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The effect of transcranial direct current stimulation on the behavioral and neurophysiological performance of healthy subjects during reaching

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THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON THE BEHAVIORAL AND NEUROPHYSIOLOGICAL PERFORMANCE OF HEALTHY SUBJECTS DURING REACHING

by

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CERTIFICATE OF APPROVAL

MASTER'S THESIS

This is to certify that the Master's thesis of

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To my parents: Drs. David and Carrie Chapman

Science is not only compatible with spirituality; it is a profound source of spirituality. When we recognize our place in an immensity of light-years and in the passage of ages, when we grasp the intricacy, beauty, and subtlety of life, then that soaring feeling, that sense of elation and humility combined, is surely spiritual...the notion that science and spirituality are somehow mutually exclusive does a disservice to both.

Carl Sagan

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LIST OF ABBREVIATIONS

CNS	Central Nervous System
M1	Primary Motor Cortex
tDCS	Transcranial Direct Current Stimulation
EMG	Electromyography
TMS	Transcranial Magnetic Stimulation
MEP	Motor Evoked Potential
3D	Three Dimensional
BB	Biceps Brachii
TB	Triceps Brachii
AD	Anterior Deltoid
PD	Posterior Deltoid
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation

CHAPTER I

INTRODUCTION

Overview

Typical adults complete multiple types of routine reaching tasks every day: we pull the covers off our beds, flip on a light switch, grab our toothbrushes, and reach for a coffee cup or a glass of water. Throughout the day, most of these types of reaching tasks are accomplished with little or no apparent conscious effort beyond the initial decision to reach for the intended object or complete a selected task; e.g. turning on the lights by flipping the light switch to the on position. Despite this apparent simplicity, reaching is indeed a complex motor task.

Successfully reaching for an object is a complex task because it requires us to control multiple functional subsystems (e.g., the musculoskeletal system, the peripheral nervous system, and the central nervous system) in light of the task we want to accomplish (Thelen & Smith, 1994). An example of controlling these subsystems is when we use our trunk muscles to provide proximal stability so that our upper extremities can move freely to execute a given reach. Additionally, we learn with experience how to successfully coordinate the multiple joints and muscles needed to reach with each upper extremity. Almost simultaneously, our central nervous system (CNS) generates the initial command to reach, processes the on-going sensory information of our reaches, and generates error correction messages in real time so that we can meet the demands of the task (Chapman, 2002). For example, to ring a doorbell we initially decide to reach out to the doorbell. Then, we generate the appropriate forces necessary to control our posture as well as flex our arm at the shoulder, extend the elbow, wrist, and fingers, and apply the

correct amount of force in order to engage the doorbell switch without injuring our finger or wrist at the point of contact. Thus, reaching is as Karniel & Inbar (1997) suggested, "…a basic motor action. It is a simple action, yet it involves almost all aspects of motor control, from vision and proprioceptors, through many parts of the nervous system, to the muscles and joints" (p. 173). In essence, reaching extends beyond its initially simple appearance, in to the realm of an ornate motor task that requires us to "master the redundant degrees of freedom of the moving organ" (Bernstein, 1967, p. 127).

The complexity of reaching is however masked in several ways. First, from the time we initially attempt to grab objects between three and five months of age (Thelen et al., 1993) until we fully utilize our ability to reach in our adult lives, it is not outside the realm of possibility that we accomplish hundreds of thousands of simple reaching tasks. Because of this high volume of repetition, we are normally well versed in even the most complex of reaching tasks. Second, although we might have the ability to access all of the information available to us about a specific reaching behavior, we tend to be only consciously aware of the most essential data needed to successfully accomplish that reach. To use ringing a doorbell as an example again, we are probably not as aware of the stiffness of our muscles or how long it takes us to reach to the doorbell. Instead, we focus on placing the end point of our fingertip directly on that doorbell and applying the appropriate amount of force needed to ring the doorbell. Many investigators have attempted to better understand the neural control of reaching through electrophysiological and lesion studies of the primary motor cortex (M1) in animal preparations. Only recently has it become possible to directly measure and alter the physiology of M1 in humans during the act of reaching in a safe and non-invasive manner. By altering the

excitability of M1, non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), can potentially allow us to study some of the aforementioned features of reaching behaviors in more depth than ever before.

Because reaching is a complex activity influenced by multiple factors, I designed this study to better understand the role of M1 in controlling particular aspects of reaching. Specifically, I set out to discover how reducing M1 excitability through cathodal tDCS alters unrestrained reaching as measured by kinematic and electromyographic (EMG) variables in healthy subjects. In light of this purpose, a systematic review of how we learn to reach in novel environments and how specific areas of the brain plan and accomplish reaching tasks will be presented. Then, the measureable kinematic and neuromuscular variables of reaching that the CNS can influence will be examined. Next, an assessment of how altered M1 activity (via tDCS) changes corticospinal excitability and the aforementioned kinematic and neuromuscular variables will be reviewed. I end with a review of what is still unknown about how altered M1 excitability via tDCS affects those variables.

Background

Coordination of reaching, as Bernstein (1967) indicated, is essentially defined by our ability to master a set of redundant degrees of freedom. In other words, we can accomplish the same reaching task utilizing multiple paths, joint angles, or other combinations of reaching features. We attempt to accomplish hundreds of thousands of these truly ornate reaching tasks throughout our lifetime in order to optimize the redundant degrees of freedom of our upper extremities. This is our primary means of

interacting with the environments that we find ourselves in (Bernstein, 1967; Wolpert, Ghahramani, & Flanagan, 2001). Whether the environment is our home and we are searching for our keys in a coat pocket or we are at work grabbing a ream of paper for the printer, these movements are generally completed without restriction with respect to time or space.

Internal Models

Because we normally reach in this unencumbered fashion, we are constantly experiencing new environments and reaching dynamics. An example of this is when we learn to adjust our upper extremities when we reach out to grab and lift an opaque bottle that appears to be full of a heavy liquid, but rather was empty instead. As a result, we are always attempting to learn new situations and scenarios in which we must successfully reach. This learning process is done through the use of what are known as internal models (Kawato, 1999; Shadmehr, Donchin, Hwang, Hemminger, & Rao, 2005; Shadmehr & Mussa-Ivaldi, 1994; Thoroughman & Shadmehr, 1999). Internal models are theoretical brain circuits that store information about the dynamics of our limbs as well as the dynamics of the environments we reach in (Conditt, Gandolfo, & Mussa-Ivaldi, 1997; Davidson & Wolpert, 2003; Sabes, 2000). By practicing in the aforementioned novel situations, internal models are utilized to increase our performance of accomplishing desired tasks (Wolpert, Ghahramani, & Flanagan, 2001). More specifically, we improve our success in reaching for items and achieving certain goals by constantly updating our internal models to more closely approximate a desired reaching behavior. This updating process occurs every time that we learn a new set of reaching dynamics. For example, internal models will update when we experience unexpected visual perturbations as well

as unanticipated limb dynamics; e.g. an object that we anticipated to be heavy, but was lighter than we expected (Shadmehr, Donchin, Hwang, Hemminger, & Rao, 2005; Shadmehr & Mussa-Ivaldi, 1994; Shadmehr & Wise, 2004).

The updating process that occurs within our reaching internal models has two major forms. The first form of updating our reaching happens as a result of feedback control (Figure 1.1). Feedback control is the process by which we modify our reaches through the use of our sensory receptors while the movement is on-going (Seidler, Noll, & Thiers, 2004). This type of control can offer a great deal of accuracy but is slow in nature.

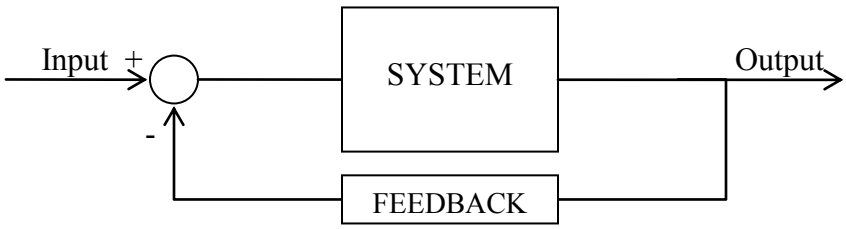

***Figure 1.1*. Simple feedback controller.**

Because of the slow operating speed of feedback control, we need a faster method for controlling our reaching movements: feedforward control (Figure 1.2) (Kawato, 1999). Unlike feedback control, feedforward control operates in the absence of any sensory input and thus allows for faster coordinated reaching movements (Kawato, 1999; Seidler, Noll, & Thiers, 2004).

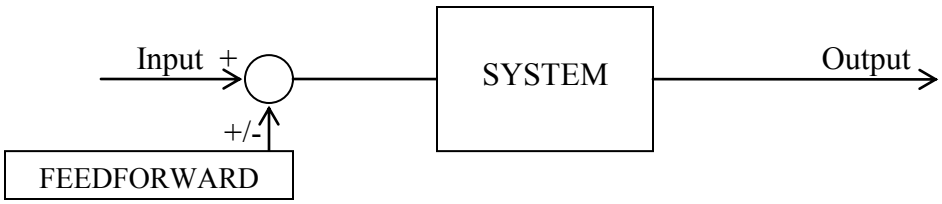

***Figure 1.2*. Simple feedforward controller.**

Internal models are one type of these faster feedforward control mechanisms and can be further divided in to two separate portions. The first is the inverse model (Figure 1.3). The inverse model is responsible for computing actual reaching commands based on all of the available sensory information (Kawato, 1999; Sabes, 2000). Once a reaching command has been computed in the inverse model, it can be executed and compared to the desired reaching behavior. If the executed reach and the desired reach do not match, we update the inverse model for that reaching behavior and recalculate our reaching command.

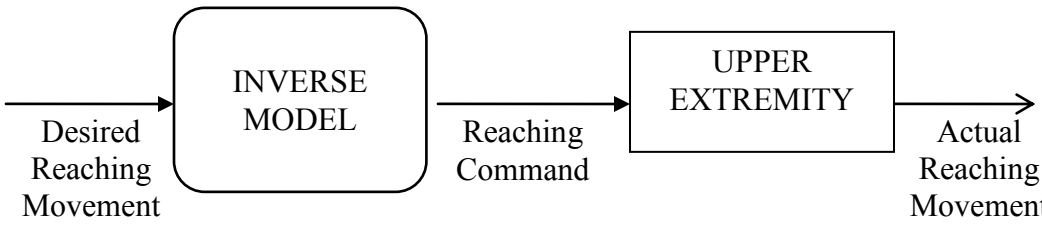

***Figure 1.3*. Example of an inverse internal model.**

In order to prevent having to try every possible reaching command for each reaching task, a copy of the reaching command that was calculated in the inverse model

is sent to the second way our internal models utilize feedforward control: the forward model (Figure 1.4). The forward model is our neurological attempt at predicting the outcome of each reaching behavior given a specific reaching command (Katsnelson, 2003; Kawato, 1999; Sabes, 2000). For example, we can imagine reaching out to press a doorbell with a certain amount of force and predict if that reach would be successful in accomplishing the desired task. If we do not believe that amount of force would have resulted in a successful reach, we can update our forward model and rerun the "neurological simulation" with a different set of reaching parameters.

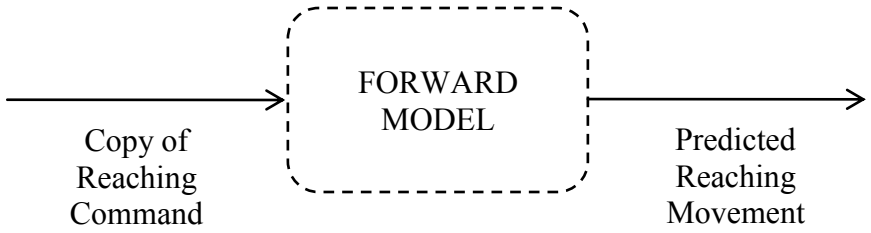

***Figure 1.4*. Example of forward internal model.**

The two aforementioned portions (inverse model and forward model) of our reaching internal model operate in unison to better perfect our reaching behaviors (Figure 1.5).

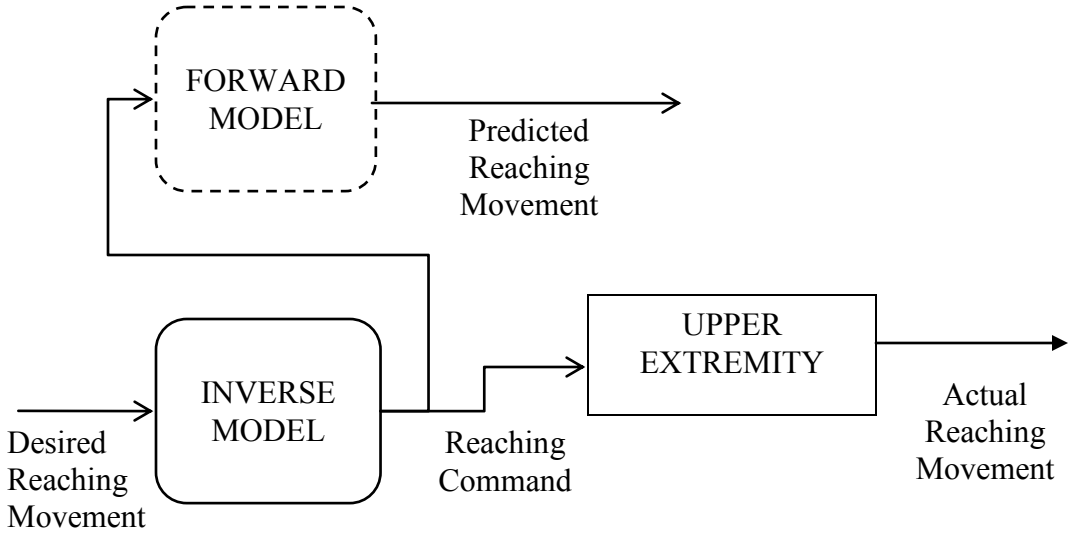

***Figure 1.5*. Example of inverse and forward models operating together.**

Central Control of Reaching

Descending Pathways

This updating process and more importantly the control of many features of reaching happens in the CNS. More specifically, there are a number of descending pathways that have some influence over the spinal motor neurons and thus the actual reaching movements we are responsible for accomplishing. Some of those descending pathways are the vestibulospinal, reticulospinal, rubrospinal, and corticospinal tracts.

