The Effect of Offline tDCS Targeting the Dorsolateral Prefrontal Cortex on Maximum Exertion Endurance Performance

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ABSTRACT

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The dorsolateral prefrontal cortex (DLPFC) plays a crucial role in cognitive functions and may impact physical endurance. Anodal transcranial direct current stimulation (a-tDCS) is a non-invasive brain stimulation technique (NIBS) that has been found to affect both cognitive and physical performance. This study investigates the effects of a-tDCS targeting the left DLPFC (L-DLPFC) on endurance performance. We hypothesize that the stimulation enhances the performance.

A sham-controlled study design was used to assess the influence of tDCS on endurance performance. All participants (N=18) underwent two maximal treadmill tests: one after actual tDCS stimulation and one after sham stimulation.

Applying a-tDCS targeting the L-DLPFC significantly improved endurance performance, as evidenced by an increase in time to exhaustion (TTE) compared to performance under sham stimulation. These findings suggest that a-tDCS of the L-DLPFC positively influences endurance at peak exertion levels, potentially through enhanced cognitive functions such as inhibitory control and pain perception. Other possible explanatory models were identified, and further research proposals were formulated.

Keywords: transcranial direct current stimulation (tDCS), dorsolateral prefrontal cortex (DLPFC), time-to-exhaustion (TTE), maximal endurance, inhibitory control

TIIVISTELMÄ

Vihervuori, Marianne & Vainio, Ville. 2024. Dorsolateraaliselle etuaivokuorelle suunnatun transkraniaalisen tasavirtastimulaation vaikutus maksimaaliseen juoksukestävyyteen. Psykologian pro gradu -tutkielma. Ohjaaja: Wikgren, Jan. Jyväskylän yliopisto. Psykologian laitos. 31 sivua.

Dorsolateraalisella etuaivokuorella (DLPFC) on keskeinen rooli kognitiivisissa toiminnoissa ja se voi vaikuttaa maksimaaliseen kestävyyssuoriutumiseen. Anodaalinen transkraniaalinen tasavirtastimulaatio (anodal transcranial direct current stimulation, a-tDCS) on ei-invasiivinen aivojen stimulaatiomenetelmä (non-invasive brain stimulation, NIBS), jonka on havaittu vaikuttavan sekä kognitiiviseen että fyysiseen suorituskykyyn.

Tässä tutkimuksessa tutkitaan vasempaan DLPFC:iin (L-DLPFC) kohdistuvan a-tDCS:n vaikutuksia maksimaaliseen juoksukestävyyteen. Hypoteesimme on, että a-tDCS parantaa suoriutumista. A-tDCS:n vaikutusta kestävyyteen arvioitiin yksinkertaisella sokkokokeella. Osallistujille (N=18) tehtiin kaksi maksimirasituskoetta juoksumatolla: toisessa koehenkilö sai oikean a-tDCS-stimulaation ja toisessa näennäisstimulaation.

L-DLPFC:n kohdistettu a-tDCS paransi kestävyyssuorituskykyä, mikä ilmeni juoksusuorituksen keston kasvuna. Tulos viittaa siihen, että L-DLPFC:n kohdistettu a-tDCS parantaa maksimaalista juoksukestävyyttä. Vaikutukset saattavat välittyä kognitiivisten toimintojen, kuten inhibitorisen kontrollin ja kivun siedon, parantumisen kautta. Tutkielmassa esitellään myös muita mahdollisia vaikutusmekanismeja sekä esitetään ehdotuksia jatkotutkimuksia varten.

Avainsanat: transkraniaalinen tasavirtastimulaatio (tDCS), dorsolateraalinen etuotsalohko (DLPFC), aika uupumukseen asti (TTE), maksimikestävyys, inhibitorinen kontrolli

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1 INTRODUCTION

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique. Stimulation can be administered before performance, often referred to as offline tDCS, or during performance, referred to as online tDCS (Friehs et al., 2021). This thesis examines the effects of offline anodal tDCS (a-tDCS) targeting the left dorsolateral prefrontal cortex (L-DLPFC) on endurance performance, more precisely time to exhaustion (TTE), at maximum exertion levels.

The prefrontal cortex (PFC) is a fundamental brain region controlling endurance performance (De Wachter et al., 2021). Fatigue, whether induced by physical or mental exertion, increases the perception of effort and impairs subsequent endurance performance (Pageaux & Lepers, 2016.)

TDCS targeting the PFC on endurance performance at maximum exertion levels has not been extensively investigated. The current research implicates that specifically L-DLPFC could potentially have a major role in endurance performance. Understanding the potential of this non-invasive brain stimulation technique to enhance endurance performance could have significant implications for athletes, military personnel, and individuals engaged in physically demanding activities. The study also aims to contribute to the overall understanding of the function of the L-DLPFC and its possible involvement in the basis of endurance performance.

1.1 Transcranial Direct Current Stimulation

Transcranial direct current stimulation is a neuromodulation technique in which an electric field is created between an anode and a cathode. This electric field may reduce the depolarization threshold in the anodal area and elevate the depolarization threshold in the cathodal area (Nitsche & Paulus 2000). However, some reports indicate that individuals may experience no effect or even opposite ef-

fects. Factors such as stimulation duration can even reverse the expected outcomes. Interindividual variability might be attributed to differences in factors such as anatomy (Laakso et al., 2019; Vergallito et al., 2022; Wiethoff et al., 2014).

The most established theory of tDCS emphasizes the polarization of neurons, leading to alterations in brain function and adaptability. However, increasing but limited proof indicates that tDCS could also directly regulate neurovascular coupling. This developing viewpoint, referred to as neurovascular modulation, proposes that the observed hemodynamic and brain fluid transport changes following tDCS are not merely coincidental occurrences but essential elements of the neuromodulation process (Bahr-Hosseini et al., 2021; Khadka et al., 2023). It has also been hypothesized that the effect of tDCS might be mediated by the blood-brain barrier (BBB), which has a critical role in brain fluid circulation (Petrovskaya et al., 2023).

