in the development of cross-bridges, and any decrease of Ca^{++} availability or kinetics will reduce the force generation capacity of the muscle fibre (38).

Peripheral fatigue has been observed during both short (38) and prolonged exercise tasks (56), and the magnitude of peripheral fatigue is affected by the type, duration and intensity of the exercise performed (46). Greater peripheral fatigue has been documented during short-duration intense exercise (38), which is also characterised by a large contribution of the anaerobic metabolism (46). The anaerobic breakdown of glycogen is well recognised to increase intracellular acids such as lactate and H^+. Accumulation of lactate and H^+ causes a decrease in pH, which has been correlated with a decline in force production (69). These mechanisms are also dependent on the level of oxygen available to the exercising muscles.

1.3.4. Task failure during physical exercise performance

The term "task failure" is defined as the point at which a subject cannot maintain the level of force needed to execute a task (70). As we discussed previously, the mechanism leading to task failure may involve the physiological process of neural (central fatigue) or muscular level (peripheral fatigue), with failure distal to the neuromuscular junction including in the peripheral component (47). For healthy individuals performing sustained whole-body dynamic exercises (i.e., cycling and running), fatigue is an expected and normal physiologic reaction that inevitably leads to task failure (47, 71). It has been shown that during submaximal or maximal contractions sustained until voluntary exhaustion, an increase in muscular activation occurs due to the progressive recruitment of muscle fibres (47).

Furthermore, task failure has been associated with an initial rise, followed by a decline, in the discharge frequency of the motor neuron pool (72) and with an increase of the neural drive to muscles (73) and the high-frequency alternations at the corticospinal level (74). Moreover, recent studies have reported peripheral fatigue's contribution at the point of task failure (75). The physiological instance of fatigue relates to the task failure of the metabolic properties in the contracting muscle. When the amount of waste is increased, the muscle difficulty in continuing its task is also increased. Overall, the muscle fatigue caused by the accumulation of lactic acid in the muscle tissue and glycogen reduction compromises the muscle's contractile properties.

1.4. PERCEPTUAL PARAMETERS DURING ENDURANCE EXERCISE

This section will discuss two important perceptual parameters measured during the cycling TTE task; RPE and exercise-induced muscle pain. Both parameters play an important role during exercise, and due to their importance in our experiment, this section aims to discuss the function they both have during endurance exercise. Knowing the processes that limit endurance performance is a fundamental element for performance enhancement. This is because, in most situations, these limiting processes must be targeted to elicit performance enhancement. As such, once a limiting process is identified, specific strategies can

be implemented to directly target or overcome this limitation and activate acute or long-term performance improvements.

Physiological factors limit endurance performance, and many performance enhancement strategies have been developed, from physical training to nutritional interventions (76). The nutritional strategy focus on the timing, quantity and proportion of micronutrient intake (77, 78). Moreover, hydrogen buffers, such as sodium bicarbonate and β alanine (79), have been used to target cardio-respiratory and biochemical processes, respectively. The research, as mentioned above strategies have demonstrated a positive effect on endurance performance. Besides, it has been recommended that the restrictions to endurance performance are regulated by psychobiological factors (20). This highlights a theoretical change towards a model where endurance performance is influenced by conscious and voluntary factors such as effort and motivation (21) as different to involuntary physiological processes (80).

1.4.1. Perception of effort (RPE)

Sensation has been defined as the specific process of instantly detecting a stimulus in the environment (81). Perception relates to how one understands the information gathered and processed by the senses resulting from this stimulus (81). Therefore, perception is a subjective interpretation of a particular inspiration (82). In the exercise context, the RPE has been defined as how hard an exercise is perceived (20). However, RPE is a fundamental component of most central models of exercise regulation. Usually, endurance exercise is related to the level of exertion that arises from the exercise task.

The RPE has been measured through the subjective rating obtained via the Borg's RPE scale, and recently the category-ratio (CR10) scale. The subjective measurement of RPE is a feature of many endurance-based exercise studies (7, 83, 84). In open-loop (until exhaustion) studies, which are defined by the absence of a known endpoint (85), RPE consistently increases with time on task (42, 86). Furthermore, when open-loop studies require the participant to exercise to exhaustion at a fixed workload, task termination coincides with a maximum or near-maximum RPE (19, 87). This remains the case when RPE is experimentally operated, for instance, by changing environmental temperatures (7) or inducing

pre-exercise muscle damage (42), and regardless of whether this causes an increase (87) or a decrease in exercise task duration (88).

Some researchers conclude that this maximum RPE causes the individual to terminate exercise (20, 89) consciously. Similarly, in closed-loop studies, which consist of a self-regulated exercise intensity towards a known endpoint (54), subjects are recommended to continually adjust their pacing to maintain an RPE that permits them to complete the task (42). This is evident when an intervention causes a change in RPE, such that individuals are compelled to reduce their workload to sustain a given RPE (90), or individuals can achieve a higher workload for an equal RPE (91). For each of these reasons, RPE is considered to be an essential factor for endurance performance (20).

Recently, researchers have proposed different theories to explain the way that RPE is generated. Some researchers contend that RPE is a product of involuntary peripheral changes within the working muscles during exercise (80), or the integration of afferent signals from group III and IV afferent receptors within the heart, muscles and lungs (38). When performing an exercise, the accumulation of exercise-induced muscle metabolites (La^-, NA^+, K^+) stimulates these peripheral receptors (92, 93). Therefore as the exercise intensity increases, the further accumulation of metabolite stimulates peripheral receptors, leading to increased RPE (94).

Another model proposed by Marcora (2009), the corollary discharge model of RPE, indicates that RPE is centrally generated by the central command's efferent neural process (20, 95). Accordingly, any increase in the of central command's magnitude should be immediately followed by a parallel development in RPE (95, 96). Recent studies have demonstrated a relationship between the motor and premotor areas' activation and the increase in RPE (97). This model provides a simple explanation for the increment in the RPE during various kinds of exercise tasks. For example, when locomotor muscle weakness is induced before an exercise task, a compensatory increase in central command is required to produce the same amount of force or power. This has been demonstrated in experiments showing a significant rise in RPE during exercise in pre-fatigued muscles (42, 97).

A progressive increase in RPE has also been observed both during prolonged isometric and dynamic exercises (20, 98). During different exercise types, the increase in RPE is likely due to the increase in central motor command required to

compensate for the exercise-induced muscle fatigue (42, 98). However, this RPE is accompanied by grown levels of fatigue (99). Athlete's exercise performance may be progressively reduced, reflected in lower power output and increased time to complete a task (100); consequently, more effort is needed to perform the same function. Thus HR increases (101). Alternatively, lowering RPE by increased power output decreased the time required to complete an exercise task, leading to an enhanced performance (100, 102). Here, it resulted in less effort needed to maintain the physical task (99).

1.4.2. Exercise-induced muscle pain

Pain is considered a human primate instinct and can be defined as a distressing sensation and as emotional experience linked to actual or potential tissue damage (103) to notify the body's defence mechanism to react towards a stimulus to avoid further tissue damages. The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (104). Pain perception was measured across the experiment in this thesis, and so this section will provide a background detailing factors affecting exercise-induced muscle pain. Principally, both the central and peripheral nervous systems are involved in the mechanism and pathways of all variations of exercise-induced muscle pain perception (6). The peripheral nervous system includes nerves and ganglia located outside the brain and spinal cord, principally permitting us to connect the CNS to organs and limbs in our body. The CNS is involved in the spinal cord and the brain, mainly for organizing and interpreting the information sent from the peripheral nervous system, and afterwards coordinating all our bodies' activities before sending response towards the effector organs (6). Peripheral nociceptors are generally classified in type III and IV muscle afferents and are sensitive to differences in concentration of metabolites, mechanical pressure, heat, cold, and endogenous substances (6). Metabolites such as H^+, K^+, La^-, and prostaglandins are the results of anaerobic metabolism during exercise. Their concentration will vary according to the exercise duration, intensity, and the size of the muscle mass involved in the task.

The peripheral pain receptors originate in and around the muscle and/or other peripheral structures and join the spinal cord's dorsal horn. When identified by the nociceptor, a nociceptive signal ascends to subcortical and cortical brain regions, such as the somatosensory cortex and the ventroposterior lateral nucleus thalamus (6, 105), where the nociceptive stimulus becomes conscious and is perceived as pain (see Figure 4). Some authors have suggested that pain tolerance could be higher in athletes than non-athletes, which might be an important requirement for athletes in specific disciplines (8). Although pain sensation is frequently quantified, the pain's role throughout the exercise has received little attention, and so its part on performance is still speculative.

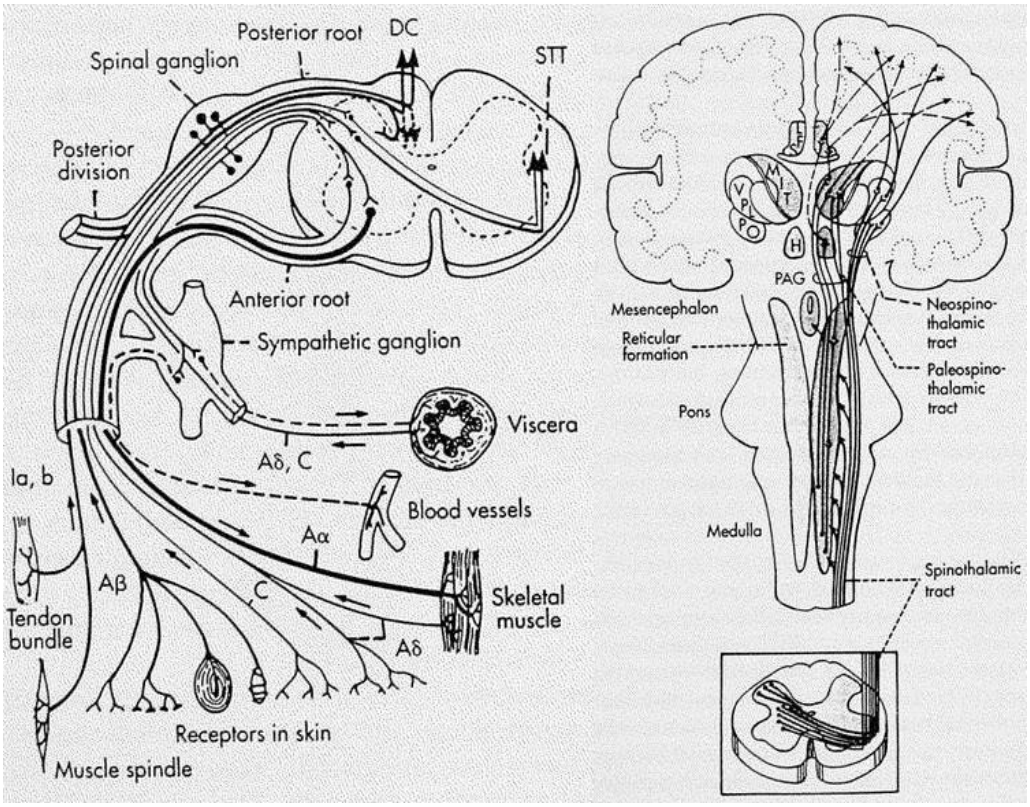

Figure 4. Peripheral and central structures involved in the processing of pain (6).

The regulation and effect of pain during exercise have been examined using different experimental procedures. These measures may explain the role of pain

during exercise (increase, decrease or block the peripheral signals from the muscle). Incremental tests performed on a cycle ergometer have demonstrated a relationship between pain ratings and exercise intensity (105). Graven et al. (106) have revealed that pain-induced through an intramuscular injection of the hypertonic saline solution decreases MVC of the knee extensors. Collectively, many studies recommend that whilst pain might not be the only factor of endurance performance, and it may play at least some role in the regulation the work rate during exercise performance. Nevertheless, methodological difficulties make this concept difficult to verify and further studies are essential to explore this paradigm.

1.5. BRAIN STIMULATION AND EXERCISE PERFORMANCE

This section will discuss non-invasive brain stimulation and its main role during exercise performance.

1.5.1. Brief evolution history of brain stimulation techniques

There has been an interest for more than 200 years in the potential use of weak intensity electrical currents to modify brain function (106). Various forms of electrical stimulation were developed during this period. The first discovery of using an electrical current to increase the different human condition by treating pain goes back to the reign of the Egyptian Empire and ancient Greece. Some physicians directed experiments applying electric fish as feasible treatment (107). As the first evidence of transcranial stimulation, Scribonius Largus, a Roman physician, described how placing a live torpedo fish over the scalp to treat headache in a patient (107). Another experiment was carried out in the 11th century, the Muslim physician in Persia, Ibn-Sidah, who using torpedo fishes to treat epilepsy (108). Concerning, fish, electricity was maybe the most popular type of electric stimulation for more than ten centuries, whether it is not clear how the effects were measured.

However, its electrical properties were only discovered a few centuries ago by Luis Galvani (1737-1798), whom first found that frogs' nerve and muscles were electrically excitable (see Figure 7). Later, two investigators, Aldini (1762-1834) and Le Roy (1723-1789) demonstrated the possibility of electrically stimulating the

human brain. Using similar techniques of those previous two scientists, Galvani has been shown responses such as blinking or opening the eye by evoking cadavers. Subsequently, Luigi Rolando (1773-1831) carried out several lesion experiments and stimulation of central nervous structures' surface. Using a voltaic pile and crude electrodes, he obtained limb movements, which became stronger in the cerebellum's vicinity. Further, he erroneously concluded that this structure was the brain's "source of vital motor energy" (109). This finding was furthered by Alexander von Humboldt (1769-1859), Carlo Matteucci (1811-1868) and Emil Heinrich du Bois-Reymond (1818-1896) discovered that muscles and nerves could generate electricity by themselves, and thus developed more advanced techniques to stimulate the central and peripheral nervous system. The pioneering work of mapping the brain cortex with electrical stimulation was done in 1870 by Eduard Hitzig (1838-1907) and Gustav Fritsch (1838-1927). Those who carry out experiments of localized electrical stimulation of several animals' brain cortex (109).

Nevertheless, with the development of advanced devices that can produce electrical or magnetic impulses, non-invasive brain stimulation (NIBS) techniques were subsequently expanded. In the 1960s, the studies of D. J. Albert confirmed the different effects of negative and positive stimulation on changing brain cortical excitability and function (110). These findings laid the base for the modern tDCS technique. After that, in 1985, Barker and colleagues introduced the first transcranial magnetic stimulation model, which permitted the non-invasive stimulation of a targeted brain area. For This thesis's purpose, one of the main NIBS technique used in sport science named transcurrent direct current stimulation (tDCS), will be discussed in the following section.

1.5.2. Transcranial direct current stimulation (tDCS)

In the last few decades, tDCS was re-evaluated and shown to modulate human cerebral cortical function (111). tDCS is a NIBS technique and differ qualitatively from other brain stimulation techniques such as transcranial electrical stimulation and transcranial magnetic stimulation by not introducing neuronal action potentials. Because the static field in this range does not yield the rapid depolarization required to produce action potentials in neural membranes (111).

Therefore, tDCS might be deemed as a neuromodulatory intervention. The exposed tissue is polarized and tDCS modifies spontaneous neuronal excitability and activity by stimulating (depolarization and hyperpolarization) the resting membrane potential (108, 112).

The brain tissue polarization is obtained by the passage of a weak constant electrical flow from the anode to the cathode electrode. As a consequence, the spontaneous firing rate increases under the anodal electrode and decreases under the cathodal. The multiple potential benefits of tDCS have revived the interest in this technique. The tDCS is a form of neurostimulation technique that has been widely accepted to be effective for the treatment of depression (113, 114), cognitive enhancement in both healthy and clinical populations (115, 116), treatment of chronic pain (106, 117) and improving motor function in post-stroke patients (118). More recently, tDCS has been used as a potential modulator of sports performance (1, 119-121).

1.5.3. Technical aspects of tDCS

1.5.3.1. tDCS electrodes preparing and contact medium

The key purpose of tDCS electrodes is to facilitate the distribution of current from the stimulation device to the scalp (122). And the electrode selection is always based on the tDCS protocol used. Generally, the following electrode arrangements are used for tDCS i) metal or conductive rubber electrode, ii) an electrode sponge, and iii) an electrolyte-based contact medium (i.e., saline, gel, or conductive cream) to facilitate the delivery of current to the scalp, iv) any materials used to shape these components (123). Moreover, during tDCS, electrodes are not recommended directly in contact with the skin. After all, these site undergo electrochemical reaction during tDCS application (124). Especially, an electrolyte is used as a buffer between the electrode and the skin; therefore, with appropriate electrolyte volume, avoiding chemicals produced at the electrode from reaching the skin (125). However, the electrolyte can be placed on a sponge encasing the electrode (e.g., saline) or the case with electrode cream, applied directly on the electrode surface. Further, it is important to obtain good contact under, and only under, the electrode

with the electrode sufficiently, but not excessively soaked (123) because this makes a critical point for investigators to take proper outcome during the experiment.

1.5.3.2. tDCS electrode placement

It is also important to know where to place electrodes on the head. Based on previous studies, physiological changes following tDCS demonstrated that the relative location of electrodes results in a significant difference in where and how much current is delivered to the brain (126, 127). For example, the relative differences of electrode locations altered whether or not tDCS impacted transcranial magnetic stimulation generated motor-evoked potentials (112). Specifically, Wood et al. (126) have demonstrated that as little as 1cm of movement in electrode position significantly changes the brain's projected current flow distributions. Moreover, electrode placement is important on the head. Regarding this, the head size and shape differ from person to person, so it is important to use a method for common localization of electrode position. The most popular way is the international 10–20 (or 10–5) electrode placement system (128). Furthermore, physiology-based placement can only be performed for motor and other primary cortices (126).

After setting the electrode location, the electrode assembly must be attached to the head to deliver the current. Non-conductive headgear is used to position the electrodes on the body or scalp (i.e., elastic straps) because they are critical for appropriate electrode placement (126). For tDCS using sponge-covered electrodes, adjustable straps are the most commonly used headgear for electrode placement. In this way, if these straps are under-or over-tightened, electrodes have a high tendency to move throughout a tDCS session. Consequently, the distribution of current delivery changes throughout a tDCS session (126). On the other hand, if electrode straps are over-tightened, there is an increase in the probability of saline evacuation from the electrode sponges. Nevertheless, the contour at the base of the skull below the inion and the forehead's flat deliver for steady placement of a strap around the head. Moreover, for the participants with long hair, order of the back of the strap under the hairline also improves the strap preparation's stability.

1.5.3.3. Blinding and sham

The typical method of blinding the subjects for plasticity inducing protocols is to apply a ''sham" stimulation protocol, which includes ramping stimulation up and down like in the real stimulation condition, but to stimulate with the target intensity only a few seconds (i.e., 30 seconds). Then subjects will feel the initial itching/tingling sensation. Moreover, the experimenter blinding concerning specific stimulation protocol is proficient by using stimulators that include a sham stimulation function, thus keeping the experimenter unaware of the particular stimulation condition. However, double-blinding, a couple of approaches are available, which should be chosen carefully considering the specific experimental design.

1.5.4. tDCS parameters

The effect of tDCS on cortical excitability mainly depends on different parameters such as the region stimulated, the intensity of the current (mA), the duration of the stimulation, the placement and size of the electrodes, and the type of task (129). Manipulation of these parameters was observed to alter the magnitude and effect of tDCS stimulation in the targeted brain area (130).

Stimulation parameters such as current intensity and the stimulation duration are crucial to consider (112). The majority of behavioural studies and clinical trials apply current intensities of 1 - 2mA with an electrode size of 25 cm^2 (5 x 5) to 35 cm^2 (5 x 7) and stimulation of 5 - 30 min, which is considered a safety protocol in humans (131). The first experiment investigating different tDCS intensity dosages was performed by Nitsche (112), who maintained the electrode size of 35 cm^2 and monitored the cortical response following an increased stimulation intensity from 0.2 to 1 mA. This experiment showed for the first time that cortical excitability was increased more using higher current intensities. The previous studies demonstrated that the 2 mA of current intensity with 35 cm^2 sizes of electrode, can increase TTE performance during cycling task (119, 132, 133). The efficacy of tDCS to induce acute modifications of membrane polarity depends on current density, which determines the induced electrical field strength (106). Density is calculated as the ratio between current intensity and the size of the

electrode. Studies have been shown that lager current densities result in more powerful effects of tDCS (112, 134).

Regarding tDCS brain stimulation area, most studies targeted the primary motor cortex (M1) (72.5%), prefrontal cortex (PFC) (9.1%) and temporal cortex (TC) (13.6%) (135). Particularly, stimulating M1 aimed to increase its excitability in order to extend the neural drive to the active muscles and delay central fatigue. The motor cortex is an efferent structure responsible for the voluntary movements on the body's contra-lateral side. The motor cortex receives inputs from both sensory pathways and other motor control regions and is ultimately responsible for planning, initiating and executing voluntary movements (136). The M1 lies within the pre central gyrus. It gives rise to many large outputs (pyramidal) cells synapse with motoneurons in the spinal cord's ventral horn responsible for evoking muscular contractions. Many studies suggest that physical exercise leads to specific changes in brain organization's functional and structural level. It is well known that M1 is a key region involved in motor control and functions in terms of perception, speed, strength, endurance and execution of the daily motor task. The PFC stimulation aims to improve top-down control over M1 output due to an enhanced physiological and psychological conditions. And the TC stimulation aimed at increasing parasympathetic control to postpone its with driving during exercise, which is related to the delay of fatigue.

