The Effect of Virtual Reality-Based Rehabilitation on Hand Motor Function and Activities of Daily Living Performance in Sub-acute Stroke Patients- A Randomized Control Trial

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Supervisor: Dr. M. Asim Waris

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No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Department of Biomedical Engineering and Sciences (BMES) in partial fulfillment of the requirements for the degree of Master of Science in the Field of Biomedical Sciences, Department of Biomedical Engineering and Sciences (BMES) National University of Sciences and Technology, Islamabad.

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To all those enduring oppression and hardship, this work is dedicated to you. Your strength and resilience are a beacon of hope and a reminder of the importance of striving for a world filled with peace and harmony.

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ADLs	Activities of Daily Living
ANOVA	Analysis of Variance
ARAT	Action Research Arm Test
BBT	Box and Block Test
BDNF	Brain-derived Neurotrophic Factor
CIMT	Constrained Induced Movement Therapy
CPT	Conventional Physical Therapy
CT	Conventional Therapy
DALYS	Disease-Adjusted Life Years
DIT	Diffusion Tensor Imaging
FMA-UE	Fugl-Meyer Assessment Scale for Upper Extremity
fMRI	Functional Magnetic Resonance Imaging
GBNDS	Global Burden of Neurological Disease Study
HMD	Head Mounted Display
IMU	Inertial Measurement Unit
IREX	Immersive Rehabilitation Exercise
LMC	Leap Motion Controller
MAS	Modified Ashworth Scale
MBI	Modified Barthel Index
ML	Motor Learning
MT	Mirror Therapy

MoU	Mobile Game-Based Upper Extremity
Myo-CI	Myoelectric Computer Interface
NMD	Neuromotor Deficit
NMES	Neuromotor Electrical Stimulation
PFC	Pre-frontal Cortex
ROM	Range of Motion
SSQOL	Stroke-Specific Quality of Life
TMS	Transcranial Magnetic Stimulation
TUG	Time Up and Go
UE	Upper Extremity
VEGF	Vascular Epithelial Growth Factor
VR	Virtual Reality
VRGI	Virtual Reality Gaming Intervention

ABSTRACT

Background: This randomized controlled trial aimed to investigate the efficacy of Virtual Reality (VR) games compared to Conventional Physical Therapy on Hand motor functions, activities of daily living, and quality of life in subacute stroke patients.

Method: Forty stroke patients who met the inclusion criteria were randomly assigned to either the experimental group receiving VR games or the control group undergoing traditional physical therapy interventions. Outcome measures included the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) to assess motor function, the Action Research Arm Test (ARAT)to evaluate functional performance, the Box and Block Test (BBT) to assess hand dexterity, the Modified Barthel Index (MBI) to measure ADL performance, and Stroke-Specific Quality of Life (SSQOL) to measure quality of life after stroke.

Results: No differences were observed in patients' demographic and clinical data at baseline between both groups. Statistical analysis revealed significant improvements in all outcome measures for both groups post-intervention. However, the experimental group exhibited notably greater improvements in hand motor function, functional ability, hand dexterity, activities of daily living (ADLs), and quality of life compared to the control group ($p<0.05$). Specifically, in the follow-up week, the VR games group continued to demonstrate sustained improvements, surpassing the improvements observed in the physical therapy group.

Conclusion: These findings underscore the potential of VR-based interventions as a promising adjunct to traditional therapy in enhancing hand motor function and overall quality of life in patients with motor impairments.

Keywords: Virtual Reality, Stroke, Upper Limb, Motor Function, Activities of Daily Living

CHAPTER 1: INTRODUCTION

1.1 Background

A stroke is a collection of neurological impairments characterized by either clogging of blood vessels (ischemic stroke) or rupture of arteries (hemorrhagic stroke) which leads to altered perfusion or bleeding in the brain. This damage causes the sudden cell death of brain tissues due to lack of oxygenation or infarction. Ischemic obstructions account for 85% of stroke casualties, whereas Hemorrhagic stroke contributes to approximately 10–15% of all strokes. [1, 2]

It is the 2nd leading cause of global mortality after coronary artery disease. A total population of 13.7 million is affected by it and approximately 5.5 million people die annually. According to a Global Burden of Neurological Disease Study, Stroke comprises the largest proportion of total Disability Adjusted Life Years (DALYS) i-e 47.3% and 67.3% in death among all other neurological disorders.[36] Illustrated in Figure 1.1. After 2016, the incidence rate of stroke has become two-fold in lower and middle-income countries. [3] By 2030, stroke prevalence is expected to rise to 21.9% globally. In Pakistan, every 1200 out of

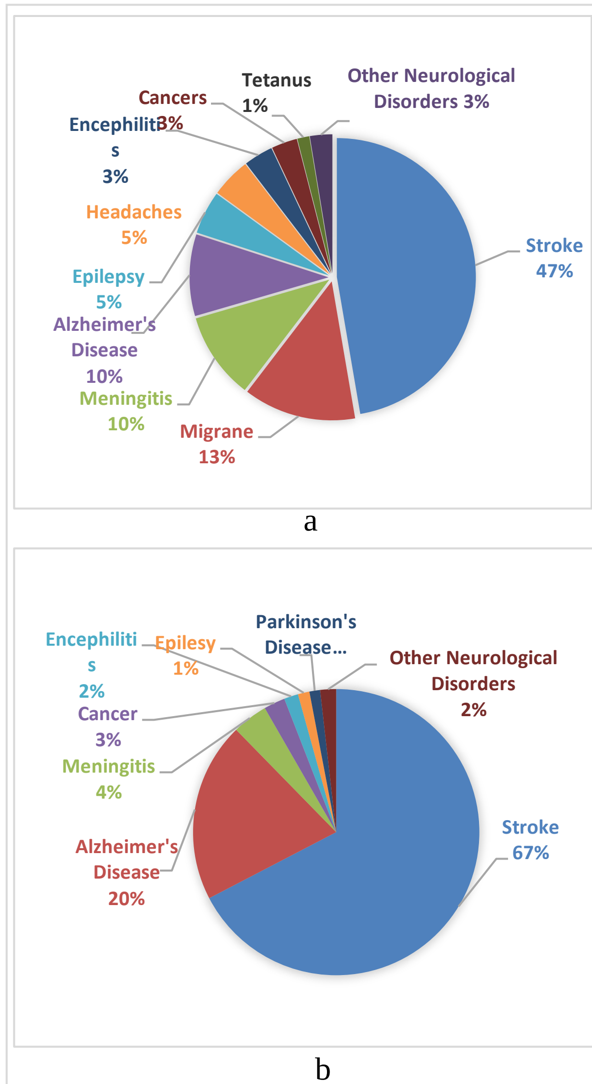

Figure 1.1 Global Burden of various neurological diseases in 2015. According to a. DALYS, b. Death

