International Doctoral Thesis / Tesis Doctoral Internacional

EXECUTIVE FUNCTIONS, SELF-PACED EXERCISE AND CYCLING PERFORMANCE

FUNCIONES EJECUTIVAS, EJERCICIO AUTORREGULADO Y RENDIMIENTO CICLISTA

UNIVERSIDAD DE GRANADA

PROGRAMA DOCTORADO EN BIOMEDICINA

DEPARTAMENTO DE EDUCACIÓN FÍSICA Y DEPORTIVA
FACULTAD DE CIENCIAS DEL DEPORTE
UNIVERSIDAD DE GRANADA

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Granada 2019

Editor: Universidad de Granada. Tesis Doctorales
Autor: Darías Manuel Holgado Núñez
ISBN: 978-84-1306-308-9
URI: http://hdl.handle.net/10481/57197

Nadie es tan pobre como
para no poder regalar una sonrisa

El doctorando D. Darías Holgado Núñez ha realizado la presente tesis doctoral internacional como beneficiario de un contrato predoctoral con cargo al programa de Formación de Profesorado Universitario (FPU) del Ministerio de Educación, Cultura y Deporte (FPU14/06229), por la resolución el 15 de julio de 2015, de la Secretaria de Estado de Educación, Formación Profesional y Universidades.

Publications from doctoral thesis

1. **Holgado, D.**, Zandonai, T., Zabala, M., Hopker, J., Perakakis, P., Luque-Casado, A., Ciria, LF, Guerra-Hernandez, E. & Sanabria, D. (2018). Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial. *Journal of Science and Medicine in Sport*, *21*(7), 654–660. https://doi.org/10.1016/j.jsams.2017.10.032 **JCR Q1, IF: 3.92**
2. **Holgado, D.,** Zandonai, T., Ciria, L. F., Zabala, M., Hopker, J., & Sanabria, D. (2019). Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: Evidence from oscillatory brain activity and power output. *PLoS ONE*, *14*(2), 1–13. https://doi.org/10.1371/journal.pone.0210873 **JCR Q1 IF:2.76**
3. **Holgado, D.,** Vadillo, M. A., & Sanabria, D. (2019). The effects of transcranial direct current stimulation on objective and subjective measures of sports performance: A systematic review and meta-analysis. *Brain Stimulation*, 12(2), 242-250. https://doi.org/10.1016/j.brs.2018.12.002. **JCR Q1 IF: 6.12**
4. **Holgado, D**., Zabala, M., & Sanabria, D. (2019). No evidence of the effect of cognitive load on self-paced cycling performance. Pl*os One (Accepted)*. **JCR Q1 2.76** https://doi.org/10.1371/journal.pone.0217825

Other publications during the doctoral thesis

1. **Holgado, D**., Hopker, J., Sanabria, D., & Zabala, M. (2018). Analgesics and Sport Performance: Beyond the Pain-Modulating Effects. *PM and R*, *10*(1), 72–82. https://doi.org/10.1016/j.pmrj.2017.07.068. JCR **Q2 IF: 1.78**
2. **Holgado, D**., Zandonai, T., & Sanabria, D. (2018). Comment on "Review of WADA Prohibited Substances: Limited Evidence for Performance-Enhancing Effects." *Sports Medicine*. https://doi.org/10.1007/s40279-019-01064-2 JCR **Q1 IF: 7.04**
3. **Holgado, D.**, Vadillo, MA. & Sanabria, D. (2019). "Brain-doping'', is it a real threat? Frontiers in Physiology, 10.3389/fphys.2019.00483. JCR **Q1 IF: 3.39**

Departamento de Educación Física y Deportiva.
Centro de Investigación, Mente, Cerebro y Comportamiento
Universidad de Granada

Título de la tesis Doctoral Internacional: Funciones ejecutivas, ejercicio autorregulado y rendimiento ciclista.

International Doctoral Thesis Tittle: Executive functions, self-paced exercise and cycling performance.

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Granada, 10 de septiembre de 2019

Agradecimientos

Quiero comenzar agradecimiento a dos profesores de bachillerato que han sido mi referente y que seguramente si hoy estoy haciendo una tesis doctoral es gracias a ellos. Antonio Puerma de Economía y Eugenio Fernández de Filosofía, gracias a ellos recuperé la ilusión por aprender después de una época convulsa. Además, por todo lo que aprendí con ellos y que hoy en día es parte fundamental de mi vida. Por un lado, todos los conceptos económicos que se pueden aplicar al día a día; y, por otro lado, la reflexión y crítica aprendida de la filosofía.

Sigo con mis directores de tesis. A Mikel por apostar por mi y apoyarme desde un principio de forma desinteresada que, aunque no lo crea le tengo muchísimo aprecio. A Dani, que sin conocerme de nada me ha apoyado desde el principio. Simplemente, un "mega crack!

A *Antonio, Thomas, Luis etc.* porque esto es en gran parte cosa vuestra al ponerle mucha pasión a lo que hacemos. Además, me sirven como consuelo de que no soy el único que está "mal" de la cabeza por dedicarle horas y horas a este trabajo, porque al final (y al principio) merece mucho la pena.

Esto tampoco hubiese sido posible sin la ayuda de todos los participantes que han venido una y otra vez a los estudios de esta tesis. Estoy gratamente sorprendido de la buena voluntad y su participación desinteresada. Al final muchos han pasado a ser buenos amigos y compañeros de fatiga sobre la bici. Me alegro de haber coincidido con José, JC, Antonio, Justo…

A mis madres…si porque para mi son dos las que tengo y son mis mayores fans incondicionales desde que tengo recuerdo y siempre lo han dado todo, incluso sin tenerlo. Aunque con suerte las veas solo 2-3 veces al año, siempre siento su cariño y apoyo de cerca. Igual que mi querido hermano, con el que tanto me he reído y hemos hecho travesuras juntas desde la infancia (y no tan infancia…). A toda mi familia del *otro lado del charco* que gracias a ella conozco la otra realidad del mundo. La familia esteponera representada por mis tías y primos. Siempre me han mostrado un cariño y apoyo desproporcional ante cualquier circunstancia.

A mis grandes amigos por entenderme como soy y compartir siempre el humor que nos caracteriza. Aunque estemos en lugares vario pintos siempre tendré en cuenta a Borja, Alberto, Minerva, Marinelli, Javi, Jose, y por supuesto Grego, por entrar siempre al trapo a mis locuras y enseñarme los Alpes. Allí siempre nos encontraremos. También, a todas las personas que he conocido en los últimos años de todas partes del mundo, que sin duda ha sido la experiencia más enriquecedora que he tenido.

Por último, abro una ventana al futuro, por toda aquella gente que acaba de llegar a mi vida o que pronto llegará porque me da la ilusión de que aún estamos a tiempo de conseguir un mundo algo mejor.

Index

Resumen

El principal objetivo de la presente tesis doctoral era entender el rol de las funciones ejecutivas (cognitivas) en el ejercicio aeróbico autorregulado (ciclismo). El ejercicio autorregulado es una actividad física en la que el esfuerzo tiene que ser distribuido de la mejor manera posible para alcanzar el objetivo de la prueba (ej., cubrir una distancia los más rápido posible o cubrir la mayor distancia posible en un tiempo dado). La autorregulación del esfuerzo físico requiere de la monitorización y control del feedback procedente de los músculos y sistemas cardiorrespiratorio hacía el cerebro. Desde un punto de vista aplicado, podríamos considerar que el ejercicio aeróbico autorregulado es un comportamiento dirigido hacia un objetivo que involucra varios procesos cognitivos, y en particular de funciones ejecutivas (ej., control inhibitorio o memoria de trabajo). En consecuencia, cualquier cambio a nivel cognitivo (y cerebral relacionado con los procesos cognitivos objeto de estudio) afectará al rendimiento físico. Para entender esta relación, en un primer capítulo introductorio resumimos el papel de las funciones ejecutivas sobre el ejercicio autorregulado, la evidencia empírica acerca de las bases neurales involucradas, y las distintas manipulaciones donde las funciones ejecutivas podrían ser relevantes sobre el ejercicio autorregulado. A continuación, presentamos una serie experimental donde estudiamos el rol de las funciones ejecutivas en el ejercicio autorregulado bajo tres manipulaciones experimentales. Primero, investigamos el efecto ergogénico del tramadol sobre el rendimiento físico y cognitivo. A continuación, intentamos comprender los efectos de la estimulación transcraneal por corriente directa (eTCD) (aplicada sobre el córtex dorsolateral prefrontal izquierdo) en índices objetivos y subjetivos del rendimiento físico. Finalmente, investigamos el papel de la carga cognitiva (ejecutiva) durante el ejercicio autorregulado. A continuación, pasamos a resumir los estudios empíricos que componen esta tesis.

Los analgésicos son fármacos ampliamente utilizados en el deporte para tratar el dolor y procesos antiinflamatorios asociados con las lesiones. Sin embargo, se ha detectado que existe una tendencia entre los atletas de todos los niveles a usar estos fármacos analgésicos, no solo para tratar lesiones menores, sino que también para entrenar y competir. Por lo tanto, además de por sus efectos periféricos, existe la posibilidad de que los atletas estén usando estos fármacos por sus efectos a nivel de sistema nervioso central para incrementar el rendimiento físico durante los entrenamientos y competiciones. Algunos de estos fármacos podrían tener un efecto sobre la activación de estructuras cerebrales superiores (por ejemplo, la corteza prefrontal o la corteza cingulada anterior) involucradas en el dolor y el procesamiento cognitivo. Uno de estos fármacos comúnmente utilizados por los ciclistas, es el tramadol. El tramadol podría mejorar el rendimiento físico mediante la reducción del esfuerzo percibido, la percepción del dolor o el estado de ánimo. Sin embargo, el tramadol es conocido por sus frecuentes efectos secundarios, como la somnolencia o las náuseas, que pueden tener un efecto negativo en las funciones cognitivas y en rendimiento

deportivo. Por lo tanto, en una serie de dos experimentos, nuestro objetivo fue estudiar el efecto del tramadol sobre el rendimiento físico y el procesamiento cognitivo en el ciclismo.

El Experimento 1 reveló que el tramadol mejoró el rendimiento físico aproximadamente un 5% durante una prueba de ciclismo autorregulada (contrarreloj) de 20 minutos. El tramadol pareció permitir a los participantes lograr una mayor potencia media sin modificar la actividad eléctrica cerebral, la percepción del esfuerzo o el estado de ánimo. Los resultados de este experimento parecían respaldar la hipótesis de que el tramadol podría mejorar el rendimiento físico, sin embargo, esto no fue corroborado en el Experimento 2.

El Experimento 2 fue diseñado para replicar el Experimento 1 y para probar la hipótesis de que el tramadol podría tener un efecto sobre la atención sostenida durante ejercicio. Para ello, los participantes completaron una tarea de discriminación de estímulos al mismo tiempo que realizaban la prueba de ciclismo de 20 minutos. La tarea cognitiva consistió en una presentación aleatoria de una secuencia de estímulos visuales de un círculo azul frecuente (no objetivo), un círculo azul raro pequeño (objetivo 1) y un cuadrado rojo (objetivo 2) en una pantalla. Contrariamente a los resultados observados en el Experimento 1, el tramadol no mejoró el rendimiento físico ni afectó la atención sostenida a nivel comportamental en comparación con la condición de placebo, es decir, ni la precisión en la respuesta ni el tiempo de reacción difirieron significativamente entre las condiciones experimentales. No obstante, durante la tarea de atención sostenida, encontramos que el tramadol provocó una actividad cerebral más baja (i.e., mayor supresión con respecto a la línea base) en la banda de frecuencia alfa vinculada al procesamiento de estímulos (relevante para la tarea) en la condición de tramadol en respecto a la de placebo. Una mayor actividad de alfa se ha considerado como un indicador de mayor alerta. Por el contrario, otro estudio que utilizó una tarea similar, interpretó la reducción de la banda alfa cuando se presentan objetivos poco comunes, como un esfuerzo mental más alto para detectar objetivos poco frecuentes. Por lo tanto, nuestros resultados podrían apuntar a la necesidad de una mayor asignación de recursos cognitivos para detectar objetivos poco frecuentes cuando los participantes reciben tramadol versus placebo.

En el siguiente estudio, siguiendo un enfoque diferente, planteamos la hipótesis de que la estimulación de las áreas cerebrales relacionadas con las funciones ejecutivas podría mejorar el rendimiento del ejercicio autorregulado, si el ejercicio autorregulado depende de funciones ejecutivas. Aunque, varios estudios habían investigado el efecto de la eTCD sobre el rendimiento físico, ninguno de ellos había abordado la cuestión de si la estimulación anódica de la corteza dorsolateral prefrontal izquierda afectaría al rendimiento en una tarea de ejercicio físico autorregulado. Curiosamente, los resultados de nuestro estudio no apoyaron la idea de que la eTCD anódica afecte ni el rendimiento autorregulado ni la actividad cerebral oscilatoria, tanto en reposo como durante el ejercicio. Este hallazgo agregó más inconsistencia a los resultados

ambiguos publicados hasta la fecha. Por lo tanto, a la vista de nuestros resultados nulos y la inconsistencia de la literatura, decidimos realizar un meta análisis para comprobar si la eTCD tenía un efecto real en índices de rendimiento físico. El meta análisis mostró que la eTCD tiene un efecto pequeño, aunque positivo, sobre el rendimiento deportivo (Hedges 'g = 0,34). Ninguno de los moderadores incluidos (ej., localización, intensidad o duración de la estimulación) en el análisis explicaba la varianza en los datos. Además de ser un tamaño de efecto pequeño, detectamos que los resultados positivos podrían estar sobreestimados por artefactos metodológicos y el sesgo de las publicaciones. A día de hoy, con los datos del meta análisis no podemos establecer que la eTCD sea una herramienta eficaz para mejorar el rendimiento deportivo.

En una etapa final, intentamos llenar un vacío existente en la literatura sobre el efecto de la carga (ejecutiva) mental durante el ejercicio autorregulado, ya que en la mayoría de los estudios previos la tarea cognitiva se ha realizado antes de un ejercicio físico. La carga cognitiva se manipuló usando una tarea de memoria de trabajo (n-back) con dos niveles de dificultad para inducir dos niveles de carga cognitiva, baja (1-back) y alta carga (2-back). Anticipamos que si el ejercicio autorregulado está determinado por el procesamiento ejecutivo y la n-back también requiere un procesamiento ejecutivo, era probable que se esperase un empeoramiento en el rendimiento físico debido a la incapacidad de autorregularse de manera eficiente. Sin embargo, a pesar de que la tarea con más demandas cognitivas fue más exigente (menor precisión y tiempos de respuestas más lentos) que la de baja carga cognitiva, y por lo tanto una mayor dificultad en términos de demandas ejecutivas, los resultados no proporcionaron evidencia suficiente para decir que la alta carga empeore el rendimiento físico o modifique la percepción del esfuerzo percibido. Estos resultados están en línea con los hallazgos anteriores de esta tesis, pudiendo especular que el ejercicio autorregulado no depende de función ejecutiva.

En conclusión, los resultados de la serie de experimentos llevados a cabo durante la tesis no apoyan la idea de que el ejercicio autorregulado dependa en gran medida de procesamiento ejecutivo. Aunque el tramadol podría afectar el rendimiento físico en el Experimento 1, la actividad cerebral oscilatoria no se vio afectada durante el ejercicio y se desconocen los mecanismos de la posible mejora (en la actualidad estamos llevando a cabo otro estudio para clarificar los resultados anteriores). Eso también fue cierto en el experimento de eTCD, ya que la estimulación cerebral no afectó el rendimiento físico o la actividad cerebral. Finalmente, una mayor carga cognitiva durante el ejercicio físico autorregulado tampoco pareció afectar el rendimiento físico. De manera crucial, los resultados de esta tesis pueden señalar que las funciones ejecutivas podrían no tener un papel decisivo en el ejercicio autorregulado, en contra de lo que se supone. Sin embargo, el papel de las funciones ejecutivas en el ejercicio podría estar mediado por varios factores como, por ejemplo, la experiencia deportiva.

Summary

The main aim of the present thesis was to understand the role of executive (cognitive) functions in self-paced aerobic exercise (cycling). A self-paced exercise is a physical activity in which the effort has to be distributed in the best possible way to achieve the objective of the event (e.g., to cover a given distance as quickly as possible or to cover the largest possible distance in a given time). Self-paced exercise requires the monitoring and control of feedback from the muscles and cardiorespiratory systems to the brain. From an applied point of view, we could consider that the self-paced aerobic exercise is a goal-directed behaviour towards an objective that involves several cognitive processes, and in particular of executive functions (e.g., inhibitory control or working memory). Consequently, any change at cognitive level (and brain related to the cognitive processes under study) will affect physical performance. To understand this relationship, in an introductory chapter we summarized the role of executive functions on the self-paced exercise, and the empirical evidence of the neural basis. We also summarized the different manipulations that have been designed to investigate the role of the executive functions on self-paced exercise. In the following chapters, we describe the three studies we have conducted to investigate the role of executive functioning on the self-paced exercise. First, we investigated the ergogenic effect of tramadol on physical and cognitive performance. Next, we attempt to understand the effects of transcranial direct current stimulation (tDCS) (applied to the left dorsolateral prefrontal cortex) on objective and subjective indices of exercise performance. Finally, we investigated the role of cognitive (executive) load during self-paced exercise.

Analgesics drugs are widely used in sports to treat pain and anti-inflammatory processes associated with injuries. However, it has been detected that there is a tendency among athletes of all levels to use these drugs, not only to treat minor injuries, but also to train and compete. Therefore, in addition to its peripheral effects, there is a possibility that athletes are using these drugs for their effects in the central nervous system to increase physical performance during training and competitions. Some of these drugs could have an effect on the activation of higher brain structures (e.g., prefrontal cortex or anterior cingulate cortex) involved in pain and cognitive processing. One of these drugs commonly used by cyclists is tramadol. Tramadol could improve physical performance by reducing perceived exertion, pain perception and/or mood. However, tramadol is known for its frequent side effects, such as drowsiness or nausea, which can have a negative effect on cognitive functions and exercise performance. Therefore, in a series of two experiments, our objective was to study the effect of tramadol on physical performance and cognitive processing in cycling.

Experiment 1 revealed that tramadol improved physical performance by approximately 5% during a self-paced (time-trial) cycling test of 20 minutes. Tramadol appeared to allow participants to achieve greater mean power output without modifying brain electrical activity, rate of perceived

exertion or mood. The results of this experiment seemed to support the hypothesis that tramadol could improve physical performance, however, this was not corroborated in Experiment 2.

Experiment 2 was designed to replicate Experiment 1 and to test the hypothesis that tramadol might have an effect on sustained attention during exercise. To do this, participants completed an oddball task while performing the 20 minutes cycling test. The cognitive task consisted of a random presentation of a sequence of visual stimuli of a frequent blue circle (non-target), a small rare blue circle (Target 1) and a red square (Target 2) on a screen. Contrary to the results observed in Experiment 1, tramadol did not improve physical performance or affect sustained attention at the behavioural level compared to the placebo condition, that is, neither the accuracy of the response nor the reaction time differed significantly between the experimental conditions. However, during the sustained attention task, we found that tramadol caused a lower brain activity (i.e., greater suppression with respect to the baseline) in the alpha frequency band linked to stimulus processing (relevant to the task) in the condition of tramadol compared to placebo. Higher alpha activity has been considered as an indicator of greater alertness. On the contrary, another study that used a similar task, interpreted the reduction of the alpha band when unusual objectives are presented, as a higher mental effort to detect infrequent objectives. Therefore, our results could point out to the need for greater allocation of cognitive resources to detect infrequent targets when participants received tramadol versus placebo.

In the next study, following a different approach, we hypothesized that the stimulation of a brain area related to executive functions could improve self-paced exercise performance, if self-paced exercise relies on executive functions. Even if several studies had investigated the effect of tDCS on physical performance, none of them had addressed the question of whether anodal stimulation over the left dorsolateral prefrontal cortex might affect self-paced aerobic exercise performance. Interestingly, the results of our study did not support the idea that anodal tDCS affects neither self-paced performance nor oscillatory brain activity, both at rest and during exercise. This finding added more inconsistency to the ambiguous results published to date. Therefore, in view of our null results and the inconsistency of the literature, we decided to perform a meta-analysis to check whether the tDCS had a real effect on indexes of exercise physical performance. The meta-analysis showed that tDCS has a small, albeit positive, effect on exercise performance (Hedges' $g = 0.34$). None of the included moderators (e.g., location of stimulation, intensity or duration) in the analysis explained the variance in the data. In addition to the small effect size, we detected that the positive results could be overestimated by methodological artefacts and publication bias. To date, with our (and others) meta-analysis we cannot establish tDCS is an effective tool to improve exercise performance.

In a final study, we try to fill an existing gap in the literature on the effect of the cognitive (executive) load during self-paced exercise, since in most of the previous studies the cognitive

task was performed prior to a physical exercise. The cognitive load was manipulated by using a working memory task (n-back) with two levels of difficulty to induce two levels of cognitive load, low (1-back) and high load (2-back). We anticipated that if the self-paced exercise is determined by executive processing and the n-back also requires executive processing, self-paced exercise performance would impair due to the inability to self-regulate efficiently. However, although the task with more cognitive demands was more demanding (lower precision and slower response times) than the one with low cognitive load, and therefore greater difficulty in terms of executive demands, the results did not provide enough evidence to affirm that high load worsens physical performance or modifies perceived perception of effort. These results are in line with the previous findings of this thesis, suggesting that self-paced exercise might not rely on executive functions.

In conclusion, the results of the series of experiments carried out during this thesis do not support the idea that self-paced exercise depends to a large extent on executive processing. Although tramadol could affect physical performance in Experiment 1, oscillatory brain activity was not affected during exercise and the mechanisms of possible improvement are unknown (we are currently conducting another study to clarify the previous results). That was also true in the tDCS' experiment, since brain stimulation did not affect physical performance or brain activity. Finally, a greater cognitive load during self-paced physical exercise did not seem to affect physical performance. Crucially, the results of this thesis may indicate that executive functions may not play a decisive role in the self-paced exercise, contrary to what is assumed. However, we acknowledge that the role of executive functions in the exercise could be mediated by several factors, such as sports expertise.

Introduction

1. Introduction

Self-paced exercise, like running a marathon, refers to any physical activity in which the effort has to be distributed over time, in order to achieve the objective of the exercise. In our marathon example, this would correspond to completing the set distance as fast as possible; other cases exist in which athletes are expected to complete the greatest possible distance in a given time as in the cycling "Hour record". In all cases, it is of the essence to complete the set goal without reaching premature exhaustion [1]. During such self-paced exercises, athletes have to continually process information in order to achieve an optimal level of performance [2]. Self-pacing requires to control and monitor the afferent feedback from the muscular and cardiopulmonary systems to the brain, which may affect directly or indirectly effort regulation [3]. Once this information is processed, athletes have to make continuous decisions to adapt the pace according to the demands of the event and the relative remaining duration or distance to cover [4]. Moreover, athletes choose their pace strategy based on the objective of the event as well as their previous experience. The higher the experience, the easier it will be to choose an adequate strategy [5]. Therefore, self-paced exercise, given its aim to adequately distribute effort along the time period of the event to avoid premature fatigue, rests on goal-directed behaviour. In doing so, it engages cognitive processes and in particular, executive functions.

Executive functions refers to a series of interrelated top-down processes which are needed for behavioural control, from selecting to monitoring behaviours that ease the achievement of goals [6]. There is a common agreement that executive functions are composed of three core components: working memory, inhibitory control and cognitive flexibility [6,7]. Working memory involves the storage of information for a short period of time after it has been experienced. It is also at play when translating instructions into action plans or update one's plan by calculating or considering others alternatives. Inhibitory control is crucial to stop automatic behaviours, as when changing one response to another one better suited to the situation. Inhibitory control is also central to selecting among many different possible choices the best memory representations, as when hearing the ambiguous word, such as "bank". Indeed, inhibitory control can be exercised at different levels or representations, from self-control and discipline (inhibition at the level of behaviour), to concentration and attention (suppression of unattended perceptual information) to cognitive inhibition (inhibition of thoughts or memories) [8]. Finally, cognitive flexibility corresponds to the ability to switch one mode of thinking, as when considering multiple alternatives in a complex situation.

This review asks the extent to which self-paced exercise engage and rely on executive functions. First, we summarize the role of executive functions on self-paced exercise. Second, we highlight the empirical evidence of the neural basis of self-paced exercise, together with the models to

explain the role of executive functions in exercise. While these first two sections are based on studies that are purely correlational, we then discuss the empirical evidence from experimental manipulations with an eye toward possible causal links. Some studies have manipulated, before or during exercise, aspects of executive function such as attentional focus, mental/cognitive fatigue and cognitive load and measured the impact on self-pacing. Other studies have asked whether self-paced exercise performance would be improved when enhancing executive functions, whether through pharmacological drugs, brain stimulation, or cognitive training. Taking stock of the available literature, we argue for the role of executive function on self-paced exercises.

2. Executive functions and self-paced exercise - Correlational approaches

2.1 Role of executive functions on perceived exertion during self-paced exercise

Self-paced exercise involves several cognitive processes, such as perception and memory, as well as executive functions, such as inhibition and working memory [9–11]. Stimulation from internal organs (e.g., muscle, lungs, heart) and from environmental factors (e.g., competitors, public, road surface) need to be processed and integrated requiring athletes to select relevant sources of information and suppress potential distractions [12]. For example, based on their breathing sensation, athletes can rate how they perceive a given physical effort. However, accurate perception of effort builds on mental template that have been previously defined through experience [13]. Indeed, athletes might perceive a given effort lighter or more strenuous depending on, not only the exercise intensity and the estimated duration until ending the exercise, but also their prior knowledge about these types of exercises [13,14]. A common measure of effort in exercise performance is the rate of perceived exertion (RPE). Briefly, RPE in sports is often described as the cognitive feeling associated to physical effort [15]. Importantly, RPE has been linked to several executive processes, such as working memory, inhibition, self-control and attention.

