Effects of transcranial direct current stimulation on long-term motor learning and retention

Marta Sevilla Sánchez

International Doctoral Thesis UDC 2022

Supervisors: Professor Miguel Ángel Fernández del Olmo
Professor Tibor Hortobágyi

PhD in Sport Science, Physical Education and Physical Activity for Health

UNIVERSIDADE DA CORUÑA

Name of department:	Departamento de Educación Física y Deportiva Research group: Motor Control Group University of A Coruña
Author:	Marta Sevilla Sánchez
Tittle:	Effects of transcranial direct current stimulation on long-term motor learning and retention
Supervisors:	Prof. Miguel Ángel Fernández del Olmo Prof. Tibor Hortobágyi
Submitted:	January 10th, 2022

The undersigned thesis supervisors,
Miguel Fernández del Olmo and Tibor Hortobágyi,
confirm that the doctoral thesis entitled
EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON LONG-TERM MOTOR LEARNING AND RETENTION

produced by the candidate
MARTA SEVILLA SÁNCHEZ
fulfill the requirements for the International PhD degree
in the University of A Coruña.

Place and date

Supervisor:
Miguel Fernández del Olmo
PhD. Professor

Supervisor:
Tibor Hortobágyi
PhD. MD. Professor

PhD. candidate:
Marta Sevilla Sánchez

Tutor UDC:
PhD. Manuel Avelino Giráldez García

A mi niño
y a mis padres

ACKNOWLEDGEMENTS

Me gustaría empezar agradeciendo a mis padres (Cati y Pascual) la educación y el amor que siempre he recibido por su parte. Ellos han confiado ciegamente en mí y me han dado alas para que sueñe y vuele. Os quiero mucho. Gracias Eva, porque, aunque estemos lejos, noto tu apoyo y cariño. A mi familia en general y también a mi familia política (Sole y Pepe) por cuidarme y tratarme como a una hija más.

A mis dos directores, Miguel has sido un guía en todo este proceso y te agradezco que me hayas enseñado esta bonita profesión. Tibor, you are an example for me of professionalism, critical spirit, and a good supervisor. Thank you for your support and for opening the doors of your laboratory.

Gracias Edu por ser compañero de vida, escucharme, entenderme y animarme siempre a aceptar nuevos retos. Tu pasión por la profesión y por la vida en general es contagiosa. Gracias también por ser tan generoso con tu tiempo y compartir muchos conocimientos conmigo que me han hecho avanzar más rápido como investigadora, profesora y como persona. Eres único, te adoro.

A mis mejores amigas, porque a pesar de la distancia, desde pequeñas seguimos creciendo juntas y me siguen transmitiendo su energía positiva y su fuerza. A mis amigas de la universidad UMH, por compartir tantos momentos y video llamadas tan necesarias. A mis amigos de Coruña por tantos ratitos de desconexión. Os quiero mucho.

A todos los compañeros y profesores de la facultad que me han aportado muchos momentos y conocimientos durante estos años y, que han conseguido que el INEF sea mi casa: Marina, Juan, María, Jessi, Pablo, Manolo, Xurxo, Eliseo, Pablo Arias, Popi, Miguel, Rafa, Alejandra, Juako, Luis, Jose …

Gracias a todos los que han aportado un granito de arena para que hoy pueda presentar este trabajo, entre los que destacan Jorge, Iván, Adrián, Kevin, y todos los alumnos/as que habéis participado en los experimentos por la gran implicación y todas las horas invertidas. También a todos los compañeros de estancias, es especial a David, Giulia, Jose, Laura, Tati, … con los que compartí risas y lágrimas. E ovviamente ringraziamo anche Giacomo per aver aperto le porte del suo laboratorio e per la sua simpatia.

En definitiva, gracias a todos los que formáis parte de mi vida.

“Somos lo que hacemos repetidamente. La excelencia,
entonces, no es un acto, es un hábito”. Aristóteles.

"El verdadero viaje del aprendizaje consiste no en buscar nuevos paisajes, sino en mirar con nuevos ojos".

Marcel Proust.

ABSTRACT

Optimizing the teaching-learning process is essential throughout life. Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) seem to be an option for optimizing the motor learning curve. This thesis aims to study the effects of tDCS on motor learning, including the retention of a motor. The first randomized controlled study explored the effects of applying tDCS before, during, or after motor practice on retention of the practiced skill in 100 participants. After a single session, similar performance changes were observed in all groups, with no significant differences in the choice reaction time task. In the second randomized controlled study, we examined the effects of tDCS on typing performance in 63 participants. Participants performed a structured program of 23 intervention sessions across 3.5-month: 20, 15-min typing practice and 3 evaluations (pre, middle, post). tDCS group performed better motor performance in the rapid learning phase compared to the sham and control groups. However, these differences dissipated from session 11th. In conclusion, tDCS appears to be a safe stimulation method when administered over multiple sessions in healthy young adults but failed to enhance motor skill acquisition and retention compared with a sham control group.

Keywords: Non-invasive brain stimulation techniques, NIBS, motor skill, typing, learning curve, complex motor skill.

RESUMEN

Optimizar el proceso de enseñanza-aprendizaje es fundamental durante la vida. La estimulación transcraneal por corriente directa (tDCS) podría optimizar la curva de aprendizaje motor. El objetivo de la tesis fue estudiar los efectos de la tDCS sobre el aprendizaje, incluyendo la fase de retención. El primer estudio controlado aleatorio exploró los efectos de la aplicación de la tDCS antes, durante, o después, de la práctica sobre la retención en 100 participantes. Después de una sesión, se observaron cambios de rendimiento similares en todos los grupos en una tarea de tiempos de reacción aleatorios. En el segundo estudio controlado aleatorio, examinamos los efectos de la tDCS sobre el rendimiento mecanográfico. Los 63 participantes realizaron un programa estructurado durante 3.5-meses que incluía 20 prácticas y 3 evaluaciones (pre-, media- y post-intervención). El grupo tDCS obtuvo un mejor rendimiento en la fase rápida del aprendizaje en comparación con el grupo placebo y el grupo control, aunque estas diferencias se disiparon desde la sesión 11 en adelante. En conclusión, la tDCS parece ser segura aplicada en sesiones múltiples en adultos jóvenes y sanos, pero no eficaz para mejorar el aprendizaje de habilidades motoras en comparación con los grupos control y placebo.

Palabras clave: Técnicas de estimulación cerebral no invasivas, NIBS, habilidad motora, mecanografía, curva de aprendizaje, habilidad motora compleja.

RESUMO

Optimizar o proceso de ensino-aprendizaxe é fundamental durante a vida. A estimulación transcraneal de corrente continua (tDCS) podería optimizar a curva de aprendizaxe motora. O obxectivo da tese foi estudar os efectos do tDCS na aprendizaxe, incluída a fase de retención. O primeiro estudo controlado aleatorizado explorou os efectos da aplicación de tDCS antes, durante ou despois da práctica sobre a retención en 100 participantes. Despois dunha sesión, observáronse cambios de rendemento similares en todos os grupos nunha tarefa aleatoria de tempos de reacción. No segundo estudo controlado aleatorizado, examinamos os efectos do tDCS no rendemento da dixitación. Os 63 participantes completaron un programa estruturado de 3.5-meses que incluía 20 prácticas e 3 avaliacións (pre-, media- e post-intervención). O grupo tDCS funcionou mellor na fase rápida de aprendizaxe en comparación co grupo placebo e o grupo control, aínda que estas diferenzas disipáronse a partir da sesión 11. En conclusión, o tDCS parece ser seguro cando se aplica en varias sesións en adultos novos sans, pero non é efectivo para mellorar a aprendizaxe das habilidades motoras en comparación cos grupos control e placebo.

Palabras chave: Técnicas de estimulación cerebral non invasivas, NIBS, habilidade motora, mecanografía, curva de aprendizaxe, habilidade motora complexa.

PREFACE

The present work, the thesis titled “Effects of transcranial direct current stimulation on long-term motor learning and retention” contains experimental work performed between 2017 and 2021 at Faculty of Sports Science and Physical Education of University of A Coruña, Department of Sports Science. Also, some work was performed during a stance in the laboratory at the Center for Human Movement Sciences, University Medical Center Groningen of University of Groningen (Netherlands), under the supervision of Dr. PhD. MD. Tibor Hortobágyi from October to November 2019, and in the Fundacion Santa Lucia IRCCS, Universidad Degli Studi Di Roma Tor Vergata (Italy) under the supervision of Dr. PhD. MD. Giacomo Koch from September to December 2020.

Three original experimental studies are included, one already published in the international peer-review journal Neuroscience. The second under review in the international peer-review journal Neuroscience Letters. The third study is a pilot study.

These studies were supported by grants from:

FPU fellowship from “Ministerio de Ciencia, Innovación y Universidades” of Spain.

FPU mobility fellowship.

CONTENTS

FIGURES INDEX

TABLES INDEX

ABBREVIATION

4-ChRT	4-choice visual-motor reaction time
BDNF	Brain-derived neurotrophic factor
CON	Control group
CON	Control group
CPM	Characters per minute
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GPI	Global performance index
iTT	Incremental typing test
LDP	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MEP	Motor-evoked potential
mTT	Maximum typing test
NMDA	N-methyl-d-aspartate
PFC	Prefrontal cortex
RT	Reaction time
SMA	Supplementary motor area
SRTT	Serial reaction time task
SVIPT	Sequential visual isometric pinch task
tDCS	Transcranial direct current stimulation
WPM	Words per minute

PUBLICATIONS INCLUDED IN THIS THESIS

Articles

Study I

The lack of timing-dependent effects of transcranial direct current stimulation (tDCS) on the performance of a choice reaction time task.

Marta Sevilla-Sanchez, Tibor Hortobágyi, Eduardo Carballeira, Noa Fogelson, Miguel Fernandez-del-Olmo.

Under review.

Study II a

Exploring the learning curve in a complex motor skill: A pilot study.

Marta Sevilla-Sanchez, Tibor Hortobágyi, Miguel Fernandez-del-Olmo.

Study II b

Small Enhancement of Bimanual Typing Performance after 20 Sessions of tDCS in Healthy Young Adults.

Marta Sevilla-Sanchez, Tibor Hortobágyi, Noa Fogelson, Elliseo Iglesias-Soler, Eduardo Carballeira, Miguel Fernandez-del-Olmo.

Neuroscience. 466 (2021) 26–35.
https://doi.org/10.1016/j.neuroscience.2021.05.001

Conference proceedings

Sevilla Sánchez, Marta; Hortobágyi, Tibor; Fernández del Olmo, Miguel Ángel. **Influencia de la estimulación cerebral eléctrica no invasiva (tDCS) sobre la retención motora**. X Congreso Internacional de la Asociación Española de Ciencias del Deporte. La Coruña; 2018.

Marta Sevilla Sánchez. **Efectos de la tDCS en el aprendizaje motor a largo plazo.** I Jornadas de Estimulación Transcraneal por Corriente Directa (tDCS): aplicaciones y tendencias actuales. Madrid; 2021.

Marta Sevilla Sánchez, Miguel Fernandez-del-Olmo, Tibor Hortobágyi. **tDCS facilitates the retention of typing skill in healthy young adults.** 30th Annual Society for the Neural Control of Movement Meeting. Victoria, Canada; 2021.

Chapter 1

Introduction

1. INTRODUCTION

1.1. MOTOR LEARNING

"Motor learning can be defined as any experience-dependent improvement in performance. Improvements at any stages of the three learning components – goal selection, action selection, or action execution - can be described as motor learning."

Krakauer et al., 2019

"Motor learning is a set of processes associated with practice or experience leading to relatively permanent changes in the capability for skilled movement."

Schmidt and Lee, 2005

An extensive review of the motor learning field is beyond the scope of the current thesis. Therefore, we focus on the elements and characteristic of the motor learning process relevant to the present thesis, being aware of this basic approach to the motor learning field and its limitations.

To begin this section is critical to distinguish between two key concepts in the motor learning domain performance and learning [3]. Performance tends to improve after a bit of practice. These improvements often occur quickly and at times substantially. However, they also tend to be temporary and may be greatly affected by external perturbations or participants' condition that I explain in the next section. When practice continues over time, tangible learning occurs, that is, the beginner retains the skill. The learner can remember what to do and can do it effectively. And these changes are sustainable over time and the skill can be performed even when external perturbations occur or when participants' state is altered [4].

Recent classifications of motor learning distinguish between online and offline learning. Online learning occurs during practice, known as adaptation, and offline learning occurs after motor practice and is known as retention. Both online and offline learning are crucial to the motor learning process. The offline gains are not affected by the practice of another novel task [5], whereby the mechanisms responsible for the acquisition phase (i.e., online learning) and the retention phase (i.e., offline learning) appear to be different. How these processes are defined, and the nature of these processes is what motor learning paradigms try to understand.

In summary, motor learning is usually a slow, constantly evolving process requiring continued practice. As wells as the preceding definition suggests, motor learning induces relatively permanent changes. But how permanent is “relatively permanent”? The lasting effect of practice -not the momentary benefits- lead to motor learning. As a result, retention intervals of 24 hours or more are commonly used before the subjects perform the retention test.

This thesis is about motor learning in heathy young humans, but animal data also provide a detailed understand of how motor learning occurs.

1.1.1. Variables that affect motor learning

Time is often limited to learn motor skills in school, sports, industry, or rehabilitation. For this reason, it is essential to organise the practice in a way that maximises the potential of learning. Therefore, it is necessary to know and adjust the main variables that affect the motor learning process (see Figure 1).

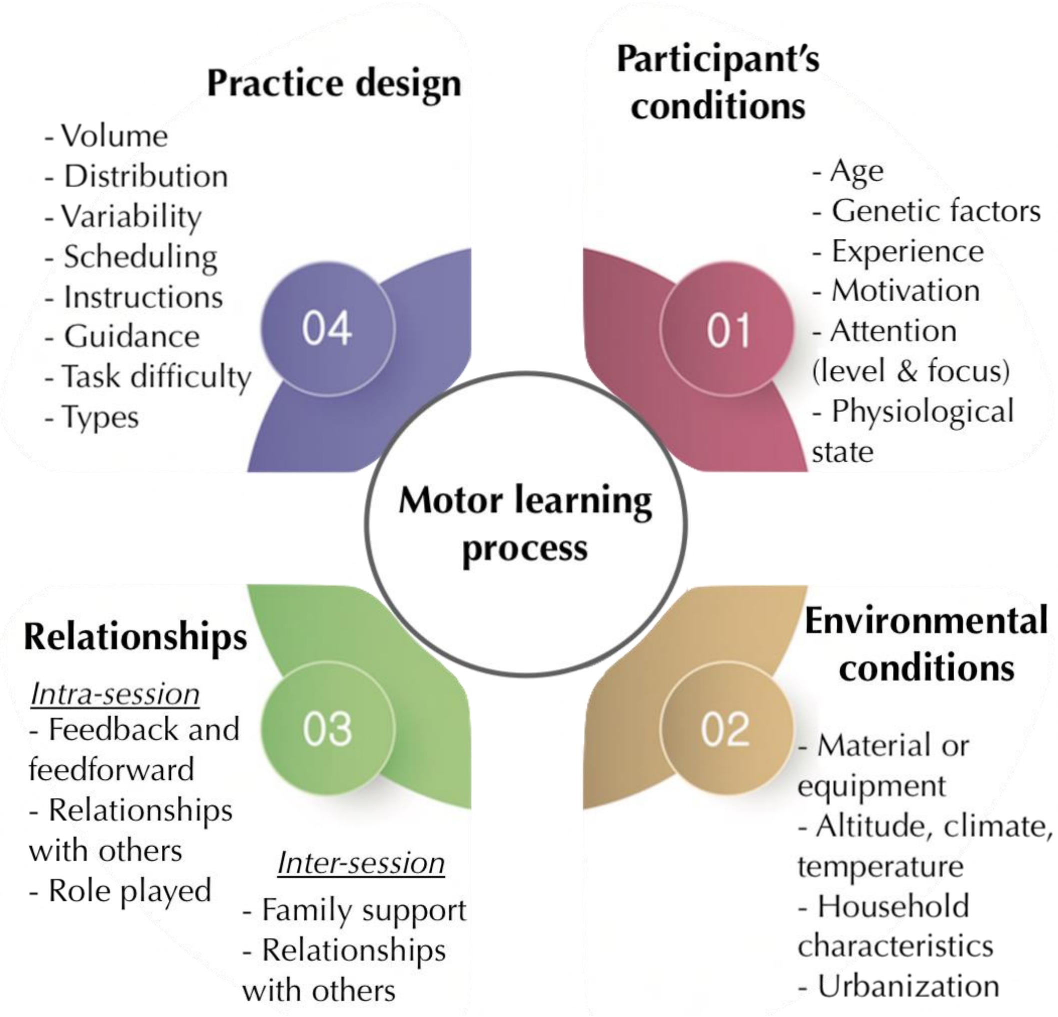


Figure 1. A summary of variables that could affect motor learning.
Figure source own elaboration based on Schmidt et al. (2019) [5].

Motor learning depends on the interactions among practice design, the participant's conditions, relationships, and environmental conditions.

The practice design and the relationships are easily modifiable categories while participant's conditions category encompass more stable variables, some hardly modifiable such as the genetic factor.

The environment conditions category is modifiable or not depending on whether the practice took place -indoors or outdoors-. If the practice takes place outdoors, we cannot be controlled the variables.

1.1.1.1. Practice design

The practice design by teacher, coach or research has an important influence over motor learning process.

Volume: the “law of practice”, more practice leads to a higher level of performance. In general, the exponential function is a good representation function of the relationship between performance and the total amount of practice time. There is a useful popular theory named the “10.000 hours rule” that establishes that it is necessary to accumulate at least 10,000 hours of practice to become expertise (journal article inspired in the Anders Ericsson’ book, [6]). Moreover, learning by doing is necessary to develop normal visual-motor coordination and form correlations between movements and perceptions [7].

Distribution: massed versus distributed practice. More extended rest periods resulted in more effective performances. Practice distribution has large effects on performance and superior retention than massed practice. For instance, Murphy (1916) concluded that practice three times a week was better than once or five times a week in a javelin throwing intervention (the total number of sessions was 34 for both groups) [8].

Variability: Transferring novel task would be enhanced after practice in variability as compared to constant practice conditions. In other words, variable practice seemed to increase generalizability, an essential criterion for motor learning. Indeed, in children, variability had a greater effect than adults on motor learning because children have considerably more to learn. There are many ways in which variability could be generated or manipulated (or both) during practice

Schedule: Randomising the order of practice increases interference levels and results in more unsatisfactory online performance but greater offline motor retention vs block practice. Even highly skilled athletes have many benefits the random practice [9]. The reason may be that the random practice supposes a greater stimulus for the learner.

Instructions: the emphasis on the part of the features of the task determines the performance of execution. For example, if the instructional set emphasised speed and accuracy, the participants were fast and accurate. However, if only speed is emphasised, participants prioritise speed over other qualities and vice versa [10].

Guidance: supposes physical assistance for the learner during the execution of the task. Mainly the objective of this rarely studied method is to prevent injuries and reduce fears.

Task difficulty: affected the motor performance but did not affect motor learning and transfer. The magnitude of learning correlated with the difficulty of the task mediated by perceived mental workload [11]. In addition, the underlying neural mechanisms (electroencephalogram or EEG) data indicated that task difficulty modulated changes in brain activation after practice. For example, the high-difficulty task is accompanied by a reduced brain activation in frontal and parietal areas and is also associated with reduced motor skill retention compared to low and medium difficulty practice specifically in older adults [12,13].

Types of practice:

> Physical, mental, and observational: there are different types of practice, and all of them are important. But physical practice is superior to both mental and observational practice [14,15]. Therefore, the mental and observational practice would complement or a tool therapeutic when necessary, such as a rehab period [16]. Observational practice means learning from a model and is based on a mirror neuron system. It is now a well-accepted notion in neurophysiology that the observation of actions performed by others activates in the perceiver the same neural structures responsible for the actual execution of those same actions [17]. The recommendations for optimising the learning through observational are (i) have previously practice the skill, (ii) self-model and opponent-model are very effective, but with the opponent-model, there was a correlation with age [18] (iii) learning from the model with mistakes vs correct, and (iv) providing advanced information of the observation increment the effects on beginner's performance and learning [19]. Mental practice is more effective when the learner imagines the performance in as much detail as possible and follow the

trajectory with their eyes while imagining [20]. The findings suggest that imagery is a process by which actions are programmed as normal movements but are inhibited from being executed.

Implicit or explicit: in implicit learning (term coined by Reber (1967) [21] and previously described by Gibson & Gibson (1955) [22]), the learning occurs in the absence of awareness or purpose, while in explicit learning, there is awareness. The most accepted model articulates that both implicit and explicit learning contributes to the process of adaptation and motor learning in a coordinated way [23].

Part or whole practice: the effects of these different types of practice depend on the nature of the task. Practice a part of a continuous task would be useful for the motor learning process. However, in the discrete tasks would appear inefficient to practice a part of the task for improvement.

1.1.1.2. Relationships

The relationships with the partners, teacher/coach and family, both intra- and inter-session, are the foundation of development and learning [24].

Relationships encompass the different types of feedback [25] and feedforward [26,27]. Feedback is information about the movement-related for the learner and has several roles (informative, motivational, attention focus). Research suggests that providing verbal technical information with high frequency after successful trials with an external focus results in more effective learning [5].

Feedforward helps distinguish the changes in the external environment caused by movement from the changes in perception caused by one's movement. Disambiguation is reduced by subtracting the difference in perception caused by the motor commands (or the internal perception representation leading to motor command) from the change in perception caused by the change in the external environment [7]. Every movement tends to reflect the combined use of feedback and feedforward.

In all, many studies have shown that providing feedback is one of the most important variables that affect motor learning process.

1.1.1.3. Participant's conditions

Genetic factors: Increasing evidence suggests that epigenetic mechanisms such as DNA play an essential role in learning and memory processes [28]. Regulation of gene expression is vital for proper memory processing because some genes must be activated, and some genes must be suppressed. These processes with genomic characteristics depend on hereditary load [29], but also the processing for expression or suppression depends on environmental factors and stimulus such as practice.

Age: the optimal age for motor learning is difficult to determine. The predispositions seem best up to early adulthood, but lifelong plasticity allows the motor learning process throughout life [30].

Experience: Humans can acquire a general improvement in motor skills learning through experience. Besides, the experience can influence transfer, that is, the ability to generalise what has been learned to task variants and even to new skill. Transfer of learning involves retrieval and modification of previously acquired representations and is neuralgy similar to the LTP [31].

Motivation: the establishment of short, medium, and long-term goals is an aspect highly correlated with motivation. Specifically, there are effects of goal setting on motor learning process. For example, in a shooting task study, the results revealed that the group of participants told to "do your best" performed slightly worse compared with the two specific goal-setting groups (assigned and participant-set goals) after five days of practice [32].

Attention: encompass level and focus, and then we are going to describe both features very briefly.

> <u>Level:</u> deliberate practice requires effort and is not inherently enjoyable. A higher level of motivation during practice leads to an optimisation of the learning process. In other words, not only is important the quantity of the practice (i.e., volume) for the performance; rather, the quality of

the practice (i.e., deliberate practice) would be the discriminant factor between the professionals and best practitioners. For example, the estimated cumulative practice of violinists classified as top performers and professionals is similar at 20 years of age. Then, deliberate practice time in acquisition likely lead to the difference in achievement performance [33]. In the same line, the similar motor performance between single and dual-task conditions [34] support the idea that attentional resources were not necessary to learn sequences. Still, it would be critical to the optimisation of the motor learning process.

Focus: the external focus of attention facilitated both performance and learning compared to internal focus [35,36]. Nevertheless, even though the use of an external focus has become popular in recent years due to its possible advantages over an internal focus, most of these studies are of low methodological quality, and the instructions given to the subjects are highly questionable.

Physiological state: the emotions (anxiety, stress, joy...) [37], quality and quantity of sleep [38], and the consumption of stimulation or relaxing substances (caffeine, alcohol, drugs...) [39] modulate the person's physiological state, which affects learning. If they increase the person's arousal state without excess (e.g., positive emotions, sleeping for long hours or taking stimulant substances), they could favour learning. Nevertheless, if they decrease the person's arousal state (e.g., negative emotions, little sleep or taking relaxers), they make learning difficult and even cause health problems [40]. Besides, the presence or absence of both diseases or injuries modulate the physiological state and therefore affects motor learning.

1.1.1.4. Environment conditions

The relationship between environmental conditions and motor learning is because the environment influences human growth and development [41]. Various environmental conditions such as material or equipment, altitude, climate, temperature, household characteristics, urbanisation, etc., interfere with the motor learning process. In conclusion, enriched environments would facilitate motor learning [42].

Taken together, in the second and third studies conducted in the current thesis, we considered most of these variables in the design to provide participants with a stable and homogeneous environment as possible to optimise the motor learning process.

1.1.2. Motor learning paradigms

There are several paradigms to study the different aspects of motor learning. In this section are described the most relevant paradigm used in the studies of this thesis.

1.1.2.1. Sequence Learning

Sequence learning paradigms describe any movement to achieve a goal as a set of elements organised in a particular temporal order. Sometimes the motor task can be subdivided into discrete movements (such as follow a recipe to make a paella). In other cases, the single movement is continuous, and the events overlap (such as the sequential muscle activations required to perform a basketball shot). Specifically, in a single movement such as a basketball shot, the quality of the resulting motor action depends on the ability of the motor system to execute each sequence element in the correct order and with the right timing, even in the subconscious elements (i.e., muscle activation) [5]. Nowadays, there is a growing interest in the motor control field to know how the sequences are learned, reproduced, and represented in the brain.

1.1.2.1.1. Choice reaction time task

The choice Reaction Time (RT) task is the most prevalent paradigm used to study sequence learning. In this task, participants usually respond to a visual stimulus in a spatially congruent manner -when at least there is more than one stimulus-response alternative. The effectors in choice RT task habitually are fingers [43], but some variants use saccadic eye movements [44], arm reaches [45], or foot stepping [46,47]. The nature of the stimulus and the type of response affect both the performance and motor learning in a choice RT task. Too, other variables affect motor learning process, as we saw in the preceding section.

In the choice RT task, the stimulus can appear in blocks (e.g., AAA – BBB – CCC), in serial (e.g., ABC – ABC - ABC) or in random order (e.g., BCA – ACB – BAC). When stimuli follow a predictable pattern, such as blocks or sequence order, people can respond to the stimulus more accurately and quickly than when the signals are unpredictable or in random order [48]. Many researchers focus on exploring the RT differences between random order and serial order, named implicit learning (i.e., participants learn without awareness a sequence) [49]. Nevertheless, the retention and motor learning seem to be facilitated in the random order conditions compared to the other conditions. The best motor retention in the random condition is probably due to the increase in the demand difficulty level of the task because, as the appearance of the stimulus is more unpredictable, the task is more complex.

The literature on RT is massive, so we will attempt to explain the most relevant results that contextualise the current thesis studies.

According to the classic study of Shea & Morgan (1979) [50], who compared blocks practice to random practice in a visuomotor choice RT task by 72 right-handed students, reported that the retention after 10-min and even 10-days after the intervention was greater for random versus blocks groups (see Figure 2).

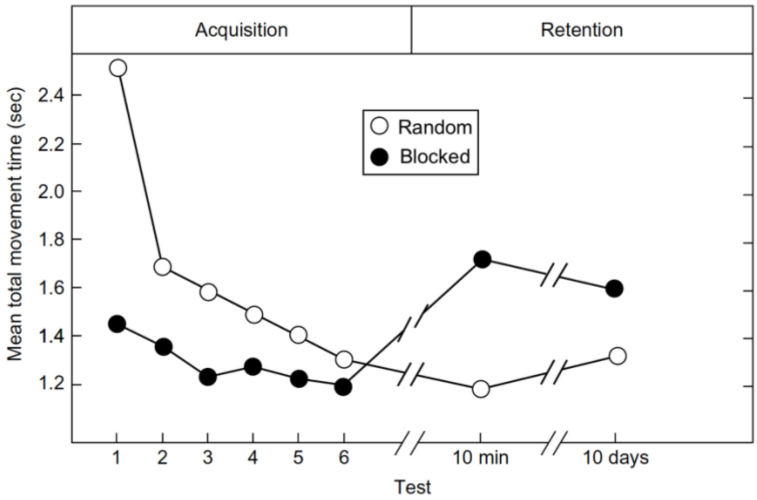


Figure 2. Blocks practice performance vs random practice performance.
Mean total movement time for a series of manual barrier strikes responded to a stimulus light when the barriers were either in a single set of locations in each block of acquisition trials (Blocked) or in varied locations (Random). The retention phase represents the average of both test blocks and random condition. Modified from Shea & Morgan (1979) in Schmidt et al. (2019) [5,50].

These findings have been replicated many times using similar and different task requirements with similar results [51–55].

The serial order condition might be considered “moderate” relative to the extremes (i.e., blocks and random order) because it combines the predictability of blocked practice with the non-repetitiveness of random practice. During the acquisition phase and a few hours after intervention, both serial and random order conditions had a similar performance [52]. However, the serial order condition would have similar retention after 24 hours to the blocks condition in a choice RT task with fingers [56].

Therefore, it would be necessary time -at least 24 h- to consolidate the knowledge acquired through random practice, according to [57].

According to Hicks' law, RT increases as the number of stimulus-response alternatives increases [58,59]. Furthermore, the linear relationship between RT and the number of stimulus-response alternatives suggests that more alternatives require more information processing and greater cognitive demand.

Taken together and following Battig’s pioneer notion [60], high contextual interference (i.e., random practice) produces decrements in performance during acquisition but facilitates the learning process (i.e., motor retention and transfer).

In the current thesis, we employed a modified version of the visuomotor choice RT task original described by Nissen & Bullemer (1987) [43]. Specifically, we employed random order conditions for both training and test tasks, and we assessed the motor retention after 24 hours. These tasks, though elementary, provide interesting information about the motor learning process in human.

1.1.2.1.2. Typing

The typing skill is framed within the sequence learning paradigm since it requires a correct order keystroke to form a message and thus be able to achieve the goal -i.e., communication. Typing is the process of writing or inputting text by pressing keys on a typewriter, computer keyboard, calculator, or cell phone. Nowadays, typing is an important skill, and it is hard to imagine that society ever functioned without it.

The first typewriting studies were done in the 1930s and '40s, and they aimed to explore what typists look at while typing. Yet, the famous typewriter was not massively commercialised until the 1800s, and after that, the typewriter began to be used habitually in human experimental studies.

Typing research has been pioneering in the motor control field, probably due to the nature of this skill. There are three key characteristics of typing that arouse the interest of researchers, that are, is an easily measurable performance skill without a known ceiling effect and very complex ecological skill. Next, I explain each key characteristics of typing.

In the past, authors used video recordings and a microcomputer to measure participants' typing performance on a typewriter [61].

Nowadays, computers became popular, and researchers usually employ software to measure performance. There are many free software that reported both the RT and the number of errors in typing immediately.

For many people, typing is a highly practiced cognitive-motor skill. Many professional typists have over 10,000 hours of practice, and after that, they can still continue to improve by typing with ever fewer errors. Numerous studies reported continuous improvements in writing speed over 100 hours or even years of practice [33,62]. For instance, in a case study with 176 typing practice sessions of 45-minutes each, the author reported a gradual improvement in participant' typing speed and a decrease in error without a ceiling effect [63].

According to the Guinness Book of World Records, Saurav Kumar Gautam uses the usual Qwerty keyboard layout to reach the fastest typing speed ever, 212 words per minute (i.e., approximately 1.060 Characters Per Minute "CPM") with an error of less than 1%. The champion is almost ten times as fast as the beginner, and only 1% of typists exceed 100 Words Per Minute “WPM” (i.e., 500 CPM) [64].

During typing acquisition, finger movements become less sequential and more overlapping with practice, without each keystroke awaiting completion of the keystroke before it. In addition, the limitation of learners’ typing would be cognitive restrictions, while the limitation of an expert would be motor and physical restrictions to improve the typing performance [65]. Besides, the automation of typing skill is possible so that expert typists can engage in dual tasking, i.e., typing and talking without little worsening of typing performance in terms of speed and accuracy [66].

Typing is a complex task that requires a high degree of system synchronisation since the behaviour elements must be ordered correctly in time. Specifically, typing involves the orchestration of sensory-motor, cognitive and linguistic skills [67,68].

The positioning of hands over the keyboard determines the ability to respond to the next stimulus would be affected or not. For example, it is a bad idea to complete the action and not return to the standard neutral hands’ position. It is usually a bad idea to stay near the edge of a tennis court after the shot to the opponent. Returning to midcourt puts you in the best position to respond to the next shot [5]. This reasoning derives from Fitts's law, which states that the time required to respond to a stimulus depends on a logarithmic relationship between its surface and the distance at which it is located [69]. Similarly, by having the hands in the middle of the keyboard at the end of a movement, the subsequent possible movements can be maximally diverse and more efficient. The typing method initially used “hunt-and-peck” - typing with two fingers- was replaced by the touch-typing model because of the better speed performance. Based on this reasoning, the most efficient typing model is the ‘touch-typing’ model [70,71], which is based on the use of both hands and all the fingers over standard position 2–5 of each hand on the respective “a”, “s”, “d”, “f” and “h”, “j”, “k”, “l” keys of a standard Qwerty keyboard. Moreover, the typist does not depend on the sight of the keyboard to know key location with the ‘touch-typing’. Typists seem to learn associations between signals and response locations, not associations between signals and finger movements. This outcome agrees with the results reviewed earlier concerning cognitive maps [72] and stimulus-response compatibility [73]. For this reason, it is very important to learn typing with a standard neutral hands' position of the finger over the keyboard.

Typing is an ecological skill that is subdivided into obvious parts, such as each letter. However, studies indicate that the letters are clustered to form "Chunks", stored/memorised as units, but that does not correspond to letters or syllables [7]. Interestingly, the intervals between keystrokes by expert typists are very irregular and maybe not follow a common pattern [74]. More studies are needed to check this hypothesis.

There is the main difficulty to interpret the results of typing studies. First, the measures of performance (e.g., accuracy and RT) usually are reported independently. To better explain this difficulty, we will provide an example, if participant A had a mean of 360 ms of RT with 97% accuracy, and participant B had a mean of 380 ms RT with 93% accuracy, whose typing performance is better? To answer this question, it is necessary to calculate the speed-accuracy tradeoff function. The calculation of the Speed-Accuracy Tradeoff (SAT) has received renewed interest in neuroscience approaches [75]. In the recent studies on the results of behavioural learning, different formulas are applied that relate both variables speed and accuracy to better understand human behaviour.

Taken together, we consider that typing is a suitable task to study the motor learning process. **We employed in Studies II and III the typing task.**

1.1.3. Phases of motor learning

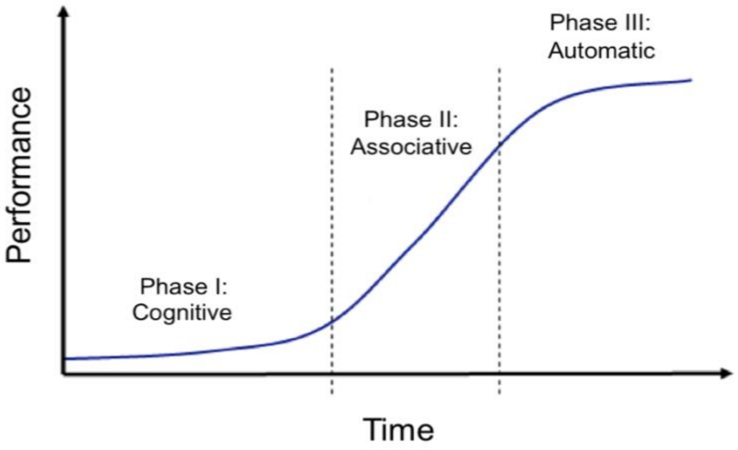


Figure 3. Graphic representation of the three stages of motor learning.
Figure source own elaboration based on the theory described by Fitts & Posner (1964) [76].

Traditionally the motor learning process is organised in three stages as they practice a skill: cognitive, associative, and automatic stage. Different names refer to each stage, but we selected this terminology according to the pioneers in this field Fitts & Posner, (1967) [76] (see Figure 3). Years later, Anderson (1981) showed that these stages apply to intellectual skills and perceptual-motor skills. These stages are not discrete and fixed stages but have "fuzzy" borders and high interindividual variability [77]. Next, we will very briefly explain each stage.

There are other types of categorization and approaches to the phases of motor learning. Recent advances in neuroimaging provide a new perspective on the functional reorganization associated with the acquisition, consolidation, and retention of motor skills and suggest that phases of learning last for shorter periods of time than previously thought [78]. However, studying traditional theories of motor learning such as Fitts & Posner helps us better understand these complex processes.

1.1.3.1. Cognitive stage

In this initial stage of motor learning, the goal is to develop a comprehensive understanding of skills. The learner must determine the goal of the skill, and for this, it is necessary a considerable amount of attention to practice. At this stage, learners mainly rely on visual cues and trial and error to guide learning.

1.1.3.2. Associative stage

Then learners begin to demonstrate a better performance through practice. During this stage, learners try out various task components and associate them with the success or failure of achieving the goal reported by the feedback. They can concentrate on the "how to do" (i.e., procedures) from the first stage of "what to do". Here, visual cues become less important, and proprioceptive cues become very important. Specifically, feedback about performance is critical during this phase [79].

1.1.3.3. Automatic stage

In the third stage, the autonomous or automatic stage, behaviour is performed quickly and consistently with greater immunity to interruption from external events. It is the least known state because there are few studies that explore this automatic stage due to the difficulty of long-term studies procedures [5]. At this last stage, learners need less attention than the previous stages to execute the task, and they can attend to other things (e.g., marker or the weather). There is a plateau visual effect of performance at this stage –i.e., the plateau of the learning curve- because the changes are mostly slight but with a positive trend.

The theoretical learning curve seems to have an "s" shape, increasing slowly at first and then increasing rapidly at the second stage, flattening out as practice continued. Still, it appears to have a positive trend from year to year in complex skills. The learning process can take different lengths of time for every individual and progression depending on many factors, as we suggested in the previous section "Variables that affect motor learning process". Yet among all the variables that can affect the learning curve, highlight the difficulty of the task because it is obvious that, for example, the learning curve of a simple reaction time task would be very different compared to the typing learning curve.

The real learning curve differs largely from theoretical in complex skills, mainly because there are large inter-individual differences and irregular learning processes. For example, in Figure 4 (A), you can see the learner's curve of typing performance across 176 sessions of practice. Figure 4 (B) shows another example of the learner' curve of typing performance across 50 practice sessions. In both case examples, the learning process is irregular and does not follow a standard similar learning curve.

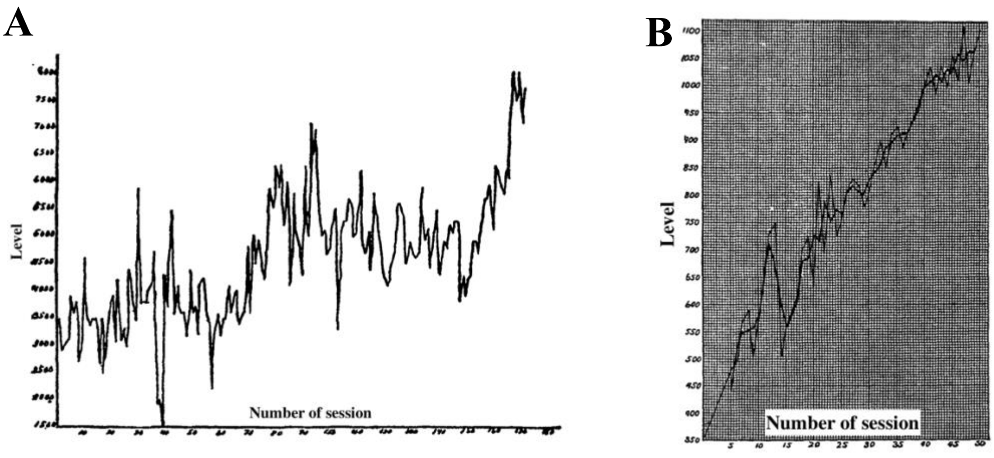


Figure 4. Examples of learning typing curves.
An individual learning typing curve (A) across 176 practice sessions and (B) across 50 practice sessions, both in a case study. Modified from Towne (1922) and Swift (1904) [63,80].