The variability in response to tDCS is notable. For example, Wiethoff et al. (2014) found that approximately 50% of their 53 participants exhibited minimal or no changes in motor evoked potentials (MEP) following 10 minutes of 2 mA tDCS applied to the M1. Similarly, López-Alonso et al. (2014) reported that only 45% of their 56 participants responded to 13 minutes of 1 mA a-tDCS applied to the left M1. The effect size of tDCS on cortical excitability directed at M1 shows considerable interindividual variability (Nitsche & Paulus, 2001). Anatomical differences among participants, along with other sources of variability, can influence the effects of tDCS (Wiethoff et al., 2014). In their study on tDCS and the Stroop task, Toth et al. (2024) observed that gender may moderate the effects of neurostimulation. Lee et al. (2018) found that higher estrogen levels in women may be associated with enhanced neuroplasticity effects of tDCS when applied to the DLPFC compared to lower estrogen levels.

The performance-enhancing effects of tDCS are most pronounced immediately after application, and these benefits tend to diminish over time. The changes in excitability of the stimulated area with one 1 mA tDCS session for 5-13 minutes has been shown to last approximately up to 90 minutes after the end of the stimulation when directed to M1. Endurance of the effect has been demonstrated to

depend on the intensity and duration of the stimulation (Nitsche & Paulus, 2001). Repetitive tDCS has been shown to induce lasting improvements in cognitive function, with benefits observed for at least a month following treatment (e.g., Doruk et al., 2014).

Reports of skin irritation or burns at electrode sites during tDCS stimulation have been noted. Additionally, temporary dizziness, fatigue, and headaches have been reported. Serious side effects are rare, and their causal relationship with tDCS remains unclear. Most adverse effects resolve after stimulation (Matsumoto & Ugawa, 2017). Rare cases of treatment-emergent mania or hypomania have been observed in depressed patients receiving tDCS; however, no significant association with these conditions was found compared to sham stimulation (Brunoni et al., 2017b). TDCS has been demonstrated to be safe based on neuronal measurements from MRI, EEG, and neuron-specific enolase (NSE). In conclusion, tDCS is considered a safe and well-tolerated technique (Matsumoto & Ugawa, 2017). However, it is important to recognize that the condition-specific risks associated with tDCS are only as well known as the response of different conditions to tDCS. For example, in the most common malignant brain tumor, glioblastoma, neuronal activity has been identified as an emerging critical regulator of glioma progression. High-grade gliomas integrate into electrical networks, and their progression is promoted by depolarizing currents (Venkatesh et al., 2019).

1.2 Transcranial Direct Current Stimulation Modulating Cognitive Function

A growing body of research has investigated the effects of tDCS targeting the DLPFC on cognitive functions. However, the understanding of the mechanism between stimulation and the effects observed in cognition need more support, e.g. from a neurophysiological perspective.

The most extensive research on the effect of tDCS concerns depression. Mutz et al. (2018) conducted in their meta-analysis that tDCS holds promise as a treatment for non-treatment-resistant depression. In a subsequent network meta-analysis, Mutz et al. (2019) compared 18 different brain stimulation techniques

and found that while tDCS is effective for treating major depressive disorder, its efficacy is lower compared to 10 other effective brain stimulation methods. Brunoni et al. (2016) found in their meta-analysis that the effect size of tDCS for depression is comparable to that of repetitive transcranial magnetic stimulation (rTMS) and antidepressant medications. Furthermore, in a double-blind noninferiority trial with 245 patients, Brunoni et al. (2017a) reported that tDCS was superior to sham stimulation but did not demonstrate superiority over the selective serotonin reuptake inhibitor (SSRI) escitalopram in treating depression. Salehinejad et al. (2017) found that 10 sessions of anodal tDCS (A-tDCS) over the L-DLPFC administered over 10 consecutive days improved executive function and reduced depression scores in patients with major depressive disorder. TDCS has been found to improve dysphoria and retardation, but not vegetative symptoms of depression (Alonzo et al., 2013). In tDCS-based treatment of depression, the brain areas stimulated have generally been the frontal regions, particularly the L-DLPFC (Nitsche et al., 2009).

Other clinical groups have also been studied. In the context of our thesis, the results related to fatigue are particularly intriguing. TDCS over the DLPFC has shown promise in treating fatigue in patient populations with multiple sclerosis (Ashrafi et al., 2020) and other conditions such as Parkinson's disease (Jagadish et al., 2024).

Support for a positive effect has also been noticed for instance in tinnitus (Martins et al., 2022), and schizophrenia (Lee et al., 2022). TDCS targeted on DLPFC may show benefits in the treatment of anxiety, especially when combined with pharmacological and cognitive behavioral therapeutic treatments (Stein et al., 2020). High-definition transcranial direct current stimulation (HD-tDCS) may be a promising treatment for traumatic brain injury (TBI), as it appears to enhance oxygen delivery to the brain (Trofimov et al., 2018). Ulam et al. (2015) investigated the effects of 1 mA a-tDCS applied to the L-DLPFC over 10 consecutive sessions in a group of 27 patients with subacute TBI. In this RCT, they observed significant cumulative changes in electroencephalography (EEG) activity in the

active tDCS group compared to the sham group. These EEG changes were associated with improvements in attention and working memory performance. Shaker et al. (2018) examined the effects of 2 mA tDCS applied for 30 minutes per session, three times per week over one month, on cognitive function in 40 male patients who had experienced a first-ever ischemic cerebrovascular stroke. They found that a-tDCS applied to the DLPFC enhanced performance on cognitive tests assessing attention, concentration, logical reasoning, and various memory tasks.

In healthy populations, tDCS-induced effects on cognition have also been observed. For instance, Doruk et al. (2014) investigated the effects of tDCS on the Trail Making Test in 18 patients with Parkinson's disease. They observed that 10 consecutive tDCS sessions over a two-week period resulted in significant improvements in Trail Making Test performance in groups that had stimulation on L-DLPFC and R-DLPFC but not in the group that had sham stimulation. These gains were sustained for a one-month follow-up period. Parasuraman et al. (2014) found that tDCS can accelerate learning in tasks that involve observing objects using rule-based judgment to assess threats. Vanderhasselt et al. (2013) found that tDCS administered to the L-DLPFC shortened reaction time in a test where the subject had to determine whether the face they saw was happy or sad. In this case, tDCS seems to have affected the neural circuitry between anterior cingulate cortex and the L-DLPFC, as evidenced by more negative polarities of the N450 component and faster reaction times, especially in response to positive emotional stimuli. It has also been found that tDCS administered to the L-DLPFC improved subjects' performance on the Purdue Pegboard Test, which measures manual dexterity and bimanual coordination (Watanabe et al., 2023). It has been found that the potential effect of tDCS administered to the L-DLPFC may be moderated by the size of the individual's cognitive reserve. In an experiment investigating the effect of tDCS on memory recall in older adults, Sandrini et al. (2024) found that higher scores on the Cognitive Reserve Index questionnaire positively correlated scores on memory recall task, but only among those who received the correct tDCS stimulation.

