NEUROMODULATION OF MOTOR LEARNING IN HEALTHY INDIVIDUALS AND PATIENTS WITH NEUROLOGICAL DISORDERS

Doctoral Thesis by: Maíra Izzadora Souza Carneiro

Supervisor: Prof. Nadia Bolognini

MILAN ‖ 2018

Doctoral School
University of Milano-Bicocca

Department of Psychology

PhD Program in Experimental Psychology, Linguistics and Cognitive Neurosciences

XXXI Cycle

Mind, Brain and Behaviour Curriculum

NEUROMODULATION OF MOTOR LEARNING IN HEALTHY INDIVIDUALS AND PATIENTS WITH NEUROLOGICAL DISORDERS

Surname: Souza Carneiro Name: Maíra Izzadora

Registration number: 810686

Supervisor: Prof. Nadia Bolognini

Coordinator: Prof. Maria Teresa Guasti

ACADEMIC YEAR 2017/2018

TABLE OF CONTENTS

Abstract

Non-invasive Brain Stimulation (NIBS) techniques, such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), have been increasingly used as tools for improving motor learning in healthy individuals. Efforts of the current neuroscientific field are now directed to the mechanistic understanding of NIBS tools with respect to their modulatory effects on different motor learning processes, among which the on-line learning (improvements occurring during practice), the retention and generalization of the learned skills. This investigation is also relevant for optimizing stimulation protocols. The enhancement effects of tDCS on motor learning have also guided the investigation of its therapeutic potential for the rehabilitation of motor disorders in neurological diseases. The present thesis aims at: (i) enriching current evidence regarding the clinical effectiveness of tDCS and rTMS as adjuvant interventions to augment the response of the motor system to behavioral trainings; (ii) exploring the role of alternative routes (via premotor and posterior parietal cortices), beyond the primary motor cortex, for improving motor learning in healthy humans and (iii) uncovering the potential of tDCS for the treatment of upper-limb motor disorders in children with cerebral palsy (CP), which represents one of the most recent field of investigation in NIBS clinical literature. Within this framework, I have performed four studies (a meta-analysis, and three empirical investigations). Results from Study 1 indicate that the quality of available evidence for the use of tDCS and TMS as add-on interventions to boost motor training effects in adult stroke patients is still *low*, although some indications for the most effective stimulation protocols for either rTMS and tDCS are emerging. Study 2 shows that, beyond the primary motor cortex, the typical tDCS target for facilitating motor learning, premotor cortex stimulation has also a merit, since it can selectively improve the generalization of motor learning to untrained skills, at least in healthy individuals. The last two studies show that in children with CP, motor learning abilities may be impaired, as compared to those of age-matched typically-developing children; motor learning deficits in CP depends on the type of corticospinal reorganization that follows a brain injury (Study 3). In this pediatric population, tDCS seems unable to enhance motor learning of the affected hand, at least when the stimulation is delivered in a single session (Study 4), suggesting that more intensive and prolonged stimulation protocols are required for improving the chronic motor dysfunctions featuring CP.

Summary

Motor learning is considered at the basis of skill acquisition in healthy individuals as well as of recovery of motor disorders in neurological patients. It is associated with high levels of practice in which the experience plays a key role for improvements in motor performance. As a very complex mechanism, motor learning is thought to be built by many cognitive processes as adaptation, retention, and consolidation of skill. Several brain areas subtend the acquisition of motor skills and, thus, motor learning. As the executive area of voluntary movements, the primary motor cortex (M1) is a source for motor commands, but other brain areas as the premotor cortex (PM), the posterior parietal cortex (PPC), the supplementary motor area (SMA), along with subcortical structures, cooperate to allow the execution and control of movements. Such brain areas play also an essential role in the acquisition of motor skills and, thus, in motor learning.

In the last years, Non-invasive Brain Stimulation (NIBS) techniques have been used to modulate behavior of healthy individuals as well as to treat a wide range of neurologic diseases as Stroke, Parkinson and Spinal Cord Injury. As an add-on technique, NIBS should be used in addition to standard therapies, rather than in substitution of them, at least in cognitive and motor rehabilitation. A series of NIBS studies have already shown that transcranial Direct Current Stimulation (tDCS) improves human motor learning if applied over M1. However, considering the role of non-primary motor areas in the acquisition of motor skills, the neuromodulation of PM and PPC activity should be considered as an alternative option to boost motor learning, especially in case of injuries affecting primary motor areas. So far, motor learning was shown to be enhanced by motor cortex stimulation, while the modulatory role of premotor and posterior parietal areas in healthy and brain-damaged adults still needs to be addressed.

A more field of investigation pertains the chance of using tDCS to affect motor learning in children with cerebral palsy (CP). Research in this field is still in infancy. The available evidence seems to prove the tolerability and safety of tDCS in such population, with few – mild – adverse effects were seldom reported in the pediatric population. With respect to motor learning, the evidence is scarce with mixed results in CP, at least for what concern upper-limb motor functions. Of importance, it is still unknown whether and how development plasticity featuring the motor system in CP may affect learning abilities and the response to tDCS.

Within this framework, this thesis aims at further increase our knowledge of the potential of tDCS for enhancing motor learning in healthy and stroke adults, as well in children with CP. In particular, through a series of experimental investigation I will provide: (i) novel evidence on the current state of art of the research assessing the facilitatory effects of the neuromodulation of motor

cortical excitability on motor learning and recovery in stroke adults – Study 1; (ii) the role of premotor and posterior parietal cortices in online and off-line motor learning processes in healthy individuals – Study 2; (iii) the impact of the type of developmental plastic motor organization following perinatal stroke on motor learning abilities in CP – Study 3 and (iv) the modulatory effects of tDCS on motor hand function of children with CP – Study 4.

CHAPTER 1

Motor Control, Learning And Neuromodulation: Theories, Cognitive Processes And Plasticity Of Neural Networks

In this first chapter, a literature review will illustrate the main theories of motor learning. Although none of these theories is capable to definitely explain all steps, each one has played an important role to build our current knowledge (Zwicker & Harris, 2009). Here, I will explore the Closed-loop theory, the Schema theory, and the Dynamic systems theory. Additionally, Hebbian Learning Theory and learning-dependent synaptic plasticity processes will be addressed to provide the physiological basis and underpinning motor learning.

The second part of this chapter will explore some neurophysiological and cognitive processes of learning as the stages of motor learning, the consciousness of learning - explicit and implicit processes, neural networks underlying motor learning and the role of sleep in off-line learning.

Finally, a brief historical overview, the technical aspects, and mechanisms of action of tDCS as well as of Transcranial Magnetic Stimulation (TMS) will be provided in the last part of this chapter.

1.1. Theories

Defined as *"a set of processes associated with practice or experience leading to relatively permanent changes in the capability for movement"* (Schmidt & Lee, 1999), motor learning is the base of every skill acquisition in healthy individuals and neurologic patients. In the last decades, particularly during the 70-90s, motor learning theories have emerged as key factors in neurological rehabilitation (Cano-De-La-Cuerda et al., 2015; Carr & Shepherd, 1989; Sabari, 1991).

1.1.1. The Closed-loop theory

Postulated by Jack Adams during the 1970s, the closed-loop theory is error-centered, which means sensory feedback is the core of learning processes and guides acquisition of motor skills (Adams, 1971). According to this theory, the movement is initiated by a memory trace and continuously analyzed by a perceptual trace in order to detect and correct possible errors. Through an extensive practice, error rate during movements is gradually reduced by comparing ongoing movement with the correct memory of such task. In this way, improvements in motor learning

reflect an increased ability to use the reference (feedback) in a closed-loop. Figure 1 provides an illustration of how works the closed-loop.

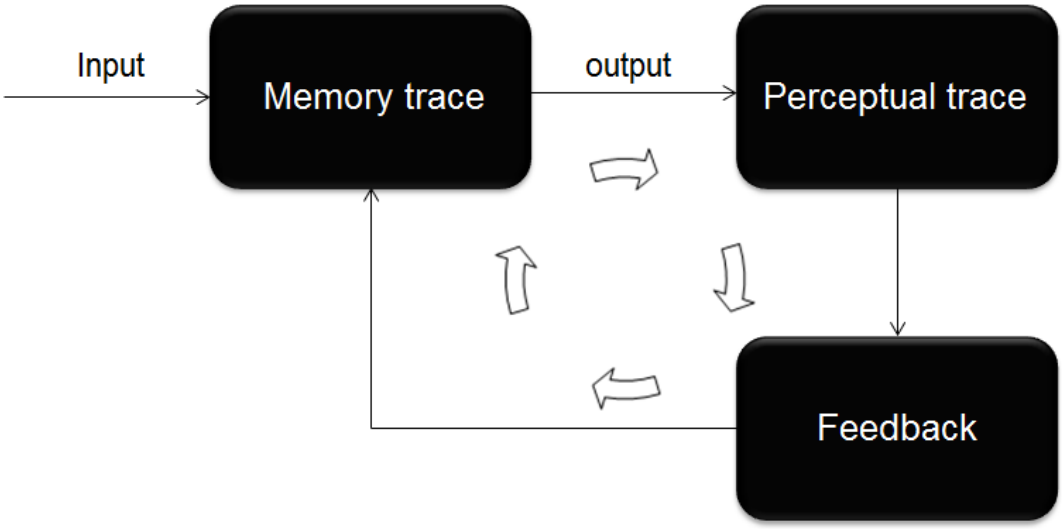

Figure 1. An illustrative diagram of theories components. Source: the author, 2018.

Such theory would have some clinical implications. First, to promote learning, motor training should be performed with the same exact movement in an extensive repetitive way. Second, the more is the practice, the more the learning rate. Third, the movement should be accurate since errors produced during learning would increase the strength of an incorrect perceptual trace. However, the closed-loop theory has some important limitations which have already been confirmed by exploratory studies. Studies performed with animals as well as humans showed that sensory feedback is not indispensable to promote motor learning (Fentress, 1973; Rothwell et al., 1982; Taub, 1976). Additionally, a variability of movements probably is better in promoting motor learning that an extensive repetitive practice of the same movement (Shea & Kohl, 1990, 1991).

1.1.2. The Schema theory

In the mid-1970s, Richard Schmidt formulated the Schema theory, which is based on an interaction between generalized motor programs (GMPs) and schemas which would allow motor skill acquisition. A motor program is "*a sequence of stored commands that are structured before the movement begins and allows the entire sequence to be carried uninfluenced by peripheral feedback*" (Keele, 1968; Keele & Summers, 1976). Thus, unlike the closed-loop theory in which sensory feedback is the core of learning processes, Schmidt proposed that each person carries

GMPs able to provide appropriate commands for a given class of movements as long as specifications about those movements are provided (Schmidt, 1975, 2003). However, such GMP could not work without motor schemas. A schema could be defined as an abstract memory representation consisting of a set of rules capable to guide movement's production (Evans, 1967). In this way, two types of schema are required to interact with GMPs and generate movements: a recall schema and a recognition schema. When a movement is about to initiate, the recall schema provides information regarding initial conditions and response specifications for the GMPs in the same way as the recognition schema provides the sensory consequences of the response produced and the outcome of this movement during and/or after performing such skill to correct or alter responses (Zwicker & Harris, 2009). Such operation results in modification of recall schemas according to movement experience and, in the same way, the larger are GMPs, the easier is the adaptation to novel situations suggesting that a variability of practice can improve motor learning. Figure 2 provides an illustration of how the two types of schema interact with each other and with various sources of information.

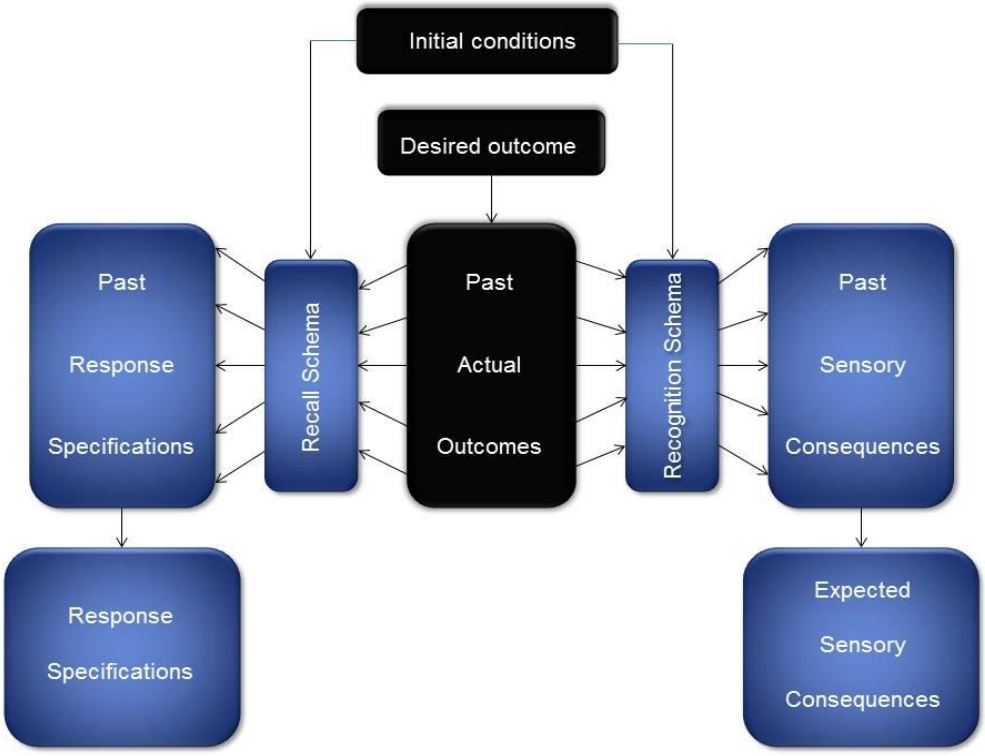

Figure 2. Diagram of recall schema and recognition schema. Source: adapted from Schmidt, 1975.

The clinical implication of such theory would be primarily task-related since optimal learning could be achieved through variable protocols. Additionally, errors result in positive effects since it is possible to learn with them and recall schemas have rules for all types of stored movements, not only those correct. As well as in closed-loop theory, Schmidt's theory has a very important

limitation, among which it does not precisely describe how GMP are formed. In a recent update article (Schmidt, 2003), Schmidt has provided some reflections about his own theory and suggests that "*GMPs are learned by a kind of successive modification resulting from efforts at reconstructing them in practice".* Previous works performed by Wulf and colleagues (1993) may reinforce this idea since randomized practice *vs.* blocked practice as well as provide less feedback seemed to be more effective strategies in promoting GMPs learning (Wulf, Schmidt, & Deubel, 1993).

1.1.3. The Dynamic systems theory

Based on the pioneering work of Thelen and Smith, this theory is centralized in the idea that movement production relies on the integration of multiple sub-systems (i.e., neurological, musculoskeletal, sensory/perceptual, etc.) within the individual, task, and environment (Thelen & Smith, 1996). As a complex and non-linear process, the movement is highly susceptible to changes in one of the sub-systems and thus, does not develop in a continuous manner (Smith & Thelen, 1993). In order to produce efficient movement patterns, sub-systems are able to self-organize and cooperatively interact with each other in a specific way with no system playing the role of commandant (Spencer, Austin, & Schutte, 2012; Zwicker & Harris, 2009). Such organization is mandatory since complex systems (as the neurologic one) have several elements which spread along multiple levels and interact creating patterns. In this way, the dynamic system theory postulates that practice leads to "attractor states". Those states are efficient patterns of movement resulting from the interaction between the mechanical system of the body (muscular or skeletal) with the environment and the demands of the task (Kugler & Turvey, 2015; Mathiowetz & Haugen, 1994).

According to such theory, the neural control of movement is only the starting point of movement production since the mechanical system of our body is susceptible to internal and external forces which can dramatically change movement's pattern. In this way, the same movements can be elicited by different commands and vice-versa. Attractor states play also an indispensable role when motor performance is in a transient phase. Learning can change attractor states in a qualitative or quantitative way. For example, when we shift from walking to running, a gradual and quantitative change in the number or type of attractors during transition phase results in sub-systems reorganization (Diedrich & Warren Jr, 1995; Spencer & Perone, 2008; van Geert, 1998). Finally, it is speculated that the dynamic system theory has the best accuracy in predicting motor behavior when compared to others learning theories since it takes into account the highly dynamic relationship between sub-systems and internal/external forces (Cano-De-La-Cuerda et al.,

2015). Figure 3 provides an illustration of the integration between individual, task, and environment to produce movement.

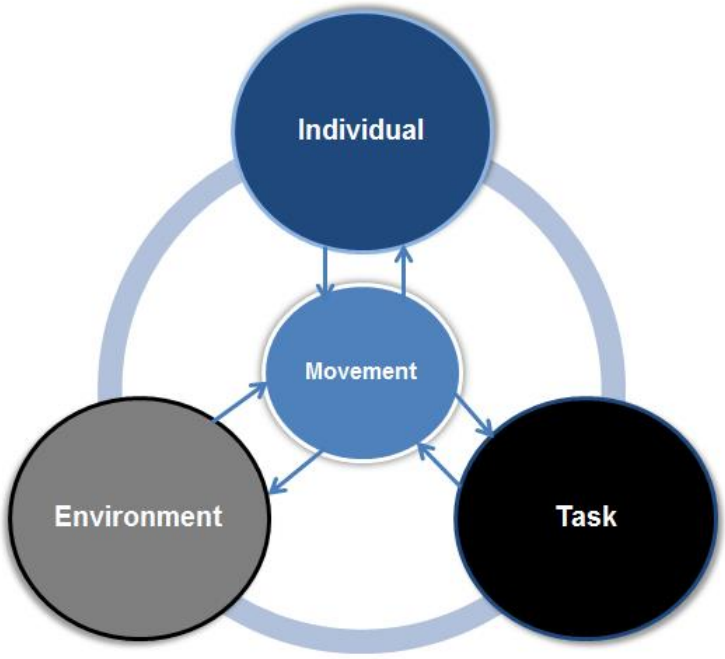

Figure 3. An illustrative diagram of how theories components work between each other. Source: adapted from Holt *et al*., 2010.

1.2. Synaptic Plasticity

1.2.1. Hebbian Learning Theory

According to Murphy and Corbett (2009), neural plasticity can be defined as "*changes in the strength of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network* "(Murphy & Corbett, 2009). In the same way, Kleim and Jones (2008) reinforced the proposal that *"neurons, among other brain cells, possess the remarkable ability to alter their structure and function in response to a variety of internal and external pressures, including behavioral training"* (Kleim & Jones, 2008). Changes in the strength of synaptic connections depend on how neurons of a given network interact with each other and are closely related to the Hebbian Learning Theory.

In the late 1940s, the Canadian psychologist named Donal Hebb combined his ideas with thoughts of philosophers and neuroscientists as William James and Eugenio Tanzi, among others, and published a manuscript called *"*The Organization of Behavior" (Hebb, 1949). In his seminal work, Hebb postulated that "*When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one*

or both cells such that A's efficiency, as one of the cells firing B, is increased." According to Hebb, such increase in synapses efficiency would be the neurological substrate for storing information in the brain and in turn for driving learning. Over the years, his theory evolved and currently, Hebbian plasticity is characterized by the interactive mechanism, the time-dependent mechanism, and the local mechanism.

The interactive mechanism implies that any modification occurring within the synaptic connection must involve both sides of the synaptic cleft, which means the presynaptic and postsynaptic neurons. At the same time, it is required a co-activation of both neurons and the time interval between these activations is the key-factor that drives synaptic modifications; this is the time-dependent mechanism. Finally, the local mechanism means that all information required for Hebbian modifications is available at the site of the synapse and depend on local variables - for example, neuronal firing rate (Brown, Zhao, & Leung, 2009).

Changes in the strength of synaptic connections can be quantified through the amplitude of excitatory/inhibitory postsynaptic potentials (EPSP/IPSP). When a presynaptic neuron fires, an action potential is generated, neurotransmitters are released into the synaptic cleft and taken up by receptors of the postsynaptic neuron. Then, postsynaptic membrane is temporarily depolarized after charged ions enter the cell as a result of opening ligand-gated ion channels. If charged ions make the intracellular concentration positive, an EPSP is produced whereas IPSP is produced when intracellular concentration becomes negative. When postsynaptic potentials are changed only for a few seconds, short-term plasticity is induced, but changes can also last minutes or hours – what is called persistent plasticity (Gerstner, 2011). Figure 6 shows the main differences between both plasticity processes.

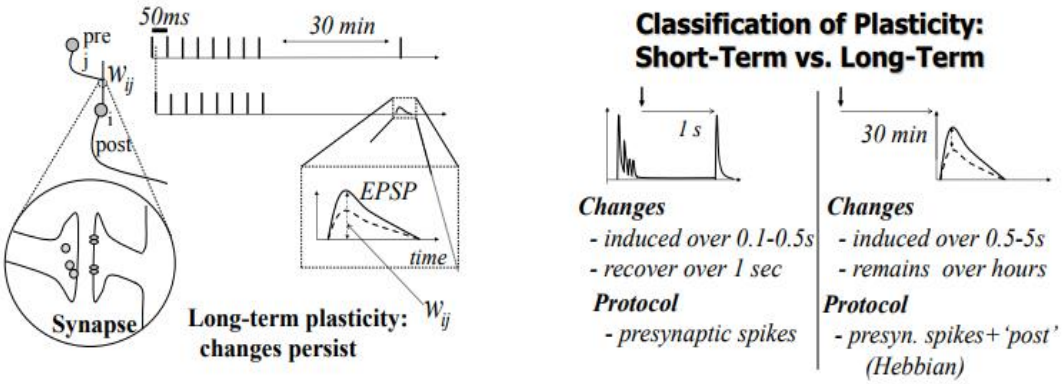

Figure 6. Mechanism of Short-term vs. Long-term neural plasticity. Source: Gerstner, 2011.

As briefly explained above, postsynaptic potential changes persisting for minutes or hours underlies persistent plasticity. Thereby, one of the most important synaptic phenomena is the long-

term potentiation (LTP). LTP mechanisms are generally induced by glutamatergic synapses. Such synapses occur through a binding of glutamate to AMPA (*2-amino-3-(3-hydroxy-5-methyl-isoxazole-4-yr) propanoic acid* and NMDA (N-methyl-D-aspartate) receptors localized on the post-synaptic neuron membrane. After the arrival of an action potential, glutamate is released by the presynaptic neuron and binds to AMPA receptors which open and allow an intracellular influx of sodium ions (Na^+), thus resulting in cellular depolarization. Concomitantly, such cellular depolarization induces a magnesium ions (Mg^{2+}) outflow from NMDA receptors and unblocking the channel, allowing also an influx of Na^+. LTP occurs only whether a higher activation of NMDA receptors is associated with a depolarization of the postsynaptic neuron. This increases a calcium (Ca^{2+}) influx to the cell, activating a cascade of protein kinases and resulting in synthesis and insertion of new AMPA receptors in the postsynaptic neuron (Gillick & Zirpel, 2012; Kułak & Sobaniec, 2004). Such an increase in the number of AMPA receptors is responsible for the reinforcement of neuronal synaptic connections and for a higher responsivity to glutamate (Pang, Cao, Xu, & Südhof, 2010) – see Figure 7.

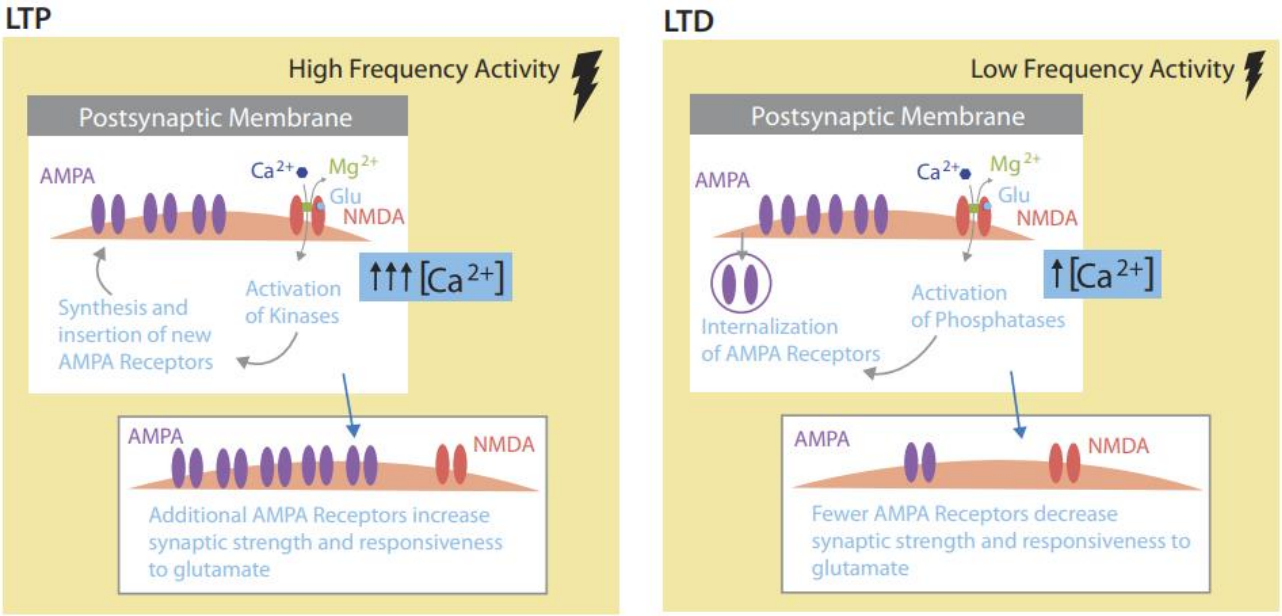

Figure 7. Neural changes during the induction of long-term potentiation (LPT) and long-term depression (LTD). Source: Gillick & Zirpel, 2012.

LTP is characterized by a persistent increase in the strength of synaptic connections that is activity-dependent. Still, in the mid-1970s, Tim Bliss and Terje Lomo performed some *in vitro* experiments in dentate gyrus tissue and observed an increment in the size of extracellular fields potentials after repetitive stimulation of afferent input to this tissue (Bliss & Lømo, 1973). A decade later, German Barrionuevo and Thomas Brown demonstrated also that LTP has an associative nature, which means that synaptic modifications are dependent on a coactivation between two

different afferent inputs to the same neuron. Through hippocampal brain slice preparations, they showed that only a coactivation of weak (small number of afferents) and strong (a large number of afferents) inputs after paired tetanic (high-frequency) stimulation induced LTP (Barrionuevo & Brown, 1983). Additionally, Thomas Brown and colleagues (1986) performed further experiments using hippocampal brain slice preparations and showed that LTP has synapses of Hebbian type through the confirmation of temporal specificity characteristic. They demonstrated that LTP induction was only possible after a coactivation of weak and strong inputs to the same neuron in which the weak input was activated during postsynaptic depolarization - see Figure 8 (Kelso, Ganong, & Brown, 1986).

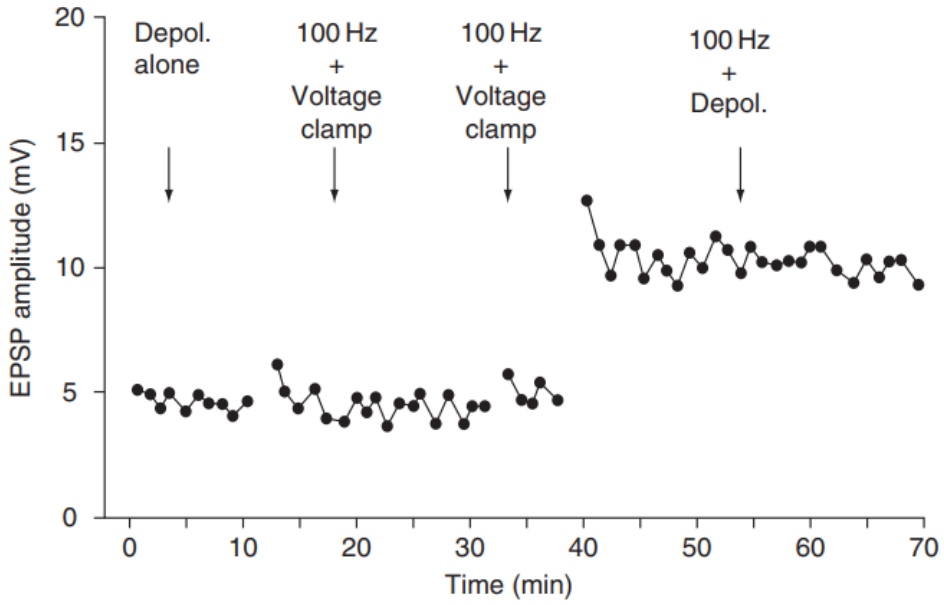

Figure 8. Results of experiments made with hippocampal brain slices showing long-term potentiation (LTP) as synapses of Hebbian type. LTP is induced after a coactivation of weak and strong inputs to the same neuron. Source: Kelson & Brown, 1986.

As the strength of synaptic connections can be increased, they also can be decreased which is described as long-term depression (LTD). A lower activation of NMDA receptors causes a reduction in the influx of Ca^{2+} to the cell, stimulating a cascade of phosphatases and resulting in a removal of AMPA receptors from the membrane. Thus, such reduction is responsible for a deterioration of synaptic connections and a lower responsivity to glutamate (Mulkey, Herron, & Malenka, 1993; Sadowski, 2008).

1.2.2. Learning-Dependent Synaptic Plasticity

After a brain damage, a cascade of structural and functional cortical changes as angiogenesis, neurogenesis, and reorganization of motor maps can occur in order to protect brain tissue and

preserve the penumbra area (Buma, Kwakkel, & Ramsey, 2013; Chopp, Zhang, & Jiang, 2007; Krakauer, 2006). Previous studies have already shown that the brain is able to encode experiences and learn new behaviors after motor training through similar plastic changes as synaptogenesis and reorganization of neural networks (Langhorne, Coupar, & Pollock, 2009; Pekna, Pekny, & Nilsson, 2012; Richards, Hanson, Wellborn, & Sethi, 2008). Indeed, nowadays there is a large body of evidence showing that synaptic plasticity occurs in association with motor training. Current literature describes the occurrence of axonal sprouting with the formation of new synapses, strengthening of ineffective cortical connections and reorganization of motor maps during plastic processes (Hluštík & Mayer, 2006; Hosp & Luft, 2011). Since, neural plasticity seems to drive brain recovery in a similar way that promotes learning (Carmichael, 2010), therapeutic strategies based in motor training has been recommended to treat neurologic patients as those who suffered stroke, for example (Arya, Pandian, Verma, & Garg, 2011; Gauthier et al., 2008; Page, Szaflarski, Eliassen, Pan, & Cramer, 2009).

Some rehabilitation studies have already shown that plastic processes are promoted by long-term motor training; such changes comprise structural and functional effects on the motor cortex (Hluštík, Solodkin, Noll, & Small, 2004; Richards, Stewart, Woodbury, Senesac, & Cauraugh, 2008). Studies with monkeys and humans have shown that extensive practice increases cortical area involved with movement carried out. Nudo and colleagues (1996) showed an expansion of cortical representations of muscles involved in training task performed over several weeks by adult squirrel monkeys (Nudo & Milliken, 1996). Additionally, in other study performed with primates, a long-term motor training induced a reactivation of some neuronal networks of the primary motor cortex (M1) which were inactive before training (Kennedy & Bakay, 1997). In humans, motor training is also able to recruit additional neurons in M1 through the growth of active neural networks and expansion of cortical territory corresponding to the muscles involved in such task (Hluštík et al., 2004; Kawashima, Roland, & O'sullivan, 1994; Alvaro Pascual-Leone, Grafman, & Hallett, 1994).

Since learning-dependent plasticity has already been extensive identified, understand how learning principles could change post-stroke motor recovery would allow therapists to develop more suitable rehabilitation protocols with maximal neural plasticity responses. Even after decades of neuroscience research, there is still not a consensus regarding motor learning components. Here I will focus on those shown to be more relevant for motor recovery after learning-induce therapies, namely the amount, intensity, progression, specificity and repetition of movements (Ammann, Knols, Baschung, De Bie, & de Bruin, 2014; Han, Wang, Meng, & Qi, 2012; Kleim & Jones, 2008; Teasell, Bitensky, Salter, & Bayona, 2005).

Concerning the amount of training, several studies have shown how the lack of use can degrade neural circuits and, conversely, how extensive practice is able to shape and boos neural plasticity, in turn resulting in better motor performance. Functional and structural plasticity processes (i.e., cortical reorganization and synaptogenesis) have already been showed after intensive training in studies with animals as well as humans (Doyon & Benali, 2005; Doyon, Ungerleider, Squire, & Schacter, 2002; Kleim et al., 2002; Kleim, Swain, et al., 1998). The current literature points out for the existence of a positive dose-response relationship between the amount of daily practice and improvement of motor performance. Lohse and colleagues (2014) reviewed data from 37 randomized clinical trials performed with post-stroke patients to explore if there is a relationship between the time scheduled for therapy and the improvement in motor performance. Results showed higher improvements for patients who received high-dose *vs.* those who received low-dose. Additionally, larger quantities of motor training were able to predict greater recovery by itself (Lohse, Lang, & Boyd, 2014). In the same way, Kwakkel and colleagues (2004) performed a systematic review to address the effects of augmented exercise therapy time on activities of daily living (ADL), walking and dexterity in post-stroke: patients significantly improve their ADL performance if they underwent an intensive therapy (at least 16-hours difference *vs.* control groups) are applied in the first six months after stroke (Kwakkel et al., 2004).

Training frequency/intensity is also a key factor for a successful intervention and should be carefully considered when rehabilitation protocols are developed (Kwakkel, Wagenaar, Koelman, Lankhorst, & Koetsier, 1997; Langhorne, Wagenaar, & Partridge, 1996; Nelles, 2004; Page, 2003). Bell and colleagues (2015) trained mice on a skilled reaching task before and after focal ischemic lesions of the sensorimotor cortex. Rehabilitative training performed after lesions was applied in a high-frequency way (twice daily), low-frequency way (once daily) or even not applied as a control group. After the end of the training sessions, mice achieved the same level of motor performance as before the ischemic lesions independently of the training frequency (high *vs.* low); however, those mice receiving the high-frequency training presented with faster functional improvements (Bell, Wolke, Ortez, Jones, & Kerr, 2015). In a similar way, a randomized clinical trial performed by Han and colleagues (2013) analyzed the effect of different motor training intensities over the recovery of the paretic upper limb of 32 post-stroke patients. Results showed that patients underwent high-intensity (3 hours daily) motor training reached the best levels of function and sensorimotor recovery after four and six weeks of ended treatment (Saucedo Marquez, Zhang, Swinnen, Meesen, & Wenderoth, 2013).

Noteworthy, despite the fact that, overall the high-intensity training is more effective, in some instances it may be even detrimental. Animal studies have shown that mice forced to use only the

paretic limb in the acute phase after unilateral lesions of the sensorimotor cortex lost more tissue and reached worse motor function levels *vs*. mice that used both limbs - paretic and non-paretic (Humm, Kozlowski, James, Gotts, & Schallert, 1998; Kozlowski, James, & Schallert, 1996).

Progression is other very important motor training principle and is defined by Ammann and colleagues (2014) as *"a gradual and systematic increase of the workload over a period of time which results in improvements in fitness without risk of injury"* (Ammann et al., 2014). Progression is closely related to exercise difficulty and requires continuous monitoring of the training to not overstep the limits of individual motor capacities. Ideally, motor training should respect hierarchical levels providing increased and continuous task-related challenges (Bowden, Woodbury, & Duncan, 2013). Kleim and colleagues (1998) used a rat model of stroke to investigate changes in functional reorganization following motor skill learning. Rats receiving 10-days of skilled reach training, featured by a progressive increase in task difficulty, presented with a cortical reorganization of motor maps (Kleim, Barbay, & Nudo, 1998). Such evidence reinforces also the importance of task-specificity. Cortical structural changes, as dendritic growth and synaptogenesis, occur as a result of motor learning and/or functional training, and not as result of a mere task repetition: a massive practice is not enough, skill learning is required for driving neural plasticity (Maldonado, Allred, Felthauser, & Jones, 2008; Nudo, 2006; Plautz, Milliken, & Nudo, 2000). Perez and colleagues (2004) assessed, in 25 healthy individuals, the effects of a 32 minutes training of a skilled, non-skilled as well as passive task performed with the ankle on the cortical excitability. Results showed changes in cortical excitability represented by an increase in recruitment curves only after the motor learning skill training, while the mere repetition of the task, without any learning component, was unable to promote neuroplastic changes (Perez, Lungholt, Nyborg, & Nielsen, 2004). Using task-specific training to improve functional independence and performance in ADL of stroke patients is a widely spread strategy in neurorehabilitation (Langhorne, Bernhardt, & Kwakkel, 2011).

Motor map plasticity represents the main neural substrate for motor learning (Conner, Culberson, Packowski, Chiba, & Tuszynski, 2003): expansion of motor maps with dendritic branching, synaptic growth, and increased synaptic connections are induced by intensive motor training (Jones, Kleim, & Greenough, 1996; Liepert, Graef, Uhde, Leidner, & Weiller, 2000). For instance, Kleim and colleagues (2004) trained rats with a skilled reaching task during three, seven or ten days, then assessing the training effect on motor map topography/synaptic activity across different motor learning phases. They found that rats trained for three or seven days significantly improved reaching accuracy, but a remarkable increase of motor representations occurred only after ten days of training (Kleim et al., 2004). These results demonstrate again that learning can occur in the early stages of training, but the consolidation of such skill requires sufficient repetition of

movements (Monfils, Plautz, & Kleim, 2005). Moreover, protocols with an adequate number of repetitions may prevent degradation of the motor skill during time, even when motor practice is not performed after the end of training sessions.

However, in post-stroke rehabilitation it is also accepted the concept that recovery mediated by training, like learning in healthy subjects, is largely task-specific at both a behavioral and a cerebral level; only the interaction between learning-based practice and spontaneous biological, recovery-related, processes would be able to improve performance across tasks and context, leading to generalization effects that may affect also non-trained skills (Kleim & Jones, 2008).

1.3. Mechanisms Of Human Motor Learning

1.3.1. Motor learning stages

Motor learning is thought to emerge from many cognitive and motor processes, as acquisition, adaptation, consolidation, and reinforcement, which give rise to use dependent-plasticity (Krakauer & Mazzoni, 2011). Motor learning also occurs through some stages that go from explicit control in the beginning to an implicit control when tasks are learned (Halsband & Lange, 2006). Of relevance, motor learning is not a linear process. Periods of great improvement mixed with plateaus or even regression in performance can occur; even when it is not apparent at a behavioral level, learning processes may be still occurring (Newell & Rosenbloom, 1981; Shadmehr & Holcomb, 1997). Therefore, classically, the whole process of motor learning can be divided into three main stages: cognitive, associative and autonomous (Anderson, 1982; Fitts, 1964; Logan, 1988).

The cognitive or verbal-motor stage of learning is characterized by an early and fast improvement of performance which can be identified even within a single training session. Firstly, individuals need to process all the information provided to perform the task (Adams, 1971; Marinelli, Quartarone, Hallett, Frazzitta, & Ghilardi, 2017). Throughout the learning phases, we need to continuously analyze task requirements and the parameters of movement, keeping in mind the goals, while taking advantage of sensory feedback, as well as of verbal instructions. When facing a novel skill task, individuals are initially inaccurate and slow, performing movements in an irregular way; this is because they are still trying to understand what needs to be done (Anderson, 1982; Schmidt, Lee, Winstein, Wulf, & Zelaznik, 2018). Very likely, the key factor of this stage is to be capable of associate sensory cues with correct motor commands. Such ability depends on attention, decision, sensory-motor coupling, and working memory (Halsband & Lange, 2006; Petersen, Corbetta, Miezin, & Shulman, 1994). After the initial period of learning, declarative and attentional processes, as well as cognitive explicit strategies, seems to mediate large and fast

performance improvements. It is not known how long can this cognitive stage lasts, but it seems to depend on available verbal instructions and the task complexity (Marinelli et al., 2017).

The second stage of learning is the associative or motor stage, which is featured by slower, progressive improvement in motor performance requiring several training sessions. In such stage, sensory feedback and attentional processing still play a critical role because sensory cues have to be retained in working memory and translated in motor output (Deiber et al., 1997; Shadmehr & Mussa-Ivaldi, 1994). Gradually, performance becomes faster, accurate and consistent because task practice reinforces motor maps, and visual inputs can be rapidly transformed into precise motor responses. Implicit mechanisms become more prominent when individuals are performing motor patterns adjustments automatically (Halsband & Lange, 2006; Marinelli et al., 2017).

Finally, in the autonomous stage of learning, motor performance becomes largely automatic since it requires minimal attentional resources. Now the performance becomes resistant to interference from other simultaneous activities and to effects of time, which means that the skill is consolidated. Long-term practice results in a faster, effortless and accurate performance most likely due to movements that seem to be planned in a motor-center coordinate system rather than in a vision-center, as in the earlier learning stages. This means that a specific input can quickly restore an associated motor map, by which the motor output is promptly and accurately generated (Logan, 1988; Marinelli et al., 2017). Figure 4 illustrates the motor learning processes and main characteristics of each stage.

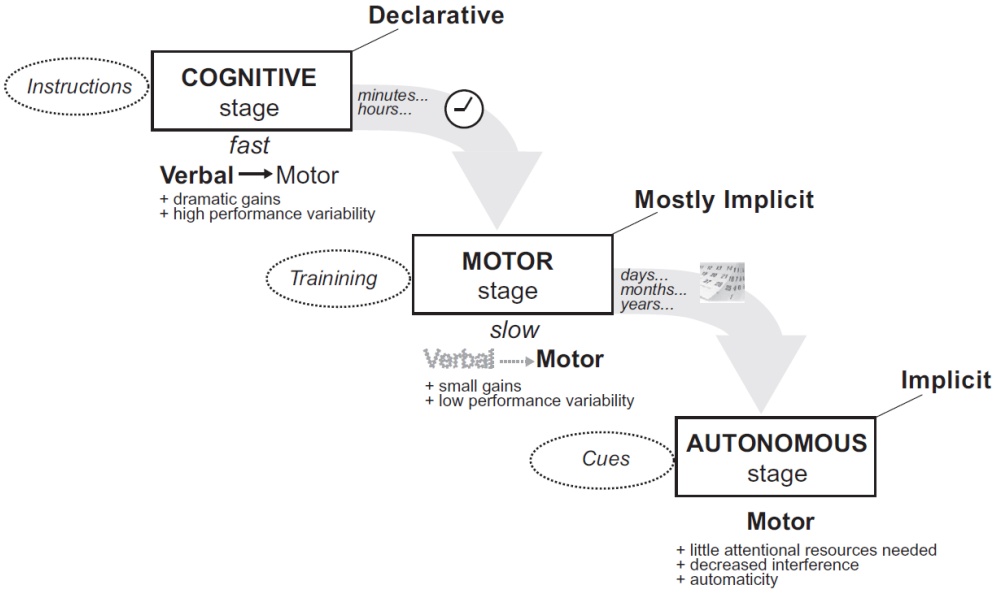

Figure 4. An illustrative diagram of motor learning stages. Source: Marinelli *et al.*, 2017.

1.3.2. Consciousness and learning: explicit and implicit processes

As previously explained, motor learning is thought to be built by many cognitive processes in which memory plays a key role: indeed, acquisition, adaptation, and consolidation of a new skill depend on it. Memory can be classified according to two systems: declarative and procedural (Nissen & Bullemer, 1987; Squire, 1987). Declarative memory refers to our conscious memory of facts, events or episodes. As in the verbal-motor stage of learning, it can be formed very quickly and it is intrinsically related to high-level cognitive processes such as planning and problem-solving (Squire et al., 1990; Vidoni & Boyd, 2007). Learning build up by declarative memories is known as explicit learning (Dennis & Cabeza, 2011; Willingham, 1998). In explicit processes, there is a conscious engagement in movement generation with a build-up of verbal and/or declarative task-relevant knowledge (Masters, 1992; Steenbergen, Van Der Kamp, Verneau, Jongbloed-Pereboom, & Masters, 2010). On the other hand, procedural memory stores information on how to do activities in our daily living (i.e., walking, playing sports). Procedural memory is formed only after long-term practice, which allows that the motor performance becomes automatic, without any need for cognitive control or attentional processes (Nissen & Bullemer, 1987; Willingham, Nissen, & Bullemer, 1989). Thus, learning build by procedural memories is known as implicit learning (Dennis & Cabeza, 2011; Willingham, 1998). In implicit processes, movement production is often made without awareness and unintentionally.

Explicit and implicit learning seems to occur through the engagement of different neural substrates (Henke, 2010), as illustrated in Figure 5 (Ashe, Lungu, Basford, & Lu, 2006). There is robust evidence from neuroimaging and neuropsychological studies as models of skill learning pointing out to the involvement of the dorsal premotor cortex, dorsolateral prefrontal cortex, supplementary motor area (Honda et al., 1998; Robertson, 2009; Vidoni & Boyd, 2007) and dorsomedial temporal lobes (Dennis & Cabeza, 2011; Eichenbaum, 2001; Squire & Zola, 1996) in explicit learning. Whereas implicit learning processes seem to involve the basal ganglia and cerebellum (Doyon et al., 2009; Hikosaka et al., 1999; Hikosaka, Nakamura, Sakai, & Nakahara, 2002). The role of the hippocampus is also hypothesized, but evidence remains inconclusive (Albouy et al., 2008; Schendan, Searl, Melrose, & Stern, 2003).

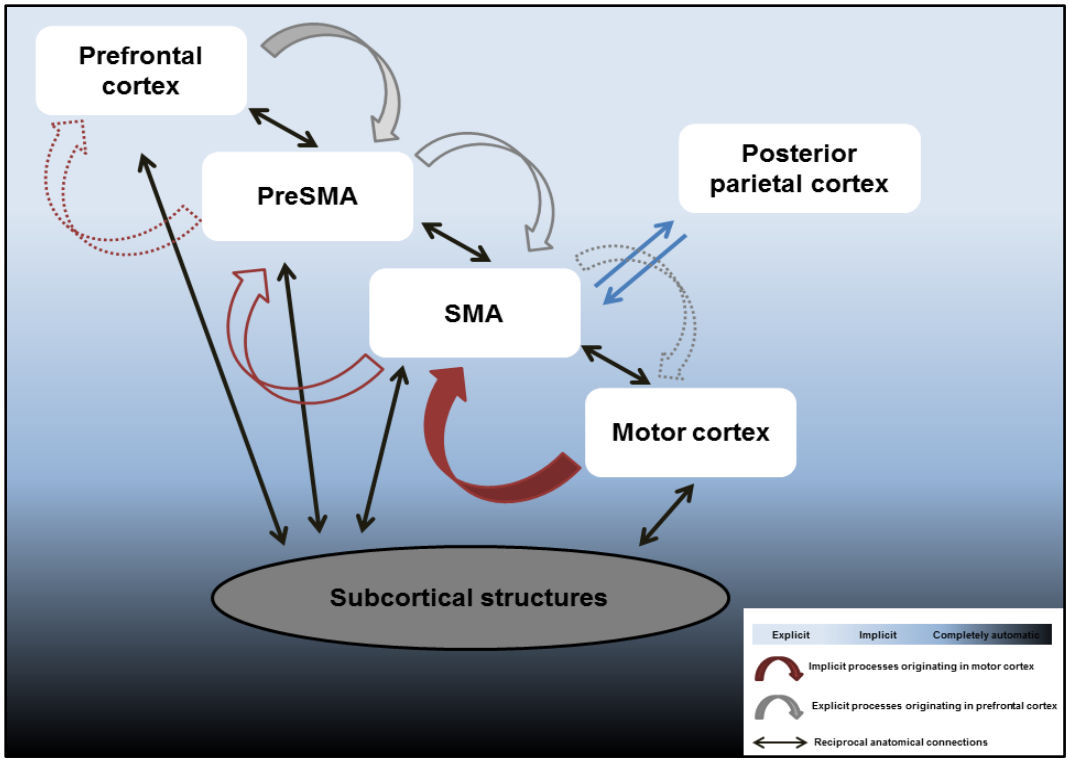

Figure 5. An illustrative diagram of neural substrates involved in implicit and explicit processes. Source: adapted from Ashe *et al*., 2006.

Although there is a recognized functional and neuroanatomic dissociation between explicit and implicit learning (Reber & Squire, 1998; Scoville & Milner, 2000), such processes do not work in an independent way. Instead, they dynamically interact during the learning process. There is even a competition between the explicit and implicit components of learning (Poldrack et al., 2001; Poldrack & Packard, 2003). Evidence from neuroimaging studies shown negative correlations between brain areas involved in explicit and implicit processes (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Poldrack et al., 2001; Poldrack & Gabrieli, 2001). For example, Poldrack and colleagues (2001) used functional magnetic resonance imaging (fMRI) to understand how human memory systems interact with each other during learning (Poldrack et al., 2001). Healthy individuals underwent different classification learning tasks designed to activate either declarative or non-declarative memory processes. Authors found reciprocal connection changes between the activation of the medial temporal lobe and striatum, which depended on the nature of learning tasks (declarative *vs*. non-declarative processes). Such changes were negatively correlated with each other, which means that while the medial temporal lobe was activated, the striatum was deactivated. Brown and Robertson (2007) have also explored whether off-line consolidation is supported by the interaction of declarative and procedural memories (Brown & Robertson, 2007). To this aim, two experiments were performed to examine the influence of declarative learning on procedural consolidation and, conversely, the influence of procedural learning on declarative

consolidation. In experiment 1, participants performed a motor skill learning through a serial reaction time task (SRTT); immediately after SRTT, they also performed a word-list learning and 12h later performance at the SRTT was retested. Authors found that the off-line motor improvement was blocked by the declarative learning tasks, over wake. Similarly, in experiment 2, participants learned a declarative word-list, immediately after that they performed the SRTT and 12h later the word-list recall was retested. Authors showed that declarative consolidation was blocked by the procedural learning over wake. Additionally, providing explicit information before performing a task seems to disrupt implicit learning as compared to learning without verbal instructions (Reber, 1976). This evidence confirms previous findings showing disruption of implicit learning by explicit processes in healthy individuals (Green & Flowers, 1991; Verdolini-Marston & Balota, 1994) as well as post-stroke patients (Boyd & Winstein, 2003, 2004, 2006). Together, such evidence highlights the existence of a competition between explicit and implicit processes.

1.3.3. Offline learning and the role of sleep

Motor learning depends on practice but does not occur only during it, rather substantial learning-induced improvements of performance may occur also offline (Robertson, Pascual-Leone, & Miall, 2004; Robertson, Press, & Pascual-Leone, 2005). Cognitive neuroscience research on motor learning indeed distinguishes the online learning and off-line learning. Online learning refers to the process that mediates fast improvements of performance during the first training sessions when individuals practice a new motor task; this mechanism leads to the initial encoding or acquisition of a memory. However, motor improvements also take place after the end of practice: this is the off-line learning, featured by gains occurring in the absence of additional practice, which are influenced by sleep (Censor, Sagi, & Cohen, 2012). During off-line learning, the online formed memories are reactivated resulting in memory modification that may be mediated by a process of reconsolidation that shapes the stabilization of memory traces after the motor acquisition phase (Krakauer & Shadmehr, 2006; McGaugh, 2000; Nemeth & Janacsek, 2010; Shadmehr & Holcomb, 1997). Successful consolidation processes include memory association and memory translocation. On one hand memory association is characterized by an integration of recently acquired information with past experiences, on the other hand, memory translocation is marked by an anatomical reorganization of representations (Walker, Brakefield, Hobson, & Stickgold, 2003; Walker & Stickgold, 2004).

