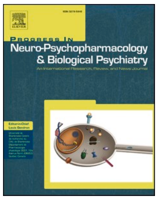
Progress in Neuropsychopharmacology & Biological Psychiatry 125 (2023) 110766

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Modulating motor learning with brain stimulation: Stage-specific perspectives for transcranial and transcutaneous delivery

Gabriel Byczynski [a,c], Sven Vanneste [a,b,c,*]

[a] Lab for Clinical and Integrative Neuroscience, Trinity College Institute for Neuroscience, School of Psychology, Trinity College Dublin, D02 PN40, Ireland
[b] School of Psychology, Trinity College Institute for Neuroscience, School of Psychology, Trinity College Dublin, D02 PN40, Ireland
[c] Global Brain Health Institute, Trinity College Dublin, D02 PN40, Ireland

ARTICLE INFO

Keywords:
Transcranial direct current stimulation (tDCS)
Transcranial alternating current stimulation (tACS)
Peripheral nerve stimulation
Non-invasive brain stimulation
Skill learning
Motor learning

ABSTRACT

Brain stimulation has been used in motor learning studies with success in improving aspects of task learning, retention, and consolidation. Using a variety of motor tasks and stimulus parameters, researchers have produced an array of literature supporting the efficacy of brain stimulation to modulate motor task learning. We discuss the use of transcranial direct current stimulation, transcranial alternating current stimulation, and peripheral nerve stimulation to modulate motor learning. In a novel approach, we review literature of motor learning modulation in terms of learning stage, categorizing learning into acquisition, consolidation, and retention. We endeavour to provide a current perspective on the stage-specific mechanism behind modulation of motor task learning, to give insight into how electrical stimulation improves or hinders motor learning, and how mechanisms differ depending on learning stage. Offering a look into the effectiveness of peripheral nerve stimulation for motor learning, we include potential mechanisms and overlapping features with transcranial stimulation. We conclude by exploring how peripheral stimulation may contribute to the results of studies that employed brain stimulation intracranially.

1. Introduction

With the growing popularity of non-invasive electrical brain stimulation techniques like transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), researchers have progressed significantly in discovering applications, proposing mechanisms, and producing interventive therapies. Non-invasive electrical stimulation of the brain is a method that employs the use of a mild electrical current between electrodes while in contact with the scalp. It has been used for the treatment of psychiatric disease (Buchanan et al., 2020; Kuo et al., 2017a), improving memory (Jo et al., 2009; Luckey et al., 2022b), tinnitus (Vanneste and De Ridder, 2011), ADHD (Buchanan et al., 2022), and motor learning (Pixa and Pollok, 2018) with relatively good success. Specific to movement and motor learning, tDCS has also been used in a range of pathological contexts including Parkinson's disease, motor stroke, and multiple sclerosis (Lefaucheur et al., 2017). Thus, brain stimulation has created an entire novel genre of neuro-modulatory research that focuses on determining new avenues which it can be applied. As research progresses, it refines the use and innovation of stimulation methodologies to achieve the most effective results. Since there are numerous reviews on the general background, mechanisms, and applications of tDCS/tACS, we put forth a focused account of brain stimulation for motor task learning modulation with novel focus on the stage of motor learning in tDCS, tACS, and peripheral stimulation.

In this article, we aim to provide an overview of tDCS and tACS and their use in stage-specific motor learning, including a review of the current methodologies and theories in motor learning and the variation between central and peripheral (i.e., transcranial and transcutaneous respectively) delivery during different stages of motor learning. We present a comparison between the alternating and direct current stimulation, and the proposed mechanisms by which the different approaches are considered to act by. We focus our approach by methodologically categorizing results based on the motor learning stage targeted, and the proposed mechanisms of stage-specific modulation. Finally, we perform the same approach for novel peripheral nerve stimulation, drawing parallels between stage-specific effects and mechanistic similarities to transcranial stimulation. Conclusively, we

---

* Corresponding author at: Lab for Clinical and Integrative Neuroscience, Institute for Neuroscience, School of Psychology, Trinity College Dublin, College Green, Dublin 2, Ireland.
E-mail address: sven.vanneste@tcd.ie (S. Vanneste).

https://doi.org/10.1016/j.pnpbp.2023.110766
Received 19 December 2022; Received in revised form 22 March 2023; Accepted 9 April 2023

aim to provide an effective account of current, stage-specific, motor task learning modulation with electrical stimulation that supports further, and indeed more focused exploration.

2. Motor task learning

Motor learning can be broadly divided into two categories; implicit and explicit learning, often describe in terms of the type of underlying motor system or the type of memory involved (e.g., procedural and declarative, respectively) (Kleynen et al., 2014). It is noted however, that it is often the case that explicit motor-learned tasks settle into the implicit, such that paradigms attempting to sequester the implicit aspect of motor learning may still have contributions in the explicit learning sphere (Krakauer et al., 2019). Implicit motor learning is described as the 'unconscious' aspect of motor learning, and is considered to be governed by procedural memory, where the participant cannot consciously recall the learned movement or sequence, however still shows training effects (Kal et al., 2018). Conversely, explicit motor learning is considered to be a conscious learning of a motor task, akin to declarative memory (Kal et al., 2018). In this way, the subject is aware of the learned movement or sequence, such that a component of performance relies on consciously recalling the sequence or movement. Motor tasks used in research can be tailored to investigate either implicit, or a combination of explicit and implicit learning. As such, when developing a motor task, researchers tend to form a consensus on how the task should be implemented, instructions given, and how learning is measured, in order to better conclude which aspect of motor learning is being measured (Kleynen et al., 2015).

The distinction between implicit and explicit motor learning is particularly relevant when performing research that aims to understand how neuromodulation can influence motor learning. Implicit motor learning is less 'at-risk' of deficits brought on by external cognitive factors. This allows for the use of dual-task paradigms, while preventing factors like fatigue or distraction from interfering with results in implicit motor learning, as is shown to occur during explicit motor learning (Rieth et al., 2010). In a recent review, the contributions of implicit and explicit aspects of motor learning are further discussed (Krakauer et al., 2019). With these considerations, a distinction between implicit and explicit motor learning will be used in this article. However, since evidence shows that tasks learned explicitly will have implicit components, we will proceed with the understanding that it is not possible to state that the processes are distinct and non-interacting.

Motor learning is also often divided into semi-structured stages, with characteristics pertaining to the behavioural implication. The first stage, *fast learning*, is the initial skill acquisition of a motor task (e.g., learning the sequence of a 4-button press task), and often occurs rapidly, showing fast improvement in measures such as reaction time and accuracy (Dayan and Cohen, 2011). Fast learning itself is a sub-component of *online learning*, which describes improvements in motor skill during training. Online learning is counterpart to *offline learning*, which reflects skill improvement that occurs after the training, but not during (Fig. 1). Also, a component of online learning is *slow learning*, which involves a form of 'refining' the task that was learned in the fast stage. In this stage, the rapid acquisition of motor skill is reduced to a fine tuning of skill performance, and a general plateau in performance improvement. Interestingly, it is believed that fast learning is generally explicit learning, while the slow learning is implicitly governed (however this is specific to the task) (Dahms et al., 2020). (See Fig. 2.)

Consolidation is often considered to follow slow learning. Consolidation is the stage that evokes the offline learning by aptly consolidating the learned motor task (Doyon and Benali, 2005). As a result, performance increases are found to occur after practice, provided no interfering task is introduced. Interestingly, some research has suggested that offline gains are only prevalent in explicit motor learning, and are not found in implicit motor tasks, since offline learning often improves aspects of declarative but not procedural memory in motor skill acquisition (Van den Berg et al., 2019). *Automatization* is a stage in which gains in motor skills are less likely to be influenced by external factors, such as typing in your pin while speaking to the cashier or dialling a friend on the phone while simultaneously having a conversation. There is preliminary evidence that implicit motor task learning leads to better automatization compared to explicit motor learning, although further research is needed to determine the accuracy of this claim (Kal et al., 2018). Lastly, *retention* describes the ability to perform the learned task with minimal losses after a prolonged period of non-practice, akin to an annual bike-ride (Doyon and Benali, 2005). Research investigating retention with stimulation may therefore attempt to determine how stimulation of the brain increases the length of time and effectiveness of the retention step (Lum et al., 2018).

We propose that by using a stage-based approach, researchers

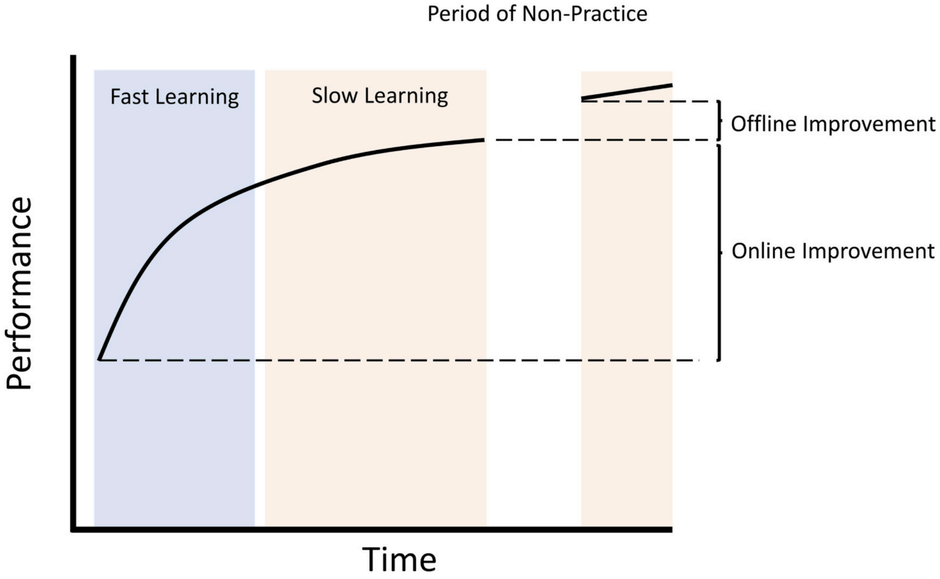


Fig. 1. Motor learning stages and related performance improvements. A schematic of motor task learning and corresponding fast and slow learning stages. A sharp increase in performance is seen during fast learning, which plateaus during slow learning, reflecting slower performance increases during refinement. A gap in which performance improves without practice reflects offline learning, while any improvement during practice is referred to as online improvement.

