Conventional Vs Robotic Stroke Therapy: Designing a Pilot study

by

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ABSTRACT

Stroke occurs when the blood supply to part of the brain is interrupted or reduced, preventing brain tissue from getting oxygen and nutrients, thus causing brain cells to die. Stroke is the 5th leading cause of death in the United States and is one of the major causes of disability. Conventional therapy is a form of stroke rehabilitation generally consisting of physical and occupational therapy. It focuses on customized exercises based on the patient's feedback. Physical therapy includes exercises such as weight bearing (affected arm), vibration of affected muscle and gravity-eliminated movement of affected arm. Overall physical therapy aims at strengthening muscle groups and aides in the relearning process. Occupational aspect of conventional therapy includes activities of daily living (ADL) such as dressing, self-feeding, grooming and toileting. Overall occupational therapy focusses on improving the daily activities performed by individuals. In comparison to conventional therapy, robotic therapy is relatively newer therapy. It uses robotic devices to perform repetitive motions and delivers high dosage and high intensity training to stroke patients. Based on the research studies reviewed, it is known that neuroplasticity in stroke patients is linked to interventions which are high in dosage, intensity, repetition, difficulty, salience. Peer-reviewed literature suggests robotic therapy might be a viable option for recovery in stroke patients. However, the extent to which robotic therapy may provide greater benefits than conventional therapy remains unclear. This thesis addresses the key components of a study design for comparing the efficacy of robotic therapy relative to conventional therapy to improve upper limb sensorimotor function in stroke survivors. The study design is based on an extensive review of the literature of stroke clinical trials and robotic therapy studies, analyses of the capabilities of a robotic therapy device (M2, Fourier

Intelligence), and pilot data collected on healthy controls to create a pipeline of tasks and analyses to extract biomarkers of sensorimotor functional changes. This work has laid the foundation for a pilot longitudinal study that will be conducted at the Barrow Neurological Institute, Phoenix, AZ, where conventional and robotic therapy will be compared in a small cohort of stroke survivors.

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CHAPTER 1

INTRODUCTION

1.1 Significance of stroke

Around 2400 years ago, Hippocrates mentioned the term “apoplexy,” which refers to the sudden loss of consciousness and motion (Engelhardt, 2017). This disorder is now generally known to us as Stroke. From around 2400 years ago, we humans have traveled so far in terms of science and technology. But even then, we have not found solutions to prevent some of the diseases and disorders that existed thousands of years ago. Stroke is still one of the leading causes of concern in the present society with rising disability. In the United States alone, stroke is 5^{th} in terms of the cause of death with the total number of stroke cases approximately being 795,000 every year (Mozaffarian Dariush et al., 2016). The total number of deaths with stroke as its cause is set to rise in the coming years as the present population lives longer and thus increasing the odds of having a stroke (Elkins Jacob S. & Johnston S. Claiborne, 2003). Thanks to extensive medical research, we have a better understanding of various diseases and medical conditions which were once impossible to understand. The advancement of this research has led to better treatments for the patients. So, if a patient has a stroke, they are more likely to survive it now compared to a few years ago. Because of this, during the last four decades, the age-adjusted mortality rate of stroke has decreased by greater than 60% in the United States (Chobanian et al., 2003). However, the odds of having a second stroke increases from the onset of stroke. One study claims that the risk of having another stroke increases up to 18% in 4 years from the first stroke (Feng et al., 2010). Hence, we can expect that the number of stroke survivors will increase in the coming years, which leads to the need for more effective approaches to stroke rehabilitation.

"Stroke is defined as a clinical syndrome, of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death" (World Health Organization 1978) (Intercollegiate Working Party for Stroke & Royal College of Physicians of London, 2012). Stroke can be broadly described to be caused by the lack of oxygen in a brain region because of blood vessels bursting, clotting, or narrowing down. The causes for blood vessel clotting, narrowing, or bursting could be due to age, gender, race/ethnicity, along with other lifestyle factors such as smoking, diet, alcohol consumption, and physical inactivity (Boehme et al., 2017). The causes of stroke are many, and the outcomes are highly variable based on where the stroke has occurred. Stroke is broadly classified into two types: Ischemic and Hemorrhagic. The reduction or loss of blood supply to the brain primarily caused by clotting or narrowing of blood vessels is known as Ischemic stroke. On the other hand, Hemorrhagic stroke is caused by the rupture of blood vessels in the brain (Donkor, 2018). Ischemic stroke occurs more frequently and contributes to almost 80% of all the stroke incidents.

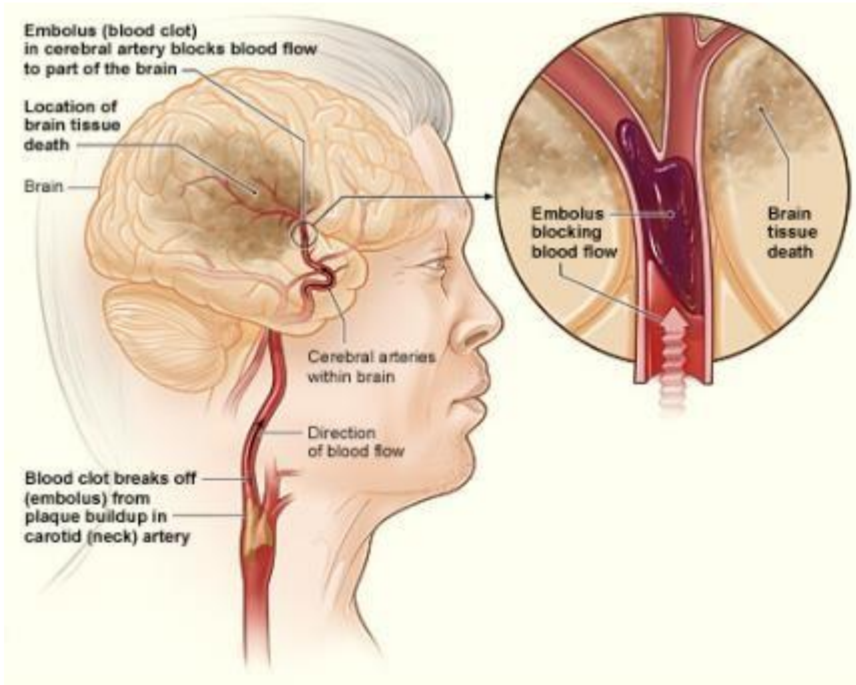

Figure 1: Ischemic Stroke (*Stroke | NHLBI, NIH,* n.d.)

Ischemic Stroke

Ischemic stroke or infarction of the brain tissue is caused by the regional reduction of cerebral blood flow for a time period (Figure 1). This results in lack of oxygen and glucose transfer to the brain, thus causing brain tissue damage (Brainin & Heiss, 2019). The reduction of blood flow could be due to the atherothrombotic changes, leading to emboli from other parts of the body reaching and blocking the blood vessels to the brain (Garcia, 1975). The brain regions affected due to reduction in blood flow are highly variable and mainly depend on the size and location of the emboli or thrombus formation.

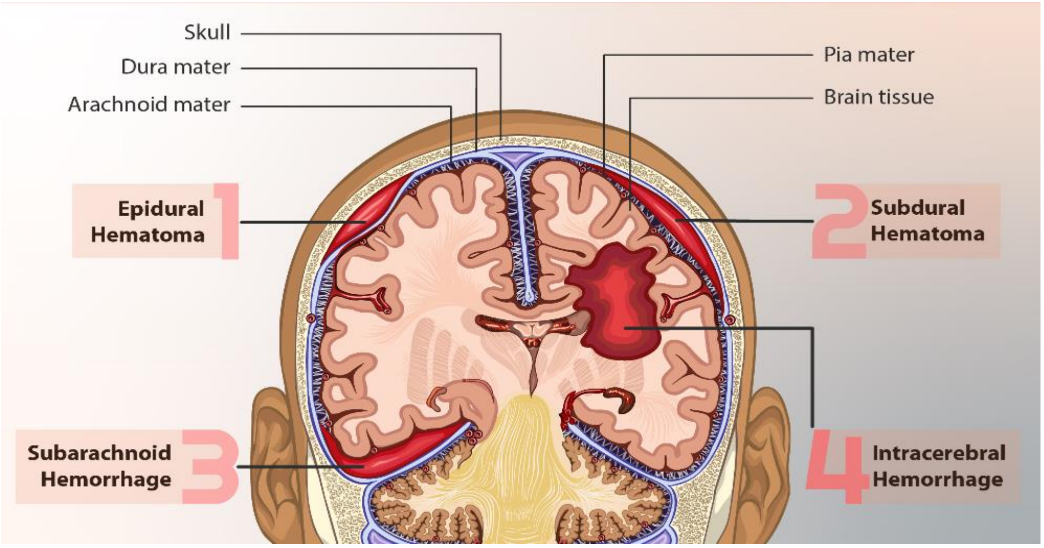

Figure 2: Types of Hemorrhagic Stroke (*Stroke | NHLBI, NIH*, n.d.)

Hemorrhagic Stroke

Hemorrhagic Stroke, as we understand, is the rupture of the blood vessels due to unwanted formations of Aneurysm or Arteriovenous Malformations (Figure 2; Garcia, 1975). Intracerebral hemorrhage is the type of hemorrhagic stroke which causes bleeding within the brain. Another type of Hemorrhage is the Subarachnoid hemorrhage, where the bleeding is around the brain. The cause of these types of hemorrhage is thought to be related to lifestyle (Boehme et al., 2017). The collection of blood between the external layer of the dura mater and the inner layer of the skull is called the Epidural hemorrhage (Kanematsu et al., 2018). Eventually, the outcome is classified as the rupturing of the blood vessel. A common cause of rupture of the blood vessel is the formation of an Aneurysm (Figure 3) (*Aortic Aneurysm | NHLBI, NIH*, n.d.). Aneurysm formation, if untreated, can lead to rupture of the blood vessel and also could lead to ischemia in the path where the blood vessel leads.

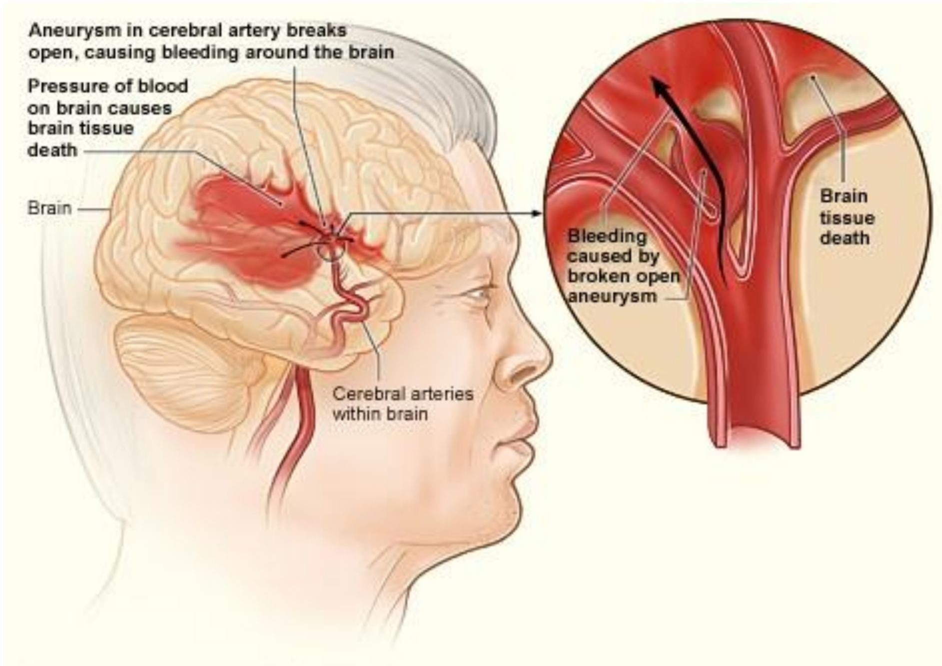

Figure 3: Aneurysm (*Stroke | NHLBI, NIH*, n.d.)