The vestibulospinal and reticulospinal tracts are considered medial brainstem pathways and pass through the ventral medial portions of the spinal cord's white matter (Lawrence & Kuypers, 1968; Kuypers, 1981). Traditionally, the pathways that are positioned accordingly have connections with interneurons located in the grey matter as well as motor neurons that are believed to primarily influence the axial muscles like our abdominals (Kuypers, 1981). As such, they are vital for portions of reaching like posture

control. More recently however, it was discovered in non-human primates that the reticulospinal tract also has some direct connections to the alpha motor neurons that control portions of the hand, forearm, and upper arm (Riddle, Edgley, & Baker, 2009). The other previously mentioned descending pathway that originates in the brain stem is the rubrospinal tract. The rubrospinal tract is a lateral brainstem pathway and as a result has connections with the interneurons found in the lateral portions of the grey matter of the spinal cord (Nyberg-Hansen & Brodal, 1964). In monkeys and in cats this is indicative of distal muscle control, but in humans this job is probably controlled by other pathways (Alstermark et al., 2011; Holstege, 1987).

The final descending pathway noted previously is the corticospinal tract. As its name indicates, this pathway originates in the cerebral cortex but has several distinct functions. First, it can be divided in to a medial and lateral portion. Similar to the medial portion of the brainstem pathways, the medial corticospinal tract directly influences the motor neurons that control the axial muscles (Kuypers, 1981; Lemon, 2008). Most important to this study however, the lateral portion of the corticospinal tract is largely considered the most direct and influential connection to the motor neurons that control the movement of our upper extremities (Lemon, 2008). As such, the focus of the following sections will be on the areas of the brain that influence the lateral corticospinal tract and more specifically our reaching behaviors.

Brain Areas involved in Reaching

There are a number of areas in the brain that play some role in controlling and executing parts of our reaching movements. They include the cerebellum, the basal ganglia, the primary visual cortex, the primary somatosensory cortex, and the posterior

parietal cortex. Additionally, several other cortical areas not only influence our reaching behaviors but also have direct access to the corticospinal pathway including the supplementary motor area, the dorsal pre-motor area, and the ventral pre-motor area. Finally, and most important to this line of research, is the cortical area largely considered the greatest contributor to the corticospinal tract as well as our reaching behaviors, the M1.

Non-Cortical Areas

The two non-cortical areas that play crucial but distinct roles in successfully accomplishing reaching tasks are the basal ganglia and the cerebellum. The basal ganglia are connected to cortical areas via the thalamus (Alexander, Crutcher, & DeLong 1991). This connection allows the basal ganglia to influence the cortex and correspondingly the corticospinal pathway. The basal ganglia are most easily observed to play some role in functional reaching via clinical observations of movement disorders like Parkinson's and Huntington's disease (Gentilucci & Negrotti, 1999; Smith, Brandt, & Shadmehr, 2000). More specifically, the basal ganglia have been linked with selecting and inhibiting specific reaching commands (Alexander & Crutcher, 1990; Doya, 2000). A dysfunction with this ability is prevalent as bradykinesia when associated with Parkinson's as a result of an inability to successfully reach when reaching without external cues (Majsak, Kaminski, Gentile, & Flanagan, 1998) or as a failure to properly sequence reaching because of a decay of the reaching command during the course of a reach (Gentilucci & Negrotti, 1999).

Our cerebellum has connections, like the basal ganglia, to cortical areas via the thalamus (Allen & Tsukahara, 1974). As a result, it can influence our reaching

movements through cortical changes and correspondingly modify parts of the corticospinal tract. More traditionally, the cerebellum is thought of as an error detector for our reaching movements. In other the words, the cerebellum plays some role in calculating and correcting the error between desired and actual reaches (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). More specifically, the cerebellum accomplishes this error detection mechanism at least in part by accounting for the interaction torques created during reaching by the multiple segments of our upper extremities (Bastian, Martin, Keating, & Thach, 1996; Schweighofer, Arbib, & Kawato, 1998).

Sensory Cortical Areas

One area responsible for supplying necessary sensory information to other areas involved in reaching is the primary visual cortex. Visual information enters our eyes and is passed initially to the lateral geniculate nucleus (Callaway, 1998; Hubel & Wiesel, 1979). From there, the visual data is then passed on to the primary visual cortex (Callaway, 1998). This brain area is then partly responsible for processing, manipulating, transforming, and passing that information to the posterior parietal cortex as well as the inferior temporal cortex (Baizer, Ungerleider, & Desimone, 1991). Information that is passed on to the posterior parietal cortex has been linked with areas of the primary visual cortex that respond to the spatial or movement features of what we see whereas the information that is sent to the inferior temporal cortex has largely been linked with portions of primary visual cortex that assess the form and color of our visual data (Baizer, Ungerleider, & Desimone, 1991). Both streams of information leaving the primary visual cortex aid us by providing not only information about our body in space, but also about

the location and other specific features of the target to which we are attempting to reach (Graziano, 1999; Sarlegna & Sainburg, 2009). More specifically, vision provides information from the external world that is needed for a successful reaching movement, e.g. the necessary spatial features needed for that movement (Gielen, Van den Oosten, & Ter Gunne, 1985). We use this information during the first portions of our reaches to select the correct kinematic plan based on that external information we receive in the primary visual cortex (Morasso, 1981). Interestingly, when the amount of visual information decreases, the directionality of our reaches becomes less successful but the amplitude of that reach remains unchanged (Monaco et al., 2010).

Unlike the primary visual cortex, the primary somatosensory cortex has direct connections to M1 (Rocco-Donovan, Ramos, Giraldo, & Brumberg, 2011). The primary somatosensory cortex is responsible for sorting through all of the somatosensory information. The somatosensory information with respect to reaching comes in the form of proprioception of the joints, stretch receptors of the muscles (the muscle spindle) and skin surrounding the joints, tension detectors of the tendons (the Golgi tendon apparatus), and cutaneous light touch receptors (Collins, Refshauge, Todd, & Gandevia, 2005; Hulliger, 1984; McGlone & Reilly, 2010; Swett & Schoultz, 1975). Without this type of information, we show large errors in the coordination of multi-joint reaching movements (Sainburg, Poizner, & Ghez, 1993). These large errors take the form of problems when controlling the aforementioned inter-segment dynamics of reaching (Sainburg, Ghilardi, Poizner, & Ghez, 1995). Not only is proprioception important for controlling inter-segment dynamics, it is also valuable for knowing the correct amplitude of a reach (Monaco et al., 2010). Finally, the information gained from proprioception is thought to

be more valuable to us than the saccades of vision are while reaching (Monaco et al., 2010).

Posterior Parietal Cortex

As mentioned in the previous section, the posterior parietal cortex receives visual information from primary visual cortex and somatosensory information from the primary somatosensory cortex that is vital to our reaching (Kalaska, 1996; Kalaska, Scott, Cisek, & Sergio, 1997). With this sensory information, the posterior parietal cortex is responsible for sensorimotor transformations that are necessary in order to correctly accomplish a reach (Kalaska, 1996; Kalaska, Scott, Cisek, & Sergio, 1997; Snyder, Batista, & Andersen, 1997). Sensorimotor transformations are calculations made by this cortical area that take the available sensory information and modify it in to at least part of a reaching motor command. In addition to its role as a sensorimotor transformer, the posterior parietal cortex is responsible for generating several preliminary motor commands based on the information it has received (Kalaska, Scott, Cisek, & Sergio, 1997). Previously, this cortical area was thought to pass these potential motor plans in a serial manner to both the ventral and dorsal pre-motor areas for further processing of grasping and reaching tasks respectively (Wise, Boussaoud, Johnson, & Caminiti, 1997). And while these connections may be the densest, the posterior parietal cortex also has parallel linkages with M1 and other frontal areas (Gharbawie, Stepniewska, Qi, & Kaas, 2011). This implies that while the posterior parietal cortex does indeed send some of its motor plans to the ventral and dorsal pre-motor areas for further processing, it may also have a more direct effect on M1 and the corticospinal tract than previously thought.

Supplementary Motor Area

The supplementary motor area is a cortical area that not only has projections to M1 but also partially forms the corticospinal tract (Maier et al., 2002; Nachev, Kennard, & Husain, 2008). The supplementary motor area is known to play a role in developing motor sub-routines (portions of actual reaching commands that contain at least part of the features needed for a successful reach) as well as correctly sequencing those commands before they are sent to M1 for final execution (Roland, Larsen, Lassen, & Skinhoj, 1980). Additionally, this area has been implicated in supplying other cortical areas with information before and during internally driven reaching rather than reaches that are driven by visual or other external stimuli (Mushiake, Inase, & Tanji, 1991). Moreover, when the functionality of the supplementary motor area has been compromised, large deficits in bimanual coordination are seen (Brinkman, 1984).

Pre-Motor Areas

The dorsal pre-motor area is responsible for several tasks in successfully controlling reaching movements. First, like the posterior parietal cortex, this area is responsible for further transforming the available visual and somatosensory information with respect to our body's relationship to objects (Caminiti, Ferraina, & Johnson, 1996; Wise, Boussaoud, Johnson, & Caminiti, 1997) as well as visual and somatosensory information in which the relationship between a stimulus and an action are arbitrary (Wise, Pellegrino, & Boussaoud, 1996) in to successful reaching behaviors. Secondly, the dorsal pre-motor area is known to be active during preparation for reaching movements (Crammond & Kalaska, 1996; Johnson, Ferraina, Bianchi, & Caminiti,

1996). This preparatory activity has been linked with calculating the extrinsic requirements of the specific reaching task (Shen & Alexander, 1997, p. 1195-1212).

The ventral pre-motor area, like the dorsal pre-motor area, plays a distinct but vital role in computing and executing reaching. This area, as with the dorsal pre-motor area, has direct connections to M1 and partially forms the corticospinal tract (Martino & Strick, 1987). This cortical area receives both visual sensory and somatosensory information about the space surrounding our bodies that is within reaching distance (Fogassi et al., 1996; Graziano, Hu, & Gross, 1997). Obviously, this information changes as the position of our bodies, arms, and eyes change. Interestingly, the activity of the cells contained within this area respond to those peripersonal sensory changes accordingly (Fogassi et al., 1996). These activity changes, like the dorsal pre-motor area, are responsible for further transforming the sensory information it receives in to a more usable reaching motor command.

Primary Motor Cortex

M1 is traditionally thought to be the major contributor and controller of our reaching movements. Indeed, M1 is the greatest cortical supplier to the corticospinal tract (Maier et al., 2002; Nudo & Masterton, 2004). As such, the primary focus of this thesis is on how altering M1 excitability affects the control and execution of the multitude of voluntary reaching movements that we must accomplish on a daily basis. M1 is responsible, at the highest level, for understanding and accounting for task related goals, cognitive aspects of sequencing tasks, and other constraints outside of actual voluntary reaching commands (Kettner, Marcario, & Port, 1996; Shen & Alexander, 1997, p. 1171-1194). At levels more critical to this line of research, M1 is partly

responsible for transforming the information it receives from other areas of the CNS and implementing/controlling a number of features needed for a successful reaching movement (Kalaska, Scott, Cisek, & Sergio, 1997). In other words, M1 is responsible for the real-time or online control of our upper extremities during reaching movements (Crammond & Kalaska, 1996; Johnson, Ferraina, Bianchi, & Caminiti, 1996; Kettner, Marcario, & Clark-Phelps, 1996; Kettner, Marcario, & Port, 1996). Obviously, accomplishing this task is more nuanced then simply outputting a successful reaching command. This output signal can contain several features of the reach including a limb-centered coordinate system, the directionality of the reach, the magnitude of the output force or torque necessary for a quality reach, and the necessary neuromuscular coordination between the joints involved in reaching (Georgopoulos, Kettner, & Schwartz, 1988; Kertzman, Schwarz, Zeffiro, & Hallett, 1997; Lukashin, Amirikian, & Georgopoulos, 1996; Kalaska, Scott, Cisek, & Sergio, 1997; Scott, 1997; Taira, Boline, Smyrnis, Georgopoulos, & Ashe, 1996).

Kinematic Measurements of Reaching

The portions of the CNS, described in previous sections, have the ability to synthesize the information necessary to create elegant and ornate reaching movements. As such, there are a number of ways in which we can monitor and assess the quality of those reaching tasks. This includes a number of kinematic features of each individual reach.

Endpoint Location

The first of these kinematic measurements is the location of our hands at the end of a reaching movement. When accomplishing a reaching task, we are usually attempting

to move our hands to a desired target or object. Morasso (1981) discovered that we plan at least part of our reaching movements with respect to the "spatial control" of our hands (p. 224). With this in mind, it is valuable to know that there is a tradeoff between the accuracy of a reach and the speed in which we accomplish that reach (Fitts, 1954; Schmidt, Zelaznik, Hawkins, Frank, & Quinn Jr., 1979; Woodworth, 1899). In other words, as the speed of a reaching movement increases, the end point accuracy of that reaching movement will decrease and vice versa. Despite that compromise, practicing a specific reaching task can decrease the variability of the location of our hands during repeated trials of that reaching movement (Georgopoulos, Kalaska, & Massey, 1981).

Velocity

A second commonly measured kinematic variable of reaching movements is velocity. The velocity of a reaching movement is a measure of how quickly and in what direction the hand moves from an initial position to a single target. When accomplishing those type of reaching tasks, the tangential velocity of that reach will have a single peaked appearance with little variation in its shape from trial to trial (Georgopoulos, Kalaska, & Massey, 1981; Morasso, 1981). Furthermore, regardless of whether the reaching path is curved or straight in nature, the single peaked and reproducible appearance of the tangential velocity remains when the velocity profile is normalized to account for distance (Atkeson & Hollerbach, 1985). In a more comprehensive study however, Abend, Bizzi, & Morasso (1982) found that when the path of a reaching movement was curved and the hand velocity profiles were not normalized with respect to distance, the velocity profiles were "irregular, with speed valleys and inflections which usually occurred at times of peaks in the trajectory curvature" (p. 343). However, with

practice, the peak velocity of reaching movements can increase a great deal (Darling, Cooke, & Brown, 1989).