1.3 Inhibitory Control

Inhibitory control refers to suppressing or inhibiting irrelevant or impulsive responses. There has been a distinction made between two types of inhibitory control: response inhibition and attentional inhibition. Response inhibition refers to the ability to stop or inhibit a prepotent motor response, while attentional inhibition involves resisting interference from distracting stimuli. However, recent studies have suggested that these two types of inhibitory control may not be completely independent and may rely on overlapping cognitive processes (Tiego et al., 2018). Inhibitory control is a multifaceted phenomenon, and research results vary significantly, likely due to differences in task types, stimulation parameters, and possibly other factors. Further research is needed to better understand the subprocesses of inhibitory control and their underlying neural mechanisms.

The neuropsychological background of inhibitory control remains unclear. It has been argued that the L-DLPFC is a vital part of inhibitory control (e.g. Angius et al., 2019). It has also been argued that the anterior cingulate cortex plays a part in inhibitory control (García et al., 2022). Also, brain areas other than cortical regions have been linked to inhibitory control, such as basal ganglia and, more precisely, the subthalamic nucleus (Frank, 2006). The caudate nucleus is linked to response interference control (Schmidt et al., 2020).

Inhibitory control can be seen as a limited resource that is consumed by various activities that require it, such as maximal sports performance. Engaging in activities that push an individual to their maximum physical performance generates a wide range of bodily signals indicating the body's exhaustion. The longer the duration of the exertion and the heavier the load, the greater the physical and psychological exhaustion experienced by the individual. When the strain exceeds the individual's tolerance, the individual stops performing the activity. Inhibitory control is thought to be related to tolerance of exertion and, thus, to maximal physical performance (Hagger et al., 2010).

The DLPFC has been implicated in the inhibition of pain (Lorenz et al., 2003). This is particularly relevant given that exercise-induced pain has been identified as a key factor in endurance performance (Astokorki & Mauger, 2017).

Elite and high-level endurance athletes have been shown to possess a significantly greater ability to tolerate pain (Pettersen et al., 2020). Consequently, one potential mechanism by which tDCS might enhance running performance in maximal endurance tests is through its ability to inhibit pain signals.

TDCS over DLPFC has been shown to influence pain perception. In their meta-analysis Vaseghi et. al. (2014), conclude that a-tDCS over DLPFC or M1 both decrease pain levels in chronic pain patients. In a RCT with 20 healthy subjects, Boggio et al. (2008) found that a-tDCS over the L-DLPFC increased the pain threshold. Similarly, Wang et al. (2014) demonstrated with 27 healthy participants that a-tDCS over the L-DLPFC modulated empathy for pain. Additionally, a-tDCS over the L-DLPFC has been shown to reduce pain in patients with multiple sclerosis (Ayache et al., 2016). In another RCT, a-tDCS over the L-DLPFC was found to modulate motor cortex excitability and reduce pain perception in a sample of 19 patients with chronic lower back pain compared to sham stimulation (Corti et al., 2022). There is support for the effectiveness of tDCS over sham stimulation for treating pain in patients with fibromyalgia (Moshfeghinia et al., 2023).

From the perspective of cognitive testing, the Stroop test is widely utilized to assess inhibitory control (Nejati et al., 2020). Loftus et al. (2015) found that 10 minutes of 2 mA anodal tDCS applied to the L-DLPFC, with the cathode on the R-DLPFC, improved reaction times but not accuracy on a modified Stroop color-word task in 28 neurologically intact young adults, compared to sham stimulation. In contrast, Angius et al. (2019) used a similar anodal electrode placement but positioned the cathode at Fp2 and extended the stimulation duration to 30 minutes. Their experiment with 12 healthy participants did not show significant improvements in Stroop test reaction times; however, they observed enhancements in accuracy. Baumert et al. (2020) studied a-tDCS applied to the L-DLPFC with the cathode placed ipsilaterally between the neck and shoulder. Although they found improved reaction times across all task types in the classical Stroop task and the Stroop Sequence Effects test, the lack of specific improvement in the interference task led them to conclude that the stimulation did not enhance inhibitory control. Toth et al. (2024) reported that a-tDCS over the L-DLPFC, with

the anode placed on the R-DLPFC, improved accuracy but not response times on congruent trials of the Stroop task, but only for male participants. They found no effect on incongruent trials and suggest that gender might contribute to the mixed results observed in previous studies.

The influence of tDCS for inhibition has also been investigated on patient groups such as ADHD. In a meta-analysis of 11 RCTs, Salehinejad et al. (2019) found that a-tDCS had an effect on inhibitory control accuracy but not speed in individuals with attention-deficit hyperactivity disorder (ADHD) when stimulation was targeted to the L-DLPFC or bilaterally to the DLPFC. They also noticed that stimulation of the right inferior frontal gyrus did not significantly increase accuracy in inhibitory control tasks. Their analysis included studies measuring inhibition on various cognitive tests: Go/No-Go, Stop Signal Task, Flanker, Stroop, Continuous Performance Test and Neuropsychological Development Assessment (NEPSY II). In their randomized controlled trial involving 25 children with ADHD, Nejati et al. (2020) found that applying 1 mA a-tDCS to the L-DLPFC for 15 minutes, with the cathode positioned over the R-DLPFC, significantly improved both accuracy and reaction times on the Stroop task. However, this stimulation did not enhance performance on the Go/No-Go task, which is designed to measure prepotent response inhibition.

In contrast, when inhibitory control has been assessed using the Stop Signal Task, the most consistent results were obtained from a-tDCS applied to the R-DLPFC (Friehs et al., 2021). Most of the studies were targeting R-DLPFC. This systematic review, which included 31 studies involving healthy adults, revealed significant heterogeneity among study methodologies.