1.2 Stroke rehabilitation

According to the International Classification of Functioning, Disability, and Health (ICF model) developed by the World Health Organization in 2001, Stroke Rehabilitation is a procedure that “aims to facilitate people with health state experiencing or likely to experience disability to attain optimal functioning in interaction with the environment” (Bindawas & Vennu, 2016; *International Classification of Functioning, Disability and Health (ICF)*, n.d.). Although this definition represents an overall aim of stroke rehabilitation in general, it lacks clarity on how we can achieve it. According to Bindawas and colleagues (2016), regaining independence and improving quality of life is key to stroke rehabilitation, and that’s to be achieved using 1. Timing of rehabilitation (Early rehabilitation intervention), 2. Qualified multidisciplinary rehabilitation team and 3. Consistent Rehabilitation for a given duration (Bindawas & Vennu, 2016).

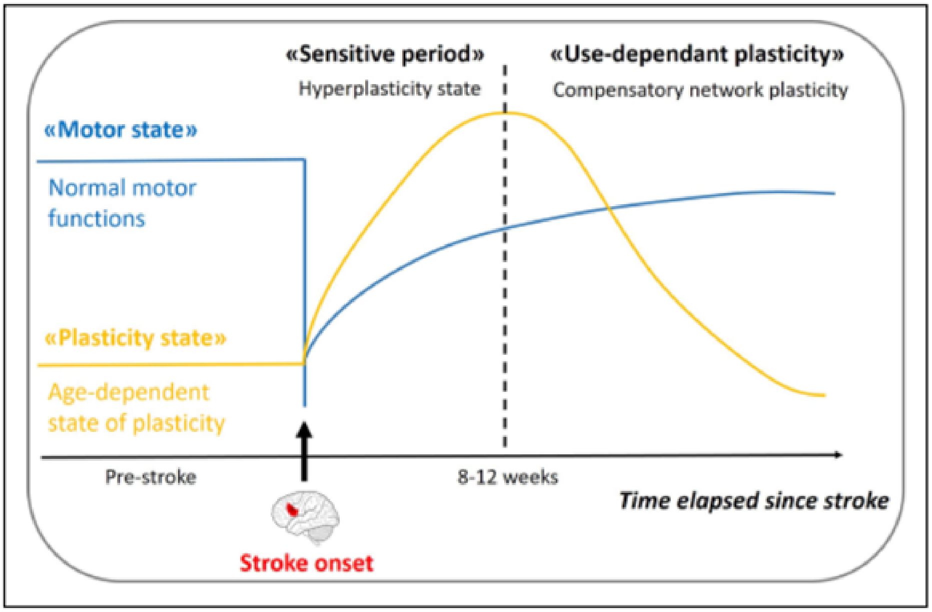

Figure 4: Sensitive and Use-dependent plasticity period (Raffin & Hummel, 2018)

Timing of rehabilitation (Early rehabilitation intervention)

In Stroke rehabilitation, time is of absolute essence, and it is highlighted in various studies. According to National Clinical Guidelines for stroke (UK), it is recommended to provide intravenous thrombolysis treatment within the first 3 to 4.5 hours of stroke, after which the significance of intravenous thrombolysis treatment declines (Intercollegiate Working Party for Stroke & Royal College of Physicians of London, 2012). Along with these early medical interventions, admission to stroke rehabilitation units as early as 24 to 48 hours from stroke is found to be beneficial in various studies (Sundseth et al., 2012). However, intervention should not begin in the first 24 hours or maybe even up to 1 week depending on the patient’s condition (Bernhardt et al., 2017). After admission to stroke rehab units, Multidisciplinary teams can access the patient’s condition and devise a personalized rehabilitation plan (Sundseth et al., 2012). As mentioned earlier, stroke is highly variable, and its outcomes are not always predictable. But there are critical periods in the path of stroke rehabilitation, and one of the important periods is believed to be the Sensitive period, also known as the hyperplasticity state (Figure 4). During this period, which initiates from the onset of stroke to the first 8 to 12 weeks, it is understood that proper training can induce higher reorganizational changes and better functional outcomes. Eventually, after this period of rapid recovery, the changes tend to normalize, and we reach a plateau (Raffin & Hummel, 2018). Looking at the overall picture, we can see that the timing of the rehabilitation makes a significant difference such that if rehabilitation procedures start early, greater recovery would be expected. This study suggests that the timing of intervention is important. However, the small number of clinical trials conducted in the acute phase of stroke prevents reaching a firm conclusion on whether early intervention is particularly effective (Coleman et al., 2017). A trial conducted by Boake and colleagues (2007) on 23 stroke patients (after 2 weeks of stroke onset) compared the Constraint-Induced movement therapy with traditional therapy (conventional) (Boake et al., 2007). The study concluded that the long-term effects on motor function did not differ between the two therapies compared. Therefore, the results of this study contradict the above-mentioned theory of early rehabilitation. Non-device assisted therapy, e.g., Constraint-Induced movement therapy, has shown no significant difference in long-term motor function compared to conventional therapy. However, a recent clinical trial conducted by Keeling and colleagues (2021) on 9 stroke patients (around 6 weeks post-stroke) (Keeling et al., 2021) found that robotic intervention during early stroke stages had a positive impact on upper-extremity motor function compared to conventional interventions. Earlier studies have also highlighted the therapeutic potential of robotic therapy when administered in the early stages of stroke (Coleman et al., 2017; Cruz et al., 2014; Forrester et al., 2014; Kuznetsov et al., 2013). In sum, although evidence is still limited, robotic stroke therapy appears to have the potential for promoting motor recovery in stroke.

Multidisciplinary teams

Another major factor of stroke rehabilitation is multidisciplinary stroke care units. Studies have shown that stroke care units as an intervention have consistently decreased deaths and dependency of stroke patients ("Collaborative Systematic Review of the Randomised Trials of Organised Inpatient (Stroke Unit) Care after Stroke," 1997; Donnan et al., 2008). According to the Stroke Unit Trialists' Collaboration (2001), 28 trials with a total of 5500+ patients were conducted to study the effectiveness of stroke care units and conventional care/therapy in terms of odds of deaths, institutionalized living, and independence (Stroke Unit Trialists' Collaboratio, 2001). The outcome indicated that conventional care/therapy was not the most effective form of stroke rehabilitation. Multidisciplinary stroke care units resulted in lower odds of death, dependency and increased the odds of living at home one year after the stroke. The stroke care units generally consist of nurses, occupational therapists, physical therapists, speech therapists, physicians. Family and community also plays an important role in bringing positivity and characterizing objectives for the therapy (Bindawas & Vennu, 2016).

Consistent rehabilitation (Duration)

Duration of rehabilitation is very important after stroke, and it is also easily neglected. There is no well-defined duration for stroke rehabilitation to continue. Generally, people focus on the first 2 to 3 months as it is known to be the sensitive period which contributes to major changes. But even after the sensitive period, stroke patients experience neuroplasticity (Raffin & Hummel, 2018). The rate of change in terms of neuroplasticity might be quite less after the sensitive period, and because of this there is an overall lack of interest in rehabilitation after 3 to 6 months of stroke. Other factors also contribute to this, such as lack of motivation, inadequate post-sensitive period rehabilitation programs, depression, expenditure. Hence, stroke rehabilitation programs need to be customized for every patient as each patient's recovery is highly variable. Long-term rehabilitation might be necessary for many stroke patients, and on a regular interval check-up need to be performed to assess the patient's function. Along with check-ups, therapy in some form or other needs to continue with the patient as long as the patient experiences complete recovery and independence in performing essential activities (Bernhardt et al., 2016; Bindawas & Vennu, 2016; Page et al., 2012; Wolf et al., 2006).

1.3 Rehabilitation and Factors of Influence

"Every stroke is unique". We might have come across this statement in various stroke research, and it is of profound importance. Stroke, as it occurs, causes damage in a unique manner to the neuronal networks which might result in impairment of sensation, movement, cognition (Murphy & Corbett, 2009). This uniqueness is critical to the rehabilitation process. Since no two types of stroke are the same, the efficacy of a certain stroke rehabilitation is almost always different for every patient. Hence, stroke rehabilitation needs to be personalized for each patient. However, this level of personalization is very difficult, even though most therapists attempt to cater to each patient's need. To understand more about how to design patient-specific therapies, a better understanding of the impairments caused by stroke is critically important. The most common type of impairment caused by stroke is motor impairment, followed by speech, vision, sensation, and other forms of impairments (Langhorne et al., 2011).

Motor impairment is the restriction or loss of muscle control or movement leading to difficulty in independent mobility. Almost 80% of stroke survivors experience some form of motor impairment such as limitation in control of muscles in the face, arm, legs of both sides, or a particular side of the body (Langhorne et al., 2009). These impairments cause the stroke survivors to be limited in motion and ultimately depend on others for their daily activity. Studies have shown that this sudden lack of motor control causes stress and emotional changes, which result in depression and lack of motivation in future rehabilitation (Nancy E. Mayo et al., 1999). Motor impairment rehabilitation is generally classified into upper and lower extremity rehabilitation, which focuses on areas around arms and legs, respectively. Classification of stroke impairment also includes hemiparetic/hemiplegic presentation, meaning there could be loss of strength in arm, leg, and sometimes face on one side of the body. Hemiparesis refers to a relatively mild loss of strength, while hemiplegia refers to a severe or complete loss of strength (*Human Phenotype Ontology*, n.d.). Another interesting aspect is the function of the head, trunk, and pelvis after stroke. The movement of these parts differs widely after stroke and that can cause difficulty in therapy sessions (Verheyden et al., 2011). In upper and lower limb rehabilitation, the function and strength of the trunk can also be a predictor of recovery (Karatas et al., 2004; Verheyden et al., 2007). For this study, we shall focus on the upper extremity motor impairments and its effects on the various types of rehabilitation therapies, especially with respect to conventional and robotic therapy.

Motor impairment is primarily caused by the injury to the motor cortex, premotor cortex, and motor pathways. These injuries are irreversible and permanent, but with proper attention and care, neuroplasticity can induce new pathways (Carey et al., 2019; Cramer & Riley, 2008). According to Langhorne et al. (2011), recovery of stroke is dependent on the site and size of the lesions in the brain. The process of recovery is through spontaneous and learning-dependent processes, such as restoring the functionality, reorganization of neural pathways, and compensation (Kwakkel et al., 2004; Langhorne et al., 2011). Neuroplasticity is the key to a stroke patient's recovery. Let's focus on some of the key factors of influence of neuroplasticity.

Repetition (Massed Practice/Repetitive Practice)

Learning or relearning a task without repetition causes little to no increase in synaptic strength. Thus, the learned skills are not going to be retained for a long time. However, repeating a task increases the synaptic strength, which implies that the skill learned will last longer, and it will improve on further repetitions (Kleim & Jones, 2008). According to de Sousa et al., 2018, they compiled data which shows that repetition as an intervention was able to influence motor recovery (de Sousa et al., 2018). The strength of the limbs involved in the repetition task also had a positive impact (de Sousa et al., 2018; French et al., 2016).