Trajectory

In addition to the aforementioned kinematic measurements, the trajectory of a reach is a valuable variable to analyze. The trajectory of a reaching movement is the path that the hand takes throughout that movement. As noted earlier, our reaching movements are thought to be centrally controlled with respect to the location of our hands. More specifically, we centrally control the trajectory of our hands during reaching tasks (Morasso, 1981). Additionally, we tend to plan these trajectories in straight line paths without further instructions about how to form the trajectories of our reaches (Abend, Bizzi, & Morasso, 1982; Georgopoulos, Kalaska, & Massey, 1981). Furthermore, even when instructed to follow a curved trajectory, we tend to segment that curvature into several straight line portions (Abend, Bizzi, & Morasso, 1982). These straight line trajectories do not vary with respect to movement speed (Soechting & Lacquaniti, 1981). However, the variability of the trajectory of reaching movements does increase when the location of the target is uncertain (Georgopoulos, Kalaska, & Massey, 1981). And, despite the general consistencies seen in the trajectories of human reaching, when we reach vertically there are regions of distinct curvature seen in our reaches (Atkeson & Hollerbach, 1985).

EMG Measurements of Reaching

Not only are kinematic measurements vital for understanding successful reaching, EMG measurements can be important as well. EMG allows us to monitor in real time the activity of a specific set of motor units in a muscle. By monitoring this activity, it has

been shown that we might be able to monitor the neural control of the major muscles involved in moving the upper arm and forearm (Halliday, Conway, Farmer, & Rosenberg, 1998). The sensorimotor cortex is responsible for controlling the major movers of the upper and lower arm: the biceps, triceps, anterior deltoid, and posterior deltoid (Daly, Vidt, Marsh, & Saul, 2011). With practice, we are able to increase the EMG activity seen in those muscles in order to alter the impedance of our arms and more effectively control reaching (Shadmehr & Thoroughman, 2000). Additionally, the activity seen in the deltoid increases greatly after a reaching movement has commenced (Soechting & Lacquaniti, 1981). Also, the activity of the biceps greatly depends on the location of the target. Finally, when accomplishing slower reaching movements, the activity of both the biceps and deltoid greatly decreases.

Transcranial Direct Current Stimulation

Overview

tDCS can alter the excitability of the human cerebral cortex (Nitsche & Paulus, 2000; Priori, 2003) and in turn potentially influence the kinematic and neuromuscular features of reaching. tDCS does not directly induce neuronal firing of action potentials. Rather, it is thought to modulate the spontaneous activity of the cortical neurons by altering the resting membrane potential of those neurons (Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). One method for measuring baseline cortical excitability as well as alterations in that cortical excitability is through the use of transcranial magnetic stimulation or TMS. TMS involves inducing a brief magnetic field from an electric current driven through a coil of wire (Hallett, 2000; Rossini & Rossi, 2007). This temporary magnetic field penetrates

the skull to reach cortical neurons when placed over M1 and induce in those neurons an electrical field capable of producing depolarization. This in turn causes a corresponding contralateral muscular response known as a motor evoked potential (MEP). These MEPs can be recorded with EMG over the responding muscle and give us a measure of the corticospinal excitability.

Neurophysiological Response to tDCS

When applying tDCS over M1, there are several basic features of tDCS and its application that have been discovered. First, we know that tDCS is polarity dependent. Anodal tDCS (anode over site of stimulation) causes an increase in the cortical excitability as measured by TMS whereas cathodal tDCS (negative cathode over site of stimulation) causes a decrease in the cortical excitability as measured by TMS (Ardolino, Bossi, Barbieri, & Priori, 2005; Furubayashi et al., 2008; Nitsche & Paulus, 2000). The effects of tDCS are also dependent on both the stimulation intensity and duration. As the stimulus intensity increases, the cortical excitability responds in an analogous fashion (Nitsche & Paulus, 2000). Similarly, as the stimulus duration increases, the duration of the altered cortical excitability increases as well (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). As a result, the effects of tDCS can outlast the stimulus duration but are reversible and eventually subside (Jeffrey, Norton, Roy, & Gorassini, 2007; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). This effect however, is greatly influenced by the cognitive and motor state of the subject (Antal, Terney, Poreisz, & Paulus, 2007; Quartarone et al., 2004). Finally, the application of tDCS depends on the location of the electrode placement on the scalp. Nitsche & Paulus (2000) first discovered that in order to see cortical excitability changes

in the M1, only the M1 and contralateral forehead arrangement yielded significant cortical alterations. More recently though, it was discovered that applying tDCS in a dual-hemisphere montage (anode over either L or R M1, cathode over opposite M1) may be more effective than the more standard uni-hemispheric application in altering the functional abilities of our upper extremities (Vines, Cerruti, & Schlaug, 2008).

Behavioral Response to tDCS

In addition to what is known about the neurophysiological responses to tDCS, we know how tDCS affects healthy individuals as measured by a number of secondary measurement protocols. First, we know that anodal tDCS improves the performance of the non-dominant hand of right handed individuals as measured by the Jebsen-Taylor hand function test (Boggio et al., 2006). Additionally, anodal tDCS improves the performance of the contralateral hand whereas cathodal tDCS improves the performance of the ipsilateral hand as measured by a keystroke task (Vines, Nair, & Schlaug, 2006). Anodal tDCS is also effective in improving the muscle endurance of the contralateral elbow flexors as measured by sub-maximal isometric contractions (Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007). We also know that anodal tDCS improves the performance of a visuomotor task as measured by a target tracking task (Antal, Nitsche, Kincses, Kruse, Hoffmann, & Paulus, 2004; Antal, Nitsche, Kincses, Kruse, Hoffmann, & Paulus, 2004), implicit learning as measured by a serial reaction time test (Nitsche et al., 2003), and motor sequence learning abilities in the contralateral arm (Lang, Nitsche, Sommer, Tergau, & Paulus, 2003). The effects of tDCS however are not present when applied prior to performing a serial reaction time test (Kuo et al., 2008).

Stroke Recovery and tDCS

The effects of tDCS that have been reported amongst healthy populations have also been demonstrated in people who have experienced a cerebrovascular accident, better known as a stroke. First, anodal tDCS applied over the lesioned hemisphere improves the naming accuracy of patients with stroke-induced aphasia for up to a week in a randomized study (Baker, Rorden, Fridriksson, 2000; Fridriksson, Richardson, Baker, & Rorden, 2011). Both anodal (applied ipsilesionally) and cathodal (applied contralesionally) tDCS applied over M1 have also been shown effective in the motor recovery of stroke patients during five and six week studies when combined with robot-assisted arm training as evidenced by improvements in the Fugl-Meyer Motor Assessment and the Modified Ashworth Scale (Hesse et al., 2007; Mitsuhiro, Satoru, Taiji, & Yasuyuki, 2013). Additionally, both anodal tDCS applied over the M1 of the lesioned hemisphere and cathodal tDCS applied over the corresponding contralesional location improved the performance of stroke patients during the Jebsen-Taylor Hand Function test for two weeks following five consecutive days of treatment (Boggio et al., 2007). When combined with constraint induced movement therapy, bihemispheric tDCS improved the performance of handgrip strength, Fugl-Meyer Motor Assessment, and the Jebsen-Taylor Hand Function test (Bolognini et al., 2011). Finally, even without any additional intervention outside of tDCS application, stroke patients show improved Jebsen-Taylor Hand function test scores after stimulation (Hummel et al., 2005).

Defining the Quality of Reaching Movements and tDCS

All of the aforementioned studies utilized clinical scales of arm movement performance to assess the functional abilities of upper extremity movements. For

example, the Jebsen-Taylor Test of hand function measures the time it takes to complete a set of tasks involving reaching movements. It does not however make any assertions about the features that can define the quality of a movement (endpoint accuracy, velocity, etc.). And, while these clinical arm movement performance scales are sufficient in some situations, they do not elucidate the features involved in normal reaching behaviors that define its quality (van Kordelaar et al., 2011). For example, while a score on the Jebsen-Taylor Test of hand function may appear stable, the features of a reaching movement that characterize its quality might still be changing. Additionally, the opposite could also possibly be true; the score on the Jebsen-Taylor Test of hand function might still be changing, but the qualitative features of a reaching behavior may not be.

Shockingly, even though we have a clear understanding of how tDCS impacts the neurophysiological and behavioral features of healthy persons in a number of ways, there have been no studies completed that assess how tDCS alters the quality of natural reaching movements comprehensively. And, while tDCS has proven effective in changing both the corticospinal excitability and functional ability of the upper extremities of healthy individuals, understanding how tDCS alters the features of natural reaching movements that describe the quality of those movements is of vital importance to understanding the mechanisms by which this form of non-invasive brain stimulation may help rehabilitate patient populations. Furthermore, by understanding how tDCS affects the quality of the reaching movements of healthy individuals, we might be able to more effectively predict how a patient population may respond. Additionally, by assessing how tDCS alters both the behavioral and neurophysiological performance of natural

dynamic reaching movements of healthy individuals, we will be able to more fully understand how M1 controls our upper extremities.

Purpose, Aims, and Hypothesis

The purpose of this study was to determine the effects of temporary M1 inhibition via cathodal tDCS on dynamic reaching. We tested whether 20 minutes of cathodal tDCS applied over M1: 1) would alter unrestrained dynamic reaching kinematics and 2) would alter the neuromuscular features of unrestrained dynamic reaching. Details are outlined in the specific aims below.

Specific Aim 1: To discover if the kinematic features that define the quality of dynamic reaching movements would be significantly altered by cathodal contralateral M1 stimulation.

Hypothesis: Following 20 minutes of 1.5 mA cathodal tDCS, reaching performance would be decreased as measured by the following kinematic variables: endpoint accuracy, velocity, time to peak velocity, and trajectory.

Rationale: Application of tDCS has been shown to alter clinical performance scores for the upper extremities in healthy persons (Boggio et al., 2006; Nitsche et al., 2003; Rosenkranz, Nitsche, Tergau, & Paulus, 2000). As such, I anticipated that we would be able to see alterations of the kinematic features of a reaching movement that define its quality when tDCS was applied during those reaching movements.

Specific Aim 2: To discover if the neuromuscular features that define the quality of dynamic reaching movements would be significantly altered by cathodal contralateral M1 stimulation.

Hypothesis: Following 20 minutes of 1.5 mA cathodal tDCS, the neuromuscular performance would decrease during a dynamic reaching task as measured by: co-contraction between the biceps and triceps, co-contraction between the anterior deltoid and posterior deltoid, and integrals of the biceps, triceps, anterior deltoid, and posterior deltoid.

Rationale: Direct evidence of neuromuscular electromyographic changes following tDCS is limited. However, different applications of tDCS have indicated the possibility for altering some neuromuscular features of our upper extremities; e.g. neuromuscular fatigue as measured by isometric contraction endurance (Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007) and the directionality of fine motor movements (Rosenkranz, Nitsche, Tergau, & Paulus, 2000). As a result, I expected that cathodal tDCS would similarly alter the neuromuscular features of a dynamic reaching task.

CHAPTER II

THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON THE BEHAVIORAL AND NEUROPHYSIOLOGICAL PERFORMANCE OF HEALTHY SUBJECTS DURING REACHING

Introduction

Transcranial direct current stimulation (tDCS) offers an exciting way to study human brain physiology that was unachievable only a few decades ago. tDCS applies a low level constant current to the human cerebral cortex via saline soaked sponges placed on the skull. This type of current alters the membrane potential of the neurons under the site of stimulation (Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Application of tDCS is most commonly administered over the primary motor cortex (M1). Under the anodal electrode, stimulated neurons increase their excitability whereas neurons under the cathode have their excitability decreased (Ardolino, Bossi, Barbieri, & Priori, 2005; Furubayashi et al., 2008; Nitsche & Paulus, 2000). The alterations to the cortical excitability outlast the period of stimulation by variable amounts (Nitsche & Paulus, 2000). In addition to the polarity dependence, the outcome of tDCS is also dependent on the simulation intensity, stimulation duration, and the distance between the two electrodes (Antal, Terney, Poreisz, & Paulus, 2007; Jeffrey, Norton, Roy, & Gorassini, 2007; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998; Quartarone et al., 2004). Following stimulation of M1, behavioral and/or physiological (cortical excitability) changes caused by tDCS can be measured by motor performance assessments and transcranial magnetic stimulation (TMS) respectively.

These corticospinal excitability changes not only allow us to understand more deeply how different areas of the central nervous system (CNS) physiologically operate but also how they are functionally connected. Moreover, the efficacy of tDCS is being investigated as an adjunct to rehabilitation interventions for patients who suffer from neurological dysfunction as often occurs following stroke. For example, anodal tDCS applied over M1 has been utilized to improve the functional performance of the contralateral upper extremity in both healthy populations (Boggio et al., 2006; Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007; Vines, Nair, & Schlaug, 2006) as well as in persons affected by stroke (Boggio et al., 2007; Bolognini et al., 2011; Hesse et al., 2007; Hummel et al., 2005; Mitsuhiro, Satoru, Taiji, & Yasuyuki, 2013). Conversely, in both healthy subjects and patient groups, cathodal tDCS improves the performance of the ipsilateral upper extremity (Hesse et al., 2007; Mitsuhiro, Satoru, Taiji, & Yasuyuki, 2013; Vines, Nair, & Schlaug, 2006) as well as decreases performance of the contralateral upper extremity (Vines, Nair, & Schlaug, 2006; Vines, Nair, & Schlaug, 2008).

These studies primarily utilize clinical measures of upper extremity functionality like the Fugl-Meyer Assessment, the Wolf Motor test, the Action Research Arm Test, the Nine Hole Peg test, the Jebsen Taylor test of hand function, and the Motor Activity Log. Other more direct measurements believed to be valuable for assessing upper extremity function post-stroke include maximal voluntary grip force and maximal voluntary pinch strength (Beebe & Lang, 2009; Boissy et al., 1999). While these outcome measures do offer some insight in to the functional ability of the upper extremities, they do not reflect all of the information available. Recent evidence has shown that three dimensional

kinematic analyses are far more sensitive than the aforementioned clinical performance scales in assessing upper extremity functionality (van Kordelaar et al., 2012). More specifically, while a stroke patient's score on tests like the Fugl-Meyer Motor Assessment may have reached a plateau; kinematic measurements like velocity and endpoint accuracy might still be improving. As a result, those kinematic measurements offer a greater insight in to the functional abilities of our upper extremities. Conversely, it is possible for the scores of the clinical scales of upper extremity function to improve in a way that can only be detected with careful kinematic analyses. In other words, only kinematic information, of a stroke patient for example, can inform the investigators whether the patient is improving their score by actually recovering natural patterns of movement or is improving their score by using compensatory mechanisms like an increased forward trunk lean.

