She Said I Love You: The Effect of StartReact and Startle Adjuvant Rehabilitation Therapy in

Post-Stroke Aphasia, Apraxia, and Dysarthria of Speech

by

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ABSTRACT

Stroke is the leading cause of long-term disability in the U.S., with up to 60% of strokes causing speech loss. Individuals with severe stroke, who require the most frequent, intense speech therapy, often cannot adhere to treatments due to high cost and low success rates. Therefore, the ability to make functionally significant changes in individuals with severe post-stroke aphasia remains a key challenge for the rehabilitation community. This dissertation aimed to evaluate the efficacy of Startle Adjuvant Rehabilitation Therapy (START), a tele-enabled, low-cost treatment, to improve quality of life and speech in individuals with severe-to-moderate stroke. START is the exposure to startling acoustic stimuli during practice of motor tasks in individuals with stroke. START increases the speed and intensity of practice in severely impaired post-stroke reaching, with START eliciting muscle activity 2-3 times higher than maximum voluntary contraction. Voluntary reaching distance, onset, and final accuracy increased after a session of START, suggesting a rehabilitative effect. However, START has not been evaluated during impaired speech. The objective of this study is to determine if impaired speech can be elicited by startling acoustic stimuli, and if three days of START training can enhance clinical measures of moderate to severe post-stroke aphasia and apraxia of speech. This dissertation evaluates START in 42 individuals with post-stroke speech impairment via telehealth in a Phase 0 clinical trial. Results suggest that impaired speech can be elicited by startling acoustic stimuli and that START benefits individuals with severe-to-moderate post-stroke impairments in both linguistic and motor speech domains. This fills an important gap in aphasia care, as many speech therapies remain ineffective and financially inaccessible for patients with severe deficits. START is effective, remotely delivered, and may likely serve as an affordable adjuvant to traditional therapy for those that have poor access to quality care.

Dedicated to

DeForest Kelly, 1920-1999

James Doohan, 1920-2005

Leonard Nimoy, 1931-2015

Nichelle Nichols, 1932-2022

for encouraging kids everywhere to fall in love with science.

And to Brad and Taffy, for their endless love.

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CHAPTER 1

INTRODUCTION

1.1 Background and Significance

Stroke is the leading cause of long-term disability in the U.S. (Anderlini et al., 2019). Up to 60% of strokes result in speech loss (Flowers et al., 2013; Mitchell et al., 2021). A survey of 66,000 long-term care residents found that the worst quality-of-life scores were associated with aphasia, higher than cancer, Huntington's, or Alzheimer's disease (Lam & Wodchis, 2010). Individuals with aphasia experience social isolation and depression due to an inability to communicate (Worrall et al., 2016), and higher financial burdens than other post-stroke deficits due to the need for long-term, high dose speech language therapies (Ellis et al., 2012). If stroke causes severe deficits, patients require even more frequent, intense therapy and often cannot adhere to treatments due to cost, lack of transportation (Blonski et al., 2014), and low therapy success rates (Wray et al., 2018). Therefore, two large barriers exist in the field of severe post-stroke speech rehabilitation: access to care and efficacy of care. Addressing these barriers remains a key challenge for the rehabilitation community.

The high incidence of speech impairment after stroke can partially be explained by neurovascular morphology (Decavel et al., 2012; Navarro-Orozco & Sánchez-Manso, 2021). The middle cerebral arteries (MCA), which are the largest of the three major arteries in the brain, supply oxygenated blood to large swathes of the lateral brain, including the frontal, temporal, and parietal lobes, and parts of the basal ganglia. The lenticulostriate vessels are small arteries that branch from the MCA stem at a right angle, making the regions supplied by the MCA highly susceptible to embolism and aneurism, especially in circumstances of anatomical variation (Decavel et al., 2012). Two of the three MCA branches specifically supply the inferior frontal lobes and superior temporal gyrus (STG), both of which are essential to speech production and comprehension, respectively (Navarro-Orozco & Sánchez-Manso, 2021). Therefore, if a stroke occurs in the MCA, speech impairments frequently follow (Briggs et al., 2019).

1.1.1 Models Of Language, Speech Motor Planning, And Execution

Speech and language sciences date back centuries. The Smith Surgical Papyrus documented symptoms of aphasia as early as 3500 B.C. The Hippocratic Corpus (400 B.C.) categorized types of speech loss. The Roman Valerius Maximus (30 A.D.) was the first to describe alexia, after a man hit in the head with a stone had intact language abilities but could not read. Speech deficits were typically documented in combination with traumatic brain injury, epilepsy, and apoplexy (stroke) (Benton, 1964; Benton & Joynt, 1960). During the Renaissance, some individual attempts began to designate functions to different brain regions, and by the 1700s, several clinical aphasia presentations were identified. Franz Joseph Gall (1810) was the first to explore the specific neuropathology of speech loss (Young, 1968). Though his work in functional localization was greatly influenced by phrenology, it attracted Paul Broca, who identified damage in the left frontal lobe (Broca's area) as the site of production impairment in 1861. Carl Wernicke (1873) recognized that not all aphasias were located in Broca's area, finding that injury to the left posterior superior temporal gyrus, now called Wernicke's area, caused language comprehension problems (Nasios et al., 2019). Wernicke was also the first to document conduction aphasia. These classical models of language provide a framework for modern language network models, which extend through the cortex and subcortex and continue to be refined through neuroimaging studies.

One of the most important modern neuropsychological models of speech and language organization in the brain is the dual stream model (Hickok & Poeppel, 2004, 2007). It describes two large-scale parallel speech processes. The "ventral" stream, mediated bilaterally by the superior temporal gyrus, converts sound into meaning, as necessary for auditory comprehension; and the "dorsal" stream, mediated unilaterally by anterior regions such as the posterior inferior frontal gyrus, insula, and area Spt, converts meaning into sound, as necessary for speech production (Fridriksson et al., 2018; Hickok, 2012; Iyer et al., 2020). During comprehension, the ventral stream uses phonological information heard from a speaker to access concepts sourced from a widely distributed, bilateral network in the cortex (Hickok, 2012). The dorsal stream works

in parallel to use these concepts to access phonological information, and subsequently build an utterance for motor control regions by incorporating word selection, phonology, syntax, and grammar.

The dual stream model can also be used to infer aphasic symptomatology. Post-stroke speech impairments can be broadly categorized into three domains: those that affect language (aphasia); those that affect speech motor planning and programming (apraxia); and those that affect muscle execution within the speech tract (dysarthria) (Jordan & Hillis, 2006). Approximately 20–40% of strokes result in acute aphasia (Engelter et al., 2006). These impairments are correlated to neuroanatomy, with lesions in the ventral, posterior regions resulting in fluent aphasias, and lesions in the anterior, dorsal regions resulting in non-fluent aphasias (Fridriksson et al., 2018; Yang et al., 2008). Therefore, an injury to the ventral stream will likely result in comprehension deficits (e.g., Wernicke's aphasia), while an injury to the dorsal stream will likely result in language production deficits (e.g., Broca's aphasia) (Fridriksson et al., 2018; Iyer et al., 2020; Yang et al., 2008). Conduction aphasia seems to result from impaired phonological encoding; both comprehension and production remain intact, as the conceptual network can still supply information to the dorsal and ventral streams (Buchsbaum et al., 2011). Instead, individuals see frequent repetition errors and paraphasias, due to impaired conversion of ventral information up into the dorsal stream. Imaging studies have shown conduction aphasia to result, not from damage to the arcuate fasciculus which connects Broca's and Wernicke's areas, but from damage to area Spt ("Sylvian Parietal Temporal")—a key dorsal stream region thought to transform sensory to motor information (Buchsbaum et al., 2011; Schwartz et al., 2012). This anatomy also supports more contemporary models which extend speech and language organization beyond the classic nineteenth century theory of Broca's and Wernicke's areas (Heilman, 2006; Nasios et al., 2019).

Apraxia of speech (AOS) is an impairment of speech motor planning, as opposed to linguistic planning upstream. AOS occurs in 57% of strokes, and up to 80% of individuals with

post-stroke aphasia have concurrent AOS (Hybbinette et al., 2021; Ziegler et al., 2022). One of the most widely used speech motor planning models is the DIVA model (Tourville & Guenther, 2011), which details the processes of speech programming, initiation, and auditory feedback integration. AOS is a disorder that results in difficulties defining and sequencing articulatory goals, impaired motor programming including motor timing anomalies; and impaired initiation (the connection between the intact linguistic areas and those governing coordinated movements has been disrupted) (Ballard et al., 2015; Pulvermüller et al., 2001). Unlike Broca's aphasia, which usually results from large, left-lateralized lesions throughout the dorsal stream, pure apraxia results from lesions directly to Broca's area and left insula (Dronkers, 1996; Graff-Radford et al., 2014). In AOS, the programming of the articulatory goals is disrupted. AOS will result in substitution errors that are inconsistent (anticipations, perseverations, and exchanges) (Bislick & Hula, 2019; Cera & Ortiz, 2010). Distortion errors are less common, as they usually result from an execution impairment (Odell et al., 1991). To that end, AOS does not result in muscle weakness or rigidity. Instead, due to difficulties in phonological sequencing and timing, individuals with AOS exhibit articulatory groping, and have difficulty with long or fast sequences of sounds (dysdiadochokinesia), e.g. counting backwards, long words, and sequences such as "pa-ta-ka" (Bislick & Hula, 2019; Moser et al., 2016). Prosody is affected, leading to slow rate of speech. Automatic speech, such as counting to ten, is preserved in AOS, as automatic speech is not as dependent on planning and programming. The most well substantiated neural mechanism of action in AOS is damage to the left insula and Broca's area (both of which help mediate phonological working memory) (Chapey, 2012b; Dronkers, 1996). The inferior frontal gyrus (IFG) is also implicated in syntax, semantics, and syllabification. Other regions that may contribute to AOS are the inferior parietal lobe (rhythm, error mapping), the presupplementary motor area (attention, working memory, encoding), and the ventral premotor cortex, which has been strongly linked to articulatory preparation processes (Chapey, 2012b; Cordella et al., 2019).

Dysarthria is a motor speech disorder occurring in over half of strokes (Mitchell et al., 2021). It affects speech execution processes, including breathing, nasality, laryngeal function,

phonation, airflow direction, and articulation, causing poor speech intelligibility (Enderby, 2013;

Jordan & Hillis, 2006). Dysarthria can be categorized by its underlying neuropathology. Flaccid

dysarthria, caused by lower motor neuron dysfunction, results in breathy, nasal speech marked

with indistinct articulation. Speech can start out sounding normal, but often deteriorates after a

few sentences. The second type is called spastic dysarthria, caused by upper motor neuron

damage in the corticobulbar tracts. If a stroke is bilateral, the presentation is more severe.

Speech is harsh, slow, and has a distinct "strain-strangle" quality. Thirdly, ataxic dysarthria is

caused by cerebellar dysfunction and results in uncoordinated speech with unusual stress and

articulation, often described as sounding intoxicated. Finally, basal ganglia lesions can cause

either hyperkinetic or hypokinetic dysarthria, leading to either under-gating or over-gating of

speech tract movement, respectively. In short, dysarthria is a complex disorder, frequently

cooccurring with other types of speech impairments after stroke and can result from lesions

throughout the corticospinal tract.

1.1.2   Current Rehabilitation In Post-Stroke Communication Disorders

1.1.2.1 Treatments for Aphasia

The efficacy of traditional speech language therapy (SLT) has been historically difficult to

study due to small study sample sizes and variability in approach. However, SLT can be broadly

categorized as being either functional, or impairment-based (Fridriksson & Hillis, 2021; Galletta &

Barrett, 2014; N. Martin et al., 2007). Functional SLT focuses on an individual's abilities and daily

life, giving them training on personally relevant words and phrases, training caregivers, and

creating an environment that is generally more accessible to the patient (Chapey, 2012a; Galletta

& Barrett, 2014). However, there is limited quantitative evidence for its efficacy (N. Martin et al.,

2007; Simmons-Mackie et al., 2014). In contrast, impairment-based SLT improves verbal

communication by targeting specific parts of speech that have been impaired (e.g. phonology,

semantics). A recent Phase III randomized clinical trial strongly supports the use of impairment-

based SLT in chronic aphasia, and showed changes after 10 hours of SLT per week for three

weeks in both language ability and quality of life (Breitenstein et al., 2017). While treatment dose and duration has not been well evaluated for SLT, about half of chronic patients continue to see gains years after their stroke (Fridriksson & Hillis, 2021; Johnson et al., 2019).

Impairment-based SLT has several factors that interact with its success, including aphasia severity, age, intensity and duration of practice, and type of SLT. According to three large randomized clinical trials (Breitenstein et al., 2017; Godecke et al., 2020; Nouwens et al., 2017), the strongest predictor by far was aphasia severity, with more severe patients benefitting less from SLT. Another predictor of improvement in SLT was age, with older individuals less likely to improve (Darley, 1972; Kristinsson et al., 2021). This may be because brain plasticity decreases with age, and is therefore less likely to reinforce recovery (Toth et al., 2008). Stroke timepoint is also a relevant factor in SLT efficacy, with individuals in the acute phase of stroke showing no difference between impairment-based SLT or no therapy, according to two RCTs (Godecke et al., 2020; Nouwens et al., 2017). Intensity of practice (increasing from 0.34 to 0.71 hours/day) also made no difference in acute patients (Godecke et al., 2020). Conversely, individuals in the chronic phase of stroke show more recovery with more intense sessions (at least 10 hours of therapy per week) (Breitenstein et al., 2017; Johnson et al., 2019). Traditional speech therapies were shown to be most effective at high doses and in group settings, over a minimum of 12 weeks(Allen et al., 2012; Breitenstein et al., 2017). Improvements were maintained after four months post treatment (Allen et al., 2012). However, another randomized control trial by Bakheit et al. reported no effect of SLT intensity on speech gains in subacute stroke, with the inability to administer at high intensity or difficulty levels (Bakheit et al., 2007).

Aphasia type seems to require slightly different therapeutic approaches (Cheng et al., 2020; Kurland et al., 2018; Pedersen et al., 2004; Plowman et al., 2012). One study found that more severe, non-fluent aphasia patients showed slightly more improvement with phonological SLT (focusing on sounds), while mild, fluent cases responded to semantic SLT (focusing on meaning), though semantic SLT was far more effective than phonological SLT on the whole (Kristinsson et al., 2021). The mechanism of action behind traditional SLT is not well understood, but several

neuroimaging studies have found lesion location was a predictor of SLT outcome. Damage to areas including middle frontal gyrus, inferior frontal gyrus, precentral gyrus, and supramarginal gyrus lead to worse phonological treatment outcomes, while no lesion locations predicted semantic outcomes (Kristinsson et al., 2021). Additionally, participants who had left middle occipital gyrus and posterior middle temporal gyrus damage showed the poorest improvement overall in the study (Kristinsson et al., 2021).

Another type of speech rehabilitation is called constraint induced aphasia therapy (CIAT). CIAT discourages "learned non-use" by constraining the unimpaired limb or function, forcing the patient to use their impaired processes (Pulvermüller et al., 2001; Zhang et al., 2017). When used in speech, patients are constrained from using writing, gestures, or other non-verbal modalities to communicate. It is usually administered at high-intensity over a short duration (most studies report 3 hours per day for 10 days) (Pulvermüller et al., 2001; Szaflarski et al., 2015; Zhang et al., 2017). As a patient's performance improves, the difficulty of tasks is increased. Several individual RCTs have demonstrated improvements in token task, naming, and comprehension (Kurland et al., 2012; Pulvermüller et al., 2001; Szaflarski et al., 2015) but sample sizes are usually small, and a recent comprehensive meta-analysis found no difference between CIAT and other types of therapy in any domain (Zhang et al., 2017). One limitation in the studies included in this meta-analysis was the variety in population, with a wide range of aphasia severities, types, and time post-stroke. Broadly speaking, the studies examining subjects in the acute phase saw fewer improvements than chronic, but when analyzed together the meta-analysis saw no effect of CIAT in any group (Zhang et al., 2017). Despite these inconclusive results, neuroimaging before and after CIAT showed that CIAT was associated with bilateral plasticity, including down-regulated ipsilesional regions and upregulated contralesional regions, indicating that CIAT encourages the patient to compensate with the contralesional (right) hemisphere as a result of discouraging learned nonuse (Kurland et al., 2012; Mohr et al., 2014; Pulvermüller et al., 2005). Limitations of CIAT include inconsistent long-term effects, variable benefits, and an unevaluated social component. This therapy may just increase self-reported benefits, not quantifiable language

performance (Pulvermüller et al., 2001; Zhang et al., 2017). Additionally, high intensity CIAT may not be different from low intensity CIAT, indicating unclear benefits. CIAT is often administered in a group setting to individuals with mild to severe chronic aphasia (Pulvermüller et al., 2001; Zhang et al., 2017).

In conclusion, traditional SLT has shown great benefit to aphasia in certain populations including less severe, younger, more fluent, and more chronic individuals (Fridriksson & Hillis, 2021). This is likely due to a higher likelihood of adaptive neural plasticity in these populations (Pedersen et al., 2004; S. M. Wilson & Schneck, 2020). Patients are often excluded due to plateaus in improvements, or discharge themselves due to lack of improvement in severe impairment, though contralesional plasticity has been demonstrated to continue over a long period (Hope et al., 2017; Zipse et al., 2012). *Therefore, therapies that are effective in severe, older, and non-fluent individuals with aphasia would constitute a welcome addition to the speech therapy repertoire.*

1.1.2.2 Treatments for Apraxia of Speech

A recent review suggests two treatment approaches effective in post-stroke AOS are the articulatory-kinematic approach and the rate/rhythm approach (Ballard et al., 2015). Articulatory-kinematic treatments employ a variety of methods to improve spatial and temporal aspects of speech production (J. Wambaugh, 2010). Repeated practice with limited verbal feedback can enhance articulation. Clinicians also use modeling ("watch me, listen to me, and say it with me" (Mauszycki & Wambaugh, 2011; Rosenbek et al., 1973; J. L. Wambaugh et al., 2006) to direct the attention to visual and auditory components of speech, as well as articulatory cueing (directing attention to the articulators, position, manner, and voicing of the phoneme) (Mauszycki & Wambaugh, 2011). Rate/rhythm-control treatments include metronomic pacing and melodic intonation therapy to manipulate the rhythm and rate of speech (Beber et al., 2018; Mauszycki & Wambaugh, 2011). This is thought to improve symptoms of AOS by giving the patient more time to prepare sensorimotor integration, increase attention to the sound, or to rebuild potential

oscillatory mechanisms involved in speech sensory processing optimization (ten Oever & Martin, 2021).

Non-invasive stimulation is an emerging form of speech rehabilitation. Two studies found that employing transcranial direct current stimulation (tDCS) as an adjuvant to speech therapy boosted accuracy beyond sham stimulation in chronic AOS (Marangolo et al., 2011, 2013). However, both studies had small sample sizes (three and eight people), and improvements varied. No research has studied the use of tDCS in early stages of AOS recovery, but the few that have evaluated it in early post-stroke aphasia suggest promising outcomes for increasing subacute plasticity (Polanowska et al., 2013; You et al., 2011)

Computerized therapy using smartphone apps is also becoming more widespread (Basilakos, 2018). A recent randomized clinical trial (n=50) showed that using software to deliver therapy in AOS improved naming and repetition in AOS and aphasia patients. The therapy consisted of a perceptual phase (auditory-verbal and auditory-picture comprehension) and a hierarchical production phase (watching a video of a word, imagined speech, and overt speech). These participants also received a sham intervention in a cross-over model using a similar software that did not include speech activities (e.g., jigsaw puzzles) (Varley et al., 2016). While naming and repetition did improve for those receiving speech therapy, the single word repetition task administered was not generalizable to other words. No trials have evaluated computerized therapy for AOS in the acute or subacute period, nor in the use of evidence-based techniques (e.g., articulatory/kinematic).

1.1.3 StartReact In Healthy And Clinical Populations

This dissertation explores a new potential rehabilitation tool for individuals with post-stroke speech impairment, making use of a phenomenon called the StartReact effect. In unimpaired individuals, reaction time can be as fast as 150-200 milliseconds (ms) if prepared in advance (e.g., starting to run during a race) (Carlsen & Maslovat, 2019). A few decades ago, Valls-Solé et al. showed that reaction time for prepared movements could be triggered as fast as

70 ms following a loud, startling acoustic stimulus (SAS) (<120 dB) (Carlsen et al., 2004; Valls-Solé et al., 1999). This was termed the StartReact effect, and is distinct from the classic startle reflex. When movements are prepared, the intended movement is elicited following the SAS. In classic startle, the movement is unprepared and results in involuntary protective movements (e.g., flinching, blinking). StartReact in healthy individuals refers to the early release of preplanned movement. Before being exposed to an SAS, participants must be completely prepared to move to achieve StartReact. A rapid (less than 120 ms latency) sternocleidomastoid muscle activation during a planned movement is the most precise method for determining the presence of StartReact (Carlsen et al., 2007).

In impaired populations (e.g., stroke (Chen et al., 2019; Honeycutt et al., 2015; Honeycutt & Perreault, 2012; Lee et al., 2022; Rahimi & Honeycutt, 2020), Parkinson's disease (Carlsen et al., 2013; Nonnekes, Geurts, et al., 2014), hereditary spastic paraplegia (Nonnekes, Oude Nijhuis, et al., 2014; van Lith et al., 2018)), StartReact not only elicits preplanned movements faster, but with greater muscle activation. In the upper extremity, StartReact can elicit muscle activity 2–3 times larger than maximum voluntary contraction in individuals with stroke with little-to-no voluntary movement (Rahimi & Honeycutt, 2020). After 1 hour of StartReact treatment, voluntary reaching in moderate-to-severe post-stroke upper extremity impairment increased in distance, muscle activity patterns, and accuracy (Rahimi et al., 2021). In these individuals, StartReact may allow movements to be triggered by alternative, intact routes similar to classic startle, bypassing injured structures (Honeycutt & Perreault, 2012; Kühn et al., 2004; Marinovic & Tresilian, 2016; Smith et al., 2019). However, these mechanisms are still unclear, and evidence is preliminary.

As StartReact response latencies were comparable to those of the startle reflex and too fast to be mediated cortically, it was originally suggested that the startle reflex activated subcortical structures containing offloaded information about the planned motor response (Carlsen & Maslovat, 2019; Valls-Solé et al., 1999). In the startle reflex circuit, there are very few synapses, projecting straight from the cochlear nuclei to motor nuclei in the caudal pontine

reticular formation (Yeomans & Frankland, 1995). Activation of this circuit results in facial grimacing and blinking because of the resulting motor engagement. Several more recent studies have presented evidence that the StartReact effect is indeed subcortical in nature. StartReact has been found to be more difficult to elicit in cortically-mediated tasks involving finger abduction, while reticulospinal-based movements such as reaching were more easily elicited by SR (Carlsen et al., 2009; Honeycutt et al., 2013). Additionally, deep brain stimulation of the pedunculopontine nucleus of Parkinson's disease patients with freezing of gait restored the StartReact effect (Thevathasan et al., 2011), indicating that the release of a prepared movement may include subcortical activity. Finally, patients with hereditary spastic paraplegia (HSP), which is characterized by degeneration of the corticospinal tract, also had an intact StartReact effect, while HSP patients had a slower voluntary reaction time than healthy controls (Nonnekes, Geurts, et al., 2014). These findings bolstered the theory that a stored response is triggered by the reticulospinal tract in the brain. If the StartReact effect is being mediated by a subcortical triggering mechanism, movements that rely more heavily on the corticospinal system than the reticulospinal system are less likely to demonstrate a reduction in reaction time in response to an SAS.

There is some evidence that StartReact may be eliciting plans using cortical structures. Two studies found that transcranial magnetic stimulation (TMS) applied over the cortex inhibited the StartReact effect, delaying reaction times for both StartReact and voluntary movements (Alibiglou & MacKinnon, 2012; Stevenson et al., 2014). While TMS is known to affect both cortical and subcortical structures, this was unlikely the case in these studies as classic startle was not affected by TMS. Other evidence for cortical involvement in the StartReact effect comes from studies that have elicited speech sounds, which is a cortically-driven process (Chiu, 2015; Chiu & Gick, 2014b; Stevenson et al., 2014). However, these studies only evaluated the syllable "ba", which, in its simplicity, cannot provide a comprehensive picture of most speech processes (e.g., grammar, semantics). One study found that picture naming, a much more complex speech task, could also be elicited by StartReact; however, this was only the case when words could be

predicted and therefore preplanned and likely stored subcortically. In conclusion, it remains unclear whether StartReact activates cortical or subcortical structures. StartReact has never been evaluated in impaired speech, which may elucidate this mechanism.

1.2   Objectives and Hypotheses

While StartReact has been evaluated in a variety of impairments and tasks described above, it is uncertain whether StartReact will be present during speech in individuals with post-stroke speech impairment. Moreover, the improvements we showed in Rahimi et al., 2021 indicate that training over time with StartReact may enhance movement. Therefore, the objective of this dissertation is to establish if StartReact is present in post-stroke speech, and to conduct a small proof-of-concept clinical trial on the potential therapeutic efficacy of StartReact training in post-stroke speech impairment.

1.2.1   Aim 1

To determine if startle affects acoustic and articulatory speech parameters in individuals with post-stroke aphasia and apraxia, I will compare quantitative metrics for startled and non-startled speech trials during word repetition. I hypothesize that (H1a) following a startling cue (~105 dB), acoustic onsets will be faster, and pitch and intensity will increase relative to non-startle cues (~77 dB). I expect vowel distance to decrease based on preliminary data. I also hypothesize that (H1b) phonemic errors will decrease for startle-evoked trials compared to non-startled speech. Specifically, startled speech will have higher incidence of fricatives due to increased respiration, and more accurate articulation during word onsets due to a higher level of preparedness.

1.2.2   Aim 2

To evaluate if training with StartReact can enhance quality of life and clinical speech measures of post-stroke aphasia and apraxia, subjects will receive 3 days of remote, high-intensity word repetition training paired with START (Startle Adjuvant Rehabilitation

Therapy) or without (Control). I hypothesize (H2a) that training with START will improve clinical assessments of speech function (WAB-R, aphasia; ABA-2, apraxia) and quality of life (SIS, stroke impact scale) compared to baseline, while Controls will see minimal change. I also hypothesize (H2b) that START gains will be retained more than Control and retention will be associated with higher quality of life measures (e.g., SIS) one-month post-START training. Finally, I hypothesize (H2c) that subjects with more severe deficits will show the greatest improvement after START, consistent with the Rahimi et al. 2021 study.

1.2.3 Aim 3

To assess the effect of START training on untrained acoustic measures of speech, I will evaluate acoustic measures of recorded speech acquired before and after training. I hypothesize (H3a) that speech intelligibility and voice quality (strained, hypernasal, breathy, etc.) will improve after START vs. Control. Additionally, I hypothesize (H3b) that Vowel duration in a multi-syllable word task will decrease after START vs. Control, signifying AOS improvement.

CHAPTER 2

IMPACT OF STARTLING ACOUSTIC STIMULI ON WORD REPETITION IN INDIVIDUALS WITH

APHASIA & APRAXIA OF SPEECH FOLLOWING STROKE.

2.1 Abstract

Purpose: The StartReact effect, whereby movements are elicited by loud, startling acoustic stimuli (SAS), allows the evaluation of movements when initiated through involuntary circuitry, before auditory feedback. When StartReact is applied during post-stroke upper extremity movements, individuals exhibit increased muscle recruitment, reaction times, and reaching distances. StartReact releases unimpaired speech with similar increases in muscle recruitment and reaction time. However, as post-stroke communication disorders have divergent neural circuitry from upper extremity tasks, it is unclear if StartReact will enhance speech post-stroke. Our objective is to determine if 1) StartReact is present in individuals with post-stroke aphasia and apraxia and 2) SAS exposure enhances speech intelligibility. **Methods:** We remotely delivered startling, 105 dB white noise bursts (SAS) and quiet, non-SAS cues to 15 individuals with post-stroke aphasia and apraxia during repetition of 6 words. We evaluated average word intensity, pitch, pitch trajectories, vowel formants F1 and F2, phonemic error rate, and percent incidence of each SAS vs. non-SAS-elicited phoneme produced under each cue type. **Results**: For SAS trials compared to non-SAS, speech intensity increased (Δ+0.6 dB), speech pitch increased (Δ+22.7 Hz), and formants (F1 and F2) changed, resulting in a smaller vowel space after SAS. SAS affected pitch trajectories for some, but not all, words. Non-SAS trials had more stops (Δ+4.7 utterances) while SAS trials had more sustained phonemes (fricatives, glides, affricates, liquids) (Δ+5.4 utterances). SAS trials had fewer distortion errors, but no change in substitution errors or overall error rate compared to non-SAS trials. **Conclusions:** We show that stroke-impaired speech is susceptible to StartReact, evidenced by decreased intelligibility due to altered formants, pitch trajectories, and articulation, including increased incidence of sounds that

could not be produced without SAS. Future studies should examine the impact of SAS on voluntary speech intelligibility and clinical measures of aphasia and apraxia.

2.2   Introduction

Stroke is the leading cause of long-term disability in the U.S. (Anderlini et al., 2019), with one-third of individuals who have had a stroke experiencing speech loss (Flowers et al., 2013). Post-stroke apraxia of speech (AOS) is one such speech disorder commonly co-occurring with aphasia and dysarthria (Duffy, 2006; Hybbinette et al., 2021). AOS is regarded as neither a purely motor (dysarthria) or linguistic (aphasia) deficit, instead considered an impairment in speech motor planning and programming. Planning deficits in AOS disrupt an individual's ability to define, program, and sequence articulatory goals (Bohland et al., 2010; Chapey, 2012b; Haley et al., 2000). Together, speech motor planning and programming deficits lead to hallmark characteristics of AOS, such as slow speech rate (Chapey, 2012b, 2012a; Pulvermüller et al., 2001), altered prosody (Odell et al., 1991), difficulty initiating speech (Chapey, 2012a), and frequent phoneme substitution errors (Cera & Ortiz, 2010; Chapey, 2012a; La Pointe & Johns, 1975). Individuals with AOS may also distort speech parameters such as lip kinematics (Basilakos et al., 2017; Hough & Klich, 1998) and vowel formants (den Ouden et al., 2018; Haley & Overton, 2001; Maas et al., 2015). Several studies have used auditory feedback masking with white noise to demonstrate that feedforward planning is disrupted, while feedback control may remain intact in AOS. Once subjects with AOS could no longer correct their speech using auditory feedback (due to masking), their vowel contrast (Lane et al., 2007; Maas et al., 2015) and fricative contrast (Lane et al., 2007) decreased. Additionally, Jacks et. al. showed that when given a bite block to induce speech errors, both individuals with and without AOS could compensate, indicating an intact feedback circuit (Jacks, 2008). Jacks and Haley et. al show that in 7 out of 10 subjects, masked auditory feedback increased syllable rates, suggesting that subjects with AOS are over-reliant on auditory feedback leading to hesitant, groping speech and effortful initiation (Jacks & Haley, 2015). This study did not report measures of intelligibility in the masked auditory

feedback condition. Together, these findings suggest that individuals with AOS have poor

feedforward planning abilities and are over-reliant on their intact feedback control. However, the

mechanisms of impaired initiation in AOS are still unclear.

A novel phenomenon called the StartReact effect, in which movements are elicited by a

loud, startling acoustic stimulus (SAS), may serve as an alternative way to investigate the effect

of speech initiation and auditory feedback in AOS. When a SAS (~117 dB) is presented during

movement preparation, movements are released 30–40 ms faster than voluntarily-initiated

movements (Carlsen et al., 2004; Carlsen & Maslovat, 2019; Valls-Solé et al., 1999). Unlike

classic startle whereby the subject reflexively crouches (Davis, 1984), StartReact movements

display in two possible ways. First, movements of unimpaired individuals maintain the features of

the planned movement in terms of accuracy, muscle activity patterns, and kinematics (Carlsen &

Maslovat, 2019; Honeycutt et al., 2015; Rahimi & Honeycutt, 2020; Valls-Solé et al., 1999).

Secondly, individuals with motor impairments (such as post-stroke) will have movements with

increased muscle activity, increased movement distance, and decreased accuracy (deviation

from linearity) (Honeycutt et al., 2015; Honeycutt & Perreault, 2012; Rahimi & Honeycutt, 2020).

StartReact movements are released as soon as 70 ms after the stimulus, generally considered

too short a latency to be initiated through voluntary pathways or correctable by auditory feedback

(Carlsen & Maslovat, 2019; Chiu & Gick, 2014b; Stevenson et al., 2014). StartReact, therefore,

allows us to evaluate a movement when 1) initiated via involuntary circuitry, and 2) elicited before

auditory feedback (Chiu, 2015).

The StartReact response has been previously generated in a variety of neurological

conditions (Parkinson's (Nonnekes, Geurts, et al., 2014), stroke (Coppens et al., 2018; Honeycutt

et al., 2015; Honeycutt & Perreault, 2012; Rahimi et al., 2021; Rahimi & Honeycutt, 2020),

hereditary spastic paraplegia (Nonnekes, Oude Nijhuis, et al., 2014)) and tasks (reaching

(Castellote & Valls-Solé, 2015; Honeycutt et al., 2015; Rahimi & Honeycutt, 2020), finger

movements (Bartels et al., 2020; Carlsen et al., 2009; Honeycutt et al., 2013), gait (Nonnekes,

Geurts, et al., 2014; Nonnekes, Oude Nijhuis, et al., 2014; van Lith et al., 2018), head rotation

(Nijhuis et al., 2007), unimpaired speech (Chiu, 2015; Chiu & Gick, 2014b; Leote et al., 2018; Stevenson et al., 2014)). In individuals with unimpaired speech, Stevenson et al. found that a simple syllable "ba" can be elicited by SAS with faster onsets and increased lip muscle activation (Stevenson et al., 2014). Lip kinematics and vowel formants were unaffected (Stevenson et al., 2014). Chiu and Gick found that speech onsets decrease and intensity and absolute pitch (fundamental frequency) increase in a similar syllable-based protocol, but found that pitch contours remain stable (Chiu & Gick, 2014a, 2014b). Though their pitch and intensity increases are consistent with the Lombard effect (i.e. that speakers will involuntary increase speech volume and pitch in loud environments due to the Lombard effect) (Luo et al., 2018), increases in reaction time and muscle activation support previous findings that StartReact is distinct from stimulus intensity effects (Carlsen et al., 2007). Chiu and Gick suggest that the effect of StartReact on speech may be used to explore pre-specified speech plans as being distinct from components of speech that are dependent on feedback integration. This is because of the timing of the speech apparatus following an SAS. Laryngeal tension (muscular activation) begins as soon as 40 ms after an unimpaired individual hears an SAS, with somatosensory (proprioceptive) feedback correction as soon as 60 ms following the SAS. Voicing onset occurs at 204 ms, followed by a second wave of somatosensory (e.g., vibrotactile) feedback around 230 ms. Auditory feedback begins 100 to 210 ms after voicing onset (i.e., at least 304 ms after SAS). Chiu and Gick found that speech was not only elicited faster after an SAS (~50 ms), but that even after auditory feedback should have begun, pitch levels did not return to a voluntary baseline (e.g. remained altered and uncorrected by feedback) (Chiu & Gick, 2014b). As such, StartReact does not seem to alter prepared speech plans themselves; instead, due to findings from the studies above, it seems to alter execution and feedback integration(Chiu, 2015; Chiu & Gick, 2014b). However, the exact impact of SR on feedforward and feedback systems is not clear.

Perhaps most provocative is StartReact's impact in individuals with stroke. In the upper extremity, StartReact can elicit muscle activity 2–3 fold greater than maximum voluntary contraction in individuals with severe stroke who have little-to-no voluntary movement (Rahimi &

Honeycutt, 2020). Following prolonged exposure to StartReact (~1 hour), we have shown that

voluntary reaching in moderate-to-severe post-stroke upper extremity impairment has increased

distance, more appropriate muscle activity patterns, and increased accuracy (Rahimi et al.,

2021). The proposed mechanism for these improvements has been that StartReact allows

movements to be initiated through alternative, intact pathways similar to classic startle, which

bypasses several structures damaged by stroke (Honeycutt & Perreault, 2012; Kühn et al., 2004;

Marinovic & Tresilian, 2016; Smith et al., 2019). However, it is unclear, and even unlikely, that

speech in AOS would follow this pattern even if StartReact is present. If the impaired feedforward

plan is initiated alone, we would expect speech to become further disrupted, regardless of the

initiation pathway. On the other hand, if exposure to SAS shows similar improvements to upper

extremity in AOS speech parameters, it would indicate 1) residual capacity for planning and 2)

deficits are driven in part by initiation via impaired structures.

