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Transcranial Alternating Current Stimulation as an Adjuvant for Nonfluent Aphasia Therapy: A Proof-Of-Concept Study

Lynsey McGrath Keator

TRANSCRANIAL ALTERNATING CURRENT STIMULATION AS AN ADJUVANT FOR NONFLUENT APHASIA THERAPY: A PROOF-OF-CONCEPT STUDY

by

Lynsey McGrath Keator

Bachelor of Arts
University of Delaware, 2013

Bachelor of Science
University of Delaware, 2013

Master of Arts
University of Massachusetts Amherst, 2016

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Accepted by:

Julius Fridriksson, Major Professor

Dirk den Ouden, Committee Member

Leigh Ann Spell, Committee Member

Christopher Rorden, Committee Member

Tracey L. Weldon, Vice Provost and Dean of the Graduate School

DEDICATION

This work is dedicated to those living with stroke and aphasia; without whom this work would not be possible. It is my hope that results from the current study and work from aphasiologists all around the world provide hope for your future and opportunities for you to continue living well with aphasia. Thank you for teaching me, inspiring me, and serving as my greatest motivation. Keep shining your light.

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ABSTRACT

Identifying effective and efficient rehabilitation tools is crucial to improve language outcomes for persons living with chronic aphasia. Speech entrainment has proved to be particularly successful in improving speech output in nonfluent aphasia. It is hypothesized that, for patients with aberrant oscillatory synchronization between anterior and posterior language regions of the left hemisphere, speech entrainment may act as an external gaiting mechanism to bolster an impaired efference copy and improve synchrony between these regions. Theoretical and empirical evidence supports this idea that speech production relies on anterior-posterior connectivity in the left hemisphere.

Transcranial alternating current stimulation (tACS) delivers low, periodically-alternating currents to improve functional connectivity between targeted brain regions through the amplification and entrainment of endogenous oscillations. Previous work suggests that *in-phase* tACS (alternating current with 0° relative phase difference) improves behavioral performance while *anti-phase* stimulation (current delivered with 180° phase difference) results in impaired behavioral performance secondary to impeded network synchronization.

The goals of the present investigation were to determine: 1) if HD-tACS boosts behavioral outcomes (as measured by speech fluency and timing in a speech entrainment task) and 2) the extent to which stroke-induced damage predicts HD-tACS-induced effects on fluency. This was a preliminary and proof-of-concept study in which high definition transcranial alternating current stimulation (HD-tACS) was paired with a

speech entrainment paradigm in a cohort of persons with nonfluent aphasia. 1 mA of HD-tACS at a theta frequency (7 Hz) was applied to anterior and posterior regions of the left hemisphere across three stimulation conditions: 1) in-phase stimulation, 2) anti-phase stimulation, 3) sham.

Group level analyses failed to support these hypotheses. Although not statistically significant, the primary behavioral outcome measure (the proportion of correct script words) and secondary measures such as the number of total correct words demonstrated a higher median for the *in-phase* condition while the number of speech errors was higher during the 'anti-phase' condition. Spectral-temporal analysis used mel-frequency cepstral coefficients in a dynamic time warping algorithm to examine the temporal distance between the AV model and patient productions during the task. Results suggest that patients' speech was better entrained (as evidenced by a smaller distance between the model and participant) during the *in-phase* stimulation condition as compared to sham.

Retrospective neuroimaging data suggest that patients who demonstrated better behavioral performance during the *in-phase* stimulation, had greater preservation of the inferior temporal gyrus ($z = 4.26$) and poorer coherence as measured by rsfMRI between anterior and posterior regions (inferior frontal gyrus, *pars opercularis* to middle temporal gyrus; $z = -2.51$).

The current study relied on a network approach and, for the first time, introduced alternating electrical current stimulation to synchronize anterior-posterior language regions in the left hemisphere. Preliminary data are encouraging and suggest that tACS may improve speech output for some speakers with nonfluent aphasia during a speech entrainment task. Data also suggest improved temporal alignment (entrainment) for some

participants with aphasia during the in-phase stimulation condition. These pilot data contribute to a growing body of research that applies noninvasive brain stimulation as an adjuvant to speech-language therapies and further inform how external modulation may facilitate neural plasticity in stroke survivors.

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LIST OF ABBREVIATIONS

Area *Spt*..... parietotemporal boundary at posterior Sylvian fissure

AV..... audiovisual

DTI..... diffusion tensor imaging

DTW ..... Dynamic Time Warping

ECoG..... electrocorticography

EEG..... electroencephalography

HD-tACS.....High-Definition Transcranial Alternating Current Stimulation

HSFC.....Hierarchical State Feedback Control Model

IFG*po* ..... Inferior Frontal Gyrus, *Pars Opercularis*

MFCC ..... mel-frequency cepstral coefficients

NFA..... Nonfluent Aphasia

NIBS .....Noninvasive Brain Stimulation

*p*MTG..... Posterior Middle Temporal Gyrus

PWA.....Persons With Aphasia

rsfMRI..... Resting State Functional Magnetic Resonance Imaging

rTMS ..... Repetitive Transcranial Magnetic Stimulation

SE..... Speech Entrainment

SFC .....State feedback control model

SLT .....Speech Language Therapy

CHAPTER 1

INTRODUCTION

1.1 Background: Etiology and Consequences of Poststroke Aphasia

It is estimated that 800,000 people suffer a stroke each year in the United States. This statistic represents only a small portion of the 80 million people who are affected by stroke annually worldwide (Johnson et al., 2019; Katan & Luft, 2018). While the overall incidence and prevalence of stroke has declined, the burden of stroke remains high due to the aging population and risk factors that contribute to increasing a lifetime stroke risk and the fact that older generations are living longer with stroke deficits (Crimmins, Zhang, Kim, & Levine, 2019; Feigin et al., 2017; Virani et al., 2020). Stroke is not only a leading cause of mortality and disability, but presents a particularly concerning public health crisis (Benjamin et al., 2018; Feigin et al., 2015). Furthermore, the number of strokes in younger populations continues to rise, and as a result, young stroke survivors are living longer with stroke-induced impairments (Kissela et al., 2012; Ramirez et al., 2016; Swerdel et al., 2016).

Aphasia results from damage to the language centers in the left hemisphere of the brain. In the context of post-stroke aphasia, brain damage is most typically caused by disrupted blood supply to the middle cerebral artery and associated vascular distributions in the left hemisphere. It is estimated that approximately 20 to 30 percent of stroke survivors experience aphasia (Engelter et al., 2006; Von Arbin et al., 2001). For many of

these patients, aphasia persists for years into the chronic stages of recovery (El Hachioui et al., 2013; Engelter et al., 2006; Poeck, 1989).

Consider the extent to which humans rely on communication to successfully engage and participate in society. The inability to effectively use language, whether as a result of an expressive language deficit (i.e. unable to say the correct word or write one's name) or receptive language deficit (i.e. unable to understand what is said or written), severely impairs access to the social world. Consequently, most people with aphasia are limited in their functional independence and in their ability to maintain interpersonal connections. For this reason, aphasia has profoundly negative effects on quality of life and is a strong predictor of negative outcomes, including those living with aphasia in long-term care facilities (Tsouli, Kyritsis, Tsagalis, Virvidaki, & Vemmos, 2009). For these individuals, health-related quality of life is significantly worse than for patients diagnosed with other chronic conditions like cancer or Alzheimer's disease (Lam & Wodchis, 2010) and the presence of aphasia is associated with a 2-fold increased risk of mortality (Von Arbin et al., 2001).

Lack of autonomy and social isolation are prevalent across most individuals living with aphasia, as many are unable to return to work or school and report significantly reduced access to their friends, families and others in their social network. Consequently, a number of psychosocial sequelae such as anxiety, loneliness, sadness, grief and depression accompany aphasia (Hemsley & Code, 1996; Hilari et al., 2003; Hilari and Byng, 2009; Franzén-Dahlin et al., 2010; Lincoln et al., 2011). These elements of emotional distress not only impact stroke survivors with aphasia to a greater degree than stroke survivors without aphasia, but severity of aphasia plays a prominent role in the

effects on psychosocial wellbeing and social health. As many as half of individuals diagnosed with aphasia meet the Diagnostic and Statistical Manual of Mental Disorders III (Pichot, 1986) criteria for depression in the first three months following a stroke and this persists into the chronic stages of recovery (Kauhanen et al., 2000). Severe aphasia more negatively impacts these outcomes than milder forms (Thomas & Lincoln 2008; Hilari et al., 2003; Hilari, 2011).

In addition to the disabling effects of aphasia and overwhelming nature of the diagnosis to an individual and their family, both immediately following the stroke and for the years of recovery that follow, the presence of post-stroke aphasia is costly. In the acute stage, patients with aphasia typically experience a longer hospital stay where the main driver of cost for these patients is rehabilitation services (Rajsic et al., 2019). In both the acute (Boehme, Martin-Schild, Marshall, & Lazar, 2016) and chronic stages, individuals with aphasia require more rehabilitation services, as compared to patients without aphasia (Pederson, Vinter, Olsen, 2004; Berthier, 2005; Gialanella & Prometti, 2009; Demaerschalk, Ha-Mill, Leung, 2010; Dickey et al., 2010; Ellis et al., 2012). Given that the projected costs for post-stroke care are expected to triple, reaching up to $184.1 billion by 2030, and the fact that there are approximately 2 million individuals living with stroke-induced aphasia, the management of deficits such as aphasia is an imminent public health concern (Rajsic et al., 2019).

As indicated, aphasia is one of the most devastating consequences of a stroke. There is an outstanding need for effective and efficient rehabilitation models to improve language outcomes and reduce the associated financial burden for this prevalent and sometimes, highly debilitating disorder. It is, therefore, a critical research priority to treat

people with aphasia to reduce the impact of aphasia by prioritizing language recovery and improved quality of life. In the sections that follow, an extensive background regarding aphasia recovery and the state of the art for aphasia management is outlined. Additionally, the neurophysiological underpinnings and behavioral variables that are particularly relevant in the context of the current study will be discussed. Importantly, this discussion is not exhaustive, but aims to highlight aspects of the field that are most relevant to this project and offer motivation for the current investigation.

1.2 The Neurobiology of Language

1.2.1 Conceptualizing Language in the Brain: Historical and Contemporary Perspectives

Neuroanatomically, aphasia most commonly occurs following an occlusion to the left middle cerebral artery (MCA) which transverses the lateral sulcus between the frontal and temporal lobes. As part of the circle of Willis, the MCA is one of the most pathologically affected blood vessels in the brain. Broadly, the MCA bifurcates into superior and inferior branches which irrigate the lateral inferior frontal lobe (Broca's area) and superior temporal gyrus (Wernicke's area). Both of these regions are classically associated with language impairment (Navarro-Orozco & Sanchez-Manso, 2020). To improve the clinical management of aphasia, it is necessary to understand the neurobiology of language in both healthy and damaged neural systems.

Classical models of aphasia, such as the Wernicke-Lichtheim model, associate language impairments with specific lesion locations (Lichtheim, 1885; Wernicke, 1874); however, it is now accepted that this is a gross oversimplification of the neural mechanisms of language processing. For example, it is well-accepted that regions outside of Broca's and Wernicke's area are implicated in speech and language (Poeppel, Hickok,

& Poeppel, 2015; Tourville & Guenther, 2011; Ueno, Saito, Rogers, & Lambon Ralph, 2011). This is evidenced by empirical data that reveal localized damage to Wernicke's or Broca's area rarely results in either a complete Wernicke's or Broca's subtype of aphasia (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Fridriksson, Fillmore, Guo, & Rorden, 2015; Lazar & Mohr, 2011; Mohr, Pessin, Finkelstein, Funkenstein, Duncan, 1978).

The underlying neural correlates of human communication have been discussed in great detail in the last few decades (Binder & Desai, 2011; Cloutman et al., 2009; DeLeon et al., 2007; Norman Geschwind, 1970; Hagoort & Indefrey, 2014; Hickok, 2012a; Hillis et al., 2006, 2001; Poeppel, Emmorey, Hickok, & Pylkkänen, 2012; C. Price, 2012; Rogalsky & Hickok, 2011; Thompson-Schill, 2014) and have offered new perspectives regarding the neurobiology of language. Unlike the Wernicke-Lichtheim model, contemporary models of language processing posit that language processing is not dependent on modular brain regions, but instead relies on a large-scale, left lateralized network and multiple sets of brain regions. The inferior frontal gyrus, anterior, posterior and inferior temporal lobes are considered to be particularly relevant (Friederici & Alter, 2004; Hickok & Poeppel, 2004) and language hubs within these regions include the inferior frontal gyrus (pars opercularis, pars triangularis), supramarginal gyrus/angular gyrus, middle temporal gyrus, and posterior superior temporal gyrus (Fridriksson et al., 2018).

Contemporary models such as the dual stream model, for example, suggest a far more detailed account and emphasize the connections between cortical regions. Hickok and Poeppel (2004) suggest that speech production and sound-articulation mapping relies on dorsal stream regions in the left hemisphere and that a bilateral ventral network

subserves comprehension and sound-to-meaning mapping. The dorsal stream involves the parietal-temporal junction (Area *Spt*) and frontal lobe regions (posterior inferior frontal gyrus [pars opercularis and pars triangularis] and lateral premotor cortex) while the ventral stream is located bilaterally into the temporal lobes (posterior middle and inferior temporal gyrus to the anterior middle temporal gyrus) and leads up to the inferior frontal gyrus.

1.2.2 Underlying neural correlates of language

Neuroimaging studies from both neurotypical (Catani et al., 2007; Catani, Jones, & Ffytche, 2005; Glasser & Rilling, 2008; Saur et al., 2008; Ueno et al., 2011) and clinical populations (Fridriksson et al., 2016; Keator, Yourganov, Faria, Hillis, & Tippett, 2021; Kümmerer et al., 2013) provide evidence for the structural-functional relationships of the dorsal and ventral streams in language processing and production. In the context of aphasia, however, one of the most comprehensive accounts regarding the anatomy of aphasia reveals a broad cortical network that supports speech and language processing (Fridriksson et al., 2018). This investigation was a follow-up to an initial investigation of the anatomical boundaries of the dorsal and ventral streams (Fridriksson et al., 2016) and offers perhaps the most accurate characterization of lesion-induced language deficits in a large cohort of patients with chronic aphasia (n = 159) (Fridriksson et al., 2018). Using region-wise and connectome lesion-symptom mapping (Yourganov, Fridriksson, Rorden, Gleichgerrcht, & Bonilha, 2016), Fridriksson and colleagues used language-specific measures to identify cortical regions and pathways where damage was associated with speech and language impairments. Consistent with the nature of the dorsal and ventral streams in the dual stream model of language processing (Hickok & Poeppel, 2007),

results revealed that motor speech impairments are likely to arise from damage to the dorsal stream while comprehension impairments are associated with disruptions to the ventral stream. Other speech and language functions such as naming, repetition and grammatical processing are posited to rely on interactions between dorsal and ventral streams. Importantly, damage not only to relevant cortical hubs for speech and language result in behavioral impairments, but damage to the connections that terminate in these hubs negatively impacts language function as well. This indicates a crucial role for not only major white matter tracts such as the arcuate fasciculus, superior longitudinal fasciculus and inferior fronto-occipital fasciculus, but also for short fibers between the angular gyrus, posterior superior temporal gyrus, and middle temporal gyrus. Results from this study emphasize the network-based structure of language in the brain and the subsequent effects of brain damage, such as a stroke, on this eloquent system.

There is now a substantial body of literature that supports the fact that language relies on local and distant neural networks across temporal, frontal and parietal regions of the brain (Friederici & Wartenburger, 2010; Hickok, 2013; Fridriksson et al., 2016, 2018a; Stockert et al., 2020). Damage to any of these neural circuits may, therefore, result in aphasia, suggesting that aphasia is a network disorder. This idea is discussed in greater detail in *Section 1.3.3: Aphasia as a Network Disorder*. Considering aphasia as a network disorder (Carrera & Tononi, 2014; Corbetta et al., 2015; Fornito, Zalesky, & Breakspear, 2015; Siegel et al., 2016), then, suggests that this same network-based organization may benefit recovery to some degree. For example, reorganization or recruitment of residual language areas and domain-general networks may compensate for

the stroke-induced damage to some extent (Crinion and Alexander, 2007; Stockert et al., 2016; Hartwigsen & Saur, 2019).

1.3 Aphasia Recovery: A Neurological Perspective

1.3.1 Neuroanatomical effects of stroke and aphasia

Aphasia recovery is complex and dynamic (Pedersen, Jorgensen, & Nakayama, 1995; Yagata et al., 2017). The process of recovery varies substantially for each person with aphasia, even in cases where the initial severity of aphasia is similar (Hope et al., 2019; Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). Language recovery relies on the re-organization of domain general and language-specific networks (Corbetta et al., 2015; Fridriksson et al., 2016; Geranmayeh, Brownsett, & Wise, 2014; Kümmerer et al., 2013; Siegel et al., 2016; Ueno et al., 2011). Although the nature of aphasia recovery has been studied extensively and technological advances have drastically improved our understanding of the underlying neural mechanisms, the process is still not completely understood and prognostication remains a challenge (Stockert et al., 2020; Wilson & Schneck, 2020; Cheng et al., 2021). While the current study aims to improve language function in a group of chronic stroke survivors, it is relevant to briefly outline the initial stages of post-stroke recovery to set the stage for the nature of neural disruption following a left-hemisphere lesion.

Brain damage induced by a stroke can result in degeneration, neurotoxicity, inflammation and apoptosis. Acutely, hypoperfusion (ischemic penumbra) and parenchymal damage negatively impact the integrity of language networks (Fridriksson, 2010; Hillis et al., 2001; Shahid et al., 2017). If critical nodes of the language network are affected by stroke, these regions, as well as connections to and from these areas

(diaschisis; von Monakow, 1906) may result in dysfunction of remote brain areas due to stroke-induced degeneration, neurotoxicity, inflammation and apoptosis (Doyle, Simon, & Stenzel-poore, 2008). It is well-understood that there is some degree of spontaneous recovery of language function during the initial days following a cerebrovascular event as the inflammatory response to stroke and diaschisis resolves (Gerstenecker & Lazar, 2019; Lomas & Kertesz, 1978).

1.3.2 Neural mechanisms to support aphasia recovery

One important mechanism for the language recovery in this acute stage is the reperfusion or restoration of blood flow to hypo-perfused language regions or penumbral tissue surround the infarct (Hillis & Heidler, 2002; Hillis et al., 2006). Randomized control trials suggest interventions such as intravenous thrombolysis (NEJM, 1995) or endovascular therapies (Berkhemer et al., 2015; Campbell et al., 2015) are beneficial for improving outcomes (Hillis, 2007). In terms of language recovery, reperfusion is associated with language improvement (Hillis et al., 2003). Spontaneous recovery may also result from cortical reorganization, neurogenesis, axonal sprouting, dendritic plasticity and angiogenesis (Castro-Alamancos and Borrell, 1995; Nudo et al., 1996; Biernaskie and Corbett, 2001; Conner et al., 2005; Ramanathan et al., 2006; Nudo, 2007; Paris, 2007). Regardless of the etiology, however, brain plasticity in the acute phase facilitates spontaneous recovery (Kerr, Cheng, & Jones, 2011). Behavioral experience may further facilitate this plasticity and is discussed in subsequent sections (Liepert et al., 2000) (see *Section 1.4.3: Treatment-induced neurophysiological changes in aphasia*).

Although the amount of language recovery is greatest in the acute phase, some spontaneous recovery may continue into the subacute phase (days and weeks following

the stroke) as edema and diaschisis continue to resolve and residual areas of the language network regain function (Saur et al., 2006), or other regions compensate for damaged areas (Brownsett et al., 2014; Geranmayeh et al., 2014). From a network perspective, a study by Saur and colleagues in 2006 suggests a three-phase model of language reorganization. Using functional MRI, this investigation revealed large increases in activation in bilateral language regions, particularly the right Broca-homologue and supplementary motor area in the sub-acute phase of recovery. Importantly this increase was associated with increased language function. This may suggest that functional connectivity is reduced in the acute phase (< 1 week post-stroke) and any remaining language ability is largely attributed to left inferior frontal gyrus activation. Direct effects of the lesion, diaschisis, and hypoperfusion likely play a role in the lack of activation in this phase and reflects the initial loss of function. In the sub-acute phase, activation improves drastically and later normalizes into the chronic phase, especially for patients who show some level of recovery (Saur et al., 2006).

The chronic stage of recovery begins approximately 6 months following the stroke and persists for months and years following the initial infarct. At this point, many of the previously described mechanisms of recovery have stabilized but residual cortical damage such as chronic hypoperfusion may persist (Richardson et al., 2011; Thompson et al., 2017). This may contribute to slower and somewhat more stable changes to spontaneous recovery (Hope et al., 2017). Importantly, however, although early evidence from animal models suggests treatment should be implemented in the acute stages of recovery when plasticity is more active, behavioral evidence from individuals with chronic aphasia suggests plasticity is evident months and even years post-stroke

(Breitenstein et al., 2017; Holland et al., 2017; Hope et al., 2017; Johnson et al., 2019). Despite these promising outcomes, not all patients improve into the chronic stages, and even with therapy, some patients may show decline (Johnson et al., 2019). This concept is discussed further in *Section 1.5: Clinical Management of Post-Stroke Aphasia: State of the Art*.

Behavioral impairments in the chronic phase have also been attributed to the increased cognitive demand of language processing for individuals with aphasia. For example, greater demands on cognitive domains such as attention, working memory, cognitive control or fluid intelligence (Woolgar et al., 2010) have been shown to play a role in effortful language processing in neurotypical controls (Fedorenko, 2014). In the context of aphasia recovery, some of these same cognitive factors (i.e. verbal working memory) predict language improvements (Dignam et al., 2017; Gilmore et al., 2019).

Given this supposed role for general cognitive domains in aphasia recovery, some have suggested that domain-general regions (i.e. middle frontal gyrus, precentral gyrus, inferior parietal cortex) may be recruited, despite not having a role in language pre-morbidly (Turkeltaub et al., 2011; Kiran et al., 2015; Sandberg et al., 2015; Meier et al., 2016; Sims et al., 2016; Cramer, 2008; Kleim, 2011). Many of these processes are attributed to therapy-induced changes and will be discussed in this context in *Section 1.4.3: Treatment-induced neurophysiological changes in aphasia*.

1.3.3 Aphasia as a network disorder

Importantly, it is now well-understood that stroke-induced infarcts result in damage to not only focal cortical areas (necrosis), but also to distal disconnections of structural and functional networks (i.e. diaschisis) (Carrera & Tononi, 2014; Corbetta,

Kincade, Lewis, Snyder, & Sapir, 2005; Grefkes & Fink, 2014; Griffis, Metcalf, Corbetta, & Shulman, 2020). Damage to white matter pathways (structural connectivity) or the neural synchrony between regions (functional connectivity) often persist despite extensive reorganization. Necrotic cortical regions and hypoconnectivity affect the integrity of the networks that support language and present clinically as chronic aphasia. The majority of research studies focus on the chronic stages of recovery, at which point language is largely reorganized (Wilson & Schneck, 2020), whereas few studies have examined the longitudinal process of reorganization in the acute-subacute phases (Saur et al., 2006).

Disruptions to white matter pathways negatively affect language function and recovery (Baldassarre, Metcalf, Shulman, & Corbetta, 2019; Carter et al., 2010; He et al., 2007; Klingbeil, Wawrzyniak, Stockert, & Saur, 2019; Park et al., 2011; Sandberg, 2017; Siegel et al., 2016; Tang et al., 2016). In chronic aphasia, the extent of damage to structural connections is related to the severity of language impairment (Bonilha, Gleichgerrcht, Nesland, Rorden, & Fridriksson, 2017; Bonilha, Rorden, & Fridriksson, 2014; Butler, Ralph, & Woollams, 2014; Griffis et al., 2020) and damage to specific white matter pathways (e.g. the arcuate fasciculus) is inversely related to the severity of language impairments (Marchina et al., 2011). In chronic aphasia, greater disruptions to left-hemisphere networks are associated with more severe aphasia (Marebwa et al., 2017).

Stroke-induced lesions in the left hemisphere also disrupt functional connectivity and this is evident even in the chronic stage (Carrera & Tononi, 2014; Grefkes & Fink, 2014; Baldassarre et al., 2016; Fox, 2018). For example, empirical data reveal abnormal

functional connectivity (particularly in left frontoparietal language and cognitive processing networks), and decreased temporal synchronization following a stroke. This has been documented with resting state connectivity data in studies of global connectivity analyses (Siegel et al., 2016; Zhu et al., 2017; Siegel et al., 2018) and specific networks such as the default mode network (Tuladhar et al., 2013); dorsal attention network (Carter et al., 2010); language network (Nair et al., 2015) and frontoparietal and cingulo-opercular cognitive control networks (Nomura et al., 2010).

A number of studies have identified specific language impairments that result from abnormal patterns of activity across different networks (Baldassarre et al., 2019; Carter et al., 2010; He et al., 2007; Park et al., 2011; Siegel et al., 2016; Tang et al., 2016). For example, Baldassarre and colleagues (2019) found that resting state functional connectivity in different networks was associated with the degree of impairment for distinctive language domains (e.g. phonology). In the chronic stages of recovery, network topology and functional connectivity remain abnormal such that more severe language deficits are correlated with more abnormal network measures (Meier, Johnson, Pan, & Kiran, 2019a; Sandberg, 2017). This and other investigations of resting state and task-based functional connectivity in language (Griffis, Nenert, Allendorfer, & Szaflarski, 2017; Klingbeil et al., 2019) and motor function (Arun, Smitha, Sylaja, & Kesavadas, 2020; Min et al., 2020) suggest resting state functional connectivity may be an important biomarker for language recovery (Keator et al., 2021; (Griffis et al., 2020; Keator et al., 2021; Wodeyar, Cassidy, Cramer, & Srinivasan, 2020; Yourganov, Stark, Fridriksson, Bonilha, & Rorden, 2021); however, the exact mechanism that supports these recovery and reorganization processes remains to be elucidated (Siegel et al., 2018).

1.3.4 Neurophysiological implications for prognostication

Advancements in the understanding of not only brain-behavior relationships, but the neurophysiology of recovery of aphasia recovery have contributed to the ability to build predictive models of recovery (Halai, Woollams, & Lambon Ralph, 2018; Hillis et al., 2018; Hope, Seghier, Leff, & Price, 2013; Osa García et al., 2020; Price, Seghier, & Leff, 2010). Over the last few decades, a number of studies have aimed to identify variables that are associated with language improvements and while results are not always consistent across studies, there are a number of variables that are expected to play a substantial role in recovery. Neurophysiological factors such as total lesion volume (Boyd et al., 2017; Hope et al., 2013; Watila & Balarabe, 2015) and behavioral factors such as initial aphasia severity (Kertesz and Mccabe, 1977; Pedersen et al., 1995; Lazar et al., 2010; Ramsey et al., 2017) have been most consistently reported such that larger lesion and greater initial severity yield poorer outcomes (Benghanem et al., 2019). Other demographic factors such as age, and education (Von Arbin et al., 2001), or clinical factors such as the number of treatment hours (Johnson et al., 2019) have been reported, but effects are not consistent across studies (Plowman, Hentz, & Ellis, 2012). Unfortunately, despite extensive work in this area, outcomes are confounded by substantial variability in intervention approaches and rehabilitation gains which contribute to considerable unexplained variance in the prediction of such outcomes. This makes prognostication and clinical management exceptionally challenging (Cheng, Worrall, Copland, & Wallace, 2020).

1.4 Neuroplastic Mechanisms for Recovery and Rehabilitation

1.4.1 Evidence for neuroplasticity in poststroke aphasia

Aphasia recovery across all stages of recovery is thought to depend on neuroplasticity. Neuroplasticity refers to the neural (structural and physiological) changes that support learning, or in the case of aphasia, re-learning, i.e., how unaffected cortical regions take on new roles following a stroke (Hartwigsen & Saur, 2019; Stefaniak, Halai, & Lambon Ralph, 2020; Turkeltaub, 2019). More specifically, structural correlates of functional plasticity may be reflected in grey matter thickness or density. In a healthy adult, it is well-understood that experience-induced brain changes take place throughout the lifespan (Kleim, 2011; Warraich & Klei, 2010; Kerr et al., 2011). Following brain injury however, this experience-dependent neural plasticity may be negatively impacted by widespread disruption to neural networks (Kerr et al., 2011). Despite this, experience can change neuronal structure and synaptic efficacy (Kleim & Jones, 2008).

While our understanding of the role of neuroplastic changes in aphasia rehabilitation is nascent, there has been a considerable number of recent studies that have positively contributed to what we know about these neural mechanisms in healthy and brain-damaged populations (Crosson et al., 2019). Recent advances in technologies, particularly functional imaging, have improved our understanding of this process, yet outcomes are variable and the exact nature of recovery and the underlying mechanisms remains unclear (Wilson & Schneck, 2020). A number of recent reviews suggest that our understanding of the neural plasticity and processes of neurophysiological re-organization that facilitate the dynamic process of post-stroke recovery are important

from a rehabilitation perspective (Abel & Lambon Ralph, 2018; Crosson et al., 2019; Hartwigsen & Saur, 2019; Kiran, Meier, & Johnson, 2019).

Post-stroke neuroanatomical changes take place through reorganization (to right-hemisphere or non-language-specific regions in the left hemisphere) or restoration (of residual left-hemisphere language-specific regions), but the exact mechanisms remain unclear (Wilson & Schneck, 2020). For example, some evidence supports residual left-hemisphere regions are critical for reorganization (Fridriksson et al., 2012) while others suggest that regions in the right hemisphere are engaged in recovery (Turkeltaub, Messing, Norise, Hamilton, 2011). For example, in cases of extensive damage to the left-hemisphere language networks, right-hemisphere and bilateral domain-general regions may contribute residual language functions (Crinion & Price, 2005; Geranmayeh, Leech, & Wise, 2016; Griffis et al., 2017; Winhuisen et al., 2005). Some even suggest that the right hemisphere may interfere with recovery (Hamilton, Chrysikou, & Coslett, 2011). Regardless of the exact nature of recovery, it is evident that while many physiological changes subside in the chronic stages of recovery, the mechanisms of neural plasticity, synaptic sprouting, for example, remain adaptable (Kleim & Jones, 2008).

As a proponent of language-specific restoration, Heiss & Thiel (2006) hypothesized a hierarchical reorganization of language where undamaged perilesional areas support language recovery (Fridriksson, 2010; Fridriksson, Richardson, Fillmore, & Cai, 2012; Karbe, Thiel, Weber-luxenburger, Kessler, & Heiss, 1998; Tyler et al., 2011; Warburton, Price, Swinburn, & Wise, 1999; Winhuisen et al., 2007). This framework has been supported by a number of studies and was recently re-visited in an effort to contextualize language recovery in terms of individual differences (Kiran et al., 2019).

Kiran and colleagues identify four emerging themes for neuroplasticity in aphasia that are largely consistent with a number of recent reviews regarding the nature of aphasia recovery (Hartwigsen & Saur, 2019; Stefaniak et al., 2020; Turkeltaub, 2019). First, naming and semantic processing rely on a bilateral network of regions and these regions are engaged in language recovery (see Kiran et al., 2019; Figure 2 for a review). Second, residual left-hemisphere language networks are engaged for language recovery and homologous regions in the right hemisphere are active when there is damage to the left inferior frontal cortex (Turkeltaub et al., 2011).

These findings have been disputed by a recent activation likelihood estimation study (Stefaniak, Alyahya, & Lambon Ralph, 2021). Stefaniak and colleagues suggest that following a stroke the language network does not expand into new territories, but instead there is considerable overlap between bilateral language-related and functional networks in PWA and controls and PWA are less likely than controls to activate certain regions, including areas proximal to the core lesion. Instead PWA are more likely to engage executive-control-related regions of the right anterior insula and IFG. It is not necessarily surprising that the involvement of left-hemisphere regions relies on the integrity of those regions. Depending on the extent to which left-hemisphere regions are spared, they are essential and engaged in language recovery, but as damage to left-hemisphere language regions increases, activation shifts to right-hemisphere, multiple-demand, or default networks (Sims et al., 2016). It is worthwhile to note, however, that these changes are dynamic and occur over time which results in consequences for the nature and opportunities for neuroplastic adaptation.

One of the most notable reviews to date is a recent systematic review from Wilson & Schneck (2020) that appraises the nature of evidence regarding the functional reorganization of language in aphasia. The authors suggest that the current body of literature does not provide a clear picture of if and how functional brain activation supports recovery from aphasia. Based on 80 articles spanning the last three decades, there are very few claims that can be made with regard to language processing and recovery. Across studies, left-hemisphere language regions are less activated in people with aphasia than in neurotypical controls, and for people with aphasia, activity in left-hemisphere language regions, as well as a temporal lobe region in the right hemisphere, is positively correlated with language function. Wilson and Schneck (2020) suggest that there is modest, equivocal evidence that people with aphasia differentially recruit right-hemisphere homotopic regions or domain-general networks and reveal there is some evidence that functional activation in the left-hemisphere language regions normalizes over time. Wilson & Schneck (2020) suggest there is no evidence for dynamic re-organization.

These findings posit that while there is some agreement that the right hemisphere, residual left-hemisphere regions, and domain-general regions may play role in language recovery, the extent and nature of these processes are largely inconclusive. Notably, Wilson and Schneck (2020) identified only three studies that compared language between two or more time points that were considered methodologically robust. Importantly, the diversity of findings may be, in part, due to the heterogeneity of patients (i.e. variable lesion size and location), a myriad of therapy approaches, and highly variable neuroimaging techniques and analyses.

At this point, it is clear from the literature that the location and extent of lesion-induced damage to language-related regions may limit the neuroplasticity that is necessary for successful recovery. It is also evident that language recovery is highly variable and dependent on lesion size and location, and stage of recovery. Despite more than thirty years of advancing neuroimaging techniques, such conclusions are quite frankly unsatisfactory and offer limited perspectives to improve prognostics and advance aphasia management. Crucially, these studies reflect a long-standing stagnancy in the field of aphasiology and it can be argued that despite an overwhelming number of neuroimaging studies that aim to investigate aphasia recovery, there are few, if any, tangible outcomes that have actually influenced how people with aphasia area treated in clinical care. Such outcomes motivate a call for innovative approaches to better delineate the nature of post-stroke aphasia recovery for the development of neurobiologically-informed therapeutic interventions.

1.4.2 Principles of learning and plasticity from a rehabilitation perspective

While a clear understanding of the neural plasticity that supports language recovery following a stroke is still emerging, it is evident that principles of neuroplasticity are relevant to the development and advancement of aphasia therapy tools and conventional approaches to aphasia rehabilitation have largely relied on experience-dependent principles of neural plasticity (Hebb, 1949; Kleim & Jones, 2008).

Hebbian learning is one prominent theory that suggests neural plasticity is facilitated by behavior. Hebbian learning proposes that synaptic strength and functional neuronal connections can be reinforced and reorganized by repeated stimulation, such as behavioral therapy (Hebb, 1949). This principle also suggests that new experiences alter

synaptic efficacy and contribute to the reorganization of neural networks (Lowel & Singer, 1992). Functional and structural network connectivity measures have served as one method to investigate the neural changes following a stroke and how these mechanisms change over time, even into the chronic stages of recovery, to facilitate language recovery (or lack thereof).

Another framework for neuroplasticity as it relates to aphasia rehabilitation is from Kleim and Jones (2008). While it is not within the context of the present study to discuss each of their ten principles of neural plasticity in detail, it is necessary to briefly discuss six principles that are specifically relevant for aphasia treatment and consequently, this study (see Kiran & Thompson, 2019 for a review). The ten principles outlined by Kleim and Jones (2008) are: 1) use it or lose it; 2) use it and improve it; 3) specificity; 4) repetition matters; 5) intensity matters; 6) time matters; 7) salience matters; 8) age matters; 9) transference; 10) interference (see Kleim and Jones, 2008 for a complete discussion of principles of neural plasticity)

First, improvement in behavior is *use-dependent*. This principle is consistent with a 'use it or lose it' concept where neural circuits that are not actively used, degrade. Following brain injury, plasticity of such networks can be induced through training. In most aphasia rehabilitation, treatment focuses on the impaired language processes. It is thought that by focusing on the language impairment, associated neural mechanisms may be recovered. Conversely, 'language-specific' systems that go unused following a stroke, may lead to a decreased ability to engage existing or new neural networks. One example of an intervention inspired by the 'use it or lose it' principle is constraint-induced

language therapy. This approach encourages the use of verbal language without the use of nonverbal aids (writing, gesture) to facilitate communication (Pulvermüller et al., 2001).

A second principle suggests *specificity* rebuilds targeted networks. In aphasia recovery, this principle can be addressed by using treatments that rely on what is known about typical language processing and representation to address the primary language impairment. There are a number of impairment-based approaches in aphasia that aim to do this (Kiran & Thompson, 2003; Thompson & Shaprio, 2005; Thompson & Shapiro, 2007; Boyle, 2010; Edmonds et al., 2014; Kendall et al., 2015). Semantic Feature Analysis (SFA) (Kiran & Thompson, 2003; Boyle, 2010) is a treatment strategy that uses what is known about semantic knowledge and connects words to one another in the mental lexicon. Phonomotor Therapy (Kendall et al., 2015) uses phonological networks that control properties of speech sounds to target word finding impairments. The Verb Network Strengthening Treatment (VNeST) (Edmonds et al., 2014) trains lexical selection properties of verbs to improve verb production. Treatment of Underlying Forms (TUF) (Thompson & Shapiro, 2005) aims to improve comprehension and production at the sentence level. This treatment uses metalinguistic steps to focus on assignment and syntactic mapping to emphasize the lexical properties of verbs.

Some suggest *salience* is essential to rehabilitation approaches. There is less empirical evidence to support this principle, but for people with aphasia salience may mean using functionally significant stimuli in treatment or training stimuli that are particularly relevant to the individual and their family. This aligns closely with functional and patient-oriented treatment approaches such as Living with Aphasia: Framework for Outcome Measure (A-FROM) and the Life Participation Approach to Aphasia (LPAA)

(Kagan et al., 2008; Simmons-Mackie & Kagan, 2007; Stahl, Mohr, Dreyer, Lucchese, & Pulvermüller, 2016). Salience may also be considered in the context of impairment-based therapy that includes personally-salient training items. The principle of salience emphasizes cognitive systems that promote encoding, motivation and attention and aligns well with empirical evidence that suggests that these domain-general mechanisms may be associated with treatment-induced recovery (Brownsett et al., 2014; Geranmayeh et al., 2014).

Sufficient *repetition* is necessary and the intensity of treatment matters. Repetition and intensity are thought to influence learning and consolidation. Greater repetition and higher intensity induced neuroplasticity in animal models (Kleim & Jones, 2008) suggest invoking long-term changes following aphasia treatment requires sufficient repetition within sessions and intensive opportunities to produce target behaviors over time. 'Sufficient repetition' is not well-defined in the literature, nor are treatment and patient-related variables clear.

Intensity of treatment matters (Kleim & Jones, 2008). In aphasia rehabilitation, however, intensity is not clearly defined (Harvey et al., 2020; Pierce et al., 2020) and is even used interchangeably with 'dose' to refer to the number of hours of therapy provided in a specific period of time or the total number of hours during a treatment study (Harnish et al., 2014). In this vein, it is well-acknowledged that there are many factors that contribute to cumulative intensity (e.g. dose, Warren et al., 2017) and that there is a complex relationship between these factors and subsequent outcomes in aphasia (Crosson et al., 2019). Therefore, optimal timing (acute versus subacute verses chronic) and nature of behavioral intervention 'dose' (Harvey, Carragher, Dickey, Pierce, Rose, 2020),

intensity (Pierce et al., 2020), or type remain inconclusive. Some evidence from the aphasia rehabilitation literature suggests that higher dosage and increased treatment in the acute stages improves rehabilitation outcomes (Godecke et al., 2013; Carpenter & Cherney, 2016), but these were small studies and largely inconclusion.

It is also argued that intensive therapy in the acute stages of recovery may not be appropriate as patients may not tolerate this intensity so soon after a stroke (Holland & Fridriksson, 2001). Other studies, such as the large-scale randomized control trial by Breitenstein and colleagues (2017) suggest that massed practice (10 hours per week) is associated with improvements as compared to deferred treatment for patients with chronic aphasia. This is consistent with other studies of chronic aphasia, though others suggest that patients in the chronic phase also benefit from lower-intensity therapy (Pierce et al., 2020). In terms of session duration, there seems to be a threshold at which longer sessions no longer yield additional benefits. Stahl and colleagues (2018), for example, found that longer intervention duration but not longer session durations improved outcomes in a randomized control trial of chronic aphasia. It is clear that more research is needed to better understand how the amount and distribution of therapy at different stages of recovery and with different treatment types impact recovery outcomes. More specifically, Pierce and colleagues (2020) suggest that more evidence, particularly from large samples and randomized control trials, is needed before we can make unequivocal claims about high versus low intensity treatments.

Finally, *transference*, or generalization, is the primary goal of impairment-based aphasia therapy and aims to extend gains achieved in therapy to real-life contexts outside of the therapy room. Patterns of generalization suggest the same neural circuits that are

engaged for trained items are engaged for untrained items. For example, in aphasia therapy, generalization is best when trained and untrained behaviors are fundamentally related (i.e. trained stimuli and generalized context may share semantic, phonological, syntactic, or orthographic features; common linguistic rules or principles, or psycholinguistic mechanisms (Kiran & Thompson, 2003; Kiran, 2008; Kendall et al., 2015; Riley & Thompson, 2015; Gray & Kiran, 2019; Thompson & Shapiro, 2005; Kiran and Thompson, 2019).

Generalization aims to avoid interference. Interference refers to the effect of learned misuse or nonuse and subsequent influences on motor reorganization from animal models (Takeuchi & Izumi, 2012; Taub & Uswatte, 2003; Taub et al., 2006). In aphasia recovery, interference suggests environmentally or treatment-induced recruitment of non-linguistic strategies may interfere with learning and the generation of optimal neural networks for linguistic processing.

Complexity may be one aspect of treatment that promotes generalization. This mechanism is demonstrated by studies that reveal generalization across behaviors increases when there is a hierarchical relationship between trained and untrained targets (Sandberg & Kiran, 2014). The complexity approach or Complexity Account of Treatment Efficacy (CATE) (Thompson et al., 2003) is in opposition with many conventional approaches of therapy that begin training with the most basic level and build to more complex features. CATE uses more complex sentence structures as a starting point. Although generalization has been demonstrated empirically, the mechanisms that are required for generalization are not completely understood.

Ideally, approaches to aphasia rehabilitation implement each of these principles to elicit the optimal response to therapy. As discussed below, however, integration of the mechanisms of neural plasticity and rehabilitation approaches fails to meet the demands of a growing population of people living with chronic aphasia. There is a need to determine how the aforementioned principles can be implemented to capitalize on recovery in post-stroke aphasia and develop efficient and effective therapy tools that not only improve language skills during treatment but demonstrate maintenance after treatment has ended.

1.4.3 Treatment-induced neurophysiological changes in aphasia

The principles of neuroplasticity that are outlined here guide behavioral rehabilitation practices and may be reflected in neurophysiological changes. Earlier sections (*Section 1.3.2: Neural mechanisms of recovery and Section 1.3.3 Aphasia as a network disorder*) describe the neurophysiological changes that occur following a stroke and provide evidence to support a variety of claims regarding the neuroplastic changes that may contribute to language recovery. In this section, it is important to expand upon these neurophysiological mechanisms to highlight those that are influenced by treatment, as opposed to spontaneous recovery. Functional and structural neuroimaging studies have indicated that aphasia treatment can recruit both residual and new neural mechanisms, likely via the principles outlined in *Section 1.4.2: Principles of learning and neuroplasticity from a rehabilitation perspective*, to improve language function (see Crosson et al., 2019 for a recent review). Ongoing advancements in neuroimaging techniques may be promising for predicting aphasia outcomes and henceforth, providing individualized and efficient care for people living with aphasia.

As indicated above in *Section 1.3.4: Neurophysiological implications for prognostication*, there is no definitive consensus regarding the nature of aphasia recovery. This is because the recovery process is highly dependent on the size and location of the lesion. Furthermore, recruitment of left-hemisphere perisylvian activity and reorganization of right-hemisphere homologues seems to be task dependent (Mohr, 2017) as cognitive processes such as salience, attention, and control may also play a role (Brownsett et al., 2014; Geranmayeh et al., 2016). This further complicates the nature of recovery and of neuroplastic changes that are induced through therapy. Recent reviews have addressed the significant heterogeneity that exists in the literature with regard to treatment-induced changes. Results vary greatly due to the heterogeneity of extrinsic and intrinsic patient characteristics (i.e. time post stroke) (Saur et al., 2006); symptom severity (Lazar et al., 2010); education and cognitive reserve (Tippett, Niparko, & Hillis, 2014)), a myriad of treatment approaches, and the manner in which the changes are assessed. Response to therapy, much like the nature of recovery itself, varies substantially across patients (Kertesz & McCabe, 1977). Therefore, while it is not straightforward to draw conclusions regarding treatment-induced changes in language, there are a number of studies that have positively contributed to our understanding of treatment-induced recovery. Below, prevalent findings regarding treatment-specific neurophysiological changes are outlined. The nature of the behavioral treatments is discussed in greater detail in *Section 1.5: Clinical Management of Post-Stroke Aphasia: State of the Art*.

Many studies have found activation in the left hemisphere is associated with favorable treatment outcomes; but right-hemisphere regions are also associated with such improvements (see reviews by Crinion & Alexander, 2007; Turkeltaub et al., 2011;

Crosson et al., 2019). Therapy-driven responses are so variable that even results from studies examining changes induced by similar types of therapy (i.e. anomia treatment) may seem paradoxical. For example, Fridriksson (2010) investigated neurophysiological changes in 26 individuals with chronic aphasia following 30 hours of anomia treatment. Treatment-related naming performance associated with increased brain activation in the anterior and posterior regions of the left hemisphere, such that improved performance in correct naming was associated with activation in these regions. The authors suggest that brain changes associated with improved naming ability rely on preservation and recruitment of language-specific regions. Contrary to these findings, Abel and colleagues (2015) identified decreased activity in the left and right hemispheres that correlates with improved naming. One reason for the contrasting findings may be that a longer duration of therapy (4 weeks; Abel et al., 2015) allows for more practice and induces more efficient processing through a neural priming effect (reduced blood oxygen level-dependent signal) such that neural networks are doing 'less work' and therefore, networks require less activation (Ward, Brown, Thompson, & Frackowiak, 2003). A more recent study by Nardo and colleagues (2017) further suggests a role of decreased activity (as indicated by fMRI) as well as the involvement of bilateral networks (i.e. right anterior insula, inferior frontal and dorsal anterior cingulate cortices and left premotor cortex) in therapy-based improvements. These empirical data suggest that implicating a dominant role in recovery for one hemisphere over the other is grossly oversimplifying the true nature of treatment response.

In addition to identifying activation in nodes of neural networks, many recent imaging studies have aimed to identify treatment effects on structural and functional

connectivity (Van Hees et al., 2014; Sandberg et al., 2015b; Bonilha et al., 2016; Meier et al., 2019b; Chang et al., 2021). Treatment-related changes in network connectivity offer evidence to support how these networks function compare to neurotypical controls and importantly, how behavioral speech-language therapy may induce neural plasticity.

In studies of treatment-induced changes in white matter tracts (as measured by structural connectivity), Bonilha and colleagues (2017b) found that left middle temporal lobe connectivity is associated with success in naming treatment. Consistent with these results, a recent longitudinal study from the same group suggest that improved naming accuracy (as measured by performance on the Philadelphia Naming Test) is associated with post-treatment structural integrity (as measured by mean kurtosis) in the left posterior superior temporal gyrus (Chang et al., 2021). Since structural connectivity in the temporal lobe engages the left acuate fasciculus, these results also implicate the role of the arcuate fasciculus in treatment-induced recovery. Earlier studies from this group have found similar results. For example, a pilot study identified fiber counts in the left inferior longitudinal fasciculus that changed as a function of anomia treatment (McKinnon et al., 2017). These studies and others suggest that white matter integrity and disorganization of neuronal networks are important predictors of long-term and treatment-induced outcomes (Bonilha et al., 2014; Griffis et al., 2017; Meier et al., 2019b).

While networks are undoubtedly disrupted following a stroke (Meier et al., 2019b; Sandberg, 2017), evidence suggests that behavioral treatment may facilitate improvements to functional connectivity (Sandberg, Bohland, Kiran, 2015). Task-based functional MRI results suggest bilateral treatment-induced changes (Vitali et al., 2010;

Kiran et al., 2015; Johnson et al., 2019). Some even suggest that this improved functional connectivity results in connectivity dynamics that are more similar to neurotypical controls (Duncan & Small, 2016; Marcotte, Perlbarg, Marrelec, Benali, & Ansaldo, 2013; Van Hees et al., 2014). While these changes, especially those that occur into the chronic stages of recovery, are promising, it is evident that patterns of recovery are heterogenous and there is substantial variability. It continues to be important to investigate how neural dynamics contribute to language recovery and identify how such mechanisms can be used to inform treatment selection and perhaps, individualized approaches to clinical management.

