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Exploring the Use of the Bimanual Arm Trainer for Improving Upper Extremity Motor Function in Stroke Patients.

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Dedication

This dissertation is dedicated to my family for their prayers, love, and support. I simply could not have done it without all of you.

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ABSTRACT

Background and purpose

There are few evidence-based treatment options to address recovery in patients with severe upper extremity impairment post-stroke. Although robotic treatment options have been widely explored with variable outcomes, the contribution of bimanual training to improve upper extremity control and coordination has not yet been fully explored. To date, the mirrored motion Bimanual Arm Trainer (BAT) has not specifically been investigated for its effectiveness in stroke patients. This study explored the usefulness of the bimanual arm trainer in improving upper extremity function in stroke patients with severe deficits and its impact on quality of life.

Methods

Twenty-three patients poststroke underwent 1 hour of training over 12 sessions provided two to three times a week on the bimanual arm trainer. The training consisted of bimanual simultaneous movements interspersed with unimanual affected arm training using the bimanual arm trainer (Mirrored Motion Works, Inc.). The Fugl- Meyer Assessment of Motor Recovery after Stroke (FMA-UE), the streamlined Wolf Motor Function Test (WMFT), the Stroke Impact Scale (SIS), and the Modified Rankin Scale (MRS- SI) were assessed pre and post intervention.

Results of study

Upper extremity arm motor impairment as measured by FMA-UE showed statistically significant change from Pre1 (M = 23.59, SD = 10.11) to Pre-2 (M = 25.00, SD = 10.57) to post bimanual arm training intervention (M = 27.45, SD = 10.22). The mean increase was 3.86, 95% CI [-1.68, -6.05], p <0.005. Upper extremity arm function as measured by the streamlined Wolf Motor Function Test showed statistically significant change from Pre-1 (M = 10.48, SD = 3.34) to Pre-2 (M = 11.10, SD = 3.29) to post bimanual arm training (M = 12.90, SD = 3.58). The mean

increase was 2.43, 95% CI [-1.45, -3.41], $p < 0.005$. The stroke impact scale did not show statistically significant change from Pre1 ($M = 213.52$, $SD = 21.04$) to Pre2 ($M = 215.30$, $SD = 21.65$) to post-intervention ($M = 220.17$, $SD = 19.46$; $F(2, 44) = 2.47$, $p > 0.05$). However, a paired samples t-test comparing SIS post intervention (220.97 ±19.46) to the Pre1 (213.52 ±21.04) showed a statistically significant increase of 6.652 (95% CI, -12.933 to -.371), $t(22) = 2.196$, $p < 0.05$).

The Modified Rankin Scale did not change from Pre1 ($M = 2.05$, $SD = 0.29$) to Pre2 ($M = 2.05$, $SD = 0.29$) to post-intervention ($M = 2.05$, $SD = 0.29$).

Discussion and conclusion

Both measures of upper extremity motor impairment and function indicated a significant increase with only 12 sessions of bimanual arm training using the bimanual arm trainer as a treatment intervention. However, although function improved, participants' perceptions of changes in quality of life were not observed, perhaps because the changes were not yet assimilated into daily life activities to impact quality of life.

Chapter I: INTRODUCTION

Stroke is the fifth leading cause of death in the United States (Mozaffarian et al., 2016). The World Health Organization (WHO) defines a stroke as "rapidly developing clinical symptoms and signs of focal, at times global, loss of cerebral function leading to death with no apparent cause other than that of vascular origin" (Hatano, 1976). Stroke reduces the blood supply to the brain and causes cell death, which leads to loss of bodily functions and mortality. Approximately 795,000 people experience a new or recurrent ischemic or hemorrhagic stroke every year in the US, which equates to a cerebrovascular event every 40 seconds and a stroke-related death approximately every four minutes (Mozaffarian et al., 2016).

In the past fifty years, the incidence of stroke and mortality rates in the US have shown regional variation. The highest rates of mortality have been observed in the southeast, a region known as the "Stroke Belt" (Borhani, 1965; El-Saed et al., 2006; Lanska, 1993; Lanska & Kryscio, 1994; Pickle, Mungiole, & Gillum, 1997), where the rates are approximately 20% higher than the national average. The stroke buckle is a region within the stroke belt comprising the coastal plains of North Carolina, South Carolina, and Georgia, with approximately 40% higher mortality rates when compared to the rest of the country. While the factors contributing to this regional phenomenon are poorly understood (Howard et al., 1997; Howard et al., 1995; Howard et al., 2001), a study conducted by Howard et al. (2011) suggests that the regional differences in the mortality rates could be due to a higher rate of stroke incidence in these regions. Additionally, access to timely stroke care may also be a factor in post-stroke outcomes, especially in rural areas (Carr, Branas, Metlay, Sullivan, & Camargo, 2009; Khan, J. A. et al., 2001; Leira, Hess, Torner, & Adams, 2008).

Despite the alarming incidence rate, stroke mortality in the US has declined in the past few decades. Between 2003 and 2013, stroke death rates showed a downward trend; the death rate decreased by 54.1% in those ≥65 years old, by 53.6% among those aged 45 to 64 years, and by 45.9% in those aged 18 to 44 years (Mozaffarian et al., 2016). The decrease in mortality rates can be attributed to advances in management, treatment, and prevention strategies that are currently being used in combating stroke. The main goal of stroke treatment is the expedient restoration of blood supply to the affected parts of the brain in addition to limiting the extent and severity of the damage. In patients with ischemic stroke, the timely restoration of blood flow to the brain by rapid and appropriate administration of the recombinant tissue-type plasminogen (rTPA) has proven to decrease morbidity and improve functional outcomes (Jauch et al., 2013). Endovascular surgery performed with stent retrievers in combination with rTPA recanalize the blood vessels affected by stroke (Powers et al., 2015). Secondary prevention strategies like control of diabetes mellitus, high cholesterol, smoking cessation programs, and aggressive hypertension treatments initiated in the 1970s have also led to the decreased incidence of stroke (Mozaffarian et al., 2016).

Despite the significant progress that has been made to reduce stroke mortality, projections for stroke prevalence between 2012 and 2030 are set to increase, based on data from 1999-2008 National Health and Nutrition Examination Survey (NHANES) and the US Census ("National Health Interview Survey," 2016; "Population Projections," n.d.). It is estimated that by 2030 nearly 4% of the population in the US will have suffered a stroke, which roughly equates to 3.4 million additional people (Ovbiagele et al., 2013). By the year 2050, the number of people above 65 who will have suffered a stroke is expected to grow from 34 million (2000) to 90 million.

Data suggests that the risk of stroke incidence increases every year by 9% in men and 10% in women (Asplund et al., 2009). The projected stroke prevalence is the greatest for people aged 45-64 years old (5%). This age group represents about one-third of all stroke survivors, which amounts to 1.3 million of the estimated 4.1 million people (Levine et al., 2007). In addition, increased incidence has been linked to lack of health insurance and lower medication affordability among people who are between 45 and 64 (Ovbiagele et al., 2013).

The direct and indirect costs of caring for patients who experience a stroke are astronomical. The direct costs include medical and nursing care needs, and the indirect costs are loss of productivity, earnings, and household productivity loss, which is defined as the loss of pay for services performed by family members (Asplund et al., 2009; Wright 387-389; "A Nationwide Framework for Surveillance of Cardiovascular and Chronic Lung Diseases," 2011). According to a policy statement issued by the American Heart Association (AHA) and the American Stroke Association (ASA) in 2013, stroke care constitutes greater than 10.7% of the Medicare budget and greater than 1.7% of the National Health Expenditure which does not include nursing home care (Trogdon, Finkelstein, Nwaise, Tangka, & Orenstein, 2007; Go et al., 2013; Cohen & Krauss, 2003). The projected direct medical cost is estimated to triple from 71.55 billion dollars to 184.13 billion between 2012 and 2030, and within the same period the indirect cost of health care is projected to increase 68% from 33.65 billion dollars in 2012 to 56.54 billion (Ovbiagele et al., 2013). The burden of stroke-related care is projected to be the fourth highest when compared to other diseases in 2020 as measured by disability-adjusted years of life (López, Murray, & Harvard School of Public Health, 1996).

Background of the Problem

Stroke is the leading cause of disability in the US, most commonly due to hemiplegia or weakness on one side of the body (Ovbiagele et al., 2013). A stroke may damage the motor cortex, premotor cortex, subcortical motor tracts, and/or other areas of the brain leading to sensory and proprioceptive deficits and/or weakness, manifested as decreased voluntary production of movement, loss of motor control, loss of coordination of fingers and hands, and compromised dexterity. These changes cause muscle shortening, and loss of function (Pollock et al., 2014). In the acute phase post-stroke, approximately 70% of individuals exhibit some form of upper extremity paresis (Nakayma, 1994), which lingers beyond six months post-stroke in over 65% of individuals, limiting the use of the upper extremity in functional tasks (Vega-Gonzalez, Bain, & Granat, 2005). Upper extremity weakness leads to decreased use of the paretic arm, up to 3-6 times less, when compared to the non-involved arm (Alberts & Wolf, 2009). Decreased use of the paretic arm in turn leads to long-term dependence in Activities of Daily Living (ADL) in 25-74% of individuals surviving a stroke (Miller et al., 2010).

Stroke care begins in the hospital with an accurate diagnosis followed by admission to a stroke unit where the median length of stay is four days for patients with ischemic stroke (Bettger et al., 2013). During the acute care hospital stay, the primary focus is stabilizing the patient. Data strongly suggests initiating multidisciplinary rehabilitation, which includes OT/ PT /SLP as soon as the patient can tolerate it (Miller et al., 2010). Following the acute care hospital stay, patients transition to post-acute care services for further rehabilitation. These services can be provided at an inpatient rehabilitation facility (IRF), a skilled nursing facility (SNF), at outpatient physical therapy centers, or at home. Individuals who have suffered a stroke in the USA stay an average of 16-17 days in acute inpatient rehabilitation (Dobkin, 2005; Dejong,

Horn, Conroy, Nichols, & Healton, 2005). This length of stay, which is often determined by insurance companies' policies for post-stroke rehab in IRFs, is often inadequate given the complex needs of these patients (O'Brien, Xue, Ingersoll, & Kelly, 2013) and the expectation that patients will return home following rehabilitation. Hence rehabilitation teams in the IRFs are focused on patients' safe return home: this focus inadvertently, out of necessity, places more emphasis on ambulation, stair training, and transfers. Although occupational therapists focus on upper limb rehabilitation and ADL training, upper limb rehabilitation is largely achieved using adaptive equipment and compensatory strategies to quickly restore function and return home safely. As part of the interdisciplinary healthcare team, physical therapists also see the need for training the upper limb to promote functional independence but given the decreased length of time spent by patients in IRF's less time is being spent rehabilitating the upper limb in physical therapy (West & Bernhardt, 2012). Hence, it is not surprising that only 5-34% achieve full upper limb function (Nijland, Wegen, Wel, & Kwakkel, 2010; Kong, Chua, & Lee, 2010).