As we mentioned before, during self-paced exercise, athletes have to continuously update their initial plan according to the current demands of the exercise. If the current performance is under or over the desired goal, athletes will have to calculate or considerer new alternatives, and switch motor plans accordingly [13]. In other words, when athletes assess their current RPE, they rely on key executive functions of working memory, inhibition and cognitive flexibility.

Moreover, the RPE also relies on inhibitory process related to the self-paced exercise [16]. During self-paced exercise, the adequate management of sensation leads to achieve an optimal level of performance, as the regulation of effort is associated with the ability to tolerate and inhibit

discomfort raised during exercise. Maintaining an exercise despite of feeling fatigue or pain in some part of the body [17] and/or hard environmental conditions [18] implies to inhibit the urge of stopping or reducing the exercise intensity [17,19]. Therefore, inhibitory process, such as focused attention or self-control [5,6], help to regulate self-paced exercise.

2.3 Neural basis of self-paced exercise

The relationship between executive functions and self-paced exercise is further supported by empirical neural evidence. The recent advances in neurophysiological techniques applied in sport, such as neuroimage (e.g., functional magnetic resonance imaging, fMRI) or electroencephalography measures (EEG), have helped to understand some neural mechanisms associated to exercise and to propose possible models in which executive functions might be relevant.

The prefrontal cortex might play a key role on self-paced exercise, with interconnection with other brain areas such as the anterior cingulate cortex and orbitofrontal cortex [20], premotor cortex and supplementary motor area [21], involved in the processing of sensorimotor information. Crucially, given the apparent role of the prefrontal cortex in self-paced exercise, Robertson and Marino [22] proposed that it acts as a control structure which integrate information raised during exercise, both centrally and peripherally, exerting a top down control [23]. The prefrontal cortex would be then responsible of integrating afferent signals provided by the anterior cingulate cortex and the orbitofrontal cortex, which have been related to motivational and emotional processing [24]. Once these signals are integrated, the prefrontal cortex would respond consequently by increasing, decreasing or maintaining the pace, or ultimately stopping exercise. Therefore, the self-paced exercise would be redefined according to the analysis of the costs and benefits made by the brain network including the prefrontal cortex, the anterior cingulate cortex and the orbitofrontal cortex during an ongoing cost-benefit analysis [25]. If the cost overcomes the benefits, the process underlying inhibitory control will be disengaged and the pace would be down-regulated [26]. Likewise, McMorris and colleagues proposed a similar interpretation to that of Robertson and Marino's model [27]. They proposed that regulation of endurance exercise is based on interoception and motivation, but in this case is the ventrolateral prefrontal cortex, which integrates the information from the supplementary motor area and the premotor motor cortex, which ultimately sets whether to continue, slow-down or stop the exercise. They also highlight the importance of the anterior insula cortex (that receives feedback from lamina I lateral spinothalamic and nucleus tractus solitarii medullo-thalamic pathways during exercise [27]) which reacts to changes of exercise intensity and perception of effort [28]. Then, this feedback is compared with the information stored in the memory in order to generate a new current status of awareness.

However, there are only a few correlational studies (and using externally-paced exercise instead of self-paced efforts) to support these models. For example, the model of Robertson and Marino [23] is based on the fact that EEG activity that would emerge from the dorsolateral and ventrolateral prefrontal cortex (note the poor spatial resolution of EEG) begins to decrease when exercise intensity overcome the ventilatory threshold, and therefore these brain areas might have a potential role on motor inhibition process. The authors argued that reduced brain activity in top-down control area may enhance the processing of unwanted stimuli which in turn, might lead to reduced pace ability or even to cease exercise. Likewise, Enders and collaborators [29] found an increased prefrontal activity which matched with onset of force production and the transition from flexion to extension in the pedaling cycle. The authors also suggested that the supplementary motor area received higher order from the prefrontal cortex exerting an executive control, motor planning and execution [30].

Executive functions are also relevant to the psychobiological model of endurance performance [2,31]. This model emphasis five different cognitive factors related to self-paced exercise: 1) perception of effort; 2) potential motivation; 3) knowledge of the distance/time to cover; 4) knowledge of the distance/time to remaining; and 5) previous experience of perception of effort during exercise. The model suggests that to overcome fatigue, the prefrontal cortex should exert inhibitory influences on the cingulate and insula cortices, both of which seem to be activated in proportion to the degree of subjective physical and mental fatigue [25]. Therefore, according to the psychobiological model, the key variable on self-paced performance is the perception of effort (c.f. [2,31]).

In any case, the limited evidence supporting the psychobiological model of endurance exercise is based on studies on mental fatigue prior to exercise. For example, Brownsberger et al. [32] and Pires et al. [33] found that cyclists with an induced state of mental fatigue presented an increased EEG brain activity in the prefrontal cortex. In Brownsberger' et al. study, twelve participants completed two consecutive self-paced cycling exercises at RPE of 11 or 15, after completing a 90-min mental fatigue task or watching a documentary. The authors found that participants produced less power during the self-paced exercise in the mental fatigue condition compared to the control condition, and it was related to a higher beta activation in the electrode position F3 for the mental fatigue condition. The authors suggested that the higher beta activation in F3 might be related to prefrontal activity. Meanwhile, Pires et al. [33] showed that a group of eight trained cyclists with an induced state of mental fatigue presented a higher theta activation during a 20km cycling time trial than in the control condition. Moreover, cyclists in the mental fatigue condition completed the 20km time-trial slower than in the control condition and the authors suggested that increase theta power might reflect their lower ability to preserve adequate inhibitory control and attentional allocation during exercise, which subsequently led to impaired performance [33].

Nonetheless, due to the small sample sizes of these studies (less than 15 participants), the level of participants (recreational athletes), and that Pires et al. [33] only placed one electrode to record EEG activity, these results should be interpreted with caution.

Finally, it is also worth mentioning the new perspective that has emerged to overcome the apparent oversimplification of the complex psychophysiological construct of exercise based mainly on the perceived exertion. Venhorst et al. [34] proposed that self-paced exercise is based on a construct of three dimensional categories. First, perceived mental and physical strain are the main components of exercise which reflect sensory-discriminatory process necessary to match the planned objective with the physiological state. Second, the core affect acts a mediatory role in regulation of effort since its two dimensions (hedonic and arousal) reflect behaviour of approaching or avoidance. Finally, the cognitive flexibility within the process between further pursuit a goal or the goal disengagement according to the boundaries set by homeostasis. Nonetheless, no study has investigated the neural basis of these proposed mechanisms.

In summary, notwithstanding the discrepancies on the main focus between these models of self-paced (endurance) performance, it seems that all of them consider the executive functions (and their neural basis) as determinant for self-paced aerobic exercise. However, as we have summarize here, there is a scarcity of empirical studies which have tested the neural mechanisms of self-paced aerobic exercise. In addition, we are still far from understanding the connection between brain areas during exercise, as it was proposed by these authors. To date, the most widespread practice is to look for manipulations that have an effect on executive functions to see how performance improves or worsens. In the following section, we summarize the evidence from experimental studies whose aim were to study the influence of executive function over self-paced aerobic exercise performance. The effect of exercise over executive functions has been discussed previously [35–37].

3. Experimental manipulations affecting executive functions and self-paced performance

3.1. Attentional focus

During self-paced exercise athletes have to allocate their attentional resources only toward relevant stimuli from the myriad of inputs (internal and external) that reach the central nervous system. Accordingly, the attentional focus during self-paced exercise has been a topic of interest for sport scientists [38]. Generally, athletes have two different strategies (associative or dissociative) with two dimensions (internal or external) to allocate their attentional resources during exercise [39]**.** On the one hand, within the associative strategy, athletes can focus their

attention towards relevant aspects of the exercise, either internal (i.e., focusing on internal body aspect of the task such as breathing, heart rate, etc.) or external (i.e., focusing on monitoring the competition such as pace, power output, remaining distance, etc.). On other hand, in the dissociative strategy, athletes divert their attention to irrelevant aspect of the exercise, such as irrelevant daydreams or math puzzles (internal dissociation) or in the scenery or other competitors (external dissociation). Therefore, when athletes adopt different focus of attention, they will mainly request the inhibitory process of cognitive inhibition (inhibition of thoughts) and focused attention.

The logic of the attentional focus theory is that focusing on the task or diverting the attention from the task might affect (mainly) subjective indexes of exercise performance, and consequently change physical performance [38]. For example, Connolly and Janelle [40] (Experiment 1) studied the effect of an associative or dissociative strategy on self-paced rowing performance. In the associative strategy, participants (n= 9) completed more distance than in dissociative strategy, although there was not difference in RPE levels between conditions. In their second experiment, they tested the two dimensions of associative and dissociative strategies (i.e., internal or external). Participants completed in five separated visits, a 2000m self-paced rowing exercise using internal/external associative or dissociative strategies and a control condition [40]. The results showed that an associative strategy either internal or external induced a higher RPE levels than a dissociative strategy or control condition during a self-paced exercise. However, the higher RPE found in Connolly and Janelle's study might be well explained by the better physical performance in the associative strategy rather than the associative strategy itself to induce higher RPE.

Williams et al. [41] suggested that focusing attention on external aspects of a self-paced exercise improves physical performance. Williams et al. used a cyclists' avatar, which simulated a competitor with higher power output than the participant at baseline, to reduce the internal associative focus during a self-paced 16.1km time-trial compared to a neutral or no avatar condition. The results of the study showed that, on average, participants (n= 15) completed the time-trial 1.4% faster and increased the average power output on 2.8% compared to the baseline. The higher performance was achieved by an altered pacing strategy throughout the time-trial, as the external (dissociative) focus might have allowed athletes to reduce negative sensation of fatigue and pain [41]. According to the authors' conclusion, the external focus helped to inhibit the rise in RPE during exercise since participants paid less attention to the RPE. In a separated study, Williams et al., [42] found that enforcing a slower initial pace during the first 4km of a 16-km cycling time-trial reduced the internal association focus compared to a fast or a neutral start. Although cyclists started slower than normal pace, the positive psychological responses during the initial phase of the time-trial reduced the RPE, but it did not affect the overall time-trial performance compared to fast and baseline start.

Robinson et al. [43] asked nine active adults to match the 80% of a 3-min all-out test, during a 3-min cycling self-paced exercise by using an internal associative strategy or external dissociative strategy. They found that using an associative strategy, participants completed the test at their 75.9% of the average power output obtained in 3-min all-out test performance, whereas with the dissociative strategy participants were only able to achieve the 70.9% of their performance. They argued that in novice participants, distracting the attention from performance can slow down the pacing, and therefore an internal (associative) focus strategy might help to maintain a more consistent performance throughout a self-paced event [43].

In conclusion, there are only a few self-paced exercise studies in which the attentional focus has been manipulated externally and the results are somewhat mixed. An associative strategy might increase RPE, but it might be mediated by an increased performance [40,43]. Yet, a dissociative strategy might improve exercise performance [41,43] without increasing RPE [42], at least in more proficient athletes, and therefore the experience of the participants may also alter the nature of the optimal strategy (see below level of expertise section). .

3.2. Cognitive load during self-paced exercise

Despite being a topic of interest, few studies evaluate the effect of cognitive load on self-paced exercise performance. Under the umbrella of cognitive load, we refer to those interventions aiming to induce different levels of cognitive (executive) load during a self-paced aerobic exercise. For instance, Epling et al. [44] found that performing a word recall task involving working memory, while participants completed a self-paced outdoor running exercise, increased the mental workload (measured with the NASA-TLX scale) compared to running without performing any cognitive task. However, they did not find that the cognitive task performed during a 5-min self-paced run affected the distance covered by the 12 athletes. Likewise, Blakely et al. [45] examined the impact of cognitive load (tone counting with two levels of difficulty) on a group running on an even surface and on a group running on an uneven (trail) surface. In Blakely' study, participants reported higher mental workload and feelings of being mentally exhausted with more difficult cognitive task. Nonetheless, they only found a linear trend in both groups for a worsening physical performance with the increasing of difficulty of the cognitive task. Malcolm et al. [46], although they did not assess an index of exercise performance, found that the increase in cognitive load (using a go/no-go response inhibition task) while participants walked in a treadmill modified the gait pattern during the more challenging task compared to the control condition.

In contrast to the above-mentioned studies, Holgado et al. [47] found that performing simultaneously a n-back task, which involves working memory and inhibition, did not affect exercise performance during a 20-min self-paced cycling exercise in 28 trained cyclists. The

results of the study did not show enough evidence to support the idea that completing a challenging cognitive task (2-back) compared to the less challenging task (1-back) affected the average power output achieved. In addition, the results of the study showed that, despite the higher cognitive demands of the 2-back condition, RPE was not affected by the cognitive load. Similarly to this finding, Daniels and Newel [48] did not find an increase in the RPE while participants completed a hard math task during a self-paced running exercise.

In conclusion, with the current evidence, it is difficult to raise any firm conclusion on the effects of cognitive load on self-paced exercise performance because of the scarcity of published studies and the degree of variation in the methodology. In any case, the current evidence does not seem to support the idea that performing simultaneously a challenging cognitive task during self-paced exercise impairs exercise performance. These data challenge the idea that self-paced exercise is regulated by top-down processing, although it is plausible that other factors, such as level of expertise, may modulate or even mask the effect of cognitive load on self-paced exercise.

3.3. Mental fatigue before self-paced exercise

It is commonly believed that performing a long and challenging cognitive task involving executive functions (e.g., inhibitory control, cognitive control, etc.) before exercise might increase the RPE in a subsequent exercise due to an induced state of mental fatigue [49]. In this state of mental fatigue, athletes would select a lower self-selected exercise intensity, as they would find harder to inhibit unpleasant stimuli related to successful exercise performance [49,50]. It is hypothesized that mental fatigue state is caused by an accumulation of adenosine within active regions of the brain during demanding cognitive task [51]. Adenosine might have two effects: first it would increase the RPE and second, it would reduce motivation towards the exercise. However, this hypothesis has not been tested in experimental studies yet and therefore, it remains speculative whether RPE increases as consequence of an accumulation of extracerebral adenosine [52].

The literature of the effects of performing a challenging cognitive task before self-paced aerobic exercise is somewhat inconsistent and scarce. For example, Pageaux et al. [51] found that performing a 30 min inhibitory control cognitive task (Stroop task) induced a higher RPE and reduced the physical performance on a 4km self-paced running exercise in 12 physically active participants compared to performing the same task without the inhibitory component. Similarly, but using a 30 min sustained attention cognitive task before exercise, Pires et al. [33] showed that the cognitive task induced a higher RPE and participants spent more time to complete a 20km time-trial in a group of 8 recreational active participants in comparison to a control condition (seated for 30 min). However, contrary to Pageaux et al. [51], Penna et al. [53] did not find that the same cognitive inhibitory task affected the RPE in 16 highly trained swimmers, although it

impaired their performance in a 1500m self-paced swimming exercise. Likewise, Martin et al. [54], using the same task and duration as in Pageaux's and Penna's studies, did not find any effect of prior mental fatigue on the RPE levels of professional cyclists (n= 11) and recreational cyclists (n= 9). However, the group of recreational cyclists impaired their physical performance in a 20 min cycling time-trial, while no changes were shown in the group of professional cyclists. Martin et al. concluded that professional riders might be more resilient to mental fatigue and have a superior inhibitory control [54]. Contrary to the findings of Martin's et al. study, Clark et al. [55] reported similar self-paced performance (6-min cycling time-trial) after completing a Stroop task or a neutral task independently of whether participants were competitive cyclists (n= 10) or untrained (n= 10).

Other studies have induced mental fatigue through longer cognitive task. However, even longer cognitive tasks do not seem to induce consistent detrimental effects on RPE or physical performance. For example, Staiano et al. [56] asked 13 young elite kayakers to perform a 60 min Stroop task before a 2000m self-paced kayaking time-trial. Participants were indeed impaired in the self-paced exercise (time to complete the 2000m) probably due to a higher RPE in the mental fatigue condition as compared to the control condition. In contrast, Filipas et al, [57] did not find that the same task and duration affected RPE or physical performance in prepubertal kayakers athletes before completing a 1500m time-trial. Performing the AX-CPT task, which involve sustained attention, working memory, response inhibition, and error monitoring, during 90 min affected neither RPE nor physical performance on a sample of 8 recreational cyclists before a 4km cycling time-trial [58]**.** In contrast, the same cognitive task impaired 3km running performance on 20 recreational runners**,** even though participants did not rate their RPE higher [59].

In summary, the above evidence seems to point out that performing a cognitive task which involve executive functions prior to self-paced exercise might at worse have a detrimental effect on RPE and self-paced exercise performance, and at best no effect. The scarcity of studies and the mixed results in the literature do not provide a strong evidence to support a systematic detrimental impact of mental fatigue on self-paced exercise.

In addition, these results should be interpreted with caution for following reasons: first, sample sizes are generally low (less than 20 participants) which may lead to overestimation of effect sizes; second, the experimental and control condition usually varies in several components, for example, the duration of the interventions [54] and doing a cognitive task versus doing nothing in the control condition [33,53,54,56,58]. Last, but not least, the effect of mental fatigue on exercise might be more likely due to random error rather than for a real effect of mental fatigue on exercise (cf. McMorris et al. 2018 [60]).

4. Interventions to enhance self-paced performance by improving executive functioning.

If executive functions have a role in the self-regulation of endurance performance, it is therefore logical that some studies have aimed to act on executive functions in order to improve self-paced aerobic exercise through the use of any technique, tool or substance. In this section, we will discuss those intervention which may have the potential to improve self-paced exercise performance by acting, directly or indirectly, on executive functions. Some examples of these interventions, but not limited to it, are cognitive training, non-invasive brain stimulation or pharmacological substances [61].

The potential role for cognitive training in sport is to develop executive functions through focusing in a specific executive functions component (e.g., working memory) for a transfer to a sporting real-world task [62]. Given that cognitive training has shown improvement in cognitive tasks related to the task used in that training (i.e., near transfer effect), there is a rationale for a possible improvement in a sport specific task (i.e., far transfer effect). Even if this is a topic of great interest, there is not enough evidence showing a positive effect of cognitive training in self-paced exercise [63]. In addition, it seems that the limited evidence comes from studies supported by commercial companies rather than peer-reviewed ones [62]. Therefore, we are still far from being able to recommend cognitive training for athletes due to the time-cost balance which supposes the training and the minimal or null gains seen after training.

Nowadays, transcranial direct current stimulation (tDCS) is the main non-invasive brain stimulation technique used in Sports science in order to improve exercise performance. The logic of tDCS is straightforward: any change in areas associated with executive functions should affect self-paced exercise, to the extent that self-paced exercise rely on executive functions. However, few studies have used self-paced exercise to test the effects of tDCS on performance. As far as we know, only four studies have tested the effect of anodal tDCS on a self-paced aerobic exercise and the results do not seem to support the idea that tDCS is an effective tool to improve performance. Anodal tDCS applied before exercise did not improve performance compared to the sham condition in a 16km self-paced time-trial in male trained cyclists [64], or during a 20km time-trial in healthy men [65], or during a 20 min time-trial on male trained cyclists [66] or in a 800m swimming test in elite triathletes [67]. Moreover, stimulating the prefrontal cortex for 20 min did not elicit any change in oscillatory brain activity either at baseline or during exercise [66]. Hence, with the current evidence available, we cannot claim that tDCS is able to improve self-paced performance. Despite the general belief that tDCS is an effective tool to improve exercise performance, the pooled effect size of the tDCS' studies on objective and subjective measures of exercise performance or muscle strength do not provide enough evidence for its ergogenic effect.

Indeed, the effect might be mainly driven by studies with low quality and by the publication bias [68,69]. Moreover, as it happened with cognitive training devices, it seems that companies with commercial interests are promoting tDCS without solid evidence of its effects on exercise performance [70].

Finally, it is worth to mention that there has been a trend for athletes from all levels to use pharmacological drugs (e.g., analgesics or opioids). Athletes might be using these drugs in order to inhibit process related to exercise induced pain or discomfort [71]. Some of these pharmacological drugs are, for example, paracetamol or tramadol. For example, paracetamol might inhibit pain sensation by decreasing the activation of the anterior cingulate or prefrontal cortices, which are involved in pain and cognitive/ affective processing. For example, Mauger et al. [72] found that paracetamol ingestion increased the average power output and reduced the time required to complete a 16.1km self-paced cycling exercise, although the RPE remained unchanged. Likewise, tramadol, might reduce the ability of the brain to respond to sensory inputs by inhibiting serotonin and norepinephrine reuptake. It is therefore possible that tramadol could improve exercise performance via its effect on central brain areas associated with perception of effort. Holgado et al. [73] conducted the first study, to the best of our knowledge, to test the hypothesis that tramadol improves self-paced performance. In their first experiment, they showed that tramadol appeared to allow trained cyclists to achieve greater mean power during a self-paced exercise without modifying brain electrical activity or RPE. In contrast, in a second experiment aimed to replicate the first experiment and to test the hypothesis that tramadol might have an effect on sustained attention during exercise, tramadol did not improve physical performance or affect sustained attention at the behavioural level compared to the placebo condition. They found, though, that tramadol caused a lower brain activity (i.e,, greater suppression with respect to the baseline) in the alpha frequency band linked to stimulus processing (relevant to the task) in the condition of tramadol compared to placebo which might suggest a detrimental impact of tramadol on stimulus processing. In any case, more research is warranted to establish the effect of tramadol on self-pacing exercise at the physical, cognitive and brain levels. For further discussion on the effect of pharmacological substance on exercise performance see the reviews by Lundberg and Howatson [74] and Holgado et al. [71].

5. Level of expertise

There is some rationale to think that the level of expertise in a given skill might be fundamental to explain the extent to which skills rely or not on the use of executive functions. It is plausible that through deliberate practice many of the exercise skills or movements might be performed, for example, with little or no reliance on executive functions [11]. Given that the use of executive functions is effortful and that of cognitive processes limited, exercise expertise would be valuable

in reaching an automatic mode in order to divert effortlessly resources where and when they are needed. According to some models, learning new skills go through different stages [75]. In a first stage, movements are performed consciously and by investing large amounts of cognitive resources. In the next stage, movements are executed in a blend of aware and automatized control strategies. Finally, some athletes reach an autonomous stage, in which the use of executive functions is reduced to a low levels and movements are performed efficiently. For instance, neuroimage studies corroborate this idea, as some studies have shown that prefrontal cortex activity change from the initial phase of learning a new skill to once the skill is already automatized [76,77]. These studies show that with increasing automaticity of movements, less brain areas are activated and that activity in participating brain areas decline [76,77]. Hence, with a high level of automaticity, processes are more efficient, rapid, smooth and require low levels of attentional capacity [78]. However, expertise is a continuum rather than an endpoint in one skill. Expertise is defined by a continuous process of acquisition that leads to reduced cognitive demands to perform any skill. Finally, it is not automaticity per se which define and expertise, but the level of proficiency of that skill that is attained [78]. Interestingly enough, studies in cognitive neuroscience investigating expertise show that those participants who recruit less brain areas, showed better performance in working memory tasks [79–81]. These results suggest that to identify the role of any brain area related to exercise, we must consider the level of expertise of those participants because the pattern and timing of brain areas recruited during exercise might change considerably [80,82].

Athletes with a higher level of expertise might, therefore, rely to a lesser extent on executive functions. For example, when athletes achieve a high level of automaticity, movements are better adjusted and require less energy expenditure and cognitive effort [83,84]. Experts might also require less cortical activity to perform the same task compared to novices. For instance, Ludyga et al [82] found that cyclists with higher fitness level have less brain cortical activity in comparison to a group of lower fitness level cyclists, during a 30 min submaximal cycling exercise below the ventilatory threshold. The results showed that alpha/beta ratio during exercise for the high fit cyclists was higher compared the lesser fit cyclists. Given that higher alpha activity is an indicator of increased alertness and arousal and a lower beta activity is associated with relaxation, the authors concluded that the high fit cyclists presented an enhanced neural efficiency, possibly due to the inhibition of task-irrelevant cognitive processes [82]. We acknowledge that the exercise intensity in this study was fixed, and therefore the results might not extrapolate to a self-paced aerobic exercise.

An example closer to self-paced aerobic exercise comes from the gait literature. Nowadays, there is evidence that different steady state walking speeds do not considerably affect prefrontal activation [85,86]. As gait is a skill that has been automatized throughout life, prefrontal activity

(with respect to rest) remains relatively stable even at different comfortable speeds. Similarly, experts' athletes through deliberate practice over years may have developed the ability to execute their skill free of much frontal cortex participation. In fact, less cortical activity within prefrontal areas might allow to divert cortical resources during exercise away from regions responsible for cognitive control, resulting in a neural efficiency [84]. Although gait and many self-paced aerobic exercises might be considered similar tasks (i.e., cyclical and continuous activities), we cannot directly extrapolate these results to these more complex self-paced exercises.