Current evidence has shown that consolidation processes depend on the length of the off-line period. Previous studies have shown that there is a “critical period” for consolidation during wakefulness (Robertson, 2004; Roth, Kishon-Rabin, Hildesheimer, & Karni, 2005), with off-line

improvements emerging 1-2 hours after the training (Robertson et al., 2005), and in some cases taking up to 5-6 hours to emerge (Press, Casement, Pascual-Leone, & Robertson, 2005; Walker et al., 2003). Beyond the duration of the off-line period, various other factors affect learning consolidation, among which the type of task (implicit or explicit) and individuals features, as the participant's age (Diekelmann, Wilhelm, & Born, 2009; Doyon et al., 2009; Hallgató, Győri-Dani, Pekár, Janacsek, & Nemeth, 2013; Nemeth & Janacsek, 2010; Siengsukon & Al-Sharman, 2011). Undoubtedly, sleep seems to play the main role in the retention of memory (for an extensive review, see Rasch & Born, 2013), and thus, in consolidation processes (Hobson & Pace-Schott, 2002; Robertson, 2004; Stickgold & Walker, 2005; Walker, 2005; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Debas and colleagues (2014) have shown that off-line consolidation is indeed associated with a greater level of integration within the cortico-striatal system which is sleep-dependent (Debas et al., 2014).

Neuronal cortical plasticity and mechanisms of sleep-dependent consolidation of learning are tightly bound (Aton et al., 2009). Consolidation occurs during sleep through a reactivation of recently encoded neuronal memory representations: the same areas activated during wakefulness are reactivated in specific sleep phases - as slow-wave sleep (Born, Rasch, & Gais, 2006; Maquet et al., 2000; Peigneux et al., 2003; Rasch & Born, 2013; Stickgold & Walker, 2005). Such reactivation could be explained by the synaptic homeostasis hypothesis which postulates that synaptic potentiation mechanisms during wakefulness are linked to the activity of the slow-wave sleep (Tononi & Cirelli, 2003, 2006). In this context, an increase of LTP expression markers in a specific cortical area during wakefulness should be followed by higher levels of activity during slow-wave sleep in the same cortical area (Cirelli & Tononi, 2000). Previous studies investigating the sleep-effects of learning tasks have shown neuronal activity changes (Ghilardi et al., 2000; Schmidt et al., 2006) in line with the findings of Cirelli & Tononi (2000). In the same way, Huber and colleagues (2004) used high-density electroencephalogram in adults to show a correlation between higher levels of activity during slow-wave sleep in learning-related areas and improvements in motor performance (Huber, Ghilardi, Massimini, & Tononi, 2004).

Sleep can also modulate neuronal connections subtending long-term memory formation (Bhatt & Pai, 2009; Lichtman & Colman, 2000; Yang, Pan, & Gan, 2009). Indeed, off-line learning rates are larger when the consolidation period includes sleep, than in absence of sleep phase between learning sessions (Borragán, Urbain, Schmitz, Mary, & Peigneux, 2015; Fischer, Hallschmid, Elsner, & Born, 2002; Stickgold & Walker, 2007; Walker, 2005; Walker & Stickgold, 2004). There is also evidence that, under some circumstances, sleep may interfere with consolidation processes, but findings are still controversial. A recent meta-analysis by Pan and

Rickard (2015), involving 34 articles and 1.296 subjects, showed that despite an overall improvement of motor performance after sleep *vs.* wakefulness periods, there is no evidence that sleep enhances learning, with several factors affecting sleep consolidation in a non-linear way. Time of testing and training duration seem to impact more on the efficacy of consolidation processes than the sleep in itself (Pan & Rickard, 2015). In conclusion, current evidence is unable to define the role of sleep in long-term memory formation.

1.4. Neural Substrates Of Motor Learning

A wide cerebral network comprising the primary motor cortex (M1), the premotor cortex (PM), the posterior parietal cortex (PPC), the supplementary motor area (SMA) and subcortical structures is responsible for action planning, execution and control (Battaglia-Mayer & Caminiti, 2009; Kaas, 2012; Kalaska, Scott, Cisek, & Sergio, 1997; Scott, 2008; Scott & Kalaska, 1995). Such brain areas also play an essential role in the acquisition of motor skills and, thus, in motor learning (Hardwick, Rottschy, Miall, & Eickhoff, 2013). In the following, I will focus on the specific contribution of M1, PM, and PPC in motor learning processes.

1.4.1. Role of M1

M1 is dorsally located in the frontal lobe of the brain and plays a crucial role in human movement control. Traditionally, M1 is considered a motor output area and thus, the executive area of voluntary movements (Porter & Lemon, 1993; Scott, 2003). Neuronal firing rates in M1 are correlated with muscle activations, joint positions as well as the generation of complex movements (Georgopoulos, Kalaska, Caminiti, & Massey, 1982; Graziano, Taylor, & Moore, 2002; Kakei, Hoffman, & Strick, 1999). Additionally, M1 plays a role in encoding kinematic aspects of movement, like force and acceleration (Ashe, 1997; Georgopoulos, Ashe, Smyrnis, & Taira, 1992). Further, there is an organization of movement categories and postures in motor cortex (Graziano, Aflalo, & Cooke, 2005; Graziano et al., 2002): indeed functional relevant movement maps described are encoded in M1, as described in rodents as well as humans (Eisenberg, Shmuelof, Vaadia, & Zohary, 2010; Harrison, Ayling, & Murphy, 2012; Matyas et al., 2010; Ramanathan, Conner, & Tuszynski, 2006; Toxopeus et al., 2011).

Beyond that, there is robust evidence showing that M1 is also involved in motor learning, motor imagery, and cognitive processes (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Lu & Ashe, 2015; Nudo & Milliken, 1996; Pascual-Leone et al., 1995; Sanes & Donoghue, 2000). Since M1 is full of dopaminergic terminals, an excitatory stimulation of their neurons would be able to

potentialize motor learning (Luft & Schwarz, 2009; Rioult-Pedotti, Donoghue, & Dunaevsky, 2007; Rioult-Pedotti, Friedman, & Donoghue, 2000). Cellular mechanisms which could explain such learning improvement may are related to the modulation of LTP - a persistent increase in the strength of synaptic connections - as well as to functioning NMDA-specific glutamate receptors (Hasan et al., 2013; Reis & Fritsch, 2011). Indeed, Molina-Luna and colleagues (2009) showed that blocking dopaminergic activity in M1 hampers LTP and consequently, the effectiveness of skill learning (Molina-Luna et al., 2009). Additionally, Hasan and colleagues (2013) showed that NMDA receptors of M1 are necessary for activity-dependent synaptic strengthening and associative learning since the loss of NMDA receptor function impaired LTP in mice with deletion of the *Grin1* gene (Hasan et al., 2013).

Although M1 is recruited in every stage of motor learning, namely acquisition, consolidation and retention of learning (Muellbacher et al., 2002; Nitsche et al., 2003), online and off-line learning differently affect M1 activity. Some evidence indicates M1 activation during the initial fast stage of learning, while other studies point out to a decrease in its activity or even no change during online learning (Doyon et al., 2002; Toni, Krams, Turner, & Passingham, 1998). M1 activity is also increased during the slow phase of learning (Dayan & Cohen, 2011; Floyer-Lea & Matthews, 2005; Karni et al., 1998). Huang and colleagues (2013) used functional magnetic resonance imaging and a classic motor training task to investigate learning-induced changes in multi-voxel spatial patterns of neural activation. The authors showed that the stability of the activation patterns after training, that is the similarity of the activation patterns between fMRI scans, was significantly increased in M1 and thus, suggested that learning shapes the brain through an increase in its activity (Huang et al., 2013). Additionally, a series of studies performed by Pascual-Leone and colleagues also showed M1 maps enlargements following motor skill learning (Pascual-Leone, Amedi, Fregni, & Merabet, 2005; Pascual-Leone et al., 1994; Pascual-Leone, Peris, Tormos, Pascual, & Catala, 1996). Healthy individuals performed a 5-finger exercise on the piano during 2h over 5 days of practice. Daily TMS mapping of M1 maps and excitability showed a significant enlargement of cortical motor areas of flexor and extensor fingers muscles only of the trained hand, along with a decrease of the motor threshold of such muscles after learning, which means that learning increased M1 activity. Such effects were obtained even when participants underwent a mental practice task (i.e., imagination without the real execution of the training). Importantly, the reorganization of M1 areas representing the trained fingers emerged immediately at the end of the training, and it was maintained in the long-term after the end of the practice.

1.4.2. Role of the Premotor Cortex

Comprising the anterior lip of the precentral gyrus, the premotor cortex (PM) occupies part of Brodmann's area (BA) 6, lying between the dorsolateral prefrontal cortex (DLPFC) and M1. Such strategic position allows the PM to play a critical role in higher level cognitive aspects of motor control: PM receives direct inputs from M1, DLPFC, and posterior parietal cortex and it projects back to M1 (Kantak, Stinear, Buch, & Cohen, 2012). PM is involved in goal-directed actions (e.g., grasping), motor planning as well as movement selection, retention and releasing (Gremel & Costa, 2013; Kroeger et al., 2010; Mochizuki, Franca, Huang, & Rothwell, 2005; Sugawara, Onishi, Yamashiro, Kirimoto, et al., 2013). Additionally, substantial sensorimotor interactions occur in PM, allowing the integration of sensory information into motor commands in order to shape movements amplitude, direction, and speed. Pesaran, Nelson, and Andersen (2006) have shown that during the elaboration of goal-oriented reach actions, PM neurons encoded the relative localization of the target, hand, and eye (Pesaran, Nelson, & Andersen, 2006). PM neurons are also activated during the preparation, decision-making and online movement control of reaching movements (Beurze, De Lange, Toni, & Medendorp, 2007; Kurata, 1993; Lee & van Donkelaar, 2006; Pardo-Vazquez, Leboran, & Acuna, 2008). Indeed, a series of studies performed by Davare and colleagues showed that a virtual lesion of the ventral PM in humans alters finger's positioning during grasping (Davare, Andres, Cosnard, Thonnard, & Olivier, 2006; Davare, Lemon, & Olivier, 2008; Davare, Montague, Olivier, Rothwell, & Lemon, 2009).

As discussed in the previous sessions, motor learning is thought to involve many cognitive processes, which include premotor cortical functions such as movement selection and planning (Hardwick et al., 2013; Taylor, Krakauer, & Ivry, 2014). For instance, Steele and Penhune (2010) used functional magnetic resonance imaging (fMRI) to explore the neural underpinnings of motor learning stages (early learning, consolidation, and retention): the results showed an activation of the dorsal portion of PM primarily during the early learning stage (Steele & Penhune, 2010). Across days of learning, as performance improves, there is a decrease in PM activity. The engagement of such area during the early stages of motor learning most likely is related to its role in movement selection and planning. Cross and colleagues (2007) examined the neural substrates of contextual interference during motor learning using fMRI and found higher blood oxygen level-dependent (BOLD) activation in PM and sensorimotor regions during random-order compared with blocked-order practice, in line with the need of improving the capacity to actively prepare motor responses when different tasks are randomly intermixed in practice (Cross, Schmitt, & Grafton, 2007).

The ventral portion of PM is specifically involved in observational and imitation learning, given the presence of *mirror neurons* (Rizzolatti & Craighero, 2004; Vogt et al., 2007). *Mirror*

neurons are visuomotor neurons that fire while activities are performed as well as when such activities (or similar ones) are merely observed (Di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Some studies have investigated which are the neural networks engaged in imitation learning and how such process could be modulated by the type of action presented as well as the tasks required during action observation. For instance, Grèzes and colleagues (2003) showed an activation of the ventral portion of PM when participants imitated gestures or executed movements in response to objects (Grèzes, Armony, Rowe, & Passingham, 2003), while Buccino and colleagues (2001) showed that imitation learning relies on a neuronal circuit comprised of the inferior parietal lobule, the posterior part of the inferior frontal gyrus and the adjacent PM (Buccino et al., 2001).

The PM is also part of a neuronal network which encodes intermanual transfer – a form of learning generalization that seems to occur in motor and perceptual domains (Censor & Sagi, 2009). The main areas of such network are PM, SMA, and M1 (Grafton, Hazeltine, & Ivry, 2002; Japikse, Negash, Howard, & Howard, 2003; Perez et al., 2007; Perez, Tanaka, Wise, Willingham, & Cohen, 2008). In conclusion, PM is a highly connected key structure that underlies human motor control, the learning of goal-oriented actions and the sensorimotor integration (Hardwick et al., 2015; Kantak, Stinear, et al., 2012).

1.4.3. Role of PPC

PPC is a multisensory area with extensive anatomical and functional connectivity with sensory areas, which mediates various sensorimotor and cognitive functions (Bucci, 2009; Goard, Pho, Woodson, & Sur, 2016; Licata et al., 2017; Vingerhoets, 2014). In particular, PPC is associated with visuomotor integration, spatial attention, spatial and body awareness and sensory integration (Capotosto, Babiloni, Romani, & Corbetta, 2011; Colby & Goldberg, 1999; Iacoboni, 2006; Mohan, de Haan, Mansvelder, & de Kock, 2017).

In the last years several studies have also pointed out to a role of PPC in some aspects of action, including movement planning, decision-making, online motor control and sensory orientation of movements (Andersen & Buneo, 2002; Convento, Bolognini, Fusaro, Lollo, & Vallar, 2014; Desmurget et al., 2009; Gold & Shadlen, 2007; Oliveira, Diedrichsen, Verstynen, Duque, & Ivry, 2010; Reichenbach, Bresciani, Peer, Bülthoff, & Thielscher, 2010). Indeed, functional connectivity changes detected between PPC and M1 in response to sensorimotor learning. Karabanov and colleagues (2012) underwent healthy individuals to 10 minutes of training in which individuals should tap their right index finger in response to a rhythmic (visual or auditory sequence) (Karabanov et al., 2012). By using TMS and electroencephalography, the authors

demonstrated an increase of the regional and interregional connectivity between PPC and M1 during the early phases of learning, which significantly decreased in the late phases. In fact, at initial phases of learning, individuals should integrate sensory information into coherent movement plans, but as soon as movements become more and more automatized, activation of PPC-M1 becomes less necessary.

Sensory guidance of movements and response selection are also mediated by PPC activity during visuomotor learning. Sugawara and colleagues (2013) used a Go/NoGo task to assess cortical visuomotor processing through magnetoencephalography (MEG) in healthy humans (Sugawara, Onishi, Yamashiro, Soma, et al., 2013). Results showed the critical role of PPC to visuomotor performance: its activation was found only during the Go condition, which can be attributed to response selection based on the visual cue. After the learning phase, changes in motor performance and neuronal activity were featured by reductions of the response time and the latency of PPC activation.

Another example is the study by Della-Maggiore and colleagues (2004), who used TMS to disrupt PPC activity and examine its role during learning new dynamics of arm movement (Della-Maggiore, Malfait, Ostry, & Paus, 2004). Healthy individuals underwent training requiring to make reaching movements with the right hand in a velocity-dependent force field. While individuals performed the task, single-pulse TMS was applied over the left PPC 40m sec after the onset of each movement. A control group performed the same training, but single-pulse TMS was applied over the visual cortex. Authors found that both groups (experimental *vs.* control) presented similar motor performance during the early stages of learning. However, at later stages of learning, while the control group presented a decrease of errors rates, the group receiving rTMS over PPC showed higher error rates. Such findings point out to the influence of PPC in tasks requiring online sensory-based adjustment of motor commands. Together, this body of evidence highlights the crucial role of PPC in a wide range of sensorimotor and cognitive functions.

1.5. Transcranial Direct Current Stimulation

1.5.1. Technical aspects and Mechanisms of action

The use of electrical stimulation to treat medical conditions dates from antique Greece when Plato and Aristotle used animal electricity (Althaus, 1873; Harris, 1908; Rockwell, 1896). Still, in the first century, a physician called Scribonius Largus used torpedo fish to deliver electric shocks to the forehead of patients and treat headache (Baldwin, 1992). Over the following 17th and 18th

centuries, transcranial current stimulators were developed and have evolved from galvanic batteries, when Volta created the first electrochemical battery, to microcontroller techniques in the 20th century. Such devices allowed the wide spreading use of direct current as a therapeutic tool (Piccolino, 2000; Priestley, 1769; Sarmiento, San-Juan, & Prasath, 2016).

In the mid-20th century, it was shown that direct current applied on the sensorimotor cortex of anesthetized rats could modulate cortical excitability with long-lasting effects - hours after the end of stimulation (Bindman, Lippold, & Redfearn, 1964). Contemporaneously, Cerletti successfully treated patients with Schizophrenia, Mania and severe Depression with brain stimulation turning electroconvulsive therapy in a popular technique (Accornero, 1988; Lewis, Thomson, Rosenfeld, & Fitzgerald, 2016). In the following years, experiments with healthy individuals as well as with psychiatric patients showed that direct current could also be used into the brain via transcranial application to induce physiological and functional effects (Dymond, Coger, & Serafetinides, 1975; Lolas, 1977; Rush & Driscoll, 1968). Finally, in the years 1998-2000, tDCS was confirmed as a neuromodulatory tool of human brain activity prompting systematically investigations of its neurophysiological and behavioral effects in healthy and pathological conditions (Lefaucheur et al., 2017; Nitsche & Paulus, 2000; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998).

tDCS differs from other NIBS techniques such as Transcranial Magnetic Stimulation because it does not induce neuronal action potentials (Nitsche et al., 2008). Rather, tDCS is a neuromodulatory tool: it applies scalp electrodes to deliver a continuous electrical current that modulates the likelihood of neuronal firing. The primary mechanisms of tDCS action is a polarity-dependent shift of cortical excitability (Stagg & Nitsche, 2011). Depending on current flow direction relative to the axonal orientation, such shifting induces a depolarization or hyperpolarization of neurons (Bindman, Lippold, & Redfearn, 1962; Purpura & McMurtry, 1965): while anodal tDCS typically increases cortical excitability, cathodal tDCS decreases it (Nitsche & Paulus, 2000). However, such pattern of polarity-specific tDCS effects should not be assumed as a general rule since behavioral changes induced by shifts in cortical excitability are also mediated by many different factors, such as the cerebral cytoarchitecture of the stimulated area and the neural state (Fertonani & Miniussi, 2017). Thus, depending on the *nature* of a particular neuronal population (whether they are excitatory or inhibitory neurons), an anodal tDCS does not always leads to excitatory responses and vice versa. Indeed, some studies have reported results in which the direct relationship between polarity-specific tDCS effects and behavioural findings was not confirmed (Antal et al., 2004; Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Hsu, Tseng, Liang, Cheng, & Juan, 2014; Moliadze, Atalay, Antal, & Paulus, 2012; Peters, Thompson, Merabet,

Wu, & Shams, 2013; Zwissler et al., 2014). Additionally, tDCS effects depended on the brain excitability state (i.e., the level of on-going activity) at the time of stimulation, which changes according to the task that is being performed (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Bortoletto, Pellicciari, Rodella, & Miniussi, 2015). Importantly, tDCS does not only modulate brain activity during the stimulation, but it also induce after-effects, namely long-lasting changes in cortical excitability maintained in the long-term. Such effects are dose-dependent. Stimulation of short duration (several seconds or few minutes) is capable to induce only short-lasting and reversible neurophysiological/behavioural effects (Priori et al., 1998; Vallar & Bolognini, 2011). Long-lasting effects require longer (several minutes), multiple and consecutive applications of tDCS (Santarnecchi et al., 2014; Touge, Gerschlager, Brown, & Rothwell, 2001). Nine to 13 minutes of tDCS is able to change cortical excitability for up than 1 hour after the end of stimulation (Nitsche & Paulus, 2001). Importantly, after effects are associated to changes in intracellular Ca^{2+} levels, protein synthesis and modulation of the responses of GABA and NMDA receptors, which in turn induce mechanisms of neuroplasticity similar to those described for LTP and LTD (Malenka & Bear, 2004; Gillick & Zirpel, 2012). Non-synaptic effects based on changes of conformation and function of axonal molecules, as well as cytoskeleton or axonal transport, may also contribute to tDCS long-lasting after effects (Ardolino, Bossi, Barbieri, & Priori, 2005; Jefferys, 1995). It should not be ruled out that non-neuronal effects as changes in endothelial cells, lymphocytes or glial cells can also contribute to the therapeutic effects of tDCS since almost all tissues/cells of our body are sensitive to electric fields (Ruohonen & Karhu, 2012), but the role of such non-neuronal effects is still poor understood.

Many factors shape the neuroplastic effects of tDCS, among them the duration, density, polarity of the current, electrodes size and montage. Electric current density determines the intensity of the electric field that is delivered in the brain tissue (Purpura & McMurtry, 1965). In humans, higher current densities tend to result in strong and long-lasting tDCS effects (Nitsche & Paulus, 2001), although there is not a linear relationship between those effects and current intensity. According to McCreery and colleagues (1990), current densities below than 25mA/cm² seem to be safe since they were not able to damage brain tissue in cats even after hours of stimulation (McCreery, Agnew, Yuen, & Bullara, 1990). It is clear the importance of adopting stimulation protocols that prioritize the safety and comfort of healthy individuals as well as patients.

Electrode's size is also an important parameter, which should be carefully taken in consideration for successful stimulation. M1 excitability can be effectively modulated via electrodes of $3.5cm^2$. If compared to larger electrodes (as those of $35cm^2$), smaller ones are able to induce more specific and focal cortical excitability changes (Nitsche et al., 2007). However, It should be

highlighted that tDCS applied via smaller electrodes is more susceptible to deviations of current in the scalp (Roth, 1994). Thus, larger electrodes have similar neuromodulation capacities of the smaller ones, but with a higher security and less heterogeneous effects (Boros, Poreisz, Münchau, Paulus, & Nitsche, 2008). Current flow and neuroplastic tDCS effects are intrinsically related to electrode's montage. Usually, the unilateral montage is the standard one, in which the *active* electrode is placed over the target area (cortical area over the scalp to be stimulated), while the *reference* electrode is placed over the contralateral supraorbital area. The 10/20 electroencephalography system is commonly used to proper localize the target cortical area. *Active* and *reference* electrode are nomenclatures adopted to distinguish which electrode is used for stimulating the brain (active) and which one is used as a reference. However, the term "reference" electrode is somewhat problematic, because the reference electrode is not physiologically inert and can contribute to activity modulation as well. This could be a potential confounder. There are different ways to positioning electrodes: when one electrode is placed below the neck, the entire montage is usually described as "unipolar". In contrast, montages with two electrodes on the head are termed usually as "bipolar" (Nitsche et al., 2008). There is also the possibility to use bilateral montages in which both electrodes are *active* and thus, are placed bilaterally over the target cortical areas.

Related to the electrodes dimension there is also the issue of the spatial resolution of tDCS, which is overall quite low. tDCS effects are not only local, they indeed arise from the modulation of the activity of a neural network, which include alteration of subcortical and cortical areas functionally and anatomically connected to the directly stimulated area. In fact, tDCS effects are mediated by changes in functional connectivity, neural synchronization and oscillatory activity (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). It is also important to keep in mind that such effects are intrinsically related to individual factors such as age, gender, baseline activity of the neural networks as well as neuronal responsivity at the stimulation time (López-Alonso, Fernández-del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015; Ziemann & Siebner, 2015). Of main relevance, tDCS-induced plastic effects depend on whether the stimulation is applied coupled to a cognitive and/or motor task or no (Antal, Terney, Poreisz, & Paulus, 2007).

1.5.2. tDCS as a neuromodulatory tool of motor learning

Evidence in healthy adults

Encompassing cognitive and motor mechanisms as acquisition and consolidation of skills, motor learning depends on practice but also occurs off-line (i.e., improvements between sessions of practice are attributed to the stabilization of memory traces after the online motor acquisition). Due to such characteristics, motor learning constitutes a vast and complex process that could be modulated by tDCS (Reis & Fritsch, 2011; Reis, Robertson, et al., 2008; Reis, Swayne, et al., 2008). Indeed, tDCS is able to facilitate synaptic plasticity mediated by LTP mechanisms and thus, it may facilitate long-term memory formation (Rroji, van Kuyck, Nuttin, & Wenderoth, 2015). Additionally, the possibility to associate tDCS with various learning paradigms allows a better understanding of the processes underlying learning, as well as how specific neuronal networks are involved in such processes (Dayan & Cohen, 2011; Doyon et al., 2002; Karni et al., 1998).

Current evidence regarding the use of tDCS protocols to modulate motor behavior in healthy individuals is extensive and, so far, many studies have defined the specific timing and polarity of tDCS effects. Stagg and colleagues (2011) investigated the timing-dependent interaction between tDCS and a sequence learning task (Stagg et al., 2011). Healthy individuals underwent a series of experiments in which anodal, cathodal or sham tDCS was applied over M1 before or during a sequence learning task. Authors found that: (i) active tDCS (anodal or cathodal) applied before the motor task resulted in slower learning rates (*vs.* sham stimulation) and (ii) anodal tDCS applied during the motor task increased motor learning, while cathodal tDCS applied during the motor task decreased it. Such results reinforced the idea that tDCS interacts with learning processes via metaplastic mechanisms. Online and/or off-line improvements of motor learning after one single session of tDCS have been identified mostly in studies using anodal stimulation concurrently to the learning task in young and old adults (Cuypers et al., 2013; Kang & Paik, 2011; Karok & Witney, 2013; Zimerman et al., 2013). Improvements in learning retention and consolidation were also identified after multiple sessions of tDCS coupled with motor training (Reis et al., 2013; Waters-Metenier, Husain, Wiestler, & Diedrichsen, 2014).

A systematic review and meta-analysis performed by Hashemirad and colleagues (2016) investigated the impact of the number of anodal tDCS sessions on motor learning and showed that multiple sessions are superior in terms of motor improvement than a single session. Authors suggested that three to five consecutive days of training is enough to boost motor learning (Hashemirad, Zoghi, Fitzgerald, & Jaberzadeh, 2016). The *nature* of the task is also a key factor to effectively change motor behavior. Nowadays, a number of tasks have been used to assess motor learning processes, but tDCS has been frequently associated to task paradigms as the serial reaction time task (SRTT), the sequential finger tapping task (SEQTAP) and the visual isometric pinch force task (SIVPT). Such paradigms allow to specifically investigate the motor *sequence* learning, which

constitutes the human inherent ability to learn sequential actions (Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003). Additionally, these tasks are easy to do but they have also the complexity that enables researchers to manipulate their characteristics and study learning over long periods (Buch et al., 2017).

Anodal tDCS applied over M1 facilitates implicit motor learning as measured by studies in which the SRTT was used. Kang and colleagues (2011) applied for 20 minutes (intensity: 2mA, electrodes of 25cm^2) in healthy right-handed adults while they performed the SRTT (Kang & Paik, 2011). In a randomized cross-over experiment, participants underwent 3 experimental sessions, during which they could receive: (i) anodal tDCS; (ii) bihemispheric tDCS or (iii) sham tDCS. Motor performance of participants was assessed before, immediately after and 24 hours after the training by the reaction time ratios. Authors found an overall decrease in mean reaction time ratios immediately after the training in all conditions, but such decrease was maintained for 24 hours only in the active tDCS groups. In the same way, Kantak and colleagues (2012) applied anodal tDCS for 15 minutes (intensity: 1mA, electrodes of 8cm^2-anode and 48cm^2 -cathode) in healthy individuals while they performed a modified version of the SRTT (Kantak, Mummidisetty, & Stinear, 2012). Active anodal tDCS was applied over M1 or over PM. Results showed that anodal tDCS applied over M1 increased implicit learning (*vs*. sham stimulation) and, additionally, promoted the off-line stabilization of such learning.

Anodal tDCS applied over M1 also facilitates online motor learning and early consolidation of procedural learning as assessed by the SEQTAP task. In healthy individuals, Saucedo Marquez and colleagues (2013) applied anodal tDCS (intensity:1mA for 20 minutes, electrodes of 25cm^2) in healthy individuals during a 5-digit SEQTAP (Saucedo Marquez et al., 2013). In a double-blind, sham-controlled design, participants underwent 2 experimental conditions separated by at least 2 months: (i) in one condition – they received anodal or sham tDCS during a 3-days training with SEQTAP; (ii) in condition two – participants underwent a different task, i.e., SIVPT. Authors showed that anodal tDCS enhanced online and off-line motor learning when coupled with the SEQTAP, while it improved long-term retention when coupled with the SIVPT. The SIVPT assesses skill acquisition of an isometric pinch force task, while the SEQTAP assesses sequential learning. Hence, the different effects on online, off-line and retention processes suggest a task-specific tDCS effect. Tecchio and colleagues (2010) applied anodal or sham tDCS (1mA for 15 minutes, electrodes of 35cm^2) immediately after healthy individuals performed a modified version of the SEQTAP (Tecchio et al., 2010). Participants were randomized in two groups: (i) anodal tDCS or (ii) sham tDCS. Authors found that only when tDCS is applied soon after the training, it improves the early consolidation of procedural learning *vs.* sham stimulation. Finally, in a series of

experiments, Rumpft and colleagues (2017) besides showing that anodal tDCS applied over M1 after a SEQTAP improves motor learning consolidation, they also found that the "optimal time window" for application of tDCS is immediately after the end of training, as compared to 60 or 120 minutes after the training (Rumpf et al., 2017), at least in elderly. Furthermore, some studies applied tDCS to the cerebellum in order to improve motor learning. Cantarero and colleagues (2015) used a bipolar electrode montage to apply anodal, cathodal or sham tDCS (2mA for 20 minutes, electrodes of 25cm^2) over the cerebellum in healthy individuals while they performed a motor skill training. Results showed that anodal cerebellar tDCS increased motor acquisition, as compared to sham and cathodal tDCS. Such effects were larger on online learning than on off-line learning (Cantarero et al., 2015).

The body of evidence presented above reinforces the rationale of using tDCS to improve online and off-line motor learning in healthy individuals, at least when M1 is the target area.

Evidence in healthy children

In the last years, an emerging body of studies is investigating tDCS effects in pediatric populations. To date, the majority of these studies assessed feasibility, safety and tolerability of tDCS protocols in children with cerebral palsy, dystonia, autism and psychiatric disorders, showing its feasibility and safety in childhood, as long as safety guidelines from adults are followed (Bikson et al., 2016; Hameed et al., 2017; Krishnan, Santos, Peterson, & Ehinger, 2015; Palm et al., 2016).

Even so, current knowledge about tDCS effects in brain function and clinical improvements in children is still very scarce. Before moving forward in this field, some concerns are being raised since such population has several structural and functional differences of the brain compared to adults. The first concern is the continuous state of developing of the brain because children are more prone to present intensive neuronal plasticity (Brunoni et al., 2012; Kolb & Teskey, 2012; Stortelder & Ploegmakers-Burg, 2010) and thus, physiological changes induced by neuromodulation might lead to different and unexpected results when compared to adults (Palm et al., 2016; Zhao et al., 2017). The second concern is related to brain structural differences: children have a smaller head, thinner cranial bone and differences in the gray and white matter (Ciechanski, Carlson, Yu, & Kirton, 2018; Rivera-Urbina, Nitsche, Vicario, & Molero-Chamizo, 2017). Thus, in order to explore the feasibility of neuromodulation in childhood, a key factor seems to be the needing of adjusting tDCS dose to compensate such structural and functional differences of the brain guaranteeing safety parameters. Minhas and colleagues explored such adjustments through computational model and showed that the tDCS-induced electric field is stronger in children

compared to adults (Minhas, Bikson, Woods, Rosen, & Kessler, 2012). Recently, some studies performed with pediatric populations have also confirmed these findings and highlighted the need for dose optimization in such population (Fiocchi, Ravazzani, Priori, & Parazzini, 2016; Gillick, Kirton, Carmel, Minhas, & Bikson, 2014; Kessler et al., 2013; Parazzini, Fiocchi, Liorni, Priori, & Ravazzani, 2014; Parazzini, Fiocchi, Liorni, & Ravazzani, 2015).

Since current knowledge regarding the underpinnings of tDCS on the developing brain is still very scarce, it is urge to understand how modulation changes brain function of typically developed children through randomized clinical trials, before move to clinical pediatric populations. In this context, with respect to motor learning, so far only one study was performed in healthy school-aged children (Ciechanski & Kirton, 2017). Twenty-four right-handed children (mean age 14 ± 3.2 years) underwent 4 tDCS conditions: (i) anodal tDCS over the right M1 at 1mA; (ii) cathodal tDCS over the left M1 at 1mA; (iii) cathodal tDCS over the left M1 at 2mA or (iv) sham tDCS. Over 3 consecutive days of motor practice, children performed with their left (non-dominant) hand the Purdue Pegboard Test (PPT) while received 20 minutes of stimulation. Results showed that motor learning increased over the training days in all children, but those who received active tDCS (in particular anodal and cathodal tDCS at 1mA) achieved better learning rates *vs*. those receiving sham tDCS. Such improvements were also achieved earlier, which means that tDCS anticipated the emergence of learning. At the Jebsen Hand Function Test, administered before and after the training, the larger gains emerged following anodal tDCS. Motor learning improvements were also maintained after 6 weeks of the end of training: children who received active tDCS still showed larger improvements than those receiving sham tDCS.

Evidence in post-stroke patients with upper limb hemiparesis

Due to its capacity to shape cortical excitability of brain areas specifically involved in motor learning, tDCS has been also widely used to improve motor function of stroke patients underwent to neurorehabilitation. Its use is particularly widespread with regard to the recovery of upper limb function of such patients since most of them do not achieve a complete recovery, especially of hand and arm function. Further, by modulating motor learning, tDCS can be used to drive neuroplastic changes promoted by rehabilitation protocols in stroke patients (Bolognini, Pascual-Leone, & Fregni, 2009; Brunoni et al., 2012).

Currently, there is a robust body of evidence showing that motor training combined with tDCS improves motor function of stroke patients (Klomjai et al., 2015; Lüdemann-Podubecká, Bösl, Rothhardt, Verheyden, & Nowak, 2014; Wessel, Zimerman, & Hummel, 2015). However,

behavioral and neurophysiological evidence specifically related to the effects of tDCS on the stages of motor learning in such patients is still scarce. Based on the model of interhemispheric imbalance, some studies assessing tDCS effects on motor learning of stroke patients have used three main approaches: (i) apply anodal tDCS over M1 of the hypo-functioning ipsilesional hemisphere; (ii) apply cathodal tDCS over M1 of the hyper-activated contralesional hemisphere or (iii) apply bilateral tDCS on both hemispheres (anodal over the ipsilesional and cathodal over the contralesional M1). So far, evidence coming from these studies have showed that tDCS of M1 in stroke patients with upper limb hemiparesis: improves online motor learning (Fleming, Rothwell, Sztriha, Teo, & Newham, 2017; Hamoudi et al., 2018; Lefebvre et al., 2014; Lefebvre et al., 2013; Zimerman et al., 2012), improves the retention of the learned motor skills (Lefebvre et al., 2014; Lefebvre et al., 2013; Zimerman et al., 2012), but it does not change generalization processes (Hamoudi et al., 2018) and may positively change functional connectivity of the ipsilesional M1 (Fleming et al., 2017; Lefebvre et al., 2017; Lefebvre et al., 2014; Zimerman et al., 2012).

Improvements in online motor learning have been reported after all types of stimulation (anodal, cathodal or bihemispheric tDCS). For instance, recently Hamoudi and colleagues (2018) performed a randomized, sham-controlled study with 36 chronic stroke patients underwent to five consecutive days of training coupled to tDCS (Hamoudi et al., 2018). Sham or anodal tDCS over the ipsilesional M1 (1mA for 20 minutes, electrodes of 25cm^2) was applied while patients performed a modified version of the SIVPT with their paretic hand for 45 minutes (5 x 20 trials). A third group with 18 patients was used as control (no training and no tDCS). Authors found that while tDCS increased more online learning *vs*. sham, it did not affect long-term retention. Conversely, training alone improved online learning less than when it was coupled with tDCS. Zimerman and colleagues (2012) performed a double-blind, crossover study in which sham or cathodal tDCS was applied over the contralesional M1 (1mA for 20 minutes, electrodes of 25cm^2) of 12 chronic stroke patients while they performed a SEQTAP with their paretic hand. Authors showed that cathodal tDCS improved online learning *vs.* sham as well as facilitated retention processes 24 hours after the training (Zimerman et al., 2012).

Retention of motor skill learning was also showed after bi-hemispheric tDCS in a series of studies performed by the same research group. In the first study, Lefebvre and colleagues (2013) performed a randomized, cross-over trial with 18 chronic stroke patients underwent to sham or bi-hemispheric tDCS (1mA for 30 minutes, electrodes of 35cm^2) applied bilaterally on M1 (Lefebvre et al., 2013). While patients received the stimulation, they used their paretic hand to training a circuit game: through a computer mouse, they should move a pointer along the circuit as quickly and accurately as possible. Bi-hemispheric tDCS was shown to increase online and off-line motor

learning and, more importantly, it increased long-term retention in 44% compared to baseline, while sham tDCS increased only 4%. In the second study, Lefebvre and colleagues (2014) performed a double-blind, cross-over trial with 19 chronic stroke patients underwent to sham or bi-hemispheric tDCS (1mA for 30 minutes, electrodes of 35cm^2) applied bilaterally on M1 (Stephanie Lefebvre et al., 2014). Participants underwent two series of experiments: (i) firstly, they trained the circuit game while received the real stimulation, but one week later an imaging session was performed using fMRI to assess the neural substrates of motor learning; (ii) secondly, they trained the circuit game while received the sham stimulation and one week later the imaging session was performed. The order of sessions was randomized across patients. Bi-hemispheric tDCS increased online motor learning and retention of skill one week after the ending of training. Additionally, the following neurophysiological changes were found: (i) a trend toward normalization of brain activation pattern (i.e., increase of ipsilesional M1 activity and decrease of contralesional M1 activity) during performance of the learned skill one week after the end of training in patients who received tDCS, this was not identified after sham tDCS; (ii) the same trend toward normalization was found during performance of an untrained skill after bi-hemispheric tDCS; (iii) the behavioural improvement found at the retention test one week after the training was accompanied by a more efficient recruitment of specific motor learning networks in the damaged hemisphere, especially the dorsal premotor cortex. The same research group performed a study to further explore changes in functional brain connectivity of stroke patients underwent to tDCS coupled with training. Lefebvre and colleagues (2017) performed a double-blind, cross-over trial with 22 chronic stroke patients underwent to: (i) a baseline fMRI session; (ii) one week later, one session of sham or bi-hemispheric tDCS coupled with motor skill learning and (iii) a retention session in which fMRI was used to assess retention of learning (Lefebvre et al., 2017). Authors found an increase in functional connectivity one week after the active tDCS condition *vs.* baseline. Furthermore, at baseline and the retention test, a strongest functional connectivity was observed between M1 and the dorsal PM of the undamaged hemisphere after sham tDCS. Conversely, such stronger functional connectivity changed its lateralization after bi-hemispheric tDCS: M1 and PM of the damaged hemisphere were stronger connected.

Although they are still preliminary, such findings highlight how tDCS can be successfully used to change motor learning of stroke patients in all of its phases, from acquisition to retention processes, and how such behavioral changes are linked to brain plasticity processes. Whether such changes could be maximized after multiple stimulation sessions and translated to the generalization of untrained skills still needs to be deepen explored.

1.6. Transcranial Magnetic Stimulation

1.6.1. Technical aspects and Mechanisms of action

Nowadays, beyond tDCS, the most widely used NIBS technique in clinical settings is Transcranial Magnetic Stimulation (TMS) (Brunoni et al., 2012; Schulz, Gerloff, & Hummel, 2013; Tatti, Rossi, Innocenti, Rossi, & Santarnecchi, 2016). However, unlike tDCS, TMS has not been used for therapeutic purposes since antique Greece. In 1831, Michael Faraday postulated the principles of electromagnetic induction suggesting that a time-varying current can create a magnetic field which is able to induce a subsequent electric field. Following such principles, in the 20th century, some primitive devices using alternating magnetic fields were designed to treat psychiatric disorders by experts as Beer, Barlow, Dunlap, and Magnusson (Lewis et al., 2016). However, the utilization of magnetic brain stimulation in the treatment of medical conditions remained speculative and poor widespread over many decades. Until when Barker and colleagues (1985) developed a device able to changes human cortical excitability through the use of magnetic fields (Barker, Jalinous, & Freeston, 1985). Following this, TMS has started to be used mostly in the neuropsychiatric field with various studies assessing its effects in patients with depression and schizophrenia (George et al., 1995; Grisaru, Yarovslavsky, Abarbanel, Lamberg, & Belmaker, 1994; Höflich, Kasper, Hufnagel, Ruhrmann, & Möller, 1993; Kolbinger, Höflich, Hufnagel, Müller, & Kasper, 1995; Pascual-Leone, Rubio, Pallardó, & Catalá, 1996). Since this, TMS studies have rapidly increased and have been performed to diagnostic and treat a wide range of cognitive and motor disorders (Ziemann, 2017).

TMS is delivered to the brain by passing a strong brief electrical current through an insulated wire coil placed on the skull. Current generates a transient magnetic field, which in turn, if the coil is held over the subject's head, induces a secondary current in the brain that is capable of depolarising neurons. TMS effects depend on various physical and biological parameters such as frequency, duration of the stimulation, the strength of the magnetic field, the shape and orientation of the coil as well as its distance from the scalp (Lefaucheur et al., 2014). Indeed, the shape of the coil changes the focality of the stimulation: while the figure-of-eight coil is more selective since it reduces the stimulation area to few square centimeters, the circular coil covers a large brain area but the stimulation has less penetration into the brain (Rossini et al., 2015; Thielscher & Kammer, 2004). The "H-coil" is also used to stimulate deep structures (Zangen, Roth, Voller, & Hallett, 2005). In the general rule, the smaller the diameter of the coil, the more focal will be the stimulation

(Deng, Lisanby, & Peterchev, 2014; Mueller et al., 2014; Peterchev, Goetz, Westin, Luber, & Lisanby, 2013).

TMS can activate or suppress activity in cortical regions (Kobayashi & Pascual-Leone, 2003) through monophasic or biphasic magnetic pulses. Even though monophasic pulses usually activate a more uniform neuronal population, stimulation performed with biphasic pulses requires less energy and seems to be more powerful specially in to its capacity to produce motor evoked potentials (MEPs) (Arai et al., 2005; Kammer, Beck, Thielscher, Laubis-Herrmann, & Topka, 2001; Sommer et al., 2006; Sommer, Lang, Tergau, & Paulus, 2002). Due to this, repetitive transcranial magnetic stimulation (rTMS) is usually performed with biphasic stimulus waveform. Long-lasting effects are induced by applying rhythmic trains of multiple TMS pulses (rTMS): when the temporal rate of rTMS is slow (<1 Hz), the inhibitory effects are accentuated, whereas at faster rates of repetition (>1 Hz) the facilitatory effects come to the fore (Siebner & Rothwell, 2003). However, such effects should not be totally accepted as a general rule since high frequency- and low-frequency rTMS can also elicit mixed excitatory/inhibitory effects (Houdayer et al., 2008). Further, an increase of MEP amplitude can also be the result of a decrease in GABA-mediated intracortical inhibition, instead of a direct increase of cortical excitability (Di Lazzaro et al., 2001; Wu, Sommer, Tergau, & Paulus, 2000; Ziemann, 2004b). The baseline level of cortical excitability (i.e., before the stimulation) is also another factor that can influence rTMS effects (Siebner & Rothwell, 2003). If cortical excitability is down-regulated by other NIBS, the inhibitory effect of low-frequency rTMS is reversed by mechanisms of metaplasticity (Siebner et al., 2004).

Since rTMS can initiate an action potential, it is considered a neuro-*stimulation* method, at the variance with tDCS that represents a neuro-*modulation* tool (Bolognini & Miniussi, 2018). The main difference between tDCS and rTMS is related to their spatial resolution: the spatial resolution of tDCS is too low to precisely stimulate functional subdivisions of a cortical area (Dayan et al., 2013). The higher spatial resolution of rTMS is highly dependent upon the shape of the stimulating coil and the duration of the train, but it is focal enough to stimulate circumscribed cortical regions, although its distant effects, within functionally and anatomically connected cortical and subcortical areas, cannot be neglected (Bikson et al., 2016; Rossini et al., 2015). Importantly, the behavioral and neural effects of both tDCS and rTMS are intrinsically related to individual factors, including age, sex, and the basal level of neuronal activity and responsivity at the time of stimulation; the last factor implies a specific caution in front of physiopathological alterations that follow a brain disease (López-Alonso et al., 2015; Ziemann & Siebner, 2015).

As far as safety guidelines are followed, rTMS is painless and safe (Rossi, Hallett, Rossini, Pascual-Leone, & Group, 2009). Further, its therapeutic efficacy has been assessed in the last years

with a wide range of studies enrolling patients with cognitive and motor disorders. So far, there is a level B of recommendation (that is probable efficacy) for applying low-frequency rTMS over the contralesional M1 in chronic stroke patients (Lefaucheur et al., 2014). Such evidence comes from studies in which rTMS was used both as stand-alone or add-on therapeutic approach; many studies have been also pointing out to the superior beneficial effects of rTMS when used in association with motor training (Grefkes & Fink, 2016). In this context, an open issue is whether rTMS can also be used coupled with training to boost motor learning skill acquisition in stroke patients.

1.6.2. TMS as a neuromodulatory tool of motor learning in stroke patients

Although largely used with diagnostic purposes (i.e., assess interhemispheric imbalance and the neuroplastic changes underlying the ictus) and to modulate the cortical excitability of sensorimotor areas of stroke patients in order to improve motor recovery, TMS has been rarely used to specifically evaluate and modulate motor skill learning of such patients. Very recently, Kantak and colleagues (2018) assessed behavioral and neurophysiological mechanisms that underlie motor skill learning in stroke patients with hemiparesis. Using a kinematic arm skill task (practiced along 3 days) and TMS measures of cortical excitability, authors evaluated short (after two and three days of practice) and long-term retention learning (after one month) of healthy and stroke individuals. Results showed that despite less accurate, stroke patients have learning rates comparable to healthy individuals, showing a similar trend for online effects and long-term retention. In stroke patients, learning was accompanied by an increase of the ipsilesional cortical excitability and a decrease of transcallosal inhibition from contralesional to ipsilesional hemisphere (Kantak, McGrath, Zahedi, & Luchmee, 2018). Such findings provide insights into how motor learning processes can be modulated to promote recovery of upper limb function in stroke patients since it was already shown that changes in transcallosal inhibition are related to motor recovery after a unilateral stroke, especially with respect to the recovery of the paretic upper-limb (Davidson & Tremblay, 2013; Harris-Love, Chan, Dromerick, & Cohen, 2016; Harris-Love, Morton, Perez, & Cohen, 2011).

So far, in the few studies assessing the impact of rTMS on motor learning of stroke patients, rTMS was typically applied to the ipsilesional M1. In this context, Kim and colleagues (2006) performed a single-blind, sham-controlled, crossover trial with 15 chronic stroke patients with hemiparesis underwent to two sessions of training coupled to sham or high-frequency rTMS (8 trains of 20 pulses at 10Hz using 80% of the resting motor threshold) applied over ipsilesional M1 (Kim et al., 2006). The training consisted of a SEQTAP in which patients should repeatedly push buttons as accurately and quickly as possible in response to a 7-digit number stimulus presented on a computer. Such task was applied immediately after each rTMS train for 40 seconds, each one.

Learning was assessed by movement accuracy and time. Additionally, MEPs were used to quantify cortical excitability changes after active or sham stimulation. Authors found that patients who received 10Hz rTMS showed a larger increase in MEPs amplitude (*vs*. sham); such increase was positively associated with higher levels of accuracy during the training. Similarly, Chang and colleagues (2012) performed a single-blind, sham-controlled, parallel group trial with 17 chronic stroke patients with hemiparesis underwent to ten daily sessions of training coupled to sham or high-frequency rTMS (20 trains of 50 pulses at 10Hz using 80% of the resting motor threshold) applied over ipsilesional M1 (Chang et al., 2012). Immediately after the placebo or active stimulation, patients were trained with the SEQTAP task. To assess motor learning, movement accuracy and movement time were recorded before and after rTMS sessions. Additionally, fMRI was performed before and after the treatment to assess changes in brain activity involving the cortico-subcortical motor learning network. Results showed: (i) higher learning rates in the active group *vs.* sham group; (ii) a higher interaction between the sensorimotor cortex, thalamus, and caudate nucleus and (iii) high levels of activation in the ipsilesional hemisphere in the group that received rTMS *vs*. participants receiving placebo stimulation.

Together, such findings indicate that rTMS can be successfully used to asses and modulate motor learning of stroke patients. The evidence is still limited in this field and more studies are necessary to move forward and deeper understand the neurophysiological and behavioral changes that underlie learning processes in stroke patients.

Concluding remarks and specific aims

In the second chapter of this thesis, I will analyze, through a meta-analysis, available published data from studies aimed at verifying the efficacy of the combined use of tDCS and TMS with motor learning paradigms for boosting recovery in adults patients with motor disorders. Despite previous reviews on this topic, the present work is innovative for two main reasons: first, I have taken into consideration a wide range of studies assessing tDCS and TMS adjuvant effects on training-induced motor recovery in patients with different neurological diseases, such as Stroke, Parkinson's disease, Spinal Cord Injury, and Leukoaraiosis; second, I have performed a more in-deep analysis in the stroke population in order to uncover the influence of the stage of illness (i.e., time elapsed from stroke), as well as the role of motor training's time of application (before vs. during tDCS or TMS). Additionally, specific effect sizes were provided for outcomes measures related to upper limb function vs. lower limb functions for each NIBS protocol.

Secondly, in the last decade, a grown body of evidence has emerged in favor of tDCS effective neuromodulator of motor learning in adulthood. In this field, the majority of evidence comes from studies in which M1 was used as the target area of stimulation for enhancing motor learning. Given that other higher-order cognitive areas (i.e., premotor cortex and posterior parietal cortex) are also involved in several motor learning processes, their stimulation may also influence motor learning, likely affecting some specific processes. Understanding how such areas work together with M1 during motor learning, and whether they can be used as alternative areas to boost motor learning in healthy conditions, and recovery in stroke patients could allow the development of new therapeutic protocols for motor rehabilitation. Thus, Chapter 3 address this issue through a study performed to evaluate the effects of tDCS on M1, PPC and PM on online and off-line motor learning in healthy individuals.

In the last few years, tDCS has also been used as a neuromodulator of motor learning in children. The potential effectiveness of tDCS for improving motor learning in children with CP and hemiparesis will be explored here by two studies, described in Chapter 4. The first study assesses motor learning abilities of the paretic upper-limb in children with CP, by using a paradigm widely used in adults, and also evaluating the impact of different types of corticospinal tract (CST) reorganization on motor learning; the second study assesses the acute effect of tDCS on motor learning in the same population, also considering whether different patterns of CST reorganization may predict the response to different tDCS strategies aimed at (i) increasing the excitability of the affected hemisphere; (ii) decreasing the excitability of the intact hemisphere or (iii) increasing the excitability of the intact hemisphere. In line with the current model of developmental plasticity after a perinatal stroke.

Finally, in Chapter 5, an in-depth discussion of the results of the present thesis will be provided, considering its merits and its limitations, as well as the implications of the findings for future research and clinical practice.