Still, an alternative possibility is that StartReact will be absent, replaced by a classic

startle response with no trace of the intended movement. For example, StartReact is only present

when a movement can be sufficiently planned (Alibiglou & MacKinnon, 2012; Honeycutt &

Perreault, 2012; Kirkpatrick et al., 2018) and is highly familiar (or trained) (Bartels et al., 2020;

Honeycutt et al., 2013; Kirkpatrick et al., 2018). Generally speaking, if a movement is highly

dependent on cortical structures (Carlsen & Maslovat, 2019; Smith et al., 2019) (e.g. individuated

finger movements) the StartReact effect is less likely to be present unless trained (Bartels et al.,

2020; Honeycutt et al., 2013; Kirkpatrick et al., 2018). Therefore, it is uncertain whether

StartReact will be present during speech in individuals with post-stroke AOS. While StartReact

has been shown to be present in speech of individuals without speech impairment, it has never

been evaluated in individuals with impaired speech, such as post-stroke AOS. StartReact is likely

mediated at least in part by subcortical structures such as the reticulospinal tract (Carlsen &

Maslovat, 2019; Choudhury et al., 2019; Marinovic & Tresilian, 2016; Nonnekes, Oude Nijhuis, et

al., 2014; Smith et al., 2019). While there is some evidence that the subcortical structures are

involved in speech planning (Jürgens, 2002a; Mena-Segovia & Bolam, 2017; Zanini et al., 2009;

Ziegler & Ackermann, 2017), speech neural processes are sufficiently distinct from the upper extremity to raise doubts if initiation via StartReact will have any impact on post-stroke AOS.

The **objectives** of this study were to determine 1) if StartReact is present in individuals with post-stroke aphasia and AOS and 2) if present, the impact it has on speech parameters. Specifically, we sought to determine if the StartReact response, if present, enhances speech intelligibility. To accomplish this, we asked subjects with post-stroke AOS to repeat simple words following a random sequence of SAS cues (105 dB) and non-startling, voluntary stimuli (77 dB). We **hypothesized** that an intact StartReact response would be present in these individuals as measured by modified speech motor execution. First, we hypothesized that SAS exposure would impact speech intelligibility by decreasing vowel space (den Ouden et al., 2018; Maas et al., 2015) and increasing phonemic error rate for StartReact trials compared to voluntary speech, as SAS trials would act in a similar manner to masked auditory feedback (Jacks & Haley, 2015; Maas et al., 2015). Moreover, we hypothesized that, similar to Chiu and Gick, increased pitch and intensity would be present (Chiu, 2015; Chiu & Gick, 2014b), and that onsets after SAS would be comparable to healthy startled onsets.

2.3   Methods

2.3.1   Subjects

Fifteen individuals with chronic stroke (4 females and 11 males), ranging in age from 39 to 81 years old (mean: 58±12.7) and a range of both aphasia and apraxia severities **(Table 1)** participated in the study. There was a consistent relationship between apraxia and aphasia severity except in the case of Subject 2, who had moderate apraxia and mild aphasia. All enrolled subjects were at least 12 months post-stroke (mean: 7.6±5.7 years). Inclusion criteria were a diagnosis of aphasia and/or apraxia following a stroke, chronic stage of stroke (> 12 months post-stroke), capacity to understand the experimental tasks, over 18 years old, English fluency, low-likelihood of COVID-19 positive diagnosis, and the ability to use video conferencing software (Zoom). All subjects were native speakers of American English, and 4 subjects were bilingual

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ID	Age (years)	Sex	Aphasia Quotient (WAB-R)	Aphasia type	Apraxia Severity (ABA-2)	Time post stroke (years)	Lesioned hemisphere (L/R)	Hemiparetic side (L/R)
1	57	M	92.2	Mild anomic	moderate	4.6	Right cortex	R
2	59	M	86.9	Mild anomic	moderate	2.9	Left cortex	R
3	48	F	79.6	Mild conduction	mild	19.9	Left hemisphere	N/A
4	71	F	63.6	Moderate Broca	moderate	12	Left cortex	R
5	64	M	41.6	Severe Wernicke	severe	3.3	Left cortex	N/A
6	39	M	90.4	Mild anomic	mild	14	Left hemisphere	R
7	46	M	82.3	Mild anomic	mild	13.3	Left cortex	R
8	81	M	63	Moderate Broca	severe	11.7	Left parietal	R
9	48	M	58.2	Moderate Broca	severe	1.1	Left cortex	R
10	59	M	42.5	Severe Broca	severe	1.8	Left cortex	N/A
11	77	F	27.5	Severe Broca	severe	2.4	Left cortex	R
12	44	M	29.4	Severe Broca	severe	2.3	Left basal ganglia	R
13	65	M	42.5	Severe Broca	severe	9.3	Right hemisphere	L
14	45	F	96.8	No aphasia	mild	6.1	Left hemisphere	R
15	66	M	66.8	Moderate conduction	moderate	8.9	Left cortex	R

Table 1. Demographic characteristics of subjects included in the study. WAB-R scores: < 50 is severe, >50 and < 76 is moderate, >76 and < 92 is mild, >93.8 indicates no aphasia.

(fluent in Hebrew, Arabic, Spanish, and Tagalog, respectively). COVID-19 status was assessed using a brief questionnaire relating to travel, possible exposures, and symptoms. Exclusion criteria included: pregnancy, dizzy spells, seizures, and/or heart conditions in the past year. Informed consent was obtained prior to participation. The study protocols were approved by the Institutional Review Board of Arizona State University STUDY00005229.

2.3.2   Protocol

Due to the COVID-19 pandemic, all experiments were conducted remotely over Zoom. After consent, baseline aphasia and apraxia severity were assessed using the Western Aphasia Battery (Revised) (WAB-R) and the Apraxia Battery for Adults, 2nd Edition (ABA-2), respectively. These tests were modified for use remotely in accordance with (Dekhtyar Maria et al., 2020; Hill et al., 2009). We also administered an online pure tone hearing test, though subjects were not excluded if they had hearing loss. No subjects had any moderate or severe hearing loss, and those who had mild hearing loss all were affected only during high frequencies (>2000 Hz) consistent with normal aging. Subjects did not report any difficulty hearing during the experiment.

Sessions were conducted remotely in the subjects' homes. An experimental testing kit was shipped to subjects. It included: a phone (Pixel 2 - Google; OS: Android 10), a LVY-01 Headphone Amplifier, and headphones (JLab Studio; Frequency: 20Hz-20kHz). A custom-built mobile phone application (app) was used to deliver randomly applied auditory cues (SAS or voluntary) per the specifications below, as well as recording speech audio. The app was controlled remotely by the experimenter using AnyDesk App for Android (AnyDesk Software GmbH, Germany). Subjects or caretakers were only responsible for charging the phone and connecting it to Wifi. Subjects were seated in a comfortable chair in front of a desk with the experimental phone. Audio and video data for each session were recorded over Zoom and offline on the mobile phone microphone as a backup. The phone recordings were lower resolution than the Zoom session recordings, with an average harmonics-to-noise ratio of 7 dB, compared to 13 dB for Zoom.

Subjects were asked to complete a word repetition task with six target words: "ball", "water", "stop", "cheese", "feet", and "please". Words were chosen based on 1) most common words that subjects wish to say post-stroke (Palmer et al., 2017) and 2) /i/ and /a/ vowels to maximize distance between the vowels and articulatory complexity. Each word was produced 45 times in blocks of 15 trials per word. Blocks were randomized for a total of 18 blocks per session.

Subjects experienced two different trial types: voluntary and SAS. During voluntary trials, a soft 77 dB tone chirp (426 Hz, 118 ms) representing "GET READY" was played, followed by an identical "GO" cue (1.5–2.5 second delay between cues). During 1/3 of trials, the GO cue was replaced with a 105 dB, 56 ms broadband white noise burst (rise/fall time < 1 ms) (Marinovic et al., 2014). Sound intensity was measured using a decibel meter during several samples of SAS cues and summed intensity throughout represented a maximum of 5s of exposure, which is well below OSHA recommendations of 3.7 minutes/day at 105 dB. All sounds were made using Praat software. Subjects were instructed to say a target word immediately following the GO or SAS cue. It is customary to use an EMG onset of < 120ms in the sternocleidomastoid muscle to indicate the presence of startle (Carlsen et al., 2011). As data were collected remotely, EMG was not collected. Instead, we used an acoustic onset of 363 ms to indicate the presence of a startle. This was obtained using prior literature of StartReact during speech. Specifically, Stevenson et. al.'s average EMG to acoustic onset yields an acoustic startle threshold of 363 ms relative to 120 ms EMG threshold. Two subjects (Subjects 7 and 8) were excluded from the analysis due to the lack of enough detectable onsets (at least 3 in each trial type).

2.3.3 Quantification of Acoustic Measures

The outcome measures for this study were acoustic and descriptive measures of speech taken during SAS and voluntary trials. We also assessed variability within each measure for SAS and voluntary trials (see Statistical Analysis). These measures were processed using custom Praat scripts (Praat 2019 version 6.1.03) which quantified speech pitch, intensity, onset, vowel space, and phoneme frequency. Two trained assessors, blinded to trial type, annotated each

recorded session in Praat (Praat 2019 version 6.1.03). Acoustic onset latencies were defined as

the time between SAS presentation to the onset of the acoustic burst of the initial consonant.

Phoneme boundaries between consonant and vowel clusters were also marked and annotated

with both the intended phoneme (prescriptive transcription) and the actual sounds achieved

(descriptive transcription). Close phonetic transcriptions were conducted perceptually according

to the manner and location of articulation, in accordance with Shuster & Wambaugh (2000), and

Shriberg and Kent (1995) (see below paragraph on phoneme categorization). Close or narrow

transcription includes transcription of sounds that do not alter the meaning of the word, but rather

attempt to omit as few details as possible. A broadband spectrogram (260 Hz bandwidth) was

used to mark the cue and phoneme onsets and offsets. We used custom Praat scripts to extract

data according to the specifications below. First (F1) and second (F2) formants and pitch levels

were extracted at ten points over the duration of each stressed vowel /i/ or /a/ (i.e. 10%, 20%,

30%, etc. of phoneme duration) to allow for pitch trajectory analysis over a normalized duration.

Therefore, each pitch trajectory has 9 samples. Pitch trajectories were averaged across subjects

to generate **Figure 5**. First and second formants was extracted via Praat using the Burg linear

predictive coding algorithm (Gray & Markel, 1978) with a ceiling of 5500 Hz for females and 5000

Hz for males. We defined absolute pitch at the midpoint of the vowel and calculated the average

intensity over the duration of each word. To calculate the distance between the two corner vowels

(/a/ and /i/), we found the Euclidian linear distance between average /a/ and /i/ formants at the

vowel midpoint.

        Using the annotations above, we calculated phoneme frequency as the number of times

an individual phoneme is uttered during the session. Because SAS trials occur less frequently

than voluntary trials, phoneme frequency was normalized between trial types by multiplying SAS

trial phoneme frequencies by the ratio of voluntary to SAS trials. Phonemes were categorized by

their manner (e.g., stops (/b, g/), glides (/w, j/)) and place (e.g. labial (/m, f/), alveolar (/l, d/)) of

articulation; if they were voiced or unvoiced; and if they were correct for the word in question

(target vs. actual). Furthermore, errors which maintained either manner or place of articulation (e.g. /p/ in place of /f/) were classified as distortions, while errors which were not similar to the target sound were classified as substitutions (Odell et al., 1991).

2.3.4   Statistical Analysis

We hypothesized that SAS-elicited words, compared to voluntary, would have higher intensity and pitch, higher frequency of sustained sounds, and larger vowel spaces. A Generalized Linear Mixed Effects model using the *lme4* package in R 2020 version 4.0.243 was used to assess dependent variables (e.g., pitch, formants, intensity, vowel space, phoneme frequency). *Trial type* (SAS vs. voluntary) and *Vowel* type (/a/ vs. /i/) were fixed factors and *Subjects* were treated as a random factor, nested within trial type. Tukey with a p-value < 0.05 was used for pos-hoc testing. Brown Forsythe tests were used to assess homogeneity of variance. We calculated Pearson correlation coefficients (r) in MATLAB 2020a version 9.8.0 to compare average pitch trajectory curves for SAS vs. voluntary trials. The *corrcoef* function in MATLAB also tests for significance of correlation. We report both r and p values for each word's pitch trajectory below. Linear regression analyses were used to investigate the effects of aphasia severity (mild, moderate, severe), and apraxia severity (mild, moderate, severe) on all dependent variables.

2.4   Results

Intensity was affected by trial type, leading to an average increase in intensity across all words for SAS trials compared to voluntary trials (*SAS*: 63.9 ± 5.16 dB, *vol*: 63.3 ± 6.11 dB; $F_{(1,1751)} = 15.15$, $p = .0001$) **(Figure 1)**. When words were assessed individually, SAS trials had increased intensity for the words "ball" ($F_{(1,319)} = 9.61$, $p = .0020$), "cheese" ($F_{(1,296)} = 15.67$, $p = .0001$), "please" ($F_{(1,273)} = 17.99$, $p < 0.0001$), and "stop" ($F_{(1,300)} = 6.32$, $p = .0125$) **(Figure 2)** but "feet" and "water" intensities were unaffected by trial type.

Pitch was affected by trial type, leading to an average increase in pitch across all words for SAS trials compared to voluntary trials (*SAS*: 193.9 ± 72.9 Hz, *vol*: 171.2 ± 64.3 Hz; $F_{(1,1305)}$

= 18.9, *p* < 0.0001) **(Figure 1)**. When words were assessed individually, SAS trials increased

pitch for the words "cheese" (F(1,239) = 23.4, *p* < 0.0001), "please" (F(1,217) = 12.6, *p* = .0005),

"stop" (F(1,146) = 9.47, *p* = .0025), and "water" (F(1,205) = 17.9, *p* < 0.0001) **(Figure 2)** but "ball"

and "feet" intensities were unaffected by trial type.
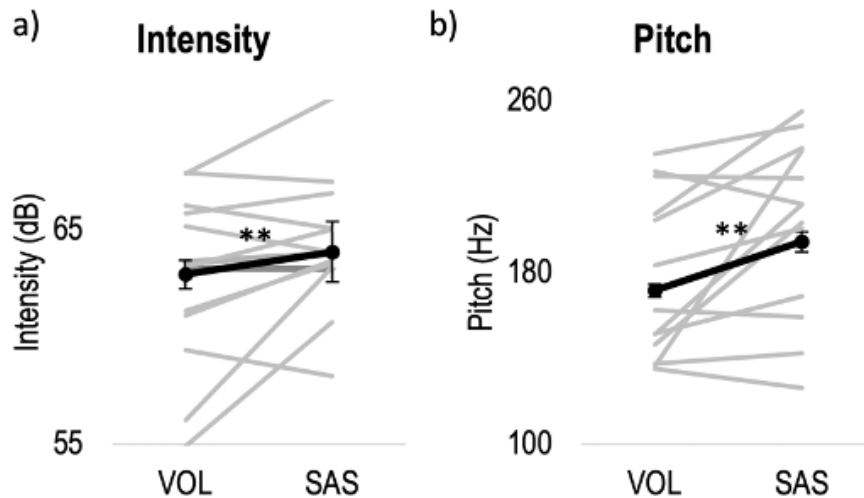
Figure 1. Average pitch and intensity changes across all words. Bold black lines represent group mean and SEM. Thin grey lines represent individual subject average changes. All subjects' a) speech intensity average over the first syllable for all 6 target words between voluntary and SAS trials and b) speech pitch at the first vowel midpoint for all 6 target words between voluntary and SAS trials. Error bars are defined as standard error (SEM = STDEV÷√ n). p < 0.01**

Midpoint formants (F1 and F2) changed for both vowels ("i" and "a") tested. For "i"

vowels, F1 increased during SAS trials (*SAS*: 485.6 ± 176.1 Hz, *vol:* 347.3 ± 91.7 Hz; F(1,717) =

185.4, p < 0.0001) while F2 decreased during SAS trials (*SAS*: 1786.9 ± 624.6 Hz, *vol:* 2212.8 ±

376.2 Hz*;* F(1,717) = 131.4, p < 0.0001) **(Figure 4)**. Conversely, for "a" vowels, F1 decreased

during SAS (*SAS*: 554.8 ± 203.9 Hz, *vol:* 671.3 ± 131.8 Hz; F(1,735) = 70.1, p < 0.0001) while F2

increased during SAS (*SAS*: 1633.2 ± 583.2 Hz, *vol:* 1194.6 ± 383.6 Hz; F(1,735) = 133.7, p <

0.0001) **(Figure 4)**. This indicates a smaller vowel space for SAS trials compared to voluntary

trials.

Brown Forsythe tests yielded increased variability during SAS trials for all outcome

measures except for intensity, which decreased. Words preceded by an SAS had more variable
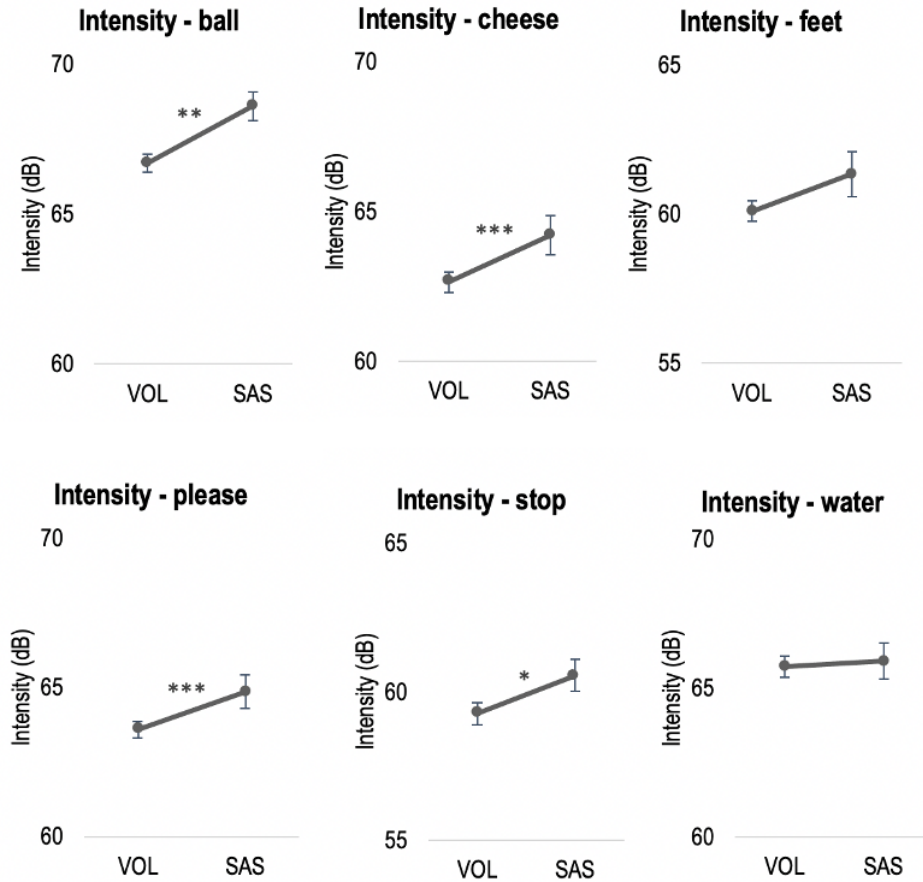
Figure 2. Intensity changes for each word. Group results for speech intensity averages over the first syllable for all 6 target words between voluntary and SAS trials. Error bars are defined as standard error (SEM = STDEV÷√ n). $p < 0.05$*, $p < 0.01$**, $p < 0.001$***

outcomes in terms of their pitch ($p = .001$) and all four formant measures (F1 and F2 for /i/ and /a/ vowels) ($p < 0.0001$). Variability in word intensity decreased (i.e., was more consistent) for SAS trials compared to voluntary trials ($p = .0013$).

Pitch trajectories were affected by trial type for some, but not all, words. While overall pitch level increased **(Figures 1 and 3)**, the trajectories had, on average, slightly more variation in SAS trials compared to voluntary. Four words had correlated (i.e., similar) pitch trajectories averaged across subjects for SAS and voluntary: "ball" (p = .009), "please" (p = .0003), "cheese"

(p < 0.0001), and "water" (p = .01) **(Figure 5)**. Pitch trajectories for "stop" and "feet, however,

showed no correlation between trial types **(Figure 5)**.
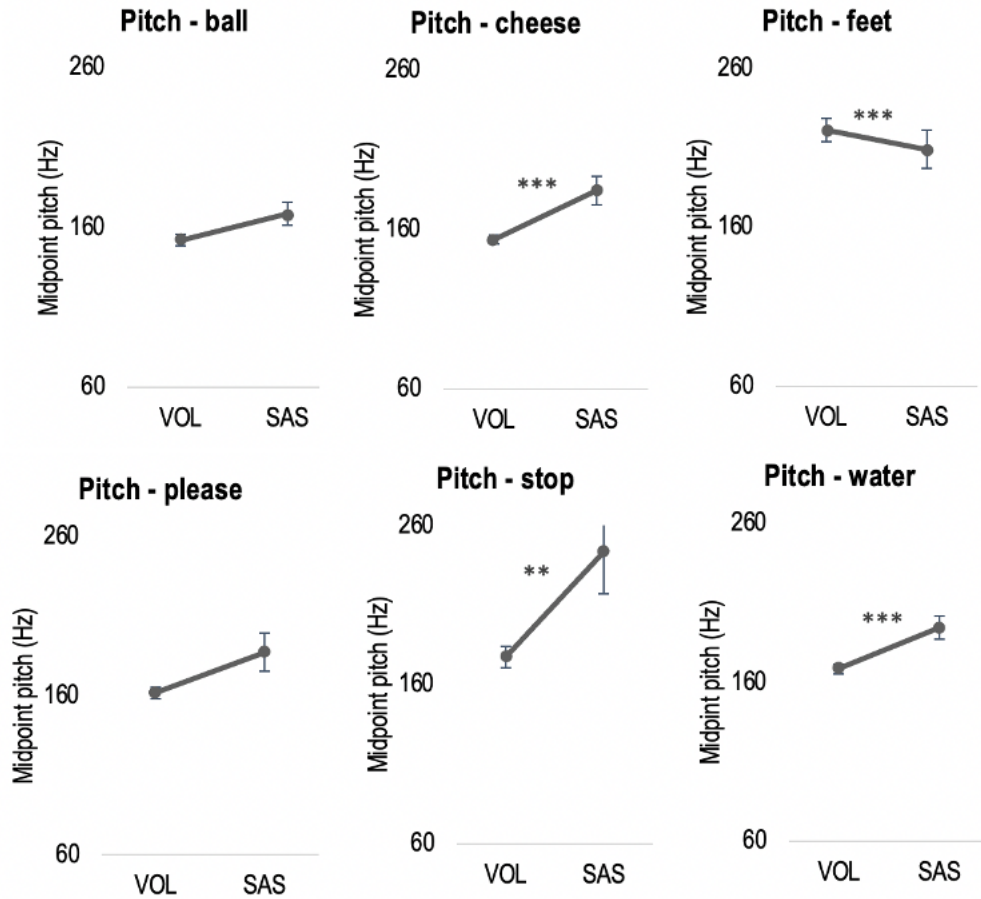
Figure 3. Pitch changes for each word. Group results speech pitch averages at the first syllable midpoint for all 6 target words between voluntary and SAS trials. Error bars are defined as standard error (SEM = STDEV÷√ n). $p < 0.05$*, $p < 0.01$**, $p < 0.001$***

Phoneme frequency was also affected by trial type. Voluntary trials had higher rates of

stops compared to SAS trials (SAS: 66.47 ± 34.4 utterances, vol: 71.1 ± 34.5 utterances, p = .01)

(Figure 6a). They were replaced with higher rates of sustained phonemes (fricatives, glides, affricates, liquids), though type varied between subjects (SAS: 111.67 ± 52.4 utterances, vol: 106.3 ± 53.9 utterances, p = .01). SAS trials had fewer distortions (p = .01), but no change in the
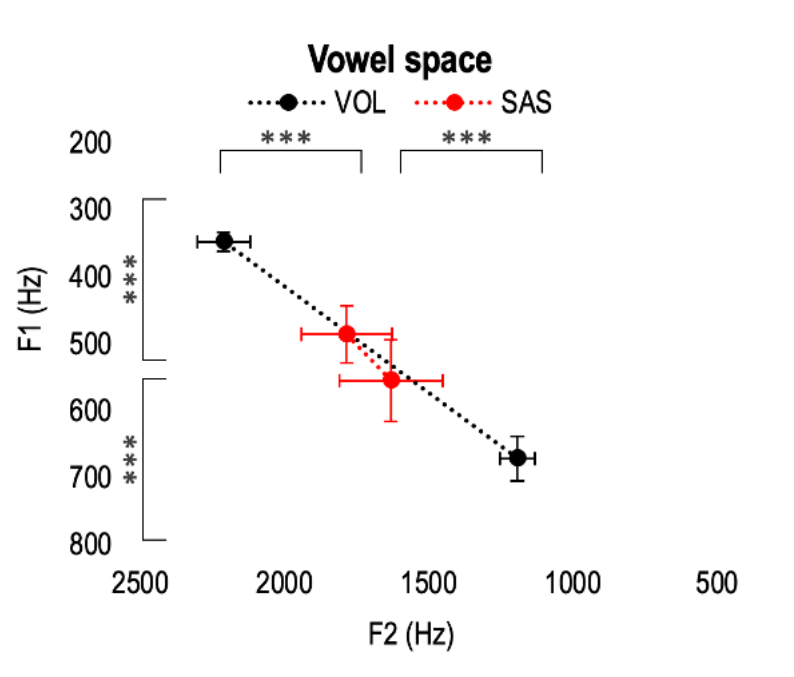
Figure 4. Vowel formant changes across /a/ and /i/ vowels. Formant frequency (F1 and F2) averages and SEM for SAS (red) and voluntary (black) trials compared across all 6 target words for all subjects. Vowel space determined by F1 and F2 formants is significantly smaller for SAS trials compared to voluntary. Error bars are defined as standard error (SEM = STDEV÷√ n). p < 0.001***

frequency of substitution errors or overall error rate compared to voluntary trials **(Figure 6b)**.

Fifty-three percent of SAS trials were found to have onset latencies below the 363 ms threshold and were therefore considered true StartReact trials. Of these, SAS acoustic onsets yielded an average latency of 244 ± 58 ms. Thirty-seven percent of SAS onsets that were included occurred faster than 205 ms— approximately the same latency of healthy startled speech (Stevenson et al., 2014).

2.5   Discussion

2.5.1   Summary
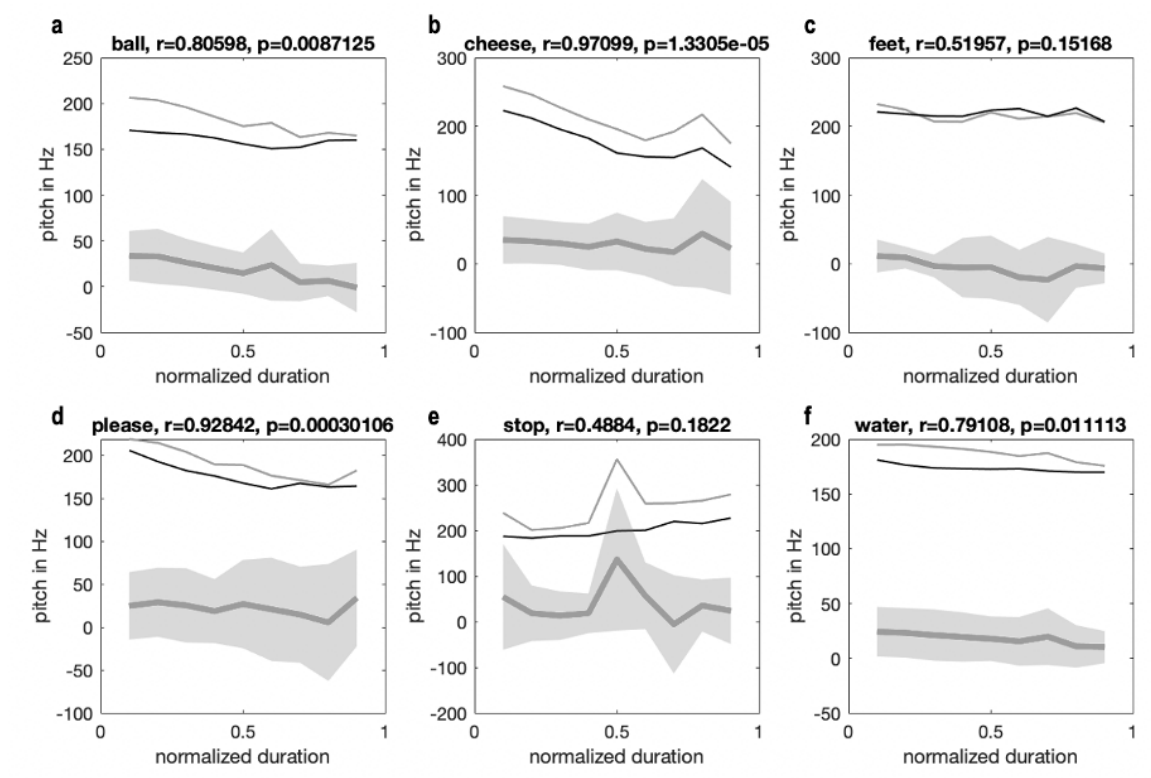
Figure 5. SAS, voluntary, and difference wave pitch trajectories for all words. Average pitch trajectories for word vowels for SAS (thin grey line) and voluntary (thin black line) trials normalized over duration for all subjects. Also plotted are average (thick grey line) difference waves calculated as the difference between SAS and voluntary trajectories with 95% confidence interval clouds in light grey. Pearson's correlation coefficient (r) and significance (p) between average SAS and voluntary trajectories are noted above each graph. Only SAS and voluntary pitch trajectories for "feet" and "stop" were not significantly correlated.

The objective of this study was to determine the impact of SAS exposure on speech parameters in individuals with post-stroke aphasia and AOS. Our data demonstrate that exposure to SAS impacts speech—by increasing intensity and pitch, centralizing vowel placement, and increasing the frequency of sustained sounds over stops, compared to voluntary words. Moreover, our data demonstrate that speech impaired by post-stroke aphasia and AOS is susceptible to StartReact, with around a third of acoustic onsets comparable to healthy startled

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speech onsets reported by Stevenson (205 ms). Finally, variability in pitch and formants

increased for SAS trials, but variability in intensity decreased. Together, these data indicate that
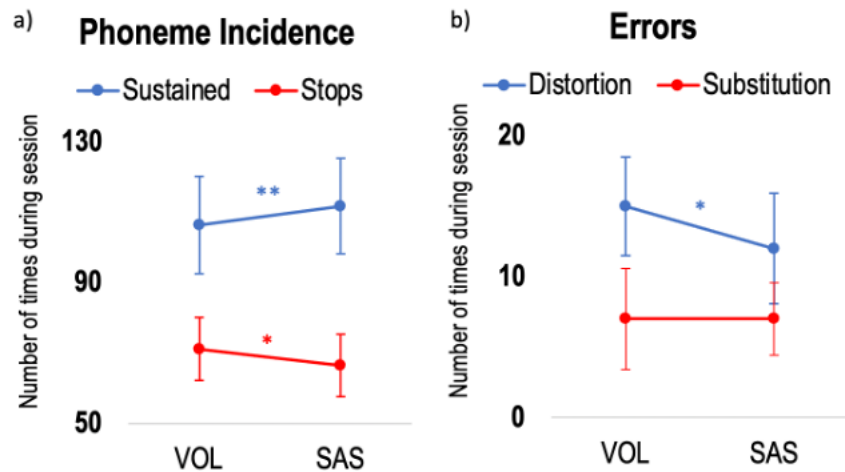
Figure 6. Phoneme frequency and error type across all words. Group averages for voluntary and SAS trials of a) how many stop phonemes (red) vs. sustained phonemes (blue) (i.e. fricatives, liquids, glides) subjects achieved on a session, and b) how many substitution errors (red) (i.e. dissimilar to target sound) vs. distortion errors (blue) (similar to target sound) individual subjects made over the session. Error bars are defined as standard error (SEM = STDEV÷√ n).

StartReact allows subjects to bypass initiation deficits to allow production of sounds that were not

present during voluntary speech but does not improve (and rather may detriment) speech

intelligibility, likely due to lack of feedback control when startled. This is in line with previous

findings from masked auditory feedback studies showing impaired intelligibility (Jacks & Haley,

2015; Maas et al., 2015). We are the first to demonstrate that startling acoustic stimuli can impact

impaired speech.

The two measures related to intelligibility we evaluated were vowel formant distance and

substitution/distortion error rate. We hypothesized that SR would act in a manner similar to

masked auditory feedback studies, due to altered feedback integration, and reduce speech

intelligibility. We hypothesized that vowel distance would decrease, and that error rate would

increase. Our data show that vowel distance decreased, and error rate did not change, with

errors becoming more consistent (in manner) and distortions decreasing. Therefore, SR decreased vowel intelligibility (distance) but did not functionally affect overall phoneme intelligibility. As individuals with AOS often exhibit inconsistent substitution errors, and substitution errors did not change because of SR, intelligibility was improved in some ways (decreased distortions), worsened in others (reduced vowel distance), and remained the same in other ways (unaffected substitutions). All in all, functional intelligibility likely was not enhanced. Increased pitch and intensity likely were not related to intelligibility in these subjects.

2.5.2 Planning and Initiation of Startled Speech

Our results showing that StartReact was present (e.g., speech parameters were altered in response to SAS) suggests that individuals with post-stroke AOS and aphasia have 1) residual capacity for speech planning and 2) AOS deficits are driven in part by initiation via impaired structures. First, the intended movement must be planned for StartReact to be present. Leote et al. found that more cortically involved tasks like picture naming could only be elicited in healthy subjects by an SAS if individuals were sufficiently prepared (i.e. could anticipate the next picture) (Leote et al., 2018). That impaired speech was susceptible to StartReact suggests that even individuals with severe aphasia and AOS retain some ability to generate feedforward plans, even if those plans are flawed. This also reinforces findings from upper limb studies, in which movement must have been sufficiently prepared to be elicited by an SAS (Carlsen et al., 2004, 2012; Kirkpatrick et al., 2018). Second, that StartReact facilitates the initiation of difficult sounds that were not present during voluntary speech indicates that subjects with AOS can access speech plans using StartReact that were voluntarily difficult or impossible to initiate. Phoneme complexity, or sounds with higher processing demands, has been well-described in the literature, with vowels being the easiest sounds to produce, followed by liquids, stops, fricatives, affricates, and clusters both for speakers with AOS and during child development (Bislick & Hula, 2019). Multisyllabic words and word initial sounds also increase motor planning load (Bislick & Hula, 2019). Here, seven subjects with apraxia achieved a phoneme during SAS trials that they could

not initiate voluntarily. These phonemes included labiodental fricatives (/f/), palato-alveolar affricates (/t͡ʃ/) and correct sequencing of consonant clusters (/pl/ and /st/)—all requiring a high degree of articulatory coordination. Subjects also produced these sounds more often during SAS trials even if they could generate them during voluntary trials. Lastly, that SAS trials were altered beyond pitch and intensity indicates that we are not merely seeing the effects of stimulus intensity but true StartReact. Intelligibility was altered by SAS, as was pitch trajectory. It is unclear why SAS exposure altered the pitch trajectories of some ("stop", "feet"), but not all words. If SAS exposure does serve as a way to limit feedback correction on speech (Chiu & Gick, 2014b; Seidler et al., 2004), semantic and emotional processing may be upregulated at an early stage of execution, before feedback correction, similar to involuntary elicitation of swear words (Hansen et al., 2019; Landis, 2006; Simonyan & Horwitz, 2011; Van Lancker & Cummings, 1999). If this was the case, then "stop", a word with high emotional weight, was accessed and deployed more intensely after an SAS compared to a word such as "ball", with low emotional weight (Bakhtiyari et al., 2015). However, this hypothesis does not account for the change in pitch trajectory for the word "feet", a word with an arguably low emotional weight.

