

APPLICATION OF TRANSCRANIAL DIRECT CURRENT STIMULATION
DURING MOTOR SKILL ACQUISITION

Anthony Wilhite Meek

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Doctoral Committee

Zachary Riley, Ph.D., Chair

Niki Munk, Ph.D., LMT

January 12, 2024

Kelly Naugle, Ph.D.

Jake Streepey, Ph.D.

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Transcranial direct current stimulation has been used to influence the acquisition of motor skills; however, most studies investigate relatively simple laboratory based motor skills tasks. Since the regions where structural and functional changes support motor learning are dependent on the qualities of the task, translation of the findings to real-world skills has been limited. In general, anodal current stimulation is associated with functional facilitation and cathodal current is associated with functional inhibition. The purpose of this dissertation is to explore the effect of transcranial direct current stimulation of the primary motor cortex and the cerebellum upon the acquisition of novel motor skills that possess varied demands comparable to everyday tasks.

In order to study motor skill learning, we investigated 4 unilateral tasks made novel by using the non-dominant hand, ensuring a discernible fast phase of learning in which to observe skill acquisition.

In study one, anodal stimulation applied over the primary motor cortex during a 20 minute practice session skill acquisition in a complex dart throwing task compared to cathodal motor cortex stimulation or SHAM. In study two, 20 minutes of anodal motor cortical stimulation while practicing a dexterous tweezer task significantly reduced post-practice pin-placing time compared to SHAM. In study three, anodal motor cortical stimulation during 20 minutes practicing a dexterous rhythmic-timing video game led to

significantly higher performance scores compared to SHAM. In study four, in the same videogame task, concurrently stimulating the primary motor cortex with 2 milliamp anodal current while stimulating the cerebellum with 2 milliamp cathodal current during 20 minutes of practice led to significantly higher performance scores compared to SHAM, whereas 2 milliamp anodal primary motor cortex, anodal cerebellar, and cathodal cerebellar stimulation alone was not different than SHAM.

These data altogether show that motor cortical transcranial direct current stimulation can facilitate skill acquisition in everyday tasks with a range of gross, fine, and visuomotor demands. They also provide the first evidence of a synergistic effect on motor learning from concurrent primary motor cortex and cerebellar stimulation, which may contribute to the development of novel stimulation protocols.

Zachary Riley, Ph.D., Chair

Niki Munk, Ph.D., LMT

Kelly Naugle, Ph.D.

Jake Streepey, Ph.D.

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LIST OF ABBREVIATIONS

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP	Action potential
a-tDCS	Anodal tDCS
BDNF	Brain derived neurotrophic factor
Ca ²⁺	Calcium
CB a-tDCS	Cerebellar anodal transcranial direct current stimulation
CB c-tDCS	Cerebellar cathodal transcranial direct current stimulation
CBI	Cerebellar brain inhibition
CMOD	Continuous modifier
c-tDCS	Cathodal tDCS
EHI	Edinburgh handedness inventory
GABA	Gamma-amino butyric acid
KER	Key error rate
LTD	Long term depression
LTP	Long-term potentiation
M1	Primary motor cortex
M1a +CBc	Primary motor cortex anodal and cerebellar cathodal transcranial direct current stimulation
M1 a-tDCS	Primary motor cortex anodal transcranial direct current stimulation
mA	Milliampere
MEP	Motor evoked potential

NIBS	Non-invasive brain stimulation
NMDA	N-methyl-D-aspartate
PI	Performance index
PMA	Premotor area
SFTT	Sequential finger tapping tasks
SMA	Supplementary motor area
SRTT	Serial reaction time tasks
SVIPT	Sequential visual isometric pinch task
TA	Temporal accuracy
tDCS	Transcranial direct current stimulation
TDR	Tap distribution ratio
TES	Transcutaneous electrical stimulation
TMS	Transcranial magnetic stimulation

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Whether it is an activity of daily living, playing a video game, or a sport specific skill, virtually all intentional movements are examples of motor skills that are acquired through practice. The process of acquiring a new skill and improving the quality of the movement with repetitive practice is referred to as motor skill learning. As a motor skill is practiced, repetitive activation of the neural representation for the movement leads to use-dependent neuroplasticity in several cortical and subcortical areas of the brain involved in motor control. The shifts in excitability provide a neural substrate for motor learning, representing changes in synaptic strength and efficacy within the neural representation of the movement. Accordingly, the primary motor cortex (M1) and the cerebellum both demonstrate changes in neuronal activity and excitability which coincides with improved performance.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique (NIBS) that induces polarity-specific changes in the excitability of cortical and cerebellar neurons. Anodal current causes a subthreshold depolarization of the neuronal membrane making it easier for neurons fire whereas cathodal stimulation causes hyperpolarization of the neuronal membrane making it harder for neurons to fire. Since anodal tDCS makes it easier for neurons to fire, it offers a means to facilitate use-dependent plasticity from practice and accelerate motor learning compared to practice alone.

Indeed, much of the literature supports tDCS as an effective adjuvant for motor skill learning. However, most studies have used relatively simple hand and finger based motor sequences to study the effect of tDCS on motor skill learning. Although much knowledge has been gleaned from these studies about tDCS and motor learning, controversy remains about whether tDCS accelerates acquisition of more complex upper body motor skills that require widely varying parameters such as dexterity, force, velocity, and timing. Thus, there is a need for more research on this topic.

1.2 Motor learning

Motor learning is a general term that encompasses two distinct processes: motor adaptation and motor skill learning. Motor adaptation is characterized by gradual improvement in performance of a skill after some type of perturbation causes performance to drop below baseline ability.^{1,2} The environmental perturbations are sensory based, such as altered visual feedback during visuomotor tasks.³ Force-fields have also been used to generate motor adaptation by interfering with limb trajectory during reaching tasks.⁴ Regardless of the method of perturbation used, the result of motor adaptation is a return to baseline performance without any additional capability or improved performance greater than what was already achievable.⁵

Alternatively, motor skill learning refers to acquisition of new motor skills through practice. Specifically, motor skill learning is defined as improved sensorimotor ability, often characterized by a shift in the speed-velocity trade-off, yielding performance capabilities or skills beyond what was possible prior to practice. Reduced

variability of a movement from trial to trial is also an indicator of motor skill learning, with smoother movements indicating greater skill.^{6,7} Another critical aspect of motor skill learning is what actually constitutes a motor 'skill'.

Motor skills consist of a sequence of component movements that are executed in a particular order and with particular parameters (force, velocity, timing, joint angles) to achieve a specific outcome, such as throwing a baseball to first base, grasping and taking a drink from a cup, or walking from place to place.⁸ The sequence of component movements is initially a critical aspect of skill execution; however, what dictates the skillfulness of a correctly ordered sequence is the optimization of the component movements. For example, to accurately throw a baseball, the component movements of the lower body, torso, and throwing arm need to be performed in the proper order, but it is crucial for the force and timing of the components to be optimized for skillful performance of an accurate throw. Although motor learning in general is conceptualized as a long term process, requiring many bouts of practice across months or years to fully optimize the movements, it has been repeatedly demonstrated that there are distinguishable phases of motor skill learning.

1.2.1 Phases of motor learning

The three main phases of motor skill learning are an initial fast phase, an intermediate consolidation phase, and a later slow phase. During the fast motor learning phase there are rapid improvements in performance that are measurable even after a single session.^{9,10} Such performance changes that happen during practice are known as 'online' changes, but there are performance improvements that also occur between

training which are known as ‘offline’ learning. Offline learning occurs during a consolidation phase¹⁰ that’s processes include stabilization of the skill and further improvement.¹¹⁻¹⁴ The third phase is a slow period where performance is optimized through further incremental gains until reaching asymptotic levels and the movement eventually becomes automatized,^{9,10} becoming implicit and requiring less attention to perform well.

Even after cessation of practice, skill improvement from online and offline learning can be retained and is often quite robust over long periods of time.^{9,15,16} Retention of motor skill is a specific phenomenon that is not itself a skill learning process, per se, but it directly results from more permanent structural and functional changes that occur as a result of motor learning.

Although the 3 primary phases of motor learning are identifiable in essentially any skill learning paradigm, the duration of the three phases is task specific, depending largely upon task difficulty. For instance, extremely difficult tasks, like learning an entire piece of music on an instrument, may have fast phases lasting many weeks where large changes in performance can be seen after a single practice session. In contrast, easier tasks, such as finger tapping sequences may have fast phases lasting minutes or hours where performance level is maximized within a single session.¹⁰ Prior experience with the task might also influence the duration of the learning phases,¹⁷ with previous experience potentially reducing the time needed to maximize performance.

1.2.2 Neuroanatomy of motor learning

Diverse experimental paradigms have been used to investigate motor learning and the involved circuitry, but all fall within two main categories: sensorimotor tasks with emphasis on learning novel movement kinematics with high motor demand; or serial reaction time tasks (SRTT) that represent learning sequential motor skills, but have minimal demands on motor execution requiring only finger taps or isometric finger squeezes. From these paradigms it is clear that motor learning, or becoming proficient at a skill, is supported by functional and structural changes in an extensive network of cortical and subcortical regions including the M1, premotor and supplementary motor areas (PMA, SMA), visuomotor cortex, the basal ganglia and the cerebellum.^{6,18} The involvement of several of these regions is task specific, showing involvement primarily if the skill possesses certain qualities. However, M1 and the cerebellum are consistently involved in motor learning, regardless of the type of skill or experimental paradigm being used, thus indicating they are vital in the core motor learning network.

The M1 and cerebellum have been extensively studied and appear to have specific roles in their contribution to motor skill learning. M1 generates neural commands that provide the primary cortical output to the descending motor systems which produces volitional movement. The descending output of M1 originates from coordinated activity of somatotopically organized neuronal ensembles whose orderly arrangement creates a motor map containing interdigitated representations of muscle synergies and basic motions.^{19,20} The M1 is consistently implicated in the use dependent acquisition and storage of muscle activation used in fast and precise movements.^{5,8}

The cerebellum serves as an error predictor during motor learning by receiving motor information from descending cortical pathways as well as sensory information from ascending peripheral pathways. For different motor skills, the cerebellum appears to maintain internal models, which are input-output comparisons between motor commands and the sensory consequences of the movements generated by those commands.²¹ The cerebellum uses the efference copy of a motor command as input to the internal model and then outputs what the predicted sensory consequences are for that action.^{22,23} The internal model allows for comparison of predicted and actual consequences of a movement, thereby allowing for the assessment of movement error that can be used to guide error correction and skill optimization.

Although the independent functions of M1 and the cerebellum are critically important in motor learning, neuroimaging studies suggest the interaction between the two areas may be equally important. For instance, interregional correlation analysis revealed activity in M1 and the cerebellum correlated during learning, which suggests interactions between these regions were associated directly to learning.⁸ Over multiple days of practice, the correlated activity between M1 and the cerebellum was greater on the fifth day than the first day. Taken together, these data suggest an integrated representation of a learned movement within M1 and the cerebellum.

1.3 Plasticity subserving motor learning

The term plasticity refers to functional or structural changes in the central nervous system in response to behavioral experience. Donald Hebb provided an early description

of a basic mechanism for synaptic plasticity, suggesting that if the firing of one neuron is associated with the persistent activation of another, then a growth process or metabolic change will occur in one or both cells that improves the efficiency of that relationship.^{24,25} When a motor skill is practiced, the motor command activates the same core neural circuitry repeatedly. The repetitious activation of the neurons in close temporal association with one another leads to increased synaptic efficacy of the involved neurons and subsequent reorganization of the neural representation of the movement. These structural and functional changes and reorganization coincide with improved performance of the skill.

1.3.1 Cellular mechanisms

Long-term potentiation (LTP) is the primary mechanism of information storage throughout the central nervous system underpinning the functional and structural changes of plasticity. For LTP to occur there must be coincident activity of pre- and post-synaptic components. This is because LTP requires an influx of calcium (Ca^{2+}) ions into the synaptic spine which is mediated through activation of N-methyl-D-aspartate (NMDA) receptors. NMDA receptors require both depolarization of the postsynaptic membrane and the binding of glutamate simultaneously to allow the influx of Ca^{2+} to occur.²⁶ Once coincident activity of the two cells occurs and Ca^{2+} enters, signaling cascades are initiated prompting insertion of ligand gated α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the post-synaptic membrane. The end result of LTP is strengthened synaptic communication between neurons such that the activity of the post-synaptic cell is 'wired' to activity in the pre-synaptic cell. In addition to improving the

efficiency of already existing synaptic connections, LTP can also lead to AMPA receptors inserting into previously “silent” synapses which allows the previously silent synapses to produce postsynaptic responses to stimulation.²⁶

Long term depression (LTD) is the converse of LTP and causes reduced efficiency at chemical synapses. The reduced efficiency is from a decrease in the number of AMPA receptors as they are internalized through endocytosis.²⁷ Like LTP, the induction of LTD-like plasticity appears to be related to the specific timing of pre- and post-synaptic activity and the corresponding influx of calcium into the post-synaptic cell, albeit a smaller influx compared to LTP requirements. It appears that LTD occurs when action potentials occur in the post-synaptic cell 0 to 50 milliseconds before excitatory input is received from the presynaptic cell.²⁸

1.3.2 Morphological and structural changes

As a result of LTP there are increases in synapse number, synaptic strength, and the topography of stimulation-evoked movement representations (i.e. number of neurons whose activity produce a movement) that reflect improved connectivity and efficiency of neural ensembles responsible for skilled movements. For instance, rats trained on complex whole body “acrobatic tasks” requiring skilled limb placement and postural control have increased synapse number within M1 compared to untrained controls.^{29,30} Moreover, rats trained on skilled reaching show increased density and complexity of motor cortical dendritic process^{31,32} and more synapses per neuron,³³ specifically within the forelimb motor areas.

These synaptic changes reflect alterations in cortical circuitry that leads to reorganization of the neural ensembles that represent and encode movements (i.e. motor maps or motor representations). This is supported by the high degree of specificity of cortical reorganization specific to the motor representations in M1 that correspond to the skill being practiced. For instance, squirrel monkeys initially trained on a skilled digit task induced expansion of digit representations exclusively. Skilled digit training was ceased and subsequently replaced with skilled wrist training which reduced the previously enlarged digit motor map and simultaneously expanded the wrist motor map within the same animals.³⁴

For map reorganization to occur there must be practice of a novel skill, not just a general increase in repetitive use of a muscle group, demonstrating another degree of specificity. Squirrel monkeys trained to acquire food pellets from a container requiring no skilled performance have no change in digit movement representations despite abundantly using their digits (approximately 13,000 digit flexions throughout training).³⁵ Likewise, rats trained to repeatedly press a simple lever,³⁶ reach for unreachable food pellets³⁷ or run on an exercise wheel³⁸ show no reorganization of cortical representations of the involved musculature.

Neuroimaging and noninvasive transcranial magnetic stimulation (TMS) have been used to demonstrate comparable changes in humans after training a novel motor skill.^{9,39-43} Motor map reorganization (i.e. expansion) has been demonstrated after training on skilled dexterous hand,⁴² ankle,⁴⁴ and tongue tasks.⁴⁵ Additionally, changes in motor representation size are accompanied by decreases in recruitment threshold and increased motor evoked potential (MEP) amplitude. Furthermore, cross-sectional

differences in motor maps consistent with differences in skill levels have been observed for both fine dexterous skills and larger gross motor skills as well. Blind braille readers have exaggerated motor representations of the braille-reading digit compared to contralateral representations of the same digit or non-braille readers.^{43,46} Highly skilled volleyball players have significantly larger and more overlapping representations of medial deltoid and carpi radialis muscles compared to running athletes.⁴⁷ Whereas volleyball athletes develop extremely honed coordinated shoulder movement sequences, runners develop no such shoulder movements.

Complex motor skill learning also leads to an increase in synapse number in the cerebellar cortex. There is a somatotopic organization of the cerebellum in rodents and humans as well.⁴⁸ Similar to M1, cerebellar plasticity is in response to complex motor skill learning, not merely extensive motor activity^{49,50} and animal studies have shown that changes in synapse number occur specifically in areas of the cerebellar lobules associated with the musculature used in the skilled activity.⁴⁹

Neuroimaging studies support similar plasticity in human cerebellar circuitry insofar as they demonstrate increased synaptic density in the cerebellum in response to training. However, somatotopic representations are less well defined in the cerebellum and thus specific changes within certain map somatotopy is difficult to directly identify in humans.⁴⁸ Despite this limitation, somatotopically specific cerebellum -M1 connectivity changes associated with motor learning have been observed.⁵¹ Within the cerebellum individually, individuals who have practiced complex motor skills, most notably athletes⁵²⁻⁵⁵ and musicians,^{56,57} display structural and functional changes in cerebellum in accord with extensive motor skill practice. What is clear is that there are changes in

cerebellum synaptic density and function in response to extensive practice of skilled movements and those changes are consistent with differing skill levels (i.e. greater skill correlates to greater cerebellar plasticity and vice versa).

The cumulative evidence demonstrates the malleable nature of the motor system during motor skill learning. This dynamic nature allows for a virtually boundless motor repertoire, particularly the ability to quickly acquire a novel motor skill and then rapidly improve its performance (i.e. fast motor learning). Universally there is a temporal relationship in the activity of neurons that enables them to either enhance or depress the synaptic communication between cells. LTP/D-like plasticity appears to be especially important for storing and refining information, like movement representations, in both the cortex and the cerebellum. Therefore, brain stimulation that modulates the excitability and spontaneous firing of neurons involved in executing a movement sequence may enable accelerated motor skill learning.

1.4 Growing interest in brain stimulation

Interest in brain stimulation has grown substantially over the last 30 years in both scientific research and clinical medicine, but also in the general public. Since the 50s it has been known that passing anodal current through dendritic fields of neurons causes an increase in their firing rate (i.e. – increased excitability) and cathodal current causes a decreased firing rate (i.e. – decreased excitability).^{58,59} This generated multiple intracranial stimulation techniques to address conditions such as Parkinson's disease,⁶⁰ obsessive compulsive disorder,⁶¹ and neuropathic pain.⁶² Though precise and effective,

these techniques are impractical for most applications because they require penetration of the skull and thus carry exorbitant costs and medical risks.⁶³ A breakthrough occurred in 1980 when brief high-intensity extracranial electrical impulses over the motor cortex were shown to induce muscle twitches.⁶⁴ This led to the development of non-invasive techniques which avoided many drawbacks of invasive techniques while still taking advantage of the ability to modulate neuronal excitability.

tDCS is one of several NIBS techniques that have been developed. In contrast to other NIBS techniques like TMS or transcutaneous electrical stimulation (TES) that use suprathreshold stimulation to cause neuronal depolarization, tDCS involves subthreshold modulation of neuronal membrane potentials with weak current that cannot independently induce neuronal activity. The efficacy of tDCS was first demonstrated in the early 2000s by Nitsche and Paulus^{65,66} who showed changes in motor cortical excitability of up to 40% that lasted several minutes to hours after stimulation ended.

tDCS has garnered much interest because it produces both substantial excitability shifts during the stimulation period, as well as relatively long-lasting after-effects. Moreover, tDCS is appealing because different brain regions can be ‘targeted’ by the current depending on the locations of the sponge electrodes on the scalp. The fact that tDCS can modulate neuronal excitability safely and with some degree of focality have made it an appealing tool to modulate motor learning in healthy and clinical populations by influencing the excitability of structures involved in motor learning.

1.5 Neurophysiology of tDCS

Neurons are electrically excitable cells whose function is dependent upon generation and conduction of action potentials (APs). APs occur when the resting membrane potential of the neuron, approximately -70 millivolts, reaches a threshold potential for AP discharge, approximately -50 millivolts. How close the neuronal membrane potential is to the firing threshold determines how much afferent activity (i.e. excitatory synaptic input) is necessary to elicit an action potential in that cell. The aim of tDCS is to directly modulate neuronal resting potentials and thereby alter the state of excitability.

Anodal stimulation causes subthreshold membrane depolarization that increases cortical excitability whereas cathodal stimulation hyperpolarizes membranes and decreases cortical excitability. However, the direction of polarization in response to a particular current depends upon the orientation of the axon and dendrites within the electric field.^{67,68} The effects of tDCS are maximized when the electric field is applied parallel to the somato-dendritic axis as this allows current to enter one end of the cell and exit the other. Neurons oriented perpendicular to the current experience negligible effects. If 2 neurons have somato-dendritic axes that are both parallel to the stimulation but have opposite orientations, the two cells will be effected oppositely by the same current. Despite these nuances, anodal and cathodal tDCS result in net excitatory or inhibitory effects, respectively.

1.6 Basic mechanisms of tDCS neuroplastic effects

It is worth disassociating between the immediate effects of tDCS observable after only a few seconds of stimulation and the longer term aftereffects of tDCS since the causal mechanisms are different. The acute effects of tDCS are the direct result of altered membrane potentials from displacement of intracellular ions by the electric field rather than changes in synaptic strength. This is clear because the acute effects of anodal tDCS are prevented by blocking the voltage-gated ion channels involved in membrane depolarization whereas glutamate receptor blockade and Gamma-amino butyric acid (GABA) agonists, both of which impact synaptic efficacy, do not prevent acute tDCS effects.⁶⁹ Furthermore, in brief exposure tDCS protocols that do not produce aftereffects, no evidence for synaptic changes have been found with TMS investigation.⁷⁰

In contrast, the aftereffects of tDCS that occur with longer stimulation exposures (~15 to 20 minutes) are the result of protein synthesis driven changes in synaptic efficacy, similar to the mechanisms in LTP/D-like plasticity. In motor cortex slices, anodal direct current accompanied by ongoing neuronal activity lead to LTP at M1 synapses.⁷¹ When protein synthesis is blocked prior to anodal polarization, the aftereffects are abolished despite increased discharge rates while the current is applied.⁷² Moreover, in animal and human individuals with diminished secretion of brain derived neurotrophic factor (BDNF), a key protein for LTP and motor learning, the ability of tDCS to enhance motor learning is also diminished.⁷¹

Altering the structure and function of synaptic spines depends on protein synthesis as well. NMDA receptors which are crucial for induction of LTP/D, are also

critical for the persistence of tDCS induced plasticity in intact humans. Pharmacological blockade of NMDA receptors prevents persistent excitability changes after both anodal and cathodal tDCS. Additionally, NMDA receptor agonists facilitate anodal tDCS-induced excitability increases.^{71,73} TMS investigations examining changes in synaptic strength (i.e. paired associative stimulation) have supported the pharmacological study results.⁷⁰

Many of the synaptic actions that support motor learning are modulated by direct current stimulation such that tDCS should enhance motor skill learning. Increased spontaneous firing rates and higher probability of AP generation in response to excitatory synaptic input increases the odds of synaptic plasticity when paired with a biologically-relevant stimulus. The directionality of tDCS aftereffects is generally the same as during stimulation with anodal tDCS enhancing, and cathodal stimulation reducing, excitability aftereffects. Although there are limits, stronger and longer stimulation enhances the efficacy of tDCS after effects. Ultimately, the effects of stimulation are dependent upon the parameters of the stimulation which are discussed in the following section.