CHAPTER 2

‖ Study 1 ‖

Augmenting motor training effects with non-invasive brain stimulation in patients with neurological diseases: a meta-analysis

2.1. Introduction

In the last 20 years, we have seen a plethora of clinical and non-clinical studies aimed at establishing the therapeutic efficacy of non-invasive brain stimulation (NIBS) techniques in various neurological diseases. Although many issues remain open, and still under investigation (as for instance, the optimal stimulation parameters, the determination of short- and long-lasting clinical and neurophysiological benefits, predictors of the patient' response) a central concept that has emerged from the scientific literature in stroke adults is that NIBS techniques should be used 'in addition' to standard therapies, rather than in 'substitution' of them, at least in cognitive and motor rehabilitation (Lefaucheur et al., 2014; Lefaucheur et al., 2017). The rationale of the combined use of NIBS and rehabilitation therapies is that, since learning-based therapies and NIBS share similar mechanisms of action for inducing plasticity, as described in Chapter 1, their mutual use should maximize the individual effects of NIBS and training, leading to more remarkable and outlasting clinical gains in rehabilitation (Bolognini et al., 2009; Convento, Russo, Zigiotto, & Bolognini, 2016). In this perspective, cortical excitability changes induced by NIBS are expected to interact with the ongoing learning processes, increasing the chance of inducing a plastic rearrangement of brain circuits that may shape and/or reinforce, the long-term effects induced by a standard – behavioural – therapy (Kleim & Jones, 2008; Murphy & Corbett, 2009).

In the motor domain, a large amount of studies has shown that mechanisms of synaptic and cortical maps plasticity sustain motor learning behavior in the healthy as well as in the damaged brain (Buma et al., 2013; Krakauer, 2006; Pekna et al., 2012). Cortical excitability shifts induced by NIBS can also drive long-term behavioral changes that rely on a re-arrangement of neural connections (Dayan et al., 2013; Malenka & Bear, 2004; Sadowski, 2008). As illustrated in the previous chapter, both motor learning and NIBS effects are accompanied by changes of synaptic efficacy, hence NIBS can be used to prime, boost or guide motor learning through a sort of

associative plasticity, in turn, fastening and strengthening motor learning (Schabrun & Chipchase, 2012). So far, a number of clinical trials have been performed to assess the enhancing effects of NIBS on the clinical outcome of motor rehabilitation for upper- and lower-limb motor impairments (Lüdemann-Podubecká et al., 2014): taken in isolation the published studies, the current evidence seems promising, but we still need a more direct assessment of the clinical validity of available results. In this framework, the aim of the present study is to verify the efficacy of using NIBS as add-on intervention to augment motor training-induced recovery in patients with motor impairments due to a central nervous system damage, based on the available literature. To this aim, I have reviewed and analyzed, by means of meta-analysis, results of published Clinical Trials (CTs) assessing the therapeutic effects of the combined approach on motor disorders of neurological origin.

Previous works had a similar goal, however, none of them has especially focused on the combined approach (i.e., NIBS + learning-based therapies), hence considering even CTs where NIBS was used alone, in substitution of standard therapies. Moreover, at variance with previous meta-analyses, I have taken into consideration a wide range of studies assessing the clinical effectiveness of the combined approach in various diseases causing motor disorders, namely Stroke, Parkinson's disease, Spinal Cord Injury, and Leukoaraiosis. A more in-depth analysis was then performed only in the Stroke population, for which there is a large body of CTs, aimed at exploring the optimal "time window" of the motor rehabilitation based on the combined approach with respect to the stage of illness (i.e., time elapsed from stroke), as well as the NIBS delivery (before vs. during motor practice). Finally, effect sizes were calculated separately for outcomes related to upper limb function *vs.* lower limb functions for each NIBS protocol.

2.2. Material and Methods

Outcome measures

This review considered outcome measures performed at the end of a given NIBS treatment period, which was associated with motor therapy. The primary analysis focused on motor function as measured with the Fugl-Meyer Scale (considering both upper- and lower-limb motor scores; noteworthy, higher score at this scale indicates the presence of a motor improvement); whenever the Fugl-Meyer scale was not administered, any other continuous clinical scales/test that evaluated the motor performance were considered. These included the following clinical assessments: Box and Block Test, Wolf Motor Function Test, Action Research Arm Test, Nine-Hole Peg Test, Purdue

Peg Test, Lower Extremity Motor Score and Postural Assessment Scale for Stroke Patients - for all these tests, higher scores represent a better motor outcome; Jebsen-Taylor Hand Function Test, Timed to Up and Go Test, 10-m/6-m Walking Test, and Unified Parkinson Disease Rating Scale – for these tests, the improvement is reflected by a reduced score. Table 1 shows scales/tests used as outcome measures as well as the main characteristics of the included studies.

Literature search and selection criteria

The literature search included only published studies on MEDLINE (via PubMed), LILACS (via BIREME) and Web of Science. Language restriction was not applied and searches were performed until November 2016, respecting the controlled vocabulary indexed on databases as well as keywords. Terms used on Medical Subject Headings (MeSH) were: "exercise", "physical therapy", "occupational therapy", "motor training", "motor performance", "repetitive transcranial magnetic stimulation" and "transcranial direct current stimulation". The descriptors in Health Sciences (DeCS) were: "exercise", "physical therapy modalities", "occupational therapy", "motor activity" and "electric stimulation therapy". All the terms were used with the Boolean Operator "AND" in a wide range of combinations to find relevant studies. Two authors (MC and DM) independently screened titles, then selected abstracts and finally full texts. In cases of doubts, such as when the abstract did not infringe any exclusion criteria, or when there was insufficient data, full-texts were analyzed. Any disagreement was solved by consensus or consulting a third author's opinion (AB). All the selected eligibility criteria are shown in Table 2.

Studies with neurological patients were included in this review according to the intervention used: motor training therapies associated with tDCS or rTMS, regardless of neurological disease.

Table 1. Characteristics of the included studies.

Author (study design)	Patients	Type (timing of stimulation)	Motor training (MT)	Groups (n)	Outcome (assessment tool)	Results
Abo *et al*., 2014 (RCT)	chronic stroke	rTMS (before MT)	OT (MT1) CIMT (MT2)	1Hz rTMS + MT1 (44) MT2 (22)	UL motor function (**FMA-UL**, WMFT)	1Hz rTMS improved 11% from baseline ($p<0.001$) MT2 improved 6% from baseline ($p<0.005$) there was difference between groups favouring 1Hz rTMS ($p<0.05$)
Allman *et al*., 2016 (RCT)	chronic stroke	tDCS (during MT)	PT	anodal tDCS + MT (11) sham tDCS + MT (13)	UL motor function (**FMA- UL,** ARAT, WMFT)	there was a difference between groups for WMFT and ARAT favoring anodal tDCS ($p<0.05$)
Ang *et al*., 2015 (RCT)	chronic stroke	tDCS (before MT)	robot-assisted training	bihemispheric tDCS + MT (10) sham tDCS+ MT (9)	UL motor function (**FMA-UL**, kinematics of movement)	there was no difference either between groups or intra-groups (over time)
Avenanti *et al*., 2012 (RCT)	chronic stroke	rTMS (before or after MT)	PT	1Hz rTMS + MT (8) MT + 1 Hz rTMS (8) sham rTMS + MT (7) MT + sham rTMS (7)	UL motor function (**JTT**, NHPT, BBT)	all groups improved from baseline ($p<0.01$) there was a difference between groups favouring 1Hz rTMS + MT and MT + 1Hz rTMS ($p<0.025$)
Benito *et al*., 2012 (RCT)	spinal cord injury	rTMS (before MT)	GT	20 Hz rTMS + MT (10) sham rTMS + MT (10)	LL motor function (**LEMS**, 10-m WT, TUG)	20 Hz rTMS improved 16% from baseline ($p<0.01$) there was no difference between groups
Bolognini *et al*., 2011 (RCT)	chronic stroke	tDCS (during MT)	CIMT	bihemispheric tDCS + MT (7) sham tDCS + MT (7)	UL motor function (**FMA-UL**, JTT, MAL)	bihemispheric tDCS improved 24% from baseline ($p<0.01$) there was a difference between groups favoring bihemispheric tDCS ($p<0.01$)
Brodie *et al*., 2014 (CT)	chronic stroke	rTMS (before MT)	serial targeting task	5 Hz rTMS + MT (11)* sham rTMS + MT (11)*	UL motor function (**WMFT**, BBT, STT)	5 Hz rTMS improved 12% from baseline sham rTMS improved 6% from baseline there was no difference between groups
Cha *et al*., 2014 (RCT)	chronic stroke	tDCS (?)	functional training	anodal tDCS + MT (10) MT (10)	UL and LL motor function (BBT, grip strength, **FMA-UL**,	all groups improved from baseline ($p<0.05$) there was a difference between groups favoring anodal tDCS + MT for the BBT, FMA-UL and

					FMA-LL, FMA-balance)	FMA-LL (p=unknown)
Cha & Kim, 2016 (RCT)	subacute stroke	rTMS (before MT)	PT	1Hz rTMS + MT (15) sham rTMS + MT (15)	UL motor function (LBT, AT, **BBT**, grip strength)	there was a difference between groups for LBT, BBT, AT and grip strength favoring 1 Hz rTMS ($p < 0.05$). The effect sizes for gains in experimental and control groups were very strong in AT, BBT (effect sizes=2.15, 0.77 respectively)
Chang *et al*., 2012 (RCT)	chronic stroke	rTMS (before MT)	sequential motor learning task	10Hz rTMS + MT (8) sham rTMS + MT (9)	UL motor function (**JTT**)	there was a difference between groups favoring 10Hz rTMS ($p<0.05$)
Chang *et al*., 2015 (RCT)	acute stroke	tDCS (during MT)	PT	anodal tDCS +MT (12) sham tDCS + MT (12)	LL motor function (**FMA- LL**, motricity index lower limb, gait analysis)	there was a difference between groups for FULG and motricity lower limb index favoring anodal tDCS
Danzl *et al*., 2013 (RCT)	chronic stroke	tDCS (before MT)	PT with robotic assistance	anodal tDCS + MT (4) sham tDCS + MT (4)	LL motor function (**10-m WT**, TUG)	there was no difference either between groups or intra-groups (over time)
Fusco *et al*., 2014a (RCT)	subacute stroke	tDCS (before MT)	PT	cathodal tDCS + MT (5) sham tDCS + MT (6)	UL and LL motor function (**FMA-UL**, NHPT, TUG, 6-m WT, 10-m WT)	there was no difference either between groups or intra-groups (over time)
Fusco *et al*., 2014b (CT)	subacute stroke	tDCS (before MT)	PT	anodal tDCS + MT (8) sham tDCS + MT (8)	UL motor function (**NHPT**)	anodal tDCS improved 22% from baseline ($p=0.007$) sham tDCS improved 16% from baseline ($p=0.006$) there was no difference between groups
Galvão *et al.*, 2014 (RCT)	chronic stroke	rTMS (before MT)	PT	1 Hz rTMS + MT (10) sham rTMS + MT (10)	UL motor function (**FMA-UL**),	1 Hz rTMS improved 23% from baseline ($p<0.05$) sham rTMS improved 35% from baseline ($p<0.05$) there was no difference between groups

Geroin *et al*., 2011 (RCT)	chronic stroke	tDCS (during MT)	robot-assisted training	anodal tDCS + MT (10) sham tDCS + MT (10)	LL motor function (**6-m WT**, 10-m WT)	anodal tDCS + MT improved 26% from baseline sham tDCS + MT improved 16% from baseline there was no difference between groups
Giacobbe *et al*., 2013 (CT)	chronic stroke	tDCS (before, during and after MT)	robot-assisted training	anodal tDCS before + MT (12)* anodal tDCS during + MT (12)* anodal tDCS after + MT (12)* anodal tDCS sham + MT (12)*	UL motor function (**volitional movement speed**)	tDCS before improved 15% from baseline (p=0.001) tDCS during worsened 15% from baseline (p=0.02) tDCS after worsened 10% from baseline (p=0.03) there was no difference between groups
Gomes-Osman *et al*., 2015 (CT)	spinal cord injury	rTMS (during MT)	fine motor task	10 Hz rTMS + RTP (11) sham rTMS + RTP (11)	UL motor function (**JTT**, pinch strength, grasp strength)	for all measures, there was no difference between conditions (p>0.05).However, the effect size was large for 10Hz rTMS (SRM=0.85) while the one for sham rTMS was small (SRM=0.42)
Hesse *et al*., 2011 (RCT)	subacute stroke	tDCS (during MT)	robot-assisted training	anodal tDCS + MT (28) cathodal tDCS + MT (29) sham tDCS + MT (28)	UL motor function (**FMA-UL**, BBT)	anodal tDCS improved 144% from baseline (p<0.001) cathodal tDCS improved 139% from baseline (p<0.001) sham tDCS improved 134% from baseline (p<0.001) there was no difference between groups
Kaski et al., 2013 (CT)	leukoaraiosis	tDCS (during MT)	GT	anodal tDCS + MT (9) sham tDCS + MT (9)	LL motor function (6-m WT, retropulsion test, **TUG**)	there was a difference between groups favoring anodal tDCS (p=0.03)
Kim *et al*., 2010 (RCT)	subacute stroke	tDCS (during MT)	OT	anodal tDCS + MT (6) cathodal tDCS + MT (5) sham tDCS + MT (7)	UL motor function (**FMA-UL**, Modified Barthel Index)	anodal and cathodal tDCS improved from baseline (p=0.001) there was a difference between groups favoring cathodal tDCS compared with sham (p<0.005)
Kumru *et al*., 2016 (RCT)	spinal cord injury	tDCS (during MT)	robot-assisted training	anodal tDCS + MT (10) sham tDCS + MT (10)	LL motor function (**LEMS**, 10-m WT, WISC-II)	there was no difference between groups
Lee & Chun, 2014 (RCT)	subacute stroke	tDCS (during MT)	VRT	cathodal tDCS + MT (20) MT (20)	UL motor function (manual muscle test, manual function test,	cathodal tDCS improved 20% from baseline (p<0.05)

					FMA-UL, BBT)	MT improved 20% from baseline ($p<0.05$) there was a difference between groups favoring cathodal tDCS ($p<0.01$)
Lefebvre *et al*., 2014a (CT)	chronic stroke	tDCS (during MT)	motor task	bihemispheric tDCS + MT (19)* sham tDCS + MT (19)*	UL motor function (**velocity, accuracy**) and motor learning (learning, performing index)	there was a difference between groups favoring bihemispheric tDCS ($p=0.002$)
Lefebvre *et al*., 2014b (CT)	chronic stroke	tDCS (during MT)	motor task	bihemispheric tDCS + MT (19)* sham tDCS + MT (19)*	UL motor function (**PPT**, grip-lifts)	bihemispheric tDCS improved 38% from baseline ($p<0.005$) there was no difference between groups
Lefebvre *et al*., 2013 (CT)	chronic stroke	tDCS (during MT)	motor task	bihemispheric tDCS + MT (19)* sham tDCS + MT (19)*	UL motor function (**PPT**) and motor learning	bihemispheric tDCS improved 10% from baseline after MT sham tDCS worsened 2.5% from baseline there was no difference between groups
Lin *et al*., 2015 (RCT)	subacute stroke	rTMS (before MT)	PT	1 Hz rTMS + MT (16) sham rTMS + MT (16)	LL motor function (**PASS**, POMA, TUG, Barthel index)	all groups improved from baseline ($p<0.001$). There was a difference between groups favouring 1 Hz rTMS ($p<0.05$)
Lindenberg *et al*., 2010 (RCT)	chronic stroke	tDCS (during MT)	PT and OT	bihemispheric tDCS + MT (10) sham tDCS +MT (10)	UL motor function (**FMA-UL**, WMFT)	bihemispheric tDCS improved 20.7% from baseline sham tDCS improved 3.2% from baseline there was no difference between groups
Lüdemann-Podubecká et al., 2015 (RCT)	subacute stroke	rTMS (before MT)	motor task	1Hz rTMS + MT (22) sham rTMS + MT (22)	UL motor function (**WMFT**, MESUPES, finger tapping)	1Hz rTMS over the contralesional M1 significantly improves the dexterity of the affected hand in patients with stroke in the dominant hemisphere ($p<0.05$), but not in those with stroke in the non-dominant hemisphere
Madhavan et al., 2011 (CT)	chronic stroke	tDCS (during MT)	visuo-motor ankle-tracking task	anodal tDCS (lesioned hemisphere) + MT (9)* anodal tDCS (non-lesioned hemisphere) + MT (9)* sham tDCS + MT (9)*	LL motor learning (**accuracy index**)	anodal tDCS (lesioned hemisphere) improved from baseline ($p=0.006$) sham tDCS improved from baseline ($p=0.001$) there was no difference between groups

Malcolm *et al*., 2007 (RCT)	chronic stroke	rTMS (before MT)	CIMT	20 Hz rTMS + MT (9) sham rTMS + MT (10)	UL motor function (**WMFT**, MAL, BBT)	20 Hz rTMS improved 43% from baseline (p=0.01) there was no difference between groups
Manenti *et al*., 2016 (CT)	PD	tDCS (during MT)	PT	anodal tDCS + MT (10) sham tDCS + MT (10)	LL motor function (**UPDRS**, TUG, sit and reach test, four square step test)	there was a difference in both groups, compared, to baseline for TUG and four square step test there was no difference between groups
Moisello *et al*., 2015 (CT)	PD	rTMS (after MT)	motor task	5Hz rTMS + MT (19)* sham rTMS + MT (19)*	UL motor learning (**adaptation and retention of the task**)	5Hz rTMS improved 73% from baseline (p<0.005) there was no difference between groups
Mortensen *et al*., 2015 (RCT)	chronic stroke	tDCS (during MT)	OT	anodal tDCS + MT (8) sham tDCS + MT (7)	UL motor function (**JTT**, SIS , grip strength)	anodal tDCS improved 45% from baseline sham tDCS improved 41% from baseline there was no difference between groups
Nair *et al*., 2011 (RCT)	chronic stroke	tDCS (during MT)	OT	cathodal tDCS + MT (7) sham tDCS + MT (7)	UL motor function (**FMA-UL**)	cathodal tDCS improved 13% from baseline (p<0.001) sham tDCS improved 6% from baseline (p<0.001) there was no difference between groups
Park *et al*., 2015 (CT)	chronic stroke	tDCS (during MT)	general exercise therapy	anodal tDCS + MT (8) sham tDCS + MT (8) MT (8)	LL motor function (**speed**, step length, symmetry)	anodal tDCS + MT and only MT increased the speed and symmetry all groups reduced the step length there was no difference between groups.
Pomeroy *et al*., 2007 (RCT)	acute and subacute stroke	rTMS (before MT)	voluntary muscle contraction	1Hz rTMS + MT (6) 1Hz rTMS + placebo MT (5) sham rTMS + MT (9) sham rTMS + placebo MT (7)	UL motor function (**ARAT**)	all groups improved from baseline (the greater was in placebo rTMS + placebo VMC - mean difference=11.43) there was no difference between groups
Raithatha *et al*., 2016 (RCT)	spinal cord injury	tDCS (before MT)	robot-assisted training	anodal tDCS + MT (9) sham tDCS + MT (6)	LL motor function (**Muscular test**; TUG; BBS; 6m -WT; 10 –m WT; SCIM-III)	both groups improved for measures compared to baseline; comparing to sham, anodal tDCS group improved scores of the manual muscular test sham tDCS improved scores for the other measures.
Rocha *et al*., 2016 (RCT)	chronic stroke	tDCS (before MT)	CIMT	anodal tDCS + MT (7) cathodal tDCS +MT (7) sham tDCS + MT (7)	UL motor function (**FMA-UL**, MAL, grip strength)	there was a difference for anodal and cathodal tDCS vs. baseline (FMA-UL); comparing to sham, only the anodal tDCS improved FMA-UL scores

Schabrun *et al.*, 2016 (RCT)	PD	tDCS (before and during MT)	walking training	anodal tDCS + MT (8) sham tDCS + MT (8)	LL motor function (**speed**, cadence, step length, TUG)	there was a difference for speed, cadence and step length for both groups compared to baseline there was no difference between groups.
Seniów *et al.*, 2012 (RCT)	acute stroke	rTMS (before MT)	PT	1 Hz rTMS + MT (20) sham rTMS + MT (20)	UL motor function (WMFT, **FMA-UL**)	1 Hz rTMS improved 16% from baseline ($p<0.01$) sham rTMS improved 18% from baseline ($p<0.01$) there was no difference between groups
Takeuchi *et al.*, 2005 (RCT)	chronic stroke	rTMS (after MT)	pinching task	1 Hz rTMS + MT (10) sham rTMS + MT (10)	UL motor function (**accelerometer**)	1 Hz rTMS improved from baseline ($p<0.01$) there was a difference between groups favoring 1 Hz rTMS ($p<0.05$)
Takeuchi *et al.*, 2008 (RCT)	chronic stroke	rTMS (before MT)	pinching task	1Hz rTMS + MT (10) sham rTMS + MT (10)	UL motor function (**accelerometer**)	1 Hz improved from baseline ($p=0.006$) there was a difference between groups favouring 1 Hz rTMS ($p=0.033$)
Triccas *et al.*, 2015 (RCT)	subacute and chronic stroke	tDCS (during MT)	robotic-assisted training	anodal tDCS + MT (12) sham tDCS + MT (10)	UL motor function (**FMA-UL**, ARAT, MAL, SIS, HPR)	anodal tDCS improved 35% from baseline sham tDCS improved 21% from baseline there was no difference between groups
Viana *et al.*, 2014 (RCT)	chronic stroke	tDCS (before MT)	VRT	anodal tDCS + VR (10) sham tDCS + VR (10)	UL motor function (**WMFT**, FMA-UL, SSQOL, MAS, grip strength)	there was a difference for WMFT, FMA-UL, MAS, grip strength and SSQOL for both groups compared to baseline for SSQOL there was no difference between groups.
Vongvaivanichakul *et al.*, 2014 (RCT)	chronic stroke	rTMS (before MT)	reach-to-grasp task	1Hz rTMS + MT (7) sham rTMS + MT (7)	UL motor function (**WMFT**, kinematics movement)	1 Hz rTMS improved from baseline ($p=0.001$) there was no difference between groups
Wang *et al.*, 2012 (RCT)	chronic stroke	rTMS (before MT)	task-oriented treatment	1Hz rTMS + MT (12) sham rTMS + MT (12)	LL motor function (**FMA-LL**, single support time ratio; step length ratio)	1 Hz rTMS improved 30% from baseline sham rTMS improved 21% from baseline there was a difference between groups favoring 1 Hz rTMS ($p<0.02$)
Wu et al., 2013 (RCT)	subacute stroke	tDCS (before MT)	PT	cathodal tDCS + PT (45) Sham tDCS + PT (45)	UL motor function (**FMA-UL**, MAS, Barthel index)	there was a difference for MAS, FMA-UL and Barthel index between groups favoring cathodal tDCS
Yang *et al.*, 2013 (RCT)	PD	rTMS (before MT)	GT	5Hz rTMS + MT (10) sham rTMS + MT (10)	LL motor function (**TUG**, 10-m WT)	5 Hz rTMS improved 27% from baseline ($p<0.000$) sham rTMS improved 10% from baseline

						(p<0.000) there was a difference between groups favouring 5 Hz rTMS (p=0.019)
Yozbatiran *et al*., 2016 (RCT)	spinal cord injury	tDCS (before MT)	robotic-assisted training	anodal tDCS + MT (4) sham tDCS + MT (4)	UL motor function (**JTT**, MAL, manual muscle test)	anodal tDCS improved 41% from baseline sham tDCS improved 7% from baseline there was no difference between groups
Zheng *et al*., 2015 (RCT)	subacute stroke	rTMS (before MT)	VRT	1Hz rTMS + MT (58)* sham rTMS + MT (58)*	UL motor function (**FMA-UL**, WMFT, Barthel index)	both 1 Hz rTMS and sham rTMS improved from baseline (p <0.01) there was a difference between groups favouring 1 Hz rTMS (p<0.01)
Zimerman *et al*., 2012 (CT)	chronic stroke	tDCS (during MT)	motor task	cathodal tDCS + MT (12) sham tDCS + MT (12)	UL motor function (**number of correct sequences**)	there was a difference for number of correct sequences favoring cathodal tDCS

PD – parkinson´s disease; rTMS - repetitive transcranial magnetic stimulation; tDCS – transcranial direct current stimulation; PT – physical therapy; OT – occupattional therapy; CIMT – constraint induced movement therapy; GT – gait training; VRT – virtual reality therapy; UL – Upper limb; LL – Lower limb; FMA – UL – Fugl Meyer assesment – upper limb; FMA – LL – Fugl Meyer assesment – lower limb; WMFT – wolf motor function test; ARAT - action research arm test; JTT – jebsen taylor test; NHPT – nine hole peg test; BBT – box and block test; STT – serial targetin task; LBT- line bisection test; AT – Albert test; LEMS – lower extremity motor score; 10-m WT – 10 meters walk test; TUG – timed and up go; PASS – postural assesment scale for stroke patients; POMA – performance oriented mobility assesment; MESUPES – motor evaluation scale for upper extremity in stroke patients; MAL – motor activity log; UPDRS – unified parkinson disease rating scale; 6-m WT – 6 minutes walk test; WISC – II – walking index for spinal cord injury; PPT – purdue pegboard test; SIS – stroke impact scale; BBS – berg balance scale; SSQOL – stroke specific quality of life; MAS – modified ashworth scale; SRM – standardized response mean; VMC – voluntary muscle contraction; HPR – Hand Path Ratio; *Studies in which the total number of patients needs to be divided by half since the same patients underwent to both - experimental and control treatment. Outcome measures in **bold** were those used to perform a meta-analysis.

Table 2. Criteria of eligibility for considering articles for the review

	INCLUSION	EXCLUSION
PARTICIPANTS	Individuals with acquired neurological disease with (age ≥ 18 years).	Hereditary neurological disease and non-CNS neurological disease.
INTERVENTION	Studies in which individuals received NIBS associated with motor training (a-tDCS, c-tDCS, bi-tDCS, low or high frequency rTMS).	Studies in which were used pharmacological intervention and/or peripheral stimulation or associated one or more NIBS techniques.
COMPARISON	Studies in which the control group received only motor training or motor training associated with sham stimulation.	Studies in which the control group received only sham stimulation without an associated motor training.
OUTCOME	Motor function or motor performance assessed by functional tests (i.e., Fugl-Meyer scale), the time taken to finish a task (i.e., Jebsen-Taylor test), number of objects moved within a time interval or number of movements repeated within a time interval.	Studies in which motor function was assessed through the same activity used to training individuals.
TRIAL DESIGN	Clinical trials, controlled clinical trials, randomized controlled trials, cross-over trials.	-
DATA REPORT	Data that enables analysis and estimation of the effects of NIBS associated with motor training on motor function must be reported.	-
TYPE OF PUBLICATIONS	Published in a peer-reviewed journal; regardless of the year of publication; studies regardless of language (except German).	-

NIBS: non-invasive brain stimulation; a-tDCS: anodal transcranial direct current stimulation; c-tDCS: cathodal transcranial direct current stimulation; bi-tDCS: bihemispheric transcranial direct current stimulation; rTMS: repetitive transcranial magnetic stimulation; CNS: central nervous system.

Studies selection and data extraction

Studies were selected through a flow diagram extracted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA – http://www.prisma-statement.org/). Data selection and extraction were performed with a structured form and checked by the third researcher (AB). Data extraction comprised: (i) study design; (ii) population; (iii) sample size; (iv) type and timing of stimulation; (v) motor training characteristics; (vi) outcome measures; (vii) tDCS protocols parameters; (viii) rTMS protocols parameters and (ix) mean ± standard deviation (SD) of motor function for experimental and control groups before and immediately after intervention; (x) items for risk of bias assessment (randomization, concealment of treatment allocation, blinding of participants, therapists and outcome assessors and selective reporting of outcomes). When necessary, the authors of a given study were contacted in order to obtain missing and incomplete data or to clarify methodological procedures. Whenever a reply to our request was not obtained, the 'uncertain' study was excluded from the meta-analysis.

Risk of bias assessment was performed independently by two researchers (MC and DM), following the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8, (Higgins & Green, 2011). Moreover, the quality of evidence was analyzed through GRADE Handbook (Grading of Recommendations, Assessment, Development, and Evaluation) which takes into account risk of bias, inconsistency, indirectness, imprecision, and publication bias. CrivoApp software was then used as an auxiliary tool to further check for the necessity to downgrade or not the quality of evidence according to the items specified by GRADE Handbook (Schunemann, 2008).

Data analysis

Quality of evidence was summarized using the GRADE profiler 3.6.1. To perform the meta-analysis, we used the mean difference between the baseline and the post-treatment motor scores at the above-mentioned tests between for the experimental group (NIBS combined with motor training), and the control group. In the studies, the control group received only the motor training or the motor training combined with the sham, placebo, NIBS. The Cochrane Collaboration's Review Manager software (RevMan 5.3) was used to calculate the treatment effect with a 95% confidence interval across trials. Effect sizes were computed for each study, using the mean difference score (MD), which was computed as the difference between the baseline and the post-treatment scores

(namely, MD_{change}= M_{final} – $M_{baseline}$) and the Standard Deviation (SD_{change}). For effect size interpretation, Cohen's *d* value was considered. Values <0.3 indicate a "small effect", values around 0.5 indicate a "medium effect", and those >0.8 a large "large effect". When the SD_{change} was not provided, it was calculated using the method of obtaining SD from confidence intervals for group means, as suggested in the Cochrane Handbook for Systematic Review of Intervention (see Section 7.7.3.2). Given that the selected studies used different outcome measures, data are presented as standardized mean differences (SMD), which was computed using a random-effects model (Higgins & Deeks, 2008).

The different outcome measures in the reviewed studies provided an index of improvement that was different in term of the direction of post-treatment scores; that is the motor improvement brought about by the treatment could be reflected by either higher or lower post-treatment scores, depending on which clinical effect was considered (i.e., for motor execution speed, the improvement is indexed by reduced scores, while motor accuracy by higher scores). To handle properly with such differences, we converted the reduced scores in increased scores by multiplying them by (-1); in this way we obtained a pool of data where, regardless of the test, in every case post-treatment improvements were indexed by increased values - see the Cochrane Handbook for Systematic Review of Intervention, Section 9.2.3.2 (Deeks, Higgins, & Altman, 2008).

Finally, meta-analyses were performed separately for neurological diseases (Stroke and Parkinson's disease), the type of brain stimulation (anodal, cathodal or bihemispheric tDCS, and low-frequency and high-frequency rTMS). Further analyses were run for stroke patients, taking into consideration: (i) the stage of illness (acute *vs.* chronic stroke), (ii) time of NIBS delivery with respect to the motor training (NIBS applied before *vs.* during the motor practice) and (iii) the affected body part (upper-limb *vs*. lower-limb motor disorder). Heterogeneity was assessed using Tau^2 test and the I^2 statistic.

2.3. Results

Identification and selection of studies

The search strategy identified a total of 2587 potentially relevant articles. After screening titles and abstracts, 926 duplicates were removed, while 1568 records were eliminated; the full-text of the remaining 93 articles were inspected. After a detailed screening, 41 articles were excluded since they did not meet our eligibility criteria; therefore, only a total of 52 papers were considered

appropriate for this review, and therefore entered in the analyses. Meta-analysis was performed with only 30 studies including 736 stroke patients and 56 patients with Parkinson disease. Figure 1 shows the flow diagram of the selection process for meta-analysis.

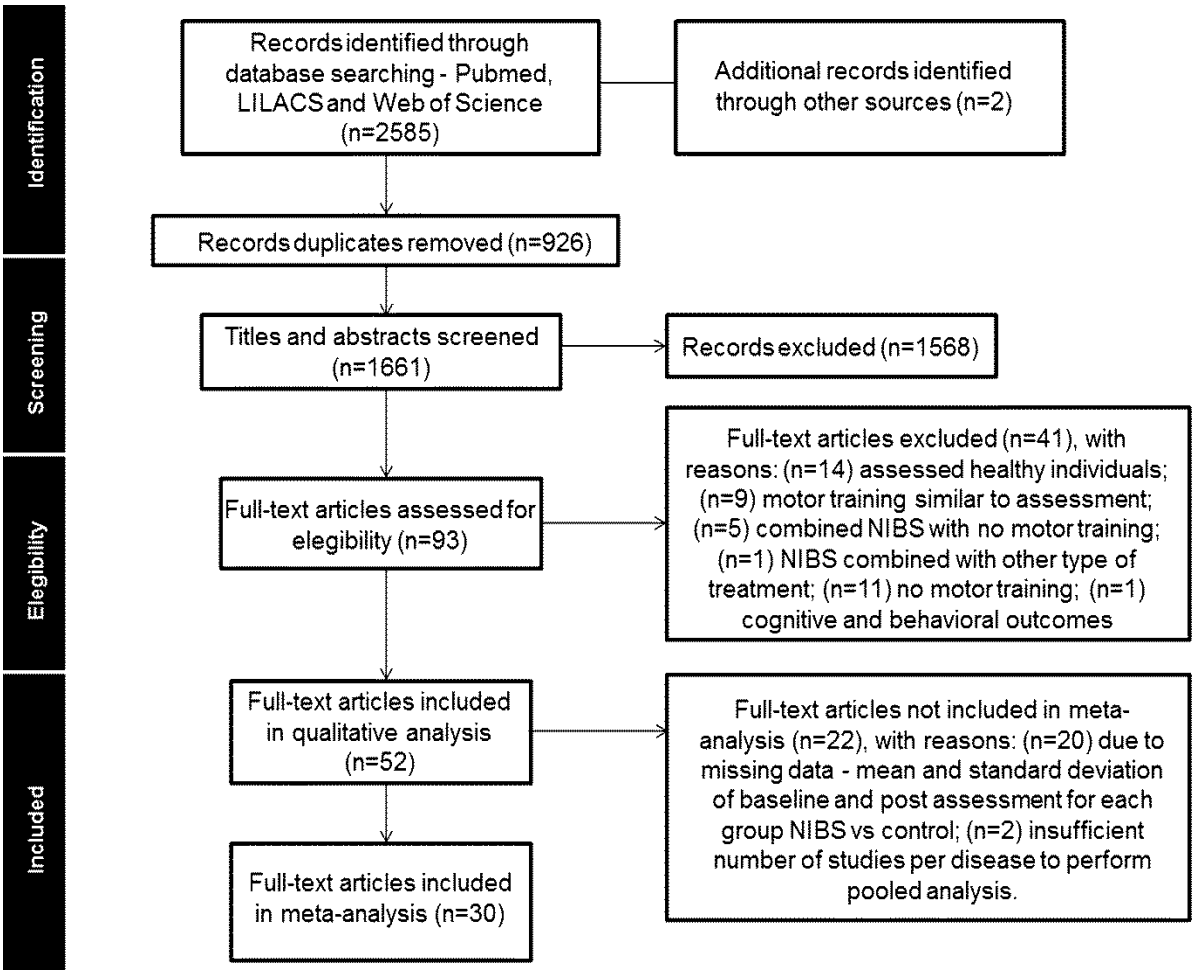

Figure 1. Flow diagram of the meta-analysis.

Characteristics of included studies

We included 42 studies involving a total of 1097 stroke patients (Abo et al., 2014; Allman et al., 2016; Ang et al., 2015; Avenanti, Coccia, Ladavas, Provinciali, & Ceravolo, 2012; Bolognini et al., 2011; Brodie, Meehan, Borich, & Boyd, 2014; Cha, Ji, Kim, & Chang, 2014; Cha & Kim, 2016; Chang, Kim, & Park, 2015; Chang et al., 2012; Danzl, Chelette, Lee, Lykins, & Sawaki, 2013; Fusco, Assenza, et al., 2014; Fusco, Iosa, et al., 2014; Galvão, dos Santos, dos Santos, Cabral, & Monte-Silva, 2014; Geroin et al., 2011; Giacobbe et al., 2013; Hesse et al., 2011; Kim et al., 2010; Lee & Chun, 2014; Lefebvre et al., 2014; Lefebvre et al., 2013; Lefebvre et al., 2014; Lin et al., 2015; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Lüdemann-Podubecká, Bösl, Theilig, Wiederer, & Nowak, 2015; Madhavan, Weber, & Stinear, 2011; Malcolm et al., 2007; Mortensen,

Figlewski, & Andersen, 2016; Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011; Park, Kim, & Song, 2015; Pomeroy et al., 2007; Rocha et al., 2016; Seniów et al., 2012; Takeuchi, Chuma, Matsuo, Watanabe, & Ikoma, 2005; Takeuchi et al., 2008; Triccas et al., 2015; Viana et al., 2014; Vongvaivanichakul, Tretriluxana, Bovonsunthonchai, Pakaprot, & Laksanakorn, 2014; Wang et al., 2012; D. Wu et al., 2013; Yozbatiran et al., 2016; Zheng, Liao, & Xia, 2015; Zimerman et al., 2012), 5 studies involving 74 patients with Spinal Cord Injury (Benito et al., 2012; Gomes-Osman & Field-Fote, 2015; Kumru, Murillo, Benito-Penalva, Tormos, & Vidal, 2016; Raithatha et al., 2016; Yozbatiran et al., 2016), 4 studies involving 75 patients with Parkinson's disease (Manenti et al., 2016; Moisello et al., 2015; Schabrun, Lamont, & Brauer, 2016; Yang et al., 2013) and 1 study with nine patients of Leukoaraiosis (Kaski, Dominguez, Allum, & Bronstein, 2013). Forty-nine studies investigated the effects of NIBS plus motor training vs. sham NIBS plus motor training (Allman et al., 2016; Ang et al., 2015; Avenanti et al., 2012; Benito et al., 2012; Bolognini et al., 2011; Brodie et al., 2014; Cha & Kim, 2016; Chang et al., 2015; Chang et al., 2012; Danzl et al., 2013; Fusco, Assenza, et al., 2014; Fusco, Iosa, et al., 2014; Galvão et al., 2014; Geroin et al., 2011; Giacobbe et al., 2013; Gomes-Osman & Field-Fote, 2015; Hesse et al., 2011; Kaski et al., 2013; Kim et al., 2010; Kumru et al., 2016; Lefebvre et al., 2014; Lefebvre et al., 2013; Lefebvre et al., 2014; Lin et al., 2015; Lindenberg et al., 2010; Lüdemann-Podubecká et al., 2015; Madhavan et al., 2011; Malcolm et al., 2007; Manenti et al., 2016; Moisello et al., 2015; Mortensen et al., 2016; Nair et al., 2011; Park et al., 2015; Pomeroy et al., 2007; Raithatha et al., 2016; Rocha et al., 2016; Schabrun et al., 2016; Seniów et al., 2012; Takeuchi et al., 2005; Takeuchi et al., 2008; Triccas et al., 2015; Viana et al., 2014; Vongvaivanichakul et al., 2014; Wang et al., 2012; Wu et al., 2013; Yang et al., 2013; Yozbatiran et al., 2016; Zheng et al., 2015; Zimerman et al., 2012), whereas three investigated the effects of NIBS plus motor training vs. motor training (Abo et al., 2014; Cha et al., 2014; Lee & Chun, 2014) .

Thirty-nine randomized clinical trials and 13 crossover trials were performed between 2005-2016; the 55.75% of them was performed in the last 3 years. Forty-four studies included one experimental group and one control group, or the study adopted a cross-over design, with patients being their own control (namely, the same patients underwent the NIBS treatment plus motor training, or the motor training alone or with sham NIBS); in 4 studies patients were divided in 2 experimental groups and one control group (Hesse et al., 2011; Kim et al., 2010; Madhavan et al., 2011; Rocha et al., 2016), in one study there were 2 experimental groups and 2 control groups (Pomeroy et al., 2007), whereas in another study there were one experimental group and 2 control groups (Park et al., 2015). Additionally, in two studies, patients received NIBS 2 or 3 times: in the

first case, NIBS was applied before or after the motor training (Avenanti et al., 2012), in the second case before, during or after the motor training (Giacobbe et al., 2013).

Thirty-six studies assessed the effects of NIBS associated with motor training on the upper-limb motor recovery, 14 studies targeted lower-limb motor functions, and 2 studies looked for motor improvement at both the upper and the lower limb.

NIBS and motor training protocols

All of the included studies used different protocols of NIBS applied over the primary motor cortex. Thirty-two studies applied tDCS protocols, while 20 studies applied rTMS protocols. The main characteristics of the tDCS protocols were: (i) current intensities ranging between 0.5-2 mA, with 25 out of 32 studies (78%) using 1 or 2 mA; (ii) 18 out of 32 studies (56.25%) applied tDCS for a mean of 20 min (durations range= 7 to 40 min); (iii) in 18 out of 32 studies (56.25%) the electrodes' size was of 35 cm^2 (range= 7 to 40 cm^2); (iv) 17 out of 32 studies (53%) combined tDCS with physical therapy or motor training (unspecified type); (v) 25 out of 32 studies (78%) trained patients for a maximum of 1 hour daily (duration range of the motor practice = 15 min - 4 hours). Table 3 shows in details the features for the tDCS protocols.

With respect to rTMS, overall the frequency ranged between 1-20 Hz: (i) in 13 out of 20 studies (65%) 1 Hz rTMS was used; (ii) 14 out of 20 studies (70%), pulses were delivered at 90% of the motor thresholds (range 80-130%); (iii) 13 out of 20 studies (65%) delivered >1000 pulses during the rTMS (number of pulses ranged between 200-2000); (iv) in 11 out of 20 studies (55%) the motor training consisted of an unspecified motor training; (v) 14 out of 20 studies (70%) trained patients for a maximum of 1 hour (duration range= 5 min – 5 hours). Table 4 reports in details the parameters of each rTMS study.

Table 3. Parameters of the tDCS protocols of the included studies

Author/year	Intensity/duration (minutes)	Number of sessions	Electrode location	Electrode size (cm^2)	Characteristics of the motor training
Ang *et al.*, 2015	1mA 20	10	target: ipsilesional M1 return: contralesional M1	not available	4 blocks of 40 trials totalizing 160 trials with 3-5min of rest between blocks (each block: 13min)
Allman *et al.*, 2016	1mA 20	9	target: C3 return: contralateral supraorbital area	35	60 minutes of physical therapy considering each patient condition
Bolognini *et al.*, 2011	2mA 40	10	target: ipsilesional M1 return: contralesional M1	35	4 hours per day of CIMT
Cha *et al.*, 2014	1mA 20	20	target: C3 or C4 return: contralateral supraorbital area	35	30 minutes per day of basic training for upper and lower limbs
Chang *et al.*, 2015	2mA 20	10	target: cortical motor area controlling the leg return: contralateral supraorbital area	target: 7.07 return: 28.26	2 hours and 30 minutes during the week and 1 hour on Saturday of general physical therapy
Danzl *et al.*, 2013	2mA 20	12	target: cortical motor area controlling the leg return: supraorbital	25/35	20 to 40 minutes per day of gait training using LOKOMAT
Fusco *et al.*, 2014b	1.5mA 10	10	target: contralesional M1 return: right shoulder	35	45 minutes of physical therapy (twice a day)
Fusco *et al.*, 2014a	1.5mA 15	2	target: anode over ipsilesional M1 return: contralateral supraorbital area	35	60 minutes of physical therapy (repetitive and resistive movements of the upper limb)
Geroin *et al.*, 2011	1.5mA 7	10	target: leg cortical representation of the affected hemisphere return: contralateral supraorbital area	35	50 minutes of gait training
Giacobe *et al.*, 2013	2mA 20	4	target: ipsilesional M1 return: contralateral supraorbital area	not available	20 minutes of robot-assisted training – flexion/extension of the wrist (4 blocks of 4 minutes each with 1 minute of rest)

Hesse *et al*., 2011	2mA 20	30	target: C3 or C4 return: contralateral supraorbital area	35	20 minutes of robot-assisted training
Kaski *et al*., 2013	2mA 15	2	target: 10-20% anterior to Cz return: inion	16/40	15 minutes of balance and gait training
Kim *et al*., 2010	2mA 20	10	target: anode over ipsilesional M1 and cathode over contralesional M1 return: contralateral supraorbital area	25	30 minutes of occupational therapy
Kumru *et al*., 2016	2mA 20	20	Target: vertex Return: contralateral supraorbital area	35	20 minutes of LOKOMAT training during tDCS plus 30 minutes after tDCS
Lee & Chun., 2014	2mA 20	15	target: contralesional M1 return: contralateral supraorbital area	25	30 minutes per day of occupational therapy and virtual reality therapy
Lefebvre *et al*., 2014	1mA 30	2	target: ipsilesional M1 return: contralesional M1	35	circuit game with blocks of training and rest
Lefebvre *et al*., 2013	1mA 30	2	target: anode over ipsilesional M1 and cathode over contralesional M1 return: -	35	30 minutes of training (5 blocks of 6 tasks each)
Lefebvre *et al*., 2012	1mA 20	2	target: anode over ipsilesional M1 and cathode over contralesional M1 return: -	35	10 trials of motor task
Lindenberg *et al*., 2010	1.5mA 30	5	target: anode over ipsilesional M1 and cathode over contralesional M1 return: -	16.3	60 minutes of physical therapy and occupational therapy (sensory-motor integration and coordination)
Madhavan *et al*., 2011	0.5mA 15	3	target: lesioned lower limb M1 or non-lesioned lower limb M1 return: contralateral supraorbital area	8	15 trials of 1 minute each with 1 minute of rest every 5 trials
Mortensen et al., 2015	1.5mA 20	5	target: ipsilesional M1 return: contralateral supraorbital area	35	30 minutes of functional tasks

Manenti *et al.*, 2016 (CT)	2mA 25	10	target: F3 or F4 return: contralateral supraorbital area	35	25 minutes of physical therapy
Nair *et al.*, 2011	1mA 30	5	target: contralesional M1 return: contralateral supraorbital area	not available	60 minutes of proprioceptive neuromuscular facilitation
Park *et al.*, 2015	2mA 15	12	target: Cz return: right supraorbital area	not available	30 minutes of general exercise therapy
Raithatha *et al.*, 2016	2mA 20	36	target: lower limb area return: contralateral supraorbital area	25/35	60 minutes of LOKOMAT training
Rocha *et al.*, 2016	1mA 13/9	12	target: affected/not affected M1 Return: contralateral supraorbital area	35	60 minutes of intensive training of paretic upper limb + immobilization of the non-paretic
Schabrun *et al.*, 2016	2mA 20	9	target: C3 return: contralateral supraorbital area	35	60 minutes of walking training with a double task
Triccas *et al.*, 2015	1mA 20	18	target: C3 or C4 return: contralateral supraorbital area	35	1 hour and 15 minutes of robotic training which targeted integrated movements of shoulder, elbow, wrist, and grip
Viana *et al.*, 2014	2mA 13	15	target: C3 or C4 return: contralateral supraorbital area	35	60 minutes per day of virtual reality therapy
Wu *et al.*, 2013	1.2mA 20	20	target: C3 or C4 return: unaffected shoulder	24.75	30 minutes per day of physical therapy
Yozbatiran *et al.*, 2016	2mA 20	10	target: C3 or c4 return: contralateral supraorbital area	35	robot-assisted arm training
Zimerman *et al.*, 2012	1mA 20	2	target: contralesional motor cortex return: contralateral supraorbital area	25	motor sequence of movements (same number of repetitions)

Abbreviations: mA – miliampère; M1 – primary motor cortex; CIMT – constraint-induced movement therapy; C3 – left primary motor cortex; C4 – right primary motor cortex; Cz – midline; F3 – left prefrontal dorsolateral cortex; F4 – right prefrontal dorsolateral cortex.

Table 4. Parameters of the rTMS protocols of the included studies

Author/year	rTMS type	Frequency (Hz)	Intensity of motor threshold (%)	Number of pulses	Number of sessions	Characteristic of the motor training
Abo *et al.*, 2014	contralesional	1	90	1200	22	120 minutes of occupational therapy (twice a day)
Avenanti *et al.*, 2012	contralesional	1	90	1500	10	45 minutes of physical therapy (manual dexterity, pinch, and force)
Brodie *et al.*, 2014	ipsilesional	5	90	1200	2	24 min of 6 blocks of 9 trials each during 4 min
Cha & Kim, 2016	contralesional	1	90	1200	20	30 minutes of conventional rehabilitation therapy (neurodevelopmental facilitation)
Chang *et al.*, 2012	ipsilesional	10	80	1000	10	10 blocks of 50 seconds each with 5 seconds of rest between them
Galvão *et al.*, 2014	contralesional	1	90	1500	10	30 minutes of physical therapy (force, flexibility, balance sensorial stimulation)
Benito *et al.*, 2012	vertex	20	90	1800	15	5 hours of motor training (including gait training)
Malcolm *et al.*, 2007	ipsilesional	20	90	2000	10	5 hours per day of home activities
Moisello *et al.*, 2015	ipsilesional	5	90	1250	2	blocks of 56-112 movements
Pomeroy *et al.*, 2007	ipsilesional	1	120	200	8	5 minutes of motor task
Seniów *et al.*, 2012	contralesional	1	90	1800	15	45 minutes of physical therapy (bobath and gait training)
Takeuchi *et al.*, 2005	contralesional	1	90	not available	1	60 or 15 minutes of a motor task (frequency between 0.3)
Takeuchi *et al.*, 2008	contralesional	1	90	1500	1	15 minutes of pinch task
Vongvaivanichakul *et al.*, 2014	contralesional	1	90	1200	1	5 min of training with 2 min of rest

Wang *et al.*, 2012	contralesional	1	90	600	10	30 minutes of gait training
Yang *et al.*, 2013	contralesional	5	100	1200	12	gait training (treadmill – initial speed 80% of the capacity and increments of 0.2Km/h for 5 minutes)
Zheng *et al.*, 2015	contralesional	1	90	1800	24	30 minutes of exercises for shoulder, elbow, and wrist
Lin *et al.*, 2015	contralesional	1	130	900	15	45 minutes of physical therapy (transfer, balance, ambulation training)
Lüdemann-Podubecká *et al.*, 2015	contralesional	1	100	900	15	30 minutes of motor training
Gomes-Osman *et al.*, 2015	contralesional	10	80	800	3	fine motor task through Nine-hole peg test

rTMS – repetitive transcranial magnetic stimulation.

Risk of bias

The risk of bias for the considered 52 studies is shown in Figure 2. For the criteria "randomization" (selection bias), we judged 26 studies (50%) as having high (n=5) or uncertain (n=21) risk of bias because it was not clear if they adopted a method for sequence generation, while 26 studies performed the random sequence allocation. The majority of studies (75%) did not report concealment of treatment allocation (selection bias) or did not describe how it was performed; therefore, we judged these studies as having high (n=28) or uncertain risk of bias (n=11). Blinding of participants and therapists (execution bias) was accomplished in 37 studies (71%) while blinding of outcome assessor (detection bias) in 33 studies (63.5%); we judged these studies as having a low risk of bias. Finally, 33 studies (63.5%) were judged as having a low risk of bias concerning selective reporting of outcome (publication bias).

