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ENHANCING APHASIA THERAPY:

TWO STUDIES OF tDCS IN CHRONIC APHASIA

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Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
Steinhardt School of Culture, Education and Human Development
New York University
2018

ACKNOWLEDGMENTS

Obtaining my doctorate has been not only an academic and professional journey, but also a personal one. So here I acknowledge those in each category. First, my advisor, Adam Buchwald, deserves the utmost thanks for guiding me on a path off which I sometimes feared falling. He challenged me as an honest critic and supported me as a staunch advocate and I will be forever grateful that he took me on as a student when my original plan fell through. Sharon Antonucci has also been an incredible role model since my early days at NYU and is a supreme example of marrying clinical practice with research. But I wouldn't have a dissertation project without Dylan Edwards, who has taught me the value in sharing one's research and maintaining loyalty to the mutual benefit of all collaborators. Thank you to Christina Reuterskiöld for your example as a compassionate and disciplined teacher and leader. I've learned so much from you beyond just the academic. To my outside readers, Tara McAllister Byun and Mira Goral and to the rest of the faculty at NYU's CSD Department, thank you for your investment in my work and in my development as an academic.

Continuing on a professional note, I'd like to thank my collaborators, especially Johanna Chang, Avrielle Rykman, Mar Cortes, Bruce Volpe, Julius Fridriksson, Regina Lin and Gabriella Liscio, who all helped these studies come to fruition. Mentors and colleagues in academic departments from Mercy College

and Sacred Heart University have also helped shape this work. Foremost among these is Rhea Paul, who has provided invaluable advice and encouragement. I wish to acknowledge the help of the entire Sacred Heart University Speech-Language Pathology Department faculty and staff during some trying times. Additional thanks go to Helen Buhler and Susan Wortman-Jutt. Thank you to Mara Steinberg Lowe, Anna Eva Hallin and Kelly Bridges for reading early drafts and scoring standardized tests and thank you to Ph.D. student peers I've met throughout the years for accompanying me on this journey. I'm indebted to both Audrey Holland and Leora Cherney for professional and personal advice and inspiration.

Personally, I have been extremely lucky to have the unwavering support of my family as I've navigated this tremendous undertaking. My success is yours! My husband, David, was beyond compare in his patience, love and understanding. Oh, and his tech support was useful too. My sons, Matthew and Andrew, who cannot remember a time when I wasn't a Ph.D. student, unconditionally believed in me. They've sometimes wondered why I haven't given up. Well guys, this is why. I did it and I believe you can accomplish your goals too. Just as you and Daddy supported me, we will be there for you. You can do hard things. Together, we can do hard things!

Then there are my parents and siblings. Mom, what can I say? What could I ever say to thank you for being the "Cadillac of Moms"? You believed in me when I didn't believe in myself. Dad, you have encouraged me when words

wouldn't come. You reminded me I was stubborn enough to persevere and you checked in with me regularly. I knew neither you, Dave, nor my boys would allow me to fail. To my siblings, in-laws and extended family, especially Ann, Kelly, Rich, Evan, Donna, Kathy, Lorraine, Amedeo, Carol Ann, Diane, Kay, Ryan, Heather, Anika, Asa, Audrey and Frank as well as my animal family members Glory, Scout, Teddy and Rosalina, thank you. A special thank you goes to my longtime friends from various stages of life, especially Kelly (Bridges), Racine, Larissa, Kevin, LeeAnn, Ted, Don, Lynn and Debbie. Thank you all for making life enjoyable while this was going on. I appreciate your proofing, laughter, distractions, prayers and love. A special thanks goes to Karen Hook for always putting me up in Boston and for looking out for me in Heaven. Thank you all for believing my work is important and worthy of sacrifice. Thank you for telling other people about aphasia and about me. Thank you for being proud of me.

So many people have contributed to this endeavor that I fear leaving someone out in acknowledging people by name. So I dedicate this work to all of those listed above, the rest of my family, friends, research assistants (especially Amanda Begley, Abrielle Gouvin, Tash Sousa, Allison Kornhaas and Gina Gallo), students and participants, who so graciously gave of their time in hopes of bettering the lives of those with aphasia.

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CHAPTER I

INTRODUCTION

Following a stroke, people often experience difficulty with speaking, reading, writing or comprehension. This acquired language impairment, called aphasia, is a consequence of neurological damage to the brain (Fridriksson, Hubbard and Hudspeth, 2012). Because language is essential to human interaction, participation in professional, economic, and family activities is limited for people with chronic aphasia (World Health Organization International Classification of Functioning , Disability and Health, 2015) and quality of life is often reduced (Ross and Wertz, 2003). People with aphasia comprise a large and growing population as approximately 795,000 individuals in the United States have new strokes every year with 20-40% of these people acquiring aphasia (Go et al., 2013). In addition to language impairment, many people with aphasia also experience a motor speech deficit called apraxia of speech (AOS) that impairs the ability to plan and program speech motor movements (McNeil, Robin and Schmidt, 2009).

Treatments of chronic aphasia and concomitant related disorders are primarily comprised of behavioral techniques designed to restore or compensate for acquired speech and language deficits. Numerous studies have shown that

people can continue to improve language well into the chronic phase of recovery (> 6 months), even decades after the stroke occurred (Meinzer, Elbert, Wienbruch, Djundja, Barthel et al., 2004; Moss & Nicholas, 2006; Falconer & Antonucci, 2012). These treatments, which can be considered learning or re-learning experiences, create structural and functional changes within the brain, particularly in the cortex (Kleim and Jones, 2008). These changes include new connections among other neurons or the strengthening of existing connections. Intact cortical regions of either hemisphere may also become engaged to perform the neurocognitive functions that damaged regions had previously performed. This capacity of the brain to change based on learning experiences (such as speech and language treatment) is referred to as experience-dependent cortical plasticity or neuroplasticity (Kleim & Jones, 2008).

While behavioral interventions alone are effective in improving speech and language skills, therapeutic progress can be slow particularly in the chronic phase. Accordingly, means of enhancing behavioral treatment have been sought. An adjunct to behavioral intervention that has recently garnered attention is non-invasive brain stimulation, which has been found to enhance recovery beyond that of behavioral techniques (such as traditional speech and language or physical therapy) alone (Fridriksson et al., 2012). The present study focuses specifically on the use of transcranial direct current stimulation (tDCS) as an adjuvant to behavioral aphasia therapy (Flöel, 2014; Holland and Crinion, 2012; Hamilton, Chrysikou and Coslett, 2011). Its use in speech and language is focused on

inducing plasticity in undamaged cortical regions most suited to language processing (i.e., left perilesional cortex or homotopic areas in the right hemisphere) in place of those destroyed by stroke (Cherney and Small, 2006; Kleim and Jones, 2008; Raymer et al., 2008). The posited mechanism by which tDCS generates neuromodulatory effects is elaborated on in Chapter II.

The current work focuses on the use of tDCS over ipsilesional primary motor cortex in two studies that investigate the relationship of tDCS to rehabilitation in individuals with chronic aphasia/apraxia of speech subsequent to stroke. The first study (Chapter III) investigated the use of tDCS over the left primary motor cortex (Meinzer et al., 2014; Meinzer, Darkow, Lindenberg & Flöel, 2016) and the effect of motor therapy on speech and language processing. That is, the effect of active tDCS over the left primary motor cortex (anodal as compared to sham with cathode placed over the right supraorbital region) combined with right upper extremity repetitive motor practice on the effects of speech and language in people with chronic stroke aphasia is evaluated. The second study (Chapter IV) investigated the role of the timing of tDCS in relation to aphasia treatment using a naming treatment in people with chronic stroke-aphasia. There is limited information about the role of timing in relation to chronic stroke treatment. One study of the rehabilitation of motor function after stroke reported differential benefits to motor recovery based on the timing of tDCS in relation to robotic hemiplegia therapy (Giacobbe, 2013). There is a paucity of research on the role of timing of tDCS in relation to speech/language

therapy to date (de Aguiar, Paolazzi and Miceli, 2015). Most current aphasia research incorporating tDCS provides language therapy concurrent to delivery of tDCS or therapy that starts concurrently with tDCS, and then continues after the tDCS session (typically 20 minutes) is completed (Fridriksson et al. 2011; Fiori et al., 2010; Baker et al., 2010).

Chapter II focuses on a description of tDCS, its posited mechanism of action and its use in the study of rehabilitation. Then the rationale for using tDCS stimulation over ipsilesional primary motor cortex and the implications of the proximity of the motor cortex and -language cortices is discussed. Finally, the need for exploring the effects of the timing of tDCS stimulation in relation to aphasia therapy is explored.

CHAPTER II

REVIEW OF RELEVANT LITERATURE

Transcranial Direct Current Stimulation (tDCS)

Mechanism of tDCS

During tDCS, a low-intensity direct electrical current is applied to the scalp to influence the electrical activity in the underlying cortex. In most experimental paradigms, tDCS is applied at an amperage insufficient to cause neurons to generate action potentials (i.e., 1-2 mA); rather, it provides sub-threshold electrical modulation, which increases or decreases the likelihood of an action potential to occur (Otal, Dutta, Foerster, Ripolles, Kuceyeski, & Miranda et al., 2016). tDCS stimulation has been shown to increase excitability in the motor cortex underlying the anode while it inhibits cortical excitability underneath the cathode (Nitsche & Paulus, 2000). *Depolarization,* associated with anodal stimulation, increases the likelihood of initiating an action potential while *hyperpolarization,* associated with cathodal stimulation, decreases the likelihood of initiating an action potential (Nitsche & Paulus, 2001; Boggio, Fregni, & Pascual-Leone, 2009; Flöel, 2014; Holland and Crinion, 2012; Hamilton et al., 2011).

These induced cortical states can persist for prolonged periods even after stimulation is removed. In the case of a single tDCS session, Nitsche and Paulus (2000 & 2001) reported that neuromodulatory effects remained up to 60 minutes after anodal tDCS over the motor cortex was applied for 9-13 minutes. The effect of multiple tDCS administrations accumulate over time to influence the ease or difficulty with which neurons fire, thereby allowing modification of cortical activity beyond the duration of stimulation (Nitsche et al., 2009). Over such cumulative sessions, anodal tDCS has been shown to result in lasting strengthening of the connections between pre- and post-synaptic neurons similar to training-induced long-term potentiation (LTP), whereas cathodal stimulation leads to lasting inhibition between pre- and post-synaptic neurons, similar to long-term depression (LTD) (Nitsche et al., 2006; Fritsch et al., 2010; Fridriksson et al., 2012).

Active tDCS stimulation

As described above, a weak sub threshold polarizing current is introduced from a battery powered tDCS device. This constant current forms an electrical circuit with electricity entering via the anode then traveling through the scalp and underlying tissue where it is discharged via the cathode (Higgins & George, 2008). The active electrode may be either the anode or the cathode, depending upon the effect investigators desire. In attempts to decrease neuronal firing, down regulation is promoted by placing the cathode over the target area. For attempts to increase neuronal firing in a specific region, the anode is place over that area. The

other electrode is often considered the "reference" electrode and is placed in an area presumed not to influence cortical regions below, usually the contralateral supraorbital cortex or sometimes off the head in an extra cephalic region such as the contralateral shoulder (Flöel et al., 2008; Iyer et al, 2005). Despite one electrode being considered "active" and the other a "reference," both electrodes stimulate underlying cortex. The most commonly reported side effects are tingling, itching or reddening of the scalp under the electrodes (Iyer et al., 2005).

Sham tDCS stimulation

Sham tDCS is used as a scientific control or placebo condition in experiments. The intent in using sham tDCS is that it replicates the placement of electrodes and sensations (often tingling or itching) experienced by participants undergoing active anodal or cathodal tDCS stimulation without the effect of modulating cortical activity. Under the sham condition used in this study, participants initially had active tDCS turned on in order to replicate the sensation of tingling; however, the device was subsequently turned off before neuromodulation could occur (Edwards et al. 2009; Ambrus, Al-Moyed, Chaieb, Sarp, Antal, & Paulus, 2012). Researchers compare the results obtained under sham stimulation with the results obtained during active stimulation (anodal or cathodal) in order to measure the differential effects of active stimulation and rule out placebo effects (Nitsche et al., 2009).

tDCS montage selection

The effect of tDCS stimulation depends on the polarity, size and placement of the electrodes on the participant's head. This configuration is known as the electrode montage (DaSilva, Volz, Bikson, & Fregni, 2011; Fusco et al., 2013). Different electrode montages – varying according to the placement site of the anodal and cathodal electrodes, electrode size, and polarity –are used to attain specific outcomes through tDCS. An additional component of tDCS design is dosage. Dosage includes the intensity in mA, the length of stimulation sessions and the frequency of sessions in multi-session investigations (Galletta, Conner, Vogel-Eyny & Marangolo, 2016). These parameters are chosen by investigators in an attempt to upregulate (Fridriksson et al. 2011) or down-regulate areas (Kang et al., 2011) of cortex targeted for intervention for specific outcomes.

Therapeutic effects of tDCS for stroke patients

In the following sections, the evidence that tDCS can enhance behavioral therapy subsequent to stroke in both the motor rehabilitation literature (e.g. Hummel et al., 2005; Boggio, Nunes, Rigonatti, Nitsche, Pascual-Leone, & Fregni, 2007; Edwards et al., 2009; Giacobbe et al., 2013) and the literature on speech and language in healthy (Meinzer et al., 2014; Cattaneo, Pisoni and Papagno, 2011; Fertonani et al., 2010; Sparing, Dafotakis, Meister, Thirugnanasambandam, and Fink, 2008; Fregni et al., 2005; Iyer et al., 2005) and impaired (Baker, Rorden and Fridriksson, 2010; Baker, 2010; Fiori, 2010;

Fridriksson, Richardson, Baker, and Rorden, 2011; Hamilton, 2011; Holland and Crinion, 2012; Flöel, 2012, 2014) individuals is reviewed. . The literature on limb recovery will be addressed first. Next, the effects of tDCS on motor speech performance in patients with mixed aphasia/AOS will be discussed. Finally, the effect of tDCS on language in healthy and impaired populations will be addressed.

tDCS and motor recovery in chronic stroke

In the stroke rehabilitation literature, tDCS has been studied most extensively in the context of upper extremity (arm/hand) motor function (Flöel, 2014), and has been shown to improve motor function recovery beyond that of motor therapy alone (Butefisch, Khurana, Kopylev, & Cohen, 2004; Hummel, Celnik, Flöel, Wu, Gerloff & Cohen , 2005; Boggio et al.,2007; Edwards et al., 2009). The following studies demonstrate some of the variables that may affect study outcomes, including intensity of tDCS; polarity of electrodes and their placement sites; number of treatment sessions; and timing of treatment compared with tDCS stimulation.