100,000 are suffering from Stroke.[4] The rate of functional disability in survivors is significantly high reaching up to 75% of all other stroke-related issues. [5]

According to epidemiological publications, 40% of stroke survivors still experience severe upper extremity impairment, and about 60% of survivors experience motor dysfunction. Moreover, only 5% to 20% of stroke patients were able to regain full use of their upper limbs, 25% were able to do so partially, and 60% had no use at all. Lower extremity motor dysfunction reduces one's capacity to execute motor functions like extending forward and gripping, which impacts one's capacity to carry out daily activities like eating, dressing, and cleaning. [6]

The impact on the person and the degree of impairment might vary from mild/moderate to severe. This alteration in upper limb function affects how people engage in daily tasks like driving and using utensils. The rehabilitation measures needed might range in duration from days to months, depending on the severity of the impairment. To restore as much function as possible to the upper limb, medicinal or surgical interventions may be given in addition to therapy measures in certain circumstances. The ailment, disease, or damage received dictates the clinical rehabilitation timelines and paths. The degree of the disability dictates the rehabilitation program's duration and level of effort. Various exercises and activities can be used as interventions to enhance mobility and participation in daily routines. To make sure that practice is up to date, it is therefore appropriate to examine rehabilitation interventions. [37]

Neuromotor deficit (NMD) is the most common consequence after stroke and is largely attributed to weakness in muscles [7], weakened control over voluntary movements due to altered corticospinal firing [8] loss of muscle mass due to disuse, abnormal increase in muscle tone, and lack of synchronization in movements [9]. These physical symptoms either occur in isolation or in combination that affect the overall muscle performance. The upper limb is more commonly involved in these multivariate impairments than the lower limb. That is because the upper limb has intricate structures and complex joints with more degrees of freedom during multi-joint actions. [10]

One of the main objectives for stroke survivors is to regain function in the upper extremities, as this is necessary for carrying out activities of daily living (ADLs). However, upper extremity limits affect about 80% of stroke survivors, and in the chronic phase, these limitations affect about half of these survivors.[5] The upper limb takes longer to recover and therefore requires significant focus in rehabilitation [10] to improve independence in performing activities of daily living. [11].

The hand is the most significant tactile organ and a valuable creative instrument that functions as an extension of the mind. It also facilitates nonverbal communication. The hand can carry out duties requiring a great deal of strength as well as incredibly delicate, fine movements. Manual dexterity and hand functions play a major role in determining the quality and performance of work-related activities of daily living and leisure. For ADLs including holding, turning movements of hands for doorknob or lock, using a phone or computer, and writing, distal upper extremity function is essential. The distal upper extremity is the last bodily portion to heal after a stroke and is severely impacted. Enhancing distal upper extremity function is therefore crucial for stroke survivors' rehabilitation. [5]

Keeping medical costs down requires seniors to maintain their activities of daily living (ADLs). This is especially important as the number of elderly people rises. Patients recovering from stroke need to engage in physiotherapy exercises such as muscle strengthening, endurance training, and active range-of-motion (ROM) exercises (extension, flexion, and rotation). A physical therapist employs diverse techniques to aid individuals in regaining their everyday mobility, such as employing assistive devices, task training, and strengthening muscles. Nonetheless, assisting a patient with physiotherapy exercises is an expensive, time-consuming, and exhausting task. [38], [39]

Stroke motor recovery is usually pronounced within 3 to 6 months following the stroke occurrence; however, motor control mostly occurs within the first-year post-stroke. Still, the window of time for the recovery of order and through the process of neural plasticity is short, and active rehabilitation approaches in the subacute stage usually are regarded as significant. The subacute stage after stroke is a critical period for motor recovery. Therefore, as suggested by the motor learning theory, task-oriented, intensive, and repetitive training during this period should be the key factor in promoting recovery.[12]

Adult brain injury is sustained by plasticity and rewiring in the wounded brain, leading to both spontaneous and secondary recovery of function following intensive rehabilitative therapy. When an adult human observes others moving, their neurons fire more frequently in that brain area. Because key nodes in the system are also active when patients conduct movements, activation of this mirror-neuron system, which includes regions of the frontal, parietal, and temporal lobes, might promote cortical reconfiguration and perhaps aid in functional recovery.

Motor learning involves a vast spectrum of events that go from relatively low-level mechanisms for maintaining the calibration of our movements to high-level cognitive decisions. The word "motor learning" is broad and covers many phenomena, methodologies, and fields. Along the motor planning pathway from stimulus to action, these learning components can be categorized into one of three basic stages: creation of a movement goal, selection of the proper action to attain that goal, and execution of the selected action. Every motor learning paradigm probably influences changes at one or more phases for acquiring motor skills. Several different areas of the brain are related to motor learning illustrated in Fig 1.1 by [40]