Most ADLs, including donning clothes, tying shoelaces, bathing, etc., require the skillful and cooperative use of both upper extremities. When patients do not regain adequate paretic upper limb function post-stroke, ADLs are usually achieved by using compensatory movement and/or with the use of adaptive equipment or assistance from another person. While such compensatory strategies may allow for the completion of many ADL tasks, the movements used to produce these tasks may be inefficient and lack fluidity and promote "learned bad use" (Raghavan 2015).

Interestingly, studies have shown that post-stroke, the ability to coordinate both upper limbs is partially retained (Harris-Love, Waller, & Whitall, 2005; Rose & Winstein, 2005). In an observational study, Michielsen et al., (2012) observed that patients use their paretic upper limb

almost exclusively in bimanual activities, although at a much lower capacity. This finding reflects what we observe in healthy adults as they tend to use both hands in functional tasks more frequently than they would either of their hands alone (Rinehart, Singleton, Adair, Sadek, & Haaland, 2008; Kilbreath & Heard, 2005; Stone, Bryant, & Gonzalez, 2012). To restore functional movements needed to successfully and efficiently execute ADLs in individuals' post-stroke, treatment should focus on rehabilitating and retraining bilateral upper extremities in order to restore patients' ability to perform ADLs and decrease their need for assistance.

The manner and type of services received following a stroke in the US vary based upon numerous factors ranging from finances, region of the country in which they receive services, age etc. With the ongoing federal changes to health care, which are currently focused on episodes of care, large-scale changes in the delivery of stroke care are inevitable (National Forum 2009) and may result in further decreases in intensive and comprehensive therapeutic services post stroke. While rehabilitation of the upper extremity is initiated during the patient's IRF stay, the bulk of their upper extremity rehabilitation occurs post discharge from the IRF during their services at SNFs, outpatient services, and at home. Given the limited number of outpatient visits provided by the insurance companies in a calendar year, or for a given condition if progress is not observed, or if patients can successfully address their needs via the use of an assistive device, patients often cannot engage in effective rehabilitation of their upper extremities.

In order to facilitate ongoing rehabilitation of the paretic upper extremity needed to impact functional change, emphasis needs to be placed on developing therapeutic techniques that can be used in the hospital, community or at home by the individual without constant oversight of a therapist. Upper limb robotic training devices continue to be investigated for their ease of

application, their interactive intention driven therapy, and their ability to provide high-intensity interactive training (Krebs, 2018). However, their potential for long-term independent use by individuals is often not possible due to potential safety risks of an external agent controlling the arm. However, with bimanual training, especially when the less affected arm is driving the movements of the more affected or paretic arm, these risks are mitigated. The central hypothesis of this current research is that simultaneous bimanual practice of homologous movements, assisted with a specially designed mechanical device, the Bimanual Arm Trainer (BAT), will improve motor control and function in the paretic upper extremity post stroke. This hypothesis was tested in the sub-acute and chronic phases of stroke recovery.

Theoretical Framework

Stroke causes irreversible damage to the motor cortices, which precipitates a loss of motor control (Nudo, 2006). Spontaneous return of upper extremity motor function is noted in less than 15% of stroke patients (Hendricks et. al, 2010). Therefore, in about 85% of stroke patients, functional motor recovery following stroke is dependent on plasticity, which is the ability of the brain to rewire itself to restore functional ability. Various areas of the cerebral cortex are specialized for processing, transmitting, and receiving information. However, when damage occurs to one functional area of the brain, other cortical areas retain the ability to reorganize and develop new functions. This type of reorganization is the primary mechanism by which functional recovery occurs post-stroke (Rossini et al., 2007). Neurorehabilitation to improve motor function in patients post stroke is dependent on physiological and anatomical plasticity (Nudo, Wise, Sifuentes, & Milliken, 1996; Taub, Uswatte, & Elbert, 2002).

The term plasticity was first used over a hundred years ago. Several scientists have been credited with both defining the term and for its usage in the medical literature. William James

(1906), in “The Principles of Psychology,” has been credited for adopting the term plasticity with reference to establishment of habits in the nerve pathways. Ernesto Lugaro, inspired by his teacher Eugenio Tanzi’s hypothesis of learning and memory put forward in 1893, is considered responsible for introducing the term the neuroplasticity. Tanzi proposed that specific learning or repetitive practice could produce hypertrophy in a neuronal pathways to enable learning, and even functional recovery after brain damage (Berlucchi & Buchtel, 2009). Hebb (1949) proposed that activity may change the effectiveness and strength of specific synapses.

Building on these initial thoughts, investigators have determined that several factors contribute to post-stroke neuroplasticity (Berlucchi & Buchtel, 2008). Synaptic changes including denervation hypersensitivity, synaptic hyper-effectiveness, and unmasking of silent synapses occur to help restore neurotransmitter synthesis and transport (Obata & Noguchi, 2006; Poncer, 2003; Kerchner & Nicoll, 2008). Studies on brain-derived neurotrophic factor (BDNF) have supported the role of genetics in neuro-recovery both post-stroke and post-brain injury. BDNF has been shown to have a strong role in CNS plasticity and repair and in motor map reorganization (Siironen et al., 2007). Research in neurogenesis is currently being performed to develop novel therapies to encourage the growth of new neurons. Stem cells are being investigated for their ability to remodel following neurological injuries such as stroke (Kernie & Parent, 2010). A meta-analysis conducted by Rossini et al. (2008) analyzed changes in neural representations post stroke using TMS, fMRI, PET, and SPECT, and concluded that focused rehabilitation of the upper extremity produced neuroplastic changes in chronic stroke patients. Behavioral experiences can influence brain reorganization by enhancing synaptic efficacy, dendritic growth, and blood supply. Experiences that have shown to have positive effects are constraint-induced therapy, skill training and behavioral compensation (Jones et al., 2008).

Interesting research outside of the rehabilitation arena, in the areas of pharmacotherapy, nervous system stimulation, stem cell research, neuroprosthetics, and rehabilitation, are being conducted concurrently to improve plasticity and predict functional outcomes post stroke (Dimyan & Cohen, 2011). It is anticipated that in the near future new technologies such as noninvasive ultrasound and optogenetics may be able to offer additional insight into studying and enhancing neural plasticity (Miesenbock, 2009, Tufail et al., 2010). Most notably, post-stroke neurogenesis has been demonstrated in caged rodents. The translation of rodent research to neurogenesis in the adult human brain is particularly tricky as the neurogenesis in the adult brain is subject to modification by the environment. Nevertheless, research in rats may offer impressive insights into this process (Ohab & Carmichael, 2008).

For decades rehabilitation of the upper extremity has been geared towards muscle strengthening, neuromuscular re-education, and functional training of the impaired arm (Bütefisch, Hummelsheim, Denzler, & Mauritz, 1995; Sunderland et al., 1994; Davies, 1985). Clearly, restoring upper limb function in patients post stroke requires skillful integration of key concepts of motor learning and motor control into treatment protocols. Theories on motor control continue to evolve as our knowledge of the nervous system expands. These ever-evolving theories provide a framework for understanding how learning and relearning of skilled movements occur in both normal and damaged nervous systems (Muratori, Lamberg, Quinn, & Duff, 2013). Motor learning happens in humans as a result of practice and experience. Motor learning comprises motor adaption, skill acquisition, and decision-making (Krakauer, 2006, Krakauer & Mazzoni, 2011). Motor learning can be affected by neurological injury. Studies have shown that damage to the cerebellum impairs motor adaptation (Morton & Bastian, 2007), however in Huntington's and Parkinson's disease, motor adaptation seems to be relatively intact

(Smith & Shadmehr, 2005; Contreras-Vidal & Buch, 2003). Studies on motor adaptation in patients post-stroke have yielded mixed results due to the heterogeneity of stroke patients. However, few studies have shown that motor learning is preserved in patients post stroke (Scheidt & Stoeckmann, 2007), nevertheless the extent to which motor learning is affected in stroke patients is still under debate. Neurorehabilitation of stroke patients is based on the concept that motor learning principles can be applied to an injured brain to promote function. It is also important to consider the role of spontaneous recovery and the type of motor learning that is being enhanced (functional compensation versus the recovery of impairments) to restore function in the extremities (Kitago & Krakauer, 2013).

Significance of the study

The projected costs of stroke-related disability, both direct and indirect, are estimated to rise above 200 billion dollars between 2012 and 2030. Six months post stroke over 65% of the patients are unable to perform their ADLs, due to persistent upper extremity motor impairment, which leads to long-term dependence on caregivers. Many patients with chronic stroke, whose deficits impacted their lives and level of independence, have exhausted their access to outpatient rehabilitation services and yet are looking for ways to continue their recovery process. These patients are younger and are very motivated to continue to recover from their stroke. Although traditional physical and occupational therapy has been effective in helping restore patient's upper extremity function, it can be expensive, time consuming, and in some cases very arduous to get to these clinics. There seems to be some consensus in the literature that, in order to enhance neuroplasticity in the injured brain, repetition and practice are essential. However, studies show that considerably fewer total movement repetitions are performed in typical rehabilitation sessions than is required for neuroplastic changes to occur (Kimberley et al., 2010). Hence

rehabilitation professionals must find creative solutions for facilitating more practice by allowing longer sessions each day, and/or multiple sessions to maximize repetition. The use of a passive mechanical bimanual training device such as the Bimanual Arm Trainer can achieve this by providing an efficient, organized way to reliably maximize repetitions. By incorporating both upper extremities in synchronous movement, the BAT may improve bilateral upper limb coordination and function. The device can also provide auditory stimuli and visual stimuli during training to enhance sensory-motor plasticity and reorganization. Furthermore, the BAT may improve motor learning by promoting movement initiation and providing lots of repetition along with guidance and feedback, all within a very interactive video gaming environment. Although we know in theory that the BAT can provide high-intensity interactive therapy based on motor learning principles and thus supports the tenets of neuroplasticity, its effect on improving functional outcomes directly in chronic stroke patients has not been studied.

