REHABILITATION IN HUNTINGTON'S DISEASE AND THOSE AT RISK FOR HUNTINGTON'S DISEASE

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REHABILITATION IN HUNTINGTON'S DISEASE AND THOSE AT RISK FOR HUNTINGTON'S DISEASE

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Abstract: Huntington's disease is a devastating genetically transmitted disorder. Until recently little has been done to rehabilitate individuals with Huntington's. This study examined the effects of cognitive and motor rehabilitation of three individuals with chorea, two of whom have a formal diagnosis of Huntington's and one who is undiagnosed, but demonstrating chorea. The treatment design was ABAB and significant improvements appeared to have been realized in each parameter treated over the 4-month video therapy trial.

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CHAPTER I

INTRODUCTION

Huntington's disease (HD) is a devastating and unfortunate disorder that results in central nervous system deterioration and ultimately loss of bodily control. A mutated gene on the short arm of chromosome 4 is casual of the disease, which is progressive and passed to successive generations genetically. The disease is characterized by motor disturbances, however, cognitive deficits are also evident and ultimately affect everyday function of the individual suffering with HD (Nehl, 2004). It is crucial that these affected individuals obtain efficient and successful methods of therapeutic intervention to address such deficits that limit these individuals in their day to day functioning.

An impairment in cognition has been distinguished as one of the central and primary symptoms of HD due to deterioration of neurons in the prefrontal cortex, hippocampus, diencephalon, and caudate nucleus of the brain (Montoya, 2006a; Dumas, 2012). Domains of cognition that have been found to be impaired are memory, attention, and executive functioning (Montoya, 2006a). Changes in cognition are often accompanied by changes in behavior. These changes greatly and negatively affect everyday living of individuals affected and their families and caregivers similarly. Eventually cognitive deficits may result in dementia, which greatly impacts the quality of life for these individuals and their caregivers

(Montoya, 2006a; Bonelli; 2004). Research has even suggested that cognitive impairments may be observable prior to the time of motor symptom appearance (Paulsen, 2001; Montoya, 2006a).

In addition, pharmacological treatment of HD-associated chorea may negatively affect cognition. In a systematic review by Bonelli and Hoffman (2004), the authors described pharmacological treatment involving antichoreic drugs [e.g. tetrabenazine (TBZ)] to reduce choreiform motor symptoms. Although the most efficacious pharmacological means of reducing chorea, such medications have serious side effects including: disturbed gait, impaired swallow, nausea, somnolence, anxiety, and depression; therefore, it is beneficial to investigate the efficacy of non-pharmacological treatment options. In addition to antichoreic medications, low doses of some neuroleptics have also been demonstrated the ability to reduce chorea. The following medications are some pharmacological options that have been shown to depress HD symptoms: Haloperidol, Fluphenaine, Olanzapine, and Risperidone (Bonelli, 2004; Bonelli, 2003), however, these neuroleptics are also commonly associated with cognitive side effects.

Although some attempts at cognitive exercise have been conducted in those with HD (Cruickshank, 2015), pharmacological treatment have been the main source of treatment for these individuals. HD has been extensively studied and targeted in pharmacologic clinical trials in order to identify likely treatment options for persons with HD (Bilney, 2003; De Tommaso, 2004; Saavedra, 2013).

A study by Saavedra discovered that cGMP (cyclic guanosine monophosphate) levels were considerably reduced in postmortem hippocampal samples of HD patients as compared to those without HD who served as controls. They suggested that the regulation of hippocampal cGMP levels in mice and humans alike with HD may improve abilities in cognition and everyday function. Because the hippocampus is an area important for memory storage, the aforementioned results specified that reduced levels of cGMP may contribute to cognitive deficits

related to the domain of memory. Improvements in cognition may be observed in those with HD once alterations in hippocampal cGMP levels are adjusted by method of PDE5 (phosphodiesterase type 5) inhibition (Saavedra, 2013).

Additionally, De Tommaso et al. (2004) looked at the effect of a cholinesterase inhibitor, Rivastigmine, on motor and cognitive impairment in individuals with HD. Treatment such as this has been observed to improve cognitive deficits in others with progressive diseases such as Alzheimer's and Parkinson's diseases. During this randomized-controlled trial, each participant was given the Mini-Mental State Examination (MMSE) in order to observe cognitive function before treatment began. Of the group, half received Rivastigmine for 6 months while the others did not and were therefore, left untreated. Results showed a significant difference in the MMSE scores of the two groups at the end of the 6-month treatment phase. The Rivastigmine group revealed an increase in MMSE scores compared to the baseline condition prior to beginning the study. Though a small (21 participants) study, as is common in this rare disease, Rivastigmine proved to be a potentially impactful treatment option for those with HD who show declines in cognitive function (De Tommaso, 2004).

Though there has been some interest in therapy for the cognitive deficits associated with HD, both the specific deficits and how to treat them have received insufficient attention. Therefore, investigators must borrow from the literature addressing cognitive therapy for other more common disorders. Verbal working memory is defined as "the temporary maintenance and manipulation of verbal information" (Baddeley, 1986). Verbal working memory is directly related to the cognitive domain of memory and may be compromised in individuals with HD. Memory training has long been a focus of cognitive therapy. In a systematic review by Gates et al., 2011, the authors found that the literature favors the use of cognitive exercise in healthy adults as well as those with mild cognitive impairment (MCI). Such exercise may help enhance cognitive function as well as slow the decline in individuals at risk for cognitive decline. Training and

intervention involving memory has been a main target of cognitive training programs. Such programs are driven by evidence that memory declines as normal aging occurs and in those with brain disease or injuries (Gates, et al., 2011). Several methods of strengthening verbal working memory have been published. These tasks and resources, according to Cognitive Atlas (Cognitive Atlas, 2011), include the doors and people test, Children's Memory Scale, Penn Word Memory Test, verbal working memory test, category fluency test, backward digit span task, and the Wechsler Memory Scale Fourth Edition (2011).

In a study by Elina Mainela-Arnold and Julia Evans (2005), word recall performance on verbal working memory span tasks using the competing language processing task (CLPT) in children with a specific language impairment (SLI) were compared to those who were typically developing at the same chronological age (CA). In a verbal working memory task, the children were read lists of short "yes/no" answer type statements. They were first asked to answer the statements based on the plausibly of the statement and then were asked to remember and recall the last word of each one of the statements. If the children were unable to repeat the target word in each statement or did not understand the task initially, they were asked if they remembered what the lady on the tape presenting the statements said. If unable to remember after that, the sentences were repeated. Each participating child demonstrated evidence of understanding the task. Word frequency and sentence length were both considered. It was found that children with the SLI did show more difficulty recalling the words than the children who were the same age and typically developing (Mainela-Arnold, 2005).

In another study by Margherita Orsolini et al., 2005, a similar task was used to observe changes or improvements in a boy with an intellectual disability. Cognitive training of verbal working memory was addressed using a task called the Listening Span Task adapted from the Daneman and Carpenter task. The child was asked to first listen to a statement (increasing in span) and judge the plausibility of the statement by stating whether it was true or false. After this

he was asked to remember the last word of each statement in the order in which the statements were presented. After 30 weeks of treatment, the participant demonstrated progress as his responses shifted from stating whether the statement was true or false. In addition, he successfully performed the second task of remembering the last word of each statement, although the task remained somewhat difficult. Results showed that treatment of verbal working memory tasks using this modified task may help improve cognition (Orsolini, 2005).

In a study by Heinzel, et al. (2014), the cognitive domain of working memory was addressed through the training of young and old adults in a total of twelve sessions. They defined older adults as adults who are aging and who often have age-related decline in cognition. Part of the treatment during the twelve sessions involved a series of forward and backward digit span tasks as well as The Consortium to Establish a Registry for Alzheimer's disease (CERAD) word list memory tasks which involved both immediate and delayed recall. For the digit span tasks, digits were read to the participants at a rate of one digit per second. Participants were instructed to repeat the digit set in the verbatim order or reversed. Two trials of each digit set were read and increased in size as correct responses were given. Assessment halted when the participant was unable to repeat back both trials. The memory task from the CERAD was performed to determine both immediate and delayed recall of a list containing 10 words. Results indicated that no changes were detected in the CERAD word list recall task with the group of younger participants; however, there was significant improvement in the older participants. Additionally, though the older group of participants showed improvement and transfer of skills resulting from forward digit span tasks, the younger group demonstrated no change from baseline (Heinzel, 2014). Such tasks can be easily transferred to tasks that address the cognitive deficit of verbal working memory.

To date there is not an identified behavioral cognitive intervention that prevents or significantly delays the progressive cognitive decline in HD (Bilney, 2003; Paulsen, 2011). As

such, the area is ripe for exploration. Examination of potential therapy to treat the cognitive aspects of HD was the purpose of this study.

CHAPTER II

LITERATURE REVIEW

Branded by the mutated autosomal dominant gene on the short-arm of chromosome 4, Huntington's disease is passed from parent to child and averts satisfactory function of the central nervous system. This disease is progressive as well as rare and unfortunately, eventually ends in death (Margolis, 2003). Relentlessly affecting both males and females, the disease typically onsets between the ages of 35 and 50; however, there have been occurrences where cases have been seen in individuals as young as 2 (Juvenile HD) and as old as 80. (Dawson, 2004; Margolis, 2003). Typically, untimely and unfortunate death occurs in those diagnosed with HD 15-20 years post disease onset. (Margolis, 2003; Duffy, 2013).

Signs of impulsiveness, disinhibition, mood swings, depression, and aggression are observable as psychiatric and emotional symptoms of the disease and worsen over time. In fact, with such change, it has been discovered that prevalence of suicide within the HD populationranges from 5-10% with additional psychiatric and emotional symptoms serving as predictors ranging from depression/anxiety, irritability, to drug abuse (Zielonka, 2015). The prevalence of depression in the HD population has been found to range from 30-40% (Bonelli, 2004). Similar to depression, apathy has been observed in individuals with HD. Pflanze et al., (1991), observed that 57% of patients had lost interest in life as well as the ability to concentrate.

Abnormal gait and involuntary jerk-like movements called 'chorea' are present and are signs of problems in control of motor movements. Additionally, speech that is slurred and difficulties in swallowing also predominate (Dawson, 2004). In addition, compromised cognition is frequent in various stages of HD (Paulsen, 2011).

Cognition

Neisser (1967) referred to cognition as "the processes by which sensory input is transformed, reduced, elaborated, stored, recovered, and used." According to Helm-Estrabrooks (2014), "cognition is often described in several behavioral domains pertaining to attention, memory, language, executive function, and visuospatial skills." Each domain is described below.