1.7 Stimulation parameters – shaping stimulation effects

The general process of applying tDCS is simple – applying weak current from a battery powered stimulator to the scalp with 2 sponge electrodes strapped to the head. However, the intricacies of tDCS are in the parameters of stimulation such as electrode location (i.e. montage), stimulation intensity, polarity, timing of stimulation in relation to

skill practice (before, during, or after) and the stimulation duration; all of these parameters can influence the effects of tDCS.

1.7.1 Montage

Where the electrodes are on the scalp dictates what tissues receive the polarizing effects of tDCS and whether the polarizing effects will be excitatory (anodal; depolarizing) or inhibitory (cathodal; hyperpolarizing). Most commonly, montages include 2 sponge electrodes, one being the “active” stimulation electrode, and the other serving as the reference electrode. In the case of excitatory montages, the anodal electrode is placed on the scalp over the cortical target and the cathode serves as the reference.

When M1 is the stimulation target, the most common electrode montage has been with an active electrode placed on the top of the head over the motor cortex and the reference electrode placed over the contralateral supraorbital.^{74,75} Another montage that has proved successful for motor learning enhancement has been bilateral M1 placement with the stimulating electrode over M1 contralateral to the hand used for the task and the reference electrode on M1 ipsilateral to the involved hand.⁷⁴

When the whole cerebellum is the desired target, effective stimulation of the cerebellum has included an active electrode centered over the cerebellum 1 to 2 cm below the inion with the return electrode placed extra-cephalically on the ipsilateral shoulder.^{74,76} With the same stimulating electrode position, effective cerebellar stimulation has also been found when the reference electrode is placed on the ipsilateral cheek over the buccinator muscle.⁷⁴ Lastly, montages for cerebellum have also included

unilateral electrode placement with the stimulating electrode 1 to 3 cm to either side of theinion in an effort to isolate which hemisphere was receiving the stimulation.⁷⁷

1.7.2 Stimulation intensity and duration

Both the current intensity and the duration of stimulation can influence the effects of tDCS.^{66,78,79} Although several studies can be found that demonstrate significant findings when using low stimulation intensities of 1mA (milliampere) or even lower,⁸⁰ it is generally accepted that higher current intensities and longer stimulation durations, within certain limits, lead to increased tDCS effects. Current intensities used for efficacious tDCS typically range from 1mA to 2 mA applied for durations ranging from 10 to 20 minutes.^{74,76}

1.7.3 Timing of stimulation

The timing of stimulation application in relation to when the skill is practiced can influence the efficacy of the stimulation. Although there have been some studies that have shown positive results with stimulation applied before practice,⁸¹ others have found prior stimulation can slow motor learning.^{82,83} Stimulation during skill practice, rather than before or after, appears to be the most effective to enhance motor learning.⁸⁴

1.8 tDCS to enhance fast motor learning

Motor skill learning improves a trade-off between the speed of skill execution and the accuracy of the intended outcome, typically achieved by reducing the variability of the motion. The network of brain areas involved in motor learning is vast, however, M1 and the cerebellum both play important roles, particularly during the fast phase of motor learning. tDCS excitability shifts are mediated by the same mechanism that mediates LTP/D-like plasticity, the putative substrates for normal motor learning⁶⁵ and indeed, early studies showed anodal tDCS (a-tDCS) of M1 improves initial learning of a motor skill.^{85,86} However, most studies have combined tDCS with motor sequence learning paradigms such as the SRTT, SFTT and the SVIPT. Though these tasks are specialized and finger/hand focal, they nevertheless have provided the basis for application of tDCS for learning any type of practical motor skills.

The SRTT is a four choice reaction time task that includes a repeating button sequence with interspersed random sequences. Participants come to predict (i.e. learn) the repeated sequence, and thus learning is quantified by reaction times to the presented cues. Anodal M1 tDCS applied during SRTT training has usually enhanced learning and retention compared to controls.^{85,87-89} There have been null effects reported, however, when M1 stimulation was not applied during SRTT training⁸³ or when single pulse TMS was used in combination with tDCS and could have interfered with tDCS effects.⁹⁰ Investigations on the effects of cerebellar tDCS on SRTT motor skill learning have been limited; however, anodal cerebellar tDCS applied during SRTT performance reportedly

reduced error rates.⁹⁰ When cerebellar stimulation was applied before performing the SRTT it led to reduced reaction times only.⁹¹

SFTT requires subjects to practice a sequence of finger movements and repeatedly execute the sequence as fast and accurately as possible. Practice with concurrent anodal M1 tDCS has improved SFTT skill by increasing the number of correct sequences executed during trials⁹² or through reduced RTs during training.⁸³ M1 a-tDCS applied between two training sessions resulted in quicker execution times for correct sequences during early consolidation, representing more rapid stabilization of the motor memory after acquiring the skill.⁹³ Over the cerebellum, anodal and cathodal tDCS during a finger tapping task decreased and increased activity in the dentate nucleus, respectively,⁹⁴ however, the effect of cerebellar tDCS on performance of conventional SFTT has not been investigated. During a sequence tapping task synchronized to auditory cues, anodal cerebellar stimulation lead to increased performance in synchronization during follow-up sessions.⁹⁴

The SVIPT task is performed by controlling a cursor on a computer screen by isometrically pinching a force transducer, in order to move a cursor as quickly and accurately as possible between a start position and a series of force “gates” or target zones. Applying anodal tDCS to M1 during SVIPT practice resulted in greater skill acquisition across consecutive training days, primarily through improved between-session¹⁶ or long-term retention.⁹² However, significant within session learning improvement was noted, but only during early training sessions.¹⁶ On the other hand, anodal cerebellar stimulation during SVIPT training appears to enhance skill acquisition within session rather than between sessions by reducing error rates.⁹⁵

Although these laboratory paradigms allow for exquisite control and measurement of learning processes, they do not fully reflect the variety of movement parameters that many real-world motor skills involve. Beyond the popular paradigms discussed above that have focused on hand/finger based skills, other studies have examined the effects of tDCS on skill learning with tasks sharing more characteristics with practical motor skills such as different visuomotor, dexterity, and gross-motor demands.

Most everyday motor skills involve some visuomotor component. Anodal M1 tDCS applied during a visuomotor coordination task improved early performance of tracking motions.⁸⁶ When applied prior to training, both a-tDCS and cathodal tDCS (c-tDCS) over M1 lead to improved performance.⁹⁶ In complicated tracing tasks including handwriting-like movements,⁹⁷ exoskeleton arm based tracking,⁹⁸ and ankle tracking movements,⁹⁹ anodal M1 tDCS applied during practice improved learning. Interestingly, cerebellar tDCS has shown a polarity-independent effect on ankle visuomotor tracking where both anodal and c-tDCS enhanced performance when applied during practice.⁹⁹

Many everyday tasks require a significant degree of dexterity for skillful performance in combination with gross movements of the arms and hands. The Jebsen-Taylor task and Purdue Pegboard tasks are designed to assess such dexterous motor skill, and evidence suggests that tDCS can facilitate training induced improvements in these tasks. Stimulation targeting M1 during non-dominant hand practice of the Purdue Pegboard task enhanced dexterous skill learning compared to practice with SHAM stimulation whether stimulation was applied during or between practice blocks.¹⁰⁰ However, when the same task was performed with lower stimulation intensity (0.2 mA vs 1 mA) and duration (10 min vs 13 min) between sessions, no beneficial effects were

found.¹⁰¹ Results from the Jebsen Taylor Task support M1 tDCS as a means to enhance learning of dexterous skills, whether applied during practice¹⁰² or between practice blocks.^{103,104}

Only a few studies have investigated the effects of M1 tDCS or cerebellar tDCS on acquisition of everyday complex motor skills. Postural control and balance are integral in most everyday motor skills, however, neither a-tDCS nor cerebellar c-tDCS during 10 minutes of practice enhanced learning of a complex whole-body balance-oriented motor skill.¹⁰⁵ In contrast, a-tDCS over M1 lead to improved performance in a similar complex dynamic balance task.¹⁰⁶ When applied during performance, anodal M1 tDCS improved learning of neurosurgical skill, with a greater effect for those who have low skill level to begin with.¹⁰⁷ Two studies have applied cerebellar stimulation to overhand throwing tasks, both showing that cerebellar stimulation can enhance acquisition of a complex upper body motor skill.^{108,109} Again, however, the benefits of cerebellar tDCS on throwing skill learning may depend upon the initial ability of the individuals, with those who perform worst benefitting the most from the stimulation.¹⁰⁸

These studies indicate that tDCS over M1 or the cerebellum during a single practice session, especially stimulation concurrent with practice, can enhance motor learning. Despite the relatively homogenous evidence for simple motor skills, the evidence for the benefits of M1 or cerebellar tDCS upon complex motor skills is sparse and less conclusive. Although the motor applications of tDCS are broad, it is specifically the effect of M1 and cerebellar tDCS during fast motor learning that is pertinent to the aims of this dissertation.

1.9 Summary and aims

1.9.1 Summary

Summarizing the previous sections, motor skill learning is a complex process that is fundamental to interacting with the environment. Skill learning has several stages and involves several brain regions with the predominant regions involved depending on the characteristics of the skill being practiced. As motor skills are acquired, the process is characterized by structural and functional changes that strengthen synaptic connections between neurons in the motor representations of the skilled movements. When learning a new skill, during fast motor learning, the motor cortex and cerebellum both demonstrate changes in excitability and structural and functional changes in the synaptic connections within the representations for the sequence of movements making up the skill. tDCS is a non-invasive brain stimulation technique that can modulate neuronal excitability and therefore increase the rate of plastic changes necessary for motor skill learning.

Although the applications of tDCS in the motor domain have been numerous, there is still a dearth of knowledge concerning tDCS efficacy for everyday motor skills. The majority of tDCS motor learning research has involved lab oriented motor skills intended to isolate specific aspect of motor skill learning. To this end, the laboratory oriented tasks have been informative. However, this has not answered the question regarding whether learning common gross and dexterous motor skills can be enhanced with tDCS. The evidence that does exist for such everyday tasks is limited in comparison to laboratory motor skill studies and the results have not been consistent. Furthermore, it is even less clear what brain regions would be ideal stimulation targets for which tasks as

the regions most involved in motor learning are depend upon the characteristics of the skill itself. Since less is known about how tDCS influences learning of everyday motor skills and what regions are the most beneficial targets, more research on this topic is needed.

1.9.2 Dissertation overview

The purpose of this dissertation was to investigate how tDCS of the M1 and the cerebellum influenced the fast phase of motor skill learning for novel everyday motor skills that possess fundamentally different movement characteristics (i.e. velocities, joint angles, visuomotor demands, dexterity). To investigate this question, a pre-post approach was used. An initial baseline assessment of skill level on each task was taken, then a practice period of the task with concurrent tDCS application was performed, followed by a retest of the skill level. The non-dominant hand was used to make the motor skills novel, ensuring a discernable fast phase of motor learning.

a.) Study one – gross motor skill with M1 tDCS

Study one of the dissertation investigated the effect of M1 tDCS on fast motor learning of a unilateral gross motor skill. The effect of M1 tDCS on gross motor skill was observed through changes in accuracy of darts thrown at a bullseye on a dartboard. Most studies that have applied tDCS to M1 to see how motor learning is affected have used motor skills limited to the hands and fingers. The results from these studies have shown that M1 tDCS can enhance acquisition of new motor skills, but research on gross motor skills like those used in sports, such as throwing, are lacking. The aim of this study was

to investigate the effect of M1 tDCS on the acquisition of a novel unilateral dart throwing skill with the goal of determining if M1 is an appropriate stimulation target for throwing skills. Sixty adults were randomized into either M1 anodal, M1 cathodal, or SHAM over M1, and practiced dart throwing while receiving the stimulation. Performance was assessed by the distance from the bullseye and measured before, during, and after practice.

b.) Study two – fine dexterity with M1 tDCS

Study two of the dissertation investigated the effect of M1 tDCS on fast motor learning of a unilateral motor skill that requires fine dexterity. The effect of M1 tDCS on fine dexterous motor skill was observed in the change in time required to place 50 pins in the O'Connor Tweezer Dexterity task. Previous studies have shown that tDCS can improve dexterous tasks with the fingers and hands. Also, neurosurgery residents have shown improved skills when training with concurrent tDCS over M1. The aim of this study was to investigate the effect of M1 tDCS on the acquisition of a novel unilateral dexterous task using tweezers, while also seeking to reproduce results of previous dexterous skills studies. Forty subjects were randomized into either M1 anodal or M1 SHAM and they practiced placing small metal pins into a pegboard with tweezers using only their non-dominant hand. During practice, subjects will place 10 pins and then rest 30 seconds for 20 minutes. Skill was assessed by the time required to place 50 pins before and after practice.

c.) Study three – visuomotor skill with M1 tDCS

Study three of the dissertation research investigated the effect of M1 tDCS on fast motor learning of a visuomotor video game with a high degree of reaction time. The effect of M1 tDCS on visuomotor learning was observed through changes in timing accuracy and movement errors during keystrokes for a timing based video game called Step Mania. Timing and coordination tasks are typically improved with cerebellar tDCS; however, tDCS of the M1 for visuomotor learning is less common and it was unknown whether it would lead to greater improvement of a visuomotor skill than practice alone. The aim of this study was to investigate the effects of M1 tDCS on the acquisition of a unilateral upper body motor skill that is highly visuomotor oriented. Sixty subjects were randomized into either M1 anodal or M1 SHAM groups and received stimulation while practicing a timing based videogame called Step Mania. Skill was assessed by analyzing how their timing accuracy of keystrokes and their movement errors changed from trial to trial. Timing accuracy was scored depending on how close their key stroke was to optimal timing based on the on-screen cues. Movement errors were indicated by incorrect key strokes, regardless of timing. The timing scores and movement errors were used to assess performance changes before, during, and after practice.

d.) Study Four –Visuomotor skill with M1 and cerebellar tDCS

i.) The first experiment of study four was done to compare the effects of M1 tDCS and cerebellar tDCS upon fast motor learning of a visuomotor video game task. The effect of tDCS of both areas was observed as they were for study three. The cerebellum, more than M1, is involved in timing and coordination of motor skills. Prior tDCS

research has shown that cerebellar tDCS can enhance visuomotor based skills, but not something such as a videogame. As tDCS has gained popularity in the gaming community, even without literature supporting its use, this is an area that must be explored. The aim of this study was to compare the effects of M1 anodal, cerebellar anodal, cerebellar cathodal, and SHAM stimulation on the acquisition of a timing based videogame skill. Additionally, visuomotor effects of tDCS have shown polarity independent results (i.e. both polarities causing the same benefits). This study sought to find any difference between anodal or cathodal cerebellar stimulation in the enhancement of skill acquisition. One hundred subjects were randomized into one of the four stimulation conditions – M1 anodal, cerebellar anodal, cerebellar cathodal, or SHAM. Skill was assessed identical to study three.

ii.) The second experiment explored the effects of complementary stimulation of both sites simultaneously upon fast visuomotor learning. Both M1 and the cerebellum serve specific roles during motor learning, however, together the M1 and the cerebellum form representations of movement sequences. Therefore, optimization of both the cerebellum and M1 function may lead to greater enhancements to motor skill than stimulation to either site individually. Although previous studies have stimulated 2 sites at once, none have investigated simultaneous stimulation of M1 and the cerebellum. Twenty-five more subjects received M1 anodal stimulation with concurrent cerebellar stimulation, but the polarity of cerebellar stimulation was based upon the results of experiment 1. The procedure and skill assessment were the same as experiment 1.

1.9.3 Aims

1. Study one aims to explore the effect of M1 tDCS on fast phase learning of a novel unilateral upper body gross motor skill.
2. Study two aims to explore the effect of M1 tDCS on fast phase learning of a novel unilateral upper body motor skill that requires high levels of dexterity.
3. Study three aims to determine if M1 is an appropriate tDCS target for enhancing learning of a novel unilateral upper body visuomotor timing-based videogame.
4. Study four (i.) aims to compare M1 a-tDCS, cerebellar c-tDCS, cerebellar a-tDCS, and SHAM stimulation to determine what the ideal targets and current directions are for improving learning of a timing based visuomotor skill videogame.
5. Study four (ii.) aims to explore the effect of complementary, simultaneous tDCS of both M1 and the cerebellum, with the cerebellar current direction based on the results of study four (i.).

1.9.4 Significance statement

Through the acquisition of new skills, motor skill learning allows for a nearly boundless variety in the repertoire of motor abilities. The fast phase of motor learning is particularly interesting as this phase enables the rapid addition of new skills when the need arises. Due to its modulatory effect and relatively simple application, interest in tDCS is growing both in and outside of the laboratory, with its applications for motor learning expanding into different activities with widely varying movement parameters.

However, there remain many questions about what brain areas are the appropriate targets to influence fast motor learning in a variety of tasks since there is a degree of task-specificity to motor learning and the brain areas involved. Although both M1 and cerebellum are active during early motor learning, whether they are ideal targets to improve real world motor skills, not just laboratory designed motor learning paradigms, remains to be conclusively determined.

CHAPTER TWO: ANODAL tDCS ACCELERATES ON-LINE LEARNING OF DART THROWING

2.1 Introduction

Practice and repetition of a task or skill promotes neuromotor adaptations that are ultimately characterized by performance improvements and/or skill acquisition. In the context of skilled task performance, this process is referred to as motor skill learning. Specifically, motor skill learning is defined as improved sensorimotor ability (often characterized by a shift in the speed-accuracy trade-off) that yields performance capabilities or skills beyond what was possible prior to practice. Reductions in movement variability between trials is also an indicator of motor skill learning, with smoother movements indicating greater skill.¹¹⁰⁻¹¹² Motor learning can also be categorized into both “slow” (late) and “fast” (early) stages. Slower phases of motor learning are generally characterized by robust and stabilized skill improvements, whereas faster phases typically demonstrate rapid, though often transient, improvements. These rapid within sessions adaptations are referred to as online skill learning.^{9,113} In most cases of online motor learning, individuals are engaging in isolated events or tasks with no intentions of regular follow up practice planned, such examples of this may include a game of pool, throwing darts, or shooting a basketball with friends. In these instances, the goal is within session improvements in task performance (e.g., closer to the target/reductions in variability).

Although it is known that M1 encodes movement parameters and modulates motor output, evidence of cortical plasticity within the region has made it clear that M1

also plays an acute role in the acquisition of motor skills.^{114,115} The descending output of M1 originates from coordinated activity of somatotopically organized neuronal ensembles whose orderly arrangement creates a motor map containing interdigitated representations of muscle synergies and basic motions.¹¹⁶ M1 is critical for the use-dependent acquisition and storage of muscle activation used in fast and precise movements; of which, most motor skill learning is targeting.^{117,118} Since it is known that a single session of online skill learning is too brief to induce long-term synaptogenesis or shifts in the M1 motor map, it is believed that there may be disinhibition of previously existing lateral connections or modulation of internal and external inputs to M1.⁹

tDCS has been used extensively as a tool for modulating performance or training effects of a skilled motor learning task via altering the excitability of targeted cortical regions.¹¹⁹ The effectiveness of tDCS on skilled motor learning has been debated considerably in the last decade. However, in the position paper by Buch et al.,¹¹⁹ it was shown that ~72% of studies reported an enhanced online learning effect with the application of tDCS in a single-day of training. Of these studies, 82% included stimulation of M1 only, or M1 with other brain regions. A variety of motor tasks have been used to demonstrate this, however, they have primarily been simple hand and finger based tasks using sequence learning, dexterity, reaction time, or movement tracking. While these simplified motor tasks offer useful insight to the benefits of tDCS in motor learning, they do not necessarily transfer to more complex, multi-joint movements requiring whole body coordination such as those seen in occupational tasks, activities of daily living, or sports.

Despite M1 being the most commonly targeted motor area for tDCS studies and the evidence for its role in skill acquisition, studies investigating M1 tDCS with complex motor skills are still limited. The vast majority of tDCS research has been focused on clinically relevant motor tasks with a translational component and not on recreational tasks or sports. It has been theorized that tDCS could be beneficial for improving performance of sport-based skills beyond a level attainable with normal training methods.^{120,121} Therefore, the purpose of this study was to examine the influence of M1 tDCS on motor skill learning during a dart throwing task.

2.2 Methods

2.2.1 Participants

Sixty subjects provided written informed consent. One SHAM subject and one c-tDCS subject were excluded from analysis after testing as their baseline dart throws were >3 standard deviations from the mean of the group, leaving 58 total subjects (n=20, n=19 cathodal and SHAM; 23.3 ± 3.9 yrs). All procedures were approved by the University's IRB and conducted according to the Declaration of Helsinki. All subjects were healthy and had no self-reported injuries to the upper limbs that would have limited their ability to perform a throwing motion. The Edinburgh Handedness Inventory (EHI) was used to determine the non-dominant hand in each of the subjects.¹²²

2.2.2 Procedures

The study was a randomized between-subjects, SHAM controlled design. As subjects were screened into the study, they were randomized to condition with a MATLAB algorithm. Subjects were blinded to their condition throughout testing and completed one session throwing darts at a dart board. The protocol (Figure 2.1) comprised a pre-test block of throws, a 20 min practice block of throws, and a post-test block of throws. During the practice block subjects received either a-tDCS, c-tDCS, or SHAM stimulation of M1.

2.2.3 tDCS

A Soterix Medical 1X1 Low Intensity transcranial direct current stimulator was placed on a cart closely behind the subjects so that it did not interfere with their throwing performance. a-tDCS and c-tDCS of M1 was delivered with previously determined safe and effective parameters (duration 20 min; current 1 mA; active electrode over M1 contralateral to the non-dominant hand and reference electrode over the supraorbital ipsilateral to the non-dominant hand). Current was delivered through rubber electrodes (25cm²) inside of saline-soaked sponges fixed in place with rubber straps. For SHAM, the current was ramped up and down over 30s.

2.2.4 Dart throwing task

Subjects threw steel-tipped, tungsten darts (26 grams) at an 18-inch diameter regulation dart board (Winmau Blade 5) with 20 radially divided sections. The board was

mounted 1.73m high on the wall and subjects stood behind a line that was marked at 3.05m in front of the board. From this location, subjects were instructed to throw at the bullseye as accurately as possible with their non-dominant hand. A researcher demonstrated basic dart throwing technique, though subjects were not required to use this form. The only instructions emphasized throughout the testing session was to use the same general dart-throwing technique during the entire session. This was done to prevent substantial changes in throwing form that may have impaired the within-session performance improvements. The dart throwing task was identical in all three conditions (a-tDCS, c-tDCS and SHAM). Each consisted of a pre-test block, a practice block and a post-test block. The electrodes were fitted and applied before the practice block and removed afterwards during a 5-minute rest period (Figure 2.1).