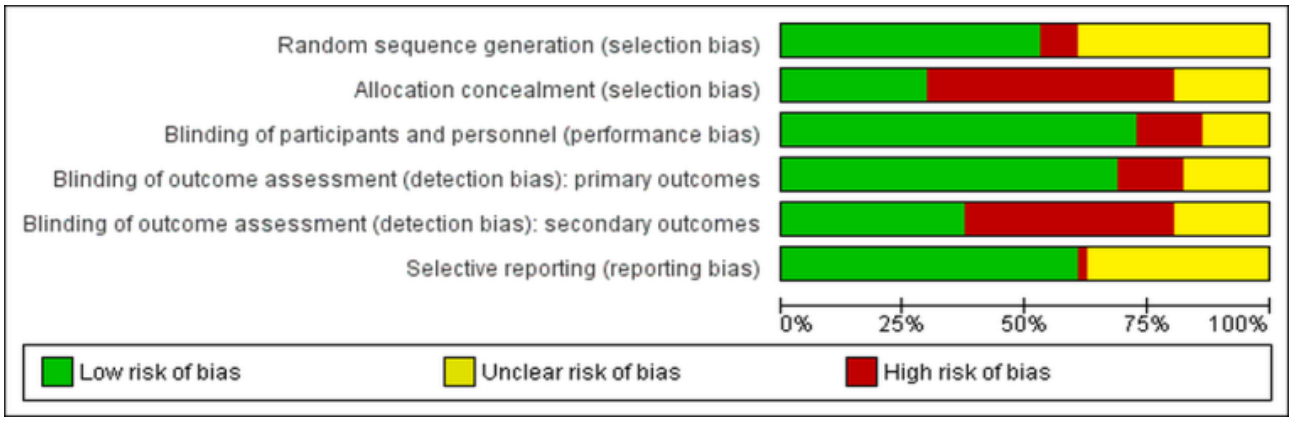

Figure 2. Assessment of risk of bias.

Effect of interventions

Stroke patients

The adjuvant effect of NIBS on motor training in neurological patients with motor disorders was assessed through a meta-analysis of 30 studies involving 736 stroke patients (Abo et al., 2014; Allman et al., 2016; Bolognini et al., 2011; Brodie et al., 2014; Cha et al., 2014; Cha & Kim, 2016; Chang et al., 2015; Galvão et al., 2014; Geroin et al., 2011; Giacobbe et al., 2013; Hesse et al., 2011; Lee & Chun, 2014; Lefebvre et al., 2013; Lefebvre et al., 2014; Lin et al., 2015; Lindenberg et al., 2010; Lüdemann-Podubecká et al., 2015; Malcolm et al., 2007; Mortensen et al., 2016; Nair et al., 2011; Park et al., 2015; Pomeroy et al., 2007; Rocha et al., 2016; Seniów et al., 2012; Triccas

et al., 2015; Viana et al., 2014; Wang et al., 2012) and 56 patients with Parkinson's disease (Manenti et al., 2016; Schabrun et al., 2016).

Since we included studies with substantial differences with respect to the sample and methodology, our results are presented according to the patient's disease and the type of NIBS technique (anodal, cathodal or bihemispheric tDCS, and low or high-frequency rTMS). Twenty-seven studies with 792 stroke patients were pooled on group analysis conducted according to stroke's chronicity. For acute and subacute stroke patients, we found only a medium effect of low frequency rTMS (SMD 0.51, 95% CI 0.17-0.85, *P*=0.003), whereas for chronic stroke patients, we found evidences for: (i) a medium effect of low frequency rTMS (SMD 0.43, 95% CI 0.03-0.83, *P*=0.04); (ii) a medium effect of anodal tDCS (SMD 0.48, 95% CI 0.09- 0.87, *P*=0.01); (iii) a large effect of cathodal tDCS (SMD 1.04, 95% CI 0.12-1.96, *P*=0.03) and (iv) of bihemispheric tDCS (SMD 0.90, 95% CI 0.45-1.34, *P*<0.0001). The total effect size for this analysis was medium (SMD 0.47, 95% CI 0.31-0.62, *P* <0.00001), although heterogeneity was significantly high (see Figure 3).

Twenty-six studies with 736 stroke patients were pooled into a group analysis conducted according to the time of NIBS application (before vs. during the motor training). For NIBS applied before the motor training, we found a medium effect of low frequency rTMS (SMD 0.40, 95% CI 0.10 – 0.70, *P*=0.009), whereas for NIBS applied during the motor training, we found: (i) a medium effect of anodal tDCS (SMD 0.37, 95% CI 0.06-0.68, *P*=0.02) and (ii) a large effect of bihemispheric tDCS (SMD 0.90, 95% CI 0.45-1.34, *P*<0.0001). The total effect size for this group analysis was medium (SMD 0.45, 95% CI 0.29- 0.61, *P* <0.00001), but the heterogeneity was significantly high (see Figure 4).

Finally, 27 studies with 792 stroke patients were pooled into a group analysis performed according to the outcome measure (upper *vs.* lower-limb motor function). When upper-limb motor improvements were measured, we found: (i) a large effect of bihemispheric tDCS (SMD 0.90, 95% CI 0.45-1.34, *P* <0.0001) and (ii) a medium effect of anodal tDCS (SMD 0.68, 95% CI 0.12-1.24, *P*=0.02); whereas for improvements of lower-limb functions, only a large effect of low frequency rTMS emerged (SMD 1.05, 95% CI 0.48-1.61, *P*=0.0003). The total effect size for this group analysis was medium (SMD 0.65, 95% CI 0.27 – 1.02, *P*=0.0007), but the heterogeneity was significantly high (see Figure 5).

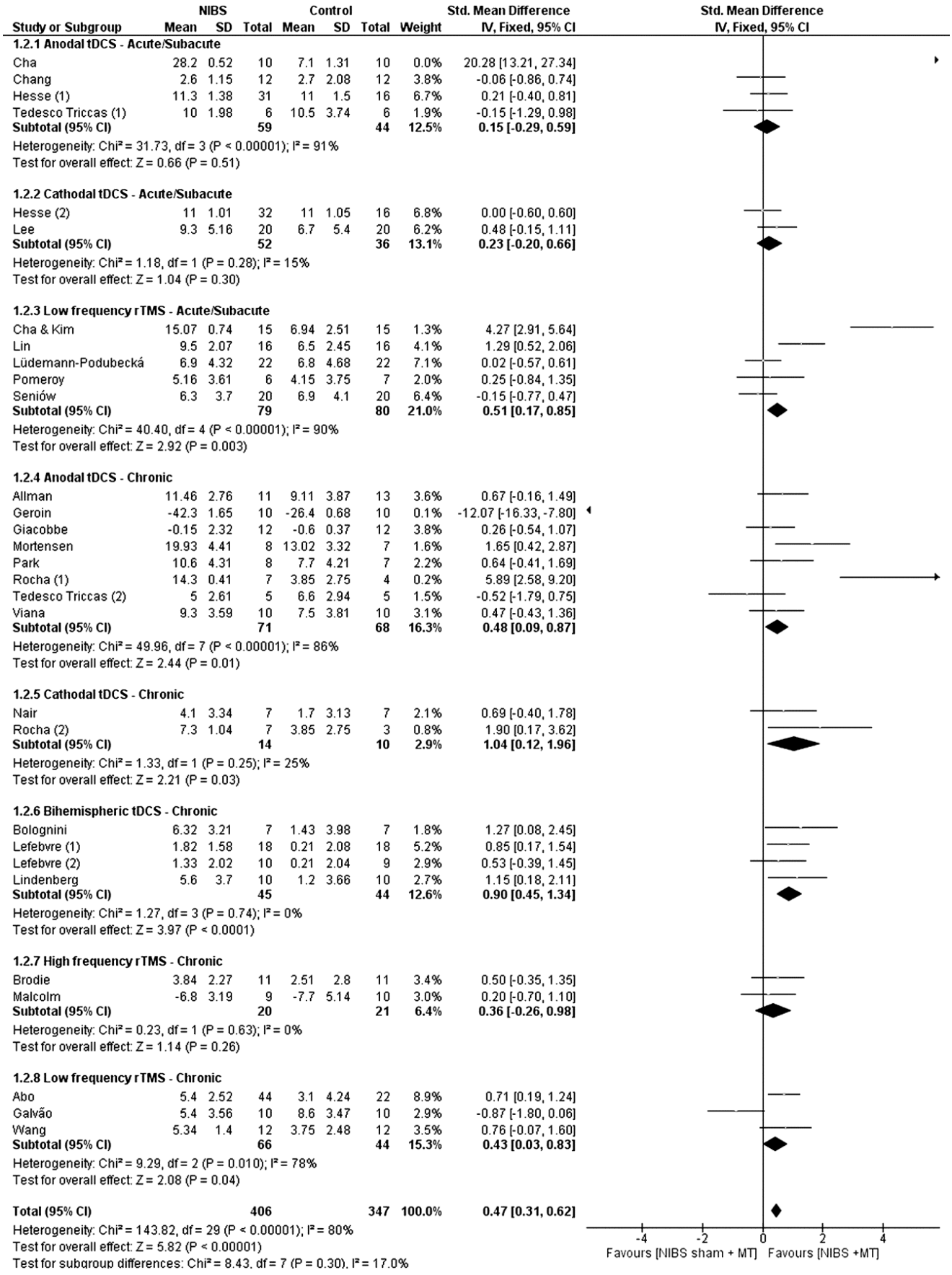

Figure 3. The effect size for group analysis conducted according to stroke's chronicity.

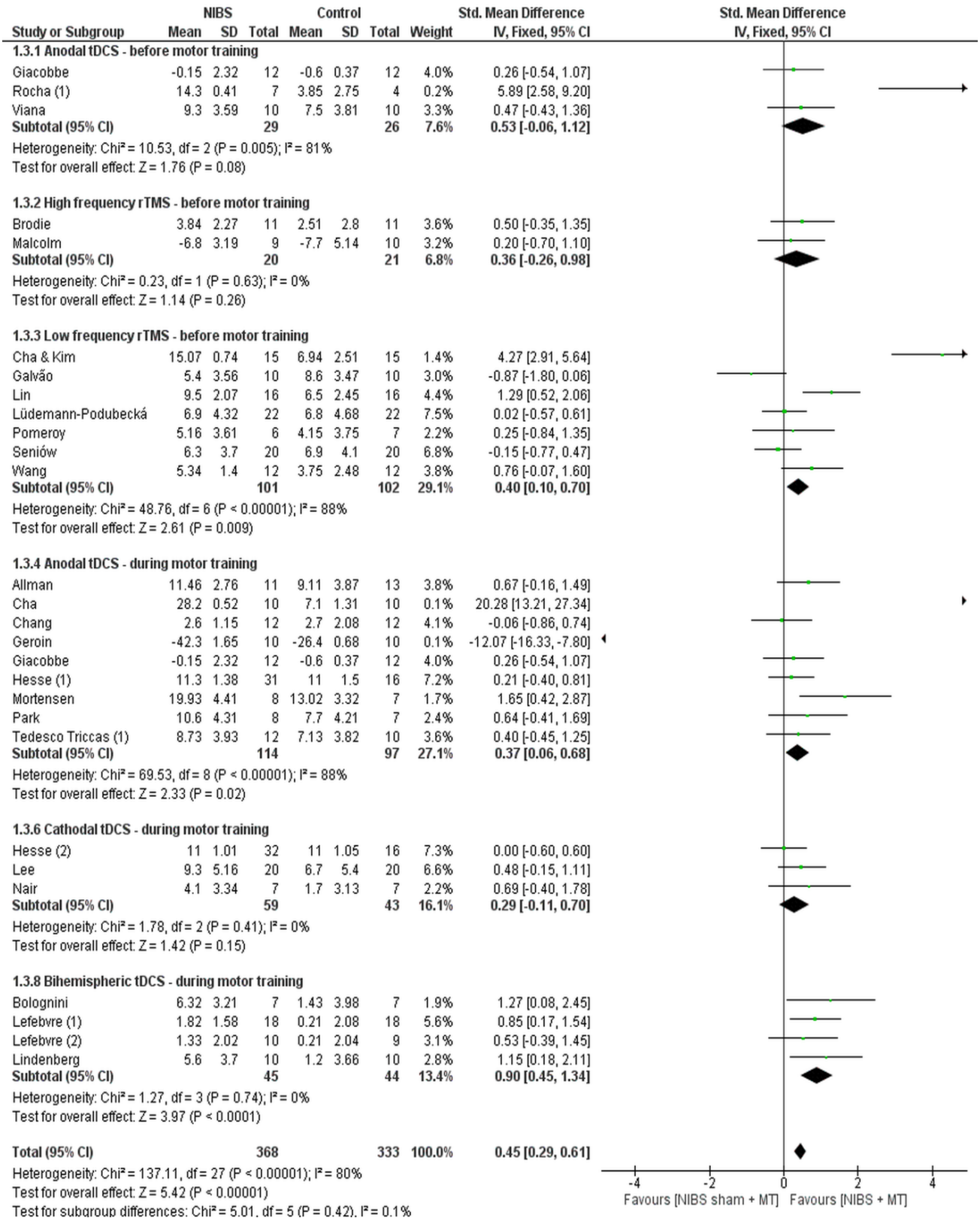

Figure 4. The effect size for group analysis conducted according to the time of NIBS application.

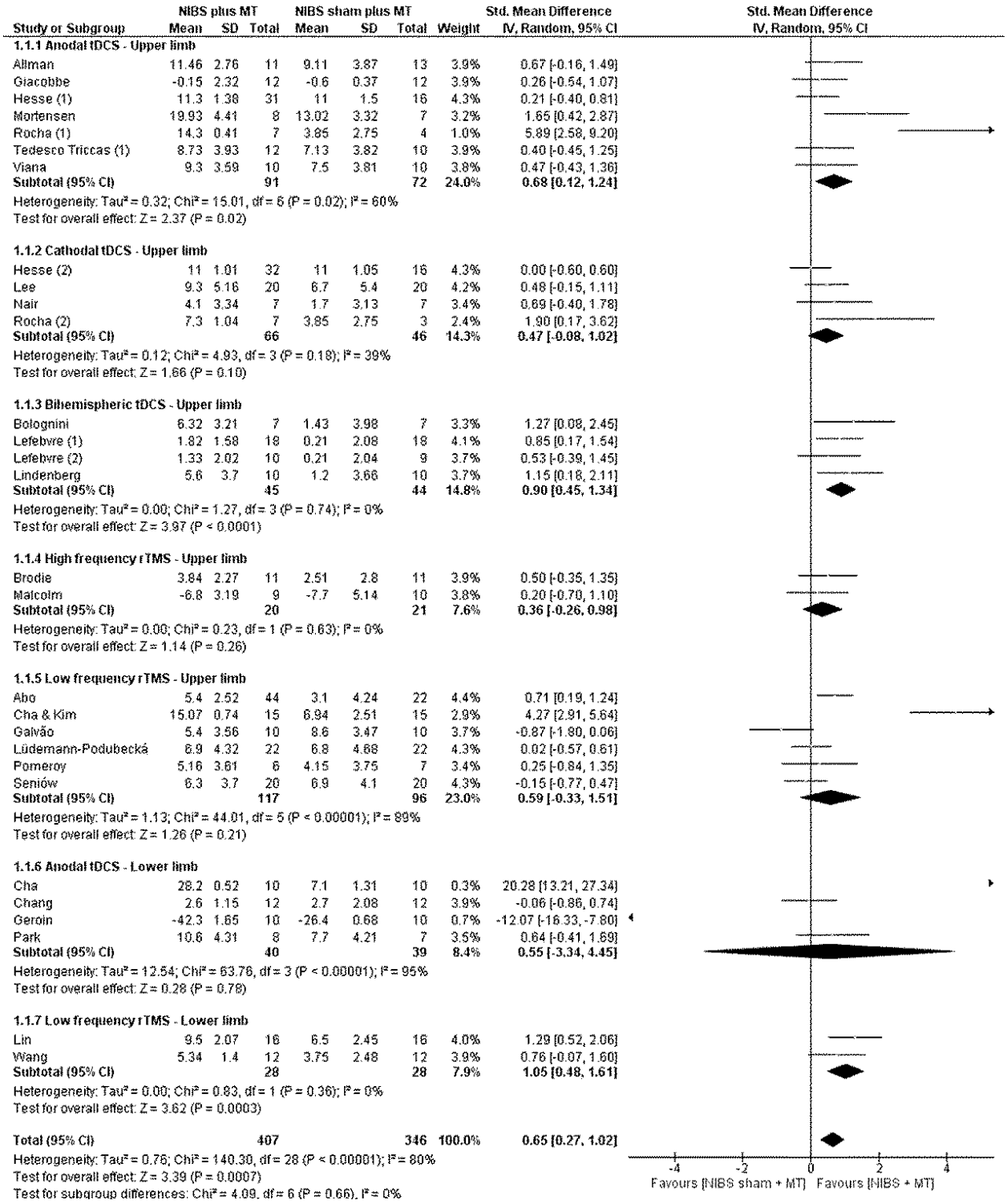

Figure 5. The effect size for group analysis conducted according to the outcome measure.

Parkinson's disease patients

Only three studies could be considered for the analysis in Parkinson's disease (Manenti et al., 2016; Schabrun et al., 2016; Yang et al., 2013); However, only 2 of them could enter into the meta-

analysis; there was no sufficient number of studies to perform a group analysis for rTMS. In this way, data from 40 patients were pooled to assess the adjuvant effect of tDCS on lower-limb motor recovery, as assessed by means of the Unified Parkinson Disease Rating Scale (Manenti et al., 2016) and considering the speed of walking (Schabrun et al., 2016). The pooled SMD for anodal tDCS was -0.15, (95% CI: -0.78-0.47) (*P*=0.63, random-effects model), which shows the absence of a facilitatory effect of on the motor training in this population (see Figure 6).

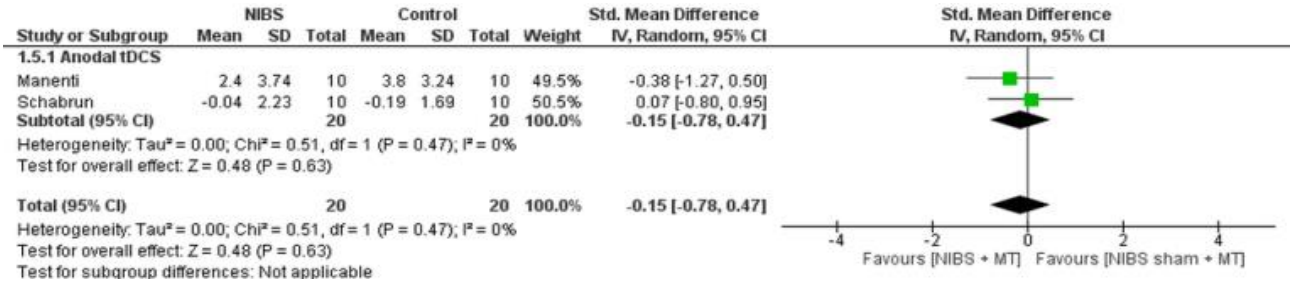

Figure 6. The effect size for group analysis of Parkinson's disease.

Spinal cord injury and Leukoaraiosis patients

Five studies conducted in 74 patients with spinal cord injury were included in this review; however, the meta-analysis was not run due to insufficient data. Only two studies assessed upper-limb motor functions (Gomes-Osman & Field-Fote, 2015; Yozbatiran et al., 2016), but their results did not show any difference between the experimental (active NIBS) and the control (sham stimulation) groups. We found a large effect size (SRM=0.85) for 10Hz rTMS applied during a repetitive motor practice, in contrast with the medium effect size (SRM=0.42) detected in the control group (sham rTMS), but without difference between the two groups. Similarly, Yozbatiran and colleagues (Yozbatiran et al., 2016) applied anodal tDCS before a robotic-assisted training and found an improvement of 41% from baseline in patients receiving anodal tDCS, vs. a 7% improvement for sham tDCS; again, no difference between the two tDCS conditions (active *vs.* sham) was found. Additionally, 3 studies (Benito et al., 2012; Kumru et al., 2016; Raithatha et al., 2016) assessing lower-limb functions did not show motor improvements by comparing the experimental and the control groups. Anodal tDCS applied before (Raithatha et al., 2016) or during (Kumru et al., 2016) the robotic-assisted training did not result in remarkable improvements. Benito and colleagues (Benito et al., 2012) found 16% of improvement after 20Hz rTMS applied before gait training, but again without difference between experimental *vs.* control treatments. Thus, at present, we cannot suggest to use NIBS combined with motor training for facilitating motor

recovery in patients with Spinal Cord Injury. So far, the few available studies applied different NIBS protocols, but none of them seems to be really effective.

Worth mentioning, only one study with 9 patients with Leukoaraiosis (Kaski et al., 2013) met our inclusion criteria and showed significant improvements in gait and balance after only 1 session of anodal tDCS applied during gait training.

Quality of evidence

Quality of evidence was assessed through GRADE approach and is shown in Figures 7 and 8. Data are presented according to the patient's disease (Stroke or Parkinson's disease) and the type of NIBS (anodal, cathodal or bihemispheric tDCS, and low and high-frequency rTMS). Additionally, for studies with stroke patients, we pooled data according to ictus chronicity (acute/subacute vs. chronic).

For studies conducted in stroke patients, 5 out of 8 of them were rated as having "very low quality". We downgraded the quality of evidence due to high risk of bias (missing data regarding concealment of treatment allocation, randomization process and/or blinding of therapists), inconsistency (nullity line crossed) and imprecision (wide confidence intervals) of effect estimates. Two out of 8 studies were rated as having "low quality" or "moderate quality". We downgraded the quality of evidence due to the low risk of bias, inconsistency and imprecision, although effect sizes were large. Only 1 study was rated as having "high quality" due to the absence of risk of bias or indirectness, and a large effect size for treatment.

Studies with Parkinson's disease patients were overall rated as having "very low quality". We downgraded the quality of evidence due to inconsistency and imprecision of effect estimates in all studies.

NIBS plus motor training compared to motor training for post stroke motor function impairment

Patient or population: patients with post stroke motor function impairment
Intervention: NIBS plus motor training
Comparison: motor training

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Motor training**	Corresponding risk **NIBS plus motor training**				
Acute/Subacute Stroke - anodal tDCS		The mean acute/subacute stroke - anodal tDCS in the intervention groups was **0.16 standard deviations higher** (0.23 lower to 0.55 higher)		119 (4 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
Chronic Stroke - anodal tDCS		The mean chronic stroke - anodal tDCS in the intervention groups was **0.53 standard deviations higher** (0.14 to 0.91 higher)		142 (8 studies)	⊕⊖⊖⊖ **very low**[4,5,6,7]	
Acute/Subacute Stroke - cathodal tDCS		The mean acute/subacute stroke - cathodal tDCS in the intervention groups was **0.18 standard deviations higher** (0.20 lower to 0.57 higher)		104 (2 studies)	⊕⊖⊖⊖ **very low**[8,9,10]	
Chronic Stroke - cathodal tDCS		The mean chronic stroke - cathodal tDCS in the intervention groups was **1.07 standard deviations higher** (0.24 to 1.89 higher)		28 (2 studies)	⊕⊕⊕⊖ **moderate**[11,12,13,14]	
Acute/Subacute Stroke - low frequency rTMS		The mean acute/subacute stroke - low frequency rTMS in the intervention groups was **0.51 standard deviations higher** (0.17 to 0.85 higher)		159 (5 studies)	⊕⊕⊖⊖ **low**[15,16,17,18]	
Chronic Stroke - low frequency rTMS		The mean chronic stroke - low frequency rTMS in the intervention groups was **0.43 standard deviations higher** (0.03 to 0.83 higher)		110 (3 studies)	⊕⊖⊖⊖ **very low**[19,20,21]	
Chronic Stroke - high frequency rTMS		The mean chronic stroke - high frequency rTMS in the intervention groups was **0.36 standard deviations higher** (0.26 lower to 0.98 higher)		41 (2 studies)	⊕⊖⊖⊖ **very low**[22,23,24]	
Chronic Stroke - bihemispheric tDCS		The mean chronic stroke - bihemispheric tDCS in the intervention groups was **0.90 standard deviations higher** (0.45 to 1.34 higher)		89 (4 studies)	⊕⊕⊕⊕ **high**[25,26,27]	

*The basis for the **assumed risk** (i.e., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Three out of four studies did not perform or did not provide data concerning concealment of treatment allocation and two out of four studies did not perform blinding of participants and therapists;
[2] Three out of four studies have crossed the nullity line;
[3] Three out of four studies have wide confidence intervals;
[4] Five out of eight studies did not perform or did not provide data regarding concealment of the treatment allocation and four out of eight studies did not perform blinding of participants/therapists;
[5] Five out of eight studies have crossed the nullity line;
[6] Five out of eight studies have very wide confidence intervals;
[7] Large effect of 0.53;
[8] All studies have crossed the nullity line;
[9] All studies have made multiple comparisons (more than one experimental group);
[10] All studies have wide confidence intervals;
[11] One out of two studies have crossed the nullity line;
[12] One out two studies have made multiple comparisons (more than one experimental group);
[13] One out of two studies has a wide confidence interval;
[14] Very large effect of 1.07;
[15] Four out of five studies did not perform or did not provide data regarding randomization process;
[16] Three out of five studies have crossed the nullity line;
[17] Two out of four studies have wide confidence intervals;
[18] Large effect of 0.51;
[19] Two out of three studies did not perform concealment of the treatment;
[20] Two out of three studies have crossed the nullity line;
[21] Two out of three studies have wide confidence intervals;
[22] All studies did not perform or did not provide data regarding concealment of the treatment and one out of two studies did not provide data regarding randomization process as well as blinding of the outcome assessor:
[23] All studies have crossed the nullity line;
[24] All studies have wide confidence intervals;
[25] Two out of four studies have crossed the nullity line;
[26] Two out of four studies have wide confidence intervals;
[27] Very large effect of 0.90.

Figure 7. Quality of the evidence for studies performed with Stroke patients.

NIBS plus motor training compared to motor training for Parkinson's disease motor function impairment

Patient or population: patients with Parkinson's disease motor function impairment
Intervention: NIBS plus motor training
Comparison: motor training

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Motor training**	Corresponding risk **NIBS plus motor training**				
Anodal tDCS		The mean anodal tDCS in the intervention groups was **0.15 standard deviations lower** (0.78 lower to 0.47 higher)		40 (2 studies)	⊕⊖⊖⊖ **very low**[1,2]	

*The basis for the **assumed risk** (i.e, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] All studies have crossed nullity line;
[2] All studies have wide confidence intervals.

Figure 8. Quality of the evidence for studies performed with patients with Parkinson's disease.

2.4. Discussion

This systematic review with meta-analysis covers 1255 patients with motor impairment due to different neurological diseases in order to assess the adjuvant effect of NIBS on motor training. The analyses reveal that NIBS can increase patient's response to motor therapies; the most robust results are those from studies conducted in stroke patients, although we should acknowledge the larger set of published data. In the stroke population, there is a good line of evidence showing the additive effect of both tDCS and rTMS on motor training. Low-frequency rTMS is more effective when applied before the motor therapy, while bihemispheric and anodal tDCS needs to be applied during the training; in every case, NIBS is effective when applied in the chronic stage of illness, but not in acute/subacute conditions. For Parkinson's disease, Spinal Cord Injury and Leukoaraiosis, definitive conclusions cannot be withdrawn.

Combining NIBS with motor training in stroke patients

In which stage of illness the treatment should be performed?

According to the meta-analysis results, only low-frequency rTMS combined with motor training shows positive, additive effects on motor recovery if applied in acute/subacute stroke patients, while patients in a chronic stage of illness benefit from the add-on use of low-frequency rTMS, and anodal, cathodal tDCS and bihemispheric tDCS. This evidence is in line with preliminary suggestions put forward by a previous review article by Adeyemo and colleagues (2012), which pointed out to the dependency of NIBS effects on the chronicity of stroke (Adeyemo, Simis, Macea, & Fregni, 2012).

After a brain damage, a cascade of neuroplastic changes occurs, such as angiogenesis, neurogenesis, and restructuring of neural networks, which act as neuroprotection of the brain tissue (Buma et al., 2013; Chopp et al., 2007; Krakauer, 2006). Moreover, brain damages determine a loss of neuronal tissue in the ipsilesional hemisphere, which in turn promotes remarkable bilateral changes in cortical excitability. Previous fMRI and PET studies showed a decrease of cortical excitability in the ipsilesional hemisphere, often paralleled by an increase of the cortical excitability in the intact hemisphere, which, in turn, increases its transcallosal inhibition over the damaged areas. Such interhemispheric imbalance causes detrimental effects on the post-stroke motor recovery of the affected limb (Alagona et al., 2001; Carey, Fregni, & Pascual-Leone, 2006; Di Lazzaro, Ziemann, & Lemon, 2008; Joachim Liepert, Bauder, Miltner, Taub, & Weiller, 2000; Manganotti et al., 2002; Marshall et al., 2000). Spontaneous neurological recovery takes place within the first 10 weeks after the stroke, and it is associated with the normalization of the

interhemispheric imbalance in favor of the damaged hemisphere (Cicinelli et al., 2003; Joachim Liepert et al., 2000). In light of this evidence, strategies for driving post-stroke motor recovery by means of NIBS may attempt either the down-regulation of contralesional cortical excitability or the up-regulation of the ipsilesional cortical excitability.

The present study shows that, overall, the combined use of NIBS and motor training is not effective for increasing motor recovery when patients are in the acute or subacute stage of illness; except for low-frequency rTMS, which seems effective even in these stages of illness. Instead, the combined use of NIBS and motor training has a merit in chronic stroke patients, regardless of the type stimulation (rTMS and tDCS). Some reflections arise from these findings. We know that spontaneous neurological recovery is strongly plasticity-dependent in the early weeks after stroke. On the other hand, the motor learning, which as the basis of the majority of motor therapies, is able to interact with brain plasticity: the brain is able to encode experience and learn new behaviors after motor learning through synaptogenesis and reorganization of neural networks (Langhorne et al., 2009; Pekna et al., 2012; Richards et al., 2008), as discussed in details in Chapter 1. Synaptic mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD), are likely recruited by NIBS after-effects (Gillick & Zirpel, 2012; Malenka & Bear, 2004). The greater brain plasticity featuring the acute phase post-stroke, which however is linked to a greater instability of the cortical networks in both hemispheres, may act as a protective mechanism that counteracts the NIBS after-effects to prevent a further disturbance of neural network functioning. This view is supported, by the study by Cosentino and colleagues, which combined rTMS with tDCS to evaluate how homeostatic plasticity can shape NIBS after-effects. Healthy subjects underwent high frequency (5-Hz) rTMS, which was pre-conditioned by 15 min of anodal or cathodal tDCS (Cosentino et al., 2012). Results showed an increase of cortical excitability (indexed by increased motor evoked potentials) when 5-Hz rTMS was applied after cathodal tDCS, whereas cortical excitability decreased when 5-Hz rTMS was applied after anodal tDCS. This evidence indicates that cortical excitability shifts by NIBS are depended on the functional state of the motor cortex at the time of stimulation.

It is worth mentioning that the negative role of contralesional hyperactivity in post-stroke motor recovery has been recently questioned (Di Pino et al., 2014): contralesional activity may act as a compensatory mechanism, depending on the extent of surviving neural tissue in the ipsilesional motor system (Cramer et al., 1997; Johansen-Berg et al., 2002). Indeed, the extension of the cortical lesion and the integrity of the corticospinal tract predict the efficacy of NIBS in the different phases of post-stroke recovery (Lefaucheur et al., 2017).

Stimulation timing with respect to the motor practice

If NIBS has to be paired with a motor training, the issue of the "stimulation timing" (i.e., *When NIBS should be delivered?*) deserves particular attention. Although evidence suggests that NIBS time window of the application is a key factor to boost behavioral and brain effects, actually a consensus regarding this optimal time is still lacking (Kubis, 2016; Simonetta-Moreau, 2014). In principle, NIBS could be applied before the motor training as a priming strategy (Antal, Polania, Schmidt-Samoa, Dechent, & Paulus, 2011; Stagg et al., 2009), during motor training for reinforcing the plastic changes boosted by learning (Cuypers et al., 2013; Madhavan et al., 2011; Reis et al., 2009), but even after the motor training to consolidate learning processes (Lefebvre & Liew, 2017).

Our meta-analysis shows positive additive effects both when NIBS is delivered before (with low-frequency rTMS) and during (with anodal and bihemispheric tDCS) the motor training. A review from Kang and colleagues had already suggested that tDCS applied before or during motor training promotes larger improvements (Kang, Summers, & Cauraugh, 2016). The efficacy of NIBS applied during motor training is more reliable, given that its success is proven by highly consistent and robust findings, as compared to the studies that applied NIBS before the motor training. Moreover, the *online* application is also supported by evidence in healthy individuals. For example, Stagg and colleagues showed faster learning rates of healthy individuals when anodal tDCS (1 mA over M1 during 10 minutes) was applied during an explicit sequence-learning task (Stagg & Nitsche, 2011). In the same way, Martin and colleagues (2014) found larger improvements when anodal tDCS (2 mA for 30 minutes) was delivered *online* during a cognitive training, as compared to when it was delivered *offline* (immediately before) (Martin, Liu, Alonzo, Green, & Loo, 2014). Sriraman and colleagues showed larger improvements when anodal tDCS (1 mA for 15 minutes) was applied during an ankle visuomotor learning task, than when it was applied before the task (Sriraman, Oishi, & Madhavan, 2014).

The optimal timing of NIBS delivery for boosting motor learning is likely linked to synaptic plasticity mechanisms. Both motor learning and NIBS after-effects rely on LTP-like changes, which can affect cortical networks functioning (Muellbacher et al., 2002; Stagg & Nitsche, 2011; Stefan et al., 2005; Ziemann, 2004a). Homeostasis is likely to respond definitively to artificial and functionally nonspecific changes in network activity, such as those induced by NIBS, in order to avoid destabilization and preserve neural activity within a reasonable physiological range (Bienenstock, Cooper, & Munro, 1982; Jung & Ziemann, 2009; Turrigiano & Nelson, 2004). Thus, if neuronal networks are already working at high levels, NIBS effects will be reduced to prevent a destabilization. This is a reasoning similar to that which explains the negative findings in acute/subacute stroke, as discussed in the previous section.

Many post-stroke patients may present an interhemispheric cortical imbalance at the time of NIBS delivery. If this is the case, the interhemispheric imbalance cannot be modulated in a linear way by a unilateral stimulation, targeting only the ipsilesional or the contralesional motor system. Our meta-analysis indeed suggests that the use of bihemispheric tDCS during motor training (effect size=0.90) may be the most effective option to improve post-stroke motor performance, likely because it can concurrently upregulate and downregulates intracortical and interhemispheric excitability. A previous study by Sehm and colleagues investigated immediate and long-lasting effects of uni- and bi-lateral tDCS over the motor cortex on intracortical and interhemispheric facilitation in healthy individuals (Sehm, Kipping, Schäfer, Villringer, & Ragert, 2013). They found that only the bihemispheric tDCS can affect both *online* and *online* (after-effects) intracortical and interhemispheric facilitation, while unilateral tDCS had only immediate effects, but not after-effects.

While the present results offer some suggestions for an optimal combination of tDCS with motor training in stroke patients, there is not enough evidence for suggesting an optimal way to combine rTMS with motor learning therapies in stroke rehabilitation.

Combining NIBS with motor training in Parkinson's disease

This review also aimed to verify the additive effects of NIBS on training-induced motor recovery in patients with motor disorders caused by Parkinson's Disease (PD), Leukoaraiosis patients or patients with Spinal cord injury. However, for these diseases, the analysis included a very limited number of studies, preventing to perform further subgroup analyses. For PD, the meta-analysis does not suggest a benefit of the combined approach, at least for coupling of anodal tDCS and motor training. Thus, the discussion of such findings remains speculative.

Different factors may affect tDCS effects in PD. First, the age: PD patients are mainly elderly; there is evidence showing that old and young individuals respond differently to NIBS (Boggio et al., 2006; Costa-Ribeiro et al., 2016; Nitsche et al., 2007; Verheyden, Purdey, Burnett, Cole, & Ashburn, 2013), likely due to changes in synaptic plasticity in aging (Kuppuswamy et al., 2011). Second, PD disrupts motor learning (in particular, sequential learning and consolidation), primarily as consequence of the basal ganglia dysfunction (Broeder et al., 2015). Third, PD duration and severity impact on brain plasticity: there is a negative correlation between the amount of cortical plasticity and the severity of clinical symptoms (Kojovic et al., 2015), as well as between the level of motor cortex activation and the disease stage, with a reduced motor cortical activity in the early stage (Buhmann et al., 2003; Haslinger et al., 2001; Sabatini et al., 2000), which turns to

hyperactivation in the advanced stage. Together, these factors may negatively affect the efficacy of NIBS in PD in unpredictable ways (Quartarone et al., 2014).

It is also important to consider others potential confounding factors related to NIBS protocols, such as the current polarity and intensity, the targeted cortical area and the intake of dopaminergic medication. Current literature in PD patients, as well in healthy individuals, shows stronger tDCS effects when the current intensity is >1 mA (up to 2.0 mA) (Boggio et al., 2006; Fregni et al., 2006; Nitsche et al., 2007). tDCS effects are also dependent on the bidirectional relationship between targeted brain area and the type motor task (Broeder et al., 2015). The assumption of dopaminergic medication also affect the patient's response to tDCS: improvements of motor performance occurs after anodal tDCS when patients are not under medication (Boggio et al., 2006; Fregni et al., 2006), while the same tDCS protocol has a negative effect on motor performance (in particular, gait) if patients are taking dopaminergic drugs (Verheyden et al., 2013). However, such finding was not confirmed by the study by Costa-Ribeiro and colleagues, which showed improvements in gait performance independently of medication intake (Costa-Ribeiro et al., 2016). Further studies are needed to confirm the role of dopaminergic medicine.

2.5. Conclusion

Results from the present work are sufficient to support and encourage an adjuvant use of NIBS at least in post-stroke motor rehabilitation, but it also highlights the influence of the disease chronicity, and the utility of some, but not all, NIBS protocols, whose efficacy relies on the type and strategy of stimulation (neurostimulation vs. neuromodulation of ipsilesional, contralesional, or bilateral motor areas, which should be timed to the motor practice).

CHAPTER 3

‖ Study 2 ‖

Neuromodulation of premotor and posterior parietal cortices for enhancing motor learning

3.1. Introduction

As illustrated in the introduction, and deeply analyzed with the study described in Chapter 2, tDCS has been extensively applied to boost motor learning in neurologically healthy and post-stroke individuals (see Chapter 1) The approach typically involves stimulating the primary motor cortex (M1). The majority of published works has applied anodal tDCS over the M1 contralateral to the trained hand, while motor learning was assessed with different motor learning tasks (i.e., finger tapping task, serial reaction time sequence (Nitsche et al., 2003; Reis & Fritsch, 2011); overall, current evidence shows the effectiveness of motor cortex stimulation by tDCS for improving motor learning processes both in healthy (i.e., Stagg & Nitsche, 2011) and post-stroke patients with motor deficits (i.e., Zimerman et al., 2012).

The almost exclusive emphasis on motor cortex stimulation for affecting motor learning has a theoretical rational: M1 is the primary cortical region of the motor system, also representing the "final common pathway" of movement execution. Indeed, M1 is the main contributor to generating neural impulses that pass down to the spinal cord (i.e., corticospinal tract) and control the execution of voluntary movements (Adkins-Muir & Jones, 2003; Plautz et al., 2003). Lesions of the precentral gyrus cause paralysis of the contralateral side of the body. M1 is also the main locus of plastic changes induced by motor learning, which in turn represent the main neural substrate for the training-induced motor improvements - see Chapter 1 (Pascual-Leone et al., 2005). From a technical point of view, the choice of applying tDCS over M1 could also reflect a bias due to the facility of targeting such area both in terms of cortical localization and measurable effects of stimulation (Lefebvre & Liew, 2017).

Notwithstanding, other cortical areas such as premotor cortex (PM) and posterior parietal cortex (PPC) are also involved in several motor learning processes, as planning, sensorimotor integration and learning consolidation (Grafton, Fagg, & Arbib, 1998; Honda et al., 1998; Nitsche

& Paulus, 2011; Nudo, 2003). In fact, while M1 sustains the planning and the execution of movements (Evarts, 1981), the motor behavior is implemented by a more widespread frontoparietal network (Albert, Robertson, & Miall, 2009). For instance, premotor (PM) areas, such as the dorsal and the ventral premotor cortex are involved in movement selection (Di Pellegrino et al., 1992; Schluter, Rushworth, Mills, & Passingham, 1998) and the supplementary motor area (SMA) is engaged in movement control and sequential motor learning (Lee, 2004; Lewis & Byblow, 2004; Lewis, Wing, Pope, Praamstra, & Miall, 2004). Due to its strategic location (it receives direct inputs from the DLPFC and PPC, and projects outputs to M1), PM plays also a critical role in higher level cognitive aspects of motor control (Kantak, Stinear, et al., 2012), such as goal-directed actions and motor planning, movement selection, retention and releasing (Gremel & Costa, 2013; Kroeger et al., 2010; Mochizuki et al., 2005; Sugawara, Onishi, Yamashiro, Kirimoto, et al., 2013). Neuroimaging and Transcranial Magnetic Stimulation (TMS) evidence in humans has demonstrated the functional connectivity of parietal and motor (PM and M1) areas during the planning and the execution of complex movements (Filimon, 2010; Koch & Rothwell, 2009), as well in sensory-motor integration for optimal motor performance (Andersen & Cui, 2009; Fattori, Breveglieri, Amoroso, & Galletti, 2004; Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003).

In addition, also the role of the Parietal Posterior Cortex (PPC) in motor learning deserves further investigation (Bolognini & Miniussi, 2018). Besides its role in visuomotor integration, spatial attention, spatial awareness and sensory integration (Capotosto et al., 2011; Iacoboni, 2006; Mohan et al., 2017). The PPC is also relevant for of action, being involved in action planning, decision-making, sensory-based control and planning of movements (Baumann, Fluet, & Scherberger, 2009; Convento et al., 2014; Oliveira et al., 2010; Reichenbach et al., 2010; Scherberger & Andersen, 2007). Different posterior parietal areas play specific roles in motor intention, execution and planning, (Kalaska et al., 1997; Lacquaniti, Guigon, Bianchi, Ferraina, & Caminiti, 1995; Mackenzie et al., 2016; Sakata, Taira, Kusunoki, Murata, & Tanaka, 1997; Verhagen, Dijkerman, Medendorp, & Toni, 2012; Desmurget et al., 2009; Weiss et al., 2013).

It should be highlighted that motor learning is a complex process, which can be defined as the plethora of different abilities necessary to the acquisition, consolidation and long-term stability (also referred to as retention) of a new motor skill. As previously described, motor acquisition through practice involves two main components: first, all the processes driving improvements during practice (*online learning*); second, the processes driving stabilization over time or improvement between sessions (*retention*) (Robertson & Cohen, 2006). Additionally, learning is expected to be specific to the trained task, with little to no improvements in untrained new tasks,

even if the necessity of a better understanding of tDCS effects in generalization processes of learning has been recently acknowledged (Waters-Metenier et al., 2014).

Since motor learning includes various processes and recruits different neuronal areas, it is likely that the neuromodulation of premotor and parietal activity may induce motor gains, as M1 does. The stimulation of premotor and parietal areas may also affect specific components of motor learning, not modulated by M1 stimulation. For instance, we know that while M1 is recruited in a later stage of learning (Dayan & Cohen, 2011; Floyer-Lea & Matthews, 2005; Karni et al., 1998), the dorsal PM is mainly activated during early learning stages (Steele & Penhune, 2010), reflecting its role in movement selection and planning.

In light of the above-mentioned evidence, the study described in this Chapter aims at assessing the modulatory effects on motor learning of premotor and parietal tDCS in healthy individuals, exploring the similarities and differences with respect to motor cortex stimulation.

3.2. Materials and methods

Participants

Thirty-three healthy participants (mean age=23.5 years, Standard Deviation = ±2.3; 30 females), all right-handed, as assessed through the Edinburgh Handedness Inventory (Oldfield, 1971) took part in the study. Participants were recruited whether fulfilling the following criteria: (1) no history or clinical evidence of disease, including neurological and psychiatric disorders; (2) no history of substance abuse or dependence; (3) no use of central nervous system-effective medication; (3) no contraindication to NIBS (Rossi et al., 2009). All participants gave their written informed consent to participate in the study, which was carried out according to the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of the IRCSS Istituto Auxologico Italiano.

Motor learning task: The Finger Tapping Task

Motor learning was assessed with a sequential Finger-Tapping Task (FTT), a widely used motor learning paradigm (Karni et al., 1998; Zimerman et al., 2012). Participants were instructed to perform a sequential pressing of a 9-element sequence (i.e., 2 4 3 1 2 1 3 4 2) on a 4-button keyboard using their left (non-dominant) hand. The numbers sequence was displayed on the computer screen; each number represented a finger of the left hand: little finger=1, ring finger=2, middle finger=3, index=4. The digits sequence was presented and controlled by the E-Prime software (version 2.0 Psychology Software Tools), which also recorded participants responses.

During the experiment, participants were instructed to perform the FTT, by using their left hand as rapidly and accurately as possible. They were also asked not to correct, in case of error, rather continue the task with no pause (i.e., Tecchio et al., 2010). An asterisk mark, appearing below each number, indicated task advancing, independently of the correctness of the pressed button. No feedback regarding accuracy was provided. Figure 1 shows the sequential FTT.

Figure 1. Illustration of the sequential finger-tapping task used in the training. Source: the author, 2018.

tDCS

tDCS was delivered by a battery-driven, constant current stimulator (BrainStim, EMS, Bologna, Italy, http://brainstim.it/), using a pair of electrodes (5 x 5 cm), covered by saline-soaked sponges. Direct, continuous, electric current was applied for 20 min (fade-in/fade-out phases=10 sec), with an intensity of 1.5 mA, following current safety data (Antal et al., 2017). By using a crossover design, active tDCS was applied over 3 different cortical areas of the right hemisphere (contralateral to the left hand, which was used to perform the FTT. For right parietal tDCS, the anode was placed over P4 (PPC of the right hemisphere, according to the 10/20 electroencephalography – EEG - system). The right premotor cortex was stimulated by positioning the anode over F4 (i.e., 10/20 EEG system). To target the right M1, the anode electrode was placed over C4 (i.e., 10/20 EEG). In all cases, the cathode (reference) electrode was placed over the contralateral (left) supraorbital area. During sham tDCS, the same parameters of the active stimulation were used, but the stimulator was turned off after 30 sec. This ensures participants an itching sensation at the beginning of tDCS, while no effective stimulation was delivered, thus allowing a successful blinding for real versus sham stimulation (Gandiga, Hummel, & Cohen, 2006).

Experimental procedure

Each participant underwent four motor training sessions during which real or sham tDCS was applied during the FTT. I adopted a sham-controlled design, which comprised four tDCS conditions, namely: (i) anodal tDCS applied over the right M1; (ii) anodal tDCS applied over the right PM; (iii) anodal tDCS applied over the right PPC and (iv) sham (placebo) tDCS applied over the right M1, PM or PPC (the target area for the sham stimulation was randomized). The order of the tDCS sessions was randomized across participants; each stimulation was separated by a wash-out period of at least 24 hours, in order to minimize carry-over effects (Monte-Silva et al., 2013). The presence of adverse effects related to the stimulation was monitored with an ad-hoc questionnaire administered at the end of every tDCS session (Brunoni et al., 2011).

As shown in Figure 2, during the training phase, participants underwent the FFT while receiving tDCS. They were instructed to repeatedly perform the same sequence (target sequence, namely the one to be learned) for 5 blocks of 3 minutes each, with 2 minutes of a break between; performance improvements during the task reflects *online learning* (Censor et al., 2012). At the end of this phase, participants were presented with a new digit sequence (i.e., untrained sequence), different from the trained one, but with the same difficulty level (Zimerman et al., 2012). The new untrained sequence was performed in a single block lasting 3 minutes; performance at the untrained sequence allows to assess *generalization* (Censor et al., 2012). The day after, namely, 24 hours after the stimulation, participants underwent a retention test: they were asked again to perform the target, trained sequence, in a single 3-minutes block; the retention test assesses consolidation/off-line learning (Censor et al., 2012).

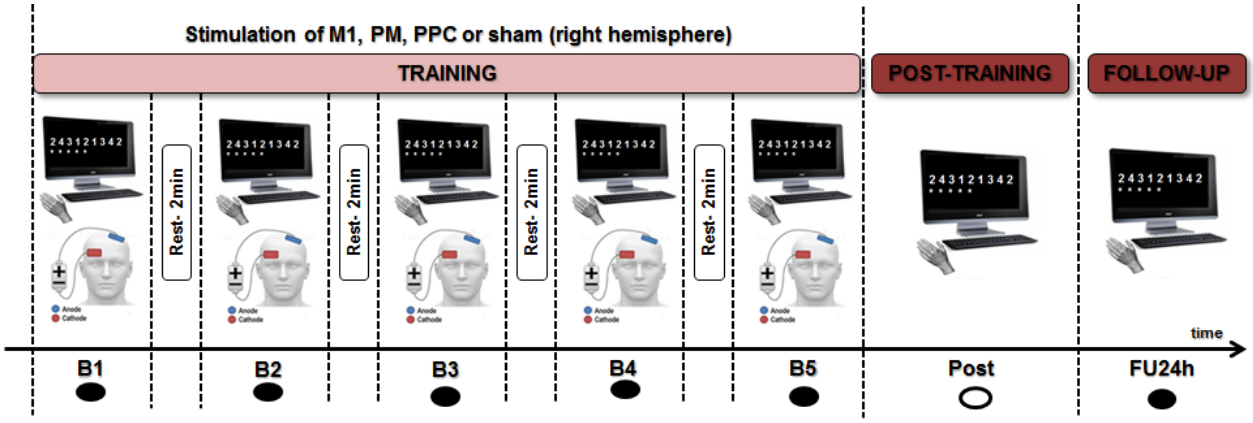

Figure 2. Schematic representation of the experimental design. Each circle represents a sequence (3 minutes each). Black circles represent the "target" sequence (namely, the one to be learned) that is repeated during the training phase (5 times, namely Blocks 1 to 5, B1-B5) and reassess and after 24 hours (FU24h). The white circle represents the "new sequence" (namely, the one not exercised during training) tested immediately after the stimulation (Post). Anodal tDCS was applied in a real or sham fashion, over PPC, PM, and M1.

3.3. Results

Statistical analyses were performed using STATISTICA for Windows, release 10 (StatSoft). Statistical significance was set at *alpha*=.05; significant main effects and interactions were further explored by means of Newman-Keuls correction. Normality of all data was assessed by the Shapiro-Wilk test. Since the assumption was not violated, online learning, retention, and generalization were analyzed via repeated measures Analysis of Variance (rm-ANOVA).

Online learning. For assessing tDCS effects on online learning and motor execution, either the total number of the performed correct sequences (accuracy), and the total number of performed sequences (regardless of the accuracy of the reproduction, i.e., correct plus incorrect sequences) were analyzed via rm-ANOVA with *tDCS* (Sham, PPC, PM and M1) and Blocks (B1, B2, B3, B4 and B5) as within factors.

With respect to accuracy, as shown in Figure 3, the rm-ANOVA reveals a significant main effect of *tDCS* [$F_{(3,96)}$=3.8, p=.01, η^2_p=.10], showing a higher number of sequences correctly performed during M1 stimulation (Mean, M=38.3) as compared to both Sham (M=35.3, p=.04), and PPC (M=34.4, p<.01) tDCS; the comparison between M1 and PM (M=36, p=.06) stimulation was marginally significant. Additionally, no differences were found between sham stimulation and both, PM (p=.55) as well as PPC stimulation (p=.45), showing that such active stimulations did not increase accuracy as compared to sham tDCS.