Active tDCS over the primary motor cortex has been shown to affect cortical electrical activity for prolonged periods after stimulation (i.e., from minutes to hours) depending on intensity and duration (Nitsche and Paulus, 2000; Nitsche and Paulus, 2001; Nitsche et al., 2005). Active tDCS with the anode placed over the ipsilesional primary motor cortex (side with lesion) has been

demonstrated to enhance effects of traditional rehabilitation techniques of the contralesional (side opposite lesion) limb's motor activity following stroke (Edwards et al., 2009). For example, Hummel, Celnik, Flöel, Wu, Gerloff & Cohen (2005) found that chronic stroke patients improved paretic hand function as measured by The Jebsen-Taylor Hand Function Test (JTT; Jebsen, Taylor, Trieschmann, Trotter & Howard, 1969), a standardized motor movement test that simulates activities of daily living. The time to complete the task decreased in all participants under the active (1mA anode over ipsilesional primary motor cortex, catrhode over contralateral supraorbital region) but not sham tDCS conditions. Improvements persisted 25 minutes after the single session of stimulation ended and these effects were still observable one to two weeks after study completion.

Boggio et al. (2007) reported that hand function improved immediately after each of four once-weekly sessions of active tDCS, both with the anode over the damaged hemisphere or with the cathode over the intact hemisphere (1mA, 20 minutes in both active conditions) as compared to sham. No cumulative improvement in motor function was found between weeks one and four, but cumulative effects were observed after *five consecutive daily* sessions of cathodal tDCS to the intact hemisphere, and these improvements persisted at follow up testing two weeks later. This suggests that dosage, in the form of frequency of tDCS application, is one variable that may affect treatment outcomes.

Another dimension that affects treatment outcomes is the timing of stimulation relative to the delivery of behavioral intervention. Giacobbe et al.

(2013) reported a differential effect of motor outcomes during different type and timing combinations of stimulation and motor training. Participants received 20 minutes of robot assisted physical therapy of the hemiplegic wrist, before, during or after 20 minutes of active (2mA) or sham tDCS with the anode placed over the ipsilesional primary motor cortex. The robotic arm therapy combined with sham tDCS improved mean speed of movement, while anodal tDCS delivered preceding robotic hemiplegia therapy improved movement smoothness. Anodal tDCS delivered during or after robotic hemiplegia therapy resulted in decreased aim and decreased mean speed respectively. While this study points to a possible effect of the timing of tDCS in relation to motor therapy, it has yet to be confirmed by replication or similar contrastive timing studies. This reflects the preliminary status of these results, though the findings here lead directly to the question of whether the timing of tDCS in relation to aphasia treatment affects language outcome measures (Chapter IV).

Translational use of tDCS from motor to speech and language research

Much of the emerging research examining the effects of tDCS on speech and language outcomes in aphasia/AOS (Marangolo et al., 2011, 2013; Boggio et al., 2007) has stemmed from methods derived from motor studies. For example, the attribution of depolarization to anodal stimulation and hyperpolarization to cathodal stimulation derives from motor evoked potentials in the primary motor cortex devoted to the hand (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). Subsequently the association of anodal stimulation with excitatory capacities and

cathodal stimulation with inhibitory processes has been applied to many forms of tDCS therapy (e.g. depression and analgesia; Kalu, Sexton, Loo and Ebmeier, 2012; Knotkova, Nitsche, and Cruciani, 2013). In addition, there is precedent for speech and language therapies being directly developed from motor therapies. For example, constraint-induced aphasia therapy (Meinzer, Elbert, Djudja, Taub and Rockstroh, 2007) was developed by modifying the principles underlying constraint-induced movement therapy (Taub, Uswatte, and Pididit, 1999) to speech and language rehabilitation.

The success of tDCS in facilitating limb motor control recovery has been extended to other motor domains including speech motor control, such as AOS. However, neurogenic motor speech disorders such as AOS have yet to be studied independently but rather have been treated as concomitant disorders associated with non-fluent aphasia (Marangolo et al., 2011, 2013; Boggio et al., 2007).

Effects of tDCS on speech production

As stated, the effects of tDCS on speech motor control in cases of only apraxia of speech or dysarthria are not yet available, a few studies have examined articulatory control in people in the chronic stages of left-hemisphere stroke recovery. Marangolo et al. (2011) applied active (1mA for 20 minutes, anode over the contralateral supraorbital region) or sham tDCS over Broca's area in three patients with chronic aphasia and motor speech disorders. In a design similar to that of Boggio et al. (2007) repetition training was provided concurrently with the

20 minutes of active tDCS stimulation (or sham) over five days for each stimulation type with a six day washout period between stimulation types to allow neuromodulatory effects to dissipate. The participants showed improvements in articulatory accuracy of target stimuli in both the sham and active tDCS conditions at a one week follow-up session, with improvement in the active tDCS condition significantly greater than in the sham condition. In a two month follow up, improvement was maintained for the participants in the active tDCS condition only.

Marangolo et al. (2013) compared sham tDCS to bihemispheric active tDCS (cathode over right Broca's area homologue and anode over left Broca's area). Ipsilesional anodal tDCS (2mA, for 20 minutes) was applied to upregulate cortical excitability in the damaged left hemisphere with concurrent contralesional right cathodal stimulation. Cathodal stimulation (2mA for 20 minutes) was applied over the right Broca's homologue to down regulate its function. Speech/language therapy was provided concurrently in both the sham and active tDCS stimulation conditions for ten consecutive days each. There was a 14 day washout period between conditions and the two conditions were counterbalanced. Measures of speed and accuracy of both trained and untrained speech stimuli of syllable, word, and sentence-length repetition tasks improved only after active tDCS stimulation. With this limited evidence, it does seem possible that tDCS with therapy for speech motor control may follow the limb literature but more extensive research is required to confirm this pattern.

tDCS studies of language effects in healthy individuals

The extension of tDCS plus motor therapy in the limb literature to that of another motor domain, speech motor control, is logical. But there is also evidence that language in healthy populations can be affected by tDCS coupled with targeted language therapy (Meinzer et al., 2014; Cattaneo, Pisoni and Papagno, 2011; Fertonani et al., 2010; Sparing, Dafotakis, Meister, Thirugnanasambandam, and Fink, 2008; Fregni et al., 2005; Iyer et al., 2005). As with motor studies, several parameters of tDCS stimulation appear to play a critical role in the outcomes obtained in language studies. These include site and polarity of tDCS, and the frequency and timing of stimulation.

Meinzer et al. (2014) assessed the effects of multiple and consecutive tDCS sessions on vocabulary learning. Healthy volunteers were randomly assigned to acquire novel vocabulary (non-words) to name both familiar and unfamiliar objects. One group received 1mA active tDCS (anode over left posterior temporo-parietal junction at EEG position Cp5, cathode over right supraorbital ridge) while the other received sham tDCS. The stimulation (or sham condition) was administered during the learning phase in which participants in both conditions were asked to memorize the non-word/object picture pairs over the duration of five consecutive days. Participants were tested with two memory tasks, free recall of learned vocabulary and forced choice recognition, immediately after each training session (Meinzer et al., 2014). One week later they were retested for retention of the vocabulary learned. Use of anodal tDCS

facilitated new language learning as compared with sham stimulation for both familiar and novel objects (Meinzer et al., 2014). More specifically, anodal tDCS led to more rapid acquisition of "vocabulary items", and allowed participants to reach ceiling levels with fewer trials and achieve more accurate responses on recognition tasks (Meinzer et al., 2014). Additionally, the effects were sustained at the one week follow-up assessment only for those in the active tDCS group.

Both the site of electrode placement and the polarity of stimulation influenced results in a study measuring verbal working memory in healthy participants. A list of letters was presented one at a time on a computer screen and participants were asked to identify whether a given letter was identical to the one presented three letters back. Stimulation over the left dorsolateral prefrontal cortex (DLPFC) was compared to stimulation over the primary motor cortex (M1). In this design 1mA of tDCS was provided for 10 minutes over the left DLPFC or left M1 in each active condition (anodal and cathodal) with the reference electrode on the contralateral supraorbital ridge. Sham replicated the active electrode placement but tDCS stimulation was turned off after 5 seconds. (Fregni et al., 2005). The order of active and sham conditions was counterbalanced across participants and the conditions were separated by a 60 minute washout period. While the DLPFC is critical to working memory tasks similar to those in the outcome measure, M1 is instead associated with motor control. A main effect of site was reported, with DLPFC stimulation associated with better verbal working memory than M1 stimulation. A main effect of

stimulation type was also found, with anodal stimulation better than cathodal or sham. Results are consistent with differential effects of tDCS based on site and polarity with anodal stimulation of the dorsolateral pre-frontal cortex showing the strongest effect for working memory. This illustrates how crucial the selection of montage variables such as electrode placement and polarity are in achieving the desired outcomes.

Another line of language research that highlights the importance of the site and polarity of stimulation examined category naming, or 'semantic fluency' (Cattaneo, Pisoni and Papagno, 2011; Iyer et al., 2005). Category naming is typically assessed with a timed word generation task in which participants are asked to produce as many exemplars from a given category as possible in one minute (i.e., animals, tools, types of transportation). Cattaneo et al. (2011) reported that participants produced significantly more items after receiving anodal tDCS than after sham tDCS. Crucially, no improvement on a visuospatial control task was reported following stimulation, reflecting the specificity of tDCS on behavioral measures and suggesting that language improvement is not due to a general improvement in cognitive function. An additional control experiment showed that this outcome was specific to anodal stimulation over *left* Broca's area. Those who received anodal tDCS applied over the right Broca's homologue (with the same conditions as the group receiving left tDCS) did not exhibit significant improvement in category naming.

Anodal stimulation to other left hemisphere regions associated with language provides additional support for the influence of tDCS on language-related behaviors. Sparing, Dafotakis, Meister, Thirugnanasambandam, and Fink (2008) measured the reaction time of healthy participants during confrontation naming of black-and-white line drawings depicting everyday objects. Responses were significantly faster after anodal tDCS was applied over the left posterior perisylvian region – approximately Wernicke's area—than cathodal or sham stimulation of the same region or anodal stimulation of the homologous region of the right hemisphere. Similarly, Fertonani et al. (2010) showed that anodal tDCS of the left DLPFC improved naming response time, while sham or cathodal stimulation over the same region did not. Anodal stimulation of the right DLPFC resulted in increased naming latency as compared to the anodal stimulation of the left DLPFC.

In another study with healthy participants, Fiori et al. (2011) investigated the effects of tDCS on associative verbal learning under three stimulation conditions (one session each of anode over Wernicke's area; sham over Wernicke's area; and anode over the right occipito-parietal area). Participants learned 20 non-words arbitrarily assigned to pictures under each stimulation condition. The results revealed that these healthy individuals experienced a facilitative effect in reaction time but not naming accuracy after anodal stimulation over Wernicke's area (left hemisphere). Right hemisphere stimulation and sham stimulation over the left hemisphere showed no significant effects.

Shorter latencies were noted during naming with anodal tDCS than with sham stimulation (Fiori et al., 2011). The aforementioned studies reviewed show that anodal tDCS, when applied to specific language-related brain regions of healthy participants, can induce improvement in confrontation naming; category naming; semantic fluency; and verbal fluency. These studies inspire investigation into whether tDCS may enhance language therapy in chronic stroke populations.

tDCS studies of language in impaired individuals

There are many variables that may affect the outcome of tDCS studies in the treatment of aphasia. Decisions include where to place the anode and cathode; whether to use multiple electrodes; their size and the strength of current introduced. These decisions depend on a number of factors including the site and size of the lesion and the behaviors targeted for neuromodulation (Galletta, Conner, Vogel-Eyny & Marangolo, 2016). The individual's time post stroke and their stage within the recovery course of aphasia is an additional consideration (Hamilton, Chrysikou & Coslett, 2011; Cherney & Small, 2006). With all of these variables, there might not be only a single montage that supports aphasia recovery. Neuroplasticity in recovery is thought to occur by ipsilateral perilesional cortex or contralateral homotopic language areas subsuming the activities of the cortical area damaged by the lesion. These processes may also vary as individuals heal. Whereas right homotopic regions may be the initial area to be recruited (Blank, Bird, Turkheimer & Wise, 2003) due to release of

transcallosal inhibition (Turkeltaub, Messing, Norise & Hamilton, 2011; Lang, Nitsche, Paulus, Rothwell & Lemon, 2004), later recovery appears to be best facilitated by a return of language function to the left perilesional cortex (Bonilha, Gleichgerrcht, Nesland, Rorden & Fridriksson, 2016; Fridriksson, Richardson, Fillmore & Cai, 2012; Hamilton, Chrysikou & Coslett, 2011).

Studies have reported a benefit of active tDCS with the anode placed over the damaged left hemisphere (Fridriksson et al., 2011; Fiori et al., 2010; Baker et al., 2010). Baker et al. (2010) used tDCS with the anode over left hemisphere cortex in individuals with chronic aphasia using a crossover design. The stimulation sites were identified separately for each individual as the area of maximal activity on a naming task during fMRI. In their crossover design, participants received sham or active tDCS (20 minutes at 1mA) during a 20 minute computerized anomia treatment therapy for five consecutive days. Each condition was followed by a one week washout period prior to administering the next condition. Picture naming accuracy was significantly improved following active tDCS condition as compared to the sham condition, with the gains maintained on follow-up testing one week later. Those who derived the most benefit received anodal stimulation closest to the perilesional area, thereby indicating the importance of choosing the best site of stimulation for improved language outcomes.

Fridriksson et al. (2011) examined the effects of active and sham tDCS on the reaction time of object naming in people with chronic aphasia. The anode was

placed over the left perilesional cortex determined individually using fMRI following the protocol of Baker et al. (2010) and the cathode over the contralateral forehead. The researchers administered 20 minutes of a computerized anomia treatment concurrent with both five consecutive days of active tDCS and five consecutive days of sham tDCS conditions separated by one week in a crossover design based on the work of Baker et al. (2010). The results indicated that language treatment with active tDCS reduced the reaction time in the naming of trained items both immediately after treatment and at three weeks follow-up testing, as compared to sham (Fridriksson et al., 2011). Taken together, these studies demonstrated that active tDCS with the anode over the damaged hemisphere during anomia training enhances the effects of such training. This is a critical result for the present work as Study 2 involves a similar training approach.

While the *anode* was placed over the left hemisphere in the studies described above, Monti et al. (2008) used a single 10 minute session of 2mA tDCS with the *cathode* placed over left hemisphere Broca's area. These participants with chronic aphasia exhibited increased naming after tDCS, as compared to their control performance before tDCS. In contrast, those who received sham tDCS and active tDCS with the anode over left Broca's area did not significantly improve in naming abilities. This result is unexpected given the prior evidence that stroke rehabilitation is enhanced from the anode placed ipsilesionally (from both the aphasia and motor literature discussed above). Thus, it is likely that the effect of polarity on neural activity is complicated, especially

in damaged brains that may rely on compensatory processes engaging broader bilateral networks of activation after injury (Jacobson et al., 2012) than what is typically seen in healthy individuals.

A study by Flöel et al. (2011) further illustrates these complexities. They performed a randomized double-blind crossover design comparing anodal (1mA), cathodal (1mA), and sham stimulation over the *right* temporo-parietal cortex in patients with aphasia with three week washout periods between conditions. Location of the reference electrode was unspecified. Participants received two hours of naming therapy concurrently with each of the tDCS conditions administered during the first 20 minutes. Participants showed improvement in naming ability in both the anodal and cathodal conditions, while no improvements were observed after sham stimulation. However, active tDCS with the anode over the right hemisphere led to the largest effect size in naming improvement in those participants with the poorest baseline Aachen Aphasia Test (a German standardized aphasia battery) scores and persisted at follow-up testing conducted 2 weeks after stimulation. These results suggest that like anodal stimulation over left perilesional cortex, anodal stimulation over the right hemisphere can also improve naming performance in certain populations.