Interestingly enough, the study of Martin et al. [54], which we discussed above, concluded that professional cyclists show better inhibitory control and are more resistant to the negative effect of a high mental fatigue. In Martin et al.'s study, the group of professional cyclists did not display impaired performance in a 20 min time-trial after completing a 30 min Stroop task compared to a 10 min seated control condition. However, the group of recreational cyclists displayed impaired physical performance in the mental fatigue condition and made more errors in the Stroop task. Likewise, Cona et al. [87] found that faster ultra-distance runner had better motor inhibition control than slower runner (but also fit runner) before an ultra-marathon running race. Furthermore, Jacobson and Matthaeus found that self-paced athletes outperformed both externally-paced athletes and non-athletes in a task involving inhibitory control [9]. These results are in line with the conclusion of Ludyga et al.'s study [82], which suggested that high fit cyclists might have a better inhibitory control. In contrast to these findings, Clark et al. [55] did not find that difference in terms of performance between untrained participants (n=10) and competitive cyclists (n=10) during a 6-min cycling time-trial after completing the inhibitory control task. However, the shorter duration (6 min vs. 20 min) of the physical exercise compared with Martin et al.'s study may explain the divergent results.

Additional evidence for the influence of expertise level on the link between executive functions and self-paced exercise comes from attentional focus strategy studies. For example, experts or those athletes with better performance, adopt different attentional strategies during self-paced exercise compared to novice athletes. For example, Silva and Appelbaum [88], found that top finishers in a marathon race spent more time using an internal associative focus of attention compared with the slower finishers. These observations are consistent with those of Morgan and Pollock [89], who determined that high-level performers runners also utilized internal associative strategy, whereas non-elite runners appealed more often to an external attentional focus strategy. This is further supported by Stevinson and Biddle [39], as they found a correlation between the use of an internal dissociative attentional focus strategy in non-elite marathon runners and "hitting the wall" in a marathon race compared with those participants that they did not use primarily this strategy. They suggested that the internal dissociation (i.e., focusing in internal aspect not relevant to the task such as daydreaming) is a hazardous strategy to achieve an optimal level of performance

during a self-paced event. Meanwhile Brick et al. [5] interviewed elite endurance runners, also reporting the predominant use of an internal associative attentional focus strategy. Finally, the outcome of Ouvrard et al.'s [90] study supports Brick et al.'s findings, this time in a sample of French elite cyclists. They studied the relationship between pacing strategies and attentional focus in elite cyclists during a time-trial championship. In the sample of 9 elite cyclists, thoughts related to active self-regulation of the performance (i.e., internal associative focus) or thought related to outward monitoring of the competition (i.e., external associative focus) were correlated with an optimal performance during a 49.3km cycling time-trial corresponding to the national championships.

In summary, the scant evidence suggests that skilled athletes could have automatized processes related to effort regulation and may need fewer resources to perform the same activity, i.e., they might be more efficient at the time of processing stimuli [91]. Although there is not much evidence on this, it is plausible that after many years of deliberate practice, expert participants could have already automatized a pacing strategy and they would not require to continuously use working memory capacity in order to update the initial plan [48–50]. Moreover, given that athletes involved in self-paced sports might have better inhibitory control [9], they would be able to inhibit thoughts unrelated to exercise performance, allowing them to invest more resources or to focus on other relevant aspects of self-paced exercise (i.e., using an associative strategy). However, this issue remains speculative, as studies which aimed to investigate the cognitive/neural factors related to experts and novices only provide a snapshot of the two endpoints of a continuum [78]. Furthermore, although elite and non-elite athletes might differ in key cognitive processing, little is known of the psychological characteristics of elite performance [92].

6. Perspective

The present review has highlighted the empirical evidence of the role of cognitive (executive) functions on self-paced aerobic exercise. Most of the manipulations described here were intended to act on cognitive/psychological process rather on physiological process. In this final section, we will briefly describe the future challenges the field has to face to understand the role of executive functions in self-pace exercise.

The present review identifies some gaps in the literature about the role of executive functions and self-paced exercise. The literature from sports science suggests that the prefrontal cortex plays a key role in exercise, because when exercise intensity increases, brain activity in prefrontal areas increase progressively until the ventilatory threshold [22,23]. Once reaching this point, prefrontal activity starts to decrease which might reduce the ability for the prefrontal area to sustain goal-directed behavior for pacing regulation at high intensities [22]**.** However, this evidence comes

from studies testing externally-paced exercises, and therefore we do not know the true role of the prefrontal cortex during self-paced exercise. In addition, we also know from cognitive neuroscience that experts in any skill request less prefrontal activity to perform their expert skills. Hence, as we have highlighted in the previous section, the prefrontal cortex might not be the key brain area responsible for regulating self-paced exercise, when athletes reach a high level of proficiency.

In the attentional focus section, we discussed the implications for self-paced exercise of adopting an associate or dissociative (either internal or external) strategy. While it is true that these studies provide valuable information, all these studies were performed in lab settings, and therefore they do not speak directly to cognitive strategies related to environmental cues or spectators. We revised some studies that provided observation from real competition scenarios, however, given that attentional focus was not manipulated, we cannot establish whether athletes with the best results would have performed equally well with another attentional focus strategy. Moreover, we should consider the duration of the self-paced exercise, since the best strategy might be different for a 5km race than for a marathon race. Finally, it would be also interesting to study which brain areas might have a role under different attentional focus strategies.

In relation to the role of the cognitive load during exercise, a key point to consider is the task characteristics. For example, we consider crucial to include (at least) two conditions with different levels of cognitive load to guarantee that any effect on exercise performance is a consequence of the cognitive load and not due to the effect of performing a single task compared to dual-tasking. Moreover, the duration and difficulty of the cognitive task and exercise should be considered according to the physical fitness of the participants, as trained/expert athletes might be more resilient to the effects of cognitive load and more challenging task given than they use to outperform their less trained counterparts.

It is fundamental to reaffirm at this point that self-paced aerobic exercise is likely to be a highly complex process, in which a multitude of factors non-related to executive functions can also contribute to the ultimate decision to upregulate or downregulate exercise intensity. Other brain areas via different mechanisms have a role on exercise regulation. For example, brain areas related to interoceptive and motivational process (e.g., anterior cingulate cortex) are linked to exercise regulation. On the one hand, interoception entails the processing of body signals and, in the case of experience athletes, might give rise to a better perception of internal cues from peripheral body systems (e.g., muscular and cardiopulmonary). This implies that interoceptive abilities might facilitate self-paced exercise regulation and to better tolerate fatigue. On the other hand, motivated athletes do not rely on greater inhibitory/self-control to resist the urge of stopping exercise or temptations. Athletes highly motivated might perceive temptations of stopping exercise as less

salient stimulus, which makes goal progress smoother [93]**.** This view implies that motivated athletes will see performance-related discomfort as a less prominent barrier to successful performance, relative to athletes less motivated or with less experience to determine these salient, negative stimuli. This implies that environmental conditions that are challenging or anxiety-provoking may substantially deteriorate performance of executive locomotor control [94]. One example is the anxiety/challenge associated with starting, for example, a race with many other competitors**.** The presence of competitors, for one side, might allow athletes to tolerate higher level of fatigue (changing the attentional focus), but for other side, it might compromise the optimal distribution of energy throughout the race [95].

In summary, self-paced exercise is a goal-directed behaviour that has been related to both bottom-up and top-down processing. As such, self-paced exercise might be seen as an effortful cognitive task involving body motion that places high demands on several brain areas related to emotional, motivational, interoception and executive processing. Athletes with high level of proficiency or expertise are likely to process these brain signals in a different way than less experienced athletes. Therefore, when we aim to study the mechanisms of self-paced exercise regulation in future studies, we should consider the level of expertise (as well as the other factors mentioned in this review) for determining the effect of these intervention which we have described in this review and for determining which brain areas have a role of exercise regulation.

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Aims

General

- To investigate the effects of tramadol on physical and cognitive performance in trained cyclists.
- Investigate the role of Prefrontal Cortex in self-paced aerobic exercise.

Specific

- To investigate the effects of tramadol vs placebo on cycling exercise performance.
- To investigate the effect of tramadol vs placebo on sustained attention, at behavioural level (precision on the stimulus and reaction time) and at the brain level (EEG) during a self-paced exercise.
- To investigate the effects of transcranial direct current stimulation (tDCS) over the left prefrontal cortex related to physical and cognitive performance.
- Investigate the role of cognitive (executive) load during self-paced aerobic exercise.

Objetivos

Generales

- Investigar la influencia del tramadol en el rendimiento físico y cognitivo en ciclistas entrenados.
- Investigar el rol del la Corteza Prefrontal en el sobre el ejercicio aeróbico autorregulado.

Específicos

- Investigar los efectos del tramadol vs placebo en índices de rendimiento fisiológicos en el ciclismo.
- Investigar el efecto del tramadol vs placebo sobre la atención sostenida, a nivel de comportamiento (precisión al estímulo y tiempo de reacción) y a nivel cerebral (EEG) durante un ejercicio autorregulado.
- Investigar los efectos de la estimulación transcraneal con corriente directa (eTCD) en la Corteza Prefrontal relacionado con el rendimiento físico y cognitivo.
- Investigar el rol de la carga mental en el ejercicio físico aeróbico autorregulado.

Material, Methods, Results and Discussion

Sections “Material and Methods”, “Results” and “Discussion” are presented below for each contribution that constitutes the doctoral thesis.

Chapter 1

Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial

Holgado, D., Zandonai, T., Zabala, M., Hopker, J., Perakakis, P., Luque-Casado, A., Ciria, LF, Guerra-Hernandez, E. & Sanabria, D. (2018). Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial. *Journal of Science and Medicine in Sport*, *21*(7), 654–660. https://doi.org/10.1016/j.jsams.2017.10.032 **JCR Q1, IF : 3.92**

Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial.

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Word count: 5176

Abstract word count: 239

Abstract

Objectives: To investigate the effect of tramadol on performance during a 20-min cycling time-trial (Experiment 1*),* and to test whether sustained attention would be impaired during cycling after tramadol intake (Experiment 2*)*.

Design: randomized, double-blind, placebo-controlled trial.

Methods: In Experiment 1, participants completed a cycling time-trial, 120-min after they ingested either tramadol or placebo. In Experiment 2, participants performed a visual Oddball task during the time-trial. Electroencephalography measures (EEG) were recorded throughout the session.

Results: In Experiment 1, average time-trial power output was higher in the tramadol vs. placebo condition (tramadol: 220 watts vs. placebo: 209 watts; $p < 0.01$). In Experiment 2, no differences between conditions were observed in the average power output (tramadol: 234 watts vs. placebo: 230 watts; $p > 0.05$). No behavioural differences were found between conditions in the Oddball task. Crucially, the time frequency analysis in Experiment 2 revealed an overall lower target-locked power in the beta-band ($p < 0.01$), and higher alpha suppression ($p < 0.01$) in the tramadol vs. placebo condition. At baseline, EEG power spectrum was higher under tramadol than under placebo in Experiment 1 while the reverse was true for Experiment 2.

Conclusions: Tramadol improved cycling power output in Experiment 1, but not in Experiment 2, which may be due to the simultaneous performance of a cognitive task. Interestingly enough, the EEG data in Experiment 2 pointed to an impact of tramadol on stimulus processing related to sustained attention.

Trial registration: EudraCT number: 2015-005056-96.

Keywords

Doping in Sport; Opioid Analgesic; Athletes; EEG; Exercise, Brain

Introduction

There is an increasing tendency to treat minor sporting injuries with the use of analgesic drugs so that an athlete is able to continue training and competing. One of these "trending" analgesics is tramadol that is an opioid agonist and is used in the treatment of moderate to severe pain. Tramadol has a dual mechanism of action, being both an μ-opioid receptor agonist, and a serotonin and norepinephrine reuptake inhibitor [1]. Activation of the μ-opioid receptor agonist can cause analgesia and sedation. Likewise, by inhibiting serotonin and norepinephrine reuptake, tramadol seems to reduce pain perception [1]. Given the negative association between pain and exercise capacity, the prophylactic use of analgesic medication (also known as "painkillers") is relatively common to reduce pain in order to enhance sport performance [2]. Similar to other painkillers [3], it is therefore possible that tramadol could improve exercise performance via its effect on effort, pain perception, or mood. However, little is known about the effect of tramadol in sporting performance, with the literature being limited to non-athletic populations [4]. Of the limited research to date, results are conflicting with some suggesting beneficial effects of reduced pain perception and improved effort based exercise performance [4], some reporting uncertain effects on cognitive function [5], and some proposing a negative effect on cognitive function and chemosomatosensory evoked potentials [6].

Informal reports from professional World-Tour cyclists and staff suggest that there may be some abuse of tramadol for potential performance enhancement reasons [7]. Indeed, results of a recent study involving young elite cyclist suggested that they identified tramadol as a potential doping agent [8]. Despite a significant media interest surrounding tramadol [9], little is known of its ergogenic effect in cycling. Currently, tramadol is not included on the list of banned substances by the World Anti-doping Agency (WADA), but it is placed on WADA's monitoring program from 2012 to 2017 to detect potential patterns of abuse [10]. According to the WADA monitoring program, 71 to 82 percent of the tramadol use between 2012 and 2015 in globally monitored sports occurred in cycling [11]. Of particular concern is the drowsiness reported following tramadol administration, which could lead to reduced perception, attention and vigilance causing possible falls in the pro-cycling peloton [12].

In this study, we aimed to test the potential ergogenic effect of tramadol during cycling, and whether it reduces sustained attention (i.e., the ability to keep focused on a particular task over the time). Sustained attention was investigated at the behavioural and brain level, by asking participants to perform a cognitive task while performing the cycling exercise and by recording electroencephalography (EEG). Specifically, we tested the hypothesis that acute oral administration of tramadol would improve 20 min cycling time-trial performance (Experiment 1*)*. We hypothesised that information processing and behavioural responses in a sustained attention task would be influenced by tramadol during the 20 min time-trial (Experiment 2*)*. Given the

aforementioned effect of painkillers on perceptual variables [3], we also investigated subjective measures of the participants' mood, perceived effort and mental fatigue. We hypothesised that tramadol would affect mood at rest and reduce perceived effort and fatigue during the 20 min time-trial.

Methods

The study involved a randomized, double blind, placebo-controlled trial. The trial was approved by the Spanish Agency of Medicines and Medical Devices (AEMPS), EudraCT number: 2015-005056-96, and the Ethical Committee of Clinical Research in Granada. All experimental procedures were designed to comply with the Declaration of Helsinki and Good Clinical Practice (GCP). The randomization process, the audit and verification of compliance of GCP rules were performed by an external clinical research organization (CRO; Delos Clinical, Seville, Spain). The sample sizes were based on power calculations using G*Power Software [13] and assuming a 0.8 power and an alpha error of 0.05. Only cyclists and triathletes with a high-medium level of physical fitness were included in the study. Exclusion criteria were the presence of symptomatic cardiopathy, metabolic disorders such as obesity (BMI >30) or diabetes, chronic obstructive pulmonary disease, epilepsy, therapy with ß-blockers and medications that would alter cardiovascular function, hormonal therapy (and estrogen-progestogen contraception for female participants) and smoking. Participants were asked to refrain from drinking alcohol (48 h abstinence) and caffeine (24 h abstinence) to keep their pre-exercise meal the same, and not to perform any exhaustive exercise in the 48 h before each experimental visit.

In Experiment 1, we recruited 30 cyclists, 20 males and 10 females. Two participants could not complete Experiment 1: one male due to nausea and drowsiness after tramadol ingestion (approximately 90min), and one female due to an ankle injury not related with the experiment. The final sample was 28 participants, 19 males and 9 females, (mean (SD) age 25.6 (5.9) years, weight 69.07 (10.3) Kg; $VO_{2max:}$ 49.17 (7.29 ml/min/kg) for Experiment 1. For male participants, tramadol dose corresponded to 1.35 mg/BM, with a dose of 1.77 mg/BM given to females**.** Participants visited the research laboratory on three separate occasions at the Mind, Brain and Behaviour Research Centre of the University of Granada, firstly for an assessment of their cardiorespiratory fitness, with two further visits for the experimental manipulation. At initial visit, participants performed a maximal incremental exercise test to establish their maximal oxygen uptake following a standard laboratory protocol [14]. During the test, participants' VO_2 was measured on a breath-by-breath basis using an online gas analyser (JAEGER MasterScreen; CareFusion GmbH, Germany). After completing the maximal incremental test, participants performed a 10-minutes time-trial in order to familiarised with protocol. The shorter duration of the familiarization test (with respect to the proper experimental time-trial) might be seen as a limitation of our study. However, two reasons motivated our choice: 1) our participants were

experienced cyclists used to performing this type of (sustained) physical effort, and given their expertise, the purpose was that of familiarize them with the laboratory setting testing procedure, 2) we were mindful that the 10' test was performed after the maximal incremental exercise test from which participants were already fatigued.

On arrival at the laboratory for visit 2 and 3 (Fig 1 for protocol schematic), participants completed a Profile of Mood States Questionnaire (POMS), and a visual analogue scale (VAS) concerning perceived activation, mental and physical fatigue. After completing the questionnaires, participants consumed either tramadol or placebo as outlined below. The experimental sessions were completed at the same time of the day (±1 h). The time-trial commenced 120 min following ingestion of the tramadol or placebo capsule (*see experimental manipulation below*). Before the beginning of the time-trial, the participant's EEG was recorded as a baseline measure and throughout the session. Next, participants performed a 10 min warm-up at 100 watts, followed immediately by a 20-min cycling time-trial on a cycle ergometer (SRM, Julich, Germany). Participants adjusted saddle and handle bar height and length, and it was kept for all sessions. The time-trial was conducted in a dimly-illuminated, sound-attenuated faraday cage. Convective cooling was provided by one fan (2.5 m/s wind speed) located 100cm from the ergometer. Participants were instructed to maintain the highest average power possible during the time-trial and were freely able to change gearing and cadence throughout. Participants were aware of the elapsed time, but did not have feedback on performance (wattage and heart rate) during, or after the time-trial. Heart rate was measured continuously throughout the protocol (V800, Polar Electro, Finland). Immediately after the time-trial participants were asked to rate their average perceived exertion during the preceding exercise. Then, participants completed 10 min cool-down (60 watts), following which another EEG recording was taken. Finally, the POMS and VAS were completed again.

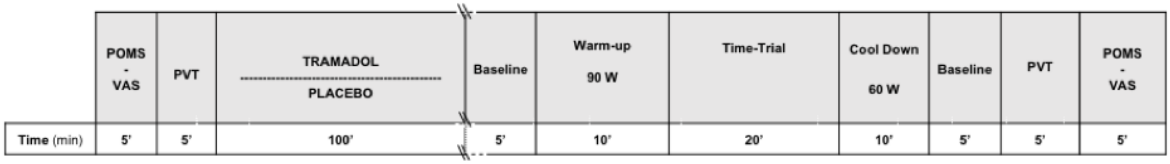

Fig 1 Experimental session's schematic protocol

As we did not find any effect of gender in Experiment 1, and given the difficulty of finding a large enough sample of females, we only recruited and tested males in Experiment 2**.** One participant only completed visit 1, and data from another was removed due to data acquisition issues, meaning

that the final sample for Experiment 2 was n = 28: age 25 (5) years, weight 73.2 (7.7) Kg; $VO_{2max:}$ 54.1 (5.7) ml/min/kg. The procedure of the Experiment 2 was the same as that of Experiment 1, except for the following: participants completed an oddball sustained attention task during the 20 min time-trial with the purpose of assessing sustained attention during exercise. Participants completed a visual three-stimulus oddball paradigm based on that used by Sawaki and Katayama [15] while performing the 20 min time-trial.

Participants consumed either a single oral dose of 100 mg of tramadol or placebo (microcrystalline cellulose) with water. The tramadol dose used in this study has been demonstrated to have effect on μ-opioid receptor (compared with placebo), with a mean time to maximum plasma concentration of 156 min (range: 87-208 min; [1]). Importantly, Bastami et al. [1], showed good tolerability to adverse events with this dose. The Hospital Pharmacology Section of the University of Granada prepared the tramadol and placebo oral doses. Tramadol and placebo were made following the good manufacturing practice (GMP) audited and approved by Spanish authority (AEMPS). The randomization was performed on a 1:1 balanced allocation where a code was assigned for tramadol and placebo to each patient in different visit order. Only a pharmacist who was not involved in the experimental work of this study knew the participant randomization. Tramadol and placebo were made in dark red hard gelatine capsules, which prevented the possibility to see the contents. Each capsule was packed in a monodose blister with the patient code and visit number in the information label. No less than 7 days were allowed between experimental sessions to allow for washout time and recovery.

We used the Spanish adapted version of the POMS [16], which has been used extensively for the assessment of mood in the sport and exercise environments. This questionnaire has 58 items and the factor structure representing six dimensions of the mood construct: Tension, Depression, Anger, Vigour, Fatigue and Confusion. Participants answered the items on a 5-point Likert scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Raw scores were transformed following the standard point table [16].

The VAS to rate participants' perceived activation, perceived mental and physical fatigue, ranging from 0 (low) to 100 (high) in response to the following questions: (a) "What is your activation level now?" (b) "What is your physical fatigue level now?" and (c) "What is your mental fatigue level now? At the end of the session, participants also rated the following question "how would you rate the overall mental load for this experimental session?". Immediately after the time-trial participants were asked to rate their average perceived exhaustion (RPE) using the 6-20 Borg scale.

An oddball task was designed to measure sustained attention by the random presentation of a sequence of visual stimuli on a computer screen situated at 100 cm from the participants' head

and at their eye level**.** A total of 600 stimuli were presented, consisting of frequent blue circle, rare blue circle, and rare red square with probabilities of .80, .10, and .10, respectively via use of computer software (E-Prime, Psychology Software Tools, Pittsburgh, PA, USA). The task lasted approximately 18 minutes, starting two minutes after the beginning of the time-trial. The small blue circle (1.15º x 1.15º) was considered as the standard stimulus. The blue circle that was slightly larger than the standard circle (1.30º x 1.30º) was defined as target 1. Finally, the rare red square (2.00º x 2.00º) was defined as target 2. Each trial begun with the presentation of a blank screen in a black background for 1200 ms. Then, the stimulus was presented in the centre of the screen in a random time interval (between 0 and 800 ms) during 150 ms (Fig 2). Participants were required to respond to both target 1 and target 2 with their thumb finger of their dominant hand by pressing a button connected to the cycle ergometer handlebar, and not to respond to the standard stimuli. Verbal and written instructions were given to the participant prior to the start of the oddball sustained attention task. Participants were instructed that the main goal of the task was to be as accurate as possible. A brief familiarization of the task was included in the screening visit. For each stimulus, the RT (in ms) and response accuracy (percentage of correct responses) were recorded.

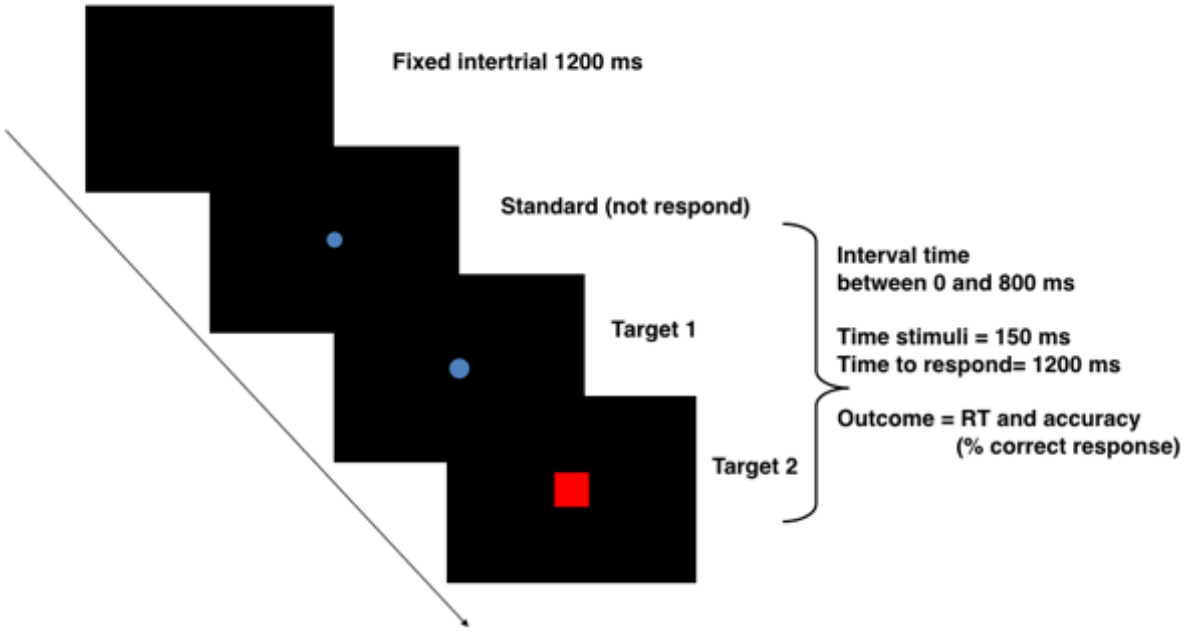

Fig 2 Schematic representation of the oddball sustained attention task

At this point, we would like to note that, while the POMS used in the present study has shown a high reliability (Cronbach alpha = 0.90) [16], we do not have a measure of reliability for the particular VAS and oddball tasks used in our study. The lack of reliability may suppose a limitation in the present investigation, but, generally, oddball tasks show an interclass correlation coefficient higher than 0.75 [17], and the VAS a Cronbach alpha higher than 0.90, showing high test-retest reliability [18,]. In any case, the purpose of these tasks were to compare performance in

within-participants experimental conditions and not to compare participants' scores with a normalized scale.

EEG data were recorded at 1000 Hz using a 62-channel actiCHamp System (Brain Products GmbH, Munich, Germany) with active electrodes positioned according to the 10-20 EEG International System and referenced to the Cz electrode. The cap was adapted to individual head size, and each electrode was filled with Signa Electro-Gel (Parker Laboratories, Fairfield, NJ) to optimize signal transduction. Participants were instructed to avoid body movements as much as possible, and to keep their gaze on the centre of a computer screen during the measurement. Electrode impedances were kept below 10 kΩ. EEG pre-processing was conducted using custom Matlab scripts and the EEGLAB [19] and Fieldtrip [20] Matlab toolboxes. EEG data were resampled at 500 Hz, bandpass filtered offline from 1 and 40 Hz to remove signal drifts and line noise, and re-referenced to a common average reference. Horizontal electrooculograms (EOG) were recorded by bipolar external electrodes for the offline detection of ocular artefacts. Independent component analysis was used to detect and remove EEG components reflecting eye blinks [21].