Despite the amount of knowledge available on how tDCS applied over M1 affects humans neurophysiologically and behaviorally, there is very little known about the kinematic changes of reaching that occur after stimulating M1 with tDCS. As a result, the primary purpose of this study was to discover how inhibitory (cathodal) tDCS applied over M1 alters contralateral reaching performance, as measured by a series of kinematic and electromyographic (EMG) variables. We hypothesized that cathodal tDCS would decrease the kinematic and neuromuscular performance of dynamic reaching in healthy individuals.

Materials and Methods

Subjects

A total of 10 young healthy right hand dominant subjects (8 females) were recruited for this study. Their mean age was 24.2 ± 1.32 years and all subjects scored 100% on the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Two of these subjects later returned to complete a second control experiment (one age 24 and the other age 26) one to two weeks after completing the main experiment.

Exclusion criteria for the study included any major diseases or disorders affecting reaching (neuromuscular or musculoskeletal dysfunction of the upper extremity), contraindications to single pulse TMS (Keel, Smith, & Wassermann, 2001) or tDCS, or currently taking one or more psychotropic drugs including selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors. This study was approved by the University of Iowa Institutional Review Board and was conducted in accordance with the Declaration of Helsinki.

Paradigm

Overview

Each subject participated in two testing sessions separated by no less than two days and no greater than seven days. The two sessions were identical except for the tDCS intervention used. The order in which subjects experienced the interventions was counterbalanced so that half of the subjects received real cathodal tDCS during session one and sham tDCS during session two while the other half received the opposite order of tDCS interventions.

During both sessions, subjects completed sets of 50 reaching trials with their non-dominant (left) arm to two different sized targets (25 each to large and small targets) both before and after receiving tDCS. For all reaches, subjects were seated in a stationary armless chair with their feet flat on the floor. A fabric brace (Carpal tunnel wrist stabilizer, Mueller® Sport Care®, Prairie du Sac, Wisconsin) was placed on the left wrist to minimize movement at the wrist joint. At the start of each reach, subjects positioned the reaching arm in the "start" position, with the shoulder in approximately zero degrees of flexion and abduction, the elbow in approximately 90 degrees of flexion, the forearm neutral, and the hand in a loose fist except for the index finger which was fully extended. Subjects were instructed to contact the center of the target with the tip of the index finger and to hold that position until each trial ended. The start of each trial was signaled with an auditory "go" tone. Between trials, subjects were verbally reminded of the specific instructions to "reach to the center of the target as quickly as you can after the 'go' tone." The inter-trial duration was kept inconsistent to force subjects to move in response to the actual "go" tone instead of guessing when the "go" tone would sound based on a learned set inter-trial duration. The target was positioned in front of the subject's chair at a distance of 95% of the fully extended upper extremity (shoulder flexed at 90 degrees and elbow/index finger fully extended) and aligned with the left shoulder vertically and laterally. The small and large targets were lightweight wooden spheres of diameter 1.0 cm and 3.5 cm, respectively. The 25 reaches to a single target were completed in a single block followed by a short (~1 minute) rest break between the two reaching blocks to manually change the targets. The order in which the targets were presented to each

subject was counterbalanced so half reached to the small target first and the other half reached to the large target first during both sessions.

Following the initial set of 50 reaches, sham or real cathodal tDCS was applied to the right M1 followed by 50 additional reaches to the same two targets as before. The timing of the tDCS was arranged so that the second set of reaching movements commenced 10 minutes in to the application of tDCS and finished approximately (+/- 1 minute) at the same time as the end of tDCS stimulation. Additionally, TMS of the right and left M1 were used to measure changes in corticomotor excitability associated with the tDCS intervention and to identify the specific target location within M1 for the tDCS to be applied. TMS measures were completed immediately before the tDCS application (after the first set of 50 reaches) and then again after the tDCS and second set of reaches. See Figure 2.1 for a depiction of the timeline of events.

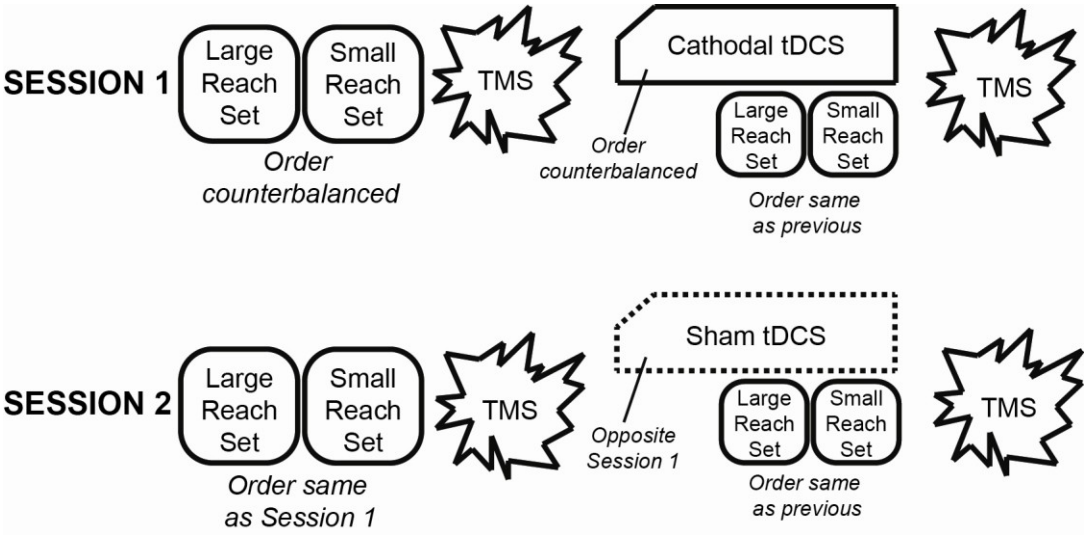

***Figure 2.1*. Example timeline of events for full two session protocol.**

Transcranial Magnetic Stimulation

TMS was used first to identify the exact location over the right M1 in which the cathodal tDCS electrode would be placed and second, to assess the excitability of both the left and right hemisphere M1s before and following tDCS. We used a Magstim 200[2] monophasic stimulating unit and a standard Magstim 70 mm figure of eight coil (The Magstim Company Limited, Whitland, UK). Subjects were seated in a barber chair with their feet flat on the foot rest, a pillow placed on the lap, shoulders in zero degrees of flexion and abduction, elbows in approximately 90 degrees of flexion, forearms pronated with palms facing downward on top of the pillow, and all fingers in a relaxed neutral position. Throughout all TMS, the coil was held tangential to the skull and at an angle approximately 45° to the midsagittal line. We used a standard search technique to locate the "hotspot" in the right M1 for the left biceps (BB) muscle. Specifically, the coil was placed on the head at a position 1 cm lateral and 1 cm posterior to the vertex. The coil was moved in 1 cm increments from the starting position until the location was found over the right M1 that elicited the largest motor evoked potentials (MEPs) in the contralateral BB consistently. This location was marked directly on the scalp utilizing permanent markers and a custom made grid system so that the coil holder was able to reproducibly place the coil over the "hotspot." After locating the left BB "hotspot," the resting motor threshold (RMT) at this location was assessed. We defined the RMT as the lowest percentage of stimulator output that elicited MEPs with a peak-to-peak amplitude greater than 50μV in at least 5 out of 10 trials. This process was then repeated for the left hemisphere in order to identify the "hotspot" and right BB RMT.

Transcranial Direct Current Stimulation

tDCS was administered by a battery driven constant current stimulator (Dual channel Chattanooga Ionto™ Iontophoresis system, Chattanooga Medical Supply Inc., Chattanooga, Tennessee). Current was applied to the scalp by two saline soaked sponge electrodes each with a surface area of 16cm^2. The cathodal electrode was placed over the right M1 "hotspot" for the left BB muscle. The anodal electrode was placed contralaterally, above the left orbit. This electrode placement has previously been shown to produce the most robust outcomes for decreasing excitability within M1 (Nitsche & Paulus, 2000). During real cathodal stimulation, the current was ramped up for 30 seconds until it reached its maximal output of 1.5 mA. The stimulation remained at 1.5 mA for 19 minutes and then ramped back down for 30 seconds. This amount of stimulation resulted in a current density of 0.09375 mA/cm^2 and a total charge of 0.1125 C/cm^2. Both of these values fall well below the industry standards (25 mA/cm^2 and 216 C/cm^2 for current density and total charge, respectively) for safe administration of tDCS (McCreery, Agnew, Yuen, & Bullara, 1990; Yuen, Agnew, Bullara, Jacques, & McCreery, 1981). During sham stimulation, the current ramped up for 30 seconds, ramped back down for 30 seconds, and then remained off for the duration of the stimulation. As shown by Gandiga, Hummel, & Cohen (2006), this ramping on and off period during sham tDCS results in similar sensations to real tDCS treatment and is thus indistinguishable from real tDCS.

Control Testing

Two subjects returned to the lab several weeks after completing the main experiment to complete a control experiment verifying that the cathodal tDCS parameters

used in the main experiment were ideal for decreasing M1 excitability. These two individuals repeated both sessions (one with real tDCS, one with sham, order counterbalanced) of the main experiment but without performing the reaching task. In this way, we were able to test the efficacy of the tDCS intervention without the confound of the motor task potentially affecting cortical excitability. For this control testing, all procedures were identical to the main experiment except that 1) reaching was omitted and 2) tDCS and TMS were targeted over the hotspot for the extensor carpi radialis (ECR) muscle rather than the BB. This was done as a convenience because ECR MEPs can be elicited at lower levels of TMS stimulator output than the more proximal BB muscle. Subjects remained seated and relatively motionless in the TMS chair throughout these sessions.

Data Collection

Kinematic Measurements

During reaching, three dimensional (3D) position measurements were collected with the Optotrak motion capture system and infrared position markers (Optotrak Certus® Motion Capture System, Northern Digital Inc., Waterloo, Ontario, Canada) placed on both the large and small targets as well as four locations on the left upper extremity: the most distal dorsal aspect of the second digit distal phalanx (index fingertip), the radial styloid process (wrist), the lateral epicondyle of the humerus (elbow), and the acromion process (shoulder). Real time 3D position data of these eight markers was collected at a sampling rate of 100 Hz and stored on a laboratory computer and analyzed offline.

Electromyography Measurements

EMG was recorded using the Motion Lab Systems unit (MA300-10 EMG system, Baton Rouge, Louisiana). Four sets of bipolar surface electrodes were placed over the muscle bellies of major muscles involved in moving the upper arm and forearm during forward reaching: the short head of the biceps (BB), the long head of the triceps (TB), the anterior deltoid (AD), and the posterior deltoid (PD) (Warfel, 1985). A ground electrode was placed over the medial epicondyle of the left humerus. EMG signals were amplified at the electrode site with a gain of x20, at the unit with a gain of x200 (total amplification x4000), and online band pass filtered at 20-500 Hz. During reaching, EMG was sampled at 1000 Hz, digitized, temporally synchronized with the kinematic measurements, and stored on the same laboratory computer as the kinematic data for offline analyses.

TMS Excitability Measures

MEPs were recorded from the surface electrodes on bilateral BB muscles using the same setup and parameters as described for the EMG recordings during reaching, except that here, EMG was recorded with a sampling rate of 4000 Hz. Here, MEPs were monitored in real time and recorded via Signal software (Signal 4.03, Cambridge Electronic Design, Cambridge, UK). Twelve single pulses of TMS were delivered, with an interpulse interval between 5.75-6.75 seconds (randomly selected), for each of two intensities, 100% and 120% of RMT, and for both the right and left M1 BB "hotspots."

Personal Activity, Visual Analog, and tDCS Experience Measures

Each subject self-reported their caffeine use, tobacco use, alcohol use, and activity levels over the previous 12, 12, 18, and eight hours respectively. In addition, before and after each testing session each subject self-reported their pain, anxiety, fatigue, and

alertness levels by making a mark of their choosing on a simple visual analog scale. After each testing session, subjects were also given a tDCS assessment survey in which they were asked to give their impressions of what sensations they felt and what intervention they believed they received.

Data Analyses

Except where otherwise noted, all analyses were completed using custom written programs in MATLAB (R2012.a, MathWorks, Natick, Massachusetts).

Reaching Kinematic Measurements

Offline, we initially interpolated any short, discreet intervals in which a marker failed to produce its complete 3D position during the course of each reach. Then, linear velocity data were created from the first derivative of the 3D position data. Following this, we determined the timing of three major events during each reach trial. The first event was the "go" tone, or the time when the auditory signal began. The second major event was movement onset, which we defined as the first frame in which the wrist marker forward velocity exceeded 5% of its maximal forward velocity. The final event was movement termination, defined as the first frame in which the wrist marker forward velocity dropped back below 5% of its maximal forward velocity. See Figure 2.2A for an example of these events.

Several kinematic calculations were then completed. First, we measured the endpoint accuracy of each reach, defined as the difference between the location of the index finger marker and the center of the target in three dimensions at movement termination. Next, we measured the peak forward velocity and the time to peak forward velocity, or the time between movement onset and the maximal forward velocity, of the

wrist marker for each reach. We also computed the reach path curvature. This measure was the ratio of the actual reach path length from the wrist marker to the ideal reach path length in three dimensions. The ideal path length was calculated as the straight line distance from the wrist marker position at the time of movement onset to the location of the wrist marker at movement termination.

Reaching Electromyography Measurements

Preliminarily, the four EMG signals (BB, TB, AD, & PD) were demeaned, filtered using a custom-made second order Butterworth low pass filter (50 Hz cutoff frequency), and rectified. The magnitude of each of the EMG signals was then normalized with respect to the average of the first session's pre-tDCS EMG, to account for any differences in electrode placement between sessions.

We then calculated EMG integrals for each of the four muscles during each reach. More specifically, this was the area under each rectified EMG trace during the time period from movement onset to peak forward velocity. From these integrals, we computed co-contraction levels between the two major agonist/antagonist pairs (BB/TB and AD/PD). Co-contraction was calculated as the ratio of the antagonist integral (TB or PD) to the sum of the antagonist integral and the agonist integral (BB or AD) during that same time period from movement onset to peak forward velocity (Hammond, Fitts, Kraft, Nutter, Trotter, & Robinson, 1988). See Figure 2.2B for a graphical example of co-contraction.