Studies indicate that repetition-based rehabilitation on animals with stroke is more effective than humans, and they also recover very quickly compared to humans (Krakauer et al., 2012; Randolph J. Nudo et al., 1996; Plautz et al., 2000). This is primarily due to the fact that animals perform relatively more repetitions when compared to humans. On average, an upper extremity treatment session for humans includes 39 repetitions in an active treatment time of 34 minutes (Lang et al., 2007). However, with the usage of modern equipment, we can achieve more repetition and training time. The best example is the use of robots in stroke rehabilitation.

Overall, review articles (e.g., Maier et al., 2019) suggest that repetition in current standing is not fruitfully quantified or measured and seems to be confounded with other factors such as dosage and difficulty. Therefore, more clinical studies are needed (Maier et al., 2019). In terms of rehabilitation, motor repetition is considered to be one of the key factors by many studies that have found positive outcomes (de Sousa et al., 2018; French et al., 2016; Kleim & Jones, 2008; Veerbeek et al., 2014).

Intensity / Dosage

Along with repetition, another key factor for inducing neuroplasticity in stroke rehabilitation is Intensity / Dosage (Kleim & Jones, 2008). Intensity in rehabilitation is a factor in which the overall amount of training given to a person is increased. Various studies have shown that performing more intensive training can result in more synaptic connections in the motor cortex, and overall there is an increase in motor recovery (Kleim & Jones, 2008).

Although intensity/dosage is recognized to be a key factor in stroke rehabilitation, what is the optimal dosage? This question is not fully answered by decades of studies conducted on the interventions for stroke rehabilitation (Lang et al., 2015). Lang and colleagues reviewed several papers and concluded that there is a significant relation between Dosage and its influence on sensorimotor functional improvement. They also state that there is a positive relation between the dosage and the time of intervention. Although the studies which are compared here are different in design, they conclude that the dosage is a good stroke rehabilitation intervention in any phase of stroke except for the most acute phase of stroke that includes the first few hours or days after stroke. The results of the study conducted by Winstein et al. (2019) are consistent with this proposition. They had 41 participants for the study and were divided randomly into 4 groups of different dosages (0hrs, 15hrs, 30hrs, 60hrs). After giving stroke rehabilitation (Accelerated Skill Acquisition Program) with the above-mentioned dosage, they analyzed the outcome using Fugl Meyer and Wolf Motor functional test. They concluded that there was a meaningful change in the motor function of the stroke participants with higher dosage (Winstein Carolee et al., 2019).

Overall, many studies have concluded that dosage is a significant factor in stroke rehabilitation. Although it is not clear when the timing is optimal to deliver a certain amount of therapy, there is general agreement that dosage/intensity is a key factor, and it should be strongly considered while performing stroke rehabilitation (Cramer et al., 2021; Lang et al., 2015; Winstein Carolee et al., 2019).

Difficulty

Increasing the difficulty of the various tasks performed during stroke rehabilitation can influence superior learning and further improve the participant's motor abilities (Maier et al., 2019). According to Pan et al., 2019, they conducted a study with variable difficulty levels on a robot-assisted stroke rehabilitation device. They derived a formula which gives a dynamic score based on which they would quantify the participant's performance. Based on the score, the level of difficulty would change and thus influence the participant to perform the task without loss of interest (this can be related to salience which could be another factor) (Maier et al., 2019; Pan et al., 2019). According to Grimm et al., 2016, they performed a study with adaptable difficulty with a Virtual Reality (VR) based system in place. They change the length of the target location based on successful attempts, and when they are not able to reach the target, the VR system induces a virtual change in the target without any passive movements. This might in one way induce motor imagery which is also considered to be a factor for intervention in stroke rehabilitation (Grimm et al., 2016; Maier et al., 2019).

Overall, stroke rehabilitation systems that can modulate task execution difficulty are on a rise and are generally used along with Virtual Reality (VR) and Robotics. Studies have shown beneficial outcomes in terms of motor recovery while using difficulty as an intervention (Maier et al., 2019).

1.4 General Strategy for Stroke Rehabilitation

Apart from the aspects mentioned above, there are some general strategies undertaken by physicians and stroke specialists. According to Langhorne et al. 2011, Stroke rehabilitation can be considered as a cyclic process. This cyclic process starts with the 1. Assessment of the patient's condition, 2. Setting Targets/Goals, 3. Plan of Rehabilitation (Interventions), 4. Reassessments and repeat (Langhorne et al., 2011).

Assessments: Therapists perform various assessments to quantify the patient's current function, spasticity, strength, and other outcomes, and using these assessments the stroke care units are able to plan the patient’s rehabilitation process.

Goal Setting: After quantifying and assessing the patient’s current condition, the stroke care units set goals for the patient to achieve within the next couple of weeks.

Intervention: In order to achieve these goals, appropriate interventions are to be given by the stroke care units at regular intervals. These interventions can be part of in-patient and out-patient rehabilitation programs. Stroke care units utilize the critical weeks of the sensitive period to induce neuroplasticity.

Reassessment: At this point of the stroke rehabilitation process, the patient undergoes assessments again, which will help determine the patient’s current condition. Based on this information further, goal setting and interventions are planned. This process is more likely to be repeated at least once until the patient recovers.

1.5 Types of stroke rehabilitation

There are several types of stroke rehabilitation interventions used currently in the world and to classify them all is very difficult. According to Cathy et al. 2020, interventions for stroke rehabilitation can be broadly classified into 4 categories such as Training Interventions, Technological Interventions, Pharmacological Interventions, and Neuromodulation interventions (Stinear et al., 2020). Currently, these interventions are seldom given individually but rather given in a mixed format involving at least 2 of the above-mentioned interventions. The focus of this report is on conventional and robotic stroke rehabilitation.

Conventional Stroke Rehabilitation

Conventional therapy is a form of stroke rehabilitation consisting of physical therapy, occupational therapy, and speech therapy, primarily focusing on improving patient's daily activities by relearning and coordination of skills (*Recovering From Stroke | Cdc.Gov*, 2020). Conventional therapy focuses on customized exercises based on the patient's feedback and functional status (Chang & Kim, 2013). Also, some therapists perform therapies using treatment approaches such as Proprioceptive Neuromuscular Facilitation (PNF) and Neuro Developmental Treatment (NDT)/ Bobath. PNF is considered to be very effective in terms of increasing the range of motion (Yıldırım et al., 2016). Bobath concept is more focused on improving both functional activities and the impairment along with efficiency of movement (Kollen et al., 2009).

Although conventional therapy is considered to be a more reliable and widely used form of therapy worldwide, in recent years, we can observe the rise in usage of assistive technology in stroke rehabilitation (Langhorne et al., 2011).

Robotic Stroke Rehabilitation

Another form of therapy which is currently on rise is robot-assisted stroke rehabilitation that delivers high dosage and high intensity training to stroke patients (Chang

& Kim, 2013). Robotic therapy used for upper extremity rehabilitation broadly combines the following (Fasoli et al., 2004; Hatem et al., 2016; Hidler et al., 2005):

1. Mechanical component which is generally motorized. The affected hand is placed or attached on to this mechanical component to provide passive or active movement training.
2. Visual feedback component through a display monitor.
3. Software which enables selection of games/tasks with an ability to automatically or manually change the difficulty of the game/task to maintain the patient's motivation.

Various studies have found that neuroplasticity in stroke patients is linked to intervention dosage, intensity, repetition, difficulty, salience (Maier et al., 2019; Roger et al., 2011). Literature suggests robotic therapy is able to induce high dosage, high repetition training to stroke patients, which makes it a viable option for recovery in stroke patients (Hatem et al., 2016; Sivan et al., 2011) (see Methods for a more description about robotic therapy). However, the extent to which robotic therapy may provide greater benefits than conventional therapy remains mostly unclear.

1.6 Gaps in literature

Conventional therapy is known to be used widely in the stroke rehabilitation process when compared to Robotic therapy. However, studies have indicated that robotic therapy provides more repetition, intensity, difficulty, which are the factors of influence of neuroplasticity (Chang & Kim, 2013; Hatem et al., 2016; Sivan et al., 2011) (see Methods for a more description about robotic therapy). The concerning factor here is that very few studies are known to compare the individual effects of these two therapies directly, and most of the studies combine robotic therapy with conventional therapy (Dehem et al., 2019; Keeling et al., 2021; Taveggia et al., 2016) (See Discussion for more details about the inconsistency). To address this gap in determining which among these two therapies have more beneficial outcomes in terms of recovery, there is a need to analyze both the therapies individually. However, before conducting such a study, it is imperative to lay down a proper experimental procedure taking into consideration how previous studies were executed (Sivan et al., 2011). Therefore, this report/thesis will try to study previous robotic therapy research and document an experiment which closely resembles conventional therapy. Ultimately, this study will further proceed to conduct an experiment over a short typical course of rehab, which replicates the time and interventions given in a typical outpatient course of therapy. At the same time, the study will analyze the recovery of the stroke patients while trying to reduce or uniformly maintain any confounding factors. The final results of the study will help identify the amount of neuroplasticity induced by the proposed conventional and robotic therapy.

CHAPTER 2

METHOD

2.1 Advances in Conventional & Robotic therapy

Conventional Stroke Rehabilitation

Conventional therapy is the most widely used therapy in stroke rehabilitation. The most fundamental components of conventional therapy are the Physical, Occupational, and Speech therapy. However, the current state-of-the-art conventional therapy is Constraint-Induced Movement Therapy (CIMT) and studies have indicated that it is an effective therapy (Bang et al., 2018; Ju & Yoon, 2018; Uswatte et al., 2018). In CIMT, the patient's unaffected arm is restrained from use and the affected arm is forced to use (Pollock et al., 2013). Although some argue that, as the unaffected arm is restrained using arm sling or something similar, CIMT should be classified as assistive technology. However, since the affected arm is performing exercise-based tasks, CIMT is classified under conventional therapy. Most importantly, CIMT induces difficulty in the tasks performed by the patients and thus it influences neuroplasticity. Along with CIMT, another promising conventional therapy is Mirror Therapy (MT). While performing mirror therapy, a mirror is placed next to the unaffected arm, blocking the view to the affected arm. As the unaffected arm moves it creates an illusion of both arms functioning. This movement of the unaffected arm is perceived as the movement of the affected arm and this thought to be inducing neuroplasticity by exciting ipsilateral motor cortex projecting to the paretic limb (Deconinck et al., 2015). Studies of MT showed motor and sensory improvements in stroke patients (Gandhi et al., 2020; M. M. Lee et al., 2012). Neurodevelopment Treatment

(NDT), also commonly known as Bobath Concept, is a treatment or evaluation approach used by therapists for individuals with motor difficulties acquired by neurological conditions such as stroke (Besios et al., 2019; *Bobath Approach*, n.d.). NDT is commonly used as part of stroke rehabilitation programs and it is considered to be effective in improving motor functions (Besios et al., 2019). Neuromuscular electrical stimulation (NMES) is a therapeutic intervention in which electrical stimulations are aimed at the recovery of the paretic limbs after stroke (Langhorne et al., 2009; Takeda et al., 2017). NMES is often used to strengthen muscles, induce motor recovery and reduce spasticity (Takeda et al., 2017). Studies have shown that NMES is effective when used in conjunction with conventional exercises performed by therapists (Knutson et al., 2015; Sahin et al., 2012; Tashiro et al., 2019). Therapists at Barrow Neurological Institute (BNI) also confirmed their use of NMES and mentioned that it is more effective to provide NMES when patients put in effort to the movement.