Although structural imaging studies show changes in gray and white matter, the relationship between functional and structural change remains unclear; however, recent work suggests there may be some independence between these two measures (Keator et al., 2021). Regardless, the integrity of functional and structural connectivity networks is highly relevant for predicting neuroplastic changes (Crosson et al., 2019; Warraich & Kleim, 2010).

It is also clear that different therapies may have different effects on the nature and extent of neuroplasticity (Crosson et al., 2019). Because the nature of aphasia recovery is not straightforward, it is difficult for professionals to provide an accurate prognosis or recommendations for the most appropriate type and duration of therapy. Given the complexity of recovery, further research is needed to better understand the interaction between neural function, language treatment and behavioral outcomes, as well as the mechanisms of neural plasticity. Future therapeutic approaches should capitalize on the

inherent nature of neuroplasticity and further elucidation of brain-behavior relationships will be critical to identify biomarkers for recovery and advance clinical practice.

1.5 Clinical Management of Post Stroke Aphasia: State of the Art and Future Directions

1.5.1 Evidence for behavioral interventions

By and large, aphasia is managed by behavioral interventions (speech-language therapy; SLT) delivered by a speech-language pathologist (SLP) (Bhogal, Teasell, & Speechley, 2003; Brady, Kelly, Godwin, Enderby, & Campbell, 2016; Fama & Turkeltaub, 2014; Robey, 1998). Given the principles of neuroplasticity, it is not necessarily surprising that behavioral interventions have become the mainstay for aphasia management. For one, behavioral therapies focus on repeated practice to induce practice-dependent learning that is reflected in neural changes (Robbins, Butler, Daniels, Lazarus, & Mccabe, 2008). Second, learning that occurs in treatment sessions is reliant on client actions (i.e. quantity of errors, number of self-corrections, adaptation to task difficulty) and clinician-related inputs (i.e. cueing and feedback) (Baker, 2012; Kleim & Jones, 2008).

In the acute phase, there is limited evidence to support intensive therapy. For example, a recent randomized control trial (RATS-3) (Nouwens & Visch-brink, 2015) did not find any group differences between patients who received therapy in the acute phase as compared to those who did not. Similarly, Godecke and colleagues (2018) have found no difference in changes to overall aphasia severity for patients who receive usual care versus patients who receive usual care plus impairment-based therapy. These null results may reflect the incredible variability that exists in patient recovery during the first

few days following a stroke. For this reason, some have argued that aphasia management in the acute phase should focus on a balance approach (Fama & Turkeltaub, 2014). This may mean prioritizing counseling and education for the patient and family while incorporating intermittent assessments to monitor progress (Holland & Fridriksson, 2001).

There are two Cochrane reviews that suggest SLT is effective in the subacute phase (Engelter et al., 2006; Seniów, Litwin, & Leśniak, 2009). Similarly, a number of studies suggest that SLT is effective in the chronic phase (Brady et al., 2016), especially when delivered at a high intensity (Bhogal et al., 2003; Breitenstein et al., 2017). The recent randomized control trial by Breitenstein and colleagues is one of the most influential studies of the last decade on this topic. In a high-powered Phase III randomized controlled trial, individuals with chronic aphasia received impairment-based SLT aimed to improve speech production. Results from this study suggest SLT not only improved the effectiveness of verbal communication (as indicated by a medium effect size; Amsterdam-Nijmegen Everyday Language Test A (Blomert, Kean, Koster, & Schokker, 1994), but importantly revealed improvements in communicative quality of life (Breitenstein et al., 2017).

The amount of SLT has even been associated with improvements in language processing years into the chronic stage and it seems behavioral treatment may be a driving factor to improve language in the chronic stages of recovery (Moss and Nicholas, 2006; Wisenburn and Mahoney, 2009; Fridriksson et al., 2018b; Mozeiko et al., 2018; Johnson et al., 2019). Taken together, this evidence suggests that there is ample opportunity for recovery throughout the lifetime for a person with aphasia (Holland et al.,

2017; Hope et al., 2017; Johnson et al., 2019). However, there are a number of caveats to this notion. While therapy in the chronic stage demonstrates improved performance at the group level, there is a wide variety of individual variability and a recent meta-analysis suggests that only a small proportion of participants respond to and maintain gains following intensive aphasia treatment (Menahemi-Falkov et al., 2021).

1.5.2 Aphasia therapy: Impairment vs. participation-based approaches

Treatment for aphasia may vary depending on aphasia type and severity (Fridriksson & Hillis, 2021). Classically, aphasia has been classified based on language impairment. Although controversial, classification systems can be beneficial to diagnose and determine patterns of language impairments following a stroke (Sheppard & Sebastian, 2021). In the western hemisphere, the most commonly used system is the Boston Classification System. Developed in the 1960's by Norman Geschwind, Frank Benson, Harold Goodglass, and Edith Kaplan, this system delineates eight subtypes of aphasia based on the presence or absence of three clinical characteristics: 1) fluency of speech; 2) ability to comprehend language; and 3) the ability to repeat. The eight subtypes are: 1) Broca's; 2) transcortical motor; 3) global; 4) mixed transcortical or isolation; 5) Wernicke's; 6) transcortical sensory; 7) conduction; and 8) anomic. In this classification system, Broca's, transcortical motor, mixed transcortical and global aphasia are all classified as nonfluent while Wernicke's, transcortical sensory, conduction and anomic aphasia are all fluent aphasias. In *Section 1.10 Nonfluent Aphasia*, a more in-depth description of nonfluent aphasia is described, as this is the population of interest for the current study.

Historically, conventional SLT paradigms tend to subscribe to one of two approaches: 1) impairment-based therapies that focus on improving specific language deficits with highly-structured tasks (Kendall et al., 2008; Boyle, 2010; Edmonds, Mammino, Ojeda, 2014) and 2) functionally-based therapies that capitalize on preserved abilities (Chapey, 2011; Elman, 2011; Simmons-Mackie & Kagan, 2007). Impairment-based approaches tend to ascribe to a medical-model where outcomes are determined based on performance on a behavioral assessment while functionally-based therapies focus on patient-centered social models that emphasize functional communication (Sheppard & Sebastian, 2021).

1.5.2.1 Impairment Based Therapy

Impairment-based therapy techniques aim to remediate language impairments (i.e., anomia, agrammatism) by targeting particular language functions (i.e. phonological, morphological, semantic, syntactic and/or pragmatic elements) in highly structured tasks in an attempt to generalize these skills and improve overall language abilities. Importantly, although the concept of 'language' either in terms of impairment or 'recovery,' is often treated as a singular entity, it is imperative that treatment approaches consider the heterogeneity and vast number of variables that are at play within each of these concepts. Different elements of language processing, for example are supported by different cognitive functions and regions, or and perhaps most importantly, the interactions between these (Fridriksson et al., 2018; Gordon, 2002; Menenti, Gierhan, Segaert, & Hagoort, 2011; Patterson & Lambon Ralph, 2015). The nature of a stroke-induced lesion may damage these systems independently or in tandem which results in the multi-dimensional and graded nature of aphasia (Kümmerer et al., 2013; Butler et al.,

2014; Mirman et al., 2015; Alyahya et al., 2020). In this vein, it is important to consider that for any language function, there are a variety of etiologies responsible for a particular clinical presentation. For example, anomia, or difficulty in word-finding, may be caused by impairment at several different levels of processing. (phonological, lexical-semantic, or due to motor speech disorders) and to various degrees of severity depending on which parts of the cortical networks that support naming were affected (DeLeon et al., 2007). This can be especially complex because naming is not associated with one singular cortical area, but rather, an expansive cortical network (Fridriksson et al., 2018). Similarly, fluency may be due to a variety of etiologies. This is discussed in further detail below in the context of nonfluent aphasia (*Section 1.10: Nonfluent Aphasia*).

Most commonly, aphasia treatments tend to incorporate semantic and/or phonological processes to improve word-finding in people with aphasia (Boyle & Coelho, 1995; Boyle, 2004, 2010; Kiran & Bassetto, 2008; Kiran & Thompson, 2003; Leonard, Rochon, & Laird, 2008; Nickels, 2002; Van Hees, Angwin, McMahon, & Copland, 2013; Wisenburn & Mahoney, 2009). Anomia is considered to be a hallmark impairment of aphasia as it pervades across all subtypes of aphasia and patients without word findings deficits are unlikely to have aphasia (Goodglass & Wingfield, 1997). Given that anomia persists, at least to some degree across all aphasia subtypes, and the fact that comprehension deficits may preclude adequate participation in therapy sessions due to reduced understanding of the task (Fleming et al., 2021), many evidence-based practices aim to improve expressive language function across many of the aforementioned communicative domains (Edmonds et al., 2014; Harnish et al., 2014; Van Der Meulen et al., 2014; Kendall et al., 2015; Stahl et al., 2016).

A complete review of the literature of aphasia rehabilitation is not within the scope of the current study, but it is important to spotlight some of the impairment-based aphasia therapies and highlight recent reviews that provide additional insight into the nature of contemporary approaches to the treatment of post-stroke aphasia (Fridriksson & Hillis, 2021). Many of the impairment-based therapies are strongly rooted in the principles of neuroplasticity and as such, are mentioned above in *Section 1.4.2 Principles of Learning*. This includes Constraint-Induced Language Therapy (CILT; (Pulvermüller et al., 2001); Melodic Intonation Therapy (MIT) (Helm-Estabrooks et al., 1989; Semantic Feature Analysis (SFA) (Boyle & Coelho, 1995); Phonological Components Analysis (PCA) (Leonard et al., 2008), Verb Network Strengthening Treatment (VNeST) (Edmonds et al., 2009), Phonomotor Therapy (Kendall et al., 2015), and Treatment of Underlying Forms (TUF) (Thompson & Shapiro, 2005) are some many evidence-based practices that have been developed in recent years.

Some approaches like CILT (Pulvermüller et al., 2001) and intensive language action therapy (Pulvermuller & Berthier, 2008) restrict therapy to the verbal modality only. CILT, as described above, encourages the use of verbal language and discourages the use of alternative modalities such as writing, drawing or gesture for communication. This is an intensive approach that emphasizes the importance of massed practice and assumes that symptoms will worsen if language is not used due to reliance on nonverbal communication.

Unlike CILT, multimodality approaches like multi-modal aphasia therapy (M-MAT) (Rose et al., 2019) aim to improve verbal output but specifically elicit nonverbal strategies. There is a large number of studies that demonstrate positive outcomes when

supplementing written communication with writing (DeDe, Parris, & Waters, 2003; Wright, Marshall, Wilson, & Page, 2008), gesture (Rose, 2006) and drawing (Farias, Davis, & Harrington, 2006). While more evidence is needed to support M-MAT, this approach may be effective by combining multimodality supports in conjunction with verbal language to elicit successful communication, especially when verbal expression fails. A recent phase III, randomized-controlled trial suggests that constraint-induced aphasia therapy and multimodal aphasia therapy, when compared to conventional SLT (usual care) were effective for word retrieval, functional communication and quality of life for participants with aphasia (Rose et al., 2022).

MIT (Helm-Estabrooks et al., 1989) will be described in greater detail in the context of nonfluent aphasia below (see *Section 1.10.5: Treatment for Nonfluent Aphasia*) but briefly, this therapy approach encourages PWA to use prosody and varied intonation in their verbal communication to improve their fluency. SFA (Boyle & Coelho, 1995) is thought to increase semantic network activation by training patients to produce relevant semantic information for a target production (i.e. for example identifying the physical properties or use for a particular target). In a similar vein, PCA (Leonard et al., 2008) elicits phonological components for a target structure to resolve word finding deficits, a hallmark clinical presentation across all types of aphasia. VNeST (Edmonds, Nadeau, & Kiran, 2009) is used to strengthen associations between verbs and related agents and patients. Similar to SFA, VNeST approach is thought to promote network activation through word retrieval at the phrase and sentence level.

To improve syntactic structures at the sentence level, TUF (Thompson & Shapiro, 2005) relies on metalinguistic training of sentence-level tasks to treat comprehension and

production of various syntactic forms in patients with Broca's aphasia. Evidence supports TUF for improving sentence processing in patients with agrammatism through a complexity approach (Barbieri et al., 2019)

The fundamental premise of aphasia therapy, particularly for impairment-based interventions, is that repeated practice of a targeted behavior results in generalization to an untrained context outside of the rehabilitation setting (Thompson & Shapiro, 2007). Impairment-based therapies serve as the majority of aphasia treatments. Unfortunately, however, outcomes from these types of approaches (i.e. naming) are not always indicative of functional communication gains (Sheppard & Sebastian, 2021).

Many have begun investigating the effects of evidence-based interventions in the context of computerized therapy. Such approaches may be especially worthwhile given that participants with aphasia can practice language skills in the absence of a speech-language pathologist. Computerized therapies may also allow for increased amounts of practice as compared to the standard of care as patients can practice at home and not just within structured therapy sessions in the clinic. Recent studies suggest that independent home practice may in fact be a viable alternative to clinician-led therapies for chronic aphasia (Kurland, Liu, & Stokes, 2018). A recent randomized control trial (Big CACTUS, n = 278) reveals enhanced naming abilities in people with chronic aphasia following self-managed computerized aphasia therapy (Palmer et al., 2019). Intensive (~85 hours) computer-based therapies also reveal improvements in auditory comprehension (Fleming et al., 2021). Given the ever-evolving presence of technology and the impacts of the ongoing COVID-19 pandemic, computer-based therapies may be a

promising application of SLT to improve access to rehabilitation and improve language outcomes.

1.5.2.2 Participation-Based Therapy

Unlike impairment-based therapies, participation (or functionally)-based therapies target communication abilities more broadly to improve how a person communicates with others using pragmatic, functional communication and pragmatic approaches (Chapey, 2011; Elman, 2011; Simmons-Mackie & Damico, 2007). In this way, functionally based approaches focus less on the underlying impairment and instead, target 'real life' communication goals and outcomes. For example, these types of approaches may establish communication abilities, and implement personally relevant stimuli. Additionally, these types of approaches aim to reduce communication barriers in the community by providing care partner training and improving the success of communication.

One community-based approach is the Life Participation Approach to Aphasia (LPAA) (Kagan et al., 2008) which strives to help stroke survivors live successfully with aphasias by improving access to the community. Programs like aphasia groups and aphasia centers aim to provide psychosocial benefits and improve communication and are very well-aligned with LPAA (Elman, 2016). Although there is a lack of large, high-quality studies to support the utility of LPAA, it seems reasonable that these approaches may be most beneficial for individuals with severe aphasia. As highlighted above, aphasia severity is one of the few reliable predictors of aphasia outcomes such that those with more severe aphasia are less likely to respond to speech and language therapy (Breitenstein et al., 2017; Godecke et al., 2020; Nouwens et al., 2017) and therefore, may

be best served with approaches that align with LPAA, or alternative approaches such as counseling, conversation coaching (Holland, 1991) and/or the inclusion of augmentative and alternative communication modalities (Purdy et al., 1994; Nicholas et al., 1998; see review by Russo et al., 2017).

Regardless of the approach, the primary goal of aphasia rehabilitation is to improve language function and ultimately, communicative ability and quality of life. To accomplish this, the most effective therapies may combine elements of functional and impairment-based therapies to yield the most positive outcomes for people living with aphasia (Galletta & Barrett, 2014).

1.5.3 Pitfalls of existing therapy approaches for aphasia

While there tends to be agreement that SLT is better than no SLT, treatment response is variable, and little is known about which factors induce the most effective therapeutic response. Many high-quality studies rely on small sample sizes or single-case study designs. Recent reviews also fail to show that any one treatment type is superior to another (Brady et al., 2016) and as highlighted above, there is still no clear answer regarding the optimal timing of treatment delivery, intensity, and dose (Harvey et al., 2020). Some report more treatment is better (Basso, 2005; Bhogal et al., 2003; Brady et al., 2016; Cherney et al., 2008; Robey, 1998) but it is unclear which treatment element and targets should be emphasized (Barthel, Meinzer, Djundja, & Rockstroh, 2008; Brady et al., 2016; Robey, 1998) and which individuals benefit from these intensive treatment schedules (Cherney, Patterson, & Raymer, 2011).

Many studies have reported treatment-related factors that are expected to play a role in positive outcomes. However, the findings are not straightforward. Patients with

aphasia present with a wide range of stroke etiologies, clinical presentations, demographics and other health-related conditions that may impact their course of recovery. Factors such as location and size of the stroke, initial aphasia severity, and demographic factors are known to affect outcomes, although these are reported inconsistently (Berthier, 2005; Plowman et al., 2012; Watila and Balarabe, 2015; Benghanem et al., 2019). Other patient characteristics such as cognitive skills (Lambon Ralph, Snell, Fillingham, Conroy, & Sage, 2010; Van De Sandt-Koenderman et al., 2008) have been found to predict therapy outcomes. Furthermore, outcomes are typically measured solely based on speech and language outcomes and few studies actually report meaningful improvements. Therapy-related gains that are reported are modest (Hope et al., 2017) and effect sizes are small or moderate (Breitenstein et al., 2017). Reviews indicate that the mean difference is small (0.28; largest effect size for studies examining effects on speech production is 1.28) (Brady et al., 2016). As a whole, there is a paucity of adequately powered, randomized-control trials that demonstrated large effect sizes.

This makes it difficult to identify an 'ideal' therapy approach for any one person living with aphasia, or accurately predict language outcomes. In sum, despite decades of aphasia research, there are a number of 'unknowns' regarding the optimal approach to aphasia therapy and the existing evidence that supports the 'effectiveness' of aphasia falls short.

1.6 Adjuvants to Behavioral Therapy and New Perspectives

1.6.1 Pharmacological approaches

Although behavioral therapy effectively improves outcomes for some individuals with aphasia, effect sizes remain modest (Hope et al., 2017). This, in combination with an

improved understanding of the neural mechanisms that underlie healthy language processing and those involved in aphasia recovery, has sparked the application of novel, adjuvant therapies for aphasia rehabilitation. Novel applications of adjuvants to behavioral therapy such pharmaceutical interventions (Enderby, Broeckx, Hospers, Schildermans, Deberdt, 1994; Berthier, 2005) or noninvasive brain stimulation (Fridriksson et al., 2018; Turkeltaub, 2015) have been explored to various degrees.

As described above, language recovery depends on neuroplasticity (*Section 1.4 Neuroplasticity*). Neuroplasticity can be facilitated by neurophysiological changes (i.e. recruitment of new connections between intact nodes of the residual language network, or compensation by undamaged nodes), behavioral acts (i.e. mass practice), and neurotransmitters such as norepinephrine, acetylcholine, serotonin and dopamine (Brzosko, Mierau, & Paulsen, 2019; Kirkwood, 2000). While the neurophysiological mechanisms and behavioral interventions that play a role in recovery are outlined extensively above, the role of neurotransmitters is discussed to a lesser degree and is important to highlight to explain why pharmacological approaches may be a viable adjuvant for SLT. Stroke-induced disruptions to neurotransmitter pathways and subsequently, the availability of neurotransmitters can mitigate stroke-related impairments (Berthier, 2011). Medications alter the availability of neurotransmitters and in the case of post-stroke aphasia, may offer an alternative method to enhance neuroplasticity (Kilgard & Merzenich, 1998).

There are no studies that show pharmacological approaches improve language function in the absence of SLT (Berthier, 2021). There is, however, inconsistent evidence that may suggest pharmacological approaches that are already approved for neurological

(i.e. Alzheimer's Disease and Parkinson's Disease) or psychiatric disorders (i.e. depression), can improve language when paired with SLT. There is evidence that the beneficial effects of SLT may not only be augmented by pharmacotherapy, but perhaps accelerated, too (see Berthier, 2021). At this point, many pharmacological trials have included drugs such as piracetam (Enderby et al., 1994; Huber et al., 1997; Orgogozo, 1998; Huber, 1999; Kessler et al., 2000), acetylcholinesterase inhibitors (Berthier et al., 2003; Berthier et al., 2006; Hong et al., 2012), dextroamphetamine (Walker-Batson, 2001) and memantine (Berthier et al., 2009). While results are promising, conclusions are confounded by the fact that most are single case studies, open level studies, or small randomized control trials and effects have been short-lasting or minor (Berthier, 2011; de Boissezon, Peran, de Boysson, & Démonet, 2007). Levadopa and bromocriptine, however, show no consistent benefit over a placebo (Seniów et al., 2009; Breitenstein et al., 2015).

In previous randomized control trials of post-stroke motor recovery (i.e. fluoxetine, Chollet 2011) and cognition (i.e. escitalopram, Jorge et al., 2010), SSRIs have been found to have a positive effect and may offer promising effects for post-stroke aphasia recovery (Hillis et al., 2018). For example, Hillis and colleagues found patients with damage to critical language regions (left posterior superior temporal gyrus, and superior longitudinal fasciculus and arcuate fasciculus, show better naming outcomes if SSRIs were administered for three months following the stroke. Continued research on pharmacotherapy for post-stroke aphasia is not futile and ongoing clinical trials may reveal more definitive outcomes for application of pharmacological approaches in aphasia therapy (Berthier, 2021).

1.6.2 Noninvasive brain stimulation

Technological advancements in neuroimaging and brain stimulation, paired with an improved understanding of the neurobiology of language and the nature of neural reorganization following a neurological trauma, such as a stroke, has sparked an interest in biologically based interventions for aphasia. One such application that gained interest in recent decades is noninvasive brain stimulation (NIBS). Noninvasive brain stimulation, the focus of the current study, is supported by a growing body of research that suggests, when paired with behavioral SLT, has the potential to 'boost' rehabilitation outcomes augmenting synaptic plasticity to induce functionally-relevant changes in the networks that support language (Goldsworthy, Müller-Dahlhaus, Ridding, & Ziemann, 2015). Unlike pharmacological approaches, noninvasive brain stimulation can be administered by a range of health professionals, and even well-trained non-professionals, and is relatively safe and easy to use (Antal et al., 2017).

Recent investigations in the field of aphasia rehabilitation have turned to NIBS to pair an exogenous source of cortical modulation with conventional behavioral therapy approaches to improve language outcomes. Studies show noninvasive brain stimulation (NIBS) techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are effective adjuvants to traditional therapy (Fridriksson et al., 2019; Naeser et al., 2010). tDCS and rTMS focally modulate neuronal activity to improve language functions or enhance neural plasticity to enable enhanced learning. Approaches to stimulation are variable and to date, there is no 'gold standard' for facilitating optimal outcomes.

In aphasia studies, NIBS is thought to facilitate activity in residual language regions or suppresses dysfunctional neural processes. For example, previous stimulation approaches include excitatory stimulation to spared perilesional LH regions, inhibitory stimulation to right-hemisphere regions that are thought to hinder recovery, combined excitatory left-hemisphere stimulation and inhibitory right-hemisphere stimulation, excitatory stimulation to compensatory right-hemisphere homologues, and stimulation to non-language regions (i.e. motor regions) (Crinion, 2016).

1.6.2.1 Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a noninvasive mild electrical stimulation that applies a weak, continuous electrical current. In tDCS, a direct current flows from anodal to cathodal electrodes. Application of tDCS typically involves 1 – 4 mA of continuous, direct electrical current which flows from anodal to cathodal electrodes that are placed on the scalp. Though the underlying mechanisms of tDCS are not completely clear, the effects are likely related to membrane depolarization. The subthreshold polarization of cortical neurons leads to increased excitation in neurons beneath the anodal electrode, and inhibition of neurons under the cathodal electrode (Purpura & McMurty, 1965; Paulus & Nitsche, 2001). When paired with a behavioral task, the effects of the stimulation prime the same neural network that is recruited by the behavioral task and alters neuronal excitability. Altered excitability augments short and long term synaptic plasticity to activate a network and induce excitability in the task-related network.

So far, the effects of tDCS on language recovery have only been demonstrated when tDCS is paired with SLT. It appears that tDCS in isolation does not affect language

(Crinion, 2015). There are over 35 randomized controlled trials supporting the language-specific effects of tDCS in post-stroke aphasia (see Biou et al., 2019 for a review). Most have been conducted in chronic aphasia and show better language outcomes in tDCS groups relative to sham or control conditions (Elsner, 2019). The largest trial to date was conducted by Fridriksson and colleagues (2018). In a double-blind randomized control trial, tDCS was applied as an adjuvant to naming therapy in a cohort of stroke survivors with chronic aphasia. Not only did accuracy of naming improve with tDCS versus sham, but investigators identified an interaction between anodal tDCS and polymorphism of the BDNF gene (Fridriksson et al., 2018).

The neural mechanisms modulated by tDCS are not completely clear and most studies to date report behavioral changes induced by tDCS. It seems likely, however, that tDCS can induce change in brain activity at the network level (Meinzer, Lindenberg, Antonenko, Flaisch, & Floel, 2013; Peña-Gómez et al., 2012). For example it has been suggested that anodal tDCS may modulate endogenous low frequency oscillations not just in the stimulated region, but across functionally connected areas of the brain (Meinzer et al., 2013). In a study of healthy older adults, anodal tDCS was applied to the left inferior frontal gyrus during a task of semantic word generation. Meinzer and colleagues found that, compared to sham the anodal tDCS condition improved task performance and they identified increased resting state functional connectivity between the left inferior frontal gyrus and other core areas of language processing (i.e. left middle temporal gyrus and bilateral inferior frontal, inferior parietal and prefrontal regions) following tDCS. These results are taken as evidence that tDCS may induce more efficient task processing in relevant network nodes.

1.6.2.2 Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) induces an electrical current from changes in magnetic fields that cause neurons to fire. TMS is thought to induce plasticity in targeted brain networks to induce functional effects in the stimulated area and connected nodes (Rossi & Rossini, 2004; Siebner & Rothwell, 2003; Ziemann et al., 2008). Repetitive pulses of this stimulation (repetitive transcranial magnetic stimulation; rTMS) can be applied to modulate neuronal activity by inducing action potentials to enhance neuroplasticity in the absence of a behavioral task. rTMS modulates neuronal activity (high frequency rTMS [$\geq$ 5 Hz) is excitatory, while low frequency rTMS [1 Hz] is inhibitory) and enhances neuroplasticity (see Naeser et al., 2010 for a review). rTMS studies in post stroke aphasia typically apply stimulation to the contralesional right hemisphere to inhibit contralateral activation and behavioral intervention is applied immediately following stimulation. Recent rTMS studies in sub-acute and chronic aphasia suggest benefits of language recovery (see review by Ren et al., 2014).

In terms of the neurophysiological mechanisms modulated by rTMS, some have found that activation patterns before treatment reveal a rightward shift of cortical activity, but following 1Hz of rTMS over right posterior inferior frontal gyrus and superior temporal lobe, a greater number of voxels in the left hemisphere were active. This suggests recruitment of left-hemisphere language networks following rTMS treatment and is in line with previous accounts of neuroplasticity in post-stroke aphasia (Thiel et al., 2013).

In conclusion, randomized control trials have demonstrated that NIBS techniques such as transcranial direct current stimulation (tDCS) (for a review, see Biou et al., 2019)

and repetitive transcranial magnetic stimulation (rTMS) (Heikkinen et al., 2019; Khedr et al., 2014) improve behavioral performance and rehabilitation outcomes of SLT when administered alone (rTMS) or when combined with therapeutic interventions (rTMS and tDCS). Transcranial electrical stimulation (tES) techniques are particularly beneficial given the low cost and ease of use, and importantly, they are typically associated with weak physical sensations (Zoefel & Davis, 2017). In general, NIBS modalities have offered a novel approach to augment synaptic plasticity and reorganization of the networks that support language.

1.6.3 Additional considerations and future directions for adjuvant therapies

At this point, evidence suggests that combining adjuvants such as noninvasive brain stimulation and pharmaceutical interventions with more traditional therapy approaches may promote the reorganization of language networks to support improved language processing (Crinion, 2015; Hartwigsen & Saur, 2019; Kilgard & Merzenich, 1998; Kiran & Thompson, 2019). However, despite a growing body of literature that supports the application of noninvasive brain stimulation as an adjuvant to aphasia therapy, studies are extremely variable in the site of stimulation and few have implemented multimodal approaches that combine noninvasive brain stimulation and neuroimaging techniques to further identify the mechanisms of neuroplasticity that are inducing these reported improvements in behavior, or the neural mechanisms that support success (Hartwigsen, 2015; Norise & Hamilton, 2017).

A recent study paired tDCS with TMS-EEG to target and modulate specific areas of excitability and resulted in language improvements (Cipollari et al., 2015). Results suggest that some regions may be potentially better suited for language processing and

that focused neuromodulation techniques like TMS and tDCS may offer a way to train optimal regions for language recovery. Furthermore, tools like advanced structural imaging, diffusion tensor imaging, diffusion spectrum imaging, and computational network modeling can continue to inform which brain regions may be the best candidate for compensation (Dijkhuizen et al., 2012; Ovadia-Caro et al., 2013). An improved understanding of the mechanisms of recovery may inform alternative montages, or as is proposed in the current study, the application of a novel technique like transcranial alternating current stimulation. Taken together, the interventions outlined above suggest that a combination of behavioral, pharmacological and NIBS may promote the reorganization of language networks to yield a more promising future for aphasia rehabilitation.

1.7 Aphasia management: Clinical translation of evidence-based practice

In clinical practice, behavioral therapy is the mainstay; however, there is no 'standard of care' for aphasia rehabilitation and treatment approaches differ greatly from clinician to clinician and patient to patient (Brady et al., 2016; Brogan, Godecke, & Ciccone, 2020). Due to the aforementioned gaps in the evidence and inconsistencies between the research standards and the reality of a highly heterogeneous approach to clinical practice, clinicians have limited evidence to inform a plan of care for a patient with aphasia (Brogan et al., 2020). The heterogeneity that exists across assessments, treatment types, delivery methods, and patient characteristics has led to inconsistent results in the aphasia treatment studies and make it nearly impossible for clinicians to identify and apply the best evidence-based practice.

From a clinical perspective, many evidence-based approaches do not reflect a typical rehabilitation setting. Most paradigms from research do not align with the productivity demands, billing standards, or time constraints of a traditional clinical care (Brady et al., 2016). In addition to the paucity of relevant, accessible, and efficient approaches for clinical application, most patients with aphasia do not receive an adequate amount of treatment (Crooke & Olswang, 2019). Many are underserved due to lack of third party reimbursement and others are limited by obstacles such as transportation or limited number of available clinicians, especially in rural areas (Simmons-Mackie & Cherney, 2018). As a result, there are a number of challenges that contribute to a substantial clinical-research gap and many unknowns that prohibit a realistic and accurate approach to a plan of care for an individual with aphasia. While aphasia therapy has shown to be effective, studies that show greater effect sizes and better inform personalized models of rehabilitation into practice are needed, including those that consider an implementation science perspective (Douglas, Feuerstein, Oshita, Schliep, & Danowski, 2022).

1.8 Final Remarks Regarding Aphasia Rehabilitation

Considering SLT has been the foundation of aphasia management for nearly a century, the current state of affairs for people living with aphasia is unsatisfactory. While many evidence-based aphasia therapies have emerged in the last few decades and our understanding of the neural mechanisms that support language processing and stroke-induced recovery have improved, substantial improvement in treatment approaches is needed to improve outcomes and maintain gains. Although treatment is shown to be better than no treatment at all, there are still a number of individuals for whom aphasia

therapy does not work and for those that do show improvements, effect sizes are modest. Current approaches simply are not effective enough. The current study not only applies a novel approach to improve language outcomes in chronic aphasia, but importantly, the nature of the paradigm has the potential to address a number of the aforementioned 'pitfalls' (see *Section 1.5.3*).

Recent work suggests that the beneficial effects of SLT can be augmented and accelerated by new approaches. Applying noninvasive brain stimulation as an adjuvant to an evidence-based behavioral paradigm may further 'boost' behavioral outcomes above and beyond what patients are capable of in conventional therapies. Greater effects in a shorter amount of time are particularly appealing given the current constraints from third party payers for post-stroke rehabilitation.

Now, more than ever, there is a critical need for a more progressive research agenda that considers novel interventions and capitalize on what is known about the neurobiology of language, nature of aphasia recovery, and ever-changing technologies to develop new treatment paradigms that directly target the underlying language impairment. In the sections that follow, a novel approach to therapy is outlined. Beginning with the specifics of the patient population (nonfluent aphasia), the theoretical basis for the behavioral intervention is described, followed by the rationale for the application of transcranial alternating current stimulation.

1.9 Motivation for the Current Study

In sum, the existing rehabilitation paradigms for people living with aphasia are unsatisfactory. There is a dire need to consider novel therapeutic approaches to treat aphasia and this paucity of effective treatments is the primary motivation for the current

study. Here, a rhythmic neuromodulatory noninvasive brain stimulation was applied as an adjuvant to an evidence-based behavioral paradigm called speech entrainment to recruit residual cortex and improve speech output in nonfluent aphasia. The proposed study is timely and may offer a novel approach to induce fluent speech in a relatively short amount of time for persons with nonfluent aphasia. The following sections describe the theoretical and empirical motivation for this approach.

1.10 Nonfluent Aphasia

1.10.1 Clinical presentation

Aphasia is a general term for several different clinical presentations. Traditionally, aphasia has been classified into subtypes or syndromes based on the presence or absence of particular language functions (De Freitas, 2012), as described above in the context of the Boston Group Classification System (Geschwind, 1965a; Goodglass and Kaplan, 1972; Goodglass, 1993; see *Section 1.5.2: Aphasia Therapy*). Consistent with this classification system, Benson (1967) identified a bimodal clustering of speech characteristics (i.e., word choice, rate of speaking, articulation, phrase length, and effort; (Howes & Geschwind, 1964) in spontaneous speech samples where patients either presented with slow, effortful speech with primarily substantive words or spoke effortlessly but lacked substantive words and produced paraphasias. Impaired fluency plays a central role in aphasia classification. This distinction was consistent with observations dating back to Hughlings Jackson's reports in 1868, where he described two classes of aphasic patients and was replicated by Kerschensteiner and colleagues in 1972. Since then, this fluent-nonfluent dichotomy has been used in the clinic and in research to describe different aphasic syndromes.

Although this dichotomy can be useful to an extent, it is important to point out the multidimensional nature of fluency. Measures such as words per minute can be used as an objective measure but are not necessarily the best index of fluency since variables such as complexity, grammaticality, presence of paraphasic and stereotypical utterances, prosodic abnormalities, and phrase-length should also be considered (Benson, 1967; Kerschensteiner et al., 1972). Therefore, despite this dichotomy, there are varying perspectives regarding the origin of nonfluent speech. Some have proposed that rate of speech is the predominant feature (Kreindler, Mihailescu, & Fradis, 1980), while others focus on rate and syntactic complexity (Wagenaar, Snow, & Prins, 1975) or semantic richness (Fillmore, 1979) in spontaneous speech. It is therefore clear that speech fluency is multifaceted with several factors that play a role and give rise to fluent speech, or in the context of post-stroke aphasia, several variables that may be negatively impacted and consequently yield nonfluent speech. These may include lexical retrieval, phonological encoding, syntactic processing, working memory and self-monitoring (Nozari & Faroqi-Shah, 2017).

Nonfluent aphasia (NFA) is a broad term that is applied to multiple underlying impairments of speech production. Individuals with NFA present with reduced verbal output, slow effortful speech, frequent pauses, short telegraphic utterances with mostly substantive words, and poor articulation (Brookshire, 2003; Geschwind, 1970; Gleason, Goodglass, Green, Ackerman, & Hyde, 1975; Poeck, 1989). Subtypes of nonfluent aphasia include Broca's, transcortical motor, and global. While nonfluent speech is the hallmark characteristic in each of these subtypes, each syndrome comprises of a specific pattern of characteristics. Patients with Broca's aphasia, for example, present with

relatively preserved comprehension but speech output is laborious and linguistically sparse and repetition abilities are impaired (Goodglass et al., 2001; Kertesz, 2006). Broadly, NFA is one of the most common types of aphasia and affects ~40% of all chronic aphasia cases (Broca, 1861; Dronkers, 1996; Geschwind, 1965).

Symptoms that are consistent across all subtypes of nonfluent aphasia include slow speech rate and reduced lexical output, but it is clear that there are a variety of factors that contribute to these clinical presentations (Feenaughty et al., 2017; 1998 Gordon, 1998; Gordon & Clough, 2020). While there is no singular behavioral factor that defines nonfluent speech, disruptions to a variety of linguistic and speech production processes, reflected by perceptual measures such as speech rate, productivity and audible struggle, are often used to define "fluency" (Park et al., 2011). Other characteristics such as phonological and phonetic encoding, articulation, and melodic line are typically used to dichotomize fluent and nonfluent speech in diagnostic assessment tools (Goodglass, Kaplan & Barresi, 2001; Kertesz, 2007). The multifaceted nature of fluency is further complicated by concomitant motor and neuromuscular control deficits or underlying cognitive-linguistic deficits. One motor speech disorder, apraxia, for example, co-exists frequently with nonfluent aphasia in clinical populations (Duffy, 1995). Apraxia of speech is a motor speech disorder that results in impaired planning and programming of speech movements that manifests primarily in errors of articulation (Darley, Arsonson, Brown, 1975; Van der Merwe, 1997).

1.10.2 Psychosocial consequences of nonfluent aphasia

NFA is debilitating and results in increased frustration and depression (Robinson & Benson, 1981). Poor fluency is detrimental to psychosocial interactions (Gordon &

Clough, 2020) and is directly associated with social isolation, decreased participation in rehabilitation, and low quality of life (Franzén-Dahlin et al., 2010; Hilari & Byng, 2009; Hilari et al., 2003; Poeck, 1989). Individuals with nonfluent aphasia often describe their speech rate, in particular, to be socially "inadequate'" and resulting in communication breakdowns and listener impatience (Feyereisen, Pillon, & de Partz de Courtray, 1991). As compared to other aphasia types, people with NFA are perceived particularly negatively (Duffy, Boyle, Plattner, 1980; Harmon et al., 2016; Khvalabov, 2019). This is reflected in perceptions of cognitive ability (i.e. competence, intelligence) and personality characteristics (i.e. extroversion, likeability) (Croteau & Le Dorze, 2001; Lasker & Beukelman, 1999; Zraick & Boone, 1991).

1.10.3 Neural correlates of nonfluent speech

Historically, anterior lesions in the left hemisphere were thought to induce NFA, especially Broca's aphasia (Broca, 1865; Geschwind, 1965). Such accounts suggest that the lesion location that causes impaired speech is in Broca's area (Hillis et al., 2004; Richardson, Fillmore, Rorden, LaPointe, Fridriksson, 2012). Contemporary research, however, suggests that lesions responsible for NFA may not be isolated solely to anterior regions. Broca's aphasia, for example, may result from damage that is pervasive across anterior and posterior (superior temporal gyrus [STG] and inferior parietal lobe) cortical structures in the left hemisphere (Fridriksson et al., 2015). The fact that nonfluent speech is induced by lesions to several cortical regions suggests there is heterogeneity in the underlying etiology.

1.10.4 Heterogeneity of Nonfluent Speech: A Theoretical Account

As referenced above, perceptual accounts of nonfluent speech suggest a variety of underlying etiologies. In the context of theoretical models, some hypothesize that nonfluent speech is due to an impairment in word production. Theoretical models suggest that word production requires at least two steps: 1) lexical retrieval and 2) phonological encoding (and later articulation) (Dell, Schwazrtz, Martin, Saffran, Gagnon et al., 1997). For patients with aphasia, impairments in word finding may result from disruptions to either or both of these stages (Schwartz, Dell, Martin, Gahl, & Sobel, 2006) and a number of studies have identified an association between impaired word production and non-fluent productions in both healthy (Hartsuiker & Lies Notebaert, 2010) and clinical populations (i.e. stuttering; Wingate, 1988; Postma and Kolk, 1993; Prins et al., 1997) and post stroke aphasia (Gordon, 2006; Luzzatti et al., 2002; McCarthy & Warrington, 1985; Wilshire & McCarthy, 2002; Zingeser & Berndt, 1990).

Alternative hypotheses suggest an association between agrammatism and nonfluent aphasia. Even if it problematic for such that grammatical production errors are also found in patients with fluent aphasia (Bird & Franklin, 1996; Edwards, 1995; Susan Edwards & Bastiaanse, 1998; Faroqi-Shah & Thompson, 2003), contemporary investigations do suggest that there is a robust connection between agrammatism and nonfluent speech in aphasia (Nozari & Faroqi-Shah, 2017). Auditory comprehension, and working memory have been proposed as potential underlying variables in speech fluency, but the extent to which they impact fluency is not well-established. Self-monitoring and repair is another process that has been implicated in speech fluency. The aforementioned study by Nozari & Faroqi-Shah (2017) demonstrates a role for word production,

comprehension and working memory in speech fluency. The authors emphasize, however, that impairments to *any* of these domains may impact fluency. Some have suggested that self-monitoring and correction may reflect the ability to produce fluent speech. For example, detecting an error may disrupt the production process and signal the need for a repair (Hartsuiker & Kolk, 2001). In patients with post-stroke aphasia and apraxia of speech, Jacks and Haley (2015) demonstrate that masking self-monitoring increased fluency suggesting that nonfluent speech may be due, at least in part, to monitoring or self-correction impairments. This is discussed in greater detail in *Section 1.11.1: A mechanism for speech fluency* in the context of altered auditory feedback, an internal model and theoretical accounts of speech production.

Other accounts suggest that nonfluent speech, at least in a subset of individuals with aphasia, may be caused by an impaired efference copy (Feenaughty et al., 2017; Fridriksson, Basilakos, Hickok, Bonilha, & Rorden, 2015; Fridriksson et al., 2012). This mechanism is presumed to be aided by a behavioral therapy called speech entrainment. Given that speech entrainment is the evidenced-based SLT that will be used in the current study, it is necessary to describe the efference copy and relevant theoretical models in more detail.

1.11 The Efference Copy

1.11.1 A mechanism for speech fluency

From a theoretical perspective, it is hypothesized that nonfluent speech may be caused by impaired motor planning and a degraded or absent efference copy, at least in a subset of patients with nonfluent aphasia (Feenaughty et al., 2017; Fridriksson, Basilakos, et al., 2015; Fridriksson et al., 2012). The efference copy is theorized to be a feed-

forward projection of the motor plans in order to predict sensory feedback. In a forward model, perceptual feedback is anticipated, and sensory consequences are predicted. The concept of an "efference copy" is not specific to speech production, rather the term has an extensive history and has been used to describe physiological movements and the related motor and sensory consequences (Holst & Mittelstaedt, 1971; Sperry, 1950). Models of motor control suggest that external sensory feedback is compared with internal predictions to produce a successful execution of a motor act (Wolpert & Miall, 1996; Golfinopoulos, Tourville, Guenther, 2010; Friston, 2011; Houde & Nagarajan, 2011).

In this vein, the efference copy is thought to underlie the skilled motor movements that are elicited during speech production (Feenaughty et al., 2017; Guenther et al., 1998; Houde & Nagarajan, 2011). Speech production is a highly complex motoric task that relies on auditory and somatosensory feedback to successfully produce language (Guenther, 1994; Hickok, 2012; Hickok & Poeppel, 2004). The efference copy is thought to be an internal representation of the motoric speech plan to predict speech behavior.

In the context of speech production, a forward model is necessary for smooth motor control and plays a role in the awareness of action by comparing the intended speech sounds with the actual production in order to minimize disparities in current and future productions (Hickok, Houde, Rong, & Hickok, Houde, Rong, 2011; Houde & Nagarajan, 2011). Given the delay between the motor command and auditory feedback in speech production (~200 milliseconds or the duration of one syllable) (Houde & Jordan, 2002), internal feedback from the forward model ensures stable feedback control of actions and can trigger early error correction instead of relying on overt sensory feedback. This allows for stable action control and self-monitoring. In well-practiced

motor acts, such as typical speech production, an efference copy predicts the sensory consequences relatively well by producing a perfect copy of the motor commands that are needed for successful execution (Niziolek, Nagarajan, & Houde, 2013). Updating future speech productions is highly dependent on the comparison between expected and actual productions, especially in the context of language development (Hickok et al., 2011; Houde & Jordan, 2002). These predictions also constitute a framework to inform fluent speech as well as clinical presentations of disordered speech (Guenther, Ghosh, & Tourville, 2006; Houde & Nagarajan, 2011; Postma, 2000).

The internal feedback (sensory predictions) is also thought to attenuate sensory areas, such as the auditory cortex (Miall, Weir, Wolpert, & Stein, 1993; Wolpert & Kawato, 1998; Wolpert & Miall, 1996). The auditory cortex attenuates sensitivity and modulates activity as a function of the expected acoustic feedback (Houde & Jordan, 2002). This is evidenced by investigations that have altered the auditory feedback and demonstrate that the altered auditory feedback signal perturbs the acoustical speech signal and creases a 'mismatch' between the predicted output and actual speech production (feedback) (Cai, Ghosh, Guenther, & Perkell, 2011; Chen, Liu, Xu, & Larson, 2007; Larson, 1998). This perturbation is due to the fact that the speaker has an internal model (efference copy) and the altered feedback does not match the motor output. In this type of task, neurotypical adults demonstrate real time modifications to compensate for the perceived speech error (Burnett, Freedland, & Larson, 1998). Individuals with an acquired language disorder such as aphasia, however, are unable to compensate for this change (Behroozmand et al., 2018). Impaired vocal feedback has been associated with

damage to anterior motor regions, particularly those associated with the dorsal stream as defined by the dual stream model (Hickok & Poeppel, 2004).

The dual stream model of speech processing is a contemporary, network-based paradigm of speech and language processing (see *Figure 1.1*). At this point, it is worthwhile to introduce this model to provide yet another theoretical account that encourages further speculation of the neural mechanisms that may underlie the function of the efference copy. The dual stream model describes two streams: (1) the dorsal stream and 2) the ventral stream that are hypothesized to be involved with the successful processing and production of speech. Importantly, this model takes into account the interconnections between cortical regions that are involved in each stream. The dorsal stream is posited to support auditory-motor integration for speech production and the ventral stream supports speech signals for conceptualization and understanding. The dorsal stream is considered to be left lateralized, projecting from the posterior superior temporal to the inferior frontal cortices. The dorsal stream maps sound to articulatory representation. By contrast, the ventral stream is considered to be bilateral and projects from the posterior middle and inferior temporal gyrus via the anterior middle temporal gyrus to the inferior frontal gyrus (Hickok & Poeppel, 2004). This model has been implemented widely in investigations of speech processing in both healthy (Catani et al., 2007; Catani et al., 2005; Saur et al., 2008; Ueno et al., 2011) and clinical populations (Fridriksson et al., 2016; Keator et al., 2021; Kümmerer et al., 2013) to better understand language processing and subsequent disorders secondary to brain injury.