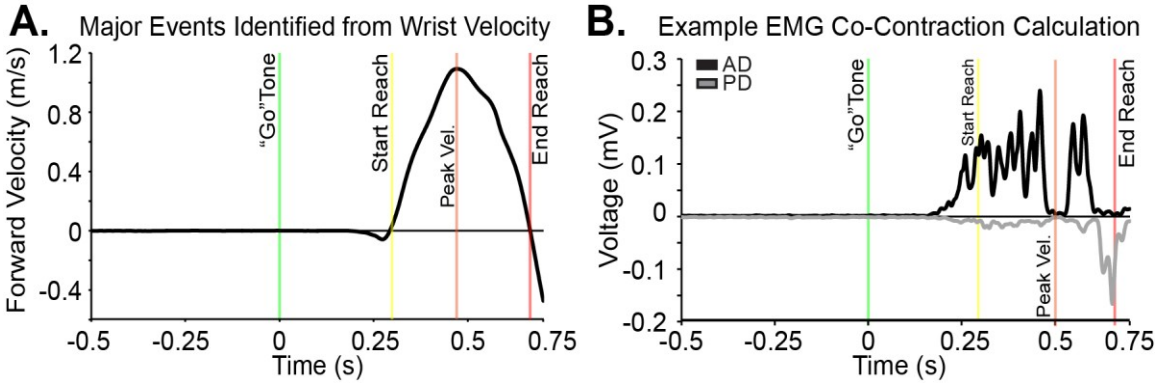

***Figure 2.2*. Example forward velocity and EMG traces. A. Individual example of how the major events of each reach were calculated from the wrist velocity data. B. Anterior deltoid (AD) and posterior deltoid (PD) co-contraction plot for the same reach in A.**

Cortical Excitability Measurements

MEP amplitude for each muscle and intensity were measured by calculating peak MEP area, which was the area under the curve of the rectified MEP. (For the two subjects returning for the follow up testing of ECR MEPs pre and post-tDCS without reaching, we measured MEP amplitude as the peak-to-peak amplitude of the MEP, because MEPs from the ECR muscle typically show a single positive and a single negative peak deflection, unlike the BB muscle MEPs.)

Personal Activity, Visual Analog, and tDCS Experience Measures

The Personal Activity Survey consisted of caffeine consumption, tobacco use, alcohol use, and activity levels. Accordingly, we quantified caffeine consumption in "servings" that corresponded to the amount of caffeine contained in one standard cup of coffee. Tobacco use was measured as the number of cigarettes, cigars, or other tobacco products consumed. For alcohol consumption, we utilized industry standard values for

serving sizes (e.g. 12 ounce beer, 5 ounces of wine, 1.5 ounces of hard liquor). Finally, for activity level, this was quantified in minutes of moderate exercise.

The Visual Analog Scales were utilized to see if there were any marked changes in the pain, anxiety, fatigue, and alertness levels in each subject. Each mark subjects made on the scale were measured in centimeters from the left most portion of scale.

The tDCS Personal Assessment Survey was a measure to discover if our sham tDCS procedure was effective. Subjects reported whether they believed they received the real cathodal tDCS treatment or the sham tDCS treatment on both days. We quantified their guesses as either a "1" for real cathodal tDCS or "0" for sham tDCS. Additionally, we quantified whether their guesses were accurate as a "1" for a correct guess and a "0" for an incorrect guess.

Statistical Analyses

For the reaching kinematic and EMG measurements, values for all reaches within a time point (pre- and post-tDCS) and session (real and sham tDCS) and target size (large and small) were averaged for each individual and then averaged across all individuals to obtain group means. MEP amplitudes during TMS excitability measures were similarly averaged. Initially, we assessed for statistically significant differences between cathodal and sham sessions during the pre-tDCS time point only, using separate paired t-tests for large and small targets for reaching data. Whenever pre-tDCS scores were found to be no different between cathodal and sham sessions, we performed the following subsequent analysis. For all reaching kinematic, reaching EMG, TMS excitability measures, and personal activity surveys/visual analog scales, we compared between cathodal and sham sessions for both the large and small targets using separate paired t-tests that compared

pre to post change scores (post-tDCS score minus pre-tDCS score). For the tDCS survey, we compared whether each individual's guess for each day was correct or not. The level for statistical significance was set at $\alpha < 0.05$. This analysis was accomplished using Statistica software (Statistica 7.0, StatSoft, Inc., Tulsa, Oklahoma). All of the values listed in the text are expressed as mean ± 1SD, whereas in any figure the error bars represent 1 standard error (SE).

Results

All subjects who participated in this study completed both sessions without requiring rest and without any complaints of fatigue or distress. There were no significant differences during the pre-tDCS time period for any outcome measure including reaching kinematic, reaching EMG, TMS excitability, and personal activity/visual analog scales (separate paired t-tests, all $p > 0.12$). Also, our sham procedure was effective in blinding subjects to the intervention group (See tDCS personal assessment survey results section below).

Reaching Kinematic Measurements

Endpoint Error

The primary measure of reaching performance was endpoint accuracy, as measured by the 3D error at movement termination. After both sham and cathodal tDCS, the endpoint error to both the large and small targets was essentially unchanged. Therefore, there was no statistical difference for the endpoint error changes between cathodal tDCS and sham tDCS interventions ($p = 0.93$ for the large target and $p = 0.76$ for the small target). See Figure 2.3.

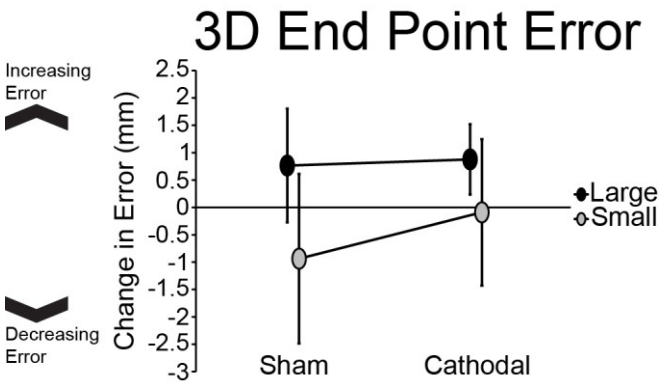

***Figure 2.3*. Endpoint error change scores comparing performance following cathodal and sham tDCS for large and small targets.**

Wrist Velocity

As with the results of the endpoint error, the wrist velocity following both sham and cathodal tDCS when reaching to the large and small target were essentially unchanged. Because these changes were minute, cathodal tDCS failed to elicit a significant difference in the forward velocity of reaching when compared to sham tDCS for both the large and small targets ($p = 0.97$ and $p = 0.66$ respectively). See Figure 2.4.

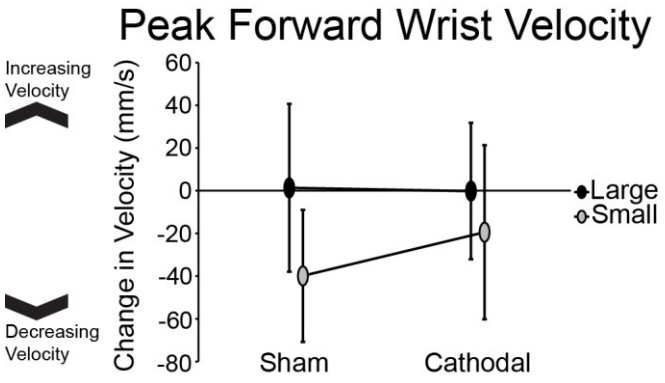

***Figure 2.4*. Peak forward wrist velocity change scores comparing performance following cathodal and sham tDCS for large and small targets.**

Time to Peak Wrist Velocity

The time to peak wrist velocity very slightly increased following sham and cathodal tDCS for both the large target and the small target. Again, these changes were not appreciable and the time to peak velocity after cathodal tDCS was not significantly different than after sham tDCS for either the large or small target ($p = 0.92$ and $p = 0.80$ respectively). See Figure 2.5.

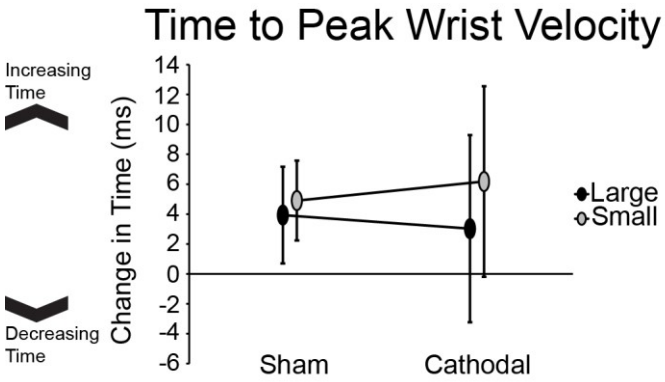

***Figure 2.5*. Time to peak wrist velocity change scores comparing performance following cathodal and sham tDCS for large and small targets.**

Reach Path Curvature

Figure 2.6 shows reach paths from the wrist marker of an exemplary subject for all reaches pre and post real and sham tDCS. Although a majority of the reach paths are indistinguishable, several of the post-tDCS reaches during the cathodal session showed an abnormally curved path.

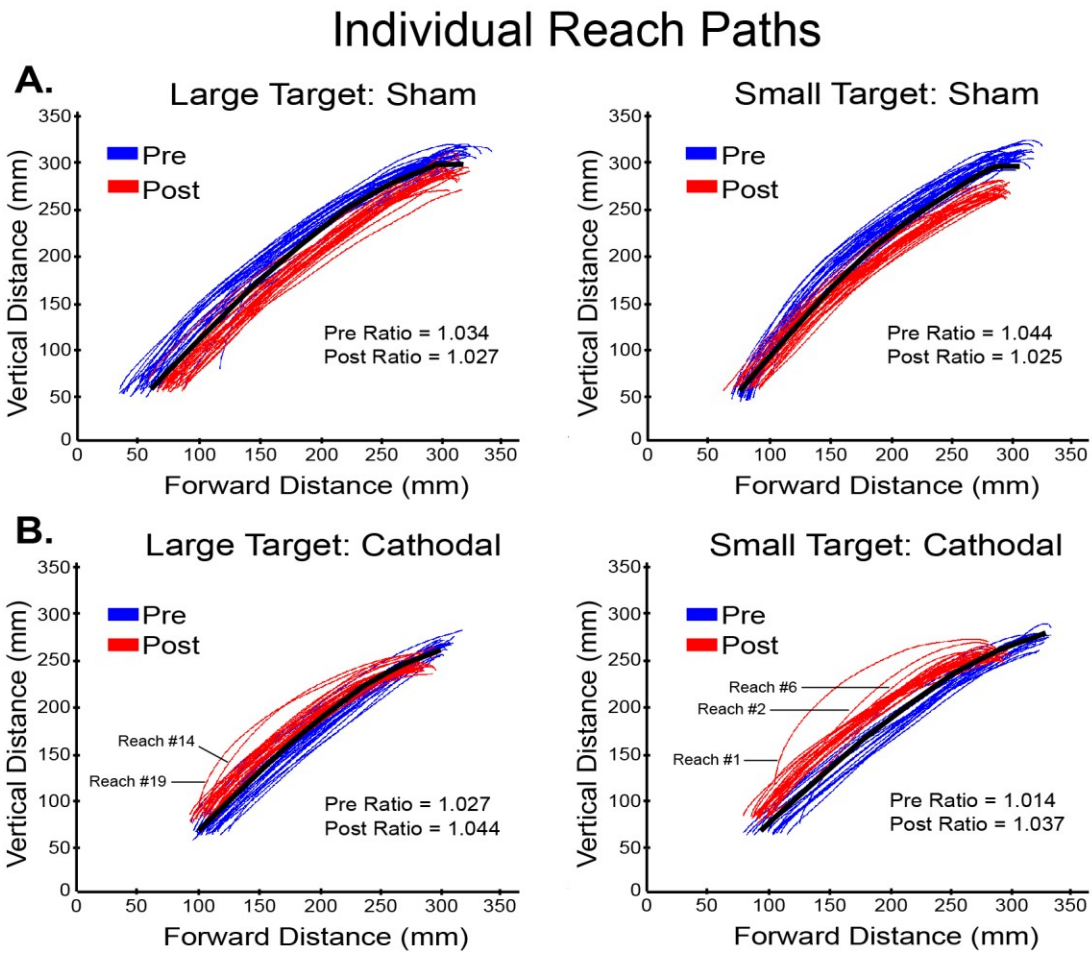

***Figure 2.6*. Reach paths from the wrist marker in the sagittal plane. A. Before and after sham tDCS and B. before and after cathodal tDCS. Average calculated path curvature ratios are shown for reference from the pre-condition.**

For the group, after sham tDCS, the path curvature decreased slightly for both the large and small targets, indicating a straighter trajectory. Conversely, the reach path curvature increased slightly following cathodal tDCS for both the large and small targets. Although these changes were in the correct direction as hypothesized, these were relatively small. Accordingly, cathodal tDCS did not alter the curvature of the reach paths significantly for either the large or small target when compared with the trajectory following sham tDCS ($p = 0.53$ and $p = 0.30$). See Figure 2.7.

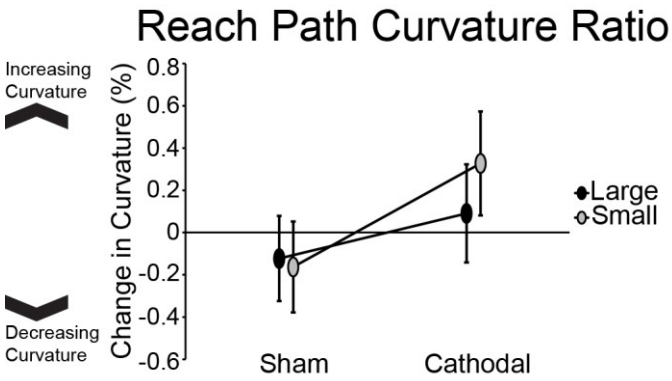

***Figure 2.7*. Reach path curvature ratio change scores comparing performance following cathodal and sham tDCS for large and small targets.**

Reaching EMG Measurements

EMG Integrals

Unlike the kinematic changes, the integrals from normalized, rectified EMG traces showed more robust effects overall from the tDCS intervention. Recall that the integrals were calculated over the period between movement onset and peak forward velocity, such that the BB and AD muscles would have been acting as the primary movers (agonists) and the TB and PD muscles would have been acting as primary brakers (antagonists) of the movement.