Attention is defined broadly as the ability to maintain a comprehendible and constant line of focus or thought over a time span. There are currently several different types of attention. Sustained attention allows individuals to directly focus on a particular stimulus, action, or object. Selective attention pertains to the ability of an individual to reject stimuli while preserving and keeping focus on another source of stimuli for processing. The ability of an individual to concentrate on more than one thing at a time is referred to as divided attention. Our ability to quickly move and shift our focus without error from one stimulus to another is called alternating attention (Helm-Estrabrooks, 2014). Shifting attention is important for carrying out activities of daily living. The American Speech-Language-Hearing Association (ASHA, 2017) states that common attentional deficits include: being easily distracted, having difficulty attending, and diminished information-processing speed-thinking/processing. Such things can greatly impact an individual's ability to communicate effectively and function independently.

One's ability to focus on, pay attention to, register, remember, process, and keep information in one's mind refers to memory. According to Helm-Estabrooks (2014), memory is

comprised of three different forms with different meanings and functions: working memory, semantic memory and episodic memory. Working memory is used when recent information is collected and manipulated to perform different tasks. This may include one's ability to add or subtract (2014). As time has progressed, working memory has replaced the concept of short-term memory (Crowder, 1982). According to Baddeley (1986), working memory has been linked to the performance of a range of tasks including language comprehension, reasoning, and learning, thus validating the relevance of the cognitive skill. Semantic memory refers to the facts and knowledge of the world that everyone experiences differently. Conceptual knowledge of the world we live in is vital for learning and functioning. Lastly, episodic memory is specific and varies per individual. It relates and pertains to an individual's experiences and past (Helm-Estabrooks, 2014). Memories from events and experiences rely on spatial and temporal cues for suitable recovery (Montoya, 2006b).

Executive functioning—also referred to the highest level of human cognition by Dumas (2012) is another aspect of cognition. Abilities related to planning, sequencing, and accomplishing goals in an well-organized and thought out manner are related to skills of executive function. Mental flexibility when things do not occur as thought or planned is also a skill related to executive function. Executive functioning is activated with planning and carrying out goals. Additionally, individuals are able to think about and consider consequences of actions because of intact executive function. (Helm-Estabrooks, 2014). In a literature review by Purpura et al. (2016), it's explained that executive function develops across one's lifespan. Currently, executive functioning is made up of several cognitive processes: response inhibition, working memory, and cognitive flexibility. Response inhibition refers to the overriding of a particular response in favor of another. Working memory refers to simultaneous maintenance and manipulation of information. Lastly, cognitive flexibility is the flexible adaptation to changes in goals or stimuli (Purpura, 2016).

HD and Cognition

The neurodegenerative nature of the disease linked with the loss of motor control and cognition make HD one of the most devastating illnesses (Montoya, 2006a; Bonelli, 2004). When deterioration of physical, cognitive, and emotional capabilities occurs, a sense of powerlessness and incapacitation occur with disease progression (Dawson, 2004). According to Dumas, primary cognitive domains affected in those with HD include memory, attention, and executive functioning. Though motor decline is one of the hallmarks of the disease, recent research findings have found that accompanying cognitive and behavioral impairments require scrutiny (Paulsen, 2011).

Results from a study by Hamilton et al., (2003) showed that behavioral changes associated with HD may be quite debilitating and unfortunately affect the ability to effectively use cognitive skills in day to day living. Eddy et al. (2012) stated that after testing quality of life in 16 patients with HD, scores were lower for individuals who presented with greater executive dysfunction in their everyday living. Further, Nehl et al., (2004) suggested that there is decline in the individuals' once intact functional abilities and a heavy burden placed on HD families due to difficulties and decline in cognition.

It has also been documented that there is evidence of an impairment in cognition and behavior 10-20 years prior to motor diagnosis of HD in some individuals (Paulsen, 2011; Montoya, 2006b). According to Montoya, the onset of deficits in cognition may be sudden or appear gradually over time and as the disorder evolves. Eventually, dementia is likely to occur as cognitive deficits such as decreased motivation, slowed information processing, depression, apathy, and changes in behavior and personality present (Montoya, 2006b; Bonelli, 2004).

Studies have validated substantial alterations in the caudate nucleus, regions of the striatum, thalamus, cortical grey matter and cerebral white matter areas in those effected by HD

(Montoya, 2006a). Structural changes in the striatum are associated with deficits as memory, attention, and executive functioning (Montoya, 2006a; Dumas, 2012.

Memory has been found to be impaired in both early and late stages of HD (Dumas, 2012). Learning new information and retrieving previously learned information becomes a challenge. Paulsen (2011) reported that tasks requiring coordination are compromised in individuals with HD due to problems and deficits in implicit memory. Another type of memory that has been shown to be affected is episodic memory. Episodic memory, as previously discussed, includes memories from individual and personal experiences. In Montoya's meta-analysis, it is discussed that recall, cued recall, and recognition are compromised in individuals with HD. In addition, it is suggested that recall and recognition are basic features of memory issues in the earlier stages of HD (Montoya, 2006b).

Cognitive impairment often gradually worsens into dementia, which is one of the three clinical features of HD (Bonelli, 2004; Bonelli, 2003). Dementia associated with HD is characterized by decreased motivation, depression, personality changes, and slowed information processing (Montoya, 2006a; Bonelli, 2004). Formally, dementia refers to "a decline in cognitive abilities which in turn results in social and occupational functioning deficits" (Peavy, 2010). Previously, the diagnosis of dementia in HD was made using the standards and criteria for dementia associated with Alzheimer's disease (Peavy, 2010). In a study by Brouwers et al. (1984), it was found that there were differences in the dementia of Alzheimer's disease and the dementia of HD. Data from this study indicate that there are different impairments in perceptual processing for individuals with dementia associated with Alzheimer's disease and dementia associated with HD. Such results only strengthen Peavy's admonition to develop and establish criteria specific to the dementia HD. Results of the Peavy study indicated that diagnosis of dementia in HD requires evidence of an impairment in at least two areas of cognition. Such

areas include attention, speed of processing, executive functioning, visuospatial abilities, and memory (2010).

Disturbances in attention span and concentration in patients with HD have been documented in the literature. In previous studies it has been documented that HD patients have difficulty shifting their attention as well as re-focusing their attention from a predictable stimulus to an unpredicted stimulus (Georgiou, 1995; Sprengelmeyer, 1995). The ability to shift and re-focus attention is important for everyday functioning. Because most activities of daily living require such skills, it is not surprising that along with attentional deficits come difficulties in other activities that require planning, organizing, and sequencing (Georgiou, 1996).

Executive functioning, aforementioned, is the most complex of all cognitive skills. Higher order functions of task-switching, flexibility and even categorization abilities are conducted through skills of executive function. Adaptation and flexibility during activities of daily living are vital for successful social interaction and communication. In several longitudinal studies, an impairment in executive functioning has been identified in individuals with HD. Because some studies have established that impairments in executive functioning herald the disease, a decline in this area of cognition in gene carriers may be a suitable behavioral marker for early detection of the disease (2012).

Overall, as progressive decline in cognition becomes more extensive, the more an individual's quality of life deteriorates (Montoya, 2006a). Loss of work, independence, and even social interaction are some life changes that may occur with disease progression, unfortunately. The impact is reflected not only on the individual, but also on the family of the individual, as it is the family who primarily provide personal care and support to HD patients. (Dawson, 2004).

Treatment

The prevalence of cognitive deficits in those that may be at risk and those diagnosed with HD dictates the need for the development of both helpful and efficacious treatment; however, personalized treatment is the gold standard. Most methods of treatment for individuals with HD are pharmacological in nature; however, in a 30-day study by Giddens et al. (2010), investigators found that an intense home therapy program involving respiratory, phonatory, and oral motor exercises resulted in improvement in motor function at the end of the trial. The ability of the participants to adequately swallow for oral feeding also appeared to be maintained and/or improved due to the treatment program (Giddens et al., 2010). This trial appeared to indicate the possible efficacy of rehabilitation in Huntington's that was not pharmacological in type.

A loss of gray matter seems to be causal of cognitive decline in individuals with HD. In a multidisciplinary rehabilitation study, an exercise program involving weekly aerobic and resistance exercises, thrice weekly muscle strengthening and fine motor exercises, and occupational therapy consisting of paper and pencil, verbal planning, memory, and problem solving exercises was conducted (Cruickshank, 2015). After 9 months, results included an increase in the volume of gray matter in the brain. This was significant, and as well some cognitive aspects in the participants with HD were noted to have improved. Together, findings from the Cruickshank study revealed that neuroplasticity of the brain may be a possibility when implementing such a treatment program—despite the degenerative nature of the disease. Ultimately, rehabilitation by multiple disciplines may be an excellent option for individuals with HD. (Cruickshank, 2015).

Further, in a review by Thom and Clare (2010), evidence suggested decline in functional independence may be reversed in those with dementia when combining both exercise and interventions that were focused on cognition. As previously discussed, dementia often occurs in

the later stages of HD, therefore, similar interventions may also maintain or even increase functional capabilities of everyday living in this population as it did in Thom and Clare's study. Cognitive exercise interventions activate task-related regions of the brain important for adequate cognitive function; therefore, such intervention should be implemented (Thom & Clare, 2010). Further, in some randomized controlled trials, at least one area of cognition has been show to improve when cognitive training was implemented. Though some domains have been shown to improve, currently, there is no evidence that demonstrates universal domain improvement of function in cognition (Thom & Clare, 2010).

Though cognitive deficits are highly associated with HD, few clinical trials addressing therapeutic options for cognitive decline have been conducted. Currently there is not a preferred treatment option for improving cognition in those living with HD; however, some cognitive aspects and behavior can be pharmacologically improved (Zielonka, 2015). The decline in cognition associated with the condition is devastating and negatively impacts the quality of life and independence of this patient population. Improvements in cognition have the capability to provide those diagnosed or at risk for diagnosis and their families greater independence in their everyday lives. Research and clinical trials involving treatment for the cognitive impairment in HD should be of high priority when implementing and conducting research in this population. The current study focuses on the implementation of behavioral cognitive exercises to improve the cognitive deficits in individuals with HD.

CHAPTER III

METHODOLOGY

The purpose of this study was to examine the effects of intense (i.e. 4 times per week or greater) treatment involving cognitive exercises to improve the cognitive deficits associated with HD.

Research Questions

The specific research questions included:

1. Do intense exercises improve or maintain impaired verbal working memory associated with HD in those diagnosed with HD and those at risk for HD?
2. If cognitive improvement results from cognitive therapy, does cognitive function return to baseline when the therapy is withdrawn and replaced with motor therapy?
3. Do cognitive therapy and motor therapy result in similar treatment effects?