The differences in the participants' learning curve could occur due to difference in the initial level, differences in the learning process, or differences in the cognitive strategies used.

Yet, there are still many questions for which this old theory has no answer [81]. For example, when does the change of associative stage and automatic stage occur or what are the functional properties of automatic versus non-automatic processes?

Further studies with large samples are needed to explore the learning curve in a complex skill such as typing. We tried to shed some light on this topic by study IIa and IIb, reporting the individual motor learning curves. **Study II would be framed within the associative stage, according to Fitt's and Posner's paradigm.**

1.1.4. Neurological changes

Repetitive motor actions induce changes in the central nervous system and these adaptations are summarized by the concept of neuronal plasticity or neuroplasticity. One form of neuroplasticity is synaptogenesis, i.e., formation of new synapses. Another form of use-dependent neuroplasticity is the strengthening the connections between synapses.

Synaptogenesis and strengthening synapsis seem to be the foundation of learning and depends on long-term potentiation (LTP) and long-term depression (LTD)-like mechanisms [82,83]. Therefore, there are three main principles of brain plasticity at the neural level: (1) synapses are modifiable, (2) they formation and strengthen with learning and practice, and (3) they disappear or weaken with disuse [84]. Besides, learning promotes neurogenesis (the formation of new neurons). For example, in rodents motor learning through practice was associated with a specific reorganization of representations of movement within the motor cortex [85]. However, in a recent systematic review of the current evidence on the effects of physical exercise (i.e., motor practice) on the brain, the authors concluded that the current evidence on the effects of physical exercise on grey matter brain volume seems inconclusive and scarce, and does not support that physical exercise is as powerful as previously proposed when it comes to affecting grey matter brain volume [86]. It is also unclear whether the white matter volume changing with motor practice in humans. For example, in a recent systematic review, eight studies (62%) suggested that motor practice increased brain structure or reduced grey and white matter atrophy. Nevertheless, five other studies (38%) did not observe any change in brain structure following exercise intervention or between groups [87]. Future research will need to focus on newer imaging techniques and longitudinal studies to provide more detailed information about neuroplasticity associated with motor practice.

From preclinical studies, the positive effects of exercise (i.e., motor practice) have been related to increased levels of neurotrophic factors, reduced levels of neuroinflammation [88], and improving brain functionality [89]. Neurochemical compounds such as brain-derived neurotrophic factor (BDNF) and Gamma-aminobutyric acid (GABA) underlie neuroplasticity in the brain. Specifically, reducing GABAergic signalling and increasing BDNF expression appears essential to the induction of long-term potentiation (LTP)-like plasticity in different brain areas such as M1 after motor practice [90]. For instance, changes inhibitory in the GABA system are thought to be essential in inducing brain plasticity after motor training. Specifically, in a study that used magnetic resonance spectroscopy in humans, the authors reported that lower primary motor cortex (M1) GABA concentration was associated with greater motor performance in a serial reaction time task [91].

1.1.5. Brain regions that contribute to motor learning

The brain's principal roles in motor learning govern motor output based on perceptual information and intentional states. Numerous regions throughout the brain have been identified as contributing in some way to motor learning.

Depending on the learning paradigm and the stage of learning, each area's involvement is different [92], and there is still some controversy about the weight of their roles (Figure 5). According to D. Ramón y Cajal, a pioneer of modern neuroscience and winner of the Medicine Nobel Prize in 1906: "The brain is the most mysterious organ of the human". To date, the brain mechanisms underlying motor learning remains unclear.

Although other areas of the brain also contribute to motor learning, in this section that follows, we focus on explaining the contribution of motor cortex in human motor learning because it is the target area in the studies of this thesis.

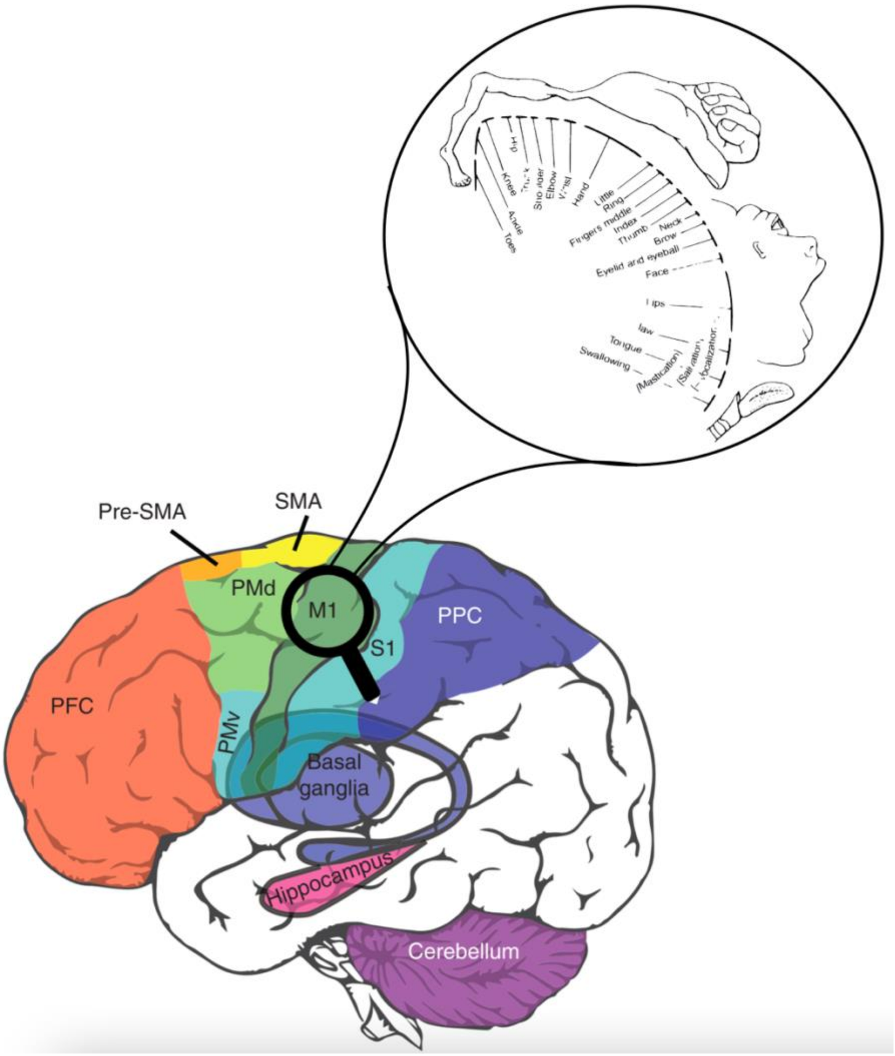


Figure 5. Several brain regions and the motor map of the body.
Modified from Krakauer et al. (2019) and from Penfield & Rasmussen (1950) [1,93]. Index to abbreviations: PFC (red): prefrontal cortex; pre-SMA (orange): presupplementary motor area; SMA (yellow): supplementary motor area; PMd (bright green): dorsal pre- motor cortex; PMv (cyan): ventral premotor cortex; M1 (dark green): primary motor cortex; S1 (cyan): primary somatosensory cortex; PPC (blue): posterior parietal cortex; basal ganglia (blue); hippocampus (pink); cerebellum (purple).

The motor cortex can be divided into three areas: a) the supplementary motor area (SMA), b) the premotor cortex, and c) the primary motor cortex. Briefly:

a) The SMA has many proposed functions, including the planning of complex movement sequences, high-level control of movement, and the coordination of the two sides of the body, such as cooperative behaviour of the two hands [94].

b) The premotor cortex is responsible for certain aspects of motor control, which may include movement preparation, sensory and spatial guidance for movement or direct control of some movements with an emphasis on control of the trunk and proximal muscles of the body, such as shoulders muscles [94].

c) The primary motor cortex (M1) is the main contributor to producing neural impulses transmitted to the spinal cord and control the movement execution, emphasising distal muscles, such as fingers. M1 is a trigger centre rather than a planning centre for movement. Besides, the motor cortex also receives feedback from the movements. M1 neurons receive sensory input from the muscle fibres they innervate [95], thereby tightly coupling efferent and afferent functions. Base on neurosurgery experimental studies, Penfield & Rasmussen (1950) developed a "motor map" of the body (Figure 5) with the representation of the different body regions in M1 [93]. According to the demands of required movements, the representation in M1 of somebody regions is diverse. For example, the mouth and hands take up a more significant motor cortex portion than do the legs or torso because the mouth and hands perform complex movements that demand a lot of control and precision.

Moreover, the learning of motor skills has been associated with plasticity in M1 [96], specifically during the early/rapid stages of motor skill acquisition [97–101]. For instance, findings in rats suggest that M1 plays an active role in motor skill acquisition up to 9 days, after which M1 can become disengaged from movement control [98] (see Figure 6). A hypothetical explanation is that the high plastic characteristics of M1 results in easy new skills codification, which can be modified during the initial stages of learning. When the skill has learned, it would be beneficial to transfer the information to other brain regions to promote automation [102] and the possibility that M1 available to learn other novel movements.

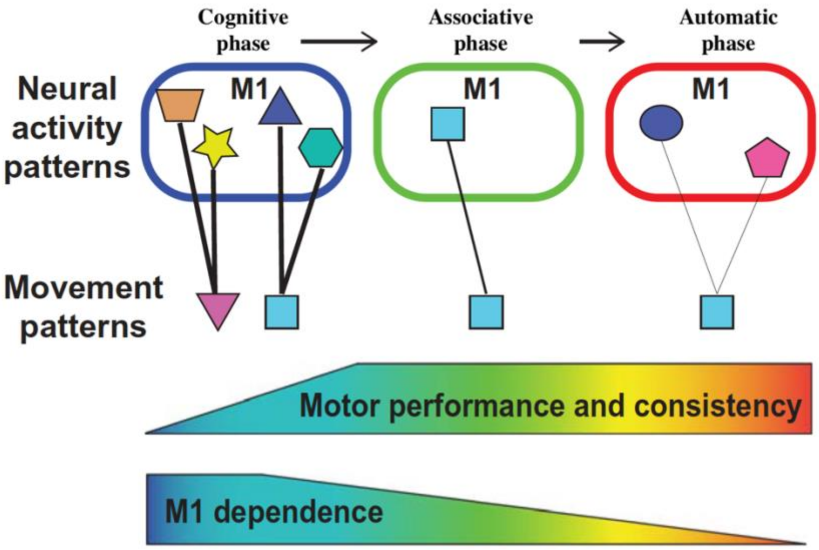


Figure 6. A graphical model of the primary motor cortex (M1) involvement in the evolution of long-term motor learning.
Adapted from Hwang et al. (2019) [98].

So far, this concise review has focused on the role of different parts of the brain in humans motor learning and related functions. However, the different parts of the brain must work together to achieve goal-oriented functional adaptability. The connections between brain regions must work correctly to ensure that each player in the neuro orchestra plays the symphony. If those regions are not properly connected, problems can arise.

1.1.6. Limitations of the studies

The major problem for motor behaviour research is that automatization phase motor skill is rarely studied in experiments on motor learning despite the immense importance of understanding high-level (i.e., complex) skills. It is challenging to convince participants to devote this kind of effort and commitment in experiments for months or even years.

Findings support the conclusion that learning new motor skills involves morphological and functional changes at the neural level (i.e., brain plasticity) [78,103]. Nevertheless, plasticity occurs as a result of cumulative practice, so the time intervention period should be more extended than those currently used, usually lasting one to three weeks with 3 to 5 intervention sessions [5], except for case studies. In addition, in the motor learning field, cross-sectional studies predominate over longitudinal studies, although this is not coherent since the learning is a process that involves a lot of time. Similarly, it is interesting to explore whether there is a standard learning curve or whether each person's learning curve is different for optimising motor learning.

Sometimes benefits of practice are most obvious when the conditions of performance exactly match the conditions of learning. This outcome is called specificity of practice and is a crucial skill-acquisition principle [4]. Yet, many studies use simple laboratory tasks with the limitations of generalizing these conclusions to practical applications of motor learning. The correlation degree between laboratory-based skill studies and actual experience is unclear, and this may depend on the effects of practice on multiple cognitive processes beyond the traditional sensorimotor structure [1].

The principles derived from the study of simple skills do not generalise to the learning of complex skills [104]. In a recent review of motor learning, Krakauer et al. (2019) suggested that although simple learning tasks may not allow us to fully understand how complex real-world skills are learned, these tasks provide basic information about the components of learning that may be necessary (if not enough) to illustrate how to learn daily life skills [1]. One possible way to address this limitation is to use ecological tasks in intervention studies

More ecological studies are needed with longer intervention periods and that individual report data to improve understanding of the learning and retention processes in the medium and long term.

1.2. TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) AND MOTOR LEARNING

1.2.1. Description and history

Electrical stimulation to treat medical conditions is not a new therapy; it has been used to treat diseases for centuries (see brief review Ref. [105]). Originally, thousands of years ago, they already used electric fish to treat pain and various pathologies. It is not until the 18th century that the first controllable artificial device electrical is created. In the 20th century, the application of tDCS in humans became popular as a tool for the potential treatments of various pathologies with fewer side effects than traditional pharmacological methods [105].

Transcranial direct current stimulation (tDCS) is a safe, portable, painless, and affordable non-invasive brain neuromodulation technique that doesn’t require a physician’s prescription.

tDCS applies a weak direct current through two electrodes (anode and cathode). These two electrodes are positioned above the human scalp, reach the neuronal tissue, and cause a polarisation shift on the resting membrane potential (that is, the current flows from the anode to the cathode) without triggering an action potential itself [105] (see Figure 7). Thus, although the individual response to stimulation is not uniformly excitatory or inhibitory, the anode tDCS is generally considered excitatory. In contrast, the cathode tDCS is generally considered inhibitory [106].

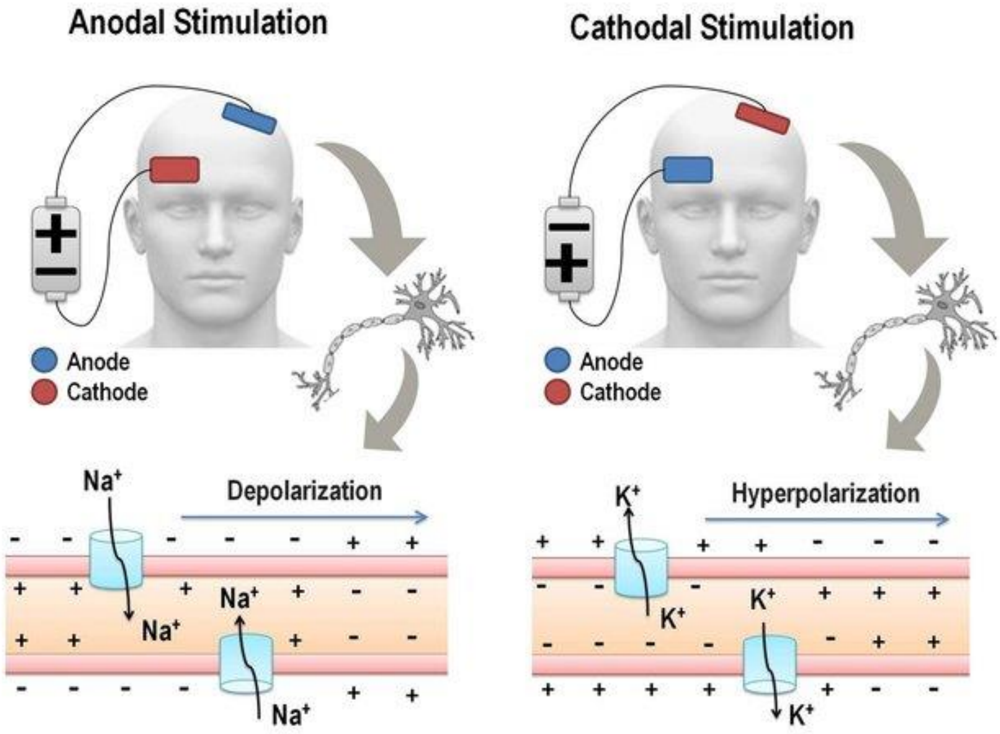


Figure 7. Effects of transcranial direct current stimulation (tDCS) on membrane polarisation. Schematic representation of the effects of anodal and cathodal on membrane polarisation. (A) The anodal electrode and (B) the cathodal electrode over primary motor cortex (M1). The anodal stimulation depolarises the neuronal membrane and enhances M1 excitability. The cathodal stimulation hyperpolarises the neuronal membrane and diminish M1 excitability. Overall, the type of stimulation determines the modulatory effect of tDCS. Adapted from Rozisky (2016) [107].

In the past few decades, progress in technology enables the creation of precision tDCS devices with superior control over stimulation parameters at reduced costs. Research into the efficacy of tDCS treatment has exploded, with over 972 peer-review scientific studies on the topic having been published in 2020 alone. This stimulation technique is becoming so popular because of its easy application, low cost, and apparent ability to improve cognitive function in treating various neurological diseases and motor performance in healthy [108]. Sensational news about the potential benefits of tDCS prompts people to self-administer stimulation at home, but further research is needed to ensure that it is a safe long-term technique and to establish the optimal settings for each treatment.

1.2.2. Physiological and behavioural changes

It is noteworthy that physiological and behavioural aspects suggest the modulation effects of tDCS are likely generated through brain plasticity-like mechanisms [108]. As discussed in the preceding section, tDCS modifies neuronal membrane polarity hence changes resting membrane threshold. In this way, the electrical current induces a sustainable response in the form of LTP by anodal stimulation or LTD plasticity by cathodal stimulation. However, the mechanisms of action of tDCS are not yet well elucidated.

Surprisingly, tDCS elicits after-effects lasting for up to 90 minutes when the duration of the stimulation is 10 minutes or more [107,109]. Hence, tDCS mechanisms of action cannot be just attributed to changes in the electrical neuronal membrane potential. Both LTP and LTD mechanisms induced by tDCS are complex, and several pathways and molecules govern these processes, including morphological and functional adaptations through cellular and molecular changes and alterations of chemical messengers that transport information from one neuron to the next (e.g. neurotrophic factors and neurotransmitters) because have electrical properties [110–112]. In this section, we will describe very briefly how tDCS could promote underlying long-lasting effects in adults.

The activities of ion-voltage channels are polarity dependent. Nevertheless, the mechanisms underlying the LTP and LTD of tDCS is attributed not exclusively to the changes of electrical neuronal membrane potential (i.e., effects in ion-voltage channels) but also to the changes on gamma-amino-butyric acid (GABA) and N-methyl-d-aspartate (NMDA) [107]. tDCS interferes with brain excitability by modulating intracortical and corticospinal neurons [113–115], triggering the modulatory effects of GABA and NMDA systems.

In healthy humans, the application of tDCS modulated the level of GABA concentrations [116]. For instance, in a recent study with 17 healthy adults, the authors reported that tDCS modulated the GABA concentration in the brain. Besides, they employed efficient techniques for the evaluation, such as magnetic resonance spectroscopy and positron emission tomography [117]. As we have discussed in previous sections, there is evidence that reducing cortical GABA has been correlated with positive increase plasticity [118]. These effects increase the possibility of LTP occurring at those synapses, and there is a similar process derived from the motor practice itself [119]. Therefore, the combination of tDCS with motor practice could have interactions such as improved brain plasticity-like mechanisms.

Moreover, tDCS appears to neuromodulate a wide range of neurotransmitters related to motor practice, such as the noradrenergic, dopaminergic and serotoninergic [90,120,121] that contribute to LTP-induced (see Figure 8). Besides the involvement of neurotransmitters in mechanisms underlying LTP and LTD induced by tDCS, the contribution of BDNF is essential for changes at the synaptic level that stimulate strengthening synapsis that induce LTP. The effects of tDCS over BDNF that contribute to neuroplasticity have demonstrated in both animals and humans' studies. For example, the tDCS applied in mice promoted BDNF-Dependent Synaptic Plasticity [122–124] and the authors suggested that BDNF is a key mediator of the LTP-induce by tDCS. However, healthy humans' studies are limited since they are of very few sessions and continuous sessions are necessary to induce a change in BDNF by cumulative stimulation [125].

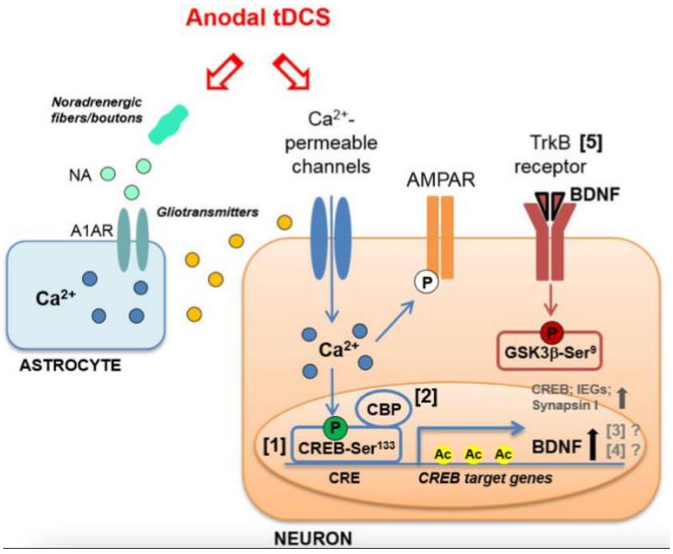


Figure 8. Physiological processes induced by transcranial direct current stimulation (tDCS). Schematic representation of molecular cascades involved in anodal tDCS induced enhancement of synaptic plasticity and memory in animal models. Index to abbreviations: BDNF: brain-derived neurotrophic factor, NA: noradrenaline. Adapted from da Silva et al. (2015) [126].

The combination of tDCS and motor practice may improve motor skill learning through augmentation of synaptic plasticity by different modulation upon neural pathways [127] and outcomes in greater enhancements of this process.

Yet, other results show a lack of physiological effects of tDCS. For instance, [127] reported in a systematic review that tDCS generates little-to-no reliable neurophysiological effect beyond Motor-Evoked Potential (MEP) amplitude modulation in healthy human participants. Furthermore, more than 80% of the studies that reported the effects of tDCS on MEP amplitude modulation did not include a CON/sham group [128].

How much current reaches the brain, and it distributes across the brain is crucial to a firm mechanistic understanding of tDCS effects. For example, in a study with human cadavers and rodents brains, authors reported that 75 to 90% of the scalp-applied current are attenuated by soft tissue and skull [129]. However, some experts argue that ~10% of the current reaching the brain does not necessarily mean that the methods are ineffective. Other experts support the idea that intensities higher than those used in current protocols are necessary to affect neural circuits. Furthermore, the use of cadavers to test these methods is problematic because dead tissue conducts electricity differently than living tissue [129,130].

Recently, computational methods have become increasingly sophisticated over the years, but experimental data are needed to justify these modelling assumptions [131]. In addition, studies in monkeys and humans have reported substantial differences among individuals concerning the electric field strengths generated [129], which might explain the variability in response between participants to tDCS. Therefore, in the current state of knowledge about the direct effects of tDCS in brain circuits and the absence of individual brain imaging measures (e.g., functional magnetic resonance imaging “fMRI”), we prefer to be cautious in the current thesis to avoid the use of computer models whose validity could be highly questionable.

1.2.3. Set up of tDCS might affect its efficacy

tDCS uses low direct current intensity through electrodes attached to the scalp. The parameters that govern the cortical excitability changes of tDCS are electrode positioning, the polarity of stimulation, the total current density of stimulus, the timing of stimulation in relation to motor practice, the number of sessions, and other parameters.

The target brain cortical area to be stimulated will depend on the purpose of stimulation. Though tDCS electrical fields are relatively non-focal because the direct electrical current can reach and modulate subcortical and deeper structures connected to the stimulated cortical area [131], the electrode positioning is critical. The tDCS is considering a "functional targeting" [107,132] because the intensity is too low and not generate de novo activity; therefore, tDCS could mainly affect networks that have already been activated [133]. This promising characteristic of specific selectivity can be considered a virtue and a controlling factor over its possible effects. Furthermore, these results explain the dependence of tDCS effects on the state of the brain [134]. For example, in studies exploring the motor cortex or treating musculoskeletal disorders, the anodal electrode is generally placed over M1 and the cathode on the contralateral area of the body (e.g., the contralateral supraorbital area) (see Figure 9). Besides, most of the tDCS articles studying motor learning have focused on M1 because of its essential role in neuroplasticity [133]. **We employed the habitual position of the electrodes in Studies I and III.**

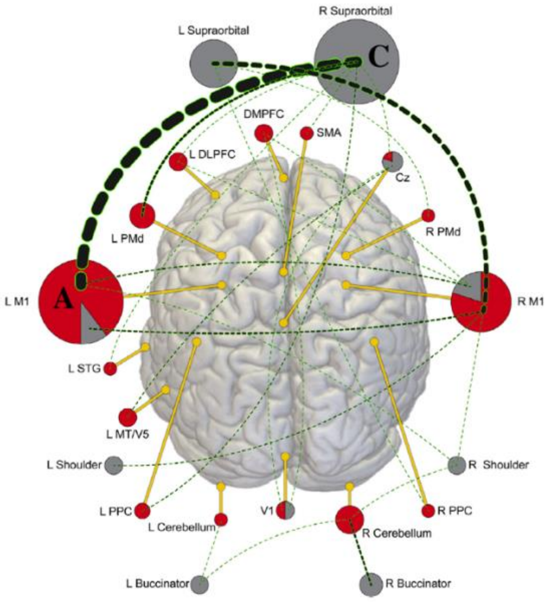


Figure 9. Usual setups transcranial direct current stimulation (tDCS).
The proportion of tDCS montages utilised in motor learning intervention. Circles for each location are proportionally filled with red (anode) and grey (cathode) to represent the relative number of studies the anode or cathode was placed at that position. The diameter of each circle is relative to the proportion of experiments that the location was used. Dashed lines represent montage connections between anode and cathode, with the line weighted relative to the ratio of experiments that particular montage was used. Index to abbreviations: L: left, R: right, M1: primary motor Cortex, PMd: dorsal premotor cortex, DLPFC: dorsolateral prefrontal cortex, DMPFC: dorsomedial prefrontal cortex, SMA: supplementary motor area, STG: superior temporal gyrus, MT/V5: middle temporal visual area, PPC: posterior parietal cortex, V1: primary visual cortex; A: anode; C: cathode. Adapted from Buch et al. (2017) [135].

As discussed previously, the tDCS has dependent polarity-effects since anodal stimulation enhances the corticospinal excitability, while cathodal diminishes it shown by the amplitude of motor-evoked potentials (MEPs) [116]. Horvath et al. (2016) compared 15 different single-session stimulation protocol over M1 (n= 150 participants), and they reported a lack of predictable or reliable effects on simple visuomotor reaction time task [128]. The authors suggest that additional research of multisession tDCS protocols or the use of a more complex task could clarify the mechanisms underlying this possible neuromodulation tool.

The most common range tDCS density is 0.28 to 0.80 A/m^2 because electrode sizes are typically 25 to 35 cm^2 and the intensity parameter is 1 to 2mA for up to 20-40 minutes [136]. tDCS conventional charge (reflecting intensity and duration) in humans is limited to 7.2 C (e.g. 3 mA for 40 minutes) to avoid tissue injuries

[136]. In addition, the number of sessions is an important parameter, as there is evidence of cumulative effects of tDCS [137] but more studies are needed to confirm these findings. Also, it is important to consider the high inter-individual variability in response to tDCS, which is around 50% [138].

Although current evidence suggests timing-dependent effects, there is controversy about what is the best moment for the tDCS stimulation before, during, or after motor practice [139]. For instance, one open question is when the application of brain stimulation is more effective for long-term effect. In the first study of this thesis, we have tried to answer this question.

On the other hand, the number of sessions seems to have a considerable positive influence on the effect of tDCS. The cumulative effect of tDCS is still unclear. It should be further investigated, mainly in terms of complex skills, because tDCS may produce more effective results based on the duration of the intervention [100,140,149,150,141–148].

Despite a large number of recent tDCS studies, there is no consensus on the configuration and protocol used (for reviews about technical tDCS guides, [151,152]); maybe because of the complexity of the human brain. A potential concern is that tDCS protocols are not universally standardised. **In the current thesis, we have used the most common tDCS setups to compare the results with the most studies.**

1.2.4. Application to enhance motor learning

tDCS has been shown to be useful to increase attention, learning, memory and other high-order processes such as problem-solving [153]. Specifically, tDCS combined with motor skill learning has been investigated as a tool for enhancing the effectiveness of training in health and disease [153]. Therefore, tDCS over the motor cortex is a useful therapeutic tool for treating different neurological pathologies such as fibromyalgia or neuropathic pain [135]. In addition, tDCS over the motor cortex can enhance cognitive abilities associated with motor skill learning in healthy people, thereby optimising the process.

Recently, evidence has emerged showing promising beneficial applications for the combined use of tDCS and motor practice to optimise the motor learning process in healthy adults. For instance, in a practical review, the authors reported the potential of anodal tDCS to enhance athletic performance [154]. Another promoting effect of tDCS is reducing fatigue [155] that may explain the relation between tDCS and motor learning. Fatigue reduces performance and consequently affects the motor learning process [156–158].

The leading paradigms combined with tDCS to research motor learning are motor sequence tasks such as serial reaction time task (SRTT) [5]. Some studies have shown the effects of a single tDCS session on M1 has a positive effect on performance in motor sequence tasks [159]; however, other studies have also proven lack of effect [152,160,161]. Variability and contradictions between studies need to be considered. Still, this is often caused by methodological differences such as the timing of application among the others. Remarkably, the timing of tDCS application is an important parameter because the effect of tDCS on the excitability of plastics in the cerebral cortex may change. The timing-dependent effects of tDCS in relation to motor practice (i.e., tDCS application before, during, or after motor practice) have already been investigated in several studies. Yet, the results are different, and so far, there is no consensus.

The tDCS effects seem to be more effective offline compared to online motor learning gains in healthy adults. In a review and meta-analysis study, [161,162] reported that a single session of tDCS did not enhance speed but did improve accuracy 24 hours after the intervention in SRTT. Hence, retention after a single day of a-tDCS was statistically significant for this type of task but not during or immediately after stimulation (see review Ref. [152]). Similar results have been obtained by other investigators reporting that a-tDCS enhances offline learning in a visuomotor stepping skill in healthy adults [163]. Perhaps the effects of a single session of tDCS on motor learning may be controversial because studies rarely measure retention (e.g., assessment after 24 hours of intervention) and usually measure during or immediately after the intervention.

Multiple sessions of tDCS induced a significantly greater motor improvement compared to a single session (see review Ref. [161]). In fact, repeated sessions of tDCS could have cumulative effects associated with greater duration and magnitude of behavioural outcomes. For instance, tDCS applied over M1 for 5 sessions induced an increase in cortical excitability, whereas a single session did not in healthy adults [152]. In another study, the authors reported that tDCS over M1 for 3 practice sessions was associated with cumulative enhanced motor learning in children that lasted up to 6 weeks after the end of stimulation [138]. Even the positive effects on motor learning of the combination of tDCS and 5-days practice appear to be sustained at 3 months in healthy adults [164]. Nevertheless, these interventions in healthy participants lasted for 3 to 5 intervention days (see Table 1), so we do not know what will happen in longer periods.

For the summary of multiple sessions tDCS in Table 1, we include articles that met the following criteria: (i) minimum two intervention sessions with the same stimulation protocol; (ii) intervention sessions separated by at least 24 hours; (iii) measurement of behavioural changes (such as movement accuracy, speed and motor skill); (iv) employing hand task with computer; (v) healthy young adults populations; (vi) having a control group (sham plus training or training only), and (vii) published in peer-reviewed journals in English.

Applying multi sessions tDCS during motor practice intervention has been shown to facilitate motor learning in healthy young adults despite methodological differences across studies (for an overview, see Table 1). The beneficial effect of anodal multi sessions tDCS has been demonstrated for many laboratory motors tasks (as shown in Table 1), such as visuomotor tracking task, SRTT and Sequential visual isometric pinch task (SVIPT). The sample sizes of the intervention groups are relatively small (less than 15 participants), and training of these tasks occurred over a period between 3 and 5 days. Interestingly, the beneficial effect of multi sessions tDCS mainly emerged through skill gains acquisition between sessions (offline effects) and was still present at long-term retention tests taking place up between 15 min to 1 month after acquisition in some studies. The effect sizes are moderate to very large, except for [165], who reports a trivial effect size.

In 2 of the 19 articles descripted [166,167], they shown a robust beneficial skill gains acquisition within sessions (online effects), without an additional improvement between session (offline effects) [166,167]. Only Prichard et al.

(2014) reported null tDCS effects in all tests (i.e., online, offline and retention tests) on behavioural or neurophysiological changes in visuomotor tracking task across 4 days of intervention [167].

Most of the studies in this summary applied tDCS over M1 excluding five studies that applied tDCS over other cortical area such as PFC or DLPFC or SMA or cerebellar [168–172]. All studies applied tDCS concurrent to the motor practice except one study [166], which applied tDCS before motor practice.

The methodological differences regarding stimulation parameters, tasks employed and evaluation tests, make it difficult to draw clear conclusions on these results. Further studies are needed that exploring multi sessions tDCS effects on motor learning and previous studies also need to be replicated with bigger sample size.

Table 1. Summary of multi sessions tDCS studies.
Effects of multisession tDCS on motor learning in healthy right-handed young adults.

Study	**Sample**	**Days**	**Electrode montage**	**Intensity (mA); Current density (mA/cm^2)**	**Duration and timing**	**Significant tDCS effects vs. sham**	**ES**	**Rating of ES**	**Conclusions**
Visuomotor tracking task									
Naros et al. 2016 [166]	N= 30, 27 ± 5y Groups: n= 10	3	EGu: A: Right M1 R: Supraorbital EGd: A: Right M1 R: Left M1	1.5; 0.06	15 min Concurrent MP	Null online ↑ Offline ↑ Offline 1w ↑ Offline 1m	- η^2_p= 0.33 η^2_p= 0.29 η^2_p= 0.37	- Large Large Large	Stimulation groups exhibited greater total learning offline than SHAM. At retention only the dual-M1 group was significantly higher when compared with sham.
Karok et al. 2017 [173]	N= 50, 28 ± 9y Groups: n=10	3	EGu: A: Right M1 R: Supraorbital EGd: A: Right M1 R: Left M1	EGu: 1; 0.06 EGd: 2; 0.06	20 min Before MP	↑ Online	Beta= 0.51		Bilateral TDCS induced larger effects than unilateral stimulation on task performance
Naros et al. 2016 [166]	N= 91, 25 ± 5y Groups: n=18	3	EGu: A: Right M1 R: Supraorbital EGd: A: Right M1 R: Left M1	1; 0.06	20 min Concurrent MP	↑ Online Null offline	η^2= 0.15 -	Large -	tDCS enhances motor skill learning over multiple sessions; specifically, by increasing on-line rather than off-line learning.
Prichard et al. 2014 [167]	N= 75, 19-30y Groups: n=15	4	A: Left M1 R: Supraorbital	2; 0.08	20 min Concurrent MP	Null online Null offline Null retention 1w	-	-	Although task performance improved over days, no significant difference between stimulation protocols was observed on behavioural or neurophysiological changes.

Study	**Sample**	**Days**	**Electrode montage**	**Intensity (mA); Current density (mA/cm^2)**	**Duration and timing**	**Significant tDCS effects vs. sham**	**ES**	**Rating of ES**	**Conclusions**
Serial reaction time task (SRTT)									
Vancleef et al. 2016b [174]	N= 48, 23 ± 4y Groups: n=12	3	A: Right M1 R: Supraorbital	2; 0.08	13 min Concurrent MP	Null online ↑ Offline	NR	-	tDCS resulted in greater sequence specific benefits compared to a single session of stimulation. But no differences in the general motor skill (i.e., random).
Debarnot et al. 2019 [175]	N= 67, 28 ± 4y Groups: n= 16, 17 and 20	3	EGu: A: Left M1 R: Supraorbital EGd: A: Left DLPFC and left M1 R: Supraorbital	EGu: 1; 0.17 EGd: 1; 0.33	20 min Concurrent MP	Null online ↑ Retention 4w	- SMD: -0.03	- Trivial	tDCS during the training led to a durable effect up to 4 weeks; however, dual-tDCS had a longer lasting (up to 4 weeks) effect on learning
Talimkhani et al. 2019 [172]	N= 20, 21 ± 1 y Groups: n= 20	3	A: Left SMA R: Supraorbital	0.4; 0.016	90 min Before, during or after MP	~ Online Null offline	NR	-	On day 2, there was a time effect only for tDCS, without differences in accuracy; Small, short-term tDCS effects in performance.
Hupfeld et al. 2017 [171]	N= 59, 21 ± 2 y Groups: n= 19 and 20	4	EGa: A: Left PFC R: Supraorbital EGc: A: Supraorbital R: Left PFC	0.7; 0.028	13 min Concurrent MP	Null offline ↑ Retention 24h ↑ Retention 15d	- η^2_p= 0.05 η^2_p= 0.11	- Moderate Moderate	Transferable performance gains when anodal tDCS is applied to the left PFC during multitasking training.
Sánchez-Kuhn et al., 2018 [169] [176]	N= 40, 21 ± 4 y Groups: n= 9, 10 and 11	3	A: Right M1 R: Contralateral trapeze	2; 0.10	20 min Concurrent MP	~ Online Null offline Null retention 20min	- - -	- - -	In the non-musicians, they found an effect of tDCS at the first and

Study	Sample	Days	Electrode montage	Intensity (mA); Current density (mA/cm^2)	Duration and timing	Significant tDCS effects vs. sham	ES	Rating of ES	Conclusions
						↑ Retention 8d	r= 0.88	Large	second session of stimulation, and at 20 min and in the 8th day follow-up test. In the musicians, we found no effect of tDCS in any of the tests.
Sánchez-Kuhn et al., 2018 [176]	N= 54, 22 ± 3 y Groups: n= 18	4	A: Left PFC R: Supaorbital	0.7; 0.028	9.5 min Concurrent MP	↑ Offline ↑ Retention 24h Null retention 15d	η^2_p= 0.11 η^2_p= 0.14 -	Moderate Large -	tDCS increased performance gains from training compared to cathodal and sham for both trained and untrained tasks.
Saucedo-Marquez et al., 2013 [177]	N= 27, 24 ± 3 y Groups: n= 13 and 14	3	A: Right M1 R: Ipsi-shoulder	1; 0.04	20 min Concurrent MP	↑ Offline SRTT Null retention 20min Null retention 1w	SMD= 1.03 - -	Large - -	tDCS improved acquisition of motor learning.
Saucedo-Marquez et al., 2013 [177]	N= 24, 22 ± 0.4y Groups: n= 12	4	A: Right M1 R: Left M1	2; 0.05	25 min Concurrent MP	↑ Offline ↑ Retention 24h	SMD= 0.92 SMD= 1.70	Large Very large	tDCS augmented synergy learning, leading subsequently to faster and more synchronized execution. This effect persisted for at least 4 weeks after training.
Waters-Metenier et al. 2014 [178]	N= 28, 27 ± 7 y Groups: n= 14	5	A: Left and right M1 R: Left and right supraorbital	1; 0.035	20 min Concurrent MP	↑ Offline Null retention 1w	d= 0.73 -	Moderate -	tDCS improved bimanual typing performance. This effect vanished after 1 week.