Craving in addiction is thought to be connected to cognitive control and closely associated with the DLPFC. Stimulation of the R-DLPFC, in particular, may play a more significant role (Chen et al., 2020). Gaudreault et al. (2021) demonstrated that 15 sessions of tDCS, applied over five weeks with the anode over the R-DLPFC and the cathode over the L-DLPFC, effectively reduced cravings in cocaine addicts. Further evidence supporting the use of tDCS over the DLPFC for managing cravings comes from a meta-analysis of 32 studies (Chen et

al., 2020), which concluded that tDCS over the DLPFC, compared to sham stimulation, has a medium effect size in reducing food and substance cravings. The analysis found no significant difference between stimulating the R-DLPFC or L-DLPFC, but it did highlight that the number of sessions significantly enhanced the effect. Additionally, Mostafavi et al. (2020) conducted a systematic review and meta-analysis of 15 studies, concluding that multi-session bilateral tDCS at 2 mA over the DLPFC is particularly effective in controlling energy intake and reducing food cravings.

1.4 Enhancing Exercise Performance Through Transcranial Direct Current Stimulation

The body's ability to produce energy through metabolism is an essential physiological factor for endurance performance. Oxygen is required for energy production, and maximal oxygen uptake is intrinsically linked to this process (Di Prampero, 2003). Maximal oxygen uptake (VO2max) quantifies the upper limit of an individual's capacity to extract, transport, and utilize oxygen during strenuous physical activity (Hill & Lupton, 1923). This determines the ability of an individual to move a given distance as quickly as possible (Di Prampero, 2003).

One method for measuring VO2max is the direct incremental treadmill test, in which participants run to exhaustion on a treadmill. In this study, we employed this protocol to assess the effect of tDCS on TTE. Billat et al. (1994) examined the reproducibility of TTE using the direct treadmill test with eight sub-elite male runners. Despite the substantial variability in performance between sessions for individual participants in their study, this variability evened out when analyzing the data from all eight participants. This suggests good reproducibility at the group level for TTE during treadmill tests conducted at one-week intervals.

Interest in utilizing tDCS to enhance sports performance has significantly grown in recent years, with multiple meta-analyses reporting encouraging outcomes from single-session tDCS interventions. For instance, Holgado et al. (2019), in their meta-analysis of 24 studies involving 386 participants, found that a-tDCS targeting M1, the prefrontal cortex (PFC), or temporal cortex (TC) may have a

small but positive impact on exercise performance. Similarly, Alix-Fages et al. (2019) analyzed 31 interventions and reported that tDCS had a small positive effect on maximal voluntary contraction (MVC) and a moderate effect on endurance, particularly in terms of time to task failure (TTF). They also observed greater benefits for full-body exercises compared to uniarticular tasks. In a more recent study, Pedreiro et al. (2023) found that applying 2 mA of a-tDCS for 20 minutes over the L-DLPFC improved TTF in a handgrip MVC test among Brazilian Jiu-Jitsu practitioners. However, no statistically significant improvements in the rate of perceived excertion (RPE) or MVC were observed compared to sham stimulation. Chinzara et al. (2022) also identified a small positive effect of tDCS on sports performance across 43 studies involving 790 participants, with more pronounced effects on strength and visuomotor skills compared to endurance. Both Holgado et al. (2019) and Chinzara et al. (2022) cautioned that the observed effects could be influenced by low-quality studies and publication bias.

Holgado et al. (2019) also noted that the effects were consistent regardless of electrode placement, the muscles involved, or the number of sessions. Furthermore, Holgado et al. (2019), Marinus et al. (2023), and Chinzara et al. (2022) found no significant correlation between tDCS effectiveness for sports performance and dose-related variables such as stimulation duration and intensity. However, Chinzara et al. (2022) suggested that factors such as gender and genetics might modulate the effect. In contrast, Alix-Fages et al. (2019) highlighted that a-tDCS over the M1 with stimulation durations exceeding 10 minutes produced the most significant improvements in TTF. The effects of a-tDCS were more pronounced during full-body exercises, such as cycling, compared to uniarticular tasks.

Some studies argue that the effects of tDCS vary depending on the targeted brain area and the type of motor performance or training. A recent systematic review by Marinus et al. (2023), encompassing 35 studies with 540 participants, concluded that tDCS targeting the DLPFC is particularly effective in enhancing sports endurance, while its effects on muscle strength and cardiopulmonary endurance remain inconclusive. They also noted that the distinction between these categories is somewhat arbitrary and may contribute to conflicting findings. A-

tDCS was found to be more effective than c-tDCS, with stimulation of the DLPFC and the M1 yielding the most promising results. Notably, all studies using c-tDCS reported negative or non-significant effects on sports performance. Additionally, it was found that online tDCS proved more effective than offline tDCS.

Research has also shown that a-tDCS over the M1 can sometimes enhance muscle strength, although results are inconsistent. It has been found to increase the excitability of the M1, which can improve the neural drive to muscles and enhance performance in strength-related tasks. Moreover, M1 stimulation may also delay the onset of central fatigue and increase pain tolerance, which can benefit endurance performance (Maudrich et al., 2022). There is also evidence suggesting that a-tDCS over the M1 may positively affect muscular endurance through isometric contractions (Lattari et al., 2018). In their randomized controlled trial (RCT) with 18 parkour practitioners, Giancatarina et al. (2024) examined the effect of tDCS on postural control, measured by the center of pressure in unipedal and bipedal stances. They found that tDCS over the M1 significantly improved unipedal stance performance, whereas stimulation over the DLPFC or sham stimulation did not yield such improvements. Additionally, the effect of tDCS was negatively correlated with parkour experience, indicating a greater influence on novice practitioners compared to more experienced individuals.

Recent studies have predominantly shown positive effects of a-tDCS over the DLPFC on various sports outcomes. A-tDCS applied to the DLPFC, but not to the M1, appears to extend the time to exhaustion, reduce the RPE, and increase the electromyographic (EMG) amplitude of the vastus medialis muscle, as well as affective response and perceived arousal under hypoxic conditions in endurance-trained males, compared to sham stimulation (Etemadi et al., 2023). Similarly, Nikooharf Salehi et al. (2022) conducted a study with 15 professional swimmers. They found that 2 mA for 20 minutes of a-tDCS, but not c-tDCS or sham tDCS, applied to the L-DLPFC decreased the impact of mental fatigue in 50-meter swimming performance. Mental fatigue in this study was induced using the modified 60-minute Stroop color-word task. Further supporting these findings, Vieira et al. (2022) found that a-tDCS applied to the DLPFC improved back squat

exercise endurance performance compared to sham stimulation in eleven healthy males with an intermediate resistance training background. Additionally, Honarmand et al. (2022) found that tDCS over the DLPFC improved visual attention and performance in stressful conditions for volleyball players.