Chapter II: LITERATURE REVIEW

Stroke causes weakness (paresis), which impairs the ability of muscles to generate force (Boissy, Bourbonnais, Kaegi, Gravel, & Arsenault, 1997; Lang, 2004), and move the joints in a coordinated manner leading to the development of abnormal synergy patterns (Dewald, Pope, Given, Buchanan, & Rymer, 1995). Both the impairment in force generation and coordination are thought to result from damage to the corticospinal tract which is thought to control the movement of one limb segment independently of the other, known as fractionation of movement (Schieber, 2001; Lemon and Griffiths, 2005). Fractionation of movement is essential for motor control and function in the upper limb (Lang, Bland, Bailey, Schaefer, & Birkenmeier, 2013). Besides the impairments seen in the paretic arm post-stroke, the ipsilesional or less-paretic arm also exhibits impaired motor control (Chollet et al., 1991; Haaland & Delaney, 1981; Sunderland, Bowers, Sluman, Wilcock, & Ardron, 1999) compared to healthy controls (Jung, Yoon, & Park, 2002). The impairments seen in the ipsilesional upper limb are not well understood. Several theories have been proposed to explain impairment in the ipsilesional arm, including disruption of the ipsilesional projections of the corticospinal tract (Desrosiers, Bourbonnais, Bravo, Roy, & Guay, 1996; Noskin et al., 2008), inhibition of the intact primary motor cortex (Nowak et al., 2007), and cognitive disorders (Sunderland, Bowers, Sluman, Wilcock, & Ardron, 1999). It has been shown that recovery of the ipsilesional upper limb can take up to nine weeks post-stroke and impairments may persist long-term even though it appears to exhibit normal function (Metrot et al., 2013).

Repetitive task training (RTT) has been recommended for treating the paretic limb post stroke. A 2007 Cochrane review concluded that there was sufficient evidence to attribute

functional improvements to lower limb RTT when compared to other forms of treatment (French et al., 2007). The functional gains realized were modest but meaningful. However, the review concluded that the evidence for upper limb RTT was insufficient and showed no significant advantage over other forms of treatment. The review acknowledged that patients included in these studies were in their acute or subacute phase post stroke, and that there were few studies conducted on chronic stroke patients. The study suggested caution in interpreting these results as patients entering the studies were of differing levels of ability. They recommended that future research should focus on the intensity of RTT, different levels of pre-intervention disability levels, cost-effectiveness of RTT, and different delivery methods such as group training, circuit type training, and practice in the home environment. However, RTT is very difficult to perform in patients who are severely impaired and have abnormal motor coordination – in these patients' repetition of abnormally coordinated movement patterns may reinforce those very patterns and impede recovery (Raghavan, 2015).

In fact, a Cochrane review conducted by Langhorne et al. (2011) noted that there were no clear standards of clinical practice relating to the treatment of upper limb impairments in patients with stroke. The Cochrane review noted that to guide future clinical practice and consensus, more research is needed to clearly define the role of specific rehabilitative interventions in specific clinical settings (Langhorne, Bernhardt, & Kwakkel, 2011). So to address the need for finding effective, timely, and cost-effective treatments for stroke, researchers continue to investigate both novel and traditional rehabilitation techniques. These techniques have been used on their own or in combination with other modalities to improve function. Treatment techniques

in these studies were administered at different intensities or dosages, frequencies, and durations (Bosch, 2014; Cooke, 2010; Kwakkel, 2006; Page, 2012).

A more recent Cochrane review conducted by Pollack et al. (2014) summarized some common techniques and modalities used in rehabilitating the upper extremity. The table below summarizes this review.

Technique or Modality	Description	Evidence	Conclusions
Biofeedback	Electromyography (EMG) biofeedback electrodes are placed on the surface of the skin or through needle electrodes, which pick up electric activity and provide feedback to the patient through a display unit or through auditory signals. This feedback can be used to enhance movement and function.	Molier 2010 (1) Systematic review	Inconclusive
Bobath approach	The bobath approach focuses on hands-on techniques to decrease abnormal muscle tone and facilitate normal movement.	Kollen 2009(2) Hatem 2016(3) Systematic review	Not superior to other modalities
Brain stimulation	The two common techniques used to stimulate the brain are Trans cranial direct current stimulation (tDCS) and Transcranial magnetic stimulation (TMS). tDCS uses surface electrodes while TMS uses rapidly changing magnetic fields to stimulate the brain. A form of TMS known as Repetitive pulse TMS (rTMS) has been proposed as a treatment option for inducing excitability of the motor cortex in stroke patients.	Hesse et al., 2011(4); Khedr et al., 2013 (5) Hatem 2016 (3)	tDCS may be a useful adjunct to therapy. rTMS may be useful as an adjuvant therapy; however, theta-burst stimulation has insufficient evidence.
Complimentary interventions	Of the complimentary interventions used to treat stroke acupuncture, a technique in which needles are inserted into meridian points, has been researched extensively; Other complimentary therapies include Chinese therapies, acupuncture, and homeopathy.	Pollock 2014(6)	Inconclusive
Constraint-induced movement therapy (CIMT)	CIMT prevents movement in the unaffected arm to encourage the use of the paretic arm.	Winstein 2016(7) AHA/ASA Guideline	Inconclusive Modified CIMT needs further investigation
Electrical stimulation	Functional electrical stimulation (FES) is provided through surface electrodes. The stimulation assists involuntary muscle contraction and can be used while a patient is performing a functional task.	Hatem 2016 (3)	Inconclusive

	Neuro muscular electrical stimulation (NMES) is a passive technique used to produce muscle contraction using frequencies of 10-50 Hz.		
Hands-on therapy (manual therapy techniques)	This movement based therapy provided by a physical therapist to decrease pain or improve joint range of motion.	Winter 2011(8) Cochrane Review	Insufficient evidence
Mental practice	Mental practice is a training method that is used to promote skill acquisition through mental rehearsal followed by the practice of the movement. Mental practice with motor imagery can be used in combination with other rehabilitation techniques.	Hatem 2016 (3)	Moderate quality evidence for the use of Mental practice with motor imagery in combination with other rehabilitation techniques
Mirror therapy	Mirror therapy is a visual stimulation based therapy using mirrors to promote functional movement.	Hartman 2016(9) Review	Further studies are recommended
Music therapy	Music therapy uses rhythmic auditory stimulation to promote functional movement.	Magee 2017(10) Cochrane Review	Insufficient low quality evidence for upper extremity function
Repetitive task training	Repetitive task training involves practicing a task repeatedly) to enhance learning and reduce muscle weakness.	French 2016 Cochrane Review	*Low-quality evidence* that RTT improves arm function
Robotics	Robotic devices are electromechanical devices that can provide assistance or resistance to movement.	Brackenridge 2016 (12) Review	Insufficient evidence
Sensory interventions	Somatosensory awareness can improve upper limb function and movement. Techniques such as sensory re-education, tactile-kinesthetic guiding, repetitive sensory practice or desensitization may be used to improve somatosensory awareness.	Doyle 2010 (13) Cochrane Review	Insufficient evidence
Strength training	Strength training muscles may be performed with assistance from a therapist or by using weights and gym equipment.	Hatem 2016 (3)	Insufficient evidence
Stretching and positioning	Stretching and positioning techniques can involve the use splints and orthoses. Orthoses are devices used in patients to provide stability and prevent or limit movement.	Pollock 2014(6)	Low-quality evidence of no benefit or harm
Task-specific training	Task-specific training involves practicing functional tasks as a part or whole to improve motor function. It is sometimes referred to functional task training.	Pelton 2012 (14) Pollock 2014 (6)	Insufficient evidence

The review found moderate quality evidence for several techniques for improving upper limb function after stroke. The study suggested the use of CIMT, mental practice, mirror therapy, interventions for sensory impairments, and virtual reality for improving upper limb function after stroke. The review concluded that there was moderate level evidence that bilateral arm training is not as effective as unilateral arm training, and that further research needs to be conducted to determine a sound theoretical rationale for the treatment and outcome measures used to establish its effectiveness in improving upper limb function after stroke. Robotics was found not to be more beneficial than conventional therapy at the same dosage. The review recommended further research into robotic devices before they are introduced into routine practice. Repetitive task training was shown not to harm or benefit the patient with moderate evidence. The patients who received the greatest number of repetitions were helped the most. The review found several interventions with low-quality evidence: biofeedback, Bobath therapy, electrical stimulation, strength training, task-specific training, and pharmacological interventions. Consistent with the findings of the 2014 Cochrane review and other reviews, bimanual training, particularly in chronic stroke patients, lacks robust studies of its effectiveness and thus further research is warranted.

Despite the results above, the literature suggests that the performance of instrumental activities of daily living (IADLs) is better when both upper limbs are used together, which emphasizes the need for bilateral training (Haaland et al., 2012). Bimanual movements have shown to improve primary motor cortex excitability when compared to unimanual movements in both the damaged and undamaged hemispheres post stroke (Staines, Mcilroy, Graham, & Black, 2001; Silvestrini, Cupini, Placidi, Diomedi, & Bernardi, 1998). Bimanual training has been shown to help rebalance the excitability of the motor cortices and thereby decrease the motor

impairments of the affected extremity (Murase, Duque, Mazzocchio, & Cohen, 2004; Calautti et al., 2007).