The state of the tDCS and aphasia literature reviewed above shows a promising, albeit complicated interaction between polarity, site of stimulation and language intervention. Results from the studies reported above, investigated in the chronic stage of stroke recovery, were all encouraging. Unfortunately, more

recent evidence garnered from a study of 58 people in the subacute phase of stroke (< 3 months post stroke) found no difference between performance on tests of naming and expressive language for those receiving active tDCS (1mA anode over ipsilesional inferior frontal gyrus) as compared with sham tDCS (Spielmann, van de Sandt-Koenderman, Heijenbrok, Kal & Ribbers (2018). It remains an open question as to what populations may or may not benefit from the use of tDCS as an adjuvant to aphasia therapy. The many variables involved in both tDCS and language recovery create a number of potential interactions which will need to be teased apart in order to judiciously use this technology to improve outcomes in aphasia.

Interconnection between motor and language systems

Language and motor cortices are proximal in the left cerebrum and as such may be affected simultaneously by disruption of blood flow in stroke (Pulvermüller, Hauk, Nikulin, & Ilmoniemi, 2005). Similarly, tDCS stimulation of one of these areas may affect the other due to the lack of focal specificity associated with this neuromodulatory technique (Edwards, Cortes, Datta, Minhas, Wasserman & Bikson, 2013). Post stroke, individuals are left with damaged cortical structures and less remaining healthy cortical regions to subsume both language and motor functions. Therefore, it would seem intuitive that both functions may compete for the use of remaining intact neural substrate, but a study by Primaßin, Scholtes, Heim, Huber, Neuschäfer, Binkofski, et al. (2015) found a facilitatory effect of motor and language treatment. Additional studies

support this finding. This apparent cross domain synergy was confirmed by both Rodriguez, McCabe, Nocera & Reilly (2012) and Harnish, Meinzer, Trinastic & Page (2009), who found that the combination of motor and language therapy benefited both functions.

Further it has been shown that anodal stimulation over left M1 can improve motor speech and category naming in healthy older adults and in post-stroke aphasia (Meinzer et al., 2014, Meinzer et al., 2016). Evidence also supports that participants receiving motor rehabilitation alone may achieve a measureable increase in speech or language production as a side effect. Hesse et al. (2007) found that 4 of 5 people in the sub-acute phase of aphasia/apraxia of speech (4-8 week post stroke) improved language on Aachen Aphasia Battery Scores, a standardized aphasia battery. Their participants received anodal tDCS (1.5mA over left ipsilesional motor cortex, cathode over contralateral orbit) for the initial 7 minutes of a concurrent 20 minute robotic arm therapy resulted in measureable language improvements in acquired aphasia. Participants received a total of 30 twenty minute sessions (5x week x 6 weeks). To date there have been no further studies or replications of the Hesse et al. (2007) study.

In this dissertation, the effect of tDCS preceding robotic right arm motor practice on language in the chronic stage of recovery was investigated. The site of electrode positioning over the primary motor cortex was informed by the interconnectedness of the motor and language cortices in healthy neural substrate. This, coupled with right upper extremity repetitive practice was predicted to

stimulate motor neurons innervating the right arm, which may increase word retrieval (Hesse et al., 2007). This intervention was predicted to increase the production of action words (those associated with movement) over object words (not associated with movement) or to more generally improve oral motor speech production. Perilesional M1 appears to be a suitable tDCS stimulation site due to its physical proximity to language cortex and the data regarding the possibility of 'spill over' effects of motor therapy on language (Fadiga & Craighero, 2006).

An additional consideration of this dissertation was to potentially provide data to address the theory of embodied semantics (detailed below) by directly comparing whether words associated with movement were preferentially affected by tDCS treatment, relative to object wordsSome views hold that these motor neurons are part of the network activated during lexical access of action words, with varying opinions about the importance of the role they play. If the role is as strong as some have suggested (Pulvermüller, 2013) then activating these neurons should differentially enhance lexical retrieval for action words. (i.e., kick, throw). A general facilitatory effect on oral motor control (e.g., diadochokinetic rate and accuracy of production of words of increasing length) may also result due to the cortical proximity of the motor speech areas to primary motor cortex.

Semantic embodiment theories posit that motor neurons active during word learning become a permanent part of that word's neural network.
One view among cognitive scientists regarding the physical instantiation of semantic networks (Gainotti, 2013; Pulvermüller, 2013) posits that the semantic

neural networks of action words are embodied within the sensorimotor system. If true, then when action words (as opposed to object words) are spoken, the motor neurons which are contained within those networks are activated (Pulvermüller, 2005) because semantic networks for action words would include motor neurons as part of their distribution, whereas non-action related object word networks would not (Hebb, 1949; Damasio, 1989, 1990; Pulvermüller,1996). A nascent conceptual language system would develop concurrent with motoric interactions such that children learn words and meanings embedded within an environment and context. For example, learning a word such as *throw* typically occurs within the context of playing with a ball while simultaneously performing a sequence of motor movements to propel the ball through the air. In this "embodied" view of semantic networks, motor neurons active during such motorically contextualized word learning would become a permanent part of the semantic neural network for the word *throw*.

One consequence of embodiment could be that the semantic network for the word "throw" could malfunction if those same motor neurons for the arm/hand were to be damaged as in acquired neurological impairments.

The focus in the current work is on why objects and actions might be differentially affected (dissociate) in aphasia (Miceli, Silveri, Nocentini, and Caramazza, 1988; Vigliocco, Vinson, Druks, Barber and Cappa, 2011). These dissociations have been used to study the organization of semantic concepts within the human brain. Converging evidence from brain imaging and TMS

studies seem to support this distinction as occurring at the level of neural networks (Perani, Cappa, Schnur, Tettamanti, Collina, Rosa, and Fazio, 1999; Pulvermüller, Hauk, Nikulin, and Ilmoniemi, 2005). When participants undergoing fMRI assessment are exposed to action words such as "kick", brain regions for the leg motor cortex show activation (Hauk, Johnsrude and Pulvermüller, 2004). Similarly, when confronted with pictures of ice cream, the brains of participants in an fMRI study showed activation in regions involving taste (Simmons, Martin, and Barsalou, 2005; Simmons et al., 2013).

Mahon (2015), however, cautions that fMRI neural activation in the regions associated with sensorimotor systems in these examples may not be a direct indication of neural instantiation. They may instead be a product of cascading activation originating from amodal conceptual representations to the sensorimotor system. This is likened to cascading activation of the phonology of alternate object names when a semantic selection is made (i.e., the phonemes of "sofa" are activated in addition to those of "couch") when confronted with a three seated piece of living room furniture (Peterson & Savoy, 1998). Just as interactivity between the semantic and phonological systems does not imply that the phonological level contains semantic information or vice versa, the fact that specific regions of the sensorimotor system are activated, does not imply that is the seat of conceptual or semantic representations. A weaker version of embodied cognition only requires that conceptual systems map into or are grounded in sensorimotor representations which Mahon & Caramazza (2008) termed

grounding by interaction. This allows that concepts are not stored directly within the sensorimotor system but interact easily with the action-perceptual systems in adjacent neural regions. This has been found in the visual perceptual system for color. While color perception was activated in the posterior regions of the occipital lobe, semantic knowledge of color was activated more anteriorly (Martin, 2009; Thompson-Schill, 2003). This is reminiscent of the of 'spill over' effects of motor therapy on language (Fadiga & Craighero, 2006) discussed earlier in this section. Chapter III focuses on the language effects of motor therapy and attempts to provide additional evidence as to whether motor activation stimulates action words as predicted by embodied semantics. But given the arguments by Mahon, even preferential improvement of action words over object words could be explained by cortical proximity and the interactivity of adjacent neural substrate.

tDCS timing effects in aphasia treatment

The optimization of dosage, timing, intensity and polarity of tDCS to treat chronic stroke patients is still being explored in all branches of rehabilitation (physical, occupational and speech/language therapy). In particular, literature is lacking on the influence of when tDCS stimulation and speech/language therapy is most beneficial. Many studies of tDCS and speech/language outcomes have shown a benefit when used concurrently (Meinzer, Darkow, Lindenberg & Flöel , 2016; Fiori et al. 2011; Baker, 2010; Monti et al, 2008). The issue of timing has been addressed more explicitly in the motor literature. Active tDCS immediately

preceding robotic hemiplegia therapy has been found to improve certain aspects of motor performance. After a single session of anodal tDCS (1mA x 20 minutes), upper extremity smoothness measures were significantly improved when administered immediately prior to robotic hemiplegia training but showed no benefit when administered concurrent to motor training and actually reduced speed when tDCS was administered after training (Giacobbe et al., 2013).

The timing of speech/language therapy in regard to tDCS administration was addressed directly by Volpato et al. (2013). Speech therapy was provided offline (at least 90 minutes before or after tDCS administration). Results showed that offline treatment performance was not enhanced by prior tDCS stimulation. But as noted, therapy was not provided during the 60 – 90 minute window of time when the electrophysiological effects from the prior administration of tDCS would be expected to prime language improvement (Nitsche & Paulus 2000, 2001). This makes interpretation of timing effects difficult since tDCS and therapy were treated as functionally separate events, and timing parameters were not systematically varied. Since one posited mechanism of action for tDCS is priming of the underlying cortex (Edwards et al., 2009; Stinear, Coxon, Fleming & Byblow , 2008), it may be that the motor therapy was given outside the period when neuromodulatory effects remained. If therapy was given hours or days after tDCS, then depolarization of the language cortex would no longer remain, and therefore no observable benefit of tDCS could have been measured. This leaves an open question of whether tDCS stimulation *immediately* preceding aphasia

therapy would improve speech and language outcomes as compared to tDCS during aphasia therapy.

If the effects on speech and language follow principles identified in the motor literature, then it would be expected that behavioral treatment immediately following tDCS may prove beneficial. That is, data from motor treatment studies addressing the timing of tDCS in relation to treatment for upper extremity rehabilitation have found that motor therapy provided immediately after 20 minutes of anodal tDCS improved motor smoothness outcomes to a greater extent than when therapy was provided during tDCS administration (Giacobbe et al., 2013). However, given the positive effects of stimulation during speech treatment, and the timing effects seen by Giacobbe et al. this remains an important, but unexplored question. This work focuses on filling that research gap.

Research questions

The specific research questions addressed in this work are:

1) Does the combination of anodal (2mA x 20 minutes, 3 times per week for 12 weeks) tDCS over left primary motor cortex immediately preceding robotic hemiplegia therapy lead to measureable increases on speech and language outcome measures in participants with chronic aphasia as compared to sham tDCS?

2) Does the relative timing of tDCS and aphasia therapy affect the word-finding abilities of people with chronic aphasia?

The first research question was addressed by comparing two groups of participants in the chronic stage of stoke. Both groups received right repetitive upper limb robotic practice 3 times per week for 12 weeks with one group receiving active tDCS and the other sham tDCS preceding motor therapy. Speech and language outcome measures were taken before and after completion of the entire 12 week protocol. The second research question was investigated using two groups of participants in a crossover design. One group received aphasia therapy during tDCS and the other received aphasia therapy *immediately* after receiving tDCS. Particpants received both anodal and sham tDCS with a week between conditions with the order of tDCS conditions counterbalanced.

Hypotheses for current work

For research question one, it was predicted that the group receiving 2mA anodal tDCS preceding robotic hemiplegia therapy would show greater improvement in language than those receiving sham tDCS. The results of this investigation may indicate certain aspects of speech and language that are most responsive to this intervention. Due to the site of stimulation and the inclusion of motor treatment this intervention may also increase word retrieval for words related to motor movements (i.e., verbs/actions) or promote a general facilitatory effect on speech motor control.

For the second research question it was predicted that the group receiving 2mA anodal tDCS *immediately preceding* aphasia therapy would increase

performance on all speech and language outcome measures more than the group receiving aphasia therapy *during* anodal tDCS. Furthermore it was expected that the anodal condition with either timing would result in better outcome measures than sham tDCS with either timing. To the best of my knowledge, these findings would be the first to demonstrate that tDCS applied immediately before aphasia therapy promotes language outcomes. The predicted results would demonstrate a cross-domain similarity in the behavior of motor and speech/language rehabilitation that has not been previously reported.

CHAPTER III

STUDY ONE: SPEECH AND LANGUAGE EFFECTS OF MOTOR REHABILITATION

Introduction

Study One examined whether intensive right repetitive upper extremity rehabilitation with sham or active tDCS in people with *chronic* stroke synergistically enhances speech and language performance *without* speech/language intervention. This study focuses on compelling evidence from Hesse et al. (2007) who reported anodal tDCS (1.5 mA over ipsilesional hand cortex, cathode over contralateral orbit) paired with robotic right arm treatment (20 minutes, 5 times per week x 6 weeks, 30 total sessions) may enhance language production in people in the sub-acute phase of aphasia. They observed that 4 out of 5 people with aphasia unexpectedly improved on a standardized aphasia battery after performing robotic arm training with active tDCS montage.

The speech and language skills of people in the chronic stage of stroke recovery (> 6 months) were measured before and after receiving multiple sessions of right repetitive upper extremity motor therapy immediately preceded by sham or active tDCS for 36 sessions (3 times per week for 12 weeks). The

motor intervention was provided as part of a larger multisite randomized control trial with active (anodal 2mA x 20 minutes) or sham tDCS over the left primary motor cortex centered at approximately C3 using the EEG 10/20 referencing system (Jurcak, Tsuzuki & Dan, 2007) preceding robotic right hemiplegia therapy. The participants were prospectively enrolled in the speech and language study if they exhibited aphasia and/or apraxia of speech along with right hemiplegia.

The speech and language outcomes in chronic aphasia were assessed after 36 sessions of active or sham tDCS applied over the left primary motor cortex (anode over M1, damaged hemisphere) preceding robotic hemiplegia therapy in the absence of direct language therapy. A comprehensive speech and language battery was assembled to assess a wide variety of areas of potential language and motor speech changes following this protocol. The posited mechanism of improvement is that tDCS stimulation over left M1 in combination with motor therapy would result in depolarization of left hemisphere cortical regions (Nitsche & Paulus, 2000). Neighboring primary motor cortex of the arm/hand (over which the anode was placed), including the oral motor cortex and Broca's area would receive neuromodulation.

Thus, it was expected that stimulating M1 would affect cortical areas associated with speech and/or language (Meinzer et al., 2014). With that in mind, a possible outcome of the combined tDCS and motor stimulation would be a general facilitatory effect over oral motor control (e.g., diadochokinetic rate and

accuracy of production of words of increasing length) or word-finding (e.g., confrontation naming and category naming). This method may also support semantic embodiment theories discussed above, which could preferentially improve the production of action words (i.e., kick, throw) over objects words not normally associated with movement (i.e., oven, pool).