However, tDCS over the DLPFC has not always yielded positive results for sports parameters. Teymoori et al. (2023) investigated in their randomized controlled trial the effects of tDCS on 15 healthy physically active men performing an anaerobic cycling task. They found that tDCS over the M1 or the L-DLPFC did not improve repeated anaerobic performance. Nevertheless, a-tDCS over the L-DLPFC positively affected RPE, EMG of the vastus lateralis muscle, qualitative affective responses, and cognitive function measured by the Stroop test. In another study, Alix-Fages et al. (2022) investigated the effects of 15 minutes of 2 mA a-tDCS and c-tDCS over the DLPFC in 25 healthy males. They found no significant impact on performance during ten 30-meter sprints, each separated by 30 seconds, compared to sham stimulation.

The evidence for tDCS over DLPFC for RPE has shown mixed results. While Holgado et al. (2019) found a non-significant effect of tDCS on RPE in their meta-analysis, Baharlouei et al. (2024), in their systematic review, concluded that a-tDCS, when applied over the M1 or the DLPFC, could decrease the rate of RPE compared to sham stimulation. On the other hand, tDCS over the temporal cortex did not show a decrease in RPE. Their meta-analysis included 33 studies with a total of 474 healthy participants aged 19–32.

To illustrate the variety of explanations for how tDCS might enhance sports performance, it's worth noting that a-tDCS applied over the temporal cortex has been shown to influence autonomic cardiac functions, as evidenced by changes in physiological indicators. For example, Okano et al. (2015) investigated the effects of a-tDCS over the left temporal cortex in cyclists, comparing it to sham stimulation. They observed that a-tDCS led to a 4% improvement in peak power output, delayed vagal withdrawal, reduced heart rate during submaximal workloads, and slowed the increase in the RPE following stimulation. Notably, maximal heart rate and RPE values were unaffected by the stimulation. The delay of

vagal withdrawal means that the activity of the vagus nerve stays higher than without stimulation, which could lead to the body perceiving a reduced sense of threat or stress. Kamali et al. (2019) conducted a study with 12 experienced bodybuilders who were randomly assigned to receive either real or sham stimulation. The results indicated that real tDCS over the M1 and left temporal cortex significantly reduced heart rate and RPE while enhancing maximal strength, endurance performance, and electrical activity in the quadriceps femoris muscle during knee extension exercises. The stimulation did not affect the participants' motivation. Additionally, in cognitive tasks, those who received tDCS outperformed the sham group in memory and verbal tasks, with corresponding changes observed in the frontopolar hemodynamic response. Marinus et al. (2023) discussed the idea in their study that an increase in DLPFC activity induced by tDCS stimulation may mitigate the exercise-induced decrease in M1 activity and its performance-reducing effect.

1.5 Research Questions and Research Aims

This study investigates the impact of a-tDCS targeting the L-DLPFC on TTE. The research question is: Does offline a-tDCS applied to the L-DLPFC extend TTE in a maximal treadmill endurance test? We hypothesize that a-tDCS targeted to the L-DLPFC lengthens the duration of an individual's TTE in the maximal endurance test.

2 RESEARCH METHODS

2.1 Participants

Originally, a total of 22 male individuals were initially recruited from the Jyväskylä area in Finland. However, four participants were later removed from the dataset, leaving a final sample size of 18 participants. Exclusions were made for the following reasons: one participant had engaged in an intense training session the day before a measurement, potentially impacting the results, and three others were excluded due to illness at the time of the measurements.

The final participants' ages ranged from 22 to 39 years (M=27.8, SD=4.6). All of the participants possessed sound general health and a history of physical activity, including endurance training. The necessity of physical activity was crucial to ensure that the study would not disproportionately enhance the participants' aerobic capacity. Participants were instructed to refrain from intense exercise for 2 days before the tests and to avoid consuming caffeine for several hours before testing. Before each measurement, they filled out a form confirming compliance with these instructions. Participants were excluded if they had acute neurological symptoms such as migraines, chronic neurological conditions like epilepsy, acute scalp irritation or wounds, psychiatric disorders requiring potent medication, heart failure, or acute respiratory infections.

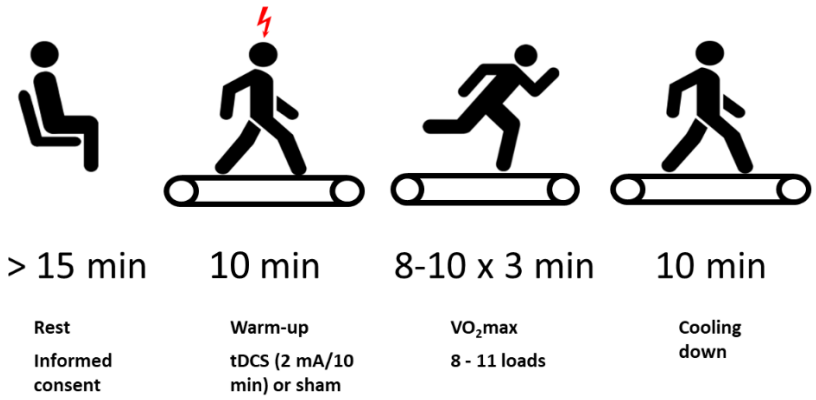
All individuals participated voluntarily in the research. They provided informed consent and confirmed their compliance with the health requirements. The participants were asked about their training background before the first measurement. After both testing sessions were completed, the participants received an evaluation of their running capabilities, including VO2 max and aerobic threshold measurements.

The first text group of nine participants was evaluated from November 2017 to June 2018, while the latter group of nine underwent assessment between March 2023 and May 2023.

2.2 Test Procedure

Figure 1

Test procedure



The study involved conducting two direct maximal oxygen uptake treadmill tests for each participant in the laboratory at the University of Jyväskylä. There was an interval of one to two weeks between the tests. The direct maximal oxygen uptake treadmill test method was chosen due to its well-known reliability in evaluating maximum exercise capacity (Alghannam et al., 2015; Billat et al., 1994; Weltman et al., 1990). The main parameter analyzed in the study was duration until exhaustion (TTE), although data on VO2max and lactate levels were also gathered.

Random allocation was utilized, with half of the participants undergoing real tDCS stimulation during their initial measurement session. The remainder received the stimulation during their subsequent session. Sham tDCS stimulation was administered during the alternate session. The participant and treadmill operator were unaware of the type of stimulation administered, while the researcher delivering the stimulation knew whether real or sham stimulation was allocated to each participant. This researcher did not intervene with the experiment.