Electrodes presenting abnormal power spectrum were identified via visual inspection and replaced by spherical interpolation. Processed EEG data from each protocol time period (baseline-pre, warm-up, time-trial, cool-down, baseline-post) were subsequently segmented to 1-s epochs. The spectral decomposition of each epoch was computed using Fast Fourier Transformation (FFT) applying a symmetric Hamming window and the obtained power values were averaged across protocol time periods.

Task-evoked spectral EEG activity was assessed by computing event-related spectral perturbations in epochs extending from –500 ms to 500 ms time-locked to stimulus onset for frequencies between 4 Hz and 40 Hz. Spectral decomposition was performed using sinusoidal wavelets with 3 cycles at the lowest frequency and increasing by a factor of 0.8 with increasing frequency. Power values were normalized with respect to a −50 ms to 0 ms pre-stimulus baseline and transformed into the decibel scale (10*log10 of the signal).

All analyses were completed using statistical non-parametric permutation tests with a Monte Carlo approach [22]. These tests do not make any assumption of the underlying data distribution, are unbiased, and as efficient and powerful as parametric statistics [23]. When statistical significance ($p < 0.05$) was found, values were corrected by the false discovery rate method. Subsequently, the effect of experimental condition (tramadol vs. placebo) on: Experiment 1 - cycling time trial power output and heart rate; and Experiment 2 - cycling time trial power output, heart rate, and RT and accuracy in the oddball task were analysed using a within-subject design condition (tramadol, placebo). Data from POMS, and VAS, were analysed using a condition (tramadol, placebo) and time point (pre, post) within-subject design.

EEG spectral power main effects of condition (tramadol, placebo) were separately tested for significance at each protocol time period. In the absence of strong a priori hypotheses, we used a stepwise, cluster-based, non-parametric permutation test [24] without prior assumptions on any frequency range or area of interest. The algorithm performed a t-test for dependent samples on all individual electrodes x frequencies pairs and clustered samples with positive and negative t-values that exceeded a threshold based on spatial and spectral adjacency. These comparisons were performed for each frequency bin of 1Hz and for each electrode without a priori assumptions on the frequency range or region of interest. Cluster-level statistics were then calculated by taking the sum of the t-values within each cluster. The trials from the two datasets (tramadol, placebo) were randomly shuffled and the maximum cluster-level statistic for these new shuffled datasets was calculated. The above procedure was repeated 5000 times to estimate the distribution of maximal cluster-level statistics obtained by chance. The two-tailed Monte-Carlo p-value was determined by the proportion of random partitions that resulted in a larger test statistic than the original. A p-value of the original cluster statistic smaller than the critical Monte-Carlo p-value indicated significant differences between the two datasets.

In Experiment 2, event-related spectral perturbation main effects of condition (tramadol, placebo) for each stimulus of the odd-ball task (target 1, target 2 and standard) were also analysed by applying the cluster-based permutation test. In order to reduce the possibility that the type II error rate was inflated by multiple comparisons correction, we set a priori criteria of collapsing data into four frequency bands: Theta (4–8 Hz), Alpha (8–14 Hz), lower Beta (14–20 Hz) and upper Beta 1 (20–40 Hz). To avoid an overlap with behavioural responses, we also limited the time windows of interest to the first 300 ms and 500 ms after the stimuli onset (based on average behavioural response times) for target and standard trials, respectively.

Results

In Experiment 1, the average power output during the 20-min time-trial (Fig 3A) was higher under tramadol condition than under placebo condition (220 W [95%CI = 203 – 240 W] vs. 209 W [95%CI = 192 – 228W] for tramadol and placebo, respectively; $p < 0.01$). An additional analysis revealed that the effect of tramadol did not depend on participants' gender: $t = 1.107$, $p = 0.83$ (critical t-score: ± 2.177).

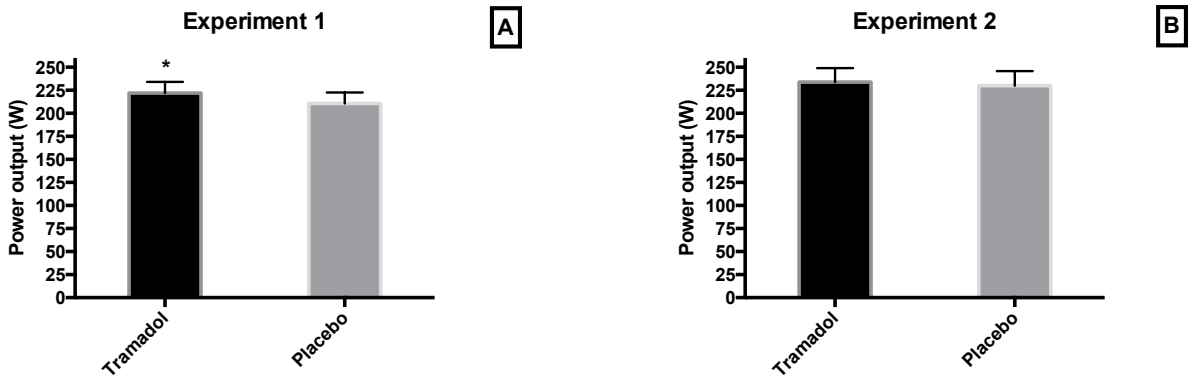

Fig 3 Power output (watts) profile for Experiment 1 (A) and 2 (B). * $p < 0.05$

The average heart rate demonstrated a significant difference between conditions (166 beats.min^{-1} [95%CI = 162 – 170 beats.min^{-1}] vs. 162 beats.min^{-1} [95%CI = 153– 166 beats.min^{-1}] for tramadol and placebo, respectively; $p < 0.01$).

The POMS data demonstrated a significant interaction between condition and time point for fatigue ($p = 0.03$), confusion ($p < 0.01$) and tension ($p < 0.01$). Under the tramadol condition, participants showed a higher fatigue (M = 52, 95%CI = 48 - 55 vs. M = 47, 95%CI = 44 - 49); $p < 0.01$) and confusion (M = 41, 95%CI =38 - 44 vs. M = 38, 95%CI = 36 - 39); $p < 0.01$) after the time-trial, while no difference where found before the time-trial for fatigue (M = 42, 95%CI = 39 - 45 vs. M = 40, 95%CI = 38 - 42), $p > 0.05$) and for confusion (M = 39, 95%CI = 37 - 40 vs. M = 38, 95%CI = 37 - 39); $p < 0.05$). There were trends for lower tension before (M = 35, 95%CI = 33 - 37 vs. M = 38, 95%CI = 35 - 39) tramadol vs. placebo, respectively; $p = 0.06$), but not after the time-trial (M = 35, 95%CI =32 - 36 vs. M = 34, 95%CI = 32 - 35), for tramadol and placebo, respectively; $p > 0.05$). The anger index showed a main effect for time point ($p < 0.01$) with higher values before the time-trial (M = 38, 95%CI = 37 – 40 vs. M = 39, 95%CI = 36 – 39), but no effect for condition or interaction between the factors. No other POMS factors (depression and vigour) demonstrated significant changes with condition or time point (ps > 0.05).

Post time-trial RPE did not demonstrate any significant differences between conditions ($p > 0.05$). VAS Mental Load demonstrated a trend for an interaction between condition and measure. Specifically, after the time-trial participants had trend for a higher mental fatigue in the tramadol vs. placebo condition (M = 34, 95%CI = 24 - 44 vs. M = 22, 95%CI =16 - 28), respectively; $p = 0.056$). The main effect for time point was not significant ($p > 0.05$).

The Activation and Fatigue indexes demonstrated a significant main effect of time point (Activation: M = 51, 95%CI = 44 - 57 vs. M = 60, 95%CI = 54 - 66; $p < 0.01$. Fatigue: M = 21, 95%CI = 13- 28 vs. M = 45, 95%CI = 36 - 52; $p < 0.01$). Before vs. after the time-trial respectively), while the main effect for condition and the interaction between both factors did not

reach significance ($p > 0.05$). Finally, the cognitive load of the session was not significantly different between conditions ($p > 0.05$).

The analysis of tonic spectral power showed a significant main effect of condition ($p < 0.01$) for the baseline period. One cluster (frequency-localization) was found and was statistically significant: a global cluster (51 electrodes) in the beta band (13-40 Hz). The analysis revealed an overall increase in the power of frequencies in the tramadol condition with regard to the placebo (Table 1).

Table 1 Power spectral values (10^{+}log10 (V2/Hz)) for tramadol and placebo in Experiment 1 and 2.

	Experiment 1		
Period	**Tramadol**	**Placebo**	***p* Value**
Baseline-pre 13-40 Hz	 38	 37	 $p < 0.01$
Warm-up 7-10 Hz	 43	 42	 *p = 0.01*
	Experiment 2		
Baseline-pre 9-15 Hz	 40	 40	 $p < 0.01$
Warm-up 3-6 Hz 26-33 Hz	 45 41	 46 43	 $p < 0.01$ $p = 0.02$
Cool-down 1-9 Hz 12-36 Hz	 47 39	 48 39	 *p = 0.01* $p < 0.01$
Baseline-post 3-7 Hz	 41	 42	 *p = 0.01*

There was a significant main effect of condition ($p = 0.01$) for the warm-up period. One cluster was statistically significant: a 33 electrodes cluster in the alpha band (7-10 Hz). The analysis revealed an overall increase in the power of frequencies in the tramadol condition in comparison to the placebo condition. There were no statistically significant terms in the analysis of the EEG data from the time-trial, cool-down and baseline-post phases ($p > 0.05$).

In Experiment 2, one participant only completed visit 1, and data from another was removed to due data acquisition issues meaning that the final sample was n = 28 for Experiment 2. The power output during the time trial was not significantly different between conditions see (Fig 3B): tramadol (234 W [95% CI = 218– 248 W]) vs. placebo (230 W [95%CI = 215– 246 W] $p > 0.05$).

The main effect of condition did not reach statistical significance for the heart rate: tramadol 176 beats.min^{-1} [95%CI = 172 – 179] vs. placebo (175 beats.min^{-1} [95%CI = 170 – 179]; $p > 0.05$.

Analysis of the POMS demonstrated a main effect of time point for the factor anger and fatigue ($p < 0.05$). Participants showed lower anger (M = 42, 95%CI = 40 - 44 vs. M = 40, 95%CI = 38 - 42) and higher fatigue (M = 44, 95%CI = 41 - 46 vs. M= 51 95%CI = 48 - 53), after the time-trial. None of the other POMS items reached statistical significance ($p > 0.05$).

There were no differences in post time-trial RPE between conditions ($p > 0.05$). An overall main effect of time point was found for fatigue and mental load in the VAS. Specifically, a higher mental fatigue (M = 31, 95%CI = 21 - 40 vs. M = 54, 95%CI = 47 - 60; $p < 0.01$) and higher mental load (M = 25, 95%CI = 17 – 32 vs. M = 44, 95%CI = 36 - 52; $p < 0.01$) were found after the time-trial. None of the others items in the analysis reached significance ($p > 0.05$).

In the Oddball task, there were no significant differences between conditions for the target1, target2 or standard stimuli, for RT and accuracy (all ps > 0.05).

The analysis of tonic spectral power revealed a significant main effect of condition ($p < 0.01$) for the baseline-pre-period. One cluster (frequency-localization) was found and was statistically significant: a global cluster (41 electrodes) in alpha band. The analysis revealed an overall increase in the power of frequencies in the placebo condition with regard to tramadol. There was a significant main effect of condition ($p < 0.01$) in the warm-up period. Two clusters were statistically significant: one cluster (17 electrodes) in the 3-6 Hz band ($p = 0.01$), and one cluster (5 electrodes) in the 26–33 Hz band ($p = 0.02$). The analysis revealed an overall increase in the power of frequencies in the placebo condition in comparison to the tramadol condition (Table 1).

The main effect of condition during the time-trial was not significant ($p>0.05$). There was a significant main effect of condition ($p < 0.05$) for the cool-down period. Two clusters were statistically significant: one cluster (29 electrodes), in the (1–9 Hz) delta and theta band ($p < 0.01$); and one global cluster (41 electrodes) in (12–36 Hz) beta band ($p < 0.01$). Similar to other period, the analysis revealed an overall increase in the power of frequencies in the placebo condition. In the baseline-post period we found a main effect of condition. One cluster was found (29 electrodes) and was statistically significant ($p = 0.01$) in the theta band. Similar to other periods, the analysis showed an increase in the power for placebo compared to tramadol.

The event-related spectral perturbation (stimulus-locked) analysis in Experiment 2 showed a main effect of condition in the alpha band for target 1, with a cluster (15 electrodes) between 118-224 ms after the onset of the target 1 ($p < 0.01$; see Fig 4 A- B). Alpha frequency band exhibited a lower spectral power in the tramadol condition with regard to the placebo condition. The Lower Beta band analysis showed a significant cluster (24 electrodes) between 136-230 ms after the onset of target 1 ($p < 0.01$). Lower Beta frequency band exhibited a higher spectral power in placebo

condition with regard to the tramadol condition (see Fig 4C). The analysis of the other frequency bands for target 1, target 2 and standard trials yielded no significant effects ($p > 0.05$).

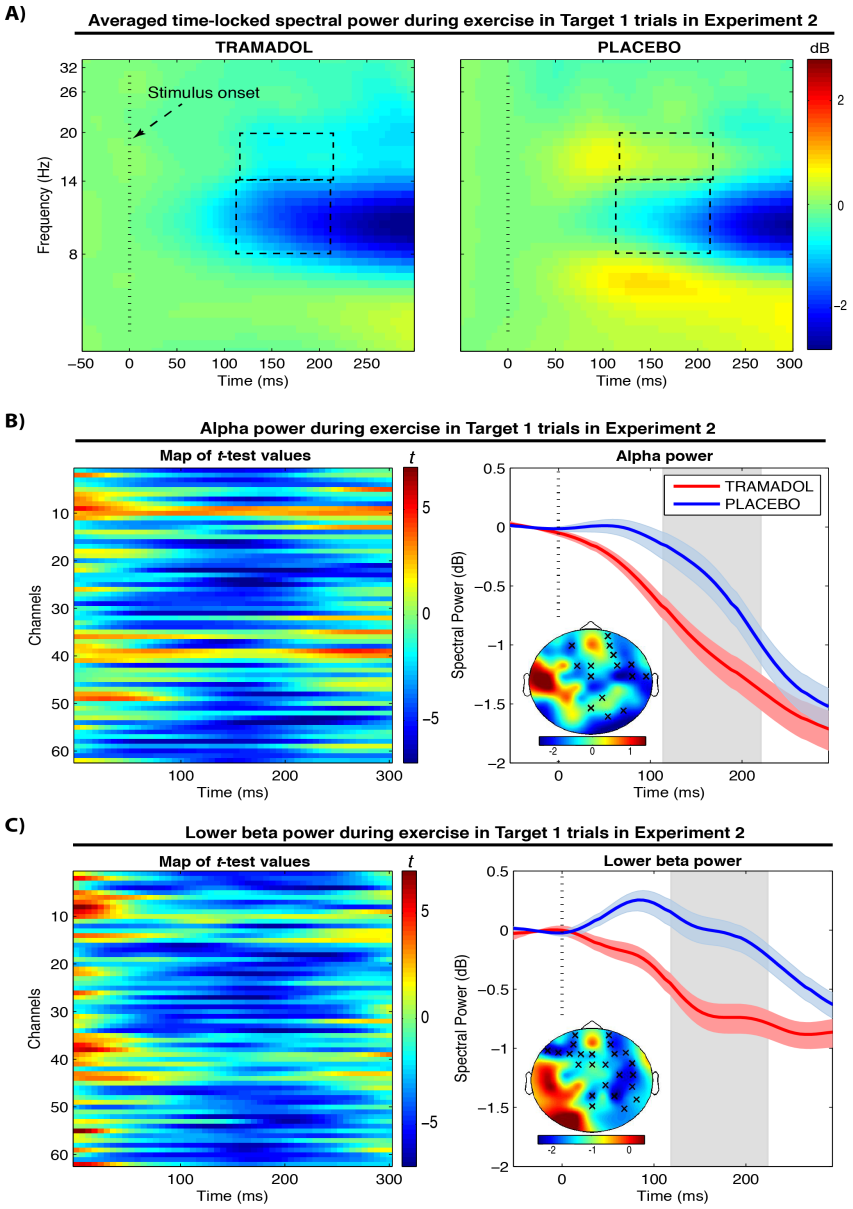

Fig 4 A Event-related spectral perturbations time-locked at Target 1 of the oddball sustained attention task. Grand averages are illustrated separately for each condition (tramadol, placebo). The enclosed areas denote significant clusters of channels and time with $p < 0.025$**. B** Main effect in event-related alpha frequency perturbations time-locked at target 1 of the oddball sustained attention task. Left panel: Non-Parametric paired t-test colormap comparing the relative power for the alpha frequency band across time (x-axis) and channels (y-axis); right panel: grand average spectral power curves showing the main effect between condition (tramadol, placebo) in the alpha frequency band. The "x" marks in the topographical map highlight the 15 electrode sites included in the significant cluster. Three electrode sites are not represented as they were present for less than 25% of the total duration of the cluster. The grey region denotes the latency range (118-224 ms) of the significant main effect between conditions. Red and blue shaded areas represent 95% confidence intervals. **C** Main effect of condition in event-related lower-beta frequency perturbations time-locked at target 1 of the oddball sustained attention task. Right panel shows grand average spectral power curves indicating the main effect of condition at the lower-beta frequency band. The topography depicts t-test distribution across surface localization, showing the 24 electrode sites included in the significant cluster. The grey region denotes the latency range (136-230 ms) of the significant main effect between conditions.

Discussion

To the best of our knowledge, this is the first study to investigate the effect of tramadol on cycling performance, sustained attention and brain dynamics in trained cyclists. Data from Experiment 1 revealed that tramadol improved 20 min cycling time-trial performance by ~5%. In contrast, there was no difference in average power output between tramadol and placebo condition in Experiment 2. Although no effect of tramadol was found on behavioural performance in the sustained attention tasks, EEG time-frequency (stimulus-locked) analysis showed effects of tramadol on brain functioning related to stimulus processing.

Tramadol allowed participants to sustain a higher power and greater cardiorespiratory stress (higher heart rate) during the 20-min time-trial than in the placebo condition in Experiment 1. However, the RPE following the time-trial was similar between both substance conditions. Similar results have been reported with other analgesics. For instance, previous research has shown that paracetamol improves performance in a 10-mile cycling time trial compared to placebo in the absence of a reduction in perceived pain or perceived exertion [3]. In another study, Foster et al. [25], also found that paracetamol improved performance compared to placebo. However, in this study testing repeated sprint ability, the authors concluded that paracetamol increased the level of performance due to an increase in participant's normal pain threshold. In the present study, although no differences were found in perceived exertion, we cannot ensure that pain perception was modulated by tramadol, since we did not ask participants to rate it. Interestingly, in Experiment 2, the effect of tramadol on time-trial power output was not significant. The reason for these divergent results between Experiment 1 and 2 is uncertain (see below for further discussion on this issue).

We only found an effect of tramadol on the POMS items for confusion and fatigue in Experiment 1. In both cases, participants showed a higher score after the time-trial with tramadol. However, it is uncertain whether tramadol caused higher fatigue and confusion, or whether these higher rating were a consequence of the greater physical effort achieved during the time-trial.

The oddball task was chosen to test the hypothesis of whether tramadol may impair cognitive function during cycling. This oddball task tests participant's ability to discriminate between a standard (frequent and irrelevant) and target (rare and infrequent) stimuli [15]. These continuous discriminations between monotonous frequent information and relevant infrequent stimuli are characteristic of those encountered in a cycling peloton (e.g., avoiding a pothole in the road or sudden breaking in front). Our hypothesis was that tramadol would impair attention level and participants would perform worse in the oddball task. However, RT and accuracy results did not show significant differences between conditions for any of the stimuli. Nevertheless, EEG data

did reveal an interesting pattern of results in relation to (brain) event-related activity following tramadol ingestion.

Specifically, there was target-locked higher suppression of the alpha activity (i.e., lower activity) and overall reduced beta frequency after tramadol intake with respect to the placebo condition. A previous study using a similar visual oddball task [26] also found a greater alpha suppression for the odd target stimuli that was interpreted as a higher mental effort to detect infrequent targets. Hence, in our study, the higher alpha suppression under tramadol condition may be interpreted as the result of participants allocating more attentional resources than in the placebo condition (which enabled them to achieve similar behavioural performance). This higher mental effort may have affected the cyclists' physical performance during the time trial, which might explain the divergent results between Experiment 1 and 2 [27] in terms of power output. Hence, while the cognitive load induced by the oddball task might have interacted with substance intake, modulating the effect of tramadol on physical performance.

Due to the analgesics properties of tramadol, it might have been expected that EEG amplitude was greater in alpha and beta bands, since a decrement in attention has been reported after the overall increase in these bands [28]. However, our EEG results present conflicting findings, as opposite results were found in Experiment 1 and 2. In Experiment 1, we found a higher spectral (tonic) power in the tramadol condition (at baseline-pre and warm-up), while in Experiment 2, the power spectral was higher in the placebo condition (at baseline-pre, post, warm-up and cool-down). Indeed, the effect of opioids at the EEG level is not clear in the previous literature as some have reported an increase in these frequencies band [29], whilst others have found the opposite effect [6].

Conclusion

The results of Experiment 1 showed that tramadol improves performance in a 20 min cycling time-trial, although the failed replication in Experiment 2 points to an influence of a concurrent cognitive task on the potential manifestation of the tramadol effect at the physical performance level. Tramadol does not seem to impair (behavioural) cognitive performance in the ability to maintain attention during exercise, although it may influence information processing as highlighted by EEG time-frequency data. It appears then that the presence of tramadol on the WADA's monitoring program seems reasonable as far as performance enhancement is concerned. Even though the present findings have to be considered with caution (as this is the first empirical approach to this issue), they open interesting venues for future research on this relevant topic.

Practical applications

Tramadol may improve cycling time-trial performance.

Tramadol influences information processing related to sustained attention at the brain level, although it was not translated into an impaired behavioural performance.

Anti-doping authorities may reconsider tramadol's status.

Acknowledgments

The authors thank Antonio Salmerón García for manufacturing the tramadol and placebo capsules and Emilio G. Cabrera for the supervision of the clinical trial.

This project was supported by grants from the World Anti-doping Agency (WADA) (REF:15C01DS) to Daniel Sanabria, Mikel Zabala, James Hopker, Darías Holgado and Thomas Zandonai, from the Spanish Ministerio de Economía, Industria y Competitividad- PSI2016-75956-P- to Daniel Sanabria and Mikel Zabala, a predoctoral grant from the Spanish Ministerio de Economía, Industria y Competitividad (BES-2014-069050) to Luis Ciria, and a Spanish "Ministerio de Educación, Cultura y Deporte" predoctoral grant (FPU14/06229) to Darías Holgado.

The authors have no potential conflicts of interest that are directly relevant to the content of this manuscript. The authors alone are responsible for the views expressed in this publication and they do not represent the decisions, policy or views of the World Anti-Doping Agency. WADA approved the final version of the manuscript. Others funding agencies were not directly involved in the data collection, data analysis or approval of the final version.

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Chapter 2

Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: Evidence from oscillatory brain activity and power output.

Holgado, D., Zandonai, T., Ciria, L. F., Zabala, M., Hopker, J., & Sanabria, D. (2019). Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance : Evidence from oscillatory brain activity and power output. *PLoS ONE*, *14*(2), 1–13. https://doi.org/10.1371/journal.pone.0210873 **JCR Q1 IF:2.76**

Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: Evidence from oscillatory brain activity and power output.

TDCS, self-paced cycling performance and brain oscillatory activity.

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DH, TZ, JH, MZ and DS designed the study; DH and TZ collected the data; DH and LC analysed the data; DH wrote the manuscript under the supervision of DS; DH and LC prepared the figures. All authors reviewed the manuscript before submission. DS coordinated the research.

Acknowledgment

The authors thank Newronika S.L. for lending their tDCS device. The company was not involved in the study.

This project was supported by grants from from the Spanish Ministerio de Economía, Industria y Competitividad-PSI2016-75956-P- to Daniel Sanabria and Mikel Zabala, a predoctoral grant from the Spanish Ministerio de Economía, Industria y Competitividad (BES-2014-069050) to Luis Ciria, and a Spanish "Ministerio de Educación, Cultura y Deporte" predoctoral grant (FPU14/06229) to Darías Holgado. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Abstract

Objectives: To test the hypothesis that transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (DLPFC) influences performance in a 20 min time-trial self-paced exercise and electroencephalographic (EEG) oscillatory brain activity in a group of trained male cyclists.

Design: The study consisted of a pre-registered (https://osf.io/rf95j/), randomized, sham-controlled, single-blind, within-subject design experiment.

Methods: 36 trained male cyclists, age 27 (6.8) years, weight 70.1 (9.5) Kg; $VO_{2max:}$ 54 (6.13) $ml.min^{-1}.kg^{-1}$, Maximal Power output: 4.77 (0.6) W/kg completed a 20 min time-trial self-paced exercise in three separate sessions, corresponding to three stimulation conditions: anodal, cathodal and sham. tDCS was administered before each test during 20 min at a current intensity of 2.0 mA. The anode electrode was placed over the DLPFC and the cathode in the contralateral shoulder. In each session, power output, heart rate, sRPE and EEG (at baseline and during exercise) was measured.