Figure 2.8 shows an exemplary individual's PD activity during individual pairs of reaches for the large target conditions pre and post real and sham tDCS. During sham tDCS, the PD EMG was quite similar during pre- and post-tDCS time points during the period between movement onset and peak velocity (shaded gray). Following cathodal tDCS however, PD EMG was clearly increased at the beginning of each reach during the post-tDCS time point compared to the pre-tDCS.

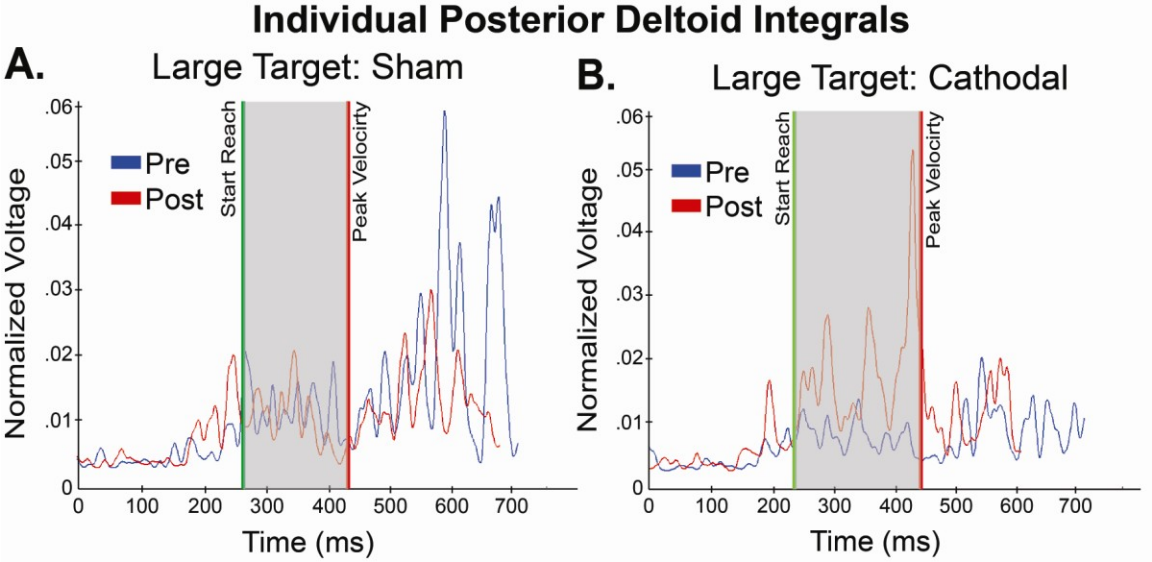

***Figure 2.8*. Individual EMG traces of the PD muscle during reaching. Prior to and following A. sham tDCS and B. cathodal tDCS. The location of movement onset and peak velocity for both reaches were within 10ms of one another.**

With respect to the group results, after sham tDCS, the (antagonist) PD integral decreased during reaches to the large and small targets. However, PD integrals increased after cathodal tDCS during reaches to both the large and to the small target. The difference between the PD EMG integral following cathodal tDCS and sham tDCS was significant for the large target ($p = 0.0499$) and nearly significant for the small target ($p = 0.06$). See Figure 2.9A.

After sham tDCS, the AD, an agonist muscle, integral increased for the large and small targets. After cathodal tDCS, the AD integral increased when reaching to the large target and decreased when reaching to the small target. Unlike the PD however, the AD integral differences between cathodal and sham tDCS lacked statistical significance ($p = 0.43$ for the large target and $p = 0.56$ for the small target). See Figure 2.9B.

For the TB muscle, another antagonist muscle like the PD, the integral increased when reaching to the large target and the small target following sham tDCS. Following cathodal tDCS, the TB integral increased for both the large target and the small target to a much greater extent than following sham tDCS. However, as with the AD, the difference between the TB integral following cathodal tDCS and following sham tDCS did not reach statistical significance ($p = 0.24$ and $p = 0.41$ for the large and small targets respectively). See Figure 2.9C.

Following sham tDCS, the agonist BB EMG integral increased when reaching to both the large and small targets. The same integral increased for the large target but decreased for the small target following cathodal tDCS. The difference between the integral of the BB EMG following cathodal tDCS and sham tDCS did not reach statistical significance for either the large or small target ($p = 0.92$ and $p = 0.33$). See Figure 2.9D.

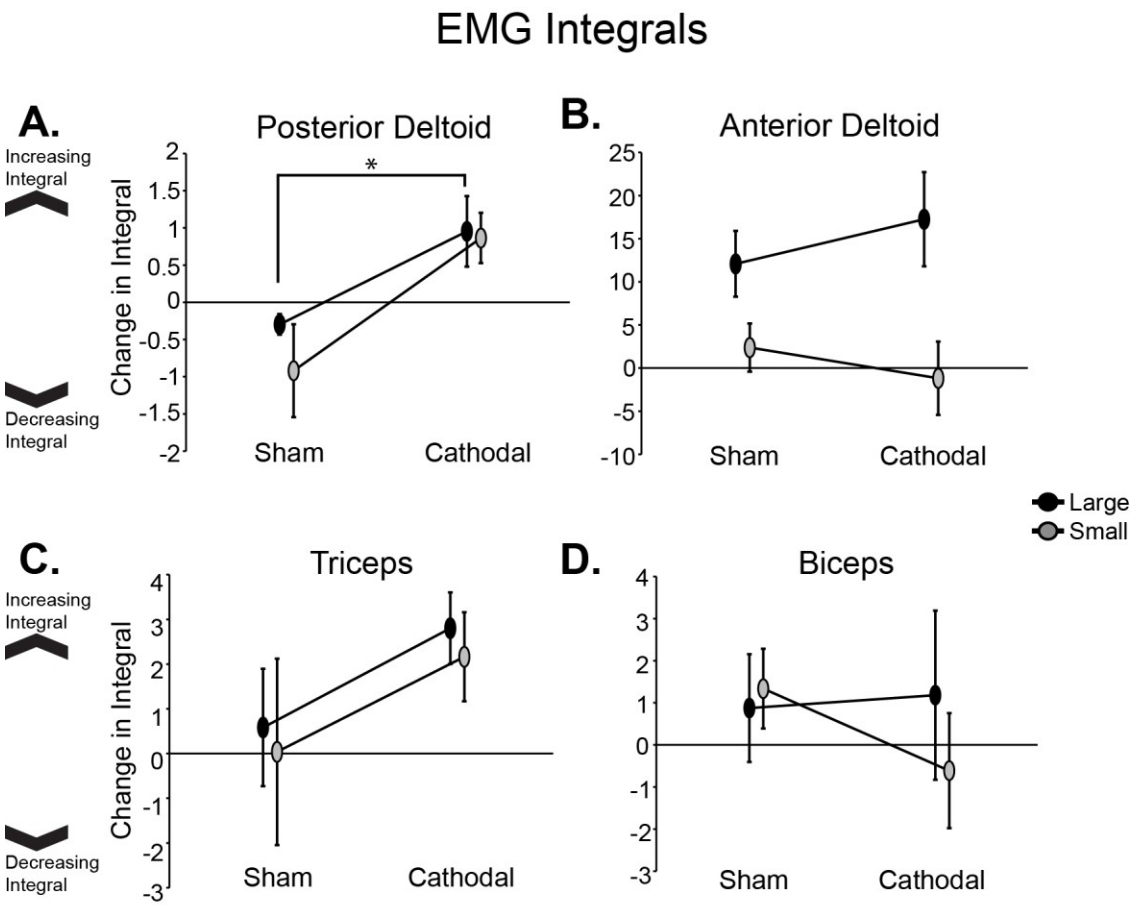

***Figure 2.9*. EMG integral change scores comparing performance following cathodal and sham tDCS for large and small targets. A. PD muscle, B. AD muscle, C. TB muscle, and D. BB muscle.**

EMG AD/PD and BB/TB Co-contraction

Figure 2.10 shows EMG from the AD and PD muscle pair from an exemplary subject during both the sham and cathodal tDCS treatment sessions and during reaching to the large target. In Figure 2.10A, it can be seen that there are no obvious differences between the pre and post traces of either the AD or the PD. Conversely, in Figure 2.10B, there are differences in the magnitude of PD activity between pre- and post-tDCS. This is a reflection of the increased PD integrals post-cathodal tDCS described above for both

targets. Accordingly, there were increases in the co-contraction between the AD and PD following cathodal tDCS.

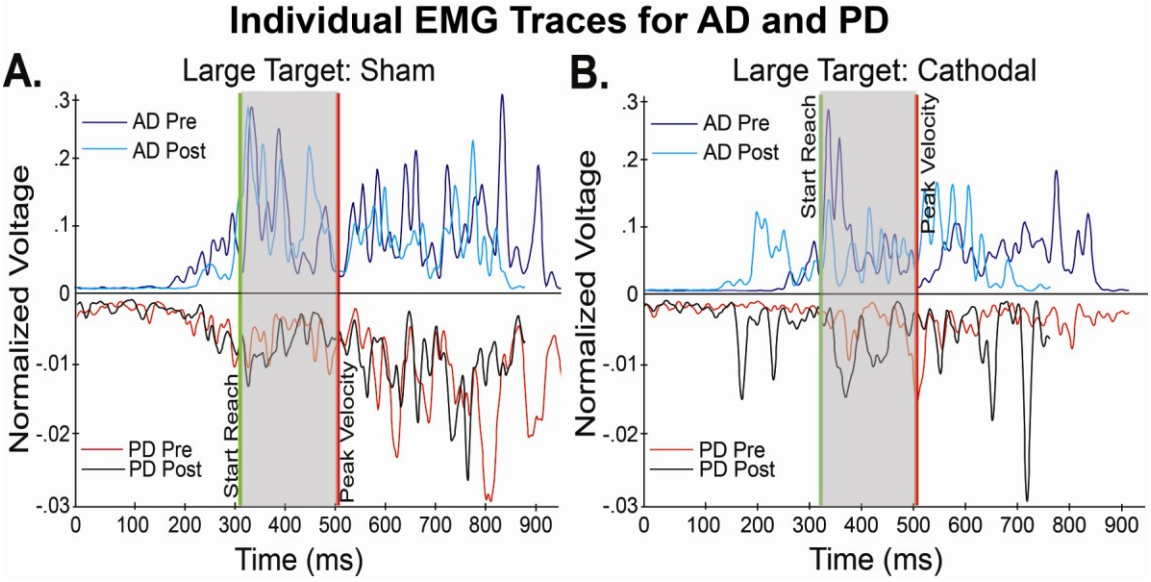

***Figure 2.10*. Individual EMG traces for AD and PD for both the large target. Before and after A. sham tDCS and B. cathodal tDCS. The location of movement onset and peak velocity for both reaches are within 10ms of one another.**

The co-contraction ratio between the AD and PD after sham tDCS for the group decreased for both the large and small targets, indicating improved coordination. After cathodal tDCS however, the co-contraction ratio between the AD and PD increased for both the large target and the small target. For the large target, the difference between cathodal and sham tDCS was nearly statistically significant ($p = 0.08$), whereas for the small target, this difference was a significant one ($p = 0.02$). See Figure 2.11A.

For sham tDCS for the group, the amount of co-contraction seen between the BB and TB increased slightly when reaching to the large target but decreased when reaching

to the small target. After cathodal tDCS, the co-contraction between the BB and TB increased for both the large and small targets. These differences did not reach statistical significance for the large target ($p = 0.34$) but were nearly significant for the small target ($p = 0.07$). See Figure 2.11B.

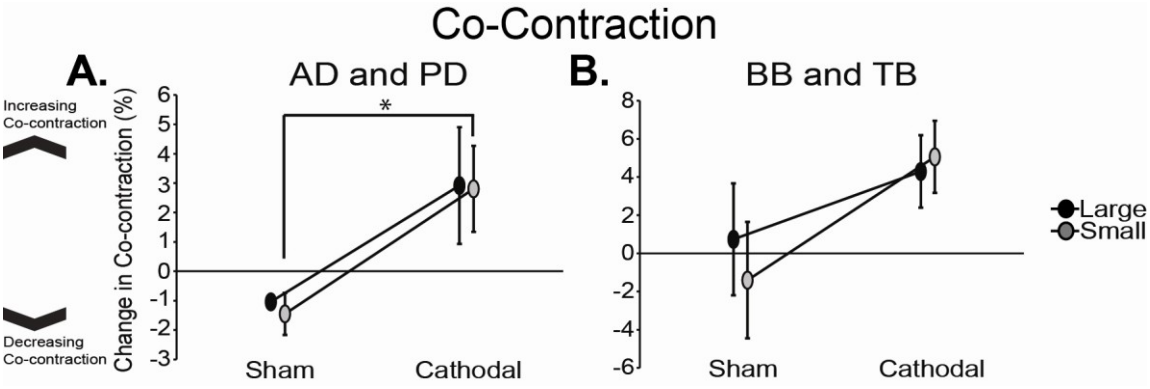

***Figure 2.11*. Co-contraction change scores comparing performance following cathodal and sham tDCS for large and small targets. Between the A. AD and the PD and B. BB and TB.**

TMS Excitability Measurements

From the TMS measures, we compared MEP areas from the right and left BB before and after right M1 cathodal and sham tDCS. For the left BB (right M1), which was the target of tDCS stimulation, following sham tDCS, the right hemisphere MEP area increased slightly at both 100% and 120% RMT. Following cathodal tDCS, in which inhibition was expected, similar but slightly greater increases were seen for both 100% and 120% RMT. The differences between the increases following sham versus

cathodal tDCS did not reach significance at either 100% RMT or 120% RMT ($p = 0.44$ and $p = 0.14$ respectively). See Figure 2.12A.

For the right BB (left M1), which did not receive any tDCS stimulation, after sham tDCS MEP areas decreased at 100% RMT and increased at 120% RMT. Following cathodal tDCS, MEP areas increased at 100% and 120% of RMT. For the 100% intensity, the differences between cathodal and sham tDCS did reach significant levels ($p = 0.03$) however at 120% RMT there was not a statistically significant increase of cathodal over sham tDCS ($p = 0.30$). See Figure 2.12B.