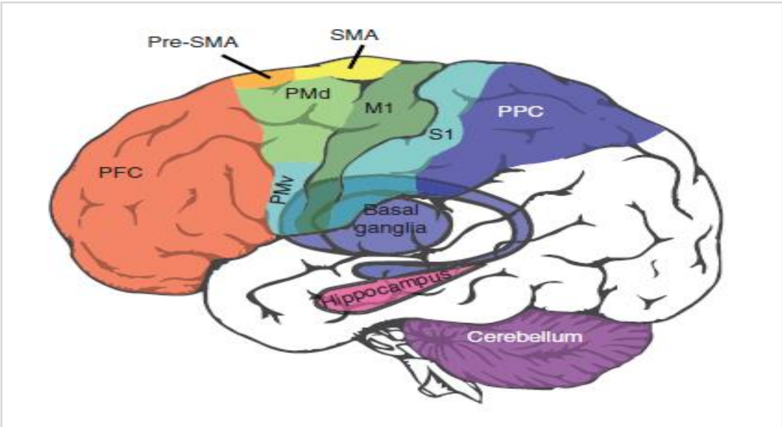

Figure 1.2 Brain Regions involved in motor learning: [PFC: prefrontal cortex; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; SMA: supplementary motor area; pre-SMA: pre-supplementary motor area; M1 primary motor cortex; S1: primary somatosensory cortex; hippocampus; cerebellum; basal ganglia; PPC: posterior parietal cortex.[40]]

1.2 Virtual Reality as an Intervention

In this regard, CTs (occupational or physical therapy) are popularly employed to ameliorate the function of the affected limbs after the patient has experienced brain injury. Nevertheless, other treatment approaches have been investigated by some researchers due to the long durations and high costs of conventional rehabilitation programs, and their outcome largely depends on the capabilities and previous background of the interveners.

To encourage brain reconfiguration and neuroplasticity, recent research has highlighted the use of concentrated, repetitive, application-relevant, and actively performed interventions. First-line CT such as occupational or physical therapy demonstrated in several studies to be effective in neurological recovery processes after stroke or head trauma. [13] Conventional rehabilitation programs, on the other hand, seem to serve as the key solution because they tend to consume a huge time and resources and the outcome of these programs depends mainly on the ability and training of the interventionist. Whereby people found that the repetition, the intensity, as well as the dose in the situations that involve CT settings are not enough to reach the desired optimal recovery. In fact, due to the aforementioned limitations, there came a piece of new information that anything that benefits the recovery of the motor function in the individuals who are affected such as VR is of great potential benefit. [14]

Various rehabilitation interventions have been developed to improve hand motor function and enhance the performance of activities of daily living in stroke patients. These interventions include conventional therapy techniques such as constraint-induced movement therapy, mirror therapy, and motor imagery. But these are poorly tolerated, and only strongly motivated patients accept its intensive training schedule. [36]

Virtual reality (VR)-based rehabilitation shows promising results for stroke patients. A wide range of VR-based rehabilitation devices, including robotics and commercial video game equipment, are now being developed and put into use. Several kinds of research have been conducted on stroke survivors in the field of upper limb rehabilitation and found that VR-based rehabilitation is more effective than traditional rehabilitation, when provided in equal amounts, at improving upper limb function. However, the majority of research on VR-based upper extremity rehabilitation focused on the proximal extremity, with scant data available on the distal extremity. [15]

In this context, cutting-edge technology like virtual reality (VR) has been added to traditional therapies. Virtual reality (VR) takes its place among the others as a tool advanced in the stroke functional recovery protocol. It focuses a task-oriented directives and an enrichment of incentives whereby a patient is trained to plan and successfully execute a therapeutic motor activity [15] Along with that, it is also suitable for a prompt interventional service where the cost is low. Researchers of a previously published meta-analysis highlighted 6 primary concepts of VR that are a direct pertinency towards the process of neuroplasticity. The principles comprise task-oriented stimulation, a high training dose (repetition count), the alteration of difficulty, real-time feedback, and users' motivation, as well as, engagement, and pleasure while practitioners conduct intensive task-relevant training. Such principles consist of motor planning related to the motor movements that the upper limbs are carrying out, and this probably leads to the much-needed improvement in motor functions for the upper limbs.[6]

To give users more input, the device can be coupled with bionic gloves, robots, or a treadmill. In addition, the content, duration, and intensity of the exercise may be adjusted in the virtual rehabilitation scenario produced by VR technology, and users can even receive timely feedback to ensure they are getting enough exercise on a tailored basis. An inventive exoskeleton, VR immersion systems like IREX, VR telerehabilitation systems, Kinect Xbox, VR coupled with Keyboard, VR combined with gloves, Nintendo Wii, and virtual tops are among the VR-related technologies that are frequently employed in the treatment of stroke victims. The primary benefit of VR training over traditional rehabilitation is that stroke patients can view it more as an entertaining game than a form of therapy. VR training has the potential to significantly improve treatment compliance and motivation by enabling users to concentrate on the job at hand fully. This can be especially advantageous for individuals recuperating from post-stroke trauma. [42]

Reduction in motivation level for regular exercise occurs because of the so frequent repetitions that require focus and attention are a basic part of conventional therapy, patients become less interested in performing few repetitions or missing out on their therapy. Aside from that, the traditional methods do not provide the proper amount of challenges to elicit the required neuroplasticity in the motor learning process.[16]

Virtual reality's capacity to provide individualized, graded programs and adaptable biofeedback in a fun, safe, and encouraging setting also makes it possible to test and implement a variety of theories to aid in motor recovery. Studies investigating the role of virtual reality in upper limb rehabilitation have revealed positive results but are limited to their operational design i.e. they are practice-dependent due to their advanced features and pose a technical challenge for the clinical staff to manipulate confidently in a clinical setting. [12, 17] Moreover, the number of studies demonstrating the effect of fully immersive game-based VR intervention at acute and subacute stages of stroke remains scarce. [17]

Due to practical issues like their labor-intensive and time-consuming nature, the difficulty of getting to specialized facilities, and the requirement for insurance coverage, conventional therapies (CT, physical therapy, and occupational therapy) do not offer enough intensity for optimizing neuroplasticity.[14] Due to the aforementioned limitations, the use of novel methods, i.e. VR, of proven benefits in regaining the affected motor function after stroke has become significantly important. The purpose of this study was to investigate how upper extremity function and ADL performance were affected in stroke patients in the subacute stage by combining CT with intense and repetitive VR training. Therefore, we hypothesize that game-based virtual reality rehabilitation has superior benefits over conventional therapy in providing greater improvements in motor function and activities of daily living (ADLs).