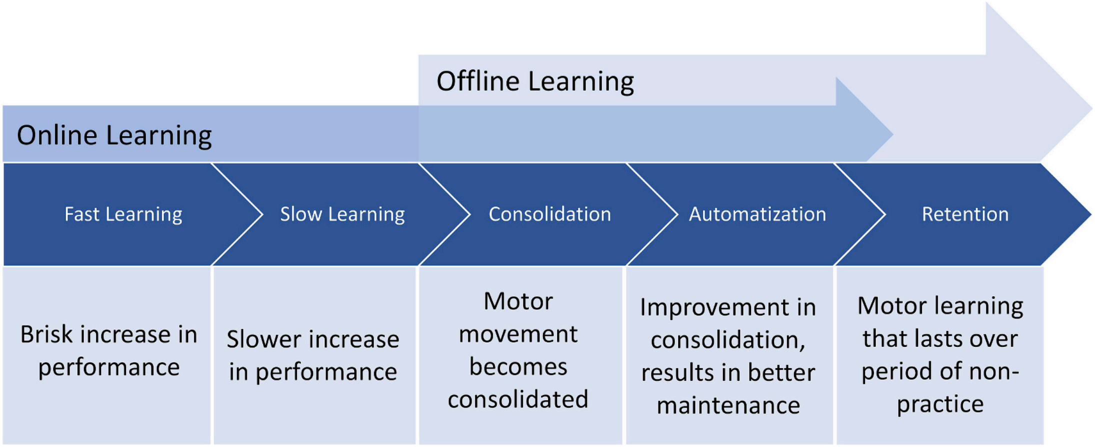


Fig. 2. Motor learning stages in online and offline learning. The stages of online and offline motor learning which including fast learning, slow learning, consolidation, automatizing, and retention. Despite being shown as individual and distinct stages, there are likely cooperative and overlapping mechanisms which govern their activity.

hypothesizing mechanisms and modulation effects can refine their approach to stage-specific targets. It is therefore necessary to consider the function, mechanistic, and behavioural contributions of each learning stage individually, to effectively approach motor learning. This is especially relevant when employing brain stimulation (e.g., tDCS) to modulate learning, as the effect of modulation may differ depending on the stage. Since there are many factors which influence the outcome of the modulation, we will first discuss the possibilities for location of delivery, type of stimulation used, and the stimulus parameters used.

The next sections will discuss individually the use of tDCS, tACS, and peripheral nerve stimulation for motor task modulation, with distinct categorization based on motor learning stage. Alongside results, the sections will also include the influence of stimulus parameters mentioned above such as location of delivery, duration, task chosen, frequency (for tACS), and duration. We will also provide stage-specific mechanistic hypotheses for modulation, with evidence and criticism.

3. Electrical stimulation and motor learning

Beginning with location of delivery of the electrical current, a common choice in motor task studies is to stimulate the primary motor cortex (M1) (Giustiniani et al., 2019; Krause et al., 2016; Reis and Fritsch, 2011). Some other brain regions that have been targeted include the premotor cortex, dorsolateral prefrontal cortex (DLPFC), supplementary motor areas (SMA), superior temporal gyrus, posterior parietal cortex, primary visual cortex, cerebellum, and middle temporal visual area (Buch et al., 2017; Ehsani et al., 2016; Miyaguchi et al., 2022; Zhu et al., 2015). The general motivation in choosing a region is that researchers suspect it has relevant function in the acquisition, consolidation, or retention of motor task learning. Delivery to M1 is intuitive, due to its essential contributions to motor learning (particularly sequence learning) (Hamano et al., 2021). Stimulation of the DLPFC might be chosen because of evidence suggesting that the DLPFC is involved in acquisition and expression of learned implicit sequences (Vékony et al., 2022). Similarly, the SMA may be targeted because it has been shown that SMA activity increases during motor skill learning (Vollmann et al., 2013). Given the variability of motor learning tasks, types of motor learning (e.g., implicit vs explicit), stage and cortical placement of stimulus delivery, the stimulation settings (i.e., frequency, current, duration), and choice study subjects, there is a wealth of possibility for applications.

3.1. TDCS

TDCS uses a direct and constant current to deliver stimulus to the brain at placed electrodes. The electrode placement, as mentioned previously, largely contributes to the effect of the stimulation as the current travels from one electrode to the other, while arcing through the underlying neural region being targeted (Unal et al., 2020). Due to the nature of electrical current, researchers have the choice between anodal and cathodal stimulation (a-tDCS and c-tDCS respectively). Anodal and cathodal describe which electrode is placed over the region of interest, with anodal stimulation being placement of the positive end, and cathodal the negative. Using this, researchers can choose to either induce either hyperpolarization (at the anode) or depolarization (at the cathode) of the neurons under effect (we further elaborate the mechanism in the forthcoming sections).

A-tDCS and c-tDCS have generally been shown to produce differing results, as for example research has shown that a-tDCS improved motor performance while c-tDCS improved offline learning (Christova et al., 2015). While studies have found motor learning improvements from tDCS, the specific effect of a/c-tDCS on motor learning isn't necessarily consistent. Some studies report improvement with both a/c-tDCS, (Ciechanski and Kirton, 2017; Khedr et al., 2013), while others report no improvement (Wiltshire and Watkins, 2020). In most cases, positive impacts on motor learning are seen in the anodal stimulation, and not cathodal - corroborated by studies finding motor learning improvements with anodal stimulation (Bastani and Jaberzadeh, 2012), and instead reduced excitability in the M1 cortex from cathodal stimulation (Brunoni et al., 2012; Sasaki et al., 2016). Other research however, have found only partial support, showing anodal stimulation increases motor excitability, and cathodal stimulation resulting in minimal inhibitory effects (Jacobson et al., 2012; Roche et al., 2015). Interestingly, it may be that these contradictory results arise from the differential activation and inhibition effects acting on cortical neurons *or* inhibitory interneurons. In this way, an inhibitory cathodal stimulation that acts on inhibitory interneurons would produce the inverse effect seen when acting on cortical neurons (Lang et al., 2004). Further research would need to quantify the possibility of this claim, and furthermore devise a way to distinguish between the two, so that researchers may be more aware of the neuron type that they are stimulating. Therefore, while considering the historical connotation of a/c-tDCS in this review, we also are conscious that there are inconsistencies in evidence that refute any definite excitatory or inhibitory activity.

It may be that to better understand the complexity of a/t-DCS, better mechanistic understanding is necessary of tDCS in general. One plausible mechanism is that tDCS changes the distribution of charge polarization across the neuron, creating a biased input of incoming connections, and changing the excitability of the cell (Rahman et al., 2013). Nitsche and Paulus also demonstrated results that corroborate a likely effect on the resting membrane potential, resulting in increases or decreases in excitability (Nitsche and Paulus, 2000). Imaging studies have revealed that increases in the blood oxygen level dependent (BOLD) signals in the M1, DLPFC, and SMA regions are associated with acquisition and retention of motor skill learning (see also review by Dayan and Cohen (2011)) (Lefebvre et al., 2012; Meehan et al., 2011). This hypothesis would therefore also be consistent with the sometimes 'inverted' effect of c-tDCS, that is, tDCS elicits its effect on the membrane potential of either cortical or inhibitory neurons, and therefore may produce opposing results. TDCS has also been suggested to improve motor learning by acting with brain-derived neurotrophic factor (BDNF). BDNF is a protein in the neurotrophic family that is established as having a role in development and synaptic plasticity (Bramham and Messaoudi, 2005). BDNF literature in plasticity is lacking however, and so its role in long-term potentiation (LTP) and subsequently motor learning is unclear (Bramham and Messaoudi, 2005). Generally, BDNF secretion is believed to occur throughout motor learning, and research has shown that tDCS improvements in motor learning are BDNF-dependent in mice (Fritsch et al., 2010). While some studies have implicated BDNF in motor learning in humans using a BDNF Val66Met genotype, grouped by homozygosity or heterozygosity (McHughen et al., 2009), other studies have found that it is not necessarily an effective predictor of motor learning alterability (Li Voti et al., 2011).

Due to the lack of understanding the exact mechanism of tDCS, stage-specificity is a relevant avenue to pursue to improve the understanding, and to direct research to specific targets. As such, the stages of motor learning, reduced here to acquisition, consolidation, and retention, may be approached as distinct period which differ in mechanism and thus in their receptivity to modulation. Here, we pursue each stage individually, highlighting the results of current research, proposed mechanisms, and stage-specific methodologies.

3.1.1. *Acquisition*

The first application of tDCS during motor learning is delivering stimulations during the motor learning task itself, possibly with the intent to improve the rate of learning, or effectiveness of automatization. We choose to combine fast learning, slow learning, and automatization stages under the general term of acquisition, as these are all aspects of online learning, and are generally suggested to follow similar processes, that is- modifications or refinements that occur during the task. Nitsche and colleagues found that when delivering anodal and cathodal tDCS to the primary motor cortex during a serial reaction time (SRT) task, reaction times decreased faster over trials, and measures of skill (the sharp increase in reaction time when blocks change from sequence to random stimulus) were larger (Nitsche et al., 2003). In another study, a-tDCS delivered over M1 in patients with Parkinson's disease was shown to improve skill acquisition, with improvements retained into the following week (Horiba et al., 2019). Thus, during motor skill acquisition, tDCS research has an agreement on the consensus that performance increases with (anodal) stimulation. Neurochemically, since GABA is often reduced during motor learning, it would be unsurprising that a-tDCS, which is suggested to reduce GABA concentrations, would correlate with improved motor learning (Stagg et al., 2011). In fact, there is evidence that the relationship between GABA and tDCS effectiveness is quite clear; as research has shown that the magnitude of GABA decreases in the M1 region brought on by a-tDCS correlates positively with motor learning and furthermore, fMRI signal changes (Stagg et al., 2011). Therefore, during motor acquisition, GABA decreases are seen resulting from tDCS. It is necessary however, to state that while research has indeed shown GABA decreases resulting from tDCS, that these GABA measures are not necessarily related to excitability. In fact to our knowledge, there have been no direct relationships shown between tDCS-altered GABA and cortical excitability (Bachtiar et al., 2015).

We emphasize that the number of papers that report significant motor task improvements during online learning with stimulation are limited compared to the number that report after-effects, or effects on testing/consolidation/retention. One study employed stimulation before and during motor task learning, and reported that delivery before the task improved acquisition of implicit learning, while delivery during the task did not elicit improvements (Kuntz et al., 2016). This trend has been shown in other research, as Fujiyama also reported that pre-conditioning tDCS improves the effect on skill acquisition (Fujiyama et al., 2017). While several studies fail to report significant during-acquisition (online) improvements with stimulation, it is common that follow-up testing is successful in detecting improvements, suggesting alteration to the consolidation of the learned task (Ehsani et al., 2016; Lang et al., 2003; Samaei et al., 2017). We further elaborate this apparent 'delay' in tDCS effectiveness in the coming section and visualize the effect in Fig. 3. Due to the trend of an apparent 'delayed' tDCS effect, there are few studies that report significant online learning improvement during tDCS in the initial visit.

3.1.2. *Consolidation*

Stimulation during the consolidation period of motor learning is used when attempting to improve the consolidation of the motor task learned, such that during for example a training/testing paradigm, improvements are seen in the testing occur after the training. Since relatively few studies focus their stimulation during the 'consolidation' period alone, it is possible that some of the effects seen on consolidation are due to excitation of the motor region that outlasts the stimulus delivery during acquisition and persists into consolidation. Research using a dual-tDCS (excitation of one hemisphere, and inhibition of the other) found that motor task performance was improved 24 h after task, but not 1 h after, providing support for a persisting excitation effect that influences consolidation of the learned motor task when delivered during the task, but not necessarily acquisition (Koyama et al., 2015).