The difference in changes to exercise enhancement arising from tDCS is potentially a consequence of different experimental and methodological configurations. According to recent evidence, a notable methodological difference has shown in the use of cephalic or extracephalic electrode montage. A cephalic electrode montage involves placing the anode electrode over the M1 (or main target area) and the cathode electrode (i.e., reference) placed over the contralateral prefrontal area (102, 137). An extracephalic montage places the cathode electrode on the opposite shoulder (120, 133, 138), rather than the head's contralateral areas. The anode (a-tDCS) electrode increases excitability over the placed areas, while the cathode decreases excitability. In this context, cephalic montage, may induced an effect under the cathode that may modulate or negate the anode's effect over M1 (138). Extracephalic montage may avoid this problem. Angius et al. (137) compared cephalic and extracephalic tDCS montages by targeting a-tDCS over the M1. They demonstrate that shoulder (extracephalic) montage is more effective than head

(cephalic) montage to improve endurance performance, likely by avoiding the cathode's adverse influence on excitability. Recently, many studies have demonstrated the effectiveness and safety of extracephalic montage (138, 139).

Regarding the duration of the tDCS, most studies report a time that oscillated between 10 and 30 min (140, 141). The duration of stimulation depends on the persistence of prolonged effect. Regarding this Nitsche et al. (2) showed an elevation of cortical excitability (increased MEP size) for up to 90 min following a 9 – 13 min stimulation protocol. However, when tDCS applied for 5 - 7 min the effects lasted for no longer than 5min (see Figure 5). However, tDCS should be applied over a sufficiently long time to modify the synaptic strength by modulating the activity of N-methyl-D-aspartate receptors (142). The relationship between the stimulation time and the duration of the effect is not linear and can be reversed beyond a certain time.

The electrode size and polarity are also important parameters contributing to the final output of stimulation. The tDCS used low amplitude direct currents applied via scalp electrodes to modulate the corticospinal excitability level (112). The direction of the changes depends on the polarity of the active electrode. Application of a-tDCS over the target brain area depolarized the resting membrane potential and caused increased excitability. The opposite is the cathode electrode, which hyperpolarizes the resting membrane potential and causes reduced excitability (140). Electrode size regulates the applied current's spatial focality, and tDCS is poorly focused using a large rectangular pad electrode configuration (143). Interesting, only one study has examined the focality of a-tDCS and the effect of a-tDCS, and the effect of a-tDCS was measured by manipulating the size of conventional pad electrodes (143). They found that a-tDCS, with 3.5 cm^2 anodes placed over the abductor digiti minimi representation over M1, did not modulate the excitability of the neighbouring representation of the first dorsal interosseus muscle, which lay just outside of the physical limit of the anode.

The parameters mentioned above change between studies and according to the objective of the stimulation. Consequently, it is not surprising that there is considerable variation in the tDCS set-up used across studies. It is also important to note that the brain does not passively accept it on receiving stimulation but reacts somehow (139). Therefore, the exact effects of tDCS on brain tissue are still not clear and yet to be defined.

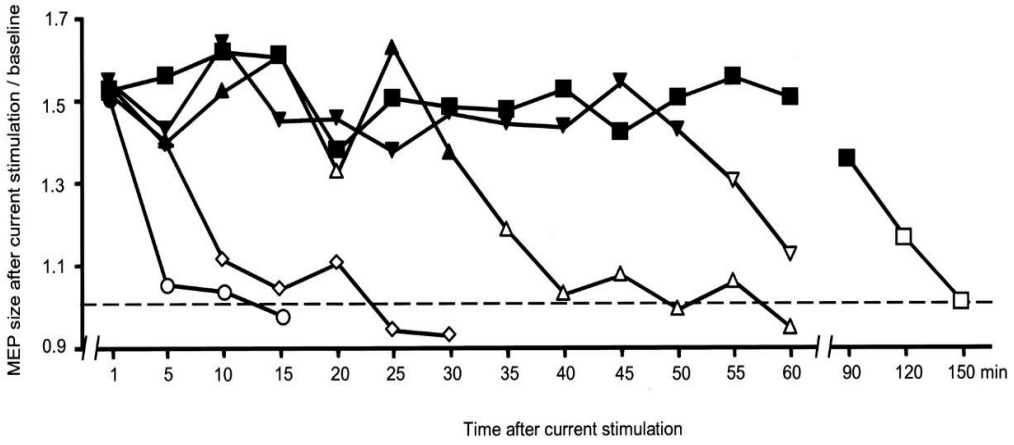

Figure 5. After-effect of a-tDCS on M1 excitability (2).

Note: Symbols indicate tDCS duration: circles = 5 min, diamonds = 7 min, upward-pointing triangles = 9 min, downward-pointing triangles =11 min, squares = 13 min.

1.5.5. Side effects and safety criteria for tDCS

tDCS is a NIBS technique that has experienced significant growth in recent years. Thus, with the growing number of tDCS protocols, new devices, and tDCS therapy, stricter safety criteria were required. Currently, a stimulation of 2 mA for 20 min is considered safe for humans (144) in both single and repeated sessions (129). In terms of intensity and duration, these parameters are frequently used to treat various neurological disorders (145). Adverse side effects of tDCS are characterized by itching sensation and tingling under the electrodes, headache, and tiredness (129).

Unlike repetitive transcranial magnetic stimulation, no cases of seizure induction have been reported (126). Post tDCS, side effects are commonly described as a mild headache or dizziness, usually disappearing in a few hours after stimulation (129, 144). Moreover, no cognitive or motor impairments have been reported following tDCS (129, 144). These studies suggest tDCS to be a safe neuromodulatory brain technique, with no or only minor side effects. However, safety procedures during a subject's preparation and contraventions to subjects are

required to reduce any possible adverse effects. However, normally applied tDCS protocols using relatively well-defined electrodes, stimulus durations and intensities seem safe and well-tolerated.

1.5.6. Brain stimulation to enhance exercise performance

In the last decade, numerous studies have demonstrated a major possibility to increase exercise performance following a-tDCS stimulation. In this section, we discuss evidence of the effect of tDCS on endurance, strength and sprint performance.

1.5.6.1. tDCS effect on muscle strength performance

Muscle strength is determined by morphological and neural factors, including motor unit recruitment, rate coding, motor unit synchronization, neuromuscular inhibition, cross-sectional muscle area, and musculotendinous stiffness (146). Muscular strength is one of the most important factors for physical performance in different sports (146). Therefore, an increase in muscle strength is recommended for all sport and non-sport population. Many investigations have examined various training methods that optimize muscle strength development in all people (147). In this regard, neuromodulatory techniques have also been used as ergogenic aids with promising results for increasing force output compared to placebo (sham) stimulation (148, 149). Previous investigations have demonstrated that a-tDCS effectively promoted the acute enhancement in submaximal strength (i.e., muscular endurance) (120, 138, 148, 149).

Given the information mentioned above regarding the importance of muscle strength, identifying a safe ergogenic aid to optimize muscle strength is of intense interest to athletes, coaches, and researchers (150). However, the effects of a-tDCS on different muscle strength have elicited inconsistent outcomes. The divergent results could be explained by the different tDCS set-ups affecting the stimulated area, current intensity and duration of a-tDCS (120, 151, 152). The potential ergogenic effects of a-tDCS applied over M1 increase corticomotoneuronal excitability in the exercising limb (153). According to many investigations, tDCS can be used as an ergogenic aid by coaches and personal trainers especially in a

task involving isometric contractions. Thereby, a-tDCS could be applied as a complementary tool in muscle strengthening programs.

1.5.6.2. tDCS effect on endurance performance

Okano et al. (102) were the first to investigate the effect of tDCS on whole-body exercise performance. In a crossover, randomized experimental design, participants performed maximal cycling exercise up to volitional exhaustion. Following a-tDCS, maximal power output improved by ~4%, and RPE and HR were lower than a sham condition. The authors suggested that a-tDCS could have affected the insular cortex's activity, thus reducing RPE and improving performance. Angius et al. (137) investigated the effect of tDCS on exercise-induced muscle pain during cycling TTE and on pain perception during a cold pressor test. The authors did not find changes in TTE performance and physiological or perceptual parameters during exercise. Another study conducted by Vitor-Costa et al. (154) found an improvement in cycling TTE performance following a-tDCS over M1.

Barwood et al. (9) have investigated the effects of tDCS on a 20km cycling ETT and a TTE test in hot conditions. The same montage used by Okano et al. (102) has applied to the hypothesis that tDCS would reduce the RPE for a given intensity and improvement in cycling performance. Angius et al.(133) have reported a significant improvement in cycling TTE performance by 23%, lower RPE, and increased corticospinal excitability following bilateral extracephalic M1 a-tDCS. The authors argued that the lower RPE values observed after a-tDCS were related to the increased M1 excitability, which in turn needs to receive less input from other brain areas (i.e., premotor cortex) to generate the output required to recruit the muscles to produce a given power output (133).

Lattari et al. (155) investigated the effect of a-tDCS over the left DLPFC in physically active women. They revealed a significant increment in exercise tolerance on cycling TTE at 100% peak power by 4%. Nevertheless, RPE values did not differ between the control and experimental conditions. However, these findings may be related to a ceiling effect in RPE during high-intensity exercise (i.e., 100%/peak power output). Another recent study conducted by Angius et al. (132) reveals that a-tDCS over the left DLPFC significantly increases TTE during cycling

with a concomitant reduction in RPE values, mainly due to improvements in the inhibitory control caused by changes in frontal lobe excitability. A part of these cycling studies, there is another study, conducted by Park et al. (156) reported an increase in running TTE performance after a-tDCS over M1 without revealing any effect on RPE values. There are also some studies where no TTE performance enhancement following tDCS protocols was observed (137, 157) and studies that did not find improvements in endurance time trial tasks following a-tDCS (1, 9, 158).

1.5.6.3. tDCS effect on sprint performance

Sprint performance is a major determinant in many athletic activities (159). Ultimately, it represents the equilibrium of propulsive power and resistance (160). Sprint performance during short-distance running or cycling gradually decreases after reaching its maximum speed or cadence (121). The most important factors limiting performance during sprints are fatigue occurring in the CNS and peripheral system (121). In this regard, it has been argued that the manipulation of supraspinal centres involved in the control of the motor output, such as M1, may reduce central fatigue and, thus, increase sprint performance (161).

Recent, only a few studies have investigate the effect of a-tDCS on sprint performance in cycling (121, 162). Sasada et al. (121) had demonstrated that 15 min of a-tDCS applied over M1 before exercise did not improve either peak or mean power output during a Wingate test (30-sec all-out test). In contrast, Huang et al. (162) have demonstrated that the application of tDCS using HALO sport© can improve repeated cycling sprint performance (162). Specifically, following 20 min of tDCS with HALO sport© subjects significantly enhanced the mean power output during a repeated cycle sprint test, but no significant differences were found in peak power output ($P = 0.47$). Therefore, it seems that the positive effect of a-tDCS described by Huang et al. (162) could be related to an improved exercise tolerance without changes in maximal force or power capacities.

Collectively, experiments mentioned above provide interesting insights regarding the possible effects of tDCS on exercise performance in healthy individuals. However, the different outcomes in terms of improvement in exercise performance make the potential benefits of tDCS still uncertain. The results'

inconsistency makes the experimental findings difficult to interpret and might be in part caused by the large differences between the experiments regarding exercise type and/or tDCS set up. The exact mechanisms underlying the effects of tDCS on exercise performance is still not clear. Researchers suggest it is likely to facilitate the M1 excitability during sports activities (120, 163). Indeed, as mentioned above, many of the studies were not designed to specifically assess the mechanism by which performance was hypothesised to improve. Therefore, more studies are needed to controlling the tDCS parameters (i.e., montage, identity, location etc.) and examining the mechanisms responsible for the effects of tDCS.

II – JUSTIFICATION

II – JUSTIFICATION

Task failure is a key determinant for defining the final effort of many sports activities. The mechanism that leads to task failure may involve different physiological processes. However, fatigue is an expected physiological reaction that inevitably leads to task failure (47). With sustained submaximal contraction, the spinal motoneurons excitability and the contractility of the muscle fibers are reduced (164). The spinal motoneuron' input must be increased to maintain the required strength or power (161). Contemporary studies have challenged the current exercise physiology model by emphasizing the crucial role played by the brain in the regulation of exercise performance (19, 20). Current evidence suggests that the PFC, IC, M1, supplementary motor area, and cerebellum play an important role in regulating physical effort and endurance exercise performance (156). Therefore, a neuromodulation intervention designed to improve exercise performance should rationally target these areas. Regarding this, interventions that can enhance the excitability of the M1 could increase output from M1 to the muscle fibres, delaying the development of supraspinal fatigue, which would lead to an increase in endurance exercise capacity (120, 163). It has been demonstrated that a neuromodulatory technique called tDCS can transiently modulate the excitability of M1 and consequently physical performance (165).

Different meta-analyses have recently been published, which shed mixing results regarding the effects of a-tDCS on strength and endurance performance (135, 141, 166, 167). Calculations conducted by pooling together different tasks performed provides unclear and confounding results on the effect of tDCS on physical performance. In particular, most of these previous meta-analyses did not consider the specificity of the task (166). Therefore, it is still unknown whether the effect of a-tDCS could be task-dependent. Considering the aspects mentioned above, we planned to perform a systematic review and meta-analysis to quantify the effect of a-tDCS on endurance cycling, and running performance, where the performance has been analysed by tasks performed such as endurance (TTE, TT), and sprint performance. It should be noted that many sports activities are based on

dynamic movements that involve multiple joints and muscles such as cycling or running. Therefore, it is relevant to clarify the specific cycling or running tasks that could benefit the most from the acute effect of a-tDCS. Furthermore, it is also important to delineate whether the effect of a-tDCS depends on the characteristics of the tasks (i.e., TTE vs. ETT or sprint), that although they share some common principles, their performance depends on different physiological and cognitive demands. TTE is considered a key parameter to define the final effort of many endurance sports. Therefore, we performed an experimental study to investigate whether TTE could be improved using bilateral extracephalic tDCS over M1.

III – OBJECTIVES

III – OBJECTIVES

3.1. General Objectives

- To investigate the ergogenic effect of a-tDCS on endurance (whole-body dynamic) exercise performance in physically active people.
- To systematically review the state of the literature with regard to the effectiveness of the acute effect of a-tDCS in endurance whole-body dynamic physical performance.
- To investigate the effect of bilateral extracephalic a-tDCS over M1 during constant-load cycling TTE task in physically active people.

3.2. Specific objectives

The specific objectives outlined for the two studies included in this present thesis are presented below:

Study - I

- To quantify the effect of a-tDCS on endurance (TTE, ETT), and sprint performance during cycling and running tasks.

Study - II

- To determine the effect of bilateral extracephalic a-tDCS over M1 on cycling time to exhaustion (TTE) performance during constant-load cycling task.
- To determine effect of bilateral extracephalic a-tDCS over M1 on HR response during constant-load cycling TTE task.
- To determine the acute effect of bilateral extracephalic a-tDCS over M1 on perception of effort (RPE) during constant-load cycling TTE task.
- To investigate the effect of bilateral extracephalic a-tDCS over M1 on exercise-induced muscle pain during constant-load cycling TTE task.

IV–HYPOTHESIS

IV– HYPOTHESIS

The specific hypothesis outlined for both studies included in this present thesis are presented below:

Study - I

- The acute effect of a-tDCS will increase the endurance (TTE, ETT), and sprint performance during cycling and running task performance compared with the sham tDCS condition.

- The acute effect of a-tDCS on endurance performance will depend on the task performed.

Study - II

- Bilateral extracephalic a-tDCS over M1, will enhance TTE performance during constant-load cycling task.

- Bilateral extracephalic a-tDCS over M1, will show no change in HR response during constant-load cycling TTE task.

- Bilateral extracephalic a-tDCS over M1, will decrease RPE values during constant-load cycling TTE task.

- Bilateral extracephalic a-tDCS over M1, will decrease exercise-induced muscle pain during constant-load cycling TTE task.

V – STUDY - I

V – STUDY - I

5.0. ACUTE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON CYCLING AND RUNNING. A SYSTEMATIC REVIEW AND META-ANALYSIS.

5.1. METHODS

The present systematic review was performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols' (PRISMA-P) 2015 guidelines (168).

5.1.1. Data source and search strategy

A comprehensive literature search was performed using Medline (via PubMed), SportDiscus and Science Direct from 1970 to September 2019. Mendeley software was used to import references and to identify duplicate studies. The search strategy was composite by two main concepts, the first one referring to transcranial direct current stimulation (i.e., "tDCS" OR "a-tDCS" OR "anodal-tDCS" OR "transcranial direct current stimulation") and the second one referring to the main performance outcomes of this review (i.e., "endurance" OR "time to task failure" OR "time limit" OR "time to exhaustion" OR "cycling" OR "running" OR "sprint"). The literature search was conducted by SKF. The authors of the studies included in this review were contacted if crucial data were not reported in the original paper. The reference list of each included study was explored to identify more potential suitable studies. The flow diagram of the search process is shown in Figure 6.

5.1.2. Study selection and eligibility criteria

After the elimination of duplicated studies, the titles and abstracts of recovered studies were screened independently by two authors (SKF and GM) to obtain relevant articles. Articles providing insufficient information in the title and abstract were full-text screened to assess whether they met the eligibility criteria.

Articles were included in the review based on the PICOS approach (168). In this approach, "P" stands for population, "I" for intervention, "C" for comparators, "O" for the main outcome, and "S" for study design. Randomized controlled trials (S) conducted with healthy people (i.e., from 18 to 50 years old) free of orthopaedic and neurological conditions (P) were included if they measured the effects of acute administration of a-tDCS (prior to the task) on cycling or running performance (I). The presence of a control condition (i.e., sham stimulation) was required to exclude a possible placebo effect (C). The dependent variables included in this systematic review were the following: (A) TTE: cycling or running at a constant or incremental intensity until participants could no longer continue with the effort; (B) ETT: completing a set distance in the shortest possible time (> 30 seconds); and (C) sprint performance: completing a set distance in the shortest possible time (≤ 30 seconds) or the maximal power recorded in a short time window (< 30 seconds). Thus, the main outcomes (O) were time (in seconds) or power (in watts). The final inclusion/exclusion decision was made by two independent researchers (SKF and GM).

5.1.3. Data extraction

Two authors (SKF and GM) independently extracted the following data from the included studies: study information (authors, published year, number of interventions, and exercise task), sample characteristic (sample size, sex, age, and training status), tDCS set-up characteristics (polarity, electrodes placement, stimulation duration, current intensity and density, and electrode size), outcomes (TTE, TT, or power output), and effectiveness (significant differences between experimental and control conditions). Authors of the original papers were contacted if the means and standard deviations of the dependent variables were not provided, but we estimated means and standard deviations from the published figure using WebplotDigitizer software (version 4.2, San Francisco, CA, USA) when authors did not respond to our request.

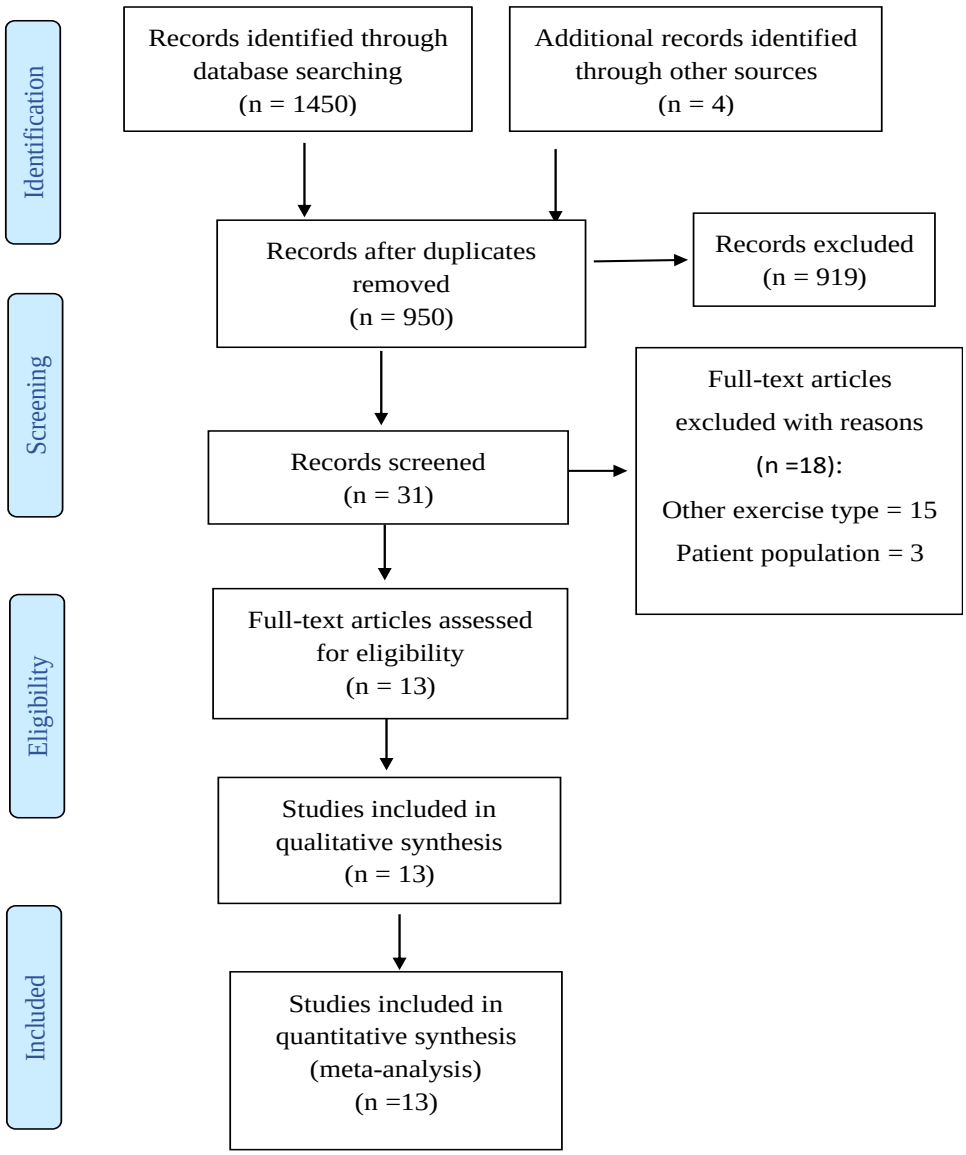

Figure 6. Study flow diagram.