CHAPTER 2: LITERATURE REVIEW

Stroke is a leading cause of long-term disability worldwide, often resulting in impairments in hand motor function and limitations in activities of daily living. The global socio-economic burden of stroke is significantly increasing over time. Hemiparesis resulting after stroke is a foremost cause of disability affecting up to 83% of total survivors out of which more than half require support in activities of daily living [18] Hemiparesis is one of the most prevalent and incapacitating disabilities that arise after a stroke.[19]

Manual dexterity is defined by Poirier et al. [2] as the capacity of an individual to rapidly coordinate voluntary gross and fine motor skills through acquiring abilities via learning, training, and experience. The authors establish a connection between manual dexterity and learning and training. Anthropometric differences, age, gender, and motor coordination all affect dexterity One's capacity to live independently can be impacted by inadequate manual dexterity, as evidenced by the strong correlation between affected dexterity and capacity to perform Activities of Daily Living. [43]

Neurological disorders have been known to have severe and undesirable effects such as abnormal dexterity and loss of motor coordination. Higgis et al. [6] have noted that the failure to regain dexterity was calamitous to stroke patients who have to resume routine life. Indeed, regaining the ability to manipulate the limb is a way of regaining control or regaining part of one’s independence. The option to carry out small tasks without help increases the level of independence of the individual with a neurological disorder, increases the self-esteem of the individual, and encourages the individual to exert more effort, especially in the process of rehabilitation.

The primary focus of inpatient physical rehabilitation is to improve the movement, balance, coordination, and upper-limb functional activities such as bending, reaching, and grasping to gain independence in performing the activities of daily living (ADL) that include transferring, grooming, dressing, feeding, and toileting. Repetitive motor retraining of the lower limb provides improved functionality but the majority of daily tasks rely on the usage of the upper limb. [11]

A combination of complex neurological mechanisms and motor relearning methods are involved in the recovery of stroke-related deficits [20] The majority of rehabilitation approaches that address this issue incorporate elements of motor learning, activating brain circuits during recovery that are comparable to those involved in motor learning. [19] The region close to the injury site is expected to experience both structural and functional reorganization during the healing process. Research has indicated that this region experiences heightened axonal sprouting and neurogenesis, as well as an increase in the migration of immature neurons from the subventricular zone to this area.

Under the crucial circumstances of inflammation, edema, metabolic disruptions, apoptosis, and nerve fiber degradation, neuroplasticity in strokes starts right after an ischemic event. It is unclear how neuroplasticity works, but it is a very complicated process that depends on the consolidation of preexisting synaptic pathways to form new connections. [44] The brain centers' surviving, albeit weaker, connections are active. Thus, in post-stroke patients, spontaneous partial recovery occurs when other cortical or subcortical structures take up the role of the damaged area, thereby restoring the deficient function. The time range for post-stroke recovery was distinctly established by the Stroke Recovery and Rehabilitation Roundtable.

Moreover, there are various phases of stroke recovery comprising hyper-acute that go from the time of injury to 24 hours, an early subacute phase that begins at 7 days until 3 months, a late subacute phase ranging from 3rd month to 6 months), and chronic phase that go start beyond 6 months. The important period for neuroplasticity is in the acute and early subacute phases. During the acute phase, secondary neural networks are used to sustain function; new synaptic connections are formed during the subacute phase; and further reorganization and remodeling take place during the chronic phase. Positive influences on all those processes can come from a variety of sources, including the surroundings, task repetition, motivation, neuromodulators, prescription drugs, and more.[45]

It is established in the literature that mechanisms based on learning are only truly operative throughout a naturally active recovery phase and hence, respond well to the therapeutic interventions. Moreover, after the incidence of stroke, the true recovery period is considered to be between 4 to 10 weeks as these first few weeks reflect the intrinsic mechanism called ‘spontaneous neurological recovery’ which is responsible for greater improvements.

Data converged at the micro level (cellular, physiological) and macro level (behavioral level) indicates a limited time window of increased neuroplasticity and enhanced receptivity of motor training to induce neurological improvements of bodily functions such as synergic patterns, alertness, and strength [21]. It is also believed that the recovery line reaches a flatland after 6 months. [21, 22]

Biomarkers can now be used to predict an individual's brain's response to neurorehabilitation due to advancements in neuroscience. This possibility makes it possible to tailor treatment regimens according to expected neuroplasticity. Diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) allow clinicians to map and visualize brain activity. These indicators help choose the right treatments and track improvement over time by revealing which parts of the brain are most responsive to neuroplastic changes. A person's inclination for neuroplasticity is also influenced by genetic factors. Clinicians can anticipate which patients will benefit from particular medications by finding genetic markers linked to neuroplastic response. This allows for a more individualized and focused approach to patient care.[46]

There is a significant potential for biomarkers such as VEGF (Vascular Epithelial Growth Factors) and BDNF (Brain-Derived Neurotrophic Factor) in assessing stroke recovery. VEGF and angiopoietins are crucial for angiogenesis, while BDNF supports neuroplasticity. These biomarkers are detected in the body in different phases of stroke recovery and can personalize treatment plans and provide early indications of recovery potential, though standardization and clinical integration remain challenges. Their effective use could optimize rehabilitation strategies and improve stroke management outcomes. Figure 2.1 illustrates the presence of biomarkers in various stages of stroke recovery.

The physiological changes in motor units' post-stroke led to altered muscle activation patterns, including decreased recruitment ability of agonist muscles, delayed initiation/termination of muscle activity, and antagonist co-activation.