It is interesting that while some studies report improvements during the task itself, and others report improvements in consolidation, in both cases, stimulation is typically delivered during the task, or during the online component. Nitsche and others reported an increase in both task acquisition and early consolidation of the SRT sequence in the tDCS group, attributing this finding to implicit motor learning modulation, and only when delivered to the motor cortex (Nitsche et al., 2003). The significant difference in performance between stimulation and control groups came in later blocks (blocks five and six). These findings suggest that the excitatory effects elicited by tDCS began not immediate, but requires a period of time to 'ramp up' and produce modulatory influence. This would explain why some studies report improvements only after the task, suggesting the task durations were shorter than the 'ramp up' period, and therefore were not long enough to see the elicited effects while measurement occurred during task. This would also explain why preconditioning with tDCS produces measurable online effects on acquisition, as it may effectively shorten, or shift earlier, the 'ramp up' period. A possible visualization of this effect is shown in Fig. 3, where the onset of the stimulus at the start of the learning stage, does not necessarily indicate that peak of effect will also occur in that stage. Evidence from tDCS in mice corroborates this story, showing motor cortex excitability increased for a period of time after stimulation was stopped (Fritsch et al., 2010).

When investigating the after-effects of tDCS in humans, as is discussed in a paper by Roche and colleagues, GABA concentration is shown to decrease after anodal stimulation, while glutamate is left unchanged (Roche et al., 2015). Furthermore, there is evidence that GABA synaptic activity is modulated by tDCS and motor learning synergistically, in a paradigm delivering tDCS after motor learning, and not during (Amadi et al., 2015). Complementary to an apparent decrease in GABA after anodal stimulation, is evidence showing a decrease in glutamate concentration post-cathodal stimulation (Stagg et al., 2009). For anodal stimulation, it appears possible that the decrease in GABA concentration is the result of decreased glutamic acid decarboxylase (GAD) activity, as it has been shown in cats that anodal tDCS in the visual cortex reduces GAD(−67) (Patel et al., 2018). GAD, an enzyme that converts glutamate

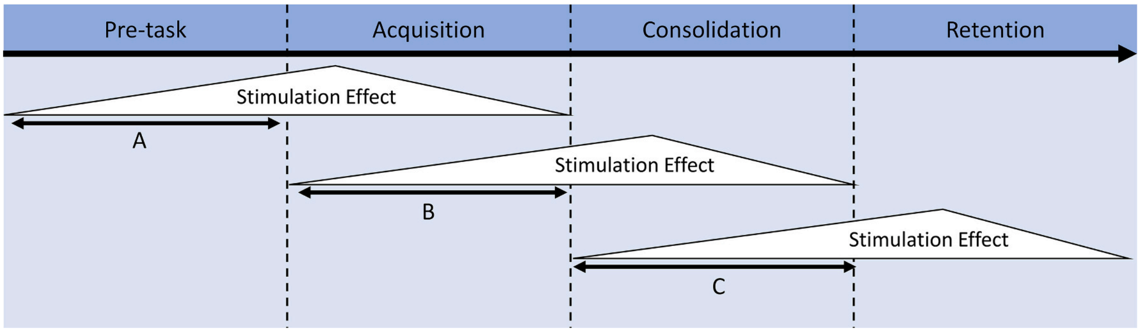


Fig. 3. Possible interaction between brain stimulation effect and motor learning stages. A schematic showing pre-task, acquisition, consolidation, and retention stages of motor learning. Arrows indicate the duration for which stimulation is delivered, and the triangle represents a theoretical effect strength that results from delivery. This illustrates a theoretical pattern by which the greatest effect of the stimulation may not occur during the targeted stage, and may instead elicit effects after stimulation has ended.

to GABA, may therefore be a possible mechanism for the after-effects of tDCS.

N-methyl-ᴅ-aspartate (NMDA) receptor sensitivity is also a possible mechanism by which tDCS' after-effects occur. Roche and colleagues note in their review that research has suggested NMDA receptor sensitivity is altered by tDCS (Roche et al., 2015). Together, the change in glutamate levels and the sensitivity change in the glutamate-agonized NMDA receptors seem to paint the picture of a possible mechanism for anodal and cathodal influence on post-stimulation excitability, where a decrease in GABA and increase in NMDA sensitivity would cooperatively contribute to cortical excitability, and a decrease in glutamate and reduced sensitivity of NMDA receptors would decrease excitability (Roche et al., 2015). Thus, the current understanding of motor task learning-modulation by tDCS is that by targeting the M1 or other motor-related regions, mechanisms like increasing excitability and modulation of EPSPs allow for plasticity changes resulting in improvements in motor learning, both online and offline (Fig. 4).

3.1.3. Retention

The effect of tDCS on motor retention refers to the improvement of how well the learned task is maintained over periods of non-practice. One study used dual-tDCS in a stroke population, it was found that tDCS resulted in improved performance during the online component, and improved long-term retention (1 week) (Lefebvre et al., 2013). This study employed 30 min of stimulation during the task training and began to see significant performance differences at the 15-min mark. This is consistent with our proposed idea that some studies fail to see online improvements because the non-preconditioned task is too short to quantify the difference, which takes a variable amount of time to begin inducing measurable plasticity changes and behavioural correlates. The improved performance was consistent for the remainder of the task, 30 min, 60 min, and 1 week after. In another study, it was reported that long-term retention of regained motor ability in individuals that suffered from stroke was better maintained 3-weeks after learning in a group that received dual-tDCS compared to those that did not (Goodwill et al., 2016).

Some adaptations of this approach, like one that used a combination of reward and tDCS delivered over the M1 region, were also successful in improving retention, finding that concurrent reward and current delivered during motor learning were effective, but neither one by themselves (Spampinato et al., 2019). In that study, the authors attribute the apparent synergistic effect to a joint use of long-term potentiation processes in both tDCS and reward. The authors also note that GABAergic synaptic modulation is a likely culprit for motor learning modulation, suggesting that reductions in M1 GABAergic inhibition lead to improved retention (Spampinato et al., 2019). Therefore, it seems that

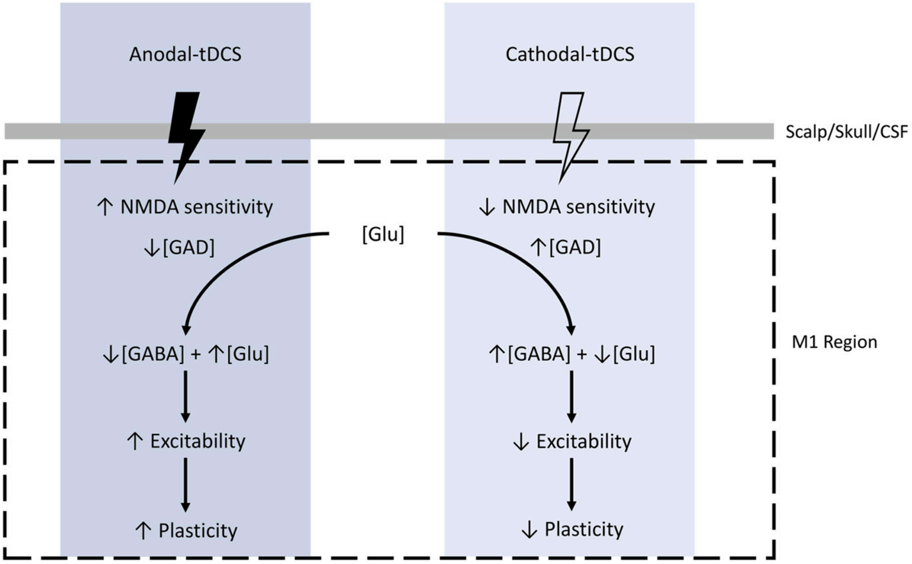


Fig. 4. Anodal and Cathodal tDCS and underlying neurochemical mechanisms. Hypothetical model of a possible mechanism for a-tDCS/c-tDCS delivered to the M1 cortical neurons, resulting in plastic changes in motor learning. ([Glu] = concentration of Glutamate, [GABA] = concentration of Gamma-aminobutyric acid, NMDA = *N*-methyl-ᴅ-aspartate (increases or decreases in sensitivity).

mechanistically, the after-effects of tDCS that act on consolidation, may similarly influence retention.

3.1.4. Conclusion

Conclusively, each of the acquisition, consolidation, and retention stages of motor learning has shown promise in motor stage learning modulation. However, when divided, it becomes apparent that each stage is distinct in the effect that tDCS elicits and the mechanisms that are believed to underly the effect. The variability in results between stages further supports the need for a stage-specific approach to tDCS and motor learning, since many studies report effects in 1 or more stages, but do not consider individual stage mechanisms in their discussion. While it may certainly be that mechanisms are shared between stages, there are likely distinct, but interacting mechanisms for acquisition, consolidation, and retention, which are often not approached as such.

3.2. TACS

TACS is applied the same as tDCS, with the only difference being the addition of a frequency in current delivery. In tACS, current is delivered in an alternating waveform with predetermined (or undetermined, in noise-delivered tACS) frequency. The appeal of tACS is the specification of the oscillatory aspect that can be used in delivery to achieve frequency-specific effects. Broadly, researchers are able to choose the delivery frequency of the stimulation, with the goal of inducing different effects based on the chosen frequency and region (Feurra et al., 2013). Such effects have included gamma-tACS (70 Hz) improvements of bimanual motor learning (Miyaguchi et al., 2022), alpha-tACS (10 Hz) for entrainment of cortical alpha waves, and beta-tACS (20 Hz) resulting in a movement speed reduction during motor task (Wach et al., 2013). This section will therefore discuss the application of tACS in motor task learning stages, the effects of varying stimulus frequencies, the underlying mechanisms, and the outcomes of tACS motor task modulation. Like tDCS, tACS for motor learning is typically delivered to the M1 or SMA region (Miyaguchi et al., 2022; Pollok et al., 2015; Wach et al., 2013), although recently researchers have begun investigating cerebellar stimulation (Naro et al., 2017). tACS delivery can be applied anywhere from 0.1 Hz to 200 kHz, and sometimes at no specific frequency at all, using frequency 'noise' in transcranial random noise stimulation (tRNS) (Antal and Paulus, 2013). Specific tACS effects on alpha waves, for example, have shown that tACS not only elicits phase entrainment of endogenous alpha waves, but also has effects on the power of the entrained oscillation (Helfrich et al., 2014). For further evidence of frequency and task specificity, (Feurra et al., 2013) presents results that show beta-tACS increases motor evoked potentials (MEP) *strictly* during rest when delivered to the motor cortex, while theta-tACS was effective during task state compared to dormancy. For implicit motor learning, low (40 Hz) gamma-tACS was shown to slow response times and decrease MEP amplitudes during an SRT task when delivered over the left M1 region (Giustiniani et al., 2019). This contrasts a higher-gamma study (Miyaguchi et al., 2022) which found the opposite, and further corroborating frequency specificity of tACS effects.

TACS acts similarly to tDCS in that it uses current to stimulate or inhibit neural activity. Studies have shown, however, that its oscillatory nature allows for entrainment of neural activity in classical alpha wave inhibition (Rumpf et al., 2019) and beta-band excitability (Yamaguchi et al., 2020). Specific to the motor cortex, tACS is believed to modulate motor excitability in the same way as anodal tDCS, however with frequency specificity being a determining factor in how long the effect lasts (Herrmann et al., 2013). Researchers must exhibit caution when theorizing the mechanism of tACS, since it is difficult to discern effects that result from stimulation (no different from tDCS), and those that result from the oscillatory aspect. In a similar fashion to tDCS-alterations of GABA, tACS has also been shown to alter $GABA_A$ activity, which in turn predicted ability to learn a motor task (Nowak et al., 2017). Unlike tDCS, however, no alteration in cortical excitability was observed in that study, suggesting again that the effect related to oscillatory mechanisms, and not those of excitability. Like tDCS, we will approach the effect of tACS on motor task learning in reference to stages, aiming to provide evidence for the benefits a stage-specific approach.