Subjects

Three study participants were recruited from HD support groups in the State of Oklahoma. Participants varied in age between 31 and 73 years. Of the three participants, two were female and one was a male. One held a professional position, one was retired, and the other was a homemaker. Participation in the study was voluntary. The participants were screened according to a protocol approved by the Institutional Review

Board at Oklahoma State University. Objective measures of baseline mental status were obtained through administration of the following tests:

- The Mini-Mental Status Examination (MMSE). Participants took a brief screening measure to ensure appropriate mental status prior to participation in the study. Acceptable mental performance ensured the participant's ability to voluntarily participate in the study and understand and perform a variety of treatment exercises. The following areas were tested and scored: orientation, attention, calculation, recall, and language. Based on the preceding measures, the participant was deemed ineligible for the study based on a composite score of <20 on the Mini-Mental State Examination (MMSE).

Baseline and Final Data Collection

The screening and examinations were conducted individually and in a private room to protect the confidentiality of the participant. Objective measures were also obtained for baseline measures through the following tests:

- Unified HD Rating Scale (UHDRS). The severity of baseline HD symptoms was documented.
- Peak Flow Measure: The individual's vital capacity at baseline was measured using a peak flow meter. The rate was re-collected at the conclusion of the study to observe changes (improvement or deterioration) following treatment.
- Blood Pressure Reading: A baseline blood pressure measure was collected by the researchers through an Omron automated sphygmomanometer as part of the study screening. None of the participants failed the blood pressure screening, therefore, glottal adduction exercises (Valsalva—pushing and pulling exercises to strengthen the voice) were conducted during Treatment B, motor therapy.

Treatment Procedures

An ABAB design was employed for the study. Following initial baseline data collection, the investigator introduced and trained the qualified participants in the use of several cognitive exercises (Treatment A). Participants underwent Treatment A four days per week during Skype or FaceTime connection with the primary investigator for a period of one month (16 sessions). The exercises addressing verbal working memory included:

Treatment A:

a. Digit Span Task (backward and forward)
    - The investigator presented a series of digits at the rate of one per second. The forward digit span task required the participant to repeat the digit set verbatim. The backward digit span task required that the participant repeat the set of numbers verbally in reverse order. Two digits were presented at first, however, the number of digits presented verbally to be repeated increased until the participant failed to repeat the digit set correctly several times in a row in both forward and backward tasks.
b. Word List Recall—Immediate and Delayed
    - The investigator verbally produced a number of unrelated single words (e.g. bear, three, oak, rice, pillow.) After the words had been presented, the participant was asked to recall and state as many of the words as possible in no particular order. The number of items accurately produced was recorded. At the conclusion of the session the participant was asked to restate the words again to complete a delayed recall task.
c. Listening Span Test
    - The participant was instructed to listen to lists of short sentences and questions that required a "yes" or "no" answer. Each sentence presented required an answer before moving to the next sentence or questions. While listening, they were

instructed to remember the final word of each sentence or question. After the participant had heard all of the sentences or questions from the list and responded to each sentence appropriately, they were asked to recall the last word of each sentence or question.

Treatment B:

Following sixteen sessions (four times per week for 4 weeks) of Treatment A, the researchers then introduced and trained the qualified participants in the use of motor (speech) exercises (Treatment B). The exercises were implemented one time per day four days out of the week for a period of one month (sixteen sessions). The speech exercises are described below. A probe of cognitive function (e.g. forward digit span task) was taken daily to monitor for maintenance, improvement, or deterioration in cognitive function.

Treatment B:

a. Breathing Exercises: inhaling and holding breath, phonating vowels as long as possible, blowing up a balloon.

b. Labial & Lingual Exercises: opening/closing, puckering, smiling with the lips. In addition, exercises involving movement of the tongue were administered. Resistance exercises using a spoon were used in attempt to retain tongue function. Speech diadochokinetic (DDK) movements were also practiced and analyzed.

c. Glottal Adduction Exercises: several voicing exercises (pushing and pulling to force the vocal folds together tightly) were administered.

Following sixteen sessions (four times per week for 4 weeks) of Treatment B, therapy reverted to Treatment A (cognitive) followed again by Treatment B (motor) during the final and fourth month. At the conclusion of the four-month long treatment program objective measures were collected again to establish final data revealing information about improvement, maintenance, or deterioration in verbal working memory over time.

CHAPTER IV

FINDINGS

The purpose of this study was to determine the treatment effects of an intense (i.e. 4 times per week) therapy program focusing on the cognitive deficits associated with HD—more specifically verbal working memory. This study was an ABAB design which took place over a span of four months. Three participants were included in the study, two diagnosed with HD as well as one at-risk individual who had been displaying chorea for several years.

Data were collected and responses recorded in the database each day for the following Treatment A components: immediate and delayed word recall, forward and backward digit span, and listening span. In addition, data was collected each day for the following Treatment B components: peak flow rate, mean phonation time, and diadochokinetic (DDK) speech rates. From the data both visual effect sizes and percentage effect sizes (Barlow, Nock, & Henson, 2009; O'Brien & Repp, 2010) were calculated for each condition. In total, each type of treatment (Treatment A & B) was conducted for 32 days. Each participant attended all therapy sessions. Data were collected and recorded into the database daily.

Results & Discussion

Immediate Word Recall

Participants were asked to listen to 10 random unrelated words produced at one word per second before immediately recalling as many words as possible. Different words were selected from a random word generator daily to be used as stimuli. Beginning and ending results for each participant differed; however, each participant showed improvement with treatment over time as can be seen in Figure 1. Although Participant 1 experienced a large effect size between Day 16 (conclusion) and Day 1 (onset) of Treatment A in month 1 (Day 1=3; Day 16=5; 66% improvement), the participant demonstrated a great deal of daily variability in her ability to perform this task (e.g. the participant recalled 3 words on Day 48 of month 3, the last day of cognitive therapy (Treatment A). Examining averages, Participant 1 was able to recall an average of 3.5 words of the 10 given at baseline. Upon final data collection, a minimal overall improvement was noted, as the participant was able to produce an average of 3.8 words.

Participant 2 also demonstrated improvement in cognitive function, but improvement appeared to be more significant following the 2nd phase of Treatment A (e.g. Day 1=6; Day 48=7; 16% improvement). At baseline, Participant 2 was able to recall on average 6.1 words of 10. Upon final data collection, this participant was able to recall an average of 6.9 words. Also consistent with Participant 1, daily variability was observed in Participant 2. Participant 2 was able to recall between 4 and 9 words over the treatment period.

Participant 3's baseline immediate word recall averaged 3.1 words of 10. Following the second phase of Treatment A at the conclusion of month 3, Participant 3 recalled an average of 4.1 words of the 10. Variability was also observed as this participant was able to recall between 3 and 6 words from day to day. Similarly, to Participants 1 and 2, however, Participant 3 did demonstrate improvement (e.g. Day 1=2; Day 48=5; a 150% improvement).

As a group, the participants averaged 4 immediately recalled words when baseline data was collected. Following cognitive therapy, the average of all participants' immediate word recall improved to5.4 words, thus demonstrating improvement of 35% post-therapy in immediate word recall.

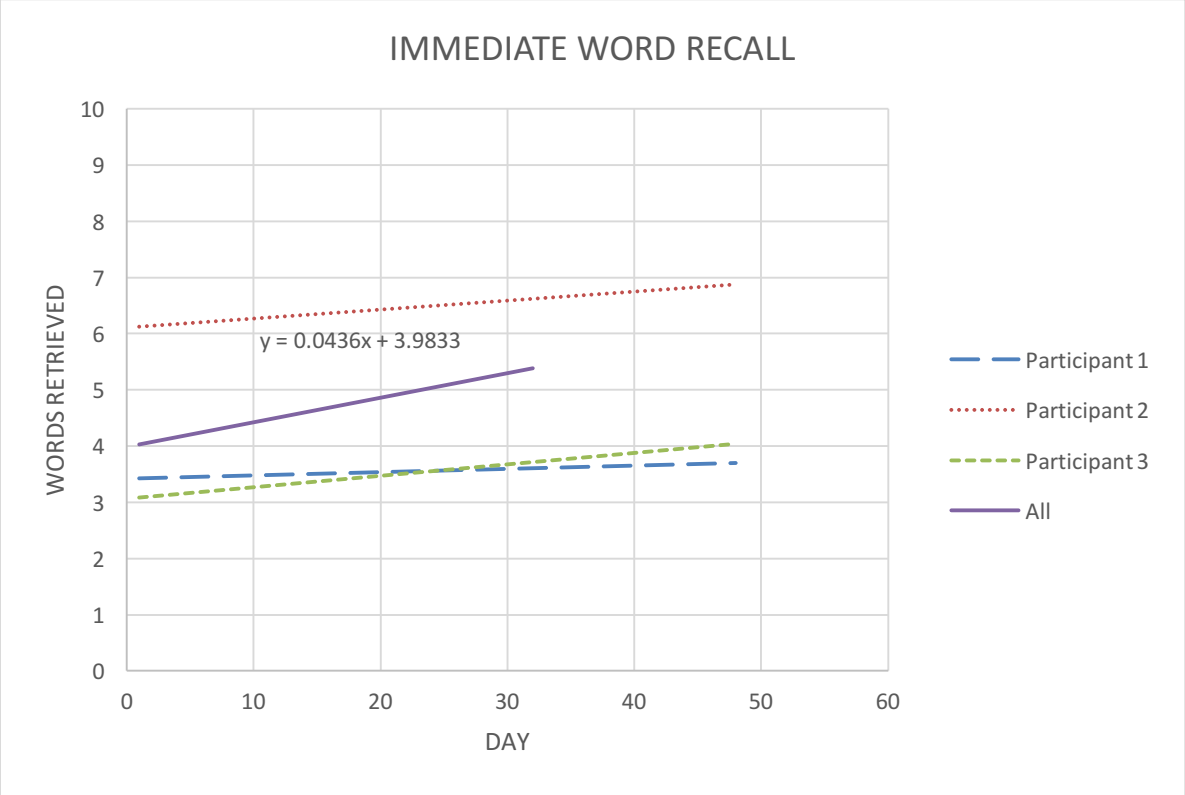

Figure 1: Immediate Word Recall

Delayed Word Recall

Participants were asked to recall a list of words ten minutes after the list had been presented aurally. The 10 words were produced at one word per second. Baseline and post-treatment results for each participant differed; however, each participant demonstrated improvement following treatment as can be observed in Figure 2. When initial data were collected, Participant 1 was able to recall post-delay an average of 2.1 words of 10. Upon final data collection, an improvement was noted, as the participant was able to recall an average of 3.9 words after delay (a 54% improvement). There was some fluctuation day to day in the number of

words recalled post-delay as this participant was observed to recall between 0 and 4 words over the four-month study.

Participant 2 also showed improvement in the delayed recall task. Initially, Participant 2 was able to recall on average 3.2 words out of 10 after delay. Upon final data collection, this participant was able to recall an average of 5.3 words (a 60% improvement). Fluctuation was noted from day to day as Participant 2 was able to recall between 2 and 8 words over the treatment period.