Post-stroke bimanual coordination is impaired when compared to controls in both symmetric and asymmetric tasks. Based upon the literature, unimanual training on its own may not improve bilateral coordination; therefore, upper limb rehabilitation must incorporate the simultaneous use of both hands to accomplish task-related goals (Kantak, Zahedi, & Mcgrath, 2016). Bilateral upper limb training protocols are rooted on the assumption that the paretic limb can be made functional by the facilitation of neutrally driven coupling effects (Carson, 2005; Cauraugh & Summers, 2005; Goble, 2006). Some possible underlying mechanisms, which support the use of bilateral training, are:

1) Activation of the ipsilateral corticospinal pathway by firing the uncrossed fibers of the tract (Muddie and Maytas, 2000)
2) Activation of the contralesional hemisphere (Luft et al., 2004)
3) Normalization of the inhibitory mechanisms between the hemispheres (Stinear et al., 2008)
4) Exploiting the symmetry constraint (Cauraugh and Summers, 2005)

Bimanual training is based on interlimb coupling, which is believed to activate the ipsilesional hemisphere by rebalancing interhemispheric inhibition (Stinear, 2008). In a systematic review, Wolf et al. (2014) concluded that in moderate to severe stroke patients, bimanual training is as efficacious as other treatment interventions in addressing upper limb impairments and activity limitations (Sakzewski, 2012; Luft et al., 2004; Delden, Peper, Beek, & Kwakkel, 2012; Coupar, Pollock, Wijck, Morris, & Langhorne, 2010). The study also suggested that when the goal of treatment is to address impairment level function and proximal control of

the upper limb, bimanual training may be more efficacious, but when the goal is to gain distal control and perception of use, CIMT may produce better results. The study indicated the need for further research in patients with varying levels of acuity and severity post-stroke (Wolf et al., 2014).

To ascertain the "Why and Who benefits" from bimanual training, Walker and Whitall (2004) conducted a review of upper extremity bimanual training. The review included twenty studies with different bimanual training devices and protocols. These studies were divided into three categories based on the training protocols used:

1. Repetitive reaching with hand fixed: Studies included in this category were training protocols in which both hands were supported or fixed at the distal end while the arms performed reaching movements repeatedly. The two devices included in the study were bilateral arm training with rhythmic auditory cueing (BATRAC) and mirror image movement enabler (MIME). The BATRAC consists of two *unyoked handles* that can be moved forward and backward in a symmetrical or an asymmetrical manner. The MIME is a robotic device that can be used in a unimanual or a bimanual training mode. In the bimanual training mode, when reaching activities are performed, the robot aids the affected arm to mirror the position of the unaffected arm. It was found that in this training protocol, patients' paretic limbs showed proximal strength gains and an improved ability to move the arm, especially in patients with mild and moderate stroke severity. One study within this category also showed an increased ability in performing bilateral tasks.

2. Isolated muscle repetitive tasks training: The first training approach that was compared in this category consisted of the Bimanutrack training, a robotic device that trains the wrist in passive, active assist, and resistance modes. The second approach that was compared in this

category was isolated repetitive muscle training, which included bimanual training in which a single upper limb motion was repeated during the treatment sessions. In this category, both training approaches showed improvement across the levels of severity. In patients with mild impairment, this training approach may promote substantial functional recovery of the paretic upper limb.

3. Whole arm function training: In this training approach, different types of the whole arm function training techniques were compared with each other. It was concluded that bimanual training improved paretic upper limb function and the speed of upper limb movement during unilateral and bimanual reaching tasks. These improvements were most appreciated in patients with mild paresis. The study concluded by emphasizing the need to match bimanual training protocols with patients' baseline characteristics and to explore the potential contributions of the paretic upper limb in a supportive role in unimanual and bimanual tasks (McCombe & Whitall, 2008; Walker S.M & Whitall J., 2004).

A pilot study conducted by Whitall et al. (2000) determined that six weeks of BATRAC training in patients with chronic stroke showed significant increases in the Fugl-Meyer Upper Extremity (FMA-UE) scale, Wolf Motor Function Test, and University of Maryland Arm Questionnaire for Stroke. The study also demonstrated strength improvements in elbow flexors and wrist flexors for the paretic upper limb, as well as elbow flexors and wrist extensors of the non-paretic upper limb. Active range of motion change was seen in shoulder extension, wrist flexion, and thumb opposition for the paretic side, and these changes were maintained in patients eight weeks post-training. The authors concluded that the BATRAC is appropriate for patients who are not candidates for CIMT and that the ease of use may permit home usage (Whitall, Waller, Silver, & Macko, 2000).

A 2015 study conducted in Amsterdam compared three interventions including CIMT, modified bilateral arm training with rhythmic auditory cueing (mBATRAC), and Dose Matched Control Treatment (DMCT), and concluded that there was a large improvement in the control of the affected upper limb after mBATRAC treatment when compared to the other two, but the coupling between the hands remained the same (Delden, Beek, Roerdink, Kwakkel, & Peper, 2014). A 2010 randomized control trial comparing the efficacy of BATRAC versus dose-matched therapeutic exercises (DMTEs) on upper limb function after six weeks of training reported that both treatment modalities improved global upper limb impairment and function in chronic stroke patients. These improvements, seen in the upper extremities as a result of both treatment modalities, were sustained over four months. The study also hypothesized that BATRAC produced results through cortical remodeling in the ipsilesional precentral gyrus and the contralesional superior frontal gyrus (premotor cortex). The DMTE, on the other hand, produced similar treatment through other neuroplastic mechanisms (Whitall et al., 2010). It has been shown in patients with chronic stroke that coupled bimanual movement with neuromuscular stimulation improved bimanual force production, as evidenced by improved bimanual coordination and improved motor synergies (Kang & Cauraugh, 2013).

A structured review and meta-analysis conducted by Cauraugh et al. (2010) compared seven different studies involving BATRAC with coupled bilateral training and EMG-triggered stimulation techniques. The study concluded that supplementing bilateral arm movements with either rhythmically paced motion or active stimulation of the impaired upper limb increased motor recovery compared to bilateral training on its own or other movement training protocols (Cauraugh, Lodha, Naik, & Summers, 2010). A similar meta-analysis of 48 stroke studies showed that although there were subtle differences between the types of bimanual training used

in the studies, overall bimanual training was effective in overcoming motor dysfunction in ADL's by activating both peripheral and central inputs (Cauraugh, Lodha, Naik, & Summers, 2015).

Stroke impairs intrinsic (proprioceptive) and extrinsic (visual and auditory) feedback controls due to the damage caused in the brain and also due to weakened muscles; this leads to impaired ability to modulate force production in the upper limb muscles (Thikey, Grealy, Wijck, Barber, & Rowe, 2012; Dokkum et al., 2012; Vliet & Wulf, 2006). Impaired feedback control leads to increased bimanual force variability and fixed force control without visual input in stroke patients. This points to an increased dependence on visual information to modulate force for chronic post-stroke patients (Kang & Cauraugh, 2015). Hence patients may need to depend on visual or auditory information to compensate for impaired feedback. A single session study conducted by Aluru et al. (2014) demonstrated the role of auditory cueing for bimanual-to-unimanual learning. The study yielded three novel findings: 1) chronic stroke patients can be stratified based on simple movement kinematics (wrist extension) to indicate their temporal stage of recovery, which can be used to select strategies for individualized stroke recovery plans; 2) auditory constraints influence motor performance differently at various stages of recovery; and 3) single session studies using bimanual-to-unimanual learning can be used to determine the type of cueing that may optimize learning (Aluru et al., 2014). The bimanual arm trainer provides patients with an immersive experience by providing auditory and visual cues for training.

Summary

Based on the review of the literature, there is a gap in answering the following questions regarding bimanual training post-stroke.

1) Do patients with chronic stroke benefit from bimanual arm training using the BAT?

2) Does bimanual training affect unimanual paretic arm function?

Thus, the purpose of this study was to investigate the usefulness of the Bimanual Arm Trainer (BAT) in improving upper extremity function in community-dwelling patients with subacute or chronic stroke.

Chapter III: RESEARCH METHODS

Participants

The participants for the study were recruited from the various New York University hospitals and outpatient clinics via advertisement using IRB-approved flyers. The age range of patients was between 18 and 90 years. This study specifically addressed the recovery of arm function after stroke in adults. Pediatric stroke is relatively rare compared to adult stroke, and the age-related mechanisms of recovery may be different. Hence children below 18 years were excluded. Adults over 90 years were also excluded to rule out possible confounding or co-morbid medical conditions. The study was conducted over a period of 18 months; all patients who met the inclusion criteria were admitted to the study. Twenty-three participants were enrolled and completed the study. Both male and female participants were included. Attempts were made to recruit 50% of male and 50% female participants. There were no gender-based enrollment restrictions.

Inclusion criteria:

- Unilateral CVA-Identified by clinical assessment.
- Between the ages of 18-90 years old. Speak the English Language.
- Able to follow instructions to adhere to protocol.
- Not currently enrolled in other upper extremity studies.

Exclusion criteria:

- Severe upper extremity spasticity suggested by an Ashworth score of >3, or restriction of full passive range of motion which impedes training.

- Evidence of alcohol, drug abuse or other relevant neuropsychiatric condition such as psychotic illness or severe depression.
- Any condition or situation that, in the investigator's opinion, may put the participant at significant risk, confound the study results, or interfere significantly with the participant's participation in the study.
- History of surgery or other significant injury to either upper extremity causing mechanical limitations that preclude task performance.
- Previous neurological illness such as head trauma, prior stroke, epilepsy, or demyelinating disease.
- Complicating medical problems such as uncontrolled hypertension, diabetes with signs of polyneuropathy, severe renal, cardiac or pulmonary disease, or evidence of other concurrent neurologic or orthopedic conditions precluding the participant from complying with the study protocol.

Study design

The study was designed to test the hypothesis that the Bimanual Arm Trainer leads to improved arm function in patients with stroke. The study design was quasi-experimental. A quasi-experimental approach means that the independent variable is active but without random assignment of participants to groups (Trochim & Donnelly, 2008, p. 158). For this study, the independent variables were active, and there was no random assignment of participants to groups, instead each subject participated in a control phase Pre 1 to Pre 2 and an experimental/training phase Pre 2 to Post.