Method

Participants

Nineteen participants with chronic aphasia and/or apraxia of speech subsequent to single left-sided ischemic strokes were recruited through Burke Medical Research Institute and The Feinstein Institute for Medical Research between March 2013 and April 2014. These participants were recruited from an ongoing NIH-funded randomized multisite clinical trial contrasting anodal and sham transcranial direct current stimulation (tDCS) preceding robotic hemiplegia therapy for right hemiplegia. All participants were in the chronic stage of stroke recovery (> 6 months post-stroke). Exclusion criteria for the multisite study included right-sided stroke, multiple/non-focal strokes, hemorrhagic stroke, history of seizures, the presence of other neurological or psychiatric conditions or implants affected by electrical current (i.e., cardiac pacemakers). The researchers at each of the two sites verified the presence or absence of these inclusion and exclusion criteria.

To be included in the study of language outcomes, participants were required to be native English speakers. Non-native speakers were included in only the motor speech outcomes. The range of baseline scores on the Western Aphasia Battery-Revised Aphasia Quotient (WAB-R AQ) was 60 -92 which are considered moderate to mild, with 93.8 considered to reflect normal language functioning (Kertesz, 2006). Non-native English speakers were included in the motor speech outcomes of the Apraxia Battery for Adults-2 (ABA-2; Dabul, 2000). Hearing was judged to be adequate for participation in the speech and language portions of testing if participants were able to perform speech and language tasks with typical conversational timing in a quiet environment and did not ask repeatedly for the stimuli to be re-administered. Since many older adults in the age range of our participants experience presbycusis, which affects hearing acuity at high frequencies, it was not deemed necessary to exclude participants with the mild high frequency losses characteristic of typical presbycusis.

As part of the multisite clinical study, participants were randomly assigned to receive either 2mA anodal tDCS or sham tDCS. Although randomization was used in the multisite robotic arm study, the subsample of participants in the speech and language testing exhibited differences in age and time post onset of stroke due to the stratification process already in place (Table 3.1). The mean age for the group receiving active tDCS (N=10) was 61.7 years (range 48 -76), while the mean age of the group receiving sham tDCS (N=9) was 69 years (range 49-81). Although randomization was used in the robotic arm study, independent

Demographic Information for Study One Participants

Anodal or Sham	Age (Years)	Months Post Onset	Gender	Ethnicity	Handedness	Stroke Type
A1	63	264	M	Caucasian	Right	Cortical
A2	76	141	M	Caucasian	Left	Subcortical
A3	61	284	M	Asian	Right	Cortical/ Mixed
A4	48	115	F	Caucasian	Right	Cortical
A5	65	283	F	Caucasian	Right	Cortical
A6	76	26	M	Caucasian	Right	Mixed
A7	70	105	M	Caucasian	Right	Mixed
A8	62	100	M	Caucasian	Right	Cortical
A9	48	584	F	Caucasian	Right	Subcortical
A10	48	792	F	Caucasian	Right	Cortical / Mixed
S1	75	26	F	African American	Right	Subcortical
S2	78	9	M	Caucasian	Right	Subcortical
S3	81	12	F	Caucasian	Right	Cortical
S4	72	120	M	Caucasian	Right	Cortical
S5	69	47	M	Caucasian	Right	Cortical
S6	49	183	F	Caucasian	Right	Cortical/ Mixed
S7	70	100	M	Indian	Right,	Cortical
S8	64	20	M	Caucasian	Right	Mixed
S9	64	36	M	African American	Right	Mixed

Table 3.1 shows variables related to each participant.

samples t-test showed that the subsample of participants in the speech and language testing exhibited significant differences in time post onset of stroke (Table 3.1). The active tDCS group had a significantly higher mean time post onset (M = 269.40, SD = 242.17) than the sham group (M = 61.44, SD = 59.91), $t(17) = 2.50$, $p = 0.023$. For some participants, data were not available for every task due to equipment problems or attrition.

Speech and Language Evaluations

To evaluate the extent to which the motor treatment with active vs. sham tDCS affected the speech and language performance of the participants, they were presented with a battery of tests to evaluate their speech and language ability. The battery was administered both before and after the 12 week treatment protocol, and was designed to allow investigation of a variety of speech and language abilities, using both common tools in clinical assessment as well as tasks designed for this study to evaluate specific aspects of the participants' performance. This section introduces these measures, and the precise timing of their administration will be described in the procedure.

Language outcome measures.

Comprehensive Speech/Language Battery. To develop a clinical picture of aphasia type and severity the Western Aphasia Battery- Revised (WAB-R, Kertesz, 2006) was administered. The WAB-R provides a composite profile of language ability which is used to classify type based on the performance on

various subtests. A measure of overall severity, the Aphasia Quotient (AQ), can also be calculated from the WAB-R results. The AQ indicates severity on a scale of 0-100, with 0 representing the most severe aphasia. Scores above 93.8 are considered to be within the normal range. Gains of five points or greater are considered functionally significant (Katz and Wertz, 1997).

Confrontation naming performance. The Philadelphia Naming Test-Short Form (PNT-30; Walker and Schwartz, 2012) is a standardized measure used to assess word-finding difficulties. In this assessment, a confrontation naming task is used whereby participants are asked to name pictured objects upon presentation. There are two matched versions (A and B), each containing 30 picture stimuli. The administration of these two versions (A and B) has been shown to be reliable (Walker and Schwartz, 2012) in assessing changes in confrontation naming over time and has the advantage of reducing practice effects (since each version contains different stimuli).

Category Naming. Rapid naming of members of specific categories often proves difficult for people with aphasia and is used as a clinical method to probe semantic processes underlying language production (Lezak, 1995; Cattaneo, Pisoni, & Papagno, 2011). In this study, participants were asked to name as many members of common categories as possible in one minute for animals, plants, transportation and tools. The change in the total number of category members named (over all categories) was compared from pre- to post-testing. Unimpaired speakers are usually able to name at least 20 members per category, 2006).

Object vs. Action Naming Test. A picture naming task was created to investigate whether word classes were differentially affected by the motor rehabilitation protocol. A 40-item confrontation naming test was created that included 10 arm-related action pictures (e.g., catch, juggle), 10 non-arm related action pictures (e.g., kick, walk), 10 objects associated with arm/hand usage (e.g., drum, comb) and 10 objects not associated with arm usage (e.g., globe, clock). Each picture was a black line drawing on a white background and was presented digitally on a laptop screen. The object and action word lists were matched list wise for length (in letters and phonemes); frequency; age of acquisition; percent name agreement and number of alternative names using data gathered from Szekely et al. (2004). Two digitized versions of the test (A and B) were created by randomly ordering the 40 pictures. One version was administered pre-treatment and the other post-treatment, with the order of administration counterbalanced across participants.

Motor Speech Outcome Measures.

Portions of the Apraxia Battery for Adults Second Edition (ABA-2, Dabul, 2000) were administered as a standardized measure of motor speech production and praxis before and after the 36 session motor therapy experimental protocol. The following subtests were administered and scored as per the ABA-2 Examiner's Manual (Dabul, 2000):

Diadochokinesis ABA – 2 Subtest 1. Diadochokinetic rate was established to document the ability to produce basic oral motor movement for rapid sequential and alternating combinations of syllables without linguistic content (e.g., "papapa"; "pataka"). The maximum number of rapid two syllable productions achieved in three seconds and three syllable productions achieved in five seconds were counted as per the instructions in the Examiner's manual of the ABA-2.

Words of Increasing Length ABA-2 Subtests 2A and B. These subtests require producing words of increasing length (e.g., "love", "loving", "lovingly"). The value used to determine AOS severity on this task is the "deterioration score" which is calculated as the difference in accuracy of production of longer words compared with shorter words. The assumption is that people with AOS will have more difficulty in oral motor planning and production of longer words as compared to shorter words. In test 2A, production of 3 syllables words is compared to the production of monosyllabic words. In test 2B, production of 4 syllable words is compared to 2 syllable words. Test 2B was only given when criteria were met as per the examiner's manual based on performance on test 2A.

Procedure

Multisite randomized clinical study

Motor therapy evaluations.

All participants were enrolled from a large randomized control trial (RCT) examining the effects of an experimental treatment of right upper extremity repetitive with active or sham tDCS on motor outcomes. A double-blind within-subjects repeated-measures study design was used to evaluate changes in motor outcome measures after 12 weeks of non-invasive brain stimulation and right robotic upper extremity therapy. Participants received this combination of tDCS and robotic hemiplegia therapy three times per week for twelve weeks (36 total sessions) immediately after 20 minutes of 2mA anodal tDCS or sham tDCS. Active tDCS of 2mA anodal or sham tDCS was delivered over the damaged left primary motor cortex preceding robotic hemiplegia therapy. As part of the large multisite clinical trial arm, shoulder and wrist motor measures were taken pre- and post- study by a licensed and certified occupational therapist or a trained researcher. No speech/language therapy was provided as part of the large multisite motor study; participants experienced only the tDCS and robotic hemiplegia therapy described in the previous paragraph. However, since the participants were originally enrolled in the multisite randomized clinical trial for motor therapy, they had not been asked to disengage from their standard speech support or therapy. Participants A4, A5, A6, A8, S7 and S9 continued to attend university or

community aphasia support groups for socialization without receiving individual speech therapy. In these cases, their attendance at the programs had been stable for over a year and had not resulted in any reported speech/language improvements. S6 and S8 received individual speech therapy 1-2 days per week on off days from this study. It was assumed that sham participants would not benefit from tDCS neuromodulation, thus there was no concern that neuromodulation could have boosted any therapeutic effect of behavioral speech therapy.

Robotic motor therapy for right hemiplegia. The Massachusetts Institute of Technology (MIT) Manus shoulder- elbow robot (Figure 2) and wrist-hand robots (Krebs et al 1998; Krebs et al 2007) were used for 36 total hours of right upper extremity therapy supervised by trained researchers. Participants were seen three times per week for twelve weeks. During robotic hemiplegia therapy participants were seated and positioned so that visual displays appeared at eye level. Computer displayed visual targets served as cues for direction and range of movement. Participants moved the robotic arms in the direction and range indicated on a computer screen in order to follow a target in a video game-like fashion.

tDCS procedure. In a 1x1 tDCS configuration, electrical current travels from the anode to the cathode to complete an electrical circuit. To stimulate the neurons of the underlying cortex, the weak electrical current generated from tDCS must penetrate the scalp, skull, meninges and cerebrospinal fluid. Thus, it was

crucial that the trained research staff for the multisite trial ensured that the electrodes were placed properly on the head. To establish a better seal between the electrodes and scalp and to increase conductivity, the electrodes were inserted into saline soaked sponges (5x7cm). These sponges containing the electrodes were then placed on the surface of the participant's head over their hair (Iyer, Mattu, Grafman, Lomarev & Sato, 2005). A positioning headband was used to retain their position throughout the experiment (Figure 3.2). Electrodes were positioned with the anode placed over the left primary motor cortex and the cathode over the right supraorbital ridge (Figure 3.2). In both active and sham conditions, participants were in a seated position and completed the tDCS (active or sham) stimulation immediately prior to robotic training.

Active stimulation. Participants in the active stimulation condition received 20 minutes of 2mA anodal tDCS stimulation through a Soterix tDCS device using a 1x1 electrode montage. The anode and cathode were inserted into 35cm^2 saline soaked sponges. Then the anode was placed over left primary motor cortex 5cm lateral to the vertex of the skull along the interaural line (centered at approximately C3 using the EEG 10/20 referencing system; Jurcak, Tsuzuki & Dan, 2007) and the cathode was placed over the right supraorbital ridge (Figure 3.1).

Depiction of the 1x1 electrode montage used in both dissertation studies.

Figure 3.1.Depiction of the electrode montage used in both Study 1 and Study 2. The red (upper) sponge represents the anodal electrode placed over the left primary motor cortex and the blue (frontal) sponge represents the cathode placed over the right supraorbital ridge.

Sham stimulation. Sham tDCS was used as a placebo condition in this investigation. Sham replicated the placement of electrodes and sensation (often tingling or itching) experienced by participants undergoing active anodal or cathodal tDCS stimulation without the effect of modulating cortical activity (Ambrus, Al-Moyed, Chaieb, Sarp, Antal, & Paulus, 2012). During this study, sham tDCS was achieved by ramping the Soterix tDCS device up to 2mA over 30 seconds, maintained for five seconds and then slowly turned off (Ambrus et al., 2012).

Speech/language assessment procedures

Data collection. The data collection for the larger R01 study was conducted under the Ethics Committee of Burke Medical Research Institute and

the Institutional Review Board of Feinstein Institute for Medical Research. The two sites followed the same protocol for all evaluations. De-identified data provided from the larger study at these sites was used in this research. As such, New York University's Institutional Review Board considered this data exempt from the University's Committee on Activities Involving Human Subjects' oversight. Participants signed an informed consent document allowing speech and language testing and permission for audio and video recording of production tasks for educational purposes. No incentives were offered for participation in this study. Audiovisual recording was conducted in a quiet testing environment. Audio was recorded on either a Sony ICD-UX70 or Olympus VN-701pc. Videos were recorded on either an iPhone 4s or a Kodak Playsport ZX5. Sound files were processed and analyzed using Praat 5.3 software (Boersma and Weenink, 2013).

Administration of speech/language measures. The speech and language measures listed above, were administered pre-intervention and repeated post-intervention by a licensed and certified Speech/Language Pathologist (SLP). In the case of the Philadelphia Naming Test-Short Form, fourteen of the participants were given either the A or B version at baseline and the alternate list at post-testing. For these participants, the order of administration was counterbalanced and at least one day passed between administrations. Later in the study, the method was changed so that both A and B versions were administered at both time periods (at least one day apart) to better account for individual variability.

Again, the order of list presentation was counterbalanced. For these later participants, the two baseline scores were averaged as were the two post-test scores so as to compare mean baseline performance to mean post-test performance and these participants are marked with asterisks in Table 3.4.

Data analysis.

Effect of tDCS with repetitive right upper extremity motor therapy on speech/language outcome measures. To determine whether tDCS coupled with repetitive right upper extremity motor therapy affects performance on speech/language outcome measures, participants receiving active and sham tDCS were compared. Pre-and post-study scores were obtained for speech/language measures discussed in the procedure section above. Dependent measures were WAB-AQ, PNT-30, Object and Action Test, category naming and the DDK and WIL subtests of the ABA-2. 2x2 repeated-measures ANOVAs with between subject factors of tDCS condition (sham vs. active) and within subject factors of time (pre- vs. post-tx) were used to compare speech/language outcomes given anodal tDCS or sham tDCS with right upper extremity motor training, in the absence of speech/language therapy.

Results

Standardized Language Outcome Measures

Western aphasia battery-r (WAB-R).

There was a main effect of time, with higher AQs at post-treatment

relative to pre-treatment ($F(1,7) = 8.85$, $p = 02$). There was no main effect of group. There was a non-significant trend towards an interaction ($F(1,7) = 3.83$, $p = .09$) between time and group, with the sham tDCS group improving by a greater magnitude than the active tDCS group. Three participants showed an improvement above or close to this threshold. One participant in the anodal group achieved a 4.6 point improvement (A8), whereas two participants in the sham group improved by 4.4 (S7) and 5.9 points (S4). The individual results for these participants are shown in bold in Table 3.2.