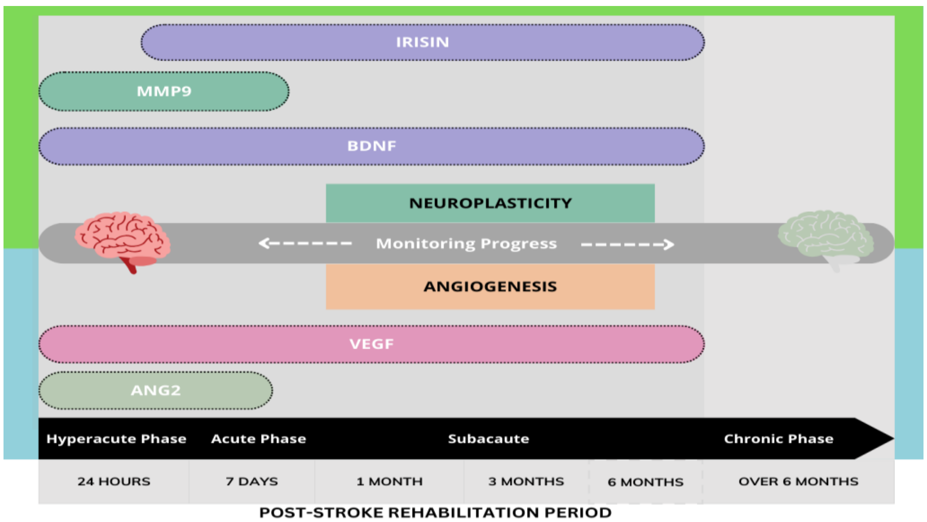

Figure 2.1 Biomarkers in different phases of Stroke. IRISN; MMP9: Metalloproteinase 9; BDNF: Brain-Derived Neurotrophic Factor; VEGF: Vascular Endothelial Growth Factor; ANG2: Angiopoietins

Early descriptions of muscle activation in hemiparesis individuals' post-stroke highlighted deficits in reaching coordination due to central nervous system damage. Recovery of reaching performance may involve improvements in muscle activation timing and decreased relative muscle recruitment capacity. These improvements may stem from the recovery of spared corticospinal components and compensatory control from other descending motor pathways. These findings provide insights into potential targets for novel rehabilitation strategies aiming to modify volitional muscle activation post-stroke.[37]

2.1 Stroke Rehabilitation Approaches

Various therapy interventions are employed in clinical settings to improve motor skills, functional abilities, and quality of life. Cardiorespiratory training and aerobic exercise benefit stroke survivors by improving walking speed and endurance, but their efficacy on specific functional tests like the TUG Test is inconclusive. Gait-oriented cardiorespiratory training enhances mobility aspects, yet mixed training approaches may have weaker effects on walking and balance. Despite positive findings, uncertainties persist regarding optimal dosing and long-term outcomes, emphasizing the need for further research. While recent reviews support their efficacy in improving disability and quality of life, concerns about evidence quality underscore the importance of cautious interpretation. Thus, while promising, cardiorespiratory exercise requires careful consideration and individualized approaches in stroke rehabilitation.[36], [38]

Therapeutic exercise, including strengthening interventions, offers numerous benefits such as increased strength, motor activity, improved balance, and enhanced walking abilities. Circuit class training and progressive strengthening exercises have shown effectiveness in improving various aspects of mobility and functional outcomes. However, passive interventions like stretching and passive exercises appear less effective, and there is insufficient evidence for some modalities such as lower limb resistance training's impact on walking and balance. Bilateral upper limb strengthening lacks sufficient evidence compared to usual therapy, while unilateral training may yield marginally significant improvements in upper limb function. Despite potential benefits, the overall efficacy of certain exercise modalities remains uncertain, emphasizing the need for high-quality randomized controlled trials to validate their effects thoroughly. [36], [39]

The analysis of 26 systematic reviews and meta-analyses on Constraint-Induced Movement Therapy (CIMT) reveals predominantly positive outcomes, including improvements in arm motor function, activity, and movement quality of the affected limb. However, implementing CIMT with high intensity poses practical challenges due to its demanding protocol, requiring over 90% participation during waking hours. Modified CIMT (mCIMT) offers a less intense alternative but still yields positive results. Despite its benefits, CIMT has limitations, with some studies indicating minimal improvements in activities of daily living, hand function, and strength. Additionally, while CIMT may sustain its effects in the short term, its impact on reducing disability over the long term remains inconclusive. Clinical applications of CIMT necessitate careful consideration, especially regarding its efficacy compared to other rehabilitation therapies and its potential as a standalone or adjunct therapy in stroke rehabilitation. [36], [41], [42]

Mental practice, combined with conventional therapies, shows potential for enhancing movement and functional recovery post-stroke. While it yields short-term gains in arm-hand ability and daily activities, conflicting evidence exists regarding its effectiveness as an adjunct therapy. However, integrating mental practice with functional task training during rehabilitation demonstrates a medium effect size for functional recovery by Cha et. al.[43] Further research is needed to clarify its efficacy and application in stroke rehabilitation.

Mirror therapy (MT) utilizes visual feedback to simulate movement in the affected hand by reflecting the movements of the unaffected hand. Most systematic reviews highlight its positive impact on upper limb functioning, with sustained outcomes observed for up to six months. However, its effectiveness in enhancing activities of daily living remains uncertain, with conflicting results reported. Further research is needed to determine optimal dosage and application methods, especially concerning stroke severity.[44]

Some of the most widely used interventions in stroke rehabilitation are mentioned in Table 2.1 However, recent advancements in technology have led to the emergence of game-based virtual reality as a potential intervention for stroke rehabilitation that has proven superior benefits than existing interventional protocols. [41], [46]

2.2 Game-Based Virtual Reality as a Rehabilitation Tool

Virtual reality training programs have gained popularity recently in the realm of enhanced stroke therapy. Virtual reality (VR) is a real-time, computer-based, interactive, multimodal simulation environment. Applications of VR to neuroplasticity include task-oriented training of the paretic extremities, repetition, and intensity. Immersive and non-immersive virtual reality environments are the two main categories.