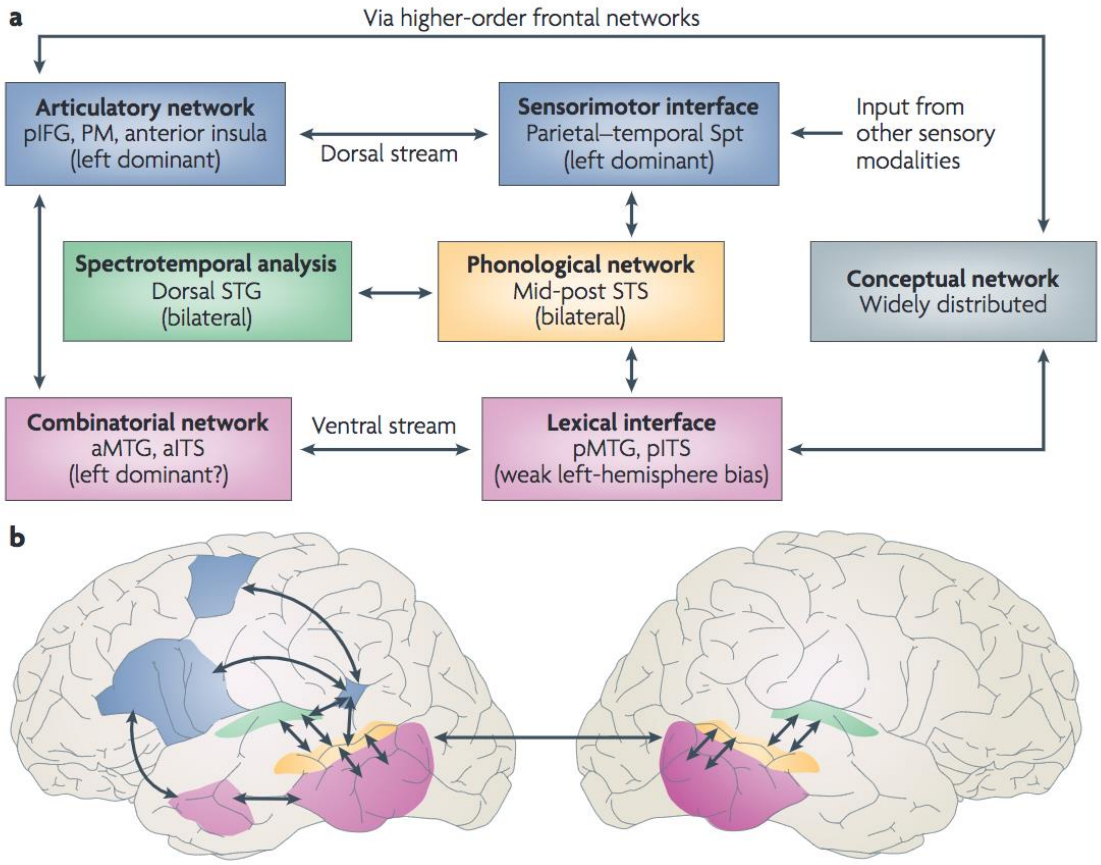


Figure 1.1: *The dual stream model of speech processing. Regions of interest implicated in the dorsal stream are shown in blue; ventral stream regions are shown in pink. Figure from Hickok & Poeppel, 2007; Figure 1.*

When considering the role of the efference copy for successful speech, it is therefore hypothesized that this left lateralized dorsal stream integrates sensorimotor networks for online monitoring of auditory feedback by comparing predicted and actual inputs. These left lateralized sensorimotor networks use internal forward models to translate the efference copies of motor commands to predict auditory consequences of the intended output. Therefore, in the context of damage to the left hemisphere and consequently, an impaired efference copy, Sangtian and colleagues (2021) suggest that damage to regions of interest in the left lateralized dorsal stream (i.e. inferior frontal gyrus, supramarginal gyrus) results in impaired vocal feedback. Earlier work by this group also suggests the involvement of the ventral stream when there is damage to auditory cortical regions within the superior and middle temporal gyrus (Behroozmand et al., 2018). The involvement of the left-hemisphere dorsal stream is further supported by more recent work from the same group (Behroozmand, Bonilha, Rorden, Hickok, & Fridriksson, 2022) and emphasizes the negative impact of left hemisphere dorsal stream damage on neural and behavioral correlates of vocal production and sensorimotor control which results in impaired sensorimotor function for speech error processing and correction in aphasia.

This failure to compensate for change may also be attributed to a damaged efference copy because the patients cannot detect and correct for the error. Pilot data have revealed that individuals who perform poorly on altered auditory feedback tasks are better at speech entrainment tasks. The proposed role of the efference copy in a forward model of speech production is evidenced by results from neuroimaging studies (Curio, Numminen, Neuloh, Jousmäki, & Hari, 2000; Numminen & Curio, 1999), which

implicate the efference copy in motor acts more generally (Haruno, Wolpert, & Kawato, 2001) but also consequences of a disordered efference copy in disordered speech patterns such as stuttering (Max, Guenther, Gracco, Ghosh, & Wallace, 2004).

To further contextualize the role of the efference copy in disordered speech such as NFA, it is critical to briefly discuss theoretical models that support speech production to outline how the efference copy is hypothesized to function in both healthy and clinical populations. Prominent speech production models such as the Direction into Velocities of Articulators (DIVA) (Guenther et al., 2006, 1998), State Feedback Control (SFC) (Hickok, Houde, Rong, 2011), and Hierarchical State Feedback (HFSC) (Hickok, 2012) describe feedforward and feedback control mechanisms that facilitate successful speech production. Each model differs with respect to the nature of the efference copy. In the DIVA model, motor plans of the efference copy project from anterior motor regions and carry internal auditory target information to the posterior auditory cortex. This is where auditory consequences are predicted and compared to the speech output (Guenther et al., 2006, 1998).

Similar to the DIVA model, SFC models (see *Figure 1.2* for reference) integrate efference copies by way of feedforward and feedback control mechanisms. Generally speaking, phonological-level representations are internal motor targets and have auditory consequences. SFC models suggest the act of speech production initiates both a motor speech plan and an efference copy of that plan to provide sensory targets. The internal feedforward model allows the motor circuit to make predictions regarding the state of the system based on sensory information. Online sensory feedback control is attributed to the efference copy and internally maintained representations of these estimates. The

estimates are then used to generate a motor command and effects of motor commands are evaluated for accuracy. The feedback system is responsible for learning the internal model and updating the model in the case of an error or perturbation.

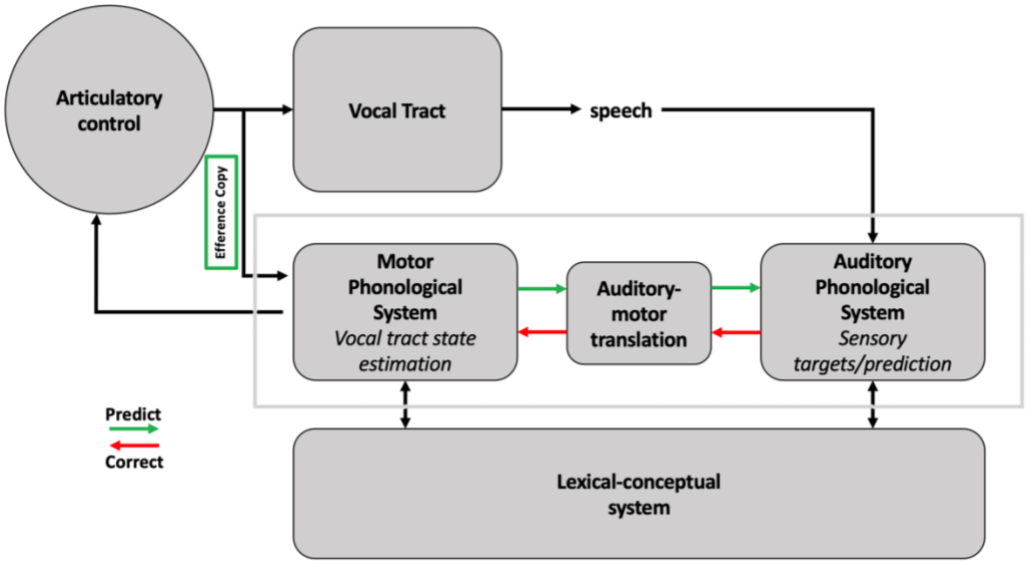


Figure 1.*2 The State Feedback Control model (Hickok & Houde, 2011). In the SFC model, the motor controller sends an efference copy (shown in green box) to the internal model to generate predictions of sensory consequences in the auditory phonological system.*

In the HSFC model (Hickok, 2012, *Figure 1.3*), the SFC model is extended to include two hierarchically organized levels: low level (somatosensory) processing in the anterior supramarginal gyrus and motor cortex and high level (auditory-motor) circuit in IFG*po*, superior temporal sulcus, superior temporal gyrus, and area *Spt*, a region located at the junction of the temporal and parietal lobes. The coordination of motor programs of speech in anterior (Broca's area) and auditory targets in posterior (superior temporal gyrus and superior temporal sulcus) are supported by area Spt. The auditory-motor circuit is thought to play a role in auditory to articulation transformations.

The DIVA, SFC, and HSFC models propose that the efference copy is an internal representation of the speech plan and plays a critical role in the initiation and monitoring of speech by predicting speech behavior (Guenther et al., 2006; Hickok & Poeppel, 2007; Hickok, Houde, Rong, 2011; Houde & Nagarajan, 2011; Houde, & Chang, 2015; Hickok, 2015). Simply put, in SFC models, speech acts initiate a motor speech plan and the efference copy copies that plan. Therefore, the efference copy is a replication of the speech motor plan and acts as an internal copy against which sensorimotor consequences can be compared in real-time (*Figures 1.2 & 1.3*). The SFC and DIVA models suggest that problems with efference mechanisms likely impact feedforward and feedback mechanisms. Efference copies are, therefore, posited to be one of the primary mechanisms of speech fluency because the efference copy generates copies of the speech motor command and projects these plans to the system to detect errors between motor commands and actual speech feedback.

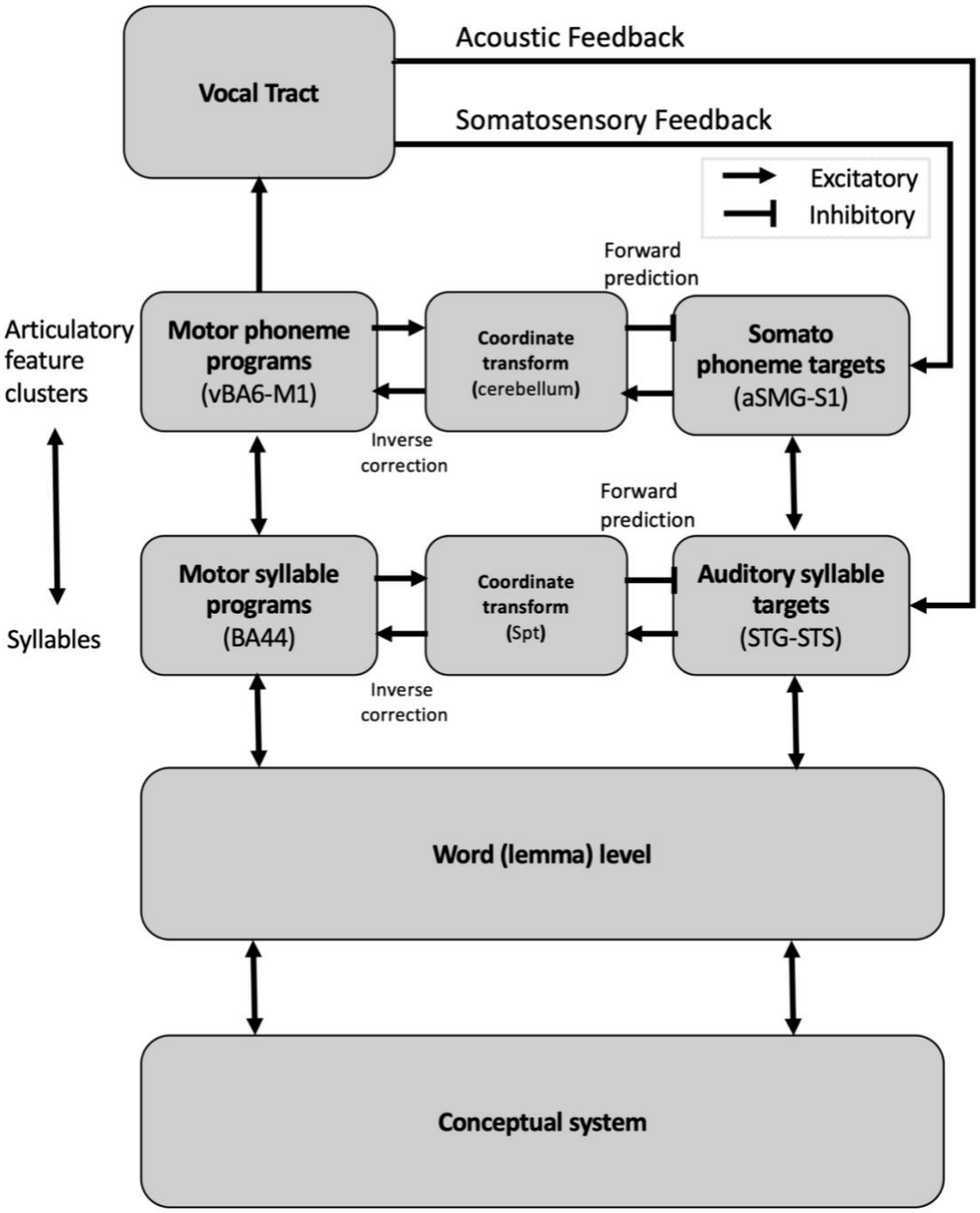


Figure 1.3 *Hierarchical State Feedback Control model (Hickok, 2012). In the HSFC model, the feedforward process of speech production activates anterior and posterior regions via area Spt. Speech entrainment is hypothesized to activate high-level auditory motor circuits and strengthen anterior-posterior synchrony to compensate for anterior damage and a disrupted internal efference copy.*

1.11.2 Efference copy integrity in nonfluent aphasia

Damage to feedforward projections (i.e. expected speech output) prohibits the generation of an efference copy, thereby hindering the initiation of the speech production mechanism (Feenaughty et al., 2017; Fridriksson et al., 2015). Consequently, an absent or degraded efference copy (i.e., speech target) compromises sensory feedback because errors cannot be detected without access to the speech sound targets (Feenaughty et al., 2017). This results in an impaired ability to generate and use an efference copy to predict sensory consequences which are necessary for successful speech production. Degradation of this mechanism, then, may result in a mismatch between the motor plan and predicted sensory consequences. Clinically, damage to the efference copy is thought to result in nonfluent, error-filled speech productions and/or poor self-corrections (Fridriksson et al., 2015; Fridriksson et al., 2012). Based on previous evidence that suggests the integrity of the efference copy is associated with speech fluency (Feenaughty et al., 2017), it seems reasonable to suggest that a therapeutic intervention that acts as an external gaiting mechanism to initiate and monitor the flow of speech in the presence of a damaged efference copy may improve speech fluency (Fridriksson et al., 2015; Fridriksson et al., 2012). These theoretical implications are discussed in the context of a specific behavioral paradigm, speech entrainment, and are described in further detail in *Section 1.13: Speech Entrainment*.

1.11.3 Anterior-Posterior coherence for language production

Further evidence for the role of the efference copy comes from more recent neurophysiological evidence that supports the aforementioned theoretical speech production models. As previously stated, speech production relies on feedforward control

mechanisms and the rapid synchronization of frontotemporal regions to accurately produce speech (Wang et al., 2014). Prior to the audible onset of speech, two parallel processes must occur. First a command is generated from anterior speech-specific regions (inferior frontal gyrus) and is sent to the motor cortex to produce the intended speech sound. Next, the efferent copy of the intended speech sound is transmitted from the anterior (IFG*po*) to posterior (STG) speech regions. Therefore, efficient coupling between frontal and temporal cortices initiates a comparison between the intended speech (efference copy) and actual speech. This is supported by neurophysiological evidence that reflects increased low frequency (theta and alpha) coherence between frontal and temporal regions and a frontocentral low-frequency negative component (Wang et al., 2014).

Anterior and posterior language regions are not only functionally connected but also structurally connected. The arcuate fasciculus, for example, is a bundle of white matter fibers that is classically defined as the connection between anterior language regions (i.e., Broca's region) and posterior regions (i.e., Wernicke's area) (Geschwind, 1970). The arcuate and frontal aslant tract (an anterior white matter pathway) are thought to facilitate transmission of the efference copy in speech production. Regions that are connected by direct and indirect paths of the arcuate fasciculus and frontal aslant have explained EEG responses to self-generated and externally generated predictable speech stimuli (Oestreich, Whitford, & Garrido, 2018). In this way, the arcuate fasciculus is thought to serve as a route for the efference copy of a motor act and the frontal aslant tract is thought to be the connection for the initiation of motor acts to trigger speech production (via connections with the supplementary motor area). This idea is not

necessarily new. Hughlings Jackson (1958) suggested an efference copy for thought. In the context of speech production, Jackson posited that inner speech may share many of the same mechanism features with overt speech. It is expected that internal forward models were developed later in evolution and may therefore be used in these higher-level cognitive processes such as inner speech (Ford & Mathalon, 2019; Oestreich et al., 2018), as online self-monitoring processes are linked to frontotemporal circuitry and this is critical for correcting errors in articulation, prosody and pitch (Doupe & Kuhl, 1999; Oller, 1980; Osberger & McGarr, 1982).

1.12 Therapy for Nonfluent Aphasia

1.12.1 Response to therapy for individuals with nonfluent aphasia

In *Section 1.5 Clinical Management of Post Stroke Aphasia: State of the Art*, current behavioral approaches are outlined. To motivate the current study, the following sections outline therapies that aim specifically to treat individuals with nonfluent aphasia.

Some patients with NFA demonstrate improved speech fluency following behavioral SLT, (Albert et al., 1973; Sparks, Holland, 1976; Kendall et al., 2008; Edmonds, Nadeau, Kiran, 2009; Fridriksson et al., 2009; Kiran & Sandberg, 2011 Fridriksson et al., 2009, 2010; Schlaug et al., 2009; Kelly, Brady, Enderby, 2010; Brady et al., 2012) but only a few recover well because impaired fluency is particularly resistant to therapy. Most speakers with NFA demonstrate a negligible response to therapy and minimal recovery of language production (Kertesz & McCabe, 1977; Marshall, Phillips, 1983; Pickersgill, & Lincoln, 1983; Bakheit et al., 2007).

As is the case for therapeutic approaches for aphasia more broadly, there is no ‘gold standard’ of treatment for severe nonfluent aphasia. Behavioral interventions for

NFA typically focus on improving speech fluency with verbal repetition or presentation of visual stimuli to elicit propositional speech. Speech production, however, is an inherently difficult task for these patients and these treatments tend to induce speech errors (Kelly, Brady, Enderby, 2010; Brady et al., 2012). In some instances, errors may outnumber correct productions and result in negative feedback due to repeated failures (Fridriksson et al, 2009; Boyle, 2015). For example, 'performance deviations' (i.e. part-word and unintelligible productions, nonword fillers, inaccurate words, false starts, unnecessary repetition, filler words, and irrelevant commentary) may be pervasive in expressive language tasks such as word-finding and discourse (Brookshire & Nicholas, 1995; Doyle et al., 2000; Boyle, 2015). Because it is difficult to elicit speech production in this population, attempts are error-filled, and patients get minimal practice to improve.

For this reason, the concept of 'errorless learning' may be critical to more successful rehabilitative approaches (Fillingham, Hodgson, Sage, & Lambon Ralph, 2003). Errorless learning relies on evidence from both empirical and clinical practices that suggest error-reduction or error-elimination techniques may promote errorless learning or control for errors during training. Fillingham and colleagues (2003), as well as more recent work (Middleton & Schwartz, 2012; Schuchard & Middleton, 2018) suggests that this may be particularly advantageous for treating anomia, a hallmark clinical presentation in post-stroke aphasia.

The theories supporting errorless learning are consistent with a Hebbian learning principle, which suggests that errorless learning strategies facilitate correct responses (Brownjohn, 2009; Strand & Morris, 1986; Wolery et al., 1992). As such, three underlying elements are proposed to underlie feedback modulation of the learning

mechanism. First, before feedback modulation can be initiated, participants much be able to monitor the accuracy of their response. Second, feedback modulation may necessitate the temporary storage or prolonged activation of the original stimulation and associated response while the underlying representations are adjusted by the learning mechanism. Finally, in terms of cognitive processes involved in errorless learning, it is likely that feedback modulation requires efficient verification and regulation of behavior and therefore, may require the deliberate manipulation of representations which may negatively impact the availability or accessibility of attentional and executive resources. This theoretical consideration is described in greater detail in the context of the principles of neuroplasticity from Kleim and Jones (2008) in *Section 1.4.2: Principles of Learning and Neuroplasticity for Rehabilitation*. See also Ludlow et al., 2008 for additional considerations regarding considerations for translating these models into clinical practice. As it stands, however, existing approaches for NFA are suboptimal (Brady et al., 2016), and re-establishing fluent speech remains the most challenging aspect of treatment for persons with NFA.

In conclusion, NFA results from a variety of lesion patterns and is expected to result from damage to the efference copy, which negatively impacts speech fluency. Disordered fluency may result from a number of distinct etiologies (reduced articulatory agility, impaired melodic prosody, or poor syntactic form) and therefore, the nature of treatment should be tailored to address the particular behavior, and ideally, neurological damage that induces these speech patterns. An external gaiting mechanism, an audiovisual model for example, may be most appropriate to externally guide speech production when the efference copy is damaged.

1.12.2 Rehabilitative approaches for nonfluent aphasia

A number of investigations have aimed to address dysfluent speech in post-stroke aphasia. Perhaps the most prominent approach has been Melodic Intonation Therapy (MIT; Sparks, Helm, Albert, 1974; Sparks, Holland, 1976; Helm-Estabrooks, Nicholas, Morgan, 1989; Schlaug et al., 2008). Originating in the 1970's, MIT relies on a hierarchically structured program that emphasizes paralinguistic aspects of speech such as production, prosodic intonation and rhythm, to improve speech production and fluency (Schlaug et al., 2008; Stahl, Kotz, Henseler, Turner, & Geyer, 2011; Van Der Meulen, Van De Sandt-Koenderman, & Ribbers, 2012; Wilson, Parsons, & Reutens, 2006). In this paradigm, patients are trained to maintain the rhythm of sentences sung by a clinician and to repeat the utterance with a matched intonation and beat. As training progresses, the intoned prosody is slowly trained back to a 'naturalistic' presentation and direct cueing is reduced. To expand upon the initial MIT studies, Stahl and colleagues (2011) provided an external source of rhythm (i.e. metronome) and found that this promotes greater speech output compared to the previous applications of MIT which relied solely on intoning (singing) speech.

Van der Meulen and colleagues have conducted two randomized clinical trials to evaluate the effects of MIT (Van Der Meulen, Van De Sandt-Koenderman, Heijenbrok, Visch-Brink, & Ribber, 2016; Van Der Meulen et al., 2014). Investigators found that subacute (2014) and chronic (2016) patients demonstrated improved repetition in trained and untrained tasks, but for patients with chronic aphasia, these effects were not maintained at follow-up. In a more recent randomized control trial, Horo-Martínez and colleagues (2019) found that MIT has a positive effect on communication skills following

therapy and at three months post-treatment. While MIT improves repetition (Van Der Meulen et al., 2014) and propositional speech (Sparks, Helm, Albert, 1974; Naeser & Helm-Estabrooks, 1985) results from randomized control trials suggest MIT may have a limited generalization effect in chronic aphasia (Van Der Meulen et al., 2016).

Script training is another paradigm that is used to improve fluency in this clinical population. This therapy relies on cue-based massed drilling to promote automatization of the production of a scripted text (Lee, Kaye, & Cherney, 2009; Youmans, Youmans, & Hancock, 2011) and offers a functional approach to rehabilitation through personalized scripts (Holland, Milman, Munoz, Bays, 2002). Script training may provide impairment-based therapy while also offering an opportunity for a patient to participate in everyday, social communication situations that require automatic speech (Cherney, Kaye, Lee, van Vuuren, 2015). One implementation of script training is a program called AphasiaScripts™ (© 2007, Rehabilitation Institute of Chicago). AphasiaScripts is a computerized conversational script training program. In one study by Cherney and colleagues (2008), participants with nonfluent aphasia practiced three individualized scripts for nine weeks. Following practice, patients demonstrated improvements in 'grammatical productivity' and production of 'script related words' with this computer-based treatment. Lee and colleagues (2009) implemented AphasiaScripts™ in a cohort of seventeen participants with nonfluent aphasia to investigate 'optimal' intensity and dose (30 minutes a day over a nine week period) and found the amount of treatment positively correlated with percent change in script content.

Other script training programs have implemented a similar paradigm in a telerehabilitation model. For example, Goldberg and colleagues (2012) used two

personally relevant scripts to train participants three times a week for three weeks. Post-treatment, investigators found improvements in accuracy, grammatical productivity, speaking rate, articulatory fluency. In a generalization probe that elicited conversation beyond the scripted topic, patients demonstrated improved use of grammatical morphemes and increased rate of speech as compared to pre-baseline samples.

Script training has also been implemented in the rehabilitation of individuals with nonfluent primary progressive aphasia, where similar benefits were found (M. L. Henry et al., 2018). Video-Implemented Script Training for Aphasia is an audiovisual approach that adapts the speech rate and linguistic and articulatory difficulty of scripts to accommodate individual needs. Following treatment, participants demonstrated significant improvement in production of scripted words and reduction of grammatical errors in trained topics and increased intelligibility in trained and untrained scripts at post-treatment. Results of these and other studies investigating script training suggest that this type of behavioral intervention may yield generalized improvement and maintenance of language function.

Others have implemented different approaches to audiovisual stimuli to treat nonfluent aphasia. For example, one program, Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effect (IMITATE), is a program for aphasia therapy that is based on action observation and imitation (Lee, Fowler, Rodney, Cherney, & Small, 2010). IMITATE consists of silent observation of audio-visually presented words and phrases and is followed by stimulus repetition. This paradigm focuses on observation-execution matching and is supported extensively in the neuropsychological literature (Skipper et al., 2005, 2007; Skipper, Goldin-Meadow, Nusbaum, Small, 2007) and by other previous

approaches to aphasia treatment (Duffy, 2005). For example, Duffy used imitation to treat NFA and suggested that the visual input of speech complemented the sensory information. This concept was also used by Rosenbek and colleagues (1973) and revealed that the patients with impaired speech can mimic the fluent speech of others in real time. Similar effects have been identified in choral reading or choral speech. These two approaches have induced fluent speech in aphasia (Oral Reading for Language; Cherney, 2004, 2010) and stuttering (Max et al., 1997; Kiefte & Armson, 2008).

Despite the number of script training studies that have and continue to be published and the reported success of this type of training for people with aphasia, like many other approaches to aphasia rehabilitation, the active ingredients of the paradigm itself are still not well-understood. However, Quique and colleagues (2022) argue that listening, repetition, and production (variables that are also engaged by and may support word-retrieval treatment response) may be considered active ingredients for script training. This is based on results from their own recent work and evidence from previous studies that propose specific components positively contribute to patient success with script training (Quique et al., 2022). These include repetition of whole sentences or words, 'choral reading', or practice with written and auditory feedback (Goldberg et al., 2012). This also includes variables commonly used to measure success with script training such as fluency, rate, and production (Cherney, Kaye, Lee, van Vuuren, 2015; Cherney et al., 2008; Cherney et al., 2011). Finally, although not within the scope of the current study, others have also considered how these proposed active ingredients and the concepts of 'ingredients' as it relates to therapy, may fit into models of rehabilitation more broadly (Hart et al., 2019).

1.13 Speech Entrainment

A recent investigation of scripted-sentence learning in Spanish speakers with aphasia aims to identify further the active ingredients of script training (Quique et al., 2022). More specifically, however, the authors suggest that speech entrainment may be a fourth active ingredient of script training. Unison production of words or sentences by the patient and clinician is not a treatment component of most other aphasia treatments (e.g. word-retrieval or sentence production) but is the essence of many in-person and computer-delivered script training programs (Cherney et al., 2008; Goldberg et al., 2012). Speech entrainment can be effectively achieved through audiovisual feedback (Fridriksson et al., 2012) and orthographic cueing, as seen in studies of choral reading (Goldberg et al., 2012; Youmans, Holland, Muñoz, & Bourgeois, 2005). Importantly, the synchronization of the clinician (model) and patient productions that is observed in speech entrainment is also highly associated rhythm. Previous work suggests that entrainment relies on the detection, integration and production of rhythmic features (Phillips-Silver, Aktipis, & Bryant, 2010) and Quique and colleagues (2022) have supported this notion with recent findings that suggest adding external rhythmic cues make the detection and alignment to the rhythmic structure easier.

1.13.1 Therapeutic Ingredients

When considering the ingredients of speech entrainment, audiovisual speech and the presence of an online model are most paramount for the context of the current speech entrainment training paradigm.

1.13.1.1 Audiovisual Speech

As mentioned earlier in *Section 1.11.2 Efference copy integrity in nonfluent aphasia*, audiovisual tasks that act as an external gaiting mechanism have the potential to promote fluent speech in patients with NFA. One such behavioral model is called speech entrainment. Unlike traditional SLT models that prompt patients with NFA to generate and produce speech, speech entrainment (SE) yields promising improvements in speech fluency among individuals with NFA by guiding or 'pulling along' the patient's speech (Fridriksson et al., 2015; Fridriksson et al., 2012). SE relies on an action observation and online rehearsal of an audiovisual script. The motivation for an audiovisual stimulus comes from the aforementioned rehabilitation approaches in aphasia (Rosenbek, Lemme, Ahern, Harris, Wertz, 1973) as well as from studies of neurotypical controls and clinical populations (Hall et al., 2005; Meister et al., 2007; Bernstein et al., 2008; Fridriksson, Moss, Davis, Baylis, Bonilha, Rorden, 2008). These studies suggest audiovisual speech improves perception and provide evidence to support the role of anterior cortical regions in the perception of auditory (Meister et al., 2007) and visual aspects of speech (Rorden, Davis, George, Borckardt, & Fridriksson, 2008). For example, studies of speech perception in healthy controls suggest that increased activity in anterior cortical areas is associated with speech perception. This is especially true when the stimuli contain both auditory and visual components (Hall et al., 2005; Bernstein et al., 2008; Fridriksson, Moss, Davis, Baylis, Bonilha, Rorden, 2008; Vander Wyk, Ramsey, Hudac, Jones, Lin, Klin, Lee, Pelphrey, 2010).

Other studies suggest the role of visual speech in production (Reisberg, McLean, Goldfield, 1987) and earlier approaches to rehabilitation have employed observation-

execution matching with audiovisual tasks (Rosenbek, Lemme, Ahern, Harris, Wertz, 1973; Duffy, 2005), as described in greater detail in *Section 1.12.2: Rehabilitative Approaches for Nonfluent Aphasia*. These previous paradigms prompted a study to determine if the nature of audiovisual stimuli improved speech production (picture naming) in a clinical population: speakers with NFA (Fridriksson et al., 2009). The authors hypothesized that an audiovisual speech perception task would recruit residual anterior cortical language regions to improve speech production. Consistent with their hypothesis, Fridriksson and colleagues found that treatment involving audiovisual stimuli improved speech production in individuals with nonfluent aphasia compared to a treatment with auditory only stimuli. More recently, Venezia and colleagues (2016) showed consistent results in a cohort of neurotypical adults and identified inferior frontal gyrus pars opercularis (IFG*po*) and posterior middle temporal gyrus (*p*MTG) as regions that respond more strongly during visual and audiovisual tasks compared to a audio only speech condition.

1.13.1.2 Online Model

In addition to the audiovisual model provided by SE, real time synchrony (via online action observation) between the audiovisual speech model and entrained speech is thought to be crucial to elicit fluency. To emphasize this point, consider two tasks: SE and speech repetition. SE relies on online rehearsal and contributes to improved speech production while speech repetition tasks do not rely on synchronous speech production and fail to induce the same effect (Fridriksson et al., 2015). It is evident then that two components: online rehearsal and audiovisual stimulus, are crucial to explain why SE induces fluent speech. These mechanisms will be discussed in further detail in *Section*

1.13.2: Behavioral Evidence for Speech Entrainment and Section 1.13.4 Underlying Neural Mechanisms.

Supported by evidence from a recent study that supports speech entrainment as an active ingredient for scripted-sentence learning, Quique and colleagues (2022) suggest that rhythmic cues (both external and those present in natural speech) may help a person with aphasia perceive and align to word stress and, in turn, support lexical retrieval. This is supported by work with healthy controls (Cutler, 1989, 2005, 2012) and Quique demonstrates the added benefit of a language such as Spanish where stress plays a crucial role in lexical retrieval (Soto-Faraco, Sebastián-Gallés, & Cutler, 2001). Quique and colleagues demonstrate patients' ability to learn significantly more scripted sentences in conditions where the scripts were rhythmically enhanced as compared to the control condition and use this to support the idea that speech entrainment may be an active ingredient for scripted-sentence learning due to the benefits for word retrieval. Second, Quique and colleagues (2022) suggest that the rhythm that is inherent to speech entrainment may facilitate scripted-sentence learning by supporting memory processing via chunking (Purnell-Webb & Speelman, 2008).

The concept of practicing speech production in real time with a model (action observation) is not necessarily a new concept in rehabilitation. This approach has been used to improve motor (Ertelt et al., 2007) and language and motor speech function in stroke patients (Dejerine & Thomas, 1914; Rosenbek, Lemme, Ahern, Harris, Wertz, 1973). In aphasia rehabilitation, action observation was also used in the aforementioned study by Fridriksson and colleagues (2009) in tandem with audiovisual stimuli to

facilitate improved naming. The authors suggest that an online audiovisual model is thought to provide external gaiting for speech production (Fridriksson et al., 2012).

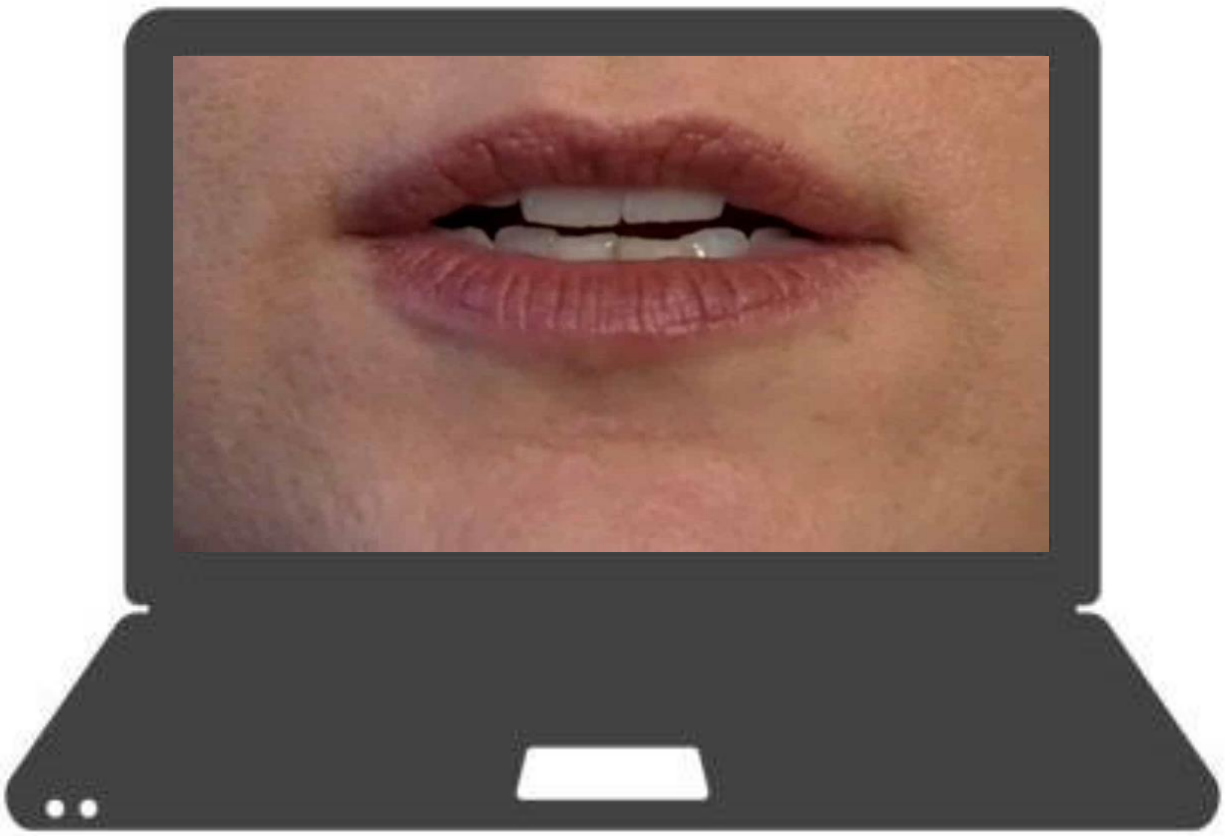


Figure 1.4 *Audiovisual stimulus for the speech entrainment task.*

1.13.2 An evidence-base for the rehabilitation of post-stroke aphasia

Following the preliminary study that revealed visual speech perception significantly improves speech production in NFA (Fridriksson et al., 2009), Fridriksson and colleagues (2012a, 2015a) conducted two studies to investigate the behavioral effects of SE and relatedly, the neural underpinnings that support successful entrainment. The initial proof-of concept study revealed that, after six weeks of practice, patients with NFA (n = 13) demonstrated greater improvements in speech fluency following SE (AV speech model) compared to treatment that involved audio-only speech models and spontaneous speech productions outside of therapy (Fridriksson et al., 2012). These findings generalized to performance on untrained scripts at 1-week and 6-weeks post-treatment. The authors suggest the audiovisual model provides an external gating for speech initiation and fluency (Fridriksson et al., 2012).

In a second study, patients with NFA (n = 15) produced more fluent speech in a SE task than in a spontaneous speech after 3 weeks of daily SE training (Fridriksson, Basilakos, et al., 2015). This study replicates the initial behavioral findings and suggests that for persons with NFA, SE induces more fluent speech production than what these participants are capable of producing in unstructured, discourse tasks. Importantly, these improvements generalize to performance in untrained scripts.

To further investigate the effects of speech entrainment on factors other than linguistic variables, Feenaughty and colleagues (2021) aimed to determine if they could identify speech timing changes during a speech entrainment paradigm. By including speakers with both fluent and nonfluent aphasia, the authors assessed 'speech fluency' using acoustic measures such as total number of syllables, speech rate, articulatory rate,

silent pause frequency and duration. Findings suggested that those with nonfluent aphasia improved speech fluency as evidenced by pause adjustments and facilitated more typical speech timing as compared to their spontaneous speech. Importantly, this study not only offers further support for the impact of speech entrainment on fluency for patients with nonfluent aphasia, but also sheds light on the acoustic-perceptual characteristics that were not previously considered. From a rehabilitation perspective, more fluent speech may positively impact perceptual judgements of speech naturalness and social acceptance for those living with nonfluent aphasia (Feenaughty et al., 2021).

Recently, speech entrainment was investigated to determine if the behavioral effects of SE generalized to spontaneous speech. Thors et al. (2019) provided SE treatment for three consecutive weeks (11.25 treatment hours) to a cohort of twenty participants with chronic aphasia and assessed maintenance at three time points: immediately post-treatment, at three months, and at six months. An overall median increase on primary discourse measures (words per minute, different words per minute, communicative efficiency and percent of content units) was noted from baseline to post-treatment as indicated by small and medium effect sizes. SE training improved spontaneous speech for some, but not all participants. Improvements in speech and language were also noted to generalize to picture naming, semantic processing and grammatical processing. Notably, following treatment, aphasia quotient scores from the Western Aphasia Battery - Revised (2007) increased, signifying reduced aphasia severity. Notably, effects from this study were confounded by a small sample size and considerable variability across participant performance. Nonetheless, this investigation provides new information regarding the effects of SE treatment and suggests small, but

perhaps meaningful generalization to structured discourse and other speech and language tasks.

Outcomes from the aforementioned studies, have encouraged further investigation of speech entrainment in a prospective, randomized, assessor-blinded multicenter phase II clinical trial (Cassarly et al., 2021). Participants in this study are randomized to 3 weeks, 4.5 weeks, or 6 weeks of speech entrainment therapy delivered via telehealth, or a control condition for 6 weeks. Outcomes from this ongoing trial will inform the dose of speech entrainment therapy that elicits the highest effect size on speech fluency and is a critical step for future definitive trials to determine the clinical utility of speech entrainment therapy.

1.13.3 Considerations for clinical translation

The behavioral findings outlined above suggest SE may be a meaningful clinical tool for the treatment of NFA (Thors et al., 2019; Fridriksson et al., 2012a, 2015a; Henry et al., 2018). Importantly, the administration of three short SE tasks increases speech output which may mean that extensive training is not necessary. Furthermore, when SE is implemented as a six-week treatment program, patients demonstrate generalization and maintenance as they produce a greater variety of words with and without SE at one and six weeks after training (Fridriksson et al., 2012). Thors and colleagues (2019) also demonstrate that generalization effects, albeit minimal, exist after a three week training period.

SE may be superior to conventional therapy approaches for nonfluent aphasia. Unlike the rapidly improved performance observed in SE, traditional behavioral aphasia therapies yield limited gains (Brady et al., 2016). Furthermore, SE ameliorates obstacles

in conventional rehabilitation approaches (Boyle, 2015) as it: 1) directly addresses the issue of learned nonuse (Taub et al., 2006; Wolf, Lecraw, Barton, & Jann, 1989), 2) allows persons with NFA to practice fluent speech with relatively few errors (Fridriksson et al., 2012), and 3) capitalizes on effective mechanisms from other treatment approaches that suggest observation, modeling, and action may modulate residual brain networks and aid recovery (Ertelt et al., 2007; Fridriksson et al., 2009; Lee et al., 2010; Small, Buccino, Solodkin, 2013; Sarasso et al., 2014).

In terms of clinical translation, SE has the potential to fulfill an unmet clinical gap. Namely, SE can be used in the absence of a trained clinician. This is especially important given limited amount of services provided to patients with aphasia and the low number of clinicians, especially in rural areas. SE is also unique because even if patients cannot improve propositional speech, they may rely on the individualized scripts in SE to facilitate conversations and increase participation in social settings. Thus, patients can still practice fluent speech despite the fact that this is their primary deficit. Adapting scripts to be personally relevant may offer a more ecologically valid task than conventional therapy stimuli. Scripts can also be modified to target underlying language deficits. In this way, speech entrainment may offer an appropriate combination of impairment and functionally-based rehabilitation to offer an individualized and efficient means of therapy.

1.13.4 *Underlying Neural Mechanisms of Speech Entrainment*

Evidence from research investigating the role of multimodal stimuli in speech perception suggests that audiovisual perception is associated with greater activation in Broca's area compared to auditory only stimuli (Fridriksson, Moss, Davis, Baylis,

Bonilha, Rorden, 2008; Vander Wyk, Ramsey, Hudac, Jones, Lin, Klin, Lee, Pelphrey, 2010). Additionally, brain stimulation in neurotypical adults suggests that Broca's area is involved in the perception of auditory (Meister et al., 2007) and visual aspects of speech (Rorden et al., 2008). These findings, in conjunction with the behavioral outcomes from SE (Fridriksson et al., 2015; Fridriksson et al., 2012) and other audiovisual models (Lee et al., 2010), prompted further investigation into the neural underpinnings of SE, to better understand the mechanism that supports successful entrainment. Functional magnetic resonance imaging (fMRI) has revealed bilateral activation of the anterior insula, IFG*po*, posterior inferior temporal cortex, left *p*MTG, and the left dorsal region of Broca's area during SE (Fridriksson et al., 2012).

A voxelwise lesion-symptom mapping analysis (Fridriksson et al., 2015) showed results that were similar to the patterns of fMRI activation: anterior damage, particularly insult to the inferior frontal (Broca's area [pars opercularis]), posterior superior temporal, inferior parietal, inferior frontal, and insular regions, predicted poor speech fluency. A positive response to speech entrainment was associated with lesions in the inferior and middle frontal gyri (Fridriksson et al., 2015). The authors posit that SE activates residual areas of the left hemisphere and may compensate for damage to language production mechanisms in the inferior frontal areas (IFG*po*) when alternative neural pathways (i.e. ventral stream regions [*p*MTG]) are intact to support the function of speech fluency. In turn, practice with the audiovisual model improves speech production. More specifically, SE is most beneficial for patients with damage to Broca's area, the neural correlate that is hypothesized to underlie successful initiation and speech fluency (Fridriksson et al., 2012). To further evaluate the critical neurological mechanisms underlying SE success,

Bonilha and colleagues (2019) used lesion mapping and machine learning to determine if a neurological model could predict which patients benefit most from SE. Consistent with previous work (Fridriksson et al., 2015; Fridriksson et al., 2012), damage to IFG*po* was associated with 'successful entrainment' (improved speech fluency gains following SE as compared to spontaneous speech), and damage to the posterior middle temporal gyrus (*p*MTG) resulted in worse SE performance (Bonilha et al., 2019).

Damage to dorsal stream regions (supra-Sylvian and associated white matter tracts [superior longitudinal fasciculus]) and preservation of ventral stream regions (infra-Sylvian and associated white matter tracts [uncinate fasciculus]) resulted in successful entrainment. It is important to note that these findings suggest that is it not isolated regions within a specific stream that promote SE success, but instead, the connections (via white matter pathways) are the substrate for successful entrainment. The ventral stream is hypothesized to serve as the auditory-motor interface (Hickok & Poeppel, 2004, 2007; Poeppel, Hickok, & Poeppel, 2000) and the integrity of ventral regions is expected to be important for SE success due to their role in early audiovisual integration and comprehension (at the word and sentence level) (Bonilha et al., 2017; Fridriksson et al., 2018; Venezia et al., 2016). Therefore, integrity of temporal white matter pathways may support dorsal-ventral stream integration and suggest why preservation of these regions is necessary to facilitate fluent speech.

Across all studies, patients with the damaged inferior frontal regions (IFG*po*), but intact ventral regions (namely, *p*MTG) demonstrate SE-related improvements. To better understand the role of the *p*MTG in SE success and audiovisual processing, this region has been studied in the context of clinical (Thors et al., 2019; Henry et al., 2018; Bonilha

et al., 2019) and healthy populations (Venezia et al., 2016). A treatment study of 20 individuals with Broca's aphasia revealed 1) success of SE treatment is associated with preservation of the *p*MTG and 2) improvements in speech fluency from pre- to post-treatment were associated with *p*MTG activity (Thors et al., 2019). In a cohort of ten patients with the nonfluent variant of primary progressive aphasia, behavioral improvements (increased verbal output and greater speech intelligibility) after training with an audiovisual SE script training task were negatively associated with atrophy in the posterior and inferior MTG (Henry et al., 2018). In a group of healthy young adults, Venezia and colleagues (2016) revealed *p*MTG activation for visual-only and audiovisual conditions while auditory-only conditions activated *p*STG. Consistent with findings from clinical populations, *p*MTG activation is associated with the perception of audiovisual speech, suggesting that this region may play a role in speech production by processing complementary visual targets. A number of previous studies have found activation of the left *p*MTG in visual or audiovisual speech (Callan et al., 2003; Calvert & Campbell, 2003; MacSweeney et al., 2001; Sekiyama, Kanno, Miura, & Sugita, 2003) and this region has even been named the temporal visual speech area (TVSA; Bernstein et al., 2011).

While neural mechanisms necessary for SE success have been investigated using lesion analyses and white matter tractography, the role of functional connectivity in this task has been explored to a lesser degree. One theory is that SE induces improved synchrony (as measured by functional connectivity) between anterior and posterior cortical speech areas. Anterior-posterior synchrony between such language regions has been shown to correlate with language ability (Fox and Raichle, 2007; Vlooswijk, Jansen,

Majoie, Hofman, de Krom, Aldenkamp, 2010; Chai et al., 2016; Baldassarre et al., 2019). This idea is discussed in further detail in *Section 1.3.3 Anterior-Posterior Coherence for Language Production*. To investigate how aberrant neural synchrony (i.e. secondary to a stroke lesion) may impact SE success, Johnson and colleagues (2021) investigated functional connectivity between regions of interest that support successful entrainment (bilateral inferior frontal gyrus, *pars opercularis* and *p*MTG) across two tasks: 1) SE and 2) free speech for a group of individuals with chronic aphasia and a group of neurotypical age-matched controls. Consistent with the hypothesis, persons with aphasia demonstrated increased functional connectivity during SE compared to free speech across two sets of anterior and posterior regions of interest: 1) left inferior frontal gyrus, *pars opercularis* and left *p*MTG (highlighted in red in *Figure 1.4*); 2) R par opercularis and L pMTG (highlighted in teal in *Figure 1.4*). Johnson and colleagues (2021) posit that improved functional connectivity between anterior (inferior frontal gyrus, *pars opercularis*) and posterior (*p*MTG) language regions improves during the SE task.

Neuroimaging findings from the aforementioned studies suggest a potential role for adjuvant approaches, such as noninvasive brain stimulation, to improve the effects on behavioral performance. This paradigm is hypothesized to serve as an external model and reinforce anterior-posterior coherence (particularly between IFG*po* and *p*MTG) in the left hemisphere. In the context of rehabilitation and neural plasticity (discussed in further detail in *Section 1.4.1 Evidence for Neural Plasticity in post stroke aphasia*), repeated training with SE (scripts with typical rhythm, syntactic structure, and speech rate) may decrease effects of cortical maladaptation associated with learned nonuse and elicit functional connectivity more similar to controls to facilitate fluent speech. Furthermore,

data suggest that the integrity of the ventral stream (cortical structures and associated white matter pathways) promote SE success.

1.13.5 Converging evidence for the current study

To conclude this section, it is relevant to consider how the neural mechanisms implicated in successful entrainment can be considered in the context of the aforementioned theoretical models. SE is hypothesized to improve neural synchrony between anterior and posterior cortical language regions and promote effortless speech production (i.e. improved fluency, and fewer speech errors) (Guenther et al., 1998; Houde & Nagarajan, 2011; Fridriksson et al., 2012). This idea that anterior-posterior coherence facilitates successful speech production is supported by neurophysiological and theoretical support (Guenther et al., 2006; Hickok, 2012; Johnson et al., 2021).