Still, though we see presentation of complex sounds that were not present during voluntary speech, these sounds were not functional to the word they were trying to say. These novel (to the subject) phonemes described above were often also inappropriate and lead to no change in substitution errors. For example, when the target word was "stop", subjects frequently were able to achieve words like "pop" or "top" during voluntary trials. During SAS trials, subjects could achieve words like "sop" or "slop", which, while requiring higher levels of articulatory coordination, were still not accurate. Interestingly, while SAS trials saw no change in substitution errors, they contained fewer distortions. It would therefore seem that substitution errors are part of the feedforward plan initiated by SAS. This is consistent with previous clinical findings that describe substitution errors as a hallmark characteristic of AOS, compared to dysarthria of speech which tends to result in consistent distortions (Chapey, 2012a, 2012b). That distortion

errors decreased when elicited by SAS suggests that SAS benefits motor initiation and execution (as in dysarthria of speech), but not planning or feedback control.

Finally, StartReact may serve as a way to remove initial feedback correction after vocalization due to its fast, involuntary action. Altered feedback control can be seen here in both the disruption of pitch trajectories and decreased vowel space during SAS trials, both of which depend somewhat on feedback correction to be accurate. That F1 increased in these words indicates SAS trials exhibited a lowered jaw and taller oral cavity compared to voluntary. Increased F2 indicates a more forward tongue placement and shallower oral cavity. Unimpaired motor execution is often followed by feedback control (Seidler et al., 2004), which is essential for error detection and compensation and to decrease noise and final error (Ao et al., 2015). Feedforward control depends solely on an individual's predictive motor planning ability and requires no time delay to fully be executed, though the execution may not be as precise without sensory feedback (Ao et al., 2015; Desmurget & Grafton, 2000). The disruption of vowel formants may be due to lack of feedback control, as in low accuracy in startled upper extremity movements (Rahimi & Honeycutt, 2020). Results from auditory feedback masking studies indicate that deficits related to AOS stem from an inability to correctly perform feedforward planning (Jacks & Haley, 2015; Maas et al., 2015), while feedback control remains intact. Here, we report similar decreases in intelligibility in the feedforward plan, marked by both centralized vowel formants and novel (to the subject) but incorrect consonant phonemes. Thus, our subjects do have some capacity to plan difficult sounds, but those plans are also inaccurate even when initiated by SAS. It is important to note that all of our subjects had both aphasia and AOS to some degree, therefore it is difficult to speculate on the impact of feedback processing in aphasia on our results. Together, our data indicate that planning of more complex sounds (e.g., fricatives, clusters) may be intact but inaccessible to motor neurons, and that feedback is certainly critical to appropriate patterns of speech. Future studies might investigate StartReact with auditory feedback masked to better isolate the intended speech movement.

2.5.3 Comparison to StartReact in the Upper Extremity

These findings are analogous to our previous work in the effect of SAS on post-stroke upper extremity impairment. In the upper extremity, StartReact allows subjects with stroke to increase the probability of muscle activity compared to voluntary (Rahimi & Honeycutt, 2020). StartReact trials were initiated faster and had increased reaching distance in severe subjects with little-to-no voluntary movement (Rahimi & Honeycutt, 2020). Therefore, StartReact allowed the initiation of novel (to the subject), larger patterns of muscle activity leading to further reaching distances. Despite these "improvements", StartReact movements were often not in the direction of the target and deviation of linearity was increased drawing into question if StartReact's novel (to the subject) movement patterns are of functional significance. We report similar tradeoffs in speech. Our results indicate that StartReact increases activity throughout the vocal tract, facilitating speech sounds that were not present during voluntary speech in individuals with AOS. An increase in speech intensity indicates increased lung pressure via higher muscle activation (Baer, 1979; Loucks et al., 2007; Mu & Sanders, 2007). Next, higher pitch indicates that laryngeal tension increases (Baer, 1979; Chiu, 2015; Dichter et al., 2018), and that this tension is graded— i.e. is not simply "on" or "off, as SAS did not affect accuracy of phoneme voicing. This is consistent with the classic startle response, during which speech gets higher and louder (Chiu, 2015; Ćosić et al., 2016; Sapir et al., 1998). Lastly, StartReact increases the frequency of sustained sounds (fricatives, liquids, glides, and affricates) which are traditionally quite difficult for people with severe apraxia to produce (Haley et al., 2000; La Pointe & Johns, 1975). That StartReact facilitates these sounds indicates increased fine motor control in the articulators (e.g., lips, tongue) allowing air to pass through in a controlled fashion. However, similar to the upper extremity, StartReact speech was not more accurate (decreased intelligibility). In conclusion, StartReact allows subjects to achieve more difficult, novel (to the subject) speech sounds requiring increased control (e.g., fricatives), and their speech motor execution increased with higher pitch and intensity; however, their speech was not accurate, with centralized formants and phonemes that were more dissimilar to the target after SAS exposure.

Previous StartReact research can be divided into two categories: effect of StartReact during a session and effect of StartReact at the end of a session. During a session, there is the possibility for movement disruption. Studies in stroke and hereditary spastic paraplegia have shown increased speed, muscle activation, reaching distance, and muscle activation probability but have also shown increased task inappropriate flexor activity (which diminished over the session), and no change in final error (accuracy) (Honeycutt & Perreault, 2012; Nonnekes, Oude Nijhuis, et al., 2014; Rahimi & Honeycutt, 2020; van Lith et al., 2018). Thus, during the session, SAS would seem to enhance execution size and speed but not accuracy, disrupting movements. In contrast, this disruption does not translate to voluntary movement. In fact, when voluntary movements were evaluated at the end of a session, disruptions decreased. Prior research evaluating voluntary reaching at the beginning and end of a session in moderate/severe stroke (Rahimi et al., 2021) found that even though task-inappropriate flexor activity and inaccuracy were present during the session, voluntary movements were enhanced by the end of the session (increased reaching distance, movement onset, and final accuracy by the end of the session)(Rahimi et al., 2021). Therefore, previous research has shown that acute SAS exposure can be disruptive, but clinically relevant at the end of a session.

The objective of this study was to determine whether or not SR could be elicited in post-stroke AOS/aphasia, and what effect it would have during the session. Our results suggest that SR may not functionally enhance speech (decreased vowel distance, increased pitch, no change in overall error rate), but this is consistent with SR studies above showing muscle activity increased but accuracy did not change. Our data do demonstrate that speech is more consistent and that distortion errors decrease under SR. Once a subject has undergone a session of SR in reaching, their voluntary reaching accuracy increases(Rahimi et al., 2021). It is unknown whether the same effect will happen in Aphasia/AOS.

2.5.4   Clinical Implications of StartReact

Our data demonstrate that StartReact is intact in individuals with AOS, even severely impaired speech. This is significant because speech is still susceptible to StartReact, despite damage to areas fundamental to speech production (Hickok & Poeppel, 2007; Stark et al., 2019; Tourville & Guenther, 2011). Together, these results show that SAS allows individuals with AOS to produce words louder and with more difficult (i.e., sustained) sounds indicating that StartReact can access and deploy improved patterns of speech more consistently, raising the possibility of StartReact's usage in therapeutics.

Still, despite these seemingly beneficial changes, formant frequency results show that SAS decreases vowel space, decreasing speech intelligibility (den Ouden et al., 2018). While these subjects can achieve novel (to the subject) and more complex consonants after an SAS, they are not accurate. Combined with centralization and increased variability of vowel formants, these results indicate startled speech has decreased intelligibility (den Ouden et al., 2018). This is in direct contrast to startled speech in healthy individuals without speech impairment, who have no changes in formants, pitch trajectories, or articulation (Chiu, 2015; Chiu & Gick, 2014b; Stevenson et al., 2014) during StartReact. These changes in phonemic and acoustic features represent a perturbation of characteristics related to AOS. All but one of the subjects in this study had co-occurring aphasia, but it is difficult to determine if SAS exposure affected aphasia presentation. Only two domains of aphasia would have impacted the experimental session: comprehension (to understand the task) and repetition (which is what we were evaluating). Only one subject had severe Wernicke's aphasia (comprehension deficits) and this individual was able to perform the task correctly in response to SAS and vol cues, with expected/reasonable speech sound errors. It is unclear to what extent comorbid aphasia influenced the results of this study, but aphasia presence did not seem to diminish ability to do the task. While still likely worthy of study, these minor changes indicate that StartReact may not have the same rehabilitative potential for speech that is afforded to upper extremity control (Rahimi et al., 2021).

While the changes seen with StartReact in upper limb are considerable (Honeycutt et al., 2015; Honeycutt & Perreault, 2012; Rahimi & Honeycutt, 2020), the changes we see in the present study are small and may not translate to clinically meaningful differences. In the first study examining the impact of StartReact in stroke (Honeycutt & Perreault, 2012), StartReact was present in 80% of trials, and doubled brachioradialis muscle activity amplitudes compared to voluntary during an extension task. Here, subjects are not only startling less frequently at ~50% of the time (though we are using a lower decibel stimulus (Carlsen, 2015; Carlsen et al., 2007)), they only see average changes an average change of 0.6 dB in speech intensity and an average change of 22.7 Hz in pitch. One reason for this difference between upper extremity and speech is that studies in upper extremity used a louder SAS at 128 dB (Honeycutt & Perreault, 2012), while the present study was constrained by remote delivery and the SAS used here was only 105 dB. An additional factor may be due to increased reliance on cortical structures while planning speech (Hickok & Poeppel, 2007), and StartReact's inability to fully access the speech plan as StartReact is likely mediated by brainstem structures (Carlsen & Maslovat, 2019; Nonnekes, Oude Nijhuis, et al., 2014). Therefore, while StartReact has been suggested as a useful clinical tool for upper extremity impairment following stroke, the current study does not necessarily support clinical efficacy in speech rehabilitation.

On the other hand, our data demonstrating changes in error rate do suggest a possible therapeutic use of SR as an adjuvant. As SR did lead to increased speech apparatus activation, consistency in errors, and was accessible in individuals with severe deficits (ranging from comprehension to AOS), SR may be able to increase the intensity of practice across several types of populations. This increase of practice intensity is further supported by previous findings that SR can lead to 2 to 3 fold increases in maximum voluntary contraction in individuals with little-to-no voluntary upper extremity movement (Rahimi & Honeycutt, 2020). Another principle of the SR task is that subjects must be fully prepared to speak before hearing the cue (Carlsen et al., 2004; Carlsen & Maslovat, 2019; Leote et al., 2018). This intensity of preparation over the course of an hour requires a massive amount of phonological working memory and attention

(Belke, 2008; Lugtmeijer et al., 2021; R. C. Martin & Schnur, 2019). Attention therapies for post-stroke aphasia have been used with moderate success (Peach et al., 2017, 2019; Zakariás et al., 2019). SR, combined with high-intensity word preparation, may make execution less effortful for individuals with severe impairment who would not be able to sustain this attention voluntarily. As such, SR may have more success used alongside traditional speech therapy as an adjuvant, assisting in fast and more stimulated speech execution.

2.5.5   Hypermetric Inspiratory Events

Previous studies evaluating reaching report StartReact-elicited movements are frequently interrupted by task-inappropriate flexor muscle activity followed by the correct extension movement (Honeycutt & Perreault, 2012; Rahimi et al., 2021; Rahimi & Honeycutt, 2020). This phenomenon is specific to individuals who have had a stroke. It has been hypothesized that this task-inappropriate flexion the result of a hypermetric classic startle response that overlays the StartReact extension response (Choudhury et al., 2019; Honeycutt & Perreault, 2012; Rahimi & Honeycutt, 2020). This is supported by known cortical disinhibition of the classic startle reflex and increased reticulospinal tract activation following a stroke (Davis & Gendelman, 1977; Karbasforoushan et al., 2019; Tresch et al., 2014).

Here, we similarly saw fast inspiratory breath that preceded speech. Sixty percent of our subjects performed at least 5 StartReact trials that were interrupted by large inhalations or gasps prior to vocalization. It is possible that this is also the result of a post-stroke hypermetric startle response (Choudhury et al., 2019; Honeycutt & Perreault, 2012; Rahimi et al., 2021). Future studies should examine the relationship between speech motor activity and vocalization in these instances of hypermetric inhalations after StartReact exposure.

2.5.6   Limitations

Due to our remote data collection during a pandemic, we could not reliably collect EMG data. The loss of EMG data limits this study in two ways. First, EMG information would have allowed us to further quantify the impact of StartReact through the evaluation of muscle activation

(e.g., amplitude, latency, timing of agonist/antagonist pairs). Second, it is customary to use activity in the sternocleidomastoid muscle to verify the presence of StartReact. Instead, we relied on the onset latencies within the acoustic speech signal. Though we lacked EMG confirmation of the StartReact effect, the change in SAS trials compared to voluntary does indicate that StartReact was present and not simply the result of a stimulus intensity effect (Luo et al., 2018). Speech volume and subglottal pressure will increase when preceded by a loud cue, regardless of StartReact being present (Baer, 1979; Chiu, 2015; Luo et al., 2018); however, our data show that speech is not just becoming louder or higher, but that the utterances themselves are changing, as seen through altered formants, phoneme frequencies, and pitch trajectories. Taken together, StartReact is likely present but further studies should do a more complete comparison with the use of the SCM muscle. Future studies evaluating the impact of StartReact on impaired speech would benefit from a healthy control group, as it would allow direct comparison to age-matched controls in terms of the voluntary speech patterns. As mentioned above, it is unclear to what extent comorbid aphasia influenced the results of this study. Future studies should further evaluate this by including one group of participants with only aphasia and another group with only AOS, matched in age and severity. Future studies should also compare the types of errors that occur under SAS and voluntary trials to determine if SAS exposure yields more error consistency and phoneme variety. If SAS exposure does result in these gains, it would be clinically meaningful for individuals with AOS who often struggle with inconsistent phonemic errors.

2.6   Conclusion

In conclusion, this study offers the first evidence that stroke-impaired speech is susceptible to the StartReact effect, marked by increased pitch, intensity, and alterations in formants, pitch trajectories, and articulation. Future studies should examine the impact of SAS training in individuals with AOS on voluntary speech intelligibility and clinical measures of aphasia and apraxia impairments.

REFERENCES FOR CHAPTER 2

Alibiglou, L., & MacKinnon, C. D. (2012). The early release of planned movement by acoustic startle can be delayed by transcranial magnetic stimulation over the motor cortex. The Journal of Physiology, 590(4), 919–936. https://doi.org/10.1113/jphysiol.2011.219592

Anderlini, D., Wallis, G., & Marinovic, W. (2019). Language as a Predictor of Motor Recovery: The Case for a More Global Approach to Stroke Rehabilitation. Neurorehabilitation and Neural Repair, 33(3), 167–178. https://doi.org/10.1177/1545968319829454

Ao, D., Song, R., & Tong, K. (2015). Sensorimotor Control of Tracking Movements at Various Speeds for Stroke Patients as Well as Age-Matched and Young Healthy Subjects. PLOS ONE, 10(6), e0128328. https://doi.org/10.1371/journal.pone.0128328

Baer, T. (1979). Reflex activation of laryngeal muscles by sudden induced subglottal pressure changes. The Journal of the Acoustical Society of America, 65(5), 1271–1275. https://doi.org/10.1121/1.382795

Bakhtiyari, J., Khatoonabadi, S. A. R., Dadgar, H., Bakhtiari, B. M., Khosravizadeh, P., & Shaygannejad, V. (2015). Comparison of emotional and non-emotional word repetitions in patients with aphasia. Advanced Biomedical Research, 4, 164. https://doi.org/10.4103/2277-9175.162540

Bartels, B. M., Quezada, M. J., Ravichandran, V. J., & Honeycutt, C. F. (2020). Experts, but not novices, exhibit StartReact indicating experts use the reticulospinal system more than novices. Journal of Motor Behavior, 0(0), 1–7. https://doi.org/10.1080/00222895.2020.1732860

Basilakos, A. (2018). Contemporary Approaches to the Management of Post-stroke Apraxia of Speech. Seminars in Speech and Language, 39(1), 25–36. https://doi.org/10.1055/s-0037-1608853

Basilakos, A., Yourganov, G., den Ouden, D.-B., Fogerty, D., Rorden, C., Feenaughty, L., & Fridriksson, J. (2017). A Multivariate Analytic Approach to the Differential Diagnosis of Apraxia of Speech. Journal of Speech, Language, and Hearing Research : JSLHR, 60(12), 3378–3392. https://doi.org/10.1044/2017_JSLHR-S-16-0443

Belke, E. (2008). Effects of working memory load on lexical-semantic encoding in language production. Psychonomic Bulletin & Review, 15(2), 357–363. https://doi.org/10.3758/PBR.15.2.357

Bislick, L., & Hula, W. D. (2019). Perceptual Characteristics of Consonant Production in Apraxia of Speech and Aphasia. American Journal of Speech-Language Pathology, 28(4), 1411–1431. https://doi.org/10.1044/2019_AJSLP-18-0169

Bohland, J. W., Bullock, D., & Guenther, F. H. (2010). Neural representations and mechanisms for the performance of simple speech sequences. Journal of Cognitive Neuroscience, 22(7), 1504–1529. https://doi.org/10.1162/jocn.2009.21306

Carlsen, A. N. (2015). A broadband acoustic stimulus is more likely than a pure tone to elicit a startle reflex and prepared movements. Physiological Reports, 3(8). https://doi.org/10.14814/phy2.12509

Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J., & Franks, I. M. (2004). Prepared movements are elicited early by startle. Journal of Motor Behavior, 36(3), 253–264. https://doi.org/10.3200/JMBR.36.3.253-264

Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J., & Franks, I. M. (2009). Differential effects of startle on reaction time for finger and arm movements. Journal of Neurophysiology, 101(1), 306–314. https://doi.org/10.1152/jn.00878.2007

Carlsen, A. N., Dakin, C. J., Chua, R., & Franks, I. M. (2007). Startle produces early response latencies that are distinct from stimulus intensity effects. Experimental Brain Research, 176(2), 199–205. https://doi.org/10.1007/s00221-006-0610-8

Carlsen, A. N., & Maslovat, D. (2019). Startle and the StartReact Effect: Physiological Mechanisms. Journal of Clinical Neurophysiology, 36(6), 452–459. https://doi.org/10.1097/WNP.0000000000000582

Carlsen, A. N., Maslovat, D., & Franks, I. M. (2012). Preparation for voluntary movement in healthy and clinical populations: Evidence from startle. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 123(1), 21–33. https://doi.org/10.1016/j.clinph.2011.04.028

Carlsen, A. N., Maslovat, D., Lam, M. Y., Chua, R., & Franks, I. M. (2011). Considerations for the use of a startling acoustic stimulus in studies of motor preparation in humans. Neuroscience and Biobehavioral Reviews, 35(3), 366–376. https://doi.org/10.1016/j.neubiorev.2010.04.009

Castellote, J. M., & Valls-Solé, J. (2015). The StartReact effect in tasks requiring end-point accuracy. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 126(10), 1879–1885. https://doi.org/10.1016/j.clinph.2015.01.028

Cera, M. L., & Ortiz, K. Z. (2010). Phonological analysis of substitution errors of patients with apraxia of speech. Dementia & Neuropsychologia, 4(1), 58–62. https://doi.org/10.1590/S1980-57642010DN40100010

Chapey, R. (2012a). Primary Progressive Aphasia and Apraxia of Speech. In Language intervention strategies in aphasia and related neurogenic communication disorders: Fifth edition (pp. 550–555).

Chapey, R. (2012b). The Nature and Management of Neuromotor Speech Disorders Accompanying Aphasia. In Language intervention strategies in aphasia and related neurogenic communication disorders: Fifth edition (pp. 1009–1030).

Chiu, C. (2015). Startling auditory stimulus as a window into speech motor planning. https://doi.org/10.14288/1.0220650

Chiu, C., & Gick, B. (2014a). Startling speech: Eliciting prepared speech using startling auditory stimulus. Frontiers in Psychology, 5. https://doi.org/10.3389/fpsyg.2014.01082

Chiu, C., & Gick, B. (2014b). Pitch planning in English and Taiwanese Mandarin: Evidence from startle-elicited responses. The Journal of the Acoustical Society of America, 136(4), EL322-328. https://doi.org/10.1121/1.4896405

Choudhury, S., Shobhana, A., Singh, R., Sen, D., Anand, S. S., Shubham, S., Baker, M. R., Kumar, H., & Baker, S. N. (2019). The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients. Neurorehabilitation and Neural Repair, 33(5), 375–383. https://doi.org/10.1177/1545968319836233

Coppens, M. J. M., Roelofs, J. M. B., Donkers, N. A. J., Nonnekes, J., Geurts, A. C. H., & Weerdesteyn, V. (2018). A startling acoustic stimulus facilitates voluntary lower extremity movements and automatic postural responses in people with chronic stroke. Journal of Neurology, 265(7), 1625–1635. https://doi.org/10.1007/s00415-018-8889-5

Ćosić, K., Popović, S., Kukolja, D., Dropuljić, B., Ivanec, D., & Tonković, M. (2016). Multimodal analysis of startle type responses. Computer Methods and Programs in Biomedicine, 129, 186–202. https://doi.org/10.1016/j.cmpb.2016.01.002

Davis, M. (1984). The mammalian startle response. In Neural stop of Startle Behavior (R. Eaton (Ed.), pp. 287–351). Plenum Publishing Corporation.

Davis, M., & Gendelman, P. M. (1977). Plasticity of the acoustic startle response in the acutely decerebrate rat. Journal of Comparative and Physiological Psychology, 91(3), 549–563. https://doi.org/10.1037/h0077345

Dekhtyar Maria, Braun Emily J., Billot Anne, Foo Lindsey, & Kiran Swathi. (2020). Videoconference Administration of the Western Aphasia Battery–Revised: Feasibility and Validity. American Journal of Speech-Language Pathology, 29(2), 673–687. https://doi.org/10.1044/2019_AJSLP-19-00023

den Ouden, D.-B., Galkina, E., Basilakos, A., & Fridriksson, J. (2018). Vowel Formant Dispersion Reflects Severity of Apraxia of Speech. Aphasiology, 32(8), 902–921. https://doi.org/10.1080/02687038.2017.1385050

Desmurget, null, & Grafton, null. (2000). Forward modeling allows feedback control for fast reaching movements. Trends in Cognitive Sciences, 4(11), 423–431. https://doi.org/10.1016/s1364-6613(00)01537-0

Dichter, B. K., Breshears, J. D., Leonard, M. K., & Chang, E. F. (2018). The Control of Vocal Pitch in Human Laryngeal Motor Cortex. Cell, 174(1), 21-31.e9. https://doi.org/10.1016/j.cell.2018.05.016

Duffy, J. R. (2006). Apraxia of speech in degenerative neurologic disease. Aphasiology, 20(6), 511–527. https://doi.org/10.1080/02687030600597358

Flowers, H. L., Silver, F. L., Fang, J., Rochon, E., & Martino, R. (2013). The incidence, co-occurrence, and predictors of dysphagia, dysarthria, and aphasia after first-ever acute ischemic stroke. Journal of Communication Disorders, 46(3), 238–248. https://doi.org/10.1016/j.jcomdis.2013.04.001

Gray, A. H., & Markel, J. D. (1978). Linear predictive coding and the Burg algorithm for speech analysis and synthesis. The Journal of the Acoustical Society of America, 64(S1), S159–S159. https://doi.org/10.1121/1.2003944

Haley, K. L., Ohde, R. N., & Wertz, R. T. (2000). Single word intelligibility in aphasia and apraxia of speech: A phonetic error analysis. Aphasiology, 14(2), 179–201. https://doi.org/10.1080/026870300401540

Haley, K. L., & Overton, H. B. (2001). Word Length and Vowel Duration in Apraxia of Speech: The Use of Relative Measures. Brain and Language, 79(3), 397–406. https://doi.org/10.1006/brln.2001.2494

Hansen, S. J., McMahon, K. L., & de Zubicaray, G. I. (2019). The neurobiology of taboo language processing: FMRI evidence during spoken word production. Social Cognitive and Affective Neuroscience, 14(3), 271–279. https://doi.org/10.1093/scan/nsz009

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. Nature Reviews Neuroscience, 8(5), 393–402. https://doi.org/10.1038/nrn2113

Hill, A. J., Theodoros, D., Russell, T., & Ward, E. (2009). Using telerehabilitation to assess apraxia of speech in adults. International Journal of Language & Communication Disorders, 44(5), 731–747. https://doi.org/10.1080/13682820802350537

Honeycutt, C. F., Kharouta, M., & Perreault, E. J. (2013). Evidence for reticulospinal contributions to coordinated finger movements in humans. Journal of Neurophysiology, 110(7), 1476–1483. https://doi.org/10.1152/jn.00866.2012

Honeycutt, C. F., & Perreault, E. J. (2012). Planning of Ballistic Movement following Stroke: Insights from the Startle Reflex. PLoS ONE, 7(8). https://doi.org/10.1371/journal.pone.0043097

Honeycutt, C. F., Tresch, U. A., & Perreault, E. J. (2015). Startling acoustic stimuli can evoke fast hand extension movements in stroke survivors. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 126(1), 160–164. https://doi.org/10.1016/j.clinph.2014.05.025

Hough, M. S., & Klich, R. J. (1998). Lip EMG activity during vowel production in apraxia of speech: Phrase context and word length effects. Journal of Speech, Language, and Hearing Research: JSLHR, 41(4), 786–801. https://doi.org/10.1044/jslhr.4104.786

Hybbinette, H., Schalling, E., Plantin, J., Nygren-Deboussard, C., Schütz, M., Östberg, P., & Lindberg, P. G. (2021). Recovery of Apraxia of Speech and Aphasia in Patients With Hand Motor Impairment After Stroke. Frontiers in Neurology, 12. https://doi.org/10.3389/fneur.2021.634065

Jacks, A. (2008). Bite block vowel production in apraxia of speech. Journal of Speech, Language, and Hearing Research: JSLHR, 51(4), 898–913. https://doi.org/10.1044/1092-4388(2008/066)

Jacks, A., & Haley, K. L. (2015). Auditory Masking Effects on Speech Fluency in Apraxia of Speech and Aphasia: Comparison to Altered Auditory Feedback. Journal of Speech, Language, and Hearing Research: JSLHR, 58(6), 1670–1686. https://doi.org/10.1044/2015_JSLHR-S-14-0277

Jürgens, U. (2002). Neural pathways underlying vocal control. Neuroscience and Biobehavioral Reviews, 26(2), 235–258. https://doi.org/10.1016/s0149-7634(01)00068-9

Karbasforoushan, H., Cohen-Adad, J., & Dewald, J. P. A. (2019). Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. Nature Communications, 10(1), 1–7. https://doi.org/10.1038/s41467-019-11244-3

Kirkpatrick, N. J., Ravichandran, V. J., Perreault, E. J., Schaefer, S. Y., & Honeycutt, C. F. (2018). Evidence for startle as a measurable behavioral indicator of motor learning. PloS One, 13(5), e0195689. https://doi.org/10.1371/journal.pone.0195689

Kühn, A. A., Sharott, A., Trottenberg, T., Kupsch, A., & Brown, P. (2004). Motor cortex inhibition induced by acoustic stimulation. Experimental Brain Research, 158(1), 120–124. https://doi.org/10.1007/s00221-004-1883-4

La Pointe, L. L., & Johns, D. F. (1975). Some phonemic characteristics in apraxia of speech. Journal of Communication Disorders, 8(3), 259–269. https://doi.org/10.1016/0021-9924(75)90018-0

Landis, T. (2006). Emotional words: What's so different from just words? Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 42(6), 823–830. https://doi.org/10.1016/s0010-9452(08)70424-6

Lane, H., Matthies, M. L., Guenther, F. H., Denny, M., Perkell, J. S., Stockmann, E., Tiede, M., Vick, J., & Zandipour, M. (2007). Effects of short- and long-term changes in auditory feedback on vowel and sibilant contrasts. Journal of Speech, Language, and Hearing Research: JSLHR, 50(4), 913–927. https://doi.org/10.1044/1092-4388(2007/065)

Leote, J., Castellote, J. M., Casanova-Molla, J., Navarro-Otano, J., Nunes, R. G., Ferreira, H. A., & Valls-Sole, J. (2018). Motor preparation in picture naming tasks. Brain and Language, 180–182, 24–30. https://doi.org/10.1016/j.bandl.2018.04.002

Loucks, T. M. J., Poletto, C. J., Simonyan, K., Reynolds, C. L., & Ludlow, C. L. (2007). Human Brain Activation during Phonation and Exhalation: Common Volitional Control for Two Upper Airway Functions. NeuroImage, 36(1), 131–143. https://doi.org/10.1016/j.neuroimage.2007.01.049

Lugtmeijer, S., Lammers, N. A., de Haan, E. H. F., de Leeuw, F.-E., & Kessels, R. P. C. (2021). Post-Stroke Working Memory Dysfunction: A Meta-Analysis and Systematic Review. Neuropsychology Review, 31(1), 202–219. https://doi.org/10.1007/s11065-020-09462-4

Luo, J., Hage, S. R., & Moss, C. F. (2018). The Lombard Effect: From Acoustics to Neural Mechanisms. Trends in Neurosciences, 41(12), 938–949. https://doi.org/10.1016/j.tins.2018.07.011

Maas, E., Mailend, M.-L., & Guenther, F. H. (2015). Feedforward and Feedback Control in Apraxia of Speech: Effects of Noise Masking on Vowel Production. Journal of Speech, Language, and Hearing Research : JSLHR, 58(2), 185–200. https://doi.org/10.1044/2014_JSLHR-S-13-0300

Marinovic, W., de Rugy, A., Riek, S., & Tresilian, J. R. (2014). The early release of actions by loud sounds in muscles with distinct connectivity. Experimental Brain Research, 232(12), 3797–3802. https://doi.org/10.1007/s00221-014-4074-y

Marinovic, W., & Tresilian, J. R. (2016). Triggering prepared actions by sudden sounds: Reassessing the evidence for a single mechanism. Acta Physiologica (Oxford, England), 217(1), 13–32. https://doi.org/10.1111/apha.12627

Martin, R. C., & Schnur, T. T. (2019). Independent contributions of semantic and phonological working memory to spontaneous speech in acute stroke. Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 112, 58–68. https://doi.org/10.1016/j.cortex.2018.11.017

Mena-Segovia, J., & Bolam, J. P. (2017). Rethinking the Pedunculopontine Nucleus: From Cellular Organization to Function. Neuron, 94(1), 7–18. https://doi.org/10.1016/j.neuron.2017.02.027

Mu, L., & Sanders, I. (2007). Neuromuscular specializations within human pharyngeal constrictor muscles. The Annals of Otology, Rhinology, and Laryngology, 116(8), 604–617. https://doi.org/10.1177/000348940711600809

Nijhuis, L. B. O., Janssen, L., Bloem, B. R., van Dijk, J. G., Gielen, S. C., Borm, G. F., & Overeem, S. (2007). Choice reaction times for human head rotations are shortened by startling acoustic stimuli, irrespective of stimulus direction. The Journal of Physiology, 584(Pt 1), 97–109. https://doi.org/10.1113/jphysiol.2007.136291

Nonnekes, J., Geurts, A. C. H., Nijhuis, L. B. O., van Geel, K., Snijders, A. H., Bloem, B. R., & Weerdesteyn, V. (2014). Reduced StartReact effect and freezing of gait in Parkinson's disease: Two of a kind? Journal of Neurology, 261(5), 943–950. https://doi.org/10.1007/s00415-014-7304-0

Nonnekes, J., Oude Nijhuis, L. B., de Niet, M., de Bot, S. T., Pasman, J. W., van de Warrenburg, B. P. C., Bloem, B. R., Weerdesteyn, V., & Geurts, A. C. (2014). StartReact restores reaction time in HSP: Evidence for subcortical release of a motor program. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 34(1), 275–281. https://doi.org/10.1523/JNEUROSCI.2948-13.2014

Odell, K., McNeil, M. R., Rosenbek, J. C., & Hunter, L. (1991). Perceptual characteristics of vowel and prosody production in apraxic, aphasic, and dysarthric speakers. Journal of Speech and Hearing Research, 34(1), 67–80. https://doi.org/10.1044/jshr.3401.67

Peach, R. K., Beck, K. M., Gorman, M., & Fisher, C. (2019). Clinical Outcomes Following Language-Specific Attention Treatment Versus Direct Attention Training for Aphasia: A Comparative Effectiveness Study. Journal of Speech, Language, and Hearing Research: JSLHR, 62(8), 2785–2811. https://doi.org/10.1044/2019_JSLHR-L-18-0504

Peach, R. K., Nathan, M. R., & Beck, K. M. (2017). Language-Specific Attention Treatment for Aphasia: Description and Preliminary Findings. Seminars in Speech and Language, 38(1), 5–16. https://doi.org/10.1055/s-0036-1597260

Rahimi, M., & Honeycutt, C. F. (2020). StartReact increases the probability of muscle activity and distance in severe/moderate stroke survivors during two-dimensional reaching task. Experimental Brain Research. https://doi.org/10.1007/s00221-020-05797-9

Rahimi, M., Swann, Z., & Honeycutt, C. F. (2021). Does exposure to startle impact voluntary reaching movements in individuals with severe-to-moderate stroke? Experimental Brain Research, 239(3), 745–753. https://doi.org/10.1007/s00221-020-06005-4

Sapir, S., McClean, M. D., & Larson, C. R. (1998). Human laryngeal responses to auditory stimulation. The Journal of the Acoustical Society of America, 73(1), 315. https://doi.org/10.1121/1.388812

Seidler, R. D., Noll, D. C., & Thiers, G. (2004). Feedforward and feedback processes in motor control. NeuroImage, 22(4), 1775–1783. https://doi.org/10.1016/j.neuroimage.2004.05.003

Shuster, L. I., & Wambaugh, J. L. (2000). Perceptual and acoustic analyses of speech sound errors in apraxia of speech accompanied by aphasia. Aphasiology, 14(5/6), 635–651. https://doi.org/10.1080/026870300401360

Shriberg, L. D., & Kent, R. D. (1995). Clinical Phonetics, Second Edition. Allyn and Bacon.

Simonyan, K., & Horwitz, B. (2011). Laryngeal Motor Cortex and Control of Speech in Humans. The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry, 17(2), 197–208. https://doi.org/10.1177/1073858410386727

Smith, V., Maslovat, D., & Carlsen, A. N. (2019). StartReact effects are dependent upon engagement of startle reflex circuits: Support for a subcortically mediated initiation pathway. Journal of Neurophysiology. https://doi.org/10.1152/jn.00505.2019

Stark, B. C., Basilakos, A., Hickok, G., Rorden, C., Bonilha, L., & Fridriksson, J. (2019). Neural organization of speech production: A lesion-based study of error patterns in connected speech. Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 117, 228–246. https://doi.org/10.1016/j.cortex.2019.02.029

Stevenson, A. J. T., Chiu, C., Maslovat, D., Chua, R., Gick, B., Blouin, J.-S., & Franks, I. M. (2014). Cortical involvement in the StartReact effect. Neuroscience, 269, 21–34. https://doi.org/10.1016/j.neuroscience.2014.03.041

Tourville, J. A., & Guenther, F. H. (2011). The DIVA model: A neural theory of speech acquisition and production. Language and Cognitive Processes, 26(7), 952–981. https://doi.org/10.1080/01690960903498424

Tresch, U. A., Perreault, E. J., & Honeycutt, C. F. (2014). Startle evoked movement is delayed in older adults: Implications for brainstem processing in the elderly. Physiological Reports, 2(6). https://doi.org/10.14814/phy2.12025

Valls-Solé, J., Rothwell, J. C., Goulart, F., Cossu, G., & Muñoz, E. (1999). Patterned ballistic movements triggered by a startle in healthy humans. The Journal of Physiology, 516(Pt 3), 931–938. https://doi.org/10.1111/j.1469-7793.1999.0931u.x

Van Lancker, D., & Cummings, J. L. (1999). Expletives: Neurolinguistic and neurobehavioral perspectives on swearing. Brain Research Reviews, 31(1), 83–104. https://doi.org/10.1016/S0165-0173(99)00060-0

van Lith, B. J. H., Coppens, M. J. M., Nonnekes, J., van de Warrenburg, B. P. C., Geurts, A. C., & Weerdesteyn, V. (2018). StartReact during gait initiation reveals differential control of muscle activation and inhibition in patients with corticospinal degeneration. Journal of Neurology, 265(11), 2531–2539. https://doi.org/10.1007/s00415-018-9027-0

Zakariás, L., Kelly, H., Salis, C., & Code, C. (2019). The Methodological Quality of Short-Term/Working Memory Treatments in Poststroke Aphasia: A Systematic Review. Journal of Speech, Language, and Hearing Research: JSLHR, 62(6), 1979–2001. https://doi.org/10.1044/2018_JSLHR-L-18-0057

Zanini, S., Moschella, V., Stefani, A., Peppe, A., Pierantozzi, M., Galati, S., Costa, A., Mazzone, P., & Stanzione, P. (2009). Grammar improvement following deep brain stimulation of the subthalamic and the pedunculopontine nuclei in advanced Parkinson's disease: A pilot study. Parkinsonism & Related Disorders, 15(8), 606–609. https://doi.org/10.1016/j.parkreldis.2008.12.003

Ziegler, W., & Ackermann, H. (2017). Subcortical Contributions to Motor Speech: Phylogenetic, Developmental, Clinical. Trends in Neurosciences, 40(8), 458–468. https://doi.org/10.1016/j.tins.2017.06.005

CHAPTER 3

WORD REPETITION PAIRED WITH STARTLING STIMULI DECREASES APHASIA AND
APRAXIA SEVERITY IN SEVERE-TO-MODERATE STROKE: A STRATIFIED, SINGLE-BLIND,
RANDOMIZED CONTROL TRIAL.