Users of immersive virtual reality (VR) can see themselves in the scenario on a computer screen or concave surface it increases users' sense of presence, making them feel as though they are truly in the virtual environment. As a result, users are more likely to interact with the computer's and linked devices' stimuli that provide haptic, aural, and visual sensations. Enabling people to feel as though they are in a computer-generated environment rather than the actual world is the primary objective of immersive virtual reality through the use of head-mounted displays, large-screen projection, tracking devices, data gloves, or video capture systems. [54]

Users of non-immersive VR engage to varying degrees with the environment seen on a computer screen, either with or without the use of haptic or computer mouse interface devices. It provides a lower sense of immersion in the virtual world to the users, which enables them to engage with the environment as observers using gadgets that can't completely overpower sensory impressions. The primary distinguishing feature of non-immersive virtual reality systems is their capacity to allow users to manipulate their environment while registering auditory, visual, and tactile stimuli.[54] Both kinds significantly improved upper limb functioning in the majority of trials.[23]

The degree of immersion can help distinguish between immersive and non-immersive situations. Since the hardware systems cover most sensory experiences, immersive VR increases immersion because it requires less mental effort to be fully immersed in virtual reality. On the other hand, immersing oneself in a virtual environment using non-immersive VR demands greater mental effort. Consequently, the degree of spatial presence—which is characterized as "the sense of being in an environment"—may be diminished by non-immersive VR.[54] The immersive VR system with the visual feedback mechanism was employed in this investigation.

Several critical components of VR training for the best motor reacquisition have been studied recently. High repetition intensity, practice with important tasks, high motivation, improved performance feedback, and using alternate motor techniques to finish the job are some of these aspects. [23, 24] Through VR training, brain remodeling, and functional recovery can be facilitated by mirror neurons that fire more frequently when they perceive a specific movement being carried out. Participants can watch and mimic the ideal movement patterns shown in the virtual scene, which makes this possible.[25]

According to certain research, virtual reality rehabilitation plans are superior to conventional rehabilitation plans in terms of enjoyment, physical accuracy, and cognitive fidelity. [26] Numerous studies have demonstrated the potential of virtual reality (VR) and interactive video games to enhance conventional clinical rehabilitation. These technologies have been applied to the recovery of independent living skills, the rehabilitation of upper limb function, and the enhancement of grip strength and motor ability[6, 27]. It can foster the development of a variety of abilities and task-based strategies that can maintain participant interest and motivation, increased range of motion in both active and passive upper limb joints, and a translation of therapeutic gains into activities of daily living (ADL) [28]

VR shows promise for focusing on particular ADLs during stroke therapy, according to recent studies. As an example, a virtual reality intervention was employed to mimic reaching, grabbing, and manipulating objects that are used in daily chores. According to the Barthel Index, patients' ADL performance significantly improved [59] A different study investigated VR's potential for post-stroke rehabilitation with an emphasis on ADLs like drinking and eating. According to their research, VR training in addition to traditional therapy improved ADL function more than traditional therapy alone. Real-time feedback on movement and task performance may be obtained in virtual reality environments, which can be very helpful for motor relearning following a stroke. With an emphasis on visual input, M. R. Mouawad et.al [64] looked at the application of VR for upper extremity rehabilitation. According to the study, stroke patients' ability to execute ADLs and increase motor learning can both be facilitated by VR's visual feedback mechanisms. Comparably, [56] investigated the application of VR for rehabilitation that included integrated biofeedback. According to their research, VR combined with biofeedback can help patients complete ADLs with better motor coordination and skill.

Table 2.1 Interventions to achieve neuroplasticity and improve functional outcomes in Stroke Patients

Rehabilitation Approaches	Neuromuscular Electrical Stimulation (NMES)	Transcranial magnetic stimulation (TMS)	Robot-Assisted Therapy	Mental Practice	Cognitive Rehabilitation
Principle of Action	Delivers electrical impulses to muscles through electrodes on the skin, causing muscle contractions and promoting neural plasticity.	Induces neural activity via magnetic fields, fostering brain plasticity and reorganization post-stroke.	Uses robotic devices to provide repetitive, precise, and controlled movements, aiding in neuroplasticity and motor relearning.	Leverages neuroplasticity by mentally rehearsing movements and tasks, activating similar brain regions as physical practice.	Employs targeted cognitive exercises and strategies to improve mental processes such as memory, attention, and problem-solving skills.
Intended Outcome	Enhanced muscle strength, improved motor function, and reduced spasticity by stimulating muscle activity and re-educating motor pathways.	Enhance motor, language, and cognitive functions by modulating brain excitability and promoting functional connectivity	Enhanced motor function and independence by improving strength, coordination, and range of motion in affected limbs.	Improved motor function and mobility by strengthening neural pathways, leading to enhanced motor recovery and functional independence	Enhanced cognitive functions and daily living skills. Improved attention, memory, and executive functions.
Key Gains	Increased muscle strength, improved functional mobility, reduced spasticity, and enhanced overall motor recovery, contributing to greater independence	Induces neuroplastic changes through modulating neural activity	Increased intensity and consistency of therapy, accelerated motor recovery, and greater patient engagement and motivation.	Facilitates motor skill relearning, reduces motor deficits, and promotes greater confidence in performing daily activities.	Boosts cognitive recovery, increases independence, and improves overall quality of life for stroke survivors.

Rehabilitation Approaches	Strengthening Interventions	Task-Oriented Training	Personalized neurorehabilitation	Mirror Therapy
Principle of Action	Involves resistance-based exercises to increase muscle strength and improve motor coordination through targeted repetitive activities.	Involves practicing specific tasks relevant to daily activities to enhance motor skills through repetitive, goal-directed actions.	Customized therapy plans based on individual patient needs, leveraging various techniques to optimize neural plasticity and recovery.	Using a mirror to create a reflection of the unaffected limb, tricking the brain into perceiving the affected limb as moving
Intended Outcome	Enhanced muscle strength and endurance. Improved functional mobility and motor skills.	Improved performance in activities of daily living (ADLs). Enhanced task-specific motor function.	Maximize functional recovery and independence by addressing specific deficits and strengths of each patient.	Improve motor function and reduce pain in the affected limb by enhancing neural plasticity and sensory-motor integration.
Key Gains	Facilitates better balance, increased independence in daily activities, and overall improvement in physical function post-stroke.	Promotes functional independence, better task performance, and increased neuroplasticity for stroke recovery.	Enhanced recovery rates, and improved overall quality of life through individualized and focused therapeutic approaches.	Improved motor function, reduced pain, increased range of motion, and greater engagement in rehabilitation exercises, leading to enhanced recovery outcomes