As described in *Section 1.13.4 Underlying Mechanisms of Successful Entrainment*, studies that have investigated the neural correlates of SE suggest that the integrity of ventral stream regions is associated with better entrainment. More recent work from Johnson and colleagues (2021) emphasizes that one particularly relevant mechanisms of entrainment is that SE acts as an external mechanism to improve coherence between anterior (IFG*po*) and posterior (*p*MTG) cortical regions in the left hemisphere. Furthermore, it is evident from the previous discussion of speech production models in *Sections 1.11: Efference Copy* and *1.13 Speech Entrainment*, that anterior-posterior cohesion is necessary for feedforward integration and successful speech production (Guenther et al., 1998, 2006; Hickok, 2014, *Figure 1.2*, *Figure 1.3*). Given that SE is shown to be most effective in patients with anterior damage to the left IFG*po* and preserved regions of the ventral stream, particularly *p*MTG, and that successful

entrainment is associated with greater functional connectivity between these two areas. It, therefore, seems reasonable that applying an external modulatory source to compensate for damage to this mechanism may boost behavioral performance, above and beyond what is seen with the effects of SE alone.

Earlier, in *Section 1.11.3: Anterior-Posterior Coherence for Language Production*, evidence is discussed regarding the anterior-posterior connectivity that supports fluent speech and how this neural mechanism may represent the efference copy. In the context of the current investigation, SE is posited to improve anterior-posterior functional connectivity in people with aphasia (Johnson et al., 2021). Therefore, neural coherence (as measured by functional connectivity) is particularly relevant to consider as a mechanism to target in rehabilitation. As outlined in *Sections 1.11.3: Anterior-Posterior Coherence for Language Production* and *Section 1.13.4: Underlying Neural Mechanisms of Successful Entrainment*, stroke-induced disruptions to anterior-posterior functional connectivity may impair the efference copy. More recent work suggests that increased anterior-posterior coherence may be facilitated by SE because it is an external audiovisual model that compensates for the damaged efference copy (Johnson et al., 2021). Such findings prompt the need for an investigation to determine how neural coherence in the left hemisphere can be modulated to 'boost' SE improvement .

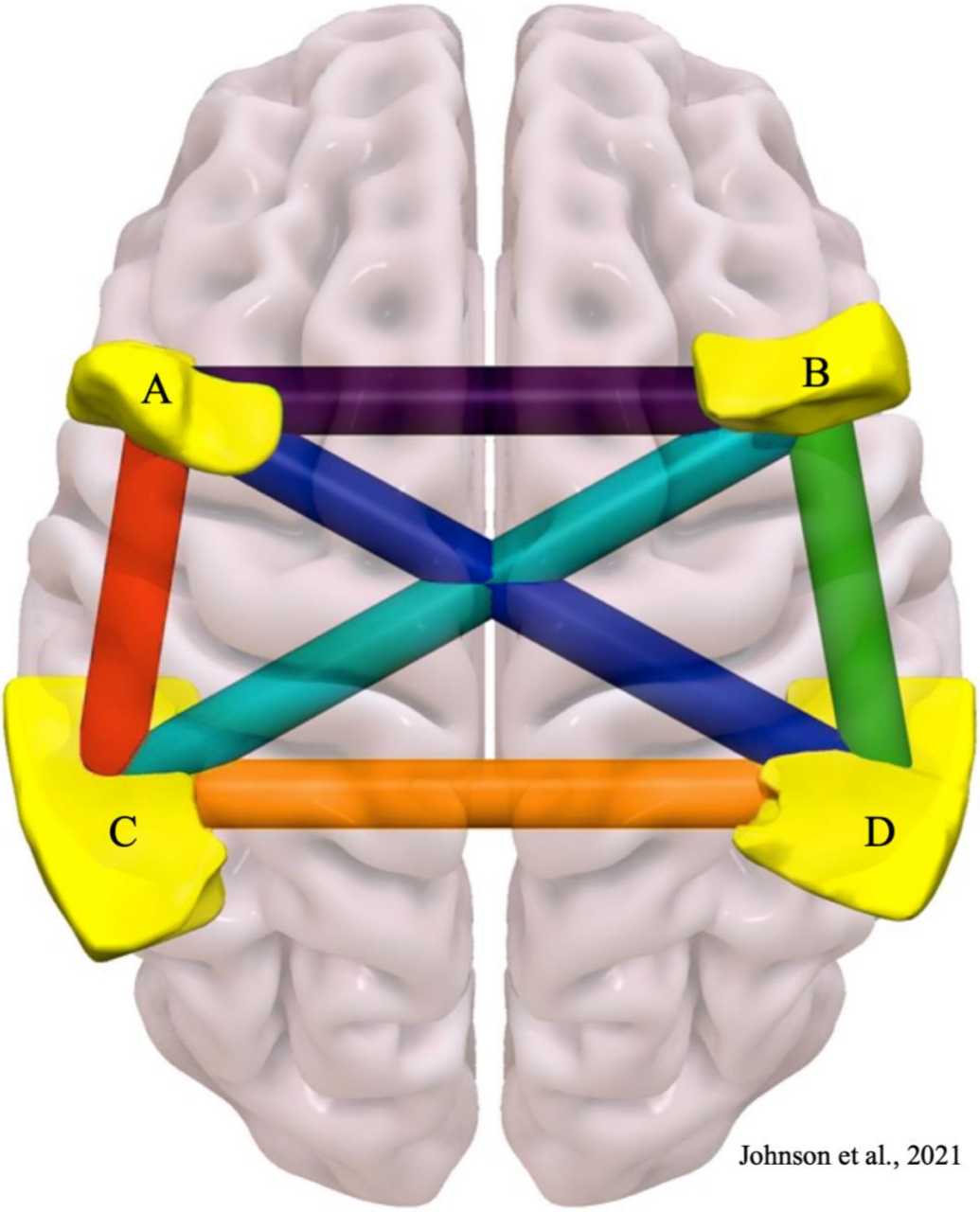


Figure 1.5 *Speech entrainment facilitates improved LH anterior (L IFG) - posterior (pMTG) neural coherence (as measured by functional connectivity). Functional connectivity between regions A (L IFG pars opercularis) and C (L pMTG) indicated in red and connectivity between regions B (R IFG pars opercularis) and C (L pMTG) indicated in teal improved with the SE task.*

A number of studies have investigated functional connectivity using fMRI (task-based and resting state) and EEG to determine the role of neural coherence. Such investigations have revealed that synchrony between anterior and posterior cortical language regions supports speech production in healthy (Chai et al., 2016; Ewald, Aristei, Nolte, & Abdel Rahman, 2012) and clinical populations (Vlooswijk, Jansen, Majoie, Hofman, de Krom, Aldenkamp, 2010; Kell et al., 2018).

In studies of neurotypical adults, EEG studies show the forward speech production model is reflected in the negative-going signal that originates from the IFG and oscillates with phase delay in the auditory cortex (Chen et al., 2011; Ford, Roach, & Mathalon, 2010; Wang et al., 2014). There is further evidence for the consequences of aberrant frontotemporal synchrony on speech production deficits in clinical populations such as developmental stuttering, autism spectrum disorder, Fragile X, and post-stroke aphasia, (Belmonte et al., 2004; Brown, Ingham, Ingham, Laird, & Fox, 2005; Budde, Barron, & Fox, 2014; Fiori et al., 2011; Mandelli et al., 2018; Marangolo et al., 2011; Paola Marangolo et al., 2013; Schmitt et al., 2020; Sengupta & Nasir, 2015).

For example, in a population of individuals with a developmental stutter, a disrupted fronto-temporal connectivity was identified prior to speech production and following speech production, this sample demonstrated under-activation of auditory language regions (Brown et al., 2005; Budde, Barron, & Fox, 2014b; Sengupta & Nasir, 2015). In a sample of individuals diagnosed with autism spectrum disorder, researchers identified reduced correlations between frontal and temporal cortices were associated with more severe expressive language deficits (Belmonte et al., 2004). Recently, Schmitt and colleagues (Schmitt et al., 2020) found fronto-temporal dysconnectivity resulted in

speech production deficits in a group of individuals diagnosed with Fragile X Syndrome. Such results implicate the role of frontotemporal circuitry in speech production and more specifically, a weakened signal from the frontal cortex may be insufficient to compare again the actual speech sound. Consequently, speech sound discrepancies may go undetected and uncorrected.

In a cohort of adults who stutter, Kell and colleagues (2009) examined neural-activity changes associated with recovery in a fluency shaping therapy program (Kassel Stuttering therapy (Euler & Wolff von Gudenberg, 2000), adapted from (Webster, 1980)). Fluency shaping therapies aim to modify paralinguistic variables (i.e., speech tempo, prosody, rhythm, onsets) and implement breathing techniques to reduce stuttering severity (Euler & Wolff von Gudenberg, 2000). Results from Kell and colleagues (Kell et al., 2009) suggest that reduced auditory-motor coupling and enhanced integration of somatosensory feedback between the supramarginal gyrus and prefrontal cortex was associated with persistent stuttering. Improved speech fluency following administration of the fluency shaping program was associated with increased functional connectivity between the articulatory motor cortex and the anterior superior temporal gyrus. Results also suggest that fluency shaping training improved auditory-motor mapping as indicated by changes in left-hemisphere neural activity (Kell et al., 2018).

Other studies reveal similar results to suggest a critical role for anterior-posterior coherence in language function. In a comparison of language performance between a control group and patients with epilepsy, Vlooswijk (2010) reported the largest difference in functional connectivity between the IFG and MTG in the left hemisphere. Ewald and colleagues (2012) showed similar patterns of anterior-posterior connectivity that support

language performance where increased connectivity between anterior (frontal) and posterior (occipital-temporal) regions was observed in an cohort of neurotypical adults during an overt language production (naming) task.

In sum, such dysconnectivity may contribute to abnormal speech development in neurodevelopmental conditions. In acquired language disorders such as post stroke aphasia, a number of investigations have found that applying a noninvasive transcranial stimulation technique, transcranial direct current stimulation, to the left inferior frontal gyrus results in reduced articulation errors and increased speech output (Fiori et al., 2011; Mandelli et al., 2018; Marangolo et al., 2011; Marangolo, Fiori, Cipollari, Campana, Razzano, Di Paola, et al., 2013).

Results from these investigations are consistent with models of speech production that suggest that 'communication' between sensory and motor units is necessary for successful (fluent) speech production. Given that fluent speech production relies on connectivity between anterior and posterior language regions (Vlooswijk, Jansen, Majoie, Hofman, de Krom, Aldenkamp, 2010; Ewald et al., 2012; Chai et al., 2016) and that additional evidence suggests maladaptive brain changes following a stroke can negatively impact recovery (Mark & Taub, 2004; Taub et al., 2006), anterior-posterior synchrony in the left hemisphere requires consideration in the context of behavioral rehabilitation. Taken together with the recent findings from Johnson and colleagues (Johnson et al., 2021), results from the aforementioned studies contribute to a growing body of literature that suggests greater anterior-posterior functional connectivity during speech production may be indicative of an intact efference-copy mechanism and therefore, may be a

reasonable target for therapeutic interventions. This is especially true for behavioral therapies, such as SE, that target the efference copy mechanism.

1.14 Neural Oscillations

1.14.1 Communication through Coherence: Processing from an Oscillatory Perspective

Communication across neural populations, termed 'communication through coherence' (Fries, 2005), is subserved by oscillatory synchrony across brain regions (Greenblatt & Pflieger, 2012). Neural oscillations are defined as peaks above the aperiodic signal of the brain (Haller et al., 2018) and refer to the endogenous rhythms that correspond with the behavior of neurons. Functional connectivity patterns are thought to be subserved by oscillatory activity (Cabral, Hugues, Sporns, & Deco, 2011).

Oscillatory brain activity is particularly important for brain processing and by extension, plays a role in normal cognitive function (Fries, 2005; Lopes da Silva, 2013; Thut, Miniussi, & Gross, 2012; S. Wang & Liu, 2010) and dysfunction (Schnitzler & Gross, 2005; Uhlhaas & Singer, 2015). Oscillatory activity serves as a prognostic factor for cognitive decline in healthy populations (i.e., normal aging) and for pathological impairments in clinical populations. Neural damage, such as the injury that results from a stroke, negatively impacts time scales of neural oscillations (functional connectivity) across the brain (Grefkes and Fink, 2011; Corbetta, 2012; Carrera and Tononi, 2014; Dijkhuizen et al., 2014; Yourganov et al., 2021). For example, a range of oscillatory frequencies (slow-5, delta, alpha and beta) have been identified in patients following brain injury as indicators of post-stroke recovery for neurophysiological (Foreman & Claassen, 2012; Wu et al., 2015) and behavioral function (Butz et al., 2004; Dubovik et al., 2012) Aberrant oscillatory patterns suggest poorer clinical outcomes may serve as an

important biomarker for stroke recovery (Laaksonen et al., 2013; Nicolo et al., 2015). In the context of stroke-induced aphasia, language impairments have been associated with aberrant oscillatory patterns, resulting in disruptions of functional connectivity networks and reduced network coherence (Baldassarre et al., 2019; Siegel et al., 2016).

1.14.2 Oscillatory Activity

Neural activity varies periodically over time (periodic oscillations) and at different frequencies (0.05 – 500 Hz), which are classified into bands (i.e., slow-5 = 0.01 = 0.027 Hz; delta = 0.5 – 4 Hz; theta = 4 - 7 Hz; alpha = 8 – 13 Hz; beta = 14 – 30 Hz; gamma = > 30 Hz). These bands represent different neural functions and strengths (as assessed with inter-trial coherence and power). For example, theta oscillations have been shown to modulate *long-distance* (fronto-parietal) network activity (Buzsaki, Draguhn, 2004; Fujisawa, Buzsaki, 2011; Karalis et al., 2016). Frequencies may compete with one another (Csicsvari, Jamieson, Wise, & Buzsáki, 2003; Klimesch, 1999; Kopell, Ermentrout, Whittington, & Traub, 2000; Singer, Engel, & Fries, 2001) or temporally co-exist in structures throughout the brain that interact with each other (Csicsvari et al., 2003; Steriade, 2001).

Oscillatory activity can be an important parameter to define spatiotemporal structures of neural activity (Fiene et al., 2020). Communication between two oscillatory populations is facilitated when the two groups are aligned to their high excitability phases. For example, there are periodic instances when neurons in designated populations are more likely to produce output or receive input. This occurs when neurons are entrained or phase-locked to oscillate at the same frequency and period as an external stimulus or internal cognitive process (other populations of entrained neurons) (Thut et

al., 2012). Effective neural communication relies on spikes in a phase of high excitability (Canolty, Edwards, Soltani, Nagarajan, Kirsch, Berger, Knight, 2006). In this way, synchronous oscillatory patterns result in successful neural communication (as measured with functional connectivity) across different regions (Fries, 2005).

The Dynamic Systems Theory (Ali, Sellers, & Frohlich, 2013) posits that neural systems have preferred ('resonant') stimulation frequencies. Therefore, neuronal modulation that is intended to enhance the inherent activation pattern of a brain network (for example, noninvasive brain stimulation) should be most effective when the exogenous stimulation frequency is at or near the brain network's resonant frequency (Ali et al., 2013). When stimulation frequencies are matched, this results in phase resetting or amplification (Lakatos, Chen, O'Connell, Mills, Schroeder, 2007). Termed *in-phase*, this mode of external stimulation induces and achieves synchronous frequencies to modulate oscillatory patterns which, in turn, can improve behavioral performance (Ali et al., 2013). *In-phase* stimulation results in enhanced synchrony between target regions and has been shown to improve cognitive performance (Helfrich et al., 2014a; Reinhart, 2017; Violante et al., 2017; Nguyen, Deng, Reinhart, 2018) while *anti-phase* stimulation (alternating current delivered with 180° relative phase difference across target areas) has the inverse effect: impeded network synchronization and impaired performance (Buzsaki, Gyorgy, Draguhn, 2004).

1.14.3 Theta Band Frequency Neural Oscillations

One particular frequency band, theta, is especially relevant in the context of the current study. Neuroanatomically, low-frequency oscillations such as those in the theta band are thought to play a primary role in long-range connectivity between anterior and

posterior regions (Von Stein and Sarnthein, 2000; Buzsaki, Gyorgy, Draguhn, 2004; Sauseng and Klimesch, 2008; Fujisawa, Buzsaki, 2011; Karalis et al., 2016; Siebenhühner et al., 2016; Palva and Palva, 2018). Phase synchronization in the theta band and increased theta coherence between prefrontal and temporal areas is associated with language and memory functions (Bastiaansen et al., 2005; Mellem et al., 2013; Doesburg, Tingling, MacDonald, Pang, 2016; Pu et al., 2020). For example, Doesburg and colleagues (2016) found increased connectivity in the theta frequency range in an expressive language task. They interpret these results to suggest that network connectivity of anterior and posterior language regions is associated with verbal language This suggests a role for theta band frequency oscillations due to the anterior-posterior synchrony that is thought to support speech production and more specifically, the generation of an efference copy.

With respect to language, multiple frequency bands have been associated with production and comprehension abilities in neurotypical populations. Theta frequency bands are strongly associated with the rhythmic patterns of human speech for perception, are thought to play a role in the extraction of semantic information (Bastiaansen et al., 2005; Hagoort, Hald, Bastiaansen, & Petersson, 2004) and are active in multisensory integration (i.e. audiovisual speech). Human speech is rhythmic and syllables (theta, 4 – 7 Hz) are nested in slower rates of phrase and word production (1-3 Hz). Low phase theta frequency oscillations in the auditory cortex are thought to synchronize with the low phase frequency of human speech during speech comprehension (Giraud & Poeppel, 2012). The magnitude of synchronization correlates with speech intelligibility (Ahissar et al., 2001; Di Liberto, Crosse, & Lalor, 2018; Keitel, Gross, & Kayser, 2017; Luo &

Poeppel, 2007; Vander Ghinst et al., 2016). Entrainment to speech is strongest at theta frequency range, the average frequency of the speech signal (Kayser, Wilson, Safaai, Sakata, & Panzeri, 2015). This cortical entrainment plays a critical role in speech processing.

Natural conversation as well as the audiovisual stimuli in SE rely on multisensory processing. It is well understood that the visual component of audiovisual speech enhances perception as compared to audio-only speech (Sumby & Pollack, 1954). More recent work has investigated the underlying mechanisms of visual speech and suggests improved perception of audiovisual speech is induced by modulation of neuronal oscillations. Auditory cortical neurons are thought to track the temporal dynamics of visual speech through slow oscillatory activity or mechanisms such as a phase reset in multisensory processing which yields more efficient and reliable cortical processing (Mégevand et al., 2020; Schroeder, Lakatos, Kajikawa, Partan, & Puce, 2008).

Theta frequency oscillations are hypothesized to play a critical role in multimodal speech. In the context of multimodal sensory processing, neural oscillations in different frequency bands reflect different aspects of processing (Keil & Senkowski, 2018). Audiovisual speech, for example, is one type of multimodal sensory processing that aids speech understanding via the orchestration of neural oscillations (see Keil and Senkowski, 2018 and Bauer et al., 2020 for a review). Previous studies suggest that oscillations are influenced by visual and auditory components of speech because the multisensory stimuli resets the phrase of low frequency oscillations in the auditory cortex (Crosse, Butler, & Lalor, 2015; Giordano et al., 2017; Luo, Liu, & Poeppel, 2010; O'Sullivan, Crosse, Di Liberto, & Lalor, 2017; Hyojin Park, Ince, Schyns, Thut, & Gross,

2018; Hyojin Park, Kayser, Thut, & Gross, 2016). Consequently, the phase reset enhances audiovisual speech processing (Mégevand et al., 2020). Oscillatory effects of visual speech occur throughout the brain, but are particularly evident in areas responsible for speech perception and production (Crosse et al., 2015; Park et al., 2018, 2016). For example, the visual component of spoken language is related to enhanced delta and theta band functional connectivity between frontal and temporal areas (Giordano et al., 2017).

In sum, studies suggest that theta frequency oscillations play a prominent role in audiovisual processing and may be particularly relevant in a task like SE, a task that relies on both language perception and production. Understanding the role of neural oscillations is important to understand the mechanisms of noninvasive neuromodulation. Other work demonstrates that modulating oscillatory patterns in the theta-frequency via transcranial electrical stimulation improves behavioral performance in speech perception (Riecke, Formisano, Sorger, Bas, & Gaudrain, 2018; Zoefel & Davis, 2017). Results from such studies are discussed in greater detail in *Section 1.15.2: Support for tACS.* Importantly, results from these studies suggest that transcranial electrical stimulation may be a promising method to facilitate improve functional coherence across anterior-posterior brain regions that communicate at a theta frequency. Coherence between these areas is evident in speech production (Vlooswijk, Jansen, Majoie, Hofman, de Krom, Aldenkamp, 2010) and processing of audiovisual stimuli (Giordano et al., 2017; Keil & Senkowski, 2018). More specifically, when paired with an audiovisual behavioral paradigm like SE that is shown to induce behavioral and neurophysiological changes, NIBS may be a promising approach to improve clinical disorders that arise due to aberrant neural synchrony.

1.15 Transcranial Alternating Current Stimulation

1.15.1 Mechanisms of tACS

Unlike tDCS, which delivers constant currents, tACS delivers low, electrical sinusoidal, periodically-alternating currents through the scalp to cortical regions of interest (Zoefel & Davis, 2017). Each electrode alternates between serving as an anode and cathode. At the cellular level, the stimulation effect of tACS is due to alterations of the transmembrane potential to modulate and entrain intrinsic neural oscillatory activity (Ali et al., 2013; Thut et al., 2011). Two assumptions need to be met for oscillatory entrainment to occur: 1) periodic modulation of membrane potentials and 2) phase alignment of intrinsic oscillations to tACS stimulation. Entrainment of endogenous oscillatory patterns induce changes in behavior (Thut et al., 2012). Oscillatory cycles establish a recurrent and dynamic temporal reference frame that allows temporal relations to be coded between groups of natural elements. Successful entrainment is dependent on a concept called the Arnold Tongue (Ali et al., 2013). This framework suggests that if the periodic input frequency matches the endogenous oscillation frequency, oscillators can be entrained at very low amplitudes. As the input amplitude increases, the range of frequencies around the endogenous frequency at which the input can entrain the oscillator expands. See *Figure 1.6*

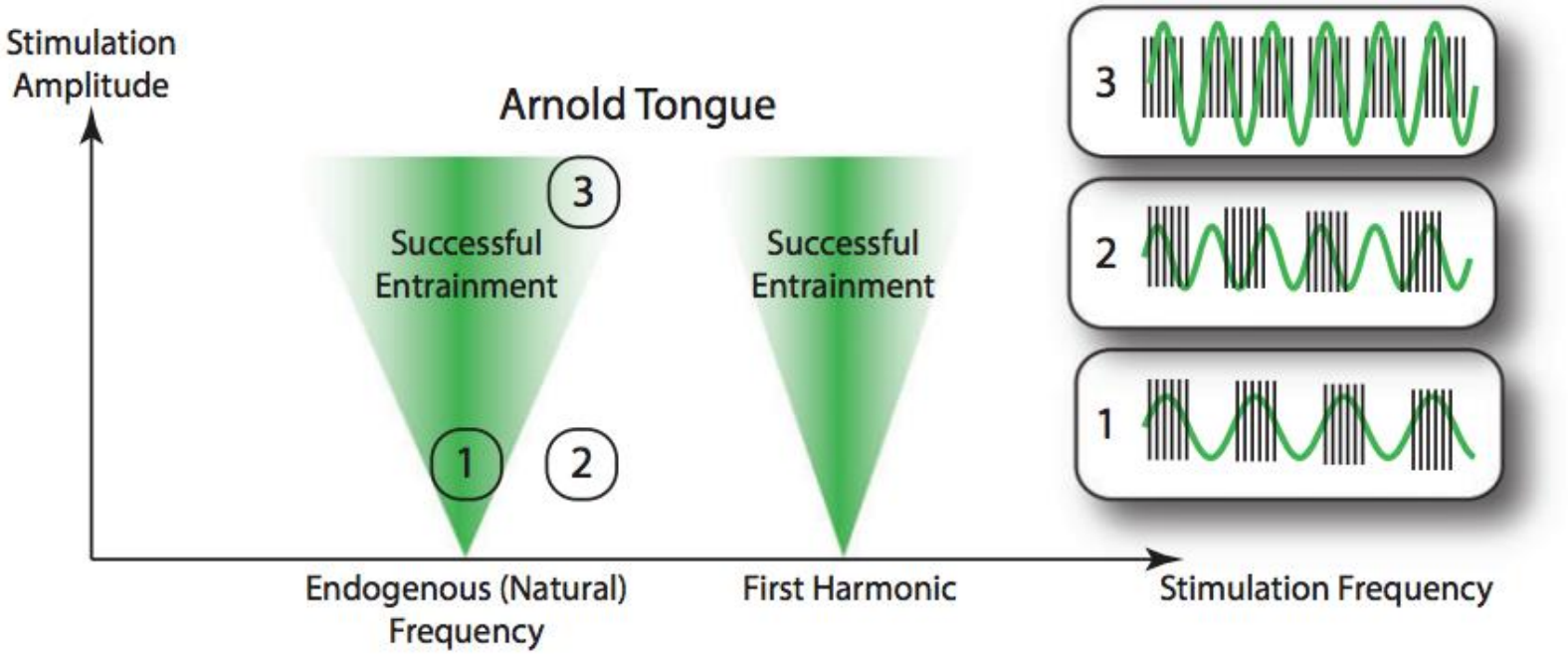


Figure 1.6: *Schematic depiction of the Arnold Tongue. Parameters (stimulation amplitude on the y axis and frequency on the x axis) that cause successful entrainment are marked in green. Image from Figure 2, Kurmann et al., 2018.*

One particularly relevant advantage of tACS is that the stimulation frequency aims to modulate task-relevant physiological processes. This effect can be magnified through synaptically connected neurons (Ali et al., 2013) and directly facilitates neuronal excitability (Buzsaki, Gyorgy, Draguhn, 2004) to induce rhythmic changes (neural oscillations) in a frequency range that corresponds to the frequency of stimulation (Buzsaki, Gyorgy, Draguhn, 2004; Helfrich, Knepper, et al., 2014; Kanai, Chaieb, Antal, Walsh, & Paulus, 2008; Pogosyan, Gaynor, Eusebio, & Brown, 2009; Zaehle, Rach, & Herrmann, 2010). Alterations to the transmembrane potential give rise to the primary mechanism of tACS: the amplification and entrainment of endogenous neuronal oscillations (Helfrich, Knepper, et al., 2014; Tavakoli & Yun, 2017; Weinrich et al., 2017; Zaehle et al., 2010). Entrainment induces synaptic changes via spike timing dependent plasticity (Vossen, Gross, & Thut, 2015; Zaehle et al., 2010).

tACS may be an alternative approach to modulate neural networks by improving coherence *between* regions, rather than overall activity levels (tDCS) and may boost or alter neural targets (Riddle & Frohlich, 2021; Tavakoli & Yun, 2017). Entrainment due to an external source of modulation such as tACS results in widespread effects, such as the functional connectivity between targeted areas (Bächinger et al., 2017; Moisa, Polania, Grueschow, & Ruff, 2016; Weinrich et al., 2017). This has been demonstrated in EEG and MEG recordings (Helfrich, Knepper, et al., 2014; Neuling et al., 2015) and indirectly using fMRI (Vosskuhl, Huster, & Herrmann, 2015). These findings further suggest that tACS can entrain neural oscillations and modulate neuronal excitability in a rhythmic fashion while improving network coherence (Thut, Schyns, & Gross, 2011).

Furthermore, tACS may induce after-effects lasting up to 70 minutes if delivered for a prolonged period of time (Kasten, Dowsett, & Herrmann, 2016). While the mechanism that supports the lasting effects is not completely clear, it may be consistent with synaptic changes (Vossen et al., 2015), or result from hyperpolarization of membrane potentials. In the context of the current study, this is particularly relevant as tACS may enhance generalization and maintenance effects of SE, above and beyond what is seen following the behavioral therapy alone. It is hypothesized that tACS may be even more efficacious than tDCS to improve cognitive abilities due to the ability to modulate neural coherence (Lang, Gan, Alrazi, & Monchi, 2019; Röhner et al., 2018). This hypothesis has yet to be explored in post-stroke aphasia as tACS has the potential to improve neural synchrony in deviant oscillatory function secondary to stroke and consequently, enhance behavioral outcomes (Riecke, Formisano, Herrmann, & Sack, 2015; Wilsch, Neuling, Obleser, & Herrmann, 2018).

1.15.2 Support for tACS: Evidence from Neurotypical and Clinical Populations

tACS has been applied in both clinical and healthy populations with documented effects on oscillatory activity and human behavior (Helfrich et al., 2014a; Brinkman et al., 2016; Lustenberger et al., 2016; Ahn, Mellin, Alagapan, Alexander, Gilmore, Jarkskog, Frohlich, 2019) and induced after effects (Tavakoli & Yun, 2017; Veniero, Vossen, Gross, & Thut, 2015; Vossen et al., 2015; Zaehle et al., 2010).

In recent years, there has been an increased number of studies investigating neural modulation with tACS in healthy controls. In this vein, tACS has been applied to examine cognitive domains such as attention (Laczó, Antal, Niebergall, Treue, & Paulus, 2012); working memory (Alekseichuk, Turi, Amador de Lara, Antal, & Paulus, 2016;

Jaušovec & Jaušovec, 2014; Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012; Reinhart & Nguyen, 2019; Santarnecchi et al., 2013; Vosskuhl et al., 2015), fluid intelligence (Santarnecchi et al., 2013), self-awareness (Voss et al., 2014), decision making (Sela, Kilim, & Lavidor, 2012), and cross-modal integration (Cecere, Rees, & Romei, 2015). More recently, Reinhart & Nguyen (2019) used tACS and EEG to determine if cognitive decline (age-related reduction in working memory) results from inefficient synchronization of neural oscillations. In a double-blind, sham-controlled, within-subjects experiment, tACS was applied to prefrontal and temporal regions to facilitate neural integration, resulting in improved working memory in a cohort of older adults. Stimulated anterior and posterior regions were selected to integrate information across spatial scales, particularly upper theta frequencies in prefrontal and temporal areas (Fries, 2005).

In neurotypical cohorts, tACS has been implemented across a variety of behavioral domains including those related specifically to speech perception (for a review, see Zoefel & Davis, 2017). Such studies have explored audiovisual perception (Cecere et al., 2015), auditory-only speech perception (Rufener, Oechslin, Zaehle, & Meyer, 2016; Wilsch et al., 2018; Zoefel & Davis, 2017), discrimination of speech in noise (Riecke et al., 2015), speech perception (Brignani, Ruzzoli, Mauri, & Miniussi, 2013; Feurra, Paulus, Walsh, & Kanai, 2011; Helfrich, Knepper, et al., 2014; Helfrich, Schneider, et al., 2014; Laczó et al., 2012; Neuling, Rach, Wagner, Wolters, & Herrmann, 2012; Riecke et al., 2015; Strüber, Rach, Trautmann-Lengsfeld, Engel, & Herrmann, 2014), and phonemic categorization (Rufener, Oechslin, et al., 2016). Still,

the number of studies that have implemented tACS in the context of speech research is surprisingly low considering the role of neural oscillations in speech processing.

In the context of speech perception, research reveals a wide variety of stimulation and experimental parameters to detect behavioral changes in neurotypical populations (Zoefel & Davis, 2017). Descriptions of some of the most recent and relevant studies to the current investigation are outlined here. In (2015), Riecke and colleagues applied tACS (4 Hz, 0.8 mA) for approximately 40 minutes to a group of fourteen participants and measured detection performance for auditory stimuli. They identified perceptual changes in the 4 Hz frequency and found sound detection was phase-dependent. More specifically, Riecke and colleagues found that changes in the relative timing of acoustic and electric stimulation caused corresponding perceptual changes that oscillate predominantly at the 4-Hz frequency. This is consistent with previous results based on 10-Hz tACS (Herrmann, Rach, Neuling, & Strüber, 2013; Nitsche et al., 2008). The authors posit that aspects of auditory cognition are modulated by temporal coherence of sound-induced cortical activity with ongoing cortical oscillations at multiple time scales.

Cecere and colleagues (2015) applied occipital tACS while participants completed a sound-induced double-flask illusion task and found correlations between alpha frequencies and the temporal window. Based on these results, the authors suggest that alpha oscillation may represent the temporal unit of visual processing that promotes audiovisual perception. Rufener and colleagues conducted two studies that employed tACS (Rufener, Oechslin, et al., 2016; Rufener, Zaehle, Oechslin, & Meyer, 2016). In the first, 40 Hz tACS was applied at 1.1 mA for 18 minutes in a cohort of 21 neurotypical young adults. Results from this study suggest that 40-Hz (but not 6 Hz) tACS impairs

learning performance in a phonetic categorization task. In the second study, 25 neurotypical older adults were recruited and a similar montage was applied (40 Hz tACS at 1.38 mA) for a shorter amount of time (8 minutes). Findings from this study were consistent with the previous and suggest that older adults, unlike the younger adults, benefitted from 40-Hz stimulation. In this group, 40-Hz stimulation yielded more precise phonetic categorization.

Of the studies that have applied tACS in stroke patients, most have investigated motor recovery (Chen et al., 2021; Feurra et al., 2013; Heise et al., 2016; Pollok, Boysen, & Krause, 2015; Wach et al., 2013) and only one reports separate analyses for individuals with aphasia (Fedorov et al., 2010). Following 12 consecutive 30-40 minute sessions of repetitive transorbital tACS in the alpha range, investigators found that following stimulation patients with aphasia demonstrated a decreased number of pauses, improved speed of speech and increased loudness of voice (Fedorov et al., 2010). It should also be noted that this study has a number of limitations: For example, it was not exclusively a study of aphasia, tACS was not paired with a behavioral task, and language outcomes were reported in the context of a coarse stroke severity measure (Stroke Severity Level, NIH-NINDS Stroke Scale), which is not a language-specific measure.

Importantly, this same study revealed neurophysiological changes following tACS. Interhemispheric connections were identified immediately following the treatment and at one month follow up coherence analyses confirmed new functional connections between temporal sites of both hemisphere in the theta range (Fedorov et al., 2010). The authors suggest that rtACS-modulated activity induced functional connectivity changes in the intact and damaged hemisphere and posit that rtACS-indued recovery relies on

residual network connections to strengthen synaptic plasticity (Chen et al., 2021; Hummel, Kirsammer, & Gerloff, 2003). The authors also suggest that this effect is not limited to localized regions, rather it applies to a more widely distributed neural network (Ali et al., 2013; Fedorov et al., 2010). The results from this and other studies that have applied tACS to stroke patients suggest that even if certain neurological mechanisms are not completely clear, tACS may be a promising approach to improve neurological function in this population.

The extensive findings from this body of literature highlight the need for further investigation of tACS in clinical populations. More recently in 2018, Wilsch and colleagues applied tACS at 3Hz while participants (n = 19) completed the Oldenburg Sentence Test (Wagner, Kühnel, Kollmeier, 2001) to determine if envelope-tACS modulated sentence comprehension in noise. Results suggest that sentence comprehension can be modulated by envelope-tACS and support other investigations that have claimed an important role for cortical entrainment in the auditory cortex for speech entrainment (Zoefel & Vanrullen, 2015). All of the studies outlined above have investigated the effects of neural modulation as it pertains to speech perception. While a few have investigated the effects of audiovisual stimuli in speech perception, none have investigated outcomes of speech production. Crucially, this topic remains unexplored for a clinical population like NFA.

1.16 Interim Chapter Summary

NFA is prevalent among stroke survivors, even into the chronic stages of recovery. While conventional rehabilitation approaches may induce language improvements, gains are often modest and most patients never fully recover (Hope et al.,

2017). One treatment paradigm, SE, is particularly effective for improving speech fluency for persons with NFA. SE is thought to compensate for stroke-induced damage to anterior cortical regions of the left hemisphere to provide an external gaiting mechanism to initiate and monitor the flow of speech. Patients with chronic NFA can practice speaking fluently with the SE task, perhaps due to generation of an external efference copy that is facilitated through synchrony between anterior (IFG*po*) and posterior (*p*MTG) regions (Bonilha et al., 2019; Johnson et al., 2021).

From a neuropsychological perspective, pairing a noninvasive brain stimulation technique with a behavioral rehabilitation paradigm has the potential to induce neural plasticity by modulating neural coherence to improve synchrony in a population with aberrant neural synchrony. Previous studies suggest the effects of SE generalize to discourse tasks, long-term effects are minimal and maintenance is not always consistent (Thors et al., 2019). These findings encourage the application of an external modulatory source to determine if behavioral performance can be improved beyond the effects seen in the behavioral paradigm alone. Implementing tACS stimulation to modulate SE performance is a novel, yet promising method to further improve speech production.

1.17 The Current Study

1.17.1 Purpose

This proof-of-concept study aims to determine if a novel application of NIBS, HD-tACS, improves speech fluency in persons with NFA. In the proposed study, HD-tACS will be applied as an adjuvant to a behavioral SE task at a theta frequency (7 Hz) to modulate neural coherence between residual anterior and posterior cortical regions of the left hemisphere. While recent work has elucidated the behavioral effects and neural

mechanisms that support successful entrainment, modulating the neural coherence with noninvasive brain stimulation may enhance these behavioral effects.

The current study aims to investigate the modulatory effects of HD-tACS on SE success. It is hypothesized that this paradigm will facilitate enhanced neural synchronization and subsequently, improve speech fluency. The proposed study is twofold: First, this study aims to determine if *in-phase* HD-tACS applied to anterior and posterior regions of the left hemisphere induces improved speech fluency in a SE task. Second, the results will provide insights into the extent to which structural and functional connectivity measures can predict HD-tACS response.

1.17.2 Abbreviated Methods and Evidence for the Current Paradigm

The methodology capitalizes on evidence from previous studies that suggest multimodal stimuli improve oscillatory synchronization particularly between anterior and posterior regions (Bauer et al., 2020; Johnson et al., 2021; see *Chapter 2: Methods*). This investigation will expand upon the existing literature about adjuvant rehabilitation approaches for aphasia by determining efficacy of HD-tACS to: 1) improve behavior and 2) modulate residual cortex. Importantly, enhanced behavioral performance (specifically, speech fluency) secondary to HD-tACS would offer a promising adjuvant to behavioral therapy for patients with nonfluent aphasia. Future research may use these preliminary data to combine HD-tACS with electroencephalographic recording to measure physiological variables such as neural oscillations to determine if HD-tACS improves network coherence in stroke survivors consistent with what has been shown in neurologically healthy populations (Helfrich, Knepper, et al., 2014; Toralf Neuling et al., 2015).

1.18 Specific Aims and Hypotheses

1.18.1 Specific Aim 1

To examine behavioral effects of HD-tACS in individuals with NFA. SE involves mimicking an audiovisual speech model in real time. The typical speech model consists of a speaker whose face is seen below the nose and presented as a video on a computer screen. As demonstrated by Fridriksson and colleagues (2012a, 2015a), most persons with NFA can produce fluent speech during the task. SE has been hypothesized to provide an external gating system that yokes the ventral language network and compensates for damage to speech production areas in the IFG (Fridriksson et al., 2012). Implementing HD-tACS stimulation to modulate SE performance is a novel, yet promising method to further improve speech production. It was hypothesized that slow oscillatory activity and poor theta phase synchronization would contribute to poor speech fluency and that an exogenous boost of *in-phase* frontotemporal theta coupling would enhance frontotemporal network connectivity, which was hypothesized to subserve successful entrainment and speech production.

Specific Aim 1a

It was expected that enhanced neural integration via this external modulatory source would improve speech output (accuracy and fluency) during speech entrainment. For the current study, the effects of stimulation condition on speech output were measured by the proportion of correct script words produced. Secondary outcome measures (number of total words produced; including those not specific to the script and proportion of errors) were also measured. Pilot data may inform future investigations regarding the maintenance and generalization of speech fluency.

It was predicted that HD-tACS would modulate anterior-posterior theta-phase synchronization and improve speech fluency was measured linguistically by proportion of correct script words. Therefore, it was predicted that *in-phase* stimulation would improve proportion of correct script words, which would suggest improved speech output. It is hypothesized that the *anti-phase* condition of HD-tACS stimulation would result in fewer correct words (as compared to the model). It was hypothesized that while the *in-phase* condition would elicit improved behavioral response, the *anti-phase* condition would result in a reduced behavioral response secondary to impaired synchrony (Buszaki, et al., 2004). For this behavioral outcome, it would therefore be hypothesized that participants would produce a greater number of errors (suggesting a more impaired behavioral response) during the *anti-phase* condition as compared to the *in-phase* and *sham* conditions. The proportion of errors for the *in-phase* condition was expected to be smaller due to improved synchrony between critical language hubs and consequently, improved behavioral performance.

Speech entrainment samples for each participant across each of the three conditions were transcribed and analyzed using CHATCLAN (MacWhinney, 2000). Medians were compared to determine the effects for each stimulation condition. Previous findings suggest that individuals with nonfluent aphasia produce more different words per minute during speech entrainment (Fridriksson et al., 2009; Fridriksson, Basilakos, et al., 2015; Fridriksson, Hubbard, et al., 2012) and more recent evidence from investigations of transcranial alternating current stimulation suggest improved behavioral performance with *in-phase* stimulation (Reinhart & Nguyen, 2019).

1.18.2: Specific Aim 1b

Enhanced coherence (as modulated by HD-tACS applied to critical anterior and posterior language centers) was expected to improve speech fluency and response to speech entrainment (Feenaughty et al., 2021; Fridriksson, Basilakos, et al., 2015; Fridriksson et al., 2012). The effect of speech entrainment on speech timing, however, is less understood. Spoken language is time-based and relies on suprasegmental features such as stress, intonation, rhythm and rate to effectively produce and understand language (Netsell, 1973). These suprasegemental cues, coupled with spectral and articulatory features, facilitate intelligible and efficient speech. In communication disorders, such as post stroke aphasia and apraxia of speech, however, these characteristics may deviate and reflect various impairments of the linguistic and motor speech systems. For example, individuals with nonfluent aphasia often produce a higher frequency of pauses during spontaneous speech compared to controls (Angelopoulou et al., 2018).

A recent article identified precise speech timing adjustments that accompany entrained speech (Feenaughty et al., 2021). Feenaughty et al. (2021) examined acoustic measures of speech timing including number of syllables, speech rate, articulatory rate, mean silent pause duration, and silent pause frequency during speech entrainment. These measures were calculated for a group of participants with nonfluent aphasia and a group of participants with fluent aphasia who were included for comparison.

To determine the effects of each stimulation condition on temporal and spectral synchronicity between the model and patient in the current study, dynamic time warping analyses that incorporate spectral and temporal features of the audiovisual model and the

participant's speech were performed to determine speech timing changes or 'entrainment success' (as measured by mel-frequency cepstral coefficients; MFCCs).

While previous studies have investigated the effects of entrainment relative to speech timing adjustments (Feenaughty et al., 2021), few have identified spectral and temporal variables relative to fluency. Such measures were examined to determine the degree to which participant productions entrain (i.e. improved vs. declined speech timing relative to the model) across each of the three conditions. It was hypothesized that during the *in-phase* condition of HD-tACS stimulation, participants would demonstrate less distance (as measured by mel-frequency cepstral coefficients) between participant productions and the audiovisual model. This would suggest better entrainment. It was predicted that during the *anti-phase* condition of HD-tACS stimulation, participants would demonstrate a poorer performance (i.e. greater distance from the model).

1.18.2 Specific Aim 2

To investigate if and to what extent brain-based predictors were associated with the behavioral response to HD-tACS. More specifically, the aim was to examine how such predictors are associated with a "tACS boost" (i.e. behavioral improvements demonstrated in the *in-phase* stimulation condition as compared to the *anti-phase* or *sham* conditions). This boost will be calculated by subtracting behavioral performance measures in the *anti-phase* condition from the *in-phase* condition ("tACs boost relative to *anti-phase*") and subtracting behavioral performance measures in the *sham* condition from the *in-phase* condition ("tACS boost relative to *sham*"). For the linguistic behavioral measure a higher number indicated a better behavioral response during the *in-phase* condition as compared to the *anti-phase* condition. For the temporal-spectral data,

a higher number indicated a greater distance between the participant and the audiovisual speech entrainment model and suggested poorer entrainment during the *in-phase* as compared to *anti-phase* condition. Proportional cortical damage to regions targeted by HD-tACS was examined and residual structural and functional connectivity between those regions were measured to determine associations with behavioral measures.

1.18.2.1 Specific Aim 2a

It was predicted that for successful modulation to occur, the targeted frontotemporal regions of the left hemisphere would need to be intact. Subsequently, it was hypothesized that a greater proportion of spared anterior (IFG*po*) and posterior (*p*MTG) would yield better HD-tACS-induced behavioral effects (i.e., a greater "tACS boost"). Previous work suggests that participants with frontal damage are more likely to have posterior integrity and for this group of participants, research suggests speech entrainment may elicit a better treatment response (Fridriksson et al., 2012). Relatedly, the preservation of ventral stream regions (including *p*MTG) seems to be critical to facilitate successful entrainment (Bonilha et al., 2019).

1.18.3 Specific Aim 2b: Anterior-posterior functional and structural connectivity were examined to determine if baseline measures predict HD-tACS response. It was hypothesized that baseline frontotemporal functional and structural connectivity would predict response to HD-tACS in participants with nonfluent aphasia due to greater potential for neural coherence facilitated by *in-phase* tACS stimulation. Specifically, it was expected that higher frontotemporal connectivity between left *p*MTG and left IFG*po* would be correlated with a greater proportion of script words during speech entrainment in the *in-phase* condition compared to the *anti-phase* and *sham* conditions. It was

predicted that effects of resting state and functional connectivity would be highly correlated with cortical integrity. Therefore, total lesion volume and damage to regions of interest were accounted for across analyses. Identifying the neurobiological mechanisms that were associated with a benefit from HD-tACS ("tACS boost") has the potential to inform future tACS studies in aphasia to distinguish between patients who are most and least likely to benefit from tACS treatment in clinical rehabilitation.

1.19 Significance

The incidence of post-stroke aphasia and associated healthcare costs for disease management are an imminent public health concern. There are approximately 100,000 new cases of aphasia diagnosed each year in the United States and projected costs for post-stroke care are expected to double due to the increased number of the at-risk, aging population and number of stroke survivors who are unable to return to work due to post-stroke deficits such as chronic aphasia (Rubin & Demaerschalk, 2014).

Existing behavioral therapies for aphasia yield modest outcomes and most patients never fully recover. Insurance caps and limited windows for service delivery also contribute to the inaccessible and ineffective nature of conventional rehabilitation models. Nonfluent speech is often intractable to therapeutic gains; however, one evidenced-based therapy, SE, suggests patients with nonfluent aphasia respond within a short time frame and have the potential to generalize this skill although more research is needed to support this (Thors, Yourganov, Rorden, Bonilha, Fridriksson, 2019; Fridriksson et al., 2012). Using an external modulatory source to stimulate anterior and posterior cortical regions of the left hemisphere, may not only boost behavioral outcomes but modulate aberrant neural oscillations to improve coherence.

SE utilizes external gaiting mechanisms to initiate and monitor the flow of speech so that patients with chronic, nonfluent speech can practice speaking more fluently and strengthen the use and generation of efference copies that are necessary for speech motor control. Current evidence regarding the neural mechanisms of SE suggests that improving communication between anterior and posterior regions of the left hemisphere may improve behavioral outcomes. While the ultimate goal of SE therapy is for patients to improve speech fluency in the context of speech, for patients for whom improved fluency does not generalize, relying on SE to produce personalized scripts in highly predictable contexts can promote greater quality of life.

Previous evidence suggests that SE has the potential to be an efficient and effective treatment for individuals with nonfluent aphasia, which is especially important when the time and duration of speech and language therapy services are limited. Identification of an HD-tACS 'boost' on speech output during speech entrainment may offer an alternative and more efficient approach to rehabilitation for this population.

CHAPTER 2

METHODOLOGY

2.1 Recruitment and Enrollment

Thirty participants were recruited to participate in the study based on retrospectively collected behavioral data from participation in previous studies in the Aphasia Laboratory at the University of South Carolina. Additional advertisements were disseminated to previous participants of the Aphasia Lab via alternative modalities, such as the quarterly laboratory newsletter. Participants were recruited based on initial inclusion criteria: presence of chronic post-stroke aphasia (>6 months post onset) nonfluent (Broca's or transcortical motor), post-stroke aphasia secondary to a single left-hemisphere ischemic stroke as confirmed by MRI or CT scan. The primary scores used for enrollment were those from the Western Aphasia Battery-Revised [WAB-R] Aphasia Quotient <93.8; score of <5 on the WAB-R Fluency subtest (fluency criteria is consistent with an ongoing Phase II trial investigating speech entrainment dosage for aphasia recovery (*SpARc Grant,* DC017521*;* Cassarly et al., 2021), score <9 on the Naming and Word Finding subtest and score of $\geq$ 4 on the WAB-R Auditory Verbal Comprehension subtest, Kertesz, 2007). Inclusion criteria for language performance is consistent with a 'nonfluent' aphasia classification on the WAB-R (Kertesz, 2007).