Study	**Sample**	**Days**	**Electrode montage**	**Intensity (mA); Current density (mA/cm^2)**	**Duration and timing**	**Significant tDCS effects vs. sham**	**ES**	**Rating of ES**	**Conclusions**
Sequential visual isometric pinch task (SVIPT)									
Gomes-Osman & Field-Fote 2013 [179]	N= 93, 28 ± 0.6 y Groups: n= 14 and 15	3	EG1: A: Left M1 R: Ipsi-shoulder EG2: A: Right M1 R: Ipsi-shoulder	1; 0.04	20 min Concurrent MP	↑ Offline	SMD= 0.72	Moderate	Left M1-tDCS induced greater skill learning than sham and a trend for greater enhancement than right M1-tDCS
Schambra et al., 2011 [180]	N= 24, 30 ± 3 y Groups: n= 12	5	A: Left M1 R: Supraorbital	1; 0.04	20 min Concurrent MP	↑ Offline ↑ Retention 3d	SMD= 1.17 SMD= 0.62	Large Moderate	Enhanced total skill acquisition with tDCS compared to sham and improved performance was sustained for up to 3 months.
Reis et al. 2009 [165]	N= 109, 28 ± 1 y Groups: n= 16	3	A: Left M1 R: Supraorbital	1; 0.06	20 min Concurrent MP	Null offline ↑ Retention 15min	- SMD= 0.69	- Moderate	tDCS applied after the training did not induce skill gains, implying that co-application of tDCS and training is required to induce offline skill gains.
Reis et al. 2015 [181]	N= 30, 22 ± 3 y Groups: n=15	5	A: Left M1 R: Supraorbital	2; 0.06	20 min Concurrent MP	↑ Offline Null retention 5d	d= 0.94 -	Large -	tDCS had a significant effect on the speed-accuracy tradeoff function only on the modified metronome-assisted task, null effects on habitual task
Fan et al. 2017 [182]	N= 30, 23 ±1 y Groups: n=11	3	A: Right cerebellar R: Right buccinator muscle	2; 0.08	20 min Concurrent MP	Null online ↑ Offline ↑ Retention 1w	- d= 0.92 d= 1.04	- Large Large	tDCS increased skill learning relative to sham and cathodal tDCS specifically

Study	Sample	Days	Electrode montage	Intensity (mA); Current density (mA/cm^2)	Duration and timing	Significant tDCS effects vs. sham	ES	Rating of ES	Conclusions
									by increasing on-line rather than off-line learning. Moreover, the larger skill improvement in the anodal group was predominantly mediated by reductions in error rate rather than changes in movement time
Cantarero et al. 2015 [168]	N= 27, 23 ± 3 y Groups: n=13 and 14	3	A: Right M1 R: Ipsi-shoulder	1; 0.04	20 min Concurrent MP	Null offline ↑ Retention 1w	- SMD= 1.66	- Very large	tDCS improved performance only at retention.

ES: Effect Sizes; A: Anode; R: Reference; M1: Primary Motor Cortex; PFC: Prefrontal Cortex; Ipsi: Ipsilateral; MP: Motor Practice; min: minutes; h: hours; d: days; w: weeks; m: months; y: years; EGu: Experimental Group uni-hemispheric; EGd: Experimental Group dual-hemispheric; EGa: Experimental Group anodal; EGc: Experimental Group cathodal; η^2_p: Partial eta squared; η^2: Eta squared; SMD: Standardized Mean Difference; d: d de Cohen; NR: Non-Reported.

NOTES:

Significant tDCS effects vs. sham

- Online: skill acquisition within-session

- Offline: skill acquisition between session

- Retention: skill performance in the short, medium, or long time after the end of the intervention.

Rating of effect sizes

- An effect of $\eta^2_p \geq 0.01$ indicated a small, ≥ 0.059 a moderate, and ≥ 0.138 a large effect, respectively (Cohen et al., 1988).

- SMD, effect size (r) for U Mann-Whitney and d de Cohen was interpreting following Cohen' guidelines: trivial, SMD < 0.2; small, SMD = 0.2 to 0.5; moderate, SMD = 0.5 to 0.8; large, SMD = 0.8 to 1.4; and, very large, SMD > 1.4.

Publication bias is a serious problem in research, which can affect the validity and generalization of results. Null findings rather than viewing these studies as failures and ruling out, these studies must be published so that all research is available to the field. Null findings are not always published, leading to the possibility of publication bias, a positively biased research base, and policies and practices based on incomplete data. In a social science review, they analyzed 221 quality unpublished studies [177]. They reported that studies with robust results were 40% more likely to be published and 60% more likely to be written than null effects papers. Therefore, Franco et al. (2014) not only reported publication bias but also that the authors do not write and submit null results to journals [183]. Specifically, Héroux et al., (2017) reported a questionable science and reproducibility in electrical brain stimulation research [184]. After a survey, 154 NIBS researchers answered that they could only replicate ~50% of the studies. They reported that approximately ~40% of the NIBS studies show both results and selective experimental conditions and an adjusted statistical analysis to optimize the results [184]. In summary, the belief that NIBS, such as tDCS, are effective tools must be replaced by a more rigorous approach so that reproducible brain stimulation methods can be designed and applied to avoid questionable research practices.

So, in the Study III of this thesis, we design a tDCS intervention across 20 practice sessions, following most of the previous considerations.

1.2.5. Adverse effects

So far, tDCS has been tested in thousands of participants worldwide with no evidence of toxic or dangerous effects [184]. Yet, many uncertainties exist regarding the prolonged administration of tDCS in healthy individuals. Generally, the prevalence of adverse effects is usually very low. For instance, in a study that included 164 tDCS stimulation sessions, only 0.11% and 0.08% of the participants reported them in the active and sham stimulation groups, respectively [137,185]. Interestingly, these effects are usually similar in the active and sham groups [186].

The most common adverse symptoms caused by tDCS are usually mild transient/short-lived and including headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, lethargy, inattention, severe mood swings... [172,187] summarised the adverse events in 567 tDCS sessions in 102 participants (77 healthy participants and 25 patients). The adverse events were a mild tingling sensation (71%), moderate fatigue (35%), and a slight itching sensation under the electrode (30%) during active stimulation was observed and even with sham tDCS. Additionally, after tDCS, the authors reported the prevalence of headache (12%), nausea (3%) and insomnia (1%) as rare adverse effects [188].

Typically, some participants showed a mild redness of the skin under the electrodes after the tDCS session, but it disappeared after few minutes of the end of stimulation without discomfort. In fact, the most severe adverse event reported is skin lesions under the electrode produced by the electrochemical field, but fairly infrequently [188]. To avoid skin burns with tDCS is important to ask the participant during the stimulation because usually preceded by pain and to check redness or skin damage after stimulation [189–193]. Also, it is recommended to use saline solution instead of tap water, and electrodes may need to be replaced periodically to avoid skin lesions [194,195].

Nevertheless, we note that most of these results were obtained from single session tDCS studies in healthy participants. In a recent systematic review, the authors showed that only 17.2 % of the studies (i.e., 5 studies in total) reported details of the adverse effects in multiple session tDCS [190]. Furthermore, the incidence of adverse effects does not appear to increase with higher levels of tDCS exposure. Likewise, little evidence that tDCS multiple session increased risk to participants within the parameters used so far (less than 3mA) compared with sham tDCS [196].

Further studies are needed to assess the safety of tDCS in multiple session design with healthy participants. In study III, we explore the possible adverse effects thought 800 tDCS-sessions in healthy participants.

1.2.6. Limitations of the studies

The extent number of tDCS protocols and the motor learning paradigms variety make it challenging to establish a relationship between both concepts. Although the mechanism of the tDCS protocols is similar, it is different in some aspect, and each motor learning task involves a different level of demands. Overall, there is a lack of consensus on the relationship between optimal tDCS protocol and the type of task to improve motor learning in health.

The controversy about the effects of tDCS on the motor learning process optimisation may be a consequence of differences in the methods employed by researchers. These differences in methods are mainly due to: the sample size, the target cortical brain area of stimulation, the tasks used, the variability intra- and inter- individual, and the duration of the intervention [196]. Next, we will briefly describe each of these aspects.

The **sample size**: the experts' recommendation summarised that each group should have more than 25 participants to reach a conclusion that can better represent the population, and the sample size between 10 to 24 participants is acceptable, including in all research a sham stimulation control group [197]. However, most studies are based on tiny samples, which might increase the probability of false positive results.

The **target stimulation cortical brain area**: as we discussed in a previous section, several studies support the conclusion that the M1 plays a pivotal role in motor learning. Therefore, the evaluation of the tDCS effects on motor learning should be achieved by preferentially positioning the anode electrode over M1. Conversely, in some studies, the position of the electrodes does not correspond with the M1position or other cortical areas involved in motor learning.

The **task**: By far, the most prevalent paradigm used to study the effects of tDCS on motor learning is through sequence learning tasks such as the SRTT [135]. Nevertheless, the improvements obtained in this type of laboratory tasks environments cannot easily be transferred into the real world. Most studies about tDCS effects have used relatively simple laboratory tasks, leading some to suggest that the potential value of this research for practical situations would be greater in more complex ecological tasks (e.g., [135]).

The **variability intra- and inter- individual**: responding to the tDCS protocol is a recent concern. In studies with more than 40 participants, the expected response to anode tDCS (i.e., increased cortical excitability) was around 50% [139,198,199]. The huge intra- and inter- variability seem to be mainly attributed to individual differences in brain physiology and anatomy and differences in the level of arousal during stimulation, among other factors [139,198,199]. Therefore, more studies are needed to explore the individual response to the combination of tDCS and practice on motor learning with large sample size.

The **duration of the intervention**: a recent review by Hashemirad et al. (2016) summarised that tDCS interventions for at least 3 days were necessary to produce improvements in motor sequence learning [152]. Whereas when tDCS was applied only during a single session, there was no consensus on the effectiveness of this technique [200,201]. As far as we know, in healthy participants, the effects of tDCS combine with practice on motor learning lasting more than 5 intervention days are unknown.

Overall, the lack of consensus in the literature regarding the benefits of tDCS in learning new motor skills in healthy participants may be due to the limitations mentioned earlier that difficult comparisons between studies. Taken together, we try to avoid the shortcomings discussed preceding in the design of this thesis to shed light on this issue.

Chapter 2

Questions of relevance

2. QUESTIONS OF RELEVANCE

After the brief review of the current data about the topic of this thesis, it remains unresolved some questions of interest:

1) Does tDCS affect motor retention in a random reaction time task?

2) When is the best time for tDCS application to be effective on retention: before, during, or after motor training?

3) Is there a standard motor learning curve in complex motor skills like typing?

4) Does tDCS optimise the motor learning process in the medium and long term?

5) Is the application of multiple session tDCS safe in healthy participants?

We tried to address these questions with this thesis. Questions 1 and 2 will be addressed in the first study. Questions 3, 4 and 5 will be addressed in the second study.

Chapter 3

Hypothesis and main aims of the studies

3. HYPOTHESIS AND MAIN AIMS OF THE STUDIES

Study I: Timing-dependent effects of transcranial direct current stimulation (tDCS) in the performance of a choice reaction time skill

a) Aims

- To explore the timing-dependent effects of anodal tDCS (i.e., before, during, or after motor practice) over M1 on motor retention 24h after in a 4-choice visual-motor reaction time task (4-ChRT).

Study II a: Exploring the learning curve in a complex motor skill: A pilot study

a) Hypothesis

We hypothesized that a structured typing program of 30 15-min sessions would improve participants' motor performance similarly.

b) Aims

- To test if a structured typing program of 30 triweekly 15-min sessions would improve the participants' motor performance.
- To explore the learning curve of 30 practice typing sessions in healthy young adults.

Study II b: Effects of 20 sessions of transcranial direct current stimulation (tDCS) on motor learning in typing skill in healthy young adults

a) Hypothesis

We hypothesised that 20 tDCS sessions over M1, applied during motor practice would improve typing performance compared with control and sham groups.

b) Aims

- To assess whether 20 sessions of tDCS over M1 would enhance the performance of a complex life motor skill, i.e., typing, in healthy young adults.
- To test the safety of tDCS over time in the medium and long term.

Chapter 4

Studies

Study I:

Timing-dependent effects of transcranial direct current stimulation (tDCS) in the performance of a choice reaction time skill

4. STUDIES

4.1. Study I: Timing-dependent effects of transcranial direct current stimulation (tDCS) in the performance of a choice reaction time skill

4.1.1. Abstract

Anodal transcranial direct current stimulation (tDCS) can enhance the retention of a previously practiced motor skill. However, the effects of tDCS on the performance of the choice reaction time task have little been investigated. The present study aimed to determine the effects of anodal tDCS over the left primary motor cortex (M1) on the retention of a 4-choice visual-motor reaction time task (4-ChRT). A hundred right-handed healthy participants were recruited and randomly assigned to five groups: three groups received anodal tDCS: before ($tDCS_{before}$), during ($tDCS_{during}$), or after ($tDCS_{after}$) motor practice. In addition, there were two control groups: performed with (CON_{mp}) and without (CON) motor practice. We evaluated the speed and precision of the 4-ChRT task before (PRE), during, and 24 h (POST) after the interventions. Thus, all the groups, including the non-stimulation (CON_{mp}) and non-practice groups (CON), significantly improved motor retention ($\Delta_{4\text{-ChRT}}$: 35.8 ± 36.0 ms). These findings suggest that the tDCS effects over M1 may differ for serial versus choice RT tasks, perhaps due to the different brain areas involved in each motor task.

4.1.2. Introduction

A critical element of motor learning is the ability to retain and recall a previously practiced motor skill. Performance may be enhanced immediately after the practice period (online skill gains). However, memory consolidation may also result in motor skill improvements that outlast the practice period (offline skill gains). The offline skill gains or motor retention occur within a specific time window after training and up to 24-48 hours later [181,202]. Newly learned motor skills are associated with functional and structural changes in the nervous system [78]. Specifically, the primary motor cortex (M1) plays an essential role in movement control during the early learning phase [1,97,98,203].

In the last two decades, non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), have gained tremendous popularity for their potential to enhance motor and cognitive functions both in healthy and patient populations. tDCS is a non-invasive, safe, and painless technique that can modulate cortical excitability and affect the function of several cortical areas [137,185]. A large number of studies have explored the effects of anodal tDCS on M1 using serial reaction time (RT) paradigms in which participants learn a motor sequence either implicitly or explicitly [100,114,146,148,149,152,160,204,205]. The results of most of these studies suggested an enhanced effect of anodal tDCS in both performance and retention. A serial RT task typically includes an embedded repeated cycle of responses, and a reduction of RT on these cycles without explicit knowledge is thought to reflect implicit learning [43]. Conversely, a 4-choice reaction time task (4-ChRT) presents the stimuli in a random and unpredictable fashion and is thought to mostly reflect response selection processes [58,206]. The 4-ChRT uses random stimuli and involves predominantly motor processes compared to other serial-learning tasks, which require more cognitive processes. Only a few studies evaluated the acute effect of tDCS in a choice RT task. In these studies, the task was used as a control condition to explore the effects of tDCS on a serial RT task [114,143,207]. The findings of these studies remain inconclusive since different tDCS protocols were used, as well as a small sample of participants. Furthermore, the effects of tDCS on a simple choice RT task can often be masked by fatigue [143] or due to a lack of attention resulting in a ceiling effect [207]. Thus, in the current study, we investigated the effects of tDCS on motor retention by evaluating the performance of the choice RT task 24 hours after the practice session.

Another important question that has been under investigation is whether the facilitation of tDCS depends on the timing of its application in relation to motor practice, that is, before, during, or after the practice. Studies have shown that applying tDCS before the motor practice enhances performance by priming M1 [100,140–143]. However, the most prevalent tDCS timing used is during motor practice [145–150,208]. Specifically, anodal tDCS applied over M1 seems to facilitate the motor retention in an serial RT task [148,149]. One other study has also shown that an application of tDCS after motor practice can improve skill retention [209].

Taken together, the aim of the present study was to determine the timing effects of tDCS, over M1, on motor retention, by evaluating the performance of a choice RT task 24 hours after the practice session.

4.1.3. Methods

The present study used a randomised blind design.

Participants

One hundred healthy, right-handed participants with no history of neurological disease, psychological disorder, drug, or alcohol abuse, or use of neuropsychiatric medication were recruited (n=100, 68 males, age 20-34 years). This sample size was determined using a power analysis (G*Power 3.1) based on medium effect size (0.25) and critical alpha and b-errors of 0.05. The participants participating in this study signed an informed consent approved by the university's ethics committee (Appendix B). The study was conducted according to the declaration of Helsinki. Participants were asked to refrain from caffeine or alcohol the day before the experimental session.

Procedures

A hundred participants were randomly assigned to five groups, 20 per group. Three groups received anodal tDCS: before ($tDCS_{before}$), during ($tDCS_{during}$), or after ($tDCS_{after}$) motor practice. Moreover, there were two control groups: performed with (CON_{mp}) and without (CON) motor practice. The pre-test or baseline (PRE) and the post-test 24h after intervention (POST) consisted of a single block of 40 trials with the right-dominant hand. Motor practice consisted of 12 blocks of 40 trials (a total of 480 trials), with 15 seconds of rest between blocks also with the right hand (Figure 10). We selected this period motor practice based on studies of serial reaction times, which establish that the participants started to decrease their performance after 480 total trials [210], possibly due to fatigue.

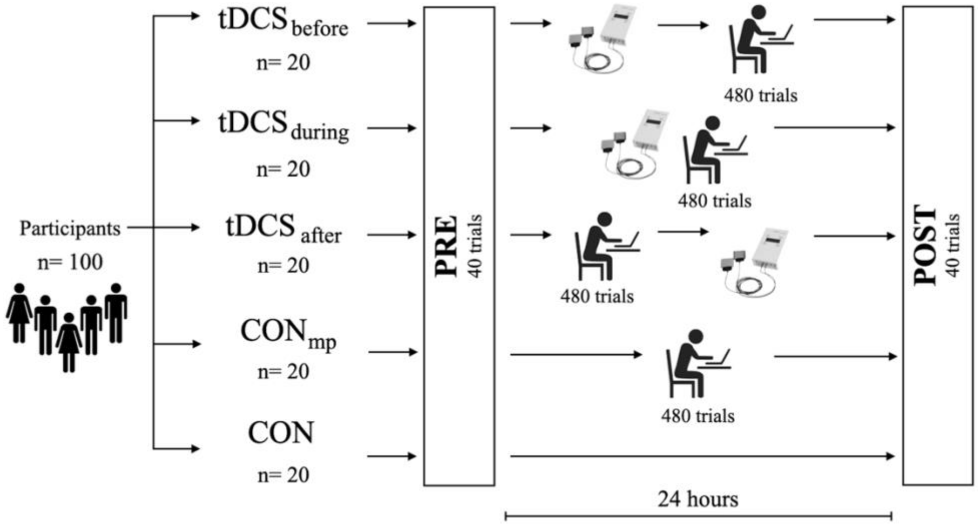


Figure 10. Study design.
Experimental protocol. tDCS, transcranial direct current stimulation; CON_{mp}, control group with motor practice; CON, control group; PRE: the pre-test or baseline; POST: the post-test 24h after intervention.

Transcranial Direct Current Stimulation (tDCS)

The 1-mA current was induced through saline-soaked sponge electrodes (size: 7x5cm; surface area: 35cm^2; current density: 0.03 mA/cm^2) for 20 min connected to aDC stimulator (tDCS Stimulator Clinical Version, TCT research Limited, Hong-Kong), with a 10-s on and off ramping. The stimulating anode electrode was positioned over electrode site C3 (international 10-20 EEG system), i.e., left M1, contralateral to the right-hand performing the tests and the motor practice. The reference cathode electrode was placed over the right supraorbital cortex. The size of the anode electrode and stimulation intensity were selected based on the findings by Ho et al. (2016) and Agboada et al. (2019) [138,211]. We applied anodal stimulation over M1 because of its role in motor retention [97,98], and based on evidence suggesting that anodal tDCS of M1 improves the retention of serial RT task [152,197].

Visuomotor reaction time task

We used a version of the RT task named 4-ChRT [43]. The participants performed the task, sitting in a chair in front of a computer screen positioned at eye level. The tests and the motor practice were performed with the right-dominant hand only. Participants placed the index, middle, ring, and pinkie fingers of their right hand on the “C”, “V”, “B”, and “N” keys of a keyboard, respectively. Four 3 × 3 cm horizontally aligned white squares with black trim were presented in the middle of a computer monitor with a white background; the squares were 1.5 cm apart. At the beginning of the 4-ChRT, the blank squares were presented for 1000ms before the first stimulus was displayed. As soon as a visual stimulus (asterisk) appeared in one of the four squares (for up to 500 ms), participants were told to make a response with the spatially corresponding key. Once a response was given, the stimulus disappeared, and then the next visual stimulus appeared. The sequence was always presented in a pseudorandom fashion order in which the stimulus appeared with the same frequency in each of the four positions. The number of errors and the RT between the appearance of the visual stimulus and the pressing of the key were recorded. The task was designed using Superlab Pro v.4.0 software (Cedrus Corporation, San Pedro, CA).

Data processing

The speed was evaluated by measuring the mean RT between the stimulus onset and the correct key press. An answer was considered correct when the participants pressed the correct key paired with a particular stimulus.

Each participant's mean RT was calculated separately for each block of trials of a given experimental condition. Individual trials exceeding two standard deviations below or above the mean score were excluded from the analysis (about 3% of trials), following the protocol from Boggio et al. (2010) [212].

One of the assessors administered tDCS and a second technician analysed the data.

Statistical analysis

All the data are reported using mean ± standard deviation (SD). We tested the data for normality using a Shapiro-Wilk test. We utilized Jamovi software [213], the GAMLj module [214], and the lme4 R package [215]. GAMLj estimates variance components with restricted (residual) maximum likelihood (REML), which produces unbiased estimates of variance and covariance parameters. To compare the online performance for RT and errors two independent mixed models was used with the following configuration: Group as the inter-subject factor ($tDCS_{before}$, $tDCS_{during}$, $tDCS_{after}$, and CON_{mp}), Block as the intra-subject factor (from block 1 to block 12), and the interaction (Group x Block). To compare the offline performance for RT and errors two independent mixed models, we used for both model Group ($tDCS_{before}$, $tDCS_{during}$, $tDCS_{after}$, CON_{mp}, and CON), Time (PRE and POST), and Group x Time interactions as independent variables (fixed effect). Sex and age were not introduced as a fixed factor and covariate, respectively, because these variables did not improve the model (i.e., parsimonious method), as evaluated by the Akaike information criterion (AIC). The participant intercept was set as the random effect. Within-subject and between-subject changes were evaluated by ANOVA F omnibus test employing the Satterthwaite approximation of degrees of freedom and by estimating the coefficients with their 95% confidence intervals for the fixed effects in the mixed model. Furthermore, the variance of the random coefficients was obtained. Simple effects analysis was applied with ANOVA (type III sums of squares) and employing the Kenward-Roger method for degrees of freedom calculation. The level of significance was established at $p < 0.05$.

4.1.4. Results

All the participants completed the entire study, and no adverse effects were reported during or after tDCS. None of the participants reported any significant discomfort, and no tDCS experiments had to be discontinued.

The effect of tDCS on speed

Figure 11 shows the speed performance during the motor practice across the groups. There were no significant RT differences between the Groups ($F_{3, 76}= 2.20$, $p= 0.09$), Blocks ($F_{11, 836}= 1.38$, $p= 0.18$) nor a significant Group*Block interaction ($F_{33, 836}= 1.01$, $p= 0.46$) ($p > 0.05$ across the comparisons, $\beta= -17$ and $CI_{95\%=}$ -41 to 7; $\beta= 14$ and $CI_{95\%}=$ -10 to 38; $\beta= -4$ and $CI_{95\%}=$ -28 to 20, for $tDCS_{before}$ vs CON_{mp}, $tDCS_{during}$ vs CON_{mp} and $tDCS_{after}$ vs CON_{mp}, respectively).

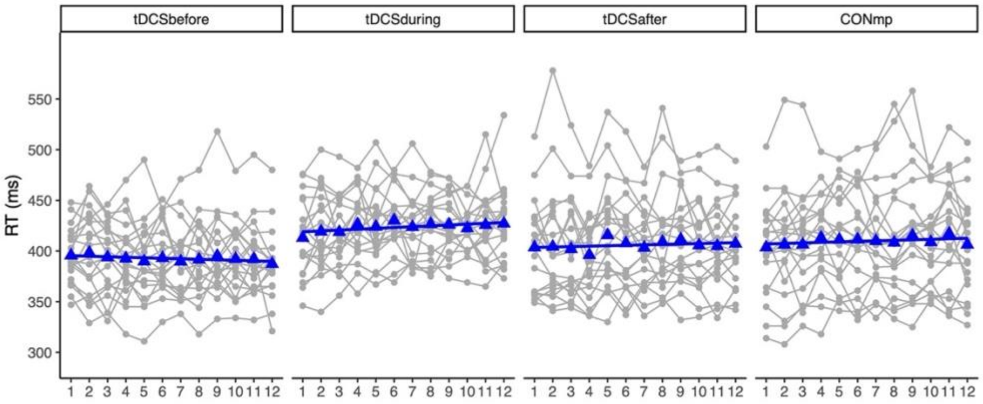


Figure 11. Online effects of tDCS on motor practice in the 4-ChRT.
Individual data cluster by groups at the motor practice are reported, and the thick blue line is the group means. No difference was seen in the motor performance between the groups. Data are mean ± 95% confident interval. tDCS, transcranial direct current stimulation; COM_{MP}, control group with motor practice.

Applying the mixed model was an appropriate decision because there was a lot of variance in the data random component (participant intercept) ($\delta = 1.449$; ICC= 0.82).

There were no significant RT differences between the groups at PRE ($p > 0.05$). Figure 12 shows the RT values by groups at PRE and POST. There were significant main effects for Time ($F_{1,97} = 99.08$, $p < .001$) and a trend for Group ($F_{4,97} = 2.13$, $p = 0.08$). However, there were no significant Time x Group interaction ($F_{4,97} = 1.66$, $p = 0.17$). The mean RT was faster at POST (384 ± 35 ms) compared to the PRE condition (419 ± 48 ms), irrespective of the stimulation condition ($ß = 35$, $CI_{95\%} = 28$ to 42, $t_{97} = 9.95$, $p < .001$) ($\Delta_{4\text{-ChRT}}$: 35.8 ± 36.0 ms). $tDCS_{after}$ was the only group that showed a higher performance in the Test compared to CON ($ß = 27$, $CI_{95\%} = 3$ to 50, $t_{97} = 2.23$, $p = 0.02$). In addition, there was no significant Time x Group interaction in the mixed model.

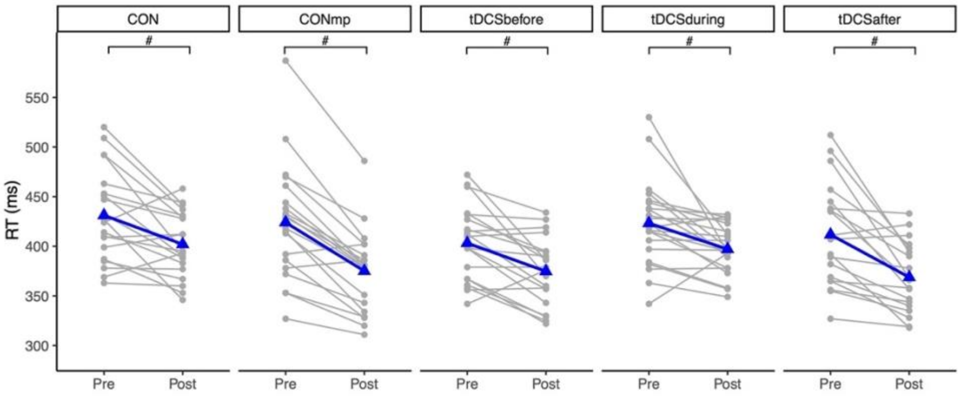


Figure 12. The performance during motor retention in the 4-ChRT.
Individual data by groups at PRE and POST are reported, and the thick blue line is the group mean. tDCS, transcranial direct current stimulation; CON_{mp}, control group with motor practice; CON, control group without motor practice. #p< .001.

The effect of tDCS on accuracy

During the motor practice, there were no significant errors differences between the Groups ($F_{3, 76}$= 0.94, p= 0.43). However, there are differences between Blocks ($F_{11, 836}$= 2.18, p= 0.01) without a significant Group*Block interaction ($F_{33, 836}$= 1.16, p= 0.25). Overall, the average errors increased in the middle of the motor practice (block numbers 3, 5, 6, 7, 8, 9, and 10) compared to block number 1 ($p < 0.05$).

There were no significant number of errors differences between the groups at PRE ($p > 0.05$). **Table 2** displays the errors by groups at PRE and POST. In the 4-ChRT, there were no significant main effects for Time ($F_{1, 97}$= 0.09, p= 0.77) or for Group ($F_{4, 97}$= 1.94, p= 0.11), nor Time x Group interaction ($F_{4, 97}$= 1.58, p= 0.19). Also, the results were not significant in the analysis by mixed model.

Table 2. Accuracy performance in the 4-ChRT.
The number of errors mean in absolute values at PRE and POST conditions by groups (Mean ± SD).

	$\text{tDCS}_{\text{before}}$ n= 20	$\text{tDCS}_{\text{during}}$ n= 20	$\text{tDCS}_{\text{after}}$ n= 20	CON_{mp} n= 20	CON n= 20
PRE	2 ± 2	2 ± 2	2 ± 1	2 ± 1	1 ± 1
POST	2 ± 2	2 ± 1	2 ± 1	2 ± 1	1 ± 2

Note: tDCS, transcranial direct current stimulation; CON_{mp}, control group with motor practice; CON, control group without motor practice. * p < .05*, *** $p < .01$.

4.1.5. Discussion

We examined the effects of the timing of tDCS, relative to the motor practice, on the performance of the 4-ChRT. Our results showed that all the groups, including the non-stimulation (CON_{mp}) and non-practice (CON) groups, significantly improved their RT in the second evaluation (24 hours after tDCS). Our findings suggest that tDCS over M1 does not have significant effects on motor retention during the performance of a 4-ChRT.

Our findings demonstrate that the groups, which performed the practice blocks, did not improve their performance compared to the control group without motor practice. This would imply that tDCS, regardless of its application time, did not induce potentiation of motor improvement during the training performed in the current study. Likewise, although the task in this study was not sensitive to the effects of motor practice, tDCS could have enhanced the effects of training per se, showing a superior performance to the control groups. The lack of effect of tDCS has been reported for simple [128] and choice RT tasks [114,117,207]. However, it is possible that the effects of tDCS were masked by fatigue or loss of concentration during the task [117,207].

All the groups improved their performance 24 hours after tDCS, regardless of whether or not they had completed the practice blocks. Thus, our findings show that the application of tDCS before, during, or after the practice blocks did not improve the retention of the task compared to the control groups. Our results align with previous studies that showed no effects of tDCS over M1 on motor retention 24-hour after practicing choice RT task [114,148,149]. Our findings differ from earlier studies that showed a potentiating effect of tDCS on motor retention before [100], during [146], and after [209] motor practice in choice RT tasks. In the study that applied tDCS before motor practice, the performance improved 48h after tDCS, but this effect manifested only through reduced variability [100]. In contrast, in the present study, we did not observe tDCS-induced improvements in accuracy, but the POST was tested 24h after. In the study that applied tDCS during motor practice [146], the authors selected a visuomotor task with 8 targets that is much complex compared to the present study task (i.e., 4-ChRT). Moreover, Drummond et al. (2017) [209] reported effects of tDCS on retention when its applied POST motor practice with a bi-hemispheric configuration, that differs from the present study configuration. Briefly, the literature about tDCS effects on motor retention in a choice RT task are inconclusive.

One possible explanation for the inconsistent findings related to the effects of tDCS on motor skill retention is the high variability in the response to tDCS. In previous studies, about 50% of healthy volunteers had no or minimal response to tDCS [139,199]. Indeed, there is increasing evidence to suggest that, at the individual level, the responses to tDCS are highly variable [198,216,217]. Another possible explanation for the lack of effect of tDCS on motor retention in the present study may be a ceiling effect associated with the choice RT task. Our results show that the control group, which did not perform the practice blocks, reached a retention level similar to that of the other groups that did perform the motor practice. These findings suggest that the test trials were sufficient for the participants to perform at their highest level.

Despite participants accumulating a volume of 480 trials during motor practice, similar to that of other RT studies [218], neither group showed substantial improvement in performance across training. However, RT have been shown to be improved by drugs [219], transcranial magnetic stimulation [220], and extensive practice [218]. Our findings suggest that the lack of tDCS effects may be due to the simplicity of the task and that more complex motor tasks may be required to observe the effects of stimulation or it may be necessary to accumulate more volume of practice [218]. Furthermore, the lack of effects of tDCS on the performance of 4-ChRT maybe be due to the stimulation area; perhaps M1 does not have a relevant role in this type of tasks. For example, recent work has shown RT reductions using anodal tDCS over the supplementary motor area (SMA) in a choice RT [221] due to its role in pre-planning and response initiation, which may be a better candidate for learning effects as shown by RT paradigms. Our findings suggest that the lack of effects of tDCS may be due to the stimulation area, and the stimulation of other cerebral areas such as SMA may be necessary to observe the effects of stimulation.

Our study has several limitations that should be mentioned. Although we used a stimulation protocol recommended by several studies [138,211] we cannot rule out that other stimulation parameters would have resulted in different outcomes. As previously suggested, one possibility is that the stimulation location did not impact the areas associated with the choice RT task. Another limitation is the lack of differences between intervention groups vs. the control group without motor practice. Another potential limitation is the absence of neurophysiological measures. Future studies using transcranial magnetic stimulation are warranted to explore further the underlying mechanisms that may explain the absence of behavioural tDCS-induced effects during a choice RT task.

4.1.6. Conclusion

To the best of our knowledge, this is the first study that explores the effects of tDCS on the motor retention during the performance of a choice RT task. Our results show that a single session of motor practice with tDCS (before, during, or after motor practice) over M1 does not enhance the retention in a choice RT task. Results show that all groups improved motor performance up to 24 hours after the intervention without differences vs control groups. Future research should consider exploring other stimulation brain areas to enhance motor retention in a choice RT. Our findings suggest that tDCS effects over M1 may differ for serial versus choice RT tasks.

Study II:

Study II a: Exploring the learning curve in a complex motor skill: A pilot study

Study II b: Effects of 20 sessions of transcranial direct current stimulation (tDCS) on motor learning in typing skill in healthy young adults

4.2. Study II a: Exploring the learning curve in a complex motor skill: A pilot study

4.2.1. Abstract

The motor learning process is crucial in all stages of life. However, the learning curve in different motor skills has been little investigated. The present study aimed to explore the effects of the structured intervention program on motor performance. Forty-five healthy participants were recruited who completed 30 typing motor practice sessions over 3.5 months. We evaluated the speed and accuracy in the maximum (mTT) and incremental (iTT) typing test 5 times: before (T_0), after the tenth session (T_{10}), after the twentieth session (T_{20}), after the thirtieth session or post-intervention (T_{30}), and three weeks after the end of the practice (R_{3w}). Participants significantly improved their speed and accuracy on the mTT and reduced the number of errors on the iTT throughout the intervention. Even those performance gains are sustained up to 3 weeks after the end of motor practice. These findings suggest that a non-massive motor practice design may mean that the intervention is more effective in typing skill programs. Considering the conclusion of this pilot study, we designed the third study of the doctoral thesis.

4.2.2. Introduction

Motor learning occurs continuously throughout daily life. Motor learning is a process associated with practice or experience that implies an improved skill relatively permanent over time [5]. Performance is commonly reported in the literature as an indirect measure of motor learning [3]. However, sometimes there is no visible change in performance, but learning still has occurred. Therefore, it is essential to implement tests that are sensitive and accurate to detect changes.

Limitations of motor learning studies include the short duration, i.e., up to 3 weeks, e.g., [222], the selection of a narrow range of tasks [simples (e.g., reaction time task) or too complex (e.g., sports initiation)], and the non-recording of the unknown variables that may affect the learning process (e.g., design of the practice, environmental conditions, conditions of the participants and its relationships) [5]. Specifically, the performance curve undergoes fluctuations throughout the motor learning process until the learners reach a relatively stable level of performance. Therefore, it is important to know the learning curve of each skill to identify if we are in a merely initial phase of the process (phase I: cognitive, described Fitts & Posner (1967) [76]) or in a more advanced stage (phase II: associative or phase III: automatic), where the changes are already relatively permanent.

Typing is a complex skill that requires the orchestration of motor and cognitive skills [7]. Yet, it is not an excessively complex skill since it involves relatively few muscle groups (mainly the upper limb). Therefore, it is an excellent skill to explore the learning curve. Some studies on typing showed that learners improved in keyboard skills immediately after an instructional program [223–226]. However, these authors reported pre-and post-intervention speed and accuracy values on a maximal typing test. These results are difficult to interpret because, for example, some participants may prioritise accuracy at the expense of speed; in contrast, others may prefer to be faster even if that means less accuracy. It would be interesting to implement more tests throughout the intervention, which provide us with information about the process and the calculation of coefficients that relate to accuracy and typing speed.

To solve these shortcomings, we designed a typing intervention study with 35 intervention sessions. Learners performed evaluations every ten practice sessions, and we evaluated motor retention at 3- and 32-weeks after finishing the practice. Moreover, in the assessments, we implemented the maximum speed test, and we designed an incremental typing test in which the speed was constant for all participants, thus limiting the motor strategy to be used. In addition, we calculated a global performance index (GPI) corresponding to a measure of performance that considers possible speed and accuracy trade-offs. In all, the study's main objective was to explore the typing performance curve throughout the motor learning process to make a better design for the third study of the doctoral thesis.

Objectives

The study aimed to clarify the following questions for the design of a long-term intervention study with non-invasive brain stimulation techniques:

To test if a structured typing program of 30 triweekly 15-min sessions would improve the participants' motor performance.

To explore the performance curve of 30 practice sessions in a complex life motor skill, i.e., typing, in healthy young adults.

To assess adherence over 35 intervention sessions in 45 participants.

4.2.3. Methods

Participants

Forty-five healthy right-hand adults (11 females, age 22 ± 3 years) participated in the study. The participants belonged to the second year of the faculty of sports sciences of the University of A Coruña. Inclusion criteria for participation were being healthy adults without prior experience in typing programs. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee. All participants signed written informed consent prior to the intervention (Appendix B). Participants were asked to refrain from caffeine or alcohol consumption the day before the experimental sessions.

Design

Forty-five participants completed 35 intervention sessions over 3.5 months (5 testing and 30 training sessions). Each training session lasted 15 minutes, and a minimum period of 48 hours was established between sessions.

Despite the fact that the structured typing programs usually employ 1–2-hour sessions [224,225], we used 15-minute sessions in our design because it is a pilot to check if it was an efficient program for the following study (study II b).

Typing familiarisation lasted two sessions when participants received instruction and practised the efficient touch-typing program (Tipp 10 freeware, Thielicke IT Solutions, Berlin, Germany), which is based on the use of both hands and all the fingers [70,71]. In the touch-typing program, the fingers position right is rest digits 2–5 of each hand on the respective a, s, d, f and h, j, k, l keys of a standard Qwerty keyboard.