Repeated Measures ANOVA Results by Test: Standardized Language Outcomesess

		WAB-AQ		PNT-30 Phonemes		PNT-30 Words	
		F	Sig	F	Sig	F	Sig
Within subject effects	Pre-post	**8.85**	**0.02**	2.06	0.19	1.34	0.28
	Pre-post * Group	3.83	0.09	0.56	0.47	1.99	0.19
Between subject effects	Group (Sham vs. Anodal)	2.91	0.13	0.16	0.70	1.38	0.27
	N	9		11		11	

Table 3.2 Table shows significance levels for repeated measures ANOVAs. Bolded figures indicate statistical significance at p< .05 or lower.

Philadelphia naming test – 30 (PNT-30).

This analysis revealed no significant main effects or interactions ($p > .05$). The analysis of both words and phonemes yielded the same pattern (Tables 3.2 and 3.3).

Non-standardized Language Outcome Measures

The non-standardized measures of language reported here are category naming, object word naming and action word naming.

Category naming.

There was a main effect of time, as participants named more words in the post-tx than pre-tx phase, (F (1, 9) = 10.9, p = 0.01). There was also a significant time by group interaction (F (1, 9) = 8.07, p = 0.02). The interaction indicates that participants in the sham group showed a greater increase in the number of words named at post-test than those in the anodal group (see Table 3.3 and 3.4). There was no significant main effect of group (F (1, 9) = 0.01, p = 0.95).

Object and action naming.

This analysis revealed no significant main effects or interactions in object or action naming (Tables 3.4).

Performance on Language Measures Pre-Therapy vs. Post-Therapy

ID	WAB AQ			PNT			Category Naming		
	Pre AQ	Post AQ	Change	Pre Words	Post Words	Change	Pre Words	Post Words	Change
A4*	-	-	-	26	23	-3.0	32.5	29	-3.5
A5*	87.6	84.7	-2.9	26	26	0	24.5	22.5	-2.0
A6	91.3	90.9	-0.4	17	15	-2.0	23	29	6.0
A8	73.3	77.9	**4.6**	19	23	4.0	12	13	1.0
A9*	89.2	91.1	1.9	29	28	-1.0	29.5	33	3.5
A10*	-	-	-	27.5	28	0.5	22	25	3.0
Mean	85.4	86.2	0.8	21	21.71	-0.25	23.9	25.3	1.3
S4	71.9	77.8	**5.9**	17	20	3.0	18	25	7.0
S6*	69.5	73.4	3.9	22.5	21	-1.5	26	29	3.0
S7	75.7	80.1	**4.4**	12	21	9.0	24	36	12
S8	89.2	91.6	2.4	28	29	1.0	33	38	5.0
S9	68.7	71.5	2.8	17	18	1.0	4.0	10	6.0
Mean	75.0	78.9	3.9	19.3	21.8	2.5	21.0	27.6	6.6

Table 3.3 Reflects pre to post results. Participants marked with asterisks performed two pre-tests and two post-tests in which case the reported figures reflect their mean scores at each time-point.

Repeated Measures ANOVA Results:
Non-Standardized Language Outcome Measures

		Category Naming		Object Words		Action Words	
		F	Sig	F	Sig	F	Sig
Within subject effects	Pre-post	**10.9**	**0.01**	0.07	0.79	0.08	0.79
	Pre-post * Group	**8.07**	**0.02**	0.71	0.42	0.08	0.79
Between subject effects	Group (Sham vs. Anodal)	0.01	0.95	0.77	0.40	0.02	0.88
	N	11		11		11	

Table 3.4 shows significance levels for repeated measures ANOVAs. Bolded figures indicate statistical significance at $p < .05$ or lower.

Motor speech outcomes as measured by the ABA-2

Diadochokinetic rate (DDK).

There was a significant main effect of time, indicating an overall increase in number of syllables produced at post-test compared to pre-test (F (1, 14) = 9.49, p = 0.008). There was no main effect of group (F (1, 14) = 0.41, p = 0.54) and the interaction between time and group was not significant (Tables 3.5 and 3.6).

The scoring system of the ABA-2 was used to evaluate any clinically significant improvement using its severity classifications. No participants increased severity (declined in motor skills in these subtests) from pre-to post testing (Table 3.6). One person in each tDCS stimulation condition decreased severity over time (A1 decreased from moderate to mild apraxia of speech and S4 decreased from moderate to mild), denoted in bold in Table 3.5. For all other numerical improvements, participants remained in the same severity category.

Words of increasing length.

This analysis revealed no significant main effects or interactions (Tables 3.5 and 3.6). Two people in each of the stimulation types decreased severities. In the anodal group, A3 decreased severity on that subtest from moderate to mild and A5 decreased from mild to no deficit. In the sham group, S4 decreased severity from moderate to no AOS while S6 went from moderate to no AOS. In part B one person in the anodal group decreased from severe to no AOS, while

two people in the sham condition decreased AOS (with S3 changing from severe to mild AOS and S7 changing from mild to none). All of these improvements are bolded Table 3.5.

There were a few instances of severity level increasing (A8, S4 and S9 in part A and A3 in part B) on this subtest. Those increases are associated with an improvement in the ability to repeat shorter words without a concomitant improvement in the ability to repeat longer words. These are marked with a + superscript (Table 3.5).

	Motor Speech Measures from ABA-2														
	DDK					Words of Increasing Length: A					Words of Increasing Length: B				
ID	Pre	Severity	Post	Severity	Change	Pre	Severity	Post	Severity	Change	Pre	Severity	Post	Severity	Change
A1	9	Mild	15	Mild	6	14	Severe	14	severe	0	-	-	-	-	-
A2	8	Mild	19	Mild	11	0	none	0	none	0	0	None	0	None	0
A3	-	-	-	-	-	7	mod	2	**mild**	-5	-	-	-	-	-
A4	5	Mod	6	Mod	1	3	mild	4	mod	1	4	Mod	7	severe^{+}	3
A5	6	Mod	10.5	**Mild**	4.5	3	mild	-1	**none**	-4	6	Severe	-1	**None**	-7
A6	32	None	33	None	1	0	none	0	none	0	0	None	0	none^{+}	0
A7	20	Mild	20	Mild	0	0	none	0	none	0	1	None	1	None	0
A8	23	Mild	22	Mild	-1	0	none	2	mild	2	7	Severe	7	severe	0
A9	28	None	29	None	0	1	none	0	none	-1	2	Mild	3	Mild	1
Mean	16.4		25.6		5.6	3.1		2.3		-0.8	2.9		2.4		-0.4
S1	30	None	35	None	5	0	none	0	none	0	0	None	0	None	0
S2	16	Mild	16	Mild	0	5	mod	1	**none**	-4	1	None	2	Mild	1
S3	12	Mild	25	Mild	13	2	mild	2	mild	0	7	Severe	3	**Mild**	-4
S4	1	Severe	5	**Mod**	4	1	none	2	mild^{+}	1	3	Mod	5	mod^{+}	2
S6	10.5	Mild	12	Mild	1.5	6	mod	0	**none**	-6	15	Severe	12	severe	-3
S7	7	Mild	8	Mild	1	3	mild	2	mild	-1	3	Mild	1	**None**	-2
S8	17	Mild	17	Mild	0	0	none	0	none	0	1	None	3	mild^{+}	2
S9	12	Mild	15	Mild	3	1	none	5	mod^{+}	4	9	Severe	7	severe	-2
Mean	13.2		16.6		3.4	2.3		1.5		-0.8	4.9		4.1		-0.8

Table 3.5 Overview of performance on all motor speech outcome measures taken from the ABA-2 (Dabul, 2000).
S5 completed only the object and action naming tasks and is not included in this table.

Repeated Measures ANOVA Results by Test:
Motor Speech Measures

		Diadochokinetic Rate Subtest		Words of Increasing Length (WIL)	
		F	Sig	F	Sig
Within subject effects	Pre-post	**9.49**	**0.008**	0.07	0.79
	Pre-post * Group	0.06	0.81	0.71	0.42
Between subject effects	Group (Sham vs. Anodal)	0.41	0.54	0.77	0.40
	N	15		12	

Table 3.6 Statistics based on stroke patients treated with anodal (2mA X 20 minutes) or sham transcranial direct stipulation (tDCS) over the left primary motor cortex with repetitive right upper extremity practice. Participants were tested prior to and following 36 sessions of therapy. Table shows significance levels for repeated measures ANOVAs. Bolded figures indicate statistical significance at $p < .05$ or lower

Relationship between Motor Change and Speech/Language change

Spearman's bivariate correlation statistics were calculated to determine whether there was a relationship between participants' change in motor skills and in their change on any of the speech/language outcome measures. The Fugl-Meyer Assessment (Fugl-Meyer et al., 1975) was used as the measure of motor change. Difference scores on the FM and each speech/language measure were computed, and Spearman's bivariate correlations were conducted for the overall sample. Results are shown in Table 3.7.

Bivariate Correlations of Pre-Post Difference Scores Reflecting Changes in Motor Skills and Language Measures for all Participants

		Correl.	Sig.	N
Correlation for Motor Skills and :				
	WAB	-0.295	0.407	10
	PNT (phonics)	0.354	0.286	15
	PNT (words)	0.153	0.653	11
	Action Naming	-0.029	0.930	12
	Object Naming	0.24	0.453	12
	Category Naming	0.167	0.623	11
	DDK	0.30	0.277	15
	WIL	-0.355	0.194	15

Table 3.7. This table reflects the Spearman's bivariate correlation statistics for motor change (change in Fugl-Meyer scores) and the change from pre-to post for all language measures

None of the correlations for the entire group (active and sham groups combined) was statistically significant. Additionally, no significant correlations were present for the anodal or sham groups individually. Due to the small number of participants in each group and the lack of statistical significance, it cannot be determined whether some numerical differences would have been significant with a larger sample size.

Discussion

A group of chronic stroke patients undergoing a multisite randomized clinical trial of intensive robotic upper extremity motor therapy coupled with active or sham tDCS was tested pre-and post- motor therapy on speech/language outcomes. Hesse et al. (2007) found that unexpected measureable changes on a standardized language battery occurred for four out of five participants in an intensive robotic hemiplegia therapy in the sub acute stage of stroke recovery. No further studies have followed up on this outcome. The participants in this study were recruited for their residual right hemiplegia and were not randomized to control for specific speech/language or demographic variables. They comprised a small sample size. Despite that, we found that several participants receiving therapy in only the motor domain made measureable positive changes in an untreated cognitive domain (speech and/or language measures) without any formal speech therapy.

Specifically, within the sham group, two individuals increased more than four points on the WAB-AQ, with one increasing by 5.9 points. A five point increase is considered functionally significant (Katz and Wertz, 1997). In the category naming task requiring participants to rapidly name members of semantic categories, there were more category members overall (all categories combined) named post-test than pre-test, indicating that participation in the motor therapy may have contributed to the improvement in this skill. In addition, those in the sham group improved more over time than those in the active tDCS group. This

was an unexpected finding and may be due to the uneven sampling method (as the speech-language testing was added onto the pre-existing multisite randomized trial) or even due to a competition for cortical resources (motor vs. speech/language) during neuroplastic changes subsequent to stroke. There was also improvement in the Diadochokinetic subtest of the ABA-2 with participants producing more syllables at post-test than at pre- test. No correlation was found between the improvement in motor performance and speech/language performance.

The improvements generated in this small sample, coupled with the earlier findings of Hesse et al. (2007) justify continued systematic investigation of possible synergistic effects between motor and language cognitive domains in stroke rehabilitation. In motor treatment, the placement of tDCS over M1 of the damaged hemisphere is a logical stimulation site to promote the neuroplasticity of motor functions. In this dissertation it was posited to be a suitable site for speech/language stimulation. In most people, language is lateralized to the left cerebral hemisphere (Kneckt, et al. 2000) and most strokes causing both right motor deficits and speech/language deficits are due to lesions of the left anterior middle cerebral artery (Alexander & Schmitt, 1980). Due to the areas served by this artery, such strokes often result in both right hemiplegia and non-fluent aphasia and/or AOS. This was a common constellation of signs in the study participants. Thus, stimulation over left M1 may stimulate the remaining cortex that housed right motor function. Additionally M1, being adjacent to typical

language cortex, may also make it a prime site for the relocation of language functions. Thus left M1 may be thought of as prime cortical real estate for neuroplastic changes leading to improved motor speech and/or language. Accordingly, tDCS stimulation over this site warrants further investigation. There is some preliminary evidence of its efficacy as a stimulation site for speech/language improvement in impaired populations (Meinzer, Darkow, Lindenberg & Flöel, 2016; Branscheidt, Hoppe, Zwitserlood & Liuzzi, 2017) and in non-impaired older adults (Meinzer et al., 2014). For these reasons, the use of tDCS stimulation over left M1 is retained in Study Two, which looks at the timing of tDCS stimulation in relation to a single session of aphasia therapy.

CHAPTER IV

STUDY 2: TIMING

Introduction

Many variables in tDCS including dosage, timing, intensity and polarity as well as the chosen behavioral therapy to pair with tDCS are still being explored (Galletta et al. 2016). In the motor domain of rehabilitation after stroke the timing of tDCS in relation to motor therapy results in differential benefits to motor recovery. As discussed above, upper extremity smoothness measures significantly improved in one study when tDCS (1mA x 20 minutes) was administered *immediately preceding* robotic hemiplegia training but showed no benefit when tDCS was administered concurrent to motor training and actually reduced speed when tDCS was administered after training (Giacobbe et al., 2013). More studies are needed to confirm this finding and determine whether timing consistently impacts outcomes in this manner.

In this work, the timing of tDCS stimulation in relation to aphasia therapy was investigated to determine whether it affects word finding in people with chronic aphasia. Two groups of participants underwent aphasia therapy in both anodal (2mA x 20 minutes) and sham tDCS conditions (Table 4.2). One group received a self-administered aphasia therapy (color picture to audiovisual cue

matching task) concurrent with tDCS (During-tDCSgroup) and the other group received tDCS *immediately* before aphasia therapy (Preceding-tDCS group). As noted earlier, the positioning of the active electrode over left M1 was retained from the first study of this dissertaton. The M1 electrode placement was motivated by the interconnection of language and motor cortices as discussed above. In addition, many standard methods used in tDCS research have stemmed from motor studies and then extended to other disciplines. For example, the attribution of depolarization to anodal stimulation and hyperpolarization to cathodal stimulation derives from motor evoked potentials in the primary motor cortex devoted to the hand (Nitsche & Paulus, 2000). Subsequently, the association of anodal stimulation with excitatory capacities and cathodal stimulation with inhibitory processes has been applied to many forms of therapy (e.g. depression and analgesia [Kalu, Sexton, Loo and Ebmeier, 2012; Knotkova, Nitsche, and Cruciani, 2013]). Similarly, there is precedence for speech/language therapies being directly developed from motor therapies. For example, constraint-induced aphasia therapy (Meinzer, Elbert, Djudja, Taub and Rockstroh, 2007) was developed by modifying the principles underlying constraint-induced movement therapy (Taub, Uswatte, and Pididit,1999) to speech/language rehabilitation.