The effect of *Block* was also significant [$F_{(4,128)}$=8.6, p<.01, η^2_p=.20], showing an overall improvement across blocks of training, which features the typical learning effect. Specifically, while the 1st (M=34.6) and the 2nd (M=35.4) blocks of training did not differ between each other (p=0.1), they were significantly lower than the 4th (M=36.8, p=.01) and 5th (M=37, p<.01) blocks of learning. The 3rd block (M=36.2) was higher than the 1st one (p<.01), but not different from the 2nd (p=.09), 4th (p=.24), and 5th (p=.2) blocks of practice. The *tDCS* X T*ime* interaction [$F_{(12,384)}$=1.5, p=.13, η^2_p=.04] did not reach significance.

With respect to the total number of sequences, as shown in Figure 4, the rm-ANOVA reveals a significant *tDCS X Time* interaction [$F_{(12,384)}$=1.8, p=.04, η^2_p=.05], as well as the main effect of *Block* [$F_{(4,128)}$=37.7, p<.01, η^2_p=.50], while no significant *tDCS* effect was found [$F_{(3,96)}$=2.2, p=.09, η^2_p=.06]. As shown in Figure 2b, during Sham tDCS, an increase of the total number of sequences is detected in the 3rd (B3, M=43.1, p<.01), the 4th (B4=43.3, p<.01) and the 5th (B5, M=43.8, p<.01) blocks, as compared to the 1st block of training (B1, M=40.7). The 2nd block of training (B2, M=42) was not different from the 1st (p=.12), as the 3rd block did not differ from the 4th (p=.8) and 5th (p=.7) block of practice. The increase in the total number of sequences occurs later during PPC

stimulation, in the 4th (M=42.8, p<.01) and 5th blocks of training (M=43.8, p<.01), as compared to the 1st block of training (M=40.7). Instead, during PM stimulation the total number of sequences significantly increases earlier: as compared to the 1st block (B1, M=39.3), a significant increase emerged as soon as in the 2nd (B2, M=41.3, p<.01), and it was still present in the 3rd (M=42.2, p<.01), the 4th (M=44.4, p<.01) and the last (B5=44.6, p<0.1) block of learning. Finally, during M1 stimulation, the number of sequences performed was higher than the other tDCS sessions since the very beginning of the stimulation (B1, M=42.8), and further improvements emerged in the following blocks: 2nd (B2, M=44.6, p=.03), the 3rd (M=45, p<.01), 4th (M=45.8, p<.01) and the last (B5=46.7, p<.01) block of learning.

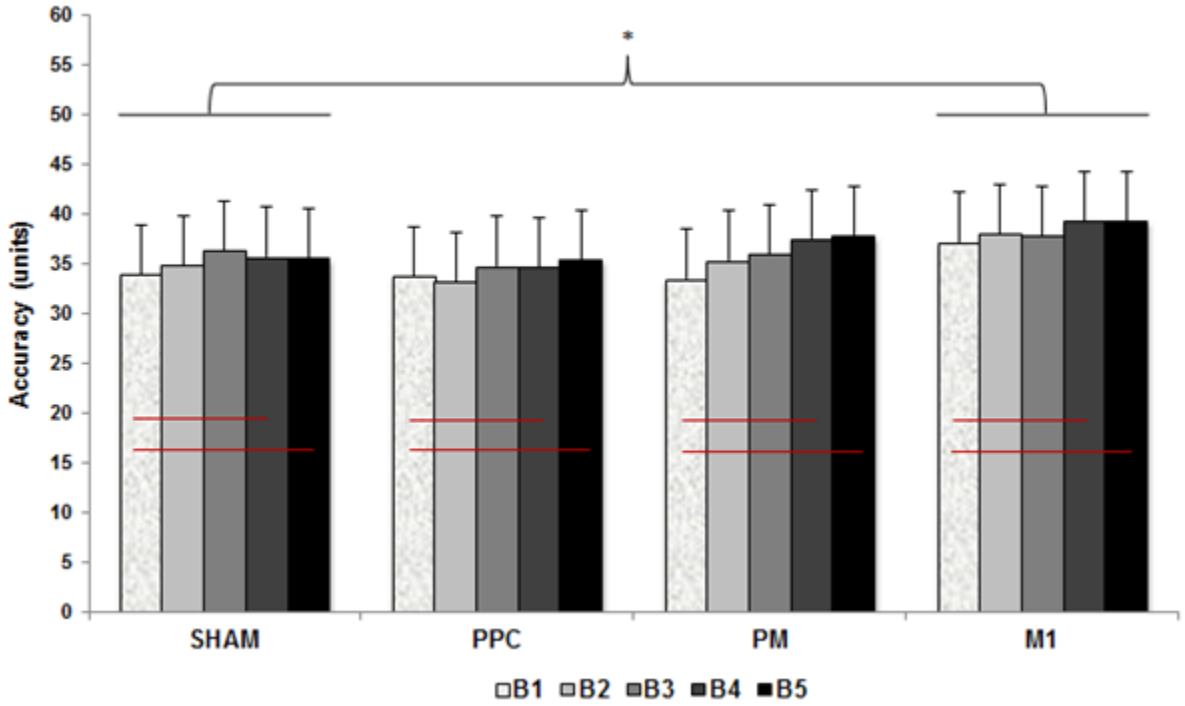

Figure 3. Online learning. Mean accuracy, i.e., the mean number of sequence correctly performed, at the FTT during the 5 blocks of training; B1=block 1, B2=Block 2, B3=block 3, B4=block 4, B5=block 5. Red lines=within-group differences; *=between-group differences (only differences as compared to sham tDCS are graphically reported). p<.05. Error bars=Mean standard error (SEM).

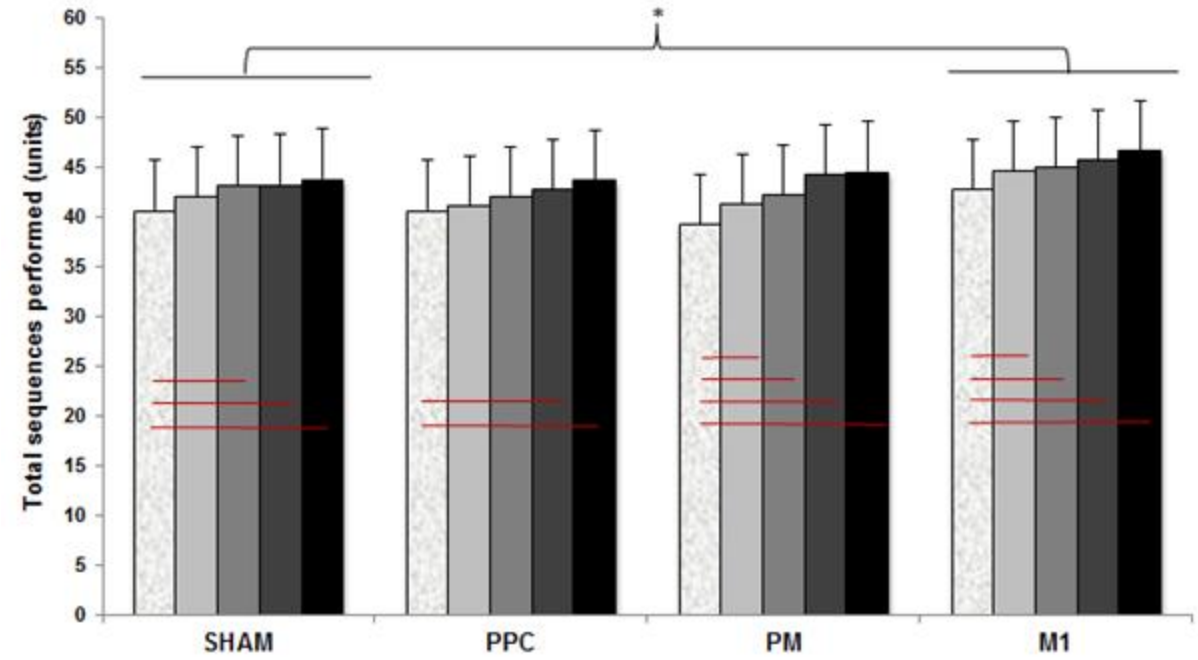

Figure 4. Online learning. Mean total number of sequences performed, regardless of their correctness, during the 5 blocks of training; B1=block 1, B2=Block 2, B3=block 3, B4=block 4, B5=block 5. Red lines=within-group differences; *=between-group differences (only statistical comparisons with sham tDCS are graphically reported). p<.05. Error bars=SEM.

Retention. For assessing tDCS effects on the retention of the trained digits sequence, either the number of correct sequences, and the total number of performed sequences (regardless of the accuracy of the reproduction, i.e., correct plus incorrect sequences) were analyzed via a rm-ANOVA with *tDCS* (Sham, PPC, PM and M1) and *Time* (B5, last block of learning, and FU24h, retention test after 24 hours) as within factor.

As shown in Figure 5, the results reveal a main effect of *tDCS* [$F_{(3,96)}$=4.7, p<.01, η^2_p=.10], with a higher number of sequences correctly performed after M1 (Mean, M=40.7) as compared to both Sham (M=37.9, p=.03), and PPC (M=37, p<.01) stimulation; PM stimulation (M=39.7) does not differ from M1 (p=.38) and sham stimulation (p=.09), while it induced a better performance than PPC stimulation (p=.04). The main effect of *Time* was also significant [$F_{(1,32)}$=28, p<.01, η^2_p=.50], showing an overall improvement of motor performance after 24 hours (FU24h, M=40.6), as compared to the last block of training (B5, M=37, p<.01). No *tDCS* X T*ime* interaction [$F_{(3,96)}$=0.7, p=.55, η^2_p=.02] was found.

With respect to the total number of performed sequences, as shown in figure 6, the rm-ANOVA reveals a significant main effect of *tDCS* [$F_{(3,96)}$=3.8, p=.01, η^2_p=.10]: M1 stimulation (M=47.5) resulted in higher retention rate, as compared to Sham (M=44.7, p=.01), as well as PPC (M=44.5, p=.02), and PM (M=45.5, p=.048) tDCS. The main effect of *Time* was also significant [$F_{(1,32)}$=11.5, p<.01, η^2_p=.30]: an overall improvement of motor performance emerged at the

retention test after 24 hours (M=46.4), as compared to the last block of practice (B5, M=44.7, p<.01). No significant *tDCS* X T*ime* [$F_{(3,96)}$=.06, p=.98, η^2_p <.01] interaction was found.

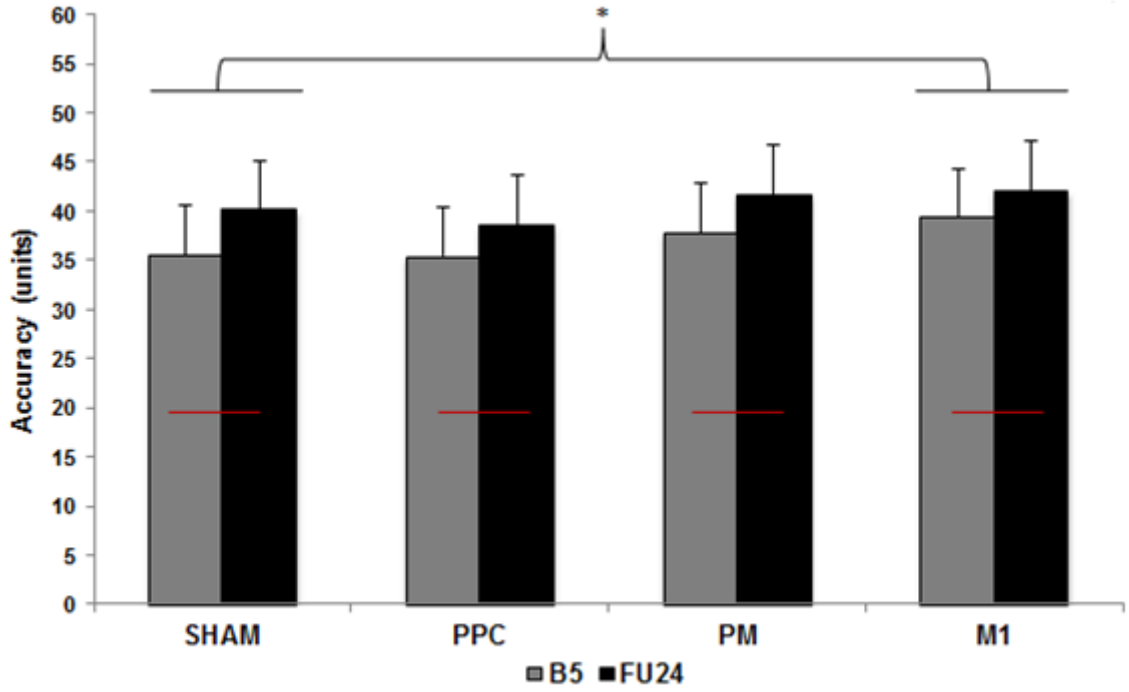

Figure 5. Retention. Mean accuracy, i.e., the mean number of sequence correctly performed in the last block at the FTT vs. 24 hours after; B5=block 5, FU24=follow-up 24 hours after the end of the training. Red lines=within-group differences; *=between-group differences (only differences as compared to sham tDCS are graphically reported). p<.05. Error bars=SEM.

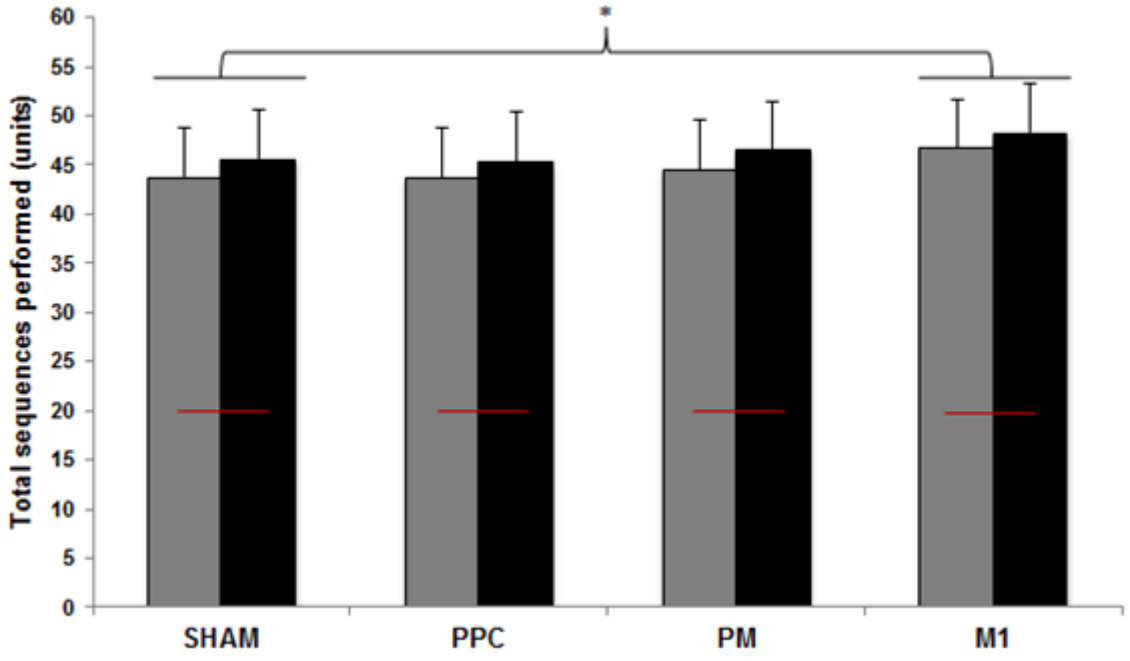

Figure 6. Retention. Mean total number of sequences performed, regardless of their correctness, in the last block of the FTT vs. 24 hours after; B5=block 5, FU24=follow-up 24 hours after the end of the training. Red lines=within-group

differences; *=between-group differences (only statistical differences as compared to sham tDCS are graphically reported). p<.05. Error bars=SEM.

Generalization. Either the number of correct sequences and the total sequences performed for the untrained sequence, after the end of training, were analyzed via one-way ANOVA with *tDCS* (Sham, PPC, PM, and M1) as within factor. As shown in Figure 7, the ANOVA reveals a significant main effect of tDCS [$F_{(3,93)}$=22.2, p<.01, η^2_p=.40]: the accuracy was higher during PM (M=37.6), as compared to Sham (M=28, p<.01), as well as PPC (M=28.3, p<.01), and M1 (M=30.2, p<.01) tDCS. Sham tDCS does not differ from M1 (p=.24) or PPC stimulation (p=.79).

With respect to the total number of sequences performed, as shown in Figure 8, the main effect of tDCS [$F_{(3,93)}$=9.6, p<.01, η^2_p=.20] shows that during premotor stimulation (Mean, M=43.6) the performance was better as compared to Sham (M=37.4, p<.01), PPC (M=37.7, p<.01), and M1 (M=40, p<.01) conditions. Conversely, sham tDCS does not differ from M1 (p=.11) and PPC (p=.85) stimulation.

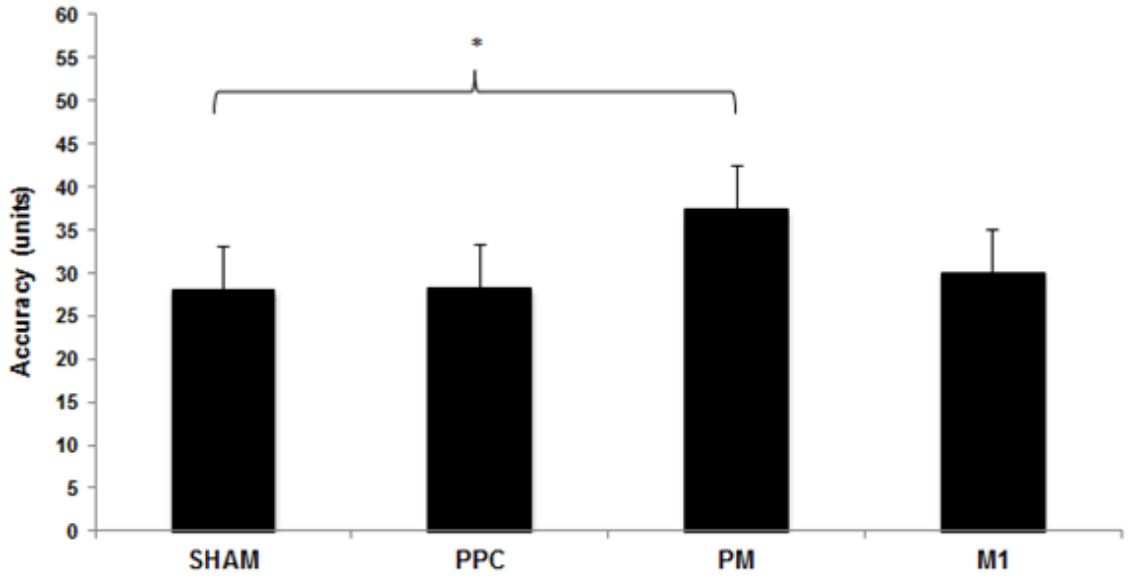

Figure 7. Generalization. Mean accuracy, i.e., the mean number of sequence correctly performed, for the "untrained sequence" after the end of training. *=between-group differences (only differences as compared to sham tDCS are graphically reported). p<.05. Error bars=SEM.

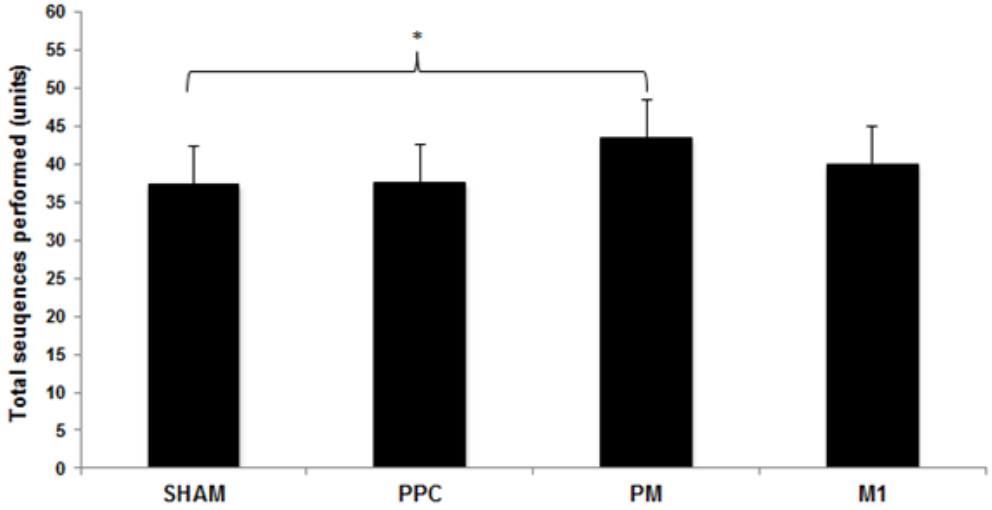

Figure 8. Generalization. Mean total number of sequences performed for the "untrained sequence" after the end of training. *=between-group differences (only differences as compared to sham tDCS are graphically reported). p<.05. Error bars=SEM.

3.4. Discussion

The aim of the present study was to assess the effects of anodal tDCS of PM and PPC, as compared to M1, on motor learning. The results seem to be featured by both elements of confirmation and novelty, as compared to previous tDCS evidence. Indeed, on one hand, results confirm that anodal M1 tDCS facilitate both *online* learning and *retention*, on the other hand, they also reveal an interesting novel finding, namely that anodal tDCS of PM promotes *generalization*. The stimulation of the posterior parietal areas does not affect motor learning processes.

In details, the present results nicely complement previous evidence (Stagg et al., 2011; Waters-Metenier et al., 2014) confirming the "supremacy" of M1 for enhancing, through a neuromodulatory approach (anodal tDCS here), o*nline* motor learning and its *retention.* Despite the neurophysiological underpinnings are still under investigation, such effects seem related to a tDCS-induced strengthening of neuroplasticity activated by the motor learning task, involving LTP mechanisms and the functioning of NMDA receptors (Hasan et al., 2013; Reis & Fritsch, 2011). When the *online* effects of the three target areas (M1, PPC, PM) are compared, it is apparent that M1 stimulation is superior than sham and PPC tDCS. PM stimulation is placed somehow in between: motor learning is driven by PM stimulation is quite similar to that induced by M1 tDCS, but not different from that induced by sham tDCS. With regard to the off-line effects, training the FTT resulted in learning, but such effect cannot be attributed to the stimulation since, for all tDCS conditions, performance at the retention test was better than that in the last, fifth, block of practice.

Further reflection is prompt by looking to the overall motor performance (regardless of its accuracy[1]). Both M1 and PM stimulations facilitate the performance from the very beginning of the stimulation. The effect induced by PM stimulation is not surprising, as previous evidence already shown premotor engagement during the early stages of motor execution and preparation (Cohen, Sherman, Zinger, Perlmutter, & Prut, 2010; Duque, Labruna, Verset, Olivier, & Ivry, 2012; Sugawara, Onishi, Yamashiro, Soma, et al., 2013). Higher levels of activity in PM seems related to the development of spatial maps/internal representations of the task (Buch, Brasted, & Wise, 2006; Nowak, Berner, et al., 2009; Taubert et al., 2010). It follows that an increased cognitive processing of information is expected during this learning stage, during which individuals should be capable of associate sensory cues with correct motor commands (Halsband & Lange, 2006; Kantak, Stinear, et al., 2012), in turn increasing their motor output. Moreover, we should consider that M1 and PM are highly interconnected through cortico-cortical pathways. For instance, TMS and tDCS studies found that PM stimulation can modulate the activity of M1 (Civardi, Cantello, Asselman, & Rothwell, 2001; Rizzo et al., 2004). Boros and colleagues (2008) found that excitatory PM tDCS reduced intracortical inhibition and increased PM-M1 excitability (Boros et al., 2008). In the same way, neuroimaging studies have demonstrated a co-activation of PM and M1 during learning tasks (Cross et al., 2007).

With respect to PPC, anodal tDCS of this area has no effect on motor learning; its seems even detrimental on the overall motor performance, delaying its practice-induced improvements, at the least in term of the overall amount of reproduced sequences, regardless of their correctness. In fact, as compared to the sham condition, the improvement of performance emerges only at the end of training (4th block) during the parietal stimulation, while it emerges sooner without tDCS (from the 3rd block during sham tDCS), and it is further anticipated during M1 and PM stimulations. A tentative explanation of such pattern could be put forward.

While the role of anterior motor areas (M1 and PM) is intrinsically motor (M1 for action execution and PM for its preparation), PPC would play a more cognitive role in movement generation. In fact, PPC is recruited not only for visuomotor transformation as traditionally thought (Goodale & Westwood, 2004; Milner & Goodale, 2006) but also in higher-order (cognitive) motor function, as motor intention and planning (Fogassi & Luppino, 2005). A paradigmatic example of higher-order motor deficit following parietal lesion is limb apraxia, featured by the inability to perform purposeful gestures, limb movement, and action; limb apraxia is typically caused by injuries to the left cerebral hemisphere (Geschwind, 1975). Accordingly, a previous tDCS study has

[1]When taking into consideration the overall performance, namely the number of reproduced sequences regardless of whether the reproduction was correct or wrong, we are not referring to learning, which is represented by increase in the correct responses only.

shown that anodal tDCS of the left PPC, but not the right hemisphere, can selectively facilitate action planning, while the anodal tDCS of the M1 of both hemispheres (contralateral to the hand involved in the motor task) only improves action execution (Convento et al., 2014). Such evidence (i.e., facilitation of motor planning after PPC stimulation) could appear in contrast with the present null effect of PPC stimulation on motor learning. However, it should be noted that here, I have stimulated only the right PPC, and the FTT was performed with the (left) non-dominant hand. Therefore, there could be a hemispheric asymmetry of the parietal effects on motor learning, as shown for motor planning. Moreover, in the present study anodal tDCS was applied with a unilateral montage, which could have induced a sort of interhemispheric imbalance (Dambeck et al., 2006; Duecker & Sack, 2015): in this view, the right-hemisphere anodal (putatively excitatory) tDCS may have disrupted the planning mediated by the left parietal cortex due to an indirect decrease in left-hemisphere excitability. These hypotheses deserve further research.

The novel finding of our study is represented by the tDCS effect on the generalization of the learned skill to a new one, which is selectively facilitated by PM stimulation, being absent for M1 and PPC. This represents an interesting dissociation between M1 and PM on motor learning processes: while M1 plays the main role in facilitating online learning and then in the retention of the learned skill, PM is recruited in a later stage, allowing the extension of the motor gains to untrained movements. The maintenance of motor improvements occurring between periods without training sessions is linked to a consolidation process, which shapes the stabilization of a memory trace after the motor acquisition phase (Krakauer & Shadmehr, 2006; McGaugh, 2000; Nemeth & Janacsek, 2010). Successful consolidation includes memory association, which means that recently acquired information is integrated with past experiences (Walker et al., 2003; Walker & Stickgold, 2004). Moreover, the integration of sensory information into motor commands is configured as one of the many functions of PM (Pesaran et al., 2006), which is also involved in movement selection, retention and releasing (Gremel & Costa, 2013; Sugawara, Onishi, Yamashiro, Kirimoto, et al., 2013). A possible speculation that follows such line of evidence is that premotor tDCS may reinforce the memory trace of the learned skill, allowing an effective movement translocation, that is the anatomical reorganization of memory representation occurs (Walker & Stickgold, 2004), which implies a better ability to recognize the new activity pattern and successfully perform it. During online learning, memory traces are formed and continuously analyzed to detect errors of execution. After the motor acquisition phase, improvements in performance are related to the consolidation of such memory traces that are reactivated in the off-line learning phase. Considering that learning is task-specific, memory traces could be partially used as a reference to learn an

untrained task and improve generalization processes as long as such tasks are of the same *nature* (i.e., trained vs. untrained sequence learning tasks). This is what was done here: generalization was assessed through the motor performance in a untrained sequence, but still, a sequence learning task, not a task of different nature (for example a visuomotor learning task.

Summarizing: the present study confirms the efficacy of M1 stimulation with anodal tDCS for improving motor learning (with the hand contralateral to the target area) in healthy individuals; such tDCS-induced gains are retained the day after. Only the stimulation of PM helps the generalization process. Finally, no facilitation of motor learning is induced by delivering tDCS to PPC, hence this area appears an inadequate cortical target for motor learning.

In conclusion, this study provides novel evidence in the effect of neuromodulation on motor learning, and the potential choice of different cortical areas for tDCS delivery. Stimulating primary motor cortex and premotor areas results in dissociable effects: whereas *online learning* and *retention* of a simple motor skill can be enhanced to a larger extent by tDCS of M1, the application of tDCS over the premotor cortex seems more useful for promoting the generalization of the acquired skill to an untrained, new, motor task. The neuromodulation of the parietal cortex seems to be ineffective for motor learning, although its role in this function deserves a more in-depth investigation.

CHAPTER 4

‖ Study 3 ‖

Motor learning in children with cerebral palsy: a behavior study

4.1. Introduction

Cerebral palsy (CP) is a neurological disorder featured by movement impairments caused by a non-progressive brain injury or malformation that occurs before birth or in early childhood (Koman, 2004). Disturbances of sensation, cognition, communication, perception, and behavior are also common, with significant impact on daily living activities (Bax et al., 2005; Riva et al., 2013). CP children typically present heterogeneous motor deficits, mainly featured by upper limb sensorimotor impairments, including spasticity, muscle contractures and weakness (Baranello et al., 2016; Rose & McGill, 1998). Such heterogeneity calls for the need to investigate thoroughly whether and to what extent clinical and physiological features could influence motor behavior of CP children. For instance, it has been suggested that the timing of brain lesion (i.e., before the birth, perinatal period or in early childhood) (Staudt et al., 2004; Steinlin et al., 1993), as well as size, severity and the type of structural pathology - i.e., brain malformations, periventricular or cortico-subcortical lesions (Feys et al., 2010; Krägeloh-Mann & Horber, 2007; Mackey, Stinear, Stott, & Byblow, 2014; Wiklund & Uvebrant, 1991) may represent critical factors. On the other hand, it seems that CP motor performance is independent of age, but it is associated with non-verbal intelligence, since implicit and explicit learning varies with intellectual levels (Fletcher, Maybery, & Bennett, 2000; Gagliardi, Tavano, Turconi, & Borgatti, 2013; Gofer-Levi, Silberg, Brezner, & Vakil, 2013). Working memory disorders also plays an important role in shaping motor behavior (Peeters, Verhoeven, & de Moor, 2009). In fact, CP children with poor working memory ability are less accurate and slower than their peers in arithmetic tests (Jenks, De Moor, & Van Lieshout, 2009). Additionally, higher-order motor planning and learning deficits further impair their physical ability (Bar-Haim et al., 2010; Steenbergen & Gordon, 2006).

In the last few years, some studies explored motor learning capabilities in CP conditions. Despite a slower pace, CP children appear to be able to explicit learn as the typically developing ones, while the implicit learning may be compromised (Gofer-Levi et al., 2013; van der Kamp,

Steenbergen, & Masters, 2017). For instance, the performance of CP children and CP adolescents in a serial reaction time task appear featured by slowness, as compared to that of typically developing (TD) peers, and the presence of a general explicit improvement in reaction times (Gofer-Levi et al., 2013). On a computerized version of the Corsi Block Test, impaired (although with heterogenous performance) sequence-learning, which comprised both explicit and implicit components, was found in CP children (Gagliardi et al., 2013). However, bilateral CP children may retain the ability to learn in an implicit manner; at least with respect to sequence learning; the integrity of this capacity seems independent of age and gross motor impairment, rather it is related to cognitive abilities (Gagliardi et al., 2013; van der Kamp et al., 2017). Of interest, the hemispheric laterality of the cerebral lesion differently affects the implicit and explicit components of learning. For instance, by using a prism-adaptation paradigm, Kamp and colleagues (2017) showed that reduced capacity for explicit motor learning in children with right-sided CP, while unimpaired implicit learning was detected in unilateral CP, regardless the side of the hemispheric damage (van der Kamp et al., 2017).

So far, the potential link between the types of plastic organization of motor functions that may develop in CP is still unknown, although it is well known that the way through which the motor system rewrites itself to respond to a cerebral insult shapes motor and cognitive disabilities, their development and recovery (Cioni, D'Acunto, & Guzzetta, 2011; Kirton, 2013).

A damage to the motor system causes a plastic reorganization of its connections and efferents, which aims at supporting the recovery of voluntary movements, that is the restoration of an adequate connection of the motor cortex with the spinal cord circuitry. Such reorganization may involve the ipsilateral motor areas, or bilateral motor projections originating in the primary motor areas, giving rise to a contralesional or a bilateral reorganization of motor functions. The last mechanism is typical for brain injuries occurring during early in life. After the first 24 weeks of gestation, each cerebral hemisphere has crossed and uncrossed descending efferent projections forming the corticospinal tract (CST). A typical development is marked by a competitive withdrawal of projections: the ipsilateral uncrossed projections of the CST generally withdraw during development, while the contralateral crossed projections are maintained and strengthen (Eyre, Taylor, Villagra, Smith, & Miller, 2001; Jaspers, Byblow, Feys, & Wenderoth, 2016). However, the ipsilateral motor projection may persist in case of a perinatal cerebral damage, giving rise to a contralesional or bilateral reorganization of motor functions - for a review, see (Staudt, 2010), which can take over the motor control of affected body part. Such reorganization can occur partially or even totally when the non-lesioned hemisphere becomes equipped with fast-conducting uncrossed projections to the affected body side (Eyre et al., 2001; Staudt et al., 2002; Thickbroom,

Byrnes, Archer, Nagarajan, & Mastaglia, 2001). This plastic reorganization of the motor system seems related to lesion extend and.

Within this framework, the present study explored motor skill learning abilities in children with CP, as compared to age-matched typically developing (TD) children, with a different pattern (ipsilateral, contralateral, bilateral) of reorganization of the motor system. To this aim, motor learning with the affected hand was measured by means of a finger tapping task – FTT (Kami et al., 1995; Zimerman et al., 2012), while the reorganization of the motor system was assessed by recording motor evoked potentials (MEPs) induced by Transcranial Magnetic Stimulation (TMS) applied to both the healthy and the damaged motor cortices (Jaspers et al., 2016).

4.2. Materials and Methods

Participants

Nine CP participants (4 males, mean age=10.9 years, SD=3.5, range=6-17 years), all presenting with upper-limb motor deficits, were recruited from the in- and an out-patient population of the Developmental Neurology Unit of the Fondazione IRCCS Istituto Neurologico Carlo Besta (Milan, Italy). Six children had unilateral brain lesions, while three bilateral lesions. Inclusion criteria were: (i) congenital hemiplegia diagnosis confirmed by clinical assessment or/and neuroimaging exams; (ii) age between 6-18 years and (iii) mild-moderate UL sensorimotor impairments ≤ III at the MACS scale. Exclusion criteria were the presence of moderate-severe intellectual disability and application of adjunctive medication to reduce spasticity as botulinum toxin.

Before the experiment, CP participants underwent a clinical and neurophysiological assessment: motor functions were assessed through the Manual Ability Classification System (MACS), Jebsen-Taylor Hand Function Test (JTT), while the motor system reorganization was evaluated with single-pulse Transcranial Magnetic Stimulation (TMS). TMS was applied following international safety guidelines (Rossi et al., 2009).

Fifteen typically developed children (TD) served as a control group. The sample included 8 males and 7 females, with a mean age of 11.7 years (SD=2.4). All participants had a normal or corrected-to-normal vision and none had history or evidence of neurological, psychiatric or other relevant disorders. According to the Oldfield's handedness questionnaire (Oldfield, 1971), 13 were right- and 2 left-handed.

The study was approved by the Ethics Committees of the IRCCS Istituto Neurologico Carlo Besta (NIBS-BIT Versione 3.0 del 10 Marzo 2016) and of the University of Milano Bicocca

(protocol number 352). The experimental procedure was in accordance with the ethical standards of the Declaration of Helsinki. Parents were informed about the aim of the study and provided written informed consent.

Clinical Assessment

The manual ability of CP children was clinically assessed through the two following tests:

i) Manual Ability Classification System – MACS (Eliasson et al., 2006). According to reports from parents or caregivers as well as physicians, MACS classifies manual ability based on how children use hands to manipulate objects in activities of daily living. The classification is made through a five-point ordinal system with each level considering the need (or not) of assistance. Better outcomes are represented by lower scores (range=I-V). For instance, level I includes children with minor limitations (i.e., they are able to handle objects easily and successfully) as those classified in level V who have severe functional limitations (i.e., they are not able to handle objects and have difficulties in performing even simple actions).

ii) Jebsen-Taylor Hand Function Test - JTT (Jebsen, Taylor, Trieschmann, Trotter, & Howard, 1969; Taylor, Sand, & Jebsen, 1973): JTT comprises 7 subtests (i.e., writing, turning cards over, picking up small objects, simulated eating, stacking checkers and moving light/heavy cans). Children are asked to perform each activity with their hemiplegic hand as quickly and accurate as possible. JTT has already been successfully used to assess hand function in TD children as well as those with CP (Eliasson et al., 2006; Klingels et al., 2012; Reedman, Beagley, Sakzewski, & Boyd, 2016). In the present study, subtests writing and simulated eating were excluded since some of CP children could not perform it with their paretic hand. The total time (in seconds) taken to finish all tasks is used as performance's score, thus lower scores represent better motor performance.

Cortical Assessment

A reliable marker of motor reorganization is provided by the assessment of the motor evoked potentials (MEPs) induced by Transcranial Magnetic Stimulation (TMS) (Jaspers et al., 2016). The TMS cortical assessment was performed before the administration of the motor learning task.

During the TMS assessment, CP children were comfortably seated on an armchair. Focal TMS pulses to M1 were delivered using an 80 mm figure-of-eight coil (Tonica Elecktronic A/S, Farum, Denmark), which was held tangential to the skull and aligned in the para-sagittal plane with the handle rotated 45° lateral. Online monitoring of the electromyographic (EMG) activity in response to TMS was performed. EMG signals were band-pass filtered (0.5 Hz - 2KHz), digitized, and stored on a computer for offline analysis (Keypoint, Alpine Biomed, Orage County, CA, USA). Ag-AgCl surface electrodes were placed bilaterally over the Abductor Brevis Pollicis (ABP) of both

hands. For the stimulation of each cerebral hemisphere, the same procedure was adopted. Firstly, we determined the motor hotspot, namely, the coil location over the M1 of each hemisphere that elicited optimal (i.e., maximal amplitude and shortest latency) motor evoked potentials (MEPs) at the lowest stimulation intensity. The resting motor threshold (rMT) was determined as follows: stimulus intensity was progressively increased at 5% steps until reached reliable MEPs in about the 50% of 10-20 consecutive pulses. Then, 10 consecutive MEPs were induced by delivering 10 TMS pulses to M1 of each hemisphere, at an intensity of 120% of the previously determined rMT. Muscle activity was visually monitored to confirm the relaxed status before the stimulation (Baranello et al., 2016). Whenever such intensity was not able to elicit MEPs, children were asked to perform voluntary contractions of their thumbs.

Through this procedure, the pattern of motor reorganization in CP children was classified as: (i) *bilateral organization*, when MEPs in the affected hand were induced in by applying TMS pulses unilaterally, to either the ipsilesional or to the contralesional M1; (ii) *ipsilateral organization*, MEPs in the affected hand induced by TMS of the contralesional M1 only, or (iii) *contralateral organization, when* MEPs in the affected hand were induced by TMS of the ipsilesional M1 only (L. Carr, Harrison, Evans, & Stephens, 1993; Jaspers et al., 2016; Staudt, 2010). Following this procedure, we could divide our CP sample into 3 experimental groups, each comprising 3 participants for each type of motor reorganization. Importantly, the three experimental groups of CP participants did not differ between each other with respect to the JTT at baseline [$F_{(2.60)}$=1.53, p=.3] scores. Demographic and clinical details of CP children according to their pattern of CST reorganization are summarized in Table 1.

Table 1. Demographic and clinical data of patients.

ID	CST organization	Gender/Age	Education	Most affected hand	MACS level	JTT score	Type of lesion
P1	Bilateral	M, 17	12	R	I	72	WMD
P2		F, 11	6	L	II	87	WMD
P3		F, 10	5	R	I	47	N/A
P4	Ipsilateral	F, 8	3	R	III	1202	N/A
P5		F, 15	9	R	III	212	MCAI
P6		M, 6	1	R	II	130	WMD
P7	Contralateral	M, 13	8	R	I	60	WMD
P8		F, 9	4	L	I	41	WMD
P9		M, 9	3	L	I	39	WMD

ID: Patients' Identification number. Gender: M=Male, F=Female. Age in years. Education in years. Affected hand: R=Right, L=Left. MACS: Manual Ability Classification System (Range=I-V); JTT: Jebsen-Taylor Hand Function

Test (total time in seconds). Brain injury: WMD=White Matter Damage, MCAI=Middle Cerebral Artery Infarct, N/A: not available.

Finger-Tapping task

The motor learning task consisting in a short-version of the sequential Finger-Tapping Task (FTT) (Kami et al., 1995; Zimerman et al., 2012), which was administered through a PC software (E-prime 2.0 Psychology Software Tools). Participants had to perform a sequential pressing of a 5-element sequence (4 1 3 2 4) on a 4-button keyboard. An asterisk mark, appearing below the corresponding number, indicated task advancing after each button press, independently of the correctness of the typing. The task comprised 3 blocks of practice, each lasting 3 minutes, with 2 minutes of break between blocks i.e., (Zimerman et al., 2012). Participants were instructed to perform the motor activity as quickly and accurately as possible, using their affected hand. In case of errors, participants were asked not to correct, but to continue the task (Tecchio et al., 2010). No feedback regarding accuracy was provided.

Figure 1 shows the design of our study. CP children had to reproduce the sequence displayed on the computer screen with the corresponding fingers of their paretic hand (or the most affected); instead, TD children did the same with their intact, non-dominant, hand. For CP children with the paretic right hand, the following correspondence between fingers and numbers was used: index=1, middle finger=2, ring finger=3, little finger=4. Conversely, for CP children with the paretic left hand, the following correspondence was used: little=1, ring=2, middle=3, and index finger=4. This same correspondence of digit/numbers was used for TD children.

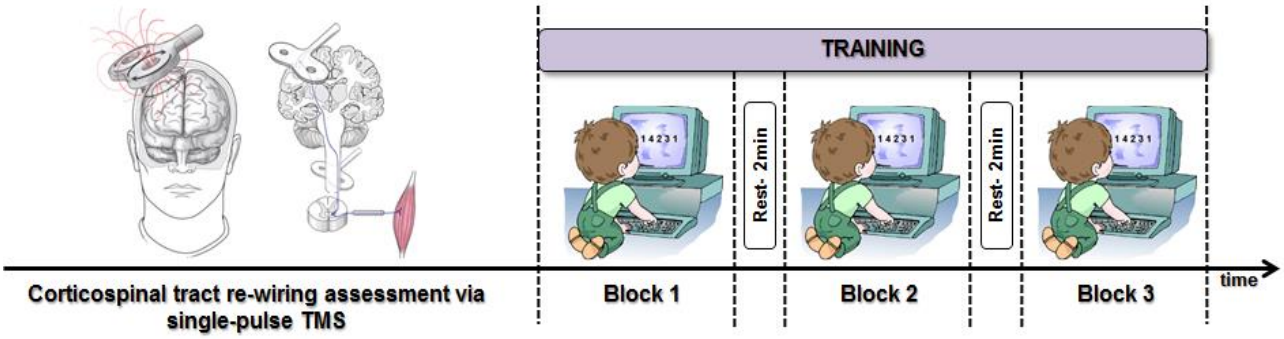

Figure 1. Study design. The experimental session starts with the determination of the motor system organization by TMS. The learning task comprises the 3 blocks of training.

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics (Version 25). Normality of all data was assessed by the Shapiro-Wilk test. Since the assumption was not violated, online learning and motor performance were analyzed via repeated measures Analysis of Variance (rm-ANOVA).

For each participant, the total number of the performed correct sequences – accuracy -and the total number of performed sequences, regardless of their accuracy, in each block of the FTT was considered (Zimerman et al., 2012). Such performance was then analyzed via a rm-ANOVA, with *Group* (4 levels: TD children, Bilateral CST, Ipsilateral CST, Contralateral CST) as between-subjects factor, and *Block* (3 levels: B1, B2, B3) as within-subjects factor. Significance was set at *alpha*=.05; main effects and interactions were further explored by means of Bonferroni correction.

4.3. Results

Online motor-learning (accuracy score)

The ANOVA revealed a significant main effect of *Group* [$F_{(3,20)}$=7.78, p<.01, η^2_p=.50] showing that TD participants have an overall better performance than CP children of every motor reorganization group (p<.02 for all comparisons). The main effect of *Block* [$F_{(2,40)}$=5.97, p<.01, η^2_p=.20] was also significant, showing a gradual improvement across blocks of practice (p<.02 for all comparisons). Most importantly, a significant *Group X Block* interaction was found [$F_{(6,40)}$=2.69, p=.03, η^2_p=.30]. To further explore this interaction, separated rm-ANOVA were performed to contrast TD participants with each group of CP children (Bilateral, Ipsilateral, and Contralateral motor organization).

TD vs. Bilateral CST reorganization

The rm-ANOVA revealed a significant main effect of *Group* [$F_{(1,16)}$=9.54, p<.01, η^2_p=.40] showing that TD participants (mean correct reproduction, M=50.3) were more accurate than CP children with bilateral CST reorganization (M=11.9, p<.01). The main effect of *Block* [$F_{(2,32)}$=8.75, p<.01, η^2_p=.35] was also significant showing that the accuracy on the second (B2, M=33.5, p<.01) and third blocks (B3, M=33.7, p=.01) was significantly higher than in the first block of practice (B1, M=26.1), with no difference between the second and the third blocks (p=.9). No significant *Group X Block* interaction was found [$F_{(2,32)}$=2.45, p=.1, η^2_p=.13].

TD vs. Ipsilateral CST reorganization

The ANOVA revealed a significant main effect of *Group* [$F_{(1,16)}$=12.75, p<.01, η^2_p=.40] and of *Block* [$F_{(2,32)}$=7.36, p<.01, η^2_p=.30]. Crucially, as shown in Figure 1, there was a significant *Group X Block* interaction [$F_{(2,32)}$=4.91, p<.01, η^2_p=.20]: only TD participants showed an improvement in accuracy from the first block (M=42.9) to the second (M=53, p<.01) and third

blocks (M=55, p<.01) of practice. On the other hand, CP children with ipsilateral CST organization did not show any improvement in accuracy across blocks of practice (B1=5 vs. B2=7 and B3=5.7, p=1 for all comparisons).

TD vs. Contralateral CST reorganization

The ANOVA revealed a significant main effect of *Block* [$F_{(2,32)}$=8.13, p<.01, η^2_p=.30], but not of *Group* [$F_{(1,16)}$=1.36, p<.261, η^2_p=.07]. As shown in Figure 1, the significant *Group X Block* interaction [$F_{(2,32)}$=3.25, p=.05, η^2_p=.20] showed again that only TD participants improved their accuracy from the first (M=42.9) to the second (M=53, p<.01) and third (M=55, p<.01) blocks of practice. CP children with contralateral CST organization did not improve their accuracy across blocks of practice (B1=34 vs. B2=37 and B3=36.3, p=1 for all comparisons) (see Figure 2).

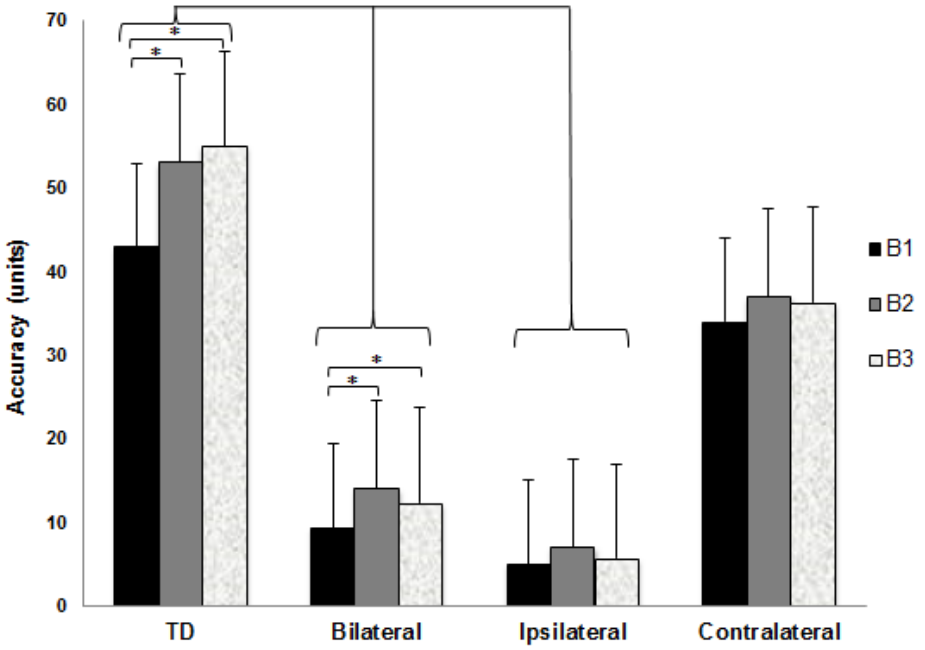

Figure 2. Online accuracy of TD *vs.* CP children. Number of sequences correctly performed during each block of training for patients with bilateral, Ipsilateral or contralateral CST reorganization, and in typically developed children (TD); **within-group differences* and lines=*between-group differences*, p<.05. Error bars=SEM.

Total Number of sequences performed by TD participants vs. children with CP

The ANOVA revealed a significant main effect of *Group* [$F_{(3,20)}$=9.34, p<.01, η^2_p=.60] showing that TD participants performed more sequences (correct or wrong) in each block of practice than CP children. The main effect of *Block* [$F_{(2,40)}$=12.06, p<.01, η^2_p=.40] showed an increasing number of the performed sequences across the three blocks of practice. The significant *Group X Block* interaction was found [$F_{(6,40)}$=4.30, p<.01, η^2_p=.40] and was further explored by separated rm-ANOVA to contrast TD participants with each group of CP children.

TD vs. Bilateral CST reorganization

The ANOVA revealed a significant main effect of *Group* [$F_{(1,16)}$=11.35, p<.01, η^2_p=.40], showing an increased number of reproduced sequences by TD participants (M=58) than CP children with bilateral reorganization (M=18, p<.01). The main effect of *Block* [$F_{(2,32)}$=18.25, p<.01, η^2_p=.50] was also significant showing an overall increase in the number of performed sequences on the second (B2, M=39.2) and third (B3, M=43.6) blocks, as compared to the first one (B1, M=31.8 *vs.* B2 p<.01 and vs. B3 p<.01, respectively), with a significant increase also from the second block to the third one (p=.04). No significant *Group X Block* interaction was found [$F_{(2,32)}$=2.91, p=.07, η^2_p=.15] (Figure 2).

TD vs. Ipsilateral CST reorganization

The ANOVA revealed a significant main effect of *Block* [$F_{(2,32)}$=10.46, p<.01, η^2_p=.40] and *Group* [$F_{(1,16)}$=16.31, p<.01, η^2_p=.50], as well as, as shown in Figure 2, a significant *Group X Block* interaction [$F_{(2,32)}$=7.78, p<.01, η^2_p=.30]: TD participants performed more sequences in the first (M=49) than in the second (M=60, p<.01) and third blocks of practice (M=65.26, p<.01). On the other hand, CP children with ipsilateral CST organization did not show any difference between blocks of practice (B1=10.7, B2=11 and B3=12, p=.9 for all comparisons).