Physical therapy (PT) aims at improving the patient's strength, mobility, movement of a limb by using various exercises. Occupational therapy (OT), on the other hand, focuses mainly on the patient's functional and purposeful tasks to improve activities of daily living (ADL), cognition, perceptual and sensory outcomes (Franceschini et al., 2020; *Rehabilitation After Stroke*, n.d.). However, the overall aim of both types of therapy is to regain as much mobility of the body within a limited timeframe. Unlike other forms of stroke therapy, conventional stroke therapy is widely dependent on manual exercises assisted by a therapist. Physical and occupational therapists progressively assess the patient's recovery. Based on the patient's recovery, they progressively increase the intensity/difficulty to the limits of the patient's ability, while adjusting in real time the delivery of the interventions to optimize recovery. In conventional therapy, there is no one exercise or sub therapy which is better than other, but based on the literature and discussion with BNI, it can be perceived that conventional therapy is reliant on mixture of all the sub therapies and exercises.

Robotic Stroke Rehabilitation

Stroke robotic therapy is a new therapy relative to conventional therapy. Robotic therapy as mentioned earlier uses motorized mechanical component on which the affected arm is placed or attached to perform passive or active training sessions. Software systems along with display screens are used to provide interactive visual feedback (Fasoli et al., 2004; Hatem et al., 2016; Hidler et al., 2005).

In terms of stroke rehabilitation, robotic devices can be classified into two categories: (1) end-effector robotic devices and (2) exoskeleton robotic devices. This classification is primarily for robotic devices used for upper extremity stroke rehabilitation. While using end-effector robotic devices, patients are dependent on using their most distal part of the affected limb for exerting force (Duret et al., 2019). In most cases, the distal part of the affected limb must be attached to the robotic device or must hold the arm of the robotic device. In contrast, exoskeleton devices are generally wearable electro-mechanical devices which mimic the kinematic configuration of the human joints (Duret et al., 2019; S. H. Lee et al., 2020). Apart from general strategies of stroke rehabilitation (Early Rehabilitation, Multidisciplinary teams, and Duration of the treatment), the patient's recovery is dependent on neuroplasticity (Pekna et al., 2012). Repetition, high-intensity training, and difficulty are some of the many known factors which influence neuroplasticity (Kleim & Jones, 2008). Currently, robotic devices both end-effector and exoskeleton provide these factors of influence with minimal supervision from the therapists. Adding to these benefits, robotic therapy is now provided along with newer forms of interventions. Studies have shown that robotic therapy with Neuromuscular Electrical Stimulation (NMES) to be effective when compared with just robotic therapy (Y. Huang et al., 2020). They showed improvement in voluntary motor recovery, muscle coordination, and reduction in spasticity for the group which combined NMES and Robotic therapy. The study concludes that robotic therapy should be combined with NMES to be an effective upper limb rehabilitation for stroke patients (Y. Huang et al., 2020). Overall, robotic therapy in stroke rehabilitation with or without additional interventions (such as NMES), still appears to be a promising approach and the results show us that robotic therapy has a great influence in a stroke patient's recovery (Bustamante Valles et al., 2016; Calabrò et al., 2019; Dehem et al., 2019; Franceschini et al., 2020; Keeling et al., 2021; Orihuela-Espina et al., 2016; Takahashi Kayoko et al., 2016; Taveggia et al., 2016). However, there are some contradictions to robotic therapy in the literature (Discussed under the title "Can stroke robotic therapy substitute conventional therapy?")

Conventional versus Robotic Stroke Therapy

Conventional therapy with its state-of-the-art Constraint-induced movement therapy, mirror therapy, neuromuscular electrical stimulation, and other approaches have improved stroke patient recovery in most of the cases (Bang et al., 2018, p. 2; Besios et al., 2019; Gandhi et al., 2020; Ju & Yoon, 2018; Langhorne et al., 2009; Takeda et al., 2017; Uswatte et al., 2018). However, when we compare conventional therapy to most of the robotic therapy, we find that conventional is not as effective. A trial conducted by Takashi and colleagues, compared robotic therapy with conventional therapy on 60 stroke patients. They concluded that robotic therapy has improved upper extremity impairments in comparison to conventional therapy. In a similar trial conducted by Dehem and colleagues on 45 acute stroke patients comparing conventional and robotic therapy, they concluded that robotic therapy resulted in more upper limb function. In similar studies, we can find that robotic therapy has improved upper limb function in comparison to conventional therapy (Bustamante Valles et al., 2016; Calabrò et al., 2019; Franceschini et al., 2020; Keeling et al., 2021; Orihuela-Espina et al., 2016; Taveggia et al., 2016). Therefore, the above-mentioned research suggests that robotic therapy is more effective in terms of upper extremity function. In that case, can we replace conventional therapy with robotic therapy? We shall look into some limitations about robotic therapy in the literature.

Can stroke robotic therapy substitute conventional therapy?

Similarly, state-of-the-art robotic therapy has been utilizing various robotic devices to improve stroke patient's recovery (Hatem et al., 2016; Langhorne et al., 2009). However, there are quite a few contradictions posed by robotic therapy. Trials conducted by Rodgers and colleagues, and another trial conducted by Sale and colleagues both used the same MIT-MANUS robotic device for their robotic intervention in comparison to conventional therapy. However, the two failed to reciprocate similar results in comparison to conventional therapy. Rodgers and colleagues, concluded that robotic therapy did not improve upper limb function when compared with usual care for stroke patients (Rodgers et al., 2019). While Sale and colleagues, concluded that robotic therapy did improve upper limb function when compared with conventional therapy (Sale et al., 2014). Another study conducted by Lo and colleagues, compared robotic therapy with usual care (Clinic visits and rehabilitation for some patients) and intensive comparison therapy (which was equivalent to conventional stroke therapy). After completing 36 sessions (over a span of 14 weeks) of the respective therapy, assessments were conducted at 12 weeks and 36 weeks. The trial concluded that robotic therapy did not improve motor function as compared to usual or intensive comparison therapy at 12 weeks. However, assessments at 36 weeks, found that motor function of robotic therapy was found to be better when compared to usual care but not with intensive comparison therapy (conventional stroke therapy). Overall, the trial concludes by stating that robotic therapy is not as effective in motor recovery when compared with intensive or usual care.

It was also noted that many studies comparing conventional and robotic therapy, did not have robotic therapy conducted alone. Instead, studies used robotic therapy as an adjunct to conventional therapy and compared that with conventional therapy alone. Trials conducted by Keeling and colleagues (2021), Takahashi and colleagues (2016), and Taveggia and colleagues (2016), used the same method of combining robotic and conventional therapy in comparison with conventional therapy and concluded that the combined group had more improvements in terms of upper limb function (Keeling et al., 2021; Takahashi Kayoko et al., 2016; Taveggia et al., 2016).

This leaves us with more questions than answers, the contradiction of results in both conventional and robotic therapy, encourages us to conduct a study which compares the individual effects of robotic therapy and conventional therapy on the changes in sensorimotor function.

2.2 Recommended features of the study

Length of the study

Based on the literature and previous studies(Aprile et al., 2020; Bustamante Valles et al., 2016; Calabrò et al., 2019; Dehem et al., 2019; Franceschini et al., 2020; Keeling et al., 2021; Massie et al., 2016; Orihuela-Espina et al., 2016; Rodgers et al., 2019; Takahashi Kayoko et al., 2016; Taveggia et al., 2016), length of the study is highly variable, and range from 2 weeks (Aprile et al., 2020) to 12 weeks (Orihuela-Espina et al., 2016; Rodgers et al., 2019). However, on average, studies concluded within 7.5 weeks of intervention with 4.75 sessions per week (Bustamante Valles et al., 2016; Calabrò et al., 2019; Franceschini et al., 2020; Keeling et al., 2021; Orihuela-Espina et al., 2016; Rodgers et al., 2019; Takahashi Kayoko et al., 2016; Taveggia et al., 2016).

Repetitive and intensive form of training is believed to be some of the factors that influence for neuroplasticity (Kleim & Jones, 2008; Maier et al., 2019). However, distributed practice is one of the best way to retain learning over time (Krakauer, 2006). A study conducted by Dettmers and colleagues (2005), compared CIMT therapy on stroke patients using two modes of practice, massed practice, and spaced practice (Dettmers et al., 2005). The massed practice group received 6 hours of training for 10 days and the distributed practice group received 3 hours of training for 20 days. The study concluded that the distributed CIMT group improved in motor function, muscle strength, and spasticity in comparison to massed CIMT group.

Therefore, it is recommended that the study be at least 7 weeks long and have a space practice of at least 4 sessions per week.

Inclusion and Exclusion

The inclusion criteria of any study need to be very specific and should be closely monitored with the requirement of the study. In terms of stroke, there are many specifications that need to be taken into account, including but not limited to age, pain tolerance, range of motion, muscle stiffness, and the phase of stroke (Aprile et al., 2020; Keeling et al., 2021). Based on the timing of rehabilitation (see Introduction), we can focus on the early stages of stroke patients for the study. However, it is important to avoid intervention in the very early stages of stroke as suggested by studies using non-device assisted therapy (Bernhardt et al., 2017; Boake et al., 2007). Therefore, it is recommended to start the study 5 to 6 weeks from the onset of stroke based on previous literature (Dehem et al., 2019; Franceschini et al., 2020; Keeling et al., 2021; Takahashi Kayoko et al., 2016). Based on the literature, the following inclusion and exclusion criteria need to be considered when designing a study on stroke patients targeting sensorimotor function of the upper limb:

1. Age (18+)
2. Had Stroke
3. How long since stroke? (Preferably 5 to 6 weeks from the onset of stroke)
4. Pain tolerance for each study session
5. Limited or no contractures
6. Range of Motion (Shoulder)
7. Have muscle strength to perform the study session

8. Ability to comply with the therapists in charge
9. Adequate cognitive and language abilities to understand the study session.

Corticospinal tract integrity

To assess the integrity of the corticospinal tract, transcranial magnetic stimulation (TMS) has been found to be a valuable tool for predicting the extent of recovery of stroke patients (Ward, 2011). According to Heald et al. 1993, when conducting TMS, the presence of Motor Evoked Potentials (MEPs) often indicated that recovery was possible with motor practice for up to 3 years. However, in the absence of Motor Evoked Potentials (MEPs), recovery was difficult to predict (Heald et al., 1993). Therefore, the presence/absence of MEPs should be considered as an additional inclusion/exclusion criterion.

Predict Recovery Potential 2 (PREP2)

Predict Recovery Potential 2 (PREP2) is an algorithm which uses clinical measures and neurological biomarkers during the first few days after the occurrence of stroke to predict upper-limb functional outcomes at 3 months (Stinear et al., 2017). This method could be used as a complementary or alternative inclusion/exclusion criterion relative to TMS if time is limited.

Functional assessments

When conducting stroke research, it is important to assess the patient's conditions on a regular basis to provide tailored rehabilitation because every stroke is unique, and one process cannot be applied to all patients. To understand the functional status of a stroke patient, functional assessments need to be conducted. Each assessment has its own strengths and weaknesses, and therefore one should consider combining some or most of clinically validated assessments. At the same time, for practical reasons, one should avoid administering functional assessment tests that provide overlapping/redundant information. In the literature reviewed, majority of the research conducted used Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA) as one of the assessments (Aprile et al., 2020; Franceschini et al., 2020; Keeling et al., 2021; Massie et al., 2016; Takahashi et al., 2005). This is primarily because FMA is considered to be the gold standard in motor recovery assessment worldwide (Teasell et al., 2009). However, the main limitation of this assessment is that FMA can be very time consuming. The Modified Ashworth Scale (MAS) is another commonly used assessment and it is generally used to assess the patient’s spasticity. It is recommended to use these two assessment tools in the proposed study design as they are accepted worldwide, can be interpreted by clinicians, and cover a broad range of motor recovery and spasticity metrics.