All recruited participants had completed an MRI at the McCausland Center at Prisma Health Richland as part of protocol for previous or ongoing studies at the Aphasia Laboratory and had fMRI data for the Naming 40 task. The Naming 40 is a behavioral

task that consists of naming pictures of high-frequency common nouns (Frances & Kucera, 1982). Participants were instructed to name every picture aloud. For additional details regarding this paradigm see (Fridriksson, Morrow, Moser, & Baylis, 2006; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006; Fridriksson et al., 2007). All participants were between the ages of 30 and 85 years and were monolingual, native English speakers. Participants provided verbal or written consent to participate in the study and passed an initial screen for exclusion criteria. Exclusion criteria included: presence of global aphasia (due to limited speech production and impaired speech comprehension), self-reported history of dementia, brain injury (excluding previous stroke) or psychiatric disorder, or alcohol abuse, or any contraindication for transcranial electrical stimulation (no implanted electronic devices, no metal implants in head, no skin sensitivity).

All participants provided written consent to procedures approved by the University of South Carolina Institutional Review Board (*Pro00091796*) and were compensated for their participation.

2.2 Experimental Design

Seventeen participants were enrolled in a within-subjects, sham-controlled, pseudorandomized block design trial. Over the course of three days (each session was separated by a minimum of 48 hours), participants participated in three trials of a HD-tACS + SE paradigm to investigate three conditions: 1) theta-tuned (7 Hz) HD-tACS *in-phase* montage; 2) theta-tuned (7Hz) HD-tACS *anti-phase* montage; 3) HD-tACS *sham condition* (See *Figure 2.1*). 1mA of HD-tACS at a theta frequency (7 Hz) was applied to residual anterior (IFG*po*, or nearest intact anterior cortex) and posterior (*p*MTG, or

nearest intact posterior cortex) regions of interest in the left hemisphere. See *Figure 2.3* and *Figure 2.4.*

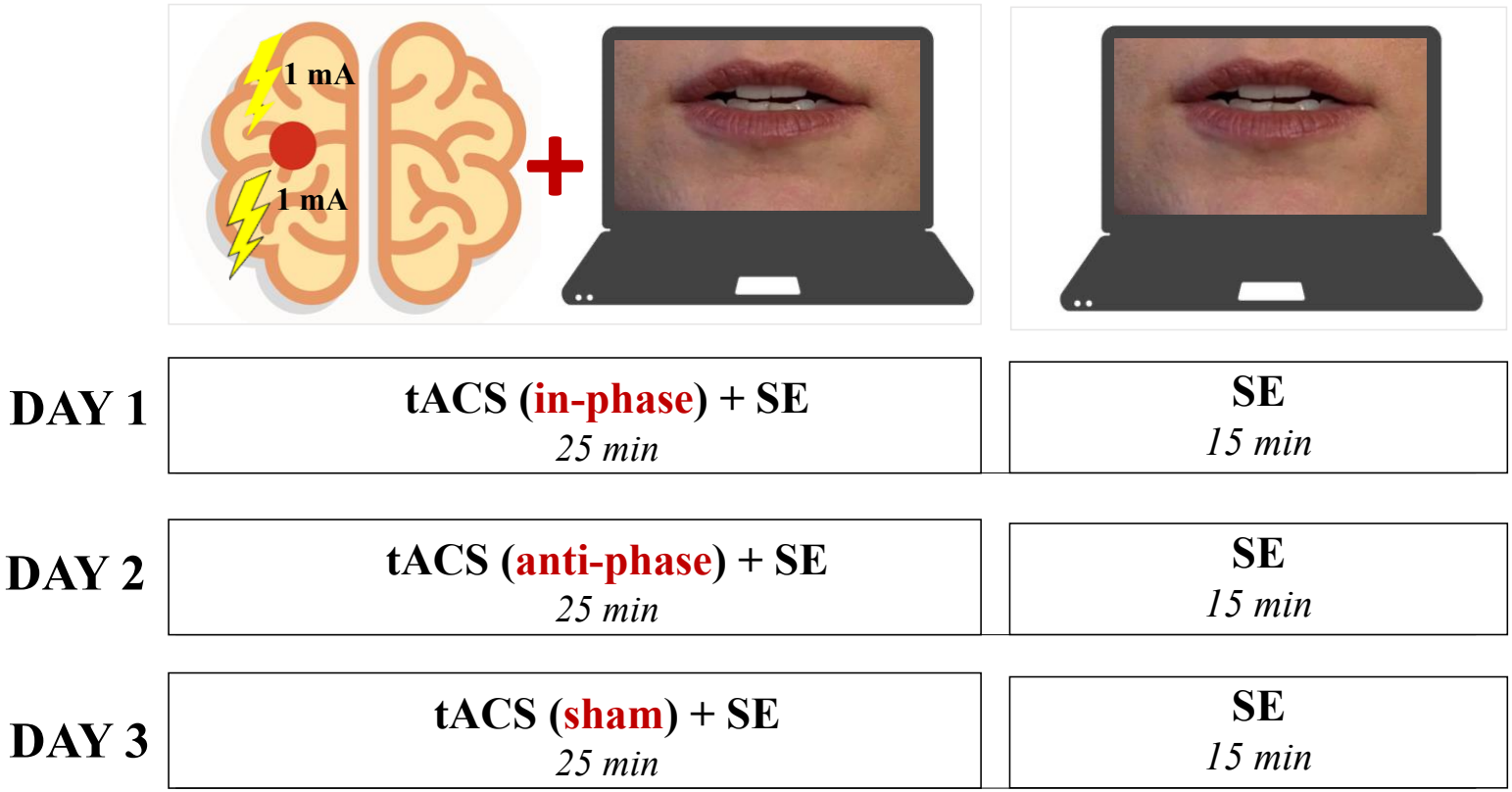


Figure 2.1 *Experimental design: Participants were recruited for three days of a paired noninvasive brain stimulation and behavioral paradigm and participated in three total conditions: 1) in-phase stimulation; 2) anti-phase stimulation; 3) no stimulation (sham).*

2.3 Testing Procedures

2.3.1 General Procedures

Prior to data collection, informed consent was collected from all participants and participants were provided with an opportunity to ask questions regarding the study protocol. A speech-language pathologist with extensive experience working with adults with neurogenic language disorders (LMK) reviewed the consent form and provided additional verbal and visual cues to ensure understanding. Appropriate breaks were provided to participants as requested and testing was conducted over the course of three days so that no single day of testing exceeded two hours.

2.3.2 Western-Aphasia Battery-Revised Administration

On the first day of data collection, the Western Aphasia Battery-Revised (WAB-R; Kertesz, 2007) was administered by a speech-language pathologist (LMK). The WAB-R consists of a number of subtests to assess a variety of language domains including: *Spontaneous Speech*, *Auditory Verbal Comprehension*, *Repetition* and *Naming and Word Finding*. In accordance with the WAB-R manual and procedures for an ongoing Phase II trial of SE (Cassarly et al., 2021), an Aphasia Quotient (a global measure of aphasia severity on a scale of 0 – 100 where a score below 93.8 indicates aphasia [0 – 25 typically indicates a very severe aphasia; 26 – 50 severe aphasia; 51 – 75 is moderate aphasia, and $\geq$ 76 suggests a mild aphasia] Kertesz, 2007) was calculated using scores for each of the following sub-domains: *Spontaneous Speech*, *Auditory Verbal Comprehension, Repetition,* and *Naming and Word Finding* for each participant. Participant scores from the WAB-R subtests and aphasia quotient (AQ) were used to

confirm the presence of nonfluent aphasia, determine current aphasia severity and type, and obtain a discourse sample (picture description).

The picture description task from the *Spontaneous Speech* subtest (see *Figure 2.1*) was used to quantify the participants' spontaneous speech. Spontaneous speech requires the integration of speech and language processing and is useful for studying spoken language (Gordon, 1998). Picture description tasks, such as the one administered in the Western Aphasia Battery-Revised (Spontaneous Speech. Subtest), are commonly used to elicit spontaneous speech from persons with aphasia (Bryant, Ferguson, & Spencer, 2016).

Figure 2.2 *Picture Description task from the Western Aphasia Battery-Revised. Spontaneous Speech subtest (Kertesz, 2007).*

2.3.2 Blinding

The current study was double-blinded. Scripts (A, B, and C) and stimulation conditions (1, 2, 3) were pseudorandomized to each participant for each session (total of three sessions per participant; 1 stimulation condition and 1 script assigned per day). A study administrator (LAJ) and undergraduate research assistant (RL) who were not involved nor present for the behavioral sessions assigned stimulation conditions to each of the three numerical values (1, 2, or 3) and prepared the HD-tES machine prior to each patient visit.

Additionally, SLP graduate student clinician scorers were blinded to the behavioral data during the transcription process. Each audio file was coded with a color (i.e. BLUE, RED, ORANGE, GREEN, PINK, YELLOW) to indicate day (Day 1, Day 2, or Day 3) and script (script number) so that scorers were unable to discern the order in which the data were collected. Data files included the participant number (specific to the study: T1 – T17), designation for picture description (WAB-R) or speech entrainment (SE) and script. For example, the script immediately post-stim was labelled as Script #6 and the script immediately following the washout period was labelled as Script #10. Colors were used to indicate the day in which each script was administered (Script #6 on the first day = BLUE; Script #10 on the first day = RED). This was an additional precaution as condition type and script sets were initially pseudorandomized for each participant and scorers did not have access to these records.

All data remained blinded to LMK until all data analyses were completed. Upon report of the final analyses, data were unblinded to reveal the nature of stimulation administered in each condition.

2.4 Data Acquisition

2.4.1 General Procedures

Data were collected in a therapy room in the Aphasia Laboratory across three separate experimental sessions which lasted approximately 2 hours on the first visit and 1 hour for each subsequent visit. The additional time during the first visit was required to review the consent, administer the Western Aphasia Battery-Revised, collect baseline discourse data and provide a practice session for the speech entrainment paradigm. This is discussed in further detail in *Section 2.3.2*. On each day, participants completed the same language task (a speech entrainment paradigm) across three different conditions: 1) *in-phase* stimulation; 2) *anti-phase* stimulation; 3) *sham*. The order of these sessions was pseudorandomized so that each participant received a different set of speech entrainment scripts and a different stimulation condition during each visit. This is described in greater detail below (See *Section 2.4.3 Behavioral Paradigm: Speech Entrainment*).

At the end of each session, a safety questionnaire (Poreisz, Boros, Antal, & Paulus, 2007) and visual analog scale (Gandiga, Hummel, & Cohen, 2006) were administered to assess pain, discomfort and sensory disturbances (See *Appendix A*). Although induction of peripheral flicker perception is typically reported with higher frequency stimulation (Turi et al., 2013), post-experiment questionnaires were administered to confirm that low-frequency stimulation did not induce peripheral flicker perception. Electrode impedance was recorded pre- and post-stimulation. Scales were presented using multi-modal communication to ensure access for all participants, given the presence of aphasia. For example, a visual description scale (Wong-Baker FACES

Pain Rating scale, Wong & Baker, 1988) and written key words (i.e. itching, tingling, etc.) were provided for all patients.

Upon the completion of each session, participants were queried regarding their experience and asked to provide an educated guess of the stimulation condition (i.e. stimulation vs. sham). Visual and verbal cueing consistent with those described above were used to ensure comprehension and validity of patient response. Similarly, the SLP (LMK) provided a guess as to which stimulation condition was administered. See *Section 2.5.3 Sham Condition* for additional details regarding these methods.

2.4.2 HD-tACS Administration

2.4.2.1 Instruments and Equipment

A MxN High Definition – Transcranial (HD-tES) Stimulation 9002A and associated equipment (CSOP-D5 Output Cable A + B; 9 HD electrodes) provided by Soterix Medical were used to administer HD-tACS. HD-tACS is a form of tACS that provides more precise targeting of cortical structures. Multiple sintered 12mm diameter Ag/AgCl electrodes attached to custom high-definition plastic holders in the Soterix Medical HD BrainCap (80 channels; sizes 56c.c. and 58c.c.; manufactured for Soterix by Bionen) was used. Four 10,000mAh Ni-MH Rechargeable Tenergy Premium Batteries (Tenergy Corporation, Fremont, CA) were used to power the HD-tES machine. High definition electrolyte HD-Gel^{TM} (60 g per tube; Soterix Medical, Inc. New York) was used to optimize conductivity and minimize impedance.

Channels 1 – 7 were used and the 8th channel served as the reference electrode. Prior to beginning each session, the primary study administrator (LMK) confirmed

channels #1 – 7 showed green and impedance levels for each channel quality display bar were recorded pre and post stimulation.

Electrode placements were determined a priori for each participant to target the left inferior frontal gyrus *pars opercularis* and left middle temporal gyrus. Individualized montages were guided by current-flow modeling (Soterix Medical; HD-Explore and HD-Targets software) to model the distribution of current flow and account for flow variations that result from differences in lesion size and location secondary to stroke.

Target regions of interest in the frontal and temporal cortices were implicated as neural correlates for successful speech entrainment (Bonilha et al., 2019; Fridriksson, Basilakos, et al., 2015; Fridriksson et al., 2012): L IFGpo and L pMTG. Anterior and posterior stimulations sites were determined by identifying peak activation from retrospective data (previously administered fMRI confrontation naming task: Naming 40; Frances & Kucera, 1982). An in-house MATLAB script was used to determine coordinates for anterior and posterior stimulation sites which were calculated from an ROI mask for each region (anterior: IFGpo; posterior: pMTG/pSTG) derived from the JHU atlas (Faria et al., 2012) and peak activation within the ROI mask, but outside of the lesioned area, was used to develop individualized montages.

Montages maximized focality using a ring montage (consistent with methods from Reinhart and Nguyen, 2019). In this set-up, eight total electrodes were used: two sets of four electrodes for each region of interest. In each set, maximal stimulation was provided via the center electrode, which overlaid the region of interest with three surrounding electrodes. Figure 2.2 shows the stimulation parameters (electrode location and intensity) for the multifocal frontotemporal montage.

During the positive cycle of alternating current stimulation, in-phase stimulation was administered and during the negative cycle, out-of-phase stimulation was administered. When the alternating current was delivered in-phase, it was delivered with 0° relative phase different across the two targeted cortical locations. This is described in further detail in *Section 2.4.1.2: Conditions*.

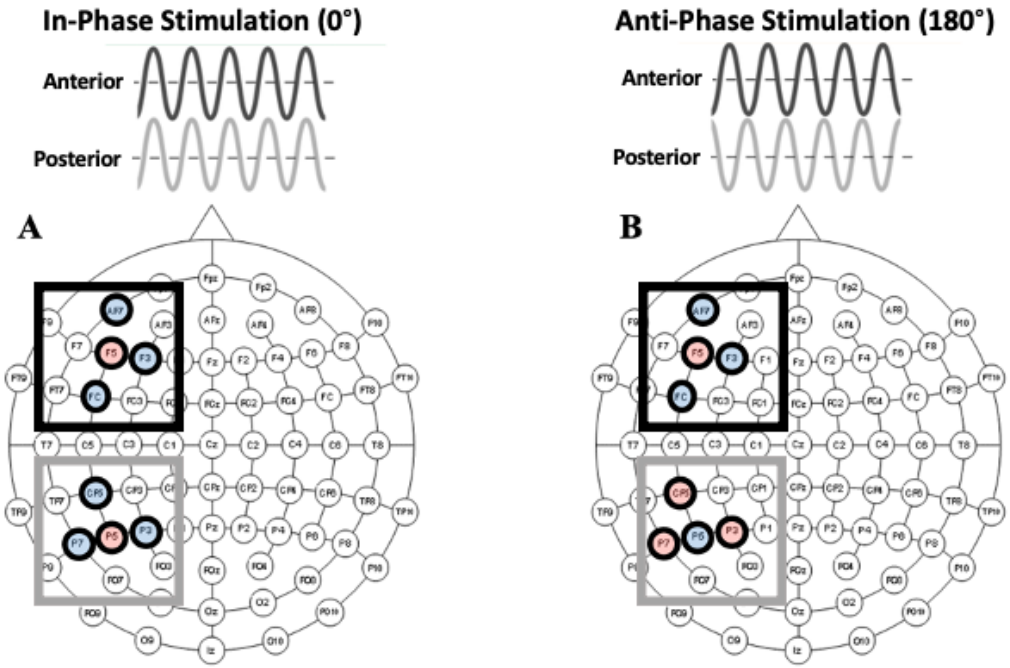
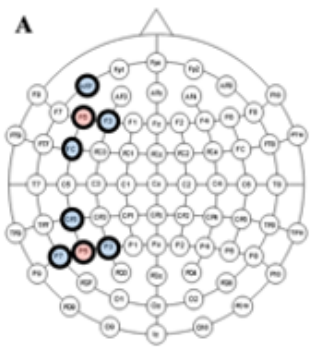
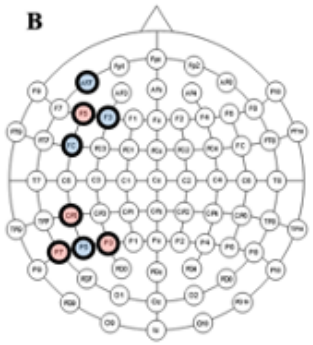


Figure 2.3 *During in-phase or positive cycle of alternating current stimulation (A, i.e. 0º offset) the central electrodes for each region of interest continuously share a current of the same polarity. During anti-phase or negative cycle of stimulation, HD-tACS is applied at the same location but central electrodes share the current of the opposite polarity (B; i.e. 180º difference across the two targeted cortical regions). Anterior region of interest is delineated with a black box and is illustrated with a black sine wave. Posterior region of interest is delineated with a grey box and is illustrated with a gray sine wave.*





In-Phase			Anti-Phase		
	Electrode Placement	*Electrode Current (mA)*		*Electrode Placement*	*Electrode Current (mA)*
Anterior	F3	-0.1665	**Anterior**	F3	-0.1665
	F5	0.50		F5	0.50
	FC5	-0.1665		FC5	-0.1665
	AF7	-0.1665		AF7	-0.1665
Posterior	B3	-0.1665	**Posterior**	B3	0.1665
	P5	0.50		CP5	-0.50
	CP5	-0.1665		P5	0.1665
	P7	-0.1665		P7	0.1665

Figure 2.4 *An example of a stimulation montage. Each stimulation site (anterior and posterior) will use four electrodes in a center-surround, course-sink pattern to achieve maximum focality. During in-phase stimulation (A, i.e. 0º offset) the central electrodes for each region of interest continuously share a current of the same polarity. During anti-phase stimulation, HD-tACS is applied at the same location but central electrodes share the current of the opposite polarity (B; i.e. 180º offset).*

2.4.2 Behavioral Paradigm: Speech Entrainment

In all three conditions, participants completed two blocks of a speech entrainment task (25 minutes with stimulation and 15 minutes following the stimulation [washout period]; see *Figure 2.1*).. This design aimed to address one of the main controversial issues with transcranial electrical current stimulation: after effects. It is unclear to what extent stimulation-induced effects persist outside of active stimulation (Fertonani & Miniussi, 2017; Galli et al., 2019; Hone-Blanchet et al., 2016; Samaei et al., 2017).

Participants were presented with a speech entrainment task in an active-stimulation and post-stimulation block across each of the three conditions (in-phase, anti-phase and sham). The task stimulus was a video of a human mouth (from the nose down) speaking a standardized, pre-recorded script (48-58 words; ~1 minute per script) at a relatively slow speaking rate and high-speed video frame rate.

Speech entrainment scripts were presented using a novel software (SE tACS App; see *Figures 2.5* and *2.6*); developed in-house by RNN; 2021 and derived from the SEAS App; see Casserly et al., 2021) through Scarlett Studio (HP60 MkIII) professional bilateral over-the-ear headphones. Audio was delivered over headphones at a comfortable listening level. All sessions were conducted on a 27-inch iMac with built-in retina display (5120x2880; AMD Radeon R9 M295 2GB Graphics; macOS Catalina, Version 10.15.7).

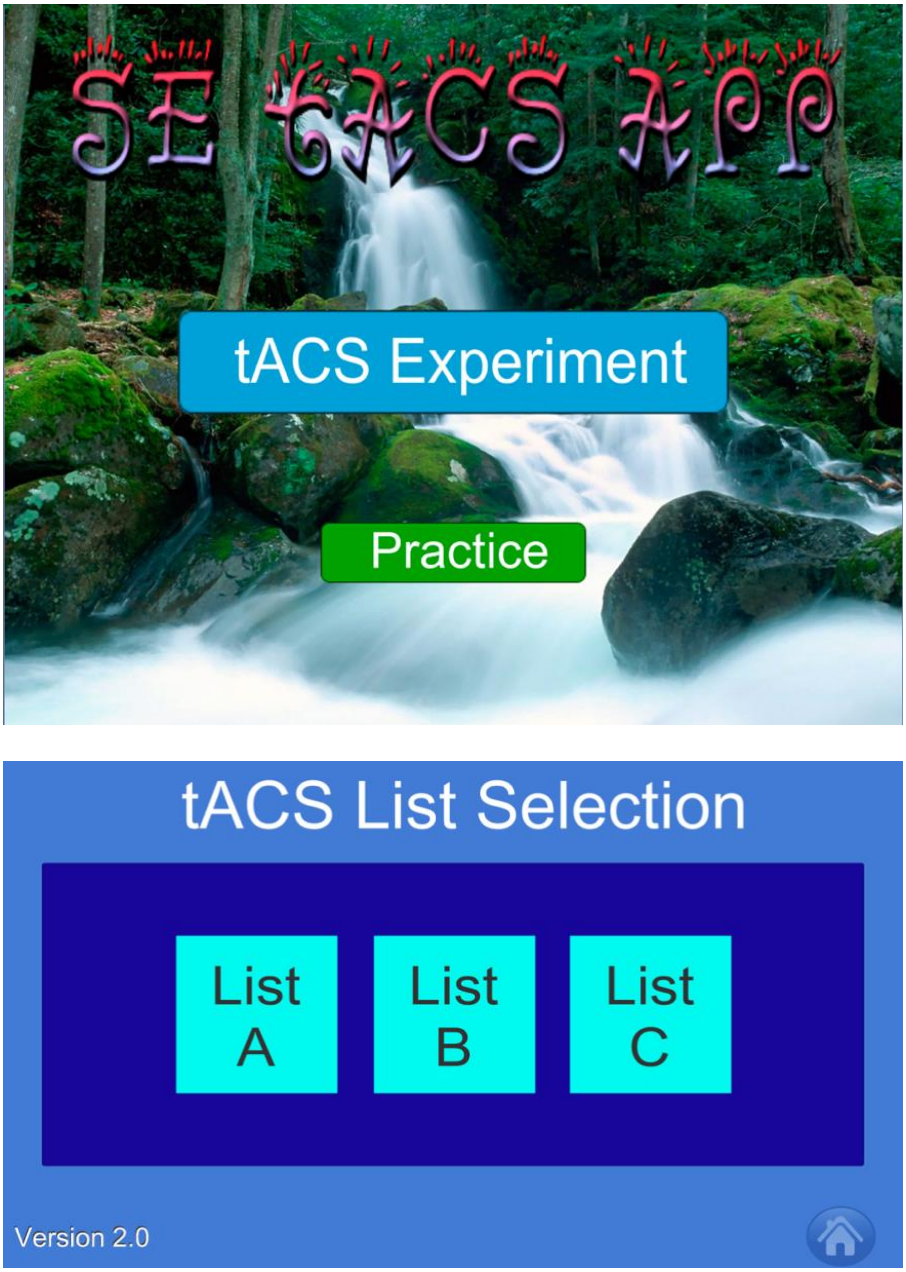


Figure 2.5: *A screenshot from the in-house software SE tACS App (RNN) that shows the Home screen and script selection menu.*

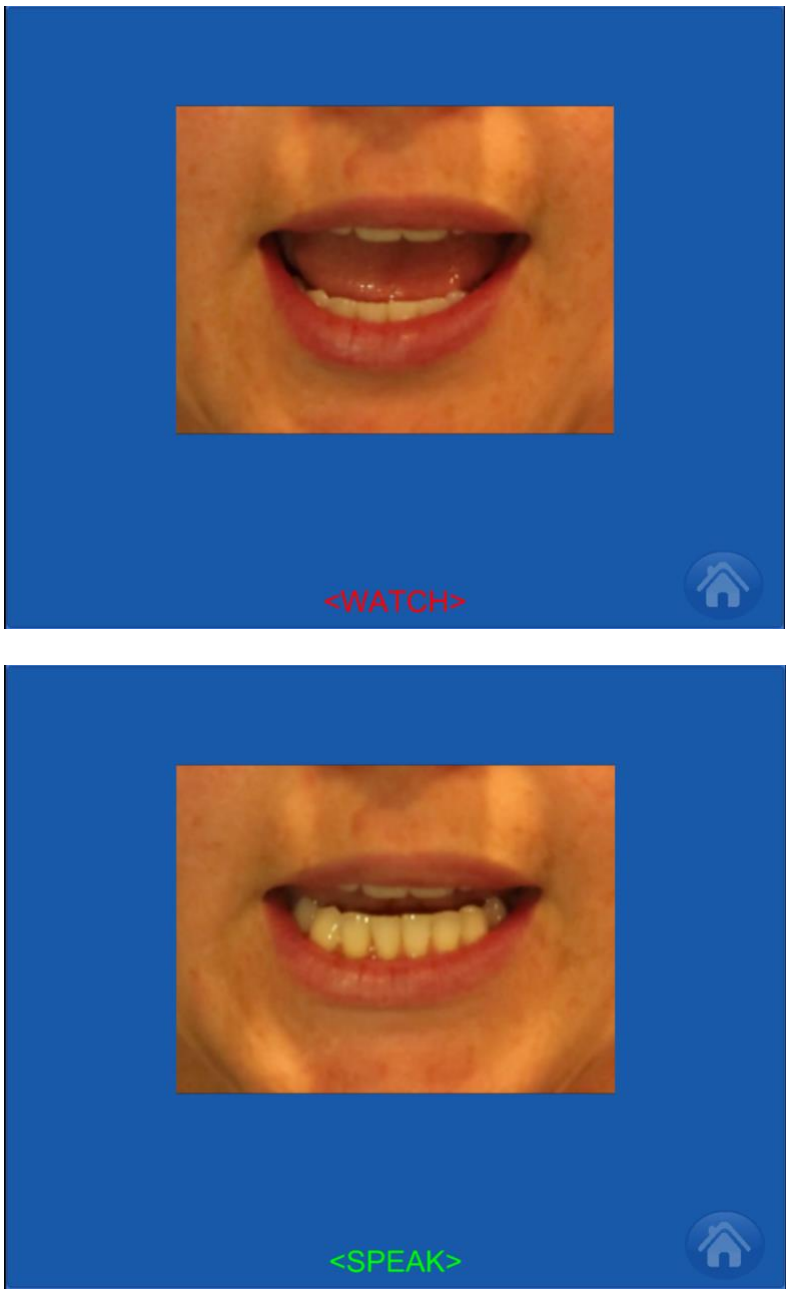


Figure 2.6: *A screenshot from the in-house software SE tACS App (RNN) with visual of instructions ("WATCH" vs. "SPEAK" that were provided to each script set.*

The scripts were selected from a pre-recorded bank of 40 scripts (recorded by a neurotypical speaker [LMK]) addressing various topics. Stimuli were consistent with those used in an ongoing Phase II Trial for Speech Entrainment: Speech entrainment for aphasia recovery (*SpARc Grant*, DC017521; PIs, Bonilha & Fridriksson*;* Cassarly et al., 2021). The content of the scripts was controlled for number of words, word class, and word frequency using CELEX (Kerkman, Piepenbrock, Baayen, van Rijn, Burnage, 1993). Scripts were matched across condition for number of words per minute, familiarity, age of acquisition, valence/salience and tokenized using *tidytext* (Silge & Robinson, 2016) and *The Glasgow Norms: Ratings of 5,500 Words on Nine Scales* (Scott, Keitel, Becirspahic, Yao, & Sereno, 2019). Only scripts with >50% of words available in the corpus were included. Scores for each category were z-scored and took into account anecdotal observations regarding script difficulty (anecdotal evidence from a trained Research SLP in a Phase II Trial of Speech Entrainment: Speech entrainment for aphasia recovery (*SpARc Grant*, DC017521*;* Cassarly et al., 2021).

A one-way ANOVA was performed prior to study commencement to compare the six scripts selected for outcome measures on each of these measures and revealed no statistically significant difference in number of words nor length across scripts: number of words ($F(1,4) = [0.627]$, $p = 0.473$ and length ($F(1,4) = [0.118]$, $p = 0.748$. Methodological details regarding the characteristics of the pre-defined script to entrain speech were previously reported in Thors et al. (2019) and used in similar studies such as, Feenaughty et al., 2017 and Fridriksson et al., 2015, 2012. The 30 scripts selected for the study are shown in Table 2.1. The scripts were matched for psycholinguistic variables and then randomized to one of three Script Sets (A, B, C). The sixth script in each set

(highlighted in yellow) was used as the outcome measure for the Stimulation period and the tenth script from each set (highlighted in blue) was used for the outcome measure for the washout phase.

Table 2.1 Script Sets

Number	Script Set A	Script Set B	Script Set C
1	Thanksgiving	Beaches	Recipe
2	Pizza	Pigs	Shoes
3	Swimming	Eggs	Teeth
4	Giraffe	Statue	Garden
5	July	Travel	Christmas
6	Routine	President	Hike
7	Piano	Olympics	Elvis
8	Advocacy	Stroke	Knit
9	Beatles	I Love Lucy	American Idol
10	Mountain	Weather	Derby

Prior to the beginning of the speech entrainment task, a sound test determined the listening level appropriate for each participant. Each participant completed a practice trial and participated with an experimental script that was not included in the test administration to ensure comprehension of and comfort with the task (see *Figure 2.7*). Verbal and visual instructions were provided prior to beginning the practice module and at the beginning of each of the three sessions.

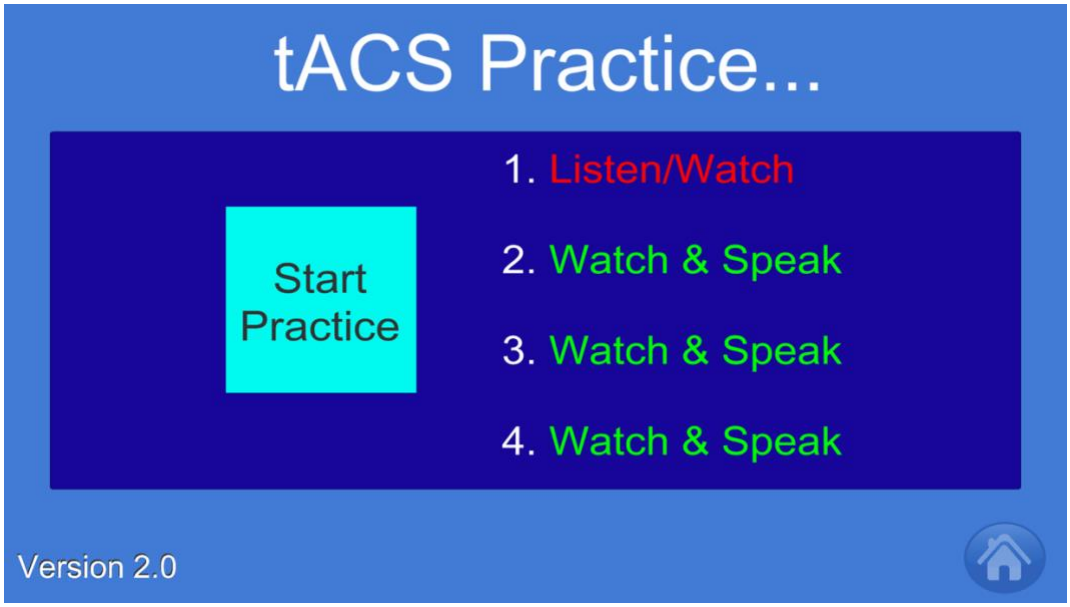


Figure 2.7: *Each participant completed a practice session prior to beginning the behavioral task. Participants were provided with verbal and visual cueing and prompts.*

The following verbal instructions were provided to the participant: “Your goal is to speak along with the video and try to match the timing of your speech as closely as possible to the video. If you miss words or fall behind, try to catch up with the video and continue speaking.” For each condition, stimulation/sham was applied for 25 minutes (consistent with Methods from Reinhart & Nguyen, 2019). Participants were asked to “mimic the speaker” in real-time for the duration of the script and were reminded that once the protocol began, additional assistance from the SLP could not be provided.

Scripts were presented in an audiovisual modality for 25 minutes. Ten scripts were presented during each day and script set presentations were pseudorandomized across participants and stimulation conditions to ensure that one script was not always paired with a particular stimulation condition and to ensure that participants received a unique script set each day to eliminate effect of learning. Each script appeared four times. The first time the script was presented, the patient was instructed to “listen to the script and watch the speakers mouth” without producing speech. The three subsequent presentations of the script required the participant to speak along with the script. Presenting the script at least three times is consistent with previous methodologies that suggest patients improve considerably from the first to the third practice of each script (Fridriksson et al., 2015; Fridriksson et al., 2012).

Participant productions were recorded using a CM25 Condenser Microphone (Focusrite Scarlett Solo USB) and Audacity (Version 3.1.3) during each behavioral session, including the initial assessment session (WAB-R test administration and picture description). All participants were audio recorded while completing the speech tasks

(both during and post-stimulation). A USB Audio Interface (Focusrite Scarlett Solo 3rd generation) was used to simultaneously record participant data and record speech entrainment scripts produced by model in a 2 (stereo) recording .wav file. Recording was collected at a project rate of 44100 Hz, 32-bit float, gain of 48v and resolution of 24-bit/192kHz. All audio recordings were saved directly to the computer (.wav) for subsequent acoustic measurement and transcription. All sessions were administered and monitored by a certified speech-language pathologist with extensive training in research protocols and clinical rehabilitation (LMK).

The final script (Script #6) from the active stimulation block was selected for transcription and analysis. After 25 minutes of stimulation, participants continued to practice with the speech entrainment task (consistent with task administration from the active-stimulation block) in the absence of stimulation for 15 minutes. The final script (Script #10) from this post-stimulation section was selected for transcription and analysis to determine after-effects of HD-tACS. (See Table 2.1).

2.4.4 *Neuroimaging Data*

MRI data for all participants were collected from previous participation in a study in the Aphasia Lab. Scans were acquired using a Siemens 3T Trio System with a 12-channel head-coil. See *Appendix C* for additional details regarding neuroimaging data acquisition.

2.5 Task Conditions

2.5.1 In-phase stimulation

HD-tACS was applied *in-phase* while the participants completed two blocks of a speech entrainment task (25 minutes with stimulation and a 15 minutes washout period;

total task duration = 40 minutes). The positioning of the HD-tACS electrodes was determined *a priori* for each individual in order to maximize the current flow to anterior (IFG*po*) and posterior (*p*MTG/*p*STG) target regions. The multi-electrode ring montage was utilized to apply *in-phase* stimulation. The HD-tACS electrodes were placed in the appropriate positions according to individualized montages. *In-phase* stimulation has been shown to facilitate network synchronization between targeted regions and improve behavioral performance (Polanía et al., 2012; Reinhart & Nguyen, 2019).

2.5.2 Anti-phase stimulation

Stimulation electrode placement and task presentation were consistent with those described for the active *in-phase* condition. The *anti-phase* montage presented an alternating current with 180 degree relative difference across targeted areas to impede network synchronization and impair performance (Reinhart, 2017).

2.5.3: Sham Condition

This task condition followed the same procedure as the *in-phase* and *anti-phase* stimulation conditions, but stimulation lasted only 30 seconds, ramping up and down to stimulate the same tingling sensation that participants typically experience and then habituate to during an active stimulation condition (Reinhart, 2017). The same ramping period was used so that participants could not distinguish the condition (Woods et al., 2016). Most subjects experience an itching sensation only initially during HD-tACS, so this sham condition aimed to prevent awareness of the stimulation conditions (Gandiga et al., 2006; Nitsche et al., 2008)

2.6 Data Analyses

2.6.1 Specific Aim 1: Behavioral Data

2.6.1.1 Specific Aim 1a: Linguistic Measures

Previous investigations of speech entrainment focused on free speech, not entrained speech as the outcome. The current study, however, focused directly on speech output during speech entrainment to examine changes in output across each of the three stimulation conditions. Behavioral measures of speech fluency were obtained, transcribed and calculated for the speech entrainment samples.

The primary outcome for this study was the *proportion of correct script words*. Secondary measures (*number of different words produced* (tokens) and *proportion of errors*) were included to assess the number of total words produced, even if not from the script, and the nature of these productions (i.e. proportion of errors) to assess the nature of speech output elicited in each condition.

Primary and secondary outcomes were examined for each stimulation condition (1: *in-phase*; 2: *anti-phase*; 3: *sham*) and for each condition, performance was assessed at two time points 1) immediately following HD-tACS stimulation and 2) fifteen minutes post-HD-tACS stimulation (washout period).

To measure effects of stimulation condition on behavioral outcomes, transcripts from speech entrainment tasks were analyzed with methods consistent with CHAT (Codes for the Human Analysis of Transcripts) format and linked to the digitized audio and video (MacWhinney, 2000). The CHAT format operates closely with CLAN (Computerized Language Analysis Tools) (MacWhinney, 2000) to analyze a wide range of linguistic and discourse structures. While this software was initially created for

research related to child language, the tool has been modified in recent years for use with populations with acquired language disorders, such as aphasia (AphasiaBank; MacWhinney, Fromm, Forbes, & Holland, 2011). MOR and FREQ commands were used to derive preliminary data (mean length of utterance), tokens, words per minute, number of errors). The SCRIPT command was used as a secondary analysis to compare participant productions to the script (proportion of total words, proportion of correct words, words per minute and proportion of errors). See the CLAN manual *Section 7.22 SCRIPT* for additional details (MacWhinney, 2000).

Graduate student clinicians supervised by certified speech-language pathologists were trained on CHATCLAN procedures (protocols consistent with clinical trials (Cassarly et al., 2021) and P50 grants through the same lab (see Spell et al., 2020) for details regarding procedures, fidelity, implementation). Each transcript was rated by one of the graduate student clinicians. Although second ratings were not completed, verbal and/or written feedback was shared across students for coding disagreements and students consulted with the Clinical Core Coordinator and project leads to resolve the disagreement. Graduate student clinicians in this group (discourse team) maintained excellent inter- and intra-rater reliability (0.82 – 0.98) over the course of previous studies (see Spell et al., 2020).

The primary outcome measure was the *proportion of correct words* produced from each script for each stimulation condition. This measure was calculated as a proportion rather than a raw number 1) to control for differences in script length and 2) to be consistent with CHATCLAN SCRIPT command analyses (output = proportion as

compared to script). The secondary outcomes were: 1) *total number of words* (tokens), and 2) *proportion of errors*.

Tokens: All words, regardless of erred productions were included in the token count (i.e. semantic or phonological errors will not be excluded from the total word count). This measure reflects *all* words produced by participants across conditions, not only the script words. Including this measure provides information about speech output and accounts for productions of tokens of the same lemma, but may not be reflected in the *proportion of correct script words* variable. Consistent with the CLAN manual and related analyses, unintelligible words, word segments, neologisms, repetition and revisions or extraneous utterances were not included in the count.

Proportion of errors: The proportion of errors reflects the proportion of each participant's script production that is coded as an error. This variable was tallied as a proportion rather than a raw number to control for differences in script length (total number of words). This measure was derived from the CLAN 'SCRIPT' Analysis. This measure was of particular relevance given the hypothesis that was set forth for *Specific Aim 1a*, regarding the impeded behavioral response that was expected to occur with application of the anti-phase stimulation.

2.6.1.2 Specific Aim 1b: Spectral and Temporal Measures

Recent studies have begun to investigate speech timing to determine speech fluency changes during speech entrainment tasks (Feenaughty et al., 2017; Kershenbaum, Nicholas, Hunsaker, & Zipse, 2019a). To further inform the mechanisms underlying the efficacy of speech entrainment for patients with nonfluent aphasia and to determine the

extent to which HD-tACS influences speech timing, temporal and spectral analyses were performed.

To determine the extent to which participants "entrain" to the audiovisual model, a dynamic time warping algorithm was used to determine the distance between the productions from the AV model and the participant. Dynamic time warping (DTW) is a method used to compare two temporal sequences that do not align. To determine distances between two such samples, DTW creates a shift in time and maps each element in one series to the closest element in the other series to find the optimum distance between the elements. The distances between points are stored in a table and the shortest paths between points are added to develop a similarity measure between the two time series. To do this, a warping path is created so that the samples are shifted and as the associated cost of a warping path becomes smaller, the similarity between the time series increases. This approach is extremely powerful when the signals being compared have similar patterns as this allows the extreme points (maximums and minimums) between two signals to be correctly mapped.

FastDTW, a dynamic time warping algorithm (Salvador & Chan, 2007), was implemented in Python to determine optimal alignments between the model and participant audio samples. A mel-frequency cepstrum (MFC) analysis was conducted to derive a metric that can be used to determine distance between two audio samples. The MFC is collectively made up of mel-frequency cepstral coefficients (MFCCs) , a spectral feature commonly used in speech recognition systems. MFCCs which are derived by taking the Fourier transform of a signal, mapping the powers of the spectrum onto the mel scale, taking the logs of the powers at each mel frequency and taking the discrete

cosine transform of the list of mel log powers. The amplitudes of the resulting spectrum are the MFCCs. Using MFCCs, an array of feature vectors can be extracted and compared with a dynamic time warping algorithm to calculate a normalized distance between the two feature vectors. The distance measure is the sum of the corrections needed to "warp" the participant onto the model. Across all samples, the distance metric was normed to resolve the discrepancy between the number of feature vectors due to variance of approximately 2% (+/-200 vectors in an average of ~10500) across audio samples.

In the current study, the librosa 0.9.1 library (Python, librosa.feature.mfcc), (McFee et al., 2015) was used to extract MFCCs and the following parameters were used: "hop length" (number of audio samples between adjacent short-time Fourier transform (STFT) columns) = 110 (audio sample rate = 44100 Hz; 110 samples ≈ 5 ms; Venkataramanan & Rajamohan, 2019); "n_mfcss" (number of MFCCs to return) = 25 (per Venkataramanan & Rajamohan, 2019); "win_length" (length in number of audio samples of the Fast Fourier Transformation) = 220 (audio sample rate = 44100Hz, 220 samples ~10ms, Venkataramanan & Rajamohan, 2019); "mfccs_pt.T, mfccs_model.T" (the MFCC arrays transposed to the correct axis); and "dist" = Euclidean (MFCCs are 1 dimensional vectors, calculated using scipy_spatial.distance library). It is important to note that because the values that were calculated from the MFCC vectors are distance, they were absolute measures and not explicitly relative. For example, two trials may have very similar distance but represent distinct speaker productions. Greater values indicated less similarity between the speaker and the model while smaller distances indicated little difference between model and speaker production.

Distances were calculated for each of the three productions of the final script of the stimulation period (Script #6, see Table 2.1) and for each of the three productions of the final script of the washout period (15 minutes post-stimulation Script #10; See Table 2.1).

Table 2.2 *Behavioral Outcome Measures*

Stimulation Conditions (Factor)	**Stimulation Time Points**		**Specific Aim**	**Dependent Variable**
1 *(in-phase)* **2** *(anti-phase)* **3** *(sham)*	**<u>Stimulation Period</u>: 25 Minutes of HD-tACS**	**<u>Washout Period:</u> 15 minutes post-HD-tACS**	**1: BEHAVIORAL MEASURES**	
			1a: LINGUISTIC VARIABLES	- Proportion of Total Script Words - Total Number of Tokens - Proportion of Errors
			1b: TEMPORAL-SPECTRAL VARIABLES	- Distance between participant production and audiovisual model (*entrainment*)
			2: BRAIN-BASED PREDICTORS	

			2a: LESION SYMPTOM MAPPING	- *"in-phase boost relative to anti-phase"*
				  - Proportion of total script words
				  - Total number of tokens
				  - Proportion of Errors
				  - Distance between participant production and audiovisual model (*entrainment*)
				
				- *"in-phase boost relative to sham"*
				  - Proportion of total script words
				  - Total number of tokens
				  - Proportion of Errors
				  - Distance between participant production and audiovisual model (*entrainment*)

			2b: CONNECTIVITY ANALYSES	

2.6.2 Statistical Analyses

All statistical analyses were conducted using R (4.1.1 GUI 1.77, 2021) and R Studio ("Ghost Orchid" Release 9-20-21, Build 351). Descriptive statistics (means and standard deviations of all behavioral outcome measures from *Specific Aims1a* and *b*) were reported for all participants across three conditions. A Kruskal-Wallis analysis of variance was used to determine differences in dependent variables across conditions for performance immediately following tACS (stimulation period) and 15 minutes following tACS administration (washout). The main factor was HD-tACS condition: 1. *in-phase*; 2. *anti-phase*; 3. *sham*.

2.6.3 Specific Aim 2: Neuroimaging Analyses

Dependent variables for the neuroimaging analyses relied on the primary and secondary behavioral outcome measures described earlier. In addition to the outcome measures, "tACS boost'" was calculated to determine the extent to which participants demonstrated a better behavioral performance in the *in-phase* condition compared to the *anti-phase* condition (*in-phase* boost relative to *anti-phase*, and/or a better behavioral performance in the *in-phase* condition compared to the *sham* condition ('in-phase boost relative to sham'. The *in-phase* "tACS boost" relative to *anti-phase* variable was calculated by subtracting the participants' performance in the *anti-phase* condition from their performance in the *in-phase* condition for each outcome measure. The *in-phase* "tACS boost" relative to *sham* was calculated by subtracting the participants' performance in the *sham* condition from their performance in the *in-phase* condition for each outcome measure. For linguistic behavioral measures, a "tACS boost", was indicated by a positive number (i.e., better performance in the *in-phase* condition relative

to the comparison condition and a greater number indicated a stronger "tACS Boost" during the *in-phase* condition. For the variable derived from the Dynamic Time Warping analysis, a larger number indicated a greater distance between the participant and the audiovisual model (i.e., poorer entrainment). See Table 2.2 for an outline of the variables.

To reduce dimensionality of the data, 40 regions of interest (ROIs) from the Johns Hopkins University atlas (Faria et al., 2012) were used to divide gray matter into regions of interest in the context of the dual stream model (i.e. 20 dual stream regions; 20 ventral stream regions). These ROIs were derived from those implicated as dorsal or ventral by Fridriksson and colleagues (2016), which relied on segmentation from the JHU atlas to identify dual stream regions in a cohort of stroke patients (Faria et al., 2012). It is important to note that the dual stream model proposed by Hickok and Poeppel (2004) is theoretical, so for the purposes of the current study, the ROIs from the aforementioned study (Fridriksson et al., 2016) were used, despite the fact that there is not a 1:1 relationship between these ROIs and the proposed dual stream model. The correspondence, however, between the model and the ROIs reported in 2016, is very high. To understand the associations between damage and behavioral performance across the stimulation conditions, we characterized brain damage using both lesion and connectome data. See Table 2.3 for a complete list of ROIs.

As indicated in the table and consistent with the methods described above, 20 dorsal stream and 20 ventral stream ROIs were included. Regions are consistent with methods and results described by Fridriksson et al., 2016. Highlighted text in the table indicates 'critical' anterior and posterior regions of interest as discussed in the context of theoretical constructs that motivate the current study and regions indicated in previous

studies that suggest coherence between these regions is associated with improved fluency during speech entrainment (Johnson et al., 2021).

Table 2.3: *Left hemisphere dual stream regions of interest*

DORSAL		VENTRAL	
Number	**ROI Name**	**Number**	**ROI Name**
7	L middle frontal gyrus	13	L inferior frontal gyrus, *pars orbitalis*
11	L inferior frontal gyrus, *pars opercularis*	29	L supramarginal gyrus
13	L inferior frontal gyrus, *pars orbitalis*	31	L angular gyrus
15	L inferior frontal gyrus, *pars triangularis*	35	L superior temporal gyrus
23	L postcentral gyrus	37	L pole of the superior temporal gyrus
25	L precentral gyrus	39	Left middle temporal gyrus
29	L supramarginal gyrus	41	Pole of the middle temporal gyrus
71	L insula	43	L inferior temporal gyrus
79	L putamen	51	L superior occipital gyrus
81	L globus pallidus	71	L insula
117	L anterior corona radiata	121	L posterior corona radiata
119	L superior corona radiata	135	L retrolenticular part of internal capsule
121	L posterior corona radiata	147	L inferior fronto-occipital fasciculus
131	L anterior limb of internal capsule	149	L posterior thalamic radiation
133	L posterior limb of internal capsule	151	L sagittal stratum
135	L retrolenticular part of internal capsule	155	L superior longitudinal fasciculus
137	L external capsule	157	L uncinate fasciculus
147	L Inferior-fronto-occipital fasciculus	182	L posterior insula
155	L superior longitudinal fasciculus	184	L posterior superior temporal gyrus
182	L posterior insula	186	L posterior middle temporal gyrus

2.6.3.1 Specific Aim 2a

2.6.3.1.1 Preprocessing

Lesions from patients' earlier available scans (from previously completed studies) were used. Preprocessing of structural scans results from the following pipeline: lesions on baseline scans were manually demarcated in MRIcron (Rorden et al., 2013) on the T2-weighted image by a neurologist. T2 images were co-registered to the T1 image, and T1 parameters were used to re-slice the lesion into the native T1 space. Re-sliced lesion maps were smoothed with a 3mm full-width half maximum Gaussian kernel to remove jagged edges associated with manual drawing and subsequently binarized using a 50% cutoff to eliminate dilation/erosion. Enantiomorphic normalization of the T1 was performed (Rorden and Brett, 2000; Rorden et al., 2013). The diffusion image was aligned with the lesion map (T2-weighted image co-registered into the T1-weighted image) and linearly normalized to the non-diffusion image (B0 image) using FSL (FMRIB Software Library) FMRIB (Functional MRI of the Brain)
Linear Image Registration Tool. The resulting spatial transform was used to register probabilistic maps of white and gray matter in native T1 space and the stroke lesion into the diffusion MRI space. This yielded spatial normalization of the atlas ROIs to diffusion space. The pre-processing was consistent with previous methods (Yourganov et al., 2016).