5.1.4. Assessment of methodological quality

The methodological quality of the selected studies was quantified through the physiotherapy evidence database (PEDro) scale (http://www.pedro.org.au). This scale consists of 10 criteria that rate the internal validity and the presence of statistically replicable information. Each criteria are rated "yes" or "no", with "yes" only awarded when a criterion is clearly satisfied. The cut-off score for rating a study as high quality was ≥ 6/10, with lower scores considered as low methodological quality. The methodological quality of each study was rated by two reviewers. When there was doubt this was resolved by discussion with another researcher until a consensus was reached.

5.1.5. Statistical analysis

Statistical analyses were performed using the Review Manager software (RevMan 5.3.5; Cochrane Collaboration, Oxford, UK). The effect size of each study was calculated as the difference in performance between the experimental (i.e., after a-tDCS application) and control (i.e., sham) conditions. The mean differences were standardized by dividing the raw difference by the within-group standard deviation. Standardized mean differences (SMD) of all interventions were pooled with a random effect model. According to Cohen's guidelines (169), SMD values of 0.2, 0.5, and 0.8 represent small, moderate, and large effect size, respectively. Heterogeneity between studies was assessed using I^2 statistics. Statistical significance was set at $P \leq 0.5$.

5.2. RESULTS

5.2.1. Study selection and characteristics

A total of 950 articles were screened and 31 full texts were assessed for eligibility. The reason for exclusion of the screening part was the use of different exercises (i.e., single-joint exercises) and the inclusion of a patient population (i.e., stroke or Parkinson) (see Figure 7). The article selection process resulted in the inclusion of 15 interventions from 13 studies: nine TTE studies (9, 102, 132, 133, 137, 154-157), three ETT studies (9, 158, 170), and two sprint studies (121, 162). Barwood et al. (9) and Andre (1) included different tDCS

Table 1. Characteristics of the included studies

Study information				Sample characteristic		tDCS set-up						Outcomes		Effect	
Authors	Exp	Exercise Type	Task	n(M/W) Age (yr)	Training status	Polarity	Stimulation Electrode	Duration (min)	Intensity (mA)	Density (mA/cm²)	Elec. Size (cm²)	TTE (M± SD) (Sec.)	Power (W)	TTE (Time)	Power
Andre et al. (2019)	2	Cycling	TT: 16.1km	9M/1W 36 ± 6	Cyclist	A	A: DLPFC, M1, V1(con) C: R-SOB	20min.	1.5	0.060	25	M1:1443.7±81.0 DL:1428.4±80.0 V1:1434.8±79.6	M1:274±44 DL:280±39 VI:279±44	NS	NS
Angius et al. (2015)	1	Cycling	TTE: 70% of PP	9M 23 ± 4	Rec. acti.	A/S	A: L-M1 C: R-DLPFC	S:30s 10min.	2	0.166	12	A: 994.8±509.4 S: 880.8±517.2		NS	
Angius et al. (2018)	1	Cycling	TTE: 70% of PP	4W/8M 24 ± 5	Rec. acti.	A/S	A: BL-M1 C:IL-Shoulder	S:30s 10min.	2	0.057	35	A: 795±260.4* C: 666±256.8 S: 645.6±181.8		⇧*	
Angius et al. (2019)	1	Cycling	TTE: 70% of PP	3W/9M 23 ± 3	Rec. acti.	A/S	A: L-DLPFC C: Fp2	S:30s 30min.	2	0.057	35	A:1020±480* S:900±480		⇧*	
Baldari et al. (2018)	1	Running	TTE: incremental ramp test	13M 27 ± 5	Rec. acti.	A/S	L & R-M1	S: 30s 20min.	1 2	0.028 0.057	35-36	A:530±44 C: 537±40 S:533±46		NS	
Brawood et al. (2015)	2	Cycling	TT: 20 km TTE: 75% of PP	6M 21 ± 2 8M 21 ± 1	Phy. Acti. Phy. acti.	A/S	A:T3 C: CLSOB	S: 30s 20min.	1.5 2	0.428 0.444	3.5 4.5	A: 2181 ± 88 S: 2181 ± 56 A: 237 ± 362 S: 314 ± 334	A:197 ± 20 S:197 ± 12	NS	NS
Holgado et al. (2018)	1	Cycling	TT: 20min.	36M 27 ± 6.8	Cyclist & Triathletes	A/S	A: L-DLPFC, C:CL-Shoulder	S:30s 20min.	2	0.080	25		A:235±38.42 S:234±41.37		NS
Huang et al. (2019)	1	Cycling	5x6-s sprint	9M 20 ± 1.2 11W 24 ± 2.2	Phy. acti.	HALO/ S	Vertex	S:30s 10min.	2	0.057	35		H:898.3±116.3 S:827.8±145.3		NS

Study information				Sample characteristic		tDCS set-up						Outcomes		Effect	
Authors	Exp	Exercise Type	Task	n(M/W) Age (yr)	Training status	Polarity	Stimulation Electrode	Duration (min)	Intensity (mA)	Density (mA/cm²)	Elec. Size (cm²)	TTE (M± SD) (Sec.)	Power (W)	TTE (Time)	Power
Lattari et al. (2018)	1	Cycling	TTE: incremental ramp test	10M 33 ± 9	Phy. acti.	A/S	A:L-DLPFC C: R-OFC	S:30s 20min.	2	0.057	35	A:199.5± 97.2* S: 137.1 ± 73.1		⇧*	
Okano et al. (2019)	1	Cycling	TTE: 70% of PP	3W/9M 23 ± 3	Cyclist.	A/S	A: L-T3 C: CL-SOB	S:30s 20min.	2	0.057	35	A: 751.4 ± 71.5* S:723.7±45.0	A:313.2±29.9* S:301.0±19.8	⇧*	⇧*
Park et al. (2019)	1	Running	TTE: 80% of PP	12M 27.4 ±2.4	Trained	A/S	A: M1 (Cz) C:c5 & C6	S: 30s 20min.	1.98	0.070	28.16	A:1270.8±427.8* S: 1106.4 ±379.2		⇧*	
Sasada et al. (2017)	1	Cycling	Wingate test	6W/17M 21±30	Athletes	A/S	A: Vertex C: R-forehead	S: 30s 15min	2	0.57	35		A:9.48±1.21 S:9.40±1.26		NS
Vitor et al. 2015	1	Cycling	TTE: 80 of PP	11M 26 ± 4	Phy. Acti	A/S	A: M1 (Cz) C: OP	S: 30s 13min	2	0.056 0.057	35-36	A:491.4 ±100* C: 443±110 S:407±69			

Note: TTE: time to exhaustion ETT: endurance time trial; M: men; W: women; Rec. acti: recreationally active; tDCS: transcranial direct current stimulation; Exp: experiment; A: anodal; C: cathodal; S: sham; M1: motor cortex; DLPFC: dorsolateral prefrontal cortex; T3: temporal cortex; Elec: electrode; Sec: second; Min: minute; PP: peak power; SOB: supraorbital; V1: visual cortex; OFC: orbitofrontal cortex; ⇧*: task improvement ; NS: no significantly difference; *: significantly difference; R: right; L: left; CL: contralateral; BL: bilateral; IL: ipsilateral; OP: occipital protuberance.

interventions within the same study and they were considered as independent interventions for the current systematic review and meta-analysis. Table 1 shows the main characteristics of the studies included in the systematic review and meta-analysis. The current intensity ranged from 1.5 to 2.0 mA, current density ranged from 0.083 to 0.166 mA/cm^2, and the duration of stimulation ranged from 10 to 30 min. Only 30 seconds of stimulation was applied in the sham condition. Four studies assessed both men and women (132, 133, 170), one study used only women (155), and the remaining studies included only men (9, 102, 137, 154, 156-158, 162). The training status of the subjects ranged from physically active to competitive athletes.

5.2.2. Study quality assessment

The quality of the studies was generally high with a mean score of 7.0 ± 0.6 in the 0-10 PEDro scale (Table S1).

5.2.3. Effect of tDCS on running and cycling performance

The systematic search identified a total 15 interventions that examined the effects of a-tDCS on TTE, ETT and sprint performance during running or cycling tasks. An overall small effect was observed in favour of the a-tDCS condition (SMD = 0.22; 90% CI = 0.05, 0.39; P = 0.04). The subgroup analysis revealed a significantly higher TTE performance for the experimental compared to the sham condition (SMD = 0.37; 90% CI = 0.13, 0.61; P = 0.01), while no significant differences were observed between the experimental and sham conditions for ETT (SMD = 0.00; 90% CI = - 0.29, 0.30; P = 1.00) or sprint performance (SMD = 0.19; 90% CI = - 0.23,0.060; P = 0.46) (Figure 7).

5.3. DISCUSSION

This systematic review and meta-analysis included 15 interventions with a total of 192 subjects examining the effects of applying a-tDCS before cycling and running tasks on endurance (TTE and ETT) and sprint performance. Our analysis revealed a significant effect of a-tDCS on cycling and running performance when

all tasks were pooled together. Moreover, the sub-group analysis evidenced a small but significant effect in favour of the a-tDCS compared to the sham condition on TTE (SMD = 0.37; 90% CI = 0.13, 0.61; P = 0.01), while ETT (SMD = 0.00; 90% CI = -0.29, 0.30; P = 1.00) and sprint performance (SMD = 0.19; 90% CI = - 0.23, 0.60; P = 0.46) did not differ between the experimental and sham conditions. Therefore, this meta-analysis suggests that the effect of a-tDCS on whole-body dynamic exercises is task dependent. However, it is important to note that only four studies analysed ETT task and two studies the sprint tasks. Therefore, more studies are apparently needed to firmly establish the effect of tDCS on these types of tasks.

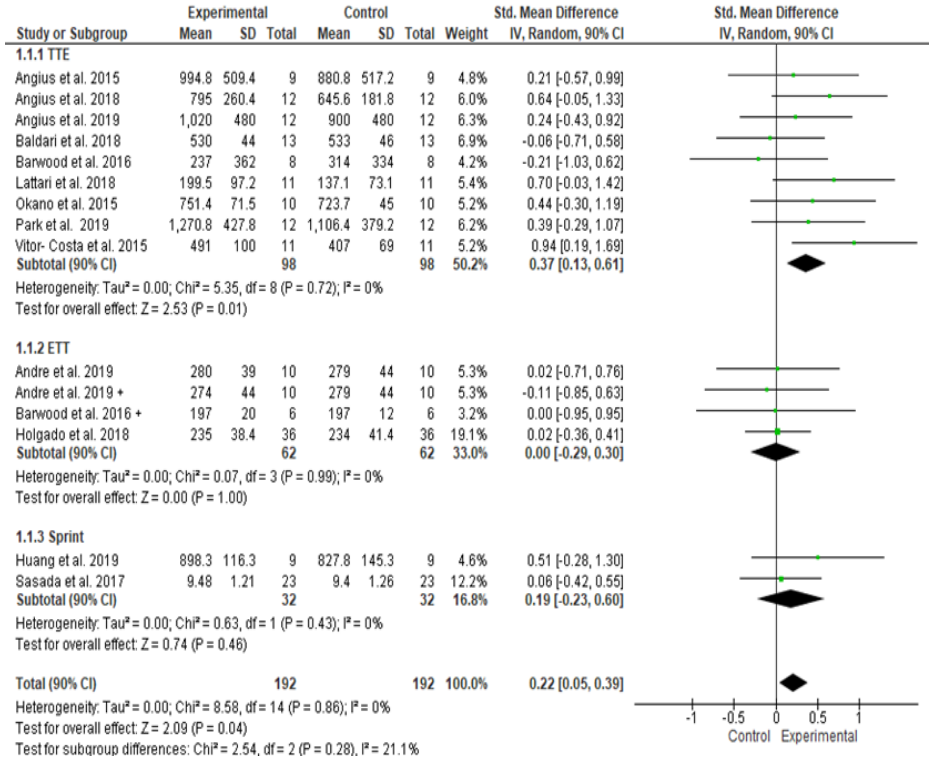

Figure 7. Forest plot with subgroup analysis for comparison of time to exhaustion (TTE), endurance time trial (ETT), and sprint performance between the experimental and sham conditions. Andre et al. (1)⁺ - subgroup that received a-tDCS over M1 before the task (cycling ETT; mean power output). Barwood et al. (9)⁺ - subgroup that received a-tDCS over T3 before the task (20 km cycling ETT; mean power output).

5.3.1. Acute effect of anodal-tDCS on TTE performance

Nine of the fifteen interventions included in the present systematic review and meta-analysis explored the effect of a-tDCS on TTE performance during running and cycling revealing a small positive effect (SMD = 0.37, P = 0.01). Interestingly, five out of nine interventions reported an improvement in TTE during cycling (102, 132, 133, 154, 155), while only one study (156) reported enhancement in TTE performance during a running task.

Okano et al.(102) were the first to report an increase of ~4% in peak power output during a maximal cycling incremental test along with lower RPE values following a-tDCS over the left TC. The authors speculated that the application of a-tDCS over the left TC could have modulated the excitability of the IC, which likely led to a decrease in RPE when exercising at submaximal intensities, improving endurance performance. This hypothesis is justified because it is known that the IC is the main area of the brain responsible for the awareness of subjective feelings from the body (171) and it is related to the RPE values reported during dynamic exercises (172). Angius et al. (133) also found significant improvements in cycling TTE performance by 23%, lower RPE, and increased corticospinal excitability following bilateral extracephalic M1 a-tDCS. The authors argued that the lower RPE values observed after a-tDCS were related to the increased M1 excitability, which in turn needs to receive less input from other brain areas (i.e., premotor cortex) to generate the output required to recruit the muscles to produce a given power output (133). These data are partially confirmed by Vitor-Costa et al. (154) who found an improvement in cycling TTE following M1 stimulation with a trend towards a reduction in RPE (P = 0.07). Another recent study conducted by Angius et al. (116) demonstrated that a-tDCS over the left DLPFC significantly increased TTE during cycling with a concomitant reduction in RPE values, mainly due to improvements in the inhibitory control caused by changes in frontal lobe excitability. In the same line, Lattari et al. (155) investigated the effect of a-tDCS over the left dorsolateral PFC in physically active women and revealed a significant increment in exercise tolerance on cycling TTE at 100% peak power by 4%. Nevertheless, RPE values did not differ between the control and experimental condition in the study of Lattari et al. (155), which may be related to a ceiling effect in RPE during high-intensity exercise (i.e., 100/peak power output) (132). However,

it should be mentioned that Park et al. (156) reported an increase in running TTE performance after a-tDCS over M1 without revealing any effect on RPE values, and other studies that applied similar tDCS protocols did not find improvements neither in TTE performance nor in RPE (137, 157, 170).

5.3.2. Acute effect of anodal-tDCS on ETT performance

A self-paced exercise is a physical activity in which the effort has to be distributed in the best possible way to cover a given distance as quickly as possible or to cover the largest possible distance in a given time (158). During self-paced exercise tasks, such as an ETT, athletes should regulate their energetic resources to maintain a submaximal sustainable intensity to avoid premature fatigue and exhaustion (172). As we know the exercise work rate is regulated by the brain based on the integration of numerous signals from various peripheral physiological systems (40). However, the role of the brain in pacing is not entirely clear, although RPE, which can be modulated by tDCS (9), is a key perceptual anchor for the regulation and distribution of effort (40) and it might provide a potential mechanism for influence exercise pacing and performance (9). However, few studies have tested the effect of a-tDCS on self-paced ETT.

Only four out of 15 interventions (9, 158, 170) included in the present meta-analysis, examined the effect of a-tDCS on self-paced cycling ETT performance revealing a trivial effect (SMD = 0.00, P = 1.00). Twenty min. of 1.5 mA a-tDCS over the left TC, the M1, or the dorsolateral PFC, before 16km self-paced ETT in male and female trained cyclist did not improve performance compared to sham condition (170). In the same line, 20 min. of a-tDCS at 2.0 mA over the DLPFC applied before a self-paced 20 min cycling ETT on male trained cyclist did not improve performance compared to sham condition (158). Therefore, this result suggests that a-tDCS does not improve cycling self-paced ETT task performance (170).

5.3.3. Acute effect of anodal-tDCS on sprint performance

Sprint performance is a major determinant in many athletic activities (159). Ultimately, it represents the equilibrium of propulsive power and resistance (160).

However, sprint performance activities such as short-distance running or cycling gradually decreases after reaching a maximum speed or cadence (121). The most important factors limiting performance during sprints are fatigue occurring in the central nervous system as well as in the peripheral system (i.e., at or distal to the neuromuscular junction) (121). In this regard, it has been argued that the manipulation of supraspinal centers involved in the control of the motor output, such as M1, may reduce central fatigue and, thus, increase sprint performance (161).

However, in the present systematic review and meta-analysis, only two studies have tested the effect of a-tDCS on sprint cycling performance (121, 162) and revealed a non-significant small effect of a-tDCS on cycling sprint performance (SMD = 0.19, P = 0.46). According to these studies, 15 min a-tDCS applied over M1 before exercise did not improve neither peak nor mean power output during a Wingate test (30-sec all-out test) (121). In contrast, Huang et al. (162) demonstrated that the application of tDCS using Halo sport© can improve repeated cycling sprint performance. Specifically, following 20 min of tDCS with Halo sport© sports subjects significantly enhanced the mean power output during a repeated cycling sprint test, but any significant differences were found in peak power output (P = 0.47). Therefore, it seems that the positive effect of a-tDCS described by Huang et al. (162) could be related to an improved exercise tolerance without changes in maximal force or power capacities, as it has been previously proposed by Alix-Fages et al. (141).

5.3.4. Characteristic of the tDCS protocol

According to the findings mentioned above, the potential ergogenic effects of a-tDCS on whole-body exercise performance are still inconclusive. Such inconsistencies may be explained by the different tDCS set-up characteristics used in the mentioned studies (i.e., stimulated brain area, electrodes montage, stimulation duration, current intensity and density, and electrode size).

Regarding the region of stimulation, numerous brain areas are known to play an important role in exercise regulation and, therefore, the rationale for using tDCS for performance improvement may differ accordingly (141). As evidenced in the present meta-analysis, these regions included the M1, DLPFC and TC. Most of the

studies that reported a positive effect of a-tDCS targeted the M1 region (133, 154, 156), which is considered a key determinant in endurance task performance (173). M1 stimulation could be effective to enhance endurance performance since increases in M1 excitability may increase the neural drive to the active muscles, delay central fatigue, or reduce the pain induced by exercise (137).

There is also evidence regarding the role of other cortical regions in endurance performance (174). In this context, studies included in our systematic review also revealed significant improvements in TTE performance following a-tDCS over dorsolateral PFC (132, 155). The DLPFC is a crucial brain region for inhibitory control, an executive function essential for both behavioral self-regulation (132) and likely exercise regulation (174). Additionally, there is evidence regarding the positive effect on endurance performance following a-tDCS over the TC (163). It is plausible that the application of a-tDCS modulated the excitability of TC and IC which have been associated with the control of the autonomic nervous system (ANS) and awareness of emotional feelings from the body (102, 171). This modulation would therefore reduce the RPE values and lead to an improvement in TTE performance (102). However, other studies did not find any effect of a-tDCS over TC on autonomic control (137). Furthermore, some studies included in the present meta-analysis have failed to find this kind of improvement in endurance performance following tDCS stimulation over the same regions mentioned above: M1 (121, 157, 162, 170), DLPFC (158) and TC (9). These results suggest that other tDCS set-up parameters in addition to the region of stimulation should modulate the ergogenic effects of tDCS on endurance performance.