3.2.1. Acquisition

In a study investigating tACS effect on motor learning, stimulation was delivered at 10 Hz, 20 Hz, and 35 Hz (Pollok et al., 2015). This study found that during an SRT task, 20 Hz tACS over the M1 region during the task resulted in faster reaction times as compared to the sham stimulation. The authors state that 10 Hz and 20 Hz tACS effects were effective in modulating implicit motor learning, while 35 Hz was ineffective in modulating performance. Another study by Antal and others found that 15 Hz tACS delivery did not improve motor performance (Antal et al., 2008). For context, the 35 Hz tACS delivery in Pollok et al., it was intended to act as a determinant of frequency specificity, which the authors suggest is therefore a similar effect in the 15 Hz (Pollok et al., 2015). Since 15 Hz did not match the endogenous beta or alpha rhythms, it did not improve motor learning, similar to 35 Hz stimulation. These findings are suggestive that tACS can elicit frequency-specific acquisitional improvement. This provides specific options for neural modulation, and suggests an additional mechanism through the modulation of cortical oscillations using tACS (Helfrich et al., 2014). It must be considered then, that if 10 Hz and 20 Hz delivery improved motor learning, while 15 Hz and 35 Hz delivery did not; do the 10 Hz and 20 Hz frequencies work by the same or different mechanisms? To add to the complexity, another study by Wach et al., which delivered tACS at both 10 Hz and 20 Hz to M1, as did Pollock et al., found that while 10 Hz tACS increased movement variability, relating to irregularities in movement implementation, 20 Hz tACS produced movement slowing (Wach et al., 2013). Their study found that 20 Hz effects were evident immediately after tACS, while 10 Hz effects occurred at 30 min following stimulation. It is thus suggested that different stimulating frequencies induce behavioural effects in different time windows, and potentially by different mechanisms. Although Pollock et al. and Wach et al. both delivered tACS at 20 Hz, their results diverged. Importantly however, is that in Pollock et al., the results indicate behavioural changes *during* stimulation, while in Wach et al., the results are changes observed *following* stimulation. This is an important distinction, since the pre/during/post effects of tACS may elicit different behavioural effects.

Interestingly and concurrent with the theory put forth in this review, Wach et al. also reported that, like tDCS-induced after effects, tACS-induced motor effects persisted up to 30 min post-stimulation (Wach et al., 2013). In the study by Pollok and others, it was determined that 10 and 20 Hz tACS facilitated learning of the implicit motor sequence (Pollok et al., 2015). The authors put forth the theory that tACS improves performance via acquisitional modulation by promoting synaptic plasticity through motor cortex excitation. The authors also draw attention to the findings that show 20 Hz stimulation was more effective in acquisition and go on to suggest that functional reorganization occurs because of stimulation, and improves not only acquisition, but also early consolidation. Similar effects have been replicated using gamma tACS (75 Hz) (Akkad et al., 2021). In their study, Akkad and colleagues used theta-amplitude-coupled gamma frequency tACS delivered to the M1 region during a thumb abduction task. The results found that the tACS group receiving 'peak' (strictly the positive component of the waveform) gamma tACS stimulation had better motor acquisition than the sham group. Research has also shown that beta-tACS (20 Hz) inhibited motor learning acquisition, while gamma-tACS (70 Hz) improved acquisition (Bologna et al., 2019). Again, studies have also found contrary results on the effect of gamma-tACS on motor acquisition, as it has been shown that gamma-tACS reduced performance improvement during an SRT task in only the last two blocks of the study (Giustiniani et al., 2019). We find again that this delayed effect is evidence that tACS, like tDCS, may have a period of time before its effects are measurable in behaviour. This highlights the importance of a stage specific approach, since overlapping effects and after-effects can confound the actual behavioural correlates of the stimulation, and indeed their effects can differ accordingly.

The mechanism underlying the after-effects of tACS are not well understood, as is apparent by the numerous, and contradicting results. It is suggested in Wach et al. that there is a likely resonance effect on neuronal membrane potentials, and furthermore that increasing oscillatory activity may lead to disruptive neuron activity, which would provide a possible explanation for the effect of the 20 Hz slowing effect presented in their study (Wach et al., 2013). It does not however, explain why other studies report improvement in motor learning at 20 Hz tACS, while delivering stimulation to the same brain region. One possible explanation is that the effect of tACS strengthens synaptic connections with similar resonance frequency to that being delivered, while weakening those with different resonance frequencies (Wach et al., 2013). If true, then the nature of the task would indeed be influential in the effectiveness of the stimulation. As for example, it has been shown that post-movement beta, parietal gamma, and prefrontal theta oscillations are associated with adaptive learning, with specific effects that include prefrontal theta influences on acquisition, and beta-related trial to trial adaptation (Struber et al., 2021). Therefore, since different motor tasks produce different endogenous rhythms (e.g., beta activity when learning a motor sequence, vs alpha activity when tracking a target), to truly compare the effect of one tACS study to another, the task, length, stimulus settings, and duration must be equivalent. This trend further highlights the need for not only stage-specific, but context-driven findings in tACS motor research. When considering the apparent inconsistent findings in tACS research, if we apply a stage specific, and furthermore task-specific context, the findings may no longer be termed contradictory, but rather highly specific.

3.2.2. *Consolidation*

Pollok and colleagues published an earlier paper that used magnetoencephalography (MEG) to understand oscillatory components of motor learning (Pollok et al., 2014). They present that, using an SRT-type task, changes in beta-band suppression were correlated with improved reaction times, which they attributed to the beta activity modulation as a marker of reorganization during motor learning and early consolidation. Combined, both studies by Pollok and colleagues (Pollok et al., 2015; Pollok et al., 2014), suggest that tACS at the beta range can modulate both learning and early consolidation.

In further support for stage specificity, is the fact that research that delivered tACS during the consolidation stage (immediately after acquisition) however, has found little evidence that suggests motor consolidation is improved by tACS (Roshchupkina et al., 2020). In their study, Roshchupkina et al. use beta-tACS to modulate motor task learning, delivering stimulation after the initial learning session, and then at two time points after learning (25 min, and 4 h). Although preliminary, this finding is potentially supportive of the earlier observation in this review, which is that some research fails to find modulatory effect during the stage of stimulus delivery, because the effect on the brain may occur after stimulation has ceased, and is therefore misaligned with motor learning stage. As mentioned, this effect has been seen in tACS already, with an approximately 30 min after-effect (Wach et al., 2013). In a different approach, Rumpf and colleagues delivered 10 and 20 Hz tACS to an elderly population and found that alpha (10 Hz) tACS delivered post-training interrupted consolidation or retention, resulting in poorer performance in testing (Rumpf et al., 2019). Interestingly, the authors suggest that these findings are not the result of modulations of cortical excitability, but instead attribute the behavioural changes to the inhibitory nature of alpha rhythm. It is suggested that the endogenous alpha activity is entrained and enhanced with delivery of alpha tACS, resulting in inhibition of consolidation. This finding is relevant because it supports that the effect of modulation is at least partially elicited via the oscillatory component in delivery, and not strictly the current intensity. Conclusively, the placement of stimulation in the task paradigm is apparently critical for interpreting findings, particularly when employing tACS, since there is the introduction of another variable (frequency) which further diversifies the field, but introduces new mechanistic theories and conditions.

3.2.3. *Retention*

Akkad et al. found that retention was also better in the tACS group compared to the sham group, with replicable results (Akkad et al., 2021). It is also reported that tACS delivered in the beta range after the acquisition stage showed improvements in performance at both 1 and 7 days post-practice (Yamaguchi et al., 2020). This finding is potentially the result of beta-band induced excitability, which is suggested to enhance retention of motor memory. The authors also note, however, that this may be the result of improved consolidation of the motor task. This is an important point, as it suggests that measurements of retention are also likely measuring a component of consolidation- since it is arguable that for a motor memory to be retained in the long-term, it must be effectively consolidated. In further support of a beta-band effect on retention, are studies that illustrate beta-tACS improved retention up to at least 7 days after acquisition (Yamaguchi et al., 2020), and furthermore that gamma-tACS improved retention 24 h after acquisition (Miyaguchi et al., 2020).

In support of the after-effect hypothesis, the study by Miyaguchi et al. did not find acquisitional differences, and only reported significant retention improvement in the tACS group, although it is important to note that Miyaguchi et al. delivered stimulus at both M1 and the cerebellum. In the previous paper mentioned by Giustiniani et al. (Giustiniani et al., 2019), it was reported that performance was disrupted by gamma-tACS delivered over M1. The authors attribute this trend to an impairment of retrieval of the learned SRT sequence. In another study, Giustiniani et al. delivered gamma-tACS instead to the cerebellum, and indeed a similar interference effect was seen, however as the authors note, in acquisition of the sequence, and not in retrieval (Giustiniani et al., 2021). The authors note that these findings are consistent with others that find that tDCS studies show contributions to acquisition by the cerebellum, and retention by the M1.

It is noted that the tACS mechanism underlying this retention improvement is likely related to oscillatory entrainment, as it is shown that for example, gamma band activity has been shown to enhance neural network activity between varying cortical regions, and thus may improve performance (Lee et al., 2003). In the study by Yamaguchi et al., tACS was delivered over M1 alone, and the authors suggest that the effect on retention may be the result of an induced long-term potentiation resultant from beta band activity, which has been shown in animal models (Yamaguchi et al., 2020). Furthermore, in reference to the apparent inconsistency in results between the effect of gamma-tACS on retention and acquisition, there are numerous explanations presented by Giustiniani et al. (Giustiniani et al., 2021). Firstly; that by modulating Purkinje cells in the cerebellar cortex, long-term depression necessary for plasticity may have been prevented, secondly; that the endogenous rhythms of the Purkinje cells was optimal during the task, and that tACS introduced interference that resulted in deteriorated performance, and third; that components of the gamma frequency in the cerebellum were entrained, but that those components were not optimally modulated, or that the component modulated was not contributory to performance or plasticity improvement. The study also failed to find differences in corticospinal excitability, leading to the hypothesis that gamma-tACS impaired cerebellar contributions to motor learning, while unaffecting M1 excitability.

In support of stage specificity, is that many of the studies presented here often find differing effects dependent on the stage placement of stimulation. Studies report that the same stimulation delivered during acquisition elicits no changes, while during retention can improve performance. Indeed the large amount of stimulation variation, task paradigms, and potential mechanisms suggests the need for consistency where possible.

3.2.4. Conclusion

Therefore, we find that although there are what appear to be growing inconsistencies in tACS literature surrounding the effect of specific frequencies, further complicated by the variation in location of delivery, we agree with the claim that this apparent inconsistency is simply the result of high specificity. Thus, it appears beneficial to categorize tACS by the motor stage under modulation, to allow for discrete categorization of effect, and to guide hypothesizing.

3.3. Criticisms of tDCS and tACS in motor learning

There are natural criticisms that arise when using tDCS and tACS to modulate motor learning. Despite our attempt to produce clarity in the variability in results of tDCS and tACS studies, the fact remains that our efforts are guided by the present literature available to us, and as such further research is necessary to better understand the mechanisms of tDCS and tACS. The evidence presented here aims to provide sufficient basis to convince the reader that by approaching brain stimulation of motor learning with stage-specificity, that further research aiming to uncover the mechanisms underlying the effects will be more applicable and specific. Further research, however, may find that stages coalesce in mechanism, or that our staging is oversimplistic. We therefore offer these recommendations as exactly that.