It can also be observed that Participant 3 displayed a very slight improvement over baseline in the ability to recall post delay. At baseline Participant 3 recalled an average of .5 word of 10 and at the termination of phase 2 of Treatment A he could recall an average of .8 words post-delay. Variability was also observed as this participant was able to recall between 0 and 2 words from day to day. As a group, the participants averaged post-delay1.8 words recalled at baseline. Following treatment, the average of all participants' delayed recall improved to 3.8 words, a greater than two-fold increase.

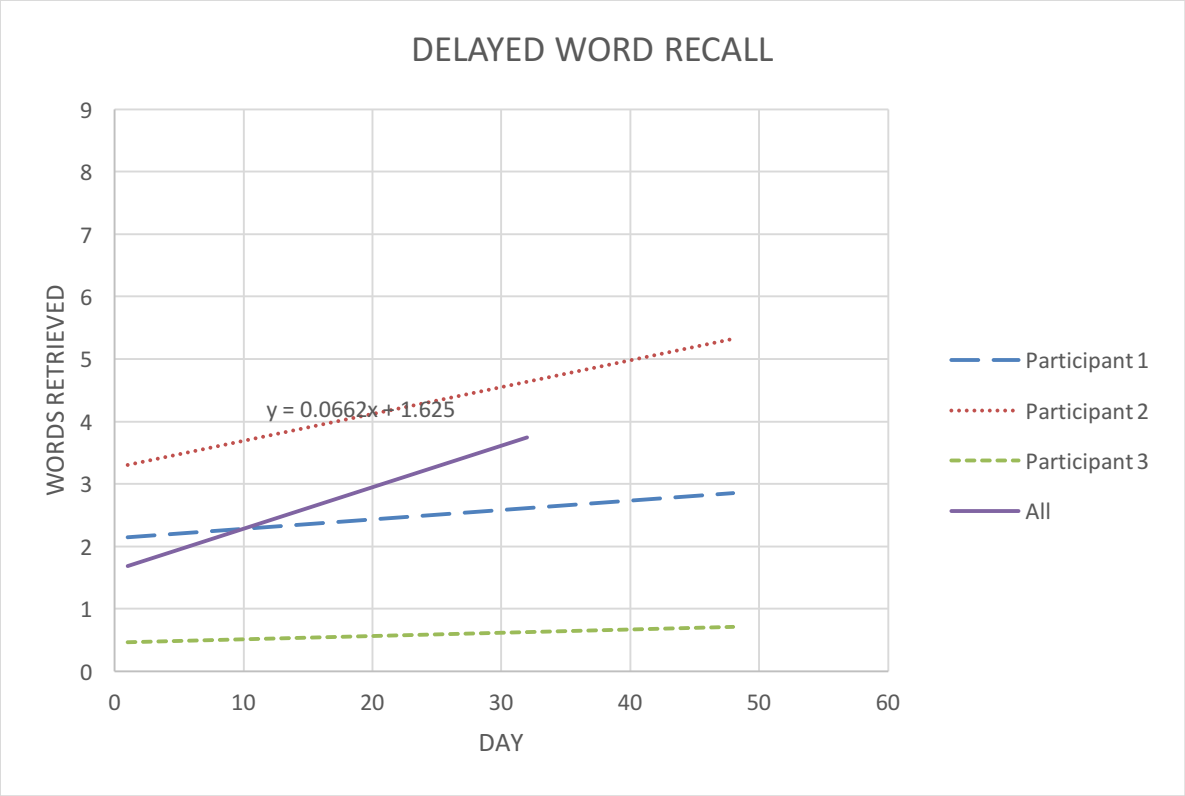

Figure 2: Delayed Word Recall

Forward Digit Span

Participants were asked to complete a forward digit span task in which numbers were presented at a rate of one per second. Numeric strings were repeated verbatim immediately following presentation. Successful repetition resulted in presentation of more complex strings. The task ceased when the participant was unable to repeat two consecutive number combinations. Individual participant and group average results can be seen in Figure 3.

This particular task served as a cognitive probe and was conducted each day over the 4-month trial. As can be observed in Figure 3, baseline and post-treatment results for each participant differed. However, overall improvement was observed in participants.

At baseline Participant 1 was able to recall combinations an average of4.9 numbers. Post trial, Participant 1 was able to repeat a 6 number string for an 82% increase. Fluctuation from

day to day was again evident. The participant successfully repeated between 3 and 7 number combinations throughout the study.

At baseline Participant 2 demonstrated the ability to repeat an average of 5.9 numeric strings verbatim. At the end of 4 months of treatment, Participant 2 demonstrated the ability to recall and repeat numeric strings an average of 9.9 digits (a 60% increase). Again, daily variability was observed with the participant repeating a range of 5 to 10 digits. However, of the three participants, Participant 2 demonstrated the greatest improvement in the forward digit span task.

Participant 3 was able to recall and repeat combinations an average of 5.1 numbers at baseline. Over the 4-month trial, improvement was demonstrated as the participant recalled and repeated numeric strings of 7 at study conclusion. Day to day variations were again observed as digit strings between 5 and 8 were repeated.

As a group, the participants averaged 5.2 digits at baseline. Upon final data collection, significant improvement was observed. The average string of digits recalled and repeated by the participant group averaged 7.8, a 50% improvement.

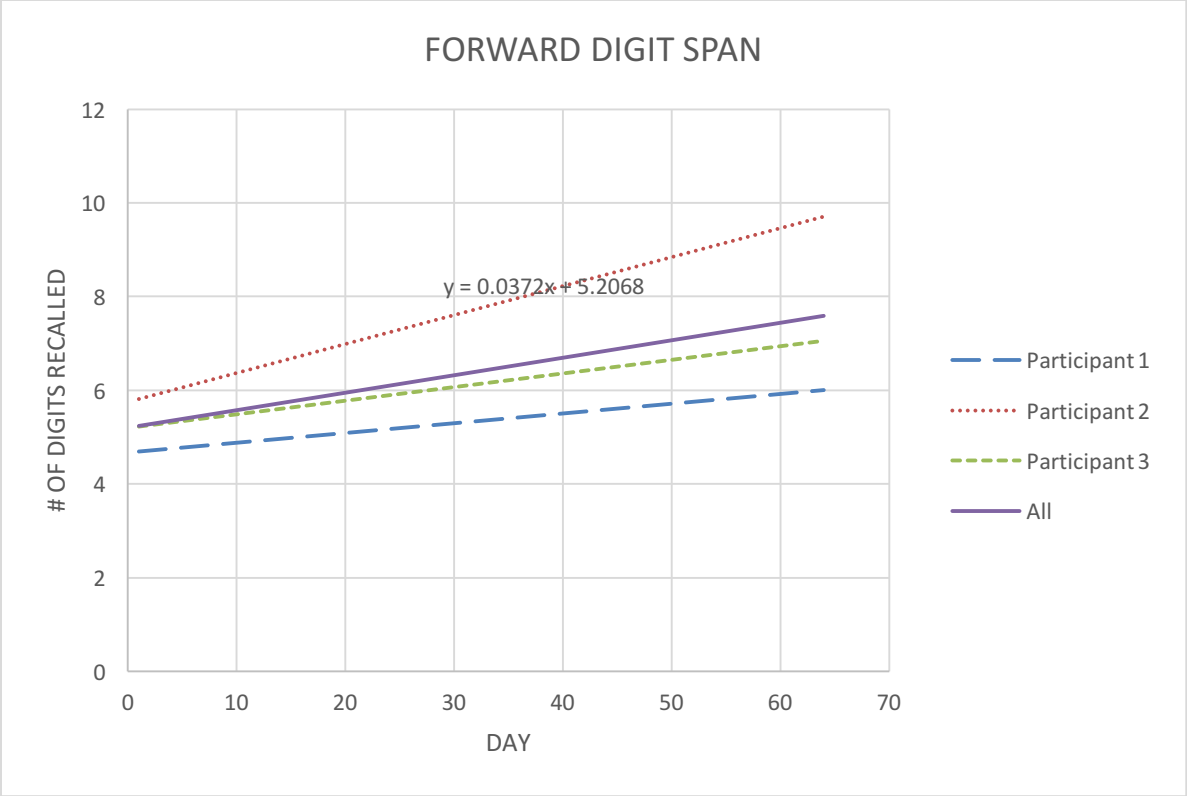

Figure 3: Forward Digit Span

Backward Digit Span

Participants were asked to complete a backward digit span task in which numbers were presented at a rate of one per second. Numeric strings were repeated in backward order by the participants and became more complex with success. The task ceased when the participant was unable to repeat back two consecutive numeric strings in backward order. Individual participant results as well as the group average can be seen in Figure 4. Although overall daily variability continued, improvement was observed over time for the participants.

Participant 1 was able to manipulate combinations an average of 3.2 numbers in backward order at baseline. Following treatment completion, only a slight improvement was evidenced by the ability to repeat an average of 3.6 numbers (a 12.5% improvement) in backwards order. Daily variability of Participant 1 was less pronounced as for the previous tasks. Participant 1 manipulated3 to 4 number combinations in a backwards order on a daily basis.

At baseline Participant 2 manipulated an average of 4.4 numbers by backward recall. This participant demonstrated significant improvement by study completion as evidenced by the ability to manipulate an average of 8.1 numbers (an 84% increase) in backward order. Daily variability continued to be evidenced by responses ranging from 4 and 9 digit responses. Consistent with the forward digit span task, of the three participants, Participant 2 demonstrated the greatest improvement in the backward digit span task.

Participant 3 was able to manipulate backwards combinations on average 2.9 numbers at baseline. Over the duration of the study, Participant 3 also improved as evident by the ability to manipulate 4.1 numbers on average (a 41% improvement) in backward order at study conclusion. Day to day variability was evidenced by the 3 to 5 digit ranges that were repeated correctly in backward order by Participant 3 over the duration of the study. The participant group on average manipulated 3.5 digits backward at baseline. The average increased to 5digits at study termination.