Swann et al., (2022). In Review. American Journal of Speech Language Pathology: AJSLP

3.1   Abstract

Purpose: The use of a startling acoustic stimuli during motor planning may initiate
otherwise inaccessible motor plans in individuals with stroke. We conducted a prospective,
single-blinded, parallel, stratified, randomized clinical trial via telehealth to determine the effect of
Startle Adjuvant Rehabilitation Therapy ("START") during a single word repetition task on
aphasia, apraxia of speech (AOS), and quality of life in individuals with chronic stroke. We
hypothesized START would have a larger effect in AOS-related measures and in more severe
individuals. **Method:** Forty-two participants with post-stroke aphasia and/or AOS were randomly
allocated to intervention type (10 mild aphasia and 11 moderate/severe aphasia in both
START/Control). For three 1-hour sessions on consecutive days, participants in START and
Control received 77-dB GET READY and GO cues during a word repetition task. Participants in
the START group received startling, 105-dB white noise GO cues during a third of trials. The
Western Aphasia Battery (Revised), Apraxia Battery for Adults, 2nd Edition, Stroke Impact Scale,
and Communication Outcomes After Stroke Scale were administered at Days 1, 5, and 1 month
follow up. **Results:** START improved performance on measures of both aphasia
(Comprehension, Repetition, Reading) and AOS (Diadochokinetic Rate, Increasing Word Length)
in individuals with moderate/severe aphasia, while moderate/severe Controls saw no changes in
any subtests. Individuals with mild aphasia receiving START had improvement in Reading, while
mild Controls saw improvement in Comprehension. Secondary measures of dysphonia and
intelligibility were unaffected in both groups. The START group had increased mood and
perceived communication recovery by Day 5 while Controls saw no changes in quality of life
measures. **Conclusions:** This study is the first to evaluate the impact of training with startling

acoustic stimuli on clinical measures of aphasia and AOS. Our findings suggest that START can improve both non-trained speech production and receptive speech tasks in moderate/severe aphasia. Future studies should assess a mechanism of action, conduct a larger and longer Phase 1 clinical trial, and evaluate retention.

3.2   Introduction

Post-stroke speech impairments can be broadly categorized into three domains: those that affect language (aphasia), speech motor planning and programming (apraxia), and muscle execution within the speech tract (dysarthria) (Jordan & Hillis, 2006). Early and correct diagnosis of speech impairment is critical to maximize therapeutic outcomes (Basilakos, 2018). However, the differential diagnosis between apraxia of speech (AOS), aphasia, and dysarthria, especially if concurrent, is challenging, and misdiagnosis can lead to improper treatment (Basilakos, 2018). This is especially true for post-stroke AOS, which rarely occurs without aphasia (Graff-Radford et al., 2014; Moser et al., 2016). According to a recent review, not only is AOS difficult to treat and diagnose quickly, but there is also a lack of acute post-stroke AOS research (Basilakos, 2018; Hickok et al., 2014). These factors diminish therapeutic outcomes in patients with AOS, and impairments can go unresolved. Neuroimaging studies controlling for concurrent aphasia found that chronic, unresolved AOS often results from lesions in Broca's area, the pre- and postcentral gyri, and the supramarginal gyrus (Basilakos et al., 2015; Graff-Radford et al., 2014; Moser et al., 2016; New et al., 2015), but the precise mechanism of AOS remains unclear.

There is growing evidence that many speech motor planning impairments may not result from a damaged motor plan but from an inaccessible motor plan. Feedforward and feedback plans are likely intact in AOS; failure may be in the readout of articulatory motor plans from the speech sound map to the primary motor cortex (Ballard et al., 2018; Bradshaw et al., 2021; Civier et al., 2013; Guenther & Vladusich, 2012). Both individuals with AOS and those who stutter fail to effectively activate the left ventral premotor cortex (vPMC) (Brown et al., 2005; Chang, 2011;

Graff-Radford et al., 2014; Salmelin et al., 2000; Watkins et al., 2008; Whitwell et al., 2013),

which is hypothesized by leading speech motor control models, such as the DIVA and GODIVA

models, to be the site of speech sound map storage because of its activity during single-syllable

repetition and association with sensorimotor interactions (Cai et al., 2014; Guenther et al., 2006;

H. E. Miller & Guenther, 2021). When the vPMC is damaged after stroke, the readout of the

speech motor plans to the primary motor cortex is likely impaired, causing the dysfluency

observed in AOS (Civier et al., 2013; Guenther, 2016; Guenther & Vladusich, 2012). Masking of

auditory feedback with noise can help individuals with dysfluency access the correct feedforward

plans fluently and quickly in both individuals with AOS and who stutter, as simulated by the DIVA

model and in clinical populations (Jacks & Haley, 2015; Kalinowski et al., 1993; Maas et al., 2015;

Terband et al., 2020). Masking auditory feedback is thought to remove the overreliance on

feedback caused by improper feedforward readout (Maas et al., 2015). If the motor plan can be

made accessible to individuals with AOS, it may provide an avenue for speech rehabilitation.

There is evidence that the use of a startling acoustic stimulus during motor planning can

initiate otherwise inaccessible plans in individuals with AOS, a phenomenon known as the

StartReact effect (Carlsen & Maslovat, 2019; Honeycutt & Perreault, 2012; Rahimi & Honeycutt,

2020; Swann et al., 2022; Valls-Solé et al., 1999). Unlike the classic startle reflex, which consists

of unplanned, protective, flexion movements, StartReact elicits intended, pre-planned involuntary,

forceful, and 30-40 milliseconds faster than voluntary execution in unimpaired individuals

(Carlsen et al., 2004; Carlsen & Maslovat, 2019; Valls-Solé et al., 1999). In individuals with little-

to-no upper extremity function post-stroke, StartReact not only elicited extension movements

quickly but also increased reaching distance and muscle activation, and muscle firing patterns

similar to unimpaired individuals (Honeycutt & Perreault, 2012; Rahimi & Honeycutt, 2020). Word

repetition can also be elicited using StartReact in individuals with concurrent aphasia and AOS

post-stroke (Swann et al., 2022). StartReact elicited more complex speech sounds that

individuals could not produce voluntarily (e.g., fricatives, clusters), but decreased overall accuracy

in vowel distance. This mirrors upper extremity findings, with individuals achieving new but

inaccurate extension movements (Rahimi & Honeycutt, 2020). Because StartReact is inaccessible without an intact motor plan (Bartels et al., 2020; Carlsen et al., 2004, 2008; Leote et al., 2018), an intact StartReact post-stroke indicates a residual capacity to form motor plans that is better than what can be initiated voluntarily (Honeycutt et al., 2015; Honeycutt & Perreault, 2012). Word repetition in AOS is susceptible to StartReact (Swann et al., 2022), there is likely a residual capacity in the AOS to form speech motor plans.

Evidence suggests that training with StartReact enhances voluntary movement (i.e., movements not elicited by StartReact but rather using the participant's own control). Rahimi et al. (2021) showed that by the end of ~1 hour of StartReact exposure (45 trials per arm), voluntary reaching movements were faster, farther, and more accurate, suggesting that StartReact has therapeutic potential (Rahimi et al., 2021). Training with StartReact may allow individuals with stroke-induced motor deficiencies to use inaccessible plans; however, it is unclear if the use of StartReact can be harnessed to allow voluntary production of improved speech motor plans.

Here, we aimed to provide evidence that StartReact can be used as a therapeutic tool to improve the performance of clinical measures for aphasia and AOS post-stroke. To date, no study has evaluated the impact of StartReact training on the clinical outcomes of speech. While the use of startling acoustic stimuli to elicit planned movement is termed the StartReact effect, therapeutic use of StartReact over time has been termed "Startle Adjuvant Rehabilitation Therapy" (START). We assessed the potential communication benefits of training with START in individuals with post-stroke AOS and/or aphasia over three days, when paired with a high-intensity word repetition task in a prospective, single-blinded (participant), parallel comparison group, stratified, randomized clinical trial via telehealth. We also performed a secondary analysis to assess the effect of START on speech dysphonia, intelligibility, and vowel duration.

As StartReact may make motor plans accessible, we hypothesized that those receiving START would show larger gains related to AOS but not aphasia symptoms. Specifically, we hypothesized that START would improve processes related to speech motor planning (e.g.,

diadochokinetic rate, polysyllabic word accuracy, utterance time, and latency time) but not upstream processes related to language (e.g., comprehension, word finding, and reading) after three days of training. We expected participants receiving START to have higher quality of life improvements than participants in the control group. We also expected individuals with more severe aphasia to have greater improvement in the measures described above after START, with relatively little change in individuals with mild aphasia and individuals in the control group. This is due to previous findings in upper extremity StartReact literature showing greater improvement with more severe impairments (Honeycutt & Perreault, 2014; Rahimi et al., 2021; Rahimi & Honeycutt, 2020). In the secondary analysis, we expected participants to have shorter vowel durations, decreased dysphonia, and enhanced intelligibility as measured by a forced choice task, likely due to more accurate motor planning abilities after START.

3.3   Method

3.3.1   Study Design

We conducted a prospective, single-blinded (participant), parallel comparison group, stratified, randomized clinical trial via telehealth to determine the therapeutic effects of startle adjuvant rehabilitation therapy (START) combined with a word repetition task on aphasia recovery, apraxia recovery, and quality of life in individuals with chronic stroke. All participants provided informed consent prior to participation in this study, which was approved by the Institutional Review Board of Arizona State University (STUDY00005229). This study was registered at ClinicalTrials.gov (identifier NCT04816799).

3.3.2   Participant Demographics and Allocation

Forty-two individuals participated in the study (**Figure 7**; see **Table 2** for baseline demographic data). Participants had a diagnosis of stroke-induced aphasia and/or apraxia and were at least 6 months post-stroke (mean:5.3 years, SD:4.6 years). START and control groups' demographic and clinical measures were not statistically different at baseline (**Table 3**). The

inclusion criteria for the study were a diagnosis of aphasia and/or apraxia following a stroke, English fluency, a low likelihood of COVID-19 positive diagnosis, and the ability to use video conferencing software (Zoom). Participants were excluded if they reported that they were pregnant or had dizzy spells, seizures, or heart conditions in the last year that posed a risk of startle exposure. We also excluded one individual who could not vocalize or understand any speech due to stroke severity. The medical history of each participant was acquired during the initial screening over Zoom and included the onset, type, and location of stroke, if known, any motor or sensory impairments (numbness, tingling, pain) following stroke; their original and current handedness; and any bilingual experience they had, regardless of fluency level (7 START and 8 Controls).
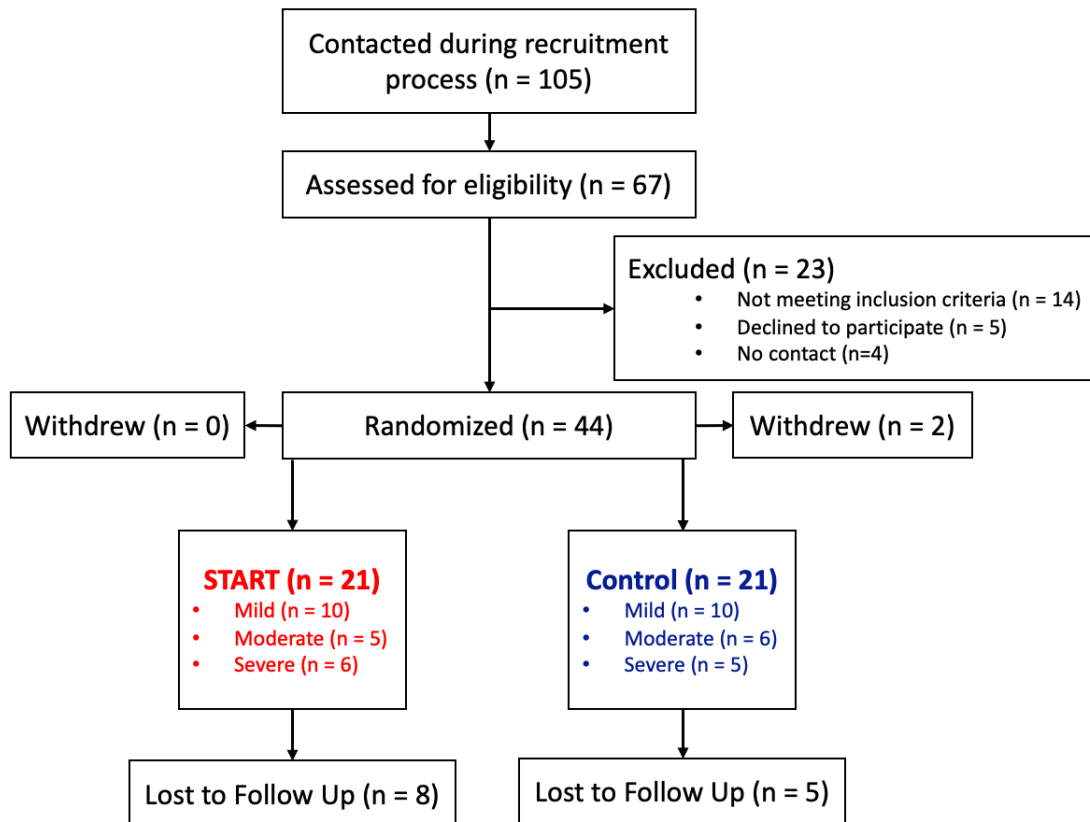
Figure 7. Flowchart of participant recruitment, enrollment, and adherence.

All participants were recruited and screened for inclusion in the study, and then randomly allocated to intervention type (START or control). Stratification by aphasia severity preceded intervention randomization, resulting in 10 participants with mild or no aphasia and 11 with moderate/severe aphasia in each group (START or control). Patients without aphasia had mild AOS (n=3). **Table 2** shows baseline severity levels and aphasia classification.

3.3.3   Primary Outcome Measures: Clinical tests and Quality of Life

The study was composed of six remote sessions for each participant: baseline clinical assessment (day 1), training days (days 2, 3, and 4), retest clinical assessment (day 5), and one-month follow-up clinical assessment (day 31). The participants were administered the Western Aphasia Battery (Revised) (WAB-R) and the Apraxia Battery for Adults, 2nd Edition (ABA-2) at baseline (day 1), retest (day 5), and follow-up (day 31) by the administrator. These clinical tests were modified for use in telerehabilitation in accordance with Dekhtyar et al., (2020) and Hill et al., (2009). The WAB-R was used to assess aphasia symptoms, as measured by the following subtests: spontaneous speech, auditory verbal comprehension, repetition, naming, word finding, and reading. ABA-2 was used to assess diadochokinetic rate, increasing word length errors, utterance time, latency time, and repeated word accuracy. Finally, we administered two quality of life questionnaires that participants completed by themselves or with the help of a caretaker on a computer: the Stroke Impact Scale (SIS) (Lin et al., 2010) and the Communication Outcome After Stroke (COAST) Scale (Long et al., 2008). The SIS was used to assess the quality of the participants' strength, memory, emotion, communication, daily activities, mobility, hand function, and participation in their community. The COAST was used to assess the specific social and emotional impacts of communication problems on participants' quality of life.

For the WAB-R, the total aphasia quotient (twice the sum of all subtests), reading quotient (sum of all reading subtests), and individual sections (spontaneous speech, auditory verbal comprehension, repetition, and word-finding) were assessed. For ABA-2, individual subtests were assessed, and overall severities were calculated using measures of utterance time,

increasing word length, repeated words, and diadochokinetic rate according to the ABA-2 manual (Dabul & Pro-Ed (Firm), 2000). After the WAB-R and ABA-2 clinical test recordings were coded, they were scored by an assessor who was blinded to the participant, intervention (START, Control), and time point (Days 1, 5, and 31).

3.3.4   Intervention and Protocol: Mobile Startle Device

A custom-built mobile phone application was created for the remote application of START. The phone application was installed on a Google Pixel 3 smartphone. The phone, amplifier, and headphones were remotely controlled by an administrator via the AnyDesk application. JLAB Studio on-ear headphones were plugged into the LVY-01 headphone amplifier, which was plugged into the smartphone via a USB-C adapter. The participants were seated in a comfortable chair at home for all sessions. On training days, they were asked to set up the mobile device, including plugging the amplifier and headphones in and connecting it to their WiFi and AnyDesk. Video and audio data for each session were recorded using Zoom, and audio data were recorded offline on a mobile device as a backup. The Zoom session recordings had an average harmonics-to-noise ratio of 13 dB, compared to 7 dB for the mobile phone microphone; therefore, Zoom audio was used for this study. Caretakers helped with the setup when necessary.

The START app generated a series of soft 77 decibel (dB) cues (GET READY) to indicate to the participants that they should prepare to say the word. Each GET READY sound was followed by an identical GO cue (1.5 - 2.5 seconds later). For the START group, one-third of the time, the GO cue was replaced with a 105 dB, 56 ms broadband white noise burst startling acoustic stimulus (SAS) (rise/fall time < 1 ms (Marinovic et al., 2014; Swann et al., 2022)). SAS and GO trials were randomized, with SAS occurring 1/3 of the time, similar to prior StartReact experiments used to elicit motor tasks (Bartels et al., 2020; Honeycutt et al., 2015; Honeycutt & Perreault, 2014; Ossanna et al., 2019; Rahimi & Honeycutt, 2020).

ID	Cohort	Age	Sex	Years post stroke	Etiology (CVA)	Aphasia classification	Aphasia severity	Apraxia severity	Education	Lesion site (self-reported)
1	START	—	F	1.17	—	TCM	Moderate	Moderate	—	—
2	START	62	M	2.16	Isch	Conduction	Mild	Mild	--	L-C
3	START	57	M	4.61	Isch	Anomic	Mild	Moderate	Undergraduate	R-C
4	START	59	M	2.89	Hem	Anomic	Mild	Moderate	Undergraduate	L-C
5	START	48	F	19.91	Hem	Conduction	Mild	Mild	Master's	L-C
6	Control	73	M	1.28	Isch	Anomic	Moderate	Mild	In Master's program	L-C
7	Control	59	M	1.47	Isch	Broca	Moderate	Severe	Some college	L-C
8	Control	49	F	0.99	Isch	Anomic	Mild	Moderate	Some college	L-C
9	Control	71	M	3.18	Hem	Broca	Moderate	Moderate	Doctoral degree	L - BG, P, Th
10	START	71	F	11.95	Hem	Broca	Moderate	Severe	Undergraduate	L-C
11	START	64	M	3.3	Hem	Wernicke	Severe	Severe	High school	L-C
13	Control	49	F	8.81	Isch	Broca	Moderate	Moderate	Some college	L-C
14	Control	48	M	2.13	Isch	Broca	Severe	Severe	Some college	L-C
15	START	39	M	14	Isch	Anomic	Mild	None	Undergraduate	L-C
16	START	46	M	13.27	Isch	Anomic	Mild	None	In doctoral program	L-C
17	Control	43	F	1.13	Isch	Anomic	Mild	Mild	Undergraduate	L-C
18	Control	72	M	3.84	Isch	Anomic	Mild	Moderate	Some college	L-C
19	Control	62	M	13.62	Hem	Broca	Moderate	Severe	—	L-C
20	START	81	M	11.73	Hem	Broca	Moderate	Severe	Did not finish high school	L-C
22	START	48	M	1.12	Isch	Broca	Moderate	Severe	Some college	L-C
23	Control	42	F	1.17	Isch	Global	Severe	Moderate	—	R-C
24	Control	50	M	1.36	Hem	Broca	Moderate	Severe	High school	L-C
25	START	59	M	1.96	Isch	Broca	Severe	Moderate	—	L-C

ID	Cohort	Age	Sex	Years post stroke	Etiology (CVA)	Aphasia classification	Aphasia severity	Apraxia severity	Education	Lesion site (self-reported)
26	START	77	F	2.36	Isch	Broca	Severe	Severe	Some college	L-C
27	Control	60	M	1.61	Hem	Anomic	Mild	Mild	Doctoral degree	L-C
28	START	44	M	2.27	Hem	Broca	Severe	Severe	—	L - BG, P, Th
29	START	65	M	9.31	Isch	Broca	Severe	Severe	Some college	R-C
30	Control	—	F	3	Hem	None	None	Mild	—	L - C, BG
31	START	65	F	0.6	Isch	Global	Severe	Severe	—	L-C
33	Control	80	M	5.5	Isch	Broca	Severe	Severe	—	R-C
34	START	45	F	6.05	Isch	None	None	Mild	Undergraduate	L-C
35	START	66	M	8.95	Isch	Conduction	Moderate	Moderate	High school	L-C
36	Control	54	M	8.57	Isch	Anomic	Mild	Mild	Did not finish high school	L-C
37	Control	70	M	5.74	Hem	Broca	Severe	Severe	Some college	L - BG, P, Th
38	Control	28	M	4.27	Isch	Broca	Severe	Moderate	Undergraduate	L-C
40	START	42	F	1.2	Isch	Anomic	Mild	Mild	Undergraduate	L-C
41	START	54	M	7.97	Isch	Anomic	Mild	Moderate	Undergraduate	L-C
42	START	57	F	6.9	Isch	Anomic	Mild	None	Doctoral degree	L-C
43	Control	—	F	7.61	Isch	None	None	Mild	Master's	L-C
45	Control	70	M	1.55	Isch	Anomic	Mild	Moderate	Undergraduate	L-C
46	Control	75	M	4.74	Hem	Anomic	Mild	Mild	Undergraduate	L-C
47	Control	61	M	7.18	Isch	Anomic	Mild	Mild	—	L-C

Table 2. Participant characteristics. All characteristics except for aphasia and apraxia severity were self-reported by the participant. *Isch = "ischemic", Hem = "hemorrhagic", "R-" = right hemisphere, "L-" left hemisphere, "C" = cortex, "BG" = basal ganglia, "P" = putamen", "Th" = thalamus, "--" unknown.*

Participants were instructed to prepare and execute their speech as follows: *"When you hear the first "get ready" sound, get ready to say the word. Breathe in, put your mouth where it needs to be to say the first sound, and focus on the word. When you hear the second sound, release the word as soon as you can".*

The target words used during training were: "stop", "ball", "water", "cheese", "please", and "feet". Words were chosen for functional relevance using a study (Palmer et al., 2017) that asked individuals with aphasia what they wished they could say, /i/ or /a/ vowels to maximize the boundaries of the vowel space and increase articulatory complexity. Each word was repeated 15 times per block, with three blocks per word per session. The blocks were randomized for 18 blocks per session; therefore, the participants said approximately 270 words per day. Participants were given optional breaks after Blocks 6 and 12 and were given the option to take more breaks if needed. All participants were provided encouragement and advice on breathing, articulation, and speech onset. Two participants were moved from the START to the control group on the first day because of 1) an inoperative amplifier and 2) inability to understand the SAS task but could repeat the words in the control task.

Demographics	START	Control	Chi sq / t test
Sex (M/F)	13/8	15/6	X^2 (1, N = 42) = 0.42, p = .5
Age (years)	57±0.6	58±0.7	p = .75
Subjects currently in speech therapy	11	14	X^2 (1, N = 42) = 0.88, p = .3
CVA (isch/hem)	16/5	14/7	X^2 (1, N = 42) = 0.46, p = .5
Days post stroke	2282±108	1584±67	p = .13
Years of education	15.8±0.23	15.9±0.2	p =.92

Table 3. Participant baseline demographics. No significant differences at baseline between START and Control in any of the above measures.

To assess the likelihood of participant bias due to encouragement from the Administrator, audio from all training days was evaluated by a blinded assessor according to the intensity of

encouragement. Each time the Administrator gave a participant encouragement it was scaled

from 0 to 5, with 0 being not related to task and 5 being explicit assistance with articulation.

According to this analysis, Controls with mild aphasia received slightly higher encouragement

than START participants with mild aphasia (p=0.03). There was no difference in participants with

moderate/severe aphasia.

3.3.5   Acoustic and Intelligibility Outcome Measures

Additional secondary measures were evaluated after data collection to supplement the

clinical measures described above with more sensitive speech measures. These included vowel

duration, Acoustic Voice Quality Index, and a forced-choice task to qualitatively measure speech

intelligibility. All data were recorded during clinical assessments using Zoom and then segmented

and processed by blinded assessors (see below). Vowel duration was used to assess the

presence of AOS, as individuals with AOS produce vowels that are longer than normal in

polysyllabic word utterances (Haley & Overton, 2001). This is thought to be because feedforward

control is impaired in AOS, causing individuals to rely more heavily on auditory feedback to

achieve their intended speech motor plan (Jacks, 2008; Maas et al., 2015). The vowel duration

assessment was taken from the second task of ABA-2: increasing word length. During ABA-2, the

participant was asked to repeat a series of words with an increasing number of bound

morphemes (e.g., *"thick, thicken, thickening"*). There were ten sets of three words each. The

vowel boundaries for all 30 target words were segmented and extracted using Praat software

(Praat 2019, Version 6.1.03), and timestamps were used to calculate vowel duration. These

vowel durations were also categorized by complexity (1, 2, or 3), according to the first, second, or

third iteration of the root word in the task.

Acoustic Voice Quality Index is used to objectively quantify the severity of dysphonia on a

1-10 scale (Faham et al., 2021; Maryn et al., 2010; Maryn & Weenink, 2015). The threshold for

dysphonia among English speakers has been found to be 3.46, with lower scores indicating

normophonia (Maryn et al., 2010; Reynolds et al., 2012). The AVQI is an objective measure of

voice quality that allows for standardization across patients and populations. This allows for the measurement of the quality of short consonant sounds as well as sustained vowels, both of which are required for a comprehensive measure of an individual's voice quality. Second, voice quality is a multivariate metric that must consider multiple different parameters that, when taken together, represent a dysphonia severity index because of their sensitivity to glottal vibratory distortions (Maryn et al., 2010). Breathiness is associated with smoothed cepstral peak prominence, glottal closure and breathiness are measured by the harmonics-to-noise ratio and spectral tilt, and irregular vocal fold vibration and roughness are associated with measures of amplitude perturbation ("shimmer") (Awan & Roy, 2006; Maryn et al., 2010). Additionally, over the past decade, the AVQI has been validated in numerous languages, age groups, and ethnicities (Batthyany et al., 2022). Thus, it is an accurate and complete metric for voice quality.

Participants repeated several words and phrases in the repetition portion of the WAB-R. Twenty-five syllables were used for the AVQI analysis: *"The telephone is ringing. He is not coming back. Delicious freshly baked bread. No ifs, ands, or buts."* The administrator's voice and any pauses were removed from the task audio between participant utterances. The audio data were otherwise unfiltered and included both voiced and unvoiced segments (i.e., whole phrases). All voice samples were recorded using Zoom with an auto-adjusted background noise-reduction setting. All parameters used to calculate AVQI were obtained using the Voice Report, spectrum, and periodicity functions in Praat: Harmonics to noise ratio (HNR), Shimmer local (SL), Shimmer local dB (SLdB), smoothed cepstral peak prominence (CPPS), slope of long-term average spectrum (Slope Ltas), and trendline tilt of the long-term average spectrum (Tilt Ltas). One AVQI value per participant before and after training was calculated using the following formula (Maryn & Weenink, 2015):

$$AVQI = 2.57(3.295 - 0.111\,CPPS - 0.073\,HNR - 0.21\,SL + 2.789\,SLdB - 0.032\,Slope\,Ltas + 0.077\,Tilt\,Ltas)$$

Finally, a forced-choice task served as a qualitative yet functional measure of intelligibility. At the beginning of their first training day and the end of the last training day, participants were asked to repeat the following words and phrases: "*peas, please, pleased, pleased to meet you, sock, stop, straw, don't stop, water, daughter, my daughters, my daughter is pretty, ball, cheese, feet".* These 15 target words were transcribed, and the boundaries at word onset and offset were segmented in Praat. A custom Python (version 3.6) script was used to extract individual target words from all Praat files using boundary timestamps and randomize the order of individual words across participants into a single mp3 file with 5 seconds between each word. Three blinded assessors independently listened to the newly generated audio file and transcribed the targets they perceived chosen from the list above. Perceived and actual targets were compared for each participant and used to calculate the percentage of words intelligible to all assessors (Boothroyd, 1985; Rogers & Dalby, 2005).

3.3.6   Assessment Fidelity and Reliability

The research team consisted of an administrator (1st author) who screened participants for eligibility and administered the clinical tests and interventions, and seven assessors who were blinded to the participant, intervention type, and study time point (baseline, retest, follow-up). Unique assessors were used for all conditions where blinding was necessary (clinical test scoring, forced-choice task, and vowel duration analysis). Only the forced choice task required more than one assessor.

3.3.7   Statistical Analysis

We hypothesized that word repetition paired with START would enhance clinical scores relating to apraxia (utterance time, diadochokinetic rate, polysyllabic word accuracy) but not those relating to aphasia (word finding, picture naming, comprehension, reading). The primary outcome measures for this study were aphasia and apraxia clinical scores (WAB-R and ABA-2), quality of life assessments (SIS and COAST), and demographic characteristics. The secondary outcome measures for this study included dysphonia as measured by the AVQI, intelligibility as measured

by a forced-choice task, and vowel duration. Participants were divided into a mild aphasia group

and moderate/severe aphasia group according to their WAB-R aphasia quotient. We used a

generalized linear mixed effects model in R 2022 version 4.2.0 (R Core Team, 2022) for all

comparisons. This model accounts for multiple comparisons using Tukey's test for multiple

comparisons. The dependent variables included all the primary and secondary outcome variables

listed above (i.e., WAB-R Aphasia Quotient, WAB-R subtests, ABA-2 subtests, SIS subtests,

COAST score, AVQI, vowel duration, and intelligibility). The fixed effects were intervention

(START, control) and study time (pre-training, post-training). The groups were separated by

aphasia severity (mild, moderate/severe) and evaluated independently. Participants were treated

as a random factor and $p < 0.05$ was considered statistically significant. A separate analysis was

conducted to assess change at 1 month follow up, including only those participants who had

completed all three timepoints (n = 29). For the quality of life assessments, groups were not

evaluated separately based on severity because several participants (n=20) did not complete the

questionnaires. In an attempt to keep sample sizes adequately high, START and Control were

not broken down by aphasia severity for the quality of life assessments.

3.4   Results

3.4.1   Speech clinical assessments

There were no differences between groups at baseline for any demographic or clinical

measure (Table 2). The results below were evaluated separately for individuals with mild aphasia

and those with moderate/severe aphasia. For a more detailed presentation of all statistical

comparisons, see **Tables 4 and 5**.

In the moderate/severe START group, two subtests within the WAB-R and three subtests

within the ABA-2 were affected by time-point from Day 1 to Day 5, while the moderate/severe

Control group saw no changes from Day 1 to Day 5 (**Figure 8 and Table** 4). This led to an

average increase for the START participants with moderate/severe aphasia in Comprehension

(*Pre*: 7.24±0.65 points, *Post*: 7.80±0.56 points; $F_{1,10}$=9.95, p=0.010); an average increase in

Diadochokinetic Rate (*Pre*: 1.91±0.97 utterances, *Post*: 4.45±1.01 utterances; $F_{1,10}$=7.69,

p=0.02); an average decrease in Increasing Word Length (*Pre*: 7.78±0.81 errors, *Post*: 4.70±0.94

errors; $F_{1,8}$=12.41, p=0.008); an average increase in Reading Quotient (*Pre*: 51.20±7.89 points,

Post: 55.93±8.03 points; $F_{1,10}$=6.15, p=0.033); an average increase in Repetition (*Pre*: 3.60±0.77

points, *Post*: 4.20±0.86 points; $F_{1,10}$=5.76, p=0.037). There were no significant differences

between moderate/severe START and Control participants at either Day 1 or Day 5.

In the mild START group, one subtest within the WAB-R was affected by timepoint from

Day 1 to Day 5, and in the mild Control group, one subtest within the WAB-R was affected by

timepoint from Day 1 to Day 5 (**Figure 8 and Table 5**). There was an average increase for the

START participants with mild aphasia in Reading Quotient (*Pre*: 82.60±4.68 points, *Post*:

85.85±4.17 points; $F_{1,9}$=9.09, p=0.015). In the mild Control group, Comprehension increased from

Day 1 to Day 5 (*Pre*: 9.45±0.15 points, *Post*: 9.75±0.12 points; $F_{1,9}$=5.95, p=0.038). There was a

Figure 8. Percent improvement in WAB-R and ABA-2 Subtests (Day 1 to Day 5).
Percent improvement was calculated as the difference between Day 5 and Day 1 scores divided by Day 1 scores and was reversed for subtests for which a lower value was closer to zero to indicate improvement (Increasing Words, Utterance Time, Latency Time). 2 participants were omitted from this figure for having no baseline Utterance Time scores due to severity. Error bars are defined as standard error (SEM = STDEV÷√n). *p < .05.

significant difference between mild START and Control participants by Day 5 in 2 subtests: Increasing Word Length (*Control:* 2.30±0.58 points, *START*: 0.60±0.31 points; $F_{1,18}=6.76$, p=0.018); and Word Finding (*Control:* 9.35±0.20 points, *START*: 8.73±0.15 points; $F_{1,18}=6.15$, p=0.023).

3.4.2   Quality of Life Clinical Assessments

In the START group, one subtest within the Stroke Impact Scale was affected by timepoint from Day 1 to Day 5. This led to an average increase in perceived Emotional recovery (*Pre:* 58.17±4.34 points, *Post*: 73.29±4.39 points; $F_{1,12}=5.60$, p=0.036) **(Figure 9)**. COAST Score was also affected by Timepoint from Day 1 to Day 5, leading to an average increase in COAST Score (*Pre:* 57.9±19.9 points, *Post*: 69.7±14.9 points; $F_{1,13}=8.70$, p=0.011) **(Figure 9)**. In the Control group, no subtests within the Stroke Impact Scale or COAST were affected by timepoint from Day 1 to Day 5 **(Table 6 and Figure 9)**.
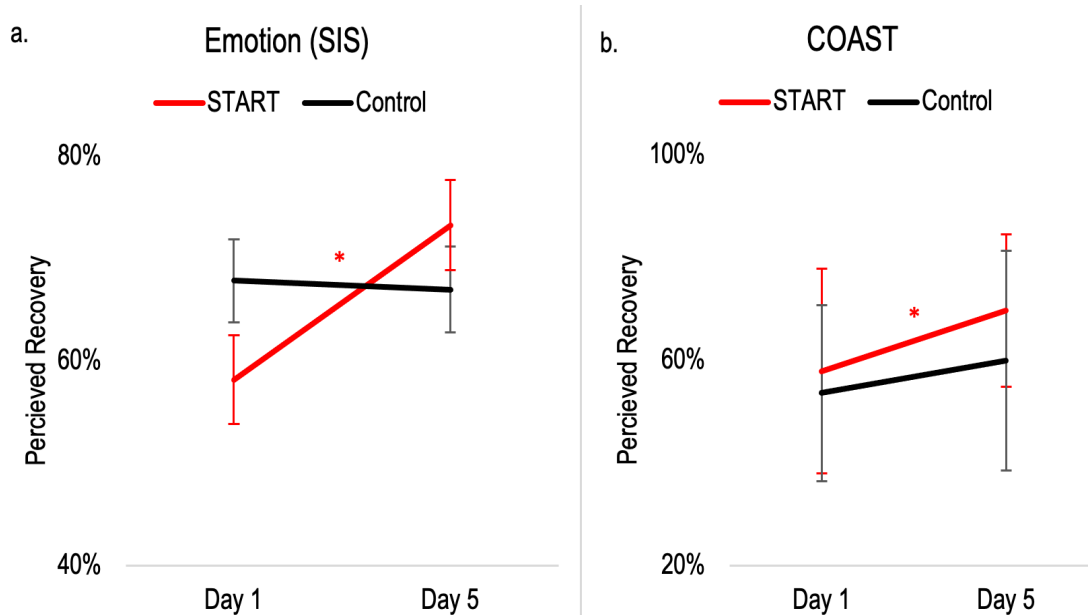
Figure 9. Perceived Recovery in Emotion and COAST Scores (Day 1 to Day 5).
Participants were given the Stroke Impact Scale (SIS) and Communication Outcomes After Stroke Scale (COAST). Participants receiving START reported higher recovery scores in Emotion and Communication Outcomes on Day 5 compared to Day 1. Error bars are defined as standard error (SEM = STDEV÷√n). *p < .05.