While the timing of tDCS in upper extremity motor rehabilitation (Giacobbe et al., 2013) and in non-speech motor therapy has been explored (Volpato et al., 2013), there have been no studies directly comparing the timing of tDCS stimulation in relation to aphasia therapy (de Aguiar, Paolazzi and Miceli,

2015). There is mention of decreased reaction time in naming with tDCS immediately preceding tDCS in healthy populations (Monti, 2008). This is consistent with what is known about the effect of single administrations of tDCS. lasting transiently beyond stimulation and about tDCS used in priming cortical regions (Edwards et al., 2009; Stinear, Coxon, Fleming & Byblow , 2008). However, the majority of recent tDCS in aphasia research provided language therapy concurrent to delivery of tDCS (Fridriksson et al. 2011; Fiori et al., 2010; Baker et al., 2010). In Volpato et al. (2013) motor speech therapy was provided 'offline' (not during tDCS administration), and did not enhance treatment outcomes. However, the exact amount of time that passed between tDCS and therapy was unspecified in their paper. Since one posited mechanism of action for tDCS is priming of the underlying cortex (Hickock, 2009), it may be that motor speech therapy was administered beyond the period of sustained neuromodulation. If behavioral speech therapy was delivered hours or days after tDCS, it is unlikely that cortical depolarization would remain. Therefore no observable benefit of tDCS could have been measured this far after tDCS administration. This leaves an open question as to whether tDCS *immediately preceding* aphasia therapy might improve language outcome in a way that behavioral therapy hours to days after neuromodulation did not. Study Two addresses this research gap.

The audiovisual matching aphasia treatment chosen for this study has previously been reported to improve confrontation naming in people with non-

fluent aphasia when used consecutively for five days (Fridriksson, et al. 2009 ; Baker, 2010). No verbal output was required to complete the therapy and no clinician bias could be introduced given the nature of the treatment. A single session of this aphasia therapy was given after participants were given 20 minutes of active or sham tDCS. A single session was used as a first step in the investigation of timing and as a proof of concept for future designs. In addition to the treatment itself being well-suited to this study, there is also precedence for the use of single treatment sessions in the study of tDCS in language improvement. For example, single treatment sessions have been shown to be effective in improving naming outcomes when provided concurrent with active tDCS in healthy populations (Monti et al., 2008).

Method

Participants

Fourteen participants were recruited for this study. A power analysis revealed the minimum number of participants required to achieve effect sizes similar to those reported previously in the literature (G*Power, Faul, Erdfelder, Buchner and Lang, 2009). Effect size estimates were based on the effects sizes reported in Baker (2010; effect size, eta squared = .14) and in Flöel et al. (2011; effect size, Cohen's d = 3.77). Using these two effect sizes as estimates for the current work, the power analysis indicated that a sample size of 10 was the minimum required to detect an effect of the size reported in Baker (2010) with a

power of .80 and an alpha of .05 using a repeated measures ANOVA within-between interaction. A sample size of 4 was the minimum required to detect an effect of the size reported in Fridriksson et al. (2011). The inclusion criteria for this study were: 1) chronic stage post single left hemisphere stroke (> six months); 2) native English speaker; 2) over the age of 18. Despite the presence of aphasia, it was required that comprehension was adequate for understanding experimental instructions. Exclusion criteria were: 1) other neurological or psychiatric disorders, especially a history of seizures; 2) people taking psychoactive medications; people with any implants or devices precluding the safe use of tDCS.

As reported above, 14 individuals were recruited and consented, but two individuals did not complete the study. Therefore, the results from 12 participants (6 male) are reported here. Attrition accounts for the uneven groups (Table 4.1). Nine participants were right hand dominant; two were left hand dominant and one was ambidextrous prior to their CVAs (Table 4.1. Participants were assigned in pseudo-random fashion to either the Preceding tDCS or During tDCS groups (described below).

The Preceding-tDCS group had a mean age of 66.1 years (range 39-82) and a mean WAB AQ of 69.8 (range 17.8-88). The During-tDCS had a mean age of 65.2 (range 42-85) and a mean WAB AQ of 81.6 (range 66.4-92). Independent sample t-tests confirmed there were no significant differences in age ($p = 0.404$); time post onset ($p = 0.385$) nor WAB AQ ($p = .316$) between two tDCS groups.

One participant (P4) was unable to provide spoken responses to confrontation naming tasks and provided written responses instead. He performed the computerized aphasia therapy independently as it did not require speech output. Three people participated in both Studies One and Two. Study One participants A8, A9 and S9 were Study Two participants P1, D1 and P7, respectively.

Demographic Information for Study Two Participants

Demographic Information for Participants in the Timing Study							
ID	**WAB AQ**	**Age (Years)**	**Years Post Onset**	**Gender**	**Ethnicity**	**Handedness**	**Stroke Type**
P1	82.8	63	4.5	M	C	Right	Cortical
P2	83.4	42	1	M	C	Ambi	cortical
P3	66.3	49	2	F	C	Right	mixed
P4*	17.8	56	1	M	C	Right	mixed
P5	73.9	82	3	M	C	Right	subcortical
P6	88	39	2	F	C	Right	mixed
P7	76.3	66	2.5	M	AA	Right	mixed
D1	92	49	20	F	C	Right	subcortical
D2	66.4	85	1	F	C	Right	cortical
D3	81.2	79	2	M	C	Right	cortical
D4	84.1	71	0.7	F	AA	Left	mixed
D5	85.6	42	2	F	C	Left	mixed

Table 4.1 This table shows the demographic characteristics of the participants in the timing study. Participants with the P identification numbers always received tDCS *immediately preceding* aphasia therapy and D participants always received tDCS *during* aphasia therapy. This is true whether sham or anodal tDCS was used. For ethnicity C = Caucasian and AA = African American. Participant P4 is marked with an asterisk to denote that all confrontation naming was produced in written form.

Behavioral Aphasia Treatment

The behavioral aphasia treatment was a self-administered, computerized picture-word matching task given on a laptop based on the work of Fridriksson et al. (2009) and Baker et al. (2010). Using a self-administered and computerized aphasia treatment ensured that no examiner bias was introduced and helped to maintain consistency across all participants. DMDX software (Forster & Forster, 2003) was used to present full color pictures on a laptop paired with an audiovisual cue of a mouth articulating a word. Some picture and audiovisual cues matched while others did not. The "A" key on the laptop was marked with green to indicate the pair matched and the "L" key was marked with red to indicate a mismatch. Participants were instructed as follows, "You are going to see a picture and then a video of a mouth saying a word. If the picture and the word that you hear are the same, press the green button, if they are not the same, press the red button. For example, if you saw a picture of a cow and heard the word "cow" (gesture to mouth) press here (gesture to green). But if you saw a picture of a cow and heard "pig" press here (gesture to red)" (Figure 4.2). During treatment (using the A or B 25 item aphasia therapy lists) pictures were presented for 3.25 seconds, followed by a 600ms interval between each picture and video stimulus pair. The video stimuli were recordings of a man's articulators as he pronounced a word.

Depiction of computerized match/mismatch task

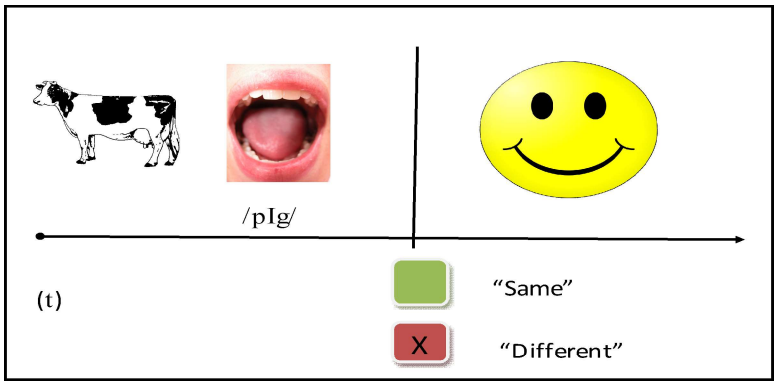

Figure 4.1 The mismatched audiovisual stimuli /pIg/ is paired with a picture of a cow. The participant clicks the red keyboard key to indicate the mismatch and receives a smiley face as feedback for the accuracy of the response.

Participants were allowed 3 seconds to respond by button push as to whether the picture and video stimulus matched or did not match. Immediate feedback was provided on the laptop indicating the accuracy of the response.

Any response taking longer than 3 seconds was counted as an error, and participants were given a written feedback message of "no response" on screen. DMDX software (Forster & Forster, 2003) was used to time and record accuracy and reaction time for each trial (button press) during the therapy task. Participants completed self-administered aphasia therapy silently and were not required to speak during the computerized therapy. Regardless of which timing group a participant was in (Preceding or During tDCS), each participant received one

treatment session with active tDCS over left M1 and one treatment session with sham tDCS over left M1, with a week-long break ("wash-out period") between conditions (Table 4.2).

Stimuli for aphasia therapy.

Two 25 item lists (A and B) consisting of low-, medium- and high-frequency nouns were created and matched on the lexical properties of word frequency; number of syllables; number of phonemes; and semantic category (Baker, 2010, Fridriksson 2011). These were used as treatment stimuli during the computerized self-administered procedure described below. Each list consisted of twenty five color pictures of nouns presented on a laptop while accompanied by either a matched or mismatched audiovisual cue of a mouth producing a word (Baker et al, 2010). Two orders of items were created for each list (A1 and A2; B1 and B2) to ensure there was no semantic benefit of stimulus presentation order for one of the two lists.

tDCS stimulation.

All equipment and positioning were identical to that described above in Study One. During active tDCS, participants received 2mA of stimulation with the anode over the left primary motor cortex and the cathode placed on the right supraorbital ridge. During sham tDCS, the electrode placement was maintained but the current ramped up to 2mA and then decreased back to 0mA within 30 seconds. All participants during all conditions wore electrodes for forty minutes

(during both 20 minutes of stimulation and 20 minutes of computerized therapy) to maintain a consistent experience between conditions.

Outcome Measures

Primary outcome measure – confrontation naming.

The 25 item aphasia treatment lists were combined with an additional 55 words matched listwise. These were used to create 80 word lists (with A and B versions) which were administered to determine the total number of words accurately named. Performance on matched lists before and after therapy (Table 4.2) was compared after each therapy was administered. This change score became the primary outcome measure. The accuracy of confrontation naming at baseline and post-treatment was compared as the primary outcome measure.

To obtain outcome measures, the 25 item treatment list (A or B) and a matched 55 word list (untrained probes A or B) were administered as a confrontation naming task. Matched lists A and B were alternated so that participants were not exposed to the same words during baseline and post-test probes administered during the same session (Figure 4.3). The primary outcome measure was the number of accurately named pictures (max = 80).

Secondary outcome measures.

The accuracy and reaction time of performance on the word-picture matching task during the self-administered treatment task served as secondary outcome measures.

Procedure

The full WAB-R AQ (Kertesz, 2006) was obtained for descriptive purposes and to determine the severity and type of aphasia present (Table 4.1). P4 scored low on the WAB (AQ = 17.8) because he was unable to answer questions verbally as is required on the WAB. However, he provided written answers to complete the confrontation naming task and was able to complete this study using that modality. Participants attended four times (Fig. 4.3). During the first session baseline testing was conducted. During the next two sessions participants received aphasia therapy as well as baseline and post-testing. Pseudo-randomization was used to balance the severity of aphasia as evenly as possible (as measured by the WAB-R AQ; Kertesz, 2006) across the Preceding-tDCS and During-tDCS groups. This was done by alternating the placement of participants with high or low WAB scores, which ranged between 60 and 92 (see procedure for the exception of P4) into the Preceding tDCS or During tDCS groups. One therapy session utilized active tDCS and one used sham (separated by one week between sessions), with the order counterbalanced across participants within each group. The pairing of lists A or B with stimulation types anodal or sham was also counterbalanced. Participants were blind to the order in which they received

tDCS. During the final visit further post-testing was administered. The testing environment was controlled with the aim of maintaining consistency between all participants and served to limit any possible interference from verbalizations prior to aphasia treatment, which was particularly relevant for the Preceding-tDCS group. Treatment sessions for both groups commenced in the same manner in an attempt to maintain a consistent experience between groups and reduce extraneous variables.

For both groups, tDCS electrodes were placed on the participant's scalp and remained for the entire 40 minutes. For the first twenty minutes (the pre-treatment phase), participants sat quietly and listened to music without lyrics (jazz or classical) and were instructed to attend to abstract artwork (abstract swirls) for 20 minutes. Preceding-tDCS participants received either active or sham tDCS during the pre-treatment period and then performed 20 minutes of computerized aphasia treatment. During-tDCS participants wore electrodes throughout the pre-treatment phase then tDCS was turned on concurrent with computerized aphasia treatment. The order of tDCS or sham conditions was counterbalanced with one week between each condition (Table 4.2).

Data Analysis

All comparisons were made to determine whether there were effects of the timing of tDCS stimulation in relation to aphasia therapy (a single self-administered computerized treatment), as well as effects of active vs. sham tDCS.

The primary outcome measure was generalized confrontation naming while the secondary outcome measures were the accuracy and reaction time on items presented during the twenty minute aphasia therapy.

Primary outcome measure: confrontation naming.

Pre- and post- performance on a confrontation naming task was used to determine whether participants named more words correctly pre- or post- therapy. A 2 x 2 repeated measures factorial ANOVA was used to evaluate any change in the number of words correctly named based on tDCS stimulation type or timing or the presence of any interaction effect. The within subjects effect was time (pre vs. post treatment) and the between subjects effect was group (Preceding-tDCS group vs. During-tDCS group).

Secondary outcome measures.

Measurements of accuracy and reaction time at six different time points were taken over the 20 minute therapy session (every 200 seconds). 2 x 2 x 2 repeated measures factorial ANOVAs were used to evaluate the accuracy of match/mismatch trials completed during the first and last timepoints. Reaction time during that 20 minute task was evaluated in the same way. The within-subject factors included stimulation type (anodal vs. sham tDCS) and session (first and last 20 minute session). The between subjects factor was timing (Preceding-tDCS vs. During-tDCS).

Study 2 Timeline Schematic

	tDCS Condition	Baseline Testing	Treatment Version	Post Testing
Session 1	**-**	**A**	**-**	**-**
One Week Off				
Session 2	**I**	**B**	**A**	**A1**
One Week Off				
Session 3	**II**	**-**	**B**	**A2 and B1**
One Week Off				
Session 4	**-**	**-**	**-**	**B2**

Table 4.2 A schematic depiction of the four sessions of the tDCS Timing Study for both the Preceding-tDCS and During-tDCS groups. Study timelines were identical for both groups. While the timing of tDCS always remained the same within group, all participants received 2mA anodal and sham tDCS separated by one week. The order of presentation of the anodal or sham tDCS conditions (I or II) was counter balanced within each group where half had condition I as sham tDCS and half as anodal tDCS. The order of treatment versions was counterbalanced over all participants.