Prior to the pre-test block, subjects were allotted 3 familiarization throws. This was so subjects could orient themselves with the task and decide on a preferred throwing form. Excluding the 3 familiarization throws, a total of 15 throws were performed in both the pre-test and the post-test blocks. During the 20-minute practice block, subjects threw at an average pace of 3 to 5 throws per minute. After each throw and before removing the dart, an investigator used a measuring tape to find the distance between the center of the bullseye and the tip of the dart. The same measuring procedure was used for any darts landing outside of the board. For each throw, subjects received visual feedback of the dart's endpoint in relation to the bullseye and the measured distance from center was called out (by a researcher) as a form of verbal feedback. This was done to facilitate error correction for subsequent throws.

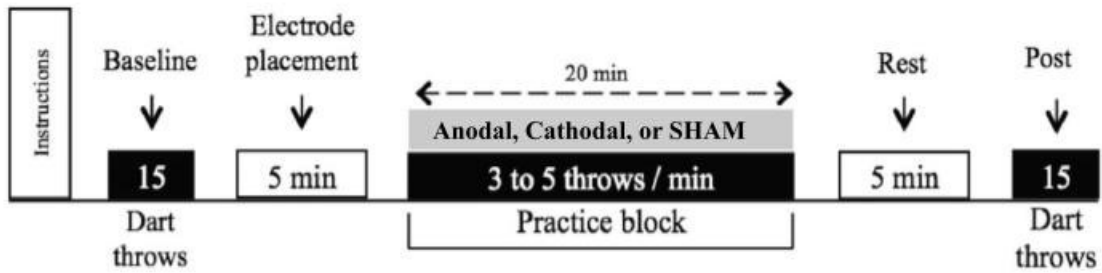


Figure 2.1. Experimental timeline

2.2.5 Statistical analysis

Large variability was expected since the subjects were learning to throw a dart with their non-dominant hand and we did note several cases where subjects indicated the dart felt unstable or uncomfortable during the throwing motion and release. Pretest and posttest scores were assessed with 15 throws; therefore, 1 extremely bad or extremely good throw could dramatically impact scores, but not actually reflect overall performance. In an effort to reduce the impact of such errant throws, the best and worst throws were dropped from the pre-test and post-tests of every subject.

Practice throws were divided into quartiles since each subject did not throw the exact same number of throws. The average number of throws per quartile were 23.2 ± 3.7 , 22.1 ± 2.4 and 21.8 ± 3.22 for anodal, cathodal, and SHAM, respectively. Gain scores (baseline mean – time point mean) were then calculated for each practice quartile and the post-test to demonstrate the change in performance over time relative to the baseline score.

Normality was tested with a Shapiro-Wilk test. Where normality was not met, normality was achieved with a square root transformation and test comparisons were

conducted to discern if non-normality caused any meaningful difference in the results. It is reported in the results where test comparisons were conducted. There were no instances where non-normal data caused any meaningful differences in the results, thus the untransformed values are reported.

Baseline performance (mean distance from bullseye) and total number of practice throws was compared across groups with a one way ANOVA. A mixed ANOVA (3 groups x 5 time points [4 quartiles, post-test]) with repeated measures on time point was used to compare the gain scores and effect sizes calculated as partial eta squared (η_p^2). A p-value of 0.05 was considered statistically significant. Bonferroni post-hoc tests were used to determine differences for multiple comparisons.

2.3 Results

There was no statistically significant difference in the amount of practice throws completed between groups ($F [2, 55] = 1.089, P = 0.344$). There was no significant interaction between the stimulation condition and time on gain scores ($F [5.896, 162.142] = 1.942, P = 0.399, \eta_p^2 = 0.037$). Mauchly's test of sphericity was significant ($P < 0.001$); thus, a Greenhouse-Geisser correction was used. Across all groups, there was significant main effect for time ($F [2.948, 162.142] = 10.295, P < 0.001, \eta_p^2 = 0.158$), indicating that gain scores increased across practice, with gain scores during the post-test significantly higher than in the first quartile of practice ($P = 0.006$, Figure 2.2). The pairwise comparisons of time, within condition, showed that a-tDCS significantly improved performance between the first and second quartile of practice ($P = 0.004$) and

the increased performance was maintained through the post-test ($P = 0.013$). Despite the significant increases between the first and second quartiles with a-tDCS, the performance did not continue to significantly improve throughout the remainder of the practice.

Neither c-tDCS nor SHAM stimulation resulted in significant increases in gain scores across time.

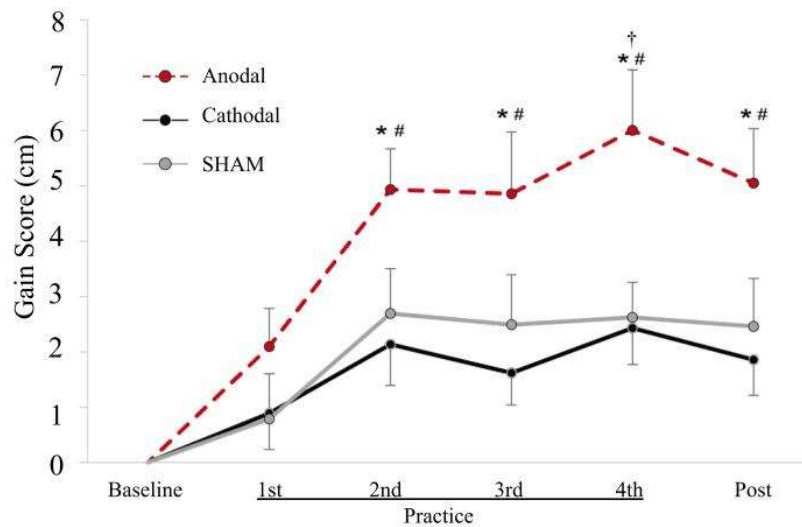


Figure 2.2. Data shows the change in gain scores over the 4 quartiles and the posttest. *Indicates the Anodal condition was increased from the second quartile through the end of the post-test. # indicates the gain score was higher for the Anodal condition compared to the Cathodal condition. † indicates the gain score was higher for the Anodal condition compared to the SHAM condition. All symbols denote significance $P < 0.05$.

There was a main effect observed for stimulation, demonstrating a statistically significant difference in mean gain scores between stimulation groups ($F [2, 55] = 4.989$, $P = 0.01$, $\eta_p^2 = 0.154$) with mean a-tDCS gain scores being significantly higher than c-tDCS ($P = 0.015$) and SHAM ($P = 0.049$). The pairwise comparisons between stimulation conditions showed no significant difference in gain scores until the 2nd quartile of practice, with a-tDCS gain scores significantly higher than c-tDCS gain scores ($P = 0.036$). Gain scores for a-tDCS remained significantly greater through the post-test

($P = 0.011$ to 0.041). There was a significant difference between a-tDCS and SHAM gain scores in the last quartile of practice, with a-tDCS showing greater improvement ($P = 0.017$). At baseline, there was a difference ($F [2, 55] = 3.997, P = 0.024$) between anodal ($18.71 \text{ cm} \pm 5.71 \text{ cm}$) and cathodal ($14.88 \text{ cm} \pm 3.06 \text{ cm}$) groups ($P = 0.036$), but not between anodal and sham ($15.40 \text{ cm} \pm 4.58 \text{ cm}$) ($P = 0.087$).

To simplify the results, we have also presented the gain scores from the pre-test to the post-test for all 3 conditions in Figure 2.3. A one way ANOVA indicated a difference between the groups in overall learning ($F [2, 55] = 4.061, P = 0.023, \eta_p^2 = 0.129$) The improvement in performance was significantly greater in a-tDCS condition than the c-tDCS condition ($P = 0.03$), but not the SHAM conditions ($P = 0.104$).

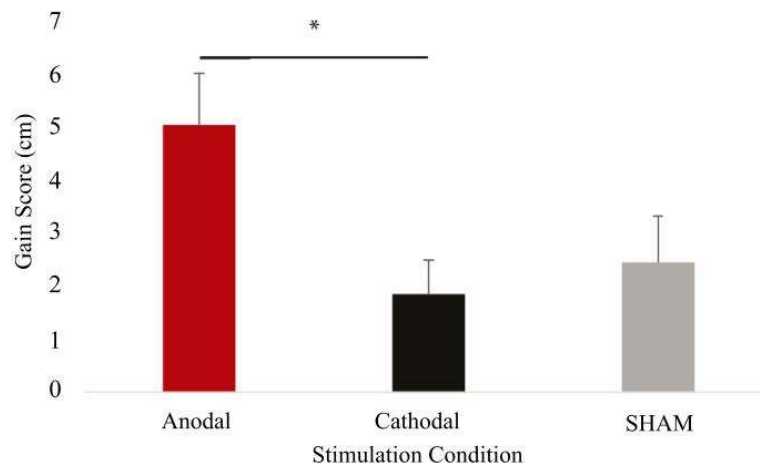


Figure 2.3. Data shows the gain score from the baseline dart throwing to the posttest dart throwing. *Significant differences were noted between a-tDCS and c-tDCS conditions

2.4 Discussion

The results of the present study indicate that there is an effect of a-tDCS of M1 on the acquisition of dart throwing skill compared with c-tDCS and SHAM conditions.

Improved performance was indicated by higher gain scores which represent distance moved towards the bullseye. The gain score for a-tDCS was significantly higher by the second quartile of practice and remained elevated through the post test. It is important to note that while the improvement was sustained above the first quartile of practice, no significant improvements were observed thereafter. If the quartiles are not considered, and only the percent improvement (pre-test to post-test) in dart throwing performance is examined, the a-tDCS condition (24.2%) was significantly greater than the c-tDCS condition (11.7%), but was not different from SHAM (13.6%, Figure 2.3).

There were small, and statistically nonsignificant performance increases (see Figure 2.2 & 2.3) in both c-tDCS and SHAM conditions. Some degree of improvement was expected in online learning the SHAM conditions. However, in comparing results with the c-tDCS condition, two interpretations can be drawn: 1. c-tDCS impaired online learning of the dart throwing skill because the results trend towards a lower (though statistically insignificant) gain score, or 2. That c-tDCS did not exhibit any effect on learning since the improvements in dart throwing were statistically consistent with the SHAM condition. Our results would suggest that the c-tDCS condition did not worsen performance of the task significantly despite evidence that showing that c-tDCS can cause inhibition of M1.^{65,123,124} Though, at first glance, our results may appear to suggest a mild inhibitory effect of c-tDCS, more research is needed to make an argument for c-tDCS impairing online learning to any meaningful degree.

M1 appears to play an important role in fast or online motor learning,¹¹⁹ though the adaptations likely involve activity in other cortical-loop circuits.^{113,125} This makes non-invasive methods of M1 stimulation interesting targets for investigation. Since tDCS

provides stimulation over an area of approximately 25cm², it can effectively reach and influence many of the cortical motor regions representing the upper limb. Considering that dart throwing is a predominantly upper limb involved task and most individuals are completely untrained in their non-dominant limb, we were able to create a complex, novel, skilled motor task and observe the effects of M1 stimulation tDCS on the early stages of motor learning.

Though our model does well to represent a novel task insofar as the non-dominant limb is concerned, important considerations must be made regarding the generalizability of these results to the dominant limb. The non-dominant limb may have a smaller, underdeveloped cortical representation than the dominant limb and therefore be prone to a more exaggerated effect from a-tDCS.¹²⁶ Alternatively, hemispheric asymmetries may contribute through greater or lesser interhemispheric inhibition depending on which hand is non-dominant.¹²⁷ It is also impossible to gauge to what degree previous dart throwing experience may have contributed to interlimb transfer of skill, however, subjects reported general naivety to darts (i.e. mostly inexperienced).

Though, our data suggests a positive effect for a-tDCS in fast motor learning, the mechanisms by which this takes place are still unclear. Plenty of studies have shown LTP-like activity resulting in greater motor cortical excitability within a single skilled training session; which may be driven by the strengthening of already established connections, or by the unmasking (disinhibition) of previously existing lateral connections between M1 neurons.^{9,114,128} The duration of practice in the present study is far too short to induce long-term synaptogenesis, motor map shifts, or potentially even

consolidation,¹²⁹ though it is likely the single practice session is enough to cause the subjects to retain some improvement in performance.¹¹³

Though all three conditions appeared to demonstrate some degree of improvement from baseline, only the improvement seen in the a-tDCS condition was statistically significant. As mentioned previously, there is an abundance of literature to suggest that the application of tDCS may accelerate motor learning likely through increases in excitability and modifying the underlying intrinsic state of the neural networks subserving the motor movements.^{119,130,131} The findings in this study appear to further confirm the positive effects of tDCS in motor learning. A noteworthy difference between our study and many others is that we used a very simple electrode montage (M1 contralateral to throwing arm), as opposite to bilateral M1 tDCS or tDCS of M1 paired with tDCS of other cortical regions. The fact that the addition of this simple electrode configuration was enough of a stimulus (at 1mA for 20 minutes) to enhance the learning of the dart throwing task, shows the promise of these stimulation methods even at relatively low intensities and commonly used durations.

Dart throwing is, perhaps, best known simply as a recreational activity or pub sport. However, it is because of the motor complexities involved in this task that it was chosen for this experiment. Dart throwing involves coordinating dexterous control of the digits while simultaneously incorporating multi-joint limb articulations. Throwing also requires dynamic body and postural stabilization to prevent unwanted perturbations during execution. Our dart throwing model more accurately depicts the practical applications of tDCS than other previous studies involving simplistic actions using just the digits or simple reaching motions.

Another thing that makes the present study unique is that we examined a task that involves a very fundamental motion to human movement (throwing), yet in a way that is specific to a sport (darts). While some sports have a large strength or endurance-based component to success, the application of tDCS has very mixed outcomes.¹³² The use of tDCS in skill centered sports such as darts may be able to significantly influence performance and ultimately a professional player's earnings in their respective sport. tDCS as a potential performance enhancing intervention is gaining more and more attention in recent years.^{120,121} Furthermore, it seems that when applied with the most common current intensity and duration recommendations ("low-intensity", 1-2mA, <30 minutes), tDCS is considered safe.¹³³ This may provide athletes with an alluring approach to augmenting the effectiveness of their practice. However, since the use of tDCS is currently unregulated in sport and in many other applications, there exists the concern for abuse either by heightened intensities, improper/imprecise application, and repeated/prolonged use. All of these things must be taken into consideration in moving forward with the use of tDCS outside of the realm of clinical or scientific applications.

2.5 Conclusion

NIBS methods such as tDCS show promise in rehabilitation and also sport and recreational setting for enhancing motor skill learning. We have shown that within a single session of dart throwing that a-tDCS of M1 can significantly improve performance over SHAM and c-tDCS conditions. Recent research has shown that M1 might not even be the primary target of neuroplasticity, at least during motor sequence learning, so the

observed effects in the present study only enhance the promise of tDCS during practice of a task.¹³⁴ While this is not a traditional rehabilitation environment where repeated practice would occur, this is representative of recreational games where faster online learning would be desirable.

CHAPTER THREE: NEUROENHANCEMENT OF A DEXTEROUS MOTOR TASK WITH ANODAL TDCS

3.1 Introduction

Motor skills consist of a sequence of component movements that are executed in a particular order and with certain parameters (force, velocity, timing, joint angles) to achieve a specific outcome; such as throwing a baseball, grasping and taking a drink from a cup, or walking from place to place.¹¹⁸ When learning a new motor skill, the M1 demonstrates changes in excitability and structural and functional changes in the synaptic connections within the representations for the movements making up the skill. The degree of cortical plasticity, therefore, can be attributed to the performance changes expected during skill practice.

The type of motor skill practiced can exhibit a large influence over the learning process and the cortical regions demonstrating plasticity. For instance, adaptation to walking and arm-reaching (e.g. split-belt treadmill and force fields, respectively) can be mediated through the cerebellum,^{135,136} whereas we know the strong contribution M1 has to fine, dexterous hand movements through large digit representations and direct cortico-motoneuronal connections.^{137,138} Dexterous movements that are precise, voluntary, and coordinated are developed over time through practice. A great example of this is with long-time musicians, where the repetitive movement causes lasting plastic changes to M1.^{139,140} Musicians, though having high inter-individual differences of obtaining, practicing and maintaining specialized motor skills, still show differences in structures

and functions of the hand motor regions of the brain compared with non-musicians.¹⁴¹ A study by Scheurich et al.¹⁴² showed that musicians have more precise control in circle drawing tasks and an increased error-correction mechanism during a tapping task, compared to non-musicians. Thus, the improvement in fine motor skill learning with the hand and digits appears to be mediated, at least in part, through M1.

NIBS techniques such as tDCS have been used to enhance or facilitate plasticity in M1.^{65,143} In particular, a-tDCS elicits an increase in excitability in the brain tissues within the region electrically activated. Through postsynaptic somatic spiking causing long-term potentiation, and enhanced neuron network effects,¹⁴⁴ the modifications in cortical plasticity after a-tDCS correspond to improvements in motor function.¹⁴³ In studies examining hand function, application of a-tDCS showed significant improvements in both dominant and non-dominant hands.^{145,146} The use of tDCS has been shown to be particularly relevant in the acquisition and early consolidation phase of motor learning, and results in changes in the amplitude of motor evoked potentials of the stimulated cortical area for up to 90 min after stimulation.^{65,145}

In recent years there has been an increased focus of neurocognitive enhancements, or the practice of improving the neurological function of healthy individuals. With the development of tDCS as a safe, non-invasive method of potential neurocognitive enhancement, more research using tDCS has been explored. The rationale behind these studies for healthy individuals is the potential to accelerate the skill acquisition and learning process in complex tasks that would otherwise take a long time to become proficient at.¹⁴⁷ The use of tDCS in healthy individuals can be used in the areas of education, military, and the medical field to enhance learning rate and performance,

where skill optimization is critical. For instance, Ciechanski et al.¹⁴⁸ used tDCS over the dominant primary motor cortex during simulation-based surgical training and showed that the addition of stimulation resulted in significantly improved pattern-cutting scores. Additional studies from Ciechanski and colleagues^{149,150} have reported similar enhancements in laparoscopic skills tasks and neurosurgical resection tasks, while robotic suturing and knot-tying tensile strength may also be improved.¹⁵¹ In a time where the demands of surgeons are high and the opportunities for training are low, tDCS may be a key technique used to enhance the speed of skill acquisition and multitasking capabilities of new surgeons.

Modulation of the M1 via tDCS to produce enhanced fine motor skills has been seen preliminarily in areas of complex task acquisition such as training for surgeons and musicians.^{142,148} The present study aimed to determine if tDCS could enhance the speed of pin placement during an O'Connor Tweezer Dexterity Task. This specific task examines the manual aptitude for work involving precision and steadiness in the use of small hand tools. Since M1 tDCS has been shown to increase the speed of skill acquisition in dexterous motor tasks, it was hypothesized that a-tDCS concurrent with practice, would result in more pins placed for the task. The possibility that tDCS could increase neurological enhancements in healthy individuals could have larger implications in the advancement of surgical training as well as in athletic, military, and other occupational realms.

3.2 Methods

3.2.1 Participants

Forty young, healthy adults (male and female, ages 22.18 ± 3.73) were recruited for this study. Subjects self-reported no history of significant neurological disorder or musculoskeletal conditions that might impact tasks of manual dexterity. All procedures in this study were reviewed by the university's IRB and subjects provided written informed consent before participating in the study. Handedness was determined with the EHI.¹²² Right handed scores were $> +40$; Left handed scores were < -40 ; scores ≥ -40 but $\leq +40$ were ambidextrous. In cases of ambidextrousness, the subject's preferred writing hand was considered their dominant with the rationale that the tweezer grip was most similar to holding a writing utensil.

3.2.2 Procedures

The study was a randomized between-subjects, SHAM controlled design. Participants were randomly assigned by MATLAB algorithm to one of two groups (a-tDCS, $n=20$ or SHAM, $n=20$) as they were screened into the study and were blinded to their condition throughout testing. a-tDCS and SHAM groups were matched for age (21.75 ± 3.46 yrs and 22 ± 4.02 yrs, respectively), sex (11 males, 9 females), and handedness (15 right, 4 left, 1 ambidextrous). Subjects completed a single testing session while receiving either a-tDCS stimulation or SHAM stimulation of the M1 region contralateral to the non-dominant (active) arm. During this session, subjects performed

the O'Connor Tweezer Dexterity task with the non-dominant arm. The time to complete a 50-pin placement task was assessed before and after 20 min of practice with either a-tDCS or SHAM stimulation (see Figure 3.1). All testing was conducted between 9:00 am and 3:00 pm.

3.2.3 Stimulation parameters

A Soterix 1x1 stimulator was used for both stimulation conditions. The stimulation parameters used in this study have been established as safe and effective in previous literature.¹⁵² A pair of rubber electrodes (5x5cm in size) were placed inside of saline soaked sponges and each were fixed on the scalp with a rubber strap. The active electrode was positioned directly above the hand representation of the M1 region contralateral to the testing hand and the reference electrode was placed on the ipsilateral scalp in the supraorbital region (Fp1 or Fp2, respectively). The a-tDCS stimulation lasted for 20 mins with a 30 second ramp up to a current of 1 mA at the beginning and a 30 second ramp down at the end. The SHAM condition simulated stimulation with a 30 second ramp up to 1mA followed by an immediate shut off. This was in an effort to blind subjects to their stimulation condition by providing a brief, superficial sensation of stimulation to the scalp.

3.2.4 O'Connor tweezer dexterity task

The O'Connor Tweezer Dexterity Task is a fine motor task that has been used as an assessment of manual dexterity and force stability in dental practitioners,¹⁵³

surgeons,¹⁵⁴ and various other occupations. Subjects completing the task must pick up small metal pins (1in long, 1/16in diameter) from an attached reservoir and place those into holes on an adjacent peg board. This task requires the subject to modulate pinch-force to allow the pins to assume a mostly upright (vertical) orientation before placement.

After completing the EHI, subjects were seated at a table with the O'Connor Tweezer Dexterity Task positioned 0.3 meters in front of them with the pin tray oriented at 90 degrees towards the testing (non-dominant) hand. Prior to testing, subjects were given standardized instructions to pick up one pin at a time and to fill the holes as fast as they could. A demonstration was provided on how to hold the tweezers, however, subjects were allowed to self-select their own specific grip strategy. Five practice pins were allotted to allow subjects to familiarize themselves with the grip and the demands of the task.

Although no explicit instructions were provided on how to best grip the tweezers, subjects were required to maintain the ulnar border of their testing hand towards the table to avoid disruption of the task via internal/external rotation. Subjects were instructed to maintain this self-selected grip throughout the entire testing session and feedback was provided from the researchers if deviation was observed.

The pre-test and post-test assessments were identical, both consisting of the placement of 50 pins. A timer was started upon placement of the first pin and stopped when the 50th pin was placed. Subjects were scored according to the time to completion. During both testing and practice blocks, subjects were instructed to ignore any dropped or spilled pins and to select a new pin from the tray. Pins were placed from top to bottom, starting at the outermost column of the board. Each column consisted of 10 holes.