Typing performance was tested five times: at baseline (T_0), after session 10th (T_{10}), after session 20th (T_{20}), after session 30th (T_{30}), and retention three weeks after the end of the intervention (R_{3w}) (Figure 13). In a complementary study, we retested six participants for retention eight months (i.e., 32 weeks approx.) after the end of the intervention (R_{32w}).

All the sessions took place at approximately the same time of day for each participant, and the experimental environment was kept constant. A college teacher taught the intervention. Lessons took place in a laboratory room allocated for the study, using standard computers and the QWERTY keyboard. Classes were held in small groups (up to 10 students). The instructor individually guided each student while using the software (e.g., ensuring they were using all their fingers, answering questions, and providing emotional support if needed).

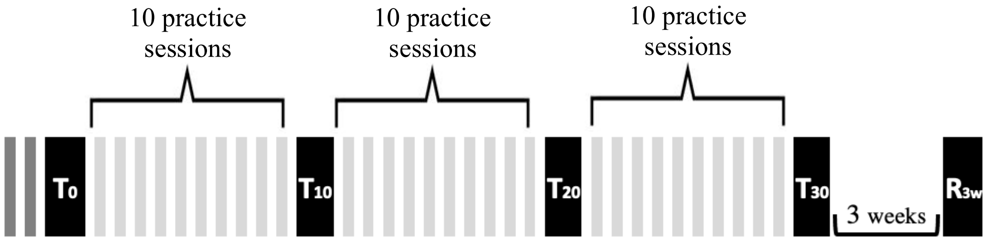


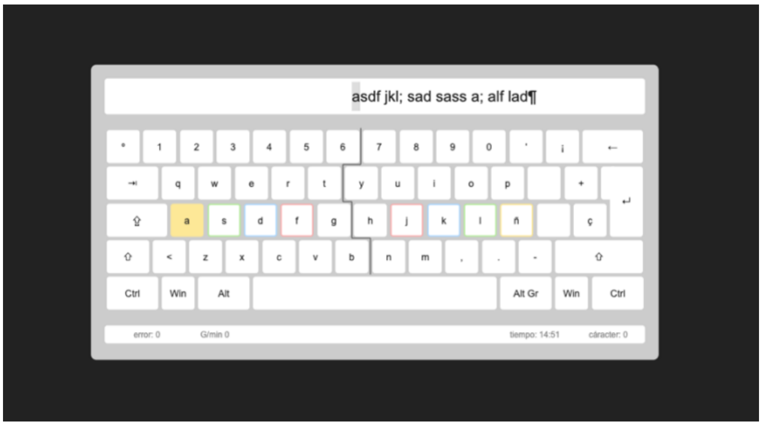
Figure 13. Study design.
Graphical representation of the distribution of both training sessions and tests in the study. T_0: pre-test or baseline, T_{10}: test after 10th practice sessions, T_{20}: test after 20th practice sessions, T_{30}: test after 30th practice sessions or post-test, R_{3w}: retention test 3 weeks after intervention.

Typing training program

The study lasted 3.5 months which a total of 30 training sessions were developed with the online "Tipp10" typing software. We chose this online open-access software because it is possible to export the data in Excel, and it is possible to do both 20 standard lessons and input external texts. For testing and training sessions, the software configuration was that regardless of whether participants keystroked the wrong letter, the text continued without demanding correction.

From session to the next training session, 2 to 4 new keys are added for practice (using transcription typing) together with the previously taught keys (which constitute 50% of the practice). The first 20 standard lessons of the software consisted of copying non-words (i.e., letter sequences that do not maintain a basic orthographic regularity). And from 21 to 30th sessions, learners copied texts composed by words frequently used in the Spanish language. During the practice of the non-words and words, immediate feedback is provided if an error is committed, but the learner can continue typing. There are 27 letters in the Spanish alphabet.

During the training sessions, participants had visual feedback they could see on the computer screen: the keyboard, the fingers position right, the number of errors, the speed, the time, and the number of characters cumulated (see Figure 14). The training sessions from the 1st to the 20th were all standard software lessons that increased difficulty by adding new letters session by session. From the 21st to the 30th training sessions, the participants performed external texts provided by researchers that changed session by session.



asdf jkl; sad sass a; alf lad¶

error: 0 G/min 0 tiempo: 14:51 cáracter: 0

Figure 14. Visual training feedback.
Screenshot of the software as viewed by participants in training sessions.

Typing Test

Typing skill assessment comprised two tests: the maximum- (mTT) and incremental- typing speed tests (iTT). For mTT, the instructions were: ‘Type as fast and accurately as possible’. The mTT was not evaluated at the baseline (T_0) because the participants were not able to type correctly at high speed even after the familiarisation period. And in the iTT, participants typed the standard text 9 times at different speeds: 50, 60, 70, 80, 90, 100, 110, 120 and 130 Characters Per Minute (CPM). A metronome was used to pace typing and, the instructions were: ‘Type as accurately as possible while following the metronome beat’ (Appendix C). The purpose of the iTT was to establish a speed-accuracy trade-off function.

For the iTT and mTT, the standard text included all the letters of the Spanish alphabet, a total of 393 characters in 72 words:

> *"El cielo es de ceniza. Los árboles son blancos, y son*
> *negros carbones los rastrojos quemados.*
>
> *Tiene sangre reseca la herida del Ocaso, y el papel*
> *incoloro del monte de color kiwi está arrugado.*
>
> *El polvo del camino se esconde en los barrancos, eso*
> *explica que estén las fuentes turbias y quietos los remansos.*
>
> *Suena en un gris rojizo la esquila del rebaño; y la noria*
> *materna acabó su rosario."*

During the typing test, participants had no visual feedback; they could only see the speed, time, and the number of characters cumulated on the computer screen (see Figure 15).

En una pequeña aldea perdida entre las m

Errors: 0
Cpm: 0
Time: 0:20
Chars: 0

Figure 15. Visual test feedback.
Screenshot of the software as viewed by participants in typing tests.

Data analysis

The dependent variables were the number of typing errors (incorrect letters or punctuation marks); and the speed of typing, i.e., the number of characters [letters and punctuation marks] typed per minute (CPM). The accuracy was calculated as the percentage between correct characters and the total number of characters (i.e., 100- (correct characters * 100/ 393 characters)).

For iTT, we calculated the (1) number of errors at each speed and (2) the total number of errors as the sum of errors performed in each speed.

For the mTT we also calculated a Global Performance Index (GPI) as a measure of typing performance that combined speed and accuracy, based on similar indices from a previous study [227]. The GPI was calculated as follows:

$$\mathrm{GPI} = \mathrm{e}^{-\mathrm{speed}} * \mathrm{e}^{-\mathrm{accuracy}}$$

where e is the mathematical constant, also known as the Euler’s number, and is defined as the base of the natural logarithm (~2.71828). Speed was the average time between correct keypresses in seconds. The accuracy was the relationship between the number of correct answers with respect to the total number of answers (e.g., 100% of accuracy= 1). The higher GPI values indicate better typing performance.

Statistical analysis

Data are presented as mean ± standard deviation (±SD). Normality was assessed using the standard distribution, the Shapiro–Wilk test, and visual inspection of Q–Q plots and box plots.

The performance was assessed using the typing speed, number of errors, and GPI scores. Changes across the time (i.e., intra-subject factor Time were set as fixed effects) for the typing speed, errors, and GPI scores, in the mTT test and the total number of errors in the iTT test, were compared using mixed models for repeated measures designs. In addition, we applied a mixed model for the complementary analysis about retention. We studied the typing speed, the number of errors and the GPI scores in mTT with the intra-subject factor time (T_{30}, R_{3w} and R_{32w}) were set as fixed effects. We utilised Jamovi software [213], the GAMLj module [214], and the lme4 R package [215]. GAMLj estimates variance components with restricted (residual) maximum likelihood (REML), which produces unbiased estimates of variance and covariance parameters. The participant intercept was set as the random effect. The estimating coefficients with their 95% confidence intervals represented the fixed effects in the mixed model. In order to evaluate the relationship between the changes in speed and accuracy and the enhancement in motor skill, we assessed the Speed–Accuracy

Tradeoff Function using the errors at 50, 60, 70, 80, 90, 100, 110, 120 and 130 CPM for the iTT, using a previously published procedure [228]. The statistical significance was established at $p < .05$.

4.2.4. Results

Forty-one participants completed all intervention sessions in the study, two participants dropped out due to external causes, and the data of two participants were not available.

Maximum typing test (mTT)

For the speed in the mTT, there was a main effect for Time ($F_{3,118}$= 34, $p< .001$) (Figure 16 A). The average typing speed in all the participants was 244 ± 78 CPM at T_{10}, 249 ± 73 CPM at T_{20}, 296 ± 62 CPM at T_{30}, and 303 ± 69 CPM at R_{3w} ($p < 0.01$ across the comparisons: β= 53, $CI_{95\%}$= 7 to 39, t_{118}= 7.61; β= 60, $CI_{95\%}$= 7 to 46, t_{118}= 8.57; β= 38, $CI_{95\%}$= 24 to 52, t_{118}= 5.31; β= 45, $CI_{95\%}$= 31 to 59, t_{119}= 6.26, for T_{10} vs T_{30}, T_{10} vs R_{3w}, T_{20} vs T_{30}, and T_{20} vs R_{3w}, respectively).

For the total number of errors in the mTT, there was a main effect for Time ($F_{3,122}$= 7, $p< .001$). The participants reduced the total number of errors committed significantly only in comparison to the initial evaluation (i.e, vs T_{10}) (see Figure 16 BFigure 16) ($p \leq 0.01$ across the comparisons: T_{10} vs T_{20}: β= 12, $CI_{95\%}$= 4 to 19, t_{122}= 3.07; T_{10} vs T_{30}: β= 15, $CI_{95\%}$= 8 to 23, t_{121}= 4.01; T_{10} vs R_{3w}: β= 15, $CI_{95\%}$= 7 to 22, t_{121}= 3.83). In all, in PRE (T_0) the accuracy was 94 ± 9 %, and in POST (T_{30}) was 98 ± 3 %.

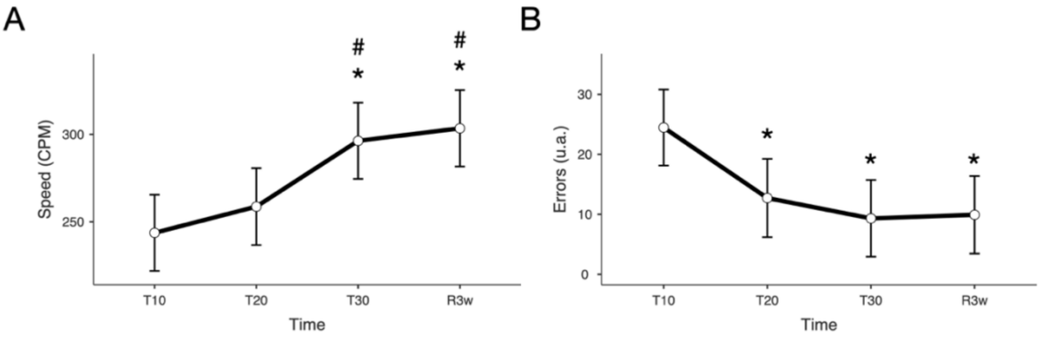


Figure 16. Participant's performance in maximum typing test (mTT).
(A) the speed and (B) the number of errors. Mixed model, Time effect versus T10, * = $p < .01$; and Time effects versus T20, # = $p < .01$. Data are Mean ± 95% Confident intervals. CPM: Characters per minute, T10: test after 10th practice sessions, T20: test after 20th practice sessions, T30: test after 30th practice sessions, R3w: retention test 3 weeks after intervention.

In the GPI scores, there was no significant Time effect (Table 3).

Table 3. Global Performance Index (GPI) in the maximum typing test (mTT).
The GPI is a relationship between speed and accuracy. The higher GPI values indicate better typing performance

Time	GPI values
$\mathbf{T_{10}}$	0.30 (0.06)
$\mathbf{T_{20}}$	0.29 (0.04)
$\mathbf{T_{30}}$	0.31 (0.02)
$\mathbf{R_{3w}}$	0.31 (0.02)

Data are Mean (SD). T10: test after 10th practice sessions, T20: test after 20th practice sessions, T30: test after 30th practice sessions, R3w: retention test 3 weeks after intervention.

Incremental typing test (iTT)

For the total number of errors, there was a main effect of Time ($F_{4,160}$= 27.9, $p< .001$). The sum of the total number of errors in iTT decreased across the Time ($p < 0.01$ across the comparisons: β= 15, $CI_{95\%}$= 10 to 21, t_{160}= 5.58; β= 21, $CI_{95\%}$= 15 to 26, t_{160}= 7.54; β= 25, $CI_{95\%}$= 19 to 30, t_{160}= 9.04; β= 24, $CI_{95\%}$= 19 to 30, t_{160}= 8.87; β= 9, $CI_{95\%}$= 4 to 15, t_{160}= 3.45; β= 9, $CI_{95\%}$= 4 to 14, t_{160}=

3.30; for T_0 vs T_{10}, T_0 vs R_{20}, T_0 vs T_{30}, T_0 vs R_{3W}, T_{10} vs R_{30}, and T_{10} vs R_{3w}, respectively) (see Figure 17). In all, in PRE (T_0) the accuracy was 92 ± 7 %, and in POST (T_{30}) was 98 ± 2 %.

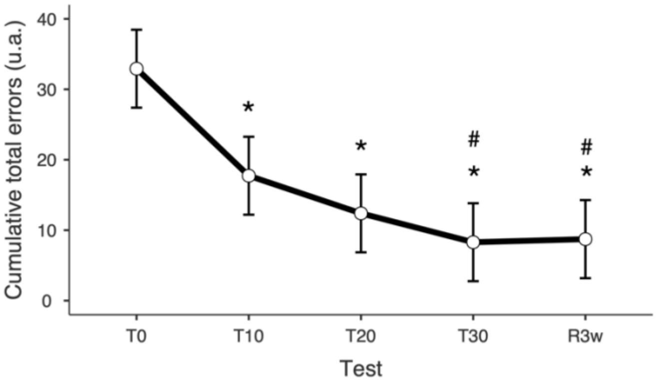


Figure 17. The cumulative total number of errors in the incremental typing test (iTT). Mixed model, Time effect versus T0 (*), and Time effects versus T10 (#), p < .01. Data are Mean ± 95% Confident intervals. T0= pre-test or baseline; T10: test after 10th practice sessions, T20: test after 20th practice sessions, T30: test after 30th practice sessions, R3w: retention test 3 weeks after intervention.

Figure 18Figure 18 shows the participant individual curve performance at each test. We were unable to characterise the Speed–Accuracy Tradeoff Function because of high inter-individual variability.

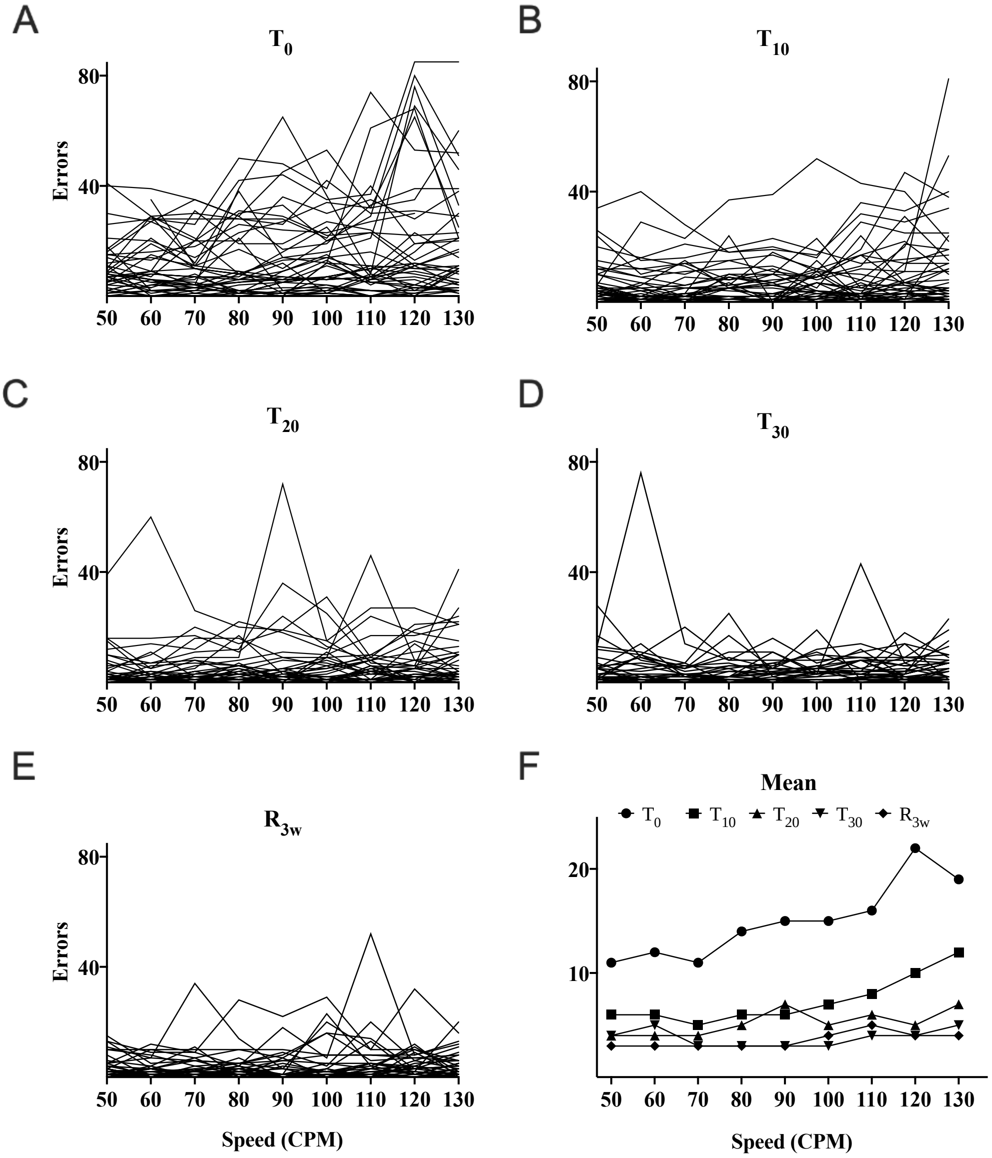


Figure 18. Speed-accuracy curves for iTT.
Errors at 50, 60, 70, 80, 90, 100, 110, 120, and 130 characters per minute (CPM). The last panel shows Mean values. CPM: Characters per minute, T0: pre-test or baseline, T10: test after 10th practice sessions, T20: test after 20th practice sessions, T30: test after 30th practice sessions or post-test, R3w: retention test 3 weeks after intervention.

Complementary study about retention in maximum typing test (mTT)

In the complementary study about retention (n=6), participants' typing performance was maintained for up to 8 months after the intervention (see Figure 19). In mTT, there were no significant Time effects in speed values

($F_{2,10}$= 3.34, p= 0.08), nor in the number of errors ($F_{2,10}$= 1.32, p= 0.31), neither GPI scores ($F_{2,10}$= 0.08, p= 0.93).

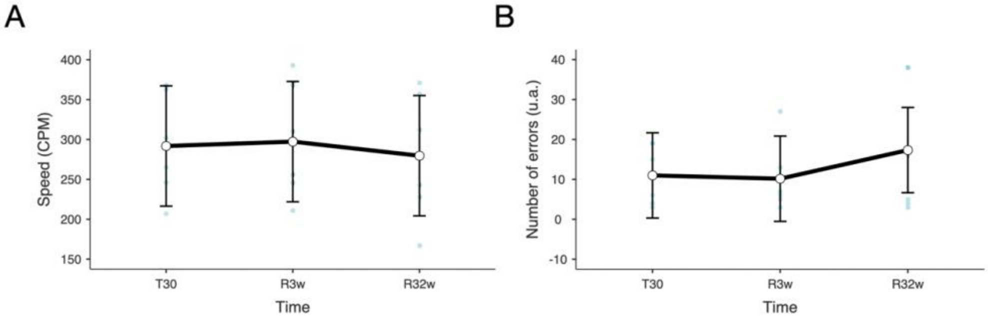


Figure 19. Typing performance on retention.
The (A) speed and (B) the total number of errors in the maximum typing test (mTT). Data are Mean ± confident intervals (95%), and the blue dots are observed scores. T30: post-test, R3w: retention test after 3 weeks of intervention, R32w: retention test after 32 weeks of intervention (i.e., 8 months).

4.2.5. Discussion

A structured 3.5-month program with a total of 30 motor practice sessions appears to be sufficient to significantly improve the performance of a complex motor skill such as typing. Participants significantly improved maximum typing speed post-intervention (after 30 sessions of motor practice or T_{30}) and this improvement was still present 3 weeks after the last training session. Also, in the maximum test, participants reduced typing errors from the 20th session (T_{20}) over time, without differences in GPI scores. In the incremental test, the participants reduce their accumulated errors from the 10th session (T_{10}) up to 3 weeks after finishing motor practice. A speed-accuracy compensation function was not identified due to the high inter-individual variability. In addition, the complementary study shows that the performance improvement was persistent up to 8 months after the end of motor practice.

In line with our results, some studies showed improved keyboard skills immediately after an instructional program [223,224,229,230]. Specifically, Yechiam et al., (2003) reported motor enhancement after intervention in the maximal typing test in young adults [224]. Yet, the authors reported maximum speed values after the intervention (approx. 150 ± 40 CPM) considerably lower than those of the present work, although with a similar accuracy (~ 97%). Likewise, in a pioneering typing study, the authors reported an enhancement in the maximum typing test post-intervention, but also the typing speeds (approximately 72 ± 8 CPM) considerably lower than those of the present work, although with a similar accuracy (~ 99.5%) [225]. In this study, participants practised and tested with a typewriter, which could justify the difference in the results obtained.

Another possible explanation for the effectiveness of our intervention compared to other studies was perhaps the distribution of practice because non-massive practice seems to favour motor performance, as pointed out by some authors in typing studies [225]. Then, in our study, the duration was 7.5 hours spaced over 3.5 months, compared to the study by Yechiam et al. (2003) in which participants practised 6 hours over two weeks (2 or more sessions per day), and compared to Baddeley & Longman (1978) that the duration was 60 to 80 hours of practice over two months (1h or two h/day) [224,225]. Additionally, in a review of the literature, the authors reported that the typing learning process required a total of 25 to 30 hours of instruction [70]. However, we employed only 7.5 hours for training in the present study, and post-intervention performance was optimal and significantly higher than the baseline in all the variables studied. In addition, the effects of the intervention on performance lasted up to 8 months after the end of the motor practice.

In contrast to our results, some authors reported a significant post-intervention decrease in typing speed in higher education students (ΔPOST-PRE = -38 CPM), without differences in accuracy (~ 98%) (14 biweekly sessions of 45min) [226]. Perhaps fatigue masks the results of this study because in the retention evaluation three months after completing the motor practice, the authors reported significant improvements compared to baseline, and in accordance with the results reported in the present work that reports the improvement of performance up to three weeks later.

Exploring the learning curve in a complex motor skill such as typing can help us structure training programs more efficiently and better understand the processes that underlie motor learning. It would be interesting to replicate the study with different age groups, in other populations, and with different skills to verify what happened.

NOTES FOR THE DESIGN OF THE FOLLOWING STUDY:

- It would be convenient to extend the familiarisation period so that learners can type with all their fingers in the baseline test.
- Twenty intervention sessions are enough to reported significant performance changes in the maximal (mTT) and the incremental (iTT) typing tests.
- The design of the intervention appears to be more efficient compared to other studies.
- Possibly adapting the difficulty in the incremental test to the level of each learner is convenient. For example, the test could be individualised in percentage concerning the maximum typing speed of each participant.
- It would be interesting to record other variables affecting motor performance in each motor practice session: quality and quantity of sleep, stress level, etc.

4.2.6. Conclusion

A structured 3.5-month program with a total of 30 motor practice sessions seems to be enough to significantly improve the performance of a complex motor skill, typing.

A common pattern of performance evolution is appraised in learning a complex ability that lasts in time. Even those performance gains are maintained when motor practice concludes up to 8 months.

It would be interesting to replicate the study with different age groups and other populations to verify what happened.

4.3. Study II b: Effects of 20 sessions of transcranial direct current stimulation (tDCS) on motor learning in typing skill in healthy young adults

4.3.1. Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that may improve motor learning. However, the long-term effects of tDCS have not been explored, and the ecological validity of the evaluated tasks was limited. To determine whether 20 sessions of tDCS over the primary motor cortex (M1) would enhance the performance of a complex life motor skill, i.e., typing, in healthy young adults. Participants (n=60) were semi-randomly assigned to 3 groups: the tDCS group (n=20) received anodal tDCS over M1; the SHAM group (n=20) received sham tDCS, both while performing a typing task; and the Control group (CON, n=20) only performed the typing task. Typing speed and errors at maximum (mTT) and submaximal (iTT) speeds were measured before training, and after 10 and 20 sessions of tDCS. Every subject increased maximum typing speed after tDCS sessions 10 and 20 with no significant differences ($p > 0.05$) between the groups. The number of errors at submaximal rates decreased significantly ($p < 0.05$) by 4% after 10 tDCS sessions compared with the 3% increase in the SHAM and the 2% increase in the CON groups. Between the 10th and 20th tDCS sessions, the number of typing errors increased significantly in all groups. While anodal tDCS reduced typing errors marginally, such performance-enhancing effects plateaued after 10 sessions without any further improvements in typing speed. These findings suggest that long-term tDCS may not have functionally relevant effects on healthy young adults' typing performance.

4.3.2. Introduction

Transcranial direct current stimulation (tDCS) is an inexpensive and safe method of neuromodulation used to enhance motor and cognitive functions in healthy adults and patients [137,185]. By delivering a weak current through the scalp, tDCS can modulate the excitability of the underlying cortical areas. Anodal tDCS modifies the resting membrane potential closer to the critical depolarization threshold, increasing excitability, while the opposite effect of a tonic hyperpolarization is associated with cathodal stimulation [112,231,232]. Pioneering studies reported that tDCS modifications in brain excitability lasted past the stimulation period [112,233] and in combination with motor practice, could enhance motor learning [210]. However, the mechanism of how tDCS might enhance motor performance following motor practice is complex [134,234].

Although anodal tDCS may enhance motor learning, only a few of studies have examined the effects of tDCS on motor learning using multiple practice sessions in a task that healthy adults often used in daily life [159,165,179,182,235]. Animal data from multisession compared with acute use of tDCS suggest that the practice effects last longer and are more stable, possibly due to a cumulative effect produced by the serial sessions [236]. Indeed, a meta-analysis of the effect of tDCS on manual motor sequence learning reported inconsistent results from single-sessions but a consistent positive effect across multiple sessions [237]. In addition, in four out of five, multi-session studies, tDCS compared with sham treatment enhanced bimanual motor skill performance [160]. The cumulative effect of multiple tDCS sessions is unclear. It could rely on increased cortical modulation across multiple tDCS sessions [235,238], although this has not always been the case [239,240]. Importantly, it is unclear whether changes in cortical plasticity are indicators of changes in motor performance [241,242]. From a behavioral point of view, the cumulative effects on motor learning may also depend on the task that is being evaluated. In a visual isometric pinch force task, the effects of M1 tDCS on motor learning was limited to the first session [165], while in a sequential finger tapping task anodal-tDCS facilitated learning gains [177]. Nevertheless, these multisession interventions in healthy participants lasted only up to 5 days and it remains unclear if the benefits of tDCS would incrementally increase with additional sessions of stimulation over weeks, or whether the performance-enhancing effects would plateau over time. In addition, the motor tasks that were evaluated in the above-mentioned studies were highly controlled and their ecological validity and transfer to life skills were limited.

The objective of the present study was to determine whether 20 sessions of tDCS over M1 would enhance the performance of a complex life motor skill, i.e., typing, in healthy young adults. We chose to evaluate typing performance because this is a bimanual motor task that is ubiquitous in young individuals' daily life. Two outcomes can characterize typing performance: typing speed and error. Learning to type on a keyboard with a few or no errors is a complex skill that demands extensive periods of practice and requires the integration of sensory-motor, language, and cognitive skills [67,243]. We stimulated M1 because brain imaging data suggest that practicing manual motor sequences induces structural and functional changes in multiple cortical regions such M1, pre-motor cortex, and the supplementary motor area [244,245]. Although the underlying mechanisms of motor skill acquisition of a complex motor task remain unclear, M1 seems to play an essential role in the early, rapid phase of motor skill acquisition [97–101]. We hypothesized that 20 tDCS sessions applied to M1, in combination with motor practice will improve typing performance compared with motor practice without tDCS. Based on the extant data we further hypothesized that the performance enhancing effects would plateau off after 10 sessions without further improvements in typing performance by session 20. This is the first study to utilize a long-term tDCS intervention in healthy volunteers.

4.3.3. Methods

All participants were right-handed [246] healthy young adults (n= 63, 42 males, age 21 ± 2 years). Exclusion criteria were: (1) age below 18 or above 30 years; (2) history of neurological diseases, psychological disorders or substance abuse; (3) personal/familial history of epilepsy or fainting; (4) traumatic brain injury, presence of a pacemaker, piece of metal implanted in the skull; (5) current usage of drugs known to influence cognition or behavior; (6) recent (< 6 months) exposure to brain stimulation; (7) disability of the fingers, hands, or wrist, and (8) any experience with typing programs. All participants signed an informed consent, approved by the university ethical committee (Appendix B). The study was conducted according to the declaration of Helsinki [247]. Participants were asked to refrain from caffeine or alcohol consumption the day before the experimental sessions.

Design

All the participants completed a familiarization period followed by 23 experimental sessions consisting of 3 testing and 20 training sessions.

The typing familiarization period began by introducing the instructions of the efficient touch-typing program (Tipp 10 freeware, Thielicke IT Solutions, Berlin, Germany), which is based on the use of both hands and all the fingers [70,71]. Participants practiced typing a specific text until they were able to use all of the fingers correctly and were at least 70% accurate, without time constraint. Participants reached this criterion in 2 to 7 training sessions. Next, participants were familiarized in one trial with the two typing tests. All participants completed the familiarization period in 14 days.

Typing performance was tested three times: at baseline (T1), after the 10th (T2) and 20th (T3) session (Figure 20). Participants were ranked based on baseline maximal typing speed from fastest to slowest and trios of participants were randomly allocated to one of three groups: tDCS, SHAM, or CON. Participants in the tDCS and SHAM groups performed 20 motor training sessions while concurrently receiving anodal or sham tDCS, respectively. Subjects in the CON group performed motor training sessions without stimulation.

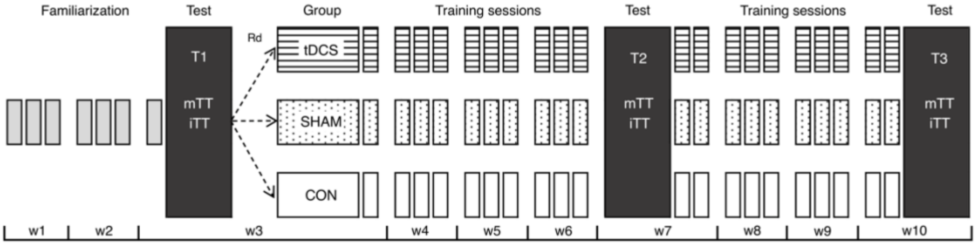


Figure 20. Experimental protocol.
Rd, pseudo-randomized; T1, Time 1; T2, Time 2; and T3, Time 3; mTT, maximum typing test; iTT, incremental typing test; w, week; w1, week 1; w2, week 2; ….

The typing training program

The training program consisted of 20 sessions over 2.5 months and was implemented using the testing software (Tipp 10 freeware, Thielicke IT Solutions, Berlin, Germany). Each training session lasted 15 minutes and was separated by a minimum of 48 hours (Figure 21). The time of day of training was kept constant throughout the 20 sessions for each participant and was similar in the three groups. Participants performed the training and testing sessions in the same laboratory room and with the same equipment.

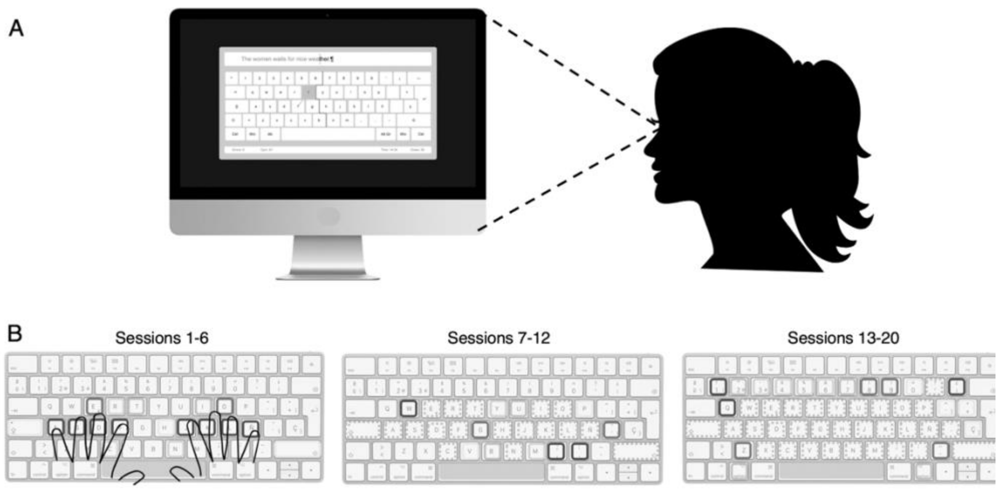


Figure 21. Typing training program.
a) During training sessions participants received visual keyboard feedback on the computer screen. Participants were sitting in a chair in front of a computer screen positioned at eye level and they always used the equal computer model, keyboard, and chair; b) Touch-typing program and representation of increasing difficulty across the sessions. The correct fingers position, i.e., rest digits 2–5 of each hand on the respective a, s, d, f and h, j, k, l keys of a standard Qwerty keyboard. The software configuration was that regardless of whether participants keystroked the wrong letter, the text continued without demanding correction. The level of difficulty increased session by session by adding new letters to the practice. In the illustration, we can see the representation of the keys that are added after each training session by colours, the darker colours keys are added before. In session 18, participants used all keys, and in sessions 19 and 20, they only used the numeric keypad with their right hand.

Typing tests

Typing skill assessment comprised two tests: the maximum and incremental typing speed tests (mTT, iTT). For mTT, the instructions were: ‘Type as fast and accurately as possible’. The text included all of the letters of the Spanish alphabet, a total of 393 characters. The iTT was conducted in order to establish an individual speed–accuracy trade-off function. Participants typed the same text 6 times at different speeds: 20%, 30%, 40%, 50%, 60%, and 70% of the individual maximum speed obtained in mTT. A metronome was used to pace typing. Instructions were: ‘Type as accurately as possible while following the metronome beat’ (Appendix C).

tDCS

Anodal tDCS was applied over the left M1 for 15 minutes concurrently with the typing practice. Stimulation intensity was set to 1.5 mA and was delivered for 15 minutes via saline-soaked sponge electrodes (size: 5x5cm; surface area: 25cm^2; current density: 0.06 mA/cm^2), connected to aDC stimulator (tDCS Stimulator Clinical Version, TCT research Limited, Hong-Kong), using 10 seconds “on” and “off” ramping. The configuration of the above parameters was based on a previous study that combined tDCS with physical therapy in patients [248]. The size of the anode electrode and stimulation intensity were based on methods detailed previously [138]. To position the electrodes, we used a 64-channel EEG cap. The anode electrode was positioned over the C3 electrode site corresponding to the left M1 cortex and the reference cathode electrode was placed over the right supra orbital cortex. Left M1 was the target area of the TDCS stimulation since it has been shown to play an essential role in motor learning [244,249,250], seems to improve motor performance in both hands in right-handed participants [251], and is the main site of stimulation in previous tDCS motor studies (see review Ref. [161]).

Participants in the SHAM group received an initial 30s of stimulation during which the current linearly increased from 0 to 1.5 mA and then the current was turned off. With this procedure participants are unable to differentiate between real and sham stimulation [185,252,253]. At the end of the last SHAM and tDCS sessions participants were asked to report whether they thought they received stimulation in order to ascertain the efficacy of the sham stimulation.

We followed established safety guidelines [137,196,254,255]. At the end of each session, we asked each participant to report any adverse effects using a questionnaire [187]. The questionnaire probed the presence of excessive symptoms related to itching, pain, tingling, burning, nausea, fatigue, difficulty of concentration or any other discomfort. Subjects were asked to answer on a scale of 1 to 4 from lowest to highest, the sensation for each symptom (1=minimal; 2=mild; 3=moderate; 4=severe).

Behavioral analysis

The dependent variables were speed of typing, i.e., the number of characters [letters and punctuation marks] typed per minute (CPM); and the number of typing errors (incorrect letters or punctuation marks). For the mTT we also calculated a Global Performance Index (GPI) as a measure of typing performance that combined speed and accuracy, based on similar indices from a previous study [227]. The GPI was calculated as follows:

$$GPI = e^{-speed} * e^{-accuracy}$$

where e is the mathematical constant, also known as the Euler’s number, and is defined as the base of the natural logarithm (~2.71828). Speed was the average time between correct keypresses in seconds. The accuracy was the relationship between the number of correct answers with respect to the total number of answers (e.g., 100% of accuracy= 1). The higher GPI values indicate better typing performance.

For iTT, we calculated the number of errors at each speed and the total number of errors as the sum of errors performed in each speed. For the adverse effects tDCS-induced questionnaire, we calculated the total mean of responses to the eight variables (itching, pain, tingling, burning, nausea, fatigue, difficulty of concentration, discomfort) across the 20 sessions.

Statistical analyses

Data are presented as mean ± standard deviation (±SD). Normality was assessed using the standard distribution, visual inspection of Q–Q plots and box plots, and the Shapiro–Wilk test. We evaluated the homoscedasticity using Levene´s test.

The tDCS-induced sensations and the psychological measures were analyzed using an independent samples t-test.

The tDCS effects were assessed using the typing speed, number of errors, and GPI scores. Changes within and between groups for the typing speed, errors and GPI scores, in the mTT test and the total number of errors in the iTT test, were compared using mixed models for repeated measures designs. We utilized

Jamovi software [213], the GAMLj module [214], and the lme4 R package [215]. GAMLj estimates variance components with restricted (residual) maximum likelihood (REML), which produces unbiased estimates of variance and covariance parameters. The inter-subject factor group (tDCS, SHAM, CON), the intra-subject factor time (T1, T2 and T3) and the interaction (group x time) were set as fixed effects. The participant intercept was set as the random effect. Bonferroni-Holm were performed to correct for multiple comparisons. Furthermore, in the iTT test since there were significant differences in the total number of errors at T1, this variable was included as a covariable in the subsequent analyses of the mixed model.

The β coefficients and their corresponding 95% confidence intervals represented the effect size. In order to evaluate the relationship between the changes in speed and accuracy and the enhancement in motor skill, we evaluated the Speed–Accuracy Tradeoff Function using the errors at 20%, 30%, 40%, 50%, 60%, and 70% of the individual maximum speed for the iTT test, using a previously published procedure [228].

The alpha level was set at $p < .05$.

4.3.4. Results

Of the original 63 participants, three dropped out: one due to a wrist injury and two participants performed the study protocol incorrectly. The remaining 60 participants (n=20 per group) completed all the sessions.