Another caveat to much of the motor research being done using tDCS is that most studies indicate that the effects seen, both mechanistically and behaviourally, are the result of non-invasive stimulation of the brain itself. Recently however, research has investigated the necessary parameters needed to induce the local effects described. Research using a cadaver approach found that nearly 6 mA of current are needed to effectively manipulate brain network activity through scalp-applied electrodes, with a nearly 66% attenuated current by scalp and skull (Vöröslakos et al., 2018). This is counterintuitive, considering that many motor task studies using on-scalp electrodes, such as tDCS, typically apply current in the range of between 1 and 2 mA (Bastani and Jaberzadeh, 2012; Buch et al., 2017; Jo et al., 2009; Khedr et al., 2013; Wiltshire and Watkins, 2020). This implies that there may be more than a localized brain-stimulation effect involved when modulating activity via scalp-electrode stimulation. tACS also raises questions in its mechanism of action in the same way as tDCS, with typical delivery voltages falling below the 6 mA level mentioned (Vöröslakos et al., 2018). Of course, a valid response to the findings of that study is that delivery of electrical current to cadaver compared to live humans is likely a confounding aspect of the research. This is valid criticism; however, it also does not rule out the possibility that peripheral nerves play a role. This therefore leads us to ponder how stimulation directed toward central regions, may actually or additionally act by peripheral mechanisms, and additionally to what extent this mechanism may be prevalent in the studies previously mentioned here, in both tDCS, and tACS.

4. Peripheral nerve stimulation and motor learning

Despite the large collection of studies and numerous proposed mechanisms, there is still a relatively low understanding of the exact mechanism by which tDCS and tACS function. This concern is highlighted by recent studies whereby it is discussed that typical current strengths applied to the scalp do not appear to maintain a significant current for neural entrainment after attenuation by tissues (Asamoah et al., 2019; Vöröslakos et al., 2018). Work by Huang and colleagues also offers an in vivo observation of electrical stimulation effects on the brain, finding similar attenuation of current to below physiologically significant levels for certain neural effects (Huang et al., 2017). There is a suggested solution to this so-called paradox occurring in the literature. Instead of being stimulated directly through the scalp, the observed neural entrainment by tACS (Asamoah et al., 2019) and activation by tDCS (van Boekholdt et al., 2021) may indeed either be partially or entirely accountable to the stimulation of peripheral nerves, which form ascending connections to the brain. The more recent suggestion that many of the effects seen in both tDCS and tACS studies may in fact be peripherally modulated is becoming more understood as researchers begin to test the effects of peripheral nerve stimulation on previously direct-stimulation effects. Up to now, disciplines such as memory (Luckey et al., 2022b), motor system modulation (Asamoah et al., 2019), tinnitus treatment (De Ridder et al., 2014), plasticity and reorganization (Hulsey et al., 2016a, 2016b; Loerwald et al., 2018), and stroke recovery (Dawson et al., 2016) have been reproduced with peripheral approaches instead of direct stimulation. To improve concision and understanding, we put forth alternative definitions for peripheral stimulation, such that tDCS and tACS delivered peripherally will be referred to in relation to the nerve under stimulation (e.g., Vagus nerve stimulation (VNS), Occipital nerve stimulation (ONS)). One such acronym that will be used in this section is Non-Invasive Transcutaneous Electrical Stimulation of the Greater Occipital Nerve (NITESGON), an approach which is currently under active investigation at the time this article is being written (Adcock et al., 2022; Luckey et al., 2022a). NITESGON involves the use of a typical tACS set-up, however with placement of the electrodes over greater occipital nerve. This arrangement has also been validated during an experiment in which a topical anaesthetic was used to block the transcutaneous mechanism (and verify NITESGON elicits its effect via peripheral effect and not transcranially). Indeed it was found that blocking the peripheral mechanism using lidocaine altered memory task performance compared to stimulation without lidocaine, providing evidence that NITESGON is effectively acting peripherally and not eliciting its effects transcranially (Vanneste et al., 2020).

To test the validity of the hypothesis that peripheral nerve stimulation is an potential contributor for the tDCS/tACS effects seen in motor learning, we turn toward the results presented in a paper by Asamoah et al. (Asamoah et al., 2019). Their findings used an encompassing approach to determine if tACS can induce effects by acting peripherally. They found that entrainment of the rat motor cortex was possible via peripheral stimulation, and in order to confirm this, used topical anaesthetic to block peripheral delivery when delivering tACS. In this instance, resulting in reduced entrainment suggesting that tACS indeed had peripheral influence in rats. The next step was to test the same finding in humans, and the results were consistent in that tACS peripherally delivered appears to be, at least a component, of the driving mechanism behind the motor cortex entrainment.

The next question is therefore *how* does stimulation delivered peripherally account for at least a partial contribution to the modulation of the brain during motor task learning? We offer here some possible mechanisms by which peripheral delivery of stimulus may modulate neural activity in motor task learning. We also delve into how these mechanisms and the concatenation of the mechanisms in this article may function cooperatively to holistically explain the findings of numerous research articles.

In direct comparison of transcranial to transcutaneous current delivery mechanisms, we first consider the biological and tissue differences. Transcranial delivery involves current that is passing through layers of skin, skull, cerebrospinal fluid (CSF), and altering activity either via oscillatory entrainment or polarity of the cortical neurons, or perhaps even deeper as is put forth by (Louviot et al., 2022). Transcutaneous stimulation, in name, does not involve current passing current through CSF or skull (which leads to current attenuation) (van Boekholdt et al., 2021). It is believed that the greater occipital and trigeminal nerve can be stimulated via peripheral stimulation, and these nerves then may functionally modulate activity in the nucleus of the solitary tract (NTS) and trigeminal nuclei (TN) (Adair et al., 2020; van Boekholdt et al., 2021). The TN is a component of the trigeminocervical complex (TCC), and has ascending connections through the quintothalamic tract, to the thalamus which further relays to the cortex, suggesting a possible motor cortex modulatory pathway for peripheral stimulation (Akerman et al., 2011). It has also been shown that the NTS has projections to the locus coeruleus (LC) (van Boekholdt et al., 2021).

This is a relevant point, as the LC is accountable for the release of norepinephrine and thus subsequent cortical excitability, of which tDCS has been implicated (increases of NE) (Kuo et al., 2017b). This however, is yet unexplainable with sound mechanistic support (van Boekholdt et al., 2021). When using VNS for treatment of epilepsy, the LC is considered to be a component of the mechanism behind the central effects (Krahl and Clark, 2012). More direct evidence has also been demonstrated, in a recent paper by Liebe and colleagues (Liebe et al., 2022), which found indeed that among numerous LC functional and anatomical connections, that the LC has a positive functional connectivity with the motor cortex, specifically parcellation 6ma, which posits further evidence for LC-driven connectivity being a feasible mechanism for NITESGON and other peripheral nerve stimulation (e.g., VNS). Using VNS in rats, a study by Hulsey and others showed that simulation induces intensity-specific activity of LC neurons (Hulsey et al., 2017). Agreeing further with the proposed pathways of activation. The same study (Hulsey et al., 2017) found that trigeminal nuclei neurons were also activated, and phase locked, to the VNS delivered. Indeed it has been shown that the occipital nerves (ON) exhibit function connection to neurons in the TCC, and furthermore that NMDA receptor antagonization reduced the responses in the TCC (García-Magro et al., 2020). This provides more context for the involvement on NMDA receptors in peripheral nerve stimulation and draws comparisons in the mechanisms of central and peripheral stimulation.

Further VNS investigations using rats have also revealed likely neurotransmitters involved in neural modulation via peripheral stimulation. In a report by Hulsey and colleagues (Hulsey et al., 2019), the hypothesis that norepinephrine (NE) and serotonin (5-HT) are involved in motor cortex plasticity changes with VNS was investigated. It was determined that VNS induced motor cortex plasticity changes however only with the presence of either NE or 5-HT. In another study (Hulsey et al., 2016a, 2016b), it was also determined that cholinergic projections are essential in inducing VNS-motor cortex reorganization. These studies create strong evidence that NE, 5-HT, and cholinergic projections are involved in the mechanism for VNS-induced motor plasticity. Since VNS and ONS have similar functional connectivity, it may be plausible that similar neurotransmitters may be implicated. This is particularly relevant, as the same findings of serotonin (Nitsche et al., 2009), NE (Adelhöfer et al., 2019), and cholinergic system (Oh et al., 2022) effects have been presented in tDCS and tACS studies.

The review by van Boekholdt et al. also draws attention to the similarity between cortical and peripheral anatomical similarities that posit cortical anodal and cathodal differences are persistent in peripheral nerve stimulation (van Boekholdt et al., 2021). This produces further explanation for the polarity-specific effects seen in previously discussed studies (Bastani and Jaberzadeh, 2012; Brunoni et al., 2012; Sasaki et al., 2016). To organize and strongly recommend the idea that tDCS/tACS may act peripherally instead of/as well as centrally, the effects and mechanisms proposed in tDCS and tACS must have a parsimonious explanation in their peripheral mechanism (Fig. 5). It has been accounted for in this article that polarity-specific effects shown in studies can be accounted for in peripheral nerve stimulation, and that commonplace neurotransmitter effects such as 5-HT and NE have presence in both central and peripheral stimulation. However, other observed correlates of CS such as GABA/Glutamate alteration, oscillatory entrainment, frequency-specificity, and delivery-location effects require peripheral equivalents. Research using VNS for epileptic patients has found that GABA receptor density (GRD) decreased after VNS, subsequently resulting in a reduction in seizure frequency, compared to an unchanged frequency and GRD distribution in the control, unstimulated, group (Marrosu et al., 2003). Memory improvements in both rats and humans as the result of VNS are attributed to processes involving the excitation of the hippocampus and associated neural networks; specifically with the presence of theta rhythm (Boyce et al., 2016; Ura et al., 2013). Research by (Broncel et al., 2019) has shown that GABAergic receptors are instrumental in producing theta rhythm, while in cooperation with cholinergic systems, and that VNS stimulation results in modulation of GABAergic processes, and as such produces a possible candidate mechanism that further implicates peripheral nerve stimulation on GABA-related processes. We return to the study by Asamoah and colleagues (Asamoah et al., 2019) to compare oscillatory entrainment in peripheral vs central stimulation delivery. In their paper, they show that transcutaneous nerve stimulation resulted in entrained beta activity as recorded via electroencephalographic recording (EEG), although the exact mechanism by which peripheral tACS elicits this entrainment was not explicitly discussed. This is suggestive that oscillatory entrainment has been shown to occur via peripheral stimulation, supporting the contributions of a peripheral mechanism.