2.3 Warm-up and Stimulation

Applying the 10-20 EEG system (Jasper, 1958), tDCS was directed towards the L-DLPFC, with an anode positioned at F3 and a cathode at F4. After the impedance check, the participant proceeded to the treadmill for a 10-minute warm-up. All the participants wore a safety vest securely fastened to a frame that was positioned over the treadmill. This precaution would prevent any risk of falling while running on the treadmill. The treadmill's speed was tailored based on the participant's reported running experience and fitness level, ensuring they could run or jog without feeling breathless. The personalized warm-up speed remained consistent across both measurement sessions.

During the warm-up phase, participants received either real or sham stimulation. Although online stimulation may be more effective (Marinus et al., 2023), the stimulation was administered during the warm-up rather than during the maximal exertion test to minimize the impact of sweating and movement, which could disrupt impedance. The active stimulation was delivered at 2 mA for 10 minutes, with a 30-second linear ramp-up at the start and a ramp-down at the end. In contrast, the sham stimulation followed the same ramp-up and ramp-down periods, but the intensity dropped to zero during the 10-minute interval in between.

After completing the warm-up, the treadmill was paused, and the electrodes were taken off. The participant then rested briefly before proceeding with the maximal treadmill endurance test. Vyntus respiratory gas collector mask was placed on their face, and their baseline lactate level was measured from their fingertip. Following this, there was a one-minute period of gas collection. During the collection, the participant remained standing without speaking to obtain baseline levels of their respiratory gasses in a resting state.

2.4 Maximal Endurance Treadmill Test

After the initial gas collection, the treadmill test commenced. The starting speed was determined based on either the warm-up pace or an increase of one kilometer per hour (km/h). The treadmill incline was standardized to 0.6 degrees to simulate air resistance. Subsequently, the test proceeded in three-minute intervals, incrementing the speed by one km/h at each stage. Brief pauses occurred between intervals for lactate sampling from participants' fingertips and to record their perceived exertion levels. These short breaks lasted no longer than 30 seconds, and their precise duration was deducted from the total test time for subsequent analysis. The RPE was measured using Borg's RPE scale, which ranges from 6 (no exertion) to 20 (maximal exertion).

Participants were instructed to sustain their running effort until they felt too fatigued to continue. To minimize differences in motivation between the two running sessions, participants were informed about their results only after both measurements were completed. However, they were made aware of the treadmill speed at the end of each three-minute interval, which inevitably provided some indication of their performance.

The research director was instructed to encourage all participants uniformly, while the individual administering the stimulation was directed not to offer any encouragement or feedback on the participants' performance. At the start of each interval, the research director would ask, 'Shall we continue?' to ensure the participant was ready and willing to proceed before the treadmill resumed. However, during the first data collection with the initial nine participants, this question was not consistently standardized.

2.5 After the Test

Following the completion of the test, participants underwent a resting gas collection procedure. Subsequently, they engaged in a 10-minute cool-down on the treadmill at their preferred intensity (running, jogging, or walking).

2.6 Data Analysis

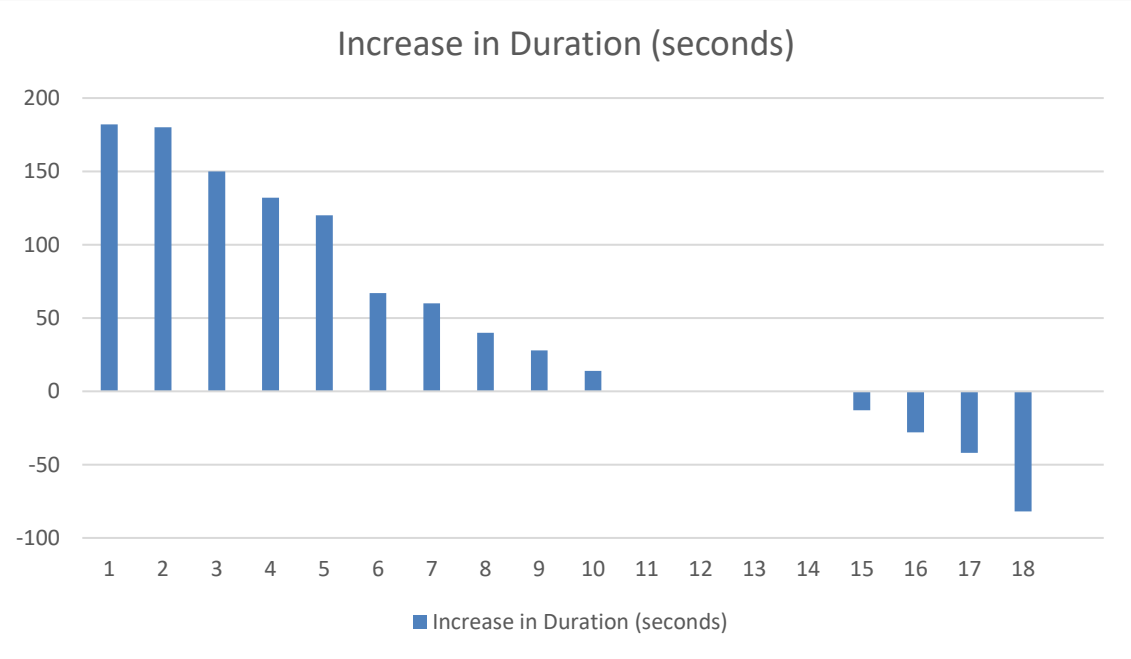
Wilcoxon signed-rank test was used to analyze the data at 5% level of confidence. Two new variables were created for comparisons between the runs. The variables were constructed by setting a constant value of 180 seconds for both performance conditions (real stimulation and sham stimulation). This constant value was added to the number of seconds that the subject could continue the trial at the speed at which he/she stopped the performance. If the participant finished the round at different speed levels, the time difference between levels (180 seconds) was added to the metric. This calculation method was chosen because it was intended to focus on the critical phase of maximal performance at the end of the exercise. All the analyzes were made using SPSS version 28.

3 RESULTS

The results of the study showed that tDCS targeted to the L-DLPFC positively affected maximal exercise performance in subjects with a background in endurance sports ($Z = 2.07$, $p = .038$). As shown in figure 2, 10 of 18 subjects showed improved performance when stimulated. In addition, 4 subjects maintained their performance levels during both stimulated and unstimulated sessions, while 4 performed worse during stimulation.