A total of 800 tDCS sessions were performed without complications. All participants in the tDCS and SHAM groups occasionally experienced mild and transient adverse effects during stimulation, such as “itching”, “burning” or “discomfort”. Transient erythema (~5 min) appeared in 7% of participants (tDCS: 2; SHAM: 1), due to the saline-soaked sponge, in participants with atopic or sensitive skin. Two participants reported a mild headache once. In no session was it necessary to interrupt the stimulation for any reason. Overall, tDCS-induced self-reported adverse effects were minimal (tDCS: 1.21 ± 0.15

vs. Sham: 1.18 ± 0.11) and were not significantly different between groups (t_{39} = 1.17, p = 0.251) (Table 4).

Table 4. Adverse effects tDCS-induced.

Stimulation sensations self-reported by the participants after each training session across the time. Stimulation sensations were assessed on a Likert 4-point scale: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe.

Sensations

Itching	**Painful**	**Tingling**	**Burning**	**Nauseous**	**Fatigue**	**Diff. Concent.**	**Discomfort**
tDCS							
1.77 (0.44)	1.12 (0.17)	1.25 (0.32)	1.24 (0.29)	1.01 (0.02)	1.15 (0.34)	1.09 (0.24)	1.02 (0.07)
Sham							
1.69 (0.35)	1.14 (0.18)	1.25 (0.28)	1.12 (0.17)	1.02 (0.06)	1.12 (0.20)	1.12 (0.21)	1.07 (0.22)

Note: Data are Mean (SD). Diff. concent.: difficulty of concentration.

In the tDCS and SHAM groups, 55% and 53% of participants reported that they were being stimulated, respectively, confirming the blinding procedure of the SHAM group.

Table 5 shows the mean of psychological measures reported by the participants session by session.

Table 5. Phycological measures.

Physiological measures were self-reported by participants in each one of 21 practice sessions.

				tDCS vs Sham		tDCS vs CON		Sham vs CON	
Phycological measures	**tDCS**	**Sham**	**CON**	t_{780}	p	t_{753}	p	t_{773}	p
Sleep duration (h)	6.7 (1.2)	7.1 (1.0)	7.3 (1.0)	-5.61	<.001	-6.83	<.001	-1.38	.0170
Sleep quality (/10)	5.1 (2.2)	5.0 (2.3)	4.5 (2.2)	0.35	0.724	3.90	<.001	3.54	<.001
Stress (/10)	5.0 (2.3)	5.2 (2.4)	5.0 (2.1)	-1.71	0.088	0.03	.976	1.80	0.072
Appetite (/10)	5.6 (1.5)	6.0 (1.9)	6.1 (1.4)	-3.06	0.002	-5.13	<.001	-1.43	0.152
Motivation (/10)	6.5 (1.7)	6.0 (1.8)	6.5 (1.5)	3.71	<.001	-0.01	.994	3.88	<.001

Practice errors (%)	2.5 (2.0)	2.7 (2.3)	4.0 (5.2)	-2.24	0.026	-3.20	.001	1.23	0.221

Note: Data are Mean of all 21 practice sessions (SD). Sleep duration was reported in hours; sleep quality, stress, appetite, and motivation were reported on a Likert scale from 0 to 10; and practice errors was reported by typing software.

Maximum typing test (mTT)

For the mTT, there was a main effect for Time ($F_{2,113}$= 88.20, p< .001). There were no significant Group or Time*Group interaction effects (Figure 22). The average typing speed in all the participants was 165 ± 55 CPM at T1, 214 ± 52 CPM at T2 (Δ_{T2-T1}= 49 CPM), and 253 ± 52 CPM at T3 (Δ_{T3-T1}= 88 CPM) (p_{holm} < 0.01 across the comparisons, β= 50 and $CI_{95\%}$= 37 to 63; β= 88 and $CI_{95\%}$= 75 to 101; β= 39 and $CI_{95\%}$= 26 to 52, for T1 vs T2, T1 vs T3 and T2 vs T3, respectively).

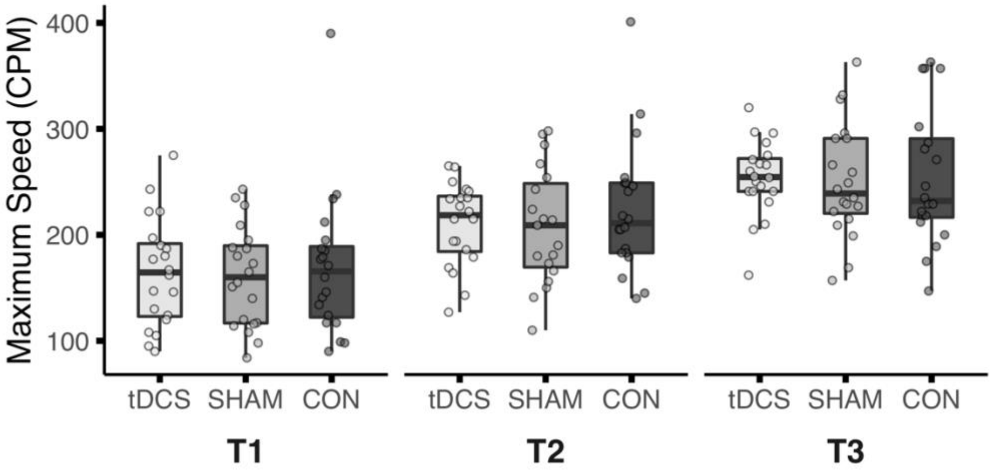


Figure 22. Speed in the maximum typing test (mTT).
The evolution of maximal typing speed across the evaluations. Dots beyond the whiskers represent outliers in the data set. Pair comparison with Holm-Bonferroni adjustment Time effect, p < .01.

There were no significant Time, Group, or Time*Group effects in the number of errors (Table 6).

Table 6**.** Number of errors in the maximum typing test (mTT).
Descriptive data and ANOVA results of the number of errors in mTT

Group	**p-value**

Time	**tDCS**	**SHAM**	**CON**	**Time**	**Group**	**Time X Group**
T1	33 ± 31	22 ± 18	21 ± 14	0.29	0.22	0.77
T2	24 ± 23	17 ± 14	21 ± 22			
T3	26 ± 17	21 ± 16	18 ± 15			

Note: Data are Mean ± SD.

In the GPI scores, there was a main effect for Time ($F_{2,114}$= 36.35, p< .001). There were no significant Group or Time*Group interaction effects. The mean GPI scores in all participants were 0.27 ± 0.04 at T1, 0.29 ± 0.03 at T2, and 0.30 ± 0.02 at T3 (p_{holm} < 0.01 across the comparisons, β= 0.02 and $CI_{95\%}$= 0.02 to 0.03; β= 0.04 and $CI_{95\%}$= 0.03 to 0.05; β= 0.01 and $CI_{95\%}$= 0.01 to 0.02, for T1 vs T2, T1 vs T3 and T2 vs T3, respectively).

Incremental typing test (iTT)

For the total number of errors, there was a main effect of Time ($F_{2,1012}$= 14.70, p< .001) and a Time*Group interaction ($F_{4,1012}$= 4.99, p< .001) but no Group effect (Figure 23 A). The total number of errors decreased in the tDCS group between T1 and T2 (ß= -4.19, $CI_{95\%}$= -5.56 to -2.82, t_{3003}= 5.99, p_{holm}< .001) and increased in the SHAM and CON groups (ß= 2.63, $CI_{95\%}$= 1.27 to 4, t_{3003}= 3.78, p_{holm}< 0.004; ß= 2.19, $CI_{95\%}$= 0.82 to 3.56, t_{3003}=3.13, p_{holm}< 0.04, respectively). Thus, errors decreased only in the tDCS group after 10 sessions ($tDCS_{\triangle T2-T1}$: -4.19 vs. $Sham_{\triangle T2-T1}$: 2.63 and, vs. $CON_{\triangle T2-T1}$: 2.19). From T2 to T3, the total number of errors increased across all the groups (ß= 3.95, $CI_{95\%}$= 1.13 to 6.79, t_{3003}= 5.65, p_{holm}< .001; ß= 4.77, $CI_{95\%}$= 1.95 to 7.59, t_{3003}= 6.84, p_{holm}< .001; ß= 2.63, $CI_{95\%}$= 0.19 to 5.46, t_{3003}= 3.81, p_{holm}= 0.004; for tDCS, Sham and Control, respectively). At T1 the total number of errors was higher in the tDCS compared to the SHAM group (ß= 5.46, $CI_{95\%}$= 0.83 to 10.09, t_{274}= 4.268, p_{holm}< .001), without significant differences between the groups at T2 and T3.

To control for the differences in the total number of errors between groups at T1, we introduced the total number of errors at T1 as a covariant of a mixed model (Figure 23 B). There were significant Time ($F_{1,625}$= 31.14, p< .001) and Group ($F_{2,56}$= 4.98, p= .01) main effects but no Time*Group interaction. Post hoc analysis confirmed the effect identified by the model, i.e., reductions in error only after tDCS but not after SHAM or CON (ß= -4.16, $CI_{95\%}$= 1.22 to 7.10, t_{56}= -2.78, p_{holm}= .02; ß= -4.00, $CI_{95\%}$= 1.12 to 6.88, t_{56}= -2.72, p_{holm}= .02; and, ß= 0.17, $CI_{95\%}$= -2.71 to 3.03, t_{56}= 0.11, p_{holm}= .91, for tDCS vs SHAM, tDCS vs CON, and SHAM vs CON respectively). From T2 to T3, the total number of errors increased in all the groups (ß= -3.79, $CI_{95\%}$= -2.46 to -5.13, t_{625}= -5.58, p_{holm}< .001).

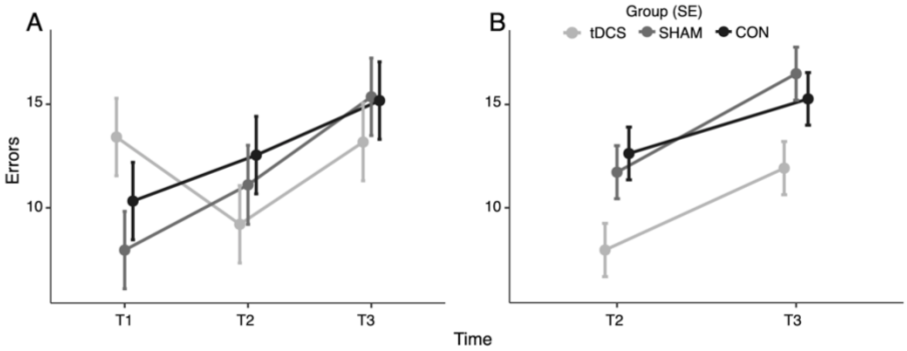


Figure 23. Total number of errors in the incremental typing test (iTT).
a) The total number of errors across the three evaluations. b) The total number of errors at T2 and T2 with T1 as covariable. See results section for a detail information of the significant effects reported by the ANOVA (A) and ANCOVA (B). Data are Mean ± 95% confidence interval (CI).

We were unable to characterize the Speed–Accuracy Tradeoff Function. As Figure 24 shows there was a high inter-individual variability in the speed-accuracy relationship and only T3 showed a clear sigmoid fit across the groups.

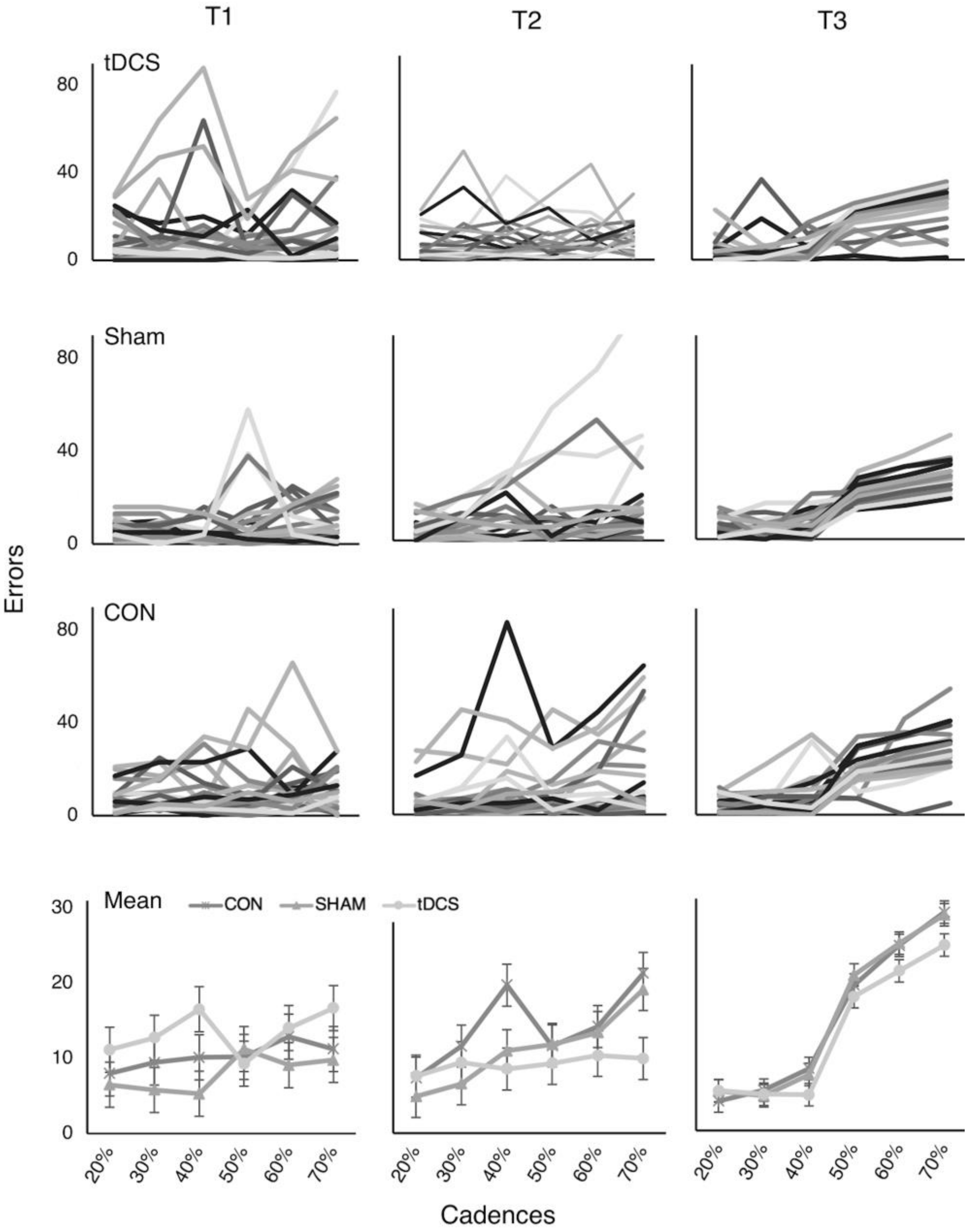


Figure 24. Speed-accuracy curves for iTT.
Errors at 20, 30, 40, 50, 60, 70% of maximal typing speed. The last panel shows Mean ± 95%C.I.

4.3.5. Discussion

The purpose of the present study was to determine whether 20 sessions of tDCS delivered to the M1 would enhance the performance of a complex motor skill, namely, typing, in healthy young adults. We found that anodal tDCS significantly reduced the total number of errors during an incremental typing test (iTT) but showed no effect on the maximal typing speed. As hypothesized, the tDCS effects were pronounced during the first 10 sessions.

To our knowledge, the present study is the first to deliver tDCS for 20 sessions in an effort to improve the performance of a life-skill in healthy young adults. We found that after 20 sessions of tDCS, participants performed iTT with 6% fewer errors compared to the SHAM and control groups. Our data agree with previous findings demonstrating favorable effects of tDCS on acquiring a bimanual motor skill [160]. Gomes-Osman and Field-Fote (2013) employed a modified version of the typing task and reported that 5 sessions of bi-hemispheric anodal tDCS improved typing performance.

In the present study, tDCS stimulation targeted M1 and its typing error-reducing effects were prominent after 10 sessions only in the tDCS group. These findings are consistent with the role of M1 in the early stages of motor skill acquisition [97,101,135,249,256,257]. Findings in rats suggest that M1 plays an active role in motor skill acquisition up to 9 days, after which M1 can become disengaged from movement control [98]. In the present study M1 plasticity, may have been the underlying mechanism for the coding of the motor skill into motor memory, during the initial 10 sessions of the typing practice [78,258].

Somewhat unexpectedly, the number of errors in iTT started to increase after the 10th session in all three groups, so that the number of typing error was still lower in tDCS compared with SHAM and CON. One possible explanation is that the participants typed increasingly faster, thus committing more errors. In the current study the performance-enhancing effects of tDCS stimulation seemed to reach a plateau and did not facilitate typing performance beyond the level reached at session 10. In other words, the effects of tDCS stimulation were not linear or cumulative. Stimulation may have helped maintain the gains achieved during the initial 10 sessions, however this is merely a speculation which cannot be compared with prior data, as studies to date only completed 5 sessions of stimulation at most [138,235,238].

The favorable effects of anodal stimulation over M1 after 5 sessions have also motivated us to assess the stimulation effects on speed-accuracy tradeoff during typing [165]. However due to large inter-individual variation in the trade-accuracy relationships, we were unable to compute individual curve fits across sessions and examine stimulation effects on the tradeoff. Participants only showed a sigmoidal speed-accuracy tradeoff relationship at T3, although the inter-subject variability remained high. This variability may reflect the complexity of the iTT assessment and may explain why previous typing studies chose to report speed and accuracy measures separately instead of using a trade-off function [71,243,259].

The positive effects of anodal tDCS were limited to the iTT and were not observed with the mTT. During the mTT, participants increased typing speed by 67%, keeping the number of errors stable across the 20 training sessions without showing significant differences between groups. The continued improvements in speed across the 20 sessions clearly rule out a celling effect in mTT. These results were expected as numerous studies reported continuous improvements in writing speed over 100 hours or even years of practice [33,62]. Both outcomes, iTT and mTT, demand asynchronous bilateral well-coordinated and skilled finger movements. However, in the iTT the metronome sets typing speed, while in the mTT participants were able to freely select their execution speed. Our mTT data suggest that the participants seemed to have developed a cognitive strategy to increase the maximum typing speed, as long as it allowed them to keep errors constant. Previous studies have also noticed this typing strategy [243,260]. In contrast, during the iTT the speed was set, increasing the cognitive demands compared to mTT. This is in line with other studies suggesting that tDCS stimulation is preferentially effective in tasks that require high cognitive demand [240,261], accounting for the effects we observed after real stimulation on iTT but not on mTT. Collectively, the findings suggest that the effects of anodal tDCS may be task dependent [149,177].

We observed no adverse effects of tDCS, and these small effects were similar across the tDCS and sham stimulation groups, suggesting that repeated sessions of tDCS with the parameters used in the present study, are safe in healthy young adult participants. These findings expand evidence from previous studies related to the safety of repeated sessions of tDCS [196].

Our study has several limitations. The first was a lack of a follow-up of typing performance. We chose typing as the motor task because it has a high ecological validity in everyday life and is thus functionally relevant, also facilitating adherence. However, for this reason it was impossible to ask the participants to refrain from typing in order to assess the retention effects of the stimulation. In addition, we were unable to control for the amount of typing participants might have performed outside the study. However, since all the participants were university students belonging to the same academic group, it is unlikely that there were systematic differences between groups in the practice time outside of the experiment. In addition, the effects of tDCS might have been limited by the stimulation of a single cortical area. In fact, our results suggest a potentially diminishing role of anodal tDCS over M1 in motor learning across 20 sessions of stimulation. Thus, future studies using other stimulation sites are warranted in order to minimize a possible plateau in motor performance. Additionally, a positive control group having tDCS applied to a region that is not expected to influence the dynamics of motor learning, will shed further light on the enhanced learning effects attributed to tDCS. Another potential limitation in our study is the absence of neurophysiological measures. Future studies using combined TMS and EEG techniques are warranted in order to further explore the underlying mechanisms that may contribute to tDCS induced enhancements.

Our findings question the functionality of tDCS effects on typing performance in healthy participants because the effect size of the observed improvements induced by real tDCS were small for iTT and absent for mTT. However, it is possible that the effects would have been more pronounced in patients with lower baseline typing performance due to a motor deficit.

4.3.6. Conclusion

In conclusion, while anodal tDCS over M1 reduced typing errors marginally, the performance-enhancing effects plateaued after 10 sessions, showing no significant improvements in typing speed. Our findings question the efficacy of tDCS for enhancing healthy young adults’ typing performance by functionally meaningful margins.

Chapter 5

Conclusions

5. CONCLUSIONS

- There is no significant effect of tDCS on motor retention 24h after in a random reaction time task for a sample of 100 participants.
- A single session of motor practice with tDCS (before, during, or after motor practice) over M1 does not enhance the retention in a choice RT task compared to control groups with and without motor practice.
- The typing learning curve following a common pattern and the performance gains are maintained even when motor practice concludes up to 3 weeks for a sample of 45 participants.
- A structured 3.5-month program with a total of thirty 15-min typing practice sessions seems to be enough to significantly improve the motor performance in general.
- There is a significant effect of tDCS on motor typing performance (6% fewer errors) after the first 10 sessions compared to sham and control groups.
- tDCS over M1 reduced typing errors marginally, the performance-enhancing effects plateaued after 10 sessions, showing no significant improvements in typing speed.
- The application of multiple session tDCS appears to be safe in healthy participants. Participants performed a total of 800 tDCS sessions without complications.
- All participants in the tDCS and SHAM groups occasionally experienced mild and transient adverse effects during stimulation, such as “itching”, “burning”, or “discomfort”, with no significant differences between them.

Chapter 6

Limitations

6. LIMITATIONS

- The sample used in the current thesis were young and healthy subjects and thus, cautions must be taken in applying our findings to other populations.
- Only one cortical area was stimulated. Although primary motor cortex has been the most often target for tDCS, it remains to be tested whether our findings are also valid for other cortical areas.
- The effects of tDCS on motor retention in the Study I of the current thesis was constraint to a single session. Therefore, it should be tested the accumulative effects of successive sessions of stimulation. In addition, the reliability of the effects induced by the tDCS protocols must be evaluated in more than two sessions because of the high inter-and intra-participants variability.
- Another potential limitation may be the non-recording of the typing practice that the participants possibly did outside the intervention, even though they belonged to the same class group.
- The absence of neurophysiological measures in the current thesis limits understanding the underlying mechanisms that contribute to the improvements induced by tDCS.
- The motor tasks used in our studies only represent a small number of the wide motor task paradigms.

Chapter 7

References

7. REFERENCES

[1] J.W. Krakauer, A.M. Hadjiosif, J. Xu, A.L. Wong, A.M. Haith, Motor learning, Compr. Physiol. 9 (2019) 613–663. https://doi.org/10.1002/cphy.c170043.

[2] M. Lee, M.R. Hinder, S.C. Gandevia, T.J. Carroll, The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice, J. Physiol. 588 (2010) 201–212. https://doi.org/10.1113/jphysiol.2009.183855.

[3] N.C. Soderstrom, R.A. Bjork, Learning Versus Performance: An Integrative Review, Perspect. Psychol. Sci. 10 (2015) 176–199. https://doi.org/10.1177/1745691615569000.

[4] R.A. Schmidt, C.A. Wrisberg, Motor learning and performance: a situation-based learning approach, 2008. https://books.google.es/books?hl=es&lr=&id=Ejc27Wrg5rMC&oi=fnd&pg=PR11&dq=motor+performance+vs+motor+learning&ots=IJ6yAhvXJT&sig=9IUFJCECw6tX4KjNc0pkLNVGqR0#v=onepage&q=motor performance vs motor learning&f=false (accessed June 25, 2021).

[5] R. Schmidt, T. Lee, C.J. Winstein, G. Wulf, H.N. Zelaznik, Motor Control and Learning: A Behavioral Emphasis, 6th Edition, Med. Sci. Sport. Exerc. 51 (2019) 226–226. https://doi.org/10.1249/01.mss.0000550736.00894.1f.

[6] A. Ericsson, R. Pool, Peak; Secrets from the New Science of Expertise, New York, 2016.

[7] D. Rosenbaum, Human Motor Control, 2010. https://doi.org/10.1016/B978-0-12-374226-1.X0001-0.

[8] H.H. Murphy, Distribution of practice periods in learning, J. Educ. Psychol. 7 (1916) 150–162. https://doi.org/10.1037/h0074113.

[9] K.G. HALL, D.A. DOMINGUES, R. CAVAZOS, CONTEXTUAL INTERFERENCE EFFECTS WITH SKILLED BASEBALL PLAYERS, Percept. Mot. Skills. 78 (1994) 835–841.

https://doi.org/10.2466/pms.1994.78.3.835.

[10] W.H. Solley, The effects of verbal instruction of speed and accuracy upon the learning of a motor skill, Res. Q. Am. Assoc. Heal. Phys. Educ. Recreat. 23 (1952) 231–240. https://doi.org/10.1080/10671188.1952.10761978.

[11] J.M. Bootsma, T. Hortobágyi, J.C. Rothwell, S.R. Caljouw, The Role of Task Difficulty in Learning a Visuomotor Skill, Med. Sci. Sports Exerc. 50 (2018) 1842–1849. https://doi.org/10.1249/MSS.0000000000001635.

[12] J.M. Bootsma, S.R. Caljouw, M.P. Veldman, N.M. Maurits, J.C. Rothwell, T. Hortobágyi, Failure to Engage Neural Plasticity through Practice of a High-difficulty Task is Accompanied by Reduced Motor Skill Retention in Older Adults, Neuroscience. 451 (2020) 22–35. https://doi.org/10.1016/J.NEUROSCIENCE.2020.10.013.

[13] J.M. Bootsma, S.R. Caljouw, M.P. Veldman, N.M. Maurits, J.C. Rothwell, T. Hortobágyi, Neural Correlates of Motor Skill Learning Are Dependent on Both Age and Task Difficulty, Front. Aging Neurosci. 13 (2021). https://doi.org/10.3389/FNAGI.2021.643132.

[14] A. Bandura, J.E. Grusec, F.L. Menlove, Observational learning as a function of symbolization and incentive set., Child Dev. 37 (1966) 499–506. https://doi.org/10.1111/j.1467-8624.1966.tb04302.x.

[15] A. Bandura, Observational Learning, in: Int. Encycl. Commun., John Wiley & Sons, Ltd, 2008. https://doi.org/10.1002/9781405186407.wbieco004.

[16] R.S. Michalski, R.E. Stepp, Learning from Observation: Conceptual Clustering, in: Mach. Learn., Springer Berlin Heidelberg, 1983: pp. 331–363. https://doi.org/10.1007/978-3-662-12405-5_11.

[17] J.J.Q. Zhang, K.N.K. Fong, N. Welage, K.P.Y. Liu, The activation of the mirror neuron system during action observation and action execution with mirror visual feedback in stroke: A systematic review, Neural Plast. 2018 (2018). https://doi.org/10.1155/2018/2321045.

[18] A.B. Cruz, Relationships among age, experience, and observational

learning of athletes based on types of model observed, J. Sports Med. Phys. Fitness. 59 (2019) 1263–1270. https://doi.org/10.23736/S0022-4707.18.08953-3.

[19] M. Andrieux, L. Proteau, Observational Learning: Tell Beginners What They Are about to Watch and They Will Learn Better, Front. Psychol. 7 (2016) 51. https://doi.org/10.3389/fpsyg.2016.00051.

[20] C. Ruffino, C. Papaxanthis, F. Lebon, Neural plasticity during motor learning with motor imagery practice: Review and perspectives, Neuroscience. 341 (2017) 61–78. https://doi.org/10.1016/j.neuroscience.2016.11.023.

[21] A. Reber, Implicit learning of Artificial Grammars, J. Verbal Learn. Verbal Behav. (1967) 855–863.

[22] J.J. Gibson, E.J. Gibson, PERCEPTUAL LEARNING: DIFFERENTIATION OR ENRICHMENT?, Psychol. Rev. 62 (1955) 32–41. https://doi.org/10.1037/h0048826.

[23] D.M. Van Es, T. Knapen, Implicit and explicit learning in reactive and voluntary saccade adaptation, PLoS One. 14 (2019). https://doi.org/10.1371/journal.pone.0203248.

[24] C.P. Edwards, H. Raikes, Extending the dance: Relationship-based approaches to infant/toddler care and education, Young Child. 57 (2002) 10–17. https://www.researchgate.net/publication/228717162_Extending_the_Dance_Relationship-Based_Approaches_to_InfantToddler_Care_and_Education (accessed April 19, 2021).

[25] L. von Bertalanffy, General Systems Theory as Integrating Factor in Contemporary Science, in: Akten Des XIV. Int. Kongresses Für Philos., Herder & Co, 1968: pp. 335–340. https://doi.org/10.5840/wcp1419682120.

[26] D.H. Bogart, Feedback, feedforward, and feedwithin: Strategic information in systems, Behav. Sci. 25 (1980) 237–249.

https://doi.org/10.1002/bs.3830250402.

[27] R.N. Scott, R.H. Brittain, R.R. Caldwell, A.B. Cameron, V.A. Dunfield, Sensory-feedback system compatible with myoelectric control, Med. Biol. Eng. Comput. 18 (1980) 65–69. https://doi.org/10.1007/BF02442481.

[28] F. Coppedè, The potential of epigenetic therapies in neurodegenerative diseases, Front. Genet. 5 (2014). https://doi.org/10.3389/fgene.2014.00220.

[29] S. Kim, B.K. Kaang, Epigenetic regulation and chromatin remodeling in learning and memory, Exp. Mol. Med. 49 (2017). https://doi.org/10.1038/emm.2016.140.

[30] P. Hirtz, W. Starosta, Sensitive and critical periods of motor coordination development and its relation to motor learning, 2002.

[31] R.D. Seidler, Neural correlates of motor learning, transfer of learning, and learning to learn, Exerc. Sport Sci. Rev. 38 (2010) 3–9. https://doi.org/10.1097/JES.0b013e3181c5cce7.

[32] B.A. Boyce, Effects of Assigned versus Participant-Set Goals on Skill Acquisition and Retention of a Selected Shooting Task, J. Teach. Phys. Educ. 11 (2016) 220–234. https://doi.org/10.1123/jtpe.11.3.220.

[33] N. Keith, K.A. Ericsson, A Deliberate Practice Account of Typing Proficiency in Everyday Typists, J. Exp. Psychol. Appl. 13 (2007) 135–145. https://doi.org/10.1037/1076-898X.13.3.135.

[34] T. Curran, S.W. Keele, Attentional and Nonattentional Forms of Sequence Learning, J. Exp. Psychol. Learn. Mem. Cogn. 19 (1993) 189–202. https://doi.org/10.1037/0278-7393.19.1.189.

[35] S. Ghorbani, A. Dana, Z. Fallah, The effects of external and internal focus of attention on motor learning and promoting learner's focus, Biomed. Hum. Kinet. 11 (2019) 175–180. https://doi.org/10.2478/bhk-2019-0024.

[36] R. Lewthwaite, G. Wulf, Optimizing motivation and attention for motor performance and learning, Curr. Opin. Psychol. 16 (2017) 38–42. https://doi.org/10.1016/j.copsyc.2017.04.005.

[37] A. Meneses, G. Liy-Salmeron, Serotonin and emotion, learning and memory, Rev. Neurosci. 23 (2012) 543–553. https://doi.org/10.1515/revneuro-2012-0060.

[38] P. Maquet, The role of sleep in learning and memory, Science (80-.). 294 (2001) 1048–1052. https://doi.org/10.1126/science.1062856.

[39] M.G. Kutlu, T.J. Gould, Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: Contributions to development and maintenance of addiction, Learn. Mem. 23 (2016) 515–533. https://doi.org/10.1101/lm.042192.116.

[40] J.H. Song, The role of attention in motor control and learning, Curr. Opin. Psychol. 29 (2019) 261–265. https://doi.org/10.1016/j.copsyc.2019.08.002.

[41] L.M. Schell, M. V. Gallo, J. Ravenscroft, Environmental influences on human growth and development: Historical review and case study of contemporary influences, Ann. Hum. Biol. 36 (2009) 459–477. https://doi.org/10.1080/03014460903067159.

[42] C. Morgan, I. Novak, N. Badawi, Enriched environments and motor outcomes in cerebral palsy: Systematic review and meta-analysis, Pediatrics. 132 (2013). https://doi.org/10.1542/peds.2012-3985.

[43] M.J. Nissen, P. Bullemer, Attentional requirements of learning: Evidence from performance measures, Cogn. Psychol. 19 (1987) 1–32. https://doi.org/10.1016/0010-0285(87)90002-8.

[44] C.M. Zingale, E. Kowler, Planning sequences of saccades, Vision Res. 27 (1987) 1327–1341. https://doi.org/10.1016/0042-6989(87)90210-0.

[45] C. Moisello, D. Crupi, E. Tunik, A. Quartarone, M. Bove, G. Tononi, M.F. Ghilardi, The serial reaction time task revisited: A study on motor sequence learning with an arm-reaching task, Exp. Brain Res. 194 (2009) 143–155. https://doi.org/10.1007/s00221-008-1681-5.

[46] Y. Du, J.E. Clark, New insights into statistical learning and chunk learning in implicit sequence acquisition, Psychon. Bull. Rev. 24 (2017) 1225–1233. https://doi.org/10.3758/s13423-016-1193-4.

[47] Y. Du, N.C. Valentini, M.J. Kim, J. Whitall, J.E. Clark, Children and adults both learn motor sequences quickly, but do so differently, Front. Psychol. 8 (2017). https://doi.org/10.3389/fpsyg.2017.00158.

[48] F. Restle, E.R. Brown, Serial pattern learning, J. Exp. Psychol. 83 (1970) 120–125. https://doi.org/10.1037/h0028530.

[49] A. Seber, R. Allen, P. Reber, Implicit versus Explicit Learning, in: Nat. Cogn., The MIT Press, Sternberg RJ, 1999. https://doi.org/10.7551/mitpress/4877.003.0019.

[50] J.B. Shea, R.L. Morgan, Contextual interference effects on the acquisition, retention, and transfer of a motor skill, J. Exp. Psychol. Hum. Learn. Mem. 5 (1979) 179–187. https://doi.org/10.1037/0278-7393.5.2.179.

[51] Kim, J. Chen, W.B. Verwey, D.L. Wright, Improving novel motor learning through prior high contextual interference training, Acta Psychol. (Amst). 182 (2018) 55–64. https://doi.org/10.1016/j.actpsy.2017.11.005.

[52] T.D. Lee, R.A. Magill, The locus of contextual interference in motor-skill acquisition, J. Exp. Psychol. Learn. Mem. Cogn. 9 (1983) 730–746. https://doi.org/10.1037/0278-7393.9.4.730.

[53] C.H.J. Lin, A.D. Wu, P. Udompholkul, B.J. Knowlton, Contextual Interference Effects in Sequence Learning for Young and Older Adults, Psychol. Aging. 25 (2010) 929–939. https://doi.org/10.1037/a0020196.

[54] D.A. Simon, Contextual interference effects with two tasks, Percept. Mot. Skills. 105 (2007) 177–183. https://doi.org/10.2466/PMS.105.1.177-183.

[55] D.L. Wright, C.B. Black, M.A. Immink, S. Brueckner, C. Magnuson, Long-Term Motor Programming Improvements Occur Via Concatenation of Movement Sequences during Random but Not during Blocked Practice, J. Mot. Behav. 36 (2004) 39–50. https://doi.org/10.3200/JMBR.36.1.39-50.

[56] K.M. Neville, M. Trempe, Serial practice impairs motor skill

consolidation, Exp. Brain Res. 235 (2017) 2601–2613. https://doi.org/10.1007/s00221-017-4992-6.

[57] T. Kim, J. Rhee, D.L. Wright, Allowing time to consolidate knowledge gained through random practice facilitates later novel motor sequence acquisition, Acta Psychol. (Amst). 163 (2016) 153–166. https://doi.org/10.1016/j.actpsy.2015.11.012.

[58] W.E. Hick, On the Rate of Gain of Information, Q. J. Exp. Psychol. 4 (1952) 11–26. https://doi.org/10.1080/17470215208416600.

[59] R. Hyman, Stimulus information as a determinant of reaction time, J. Exp. Psychol. 45 (1953) 188–196. https://doi.org/10.1037/h0056940.

[60] W.F. Battig, Facilitation and Interference, in: Acquis. Ski., 1966: pp. 215–253.

[61] D.R. Gentner, The acquisition of typewriting skill, Acta Psychol. (Amst). 54 (1983) 233–248. https://doi.org/10.1016/0001-6918(83)90037-9.

[62] C.J. Chapman, The learning curve in type writing, J. Appl. Psychol. 3 (1919) 252–268. https://doi.org/10.1037/h0072933.

[63] B.M. Towne, An Individual Curve of Learning: a Study in Typewriting, J. Exp. Psychol. 5 (1922) 79–92. https://doi.org/10.1037/h0073872.

[64] J. Long, I. Nimmo-Smith, A. Whitefield, Skilled Typing: A Characterization Based on the Distribution of Times Between Responses, Cogn. Asp. Ski. Typewriting. (1983) 145–195. https://doi.org/10.1007/978-1-4612-5470-6_7.

[65] D.R. Gentner, S. Larochelle, J. Grudin, Lexical, sublexical, and peripheral effects in skilled typewriting, Cogn. Psychol. 20 (1988) 524–548. https://doi.org/10.1016/0010-0285(88)90015-1.

[66] L.H. Shaffer, Control Processes in Typing, Q. J. Exp. Psychol. 27 (1975) 419–432. https://doi.org/10.1080/14640747508400502.

[67] J. Grabowski, The internal structure of university students' keyboard skills, J. Writ. Res. 1 (2008) 27–52. https://doi.org/10.17239/jowr-2008.01.01.2.

[68] N. Weintraub, N. Gilmour-Grill, P.L. Weiss, Relationship between handwriting and keyboarding performance among fast and slow adult keyboarders, Am. J. Occup. Ther. 64 (2010) 123–132. https://doi.org/10.5014/ajot.64.1.123.

[69] P.M. Fitts, C.M. Seeger, S-R compatibility: spatial characteristics of stimulus and response codes, J. Exp. Psychol. 46 (1953) 199–210. https://doi.org/10.1037/h0062827.

[70] A.R. Freeman, J.R. Mackinnon, L.T. Miller, Keyboarding for Students with Handwriting Problems, Phys. Occup. Ther. Pediatr. 25 (2005) 119–147. https://doi.org/10.1080/j006v25n01_08.

[71] H. Weigelt Marom, N. Weintraub, The effect of a touch-typing program on keyboarding skills of higher education students with and without learning disabilities, Res. Dev. Disabil. 47 (2015) 208–217. https://doi.org/10.1016/j.ridd.2015.09.014.

[72] E.C. Tolman, Cognitive maps in rats and men, Psychol. Rev. 55 (1948) 189–208. https://doi.org/10.1037/h0061626.

[73] J. Brebner, S-R compatibility and changes in RT with practice, Acta Psychol. (Amst). 37 (1973) 93–106. https://doi.org/10.1016/0001-6918(73)90023-1.

[74] J.E. Coover, A method of teaching typewriting based on a psychological analysis of expert typing., Natl. Educ. Assoc. (1923) 561–567. http://scholar.google.com/scholar?hl=en&q=coover+a+method+of+teaching+typewriting&btnG=&as_sdt=1,3&as_sdtp=#0.

[75] R.P. Heitz, The speed-accuracy tradeoff: History, physiology, methodology, and behavior, Front. Neurosci. 8 (2014) 1–19. https://doi.org/10.3389/fnins.2014.00150.