2.6.2.1.2 Analysis: Lesion-Symptom Mapping:

To understand the effect of lesion volume and location for tACS-related "boost" a region-based lesion-symptom mapping analysis were conducted. All univariate statistical analyses were implemented using NiiStat toolbox for MATLAB

(https://www.nitrc.org/projects/niistat/). The 40 ROIs described above (see Table 2.3) were used and analyses were controlled for total lesion volume. Only voxels where at least 2 individuals had damage were included in the analysis. The univariate analyses used conventional lesion-symptom mapping: General Linear Model (GLM) with $P < 0.05$ and controlled for multiple comparisons using permutation thresholding (5000 permutations). These analyses examined associations between the dependent variable (primary and secondary outcome measures) and neuroanatomical damage to left-hemisphere dual stream regions, Total lesion volume was be regressed to account for lesion size.

2.6.3.2 Specific Aim 2b

2.6.3.2.1 Preprocessing

Structural Connectivity: Probabilistic tractography was applied to evaluate pairwise gray matter structural connectivity (Bonilha et al., 2015; Gleichgerrcht, Fridriksson, Rorden, & Bonilha, 2017). Tractography was estimated using the FMRIB Diffusion Toolbox probabilistic method (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) with FDT's BEDPOST (default parameters: 3 fibers per voxel, ARD weight of 1, burin period of 1000, 1250 jump, and one sample every 25) to build default distributions of diffusion parameters at each voxel. Structural connectivity was qualified as fiber count between the aforementioned 40 ROIs (number of streamlines arriving in one region when another ROI was seeded and vice versa). All possible connections between nodes were included, without any a priori constraints regarding plausibility, with the subsequent analyses identifying those were connectivity strength was reliably associated with behavioral impairment.

Functional Connectivity: The resting-state fMRI data were corrected for motion using the SPM12 "realign and unwarp" procedure with default settings during preprocessing. Brain extraction was performed using the SPM12 script *spm_brain_mask* with default settings. The mean fMRI volume for each participant was aligned to the corresponding T2-weighted image to compute the spatial transformation between the fMRI data and the lesion mask. The fMRI data were then spatially smoothed with a Gaussian kernel with FWHM = 6 mm. The voxel-wise fMRI time courses were detrended using the following regressors: mean signals from the white matter and from cerebro-spinal fluid; time courses of the six motion parameters estimated at the motion correction step; linear, quadratic and cubic trends. Then, the time courses were bandpass-filtered using the 0.01-0.1 Hz frequency band. To remove artifacts driven by lesions, the procedure described by Yourganov and colleagues (2018) was used. To decompose data into independent components, the FSL MELODIC package was used to compute the z-scored spatial maps for each independent component. The spatial maps were thresholded at $p < 0.05$ and compared with the lesion mask for that participant. If the spatial overlap (measured with Jaccard index) between the lesion mask and the thresholded IC map was greater than 5%, the corresponding component was deemed to be significantly overlapping with the lesion mask. All such components were regressed out of the fMRI data using the fsl_regfilt script from the FSL package. After these steps, individual rsFC connectomes were built for each participant by 1) segmenting probabilistic grey matter maps from T1- weighted images; 2) division of grey matter map into regions of interest; 3) computation of ROI-specific time courses of the BOLD signal by averaging time courses across the voxels within each ROI. Functional connectivity for

a pair of ROIs was computed as bivariate Pearson's correlation coefficients between their mean BOLD fMRI time courses.

2.6.2.2.2 Connectivity Measures and Analyses

Analyses of structural and resting state functional connectivity was performed to determine the extent to which network integrity predicts successful entrainment. Associations between primary and secondary outcome measures and residual structural and functional connectivity between targeted regions were examined in an ROI-based connectome analysis. The connectome analysis used information from diffusion tensor imaging (DTI) and resting state functional connectivity (rsFC). DTI images can be used to determine the measure and direction of water diffusion in the brain to provide an estimate of the location and trajectory of white matter pathways (Hagmann et al., 2010). Resting state functional connectivity (rsFC) measured temporal coherence of the BOLD signal between grey matter regions (Biswal, Yetkin, Haughton, Hyde, 1995; Fox and Raichle, 2007).

This analysis measured structural and resting state functional connectivity across the brain and determine how white matter integrity and baseline neural coherence relates to the ability to entrain, secondary to the effect of *in-phase* tACS (see *Section 2.6.3*). The 'tACS-boost' was calculated as two dependent variables: 1) the difference between performance during the *in-phase* stimulation condition and the *anti-phase* stimulation condition and, 2) the difference between performance during the *in-phase* and *sham* conditions.

NiiStat was used to compute a GLM where behavioral scores served as dependent variables and functional/structural scores between each pair of ROIs were included as

independent variables. Statistical thresholding for all analyses were correct for multiple comparisons using permutation analyses (5000 permutations). Due to the inter-subject variability in whole brain white matter and resting state functional connectivity, fiber counts and coherence from select connections between regions of interest in the dual stream model of language processing (Hickok & Poeppel, 2007) were included.

Structural Connectivity: Univariate analyses consistent with those used for lesion-symptom mapping were performed. All analyses controlled for total lesion volume and corrected for multiple comparisons using permutation analyses (5000 permutations).

Resting State Functional Connectivity: NiiStat (https://github.com/neurolabusc/NiiStat) was used to analyze the association between resting state functional connectivity (rsFC) within the dual stream regions of interest and *tACS-related boost*. To examine the association between the association between rsFC across ROIs and performance in the *in-phase* tACS condition, a general linear model (GLM) was computed where behavioral scores served as dependent variables and functional connectivity scores between each pair of ROIs were the independent variables. Values for each predictor ($p < 0.05$) were z-transformed using SPM's smp_t2z function. The statistical threshold for all analyses was corrected for multiple comparisons using permutation analyses (5000 permutations).

2.7 Hypotheses

Previous research suggests a behavioral paradigm, speech entrainment, acts as an external gating mechanism to help compensate for an impaired efference copy and facilitate fluent speech in individuals with nonfluent aphasia (Fridriksson et al., 2015, 2012). The neural substrates underlying this effect have been elucidated through this

work and recent investigations of the structural and functional connectivity that underlie "successful entrainment" (Johnson, 2021; Bonilha et al., 2019).

2.7.1 Specific Aim 1

It was hypothesized that slow oscillatory activity and poor theta phase synchronization contributes to poor SE performance and that an exogenous boost of *in-phase* frontotemporal theta coupling would enhance frontotemporal network connectivity, which is hypothesized to subserve successful entrainment. It was expected that enhanced neural integration via this external modulatory source would improve speech fluency (*number of different script words*) and reduce the proportion of errors produced during the *in-phase* stimulation condition.

2.7.2 Specific Aim 2

2.7.2.1 Specific Aim 2a

Previous literature suggests anterior damage, particularly to the left IFG results in nonfluent aphasia (Broca, 1865; Dronkers, 1996; Geschwind, 1965). SE is thought to serve as an external gating mechanism to support anterior damage (Fridriksson 2015; Fridriksson et al., 2012). Related work in healthy controls (Venezia et al., 2016) and clinical populations suggests that the left *p*MTG is crucial for audiovisual integration and that successful entrainment relies on intact ventral regions (particularly *p*MTG; Fridriksson et al., 2015; Bonilha et al., 2019). The theta band frequency of stimulation (7 Hz) to be applied in the proposed study is consistent with human speech syllable processing (Giraud & Poeppel, 2012), and importantly, is associated neural oscillatory patterns for audiovisual processing (Bauer et al., 2020; Keil & Senkowski, 2018). In the present study, it was hypothesized that an exogenous boost of

in-phase theta coupling via HD-tACS would enhance frontotemporal network connectivity to facilitate neural integration and improve SE performance. It was expected that greater proportion of intact anterior, dorsal regions (IFG*po*) and ventral, posterior regions (*p*MTG) would yield improved entrainment when paired with HD-tACS.

2.7.2.2 Specific Aim 2b

Previous literature suggests anterior and posterior coherence, particularly between the left IFG (Fridriksson et al., 2015, 2012) and the left *p*MTG (Bonilha et al., 2019; Fridriksson, Basilakos, et al., 2015), is facilitated by the speech entrainment task (Johnson et al., 2021). It was hypothesized that slow oscillatory activity and poor theta phase synchronization, secondary to a stroke-induced lesion contributes to poor speech fluency. With regard to neural modulation via HD-tACS, it was expected that reduced connectivity between intact perilesional frontotemporal regions negatively would affect the response to HD-tACS. It was also hypothesized that a greater proportion of spared frontotemporal cortical regions (proportion of IFG*po* and *p*MTG) and greater frontotemporal neural coherence (as measured by functional connectivity) would yield better modulatory effects of HD-tACS during *in-phase* stimulation. It was expected that application of HD-tACS at a theta frequency (7 Hz) would provide neural modulation at a rate consistent with long range (anterior-posterior) fibers (Buzsaki, Gyorgy, Draguhn, 2004; Fujisawa & Buzsaki, 2011; Karalis et al., 2016).

CHAPTER 3

RESULTS

3.1 PARTICIPANTS

3.1.1 Enrollment

Seventeen participants were enrolled and 16 completed the study. One participant (T15) enrolled in the study and did not complete all three sessions, which yielded a 6% attrition rate for this study. The remaining 16 participants are included in the data analysis and subsequent discussion.

3.1.2 Screen Fails

Those contacted regarding the study and not enrolled (due to failure to meet study inclusion criteria [including contraindication for noninvasive brain stimulation], declining to participate) are, for the purposes of this study, considered 'screening failures' (n = 13). See Appendix B for additional information.

3.1.3 Demographic Data

A total of 16 participants completed the study (4 women; 25%). All participants had incurred a left hemisphere stroke and were at least one-year post-stroke at the time of the study (mean MPO =77.53, SD= 48.33; range = 13 - 190). The average age of participants was 65.13 years (SD: 10.30, range = 47 - 82.) and the average number of completed years of education was 15.20 (SD = 2.70, range = 12 - 20). Participants identified as White (n = 12), or Black or African American (n = 4) and no participants indicated Hispanic or Latinx ethnicity. Demographic data are available in Table 3.1.

Table 3.1 *Patient demographic data*

Pt Identifier	**Age** *(years)*	**Education** *(years)*	**Sex** *(reported by pt)*	**Race** *(reported by pt)*	**MPO** *(months)*	**WAB-R AQ** *(1 – 100)*	**AOS** *(1 = presence; 0 = absence)*
T1	75	12	Female	White	93	30.8***	1
T2	60	16	Male	White	135	52.8**	1
T3	65	16	Male	White	75	66.5**	0
T4	47	16	Female	White	190	62.5**	1
T5	62	12	Male	Black	41	80.8	0
T6	71	16	Male	White	82	63.2**	1
T7	63	18	Male	White	153	74.7**	0
T8	70	14	Male	White	38	82*	0
T9	82	12	Female	White	38	48***	1
T10	48	16	Male	Black	68	79.9*	1
T11	63	12	Male	Black	69	27.5***	1
T12	54	12	Male	Black	63	72.5**	0
T13	79	18	Female	White	36	81.6*	0
T14	65	20	Male	White	69	78.1*	0
T15	69	27	Female	Black	45	24.7****	1
T16	73	18	Male	White	13	19.5****	1
T17	77	16	Male	White	298	40.2***	0

MPO = months post onset; WAB-R AQ = Western Aphasia Battery-Revised Aphasia Quotient; AOS = apraxia of speech

3.1.4 Behavioral Data

All patients presented with nonfluent aphasia (based on clinical judgement, test administration of the WAB-R, and inclusion criteria for nonfluent aphasia consistent with Casserly at al., 2021) and varying degrees of aphasia severity, as represented by Aphasia Quotient (AQ) scores ranging from 19.5 (very severe aphasia) to 82 (mild aphasia) (mean AQ = 60.04; moderate aphasia). See Table 3.1.

3.1.5 Stimulation Montages

Individualized montages were created for each participant to map the optimal current flow after accounting for the lesion size and location and identifying residual cortex that was active during a language task (see *Methods Section 2.4.2* for details). Coordinates for each patient are shown in Table 3.2. Pt 15 completed 2/3 behavioral sessions and did not complete the third session secondary to attrition. Coordinates for this patient are included above but attrition is indicated by the grey color. Individualized stimulation montages can be visualized in Appendix E.

Table 3.2 *Individualized participant stimulation montages*

Pt Number	Anterior MNI Coordinates	Anterior Central Electrode	Anterior Ring Electrodes	Posterior MNI Coordinates	Posterior Central Electrode	Posterior Ring Electrodes
T1	-57; 10; 7	FC5	F3, C3, FT7	-67; -33; -3	TP7	C5, P5, F9
T2	-37; 7; 30	FC5	F3, C3, FT7	-57; -39; -5	TP7	C5, P5, F9
T3	-47; 16; 3	F5	F3, FC5, AF7	-57; -19; -33	P5	CP5, P3, PO7
T4	-47; 17; -7	F3	F5, FC5, AF7	-61; -50; 23	P3	CP5, P5, PO7
T5	-43; 6; 29	FC5	FT7, F3, C1	-49; -44; 27	P5	TP7, P9, P3
T6	-57; 11; 2	F7	AF7, FC5, F9	-59; -45; 11	CP5	C3, P3, TP7
T7	-58; 19; 10	F3	F5, FC5, AF7	-57; - 53; 13	P3	CP5, P5, PO7
T8	-41, 25, 41	F3	AF3, FC1, FC5	-61, -55, 11	P5	P3, PO7, CP5
T9	-31, 13, 12	FC5	AF3, C3, F9	-52, -64, 12	P5	P3, PO7, CP5
T10	-51; 21; 26	F5	FT7, FC3, AF7	-59; -45; 11	CP5	T7, P7, C3
T11	-24, 21, 51	FC1	C3, C1, Fz	-53, -64, 13	P7	CP5, PO7, P9
T12	-57; 11; 11	FC5	FT7, F7, FC3	-65; -25; 15	TP7	CP3, FT9, P9
T13	-40, 21, 50	FC3	C3, F1, F5	-36, -48, 20	P5	P3, PO7, CP5
T14	-41, 17, -3	F7	F9, AF7, FC5	-36, -50, 17	P5	P3, PO7, CP5
T15	-41, 13, 1	FT7	C5, F7, FT9	-58, -55, -3	P7	CP5, PO7, P9
T16	-49, 13, 31	FC5	FT7, F7, C3	-65, -41, -7	TP7	CP3, FT9, P9

3.1.6 Neuroimaging Data

Consistent with the inclusion criteria, all participants suffered a left hemisphere cerebrovascular event that resulted in aphasia. The mean number of months post stroke was equivalent to 88.59 (SD: 70.84, range = 13 - 298). Average lesion volume across participants was equal to 140195.53 mm^3 (SD = 85034.024 mm^3; range = 20257 – 272347 mm^3). The total lesion volume and proportion damage to regions of interest (ROIs) for this particular study are available in Table 3.3. See Figure 3.1 for lesion overlap map and Table 2.3 in the *Methods* chapter for a list of dual stream ROIs.

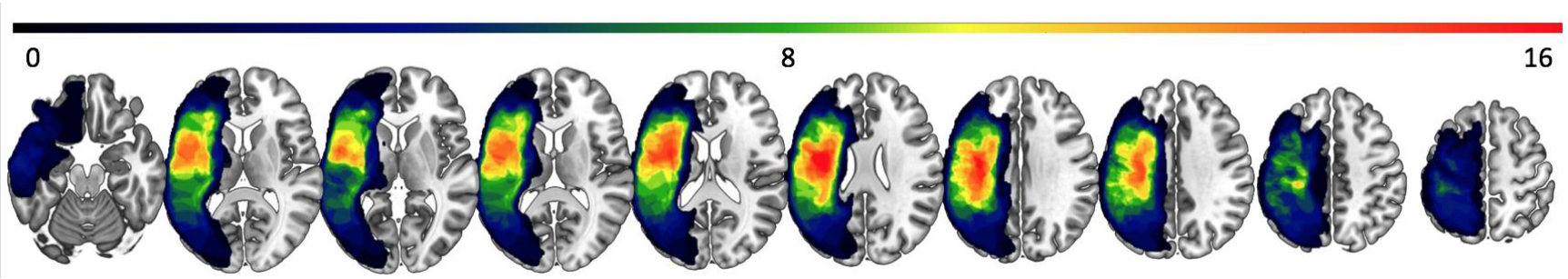


Figure 3.1: *Lesion overlay map for study participants (n = 16). The color scale indicates the number of participants with lesion damage at a particular location. The upper boundary (n = 16) of the color scale represents the highest lesion overlap.*

Table 3.3 *Proportion of damage to 'critical' anterior (inferior frontal gyrus) and posterior (middle temporal gyrus) regions of interest for each enrolled participant.*

Pt Number	**L Inferior Frontal Gyrus *pars opercularis***	**L Inferior Frontal Gyrus *pars orbitalis***	**L Inferior Frontal Gyrus *pars triangularis***	**L Middle Temporal Gyrus**	**L Posterior Middle Temporal Gyrus**	**Lesion Volume (mm^3)**
T1	0.41	0	0.14	0	0.56	113410
T2	1	1	1	0.39	0.44	243361
T3	0.01	0	0	0.66	0.99	219675
T4	0.21	0	0.06	0.04	0.01	59149
T5	0.53	0	0.17	0	0	42579
T6	0.99	0.89	0.97	0	0	210969
T7	0.97	0.22	0.95	0.35	0.23	148221
T8	0.45	0	0.11	0	0	57123
T9	0.86	0	0.20	0	0	68965
T10	0.74	0.31	0.77	0	0	53438
T11	0.96	0.12	0.73	0	0	114454
T12	0.13	0	0	0	0.01	177110
T13	0.96	0.05	0.75	0	0	95419
T14	0	0.05	0.08	0	0.03	20257
T15	0.46	0.10	0.32	0.08	0.91	272347
T16	0.84	0.97	0.93	1	0.95	252111
T17	0.99	0.78	0.97	0.04	0.57	234736

3.1.7 Protocol

From November 2021 to April 2022, a total of 54 behavioral sessions were conducted. Due to attrition (n = 1), data from a total of 48 sessions were included in the subsequent analyses. All participants tolerated tACS well and no adverse effects related to the application of tACS were demonstrated. Technological errors were experienced for 2 of the 54 sessions (4%) for two independent participants (T6 and T14). Technological errors were due to computer and software updates which resulted in the session data not being recorded. To ensure clean data, these participants were asked to return for one additional session to obtain data. Stimulation conditions and the speech entrainment scripts were identical to the missed session.

3.1.8 Blinding

As reported previously, this study was a double-blind pseudorandomized study. Upon the completion of each behavioral session, participants were queried regarding whether they believed they received active stimulation during the session (in-phase or anti-phase), or the sham condition. The SLP administering behavioral sessions also completed the query. Patient reports and actual stimulation condition were not significantly different from chance ($p < 0.48$). SLP reports were also not significantly different from chance ($p < 0.92$). This suggests that neither patients nor the SLP guessed better than chance regarding the stimulation. Furthermore, this provides evidence that the nature of the stimulation (active vs. Sham) was not discernable due to differences in behavior, nor performance as assessed by the SLP.

3.1.9 Discomfort Ratings

Patients discomfort / pain ratings were = 0 out of 10 (mean = 0; SD = 0) during sham conditions and ranged between 0 and 1 out of 10 (mean = 0.08; SD = 0.27) during active stimulation conditions. Statistical analysis revealed that the discomfort ratings were comparable between sham and active stimulation conditions (Mann-Whitney U; p = 0.23), indicating that patients did not report a difference in discomfort level between the two conditions.

3.2 BEHAVIORAL RESULTS

A Shapiro-Wilk test of normality revealed that the linguistic behavioral variables were not normally distributed ($p > 0.05$). Therefore, non-parametric methods of analysis, namely, Kruskal-Wallis analysis of variances and post-hoc Dunn tests were used. For three participants (T9, T11, T16), behavioral data were considered outliers per the interquartile range criterion where observations outside the first and third quartiles were considered outliers. These data were removed for subsequent analyses. Outliers likely resulted from limited verbal output due to severity of aphasia and presence of motor speech disorders (e.g. apraxia of speech).

3.2.1 Specific Aim 1a:Primary outcome measure: Proportion of correct script words

No significant main effect was detected with a Kruskal-Wallis analysis of variances for the proportion of correct script words between the three stimulation conditions: $\chi^2(5) = 0.91$, $p = 0.96$ (see *Figure 3.2*). Participants produced a greater proportion of correct words during the in-phase condition during stimulation (median = 0.85) as compared to the anti-phase (median = 0.78) and sham conditions (median = 0.75). The proportion of correct words remained higher in the washout period where the

proportion of correct words was less than the stimulation phase for both anti-phase and in-phase conditions; however, the proportion of correct words produced after the in-phase condition remained higher than production after the anti-phase condition, even if not significantly so ($p = 0.96$). See Table 3.4.

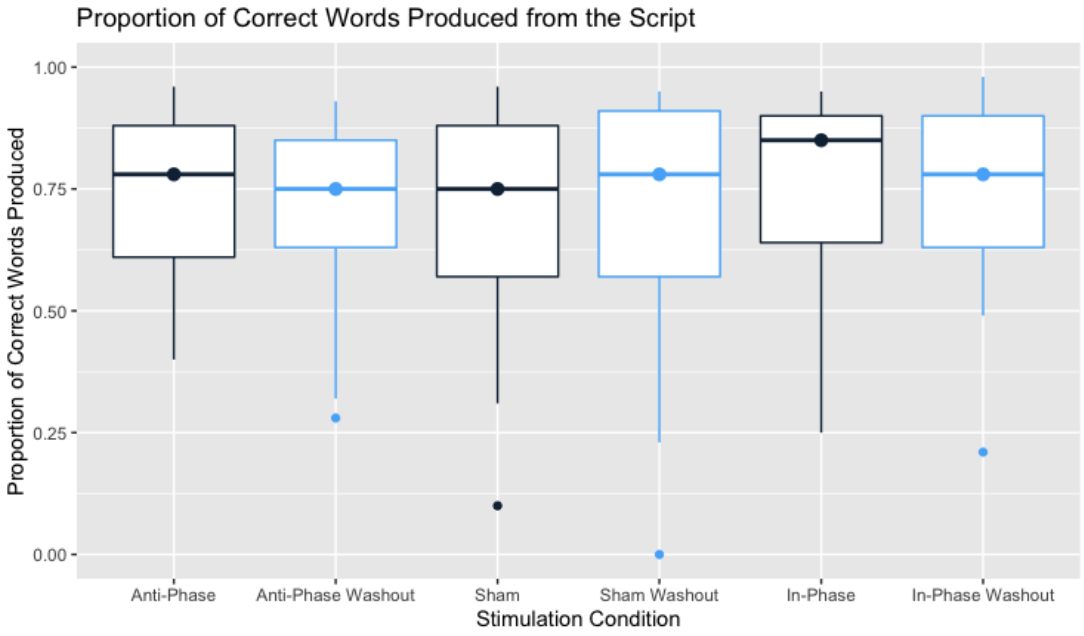


Figure 3.2*: Proportion of correct words produced from the script across all three stimulation conditions; and compared for simulation vs. washout periods. Despite nonsignificant effects, the trend was for participants to produce a greater proportion of correct words from the script during the in-phase condition during stimulation as compared to the anti-phase and sham conditions.*

Table 3.4: Statistics for the primary outcome measure: proportion of correct words.

Proportion of Correct Words (derived from CHATCLAN SCRIPT Command; n = 13)		
Kruskal-Wallis H	**Degrees of Freedom**	**p-value**
0.91	5	0.96
	Post Stim vs Washout	
	Stimulation	***Washout***
Stimulation Condition	*Median (IQR)*	*Median (IQR)*
Anti-Phase	0.78 (0.27)	0.75 (0.22)
Sham	0.75 (0.31)	0.78 (0.34)
In-Phase	0.85 (0.26)	0.78 (0.27)

3.2.2 Specific Aim 1a: Secondary outcome measure results

Number of Tokens

Kruskal-Wallis analysis of variances did not reveal a significant main effect of condition for number of tokens: $\chi^2(5) = 7.09$, $p = 0.21$. Although not significant, a greater number of tokens were produced in the in-phase condition, as compared to anti-phase and sham conditions during stimulation. During the washout period, participants produced more tokens during the anti-phase and in-phase conditions than in the sham condition, although not significantly so (*Figure 3.3*).

To examine the effects of condition during the stimulation period *only* (not considering the wash-out period), another Kruskal-Wallis analysis of variance was conducted to compare the number of tokens produced across anti-phase, sham, and in-phase stimulation conditions following the 25 minutes of stimulation. This analysis did reveal a significant main effect of condition for number of tokens: $\chi^2(2) = 5.94$, $p = 0.05$ (see *Figure 3.4*). Pairwise comparisons revealed that the in-phase stimulation condition (median = 51) yielded a numerically greater number of tokens than both the 'anti-phase'(median = 47) and 'sham' conditions (median = 41), but only the comparison between 'in-phase' and 'sham' was statistically significant (per a pairwise post-hoc Dunn test; $p = 0.05$).

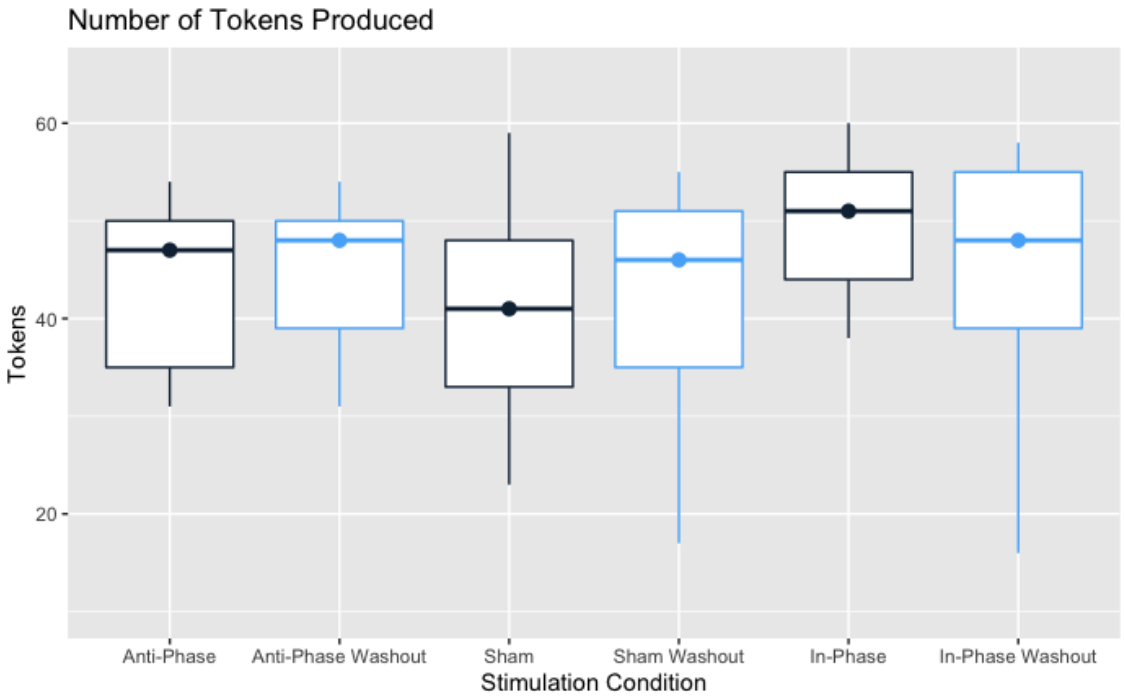


Figure 3.3*: Number of tokens produced form the script across all three stimulation conditions; and compared for simulation vs. washout periods. Despite nonsignificant effects, participants produced a greater proportion of tokens during the in-phase condition during stimulation as compared to the anti-phase and sham conditions. n = 13.*

Table 3.5: Statistics for secondary outcome measure: number of tokens produced.

Number of Tokens Produced (n = 13)		
Kruskal-Wallis H	**Degrees of Freedom**	**p-value**
7.09	5	0.21
	Post Stim vs Washout	
	Stimulation	***Washout***
Stimulation Condition	*Median (IQR)*	*Median (IQR)*
Anti-Phase	47 (15)	48 (11)
Sham	41 (15)	46 (16)
In-Phase	51 (11)	48 (16)

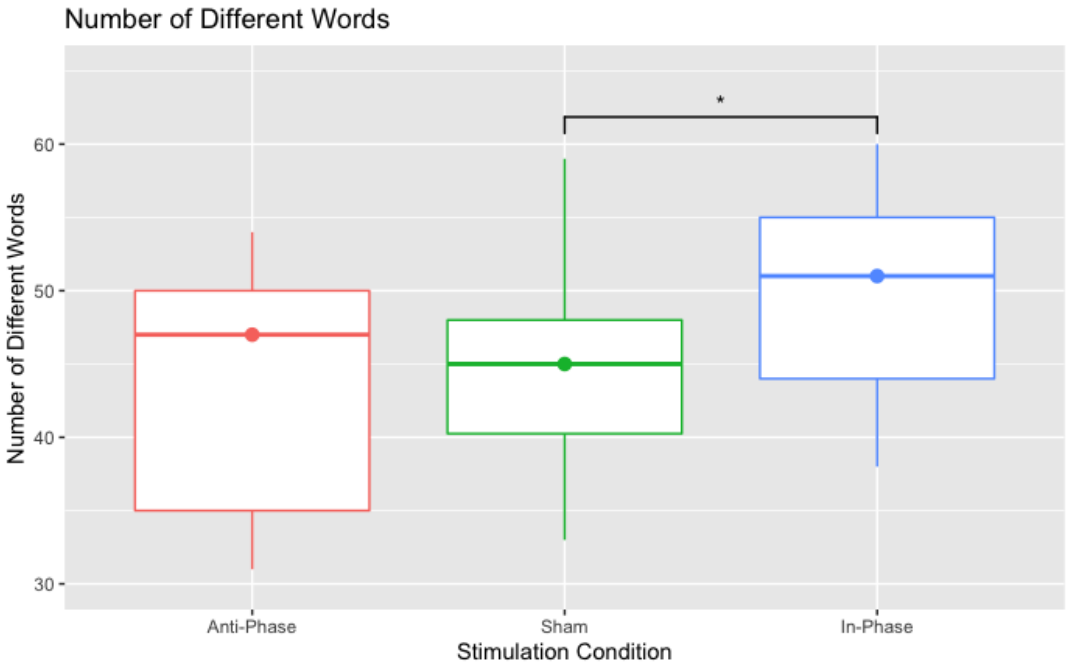


Figure 3.4*: Number of tokens produced in all three stimulation conditions. In a comparison of all three stimulation conditions during only the stimulation phase (not washout), participants produced significantly more tokens during the in-phase stimulation phase than in the sham condition.*

Table 3.6: Statistics for secondary outcome measure: stimulation phase only.

Number of Tokens Produced (n = 13)		
Kruskal-Wallis H	**Degrees of Freedom**	**p-value**
5.94	2	0.05
Dunn Kruskal-Wallis (Bonferroni applied)		
Comparison	**Z**	**p-value**
Anti-Phase – Sham	0.81	1.0
Anti-Phase – In-Phase	-1.59	0.33
Sham – In-Phase	-2.40	0.05*
	Median (IQR)	
Stimulation Condition		
Anti-Phase	47 (15)	
Sham	41 (15)	
In-Phase	51 (11)	

Proportion of Errors

No significant main effect was detected with a Kruskal-Wallis analysis of variances for the proportion of errors produced: $\chi^2(5) = 2.09$, $p = 0.83$. Despite nonsignificant effects, participants produced a numerically greater proportion of errors per during the anti-phase condition of the stimulation period (median = 0.41) as compared to the in-phase (median = 0.31) and sham conditions (median = 0.40). This effect remained unsignificant in the washout period but the same trend persisted (median of anti-phase condition = 0.42; median of sham condition = 0.38; median of in-phase condition = 0.36). See *Figure 3.5*.

Figure 3.5*: Proportion of errors produced across all three stimulation conditions; and compared for simulation vs. washout periods. Despite nonsignificant effects, participants produced a smaller number of errors during the in-phase condition as compared to the anti-phase and sham conditions. N = 13.*

Table 3.7: Statistics for secondary outcome measure: Proportion of errors.

Proportion of Errors (n = 13)		
Kruskal-Wallis H	**Degrees of Freedom**	**p-value**
2.09	5	0.83
	Post Stim vs Washout	
	Stimulation	***Washout***
Stimulation Condition	*Median (IQR)*	*Median (IQR)*
Anti-Phase	0.41 (0.21)	0.42 (0.26)
Sham	0.40 (0.29)	0.38 (0.16)
In-Phase	0.31 (0.14)	0.36 (0.22)

3.2.3 Specific Aim 1b:Dynamic Time Warping Results

A Shapiro-Wilk test of normality revealed that the temporal-acoustic behavioral variables were not normally distributed ($p < 0.05$). Therefore, non-parametric methods of analysis, namely Kruskal-Wallis analysis of variances and post hoc Dunn tests were used. *Average Distance Across All Three Script Productions:* No significant main effect was detected with a Kruskal-Wallis analysis of variances: $\chi^2(2) = 2.60$, $p = 0.27$ during the stimulation phase (see *Figure 3.6*). Despite nonsignificant effects, participants demonstrated a smaller distance (i.e. better temporal alignment with the model) during the in-phase stimulation condition as compared to the anti-phase condition and sham conditions.

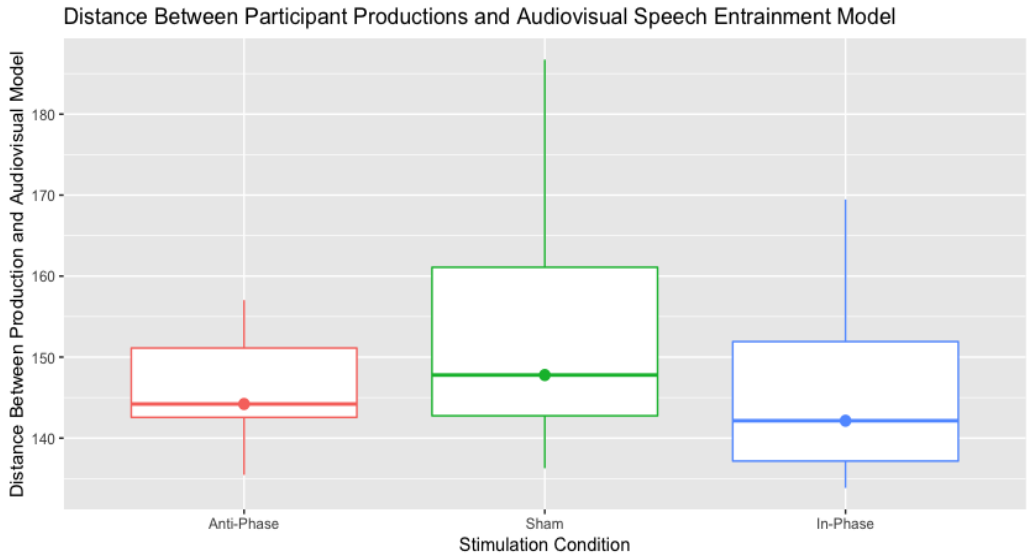


Figure 3.6: *Results from the Kruskal-Wallis Analysis of Variance examining differences across the stimulation condition (not washout) for distance between participant production and audiovisual speech entrainment model productions. Smaller distances demonstrate better alignment or 'entrainment' to the model.* n = 13.

Table 3.8: Statistics for time warping analysis to determine degree of entrainment across conditions.

Distance Between Participant and Model (n = 13)		
Kruskal-Wallis H	**Degrees of Freedom**	**p-value**
2.60	2	0.27
Stimulation	**Median**	**Interquartile Range**
Anti-Phase	144	8.56
Sham	148	18.3
In-Phase	142	14.7

3.3 Power Analysis

Although the analyses above did not yield significant results, a power analysis is included in *Figure 3.7* to demonstrate that 37 participants are needed to demonstrate a medium effect size (Cohen, 1988).

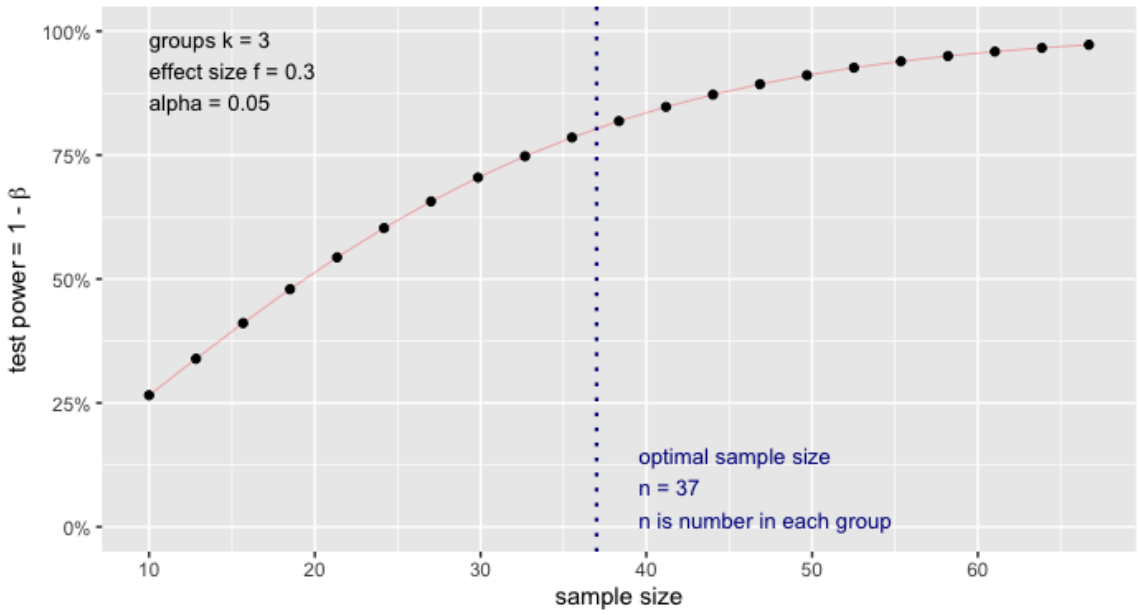


Figure 3.7: *A power analysis was conducted for sample size estimation. The effect size was considered to be medium using Cohen's (1988) criteria. With a significance criterion of* $\alpha = 0.05$ *and power = 0.05, the minimum sample size needed with this effect size is N = 37.*

3.4 Brain-based Predictors of Success

As described above (*Chapter 2; Section 2.6.3*), the dependent variables for the subsequent analyses were calculated to reflect the extent to which participants' benefited from 'in-phase' tACS stimulation. The dependent variables were calculated by subtracting the participants' performance in the anti-phase condition from performance during the in-phase condition and similarly, subtracting performance in the sham condition from performance during the in-phase condition. To illustrate an example the primary outcome measure, proportion of correct script words, is plotted against total lesion volume. See *Figures 3.8* and *3.9*. Importantly, not all participants demonstrated a "tACS boost" and for that reason, the dependent variable is not always a positive integer.

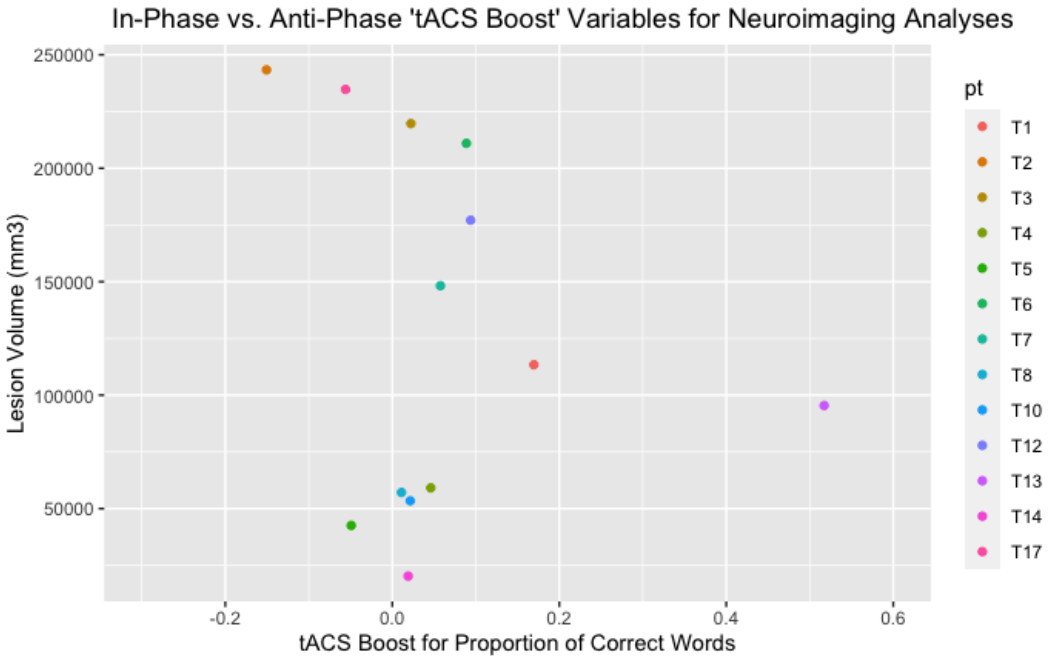


Figure 3.8: *"tACS boost", in-phase vs. anti-phase stimulation for the primary behavioral outcome measure: proportion of correct script words. Positive values on the x-axis indicate better performance (i.e. greater proportion of correct words) during the in-phase as compared to the anti-phase condition. Negative values indicate a greater proportion of correct script words were produced in the anti-phase condition. Each colored point represents a participant in the study. N = 13. 3 participants (T9, T11, T16) were excluded secondary to limited verbal expression.*

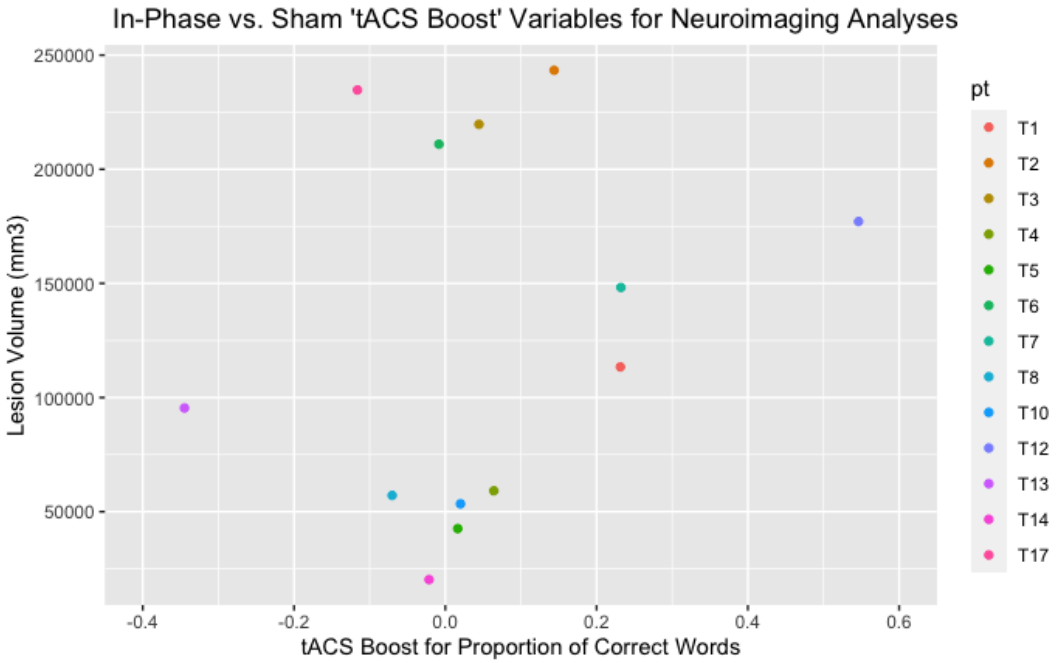


Figure 3.9: *"tACS boost", in-phase stimulation vs. sham for the primary behavioral outcome measure: proportion of correct script words. Positive values on the x-axis indicate better performance (i.e. greater proportion of correct words) during the in-phase as compared to the sham condition. Negative values indicate a greater proportion of correct script words were produced in the sham condition. Each colored point represents a participant in the study. N = 13. 3 participants (T9, T11, T16) were excluded secondary to limited verbal expression.*

3.3.1 Lesion-Symptom Mapping

A region-based lesion-symptom mapping analysis (n = 16) revealed that there were no significant associations between lesion damage and the primary behavioral outcome measure: proportion of script words. When considering associations between lesion damage and secondary behavioral measures, preservation of the inferior temporal gyrus (ITG, z = -4.26) was associated with larger 'tACS boost' in number of different words (as defined by 'tACS boost' in the in-phase condition vs. sham condition). After controlling for total lesion volume, there were no significant predictors of behavioral outcome measures. See *Figure 3.10*.

Because this study is a proof-of-concept design and exploratory in nature, the three participants who were removed from previous behavioral analyses were removed for subsequent analyses. After removing these three participants, there were no significant associations between lesion damage and the primary behavioral outcome measure: proportion of script words. In an analysis of lesion damage and secondary behavioral measures, greater damage to the left post-central gyrus was associated a greater number of tokens in the in-phase condition as compared to the sham condition (z = -3.55). This association did not survive after controlling for total lesion volume.

In a final lesion-symptom mapping analysis, a significant association was identified between damage to the external capsule (z = 2.85) and 'tACS boost' in the in-phase vs. anti-phase condition for distance between the participant and the audiovisual speech entrainment model. Where greater damage to the external capsule resulted in greater distance (i.e., poorer entrainment) during the in-phase condition as compared to

anti-phase stimulation condition. This association did not survive after controlling for total lesion volume.

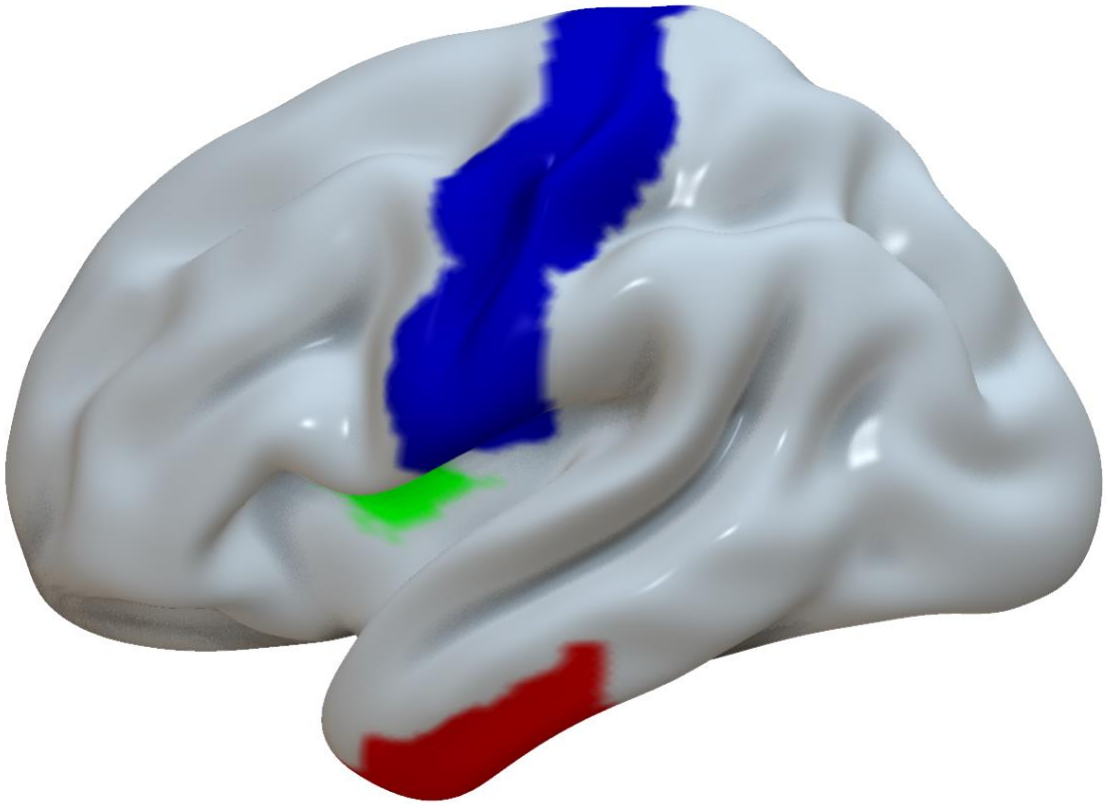


Figure 3.10: *Lesion-symptom mapping for behavioral performance. Linguistic behavioral variables (number of tokens are shown in red and blue where preservation of the inferior temporal gyrus (shown in blue; z = -4.26) and damage to the left post-central gyrus (red; z = 3.55) was associated with better response to tACS. Greater damage to the external capsule (green; z = 2.85) was associated with poorer entrainment during the 'in-phase' condition.*

3.3.2 Structural Connectivity

In an analysis of all 16 participants, there were no structural connections that were associated with behavioral performance. After removing the three outliers mentioned above, there were no significant white matter connections that were associated with the primary outcome measure: proportion of correct script words. In an analysis of secondary behavioral outcomes, interhemispheric structural pathways predicted tACS response. These associations remained significant even after accounting for total lesion volume. Poorer connectivity of the left hemisphere pathways between the left superior temporal gyrus and the globus pallidus ($z = -3.15$) was associated with a better behavioral response during the in-phase condition, as compared to the sham condition for performance on number of tokens.