Results: There were no differences ($F = 0.31$, $p > 0.05$) in power output between the stimulation conditions: anodal (235 W [95%CI 222 - 249 W]; cathodal (235 W [95%CI 222 - 248 W] and sham (234 W [95%CI 220 - 248 W]. Neither heart rate, sRPE nor EEG activity were affected by tDCS (all Ps > 0.05).

Conclusion: tDCS over the left DLFC did not affect self-paced exercise performance in trained cyclists. Moreover, tDCS did not elicit any change on oscillatory brain activity either at baseline or during exercise. Our data suggest that the effects of tDCS on endurance performance should be taken with caution.

Keywords

Endurance Performance, Brain stimulation, time-trial, neuromodulation, cognitive performance

Introduction

Self-paced exercise refers to a physical activity in which the effort needs to be evenly distributed and monitored in order to complete the task without reaching premature exhaustion [1]. Performance in self-paced exercise is undoubtedly related to the functioning of peripheral body systems, such as the muscles, heart, lungs etc., as well as the brain. In this respect, self-pacing during exercise is a challenging cognitive task [2], as it requires constant control and monitoring of internal (e.g., heart rate) and external inputs (e.g., a bump on the road while cycling), while maintaining the goals of the task (e.g., completing a set distance as fast as possible). In other words, self-paced exercise can be regarded as an executive task, with high demands of self-control, goal-monitoring and inhibition [2].

Research in cognitive neuroscience has long pointed to the prefrontal cortex as a key brain area involved in executive processing [3]. Interestingly, the few neuroimaging studies testing participants while exercising have shown activation of the prefrontal cortex, together with the expected sensory-motor recruitment [4,5], which reinforces the hypothesis of the crucial role of executive processing on self-paced exercise. It has been proposed that the prefrontal cortex acts as a control structure by integrating central and peripheral information during exercise, exerting top-down control. The prefrontal cortex would be responsible for merging afferent signals together with inputs provided by the anterior cingulate cortex and the orbitofrontal cortex [6], which has been related to motivational and emotional processing. Therefore, the rationale of the present study was that anodal stimulation of the prefrontal cortex via transcranial direct current would improve self-paced exercise performance, supporting previous evidence (see below).

Transcranial direct current stimulation (tDCS) is a non-invasive electrical brain stimulation technique that is able to induce cortical changes by depolarizing (anodal) or hyperpolarizing (cathodal) a neuron's resting membrane potential [7]. Recently, there have been an increasing interest in the use of tDCS to enhance endurance performance [8–10]. For example, Angius et al. [9] and Vitor-Costa et al. [10] found an increased time to exhaustion in a cycling test after acute stimulation of the primary motor cortex (M1). Angius et al. [9] attributed that performance enhancement to a reduction of the perceived effort (RPE), although Vitor-Costa et al. [10] did not find such a reduction perceived exertion. These apparently contradictory results leave open the question of whether tDCS affects people's RPE when stimulating the motor cortex. Meanwhile, Okano et al. [11] found improved cycling performance (greater peak power output) in the anodal condition than in the sham condition after stimulating the temporal cortex of ten trained cyclists. The authors argued that their anodal condition might have influenced activity in the insular cortex, which has been linked to autonomic regulation and to self-perception and awareness of body

sensations [12]. Most of research on the effect of tDCS on endurance performance has hitherto been focused on activation or inhibition of the motor and temporal cortices.

To the best of our knowledge, only two studies have targeted the prefrontal cortex. Lattari et al. [13] found increased exercise tolerance in a time to exhaustion at 100% of the peak power after stimulating the left dorsolateral prefrontal cortex for 20 min in eleven physically active women. This improvement was not accompanied by a reduction in the RPE. Meanwhile, Borducchi et al. [14] found an improvement in cognitive performance and mood in elite athletes of different sport modalities (n = 10) after ten days of anodal stimulation over the left dorsolateral prefrontal cortex, which, according the authors, may contribute to performance gains, greater well-being and faster recovery. However, due to the lack of a control condition (Borducchi et al.) and small sample sizes in their studies (like in almost every previous study on tDCS and sport performance), the above results should be considered with caution.

The present (pre-registered, https://osf.io/rf95j/) research is novel, as it is the first to directly test the hypothesis that stimulation of the prefrontal cortex would affect performance in a 20 min time-trial self-paced exercise bout in trained male cyclists. More precisely, we expected that activation via anodal stimulation would improve performance, whilst inhibition of the prefrontal cortex via cathodal stimulation would impair performance (compared to a sham condition). The indexes of physical performance were the power output during exercise and the RPE after the self-paced exercise. Additionally, we asked participants to perform an executive task [15] after the exercise. The purpose was to test the hypothesis that any change on physical performance produced by the tDCS over the prefrontal cortex would modulate the subsequent (known [16]) effect of exercise on inhibitory control. This is in line with the idea of a bi-directional relationship between exercise, brain and cognition [16], i.e., brain and cognitive functioning influences exercise performance and vice versa. Brain electrical activity was measured at rest, during exercise, and during the cognitive task by recording electroencephalography (EEG) in order to examine the effects of tDCS at brain level. Even though the literature over the effect of tDCS on EEG is scarce and inconclusive [17], we anticipated an increase in the alpha and beta band after stimulation in the anodal condition compared to cathodal and sham condition.

Methods

Following institutional ethical approved by the University of Granada Ethics Committee (287/CEIH/2017), a randomized, sham-controlled, single-blind, within-subject experimental design was conducted on male trained cyclists and triathletes with a reported weekly training of more than 7h/week. All experimental procedures were designed to comply with the Declaration of Helsinki. Before being recruited, participants provided written informed consent having previously read a participant information sheet. All data were entered in a case report form, and

subsequently in a computerized database and stored at the Mind, Brain and Behaviour Research Centre (MBBRC) of the University of Granada. Exclusion criteria was the presence of symptomatic cardiomyopathy, metabolic disorders such as obesity (BMI >30) or diabetes, chronic obstructive pulmonary disease, epilepsy, therapy with b-blockers and medications that would alter cardiovascular function, hormonal therapy, smoking, and neurological disorders, as well as the presence of implanted metal devices (e.g., pacemakers, metal plates or wires).

The method and planned analyses of this study were pre-registered on the Open Science Framework. This was done on June 29, 2017, and can be found at https://osf.io/rf95j/.

Additionally, we considered that a medium effect would be appropriate in terms of the potential future practical application of the findings from this type of research to elite cyclists. Therefore, according to the G*Power software [18], 36 participants were required for a power of .8 and a medium effect size, (partial eta-squared $\eta^2 = .13$) for a 3 conditions (anodal, cathodal, sham) design. During the data collection, two of the participants could not complete the three experimental sessions and were replaced by two other participants. Accordingly, data collection stopped when complete datasets (successful completion of all three condition) were obtained for 36 endurance trained cyclists and triathletes. The physiological characteristics of the participants are (mean and SD): age = 27 (6.8) years, weight = 70.1 (9.5) Kg; VO_{2max} = 54 (6.13) $ml.min^{-1}.kg^{-1}$ and Maximal Power Output: 4.77 (.6) W/kg

Participants visited the MBBRC four times (one screening visit and three experimental sessions). Participants initially attended the MBBRC for a screening visit. After verifying that the participants met the inclusion criteria, they performed a maximal incremental exercise test in order to identify their maximal oxygen consumption using a standard laboratory protocol [19]. After completing the maximal incremental test, participants performed a 10 min time-trial self-paced exercise test in order to familiarize themselves with the protocol to be used in subsequent visits. The shorter duration of the familiarization test (with respect to the proper experimental self-paced exercise) was motivated for the following reasons: 1) our participants were experienced cyclists used to performing self-paced exercise during training and competitions (at high intensity and even for longer durations than that of the experimental self-paced test); 2) most of the participants had already enrolled on previous studies from our lab in which we also used the same test; 3) we were aware that the 10 min test was performed after the maximal incremental exercise test and participants were already fatigued.

After the screening visit, participants attended the lab on three separate occasions to perform the 20 min time-trial self-paced exercise (all procedures were the same, except for the stimulation condition). Participants were asked to refrain from drinking alcohol (48 h abstinence) and caffeine (24 h abstinence) and instructed not to perform any exhaustive exercise in the 48 h before each

experimental session. Participants were also asked to keep their pre-exercise meal the same for every session. The experimental sessions were completed at the same time of the day to avoid diurnal variations. EEG was recorded throughout the session, except for the stimulation period. Before the beginning of the stimulation, we recorded 5 min EEG with open-eyes as a baseline measure. After the baseline measure, we delivered 20 min of tDCS stimulation: anodal, cathodal or sham. The order of presentation of the three experimental conditions was counterbalanced across participants to control for a potential learning effect. Next, we repeated the 5 min baseline EEG measure with open-eyes. After that, participants performed the 20 min self-paced exercise preceded by 5 min warm-up (at 120 watts) on the cycle ergometer (SRM, Julich, Germany). During the data collection, the SRM broke and we had to replace it for a Phantom 5 ergometer (CyleOps, Madison, USA). The Phantom 5 measure the power output using an on-board power meter PowerTap (PowerTap, Madison, USA) with power accuracy of +/- 1.5%. Every participant completed the time-trial self-paced exercise on the same ergometer: seventeen participants completed the trial on the SRM and nineteen on the Phantom 5. Participants were instructed to achieve the highest average power possible during time-trial self-paced exercise and were freely able to change gearing and cadence throughout. Participants were aware of the elapsed time, but they did not have feedback on performance (wattage and heart rate) during, or after the self-paced exercise. Heart rate was measured continuously throughout the protocol (V800, Polar Electro, Finland). Immediately after exercise, we asked the participant to rate their session RPE (sRPE) [20]. Finally, participants completed a 5 min cool-down and the executive task. The interval between the different sessions was at least 48h to allow the full recovery and to minimize carryover effects.

Stimulation was delivered using battery powered DC stimulators (Newronika S.r.l, Milan, Italy) and delivered through a saline soaked pair of surface sponge electrodes (5 x 5 cm). For the anodal (increased excitability) or cathodal (decreased excitability) we targeted the prefrontal cortex. The anode or cathode electrode was placed over F3 area according to the international EEG 10-20 system [21]. The opposite electrode was placed over the contralateral shoulder area in order to avoid the delivery of current on the participant's scalp. Current was set at 2 mA and was delivered for 20 min, which has previously been shown to provoke cortical changes [22]. The sham stimulation (control) was similar to the anodal and cathodal stimulation but the device only provided 2mA for 30s after which was turned off without the participant's awareness. This method replicates the sensory feelings experienced in the tDCS trial (i.e., itching and tingling sensations) and cannot be distinguished from it, whether the stimulation is continued or stopped [23]. The EEG cap was kept over the sponges during stimulation period, but the EEG activity was not recorded. At the end of the session (after completing the cognitive task), participants answered a questionnaire regarding their experience during and after the tDCS sessions [24]. The

questionnaire included a set of 19 items (e.g., did you have itching during the stimulation?) scored on a scale that ranged from 0 (no effect at all) to 4 (severe effect).

Participants completed a modified flanker task [15], via use of computer software (E-Prime, Psychology Software Tools, Pittsburgh, PA, USA), to assess inhibitory control, a form of executive processing after the self-paced exercise. Here, the flanker task involves the response to the direction of a central arrow surrounded by other arrows pointing in the same or opposite direction. Congruent trials consist of a central target arrow being flanked by other arrows that faced the same direction (e.g., <<<<< or >>>>>). The incongruent trials consist of the target arrow being flanked by other arrows that faced the opposite directions (e.g., <<><< or >><>>). Participants pressed a button with their left index finger when the target arrow (regardless of condition) faced to the left (e.g., '<') and a button with their right index finger when the target arrow faced to the right (e.g., '>'). Each trial started with the presentation of a cross (fixation point) that remained on a steady until the appearance of the target arrows 2 seconds later. The target was presented in the middle of the screen for 150 ms and a response window of 1350 ms was allowed. The next trial started 1500 ms after the response. Total task duration was approximately 7-min. Participants completed one block of 160 trials with equal probability for congruent and incongruent trials, randomized across task conditions. A brief familiarization of the task was included in the screening visit. RT (in ms) and response accuracy (percentage of correct responses) for each stimulus were recorded.

EEG were recorded at 1000 Hz using a 30-channel actiCHamp System (Brain Products GmbH, Munich, Germany) with active electrodes positioned according to the 10-20 EEG International System and referenced to the Cz electrode. The cap was adapted to the individual head size for each participant (mean of 57 cm), and each electrode was filled with Signa Electro-Gel (Parker Laboratories, Fairfield, NJ) to optimize signal transduction. Participants were instructed to avoid body movements as much as possible, and to keep their gaze on the center of a computer screen during the measurement. Electrode impedances were kept below 10 kΩ. EEG pre-processing was conducted using custom Matlab scripts and the EEGLAB and Fieldtrip Matlab toolboxes. Each period and stimuli for the analysis were detected by triggers sent through a parallel port from the E-prime software to the EEG recorder. EEG data were resampled at 500 Hz, with a butter filter design and bandpass filtered offline from 1 and 40 Hz to remove signal drifts and line noise, and re-referenced to a common average reference. Horizontal electrooculograms (EOG) were recorded by bipolar external electrodes for the offline detection of ocular artefacts. Independent component analysis was used to detect and remove EEG components reflecting eye blinks. The potential influence of electromyography activity in the EEG signal was minimized by using the available EEGLAB routines [25]. Independent component analysis was used to detect and remove EEG components reflecting eye blinks [26]. Abnormal spectra epochs which spectral power deviated

from the mean by +/- 50 dB in the 0-2 Hz frequency window (useful for catching eye movements) and by +25 or -100 dB in the 20-40 Hz frequency window (useful for detecting muscle activity) were rejected. On average, 2.25 % of epochs per participant were discarded.

All analyses were completed using statistical nonparametric permutation tests with a Monte Carlo approach. These tests do not make any assumption of the underlying data distribution, are unbiased, and as efficient and powerful as parametric statistics. When statistical significance ($p < 0.05$) was found, values were corrected by the false discovery rate method. The effect of experimental condition (anodal, cathodal, sham) on self-paced exercise power output, heart rate and RPE were analyzed using a within-subject design condition.

Spectral power was analyzed using a within-participants' design with the factor of stimulation (anodal, cathodal, sham). Each period (Baseline, Warm-Up, Exercise, Cool-Down) was tested separately for significance. In the absence of strong a priori hypotheses over the frequency range and channels which tDCS may induce a change, we use a stepwise, cluster-based, non-parametric permutation test [27]. The spectral decomposition of each epoch (1s) was computed using Fast Fourier Transformation (FFT) applying a symmetric Hamming window (0.5s) and the obtained power values were averaged across experimental periods.

For the cognitive task, we analyzed the event-related spectral perturbation main effects of stimulation (anodal, cathodal, sham) for each stimulus (congruent, incongruent) by applying the cluster-based approach [28]. In order to reduce the possibility that the type II error rate was inflated by multiple comparisons correction, we set an a priori criteria of collapsing data into four frequency bands: Theta (4–8 Hz), Alpha (8–14 Hz), lower Beta (14–20 Hz) and upper Beta 1 (20–40 Hz). Task-evoked spectral EEG activity was assessed by computing event-related spectral perturbation in epochs extending from -500 ms to 500 ms time-locked to stimulus onset for frequencies between 4 and 40 Hz. Spectral decomposition was performed using sinusoidal wavelets with 3 cycles at the lowest frequency and increasing by a factor of 0.8 with increasing frequency. Power values were normalized with respect to a -300 ms to 0 ms pre-stimulus baseline and transformed into the decibel scale [29].

Results

Side effects

The intervention was well tolerated and participants reported common side effects such as tingling (anodal: 22%, cathodal: 8% and sham: 11%), or "itchy sensation in the scalp (anodal: 30%, cathodal: 8% and sham: 16%).

Exercise performance

The average power output during the time trial self-paced exercise was not significantly different ($F(2,34) = 0.31$, $p > 0.05$) between conditions (see Fig 1): Anodal (234 W [95%CI 222 - 249 W]; Cathodal (235 W [95%CI 222 - 248 W] and Sham (234 W [95%CI 220 - 248 W].

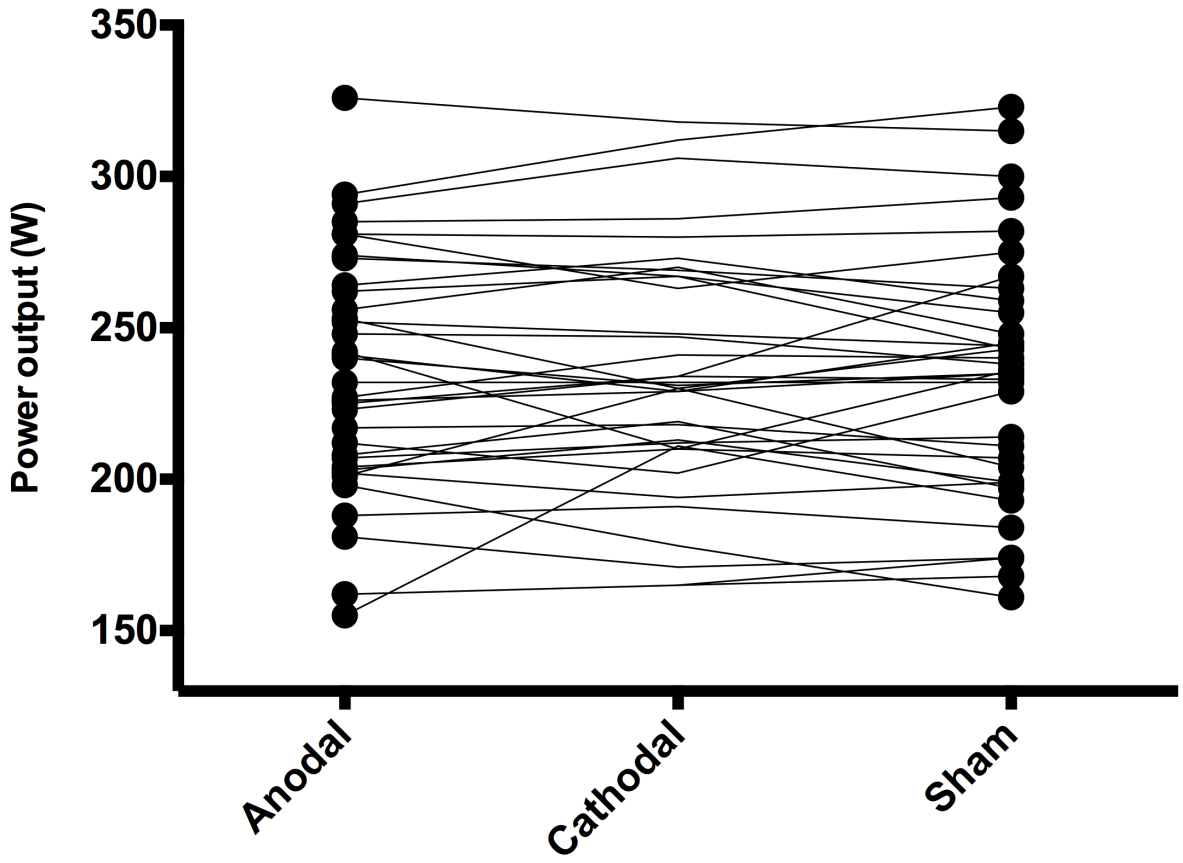

Fig 1. Power output (watts) profile for each participant during the 20-min self-paced exercise.

The heart rate signal for three participants was lost during the 20 min time-trial self-paced exercise, consequently they were removed from the subsequent analysis (n= 33). The average heart rate during the time trial was not significantly different ($F(2,34) = 1.02$, $p > 0.05$) between conditions: Anodal (161 beats min−1 [95%CI 157 - 166 beats min−1]; Cathodal (162 beats min−1 [95%CI 158 - 167 beats min^{-1}] and Sham (162 beats min^{-1} [95%CI 157 - 167 beats min^{-1}].

Post time-trial sRPE did not show any significant differences between conditions: Anodal (17.02 [95%CI 16.5 - 17.5]; Cathodal (17 [95%CI 16.8 - 17.4] and Sham (17.02 [95%CI 16.5 - 17.5], $F(2,34) = 1.69$; $p > 0.05$.

Electrical brain activity (EEG)

Due to excessive noise in the EEG signal, five participants were not included in the EEG analysis (n= 31). The analysis of tonic spectral power (see Fig. 2) did not provide any significant difference (all ps > 0.05) between conditions (anodal, cathodal and sham), and for each period of time (baseline-pre; baseline-post, warm-up, self-paced exercise and cool-down).

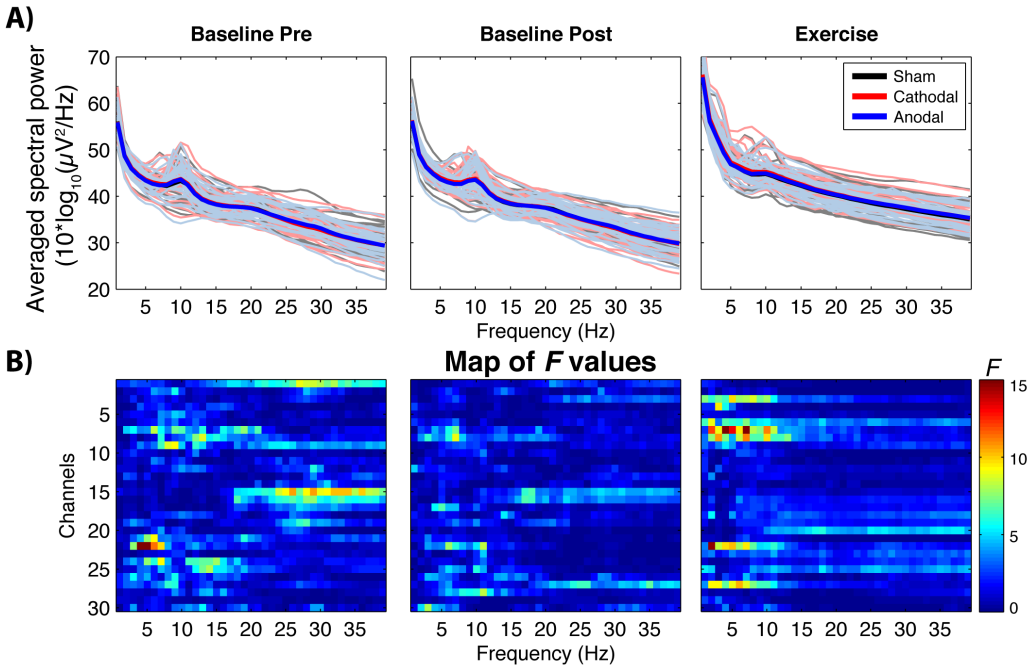

Fig 2. Differences in brain power spectrum as a function of tDCS condition.

A) Average EEG power spectrum across participants among anodal (blue lines), cathodal (red line) and sham (black lines) condition at baseline pre, baseline post and exercise period. The shaded lines denote the average tonic spectral power for each participant and condition (given that there were not significant differences between conditions, the lines tend to overlap). B) Parametric F-test colormap comparing the relative power across frequency (x-axes) and channels (y-axes). Note that the analysis of the other periods (warm-up and cool-down) did not yield significant between-intensity differences.

The event-related spectral perturbation (stimulus-locked) analysis in the flanker task (see Fig. 3) did not reveal any main effect of condition for the congruent or incongruent trial (both ps > 0.05).

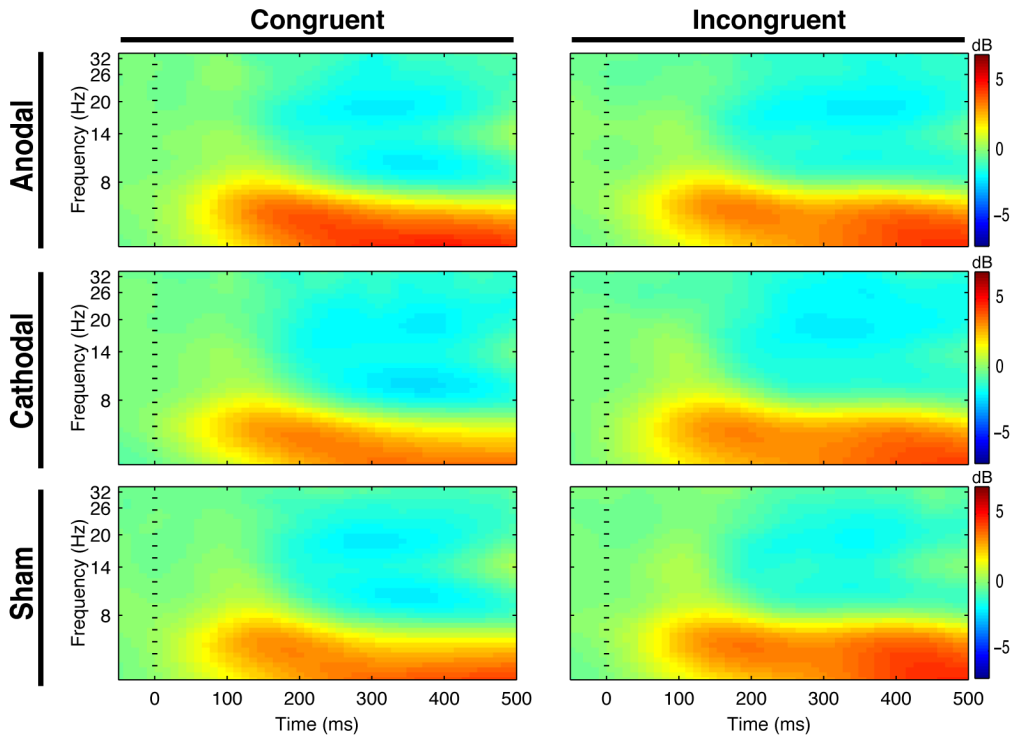

Fig 3. Event-related spectral perturbation during the flanker task.