Regarding electrodes montage, in those studies which used a cephalic montage (i.e., anodal electrode over the target area and the cathodal electrode over the contralateral prefrontal cortex) (137, 163), it is plausible that the lower excitability expected in the brain area under the cathode may have counteracted the positive effect of the anodal stimulation. An extracephalic montage (i.e., anode over the main area and cathode on the shoulder) may avoid this problem and this could explain the large ergogenic effects of a-tDCS in studies that use an extracephalic montage (120). The duration of stimulation is another key parameter that may influence tDCS aftereffects (175). Alix-Fages et al. (141), demonstrated a higher endurance performance when stimulating the cerebral cortex for 15-20 min

compared to 10 min (ES = 0.31 and 0.17, respectively). However, the present systematic review and meta-analysis revealed a significant effect on TTE performance during cycling regardless of the stimulation duration: 30 min (170), 20 min (102, 155), 13 min (154), or 10 min. (133). Regarding the current intensity, Nitsche et al. (112) reported that cortical excitability was increased more using higher (1.5 - 2.0 mA) compared to lower (0.5 mA) intensities.

However, no study has directly compared the effects of different intensities of tDCS on the performance during the tasks included in the current systematic review. Furthermore, the stimulation intensity used in the studies analyzed in the present meta-analysis was very homogeneous, ranging from 1.5 mA (170), 1.98 (156) and 2 mA (the other 13 interventions). To the best of our knowledge, only one study has investigated the effect of tDCS intensity (2 vs 4 mA) on knee extensor performance during an isokinetic fatiguing task (176).

VI – STUDY – II

VI- STUDY - II

6.0. EFFECT OF BILATERAL EXTRACEPHALIC TRANSCRANIAL DIRECT CURRENT STIMULATION OVER M1 ON CONSTANT-LOAD CYCLING TIME TO EXHAUSTION TASK PERFORMANCE

6.1. METHOD AND MATERIALS

In this section, we describe methodological procedures and materials used in the experimental study of this thesis. All the data collection and sample analysis in this thesis were carried out in the neuroscience laboratory of Catholic University in Murcia.

6.1.1. Study design

We conducted a crossover double-blind, randomized and placebo-controlled design to investigate the effect of bilateral extracephalic tDCS over M1 during a constant-load cycling TTE task with 16 healthy active subjects. The independent variable, tDCS (anodal and sham conditions), was applied over bilateral M1 before the constant-load cycling TTE task. The dependent variables (HR, RPE, exercise-induced muscle pain, and TTE) were assessed during the constant-load cycling TTE task after tDCS. Control variables (profile of mood state (POMS), beck anxiety inventory (BAI), pittsburgh sleep quality index (PSQI)) were collected before the application of tDCS. Each subject visited the laboratory on three occasions, each separated by at least seven days. During the visit 1, the purpose was to familiarize the subject with all procedures performed during the experimental protocol and determine their 10 min maximal aerobic power. During visits 2 and 3, each participant performed both tDCS experimental sessions in a counterbalanced order (A/B – B/A design).

6.1.2. Description of the study population

All subjects were students at the Catholic University of Murcia or residents of the local community. For this study, the subjects were recruited mainly through personal contacts and emails. All subjects were between 18 and 40 years old and free from any cardiometabolic, neuromuscular, musculoskeletal diseases or medication. The demographic information of the subjects from the first session is shown in the table 2. Each subject was informed about the procedures, benefits and risks before giving their written informed consent (see Annex 1). A total of 16 subjects were recruited for the study, and they were instructed to avoid strenuous physical activity, take caffein, and to rest well the day before and on the same day of testing for all the sessions.

Table 2: Characteristics of the subjects

	N	Media	SD	Minimum	Maximum
Age (years)	16	23.1	4.5	20	39
Weight (kg)	16	70.1	10.7	56.4	88.1
Height (m)	16	1.74	0,06	1.64	1.82
10-min power test	16	193.5	27.22	129	245

Note: SD: standard deviation

6.1.3. Inclusion and exclusion criteria

Inclusion criteria for subject participation were age between 18 to 40 years, physically active participants (who are physical activity for at least one hour per day and 4 - 5 days per week), and free from certain medical conditions (cardiovascular diseases, respiratory diseases, and neurological diseases). All the subjects had to fill in two screening questionnaires. The first of these questionnaires was a tDCS screening questionnaire (see Annex 2). Due to the nature of tDCS, the subjects were excluded if they had undergone brain surgery, were pregnant, had

metal in their brain or an implanted neurostimulator. The second was the Physical Activity Readiness Questionnaire (Par-Q+) (see Annex 3).

6.1.4. Variables of the investigation

The research variables used for this study are described in the following section.

6.1.4.1. Independent variable

The type of stimulation: a-tDCS (experimental) and s-tDCS (sham (control)).

Transcranial direct current stimulation (tDCS)

The tDCS was administered by two transcranial direct current stimulators using two rubber electrodes (Anodal 7 x 5 cm, Cathodal 6 x 4 cm) and a water-soaked synthetic sponge (see Figure 8). The tDCS protocol used by Angius et al. (133) was used for this experiment. Two anodal electrodes were placed over

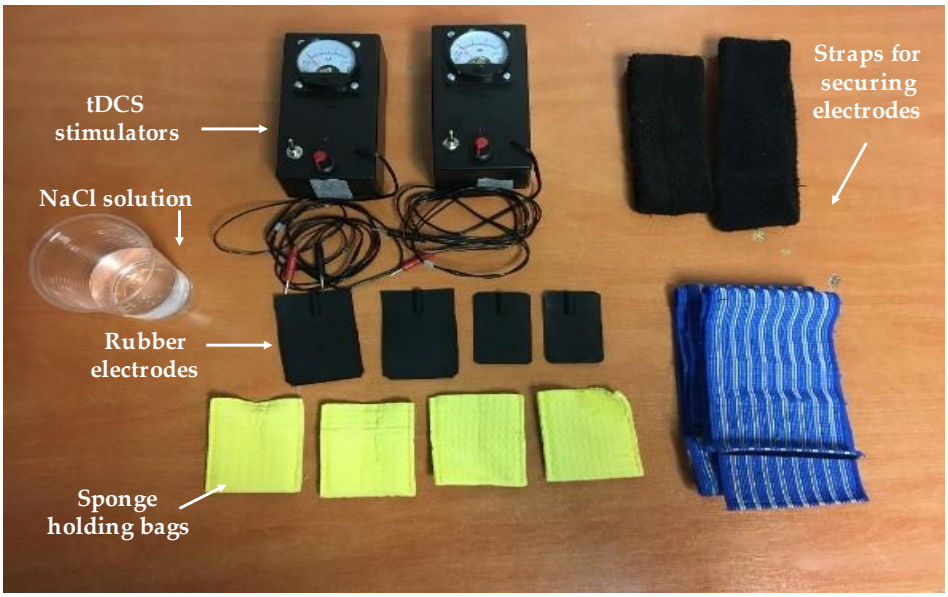

Figure 8. Materials for instrumentation of the subject. Own elaboration.

bilateral M1, while the two cathodal electrodes were placed on the ipsilateral shoulders. Electrical current was delivered at an intensity of 2.0 mA for 10 min. The same montage was used for the sham condition, but the tDCS time lasted 30 seconds and was subsequently ramped down to no stimulation. This induced a slight itching sensation, which is commonly experienced during tDCS at the beginning of the stimulation, but does not produce cortical changes (177).

6.1.4.2. Dependent variable

The dependent variables used in this study were: cycling TTE, HR response, RPE, and exercise-induced muscle pain. These are described one by one below.

Time to Exhaustion (TTE)

In sports science, performance tests are often used to control the effectiveness of interventions, and therefore each test must be able to provide a reliable and consistent measure of performance. Endurance performance is measured in laboratories using two types of tests: the ETT and TTE tests. In the ETT test, subjects work at a self-selected intensity to complete a set distance or to work as fast as possible, whereas, in the TTE tests, work is usually carried out at a predetermined and constant work rate until volitional exhaustion, that is, the point where the subjects are unable to maintain the required force or intensity. TTE tests have a subjective endpoint, as the subject's task disengagement usually determines the termination (10).

The study by Laursen et al. (178) reported that TTE tests show greater variability than ETT. During the ETT tests, athletes can up/down their exercise intensity according to their perception of fatigue and external motivational cues. While during TTE tests, exercise intensity or power output is constant. This constant intensity allows a better analysis of the physiological and psychological response during the TTE test (154). This is not possible during ETT because each subject can self-regulate power or speed (i.e., pace), making it difficult to interpret the results (178). Therefore, for this thesis, we used a constant-load cycling TTE test. To reduce the potential variability in the TTE test, participants were always strongly motivated and the experimental sessions were counterbraced to avoid any learning effect for the TTE.

Heart Rate Measurement

The HR response was recorded during the cycling TTE test with a wireless chest strap heart rate sensor (M400, Polar Electro, Finland). Before the test, the chest strap was moistened and securely fastened to the subject's chest, according to the manufacturer's guidelines.

Rating of perceived exertion (RPE)

RPE was measured using the Category Ratio 10 (CR 0-10) scale developed by Borg (179). The scale shows a list of numbers starting from 0 to 10 in the upper left-hand corner. On the right side of the scale is a list of words used to anchor the perceived feeling, corresponding to the corresponding number (see Figure 9).

Rating	Description
0	Rest
1	Very Easy
2	Easy
3	Moderate
4	Somewhat Hard
5	Hard
6	-
7	Very Hard
8	Very, Very Hard
9	Nearly Maximal
10	Maximal

Figure 9. Modified Borg RPE scale (8)**.**

RPE scale was originally developed to monitor the effort perceived during exercise. It has recently also been used to monitor the effort perceived during various training sessions (180, 181). During the experiment, subjects were asking to

rate how hard the exercise is. All standardized instructions for the RPE were provided during the familiarization visit, as follows:

- *While doing the cycling task, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining sensations and feelings of physical stress, effort, and fatigue.*

- *Do not concern yourself with any one factor such as leg pain or shortness of breath, but try to focus on your real feeling of exertion.*

- *Look at the rating scale ahead of you while you are engaging in a cycling task; it ranges from 0 to 10, where 0 means "no exertion at all" and then relates to extremely strong, almost maximal.*

A printed copy of the scale of RPE scale was affixed in front of the place where the subject performed the exercise, making it easier to identify their perceived exertion without difficulties.

Exercise – induced muscle pain sensation

Exercise-induced muscle pain was assessed using an accurate and reliable pain scale (0-10) by Cook et al. (182) (see Figure 10). This scale has been used in several experiments to quantify the level of exercise-induced muscle pain. Similarly, to the RPE scale, this scale presents numbers corresponding to the magnitude of the perceived discomfort, rating from 0 (no pain) at the top of the scale to 10 (extremely intense pain). The description of each item is located to the right of the number. The following instructions of the pain scale were used:

- *The scale contains the numbers 0 to 10. You will use this scale to assess the perceptions of pain in your legs during the TTE test. In this context, pain is defined as the intensity of hurt that you feel. Don't underestimate or overestimate the degree of hurt you feel; try to estimate it as honestly and objectively as possible.*

- *The numbers on the scale represent a range of pain intensity from "very faint pain" (number ½) to "extremely intense pain-almost unbearable" (number 10). When you feel no pain in your legs, you should respond with the number zero. When the pain*

in your legs becomes just noticeable, you should respond with the number ½. If your legs feel almost unbearable extremely strong pain, you should respond with the number 10.

- *Repeatedly during the test, you will be asked to rate the feelings of pain in your legs. When rating these pain sensations, be sure to attend only to your legs' specific sensations and not report other pains you may be feeling.*

- *Your rating of pain intensity must reflect only the degree of hurt you are feeling in your legs. Do not use your ratings to expression fatigue (i.e., Inability of the muscle to produce force) or believe that the exercise task is completed.*

- *In summary, you will be asked to: (a) provide pain intensity ratings in your legs only, (b) give ratings as accurate as possible, and (c) not under-or-over- estimate the pain, but rate your pain honestly. It would be best if you used verbal expressions to help rate your sensations.*

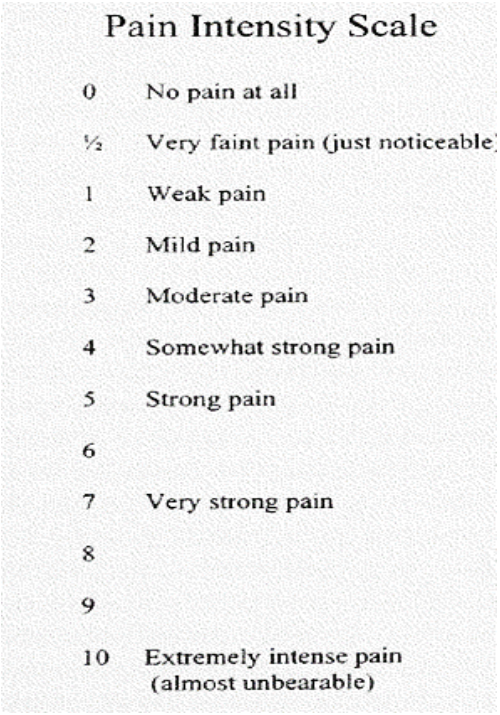

Figure 10. Category ratio scale for assessing pain (6).

A printed copy of the scale was placed in front of the subject. Pain ratings were obtained every minute until the participant was unable to maintain the minimum pedal rate. In this thesis, the instructions for each scale were given at the beginning of the experimental session. The subjects were fully familiarized during the first visit to neither overestimate nor underestimate each parameter.

6.1.4.3. Control variable

Profile of mood state (POMS)

The mood was measured using the POMS instrument developed by McNair et al. (183) (Annexe 5), which measures the variability of tension, depression, anger, vigour-activity, fatigue, and confusion. The POMS is one of the most widely used and accepted instruments for mood measures in sports and physical activity settings (184) and assesses temporary different mood states. The advantages of using this assessment include the simplicity of use and ease of understanding for the participant. A five-point scale ranging from "not at all" to "extreme" is administered to subject by experimenters to assess their mood states. Completing the assessment may take 5 – 15 min. For current experiment, we used the short form of the POMS, which was applied before the initiation of each session. The examiner explained the questionnaire to the subjects during the first session (familiarization).

Read each word/statement below, decide how you have been feeling, in respect to the word/statement, in today (before the start of the session), and select the appropriate statement "Not at All", "A Little", "Moderately", "Quite a Lot" or "Extremely" to indicate your feeling.

Beck Anxiety Inventory (BAI)

BAI is a widely used anxiety scale in both clinical practice and research. The BAI by Beck et al. (185) is a 21-point self-report questionnaire that uses a Likert scale that measures common symptoms of clinical anxiety, such as nervousness and loss of control. The subjects' degree of discomfort corresponds to a sign and is rated on a 4-point scale from 0 (not at all) to 3 (severely, I could barely stand it). In

the inventory, total scores range from 0 to 63. The anxiety level is directly proportional to the higher scores. 13 of the 21 symptoms assess psychological symptoms, 5 of which consider cognitive aspects, and 3 assess both somatic and cognitive symptoms. Various psychometric studies guarantee the reliability and validity of the BAI in different subjects (psychiatric patients, patients with anxiety disorder, adolescents with mental disorders, elderly people, university students) (186), including adults from the general population (187). In the present experiment, we use the BAI (Annexe 6) before the start of each tDCS session. The investigator explained the questionnaire to the participants during the first session (familiarization).

Pittsburgh sleep quality index (PSQI)

The PSQI was developed in 1988 by Buysse et al. (188) (Annex 7) to provide a standardized measure that could collect consistent information about the subjective nature of people's sleep habits and provide a clear index that could be used by clinicians and patients alike (188). It has gained popularity as a measure that could research how sleep might be associated with sleep disorders, depression, and bipolar disorders. The PSQI consists of 19 questions about sleep during the last month, resulting in seven components: subjective sleep quality, sleep latency, sleep duration, sleep disturbances, sleep efficiency, sleep disturbances, sleep medication and daytime dysfunction. Each element contains four-level Likert scales (0-3) with higher scores indicating poor sleep. The sum of the score these seven components' score gives a global score ranging from 0 to 21, which is composed of sleep quantity (189). Acceptable measures of internal homogeneity, reliability and validity were obtained for the PSQI (188). For this experiment, we used PSQI questionnaire before they start each session. We explained the questionnaire to the subjects during their first session (familiarization).

6.1.5. Experimental Procedure

Familiarization session

Before participating in the study, all subjects attended a familiarization session that corresponded to the study's first visit. In this session, each subject was familiarized with all the methodological procedures performed in the subsequent visits. In this session, individual subjects' information was recorded together with their anthropometric data (see Table 2). Before starting the study, subjects completed a tDCS screening questionnaire, and Physical Activity Readiness questionnaire (PAR-Q). PAR-Q was used to monitor individual health status and recognize any medication or pathologies that would have excluded them from participate in the study. If the subject fulfilled all the inclusion criteria for stimulation and health status, they were offered to sign the consent form and also permitted to withdraw from the study at any time and for any reason. Following anthropometric measurements, the subject fulfilled different questionnaires. International physical activity questionnaire (IPAQ) was used to analyse the subject physical activity level in the last 7 days (see Annex 4). POMS was used to assess transient and distinct mood states (see Annex 5). The BAI was used to measure the severity of anxiety before starting the study (see Annex 6), and finally, PSQI was used to evaluate the subject's sleep quality (see Annex 7). Afterwards, they were instructed to perform a 10-min maximum aerobic power test in a cycle ergometer.

10-minute power test

During the familiarization visit, subjects performed a 10 min power test on a cycle ergometer (Exite, TechnoGym, Italy) to determine the power each subject could maintain during 10 min. Before the test, subjects performed a 5 min warm-up, and they allowed 5 min rest period. Then they were started 10 min power test, which consisted of cycling at a cadence of 65-70 revolution/min (rpm) with the self-selected maximal power that they believed they were able to maintain during 10 min. The cycle ergometer rider position was recorded for each subject to be reproduced for all the subsequent visits. Besides, the examiner recorded the appropriate power level at each end of the minute during the entire 10 min to

obtain the mean value required to perform the constant-load cycling TTE test. Besides, the HR, RPE, and exercise-induced pain were recorded in each minute to familiarize with the procedure. Finally, familiarization with the TTE was performed in the same session following 30 min of recovery. During the test, each subject was strongly verbally encouraged during all the 10 min power test.

Experimental session I and II

The remaining two sessions were completed using identical methodology. The two sessions were separated with at least 7 days of rest to allow the full recovery and minimize carryover effects. First, subjects completed the three questionnaires (i.e., POMS, BAI, PSQI), and the subjects were prepared for the administration of tDCS.

We used a bilateral extracephalic tDCS montage with the anodes (size: 7 x 5 cm) over the bilateral M1 (C3 and C4 according to the 10-20 EEG system) and the cathodes (size: 4 x 6 cm) placed over the ipsilateral shoulders. We used this montage because it was previously recommended by Angius et al. (133), showing favourable effects during the constant-load cycling TTE test performance. Ensure good conduction, each electrode sponges were soaked with saline solution (NaCl), and elastic straps were used to maintain the electrodes on the scalp and both shoulders. During a-tDCS condition, stimulation lasted 10 min at 2mA of current intensity. In contrast, in the sham condition, the current was disconnected at 30 seconds after the beginning of the stimulation (duration of the fade in and fade out period-10 seconds). In this manner, the subject felt the itching sensation below the electrode at the beginning and that the end of the stimulation, making this condition indistinguishable from the real stimulation (190). Moreover, this procedure allows the subjects to blind to the type of stimulation they are receiving during the test, ensuring a control effect (177).

After the tDCS period, the subject performed a 5 min warm-up at 50 watts, followed by a constant-load cycling TTE test at the mean value of their 10 min power test. The TTE test ended when the subjects could not maintain a pedal frequency between 65-70 rpm for more than five seconds despite strong verbal encouragement. During the constant-load cycling TTE test, RPE values and exercise-induced muscle pain were recorded respectively, using the 10-point RPE

scale and a 10-point numerical scale for Pain. HR response was monitored using an HR monitor (polar M400, polar electro, Finland) in each minute until they stopped the test. Subjects were not aware of the elapsed time or feedback on performance during or after the TTE task. The experimental protocol is represented in Figure 11.