TD vs. Contralateral CST reorganization

The ANOVA revealed a significant main effect of *Block* [$F_{(2,32)}$=13.81, p<.01, η^2_p=.50], but not of *Group* [$F_{(1,16)}$=1.59, p=.225, η^2_p=.09]. As shown in Figure 2, the significant *Group X Block* interaction [$F_{(2,32)}$=4.19, p=.025, η^2_p=.20] showed that only TD participants performed more sequences from the first block (M=42.9) to the second (M=53, p<.01) and third blocks of practice (M=55, p<.01). In CP children with contralateral reorganization, there was no increase in the number of sequences performed across blocks of practice (B1=40.7 vs. B2=44 and B3=45.3, p=.9 for all comparisons) (see Figure 3).

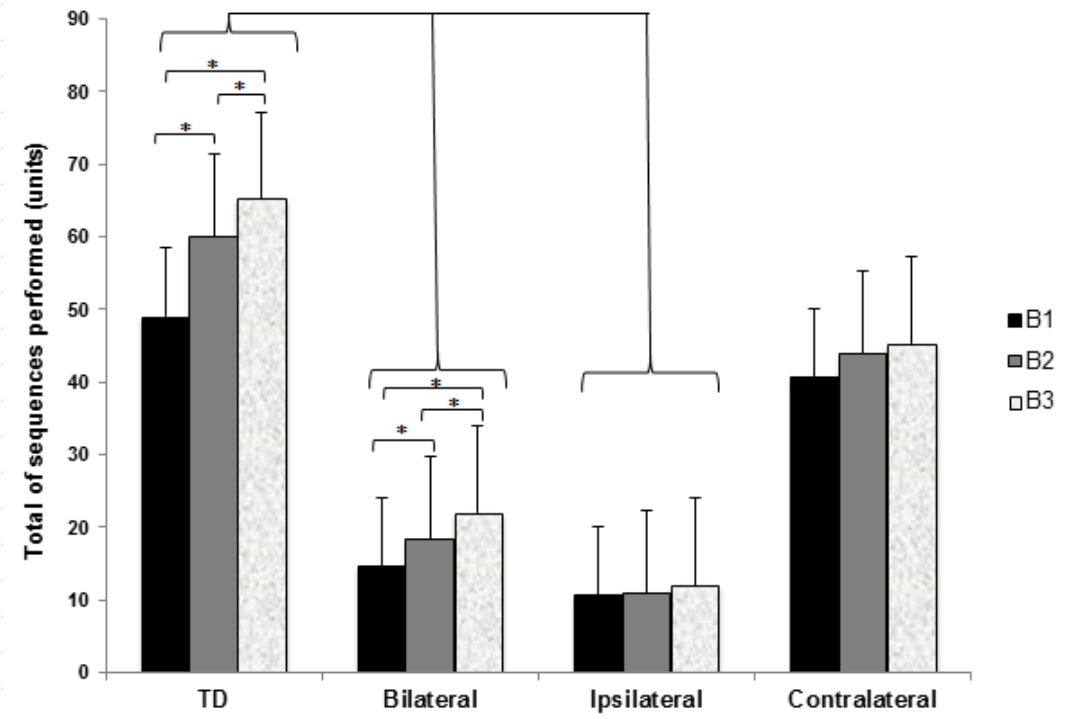

Figure 3. Total number of sequences performed by TD *vs.* CP children. Motor performance during each block of training for patients with Bilateral, Ipsilateral or Contralateral CST reorganization, and in typically developed children (TD); lines=*between-group differences and *within-group differences*, $p<.05$. Error bars=SEM.

4.4. Discussion

The present evidence shows that the way by which the motor system reorganizes in CP impact motor learning abilities: indeed, only when there is a bi-hemispheric control of the affected hand, CP children show a motor learning performance comparable to that of TD children. Conversely, ipsilateral and contralateral CP children do not show online motor learning in terms of quality (accuracy) and quantity (number of sequences performed) when confronted to TD children. In particular, children with a bilateral CST reorganization are able to learn a simple FTT, while those with ipsilateral or contralateral CST reorganization seem not to be capable. Such finding points out to the possibility of different levels of motor network engagement during learning in CP children which depends on the pattern of CST reorganization.

Hung and Gordon (2013) have already shown that unilateral CP children are able to improve their performance in a bimanual speed task, but their rate of improvement and learning are quite different from those of TD children (Hung & Gordon, 2013). In the same way, Gagliardi and colleagues (2011) showed that sequence-learning skills of CP children are lower than those of TD children in terms of visual memory and accuracy. Such impairments seem not to be related to motor impairments assessed through the Gross Motor Function Classification System (Gagliardi, Tavano, Turconi, Pozzoli, & Borgatti, 2011). Similarly, Hakkarainen and colleagues (2012) investigated the motor planning of patients with mild spastic CP and a peer control group of TD children. Author's

findings pointed out an overall slowness and inaccurate reaction time performance of CP vs. TD children, which could reflect poor motor execution processes (Hakkarainen, Pirilä, Kaartinen, & Meere, 2012). Such findings provide robust evidence for the existence of different patterns of motor learning in CP and TD children.

The present results show that motor learning abilities with a paretic limb are associated with the pattern of motor system reorganization. A child with typical motor development has a contralateral pattern of movement control (Eyre et al., 2001; Jaspers et al., 2016). Such contralateral pattern is the result of a competitive withdrawal of brain projections in which the ipsilateral uncrossed projections of the CST gradually weaken, while the contralateral crossed projections strengthen in the first months of life. On the other hand, this lateralization of movement control may be disrupted in CP children. Due to the brain lesion, CP children may develop weakened crossed projections from the motor areas of the affected hemisphere (Eyre, 2007; Staudt et al., 2004), while strengthened uncrossed projections from the intact hemisphere which can take (or not) control of the affected body side movement. The present results showed that only bilateral CP children were able to improve their accuracy as well as the number of total sequences performed along the FTT, while ipsilateral and contralateral CP children did not show this online motor learning. This evidence suggests that after a brain damage the greater the neural resources available to compensate for the lost abilities, the greater the outcome: at least with respect to motor learning, this function seems to require an extensive recruitment of preserved motor areas in both hemispheres. It follows that bilateral CP children may have improved their performance more effectively than ipsilateral CP children due to such "reinforced" bilateral recruitment of motor areas.

To note, 2 out of 3 bilateral CP children of our sample had a left-hemisphere brain damage, and thus, uncrossed projections from the right hemisphere were preserved. Goldberg and colleagues (1994) have already proposed that external environment drives right hemisphere's processing (Goldberg, 1994). It is well known that declarative memories can be formed very quickly as well as being intrinsically related to high-level cognition processes in which sensory guidance and verbal instructions are present (Squire et al., 1990; Vidoni & Boyd, 2007). A speculation could be that bilateral CP children with a left-hemisphere brain damage perhaps achieved better performance due to the preservation of their uncrossed projections from the right hemisphere which allowed a boosting in their explicit learning.

Moreover, we found that CP children with ipsilateral CST reorganization of the present sample showed the worst quantitative and qualitative performance (and they also do not show a normal learning rate) during the task, while children with a contralateral pattern perform as TD ones. This evidence is in line with previous studies which suggested a poorer motor performance of

children with an ipsilateral motor reorganization (Baranello et al., 2016; Holmstrom et al., 2010; Rich, Menk, Rudser, Feyma, & Gillick, 2017; Smorenburg et al., 2017). Rich and colleagues (2017) compared hand function and grip strength of unilateral CP children (only those with a ipsilateral or contralateral reorganization of the motor system) to TD peers and showed that those with contralateral motor pattern had the best motor performance by means of JTT, as compared to children with an ipsilateral reorganization (Rich et al., 2017). However, it is estimated that 30% of pediatric unilateral CP children present a bi-hemispheric motor reorganization pattern (Friel et al., 2016). Rich and colleagues (2017) did not include CP children with a "mixed" motor reorganization (i.e., bilateral), but raised the hypothesis that the contralateral motor pattern group had also children with such "mixed" pattern (Rich et al., 2017). Marneweck and colleagues (2018) used single-pulse transcranial magnetic stimulation to measure the size and excitability of motor representation of both hands as well as their overlap in the contralesional hemisphere of 50 unilateral CP children (Marneweck et al., 2018). They showed a large amount of overlap in contralesional motor representations of both hands in CP children which seem to be in some extent a positive functional plastic processes, since the size, as well as excitability of overlapping motor representations are related to motor abilities and recovery. The greater and stronger is such overlapping, the better is the unimanual and bimanual performance of children.

A parallel may be done with learning processes of CP children and of adult stroke patients with respect to cortical reorganization of neuronal networks after a stroke. A key factor seems to be the interhemispheric connectivity. Healthy adults present with a balanced motor network activity in both hemispheres, with a mutual inhibitory control allows performing movements (Kinsbourne, 1974). Unilateral hand movements are associated with a predominant activation of contralateral motor areas as well as with an increase of the inhibitory control of such areas over the ipsilateral hemisphere - which occurs via transcallosal fibers (Bütefisch, Weβling, Netz, Seitz, & Hömberg, 2008; Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008). However, such interhemispheric balance is altered in stroke patients due to the unilateral brain injury. Evidence from studies with fMRI have shown that movements of the affected hand in stroke patients elicit an increase in cortical activity of motor areas in both hemispheres (injured and not-injured) and such pattern is also commonly found in patients with poorer prognosis (Rehme, Fink, von Cramon, & Grefkes, 2010; Ward, Brown, Thompson, & Frackowiak, 2003). Rehme and colleagues (2010) have already shown a decrease in interhemispheric inhibitory M1-M1 coupling in the acute stroke which gradually returns to the normality in patients showing a good motor recovery of the paretic hand (Rehme et al., 2010). Additionally, neural networks involved in a simple implicit learning task are divergent in chronic stroke patients whether confronted with healthy individuals. Using fMRI,

Wadden and colleagues (2015) showed that healthy individuals have a bihemispheric activation during implicit motor sequence learning which encompasses motor and sensory cortices as well as the parietal lobule. However, authors found a limited neuronal activity within the M1-premotor-parietal-cerebellar circuit as well as a high degree of inter-individual variability in network activity within the injured hemisphere of stroke patients (Wadden et al., 2015). Such compensatory mechanisms likely are related to changes in functional connectivity and may support our findings of preserved motor learning in CP children with bilateral CST reorganization. Unlike stroke adults, bilateral CP children seem to benefit of a "bilateral" motor control of the affected hand, while adults usually present better motor performance when cortical reorganization resembles the "normal" (i.e., contralateral) one.

‖ Study 4 ‖

tDCS modulation of motor learning in children with cerebral palsy

4.5. Introduction

Given the results from the previous experiment showing impaired motor learning in CP, a second experiment was performed to verify the possibility of improving motor performance of the affected hand in CP by means of tDCS. So far, there is no definitive evidence that tDCS may modulate upper-limb motor disorders in CP. Ciechanski and Kirton (2017) assessed safety, tolerability and tDCS effects in 24 healthy school-aged children. Such pediatric population underwent 3 consecutive days of motor task practice performing the Purdue Pegboard Test (PPT); in a between-subjects design, participants were randomized to receive, during the PPT, different tDCS conditions: anodal tDCS (duration= 20 minutes) at an intensity of 1mA, cathodal tDCS at 1mA, cathodal tDCS at 2mA or sham over the right M1 or left M1. Authors showed that all tDCS conditions were able to enhance motor performance at PPT, as compared to sham tDCS, and such effects were sustained after 6 weeks of the training ends. Additionally, tDCS was well-tolerated with no serious adverse effects (Ciechanski & Kirton, 2017). Only two rehabilitation studies were performed in children with CP: in both studies, the cathodal stimulation was administered as adjuvant of the motor therapy to improve upper-limb motor functions (B. Gillick et al., 2018). Negative results were obtained: the cathodal stimulation applied to the healthy hemisphere was overall unable to increase the gains of the motor training (as compared to the add-on use of sham tDCS), with respect to objective motor outcomes.

Within this framework, the present study explores the effect of a single application of anodal tDCS on motor performance of the affected hand in children with CP. I adopted the same experimental design of the seminal study in stroke adults performed by Boggio and colleagues (Boggio et al., 2007). Participants underwent, in a sham-controlled cross-over experiment, 4 tDCS conditions: (i) anodal tDCS over the ipsilesional M1; (ii) anodal tDCS over the contralesional M1; (iii) cathodal tDCS over the contralesional M1; (iv) sham tDCS. Motor improvements were assessed with the Jebsen Hand Function Test (Boggio et al., 2007). Given the observation that the

pattern of CST reorganization (Study 3) impact on motor performance, I have also verified whether CST pattern impacted on the modulatory effects of tDCS on motor learning.

4.6. Material and Methods

Participants

Nine children with CP and upper-limb motor deficits tested in this experiment were the same of the Study 3, five additional children, all of them with unilateral brain lesions were added to that sample; also these participants were from the in- and an out-patient population of the Developmental Neurology Unit of the Fondazione IRCCS Istituto Neurologico Carlo Besta (Milan, Italy). Hence, a total of 14 participants (see Table 1 for details about the five additional children) were tested in this experiment. The same inclusion/exclusion criteria of Study 3 were adopted. No participant had contraindication to tDCS (Rossi et al., 2009), particularly with respect to having had epileptic seizures in the two years prior to the experiment or being under anti-epileptic treatment at the time of testing.

The study was approved by the Ethics Committees of the IRCCS Istituto Neurologico Carlo Besta (NIBS-BIT version 3.0). The experimental procedure was in accordance with the ethical standards of the Declaration of Helsinki. Parents were informed about the aim of the study and provided written informed consent.

Table 1. Demographic and clinical data of patients.

ID	CST organization	Gender/Age	Education	Most Affected Hand	MACS level	JTT score (baseline)	Type of lesion
P1	Bilateral	M, 6	0	R	III	67	WMD
P2		M, 6	1	L	III	62	WMD
P3	Ipsilateral	M, 7	1	R	II	412	MCAI
P4		M, 6	1	R	II	125	WMD
P5	Contralateral	F, 14	8	L	III	243	WMD

ID: Patients' Identification number. Gender: M=Male, F=Female. Age in years. Education in years. Affected hand: R=Right, L=Left. MACS: Manual Ability Classification System (Range=I-V); JTT: Jebsen-Taylor Hand Function Test (total time in seconds).Type of lesion: WMD=White Matter Damage, MCAI=Middle Cerebral Artery Infarct, N/A: not available.

Study design

In a cross-over and randomized order, CP children received 4 tDCS conditions during 4 experimental days with at least 24 hours between sessions to avoid tDCS *carry-over* effects

(Brunoni et al., 2012): (i) anodal tDCS over the ipsilesional M1; (ii) anodal tDCS over the contralesional M1; (iii) cathodal tDCS over the contralesional M1; (iv) sham tDCS over the ipsilesional or contralesional M1 (randomized across participants). Figure 1 shows the experimental design.

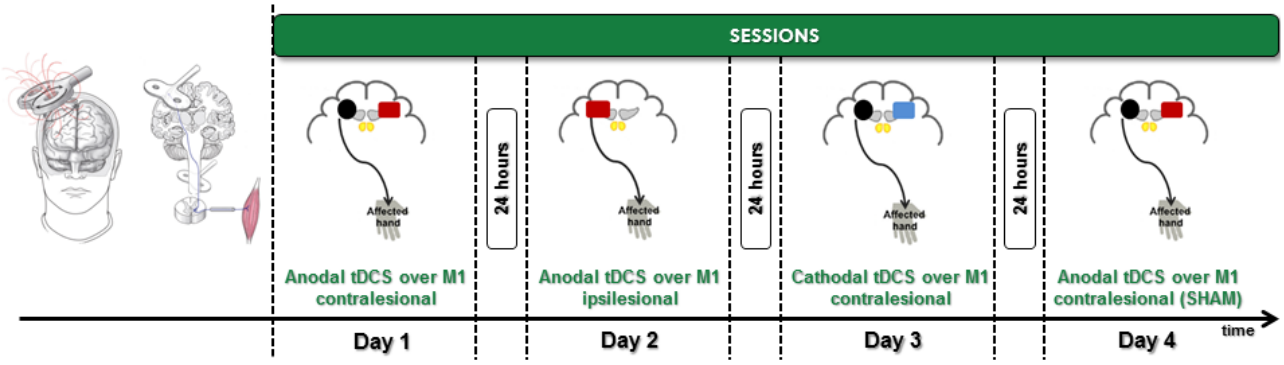

Figure 1. Study design. Children underwent, in a randomized order, 4 tDCS sessions, during which different types of tDCS were applied. Before the experiment, the determination of the CST re-organization was made by TMS.

The Jebsen-Taylor Hand Function Test - JTT (Jebsen et al., 1969; Taylor et al., 1973) was applied immediately after the end of tDCS to assess changes in motor function after stimulation (Boggio et al., 2007). The JTT assess fine and gross motor hand function using simulated activities of daily living (i.e., picking up small objects, moving light/heavy cans, etc.). The total time (in seconds) taken to complete the tasks represents the performance's score, thus lower scores represent better motor performance. Children were ask to perform the tasks of the JTT with their affected hand as quickly and accurate as possible.

tDCS

Direct current stimulation was delivered by a battery-driven stimulator (BrainStim, EMS, Bologna, Italy, http://brainstim.it/) via a pair of electrodes covered by saline-soaked sponges (5 x 5 cm – 25 cm^2). Active stimulation was applied for 20 min (fade-in/fade-out phases=10 sec), with an intensity of 1 mA, following current safety data (Antal et al., 2017). For the anodal stimulation of the ipsilesional hemisphere, the anode was placed over the ipsilesional motor cortex (C4 or C3, according to the 10/20 EEG system for electrodes placement) and the cathode (reference) electrode was placed over the contralateral supraorbital area. The opposite electrodes' montage was used for the cathodal stimulation or the anodal stimulation of the intact motor cortex. For sham stimulation, the same parameters of the active stimulation were used, but the stimulator was turned off after 30 sec (Gandiga et al., 2006).

Clinical and Cortical Assessment

Before the experiment, CP participants underwent a clinical and neurophysiological assessment. Reorganization of the motor system was assessed via MEPs induced by TMS (Jaspers et al., 2016): for the detailed protocol of assessments, consult the methods of Study 3 in this thesis – section 4.2).

Statistical analyses

Statistical analyses were performed using Statistica (Version 10). Normality of all data was assessed by the Shapiro-Wilk test. Since the assumption was not violated, learning and motor performance were analyzed via repeated measures Analysis of Variance (rm-ANOVA).

The total response time at the JTT was analyzed via rm-ANOVA, with *Group* (3 levels: Bilateral CST, Ipsilateral CST, Contralateral CST) as between-subjects factor, and *tDCS* (4 levels: anodal tDCS over the ipsilesional M1, anodal tDCS over the contralesional M1, cathodal tDCS over the contralesional M1, sham tDCS) as within-subjects factor. Significance was set at *alpha*=.05; main effects and interactions were further explored by means of Newman-Keuls correction.

Further, we looked for an association (Spearman correlation test) between the manual ability (JTT score at baseline and MACS) and the effect of active tDCS conditions (tDCS effect index=JTT score post-active tDCS *minus* JTT score after sham tDCS).

4.7. Results

The rm-ANOVA did not reveal any significant main effects, or significant interactions between factors: *Group* [$F_{(3,11)}$=3.03, p=.08, η^2_p=.35]; *tDCS* [$F_{(3,33)}$=0.93, p=.43, η^2_p=.07] and the *Group X tDCS* interaction [$F_{(6,33)}$=1.06, p=.40, η^2_p=.16] (see Figure 2).

Correlation analyses showed a significant negative association between the JTT score at baseline and the tDCS effect index only for the anodal stimulation of the contralesional M1 (r= -.55, p=.04); this means that the higher is the improvement in motor performance after the anodal tDCS of the contralesional M1, the lower is the JTT score at baseline (i.e., better motor performance of the children). No correlation was found between the JTT score at baseline and the tDCS index for the other tDCS conditions, nor between the level of MACS and the tDCS index for all stimulation conditions (see Table 2).

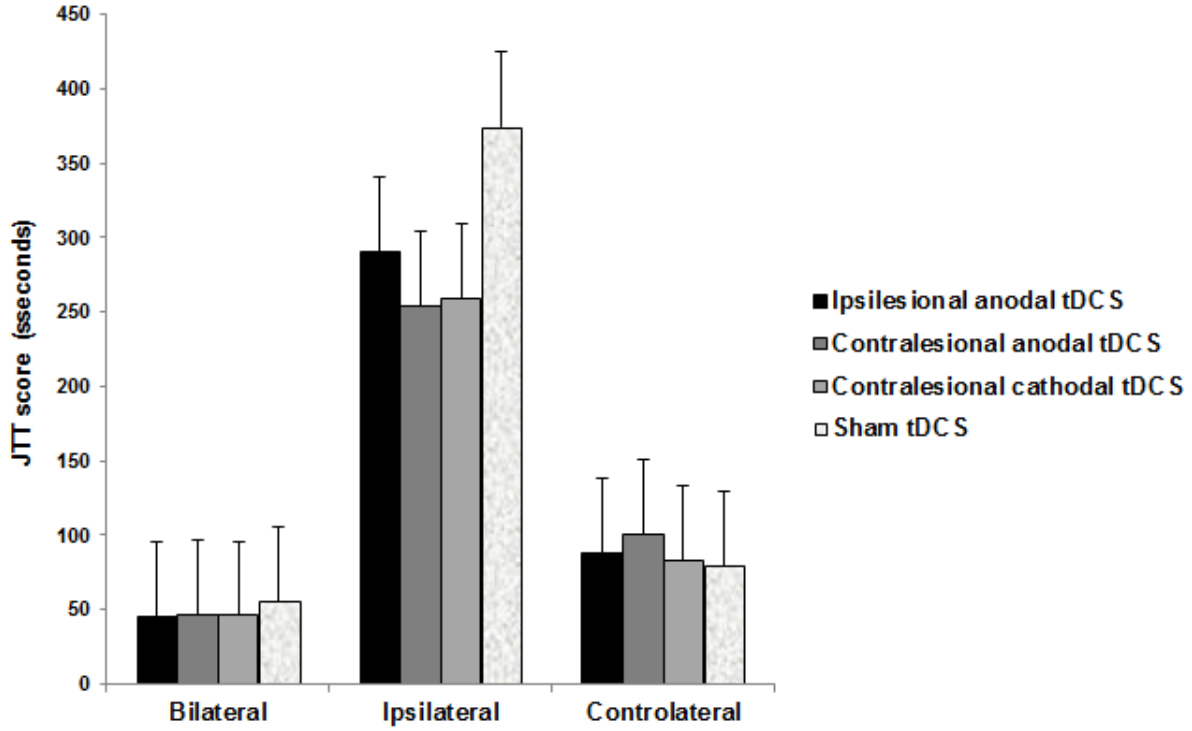

Figure 2. Total score at the Jebsen-Taylor Test for patients with Bilateral, Ipsilateral or Contralateral CST reorganization in each stimulation condition; Error bars=SEM.

Table 2. Correlation between manual ability and the increase of the tDCS index after each active condition.

		Ipsilesional anodal tDCS	Contralesional anodal tDCS	Contralesional cathodal tDCS
MACS score	Spearman Correlation	.084	-.252	-.147
	p-level	.776	.386	.617
	N	14	14	14
JTT score at baseline	Spearman Correlation	.116	-.556	-.218
	p-level	.692	***.039****	.455
	N	14	14	14

MACS: Manual Ability Classification System; JTT: Jebsen-Taylor Hand Function Test;
*Correlation at .05 (2-tailed)

4.8. Discussion

The present evidence shows that a single application of tDCS does not seem to change the motor performance of the affected hand of CP children; the pattern of CST reorganization affects children's motor performance, but it does not influence tDCS efficacy. However, at least for the anodal contralesional tDCS, an association was found between the tDCS improvements and the severity of motor disorder.

Our results are in line with previous findings showing the absence of TDCS facilitation of motor performance of the affected hand in CP children. Indeed, in such pediatric population, anodal

tDCS over the affected M1, combined with standard physiotherapeutic training, was shown to improve mobility, gait, body sway velocity, balance as well as spasticity - for a review see (Palm et al., 2016). So far, two three studies explored tDCS effects on hand functions of CP children. Results showed that contralesional cathodal tDCS with an intensity equal or below 1 mA (i.e. 0.7 mA) was unable to increase upper-limb motor functions in such population (Gillick et al., 2018). Instead, multiple applications of ipsilesional anodal tDCS (1mA, 20 min) applied during motor training improves only subjective (Canadian Occupational Performance measure), but not objective (i.e., scores at JTT) motor outcomes. Using a design similar to the present experiment, Moura and colleagues (2017) showed that a single application of anodal tDCS (1mA, 20 min) over the ipsilesional M1 combined with a functional training may improve upper-limb function (i.e., movement duration and returning movement duration of paretic and non-paretic limbs) in children with spastic hemiparesis (Moura et al., 2017). Although the authors used the same tDCS parameters of the present study (current intensity, duration of the stimulation and the same size of electrodes), two main differences should be considered. Firstly, in Moura et al. Study, tDCS was delivered during a functional training. Secondly, the authors did not assess the effects on daily living activities, nor on fine motor skills, as instead measured by the JTT.

We should also acknowledge some methodological limitations of the present experiment. Firstly, the small sample size (about 4/5 individuals for CST group), with heterogeneous levels of motor impairments (MACS and JTT scores at baseline). In this regard, it is worth noting that the less impaired was the children at the JTT, the greater were the effects of contralesional anodal tDCS. This finding supports a more in-depth exploration of the role of the intact hemisphere in driving motor recovery in CP children. So far, tDCS approaches in such children were based on the model of interhemispheric imbalance, which posits that supressing the excitability of the non-lesioned hemisphere should enhance post-stroke motor recovery by reducing interhemispheric inhibition over the lesioned hemisphere. However, this model primarily refers to stroke occurring in adulthood (Nowak, Grefkes, Ameli, & Fink, 2009). An increasing number of evidence is showing that the interhemispheric competition model may be over simplified, since functional recovery also depend on structural reserve spared by the lesion (Bradnam, Stinear, & Byblow, 2013; Di Pino et al., 2014; Lotze et al., 2012; Lotze et al., 2006). The present finding support this view in CP.

Secondly, as pointed out in the introduction (Chapter 1), tDCS effects are intrinsically associated with the parameters of stimulation (i.e., duration of stimulation, current density, polarity, electrodes size, and montage, among others). In pediatric populations, at variance with the more advanced state of the research in adults (Chapter 1), there is insufficient evidence to establish the optimal stimulation parameters, either in healthy and children with neurological diseases such as CP

(Gillick et al., 2014; Kessler et al., 2013; Moliadze et al., 2015). So far, studies investigating tDCS effects in pediatric populations adopted a current intensity ranging between 0.3mA and 2 mA, and a duration up to 20 minutes (Krishnan et al., 2015). Moreover, the persistence of tDCS effects in children is still unknown (Antal et al., 2017). It is also important to keep in mind that tDCS does not function in a linear manner, so that the physiological and behavioral outcomes (in term of facilitation or inhibition) of the cortical excitability modulation depends on the interaction of several factors related not only to technical parameters (such as the current polarity and duration), but also to individual and task characteristics, as well to metaplasticity-related effects (Fertonani & Miniussi, 2017); this is especially relevant, and even more complex, in a developing brain (Davis, 2014).

4.9. General conclusion (studies 3 & 4)

The two studies described in this chapter showed that CP children with an Ipsilateral or Bilateral CST reorganization showed a more impaired motor performance, as compared to TD children and CP children with a Contralesional CST reorganization (Study 3); this finding agrees with the view that abnormal projections from the non-lesioned hemisphere to the paretic hand, common in hemiparetic CP, are associated with worse motor function and recovery. The novel finding is that, despite an important impairment of the paretic hand, CP children with a Bilateral CST reorganization show preserved motor learning abilities, at variance of CP with either Ipsilateral and Contralateral CST reorganization. This evidence indicates that in CP children, motor execution and learning are dissociable, being differently affected by the patter of CST reorganization. tDCS seems unable to improve motor performance in CP children (Study 4): a single application of tDCS, either to the intact or to the damaged hemisphere, does not change motor performance of the affected hand in such pediatric population, independently of the type of CST reorganization. However, the severity of the motor hand impairment seems to influence the effect of the contralesional anodal tDCS applied over M1.

CHAPTER 5

General discussion

The present dissertation comprises four studies. The first study was a systematic review with meta-analysis of the published scientific literature from clinical trials in order to verify the efficacy of NIBS techniques as add-on tools to boost motor training effects in individuals with neurological diseases. Then, I have conducted three empirical investigations to extent the scientific knowledge about tDCS effects on motor learning in healthy adults, and potential disorders of motor learning in children with CP. In this case, even allowing a chance of improving with tDCS the upper-limb function of such children.

Summarizing the main findings of my work, in Chapter 2, the first Study covered the results from 30 CTs and 1255 patients with motor impairments due to different neurological diseases (i.e., Stroke, Parkinson's disease, Spinal Cord Injury and Leukoaraiosis). The results reveal that NIBS can increase a patient's response to motor therapies, with a major effect induced by combining rTMS or tDCS with motor training in stroke patients. In particular, in such population, low-frequency rTMS is more effective when applied before the motor therapy, while bihemispheric and anodal tDCS should be applied during the training; in every case, NIBS is effective in chronic post-stroke patients. For Parkinson's disease, Spinal Cord Injury, and Leukoaraiosis, any definitive conclusion cannot be drawn due to the few published studies.

In Chapter 3, the second Study addressed the modulatory effects of tDCS applied over different cortical areas (namely, M1, PPC, and PM) on motor learning processes of healthy individuals. I have obtained evidence indicating that anodal tDCS modulate differently learning processes, as acquisition and retention of the learned skill, as well as its generalization, depending on which area is targeted: the anodal stimulation of M1 facilitates both *online learning* and *retention*. However, anodal tDCS on PM facilitates only the *generalization*. Parietal stimulation was unable to affect motor learning processes.

In Chapter 4, the third and fourth studies showed that the type of corticospinal tract reorganization that takes place in CP children might disrupt motor learning; in this paediatric population, a single application of anodal tDCS does not improve motor performance of the affected hand.

In the following sessions, I will discuss the main findings of this thesis providing perspectives for the future and analyzing the limitations of my studies.

Non-invasive brain stimulation as a tool to boost the motor function of adults patients with neurological disorders

In the last years, plenty of systematic reviews have provided promising results regarding the efficacy of NIBS in the treatment of neurological patients with motor disorders (Butler et al., 2013; Corner, 2016; Gunduz, Rothwell, Vidal, & Kumru, 2017; Lüdemann-Podubecká et al., 2015; Zhu et al., 2015). A still open issue and a big challenge in the field of neuroscience is its use as an add-on approach. Since many issues remain unanswered and are under investigation (i.e., optimal stimulation parameters, predictors of the patient' response, among others), an increasing number of studies has investigated the potential of tDCS and rTMS to enhance the clinical efficacy of a wide range of therapies (i.e., physical therapy, occupational therapy). Tedesco Triccas (2016) reviewed the effect of multiple sessions of tDCS associated with post-stroke rehabilitation for upper extremities. Covering 9 studies with 371 patients, authors have found a small non-significant beneficial effect of tDCS combined with rehabilitation (Triccas et al., 2016). In the same way, Graef and colleagues (2016) considered 8 studies with 199 patients: authors have concluded that the state of the current literature does not support the idea that rTMS associated with upper-limb training is able to improve motor function of post-stroke patients, as compared to training as stand-alone therapy (Graef, Dadalt, da Silva Rodrigués, Stein, & de Souza Pagnussat, 2016). So far, only Kang and colleagues (2016) have shown positive effects of associating tDCS and motor training in post-stroke patients (Kang et al., 2015).

The study 1 extends such literature, also considering patients with Parkinson's disease, Spinal Cord Injury or Leukoaraiosis. However, for these diseases, the evidence is still poor to demonstrate positive/negative NIBS effects. Regarding Stroke, my original results have showed positive effects of low-frequency rTMS applied in the acute/subacute phases, while patients in a chronic stage benefit from almost every type of NIBS, namely low-frequency rTMS, and anodal, cathodal and bihemispheric tDCS. Moreover, NIBS has been demonstrated to be effective both when delivered before (in the case of low-frequency rTMS) and during motor training (anodal and bihemispheric tDCS). In light of these findings, some implications for research and practice can be drawn.

Before discussing the limitations of the Study 1, it is important to highlight its conceptual advance, value for clinical practice and its importance to improve the quality of future meta-analyses. The most important limitation from Study 1 is the small number of studies included in the quantitative analysis, along with the fact that the majority of them did not provide satisfactory data to perform a more reliable meta-analysis. Secondly, the heterogeneity of both NIBS protocols and the combined motor training made it difficult to generalize the findings. I took into consideration only one outcome measure in the meta-analysis, namely the motor performance, which was

assessed, however, using a mix of functional scales and behavioral tasks. The uniformity across studies is required even in this regard. Another aspect is the subgroups analyses, which were performed in order to identify factors influencing NIBS effects on motor learning. The emerging picture is that multiple interacting factors could have be found, from the technical aspects of NIBS to the individual features of the neurological patient. They all need to be systematically controlled, or at least carefully considered, especially when planning a clinical trial with NIBS. In addition, it is relevant to have described details for optimizing data selection and analysis.

It is important to take into consideration that methodological recommendations for clinical trial were not followed by many studies, especially with respect to the randomization procedure and the concealment of treatment allocation. For this reason, I have selected only CTs adopting moderate to high-quality methodological standards. In future clinical trials, it will be important to increase the overall sample size and to share some parameters of NIBS, to facilitate comparisons and merging of data from different studies. In the perspective of implementing more informative meta-analyses, I encourage researchers to ensure that the details of their ongoing protocols are registered in relevant databases or, at least, they could be shared upon request.

For clinical decision-making, results from Study 1 suggest that bihemispheric and cathodal tDCS applied as add-on intervention to motor therapies have the potential for facilitating training-induced motor recovery, but only in chronic stroke patients (quality of evidence: *moderate* to *high*). Instead, the quality of evidence is too low for recommending the combined use of anodal tDCS, and high or low-frequency rTMS, in chronic stroke patients. Finally, the use of NIBS in acute/subacute stroke and Parkinson's disease cannot be recommended at the moment (quality of evidence: *low* to *very low*).

tDCS as a tool to boost motor learning in healthy individuals

In the last decade, tDCS has been successfully used to promote behavioral changes and enhance motor learning in healthy individuals. It is unquestionable that its use has spread in the motor learning domain very likely due to the low-cost, easy utilization and the fact that it is a painless technique. So far, some recent reviews have shown mixed effects of tDCS on motor learning in healthy adults. Hashemirad and colleagues (2016) showed that anodal tDCS applied over M1 for 3 to 5 consecutive days is able to improve motor sequence learning (Hashemirad et al., 2016). The median effect size was 0.71, but effects across all studies ranged from 0.02 to 1.70, which highlights the inconsistency of the findings. On the other hand, evidence coming from a meta-analysis performed by Bastani and Jaberzadeh (2012) showed a small, but significant effect of anodal tDCS applied over M1 to increase cortical excitability of healthy individuals, but the same cannot be affirmed to improvements of motor function (Bastani & Jaberzadeh, 2012). Indeed, in a

critical paper, Buch and colleagues (2017) stated that a growing body of evidence continues to support the use of tDCS as a tool to facilitate motor learning in healthy individuals, but some critical points still need to be addressed. Those points are mainly related to methodological and design requirements of tDCS studies and thus, authors have suggested a reporting checklist to be used. In the future, it will allow an optimization of stimulation dose and reduce inter-study variabilities (Buch et al., 2017).

Besides confirming the benefits of anodal tDCS applied over M1 for motor learning in healthy individuals, my Study 2 provides also novel evidence for the role of other cortical areas in learning processes. Indeed, tDCS of PM induces effects similar to that of M1 stimulation in terms of *online* and *retention*, but it additionally facilitates generalization of the learned skill. This finding represents a step forward in the current literature since it paves the way for the application of tDCS to facilitate not only learning, but also to aid its generalization to other motor activities. This is of main importance in clinical context, where the main goal of any treatment is to improve performance in a particular task that could be transferred to other functions. Moreover, the present results also suggests that different areas may be targeted to drive specific effects on motor recovery, depending on the extend of M1 lesion (Plow, Cunningham, Varnerin, & Machado, 2015). For instance, with respect to the results of Study 2, PM could represent a potential candidate to facilitate the transfer of tDCS-induced gains on daily living. On the other hand, PPC may represent a more promising target, whenever higher order levels of motor programming and execution are affected (Bolognini et al., 2014; Fogassi & Luppino, 2005; Gardner, 2017), rather than low-level learning processes as found here. In this perspective, assessing the therapeutic effects of premotor and parietal stimulations could pave the way to offer more rehabilitation alternatives for the treatment of post-stroke hemiparesis patients.

tDCS as a tool to boost motor learning and function of children with cerebral palsy

Considering the potential of NIBS techniques in change motor and cognitive behavior of healthy individuals, as well as adult patients with neurologic disorders, neuromodulation has been increasingly used also in pediatric populations. The main concern is the feasibility and safety of such approach since children have important anatomical differences when confronted to adults, as the diameter and thickness of the skull (Gillick et al., 2014; Kessler et al., 2013; Moliadze et al., 2015). Such factors are important due to the fact that tDCS-dose should be adjusted or attenuated to induce similar plastic neuronal changes without harming effects. Some reviews have assessed tDCS adverse events in childhood, and so far, it seems to be a well-tolerated and safe technique (Krishnan et al., 2015). However, the therapeutic use of tDCS in children/adolescents has some ethical deliberations that should be carefully considered (Palm et al., 2016). Davis (2014) calls attention for

the lack of knowledge regarding the effects of treatment, the lack of clear guidelines for dosage and especially, the lack of translational studies from adults to children (Davis, 2014). It should also be considered the fact that a child's brain is still developing and tDCS protocols must ensure safety and positive effects along with all the stages of cognitive and motor development.

Before trying to verify the modulatory effects of tDCS on the impaired motor function of children with CP, I have performed a behavioral investigation to assess whether motor learning abilities are spared in CP, and then to understand the role of CST reorganization in motor learning of such paediatric population. Results from Study 3 showed that motor learning abilities are disrupted in CP children, except for those children with a Bilateral reorganization of the CST. Based on this, it may be suggested that CP children with such reorganization pattern could benefit more of treatment approaches in which cortical excitability balance is bilaterally modulated. This could be done through the application of anodal tDCS over either the injured or the intact hemisphere, in combination with a bimanual training which also modulates interhemispheric interactions. Conversely, CP children with an Ipsilateral or a Contralateral CTS pattern, who do not show online motor learning, might benefit more of treatment approaches in which cortical excitability balance is unilaterally modulated. For example, Islam and colleagues (2014) showed that constraint-induced movement therapy improved hand functions both, at the JTT and at the Assisting Hand Assessment, in CP children presenting projections from the uninjured or the injured hemisphere to the paretic hand (Islam et al., 2014).

Being preliminary to a clinical study assessing whether tDCS can be used to improve paretic hand functions in CP, Study 4 has explored the effects of a single application of tDCS taking into consideration the impact of the pattern of CST reorganization. The results did not show any benefit from tDCS, regardless of whether it was the intact or the damaged M1 to be stimulated, the polarity of the current, and their interaction with respect to the CST pattern. Such negative results may be explained by some methodological aspects already discussed in Chapter 4 (i.e., small sample size, different levels of preserved functional ability of the paretic limb, tDCS parameters). Clinical trials applying multiple sessions of tDCS associated with a motor training still need to confirm or refute the results from 'one-shot' sessions. The finding that the effects of contralesional anodal tDCS seem to be influenced by severity of the hand impairment in CP children also opens new perspectives to individualize protocols of tDCS in such paediatric population.

Additionally, facing the fact that a child's brain is in constant development and there is no consensus regarding the most suitable tDCS dosage to induce after-effects before applying tDCS, the child's anatomical particularities should be taken into consideration. According to the singularities of each developmental disorder, as well as the age of the child, parameters of

stimulation and tDCS montages should be able to precisely reproduce brain current densities which have been consolidated as effective and safe for adults by the scientific literature. It is noteworthy that in the present sample, none of the CP children reported adverse events after the tDCS protocol used.

Concluding remarks

In the neuroscience field, NIBS techniques are currently used as neuromodulation tools for diagnostic and treat plenty motor disorders. Its use has grown due to efforts in understanding the underlying mechanisms of learning and motor control as well as how therapeutic approaches could be used to maximize the patient's response. Within this framework, the present thesis has contributed clarifying the state of the art of the combined approach which posits an adjuvant effect of NIBS (and tDCS in particular) on motor training in neurological and paediatric populations. Further, an advance of knowledge is offered by the empirical investigation showing, on one hand, that M1 is not the only area that should be considered in post-stroke motor rehabilitation, at least in adults; on the other hand, CP may disrupt motor learning processing in children, depending on how the lesion impacts the recruitment of ipsilateral or contralateral motor projections to the paretic hand. The application of tDCS without any motor training cannot restore upper-limb motor functions, at least when it is delivery with a low dosage.

Acknowledgments

From the bottom of my heart, I am really grateful to all the persons who helped me, supported me and trusted me along these three years of hard work. I had been through tuff days until arrive here and, for sure, it's a dream coming true.

Firstly, I would like to express my deepest thankfulness to my supervisor, Nadia Bolognini, who received me here in Milan without any hesitation even though she did not know me before the Ph.D. It was three years of intensive, challenger and exciting work that transformed me in a better researcher, but also in a better person. She knew how to manage her work, give support and, at the same time, leave space so that I could grow up by myself and build my own knowledge. For sure, she is an inspiring person who puts in evidence the great work of female researchers in Italy.

I cannot forget of all professionals of the *Istituto Auxologico Italiano, Fondazione IRCCS Istituto Neurologico Carlo Besta* and of the undergraduate students of the University of Milano-Bicocca, who welcomed me and made my experiments feasible from the very beginning of the Ph.D. In the same way, my sincere gratitude to the families of all children who took part in my experiments. Thank you for respect me, for trust in my work and for being so patience during the countless clinical evaluations and experimental sessions. I have learned a lot with each one of you and your children.

It is difficult to express also my thankfulness to colleagues and friends of the thirty-first doctoral cycle who made me feel like I was at home since my arrival in Italy. I will never forget how each one of you was receptive, generous and loving. You guys, made my journey here lighter and easier, even in the hardest days.

Finally, I really should say how blessed am I for having a huge support from my Brazilian family and friends. Since the beginning of my dream, when I did not even know if I would be able to achieve it, they have always encouraged me relentlessly. Mother, father, brother/sister and lovely friends, you have kindly renounced my presence for three years and understood how important to me was having all of you by my "side". I could not do this without such support. In particular, I should say that while my Brazilian family and friends were my emotional pillar during the Ph.D., the clinical team of the Hospital Memorial São José/Núcleo Especializado em Oncologia e Hematologia (in special Dr. Jurema Telles, Dr. Christine Miranda, and Ivo) literally saved my life and gave me a new chance to finish my studies in Italy.

I would like to dedicate this thesis to my grandmother, Maria Celina. She is my infinite source of love!

References

Abo, M., Kakuda, W., Momosaki, R., Harashima, H., Kojima, M., Watanabe, S., . . . Sasanuma, J. (2014). Randomized, multicenter, comparative study of NEURO versus CIMT in poststroke patients with upper limb hemiparesis: the NEURO-VERIFY Study. *International Journal of Stroke, 9*(5), 607-612.

Accornero, F. (1988). An eyewitness account of the discovery of electroshock. *Convuls Ther, 4*(1), 40-49.

Adams, J. A. (1971). A closed-loop theory of motor learning. *Journal of motor behavior, 3*(2), 111-150.

Adeyemo, B. O., Simis, M., Macea, D., & Fregni, F. (2012). Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke. *Frontiers in psychiatry, 3*, 88.

Adkins-Muir, D. L., & Jones, T. A. (2003). Cortical electrical stimulation combined with rehabilitative training: enhanced functional recovery and dendritic plasticity following focal cortical ischemia in rats. *Neurological research, 25*(8), 780-788.

Alagona, G., Delvaux, V., Gérard, P., De Pasqua, V., Pennisi, G., Delwaide, P. J., . . . de Noordhout, A. M. (2001). Ipsilateral motor responses to focal transcranial magnetic stimulation in healthy subjects and acute-stroke patients. *Stroke, 32*(6), 1304-1309.

Albert, N. B., Robertson, E. M., & Miall, R. C. (2009). The resting human brain and motor learning. *Current Biology, 19*(12), 1023-1027.

Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., . . . Degueldre, C. (2008). Both the hippocampus and striatum are involved in consolidation of motor sequence memory. *Neuron, 58*(2), 261-272.

Allman, C., Amadi, U., Winkler, A. M., Wilkins, L., Filippini, N., Kischka, U., . . . Johansen-Berg, H. (2016). Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke. *Science translational medicine, 8*(330), 330re331-330re331.

Althaus, J. (1873). *A Treatise on Medical Electricity, Theoretical and Practical: And Its Uses in the Treatment of Paralysis, Neuralgia and Other Diseases*: Longmans, Green.

Ammann, B. C., Knols, R. H., Baschung, P., De Bie, R. A., & de Bruin, E. D. (2014). Application of principles of exercise training in sub-acute and chronic stroke survivors: a systematic review. *BMC neurology, 14*(1), 167.

Andersen, R. A., & Buneo, C. A. (2002). Intentional maps in posterior parietal cortex. *Annual review of neuroscience, 25*(1), 189-220.

Andersen, R. A., & Cui, H. (2009). Intention, action planning, and decision making in parietal-frontal circuits. *Neuron, 63*(5), 568-583.

Anderson, J. R. (1982). Acquisition of cognitive skill. *Psychological review, 89*(4), 369.

Ang, K. K., Guan, C., Phua, K. S., Wang, C., Zhao, L., Teo, W. P., . . . Chew, E. (2015). Facilitating effects of transcranial direct current stimulation on motor imagery brain-computer interface with robotic feedback for stroke rehabilitation. *Archives of physical medicine and rehabilitation, 96*(3), S79-S87.

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A., Chen, R., . . . Flöel, A. (2017). Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology, 128*(9), 1774-1809.

Antal, A., Nitsche, M. A., Kruse, W., Kincses, T. Z., Hoffmann, K.-P., & Paulus, W. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of cognitive neuroscience, 16*(4), 521-527.

Antal, A., Polania, R., Schmidt-Samoa, C., Dechent, P., & Paulus, W. (2011). Transcranial direct current stimulation over the primary motor cortex during fMRI. *Neuroimage, 55*(2), 590-596.

Antal, A., Terney, D., Poreisz, C., & Paulus, W. (2007). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience, 26*(9), 2687-2691.

Arai, N., Okabe, S., Furubayashi, T., Terao, Y., Yuasa, K., & Ugawa, Y. (2005). Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. *Clinical Neurophysiology, 116*(3), 605-613.

Ardolino, G., Bossi, B., Barbieri, S., & Priori, A. (2005). Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *The Journal of physiology, 568*(2), 653-663.

Arya, K. N., Pandian, S., Verma, R., & Garg, R. (2011). Movement therapy induced neural reorganization and motor recovery in stroke: a review. *Journal of bodywork and movement therapies, 15*(4), 528-537.

Ashe, J. (1997). Force and the motor cortex. *Behavioural brain research, 86*(1), 1-15.

Ashe, J., Lungu, O. V., Basford, A. T., & Lu, X. (2006). Cortical control of motor sequences. *Current opinion in neurobiology, 16*(2), 213-221.

Aton, S. J., Seibt, J., Dumoulin, M., Jha, S. K., Steinmetz, N., Coleman, T., . . . Frank, M. G. (2009). Mechanisms of sleep-dependent consolidation of cortical plasticity. *Neuron, 61*(3), 454-466.

Avenanti, A., Coccia, M., Ladavas, E., Provinciali, L., & Ceravolo, M. (2012). Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke A randomized trial. *Neurology, 78*(4), 256-264.

Baldwin, B. (1992). The career and work of Scribonius Largus. *Rheinisches Museum für Philologie, 135*(H. 1), 74-82.

Bar-Haim, S., Harries, N., Nammourah, I., Oraibi, S., Malhees, W., Loeppky, J., . . . Lahat, E. (2010). Effectiveness of motor learning coaching in children with cerebral palsy: a randomized controlled trial. *Clinical rehabilitation, 24*(11), 1009-1020.

Baranello, G., Sebastiano, D. R., Pagliano, E., Visani, E., Ciano, C., Fumarola, A., . . . Marchi, A. (2016). Hand function assessment in the first years of life in unilateral cerebral palsy: correlation with neuroimaging and cortico-spinal reorganization. *european journal of paediatric neurology, 20*(1), 114-124.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *The Lancet, 325*(8437), 1106-1107.

Barrionuevo, G., & Brown, T. H. (1983). Associative long-term potentiation in hippocampal slices. *Proceedings of the National Academy of Sciences, 80*(23), 7347-7351.

Bastani, A., & Jaberzadeh, S. (2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clinical Neurophysiology, 123*(4), 644-657.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of physiology, 591*(7), 1987-2000.

Battaglia-Mayer, A., & Caminiti, R. (2009). Posterior Parietal Cortex and Arm Movement.

Baumann, M. A., Fluet, M.-C., & Scherberger, H. (2009). Context-specific grasp movement representation in the macaque anterior intraparietal area. *Journal of Neuroscience, 29*(20), 6436-6448.

Bax, M., Goldstein, M., Rosenbaum, P., Leviton, A., Paneth, N., Dan, B., . . . Damiano, D. (2005). Proposed definition and classification of cerebral palsy, April 2005. *Developmental medicine and child neurology, 47*(8), 571-576.

Bell, J. A., Wolke, M. L., Ortez, R. C., Jones, T. A., & Kerr, A. L. (2015). Training intensity affects motor rehabilitation efficacy following unilateral ischemic insult of the sensorimotor cortex in C57BL/6 mice. *Neurorehabilitation and neural repair, 29*(6), 590-598.

Benito, J., Kumru, H., Murillo, N., Costa, U., Medina, J., Tormos, J., . . . Vidal, J. (2012). Motor and gait improvement in patients with incomplete spinal cord injury induced by high-frequency repetitive transcranial magnetic stimulation. *Topics in spinal cord injury rehabilitation, 18*(2), 106-112.

Benwell, C. S., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: evidence from biparietal tDCS influence on lateralized attention bias. *cortex, 69*, 152-165.

Bestmann, S. (2015). Computational neurostimulation in basic and translational research Preface. *COMPUTATIONAL NEUROSTIMULATION, 222*, XV-XX.

Beurze, S. M., De Lange, F. P., Toni, I., & Medendorp, W. P. (2007). Integration of target and effector information in the human brain during reach planning. *Journal of neurophysiology, 97*(1), 188-199.

Bhatt, T., & Pai, Y.-C. (2009). Prevention of slip-related backward balance loss: the effect of session intensity and frequency on long-term retention. *Archives of physical medicine and rehabilitation, 90*(1), 34-42.

Bienenstock, E. L., Cooper, L. N., & Munro, P. W. (1982). Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *Journal of Neuroscience, 2*(1), 32-48.