Here is a summary of the recommended assessments:

1. **Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA):** It is used to assess motor function, sensation, balance, joint function, and pain in post-stroke patients. It is considered a gold standard in research and can be used as an assessment to reflect patient recovery. However, it is a time-consuming process and is also referred to be not very responsive to chronic stroke patients (Teasell et al., 2009; J. H. van der Lee et al., 2001).

2. **Modified Ashworth Scale (MAS):** This scale is used as the primary clinical measure for tone as perceived by the examiner. It is widely accepted and can be considered the clinical standard test for tone. Even though it is considered a standard, there is no standardized testing protocol or guideline mentioned for MAS. In the study conducted by Balkburn and colleagues (2002), the assessors were not trained well enough and therefore it resulted in poor levels of interrater reliability (Blackburn et al., 2002; Teasell et al., 2009).

3. **The Action Research Arm Test (ARAT):** It is based on performance of the stroke patient's upper extremity function and dexterity (Hsueh & Hsieh, 2002). It is a relatively short assessment tool with simple measures of upper limb function. It covers a wide range of aspects such as arm function, including proximal control and dexterity. The administering of the test can take more than 20 mins in relatively more impaired patients (Teasell et al., 2009). According to Van der Lee and colleagues (2002), the test might not be sensitive enough to detect changes in severely impaired patients (Johanna H. van der Lee et al., 2002).

4. **Barthel Index (BI):** Intended to quantify the ability of a patient with neuromuscular or musculoskeletal disorder to selfcare on a simple index of independence (Teasell et al., 2009). The major advantage of BI is its simplicity and ease to administer. Major drawback in BI is the lack of agreement with respect to the threshold of dependence/independence and also the different scoring systems presently used.

5. **Motor Assessment Scale:** Developed to assess everyday motor functions after stroke, it evaluates motor performance of functional tasks (Malouin et al., 1994;

Teasell et al., 2009). It is a short and simple test to perform and that is one of its advantages. However, the scoring hierarchy had some issues. According to Poole and Whitney (1988) and Moulin et al. (1994), patients were able to perform the most difficult task in the test and at the same time find it hard to complete the easier task (Malouin et al., 1994; Poole & Whitney, 1988).

6. **Nine-hole Peg Test (NHPT)** is one of the fastest amongst the assessment mentioned here. It quantifies fine manual dexterity. NHPT is considered very reliable and is widely accepted for adults and pediatric populations. However, according to Cohen & Marino (2000), NHPT results are set to improve with practice which is a drawback (Cohen & Marino, 2000; Teasell et al., 2009).

Timing of functional assessment is another important factor. Ideally, the assessment should be conducted after every session of intervention. However, practically it consumes a lot of time, and therefore, the best and most common method is to perform the assessment pre- and post-intervention. Hence, it is recommended that a mixture of assessments or an extensive assessment like Fugl-Meyer be conducted before and after the entire intervention period.

Robotic functional assessment

Robotic devices are equipped with sensors and various hardware that can analyze patient's functional capabilities such as patient's movement trajectory, forces applied, range of motion, displacement and velocity. These data sets are not standardized in terms of clinical assessments mentioned earlier but they can provide very valuable and objective information. Specifically, these data sets can help understand the patient's recovery trajectory throughout the course of intervention. In addition, these raw data are generated as the patient is performing training, which saves time for both the therapist and the patient. It is recommended to use these robotic assessments if available and feasible.

Equipment

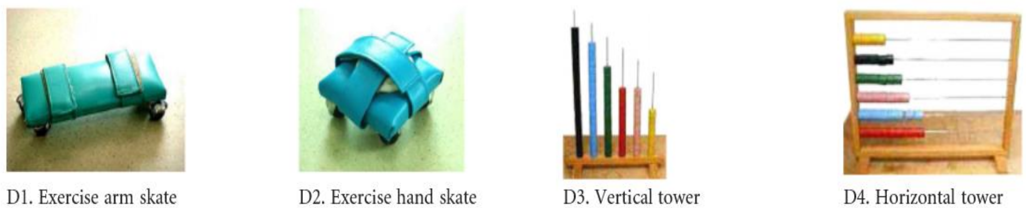

Figure 5: Some equipment used in conventional therapy. (L.-L. Huang et al., 2013)

Conventional therapy

Conventional therapy is highly reliant on physical exercises performed under therapist's supervision. But there is various equipment used for conventional therapy and each one of them has its significance. The figures 5, 6, and 7, show some of the equipment used in conventional therapy. The literature does not explicitly focus on the equipment or brand of equipment used in conventional therapy.

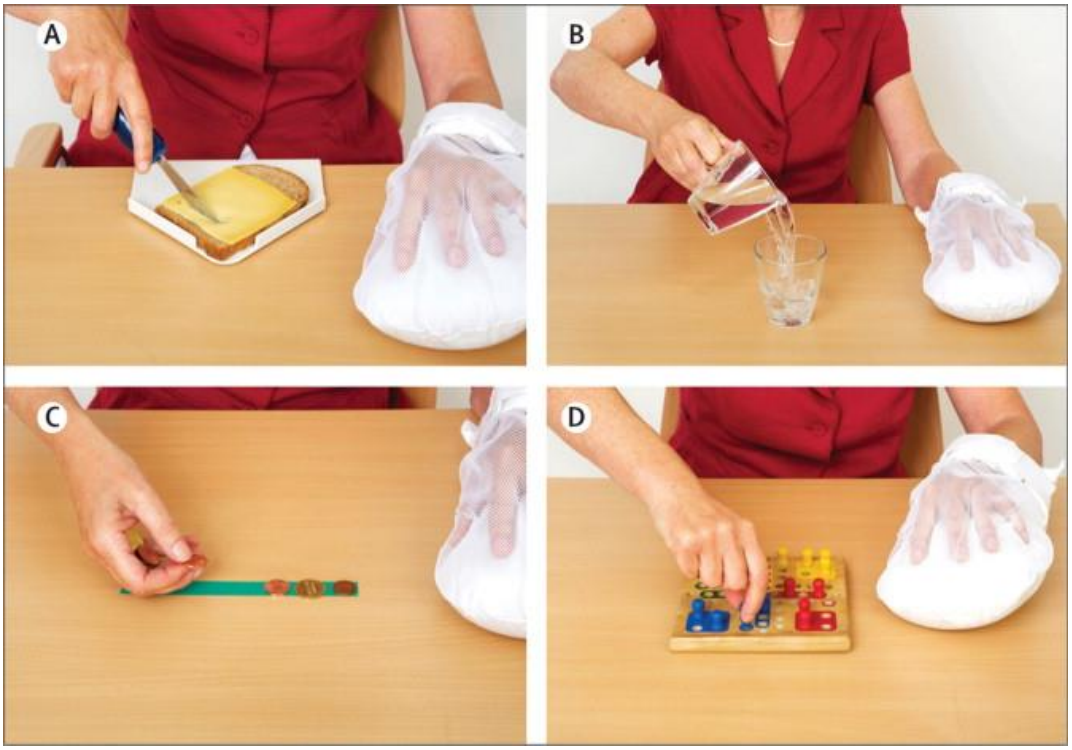

Figure 6: Constraint-induced movement therapy performed in a study. (Kwakkel et al., 2015)

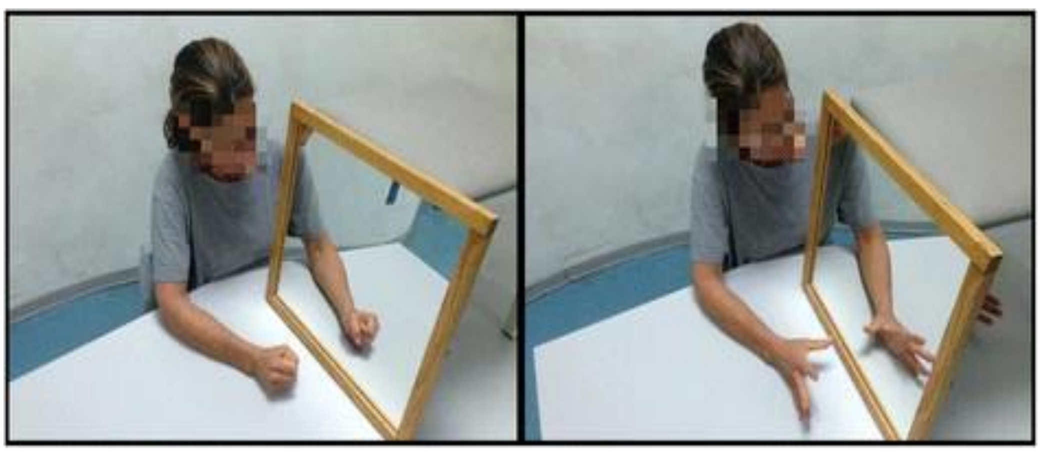

Figure 7: Mirror therapy (Corbetta et al., 2018)

Robotic therapy

Robotic devices for upper limb rehabilitation, as mentioned earlier, are broadly classified under two categories end-effector and exoskeleton. Which of the two is more effective in promoting functional recovery in stroke according to the literature? Peer-reviewed literature shows that both exoskeleton and end-effector based devices are effective and provided improvement in patient's overall recovery (Corbetta et al., 2018; Dehem et al., 2019; Keeling et al., 2021; Taveggia et al., 2016). A study conducted by Lee and colleagues (2020), compared an end-effector robotic device with an exoskeleton robotic device. They concluded that the end-effector robotic device is better than exoskeleton device in terms of activity (using Wolf Motor Function Test - Functional ability rating scale and Time) and participation (using stroke impact scale) (S. H. Lee et al., 2020). Although studies have used exoskeleton robotic device, it is recommended to use end-effector robotic device as it is found to be better than exoskeleton devices. The ArmMotus M2 which is an end-effector robotic device seems to be a good candidate. The device is capable of providing high-level customized intervention. Different modes of training can be provided based on the level of impairment present in the stroke patient. The mode of training can be manipulated further to personalize the intervention provided. There are various patterns of movement which can be performed using the M2 robotic device. There are many games in the M2 device which is highly salient will help in inducing neuroplasticity. (More details mentioned below under the Study Intervention section)

 

Figure 8: Fourier Intelligence ArmMotus M2 (left side) (a typical end-effector robotic device used for upper extremity stroke rehabilitation) Figure 9: Kinarm Exoskeleton (right side) (a typical exoskeleton robotic device used for upper extremity stroke rehabilitation)(*Kinarm Exoskeleton Lab*, n.d.)

Study Interventions

In conventional rehabilitation, there are several exercises and sub therapies being used presently (many of which are mentioned in the previous paragraphs). Based on the literature review conducted for this thesis, it is recommended that conventional therapy in the pilot study include the newer and the more effective interventions along with the traditional ones. As we know that repetition is a key factor of neuroplasticity, it is a good practice to quantify the number of repetitions performed in the study. Studies conducted by Lang and colleagues have attempted to quantify the number of repetitions used for stroke rehabilitation in a clinical setting (Lang et al., 2009, 2015). These studies found that the average number of repetitions for upper extremity rehabilitation was close to 32 in clinical setting. However, this number of repetitions are significantly smaller than those needed to promote improvement in upper limb motor function (Lang et al., 2009). In animal studies, which includes healthy monkeys and rats, around 400 to 600 upper extremity task repetitions were necessary to observe skill learning changes in cortical representations (Kleim et al., 1998; R. J. Nudo et al., 1996). In a similar stroke model animal study, monkeys performed an upper limb task with around 600 repetitions per day. This number of repetitions was able to reverse the harmful effects of the cortical lesion (Randolph J. Nudo et al., 1996). Overall, we can see that animal studies required far more repetitions to induce improvements in lesioned cortical areas after stroke. Even though it is often not feasible to increase the number of movement repetitions in clinical settings, keeping track of the number of repetitions should be one of the key features of stroke studies to allow comparison with previous work. Therefore, we recommend that the therapist performing both conventional and robotic therapy quantify the number of repetitions provided during both interventions. Tally counters or a checklist can be used during conventional therapy. However, during robotic therapy the therapist can choose to do the same or use the robotic assessment system to track the movement repetitions.