In a post hoc ROI-based analysis including the anterior and posterior regions of interest that were used in the stimulation montages of the current study, the left inferior frontal gyrus and left middle temporal gyrus were included. White matter connectivity between the left inferior frontal gyrus pars opercularis and the left middle temporal gyrus was not significantly associated with any of the behavioral variables. There were no significant associations between white matter damage and entrainment (as measured by the dynamic time warping analysis).

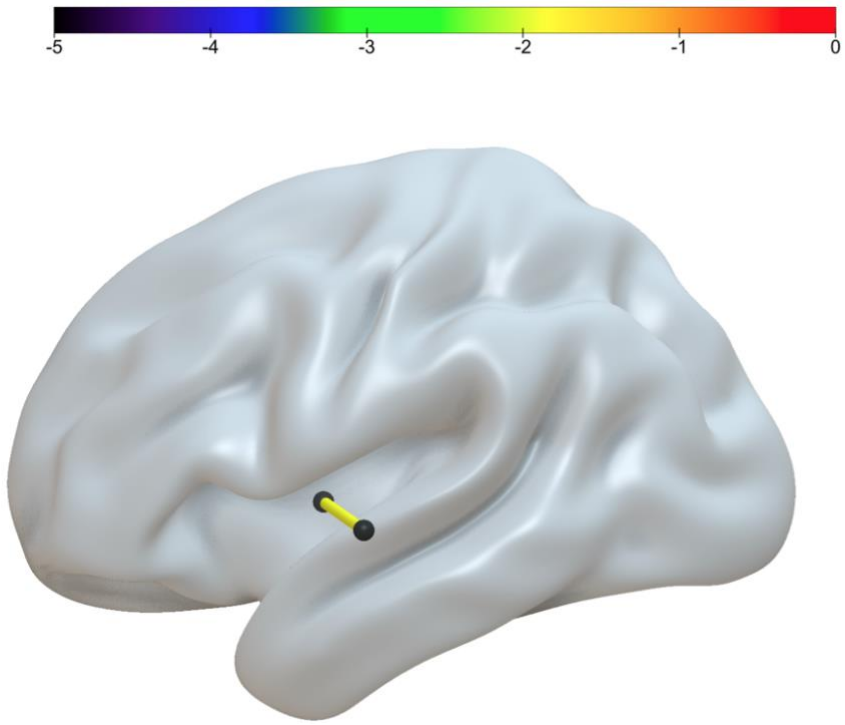


Figure 3.11: *White matter connectivity associated with behavioral performance where greater damage to white matter tracts was associated with improved performance during the in-phase condition, as compared to the sham condition. Reduced structural connectivity between the left superior temporal gyrus and globus pallidus was associated with a greater number of different words produced in the in-phase condition as compared to sham.*

3.3.3 Resting State Functional Connectivity

In an analysis of all 16 participants, there were no resting state functional connections that were associated with behavioral performance. After removing the three outliers mentioned above, interhemispheric structural pathways predicted tACS response. These associations remained significant even after accounting for total lesion volume. Left hemisphere pathways between the left putamen and left globus pallidus (z = -4.65) were negatively associated with a 'tACS boost' for the in-phase versus anti-phase stimulation condition, see *Figure 3.12 A.* Reduced synchrony between the left putamen and left globus pallidus was associated a greater proportion of correct words during the in-phase condition, as compared to the anti-phase condition.

To consider the resting state functional connectivity between the regions targeted in stimulation, in a post hoc ROI-based analysis was conducted. This analysis included the anterior (left inferior frontal gyrus, pars opercularis, pars orbitalis, and pars triangularis) and posterior (left posterior middle temporal gyrus) regions of interest that were targeted for stimulation. There were no significant associations between anterior-posterior coherence between these regions and 'tACS boost' for the primary behavioral outcome measure.: proportion of correct script words.

Resting state functional connectivity between the left inferior frontal gyrus pars opercularis and the left middle temporal gyrus was significantly associated with one secondary behavioral outcome measure: the *number of tokens* produced in the in-phase as compared to the sham condition (z = -2.51); see *Figure 3.12 B.* This association remained significant even after controlling for total lesion volume. The negative association suggests that poorer anterior-posterior synchrony was associated with a greater benefit

from tACS stimulation. There were no significant associations between white matter damage and entrainment (as measured by the dynamic time warping analysis).

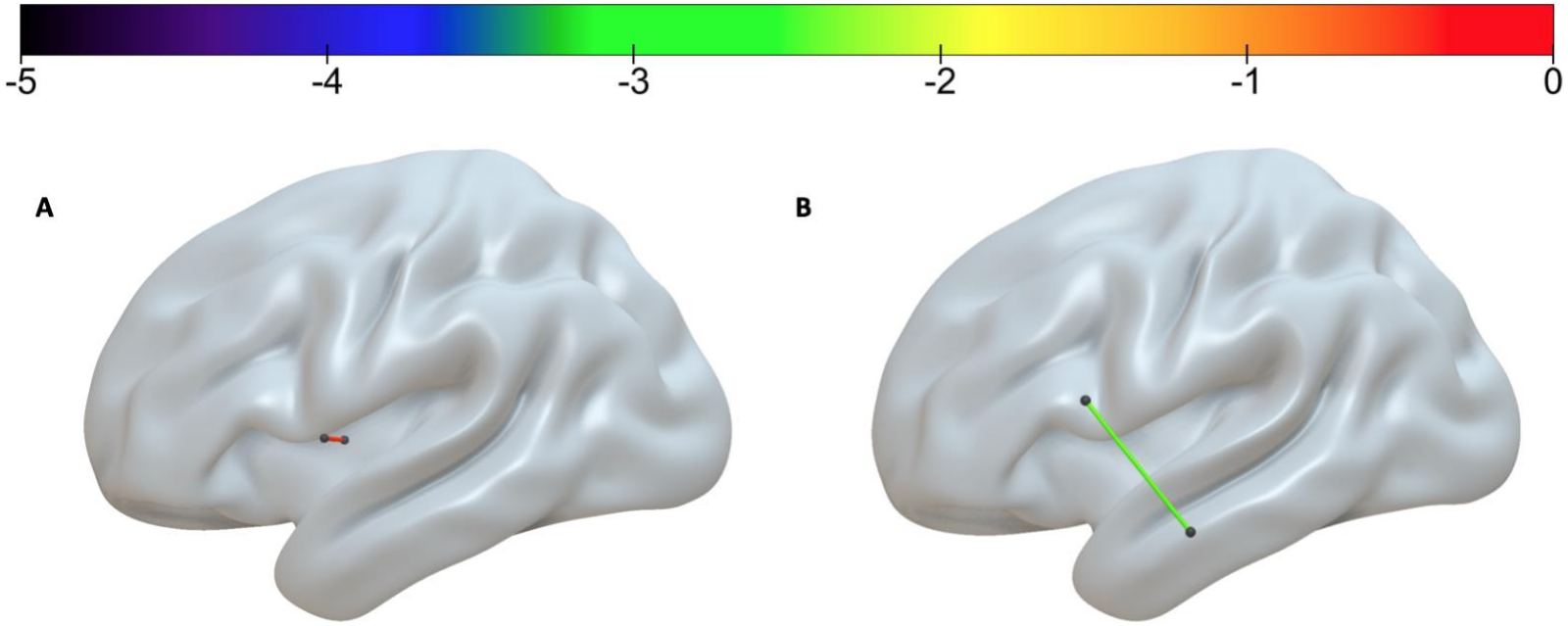


Figure 3.12: *Resting state functional connections associated with behavioral performance where greater damage to white matter tracts indicated improved performance during the in-phase condition, as compared to the sham condition.* ***A:*** *Reduced synchrony (as measured by resting state functional connectivity) between left putamen and left globus pallidus (z = -4.65) was associated with greater proportion of correct words in the in-phase condition, as compared to out-of-phase.* ***B:*** *A post-hoc analysis revealed that reduced synchrony between the inferior frontal gyrus and middle temporal gyrus was associated with a greater number of different words in the in-phase condition, as compared to the sham condition (z = -2.51). These associations remained significant even after accounting for total lesion volume.*

CHAPTER 4

DISCUSSION

4.1 Summary of Study and Specific Aims:

The primary goal of the current investigation was to conduct a proof-of-concept study to determine if the application of HD-tACS at 7 Hz improves speech output during speech entrainment in a cohort of speakers with chronic, nonfluent aphasia during a speech entrainment task. The study investigated speech production using two behavioral measures: 1) linguistic (e.g. proportion of words script words produced, number of total words produced, and proportion of errors) and 2) temporal-acoustic measures (e.g. 'distance' between model and patient productions, *entrainment*). Retrospective neuroimaging data were used to determine which structural and connectome characteristics are associated with behavioral performance during rhythmic neuromodulation (HD-tACS).

With regard to the behavioral effects of tACS, it was postulated that HD-tACS would improve language output as measured by proportion of correct words produced from the model script. More specifically, it was predicted that *in-phase* stimulation would improve the proportion of correct script words and that *anti-phase* stimulation would result in fewer correct words. Similarly, it was predicted that secondary linguistic outcome measures such as *number of total words*, would be greater during

the *in-phase* stimulation condition as compared to the *sham* and *anti-phase* conditions. On the contrary, the behavioral variable *proportion of script errors* was hypothesized to be greatest in the *anti-phase* condition compared to *in-phase* and *sham*, due to the fact that *anti-phase* tACS is thought to impair behavioral performance secondary to interrupted neural synchrony.

Concerning the temporal alignment or 'entrainment' of the participants' speech to the audiovisual model, it was hypothesized that participants would demonstrate better alignment with or entrainment to the model (as measured by distance between the model and the participants' productions using dynamic time warping) during the *in-phase* condition, as compared to the *anti-phase* and *sham* conditions. The distance between the model and participant output during the *anti-phase* condition was expected to be greatest (suggesting poorer temporal alignment) as compared to *in-phase* and *sham* conditions.

Finally, with respect to the neuroanatomical predictors of a "tACS boost" for the *in-phase* stimulation condition (as compared to *anti-phase* and *sham* conditions), it was expected that at least some degree of frontotemporal cortical regions of the left hemisphere needed to be intact for the alternating current to modulate exogenous oscillations. Therefore, it was postulated that participants with preserved anterior and posterior regions of interest in the left hemisphere would yield greater HD-tACS induced behavioral effects. Similarly, it was predicted that connectometric measures (DTI and rsfMRI) would be highly correlated with cortical integrity but that higher frontotemporal connectivity between anterior and posterior left hemisphere regions of interest would be associated with greater "tACS boost" in performance (as demonstrated by better

performance during the *in-phase* stimulation condition, as compared to *anti-phase* and *sham* conditions).

4.2 Summary of Findings:

The results from the current study fail to support the initial hypotheses. No significant results exist when examining differences in conditions (three conditions: 1) in-phase; *anti-phase*; *sham*) *and* two time periods (1) stimulation, 2) washout). The reasons for nonsignificant results are explored extensively in the Limitations and Future Directions sections of this chapter, but given the promising trend of the results, a large portion of this chapter will consider the nature of the results. Although not significant at the group level, the outcomes reported here offer a greater insight into the heterogeneity of nonfluent aphasia and mechanisms of action that may be involved with the recovery of speech fluency and language output. Overall, the behavioral results from this proof-of-concept study are encouraging and suggest that future explorations of the application of tACS for post-stroke aphasia rehabilitation are worthwhile.

While planned analyses did not reveal significant results at the group level, there was a significant difference between the *number of tokens* produced *in-phase* as compared to the *sham* condition in an analyses that only analyzed variances during the *stimulation* phase. Although this was the only significant finding, and the difference is reflected in a secondary behavioral outcome measure, not primary, the results as a whole are encouraging, especially in the context of a proof-of-concept study.

For the remaining analyses, although the results are nonsignificant, numerical trends in the data are consistent and suggest that participants produced a greater proportion of script words during the *in-phase* condition, as compared to *anti-phase* and

sham conditions. These trends in the data are further supported by the results that show a greater number of overall words were produced in the in-phase condition and that participants demonstrated greater entrainment to the model during the in-phase condition. It was also encouraging to see that participants produced fewer errors (although not significantly so) during the *in-phase* condition as compared to *anti-phase* and *sham* conditions.

Results from the dynamic time warping analysis, although not significant, also demonstrate improved entrainment numerically (as measured by distance between the speaker and the audiovisual model) during the *in-phase* stimulation condition as compared to the *anti-phase* and *sham* conditions. It was hypothesized that slow oscillatory activity and poor theta phase synchronization contribute to nonfluent speech and that an exogenous boost of *in-phase* frontotemporal theta coupling can enhance frontotemporal connectivity due to the fact that the stimulation was applied at a frequency of 7 Hz, a frequency that aligns with the internal oscillatory frequency of speech perception. This measure, in the context of the current study, serves as a proxy for entrainment as it considers temporal and spectral data to determine the alignment between the productions of the model and the person with aphasia.

Based on the results, it seems likely that for at least some participants, the *in-phase* stimulation elicited more speech and better entrainment. Because this study was a proof-of concept design, results were considered at the group level. In *Appendix F*; however, individual data points are included to provide some insight into the variability that exists during the stimulation phase for one linguistic behavioral variable (number of tokens produced). Statistical analyses were not performed to determine individual

characteristics that contribute to speech entrainment success (primarily due to the nature of this study and small sample size) but it is worthwhile to consider the patterns of performance that are evidenced in the descriptive data as displayed in *Appendix F*.

For both sets of behavioral data (1. linguistic and 2. temporal spectral) it is worthwhile to consider individual trends in the data. For some participants, performance aligns well with the aforementioned hypothesis, where performance (as demonstrated by improved behavioral performance for the linguistic variables, or better entrainment for the dynamic time warping analysis) is best during the *in-phase* stimulation condition and most impaired during the *anti-pha*se stimulation condition. For others, however, behavioral performance is most impaired and participants are less 'entrained' during the *sham* condition as compared to either the *in-phase* and *anti-phase* conditions. While the nature of the differences is not necessarily within the scope of the current investigation, it is crucial to consider these variations. It seems reasonable to speculate that for those who performed better in the *anti-phase* condition as compared to the *sham* condition, stimulation recruited at least some residual cortical areas or elicited some degree of coherence in the left hemisphere. It may also be the case for these participants, that the benefit of anti-phase stimulation lies not so much in the synchronization between two areas, but rather in the local stimulation itself. Again, this speculation is outside the scope of the current study but will be important to consider for future investigations. This is discussed further in the sections that follow.

Behavioral outcome measures (both linguistic and temporal) were considered to determine which underlying cortical regions, white matter pathways and functional connections, may be associated with improved performance during the in-phase tACS

condition. Improvement in the *in-phase* condition, or a "tACS-boost", was calculated as the difference between performance during the *in-phase* condition as compared to either the *anti-phase* or *sham* conditions, where a greater, positive number suggests a larger "tACS-boost" and a smaller number indicates a smaller "tACS-boost." Negative values here would suggest that performance was better during either the *anti-phase* or *sham* condition, as compared to the *in-phase* stimulation. Neuroimaging results examining the integrity of cortical gray matter regions, align with previous work from our group that suggests successful entrainment requires an at least partially intact ventral stream (Bonilha et al., 2019). Findings from the present study also provide supplemental information about specific lesion and connectome (resting state and white matter) characteristics regarding who may benefit from tACS, generally, or as an adjuvant to speech entrainment.

For example, patients with a greater proportion of intact inferior temporal gyrus demonstrated a better behavioral response (i.e. number of words) during the *in-phase* condition. By contrast, disrupted or reduced white matter connectivity was associated with improved language performance during the *in-phase* condition, as compared to *sham*, where less white matter connectivity between the left globus pallidus and superior temporal gyrus facilitated a better response to *in-phase* tACS as compared to *sham* (i.e. accuracy: greater number of words). Similarly, participants with reduced synchrony between anterior and posterior regions of interest (e.g. left inferior frontal gyrus, *pars opercularis* and left middle temporal gyrus, $z = -2.51$; as measured by rsfMRI) demonstrated a greater performance during *in-phase* tACS. It is important to note that the

connectivity results appear to be contrastive with the lesion-symptom-mapping results where preservation of cortical areas yielded a "tACS boost."

The DTI and rsfMRI results are contrary to the initial hypothesis. It was postulated that in order to benefit from a rhythmic neuromodulation such as HD-tACS, there would need to be some degree of preserved coherence between anterior and posterior regions; and that those with more intact structural or resting state connections, would demonstrate a greater benefit from tACS. On the contrary, however, the results suggest that patients with more damage (i.e. more damage to white matter and less coherence) between anterior and posterior regions benefitted most from tACS. It can be speculated that perhaps the rhythmic neuromodulation, when applied at 7Hz, induced improved synchrony and that this elicited an improved behavioral response. These results are discussed in greater detail below in the context of neural oscillations and expected underlying mechanisms of tACS. However, preliminary results offer a promising insight into facilitating recovery for nonfluent aphasia. Although further investigations are needed, preliminary data from this proof of concept study provide evidence to suggest that for some speakers with nonfluent aphasia (i.e., those with greater incoherence secondary to brain damage) the application of external, rhythmic stimulation was beneficial.

In the current study, entrainment was explored through the application of a rhythmic neuromodulation: high definition transcranial alternating current stimulation. This external modulatory source was paired with a behavioral paradigm: speech entrainment, an audiovisual paradigm that is shown to improve speech output in participants with nonfluent aphasia. The data that are described above, provided

preliminary behavioral evidence from the linguistic outcome measures mildly suggesting that the application of a rhythmic noninvasive brain stimulation (HD-tACS) during a speech entrainment paradigm improves speech production and fluency (*Specific Aim 1a*). Results from the dynamic time warping analysis provide mild support for improved temporal alignment (termed *entrainment*, for the purpose of the current study) in the context of an audiovisual model for speakers with nonfluent aphasia (*Specific Aim 1a*). Although cortical tracking or electrophysiological methods were not explicitly tested in the current study, neurophysiological predictors of improved performance with *in-phase* tACS from this proof-of-concept study provide additional information regarding potential neural mechanisms that facilitate such entrainment (*Specific Aims 2a + b*). In the sections that follow, each of these aims and the associated findings are discussed in greater detail with respect to existing literature. Largely, the results are described within the context of rhythm and entrainment. Entrainment will be re-visited from a broad sense and discussed further at the level of speech entrainment and ultimately, neuronal entrainment. Given that rhythm is a critical component of both the behavioral paradigm as well as the noninvasive brain stimulation that were used in the current study, rhythm is discussed extensively and embedded into the many levels of entrainment that are of interest for this study.

4.3 'Entrainment' : Considerations from behavioral, neurophysiological and theoretical perspectives

In this section, the concept of entrainment will be reviewed and discussed in the context of behavioral outcomes from the current study to address how behavioral (linguistic and temporal-acoustic results; *Specific Aims 1a + b*) may elucidate underlying

mechanisms of tACS at the neuronal level (oscillatory entrainment). In particular, rhythm will be considered as a necessary ingredient for entrainment and discussed in the context of the current study and rehabilitation paradigms, more broadly. Later, the underlying neurophysiological mechanisms that were shown to support a tACS-related 'boost' will be explored in greater detail.

Broadly, entrainment refers to the integration of information across sensory modalities. From the classic pendulum clock example proposed by Dutch physicist Huygens 1893) in the 21st century, both speech specific (Fridriksson et al., 2012) and otherwise (i.e. musical entrainment, Large, 2000; Phillips-Silver et al., 2010), it is well-recognized that this process involves the integration between independent systems and evidently occurs not just in human behavior but in a variety of different scales of time and space. It is understood that rhythmic brain activity interacts with rhythms in internal and external environments through neuronal entrainment (Lakatos, Gross, & Thut, 2019). Examples of entrainment have been presented in both biological and mechanical systems and from the neuronal level ('pacemaker' cells in the heart) to more global biological systems (evidenced by the 'resetting' of internal clocks by sunlight) (Clayton, 2012). Across each of these examples, entrainment describes different phenomena in relation to the synchronization between two or more signals (Clayton, 2012).

In communication, entrainment may refer to synchrony at different hierarchical levels: 1) conversational; 2) speech; 3) coordinated rhythmic movement in response to an external stimulus and 4) cortical entrainment or cortical tracking (Quique, 2020). Importantly, each level defines entrainment in the context of the internal and external systems that are at play. For example, conversational entrainment is considered to be

alignment that takes place between two partners involved in conversation (Borrie, Lubold, & Pon-Barry, 2015) while speech entrainment is the *unison* production of language (i.e. simultaneous productions by a clinician and patient). Another unison production, rhythmic movement, refers to actions that are produced in response to an external stimulus. This includes clapping, dancing, or walking. These types of actions have been considered in the realm of musical entrainment (Phillips-Silver et al., 2010) Finally, cortical entrainment (or tracking) refers to the coupling between low frequency brain responses and speech rhythm as reflected by the speech envelope (Ding & Simon, 2014). In the interest of the current study, entrainment at the level of speech and entrainment at the cortical level are of particular interest. Cortical entrainment will be discussed in greater detail in *Section 4.5.1: Cortical Tracking* of the this chapter.

4.3.1 Rhythmicity for Entrainment

The nature of speech entrainment, particularly as a rehabilitation paradigm for nonfluent aphasia, has been investigated primarily by Fridriksson and colleagues (Bonilha et al., 2019; Fridriksson et al., 2012; Johnson et al., 2021) with an increasing number of investigations shedding light on this type of entrainment in recent years (Kershenbaum, Nicholas, Hunsaker, & Zipse, 2019b; Quique et al., 2022). It is important, however, to consider and discuss speech entrainment from a perspective that considers all possible active ingredients, in particular, rhythm; prior to discussing entrainment purely in the context of a paradigm for disordered speech and language and how the current results further support the use of this paradigm in the presence of rhythmic neuromodulation.

The underlying nature of entrainment and the rhythmicity of human speech likely plays an important role in the entrainment that is demonstrated in the current study. One consideration of entrainment comes from Lakatos and colleagues (2019), who explored entrainment from a theoretical account and proposed a new account of the role of neuronal entrainment. In their Unified Theory of Entrainment, Lakatos and colleagues posit that spatiotemporal coordination results from rhythmic responsiveness to a perceived rhythmic signal: 1) rhythmic features need to be detected, 2) integrated (sensory information and motor production integrate to enable adjustment of motor output based on rhythmic input, and 3) produced (Lakatos et al., 2019; Wilson & Wilson, 2005). The nature of rhythm in the context of clinical approaches for nonfluent aphasia is not new and has been used extensively to improve language fluency for speakers with nonfluent aphasia for decades. Speech entrainment, as described in the Introduction (see *Section 1.13*) is thought to capitalize on errorless learning, in support of Hebbian learning, and more recent research suggests the active role of rhythm as a primary ingredient for speech entrainment (Quique et al., 2022). While rhythm has been suggested to be a primary ingredient in the entrainment process, the precise role of rhythmic features is not well understood. In a context specific to speech entrainment, this process has been described hierarchically as: 1) listening; 2) repeating; 3) entraining (choral reading); 4) and independently producing.

Human speech is rhythmic and has been conceptualized as such in terms of duration, spacing between elements and relative intensity (alteration of stressed and unstressed syllables) (Kotz, Ravignani, & Fitch, 2018). English, the language used in the current study, is also stress-timed language (Pike, 1945). The rhythm of speech is thought

to bind events into organized sequences under a superordinate prosodic cycle to coordinate multiple movements, timings, and processes that are necessary for speech production and perception. Speech processing is thought to rely on rhythmic activity (Henry, Herrmann, & Obleser, 2014; Kayser, Ng, & Schroeder, 2012; Neuling et al., 2012; Strauß, 2015). Empirical studies of auditory perception also suggest rhythm plays a role as auditory cortical delta-entrainment interacts with oscillatory power in multiple frontoparietal networks (Keitel, Ince, Gross, & Kayser, 2017). Finally, the rhythm of speech production and processing have been shown to occur at lower frequencies (< 20 Hz; Giraud & Poeppel, 2012).

It is seems likely that the audiovisual speech entrainment paradigm heavily relies on rhythm as an active ingredient. Furthermore, another component that may have contributed to the improved performance during the in-phase stimulation condition was the frequency at which the brain was stimulated (7 Hz; a frequency that is thought to facilitate speech processing; Ding & Simon, 2014).

4.3.2 The Role of Cognitive-Linguistic Domains and Learning in Entrainment

Empirical data, such as that from Phillips-Silver and colleagues (2010) suggest that simultaneous speech production is based on rhythm, rhythm that is either derived from the rhythmic nature of human speech or from another type of rhythm (i.e. metronomic beats), and that regardless of the source of rhythm, these features underlie speech entrainment and have a facilitatory effect on sentence learning. A growing body of literature has aimed to further investigate the faciliatory effects of rhythm, out of which the following two hypotheses have emerged: 1) unison production of scripted sentences enables people with aphasia to align word stress, which facilitates lexical

retrieval (Kimelman & Mcneil, 1987; Soto-Faraco et al., 2001) and 2) the unison production of scripted sentences enhances sentence memorization via chunking (Purnell-Webb & Speelman, 2008; Stahl et al., 2011). In terms of supporting lexical retrieval, some have considered the fact that rhythmic properties (i.e. word stress, retrieval of lexical/phonological representations and encoding of such representations) are related to lexical access and that the innate rhythmic properties of speech may induce an entrainment effect secondary to the hierarchical organization of temporally coordinated prosodic units (Cummins & Port, 1998). This can be particularly helpful in the context of language comprehension and production where emphatic stress, for example, may amplify processes to support lexical access in people with aphasia.

The second hypothesis that suggests sentence memorization occurs via 'chunking' or 'grouping' states that when speech is produced in unison, this results in regular, rhythmic patterns that can facilitate memorization (see Gobert et al., 2001)for a review specific to memory). As mentioned above, work from Cummins and Port (1998) suggests entrainment to beats is possible because the metronomic beats provide a rhythmic structure over which entrainment can occur. In a subsequent investigation, words and sentences were produced with regular prosodic patterns and results suggest that speech entrainment to beats was also possible (Port, 2003). During tasks such as these, the cognitive load for language production is assumed to be low due to multiple repetitions that do not require lexical access and the efficiency that rhythm provides for coordinating structures in motor sequences.

While this study investigated unison sentence production, rather than lexical learning, perhaps the rhythmicity of the speech entrainment stimuli lessened the cognitive

load and elicited lexical production. It does seems likely, especially in consideration of the literature discussed above, that the nature of the behavioral task (an audiovisual tasks that relies on the processing and production of human speech) paired with a rhythmic neuromodulation technique may have resulted in the improved entrainment that was observed during the *in-phase* stimulation across linguistic and temporal behavioral variables. Such conclusions cannot be deduced from the current study as cognitive-linguistic measures were not acquired nor considered; but it seems reasonable to posit the involvement of such factors.

4.3.3 Clinical Applications of Rhythm and Entrainment

The rhythm of human speech has been considered to be an active ingredient in rehabilitative paradigms such as choral reading, Melodic Intonation Therapy, and in the context of the current study, speech entrainment. Importantly, entrainment and naturally, rhythm, have been identified as key ingredients in well-established rehabilitation paradigms such as script training, which is strongly related to the nature of the behavioral paradigm in the current study (Quique et al., 2022). Rhythm has also shown to be beneficial for language learning in people with aphasia (Kershenbaum et al., 2019b; Quique, 2020; Quique et al., 2022; Stahl, Henseler, Turner, Geyer, & Kotz, 2013; Stahl et al., 2011; Zipse, Worek, Guarino, & Shuattuck-Hufnagel, 2014) and for speech production in the presence of motor speech disorders such as dysarthria and apraxia of speech (Brendel & Ziegler, 2008; Dworkin, Arkarian, & Johns, 1988; Wambaugh & Martinez, 2000). For example, Zipse et al. (2014) investigated the discrimination and production of rhythmic patterns in post-stroke aphasia and found patients with aphasia performed significantly worse than the control group on five out of six tasks. These data

suggested that patients with aphasia had more difficult accurately discriminating between rhythm patterns and showed more variability when tapping to a rhythm from memory. The only task where patients with aphasia did not differ from control participants was a task where they were asked to tap along (entrain). Authors suggest that these findings may suggest that entrainment to rhythm is at least partially preserved and suggests a potential use of entrainment to rhythmic beats for people with aphasia.

To expand upon these findings, Kershenbaum and colleagues investigated the role of rhythm during a language task by adding text to metronomic beats (2019). For patients with aphasia, entraining to linguistic and rhythmic information improved learning and memorization of sentences as demonstrated by an improved ability to learn from the use of speech entrainment, singing/speaking along, as compared to solo productions. Such findings are aligned with earlier investigations from Stahl and colleagues (2011, 2018) and suggest that patients with aphasia can entrain to rhythmic beats and encourage the use of rhythm in rehabilitation for this population. With respect to the results from the current study that suggest patients were more temporally aligned (i.e. 'entrained') during the *in-phase* stimulation condition versus the *sham* or *anti-phase* condition, it seems likely that, at least for some patients, the application of HD-tACs provided a 'boost', above and beyond what the traditional speech entrainment paradigm yields.

Feenaughty and colleagues (2021) recently examined results from a behavioral speech entrainment study and found that patients with nonfluent aphasia demonstrated speech timing changes, consistent with improved fluency. Speech timing was considered in terms of a number of acoustic measures of speech timing (i.e. total number of syllables, speech rate, articulatory rate, silent pause frequency, and duration). The

primary finding from Feenaughty and colleagues was evidenced by pause adjustments in the group of participants with nonfluent aphasia during the speech entrainment task. Such findings align well with findings from the current study as well as other studies that have identified a greater number of syllables and greater 'synchrony' during a unison production task with beat-based timing structure in people with aphasia as compared to conversational speech and suggests a role for rhythm in the success of people with nonfluent aphasia during unison productions.

4.4 Speech Entrainment

4.4.1 Theoretical Implications for Speech Entrainment

Although speech entrainment has been demonstrated to be an effective tool to elicit fluent speech in people with nonfluent aphasia, the exact ingredients of speech entrainment as a clinical paradigm remain understudied. However, given the evidence above, it is likely that the role of rhythm plays an active role in successful entrainment. This has been shown most recently by groups who have explicitly investigated rhythmic versus conversational speech in entrainment paradigms (Kershenbaum et al., 2019b; Quique et al., 2022). Results from the current study support this notion, as evidenced by the improved accuracy and fluency of participant productions in the context of speech entrainment plus HD-tACS.

As discussed in Chapter 1 (*Section 11.1*) the efference copy is hypothesized to be an important mechanisms for speech entrainment success in people with aphasia. The hypotheses as to why speech entrainment elicits fluent speech in speakers with nonfluent aphasia served as a primary motivation for the current study; both from the theoretical perspective (the suggested role of the efference copy in entrainment; (Fridriksson et al.,

2015; Fridriksson et al., 2012), as well as the neurophysiological perspective, in terms of the hypothesized neural underpinnings (Johnson et al., 2021). The two hypotheses that are proposed by Fridriksson and colleagues regarding successful entrainment are: 1) speech entrainment works at the somatosensory motor circuit level, a lower level system that supports the production of individual phonemes by providing multisensorial phonemic support to enhance speech production and 2) speech entrainment works as a higher syllable level system by providing auditory visual syllabic information that can be mapped onto articulation. For example, the first hypothesis suggests that the visual and auditory perceptual system that is associated with phonemic proprioception facilitates speech production.

4.4.2 Proposed Mechanisms of Speech Entrainment

While speech production models certainly were not constructed with the SE paradigm in mind, the mechanisms outlined by theoretical speech production models may provide insight into the mechanisms of SE that induce fluent speech. Prior to discussing the proposed role of SE in speech production, it is necessary to discuss theoretical models of speech production in greater detail. These models are discussed briefly to describe the location and function of the efference copy in Chapter 1 (*Section 1.3: The Efference Copy)*. Here, the focus is on the most recently proposed speech production model, the HSFC (Hickok, 2014). As previously discussed, the HSFC is extended to include two hierarchically organized levels: low level (somatosensory) processing in the anterior supramarginal gyrus and motor cortex and high level (auditory-motor) circuit in IFG*po*, superior temporal sulcus, superior temporal gyrus, and area *Spt*, a region located at the junction of the temporal and parietal lobes. The coordination of motor programs of

speech in anterior (Broca's area) and auditory targets in posterior (superior temporal gyrus and superior temporal sulcus) are supported by area *Spt*. The auditory-motor circuit is thought to play a role in auditory to articulation transformations.

Because some patients with NFA are able to produce fluent speech under the conditions of speech entrainment, it seems lower-level motor commands (primary motor cortex and precentral sulcus) are relatively intact. One etiology of nonfluent speech is thought be damage to motor syllable programs in the auditory-motor circuit in IFG*po*. IFG*po* is thought to be a crucial area for the formation of speech syllable programs (Hierarchical State Feedback Control Model, Hickok, 2012; see *Figure 1.3*). These programs are expected to guide internal monitoring prior to programming motor actions in primary and supplementary motor areas. Damage to IFG*po*, therefore, prohibits access to lower-level motor commands, which means that the system cannot successfully utilize feedforward error correction mechanisms. It is possible that SE facilitates fluent speech production at a lower-level somatosensory motor circuit, as hypothesized by the HSFC model, but seems unlikely that this is the case as IFG*po* is not included in this circuit. Instead, it seems more likely that SE is effective because it affects higher-level cortical auditory-motor circuits of processing. More specifically, it is hypothesized that audiovisual stimuli activate audiovisual syllable targets in the *p*MTG and audiovisual targets are integrated via area *Spt*. (Fridriksson et al., 2015; Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Hickok, Okada, & Serences, 2009; Isenberg, Vaden, Saberi, Muftuler, & Hickok, 2012; Pa & Hickok, 2008; Poeppel et al., 2012; Venezia et al., 2016; see *Figure 1.2*).

4.4.3 Multisensory stimuli may facilitate improved processing via the efference copy

Although the exact nature of the external gaiting mechanism is not completely clear, there are a number of hypotheses that may explain how and why this particular mechanism is crucial to successful entrainment. In the context of audiovisual speech, theoretical models of audiovisual speech perception suggest a multisensory hypothesis that incorporates the efference copy (Skipper et al., 2005, 2007; Wassenhove, Grant, & Poeppel, 2004). This multisensory hypothesis suggests that early multisensory (audiovisual) speech representations are derived from sound and facial patterns. This sensory information is mapped onto motor commands and is employed during speech production. The activated motor commands are then able to predict acoustic and somatosensory consequences of speech production by way of an efference copy at a relatively low-level. This concept is consistent with previous work (von Holst & Mittelstaedt, 1950).

A recent study by Skipper and colleagues (Skipper & Hasson, 2017) aimed to determine the adaptations that allow humans to produce and perceive speech in 'natural' audiovisual speech conditions. In the study, researchers investigated the cortical thickness, white matter structural connectivity and task-free functional connectivity of two seed regions (one anterior primary/pre-motor region and one posterior auditory region) to determine if connectivity between the central sulcus (CS) and transverse temporal gyrus (TTG) was implicated during audiovisual speech perception and language comprehension. The authors also investigated the extent to which this neural circuit may inform the role of the efference copy in speech production.

Results suggest that the central sulcus (or primary motor and somatosensory cortex) and transverse temporal gyrus (or primary auditory cortex) constitute a 'speech core.' These two regions are not only functionally connected at rest, but demonstrate coherence during natural audiovisual speech perception tasks and coactivate across a variety of linguistic tasks. The authors posit that these areas constitute an interface for the exchange of articulatory and acoustic information. These findings are consistent with the idea that sensory consequences that are activated by the efference copy in the CS-TTG are relatively low-level. It is further hypothesized by Skipper et al. that this circuit develops early on and therefore, can act as a foundational learning mechanism for speech development and, later, production. This hypothesis would suggest that this circuit and the underlying mechanisms (i.e. efference copy), allow for maintenance and error-adjustment during speech production. Importantly, the authors highlight that while this circuit is considered in some speech production models (Guenther et al., 2006; Hickok, 2012), it is implicated to a lesser degree in contemporary neurobiological models of speech perception and language comprehension (i.e. the dual stream model; Hickok & Poeppel, 2007b).

Fridriksson and colleagues (2015; 2012) have hypothesized a similar role for the efference copy in the context of an audiovisual model of speech; primarily, the speech entrainment task. Based on prior evidence, it seems that there is something specific about an audiovisual stimulus that induces fluent speech. More specifically, recruitment of the visual stream may induce speech fluency in patients with nonfluent aphasia. As described above, speech entrainment is hypothesized to work because it provides an external model (efference copy) that activates visual speech units in the *p*MTG. In turn, theses visual

speech units activate the lower-level motor circuit that allows for fluent speech production. Fridriksson and colleagues have previously hypothesized that one cause of nonfluent speech in aphasia may be impaired motor planning and a degraded or absent efference copy, secondary to damage to anterior left-hemisphere speech regions. The idea that the efference model can activate visual units in posterior regions (*p*MTG) and consequently activate lower-level motor circuits, is similar to accounts that posit a role for this same route in typical language development. Due to the reliance on the visual aspects of speech in an audiovisual model, congenitally blind children typically demonstrate delayed development of speech articulation.

In sum, repeated practice with SE is thought to: 1) activate auditory-motor circuits and 2) strengthen the efference copy. As discussed in *Section 1.3: Efference Copy*, when the efference copy is impaired, the speech production mechanism cannot be implemented or initiated. To repair a damaged efference copy, SE provides an external model (efference copy) to compensate for damage to the internal online model and in turn, promotes fluent speech (Fridriksson et al., 2012; Hickok et al., 2011). To this end, speech entrainment response may be indicative of the integrity of the efference copy (Feenaughty et al., 2017).

Although Fridriksson and colleagues have proposed two possible explanations regarding the benefits of speech entrainment, the underlying mechanisms of are still not entirely clear. Neither of the aforementioned hypothesized mechanisms account for the simultaneous production of speech; a feature that is critical for speech entrainment (as opposed to tasks such as repetition with visual and auditory feedback. Despite this, the evidence that an audiovisual speech entrainment paradigm acts as an external efference

copy to compensate for stroke-induced damage in people with nonfluent aphasia, served as a primary motivation to include this task as the behavioral paradigm in the current study. In the sections that follow, neural bases and potential theoretical implications are discussed to elucidate additional reasons as to why the application of HD-tACS may have elicited behavioral gains above and beyond what has been shown with speech entrainment alone.

4.5 The Mechanisms of Entrainment: Contextualizing the success of tACS

Above, the underlying mechanisms of speech entrainment are discussed in the context of theoretical models. More recently, however, work from the same group considers neurophysiological implications of successful entrainment (Bonilha et al., 2019; Johnson et al., 2021). Results from the current study are seemingly paradoxical: "tACS boost" is predicted by preservation of inferior temporal gyrus as well as reduced baseline anterior-posterior connectivity. Results from the lesion-symptom-mapping analysis is, in part, consistent with the hypothesis for *Specific Aim 2a.* It was hypothesized that greater proportion of intact anterior, dorsal regions (i.e. IFG*po*) and posterior, ventral regions (i.e. *p*MTG) would result in improved entrainment during the *in-phase* tACS. There were no associations with anterior, or other posterior cortical regions and behavioral outcomes in the present study. This may be due to the current sample size, or may be due to a limited amount of variance in the current sample, as many participants had similar lesion profiles given the inclusion criteria.

Previous results from Bonilha and colleagues suggest that preservation of the ventral stream elicits better entrainment success (2019). For example, after controlling for lesion size, significant correlations between damage to specific ROIs and patient

performance in the speech entrainment task, as compared to spontaneous speech, were identified. Namely, preservation of the inferior temporal gyrus (and other ventral stream regions of interest) led to more fluent speech during the entrainment paradigm ($r = -0.35$; $p = 0.01$; see (Bonilha et al., 2019, *Table 1* for additional details). Other work suggests a similar role for residual posterior regions in a paradigm such as speech entrainment. Johnson and colleagues, for example, propose that the speech entrainment model provides an external efference copy by recruiting posterior regions to induce more fluent speech production (2021). Not only is this a consistent finding with speech entrainment research, but it also aligns well with other studies that have examined the role of the inferior temporal cortex for coding synergistic auditory information (Bourguignon, Baart, Kapnoula, & Molinaro, 2020; Park et al., 2018).

Although the preservation of the inferior temporal gyrus was associated with a better behavioral response to tACS in the present study, results from the connectometric data suggest that patients who demonstrated better behavioral performance during the *in-phase* stimulation, had *poorer* coherence (as measured by rsfMRI) between anterior and posterior regions prior to stimulation (e.g. inferior frontal gyrus to middle temporal gyrus; $z = -2.51$). It can be hypothesized that an additional benefit of tACS was evident in participants for whom the benefits of the behavioral paradigm alone were not enough to elicit entrainment to the audiovisual model. It is also likely that the "tACS boost" that was demonstrated by some participants, may be due to the etiology of their deficit. To relate these findings to existing hypotheses of successful entrainment in audiovisual speech entrainment paradigms (*Section 4.4*), it is likely that participants with nonfluent aphasia with greatest damage to the theoreticized 'efference copy' benefitted most from

the *in-phase* stimulation. This is evidenced by the degree to which participants performed during the stimulation block of the *in-phase* condition; but also as observed by the changes from the stimulation to washout periods. It is clear that application of 1mA of HD-tACS at 7Hz boosted performance during the *in-phase* stimulation condition; but these effects do not persist into the washout phase to the same extent.

As described above, the Hierarchical State Feedback Control (HSFC) model suggests that speech production relies on the coordination between posterior temporal (*p*MTG and *p*STG) and anterior frontal (IFG *pars opercularis*) language regions. This suggests anterior-posterior connectivity is necessary, perhaps even critical, to recruit the efference copy for speech due to its role in speech motor programming and the role of intact feedforward and feedback projections (Hickok, 2012a; Johnson et al., 2021) and that *in-phase* HD-tACS may serve as a modulatory source to strengthen the damaged efference copy. From the group level analyses, it seems reasonable that those with more severe damage to anterior and posterior connections, and subsequently, a more profoundly affected efference copy, benefitted most from the presence of the external efference copy (i.e. audiovisual speech entrainment model) when it was *paired* when with *in-phase* tACS. Perhaps the presence of an audiovisual model *and* the rhythm of an external neuromodulatory stimulus in the context of greater physiological damage resulted in greater behavioral gains by increasing neural synchrony and eliciting plasticity is a manner that is not facilitated by administration of the behavioral paradigm in isolation. It is also likely, due to the multifactorial nature of nonfluent aphasia, that nonfluent aphasia results from different etiologies (Feenaughty et al., 2017; Gordon & Clough, 2020; Gordon, 1998; Nozari & Faroqi-Shah, 2017; see Chapter 1: *Section 10.1*)

and therefore, tACS may assist some of these patients (i.e. those with reduced coherence). This is discussed in greater detail in the sections that follow.

4.6 Rhythmicity from a Neuronal Perspective: Fundamental and defining features of neuronal activity

In the sections that follow, the rhythmic nature of tACS and intrinsic neural oscillations will be considered. The current study relied on the natural rhythmic structure of language provided via audiovisual stimuli and an external source of rhythmic stimulation (HD-tACS). By relying on a task that inherently relies on the rhythm of human speech and is thought to serve as an external gaiting mechanism, and applying an external modulatory source (i.e. tACS), it was hypothesized that tACS at 7 Hz would result in increased neural synchrony and that this would be reflected in that improved behavioral outcomes during stimulation. The current work administered HD-tACS at a frequency of 7 Hz. As described in Chapter 1 (*Section 1.14.3*), this particular frequency was selected due to theoretical accounts (Giraud & Poeppel, 2012; Peelle & Davis, 2012) and existing empirical evidence that supports entrainment at these frequencies is important for communication through speech (Ding et al., 2017; Doelling, Arnal, Ghitza, & Poeppel, 2014; Ghitza, 2012, 2014). Furthermore, empirical work suggests that when rhythms of motor production and sensory perception are matched in intrinsic frequencies, coupling is facilitated (Giraud & Poeppel, 2012).

Neuronal oscillations reflect a rhythmic fluctuation of neuronal excitability (between high and low frequency states). Although the exact nature of oscillations remains debated, the literature suggests that oscillations are instrumental rather than incidental to brain operations (Buzsaki, Gyorgy, Draguhn, 2004; Fujisawa, Buzsaki,

2011). When sensory inputs are rhythmic, evidence suggests that the brain aligns neuronal oscillations at a frequency that is most closely matched to the temporal structures of the incoming stimuli (Lakatos et al., 2019). As a result, internally, there is a constant oscillatory phase alignment to the external, rhythmic stimulus by way of stabilization and adjustment. Therefore, many have suggested that intrinsic brain oscillations might synchronize (or entrain) with external rhythms. In a recent review, Lakatos and colleagues go as far as to say that such entrainment might facilitate sensory processing of further input that occurs in-sync with this rhythm (Lakatos et al., 2019). Optimal processing is expected to occur when high-excitability oscillatory phases coincide with task-relevant sensory input and consequently, this input is thought to undergo optimal processing (Haegens & Zion Golumbic, 2018; Large & Jones, 1990; Schroeder et al., 2008), either by way of automatic, bottom-up processing or mechanisms of temporal prediction (Nobre, Correa, & Coull, 2007).

4.6.1 Cortical Tracking

Above (*Section 4.3*), cortical tracking is named as a fourth type of entrainment. Cortical tracking refers to the coupling of low frequency oscillations and the speech envelope (Ding & Simon, 2014) and reflects the successful alignment of brain responses with rhythmic features that are present in the speech signal. This synergy that is facilitated by oscillatory coupling enables the efficient processing of linguistic features (Peelle & Davis, 2012; Peelle, Gross, & Davis, 2013). Although no measures of cortical tracking were obtained in the current study, it is crucial to consider this level of entrainment to both determine the underlying mechanisms of the behavioral success that was demonstrated in the *in-phase* tACS condition, and to consider future directions to

further illuminate the underlying neural mechanisms of entrainment, both at the neural and linguistic levels. In a recent review, Hamilton and Huth (2020) suggest that cortical tracking may index individual perceptions of speech rhythmic properties in connected sentences and that, therefore, cortical tracking may predict an individual's ability to learn or entrain to sentences. Cortical tracking will be discussed in greater detail in *Future Directions*, but generally speaking, this measure of perception may provide valuable evidence about whether perceiving speech-rhythmic information facilitates scripted sentence learning when enhancing speech rhythmic properties during speech entrainment. Although not explicitly tested in the current study, one explanation for the current results may be found in the cortical tracking that is induced by the application of HD-tACS. For example, speech entrainment may improve anterior-posterior synchrony in an impaired system (secondary to stroke; Johnson et al., 2021) and though not directly assessed in the current study, it is likely that the application of HD-tACS at 7Hz, when paired with the speech entrainment task, may elicit different individual responses due to varying degrees of nonfluent aphasia and the multifaceted nature of the deficit.

It is possible that, as described by Fridriksson and colleagues, the efference copy is supported by the audiovisual speech entrainment model and that perhaps, for some, an adjuvant such as *in-phase* tACS, boosts this effect above and beyond the behavioral effect alone. It also seems likely that due to reduced frontotemporal coherence, some participants may benefit more than others from this adjuvant stimulation. The precise nature of the mechanism of stimulation was not examined in the current study. It is crucial to consider that although the effects were not significant at the group level, participants with compromised anterior-posterior connectivity do seem to benefit from

cortical synchronization secondary to tACS. The heterogeneity of not only the nature of nonfluent aphasia, but also the variance in lesion size and location, may contribute to the varying effects of stimulation and lack of overall effects at the group level.