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., . . . Boggio, P. (2016). Safety of transcranial direct current stimulation: evidence based update 2016. *Brain stimulation, 9*(5), 641-661.

Bindman, L. J., Lippold, O., & Redfearn, J. (1962). Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature, 196*(4854), 584.

Bindman, L. J., Lippold, O., & Redfearn, J. (1964). 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. *The Journal of physiology, 172*(3), 369-382.

Bliss, T. V., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of physiology, 232*(2), 331-356.

Boggio, P. S., Ferrucci, R., Rigonatti, S. P., Covre, P., Nitsche, M., Pascual-Leone, A., & Fregni, F. (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *Journal of the neurological sciences, 249*(1), 31-38.

Boggio, P. S., Nunes, A., Rigonatti, S. P., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2007). Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restorative neurology and neuroscience, 25*(2), 123-129.

Bolognini, N., Convento, S., Banco, E., Mattioli, F., Tesio, L., & Vallar, G. (2014). Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex. *Brain, 138*(2), 428-439.

Bolognini, N., & Miniussi, C. (2018). Noninvasive brain stimulation of the parietal lobe for improving neurologic, neuropsychologic, and neuropsychiatric deficits. *Handbook of clinical neurology, 151*, 427-446.

Bolognini, N., Pascual-Leone, A., & Fregni, F. (2009). Using non-invasive brain stimulation to augment motor training-induced plasticity. *Journal of neuroengineering and rehabilitation, 6*(1), 8.

Bolognini, N., Vallar, G., Casati, C., Latif, L. A., El-Nazer, R., Williams, J., . . . Chessa, C. (2011). Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabilitation and neural repair, 25*(9), 819-829.

Born, J., Rasch, B., & Gais, S. (2006). Sleep to remember. *The Neuroscientist, 12*(5), 410-424.

Boros, K., Poreisz, C., Münchau, A., Paulus, W., & Nitsche, M. A. (2008). Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. *European Journal of Neuroscience, 27*(5), 1292-1300.

Borragán, G., Urbain, C., Schmitz, R., Mary, A., & Peigneux, P. (2015). Sleep and memory consolidation: motor performance and proactive interference effects in sequence learning. *Brain and cognition, 95*, 54-61.

Bortoletto, M., Pellicciari, M. C., Rodella, C., & Miniussi, C. (2015). The interaction with task-induced activity is more important than polarization: a tDCS study. *Brain stimulation, 8*(2), 269-276.

Bowden, M. G., Woodbury, M. L., & Duncan, P. W. (2013). Promoting neuroplasticity and recovery after stroke: future directions for rehabilitation clinical trials. *Current opinion in neurology, 26*(1), 37-42.

Boyd, L. A., & Winstein, C. J. (2003). Impact of explicit information on implicit motor-sequence learning following middle cerebral artery stroke. *Physical Therapy, 83*(11), 976-989.

Boyd, L. A., & Winstein, C. J. (2004). Providing explicit information disrupts implicit motor learning after basal ganglia stroke. *Learning & memory, 11*(4), 388-396.

Boyd, L. A., & Winstein, C. J. (2006). Explicit information interferes with implicit motor learning of both continuous and discrete movement tasks after stroke. *Journal of Neurologic Physical Therapy, 30*(2), 46-57.

Bradnam, L. V., Stinear, C. M., & Byblow, W. D. (2013). Ipsilateral motor pathways after stroke: implications for non-invasive brain stimulation. *Frontiers in human neuroscience, 7*, 184.

Brodie, S. M., Meehan, S. K., Borich, M., & Boyd, L. A. (2014). 5 Hz repetitive transcranial magnetic stimulation over the ipsilesional sensory cortex enhances motor learning after stroke. *Frontiers in human neuroscience, 8*, 143.

Broeder, S., Nackaerts, E., Heremans, E., Vervoort, G., Meesen, R., Verheyden, G., & Nieuwboer, A. (2015). Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects. *Neuroscience & Biobehavioral Reviews, 57*, 105-117.

Brown, R. M., & Robertson, E. M. (2007). Off-line processing: reciprocal interactions between declarative and procedural memories. *Journal of Neuroscience, 27*(39), 10468-10475.

Brown, T., Zhao, Y., & Leung, V. (2009). Hebbian plasticity.

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology, 14*(8), 1133-1145.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Pascual-Leone, A. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain stimulation, 5*(3), 175-195.

Bucci, D. J. (2009). Posterior parietal cortex: an interface between attention and learning? *Neurobiology of learning and memory, 91*(2), 114-120.

Buccino, G., Binkofski, F., Fink, G. R., Fadiga, L., Fogassi, L., Gallese, V., . . . Freund, H. J. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *European Journal of Neuroscience, 13*(2), 400-404.

Buch, E. R., Brasted, P. J., & Wise, S. P. (2006). Comparison of population activity in the dorsal premotor cortex and putamen during the learning of arbitrary visuomotor mappings. *Experimental brain research, 169*(1), 69-84.

Buch, E. R., Santarnecchi, E., Antal, A., Born, J., Celnik, P. A., Classen, J., . . . Nitsche, M. A. (2017). Effects of tDCS on motor learning and memory formation: a consensus and critical position paper. *Clinical Neurophysiology, 128*(4), 589-603.

Buhmann, C., Glauche, V., Stürenburg, H., Oechsner, M., Weiller, C., & Büchel, C. (2003). Pharmacologically modulated fMRI---cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients. *Brain, 126*(2), 451-461.

Buma, F., Kwakkel, G., & Ramsey, N. (2013). Understanding upper limb recovery after stroke. *Restorative neurology and neuroscience, 31*(6), 707-722.

Bütefisch, C. M., Weβling, M., Netz, J., Seitz, R. J., & Hömberg, V. (2008). Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. *Neurorehabilitation and neural repair, 22*(1), 4-21.

Butler, A. J., Shuster, M., O'hara, E., Hurley, K., Middlebrooks, D., & Guilkey, K. (2013). A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *Journal of Hand Therapy, 26*(2), 162-171.

Cano-De-La-Cuerda, R., Molero-Sánchez, A., Carratalá-Tejada, M., Alguacil-Diego, I., Molina-Rueda, F., Miangolarra-Page, J., & Torricelli, D. (2015). Theories and control models and motor learning: clinical applications in neurorehabilitation. *Neurología (English Edition), 30*(1), 32-41.

Cantarero, G., Spampinato, D., Reis, J., Ajagbe, L., Thompson, T., Kulkarni, K., & Celnik, P. (2015). Cerebellar direct current stimulation enhances on-line motor skill acquisition through an effect on accuracy. *Journal of Neuroscience, 35*(7), 3285-3290.

Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. (2011). Differential contribution of right and left parietal cortex to the control of spatial attention: a simultaneous EEG–rTMS study. *Cerebral cortex, 22*(2), 446-454.

Carey, J. R., Fregni, F., & Pascual-Leone, A. (2006). rTMS combined with motor learning training in healthy subjects. *Restorative neurology and neuroscience, 24*(3), 191-199.

Carmichael, S. T. (2010). Targets for neural repair therapies after stroke. *Stroke, 41*(10 suppl 1), S124-S126.

Carr, J. H., & Shepherd, R. B. (1989). A motor learning model for stroke rehabilitation. *Physiotherapy, 75*(7), 372-380.

Carr, L., Harrison, L., Evans, A., & Stephens, J. (1993). Patterns of central motor reorganization in hemiplegic cerebral palsy. *Brain, 116*(5), 1223-1247.

Censor, N., & Sagi, D. (2009). Global resistance to local perceptual adaptation in texture discrimination. *Vision research, 49*(21), 2550-2556.

Censor, N., Sagi, D., & Cohen, L. G. (2012). Common mechanisms of human perceptual and motor learning. *Nature Reviews Neuroscience, 13*(9), 658.

Cha, H.-K., Ji, S.-G., Kim, M.-K., & Chang, J.-S. (2014). Effect of transcranial direct current stimulation of function in patients with stroke. *Journal of physical therapy science, 26*(3), 363-365.

Cha, H. G., & Kim, M. K. (2016). Effects of repetitive transcranial magnetic stimulation on arm function and decreasing unilateral spatial neglect in subacute stroke: a randomized controlled trial. *Clinical rehabilitation, 30*(7), 649-656.

Chang, M. C., Kim, D. Y., & Park, D. H. (2015). Enhancement of cortical excitability and lower limb motor function in patients with stroke by transcranial direct current stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8*(3), 561-566.

Chang, W. H., Kim, Y.-H., Yoo, W.-K., Goo, K.-H., Park, C.-h., Kim, S. T., & Pascual-Leone, A. (2012). rTMS with motor training modulates cortico-basal ganglia-thalamocortical circuits in stroke patients. *Restorative neurology and neuroscience, 30*(3), 179-189.

Chopp, M., Zhang, Z. G., & Jiang, Q. (2007). Neurogenesis, angiogenesis, and MRI indices of functional recovery from stroke. *Stroke, 38*(2), 827-831.

Cicinelli, P., Pasqualetti, P., Zaccagnini, M., Traversa, R., Oliveri, M., & Rossini, P. M. (2003). Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. *Stroke, 34*(11), 2653-2658.

Ciechanski, P., Carlson, H., Yu, S., & Kirton, A. (2018). Modeling Transcranial Direct-Current Stimulation-Induced Electric Fields in Children and Adults. *Frontiers in human neuroscience, 12*, 268.

Ciechanski, P., & Kirton, A. (2017). Transcranial direct-current stimulation can enhance motor learning in children. *Cerebral cortex, 27*(5), 2758-2767.

Cioni, G., D'Acunto, G., & Guzzetta, A. (2011). Perinatal brain damage in children: neuroplasticity, early intervention, and molecular mechanisms of recovery *Progress in brain research* (Vol. 189, pp. 139-154): Elsevier.

Cirelli, C., & Tononi, G. (2000). Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *Journal of Neuroscience, 20*(24), 9187-9194.

Civardi, C., Cantello, R., Asselman, P., & Rothwell, J. C. (2001). Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. *Neuroimage, 14*(6), 1444-1453.

Classen, J., Liepert, J., Wise, S. P., Hallett, M., & Cohen, L. G. (1998). Rapid plasticity of human cortical movement representation induced by practice. *Journal of neurophysiology, 79*(2), 1117-1123.

Cohen, O., Sherman, E., Zinger, N., Perlmutter, S., & Prut, Y. (2010). Getting ready to move: transmitted information in the corticospinal pathway during preparation for movement. *Current opinion in neurobiology, 20*(6), 696-703.

Colby, C. L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annual review of neuroscience, 22*(1), 319-349.

Conner, J. M., Culberson, A., Packowski, C., Chiba, A. A., & Tuszynski, M. H. (2003). Lesions of the basal forebrain cholinergic system impair task acquisition and abolish cortical plasticity associated with motor skill learning. *Neuron, 38*(5), 819-829.

Convento, S., Bolognini, N., Fusaro, M., Lollo, F., & Vallar, G. (2014). Neuromodulation of parietal and motor activity affects motor planning and execution. *Cortex, 57*, 51-59.

Convento, S., Russo, C., Zigiotto, L., & Bolognini, N. (2016). Transcranial electrical stimulation in post-stroke cognitive rehabilitation. *European Psychologist*.

CORNER, C. (2016). Transcranial direct current stimulation for improving idiopathic Parkinson's syndrome. An abridged version of a Cochrane review. *European journal of physical and rehabilitation medicine, 52*(6), 902-906.

Cosentino, G., Fierro, B., Paladino, P., Talamanca, S., Vigneri, S., Palermo, A., . . . Brighina, F. (2012). Transcranial direct current stimulation preconditioning modulates the effect of high-frequency repetitive transcranial magnetic stimulation in the human motor cortex. *European Journal of Neuroscience, 35*(1), 119-124.

Costa-Ribeiro, A., Maux, A., Bosford, T., Tenório, Y., Marques, D., Carneiro, M., . . . Monte-Silva, K. (2016). Dopamine-Independent Effects of Combining Transcranial Direct Current Stimulation with Cued Gait Training on Cortical Excitability and Functional Mobility in Parkinson's Disease. *Journal of rehabilitation medicine, 48*(9), 819-823.

Cramer, S. C., Nelles, G., Benson, R. R., Kaplan, J. D., Parker, R. A., Kwong, K. K., . . . Rosen, B. R. (1997). A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke, 28*(12), 2518-2527.

Cross, E. S., Schmitt, P. J., & Grafton, S. T. (2007). Neural substrates of contextual interference during motor learning support a model of active preparation. *Journal of cognitive neuroscience, 19*(11), 1854-1871.

Cuypers, K., Leenus, D. J., van den Berg, F. E., Nitsche, M. A., Thijs, H., Wenderoth, N., & Meesen, R. L. (2013). Is motor learning mediated by tDCS intensity? *PloS one, 8*(6), e67344.

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Topper, R., & Boroojerdi, B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain research, 1072*(1), 194-199.

Danzl, M. M., Chelette, K. C., Lee, K., Lykins, D., & Sawaki, L. (2013). Brain stimulation paired with novel locomotor training with robotic gait orthosis in chronic stroke: a feasibility study. *NeuroRehabilitation, 33*(1), 67-76.

Davare, M., Andres, M., Cosnard, G., Thonnard, J.-L., & Olivier, E. (2006). Dissociating the role of ventral and dorsal premotor cortex in precision grasping. *Journal of Neuroscience, 26*(8), 2260-2268.

Davare, M., Lemon, R., & Olivier, E. (2008). Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. *The Journal of physiology, 586*(11), 2735-2742.

Davare, M., Montague, K., Olivier, E., Rothwell, J. C., & Lemon, R. N. (2009). Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. *Cortex, 45*(9), 1050-1057.

Davidson, T., & Tremblay, F. (2013). Hemispheric differences in corticospinal excitability and in transcallosal inhibition in relation to degree of handedness. *PloS one, 8*(7), e70286.

Davis, N. J. (2014). Transcranial stimulation of the developing brain: a plea for extreme caution. *Frontiers in human neuroscience, 8*, 600.

Dayan, E., Censor, N., Buch, E. R., Sandrini, M., & Cohen, L. G. (2013). Noninvasive brain stimulation: from physiology to network dynamics and back. *Nature neuroscience, 16*(7), 838.

Dayan, E., & Cohen, L. G. (2011). Neuroplasticity subserving motor skill learning. *Neuron, 72*(3), 443-454.

de Xivry, J.-J. O., Marko, M. K., Pekny, S. E., Pastor, D., Izawa, J., Celnik, P., & Shadmehr, R. (2011). Stimulation of the human motor cortex alters generalization patterns of motor learning. *Journal of Neuroscience, 31*(19), 7102-7110.

Debas, K., Carrier, J., Barakat, M., Marrelec, G., Bellec, P., Tahar, A. H., . . . Doyon, J. (2014). Off-line consolidation of motor sequence learning results in greater integration within a cortico-striatal functional network. *Neuroimage, 99*, 50-58.

Deeks, J. J., Higgins, J., & Altman, D. G. (2008). Analysing data and undertaking meta-analyses. *Cochrane handbook for systematic reviews of interventions: Cochrane Book Series*, 243-296.

Deiber, M.-P., Wise, S., Honda, M., Catalan, M., Grafman, J., & Hallett, M. (1997). Frontal and parietal networks for conditional motor learning: a positron emission tomography study. *Journal of Neurophysiology, 78*(2), 977-991.

Della-Maggiore, V., Malfait, N., Ostry, D. J., & Paus, T. (2004). Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. *Journal of Neuroscience, 24*(44), 9971-9976.

Deng, Z.-D., Lisanby, S. H., & Peterchev, A. V. (2014). Coil design considerations for deep transcranial magnetic stimulation. *Clinical Neurophysiology, 125*(6), 1202-1212.

Dennis, N. A., & Cabeza, R. (2011). Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. *Neurobiology of aging, 32*(12), 2318. e2317-2318. e2330.

Desmurget, M., Reilly, K. T., Richard, N., Szathmari, A., Mottolese, C., & Sirigu, A. (2009). Movement intention after parietal cortex stimulation in humans. *science, 324*(5928), 811-813.

Di Lazzaro, V., Oliviero, A., Saturno, E., Pilato, F., Insola, A., Mazzone, P., . . . Rothwell, J. (2001). The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. *Experimental brain research, 138*(2), 268-273.

Di Lazzaro, V., Ziemann, U., & Lemon, R. N. (2008). State of the art: physiology of transcranial motor cortex stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 1*(4), 345-362.

Di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Experimental brain research, 91*(1), 176-180.

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., . . . Rothwell, J. C. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nature Reviews Neurology, 10*(10), 597.

Diedrich, F. J., & Warren Jr, W. H. (1995). Why change gaits? Dynamics of the walk-run transition. *Journal of Experimental Psychology: Human Perception and Performance, 21*(1), 183.
Diekelmann, S., Wilhelm, I., & Born, J. (2009). The whats and whens of sleep-dependent memory consolidation. *Sleep medicine reviews, 13*(5), 309-321.
Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., . . . Benali, H. (2009). Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behavioural brain research, 199*(1), 61-75.
Doyon, J., & Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Current opinion in neurobiology, 15*(2), 161-167.
Doyon, J., Ungerleider, L. G., Squire, L., & Schacter, D. (2002). Functional anatomy of motor skill learning. *Neuropsychology of memory, 3*, 225-238.
Duecker, F., & Sack, A. T. (2015). The hybrid model of attentional control: New insights into hemispheric asymmetries inferred from TMS research. *Neuropsychologia, 74*, 21-29.
Dumel, G., Bourassa, M.-È., Charlebois-Plante, C., Desjardins, M., Doyon, J., Saint-Amour, D., & De Beaumont, L. (2018). Multisession anodal transcranial direct current stimulation induces motor cortex plasticity enhancement and motor learning generalization in an aging population. *Clinical Neurophysiology, 129*(2), 494-502.
Duque, J., Labruna, L., Verset, S., Olivier, E., & Ivry, R. B. (2012). Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. *Journal of Neuroscience, 32*(3), 806-816.
Dymond, A., Coger, R., & Serafetinides, E. (1975). Intracerebral current levels in man during electrosleep therapy. *Biological Psychiatry, 10*(1), 101.
Eichenbaum, H. (2001). The hippocampus and declarative memory: cognitive mechanisms and neural codes. *Behavioural brain research, 127*(1-2), 199-207.
Eisenberg, M., Shmuelof, L., Vaadia, E., & Zohary, E. (2010). Functional organization of human motor cortex: directional selectivity for movement. *Journal of Neuroscience, 30*(26), 8897-8905.
Eliasson, A.-C., Krumlinde-Sundholm, L., Rösblad, B., Beckung, E., Arner, M., Öhrvall, A.-M., & Rosenbaum, P. (2006). The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Developmental medicine and child neurology, 48*(7), 549-554.
Evans, S. H. (1967). A brief statement of schema theory. *Psychonomic Science, 8*(2), 87-88.
Evarts, E. V. (1981). Role of motor cortex in voluntary movements in primates. *Handbook of physiology, 2*, 1083-1120.
Eyre, J. (2007). Corticospinal tract development and its plasticity after perinatal injury. *Neuroscience & Biobehavioral Reviews, 31*(8), 1136-1149.
Eyre, J., Taylor, J., Villagra, F., Smith, M., & Miller, S. (2001). Evidence of activity-dependent withdrawal of corticospinal projections during human development. *Neurology, 57*(9), 1543-1554.
Fattori, P., Breveglieri, R., Amoroso, K., & Galletti, C. (2004). Evidence for both reaching and grasping activity in the medial parieto-occipital cortex of the macaque. *European Journal of Neuroscience, 20*(9), 2457-2466.
Fentress, J. C. (1973). Development of grooming in mice with amputated forelimbs. *Science, 179*(4074), 704-705.
Fertonani, A., & Miniussi, C. (2017). Transcranial electrical stimulation: what we know and do not know about mechanisms. *The Neuroscientist, 23*(2), 109-123.
Feys, H., Eyssen, M., Jaspers, E., Klingels, K., Desloovere, K., Molenaers, G., & De Cock, P. (2010). Relation between neuroradiological findings and upper limb function in hemiplegic cerebral palsy. *european journal of paediatric neurology, 14*(2), 169-177.
Filimon, F. (2010). Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. *The Neuroscientist, 16*(4), 388-407.
Fiocchi, S., Ravazzani, P., Priori, A., & Parazzini, M. (2016). Cerebellar and spinal direct current stimulation in children: computational modeling of the induced electric field. *Frontiers in human neuroscience, 10*, 522.
Fischer, S., Hallschmid, M., Elsner, A. L., & Born, J. (2002). Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences, 99*(18), 11987-11991.
Fitts, P. M. (1964). Perceptual-motor skill learning *Categories of human learning* (pp. 243-285): Elsevier.

Fleming, M. K., Rothwell, J. C., Sztriha, L., Teo, J. T., & Newham, D. J. (2017). The effect of transcranial direct current stimulation on motor sequence learning and upper limb function after stroke. *Clinical Neurophysiology*, *128*(7), 1389-1398.

Fletcher, J., Maybery, M. T., & Bennett, S. (2000). Implicit learning differences: A question of developmental level? *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *26*(1), 246.

Floyer-Lea, A., & Matthews, P. M. (2005). Distinguishable brain activation networks for short-and long-term motor skill learning. *Journal of neurophysiology*, *94*(1), 512-518.

Fogassi, L., & Luppino, G. (2005). Motor functions of the parietal lobe. *Current opinion in neurobiology*, *15*(6), 626-631.

Fregni, F., Boggio, P. S., Santos, M. C., Lima, M., Vieira, A. L., Rigonatti, S. P., . . . Pascual-Leone, A. (2006). Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Movement Disorders*, *21*(10), 1693-1702.

Friel, K. M., Kuo, H.-C., Fuller, J., Ferre, C. L., Brandão, M., Carmel, J. B., . . . Rowny, S. B. (2016). Skilled bimanual training drives motor cortex plasticity in children with unilateral cerebral palsy. *Neurorehabilitation and neural repair*, *30*(9), 834-844.

Fusco, A., Assenza, F., Iosa, M., Izzo, S., Altavilla, R., Paolucci, S., & Vernieri, F. (2014). The ineffective role of cathodal tDCS in enhancing the functional motor outcomes in early phase of stroke rehabilitation: an experimental trial. *BioMed research international*, *2014*.

Fusco, A., Iosa, M., Venturiero, V., De Angelis, D., Morone, G., Maglione, L., . . . Paolucci, S. (2014). After vs. priming effects of anodal transcranial direct current stimulation on upper extremity motor recovery in patients with subacute stroke. *Restorative neurology and neuroscience*, *32*(2), 301-312.

Gagliardi, C., Tavano, A., Turconi, A. C., & Borgatti, R. (2013). Sequence memory skills in Spastic Bilateral Cerebral Palsy are age independent as in normally developing children. *Disability and rehabilitation*, *35*(6), 506-512.

Gagliardi, C., Tavano, A., Turconi, A. C., Pozzoli, U., & Borgatti, R. (2011). Sequence learning in cerebral palsy. *Pediatric neurology*, *44*(3), 207-213.

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*(2), 593-609.

Galletti, C., Kutz, D. F., Gamberini, M., Breveglieri, R., & Fattori, P. (2003). Role of the medial parieto-occipital cortex in the control of reaching and grasping movements. *Experimental Brain Research*, *153*(2), 158-170.

Galvão, S. C. B., dos Santos, R. B. C., dos Santos, P. B., Cabral, M. E., & Monte-Silva, K. (2014). Efficacy of coupling repetitive transcranial magnetic stimulation and physical therapy to reduce upper-limb spasticity in patients with stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation*, *95*(2), 222-229.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical neurophysiology*, *117*(4), 845-850.

Gardner, E. P. (2017). Neural pathways for cognitive command and control of hand movements. *Proceedings of the National Academy of Sciences*, 201702746.

Gauthier, L. V., Taub, E., Perkins, C., Ortmann, M., Mark, V. W., & Uswatte, G. (2008). Remodeling the brain plastic structural brain changes produced by different motor therapies after stroke. *Stroke*, *39*(5), 1520-1525.

George, M. S., Wassermann, E. M., Williams, W. A., Callahan, A., Ketter, T. A., Basser, P., . . . Post, R. M. (1995). Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience*.

Georgopoulos, A. P., Ashe, J., Smyrnis, N., & Taira, M. (1992). The motor cortex and the coding of force. *Science*, *256*(5064), 1692-1695.

Georgopoulos, A. P., Kalaska, J. F., Caminiti, R., & Massey, J. T. (1982). On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *Journal of Neuroscience*, *2*(11), 1527-1537.

Geroin, C., Picelli, A., Munari, D., Waldner, A., Tomelleri, C., & Smania, N. (2011). Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: a preliminary comparison. *Clinical rehabilitation*, *25*(6), 537-548.

Gerstner, W. (2011). Hebbian learning and plasticity. *From neuron to cognition via computational neuroscience*, 0-25.
Geschwind, N. (1975). The apraxias: Neural mechanisms of disorders of learned movement: The anatomical organization of the language areas and motor systems of the human brain clarifies apraxic disorders and throws new light on cerebral dominance. *American scientist, 63*(2), 188-195.
Ghilardi, M.-F., Ghez, C., Dhawan, V., Moeller, J., Mentis, M., Nakamura, T., . . . Eidelberg, D. (2000). Patterns of regional brain activation associated with different forms of motor learning. *Brain research, 871*(1), 127-145.
Giacobbe, V., Krebs, H., Volpe, B., Pascual-Leone, A., Rykman, A., Zeiarati, G., . . . Edwards, D. (2013). Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: the dimension of timing. *NeuroRehabilitation, 33*(1), 49-56.
Gillick, B., Rich, T., Nemanich, S., Chen, C.-Y., Menk, J., Mueller, B., . . . Feyma, T. (2018). Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: A randomized, blinded, sham-controlled clinical trial. *European Journal of Paediatric Neurology, 22*(3), 358-368.
Gillick, B. T., Kirton, A., Carmel, J. B., Minhas, P., & Bikson, M. (2014). Pediatric stroke and transcranial direct current stimulation: methods for rational individualized dose optimization. *Frontiers in human neuroscience, 8*, 739.
Gillick, B. T., & Zirpel, L. (2012). Neuroplasticity: an appreciation from synapse to system. *Archives of physical medicine and rehabilitation, 93*(10), 1846-1855.
Goard, M. J., Pho, G. N., Woodson, J., & Sur, M. (2016). Distinct roles of visual, parietal, and frontal motor cortices in memory-guided sensorimotor decisions. *Elife, 5*, e13764.
Gofer-Levi, M., Silberg, T., Brezner, A., & Vakil, E. (2013). Deficit in implicit motor sequence learning among children and adolescents with spastic cerebral palsy. *Research in developmental disabilities, 34*(11), 3672-3678.
Gold, J. I., & Shadlen, M. N. (2007). The neural basis of decision making. *Annual review of neuroscience, 30*.
Goldberg, E. (1994). Cognitive Novelty'. *Neurosciences, 6*, 371-378.
Gomes-Osman, J., & Field-Fote, E. C. (2015). Improvements in hand function in adults with chronic tetraplegia following a multi-day 10Hz rTMS intervention combined with repetitive task practice. *Journal of neurologic physical therapy: JNPT, 39*(1), 23.
Goodale, M. A., & Westwood, D. A. (2004). An evolving view of duplex vision: separate but interacting cortical pathways for perception and action. *Current opinion in neurobiology, 14*(2), 203-211.
Graef, P., Dadalt, M. L. R., da Silva Rodrigués, D. A. M., Stein, C., & de Souza Pagnussat, A. (2016). Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: a systematic review and meta-analysis. *Journal of the neurological sciences, 369*, 149-158.
Grafton, S., Fagg, A., & Arbib, M. (1998). Dorsal premotor cortex and conditional movement selection: A PET functional mapping study. *Journal of Neurophysiology, 79*(2), 1092-1097.
Grafton, S. T., Hazeltine, E., & Ivry, R. B. (2002). Motor sequence learning with the nondominant left hand. *Experimental brain research, 146*(3), 369-378.
Graziano, M. S., Aflalo, T. N., & Cooke, D. F. (2005). Arm movements evoked by electrical stimulation in the motor cortex of monkeys. *Journal of neurophysiology, 94*(6), 4209-4223.
Graziano, M. S., Taylor, C. S., & Moore, T. (2002). Complex movements evoked by microstimulation of precentral cortex. *Neuron, 34*(5), 841-851.
Green, T. D., & Flowers, J. H. (1991). Implicit versus explicit learning processes in a probabilistic, continuous fine-motor catching task. *Journal of motor behavior, 23*(4), 293-300.
Grefkes, C., Eickhoff, S. B., Nowak, D. A., Dafotakis, M., & Fink, G. R. (2008). Dynamic intra-and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage, 41*(4), 1382-1394.
Grefkes, C., & Fink, G. R. (2016). Noninvasive brain stimulation after stroke: it is time for large randomized controlled trials! *Current opinion in neurology, 29*(6), 714-720.
Gremel, C., & Costa, R. (2013). Premotor cortex is critical for goal-directed actions. *Frontiers in computational neuroscience, 7*, 110.
Grèzes, J., Armony, J. L., Rowe, J., & Passingham, R. E. (2003). Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. *Neuroimage, 18*(4), 928-937.
Grisaru, N., Yarovslavsky, U., Abarbanel, J., Lamberg, T., & Belmaker, R. (1994). Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology, 4*(3), 287-288.

Gunduz, A., Rothwell, J., Vidal, J., & Kumru, H. (2017). Non-invasive brain stimulation to promote motor and functional recovery following spinal cord injury. *Neural regeneration research, 12*(12), 1933.
Hakkarainen, E., Pirilä, S., Kaartinen, J., & Meere, J. J. v. d. (2012). Stimulus evaluation, event preparation, and motor action planning in young patients with mild spastic cerebral palsy: an event-related brain potential study. *Journal of child neurology, 27*(4), 465-470.
Hallgató, E., Győri-Dani, D., Pekár, J., Janacsek, K., & Nemeth, D. (2013). The differential consolidation of perceptual and motor learning in skill acquisition. *cortex, 49*(4), 1073-1081.
Halsband, U., & Lange, R. K. (2006). Motor learning in man: a review of functional and clinical studies. *Journal of Physiology-Paris, 99*(4-6), 414-424.
Hameed, M. Q., Dhamne, S. C., Gersner, R., Kaye, H. L., Oberman, L. M., Pascual-Leone, A., & Rotenberg, A. (2017). Transcranial magnetic and direct current stimulation in children. *Current neurology and neuroscience reports, 17*(2), 11.
Hamoudi, M., Schambra, H. M., Fritsch, B., Schoechlin-Marx, A., Weiller, C., Cohen, L. G., & Reis, J. (2018). Transcranial Direct Current Stimulation Enhances Motor Skill Learning but Not Generalization in Chronic Stroke. *Neurorehabilitation and neural repair, 32*(4-5), 295-308.
Han, C., Wang, Q., Meng, P.-p., & Qi, M.-z. (2012). Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. *Clinical rehabilitation*, 0269215512447223.
Hardwick, R. M., Lesage, E., Eickhoff, C. R., Clos, M., Fox, P., & Eickhoff, S. B. (2015). Multimodal connectivity of motor learning-related dorsal premotor cortex. *Neuroimage, 123*, 114-128.
Hardwick, R. M., Rottschy, C., Miall, R. C., & Eickhoff, S. B. (2013). A quantitative meta-analysis and review of motor learning in the human brain. *Neuroimage, 67*, 283-297.
Harris-Love, M. L., Chan, E., Dromerick, A. W., & Cohen, L. G. (2016). Neural substrates of motor recovery in severely impaired stroke patients with hand paralysis. *Neurorehabilitation and neural repair, 30*(4), 328-338.
Harris-Love, M. L., Morton, S. M., Perez, M. A., & Cohen, L. G. (2011). Mechanisms of short-term training-induced reaching improvement in severely hemiparetic stroke patients: a TMS study. *Neurorehabilitation and neural repair, 25*(5), 398-411.
Harris, W. (1908). *Electrical treatment*: Cassell.
Harrison, T. C., Ayling, O. G., & Murphy, T. H. (2012). Distinct cortical circuit mechanisms for complex forelimb movement and motor map topography. *Neuron, 74*(2), 397-409.
Hasan, M. T., Hernández-González, S., Dogbevia, G., Trevino, M., Bertocchi, I., Gruart, A., & Delgado-García, J. M. (2013). Role of motor cortex NMDA receptors in learning-dependent synaptic plasticity of behaving mice. *Nature communications, 4*, 2258.
Hashemirad, F., Zoghi, M., Fitzgerald, P. B., & Jaberzadeh, S. (2016). The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: a systematic review and meta-analysis. *Brain Cogn, 102*, 1-12.
Haslinger, B., Erhard, P., Kämpfe, N., Boecker, H., Rummeny, E., Schwaiger, M., . . . Ceballos-Baumann, A. (2001). Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain, 124*(3), 558-570.
Hebb, D. O. (1949). The organization of behavior: A neurophysiological approach: Wiley.[JH].
Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience, 11*(7), 523.
Hesse, S., Waldner, A., Mehrholz, J., Tomelleri, C., Pohl, M., & Werner, C. (2011). Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized multicenter trial. *Neurorehabilitation and neural repair, 25*(9), 838-846.
Higgins, J., & Deeks, J. J. (2008). Selecting studies and collecting data. *Cochrane handbook for systematic reviews of interventions: Cochrane Book Series*, 151-185.
Higgins, J. P., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions* (Vol. 4): John Wiley & Sons.
Hikosaka, O., Nakahara, H., Rand, M. K., Sakai, K., Lu, X., Nakamura, K., . . . Doya, K. (1999). Parallel neural networks for learning sequential procedures. *Trends in neurosciences, 22*(10), 464-471.
Hikosaka, O., Nakamura, K., Sakai, K., & Nakahara, H. (2002). Central mechanisms of motor skill learning. *Current opinion in neurobiology, 12*(2), 217-222.
Hluštík, P., & Mayer, M. (2006). Paretic hand in stroke: from motor cortical plasticity research to rehabilitation. *Cognitive and behavioral neurology, 19*(1), 34-40.

Hluštík, P., Solodkin, A., Noll, D. C., & Small, S. L. (2004). Cortical plasticity during three-week motor skill learning. *Journal of Clinical Neurophysiology, 21*(3), 180-191.
Hobson, J. A., & Pace-Schott, E. F. (2002). The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. *Nature Reviews Neuroscience, 3*(9), 679.
Höflich, G., Kasper, S., Hufnagel, A., Ruhrmann, S., & Möller, H. J. (1993). Application of transcranial magnetic stimulation in treatment of drug-resistant major depression—a report of two cases. *Human Psychopharmacology: Clinical and Experimental, 8*(5), 361-365.
HolmstrÖm, L., Vollmer, B., Tedroff, K., Islam, M., Persson, J. K., Kits, A., . . . ELIASSON, A. C. (2010). Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. *Developmental Medicine & Child Neurology, 52*(2), 145-152.
Honda, M., Deiber, M.-P., Ibánez, V., Pascual-Leone, A., Zhuang, P., & Hallett, M. (1998). Dynamic cortical involvement in implicit and explicit motor sequence learning. A PET study. *Brain: a journal of neurology, 121*(11), 2159-2173.
Hosp, J. A., & Luft, A. R. (2011). Cortical plasticity during motor learning and recovery after ischemic stroke. *Neural plasticity, 2011*.
Houdayer, E., Degardin, A., Cassim, F., Bocquillon, P., Derambure, P., & Devanne, H. (2008). The effects of low-and high-frequency repetitive TMS on the input/output properties of the human corticospinal pathway. *Experimental brain research, 187*(2), 207-217.
Hsu, T.-Y., Tseng, P., Liang, W.-K., Cheng, S.-K., & Juan, C.-H. (2014). Transcranial direct current stimulation over right posterior parietal cortex changes prestimulus alpha oscillation in visual short-term memory task. *Neuroimage, 98*, 306-313.
Huang, Y., Zhen, Z., Song, Y., Zhu, Q., Wang, S., & Liu, J. (2013). Motor training increases the stability of activation patterns in the primary motor cortex. *PloS one, 8*(1), e53555.
Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature, 430*(6995), 78.
Humm, J. L., Kozlowski, D. A., James, D. C., Gotts, J. E., & Schallert, T. (1998). Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period. *Brain research, 783*(2), 286-292.
Hung, Y.-C., & Gordon, A. M. (2013). Motor learning of a bimanual task in children with unilateral cerebral palsy. *Research in developmental disabilities, 34*(6), 1891-1896.
Iacoboni, M. (2006). Visuo-motor integration and control in the human posterior parietal cortex: evidence from TMS and fMRI. *Neuropsychologia, 44*(13), 2691-2699.
Islam, M., Nordstrand, L., Holmström, L., Kits, A., Forssberg, H., & Eliasson, A. C. (2014). Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? *Developmental Medicine & Child Neurology, 56*(3), 252-258.
Japikse, K. C., Negash, S., Howard, J. H., & Howard, D. V. (2003). Intermanual transfer of procedural learning after extended practice of probabilistic sequences. *Experimental brain research, 148*(1), 38-49.
Jaspers, E., Byblow, W. D., Feys, H., & Wenderoth, N. (2016). The corticospinal tract: a biomarker to categorize upper limb functional potential in unilateral cerebral palsy. *Frontiers in pediatrics, 3*, 112.
Jebsen, R. H., Taylor, N., Trieschmann, R., Trotter, M. J., & Howard, L. A. (1969). An objective and standardized test of hand function. *Archives of physical medicine and rehabilitation, 50*(6), 311-319.
Jefferys, J. (1995). Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiological reviews, 75*(4), 689-723.
Jenkins, I., Brooks, D., Nixon, P., Frackowiak, R., & Passingham, R. (1994). Motor sequence learning: a study with positron emission tomography. *Journal of Neuroscience, 14*(6), 3775-3790.
Jenks, K. M., De Moor, J., & Van Lieshout, E. C. (2009). Arithmetic difficulties in children with cerebral palsy are related to executive function and working memory. *Journal of Child Psychology and Psychiatry, 50*(7), 824-833.
Johansen-Berg, H., Dawes, H., Guy, C., Smith, S. M., Wade, D. T., & Matthews, P. M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain, 125*(12), 2731-2742.
Jones, T. A., Kleim, J. A., & Greenough, W. T. (1996). Synaptogenesis and dendritic growth in the cortex opposite unilateral sensorimotor cortex damage in adult rats: a quantitative electron microscopic examination. *Brain research, 733*(1), 142-148.

Jung, P., & Ziemann, U. (2009). Homeostatic and nonhomeostatic modulation of learning in human motor cortex. *Journal of Neuroscience, 29*(17), 5597-5604.
Kaas, J. H. (2012). Somatosensory system *The Human Nervous System (Third Edition)* (pp. 1074-1109): Elsevier.
Kakei, S., Hoffman, D. S., & Strick, P. L. (1999). Muscle and movement representations in the primary motor cortex. *Science, 285*(5436), 2136-2139.
Kalaska, J. F., Scott, S. H., Cisek, P., & Sergio, L. E. (1997). Cortical control of reaching movements. *Current opinion in neurobiology, 7*(6), 849-859.
Kami, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature, 377*(6545), 155.
Kammer, T., Beck, S., Thielscher, A., Laubis-Herrmann, U., & Topka, H. (2001). Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clinical Neurophysiology, 112*(2), 250-258.
Kang, E. K., & Paik, N.-J. (2011). Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subjects. *Experimental & translational stroke medicine, 3*(1), 4.
Kang, N., Summers, J. J., & Cauraugh, J. H. (2015). Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*, jnnp-2015-311242.
Kang, N., Summers, J. J., & Cauraugh, J. H. (2016). Non-invasive brain stimulation improves paretic limb force production: a systematic review and meta-analysis. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 9*(5), 662-670.
Kantak, S., McGrath, R., Zahedi, N., & Luchmee, D. (2018). Behavioral and neurophysiological mechanisms underlying motor skill learning in patients with post-stroke hemiparesis. *Clinical Neurophysiology, 129*(1), 1-12.
Kantak, S. S., Mummidisetty, C. K., & Stinear, J. W. (2012). Primary motor and premotor cortex in implicit sequence learning–evidence for competition between implicit and explicit human motor memory systems. *European Journal of Neuroscience, 36*(5), 2710-2715.
Kantak, S. S., Stinear, J. W., Buch, E. R., & Cohen, L. G. (2012). Rewiring the brain: potential role of the premotor cortex in motor control, learning, and recovery of function following brain injury. *Neurorehabilitation and neural repair, 26*(3), 282-292.
Karabanov, A., Jin, S.-H., Joutsen, A., Poston, B., Aizen, J., Ellenstein, A., & Hallett, M. (2012). Timing-dependent modulation of the posterior parietal cortex–primary motor cortex pathway by sensorimotor training. *Journal of neurophysiology, 107*(11), 3190-3199.
Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences, 95*(3), 861-868.
Karok, S., & Witney, A. G. (2013). Enhanced motor learning following task-concurrent dual transcranial direct current stimulation. *PloS one, 8*(12), e85693.
Kaski, D., Dominguez, R. O., Allum, J. H., & Bronstein, A. M. (2013). Improving gait and balance in patients with leukoaraiosis using transcranial direct current stimulation and physical training: an exploratory study. *Neurorehabilitation and neural repair, 27*(9), 864-871.
Kawashima, R., Roland, P. E., & O'sullivan, B. (1994). Fields in human motor areas involved in preparation for reaching, actual reaching, and visuomotor learning: a positron emission tomography study. *Journal of Neuroscience, 14*(6), 3462-3474.
Keele, S. W. (1968). Movement control in skilled motor performance. *Psychological bulletin, 70*(6p1), 387.
Keele, S. W., Ivry, R., Mayr, U., Hazeltine, E., & Heuer, H. (2003). The cognitive and neural architecture of sequence representation. *Psychological review, 110*(2), 316.
Keele, S. W., & Summers, J. J. (1976). The structure of motor programs *Motor Control* (pp. 109-142): Elsevier.
Kelso, S. R., Ganong, A. H., & Brown, T. H. (1986). Hebbian synapses in hippocampus. *Proceedings of the National Academy of Sciences, 83*(14), 5326-5330.
Kennedy, P. R., & Bakay, R. A. (1997). Activity of single action potentials in monkey motor cortex during long-term task learning. *Brain research, 760*(1), 251-254.
Kessler, S. K., Minhas, P., Woods, A. J., Rosen, A., Gorman, C., & Bikson, M. (2013). Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. *PloS one, 8*(9), e76112.

Kim, D.-Y., Lim, J.-Y., Kang, E. K., You, D. S., Oh, M.-K., Oh, B.-M., & Paik, N.-J. (2010). Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. *American journal of physical medicine & rehabilitation, 89*(11), 879-886.

Kim, Y.-H., You, S. H., Ko, M.-H., Park, J.-W., Lee, K. H., Jang, S. H., . . . Hallett, M. (2006). Repetitive transcranial magnetic stimulation–induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke, 37*(6), 1471-1476.

Kinsbourne, M. (1974). Mechanisms of hemispheric interaction in man.

Kirton, A. (2013). Modeling developmental plasticity after perinatal stroke: defining central therapeutic targets in cerebral palsy. *Pediatric neurology, 48*(2), 81-94.

Kleim, J. A., Barbay, S., Cooper, N. R., Hogg, T. M., Reidel, C. N., Remple, M. S., & Nudo, R. J. (2002). Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiology of learning and memory, 77*(1), 63-77.

Kleim, J. A., Barbay, S., & Nudo, R. J. (1998). Functional reorganization of the rat motor cortex following motor skill learning. *Journal of neurophysiology, 80*(6), 3321-3325.

Kleim, J. A., Hogg, T. M., VandenBerg, P. M., Cooper, N. R., Bruneau, R., & Remple, M. (2004). Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *Journal of Neuroscience, 24*(3), 628-633.

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of speech, language, and hearing research, 51*(1), S225-S239.

Kleim, J. A., Swain, R. A., Armstrong, K. A., Napper, R. M., Jones, T. A., & Greenough, W. T. (1998). Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning. *Neurobiology of learning and memory, 69*(3), 274-289.

Klingels, K., Feys, H., De Wit, L., Jaspers, E., Van de Winckel, A., Verbeke, G., . . . Molenaers, G. (2012). Arm and hand function in children with unilateral cerebral palsy: a one-year follow-up study. *European journal of paediatric neurology, 16*(3), 257-265.

Klomjai, W., Lackmy-Vallee, A., Roche, N., Pradat-Diehl, P., Marchand-Pauvert, V., & Katz, R. (2015). Repetitive transcranial magnetic stimulation and transcranial direct current stimulation in motor rehabilitation after stroke: an update. *Annals of physical and rehabilitation medicine, 58*(4), 220-224.

Kobayashi, M., & Pascual-Leone, A. (2003). Transcranial magnetic stimulation in neurology. *The Lancet Neurology, 2*(3), 145-156.

Koch, G., & Rothwell, J. C. (2009). TMS investigations into the task-dependent functional interplay between human posterior parietal and motor cortex. *Behavioural brain research, 202*(2), 147-152.

Kojovic, M., Kassavetis, P., Bologna, M., Pareés, I., Rubio-Agusti, I., Beraredelli, A., . . . Bhatia, K. P. (2015). Transcranial magnetic stimulation follow-up study in early Parkinson's disease: A decline in compensation with disease progression? *Movement Disorders, 30*(8), 1098-1106.

Kolb, B., & Teskey, G. C. (2012). Age, experience, injury, and the changing brain. *Developmental psychobiology, 54*(3), 311-325.

Kolbinger, H. M., Höflich, G., Hufnagel, A., Müller, H. J., & Kasper, S. (1995). Transcranial magnetic stimulation (TMS) in the treatment of major depression—a pilot study. *Human Psychopharmacology: Clinical and Experimental, 10*(4), 305-310.

KOMAN, A. (2004). PATERSON SMITH B, SHLIT JS. *The Lancet, 363*.

Kozlowski, D. A., James, D. C., & Schallert, T. (1996). Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. *The Journal of Neuroscience, 16*(15), 4776-4786.

Krägeloh-Mann, I., & Horber, V. (2007). The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Developmental Medicine & Child Neurology, 49*(2), 144-151.

Krakauer, J. W. (2006). Motor learning: its relevance to stroke recovery and neurorehabilitation. *Current opinion in neurology, 19*(1), 84-90.

Krakauer, J. W., & Mazzoni, P. (2011). Human sensorimotor learning: adaptation, skill, and beyond. *Current opinion in neurobiology, 21*(4), 636-644.

Krakauer, J. W., & Shadmehr, R. (2006). Consolidation of motor memory. *Trends in neurosciences, 29*(1), 58-64.

Krishnan, C., Santos, L., Peterson, M. D., & Ehinger, M. (2015). Safety of noninvasive brain stimulation in children and adolescents. *Brain stimulation, 8*(1), 76-87.

Kroeger, J., Bäumer, T., Jonas, M., Rothwell, J. C., Siebner, H. R., & Münchau, A. (2010). Charting the excitability of premotor to motor connections while withholding or initiating a selected movement. *European Journal of Neuroscience, 32*(10), 1771-1779.

Kubis, N. (2016). Non-invasive brain stimulation to enhance post-stroke recovery. *Frontiers in neural circuits, 10*, 56.

Kugler, P. N., & Turvey, M. T. (2015). *Information, natural law, and the self-assembly of rhythmic movement*: Routledge.

Kułak, W., & Sobaniec, W. (2004). Molecular mechanisms of brain plasticity: neurophysiologic and neuroimaging studies in the developing patients. *Rocz Akad Med Bialymst, 49*, 227-236.

Kumru, H., Murillo, N., Benito-Penalva, J., Tormos, J. M., & Vidal, J. (2016). Transcranial direct current stimulation is not effective in the motor strength and gait recovery following motor incomplete spinal cord injury during Lokomat® gait training. *Neuroscience letters, 620*, 143-147.

Kuppuswamy, A., Balasubramaniam, A., Maksimovic, R., Mathias, C., Gall, A., Craggs, M., & Ellaway, P. (2011). Action of 5 Hz repetitive transcranial magnetic stimulation on sensory, motor and autonomic function in human spinal cord injury. *Clinical Neurophysiology, 122*(12), 2452-2461.

Kurata, K. (1993). Premotor cortex of monkeys: set-and movement-related activity reflecting amplitude and direction of wrist movements. *Journal of neurophysiology, 69*(1), 187-200.

Kwakkel, G., van Peppen, R., Wagenaar, R. C., Wood Dauphinee, S., Richards, C., Ashburn, A., . . . Wellwood, I. (2004). Effects of augmented exercise therapy time after stroke: a meta-analysis. *stroke, 35*(11), 2529-2539.

Kwakkel, G., Wagenaar, R. C., Koelman, T. W., Lankhorst, G. J., & Koetsier, J. C. (1997). Effects of intensity of rehabilitation after stroke a research synthesis. *Stroke, 28*(8), 1550-1556.

Lacquaniti, F., Guigon, E., Bianchi, L., Ferraina, S., & Caminiti, R. (1995). Representing spatial information for limb movement: role of area 5 in the monkey. *Cerebral cortex, 5*(5), 391-409.

Langhorne, P., Bernhardt, J., & Kwakkel, G. (2011). Stroke rehabilitation. *The Lancet, 377*(9778), 1693-1702.

Langhorne, P., Coupar, F., & Pollock, A. (2009). Motor recovery after stroke: a systematic review. *The Lancet Neurology, 8*(8), 741-754.

Langhorne, P., Wagenaar, R., & Partridge, C. (1996). Physiotherapy after stroke: more is better? *Physiotherapy Research International, 1*(2), 75-88.

Lee, D. (2004). Behavioral context and coherent oscillations in the supplementary motor area. *Journal of Neuroscience, 24*(18), 4453-4459.

Lee, J.-H., & van Donkelaar, P. (2006). The human dorsal premotor cortex generates on-line error corrections during sensorimotor adaptation. *Journal of Neuroscience, 26*(12), 3330-3334.

Lee, S. J., & Chun, M. H. (2014). Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Archives of physical medicine and rehabilitation, 95*(3), 431-438.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., . . . De Ridder, D. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology, 125*(11), 2150-2206.

Lefaucheur, J.-P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., . . . Langguth, B. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology, 128*(1), 56-92.

Lefebvre, S., Dricot, L., Laloux, P., Desfontaines, P., Evrard, F., Peeters, A., . . . Vandermeeren, Y. (2017). Increased functional connectivity one week after motor learning and tDCS in stroke patients. *Neuroscience, 340*, 424-435.

Lefebvre, S., Dricot, L., Laloux, P., Gradkowski, W., Desfontaines, P., Evrard, F., . . . Vandermeeren, Y. (2014). Neural substrates underlying stimulation-enhanced motor skill learning after stroke. *Brain, 138*(1), 149-163.

Lefebvre, S., Laloux, P., Peeters, A., Desfontaines, P., Jamart, J., & Vandermeeren, Y. (2013). Dual-tDCS enhances online motor skill learning and long-term retention in chronic stroke patients. *Frontiers in human neuroscience, 6*, 343.

Lefebvre, S., & Liew, S.-L. (2017). Anatomical parameters of tDCS to modulate the motor system after stroke: a review. *Frontiers in neurology, 8*, 29.

Lefebvre, S., Thonnard, J.-L., Laloux, P., Peeters, A., Jamart, J., & Vandermeeren, Y. (2014). Single session of dual-tDCS transiently improves precision grip and dexterity of the paretic hand after stroke. *Neurorehabilitation and neural repair, 28*(2), 100-110.