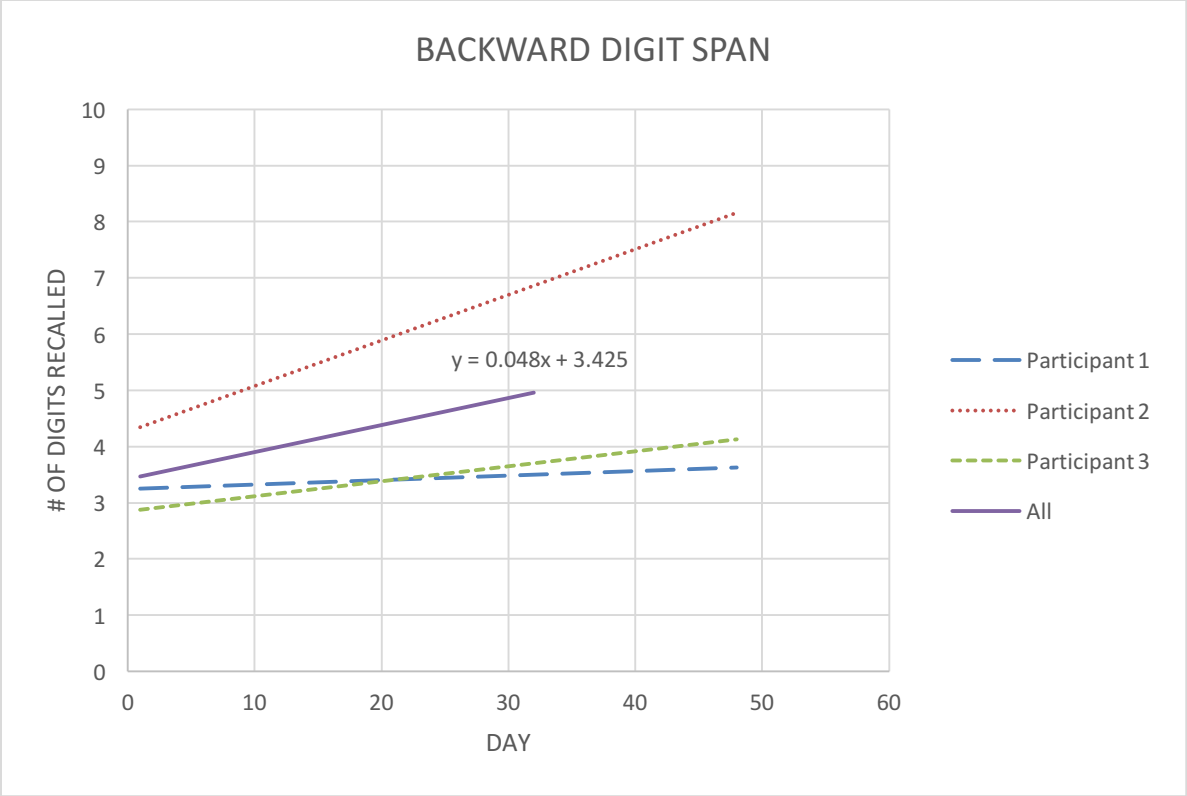

Figure 4: Backward Digit Span

Listening Span Test

Participants were instructed to listen to five short sentences and questions that required a "yes" or "no" answer. Each statement or question presented required an answer before moving to the next. While listening, they were instructed to remember the final word of each of the five sentences or questions. After the participant had heard all of the sentences or questions from the list and responded to each sentence appropriately, they were asked to recall the last word of each sentence or question stated. Results from the listening span task can be observed in Figure 5.

For two of the participants, the ability to recall the final word in each question improved over the trial; however, Participant 1did not improve. Daily variability varied significantly with responses ranging from 1 to 4 words. At final data collection, a very slight decline in ability to recall observed as recalled an average of 2.4 words.

Participant 2 was able to recall an average of 3.8 of the final words from the questions at baseline. Upon collection of final data, Participant 2 was observed to recall an average of 4.8 words (a 26% improvement). Participant 2's daily performance on the task ranged from 2 to 5 words recalled. Again, Participant 2 demonstrated the greatest improvement for the task.

At baseline, Participant 3 could recall an average of 1.8 words from the five questions. At study conclusion, Participant 3 could recall an average of 3 words (an improvement of 66%). Daily performance variability was again great with responses ranging between 1 and 4 words recalled. As a group, the participants averaged 2.5 words of five recalled at baseline. Final data collection revealed the group could recall an average of 4 words (a 60% improvement).

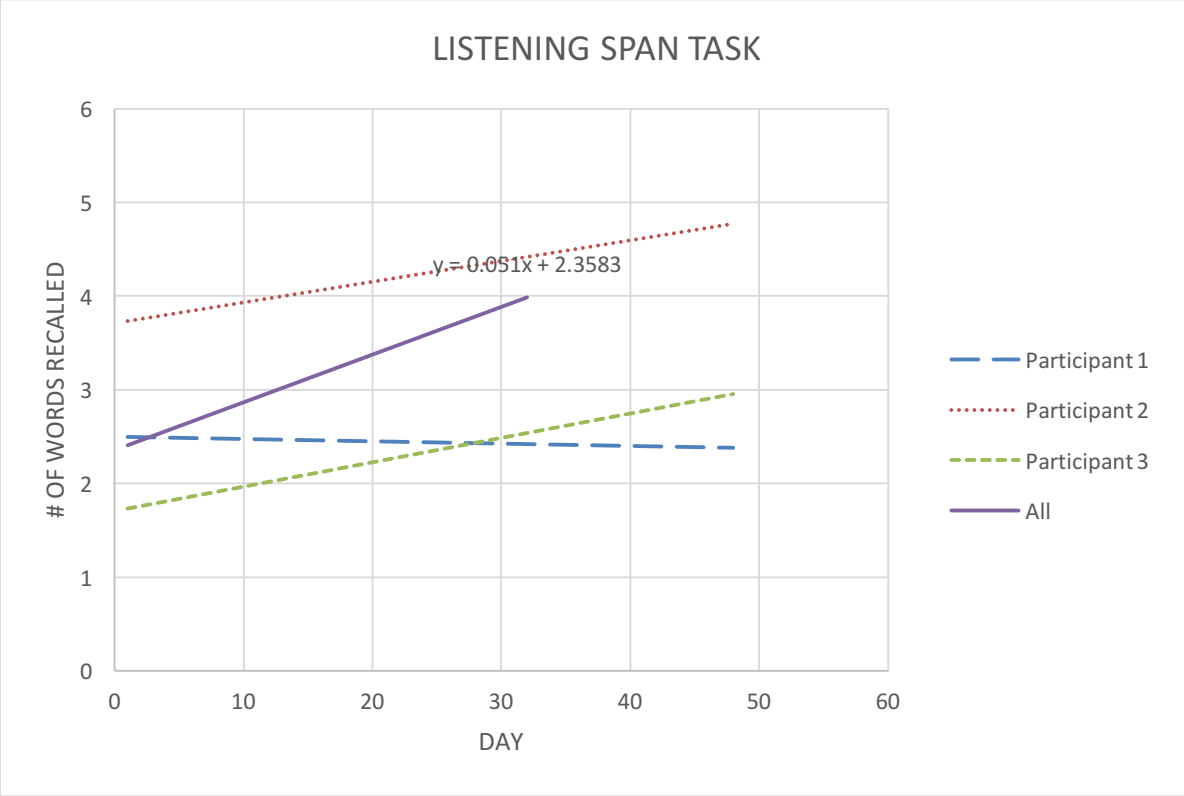

Figure 5: Listening Span Task

Peak Flow Rate

During the four treatment phases, the participants' vital capacity was measured using a peak flow meter. Three trials were collected and averaged each day. Although one participant saw a somewhat significant improvement in peak flow, the other participants' peak flow rates either diminished or were maintained as can be observed in Figure 6. The group average for baseline peak flow was 340 liters/minute (LPM), but by study conclusion the group average was 325 LPM. Upon admission to the study, Participant 1's vital capacity measured an average of 290 LPM. After the four month-trial, Participant 1's vital capacity was observed to diminish to an average of 255 LPM. Peak flow readings for participant 1 varied significantly on a daily basis, ranging from 200 LPM to 350 LPM

Participant 2 demonstrated peak flow maintenance over the four-month trial. At baseline, Participant 1's peak flow averaged 355 LPM. At study conclusion, Participant's 2's peak flow rate averaged 360 LPM. This participants peak flow rates varied from 310 LPM to 397 LPM throughout the study.

The participant demonstrating the greatest improvement in vital capacity was Participant 3. Upon collection of baseline data, a peak flow rate average of 310 LPM was observed. A gradual increase was observed over the trail. By study conclusion, Participant 3's peak flow rate averaged 365 LPM, an improvement of 18%.

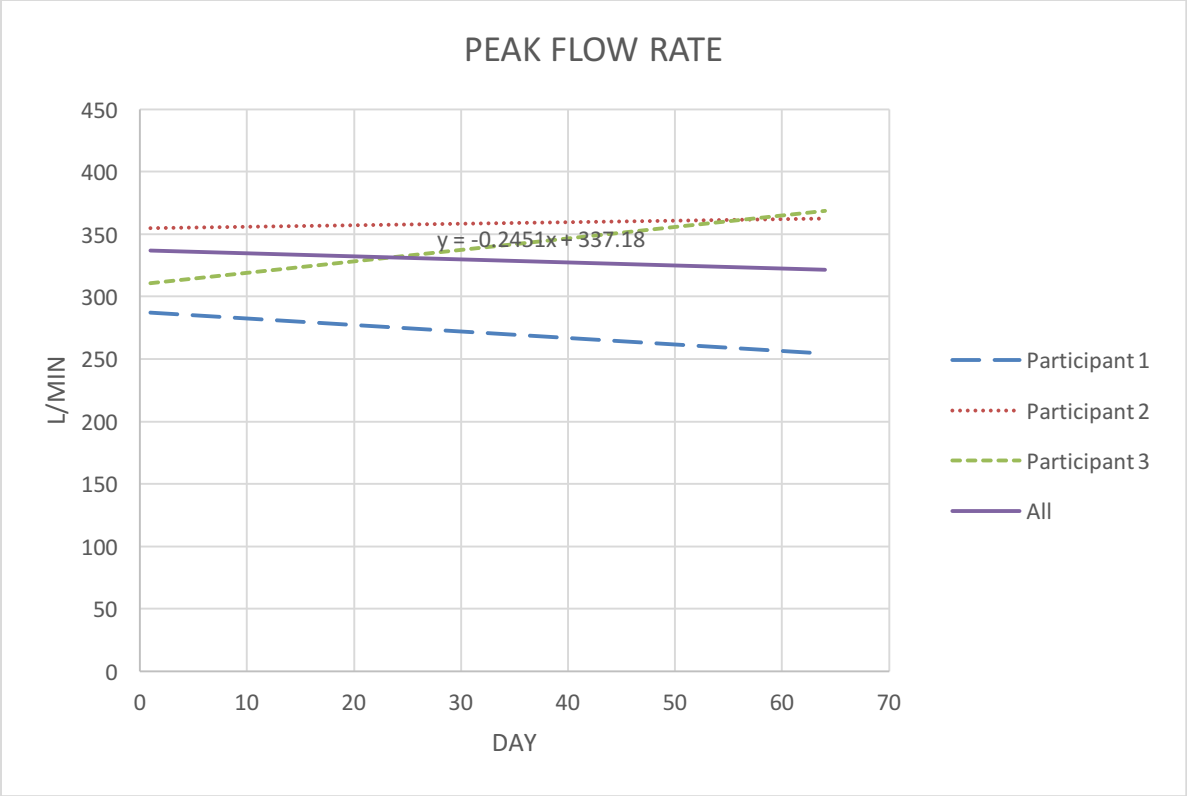

Figure 6: Peak Flow Rate

Mean Phonation Time

During the motor intervention, Treatment B, sustained phonation was calculated daily. Participants were asked to sustain the vowel "ah" for as long as their breath would allow five times. The average of each sustained phonation trial was calculated for each participate each day during Treatment B. As observed in Figure 7, both maintenance and improvement of mean phonation time (MPT) values were observed. Participant 1 began with a mean phonation time average of 12 seconds at baseline. Final data collection revealed neither improvement or decline, but maintenance of MPT at 12 seconds. Daily averages for Participant 1 were again highly variable, ranging from 6.9 to 15.3 seconds.