Here is a list of potential new and effective exercise and sub therapies (It is important to note that the therapies are not limited to these mentioned below and that it is imperative to include other physical and occupational exercises):

1. Constraint induced movement training (CIMT): Constraint-induced movement therapy has shown clinical improvements in stroke patient’s force control (force and torque regulation) and overall motor function (Alberts et al., 2004; Batool et al., 2015). CIMT in acute/subacute phases of stroke is known to be effective in improving muscle strength and spasticity (Teasell et al., n.d.). However, according to Marcus and colleagues (2018), they state that CIMT trials have a lot

of contradictory conclusions in terms of the improvements in motor function (Marcus Saikaley et al., 2018).

2. Mirror therapy: Mirror therapy studies have indicated that the therapy improves motor function and dexterity (Bai et al., 2019; Chaudhari et al., 2019; Chinnavan et al., 2020; Madhoun et al., 2020). However, studies have mixed conclusions regarding the improvements in activities of daily living (ADLs), spasticity, and muscle strength on stroke patients (Antoniotti et al., 2019; Marcus Saikaley et al., 2018; Teasell et al., n.d.).
3. Neuromuscular electrical stimulation (NMES): NMES has shown improvements in stroke patient's motor function and motor coordination (Y. Huang et al., 2020). However, mixed conclusions were found in terms of spasticity and range of motion (Teasell et al., n.d.).
4. Process: Neuro Developmental Treatment (NDT)/ Bobath Concept: Bobath concept focuses on motor recovery of an individual's affected region (Michielsen et al., 2019). NDT/Bobath are approaches that focuses on motor recovery such as motor function, movement, and tone.
5. Occupational therapy: Activities of daily living (ADL) tasks such as self-feeding, grooming, and functional purposeful activities such as writing, sorting objects, reaching for glass.
6. Physical Therapy: Physical therapy includes exercises that help strengthen muscles for mobility, movement of a limb by using various exercises. Exercises generally include but are not limited to stretching, passive/active movements, weight bearing on affected arm (*Rehab Therapy After a Stroke*, n.d.).

In robotic therapy, intervention can be highly customized to the patient. The ability to make these customizations on a real-time basis on robotic devices and to mimic the customization that physical or occupational therapists implement when working with stroke patients on a real-time basis is very important. To make the pilot study informative, it is imperative that the functions targeted by exercises and other activities performed by both conventional and robotic therapy are very similar. At the same time, it is necessary that the unique strengths of each type of therapy are optimally leveraged. One of the main customizations that can be implemented when using robotic devices is the gamification of exercises. By using the movements of the exercises to be part of a game, therapy can be customized according to the clinical status of the patient and the specific objective of the therapy. Currently, most of the end-effector devices are already developed with this feature. Figure 10 to Figure 16 shows us the games used in Fourier Intelligence ArmMotus M2 end-effector robotic device. While selecting games in robotic devices, it is recommended to have games which mimic or closely resembles the functions targeted by conventional therapy. These games should also allow adjusting motor execution difficulty, e.g., amount of force to be exerted and the level of difficulty. Since games in ArmMotus M2 have these features, a detailed analysis of the games in ArmMotus M2 was conducted.

Review of Games and features in ArmMotus M2

1. Botanical Garden

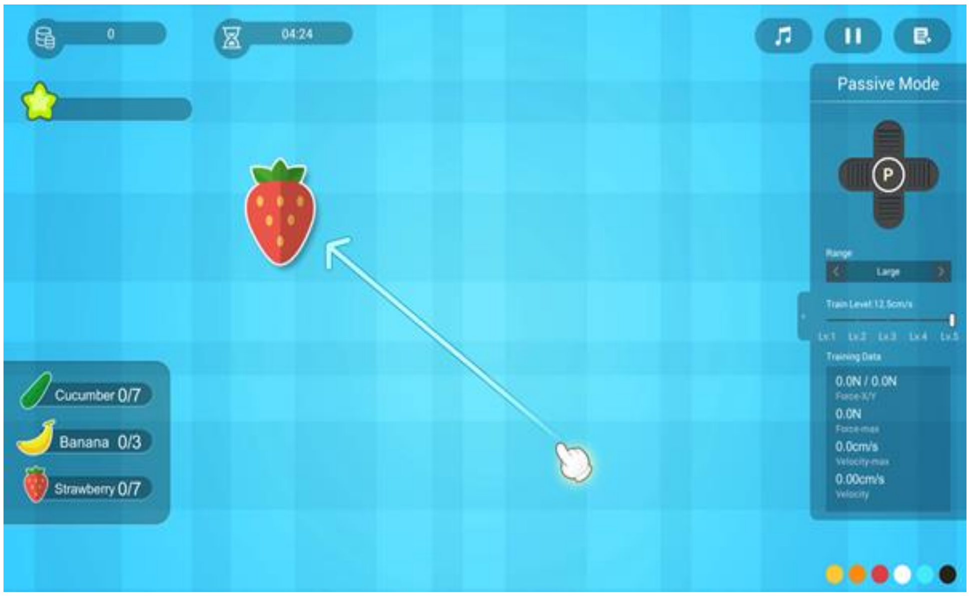

Figure 10: Game on ArmMotus M2 (Botanical Garden)

Game Gist: The game wants the subject to move towards the target vegetable or fruit. The vegetable or fruit is placed in a different location one at a given time. The cursor on the screen is to be moved using the robotic arm. As the cursor reaches the target the subject will have to wait for a second or two which results in points scored and a new target appears. There are bonus points when the subject has reached a fixed number of targets.

2. Ball

Figure 11: Game on ArmMotus M2 (Ball)

Game Gist: Ball is a very simple game and is quite similar to Botanical garden. The ball in the game needs to be moved using the robotic arm to the target animal in the game. Reaching the target will result in 50 points. The target animal disappears in 10 seconds and a new animal appears.

3. Magic Ball

Figure 12: Game on ArmMotus M2 (Magic Ball)

Game Gist: The goal of the game is to move the ball to the target yellow circle. After reaching the target the subject will wait for 1 or 2 seconds and a new target location will appear. The closer you are to the circle the more points you receive.

4. Defense Base

Figure 13: Game on ArmMotus M2 (Defense Base)

Game Gist: The game is basically a shooting task where bird-like creatures are shooting stone-like objects at you and you have to shoot those birds with a gun. The subject will have to move the robotic arm to move the pointer on the screen towards the birds and as the pointer is in line with the bird in a second or two the gun shoots the bird down. If the subject is unable to reach the target bird, then after a few seconds a timer of 10 seconds will be displayed. Upon the timer being exhausted the target bird will vanish and a new target bird will be displayed. Appropriate score is given for hitting each target bird and if many birds are shot quickly additional points will be given. After hitting a certain amount of birds, a bigger bird will pop up. This change in game difficulty will induce salience in the subject playing the game. However, it becomes repetitive after some rounds of the game.

5. **Cube War**

Figure 14: Game on ArmMotus M2 (Cube War)

Game Gist: The game is relatively intense with a lot of graphics and an overall goal of shooting down objects like blocks and various sizes of spaceships. The game also comes with choices of weapon and environment. This feature can only be unlocked with coins that were collected previously. The game features a laser shooting cannon to destroy many target objects/spaceships. The pointer of the cannon is controlled by the subject using the robotic arm and moved towards the objects/spaceship. The game pauses as the main spaceship is destroyed and the game proceed to the next level of game difficulty. The game because of its graphics and overall gameplay seems to be attractive. The complexity and change in game levels will induce salience in stroke subject.

6. Star/Galaxy Wars

Figure 15: Game on ArmMotus M2 (Star/Galaxy Wars)

Game Gist: The goal of the game is to destroy objects and spaceships coming towards you. We have a weapon to shoot the oncoming object and as we destroy the object, we earn points. At one stage we are supposed to just avoid the rocks coming towards us. There is a possibility of only moving along the x-axis and still proceeding with the game.

This could be decreasing the difficulty and number of movement repetitions in the game. Overall, the game seems to be not very easy neither very difficult.

7. Color Rush/Dodgeball

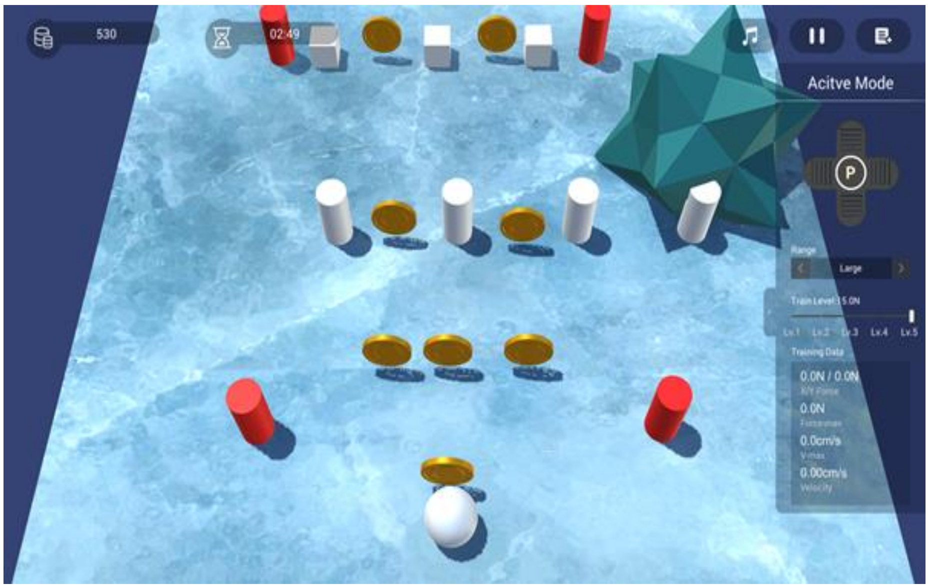

Figure 16: Game on ArmMotus M2 (Color Rush/ Dodgeball)

Game Gist: The goal of the game is to move forward as much as possible without touching certain objects. The ball in the game is controlled by the robotic arm. The color of the ball determines which objects can be touched. If the color of the ball is white, then all white objects can be touched. The game also requires the subject to collect as many coins as possible by touching them. As we move forward there shall be few large objects [Figure 16 – large object on the upper right corner] passing with more speed and these objects should be avoided. The subject also cannot go to extreme corners of the pathway on which the ball is moving forward, as it will end the game. Due to these various features of the game, the subject might not be able to process everything and hence, find it difficult to understand. Overall, this can be considered the most difficult game in the M2 system.

But the issue here in the game is the possibility of avoiding objects without making any movements along the y-axis.

Modes of training in ArmMotus M2

The Fourier Intelligence ArmMotus M2 is equipped with four modes of training:

1. Passive Mode: Using the passive mode, the robotic arm will make the movements to the targets by itself. The subject’s affected limb is placed on the robotic arm and this will help the subject who are severely impaired to start making movements. The parameter that can be changed in this mode is velocity of the robotic arm to the targets (2.5cm/s to 12.5cm/s).
2. Assistive Mode: Using the Assistive mode, subjects will be able to move the robotic arm in accordance to the game. However, the robotic arm will also provide some form of assistance and this can be adjusted by the therapist when required. The range of assistance is 15 N to 32 N.
3. Active Mode: In the active mode, the subject will be performing the movements with friction or resistance provided by the robotic device. The range of friction is 1 N to 15 N.
4. Resistive Mode: The resistive mode is similar to the active mode. However, the range of resistance provided by the device is larger. The range of resistance is 10 N to 25 N.