The last aspect of the stimulation mechanism which persists the possibility that tACS and tDCS may have some central/direct delivery component, is location specificity. Motor studies using brain stimulation to modulate motor learning typically deliver stimulus at the M1 region,

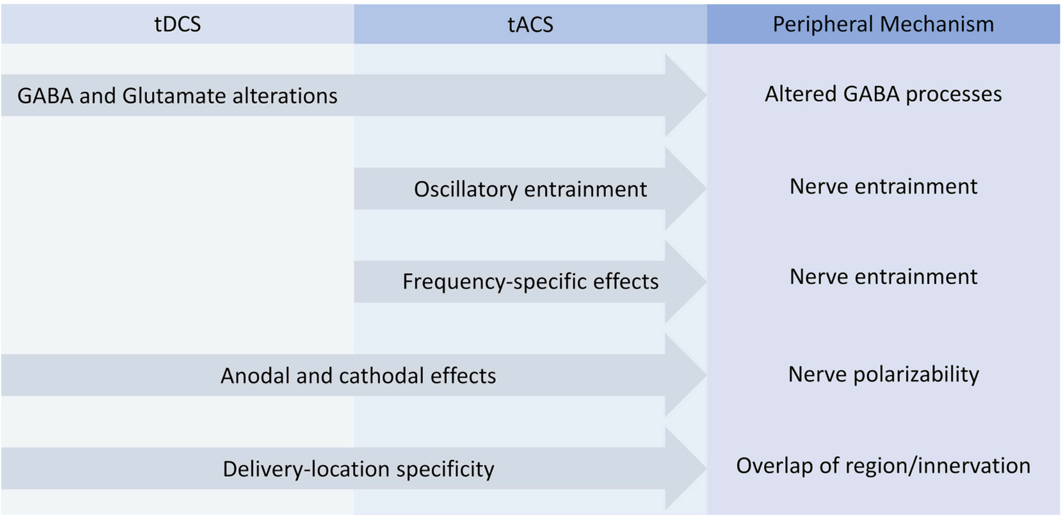


Fig. 5. TDCS and tACS mechanisms and corresponding peripheral explanations. An illustration that shows how each mechanism for either tDCS or tACS has a plausible peripheral mechanism which may produce a similar result. For tDCS, GABA and Glutamate alterations exist in peripheral GABA processes. In tACS, oscillatory and frequency-related effects have been shown to result from nerve entrainment. For both tDCS and tACS, anodal and cathodal difference and location-specific activation may be explained or supported by nerve polarizability and regional innervation of peripheral nerves.

although as mentioned, there are numerous other targets which are sometimes chosen. This raises the question of whether innervation of the scalp correctly correlates with the locations chosen in motor studies, such that peripheral nerve stimulation is still a viable mechanism? It appears that nerves such as the ON do indeed innervate the scalp as far as the vertex, which would corroborate the possibility that M1 stimulation does indeed stimulate the ON, while stimulating the cortical region directly (Yu and Wang, 2021). Further possibility is that cerebellar tDCS or tACS is also spatially similar to ONS study placement, creating the possibility that peripheral nerve stimulation is an additional contributor to the effects.

A study that investigated the central effects of occipital nerve (ON) stimulation using functional magnetic resonance imaging (fMRI) provides more evidence for this claim, showing that ONS both increased and decreased activity various areas of the brain, with decreased activity in the auditory cortex, visual cortex, somatosensory cortex, and amygdala, and increased activity in the thalamus, frontal, parietal, and cerebellar regions (Kovacs et al., 2011; Naro et al., 2017). As mentioned, the analysis in an article by Kovacs and colleagues suggested frequency dependency effects during nerve stimulation, which mirrors the frequency specificity cited in tACS studies mentioned earlier in this paper (Kovacs et al., 2011).

5. Future directions and criticisms

It is presented here that peripheral nerve stimulation causes widespread-activation, with frequency and location dependency, reflecting polarity-sensitivity, and with preliminary evidence of neurochemical similarities between central and peripheral delivery. There then appears a growing body of evidence to suggest that many studies using tDCS and tACS for delivery of central stimulation during motor task learning modulation, may be acting by an unconsidered and understudied mechanism. We therefore suggest that as research continues to further the understanding of the mechanisms of tDCS and tACS in motor modulation that there be careful consideration for the possibility of peripheral stimulatory effects and mechanisms of action, and indeed consideration for the motor learning stage and parameters which are chosen. It is additionally worth noting that much of the literature on peripheral nerve stimulation cited in this section was provided in the scope of epilepsy, migraine, tinnitus, and motor studies in animals. It may be considered that future research aims to fill gaps that obscure key understanding of how both central and peripheral nerve stimulation work. We highlight some key points here in order to support researchers in identifying where research can be directed.

1) Necessity to further investigate the mechanism of action of peripheral and central nerve stimulation including the vagus, occipital, and trigeminal nerves, and a suggestion for researchers to investigate the distinction of transcranial from transcutaneous stimulation via methodologies such as those presented in (Asamoah et al., 2019).
2) The need to clearly outline target motor learning stage, and outcome in a stage-specific manner, such that mechanisms, interpretations, and reproducibility are streamlined and operationalized.
3) Consideration for motor task used, electrode placement, and duration when reproducing or comparing studies, in order to reduce the apparent inconsistency in the field, and to allow for relevant comparisons to be made between findings.

6. Conclusion

We present here a brief overview of motor task learning, the stages of motor learning, common experimental approaches, and key features and anatomy of motor learning. With this background, we further explored the use of tDCS and tACS for manipulating motor task learning, including a specific focus on the stage of delivery, and the outcomes of numerous studies. The results of the studies and their findings led to an additionally, underlying mechanism of motor task modulation; that peripheral nerve stimulation may be acting to functionally modulate the motor cortices. We presented further evidence for this possibility, including accounting for central mechanisms in the peripheral domain and preliminary data showing effectiveness of peripheral nerve stimulation. We conclude with recommendations for additional consideration for a peripheral mechanism. It is our aim in this review to provide an overview of motor task modulation by stage, via tDCS and tACS – and in the hopes that future research may be able to refine approaches with greater specificity and context.

Data availability

No data was used for the research described in the article.

References

Adair, D., Truong, D., Esmaeilpour, Z., Gebodh, N., Borges, H., Ho, L., Bremner, J.D., Badran, B.W., Napadow, V., Clark, V.P., 2020. Electrical stimulation of cranial nerves in cognition and disease. Brain Stimul. 13 (3), 717–750.

Adcock, K.S., Lawlor, B., Robertson, I.H., Vanneste, S., 2022. Diminishing accelerated long-term forgetting in mild cognitive impairment: study protocol for a prospective, double-blind, placebo-controlled, randomized controlled trial. Contemp. Clin. Trials Commun. 30, 100989 https://doi.org/10.1016/j.conctc.2022.100989.

Adelhöfer, N., Mückschel, M., Teufert, B., Ziemssen, T., Beste, C., 2019. Anodal tDCS affects neuromodulatory effects of the norepinephrine system on superior frontal theta activity during response inhibition. Brain Struct. Funct. 224 (3), 1291–1300.

Akerman, S., Holland, P.R., Goadsby, P.J., 2011. Diencephalic and brainstem mechanisms in migraine. Nat. Rev. Neurosci. 12 (10), 570–584.

Akkad, H., Dupont-Hadwen, J., Kane, E., Evans, C., Barrett, L., Frese, A., Tetkovic, I., Bestmann, S., Stagg, C.J., 2021. Increasing human motor skill acquisition by driving theta–gamma coupling. eLife 10, e67355.

Amadi, U., Allman, C., Johansen-Berg, H., Stagg, C.J., 2015. The homeostatic interaction between anodal transcranial direct current stimulation and motor learning in humans is related to GABAA activity. Brain Stimul. 8 (5), 898–905. https://doi.org/10.1016/j.brs.2015.04.010.

Antal, A., Paulus, W., 2013. Transcranial alternating current stimulation (tACS) [review]. Front. Hum. Neurosci. 7 https://doi.org/10.3389/fnhum.2013.00317.

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., Paulus, W., 2008. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 1 (2), 97–105.

Asamoah, B., Khatoun, A., Mc Laughlin, M., 2019. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat. Commun. 10.

Bachtiar, V., Near, J., Johansen-Berg, H., Stagg, C.J., 2015. Modulation of GABA and resting state functional connectivity by transcranial direct current stimulation. eLife 4, e08789. https://doi.org/10.7554/eLife.08789.

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. Clin. Neurophysiol. 123 (4), 644–657. https://doi.org/10.1016/j.clinph.2011.08.029.

van Boekholdt, L., Kerstens, S., Khatoun, A., Asamoah, B., Mc Laughlin, M., 2021. tDCS peripheral nerve stimulation: a neglected mode of action? Mol. Psychiatry 26 (2), 456–461.

Bologna, M., Guerra, A., Paparella, G., Colella, D., Borrelli, A., Suppa, A., Di Lazzaro, V., Brown, P., Berardelli, A., 2019. Transcranial alternating current stimulation has frequency-dependent effects on motor learning in healthy humans. Neuroscience 411, 130–139. https://doi.org/10.1016/j.neuroscience.2019.05.041.

Boyce, R., Glasgow, S.D., Williams, S., Adamantidis, A., 2016. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 352 (6287), 812–816. https://doi.org/10.1126/science.aad5252.

Bramham, C.R., Messaoudi, E., 2005. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog. Neurobiol. 76 (2), 99–125. https://doi.org/10.1016/j.pneurobio.2005.06.003.

Broncel, A., Bocian, R., Kłos-Wojtczak, P., Konopacki, J., 2019. GABAergic mediation of hippocampal theta rhythm induced by stimulation of the vagal nerve. Brain Res. Bull. 147, 110–123. https://doi.org/10.1016/j.brainresbull.2019.02.010.

Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D.J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., Fregni, F., 2012. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 5 (3), 175–195. https://doi.org/10.1016/j.brs.2011.03.002.

Buch, E.R., Santarnecchi, E., Antal, A., Born, J., Celnik, P.A., Classen, J., Gerloff, C., Hallett, M., Hummel, F.C., Nitsche, M.A., Pascual-Leone, A., Paulus, W.J., Reis, J., Robertson, E.M., Rothwell, J.C., Sandrini, M., Schambra, H.M., Wassermann, E.M., Ziemann, U., Cohen, L.G., 2017. Effects of tDCS on motor learning and memory formation: a consensus and critical position paper. Clin. Neurophysiol. 128 (4), 589–603. https://doi.org/10.1016/j.clinph.2017.01.004.

Buchanan, D.M., Robaey, P., D'Angiulli, A., 2020. What do we know about transcranial direct current stimulation for major depression? Brain Sci. 10 (8), 480. https://www.mdpi.com/2076-3425/10/8/480.

Buchanan, D.M., D'Angiulli, A., Samson, A., Maisonneuve, A.R., Robaey, P., 2022. Acceptability of transcranial direct current stimulation in children and adolescents with ADHD: the point of view of parents. J. Health Psychol. 27 (1), 36–46. https://doi.org/10.1177/1359105320937059.

Christova, M., Rafolt, D., Gallasch, E., 2015. Cumulative effects of anodal and priming cathodal tDCS on pegboard test performance and motor cortical excitability. Behav. Brain Res. 287, 27–33. https://doi.org/10.1016/j.bbr.2015.03.028.

Ciechanski, P., Kirton, A., 2017. Transcranial direct-current stimulation can enhance motor learning in children. Cereb. Cortex 27 (5), 2758–2767. https://doi.org/10.1093/cercor/bhw114.

Dahms, C., Brodoehl, S., Witte, O.W., Klingner, C.M., 2020. The importance of different learning stages for motor sequence learning after stroke. Hum. Brain Mapp. 41 (1), 270–286. https://doi.org/10.1002/hbm.24793.