Participant 2 demonstrated an average MPT of 24 seconds at baseline. At study termination, Participant 2 had improved to an average MPT of 37 seconds. Daily averages

gradually increased overtime as treatment progressed. The highest average calculated for this participant was 43.6 seconds. Participant 2 demonstrated the greatest improvement in MPT during the study.

At baseline, Participant 3 demonstrated the ability to sustain a vowel an average of only 4 seconds. Upon final data collection, Participant 3's MPT, although still deficient, had increased to an average of 7 seconds (a 75% increase). Consistent with Participant 2, mean phonation time (MPT) gradually improved for Participant 3 as treatment progressed. The overall group average MPT was 13seconds at baseline. At study conclusion, the group average was 19 seconds, a 46% increase.

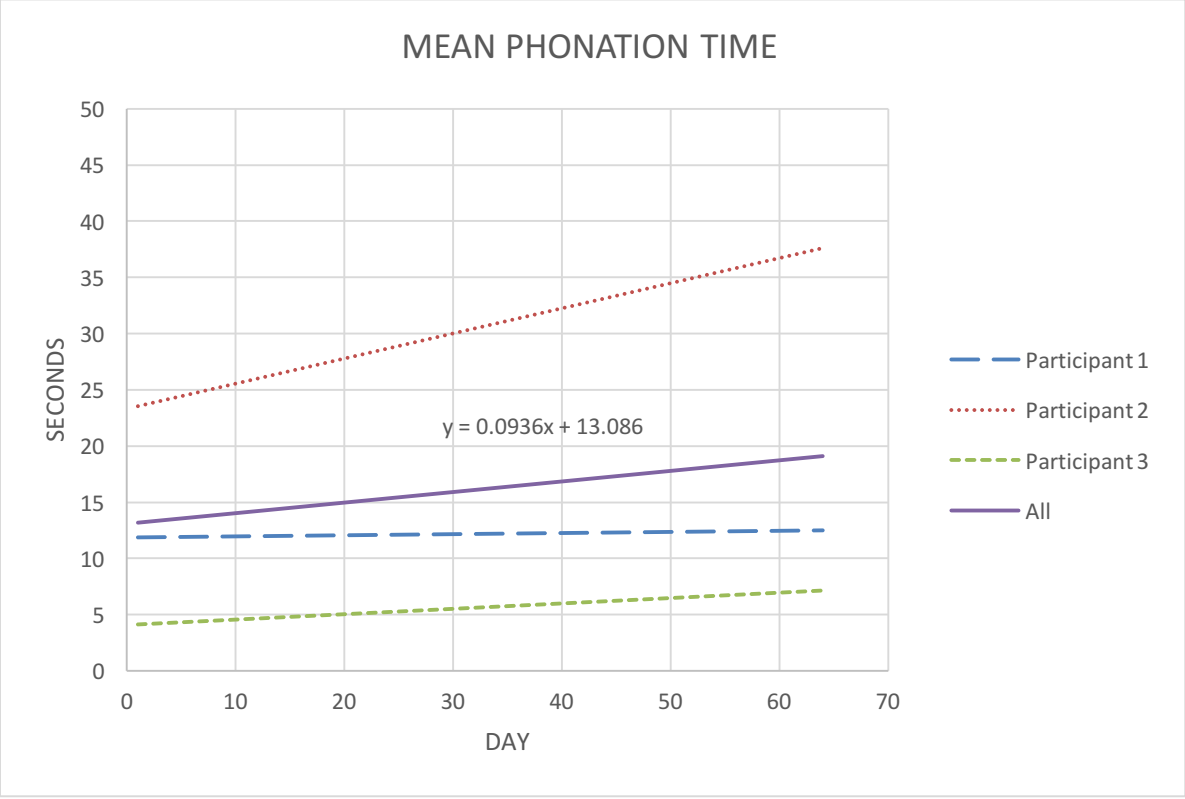

Figure 7: Mean Phonation Time

Diadochokinetic Rate: /ma/

Diadochokinetic (DDK) rate was measured to observe the speed and accuracy of movement of articulators. During the motor treatment portion of the study, Treatment B, "ma" was recorded and repeated rapidly for5 seconds. The number of single "ma" productions was counted and divided by the number of seconds sustained for production. As seen in Figure 8 below, Participant 1 showed a reduction over treatment in the DDK rate of "ma". Participant 1 produced an average of 3.9 "ma" productions per second. Following Treatment B, Participant 1 produced an average of 3.2 "ma" productions per second. Participant 1's daily variability was again great as evidenced by daily productions ranging from 2 to 4.9 productions per second.

Participant 2's DDK rate for "ma," at baseline averaged 5.9 per second. Improvement in DDK rate of "ma" was observed when final data were collected. Participant 2 was able to produce "ma" at a average rate of 7.5 productions per second (a 27% increase).

At baseline Participant 3 on average produced "ma" at a rate of 3.3 per second. At the conclusion of motor therapy, Treatment B, the DDK rate of "ma" was produced at an average of 4.5 productions per second (a 36% increase). The participants as a group produced "ma" at an average of 4.4 per second. Final data revealed that on average, the participants as a group increased slightly in the DDK rate for "ma". Post Treatment B, the group average was 5.1 per second (an average improvement of 15.9%).

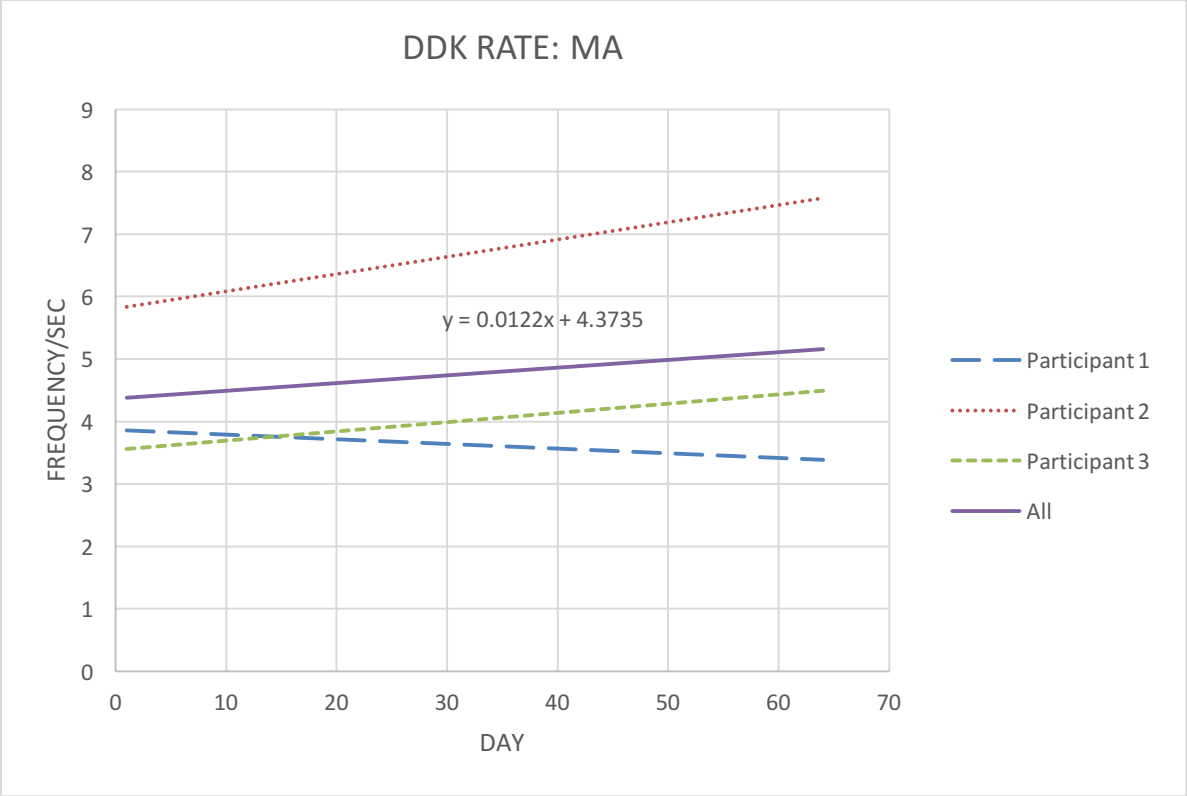

Figure 8: DDK Rate—MA

Diadochokinetic Rate: /la/

The number of single "la" productions were counted and divided by the number of seconds. As observed in Figure 9, Participant 1 produced "la," at the average rate of 3.4 productions per second at baseline. Post Treatment B, the production rate was unchanged at an average of 3.4 productions per second. Daily variability ranged from 2.81 to 5 productions per second.

At baseline Participant 2 produced "la" at an average rate of 4 per second. Improvement in DDK rate of "la" was observed when final data were collected post therapy with Treatment B, at which time Participant 2's average production rate was 5.8 per second (an increase of 45%).

Participant 3 on average produced "la" at a rate of 3.8 per second at baseline. At the conclusion of motor therapy, Treatment B, "la" was produced at an average of 3.5 productions

per second, an 8.5% reduction. The baseline group average for production of "la" was 3.6 per second. Although final data revealed an improvement in the group average to 4.2 productions per second, an improvement of 16.5%, the average is driven by the large improvement observed by Participant 2. Participant 1 maintained her baseline rate post treatment and Participant 3 demonstrated a reduction in rate post treatment.