The practice block, during which subjects received a-tDCS or SHAM stimulation, subjects were asked to continuously place pins for the entire 20-min practice time. The subjects were required to sit the tweezers down and to rest their hand for 30 seconds after completing each column (10 pins) to avoid fatigue. Dropped pins were cleared from the board between each column. Additionally, if the subjects were reaching the last column then the pins were cleared on that column during the rest period so that the subject had somewhere to continue placing the pins. Subjects were given 5 minutes of rest time between the pre-test, practice, and post-test blocks.

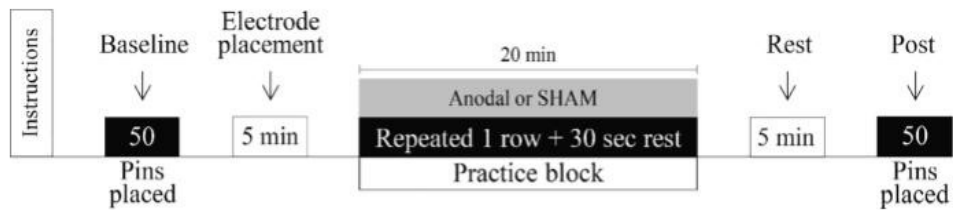


Figure 3.1. Experimental timeline

3.2.5 Statistical analysis

The time (seconds) required to place 50 pins was the main outcome variable. For the pre-test and post-test, this was just the time to complete the 50 pin task. For the 20 min practice, the time actively placing the first 5 columns of 10 pins (excluding rest) was used. To further investigate changes in performance during practice, the average time per column was calculated for the first and the second halves of practice since each subject did not complete the same amount of practice. Normality was tested with a Shapiro-Wilk test and a Log10 transformation was used to improve normality in all non-normally distributed time data. Since ANOVAs are robust to violations of normality, tests were

performed on both the original non-normal data and the transformed data to determine if the lack of normality was affecting the results in any meaningful way. Any discrepancies are highlighted in the results section. A mixed ANOVA (2 groups [a-tDCS, SHAM] \times 3 time points [Pretest, Practice, Post]) with repeated measures on time point was used to compare the time to place 50 pins. A second mixed ANOVA (2 groups [a-tDCS, SHAM] \times 2 time points [first half, second half]) with repeated measures on time point was used to compare the average time per row for the first and second halves of practice. Overall learning was calculated as the percent change in time required to place 50 pins between the pre- and post-tests. All between group comparisons were assessed using two-tailed independent t-tests. Bonferroni corrections were used for repeated measures. All statistics were performed using SPSS (v.26).

3.3 Results

Groups performed a similar amount of practice overall with 143.15 ± 19.8 pins and 139.90 ± 30.08 pins for a-tDCS and SHAM, respectively ($P = 0.690$, Figure 3.2). All time data were non-normally distributed ($p < 0.05$), except for the Anodal group practice ($p = 0.086$), as assessed by Shapiro-Wilk tests. The skewness of time data were assessed and found to all be positively skewed, ranging from 0.441 to 2.021. After Log10 transformation, all time data were normal ($P > 0.05$) or approximately normal (Anodal post-test $p = 0.026$)

The meaningful effect of the non-normality was on the determination of a statistically significant interaction. For the transformed time data there was a significant

interaction of between the stimulation condition and time ($F[1.728, 65.662] = 4.136, P = 0.025$) whereas the analysis of the raw time data was not statistically significant; however, it did approach significance despite the non-normal distribution ($F[1.808, 68.72] = 2.898, P = 0.067$). In both cases, Mauchly's test of sphericity was significant ($P = 0.007$ and $P = 0.024$) and a Huyhn-Feldt correction was used. Post hoc analyses of the interaction indicated that the time to place 50 pins was statistically significantly lower for a-tDCS group than SHAM group in the post-test ($P = 0.007$, Figure 3.4).

For the assessment of practice performance, there was a significant main effect of time ($F[1, 38] = 27.119, P < 0.001$). Pairwise comparisons within condition showed that a-tDCS and SHAM both had significantly lower times for the last half or practice compared to the first ($P = 0.01$ and $P < 0.001$, respectively; Figure 3.3). There was no significant interaction between time and condition for the practice ($F[1, 38] = 0.113, P = 0.718$). The main effect of group was also not significant ($F[1, 38] = 0.131, P = 0.72$). Non-normality had no meaningful effect on the results.

To summarize the results, we have also presented the percent change from pretest to posttest. A two-tailed independent t-test showed that the a-tDCS group had a greater improvement than SHAM ($P = 0.028$, Figure 3.5).

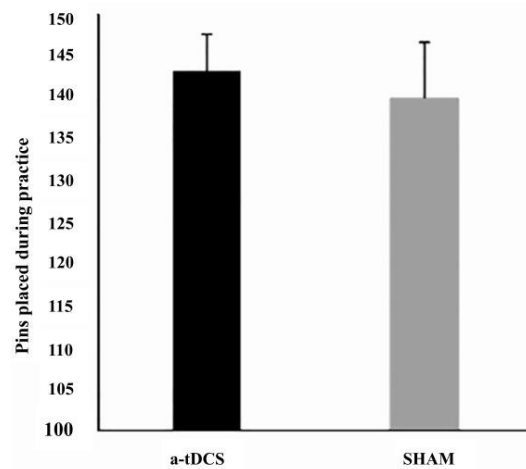


Figure 3.2. Total number of pins placed during the 20 min practice period. There were no differences between the two conditions. Error lines denote standard error.

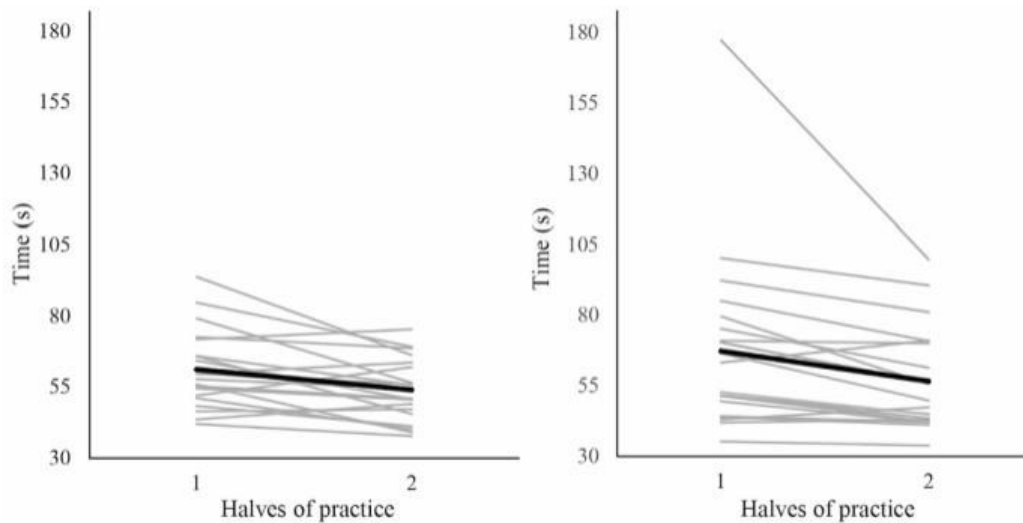


Figure 3.3. Average time per 10-pin column (seconds/row) for the first and second halves of the 20 min practice for each individual subject in the a-tDCS (Left) and SHAM (Right) group. Black solid line denotes mean change for the group. Both groups improved significantly from the first half of practice to the second (a-tDCS $P=0.01$; SHAM $P<0.01$). There were no differences between groups.

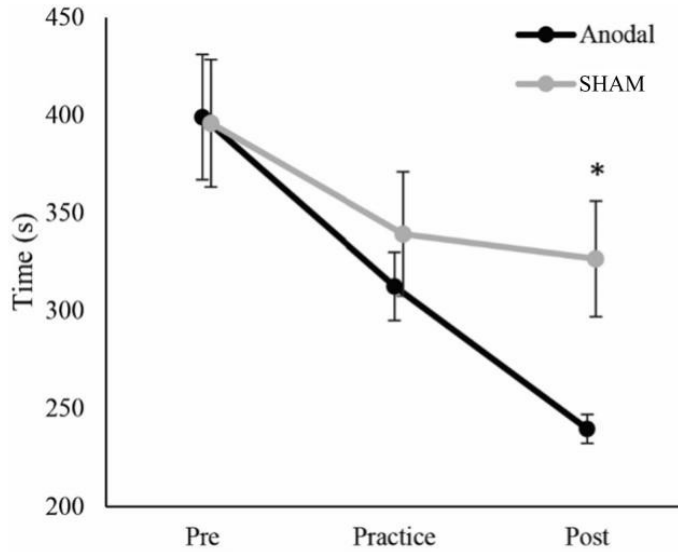


Figure 3.4. Time (seconds) to complete placing 50 pins for the pre-test, practice, and post test across the a-tDCS and SHAM conditions. Error lines denote standard error. There was a significant stimulation X time interaction and the posthoc analysis showed a significant difference between the a-tDCS and SHAM conditions at the post-test (* <0.05).

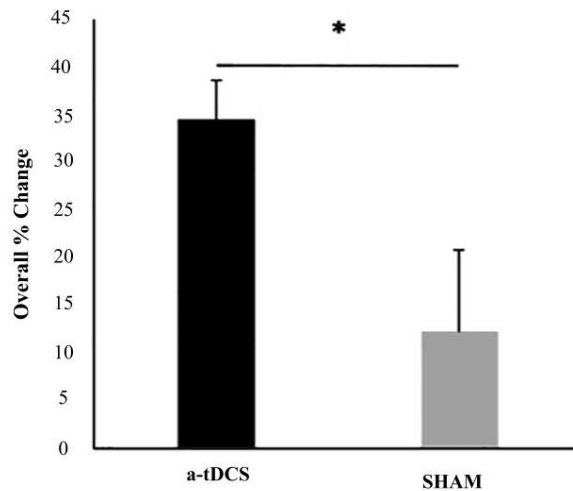


Figure 3.5. The percent change in time to place 50 pins (pre- and post-test time) showing the overall improvement in the O'Connor Tweezer Dexterity Test. The a-tDCS condition showed a significantly greater percent improvement compared to SHAM (* <0.05). Error lines denote standard error.

3.4 Discussion

The main finding of the present study is that a-tDCS over M1 improves the rate of fine motor skill learning as evidenced by an increased speed of pin placement in the O'Connor Tweezer Dexterity Task. The a-tDCS condition demonstrated a significantly lower time to place 50 pins and a greater overall percent improvement in time from pre- to post-test compared with the SHAM condition. Both groups performed similarly in the pretest and both placed similar amounts of pins during the practice session, indicating that no significant differences existed in baseline ability and practice quantity. The only notable difference between groups was the application of brain stimulation. It can therefore be assumed that any differences in outcomes between the conditions were likely the result of neuroplastic changes enhanced with a-tDCS stimulation.

Our findings are in line with the previous literature indicating tDCS as an effective tool for enhancing the rate of motor learning and fine motor task performance.^{145,146} The majority of previous tDCS dexterity studies have focused largely on non-tool tasks such as the Purdue Pegboard Test, cup stacking, or finger tapping, where reaction time and execution time are the most important variables to task performance.¹⁵⁵ Recent work by Ciechanski and colleagues suggests that the benefits of tDCS may extend to fine motor tasks involving the skilled manipulation of surgical tools and instruments, where execution time and force steadiness will primarily determine the success of the procedure.¹⁴⁸⁻¹⁵⁰ The O'Connor Tweezer Dexterity Task is a good representation of the experimental control of small, specialized tools that would be seen in occupations such as medicine and engineering. A 2009 review of various dexterity

tasks found the O'Connor Tweezer Dexterity Task to demonstrate “good-to-excellent predictive validity” when assessing disability and Activities Daily Living subscale scores,¹⁵⁶ though additional evidence suggests that O'Connor Tweezer Dexterity Task performance may predict success in various medical settings.^{157,158} Although this task has been utilized in many areas, to our knowledge, ours is the first study using this task in combination with a-tDCS.

The precise modulation of grip force is key to performance in tasks of manual dexterity.¹⁵⁹ This is especially true in tasks involving the use of fine instruments.^{160,161} It is important to note that during our study subjects were instructed to point their elbow towards the floor and to focus on adjusting grip force to change the pin angle. If subjects applied too much grip force, this often resulted in a fixed pin angle that was difficult to place within the board. A common strategy employed when grip force resulted in a fixed pin angle was to rotate the arm to reorient the pin. To mitigate this, researchers provided subjects with a verbal reminder to maintain a downward elbow if arm rotation was noticed. This ensured that pinch force was the primary determinant of task performance. Since strategies of pin manipulation were similar between groups, our use of a-tDCS over the M1 region should therefore explain differences in task performance between groups.

To ensure we used a novel task, we required subjects to use their non-dominant hand. However, important considerations should be made regarding the generalizability of these results to the dominant hand. One such consideration is the likelihood of asymmetry between hemispheres. It is well established that asymmetries exist between the cortices, especially in relation to the upper extremities and hand dominance. With somatotopic mapping of the M1, it has been shown that the dominant hand motor cortex

representation is more developed than for the non-dominant hand.^{126,162} This apparent lesser development within the non-dominant cortex may result in a more pronounced learning effect with any sort of practice or stimulation compared to the dominant side. The results of our study may, therefore, slightly overestimate the effect of a-tDCS in motor task learning if applied to the dominant limb.

Finally, since our study tested the non-dominant hand, it is fair to assume that the O'Connor Tweezer Dexterity Task was a mostly novel task regardless of prior exposure. During the initial screening, subjects reported little to no experience with the O'Connor Tweezer Dexterity Task, or even tweezers, specifically. However, the possibility of interlimb transfer still persists if any subjects possessed extensive experience with similar manual dexterity tasks involving the use of small tools. To our knowledge, none of the subjects included in this study were involved in occupations or hobbies involving these sorts of tasks. Regardless, our decision to test the non-dominant hand should be sufficient to ensure a degree of subjective novelty with the task.

As previously mentioned, the only differences between groups within our study was the type of stimulation received (anodal vs SHAM). Since subjects in the a-tDCS group demonstrated a faster time in the post-test, it is reasonable to assume that they would have also placed more pins during the timed practice block. However, our analysis revealed no significant differences between groups in the total number of pins placed. This is important to note because a-tDCS appears to have improved performance directly from stimulation and not as a byproduct of greater total quantity of practice, since the quantity of practice directly influences the degree of motor adaptation.¹⁶³⁻¹⁶⁵ Furthermore, since the pre-test scores between groups were not significantly different, we can also

assume that neither previous experience, nor interlimb variability influenced our results in a significant way.

3.5 Conclusion

Previous a-tDCS studies examining tasks of manual dexterity have demonstrated results congruent with our findings. As discussed in the review paper by Patel and colleagues, a modest body of literature exists to support the efficacy of M1 a-tDCS as a tool for enhancing learning during tasks of manual dexterity.¹⁵⁵ These findings add to, and build upon, that body of literature by demonstrating that a-tDCS applied to M1 can increase the aptitude for manual precision and steadiness that is necessary for delicate and skillful manipulation of small tools at a fast rate. Future studies should explore the use of a-tDCS in occupation-specific tasks such as surgery, model building, or microelectronics.

CHAPTER FOUR: ANODAL M1 tDCS ENHANCES ONLINE LEARNING OF RHYTHMIC TIMING VIDEOGAME SKILL

4.1 Introduction

Motor learning is fundamental in everyday life for acquiring and honing skills that range in complexity from relatively simple, like reaching and pressing a button, to more complex skills requiring coordinated sequential actions such as learning a piece of music on an instrument or throwing a ball. Motor skill improvements can accrue during a single practice session (online) or after practice is completed (offline), with both contributing over time to long-term retention.¹⁶⁶ The online and offline skill changes comprise fast and slow stages of learning, with fast stage learning occurring early on, markedly during skill acquisition, and slow stage occurring later with incremental gains over multiple practice sessions.^{9,10} The motor learning process is underpinned by neuroplastic changes across a spatially distributed network of interconnected brain regions.¹⁶⁷ Which areas are involved and the extent to which plasticity within them may subserve learning, largely depends upon the characteristics of task and the stage learning.¹⁶⁸

Evidence of learning related cortical plasticity in the M1 after skill practice has indicated that it contributes to motor skill acquisition. M1 is crucial for the use-dependent acquisition and storage of muscle activation for fast and precise motions associated with skillful performance.^{5,8} When a motor skill is practiced, somatotopically specific changes arise via LTP-like plasticity within M1 that improve synaptic connectivity and efficiency amongst the ensemble of cells activated to generate the movements of the skill.^{169,170} The

principal result of this process is enlarged cortical representations of the muscles involved in the task and/or facilitation of MEPs, indicative of increased cortical excitability, as assessed by TMS.^{171,172} Short bouts of skill practice (10 to 30 minutes) have been shown to elicit acute increases in M1 excitability.^{172,173} Although early practice-related plasticity is relatively transient in the short term,¹⁷⁴ it is believed to be an important initial step of fast motor learning and skill acquisition.^{9,172} Based on these short term mechanisms as well as the more permanent structural and functional cortical reorganization associated with extensive practice and skill expertise,^{34,47,171,175} M1 is a site of particular interest for investigating motor learning.

tDCS is a NIBS technique for modulating cortical excitability. By passing a current between two electrodes placed on the scalp, tDCS provides a sub-threshold, transcranial stimulation to the underlying cortical surface. Directional flow of the current between these electrodes determines the stimulation polarity (positive, Anodal; negative, Cathodal).¹⁷⁶ a-tDCS in particular has been used to enhance cortical excitability and LTP-like plasticity in M1 corresponding with improved motor function.^{74,100,177} tDCS has been shown to be particularly relevant in the acquisition and early consolidation phase of motor learning and evidence suggests that it is safe for facilitating motor learning in healthy individuals^{74,84} as well as those suffering from neurological disorders.^{178,179}

Improved performance from tDCS application to M1 during practice has been reported for several upper limb motor tasks where skill is usually assessed through changes in speed (reaction or movement time), accuracy, the relationship between those two qualities, or reduced variability.¹⁷⁷ Most studies have used laboratory based tasks,

such as the SRTT, SFTT, and SVIPT that offer highly controlled, simplified environments.^{74,81,177} Although lab-based tasks provide precise measurements and high degrees of control, they lack the complexity and visual-motor demands that most normal everyday tasks often involve, making generalization to real-world tasks limited. Nevertheless, these studies lend support to M1's important role in fast stage learning and potential as a target for tDCS to benefit learning.

The benefit of M1 tDCS on motor skill acquisition has been demonstrated with an increasing number of tasks with expanding complexity.¹⁸⁰⁻¹⁸³ Videogames are emerging as a potentially useful tool to study motor learning since they involve diverse combinations of perceptual, attentional, cognitive, and motor skills, and practice can lead to training-induced learning.^{184,185} Although there are reports of competitive gamers using tDCS to enhance performance,¹⁸⁶ the effect of M1 tDCS in the context of gaming-based motor skill has only recently been initially investigated.¹⁸¹ With comparable motor demands to laboratory tasks, but more visually complex environments and precise temporally-constrained inputs, video games present a novel way to study the effects of M1 tDCS on motor learning. Given the task dependency of tDCS effects for relatively simple tasks,^{91,177,187} it is unclear how M1 tDCS will influence the acquisition of a rhythmic sequence tapping task with complex visuomotor and auditory processing demands. Therefore, the purpose of this study was to investigate how M1 a-tDCS influences the acquisition of a timing-based video game skill.

4.2 Methods

4.2.1 Participants

58 total subjects participated in the study ($n = 29$ per group; age 22.27 ± 2.78 yrs). Participants were free of neurological or musculoskeletal impairments that could impact performance of the task. Participants that were taking medications that could influence learning, such as stimulants for ADHD, were also excluded. Handedness was determined with the EHI.¹²² Right-hand dominance was identified with scores $> +40$, left-hand dominance with scores < -40 , while scores ≥ -40 and $\leq +40$ were ambidextrous. In cases of ambidextrousness, the subject's preferred writing hand was considered their dominant.

The study was a randomized, between-subjects, SHAM controlled design. Participants were randomized to an a-tDCS or SHAM stimulation group (SHAM) as they were screened into the study and were blinded to their condition for the duration of testing. The two groups were relatively matched for age (a-tDCS = 22.70 ± 2.96 yrs and SHAM = 22.34 ± 2.64 yrs) and sex (a-tDCS = 14 males, 15 females; SHAM = 15 males, 14 females). For handedness, considering preferred writing hand in the case of an ambidextrous inventory result, each group had 25 right-handed individuals and 4 left-handed individuals. All procedures were approved by Indiana University's IRB and conducted according to the Declaration of Helsinki and all subjects provided their written informed consent before participation in the study.

4.2.2 Procedures

Participants completed a single testing session while receiving a-tDCS or SHAM stimulation over M1 contralateral to the non-dominant (active) hand. During the session, subjects performed a timing-based dexterous video game task with the non-dominant hand. The protocol included 2 familiarization pre-test blocks, 5 practice blocks while receiving either a-tDCS or SHAM, and a post-test block 5 min after cessation of practice. Familiarization pre-test scores were used to determine whether the task difficulty was adequate to demonstrate motor learning during the practice period. If the task was too easy or too hard based on the familiarization trial performance, the difficulty was increased or decreased accordingly in the video game settings, and one additional familiarization trial was given at the new speed (Figure 4.1B).

4.2.3 Step mania task

Step Mania (<https://www.stepmania.com/>) is an open-source videogame where sequences of directional arrow icons (up, down, left, right) scroll upwards toward stationary arrow silhouettes (Figure 4.1A) and the objective is to press the appropriate arrow keys whenever a corresponding scrolling icon is perfectly aligned with (i.e. centered on) its silhouette.

Participants sat at a desk with a keyboard positioned with the arrow keys in front of the non-dominant hand. Subjects were instructed to only use one hand to tap the keys and to only tap keys one time per cue. However, no explicit instructions were given assigning specific digits to particular keys. A brief demonstration of the gameplay was

shown to the participants as the objective was explained (*i.e.* press correct keys with optimal timing and avoid unnecessary/incorrect key strokes).

The same 219 cue pattern was used for all test blocks. One of the 219 cues required the left and right arrow key to be struck simultaneously, thus the pattern consisted of 55 up, 56 down, 55 left and 54 right key strokes (220 total key taps). This could not be changed through the available settings. Each testing block comprised one complete pattern. Each keystroke was categorized relative to a time window centered (time = 0s) on perfect overlap of the scrolling icon and its stationary silhouette. These timing windows were built into the program as flawless (0 to ± 0.0225 s), perfect (± 0.0225 to ± 0.045 s), great (± 0.045 to ± 0.090 s), good (± 0.090 to ± 0.135 s), boo (± 0.135 to ± 0.180 s), and miss ($> \pm 0.180$ s). To note, the first two time windows (flawless and perfect) were 22.5ms, while the other windows were 45ms.