Lewis, G. N., & Byblow, W. D. (2004). The effects of repetitive proprioceptive stimulation on corticomotor representation in intact and hemiplegic individuals. *Clinical neurophysiology, 115*(4), 765-773.

Lewis, P. A., Wing, A., Pope, P., Praamstra, P., & Miall, R. (2004). Brain activity correlates differentially with increasing temporal complexity of rhythms during initialisation, synchronisation, and continuation phases of paced finger tapping. *Neuropsychologia, 42*(10), 1301-1312.

Lewis, P. M., Thomson, R. H., Rosenfeld, J. V., & Fitzgerald, P. B. (2016). Brain neuromodulation techniques: a review. *The Neuroscientist, 22*(4), 406-421.

Licata, A. M., Kaufman, M. T., Raposo, D., Ryan, M. B., Sheppard, J. P., & Churchland, A. K. (2017). Posterior parietal cortex guides visual decisions in rats. *Journal of Neuroscience*, 0105-0117.

Lichtman, J. W., & Colman, H. (2000). Synapse elimination and indelible memory. *Neuron, 25*(2), 269-278.

Liepert, J., Bauder, H., Miltner, W. H., Taub, E., & Weiller, C. (2000). Treatment-induced cortical reorganization after stroke in humans. *Stroke, 31*(6), 1210-1216.

Liepert, J., Graef, S., Uhde, I., Leidner, O., & Weiller, C. (2000). Training-induced changes of motor cortex representations in stroke patients. *Acta neurologica scandinavica, 101*(5), 321-326.

Lin, Y.-N., Hu, C.-J., Chi, J.-y., Lin, L.-F., Yen, T.-H., Lin, Y.-K., & Liou, T.-H. (2015). Effects of repetitive transcranial magnetic stimulation of the unaffected hemisphere leg motor area in patients with subacute stroke and substantial leg impairment: a pilot study. *Journal of rehabilitation medicine, 47*(4), 305-310.

Lindenberg, R., Renga, V., Zhu, L., Nair, D., & Schlaug, G. (2010). Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology, 75*(24), 2176-2184.

Logan, G. D. (1988). Toward an instance theory of automatization. *Psychological review, 95*(4), 492.

Lohse, K. R., Lang, C. E., & Boyd, L. A. (2014). Is more better? Using meta-data to explore dose-response relationships in stroke rehabilitation. *Stroke; a journal of cerebral circulation, 45*(7), 2053.

Lolas, F. (1977). Brain polarization: behavioral and therapeutic effects. *Biological Psychiatry, 12*(1), 37-47.

López-Alonso, V., Fernández-del-Olmo, M., Costantini, A., Gonzalez-Henriquez, J. J., & Cheeran, B. (2015). Intra-individual variability in the response to anodal transcranial direct current stimulation. *Clinical Neurophysiology, 126*(12), 2342-2347.

Lotze, M., Beutling, W., Loibl, M., Domin, M., Platz, T., Schminke, U., & Byblow, W. D. (2012). Contralesional motor cortex activation depends on ipsilesional corticospinal tract integrity in well-recovered subcortical stroke patients. *Neurorehabilitation and neural repair, 26*(6), 594-603.

Lotze, M., Markert, J., Sauseng, P., Hoppe, J., Plewnia, C., & Gerloff, C. (2006). The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. *Journal of Neuroscience, 26*(22), 6096-6102.

Lu, X., & Ashe, J. (2015). Dynamic reorganization of neural activity in motor cortex during new sequence production. *European Journal of Neuroscience, 42*(5), 2172-2178.

Lüdemann-Podubecká, J., Bösl, K., Rothhardt, S., Verheyden, G., & Nowak, D. A. (2014). Transcranial direct current stimulation for motor recovery of upper limb function after stroke. *Neuroscience & biobehavioral reviews, 47*, 245-259.

Lüdemann-Podubecká, J., Bösl, K., Theilig, S., Wiederer, R., & Nowak, D. A. (2015). The effectiveness of 1Hz rTMS over the primary motor area of the unaffected hemisphere to improve hand function after stroke depends on hemispheric dominance. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8*(4), 823-830.

Luft, A. R., & Schwarz, S. (2009). Dopaminergic signals in primary motor cortex. *International Journal of Developmental Neuroscience, 27*(5), 415-421.

Mackenzie, T. N., Bailey, A. Z., Mi, P. Y., Tsang, P., Jones, C. B., & Nelson, A. J. (2016). Human area 5 modulates corticospinal output during movement preparation. *NeuroReport, 27*(14), 1056-1060.

Mackey, A., Stinear, C., Stott, S., & Byblow, W. D. (2014). Upper limb function and cortical organization in youth with unilateral cerebral palsy. *Frontiers in neurology, 5*, 117.

Madhavan, S., Weber, K. A., & Stinear, J. W. (2011). Non-invasive brain stimulation enhances fine motor control of the hemiparetic ankle: implications for rehabilitation. *Experimental brain research, 209*(1), 9-17.

Malcolm, M. P., Triggs, W. J., Light, K. E., Rothi, L. J. G., Wu, S., Reid, K., & Nadeau, S. E. (2007). Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an

exploratory randomized controlled trial. *American journal of physical medicine & rehabilitation/Association of Academic Physiatrists, 86*(9), 707.
Maldonado, M. A., Allred, R. P., Felthauser, E. L., & Jones, T. A. (2008). Motor skill training, but not voluntary exercise, improves skilled reaching after unilateral ischemic lesions of the sensorimotor cortex in rats. *Neurorehabilitation and neural repair, 22*(3), 250-261.
Malenka, R. C., & Bear, M. F. (2004). LTP and LTD: an embarrassment of riches. *Neuron, 44*(1), 5-21.
Manenti, R., Brambilla, M., Benussi, A., Rosini, S., Cobelli, C., Ferrari, C., . . . Borroni, B. (2016). Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. *Movement Disorders, 31*(5), 715-724.
Manganotti, P., Patuzzo, S., Cortese, F., Palermo, A., Smania, N., & Fiaschi, A. (2002). Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. *Clinical Neurophysiology, 113*(6), 936-943.
Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., . . . Meulemans, T. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nature neuroscience, 3*(8), 831.
Marinelli, L., Quartarone, A., Hallett, M., Frazzitta, G., & Ghilardi, M. F. (2017). The many facets of motor learning and their relevance for Parkinson's disease. *Clinical Neurophysiology, 128*(7), 1127-1141.
Marneweck, M., Kuo, H.-C., Smorenburg, A. R., Ferre, C. L., Flamand, V. H., Gupta, D., . . . Friel, K. M. (2018). The Relationship Between Hand Function and Overlapping Motor Representations of the Hands in the Contralesional Hemisphere in Unilateral Spastic Cerebral Palsy. *Neurorehabilitation and neural repair, 32*(1), 62-72.
Marshall, R. S., Perera, G. M., Lazar, R. M., Krakauer, J. W., Constantine, R. C., & DeLaPaz, R. L. (2000). Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke, 31*(3), 656-661.
Martin, D. M., Liu, R., Alonzo, A., Green, M., & Loo, C. K. (2014). Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Experimental brain research, 232*(10), 3345-3351.
Masters, R. S. (1992). Knowledge, knerves and know-how: The role of explicit versus implicit knowledge in the breakdown of a complex motor skill under pressure. *British journal of psychology, 83*(3), 343-358.
Mathiowetz, V., & Haugen, J. B. (1994). Motor behavior research: implications for therapeutic approaches to central nervous system dysfunction. *American Journal of Occupational Therapy, 48*(8), 733-745.
Matyas, F., Sreenivasan, V., Marbach, F., Wacongne, C., Barsy, B., Mateo, C., . . . Petersen, C. C. (2010). Motor control by sensory cortex. *Science, 330*(6008), 1240-1243.
McCreery, D. B., Agnew, W. F., Yuen, T. G., & Bullara, L. (1990). Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *IEEE Transactions on Biomedical Engineering, 37*(10), 996-1001.
McGaugh, J. L. (2000). Memory--a century of consolidation. *Science, 287*(5451), 248-251.
Milner, D., & Goodale, M. (2006). *The visual brain in action*: Oxford University Press.
Minhas, P., Bikson, M., Woods, A. J., Rosen, A. R., & Kessler, S. K. (2012). *Transcranial direct current stimulation in pediatric brain: a computational modeling study.* Paper presented at the Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE.
Mochizuki, H., Franca, M., Huang, Y.-Z., & Rothwell, J. C. (2005). The role of dorsal premotor area in reaction task: comparing the "virtual lesion" effect of paired pulse or theta burst transcranial magnetic stimulation. *Experimental Brain Research, 167*(3), 414-421.
Mohan, H., de Haan, R., Mansvelder, H. D., & de Kock, C. P. (2017). The posterior parietal cortex as integrative hub for whisker sensorimotor information. *Neuroscience*.
Moisello, C., Blanco, D., Fontanesi, C., Lin, J., Biagioni, M., Kumar, P., . . . Abbruzzese, G. (2015). TMS enhances retention of a motor skill in Parkinson's disease. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8*(2), 224-230.
Moliadze, V., Atalay, D., Antal, A., & Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain stimulation, 5*(4), 505-511.
Moliadze, V., Schmanke, T., Andreas, S., Lyzhko, E., Freitag, C. M., & Siniatchkin, M. (2015). Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. *Clinical Neurophysiology, 126*(7), 1392-1399.

Molina-Luna, K., Pekanovic, A., Röhrich, S., Hertler, B., Schubring-Giese, M., Rioult-Pedotti, M.-S., & Luft, A. R. (2009). Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. *PloS one, 4*(9), e7082.

Monfils, M.-H., Plautz, E. J., & Kleim, J. A. (2005). In search of the motor engram: motor map plasticity as a mechanism for encoding motor experience. *The Neuroscientist, 11*(5), 471-483.

Monte-Silva, K., Kuo, M.-F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation, 6*(3), 424-432.

Mortensen, J., Figlewski, K., & Andersen, H. (2016). Combined transcranial direct current stimulation and home-based occupational therapy for upper limb motor impairment following intracerebral hemorrhage: a double-blind randomized controlled trial. *Disability and rehabilitation, 38*(7), 637-643.

Moura, R. C. F., Santos, C., Collange Grecco, L., Albertini, G., Cimolin, V., Galli, M., & Oliveira, C. (2017). Effects of a single session of transcranial direct current stimulation on upper limb movements in children with cerebral palsy: A randomized, sham-controlled study. *Developmental neurorehabilitation, 20*(6), 368-375.

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., . . . Hallett, M. (2002). Early consolidation in human primary motor cortex. *Nature, 415*(6872), 640.

Mueller, J. K., Grigsby, E. M., Prevosto, V., Petraglia III, F. W., Rao, H., Deng, Z.-D., . . . Platt, M. L. (2014). Simultaneous transcranial magnetic stimulation and single-neuron recording in alert non-human primates. *Nature neuroscience, 17*(8), 1130.

Mulkey, R. M., Herron, C. E., & Malenka, R. C. (1993). An essential role for protein phosphatases in hippocampal long-term depression. *Science, 261*(5124), 1051-1055.

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: from synapse to behaviour. *Nature Reviews Neuroscience, 10*(12), 861.

Nair, D. G., Renga, V., Lindenberg, R., Zhu, L., & Schlaug, G. (2011). Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tDCS. *Restorative neurology and neuroscience, 29*(6), 411-420.

Nelles, G. (2004). Cortical reorganization-effects of intensive therapy. *Restorative neurology and neuroscience, 22*(3), 239-244.

Nemeth, D., & Janacsek, K. (2010). The dynamics of implicit skill consolidation in young and elderly adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 66*(1), 15-22.

Newell, A., & Rosenbloom, P. S. (1981). Mechanisms of skill acquisition and the law of practice. *Cognitive skills and their acquisition, 1*(1981), 1-55.

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive psychology, 19*(1), 1-32.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., . . . Fregni, F. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain stimulation, 1*(3), 206-223.

Nitsche, M. A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of neurophysiology, 97*(4), 3109-3117.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology, 527*(3), 633-639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation–update 2011. *Restorative neurology and neuroscience, 29*(6), 463-492.

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *Journal of cognitive neuroscience, 15*(4), 619-626.

Nowak, D. A., Berner, J., Herrnberger, B., Kammer, T., Grön, G., & Schönfeldt-Lecuona, C. (2009). Continuous theta-burst stimulation over the dorsal premotor cortex interferes with associative learning during object lifting. *cortex, 45*(4), 473-482.

Nowak, D. A., Grefkes, C., Ameli, M., & Fink, G. R. (2009). Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabilitation and neural repair, 23*(7), 641-656.

Nudo, R. (2003). Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. *Journal of Rehabilitation Medicine-Supplements, 41*, 7-10.
Nudo, R. J. (2006). Plasticity. *NeuroRx, 3*(4), 420-427.
Nudo, R. J., & Milliken, G. W. (1996). Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *Journal of neurophysiology, 75*(5), 2144-2149.
Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.
Oliveira, F. T., Diedrichsen, J., Verstynen, T., Duque, J., & Ivry, R. B. (2010). Transcranial magnetic stimulation of posterior parietal cortex affects decisions of hand choice. *Proceedings of the National Academy of Sciences, 107*(41), 17751-17756.
Page, S. J. (2003). Intensity versus task-specificity after stroke: how important is intensity? *American Journal of Physical Medicine & Rehabilitation, 82*(9), 730-732.
Page, S. J., Szaflarski, J. P., Eliassen, J. C., Pan, H., & Cramer, S. C. (2009). Cortical plasticity following motor skill learning during mental practice in stroke. *Neurorehabilitation and neural repair*.
Palm, U., Segmiller, F. M., Epple, A. N., Freisleder, F.-J., Koutsouleris, N., Schulte-Körne, G., & Padberg, F. (2016). Transcranial direct current stimulation in children and adolescents: a comprehensive review. *Journal of neural transmission, 123*(10), 1219-1234.
Pan, S. C., & Rickard, T. C. (2015). Sleep and motor learning: is there room for consolidation? *Psychological bulletin, 141*(4), 812.
Pang, Z. P., Cao, P., Xu, W., & Südhof, T. C. (2010). Calmodulin controls synaptic strength via presynaptic activation of calmodulin kinase II. *Journal of Neuroscience, 30*(11), 4132-4142.
Parazzini, M., Fiocchi, S., Liorni, I., Priori, A., & Ravazzani, P. (2014). Computational modeling of transcranial direct current stimulation in the child brain: implications for the treatment of refractory childhood focal epilepsy. *International journal of neural systems, 24*(02), 1430006.
Parazzini, M., Fiocchi, S., Liorni, I., & Ravazzani, P. (2015). Effect of the interindividual variability on computational modeling of transcranial direct current stimulation. *Computational intelligence and neuroscience, 2015*, 73.
Pardo-Vazquez, J. L., Leboran, V., & Acuna, C. (2008). Neural correlates of decisions and their outcomes in the ventral premotor cortex. *Journal of Neuroscience, 28*(47), 12396-12408.
Park, S. D., Kim, J. Y., & Song, H. S. (2015). Effect of application of transcranial direct current stimulation during task-related training on gait ability of patients with stroke. *Journal of physical therapy science, 27*(3), 623-625.
Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human brain cortex. *Annu. Rev. Neurosci., 28*, 377-401.
Pascual-Leone, A., Grafman, J., & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science, 263*(5151), 1287-1289.
Pascual-Leone, A., Nguyet, D., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., & Hallett, M. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *Journal of neurophysiology, 74*(3), 1037-1045.
Pascual-Leone, A., Peris, M., Tormos, J., Pascual, A. P.-L., & Catala, M. (1996). Reorganization of human cortical motor output maps following traumatic forearm amputation. *Neuroreport, 7*(13), 2068-2070.
Pascual-Leone, A., Rubio, B., Pallardó, F., & Catalá, M. D. (1996). Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet, 348*(9022), 233-237.
Peeters, M., Verhoeven, L., & de Moor, J. (2009). Predictors of verbal working memory in children with cerebral palsy. *Research in developmental disabilities, 30*(6), 1502-1511.
Peigneux, P., Laureys, S., Fuchs, S., Destrebecqz, A., Collette, F., Delbeuck, X., . . . Degueldre, C. (2003). Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *Neuroimage, 20*(1), 125-134.
Pekna, M., Pekny, M., & Nilsson, M. (2012). Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke, 43*(10), 2819-2828.
Perez, M., Tanaka, S., Wise, S., Sadato, N., Tanabe, H., Willingham, D., & Cohen, L. (2007). Neural substrates of intermanual transfer of a newly acquired motor skill. *Current Biology, 17*(21), 1896-1902.

Perez, M. A., Lungholt, B. K., Nyborg, K., & Nielsen, J. B. (2004). Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. *Experimental brain research, 159*(2), 197-205.

Perez, M. A., Tanaka, S., Wise, S. P., Willingham, D. T., & Cohen, L. G. (2008). Time-specific contribution of the supplementary motor area to intermanual transfer of procedural knowledge. *Journal of Neuroscience, 28*(39), 9664-9669.

Pesaran, B., Nelson, M. J., & Andersen, R. A. (2006). Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. *Neuron, 51*(1), 125-134.

Peterchev, A. V., Goetz, S. M., Westin, G. G., Luber, B., & Lisanby, S. H. (2013). Pulse width dependence of motor threshold and input–output curve characterized with controllable pulse parameter transcranial magnetic stimulation. *Clinical Neurophysiology, 124*(7), 1364-1372.

Peters, M. A., Thompson, B., Merabet, L. B., Wu, A. D., & Shams, L. (2013). Anodal tDCS to V1 blocks visual perceptual learning consolidation. *Neuropsychologia, 51*(7), 1234-1239.

Petersen, S., Corbetta, M., Miezin, F., & Shulman, G. (1994). PET studies of parietal involvement in spatial attention: comparison of different task types. *Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale, 48*(2), 319.

Piccolino, M. (2000). The bicentennial of the Voltaic battery (1800–2000): the artificial electric organ. *Trends in neurosciences, 23*(4), 147-151.

Plautz, E. J., Barbay, S., Frost, S. B., Friel, K. M., Dancause, N., Zoubina, E. V., . . . Nudo, R. J. (2003). Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurological research, 25*(8), 801-810.

Plautz, E. J., Milliken, G. W., & Nudo, R. J. (2000). Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiology of learning and memory, 74*(1), 27-55.

Plow, E. B., Cunningham, D. A., Varnerin, N., & Machado, A. (2015). Rethinking stimulation of the brain in stroke rehabilitation: why higher motor areas might be better alternatives for patients with greater impairments. *The Neuroscientist, 21*(3), 225-240.

Poldrack, R. A., Clark, J., Pare-Blagoev, E., Shohamy, D., Moyano, J. C., Myers, C., & Gluck, M. A. (2001). Interactive memory systems in the human brain. *Nature, 414*(6863), 546.

Poldrack, R. A., & Gabrieli, J. D. (2001). Characterizing the neural mechanisms of skill learning and repetition priming: evidence from mirror reading. *Brain, 124*(1), 67-82.

Poldrack, R. A., & Packard, M. G. (2003). Competition among multiple memory systems: converging evidence from animal and human brain studies. *Neuropsychologia, 41*(3), 245-251.

Pomeroy, V. M., Cloud, G., Tallis, R. C., Donaldson, C., Nayak, V., & Miller, S. (2007). Transcranial magnetic stimulation and muscle contraction to enhance stroke recovery: a randomized proof-of-principle and feasibility investigation. *Neurorehabilitation and neural repair, 21*(6), 509-517.

Porter, R., & Lemon, R. (1993). *Corticospinal function and voluntary movement*: Oxford University Press, USA.

Press, D. Z., Casement, M. D., Pascual-Leone, A., & Robertson, E. M. (2005). The time course of off-line motor sequence learning. *Cognitive Brain Research, 25*(1), 375-378.

Priestley, J. (1769). *The history and present state of electricity, with original experiments*: J. Dodsley... J. Johnson and J. Payne... and T. Cadell.

Priori, A., Berardelli, A., Rona, S., Accornero, N., & Manfredi, M. (1998). Polarization of the human motor cortex through the scalp. *Neuroreport, 9*(10), 2257-2260.

Purpura, D. P., & McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *Journal of neurophysiology, 28*(1), 166-185.

Quartarone, A., Rizzo, V., Terranova, C., Bruschetta, D., Milardi, D., Girlanda, P., & Ghilardi, M. F. (2014). Cortical plasticity in patients with Parkinson's disease a window for therapeutic non-invasive neuromodulation. *Archives italiennes de biologie, 152*(4), 239-246.

Raithatha, R., Carrico, C., Powell, E. S., Westgate, P. M., Chelette, I., Kenneth, C., . . . Sawaki, L. (2016). Non-invasive brain stimulation and robot-assisted gait training after incomplete spinal cord injury: a randomized pilot study. *NeuroRehabilitation, 38*(1), 15-25.

Ramanathan, D., Conner, J. M., & Tuszynski, M. H. (2006). A form of motor cortical plasticity that correlates with recovery of function after brain injury. *Proceedings of the National Academy of Sciences, 103*(30), 11370-11375.

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological reviews, 93*(2), 681-766.

Reber, A. S. (1976). Implicit learning of synthetic languages: The role of instructional set. *Journal of Experimental Psychology: Human Learning and Memory, 2*(1), 88.
Reber, P. J., & Squire, L. R. (1998). Encapsulation of implicit and explicit memory in sequence learning. *Journal of cognitive neuroscience, 10*(2), 248-263.
Reedman, S. E., Beagley, S., Sakzewski, L., & Boyd, R. N. (2016). The jebsen taylor test of hand function: a pilot test–retest reliability study in typically developing children. *Physical & occupational therapy in pediatrics, 36*(3), 292-304.
Rehme, A. K., Fink, G. R., von Cramon, D. Y., & Grefkes, C. (2010). The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal FMRI. *Cerebral cortex, 21*(4), 756-768.
Reichenbach, A., Bresciani, J.-P., Peer, A., Bülthoff, H. H., & Thielscher, A. (2010). Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. *Cerebral Cortex, 21*(7), 1602-1612.
Reis, J., Fischer, J. T., Prichard, G., Weiller, C., Cohen, L. G., & Fritsch, B. (2013). Time-but not sleep-dependent consolidation of tDCS-enhanced visuomotor skills. *Cerebral cortex, 25*(1), 109-117.
Reis, J., & Fritsch, B. (2011). Modulation of motor performance and motor learning by transcranial direct current stimulation. *Current opinion in neurology, 24*(6), 590-596.
Reis, J., Robertson, E., Krakauer, J. W., Rothwell, J., Marshall, L., Gerloff, C., . . . Celnik, P. A. (2008). Consensus:"Can tDCS and TMS enhance motor learning and memory formation?". *Brain stimulation, 1*(4), 363.
Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., . . . Krakauer, J. W. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences, 106*(5), 1590-1595.
Reis, J., Swayne, O. B., Vandermeeren, Y., Camus, M., Dimyan, M. A., Harris-Love, M., . . . Cohen, L. G. (2008). Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *The Journal of physiology, 586*(2), 325-351.
Rich, T. L., Menk, J. S., Rudser, K. D., Feyma, T., & Gillick, B. T. (2017). Less-Affected Hand Function in Children With Hemiparetic Unilateral Cerebral Palsy: A Comparison Study With Typically Developing Peers. *Neurorehabilitation and neural repair, 31*(10-11), 965-976.
Richards, L., Hanson, C., Wellborn, M., & Sethi, A. (2008). Driving motor recovery after stroke. *Topics in stroke rehabilitation, 15*(5), 397-411.
Richards, L. G., Stewart, K. C., Woodbury, M. L., Senesac, C., & Cauraugh, J. H. (2008). Movement-dependent stroke recovery: a systematic review and meta-analysis of TMS and fMRI evidence. *Neuropsychologia, 46*(1), 3-11.
Rioult-Pedotti, M.-S., Donoghue, J. P., & Dunaevsky, A. (2007). Plasticity of the synaptic modification range. *Journal of neurophysiology, 98*(6), 3688-3695.
Rioult-Pedotti, M.-S., Friedman, D., & Donoghue, J. P. (2000). Learning-induced LTP in neocortex. *Science, 290*(5491), 533-536.
Riva, D., Franceschetti, S., Erbetta, A., Baranello, G., Esposito, S., & Bulgheroni, S. (2013). Congenital brain damage: cognitive development correlates with lesion and electroencephalographic features. *Journal of child neurology, 28*(4), 446-454.
Rivera-Urbina, G. N., Nitsche, M. A., Vicario, C. M., & Molero-Chamizo, A. (2017). Applications of transcranial direct current stimulation in children and pediatrics. *Reviews in the Neurosciences, 28*(2), 173-184.
Rizzo, V., Siebner, H. R., Modugno, N., Pesenti, A., Münchau, A., Gerschlager, W., . . . Rothwell, J. C. (2004). Shaping the excitability of human motor cortex with premotor rTMS. *The Journal of physiology, 554*(2), 483-495.
Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu. Rev. Neurosci., 27*, 169-192.
Robertson, E. M. (2004). Skill learning: putting procedural consolidation in context. *Current Biology, 14*(24), R1061-R1063.
Robertson, E. M. (2009). From creation to consolidation: a novel framework for memory processing. *PLoS biology, 7*(1), e1000019.
Robertson, E. M., & Cohen, D. A. (2006). Understanding consolidation through the architecture of memories. *The Neuroscientist, 12*(3), 261-271.
Robertson, E. M., Pascual-Leone, A., & Miall, R. C. (2004). Current concepts in procedural consolidation. *Nature Reviews Neuroscience, 5*(7), 576.

Robertson, E. M., Press, D. Z., & Pascual-Leone, A. (2005). Off-line learning and the primary motor cortex. *Journal of Neuroscience, 25*(27), 6372-6378.
Rocha, S., Silva, E., Foerster, Á., Wiesiolek, C., Chagas, A. P., Machado, G., . . . Monte-Silva, K. (2016). The impact of transcranial direct current stimulation (tDCS) combined with modified constraint-induced movement therapy (mCIMT) on upper limb function in chronic stroke: a double-blind randomized controlled trial. *Disability and rehabilitation, 38*(7), 653-660.
Rockwell, A. D. (1896). *The Medical and Surgical Uses of Electricity*: W. Wood.
Rose, J., & McGill, K. C. (1998). The motor unit in cerebral palsy. *Developmental Medicine & Child Neurology, 40*(4), 270-277.
Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Group, S. o. T. C. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology, 120*(12), 2008-2039.
Rossini, P. M., Burke, D., Chen, R., Cohen, L., Daskalakis, Z., Di Iorio, R., . . . George, M. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an IFCN Committee. *Clinical Neurophysiology, 126*(6), 1071-1107.
Roth, B. J. (1994). Mechanisms for electrical stimulation of excitable tissue. *Critical reviews in biomedical engineering, 22*(3-4), 253-305.
Roth, D. A.-E., Kishon-Rabin, L., Hildesheimer, M., & Karni, A. (2005). A latent consolidation phase in auditory identification learning: Time in the awake state is sufficient. *Learning & Memory, 12*(2), 159-164.
Rothwell, J., Traub, M., Day, B., Obeso, J., Thomas, P., & Marsden, C. (1982). Manual motor performance in a deafferented man. *Brain, 105*(3), 515-542.
Rroji, O., van Kuyck, K., Nuttin, B., & Wenderoth, N. (2015). Anodal tDCS over the primary motor cortex facilitates long-term memory formation reflecting use-dependent plasticity. *PloS one, 10*(5), e0127270.
Rumpf, J.-J., Wegscheider, M., Hinselmann, K., Fricke, C., King, B. R., Weise, D., . . . Karni, A. (2017). Enhancement of motor consolidation by post-training transcranial direct current stimulation in older people. *Neurobiology of aging, 49*, 1-8.
Ruohonen, J., & Karhu, J. (2012). tDCS possibly stimulates glial cells. *Clinical Neurophysiology, 123*(10), 2006-2009.
Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia & Analgesia, 47*(6), 717-723.
Sabari, J. S. (1991). Motor learning concepts applied to activity-based intervention with adults with hemiplegia. *American Journal of Occupational Therapy, 45*(6), 523-530.
Sabatini, U., Boulanouar, K., Fabre, N., Martin, F., Carel, C., Colonnese, C., . . . Chollet, F. (2000). Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. *Brain, 123*(2), 394-403.
Sadowski, B. (2008). Plasticity of the cortical motor system. *Journal of Human Kinetics, 20*, 5-22.
Sakata, H., Taira, M., Kusunoki, M., Murata, A., & Tanaka, Y. (1997). The TINS Lecture The parietal association cortex in depth perception and visual control of hand action. *Trends in neurosciences, 20*(8), 350-357.
Sanes, J. N., & Donoghue, J. P. (2000). Plasticity and primary motor cortex. *Annual review of neuroscience, 23*(1), 393-415.
Santarnecchi, E., Feurra, M., Barneschi, F., Acampa, M., Bianco, G., Cioncoloni, D., . . . Rossi, S. (2014). Time course of corticospinal excitability and autonomic function interplay during and following monopolar tDCS. *Frontiers in psychiatry, 5*, 86.
Sarmiento, C., San-Juan, D., & Prasath, V. (2016). Letter to the Editor: Brief history of transcranial direct current stimulation (tDCS): from electric fishes to microcontrollers. *Psychological medicine, 46*(15), 3259-3261.
Saucedo Marquez, C. M., Zhang, X., Swinnen, S. P., Meesen, R., & Wenderoth, N. (2013). Task-specific effect of transcranial direct current stimulation on motor learning. *Frontiers in human neuroscience, 7*, 333.
Schabrun, S. M., & Chipchase, L. S. (2012). Priming the brain to learn: the future of therapy? *Manual therapy, 17*(2), 184-186.

Schabrun, S. M., Lamont, R. M., & Brauer, S. G. (2016). Transcranial Direct Current Stimulation to Enhance Dual-Task Gait Training in Parkinson's Disease: A Pilot RCT. *PloS one, 11*(6), e0158497.
Schendan, H. E., Searl, M. M., Melrose, R. J., & Stern, C. E. (2003). An FMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron, 37*(6), 1013-1025.
Scherberger, H., & Andersen, R. A. (2007). Target selection signals for arm reaching in the posterior parietal cortex. *Journal of Neuroscience, 27*(8), 2001-2012.
Schluter, N., Rushworth, M., Mills, K., & Passingham, R. (1998). Signal-, set-, and movement-related activity in the human premotor cortex. *Neuropsychologia, 37*(2), 233-243.
Schmidt, C., Peigneux, P., Muto, V., Schenkel, M., Knoblauch, V., Münch, M., . . . Cajochen, C. (2006). Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. *Journal of Neuroscience, 26*(35), 8976-8982.
Schmidt, R. A. (1975). A schema theory of discrete motor skill learning. *Psychological review, 82*(4), 225.
Schmidt, R. A. (2003). Motor schema theory after 27 years: Reflections and implications for a new theory. *Research quarterly for exercise and sport, 74*(4), 366-375.
Schmidt, R. A., Lee, T., Winstein, C., Wulf, G., & Zelaznik, H. (2018). *Motor Control and Learning, 6E*: Human kinetics.
Schmidt, R. A., & Lee, T. D. (1999). *Motor control and learning: A behavioral emphasis*: Human Kinetics.
Schulz, R., Gerloff, C., & Hummel, F. C. (2013). Non-invasive brain stimulation in neurological diseases. *Neuropharmacology, 64*, 579-587.
Schunemann, H. (2008). GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2. *http://www. cc-ims. net/gradepro*.
Scott, S. H. (2003). The role of primary motor cortex in goal-directed movements: insights from neurophysiological studies on non-human primates. *Current opinion in neurobiology, 13*(6), 671-677.
Scott, S. H. (2008). Inconvenient truths about neural processing in primary motor cortex. *The Journal of physiology, 586*(5), 1217-1224.
Scott, S. H., & Kalaska, J. F. (1995). Changes in motor cortex activity during reaching movements with similar hand paths but different arm postures. *Journal of neurophysiology, 73*(6), 2563-2567.
Scoville, W. B., & Milner, B. (2000). Loss of recent memory after bilateral hippocampal lesions. *The Journal of neuropsychiatry and clinical neurosciences, 12*(1), 103-a-113.
Sehm, B., Kipping, J. A., Schäfer, A., Villringer, A., & Ragert, P. (2013). A comparison between uni-and bilateral tDCS effects on functional connectivity of the human motor cortex. *Frontiers in human neuroscience, 7*, 183.
Seniów, J., Bilik, M., Leśniak, M., Waldowski, K., Iwański, S., & Członkowska, A. (2012). Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: a randomized, double-blind, placebo-controlled study. *Neurorehabilitation and neural repair, 26*(9), 1072-1079.
Shadmehr, R., & Holcomb, H. H. (1997). Neural correlates of motor memory consolidation. *Science, 277*(5327), 821-825.
Shadmehr, R., & Mussa-Ivaldi, F. A. (1994). Adaptive representation of dynamics during learning of a motor task. *Journal of Neuroscience, 14*(5), 3208-3224.
Shea, C. H., & Kohl, R. M. (1990). Specificity and variability of practice. *Research quarterly for exercise and sport, 61*(2), 169-177.
Shea, C. H., & Kohl, R. M. (1991). Composition of practice: Influence on the retention of motor skills. *Research quarterly for exercise and sport, 62*(2), 187-195.
Siebner, H., & Rothwell, J. (2003). Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Experimental brain research, 148*(1), 1-16.
Siebner, H. R., Lang, N., Rizzo, V., Nitsche, M. A., Paulus, W., Lemon, R. N., & Rothwell, J. C. (2004). Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *Journal of Neuroscience, 24*(13), 3379-3385.
Siengsukon, C. F., & Al-Sharman, A. (2011). Sleep promotes offline enhancement of an explicitly learned discrete but not an explicitly learned continuous task. *Nature and science of sleep, 3*, 39.
Simonetta-Moreau, M. (2014). Non-invasive brain stimulation (NIBS) and motor recovery after stroke. *Annals of physical and rehabilitation medicine, 57*(8), 530-542.

Smith, L. B., & Thelen, E. E. (1993). *A dynamic systems approach to development: Applications*. Paper presented at the This book grew out of a workshop," Dynamic Systems in Development," held for the Society for Research in Child Development in Kansas City, KS, Apr 1989.

Smorenburg, A. R., Gordon, A. M., Kuo, H.-C., Ferre, C. L., Brandao, M., Bleyenheuft, Y., . . . Friel, K. M. (2017). Does corticospinal tract connectivity influence the response to intensive bimanual therapy in children with unilateral cerebral palsy? *Neurorehabilitation and neural repair, 31*(3), 250-260.

Sommer, M., Alfaro, A., Rummel, M., Speck, S., Lang, N., Tings, T., & Paulus, W. (2006). Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clinical Neurophysiology, 117*(4), 838-844.

Sommer, M., Lang, N., Tergau, F., & Paulus, W. (2002). Neuronal tissue polarization induced by repetitive transcranial magnetic stimulation? *Neuroreport, 13*(6), 809-811.

Spencer, J. P., Austin, A., & Schutte, A. R. (2012). Contributions of dynamic systems theory to cognitive development. *Cognitive Development, 27*(4), 401-418.

Spencer, J. P., & Perone, S. (2008). Defending qualitative change: The view from dynamical systems theory. *Child Development, 79*(6), 1639-1647.

Squire, L. R. (1987). Memory and brain.

Squire, L. R., Zola-Morgan, S., Cave, C., Haist, F., Musen, G., & Suzuki, W. (1990). *Memory: organization of brain systems and cognition.* Paper presented at the Cold Spring Harbor symposia on quantitative biology.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences, 93*(24), 13515-13522.

Sriraman, A., Oishi, T., & Madhavan, S. (2014). Timing-dependent priming effects of tDCS on ankle motor skill learning. *Brain research, 1581*, 23-29.

Stagg, C., Jayaram, G., Pastor, D., Kincses, Z., Matthews, P., & Johansen-Berg, H. (2011). Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. *Neuropsychologia, 49*(5), 800-804.

Stagg, C., O'shea, J., Kincses, Z., Woolrich, M., Matthews, P., & Johansen-Berg, H. (2009). Modulation of movement-associated cortical activation by transcranial direct current stimulation. *European Journal of Neuroscience, 30*(7), 1412-1423.

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17*(1), 37-53.

Staudt, M. (2010). Reorganization after pre-and perinatal brain lesions. *Journal of Anatomy, 217*(4), 469-474.

Staudt, M., Gerloff, C., Grodd, W., Holthausen, H., Niemann, G., & Krägeloh-Mann, I. (2004). Reorganization in congenital hemiparesis acquired at different gestational ages. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 56*(6), 854-863.

Staudt, M., Grodd, W., Gerloff, C., Erb, M., Stitz, J., & Krägeloh-Mann, I. (2002). Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. *Brain, 125*(10), 2222-2237.

Steele, C. J., & Penhune, V. B. (2010). Specific increases within global decreases: a functional magnetic resonance imaging investigation of five days of motor sequence learning. *Journal of Neuroscience, 30*(24), 8332-8341.

Steenbergen, B., & Gordon, A. M. (2006). Activity limitation in hemiplegic cerebral palsy: evidence for disorders in motor planning. *Developmental medicine and child neurology, 48*(9), 780-783.

Steenbergen, B., Van Der Kamp, J., Verneau, M., Jongbloed-Pereboom, M., & Masters, R. S. (2010). Implicit and explicit learning: applications from basic research to sports for individuals with impaired movement dynamics. *Disability and Rehabilitation, 32*(18), 1509-1516.

Stefan, K., Wycislo, M., Gentner, R., Schramm, A., Naumann, M., Reiners, K., & Classen, J. (2005). Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training. *Cerebral Cortex, 16*(3), 376-385.

Steinlin, M., Good, M., Martin, E., Bänziger, O., Largo, R., & Boltshauser, E. (1993). Congenital hemiplegia: morphology of cerebral lesions and pathogenetic aspects from MRI. *Neuropediatrics, 24*(04), 224-229.

Stickgold, R., & Walker, M. P. (2005). Memory consolidation and reconsolidation: what is the role of sleep? *Trends in neurosciences, 28*(8), 408-415.

Stickgold, R., & Walker, M. P. (2007). Sleep-dependent memory consolidation and reconsolidation. *Sleep medicine, 8*(4), 331-343.
Stortelder, F., & Ploegmakers-Burg, M. (2010). Adolescence and the reorganization of infant development: a neuro-psychoanalytic model. *Journal of the American Academy of Psychoanalysis and Dynamic Psychiatry, 38*(3), 503-531.
Sugawara, K., Onishi, H., Yamashiro, K., Kirimoto, H., Tsubaki, A., Suzuki, M., . . . Kameyama, S. (2013). Activation of the human premotor cortex during motor preparation in visuomotor tasks. *Brain topography, 26*(4), 581-590.
Sugawara, K., Onishi, H., Yamashiro, K., Soma, T., Oyama, M., Kirimoto, H., . . . Kameyama, S. (2013). Repeated practice of a Go/NoGo visuomotor task induces neuroplastic change in the human posterior parietal cortex: an MEG study. *Experimental brain research, 226*(4), 495-502.
Takeuchi, N., Chuma, T., Matsuo, Y., Watanabe, I., & Ikoma, K. (2005). Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke, 36*(12), 2681-2686.
Takeuchi, N., Tada, T., Toshima, M., Chuma, T., Matsuo, Y., & Ikoma, K. (2008). Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *Journal of rehabilitation medicine, 40*(4), 298-303.
Tatti, E., Rossi, S., Innocenti, I., Rossi, A., & Santarnecchi, E. (2016). Non-invasive brain stimulation of the aging brain: State of the art and future perspectives. *Ageing research reviews, 29*, 66-89.
Taub, E. (1976). Motor behavior following deafferentation in the developing and motorically mature monkey *Neural control of locomotion* (pp. 675-705): Springer.
Taubert, M., Dafotakis, M., Sparing, R., Eickhoff, S., Leuchte, S., Fink, G. R., & Nowak, D. A. (2010). Inhibition of the anterior intraparietal area and the dorsal premotor cortex interfere with arbitrary visuo-motor mapping. *Clinical Neurophysiology, 121*(3), 408-413.
Taylor, J. A., Krakauer, J. W., & Ivry, R. B. (2014). Explicit and implicit contributions to learning in a sensorimotor adaptation task. *Journal of Neuroscience, 34*(8), 3023-3032.
Taylor, N., Sand, P., & Jebsen, R. (1973). Evaluation of hand function in children. *Archives of physical medicine and rehabilitation, 54*(3), 129-135.
Teasell, R., Bitensky, J., Salter, K., & Bayona, N. A. (2005). The role of timing and intensity of rehabilitation therapies. *Topics in stroke rehabilitation, 12*(3), 46.
Tecchio, F., Zappasodi, F., Assenza, G., Tombini, M., Vollaro, S., Barbati, G., & Rossini, P. M. (2010). Anodal transcranial direct current stimulation enhances procedural consolidation. *Journal of neurophysiology, 104*(2), 1134-1140.
Thelen, E., & Smith, L. B. (1996). *A dynamic systems approach to the development of cognition and action*: MIT press.
Thickbroom, G. W., Byrnes, M. L., Archer, S. A., Nagarajan, L., & Mastaglia, F. L. (2001). Differences in sensory and motor cortical organization following brain injury early in life. *Annals of neurology, 49*(3), 320-327.
Thielscher, A., & Kammer, T. (2004). Electric field properties of two commercial figure-8 coils in TMS: calculation of focality and efficiency. *Clinical Neurophysiology, 115*(7), 1697-1708.
Toni, I., Krams, M., Turner, R., & Passingham, R. E. (1998). The time course of changes during motor sequence learning: a whole-brain fMRI study. *Neuroimage, 8*(1), 50-61.
Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: a hypothesis. *Brain research bulletin, 62*(2), 143-150.
Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep medicine reviews, 10*(1), 49-62.
Touge, T., Gerschlager, W., Brown, P., & Rothwell, J. C. (2001). Are the after-effects of low-frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses? *Clinical Neurophysiology, 112*(11), 2138-2145.
Toxopeus, C. M., de Jong, B. M., Valsan, G., Conway, B. A., Leenders, K. L., & Maurits, N. M. (2011). Direction of movement is encoded in the human primary motor cortex. *PLoS One, 6*(11), e27838.
Triccas, L. T., Burridge, J. H., Hughes, A.-M., Pickering, R. M., Desikan, M., Rothwell, J. C., & Verheyden, G. (2016). Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: a review and meta-analysis. *Clinical Neurophysiology, 127*(1), 946-955.

Triccas, L. T., Burridge, J. H., Hughes, A., Verheyden, G., Desikan, M., & Rothwell, J. (2015). A double-blinded randomised controlled trial exploring the effect of anodal transcranial direct current stimulation and uni-lateral robot therapy for the impaired upper limb in sub-acute and chronic stroke. *NeuroRehabilitation, 37*(2), 181-191.

Turrigiano, G. G., & Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nature Reviews Neuroscience, 5*(2), 97.

Vallar, G., & Bolognini, N. (2011). Behavioural facilitation following brain stimulation: implications for neurorehabilitation. *Neuropsychological Rehabilitation, 21*(5), 618-649.

van der Kamp, J., Steenbergen, B., & Masters, R. S. (2017). Explicit and implicit motor learning in children with unilateral cerebral palsy. *Disability and rehabilitation*, 1-8.

van Geert, P. (1998). A dynamic systems model of basic developmental mechanisms: Piaget, Vygotsky, and beyond. *Psychological review, 105*(4), 634.

Verdolini-Marston, K., & Balota, D. A. (1994). Role of elaborative and perceptual integrative processes in perceptual-motor performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20*(3), 739.

Verhagen, L., Dijkerman, H. C., Medendorp, W. P., & Toni, I. (2012). Cortical dynamics of sensorimotor integration during grasp planning. *Journal of Neuroscience, 32*(13), 4508-4519.

Verheyden, G., Purdey, J., Burnett, M., Cole, J., & Ashburn, A. (2013). Immediate effect of transcranial direct current stimulation on postural stability and functional mobility in Parkinson's disease. *Movement Disorders, 28*(14), 2040-2041.

Viana, R., Laurentino, G., Souza, R., Fonseca, J., Silva Filho, E., Dias, S., . . . Monte-Silva, K. (2014). Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: a pilot randomized controlled trial. *NeuroRehabilitation, 34*(3), 437-446.

Vidoni, E. D., & Boyd, L. A. (2007). Achieving enlightenment: what do we know about the implicit learning system and its interaction with explicit knowledge? *Journal of Neurologic Physical Therapy, 31*(3), 145-154.

Vingerhoets, G. (2014). Contribution of the posterior parietal cortex in reaching, grasping, and using objects and tools. *Frontiers in psychology, 5*, 151.

Vogt, S., Buccino, G., Wohlschläger, A. M., Canessa, N., Shah, N. J., Zilles, K., . . . Fink, G. R. (2007). Prefrontal involvement in imitation learning of hand actions: effects of practice and expertise. *Neuroimage, 37*(4), 1371-1383.

Vongvaivanichakul, P., Tretriluxana, J., Bovonsunthonchai, S., Pakaprot, N., & Laksanakorn, W. (2014). Reach-to-grasp training in individuals with chronic stroke augmented by low-frequency repetitive transcranial magnetic stimulation.

Wadden, K. P., Woodward, T. S., Metzak, P. D., Lavigne, K. M., Lakhani, B., Auriat, A. M., & Boyd, L. A. (2015). Compensatory motor network connectivity is associated with motor sequence learning after subcortical stroke. *Behavioural brain research, 286*, 136-145.

Walker, M. P. (2005). A refined model of sleep and the time course of memory formation. *Behavioral and brain sciences, 28*(1), 51-64.

Walker, M. P., Brakefield, T., Hobson, J. A., & Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature, 425*(6958), 616.

Walker, M. P., & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron, 44*(1), 121-133.

Walker, M. P., Stickgold, R., Alsop, D., Gaab, N., & Schlaug, G. (2005). Sleep-dependent motor memory plasticity in the human brain. *Neuroscience, 133*(4), 911-917.

Wang, R.-Y., Tseng, H.-Y., Liao, K.-K., Wang, C.-J., Lai, K.-L., & Yang, Y.-R. (2012). rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. *Neurorehabilitation and neural repair, 26*(3), 222-230.

Ward, N., Brown, M., Thompson, A., & Frackowiak, R. (2003). Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain, 126*(11), 2476-2496.

Waters-Metenier, S., Husain, M., Wiestler, T., & Diedrichsen, J. (2014). Bihemispheric transcranial direct current stimulation enhances effector-independent representations of motor synergy and sequence learning. *Journal of Neuroscience, 34*(3), 1037-1050.

Weiss, P. H., Achilles, E. I., Moos, K., Hesse, M. D., Sparing, R., & Fink, G. R. (2013). Transcranial direct current stimulation (tDCS) of left parietal cortex facilitates gesture processing in healthy subjects. *Journal of Neuroscience, 33*(49), 19205-19211.

Wessel, M. J., Zimerman, M., & Hummel, F. C. (2015). Non-invasive brain stimulation: an interventional tool for enhancing behavioral training after stroke. *Frontiers in human neuroscience, 9*, 265.

Wiklund, L. M., & Uvebrant, P. (1991). Hemiplegic cerebral palsy: correlation between CT morphology and clinical findings. *Developmental Medicine & Child Neurology, 33*(6), 512-523.

Willingham, D. B. (1998). A neuropsychological theory of motor skill learning. *Psychological review, 105*(3), 558.

Willingham, D. B., Nissen, M. J., & Bullemer, P. (1989). On the development of procedural knowledge. *Journal of experimental psychology: learning, memory, and cognition, 15*(6), 1047.

Wu, D., Qian, L., Zorowitz, R. D., Zhang, L., Qu, Y., & Yuan, Y. (2013). Effects on decreasing upper-limb poststroke muscle tone using transcranial direct current stimulation: a randomized sham-controlled study. *Archives of physical medicine and rehabilitation, 94*(1), 1-8.

Wu, T., Sommer, M., Tergau, F., & Paulus, W. (2000). Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neuroscience letters, 287*(1), 37-40.

Wulf, G., Schmidt, R. A., & Deubel, H. (1993). Reduced feedback frequency enhances generalized motor program learning but not parameterization learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19*(5), 1134.

Yang, G., Pan, F., & Gan, W.-B. (2009). Stably maintained dendritic spines are associated with lifelong memories. *Nature, 462*(7275), 920.

Yang, Y.-R., Tseng, C.-Y., Chiou, S.-Y., Liao, K.-K., Cheng, S.-J., Lai, K.-L., & Wang, R.-Y. (2013). Combination of rTMS and treadmill training modulates corticomotor inhibition and improves walking in Parkinson disease: a randomized trial. *Neurorehabilitation and neural repair, 27*(1), 79-86.

Yozbatiran, N., Keser, Z., Davis, M., Stampas, A., O'Malley, M., Cooper-Hay, C., . . . Francisco, G. E. (2016). Transcranial direct current stimulation (tDCS) of the primary motor cortex and robot-assisted arm training in chronic incomplete cervical spinal cord injury: a proof of concept sham-randomized clinical study. *NeuroRehabilitation, 39*(3), 401-411.

Zangen, A., Roth, Y., Voller, B., & Hallett, M. (2005). Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clinical Neurophysiology, 116*(4), 775-779.

Zhao, H., Qiao, L., Fan, D., Zhang, S., Turel, O., Li, Y., . . . He, Q. (2017). Modulation of brain activity with noninvasive transcranial direct current stimulation (tDCS): clinical applications and safety concerns. *Frontiers in psychology, 8*, 685.

Zheng, C.-j., Liao, W.-j., & Xia, W.-g. (2015). Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: a double-blind randomized controlled trail. *Journal of Huazhong University of Science and Technology [Medical Sciences], 35*(2), 248-254.

Zhu, H., Lu, Z., Jin, Y., Duan, X., Teng, J., & Duan, D. (2015). Low-frequency repetitive transcranial magnetic stimulation on Parkinson motor function: a meta-analysis of randomised controlled trials. *Acta neuropsychiatrica, 27*(2), 82-89.

Ziemann, U. (2004a). LTP-like plasticity in human motor cortex *Supplements to Clinical neurophysiology* (Vol. 57, pp. 702-707): Elsevier.

Ziemann, U. (2004b). TMS induced plasticity in human cortex. *Reviews in the Neurosciences, 15*(4), 253-266.

Ziemann, U. (2017). Thirty years of transcranial magnetic stimulation: where do we stand? *Experimental brain research, 235*(4), 973-984.

Ziemann, U., & Siebner, H. R. (2015). Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: boon or bane? *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8*(3), 662-663.

Zimerman, M., Heise, K. F., Hoppe, J., Cohen, L. G., Gerloff, C., & Hummel, F. C. (2012). Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. *Stroke, 43*(8), 2185-2191.

Zimerman, M., Nitsch, M., Giraux, P., Gerloff, C., Cohen, L. G., & Hummel, F. C. (2013). Neuroenhancement of the aging brain: restoring skill acquisition in old subjects. *Annals of neurology, 73*(1), 10-15.

Zwicker, J. G., & Harris, S. R. (2009). A reflection on motor learning theory in pediatric occupational therapy practice. *Canadian Journal of Occupational Therapy, 76*(1), 29-37.

Zwissler, B., Sperber, C., Aigeldinger, S., Schindler, S., Kissler, J., & Plewnia, C. (2014). Shaping memory accuracy by left prefrontal transcranial direct current stimulation. *Journal of Neuroscience, 34*(11), 4022-4026.