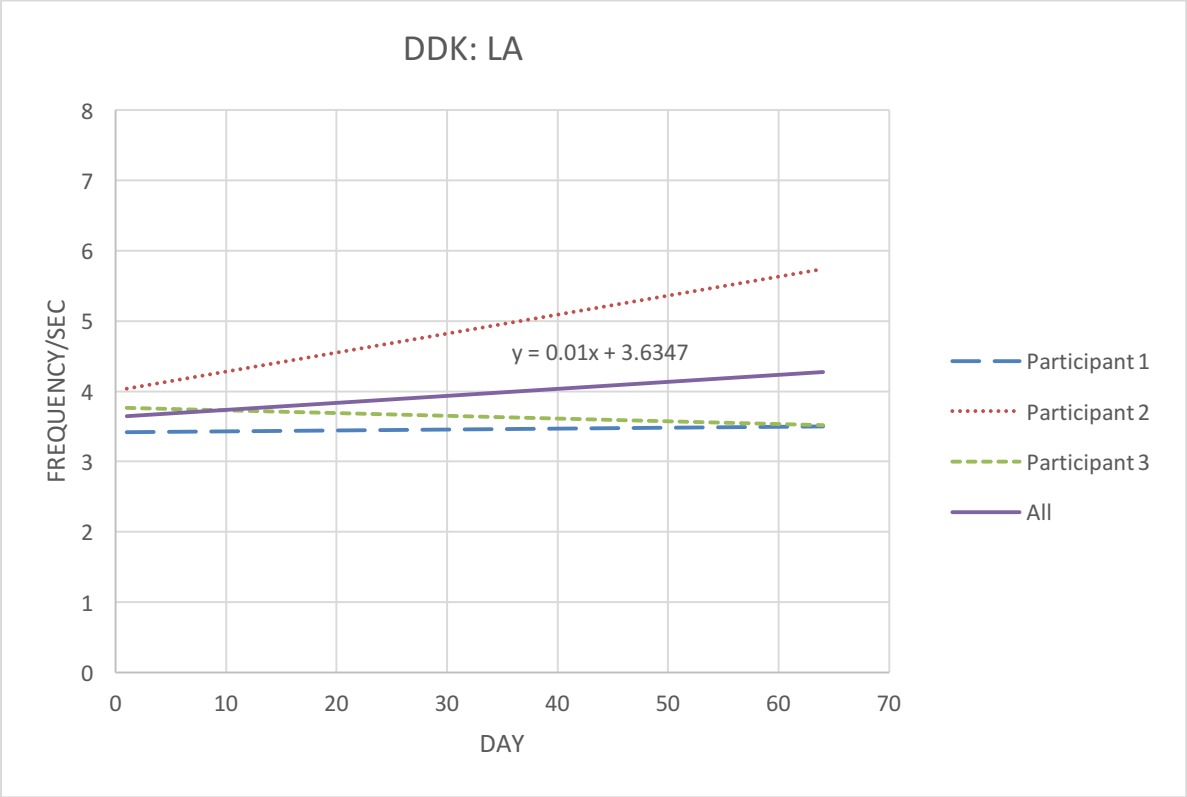

Figure 9: DDK Rate--LA

Diadochokinetic Rate: KA

As demonstrated in Figure 10, Participant 1 demonstrated a very slight (11%) improvement in the DDK rate of "ka," from the average of 3.6 syllables per second at baseline to an average of 4 per second post therapy with Treatment B. Participant 2 produced "ka" at an average rate of3.9 per second at baseline that improved to an average of 5.4 productions per second (a 38% increase) post-Treatment B. Participant 3 produced an average of 2.6 syllables per

second at baseline which improved to an average of 3.9 productions per second post-therapy. Participant 3's demonstrated a 50% improvement in production post therapy.

The baseline group mean DDK rate for “ka” was 3.3 per second. Final data revealed that on average, the participants as a group produced4.1syllables per second post-treatment. per second. Overall, the participants' ability to rapidly produce “ka” increased 24% with treatment.

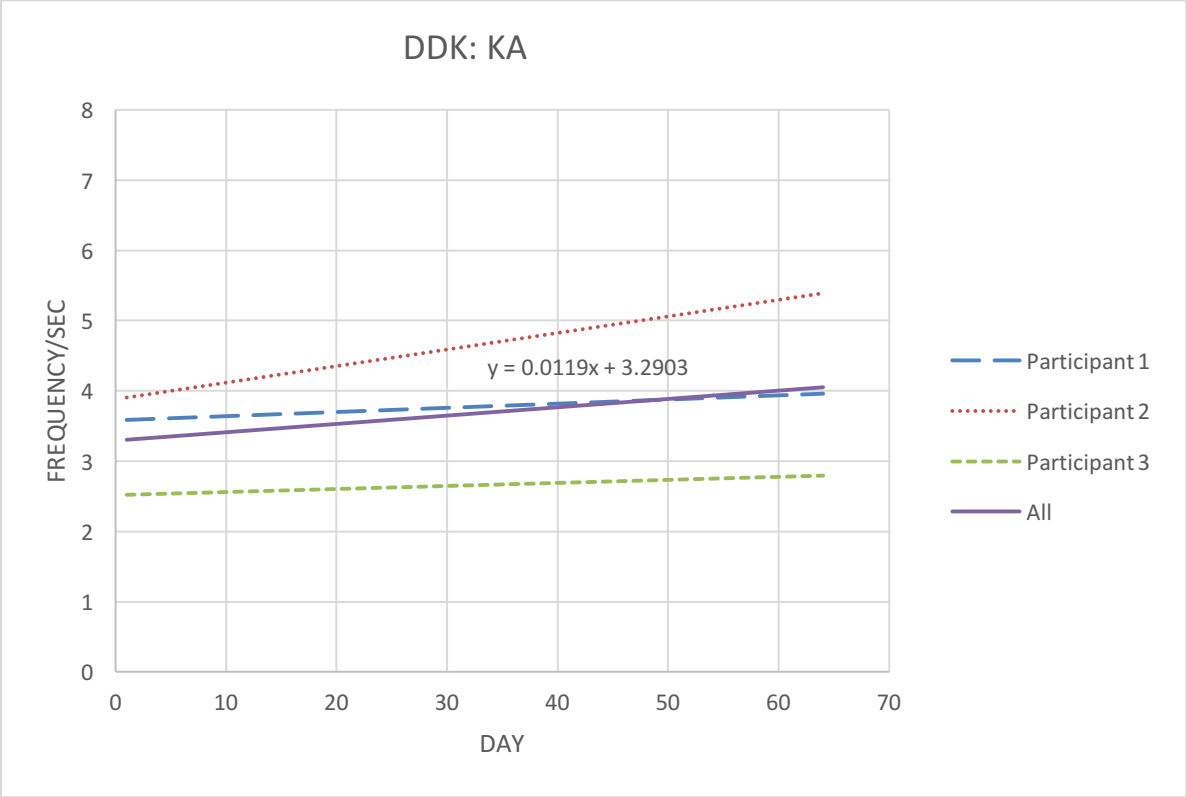

Figure 10: DDK Rate—KA

Diadochokinetic Rate: KALA

The CV sound combination, "kala" was calculated to demonstrate each participant’s ability to shift and coordinate the use of articulators while carrying out the task. As demonstrated in Figure 11, Participant 1 showed slight improvement in the DDK rate of “kala,” from a baseline average rate of 2.3 “kala” productions per second to a post Treatment B rate of 2.9 “kala” productions per second, a 26% improvement.

Participant 2 produced “kala” at an average rate of 2.8 per second at baseline. At the completion of Treatment B, the participant's production rate improved to an average of 3.7 productions per second. This represents a 32% improvement in production.

Participant 3 on average produced “kala” at a rate of 1.9 per second at baseline. At the conclusion of motor therapy, Treatment B, “kala” was produced at ~1.9 productions per second, demonstrating maintenance but not improvement.

The group mean for production of "kala" was 2.3 syllables per second at baseline. Final data collection revealed that on average, the participants produced “kala” at a rate of ~2.8 per second. The mean change equaled a 21.7% increase.

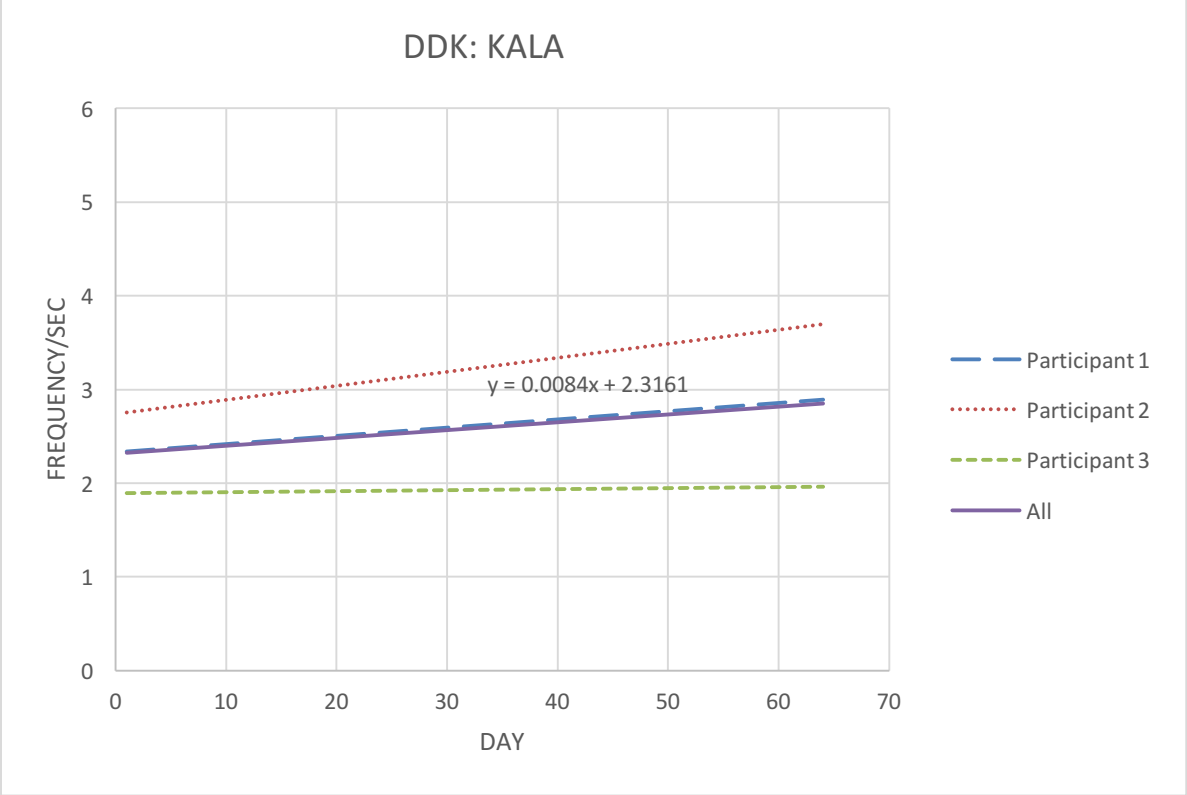

Figure 11: DDK Rate--KALA

Group mean percentage effect sizes and effect trend lines indicate that the participants as a whole demonstrated improvement in each cognitive task following treatment. As well the group appeared to experience motor improvement, but less so that was observed following cognitive treatment. In addition, peak flow, an index of vital capacity declined on average during the trial.