Variables

The independent variable was bimanual training using the Bimanual Arm Trainer (BAT). The dependent variables were the Fugl-Meyer Assessment (FMA-UE), the Wolf Motor Function Test (WFMT), the Stroke Impact Scale (SIS), and Modified Rankin Scale (MRS – SI).

Intervention

Each patient received 1 hour of training over 12 sessions with the bimanual arm trainer. The training consisted of bimanual simultaneous movements interspersed with unimanual affected arm movements with the bimanual arm trainer.

Figure 1. Bimanual Arm Trainer

(Raghavan, MD, Weisz, PhD, & Lohmeyer, 2019)

Description of the Bimanual Arm Trainer (BAT): The BAT (Fig. 1) operates by a system of cables which connect the two arms. The participant rests their forearms on two forearm rests. The participant is instructed to move the unaffected arm outwards, which leads to the affected arm moving in the same manner (simultaneous bimanual training). The movement facilitated is shoulder external rotation and elbow extension. The movement can also be performed solely using the affected arm (unimanual training). During training, a sensor captures the movement and displays it to the participant for feedback. The movements are encouraged by engaging the participant in a virtual reality environment with visually pleasing graphics.

Outcome measures

Below are the listed outcome measures used in this study and their characteristics:

Fugl-Meyer Assessment of Motor Recovery after Stroke – FMA-UE:

- One of the most widely used quantitative measures of motor impairment (Gladstone et al, 2002).
- Evaluates and measures recovery in post-stroke hemiplegic patients.
- Used in both clinical and research settings.
- Test-retest reliability is excellent (ICC =0.97).
- Inter-rater reliability for the upper extremity is excellent (r=0.995-0.996) (Duncan et al, 1993).
- Intra-rater reliability is excellent (ICC =0.95).

The maximum upper extremity score that can be achieved is 66; a 10-point increase in FMA-UE is considered to be clinically significant (Shelton et al., 2001).

Wolf Motor Function Test:

- Quantitative measure of upper extremity motor ability through timed and functional tasks (Wolf et al., 2005).
- Test-retest reliability is excellent (r =0.95) (Morris et al 2001).
- Inter-rater reliability is excellent (ICC 0.93) (Morris et al 2001).

A streamlined version of WMFT (6 tasks) was used in which a maximum score of 30 can be obtained by the participants. The streamlined WMFT has been shown to have better clinical utility compared to the original scale as it is shorter (Wu, Ching-Yi et al., 2010).

Stroke Impact Scale (SIS):

- Assesses health status following a stroke.

- Test-retest reliability is adequate to excellent (ICC =0.70- 0.92) (Duncan et al, 1999).
- Inter-rater reliability is excellent (ICC =0.82) (Carod et al, 2009).
- SIS is a 59-item measure that assesses post-stroke quality of life in 8 domains.

Each item is rated on a 5-point Likert scale. The summative scores for each domain range from 0-100. A transformed scale is obtained for each domain as follows: transformed scale = [actual raw score – lowest possible raw score)/possible raw score *100]. An individual participant score change has to reach 24.0 on the SIS strength; 17.3 on the ADL/IADL; 15.1 on the mobility; and 25.9 on the hand function subscales to indicate clinically significant improvement (Lin et al., 2010).

Modified Rankin Scale (MRS – SI):

- A clinician-reported measure of global disability - it is widely applied for evaluating stroke patient outcomes and as an end point in acute stroke randomized clinical trials.
- Inter-rater reliability with the mRS is moderate and improves with structured interviews (kappa 0.56 versus 0.78).
- Strong test-re-test reliability (kappa=0.81 to 0.95) (Wilson et al, 2005).

The Modified Rankin Scale (MRS – SI) is a 6-point disability scale with possible scores ranging from 0 to 5. MRS – SI improvement of _>1 post stroke is considered meaningful improvement (Tilson, et al.2010).

Procedures

Following receipt of NYU Medical Center, Hackensack Medical Centers and SHU's IRB approvals of this study, participants were recruited via advertisement using flyers within the New York metropolitan area. Participants who contacted the PI via the telephone and were found

eligible for the study were required to provide informed consent prior to participation in the study. They were then given an appointment to come in person to the research facility.

Written consent was obtained at the first visit. Then the study coordinator discussed one-on-one with the participant the nature of the study, the costs, and the time commitment involved in their participation. The participants did not incur any cost to participate in the study but had to make their own way to the clinic. Participants were given adequate time to ask questions regarding the study. After consent was obtained, the participants were screened using the inclusion and exclusion criteria mentioned above to ascertain eligibility for the study. Once deemed suitable for the study, participants were shown the bimanual arm trainer and provided a brief demonstration of the device. If the participant wished to proceed with the study, they were scheduled for their clinical assessment session, and assigned a study ID. The participant was given a copy of the consent forms and appointments for subsequent visits were made.

During the first clinical assessment session, each participant was asked to complete the stroke impact scale after brief instructions were provided and the participant was given adequate time to fill out the form on their own. The Fugl-Meyer Assessment, Wolf Motor Function Test, and the Modified Rankin Scale were then administered. All participants were given rest breaks between the clinical assessments. These clinical assessments were labelled Pre1 and the data were entered in REDCap subsequently. After the clinical assessments were complete, the participant was set up on the bimanual arm trainer. The setup included adjusting the height of the table to ensure that he or she was sitting upright in a comfortable position. The shoulder width and length of the arms were set to avoid discomfort. The measurements were recorded for subsequent visits. The participants were advised to continue with their regular therapy/exercises

during the course of the study but asked to document these in an exercise log which was provided.

The second clinical assessment appointment occurred six weeks later to repeat the same assessments that were performed at baseline prior to beginning training on the BAT. The assessments were labelled as Pre2 and data were entered in REDCap subsequently. Participants then began training sessions with the device for 12 sessions over approximately 4-6 weeks, as their schedule allowed. Training visits could be once, twice, or thrice per week. Participants were enrolled for a total of approximately 12 weeks, but the duration may have been shorter or longer based on travel and transportation constraints. There were approximately 9 testing sessions and 12 training sessions with the BAT overall. Participants were advised to continue with their regular therapy/exercises during this time and continue to document these in the exercise log. After completion of training with the BAT, the participants came in for a final clinical assessment session. Data from this session were labelled as Post and were entered into REDCap subsequently.

Data Analysis:

All clinical measures of upper extremity function, quality of life, and disability were first captured on paper and then entered into REDCap. Study data were managed using REDCap, an electronic data capture tool hosted at NYU Rusk Rehabilitation. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies by providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources Harris et al. (2009). The chosen data—Fugl-Meyer Assessment (FMA-UE), Wolf Motor

Function Test (WFMT), stroke impact scale (SIS), and Modified Rankin Scale (MRS – SI) were exported from REDCap via Excel files to SPSS (Version 24). The paper copies of the clinical assessments were filed and securely locked in the PI's lab.

For the purpose of this study, repeated measures analysis of variance (ANOVA) was employed to analyze the data because the same dependent variables were measured at different time points. Repeated measures ANOVA is an extension of a paired-samples t-test. Repeated measures ANOVA is also known as 'within-subjects' ANOVA.

The assumptions for a repeated measures analysis of variance are 1) normality; 2) homogeneity of variances; 3) absence of outliers; and 4) sphericity, or the assumption that variances of the differences between all combinations of the related conditions and time points are equal—much like the assumption of equal variances in ANOVA (www.statstutor.ac.uk). If the assumptions were violated, data transformation was attempted using data inverse transformation, square transformation, and logarithmic transformation. If the data transformations did not work, then non-parametric tests were used.

For the Fugl-Meyer Assessment Scale (FMA- UE) and the Stroke Impact Scale (SIS),the Mauchly's test of sphericity indicated that the assumption of sphericity had not been violated; therefore, the F values partial Eta squared and observed power were reported from the sphericity assumed row. However, for the Wolf Motor Function Test (WMFT), the Mauchly's test of sphericity indicated that the assumption of sphericity had been violated. Hence the Huynh Feldt was reported. There was no significant change in the Modified Rankin Scale (MRS – SI) between the different points of measurement.

Chapter IV: RESULTS

Summary

The data were analyzed using SPSS 26 (IBM Corp., 2018). Repeated measures ANOVA was performed on the Upper Extremity component of the Fugl-Meyer Assessment Scale (FMA-UE), the 6-item Wolf Motor Function Test (WMFT), the Stroke Impact Scale (SIS), and the Modified Rankin Scale (MRS – SI) scores across the three time points. The FMA- UE, which measures upper extremity motor impairment, and the WMFT, which measures upper extremity function, showed statistically significant changes which were also clinically significant. The MRS – SI did not show statistically significant change. The SIS scale did not show a statistically significant change on the ANOVA, however the paired-samples t-test performed on Pre1 and Post SIS data showed statistically significant change indicating that the patient's quality of life had improved.

Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA-UE)

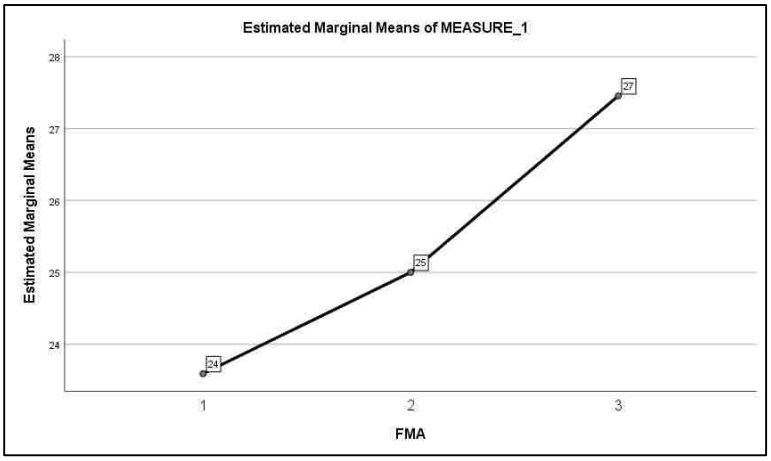

Figure 2. The mean Fugl-Meyer scores increased between pre1 and post.

Table 1. Means and standard deviation of Fugl-Meyer.