[76] P.M. Fitts, M.A. Posner, Human Performance, Brooks/Col, Belmont, CA, 1967. https://www.worldcat.org/title/human-performance/oclc/00480476 (accessed June 29, 2021).

[77] J.R. Anderson, Cognitive Skills and Their Acquisition , Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1981.

https://books.google.es/books?hl=es&lr=&id=PDzFBQAAQBAJ&oi=fnd&pg=PA57&dq=Neves,+D.+M.,+%26+Anderson,+J.+R.+(1981).+Knowledge+compilation:+Mechanisms+for+the+automatization+of+cognitive+skills&ots=OioWMuqB7F&sig=-pn3EJmvVNXyLkoxk_hoVQLGVbM#v=onepage&q&f=false (accessed February 12, 2021).

[78] E. Dayan, L.G. Cohen, Neuroplasticity subserving motor skill learning, Neuron. 72 (2011) 443–454. https://doi.org/10.1016/j.neuron.2011.10.008.

[79] P. Johnson, The acquisition of skill, in: M.M. Smyth, A.M. Wing (Eds.), Phychology Hum. Mov., Academic Press, London, 1984: pp. 215–240. https://scholar.google.com/scholar?cluster=13714197537371583838&hl=es&as_sdt=2005&sciodt=0,5 (accessed February 11, 2021).

[80] E.J. Swift, The acquisition of skill in type-writing; A contribution to the psychology of learning, Psychol. Bull. 1 (1904) 295–305. https://doi.org/10.1037/h0072241.

[81] O. Neumann, Automatic Processing: A Review of Recent Findings and a Plea for an Old Theory, in: Cogn. Mot. Process., Springer Berlin Heidelberg, 1984: pp. 255–293. https://doi.org/10.1007/978-3-642-69382-3_17.

[82] M. Baudry, J.L. Davis, Long-term Potentiation: A Debate of Current Issues, Volume 1, 1991. https://books.google.com/books?hl=es&lr=&id=AQe75vXBtSMC&oi=fnd&pg=PR9&ots=f02EIwaxF_&sig=M_L5QUDVGQNYDrqeWassF1pM3Po (accessed May 4, 2021).

[83] A. Artola, S. Bröcher, W. Singer, Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex, Nature. 347 (1990) 69–72. https://doi.org/10.1038/347069a0.

[84] M.S. Rioult-Pedotti, D. Friedman, J.P. Donoghue, Learning-induced LTP in neocortex, Science (80-.). 290 (2000) 533–536. https://doi.org/10.1126/science.290.5491.533.

[85] J.A. Kleim, S. Barbay, R.J. Nudo, Functional reorganization of the rat motor cortex following motor skill learning, J. Neurophysiol. 80 (1998) 3321–3325. https://doi.org/10.1152/jn.1998.80.6.3321.

[86] L.G. Hvid, D.L. Harwood, S.F. Eskildsen, U. Dalgas, A Critical Systematic Review of Current Evidence on the Effects of Physical Exercise on Whole/Regional Grey Matter Brain Volume in Populations at Risk of Neurodegeneration, Sport. Med. 51 (2021) 1651–1671. https://doi.org/10.1007/s40279-021-01453-6.

[87] F.T. Chen, R.J. Hopman, C.J. Huang, C.H. Chu, C.H. Hillman, T.M. Hung, Y.K. Chang, The effect of exercise training on brain structure and function in older adults: A systematic review based on evidence from randomized control trials, J. Clin. Med. 9 (2020). https://doi.org/10.3390/jcm9040914.

[88] M. Svensson, J. Lexell, T. Deierborg, Effects of Physical Exercise on Neuroinflammation, Neuroplasticity, Neurodegeneration, and Behavior: What We Can Learn From Animal Models in Clinical Settings, Neurorehabil. Neural Repair. 29 (2015) 577–589. https://doi.org/10.1177/1545968314562108.

[89] M.S. De Sousa Fernandes, T.F. Ordônio, G.C.J. Santos, L.E.R. Santos, C.T. Calazans, D.A. Gomes, T.M. Santos, Effects of Physical Exercise on Neuroplasticity and Brain Function: A Systematic Review in Human and Animal Studies, Neural Plast. 2020 (2020). https://doi.org/10.1155/2020/8856621.

[90] T. Inoue, S. Ninuma, M. Hayashi, A. Okuda, T. Asaka, H. Maejima, Effects of long-term exercise and low-level inhibition of GABAergic synapses on motor control and the expression of BDNF in the motor related cortex, Neurol. Res. 40 (2018) 18–25. https://doi.org/10.1080/01616412.2017.1382801.

[91] J. Kolasinski, E.L. Hinson, A.P. Divanbeighi Zand, A. Rizov, U.E. Emir, C.J. Stagg, The dynamics of cortical GABA in human motor learning, J. Physiol. 597 (2019) 271–282. https://doi.org/10.1113/JP276626.

[92] C. Smyth, J.J. Summers, M.I. Garry, Differences in motor learning

success are associated with differences in M1 excitability, Hum. Mov. Sci. 29 (2010) 618–630. https://doi.org/10.1016/j.humov.2010.02.006.

[93] W. Penfield, T. Rasmussen, The Cerebral Cortex of Man: A Clinical Study of Localization of Function, J. Am. Med. Assoc. 144 (1950) 1412. https://doi.org/10.1001/jama.1950.02920160086033.

[94] M. Wiesendanger, Organization of Secondary Motor Areas of Cerebral Cortex, in: Compr. Physiol., John Wiley & Sons, Inc., Hoboken, NJ, USA, 2011: pp. 1121–1147. https://doi.org/10.1002/cphy.cp010224.

[95] H. Asanuma, The Pyramidal Tract, in: Compr. Physiol., John Wiley & Sons, Inc., Hoboken, NJ, USA, 2011: pp. 703–733. https://doi.org/10.1002/cphy.cp010215.

[96] J.A. Kleim, S. Barbay, N.R. Cooper, T.M. Hogg, C.N. Reidel, M.S. Remple, R.J. Nudo, Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex, Neurobiol. Learn. Mem. 77 (2002) 63–77. https://doi.org/10.1006/nlme.2000.4004.

[97] W. Muellbacher, U. Zlemann, J. Wissel, N. Dang, M. Kofler, S. Facchini, B. Boroojerdi, W. Poewe, M. Hallett, Early consolidation in human primary motor cortex, Nature. 415 (2002) 640–644. https://doi.org/10.1038/nature712.

[98] E.J. Hwang, J.E. Dahlen, Y.Y. Hu, K. Aguilar, B. Yu, M. Mukundan, A. Mitani, T. Komiyama, Disengagement of motor cortex from movement control during long-term learning, Sci. Adv. 5 (2019) 1–12. https://doi.org/10.1126/sciadv.aay0001.

[99] A.E. Papale, B.M. Hooks, Circuit Changes in Motor Cortex During Motor Skill Learning, Neuroscience. 368 (2018) 283–297. https://doi.org/10.1016/j.neuroscience.2017.09.010.

[100] F. Ehsani, A.H. Bakhtiary, S. Jaberzadeh, A. Talimkhani, A. Hajihasani, Differential effects of primary motor cortex and cerebellar transcranial direct current stimulation on motor learning in healthy individuals: A randomized double-blind sham-controlled study, Neurosci. Res. 112 (2016) 10–19. https://doi.org/10.1016/j.neures.2016.06.003.

[101] A. Yokoi, S.A. Arbuckle, J. Diedrichsen, The role of human primary motor cortex in the production of skilled finger sequences, J. Neurosci. 38 (2018) 1430–1442. https://doi.org/10.1523/JNEUROSCI.2798-17.2017.

[102] R.S. Bapi, K. Doya, A.M. Harner, Evidence for effector independent and dependent representations and their differential time course of acquisition during motor sequence learning, Exp. Brain Res. 132 (2000) 149–162. https://doi.org/10.1007/s002219900332.

[103] T. Elbert, C. Pantev, C. Wienbruch, B. Rockstroh, E. Taub, Increased cortical representation of the fingers of the left hand in string players, Science (80-.). 270 (1995) 305–307. https://doi.org/10.1126/science.270.5234.305.

[104] G. Wulf, C.H. Shea, Principles derived from the study of simple skills do not generalize to complex skill learning, Psychon. Bull. Rev. 9 (2002) 185–211. https://doi.org/10.3758/BF03196276.

[105] C.I. Sarmiento, D. San-Juan, V.B.S. Prasath, Letter to the Editor: Brief history of transcranial direct current stimulation (tDCS): From electric fishes to microcontrollers, Psychol. Med. 46 (2016) 3259–3261. https://doi.org/10.1017/S0033291716001926.

[106] M.A. Nitsche, L.G. Cohen, E.M. Wassermann, A. Priori, N. Lang, A. Antal, W. Paulus, F. Hummel, P.S. Boggio, F. Fregni, A. Pascual-Leone, Transcranial direct current stimulation: State of the art 2008., Brain Stimul. 1 (2008) 206–223. https://doi.org/10.1016/j.brs.2008.06.004.

[107] J.R. Rozisky, L. da Conceição Antunes, A.P. Brietzke, A.C. de Sousa, W. Caumo, Transcranial direct current stimulation and neuroplasticity, in: Transcranial Direct Curr. Stimul. Emerg. Uses, Saf. Neurobiol. Eff., Nova Science Publishers, Inc., 2016: pp. 1–26.

[108] E. Morya, K. Monte-Silva, M. Bikson, Z. Esmaeilpour, C.E. Biazoli, A. Fonseca, T. Bocci, F. Farzan, R. Chatterjee, J.M. Hausdorff, D.G. Da Silva Machado, A.R. Brunoni, E. Mezger, L.A. Moscaleski, R. Pegado, J.R. Sato, M.S. Caetano, K.N. Sá, C. Tanaka, L.M. Li, A.F. Baptista, A.H. Okano, Beyond the target area: an integrative view of tDCS-

induced motor cortex modulation in patients and athletes, J. Neuroeng. Rehabil. 16 (2019) 1–29. https://doi.org/10.1186/s12984-019-0581-1.

[109] W. He, P.Y. Fong, T.W.H. Leung, Y.Z. Huang, Protocols of non-invasive brain stimulation for neuroplasticity induction, Neurosci. Lett. 719 (2020) 133437. https://doi.org/10.1016/j.neulet.2018.02.045.

[110] M.A. Nitsche, W. Paulus, Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans, Neurology. 57 (2001) 1899–1901. https://doi.org/10.1212/WNL.57.10.1899.

[111] Nitsche, L.G. Cohen, E.M. Wassermann, A. Priori, N. Lang, A. Antal, W. Paulus, F. Hummel, P.S. Boggio, F. Fregni, A. Pascual-Leone, Transcranial direct current stimulation: State of the art 2008, Brain Stimul. 1 (2008) 206–223. https://doi.org/10.1016/j.brs.2008.06.004.

[112] Nitsche, W. Paulus, Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation, J. Physiol. 527 (2000) 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.

[113] D. Liebetanz, M.A. Nitsche, F. Tergau, W. Paulus, Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability, Brain. 125 (2002) 2238–2247. https://doi.org/10.1093/brain/awf238.

[114] M.A. Nitsche, A. Schauenburg, N. Lang, D. Liebetanz, C. Exner, W. Paulus, F. Tergau, Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human, J. Cogn. Neurosci. 15 (2003) 619–626. https://doi.org/10.1162/089892903321662994.

[115] C.J. Stagg, J.G. Best, M.C. Stephenson, J. O'Shea, M. Wylezinska, Z.T. Kineses, P.G. Morris, P.M. Matthews, H. Johansen-Berg, Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation, J. Neurosci. 29 (2009) 5202–5206. https://doi.org/10.1523/JNEUROSCI.4432-08.2009.

[116] M.A. Nitsche, A. Seeber, K. Frommann, C.C. Klein, C. Rochford, M.S.

Nitsche, K. Fricke, D. Liebetanz, N. Lang, A. Antal, W. Paulus, F. Tergau, Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex, J. Physiol. 568 (2005) 291–303. https://doi.org/10.1113/jphysiol.2005.092429.

[117] C.J. Stagg, G. Jayaram, D. Pastor, Z.T. Kincses, P.M. Matthews, H. Johansen-Berg, Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning, Neuropsychologia. 49 (2011) 800–804. https://doi.org/10.1016/j.neuropsychologia.2011.02.009.

[118] T. Bunai, T. Hirosawa, M. Kikuchi, M. Fukai, M. Yokokura, S. Ito, Y. Takata, T. Terada, Y. Ouchi, tDCS-induced modulation of GABA concentration and dopamine release in the human brain: A combination study of magnetic resonance spectroscopy and positron emission tomography, Brain Stimul. 14 (2021) 154–160. https://doi.org/10.1016/j.brs.2020.12.010.

[119] U. Ziemann, R. Chen, L.G. Cohen, M. Hallett, Dextromethorphan decreases the excitability of the human motor cortex, Neurology. 51 (1998) 1320–1324. https://doi.org/10.1212/WNL.51.5.1320.

[120] M.A. Castro-Alamancos, J.P. Donoghue, B.W. Connors, Different forms of synaptic plasticity in somatosensory and motor areas of the neocortex, J. Neurosci. 15 (1995) 5324–5333. https://doi.org/10.1523/jneurosci.15-07-05324.1995.

[121] C. Trepel, R.J. Racine, GABAergic modulation of neocortical long-term potentiation in the freely moving rat, Synapse. 35 (2000) 120–128. https://doi.org/10.1002/(SICI)1098-2396(200002)35:2<120::AID-SYN4>3.0.CO;2-6.

[122] C. Fonteneau, J. Redoute, F. Haesebaert, D. Le Bars, N. Costes, M.-F. Suaud-Chagny, J. Brunelin, Frontal Transcranial Direct Current Stimulation Induces Dopamine Release in the Ventral Striatum in Human, Cereb. Cortex. 28 (2018) 2636–2646. https://doi.org/10.1093/cercor/bhy093.

[123] R. Meeusen, K. De Meirleir, Exercise and Brain Neurotransmission, Sport. Med. 20 (1995) 160–188. https://doi.org/10.2165/00007256-199520030-00004.

[124] S. Cocco, M. V. Podda, C. Grassi, Role of BDNF Signaling in Memory Enhancement Induced by Transcranial Direct Current Stimulation, Front. Neurosci. 12 (2018) 427. https://doi.org/10.3389/fnins.2018.00427.

[125] B. Fritsch, J. Reis, K. Martinowich, H.M. Schambra, Y. Ji, L.G. Cohen, B. Lu, Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning, Neuron. 66 (2010) 198–204. https://doi.org/10.1016/j.neuron.2010.03.035.

[126] N.R.J. da Silva, G. Laste, A. Deitos, L.C. Stefani, G. Cambraia-Canto, I.L.S. Torres, A.R. Brunoni, F. Fregni, W. Caumo, Combined neuromodulatory interventions in acute experimental pain: Assessment of melatonin and non-invasive brain stimulation, Front. Behav. Neurosci. 9 (2015) 77. https://doi.org/10.3389/fnbeh.2015.00077.

[127] B.C. Lopes, L.F. Medeiros, D.J. Stein, S.G. Cioato, V.S. de Souza, H.R. Medeiros, P.R.S. Sanches, F. Fregni, W. Caumo, I.L.S. Torres, tDCS and exercise improve anxiety-like behavior and locomotion in chronic pain rats via modulation of neurotrophins and inflammatory mediators, Behav. Brain Res. 404 (2021) 113173. https://doi.org/10.1016/j.bbr.2021.113173.

[128] J.C. Horvath, O. Carter, J.D. Forte, No significant effect of transcranial direct current stimulation (tDCS) found on simple motor reaction time comparing 15 different simulation protocols, Neuropsychologia. 91 (2016) 544–552. https://doi.org/10.1016/j.neuropsychologia.2016.09.017.

[129] M. Vöröslakos, Y. Takeuchi, K. Brinyiczki, T. Zombori, A. Oliva, A. Fernández-Ruiz, G. Kozák, Z.T. Kincses, B. Iványi, G. Buzsáki, A. Berényi, Direct effects of transcranial electric stimulation on brain circuits in rats and humans, Nat. Commun. 9 (2018). https://doi.org/10.1038/s41467-018-02928-3.

[130] E. Underwood, Cadaver study challenges brain stimulation methods:

Unusual test of transcranial stimulation shows that little electrical current penetrates the skull, Science (80-.). 352 (2016) 397. https://doi.org/10.1126/science.352.6284.397.

[131] A. Opitz, A. Falchier, G.S. Linn, M.P. Milham, C.E. Schroeder, Limitations of ex vivo measurements for in vivo neuroscience, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 5243–5246. https://doi.org/10.1073/pnas.1617024114.

[132] P. Ruhnau, K.S. Rufener, H.J. Heinze, T. Zaehle, Sailing in a sea of disbelief: In vivo measurements of transcranial electric stimulation in human subcortical structures, Brain Stimul. 11 (2018) 241–243. https://doi.org/10.1016/j.brs.2017.09.015.

[133] M. Bikson, A. Rahman, Origins of specificity during tDCS: Anatomical, activity-selective, and input-bias mechanisms, Front. Hum. Neurosci. 7 (2013). https://doi.org/10.3389/fnhum.2013.00688.

[134] G. Kronberg, M. Bridi, T. Abel, M. Bikson, L.C. Parra, Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects, Brain Stimul. 10 (2017) e23–e24. https://doi.org/10.1016/j.brs.2017.04.014.

[135] E.R. Buch, E. Santarnecchi, A. Antal, J. Born, P.A. Celnik, J. Classen, C. Gerloff, M. Hallett, F.C. Hummel, M.A. Nitsche, A. Pascual-Leone, W.J. Paulus, J. Reis, E.M. Robertson, J.C. Rothwell, M. Sandrini, H.M. Schambra, E.M. Wassermann, U. Ziemann, L.G. Cohen, Effects of tDCS on motor learning and memory formation: A consensus and critical position paper., Clin. Neurophysiol. 128 (2017) 589–603. https://doi.org/10.1016/j.clinph.2017.01.004.

[136] A.R. Brunoni, M.A. Nitsche, N. Bolognini, M. Bikson, T. Wagner, L. Merabet, D.J. Edwards, A. Valero-Cabre, A. Rotenberg, A. Pascual-Leone, R. Ferrucci, A. Priori, P.S. Boggio, F. Fregni, Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions, Brain Stimul. 5 (2012) 175–195. https://doi.org/10.1016/j.brs.2011.03.002.

[137] M. Bikson, P. Grossman, C. Thomas, A.L. Zannou, J. Jiang, T. Adnan,

A.P. Mourdoukoutas, G. Kronberg, D. Truong, P. Boggio, A.R. Brunoni, L. Charvet, F. Fregni, B. Fritsch, B. Gillick, R.H. Hamilton, B.M. Hampstead, R. Jankord, A. Kirton, H. Knotkova, D. Liebetanz, A. Liu, C. Loo, M.A. Nitsche, J. Reis, J.D. Richardson, A. Rotenberg, P.E. Turkeltaub, A.J. Woods, Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016., Brain Stimul. 9 (2016) 641–661. https://doi.org/10.1016/j.brs.2016.06.004.

[138] K.A. Ho, J.L. Taylor, T. Chew, V. Gálvez, A. Alonzo, S. Bai, S. Dokos, C.K. Loo, The Effect of Transcranial Direct Current Stimulation (tDCS) Electrode Size and Current Intensity on Motor Cortical Excitability: Evidence from Single and Repeated Sessions, Brain Stimul. 9 (2016) 1–7. https://doi.org/10.1016/j.brs.2015.08.003.

[139] V. López-Alonso, B. Cheeran, D. Río-Rodríguez, M. Fernández-Del-Olmo, Inter-individual variability in response to non-invasive brain stimulation paradigms, Brain Stimul. 7 (2014) 372–380. https://doi.org/10.1016/j.brs.2014.02.004.

[140] A. Molero-Chamizo, J.R. Alameda Bailén, T. Garrido Béjar, M. García López, I. Jaén Rodríguez, C. Gutiérrez Lérida, S. Pérez Panal, G. González Ángel, L. Lemus Corchero, M.J. Ruiz Vega, M.A. Nitsche, G.N. Rivera-Urbina, Poststimulation time interval-dependent effects of motor cortex anodal tDCS on reaction-time task performance, Cogn. Affect. Behav. Neurosci. 18 (2018) 167–175. https://doi.org/10.3758/s13415-018-0561-0.

[141] T. Bocci, M. Caleo, S. Tognazzi, N. Francini, L. Briscese, L. Maffei, S. Rossi, A. Priori, F. Sartucci, Evidence for metaplasticity in the human visual cortex, J. Neural Transm. 121 (2014) 221–231. https://doi.org/10.1007/s00702-013-1104-z.

[142] H.R. Siebner, N. Lang, V. Rizzo, M.A. Nitsche, W. Paulus, R.N. Lemon, J.C. Rothwell, Preconditioning of Low-Frequency Repetitive Transcranial Magnetic Stimulation with Transcranial Direct Current Stimulation: Evidence for Homeostatic Plasticity in the Human Motor Cortex, J. Neurosci. 24 (2004) 3379–3385.

https://doi.org/10.1523/JNEUROSCI.5316-03.2004.

[143] C.J. Stagg, G. Jayaram, D. Pastor, Z.T. Kincses, P.M. Matthews, H. Johansen-Berg, Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning, Neuropsychologia. 49 (2011) 800–804. https://doi.org/10.1016/j.neuropsychologia.2011.02.009.

[144] G.G. Ambrus, L. Chaieb, R. Stilling, H. Rothkegel, A. Antal, W. Paulus, Monitoring transcranial direct current stimulation induced changes in cortical excitability during the serial reaction time task, Neurosci. Lett. 616 (2016) 98–104. https://doi.org/10.1016/j.neulet.2016.01.039.

[145] H.L. Filmer, P.E. Dux, J.B. Mattingley, Applications of transcranial direct current stimulation for understanding brain function, Trends Neurosci. 37 (2014) 742–753. https://doi.org/10.1016/j.tins.2014.08.003.

[146] J.M. Galea, A. Vazquez, N. Pasricha, J.J. Orban De Xivry, P. Celnik, Dissociating the roles of the cerebellum and motor cortex during adaptive learning: The motor cortex retains what the cerebellum learns, Cereb. Cortex. 21 (2011) 1761–1770. https://doi.org/10.1093/cercor/bhq246.

[147] R. Greinacher, L. Buhôt, L. Möller, G. Learmonth, The time course of ineffective sham-blinding during low-intensity (1 mA) transcranial direct current stimulation, Eur. J. Neurosci. (2019) 1–9. https://doi.org/10.1111/ejn.14497.

[148] E.K. Kang, N.J. Paik, Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subjects, Exp. Transl. Stroke Med. 3 (2011) 2–7. https://doi.org/10.1186/2040-7378-3-4.

[149] S.S. Kantak, C.K. Mummidisetty, J.W. Stinear, Primary motor and premotor cortex in implicit sequence learning - Evidence for competition between implicit and explicit human motor memory systems, Eur. J. Neurosci. 36 (2012) 2710–2715. https://doi.org/10.1111/j.1460-9568.2012.08175.x.

[150] M.A. Nitsche, A. Schauenburg, N. Lang, D. Liebetanz, C. Exner, W. Paulus, F. Tergau, Facilitation of implicit motor learning by weak

transcranial direct current stimulation of the primary motor cortex in the human, (2002) 619–626. https://doi.org/10.1007/s10973-012-2225-6.

[151] K. Monte-Silva, M.F. Kuo, S. Hessenthaler, S. Fresnoza, D. Liebetanz, W. Paulus, M.A. Nitsche, Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation, Brain Stimul. 6 (2013) 424–432. https://doi.org/10.1016/j.brs.2012.04.011.

[152] F. Hashemirad, M. Zoghi, P.B. Fitzgerald, S. Jaberzadeh, The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: A systematic review and meta-analysis, Brain Cogn. 102 (2016) 1–12. https://doi.org/10.1016/j.bandc.2015.11.005.

[153] B.A. Coffman, V.P. Clark, R. Parasuraman, Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation., Neuroimage. 85 Pt 3 (2014) 895–908. https://doi.org/10.1016/j.neuroimage.2013.07.083.

[154] J.-P. Lefaucheur, A. Antal, S.S. Ayache, D.H. Benninger, J. Brunelin, F. Cogiamanian, M. Cotelli, D. De Ridder, R. Ferrucci, B. Langguth, P. Marangolo, V. Mylius, M.A. Nitsche, F. Padberg, U. Palm, E. Poulet, A. Priori, S. Rossi, M. Schecklmann, S. Vanneste, U. Ziemann, L. Garcia-Larrea, W. Paulus, Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)., Clin. Neurophysiol. 128 (2017) 56–92. https://doi.org/10.1016/j.clinph.2016.10.087.

[155] L. Angius, A. Pascual-Leone, E. Santarnecchi, Brain stimulation and physical performance, 1st ed., Elsevier B.V., 2018. https://doi.org/10.1016/bs.pbr.2018.07.010.

[156] A.H. Okano, E.B. Fontes, R.A. Montenegro, P. De Tarso Veras Farinatti, E.S. Cyrino, L.M. Li, M. Bikson, T.D. Noakes, Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise, Br. J. Sports Med. 49 (2015) 1213–1218. https://doi.org/10.1136/bjsports-2012-091658.

[157] D.M.M. Borducchi, J.S. Gomes, H. Akiba, Q. Cordeiro, J.H.M. Borducchi, L.S.S. Valentin, G.M. Borducchi, Á.M. Dias, Transcranial direct current stimulation effects on athletes' cognitive performance: An

exploratory proof of concept trial, Front. Psychiatry. 7 (2016) 183. https://doi.org/10.3389/fpsyt.2016.00183.

[158] S. Reardon, "Brain doping" may improve athletes' performance, Nature. 531 (2016) 283–284. https://doi.org/10.1038/nature.2016.19534.

[159] C. Ammann, D. Spampinato, J. Márquez-Ruiz, Modulating motor learning through transcranial direct-current stimulation: An integrative view, Front. Psychol. 7 (2016). https://doi.org/10.3389/fpsyg.2016.01981.

[160] N.H. Pixa, B. Pollok, Effects of tDCS on bimanual motor skills: A brief review, Front. Behav. Neurosci. 12 (2018). https://doi.org/10.3389/fnbeh.2018.00063.

[161] R. Patel, J. Ashcroft, A. Patel, H. Ashrafian, A.J. Woods, H. Singh, A. Darzi, D.R. Leff, The Impact of Transcranial Direct Current Stimulation on Upper-Limb Motor Performance in Healthy Adults: A Systematic Review and Meta-Analysis, Front. Neurosci. 13 (2019). https://doi.org/10.3389/fnins.2019.01213.

[162] J.C. Horvath, J.D. Forte, O. Carter, Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS)., Brain Stimul. 8 (2015) 535–550. https://doi.org/10.1016/j.brs.2015.01.400.

[163] S.C. Tseng, S.H. Chang, K.M. Hoerth, A.T.A. Nguyen, D. Perales, Anodal Transcranial Direct Current Stimulation Enhances Retention of Visuomotor Stepping Skills in Healthy Adults, Front. Hum. Neurosci. 14 (2020). https://doi.org/10.3389/fnhum.2020.00251.

[164] P. Ciechanski, A. Kirton, Transcranial Direct-Current Stimulation Can Enhance Motor Learning in Children, Cereb. Cortex. 27 (2017) 2758–2767. https://doi.org/10.1093/cercor/bhw114.

[165] J. Reis, H.M. Schambra, L.G. Cohen, E.R. Buch, B. Fritsch, E. Zarahn, P.A. Celnik, J.W. Krakauer, Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 1590–1595.

https://doi.org/10.1073/pnas.0805413106.

[166] G. Naros, M. Geyer, S. Koch, L. Mayr, T. Ellinger, F. Grimm, A. Gharabaghi, Enhanced motor learning with bilateral transcranial direct current stimulation: Impact of polarity or current flow direction?, Clin. Neurophysiol. 127 (2016) 2119–2126. https://doi.org/10.1016/j.clinph.2015.12.020.

[167] G. Prichard, C. Weiller, B. Fritsch, J. Reis, Effects of different electrical brain stimulation protocols on subcomponents of motor skill learning, Brain Stimul. 7 (2014) 532–540. https://doi.org/10.1016/j.brs.2014.04.005.

[168] G. Cantarero, D. Spampinato, J. Reis, L. Ajagbe, T. Thompson, K. Kulkarni, P. Celnik, Cerebellar direct current stimulation enhances on-line motor skill acquisition through an effect on accuracy, J. Neurosci. 35 (2015) 3285–3290. https://doi.org/10.1523/JNEUROSCI.2885-14.2015.

[169] H.L. Filmer, M. Lyons, J.B. Mattingley, P.E. Dux, Anodal tDCS applied during multitasking training leads to transferable performance gains, Sci. Rep. 7 (2017) 1–11. https://doi.org/10.1038/s41598-017-13075-y.

[170] H.L. Filmer, E. Varghese, G.E. Hawkins, J.B. Mattingley, P.E. Dux, Improvements in Attention and Decision-Making Following Combined Behavioral Training and Brain Stimulation, Cereb. Cortex. 27 (2017) 3675–3682. https://doi.org/10.1093/cercor/bhw189.

[171] K.E. Hupfeld, C.J. Ketcham, H.D. Schneider, Transcranial direct current stimulation (tDCS) to the supplementary motor area (SMA) influences performance on motor tasks, Exp. Brain Res. 235 (2017) 851–859. https://doi.org/10.1007/s00221-016-4848-5.

[172] A. Talimkhani, I. Abdollahi, M.A. Mohseni-Bandpei, F. Ehsani, S. Khalili, S. Jaberzadeh, Research paper: Differential effects of unihemispheric concurrent dual-site and conventional tDCS on motor learning: A randomized, sham-controlled study, Basic Clin. Neurosci. 10 (2019) 59–71. https://doi.org/10.32598/bcn.9.10.350.

[173] S. Karok, D. Fletcher, A.G. Witney, Task-specificity of unilateral anodal

and dual-M1 tDCS effects on motor learning, Neuropsychologia. 94 (2017) 84–95. https://doi.org/10.1016/j.neuropsychologia.2016.12.002.

[174] K. Vancleef, R. Meesen, S.P. Swinnen, H. Fujiyama, TDCS over left M1 or DLPFC does not improve learning of a bimanual coordination task, Sci. Rep. 6 (2016) 1–11. https://doi.org/10.1038/srep35739.

[175] U. Debarnot, R. Neveu, Y. Samaha, E. Saruco, T. Macintyre, A. Guillot, Acquisition and consolidation of implicit motor learning with physical and mental practice across multiple days of anodal tDCS, Neurobiol. Learn. Mem. 164 (2019) 107062. https://doi.org/10.1016/j.nlm.2019.107062.

[176] A. Sánchez-Kuhn, C. Pérez-Fernández, M. Moreno, P. Flores, F. Sánchez-Santed, Differential effects of transcranial direct current stimulation (tDCS) depending on previous musical training, Front. Psychol. 9 (2018) 1–9. https://doi.org/10.3389/fpsyg.2018.01465.

[177] C.M. Saucedo-Marquez, X. Zhang, S.P. Swinnen, R. Meesen, N. Wenderoth, Task-specific effect of transcranial direct current stimulation on motor learning, Front. Hum. Neurosci. 7 (2013) 1–12. https://doi.org/10.3389/fnhum.2013.00333.

[178] S. Waters-Metenier, M. Husain, T. Wiestler, J. Diedrichsen, Bihemispheric transcranial direct current stimulation enhances effector-independent representations of motor synergy and sequence learning, J. Neurosci. 34 (2014) 1037–1050. https://doi.org/10.1523/JNEUROSCI.2282-13.2014.

[179] J. Gomes-Osman, E.C. Field-Fote, Bihemispheric anodal corticomotor stimulation using transcranial direct current stimulation improves bimanual typing task performance, J. Mot. Behav. 45 (2013) 361–367. https://doi.org/10.1080/00222895.2013.808604.

[180] H.M. Schambra, M. Abe, D.A. Luckenbaugh, J. Reis, J.W. Krakauer, L.G. Cohen, Probing for hemispheric specialization for motor skill learning: A transcranial direct current stimulation study, J. Neurophysiol. 106 (2011) 652–661. https://doi.org/10.1152/jn.00210.2011.

[181] J. Reis, J.T. Fischer, G. Prichard, C. Weiller, L.G. Cohen, B. Fritsch, Time- but not sleep-dependent consolidation of tDCS-enhanced visuomotor skills, Cereb. Cortex. 25 (2015) 109–117. https://doi.org/10.1093/cercor/bht208.

[182] J. Fan, J. Voisin, M.H. Milot, J. Higgins, M.H. Boudrias, Transcranial direct current stimulation over multiple days enhances motor performance of a grip task, Ann. Phys. Rehabil. Med. 60 (2017) 329–333. https://doi.org/10.1016/j.rehab.2017.07.001.

[183] A. Franco, N. Malhotra, G. Simonovits, Publication bias in the social sciences: Unlocking the file drawer, Science (80-.). 345 (2014) 1502–1505. https://doi.org/10.1126/science.1255484.

[184] M.E. Héroux, C.K. Loo, J.L. Taylor, S.C. Gandevia, Questionable science and reproducibility in electrical brain stimulation research, PLoS One. 12 (2017). https://doi.org/10.1371/journal.pone.0175635.

[185] A. Antal, I. Alekseichuk, M. Bikson, J. Brockmöller, A.R. Brunoni, R. Chen, L.G. Cohen, G. Dowthwaite, J. Ellrich, A. Flöel, F. Fregni, M.S. George, R. Hamilton, J. Haueisen, C.S. Herrmann, F.C. Hummel, J.P. Lefaucheur, D. Liebetanz, C.K. Loo, C.D. McCaig, C. Miniussi, P.C. Miranda, V. Moliadze, M.A. Nitsche, R. Nowak, F. Padberg, A. Pascual-Leone, W. Poppendieck, A. Priori, S. Rossi, P.M. Rossini, J. Rothwell, M.A. Rueger, G. Ruffini, K. Schellhorn, H.R. Siebner, Y. Ugawa, A. Wexler, U. Ziemann, M. Hallett, W. Paulus, Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines, Clin. Neurophysiol. 128 (2017) 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001.

[186] L. Tadini, R. El-Nazer, A.R. Brunoni, J. Williams, M. Carvas, P. Boggio, A. Priori, A. Pascual-Leone, F. Fregni, Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents, J. ECT. 27 (2011) 134–140. https://doi.org/10.1097/YCT.0b013e3181e631a8.

[187] A.R. Brunoni, J. Amadera, B. Berbel, M.S. Volz, B.G. Rizzerio, F. Fregni, A systematic review on reporting and assessment of adverse

effects associated with transcranial direct current stimulation., Int. J. Neuropsychopharmacol. 14 (2011) 1133–1145. https://doi.org/10.1017/S1461145710001690.

[188] C. Poreisz, K. Boros, A. Antal, W. Paulus, Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients, Brain Res. Bull. 72 (2007) 208–214. https://doi.org/10.1016/j.brainresbull.2007.01.004.

[189] U. Palm, D. Keeser, C. Schiller, Z. Fintescu, E. Reisinger, F. Padberg, M. Nitsche, Skin lesions after treatment with transcranial direct current stimulation (tDCS), Brain Stimul. 1 (2008) 386–387. https://doi.org/10.1016/j.brs.2008.04.003.

[190] N. Rodríguez, E. Opisso, Á. Pascual-Leone, M. Dolors Soler, Skin Lesions Induced by Transcranial Direct Current Stimulation (tDCS), Brain Stimul. (2014). https://doi.org/10.1016/j.brs.2014.06.005.

[191] E. Frank, S. Wilfurth, M. Landgrebe, P. Eichhammer, G. Hajak, B. Langguth, Anodal skin lesions after treatment with transcranial direct current stimulation, Brain Stimul. 3 (2010) 58–59. https://doi.org/10.1016/j.brs.2009.04.002.

[192] J. Wang, Y. Wei, J. Wen, X. Li, Skin burn after single session of transcranial direct current stimulation (tDCS), Brain Stimul. 8 (2015) 165–166. https://doi.org/10.1016/j.brs.2014.10.015.

[193] K. Kasahara, S. Tanaka, K. Watanabe, T. Hanakawa, M. Honda, Small skin lesion after treatment with repeated daily transcranial direct current stimulation, 臨床神経生理学 Japanese J. Clin. Neurophysiol. 39 (2011) 24–27.

[194] C.K. Loo, D.M. Martin, A. Alonzo, S. Gandevia, P.B. Mitchell, P. Sachdev, Avoiding skin burns with transcranial direct current stimulation: Preliminary considerations, Int. J. Neuropsychopharmacol. 14 (2011) 425–426. https://doi.org/10.1017/S1461145710001197.

[195] H. Matsumoto, Y. Ugawa, Adverse events of tDCS and tACS: A review, Clin. Neurophysiol. Pract. 2 (2017) 19–25.

https://doi.org/10.1016/j.cnp.2016.12.003.

[196] S. Nikolin, C. Huggins, D. Martin, A. Alonzo, C.K. Loo, Safety of repeated sessions of transcranial direct current stimulation: A systematic review, Brain Stimul. 11 (2018) 278–288. https://doi.org/10.1016/j.brs.2017.10.020.

[197] B. Savic, B. Meier, How transcranial direct current stimulation can modulate implicit motor sequence learning and consolidation: A brief review, Front. Hum. Neurosci. 10 (2016). https://doi.org/10.3389/fnhum.2016.00026.

[198] V. López-Alonso, M. Fernández-del-Olmo, A. Costantini, J.J. Gonzalez-Henriquez, B. Cheeran, Intra-individual variability in the response to anodal transcranial direct current stimulation, Clin. Neurophysiol. 126 (2015) 2342–2347. https://doi.org/10.1016/j.clinph.2015.03.022.

[199] S. Wiethoff, M. Hamada, J.C. Rothwell, Variability in response to transcranial direct current stimulation of the motor cortex, Brain Stimul. 7 (2014) 468–475. https://doi.org/10.1016/j.brs.2014.02.003.

[200] J.J. Summers, N. Kang, J.H. Cauraugh, Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta- analysis, Ageing Res. Rev. 25 (2016) 42–54. https://doi.org/10.1016/j.arr.2015.11.004.

[201] A. Guerra, V. López-Alonso, B. Cheeran, A. Suppa, Variability in non-invasive brain stimulation studies: Reasons and results, Neurosci. Lett. 719 (2020). https://doi.org/10.1016/j.neulet.2017.12.058.

[202] M.R. Borich, T.J. Kimberley, Both sleep and wakefulness support consolidation of continuous, goal-directed, visuomotor skill, Exp. Brain Res. 214 (2011) 619–630. https://doi.org/10.1007/s00221-011-2863-0.

[203] A. Antal, M.A. Nitsche, T.Z. Kincses, W. Kruse, K.P. Hoffmann, W. Paulus, Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans, Eur. J. Neurosci. 19 (2004) 2888–2892. https://doi.org/10.1111/j.1460-9568.2004.03367.x.

[204] M. Mosayebi Samani, D. Agboada, M. Kuo, M.A. Nitsche, Probing the relevance of repeated cathodal transcranial direct current stimulation over the primary motor cortex for prolongation of after-effects, J. Physiol. 598 (2020) 805–816. https://doi.org/10.1113/JP278857.

[205] E. Ghasemian-Shirvan, L. Farnad, M. Mosayebi-Samani, S. Verstraelen, R.L.J. Meesen, M.-F. Kuo, M.A. Nitsche, Age-related differences of motor cortex plasticity in adults: A transcranial direct current stimulation study, Brain Stimul. 13 (2020) 1588–1599. https://doi.org/10.1016/j.brs.2020.09.004.