4.2.4 Baseline assessment and testing

Subjects performed 2 familiarization trials with 500 continuous modifier (CMOD) difficulty (sets the arrow scroll speed; “arrow heights” moved per minute). An initial proficiency score was calculated (*Eq. 1*) indicative of the number of cues being met with a tap within scoring distance. This allowed for difficulty adjustment to ensure that the task was appropriately difficult for performance gains to be demonstrated within a single practice session. It was determined in pilot testing that if too many cues were entirely missed or nearly unscored based on the inbuilt timing windows, the task overwhelmed participants and they struggled to improve. Conversely, individuals who, in their

familiarization trials demonstrated very precise timing and few misses, had little room for growth.

Eq. 1) Familiarization Proficiency

$$FP = \left(\frac{(Flawless * 1) + (Perfect * 0.75) + (Great * 0.5) + (Good * 0.25) + (Boo * 0) + (Miss * -1)}{219} \right) * 100$$

For familiarization proficiency scores between 20 and 60, the default 500 CMOD was maintained throughout testing. For scores > 60 or < 20, the scrolling speed was adjusted up or down by 200, respectively (Figure 4.1B). The music tempo (210 beats per minute) was not affected by the CMOD change, it only affected the cue scrolling speed. Skill-adjusted subjects performed an additional familiarization block at the new speed that was used for all subsequent blocks. The last familiarization block was used as the pre-test measure for all subjects.

After familiarization and pre-test, tDCS electrodes were positioned during a 5 minute break. Subjects then completed a 20 minute practice period while they received either a-tDCS or SHAM during 5 practice blocks with 2 minutes of rest between blocks. The stimulation electrodes were then removed and subjects completed a post-test trial 5 minutes after completing practice.

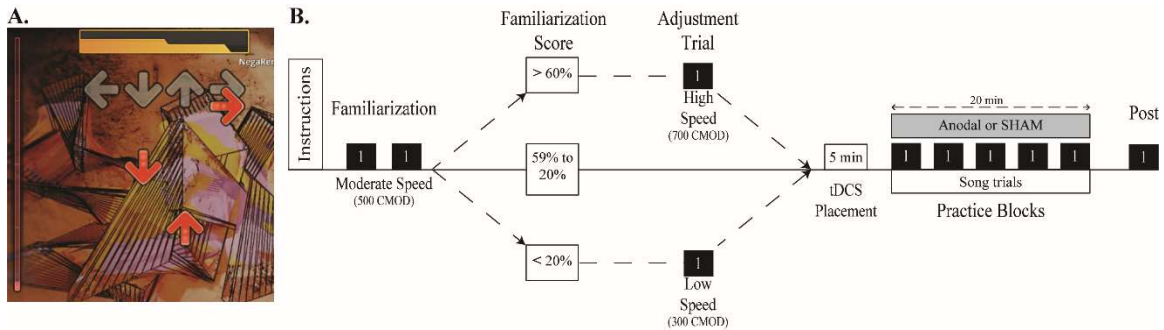


Figure 4.1. Gameplay and experimental procedures timeline. (A) Screen shot of step mania gameplay showing scrolling arrow icons and stationary arrow silhouettes. (B) Study procedures timeline.

4.2.5 Evaluating performance

At the end of each trial, the game provides feedback in the form of a numerical "game score" as well as an aggregate overview of the categorization of each keystroke timing (i.e. miss, boo, good, great, perfect, and flawless). However, this fails to account for any excess or aberrant keystrokes that fall outside of the inbuilt timing windows. For this reason, we opted to collect additional data using a separate keystroke logging software. This allowed us to devise an alternate scoring mechanism, or performance index (PI), that better reflects changes in task performance.

Two aspects of Step Mania performance are related to skill – hitting only the correct inputs and hitting them at the correct time. Both are interrelated as qualities of the task, but a change in one does not necessarily precipitate a proportional change in the other. With the guiding premise that newly acquired movement sequences are segmented, inaccurate, and jerky, whereas learned sequences are cohesive, accurate and smooth⁸, a PI was calculated to incorporate incorrect inputs (Key Error Rate, KER) and temporal

accuracy (2 values: Temporal Accuracy, TA; Tap Distribution Ratio, TDR) into a single value to reflect the skill associated with a certain quality of performance:

Eq. 2) Performance Index (PI)

$$PI = (TA - KER) \times TDR$$

A description is provided below for each of the constituent variables in the PI equation and how they are derived from the data provided by the game. Example data are shown after each equation to illustrate each step of the process.

4.2.6 Temporal accuracy (TA)

TA was quantified by assigning point values to the timing windows, so that “flawless” keystrokes awarded 1.0 pt and each subsequent window awarded 0.2 pts less, resulting in 0 pts for each “miss”. TA provided a base value reflecting temporal accuracy of the entire 220 constituent inputs of each trial.

This is different from the Familiarization Proficiency equation we used to evaluate initial ability because we did not want to penalize a “miss” with a negative score and instead just not award any points in that case. This distinction was made because in the initial familiarization, if the speed of the game was too fast for the subject they would get overwhelmed and miss several arrows in a row without even attempting any inputs, in which case a measure was needed to clearly inform us to slow the game down. In the case

of the TA measure (Eq. 3), the subject would typically only miss an arrow occasionally and therefore just not be awarded points for it.

Eq. 3) Temporal Accuracy (TA)

$$TA = ((Flawless * 1) + (Perfect * 0.8) + (Great * 0.6) + (Good * 0.4) + (Boo * 0.2) + (Miss * 0))$$

For a subject with 72 Flawless, 69 Perfect, 58 Great, 10 good, 3 Boo and 7 miss:

$$TA = (72 * 1) + (69 * 0.8) + (58 * 0.6) + (10 * 0.4) + (3 * 0.2) + (7 * 0) = 166.6$$

4.2.7 Key error rate (KER)

KER evaluated execution errors such as pressing multiple keys simultaneously, tapping the same key several times, or pressing a cycle of keys ‘searching’ for the correct one. Imprecise and unstable finger movements relate to learning in aspects of the skill, irrespective of timing (i.e. key sequence order, hand positioning, etc). Utilizing the extra keystroke data collected during the game, the differences between actual key stroke totals and the number of times the arrow keys appear in the sequence were calculated for each trial and used in Eq. 4 to produce a scaled error value relative to the total number of cues.

Eq. 4) Key Error Rate

$$KER = \left(\frac{(up - 55) + (down - 56) + (left - 55) + (right - 54)}{220} \right) * 100$$

For a subject with 56 up, 57 down, 53 left and 53 right arrow:

$$KER = \left(\frac{(|56 - 55|) + (|57 - 56|) + (|53 - 55|) + (|53 - 54|)}{220} \right) * 100 = 2.273$$

4.2.8 Tap distribution ratio (TDR)

In rhythm gaming, ratios of the tap totals in the different timing windows are commonly used in conjunction with timing scores because, as a consequence of binning taps into scored timing windows that are relatively wide, attempts can yield arbitrarily similar TAs despite the distribution of taps in the windows reflecting different levels of play. We adapted this strategy to further differentiate skill in the task and enhance sensitivity in the measure to changes in the quality of performance. TDR adjusts scores based on the concentration of taps in the two best and two worst categories, with additional weighting based on the proportion of those that are in the best (Flawless; most skillful) and worst (Miss; least skillful) timing windows. To properly illustrate the function of this variable, the original TA data from above will be used as well as a second example that produces an identical 166.6 TA value.

Eq. 5) Tap Distribution Ratio (TDR)

$$TDR = \frac{\left(1 + \left(\frac{Flawless + Perfect}{219}\right)\right) * \left(1.5 + \left(\frac{Flawless}{219}\right)\right)}{\left(1 + \left(\frac{Boo + Miss}{219}\right)\right) * \left(1.5 + \left(\frac{Miss}{219}\right)\right)}$$

For a subject with 72 Flawless, 69 Perfect, 58 Great, 10 good, 3 Boo and 7 Miss:

$$TDR = \frac{\left(1 + \left(\frac{72+69}{219}\right)\right) * \left(1.5 + \left(\frac{72}{219}\right)\right)}{\left(1 + \left(\frac{3+7}{219}\right)\right) * \left(1.5 + \left(\frac{7}{219}\right)\right)} = 1.877$$

For a second subject with 82 Flawless, 46 Perfect, 67 Great, 18 Good, 2 Boo, 4 Miss:

$$TDR = \frac{\left(1 + \left(\frac{82 + 46}{219}\right)\right) * \left(1.5 + \left(\frac{82}{219}\right)\right)}{\left(1 + \left(\frac{2 + 4}{219}\right)\right) * \left(1.5 + \left(\frac{4}{219}\right)\right)} = 1.904$$

Assuming a similar KER value for both of these trials, the PI for each would be:

$$PI = (TA - KER) * TDR$$

$$A.) PI = (166.6 - 2.273) * 1.877 = 307.32$$

or

$$B.) PI = (166.6 - 2.273) * 1.904 = 311.7$$

In utilizing a TDR factor to modify PI scores, we are able to better reflect the more subtle changes in subject performance that might otherwise be missed when relying on TA and KER values alone.

4.2.9 tDCS

The location of M1 was approximated using the BA9 BA8 BA42 Location System¹⁸⁸ and a marker was used to denote this location on the scalp. A Soterix Medical 1x1 Low Intensity transcranial direct current stimulator was used to deliver a-tDCS with parameters previously determined to be effective and safe (duration 20 min; current 1mA; active electrode over M1 contralateral to the non-dominant hand and reference electrode over the ipsilateral supraorbital). Current was delivered through 5cm x 5cm (25cm²) rubber electrodes inside of saline-soaked sponges affixed to the head with rubber straps. For SHAM, the current was ramped up and down over 30s.

4.2.10 Statistical analysis

A PI value was calculated for each trial. PI gain scores (block PI – baseline PI) were calculated for each practice block and the post-test to demonstrate the change in performance over time relative to baseline performance. Normality was tested with a Shapiro-Wilk test. Baseline PI scores were compared between groups with an independent *t*-test to test for baseline differences before gain scores were calculated.

Separate comparisons were performed for the practice blocks and the post-test block. A mixed ANOVA (2 groups x 5 blocks) with repeated measures on block was

used to compare the practice gain scores and effect size were calculated as partial eta squared (η_p^2). For the post-test block, an independent *t*-test was used to compare the gain scores between the conditions and effect size was calculated as Cohen's *d*. A *p*-value of 0.05 was considered statistically significant. Bonferroni post-hoc tests were used to determine differences for multiple comparisons. Data are presented as mean \pm standard deviation in text and as mean \pm standard error in figures. All data analysis was performed with SPSS 24.

4.3 Results

4.3.1 Practice blocks

Over the course of practice (B1 through B5), both groups gradually improved TA (range: 147.78 to 160.72) and TDR also modestly increased (range: 1.56 to 1.80). The KER also improved (i.e. reduced) across practice for both groups (range: 3.83 to 2.71) (Table 4.1). The calculated PI score for each block incorporated all 3 of these metrics.

Table 4.1. Mean TA, KER, and TDR values for each test block.

	Practice						Post-Test
	Baseline	B1	B2	B3	B4	B5	
a-tDCS							
TA	135.66(19.81)	149.84(19.16)	152.85(20.02)	154.31(15.99)	159.42(15.04)	160.72(16.01)	166.63(15.57)
KER	5.36(4.53)	3.83(3.42)	3.30(2.59)	3.15(2.06)	3.26(2.33)	2.82(1.91)	2.63(1.93)
TDR	1.35(0.29)	1.59(0.32)	1.65(0.34)	1.66(0.28)	1.76(0.28)	1.80(0.31)	1.92(0.31)
SHAM							
TA	134.96(27.41)	147.78(22.42)	150.78(22.32)	154.21(19.79)	152.66(17.71)	155.36(19.73)	159.62(18.98)
KER	3.82(2.99)	3.32(1.97)	2.74(2.33)	2.90(2.16)	2.98(2.30)	2.71(1.82)	2.03(1.79)
TDR	1.37(0.36)	1.56(0.35)	1.62(0.35)	1.68(0.35)	1.64(0.32)	1.69(0.37)	1.78(0.37)

TA - Temporal Accuracy; KER - Key error rate; TDR - Tap Distribution Ratio; values are Mean (SD)

Practice block PI gain scores were calculated relative to baseline to evaluate how overall performance of the two groups changed during practice. An independent *t*-test on the baseline PI values showed a-tDCS (181.80 pts \pm 66.04) and SHAM (188.97 pts \pm 79.39) performance was similar prior to practice ($t(56) = -0.37, P = 0.71$). An a-tDCS subject was missing error data for two practice trials and thus was excluded from the practice block analysis (a-tDCS $n = 28$, SHAM $n = 29$).

A Shapiro-Wilk test showed normally distributed gain scores ($P = 0.278$ to 0.977) for all cells of the design except a-tDCS B1 ($P = 0.004$) and a-tDCS B4 ($P = 0.01$). Since ANOVA type I error rate is fairly robust to normality violations¹⁸⁹⁻¹⁹¹ the mixed ANOVA was still performed. Homogeneity of variances was confirmed by Levene's test ($P = 0.25$ to 0.65). A Huynh-Feldt correction was used to adjust for a sphericity violation ($P = 0.003$). There was a statistically significant interaction between the stimulation group and block on practice gain scores ($F[3.466, 190.605] = 3.042, P = 0.024, \eta_p^2 = 0.052$). Post hoc analysis of the simple main effects for group revealed a significant difference between conditions at B4 ($P = 0.008$) and B5 ($P = 0.046$), where a-tDCS (B4:

100.02pts \pm 47.21; B5: 109.05pts \pm 60.92) resulted in greater PI improvement than SHAM (B4: 62.05pts \pm 55.75; B5: 76.58pts \pm 59.16). Post hoc analysis for block showed that B3 and B5 SHAM gain scores were significantly different from B1 ($P = 0.002$ and $P = 0.005$). For a-tDCS, B4 and B5 gain scores were statistically significantly higher than blocks 1 (both, $P < 0.001$), 2 ($P = 0.049$ and $P = 0.008$) and 3 ($P = 0.005$ and $P = 0.002$).

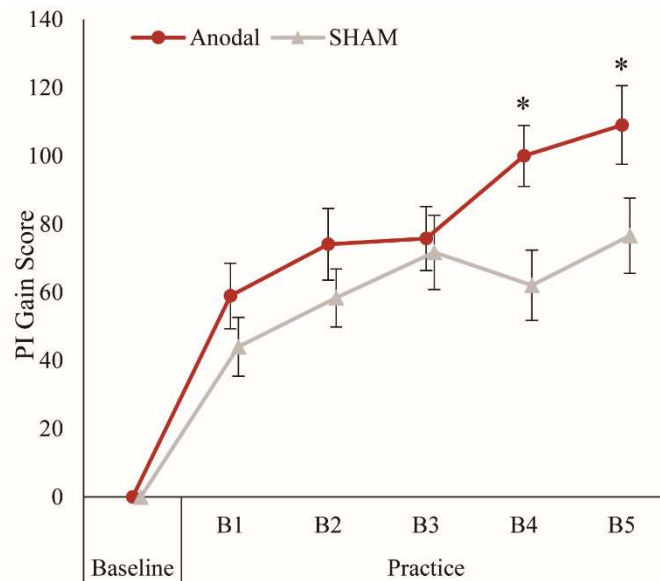


Figure 4.2. Practice block gain scores. Data show the practice block PI gain scores relative to baseline (i.e. last familiarization block) for a-tDCS ($n=28$) and SHAM ($n=29$) conditions. Whiskers denote the standard error. Both groups displayed significant increases in performance across practice. a-tDCS gain scores were significantly greater than SHAM at B4 and B5. *Indicates significant difference for SHAM ($P < 0.05$).

4.3.2 Pre-test to post-test

One SHAM subject was missing error data for the post-test and thus was excluded from analysis (a-tDCS $n = 29$, SHAM $n = 28$). Normality of the gain scores was confirmed with a Shapiro-Wilk test ($P = 0.661$ to 0.540). An independent t -test on the gain scores from baseline to post-test showed a statistically significant difference between conditions ($t(55) = 2.234$, $P = 0.030$, Cohen's $d = 0.592$), with a-tDCS

(137.844pts \pm 66.218) leading to greater improvement compared to SHAM (99.501pts \pm 63.28) (Figure 4.3).

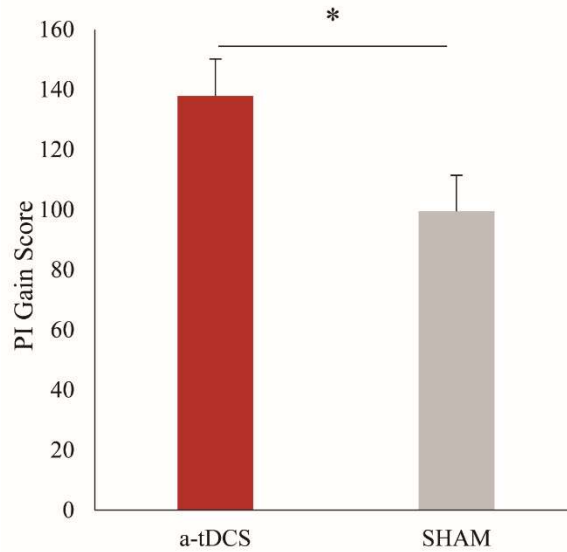


Figure 4.3. Overall gain scores. Data show the gain scores from the baseline to the post-test block for a-tDCS ($n = 29$) and SHAM ($n = 28$) conditions. Whiskers denote the standard error. *Significant difference between a-tDCS and SHAM ($P < 0.05$).

4.4 Discussion

These results indicate M1 a-tDCS has a beneficial effect on the acquisition of a dexterous timing-based video game compared to SHAM stimulation. Task improvement was indicated by higher gain scores, representing increased cumulative performance with better temporal accuracy and reduced error rate. Although both conditions demonstrated significant differences in performance across practice, the level of improvement with a-tDCS at B4 and B5 was significantly greater than that attained by SHAM (Figure 4.2). Likewise, considering only the change in performance from baseline to post-test, a-tDCS

during practice resulted in a greater overall change in PI compared to SHAM stimulation (Figure 4.3).

Our results align with previous findings that indicate M1 a-tDCS is a beneficial tool to enhance acquisition and performance of dexterous motor skills.^{85,91,177} However, most of the previous evidence is based on simple laboratory tasks that do well isolating and measuring specific learning processes, but lack the variety of parameters many real-world motor skills involve. Step Mania is a complex rhythmic timing video game that provides ample explicit feedback. Even though M1 is important in skill acquisition, the effects of tDCS on motor learning are known to be task-dependent^{91,187} and when several areas outside M1 influence task performance, it has been suggested that M1 modulation alone may be insufficient to enhance motor learning.¹⁷⁷ Within this context, our finding that M1 was a viable target for tDCS to enhance acquisition and performance of a novel complex task are particularly interesting.

A potential issue with a global PI score is that it may indicate performance changes, but lack detail about how specific aspects of execution changed to improve performance. Partly due to our hypothesis that a-tDCS would enhance learning in a complicated task not singularly defined by one aspect of performance, but also due to game data extraction limitations, our methodology lacked the resolution and granularity typically needed to detect differences in individual aspects of performance. Although no statistical analysis was performed on the component variables individually, visual inspection of the general raw data trends seems to suggest the timing element of the task may have differentiated performance gains between the groups (Figure 4.4 A-C). Both groups appear to display an initial decrease in KER that is characteristic of sequence

learning tasks⁸ with seemingly similar trends across practice and post-test (Figure 4.4C) suggesting the groups likely acquired the sequence order similarly. Regarding timing quality, looking purely at raw group means, a-tDCS and SHAM had more taps in the best TA window (Flawless) with a concurrent decrease in the worst window (Miss, Figure 4.4B). Although it was not statistically analyzed, by practice B5 and post-test, however, there seems to be an advantage in TA favoring a-tDCS with 10.3 and 13.3 more taps on average than SHAM in the best two timing windows combined and 2.9 and 2.7 fewer misses in B5 and the post-test, respectively (Figure 4.4A).

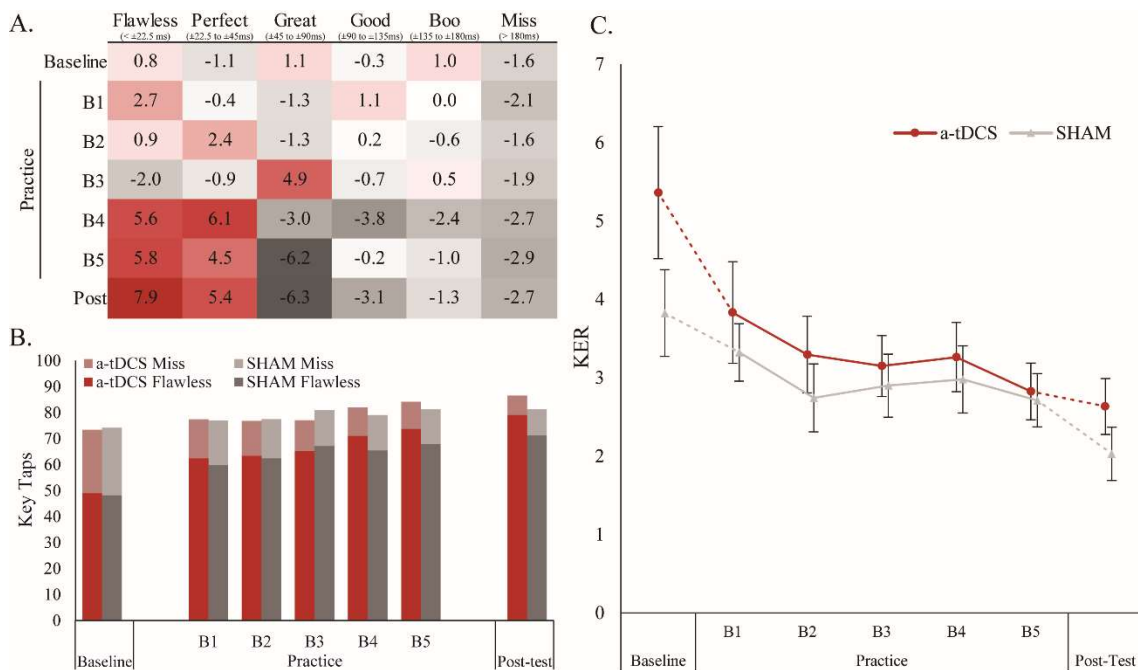


Figure 4.4. Timing window tap concentrations and key error rates. (A) Gradient table showing difference between the average a-tDCS and SHAM tap distributions (a-tDCS total – SHAM total) for each trial. Darker red signifies more a-tDCS taps (positive values) and darker grey signifies more SHAM taps (more negative). (B) Stacked bar graph showing the total taps in the best (“Flawless”, 0 to ± 0.0225s) and worst (“Miss”, > ± 0.180s) timing windows. Total bar height represents the combined total taps within those two windows. Dark bottom bars indicate the proportion of flawless taps and light top bars represent misses. (C) Line graph showing KER trend from baseline, across practice to the post-test. Whiskers denote standard error.