Results

Primary outcome measure: Confrontation naming

There was no significant interaction between the type of tDCS stimulation (Active or Sham) and the timing (preceding or during) on the change in naming accuracy pre- and post-trial, F (1, 10) = 0.952, p = 0.352. There was also no significant difference in the change in naming accuracy between Active (M = 5.17, SD = 4.78) or Sham tDCS stimulation (M = 6.00, SD = 5.26), F (1, 10) =

0.069, p = 0.799. There was a significant main effect of the timing of stimulation (F (1, 10) = 5.179, p = .046), with the preceding-tDCS group having a bigger change in naming accuracy between pre- and post-trial (M = 7.36, SD = 4.63) than the during-tDCS group (M = 3.10, SD = 4.41). See Table 4.3 and Figure 4.2.

Repeated Measures ANOVA Results for the Confrontation Naming Test

		Confrontation Naming	
		F	Sig
Within subject effects	tDCS stimulation (Anodal vs. Sham)	0.069	0.799
	tDCS * Group	0.952	0.352
Between subject effects	Group (Preceding vs. During)	**5.18**	**0.046**
	N	12	

Table 4.3 Change in the naming accuracy pre- and post-stimulation were used. Table shows significance levels for repeated measures ANOVAs. Bolded figures indicate statistical significance at p< .05 or lower.

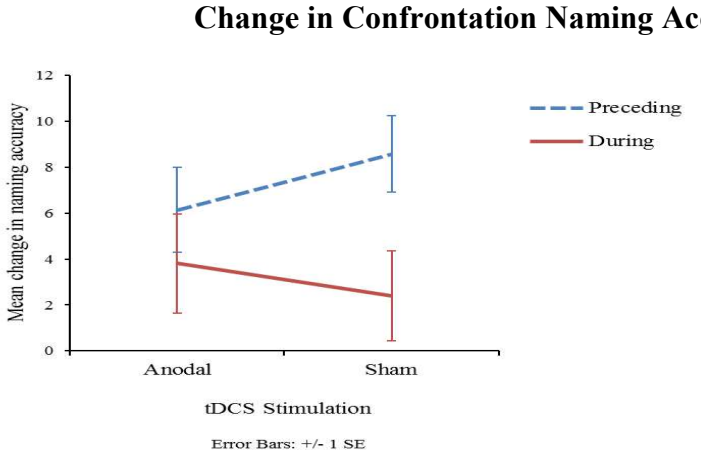

Figure 4.2 Average number of words named when anodal or sham tDCS was provided immediately preceding (dashed) or during (solid) a computerized naming therapy.

Secondary Outcome Measures

Matching accuracy within a treatment session.

Contrary to the hypothesis, there was no significant interaction between the type of tDCS stimulation (Active or Sham) and the timing (preceding or during) on the naming accuracy, $F(1,8) = 0.563$, $p = 0.475$. There was no significant main effect of tDCS stimulation type, session, or timing, as well as no significant interactions, $p > .05$. See Repeated measures ANOVA for match/mismatch accuracy (Tables 4.4 and 4.5).

Match/Mismatch accuracy during a 20 minute treatment session

		Matching Accuracy	
		F	Sig
Within subject effects	tDCS stimulation (Anodal vs. Sham)	0.071	0.797
	tDCS * Timing	0.563	0.475
	Sessions	3.472	0.099
	Sessions * Timing	0.017	0.899
	tDCS*Sessions	0.524	0.490
	tDCS*Sessions*Timing	0.096	0.764
Between subject effects	Timing (Preceding vs. During)	1.273	0.292
	N	10	

Table 4.4 Match/mismatch accuracy means comparing the 1st and 6th measures taken at 6 time points during a 20 minute aphasia treatment task (every 200 seconds). Table shows significance levels for repeated measures ANOVAs. No comparisons reached statistical significance

Mean match/mismatch accuracy at six timepoints during aphasia treatment.

	Mean Accuracy measured every 200 seconds						
	200s	400s	600s	800s	1000s	1200s	Mean (SE)
Anodal Preceding	0.91	0.95	0.90	0.97	0.97	0.99	0.95 (.04)
Anodal During	0.82	0.89	0.93	0.94	0.88	0.90	0.88 (.06)
Sham Preceding	0.91	0.98	0.94	0.98	0.94	0.96	0.95 (.04)
Sham During	0.90	0.88	0.89	0.90	0.95	0.93	0.89 (.06)

Table 4.5 Measures taken at 6 timepoints (every 200 seconds) during a 20 minute aphasia treatment task.

Reaction time within a single treatment session.

Similar to the match/mismatch accuracy, there was no significant interaction between the type of tDCS stimulation (Active or Sham) and the timing (preceding or during) on the naming reaction time, $F(1,8) = 0.658$, $p = 0.441$. There was no significant main effect of tDCS stimulation type, session, or timing, as well as no significant interactions, $p > .05$. (Tables 4.6 and 4.7).

Discussion

A single session of a self-administered computerized based aphasia treatment was administered in a sham-controlled crossover design that compared the timing of tDCS stimulation across participants. One group of participants received 20 minutes of tDCS stimulation immediately preceding 20 minutes of aphasia treatment and the other group received stimulation during 20 minutes of

Results of repeated measures ANOVA of reaction time during aphasia treatment task.

		Matching Reaction Time	
		F	Sig
Within subject effects	tDCS stimulation (Anodal vs. Sham)	0.004	0.951
	tDCS * Timing	0.658	0.441
	Sessions	4.177	0.075
	tDCS*Sessions	0.121	0.737
	tDCS*Sessions*Timing	0.134	0.724
Between subject effects	Timing (Preceding vs. During)	0.134	0.724
	N	10	

Table 4.6 Reaction time means comparing the 1st and 6th measures taken at 6 timepoints during a 20 minute aphasia treatment task (every 200 seconds). Table shows significance levels for repeated measures ANOVAs. No comparisons reached statistical significance.

Mean reaction time during a 20 minute online aphasia treatment.

	Mean reaction time every 200 seconds						
	200s	400s	600s	800s	1000s	1200s	Mean (SE)
Anodal Preceding	2.26	2.17	2.15	2.14	2.23	2.08	2.17 (.08)
Anodal During	2.32	2.26	2.30	2.23	2.25	2.23	2.27 (.12)
Sham Preceding	2.31	2.18	2.22	2.13	2.22	2.14	2.27 (.12)
Sham During	2.20	2.17	2.18	2.20	2.15	2.17	2.18 (.15

Table 4.7 Measures taken at 6 time points (every 200 seconds) during a 20 minute aphasia treatment task.

aphasia therapy. Because the treatment was automatized and self-administered requiring no speech output, evaluator bias was reduced.

For the primary outcome measure of confrontation naming, there was no interaction between the timing of tDCS (preceding vs. during tDCS groups) with tDCS stimulation type (active vs. sham tDCS conditions) which should have been present if the timing of tDCS preceding aphasia treatment was more beneficial than receiving the two concurrently. The secondary outcome measures of match/mismatch accuracy and reaction time throughout a single treatment task were measured by computer software. Mean match/mismatch accuracy was measured during aphasia treatment task at 6 equal time points (every 200 seconds). There was no interaction between stimulation timing and stimulation type, indicating that there was no clear benefit for either approach to pairing stimulation with treatment. The same pattern held with reaction time measured at six probes across a single 20 minute aphasia treatment session. These findings are discussed further in Chapter V.

CHAPTER V

GENERAL DISCUSSION

Overview

This dissertation addressed research gaps in the literature on the use of tDCS on chronic aphasia/apraxia of speech that warrant further empirical investigation. Both utilized 2mA active tDCS with the anode over the primary motor cortex (the C3 position in the 10/20 EEG coordinates) and the cathode over the right supraorbital region.

The first study (Chapter III) investigated the effects of repeated tDCS over the left primary motor cortex combined with right robotic hemiplegia therapy for 12 weeks (3 times per week for a total of 36 sessions) on the speech and language of chronic stroke-aphasia patients. A broad range of speech/language skills was administered via a constructed testing battery (see Appendix I). This included measures of overall language function, confrontation naming, category member naming, object vs. action naming, and measures of speech motor control. Comparisons of pre-and post scores on these outcome measures were compared to determine whether active or sham tDCS conditions were associated with enhanced performance.

Discussion of Findings in Relation to the Original Hypotheses

Effect of tDCS and right robotic motor therapy on speech and language

The original hypothesis for study one was that the results would indicate which aspects of speech and/or language that are most responsive to this intervention. A general facilitatory effect on speech motor control was also predicted. In fact, the results of the comprehensive speech-language battery performed at pre- and post-testing did reveal areas of speech and language that improved more than others. These included WAB Aphasia Quotient scores, category naming and diadochokinesis.

It was hypothesized that the group receiving active tDCS would show greater gains on speech and language outcomes than a group receiving sham tDCS under the same conditions. In contrast, results from the WAB-R showed a main effect of time with higher scores post-treatment than at pre-treatment with no effect of the type of tDCS stimulation (anodal vs. sham). For category naming, the same pattern was observed, with a significant interaction between time and group. Those who received sham tDCS named more category members than those who received active tDCS.

Contrary to the predicted hypothesis that action words may preferentially benefit from motor therapy and tDCS stimulation of the left primary motor cortex, no statistically significant improvements in either word class was found. While there was a numerical increase in accuracy on action words with anodal tDCS and

for object words with sham tDCS, nothing can be assumed about this relationship from this study.

The outcomes on the ABA-2 diadochokinetic rate subtest revealed a main effect of time with the mean post-test scores higher than the mean pre-test scores. This indicates that participants were able to increase the number of rapid syllable productions in a timed task after completing 36 sessions of motor therapy preceded by anodal or sham tDCS over 12 weeks. But, the hypothesis that those receiving 2mA anodal tDCS prior to motor treatment would increase on outcome measures of speech motor control (in this case the diadochokinetic rate and words of increasing length subtests of the ABA-2) did not bear out. There was no significant main effect of tDCS group. The words of increasing length subtest revealed no significant results.

The second study (Chapter IV) investigated the role of the relative timing of tDCS in regards to aphasia therapy for people in the chronic stage of aphasia. Two groups of participants underwent both anodal and sham tDCS over the left primary motor cortex (C3 on the 10/20 EEG system) in a crossover design with one week between active or sham tDCS stimulation conditions (Figure 4.3). The Preceding-tDCS group received a self-administered aphasia therapy (audiovisual cue to picture matching task) *immediately preceding* tDCS and the During-tDCS group received aphasia therapy *during* tDCS administration (standard care). A single session of aphasia therapy was given under each condition. Comparisons of active vs. sham tDCS and the timing of tDCS (preceding or during aphasia

therapy) were compared to determine whether either main effect or an interaction resulted in better outcomes.

The hypotheses for study two were that the group receiving 2mA anodal tDCS *immediately preceding* aphasia therapy would increase performance on all speech and language outcome measures more than the group receiving aphasia treatment *during* anodal tDCS. Improved outcome measures with 2mA anodal tDCS were expected in both the *preceding-tDCS* and *during-tDCS* groups.

The results reported here are in opposition to the original hypothesis as there was no interaction between the timing of tDCS (preceding-tDCS and during-tDCS) and tDCS stimulation (active vs. sham). The preceding-tDCS group did achieve significantly greater gains in the primary outcome measure of confrontation naming than the during tDCS group but they started lower and had more room to increase than the during-tDCS group (Figure 4.5). If neuromodulation achieved during active tDCS in the first week lasted beyond the week between sessions then cortical excitability may have remained elevated during the second week of treatment. This continued excitatory capacity might then influence performance during sham tDCS when neuromodulation should not have occurred. Other explanations for this order effect include enhanced learning during active tDCS or could point to a reversal of the tDCS effect as seen in some studies involving 2mA active tDCS (Batsikadze et al., 2013). These possibilities are further discussed below.

Implications

Stimulation over left primary motor cortex

Both studies in this dissertation used the left primary motor cortex as the site of tDCS stimulation to enhance speech and language outcomes in people with chronic aphasia. This site has shown to be a viable location as it is likely perilesional to infarcts causing aphasia (especially non-fluent aphasia which may be accompanied by apraxia of speech). This neural substrate has been found to subsume language functions through neuroplasticity and cortical remapping over the course of recovery. (Meinzer et al, 2016; Branscheidt et al.,2017; Fadiga & Craighero, 2006). In study one, after participating in a right repetitive upper extremity therapy protocol for twelve weeks, people with aphasia showed improvements in measures on a comprehensive language battery; increased the number of syllables produced during a timed task and increased the number of category members named in a timed task. These data extend Hesse et al.'s (2007) findings of language improvement in a group of participants undergoing right robotic upper limb training in the subacute stage of stroke to those under similar conditions in the chronic phase of recovery. The fact that participants tended to perform better in the sham tDCS condition rather than the active condition (2mA anodal) suggests the active condition interfered with speech/language improvements. Therefore, the effects of the selected intensity of active anodal tDCS will be discussed below in more detail. Of note, in this small sample, there was no statistical relationship found between speech/language improvement and

motor improvement. It was hypothesized that tDCS stimulation over the left primary motor cortex would be viable neuromodulatory location to effect speech and language change in chronic stoke. This was due to the cortical proximity of both language and motor cortices in healthy brains and intact motor cortex as a prime area for cortical remapping of language to perilesional areas in stroke (Meinzer et al, 2016; Branscheidt et al., 2017). But the performance of participants in both study one and study two was better in the sham condition than in the active tDCS condition. Future investigations should test this cortical target as a location for language improvement at different intensities of stimulation.

Competition for cognitive resources?

After a unilateral left hemisphere stroke of the middle cerebral artery resulting in damage to regions controlling language and the right upper limb, both functions need healthy neural substrate to subsume their functions. It might seem intuitive that both functions would compete for perilesional intact neural substrate, since two functions have been lost and there is limited healthy cortex. However, a facilitatory rather than competitive effect was found between the motor and language systems in several studies using both healthy and impaired population. This apparent cross domain synergy was seen in healthy adults when motor and semantic tasks were combined and both benefited (Rodriguez, McCabe, Nocera & Reilly, 2012). Primaßin et al. (2015) confirmed this synergy in impaired populations as a facilitatory effect of motor and language treatment was found in a case series. Participants received functional tests evaluating both

motor and language skills and the outcome measures resulted in improvements in both domains. They found no evidence of competition for intact cortical resourcs. Similarly, Harnish et al. (2009) also reported improved language outcomes after motor therapy subsequent to the surgical implantation of a neuroprostheses in the right hemiparetic arm. In sum, the relationship of motor and speech/language recovery may not fit the presumed competitive model of recovery with both functions vying for use of the same healthy cortex. In fact, improvement in both systems after combined speech and motor intervention points to a cross domain cognitive synergy with both motor and speech/language improving in parallel (Wortman-Jutt & Edwards, 2017).