[206] F.C. Donders, On the speed of mental processes, Acta Psychol. (Amst). 30 (1969) 412–431. https://doi.org/10.1016/0001-6918(69)90065-1.

[207] M.-F. Kuo, M. Unger, D. Liebetanz, N. Lang, F. Tergau, W. Paulus, M.A. Nitsche, Limited impact of homeostatic plasticity on motor learning in humans, Neuropsychologia. 46 (2008) 2122–2128. https://doi.org/10.1016/j.neuropsychologia.2008.02.023.

[208] G.G. Ambrus, L. Chaieb, R. Stilling, H. Rothkegel, A. Antal, W. Paulus, Monitoring transcranial direct current stimulation induced changes in cortical excitability during the serial reaction time task, Neurosci. Lett. 616 (2016) 98–104. https://doi.org/10.1016/j.neulet.2016.01.039.

[209] N.M. Drummond, G. Hayduk-Costa, A. Leguerrier, A.N. Carlsen, Effector-independent reduction in choice reaction time following bi-hemispheric transcranial direct current stimulation over motor cortex, PLoS One. 12 (2017) 1–12. https://doi.org/10.1371/journal.pone.0172714.

[210] M.A. Nitsche, A. Schauenburg, N. Lang, D. Liebetanz, C. Exner, W. Paulus, F. Tergau, Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human, J. Cogn. Neurosci. 15 (2003) 619–626. https://doi.org/10.1162/089892903321662994.

[211] D. Agboada, M. Mosayebi Samani, A. Jamil, M.F. Kuo, M.A. Nitsche, Expanding the parameter space of anodal transcranial direct current stimulation of the primary motor cortex, Sci. Rep. 9 (2019).

https://doi.org/10.1038/s41598-019-54621-0.

[212] P.S. Boggio, C. Campanhã, C.A. Valasek, S. Fecteau, A. Pascual-Leone, F. Fregni, Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation, Eur. J. Neurosci. 31 (2010) 593–597. https://doi.org/10.1111/j.1460-9568.2010.07080.x.

[213] AA.VV., The jamovi project (version 1.2), Jamovi.Org. (2020) 1. https://www.jamovi.org.

[214] M. Gallucci, GAMLj: General analyses for linear models. [jamovi module], (2019). https://gamlj.github.io/.

[215] R, R Core Team, R A Lang. Environ. Stat. Comput. R Found. Stat. Comput. Vienna, Austria. (2018) Language and envionment for statistical computing. https://cran.r-project.org/.

[216] M.E. Berryhill, K.T. Jones, tDCS selectively improves working memory in older adults with more education, Neurosci. Lett. 521 (2012) 148–151. https://doi.org/10.1016/j.neulet.2012.05.074.

[217] P. Tseng, T.Y. Hsu, C.F. Chang, O.J.L. Tzeng, D.L. Hung, N.G. Muggleton, V. Walsh, W.K. Liang, S.K. Cheng, C.H. Juan, Unleashing potential: Transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals, J. Neurosci. 32 (2012) 10554–10561. https://doi.org/10.1523/JNEUROSCI.0362-12.2012.

[218] G.H. Mowbray, M. V. Rhoades, On the Reduction of Choice Reaction Times with Practice, Q. J. Exp. Psychol. 11 (1959) 16–23. https://doi.org/10.1080/17470215908416282.

[219] M. Farre, R. De la Torre, M. Llorente, X. Lamas, B. Ugena, J. Segura, J. Cami, Alcohol and cocaine interactions in humans, J. Pharmacol. Exp. Ther. 266 (1993) 1364–1373.

[220] A. Pascual-Leone, J. Valls-Solé, E.M. Wassermann, J. Brasil-Neto, L.G. Cohen, M. Hallett, Effects of focal transcranial magnetic stimulation on simple reaction time to acoustic, visual and somatosensory stimuli, Brain. 115 (1992) 1045–1059. https://doi.org/10.1093/brain/115.4.1045.

[221] A.N. Carlsen, J.S. Eagles, C.D. MacKinnon, Transcranial direct current stimulation over the supplementary motor area modulates the preparatory activation level in the human motor system, Behav. Brain Res. 279 (2015) 68–75. https://doi.org/10.1016/J.BBR.2014.11.009.

[222] M.G. Gamero, J.M. García-Ceberino, S.J. Ibáñez, S. Feu, Analysis of Declarative and Procedural Knowledge According to Teaching Method and Experience in School Basketball, Sustain. 2021, Vol. 13, Page 6012. 13 (2021) 6012. https://doi.org/10.3390/SU13116012.

[223] R.M. Britten, The Effects of Instruction on Keyboarding Skills in Grade 2, Technology. 28 (1988) 34–37.

[224] E. Yechiam, I. Erev, V. Yehene, D. Gopher, Melioration and the Transition from Touch-Typing Training to Everyday Use, in: Hum. Factors, 2003: pp. 671–684. https://doi.org/10.1518/hfes.45.4.671.27085.

[225] D. Baddeley, D.J.A. Longman, The influence of length and frequency of training session on the rate of learning to type, Ergonomics. 21 (1978) 627–635. https://doi.org/10.1080/00140137808931764.

[226] H. Weigelt Marom, N. Weintraub, The effect of a touch-typing program on keyboarding skills of higher education students with and without learning disabilities, Res. Dev. Disabil. 47 (2015) 208–217. https://doi.org/10.1016/j.ridd.2015.09.014.

[227] S. Laventure, S. Fogel, O. Lungu, G. Albouy, P. Sévigny-Dupont, C. Vien, C. Sayour, J. Carrier, H. Benali, J. Doyon, NREM2 and Sleep Spindles Are Instrumental to the Consolidation of Motor Sequence Memories, PLOS Biol. 14 (2016) e1002429. https://doi.org/10.1371/journal.pbio.1002429.

[228] J. Reis, B. Fritsch, Modulation of motor performance and motor learning by transcranial direct current stimulation., Curr. Opin. Neurol. 24 (2011) 590–596. https://doi.org/10.1097/WCO.0b013e32834c3db0.

[229] L.M. Nichols, A Comparison of Two Methods for Teaching Keyboarding in the Elementary School, Comput. Sch. Interdiscip. J. Pract. Theory,

Appl. Res. 11 (1995) 15–25. https://doi.org/10.1300/J025v11n04_03.

[230] C. Sormunen, A Comparison of Speed Achievement of Students in Grades 3-6 Who Learn Keyboarding on the Microcomputer., Delta Pi Epsil. J. 30 (1988) 47–57. https://search.proquest.com/openview/9ebf8b1e211bab7978df04f5f203ece8/1?pq-origsite=gscholar&cbl=1817376 (accessed November 25, 2021).

[231] L.J. Bindman, O.C.J. Lippold, J.W.T. Redfearn, The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects, J. Physiol. 172 (1964) 369–382. https://doi.org/10.1113/jphysiol.1964.sp007425.

[232] L.J. Romero Lauro, M. Rosanova, G. Mattavelli, S. Convento, A. Pisoni, A. Opitz, N. Bolognini, G. Vallar, TDCS increases cortical excitability: Direct evidence from TMS-EEG, Cortex. 58 (2014) 99–111. https://doi.org/10.1016/j.cortex.2014.05.003.

[233] M.A. Nitsche, W. Paulus, Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans, Neurology. 57 (2001) 1899–1901. https://doi.org/10.1212/WNL.57.10.1899.

[234] C.J. Stagg, M.A. Nitsche, Physiological Basis of Transcranial Direct Current Stimulation, Neurosci. 17 (2011) 37–53. https://doi.org/10.1177/1073858410386614.

[235] V. Gálvez, A. Alonzo, D. Martin, C.K. Loo, Transcranial direct current stimulation treatment protocols: Should stimulus intensity be constant or incremental over multiple sessions?, Int. J. Neuropsychopharmacol. 16 (2013) 13–21. https://doi.org/10.1017/S1461145712000041.

[236] M.A. Rueger, M.H. Keuters, M. Walberer, R. Braun, R. Klein, R. Sparing, G.R. Fink, R. Graf, M. Schroeter, Multi-Session Transcranial Direct Current Stimulation (tDCS) Elicits Inflammatory and Regenerative Processes in the Rat Brain, PLoS One. 7 (2012) e43776. https://doi.org/10.1371/journal.pone.0043776.

[237] F. Hashemirad, M. Zoghi, P.B. Fitzgerald, S. Jaberzadeh, The effect of

anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: A systematic review and meta-analysis., Brain Cogn. 102 (2016) 1–12. https://doi.org/10.1016/j.bandc.2015.11.005.

[238] A. Alonzo, J. Brassil, J.L. Taylor, D. Martin, C.K. Loo, Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation, Brain Stimul. 5 (2012) 208–213. https://doi.org/10.1016/j.brs.2011.04.006.

[239] F. Zappasodi, G. Musumeci, R. Navarra, V. Di Lazzaro, M. Caulo, A. Uncini, Safety and effects on motor cortex excitability of five cathodal transcranial direct current stimulation sessions in 25 hours, Neurophysiol. Clin. 48 (2018) 77–87. https://doi.org/10.1016/j.neucli.2017.09.002.

[240] J.C. Horvath, O. Carter, J.D. Forte, No significant effect of transcranial direct current stimulation (tDCS) found on simple motor reaction time comparing 15 different simulation protocols, Neuropsychologia. 91 (2016) 544–552. https://doi.org/10.1016/j.neuropsychologia.2016.09.017.

[241] A. Abdelmoula, S. Baudry, J. Duchateau, Anodal transcranial direct current stimulation enhances time to task failure of a submaximal contraction of elbow flexors without changing corticospinal excitability, Neuroscience. 322 (2016) 94–103. https://doi.org/10.1016/j.neuroscience.2016.02.025.

[242] V. Lopez-Alonso, S.L. Liew, M.F. del Olmo, B. Cheeran, M. Sandrini, M. Abe, L.G. Cohen, A preliminary comparison of motor learning across different non-invasive brain stimulation paradigms shows no consistent modulations, Front. Neurosci. 12 (2018). https://doi.org/10.3389/fnins.2018.00253.

[243] D. Rosenbaum, 9. Keyboarding, in: Hum. Mot. Control, Elsevier, 2010: pp. 279–321. https://doi.org/10.1016/B978-0-12-374226-1.X0001-0.

[244] K. Kansaku, S. Muraki, S. Umeyama, Y. Nishimori, T. Kochiyama, S. Yamane, S. Kitazawa, Cortical activity in multiple motor areas during

sequential finger movements: An application of independent component analysis, Neuroimage. 28 (2005) 669–681. https://doi.org/10.1016/j.neuroimage.2005.06.022.

[245] O. Hikosaka, K. Nakamura, K. Sakai, H. Nakahara, Central mechanisms of motor skill learning, Curr. Opin. Neurobiol. 12 (2002) 217–222. https://doi.org/10.1016/S0959-4388(02)00307-0.

[246] R.C. Oldfield, The assessment and analysis of handedness: The Edinburgh inventory, Neuropsychologia. 9 (1971) 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.

[247] WHO, World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects, J. Postgrad. Med. 48 (2002) 206–208.

[248] A. Middleton, S.L. Fritz, D.M. Liuzzo, R. Newman-Norlund, T.M. Herter, Using clinical and robotic assessment tools to examine the feasibility of pairing tDCS with upper extremity physical therapy in patients with stroke and TBI: A consideration-of-concept pilot study, NeuroRehabilitation. 35 (2014) 741–754. https://doi.org/10.3233/NRE-141178.

[249] I.A.M. Beets, J. Gooijers, M.P. Boisgontier, L. Pauwels, J.P. Coxon, G. Wittenberg, S.P. Swinnen, Reduced Neural Differentiation between Feedback Conditions after Bimanual Coordination Training with and without Augmented Visual Feedback, Cereb. Cortex. 25 (2015) 1958–1969. https://doi.org/10.1093/cercor/bhu005.

[250] J.L. Neva, M. Vesia, A.M. Singh, W.R. Staines, Modulation of left primary motor cortex excitability after bimanual training and intermittent theta burst stimulation to left dorsal premotor cortex, Behav. Brain Res. 261 (2014) 289–296. https://doi.org/10.1016/j.bbr.2013.12.029.

[251] B.W. Vines, D. Nair, G. Schlaug, Modulating activity in the motor cortex affects performance for the two hands differently depending upon which hemisphere is stimulated, Eur. J. Neurosci. 28 (2008) 1667–1673. https://doi.org/10.1111/j.1460-9568.2008.06459.x.

[252] G.G. Ambrus, H. Al-Moyed, L. Chaieb, L. Sarp, A. Antal, W. Paulus, The fade-in - Short stimulation - Fade out approach to sham tDCS - Reliable at 1 mA for naïve and experienced subjects, but not investigators, Brain Stimul. 5 (2012) 499–504. https://doi.org/10.1016/j.brs.2011.12.001.

[253] P.C. Gandiga, F.C. Hummel, L.G. Cohen, Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation, Clin. Neurophysiol. 117 (2006) 845–850. https://doi.org/10.1016/j.clinph.2005.12.003.

[254] L.V.M. Aparicio, F. Guarienti, L.B. Razza, A.F. Carvalho, F. Fregni, A.R. Brunoni, A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials., Brain Stimul. 9 (2016) 671–681. https://doi.org/10.1016/j.brs.2016.05.004.

[255] B. Paneri, P. Toshev, N. Khadka, V. Patel, C. Thomas, W. Tyler, L. Parra, M. Bikson, The tolerability of transcranial electrical stimulation used across extended periods in a naturalistic context by healthy individuals, (2015). https://doi.org/10.7287/peerj.preprints.1097v1.

[256] S. Broeder, E. Nackaerts, K. Cuypers, R. Meesen, G. Verheyden, A. Nieuwboer, tDCS-Enhanced Consolidation of Writing Skills and Its Associations With Cortical Excitability in Parkinson Disease: A Pilot Study, Neurorehabil. Neural Repair. (2019) 154596831988768. https://doi.org/10.1177/1545968319887684.

[257] R. Kawai, T. Markman, R. Poddar, R. Ko, A.L. Fantana, A.K. Dhawale, A.R. Kampff, B.P. Ölveczky, Motor Cortex Is Required for Learning but Not for Executing a Motor Skill, Neuron. 86 (2015) 800–812. https://doi.org/10.1016/j.neuron.2015.03.024.

[258] D.J. Ostry, P.L. Gribble, Sensory Plasticity in Human Motor Learning, Trends Neurosci. 39 (2016) 114–123. https://doi.org/10.1016/j.tins.2015.12.006.

[259] A. Kalava, S. Ravindranath, I. Bronshteyn, R.S. Munjal, J. SchianodiCola, J.M. Yarmush, Typing Skills of Physicians in Training,

J. Grad. Med. Educ. 6 (2014) 155–157. https://doi.org/10.4300/jgme-d-13-00164.1.

[260] H. Weigelt-Marom, N. Weintraub, Keyboarding versus handwriting speed of higher education students with and without learning disabilities: Does touch-typing assist in narrowing the gap?, Comput. Educ. 117 (2018) 132–140. https://doi.org/10.1016/j.compedu.2017.10.008.

[261] J.A.G. Lum, A. Mills, J.M.A. Plumridge, N.P. Sloan, G.M. Clark, M. Hedenius, P.G. Enticott, Transcranial direct current stimulation enhances retention of a second (but not first) order conditional visuo-motor sequence, Brain Cogn. 127 (2018) 34–41. https://doi.org/10.1016/j.bandc.2018.09.006.

Chapter 8

Appendix

Appendix A:

Abstract of at least 3000 words in an official language

APPENDIX A

Abstract of at least 3000 words in an official language

i- INTRODUCCIÓN

Aprendizaje motor

El aprendizaje motor es crucial a lo largo de la vida y se define como un conjunto de procesos asociados con la práctica o la experiencia que conducen a cambios en el rendimiento relativamente permanentes. Las clasificaciones recientes del aprendizaje motor distinguen entre aprendizaje en línea y fuera de línea. El aprendizaje en línea ocurre durante la práctica, conocido como adaptación, y el aprendizaje fuera de línea ocurre después de la práctica motora y se conoce como retención. Tanto el aprendizaje en línea como fuera de línea son cruciales para el proceso de aprendizaje motor. Las ganancias fuera de línea no se ven afectadas por la práctica de otra nueva tarea, lo que sugiere que los mecanismos responsables de la fase de adquisición (es decir, aprendizaje en línea) y la fase de retención (es decir, aprendizaje fuera de línea) parecen ser diferentes.

El tiempo suele ser limitado para aprender las habilidades motoras en la escuela, en el deporte, en la industria o en rehabilitación. Por este motivo, es fundamental organizar la práctica de forma que se optimice al máximo el proceso de aprendizaje motor. Por tanto, es necesario conocer y ajustar las principales variables que inciden sobre este proceso. El aprendizaje motor depende de las interacciones entre el diseño de la práctica, las condiciones del participante, las relaciones que se establecen y las condiciones ambientales. El diseño de la práctica y las relaciones interpersonales son categorías fácilmente modificables, mientras que la categoría de condiciones del participante abarca variables más estables, algunas difícilmente modificables como el factor genético. Además, existen numerosas estrategias que pueden potenciar o ralentizar el aprendizaje motor, como por ejemplo el uso de drogas o medicamentos.

Existen varios paradigmas que estudian el aprendizaje motor, empleando diferentes habilidades motoras y explorando los cambios comportamentales en diferentes momentos temporales. Tradicionalmente, el proceso de aprendizaje motor se organiza en tres etapas a medida que se practica una habilidad: etapa cognitiva, asociativa y automática. Estas etapas no son discretas y fijas, sino que tienen bordes "difusos" y una alta variabilidad interindividual. De hecho, una de las grandes limitaciones de la investigación sobre el aprendizaje motor es que la habilidad motora en la fase de automatización rara vez se estudia en intervenciones sobre aprendizaje motor a pesar de la inmensa importancia de comprender las habilidades complejas. Es un desafío convencer a los participantes e investigadores de que dediquen este tipo de esfuerzo y compromiso en experimentos durante meses o incluso años.

Otra gran limitación de los estudios sobre aprendizaje motor es la complejidad de hacer coincidir las condiciones de ejecución exactamente con las condiciones de aprendizaje, ya que condiciona los resultados del proceso. Este fenómeno se denomina especificidad de la práctica y es un principio crucial para la adquisición de habilidades. Sin embargo, muchos estudios utilizan tareas de laboratorio simples con las limitaciones de generalizar estas conclusiones a aplicaciones prácticas del aprendizaje motor. El grado de correlación entre los estudios de habilidades de laboratorio y la experiencia real no está claro, y esto puede depender de los efectos de la práctica en múltiples procesos cognitivos más allá de la estructura sensoriomotora tradicional. Una forma posible solución para de abordar esta limitación es utilizar tareas ecológicas, con periodos más prolongados de intervención y que reporten los resultados individuales para mejorar la comprensión de los procesos de aprendizaje y retención a medio y largo plazo.

El aprendizaje de nuevas habilidades motoras implica cambios morfológicos y funcionales a nivel neural (es decir, plasticidad cerebral). Sin embargo, la plasticidad se produce como resultado de la práctica acumulativa, por lo que períodos de intervención debería ser más prolongados que los que se utilizan actualmente (habitualmente de una a tres semanas, y de tres a cinco sesiones de intervención; exceptuando los estudios de caso). Además, en el campo del aprendizaje motor predominan los estudios transversales sobre los longitudinales, aunque esto no es coherente ya que el aprendizaje es un proceso que implica generalmente periodos largos de tiempo. De manera similar, es interesante explorar si existe una curva de aprendizaje estándar o si la curva de aprendizaje es diferente para cada persona, para tratar de optimizar el proceso de aprendizaje motor.

Se han identificado numerosas regiones del cerebro que contribuyen de alguna manera al aprendizaje motor. Dependiendo del paradigma de aprendizaje y la etapa de aprendizaje, la participación de cada área difiere, y todavía existe cierta controversia sobre el peso de sus roles. Aunque otras áreas del cerebro también contribuyen al aprendizaje motor, la aportación de la corteza motora es incuestionable. Específicamente, la corteza motora primaria (M1) es el principal contribuyente para producir los impulsos neurales que se transmiten a la médula espinal y controlar la ejecución del movimiento, haciendo hincapié en los músculos distales, como los dedos. M1 es un centro de activación más que un centro de planificación para el movimiento. Además, la corteza motora también recibe retroalimentación de los movimientos. Las neuronas M1 reciben información sensorial de las fibras musculares que inervan, por lo que acoplan estrechamente las funciones eferentes y aferentes.

Asimismo, el aprendizaje de las habilidades motoras se ha asociado con la plasticidad en M1, concretamente durante la etapa temprana o rápida de la adquisición de las habilidades motoras.

Estimulación transcraneal por corriente directa (tdcs) y aprendizaje motor

La estimulación transcraneal por corriente directa (tDCS) es una técnica de neuromodulación cerebral no invasiva, aparentemente segura, portátil, indolora y asequible, que no requiere prescripción médica. En el siglo XX, la aplicación de la tDCS en humanos se hizo popular como una herramienta para tratamientos potenciales de diversas patologías con menos efectos secundarios que los métodos farmacológicos tradicionales. La tDCS consiste en la aplicación una corriente continua débil a través de dos electrodos: ánodo y cátodo. Estos dos electrodos se colocan sobre el cuero cabelludo humano, alcanzan el tejido neuronal y provocan un cambio de polarización en el potencial de membrana en reposo (es decir, en teoría la corriente fluye desde el ánodo al cátodo) sin desencadenar un potencial de acción en sí mismo. Por tanto, aunque la respuesta individual a la estimulación no es uniformemente excitadora o inhibidora, la aplicación de la tDCS anódica generalmente se considera excitadora. Por el contrario, la aplicación de la tDCS catódica generalmente se considera inhibidora.

Los efectos de modulación de la tDCS probablemente se generen a través de mecanismos similares a la plasticidad cerebral. Sin embargo, los mecanismos de acción de la tDCS aún no están claros. Curiosamente, la tDCS provoca secuelas que duran hasta 90 minutos después del fin de la estimulación. Por lo tanto, los mecanismos de acción de la tDCS no pueden atribuirse simplemente a cambios en el potencial eléctrico de la membrana neuronal. Algunos estudios sugieren que la tDCS podría promover efectos subyacentes duraderos a través de alteraciones en los mensajeros químicos que tienen propiedades eléctricas (por ejemplo, factores neurotrópicos y neurotransmisores) y son facilitadores también de la neuroplasticidad. Por lo tanto, la combinación de tDCS con la práctica motora podría tener interacciones tales como mecanismos mejorados o potenciadores de la plasticidad cerebral mediante una modulación diferente en las vías.

Sin embargo, otros resultados muestran una falta de efectos fisiológicos de la tDCS. Por ejemplo, en una revisión sistemática reciente se concluyó que la tDCS genera poco o ningún efecto neurofisiológico confiable más allá de la modulación de amplitud potencial motor evocado (MEP) en participantes sanos. Además, más del 80% de los estudios que informaron de los efectos de la tDCS sobre la modulación de amplitud del MEP no incluyeron un grupo control o placebo. La cantidad de corriente que llega al cerebro y se distribuye a través del cerebro es crucial para una sólida comprensión mecanicista de los efectos de la tDCS. Por ejemplo, en un estudio con cadáveres humanos y cerebros de roedores, los autores informaron que entre 75 y el 90% de la corriente aplicada en el cuero cabelludo se atenúa por los tejidos blandos y el cráneo. Sin embargo, algunos expertos sostienen que ~ 10% de la corriente que llega al cerebro no significa necesariamente que los métodos sean ineficaces. Otros expertos apoyan la idea de que son necesarias intensidades superiores a las utilizadas en los protocolos actuales para afectar los circuitos neuronales. Además, el uso de cadáveres para probar estos métodos es problemático porque el tejido muerto conduce la electricidad de manera diferente que el tejido vivo.

La configuración de la tDCS podría afectar a su eficacia. Los parámetros que gobiernan los cambios de excitabilidad cortical de la tDCS son (1) la posición de los electrodos, (2) la polaridad de la estimulación, (3) la densidad de corriente total, (4) el momento de la estimulación en relación con la práctica motora, (5) el número de sesiones y (6) otros parámetros. A pesar de un gran número de estudios recientes sobre la tDCS, no hay consenso sobre la configuración y el protocolo a emplear; quizás debido a la complejidad del cerebro humano. Los protocolos de la tDCS en función del objetivo y/o grupo poblacional no están estandarizados universalmente.

La tDCS sobre la corteza motora podría mejorar las habilidades cognitivas asociadas con el aprendizaje de habilidades motoras en personas sanas, optimizando así el proceso. Algunos estudios han demostrado que una sola sesión de tDCS sobre M1 tienen un efecto positivo sobre el rendimiento en tareas de secuencia motora; sin embargo, otros estudios también han demostrado una falta de efecto. Es necesario considerar la variabilidad y las contradicciones entre los estudios. Aún así, esto a menudo se debe a diferencias metodológicas, como el momento de la aplicación, entre otros. Quizás los efectos de una sola sesión de tDCS sobre el aprendizaje motor puedan ser controvertidos porque los estudios rara vez miden la retención (por ejemplo, evaluación después de 24 horas de intervención) y generalmente miden durante o inmediatamente después de la intervención. Por otro lado, según reporta una reciente revisión, varias sesiones de tDCS indujeron una mejora motora significativamente mayor en comparación con una sola sesión. De hecho, las sesiones repetidas de tDCS podrían tener efectos acumulativos asociados con una mayor duración y magnitud de los resultados conductuales. Incluso los efectos positivos sobre el aprendizaje motor de la combinación de tDCS y 5 días de práctica parecen mantenerse hasta 3 meses después de la intervención en adultos sanos. Sin embargo, las diferencias metodológicas en cuanto a parámetros de estimulación, tareas empleadas y pruebas de evaluación dificultan sacar conclusiones claras sobre estos resultados. Se necesitan más estudios que exploren los efectos de la tDCS en sesiones múltiples sobre el aprendizaje motor y también deberían replicarse los estudios previos con un tamaño de muestra más grande.

Otra limitación importante es comprobar la seguridad de la técnica a largo plazo. Hasta ahora, la tDCS se ha probado en miles de participantes en todo el mundo sin evidencia de efectos tóxicos o peligrosos. Sin embargo, existen mucha incertidumbre con respecto a la administración prolongada de tDCS en individuos sanos y/o con patologías.

El número de protocolos tDCS y la variedad de paradigmas de aprendizaje motor dificultan el establecimiento de una relación entre ambos conceptos. En general, existe una falta de consenso sobre la relación entre el protocolo tDCS óptimo y el tipo de tarea para mejorar el aprendizaje motor. La controversia sobre los efectos de la tDCS en la optimización del proceso de aprendizaje motor puede ser una consecuencia de las diferencias en los métodos empleados por los investigadores. Estas diferencias en los métodos se deben principalmente a: (a) el tamaño de la muestra (habitualmente muy pequeñas), (b) el área de estimulación cerebral cortical objetivo (que sea relevante en el aprendizaje motor, por ejemplo corteza motora), (c) las tareas utilizadas (se necesitan más estudios con tareas ecológicas), (d) la variabilidad intra- e inter-individual (es importante reportar las respuestas individuales); y, (e) la duración de la intervención (que habitualmente en la literatura es muy breve, de 3 a 5 días). En general, la falta de consenso en la literatura con respecto a los beneficios de la tDCS sobre el aprendizaje motor en participantes sanos puede deberse a las limitaciones mencionadas anteriormente que dificultan las comparaciones entre estudios. En conjunto, en el diseño de la presente tesis intentamos evitar algunas de las deficiencias discutidas anteriormente para arrojar luz sobre este tema.

ii- CUESTIONES DE RELEVANCIA

Tras la breve revisión de los datos actuales sobre el tema de esta tesis, quedan sin resolver algunas cuestiones de interés:

1) ¿La tDCS afecta a la retención del motor en una tarea de tiempos de reacción aleatorios?

2) ¿Cuándo es el mejor momento para que la aplicación de la tDCS sea eficaz sobre la retención motora: ¿antes, durante o después de la práctica motora?

3) ¿Existe una curva de aprendizaje motora estándar en habilidades motoras complejas, como la mecanografía?

4) ¿Optimiza la tDCS el proceso de aprendizaje motor a medio y largo plazo?

5) ¿Es segura la aplicación de la tDCS en sesiones múltiples para participantes sanos?

Intentamos abordar estas cuestiones con esta tesis. Las preguntas 1 y 2 se abordarán en el primer estudio. Las preguntas 3, 4 y 5 se abordarán en el segundo estudio.

iii- HIPÓTESIS Y OBJETIVOS PRINCIPALES DE LOS ESTUDIOS

Estudio I: Los efectos dependientes del tiempo de la estimulación transcraneal por corriente directa (tDCS) en el desempeño de una habilidad de tiempos de reacción aleatorios.

b) Objetivo

- Explorar los efectos dependientes del tiempo de la tDCS anódica (es decir, antes, durante o después de la práctica motora) sobre M1 en la retención motora 24 horas después, en una tarea de tiempos de reacción visual-motora de 4 opciones (4-ChRT).

Estudio II a: Exploración de la curva de aprendizaje en una habilidad motora compleja: un estudio piloto.

a) Hipótesis

Planteamos la hipótesis de que un programa estructurado de mecanografía de 30 sesiones de 15 minutos mejoraría el rendimiento motor de los participantes de manera similar.

b) Objetivos

- Probar si un programa estructurado de mecanografía de 30 sesiones trisemanales de 15 minutos mejoraría el rendimiento motor de los participantes.

- Explorar la curva de aprendizaje de 30 sesiones de práctica de mecanografía en adultos jóvenes y sanos.

Estudio II b: Efectos de 20 sesiones de estimulación transcraneal por corriente directa (tDCS) sobre el aprendizaje motor en la habilidad de mecanografía en adultos jóvenes y sanos.

a) Hipótesis

Presumimos que 20 sesiones de tDCS aplicadas sobre el área motora primaria durante la práctica motora, mejorarían el rendimiento de mecanografía en comparación con los grupos placebo y control.

b) Objetivos

- Evaluar si 20 sesiones de tDCS sobre M1 mejorarían el desempeño de una habilidad motora compleja de la vida, es decir, la mecanografía, en adultos jóvenes y sanos.

- Comprobar la seguridad de la tDCS a lo largo del tiempo a medio y largo plazo.

iv- ESTUDIOS

Estudio I: Los efectos dependientes del tiempo de la estimulación transcraneal de corriente continua (tDCS) en el desempeño de una habilidad de tiempo de reacción aleatorios.

La estimulación anódica transcraneal por corriente directa (tDCS) puede mejorar la retención de una habilidad motora previamente practicada. Sin embargo, los efectos de tDCS sobre el desempeño de la tarea de tiempo de reacción de reacción aleatorios se han investigado poco. El presente estudio tuvo como objetivo determinar los efectos de la tDCS anódica sobre la corteza motora primaria izquierda (M1) sobre la retención en una tarea de tiempos de reacción visual-motora de 4 opciones (4-ChRT). Se reclutaron 100 participantes sanos diestros y se asignaron al azar a cinco grupos: tres grupos recibieron tDCS anódica: antes ($\text{tDCS}_{\text{before}}$), durante ($\text{tDCS}_{\text{during}}$) o después ($\text{tDCS}_{\text{after}}$) de la práctica motora. Además, había dos grupos control: con (CON_{mp}) y sin (CON) práctica motora. Evaluamos la velocidad y precisión de la tarea 4-ChRT antes (PRE), durante y 24 h (POST) después de la intervención. En general, todos los grupos, incluidos los grupos control con práctica (CON_{mp}) y sin práctica (CON) motora, mejoraron significativamente la retención ($\Delta_{\text{4-ChRT}}$: 35,8 ± 36,0 ms). Estos hallazgos sugieren que los efectos de la tDCS sobre M1 pueden diferir para las tareas de RT en serie frente a las de RT aleatorias, quizás debido a las diferentes áreas del cerebro involucradas para dar respuesta a las demandas de cada tarea motora.

Estudio II a: Exploración de la curva de aprendizaje en una habilidad motora compleja: un estudio piloto.

El proceso de aprendizaje motor es fundamental en todas las etapas de la vida. Sin embargo, la curva de aprendizaje en diferentes habilidades motoras ha sido poco investigada. El presente estudio tuvo como objetivo explorar los efectos de un programa de intervención estructurado sobre el rendimiento motor. Se reclutó a 45 participantes sanos que completaron 30 sesiones de práctica motora de mecanografía durante 3.5 meses. Evaluamos la velocidad y precisión en la prueba de mecanografía máxima (mTT) e incremental (iTT) 5 veces: antes (T_0), después de la décima sesión (T_{10}), después de la vigésima sesión (T_{20}), después de la trigésima sesión o post- intervención (T_{30}), y tres semanas después del final de la práctica (R_{3w}). Los participantes mejoraron significativamente su velocidad y precisión en la mTT y redujeron el número de errores en la iTT a lo largo de la intervención. Incluso esas ganancias de rendimiento se mantienen hasta 3 semanas después del final de la práctica motora. Estos hallazgos sugieren que un diseño de práctica motora no masiva puede significar que la intervención sea más efectiva para diseñar los programas de habilidades complejas como la mecanografía. Teniendo en cuenta las conclusiones de este estudio piloto, diseñamos el tercer estudio de la tesis doctoral.

Estudio II b: Efectos de 20 sesiones de estimulación transcraneal por corriente directa (tDCS) sobre el aprendizaje motor en la habilidad de mecanografía en adultos jóvenes y sanos.

La estimulación transcraneal por corriente directa (tDCS) es una técnica de estimulación cerebral no invasiva que puede mejorar el aprendizaje motor. Sin embargo, no se han explorado los efectos a largo plazo de la tDCS, y el estudio de la validez de esta técnica en tareas ecológicas es muy limitado. El objetivo del estudio fue determinar si 20 sesiones de tDCS sobre la corteza motora primaria (M1) mejorarían el desempeño de una habilidad motora compleja de la vida cotidiana, como la mecanografía, en adultos jóvenes y sanos. Los participantes (n = 60) fueron asignados de forma pseudoaleatoria a 3 grupos: el grupo tDCS (n = 20) recibió tDCS anódica sobre M1; el grupo SHAM (n = 20) recibió tDCS simulado/placebo, ambos mientras realizaba la práctica motora de mecanografía; y el grupo de Control (CON, n = 20) que solo realizó la práctica motora. La velocidad de escritura y los errores a velocidades máxima (mTT) e incremental (iTT) se midieron antes, a mitad (después de 10 sesiones) y, al final de la intervención (después de 20 sesiones). Los participantes aumentaron la velocidad máxima de escritura después de las sesiones de tDCS número 10 y número 20, sin diferencias significativas ($p > 0.05$) entre los grupos. El número de errores en la prueba incremental disminuyó significativamente ($p < 0.05$) en un 6% después de 10 sesiones de tDCS en comparación con el aumento del 3% en el grupo SHAM y el aumento del 2% en el grupo CON. Entre la décima y la vigésima sesión de tDCS, el número de errores de mecanografía aumentó significativamente en todos los grupos. Si bien el tDCS anódico redujo los errores de mecanografía marginalmente, estos efectos de mejora del rendimiento se estabilizaron después de 10 sesiones, sin ninguna mejora adicional en la velocidad de escritura. Estos hallazgos sugieren que la tDCS a largo plazo puede no tener efectos funcionalmente relevantes en el rendimiento de mecanografía de los adultos jóvenes y sanos.

v- CONCLUSIONES

- No hay un efecto significativo de la tDCS sobre la retención motora 24 h después en una tarea de RT aleatoria para una muestra de 100 participantes.

- Una sola sesión de práctica motora combinada con tDCS (antes, durante o después de la práctica motora) sobre M1 no mejoría la retención en una tarea de RT aleatoria en comparación con los grupos de control (con y sin práctica motora).

- La curva de aprendizaje de mecanografía sigue un patrón común y las ganancias de rendimiento se mantienen incluso cuando la práctica motora concluye hasta 3 semanas después, para una muestra de 45 participantes.

- Un programa estructurado de 3.5 meses con un total de 30 sesiones de práctica de mecanografía de 15 minutos/sesión parece ser suficiente para mejorar significativamente el rendimiento motor en dicha habilidad.

- Existe un efecto significativo de la tDCS sobre el rendimiento en mecanografía (6% menos de errores) después de las primeras 10 sesiones en comparación con los grupos control y placebo.

- tDCS sobre M1 redujo los errores de escritura marginalmente, los efectos de mejora del rendimiento se estabilizaron después de 10 sesiones, sin mostrar mejoras significativas en la velocidad máxima de mecanografía respecto a los grupos control y placebo.

- La aplicación de la tDCS en sesiones múltiples parece ser segura en participantes sanos. Los participantes realizaron un total de 800 sesiones de tDCS sin complicaciones.

- Todos los participantes de los grupos tDCS y placebo/simulado experimentaron ocasionalmente efectos adversos leves y transitorios durante la estimulación, como "picazón", "ardor" o "malestar", sin diferencias significativas entre grupos.

vi- LIMITACIONES

- La muestra utilizada en la tesis actual fueron sujetos jóvenes y sanos, por lo que hay que tener cuidado al extrapolar nuestros hallazgos a otras poblaciones.

- Solo se estimuló una zona cortical. Aunque la corteza motora primaria ha sido el objetivo más frecuente de los estudios con la tDCS, queda comprobar si nuestros hallazgos también son válidos para otras áreas corticales.

- Los efectos de la tDCS sobre la retención motora en el Estudio I de la tesis actual se limitaban a una sola sesión. Por tanto, conviene probar los efectos acumulativos de sucesivas sesiones de estimulación. Además, la confiabilidad de los efectos inducidos por los protocolos tDCS debe evaluarse en más de dos sesiones debido a la alta variabilidad entre- e intra-participante.

- En el Estudio II, una posible limitación puede ser el no registro de la práctica de mecanografía que posiblemente realizaron los participantes fuera de la intervención, aunque pertenecieran al mismo grupo de clase.

- La ausencia de medidas neurofisiológicas en la tesis actual limita la comprensión de los mecanismos subyacentes que contribuyen a las mejoras inducidas por tDCS.

- Las tareas motoras utilizadas en nuestros estudios solo representan un pequeño número de los paradigmas de las tareas motoras empleadas.

Appendix B:

Informed consent

APPENDIX B

Study I

Cuestionario para identificar posibles contraindicaciones para la tDCS

TÍTULO: EFECTO DE LA tDCS SOBRE LA RETENCIÓN MOTORA

INVESTIGADOR PRINCIPAL: MIGUEL ANGEL FERNÁNDEZ DEL OLMO

NOMBRE Y APELLIDOS: ____

DNI: ____________________FECHA DE NACIMIENTO: ______________________

Para evitar cualquier riesgo en la aplicación de la estimulación de corriente directa transcraneal, necesitará responder a las siguientes cuestiones. Es importante que lea atentamente cada una de ellas y sea honesto en su respuesta. Si tiene alguna duda diríjase al investigador para cualquier aclaración. Marca con una "X":

1. ¿Padece actualmente algún tipo de patología? SI_____ NO____
2. ¿Ha padecido alguna vez un ataque epiléptico? SI_____ NO____
3. ¿Alguien en su familia ha sufrido un ataque epiléptico? SI_____ NO____
4. ¿Ha sufrido algún desorden neurológico? SI_____ NO____
    4a. ¿un traumatismo craneal? SI_____ NO____
    4b. ¿un infarto cerebral? SI_____ NO____
    4c. ¿algún tipo de cirugía en el cerebro? SI_____ NO____
5. ¿Padece de migraña o dolores de cabeza habituales? SI_____ NO____
6. ¿Tiene implantado un marcapasos u otro tipo de aparato médico? SI_____ NO____

Si ha contestado SI a alguna de las cuestiones de la lista anterior no podrá participar en el presente estudio. Aunque no existen riesgos conocidos asociados con alguna de estas condiciones, creemos conveniente la no participación en este experimento. Si ha sido excluido de este estudio la información de esta hoja será destruida.