4.7 Aphasia as an Oscillopathy

Another potential rationale for the findings from the current study, is due to the *nature* of the clinical disorder that was investigated. As discussed in Chapter 1 (*Section 1.3.3*) aphasia is a network-based disorder, due in large part to the fact that expansive structural and functional networks support language (Corbetta, Siegel, & Shulman, 2018; Julius Fridriksson, Den Ouden, et al., 2018; Hope et al., 2017; Salvalaggio, De Filippo De Grazia, Zorzi, Thiebaut de Schotten, & Corbetta, 2020; Siegel et al., 2016; Stockert et al., 2016). It is evident that frank cortical damage affects overall network connectivity (Cramer, 2008; Kreisel, Bazner, Hennerici, 2006; Nudo, Friel, 1999; Stockert et al., 2016; Witte, Bidmon, Schiene, Redecker, & Hagemann, 2000). Spontaneous amplitude-based connectivity during the resting state is thought to reflect oscillatory amplitude or power-envelope fluctuations and capture the slower aspects of interregional communication (Cox, Schapiro, & Stickgold, 2018).

A stroke, for example, may cause disconnections of cortical regions and interrupt resting state functional connectivity (Zhu et al., 2017). As discussed in *Section 1.14* of Chapter 1, neural oscillations reflect a measure of functional connectivity and overall network organization (Nicolo et al., 2015). In a neurologically intact system, neural oscillations occurring at 7 – 13 Hz are considered to be the primary carriers for phase synchronization at rest (Guggisberg, Honma, Findlay, Dalal, Kirsch, Berger, Nagarajan, 2008; Hillebrand, Barnes, Bosboom, Berendse, & Stam, 2012). Following a stroke,

oscillations deviate from their typical frequencies as they adapt and re-adapt to compensate for disruptions due to the trauma and in this way, decrease the coupling between functional and structural networks (Dubovik, 2012; Nicolo et al., 2015). Disruptions in neural oscillatory function have been associated with neurological deficits and behavioral impairments in the acute and sub-acute phase of stroke recovery (Dubovik, 2012), and has been shown in other clinical pathologies, such as epilepsy (Chiang, Stern, Engel, Haneef, 2015; Zhang et al., 2011).

For patients with aphasia, there are reports of slower oscillatory activity and alterations in signal complexity (Chu, Tanaka, Diaz, Edlow, Wu, Hamalainene, Stufflebeam, Cash, Kramer, 2015; Laaksonen et al., 2013). It is hypothesized that the slowed oscillatory activity indicates dysfunction in otherwise intact brain tissue and such evidence suggests that this may hinder the recovery process. This has been evidenced by recent work in chronic aphasia where poor synchrony is associated with language impairments, even after controlling for damage to structural connectivity (Keator et al., 2021) and success in behavioral language therapy (Johnson et al., 2021). Above, the theoretical accounts of speech entrainment were discussed in great detail. Many of these accounts posit that nonfluent speech in speakers with aphasia results from poor synchrony between critical language regions (Johnson et al., 2021), which aligns with more general findings (not specific to speech language) in the stroke literature that reflect not only slower oscillatory activity, but widespread disconnection and interruption to distal regions after a brain injury.

Plasticity following a traumatic injury such as a stroke is associated with the synchronization of spontaneous neural oscillations between brain areas. This is supported

by empirical evidence that has shown that greater oscillatory synchronization of language regions is linked to improvement in clinical functions (Nicolo et al., 2015) and more specifically, coherent synchrony in alpha and beta frequencies have been associated with post-stroke cognitive and motor recovery (Dubovik, 2012; Petrovic et al., 2017; Westlake, Hinkley, Bucci, Guggisberg, Findlay, Byl, Henry, Nagarajan, 2012). While there is emerging evidence for the role of oscillatory function in post-stroke aphasia, little is known about long-range connectivity patterns that may underpin spared language functions in this population. What is understood, however, is that slow oscillations seem to extend over larger brain regions (Buzsaki, Gyorgy, Draguhn, 2004). This served as a primary motivation for the application of theta band frequencies in the current study. Low frequency brain rhythms assume a role in speech perception (Giraud & Poeppel, 2012) and the mediation of top-down predictions, such as those in entrainment to speech using an audiovisual model (Park et al., 2016). Furthermore, and most importantly in the context of neural synchrony and the neurophysiological underpinnings of speech, this band is thought to traverse larger brain regions, such as anterior to posterior regions of interest (Buzsaki, Gyorgy, Draguhn, 2004; Fujisawa, Buzsaki, 2011).

Based on results from a growing number of studies, including patients with aphasia as well as other degenerative diseases such a primary progressive aphasia, Alzheimer's disease, Huntington's disease and frontotemporal dementia, some aphasic deficits may be the result of impaired oscillatory function. For this reason, some aphasia, subtypes may be considered an 'oscillopathy', or a clinical symptom associated with impaired oscillatory function or deviant synchrony. It is important to note here, that although the nature of neuronal oscillations is discussed here, given the context of the

current study, it is clear that not all types of aphasic symptoms are a result of mis-timed oscillations. The point here is that some subtypes or perhaps even some aspects of language impairments, *may* result from oscillatory dysfunction.

'Oscillopathy' refers to network dysfunction that is hypothesized to be a direct consequence of spatial disintegration of highly organized neuronal networks (Schnitzler & Gross, 2005). Although the cellular pathology leading to network dysfunction is not well understood, measures such as EEG have been used to investigate neuronal oscillations and have revealed causal links between network oscillatory function and systemic behaviors (Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009; Lozano & Lipsman, 2013; Polanía et al., 2012). Similar findings have also been found in clinical pathologies, such as post-stroke (Kawano et al., 2021) and primary progressive aphasia (Kielar, Deschamps, Jokel, & Meltzer, 2018; Kielar, Shah-Basak, Deschamps, Jokel, & Meltzer, 2019). For example, Kewano and colleagues (2021) identified associations between aphasia severity and brain network alterations using an electroencephalographic phase synchrony index and suggest these findings further contribute to the classification of post-stroke aphasia as a network disorder.

Furthermore, as described above and in greater detail in Chapter 1, nonfluent aphasia is multifactorial (Feenaughty et al., 2017; Gordon & Clough, 2020; Nozari & Faroqi-Shah, 2017) and while there are certainly similarities in lesion location for participants with nonfluent aphasia there is substantial heterogeneity. In a recent study, investigating nonfluent primary progressive aphasia (nfaPPA), Mandelli and colleagues (2018) applied graph theory to study network architecture in patients and found less efficient and less robust network in the 'speech and language production network' (left

fronto-insula region). Importantly, network characteristics that were primarily associated with behavior were accounted for through functional rather than structural changes. Although the etiologies of nonfluent post stroke and primary progressive aphasia vary greatly, this finding may shed some light on the biomarkers that are involved with speech production.

4.6.1 The Role of Rhythmic Neuromodulation in Oscillopathies

Rhythmic neuromodulation enables direct perturbation of local brain areas. Given that aphasia has an aspect of a network disorder (Kawano et al., 2021) and that speech entrainment is thought to improve anterior-posterior coherence (Johnson et al., 2021) an external source of rhythmic modulation applied in this proof-of-concept study to capitalize on these theoretically and empirically-based notions to coherence in a clinical population. The effects of entrainment that are demonstrated here, suggest that tACS may predictively align neuronal oscillations to certain phases across distinct brain regions. When neuronal oscillations are predictively aligned to certain phases across distinct brain regions via entrainment, this results in communication through coherence (Fries, 2005; Lakatos et al., 2013). Furthermore, when high excitability phases are matched, sensory information can be effectively bound and information can be transformed across distinct brain regions (Engel & Fries, 2010; Gray & Singer, 1989; Nakayama & Motoyoshi, 2019). On the contrary, in the case of *anti-phase* alternating currents, these phases are mismatched and result in incoherent or *deviant* coherence.

Most recently, Okazaki and colleagues (2021) aimed to treat clinical 'oscillopathies' using rTMS and identified frequency and area-specific phase entrainment of intrinsic oscillations. Results suggest that local phase entrainment may lead to global

phase entrainment of neural oscillators with the same natural frequency in functionally coupled regions. In the context of post stroke aphasia, Shah-Basak and colleagues (2022) identified electrophysiological connectivity markers of preserved language functions and found that connectivity in the left hemisphere of patients with aphasia was greatly reduced compared to healthy controls. Greater connectivity in the alpha band was associated with better naming performance and greater connectivity in both alpha and beta bands was associated with better speech fluency. Results suggest a critical role of coherent activity within the alpha and beta bands for distinct language functions after a stroke. Furthermore, these results provide insights into the electrophysiological connectivity profiles (frequency and spatial topology) that underlie preserved language abilities in people with aphasia.

4.6.2 A Dynamic Systems Perspective

From the perspective of a nonlinear dynamical systems theory (see Chapter 1, *Section 1.14.2*), the degree of entrainment to an oscillatory system to the rhythmic stimulation changes as a function of the stimulation and amplitude (Pikovsky et al., 2001). This relationship is referred to as the 'Arnold Tongue' (Ali et al., 2013); see *Figure 1.6*. For example, in a model evaluating the degree of entrainment by tACS under a comprehensive array of stimulation conditions, tACS matched to the natural frequency was most efficient in entraining network activity at the lowest amplitude. When considering the relationship between entrainment and amplitude, if the stimulation amplitude is low, only rhythms close to the natural frequency can entrain the system. As stimulation amplitude increases, the system is entrained to a wider range of stimulation frequencies. Therefore, rhythmic stimulation such as rTMS or tACS at a frequency that

matches physiological rhythms is the most efficient to modulate behaviors via the entrainment of task-related oscillations (Klimesch et al., 2003; Sauseng et al., 2009; Romei et al., 2011).

One explanation for why *in-phase* tACS improved behavior for some participants may the fact that neuronal oscillations sample sensory input (in this case, audiovisual speech) and in response, induce rhythmic fluctuations of neuronal oscillations. Simply put, when the brain is presented with a rhythmic input stream (like human speech), it tends to produce a rhythmic response (Lakatos et al., 2019). Although the underlying mechanisms of tACS are not entirely understood, phase entrainment is thought to be established by a sequential phase shift (Lakatos et al., 2019) when there is an effective relationship between the rhythm of the oscillating system and the external force (Lakatos et al., 2019). A phase shift that is induced by a periodic external force, such as the rhythmic stimulation of tACS, at an appropriate intensity and an appropriate frequency, will result in a gradual increase in phase locking across trials (Thut et al., 2011). It is recognized that it does take time for the oscillatory system (here the post-stroke brain) and the external rhythm (the audiovisual speech entrainment stimulus and the rhythmic application of tACS at 7 Hz) to synchronize completely. In the case of strong entrainment to the external rhythm(s), the phase locking at that frequency is sustained. When considering the current study, this effect may explain why behavioral effects were seen for the *in-phase* (and in some cases, the stimulation phase more generally).

By contrast, the more the frequency differs, the more time it will take the two targets to synchronize; in some cases, synchronization may not even occur. When the external force (i.e. audiovisual stimulus and/or tACS) is terminated, the entrained

oscillations slowly revert back to their natural frequencies (Lakatos et al., 2019). Empirical and theoretical data such as these may indicate why the washout period of the current study did not reveal persistent behavioral gains for the *in-phase* stimulation condition, even for participants who demonstrated gains from the *in-phase* stimulation period. It is likely that following the 25 minutes of stimulation, gains did not persist because neural oscillations began to assimilate to their pre-stimulation status, which was likely disrupted due to the presence of the lesion. This will be discussed in greater details in the *Limitations* section, but it seems reasonable to consider that a longer period of stimulation (i.e. greater than the 25 minute administered in the current study), or a greater amplitude of stimulation (i.e. > 1mA), may elicit a greater carryover or generalization effect.

This notion is supported by trends in the data from the current study that favor *in-phase* stimulation as well as empirical evidence that demonstrates a striking match between the rhythmic structures of natural, behaviorally-relevant events (such as human speech) and intrinsic brain oscillations (Schroeder et al., 2008; Zion Golumbic et al., 2013). A recently proposed theoretical framework of entrainment suggests that speech entrainment (typically delivered at a rate of ~5 syllables per second) establishes communication channels between interlocutors who can expect to receive syllables at this particular rate. The predictive nature establishes temporal synchrony between the speaker and listeners' forward models. Consistent with this observation, speech entrainment is most strongly observed at frequencies below 10 Hz and is thought to result from phase resetting of ongoing oscillations in the auditory cortex caused by rapid changes in the speech waveform (i.e. onsets). As a result of phase resetting, neural oscillations may

temporally align to quasi-rhythmic structures in speech (Lakatos et al., 2019). It has also been observed that entrainment to a speech signal is strongest for intelligible and attended speech in healthy controls.

4.7 Clinical Relevance and Future Directions

4.7.1 *Modulating functional connectivity: Clinical Considerations*

Many studies suggest that functional connectivity may be associated with treatment-induced behavioral changes in aphasia (Marcotte et al., 2013; Price, Crinion, & Friston, 2006). By investigating the dynamic changes of functional connectivity in the context of behavioral interventions, and understanding how such changes are mediated by lesion size and location, clinicians and researchers can continue to improve their understanding of the relationships between brain and behavior. In the context of speech-language pathology, an improved understanding may facilitate rehabilitative efforts contributing to improved patient outcomes and quality life. Considerations of how we can apply external methods to modulate neural synchrony with adjuvants such as HD-tACS, in conjunction with traditional behavioral speech and language, may offer rehabilitative advances and better outcomes for this population.

In a clinic setting, the implementation of speech entrainment as a behavioral paradigm is feasible and potentially offers an alternative for typical service delivery. It can be speculated that a computerized therapy model like speech entrainment (discussed in greater detail in Chapter 1, *Section 1.13 Speech Entrainment*) not only allows participants to practice their speech at home and in the absence of a speech-language pathologist but can be personalized for personally relevant and functional goals, thereby improving salience and accessibility to care. Individualized scripts can be created to

encourage patients to supplement their speech with entrainment, either fully or in part, to improve fluency. In this way, patients can practice for longer than would typically be reimbursed in the clinical setting and reimbursed visits could be prioritized for adjuvant approaches that patients may not be able to implement at home independently. For example, to capitalize on results from the current study, clinic sessions could be used to apply NIBS in the context of the SLT while the patient relies on home practice to continue the treatment.

From the perspective of an impairment-based approach, clinicians may adapt speech entrainment scripts to address specific linguistic impairments (i.e. syntactic structure). However, most relevant in the context of the current study is the idea that pairing an adjuvant like noninvasive brain stimulation may improve the effectiveness and efficiency of rehabilitation.

It is clear that noninvasive brain stimulation is an effective adjuvant to aphasia therapy (Fridriksson et al., 2018). What is not clear, however, is how and when NIBS will be successfully integrated into clinical practice. In a recent study, SLPs indicated that they are receptive to the use of NIBS in clinical practice, but there are a number of obstacles that prohibit an immediate translational approach (Keator et al., 2020). The first being the need for a large Phase III trial to determine efficacy. Recent work in the scope of implementation science has begun to address the obstacle of neuromodulation in the clinic. Keator and colleagues administered a survey in 2019 to determine the extent to which SLPs would need to see behavioral improvement secondary to noninvasive brain stimulation (transcranial direct current stimulation; tDCS) for them to consider implementing this tool into practice. Despite realistic hesitations secondary to facility

logistics, insurance and billing procedures, and lack of training, SLPs were largely receptive to the opportunity to apply noninvasive brain stimulation in a clinical setting.

More recently, Duncan and colleagues (2022) followed up with a survey specifically for people with aphasia to gauge their perspectives about noninvasive brain stimulation (tDCS) in a clinical setting. Results from the survey suggest that people with aphasia may be open to receiving tDCS if it would ameliorate their aphasia. There is a general need for work that spans the growing research-clinic gap in the field of speech-pathology, especially in terms of implementation science, translational research and a drive to involve stakeholders at a variety of levels (Palmer & Paterson, 2013).

Finally, it is evident that imaging data, particularly structural and functional scans and the related preprocessing and analytical tools are likely not available for clinicians. Determining the lesion patterns that best support successful entrainment will allow clinicians to at least identify 'potential' candidates for this type of treatment. If neuroimaging data are not at all available, preliminary evaluation outcomes can help clinicians determine 'potential candidacy' for this type of paradigm by recruiting patients with nonfluent aphasia (Fridriksson et al., 2015; Fridriksson et al., 2012).

4.7.2 Future Applications of tACS in aphasia

This proof-of-concept study offers promising results for future investigations of implementing tACS in aphasia. Future investigations may be fueled by a myriad of unanswered questions regarding not only this approach, but the number of applications for aphasia and other clinical disorders. For example, in the current study behavioral outcomes measures were collected to determine if tACS is beneficial for people with

aphasia. This was an important initial step; however, it will be crucial to consider the underlying neural mechanisms of this modulatory source.

One initial next step may be to take the current experimental design and apply it to a larger cohort of participants with aphasia who meet the inclusion criteria. A power analysis suggests that at least 37 participants are necessary to show medium effect sizes (f = 0.3; see *Figure 3.7*). An increased sample size likely ameliorate the issue of the nonsignificant results presented here.

A second consideration would be to consider adding an electrophysiological measure, such as electroencephalography (EEG) or magnetoencephalography (MEG) to provide information regarding neural coherence and how these measures change in each stimulation condition. EEG or MEG could be used to interact with the ongoing brain activity and guide the transcranial stimulation (Liu et al., 2018). EEG, for example, contributes information about synchronized activity between networks by measuring oscillatory changes with a high temporal resolution and offers information about the frequency ranges of these oscillations. This would inform our understanding of the network connectivity dynamics in chronic aphasia and how such dynamics are modulated during stimulation. Additionally, this would also help to elucidate underlying factors (intrinsic and extrinsic) that may impact an individuals' response to tACS.

It is also worthwhile to consider how the effect of tACS compares to that of other neuromodulatory methods, such as transcranial direct current stimulation (tDCS), which has been shown to improve language when paired with a myriad of behavioral interventions in people who have aphasia. An important consideration prior to moving forward with any type of clinical trial would be to determine if either of these (or other)

noninvasive brain stimulation methods demonstrate an advantage, in what capacity they show the greatest benefit and for whom these methods are most effective.

A final possibility, and certainly the most invasive, would be to replicate the hypothesis that disrupted anterior-posterior connectivity yields nonfluent speech, with the use of electrocorticography (ECoG). This approach would require invasive stimulation, but would ultimately serve as a springboard to more extensive investigations of how tACS and other stimulations may be applied to modulate behavior. ECoG uses electrodes to record electrical activity from the exposed surface of the brain. Integration of neuromodulatory sources and ECoG offer countless applications, both from a clinical and research perspective, including those related to speech and language (Kojima et al., 2020; Li, Tang, Lu, Wu, & Chang, 2021), and especially when considering technologies such as neuroprostheses (Moses et al., 2021).

In an age of rapidly advancing healthcare technologies, it seems reasonable that brain-computer interfaces (BCIs) or neural prostheses may, at some point, assist with aphasia recovery. BCIs are direct neural interfaces that provide control of external devices via brain signals (Moses et al., 2021). A number of researchers are considering this application to speech and language in clinical populations outside of aphasia (Brumberg, Pitt, Mantie-Kozlowski, & Burnison, 2018; Cooney, Folli, & Coyle, 2018; Rabbani, Milsap, & Crone, 2019), including applications of BCI + ECog (Pailla, Jiang, Dichter, Chang, & Gilja, 2016) and although the application to a disorder like aphasia may be challenging, it is certainly a consideration for the future.

4.8 Limitations

This proof-of-concept study is the first to apply HD-tACS, a noninvasive brain stimulation, in a cohort of participants with aphasia. While this paradigm offers a potential adjuvant to conventional speech language therapies for chronic aphasia, it is acknowledged that there are important clinical translation hurdles to address and importantly, that while this work may have implications for future practice, this is a preliminary study that will offer insight into the effectiveness of HD-tACS and the potential neural mechanisms that support this success.

First and foremost, it is important to recognize the limitations of tACS. While there have been a number of studies that provide ample evidence to support the use of tACS and much of this work has elucidated the underlying mechanism of tACS, there is still much to be learned. This is especially true when considering behavioral outcomes, as was done in the current study. It is crucial to consider that just because the effect of entrainment is observable in behavioral performance or even electrophysiological measures, it does not necessarily mean that it contributes to the specific task that the individual or their brain is performing (Lakatos et al., 2019). As described above, a measures such as EEG may show that entrainment meaningfully modulates some other variable. In this vein, the concept of 'entrainment' continues to be controversial in the literature. However, it is not within the scope of the current work to discuss this at length.

Another limitation of tACS is the presence of a *sham* condition. Many studies cite *sham* stimulation conditions as the 'gold standard.' Despite this, evidence to support a true *sham* condition is not straightforward as perceptual effects of alternating current stimulation vary across individuals and as a result of varying stimulation parameters

which may increase sensation on the scalp, compared to that induced by direct-current stimulation. For example greater sensations tend to be reported during high frequency stimulation (i.e. beta and gamma frequency range) (Turi et al., 2013). Some studies have assessed this by providing subjective evaluations to participants and have found that when blinded to conditions, participants cannot identify the *sham* condition (Ahn et al., 2019; Ergo, de Loof, Debra, Pastötter, & Verguts, 2020; May et al., 2021), nor can they determine whether anterior and posterior regions are stimulated in or out of phase from each other (Kleinert, Szymanski, & Müller, 2017). Other reviews of tACS suggest there is an absence of somatosensory sensations during tACS which allows for easy control conditions (Herrmann et al., 2013). Although there was no evidence to support that the patients nor the administering speech-language pathologist were able to determine the difference between *sham* and stimulation conditions in the current study, this remains a limitation and consideration for future studies. It is also likely that the amplitude used in the current study (and/or the frequency of stimulation) did not elicit the effects described above and this should be taken into consideration for future work.

Furthermore, as tACS continues to be applied to clinical populations, more work is needed to identify a standardized approach for inclusion criteria, stimulation parameters (amplitude, duration, frequency, number of sessions), montage implementation (i.e. low vs high electrode counts, focality vs intensity) and 'offline' effects of stimulation and underlying mechanisms of action (see Riddle & Frohlich, 2021b for a review). In line with this, it will also be important to consider patient factors that may negatively or positively impact the response to tACS. For example, the presence of motor speech disorders (e.g. apraxia of speech, dysarthria) was not considered an

exclusion criteria in the current study. The impact of these motor speech disorders needs to be considered from both behavioral and neuromodulatory perspectives. Standardizing and optimizing these elements will be important to lead double-blind placebo controlled clinical trials, enhance effect sizes and compare results (Lakatos et al., 2019; Riddle & Frohlich, 2021).

Despite these hurdles, this study offers preliminary data to support future investigations of tACS in aphasia. It is clear that SE improves speech fluency for individuals with nonfluent aphasia, outcomes that are particularly appealing given the limited time and duration of speech and language services that are available to this target population. A tACS related performance 'boost' may suggest additional research related to tACS and aphasia are warranted.

4.9 Summary of Findings and Conclusions

Building upon previous work that suggests speech entrainment induces fluent speech in people with nonfluent aphasia, this proof-of-concept study provides encouraging evidence to support further investigations of tACS in post-stroke aphasia. Preliminary results suggest that a positive response to tACS (i.e., 'tACS boost') may be driven by reduced baseline connectivity between anterior and posterior speech regions. Following a stroke, this connectivity is disrupted, resulting in cognitive-linguistic impairments. Results suggest, that for at least some participants with nonfluent aphasia, application of a rhythmic neuromodulatory source to residual cortical regions in the anterior and posterior regions of the left hemisphere, when paired with a speech entrainment paradigm, elicits improved greater speech output. The numerical behavioral results from this study, even where statistically nonsignificant are encouraging, especially

given the small sample size and novel approach. The results presented here are particularly exciting given that this is the first application of HD-tACS in a population of people with aphasia, and that the preliminary results certainly suggest further investigations with a larger sample of participants with nonfluent aphasia are warranted. It will be worthwhile to proceed with a larger study that further investigates the nature and extent of a ‘tACS boost’.

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APPENDIX A

PAIN AND DISCOMFORT SCREENING

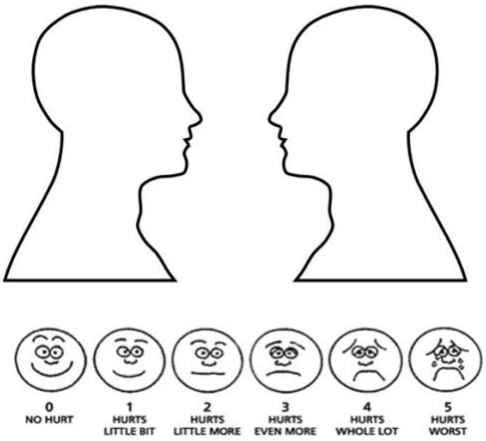
HD-tACS Run Sheet

Participant ID: _____

Date: _____

Condition: _____

Researcher(s): _____



HD-tACS Run Sheet

Participant ID: _____

Date: _____

Condition: _____

Researcher(s): _____

Channel	Electrode	Impedance Pre-Stim	Impedance Post-Stim

Pain 1 2 3 4 5 6 7 8 9 10

Unpleasantness 1 2 3 4 5 6 7 8 9 10

PT GUESS

STIMULATION	SHAM

SLP GUESS

STIMULATION	SHAM

Comments:

APPENDIX B

SCREENING FAILURES

Master Number	**Reason for Screen Fail**
M2072	Scheduling conflicts
M2118	Scheduling conflicts
M2198	Declined to participate
M2199	Illness
M2215	Not vaccinated
M2216	Declined to participate
M2239	Titanium implants 2/2 craniotomy
M2248	MRI not completed
M2253	MRI not completed
M2254	Missing fMRI data
M2260	Scheduling conflicts
M2268	Scheduling conflicts
M2269	Declined to participate

APPENDIX C

SPEECH ENTRAINMENT SCRIPTS

Narrative 1: Christmas

Christmas is a popular holiday all over the world. People have many different traditions to celebrate this holiday. Many people travel far to see their family on this holiday. A common Christmas tradition is decorating a pine tree with ornaments and lights and placing gifts under the tree for loved ones. (Total words = 51).

Narrative 2: Brushing Teeth

I brush my teeth in the morning after I eat breakfast. To brush my teeth, I wet a toothbrush and place a small amount of toothpaste on top of the brush. Then I move the toothbrush back and forth across my teeth. Once I am done brushing, I rinse the toothbrush and my mouth with water. (Total words = 56).

Narrative 3: South Carolina

South Carolina is a state located in the Southeast of the United States. The capital of the state is Columbia. The state dance of South Carolina is the Shag and the state bird is the Carolina Wren. South Carolina is also known for its beautiful beaches, lakes and mountains. (Total Words = 49).

Narrative 4: Days of the Week

A week has seven days in it. Each week begins on Monday and ends on Sunday. There are fifty-two weeks in each year. The most popular days of the week are Saturday and Sunday because many people do not work on these days. The least popular day is Monday since it is the beginning of the week. (Total Words = 57).

Narrative 5: Pizza

Pizza is a popular Italian food. It consists of a baked thin crust with a tomato sauce on top. Pizza also has melted cheese on top. There are many different pizza toppings. Many people put vegetables, extra cheese, or different types of meat on their pizza. Pizza is a favorite food for many people. (Total Words = 54).

Narrative 6: 4th of July

The 4th of July is an American holiday that is celebrated every year. This holiday celebrates when Americans declared their independence from the British a long time ago. Many people celebrate the 4th of July by having a cookout with friends and family. Another common 4th of July activity is watching fireworks. (Total Words = 52).

Narrative 7: The Beatles

The Beatles were a popular English rock band that formed in 1960. The Beatles came to America by plane and landed in New York City in 1964. The Beatles won many music awards and people still listen to their music today. Two of the original members of The Beatles are still living today. (Total Words = 53).

Narrative 8: Grand Canyon

The Grand Canyon is a large canyon found in Arizona in the United States. It is contained within Grand Canyon National Park. The weather at The Grand Canyon is usually dry. The Grand Canyon can reach a depth over a mile. Many people visit The Grand Canyon to enjoy the scenery, raft in the rivers, hike, and run. (Total Words = 58).

Narrative 9: The President

The President of the United States is the head of the government and enforces the laws of the land. The President is elected every four years and the president's term also lasts four years. The White House in Washington, D.C., is the official home and workplace of the president. (Total Words = 49).

Narrative 10: The Beach

Beaches are a type of land found along the ocean or the sea. Many beaches have sand, which are very small pieces of rock. Many people visit beaches in the summertime. Common beach activities are swimming, making a sandcastle, or walking along the shore. People also like to search for seashells along the beach. (Total Words = 54).

Narrative 11: Swimming

Swimming is a fun outdoor activity during the summer, and it is also great exercise. Make sure you have a good kick. Your kick is like a motor on a boat. Keep the kicks small and fast with straight legs. Remember to lay flat to make it easier to move forward. (Total Words = 51).

Narrative 12: Peanut Butter Cookies

Here is a simple recipe for peanut butter cookies. Mix one cup of peanut butter and one cup of sugar together. Put spoonfuls of the mix on a cookie sheet. I like to put a Hershey's kiss on top. After baking, make sure to let the chocolate cool completely so it keeps its shape. (Total Words = 54).

Narrative 13: Gardening

I enjoy gardening. Every spring I buy new flowers, herbs, and trees to plant all around the house. I enjoy picking and eating all the fruits and vegetables from the backyard. This year I am going to plant tomatoes so I can have fresh ones in my salsa. (Total Words = 48).

Narrative 14: Traveling

Most people like to travel. Whether it is within the United States or to a different country, it is nice to get away from work. Some people prefer to relax on vacation. Others like to make an adventure out of their trip and explore somewhere new. Where do you like to travel? (Total Words = 52).

Narrative 15: Gold Rush

During the California gold rush, families traveled by covered wagons and ships to California. The forty-niners spent long days panning for gold. They filled pans with sand and water from streams and shook them in a circular motion. The gold sank to the bottom of the pan while dirt fell out. (Total Words = 51).

Narrative 16: Knitting

Knitting is a hobby enjoyed by many people. It takes some practice at first, but many knitters become very good. It can be useful to make your own scarves, hats, and even sweaters for winter. Craft stores carry many different kinds of yarn to choose from. (Total Words = 46).

Narrative 17: Piano

The piano is one of the most played instruments. A piano has 88 keys, 52 white keys and 36 black keys. Three types of pianos are the grand piano, the upright piano, and the electric keyboard. Many famous composers have created beautiful piano music that is well-known around the world. (Total Words = 50).

Narrative 18: University of South Carolina

The University of South Carolina is a large school in Columbia, South Carolina. The mascot of the school is a gamecock. The school colors are garnet and black. A major landmark of the school is the Horseshoe, which contains many historic buildings from as early as 1805. (Total Words = 47).

Narrative 19: Cats

Cats are a four-legged animal that many people have as a pet. Cats can be many different colors such as white, gray, brown, or black. Some cats have spots on their fur or are more than one color. Some people have more than one cat, because they are an easy pet to take care of. (Total Words = 55).

Narrative 20: Hiking

Hiking is a common leisure activity. People wear hiking boots and will go to a local trail to walk and enjoy the scenery. The scenery people enjoy the most while hiking are trees, waterfalls, or tops of mountains. Many people will pack a lunch in a backpack to take with them while hiking to eat and enjoy the scenery. (Total Words = 59).

Narrative 21: Morning Routine

My alarm wakes me up at 7 AM. I get up, take a shower, brush my teeth, and put on clothes for work. Then, I make breakfast and eat. Next, I feed the dog and let it outside to use the restroom. I make sure to pack my laptop, phone, wallet, and keys. (Total Words = 53).

Narrative 22: I Love Lucy

I Love Lucy was a popular TV show in the 1950s. This sitcom was set in Lucy's apartment in New York City where she lived with her singer husband, Ricky Ricardo, and their son, Little Ricky. Lucy is very ambitious and wants to get into show business, but usually ends up getting in trouble. (Total Words = 54).

Narrative 23: Mars

Mars is the fourth planet from the sun. It is small and has a reddish tint. No astronaut has ever visited Mars, but NASA has sent rovers to explore the planet. Because there are polar ice caps that contain water on Mars, some people believe that there may have been life on the planet. (Total Words = 54).

Narrative 24: Giraffes

The giraffe is a mammal native to Africa. Their long legs and necks allow them to eat the leaves off of tall trees that other animals cannot reach. At the Columbia Riverbanks Zoo, you can feed the giraffes. Many children and adults enjoy taking pictures with these gentle animals. (Total Words = 49).

Narrative 25: Three Little Pigs

There is a famous story of three little pigs. One built his house out of straw. The other built his house out of wood. The last pig built his house out of bricks. The big, bad wolf huffed and puffed and blew the first two houses down but could not destroy the brick house. (Total Words = 54).

Narrative 26: Shakespeare

William Shakespeare was a famous poet, playwright, and actor in England during the late 1500s. His most famous play is probably *Romeo and Juliet*. This tragic story is about two young lovers from enemy families. They try to be together against their families' wishes but ultimately die trying. (Total Words = 48).

Narrative 27: Statue of Liberty

The Statue of Liberty is a symbol of freedom that welcomes immigrants into the country. It was originally a gift from France and now stands in New York. The statue is made of copper, but because of a reaction with water and air, it looks green today. (Total Words = 47).

Narrative 28: Home

I live in a house. There is a big kitchen perfect for cooking meals. The dining room is just big enough for my family to sit down and eat together. I like to unwind in the comfy living room. And after a long day at work, I like sleeping in my soft bed. (Total Words = 53).

Narrative 29: Kentucky Derby

The Kentucky Derby is a famous horse race. The race is held on the first Saturday of May each year. The race is often called “the most exciting two minutes in sports”. Many women wear a nice dress and a fancy hat and men wear a suit. A famous drink served at the race is the Mint Julep. (Total Words = 58).

Narrative 30: Shoes

There are many different kinds of shoes. In the summer, most people like to wear sandals or flip flops. In the winter, many people wear boots or sneakers. When running or walking for long distances, it is best to wear shoes with good arch support. When dressing up, many women like to wear high heels. (Total Words = 55).

Narrative 31: The Olympics

The Olympics is a worldwide event that hosts both summer and winter sports competitions. The Olympic games started in Athens, Greece. Today, over 200 countries participate in the games. Thousands of athletes train and compete in the games. Some of

the more popular events are track, swimming, skiing, snowboarding, and ice skating. (Total Words = 52).

Narrative 32: American Idol

American Idol is a popular singing competition and a TV show. People can try out in cities across the country and four judges decide who gets to go to Los Angeles to compete. Every week, contestants perform a song. Viewers can text to vote for their favorite singer. Contestants are eliminated every week until there is one winner. (Total Words = 58).

Narrative 33: Weather

The weather in the Southern United States is usually very pleasant. During the spring, it is warm and sunny. During the summer, it is very hot with frequent thunderstorms. During the fall it is cool, and the leaves change colors. The winter is usually cold and dry, and it rarely snows. (Total Words = 51).

Narrative 34: Advocacy

I have Aphasia. This means I have difficulty with language. Aphasia affects my language, not my intelligence. It is hard for me to understand what people are saying and to find the words to speak my thoughts. Please speak directly to me and give me time to communicate. (Total Words = 48).

Narrative 35: Eggs

I like to eat scrambled eggs for breakfast. I like them because they are fast and easy. To make eggs I get out a pan and melt some butter over medium heat. I crack the eggs into the pan and stir. I like scrambled eggs best, so I stir until they are done. (Total Words = 53).

Narrative 36: Smoky Mountain

Have you been to the Smoky Mountain National Park? It is a great place for a family vacation. When it is warm, people like to camp and hike. In the fall, the leaves change colors and it is the perfect time for bird watching. The Smoky Mountain National Park is the most visited national park. (Total Words = 55).

Narrative 37: Elvis

Elvis Presley is known as the King of Rock and Roll. He lived at Graceland in Memphis Tennessee. Elvis spent more weeks at the top of the charts than any other artist. He also made more than thirty movies. The King died in 1977, but some say he still lives at Graceland. (Total Words = 52).

Narrative 38: MLK

Martin Luther King Jr. was a leader in the Civil Rights Movement. He was active during bus boycotts that ended segregation on public buses. King led the March on Washington where he delivered his famous "I Have a Dream" speech. In 1964, he received the Nobel Peace Prize. He is honored every January. (Total Words = 53).

Narrative 39: Stroke

Stroke is a serious medical condition. A stroke is when blood flow to the brain is disrupted. Blood carries oxygen and nutrients all over the body. Without blood to parts of the brain the tissue dies. Stroke is the leading cause of adult disability in the United States. (Total Words = 48).

Narrative 40: Thanksgiving

Thanksgiving is a popular American holiday. At the end of November many families come together for a big meal and to give thanks. People travel all over the world to see family at Thanksgiving. The most common Thanksgiving dishes are turkey and dressing, cranberry sauce, green bean casserole, and pumpkin pie. (Total Words = 51).

APPENDIX D

NEUROIMAGING DATA ACQUISITION

MRI scanning was performed within two days of language testing. Images were acquired on Siemens 3T scanners that were upgraded from a Trio (12-channel head coil) to a Prisma (20-channel head/neck coil) at the University of South Carolina or at the Medical University of South Carolina. Structural (T1, T2), diffusion tensor imaging, and resting state fMRI scans were acquired. Parameters were as follows:

T1-weighted images: 3D MP-RAGE sequence with 1 mm^3 isotropic voxels, a 256 x 256 matrix size, 256 x 256 FOV, a 9-degree flip angle and 192 slice sequence, TR = 2250 ms, TE = 4.11 ms, TI = 925 ms, echo time = 4.11 ms with parallel imaging (GRAPPA = 2, 80 reference lines).

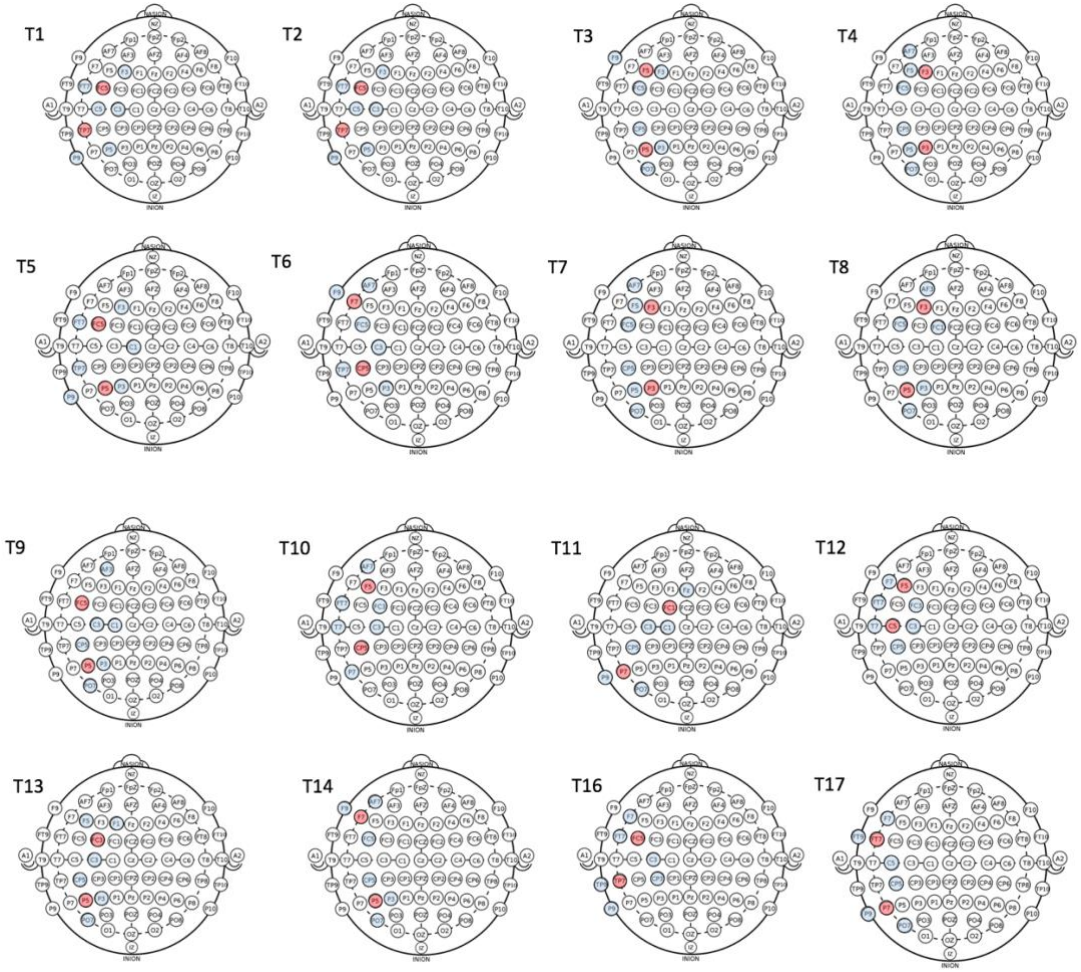
T2-weighted images: utilized a sampling perfection with application optimized contrasts using a different flip angle evolution (3D-SPACE) sequence with 1mm^3 voxels. TR = 3200 ms, TE = 567 ms, variable flip angle, 256 x 256 matrix scan with 176 slices (1-mm thick), using parallel imaging (GRAPPA = 2, 80 reference lines). This series was acquired with the same slice center and angulation as the T1-weighted sequence.

Diffusion tensor imaging using a Prisma in four series, a pair with b = 1000 s/mm2 (43 volumes of which 7 were b = 0, TR = 5250 ms, TE = 80.0 ms) and a pair with b = 2000 s/mm2 (56 volumes of which 6 were b = 0, TR = 5470 ms, TE = 85.4 ms, TA = 5:23). The pairs were identical except for reversed phase encoding polarity (A>P vs P>A). Scans used a monopolar sequence with a 140x140 matrix, 210x210 mm FOV, multi-band x2, 6/8 partial Fourier, 80 contiguous 1.5 mm axial slices.

Resting state fMRI: EPI sequence was acquired with 216 x 216 mm FOV, 90 x 90 matrix size, and a 72-degree flip angle, 50 axial slices (2 mm thick with 20% gap yielding 2.4 mm between slice centers), TR = 1650 ms, TE = 35 ms, GRAPPA = 2, multi-band x2, sequential descending acquisition. A total of 427 volumes were acquired.

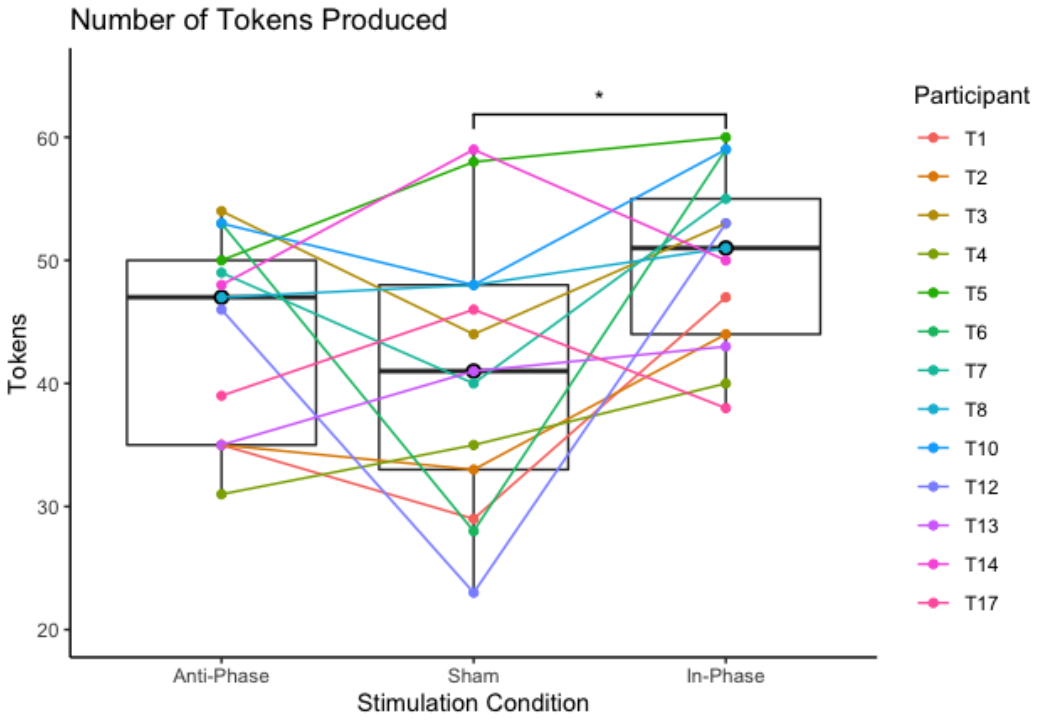
APPENDIX E

INDIVIDUALIZED STIMULATION MONTAGES

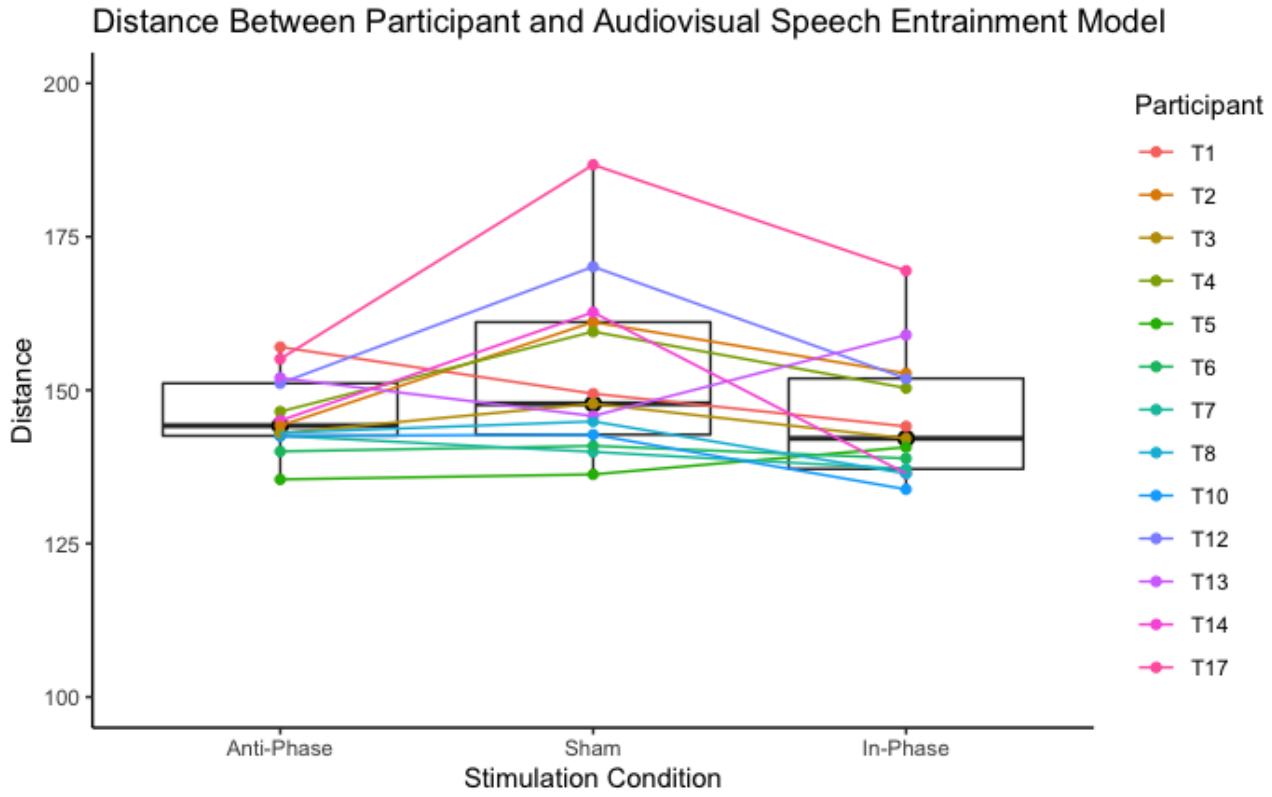


APPENDIX F

INDIVDUAL RESPONSES TO STIMULATION CONDITION



Individual behavioral outcomes are displayed here. Each colored point represents a participant in the study, lines connecting the dots represent change from one condition to the next. N = 13. 3 participants (T9, T11, T16) were excluded secondary to limited verbal expression.



Individual behavioral outcomes from the dynamic time warping analysis are displayed here. Each colored point represents a participant in the study, lines connecting the dots represent change from one condition to the next. N = 13. 3 participants (T9, T11, T16) were excluded secondary to limited verbal expression.