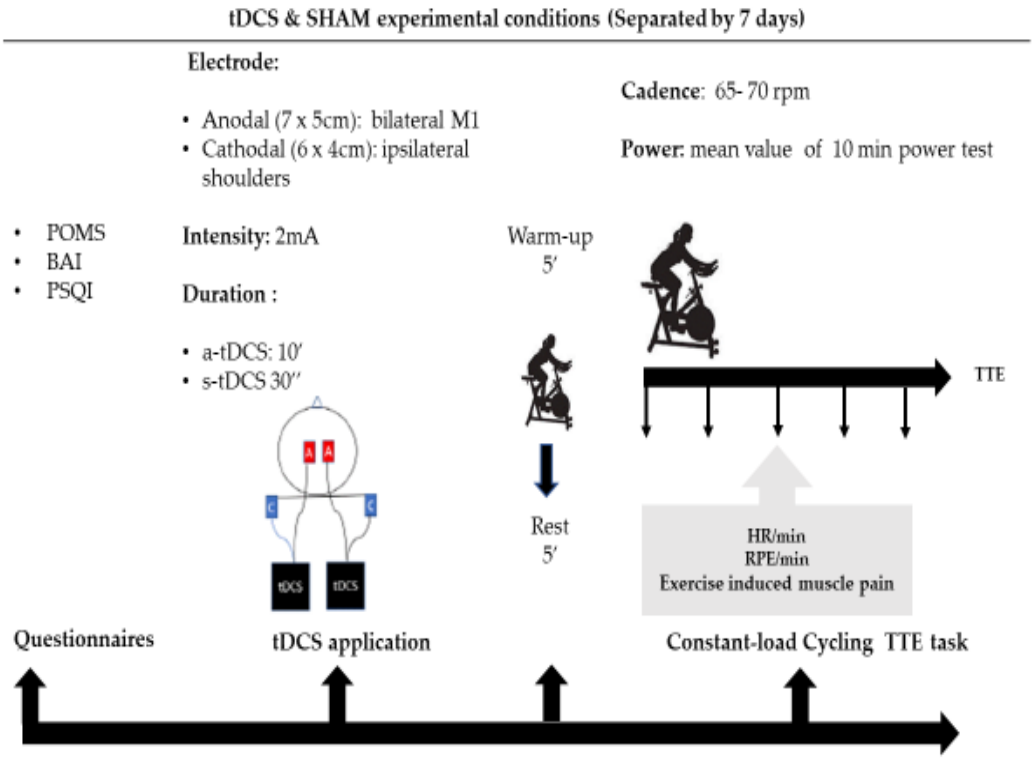

Figure 11. Schematic view of the set-up and protocol.

6.1.6. Data analysis

Once the data of the variables of interest were collected, they were dumped and ordered in an Excel matrix datasheet. The iso-time data of HR, RPE and exercise-induced muscle pain were measured at the selected time points (0%, 25%, 50%, 75% and 100%) to allow the within-subjects comparison of temporal changes during the constant-load cycling TTE test. According to Niccolò et al. (191), in the individual iso-time data method, each subject was considered in isolation when dividing the test into time points. Consequently, that allows for the estimating an experimental intervention's effect while greatly reducing the data loss during experimental interventions. The shortest TTE was identified for each subject over the two experimental sessions and considered as 100% iso-time to obtain these iso-time data. The value for each variable attained during the final full minute of the shortest TTE test was then compared to the value achieved during the equivalent minute of the longer TTE test. The respective 25%, 50% and 75% iso-time were obtained by multiplying the minute identified as 100% (shortest TTE) iso-time for 0.25, 0.50 and 0.75. Iso-time values for 0% were attained by comparing values for the first full minute of each TTE test (133, 192).

6.1.7. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 25 (SPSS Inc., An IBM Company, Chicago, IL, USA), and significance was based on an alpha level of .05. All data are presented as mean ± SD unless otherwise stated. Each variable was examined with the Shapiro-Wilk normality test. Two-way repeated measures analysis of variance (RM-ANOVA) were performed with the condition (a-tDCS and s-tDCS) and time (0%, 25%, 50%, 75%, 100% of TTE) as factors for the following variables: HR, RPE, and exercise-induced muscle pain during constant-load cycling TTE test. Post hoc analysis was performed using paired comparisons with Bonferroni correction. A paired *t*-test was performed to verify the effect of experimental conditions on constant-load cycling TTE performance and the POMS, BAI and PITTSBURGH influences on experimental conditions. Partial eta-squared (η_P^2) values and Cohen-*d* were calculated as effect sizes.

6.2. RESULTS

6.2.1. TTE performance

The results of the cycling TTE task performance are shown in Figure 12. A paired *t*-test was conducted to compare the effect of bilateral extracephalic tDCS applied over M1 during constant-load cycling TTE task between a-tDCS and s-tDCS conditions. There was a significant difference in the cycling TTE between the experimental (M = 684.0, SD = 230.11) and sham (M = 609.0, SD = 193.00) tDCS conditions (t (15) = 2.25, p = 0.04; d = .58). And this indicated that there is a tended to increase in TTE performance following a-tDCS stimulation.

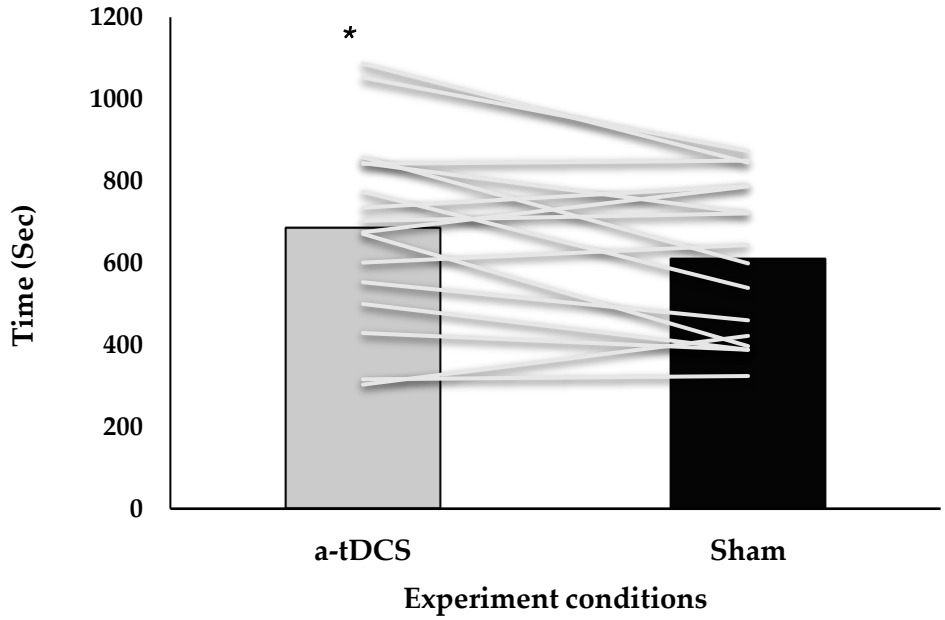

Figure 12. Effect of tDCS on performance during constant-load cycling TTE test under the experimental conditions. * Significant difference compared to the sham condition (P = 0.04). Data are presented as mean ± SD.

6.2.2. HR during constant-load cycling TTE task performance

The results of RM-ANOVA revealed that there was no significant main effect for HR response between a-tDCS and sham conditions (F (1,15) = 2.7, p = .120, η_p^2 =.15) (see figure 13). However, significant main effect for time was observed (F (2, 32) = 238.5, p = < .01, η_p^2 = .94). The interaction effect (condition * time) was not significant (F (4,60) = 2, p =. 11).

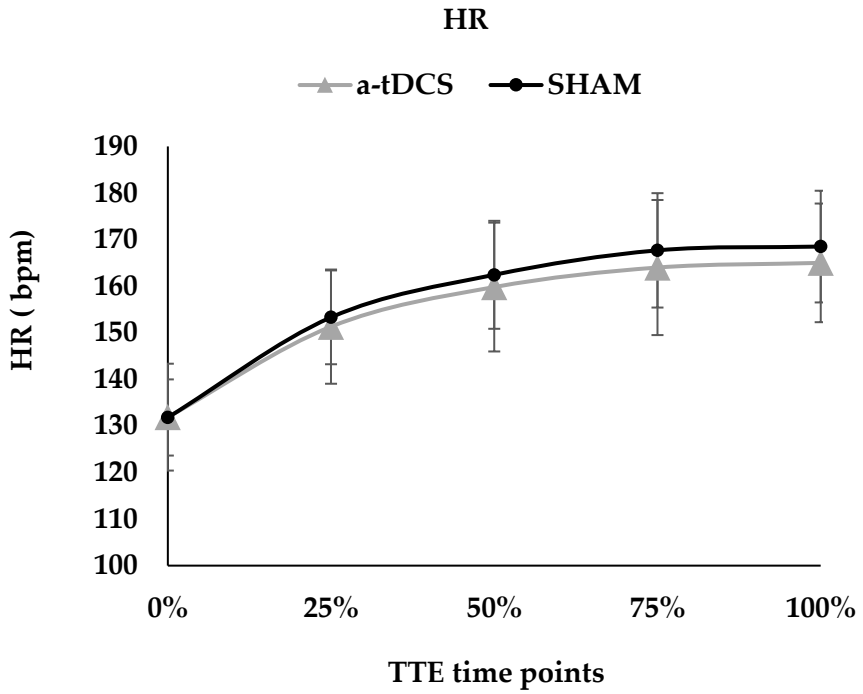

Figure 13. Effect of tDCS on HR response during constant-load cycling TTE task between a-tDCS and sham conditions. Data are presented as mean ± SD.

6.2.3. RPE during constant-load cycling TTE task performance

The ANOVA for the RPE did not show a significant main effect for the condition factor (F (1,15) = 2.51, p = .134, η2 =.14) However, there was a significant main effect of time for RPE (F (2,35) = 270.89, P = < .01, η_p^2 =. 95). RPE increased significantly from the beginning to the end of the TTE task in both conditions (p < 0.001; see Figure 14). The interaction effect (condition * time) was not significant, (F (4,60) = 1.83, P =. 136).

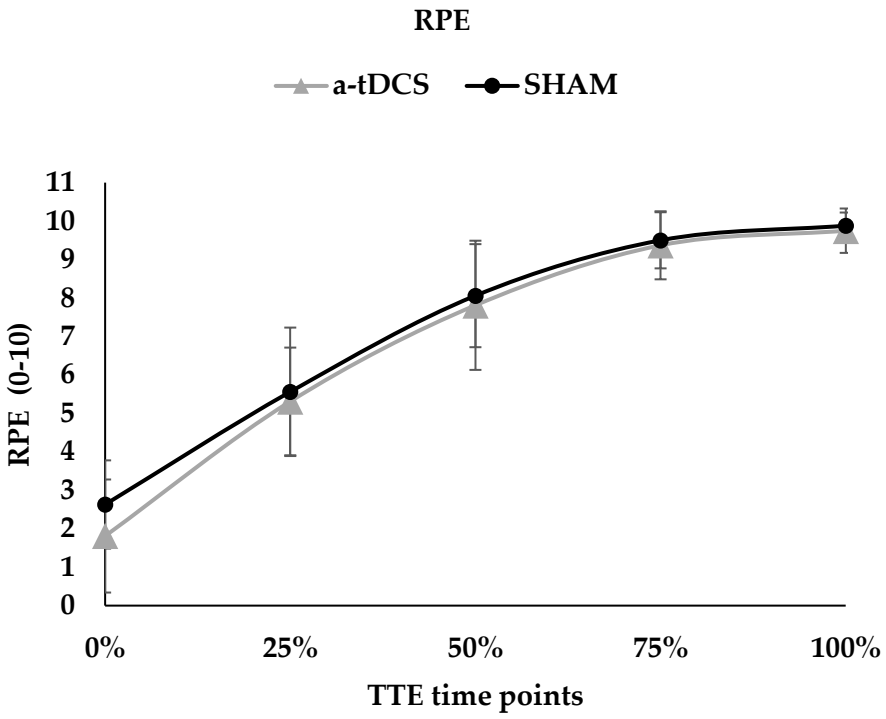

Figure 14. Effect of tDCS on RPE during constant-load cycling TTE task between a-tDCS and sham conditions. Data are presented as mean ± SD.

6.2.4. Exercise-induced muscle pain during constant-load cycling TTE task performance

The results of RM ANOVA revealed no significant main effect for exercise-induced muscle pain between a-tDCS and sham conditions (F (1,15) = 2.21, p = .16, η_p^2 =. 13). However, significant effects were observed for the time factor (F (2, 38) = 316.1, p = < .01, η_p^2 =. 96). Exercise-induced muscle pain was increased significantly from the beginning to the end of the TTE test in both conditions (P < 0.003; see Figure 15). The interaction effect (condition * time) was not significant (F (4,60) = 1.8, P = 0.15).

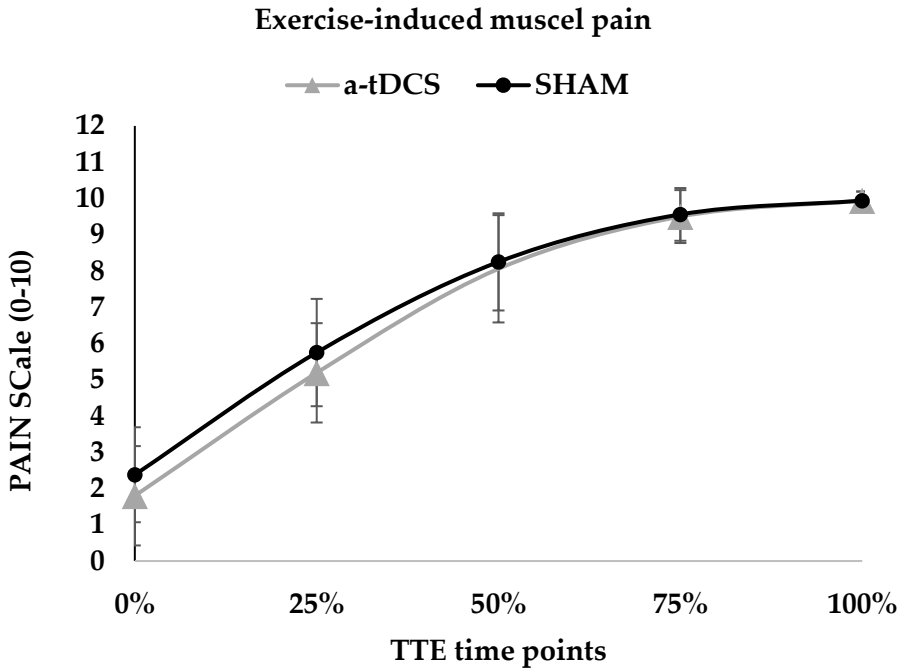

Figure 15. Effect of tDCS on exercise-induced muscle pain during constant-load cycling TTE task between a-tDCS and sham conditions. Data are presented as mean ± SD.

6.2.5. Control variables

Our results yielded no significant differences for any control variables (see Table 3).

Table 3: Results of the questionnaires

Questionnaire	Sub scales	N	a-tDCS	Sham	*t*	*p*
			M ± SD	M ± SD		
POMS	Tension	16	19.5 ± 10	16.9 ± 8	1.10	0.29
	Depression	16	2.5 ± 4.5	2.8 ± 5.2	- 0.24	0.82
	Anger	16	10.8 ± 12.5	10.4 ± 7	0.21	0.83
	Vigour	16	47.2± 21.8	50.9 ± 18.3	-1.22	0.24
	Fatigue	16	14.1 ± 10.5	16.9 ± 14.8	- 0.79	0.44
BAI		16	3.8 ± 4.1	3.1 ± 2.7	0.87	0.40
PITTSBURGH		16	4.4 ± 2.3	4.6 ± 2.4	-0.38	0.71

6.3. DISCUSSION

The main objective of the present study was to determine the effect of bilateral extracephalic tDCS over M1 during constant-load cycling TTE task in physically active people. We also analyzed HR response, RPE, and exercise-induced muscle pain during the abovementioned task.

6.3.1. Effect of a-tDCS over M1 on TTE performance

We hypothesized that extracephalic a-tDCS over bilateral M1 would increase TTE performance during the constant-load cycling TTE task. Likewise, we also consider that tDCS over M1 could decrease HR response, RPE, and exercise-induced muscle pain.

As hypothesized, the main finding of our study is that a-tDCS increased cycling TTE performance by 12%. This finding coincides with previous studies that showed increases of TTE following a-tDCS over the M1 (133, 137, 138, 154, 156). For example, Angius et al. (133) found that TTE performance was improved remarkably by 23%, and Vitor-Costa et al. (154) showed an increase in exercise tolerance during constant-load cycling TTE test after a-tDCS stimulation over the Cz region. In contrast, Angius et al. (137) did not show improvements in cycling TTE after a-tDCS than a sham condition. These differences might be related to the electrode montage used in those studies (165). According to Angius et al. (138), cephalic montage (anode over M1 and cathode over right DLPFC) may induce an effect under the cathode that may modulate or even negate the anode effect over M1. Moreover, in their follow-up study, they compared cephalic and extracephalic tDCS montage by targeting anode over M1. They observed a significant increase in TTE of knee extensor muscles when the extracephalic montage was used. In additionally, our tDCS electrode montage those described by Angius et al. (133) (anode: M1 and cathode: shoulder) and Vitor-Costa et al. (154) (anode: Cz and cathode: occipital protuberance) have also found increment in TTE performance during constant-load cycling.

Furthermore, it should be noted that other electrode montages, such as the stimulation of the DLPFC (132, 155) or the TC (102), are also effective to increase cycling TTE. According to the authors mentioned above, the possible mechanism of longer exercise tolerance mediated by a-tDCS could be related to an increase in motor cortex excitability. This increased excitability would counteract supraspinal fatigue leading to a prolonged cycling time during the TTE task (i.e., more exercise tolerance). However, there is no direct evidence about this, and further studies are needed to test this hypothesis.

6.3.2. **Effect of a-tDCS over M1 on HR response during constant-load cycling TTE task performance**

However, whether HR responses are affected by tDCS during physical exercise remains unclear. Like these previous studies, the present study also did not find the change in HR response after bilateral extracephalic tDCS applied over M1 compared to the sham condition as we hypothesized previously. This result is

consistent with previous studies findings whereas described that there was no significant effect induced by tDCS over M1 on HR response during the constant-load cycling and running. For an example, Vitor-Costa et al, (154) failed to observe any significant HR response changes between three experimental sessions (anodal, cathodal and sham), whereas exercise tolerance was a higher under the a-tDCS condition. Angius et al. (133), have found no difference in HR between experimental conditions while reported a significant increment in constant-load cycling TTE test. Besides, Park et al. (156), have reported no changes in HR response changes during a constant-load running test at 80% intensity following tDCS over M1, whereas running TTE increased following a-tDCS.

Recent studies have discussed that tDCS affects different brain areas on HR response during different physical exercise. Okano et al. (102) reported that the ANS activity modulates following tDCS over the TC, reduction in HR response during the initial phases of maximal incremental cycling test. Besides, Angius et al. (132), for the first time, have demonstrated that the tDCS over left DLPFC reduction in HR response during constant-load cycling TTE test with longer exercise tolerance in TTE test. This may be the PFC, whereas identified to modulate brain areas involved in the regulating the cardiovascular autonomic control (132). Therefore, observed HR response could be related to the ANS differential function following this brain region stimulation (PFC). Taking together, these results propose that tDCS could increase ANS activity during physical exercise.

Finally, as in previous studies, the present study finding supports the theory that tDCS does not affect the physiological variable such as HR. Moreover, it recommended that the connection between the CNS and motor units is entirely regulated by afferent responses (156). Although tDCS, montage used in each study may differ, the findings reported up to date implies that tDCS on motor M1 has no effect on HR response during physical exercise such as constant-load cycling and running TTE test (133, 137, 154, 156).

6.3.3. Effect of a-tDCS over M1 on RPE during constant-load cycling TTE task performance

In contrast to our initial hypothesis, we did not find any changes between experimental conditions in the RPE value during the constant-load cycling TTE

task following tDCS over bilateral M1. When voluntary action involves dynamic contractions of a large muscle group, RPE is an important aspect of volition subjective experience. The conscious sensation of effort provides information about task difficulty. RPE during physical tasks is the conscious awareness of the central motor command sent to the active muscle (97).

The present study results are consistent with the findings of Vitor-Costa et al. (154), who also failed to observe an alteration in RPE value after applying tDCS over the Cz region. In the same line, the study conducted by Angius et al. (137) showed that cephalic tDCS montage over M1 did not alter RPE value during the cycling task. This montage, can negatively affect M1 excitability; therefore, it did not observe any enhancement of the performance or perceptual parameters. In the present study, we used bilateral extracephalic montage (anode: both M1 and cathode: ipsilateral shoulders). Still, we did not observe a decrement in RPE following a-tDCS compared with a sham condition. Moreover, Park et al. (156) have shown an improvement in TTE during running at 80% intensity by applying an a-tDCS to M1 without any alteration in RPE values.

Our study found that RPE was unchanged, whereas other studies found that the manipulation of M1 decreases RPE and increased TTE performance. These results demonstrated that an RPE decrease following a-tDCS could increase M1 excitability, increase central motor command and show a lower RPE. For example, Angius et al. (133) demonstrated that bilateral extracephalic tDCS over M1 induced lower RPE values related to improved cycling TTE. In the same line Angius et al. (138) have found longer isometric TTE of knee extensors with lower RPE following extracephalic a-tDCS. It has been documented that the RPE change is related to various activities across different regions in the motor cortex, including premotor cortex, M1, prefrontal cortex, supplementary motor areas (97).