En A Coruña, a ____ de ____________ de 2018

Firmas

Participante Investigador presente

____________________________ Marta Sevilla Sánchez

Nombre y apellidos

Consentimiento informado para participar en un estudio de investigación

TÍTULO: EFECTO DE LA tDCS SOBRE LA RETENCIÓN MOTORA

INVESTIGADOR PRINCIPAL: MIGUEL ANGEL FERNÁNDEZ DEL OLMO

Yo, ____

(Marca con una "X" dentro del cuadrado en caso de estar de acuerdo)

- He leído la hoja de información al participante del estudio arriba mencionado que se me entregó, he podido hablar con la investigadora Marta Sevilla Sánchez y hacerle todas las preguntas sobre el estudio necesarias para comprender sus condiciones y considero que he recibido la información suficiente sobre el estudio. ☐
- Comprendo que mi participación es voluntaria, y que puedo retirarme del estudio cuando quiera, sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos. ☐
- Accedo a que se utilicen mis datos en las condiciones detalladas en la hoja de información al participante. ☐
- Presto libremente mi conformidad para participar en el estudio. ☐
- Accedo a que los datos y/o muestras se conserven para usos posteriores en líneas de investigación relacionados con la presente, y en las condiciones mencionadas, siempre y cuando sea imposible identificarlos por ningún medio. ☐

En cuanto a los resultados de la prueba realizada:

☐ **DESEO** conocer los resultados de mis pruebas.

☐ **NO DESEO** conocer los resultados de mis pruebas.

En A Coruña, a ____ de ____________ de 2018

Fdo.

Participante Investigador presente

Hoja de información al participante para participar en un estudio de investigación

TÍTULO: EFECTO DE LA tDCS SOBRE LA RETENCIÓN MOTORA

INVESTIGADOR PRINCIPAL: MIGUEL FERNÁNDEZ DEL OLMO

El presente experimento versa sobre la retención motora a través del estudio del tiempo de reacción en diferentes situaciones. Cada participante del experimento deberá completar las siguientes fases:

- Fase 1: Evaluación individual de tiempo de reacción en laboratorio + práctica motora (con estimulación de corriente directa transcraneal, tDCS).

Tiempo estimado 1h 30 minutos.

- Fase 2: A las 24 horas de haber realizado el apartado anterior, se evaluará de nuevo el tiempo de reacción en laboratorio. Tiempo estimado 20 minutos.

Riesgos

La estimulación de corriente directa transcraneal es una modalidad no invasiva de estimulación cerebral que se considera segura. Sin embargo, puede provocar efectos secundarios.

Efectos secundarios poco frecuentes de carácter leve o moderado:

- Dolor de cabeza
- Molestia en el cuero cabelludo en el lugar de la estimulación
- Hormigueo, espasmos o fasciculaciones de los músculos faciales
- Sensación de vértigo

Se necesitan más estudios para determinar si la estimulación de corriente directa transcraneal puede tener efectos secundarios a largo plazo.

Study II

Documentación del estudio de investigación titulado Efectos de la estimulación de corriente directa transcraneal en el aprendizaje y retención motora a largo plazo.

a) Hoja de información al participante

b) Compromiso de confidencialidad

c) Consentimiento informado para la participación en el estudio de investigación

d) Consentimiento informado ante testigos para la participación en el estudio de investigación

e) Revocación del consentimiento

a) HOJA DE INFORMACIÓN AL PARTICIPANTE

TÍTULO: Efectos de la estimulación de corriente directa transcraneal en el aprendizaje y retención motora a largo plazo.

INVESTIGADORES:

Miguel Ángel Fernández del Olmo (catedrático de la universidad).

Marta Sevilla Sánchez (investigadora en formación, FPU).

Grupo de investigación: Motor control group.

Departamento de Educación Física y Deportiva.

El objetivo de este documento es ofrecerle información sobre un estudio de investigación en el que está invitado a participar. Este estudio se está llevando a cabo en la Facultad de Ciencias del Deporte y Educación Física (INEF Galicia), Universidad de A Coruña y ha sido aprobado por el Comité Ético de la universidad.

Si decide participar en el mismo, debe recibir información personalizada del investigador, lea este documento de antemano y haga todas las preguntas que necesite para comprender los detalles al respecto. Si lo desea, puede tomar el documento, consultarlo con otros y tomarse el tiempo para decidir si desea participar o no.

La participación en este estudio es completamente voluntaria. Vd. Puede decidir no participar o, si acepta hacerlo, puede cambiar su opinión retirando su consentimiento en cualquier momento sin tener que dar explicaciones. Le aseguramos que esta decisión no afectará la relación con ningún profesor de la facultad.

¿Cuál es el propósito del estudio?

La principal contribución del estudio será la identificación de los efectos principales o la ausencia de efectos de la estimulación cerebral sobre la curva de aprendizaje y la retención de motora a medio y largo plazo, y contribuir así a mejorar el proceso de enseñanza-aprendizaje en poblaciones sanas y en poblaciones especiales.

¿Por qué me ofrecen participar?

La selección de las personas invitadas a participar depende de algunos criterios que se describen a continuación. Estos criterios sirven para seleccionar la población en la que se responderá la pregunta de la investigación. Vd. Le invitamos a participar porque potencialmente cumple con estos criterios, ya que es un sujeto joven, sano y que no ha realizado un curso de mecanografía con anterioridad.

Se espera que alrededor de 65 personas participen en este estudio.

¿En qué consiste mi participación?

El estudio consiste en una evaluación inicial seguida de un programa de entrenamiento de mecanografía en el aula de informática de tres meses, con tres sesiones semanales, dos evaluaciones intermedias (durante el programa) y una evaluación posterior (una vez finalizados todos los entrenamientos).

Cada uno de los 20 entrenamientos de mecanografía tendrá una duración de 15 minutos y, las cuatro sesiones de evaluación tendrán una duración de 1 hora y 30 minutos aproximadamente cada una de ellas.

A la mayor parte de los participantes seleccionados de forma aleatoria, se os colocará dos electrodos en el cuero cabelludo para recibir una estimulación de baja intensidad de forma concurrente a la realización de los entrenamientos de mecanografía. La técnica se explica con más detalle en el siguiente apartado.

Tanto el investigador como el participante pueden decidir finalizar el estudio antes de lo programado o interrumpir su participación debido a la aparición de nueva información relevante, por razones de seguridad o por incumplimiento de los procedimientos del estudio.

¿Qué riesgos o desventajas tienes?

La técnica de estimulación cerebral por corriente directa es una técnica indolora y segura (Tremblay et al 2016). Numerosos estudios han aplicado la tDCS en un mayor número de sesiones a las del actual proyecto sin haber reportado efectos adversos o molestias (Hesse et al., 2011; Lefaucheur et al., 2017). Consiste en colocar un par de electrodos sobre el cuero cabelludo entre los cuales pasará una corriente eléctrica de muy baja intensidad y casi imperceptible. Esta técnica se ha aplicado hasta el momento en más de 8.000 personas y el único posible efecto adverso de la estimulación eléctrica transcutánea es cierta irritación de la piel por una incorrecta aplicación de la técnica y relacionada con un mal contacto entre el electrodo y la piel. Para evitar esto usaremos electrodos de estimulación más grandes de lo habitual junto con estimuladores que automáticamente dejan de funcionar cuando el contacto entre el electrodo y la piel no es el idóneo.

En este estudio, la estimulación eléctrica se aplicará sobre el hemisferio izquierdo de la corteza motora primaria (F3, ubicada a través del sistema de posicionamiento internacional 10-20) y sobre el área supra-orbital del ojo derecho.

Los participantes que pertenecen a grupos de estimulación recibirán estimulación eléctrica durante la práctica motora, de forma simultánea. En el supuesto de notar alguna molestia durante la intervención se detendría automáticamente la estimulación. Y si usted percibe cualquier efecto adverso que pueda estar asociado a la participación en el estudio, no dude en contactar con cualquier de los investigadores.

¿Obtengo algún beneficio por participar?

No se espera que los participantes consigan ningún beneficio económico por participar en el estudio. Sin embargo, si Vd. Participa en el estudio mejorará notablemente su nivel de mecanografía.

¿Recibiré la información que se obtenga del estudio?

Si Vd. lo desea y así lo registra en el anexo "DOCUMENTO DE CONSENTIMIENTO PARA LA PARTICIPACIÓN EN UN ESTUDIO DE INVESTIGACIÓN", se le dará un resumen individualizado de los resultados del estudio. En el supuesto de que quiera modificar su decisión al respecto, simplemente tendría que enviar un email a cualquier de los investigadores.

Es posible que estos resultados no tengan una aplicación clínica ni una interpretación clara, por lo que, si desea tenerlos, debe analizarlos con los principales investigadores del estudio.

¿Se publicarán los resultados de este estudio?

Los resultados de este estudio se enviarán a dos congresos internacionales y serán publicados como artículos en revistas científicas para su difusión, pero no se transmitirá ninguna información que pueda conducir a la identificación de los participantes. Los artículos científicos generados a partir de la presente intervención les serán remitidos vía email a todos los participantes que así lo deseen.

¿Cómo se protegerá la confidencialidad de mis datos?

El procesamiento, la comunicación y la asignación de sus datos se realizarán de conformidad con las disposiciones de la Ley Orgánica 15/1999, de 13 de diciembre, sobre la protección de datos personales de carácter sensible. En todo momento tiene derecho a consultar sus datos, corregirlos, cancelarlos, o a la limitación del tratamiento de estos, contactando con cualquiera de los investigadores vía email.

Solo el equipo de investigación y los colaboradores, que tienen el deber de mantener la confidencialidad, tendrán acceso a todos los datos recopilados por el estudio. En caso de que alguna información se transmita a otros países, se llevará a cabo con un nivel de protección de los datos equivalentes, al menos, que exige la normativa de nuestro país. La transmisión de estos datos tendría el propósito de realizar un análisis más exhaustivo en algunos de los parámetros registrados que, por razones técnicas, no es posible analizarlos en nuestro laboratorio.

¿Hay intereses económicos en este estudio?

Esta investigación es promovida por Miguel Fernández del Olmo y Marta Sevilla Sánchez con fondos aportados por el Ministerio de Ciencia, Innovación y Universidades de España.

Los investigadores no recibirán retribución específica por su dedicación al estudio.

Es posible que los resultados del estudio se deriven de productos comerciales o de patentes. En este caso, Vd. no participará en los beneficios económicos originados.

¿Quién me puede dar más información?

Marta Sevilla Sánchez, estudiante de doctorado. Facultad de CCs de la Actividad Física y del Deporte – Universidade da Coruña, Avenida Ernesto Che Guevara, 121, 15179 Oleiros, A Coruña, Galicia, España.

Teléfono: +34 981 167 000 (ext. 4017); E-mail: marta.sevilla@udc.es

……………………………………

Recordamos que su participación es totalmente voluntaria y en cualquier momento puede decidir no continuar en el estudio. **Muchas gracias por su colaboración.**

b) COMPROMISO DE CONFIDENCIALIDAD

TÍTULO DEL ESTUDIO: Efectos de la estimulación de corriente directa transcraneal en el aprendizaje y retención motora a largo plazo.

Se han tomado las medidas apropiadas para garantizar la total confidencialidad de sus datos personales, de conformidad con las disposiciones de LO 3/2018, de 5 de diciembre, sobre la protección de datos personales y la garantía de los derechos digitales y el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo del 27/04/2016, sobre la protección de las personas físicas con respecto al tratamiento de datos personales y la libre circulación de dichos datos y por la que se deroga la Directiva 95 / 46CE (Reglamento general de protección de datos).

Los datos necesarios para llevar a cabo este estudio se recopilarán y almacenarán de la siguiente manera:

Seudónimos (o codificados), es decir, los datos se procesarán de tal manera que no se puedan atribuir a un participante sin que se utilice información adicional. En este estudio, solo el equipo de investigación conocerá el código que permitirá conocer su identidad.

Al utilizar los resultados del estudio con fines de enseñanza, investigación, publicación y/o difusión, siempre se respetará la confidencialidad de los datos personales, de modo que los participantes no serán identificados ni identificables.

Vd. Tiene derechos de acceso a sus datos, de rectificación, de supresión, de limitación del tratamiento, de portabilidad y de oposición al uso de sus datos en cualquier momento. Puede ejercer su derecho enviando una solicitud por escrito o vía email a cualquiera de los investigadores. En el supuesto de que se realice dicha solicitud, la persona que participa en la investigación recibirá una respuesta por escrito.

Marta Sevilla Sánchez, Facultad de CCs de la Actividad Física y del Deporte – Universidade da Coruña, Avenida Ernesto Che Guevara, 121, 15179 Oleiros, A Coruña, Galicia, España. Teléfono: +34 981 167 000 (ext. 4017). E-mail: marta.sevilla@udc.es

En ocasiones, los datos obtenidos en esta investigación/estudio pueden ser útiles para futuras investigaciones. Por esta razón, al final de este documento se le solicita específicamente su autorización para la cesión/reutilización de sus datos.

c) CONSENTIMIENTO INFORMADO PARA LA PARTICIPACIÓN EN EL ESTUDIO DE INVESTIGACIÓN

TÍTULO:

Efectos de la estimulación de corriente directa transcraneal en el aprendizaje y retención motora a largo plazo.

Yo,____________________________________con DNI_________________ y domicilio en____

DECLARO que

Fui informado/a de las características del estudio	Si ☐	No ☐
Leí la hoja de información que me entregaron	Si ☐	No ☐
Pude realizar observaciones o preguntas y fueron aclaradas mis dudas	Si ☐	No ☐
Comprendí las explicaciones que se me facilitaron y en que consiste mi participación en el estudio	Si ☐	No ☐
Se como y a quien dirigirme para realizar preguntas sobre el estudio en el presente y en el futuro	Si ☐	No ☐
Fui informado/a de los riesgos asociados a mi participación	Si ☐	No ☐
Soy conocedor/a de que no cumplo ninguno de los criterios de exclusión como participante y que si esto cambiase a lo largo del estudio debo hacérselo saber al equipo de investigación	Si ☐	No ☐
Confirmo que mi participación es voluntaria	Si ☐	No ☐
Comprendo que podo revocar el consentimiento en cualquier momento sin tener que dar explicaciones y sin que repercuta negativamente en mi persona	Si ☐	No ☐

CONSINTO

Participar en el estudio	Si ☐	No ☐
Que se utilicen los datos facilitados para a investigación	Si ☐	No ☐
Que se utilicen los datos facilitados en publicaciones científicas	Si ☐	No ☐
Que se utilicen los datos facilitados en reuniones y congresos	Si ☐	No ☐
Que se utilicen los datos facilitados para a docencia	Si ☐	No ☐
Que se realicen fotografías para a obtención dos datos	Si ☐	No ☐
Que se use material sensible (fotografías, audio, vídeo) con fines de docencia	Si ☐	No ☐
Que se use material sensible (fotografías, audio, vídeo) en publicaciones	Si ☐	No ☐
Que se conserven os datos de forma anónima al finalizar el estudio para su uso en futuras investigaciones	Si ☐	No ☐
Que se conserven os datos codificados al finalizar el estudio para su uso en futuras investigaciones siempre que garanticen el tratamiento de los datos conforme a este consentimiento	Si ☐	No ☐

SOLICITO

Acceder a los resultados generales del estudio	Si ☐	No ☐
Acceder á información sobre mí derivada del estudio	Si ☐	No ☐
Acceder a los artículos científicos una vez sean publicados	Si ☐	No ☐
La destrucción de mis datos una vez finalizado el estudio	Si ☐	No ☐
Incluir las siguientes restricciones al uso de mis datos:		

Y en prueba de conformidad, firmo el presente documento en el lugar y en la fecha que se indican a continuación.

A Coruña, a_______ de _____________________ de _______.

Nombre y apellidos del/a participante:	Nombre y apellidos del/a investigador/a que solicita el consentimiento: Marta Sevilla Sánchez
Firma:	Firma:

d) CONSENTIMIENTO INFORMADO ANTE TESTIGOS PARA LA PARTICIPACIÓN EN EL ESTUDIO DE INVESTIGACIÓN

(Para los casos en los que el participante no pueda leer/escribir)

El testigo imparcial ha de identificarse y ser una persona ajena al equipo investigador.

TÍTULO: Efectos de la estimulación de corriente directa transcraneal en el aprendizaje y retención motora a largo plazo.

Yo,____con DNI____________

y domicilio en ____

como testigo imparcial, afirmo que en mi presencia el participante respondió a las siguientes preguntas tal y como queda reflejado a continuación:

QUE EL PARTICIPANTE DECLARA que

Fui informado/a de las características del estudio	Si ☐	No ☐
Leí la hoja de información que me entregaron	Si ☐	No ☐
Pude realizar observaciones o preguntas y fueron aclaradas mis dudas	Si ☐	No ☐
Comprendí las explicaciones que se me facilitaron y en que consiste mi participación en el estudio	Si ☐	No ☐
Se como y a quien dirigirme para realizar preguntas sobre el estudio en el presente y en el futuro	Si ☐	No ☐
Fui informado/a de los riesgos asociados a mi participación	Si ☐	No ☐
Soy conocedor/a de que no cumplo ninguno de los criterios de exclusión como participante y que si esto cambiase a lo largo del estudio debo hacérselo saber al equipo de investigación	Si ☐	No ☐
Confirmo que mi participación es voluntaria	Si ☐	No ☐
Comprendo que podo revocar el consentimiento en cualquier momento sin tener que dar explicaciones y sin que repercuta negativamente en mi persona	Si ☐	No ☐

QUE EL PARTICIPANTE CONSINTE

Participar en el estudio	Si ☐	No ☐
Que se utilicen los datos facilitados para a investigación	Si ☐	No ☐
Que se utilicen los datos facilitados en publicaciones científicas	Si ☐	No ☐
Que se utilicen los datos facilitados en reuniones y congresos	Si ☐	No ☐
Que se utilicen los datos facilitados para a docencia	Si ☐	No ☐
Que se realicen fotografías para a obtención dos datos	Si ☐	No ☐
Que se use material sensible (fotografías, audio, vídeo) con fines de docencia	Si ☐	No ☐
Que se use material sensible (fotografías, audio, vídeo) en publicaciones	Si ☐	No ☐
Que se conserven os datos de forma anónima al finalizar el estudio para su uso en futuras investigaciones	Si ☐	No ☐
Que se conserven os datos codificados al finalizar el estudio para su uso en futuras investigaciones siempre que garanticen el tratamiento de los datos conforme a este consentimiento	Si ☐	No ☐

QUE EL PARTICIPANTE SOLICITA

Acceder a los resultados generales del estudio	Si ☐	No ☐
Acceder á información sobre mí derivada del estudio	Si ☐	No ☐
Acceder a los artículos científicos una vez sean publicados	Si ☐	No ☐
La destrucción de mis datos una vez finalizado el estudio	Si ☐	No ☐
Incluir las siguientes restricciones al uso de mis datos:		

Y en prueba de conformidad, firmo el presente documento en el lugar y en la fecha que se indican a continuación.

A Coruña, a_______ de _____________________ de _______.

Nombre y apellidos del testigo:	Nombre y apellidos del/a investigador/a que solicita el consentimiento: Marta Sevilla Sánchez
Firma:	Firma:

e) REVOCACIÓN DEL CONSENTIMIENTO

Revoco el consentimiento prestado el día ______________________ para participar en la investigación/estudio titulado “Efectos de la estimulación de corriente directa transcraneal en el aprendizaje y retención motora a largo plazo”.

Consiento que los datos recogidos hasta este momento sean utilizados conforme se explicó en el documento de información (y consentimiento) Si ☐ Non ☐

Para que así conste, firmo la presente revocación.

En A Coruña, a________ de _________________________ de 202__.

Nombre y apellidos del/a participante:	Nombre y apellidos del/a investigador/a principal: Marta Sevilla Sánchez
Firma:	Firma:

Appendix C:

Evaluation’s instructions

APPENDIX C

Evaluation's instructions Study II a

EXPERIMENTO MECANOGRAFÍA 2018

-Prueba de Evaluación X-

Índice

1. DESCRIPCIÓN DE LA PRUEBA

- ✓ Antes de iniciar la prueba de evaluación, recuerda:
- ✓ Ajusta lo mejor posible cada letra a cada pulso marcado por el metrónomo.
- ✓ Intenta cometer los menores errores posibles.
- ✓ Mantén la máxima concentración posible durante toda la prueba.

Para comenzar la evaluación, accede a tipp10 -> "Online versión" -> "Training" -> "Own lessons" -> "Prueba de evaluación 1", realiza de nuevo la prueba completa 10 veces, configurando el metrónomo online a las siguientes pulsaciones y marcando en las opciones del software "Entire Lesson":

- 50 pulsaciones/minuto
- 60 pulsaciones/minuto
- 70 pulsaciones/minuto
- 80 pulsaciones/minuto
- 90 pulsaciones/minuto
- 100 pulsaciones/minuto
- 110 pulsaciones/minuto

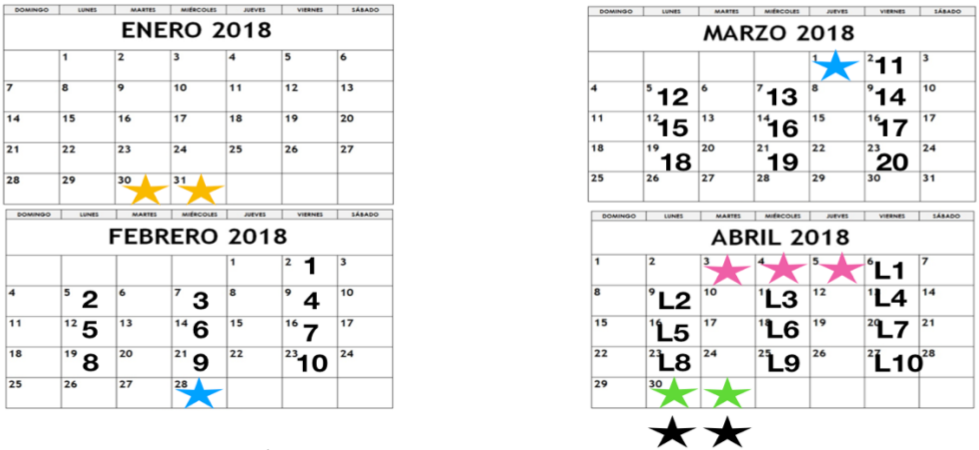
- 120 pulsaciones/minuto

- 130 pulsaciones/minuto

- SIN METRÓNOMO a la mayor velocidad posible

✓ Muy importante, cuando finalices la evaluación **envía todos los resultados que tengas registrados hasta la fecha (4 pruebas completas de evaluación + 30 entrenamientos) en formato Excel renombrando el archivo con el código que tengas asignado a: experimentoinef@gmail.com**

2. SEGUIMIENTO SESIONES-TEMPORALIZACIÓN



ENERO 2018

DOMINGO	LUNES	MARTES	MIÉRCOLES	JUEVES	VIERNES	SÁBADO
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30 ★	31 ★			

FEBRERO 2018

DOMINGO	LUNES	MARTES	MIÉRCOLES	JUEVES	VIERNES	SÁBADO
				1	2 **1**	3
4	5 **2**	6	7 **3**	8	9 **4**	10
11	12 **5**	13	14 **6**	15	16 **7**	17
18	19 **8**	20	21 **9**	22	23 **10**	24
25	26	27	28 ★			

MARZO 2018

DOMINGO	LUNES	MARTES	MIÉRCOLES	JUEVES	VIERNES	SÁBADO
				1 ★	2 **11**	3
4	5 **12**	6	7 **13**	8	9 **14**	10
11	12 **15**	13	14 **16**	15	16 **17**	17
18	19 **18**	20	21 **19**	22	23 **20**	24
25	26	27	28	29	30	31

ABRIL 2018

DOMINGO	LUNES	MARTES	MIÉRCOLES	JUEVES	VIERNES	SÁBADO
1	2	3 ★	4 ★	5 ★	6 **L1**	7
8	9 **L2**	10	1 **L3**	12	1 **L4**	14
15	16 **L5**	17	18 **L6**	19	20 **L7**	21
22	23 **L8**	24	25 **L9**	26	27 **L10**	28
29	30 ★	★				

★ ★

★ **Evaluaciones**

Nº1 al 20 **Niveles ordenados por dificultad del software Tipp10**

L **10 sesiones práctica con texto que os enviaré por email**

Se os invitará a una reunión informativa en el **mes de junio** para presentar los resultados obtenidos del experimento.

3. PREMIOS

- ✓ 3 premios a los alumnos que cometan **menos errores**.
- ✓ 3 premios a los alumnos más **rítmicos**.
- ✓ 3 premios **sorpresa.**
- ✓ 3 premios a los alumnos más **responsables**

-> 8 premios.

motor control group

Marta Sevilla
experimentoinef@gmail.com

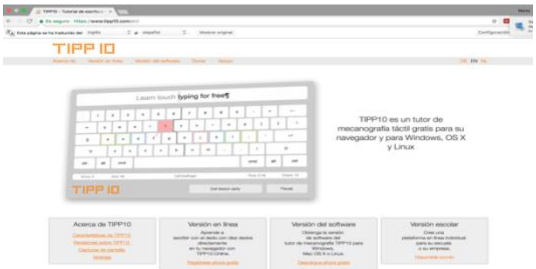
Evaluation instructions Study II b

A. Repasa la **imagen** que hay en la **carpeta** sobre la **forma correcta de colocar** los dedos en el teclado e intenta durante todos los entrenamientos llevarla a cabo.

B. Sigue las siguientes instrucciones para completar la evaluación 1 paso a paso

---

1er paso

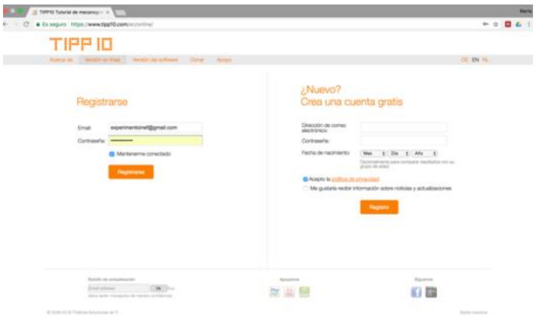


TIPP10 es un tutor de mecanografía táctil gratis para su navegador y para Windows, OS X y Linux

Acceder a la página web https://www.tipp10.com/en/

Haz clic en **“Online versión”**

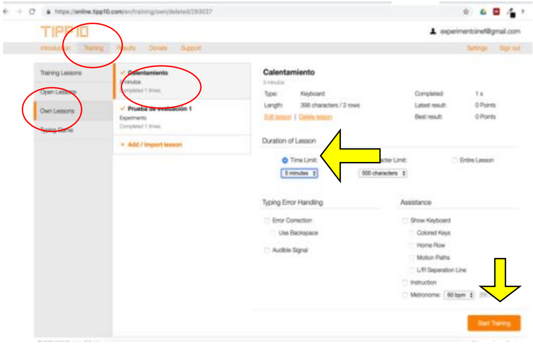
2º paso



Email: experimentoinef@gmail.com

Inicia sesión desde la web con tu nombre de usuario (**email de la UDC**) y contraseña (**DNI**, 8 dígitos seguidos de la letra en mayúscula).

3er paso



Calentamiento

Type: Keyboard

Length: 398 characters / 2 rows

Completed: 1 x

Latest result: 0 Points

Best result: 0 Points

● Time Limit: 5 minutes

○ Character Limit: 500 characters

○ Entire Lesson

☐ Error Correction

☐ Use Backspace

☐ Audible Signal

☐ Show Keyboard

☐ Colored Keys

☐ Home Row

☐ Motion Paths

☐ L/R Separation Line

☐ Instruction

☐ Metronome: 60 bpm

Haz click en “Ejercicios de teclear” y luego haz click en lección **“Calentamiento”** (asegúrate que la barra naranja esté a la izquierda de calentamiento).

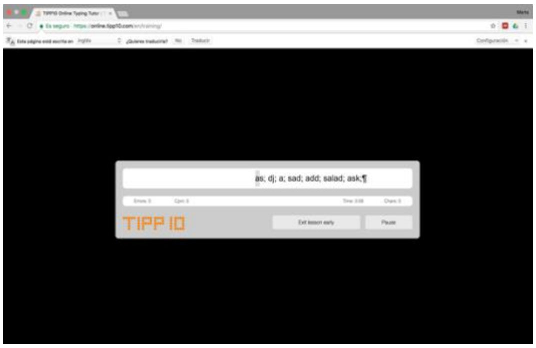
En las opciones de la lección

SÓLO marcar “Time Limit” y configurar 3 minutos.

Inicia el entrenamiento dándole a “Start Training”.

Antes de comenzar concéntrate e intenta ser lo más rápido y preciso posible.

4º paso



as; dj; a; sad; add; salad; ask;¶

Una vez transcurridos los 3 minutos programados, el entrenamiento se

detendrá y quedará guardado automáticamente.

PRUEBA INCREMENTAL: PRUEBA CON METRÓNOMO

- **Conecta los auriculares a tu móvil y en el buscador de google escribe la palabra "metrónomo". Configura el metrónomo de google online a las pulsaciones que te indiquen los investigadores.**

ACLARACIÓN 1

En el caso de que no te aparezca el metrónomo de google en tu móvil, busca en YouTube "100 ppm metrónomo"

Consulta a los investigadores o colaborados cuáles son tus 3 velocidades, ya que son personales y están adaptadas a tu nivel de forma individual 50%, 60%, 70% de tu velocidad máxima de mecanografía.

Por tanto, tendrás realizar esta prueba de evaluación (con el mismo texto) un total de 3 veces, con el metrónomo configurado a diferentes velocidades (pulsaciones por minuto).

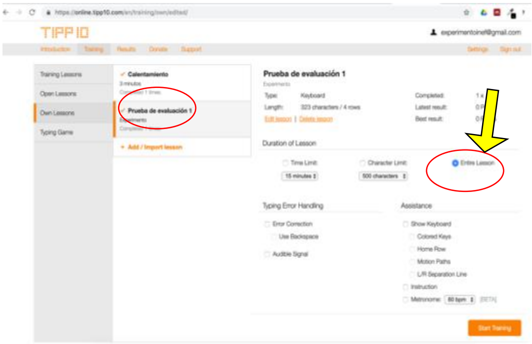
Son velocidades distintas a las del último día.

Antes de comenzar concéntrate e intenta **ser lo más rápido y preciso posible**, **ajustando cada pulso al ritmo de golpeo que establece el metrónomo**.

ACLARACIÓN 2

Cuando aparece una tilde hay que cuadrar el golpeo de las 2 teclas dentro de un mismo pulso.

5º paso


https://online.tipp10.com/en/training/own/edited/

TIPP10

experimentoinef@gmail.com

Introduction | Training | Results | Donate | Support | Settings | Sign out

Training Lessons

Open Lessons

Own Lessons

Typing Game

✓ Calentamiento
3 minutos

✓ Prueba de evaluación 1
Experimento

+ Add / Import lesson

Prueba de evaluación 1
Experimento

Type: Keyboard

Length: 323 characters / 4 rows

Edit lesson | Delete lesson

Duration of Lesson

○ Time Limit: 15 minutes

○ Character Limit: 500 characters

● Entire Lesson

Typing Error Handling

☐ Error Correction

☐ Use Backspace

☐ Audible Signal

Assistance

☐ Show Keyboard

☐ Colored Keys

☐ Home Row

☐ Motion Paths

☐ L/R Separation Line

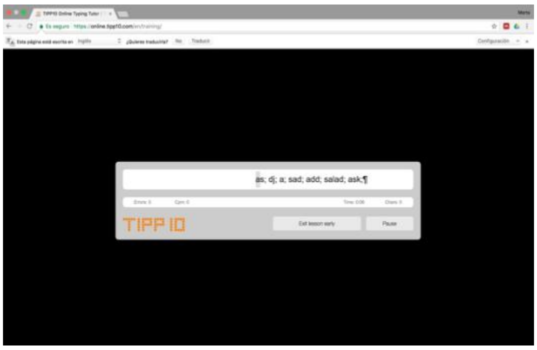
☐ Instruction

☐ Metronome: 80 bpm [BETA]

Start Training

En las opciones de la lección **SÓLO marcar “Enteri lesson”**, para realizar el texto completo. Inicia el entrenamiento dándole a “Start Training” y asegúrate de tener los auriculares bien conectados y de escuchar el sonido antes de comenzar la prueba. Haz click en “Ejercicios de teclear” y luego haz click en la lección “**prueba de evaluación**” (asegúrate que la barra naranja esté a la izquierda de dicha sección).

6º paso


TIPP10 Online Typing Tutor

https://online.tipp10.com/en/training/

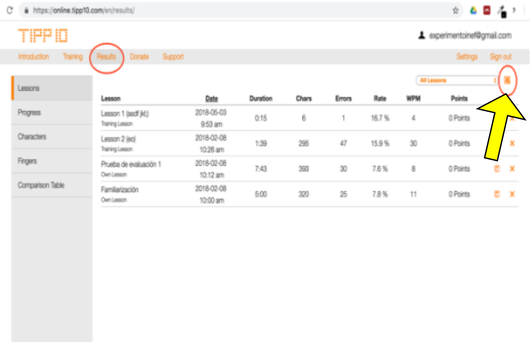
as; dj; a; sad; add; salad; ask;¶

TIPP10

Exit lesson early | Pause

Una vez completado el texto, el entrenamiento se detendrá y quedará guardado automáticamente.

7º paso



Lesson	Date	Duration	Chars	Errors	Rate	WPM	Points
Lesson 1 (asdf jkl;) Training Lesson	2018-05-03 9:53 am	0:15	6	1	16.7 %	4	0 Points
Lesson 2 (ei) Training Lesson	2018-02-08 10:26 am	1:39	295	47	15.9 %	30	0 Points
Prueba de evaluación 1 Own Lesson	2018-02-08 10:12 am	7:43	393	30	7.6 %	8	0 Points
Familiarización Own Lesson	2018-02-08 10:00 am	5:00	320	25	7.8 %	11	0 Points

Tras realizar la prueba, debes descargar y enviar el informe en formato Excel, accediendo a “Results” y pulsando en la “X” que hay arriba a la derecha. Una vez descargado el archivo (búscalo en la carpeta de descargas) y **renómbralo** con tu **DNI**. Abre tu correo personal e indicando en el **asunto: “Evaluación 2”, envíalo** a

experimentoinef@gmail.com

8 paso

Cumplimenta el siguiente cuestionario:

https://forms.gle/BqDFStCaHANU1XT37

Marta Sevilla
experimentoinef@gmail.com

Appendix D:

Other scientific contributions

APPENDIX D

Other scientific contributions

During these four years of PhD training, I also participated in other 7 studies with the Department of Physical and Sports Education (University of A Coruña), and in other in collaboration with other universities.

Articles

S.F. Gómez, C. Homs, J. Wärnberg, M. Medrano, M. Gonzalez-Gross, N. Gusi, S. Aznar, E.M. Cascales, M. González-Valeiro, L. Serra-Majem, N. Terrados, J.A. Tur, M. Segú, C. Lassale, J.C. Benavente-Marín, I. Labayen, A.G. Zapico, J. Sánchez-Gómez, F. Jiménez-Zazo, P.E. Alcaraz, **M. Sevilla-Sanchez**, E. Herrera-Ramos, S. Pulgar, M.D.M. Bibiloni, O. Sancho, H. Schröder, Study protocol of a population-based cohort investigating Physical Activity, Sedentarism, lifestyles and Obesity in Spanish youth: The PASOS study, BMJ Open. 10 (2020) 1–6. https://doi.org/10.1136/bmjopen-2019-036210

J. Wärnberg, N. Pérez-Farinós, J.C. Benavente-Marín, S.F. Gómez, I. Labayen, A. G. Zapico, N. Gusi, S. Aznar, P.E. Alcaraz, M. González-Valeiro, L. Serra-Majem, N. Terrados, J.A. Tur, M. Segú, C. Lassale, C. Homs, M. Oses, M. González-Gross, J. Sánchez-Gómez, F. Jiménez-Zazo, E. Marín-Cascales, **M. Sevilla-Sánchez**, E. Herrera-Ramos, S. Pulgar, M. del M. Bibiloni, O. Sancho-Moron, H. Schröder, F.J. Barón-López, Screen Time and Parents' Education Level Are Associated with Poor Adherence to the Mediterranean Diet in Spanish Children and Adolescents: The PASOS Study, J. Clin. Med. 10 (2021) 795. https://doi.org/10.3390/jcm10040795

A. Luque-Casado, S. Novo-Ponte, J.A. Sanchez-Molina, **M. Sevilla-Sanchez**, D. Santos-Garcia, M. Fernandez-del-Olmo, Test-Retest Reliability of the Timed Up and Go Test in Subjects with Parkinson's Disease: Implications for Longitudinal Assessments, J. Parkinsons. Dis. (2021) 1–9. https://doi.org/10.3233/jpd-212687

H. Schröder, I. Subirana, J. Wärnberg, M. Medrano, M. González-Gross, N. Gusi, S. Aznar, P.E. Alcaraz, M.A. González-Valeiro, L. Serra-Majem, N. Terrados, J.A. Tur, M. Segú, C. Homs, A. Garcia-Álvarez, J.C. Benavente-Marín, F.J. Barón-López, I. Labayen, A.G. Zapico, J. Sánchez-Gómez, F. Jiménez-Zazo, E. Marín-Cascales, **M. Sevilla-Sanchez**, E. Herrera-Ramos, S. Pulgar, M. del Mar Bibiloni, C. Sistac-Sorigué, S.F. Gómez, Validity, reliability, and calibration of the physical activity unit 7 item screener (PAU-7S) at population scale, Int. J. Behav. Nutr. Phys. Act. 18 (2021) 1–13. https://doi.org/10.1186/s12966-021-01169-w

M. Fernández-del-Olmo, **M. Sevilla-Sanchez**, G.M. Sanchez, D. Kidgell, M.H. Milot, R.W. Selles, J. Rothwell, T. Hortobágyi, Neuromodulation by non-invasive brain stimulation (NIBS): a step back to move forward, Brazilian J. Mot. Behav. 15 (2021) 61–64. https://doi.org/10.20338/bjmb.v15i2.213

A. Nieto-Guisado, M. Solana-Tramunt, A. Marco-Ahulló, **M. Sevilla-Sánchez**, C. Cabrejas, J. Campos-Rius, J. Morales, The Mediating Role of Vision in the Relationship between Proprioception and Postural Control in Older Adults, as Compared to Teenagers and Younger and Middle-Aged Adults, Healthcare. 10 (2022) 103. https://doi.org/10.3390/healthcare10010103

M. Bibiloni, L. Gallardo-alfaro, F.G. Santiago, J. Wärnberg, M. Oses, M. Gonzalez, S. Aznar, E. Mar, M. Gonzalez, L. Serra-Majem, M. Segu, C. Lassale, C. Homs, J. Carlos, I. Labayen, A.G. Zapico, F. Jim, P.E. Alcaraz, **M. Sevilla-Sanchez**, E. Herrera-ramos, S. Pulgar, C. Sistac, H. Schröder, C. Bouzas, J.A. Tur, Combined Body Mass Index and Waist-to-Height Ratio and Its Association with Lifestyle and Health Factors among Spanish Children: The PASOS Study, Nutrients. (2022). https://doi.org/https://doi.org/10.3390/nu14020234