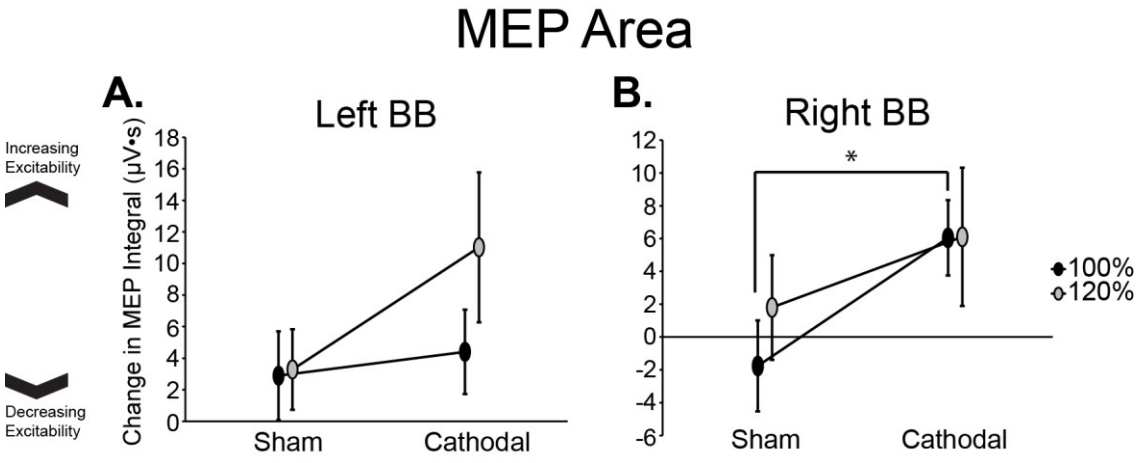

***Figure 2.12*. MEP area change scores comparing performance following cathodal and sham tDCS for TMS intensities of 100% and 120% of RMT. In the A. left BB muscle and B. right BB muscle.**

For the two subjects who completed the additional control experiment testing excitability changes pre- and post-tDCS without reaching, we compared MEP amplitudes from the right and left ECR before and after right M1 cathodal and sham tDCS. For the

left ECR (right M1), which was the target of tDCS stimulation, following sham tDCS, the right hemisphere MEP amplitude increase at both 100% and 120% RMT. Conversely, after cathodal tDCS, in which inhibition was expected, the MEP amplitude decreased at both 100% and 120% RMT. The differences between the increases following sham versus the decreases following cathodal tDCS did not reach significance at either 100% RMT or 120% ($p = 0.15$and $p = 0.57$ respectively). See Figure 2.13A.

For the right ECR (left M1), which did not receive any tDCS stimulation, after sham tDCS MEP amplitudes increased at 100% RMT but decreased slightly at 120% RMT. Following cathodal tDCS however, MEP amplitudes increased greatly at both 100% and 120% of RMT. For the 100% and 120% intensity, the differences between cathodal and sham tDCS were nearly significant ($p = 0.09$ and $p = 0.11$ respectively). See Figure 2.13B.

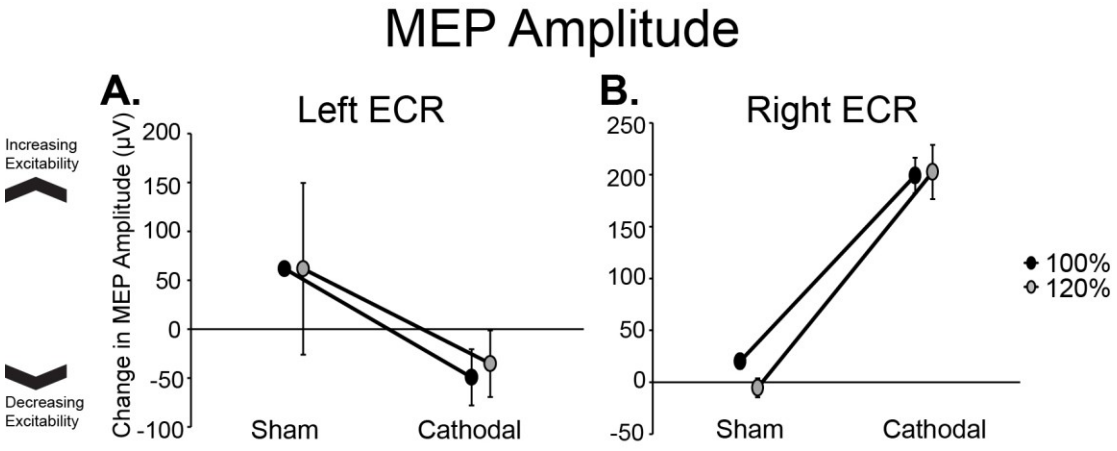

***Figure 2.13*. MEP amplitude change scores comparing performance following cathodal and sham tDCS for TMS intensities of 100% and 120% of RMT. In the A. left ECR muscle and B. right ECR muscle.**

Personal Activity, Visual Analog, & tDCS Experience Measures

There were no statistical differences in the variables contained within the Personal Activity Survey (caffeine, tobacco, alcohol, and activity) when comparing pre and post real- and sham-tDCS. Additionally, there were no changes in the pain, anxiety, fatigue, or alertness levels for any subject between pre and post real- and sham-tDCS. Finally, all subjects reported on the tDCS personal assessment survey a tingling, itching, or burning sensation during both sessions. Five of the ten subjects believed that they received real cathodal tDCS during both sessions. Two subjects guessed correctly about what intervention they received during both sessions. Two other subjects guessed incorrectly about what intervention they received during both sessions. The remaining subject believed that they received sham tDCS during both sessions.

Discussion

To the best of our knowledge, this is the first study to systematically analyze how cathodal tDCS affects unrestrained reaching movements as measured by a series of kinematic, neuromuscular, and TMS excitability variables. Despite the modest body of knowledge available on how tDCS affects both healthy and patient populations (Nitsche & Paulus, 2000; Priori, 2003; Boggio et al., 2006; Hesse et al., 2007), the majority of these studies utilize relatively gross clinical scales of extremity functionality that do not take into account movement quality or solely measure cortical excitability. As such, the novelty of this study was in the use of more sensitive kinematic measures to assess the quality of a reaching behavior to assess the performance of our upper extremities following cathodal tDCS.

It is well known that cathodal tDCS has the ability to inhibit the cerebral cortex (Ardolino, Bossi, Barbieri, & Priori, 2005; Furubayashi et al., 2008; Nitsche & Paulus, 2000). The secondary testing of two subjects was utilized to confirm that our protocol for cathodal tDCS over right M1 does in fact produce inhibition of that brain region. Indeed, by collecting TMS excitability measures while having the subjects remain stationary (i.e., without reaching) we established that our protocol is capable of inhibiting the treatment M1 and exciting the corresponding contralateral M1 (assumed to occur through transcallosal interhemispheric pathways that have a net inhibitory effect) (Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004). Even though the results were not significant in the target hemisphere, with only two subjects this was not expected. Like the right M1, the left hemisphere (non-treatment) results were in line with the literature but more robust.

Kinematic Measurements

A number of studies have shown that upper extremity performance can be decreased in healthy subjects through the use of cathodal tDCS (Vines, Nair, & Schlaug, 2006; Vines, Nair, & Schlaug, 2008). However, the overwhelming majority of this information is shown through the use of standardized clinical scales that lump movements into broad categories or only measure time to complete a certain set of tasks. And while there is no literature to indicate whether or not the same would occur for the kinematic features of unrestrained reaching movements in healthy subjects, our expectation was that a similar decrease in performance would be seen in this study. Specifically, we hypothesized that cathodal tDCS would increase endpoint error, decrease peak velocity, increase the time to peak velocity, and increase the curvature of the reach path.

This was however not seen for any of our kinematic measures. Even more, the peak forward velocity increased and the time to that peak forward velocity decreased when reaching to the small target following cathodal tDCS. In other words, these two measures indicated an improvement in performance after cathodal tDCS. Conversely, the endpoint accuracy when reaching to both the large and small target, peak velocity for the large target, and time to peak velocity for the large target could potentially show significant differences in the expected direction with enough subjects. With $\alpha = 0.05$ and a desired power of 80%, to achieve significance for all of those performance measures, 67,778 subjects are needed. This number is clearly out of the realm of possibility, and underscores a very small effect size of cathodal tDCS on these measures.

Interestingly though for the trajectory curvature, differences between cathodal and sham sessions were fairly robust and might reveal a significant increase in path curvature following cathodal tDCS if given enough subjects. In fact, with $\alpha = 0.05$ and a desired power of 80%, sample size calculations indicated that statistical significance would be reached with 128 and 28 subjects for the large and small targets respectively. A sample size of 128 was not a feasible number of subjects to recruit for this study. Instead, a more practical solution would be to either recruit more subjects with only the small target or conduct a more detailed analysis on the current data to discover if the significant differences when reaching to the small target were occurring during a specific subset of reaches within each reaching set. Moreover, the decrease in performance in the trajectory that was caused by cathodal tDCS was a mere 0.5% increase in the total path length or approximately 2.10 mm over an average total reach distance of 42 cm. How meaningful that change is for functional reaching performance is up for debate.

Hence, despite the evidence presented in the studies completed by Vines, Nair, and Schlaug (2006 & 2008) showing that upper extremity performance can decline following cathodal tDCS, we found that for a young healthy sample of subjects, cathodal tDCS was not sufficient to significantly alter any of the qualitative kinematic features of reaching. Several potential reasons for the lack of kinematic changes following cathodal tDCS exist and will be explored at the end of this section.

Electromyographic Measurements

When learning a new movement the co-contraction between the agonist and antagonist muscle pairs is greatest during our first attempts at that movement and progressively decreases as we increase the performance of that movement (Vereijken, van Emmerik, Whiting, & Newell, 1992). In other words, a rise in the co-contraction levels between opposing muscles is indicative of a decrease in performance. Both pairs of muscles (BB/TB and AD/PD) were altered by cathodal tDCS as shown by increases in the co-contraction levels. With respect to the BB and TB, the increases in the co-contraction seen were caused by some combination of both the BB and TB changing as indicated by a lack of statistically significant alterations to both the BB and TB integrals. The increases in the co-contraction levels between the AD and PD were caused by a significant increase in the PD activity follow cathodal tDCS as compared to sham tDCS. In other words, cathodal tDCS seemed to be causing an interruption of the normal decrease in co-contraction that is seen when we begin perfecting a movement.

Reasons for this Result

There are a number of potential reasons why we did not see the kinematic decreases in performance that we expected.

Ineffective tDCS Treatment

The first and most obvious conclusion that could be potentially drawn from the results of this study is that our tDCS treatment was simply ineffective. The lack of inhibition in the M1 of the right hemisphere during the main experiment is the most compelling evidence for this possibility. It is well established that M1 is the primary contributor to the lateral corticospinal tract and correspondingly the voluntary movements of our upper extremities (Lemon, 2008). As such, it was reasonable to expect based on the literature (Nitsche & Paulus, 2000; Priori, 2003; Vines, Nair, & Schlaug, 2006; Vines, Nair, & Schlaug, 2008) that the performance of the contralateral upper extremity would degrade when cathodal tDCS was applied to the right hemisphere's M1. Because we did not see cortical excitability decreases in the right hemisphere, it is not surprising that we did not see reaching performance decreases as measured by kinematics. This is further support for the theory that we ineffectively applied cathodal tDCS over the right hemisphere. Conversely however, through our follow-up testing of two individuals, we confirmed that our cathodal tDCS protocol is successful in inhibiting M1. As such, the possibility that we unsuccessfully applied tDCS over the right M1 seems unlikely. Additionally, the increased excitability in the (non-treatment) left hemisphere and the increases in co-contraction following real cathodal tDCS suggest that the tDCS intervention was effective.

tDCS Alters Motor Learning not Motor Performance

Another possibility is that cathodal tDCS may selectively alter motor learning and not motor performance. For example, Vines, Nair, & Schlaug (2006 & 2008) measured the decreases in "performance" by counting the number of correctly sequenced

keystrokes. It could be argued that this is actually more of a motor learning task than a pure motor performance task, because the movements required to accomplish the keystroke sequence may remain unchanged but the person completing them has simply remembered the sequence more or less effectively due to tDCS treatment. The possibility that tDCS actually affects motor learning rather than motor performance may be further supported by the fact we saw no changes in the kinematics of the reaches but we did see a change in the EMG measures of those reaches that are associated with motor learning (Thoroughman & Shadmehr, 1999).

Co-contraction Compensates for Kinematic Changes

tDCS may have also been effective by causing co-contraction increases that are known to be a compensatory mechanism for decreasing kinematic motor performance. For example, co-contracting an agonist/antagonist pair of muscles is one method for maintaining accuracy when accuracy demands are increased (Gribble, Mullin, Cothros, & Mattar, 2003; van Roon, Steenberg, & Meulenbroek, 2005). During this study, co-contraction increases following cathodal tDCS treatment similarly might have occurred in order to keep the kinematic performance of those reaches at a maximal level. Accordingly, it is possible that in order to maintain the kinematic performance at an optimum level while experiencing a disturbing stimulus like cathodal tDCS, co-contraction levels were forced to increase. Cathodal tDCS then might actually be influencing the kinematic performance of our reaching movements but those changes are masked by compensatory increases in the co-contraction levels between the BB/TB and AD/PD pairs.

Co-contraction at the Shoulder versus Elbow

While it is possible that the increases in co-contraction seen in this experiment were partly responsible for maintaining the kinematic performance of the reaching movements, it is imperative to note that the measures of co-contraction utilized in this study might be an oversimplification of the true muscle activity. More specifically, it was assumed that the agonist/antagonist pairs of the shoulder and elbow were the anterior deltoid/posterior deltoid and biceps/triceps respectively. This assumption however may have been too simple.

The movement completed in this study required shoulder flexion. Accordingly, the muscles needed for the movement at the shoulder are more likely the anterior deltoid and biceps (agonists) as well as the posterior deltoid and triceps (antagonists). Because the biceps and triceps are much lesser contributors to shoulder motion, it was appropriate to simplify the co-contraction measurement at the shoulder down to only the anterior and posterior deltoids. As such, our result of increased co-contraction at the shoulder (anterior and posterior deltoid) is correct. In addition to flexing the shoulder, subjects were required to extend the elbow throughout each reach in this study. To accomplish such an action, the triceps operates as the agonist whereas the biceps is the antagonist. Therefore, our assumption that the biceps and triceps are the agonist and antagonist of this movement may actually be reversed. Consequently, the result of non-significant increases in co-contraction between the biceps and triceps following cathodal tDCS may be actually non-significant decreases in co-contraction between those two muscles.