Dawson, J., Pierce, D., Dixit, A., Kimberley, T.J., Robertson, M., Tarver, B., Hilmi, O., McLean, J., Forbes, K., Kilgard, M.P., Rennaker, R.L., Cramer, S.C., Walters, M., Engineer, N., 2016. Safety, feasibility, and efficacy of Vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. Stroke 47 (1), 143–150. https://doi.org/10.1161/STROKEAHA.115.010477.

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

De Ridder, D., Vanneste, S., Engineer, N.D., Kilgard, M.P., 2014. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation 17 (2), 170–179. https://doi.org/10.1111/ner.12127.

Doyon, J., Benali, H., 2005. Reorganization and plasticity in the adult brain during learning of motor skills. Curr. Opin. Neurobiol. 15 (2), 161–167.

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

Feurra, M., Pasqualetti, P., Bianco, G., Santarnecchi, E., Rossi, A., Rossi, S., 2013. State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters. J. Neurosci. 33 (44), 17483–17489.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H.M., Ji, Y., Cohen, L.G., Lu, B., 2010. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 66 (2), 198–204.

Fujiyama, H., Hinder, M.R., Barzideh, A., Van de Vijver, C., Badache, A.C., Manrique-C, M.N., Reissig, P., Zhang, X., Levin, O., Summers, J.J., Swinnen, S.P., 2017. Preconditioning tDCS facilitates subsequent tDCS effect on skill acquisition in older adults. Neurobiol. Aging 51, 31–42. https://doi.org/10.1016/j.neurobiolaging.2016.11.012.

García-Magro, N., Negredo, P., Martin, Y.B., Nuñez, Á., Avendaño, C., 2020. Modulation of mechanosensory vibrissal responses in the trigeminocervical complex by stimulation of the greater occipital nerve in a rat model of trigeminal neuropathic pain. J. Headache Pain 21 (1), 96. https://doi.org/10.1186/s10194-020-01161-y.

Giustiniani, A., Tarantino, V., Bonaventura, R.E., Smirni, D., Turriziani, P., Oliveri, M., 2019. Effects of low-gamma tACS on primary motor cortex in implicit motor learning. Behav. Brain Res. 376, 112170 https://doi.org/10.1016/j.bbr.2019.112170.

Giustiniani, A., Tarantino, V., Bracco, M., Bonaventura, R.E., Oliveri, M., 2021. Functional role of cerebellar gamma frequency in motor sequences learning: a tACS study. Cerebellum 20 (6), 913–921. https://doi.org/10.1007/s12311-021-01255-6.

Goodwill, A.M., Teo, W.-P., Morgan, P., Daly, R.M., Kidgell, D.J., 2016. Bihemispheric-tDCS and upper limb rehabilitation improves retention of motor function in chronic stroke: a pilot study [original research]. Front. Hum. Neurosci. 10 https://doi.org/10.3389/fnhum.2016.00258.

Hamano, Y.H., Sugawara, S.K., Fukunaga, M., Sadato, N., 2021. The integrative role of the M1 in motor sequence learning. Neurosci. Lett. 760, 136081 https://doi.org/10.1016/j.neulet.2021.136081.

Helfrich, Randolph F., Schneider, Till R., Rach, S., Trautmann-Lengsfeld, Sina A., Engel, Andreas K., Herrmann, Christoph S., 2014. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr. Biol. 24 (3), 333–339. https://doi.org/10.1016/j.cub.2013.12.041.

Herrmann, C., Rach, S., Neuling, T., Strüber, D., 2013. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes [review]. Front. Hum. Neurosci. 7 https://doi.org/10.3389/fnhum.2013.00279.

Horiba, M., Ueki, Y., Nojima, I., Shimizu, Y., Sahashi, K., Itamoto, S., Suzuki, A., Yamada, G., Matsukawa, N., Wada, I., 2019. Impaired motor skill acquisition using mirror visual feedback improved by transcranial direct current stimulation (tDCS) in patients with Parkinson's disease. Front. Neurosci. 13, 602.

Huang, Y., Liu, A.A., Lafon, B., Friedman, D., Dayan, M., Wang, X., Bikson, M., Doyle, W. K., Devinsky, O., Parra, L.C., 2017. Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. eLife 6, e18834. https://doi.org/10.7554/eLife.18834.

Hulsey, D.R., Hays, S.A., Khodaparast, N., Ruiz, A., Das, P., Rennaker II, R.L., Kilgard, M. P., 2016a. Reorganization of motor cortex by vagus nerve stimulation requires cholinergic innervation. Brain Stimul. 9 (2), 174–181.

Hulsey, D.R., Hays, S.A., Khodaparast, N., Ruiz, A., Das, P., Rennaker, R.L., Kilgard, M.P., 2016b. Reorganization of motor cortex by vagus nerve stimulation requires cholinergic innervation. Brain Stimul. 9 (2), 174–181. https://doi.org/10.1016/j.brs.2015.12.007.

Hulsey, D.R., Riley, J.R., Loerwald, K.W., Rennaker, R.L., Kilgard, M.P., Hays, S.A., 2017. Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. Exp. Neurol. 289, 21–30. https://doi.org/10.1016/j.expneurol.2016.12.005.

Hulsey, D.R., Shedd, C.M., Sarker, S.F., Kilgard, M.P., Hays, S.A., 2019. Norepinephrine and serotonin are required for vagus nerve stimulation directed cortical plasticity. Exp. Neurol. 320, 112975 https://doi.org/10.1016/j.expneurol.2019.112975.

Jacobson, L., Koslowsky, M., Lavidor, M., 2012. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp. Brain Res. 216 (1), 1–10.

Jo, J.M., Kim, Y.-H., Ko, M.-H., Ohn, S.H., Joen, B., Lee, K.H., 2009. Enhancing the working memory of stroke patients using tDCS. Am. J. Phys. Med. Rehabil. 88 (5), 404–409.

Kal, E., Prosée, R., Winters, M., van der Kamp, J., 2018. Does implicit motor learning lead to greater automatization of motor skills compared to explicit motor learning? A systematic review. PLoS One 13 (9), e0203591. https://doi.org/10.1371/journal.pone.0203591.

Khedr, E.M., Shawky, O.A., El-Hammady, D.H., Rothwell, J.C., Darwish, E.S., Mostafa, O. M., Tohamy, A.M., 2013. Effect of anodal versus cathodal transcranial direct current stimulation on stroke rehabilitation: a pilot randomized controlled trial. Neurorehabil. Neural Repair 27 (7), 592–601.

Kleynen, M., Braun, S.M., Bleijlevens, M.H., Lexis, M.A., Rasquin, S.M., Halfens, J., Wilson, M.R., Beurskens, A.J., Masters, R.S.W., 2014. Using a Delphi technique to seek consensus regarding definitions, descriptions and classification of terms related to implicit and explicit forms of motor learning. PLoS One 9 (6), e100227. https://doi.org/10.1371/journal.pone.0100227.

Kleynen, M., Braun, S.M., Rasquin, S.M.C., Bleijlevens, M.H.C., Lexis, M.A.S., Halfens, J., Wilson, M.R., Masters, R.S.W., Beurskens, A.J., 2015. Multidisciplinary views on applying explicit and implicit motor learning in practice: an international survey. PLoS One 10 (8), e0135522. https://doi.org/10.1371/journal.pone.0135522.

Kovacs, S., Peeters, R., De Ridder, D., Plazier, M., Menovsky, T., Sunaert, S., 2011. Central effects of occipital nerve electrical stimulation studied by functional magnetic resonance imaging. Neuromodulation 14 (1), 46–57. https://doi.org/10.1111/j.1525-1403.2010.00312.x.

Koyama, S., Tanaka, S., Tanabe, S., Sadato, N., 2015. Dual-hemisphere transcranial direct current stimulation over primary motor cortex enhances consolidation of a ballistic thumb movement. Neurosci. Lett. 588, 49–53. https://doi.org/10.1016/j.neulet.2014.11.043.

Krahl, S.E., Clark, K.B., 2012. Vagus nerve stimulation for epilepsy: a review of central mechanisms. Surg. Neurol. Int. 3 (Suppl. 4), S255–S259. https://doi.org/10.4103/2152-7806.103015.

Krakauer, J.W., Hadjiosif, A.M., Xu, J., Wong, A.L., Haith, A.M., 2019. Motor learning. Compr. Physiol. 9 (2), 613–663.

Krause, V., Meier, A., Dinkelbach, L., Pollok, B., 2016. Beta band transcranial alternating (tACS) and direct current stimulation (tDCS) applied after initial learning facilitate retrieval of a motor sequence. Front. Behav. Neurosci. 10, 4.

Kuntz, T., Sturm, A.P., Krause, V., Pollok, B., Keitel, A., 2016. EP 129. The effect of tDCS over M1 prior to and during implicit motor sequence learning. Clin. Neurophysiol. 127 (9), e295 https://doi.org/10.1016/j.clinph.2016.05.170.

Kuo, M.-F., Chen, P.-S., Nitsche, M.A., 2017a. The application of tDCS for the treatment of psychiatric diseases. Int. Rev. Psychiatry 29 (2), 146–167.

Kuo, H.I., Paulus, W., Batsikadze, G., Jamil, A., Kuo, M.F., Nitsche, M.A., 2017b. Acute and chronic effects of noradrenergic enhancement on transcranial direct current stimulation-induced neuroplasticity in humans. J. Physiol. 595 (4), 1305–1314.

Lang, N., Nitsche, M.A., Sommer, M., Tergau, F., Paulus, W., 2003. Chapter 28 modulation of motor consolidation by external DC stimulation. In: Paulus, W., Tergau, F., Nitsche, M.A., Rothwell, J.G., Ziemann, U., Hallett, M. (Eds.), Supplements to Clinical Neurophysiology, vol. 56. Elsevier, pp. 277–281. https://doi.org/10.1016/S1567-424X(09)70231-4.

Lang, N., Nitsche, M., Paulus, W., Rothwell, J., Lemon, R., 2004. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp. Brain Res. 156 (4), 439–443.

Lee, K.-H., Williams, L.M., Breakspear, M., Gordon, E., 2003. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. Brain Res. Rev. 41 (1), 57–78.

Lefaucheur, J.-P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M.A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Paulus, W., 2017. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin. Neurophysiol. 128 (1), 56–92. https://doi.org/10.1016/j.clinph.2016.10.087.

Lefebvre, S., Dricot, L., Gradkowski, W., Laloux, P., Vandermeeren, Y., 2012. Brain activations underlying different patterns of performance improvement during early motor skill learning. NeuroImage 62 (1), 290–299. https://doi.org/10.1016/j.neuroimage.2012.04.052.

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 [clinical trial]. Front. Hum. Neurosci. 6 https://doi.org/10.3389/fnhum.2012.00343.

Li Voti, P., Conte, A., Suppa, A., Iezzi, E., Bologna, M., Aniello, M.S., Defazio, G., Rothwell, J.C., Berardelli, A., 2011. Correlation between cortical plasticity, motor learning and BDNF genotype in healthy subjects. Exp. Brain Res. 212 (1), 91–99. https://doi.org/10.1007/s00221-011-2700-5.

Liebe, T., Kaufmann, J., Hämmerer, D., Betts, M., Walter, M., 2022. In vivo tractography of human locus coeruleus—relation to 7T resting state fMRI, psychological measures and single subject validity. Mol. Psychiatry 1–10.