Cognitive Maintenance

Due the ABAB (treatment/withdrawal) design of the study a cognitive probe was measured daily to monitor for any change in cognition that might have occurred during the shift to Treatment B, motor therapy. As can be observed in Figure 12, cognitive improvement realized during Treatment A was observed to remain largely maintained during (motor) Treatment B for each of the participants with the exception of Participant 2. Both Participants 1 and 3 demonstrated a net improvement in forward digit span at study conclusion with no declination in forward digit span performance after withdrawal from cognitive therapy. Interestingly Participant 2, the participant who displayed the greatest treatment gains for most cognitive and motor variables, also displayed the predicted return to baseline following Treatment B, trial 2. It should be noted, however, that Participant 2 did not display the predicted gain in forward digit span performance post trial 1, Treatment A, cognitive therapy.

Participant	gender	AGE	D1 forward	D16forwar	D33forwar	D48 forward	D64 forward
1	F	31;11	4	5	5	7	6
2	F	39;10	8	7	8	10	8
3	M	73;2	5	5	5	6	8

Figure 12: Forward Digit Span Prob

CHAPTER V

DISCUSSION & CONCLUSION

Cognitive decline is a well-documented hallmark of the progressive disorder of Huntington's disease (HD). The literature documents that treatment of this disease is pharmacological in nature with scarce research indicating that behavioral intervention may also be beneficial. The primary focus of this study was to document any improvements in cognition in those with HD and those at risk for the disease when treated with a variety of cognitive and motor tasks over a four-month period. It was hypothesized that the cognitive exercises would improve ability in the area of verbal working memory. Such improvement would greatly enhance an individual's quality of life and independence. During the withdraw period from cognitive exercise, motor therapy was implemented. It was also hypothesized that the motor exercises might improve breath support, and such speech parameters as articulatory accuracy. A benefit of speech improvement can in some cases translate to improvement in swallow function.

This study was conducted as an ABAB design in which cognitive treatment was carried out for one month (sixteen sessions) before replacing cognitive exercise with motor tasks for a duration of 1 month. At the end of the second month, cognitive exercises were re-implemented before withdrawing for the fourth and final month of motor exercise. Baseline measures were taken at the beginning of each month and final data collected at the end of each month to track

Progress. A linear equation was created using the best fit line of the average results from all participants of the current study for the purpose of (visual) effect trends. The mathematical equation located on each of the graphs in earlier chapters may be used to predict or determine improvement and change in each of the measured variables over time in other participants. In addition, percentage effect sizes were calculated for each variable.

All participants screened were eligible for participation in the study. They each had an official diagnosis of the disease or were at risk for the disease and ranged in age from 31 to 73. Each participant was given the Mini Mental Status Exam (MMSE), Unified HD Rating Scale (UHDRS), a voice screening (i.e. prolonged vowel, s to z ratio), a peak flow reading, and a blood pressure screening. Direct instruction on each exercise—both motor and cognitive—was provided by the investigator during the sessions which were conducted through Skype and FaceTime. Sessions lasted no longer than 30 minutes in duration. At the conclusion of the four months, the MMSE, vocal screening, and cognitive exercise tasks were completed once again to document post-treatment data. In addition, a cognitive probe and a motor probe were conducted each of the 64 days therapy was delivered.

Primary Findings

The primary findings of the current study concluded that:

1. Cognitive treatment involving word recall, digit span, and listening span tasks improved the cognitive aspect of verbal working memory for the individuals participating in the study.
2. Breathing, oral motor, and glottal adduction exercises improved the motor function of the individuals participating in the study, but not to the extent observed following cognitive therapy.

3. Only one participant demonstrated the expected pattern of improvement in cognitive function followed by the declination in function during the withdrawal phase as measured by the cognitive probe.
4. Skype therapy was a viable option for those diagnosed with and those at risk for HD who participated in this study.

This is one of but a few studies documenting objective improvement in cognitive function following rehabilitation for individuals with HD(Cruickshank, 2015). In addition, improvement, albeit minimal, was observed in the (sham) motor condition variables. Since HD is a somewhat rapidly progressive disease, documentation of improvement in function over a period of 4 months is significant. A previously conducted study by Giddens et al. (2010) of rehabilitation in HD documented improvement in motor function during a 30-day trial; however, for fewer variables. In addition, the findings are exciting in that individuals with HD are often limited in their ability to travel to a clinic for rehabilitation. This study was conducted via tele-therapy and improvements using this means of therapeutic intervention were apparent. All sessions with the exception of baseline data collected and consent into study were conducted via Skype and FaceTime. This finding offers a degree of optimism to people with an otherwise hopelessly progressive condition. Individuals with HD who can no longer walk or drive can still have access to rehabilitation and from the comfort of their homes or places of work. as the case may be.

Directions for Future Study

The small sample size of the current study unfortunately weakens the generalizability of the study findings to the HD population as a whole. Because HD is a rare disease, the availability of participants for the study was limited. The study should be replicated on a larger sample size. In addition, social engagement and perhaps an increased motivation to improve associated with daily treatment may have had an effect that was beneficial to the overall

performance of the participants. There was no way to determine if such interaction had a significant impact on the observed improvements.

Of the three participants in the study, only two had an official HD diagnosis. The remaining participant was at risk and had displayed chorea for several years. However, without an official diagnosis of the disease, it is difficult to (officially) generalize that participant's improvement or declination in function to the HD population in general.

In addition, several other aspects of each participant's life should be taken into consideration when analyzing and determining the results. Medication could have greatly affected the results of treatment. Participant 1 did not report being on any type of medication prior to or during treatment. Participant 2 reported being on an anti-depressant medication as well as medication to address attentional deficits related to HD-associated attention deficit. Such medication could have greatly impacted the long term results as well as data gathered on a day to day basis. Lastly, participant 3 reported that he began taking Tetrabenazine for chorea early in the study. This could be hypothesized to have depressed his cognitive function during the study.

In addition to medication an additional aspect which may have affected the results may have been degree of daily activity. The participant's social lives and activity levels varied. Two participants were home during the day, one being a homemaker and the other a retiree. The remaining participant is a fully-employed professional. Daily involvement can greatly reduce the feelings of isolation that contribute to depression, which can greatly alter cognitive function. It should be noted, however, that all the participants lived with and were very involved with family, attended church regularly, and also regularly saw friends outside the home (e.g. went out to dinner). However, the participant who demonstrated the most significant improvement was the individual who worked outside the home full time.

In addition, the participant sample consisted of individuals who varied significantly in age and severity of the disease. The senior participant might not have been expected to improve to the degree observed by the other two participants. The age range employed in this study may, however, improve the generalizability of the study findings to the HD population as a whole.

Counting diadochokinetic (DDK) rates via tele-therapy may have added an element of subjectivity to the DDK rate findings of the study. Visual signal breakdown, although rare, did impact the ability for participants to properly see, hear, and replicate the investigators during some of the DDK instructions. In future studies, recorded sessions for ensuring objective measurement of DDK rates might be beneficial. Although face-to-face (in person) therapy is preferable to Skype and FaceTime connections that are susceptible to connection failure, the method appears to be the most viable option for service delivery to most individuals with HD. As such, this 4-month trial may be a landmark study documenting the utility of such.

In summary, cognition improved for most-to-all participants for most of the aspects treated. Such improvement can greatly enhance social and communicative abilities of people in this population. In addition, motor function improved, but the improvement was not significant as contrasted with that observed in the cognitive domain. The participant who demonstrated the greatest improvement in both domains is engaged in full-time professional work and takes medication to reduce attention deficit. As such, perhaps behavioral therapy is best conducted as adjunctive to pharmacological treatment of HD. The current wisdom that cognitive function is best preserved in those maintaining both physical and mental activity is borne out in this sample of individuals with HD. The findings serve as an exciting beginning to learning more about how best to serve the HD population in terms of remediation of cognitive and motor deficits.

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APPENDICES

Oklahoma State University Institutional Review Board

Date:	Tuesday, September 13, 2016
IRB Application No	#Type!
Proposal Title:	Rehabilitation in Huntington's disease and those at risk for Huntington's disease
Reviewed and Processed as:	Expedited

Status Recommended by Reviewer(s): Approved Protocol Expires: 9/12/2017

Principal Investigator(s):

Jessica Grace
Stillwater, OK 74078

Cheryl L. Giddens
042 Murray
Stillwater, OK 74078

The IRB application referenced above has been approved. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

☐ The final versions of any printed recruitment, consent and assent documents bearing the IRB approval stamp are attached to this letter. These are the versions that must be used during the study.

As Principal Investigator, it is your responsibility to do the following:

1.Conduct this study exactly as it has been approved. Any modifications to the research protocol must be submitted with the appropriate signatures for IRB approval. Protocol modifications requiring approval may include changes to the title, PI advisor, funding status or sponsor, subject population composition or size, recruitment, inclusion/exclusion criteria, research site, research procedures and consent/assent process or forms
2.Submit a request for continuation if the study extends beyond the approval period. This continuation must receive IRB review and approval before the research can continue.
3.Report any adverse events to the IRB Chair promptly. Adverse events are those which are unanticipated and impact the subjects during the course of the research; and
4.Notify the IRB office in writing when your research project is complete.

Please note that approved protocols are subject to monitoring by the IRB and that the IRB office has the authority to inspect research records associated with this protocol at any time. If you have questions about the IRB procedures or need any assistance from the Board, please contact Dawnett Watkins 219 Scott Hall (phone: 405-744-5700, dawnett.watkins@okstate.edu).

Sincerely,

Hugh Crethar, Chair
Institutional Review Board

Figure 13: IRB Approval

VITA

Jessica Layne Grace

Candidate for the Degree of

Master of Science

Thesis: REHABILITATION IN HUNGTINGTON'S DISEASE AND THOSE AT RISK FOR HUNTINGTON'S DISEASE

Major Field: Communication Sciences & Disorders

Biographical:

Education:

Completed the requirements for the Master of Science/Arts in Communication Sciences and Disorders at Oklahoma State University, Stillwater, Oklahoma in May 2017.

Completed the requirements for the Bachelor of Science/Arts in Communication Sciences and Disorders at Oklahoma State University, Stillwater, Oklahoma in May 2015.

Experience:

Graduate Teaching Assistant
Graduate Advisor for Alpha Sigma Phi Fraternity
Huntington's Disease Society of America Education Day Presenter
OSU's Grandparent's University AAC Presentation Presenter
Master's Thesis Presentation
Huntington's Disease Treatment Program
Aviation Research Program
Extern at Will Roger's Elementary
Extern at Integris Jim Thorpe Outpatient Rehabilitation
Graduate Clinician at the OSU Speech-Language-Hearing Clinic

Professional Memberships:

OSU NSSLHA
National NSSLHA