Increases in co-contraction at the shoulder indicate a decrease in performance at that joint whereas decreases (NS) in co-contraction at the elbow indicate an increase in

performance at that joint. Accordingly, it seems possible that the elbow movement improved to compensate for a decrease in performance at the shoulder. Similarly, it is possible then that cathodal tDCS may be selectively decreasing the performance of the shoulder but improving the performance of the elbow.

Other Brain Regions Compensate for M1

One final piece of evidence that might explain our results is that other brain areas have the ability to compensate for deficiencies in M1. Accordingly, it is possible that tDCS was unable to alter the kinematic performance during reaching because other brain areas were compensating for those deficiencies in M1. One example of this type of compensation occurring from other brain areas has been postulated to be from the ipsilateral (also contralesional) M1 in persons recovering from a stroke and those that suffer from other neuromuscular dysfunction like multiple sclerosis (Strens, Fogelson, Shanahan, Rothwell, & Brown, 2003; Zeller, Dang, Stefan, & Classen, 2009; Zeller et al., 2011). In addition, Frost, Barbay, Friel, Plautz, and Nudo (2002) showed that the ipsilesional ventral pre-motor area functionally compensates for a lesioned M1 by directly replacing lost cortical space in M1 with cortical space in ventral pre-motor area. Moreover, patients who suffer from Parkinson's disease, show increased connections between M1 and the supplementary area, pre-motor area, posterior parietal cortex, and the cerebellum (Wu et al., 2010).

This phenomenon of other brain areas compensating for deficits seen in M1 was confirmed in a repetitive transcranial magnetic stimulation study (rTMS) in healthy persons (Lee et al., 2003; Strens, Fogelson, Shanahan, Rothwell, & Brown, 2003) that demonstrated these compensatory mechanisms can occur in very short periods of time (as

required in this study) rather than what was previously thought to occur in patient populations over much longer periods of time. The results obtained from the cortical excitability measures of the left hemisphere in this study could be interpreted as further proof of this phenomenon (Schaefer, Haaland, & Sainburg, 2009). Furthermore, even though we do not have any excitability measures from other areas of the brain (ventral pre-motor area, supplementary motor area, posterior parietal cortex, and cerebellum) that have been associated with compensatory mechanisms, it is possible that during this study, we might not have seen kinematic alterations of movement because other brain regions were compensating for the deficiencies in the treatment M1.

Conclusion

Despite our expectation that inhibitory cathodal tDCS applied over the right hemisphere M1 would decrease the performance of reaches performed with the left upper extremity, we were unable to elucidate any changes in the detailed kinematic features of reaching behavior following cathodal tDCS. This may have occurred for a number of reasons. The first reason might be that cathodal tDCS selectively affects motor learning as evidenced by increases in co-contraction and not motor performance as we previously hypothesized. Second, cathodal tDCS could be causing kinematic performance decreases but the aforementioned co-contraction increases compensate for those kinematic performance declines. Additionally, it is possible that in actuality cathodal tDCS caused co-contraction changes at the elbow (potential increased performance) that were compensating for actual decreases in performance at the shoulder joint. Finally, compensatory mechanisms from other brain regions might mask major kinematic

performance declines. Further study of different types of motor tasks and how they respond to the cathodal tDCS is necessary to parse out which of these possibilities is most likely.

CHAPTER III

DISCUSSION

Overview

In previous chapters, it was well established that reaching is a complex task that we are responsible for accomplishing on a daily basis. Moreover, the complexity of reaching may not arise only as a result of the tasks we must accomplish, but also the fact that we must successfully control and coordinate multiple joints interacting in a variety of environments. Despite the inherent complexity of reaching, these types of tasks are often over learned by humans and as a result are relatively automatic. Because we have still not fully elucidated all the details of how we control these relatively automatic reaching movements, in this study tDCS was used to alter the cortical excitability of M1 and assess its effects on reaching behaviors.

This is the first study, to the best of our knowledge, which investigated the effect of tDCS over the contralateral M1on the detailed kinematics and EMG during dynamic reaching in healthy adults. While there is some knowledge on the effects of tDCS on the upper extremity function of both healthy and patient populations, there is nearly no information available on how tDCS changes the more nuanced kinematic features of the upper extremity. Moreover, there is even less information about how tDCS affects the kinematic features of the upper extremity while completing relatively unrestrained dynamic reaching movements. Therefore, the novel piece of this study was in utilizing three dimensional kinematic analyses instead of clinical measures of upper extremity functional ability to assess the functionality of our upper extremities.

Kinematic Measurements

As established throughout this paper, reaching and functional extremity movements can be quantified in a number of ways including standardized clinical performance measures, more direct performance measurements of isometrics like grip and pinch strength, or as in this study, kinematic measurements of a specific reaching behavior. More specifically, we selected key reaching parameters including the endpoint accuracy, peak velocity, time to peak velocity, and reach path curvature of those reaching movements. Because of previous work showing decrements in performance following cathodal tDCS over M1 as measured by standardized scores (Baudewig, Nitsche, Paulus, & Frahm, 2001; Nitsche & Paulus, 2000; Vines, Nair, and Schlaug, 2006; Vines, Nair, & Schlaug, 2008), I hypothesized that cathodal tDCS applied over contralateral M1 would alter the kinematic features of reaching behaviors in a similar fashion. Despite these expectations, we did not however see any kinematic performance changes.

Electromyographic Measurements

Traditionally, agonist and antagonist muscle pairs, like the biceps/triceps and anterior deltoid/posterior deltoid pairs, fire in a "triphasic burst pattern" when accomplishing movements like the reaches completed in this study (Pampiglione, 1966; Sanes & Jennings, 1984). In this perfect theoretical model there is no temporal overlapping of either agonist burst with the antagonist burst, implying no co-contraction. In real world movements however, there is always some level of co-contraction. And, as noted earlier, when learning new movements, co-contraction levels are initially much higher than when we begin to improve our performance with that movement (Vereijken, van Emmerik, Whiting, & Newell, 1992). So, any increase in co-contraction levels of the

primary movers of reaching movements would indicate a decrease in performance. This decrease in performance (increase in the co-contraction) is what we hypothesized would occur following cathodal tDCS to both the BB/TB and AD/PD agonist/antagonist muscle pairs and is indeed what we found.

Reasons for Lack of Kinematic Changes and Presence of EMG Changes

There are a number of potential reasons for why there were no performance declines in kinematic measures but there were performance declines in the EMG measurements. The first of these reasons might simply be that we ineffectively applied cathodal tDCS. Primarily, this is refuted by our follow-up testing that showed our protocol is successful at inhibiting M1 in the right hemisphere and exciting M1 in the left, non-stimulated hemisphere. Additionally, this is also refuted by the cortical excitability results in the left M1 (increased excitability following cathodal tDCS over right M1) and the EMG results from the main experiment. A second potential reason for this mixed result was that tDCS might selectively impact motor learning and not motor performance as previously believed. This theory might be buoyed by the fact that we did not see kinematic changes but we did see EMG changes that Thoroughman and Shadmehr (1998) have suggested are linked with motor learning. Additionally, the co-contraction increases may also be associated with a compensation for rising kinematic demands. Those same co-contraction increases seen at the shoulder were potentially compensated by improvement in the neuromuscular performance at the elbow indicating that tDCS might selectively inhibit and improve the functionality of the shoulder and elbow respectively. Finally, it is possible that other brain areas were compensating for a relatively inhibited right (stimulated) M1.

Limitations

As with any study, there are limitations in both the study design and the interpretation of the results. The first limitation with our study is the possibility that our task was too simple relative to the skill level of our young healthy subjects. Reaching, by and large, is an overlearned task in humans and is therefore relatively automatic in nature. No matter how difficult the reaching task might seem, we have practiced potentially hundreds of thousands of different reaching movements so that even the most difficult reaches are actually quite simple to the well versed subject. Accordingly, having subjects reach to an object with approximately the same surface area as something we reach to frequently (a standard doorbell) in a location that we frequently reach to objects for (in line with our upper extremities) might have been far too simple. Moreover, because the task may have been far too easy for our subjects, cathodal tDCS may have had very little disruption of this highly skilled and automatic behavior.

A second limitation that is present in this study has to do with the application of tDCS while performing a motor task. There are a number of studies that have indicated that for the application of tDCS to be effective in altering motor performance and learning in both healthy and patient populations, it needs to be administered during actual performance of that task (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Galea & Celnik, 2009; Hunter, Sacco, Nitsche, & Turner, 2009; Nitsche et al., 2003; Nitsche et al., 2007). Accordingly, we chose to apply tDCS during completion of the reaching task. Interestingly though, it was recently shown that performing a motor task during cathodal tDCS may result in reduced or even reversed cortical excitability changes (Thirugnanasambandam et al., 2011). If this held true for the task completed in our study

as well, it would be unsurprising that the TMS excitability measures we collected from the stimulated right M1 were not decreased.

A final limitation with this study has to do with potential sources of variability within TMS measures. A first possible source of variability was our use of a two day protocol. Inclusion of a third day that would have served as a familiarization session may have avoided the potential for some subjects experiencing the "white coat effect." In this case, the "white coat effect" is when a subject is particularly anxious about being in the laboratory setting or about participating in unfamiliar activities (TMS and tDCS) to the point that performance is compromised and/or excitability is altered. A second source of variability may come from unexpected stimuli when collecting TMS excitability measures. The stimuli can come from some external source, e.g. ambient noise, or from an internal source, e.g. a disturbing memory. Any fluctuation in the overall arousal level can alter the cortical excitability measures outside of what is caused by tDCS.

Future Studies

Having completed this study, it is apparent that there were aspects of the study that did not work as well as planned, other aspects that went as expected, and still other aspects of the study that exceeded our expectations. Knowing what we know now, there are a number of logical "next steps" for this line of research.

The first set of "next steps" falls in the category of improvements for this particular study protocol. Obviously, there were some limitations encountered (both foreseeable and unforeseeable) during the course of this study. I suggest creating a protocol that utilizes the same reaching task, but maximizes the potential to see cortical

excitability changes alongside the neuromuscular variables that did in fact change as a result of cathodal tDCS. This includes creating a three day protocol where the first day is used as a "subject familiarization" period. In other words, everything will appear the same to the subject, but the information will simply be set aside and not used in the final data analysis. Also, in order to effectively decrease the uncontrollable outside stimuli (e.g., loud disruptive noises), playing "low tone easy listening" music might more effectively level out the concentration of the subject as well as dampen any other external noises.

Having discussed a number of the different structures in the central nervous system that control different facets of reaching, a second logical place to guide this research would be to look at how tDCS stimulation over some of those areas affects the same variables of our reaching measured in this study. For example, it is known that the supplementary motor area has direct connections to the spinal cord via the corticospinal tract and is at least partly responsible for planning and controlling the sequencing and coordination of our reaching movements (Kazennikov et al., 1999; Maier et al., 2002; Nachev, Kennard, & Husain, 2008). It would be of interest to see how cathodal tDCS over this area then influenced the unrestrained dynamic reaching behaviors of young healthy individuals. This type of study would give us a better understanding of how the supplementary motor area is functionally connected with our reaching behaviors. Other similar experiments could be completed with any number of other central structures (e.g., cerebellum, pre-motor areas, etc.).

A third direction in which this line of research should be extended is as a direct result of what was discovered in this study. We found that primarily, cathodal tDCS

appears to be interrupting the neuromuscular features of our reaching behaviors (increases in co-contraction) as well as causing an excitation of the hemisphere opposite the treatment and ipsilateral to the moving upper extremity. As such, a logical step would be to see if this increase in excitability in the left hemisphere caused by cathodal tDCS over the right primary motor cortex could potentially influence the movements in our right upper extremity reaching behaviors. Obviously, because we utilized young healthy individuals, it might be nearly impossible to see improvements in the kinematic features of those reaching behaviors (ceiling effect). But, it might be possible to see neuromuscular improvements (decreases in co-contraction) beyond what is normally found when practicing a new movement.

A fourth line of inquiry arises from the previously mentioned increases in co-contraction. We previously asserted that this may be because cathodal tDCS is actually influencing motor learning and not true motor performance. As such, it would be interesting and fruitful to investigate whether this is actually true with a series of similar experiments to the one completed in this study but incorporating a true motor learning component. The task might need to be updated to include reaching to a series of randomly selected targets located in various positions rather than the single target utilized in this experiment.

Obviously, understanding how the primary motor cortex influences our unrestrained dynamic reaching movements is important. Probably more so though is utilizing the information gleaned from this study to help individuals who are affected by neurological dysfunctions that impair the functional abilities of their upper extremities. For example, tDCS has been shown to be effective in improving the upper extremity

functionality of persons having experienced a stroke (Boggio et al., 2007; Hesse et al., 2007; Mitsuhiro, Satoru, Taiji, & Yasuyuki, 2013). It would be important however to go beyond the more standard secondary measurement protocols to gain a further understanding of how tDCS is actually "improving" the upper extremity performance of these patient populations. For example, by utilizing this task and measurement protocol, one might be able to see whether tDCS is causing improvements by improving neuromuscular features (co-contraction reduction) like the ones seen in this study or if it is through other kinematic measures like velocity, end point error, or trajectory.

Conclusion

The task completed during this study more closely attempted to approximate actual reaching movements that we encounter on a daily basis. tDCS allows us to alter the cortical excitability of the primary motor cortex and potentially the features of reaching as defined by kinematic properties and neuromuscular properties. We were unable to elucidate any changes to the kinematic features of their reaching behaviors following cathodal tDCS. This may have occurred for a number of reasons including compensatory mechanisms from other brain regions, tDCS actually altering motor learning and not motor performance, or the co-contraction increases compensating for any kinematic dysfunction just to name a few. Additionally, we were unable to elicit any cortical excitability changes in the stimulated hemisphere. This may have been due to the fact that applying tDCS during actual performance of a motor task (as was done in this study) caused an increase in right M1 excitability (due to repetitive motor activity) that overpowered the inhibitory effects of cathodal stimulation. Finally, we were able to see a

disruption in the normal reduction of co-contraction levels seen when learning a new motor task.

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