Time-locked spectral power averaged over all electrodes for each condition. Each panel illustrates time-frequency power across time (x-axes) and frequency (y-axes) for the congruent and incongruent stimuli (blue: decreases; red: increases). Dashed vertical line represents stimulus onset.

Executive task

A main effect of stimulus was reported in the flanker task, with participants being less accurate (M = 98 vs 91 % correct responses; $F(2,34) = 13.17$, $p < 0.01$) and slower (423 vs 515 ms; $F(2,34) = 182.39$, $p < 0.05$) in the incongruent stimulus compared to the congruent stimulus. There were no significant differences between conditions for the congruent and incongruent target, for RT and accuracy ($Fs < 1$, all $ps > 0.05$).

Discussion

To the best of our knowledge, this is the first study testing the influence of prefrontal cortex tDCS' stimulation on self-paced exercise and brain activity during exercise. The main finding of this study was that 20 min anodal or cathodal tDCS (relative to sham) over the left dorsolateral prefrontal cortex did not affect exercise performance or brain electrical activity. Moreover, neither sRPE, EEG or cognitive performance were affected by the stimulation. Our findings indicated that anodal or cathodal tDCS applied over the left dorsolateral prefrontal cortex before exercise did

not modulate exercise performance during a 20-min time-trial self-paced exercise. This finding contrasts the results of the only previous study testing the effect of tDCS on cycling over the same brain area [13], as well as previous studies reporting positive effects of tDCS.

The rationale of our study was that the prefrontal cortex is involved in the control of self-paced exercise, and therefore stimulating it via tDCS would increase performance. In view of our null results, it may be possible that, through experience, self-pacing the effort became a more automatic task for our experienced cyclists, requiring less involvement of brain areas typically linked to executive processing. This may account for the apparent discrepancy of our results with those of the only previous study [13] testing the effect of tDCS over the prefrontal cortex on performance in a cycling task (a time to exhaustion test performed in the cycle ergometer). Indeed, participants in Lattari et al.'s study only reported 3 hours per week of aerobic physical activity the last six months, and hence could clearly not be classified as experienced cyclists. Therefore, the stimulation of the prefrontal cortex, instead of M1 as in the majority of previous positive findings, would explain the lack of effect of tDCS in our experiment.

Another factor that could help explaining our null results refers to the intensity of the stimulation. It is possible that 2 mA (the most commonly used tDCS intensity in this research domain) was not high enough to affect neuronal circuits and hence to modulate exercise performance. Indeed, a study by Vöröslakos et al. [30] suggests that much higher current intensities are necessary to induce observable effects of electric brain stimulation. However, Vöröslakos et al. used transcranial alternating current stimulation (tACS) in their experiment which somewhat limits a direct comparison with studies using tDCS. It could be also possible that an individualized current intensity would be necessary to affect exercise performance due to the high inter-variability across participants (see [31], for discussion on this issue).

The hypothesis that anodal stimulation would increase EEG amplitude was not confirmed in the present study. After the 20 min stimulation, the EEG spectral power was similar across all condition for each period of time. This null effect is in line with the outcome of a review by Horvath et al. [34] who found that tDCS does not appear to modulate EEG power spectrum measures or event-related potential measures. This is also supported by the inconsistence aftereffect of tDCS on brain oscillations reported across studies [32]. Once again, the null effect of tDCS on the EEG signal could be explained by the low intensity of the stimulation. Indeed, using tACS, Vöröslakos et al. [30] found that currents between 4-6 mA should be delivered to modulate EEG amplitude.

The rationale of including the flanker task after the cycling self-paced exercise was that any change in physical performance and brain activity via tDCS would modulate the subsequent influence of cycling on cognitive (inhibition) performance. The lack of differences in physical

exertion, RPE and EEG between the three experimental conditions make reasonable to have found no difference in RT or accuracy as a function of tDCS.

Apart from the above-mentioned alternative explanations, we believe that a key methodological aspect could explain the discrepancy between our null findings and previous published studies, as well as the inconsistencies found in this literature (see [8] for discussion on this issue): the sample size of previous reports. The sample size of the vast majority of the tDCS studies in the Sport Science domain are low. According to a recent review, to date, the average sample size in tDCS' experiment is N=14 [8]. If one assume that there is a true effect of tDCS over exercise performance, by testing 14 participants one would be assuming an effect size of dz=0.81 for a paired-sample two-tailed t-test (anodal vs. sham) and an a priori power of 1-β=.8 [18]. Testing a lower sample size (like in [9,11,13]) would assume an even larger effect size. However, such large effects are very unlikely in the tDCS research domain. For instance, the estimate average effect size for tDCS studies in cognition is dz=0.45 [33]. This would suggest, together with the low reproducibility of tDCS' studies [33,34], that a statistically significant effect from a published tDCS-exercise study with a small sample size (which would not ensure sufficient statistical power) may easily reflect a false positive [35]. In view of our null result, one might wonder whether our study, assuming there is a true small effect of tDCS over self-paced exercise, was also underpowered even if we performed an a priori power analysis (based on an expected medium effect size). In that respect, it is worth noting that, to the best of our knowledge, our study has tested the largest sample size ever in this research domain. At this point, we believe that a meta-analytical review is necessary to unveil the overall effect (if any) of tDCS over exercise/sport performance and the effect of potential moderators (e.g., electrode site). Finally, we believe that the "file drawer effect" (i.e., the tendency to only publish positive outcomes) might be biasing the literature to positive findings [36].

Conclusion

tDCS is an increasingly popular technique used within a wide range of settings, from treatment of neurological disorders, to attempting to improve exercise performance. Our data, however, add further to the mixed evidence in this area, challenging the idea that an acute session of tDCS can improve physical performance. At this point, we believe that research on this topic will benefit from further methodologically sound research in order to accumulate evidence on whether an acute session of tDCS affect sport performance or not.

Practical applications

The use of tDCS is increasing in popularity in sport science

tDCS over the left prefrontal cortex does not improve performance in trained cyclists

tDCS does not seem to change EEG activity at rest or during exercise

Acknowledgments

The authors thank Newronika S.L. for lending their tDCS device. The company was not involved in the study.

Additional information

Data availability: All data can be found in https://doi.org/10.5281/zenodo.1313703

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Chapter 3

The effects of transcranial direct current stimulation on objective and subjective indexes of exercise performance: a systematic review and meta-analysis

Holgado, D., Vadillo, M. A., & Sanabria, D. (2019). The effects of transcranial direct current stimulation on objective and subjective measures of sports performance: A systematic review and meta-analysis. *Brain Stimulation*, 12(2), 242-250. https://doi.org/10.1016/j.brs.2018.12.002. **JCR Q1 IF: 6.12**

The effects of transcranial direct current stimulation on objective and subjective indexes of exercise performance: a systematic review and meta-analysis.

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Abstract

Objective: To examine the effects of transcranial direct current stimulation (tDCS) on objective and subjective indexes of exercise performance.

Design: Systematic review and meta-analysis.

Data Sources: A systematic literature search of electronic databases (PubMed, Web of Science, Scopus, Google Scholar) and reference lists of included articles up to June 2018.

Eligibility Criteria: Published articles in journals or in repositories with raw data available, randomized sham-controlled trial comparing anodal stimulation with a sham condition providing data on objective (e.g. time to exhaustion or time-trial performance) or subjective (e.g. rate of perceived exertion) indexes of exercise performance.

Results: The initial search provided 420 articles of which 31 were assessed for eligibility. Finally, the analysis of effect sizes comprised 24 studies with 386 participants. The analysis indicated that anodal tDCS had a small but positive effect on performance $g = 0.34$, 95% CI [0.12, 0.52], $z = 3.24$, $p = 0.0012$. Effects were not significantly moderated by type of outcome, electrode placement, muscles involved, number of sessions, or intensity and duration of the stimulation. Importantly, the funnel plot showed that, overall, effect sizes tended to be larger in studies with lower sample size and high standard error.

Summary: The results suggest that tDCS may have a positive impact on exercise performance. However, the effect is probably small and most likely biased by low quality studies and the selective publication of significant results. Therefore, the current evidence does not provide strong support to the conclusion that tDCS is an effective means to improve exercise performance.

Keywords

Brain stimulation, exercise, tdcs, sports, physical activity

Introduction

Improving exercise performance represents the daily goal for many athletes. In the increasingly competitive context of sports, athletes are pressed to push their physical boundaries to run faster, increase power output, lift more weight or jump farther. As a consequence, athletes from all levels are willing to use cutting-edge methods to enhance their performance. Elevation training masks [1], iced garments [2] and virtual reality [3] are some remarkable examples. Another technique that is awakening interest in sports is transcranial direct current stimulation (tDCS) [4]. In fact, some companies have started to sell stimulation kits (sometimes in a do-it-yourself fashion) and professional and Olympic athletes have promoted them as an effective means to improve performance [5,6].

tDCS is a non-invasive brain stimulation technique that has been widely used in Neuroscience, as it has been deemed an effective and safe method to induce cortical changes by depolarizing (anodal) or hyperpolarizing (cathodal) neurons' resting membrane potential [7]. In a common tDCS set-up, researchers use two electrodes; one electrode is the target electrode (i.e., deliver the weak current) and another is the reference electrode [8]. The reference electrode is normally placed on the contralateral brain area targeted or away of the head (e.g., in the shoulder) to avoid the delivery of current on the participant's scalp (i.e., extracephalically). Electrodes can be also placed bilaterally to deliver dual stimulation to two parallel brain areas [9]. The electrodes are connected to a battery which delivers a weak electrical current (usually between 1 and 2 mA) through the electrodes, which seems able to cross the scalp. The results of some studies suggest that the effects of tDCS could last up to 90 minutes after only 10-20 minutes of stimulation [7]. However, recently, Vöröslakos et al. [10] suggested that much higher current intensities (> 4.5 mA) might be necessary to be able to cross human's scalp. Note, though, that Vöröslakos et al. used transcranial alternating current stimulation (tACS) in their experiment which somewhat limits a direct comparison with the potential effects of tDCS. Moreover, it has been argued that a higher stimulation intensity in a given brain area may not imply a greater effect [11,12].

Findings to date point to the potential use of tDCS as a tool to enhance performance in the sports context. The rationale behind using tDCS as a tool in sports is that stimulating brain areas related to exercise could boost athletes' physical performance or reduce perceived exertion. For instance, an acute session of tDCS has been shown to improve both single-joint exercise and whole-body endurance [9,13]. However, despite the increasing use amongst researchers, the mechanisms underlying their possible ergogenic effects are far from clear [14,15]. Some authors have argued that tDCS is able to modulate cortical neurons or affective responses, leading to a reduced rate of perceived exertion (RPE) or reduced pain perception. However, the reduction of perceived exertion has not been reported in all cases [16,17].

Given the growing interest in this topic and in light of the inconsistent findings reported in the literature, the aim of the present systematic review and meta-analysis was to synthesize the evidence available so far regarding the impact of tDCS on objective (e.g., time-trial performance) and subjective (e.g., perceived exertion) indexes of exercise performance.

Methods

Literature Search

We used the PRISMA statement [18] as a basis for the procedures described herein. We carried out a literature search in PubMed, Scopus, Web of Science and Google Scholar (most of the journals in the field of sports and neuroscience can be found in any of these databases) using the following terms and Boolean operators: (“tDCS” OR "transcranial direct current stimulation") AND ("exercise" OR "sport" OR "physical activity" OR "physical performance" OR "sport performance"). Searches were limited to papers published in English before July 2018. The reference lists of the retrieved studies were also reviewed to find additional studies that might not have appeared in the databases with our search terms.

Inclusion and Exclusion Criteria

We considered for review any study meeting the following inclusion criteria: 1) available in English; 2) randomized sham-controlled trials; 3) anodal stimulation in any brain region and any type of electrode montage (i.e., either single or bicephalic) was the main stimulation; 4) the main outcome of the study was a measure of exercise performance, such as time to exhaustion (TTE), time to fatigue (TTF), time-trial (TT) performance, total volume of repetition, muscle strength (1 repetition maximum); or a subjective measure of performance, such as rate of perceived exertion (RPE). Studies were excluded following these criteria: 1) participants were symptomatic or in poor health condition; 2) studies were not published in full in a peer-reviewed journal or accessible in an open-access repository with the raw data available.

Study Selection

Fig. 1 summarizes the study selection process. The initial search returned 420 publications. Five additional records were identified as a potentially relevant for this topic via a manual inspection of the reference list of reviews and empirical articles identified in the initial search. All records were then introduced in the Rayyan web service [19] to facilitate the following steps of the study selection. Rayyan is free web application (https://rayyan.qcri.org) designed to facilitate several steps of systematic reviews, like finding and removing duplicate articles, or classifying studies. After identifying 144 duplicate articles, 280 articles were screened by the title and the abstract. Thirty-one full articles were assessed for eligibility and 24 were included in the qualitative analysis. When the potential inclusion of a study was not evident, the article was discussed by all

three authors to reach an agreement. The final selection of all shortlisted articles was approved by the three authors.

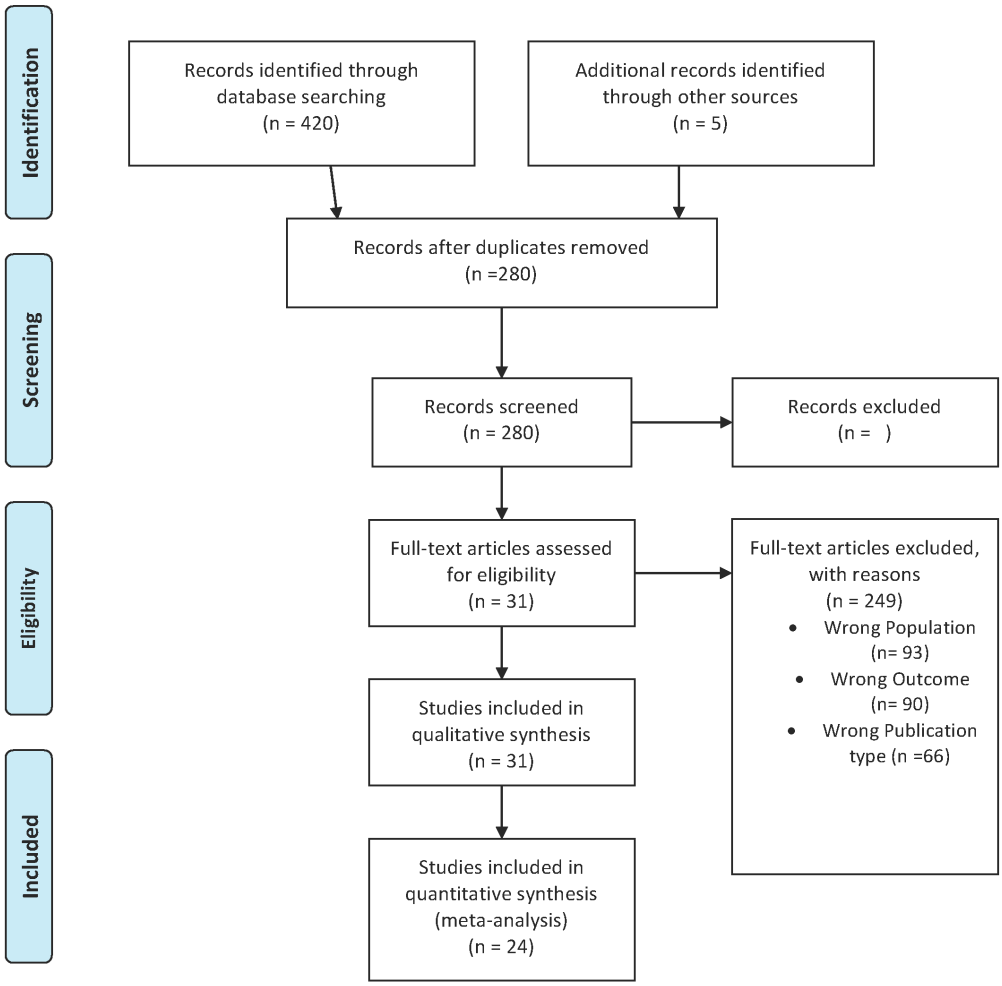

Fig. 1 PRISMA summary of the study selection process

Quality Assessment of Results

We used the Physiotherapy Evidence Database (PEDro) to assess the methodological quality of the 24 studies included in the meta-analysis [20]. Although the original scale includes 11 items,

for our present purposes we ignored item 1 (eligibility criteria), because it does not assess internal quality. Consequently, studies were rated on a 0-10 scale, depending upon the number of items satisfied by each study (10 = study possesses excellent internal validity, 0 = study has poor internal validity). None of the studies were excluded based upon their PEDro scale score (M = 8.92 ± 1.07). Two independent researchers assessed 20% of the includes articles and the inter-rater agreement was of 96%.

Data Extraction

Data were extracted by DH and entered into a custom excel spreadsheet, summarized in Table 1 (the quantitative data and moderators used for the meta-analysis can be found at https://osf.io/bh3g9/). We limited the extraction of data for anodal and sham conditions of the included articles because they are the most common experimental set up and to improve the comparability between studies. The data collected included: 1) descriptive data; 2) study design; 3) characteristic of the stimulation including electrode placement, intensity and duration; 4) exercise protocol and type of test, and 5) the main findings. Given the variety of experimental designs used in this literature, we decided to test the role of a series of common moderators on these studies to explain their possible impact on the effects of tDCS. These moderators were 1) the type of outcome (objective vs. subjective outcomes), 2) the exercise mode (whole-body exercise vs. single muscle group), 3) the location of the anode electrode (and, therefore, the target brain area), 4) the duration of the stimulation, 5) the intensity of the stimulation, and 6) the number of sessions (acute vs. several sessions).

Table 2. Studies examining the effects of tDCS on objective and subjective outcomes. Studies included in the meta-analysis are marked with *. M1: Motor cortex; PC: Prefrontal Cortex; TC: Temporal Cortex; TTF: Time to fatigue test; TTE: Time to exhaustion test; MVC: Maximal voluntary contraction test; TT: Time-trial; RM: Repetition Maximum; PPO: Peak power output; CMJ: Countermovement jump; HRVt: Heart rate variability threshold.

Cogiamanian et al. (2007) [21]*	Between	Performance	M1	10	1.5	Single	35%MVC	One	Yes
Hendy & Kidgell (2013) [22]*	Between	Performance	M1	20	2	Single	1RM test	Several	No
Kan et al. (2013) [23]*	Within	Performance Subjective	M1	10	2	Single	TTF 30%MVC	One	No
Lampropoulou et al. (2013)[24]	Within	Performance Subjective	M1	10	1.5	Single	Isometric MVC	One	No
Muthalib et al. (2013) [25]*	Within	Performance	M1	10	2	Single	TTF 30%MVC	One	No
Williams et al. (2013) [26]*	Within	Performance Subjective	M1	20	1.5	Single	TTF 20%MVC	One	No
Angius et al. (2015) [27]*	Within	Performance Subjective	M1	10	2	Whole-body	TTE 70% PPO	One	No
Hendy et al. (2015) [28]*	Between	Performance	M1	15	1.5	Single	1RM test	Several	Yes
Okano et al. (2015) [29]*	Within	Performance Subjective	TC	20	2	Whole-body	MIT	One	Yes
Vitor-Costa et al. (2015)[30]*	Within	Performance Subjective	M1	13	2	Whole-body	TTE 80% PPO	One	Yes
Abdelmoula et al. (2016) [16]*	Within Within	Performance Subjective	M1	10	1.5	Single	TTF 35% MVC	One	Yes
Angius et al. (2016)[31]*	Within	Performance Subjective	M1	10	2	Single	TTE 20% MVC	One	Yes
Barwood et al. (2016)[32]*	Within	Performance Subjective Performance Subjective	M1	20	1.5	Whole-body	20km TT TTE 75% PPO	One One	No No
Frazer et al. (2016)[33]*	Within	Performance	M1	20	2	Single	MVC	Several	Yes

Lattari et al. (2016)[34]*	Within	Performance Subjective	PC	20	2	Single	10RM Test	One	Yes
Oki et al. (2016)[35]*	Within	Performance	M1	Max20	1.5	Single		One	No
Montenegro et al. (2016)[36]*	Within	Subjective	M1	20	2	Single	Resistance Exercise	One	No
Okano et al. (2017)[37]	Within	Subjective	TC	20	2	Whole-body	120% HRVt	One	No
Flood et al. (2017)[38]*	Within	Performance	M1	20	2	Single	MVC	One	No
Hazime et al. (2017)[39]*	Within	Performance	M1	20	2	Single	MVC	One	Yes
Radel et al. (2017)[40]*	Within	Performance Subjective	M1	Min10	2	Single	TTF 35%	One	No
Angius et al. (2018)[9]*	Within	Performance Subjective	M1	10	2	Whole-body	TTE 70% PPO	One	Yes
		Performance				Single	MVC	One	No
Holgado et al. (2018)[41]*	Within	Performance Subjective	PC	20	2	Whole-body	20-min TT	One	No
Lattari et al. (2018)[17]*	Within	Performance Subjective	PC	20	2	Whole-body	TTE 100% PPO	One	Yes
Vargas et al. (2018)[13]*	Within	Performance	M1	20	2	Single	MVC	One	Yes
Lattari et al. (in press-a)[42]*	Within	Performance	M1	20	2	Whole-body	CMJ	One	Yes
Lattari et al. (in pess-b) [43]*	Within	Performance Subjective	PC	20	2	Single	10RM	One	Yes

Statistical Analysis

The effect size estimate used in all the analyses reported in this study is Hedges' *g*, a standardised mean difference score that corrects for an upward bias in small studies. For all studies, this measure was computed from the means, standard deviations and sample sizes of the experimental (anodal) and control (sham) conditions. When these data were not directly available in the articles themselves, we contacted the authors for further information.

Given that some studies measured performance (objective and/or subjective) before and after the stimulation and other studies only measured performance after the stimulation, we decided to use only post scores in all cases to improve the comparability of studies. Similarly, as some of the selected studies used within-subjects designs and others used between-groups designs, we computed between-groups effect sizes for all studies, also for those with within-subjects designs. In these cases, we used the standard deviation of the sham condition to standardise the difference of means.

The variances of effect sizes were computed using the equations provided by Morris and DeShon [44]. For within-subjects studies, the computation of variance requires an estimate of the correlation between dependent measures. As this information is rarely reported in empirical articles, we assumed a correlation of $r = .50$ for all within-subjects studies. To ensure that this arbitrary choice did not affect the results, we conducted sensitivity analyses assuming correlations of .25 and .75. None of these assumptions made a meaningful change in the results and, consequently, we do not report them in detail.

Some studies contained sufficient information to compute more than one effect size. For instance, some studies measured both objective and subjective performance variables. Treating these effect sizes as statistically independent would violate the assumptions of traditional meta-analysis and could potentially bias the results. To control for dependencies between effect sizes, we fitted a multi-level model using the rma.mv function of the "metafor" R package [45]**,** clustering effect sizes at the sample level.

Results

Study characteristics

The effects analyzed included data from 386 participants (75% male participants) following tDCS' stimulation. The number of participants per study ranged from 6 to 36 participants (14.8 ± 7.2). Of the included studies in the quantitative analysis, 63% assessed the effect of stimulation on a single muscle group, while 37% studies used a whole-body exercise test. In relation to the anodal electrode placement, the design varied between studies, targeting the Motor Cortex (79%), the Prefrontal Cortex (18%) or the Temporal Cortex (3%). Regarding the intensity of the tDCS, it

varied between 2 mA (70%), 1.5 mA (30%) whereas the duration was 20 min (54%), 10 min (30%) and others (16%).

Overall Meta-Analysis

In total, we were able to compute 36 effect sizes from the information reported in the original articles or sent by the authors upon request. The results of the overall meta-analysis are summarized in the forest plot (Fig. 2). The overall effect size across all the effect sizes is $g = 0.34$, 95% CI [0.14, 0.55], which is significantly different from zero, $z = 3.26$, $p = .0011$. This result suggests that anodal tDCS may have a small, but positive impact over the objective and subjective outcomes measured in these studies. The meta-analysis also reveals substantial heterogeneity across effect sizes, $Q(35) = 81.30$, $p < .001$, suggesting that the differences among effect sizes cannot be solely attributed to sampling error.