3.4.3   Secondary Outcome Measures

In the moderate/severe START group, neither AVQI, Forced Choice, or Vowel Duration were significantly affected by timepoint from Day 1 to Day 5, while the moderate/severe Control group also saw no significant changes from Day 1 to Day 5 **(Table 4)**. In the mild START group, Vowel Duration was affected by timepoint from Day 1 to 5 with an average increase for the START participants with mild aphasia in single-syllable repetitions (*Pre:* 0.17±0.9 points, *Post*: 0.18±0.008 points; $F_{1,160}$=5.15, p=0.025). The mild Control group saw no significant changes in AVQI, Forced Choice, or Vowel Duration from Day 1 to Day 5 **(Table 5)**.

3.4.4   One Month Follow Up Analysis

One month follow up scores were compared to baseline in a separate analysis including only participants who had completed all three clinical assessment sessions (n=29). In the moderate/severe START group, one subtest within the WAB-R and one subtest within the ABA-2 were significantly affected by timepoint from Day 1 to Day 31, and in the moderate/severe Control group, three subtests within the WAB-R were affected by timepoint from Day 1 to Day 31. There was an average increase for the moderate/severe START participants in Comprehension (*Pre*: 7.57±0.34 points, *Post*: 8.46±0.36 points; $F_{1,5}$=67.75, p=0.0004) and an average decrease in Increasing Word Length (*Pre*: 8.20±1.45 errors, *Post*: 5.83±1.01 errors; $F_{1,4}$=7.94, p=0.048). In the moderate/severe Control group, Aphasia Quotient (*Pre*: 52.04±4.82 points, *Post*: 57.87±5.92 points; $F_{1,8}$=8.10, p=0.02), Spontaneous Speech (*Pre*: 5.56±0.44 points, *Post*: 7.33±0.62 points; $F_{1,8}$=10.56, p=0.01), and Information (*Pre*: 8.78±0.92 points, *Post*: 11.56±1.18 points; $F_{1,8}$=11.21, p=0.01) increased from Day 1 to Day 31.

In the mild START group, no subtests within the WAB-R or ABA-2 were significantly affected by timepoint from Day 1 to Day 31. In the mild Control group, one subtest within the WAB-R was affected by timepoint from Day 1 to Day 31, i.e.an average increase for the mild Control participants in Comprehension (*Pre*: 9.39±0.18 points, *Post*: 9.81±0.09 points; $F_{1,6}$=6.87, p=0.04) from Day 1 to Day 31.

3.5   Discussion

3.5.1   Summary

The objective of the current study was to evaluate whether training with START for three days could generate clinically meaningful changes in speech for individuals with aphasia and/or apraxia due to stroke. Our hypothesis that more clinical test measures would improve following START in the moderate/severe group than in the mild group was upheld. However, contrary to our hypothesis, START improved measures of both aphasia (comprehension, repetition, reading) and AOS (diadochokinetic rate, increasing word length accuracy) in individuals with moderate/severe aphasia. Moderate/severe controls showed no changes in any of the WAB-R or ABA-2 subtests. Contrary to our hypothesis, individuals with mild aphasia receiving START showed an improvement in the WAB-R reading quotient, whereas individuals with mild impairment in the control group showed improvement in the WAB-R Comprehension subtest. Furthermore, measures relating to dysphonia and intelligibility were unaffected by intervention type, contrary to our hypothesis. Vowel duration in monosyllabic words increased for individuals with mild aphasia receiving START, whereas the mild aphasia control group showed no changes in vowel duration measures. Our hypothesis regarding quality of life measures was upheld, as the START group had increased mood (SIS) and perceived communication recovery (COAST) after three days of START, while controls saw no changes in quality of life measures. Our findings are surprising and suggest that START generalizes not only to non-trained speech production, but also receptive speech tasks.

Neither the severe/moderate or mild START groups achieved a clinically meaningful difference of 5 points in the WAB-R Aphasia Quotient (Gilmore et al., 2018; Hula et al., 2010; Katz & Wertz, 1997), an overall measure of aphasia severity. One method of determining clinically meaningful changes in AOS is a change in severity classification, as defined by ABA-2 (i.e., none, mild, moderate, and severe) (Dabul & Pro-Ed (Firm), 2000). Two START participants achieved a change across the two severity levels, improving from moderate to no AOS and

severe to mild AOS, respectively (**Figure 10**). None of the controls achieved more than one change in severity. In conclusion, while individuals with moderate/severe aphasia receiving START showed significant changes in several clinical subtests, they did not achieve clinical significance. Further studies are required to determine whether START is a viable strategy for generating clinically meaningful changes. The current study was a short, three-session, proof-of-concept trial, and future studies should evaluate the effect of more sessions of START over a greater number of days.
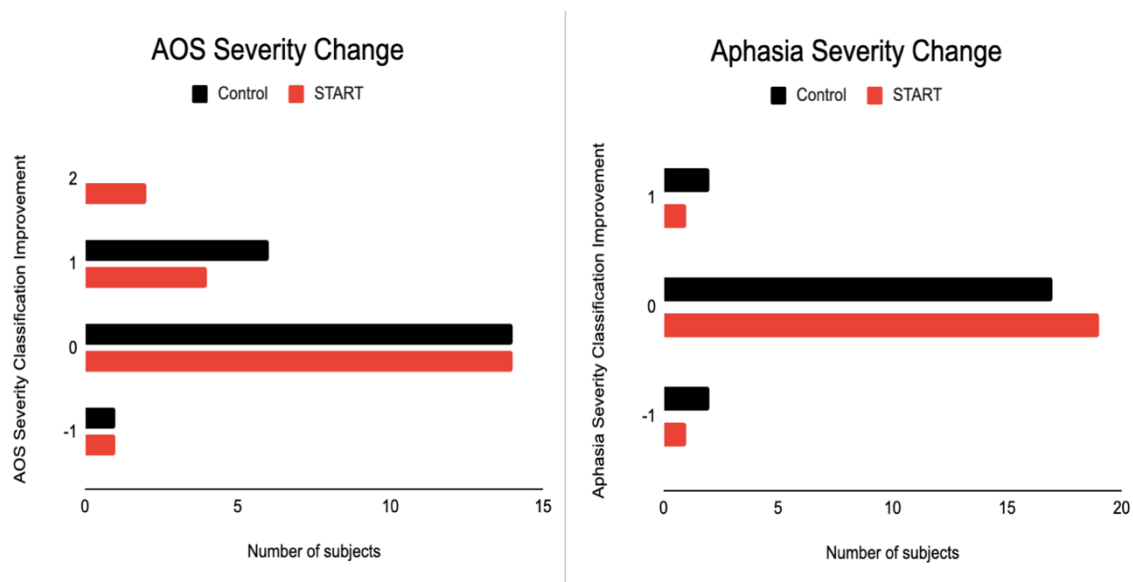
Figure 10. Number of subjects with clinically meaningful changes from Day 1 to Day 5. A clinically meaningful change is defined here as a change in severity classification (e.g., from moderate to mild). The two START participants who achieved a score of 2 above improved from moderate to no AOS and severe to mild AOS, respectively. Most subjects did not change in aphasia or AOS severity classification (represented by 0 on the y axis).

Although 30% of participants were lost to one month post-follow-up clinical assessments, the remaining participants in the moderate/severe START group maintained their improvements on the WAB-R's Comprehension subtest and the ABA-2's Increasing Word Length test at Day 31. The Aphasia Quotient for the moderate/severe START group also approached a clinically meaningful increase at one-month (+4.88 points, $p=0.058$). Comprehension gains were

maintained for the mild controls, while moderate/severe controls saw a clinically meaningful increase of 5.8 points in Aphasia Quotient, mostly accounted for by improved Information scores in the spontaneous speech subtest on day 31. In conclusion, both the START and control groups showed improvements in some aphasia and AOS measures on day 31, but the control group showed improvements in more areas and overall aphasia severity. These changes may be related to two-thirds of the control group and half of the START group concurrently participating in some form of speech therapy. These results should also be considered carefully due to high dropout rates at the one-month mark.

3.5.2   START Affects Measures of Both AOS and Aphasia

We hypothesized that individuals receiving START would exhibit improvements in AOS symptoms but not aphasia. However, we found that START generated changes in subtests within both the aphasia and AOS clinical assessments. The domains improved by START include speech motor sequencing and timing (diadochokinetic rate); sequencing accuracy in multisyllabic words not trained during START days (ABA-2's increasing word length); accuracy in single words, phrases, and longer sentences not trained during START days (WAB-R Repetition subtest); accuracy in tasks related to reading commands and multiple-choice questions (WAB-R Reading subtests); and accuracy in understanding spoken single words, questions, and commands (WAB-R Comprehension subtest). These improvements imply that START may affect speech tasks in multiple ways, including by improving motor encoding.

While previous research has proposed that StartReact makes intact motor plans accessible post-stroke (Honeycutt & Perreault, 2012), here, we show that START affects activities further upstream of motor planning, such as comprehension and reading, which are mediated by widely distributed areas. Several reading tasks included in the WAB-R involve comprehension of sentences, which is likely mediated in part by regions in the occipital, parietal, and temporal lobes to retrieve familiar words encoded in lexical memory (Borowsky et al., 2006). The comprehension portion of the WAB-R involves spectrotemporal analysis and phonological

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processing of the auditory speech stimulus, lexical retrieval, production of speech or hand movements in response to the examiner, and correct understanding of complex grammatical constructs. It is surprising that a simple word repetition task paired with START would affect widely distributed neural activity. However, improvements related to AOS (diadochokinetic rate and increased polysyllabic word accuracy) are potentially a result of improved access to speech motor plans. We observed no changes in the ABA-2 utterance time, which reflects speech rate difficulties common in AOS, or latency, which reflects word-finding difficulties common in aphasia (Dabul & Pro-Ed (Firm), 2000). Therefore, sequencing and articulatory accuracy seem to be improved in moderate/severe participants receiving START, whereas execution speed is not. In conclusion, START seems to improve auditory speech comprehension and reading performance beyond speech-motor encoding, and these mechanisms should be investigated further.

3.5.3   Updated Neural Mechanisms of StartReact

As StartReact response latencies are comparable to those of the startle reflex, it was originally suggested that StartReact activates subcortical structures containing offloaded information about the planned motor response (Carlsen & Maslovat, 2019; Valls-Solé et al., 1999). StartReact has been found to be more difficult to elicit in tasks involving the cortex, such as picture naming or finger abduction, while reticulospinal based movements were more easily elicited by StartReact (Bartels et al., 2020; Carlsen et al., 2009; Honeycutt et al., 2013, 2013; Leote et al., 2018; Stevenson et al., 2014). Highly trained tasks are also more susceptible to the StartReact effect than novice tasks, further supporting subcortical mechanisms (Bartels et al., 2020; Kirkpatrick et al., 2018; Rangarajan et al., 2022). Additionally, deep brain stimulation of the pedunculopontine nucleus in Parkinson's disease patients with freezing of gait restored the StartReact effect (Thevathasan et al., 2011) indicating that StartReact releases movement via subcortical structures. Patients with hereditary spastic paraplegia (HSP), characterized by degeneration of the corticospinal tract, also exhibit an intact StartReact effect (Nonnekes, Geurts,

et al., 2014). These findings support the theory that the reticulospinal tract in the brain triggers a stored response within subcortical structures.

Conversely, StartReact may elicit plans by using a larger repertoire of structures, including the cortex. Two studies found that transcranial magnetic stimulation (TMS) applied over the contralateral primary motor cortex inhibited the StartReact effect and delayed reaction times for both StartReact and voluntary movements during wrist extension (Alibiglou & MacKinnon, 2012; Stevenson et al., 2014). Although TMS is known to affect both cortical and subcortical structures, in these studies classic startle was not affected by TMS, implicating the cortex as the mechanism of action. StartReact can also elicit speech, which is a cortically driven process (Chiu, 2015; Chiu & Gick, 2014b; Stevenson et al., 2014; Swann et al., 2022). One study found that picture naming could also be elicited by StartReact in unimpaired individuals but only when words could be preplanned and likely offloaded to intact subcortical structures (Leote et al., 2018). Others have hypothesized that StartReact's mechanism may vary depending on the task (Marinovic & Tresilian, 2016). The results of the present study show changes in tasks known to be highly supported in cortical language networks (e.g., reading and auditory comprehension), suggesting that the mechanisms of StartReact may need to be reconsidered.

START may facilitate activity in the premotor cortex by ameliorating cortical suppression after stroke. Following a stroke, ipsilesional cortex suppression often occurs, paired with contralesional disinhibition (Bütefisch et al., 2003; Dodd et al., 2017; Du et al., 2018; Prashantha et al., 2013). Higher cortical suppression leads to a higher degree of impairment (Du et al., 2018). Transcranial magnetic stimulation (TMS) studies have shown that after stroke, more intensity is required to generate motor evoked potentials in the ipsilesional hemisphere (Bütefisch et al., 2003; Du et al., 2018; Favre et al., 2014). Therefore, damaged neurons likely have higher thresholds required to generate action potentials. Other studies have shown that stimulation does not have to be local; an experiment in intact and post-stroke rats found that epidural cerebellar stimulation improved M1 function by modifying neuronal firing rates, enhancing neural synchronization, and strengthening the activation of neuronal assemblies (Abbasi et al., 2021).

The results of the current study show that StartReact post-stroke can enhance cortically mediated tasks and suggest that StartReact can make speech plans accessible to the motor cortex. StartReact consists of two steps: planning movement and exposure to a startling acoustic stimulus. StartReact may then serve to load the articulatory plan in the vPMC and then overexcite suppressed neurons between the reticular formation and M1 to elicit the indented plan and enhance the resulting movement(Honeycutt & Perreault, 2012). As in the present study, over several days of training, these thresholds might be reset to lower levels so that voluntary speech and movement are easier to access via the vPMC-M1 pathway. The effect of START in the moderate/severe group aligns with previous upper-extremity work (Rahimi & Honeycutt, 2020) and may be due to heightened contralesional plasticity and reticular formation disinhibition following more severe stroke (Li & Francisco, 2015; McPherson et al., 2018).

3.5.4   Comparison to Existing Speech Language Therapies

We found that individuals with moderate/severe aphasia saw the most benefit from START; this contrasts with most speech therapies. Recent reviews suggest that most new intervention strategies fail to benefit individuals with severe aphasia (Breitenstein et al., 2017; Fridriksson & Hillis, 2021; Godecke et al., 2020; Plowman et al., 2012). Individuals with severe aphasia can experience higher financial burdens than other post-stroke deficits due to the need for long-term, high dose speech language therapies (Ellis et al., 2012), and often cannot adhere to treatments due to cost, lack of transportation (Blonski et al., 2014), and low therapy success rates (Schindel et al., 2022; Wray et al., 2018). According to three large RCTs, more individuals with severe aphasia benefit less from SLT than more mild patients (Breitenstein et al., 2017; Godecke et al., 2020; Nouwens et al., 2017). One study found no differences between individuals with severe aphasia receiving 40 hours of traditional SLT, and those who did not receive any therapy (Sarno Martha Taylor et al., 1970). In conclusion, while individuals with severe aphasia are less likely to benefit from existing speech therapies, our moderate/severe group, including 6 individuals with severe aphasia, saw the highest number of subtests affected by START.

There is some evidence that high-intensity speech therapy (at least 10 hours of therapy per week for at least 12 weeks (Breitenstein et al., 2017; Johnson et al., 2019) is more effective for individuals with severe aphasia. Similarly, constraint-induced aphasia therapy (CIAT) is usually administered at high intensity in group settings (3 hours per day for 10 days) (Pulvermüller et al., 2001; Szaflarski et al., 2015; Zhang et al., 2017). However, high-intensity therapies are expensive, intense, and may still be ineffective in severe aphasia, leading to high dropout rates (Brogan et al., 2019; Harrison et al., 2020). The present study shows that START can be used via telehealth and is most effective in moderate/severe individuals, with improvements noted after only three days of administration. The participants in the present study were trained on a high-intensity word repetition task (three consecutive days, 270 words per session). StartReact may be useful as an adjuvant to existing speech therapies, helping to increase the intensity of practice inexpensively and quickly and make eliciting speech motor programs less effortful for individuals with severe impairment who struggle to elicit them voluntarily. Previous work has shown that StartReact increases maximum voluntary contraction 2 to 3 fold in individuals with little-to-no voluntary upper extremity movement (Rahimi & Honeycutt, 2020), indicating that StartReact increases practice intensity. StartReact also elicits involuntary movements, which may make speech less effortful (Smith et al., 2019; Swann et al., 2022; Valls-Solé et al., 1999). If START does in fact increase the intensity of practice during speech tasks, it has the potential to be successfully administered as an adjuvant to traditional speech therapies.

A recent meta-analysis (Allen et al., 2012) defined five types of interventions for post-stroke aphasia: traditional speech therapy, technological, pharmaceutical, stimulation, and constraint-induced (i.e., discouraging non-verbal communication) therapies. Speech therapies were most effective at high doses and in group settings for a minimum of 12 weeks. Computer games were similarly effective at high intensity, with a minimum timeframe of 2 months. Pharmaceutical interventions were inconsistently successful, with approximately half of the studies reporting significant changes in the aphasia scores after at least 16 weeks. CIAT, which discourages "learned non-use" by constraining writing, gestures, or other non-verbal modalities,

forces the patient to use their impaired processes (Pulvermüller et al., 2001; Zhang et al., 2017). The efficacy of CIAT remains unclear compared with that of other treatments. A recent comprehensive meta-analysis found no difference between CIAT and other types of therapy in any domain (Zhang et al., 2017), while individual studies suggested that CIAT benefits individuals across all severities and domains tested (Meinzer et al., 2005; Szaflarski et al., 2015). The fastest reported therapies were CIAT and brain stimulation therapies (TMS and tDCS) over the course of at least 10 days. CIAT demonstrated efficacy in multiple language domains (comprehension, naming, repetition), but can be expensive; therefore, it is most practically delivered in groups (Zhang et al., 2017) and is not specific to each individual's needs. Similar to high-dose traditional SLT, higher CIAT dose/intensity is often not tolerated (Woldag et al., 2017; Zhang et al., 2017). Like CIAT, START discourages learned nonuse/nonverbal communication. The current study suggests that future work should investigate whether START is an appropriate alternative or adjuvant to CIAT, as START is inexpensive, can be tailored to the individual, and shows improvements after a shorter duration (3 days). Although the results from this study suggest that individuals in the control group showed more gains than those in the START group at the one-month follow-up time point, this study evaluated speech after only three sessions. It is unknown whether START would benefit speech in the long term if participants received at least 10 days of START, which is comparable to the typical CIAT duration. The results from a satisfaction survey administered to our participants at the end of training provided anecdotal evidence that START may be more tolerable for some individuals.

Finally, the results of this study suggest that START can affect speech beyond the six words in the trained word repetition task and is generalizable to other tasks, from syllable repetition in the diadochokinetic rate test in ABA-2 to understanding sequential commands in the WAB-R comprehension subtest. Previous work has disagreed whether training specific words is effective for aphasia. Some studies found that word repetition or script training alone may be generalizable to other words (Goldberg Samantha et al., 2012; R. Holland et al., 2018; Kaye & Cherney, 2016; Schuchard & Middleton, 2018), while others found that training specific words,

even when combined with gestural therapy, improved untrained words in only 33% of participants (Rose et al., 2013). Our results indicate that START generalizes not only to the production of non-trained speech but also to receptive speech tasks.

3.5.5   Limitations

While the changes we observed in moderate/severe participants receiving START were statistically significant, they were small. These changes do not meet the clinically important differences for WAB-R: spontaneous speech (+2 points), comprehension, repetition, word finding (+1.5 points), or overall Aphasia Quotient (+5 points) (A. Holland et al., 2017). The standard error of measurement for AQ is considered a clinically meaningful difference and can be estimated to be approximately five points (Shewan & Kertesz, 1980). Although the START group saw improvements in speech and language measures from Day 1 to Day 5, the START and control groups did not differ from each other by Day 5, likely due to high variability in each group. However, this study evaluated only a small population (n=42) with a wide range of aphasia, AOS symptoms, and severity levels. Additionally, the finding that the START group had increased mood (SIS and perceived communication recovery (COAST) after three days of START training) should be considered carefully, as only half of the participants completed both day 1 and day 5 quality of life assessments (likely because participants were asked to complete these surveys on their own time, not while virtually connected with the experimenters). By including all types of aphasia, we increased the noise in our sample, making the large number of clinical subtests that changed after START even more remarkable. However, START may affect expressive and receptive aphasia differently; therefore, future studies should selectively recruit specific aphasia types to investigate this.

The clinical measures used in this study (WAB-R and ABA-2) are standard for detecting the presence and severity of aphasia and AOS, respectively, and have excellent test-retest reliability (over 90%) (Ahmed et al., 2020; Bond, 2019). However, certain subtests of the WAB-R have limitations in the research setting. The AQ may be overly sensitive to the presence of motor

speech disorders owing to the high number of expressive speech tasks used. Additionally, fluency and information content scores are more qualitative measures and account for 40% of AQ (Hula et al., 2010). Therefore, it is prudent to evaluate individual subtests rather than solely rely on AQ for aphasia improvement. The ABA-2 overcomes some of these challenges by scoring the severity of individual subtests separately and relying on an informed clinical opinion to find an overall measure of AOS severity based on the overall patient history (Dabul & Pro-Ed (Firm), 2000).

Another limitation of this study was our inability to reliably detect whether a participant achieved StartReact (as opposed to the classic startle) following the startling acoustic stimulus. Traditionally, the StartReact effect has been measured by fast peaks of sternocleidomastoid muscle activity using electromyography (EMG) (Carlsen et al., 2003, 2004). Here, we were unable to use EMG due to the teletherapy design. However, we previously showed that subjects startle ~50% of the time in an identical protocol, well below other studies, because of the lower decibel stimulus we used (Swann et al., 2022). Despite this limitation, we showed that START does have an impact on some aphasia and AOS symptoms after stroke at the group level, regardless of the degree to which individuals achieve startle responses. Sternocleidomastoid EMG is an excellent metric to include in future studies to assess neuromotor behavior both during and after training.

3.5.6   Future Directions

Training over three days with START increases WAB-R measures of Comprehension, Repetition and Reading, as well as ABA-2 measures of Diadochokinetic Rate, and Increasing Word Accuracy in individuals with moderate/severe aphasia. Future studies should determine if longer sessions over more days in a larger sample would increase the small changes we see to clinically meaningful thresholds. Unlike participants with moderate/severe aphasia, participants with mild aphasia did not improve in the diadochokinetic rate task, so future studies should consider that START may decrease speech rate or affect vowel distance and intelligibility in more

mild individuals. We saw no effect of START training on measures of dysphonia or intelligibility, indicating execution parameters like phonation, articulation, and nasality remain unaffected by START. Future studies should examine the effect of START on other speech and voice-related acoustic measures, such as pitch, vowel distance, phonemic error rate, and changes in breathing activity. START's effect in both aphasia and apraxia subtests, especially in moderate/ severe participants, indicates that START's mechanism of action may not directly target any specific circuit, but increase communication abilities more broadly. In this way, START may operate by modifying a physiologic response, such as cortisol (Bronson & Preuss, 2017; M. W. Miller & Gronfier, 2006) or oxygen (Hadanny et al., 2020; Swann et al., 2022). This possibility is supported by our previous work showing that StartReact in post-stroke aphasia and apraxia often leads to hypermetric inspiratory events, which could increase oxygen and cortisol and thereby affect learning and memory. Alternatively, the intense articulatory planning phase of the START paradigm could affect working memory (R. C. Martin & Schnur, 2019), or attention (Peach et al., 2017), leading to a general mechanism for cognitive improvements. Attention therapies for post-stroke aphasia have been used with moderate success (Peach et al., 2017, 2019; Zakariás et al., 2019). Future studies should evaluate both physiological and cognitive markers in relation to START to further assess its potential mechanism.

3.6 Conclusions

In conclusion, training over three days with START increases WAB-R measures of Comprehension, Repetition and Reading, as well as ABA-2 measures of Diadochokinetic Rate, and Increasing Word Accuracy in moderate/severe aphasia. Reading Quotient is also increased in mild aphasia. Control participants with mild aphasia saw increased Comprehension. These changes in clinical scores lead to an increase in perceived mood (SIS) and communication ability (COAST) for the START group, compared to Controls who saw no changes. Measures of dysphonia, vowel duration, and intelligibility were largely unaffected by START training. This study is the first to evaluate the impact of training with StartReact on clinical outcomes. Future

studies should assess a mechanism of action that may relate to speech motor planning abilities,

as well as run a longer Phase 1 clinical trial with more training days, longer sessions, a larger

population, and evaluate retention of outcomes.

Subtest	MODERATE/SEVERE START GROUP				MODERATE/SEVERE CONTROL GROUP			
	Pre Mean(SEM)	Post Mean(SEM)	F-value	p-value	Pre Mean(SEM)	Post Mean(SEM)	F-value	p-value
AQ	46.91(6.30)	49.79(6.75)	2.598	0.138	47.13(5.17)	48.51(4.73)	0.55	0.475
Information	5.18(0.69)	5.00(0.83)	0.313	0.588	5.09(0.49)	5.45(0.53)	1.702	0.221
Fluency	3.55(0.62)	3.55(0.67)	0	1	3.00(0.54)	3.00(0.49)	0	1
Spontaneous speech	8.73(1.18)	8.55(1.38)	0.102	0.756	8.09(0.97)	8.45(0.87)	0.342	0.572
Comprehension	7.24(0.65)	7.80(0.56)	9.955	0.01	7.27(0.64)	7.57(0.57)	1.845	0.204
Repetition	3.60(0.77)	4.20(0.86)	6.149	0.033	4.09(0.67)	4.30(0.67)	0.464	0.511
Word finding	3.89(0.92)	4.35(0.89)	3.159	0.106	4.11(0.75)	3.93(0.65)	0.313	0.588
Reading	51.20(7.89)	55.93(8.03)	5.761	0.037	37.68(9.65)	39.50(9.73)	0.461	0.512
Diadochokinetic Rate	1.91(0.97)	4.45(1.01)	7.686	0.02	6.09(2.16)	8.45(2.52)	1.395	0.265
Increasing Words	7.78(0.81)	4.70(0.94)	12.412	0.008	6.00(0.94)	5.55(1.30)	0.217	0.651
Utterance Time	10.79(0.75)	9.67(0.79)	1.1	0.329	7.81(1.01)	8.62(0.89)	0.711	0.421
Latency TIme	97.33(14.08)	105.54(21.05)	5.31	0.055	140.00(24.58)	152.17(30.06)	0.992	0.345
Repeated Words	12.80(3.06)	14.10(2.71)	1.246	0.293	16.70(3.17)	16.18(3.01)	0.167	0.692
CPPS	5.10(0.26)	4.77(0.28)	0.896	0.3753	4.83(0.22)	4.66(0.18)	1.2434	0.3016
HNR	11.63(1.17)	11.08(1.03)	0.022	0.8859	13.12(0.72)	12.25(0.57)	1.1453	0.32
SL	11.63(1.12)	11.60(1.78)	0.739	0.4185	10.40(0.74)	11.51(0.70)	1.0533	0.3389
SLdB	1.14(0.08)	1.20(0.09)	0.015	0.9062	1.05(0.06)	1.15(0.06)	1.3047	0.2909
Slope (Ltas)	-18.60(1.57)	-17.73(1.17)	0.875	0.3807	-17.17(1.57)	-16.93(1.42)	0.68561	0.435
Tilt (trendline)	-7.88(0.79)	-7.76(0.82)	0	0.9992	-9.64(0.54)	-8.33(0.61)	2.4035	0.165
AVQI	6.64(0.28)	7.18(0.35)	1.231	0.3038	5.93(0.25)	6.52(0.27)	4.1857	0.08
Vowel Duration (1 syll.)	0.245(0.014)	0.265(0.018)	0.06011	0.8067	0.227(0.010)	0.231(0.012)	1.5769	0.2109
Vowel Duration (2 syll.)	0.229(0.014)	0.223(0.013)	1.02986	0.312	0.184(0.008)	0.180(0.009)	0.0716	0.7894
Vowel Duration (3 syll.)	0.233(0.013)	0.245(0.016)	0.00376	0.9512	0.203(0.012)	0.188(0.008)	0.56417	0.4537
Forced choice % All Correct	67.41(6.79)	72.59(7.15)	1.16003	0.3129	71.36(6.27)	81.31(5.98)	4.15022	0.0721

Table 4. Statistical Comparisons for participants with Moderate/Severe Aphasia.

Subtest	MILD START GROUP				MILD CONTROL GROUP			
	Pre Mean(SEM)	Post Mean(SEM)	F-value	p-value	Pre Mean(SEM)	Post Mean(SEM)	F-value	p-value
AQ	85.78(1.85)	85.36(2.07)	0.281	0.609	89.07(1.97)	91.56(2.37)	2.699	0.135
Information	8.60(0.27)	8.70(0.26)	0.101	0.758	8.90(0.28)	9.00(0.33)	0.184	0.678
Fluency	7.90(0.35)	7.50(0.43)	1.385	0.27	8.20(0.39)	8.60(0.54)	2.25	0.168
Spontaneous speech	16.50(0.54)	16.20(0.53)	0.503	0.496	17.10(0.62)	17.60(0.82)	1.364	0.273
Comprehension	9.22(0.29)	9.45(0.21)	4.804	0.056	9.45(0.15)	9.74(0.12)	5.946	0.038
Repetition	8.50(0.35)	8.30(0.41)	2.903	0.123	8.93(0.29)	9.09(0.25)	0.36	0.563
Word finding	8.67(0.24)	8.73(0.15)	0.165	0.694	9.06(0.18)	9.35(0.20)	3.366	0.1
Reading	82.60(4.68)	85.85(4.17)	9.086	0.015	80.30(9.19)	81.20(9.29)	0.377	0.554
Diadochokinetic Rate	23.40(4.55)	24.60(3.88)	0.408	0.539	13.30(1.69)	15.00(2.57)	0.681	0.431
Increasing Words	1.50(0.48)	0.60(0.31)	4.893	0.054	3.10(1.02)	2.30(0.58)	1.946	0.197
Utterance Time	11.16(3.44)	11.73(4.67)	0.174	0.686	8.41(0.75)	7.79(0.61)	1.557	0.244
Latency TIme	32.80(4.60)	31.05(4.65)	0.131	0.726	37.70(7.28)	26.46(5.22)	3.529	0.093
Repeated Words	27.00(1.02)	28.20(0.49)	2.25	0.168	26.00(1.72)	27.60(1.36)	1.419	0.264
CPPS	4.88(0.19)	5.10(0.16)	2.8517	0.1297	3.97(0.54)	5.20(0.23)	2.4715	0.1546
HNR	11.30(0.80)	10.66(0.75)	1.10082	0.3247	9.32(1.46)	11.72(0.77)	0.35487	0.5678
SL	11.30(1.10)	12.20(0.96)	1.52755	0.2515	8.69(1.45)	11.45(0.94)	2.71883	0.1378
SLdB	1.11(0.08)	1.18(0.07)	1.95873	0.1992	0.98(0.08)	1.11(0.06)	3.0508	0.1188
Slope (Ltas)	-15.62(1.02)	-16.15(1.41)	0.33627	0.5779	-12.10(2.22)	-16.71(1.27)	0.45705	0.5181
Tilt (trendline)	-9.01(0.99)	-8.38(1.03)	2.25806	0.1713	-6.53(1.23)	-9.17(0.87)	0.07124	0.7963
AVQI	6.24(0.28)	6.48(0.30)	2.2396	0.1729	4.83(0.71)	6.01(0.25)	0.1118	0.7467
Vowel Duration (1 syll.)	0.166(0.009)	0.184(0.008)	5.15241	0.0245	0.182(0.010)	0.177(0.011)	0.31557	0.575
Vowel Duration (2 syll.)	0.130(0.006)	0.132(0.005)	0.29988	0.5847	0.149(0.008)	0.143(0.008)	0.77494	0.3798
Vowel Duration (3 syll.)	0.123(0.006)	0.127(0.005)	0.34508	0.5577	0.170(0.011)	0.149(0.010)	3.03262	0.0833
Forced choice % All Correct	86.76(3.27)	93.33(3.45)	2.0032	0.1999	87.95(1.65)	93.33(1.74)	5.284	0.0506

Table 5. Statistical Comparisons for participants with Mild Aphasia.

Subtest	START GROUP				CONTROL GROUP			
	Pre Mean(SEM)	Post Mean(SEM)	F-value	p-value	Pre Mean(SEM)	Post Mean(SEM)	F-value	p-value
Strength	46.18%(5.08%)	57.21%(7.25%)	2.639	0.13	49.70%(6.18%)	48.61%(10.56%)	0.79	0.4
Memory	68.03%(4.54%)	73.35%(4.02%)	1.384	0.262	72.79%(4.54%)	74.21%(5.64%)	0.68	0.433
Emotion	58.17%(4.34%)	73.29%(4.39%)	5.602	0.036	67.86%(4.05%)	66.98%(4.20%)	0.172	0.689
Communication	53.01%(5.45%)	64.29%(7.65%)	2.059	0.177	51.53%(5.49%)	61.90%(6.89%)	2.886	0.128
Daily Activities	76.56%(4.14%)	77.74%(4.52%)	0.393	0.544	73.69%(4.56%)	72.50%(8.21%)	0.282	0.61
Mobility	80.07%(4.34%)	81.20%(3.71%)	0.785	0.393	79.50%(4.34%)	81.17%(5.68%)	0.144	0.714
Hand function	35.29%(9.22%)	42.69%(10.66%)	0.016	0.901	37.26%(8.24%)	38.89%(14.78%)	0.009	0.926
Participation	53.49%(6.02%)	59.27%(5.62%)	0.51	0.489	45.64%(5.43%)	55.10%(10.51%)	0.729	0.418
Total (SIS)	63.74(4.41)	73.46(3.04)	3.515	0.085	68.52(2.78)	70.11(4.79)	0.043	0.841
COAST	57.90%(19.90%)	69.70%(14.90%)	8.696	0.011	53.60%(17.20%)	60.00%(21.40%)	2.866	0.134

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Table 6. Statistical Comparisons for Quality of Life Measures

CHAPTER 4

CONCLUSIONS

4.1 Summary

The objective of this dissertation was to establish if the StartReact phenomenon is present in post-stroke speech, and to conduct a small proof-of-concept clinical trial on the potential therapeutic efficacy of StartReact training ("START") in post-stroke speech impairment. Chapter 2 represents the first experiment to study if impaired speech can be elicited using startling acoustic stimuli. The results of that study not only show an expected stimulus intensity effect on pitch and loudness (Luo et al., 2018), but also indicate a robust StartReact effect marked by changes to vowel space, error rate, and novel phoneme achievement compared to voluntary (non-startled) words. Chapter 3 represents the first study to evaluate the impact of training with StartReact on clinical outcomes, in any therapy domain e.g., speech or upper extremity, in a randomized control clinical trial. Participants receiving 3 days of training with StartReact, or "Startle Adjuvant Rehabilitation Therapy" (START) paired with a word repetition task saw improvement in clinical scores related to aphasia, apraxia of speech, and quality of life. Controls, who received three days of a sham word repetition task, did not see changes in these measures. Speech intelligibility and dysphonia were unaffected by START, though mild participants receiving START saw a small increase in vowel duration in monosyllabic words. Individuals receiving START had improved mood and communicative quality of life compared to Controls who saw no changes. START was administered via telehealth and showed the greatest number of improved assessments in individuals with moderate-to-severe speech impairment. In summary, this dissertation has shown that StartReact 1) is present in impaired speech and 2) has potential for efficacy in therapy. This represents the first study to look at therapeutic potential of StartReact in any modality, so future studies should examine if START improves upper or lower extremity control. This dissertation has further brought into question the mechanisms of StartReact. In Chapter 3, START affected activities further upstream of motor planning (e.g.,

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comprehension and reading) and generalizes not only to production of non-trained speech, but also to receptive speech tasks as well. Future studies should evaluate the ability of StartReact to elicit widely distributed cortical tasks and determine if START is effective in a larger clinical trial.