The usage of passive and assistive mode seems to be useful for severely impaired and sensitive stroke patients. Active and resistive mode can induce an intensive form of therapy. Therefore, to provide a more intensive form of therapy it is recommended that we use Active and Resistive mode of training in M2.

Summary of the games in terms of salience

Table 1: Summary of games in terms of salience

Game	Interaction	Game Difficulty	Salience
Botanical Garden	Single Target	Very Easy	Low: No change in environment and some changes to objects
Ball	Single Target	Easy	Low: No change in environment and objects
Magic Ball	Single Target	Very Easy	Low: No change in environment and objects
Defense Base	Single Target	Moderate	Moderate: Change in environment and targets.
Cube wars	Multiple Target	Moderate	High: Interactive environment and optimate difficulty
Star/Galaxy war	Multiple Target	Moderate	High: Interactive environment and optimate difficulty
Color Dodgeball	Multiple Target	Hard	Moderate: Interactive environment and optimate difficulty but might be difficulty to learn

Salience is an important factor that influences neuroplasticity in stroke patients. In robotic devices, games and its features are an optimal component to induce salience.

Therefore, the study has tried to classify the games based on the salience it might induce (Table 1). Games with multiple targets and interactive environment were more salient than a single target and non-interactive games. It is recommended to use Cube Wars, Star/Galaxy War, Defense Base, and Color Dodgeball as they are the 4 best games in terms of the salience and game difficulty.

Difficulty of the intervention

Difficulty is another important factor that influences neuroplasticity in stroke patients. Maintaining optimal difficulty is tough as it involves making decisions if the subject has fulfilled requirements to progress to the next level of difficulty. In the M2, there are modes which provide key features such as resistance or assistance to the movement. Using these modes, the therapist can induce different levels of difficulty by increasing or decreasing resistance or assistance.

Therefore, the study recommends that the therapists make judgements on the patient’s progress and progressively increase or decreases the parameters of the recommended modes of training (Active and Resistive mode).

Similarity of the conventional and robotic therapy

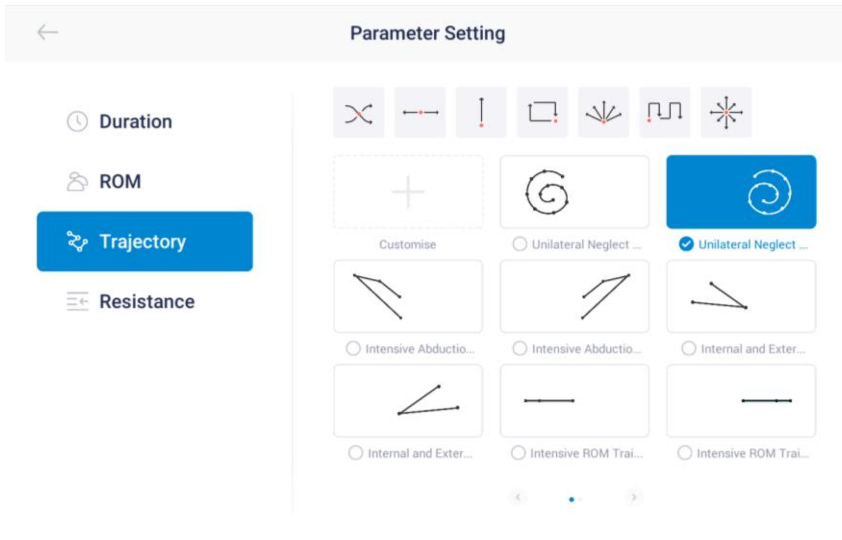

Figure 17: Pre-defined patterns of movement

The attempt to make robotic therapy similar to conventional therapy is difficult and practically not always possible. Conventional therapy has a wide range of activities/exercises conducted under it such as weight bearing, NMES, CIMT, Mirror therapy, and freedom of motion. However, Robotic therapy is limited to the features of the device. Particularly in the M2, we cannot have a 3-Dimensional free form of movement, NMES, and mirror therapy. However, attempt was made to select the correct form of training which closely resembles the conventional therapy. Constraint-induced movement training is very similar to the active and resistive modes of training in the M2. The repetition of a particular movement which is necessary for targeting a particular muscle can be addressed in conventional therapy by the therapist instructing and helping in performing the action. However, we can recreate such actions using the M2 device. In the M2 device, there are few preinstalled patterns of movement which can be used during the training (Figure 17). Additionally, the M2 device also provides the feature to customize and develop a new pattern of movement (Figure 18). Therefore, it is recommended that in order to make robotic therapy similar to conventional therapy, the therapists should use the features such as customizing movement patterns to target a region, or a particular muscle based on their judgement. Similarly, it is also recommended to use Active and Resistive mode to conduct intensive form of therapy.

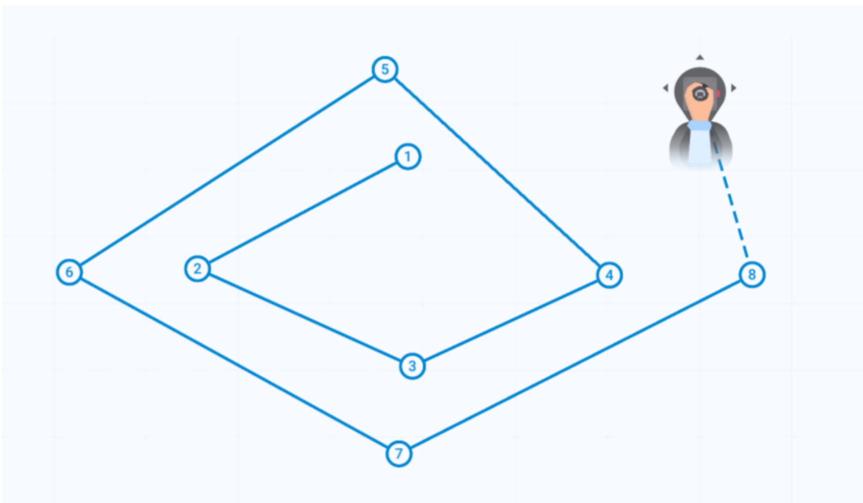

Figure 18: Developing customized patterns of movement

Summary of ArmMotus M2 robotic device interventions:

- **Recommended games:** Color Dodgeball/Rush, Cube wars, Defense Base and Galaxy/Star war
- **Recommended mode of training:** Active and Resistive mode
- **Recommended features:**
    1. Pattern customization to replicate conventional therapy patterns.
    2. Progressive increase and decrease of difficulty.

CHAPTER 3

RESULTS

The proposed design of the pilot study comparing conventional and robotic stroke therapy is based on the review of the literature and extensive discussion with the physical and occupational therapists at Barrow Neurological Institute (BNI) and faculty at Arizona State University.

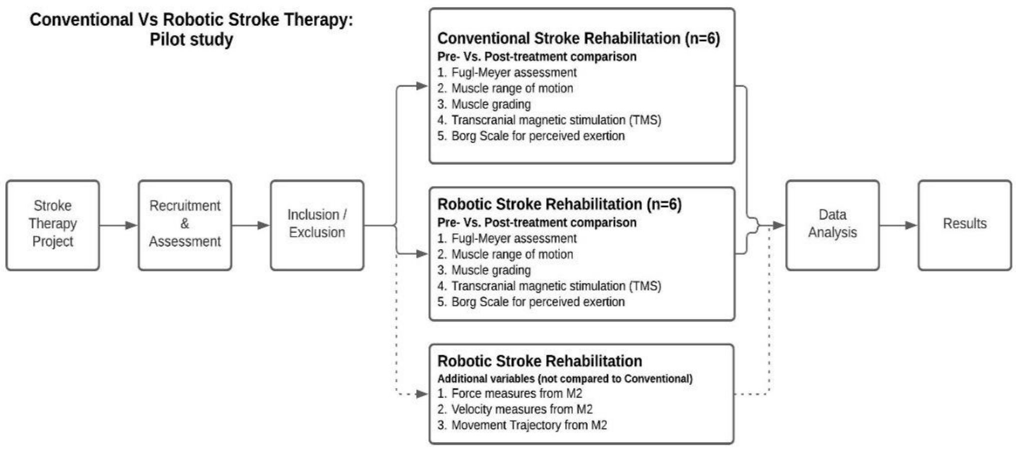

Figure 19: Conventional versus Robotic Stroke therapy (Pilot study design)

3.1 Actual features of the study

Number of Participants

After meeting the inclusion and exclusion criteria, at least 12 participants will be recruited for the pilot study. The participants will be enrolled into the following groups:

1. Conventional stroke therapy group (n=6)
2. Robotic stroke therapy group (n=6)

Length of the study:

The study will consist of nine therapy sessions and two assessment sessions conducted at the beginning and end of the study. Based on the logistics of conducting the study as discussed with therapists at BNI, overall length of the pilot study will be close to 4 to 5 months. In Figure 20, we can see the expected timeline of the pilot study.

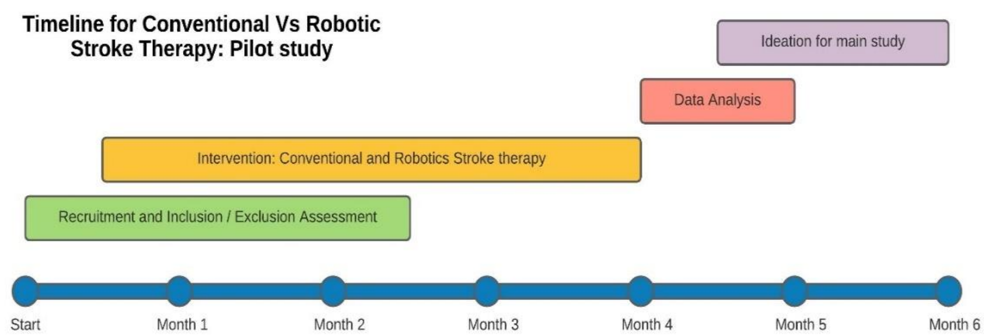

Figure 20: Expected timeline of the pilot study.

Assessments

Based on the evaluation of the various assessments the following were included in the study:

A. Clinical Assessments:

1. Fugl Meyer Assessment for Upper extremity stroke (FMA): FMA has been selected to be the main assessment tool and will be conducted before and after the entire series of intervention. It is a standardized test conducted to worldwide

and is very extensively used in research studies. Moreover, this covers a vast range of upper-extremity assessments in a single test.

2. Range of motion (ROM): Range of Motion testing will be conducted before and after the study. The difference in the ROM before and after will be a good assessment of the patient's recovery.
3. Manual Muscle Test (MMT): Manual muscle test is a standardized tool to assess the patient's muscle strength. Apart from being an assessment, it will be also used in the inclusion/exclusion criteria to determine if the participant will be able to interact with the robotic device. If muscle strength is low then participants can only use the device on passive mode, which limits the scope of the therapy.
4. Corticospinal tract integrity using Transcranial Magnetic Stimulation (TMS): Conducting TMS will help determine the magnitude or occurrence of Motor Evoked Potentials (MEPs). These MEPs can be a predictor of recovery and hence conducting them will give access to very important data. In addition to being an assessment tool, the presence of MEPs will be considered as a potential inclusion/exclusion criterion.
5. Borg Scale for perceived exertion: Borg Scale for perceived exertion is a measure of perceived intensity of physical activity. This assessment will assess each participant's perceived physical activity during each study session. The intention of Borg's scale is to understand the influence of difficulty in patient's recovery (*Perceived Exertion (Borg Rating of Perceived Exertion Scale) | Physical Activity | CDC*, 2020).