Figure 2

Difference in seconds between the lengths of participants' runs (with stimulation and with sham-stimulation)



On average, participants ran 45 seconds longer during the performance period when they received actual stimulation compared to the period when they received sham stimulation. Across the study participants, the range of performance between sham and real stimulation was -82 to 182 seconds with a standard deviation of 78 seconds.

4 DISCUSSION

The main finding of this research is that offline a-tDCS targeted on L-DLPFC might have a performance-enhancing effect in a test where the subject is required to run on a treadmill for as long as possible in the maximum endurance zone. In average the improvement was 44 seconds with 78 seconds standard deviation (p=.038). 10 out of 18 participants demonstrated improved performance, while 4 performed worse with stimulation. The remaining four participants had the same result in both measurements as they stopped their run at the short break between speed increases. This result aligns with previous studies.

A potential mechanism that may underlie the observed effect may be inhibitory control. Inhibitory control has been shown to influence pain tolerance and thus maximal physical performance (Hagger et al., 2010.) The DLPFC, on the other hand, has been found to be an essential region underlying inhibitory control (e.g. Angius et al., 2019). However, the findings are not entirely consistent (e.g. Baumert et al., 2020). Our findings, where participants' performance after L-DLPFC stimulation was longer, support previous research (Etemadi et al., 2023; Marinus et al., 2023).

Understanding the relationship between exercise and pain modulation could open new avenues for research aimed at improving public health. This understanding could lead to strategies for enhancing the exercise experience for individuals who find physical activity less enjoyable or motivating. Non-invasive brain stimulation (NIBS), along with other interventions such as psychotherapeutic approaches, could be explored for their potential to modulate exercise-induced pain. However, further research is required to better understand the complexities of pain experience and inhibition during physical activity across diverse populations and different types of exercise.

As we mentioned in section 1.1, it is not uncommon for some participants to show little or no response to stimulation. This is relevant for further research

because standardizing the protocol associated with tDCS and adding more diverse background variables to the study can achieve a more unbiased picture of the effect of tDCS.

There is still no coherent, comprehensive understanding of the overall mechanism by which tDCS might alter brain functioning. The vast majority of research on this topic has been conducted under the assumption that the effect might be due to changes in neuronal activity induced by an electric current. A more recent explanation, however, is that the electrical current would directly affect brain hemodynamics and fluid flow and thereby cause noticeable changes in cognition and other performance (Khadka et al., 2023; Bahr-Hosseini et al., 2021).

To better understand the mechanisms underlying the effect, research designs should be able to measure explicit, quantitative changes in brain function, such as blood flow or other fluid circulation. A recent study by Khadka et al. (2023) aims to move in this direction by creating a comprehensive computer simulation model. Research on tDCS should incorporate more interdisciplinary work in sports science, neurology, anatomy, and medical science. The literature review for this thesis found limited inclusion of relevant concepts, such as cerebral blood flow and neurovascular coupling, in the theoretical foundations of studies on similar phenomena in medical, neurological, and anatomical research. Incorporating these concepts could aid future research designs in exploring the issue more deeply. Additionally, case studies of individuals with different states, e.g., traumatic brain injuries or brain tumors, could provide valuable insights into the topic.

4.1 Limitations

Some studies utilizing tDCS stimulation and sham control groups have reported that participants can perceive whether they received active or sham stimulation beyond chance levels (e.g., Brunoni et al., 2014; Greinacher et al., 2019; O'Connell et al., 2012; Wallace et al., 2016), while others found no distinction between real

and sham stimulation (e.g., Gandiga et al., 2006; Palm et al., 2013). In a meta-analysis of 23 studies encompassing a total of 501 participants, De Smet et al. (2021) identified a significant response to sham tDCS in the context of depression treatment. Notably, sham protocols incorporating ramp-up/ramp-down times exhibited a smaller sham response. These findings underscore the necessity for standardized sham protocols and proper blinding. Workman et al. (2020) conducted a review focusing on tDCS studies in Parkinson's disease patients. They found that only 17 out of 70 potentially reviewable studies quantitatively assessed blinding or tolerability. Future studies should consider systematically collecting such data, a practice omitted in our study. This assessment should occur post-measurements to prevent any potential impact on running performance. In our study, the participants received stimulation during their warm-up phase. We assume this might have diverted their attention from the stimulation, compared to receiving it while staying still.

The lack of a clear theoretical framework regarding the mechanism of action of tDCS constitutes a limitation of our study. For the results to be considered reliable, the mediating mechanism of the method itself should be more clearly understood and described. A research track in which the effect of tDCS is hypothesized to affect cerebral blood flow via neurovascular coupling could potentially add further discriminatory power to the theoretical background. In this case, improved performance due to tDCS can be described by a richer set of concepts and their dialogue: neuromodulation and neurovascular modulation.

Eight of our 18 subjects did not improve their TTE under the tDCS condition. Several factors might explain why tDCS does not enhance TTE for all participants. Uncontrollable variables such as fatigue, mood, and motivation could influence performance. Although impedance was verified to be within the acceptable range before stimulation, factors like thicker hair or skull density could still alter current distribution. Additionally, individual differences in sweating, both in quantity and composition, could impact impedance during the stimulation process (Vergallito et al., 2022; Wiethoff et al., 2014). Future studies should consider these anatomical and physiological differences by integrating advanced

imaging techniques to assess skull thickness and brain structure, ensuring a more tailored approach to tDCS application.

When evaluating the study results and comparing them with other research findings, it should be noted that the experiment was not conducted in a way that fully complies with the definition of a double-blind experiment. Specifically, the researcher administering the stimulation was aware of whether the participant received real or sham stimulation. However, we believe this did not significantly impact the study's outcomes.

The study underwent a change in personnel between the first and second phases of data collection, which could have led to procedural differences, especially in the way participants were encouraged during their running sessions. Additionally, some study personnel and participants were acquainted before the study commenced. Although we do not believe this significantly influenced participant performance, the potential for such familiarity to impact outcomes cannot be entirely ruled out. We also aimed to have the same personnel present for both measurements of each participant, but this was not always possible. However, it is unlikely that this had a significant effect, as any marginal influence would likely be outweighed by the sample size.