It is likely that M1 tDCS facilitated chunking of Step Mania subsequences as previous work has demonstrated that M1 tDCS can accelerate chunk formation in early motor learning within the first training session.¹⁹² The chunk formation process can be thought of as a transition from high uncertainty to low uncertainty in the execution of a motor skill that leads to sequence accuracy increases as the transition occurs.¹⁹³ In early stages of sequence learning with internally cued movements, efficient learning appears to prioritize learning of spatial elements and then shift to temporal components.¹⁹³ Our results seem to align with this pattern for externally cued sequences as well, based on the visually identified quick initial improvements in KER and the similar learning curve in both groups (Figure 4.4C). Whether performance differences potentially resulted from enhanced encoding of temporal sequence elements across the motor network or enhanced local M1 circuitry (enlarged representation or improved activity pattern), the behavioral output that increased PI scores resulted from M1 tDCS, which supports the important role of M1 for fast motor learning and as a sequence learning substrate.¹⁹⁴

tDCS may have augmented Step Mania skill acquisition by hastening development of co-occurring spatiotemporal muscle patterns (i.e. ‘synergies’¹⁹⁵) for coarticulations¹⁹⁶ and anticipatory finger movements,¹⁹⁷ that can facilitate improved transitions between taps. Transition improvements arise as sequence elements are chunked¹⁹⁸ and are believed to represent temporal control optimization of sequence movements.¹⁹⁹⁻²⁰¹ Due to the order and quick succession of externally paced cues with the irregular key layout, coordinated finger motions either preparing to press the next cue or making a subsequent key accessible while tapping another could have benefited rhythmic performance of the subsequences. Coarticulation is the tendency for one element of a

movement sequence to be generated in a manner facilitating other movements needed for the preceding or subsequent elements.¹⁹⁶ Therefore, M1 tDCS accelerating the emergence of coarticulations that facilitated element-to-element transitions is a plausible explanation for our findings. Furthermore, the timescale of our results is consistent with that of tDCS-associated synergy learning advantages that emerged primarily within session.¹⁹⁵

Timing is not often a tightly controlled parameter of tasks in most sequence learning studies²⁰² despite timing²⁰³ and rhythm²⁰⁴ being critically important to motor skill learning and performance. Relative timing is the theoretical correlate to rhythm and it refers to the relative ratio of timing components of a skill.²⁰⁴ Since M1 tDCS improved tapping sequences with correct rhythm, it appears to have improved relative timing, which differs from previous evidence that indicated M1 tDCS affected only absolute timing.²⁰⁵ However, in contrast to the present study where the context was consistent within subjects across baseline, practice, and post-test blocks, the M1 tDCS effects on timing observed by Apolinário-Souza et al.²⁰⁵ were during contextual changes for a transfer task rather than when learning was analyzed under the practiced conditions. Additionally, as complex movements may be more susceptible to tDCS accelerated learning than simpler tasks,²⁰⁶ the complexity of Step Mania (chunking rapid coordinated multi-finger motions; visual guidance/pre-selection;²⁰⁷ visual/audio feedback action-effects^{208,209}) may be more conducive to relative timing changes to improve execution of the component finger movements versus the comparatively simpler one-finger task studied by Apolinário-Souza and colleagues.²⁰⁵

Our results may also support that M1 is an important neural substrate for motor sequence learning when optimized timing between movements is important for the

quality of the skill, such as with playing an instrument or shooting a jump shot, rather than the fastest possible performance of correctly ordered elements. tDCS may have impacted the neural representation of the sequence locally within M1 circuitry since it has recently been shown to have this effect in animals. In mice, increased performance after training with tDCS resulted from increased learning associated modification of specific motor circuits in M1 via enhanced correlated firing that induces Hebbian LTP within task related neural populations.²¹⁰ A similar process has been demonstrated in human auditory cortex where tDCS preferentially influenced neurons coactive with stimulation over inactive neurons.²¹¹ On the other hand, imaging studies suggest temporal and spatial aspects of sequences may be independently encoded upstream from M1 in premotor areas²¹² with only a minor component of the activity in M1 reflecting sequential characteristics.²¹³ During early, as compared to late, explicit sequence learning there is increased within-session coupling of M1, PMA, and SMA, likely reflecting interaction functions important for fast motor learning.^{167,214} Therefore, tDCS-modulated M1 excitability may have influenced encoding of temporal aspects in premotor areas since these areas are closely reciprocally interconnected with M1 in primates²¹⁵ and Hebbian type plasticity has been demonstrated in the human M1-SMA network.²¹⁶

Successful goal-directed hand movements are highly dependent upon sensory feedback and there is extensive communication cortically between sensory and motor areas, with M1 receiving projections from many regions.²¹⁷ Based on the apparent activity-selectivity of tDCS,^{210,211,218} we speculate that tDCS could have increased utilization of task relevant feedback by heightening sensitivity of task related M1 neural populations to converging visual and somatosensory inputs.²¹⁹ Layer II/III pyramidal

cells form a broad intrinsic horizontal projection system in M1 with synaptic connections that are strengthened by LTP-like plasticity during normal motor learning,¹²⁸ and within this layer are neurons that respond rapidly to somatosensory and visual feedback that converges in M1.²²⁰⁻²²² Furthermore, many reciprocal interconnections between M1 and the premotor areas exist within this same layer II/III with no apparent bias in information flow.²¹⁵ Therefore, tDCS may have exacerbated the process of task related somatosensory and visual feedback shaping the neural representation in M1 locally and/or, by way of enhanced M1 activity patterns, facilitated encoding of the temporal features of the sequence in premotor areas. Considering the timing between the sequence elements was conveyed visually by the vertical distance between the scrolling arrows (Figure 4.1B) and improved timing between motions of multiple fingers is inherent to improved Step Mania performance, tDCS enhancing visual and somatosensory input integration in M1 is an appealing potential explanatory mechanism as it would be consistent with both the activity-selectivity hypothesis within M1 and the interrelated roles of premotor areas and M1 in sequence learning.

Task difficulty and baseline ability can factor into the likelihood and potential magnitude of tDCS learning effects,²²³ with tDCS usually benefitting novices/low performers most.^{108,181} Since our participants were naïve to rhythm games and played with their non-dominant hand, our results further support tDCS efficacy in enhancing novice skill acquisition. However, despite similar naiveté, a complex task may be easy for one person but difficult for another. This was observed while pilot testing Step Mania under normal conditions where high familiarization aptitude led to rapid performance plateaus during practice and low aptitude caused too much difficulty that rendered

practice ineffective and impeded learning. M1 tDCS can improve visuomotor learning,⁸⁶ but benefits may be optimized for moderately difficult (set by speed) tasks as opposed to high or low difficulty.²²⁴ Taking this into consideration, we increased or decreased the visual cue scrolling speed for high and low baseline aptitudes, respectively, which shifted *relative* difficulty towards moderate and minimized interference from floor and ceiling effects on the emergence of tDCS effects. Therefore, task novelty notwithstanding, our results suggest that tDCS learning benefits may still be had by more experienced/skilled individuals, provided the practiced task demands moderately exceed those already managed by existing skill.

To our knowledge this is only the second study demonstrating M1 tDCS can enhance acquisition of video gaming motor skill,¹⁸¹ and the first specifically within the rhythm gaming genre. Video gaming inputs (i.e. controllers, keyboard and mouse) require dexterous hand and gross arm skills that, when combined with the complex visual processing and attentional demands of video games, can create motor learning paradigms to study tDCS effects with greater generalizability than traditional paradigms.¹⁸¹ With the emergence of gaming as a lucrative competitive endeavor (e.g. eSports, streaming) and participants training and attempting to gain a competitive advantage, tDCS has reportedly been used to improve gaming skill.¹⁸⁶ Due to growing interest in such applications, commercial availability of tDCS has increased (i.e. foc.us or Halo devices); however, which regions are ideal targets for effective enhancement of specific aspects of gaming is unclear. Our results support and extend the evidence that M1 tDCS can improve gaming based motor skills. Additionally, our results also provide further indication that M1 tDCS may be able to enhance rehabilitation motor outcomes, especially given the growing

interest in video game-based rehabilitation interventions and their use in conjunction with tDCS.²²⁵

4.5 Conclusion

tDCS shows promise as a motor learning adjuvant in many settings, but due to the task specific nature of tDCS effects on simplified laboratory tasks, there is little consensus on ideal stimulation targets to enhance motor learning for more complex real-world tasks. We have demonstrated that, compared to SHAM stimulation, M1 a-tDCS can significantly improve acquisition and performance of a complex dexterous video game skill within a single practice session. In contrast to simpler sequence learning tasks frequently used to study tDCS effects, Step Mania better represents real world skills where timing between component motions and processing incoming information relevant to task success are pivotal for learning and performance. In light of recent work highlighting that M1 might not be the primary site for plasticity that supports learning in traditional lab-based sequence tasks,^{213,226} and that lab-based tasks may not probe learning a skilled continuous sequential action with high fidelity,²²⁷ the observed effects in the present study provide interesting evidence that supports the potential of M1 a-tDCS for practical real-world applications.

CHAPTER FIVE: CONCURRENT M1 ANODAL AND CEREBELLAR CATHODAL
tDCS ENHANCES ACQUISITION OF A DEXTEROUS RHYTHMIC-TIMING
VIDEO GAME

5.1 Introduction

Motor learning consists of neuromotor adaptations that are behaviorally observed as performance improvements and/or skill acquisition. Motor learning manifests through online (during practice) and offline (outside of practice) skill changes that comprise fast and slow stages of learning.²²⁸ During early motor learning, where performance changes occur rapidly even in as little as a single practice session, the M1 and the cerebellum both demonstrate learning-related neuroplastic changes.^{118,228,229} M1 is crucial for the use-dependent acquisition and storage of muscle activation for fast and precise motions associated with skillful performance.^{117,118} In response to practice, rapid changes may occur in the output organization of M1^{42,114,230} due to LTP mediated changes in synaptic strength amongst the task related cortical circuitry.^{170,231}

The cerebellum serves a role in error-dependent learning, updating motor commands in response to differences between the anticipated sensory consequence of a descending motor command and the resulting sensory feedback from the movement. The cerebellum has been implicated in error-correction during early learning, contributing to skill acquisition.^{118,232} Evidence has shown that the cerebellum is densely interconnected with M1 via multiple closed loop circuits which allow for the optimization of motor control and learning through refined motor inhibition.^{233,234} The cerebellar contributions

to motor learning are at least partly mediated by LTD mechanisms in cerebellar cortex.²³⁵⁻²³⁷ In addition to neuroplastic changes locally within M1 and cerebellum, there are connectivity changes between the two regions which occur with learning,^{118,238,239} and the changes appear in an effector specific manner.²⁴⁰

tDCS is a form of non-invasive, subthreshold electrical brain stimulation that has been shown to modulate excitability within the underlying cortical structures and facilitate motor learning.^{65,241-247} Typically, tDCS is performed by passing a weak electrical current (~1-2 mA) between two or more electrodes positioned on the scalp. The direction of current flow between the electrodes determines the stimulation polarity (positive, Anodal; negative, Cathodal).²⁴⁸ a-tDCS is usually associated with subthreshold depolarization that increases neuronal excitability, whereas c-tDCS is associated with hyperpolarization that reduces neuronal excitability.²⁴⁹ The a-tDCS and c-tDCS excitability shifts are attributed to LTP and LTD-like mechanisms which has made tDCS an appealing tool to probe processes, like motor learning, that are underpinned by timing-dependent mechanisms within different structures.^{250,251} Specifically, M1 focused a-tDCS appears to enhance cortical excitability and LTP-like plasticity within M1 and improved motor function in a variety of motor tasks including, SRTT, SFTT, and SVIPT.^{119,143,155}

The cerebellum similarly demonstrates excitability changes that depend on the direction of stimulation;²⁴⁹ however, the polarity-specific functional changes are less clear as a-tDCS and c-tDCS can produce similar behavioral effects.²⁵² The many cerebellar tDCS studies have focused on error-based learning tasks (i.e. adaptation tasks)^{119,253} with some findings showing a-tDCS enhancing learning²⁴⁹ while others show a beneficial effect on learning from c-tDCS.²⁵⁴ Likewise, studies investigating cerebellar

stimulation effects for skill acquisition paradigms show similarly mixed findings, even when task demands are similar. For instance, a-tDCS enhanced acquisition of complex overhand throwing task,¹¹² whereas c-tDCS enhanced learning in a dart throwing task.¹⁰⁸ Likewise, cerebellar a-tDCS has been shown to both increase²⁴⁷ and decrease²⁵⁵ performance in the SRTT.

Imaging and TMS studies have shown that M1 and the cerebellum are densely interconnected structurally and functionally.²⁵⁶ When learning a movement sequence task that involves specific timing demands, there are changes in M1 and cerebellar interaction that relate directly to task learning.^{238,239} The vast majority of studies have stimulated either M1 or the cerebellum individually,^{119,243} however dual-site concurrent stimulation of both areas may modulate learning processes to a greater extent than stimulating either site individually.^{257,258} A previous study has investigated concurrent bilateral a-tDCS over M1 and cerebellum and found increased corticospinal excitability, but no behavioral effects were measured.²⁵⁹

Based on the importance of M1 and the cerebellum in early motor learning, as well as the lack of polarity-dependent facilitatory behavioral effects in cerebellar literature, we developed 2 experiments to first investigate the effects of cerebellar tDCS and M1 tDCS on a complex rhythmic-timing video game task and then devise a concurrent M1+CB tDCS protocol to apply complementary stimulation to both sites simultaneously. In experiment 1, 2mA M1 anodal stimulation (M1 a-tDCS), cerebellar a-tDCS, cerebellar c-tDCS, and SHAM stimulations were compared to determine if any would enhance online learning of the video game skill. In experiment 2, concurrent

stimulation of M1 a-tDCS and cerebellar c-tDCS was applied alongside practice and the results were compared to the SHAM group from experiment 1.

5.2 Methods

5.2.1 Participants

One hundred and twenty-five subjects were screened to be in the study ($n = 25$ per group; age 21.17 ± 2.91 yrs, 60 males and 65 females total). Only individuals free of neurological/musculoskeletal impairments that could impact performance of the task and medications that could influence learning, such as stimulants for ADHD, participated in the study. Subjects were required to achieve a minimum level of task competency because some subjects would forgo large segments of the cues when they got off track. As a result, these subjects typically did not try as hard for the remainder of the trial and became outliers. After screening criteria, there were 103 participants across the 5 total groups that comprised experiment 1 and experiment 2 (M1 a-tDCS $n = 17$, cerebellar a-tDCS $n = 24$, cerebellar c-tDCS $n = 20$, SHAM $n = 18$, M1a+CBc $n = 24$). Handedness was determined with the EHI.¹²² Right-hand dominance was identified with scores $> +40$, left-hand dominance with scores < -40 , while scores ≥ -40 and $\leq +40$ were ambidextrous. In cases of ambidextrousness, the subject's preferred writing hand was considered their dominant.

Participants were randomized to one of five tDCS conditions as they were screened into the study: M1 a-tDCS, cerebellar a-tDCS, cerebellar c-tDCS, SHAM stimulation (SHAM), or the combined stimulation group planned to be based on the

results of experiment 1 (concurrent M1 anodal and cerebellar c-tDCS, M1a+CBc tDCS). Subjects were blinded to their condition for the duration of testing. The groups were matched for age (M1 a-tDCS = 20.35 ± 3.08 yrs; cerebellar a-tDCS = 22.33 ± 3.32 yrs; cerebellar c-tDCS = 21.00 ± 3.01 yrs; SHAM = 20.94 ± 2.21 ; M1a+CBc = 21.96 ± 1.90 yrs). However, they were less balanced on sex (M1 a-tDCS = 10 males, 7 females; cerebellar a-tDCS = 12 males, 12 females; cerebellar c-tDCS = 15 males, 5 females yrs; SHAM = 14 males, 4 females; and M1a+CBc = 10 males, 14 females).

5.2.2 Procedures

In experiment one, participants took part in a single testing session while receiving either M1 a-tDCS, cerebellar a-tDCS, cerebellar c-tDCS or SHAM stimulation. a-tDCS was applied to M1 contralateral to the non-dominant (active) hand, while both a-tDCS and c-tDCS were performed with the active electrode over the cerebellum and the reference electrode over the buccinators ipsilateral to the non-dominant hand. During the session, subjects performed a timing-based dexterous video game task with the non-dominant hand on the arrow keys of a standard computer keyboard. The protocol included 2 familiarization pre-test blocks, 5 practice blocks while receiving either a-tDCS or SHAM, and a post-test block 5 min after cessation of practice. Familiarization pre-test scores were used to determine whether the task difficulty was adequate to demonstrate motor learning during the practice period. If the task was too easy based on the familiarization trial performance, the difficulty was increased accordingly in the video game settings, and one additional familiarization trial was given at the new speed. Subjects who were unable to meet the minimum performance proficiency were excluded.

For experiment 2, the procedures were identical except that participants received M1a+CBc tDCS.

5.2.3 Step mania task

Step Mania is an open-source videogame where sequences of directional arrow icons (up, down, left, right) scroll upwards toward stationary arrow silhouettes (Figure 5.1A) and the objective is to press the appropriate arrow keys whenever a corresponding scrolling icon is perfectly aligned with (i.e. centered on) its silhouette.

Participants sat at a desk with a keyboard positioned with the arrow keys in front of the non-dominant hand. Subjects were instructed to only use one hand to tap the keys and to only tap keys one time per cue. However, no explicit instructions were given assigning specific digits to particular keys. A brief demonstration of the gameplay was shown to the participants as the objective was explained (*i.e.* press correct keys with optimal timing and avoid unnecessary/incorrect key strokes).

The same 219 cue pattern was used for all test blocks. One of the 219 cues required the left and right arrow key to be struck simultaneously, thus the pattern consisted of 55 up, 56 down, 55 left and 54 right key strokes (220 total key taps). Each testing block comprised one complete pattern. Each keystroke was categorized relative to a time window centered (time = 0s) on perfect overlap of the scrolling icon and its stationary silhouette. These timing windows were built into the program as flawless (0 to ± 0.0225 s), perfect (± 0.0225 to ± 0.045 s), great (± 0.045 to ± 0.090 s), good (± 0.090 to ± 0.135 s), boo (± 0.135 s to ± 0.180 s), and miss ($> \pm 0.180$ s). To note, the first two time windows (flawless and perfect) were 22.5ms, while the other windows were 45ms.

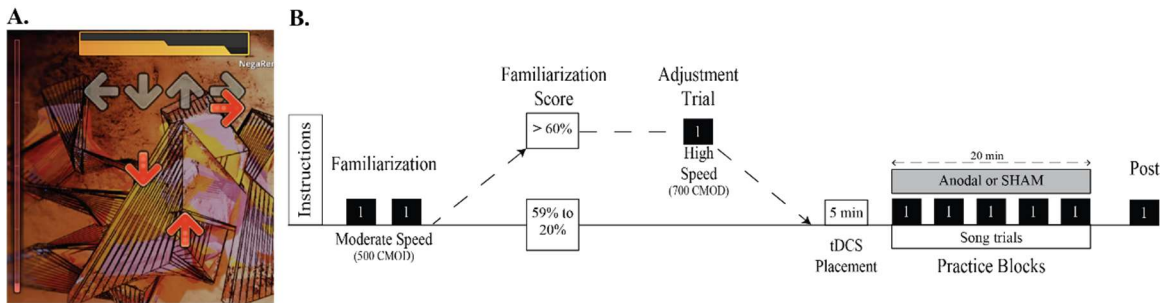


Figure 5.1. (A) Screenshot of step mania gameplay. (B) Experimental procedures timeline

5.2.4 Baseline assessment and testing

Subjects performed 2 familiarization trials with 500 CMOD difficulty (sets the arrow scroll speed; “arrow heights” moved per minute). An initial proficiency score was calculated (*Eq. 1*) that indicated the amount of sequence cues that were met with a tap within scoring distance. This allowed for difficulty adjustment to ensure that the task was appropriately difficult for performance gains to be demonstrated within a single practice session. This also produced a criterion to identify subjects who became overwhelmed with the task for exclusion from the study. It was determined in pilot testing that if too many cues were entirely missed or nearly unscored, the task tended to overwhelm participants and their effort diminished as they struggled to improve.

Eq. 1) Familiarization Proficiency

$$FP = \left(\frac{(Flawless * 1) + (Perfect * 0.75) + (Great * 0.5) + (Good * 0.25) + (Boo * 0) + (Miss * -1)}{219} \right) * 100$$

For familiarization proficiency scores between 20 and 60, the default 500 CMOD was maintained throughout testing. For scores > 60, the scrolling speed was adjusted up

by 200, (Figure 5.1B). The music tempo (210 beats per minute) was unaffected by this change as it only affected the cue scrolling speed. Skill-adjusted subjects performed an additional familiarization block at the new speed that was used for all subsequent blocks. Those with familiarization proficiency < 20 were excluded from analysis. The last familiarization block was used as the pre-test measure for all subjects.

After familiarization and pre-test, tDCS electrodes were positioned during a 5 min break. Subjects then completed a 20 min practice period while they received either a-tDCS or SHAM during 5 practice blocks with 2 minutes of rest between blocks. The stimulation electrodes were then removed and subjects completed a post-test trial 5 minutes after completing practice.

5.2.5 Evaluating performance

At the end of each trial, the game provides feedback in the form of a numerical "game score" as well as an aggregate overview of the categorization of each keystroke timing (i.e. miss, boo, good, great, perfect, and flawless). However, this fails to account for any excess or aberrant keystrokes that fall outside of the inbuilt timing windows. For this reason, we opted to collect additional data using a separate keystroke logging software. This allowed us to devise an alternate scoring mechanism, or PI, that better reflects changes in task performance.

Two aspects of Step Mania performance are related to skill – hitting only the correct inputs and hitting them at the correct time. While they are generally interrelated as qualities of the task, a change in one does not necessarily precipitate a proportional change in the other. Based on the premise that well learned sequences are cohesive,

accurate and smooth, whereas recently acquired movement sequences are unconnected, inaccurate, and jerky, ¹¹⁸ a PI was calculated to incorporate incorrect inputs, KER, and 2 related values, TA and TDR, into one score to reflect the skill associated with a certain quality of performance.

Eq. 2) Performance Index (PI)

$$PI = (TA - KER) \times TDR$$

How each of the component variables were derived from the data provided by the game was explained in detail in the previous chapter (Sections 4.2.5 through 4.2.8) with example data. Therefore, a brief explanation for each of the constituent variables in the PI equation are provided below without the example subject data.