Descriptive Statistics

	Mean	Std. Deviation	N
FMAPre	23.59	10.112	22
FMAPre2	25.00	10.574	22
FMAPost	27.45	10.220	22

A repeated measures analysis of variance (ANOVA) was performed to determine if there was a significant improvement in upper extremity arm motor impairment over time. The upper extremity Fugl-Meyer score increased from Pre1 (M = 23.59, SD = 10.11) to Pre-2 (M = 25.00, SD = 10.57) to post-intervention (M = 27.45, SD = 10.22). Mauchly's test of sphericity indicated that the assumption of sphericity has not been violated, χ^2 (2) =5.89, p = 0.053.

Table 2. ANOVA – Fugl-Meyer.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
FMA	Sphericity Assumed	168.212	2	84.106	16.270	.000	.437	32.539	.999
	Greenhouse-Geisser	168.212	1.594	105.547	16.270	.000	.437	25.929	.997
	Huynh-Feldt	168.212	1.704	98.736	16.270	.000	.437	27.718	.998
	Lower-bound	168.212	1.000	168.212	16.270	.001	.437	16.270	.970
Error(FMA)	Sphericity Assumed	217.121	42	5.170					
	Greenhouse-Geisser	217.121	33.468	6.487					
	Huynh-Feldt	217.121	35.777	6.069					
	Lower-bound	217.121	21.000	10.339					

a. Computed using alpha = .05

Training with the BAT elicited statistically significant changes in upper extremity arm motor impairment over time, F (2, 42) = 16.27, $p < 0.005$, partial $\eta^2 = 0.44$ (large effect size), and an observed power greater than 99%.

Table 3. Pairwise comparisons – Fugl-Meyer.

Pairwise Comparisons

Measure: MEASURE_1

(I) FMA	(J) FMA	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	-1.409	.584	.075	-2.927	.109
	3	-3.864*	.841	.000	-6.051	-1.676
2	1	1.409	.584	.075	-.109	2.927
	3	-2.455*	.602	.002	-4.021	-.888
3	1	3.864*	.841	.000	1.676	6.051
	2	2.455*	.602	.002	.888	4.021

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

There was a small but non-significant increase in the FMA-UE scores between Pre1 (M = 23.59, SD = 10.11) to Pre-2 (M = 25.00, SD = 10.57). There was a significant increase in FMA-UE scores from Pre-2 (M = 25.00, SD = 10.57) to Post (M = 27.45, SD = 10.22). The mean increase was 2.46, 95% CI [-.89, -4.02], $p < 0.005$. There was a significant increase in FMA-UE from Pre1 (M = 23.59, SD = 10.11) to Post (M = 27.45, SD = 10.22). The mean increase was 3.86, 95% CI [-1.68, -6.05], $p < 0.005$.

There was a statistically significant difference between means, therefore we can reject the null hypothesis in favor of the alternative hypothesis.

Wolf Motor Function Test (WFMT)

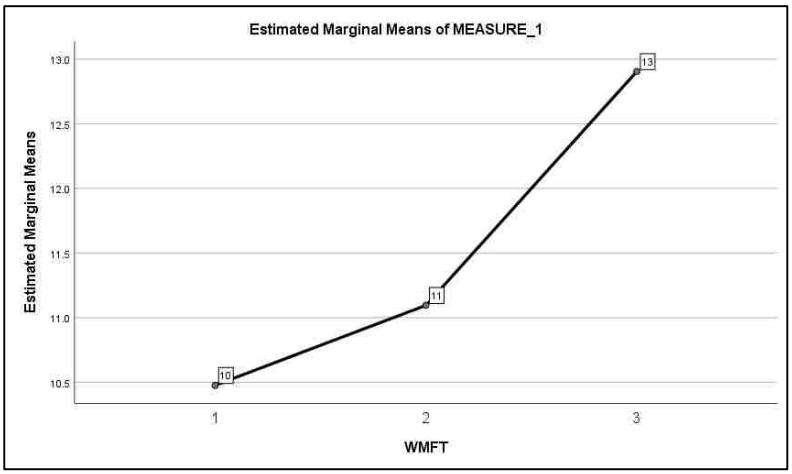

Figure 3. The mean Wolf Motor Function scores increased between pre1 and post.

Table 4. Means and standard deviations on the Wolf Motor Function Test.

Descriptive Statistics

	Mean	Std. Deviation	N
wmfPre	10.48	3.341	21
wmfPre2	11.10	3.285	21
wmfPost	12.90	3.576	21

A repeated measures analysis of variance (ANOVA) was conducted to determine if there was a significant increase in upper extremity arm function over time. Upper extremity arm function increased from Pre1 (M = 10.48, SD = 3.34) to Pre-2 (M = 11.10, SD = 3.29) to post-intervention Post (M = 12.90, SD = 3.58).

Mauchly's test of sphericity indicated that the assumption of sphericity has been violated, $\chi^2(2) = 6.31$, $p = 0.045$. The Greenhouse Geisser Epsilon = 0.78, hence the Huynh Feldt is being reported.

Table 5. ANOVA - Wolf Motor Function Test.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
WMFT	Sphericity Assumed	66.889	2	33.444	31.518	.000	.612	63.037	1.000
	Greenhouse-Geisser	66.889	1.559	42.897	31.518	.000	.612	49.147	1.000
	Huynh-Feldt	66.889	1.667	40.119	31.518	.000	.612	52.549	1.000
	Lower-bound	66.889	1.000	66.889	31.518	.000	.612	31.518	1.000
Error(WMFT)	Sphericity Assumed	42.444	40	1.061					
	Greenhouse-Geisser	42.444	31.186	1.361					
	Huynh-Feldt	42.444	33.345	1.273					
	Lower-bound	42.444	20.000	2.122					

a. Computed using alpha = .05

There were statistically significant changes in upper extremity arm function over time, $F(2, 40) = 31.52$, $p < 0.005$, partial $\eta^2 = 0.62$ (large effect size), and an observed power of 99%

Table 6. Pairwise comparisons – Wolf Motor Function Test

Pairwise Comparisons

Measure: MEASURE_1

(I) WMFT	(J) WMFT	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	-.619*	.223	.035	-1.203	-.036
	3	-2.429*	.375	.000	-3.409	-1.448
2	1	.619*	.223	.035	.036	1.203
	3	-1.810*	.335	.000	-2.686	-.933
3	1	2.429*	.375	.000	1.448	3.409
	2	1.810*	.335	.000	.933	2.686

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

There was a small but non-significant increase in upper extremity arm function between Pre1 (M = 10.48, SD = 3.34) to Pre-2 (M = 11.10, SD = 3.29) There was a significant increase in upper extremity arm function from Pre-2 (M = 11.10, SD = 3.29) to Post (M = 12.90, SD = 3.58) The mean increase was 2.43, 95% CI [-0.93, -2.69], $p < 0.05$. There was a significant increase in upper extremity arm function from Pre1 (M = 10.48, SD = 3.34) to Post (M = 12.90, SD = 3.58) The mean increase was 2.43, 95% CI [-1.45, -3.41], $p < 0.005$.

There was a statistically significant difference between means, therefore we can reject the null hypothesis in favor of the alternative hypothesis.

Stroke Impact Scale (SIS)

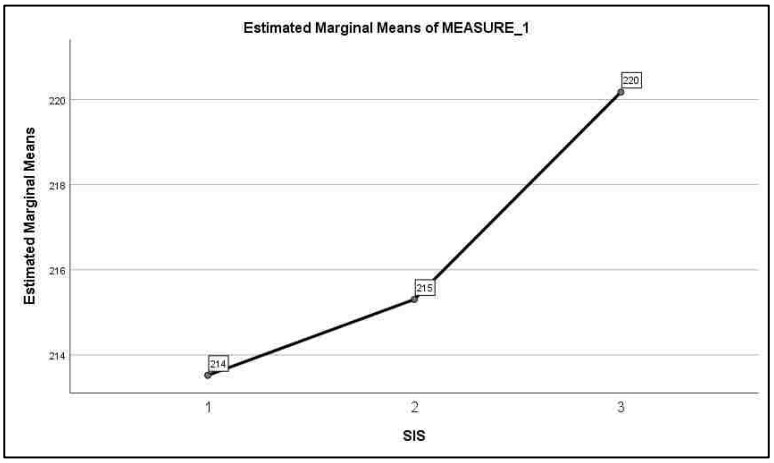

Figure 4. The mean Stroke Impact Scale scores increased between pre1 and post.

Table 7. Means and standard deviation of Stroke Impact Scale.

Descriptive Statistics

	Mean	Std. Deviation	N
SIS Pre	213.52	21.041	23
SIS Pre2	215.30	21.653	23
SIS Post	220.17	19.460	23

A repeated measures analysis of variance (ANOVA) was performed to determine if there was a significant increase in quality of life as measured by SIS over time. The stroke impact scale increased from Pre1 (M = 213.52, SD = 21.04) to Pre2 (M = 215.30, SD = 21.65) to post-intervention Post (M = 220.17, SD = 19.46). Mauchly's test of sphericity indicated that the assumption of sphericity has not been violated, $\chi^2(2) = 1.31$, $p = 0.519$

Table 8. ANOVA – Stroke Impact Scale.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
SIS	Sphericity Assumed	545.420	2	272.710	2.466	.097	.101	4.933	.470
	Greenhouse-Geisser	545.420	1.886	289.228	2.466	.100	.101	4.651	.455
	Huynh-Feldt	545.420	2.000	272.710	2.466	.097	.101	4.933	.470
	Lower-bound	545.420	1.000	545.420	2.466	.131	.101	2.466	.324
Error(SIS)	Sphericity Assumed	4865.246	44	110.574					
	Greenhouse-Geisser	4865.246	41.487	117.271					
	Huynh-Feldt	4865.246	44.000	110.574					
	Lower-bound	4865.246	22.000	221.148					

a. Computed using alpha = .05

The SIS showed non-significant changes in quality of life over time, F (2, 44) = 2.47, $p >$ 0.05.

Table 9. Pairwise Comparisons SIS.