4.2   Clinical Impact of Findings

This dissertation contributes new evidence to support the use of StartReact in therapeutic settings in terms of efficacy, feasibility, and safety. The changes reported in Chapter 3 indicate a small effect of START that provides the framework to determine if the impact can be amplified through longer and more sessions in a Phase 1 clinical trial. Our results indicate, at the least, that START does not worsen speech outcomes. Moreover, the dose and duration of StartReact used in this dissertation were well tolerated. Subjects who were exposed to StartReact did not report any discomfort, and instead reported higher levels of motivation to keep speaking. Five subjects reported boredom or sleepiness during the sessions regardless of treatment type (START/Control). One test subject reported one night she had trouble sleeping but it is unclear if this was related to START. Five subjects went out of their way to report they wished the sessions had been longer regardless of treatment type (START/Control). Given the improvements in language outcomes, motor planning outcomes, mood, and communicative quality of life shown in this dissertation, the use of START in a Phase 1 clinical trial is likely to be safe. Future trials should also assess the influence of START on other measures impacting quality of life, such as sleep and mental health. Future studies should determine if START can be used in individuals with mild hearing impairment typical in older individuals. Compared to other forms of treatment, START is inexpensive, can be delivered via telehealth, and could be used as an effective adjuvant to existing speech therapies.

Our recruitment efforts were focused on a demographically diverse population to better evaluate the efficacy of START among different groups. START was accessible to even the most underserved participants. Seventeen participants reported at least a bachelor's degree, while two

did not finish high school. Most participants (n=23) considered themselves to be middle class, with twelve reporting their yearly combined household income as over $100,000, while eight reported under $40,000. Twenty-nine participants reported their ethnicity as white, with the remaining participants reporting their ethnicities as either Black, Hispanic/Latinx, or Asian. Finally, three participants reported themselves as living in a rural community, and the remainder reported either urban or suburban neighborhoods. While our results suggest START to be easily deployable to patients regardless of socioeconomic status, future studies should evaluate the effect of socioeconomic status on access to care with START.

4.3   Brief Discussion of Neural Mechanisms

This dissertation also demonstrates the need to reevaluate the neural mechanisms of StartReact. As discussed in Chapter 1, StartReact's latency and higher rate in trained, proximal movements suggest it is mediated by subcortical structures, while other studies in speech and using TMS suggest a cortical component. This dissertation shows that impaired speech in individuals with cortical stroke have an intact StartReact response. It is unlikely that processes related to reading, sentence repetition, and comprehension, which improved in the clinical assessments used in Chapter 3, could be governed entirely by subcortical structures. Though we did not study mechanisms in this study, the following are observations that add to the understanding of the mechanisms governing this response. Future studies are needed to specifically determine if these implications are accurate.

As discussed in Chapter 3, cortical suppression is common after stroke (Bütefisch et al., 2003; Dodd et al., 2017; Du et al., 2018; Prashantha et al., 2013), and the simplest mechanism here may be that StartReact over-activates suppressed neurons throughout the corticospinal tract, thereby releasing voluntarily inaccessible speech tasks. This would indicate the StartReact effect, in stimulating the corticospinal tract, may be mediated by cortical structures, at least where the word repetition task in this dissertation is concerned. A recent review suggested that StartReact's mechanism may be more diffuse than previously thought. The type of task (e.g.

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reaching vs. distal finger movement vs. posture) may weight the region of action following reticular formation activation via the startle response (Marinovic & Tresilian, 2016). If this were the case, StartReact would access motor plans stored in subcortical structures for certain tasks (e.g., proximal joint, trained) and access motor plans stored in cortical structures for others (e.g., distal joint, untrained, speech).

If StartReact is overstimulating additional cortical circuitry to elicit speech, it still unclear how StartReact accesses the cortex, especially in cases of cortical damage. Given our results in Chapter 2 that startled speech is more forceful and less accurate than voluntary speech, StartReact may make use of emotional limbic circuitry. Specifically, StartReact may interact with two speech pathways: one for innate, emotional vocalizations (indirect); and one for voluntary, complex speech (direct) (Conant et al., 2014; Jürgens, 2002a, 2002b, 2009; Simonyan & Horwitz, 2011; Simonyan & Jürgens, 2002; Willemse et al., 2006). Most human speech will be mediated by the direct pathway, involving projections from the laryngeal motor cortex to the reticular formation in the brainstem via the basal ganglia. The direct pathway also involves reciprocal projections from the laryngeal motor cortex (LMC) to the anterior cingulate cortex (ACC), which is involved in many cognitive, limbic, and motor processes including voluntary speech initiation and emotional inflection (Simonyan & Horwitz, 2011). The indirect pathway is active in both human and non-human primate emotional vocalizations, such as laughing, crying, mating noises, and shouting (Jürgens, 2009; Simonyan & Horwitz, 2011). It is governed by a distinct pathway extending directly from the ACC to the periaqueductal grey (PAG) within the brainstem, which then projects to the reticular formation, the site of vocal execution and coordination. Therefore, the direct and indirect pathways converge in two areas: the ACC and the reticular formation. The latter also mediates the startle response (Yeomans & Frankland, 1995), and the StartReact phenomenon has been proposed to represent activation of the reticular formation (Bartels et al., 2020; Honeycutt et al., 2013; Rangarajan et al., 2022).

It is possible, then, that StartReact would use the ACC-PAG-RF pathway during speech tasks, and gain access to cortical structures by avoiding damaged circuitry. Both the brainstem and the cingulate are often spared in most strokes that cause aphasia, as neither are supplied by the middle cerebral artery. In fact, individuals with stroke likely have increased ipsilateral projections of the reticulospinal tract (Herbert et al., 2015; Karbasforoushan et al., 2019) as a potential compensatory mechanism following cortical damage (Pineiro et al., 2001; Stinear et al., 2007). If StartReact causes activation throughout this pathway, starting with the reticular formation, it may serve as a mechanism for adaptive plasticity in post-stroke speech and lead to the improvements seen in this dissertation. The ACC mediates a wide array of potentially helpful neural activities including initiation, motivation, and attentional control during speech production (Piai et al., 2013; Simonyan & Horwitz, 2011), as well as conflict monitoring, social awareness, and emotional inflection of speech. The ACC also serves as a hub within the direct pathway and may serve as a mechanism for StartReact to access the direct pathway and impact elements of voluntary speech planning, such as semantics, word selection, and articulatory sequencing (Simonyan & Horwitz, 2011).

I hypothesize that StartReact likely carries out four phases: 1. Priming the laryngeal motor cortex, 2. Activating the ACC-PAG pathway, 3. Resetting laryngeal motor cortex activation thresholds, and 4. Executing the speech plan voluntarily. First, actions must be sufficiently and completely prepared in advance to be elicited by StartReact. Without sufficient planning, either classic startle or slow, voluntary movement is achieved. In the word repetition task used in this dissertation, participants were asked to plan each word well in advance through covert speech, thereby "priming" the LMC. The second phase of StartReact is fast, involuntary, ballistic execution. Movements are gross and inaccurate but have higher motor intensity compared to voluntary movements. Subjects with stroke can also achieve movements they were not able to on their own (Honeycutt & Perreault, 2012; Rahimi et al., 2021; Swann et al., 2022). StartReact may use the intact indirect pathway structures for this step. Startled reaching movements are initially contaminated by inappropriate classic startle (ballistic flexion), followed by the intended
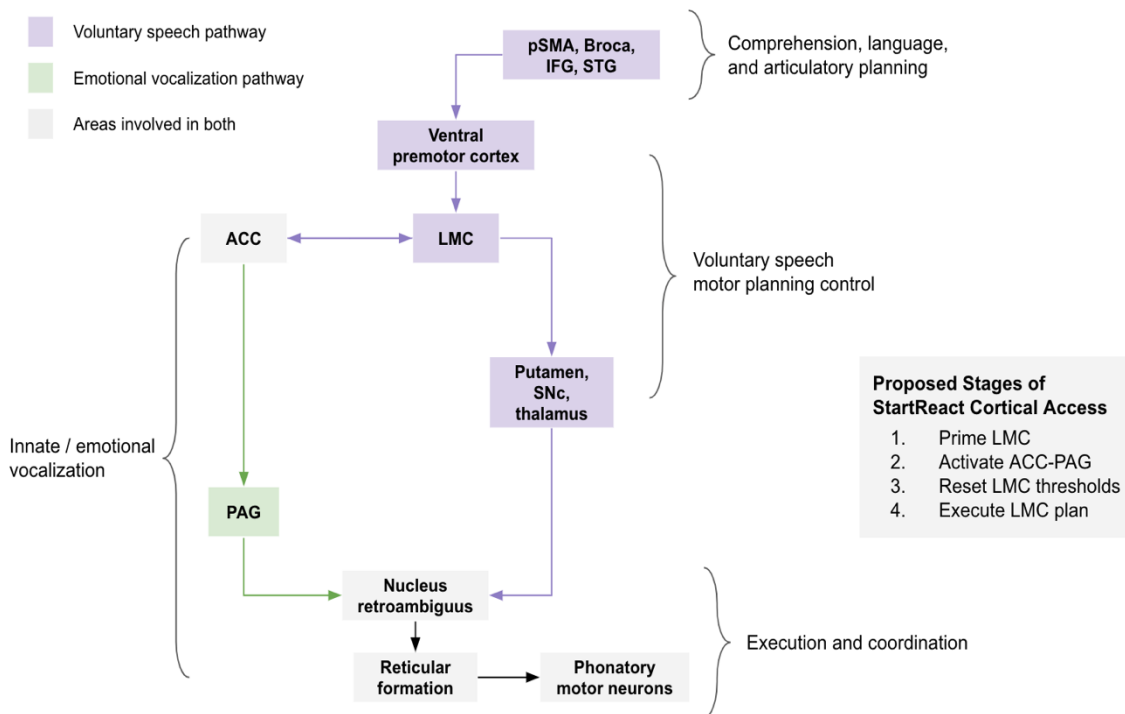
Figure 11. Potential Mechanisms of StartReact Access to Cortex. *pSMA = presupplementary motor area; IFG = inferior frontal gyrus; STG = supratemporal gyrus; ACC = anterior cingulate cortex; LMC = laryngeal motor cortex; SNc = substantia nigra pars compacta; PAG = periaqueductal grey.*

movement (extension) (Rahimi & Honeycutt, 2020). This initial contamination suggests the

properly gated movement is preceded by uninhibited subcortical activation. In the case of speech,

the ACC-PAG ("indirect") pathway is a likely target for this subcortical activation, with direct

connections to the reticular formation and heavy involvement in emotional vocalizations. This

pathway may be activated during startled speech and StartReact may then use this pathway to

gain access to the ACC, and its reciprocal connection with the LMC (Simonyan & Horwitz, 2011).

The third phase is cortical reactivation. After a stroke, ipsilesional cortical suppression and

contralesional disinhibition occur, causing impairment (Bütefisch et al., 2003; Dodd et al., 2017;

Du et al., 2018; Prashantha et al., 2013). These damaged neurons have greater action potential

thresholds, and higher stimulation intensity is needed to elicit motor evoked potentials in the

ipsilesional hemisphere (Bütefisch et al., 2003; Du et al., 2018; Favre et al., 2014). StartReact

may overexcite suppressed neurons to elicit the intended word. The fourth phase represents

several days of training, as in the current study, which may reset these thresholds to lower levels,

making voluntary speech and movement less effortful to access via the direct pathway.

4.4   Future Directions

This dissertation marks the start of the use of StartReact in impaired speech. Future

studies should evaluate the susceptibility of impaired speech to START during other speech tasks

such as multi-syllable words, sentence completion, and picture naming, as well as evaluate the

impact of emotional words (e.g., neutral words, swear words, positive words, non-words) on

StartReact presence. Future studies should take care to evaluate EMG onset and muscle

activation data during these tasks to ensure the presence of StartReact and to identify the effect

of respiration on speech tasks (see: Hypermetric inspiratory events in Chapter 2).

This dissertation also marks the first clinical trial to evaluate START in any population.

While our results indicate a small effect of START, future studies should conduct a larger clinical

trial with a longer duration of therapy, longer individual sessions, and a larger sample size. Future

clinical trials should also evaluate the effect of START on individuals with dysarthria. While

several of the participants in these studies likely had co-occurring dysarthria, it was not clinically

assessed. Additionally, retention, feasibility, and safety should continue to be evaluated in a

larger clinical trial to maximize patient outcomes.

REFERENCES

Abbasi, A., Danielsen, N. P., Leung, J., Muhammad, A. K. M. G., Patel, S., & Gulati, T. (2021). Epidural cerebellar stimulation drives widespread neural synchrony in the intact and stroke perilesional cortex. *Journal of NeuroEngineering and Rehabilitation*, *18*(1), 89. https://doi.org/10.1186/s12984-021-00881-9

Ahmed, M. S., Naznin, N., & Alam, M. J. (2020). Adaptation of Apraxia Battery for Assessing the Patient with Apraxia. *Journal of Medical Research and Health Sciences*, *3*(10), 1114–1123. https://doi.org/10.15520/jmrhs.v3i10.263

Alibiglou, L., & MacKinnon, C. D. (2012). The early release of planned movement by acoustic startle can be delayed by transcranial magnetic stimulation over the motor cortex. *The Journal of Physiology*, *590*(4), 919–936. https://doi.org/10.1113/jphysiol.2011.219592

Allen, L., Mehta, S., McClure, J. A., & Teasell, R. (2012). Therapeutic Interventions for Aphasia Initiated More than Six Months Post Stroke: A Review of the Evidence. *Topics in Stroke Rehabilitation*, *19*(6), 523–535. https://doi.org/10.1310/tsr1906-523

Anderlini, D., Wallis, G., & Marinovic, W. (2019). Language as a Predictor of Motor Recovery: The Case for a More Global Approach to Stroke Rehabilitation. *Neurorehabilitation and Neural Repair*, *33*(3), 167–178. https://doi.org/10.1177/1545968319829454

Ao, D., Song, R., & Tong, K. (2015). Sensorimotor Control of Tracking Movements at Various Speeds for Stroke Patients as Well as Age-Matched and Young Healthy Subjects. *PLOS ONE*, *10*(6), e0128328. https://doi.org/10.1371/journal.pone.0128328

Awan, S. N., & Roy, N. (2006). Toward the development of an objective index of dysphonia severity: A four-factor acoustic model. *Clinical Linguistics & Phonetics*, *20*(1), 35–49. https://doi.org/10.1080/02699200400008353

Baer, T. (1979). Reflex activation of laryngeal muscles by sudden induced subglottal pressure changes. *The Journal of the Acoustical Society of America*, *65*(5), 1271–1275. https://doi.org/10.1121/1.382795

Bakheit, A. M. O., Shaw, S., Barrett, L., Wood, J., Carrington, S., Griffiths, S., Searle, K., & Koutsi, F. (2007). A prospective, randomized, parallel group, controlled study of the effect of intensity of speech and language therapy on early recovery from poststroke aphasia. *Clinical Rehabilitation*, *21*(10), 885–894. https://doi.org/10.1177/0269215507078486

Bakhtiyari, J., Khatoonabadi, S. A. R., Dadgar, H., Bakhtiari, B. M., Khosravizadeh, P., & Shaygannejad, V. (2015). Comparison of emotional and non-emotional word repetitions in patients with aphasia. *Advanced Biomedical Research*, *4*, 164. https://doi.org/10.4103/2277-9175.162540

Ballard, K. J., Halaki, M., Sowman, P., Kha, A., Daliri, A., Robin, D. A., Tourville, J. A., & Guenther, F. H. (2018). An Investigation of Compensation and Adaptation to Auditory Perturbations in Individuals With Acquired Apraxia of Speech. *Frontiers in Human Neuroscience*, *12*. https://www.frontiersin.org/articles/10.3389/fnhum.2018.00510

Ballard, K. J., Wambaugh, J. L., Duffy, J. R., Layfield, C., Maas, E., Mauszycki, S., & McNeil, M. R. (2015). Treatment for Acquired Apraxia of Speech: A Systematic Review of Intervention Research Between 2004 and 2012. *American Journal of Speech-Language Pathology*, *24*(2), 316–337. https://doi.org/10.1044/2015_AJSLP-14-0118

Bartels, B. M., Quezada, M. J., Ravichandran, V. J., & Honeycutt, C. F. (2020). Experts, but not novices, exhibit StartReact indicating experts use the reticulospinal system more than novices. *Journal of Motor Behavior*, *0*(0), 1–7. https://doi.org/10.1080/00222895.2020.1732860

Basilakos, A. (2018). Contemporary Approaches to the Management of Post-stroke Apraxia of Speech. *Seminars in Speech and Language*, *39*(1), 25–36. https://doi.org/10.1055/s-0037-1608853

Basilakos, A., Rorden, C., Bonilha, L., Moser, D., & Fridriksson, J. (2015). Patterns of poststroke brain damage that predict speech production errors in apraxia of speech and aphasia dissociate. *Stroke*, *46*(6), 1561–1566. https://doi.org/10.1161/STROKEAHA.115.009211

Basilakos, A., Yourganov, G., den Ouden, D.-B., Fogerty, D., Rorden, C., Feenaughty, L., & Fridriksson, J. (2017). A Multivariate Analytic Approach to the Differential Diagnosis of Apraxia of Speech. *Journal of Speech, Language, and Hearing Research : JSLHR*, *60*(12), 3378–3392. https://doi.org/10.1044/2017_JSLHR-S-16-0443

Batthyany, C., Latoszek, B. B. V., & Maryn, Y. (2022). Meta-Analysis on the Validity of the Acoustic Voice Quality Index. *Journal of Voice*. https://doi.org/10.1016/j.jvoice.2022.04.022

Beber, B. C., Berbert, M. C. B., Grawer, R. S., & Cardoso, M. C. de A. F. (2018). Rate and rhythm control strategies for apraxia of speech in nonfluent primary progressive aphasia. *Dementia & Neuropsychologia*, *12*(1), 80–84. https://doi.org/10.1590/1980-57642018dn12-010012

Belke, E. (2008). Effects of working memory load on lexical-semantic encoding in language production. *Psychonomic Bulletin & Review*, *15*(2), 357–363. https://doi.org/10.3758/PBR.15.2.357

Benton, A. L. (1964). Contributions to Aphasia Before Broca. *Cortex*, *1*(3), 314–327. https://doi.org/10.1016/S0010-9452(64)80006-X

Benton, A. L., & Joynt, R. J. (1960). Early descriptions of aphasia. *Archives of Neurology*, *3*, 205–222. https://doi.org/10.1001/archneur.1960.00450020085012

Bislick, L., & Hula, W. D. (2019). Perceptual Characteristics of Consonant Production in Apraxia of Speech and Aphasia. *American Journal of Speech-Language Pathology*, *28*(4), 1411–1431. https://doi.org/10.1044/2019_AJSLP-18-0169

Blonski, D. C., Covert, M., Gauthier, R., Monas, A., Murray, D., O'Brien, K. K., Mendelson, A. D., & Huijbregts, M. (2014). Barriers to and Facilitators of Access and Participation in Community-Based Exercise Programmes from the Perspective of Adults with Post-stroke Aphasia. *Physiotherapy Canada*, *66*(4), 367–375. https://doi.org/10.3138/ptc.2013-70

Bohland, J. W., Bullock, D., & Guenther, F. H. (2010). Neural representations and mechanisms for the performance of simple speech sequences. *Journal of Cognitive Neuroscience*, *22*(7), 1504–1529. https://doi.org/10.1162/jocn.2009.21306

Bond, B. (2019). *The test-retest reliability of the Western Aphasia Battery-Revised* [Thesis, University of Kansas]. https://kuscholarworks.ku.edu/handle/1808/30075

Boothroyd, A. (1985). Evaluation of speech production of the hearing impaired: Some benefits of forced-choice testing. *Journal of Speech and Hearing Research*, *28*(2), 185–196. https://doi.org/10.1044/jshr.2802.185

Borowsky, R., Cummine, J., Owen, W. J., Friesen, C. K., Shih, F., & Sarty, G. E. (2006). FMRI of ventral and dorsal processing streams in basic reading processes: Insular sensitivity to phonology. *Brain Topography*, *18*(4), 233–239. https://doi.org/10.1007/s10548-006-0001-2

Bradshaw, A. R., Lametti, D. R., & McGettigan, C. (2021). The Role of Sensory Feedback in Developmental Stuttering: A Review. *Neurobiology of Language*, *2*(2), 308–334. https://doi.org/10.1162/nol_a_00036

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., Huber, W., Willmes, K., Ringelstein, E. B., Haeusler, K. G., Abel, S., Glindemann, R., Domahs, F., Regenbrecht, F., Schlenck, K.-J., Thomas, M., Obrig, H., de Langen, E., Rocker, R., … FCET2EC study group. (2017). Intensive speech and language therapy in patients with chronic aphasia after stroke: A randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet (London, England)*, *389*(10078), 1528–1538. https://doi.org/10.1016/S0140-6736(17)30067-3

Briggs, R. G., Pryor, D. P., Conner, A. K., Nix, C. E., Milton, C. K., Kuiper, J. K., Palejwala, A. H., & Sughrue, M. E. (2019). The Artery of Aphasia, A Uniquely Sensitive Posterior Temporal Middle Cerebral Artery Branch that Supplies Language Areas in the Brain: Anatomy and Report of Four Cases. *World Neurosurgery*, *126*, e65–e76. https://doi.org/10.1016/j.wneu.2019.01.159

Brogan, E., Ciccone, N., & Godecke, E. (2019). Treatment fidelity in aphasia randomised controlled trials. *Aphasiology*, *33*(7), 759–779. https://doi.org/10.1080/02687038.2019.1576442

Bronson, D. R., & Preuss, T. (2017). Cellular Mechanisms of Cortisol-Induced Changes in Mauthner-Cell Excitability in the Startle Circuit of Goldfish. *Frontiers in Neural Circuits*, *11*. https://www.frontiersin.org/articles/10.3389/fncir.2017.00068

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., & Fox, P. T. (2005). Stuttered and fluent speech production: An ALE meta-analysis of functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 105–117. https://doi.org/10.1002/hbm.20140

Buchsbaum, B. R., Baldo, J., Okada, K., Berman, K. F., Dronkers, N., D'Esposito, M., & Hickok, G. (2011). Conduction Aphasia, Sensory-Motor Integration, and Phonological Short-term Memory – an Aggregate analysis of Lesion and fMRI data. *Brain and Language*, *119*(3), 119–128. https://doi.org/10.1016/j.bandl.2010.12.001

Bütefisch, C. M., Netz, J., Weßling, M., Seitz, R. J., & Hömberg, V. (2003). Remote changes in cortical excitability after stroke. *Brain*, *126*(2), 470–481. https://doi.org/10.1093/brain/awg044

Cai, S., Tourville, J. A., Beal, D. S., Perkell, J. S., Guenther, F. H., & Ghosh, S. S. (2014). Diffusion imaging of cerebral white matter in persons who stutter: Evidence for network-level anomalies. *Frontiers in Human Neuroscience*, *8*, 54. https://doi.org/10.3389/fnhum.2014.00054

Carlsen, A. N. (2015). A broadband acoustic stimulus is more likely than a pure tone to elicit a startle reflex and prepared movements. *Physiological Reports*, *3*(8). https://doi.org/10.14814/phy2.12509

Carlsen, A. N., Almeida, Q. J., & Franks, I. M. (2013). Using a startling acoustic stimulus to investigate underlying mechanisms of bradykinesia in Parkinson's disease. *Neuropsychologia*, *51*(3), 392–399. https://doi.org/10.1016/j.neuropsychologia.2012.11.024

Carlsen, A. N., Chua, R., Dakin, C. J., Sanderson, D. J., Inglis, J. T., & Franks, I. M. (2008). Startle reveals an absence of advance motor programming in a Go/No-go task. *Neuroscience Letters*, *434*(1), 61–65. https://doi.org/10.1016/j.neulet.2008.01.029

Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J., & Franks, I. M. (2003). Startle response is dishabituated during a reaction time task. *Experimental Brain Research*, *152*(4), 510–518. https://doi.org/10.1007/s00221-003-1575-5

Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J., & Franks, I. M. (2004). Prepared movements are elicited early by startle. *Journal of Motor Behavior*, *36*(3), 253–264. https://doi.org/10.3200/JMBR.36.3.253-264

Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J., & Franks, I. M. (2009). Differential effects of startle on reaction time for finger and arm movements. *Journal of Neurophysiology*, *101*(1), 306–314. https://doi.org/10.1152/jn.00878.2007

Carlsen, A. N., Dakin, C. J., Chua, R., & Franks, I. M. (2007). Startle produces early response latencies that are distinct from stimulus intensity effects. *Experimental Brain Research*, *176*(2), 199–205. https://doi.org/10.1007/s00221-006-0610-8

Carlsen, A. N., & Maslovat, D. (2019). Startle and the StartReact Effect: Physiological Mechanisms. *Journal of Clinical Neurophysiology*, *36*(6), 452–459. https://doi.org/10.1097/WNP.0000000000000582

Carlsen, A. N., Maslovat, D., & Franks, I. M. (2012). Preparation for voluntary movement in healthy and clinical populations: Evidence from startle. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *123*(1), 21–33. https://doi.org/10.1016/j.clinph.2011.04.028

Carlsen, A. N., Maslovat, D., Lam, M. Y., Chua, R., & Franks, I. M. (2011). Considerations for the use of a startling acoustic stimulus in studies of motor preparation in humans. *Neuroscience and Biobehavioral Reviews*, *35*(3), 366–376. https://doi.org/10.1016/j.neubiorev.2010.04.009

Castellote, J. M., & Valls-Solé, J. (2015). The StartReact effect in tasks requiring end-point accuracy. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *126*(10), 1879–1885. https://doi.org/10.1016/j.clinph.2015.01.028

Cera, M. L., & Ortiz, K. Z. (2010). Phonological analysis of substitution errors of patients with apraxia of speech. *Dementia & Neuropsychologia*, *4*(1), 58–62. https://doi.org/10.1590/S1980-57642010DN40100010

Champely, S. (2020). *Stephane Champely (2020). Pwr: Basic Functions for Power Analysis.* (R package version 1.3-0). https://CRAN.R-project.org/package=pwr

Chang, S.-E. (2011). Using brain imaging to unravel the mysteries of stuttering. *Cerebrum: The Dana Forum on Brain Science*, *2011*, 12.

Chapey, R. (2012a). Primary Progressive Aphasia and Apraxia of Speech. In *Language intervention strategies in aphasia and related neurogenic communication disorders: Fifth edition* (pp. 550–555).

Chapey, R. (2012b). The Nature and Management of Neuromotor Speech Disorders Accompanying Aphasia. In *Language intervention strategies in aphasia and related neurogenic communication disorders: Fifth edition* (pp. 1009–1030).

Chen, Y.-T., Li, S., Zhou, P., & Li, S. (2019). A startling acoustic stimulation (SAS)-TMS approach to assess the reticulospinal system in healthy and stroke subjects. *Journal of the Neurological Sciences*, *399*, 82–88. https://doi.org/10.1016/j.jns.2019.02.018

Cheng, B. B. Y., Worrall, L. E., Copland, D. A., & Wallace, S. J. (2020). Prognostication in post-stroke aphasia: How do speech pathologists formulate and deliver information about recovery? *International Journal of Language & Communication Disorders*, *55*(4), 520–536. https://doi.org/10.1111/1460-6984.12534

Chiu, C. (2015). *Startling auditory stimulus as a window into speech motor planning*. https://doi.org/10.14288/1.0220650

Chiu, C., & Gick, B. (2014a). Startling speech: Eliciting prepared speech using startling auditory stimulus. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.01082

Chiu, C., & Gick, B. (2014b). Pitch planning in English and Taiwanese Mandarin: Evidence from startle-elicited responses. *The Journal of the Acoustical Society of America*, *136*(4), EL322-328. https://doi.org/10.1121/1.4896405

Choudhury, S., Shobhana, A., Singh, R., Sen, D., Anand, S. S., Shubham, S., Baker, M. R., Kumar, H., & Baker, S. N. (2019). The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients. *Neurorehabilitation and Neural Repair*, *33*(5), 375–383. https://doi.org/10.1177/1545968319836233

Civier, O., Bullock, D., Max, L., & Guenther, F. H. (2013). Computational modeling of stuttering caused by impairments in a basal ganglia thalamo-cortical circuit involved in syllable selection and initiation. *Brain and Language*, *126*(3), 263–278. https://doi.org/10.1016/j.bandl.2013.05.016

Conant, D., Bouchard, K. E., & Chang, E. F. (2014). Speech Map in the Human Ventral Sensory-Motor Cortex. *Current Opinion in Neurobiology*, *0*, 63–67. https://doi.org/10.1016/j.conb.2013.08.015

Coppens, M. J. M., Roelofs, J. M. B., Donkers, N. A. J., Nonnekes, J., Geurts, A. C. H., & Weerdesteyn, V. (2018). A startling acoustic stimulus facilitates voluntary lower extremity movements and automatic postural responses in people with chronic stroke. *Journal of Neurology*, *265*(7), 1625–1635. https://doi.org/10.1007/s00415-018-8889-5

Cordella, C., Quimby, M., Touroutoglou, A., Brickhouse, M., Dickerson, B. C., & Green, J. R. (2019). Quantification of motor speech impairment and its anatomic basis in primary progressive aphasia. *Neurology*, *92*(17), e1992–e2004. https://doi.org/10.1212/WNL.0000000000007367

Ćosić, K., Popović, S., Kukolja, D., Dropuljić, B., Ivanec, D., & Tonković, M. (2016). Multimodal analysis of startle type responses. *Computer Methods and Programs in Biomedicine*, *129*, 186–202. https://doi.org/10.1016/j.cmpb.2016.01.002

Dabul, B. & Pro-Ed (Firm). (2000). *ABA-2: Apraxia Battery for Adults*. Pro-Ed.

Darley, F. L. (1972). The efficacy of language rehabilitation in aphasia. *The Journal of Speech and Hearing Disorders*, *37*(1), 3–21. https://doi.org/10.1044/jshd.3701.03

Davis, M. (1984). The mammalian startle response. In *Neural stop of Startle Behavior* (R. Eaton (Ed.), pp. 287–351). Plenum Publishing Corporation.

Davis, M., & Gendelman, P. M. (1977). Plasticity of the acoustic startle response in the acutely decerebrate rat. *Journal of Comparative and Physiological Psychology*, *91*(3), 549–563. https://doi.org/10.1037/h0077345

Decavel, P., Vuillier, F., & Moulin, T. (2012). Lenticulostriate infarction. *Frontiers of Neurology and Neuroscience*, *30*, 115–119. https://doi.org/10.1159/000333606

Dekhtyar Maria, Braun Emily J., Billot Anne, Foo Lindsey, & Kiran Swathi. (2020). Videoconference Administration of the Western Aphasia Battery–Revised: Feasibility and Validity. *American Journal of Speech-Language Pathology*, *29*(2), 673–687. https://doi.org/10.1044/2019_AJSLP-19-00023

den Ouden, D.-B., Galkina, E., Basilakos, A., & Fridriksson, J. (2018). Vowel Formant Dispersion Reflects Severity of Apraxia of Speech. *Aphasiology*, *32*(8), 902–921. https://doi.org/10.1080/02687038.2017.1385050

Desmurget, null, & Grafton, null. (2000). Forward modeling allows feedback control for fast reaching movements. *Trends in Cognitive Sciences*, *4*(11), 423–431. https://doi.org/10.1016/s1364-6613(00)01537-0

Dichter, B. K., Breshears, J. D., Leonard, M. K., & Chang, E. F. (2018). The Control of Vocal Pitch in Human Laryngeal Motor Cortex. *Cell*, *174*(1), 21-31.e9. https://doi.org/10.1016/j.cell.2018.05.016

Dodd, K. C., Nair, V. A., & Prabhakaran, V. (2017). Role of the Contralesional vs. Ipsilesional Hemisphere in Stroke Recovery. *Frontiers in Human Neuroscience*, *11*. https://www.frontiersin.org/articles/10.3389/fnhum.2017.00469

Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature*, *384*(6605), 159–161. https://doi.org/10.1038/384159a0

Du, J., Hu, J., Hu, J., Xu, Q., Zhang, Q., Liu, L., Ma, M., Xu, G., Zhang, Y., Liu, X., Lu, G., Zhang, Z., & Yang, F. (2018). Aberrances of Cortex Excitability and Connectivity Underlying Motor Deficit in Acute Stroke. *Neural Plasticity*, *2018*, e1318093. https://doi.org/10.1155/2018/1318093

Duffy, J. R. (2006). Apraxia of speech in degenerative neurologic disease. *Aphasiology*, *20*(6), 511–527. https://doi.org/10.1080/02687030600597358

Ellis, C., Simpson, A. N., Bonilha, H., Mauldin, P. D., & Simpson, K. N. (2012). The one-year attributable cost of poststroke aphasia. *Stroke*, *43*(5), 1429–1431. https://doi.org/10.1161/STROKEAHA.111.647339

Enderby, P. (2013). Disorders of communication: Dysarthria. *Handbook of Clinical Neurology*, *110*, 273–281. https://doi.org/10.1016/B978-0-444-52901-5.00022-8

Engelter, S. T., Gostynski, M., Papa, S., Frei, M., Born, C., Ajdacic-Gross, V., Gutzwiller, F., & Lyrer, P. A. (2006). Epidemiology of aphasia attributable to first ischemic stroke: Incidence, severity, fluency, etiology, and thrombolysis. *Stroke*, *37*(6), 1379–1384. https://doi.org/10.1161/01.STR.0000221815.64093.8c

Faham, M., Laukkanen, A.-M., Ikävalko, T., Rantala, L., Geneid, A., Holmqvist-Jämsén, S., Ruusuvirta, K., & Pirilä, S. (2021). Acoustic Voice Quality Index as a Potential Tool for Voice Screening. *Journal of Voice*, *35*(2), 226–232. https://doi.org/10.1016/j.jvoice.2019.08.017

Favre, I., Zeffiro, T. A., Detante, O., Krainik, A., Hommel, M., & Jaillard, A. (2014). Upper Limb Recovery After Stroke Is Associated With Ipsilesional Primary Motor Cortical Activity. *Stroke*, *45*(4), 1077–1083. https://doi.org/10.1161/STROKEAHA.113.003168

Flowers, H. L., Silver, F. L., Fang, J., Rochon, E., & Martino, R. (2013). The incidence, co-occurrence, and predictors of dysphagia, dysarthria, and aphasia after first-ever acute ischemic stroke. *Journal of Communication Disorders*, *46*(3), 238–248. https://doi.org/10.1016/j.jcomdis.2013.04.001

Fridriksson, J., den Ouden, D.-B., Hillis, A. E., Hickok, G., Rorden, C., Basilakos, A., Yourganov, G., & Bonilha, L. (2018). Anatomy of aphasia revisited. *Brain*, *141*(3), 848–862. https://doi.org/10.1093/brain/awx363

Fridriksson, J., & Hillis, A. E. (2021). Current Approaches to the Treatment of Post-Stroke Aphasia. *Journal of Stroke*, *23*(2), 183–201. https://doi.org/10.5853/jos.2020.05015

Galletta, E. E., & Barrett, A. M. (2014). Impairment and Functional Interventions for Aphasia: Having it All. *Current Physical Medicine and Rehabilitation Reports*, *2*(2), 114–120. https://doi.org/10.1007/s40141-014-0050-5

Gilmore, N., Dwyer, M., & Kiran, S. (2018). Benchmarks of Significant Change After Aphasia Rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *100*. https://doi.org/10.1016/j.apmr.2018.08.177

95

Godecke, E., Armstrong, E., Rai, T., Ciccone, N., Rose, M. L., Middleton, S., Whitworth, A., Holland, A., Ellery, F., Hankey, G. J., Cadilhac, D. A., Bernhardt, J., & VERSE Collaborative Group. (2020). A randomized control trial of intensive aphasia therapy after acute stroke: The Very Early Rehabilitation for SpEech (VERSE) study. *International Journal of Stroke: Official Journal of the International Stroke Society*, 1747493020961926. https://doi.org/10.1177/1747493020961926

Goldberg Samantha, Haley Katarina L., & Jacks Adam. (2012). Script Training and Generalization for People With Aphasia. *American Journal of Speech-Language Pathology*, *21*(3), 222–238. https://doi.org/10.1044/1058-0360(2012/11-0056)

Graff-Radford, J., Jones, D. T., Strand, E. A., Rabinstein, A. A., Duffy, J. R., & Josephs, K. A. (2014). The neuroanatomy of pure apraxia of speech in stroke. *Brain and Language*, *129*, 43–46. https://doi.org/10.1016/j.bandl.2014.01.004

Gray, A. H., & Markel, J. D. (1978). Linear predictive coding and the Burg algorithm for speech analysis and synthesis. *The Journal of the Acoustical Society of America*, *64*(S1), S159–S159. https://doi.org/10.1121/1.2003944

Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural Modeling and Imaging of the Cortical Interactions Underlying Syllable Production. *Brain and Language*, *96*(3), 280–301. https://doi.org/10.1016/j.bandl.2005.06.001

Guenther, F. H., & Vladusich, T. (2012). A Neural Theory of Speech Acquisition and Production. *Journal of Neurolinguistics*, *25*(5), 408–422. https://doi.org/10.1016/j.jneuroling.2009.08.006

Hadanny, A., Rittblat, M., Bitterman, M., May-Raz, I., Suzin, G., Boussi-Gross, R., Zemel, Y., Bechor, Y., Catalogna, M., & Efrati, S. (2020). Hyperbaric oxygen therapy improves neurocognitive functions of post-stroke patients—A retrospective analysis. *Restorative Neurology and Neuroscience*, *38*(1), 93–107. https://doi.org/10.3233/RNN-190959

Haley, K. L., Ohde, R. N., & Wertz, R. T. (2000). Single word intelligibility in aphasia and apraxia of speech: A phonetic error analysis. *Aphasiology*, *14*(2), 179–201. https://doi.org/10.1080/026870300401540

Haley, K. L., & Overton, H. B. (2001). Word Length and Vowel Duration in Apraxia of Speech: The Use of Relative Measures. *Brain and Language*, *79*(3), 397–406. https://doi.org/10.1006/brln.2001.2494

Hansen, S. J., McMahon, K. L., & de Zubicaray, G. I. (2019). The neurobiology of taboo language processing: FMRI evidence during spoken word production. *Social Cognitive and Affective Neuroscience*, *14*(3), 271–279. https://doi.org/10.1093/scan/nsz009

Harrison, M., Palmer, R., & Cooper, C. (2020). Factors Associated With Adherence to Self-Managed Aphasia Therapy Practice on a Computer—A Mixed Methods Study Alongside a Randomized Controlled Trial. *Frontiers in Neurology*, *11*, 582328. https://doi.org/10.3389/fneur.2020.582328

Heilman, K. M. (2006). Aphasia and the Diagram Makers Revisited: An Update of Information Processing Models. *Journal of Clinical Neurology (Seoul, Korea)*, *2*(3), 149–162. https://doi.org/10.3988/jcn.2006.2.3.149

Herbert, W. J., Powell, K., & Buford, J. A. (2015). Evidence for a role of the reticulospinal system in recovery of skilled reaching after cortical stroke: Initial results from a model of ischemic cortical injury. *Experimental Brain Research*, *233*(11), 3231–3251. https://doi.org/10.1007/s00221-015-4390-x

Hickok, G. (2012). The cortical organization of speech processing: Feedback control and predictive coding the context of a dual-stream model. *Journal of Communication Disorders*, *45*(6), 393–402. https://doi.org/10.1016/j.jcomdis.2012.06.004

Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition*, *92*(1–2), 67–99. https://doi.org/10.1016/j.cognition.2003.10.011

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, *8*(5), 393–402. https://doi.org/10.1038/nrn2113

Hickok, G., Rogalsky, C., Chen, R., Herskovits, E. H., Townsley, S., & Hillis, A. E. (2014). Partially overlapping sensorimotor networks underlie speech praxis and verbal short-term memory: Evidence from apraxia of speech following acute stroke. *Frontiers in Human Neuroscience*, *8*, 649. https://doi.org/10.3389/fnhum.2014.00649

Hill, A. J., Theodoros, D., Russell, T., & Ward, E. (2009). Using telerehabilitation to assess apraxia of speech in adults. *International Journal of Language & Communication Disorders*, *44*(5), 731–747. https://doi.org/10.1080/13682820802350537

Holland, A., Fromm, D., Forbes, M., & MacWhinney, B. (2017). Long-term Recovery in Stroke Accompanied by Aphasia: A Reconsideration. *Aphasiology*, *31*(2), 152–165. https://doi.org/10.1080/02687038.2016.1184221

Holland, R., Johns, S. L., & Woollams, A. M. (2018). The impact of phonological versus semantic repetition training on generalisation in chronic stroke aphasia reflects differences in dorsal pathway connectivity. *Neuropsychological Rehabilitation*, *28*(4), 548–567. https://doi.org/10.1080/09602011.2016.1190384

Honeycutt, C. F., Kharouta, M., & Perreault, E. J. (2013). Evidence for reticulospinal contributions to coordinated finger movements in humans. *Journal of Neurophysiology*, *110*(7), 1476–1483. https://doi.org/10.1152/jn.00866.2012

Honeycutt, C. F., & Perreault, E. J. (2012). Planning of ballistic movement following stroke: Insights from the startle reflex. *PloS One*, *7*(8), e43097. https://doi.org/10.1371/journal.pone.0043097

Honeycutt, C. F., & Perreault, E. J. (2014). Deficits in startle-evoked arm movements increase with impairment following stroke. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *125*(8), 1682–1688. https://doi.org/10.1016/j.clinph.2013.12.102

Honeycutt, C. F., Tresch, U. A., & Perreault, E. J. (2015). Startling acoustic stimuli can evoke fast hand extension movements in stroke survivors. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *126*(1), 160–164. https://doi.org/10.1016/j.clinph.2014.05.025

Hope, T. M. H., Leff, A. P., Prejawa, S., Bruce, R., Haigh, Z., Lim, L., Ramsden, S., Oberhuber, M., Ludersdorfer, P., Crinion, J., Seghier, M. L., & Price, C. J. (2017). Right hemisphere structural adaptation and changing language skills years after left hemisphere stroke. *Brain: A Journal of Neurology*, *140*(6), 1718–1728. https://doi.org/10.1093/brain/awx086

Hough, M. S., & Klich, R. J. (1998). Lip EMG activity during vowel production in apraxia of speech: Phrase context and word length effects. *Journal of Speech, Language, and Hearing Research: JSLHR*, *41*(4), 786–801. https://doi.org/10.1044/jslhr.4104.786

Hula, W., Donovan, N. J., Kendall, D. L., & Gonzalez-Rothi, L. J. (2010). Item response theory analysis of the Western Aphasia Battery. *Aphasiology*, *24*(11), 1326–1341. https://doi.org/10.1080/02687030903422502

Hybbinette, H., Schalling, E., Plantin, J., Nygren-Deboussard, C., Schütz, M., Östberg, P., & Lindberg, P. G. (2021). Recovery of Apraxia of Speech and Aphasia in Patients With Hand Motor Impairment After Stroke. *Frontiers in Neurology*, *12*. https://www.frontiersin.org/articles/10.3389/fneur.2021.634065

Iyer, K. K., Angwin, A. J., Van Hees, S., McMahon, K. L., Breakspear, M., & Copland, D. A. (2020). Alterations to dual stream connectivity predicts response to aphasia therapy following stroke. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *125*, 30–43. https://doi.org/10.1016/j.cortex.2019.12.017

Jacks, A. (2008). Bite block vowel production in apraxia of speech. *Journal of Speech, Language, and Hearing Research: JSLHR*, *51*(4), 898–913. https://doi.org/10.1044/1092-4388(2008/066)

Jacks, A., & Haley, K. L. (2015). Auditory Masking Effects on Speech Fluency in Apraxia of Speech and Aphasia: Comparison to Altered Auditory Feedback. *Journal of Speech, Language, and Hearing Research: JSLHR*, *58*(6), 1670–1686. https://doi.org/10.1044/2015_JSLHR-S-14-0277

Johnson, L., Basilakos, A., Yourganov, G., Cai, B., Bonilha, L., Rorden, C., & Fridriksson, J. (2019). Progression of Aphasia Severity in the Chronic Stages of Stroke. *American Journal of Speech-Language Pathology*, *28*(2), 639–649. https://doi.org/10.1044/2018_AJSLP-18-0123

Jordan, L. C., & Hillis, A. E. (2006). Disorders of speech and language: Aphasia, apraxia and dysarthria. *Current Opinion in Neurology*, *19*(6), 580–585. https://doi.org/10.1097/WCO.0b013e3280109260

Jürgens, U. (2002a). Neural pathways underlying vocal control. *Neuroscience and Biobehavioral Reviews*, *26*(2), 235–258. https://doi.org/10.1016/s0149-7634(01)00068-9

Jürgens, U. (2002b). A study of the central control of vocalization using the squirrel monkey. *Medical Engineering & Physics*, *24*(7), 473–477. https://doi.org/10.1016/S1350-4533(02)00051-6

Jürgens, U. (2009). The neural control of vocalization in mammals: A review. *Journal of Voice: Official Journal of the Voice Foundation*, *23*(1), 1–10. https://doi.org/10.1016/j.jvoice.2007.07.005

Kalinowski, J., Armson, J., Stuart, A., & Gracco, V. L. (1993). Effects of Alterations in Auditory Feedback and Speech Rate on Stuttering Frequency. *Language and Speech*, *36*(1), 1–16. https://doi.org/10.1177/002383099303600101

Karbasforoushan, H., Cohen-Adad, J., & Dewald, J. P. A. (2019). Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. *Nature Communications*, *10*(1), 1–7. https://doi.org/10.1038/s41467-019-11244-3

Katz, R. C., & Wertz, R. T. (1997). The efficacy of computer-provided reading treatment for chronic aphasic adults. *Journal of Speech, Language, and Hearing Research: JSLHR*, *40*(3), 493–507. https://doi.org/10.1044/jslhr.4003.493

Kaye, R. C., & Cherney, L. R. (2016). Script Templates: A Practical Approach to Script Training in Aphasia. *Topics in Language Disorders*, *36*(2), 136–153. https://doi.org/10.1097/TLD.0000000000000086

Kirkpatrick, N. J., Ravichandran, V. J., Perreault, E. J., Schaefer, S. Y., & Honeycutt, C. F. (2018). Evidence for startle as a measurable behavioral indicator of motor learning. *PloS One*, *13*(5), e0195689. https://doi.org/10.1371/journal.pone.0195689

Kristinsson, S., Basilakos, A., Elm, J., Spell, L. A., Bonilha, L., Rorden, C., den Ouden, D. B., Cassarly, C., Sen, S., Hillis, A., Hickok, G., & Fridriksson, J. (2021). Individualized response to semantic versus phonological aphasia therapies in stroke. *Brain Communications*, *3*(3), fcab174. https://doi.org/10.1093/braincomms/fcab174

Kühn, A. A., Sharott, A., Trottenberg, T., Kupsch, A., & Brown, P. (2004). Motor cortex inhibition induced by acoustic stimulation. *Experimental Brain Research*, *158*(1), 120–124. https://doi.org/10.1007/s00221-004-1883-4

Kurland, J., Liu, A., & Stokes, P. (2018). Effects of a Tablet-Based Home Practice Program With Telepractice on Treatment Outcomes in Chronic Aphasia. *Journal of Speech, Language, and Hearing Research: JSLHR*, *61*(5), 1140–1156. https://doi.org/10.1044/2018_JSLHR-L-17-0277

Kurland, J., Pulvermüller, F., Silva, N., Burke, K., & Andrianopoulos, M. (2012). Constrained versus unconstrained intensive language therapy in two individuals with chronic, moderate-to-severe aphasia and apraxia of speech: Behavioral and fMRI outcomes. *American Journal of Speech-Language Pathology*, *21*(2), S65-87. https://doi.org/10.1044/1058-0360(2012/11-0113)

La Pointe, L. L., & Johns, D. F. (1975). Some phonemic characteristics in apraxia of speech. *Journal of Communication Disorders*, *8*(3), 259–269. https://doi.org/10.1016/0021-9924(75)90018-0

Lam, J. M. C., & Wodchis, W. P. (2010). The Relationship of 60 Disease Diagnoses and 15 Conditions to Preference-Based Health-Related Quality of Life in Ontario Hospital-Based Long-Term Care Residents. *Medical Care*, *48*(4), 380–387. https://doi.org/10.1097/MLR.0b013e3181ca2647

Landis, T. (2006). Emotional words: What's so different from just words? *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *42*(6), 823–830. https://doi.org/10.1016/s0010-9452(08)70424-6

Lane, H., Matthies, M. L., Guenther, F. H., Denny, M., Perkell, J. S., Stockmann, E., Tiede, M., Vick, J., & Zandipour, M. (2007). Effects of short- and long-term changes in auditory feedback on vowel and sibilant contrasts. *Journal of Speech, Language, and Hearing Research: JSLHR*, *50*(4), 913–927. https://doi.org/10.1044/1092-4388(2007/065)

Lee, H., Honeycutt, C., & Perreault, E. (2022). Influence of task complexity on movement planning and release after stroke: Insights from startReact. *Experimental Brain Research*. https://doi.org/10.1007/s00221-022-06368-w

Leote, J., Castellote, J. M., Casanova-Molla, J., Navarro-Otano, J., Nunes, R. G., Ferreira, H. A., & Valls-Sole, J. (2018). Motor preparation in picture naming tasks. *Brain and Language*, *180–182*, 24–30. https://doi.org/10.1016/j.bandl.2018.04.002

Li, S., & Francisco, G. E. (2015). New insights into the pathophysiology of post-stroke spasticity. *Frontiers in Human Neuroscience*, *9*, 192. https://doi.org/10.3389/fnhum.2015.00192

Lin, K., Fu, T., Wu, C.-Y., Wang, Y., Liu, J., Hsieh, C., & Lin, S. (2010). Minimal Detectable Change and Clinically Important Difference of the Stroke Impact Scale in Stroke Patients. *Neurorehabilitation and Neural Repair*, *24*, 486–492. https://doi.org/10.1177/1545968309356295

Long, A., Hesketh, A., Paszek, G., Booth, M., & Bowen, A. (2008). Development of a reliable self-report outcome measure for pragmatic trials of communication therapy following stroke: The Communication Outcome after Stroke (COAST) scale. *Clinical Rehabilitation*, *22*(12), 1083–1094. https://doi.org/10.1177/0269215508090091

Loucks, T. M. J., Poletto, C. J., Simonyan, K., Reynolds, C. L., & Ludlow, C. L. (2007). Human Brain Activation during Phonation and Exhalation: Common Volitional Control for Two Upper Airway Functions. *NeuroImage*, *36*(1), 131–143. https://doi.org/10.1016/j.neuroimage.2007.01.049

Lugtmeijer, S., Lammers, N. A., de Haan, E. H. F., de Leeuw, F.-E., & Kessels, R. P. C. (2021). Post-Stroke Working Memory Dysfunction: A Meta-Analysis and Systematic Review. *Neuropsychology Review*, *31*(1), 202–219. https://doi.org/10.1007/s11065-020-09462-4

Luo, J., Hage, S. R., & Moss, C. F. (2018). The Lombard Effect: From Acoustics to Neural Mechanisms. *Trends in Neurosciences*, *41*(12), 938–949. https://doi.org/10.1016/j.tins.2018.07.011

Maas, E., Mailend, M.-L., & Guenther, F. H. (2015). Feedforward and Feedback Control in Apraxia of Speech: Effects of Noise Masking on Vowel Production. *Journal of Speech, Language, and Hearing Research : JSLHR*, *58*(2), 185–200. https://doi.org/10.1044/2014_JSLHR-S-13-0300

Marangolo, P., Fiori, V., Cipollari, S., Campana, S., Razzano, C., Di Paola, M., Koch, G., & Caltagirone, C. (2013). Bihemispheric stimulation over left and right inferior frontal region enhances recovery from apraxia of speech in chronic aphasia. *The European Journal of Neuroscience*, *38*(9), 3370–3377. https://doi.org/10.1111/ejn.12332

Marangolo, P., Marinelli, C. V., Bonifazi, S., Fiori, V., Ceravolo, M. G., Provinciali, L., & Tomaiuolo, F. (2011). Electrical stimulation over the left inferior frontal gyrus (IFG) determines long-term effects in the recovery of speech apraxia in three chronic aphasics. *Behavioural Brain Research*, *225*(2), 498–504. https://doi.org/10.1016/j.bbr.2011.08.008

Marinovic, W., de Rugy, A., Riek, S., & Tresilian, J. R. (2014). The early release of actions by loud sounds in muscles with distinct connectivity. *Experimental Brain Research*, *232*(12), 3797–3802. https://doi.org/10.1007/s00221-014-4074-y

Marinovic, W., & Tresilian, J. R. (2016). Triggering prepared actions by sudden sounds: Reassessing the evidence for a single mechanism. *Acta Physiologica (Oxford, England)*, *217*(1), 13–32. https://doi.org/10.1111/apha.12627

Martin, N., Thompson, C. K., & Worrall, L. (2007). *Aphasia Rehabilitation: The Impairment and Its Consequences*. Plural Publishing.

Martin, R. C., & Schnur, T. T. (2019). Independent contributions of semantic and phonological working memory to spontaneous speech in acute stroke. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *112*, 58–68. https://doi.org/10.1016/j.cortex.2018.11.017

Maryn, Y., De Bodt, M., & Roy, N. (2010). The Acoustic Voice Quality Index: Toward improved treatment outcomes assessment in voice disorders. *Journal of Communication Disorders*, *43*(3), 161–174. https://doi.org/10.1016/j.jcomdis.2009.12.004

Maryn, Y., & Weenink, D. (2015). Objective Dysphonia Measures in the Program Praat: Smoothed Cepstral Peak Prominence and Acoustic Voice Quality Index. *Journal of Voice*, *29*(1), 35–43. https://doi.org/10.1016/j.jvoice.2014.06.015

Mauszycki, S., & Wambaugh, J. (2011). Acquired Apraxia of Speech: A Treatment Overview. *ASHA Leader*, *16*, 16. https://doi.org/10.1044/leader.FTR2.16052011.16

McPherson, J. G., Chen, A., Ellis, M. D., Yao, J., Heckman, C. J., & Dewald, J. P. A. (2018). Progressive recruitment of contralesional cortico-reticulospinal pathways drives motor impairment post stroke. *The Journal of Physiology*, *596*(7), 1211–1225. https://doi.org/10.1113/JP274968

Meinzer, M., Djundja, D., Barthel, G., Elbert, T., & Rockstroh, B. (2005). Long-Term Stability of Improved Language Functions in Chronic Aphasia After Constraint-Induced Aphasia Therapy. *Stroke*, *36*(7), 1462–1466. https://doi.org/10.1161/01.STR.0000169941.29831.2a

Mena-Segovia, J., & Bolam, J. P. (2017). Rethinking the Pedunculopontine Nucleus: From Cellular Organization to Function. *Neuron*, *94*(1), 7–18. https://doi.org/10.1016/j.neuron.2017.02.027

Miller, H. E., & Guenther, F. H. (2021). Modelling speech motor programming and apraxia of speech in the DIVA/GODIVA neurocomputational framework. *Aphasiology*, *35*(4), 424–441. https://doi.org/10.1080/02687038.2020.1765307

Miller, M. W., & Gronfier, C. (2006). Diurnal variation of the startle reflex in relation to HPA-axis activity in humans. *Psychophysiology*, *43*(3), 297–301. https://doi.org/10.1111/j.1469-8986.2006.00400.x

Mitchell, C., Gittins, M., Tyson, S., Vail, A., Conroy, P., Paley, L., & Bowen, A. (2021). Prevalence of aphasia and dysarthria among inpatient stroke survivors: Describing the population, therapy provision and outcomes on discharge. *Aphasiology*, *35*(7), 950–960. https://doi.org/10.1080/02687038.2020.1759772

Mohr, B., Difrancesco, S., Harrington, K., Evans, S., & Pulvermüller, F. (2014). Changes of right-hemispheric activation after constraint-induced, intensive language action therapy in chronic aphasia: FMRI evidence from auditory semantic processing. *Frontiers in Human Neuroscience*, *8*, 919. https://doi.org/10.3389/fnhum.2014.00919

Moser, D., Basilakos, A., Fillmore, P., & Fridriksson, J. (2016). Brain damage associated with apraxia of speech: Evidence from case studies. *Neurocase*, *22*(4), 346–356. https://doi.org/10.1080/13554794.2016.1172645

Mu, L., & Sanders, I. (2007). Neuromuscular specializations within human pharyngeal constrictor muscles. *The Annals of Otology, Rhinology, and Laryngology*, *116*(8), 604–617. https://doi.org/10.1177/000348940711600809

Nasios, G., Dardiotis, E., & Messinis, L. (2019). From Broca and Wernicke to the Neuromodulation Era: Insights of Brain Language Networks for Neurorehabilitation. *Behavioural Neurology*, *2019*, e9894571. https://doi.org/10.1155/2019/9894571

Navarro-Orozco, D., & Sánchez-Manso, J. C. (2021). Neuroanatomy, Middle Cerebral Artery. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK526002/

New, A. B., Robin, D. A., Parkinson, A. L., Duffy, J. R., McNeil, M. R., Piguet, O., Hornberger, M., Price, C. J., Eickhoff, S. B., & Ballard, K. J. (2015). Altered resting-state network connectivity in stroke patients with and without apraxia of speech. *NeuroImage. Clinical*, *8*, 429–439. https://doi.org/10.1016/j.nicl.2015.03.013

Nijhuis, L. B. O., Janssen, L., Bloem, B. R., van Dijk, J. G., Gielen, S. C., Borm, G. F., & Overeem, S. (2007). Choice reaction times for human head rotations are shortened by startling acoustic stimuli, irrespective of stimulus direction. *The Journal of Physiology*, *584*(Pt 1), 97–109. https://doi.org/10.1113/jphysiol.2007.136291

Nonnekes, J., Geurts, A. C. H., Nijhuis, L. B. O., van Geel, K., Snijders, A. H., Bloem, B. R., & Weerdesteyn, V. (2014). Reduced StartReact effect and freezing of gait in Parkinson's disease: Two of a kind? *Journal of Neurology*, *261*(5), 943–950. https://doi.org/10.1007/s00415-014-7304-0

Nonnekes, J., Oude Nijhuis, L. B., de Niet, M., de Bot, S. T., Pasman, J. W., van de Warrenburg, B. P. C., Bloem, B. R., Weerdesteyn, V., & Geurts, A. C. (2014). StartReact restores reaction time in HSP: Evidence for subcortical release of a motor program. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(1), 275–281. https://doi.org/10.1523/JNEUROSCI.2948-13.2014

Nouwens, F., de Lau, L. M., Visch-Brink, E. G., van de Sandt-Koenderman, W. (Mieke), Lingsma, H. F., Goosen, S., Blom, D. M., Koudstaal, P. J., & Dippel, D. W. (2017). Efficacy of early cognitive-linguistic treatment for aphasia due to stroke: A randomised controlled trial (Rotterdam Aphasia Therapy Study-3). *European Stroke Journal*, *2*(2), 126–136. https://doi.org/10.1177/2396987317698327

Odell, K., McNeil, M. R., Rosenbek, J. C., & Hunter, L. (1991). Perceptual characteristics of vowel and prosody production in apraxic, aphasic, and dysarthric speakers. *Journal of Speech and Hearing Research*, *34*(1), 67–80. https://doi.org/10.1044/jshr.3401.67

Ossanna, M. R., Zong, X., Ravichandran, V. J., & Honeycutt, C. F. (2019). Startle evokes nearly identical movements in multi-jointed, two-dimensional reaching tasks. *Experimental Brain Research*, *237*(1), 71–80. https://doi.org/10.1007/s00221-018-5399-8

Palmer, R., Hughes, H., & Chater, T. (2017). What do people with aphasia want to be able to say? A content analysis of words identified as personally relevant by people with aphasia. *PLoS ONE*, *12*(3). https://doi.org/10.1371/journal.pone.0174065

Peach, R. K., Beck, K. M., Gorman, M., & Fisher, C. (2019). Clinical Outcomes Following Language-Specific Attention Treatment Versus Direct Attention Training for Aphasia: A Comparative Effectiveness Study. *Journal of Speech, Language, and Hearing Research: JSLHR*, *62*(8), 2785–2811. https://doi.org/10.1044/2019_JSLHR-L-18-0504

Peach, R. K., Nathan, M. R., & Beck, K. M. (2017). Language-Specific Attention Treatment for Aphasia: Description and Preliminary Findings. *Seminars in Speech and Language*, *38*(1), 5–16. https://doi.org/10.1055/s-0036-1597260

Pedersen, P. M., Vinter, K., & Olsen, T. S. (2004). Aphasia after stroke: Type, severity and prognosis. The Copenhagen aphasia study. *Cerebrovascular Diseases (Basel, Switzerland)*, *17*(1), 35–43. https://doi.org/10.1159/000073896

Piai, V., Roelofs, A., Acheson, D. J., & Takashima, A. (2013). Attention for speaking: Domain-general control from the anterior cingulate cortex in spoken word production. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00832

Pineiro, R., Pendlebury, S., Johansen-Berg, H., & Matthews, P. M. (2001). Functional MRI Detects Posterior Shifts in Primary Sensorimotor Cortex Activation After Stroke. *Stroke*, *32*(5), 1134–1139. https://doi.org/10.1161/01.STR.32.5.1134

Plowman, E., Hentz, B., & Ellis, C. (2012). Post-stroke aphasia prognosis: A review of patient-related and stroke-related factors. *Journal of Evaluation in Clinical Practice*, *18*(3), 689–694. https://doi.org/10.1111/j.1365-2753.2011.01650.x

Polanowska, K. E., Leśniak, M. M., Seniów, J. B., Czepiel, W., & Członkowska, A. (2013). Anodal transcranial direct current stimulation in early rehabilitation of patients with post-stroke non-fluent aphasia: A randomized, double-blind, sham-controlled pilot study. *Restorative Neurology and Neuroscience*, *31*(6), 761–771. https://doi.org/10.3233/RNN-130333

Prashantha, D. K., Sriranjini, S. J., Sathyaprabha, T. N., Nagaraja, D., & Pal, P. Kr. (2013). Evaluation of the motor cortical excitability changes after ischemic stroke. *Annals of Indian Academy of Neurology*, *16*(3), 394–397. https://doi.org/10.4103/0972-2327.116955

Pulvermüller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *NeuroImage*, *28*(2), 481–489. https://doi.org/10.1016/j.neuroimage.2005.06.038

Pulvermüller, F., Neininger, B., Elbert, T., Mohr, B., Rockstroh, B., Koebbel, P., & Taub, E. (2001). Constraint-induced therapy of chronic aphasia after stroke. *Stroke*, *32*(7), 1621–1626. https://doi.org/10.1161/01.str.32.7.1621

R Core Team. (2022). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Rahimi, M., & Honeycutt, C. F. (2020). StartReact increases the probability of muscle activity and distance in severe/moderate stroke survivors during two-dimensional reaching task. *Experimental Brain Research*. https://doi.org/10.1007/s00221-020-05797-9

Rahimi, M., Swann, Z., & Honeycutt, C. F. (2021). Does exposure to startle impact voluntary reaching movements in individuals with severe-to-moderate stroke? *Experimental Brain Research*, *239*(3), 745–753. https://doi.org/10.1007/s00221-020-06005-4

Rangarajan, V., Schreiber, J. J., Barragan, B., Schaefer, S. Y., & Honeycutt, C. F. (2022). Delays in the Reticulospinal System Are Associated With a Reduced Capacity to Learn a Simulated Feeding Task in Older Adults. *Frontiers in Neural Circuits*, *15*. https://www.frontiersin.org/articles/10.3389/fncir.2021.681706

Reynolds, V., Buckland, A., Bailey, J., Lipscombe, J., Nathan, E., Vijayasekaran, S., Kelly, R., Maryn, Y., & French, N. (2012). Objective assessment of pediatric voice disorders with the acoustic voice quality index. *Journal of Voice: Official Journal of the Voice Foundation*, *26*(5), 672.e1-7. https://doi.org/10.1016/j.jvoice.2012.02.002

Rogers, C. L., & Dalby, J. (2005). Forced-Choice Analysis of Segmental Production by Chinese-Accented English Speakers. *Journal of Speech, Language & Hearing Research*, *48*(2), 306–322. https://doi.org/10.1044/1092-4388(2005/021)

Rose, M. L., Raymer, A. M., Lanyon, L. E., & Attard, M. C. (2013). A systematic review of gesture treatments for post-stroke aphasia. In *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*. Centre for Reviews and Dissemination (UK). https://www.ncbi.nlm.nih.gov/books/NBK169255/

Rosenbek, J., Lemme, M., Ahern, M., Harris, E., & Wertz, R. (1973). A Treatment for Apraxia of Speech in Adults. *The Journal of Speech and Hearing Disorders*, *38*, 462–472. https://doi.org/10.1044/jshd.3804.462

Salmelin, R., Schnitzler, A., Schmitz, F., & Freund, H. J. (2000). Single word reading in developmental stutterers and fluent speakers. *Brain: A Journal of Neurology*, *123 (Pt 6)*, 1184–1202. https://doi.org/10.1093/brain/123.6.1184

Sapir, S., McClean, M. D., & Larson, C. R. (1998). Human laryngeal responses to auditory stimulation. *The Journal of the Acoustical Society of America*, *73*(1), 315. https://doi.org/10.1121/1.388812

Sarno Martha Taylor, Silverman Marla, & Sands Elaine. (1970). Speech Therapy and Language Recovery in Severe Aphasia. *Journal of Speech and Hearing Research*, *13*(3), 607–623. https://doi.org/10.1044/jshr.1303.607

Schindel, D., Mandl, L., Schilling, R., Meisel, A., & Schenk, L. (2022). Guideline adherence in speech and language therapy in stroke aftercare. A health insurance claims data analysis. *PLoS ONE*, *17*(2), e0263397. https://doi.org/10.1371/journal.pone.0263397

Schuchard, J., & Middleton, E. L. (2018). Word Repetition and Retrieval Practice Effects in Aphasia: Evidence for Use-dependent Learning in Lexical Access. *Cognitive Neuropsychology*, *35*(5–6), 271–287. https://doi.org/10.1080/02643294.2018.1461615

Schwartz, M. F., Faseyitan, O., Kim, J., & Coslett, H. B. (2012). The dorsal stream contribution to phonological retrieval in object naming. *Brain*, *135*(12), 3799–3814. https://doi.org/10.1093/brain/aws300

Seidler, R. D., Noll, D. C., & Thiers, G. (2004). Feedforward and feedback processes in motor control. *NeuroImage*, *22*(4), 1775–1783. https://doi.org/10.1016/j.neuroimage.2004.05.003

Shewan, C. M., & Kertesz, A. (1980). Reliability and Validity Characteristics of the Western Aphasia Battery (WAB). *Journal of Speech and Hearing Disorders*, *45*(3), 308–324. https://doi.org/10.1044/jshd.4503.308

Simmons-Mackie, N., Savage, M. C., & Worrall, L. (2014). Conversation therapy for aphasia: A qualitative review of the literature. *International Journal of Language & Communication Disorders*, *49*(5), 511–526. https://doi.org/10.1111/1460-6984.12097

Simonyan, K., & Horwitz, B. (2011). Laryngeal Motor Cortex and Control of Speech in Humans. *The Neuroscientist*, *17*(2), 197–208. https://doi.org/10.1177/1073858410386727

Simonyan, K., & Jürgens, U. (2002). Cortico-cortical projections of the motorcortical larynx area in the rhesus monkey. *Brain Research*, *949*(1–2), 23–31. https://doi.org/10.1016/s0006-8993(02)02960-8

Smith, V., Maslovat, D., & Carlsen, A. N. (2019). StartReact effects are dependent on engagement of startle reflex circuits: Support for a subcortically mediated initiation pathway. *Journal of Neurophysiology*, *122*(6), 2541–2547. https://doi.org/10.1152/jn.00505.2019

Stark, B. C., Basilakos, A., Hickok, G., Rorden, C., Bonilha, L., & Fridriksson, J. (2019). Neural organization of speech production: A lesion-based study of error patterns in connected speech. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *117*, 228–246. https://doi.org/10.1016/j.cortex.2019.02.029

Stevenson, A. J. T., Chiu, C., Maslovat, D., Chua, R., Gick, B., Blouin, J.-S., & Franks, I. M. (2014). Cortical involvement in the StartReact effect. *Neuroscience*, *269*, 21–34. https://doi.org/10.1016/j.neuroscience.2014.03.041

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain*, *130*(1), 170–180. https://doi.org/10.1093/brain/awl333

Swann, Z., Daliri, A., & Honeycutt, C. F. (2022). Impact of Startling Acoustic Stimuli on Word Repetition in Individuals With Aphasia and Apraxia of Speech Following Stroke. *Journal of Speech, Language, and Hearing Research : JSLHR*, *65*(5), 1671–1685. https://doi.org/10.1044/2022_JSLHR-21-00486

Szaflarski, J. P., Ball, A. L., Vannest, J., Dietz, A. R., Allendorfer, J. B., Martin, A. N., Hart, K., & Lindsell, C. J. (2015). Constraint-Induced Aphasia Therapy for Treatment of Chronic Post-Stroke Aphasia: A Randomized, Blinded, Controlled Pilot Trial. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *21*, 2861–2869. https://doi.org/10.12659/MSM.894291

ten Oever, S., & Martin, A. E. (2021). An oscillating computational model can track pseudo-rhythmic speech by using linguistic predictions. *ELife*, *10*, e68066. https://doi.org/10.7554/eLife.68066

Terband, H., Rodd, J., & Maas, E. (2020). Testing hypotheses about the underlying deficit of apraxia of speech through computational neural modelling with the DIVA model. *International Journal of Speech-Language Pathology*, *22*(4), 475–486. https://doi.org/10.1080/17549507.2019.1669711

Thevathasan, W., Pogosyan, A., Hyam, J. A., Jenkinson, N., Bogdanovic, M., Coyne, T. J., Silburn, P. A., Aziz, T. Z., & Brown, P. (2011). A block to pre-prepared movement in gait freezing, relieved by pedunculopontine nucleus stimulation. *Brain*, *134*(7), 2085. https://doi.org/10.1093/brain/awr131

Toth, E., Gersner, R., Wilf-Yarkoni, A., Raizel, H., Dar, D. E., Richter-Levin, G., Levit, O., & Zangen, A. (2008). Age-dependent effects of chronic stress on brain plasticity and depressive behavior. *Journal of Neurochemistry*, *107*(2), 522–532. https://doi.org/10.1111/j.1471-4159.2008.05642.x

Tourville, J. A., & Guenther, F. H. (2011). The DIVA model: A neural theory of speech acquisition and production. *Language and Cognitive Processes*, *26*(7), 952–981. https://doi.org/10.1080/01690960903498424

Tresch, U. A., Perreault, E. J., & Honeycutt, C. F. (2014). Startle evoked movement is delayed in older adults: Implications for brainstem processing in the elderly. *Physiological Reports*, *2*(6). https://doi.org/10.14814/phy2.12025

Valls-Solé, J., Rothwell, J. C., Goulart, F., Cossu, G., & Muñoz, E. (1999). Patterned ballistic movements triggered by a startle in healthy humans. *The Journal of Physiology*, *516*(Pt 3), 931–938. https://doi.org/10.1111/j.1469-7793.1999.0931u.x

Van Lancker, D., & Cummings, J. L. (1999). Expletives: Neurolinguistic and neurobehavioral perspectives on swearing. *Brain Research Reviews*, *31*(1), 83–104. https://doi.org/10.1016/S0165-0173(99)00060-0

van Lith, B. J. H., Coppens, M. J. M., Nonnekes, J., van de Warrenburg, B. P. C., Geurts, A. C., & Weerdesteyn, V. (2018). StartReact during gait initiation reveals differential control of muscle activation and inhibition in patients with corticospinal degeneration. *Journal of Neurology*, *265*(11), 2531–2539. https://doi.org/10.1007/s00415-018-9027-0

Varley, R., Cowell, P. E., Dyson, L., Inglis, L., Roper, A., & Whiteside, S. P. (2016). Self-Administered Computer Therapy for Apraxia of Speech. *Stroke*, *47*(3), 822–828. https://doi.org/10.1161/STROKEAHA.115.011939

Wambaugh, J. (2010). Sound Production Treatment for Acquired Apraxia of Speech. *Perspectives on Neurophysiology and Neurogenic Speech and Language Disorders*, *20*(3), 67–72. https://doi.org/10.1044/nnsld20.3.67

Wambaugh, J. L., Duffy, J. R., McNeil, M. R., Robin, D. A., & Rogers, M. A. (2006). Treatment guidelines for acquired apraxia of speech: A synthesis and evaluation of the evidence. *Journal of Medical Speech - Language Pathology*, *14*(2), xv–xv. https://go.gale.com/ps/i.do?p=AONE&sw=w&issn=10651438&v=2.1&it=r&id=GALE%7CA147007295&sid=googleScholar&linkaccess=abs

Watkins, K. E., Smith, S. M., Davis, S., & Howell, P. (2008). Structural and functional abnormalities of the motor system in developmental stuttering. *Brain : A Journal of Neurology*, *131*(Pt 1), 50–59. https://doi.org/10.1093/brain/awm241