Loerwald, K.W., Buell, E.P., Borland, M.S., Rennaker, R.L., Hays, S.A., Kilgard, M.P., 2018. Varying stimulation parameters to improve cortical plasticity generated by VNS-tone pairing. Neuroscience 388, 239–247. https://doi.org/10.1016/j.neuroscience.2018.07.038.

Louviot, S., Tyvaert, L., Maillard, L.G., Colnat-Coulbois, S., Dmochowski, J., Koessler, L., 2022. Transcranial electrical stimulation generates electric fields in deep human brain structures. Brain Stimul. 15 (1), 1–12. https://doi.org/10.1016/j.brs.2021.11.001.

Luckey, A.M., McLeod, S.L., Huang, Y., Mohan, A., Vanneste, S., 2022a. Making memories last: The peripheral effect of direct current stimulation on strengthening memories. bioRxiv. https://doi.org/10.1101/2022.07.06.498966, 2022.2007.2006.498966.

Luckey, A.M., McLeod, S.L., Mohan, A., Vanneste, S., 2022b. Potential role for peripheral nerve stimulation on learning and long-term memory: a comparison of alternating and direct current stimulations. Brain Stimul. 15 (3), 536–545. https://doi.org/10.1016/j.brs.2022.03.001.

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

Marrosu, F., Serra, A., Maleci, A., Puligheddu, M., Biggio, G., Piga, M., 2003. Correlation between GABAA receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. Epilepsy Res. 55 (1), 59–70. https://doi.org/10.1016/S0920-1211(03)00107-4.

McHughen, S.A., Rodriguez, P.F., Kleim, J.A., Kleim, E.D., Crespo, L.M., Procaccio, V., Cramer, S.C., 2009. BDNF Val66Met polymorphism influences motor system function in the human brain. Cereb. Cortex 20 (5), 1254–1262. https://doi.org/10.1093/cercor/bhp189.

Meehan, S.K., Randhawa, B., Wessel, B., Boyd, L.A., 2011. Implicit sequence-specific motor learning after subcortical stroke is associated with increased prefrontal brain activations: an fMRI study. Hum. Brain Mapp. 32 (2), 290–303. https://doi.org/10.1002/hbm.21019.

Miyaguchi, S., Inukai, Y., Matsumoto, Y., Miyashita, M., Takahashi, R., Otsuru, N., Onishi, H., 2020. Effects on motor learning of transcranial alternating current stimulation applied over the primary motor cortex and cerebellar hemisphere. J. Clin. Neurosci. 78, 296–300. https://doi.org/10.1016/j.jocn.2020.05.024.

Miyaguchi, S., Inukai, Y., Mitsumoto, S., Otsuru, N., Onishi, H., 2022. Gamma-transcranial alternating current stimulation on the cerebellum and supplementary motor area improves bimanual motor skill. Behav. Brain Res. 424, 113805 https://doi.org/10.1016/j.bbr.2022.113805.

Naro, A., Bramanti, A., Leo, A., Manuli, A., Sciarrone, F., Russo, M., Bramanti, P., Calabrò, R.S., 2017. Effects of cerebellar transcranial alternating current stimulation on motor cortex excitability and motor function. Brain Struct. Funct. 222 (6), 2891–2906.

Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527 (Pt 3), 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.

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. J. Cogn. Neurosci. 15 (4), 619–626.

Nitsche, M.A., Kuo, M.-F., Karrasch, R., Wächter, B., Liebetanz, D., Paulus, W., 2009. Serotonin affects transcranial direct current–induced neuroplasticity in humans. Biol. Psychiatry 66 (5), 503–508.

Nowak, M., Hinson, E., Van Ede, F., Pogosyan, A., Guerra, A., Quinn, A., Brown, P., Stagg, C.J., 2017. Driving human motor cortical oscillations leads to behaviorally relevant changes in local GABAA inhibition: a tACS-TMS study. J. Neurosci. 37 (17), 4481–4492.

Oh, E., Park, J., Youn, J., Jang, W., 2022. Anodal transcranial direct current stimulation could modulate cortical excitability and the central cholinergic system in Akinetic rigid-type Parkinson's disease: pilot study. Front. Neurol. 13.

Patel, H.J., Romanzetti, S., Pellicano, A., Reetz, K., Binkofski, F., 2018. PB11. Long term GABA alterations induced by anodal transcranial direct current stimulation (tDCS) in motor cortex: a proton magnetic resonance spectroscopy study. Clin. Neurophysiol. 129 (8), e59–e60. https://doi.org/10.1016/j.clinph.2018.04.636.

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

Pollok, B., Latz, D., Krause, V., Butz, M., Schnitzler, A., 2014. Changes of motor-cortical oscillations associated with motor learning. Neuroscience 275, 47–53.

Pollok, B., Boysen, A., Krause, V., 2015. The effect of transcranial alternating current stimulation (tACS) at alpha and beta frequency on motor learning. Behav. Brain Res. 293, 234–240.

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C., Bikson, M., 2013. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J. Physiol. 591 (10), 2563–2578.

Reis, J., Fritsch, B., 2011. Modulation of motor performance and motor learning by transcranial direct current stimulation. Curr. Opin. Neurol. 24 (6), 590–596.

Rieth, C.A., Cai, D.J., McDevitt, E.A., Mednick, S.C., 2010. The role of sleep and practice in implicit and explicit motor learning. Behav. Brain Res. 214 (2), 470–474. https://doi.org/10.1016/j.bbr.2010.05.052.

Roche, N., Geiger, M., Bussel, B., 2015. Mechanisms underlying transcranial direct current stimulation in rehabilitation. Ann. Phys. Rehabil. Med. 58 (4), 214–219.

Roshchupkina, L., Stee, W., Peigneux, P., 2020. Beta-tACS does not impact the dynamics of motor memory consolidation. Brain Stimul. 13 (6), 1489–1490.

Rumpf, J.-J., Barbu, A., Fricke, C., Wegscheider, M., Classen, J., 2019. Posttraining alpha transcranial alternating current stimulation impairs motor consolidation in elderly people. Neural Plasticity 2019.

Samaei, A., Ehsani, F., Zoghi, M., Hafez Yosephi, M., Jaberzadeh, S., 2017. Online and offline effects of cerebellar transcranial direct current stimulation on motor learning in healthy older adults: a randomized double-blind sham-controlled study. Eur. J. Neurosci. 45 (9), 1177–1185. https://doi.org/10.1111/ejn.13559.

Sasaki, R., Miyaguchi, S., Kotan, S., Kojima, S., Kirimoto, H., Onishi, H., 2016. Modulation of cortical inhibitory circuits after cathodal transcranial direct current stimulation over the primary motor cortex. Front. Hum. Neurosci. 10, 30.

Spampinato, D.A., Satar, Z., Rothwell, J.C., 2019. Combining reward and M1 transcranial direct current stimulation enhances the retention of newly learnt sensorimotor mappings. Brain Stimul. 12 (5), 1205–1212.

Stagg, C.J., Best, J.G., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kincses, Z.T., Morris, P.G., Matthews, P.M., Johansen-Berg, H., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J. Neurosci. 29 (16), 5202–5206. https://doi.org/10.1523/jneurosci.4432-08.2009.

Stagg, C.J., Bachtiar, V., Johansen-Berg, H., 2011. The role of GABA in human motor learning. Curr. Biol. 21 (6), 480–484. https://doi.org/10.1016/j.cub.2011.01.069.

Struber, L., Baumont, M., Barraud, P.-A., Nougier, V., Cignetti, F., 2021. Brain oscillatory correlates of visuomotor adaptive learning. NeuroImage 245, 118645. https://doi.org/10.1016/j.neuroimage.2021.118645.

Unal, G., Ficek, B., Webster, K., Shahabuddin, S., Truong, D., Hampstead, B., Bikson, M., Tsapkini, K., 2020. Impact of brain atrophy on tDCS and HD-tDCS current flow: a modeling study in three variants of primary progressive aphasia. Neurol. Sci. 41 (7), 1781–1789. https://doi.org/10.1007/s10072-019-04229-z.

Ura, H., Sugaya, Y., Ohata, H., Takumi, I., Sadamoto, K., Shibasaki, T., Maru, E., 2013. Vagus nerve stimulation induced long-lasting enhancement of synaptic transmission and decreased granule cell discharge in the hippocampal dentate gyrus of urethane-anesthetized rats. Brain Res. 1492, 63–71.

Van den Berg, N., Al-Kuwatli, J., Paulin, J., Ray, L., Owen, A., Fogel, S., 2019. Sleep preferentially enhances memory for a cognitive strategy but not the implicit motor skills used to acquire it. Neurobiol. Learn. Mem. 161, 135–142.

Vanneste, S., De Ridder, D., 2011. Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur. J. Neurosci. 34 (4), 605–614.

Vanneste, S., Mohan, A., Yoo, H., Huang, Y., Luckey, A., McLeod, S., Tabet, M., Souza, R., McIntyre, C., Chapman, S., Robertson, I., To, W. T, 2020. The peripheral effect of direct current stimulation on brain circuits involving memory. Sci. Adv. 6 https://doi.org/10.1126/sciadv.aax9538.

Vékony, T., Ambrus, G.G., Janacsek, K., Nemeth, D., 2022. Cautious or causal? Key implicit sequence learning paradigms should not be overlooked when assessing the role of DLPFC (commentary on Prutean et al.). Cortex 148, 222–226. https://doi.org/10.1016/j.cortex.2021.10.001.

Vollmann, H., Conde, V., Sewerin, S., Taubert, M., Sehm, B., Witte, O.W., Villringer, A., Ragert, P., 2013. Anodal transcranial direct current stimulation (tDCS) over supplementary motor area (SMA) but not pre-SMA promotes short-term visuomotor learning. Brain Stimul. 6 (2), 101–107. https://doi.org/10.1016/j.brs.2012.03.018.

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., Kozák, G., Kincses, Z.T., Iványi, B., Buzsáki, G., 2018. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat. Commun. 9 (1), 1–17.

Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A., Pollok, B., 2013. Effects of 10Hz and 20Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. Behav. Brain Res. 241, 1–6. https://doi.org/10.1016/j.bbr.2012.11.038.

Wiltshire, C.E.E., Watkins, K.E., 2020. Failure of tDCS to modulate motor excitability and speech motor learning. Neuropsychologia 146, 107568. https://doi.org/10.1016/j.neuropsychologia.2020.107568.

Yamaguchi, T., Svane, C., Forman, C.R., Beck, M.M., Geertsen, S.S., Lundbye-Jensen, J., Nielsen, J.B., 2020. Transcranial alternating current stimulation of the primary motor cortex after skill acquisition improves motor memory retention in humans: a double-blinded sham-controlled study. Cerebr. Cortex Commun. 1 (1), tgaa047.

Yu, M., Wang, S.-M., 2021. Anatomy, head and neck, occipital nerves. In: StatPearls [Internet]. StatPearls Publishing.

Zhu, F.F., Yeung, A.Y., Poolton, J.M., Lee, T.M.C., Leung, G.K.K., Masters, R.S.W., 2015. Cathodal transcranial direct current stimulation over left dorsolateral prefrontal cortex area promotes implicit motor learning in a golf putting task. Brain Stimul. 8 (4), 784–786. https://doi.org/10.1016/j.brs.2015.02.005.