Pairwise Comparisons

Measure: MEASURE_1

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	-3.422	11.615	1.000	-33.520	26.676
	3	-23.372*	8.642	.039	-45.764	-.980
2	1	3.422	11.615	1.000	-26.676	33.520
	3	-19.950	10.228	.192	-46.452	6.552
3	1	23.372*	8.642	.039	.980	45.764
	2	19.950	10.228	.192	-6.552	46.452

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Although the ANOVA did not show significance, the pairwise comparisons showed a significant difference from Pre1 ($M = 213.52$, $SD = 21.04$) to Post ($M = 220.17$, $SD = 19.46$). The mean increase was 23.37, 95% CI [-0.98, -45.76], $p < 0.05$.

Table 10. Paired Samples t test SIS.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	SIS Pre - SIS Post	-6.652	14.525	3.029	-12.933	-.371	-2.196	22	.039

A paired t-test was run to determine whether there was a statistically significant mean difference in the Stoke Impact Scale pre and post intervention Participants scored higher on the

SIS post intervention (220.97 ±19.46) as opposed to the Pre1 (213.52 ±21.04); a statistically significant increase of 6.652 (95% CI, -12.933 to -.371), $t(22) = 2.196$, $p < 0.05$ was noted.

Modified Rankin Scale

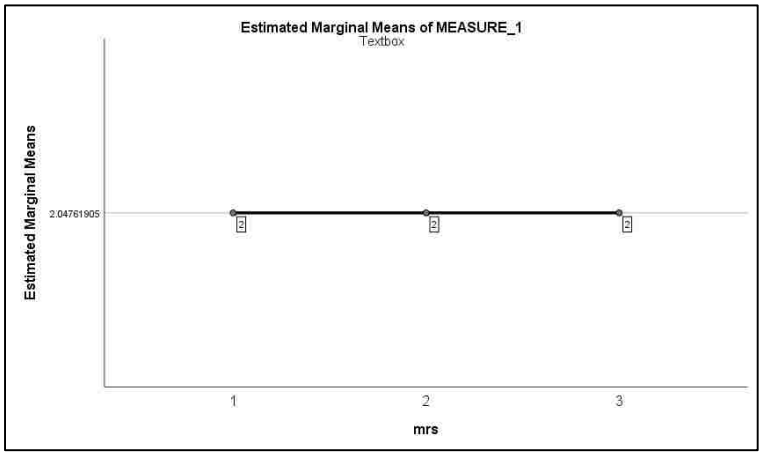

Figure 5. The mean Modified Rankin Scale scores between pre1 and post.

Table 11. Means and standard deviation of Modified Rankin Scale.

Descriptive Statistics

	Mean	Std. Deviation	N
modRankinPre	2.05	.218	21
modRankinPre2	2.05	.218	21
modRankinPost	2.05	.218	21

A repeated measures analysis of variance (ANOVA) was performed to determine if there was a significant change in disability as measured by MRS-SI over time. The Modified Rankin

score stayed the same from Pre1 ($M = 2.05$, $SD = 0.29$) to Pre2 ($M = 2.05$, $SD = 0.29$) to post-intervention ($M = 2.05$, $SD = 0.29$).

There was no statistically significant difference between the means at the different time points ($p > 0.05$) and, therefore we cannot reject the null hypothesis in favor of the alternative hypothesis.

Chapter V: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Discussion

The purpose of the study was to assess the extent to which training using the Bimanual Arm Trainer (BAT) is effective in improving arm function in stroke patients as measured by the Fugl-Meyer Assessment (FMA-UE), the Wolf Motor Function Test (WFMT), the Stroke Impact Scale (SIS), and the Modified Rankin Scale (MRS – SI). While the advantages of bimanual arm training have been discussed in the literature review (Chapter 2), the Bimanual Arm Trainer in particular has not been researched with this population.

It was not easy to recruit community dwelling participants willing to commute to a research facility for over 15 sessions. Hence, we recruited a convenience sample of patients who met the inclusion criteria, with a final sample size of N=23. Although the sample size was small, we had excellent retention of the participants.

For the first research question, the research hypothesis can be accepted as there was a significant increase in the Fugl-Meyer scores between the different points of measurement. For the second research question, the research hypothesis can be accepted as there was a significant increase in the Wolf Motor Function Test between the different points of measurement. For the third research question, the research hypothesis can be rejected as there was no significant increase in the Stroke Impact Scale between the different points of measurement. For the fourth research question, the research hypothesis can be rejected as there was no significant change in the Modified Rankin Scale between the different points of measurement. These results indicate that patients have made meaningful recovery of their upper limb function with bimanual arm training using the BAT device. Both measures of upper extremity impairment and function

indicated a significant improvement with just 12 sessions of bimanual arm training with the Bimanual Arm Trainer. Quality of life measures did not show a significant change.

Although many studies have reported that bimanual therapy may be used for adjunct therapy in restoring patient's upper limb function, large systematic reviews, including Cochran reviews, have failed to conclude its effectiveness in patients with chronic stroke. This study indicates that patients with stroke continue to benefit from bimanual arm training in the chronic stage of the disease. The study also serves as a reminder to extend the rehabilitation window by offering patients a way to continue to work even after formal physical and occupational therapy end. Using Bimanual Arm Trainers in clinics, community centers, and gyms can help to achieve this.

Approximately, 4% of the population in the US is likely to be affected by a stroke by 2030, which roughly equates to 3.4 million additional people (Ovbiagele et al., 2013). These projections are the greatest for people aged 45-64 years old (5%), which represents about one-third of all stroke survivors, amounting to 1.3 million of the estimated 4.1 million (Levine et al., 2007). Only 5-34% achieve full upper limb function (Nijland, Wegen, Wel, & Kwakkel, 2010; Kong, Chua, & Lee, 2010) when they leave the acute rehab facility due to the limited number of days of treatment afforded to them by insurance companies (West & Bernhardt, 2012).

These younger stroke survivors need an effective, and easy to use upper limb rehabilitation device/strategy over an extended period to improve their function and decrease their dependence on human assistance to complete their daily tasks. This study has demonstrated that the patients can continue to benefit from using the BAT well into the chronic phase when they have usually exhausted all their resources.

Summary

This is the first study to examine the effect of a passive mechanical bimanual robotic device, the Bimanual Arm Trainer, on upper limb function by providing improved access and convenience in post-stroke patients. The BAT enabled the patient to train independently using the device, with high intensity repetition. While powered robotic devices have shown promise in improving upper limb function post-stroke, their usefulness in providing ongoing rehabilitation and recovery in stroke is questionable due to the requirement for supervision in addition to the device. Bimanual arm training using the BAT is grounded in the principles of motor control and learning which suggest that the brain, with practice and training, can reorganize itself to re-enable patients recovering from a stroke, and that movements of the non-involved limb can aid the recovery of movement in the impaired limb.

This study investigated the use of the BAT in improving upper limb function in stroke patients. Improvements in the FMA and the WMFT scores speak to the usefulness of the device in improving upper limb motor impairment and function for stroke patients.

Limitations.

Since the study was quasi-experimental, it presents a few limitations. Each subject was their own control and there was no randomization. The sample size was small.

Inter validity considerations.

- Maturation – Natural changes, biological or psychological, within the participants over the time of the study may have an impact on the results. Test participants may become bored, tired, hungry, and so forth during the time of the study. This is more of an issue with long-term studies.

- Testing – Experiments that pretest the participants may influence the performance of participants on subsequent tests simply because participants have already seen or completed the test before. People tend to perform better in any activity the more they are exposed to it.
- Statistical Regression – Statistical regression, or regression to the mean, can be a concern in studies with extreme scores, either particularly high or low. Scores are typically not as extreme in subsequent testing in most situations, making meaningful pretest and post-test comparisons more difficult.
- Selection Interaction – The selection method may interact with one or more of the other threats and impact results. For example, groups with larger numbers of elderly participants may be impacted more by maturation during the study.

External validity considerations

- Interaction Effects of Testing – The pretest may make the participants more aware of or sensitive to the treatment that will be applied and therefore, may influence the response to the treatment.
- Selection Bias – This occurs when participants are selected in a manner that does not ensure that they are representative of the overall population. The random selection of participants is a critical factor in determining external validity.
- Reactive Effects of Experimental Testing – The fact that treatments in a controlled, laboratory setting may differ from those in a less controlled, real-world environment. The performance of the participants may actually be more due to the setting than the independent variable.

- Multiple Treatment Interference – When participants receive more than one treatment, the effects of previous treatments may influence responses. Early treatments may have a cumulative effect on how participants perform or respond.

Conclusion

This study sought to address the gap in the literature in understanding the effectiveness of bimanual training using the BAT in stroke patients. The findings of this study support the use of the BAT for improving arm function in patients with stroke. Patient quality of life measures did not show a statistical significance; we believe this may be due to the fact that not enough time had elapsed for patients to fully assimilate and comprehend the effects of improved upper limb function on their quality of life.

Recommendations

The study serves as a pilot for subsequent bimanual studies using the BAT. Results from this study, as presented here, show promise for the use of the BAT in treating stroke patients. Future studies should focus on the ability to determine how an individual patient may learn best, i.e. with auditory stimulus, visual stimulus (Arulu et al., 2014), a combination of both, or neither, which may enable treatment sessions to be tailored to patients. Future research should have a larger sample size and randomize patients into different therapy groups. It is also recommended that future research be conducted on patients while they are in acute rehab, while the patients are in the acute phase of recovery. However, given the decreased number of days patients stay in acute rehab, if bimanual arm training can be continued in subacute rehab or an outpatient facility, the data will be more robust. This type of study can inform the clinician about the appropriate time in the recovery process to employ bimanual arm training. Although this study did not show improvements in patient quality of life measures, future studies can be geared towards finding a

correlation with the increased ability to use the arm and improved quality of life measures. Further studies should also consider the impact of decreased reliance of patients on human assistance once they are able to use the upper limb better. Studies may also want to focus on the long-term benefits from improved arm function by allowing patients to access devices such as the BAT in their community centers, gyms, and homes.