Whitwell, J. L., Duffy, J. R., Strand, E., Machulda, M. M., Senjem, M. L., Gunter, J. L., Kantarci, K., Eggers, S. D., Jack, C. R., & Josephs, K. A. (2013). Neuroimaging comparison of Primary Progressive Apraxia of Speech & Progressive Supranuclear Palsy. *European Journal of Neurology : The Official Journal of the European Federation of Neurological Societies*, *20*(4), 629–637. https://doi.org/10.1111/ene.12004

Willemse, N., Viljoen, M., & Govender, C. (2006). Neurological aspects of stuttering: Summary overview of scientific findings. *Health SA Gesondheid*, *11*(1), Article 1. https://doi.org/10.4102/hsag.v11i1.215

Wilson, K., Bell, C., Wilson, L., & Witteman, H. (2018). Agile research to complement agile development: A proposal for an mHealth research lifecycle. *Npj Digital Medicine*, *1*(1), 1–6. https://doi.org/10.1038/s41746-018-0053-1

Wilson, S. M., & Schneck, S. M. (2020). Neuroplasticity in Post-Stroke Aphasia: A Systematic Review and Meta-Analysis of Functional Imaging Studies of Reorganization of Language Processing. *Neurobiology of Language*, *2*(1), 22–82. https://doi.org/10.1162/nol_a_00025

Woldag, H., Voigt, N., Bley, M., & Hummelsheim, H. (2017). Constraint-Induced Aphasia Therapy in the Acute Stage: What Is the Key Factor for Efficacy? A Randomized Controlled Study. *Neurorehabilitation and Neural Repair*, *31*(1), 72–80. https://doi.org/10.1177/1545968316662707

Worrall, L., Ryan, B., Hudson, K., Kneebone, I., Simmons-Mackie, N., Khan, A., Hoffmann, T., Power, E., Togher, L., & Rose, M. (2016). Reducing the psychosocial impact of aphasia on mood and quality of life in people with aphasia and the impact of caregiving in family members through the Aphasia Action Success Knowledge (Aphasia ASK) program: Study protocol for a randomized controlled trial. *Trials*, *17*(1), 153. https://doi.org/10.1186/s13063-016-1257-9

Wray, F., Clarke, D., & Forster, A. (2018). Post-stroke self-management interventions: A systematic review of effectiveness and investigation of the inclusion of stroke survivors with aphasia. *Disability and Rehabilitation*, *40*(11), 1237–1251. https://doi.org/10.1080/09638288.2017.1294206

Yang, Z.-H., Zhao, X.-Q., Wang, C.-X., Chen, H.-Y., & Zhang, Y.-M. (2008). Neuroanatomic correlation of the post-stroke aphasias studied with imaging. *Neurological Research*, *30*(4), 356–360. https://doi.org/10.1179/174313208X300332

Yeomans, J. S., & Frankland, P. W. (1995). The acoustic startle reflex: Neurons and connections. *Brain Research. Brain Research Reviews*, *21*(3), 301–314. https://doi.org/10.1016/0165-0173(96)00004-5

You, D. S., Kim, D.-Y., Chun, M. H., Jung, S. E., & Park, S. J. (2011). Cathodal transcranial direct current stimulation of the right Wernicke's area improves comprehension in subacute stroke patients. *Brain and Language*, *119*(1), 1–5. https://doi.org/10.1016/j.bandl.2011.05.002

Young, R. M. (1968). The Functions of the Brain: Gall to Ferrier (1808-1886). *Isis*, *59*(3), 250–268. https://www.jstor.org/stable/227880

Zakariás, L., Kelly, H., Salis, C., & Code, C. (2019). The Methodological Quality of Short-Term/Working Memory Treatments in Poststroke Aphasia: A Systematic Review. *Journal of Speech, Language, and Hearing Research: JSLHR*, *62*(6), 1979–2001. https://doi.org/10.1044/2018_JSLHR-L-18-0057

Zanini, S., Moschella, V., Stefani, A., Peppe, A., Pierantozzi, M., Galati, S., Costa, A., Mazzone, P., & Stanzione, P. (2009). Grammar improvement following deep brain stimulation of the subthalamic and the pedunculopontine nuclei in advanced Parkinson's disease: A pilot study. *Parkinsonism & Related Disorders*, *15*(8), 606–609. https://doi.org/10.1016/j.parkreldis.2008.12.003

Zhang, J., Yu, J., Bao, Y., Xie, Q., Xu, Y., Zhang, J., & Wang, P. (2017). Constraint-induced aphasia therapy in post-stroke aphasia rehabilitation: A systematic review and meta-analysis of randomized controlled trials. *PloS One*, *12*(8), e0183349. https://doi.org/10.1371/journal.pone.0183349

Ziegler, W., & Ackermann, H. (2017). Subcortical Contributions to Motor Speech: Phylogenetic, Developmental, Clinical. *Trends in Neurosciences*, *40*(8), 458–468. https://doi.org/10.1016/j.tins.2017.06.005

Ziegler, W., Aichert, I., Staiger, A., Willmes, K., Baumgaertner, A., Grewe, T., Flöel, A., Huber, W., Rocker, R., Korsukewitz, C., & Breitenstein, C. (2022). The prevalence of apraxia of speech in chronic aphasia after stroke: A bayesian hierarchical analysis. *Cortex*, *151*, 15–29. https://doi.org/10.1016/j.cortex.2022.02.012

Zipse, L., Norton, A., Marchina, S., & Schlaug, G. (2012). When right is all that is left: Plasticity of right-hemisphere tracts in a young aphasic patient. *Annals of the New York Academy of Sciences*, *1252*, 237–245. https://doi.org/10.1111/j.1749-6632.2012.06454.x

APPENDIX A

PRELIMINARY LINEAR REGRESSION ANALYSIS TO DETERMINE EFFECT OF APHASIA

AND APRAXIA SEVERITY ON START EFFICACY

The results of Chapter 3 indicate that individuals with moderate-to-severe impairment improved in domains related to both aphasia and AOS. Our objective is to determine to what extent aphasia and AOS severity are contributing to those results. We ran a multiple linear regression analysis comparing baseline aphasia severity and apraxia severity to the change in each WAB-R and ABA-2 subtest from Day 1 to Day 5. As this dataset was not powered to run a multiple linear regression in this way, these results should be considered preliminary data for a future study. The results from this analysis indicate that:

1. There is a negative linear relationship between aphasia severity and Comprehension change in the START group. Participants with more severe aphasia show more improvement in the Comprehension tasks.

2. There is a positive linear relationship between aphasia severity and Diadochokinetic Rate change in the START group. Participants with more mild aphasia show more improvement in the Diadochokinetic Rate task.

3. There is a positive linear relationship between apraxia severity and Diadochokinetic Rate change in the START group. Participants with more mild apraxia show more improvement in the Diadochokinetic Rate task.

4. There is a negative linear relationship between apraxia severity and Increasing Word Length change in the Control group. Participants with more mild apraxia have fewer errors in the Increasing Word Length task.

5. There is a negative linear relationship between apraxia severity and Utterance Time change in the Control group. Participants with more mild apraxia have shorter utterance duration in the Utterance Time task

START Comprehension

Regression Statistics

Multiple R	0.5647
R Square	0.3189
Adjusted R Square	0.2432
Standard Error	0.4354996
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	1.5985	0.799	4.2141	0.0315
Residual	18	3.4139	0.190		
Total	20	5.0124			

	Coefficients	SE	P-value
Intercept	1.3064	0.5611	0.0317
AOS	-0.0440	0.1254	0.7298
Aphasia	-0.0126	0.0055	0.0357

Control Comprehension

Regression Statistics

Multiple R	0.2037
R Square	0.0415
Adjusted R Square	-0.0650
Standard Error	0.5965
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	0.2774	0.139	0.3898	0.6828
Residual	18	6.4050	0.356		
Total	20	6.6824			

	Coefficients	SE	P-value
Intercept	0.6653628	0.9245	0.4810
AOS	-0.014795	0.2374	0.9510
Aphasia	-0.005061	0.0079	0.5294

Multiple Regression Results for START and Control Aphasia and Apraxia Severity vs. Comprehension Change from Day 1 to Day 5.

START Diadochokinetic Rate

Regression Statistics

Multiple R	0.7131
R Square	0.5085
Adjusted R Square	0.4539
Standard Error	3.3856
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	213.4882	106.744	9.3126	0.0017
Residual	18	206.3213	11.4623		
Total	20	419.8095			

	Coefficients	SE	P-value
Intercept	-13.6332	4.3621	0.0058
AOS	4.1844	0.9746	0.0004
Aphasia	0.1187	0.0431	0.0130

Control Diadochokinetic Rate

Regression Statistics

Multiple R	0.1845
R Square	0.0340
Adjusted R Square	-0.0733
Standard Error	6.6536
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	28.0820	14.041	0.3172	0.7322
Residual	18	796.870	44.2706		
Total	20	824.952			

	Coefficients	SE	P-value
Intercept	9.3792	10.3120	0.3751
AOS	-1.3937	2.6484	0.6051
Aphasia	-0.0697	0.0880	0.4387

Multiple Regression Results for START and Control Aphasia and Apraxia Severity vs. Diadochokinetic Rate Change from Day 1 to Day 5.

Multiple Regression Results for START and Control Aphasia and Apraxia Severity vs. Polysyllabic Word Accuracy Change from Day 1 to Day 5.

START Increasing Word Length

Regression Statistics	
Multiple R	0.0513
R Square	0.0026
Adjusted R Square	-0.1082
Standard Error	3.2037
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	0.4877	0.2439	0.0238	0.9766
Residual	18	184.7503	10.2639		
Total	20	185.2381			

	Coefficients	SE	P-value
Intercept	-0.8600	4.1277	0.8373
AOS	-0.0725	0.9222	0.9382
Aphasia	-0.0081	0.0407	0.8448

Control Increasing Word Length

Regression Statistics	
Multiple R	0.4622
R Square	0.2136
Adjusted R Square	0.1262
Standard Error	2.4282
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	28.8249	14.4124	2.4445	0.1150
Residual	18	106.128	5.8960		
Total	20	134.952			

	Coefficients	SE	P-value
Intercept	7.4894	3.7632	0.0620
AOS	-1.7883	0.9665	0.0808
Aphasia	-0.0701	0.0321	0.0426

Multiple Regression Results for START and Control Aphasia and Apraxia Severity vs. Utterance Time Change from Day 1 to Day 5.

START Utterance Time

Regression Statistics	
Multiple R	0.3375
R Square	0.1139
Adjusted R Square	0.0155
Standard Error	3.7429
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	32.4209	16.2104	1.1571	0.3367
Residual	18	252.1663	14.0092		
Total	20	284.5872			

	Coefficients	SE	P-value
Intercept	7.5362011	4.8224	0.1355
AOS	-1.471379	1.0774	0.1889
Aphasia	-0.068726	0.0476	0.1660

Control Utterance Time

Regression Statistics	
Multiple R	0.5277
R Square	0.2784
Adjusted R Square	0.1982
Standard Error	2.1567
Observations	21

ANOVA

	df	SS	MS	F	P-value
Regression	2	32.3066	16.1533	3.4727	0.0530
Residual	18	83.7276	4.6515		
Total	20	116.034			

	Coefficients	SE	P-value
Intercept	6.3953947	3.34259	0.0718
AOS	-0.895015	0.85848	0.3110
Aphasia	-0.068599	0.02853	0.0272

APPENDIX B

EFFECT OF START ON GRAMMAR ANALYSIS

DURING SPONTANEOUS SPEECH

Clinical tests tend to have low sensitivity, despite being excellent measures of broad and meaningful speech improvements. Individuals with Broca's aphasia often eliminate adverbs, articles, adjectives, and tense. To increase the sensitivity of these tests to examine more specific components of speech, we used the Spontaneous Speech subtest of the WAB-R to assess grammar before and after training. Trained assessors blinded to treatment and timepoint quantified the total number of words, sentences, verbs, nouns, closed class words, correct verbs, grammatical sentences, ungrammatical sentences, nonutterances (incomplete sentences), semantic errors, syntactic errors (word order), and complex sentences (>1 clauses) said by each participant while they described a line drawing of a four-year old girl's birthday party. Assessors also evaluated whether participants were able to discuss the picture. A more detailed methodology is described in the table below.

Category	Methodology
Closed Class	Count all closed class words (and, a, the, but, on, etc.) excluding pronouns.
Complex Sentences	Count all sentences which are lengthy and/or complicated (involving more than one clause).
Correct Verbs	Count all verbs that are grammatically incorrect (wrong tense, for example) and subtract them from the total verbs.
Grammatical Sentences	Count all phrases which include a subject and a verb and have little or no grammatical errors.
Nonutterances	Count all phrases which do not include both a subject and a verb.
Semantic Errors	Count all words which seem inaccurately used to describe the picture.
Syntactic Errors	Count all words which seem accurate in meaning but out of place in terms of location in the sentence.
Total Nouns	Count all nouns, including pronouns.
Total Sentences	Count all phrases with a subject and verb
Total Verbs	Count all verbs, including personal asides ("I think", "I see", etc.)
Total words	Count all words except for "um"s or "uh"s or similar nonwords. Also do not count direct repetitions (consecutive repetitions of single words).
Ungrammatical Sentences	Count all phrases which include a subject and a verb but have many grammatical errors.

The results of this grammar analysis indicate that following three days of START, participants with mild aphasia had decreased ungrammatical sentences (Pre: 2.8±0.7, Post: 1.5±0.7, p=0.024). Moderate/severe participants receiving START saw no change in any grammar category. Following three days of Control intervention (a word repetition task with no startling cues), moderate/severe participants had decreased total nouns (Pre: 13.3±3.2, Post: 11.6±2.8, p=0.011) and semantic errors (Pre: 2.8±0.8, Post: 2.3±0.7, p=0.026). Mild participants receiving Control saw no change in any grammar category.

These results suggest a small effect on grammar regardless of intervention. While ungrammatical sentences decreased after START, there was no significant effect on other factors to ungrammatical sentences, such as number of total sentences, closed class words, non-utterances, or syntactic errors. This change represents an average improvement of less than two sentences for both START and Control participants and it is unlikely that these changes are clinically relevant.

	MOD/SEV CONTROL				MILD CONTROL			
	Mean Pre	Mean Post	F-value	p-value	Mean pre	Mean Post	F-value	*p-value*
total words	35.3(9.4)	34.8(8.5)	3.8	0.146	24.4(7.4)	47.6(9.2)	5.23	*0.084*
total sentences	4.6(1.1)	4.2(0.6)	0.1	0.771	3(0.7)	5.3(0.9)	5.48	*0.079*
total verbs	5(2.0)	4.7(1.7)	0.48	0.538	3.3(1.1)	6.7(1.7)	2.59	*0.183*
total nouns	13.3(3.2)	11.6(2.8)	32.16	0.011	8.4(2.1)	13.7(2.6)	2.57	*0.184*
closed class words	8(2.1)	7.3(1.9)	0.17	0.709	5.7(2.1)	9.8(2.5)	1.84	*0.247*
correct verbs	4.4(1.7)	3.2(1.5)	0.16	0.716	2.4(0.9)	6.1(1.4)	5.35	*0.082*
grammatical sentences	0.5(0.3)	0.8(0.3)	0.27	0.638	0.2(0.2)	0.9(0.3)	2.91	*0.163*
ungrammatical sentences	1.9(0.8)	1.3(0.4)	0.38	0.579	1.4(0.6)	2.5(0.6)	2.19	*0.213*
nonutterances	2.2(0.6)	2.1(0.4)	0.01	0.938	1.3(0.2)	1.9(0.7)	0.71	*0.448*
semantic errors	2.8(0.8)	2.3(0.7)	16.79	0.026	1.4(0.6)	3.6(0.9)	5	*0.089*
syntactic errors	0.9(0.5)	1(0.4)	0.02	0.897	0.2(0.2)	0.9(0.4)	2.28	*0.206*
complex sentences	1.4(0.7)	1.2(0.4)	1.01	0.39	0.6(0.3)	1.6(0.4)	3.89	*0.12*

Results of grammar analysis for moderate/severe and mild Controls. Pre and Post refer to Day1 and Day 5. Units are in number of utterances. Parentheses indicate standard error.

APPENDIX C

POWER ANALYSES AND VARIABILITY OF PARTICIPANTS

Power analyses were conducted using the WAB-R Aphasia Quotient score to estimate the minimum sample size required for the null hypothesis to be rejected (i.e., that the Aphasia Quotient will change after 3 days of intervention). To calculate this, I used the pwr.f2.test in R, which tests for the general linear model (Champely, 2020). To be conservative, I used the measure with the smallest effect size (WAB Δ=+3.5%) and the most clinically meaningful effect as the basis for power calculations. Based on the data from the 42 subjects in this study, I identified effect sizes (Cohen's d) for moderate/severe aphasia START vs. Control and mild aphasia START vs. Control comparisons. For a power of 80% at 5% significance level, a future study would require an estimated 55 (rounded up from 54.3) subjects per group to see a difference in overall Aphasia Quotient between moderate/severe START vs Control by Day 5. This would represent a Phase II or III clinical trial (K. Wilson et al., 2018). In contrast, only 12 subjects per group would be required to see a difference in Aphasia Quotient between mild START vs Control by Day 5. Notably, the current study enrolled all types of aphasia; a future study which controls for aphasia type would likely not require as many participants to see a difference in Aphasia Quotient.

Aphasia	Group 1	Group 2	Cohen's d	N (p=0.05)
moderate/severe	Test Day 5	Control Day 5	0.357	54.32
mild	Test Day 5	Control Day 5	-0.829	11.73

Power Analysis Results for Aphasia Quotient change for START and Control.

Another factor in achieving statistical significance is variability within a sample. The high variability in our START and Control groups explains why START and Control groups were not different when compared to each other by Day 5, while there was significant change in several subtests for within-group comparisons. The box plots below exemplify the change within groups that did not result in differences between START and Control groups due to high variability. A larger sample size would likely decrease this variability and yield significant between-group changes.
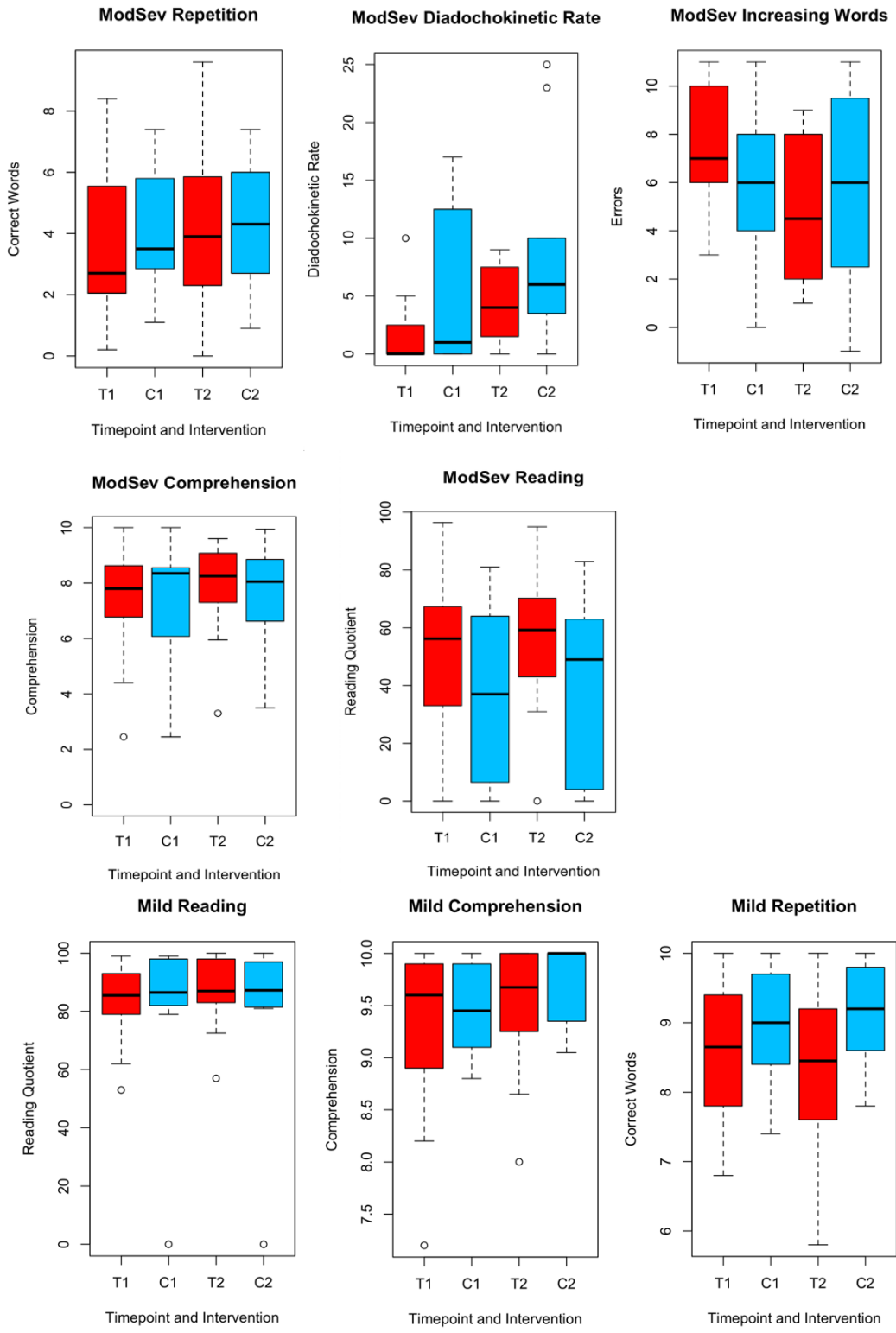
Boxplots for START (red) and Control (blue) before and after training for statistically different clinical subtests. Note within group vs. between group variability.

APPENDIX D

CLINICAL TRIAL DATA SUMMARY TABLES

The below table contains all speech clinical assessment (WAB-R and ABA-2) results for all participants. The table header descriptions are as follows: ID (Participant identification number); Aphasia at Timepoint (Severity of Aphasia as measured by Aphasia Quotient at the timepoint specified (Pre/Post intervention); AOS at Timepoint (Severity of Apraxia of speech as measured by Aphasia Quotient at the timepoint specified (Pre/Post intervention); Timepoint (Pre/Post intervention); Intervention (START vs. Control group); AQ (WAB-R Aphasia Quotient Score); SS (WAB-R Spontaneous Speech Score); AVC (WAB-R Auditory Verbal Comprehension Score); R (WAB-R Repetition Score); NWF (WAB-R Naming and Word Finding Score); RQ (WAB-R Reading Quotient Score); DKR (ABA-2 Diadochokinetic Rate Score); IW (ABA-2 Increasing Word Length Score); UT (ABA-2 Utterance Time Score); LT (ABA-2 Latency Time Score); RW (ABA-2 Repeated Words Score). A Score of N/A indicates an individual could not complete the task due to severity. For more detail on these clinical assessments, see Chapter 3.

ID	Aphasia at Timepoint	AOS at Timepoint	Time point	Intervention	AQ	SS	AVC	R	NWF	RQ	DKR	IW	UT	LT	RW
1	moderate	moderate	Pre	START	75.6	11	10	8.4	8.4	96.5	10	9	10.69	17.35	19
2	mild	mild	Pre	START	80.1	13	9.95	8.4	8.7	98	41	2	40.68	47.58	24
3	mild	moderate	Pre	START	92.2	18	9.9	9.4	8.8	86	6	2	8.66	38.99	25
4	mild	moderate	Pre	START	86.9	16	9.85	9	8.6	85	9	5	14.7	25.14	20
5	mild	mild	Pre	START	79.6	16	8.2	6.8	8.8	88	15	1	11.6	26.85	30
6	moderate	mild	Pre	Control	65.3	12	8.45	7.4	4.8	48.5	12	0	6.04	142.86	30
7	moderate	severe	Pre	Control	52.3	10	8.35	3.5	4.3	0	0	6	9.31	131.77	6
8	mild	moderate	Pre	Control	86.2	17	9.1	7.8	9.2	87	8	7	7.75	25.37	23
9	moderate	moderate	Pre	Control	55.2	7	10	7	3.6	71	13	5	9.68	341.21	27
10	moderate	severe	Pre	START	63.6	10	8	6.4	7.4	73	1	6	10.37	65.05	23
11	severe	severe	Pre	START	41.6	11	7.3	2.1	0.4	32	0	N/A	N/A	N/A	0
13	moderate	moderate	Pre	Control	74.4	13	8.8	6.8	8.6	81	17	3	6.13	25.46	20
14	severe	severe	Pre	Control	46.8	8	7.4	2.6	5.4	27	0	11	5.51	116.15	27
15	mild	none	Pre	START	90.4	17	9.9	9.7	8.6	93	44	0	3.7	21.91	30
16	mild	none	Pre	START	82.3	15	9.35	8	8.8	83	26	0	4.79	37.7	28
17	mild	mild	Pre	Control	76.8	12	8.8	8.4	9.2	79	20	1	6.59	66.83	27
18	mild	moderate	Pre	Control	88	17	9.8	8.6	8.6	86	9	10	11.85	71.52	17
19	moderate	severe	Pre	Control	52.7	7	8.45	4.3	6.6	57	0	9	12.98	87.99	18
20	moderate	severe	Pre	START	63	11	8.8	6.2	5.5	31	0	6	12.88	102.77	15
22	moderate	severe	Pre	START	58.2	13	8.7	3.5	3.9	65.5	0	11	8.41	137.41	25

ID	Aphasia at Timepoint	AOS at Timepoint	Time point	Intervention	AQ	SS	AVC	R	NWF	RQ	DKR	IW	UT	LT	RW
23	severe	moderate	Pre	Control	18.9	2	2.45	3.1	1.9	0	16	3	5.82	145.4	24
24	moderate	severe	Pre	Control	53.3	8	8.65	4.8	5.2	80	1	8	10.48	179.61	7
25	severe	moderate	Pre	START	42.5	7	7.35	2.7	4.2	59	4	11	9.83	133.43	15
26	severe	severe	Pre	START	27.5	5	6.25	2	0.5	34	0	10	N/A	N/A	3
27	mild	mild	Pre	Control	89.7	18	9.35	9.4	8.1	88	19	0	9.48	34.21	29
28	severe	severe	Pre	START	29.4	6	4.4	2.2	2.1	47	1	7	7.36	149.99	4
29	severe	severe	Pre	START	42.5	9	8.55	1	2.7	56	0	7	15.3	116.84	0
30	none	mild	Pre	Control	97.6	19	10	9.8	10	99	18	2	8.41	14.68	30
31	severe	severe	Pre	START	5.3	0	2.45	0.2	0	0	0	N/A	N/A	N/A	N/A
33	severe	severe	Pre	Control	31.1	8	5.95	1.1	0.5	13	0	6	N/A	N/A	N/A
34	none	mild	Pre	START	96.8	19	10	10	9.4	99	13	2	8.31	19.4	27
35	moderate	moderate	Pre	START	66.8	13	7.8	4.9	7.7	69	5	3	11.48	55.76	24
36	none	mild	Pre	Control	94.8	18	10	9.7	9.7	98	16	3	7.44	26.31	30
37	severe	severe	Pre	Control	21.6	4	5.3	1.1	0.4	0	0	8	1.62	116.74	2
38	severe	moderate	Pre	Control	46.8	10	6.2	3.3	3.9	37	8	7	10.48	112.83	6
40	mild	mild	Pre	START	79.8	18	7.2	7.8	6.9	53	17	0	4.93	64.6	29
41	mild	moderate	Pre	START	86.3	17	8.95	8.9	8.3	62	20	1	6.63	26.62	27
42	mild	none	Pre	START	83.4	16	8.9	7	9.8	79	43	2	7.61	19.24	30
43	none	mild	Pre	Control	95.6	19	9.9	10	8.9	0	8	0	3.77	72.18	29
45	mild	moderate	Pre	Control	83.6	17	8.8	7.4	8.6	86	5	3	11.74	23.57	16
46	mild	mild	Pre	Control	91.5	17	9.55	9.7	9.5	98	14	1	9.23	18.34	30
47	mild	mild	Pre	Control	86.9	17	9.15	8.5	8.8	82	16	4	7.88	24	29

ID	Aphasia at Timepoint	AOS at Timepoint	Time point	Intervention	AQ	SS	AVC	R	NWF	RQ	DKR	IW	UT	LT	RW
1	mild	none	Post	START	82.8	13	9.6	9.6	9.2	95	8	1	7.81	18.51	22
2	mild	mild	Post	START	82.3	15	9.95	7.8	8.4	99	46	1	53.08	58.09	27
3	mild	mild	Post	START	87.9	16	9.75	9	9.2	85	12	1	6.05	30.44	27
4	mild	moderate	Post	START	86.2	15	10	9.2	8.9	89	11	2	11.9	31.57	26
5	moderate	mild	Post	START	75.5	15	8.65	5.8	8.3	90	21	0	11.05	19.95	30
6	moderate	mild	Post	Control	65.3	13	8.05	7.4	4.2	60	25	2	3.58	139.44	29
7	moderate	severe	Post	Control	57.9	10	8.35	4.8	5.8	0	0	8	10.79	149.49	4
8	mild	moderate	Post	Control	92.1	19	9.75	8	9.3	86	18	5	8.1	21.2	26
9	moderate	mild	Post	Control	56.1	8	9.95	6.9	3.2	78	10	0	10.83	404.35	29
10	moderate	mild	Post	START	67.9	11	8.25	7	7.7	71	8	1	10.03	63.78	19
11	severe	severe	Post	START	45.5	11	8.05	2.9	0.8	46	4	7	N/A	230.52	5
13	moderate	moderate	Post	Control	73.7	12	9.35	7.1	8.4	83	6	0	6.74	22.67	27
14	severe	moderate	Post	Control	48.5	7	8.05	3.9	5.3	39	10	11	6.72	74.64	20
15	mild	none	Post	START	91.2	17	10	9.6	9	98	38	0	5.21	23.29	29
16	mild	mild	Post	START	79.9	14	9.25	7.9	8.8	83	20	0	4.31	55.67	30
17	moderate	mild	Post	Control	73.3	11	9.05	7.8	8.8	81	18	1	7.75	21.1	29
18	mild	severe	Post	Control	93.4	19	10	8.6	9.1	88.5	0	6	11.94	71.54	16
19	severe	moderate	Post	Control	43.2	8	7.1	2.7	3.8	49	3	6	10.01	141.32	11
20	moderate	moderate	Post	START	58.8	10	9.4	5.4	4.6	40	4	2	11.34	101.37	23
22	moderate	moderate	Post	START	73.4	16	9.4	5.4	5.9	69.5	7	8	6.19	66.07	24

ID	Aphasia at Timepoint	AOS at Timepoint	Time point	Intervention	AQ	SS	AVC	R	NWF	RQ	DKR	IW	UT	LT	RW
23	severe	moderate	Post	Control	31.8	5	3.5	5.1	2.3	0	23	3	7.98	189.49	21
24	moderate	moderate	Post	Control	60.9	12	9.65	4.3	4.5	66	6	3	7.29	126.97	10
25	severe	moderate	Post	START	49.5	7	8.75	3.9	5.1	68.5	9	8	14.7	102.34	12
26	severe	severe	Post	START	29.6	5	6.6	1.9	1.3	31	0	5	7.44	214.69	6
27	mild	mild	Post	Control	85.9	16	9.35	9.2	8.4	81.5	20	2	7.75	29.58	27
28	severe	severe	Post	START	32.9	5	5.95	2.7	2.8	50	1	4	7.91	128.59	5
29	severe	severe	Post	START	36.7	5	8.45	1.1	3.8	59	2	9	11.09	92.98	2
30	none	none	Post	Control	97.6	19	10	9.2	10.6	100	26	1	5.63	13.45	30
31	severe	severe	Post	START	6.6	0	3.3	0	0	0	0	N/A	N/A	N/A	N/A
33	severe	severe	Post	Control	29.5	6	6.05	1.5	1.2	8	4	10	N/A	N/A	17
34	none	mild	Post	START	98.2	20	10	10	9.1	100	11	1	8.64	21.3	30
35	moderate	moderate	Post	START	64	11	8	6.3	6.7	85	6	2	10.54	36.59	23
36	none	mild	Post	Control	94.6	18	10	9.7	9.6	99	12	1	7.81	26.54	30
37	severe	severe	Post	Control	25.7	5	6.15	0.9	0.8	0	0	10	7.99	125.32	0
38	severe	moderate	Post	Control	41	7	7.1	2.7	3.7	51.5	6	9	14.22	147.99	10
40	mild	mild	Post	START	79	16	8	7.6	7.9	57	22	0	4.5	25.98	29
41	mild	mild	Post	START	87.2	17	9.3	9	8.3	72.5	29	2	5.71	30.51	27
42	mild	none	Post	START	86.2	17	9.6	7.1	9.4	85	36	-1	6.89	13.73	27
43	none	mild	Post	Control	97.8	20	10	10	8.9	0	10	1	4.64	24.01	30
45	none	mild	Post	Control	95.6	18	10	9.8	10	85	10	1	8.15	18.6	29
46	none	mild	Post	Control	96.6	19	10	9.8	9.5	97	10	2	8.94	16.72	30
47	mild	mild	Post	Control	88.7	17	9.25	8.8	9.3	94	26	3	7.17	21.89	29

APPENDIX E

ARIZONA STATE UNIVERSITY INSTITUTIONAL REVIEW BOARD APPROVAL

ASU Knowledge Enterprise Development

APPROVAL: EXPEDITED REVIEW

Claire Honeycutt
Biological and Health Systems Engineering, School of (BHSE)
-
Claire.Honeycutt@asu.edu

Dear Claire Honeycutt:

On 1/30/2017 the ASU IRB reviewed the following protocol:

Type of Review:	Initial Study
Title:	The application of startle-evoked movements with facial muscles for speech
Investigator:	Claire Honeycutt
IRB ID:	STUDY00005229
Category of review:	(6) Voice, video, digital, or image recordings, (4) Noninvasive procedures, (7)(a) Behavioral research
Funding:	None
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Screening Script with Questionnaire, Category: Screening forms; • IRB_Protocol_Updated.docx, Category: IRB Protocol; • Consent Form Updated.pdf, Category: Consent Form; • Healthy Subjects Flyer, Category: Recruitment Materials; • Flyer for research Updated.pdf, Category: Recruitment Materials;

The IRB approved the protocol from 1/30/2017 to 1/29/2018 inclusive. Three weeks before 1/29/2018 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 1/29/2018 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator

cc: Zachary Ticktin
       Xi Zong
       Claire Honeycutt
       Zachary Ticktin

ASU Knowledge Enterprise Development

EXEMPTION GRANTED

Claire Honeycutt
IAFSE-BHSE: Bioengineering, Harrington Department of
480/965-8453
Claire.Honeycutt@asu.edu

Dear Claire Honeycutt:

On 8/22/2022 the ASU IRB reviewed the following protocol:

Type of Review:	Continuing Review
Title:	The application of startle-evoked movements with facial muscles for speech
Investigator:	Claire Honeycutt
IRB ID:	STUDY00005229
Funding:	None
Grant Title:	None
Grant ID:	None
Documents Reviewed:	None

The IRB determined that the protocol is considered exempt pursuant to Federal Regulations 45CFR46 (4) Data, documents, or specimens on 8/22/2022.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

If any changes are made to the study, the IRB must be notified at research.integrity@asu.edu to determine if additional reviews/approvals are required. Changes may include but not limited to revisions to data collection, survey and/or interview questions, and vulnerable populations, etc.
including face coverings, health checks, facility access, etc. are governed by current ASU policy.

Sincerely,

IRB Administrator

APPENDIX F

PREVIOUSLY PUBLISHED WORKS CO-AUTHOR APPROVAL STATEMENT

This certifies that all co-authors (Drs. Ayoub Daliri and Claire Honeycutt) have granted their permission for the previously published work "Impact of Startling Acoustic Stimuli on Word Repetition in Individuals With Aphasia and Apraxia of Speech Following Stroke.", published in the Journal of Speech, Language, and Hearing Research : JSLHR, 65(5), pages 1671–1685, to be used in the second chapter of this dissertation in its entirety.

<u>Full citation:</u> Swann, Z., Daliri, A., & Honeycutt, C. F. (2022). Impact of Startling Acoustic Stimuli on Word Repetition in Individuals With Aphasia and Apraxia of Speech Following Stroke. Journal of Speech, Language, and Hearing Research : JSLHR, 65(5), 1671–1685. https://doi.org/10.1044/2022_JSLHR-21-00486