In experimental designs measuring the duration a subject can sustain maximal effort, continuous performance from start to exhaustion is ideal. However, lactate sampling during incremental speed tests introduces brief interruptions in performance between intervals. In this study, lactate samples were collected during pauses of no more than 30 seconds. To mitigate the impact of these interruptions in future research, adopting a standardized sampling duration, such as 30 seconds, could help maintain consistency across tests. However, the pauses might influence participants' motivation, as the participants may decide to continue until the end of the interval, and on the other hand, the breaks between intervals pose a risk of participants discontinuing. The type of encouragement provided could play a significant role in this context. For example, using phrases like "continue" versus "stop" may impact participants' choices, as people tend to opt for the default option presented to them (Samuelson & Zeckhauser, 1988).

There may have been differences between the first and second dataset collections due to non-standardized encouragement. In the first dataset, all participants quit between intervals, whereas in the second dataset, no participants quit between sets. Since the encouragement was not standardized, we are uncertain what differed in the first dataset. However, during the second dataset collection, personnel attempted to use the phrase "Do we continue?"

The study involved 18 male subjects, which restricts the generalizability of the findings to this specific demographic. As mentioned in section 1.1, the effects of tDCS have sometimes been reported to vary based on gender and may be influenced by estrogen levels. Most participants were from the Jyväskylä region in Finland and identified as physically active, though not elite athletes, with approximately five participants being floorball players.

4.2 Future Research Propositions

The research on the effectiveness of tDCS on the L-DLPFC is still insufficient. More studies with larger sample sizes and diverse populations, including women, are needed to validate these findings. Employing different methodologies, such as endometrial biopsies, could yield new insights into the mechanisms and reproducibility of the effects observed.

The precise mechanisms by which the L-DLPFC influences endurance performance remain unclear and warrant further investigation. Several cognitive processes, such as inhibitory control and mood, might modulate this effect. Examining participants' background variables and survey data on mood could help clarify these underlying processes.

Also, comparing subjects with varied training backgrounds could provide deeper insights into how tDCS influences endurance performance. For instance, investigating whether novice runners benefit more from the stimulation than experienced runners would be valuable. Professional runners may have developed a higher tolerance for pain and exhaustion through extensive training. Thus, comparing novice and professional runners could elucidate the neurological

mechanisms underlying the impact of tDCS on the L-DLPFC. This comparison should be made by looking at a task where performance may be affected by inhibition, for example, from a pain tolerance perspective (e.g., maximal incremental running test and RPE, but also where absolute, physiological measures can be collected (e.g., heart rate variability). This would allow us to compare how the experience is affected: whether or not the changes occur at the same rate in both dimensions.

One crucial consideration of the tDCS method is whether such a weak electric current can affect brain function. In addition to the growing body of research demonstrating the cognitive and sports performance effects of tDCS stimulation, physiological measurements have also been investigated. For example, Okano et al. (2015) and Kamali et al. (2019) found tDCS to affect autonomic cardiac functions such as heart rate and vagal withdrawal along with enhancing effects on sports performance.

Combining knowledge of brain chemistry with research also creates different ways forward in situations where, for example, certain physiological changes (change in magnetic field, fluid flow) cannot be detected (e.g., absence of certain measurement devices). For example, in the study of Alzheimer's disease, it has been found that neuronal cell loss causes an increase in cytokine levels, and cytokine is an early biomarker of the disease (Rani et al., 2022). In rat studies, tDCS has been found to affect brain cytokine levels (Ethridge et al., 2022). Thus, the potential impact of tDCS on Alzheimer's disease could potentially be investigated in the future using information from blood tests if the link between tDCS and changes in cytokine levels is proven. This trajectory may also help to identify links between tDCS and performance, as indirect measures of improved endurance performance can be developed.

4.3 Safety and Ethical Considerations

Research into the safety of tDCS and other noninvasive brain stimulation methods (NIBS) requires interdisciplinary dialogue. This need arises when we examine the potential impact of tDCS on a condition-specific basis, expecting both positive and negative outcomes.

For example, a scientific perspective article by Petrovskaya et al. (2023) looks at the issue from an Alzheimer's disease perspective. The article describes the effect of NIBS on BBB. The article presents that if tDCS is used to influence BBB function, this may lead to better drug delivery. A potential explanation for this could be, e.g., that the permeability of BBB increases (Shin et al., 2020). However, it is possible that increasing BBB permeability will accelerate disease progression through BBB degeneration if BBB function, already impaired by Alzheimer's disease, is further impaired (e.g., if the BBB is permeated by more agents that accelerate endothelial layer degeneration). Petrovskaya et al. (2023) underline that further research is needed to understand risks better. By study design, researchers can mitigate the possible risk by limiting the age of the subjects. By this, it is possible to exclude undiagnosed Alzheimer's disease patients from the study largely, but replicating the study in elderly subjects is immediately subject to further ethical scrutiny, as Alzheimer's disease usually takes years to be diagnosed after the onset of disease development.

A similar analysis can be made from the perspective of glioblastoma. As we noted in section 1.1., it has been observed that glioblastoma growth progression is promoted by depolarising currents. In line with the precautionary principle, one must assume that tDCS could potentially induce growth acceleration and worsen prognosis. On the other hand, it is known that tDCS can affect BBB permeability (Shin et al., 2020), so that, for example, the delivery of temozolomide used in the treatment of glioblastoma could be supported by tDCS. By contrast, as with Alzheimer's disease, undiagnosed glioblastoma patients cannot be eliminated by any known parameter at present, as the cancer type is also relatively prevalent in non-elderly people.

Ethical reflection on the use of tDCS should be kept active, and a useful model could be to establish a separate ethical reflection alongside the individual studies themselves. A multidisciplinary consortium of researchers should organize this medium. A broad perspective could provide essential information on, for example, how different psychiatric and physiological conditions respond to tDCS, thus creating a framework for conducting research elsewhere. This could help to increase knowledge in borderline cases where no established safety threshold is crossed but where, for example, the effect of tDCS on a particular condition is unclear, in which case the ethics of the study may be considered to be compromised.

There is an ethical consideration regarding whether the use of tDCS could increase the risk of injury when used to push an individual to their physical limits. We speculate that the brain may impose a natural limit to prevent maximal exertion, and surpassing this limit could entail significant risks.

Finally, the use of tDCS in sports calls for ethical considerations regarding its use as a doping method. However, as noted in section 4.5, the impact of tDCS may not be as beneficial for elite athletes as it is for novice athletes, diminishing its potential as a doping method in professional sports. This requires further investigation in future studies. Pugh & Pugh (2021) concluded that tDCS should be monitored rather than prohibited.

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