Rehabilitation Approaches	Combination of brain stimulation with rehabilitation	Hybrid virtual reality-based therapy	Multimodal Rehabilitation	Sensorimotor Integration Training
Principle of Action	Techniques like transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) alongside traditional rehabilitation to enhance neural plasticity and recovery.	Combines virtual reality (VR) environments with real-world physical activities to stimulate and engage the brain, promoting neuroplasticity and motor learning.	Integrates various therapeutic approaches such as physical, occupational, speech, and cognitive therapies to target different aspects of recovery, enhancing overall brain and body rehabilitation	Combines sensory input with motor exercises to enhance the brain's ability to process and integrate sensory information, improving motor control and coordination.
Intended Outcome	Improved motor and cognitive functions by synergistically boosting brain activity and optimizing the effects of physical, occupational, and cognitive therapies.	Enhanced motor function, cognitive abilities, and daily living skills by providing immersive, interactive, and adaptive therapeutic experiences.	Comprehensive functional improvement by addressing multiple deficits simultaneously, promoting holistic recovery and independence.	Improved motor function and coordination by strengthening the connections between sensory and motor pathways, leading to better movement quality and precision.
Key Gains	Enhances effectiveness of rehabilitation exercises, and amplifies overall functional outcomes	Increased motivation and engagement, personalized and adjustable therapy, and improved functional outcomes through immersive and repetitive practice in a controlled environment.	The balanced recovery process, improved functional outcomes across multiple domains, and increased patient satisfaction and engagement through diverse and complementary therapies.	Enhanced motor skills, improved coordination, and increased functional independence, resulting from the integration of sensory feedback with motor activities

Rehabilitation Approaches	Brain-computer interfaces	Virtual reality and gamification	Constraint-induced movement therapy	Cardiorespiratory training and aerobic exercise
Principle of Action	Utilizes neural signals from the brain to control external devices, facilitating motor function recovery through neurofeedback and targeted exercises.	Uses immersive and interactive digital environments to simulate real-world tasks, providing engaging and repetitive practice with real-time feedback.	Restricts the use of the unaffected limb to encourage intensive use of the affected limb through repetitive, task-specific practice.	Engages heart and lungs through sustained activities and involves rhythmic movements like walking or cycling
Intended Outcome	Restoration of motor functions and improved muscle control. Enhanced communication between the brain and muscles.	Improved upper limb motor function and ADL performance. Enhanced cognitive engagement and motivation.	Increased use and function of the affected limb. Improved motor skills and functional independence.	Enhanced aerobic capacity, muscle endurance, and metabolic rate
Key Gains	Promotes neuroplasticity, aids in regaining motor skills, and offers personalized rehabilitation strategies to improve daily function.	Boosts neuroplasticity, increases patient motivation and translates therapeutic gains into daily functional improvements	Enhances limb strength and coordination, reduces learned non-use, and improves overall functional abilities in daily activities.	Improves cardiovascular efficiency and helps avoid recurrent episodes

Research indicates that augmenting hand motor abilities via virtual reality instruction may result in increased self-sufficiency for stroke victims when executing activities of daily living. In a study on VR for upper limb rehabilitation, [57]discovered that patients who got VR training showed appreciable gains in ADL function, making it easier for them to carry out everyday duties. A follow-up investigation into the long-term impact of VR therapy on ADLs was also conducted. According to the findings, VR can help stroke patients become more virtual reality-independent in their daily activities by resulting in long-lasting improvements in ADL function.

To make therapeutic activity enjoyable and relevant, interactive computer gaming has made inroads into rehabilitation. Among them is the Nintendo WiiTM (NW) game system, which hit stores at the close of 2006. With the help of a wireless portable pointing device (Wiimote) with an accelerometer and gyroscope built into it, NW can detect the user's movement and acceleration in three dimensions. Using a variety of commercially available games (including sports-themed games), the user can accomplish activities with part or all of their upper limb (e.g., throwing a virtual bowling ball or swinging a virtual tennis racket). With scores and other inspirational elements (such as in-game medals, inspirational commentary, video replays, bonuses, music, etc.), the games are entertaining and participatory to encourage the patients to improve their activity performance.[58] Using real-time visual biofeedback, the VR Nintendo Wii shows the necessary training of the target hand that results in the effective development of its functional capacity. Furthermore, it provides the patients with a secure environment where the repetition of the activities of daily life in the form of intensified, specific, and high-intensity tasks is imitated. Moreover, such an option makes it possible to adapt to the severity of the condition and thereby the patient's neuroplasticity and ability to recover are increased.[23, 29]

A study investigated the impact of integrating virtual reality (VR) games into conventional therapy for acute stroke patients. Utilizing the IREX VR system, participants engaged in VR interventions comprising interactive games designed to enhance reaching and lifting motor skills of the upper limb. Results revealed significant improvements in upper extremity function, assessed through the Fugl-Meyer Assessment

(FMA), and activities of daily living (ADL) performance, measured by the Korean version of the Modified Barthel Index (K-MBI). These findings underscore the potential of VR game-based interventions as effective tools for stroke rehabilitation, highlighting their role in augmenting traditional therapy approaches.[24]

A Kinect-based, low-cost, top limb rehabilitation system was developed which proved its efficacy (in the sense of being more successful in comparison with the active sham VR control) when compared in a randomized, controlled, double-blind trial with subacute stroke patients. However, the compliance in VR was good and the VR system provided more arm motion than the conventional therapy and similar activity of the desired conventional therapy. This system feature allowed the researchers to consider this method as an auxiliary to traditional treatment in neurologic rehabilitation wards.[48]