In this context, there is an evidence that the effect of a-tDCS over other brain areas such as IC also reduced the RPE value. However, these results are contradictory. For example, Okano et al. (102) reported a reduction in RPE and ~4% improvement in peak power output during an incremental cycling test. In contrast, Barwood et al. (9) did not find any perceptual or performance improvement during a fixed intensity cycling TTE in hot condition (33°C). According to these authors, differences in the testing procedures and the

environmental conditions may explain these contrasting results. In addition, Angius et al. (132) have found lower RPE values in the real-tDCS applied over the left DLPFC with longer cycling TTE performance than the s-tDCS condition. Unlike the DLPFC, which is directly related to emotions such as discomfort levels, the montage used in this study applies an a-tDCS to both M1, which is not generally associated with emotion control. The high-intensity physical task requires inhibitory control to prevent task failure, and this cognitive process is associated with a subjective feeling of effort that might contribute positively to the overall RPE during exercise (132).

RPE might have been different owing to the subjects' motivational level. The interoceptive model considers various factors that can be used to explain our study results. According to the interoceptive model, different factors including afferent feedback, sensory, emotion, and motivation, collectively involves central fatigue based on the whole-body exercise physiological state (193). However, recent evidence suggests that a-tDCS might increases TTE performance by altering RPE value. Thus, further study is needed to understand the effect of tDCS on RPE during physical performance.

6.3.4. **Effect of a-tDCS over M1 on exercise-induced pain during constant-load cycling TTE task performance**

In contrast to our expectation, exercise-induced muscle pain did not differ between experimental conditions following bilateral extracephalic tDCS over M1, during constant-load cycling. Our result is consistent with Angius et al. (133). They observed a lack of variations in exercise-induced muscle pain during constant-load cycling TTE test following bilateral extracephalic tDCS over M1 compared to a sham condition while showed an increase in TTE performance. Further, these findings were also consistent with their previous studies. The study conducted by Angius et al. (137) investigated the effect of tDCS on exercise-induced muscle pain during fixed intensity cycling TTE and on pain perception during a cold pressor test. The authors observed significant reduction in perceived pain during the cold pressor test following cephalic tDCS montage over M1. Moreover, our result contrarily to some previous studies where a-tDCS over M1 induced pain perception changes during different experimentally induced pain types (177, 194).

Exercise-induced muscle pain is considered an important factor in exercise performance regulation (195). Recently, have reported several key factors that may explain why exercise-induced muscle pain appears to be insensitive to the effects of tDCS over M1 (137, 138) which to include the type of nociceptive stimulus, attentional factors, release of endogenous opioids or catecholamines and supraspinal nociceptive inhibitory mechanism (137). Exercise-induced muscle pain plays an essential role in exercise tolerance because of its afferent feedback (165). It has been documented that the effect of tDCS over M1 reduces thermal and electrical pain that (137). It has been suggested that key areas for exercise-induced pain include the primary sensorimotor cortex, secondary somatosensory cortex, and anterior insular and cingulate cortex and thalamus (6). tDCS application of M1 has been proposed to induce analgesia through a corticothalamic inhibition of epicritic (consistent with type III afferents) and nociceptive sensation at the ventral posterolateral and ventral posteromedial thalamic nuclei (177). But, as skeletal muscle is more densely populated by type IV afferents, which are more related to a progressive build-up of pain that is dull, burning and painful (6), it may be tDCS over M1 produces a small analgesic effect to exercise-induced muscle pain.

There is a strong emotional response to exercise-induced pain. tDCS applied over DLPFC may reduce the emotional response to pain (196). The DLFPC has been proposed to play an important role in the affective, cognitive, and attentional aspect of pain (197). Studies applying tDCS over left DLPFC found a reduction in cold pain perception (198), increase in thermal pain threshold (197) or decreased of self-unpleasantness when viewing emotionally aversive pictures (196). But still, Angius et al. (132) have reported that exercise-induced pain was not affected by tDCS applied over left DLFPC. Several methodological aspects, as well as the different type of pain investigated may explain these discrepancies.

With the lack of analgesic effect of tDCS over M1 on exercise-induced muscle pain, it may be the case that the constant-load cycling TTE task did not produce the level of pain high enough for an analgesic effect to be detected. This may be in part due to intense exercise stimulating the body's inherent analgesic system, including the release of endogenous opioids. The endogenous pain inhibition acts by inhibiting nociceptive input in the CNS at both spinal and supraspinal levels. Descending neural pathways with inputs from cortical, subcortical and spinal

regions have been propose to be involved in this modulatory process (199, 200). all of which are likely to mitigate the strength of pain signal reaching the brain. Consequently, the additive effect of tDCS may not improve this powerful natural analgesic response to exercise. Additionally, the stimuli direct attention is one of the requisites of the pain perception, and any distraction from pain sensation can reduce reporting of pain. During the constant-load cycling TTE, the subject provides more attention to the exercise task (201). Finally, all these factors during exercise might reduce the benefits of tDCS.

VII – GENERAL DISCUSSION

VII – GENERAL DISCUSSION

The present thesis aimed to investigate the ergogenic effect of a-tDCS on endurance exercise performance in physically active people. For this purpose, it has been performed a systematic review of the literature and meta-analysis concerning the effectiveness of a-tDCS on endurance whole-body dynamic physical performance. Finally, the experiment investigated the effect of bilateral extracephalic a-tDCS over M1 during a constant-load cycling TTE task in 16 physically active people.

For that purpose, we performed two studies. First, the systematic review and meta-analysis to quantify the effect of a-tDCS on endurance (TTE, ETT) and sprint performance during cycling and running tasks, where we compared the effect of a-tDCS against sham stimulation. The results showed that a-tDCS could increase TTE performance during cycling and running task but not during ETT or sprint task, and the task should be considered as it probably influences the results obtained through a-tDCS (202). In the second study we found that bilateral extracephalic a-tDCS over M1 increases TTE performance by 12% compared with the sham condition, without a change in HR response consistent with our initial hypothesis. However, in contrast to our expectations, RPE values and exercise-induced muscle pain variables did not differ between experimental conditions. It has been documented that the endurance task involving cycling, running or sustained submaximal isometric contraction promote a progressive decline in the excitability of the spinal motoneurons and contractile capacity of the active muscle fibres (68, 98) so that to maintain the required force or power, the input to the spinal motoneurons must increase (203). Previous studies have suggested that increasing M1 excitability may lead to a more efficient motor command that can ultimately enhance TTE performance (120). This hypothesis has been examined in different studies using tDCS.

Previous systematic reviews and meta-analyses shed mixed results concerning the effect of a-tDCS on endurance and strength performance (135, 166, 167). Moreover, most of these meta-analyses did not consider the nature of the task performed when assessing the effect of a-tDCS. Calculations conducted by pooling

together such different task provide unclear and confounding results on the possible after effect of tDCS on physical performance. Therefore, we conducted a systematic review to identify the state of the literature regarding the effectiveness of the acute effect of a-tDCS in endurance physical performance to identify whether the effect of tDCS depends on the characteristic of the task performed (i.e., TTE, TT and sprint). However, it is important to note that only four studies analyzed the ETT task and two studies the sprint tasks (202). Therefore, more studies are apparently needed to firmly establish the effect of a-tDCS on these types of tasks.

The inconsistency in the results of the included studies regarding the potential ergogenic effect of a-tDCS on endurance cycling and running exercise could be related to differences in multiple parameters such as brain stimulation area, electrode size, electrode montage, current intensity and duration (141). The present review shows that most of the above mentioned experiments targeted brain areas such as M1 (133), DLPFC (132), TC (102). All included studies have used endurance (TTE, ETT) and sprint tasks during cycling and running. Authors suggested that the TTE test has more sensitivity evaluating factors that alter endurance exercise performance, such as physiological and perceptual responses in a controlled manner (27).

Nine of fifteen interventions in current systematic review and meta-analysis have reported the positive ergogenic effect of a-tDCS on TTE performance during cycling and running. Some of these included studies demonstrated an increase of cycling TTE performance related to a lower RPE value after tDCS applied over M1 (133). The increased excitability of the M1 could have increased the output to the working muscles by reducing the central command required. This could have caused the lower RPE, thus, exercise feels easier for a given intensity (138, 163). Additionally, Angius et al. (132) reported that a-tDCS targeting the left-DLPFC increased cycling TTE performance in parallel to a lower RPE. Authors have argued that tDCS can modulate cortical neurons or affective responses, leading to a lower RPE or reduced pain perception. However, the redaction of RPE has not been reported in all cases (154, 155).

The acute effect of a-tDCS on ETT performance is not entirely clear. Considering the limited available literature of tDCS on ETT task (9, 156), a-tDCS applied to brain areas such as M1, DLPFC, TC are unlike to increase performance

during this type of task. It is, therefore, possible that the effect of a-tDCS on exercise performance is task-dependent. The most important factors limiting performance during the sprint activities are fatigue occurring in the CNS. Therefore, the manipulation of supraspinal centres involved in the control of the motor output such as the M1 could reduce CNS fatigue and thus enhance performance (47). However, only two studies have been performed to investigate the effect of a-tDCS on sprint performance (121, 162). The results of these studies demonstrated that the tDCS do not induced improvement in sprint performance. Further studies are needed to clarify the deferent mechanism by which tDCS could improve performance in such a task (i.e., sprint).

Based on the systematic review and meta-analysis, we performed a second study to determine the effect of bilateral extracephalic a-tDCS over M1 during a constant-load cycling TTE test. During the TTE test, we measured HR response, RPE, and exercise-induced muscle pain. Results show that the bilateral extracephalic a-tDCS over M1 increase TTE performance by 12% during constant-load cycling task, without any change on HR response, RPE, and exercise-induced muscle pain between both experimental conditions. The results from the previous experiment suggest that endurance cycling TTE performance can be increased by a-tDCS (133, 154). The increased M1 excitability could have made exercise feel easier due to a lowered RPE (165). However, this hypothesis could not be confirmed because we did not measure the excitability of M1 following a-tDCS during this study. Furthermore, we did not find any alterations in RPE values with longer exercise tolerance. There are also some studies that demonstrated increased TTE without changes in RPE (154, 156).

It was hypothesized that bilateral extracephalic tDCS over M1 would not change HR response. This finding supports our initial hypothesis; there was no change observed in HR during cycling TTE test following a-tDCS. In this regard, HR is well controlled in the TTE test as suggested by Amann et al. (27) because the load was constant through the test, and it is used across all the experimental conditions. It has been documented that the HR responses did not change after a-tDCS over M1 during the constant-load cycling TTE task (133, 137, 154). However, Angius et al. (132) have reported lower HR response in the a-tDCS applied over left DLPFC during constant-load cycling. It has been identified that the PFC is linked

to brain areas involved in the regulation of cardiovascular autonomic control (204). Increased PFC activity is related to an increased parasympathetic tone that induced variations in HR (204). In light of this evidence, the reduction in HR during exercise task, can result from an increased parasympathetic activity induced by tDCS. It should be considered that we did not monitor heart rate variability during the current study; therefore, further investigation should be performed to explore mechanisms leading to lower HR during constant load cycling following tDCS.

The results of the current study demonstrated that the exercise-induced pain during constant-load cycling was not affected by tDCS. A lack of effect of tDCS on exercise-induced muscle pain during constant-load cycling TTE test has been previously reported (133). It was likely caused by the different type of pain stimulus, pain intensity perceived, or the attentional focus. Therefore, it might be still difficult to understand the mechanism underlining tDCS effects on exercise-induced muscle pain. In contrast, a-tDCS over the M1 produced a significant reduction in cold pain perception (137) while exercise-induced muscle pain did not show any change during fixed intensity TTE cycling test (133, 137). Additionally, studies have reported an increase in thermal pain threshold (197). Probably, different methodological aspect as well as different kind of pain investigated, may explain discrepancies.

To sum up, the present thesis aimed to investigate the ergogenic effect of a-tDCS on endurance exercise performance in healthy people. At the actual level, the overall result from the present thesis shows that the ergogenic effect of tDCS can potentially increase endurance cycling and running TTE performance. However, the task should be considered as it probably influences the result obtained though acute a-tDCS. In the second study of the present thesis, despite the increase in constant-load cycling TTE following bilateral extracephalic tDCS over M1 agrees with the results of other studies (133, 154). Further, no changes observed in HR, RPE, and exercise-induced muscle pain.

VIII - CONCLUSIONS

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General conclusions

The results of the present thesis suggested that the ergogenic effect of tDCS can potentially increase endurance TTE performance during cycling and running in physically active people. However, the task should be considered when examining the effect of tDCS on physical exercise. This is due to the influence of individuals' anatomical, physiological, perceptual, and tDCS parameters. Further, bilateral extracephalic a-tDCS montage over M1 can effectively enhance TTE performance during constant-load cycling task. This finding implies that tDCS is a sports supportive tool. Precisely, need more studies to understand the specific mechanism that associating with different targeted brain areas during different kinds of physical activities.

Specific conclusions

Study 1

- The acute increase in performance during the endurance cycling and running in whole-body dynamic exercise occurred after a-tDCS.
- Only increased the TTE performance during endurance cycling and running after a-tDCS over targeted brain areas, but no changes occurred in the ETT and sprint performance. Therefore, the task should be considered, as it influences the result obtained following a-tDCS.
- It should be noted that only four studies have analyzed the ETT task and two studies have analyzed the sprint task. Therefore, further studies are needed to establish the effect of tDCS on this type of task.

Study 2

- Bilateral extracephalic a-tDCS over M1 increase TTE performance by 12%, during constant-load cycling task. The performance was enhanced in the absence of changes in HR, RPE, exercise induce muscle pain variables.
- The acute effect of bilateral extracephalic a-tDCS applied over M1 was not associated with reducing HR response during the constant-load cycling TTE test.
- The RPE value during constant-load cycling was not decreased after bilateral extracephalic a-tDCS applied over M1 due to subjective motivational level.
- The exercise-induced muscle pain did not decrease during constant-load cycling task performed after bilateral extracephalic tDCS applied to M1.

IX – LIMITATIONS

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Considering, contradictory evidence regarding the effect of a-tDCS on whole-body dynamic exercise such as cycling and running, it is still challenging to understand the exact mechanism that underline the effect of tDCS on brain stimulation during physical performance. There are some limitations of two studies composing the present thesis must be addressed.

Study 1:

- The limited number of studies included in the systematic review and meta-analysis, due to the few existing publications in the relative literature that attempt to analyse the acute effect of a-tDCS on endurance cycling and running performance. In particular, only four studies have been examined ETT, and the other two studies have evaluated the effect of tDCS on sprinting performance.

Study 2:

- Application of bilateral extracephalic tDCS to M1 does not modulate HR, RPE and exercise-induced muscle pain during constant-load cycling TTE task. However, the results are applicable to the type of tDCS protocol used including, the modification in the brain stimulation area, current intensity, duration and electrode size could be substantially altering these variable responses. Furthermore, this may also have an impact by each individual's anatomical, physiological characteristics.
- In this study, the tDCS mechanism is not entirely understood. We supposed that a-tDCS modulate M1 excitability, and therefore, increased TTE performance. In this study, we did not measure parameters that allowed to assess the M1 excitability. Hence, it is unknown how a-tDCS intervention affected to enhance TTE performance. during constant-load cycling TTE task
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X – FUTURE LINES OF INVESTIGATION

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After the completion of the present thesis, future investigation lines arise from the results achieved. In this regard, potential future investigations that could bring further understanding on the topics studied herein are presented below:

- Considering the findings of the systematic review and meta-analysis, the effect of tDCS is depended on the nature of the task performed. Future research should explore this concept to better understand the mechanism which underlines tDCS during different sports activities.

- It is considered that the heterogeneity of the tDCS protocols makes the comparison between studies difficult and is probably one of the reasons why contradictory results are found. Therefore, when preparing tDCS protocols, it should take into account the selected tDCS parameters. In particular, electrode montage, electrode size (i.e., 35 cm, 12cm, 24cm), stimulation time (i.e., ≥ 10min), brain stimulation area (i.e., M1, DLPFC, TC… etc…).

- Future research should take into account the effect of tDCS stimulation on other cortical areas (IC, PFC), which has associated with regulating the HR responses, RPE, exercise-induce pain during endurance whole-body dynamic exercise.

- Elaborate a long-term training program that allows investigating the long-term effect of a-tDCS on M1.

XI – REFERENCES

XI–REFERENCES

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XII– ANNEXES

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Annex 1. Informed Consent form

ANEXO II

CONSENTIMIENTO INFORMADO

Yo, ..., con DNI: .....

DECLARO:

Haber sido informado/a del estudio y procedimientos de la investigación del Proyecto titulado: "La estimulación cerebral por corriente directa como ayuda ergogénica en tareas de fuerza y resistencia. Parámetros óptimos de estimulación y aplicación al alto rendimiento".

Los investigadores que van a acceder a mis datos personales y a los resultados de las pruebas son: Shyamali Kaushalya, Gonzalo Márquez Sánchez, Salvador Romero Arenas, Carlos Alix, Giancarlo de Jesús y Agustín Jerez Martinez.

Asimismo, he podido hacer preguntas del estudio, comprendiendo que me presto de forma voluntaria al mismo y que en cualquier momento puedo abandonarlo sin que me suponga perjuicio de ningún tipo.

CONSIENTO:

1.-) Someterme a las siguientes pruebas exploratorias (en su caso): Estimulación eléctrica por corriente directa, test incremental en cicloergómetro, test de tiempo de esfuerzo hasta la extenuación.

2.-) El uso de los datos obtenidos según lo indicado en el párrafo siguiente:

En cumplimiento del Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, Real Decreto-Ley 5/2018, de 27 de julio y Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal, le comunicamos que la información que ha facilitado y la obtenida como consecuencia de las exploraciones a las que se va a someter pasará a formar parte del fichero automatizado INVESALUD, cuyo titular es la FUNDACIÓN UNIVERSITARIA SAN ANTONIO, con la finalidad de INVESTIGACIÓN Y DOCENCIA EN LAS ÁREAS DE CONOCIMIENTO CIENCIAS EXPERIMENTALES Y CIENCIAS DE LA SALUD. Tiene derecho a acceder a esta información y cancelarla o rectificarla, dirigiéndose al domicilio de la entidad, en Avda. de los Jerónimos de Guadalupe 30107 (Murcia). Esta entidad le garantiza la adopción de las medidas oportunas para asegurar el tratamiento confidencial de dichos datos.

En Guadalupe (Murcia) a ..... de ..... de 20

El investigador,

Fdo:..... Fdo:.....

Annex 2. tDCS screening questionnaire (205).

Es importante que responda todas las preguntas siguientes con sinceridad. Si alguna de las preguntas / términos de este formulario no está clara, o si no está seguro de cómo responderlas, no dude en preguntar al investigador del estudio.		
	Yes	**No**
¿Ha tenido convulsiones alguna vez?		
¿Alguna vez ha tenido una lesión en la cabeza que haya provocado la pérdida del conocimiento?		
¿Sufre de migrañas?		
¿Tiene actualmente un diagnóstico médico de una condición psicológica o neurológica?		
¿Tiene algún metal en la cabeza (fuera de la boca) como metralla o clips quirúrgicos?		
¿Tiene algún dispositivo implantado (por ejemplo, marcapasos cardíaco, estimulador cerebral)?		
¿Tiene una afección cutánea en el cuero cabelludo? (por ejemplo, psoriasis)		
¿Tiene una herida en la cabeza que no ha sanado por completo?		
¿Ha tenido una reacción adversa al tDCS/TMS?		
Para las mujeres participantes: ¿Existe la posibilidad de que esté embarazada?		
¿Está tomando actualmente algún medicamento?		
He comprendido la información que antecede y que me ha sido explicada satisfactoriamente		
Fdo: El voluntario: Nombre: …….. DNI……		

Annex 3. The Physical activity readiness questionnaire (PAR-Q & YOU).

Physical Activity Readiness Questionnaire – PAR-Q (revisado en 2002)

PAR-Q* Y TÚ

Cuestionario para persona entre 15 y 69 años

Con el propósito de asegurar su participación en el estudio de la forma más segura posible, conteste de la forma más honrada posible a las siguientes preguntas marcando una cruz en SÍ o NO.

Sí	No		
☐	☐	1.	¿Le ha dicho alguna vez su médico que tiene una enfermedad del corazón y le ha recomendado realizar actividad física solamente con supervisión médica?
☐	☐	2.	¿Nota dolor en el pecho cuando practica alguna actividad física?
☐	☐	3.	¿Ha notado dolor en el pecho en reposo durante el último mes?
☐	☐	4.	¿Ha perdido la consciencia o el equilibrio después de notar sensación de mareo?
☐	☐	5.	¿Tiene algún problema en los huesos o articulaciones que podría empeorar a causa de la actividad física que se propone realizar?
☐	☐	6.	¿Le ha prescrito su médico medicación arterial o para algún problema del corazón (p. ej. diuréticos)?
☐	☐	7.	¿Está al corriente, ya sea por su propia experiencia o por indicación de un médico, de cualquier otra razón que le impida hacer ejercicio sin supervisión médica?

Si ha contestado	Sí a una o más preguntas	No a todas las preguntas
	Hable con el médico por teléfono o en persona ANTES de realizar el estudio. Hable con el médico del PAR-Q y de las preguntas a las que dio contestación afirmativa.	**Si contestó NO honradamente a todas las preguntas del PAR-Q, puede estar razonablemente seguro de poder realizar el estudio.**

NOTAS:

1. Si no se siente bien por una enfermedad temporal como yn resfriado o fiebre, espere hasta estar mejor.
2. Si está o puede estar embarazada, hable con el médico antes de volver a ser más activa.
3. Si su salud cambia de tal forma que contesta Sí a alguna de las preguntas anteriores, háganoslo saber.