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Appendix A

Seton Hall University IRB Approval Form

Hackensack
Meridian *Health*

August 10, 2017

Seton Hall University
School of Health and Medical Sciences,
400 South Orange Ave, South Orange NJ 07079

Dear Dr. Zipp,

This letter is to confirm that the Hackensack UMC IRB (IRB of record for the Seton Hall School of Biomedical Science) will allow New York University to serve as the IRB of record for the research conducted for the Ph.D in Health Sciences requirements for Manuel Wilfred, PT DPT.

This cede of review is based on the following factors:

a) The study will be conducted an overseen by an investigator at NYU
b) The Hackensack Meridian Health Network is not engaged in this research

If there are any additional questions or concerns, please feel free to contact me.

Sincerely,

Kim Bazylewicz
Director, Human Research Protection Program
Office of Research Administration
Hackensack University Medical Center
30 Prospect Avenue, Hackensack, NJ 07601
T: 551-996-5977 | F: 551-996-1882
Kimberly.Bazylewicz@HackensackMeridian.org

Appendix B

New York School of Medicine IRB Approval Forms

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Office of Science and Research
Institutional Review Board
1 Park Ave.| 6th Floor, | New York, NY 10016

Approval of Submission February 16, 2017

Dear Preeti Raghavan:

On 2/14/2017 8:36 PM EST, the IRB reviewed the submission below: All conditions for approval were met on 2/14/2017.

principal investigator	Preeti Raghavan
email	raghap01@nyumc.org
study number	i11-00118
study title	Simultaneous Bimanual Training to Improve Motor Function Post-Stroke
performance period	2/14/2017 - to 12/20/2017 inclusive. Before 12/20/2017 or within 30 days of study closure, whichever is earlier, you are to submit a continuing review with required explanations. You can submit a continuing review by navigating to the active study and clicking Create Modification / CR. If continuing review approval is not granted before the expiration date of 12/20/2017, approval of this study expires on that date.
location(s)	Rusk Rehabilitation (34th Street) (NYUMC Locations), Ambulatory Care Center (NYUMC Locations)
sponsor(s)	Name: Rehabilitation Medicine;
review type	Modification
board name	Reported to all boards
materials approved for use	• Main ICF - R#11-00118 _2017_02_07_Clean.pdf, • Protocol_2017_02_07_Clean.pdf, • Exercise Log_2017_02_07_clean.pdf,
#of subjects approved to consent	
vulnerable populations approved for participation in this study	

The current IRB Status of your study is: Approved . This study was reviewed by the NYU School of Medicine's Institutional Review Board (IRB). During the review of your study, the IRB specifically considered:

1. the risks and anticipated benefits (if any) to your subjects
2. the selection of subjects
3. the procedures for securing and documenting informed consent
4. the safety of your subjects
5. the privacy of your subjects and confidentiality of the data

Your study cannot commence until all ancillary review decisions are complete. In order to determine the state of all ancillary reviews please go the My Studies page of this study in Research Navigator. Ancillary review statuses will be found on the right side of the header section.

Please note; if your study includes a clinical trial agreement or budget you will need to ensure approval has been issued from My Agreements/CRMS and The Office of Clinical Trials before you proceed with any aspects of this study including the enrollment of human subjects.

Review Notes
For NIH Grant funded research: the IRB has found the IRB approved protocol referenced above to be consistent with the NIH grant application.

Helen Panageas February 16, 2017

RE: Study#i11-00118
Helen Panageas, Director, Institutional Review Board OHRP #FWA00004952

Notes

- You must submit all changes to this study (e.g., protocol, recruitment materials, consent forms, etc.) via eSubmission to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.
- You must report all adverse and/or unanticipated event(s) that occur during the course of this study to IRB via eSubmission in accordance with IRB Policy.
- Use only IRB-approved copies of your consent form(s), questionnaire(s), letter(s), advertisement(s), etc. in your study. Do not use expired consent forms.
- You must inform all research staff listed on this study of changes or adverse events that occur.
- IRB's approval is valid until the end date of the performance period indicated above. A reminder for renewal should be e-mailed to you from the IRB 90, 60 and 30 days before this study's approval is scheduled to expire. However, you are responsible for submitting all renewal materials at least eight weeks before expiration regardless of whether or not you receive a reminder notice.
- All IRB policy documents can be found on our website: http://irb.med.nyu.edu/library
- Prior to initiating an IRB-approved study, you must receive written approval from an authorized representative for each site where your study will take place. Key contacts are:
    - **Bellevue Hospital**: when Bellevue Hospital is listed as a site where your study can take place, please note that you may have to complete additional work in BHC's Reason system. Bellevue will be contacting you with any additional needed information. For questions on Bellevue Hospital research, please contact *BellevueResearch@bellevue.nychhc.org*
    - CTSI - Clinical and Translational Science Institute, NYU School of Medicine [formerly General Clinical Research Center (GCRC)], ctsi@nyumc.org.
    - NYU Langone Medical Center (Tisch Hospital/Rusk Institute/Co-op Care/HJD/Perlmutter Cancer Center) site approval is handled for you automatically (as needed) by the Office of Clinical Trials
- The IRB may terminate studies that are not in compliance with NYU Langone Medical Center/School of Medicine Policies & Procedures and the requirements of the Institution's Federal Wide Assurance with the Federal Government. Direct IRB questions, correspondence and forms (e.g., continuing reviews, amendments, adverse events, etc.) to 212-263-4110 or IRB-INFO@nyumc.org.
- Prior to initiating an IRB-approved study, you must receive written approval from an authorized representative of the Office of Clinical Trials. You may contact the Office of Clinical Trials at 212.263.4210 or clinicaltrials@nyumc.org.

NYU SoM IRB operates in accordance with Good Clinical Practices (GCP) and applicable laws and regulations. The NYU SoM IRB Federal Wide Assurance number is 00004952.

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Office of Science and Research
Institutional Review Board
1 Park Ave.| 6th Floor, | New York, NY 10016

Approval of Submission

March 28, 2016

Preeti Raghavan

raghap01@nyumc.org

Dear Dr. Preeti Raghavan:

On 3/28/2016 3:00 PM EDT, the IRB reviewed the submission below: All conditions for approval were met on 3/28/2016.

principal investigator	Preeti Raghavan
email	raghap01@nyumc.org
study number	i11-00118
study title	Simultaneous Bimanual Training to Improve Motor Function Post-Stroke
performance period	3/28/2016 - to 1/31/2017 inclusive. Before 1/31/2017 or within 30 days of study closure, whichever is earlier, you are to submit a continuing review with required explanations. You can submit a continuing review by navigating to the active study and clicking Create Modification / CR. If continuing review approval is not granted before the expiration date of 1/31/2017, approval of this study expires on that date.
location(s)	Rusk Rehabilitation (34th Street) (NYUMC Locations), Ambulatory Care Center (NYUMC Locations)
sponsor(s)	Name: Rehabilitation Medicine;
review type	Modification
board name	
materials approved for use	The following personnel change has been noted: Adding Manuel Wilfred as personnel

The current IRB Status of your study is: Approved . This study was reviewed by the NYU School of Medicine's Institutional Review Board (IRB). During the review of your study, the IRB specifically considered:

1. the risks and anticipated benefits (if any) to your subjects
2. the selection of subjects
3. the procedures for securing and documenting informed consent
4. the safety of your subjects
5. the privacy of your subjects and confidentiality of the data

Your study cannot commence until all ancillary review decisions are complete. In order to determine the state of all ancillary reviews please go the My Studies page of this study in Research Navigator. Ancillary review statuses will be found on the right side of the header section.

Please note; if your study includes a clinical trial agreement or budget you will need to ensure approval has been issued from My Agreements/CRMS and The Office of Clinical Trials before you proceed with any aspects of this study including the enrollment of human subjects.

Review Notes:

For NIH Grant funded research: the IRB has found the IRB approved protocol referenced above to be consistent with the NIH grant application.

Helen Panagopoulos

March 28, 2016

RE: Study#i11-00118
Helen Panageas Director (Acting), Institutional Review Board OHRP #FWA00004952

Notes

- You must submit all changes to this study (e.g., protocol, recruitment materials, consent forms, etc.) via eSubmission to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.
- You must report all adverse and/or unanticipated event(s) that occur during the course of this study to IRB via eSubmission in accordance with IRB Policy.
- Use only IRB-approved copies of your consent form(s), questionnaire(s), letter(s), advertisement(s), etc. in your study. Do not use expired consent forms.
- You must inform all research staff listed on this study of changes or adverse events that occur.
- IRB's approval is valid until the end date of the performance period indicated above. A reminder for renewal should be e-mailed to you from the IRB 90, 60 and 30 days before this study's approval is scheduled to expire. However, you are responsible for submitting all renewal materials at least eight weeks before expiration regardless of whether or not you receive a reminder notice.
- All IRB policy documents can be found on our website: http://irb.med.nyu.edu/library
- Prior to initiating an IRB-approved study, you must receive written approval from an authorized representative for each site where your study will take place. Key contacts are:
    - ***Bellevue Hospital****: when Bellevue Hospital is listed as a site where your study can take place, please note that you may have to complete additional work in BHC's Reason system. Bellevue will be contacting you with any additional needed information. For questions on Bellevue Hospital research, please contact BellevueResearch@bellevue.nychhc.org*
    - CTSI - Clinical and Translational Science Institute, NYU School of Medicine [formerly General Clinical Research Center (GCRC)], ctsi@nyumc.org.
    - NYU Langone Medical Center (Tisch Hospital/Rusk Institute/Co-op Care/HJD/Perlmutter Cancer Center) site approval is handled for you automatically (as needed) by the Office of Clinical Trials
- The IRB may terminate studies that are not in compliance with NYU Langone Medical Center/School of Medicine Policies & Procedures and the requirements of the Institution's Federal Wide Assurance with the Federal Government. Direct IRB questions, correspondence and forms (e.g., continuing reviews, amendments, adverse events, etc.) to 212-263-4110 or IRB-INFO@nyumc.org.
- Prior to initiating an IRB-approved study, you must receive written approval from an authorized representative of the Office of Clinical Trials. You may contact the Office of Clinical Trials at 212.263.4210 or clinicaltrials@nyumc.org.

NYU SoM IRB operates in accordance with Good Clinical Practices (GCP) and applicable laws and regulations. The NYU SoM IRB Federal Wide Assurance number is 00004952.