B. **Robotic Assessment:** ArmMotus M2 is equipped with sensors which records various parameters during the study session. Parameters such as velocity, movement trajectory, and force exerted will help understand the patient's recovery during the entire study session.

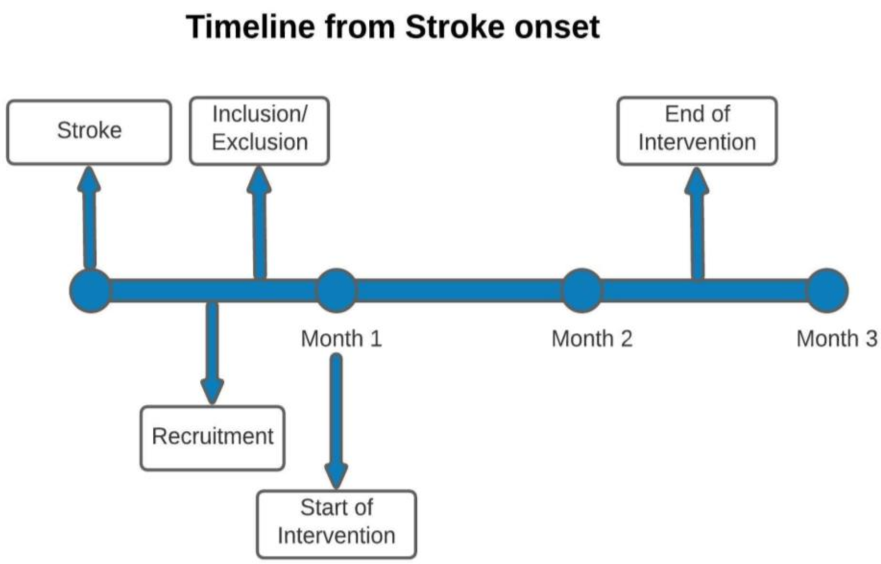

Figure 21: Expected timeline of the pilot study from stroke onset.

Inclusion and Exclusion

After taking into consideration all the recommendations and discussion with BNI resulted in the following inclusion and exclusion criteria.

Inclusion: Participants must meet all the following eligibility criteria at the time of entry:

1. Male or female, age 18 years - 85 years inclusive.
2. Stroke with hemiparesis with Manual Muscle Test (MMT) 2-/5 or greater in the shoulder.
3. Acute Hemorrhagic or ischemic stroke patient.

4. Can tolerate greater than 1 hour of upper extremity (UE) therapy.
5. Ability to follow one step commands.
6. Shoulder Range of Motion (ROM) for use of device (shoulder flex to 90 degrees of flex required).
7. No presence of contractures, particularly lacking greater than 20 degrees of elbow extension
8. Informed consent.

Exclusion: Participants missing out any one of the following will be excluded from the study:

1. Shoulder pain greater than 4/10.
2. Modified Ashworth of 1+ or greater.
3. People with skin integrity issues at the sites of device human interaction.
4. Upper Extremity fractures.
5. Hemispatial neglect of the affected Upper Extremity.
6. Heterotrophic ossification of the shoulder or elbow.
7. Unwilling or unable to comply with the requirements of the study.

Equipment & Experiment Intervention:

1. Conventional therapy: Based on the recommendations mentioned in the method section and discussions with therapists at BNI a list of exercises and sub therapies were finalized for the therapy. These interventions will be performed by therapists based on their judgement and progressively the difficulty of each exercise will be increased based on the patient's condition. Following are some of the Conventional neuromuscular re-education for upper extremity which will be conducted at Barrow Neurological Institute during the pilot study:

- Weight bearing on affected arm
- Use of vibration for facilitation of affected muscle groups
- Focus on proximal muscles then distal as active movement emerges
- Reducing gravity/friction to increase active movements
- Neuromuscular electrical stimulation (NMES)
- Proprioceptive Neuromuscular Facilitation (PNF) patterns
- Neuro Developmental Treatment (NDT)/ Bobath
- Activities of daily living tasks (Dressing, self-feeding, grooming)
- Manual contact, verbal feedback, visual integration/use of mirror, pressure/proprioceptive input.
- Functional purposeful activities (example: reaching for glass in kitchen, playing tabletop game, writing, sorting medications, etc.)
- Range of motion (Decrease flexor tone - focus on abduction, extension, external rotation)
- Kinesiotaping (Used to decreased flexor tone, support shoulder with subluxation, increase proprioceptive input)

2. Robotic therapy: Based on the recommendations provided, ArmMotus M2 seemed to be a good equipment to be used in the study, as it fulfilled many characteristics required for the study. In order to keep the therapy sessions consistent between conventional and robotics, a detailed analysis of the robotic intervention was conducted. As the interventions are delivered in the form of games and hence, all the games were analyzed. Out of the many games in ArmMotus M2, 3 games (Cube war, Color Rush/Dodgeball, Galaxy/Star War) were chosen based on factors promoting neuroplasticity (Salience). Out of the many modes of training in the M2 robotic device, Active and Resistive mode of training was selected based on the difficulty and intensity that it provides. Therapists will judge the stroke patient's ability and progressively increase or decrease the level of difficulty and intensity of the intervention provided. Finally, in order to replicate conventional therapy as much as possible, therapists will customize or use pre-defined patterns of motion on the M2 robotic device.

CHAPTER 4

DISCUSSION

In this thesis, a pilot study design was developed to compare the individual effects of robotic stroke therapy with conventional stroke therapy using acute stroke patients. The design of this study was developed using recent stroke literature and discussions conducted between therapists at Barrow Neurological Institute (Phoenix, Arizona) and faculty at Arizona State University.

4.1 Addressing gaps in the clinical trial literature

The study designed here tried to address the main gaps and limitations of previous studies by proposing potential solutions as described below.

Lack of details about conventional therapy

It has been a standard practice to compare an upcoming intervention with a traditional one to understand the benefits of the newer intervention. Generally, conventional therapy is used as the "baseline" for comparison with newer intervention, e.g. Robotic Gym with 6 robotic devices (Bustamante Valles et al., 2016), robot therapy using Amadeus Tyromotion (Orihuela-Espina et al., 2016), robot-assisted arm therapy, and hand functional electrical stimulation (Straudi et al., 2020). However, in reviewing the literature, it was noted that many stroke clinical trials do not provide sufficient details about what the conventional therapies entailed. For example, Dehem and colleagues (2019) compared robotic therapy with conventional therapy. Although this study provided details about the robotic therapy, the only detail being mentioned about the conventional therapy was that it had delivered for same amount of time as the robotic therapy (Dehem et al., 2019). In a similar stroke study conducted by Rodgers and colleagues, conventional therapy was provided as the baseline in comparison to robotic therapy (Rodgers et al., 2019). They mentioned conventional therapy was conducted per NHS Care (UK) guidelines, which include physical therapy and occupational therapy. However, even though physical therapy and occupational therapy include a wide range of exercises and sub-therapies, there was no mention of what specific exercises were performed by the patients (Rodgers et al., 2019). In sum, lack of details about conventional therapy used in clinical trials prevents the assessment of whether robotic therapy might offer advantages relative to conventional intervention. *To address this gap, this study was designed by including a detailed list of conventional therapies that should be used in future studies*.

Inconsistent results from clinical trials comparing conventional versus robotic therapy.

The variation in the conventional therapy, can be a factor for change in the baseline for each study. A clinical trial Lo and colleagues (2010) conducted compared the robotic therapy with conventional and intensive therapy and concluded robotic therapy did not significantly improve upper limb motor function in comparison to conventional and intensive therapy (Lo et al., 2010). A clinical trial conducted by Sale and colleagues (2014), comparing conventional and robotic therapy concluded that robot therapy contributed to greater motor recovery of the upper limb in comparison to conventional therapy (Sale et al., 2014). A later clinical trial conducted by Rodgers and colleagues (2019), used the same robotic device used by Sale and colleagues (MIT-MANUS) concluded that robotic therapy did not provide more upper-limb function in comparison to conventional therapy (Rodgers et al., 2019). Another clinical trial (Aprile et al., 2020) using 4 robotic devices in comparison to conventional therapy concludes that both robotic therapy and conventional therapy improved upper-limb motor function significantly but there was no difference between to the two. In sum, the results of clinical trials comparing robotic versus conventional therapy have yielded contradictory results. Part of this issue could be due to different methodologies used, including differences in the conventional therapy exercises (see above), the use of different robotic devices, and differences in delivery modalities (e.g., intensity, frequency) of either type of therapy. *To address this issue, we analyzed the M2 robotic device and found variables that will focus on factors that influence neuroplasticity. Using these variables, such as salient games, difficulty level progression and optimal training modes, we shall conduct a pilot study. In addition, we have tried to replicate conventional stroke therapy using customized and pre-defined movement patterns on M2 robotic device. We will then map the sensorimotor functions targeted by conventional therapy and robotic therapy groups using assessments tools such as Fugl-Meyer Assessment.*

Inconsistency in design of clinical trials comparing conventional versus robotic therapy

An interesting aspect of many clinical trials comparing conventional versus robotic therapy is that they combine robotic therapy together with conventional therapy as the experimental group (RT+CT) and compare it with a group of conventional therapy (CT) as a baseline. Many hospitals refer robotic therapy as an adjunct to conventional therapy and studies have also found them to be reflecting positive results supporting combination RT+CT group to provide better upper-limb function (Dehem et al., 2019; Keeling et al., 2021; Taveggia et al., 2016). However, the major concern here is that we are still not clear which of the two is causing the difference. Reviewing the literature, our understanding is that robotic therapy does improve upper-extremity function for stroke patients (Bustamante Valles et al., 2016; Calabrò et al., 2019; Dehem et al., 2019; Franceschini et al., 2020; Keeling et al., 2021; Orihuela-Espina et al., 2016; Sale et al., 2014; Takahashi Kayoko et al., 2016; Taveggia et al., 2016). However, some of those studies still recommend further investigation with larger population (Calabrò et al., 2019; Chinembiri et al., 2021; Keeling et al., 2021; Orihuela-Espina et al., 2016; Takahashi Kayoko et al., 2016). Hence, it is still not clear whether the extent to which robotic therapy is better than conventional therapy. *To address this issue, we decided to have two groups of participants, that is, one group of participants with only conventional therapy and other group with only robotic therapy as intervention. We also made sure that the robotic therapy intervention closely resembles conventional therapy, thus we expect the results to provide a clear analysis of the two therapies.*

Ethical standpoint regarding the timing of the study

This leads to an ethical standpoint where the study is providing robotics to a set of acute stroke patients and denying the same to the other set who will be performing conventional therapy. The timing of stroke is of importance here, especially since the study aims to deal with acute stroke patients. As mentioned earlier, the sensitive period is where most of the neuroplasticity is expected to occur (Langhorne et al., 2011; Raffin & Hummel, 2018). *To address this issue, we will not include patients at an early stage of stroke. Instead, we will wait for the primary form of stroke rehabilitation to be completed, and after which the participant recruitment will be conducted. Thus, the study will not deny standard therapy to any participant instead additional therapy will be provided to the recruited participants free of cost.*

4.2 Future Work

The aim of this thesis is to develop a design that can conduct a fair pilot study. The results of the pilot study should be a good representation of the individual sensorimotor functions targeted by conventional therapy and robotic therapy. Analyzing the results of the study, a full-scale study should be devised to further validate the findings. Adding further to this, the factors that influence neuroplasticity can be studied in detail and quantified. The scope of the study can also result in inclusion of newer technologies such as Virtual Reality (VR) and Neurostimulation along with robotic therapy in future studies.

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