<<He leído, entendido y completado este cuestionario. He respondido a todas las preguntas con mi aprobación.>>

Nombre:_____Fecha:_____

Firma del participante Firma del testigo

Annex 4. International physical activity questionnaire (IPAQ).

CUESTIONARIO INTERNACIONAL DE ACTIVIDAD FÍSICA (IPAQ)

Estamos interesados en averiguar acerca de los tipos de actividad física que hace la gente en su vida cotidiana. Las preguntas se referirán al tiempo que usted destinó a estar físicamente activo en los **últimos 7 días.** Por favor responda a cada pregunta aún si no se considera una persona activa. Por favor, piense acerca de las actividades que realiza en su trabajo, en las tareas domésticas o en el jardín, en sus desplazamientos, en el tiempo libre, el ejercicio o el deporte.

Piense en todas las actividades **INTENSAS** que usted realizó en los **últimos 7 días.** Las actividades físicas **intensas** se refieren a aquellas que implican un esfuerzo físico intenso y que lo hacen respirar mucho más intensamente que lo normal. Piense ***solo*** en aquellas actividades físicas que realizó durante por lo menos **10 minutos** seguidos.

1. Durante los últimos 7 días, ¿en cuantos realizó actividades físicas intensas tales como levantar cargas pesadas, cavar, hacer ejercicios aeróbicos o pedalear en bicicleta de forma intensa?

_____ **días por semana** ☐ **Ninguna actividad física intensa** ⇨ *Vaya a la pregunta 3*

2. Habitualmente, ¿cuánto tiempo en total dedicó a una actividad física intensa en uno de esos días?

_____ **horas por día** _____ **minutos por día** ☐ **No sabe / No está seguro**

Piense en todas las actividades **MODERADAS** que usted realizó en los **últimos 7 días**. Las actividades **moderadas** son aquellas que requieren un esfuerzo físico moderado que lo hace respirar algo más intensamente que lo normal. Piense solo en aquellas actividades físicas que realizó durante por lo menos **10 minutos** seguidos.

3. Durante los últimos 7 días, ¿en cuántos días hizo actividades físicas moderadas como transportar pesos livianos, pedalear en bicicleta a velocidad normal o jugar dobles a tenis? No incluya caminar.

_____ **días por semana** ☐ **Ninguna actividad física moderada** ⇨ *Vaya a la pregunta 5*

4. Habitualmente, ¿cuánto tiempo en total dedicó a una actividad física moderada en uno de esos días?

_____ **horas por día** _____ **minutos por día** ☐ **No sabe / No está seguro**

Piense en el tiempo que usted dedicó a **CAMINAR** en los **últimos 7 días**. Esto incluye caminar en el trabajo o en la casa, para trasladarse de un lugar a otro, o cualquier otra caminata que usted podría hacer solamente para la recreación, el deporte, el ejercicio o el ocio.

5. Durante los últimos 7 días, ¿En cuántos caminó por lo menos 10 minutos seguidos?

_____ **días por semana** ☐ **Ninguna caminata** ⇨ *Vaya a la pregunta 7*

6. Habitualmente, ¿cuánto tiempo en total dedicó a caminar en uno de esos días?

_____ **horas por día** _____ **minutos por día** ☐ **No sabe / No está seguro**

La última pregunta es acerca del tiempo que pasó usted **SENTADO** durante los días laborables de los **últimos 7 días**. Esto incluye el tiempo dedicado al trabajo, en la casa, en una clase, y durante el tiempo libre. Puede incluir el tiempo que pasó sentado ante un escritorio, visitando amigos, leyendo, viajando en automóvil o autobús, sentado o recostado mirando la televisión.

7. Durante los últimos 7 días ¿cuánto tiempo pasó sentado durante un día hábil?

_____ **horas por día** _____ **minutos por día** ☐ **No sabe / No está seguro**

Annex 5. Profile of state (POMS)

PERFIL DE ESTADOS DE ANIMO (POMS). FORMA ABREVIADA

NOMBRE:	FECHA:
DEPORTE:	EDAD:

Más abajo hay una lista de palabras que describen sensaciones que tiene la gente. Por favor, lea cada una cuidadosamente. Después rodea con un círculo, o tache con una X uno de los números que hay al lado, el que mejor describa como se ha sentido usted durante la semana pasada incluyendo el día de hoy.

Los números significan:
0 = Nada; 1 = Un poco; 2 = Moderadamente; 3 = Bastante; 4 = Muchísimo.

1. Intranquilo	0	1	2	3	4
2. Enérgico	0	1	2	3	4
3. Desamparado	0	1	2	3	4
4. Furioso	0	1	2	3	4
5. Sin fuerzas	0	1	2	3	4
6. Deprimido	0	1	2	3	4
7. Lleno de energía	0	1	2	3	4
8. Inquieto	0	1	2	3	4
9. Molesto	0	1	2	3	4
10. Agotado	0	1	2	3	4
11. Agitado	0	1	2	3	4
12. Luchador	0	1	2	3	4
13. Desdichado	0	1	2	3	4
14. Irritable	0	1	2	3	4
15. Cansado	0	1	2	3	4
16. Amargado	0	1	2	3	4
17. Animado	0	1	2	3	4
18. Nervioso	0	1	2	3	4
19. Enfadado	0	1	2	3	4
20. Exhausto	0	1	2	3	4
21. Tenso	0	1	2	3	4
22. Vigoroso	0	1	2	3	4
23. Triste	0	1	2	3	4
24. Enojado	0	1	2	3	4
25. Fatigado	0	1	2	3	4
26. Infeliz	0	1	2	3	4
27. Activo	0	1	2	3	4
28. Relajado	0	1	2	3	4
29. De mal genio	0	1	2	3	4

Annex 6. Beck Anxiety Inventory (BAI)

En el cuestionario hay una lista de síntomas comunes de la ansiedad. Lea cada uno de los ítems atentamente, e indique cuanto le ha afectado en la última semana incluyendo hoy:

Inventario de Ansiedad de Beck (BAI)

		En absoluto	Levemente	Moderadamente	Severamente
1	Torpe o entumecido.	○	○	○	○
2	Acalorado.	○	○	○	○
3	Con temblor en las piernas.	○	○	○	○
4	Incapaz de relajarse	○	○	○	○
5	Con temor a que ocurra lo peor.	○	○	○	○
6	Mareado, o que se le va la cabeza.	○	○	○	○
7	Con latidos del corazón fuertes y acelerados.	○	○	○	○
8	Inestable.	○	○	○	○
9	Atemorizado o asustado.	○	○	○	○
10	Nervioso.	○	○	○	○
		En absoluto	**Levemente**	**Moderadamente**	**Severamente**
11	Con sensación de bloqueo.	○	○	○	○
12	Con temblores en las manos.	○	○	○	○
13	Inquieto, inseguro.	○	○	○	○
14	Con miedo a perder el control.	○	○	○	○
15	Con sensación de ahogo.	○	○	○	○
16	Con temor a morir.	○	○	○	○
17	Con miedo.	○	○	○	○
18	Con problemas digestivos.	○	○	○	○
19	Con desvanecimientos.	○	○	○	○
20	Con rubor facial.	○	○	○	○
		En absoluto	**Levemente**	**Moderadamente**	**Severamente**
21	Con sudores, frios o calientes.	○	○	○	○

Annex 7. Pittsburgh Sleep Quality Index (PSQI)

Apellidos y nombre_____ Nº HªC._____

Sexo_____ Estado civil_____ Edad_____ Fecha___/___/___

Intrucciones:
Las siguientes preguntas hacen referencia a cómo ha dormido usted normalmente durante el último mes. Intente ajustarse en sus respuetas de la manera más exacta posible a lo ocurrido durante la mayor parte de los días y noches del último mes.
¡Muy importante! CONTESTE A TODAS LAS PREGUNTAS

1. Durante el último mes, ¿cuál ha sido, normalmente, su hora de acostarse?
   APUNTE SU HORA HABITUAL DE ACOSTARSE:_____

2. ¿Cuánto tiempo habrá tardado en dormirse, normalmente, las noches del último mes?
   APUNTE EL TIEMPO EN MINUTOS:_____

3 Durante el último mes, ¿a qué hora se ha levantado habitualmente por la mañana?
   APUNTE SU HORA HABITUAL DE LEVANTARSE:_____

4. ¿Cuántas horas calcula que habrá dormido verdaderamente cada noche durante el último mes? (El tiempo puede ser diferente al que usted permanezca en la cama)
   APUNTE LAS HORAS QUE CREA HABER DORMIDO:_____

Para cada una de las siguientes preguntas, elija la respuesta que más se ajusta a su caso. Intente contestar a TODAS las preguntas.

5. Durante el último mes, cuántas veces ha tenido usted problemas para dormir a causa de:

   a) No poder concliliar el sueño en la primera media hora:
   Ninguna vez en el último mes ☐
   Menos de una vez a la semana ☐
   Una o dos veces a la semana ☐
   Tres o más veces a la semana ☐

   b) Despertarse durante la noche o de madrugada:
   Ninguna vez en el último mes ☐
   Menos de una vez a la semana ☐
   Una o dos veces a la semana ☐
   Tres o más veces a la semana ☐

   c) Tener que levantarse para ir al servicio:
   Ninguna vez en el último mes ☐
   Menos de una vez a la semana ☐
   Una o dos veces a la semana ☐
   Tres o más veces a la semana ☐

   d) No poder respirar bien:
   Ninguna vez en el último mes ☐
   Menos de una vez a la semana ☐
   Una o dos veces a la semana ☐
   Tres o más veces a la semana ☐

   e) Toser o roncar ruidosamente:
   Ninguna vez en el último mes ☐
   Menos de una vez a la semana ☐
   Una o dos veces a la semana ☐
   Tres o más veces a la semana ☐

   f) Sentir frío:
   Ninguna vez en el último mes ☐
   Menos de una vez a la semana ☐
   Una o dos veces a la semana ☐
   Tres o más veces a la semana ☐

g) Sentir demasiado calor:
- Ninguna vez en el último mes ☐
- Menos de una vez a la semana ☐
- Una o dos veces a la semana ☐
- Tres o más veces a la semana ☐

h) Tener pesadillas o «malos sueños»:
- Ninguna vez en el último mes ☐
- Menos de una vez a la semana ☐
- Una o dos veces a la semana ☐
- Tres o más veces a la semana ☐

i) Sufrir dolores:
- Ninguna vez en el último mes ☐
- Menos de una vez a la semana ☐
- Una o dos veces a la semana ☐
- Tres o más veces a la semana ☐

j) Otras razones (por favor, descríbalas a continuación):_____

_____

_____

6. Durante el último mes, ¿cómo valoraría en conjunto, la calidad de su sueño?
- Bastante bueno ☐
- Bueno ☐
- Malo ☐
- Bastante malo ☐

7. Durante el último mes, ¿cuántas veces habrá tomado medicinas (por su cuenta o recetadas por el médico) para dormir?
- Ninguna vez en el último mes ☐
- Menos de una vez a la semana ☐
- Una o dos veces a la semana ☐
- Tres o más veces a la semana ☐

8. Durante el último mes, ¿cuántas veces ha sentido somnolencia mientras conducía, comía o desarrollaba alguna otra actividad?
- Ninguna vez en el último mes ☐
- Menos de una vez a la semana ☐
- Una o dos veces a la semana ☐
- Tres o más veces a la semana ☐

9. Durante el último més, ¿ha representado para usted mucho problema el «tener ánimos» para realizar alguna de las actividades detalladas en la pregunta anterior?
- Ningún problema ☐
- Sólo un leve problema ☐
- Un problema ☐
- Un grave problema ☐

10. ¿Duerme usted solo o acompañado?
- Solo ☐
- Con alguien en otra habitación ☐
- En la misma habitación, pero en otra cama ☐
- En la misma cama ☐

Annex 8. Study 1. Reference: Fernando Shyamali Kaushalya, Salvador Romero-Arenas, Amador García-Ramos, David Colomer-Poveda & Gonzalo Marquez (2020) Acute effects of Transcranial Direct Current Stimulation on Cycling and Running Performance. A Systematic Review and Meta-Analysis, European Journal of Sport Science, DOI: 10.1080/17461391.2020.1856933

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REVIEW

Acute effects of transcranial direct current stimulation on cycling and running performance. A systematic review and meta-analysis

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Abstract
Transcranial direct current stimulation (tDCS) has been proven to induce positive effects on athletic performance. The present study aimed to analyse the effect of anodal-tDCS on endurance (time to exhaustion [TTE] or endurance time trial [ETT]) and sprint performance during cycling and running tasks. We performed a systematic literature review in the databases Medline (via PubMed), SPORTDiscus and Science Direct. We included only randomised controlled trials conducted with healthy individuals in which an anodal-tDCS protocol was applied prior to cycling or running tests. The effect of anodal-tDCS (experimental condition) was compared against sham stimulation (control condition). A total of 15 interventions from 13 studies were included. The sub-group analysis revealed a positive effect of anodal-tDCS on TTE (standardised mean differences [SMD] = 0.37; 90% confidence interval [CI] = 0.13, 0.61; $p = 0.01$), but not on ETT (SMD = 0.00; 90% CI = −0.29, 0.30; $p = 1.00$) or sprint performance (SMD = 0.19; 90% CI = −0.23, 0.60; $p = 0.46$). The current meta-analysis suggests that the effect of anodal-tDCS on whole-body dynamic exercises (running and cycling) could be task dependent. Specifically, anodal-tDCS enhance running and cycling time to exhaustion performance during TTE tasks but not ETT or sprint tasks. The increase in cortical excitability induced by anodal-tDCS may lead to lower ratings of perceived exertion by reducing the input required to perform the physical task. Task should be taken into account, because it is probably influencing the result obtained by anodal-tDCS.

Keywords: *TDCS, time to exhaustion, endurance performance, sprint performance*

Highlights
- Transcranial Direct Current Stimulation (tDCS) is a neuromodulatory technique which can transiently modulate the neuronal activity in resting membrane potential and consequently increase (anodal) or decrease (cathodal) the excitability of the targeted brain area.
- The present systematic review and meta-analysis showed that anodal-tDCS enhances the time to exhaustion (TTE) performance during running and cycling tasks, but not during endurance time trials (ETT) or sprint tasks.
- The task should be considered as it probably influences the results obtained through acute anodal-tDCS.
- Most studies used small samples that likely inflated the effect sizes and therefore might affect the pooled result and, therefore, it should be recommended further studies with higher sample sizes.

1. Introduction

Endurance tasks involving cycling, running or sustaining a submaximal isometric torque promote a progressive decline in the capacity of the muscles to produce force and power that is usually termed exercise induced muscle fatigue. Exercise induced muscle fatigue involves processes at various level of the motor pathway, from the brain to the muscle (Gandevia, 2001). These processes involve

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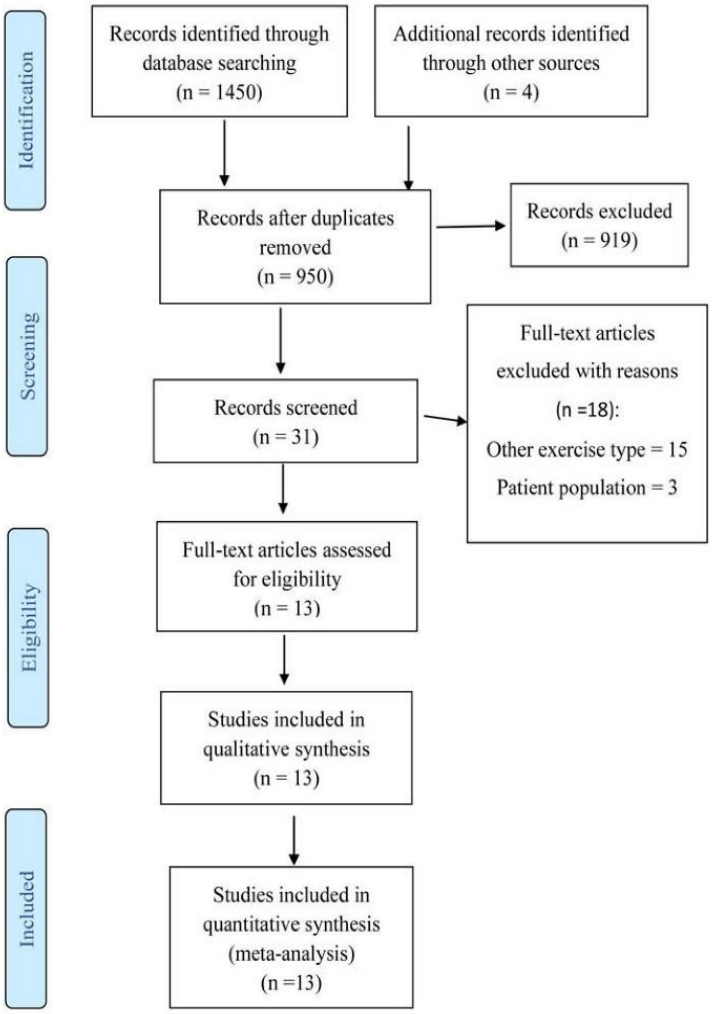

Figure 1. Flow diagram of the literature search.

evidence database (PEDro) scale (http://www.pedro.org.au). This scale consists of 10 criteria that rate the internal validity and the presence of statistically replicable information. Each criteria is rated "yes" or "no", with "yes" only awarded when a criterion is clearly satisfied. The cut-off score for rating a study as high quality was ≥ 6/10, with lower scores considered as low methodological quality. The methodological quality of each study was rated by two reviewers. When there was doubt this was resolved by discussion with another researcher until a consensus was reached.

2.4. Statistical analysis

Statistical analyses were performed using the Review Manager software (RevMan 5.3.5; Cochrane Collaboration, Oxford, UK). The effect size of each study was calculated as the difference in performance between the experimental (i.e. after anodal-tDCS application) and control (i.e. sham) conditions. The mean differences were standardised by dividing the raw difference by the within-group standard deviation. Standardised mean differences (SMD) of all interventions were pooled with a random effect model. According to Cohen's guidelines (Cohen et al., 1988) , SMD values of 0.2, 0.5, and 0.8 represent

small, moderate, and large effect size, respectively. Heterogeneity between studies was assessed using I^2 statistics. Statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Study selection and characteristics

A total of 950 articles were screened and 31 full texts were assessed for eligibility. The reason for exclusion at the screening part was the use of different exercises (e.g. single-joint exercises) and the inclusion of a patient population (e.g. stroke or Parkinson) (Figure 1). The article selection process resulted in the inclusion of 15 interventions from 13 studies: nine TTE studies (Angius et al., 2015; Angius et al., 2018; Angius et al., 2019; Baldari et al., 2018; Barwood et al., 2016; Lattari et al., 2018; Okano et al., 2015; Park et al., 2019; Vitor-Costa et al., 2015), three ETT studies (Andre et al., 2019; Barwood et al., 2016; Holgado et al., 2019), and two sprint studies (Huang et al., 2019; Sasada et al., 2017). Barwood et al. (2016) and Andre et al. (2019) included different tDCS interventions within the same study and they were considered as independent interventions for the current systematic review and meta-analysis. Table I shows the main characteristics of the studies included in the systematic review and meta-analysis. The current intensity ranged from 1.5–2.0 mA, current density ranged from 0.083–0.166 mA/cm^2, and the duration of stimulation ranged from 10 to 30 min. Only 30 s of stimulation was applied in the sham condition. Four studies assessed both men and women (Andre et al., 2019; Angius et al., 2018; Angius et al., 2019), one study used only women (Lattari et al., 2018), and the remaining studies included only men (Angius et al., 2015; Baldari et al., 2018; Barwood et al., 2016; Holgado et al., 2019; Huang et al., 2019; Okano et al., 2015; Park et al., 2019; Vitor-Costa et al., 2015). The training status of the subjects ranged from physically active to competitive athletes.

3.2. Study quality assessment

The quality of the studies was generally high with a mean score of 7.0 ± 0.6 in the 0–10 PEDro scale (Table S1).

3.3. Effect of tDCS on running and cycling performance

The systematic search identified a total 15 interventions that examined the effects of anodal-tDCS on TTE, ETT and sprint performance during running or cycling tasks. An overall small effect was observed in favour of the anodal-tDCS condition (SMD = 0.22; 90% CI = 0.05, 0.39; $P = 0.04$). The subgroup analysis revealed a significantly higher TTE performance for the experimental compared to the sham condition (SMD = 0.37; 90% CI = 0.13, 0.61; $P = 0.01$), while no significant differences were observed between the experimental and sham conditions for ETT (SMD = 0.00; 90% CI = −0.29, 0.30; $P = 1.00$) or sprint performance (SMD = 0.19; 90% CI = - 0.23, 0.60; $P = 0.46$) (Figure 2).