5.2.6 Temporal accuracy (TA)

TA provided a base value reflecting temporal accuracy of the entire 220 constituent inputs of each trial by assigning point values to the timing windows. “Flawless” keystrokes awarded 1.0 pt and each subsequent window awarded 0.2 pts less, resulting in 0 pts for each “miss”.

Unlike the Familiarization Proficiency equation we used to evaluate initial ability, we did not want to penalize a “miss” with a negative score and instead just not award any points in that case. This distinction was made because in the initial familiarization, if the speed of the game was too fast for the subject they would get overwhelmed and miss several arrows in a row without even attempting any inputs, thus a measure was needed

to clearly indicate their exclusion. In the case of the TA measure (Eq. 3), subjects would typically only miss an arrow occasionally and therefore just receive no points for it.

Eq. 3) Temporal Accuracy (TA)

$$TA = (\text{Flawless} * 1) + (\text{Perfect} * 0.8) + (\text{Great} * 0.6) + (\text{Good} * 0.4) + (\text{Boo} * 0.2) + (\text{Miss} * 0)$$

5.2.7 Key error rate (KER)

KER evaluated execution errors such as pressing multiple keys simultaneously, tapping the same key several times, or pressing a cycle of keys ‘searching’ for the correct one. Imprecise and unstable finger movements relate to learning in aspects of the skill, irrespective of timing (i.e. key sequence order, hand positioning, etc). Utilizing the extra keystroke data collected during the game, the differences between actual key stroke totals and the number of times the arrow keys appear in the sequence were calculated for each trial and used in Eq. 4 to produce a scaled error value relative to the total number of cues.

Eq. 4) Key Error Rate

$$KER = \left(\frac{(\text{up} - 55) + (\text{down} - 56) + (\text{left} - 55) + (\text{right} - 54)}{220} \right) * 100$$

5.2.8 Tap distribution ratio (TDR)

In rhythm gaming scoring, ratios of the timing window tap totals are commonly used in conjunction with timing scores because, as a consequence of binning taps into scored timing windows that are relatively wide, TAs can be arbitrarily similar between

two attempts, even though the distribution of taps in the windows reflects different levels of play. This strategy was adapted to further differentiate skill in the task and enhance measure sensitivity to changes in performance quality. TDR adjusts scores based on the concentration of taps in the two best and two worst categories, with additional weighting based on the proportion of those that are in the best (Flawless; most skillful) and worst (Miss; least skillful) timing windows.

Eq. 5) Tap Distribution Ratio (TDR)

$$TDR = \frac{\left(1 + \left(\frac{Flawless + Perfect}{219}\right)\right) * \left(1.5 + \left(\frac{Flawless}{219}\right)\right)}{\left(1 + \left(\frac{Boo + Miss}{219}\right)\right) * \left(1.5 + \left(\frac{Miss}{219}\right)\right)}$$

In utilizing a TDR factor to modify PI scores, we are able to better reflect the more subtle changes in subject performance that might otherwise be missed when relying on TA and KER values alone.

5.2.9 tDCS

Two Soterix Medical 1x1 Low Intensity transcranial DC stimulators were used to deliver a-tDCS with parameters previously determined to be effective and safe (duration 20 min; current 2mA). One stimulator had electrodes placed in a motor cortical montage with the active electrode over M1 contralateral to the non-dominant hand and reference electrode over the ipsilateral supraorbital. The second stimulator had the active electrode placed 1cm below the inion, centered over the cerebellar hemispheres and the reference

electrode over the buccinator muscle ipsilateral to the non-dominant hand. All subjects in experiment 1 and 2 had all 4 electrodes attached during testing.

Current was delivered through 5cm x 5cm (25cm²) rubber electrodes inside of saline-soaked sponges affixed to the head with rubber straps. Four stimulation conditions were used in experiment 1: M1 a-tDCS, cerebellar a-tDCS, cerebellar c-tDCS, and SHAM. For SHAM stimulation, the current was ramped up and down over 30s. In experiment 1, when M1 was targeted, SHAM stimulation was delivered to the cerebellar electrodes. Similarly, when cerebellum was targeted, SHAM stimulation was delivered over M1. In experiment 2, both sets of electrodes delivered active stimulation concurrently (M1 a-tDCS and cerebellar c-tDCS).

5.2.10 Statistical analysis

For both experiments, a PI was calculated for each block which incorporated the various aspects of gameplay into a single cumulative assessment of skill. A one-way ANOVA and an independent t-test were performed for experiment 1 and 2, respectively, to confirm groups had similar PIs at baseline. PI gain scores were calculated for each practice block (Block PI - Baseline PI) to show how performance changed across practice relative to baseline. These data were then analyzed using Group by Block mixed ANOVAs with a repeated measures on block (Experiment 1: 4 groups x 5 blocks; Experiment 2: 2 groups x 5 blocks).

To assess overall learning, the mean post-test PIs were analyzed with an ANCOVA which compared the effect of stimulation on PI after controlling for baseline performance. In experiment 2, the results from the stimulation protocol with M1a+CBc

stimulation were compared to the SHAM condition from experiment 1. Shapiro-Wilk tests were used to confirm normality. A p-value of 0.05 was considered statistically significant and effect size were calculated as partial eta squared (η_p^2). Bonferroni post-hoc tests were used to determine differences for multiple comparisons. Data are presented as mean \pm standard deviation in text and as mean \pm standard error in figures unless otherwise stated. All data analysis was performed with SPSS 24.

5.3 Results

5.3.1 Experiment 1

The calculated PI score for each block incorporated TA, KER, TDR. The means \pm SD for each of the component variables are summarized for each group at each time point in Table 5.1. Approximate normality was confirmed for mean baseline PIs (P s = 0.03 to 0.88) by Shapiro-Wilk test. A one-way ANOVA on the baseline PIs showed that the performances of M1 a-tDCS (192.990 pts \pm 62.568), cerebellar a-tDCS (250.076 pts \pm 100.957), cerebellar c-tDCS (208.153 \pm 105.670), and SHAM (216.237 \pm 66.456) groups were comparable at baseline ($F [3, 75] = 1.59, P = 0.199$).

5.3.2 Practice blocks

Normality of the PI gain scores was confirmed with a Shapiro-Wilk test (P s = 0.10 to 0.97). A Greenhouse-Geisser correction was used to adjust for a sphericity-violation ($P < 0.001$). For the practice block analysis, a 4 x 5 (Stimulation Group x

Block) mixed ANOVA showed there was no significant Stimulation Group by Block interaction effect on PI gain scores ($F[9.029, 225.731] = 1.318, P = 0.228$). The main effect of Block was statistically significant ($F[3.010, 225.731] = 20.099, P < 0.001, \eta_p^2 = 0.211$), indicating that, collapsed across conditions, there was a statistically significant difference in mean PI between the practice Blocks (Figure 5.2). The main effect of Stimulation Group was not statistically significant ($F[3, 75] = 1.230, P = 0.305$).

Table 5.1. Mean TA, KER, and TDR values for each test block.

	Baseline	Practice					Post-Test
		B1	B2	B3	B4	B5	
M1a-tDCS							
TA	140.12(17.73)	162.07(14.70)	162.34(16.87)	165.09(18.09)	163.49(17.37)	168.38(15.93)	173.45(12.79)
KER	8.24(8.35)	4.71(4.30)	4.30(3.67)	3.80(2.31)	3.72(1.78)	3.53(2.40)	2.89(2.29)
TDR	1.42(0.27)	1.82(0.29)	1.84(0.35)	1.90(0.37)	1.86(0.36)	1.97(0.36)	2.07(0.30)
CBa-tDCS							
TA	151.74(21.25)	163.07(18.82)	168.52(15.84)	169.97(17.36)	172.38(17.00)	172.98(15.21)	174.43(16.11)
KER	4.66(4.11)	3.13(3.78)	2.78(2.61)	2.58(1.90)	3.48(3.20)	3.05(2.51)	2.67(2.12)
TDR	1.64(0.41)	1.86(0.42)	1.96(0.36)	2.00(0.40)	2.05(0.40)	2.06(0.38)	2.10(0.39)
CBc-tDCS							
TA	141.15(24.43)	156.40(20.39)	164.03(19.54)	163.09(20.37)	169.81(18.02)	170.24(19.23)	175.46(16.46)
KER	6.25(4.87)	4.39(2.70)	4.14(2.61)	4.82(3.24)	4.23(2.40)	3.98(3.41)	3.80(2.44)
TDR	1.46(0.44)	1.72(0.39)	1.88(0.40)	1.85(0.43)	2.00(0.39)	2.01(0.40)	2.12(0.37)
SHAM							
TA	145.21(18.14)	159.23(20.56)	159.72(22.26)	164.50(18.59)	167.69(16.18)	167.56(14.52)	173.57(14.12)
KER	5.08(4.21)	4.17(2.70)	3.59(2.87)	3.74(2.94)	3.36(3.43)	3.38(2.45)	3.01(3.23)
TDR	1.50(0.29)	1.78(0.40)	1.79(0.43)	1.88(0.38)	1.93(0.34)	1.93(0.29)	2.07(0.32)
M1a+CBc							
TA	149.97(21.53)	171.53(15.96)	176.51(13.37)	176.90(13.58)	176.65(13.77)	180.13(14.28)	183.47(11.71)
KER	5.51(4.14)	2.86(1.68)	2.48(1.67)	2.65(1.79)	2.50(1.84)	2.61(1.59)	2.01(1.17)
TDR	1.61(0.41)	2.03(0.36)	2.14(0.32)	2.15(0.33)	2.14(0.33)	2.23(0.35)	2.30(0.31)

M1a-tDCS – M1 anodal tDCS; CBa-tDCS – cerebellar anodal tDCS; CBc-tDCS – cerebellar cathodal tDCS; SHAM – SHAM stimulation; M1a+CBc – concurrent M1 anodal and cerebellar cathodal tDCS

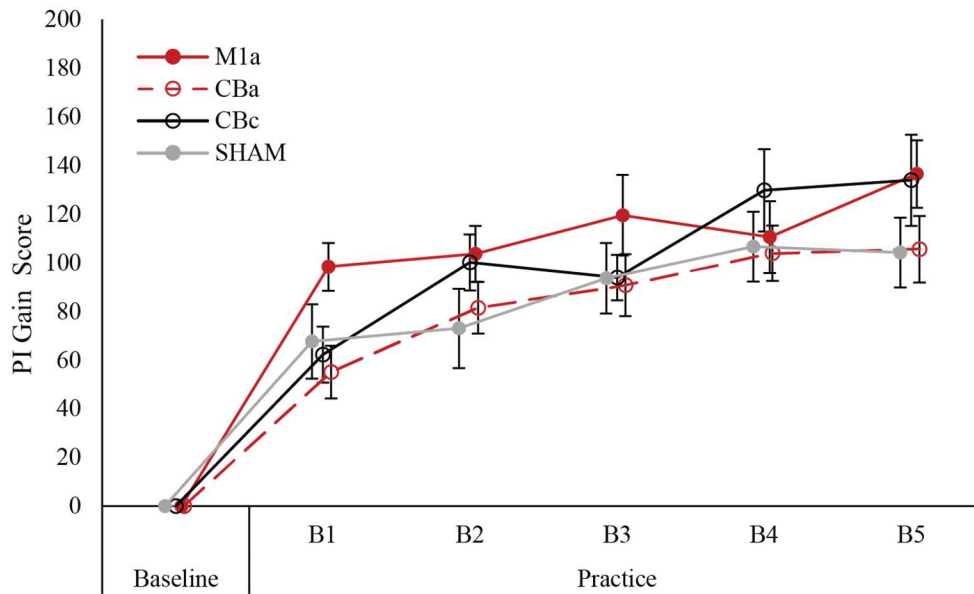


Figure 5.2. Practice performance relative to baseline. There were no significant differences between any of the conditions at any time point. Whiskers denote standard error.

5.3.3 Pre-test to post-test

A Shapiro-Wilk test confirmed normality of the post-test PIs ($P = 0.19$ to 0.868). A one way ANCOVA showed that, after adjustment for baseline performance, there was no difference in PIs between the 4 stimulation groups after practice ($F[3, 74] = 0.685$, $P = 0.564$) (Figure 5.3).

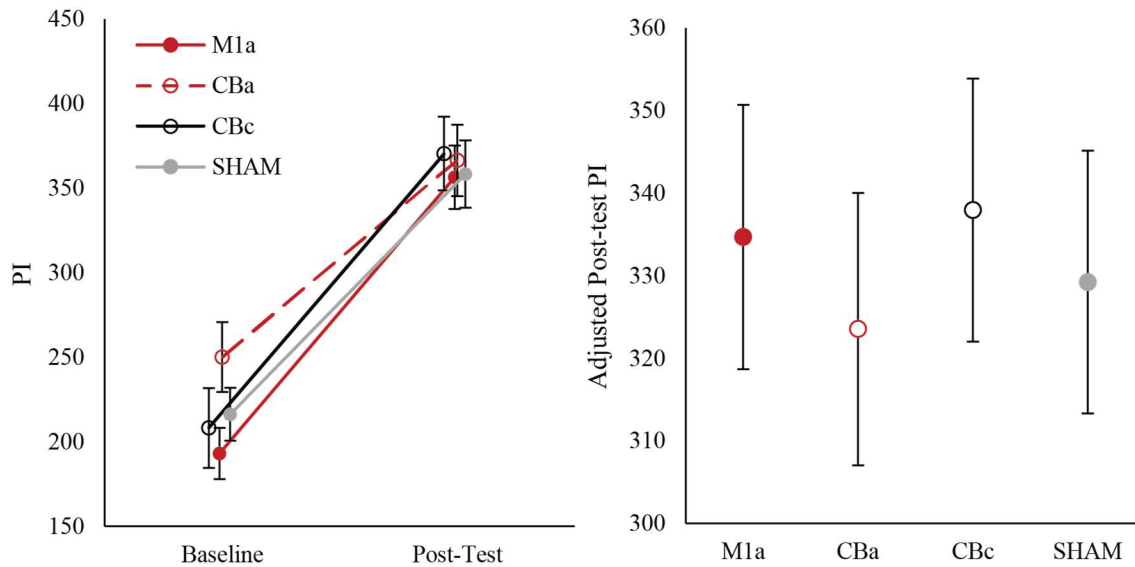


Figure 5.3. Overall performance change. Left panel shows group means before and after practicing for 20 minutes with tDCS. Right shows the comparison between post-test means for the 4 groups after adjusting for baseline. There were no significant differences between groups. Whiskers denote standard error.

5.3.4 Experiment 2

Normality of baseline PIs for SHAM ($P = 0.10$) and M1a+CBc ($P = 0.08$) were confirmed with Shapiro-Wilk test. An independent t-test on baseline PIs showed that the M1a+CBc ($241.633 \text{ pts} \pm 104.071$) and SHAM (216.237 ± 66.456) groups had comparable performance at baseline ($t(40) = -0.905, P = 0.371$).

5.3.5 Practice blocks

Normality of the PI gain scores was confirmed with a Shapiro-Wilk test (P s = 0.09 to 0.97). A Greenhouse-Geisser correction was used to adjust for a sphericity-violation ($P = 0.008$). For the practice blocks, a 2 x 5 (Stimulation Group x Block) mixed ANOVA showed there was no significant Stimulation Group by Block interaction effect

on PI gain scores ($F[3.00, 119.994] = 1.150, P = 0.332$). The main effect of Block was statistically significant ($F[3.00, 217.337] = 7.925, P < 0.001, \eta_p^2 = 0.165$), indicating that, collapsed across condition, there was a statistically significant difference in mean PI between the practice Blocks (Figure 5.4). There was a significant main effect of Stimulation Group ($F[1, 40] = 5.789, P = 0.021, \eta_p^2 = 0.126$) that showed a statistically significant difference in mean PI gain scores across practice ($mean \pm SE$) with M1a+CBc tDCS (134.776 ± 12.47 pts) over SHAM (89.031 ± 14.373 pts).

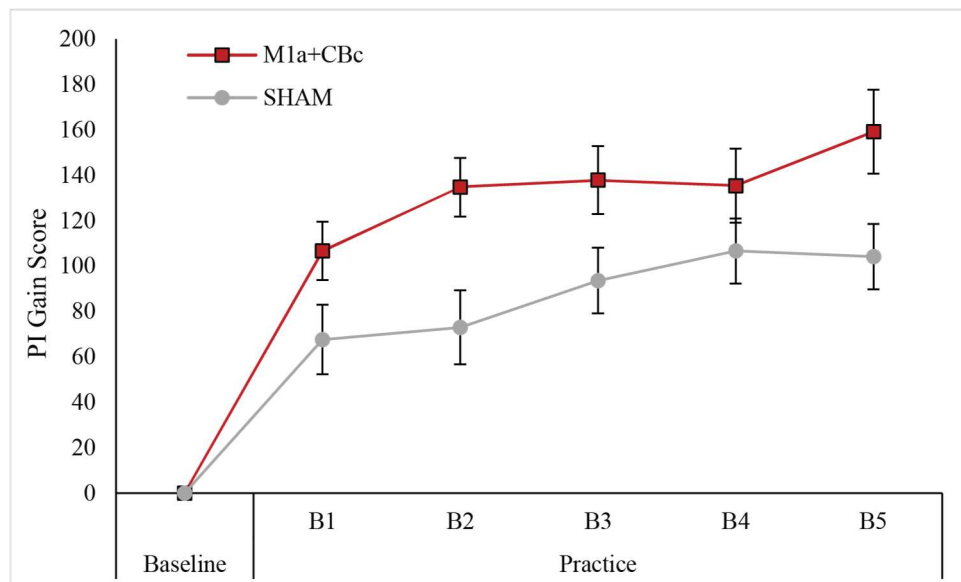


Figure 5.4. Practice performance relative to baseline. Across the practice blocks, M1a+CBc resulted in a mean PI gain score that was greater than SHAM. $P < 0.05$ Whiskers denote standard error.

5.3.6 Pre-test to post-test

A Shapiro-Wilk test confirmed normality of the post-test PIs for SHAM ($P = 0.65$) and M1a+CBc ($P = 0.48$). A one way ANCOVA showed that, after adjustment for baseline performance, there was a statistically significant difference between M1a+CBc

tDCS and SHAM after practice ($F[1, 39] = 4.810, P = 0.034 \eta_p^2 = 0.110$), with M1a+CBc tDCS post-test PI ($mean \pm SE$) ($416.456 \text{ pts} \pm 15.274$) statistically significantly greater than SHAM ($364.992 \text{ pts} \pm 17.662$) (Figure 5.5).

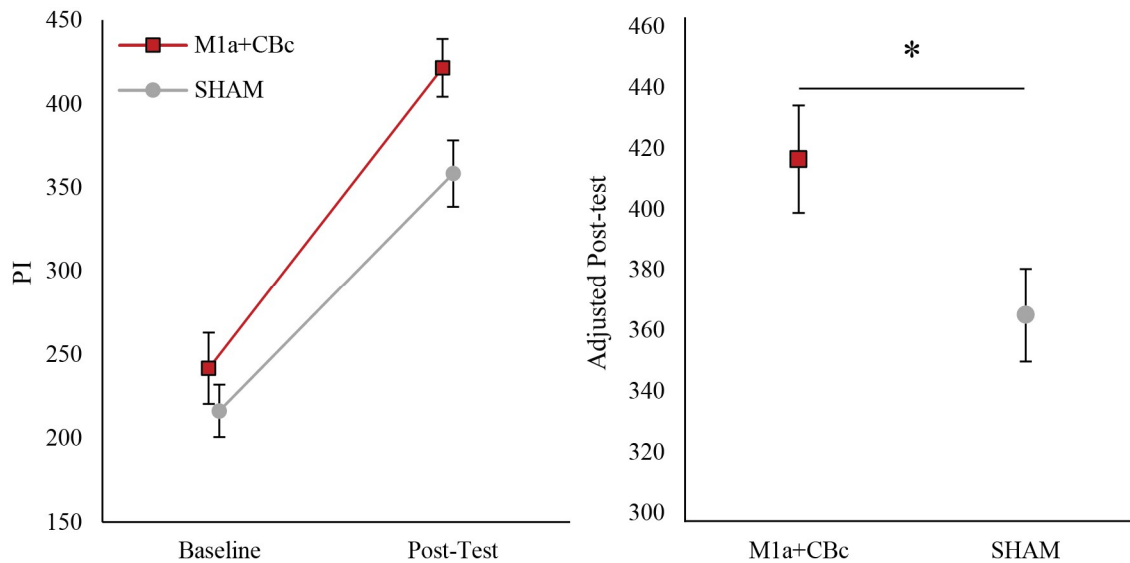


Figure 5.5. Overall performance change. Left panel shows group means before and after practicing for 20 minutes with M1a+CBc tDCS or SHAM. Right shows the comparison between the baseline adjusted post-test means. After adjusting for baseline, M1a+CBc tDCS produced significantly greater PI at post-test compared to SHAM. Whiskers denote standard error.

5.4 Discussion

The main findings of the two experiments were: (1) 2mA a-tDCS applied to M1 did not yield a statistically significant effect on acquisition of skill in the Step Mania task; (2) 2mA of cerebellar tDCS failed to elicit a significant difference in performance regardless of current polarity. Though non-significant, a trend towards improved performance was apparent in both the M1 a-tDCS and cerebellar c-tDCS groups; (3) the concurrent application of 2mA M1 a-tDCS and 2mA cerebellar c-tDCS stimulation

significantly enhanced acquisition of skill in the Step Mania task compared to SHAM. Since tDCS of M1 and cerebellum individually did not produce differences compared to SHAM, it can be assumed that the enhanced learning demonstrated by the concurrent group is the result of neuroplastic changes specifically brought on by stimulating both sites simultaneously. To our knowledge, this is the first study to investigate the effect of concurrent stimulation of M1 and the cerebellum on motor learning.

In contrast with the early tDCS literature which demonstrated a dose-response relationship of tDCS effects,^{65,244} more recent literature has demonstrated diminishing effects of tDCS at higher intensities and durations.^{260,261} Nevertheless, some previous studies have found that 2mA anodal stimulation over M1 enhanced motor learning.²⁶²⁻²⁶⁴ When compared with our previous study showing that 1mA of M1 a-tDCS enhances Step Mania task performance,²⁶⁵ our current results support a dose-response ceiling effect of anodal tDCS of M1. Compared to 1mA in our previous study, the reduced efficacy of 2mA may reflect higher spontaneous activity (noise) relative to the task-related activity (signal) such that normal acquisition was still able to occur, but tDCS benefits were minimal.^{266,267} Ultimately, these results, together with our previous findings, suggest the beneficial effects of monofocal M1 tDCS do not scale linearly with stimulation intensity. Although 2mA M1 a-tDCS did not enhance learning, our findings also suggest that, at least for M1, dual-site stimulation may be able to leverage intrinsic network connectivity and allow a higher stimulation intensity to be used before reaching a ceiling effect.