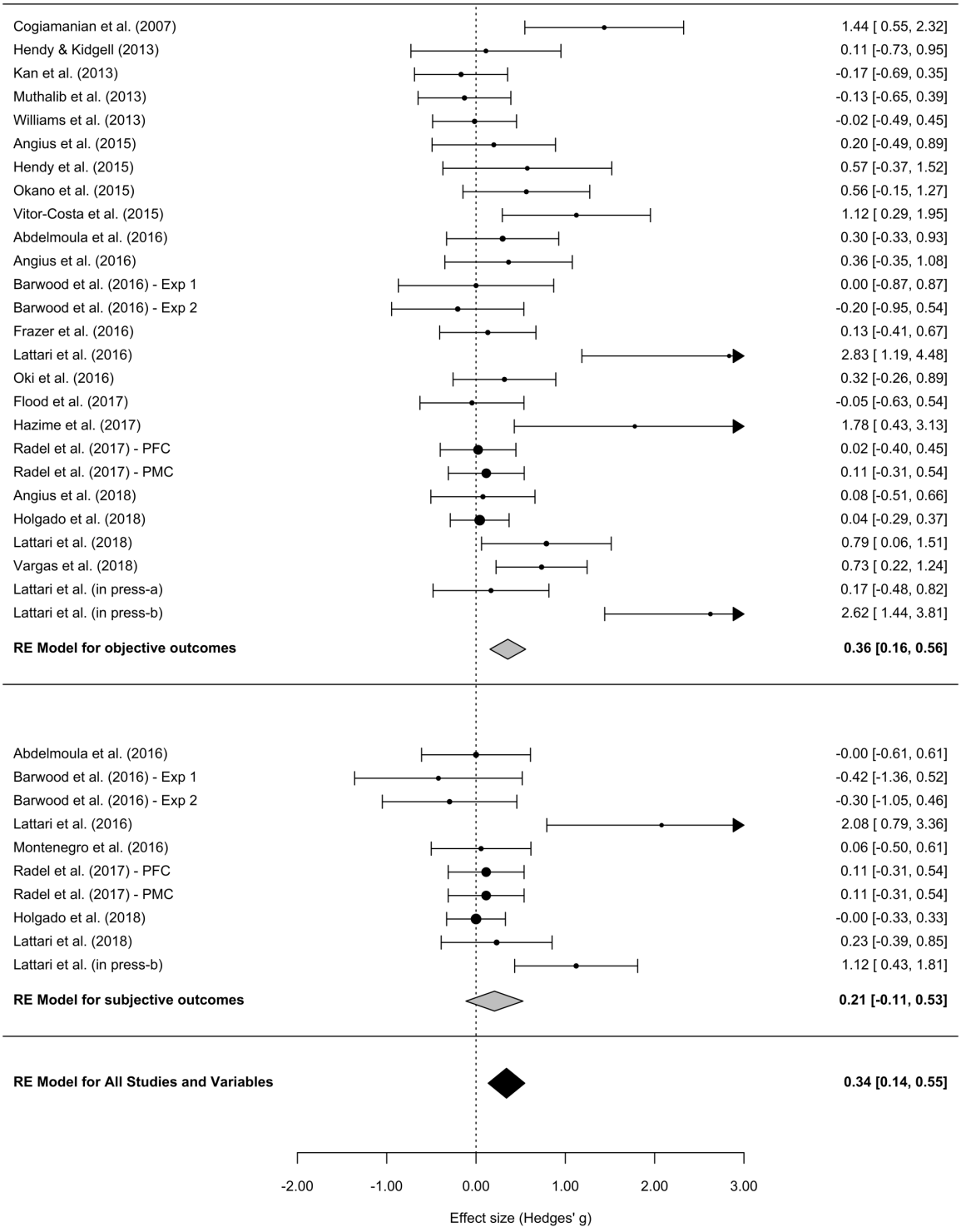

Fig. 2 Forest plot of the effect size of tDCS on objective and subjective indexes

The funnel plot (Fig. 3) shows that, overall, effect sizes tended to be particularly large (in some cases, larger than 2) in studies with smaller sample sizes and a higher standard error. In contrast, studies with larger samples tended to yield smaller effect sizes, in many cases close to zero. To explore funnel plot asymmetry, we run a multi-level meta-regression predicting effect sizes (clustered at the sample level) from the standard error. The results revealed a statistically significant intercept, b_0=-0.87, SE = 0.25, z = -3.44, p < .001, and slope, b_1 = 3.64, SE = 0.85, z = 4.9, p < .001, confirming that effect sizes do differ depending on the level of precision. With some caveats, this asymmetric distribution of effect sizes is usually taken as indicative of publication or reporting biases, as it is typically due to the absence of studies with small sample sizes and non-significant results. The main practical implication of this finding is that the overall effect size estimate reported in the previous paragraph is likely to overestimate the true effects of tDCS.

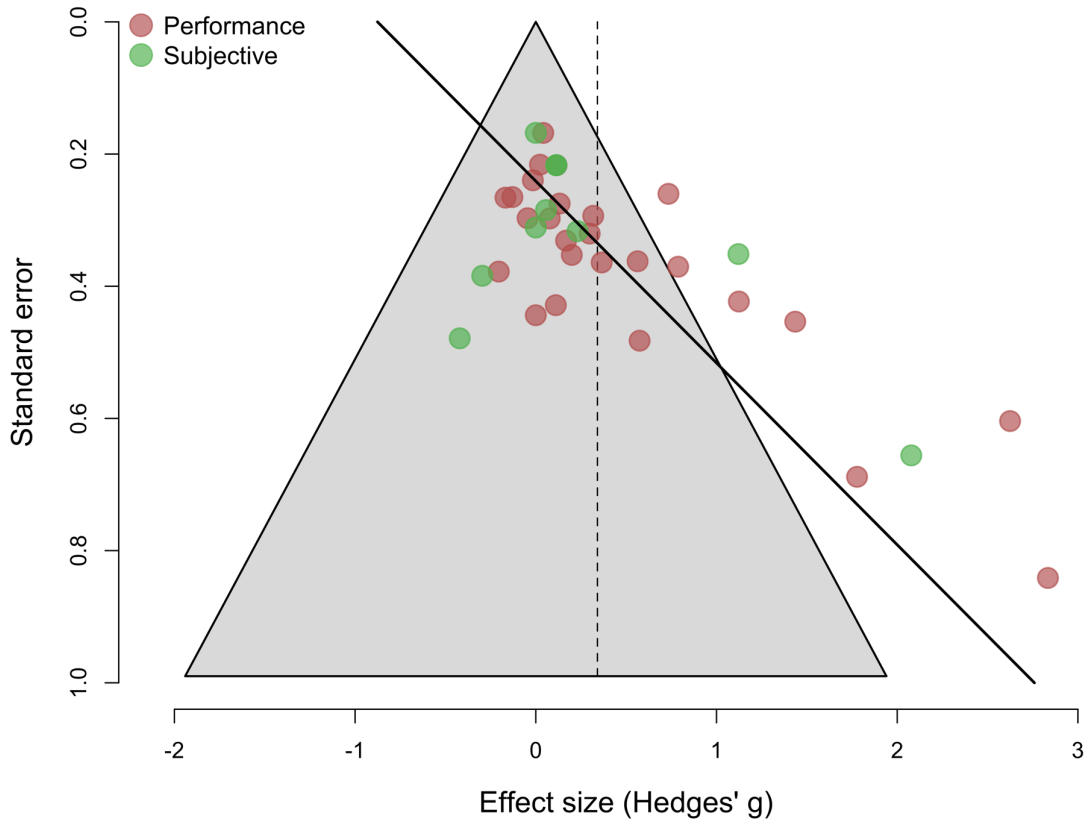

Fig. 3 Funnel plot of Hedges' g effect size versus study standard error. The aggregated Hedges' g is the random-effects mean effect size for tDCS on objective and subjective indexes

Moderator and Sub-Group Analyses

Tables 2 and 3 summarize the results of the moderator analyses. As can be seen, none of the moderators made a statistically significant difference in effect sizes, as revealed by the results of the Q-tests. Numerically, effect sizes tended to be somewhat larger for objective exercise performance indexes than for subjective measures. Similarly, studies tended to yield larger effect sizes if they involved training a single muscle, if they included a single session, and if the anode

electrode was placed on the motor or prefrontal cortex. All these trends should be interpreted with caution, given that none of the moderator analyses reached statistical significance and that there was a substantial overlap between the confidence intervals of all sub-groups. The analysis of continuous moderators (Table 3) revealed that studies with longer and more intense stimulation tended to yield numerically larger effects, but again these effects were far from statistical significance.

Table 2. Results of moderation analyses (Categorical moderators)

Moderator / Sub-group	***g***	**LL**	**UL**	***z***	***p***	***k***	***Q***	***df***	***p***
Type of outcome							0.84	1	.360
Performance***	0.36	0.16	0.55	3.50	<.001	26			
Subjective	0.21	-0.11	0.53	1.27	.204	10			
Muscular group							0.91	1	.340
Single muscle**	0.44	0.14	0.75	2.85	.004	23			
Whole body	0.17	-0.05	0.39	1.51	.131	13			
Number of sessions							0.09	1	.759
One**	0.36	0.13	0.59	3.06	.002	33			
Several	0.21	-0.20	0.62	1.00	.315	3			
Stimulation location†							5.10	2	.078
Motor cortex*	0.17	0.03	0.30	2.44	.015	27			
Prefrontal cortex*	1.01	0.02	2.01	1.99	.046	8			
Temporal cortex	0.56	-0.15	1.27	1.56	.120	1			

Note: *g* = effect size. LL = lower limit of the 95% CI; UL = upper limit of the 95% CI; *z* = *z*-score associated with the *g* value in the same row; *p* = *p*-value associated with the *z*-score in the same row; *k* = number of effect sizes contributing to *g* in the same row; *Q* = result of the *Q*-test for moderation; *df* = degrees of freedom of the *Q*-test for moderation; *p* = *p*-value of the *Q*-test for moderation. † $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 3. Results of moderation analyses (Continuous moderators)

Moderator / Coefficients	*Estimate*	SE	LL	UL	*z*	*p*	*Q*	*df*	*p*
Stimulation duration							0.18	1	.669
Intercept	0.18	0.45	-0.71	1.07	0.40	.687			
Slope	0.01	0.03	-0.04	0.06	0.43	.669			
Stimulation intensity							0.55	1	.457
Intercept	-0.32	0.90	-2.09	1.44	-0.36	.720			
Slope	0.36	0.48	-0.58	1.30	0.74	.584			

Note: SE = standard error of the coefficient. LL = lower limit of the 95% CI; UL = upper limit of the 95% CI; *z* = *z*-score associated with the coefficient value in the same row; *p* = *p*-value associated with the coefficient in the same row; *Q* = result of the *Q*-test for moderation; *df* = degrees of freedom of the *Q*-test for moderation; *p* = *p*-value of the *Q*-test for moderation.

Discussion

The present study is the first meta-analysis to investigate the effects of tDCS on exercise performance. Overall, the main finding is that if tDCS has any effect, it is small ($g = 0.34$) and most likely influenced by publication and reporting biases. The moderator and sub-group analyses failed to find effects for any of the tested moderators. There were no significant differences between studies involving whole-body exercise and studies training a single muscle group. Similarly, there was no influence of either the electrode placement, the intensity or duration of the stimulation.

Assuming there is a true effect of tDCS on exercise performance, the reasons for the possible improvements are still unclear. For example, Angius et al. [9] and Vitor-Costa et al. [30] found an improvement in a cycling TTE test after anodal tDCS and Cogiamanian et al. [21] also found a prolonged endurance time in an elbow flexor TTF test. Together with the improvement in exercise performance, Cogiamanian et al. showed that anodal stimulation increased the motor evoked response. The authors suggested that the increase in the motor evoked response amplitude is consistent with an enhanced corticospinal excitability, which might reflect an augmentation in the voluntary drive sent to the muscle, although Cogiamanian et al. did not measure that parameter. Consequently, the performance benefit could be mediated by an increase in motor cortex

excitability after the anodal stimulation. However, contrary to these findings, Radel et al. [40] found no improvement in performance in a TTF arm flexion or changes in cerebral O_2Hb measured with near infrared spectroscopy and Holgado et al. [41] failed to find any change in the electroencephalography brain electrical activity at rest or during exercise in a 20-min cycling time-trial after anodal stimulation of the prefrontal cortex. These mixed results are a clear sign of the variety of outcomes and converge to the conclusion that the effects may be small and possibly biased.

The present meta-analysis also challenges the idea that tDCS has an effect on subjective indexes related to exercise performance. The subgroup analysis (see Fig. 2 and Table 2) showed that tDCS had a small (g = 0.21) and non-significant effect on subjective indexes related to exercise performance. This suggests that tDCS is not as effective as it appear to reduce perceived exertion. For instance, after an acute stimulation of the motor cortex in a cycling TTE [30], temporal cortex in a cycling incremental test [29] and prefrontal cortex in a resistance strength exercise [43], the authors found an improvement in physical performance accompanied by a reduction in the RPE in the anodal condition compared to the sham condition. Despite the different protocols used in these studies, all of them suggested that the reduction in RPE was as a consequence of tDCS affecting other brain areas, such as the insular cortex, which has been linked to autonomic regulation and to self-perception and awareness of body sensations [46]. Contrary to these findings, Vitor-Costa et al. [30] did not find such reduction in RPE (p = .07) in a group of recreational cyclists who did show and improved performance in the TTE test. Therefore, given the results of the present meta-analysis and the mixed results in the literature, we cannot conclude that tDCS modulates subjective outcomes of exercise performance.

The sub-group analyses also revealed that the intensity of the tDCS did not moderate effect sizes. As mentioned above, the intensities used in all these studies ranged from 1 to 2 mA. Regarding this issue, a recent study [10] showed that an intensity of 2 mA (the maximum intensity used in tDCS-sports research) does not seem enough to affect neuronal circuits [41]. As we mentioned before, by testing tACS (instead of tDCS, which might limit the comparison with the topic addressed here), the authors argued that at least 4.5 mA would be necessary to affect neural circuits, because a significant fraction of the current is lost due to skin and soft tissue and to the resistance of the skull. This is in line with previous reviews where tDCS does not seem to have a reliable neurophysiologic effect beyond motor evoke response modulation in healthy participants [47]. Nonetheless, due to the limited evidence in regard to the safety of stimulation intensity higher than 2mA in healthy human participants [48] and given the fact that higher intensities of electric field to a given brain area may not induce further benefits [11,12], this should be taken with special caution. In addition, due to the high inter-individual variability, it seems that the most effective approach would be to apply an individualized current intensity for each individual [11].

The moderator analyses did not suggest that studies comprising several sessions (three to date) tend to report larger effects. If anything, a single acute session seemed to be numerically more effective. Once again, the limited number of studies and the methodological issues present in this literature nuance any interpretation and explanation of the (potential) effect of repetitive vs. single sessions of tDCS on exercise performance.

Based on the PEDro quality scores, we might conclude that the results obtained in this review were not influenced by poor methodological designs, as on average studies received a score of 8.8/10 in the PEDro scale. Nonetheless, over the course of the systematic review we detected several limitations in the literature [49]. One of them is the overly low statistical power of most studies. For a between-groups study with two conditions (anodal, sham), 274 participants would be needed to reach .80 power to detect an effect of $g = 0.34$ in a two-tailed test with an alpha of .05. Likewise, for a within-participants design and assuming a correlation of 0.5 between dependent variables, we would need 70 participants. However, the average sample size of the studies included in this meta-analysis was only 14 participants (this would yield sufficient power only if a much higher effect size, $d_z = 0.81$, is assumed). This fact suggests that most published studies are underpowered, reducing the probability of detecting a true effect [50]. In combination with the evidence of publication bias in this literature, low statistical power can result in a dramatic overestimation of effect sizes and reduce the reproducibility of results [50].

Limitations

The main findings of this systematic review need to be considered in the context of some limitations. The meta-analysis showed that there was a significant degree of heterogeneity between the studies and none of the moderators included in the analysis could explain this heterogeneity. Publication bias was also evident, as aforementioned in the manuscript. Moreover, some data could not be included in the meta-analysis due to the lack of detailed information on the original articles and because some authors did not provide it upon request. Finally, the quality of studies must improve, as many studies had small sample sizes.

Conclusion

Research on tDCS has produced inconsistent findings regarding the effects of brain stimulation on exercise performance. In this report, we point to four issues that may explain the diversity of results and that should be taken into consideration in future studies: 1) low statistical power, 2) intensity of the stimulation and high inter-individual variability across participants, 3) gender and fitness level of the participants, and 4) publication bias. Thereby, the small positive effect detected in our meta-analysis is likely to be an overestimation of the true effects of tDCS, leading us to conclude that the extant evidence does not support conclusively the use of tDCS to improve

exercise performance. However, given the growing interest and the potential applications of these studies, we think that this line of research should not be neglected or abandoned. Beside the aforementioned methodological issues, we propose some means to improve the credibility of the results in future studies, so that we can establish conclusively whether there is a real effect of tDCS or not: a priori power calculation (leading to larger sample sizes that those used in previous studies), pre-registration of studies [51], and data sharing (e.g., some authors did not send us the data), that might help to reduce the likelihood of *p*-hacking, HARKing and publication bias.

Acknowledgments

We would like to thank all authors who kindly provided us with the data needed to perform this meta-analysis.

Compliance with ethical standards

Contributors: All authors have made substantial contributions to various elements of the study.

Funding: This project was supported by grant PSI2016-75956-P from Ministerio de Economía, Industria y Competitividad, awarded to Daniel Sanabria, grant FPU14/06229 from Ministerio de Educación, Cultura y Deporte, awarded to Darías Holgado, and grants 2016-T1/SOC-1395, from Comunidad de Madrid (Programa de Atracción de Talento Investigador, 2016) and PSI2017-85159-P from Ministerio de Ciencia, Innovación y Universidades, awarded to Miguel A. Vadillo. The funders were not involved directly in the preparation of this manuscript-

Conflict of interests: none declared

Data availability: data and code for the meta-analysis can be found here: https://osf.io/bh3g9/

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Chapter 4

No evidence of the effect of cognitive load on self-paced cycling performance

Holgado, D., Zabala, M., & Sanabria, D. (2019). No evidence of the effect of cognitive load on self-paced cycling performance. Pl*os One (Accepted)*. **JCR Q1 2.72**
https://doi.org/10.1371/journal.pone.0217825

No evidence of the effect of cognitive load on self-paced cycling performance

Executive functions, self-paced exercise and cycling performance.

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Funding

This project was supported by grant PSI2016-75956-P from Ministerio de Economía, Industria y Competitividad, awarded to Daniel Sanabria and Mikel Zabala and grant FPU14/06229 from Ministerio de Educación, Cultura y Deporte, awarded to Darías Holgado. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Objectives: to test the hypothesis that cognitive load (low vs. high load) during a 20 min self-paced cycling exercise affects physical performance.

Design: A pre-registered (https://osf.io/qept5/), randomized, within-subject design experiment.

Methods: 28 trained and experienced male cyclists completed a 20 min self-paced cycling time-trial exercise in two separate sessions, corresponding to two working memory load conditions: 1-back or 2-back. We measured power output, heart rate, RPE and mental fatigue.

Results: Bayes analyses revealed extreme evidence for the 2-back task being more demanding than the 1-back task, both in terms of accuracy (BF_{10} = 4490) and reaction time (BF =1316). The data only showed anecdotal evidence for the alternative hypothesis for the power output (BF_{10}= 1.52), moderate evidence for the null hypothesis for the heart rate (BF_{10} = 0.172), anecdotal evidence for RPE (BF_{10} = 0.72) and anecdotal evidence for mental fatigue (BF_{10} = 0.588).

Conclusions: Our data seem to challenge the idea that self-paced exercise is regulated by top-down processing, given that we did not show clear evidence of exercise impairment (at the physical, physiological and subjective levels) in the high cognitive load condition task with respect to the low working memory load condition. The involvement of top-down processing in self-pacing the physical effort, however, cannot be totally discarded. Factors like the duration of the physical and cognitive tasks, the potential influence of dual-tasking, and the participants' level of expertise, should be taken into account in future attempts to investigate the role of top-down processing in self-pace exercise.

Keywords

dual-task; time-trial; top-down; pacing; working memory; executive functions

Introduction

Self-paced exercise is a goal-directed behavior that has been related to both bottom-up [1,2] and top-down processing [3]. Self-paced exercise or pacing refers to a physical activity (e.g., a cycling time trial or a marathon), in which the effort has to be evenly distributed in order to achieve the objective of the exercise (to complete a given distance as fast as possible, or to complete the maximum possible distance in a given time), but without reaching premature exhaustion, based on previous experiences and the perceived duration/distance to cover [4]. Thus, self-paced exercise might be seen as an effortful cognitive task involving body motion that places high demands on the brain and request top-down processing [5], for it involves goal monitoring, cognitive control etc. For example, during a cycling time-trial, cyclists have to make continuous decisions to adapt the pace according to the demands of the event [6], to focus their attention toward relevant stimuli [7] and to inhibit the urge of slowing down [8]. Indeed, Sport Scientists are beginning to recognize the brain and cognitive functioning (e.g., inhibitory control, working memory) as decisive in the control of exercise, in particular self-paced aerobic exercise [4]. Interestingly, the few neuroimaging studies testing participants while exercising have shown activation of the prefrontal cortex, together with the expected sensorio-motor recruitment [9,10], which reinforces the hypothesis of the crucial role of top-down processing on self-paced exercise.

The above-mentioned research is in line with the cognitive resource theory or Reticular-Activating Hypofrontality [11]. This theory proposes that humans have a limited set of metabolic resources and when these resources are shared amongst several tasks, interference occurs between each other [11]. However, other authors have questioned that metabolic resources are a limiting factor and they indicate that the impairment might be rather due to the attentional limitations when perform both tasks [12,13]. Nonetheless, there is evidence showing that concurrent exercise (which might tap the same underlying cognitive processes) can impair cognitive performance compared to when the cognitive a task is performed alone [14–16]. For instance, Epling et al. [17] found a decrement in the number of words recalled when participants completed a 5 min self-paced (outdoor) running exercise.

To date, in the majority of studies interested on the interplay between top-down cognitive processing (cognitive load) and exercise performance, participants performed the cognitive task prior to the exercise session (c.f. Van Cutsem et al. [18]; Pageaux & Lepers [19]). Little is known regarding the impact of top-down processing (cognitive load) during self-paced exercise. For example, Blakely et al., [20] examined the impact of cognitive load (tone counting with two levels of difficulty) on a group running on an even surface and in a group running on an uneven (trail) surface. They found a linear trend in both groups for a worsening performance with increasing of difficulty of the cognitive task and also higher reports of workload, task-focus and feelings of

being mentally exhausted with the increased cognitive load. Similarly, Malcolm et al. [21] found that the increase in cognitive load while participants walked in a treadmill, modified the gait pattern during the more challenging task compared to the control condition. Likewise, Daniel and Newell [22] evaluated the influence of solving a mental arithmetic task with two levels of difficulty (easy and hard, and with respect to a control condition without mental task) on the walk-run transition speed. Authors hypothesized that the walk-run transition would occur later while participants solved the mental arithmetic because the distraction created by focusing on the math task would mitigate perception of effort that contribute to triggering the switch to running. Despite the run-walk transition speed occurred later compared to the control condition (i.e., participants started to run later, although walking at higher speed would require higher capacity of attention), they did not find difference between the easy and the hard (cognitive) condition.

Here, we provide novel evidence on self-pacing during (cycling) exercise under two different conditions of cognitive load. We chose a n-back task with two levels of cognitive demands (low 1-back and high 2-back) during cycling self-paced exercise. The n-back task has been shown to involve both inhibitory control and working memory [23,24]. Therefore, performing an executive task with low or high demands would affect self-paced exercise performance, if self-paced exercise depends on top-down processing. In particular, we expected lower performance and increased perceived effort during the high-load condition than during the low-load condition. By including two conditions with different levels of cognitive (top-down) load, we tried to ensure that any effect on physical performance would be a consequence of the cognitive load and not the effect of performing a single task compared to dual-tasking. In others words, finding impaired exercise performance in a dual-task (cognitive + physical) compared to a single (physical) task could point to both an effect of cognitive load or to the mere effect of dual-tasking (irrespective of the level of cognitive load). Note that this is common practice in the literature that investigates the effects of physical load on cognitive performance (i.e., physical demands are manipulated while the cognitive task remains the same [25–27]). And, more importantly, in the previous studies investigating the impact of mental fatigue on subsequent physical performance [28]. In sum, our study tests the hypothesis that self-pacing effort during exercise rely on top-down processing.

Material and Methods

Design

A randomized, counterbalanced, within-participant procedure was carried out. This study was approved by the University of Granada Ethics Committee (287/CEIH/2017). All experimental procedures have been designed to comply with the Declaration of Helsinki. Before being recruited to the study, participants read and signed the informed consent. All data was entered in a case

report form and subsequently in a computerized database. Participants were naïve to the aim of the study in order to avoid an expectation effect. Once they completed their participation, they were debriefed with the purpose of the study. We pre-registered the methods and planned analyses of this study on the Open Science Framework. This was done on April 4, 2018, and can be found at https://osf.io/qept5/registrations/ together with the raw data files.

Participants

Participants were recruited by local advertisements in the Granada area, in Spain. Experimental sessions took place in the Faculty of Sport Sciences, in the University of Granada, Spain. Only male trained cyclists with a reported weekly training of more than 6h/week and between 18 to 40 years were included in the study. We decided to include only trained (although not elite) cyclists because they are used to performing bouts of self-paced exercise at the highest possible intensity. Untrained individuals might stop exercising because of the inability to sustained the effort, discomfort due to the body posture on the ergometer or any related factors. Exclusion criteria were the presence of symptomatic cardiomyopathy, metabolic disorders such as obesity (BMI >30) or diabetes, chronic obstructive pulmonary disease, epilepsy, therapy with b-blockers and medications that would alter cardiovascular function, hormonal therapy, smoking, and neurological disorders.

The sample size was determined following a Bayesian approach. We planned to collect data from a minimum of 20 participants. Then, we monitored the Bayes factor (for the average power output) and stopped the experiment whenever the Bayes factor reached a moderate evidence to either support ($BF > 6$) or to reject the null hypothesis ($BF < 1/6$). We also planned to stop the experiment when we reached the maximum number of participants (40 participants) which we expected to be able to recruit. In any case, even if we were not able to reach the 40 participants sample, we would stop the experiment on June 30th, 2018 when the academic year ends. A final sample of 28 male trained cyclists' participants completed the study (27.03 ± 7.41 years).