Active vs. sham tDCS and the intensity of active tDCS

As reported above and in opposition to the a priori hypotheses, in both studies, participants receiving active 2mA anodal tDCS stimulation over the left primary motor cortex did not outperform those receiving sham stimulation. In some measures sham gains were greater than active gains. The tDCS literature centered on aphasia continues to grow but there are many variables that still require more systematic investigation. As reviewed in Chapter II, montage variables are important in creating a desired treatment effect in targeted underlying cortex. Very few studies have examined the selection and neuromodulatory effects of specific amperages of active tDCS (e.g., 1mA, 1.5mA or 2mA). One study found that healthy individuals did not benefit from 1mA and 1.5mA active tDCS on word retrieval tasks. This was attributed to the possibly

that these amperages were insufficient to modulate cortical excitability above an already typical healthy background of neural activity. The authors express doubt as to whether tDCS is a reliable method of neuromodulation in all populations, especially in single session methodologies (Westwood, Olson, Nappo, & Romani, 2017). It ispossible that individualized montage selection, including amperage, because many inter-individual variables nay be necessary since all of these can affect the outcome of different montage configurations (Shah-Basak, Norise, Garcia, Torres, Faseyitan & Hamilton, 2015). Similarly, Westwood et al. (2017) propose that novel tasks, higher tDCS dosages and longer or repeated tDCS sessions may increase benefits to healthy and harder to treat impaired populations. But Batsikadze, Moliadze, Paulus, Kuo, Nitsche (2013) found that longer dosages and more intense stimulation do not always increase tDCS efficacy. In fact, at 2mA, the expected effects of anodal or cathodal stimulation were reversed with cathodal stimulation at 2mA acting in an excitatory capacity. This paradoxical effect at 2mA is consistent with the outcomes of the studies reported in this work and this study may support the findings by Batsikadze et al (2013).

Timing of tDCS *immediately preceding* aphasia treatment.

The results of study two did not show an interaction of tDCS condition and timing of tDCS as was predicted. A group of participants receiving tDCS *immediately preceding* aphasia treatment named significantly more words than a group receiving tDCS *during* aphasia treatment. This indicates that the Preceding-tdcs performed better but there was no interaction. However, this is primarily

driven by the Preceding-tDCS group in the sham condition and does not reflect an improvement associated with the interaction of the dependent variables relevant in this experiment (Figure 4.5). The positive gain in the Preceding-tDCS group is misleading, as the participants receiving anodal tDCS preceding tDCS exhibited the lowest outcomes.

The timing of tDCS in most experiments of tDCS and aphasia or language has been to run tDCS and behavioral treatments concurrently or to start them together and continue behavioral treatment after tDCS has been turned off (Meinzer, Darkow, Lindenberg & Flöel , 2016; Fiori et al. 2011; Baker, 2010; Monti et al, 2008). For those studies that began with simultaneous tDCS and aphasia therapy but continued aphasia therapy after tDCS was turned off, it is not possible to separate out which, if any, gains could be attributed to the during or preceding portion of the experiment. That methodology is functionally equivalent to some tDCS during and some tDCS preceding aphasia treatment.

Limitations

Sample size

The sample size for study one (Chapter III) was based on the number of people with aphasia available during the cohorts tested between March 2013 and April 2014 as part of a larger study of robotic motor therapy and tDCS. This was a pragmatic means of obtaining participants for this initial investigation and was not chosen scientifically. But it may have limited the ability to find significant

results and limits the interpretations that can be made from the trends found as discussed in the section above on the object vs. action test.

In contrast, study two (Chapter IV) used a power analysis to determine a minimum number of participants to achieve moderate effect sizes in study two. The power analysis conducted for study two used effect sizes generated from Baker (2010) and Fridriksson et al. (2011). Their methodology included 5 consecutive days of self-administered computerized aphasia treatment whereas only a single session was used in the current study. In hindsight, an adjustment in group size was likely necessary because of the difference in treatment sessions between their method and the one employed here. In general, it is assumed that a larger sample size will yield results that most closely approximate that of a population. For future investigations related to either study reported here, a larger sample size is recommended and the increased power associated with such might allow some trends to reveal statistically significant differences. This remains for further empirical studies with a larger sample size to clarify.

Individual and Group differences

Many factors influence the recovery trajectory of aphasia after stroke. These include severity of impairment, age, time post onset, years of formal education and lesion size, among others. When conducting group studies on these populations, scientists attempt to control such variables so there is an equal representation of each of them contained within each experimental group. However, in study one, it was impossible to control for these variables as the

larger project had already been stratified for a number of variables by an epidemiologist and no stratification for aphasia could be added by the time the speech-language pathologist began testing. This unfortunately resulted in significant differences between groups for Study 1 participants in sham and anodal were significantly different in age and time since stroke onset. The sham group began with lower scores on the WAB-R (Kertesz, 2006) which allowed more room for improvement. This pattern may have masked improvement in the anodal group (Lazar, Minzer, Anoniello, Festa, Krakauer & Marshall, 2010).

Lack of procedural control in study one

Study one was conducted under procedures originally developed for a larger study of the effect of tDCS preceding robotic right repetitive upper extremity motor practice on right hemiplegia in chronic stroke. It was not designed to control for linguistic variables. As discussed in Chapter III, some participants continued speech/language therapy during the 12 weeks of motor practice albeit outside times when the neuromodulatory effects of tDCS should have persisted. During the motor practice, talking between researchers and other participants was encouraged and supported which resulted in a collegial cohort atmosphere. By participating in this lengthy study participants were afforded frequent social opportunities. Additionally, the three times per week schedule provided participants with something to look forward to and provided more topics for conversation. People reported they were more active and got out of the house

frequently while participating in the study. Increased social opportunities are known to improve mood and depression in people with aphasia which may increase attempts to communicate (Code & Herrmann, 2013). A positive expectation was set up regarding the ability to improve (motor) function during the chronic stage of stroke recovery which may have carried over to views about speech/language function. It is not possible to tease apart variables, which may have contributed to the speech/language changes reported in study one of this dissertation. Future studies should attempt to tighten control on these variables to ascertain which specifically contribute most to speech/language improvements and determine whether robotic right repetitive motor practice alone could reproduce the results found here.

Lack of focal specificity of 1x1 tDCS

The tDCS montage used in the studies reported above consisted of two electrodes inserted into saline soaked sponges with a total area of 35cm^2 each. In computational models, this electrode constellation has been associated with diffuse modulation of underlying cortex (Edwards et al, 2013; Bikson, Datta, Rahman, & Scaturro, 2010). Given a 1x1 constellation, tDCS causes widespread, rather than focal changes in cortical regions (Lang et al., 2005). As such, neuromodulatory effects may not be as tightly restrained within the cortical regions that investigators assume they are targeting. Another form of non-invasive neuromodulation, Transcranial Magnetic Stimulation (TMS), has a different mechanism of action with the ability to force or inhibit action potentials. Through

focusing of an electromagnetic coil, TMS has the advantage of targeting circumscribed brain regions (Wortman-Jutt & Edwards, 2017; Edwards et al., 2013). There is current interest in using tDCS in a more focal approach to target cortex more discretely, as found in TMS. High-Definition tDCS (HD-tDCS) uses smaller electrodes in various formations to better target specific cortical regions. These montages may take various forms. For example, in a ring cluster with the anode at the center of the ring surrounded by four small cathodes, current is dispersed and focused on the centered anode (Datta, Elwassif, Battaglia & Biksom, 2009). For the reverse effect, the cathode can be centered with four return electrodes (anodes in this case). Though with the complexities of HD-tDCS electrode configurations, the neuromodulatory effects may not coincide with the traditional definitions of anodal and cathodal stimulation (Garnett, Malyutina, Datta & den Outen (2015). It has been shown to be at least as safe and effective as 1x1 tDCS using saline soaked sponges. High definition tDCS has been combined with aphasia therapy to better focus neuromodulation on healthy perilesional cortex while maintaining the safety associated with traditional 1x1 tDCS. In a feasibility study, Richardson, Datta, Dmochowski, Parra and Fridriksson (2015) conducted computational modeling and determined individualized stimulation sites with two anodes and two cathodes. When combined with computerized aphasia treatment, outcomes with HD-tDCS were on par with traditional 1x1 tDCS. Other HD-tDCS studies of the effects on the language of healthy adults have shown increased rate of verbal learning (Nikolin, Loo, Bai, Dokos & Martin,

2015; Malyutina & den Ouden, 2017) and increased accuracy in learning new words (Perceval, Martin, Copland, Laine & Meinzer, 2017). Malyutina and den Ouden (2016) found that cathodal stimulation in healthy adults improved naming accuracy, which aligns with their earlier work suggesting that HD-tDCS excitatory capacities may not fit within a strict anodal/cathodal paradigm. They also found order effects suggesting that neuromodulation may remain active beyond the expected time period thereby affecting later tasks. This may be similar to the order effects found in study two of this work. This is discussed in the next section on the conclusions and future directions of the two studies reported in this dissertation.

Conclusions and future directions

Study one

This study contributed to the understanding of whether tDCS and robotic hemiplegia therapy improve acquired chronic motor speech or language impairments and extend the findings of Hesse et al (2007). Their results showed that some participants in the subacute phase of stroke recovery improved scores on a comprehensive aphasia examination after participating in a robotic right hemiplegia therapy program. The results reported here provide further evidence for a cross domain synergy between language improvement associated with motor therapy and left primary motor cortex stimulation. With the small sample here no

relationship between motor improvement and speech improvement could be established

Since the active condition of anodal tDCS at 2mA may have impeded speech/language gains (Batsikadze et al, 2013), investigation of the effect of intense repetitive robotic right upper limb therapy alone are warranted to determine their singular effect on speech and language. In addition, lower intensity anodal tDCS amperages of 1-1.5mA should be paired with robotic motor therapy to examine whether these intensities enhance rather than impede the effect on speech and language outcomes. Comparing the same schedule with robotic and more traditional behavioral PT should also be examined for their effects on speech and language.

Using linguistic right upper extremity motor movements (i.e., writing) may improve cross domain extension of cognitive resources better than the visual targets currently provided by the MIT robots and associated software (Krebs, Hogan, Aisen & Volpe, 1998). Here the targets on screen were clock-like and horizontal layout of circles requiring participants to move the cursor from the center out radially to a circle of points or laterally out to each side. If the onscreen targets could include linguistic material instead, tracing letters or answering onscreen written questions by moving the cursor to the correct answer, perhaps a better language outcome benefit could be established. Another thought is that if the robots could be programmed to allow free range of motion and just support the user in controlling the impaired arm, then participants could use the system to

allow free writing of letters or words. This is only one of many ways that the motor and language systems may be harnessed simultaneously to achieve gains in both systems as suggested above. This could also more easily allow for assessment of connected speech in the written modality. Outcome measures should be expanded to include discourse in both the written and spoken modalities.

Study two

While the effects of single sessions, as reported here, are an important first step, systematic study of the timing of tDCS in aphasia recovery is in its infancy (Wortman-Jutt & Edwards, 2017). Study two results were equivocal as there was no interaction between the timing of stimulation and tDCS type. The majority of aphasia studies are conducted with behavioral treatment run concurrent with tDCS stimulation (Meinzer, Darkow, Lindenberg & Flöel , 2016; Fiori et al. 2011; Baker, 2010; Monti et al, 2008), that standard treatment may not be the only or best choice of timing for maximizing speech/language outcomes and further investigation is warranted. Unfortunately, this study does not provide evidence for or against current practice. Beyond tDCS timing, it is also important to consider not just the tDCS parameters in such studies but also the appropriateness of the behavioral therapy best paired with a particular montage configuration and individual psychosocial, linguistic and lesion variables (Gallettta & Vogel-Eyny,

2017). More knowledge is needed about the underlying mechanisms of tDCS neuromodulation to best harness its potential in optimizing rehabilitation gains.

The limb motor literature is the most consistent in reporting positive outcomes of tDCS paired with therapy. This is understandable since the primary motor cortex has been well mapped, allowing scientists to focus on varying tDCS parameters with more certainty as to the role of the underlying substrate. However, the nature of the neural instantiation of language differs greatly from the motor system. Language is organized in networks of neurons both ipsi- and contralaterally and the time within the recovery course affects neuroplastic changes (Fridriksson, Bonilha, Baker, Moser & Rorden, 2009; Thie & Zumbansen, 2016). Coupling that complexity with the number of combinations of tDCS variables (i.e., site, polarity, amperage, delivery schedule, etc.) is a major challenge to the elucidation of best practices for language improvement. These must be studied systematically and until the effects of how different tDCS variables interact with the language system (both healthy and impaired) are known, it is not advisable for clinicians or individuals to be using tDCS independently (Wurzman, Hamilton, Pascual-Leone, & Fox, 2016).

Study two was an important first step in determining whether there are differential effects of the timing of anodal tDCS in relation to the administration of behavioral aphasia treatment. Future studies with consecutive sessions of aphasia therapy will help answer additional questions regarding tDCS timing and the durable effects of tDCS on speech and language in acquired neurological

disorders. Time post onset of stroke is another important variable to address in future studies seeking to differentiate treatment effects from spontaneous recovery. Participants in the chronic stage of recovery were used because untreated improvement is no longer expected. This may be a disadvantage as stroke survivors often make greater gains in therapy during the acute and sub acute recovery phases. The use of active tDCS as an adjuvant may provide greater gains when combined with therapies in earlier stages of recovery (Johansson, 2011).

Nevertheless, this is an exciting time in aphasia research as tDCS and other forms of neuromodulation have the potential to improve speech and language outcomes for those with chronic aphasia. Systematic study of the variables involved with neuromodulation could help establish a set of principles to maximize gains and improve the lives of those living with this chronic impairment. This work has attempted to contribute to this worthy endeavor.

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Appendix A. Study One Outcome measures and scoring protocols

Assessment	Task	Scoring Protocol
Comprehensive Battery	Western Aphasia Battery - Revised (WAB-R)	1) Score as per manual to calculate AQ 2) Max AQ = 100 3) Classify aphasia type
Confrontation Naming	Philadelphia Naming Test Short Form (PNT-30)	1) First full response is scored 2) Calculate word and phoneme accuracy (Max words=30)
Category naming	Name members of each category for one minute: animals, tools, plants and transportation	1) Timed task. 2) Prompt: "You have one minute to name as many ____ as you can. Go."
Object vs. Action	Object vs. Action Naming	1) Count number of objects correct (max=20) 2) Count number of actions correct (max=20)
Motor Speech	ABA-2 Subtest 1: Diadochokinetic Rate	1) Score as per manual. 2) Count highest number of repetitions of single syllables per second.
	Subtest 2: Increasing Word Length	Score as per manual.
	Subtest 3: Limb and Oral Apraxia	Score as per manual

Appendix B.

Spearman Correlation Matrix for Change in Motor and Speech/Language Measures

Measure			Change in Fugl-Meyer
	N	Sig. (2-tailed)	Correlation Coefficient
Change in Fugl-Meyer	18		1.000
Change in DDK (ABA-2)	15	0.277	0.300
Change in Words of Increasing Length (ABA-2)	15	0.194	-0.355
Change in PNT in Phonemes	11	0.286	0.354
Change in PNT in Words	11	0.653	0.153
Change in WAB-R	10	0.407	-0.295
Change in Object Naming	12	0.453	0.240
Change in Action Naming	12	0.930	-0.029
Change in Category Naming	11	0.623	0.167