Like M1, the cerebellum experiences anodal-cathodal polarity dependent changes in excitability with tDCS,²⁴⁹ however, similarly polarity-dependent functional effects are less apparent. Both a-tDCS^{112,232,247} and c-tDCS^{108,254,268} have resulted in learning

outcomes that are consistent with having facilitated cerebellar function.²⁵² In some cases, the effects of stimulation have been polarity independent, with the opposite polarities yielding the same facilitated effects.^{269,270} In regards to the current study, neither a-tDCS nor c-tDCS alone resulted in any significant differences in the acquisition of SM skill compared to SHAM. Although the exact cellular mechanisms underlying the effects of tDCS in the cerebellum are not well understood, it seems a-tDCS and c-tDCS modulate cerebellar output through an increase or decrease Purkinje cell excitability, respectively.²⁴⁹ Whether a-tDCS or c-tDCS will result in a facilitatory or inhibitory outcome on behavior depends on the activity of the cerebellum during task performance.^{252,271}

In contrast to the findings with monofocal M1 and cerebellar groups in experiment 1, concurrent 2mA M1a+CBc resulted in significantly improved performance compared to the SHAM condition. Under normal circumstances, M1 and the cerebellum interact when learning a tapping sequence with specific timing demands.²³⁹ When performance is poor initially, cerebellar activity is high, likely owing to error-correction mechanisms related to optimization of movements.^{239,272} As skill improves, cerebellar activity decreases and M1 activity increases. This M1-cerebellar interaction pattern is directly related to within-day learning in the task.^{118,239} Whereas the single site protocols only influenced one side of the interaction, applying M1a+CBc tDCS influenced both ends of the interaction, thereby facilitating their cooperative roles.

Due to the state-dependency of tDCS effects,²⁶⁷ and the lack of excitability measures in the current study, it cannot be concluded from these data how M1a+CBc tDCS affected learning mechanisms differently than the single-site stimulation of either

M1 or cerebellum alone. However, based on the presumed effect of each polarity on the excitability of the respective regions, we broadly speculate that the 2mA cerebellar c-tDCS increased task-specific excitatory input to M1, which increased the task-related neural activity (signal) in M1 relative to the random neural activity (noise) from M1 2mA a-tDCS. This may have been due to a general decrease in the tonic inhibitory tone that the cerebellum exerts over M1 (cerebellar brain inhibition, CBI) through suppression of Purkinje cell excitability by cathodal tDCS.²⁴⁹ However, it has been suggested that cathodal tDCS acts a neural noise filter by hyperpolarizing cells which suppresses spontaneous firing rates/irrelevant inputs, thereby improving the strength of the neural signal (task-related neural activity).^{266,273} Such a mechanism may have provided more refined feedback in addition to generally reduced CBI. In the absence of excitability measures, these interpretations are only conjecture, as there may have been other homeostatic mechanisms²⁷⁴ affecting neurophysiological changes while both currents were applied.

The majority of studies investigating the use of tDCS in motor learning have targeted either M1 or the cerebellum while subjects performed laboratory tasks intended to isolate specific learning processes.^{119,155} However, as task complexity increases, more areas outside of M1 are recruited in the learning process. As a result, it has been suggested that stimulus of a single region may be inadequate for learning benefits.¹⁵⁵ The results of this study suggest that multi-site concurrent stimulation may be useful in addressing this potential shortcoming.

The potential for tDCS to enhance motor learning or performance has led to increased consumer interest outside of the lab where devices are now becoming

commercially available to consumers.^{275,276} However, there is a task dependency for tDCS effects that must be considered. For instance, video games require dexterous temporally-constrained inputs with varying degrees of visuomotor processing and cognitive demands. Despite reports of gamers using tDCS to improve performance,¹⁸⁶ it is still unclear what regions should be targeted to optimize tDCS benefits. a-tDCS has recently been shown to enhance acquisition of different video game based skills.^{181,265} Our results indicate that, for gaming enhancement, a dual site M1 and cerebellum approach may be more effective than traditional single single-site stimulation protocols. However, as most videogames are bimanual tasks, our results may not translate to controller-based videogaming.

In this study, there were no measurements taken to assess the excitability changes that accompanied the M1a+CBc concurrent montage or to investigate how the connectivity changes between M1 and the cerebellum were affected. Since tDCS of M1 and cerebellum individually did not produce differences compared to SHAM, it seems that the enhanced learning demonstrated by the M1a+CBc group is a direct result of neuroplastic changes specifically brought on by stimulating both sites simultaneously. However, given the influence of state dependent effects on tDCS outcomes,²⁶⁷ as well as the uncertainty of the mechanisms of action in cerebellar tDCS,²⁵² how the concurrent montage affected the excitability of either region, or the pathways connecting them, differently than the single site approaches remains unclear and should be investigated further.

Future studies investigating concurrent M1-cerebellar stimulation should investigate the effects of combining 1mA M1 a-tDCS with the 2mA cerebellar current.

Over M1, 1 mA is more commonly used than 2mA to produce beneficial learning outcomes.^{119,155} Considering 2mA M1 stimulation in the current study was only effective when combined with cerebellar stimulation, 1mA may increase the probability of learning benefits. Furthermore, functional enhancement from dual-site simulation of M1 and the cerebellum may be polarity specific depending on the effector for the task. Whereas c-tDCS over the cerebellum enhanced hand adaptation movements, it led to significantly impaired whole arm adaptation movements.²⁵⁴ The error-dependent mechanisms in early skill acquisition may be similarly influenced by the different polarities over the cerebellum in a dual-site approach. Lastly, in the current study we did not assess retention. Evidence suggests M1 has a significant role in motor retention while the cerebellum is more involved with early learning processes.²⁷⁷ Concurrent M1 and cerebellum applications may result in greater retention by optimizing plasticity in both structures simultaneously.

5.6 Conclusion

While there may be a dose-dependent effect stimulation, it seems that at higher stimulation intensities, tDCS may yield diminishing returns. This is important because the effects of traditional, monofocal tDCS protocols appear to be inconsistent in more complex, real-world tasks. This is likely because as task complexity scales, the network-wide activity within the brain does also.^{165,278,279} In particular, the cerebellum is one such region of the brain that is exceedingly important in the early stages of motor learning when high amounts of sensorimotor feedback and error correction are present^{117,239,272}. Our findings show that anodal stimulation of M1 concurrent with cathodal stimulation of

the cerebellum results in improvements in task performance that are significantly different than SHAM stimulation. It is our hope that these findings will provide future researchers and clinicians with a better understanding of how dual site tDCS can be employed to better facilitate motor learning in complex tasks.

CHAPTER SIX: SUMMARY AND FUTURE DIRECTIONS

6.1 Dissertation summary

The studies in this dissertation investigated how tDCS applied to M1 and the cerebellum affects skill acquisition during the fast phase of motor learning for novel everyday tasks, with an emphasis on tasks that have diverse motor demands. Previous tDCS motor learning research has focused mostly on M1 or cerebellar stimulation that is applied while practicing relatively simple, highly controlled laboratory tasks that isolate learning processes. However, as real-world tasks tend to have more complex motor demands, generalization of these results to practical applications outside of the lab has had inconsistent results. To increase the amount of research related to tDCS-based applications for the acquisition of complex motor skills, we studied the acquisition of 4 everyday motor tasks. For each of the tasks, the non-dominant hand was used to make tasks novel, which ensured there was a discernible fast phase of learning to observe skill acquisition.

In study one, 1mA of M1 a-tDCS applied during a single practice session was found to enhance skill acquisition in a complex dart throwing task compared to SHAM and 1mA of M1 c-tDCS. In study two, 1mA M1 a-tDCS improved the rate of motor learning in the O'Connor Tweezer Dexterity Task compared to SHAM. In study three, 1mA of M1 a-tDCS while practicing a dexterous rhythmic-timing video game led to significantly higher performance scores compared to SHAM, demonstrating increased motor acquisition. In study four, concurrently applying 2mA M1 a-tDCS and 2mA cerebellar c-tDCS significantly improved skill acquisition in the rhythmic-timing video

game task, whereas 2mA M1 of a-tDCS, 2mA of cerebellar a-tDCS and c-tDCS alone was no different than SHAM. Taken together, the data from everyday tasks possessing a range of gross, fine, and visuomotor demands demonstrates the capability of tDCS to enhance skill acquisition in a variety of real-world tasks. They also provide evidence suggesting a synergistic effect on learning may occur when M1 and the cerebellum are stimulated concurrently, which a novel finding.

6.2 Strengths, limitations and future directions

Using a series of novel everyday tasks with a variety of motor demands, the studies found that tDCS can influence the underlying neuroplastic mechanisms in M1 and the cerebellum that underpin the acquisition of skill in complex tasks. However, there are strengths and limitations of the studies that should be noted. Future research on tDCS in motor learning should address these limitations.

In study one, there was no background demographic information collected from the subjects in regards to their past or current involvement in sports that involve skilled throwing. Although the task was performed with the non-dominant arm, previous motor experience can influence the rate that skill learning takes place.¹⁷ Baseline aptitude for a task, and the difficulty of the task, also have an influence on the development of measurable tDCS learning outcomes due to ceiling/floor effects (high aptitude, low difficulty; low aptitude, high difficulty).^{224,280,281} These influential factors should be addressed in future studies by collecting sport participation history, as well as an initial aptitude assessment, and take these into consideration when comparing group demographics, and possibly control for their influence on learning.

In study two, subjects were required to use a uniform technique when placing pins, which prevented subjects using strategies that made placing pins easier as a result of accessory hand or wrist movement. This strengthened the results of the study by ensuring that improvements in performance placing pins was the result of gained motor skill, rather than by implementation of a different strategy. Fatigue is also a concern during motor learning as it affects performance of the task and interferes with motor learning.²⁸² The rest periods implemented in between completion of rows effectively eliminated the detrimental effects of fatigue on the practice period that had been observed in pilot testing. We did not limit the amount of practice individuals could complete during the 20 minute practice session, so individuals with better performance completed more practice, which could have influenced our results. Future studies may address such a concern by having subjects perform a set number of trials during the stimulation period, with timed rest periods, and excluding subjects who are unable to complete a certain number of trials.

In study three, the use of adjustable task difficulty provided a unique strength in this study that is not easily achievable with other complex motor skills in the context of tDCS research. It is a common observation in tDCS motor learning literature that individuals with novice/low baseline ability benefit more from stimulation than those with more expertise/ability.^{108,181,280} The difficulty adjustment used in Step Mania decreases the influence of performance floor and ceiling effects preventing the development of observable tDCS performance effects. An important limitation note is that there was no data collected on subject videogame experience. It has been shown that those with more experience playing videogames benefit less from M1 a-tDCS when

acquiring video game based motor skills compared to less experienced counterparts.¹⁸¹ Future research on tDCS effects in videogame based motor skills would be strengthened by parsing data based on subject gaming history or skill level. Lastly, individuals who have been involved with rhythm based activities, such as musicians or dancers, may have increased motor timing²⁸³ and/or temporal processing abilities compared to those lacking rhythmic task experience; however, we did not collect any data on musical/dance experience. Future studies using rhythmic matching motor tasks should exclude or control for individuals with developed temporal skills who will likely not demonstrate a measureable learning benefit, or who may even experience a diminished ability, from tDCS applied during practice.²⁸¹

In study four, the same motor task was used as in study three; therefore, the strengths and limitations associated with study three also apply to study four. Additionally, however, the greatest limitation in study four was the lack of cortical excitability or M1-cerebellum connectivity (assessed by CBI) measures to assess the neuroplastic effects of the novel M1-cerebellar stimulation that was used. Although the behavioral data suggests a robust effect, what functional changes, and in which structures, that potentially led to the effect cannot be surmised because of potential homeostatic effects in the cerebellar-cortical loop circuitry from altering excitability in both structures at once. Future studies investigating M1-cerebellar dual-site concurrent stimulation protocols should include neurophysiological measures or neuroimaging to address this shortcoming. Additionally, the distribution of genders in the different groups may have impacted the results as there is emerging evidence of sex-based differences in responses to tDCS.^{284,285} Considering the influence that factors such as baseline ability,

sports or music background, and gender may have on tDCS, future tDCS studies may find more consistent reproducible results if these different participant characteristics are considered for inclusion in the study and group allocation.

Despite the limitations of these studies, the evidence they provide generally supports the beneficial effects of tDCS for applications in motor skill acquisition. However, as all of the tasks were unilateral, these results may not generalize to bimanual tasks. Additionally, all tasks were performed with the non-dominant hand to model early learning of a new skill. Therefore, tDCS may not necessarily translate to improving skill acquisition in the dominant hand. However, this may depend on how novel or new the skill being learned with the dominant hand is. Nevertheless, the novel finding that concurrent stimulation of M1 and the cerebellum synergistically impact motor learning is interesting and interesting proof-of-concept and may influence the development of promising new protocols in the future.

APPENDIX

Edinburgh Handedness Inventory¹²²

Please indicate with a one (1) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put a two (2).

If you are indifferent, put a one in each column (1 | 1).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH - LH =	
Result	R = (D / CT) × 100 =	
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)		

← Please stop here

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282. Branscheidt M, Kassavetis P, Anaya M, et al. Fatigue induces long-lasting detrimental changes in motor-skill learning. *Elife*. 2019;8.
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284. Workman CD, Fietsam AC, Rudroff T. Transcranial Direct Current Stimulation at 4 mA Induces Greater Leg Muscle Fatigability in Women Compared to Men. *Brain Sci*. 2020;10(4).
285. Weller S, Derntl B, Plewnia C. Sex matters for the enhancement of cognitive training with transcranial direct current stimulation (tDCS). *Biol Sex Differ*. 2023;14(1):78.

CURRICULUM VITAE

Anthony Wilhite Meek

EDUCATION

Indiana University, Indianapolis, IN

- Doctor of Philosophy in Health and Rehabilitation Sciences, a concentration in Neuroscience (2024)

Indiana University, Indianapolis, IN

- Master of Science in Kinesiology (2014)

DePauw University, Greencastle, IN

- Bachelor of Science in Education Studies, Minor in Kinesiology; graduated *Cum Laude* (2012)

PROFESSIONAL EXPERIENCE

Indiana University, Indianapolis, IN

Aug 2012 – May 2020

Graduate Teaching Assistant, Department of Kinesiology, School of Health and Human Sciences, IUPUI, Indianapolis, IN.

Researcher, Dr. Riley Neural Control Lab,

March 2014 - Present

Department of Kinesiology, School of Health and Human Sciences

TEACHING EXPERIENCE

Indiana University-Purdue University-Indianapolis (IUPUI)

Undergraduate

- (P397) Biomechanics – 6 semesters (3 cr.)
- (P391) Biomechanics Laboratory – 10 semesters (3 cr.)
- (P215) Introduction to Kinesiology Laboratory – 3 semesters (3 cr.)
- (P200) Microcomputers (Technology) in Kinesiology – 9 semesters (3 cr.)
- (E111) Introduction to Basketball – 10 semesters (1 cr.)
- (E121) Conditioning and Weight Training – 2 semesters (1 cr.)
- (E 211) Advanced Basketball – 1 semester (1 cr.)
- Intermediate Weight Training – 2 semesters (1 cr.)
- (E102) Group Exercise – 2 semesters (1 cr.)

Invited Lecturer

Franklin College

- “Kinesiology Research Laboratory,” Organization and Administration, 2018.
Instructor: Adam Heavrin
- “Olympic lifting for athletic power development,” Methods of Strength and Conditioning, 2015.
Instructor: Adam Heavrin
- “The basics of Olympic lifting,” Methods of Strength and Conditioning, 2014.
Instructor: Adam Heavrin

RESEARCH EXPERIENCE

Peer-reviewed manuscripts

1. **A.W. Meek**, D. Greenwell, B.J. Poston, Z.A. Riley. Anodal M1 tDCS enhances online learning of rhythmic timing videogame skill. *bioRxiv [In Review]*. 2023.11.22.568299. <https://doi.org/10.1101/2023.11.22.568299>
2. M.A. Wilson, D. Greenwell, **A.W. Meek**, B.J. Poston, and Z.A. Riley. Neuroenhancement of a dexterous motor task with anodal tDCS. *BrainRes*.2022; 1790,147993. <https://doi.org/10.1016/j.brainres.2022.147993>
3. **A.W. Meek**, A.M. Heavrin, A.E. Mikesky, N.A. Segal, and Z.A. Riley. Subject factors influencing blood flow restriction in the arm at low cuff pressures. *Clin Physiol Funct Imaging*. 2022; 42(4):233-240. <https://doi.org/10.1111/cpf.12752>
4. **A.W. Meek**, J. Perez, B.J. Poston, and Z.A. Riley. Cortical Representation and excitability increases for a Thenar Muscle Mediate Improvement in Short-Term Cellular Phone Text Messaging Ability. *Brain Sci*. 2021; 11(3):406. <https://doi.org/10.3390/brainsci11030406>
5. **Meek, A. W.**, Greenwell, D., Poston, B.J., & Riley, Z. A. Anodal tDCS accelerates on-line learning of dart throwing. *Neurosci lett*. 2021; 764, 136211. <https://doi.org/10.1016/j.neulet.2021.136211>

Abstracts

1. **A.W. Meek**, A. Heavrin, N.A. Segal, and A.E. Mikesky. KAATSU Cuff Tightness and Limb Anthropometry: Effect on Blood Flow Restriction. *Medicine and Science in Sports and Exercise*. Abstracts #3006, 2014.
2. Heavrin, **A.W. Meek**, N.A. Segal, and A.E. Mikesky. Initial KAATSU Cuff Tightness: Effect of Limb Anthropometrics on Blood Flow Restriction. IV NSCA International Conference, Murcia, Spain, June 26 – 28, 2014.
3. **A.W. Meek**, A. Heavrin, A., N.A. Segal, and A.E. Mikesky. KAATSU Cuff Tightness and Limb Anthropometry: Effect on Blood Flow Restriction. Poster session presented at IUPUI Research Day, 2014.
4. Heavrin, **A.W. Meek**, A., N.A. Segal, and A.E. Mikesky. Initial KAATSU Cuff Tightness: Effect of Limb Anthropometrics on Blood Flow Restriction. IUPUI Research Day, 2014.
5. N.R. Eckert, **A.W. Meek**, K. Smith, J.C. Williams and Z.A. Riley. Cutaneous Silent Period Characteristics are Dependent on the Organization of Upper Limb Muscles. IUPUI Research Day, 2014.
6. N.R. Eckert, **A.W. Meek**, K. Smith, J.C. Williams, and Z.A. Riley. Cutaneous Silent Period Characteristics are Dependent on the Organization of Upper Limb Muscles. *Society for Neuroscience Abstracts* #63.04, 2014.
7. **A.W. Meek**, N.R. Eckert, K. Smith, J.C. Williams, and Z.A. Riley. Effect of Cutaneous Silent Period on Cortical Output in Proximal-Distal Muscles in the Upper Limb. *Society for Neuroscience Abstracts* #63.07, 2014.
8. Z.A. Riley, **A.W. Meek**, J. Williams, and N.R. Eckert. Correlates between Motor Cortical Output and Control of the Digits during Common-Practiced Hand Dexterity Tasks. *Society for Neuroscience Abstracts* #249.15, 2014.
9. **A.W. Meek**, J.W. Streepey, and Z.A. Riley. Determinants of Fatigue in the Biceps Brachii During Blood Flow Restriction Training. *Medicine and Science in Sports and Exercise*: S000, 2016.
10. B. Wind, **A.W. Meek**, M. Godza, and Z.A. Riley, K.M. Naugle. The Effect of Transcranial Direct Current Stimulation on Conditioned Pain Modulation in Healthy Older Adults. *Society for Neuroscience Abstracts* #390.08, 2018
11. N. Zdanowicz, **A.W. Meek**, D. Greenwell, M. Wolfe, and Z.A. Riley. M1 tDCS does not influence performance of a fine-motor skill tweezer task. *Society for Neuroscience Abstracts* #402.02, 2018

12. **A.W. Meek**, D. Greenwell, M. Wolfe, B.J. Poston, and Z.A. Riley. The use of tDCS to enhance learning of a dart throwing task. Society for Neuroscience Abstracts #402.10, 2018
13. M. Wolfe, A. Zakeresfahani, M. Wilson, **A.W. Meek**, B.J. Poston, and Z.A. Riley. Performance of a timing-based hand dexterity video game with M1 tDCS. Society for Neuroscience Abstracts #402.12, 2018
14. J. Perez, **A.W. Meek**, and Z.A. Riley. Variant Target Effects on Motor Learning through tDCS. Annual Biomedical Research Conference for Minority Students Abstracts #267, 2018
15. M. Wolfe, J. Perez, **A.W. Meek**, B.J. Poston, Z.A. Riley. Cerebellar tDCS Improves Performance of a Timing-Based Video Game More than M1 tDCS or Practice Alone. Society for Neuroscience Abstracts #759.06, 2019
16. **A.W. Meek**, J. Perez, M. Wolfe, A. Bockelman, K. Harbison, C. Lasher, B.J. Poston, Z.A. Riley. Dextrous Timing-Based Video Game Performance with Complementary Transcranial Direct Current Stimulation of the Primary Motor Cortex and Cerebellum. Society for Neuroscience Abstracts #759.11, 2019

PRESENTATIONS

- J. W. Streepey, M. Urtel, and **A.W. Meek**. How tablets are used to improve technology knowledge in kinesiology students. Advanced Learning Symposium, IUPUI, 2014.
- **A.W. Meek**. “Transcranial Direct Current Stimulation – Augmenting neuroplasticity to improve neurorehabilitative outcomes.” Medicine beyond Medication: Rethinking Brain Health Conference, Grand Rapids, MI. Oct. 9, 2015. (Invited Speaker)

SERVICE

Committees

- PETM Graduate Research Committee Co-Student Representative, 2015 – 2017
- PETM Graduate Research Committee Student Representative, 2013 – 2015

Service to the Field

- Volunteer Resistance Training Consultant, Football and Girls Basketball, Rushville Consolidated High School, 2020 – 2023
Coach: Isaac Sliger
- Volunteer speaker, after school program for athletes, “Nutrition for Recovery and Supplements,” Rushville Consolidated High School, 2019
Leader: Greg Pratt
- Consultant Motor Learning projects for motor learning studies, 2019
Instructor: Dr. Kyra Noerr
- Invited presentation, Advanced Health Topics, “Supplements and PEDs,” Rushville Consolidated High School, Fall 2017
Teacher: Jake Hedrick
- Consultant Biomechanics Lab and Course Content, 2017 – 2021
Instructor: Adam Heavrin
- Consultant Doppler ultrasound blood flow measure and Kaatsu protocols, 2015 – 2016.
Instructor: Adam Heavrin

Service to the Profession

- Peer reviewer – European Journal of Applied Physiology

PROFESSIONAL MEMBERSHIPS

- Society for Neuroscience
- National Strength and Conditioning Association
 - Certified Personal Trainer
 - Certified Strength and Conditioning Specialist