4. Discussion

This systematic review and meta-analysis included 15 interventions with a total of 192 participants examining the effects of applying anodal-tDCS before cycling and running tasks on endurance (TTE and ETT) and sprint performance. Our analysis revealed a significant effect of anodal-tDCS on cycling and running performance when all tasks were pooled together. Moreover, the subgroup analysis evidenced a small but significant effect in favour of the anodal-tDCS compared to the sham condition on TTE (SMD = 0.37; 90% CI = 0.13, 0.61; $P = 0.01$), while ETT (SMD = 0.00; 90% CI = −0.29, 0.30; $P = 1.00$) and sprint performance (SMD = 0.19; 90% CI = - 0.23, 0.60; $P = 0.46$) did not differ between the experimental and sham conditions. Therefore, this meta-analysis suggests that the effect of anodal-tDCS on whole-body dynamic exercises is task dependent. However, it is important to note that only four studies analysed ETT task and two studies the sprint tasks. Therefore, more studies are apparently needed to firmly establish the effect of tDCS on these types of task.

4.1. Acute effect of anodal-tDCS on TTE performance

Nine of the fifteen interventions included in the present systematic review and meta-analysis explored the effect of anodal-tDCS on TTE performance during running and cycling revealing a small positive effect (SMD = 0.37, $P = 0.01$). Interestingly, five out of nine interventions reported an improvement in TTE during cycling (Angius et al., 2018; Angius et al., 2019; Lattari et al., 2018; Okano et al., 2015; Vitor-Costa et al., 2015), while only one study (Park et al., 2019) reported enhancement in TTE performance during a running task.

Okano et al. (2015) were the first to report an increase of ~4% in peak power output during a

Table I. Main characteristic of the included studies.

Study information				Sample characteristic		tDCS set-up					Outcomes		Effect	
Authors	Exp	Exercise	Task	n(M/W) Age (yr)	Training status	Polarity	Stimulation Electrode	Duration (min)	Intensity (mA)	Density (mA/cm 2)	Elec. Size (cm2)	TTE (M± SD) (Sec.)	Power (W)	TTE (Time)	Power
Andre et al. (2019)	2	Cycling	TT: 16.1 km	9M / 1W 36 ± 6	Cyclist	A	A: DLPFC, M1, V1(con) C: R-SOB	20min.	1.5	0.060	25	M1:1443.7 ±81.0 DL:1428.4 ±80.0 V1:1434.8 ±79.6	M1:274 ±44 DL:280 ±39 VI:279 ± 44	NS	NS
Angius et al. (2015)	1	Cycling	TTE: 70% of PP	9M 23 ± 4	Rec. acti.	A/S	A: L-M1 C: R-DLPFC	S:30s 10min.	2	0.166	12	A: 994.8 ±509.4 S: 880.8 ±517.2		NS	
Angius et al. (2018)	1	Cycling	TTE: 70% of PP	4W / 8M 24 ± 5	Rec. acti.	A/S	A: BL-M1 C: IL-Shoulder	S:30s 10min.	2	0.057	35	A: 795 ±260.4* C: 666±256.8 S: 645.6 ±181.8		⇑*	
Angius et al. (2019)	1	Cycling	TTE: 70% of PP	3W / 9M 23 ± 3	Rec. acti.	A/S	A: L-DLPFC C: Fp2	S:30s 30min.	2	0.057	35	A:1020 ± 480* S:900 ± 480		⇑*	
Baldari et al. (2018)	1	Running	TTE: incremental ramp test	13M 27 ± 5	Rec. acti.	A/S	L & R-M1	S: 30s 20min.	1 2	0.028 0.057	35 - 36	A:530±44 C: 537±40 S:533± 46		NS	
Barwood et al. (2016)	2	Cycling	TT: 20 km TTE: 75% of PP	6M 21 ± 2 8M 21 ± 1	Phy. acti. Phy. acti.	A/S	A: T3 C: CLSOB	S: 30s 20min.	1.5 2	0.428 0.444	3.5 4.5	A: 2181± 88 S: 2181± 56 A: 237 ± 362 S: 314 ±334	A:197±20 S:197±12	NS	NS
Holgado et al. (2019)	1	Cycling	TT: 20min.	36M 27 ± 6.8	Cyclist & Triathletes	A/S	A: L-DLPFC C: CL-Shoulder	S: 30s 20min.	2	0.080	25		A:235 ±38.42 S:234 ±41.37		NS
Huang et al. (2019)	1	Cycling	5x6-s sprint	9M 20 ± 1.2	Phy. acti	HALO/ S	Vertex	S:30s 20min.	2	0.083	24		H:898.3 ±116.3 S:827.8 ±145.3		NS
Lattari et al. (2018)	1	Cycling	TTE: 100% of PP	11W 24 ± 2.2	Phy. acti.	A/S	A: L-DLPFC C: R-OFC	S: 30s 20min.	2	0.057	35	A:199.5 ± 97.2* S: 137.1 ± 73.1		⇑*	

Study information				Sample characteristic		tDCS set-up						Outcomes		Effect	
Authors	Exp	Exercise	Task	n(M/W) Age (yr)	Training status	Polarity	Stimulation Electrode	Duration (min)	Intensity (mA)	Density (mA/cm 2)	Elec. Size (cm2)	TTE (M± SD) (Sec.)	Power (W)	TTE (Time)	Power
Poreisz et al. (2007)	1	Cycling	TTE: incremental ramp test	10M 33 ± 9	Cyclist	A/S	A: L-T3 C: CL-SOB	S: 30s 20min.	2	0.057	35	A: 751.4 ± 71.5* S: 723.7 ± 45.0	A:313.2 ±29.9* S:301.0 ±19.8	⇑*	ñ*
Robertson and Marino (2016)	1	Running	TTE: 80% of PP	12M 27.4 ± 2.4	Trained	A/S	A: M1 (*Cz*) C: C5 & C6	S: 30s 20min.	1.98	0.070	28.16	A:1270.8 ±427.8* S: 1106.4 ±379.2		⇑*	
Segaard et al. (2006)	1	Cycling	Wingate test	6W / 17M 21 - 30	Athletes	A/S	A: Vertex C: R-Forehead	S:15s 15min.	2	0.057	35		A:9.48 ±1.21 S:9.40± 1.26		NS
Williams et al. (2013)	1	Cycling	TTE: 80% of PP	11M 26 ± 4	Phy. acti.	A/S	A:M1 (*Cz*) C: OP	S: 30s 13min.	2	0.056 0.057	35 - 36	A: 491.4 ± 100* C: 443 ± 110 S: 407 ± 69		⇑*	NS

Note: TTE: time to exhaustion ETT: endurance time trial; M: men; W: women; Rec. acti: recreationally active; tDCS: transcranial direct current stimulation; Exp: experiment; A: anodal; C: cathodal; S: sham; M1: motor cortex; DLPFC: dorsolateral prefrontal cortex; T3: temporal cortex; Elec: electrode; Sec: second; Min: minute; PP: peak power; SOB: supraorbital; V1: visual cortex; OFC: orbitofrontal cortex; ñ*: task improvement; NS: no significantly difference; *: significantly difference; R: right; L: left; CL: contralateral; BL: bilateral; IL: ipsilateral; OP: occipital protuberance.

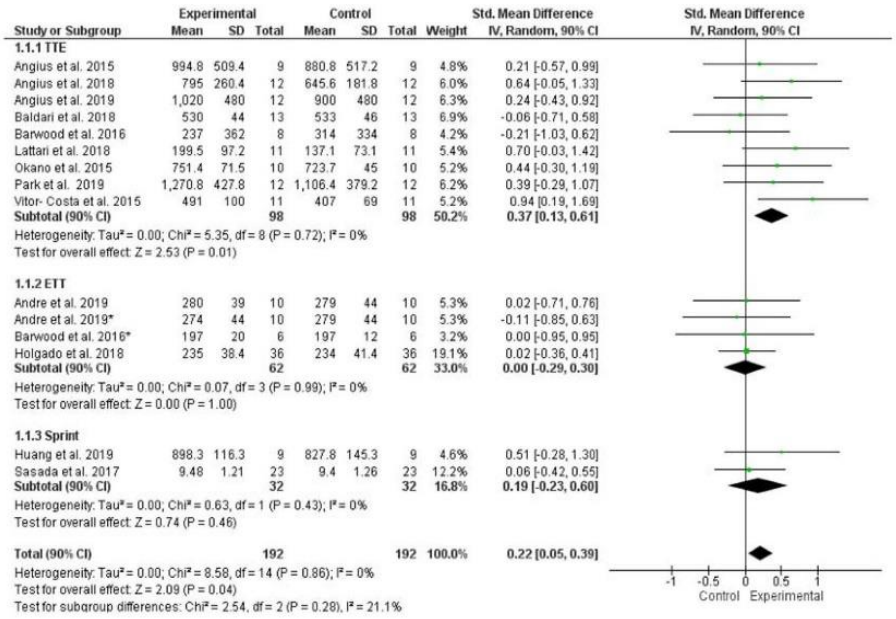

Figure 2. Forest plot with subgroups analyses for the comparison of time to exhaustion (TTE), endurance time trial (ETT), and sprint performance between the experimental and sham conditions. Andre et al. (2019)* - subgroup that received anodal-tDCS over M1 before the task (cycling ETT; mean power output). Barwood et al. (2016)*- subgroup that received anodal-tDCS over T3 before the task (20 km cycling ETT; mean power output).

maximal cycling incremental test along with lower RPE values following anodal-tDCS over the left temporal cortex (TC). Authors speculated that the application of anodal-tDCS over the left TC could have modulated the excitability of the insular cortex (IC), which likely led to a decrease in RPE when exercising at submaximal intensities, improving endurance performance. This hypothesis is justified because it is known that the IC is the main area of the brain responsible for the awareness of subjective feelings from the body (Craig & Craig, 2009) and it is related to the RPE values reported during dynamic exercises (Abbiss & Laursen, 2008). Angius et al. (2018) also found significant improvements in cycling TTE performance by 23%, lower RPE, and increased corticospinal excitability following bilateral extracephalic M1 anodal-tDCS. The authors argued that the lower RPE values observed after anodal-tDCS were related to the increased M1 excitability, which in turn needs to receive less input from other brain areas (e.g. premotor cortex) to generate the output required to recruit the muscles to produce a given power output (Angius et al., 2018). These data are partially confirmed by Vitor-Costa et al. (2015) who found an improvement in cycling TTE following M1 stimulation with a trend towards a reduction in RPE ($P = 0.07$). Another recent study conducted by Angius et al. (2019) demonstrated that anodal-tDCS over the left dorsolateral prefrontal cortex (DLPFC) significantly increased TTE during cycling with a concomitant reduction in RPE values, mainly due to improvements in the inhibitory control caused by changes in frontal lobe excitability. In the same line, Lattari et al. (2018) investigated the effect of anodal-tDCS over the left DLPFC in physical active women and revealed a significant increment in exercise tolerance on cycling TTE at 100% peak power by 4%. Nevertheless, RPE values did not differ between the control and experimental condition in the study of Lattari et al. (2018), which may be related to a ceiling effect in RPE during high-intensity exercise (i.e.: 100/peak power output) (Angius et al., 2019). However, it should be mentioned that Park et al. (2019) reported an increase in running TTE performance after anodal-tDCS over M1 without revealing any effect on RPE values, and other studies that applied similar tDCS protocols did not find improvements neither in TTE performance nor in RPE (Andre et al., 2019; Angius et al., 2015; Baldari et al., 2018).

4.2. Acute effect of anodal-tDCS on ETT performance

A self-paced exercise is a physical activity in which the effort has to be distributed in the best possible way to cover a given distance as quickly as possible or to cover the largest possible distance in a given time (Holgado et al., 2019). During self-paced exercise tasks, such as an ETT, athletes should regulate their energetic resources to maintain a submaximal sustainable intensity to avoid premature fatigue and exhaustion (Abbiss & Laursen, 2008). As we know the exercise work rate is regulated by the brain based on the integration of numerous signals from various peripheral physiological systems (Tucker, 2009). However, the role of the brain in pacing is not entirely clear although RPE, which can be modulated by tDCS (Barwood et al., 2016), is a key perceptual anchor for the regulation and distribution of effort (Tucker, 2009) and it might provide a potential mechanism for influence exercise pacing and performance (Barwood et al., 2016). However, few studies have tested the effect of anodal-tDCS on self-paced ETT.

Only four out of 15 interventions (Andre et al., 2019; Barwood et al., 2016; Holgado et al., 2019) included in the present meta-analysis, examined the effect of anodal-tDCS on self-paced cycling ETT performance revealing a trivial effect (SMD = 0.00, $P = 1.00$). Twenty minutes of 1.5 mA anodal-tDCS over the left TC, the M1, or the DLPCF, before 16 km self-paced TT in male and female trained cyclist did not improve performance compared to sham condition (Andre et al., 2019). In the same line, 20 min of anodal-tDCS at 2.0 mA over the DLFPC applied before a self-paced 20 min cycling TT on male trained cyclist did not improve performance compared to sham condition (Holgado et al., 2019). Therefore this results suggest that anodal-tDCS does not improve cycling self-paced ETT tasks performance (Andre et al., 2019).

4.2. Acute effect of anodal-tDCS on sprint performance

Sprint performance is a major determinant in many athletic activities (Rumpf, Lockie, Cronin, & Jalilvand, 2016). Ultimately, it represents equilibrium of propulsive power and resistance (Martin, Davidson, & Pardyjak, 2007). However, sprint performance activities such as short-distance running or cycling gradually decreases after reaching a maximum speed or cadence (Sasada et al., 2017). The most important factors limiting performance during sprints are fatigue occurring in the central nervous system as well as in the peripheral system (i.e. at or distal to the neuromuscular junction) (Sasada et al., 2017). In this regard, it has been argued that the manipulation of supraspinal centres involved in the control of the motor output, such as M1, may reduce central fatigue and, thus, increase sprint performance (Gandevia et al., 1996).

However, in the present systematic review and meta-analysis, only two studies have tested the effect of anodal-tDCS on sprint cycling performance (Huang et al., 2019; Sasada et al., 2017) and revealed a non-significant small effect of anodal-tDCS on cycling sprint performance (SMD = 0.19, $P = 0.46$). According to these studies, 15 min anodal-tDCS applied over M1 before exercise did not improve neither peak nor mean power output during a Wingate test (30-sec all-out test) (Sasada et al., 2017). In contrast, Huang et al. (2019) demonstrated that the application of tDCS using Halo sport© can improve repeated cycling sprint performance. Specifically, following 20 min of tDCS with halo sports subjects significantly enhanced the mean power output during a repeated cycling sprint test, but any significant differences were found for peak power output ($P = 0.47$). Therefore, it seems that the positive effect of anodal-tDCS described by Huang et al. (2019) could be related to an improved exercise tolerance without changes in maximal force or power capacities, as it has been previously proposed by Alix-Fages et al. (2019).

4.3. Characteristic of the tDCS protocol

According to the findings mentioned above, the potential ergogenic effects of anodal-tDCS on whole-body exercise performance are still inconclusive. Such inconsistencies may be explained by the different tDCS set-up characteristics used in the mentioned studies (i.e. stimulated brain area, electrodes montage, stimulation duration, current intensity and density, and electrode size).

Regarding the region of stimulation, numerous brain areas are known to play an important role in exercise regulation and, therefore, the rationale for using tDCS for performance improvement may differ accordingly (Alix-Fages et al., 2019). As evidenced in the present meta-analysis, these regions included the M1, DLPFC and TC. Most of the studies that reported a positive effect of anodal-tDCS targeted the M1 region (Angius et al., 2018; Park et al., 2019; Vitor-Costa et al., 2015), which is considered a key determinant in endurance tasks performance (Taylor, Amann, Duchateau, Meeusen, & Rice, 2016). M1 stimulation could be effective to enhance endurance performance since increases in M1 excitability may increase the neural drive to the

active muscles, delay central fatigue, or reduce the pain induced by exercise (Angius et al., 2015).

There is also evidence regarding the role of other cortical regions in endurance performance (Robertson & Marino, 2016). In this context, studies included in our systematic review also revealed significant improvements in TTE performance following anodal-tDCS over DLPFC (Angius et al., 2019; Lattari et al., 2018). The DLPFC is a crucial brain region for inhibitory control, an executive function essential for both behavioural self-regulation (Angius et al., 2019) and likely exercise regulation (Robertson & Marino, 2016). Additionally, there is evidence regarding the positive effect on endurance performance following anodal-tDCS over the TC (Williams et al., 2013). It is plausible that the application of anodal-tDCS modulated the excitability of TC and IC which have been associated with the control of the autonomic nervous system and awareness of emotional feelings from the body (Craig & Craig, 2009; Okano et al., 2015). This modulation would therefore reduce the RPE values and lead to an improvement in TTE performance (Okano et al., 2015). However, other studies did not find any effect of anodal-tDCS over TC on autonomic control (Angius et al., 2015). Furthermore, some studies included in the present meta-analysis have failed to find this kind of improvement in endurance performance following tDCS stimulation over the same regions mentioned above: M1 (Andre et al., 2019; Baldari et al., 2018; Huang et al., 2019; Sasada et al., 2017), DLPFC (Holgado et al., 2019) and TC (Barwood et al., 2016). These results suggest that other tDCS set-up parameters in addition to the region of stimulation should modulate the ergogenic effects of tDCS on endurance performance.

Regarding electrodes montage, in those studies which used a cephalic montage (i.e. anodal electrode over the target area and the cathodal electrode over the contralateral prefrontal cortex) (Angius et al., 2015; Williams et al., 2013), it is plausible that the lower excitability expected in the brain area under the cathode may have counteracted the positive effect of the anodal stimulation. An extracephalic montage (i.e. anode over the main area and cathode on the shoulder) may avoid this problem and this could explain the large ergogenic effects of anodal-tDCS in studies that use an extracephalic montage (Cogiamanian et al., 2007). The duration of stimulation is another key parameter that may influence tDCS aftereffects (Nitsche & Bikson, 2017). Alix-Fages et al. (2019) demonstrated a higher endurance performance when stimulating the cerebral cortex for 15–20 min compared to 10 min (ES = 0.31 and 0.17, respectively). However, the present systematic review and meta-analysis revealed a significant effect on TTE performance during cycling regardless of the stimulation duration: 30 min (Andre et al., 2019), 20 min (Lattari et al., 2018; Okano et al., 2015), 13 min (Vitor-Costa et al., 2015), or 10 min (Angius et al., 2018). Regarding the current intensity, Nitsche and Paulus (2000) reported that cortical excitability was increased more using higher (1.5–2.0 mA) compared to lower (0.5 mA) intensities. However, no study has directly compared the effects of different intensities of tDCS on the performance during the tasks included in the current systematic review. Furthermore, the stimulation intensity used in the studies analysed in the present meta-analysis was very homogeneous, ranging from 1.5 mA (Andre et al., 2019), 1.98 (Park et al., 2019) and 2 mA (the other 13 interventions). To the best of our knowledge, only one study has investigated the effect of tDCS intensity (2 vs 4 mA) on knee extensor performance during an isokinetic fatiguing task (Workman, Kamholz, & Rudroff, 2020).

5. Limitations, recommendations

The present systematic review and meta-analysis yield mixed results on the efficacy of anodal-tDCS as an ergogenic aid to enhance cycling and running performance during TTE, ETT and sprint tasks. While anodal-tDCS revealed a small but significant effect on TTE task performance, it did not improve self-paced ETT or sprinting performance. However, most studies used small samples (median n = 14) that likely inflated the effect sizes and therefore might affect the pooled result (Holgado et al.,2019a). Furthermore, it should be noted that the exact neurophysiological mechanisms between the excitability of different brain regions and RPE are not fully understood and, therefore, the relationship between RPE and brain excitability might not be direct. However, the contradictory results about the effects of anodal-tDCS on cycling and running TTE, ETT and sprint performance may be related to differences in the tDCS set-up, which can influence the amount of electrical current applied to nominal target areas and, therefore, impact the efficacy of anodal-tDCS as an ergogenic aid. Furthermore, an assessment of a wider range of tDCS intensities, particularly those above 2 mA, would be helpful to identify whether there is a dose–response relationship (Nitsche & Bikson, 2017).

6. Conclusions

The present systematic review and meta-analysis showed a statistically positive small effect on

endurance TTE cycling and running performance, whereas no significant effect was observed for ETT and sprint. Therefore, the task should be considered, as it probably influences the result achieved following **anodal**-tDCS. Furthermore, it should be noted that only four studies have analysed the ETT task and two studies have analysed the sprint task. Therefore, further studies are needed to establish the effect of tDCS on this type of tasks.

7. Practical applications

tDCS is a neuromodulatory technique that transiently modulate the neuron resting membrane potential and consequently increase (anodal) or decrease (cathodal) the excitability of the targeted brain area by applying a very low direct current from electrodes placed on the scalp. It has been suggested that the potential mechanism underlining the ergogenic effect of anodal-tDCS on endurance motor performance could be related to improved cortical excitability within the primary motor cortex which in turn lead to decreases in supraspinal fatigue and rating of perceived exertion. Our meta-analysis demonstrated that applying anodal-tDCS as a supportive tool in athletes' performance enhancement can increase time to exhaustion performance during cycling and running exercise task. These findings are extremely related to sports performance, as time to exhaustion is one of the most important factors to define the final effort of many sports such as cycling, running, soccer, basketball, among others. Therefore, tDCS can be considered as a supportive training tool that allowing to enhance training effectiveness athletes and coaches.

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