Apparatus and materials

We used an indoor cycling trainer Phantom 5 ergometer (CyleOps, Madison, USA) to conduct the experimental self-paced exercise. The Phantom 5 measures the power output using an onboard power meter PowerTap (PowerTap, Madison, USA) with power accuracy of +/- 1.5%. We used the Rouvy app to monitor and record power output and heart rate (HR) through a sensor band attached to the participant's chest (SmartLab, Dossenheim, Germany) during the experiments. We used a PC and the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) to control the stimulus presentation and response collection for the n-back task. The center of the PC screen was situated at 100 cm (approx.) from the participants' head and at his eye level.

Procedure

Screening visit

The first day of the study, participants attended to the Faculty of Sport Sciences for a familiarization visit. After verifying that the participants met the inclusion criteria, participants performed the two levels of the n-back task (1-back and 2-back) (counterbalanced across participants) and a 10-minutes self-paced exercise. The aim of this session was that of familiarize the participants with the lab and cycle ergometer. Participants were experienced cyclists and used to performing self-paced effort such as the 20 min self-paced cycling test.

Experimental sessions

After the familiarization visit, participants attended to the lab in two separate visits to perform the 20 min self-paced cycling exercise and the n-back task during exercise. Participants were asked to refrain from drinking alcohol (48 h abstinence) and instructed not to perform any exhaustive exercise in the 48 h before the experimental session. Upon the arrival at the laboratory, participants performed the 20 min self-paced exercise preceded by 10 min warm-up in the ergometer. Participants were instructed to achieve the highest average power output (watts) during the self-paced exercise and perform the n-back task as accurately as possible (see below n-back task). They were allowed to modify the power load during the exercise by pressing two buttons attached to the handlebar (± 10 watts) on the side of their non-dominant hand. Participants were aware of the elapsed time (helping them to self-regulated the effort), but they were blinded to performance variables (watts and heart rate) during the self-paced exercise. The experimenter did not intervene (e.g., encouraging participants) during the test. Participants were instructed to do their best in both tasks, the self-paced exercise and the cognitive task.

N-back task

Participants completed a 1-back and a 2-back task (counterbalanced across participants). One of four digits (1, 2, 3 or 4; 2.67º x 1.53º; 2.67º x 1.62º; 2.67°x 1.62º and 2.67°x 1.81º, respectively) was presented for 500 ms, followed by a fixed delay of 2500 ms (see Luque-Casado, et al., 2015 [29] for a similar procedure). In the 2-back condition, participants had to respond, at any time during the presentation of the stimulus or the delay period, only when the current stimulus was the same as the stimulus presented two trials before. If the stimulus on the screen matched the stimulus presented two trials before, the participant had to press a USB button attached to the handlebar of the ergometer on the side of their dominant hand. Otherwise, the participants had to withhold the response. A new stimulus was presented every 3000 ms (i.e., 500 ms of stimulus presentation and 2500 ms of fixed delay). For the 1-back condition the procedure was similar of that of the 2-back, but they had to respond only when the current stimulus was the same as the

previous stimulus. The digit appearing on each trial was randomly selected, which means that, on average, the current digit was the same as the one presented one or two trials earlier in 25% of the trials. There was not feedback after each trial. The overall duration of the task was 20 min, divided in 4 blocks. At the end of each block participants rated their perceived exertion. The N-back task was reset after each block. Participants completed the first minute of the self-paced exercise without the task so that they could increase the power output load. For each stimulus, the response accuracy (percentage of correct responses) and reaction time were recorded. Accuracy was stressed over response speed.

Subjective scales

We assessed the subjective mental workload of both the 1-back and 2-back sessions with a visual analog scale (VAS). We used a VAS ranging from 0 (low) to 100 (high) in response to the following question before and after each experimental session: “What is your mental fatigue level now?” [30].

Rate of perceived exertion (RPE): we asked the participant to rate their perceived effort in the 6-20 RPE [31] scale after each block of the n-back during the test (i.e., 4 time points). The scale appeared in the screen for 10 seconds and they rated the perceived exertion. All participants were familiarized with the scale, since they had already participated in previous (similar) studies. Nonetheless, we stressed that they should only rate the feeling of effort experienced during the physical exercise, not during the cognitive task.

Statistical analysis

Confirmatory analysis

We calculated the default Bayes factor for a paired, one-sided t-test (2-back vs 1-back) using the open-source JASP statistical package. We used a one-sided Bayesian hypothesis test with a prior of d = 0.4 for (small-medium) effect size on the alternative hypothesis to quantify the evidence for the hypothesis that the high cognitive load induced by the 2-back task would impair the performance in the self-paced exercise with respect to the 1-back condition. Note that in the pre-registration form, we incorrectly stated the we would use a Cauchy prior r = 1 as effect size.

The dependent variables for the self-paced exercise were the average power output, the average heart rate and RPE. The dependent variable for the n-back task was the global accuracy. We used the VAS to check the task demands of n-back after each experimental session. It was analyzed by (normalized) rating change: post-test rating minus pre-test rating divided by post-test ratting plus pre-test rating.

Exploratory analysis

We tested if self-paced exercise performance and RPE during the cognitive task varied as a function of time by including the variable block in the analysis (i.e., four blocks of 5 min).

Furthermore, we correlated the effect of the intervention (difference of power output between the low and high cognitive load) with the effect of the cognitive load (difference of accuracy in the n-back task between low and high load condition).

Even if we did not mention it in the pre-registration form, we also analyzed the reaction time from the n-back task following the recommendation of the Reviewers of a previous version of this article. Note, though, that we considered the accuracy in the n-back task as the main manipulation check.

Results

Confirmatory analysis

N-back task

The Bayes factor for the accuracy in the n-back task during the self-paced exercise was BF_{10} = 4490, indicating that the observed data are more likely under the alternative hypothesis that indicate the presence of effect. According to the classification system proposed by Jeffrey [32], this represents an extreme evidence for the alternative hypothesis that there is a difference on accuracy in the low and in the high cognitive load. The accuracy (percentage of correct responses) for both conditions were: 0.96 (95% Credible Interval (CI) 0.92 - 0.98) and 0.88 (95% CI 0.85-0.91) for the low and the high cognitive load conditions, respectively.

Performance

The Bayes factor for the average power output of self-paced exercise was BF_{10} = 1.524, indicating that the observed data are more likely under the alternative hypothesis. However, this represents an anecdotal evidence for the alternative hypothesis that there is a difference on physical performance between the low and the high cognitive load. The average power output for both conditions were: 222 (95%CI 206.4-237.6) watts, and 217 (95%CI 201.9 - 232.1) watts for the low and the high cognitive load conditions, respectively (Fig 1).

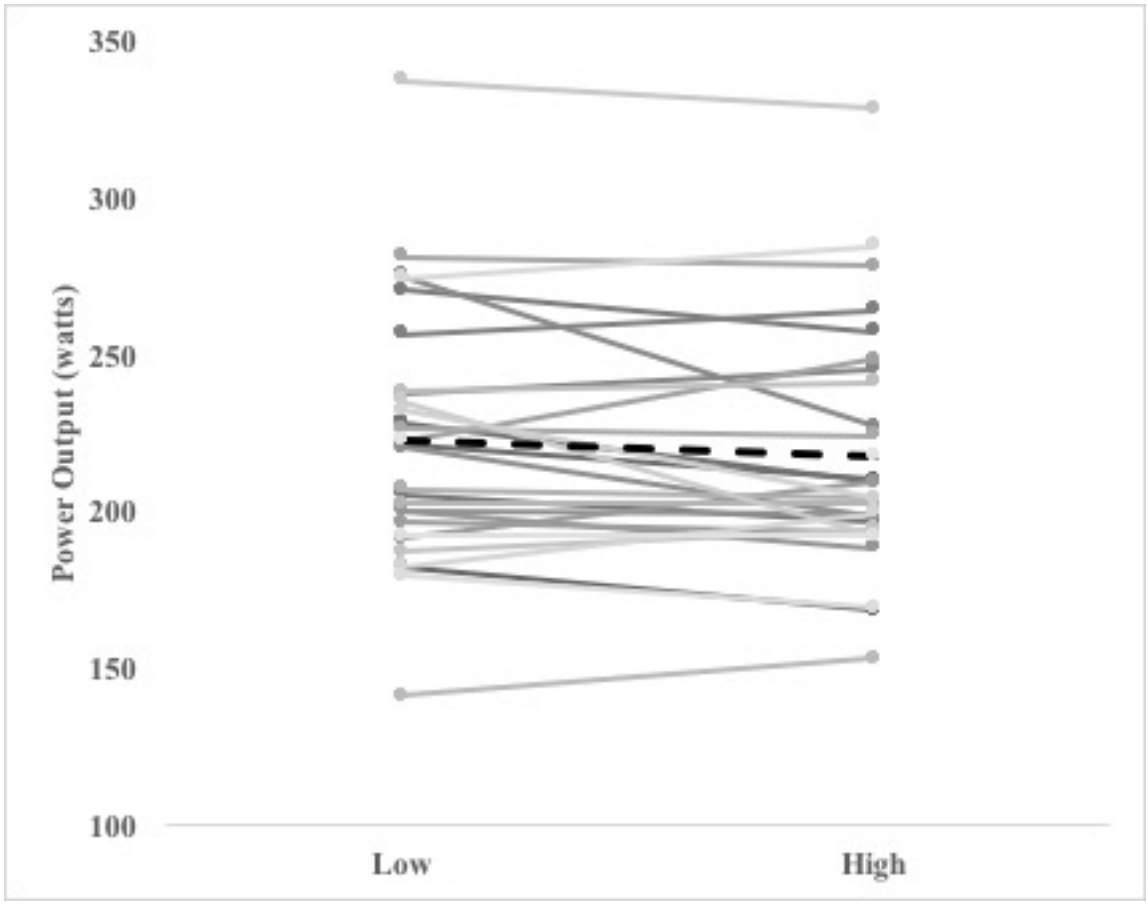

Fig 1. Power output (watts) profile. Power output for each participant and condition during the 20' self-paced exercise. Dashed line represents the overall mean.

The Bayes factor for the average heart rate during the self-paced exercise was BF_{10} = 0.172, indicating that observed data are more likely under the null hypothesis. The BF indicated a strong evidence in favor of the null hypothesis that the average heart rate during the exercise was not different between both conditions. The heart rate for both conditions were: 159 (95%CI 154 - 163) bpm and 160 (95%CI 156 - 165) bpm for the low and the high cognitive load conditions, respectively.

The Bayes factor for the average RPE in the self-paced exercise was BF_{10} = 0.720, which indicate an anecdotal evidence in favor of the null hypothesis indicating the absence of effect between low and high load conditions. The average RPE for both conditions were: 14.88 (95%CI 14.2 - 15.5) and 15 (95%CI 14.45 - 15.65) for the low and the high cognitive load conditions, respectively.

The Bayes factor for the normalized VAS score after the self-paced exercise was BF_{10} = 0.588. The Bayes factor supports the null hypothesis and yield anecdotal evidence in favor of the null hypothesis. The normalized VAS score for both conditions were: 0.31 (95%CI 0.15 - 0.47) IU and 0.37 (95%CI 0.21 - 0.54) IU for the low and the high cognitive load conditions, respectively.

Exploratory analysis

To explore our data further in order to find an alternative explanation (to that of the absence of a

true effect of cognitive load on physical performance) to our null finding, we performed additional exploratory analyses.

The results showed that there was strong evidence against the interaction Cognitive load x Block (i.e., stronger evidence for the model without interaction) for the power output in the self-paced exercise, BF_{10}= 0.085. Similarly, the results yielded that there was a strong evidence against the interaction for the RPE in the self-paced exercise BF_{10}= 0.093.

The results showed that there was not a correlation between difference in the power output and the difference in accuracy in the n-back task, r = 0.022, BF_{10} = 0.381.

The Bayes factor for the reaction time in the n-back task was BF_{10} = 1316 and also represented extreme evidence for the alternative hypothesis that indicate the presence of an effect. The reaction times for both conditions were 614.8 (95%CI 549.1 - 680.4) ms and 801.1 (95%CI 709.9- 892.3) ms for the low and the high cognitive load conditions, respectively.

Discussion

The purpose of this study was to test the hypothesis that executive (cognitive) load would interfere with exercise performance in a 20 min cycling self-paced exercise. The results of the accuracy (and reaction time) in the cognitive task suggest that the high cognitive load condition was more demanding than the low cognitive load. However, despite of the increased executive (cognitive) demands, participants did not seem to impair their physical performance or changed the perceived exertion. In turn, the difference in cognitive performance between the high and low cognitive load conditions cannot be explained by difference in physical performance (at the objective and subjective levels). The results only provided anecdotal evidence for the alternative hypothesis that high cognitive load during exercise might affect physical performance. However, heart rate and RPE data showed moderate to anecdotal evidence in support of the null hypothesis. Moreover, the exploratory analysis also indicated that the effect did not vary as a function of time, i.e., the power output, heart rate and RPE were similar across conditions and time. Finally, the VAS question: What is your mental fatigue level now?" only showed anecdotal evidence for the null hypothesis. During the process of reviewing this manuscript, Reviewers noted that the question we asked to participants could not address correctly the cognitive load of the task. Even if this could be interpreted as a limitation for this study, the purpose was only to obtain an additional measure of cognitive load during the n-back task. In any case, as we have previously mentioned, the results of the accuracy and reaction time data from the n-back task clearly showed a higher cognitive load for the 2-back compared to the 1-back task.

Self-paced exercise might be considered an effortful cognitive task which require the activation of brain areas related to goal monitoring, cognitive control, etc. It has been proposed that self-

paced exercise is continuously monitored by feedforward and feedback between peripheral systems and the brain [33]. However, in most of the related studies the athletes have performed the cognitive task prior to exercise [34] and little is known about the effect of performing a challenging cognitive task during a cycling self-paced exercise. To date, we have only found similarities to cycling exercise in studies investigating gait/running pattern. Indeed, gait is also an attention-demanding task that, according to some authors [35], demands high levels of executive processing and memory. When participants perform a cognitive task during the gait, they seem to alter the normal walk pattern to counter the demands of the cognitive task [21,22]. Although gait and cycling might be considered similar tasks (i.e., cyclical and continuous activities), we cannot extrapolate these results to our experiment.

The logic of our study was straightforward: if self-paced exercise is regulated by top-down processing and the n-back also requires top-down processing [24], it was plausible to expect an impairment in physical performance due to the inability to self-pace efficiently. Moreover, we expected that participants would perceive the physical effort harder in the high cognitive load condition than in the low cognitive load condition. The analysis showed anecdotal evidence for the null hypothesis i.e., no effect of cognitive load at subjective levels of physical performance, than for the alternative hypothesis and it similar to previous studies in which the cognitive load did not affect RPE during exercise [36]. Contrary to the impairment when two cognitive tasks demanding top-down processing are performed simultaneously [37], we may speculate that self-paced exercise does not rely on top-down processing.

Alternatively, as a Reviewer of this manuscript pointed out, a potential dual-task effect could not be discarded [38] in our study, suggesting the involvement of top-down processing in both the cycling and n-back tasks. Indeed, there was a rather large difference in RT (30.46%) between the 2-back and the 1-back condition, which might be a sign of interference between the physical and cognitive task. For example, Jaeggi et al. [39] found that the difference in RT between the 2-back and 1-back tasks in dual-task conditions was 20.64%, whereas in single task conditions it was only 7.38%. The magnitude of the change in performance between conditions in our study was larger in the cognitive than in the physical task, which might suggest that, even though both tasks relied on top-down processes, participants prioritized the first over the latter. Nonetheless, this interpretation is speculative, as the purpose of our study was not to test potential dual-task effects, but to control for them [39].

There are, however, other possible explanation. We propose that despite the task was challenging enough, our sample of experienced cyclists (even though they were not elite cyclists) could have already automatized the self-paced effort so that they would not require high demands of top-down processing to self-regulate during the 20 min exercise [40]. Indeed, although there are not previous published attempts to measure the impact of cognitive load during self-paced cycling

exercise, previous related findings would suggest that cyclists with a higher level of expertise might be more resistant to the negative effect of a high cognitive load [41]. In Martin et al.'s study, professional cyclists did not impair their performance in a 20 min time-trial after completing a 30 min mental exertion task (Stroop task) compared to a control condition. However, the group of recreational cyclists impaired their performance in the mental exertion condition and completed less correct answer in the Stroop task. Therefore, it would seem that there was also difference between trained and professional cyclists. However, the control condition in Martin et al.'s study did not involve any cognitive activity (10 min seated), so any effect of the cognitive task on exercise performance could have been due to the mere effect of doing a cognitive task versus doing nothing.

The present research needs to be considered in the context of some limitations. The Bayes factor indicated that there was an anecdotal evidence in favor of the alternative hypothesis. Therefore, if there was a small effect, we could not have been able to find with our sample size (n=28). Additionally, the duration of the self-paced exercise and cognitive tasks could have not been long enough to induce a high cognitive load in trained cyclists. Finally, as noted above, the level of expertise might be a crucial factor to explain the effect of cognitive (executive) load on self-paced exercise.

Conclusion

The effect of cognitive load on concurrent self-paced exercise performance is scarce, even if the role of cognition of exercise and sport performance is a current topic of debate. Our data appear to challenge the idea that self-paced exercise is regulated by top-down processing given that despite of the evident difference in cognitive load between the two conditions, participants did not seem to impair their performance. Our study, however, does not provide the definitive answer on whether self-pacing the physical effort rely on top-down processing, but opens new interesting avenues for future research on this topic that should consider factors like potential dual-task effects and sport expertise.

Additional information

Competing interests: The authors declare no competing interests.

Data availability: All data can be found in Open Science framework platform: https://osf.io/qept5/

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Chapter 5

General Conclusions

The main aim of the present thesis was to understand the role of cognitive (executive) functions on self-paced cycling exercise. The thesis follows the logic of the bi-directional relationship between the brain, cognition and exercise, i.e., any change at brain level will subsequently affect exercise performance and vice-versa. Here, we address this issue from a cognitive neuroscience perspective with behavioural and neural (brain oscillations) measures. The general conclusions of this thesis based on the obtained results are:

1. The results from the series of experiments carried out during the thesis does not provide a strong evidence that self-paced aerobic exercise rely on executive processing. High cognitive (executive) load during self-paced exercise does not seem to impair exercise performance at objective (physical) or subjective (RPE) level in trained male cyclists. Self-paced aerobic exercise is likely to be a highly complex process, in which a multitude of factors contribute to the ultimate decision to upregulate or downregulate exercise intensity. In particular, we believe that athletes' level of expertise might be a key factor to explain the relationship between executive processing and self-paced exercise.
2. Although tramadol might improve physical performance, the results are not conclusive. In addition, tramadol does not seem to impair cognitive performance, even though it might affect information processing during exercise, as it was highlighted by the brain oscillatory activity.
3. Our data challenge the idea that an acute brain stimulation (tDCS) session affects physical performance or brain oscillatory activity, either at rest or during exercise.
4. Despite the increasing popularity of tDCS in Sport Science, the current evidence does not provide a strong evidence to support the idea that tDCS is an effective technique to improve exercise performance. The smallest positive effect detected in the meta-analysis might be an overestimation of the true effect of the tDCS and a consequence of the publication bias.

Short CV

CV Date	12/05/2019

Part A. Personal information

Name, Surname	Darías Holgado		
Nationality	Spanish	DOB	07/09/1991
Researcher Identification	Researcher ID	S-7682-2017	
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A.1. Current employment

University	University of Granada			
Department	Physical Education and Sport and Brain and Behavior Research Centre			
Address	Facultad de Ciencias del Deporte, Carretera de Alfacar s/n, 18011, Granada			
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Position	PhD Fellow with a predoctoral grant by the Spanish Ministry of Education		Start date	Oct-2015
			End date	Jun-2019
Keywords	Sport performance; Sport Psychology; Brain Stimulation; Anti-doping; Exercise performance; EEG			

A.2. Education

Title	University	Year
PhD in Biomedicine. Physical Activity and Health	University of Granada	-
MRes. in Sport and Physical Activity	University of Granada	2015
BSc. in Sport Sciences (Hons)	University of Granada	2014

Part B. Brief summary

I currently work at the Department of Physical Education and Sport and the Brain and Behavior Research Centre in the University of Granada. My research line is interdisciplinary since I have worked on exercise performance under the focus of Cognitive Science, Experimental Psychology and Sport Psychology. My current projects are 'Putting the brain to work: Self-paced acute aerobic exercise and executive control and "Clinical trial on the effects of the combination of tramadol and paracetamol on physical, cognitive and brain performance during cycling" Moreover, my research group have adopted a policy for the Open Science (e.g. preregistration of studies).

Part C. More relevant scientific merits

C.1. Publications

1. **Darías Holgado**; Miguel A. Vadillo; Daniel Sanabria. 2019. **"**Brain-doping'', is it a real threat? Frontiers in Physiology, 10.3389/fphys.2019.00483.
2. **Darías Holgado**.; Mikel Zabala; Daniel Sanabria. 2019. No evidence of the effect of cognitive load on self-paced cycling performance. Plos One. 10.1371/journal.pone.0217825
3. **Darías Holgado**; Thomas Zandonai; Luis F Ciria; Mikel Zabala; James Hopker; Daniel Sanabria. 2019. Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: Evidence from oscillatory brain activity and power output. Plos One.10.1371/journal.pone.0210873
4. **Darías Holgado**; Thomas Zandonai; Daniel Sanabria.; 2019. Comment on "Review of WADA Prohibited Substances: Limited Evidence for Performance-Enhancing Effects." Sports Medicine. https://doi.org/10.1007/s40279-019-01064-2
5. **Darías Holgado**; Miguel A. Vadillo; Daniel Sanabria; 2019. The effects of transcranial direct current stimulation on objective and subjective measures of sports performance: A systematic review and meta-analysis. Brain Stimulation. https://doi.org/10.1016/j.brs.2018.12.002.
6. Ana Peinado; **Darías Holgado**; Antonio Luque Casado; Miguel Rojo Tirado; Daniel Sanabria Lucena; Coral González; Manuel Mateo-March; Cristobal Sanchez Muñoz; Francisco Calderón; Mikel Zabala. 2018. Effect of induced alkalosis on performance during a field-simulated BMX cycling competition. Journal of Science and Medicine in Sport., 08/2018. https://doi.org/10.1016/j.jsams.2018.08.010
7. **Darías Holgado**; Thomas Zandonai; Mikel Zabala; James Hopker; Pandelis Perakakis; Antonio Luque Casado; Luis Ciria; Eduardo Guerra Hernandez; Daniel Sanabria. 2017. Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial. Journal of Science and Medicine in Sport. 01/11/2017. https://doi.org/10.1016/j.jsams.2017.10.032
8. Luis F Ciria; Antonio Luque-Casado; Daniel Sanabria; **Darías Holgado**; Plamen Ch Ivanov; Pandelis Perakakis. 2018. Oscillatory brain activity during acute exercise: Tonic and transient neural response to an Oddball task. Psychophysiology. 11/2018. 10.1111/psyp.13326
9. **Darías Holgado**; James Hopker; Daniel Sanabria; Mikel Zabala. 2017. Analgesics and Sport Performance: Beyond the Pain Modulating Effects. PM&R. 10.1016/j.pmrj.2017.07.068

C.2. Projects

1. Participating member: Putting the brain at work: Self-regulated acute aerobic exercise and executive control. Spanish Ministerio de Economía y Hacienda. Pi: Daniel Sanabria. (University of Granada) 01/01/2017-31/12/2020. 54.500 €.
2. Participating member: Clinical trial on the effects of the combination of tramadol and paracetamol on physical, cognitive and brain performance during cycling. World Anti- Doping Agency (WADA). Pi: Daniel Sanabria. (University of Granada). 01/07/2018- 01/07/2020. 94.556,01 €.
3. Participating member: Tramadol and sport: Effects on physical and sustained attention performance during cycling exercise. World Anti-Doping Agency (WADA). Pi: Daniel Sanabria. (University of Granada). 15/02/2016-15/02/2016. 67.000 €.

Part D. Additional formation

D.1. Languages

Language	Listening	Reading	Speaking	Writing
German (Hochdeutsch)	**B2**	**B2**	**B1**	**B1**
French	**B2**	**B2**	**B2**	**B2**
Italian	**C1**	**C1**	**B2**	**B2**
English	**C1**	**C1**	**C1**	**C1**

D.2 University Lectures

- Course: Fundamentals of Sport IV: Cycling. Degree: BSc. Sport Sciences. Academic Year: 2017/2018, 2018/2019. Credits ECTS: 6 Faculty: Sport Sciences
- Course: Sport Specialization: Cycling. Degree: BSc. Sport Sciences. Academic Year: 2016/2017, 2018/2019. Credits ECTS: 4.5 Faculty: Sport Sciences
- Course: Sport Advanced Course: Cycling. Degree: BSc. Sport Sciences. Academic Year: 2017/2018. Credits ECTS: 3. Faculty: Sport Sciences

D.3. Relevant courses

- Matlab programming. 20h. University of Granada.
- Data Science in R. Basics Course; Inference and Modeling; Probability; Visualization. 60h. edX (Harvard).
- Advanced design and multivariate analysis. 20h. University of Granada.

- EEG/ERPs data analysis with EEGLAB-ERPLAB Matlab tool. 10h. Mind, brain and Behavior Research Centre, University of Granada.
- Methodology in Psychology: preparing experimental studies with E-prime. 15h. Mind, Brain and Behavior Research Centre, University of Granada.
- Triathlon national coach. Federación Española de Triatlón.

D.4 International stays

- PhD. Internship in Campus Biotech. University of Geneva. Geneva, Switzerland. Start date-end 03/09/2018 - 03/12/2018. Supervisor: Prof. Dapnhe Bavelier
- Visiting student at the School of Sport and Exercise Sciences, University of Kent, Canterbury, Kent, United Kingdom. Start date-end. 08/07/2015 - 08/10/2015. Supervisor: Dr. James Hopker