The Leap Motion Controller (LMC), utilized as a cost-effective semi-immersive VR device, captured upper extremity (UE) movements of stroke patients within a virtual environment housing specially designed games via Unity3D Game Engine software. These serious games aimed to mimic conventional rehabilitation exercises, targeting UE functionality improvement. This showed improvements in hand manual dexterity, grip strength, and functional performance of the upper extremity along with increased feasibility and motivation. However, notable limitations include the inability to generalize results to all stroke patients due to varying stroke severity and evolution time, small sample size, heterogeneous patient population, absence of follow-up, and lack of a control group for efficacy assessment. [59]

The Oculus hand-tracking Software Development Kit was made available in year 2019. Hand tracking combined with immersive Virtual Reality can produce movements that more closely resemble actions in the real world. In 2017, Coox et al.[37] studied the Virtual Reality application's comfort and usability, utilizing hand-tracking technology. To imitate everyday tasks like gesturing, this study constructed an application programming interface rehabilitation library with a variety of hand interactions. It was indicated that the application programming interface rehabilitation library and immersive VR technology were inexpensive and may be used in conjunction with occupational therapy for the rehabilitation of upper limbs.

With the use of motion tracking sensors, HMDs (Head Mounted Display) enable users to interact with virtual objects and provide a more immersive 3D artificial environment. Given the duration of therapy and the dynamic nature of rehabilitation, the head-mounted display (HMD) needs to be lightweight, pleasant to wear, stable on the head, and sufficiently cold to operate (most HMDs produce heat). The HMD's wireless design (with an adequate battery life) might be advantageous. [54] Physical objects or devices positioned in the real world could also enhance HMD-based immersive VR by tracking their exact locations concerning the user's position. Because the physical object is tracked to be placed at the same position as that in the virtual space, the user touches the physical object when they touch the virtual object, allowing the user to perceive the texture or temperature of objects without feeling awkward when touching them.

The immersive Virtual Reality Gaming Intervention (VRGI) can offer a cost-effective solution, poised to complement occupational therapy for upper limb rehabilitation. Published evidence for novel hand-tracking tools in upper limb rehabilitation remains scarce. Current studies often rely on external input devices such as sensor systems and motion-tracking gloves, highlighting technical challenges that hinder widespread clinical adoption. Moreover, the utilization of VR headsets alone presents additional hurdles, including staff confidence issues and limited technical support availability. Various Gamified versions of VR are available commercially that are discussed in Table 2.2 [54], [59], [60], [61]

Thus, there is a pressing need to explore self-contained VR systems capable of catering to diverse groups undergoing occupational therapy for upper limb rehabilitation. The primary purpose of this study is to utilize the subacute phase which has a maximum percentage of neuroplasticity to induce motor improvements that can be translated into Activities of Daily Living and eventually to the overall quality of life. It also aims to find out the dosage and frequency of VR intervention that is adequate to bring neural learning if given alone or in adjunct with Conventional Physical Therapy.

Table 2.2 Gamified Virtual Reality Interventions for Stroke Survivors.

Game	MoU Rehab	Microsoft Kinect (Bowling, Boxing, 360)	Nintendo Wii (Fit, Sports, Arcade)
Type of gamification	Game-Based VR	Camera Motion Tracking System	Hand-held controller-based system
VR Type	Non- Immersive	Immersive	Semi-Immersive
Targeted Body Area	Shoulder, Elbow, Wrist	Upper Extremity	Upper Extremity
Targeted Goals	Upper Limb Mobilization	Functional use of arm e.g. Reaching, Range of Motion, Balance in Sitting and Standing	Upper Limb Movement. Speed Control, Coordination, Endurance, and Accuracy of Arm Movement.
Effectiveness	Results showed significant improvement in FMA-UE, Manual Muscle Testing scores than in Conventional Therapy Group	The findings showed that video games combined with Conventional Therapy showed improved functionality of the upper limb and Quality of Life	This Game based VR showed significant improvement in all outcomes after the Intervention

Game	IREX (Immersive Rehabilitation Exercise)	Rehab MASTER	Myo-CI
Type of gamification	Video Capture System	Game-Based	Video Game Based
VR Type	Immersive	Non- Immersive	Non-Immersive
Targeted Body Area	Upper Limb and Lower Limb	Upper Extremity and Trunk	Arms and Hand
Targeted Goals	Mobilization of all limbs and Balance Training	Mobilization of Upper Limb and shifting of balance	Muscle Strengthening and reducing Muscle Co-activation
Effectiveness	It shows more profound effects on mobility-related Outcomes	This game-based VR specifically affects upper limb functions and health-related quality of life.	This study reveals no significant improvements in Motor function over Conventional Therapy.

Game	The RAPEAL Smart Glove	LMC (Leap Motion Controller)	Jintronix System
Type of gamification	IMU sensors based	Camera Motion Tracking	Kinect-Based
VR Type	Non- Immersive	Non-Immersive	Non-Immersive
Targeted Body Area	Wrist and Hands	Upper Extremity	Upper Extremity
Targeted Goals	Gripping, Releasing, pinching, holding	Mobilization of Upper Limb	Mobilization of Upper Limb
Effectiveness	This game system might be a good rehabilitation tool for the distal upper extremity in stroke Patients	The findings indicated Improved hand motor function and increased participation	Results revealed that Exergaming may be beneficial to Upper Limb Functional Recovery

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Instrumentation

3.1.1 Virtual Reality Setting

This study method has VR settings shown in Figure 3.1. The development was performed under the Unity3D game engine to make therapeutic games for hand rehabilitation. The Android Package Kit (APK) file was used to play the games on the Oculus Quest 2 Virtual Reality device. Meta produces Quest 2 independently from other devices including a Head Mounted Device (HMD) and controllers. The patient is asked to sit on a comfortable chair for the entire gaming experience while wearing the device. Furthermore, the tool is combined with hand-tracking technology that allows to design of virtual scenes with the subject hands. In the beginning, the patients were instructed to draw their hands inside the VR device and then the device gave an immediate response to the patient's hand movements in real-time.

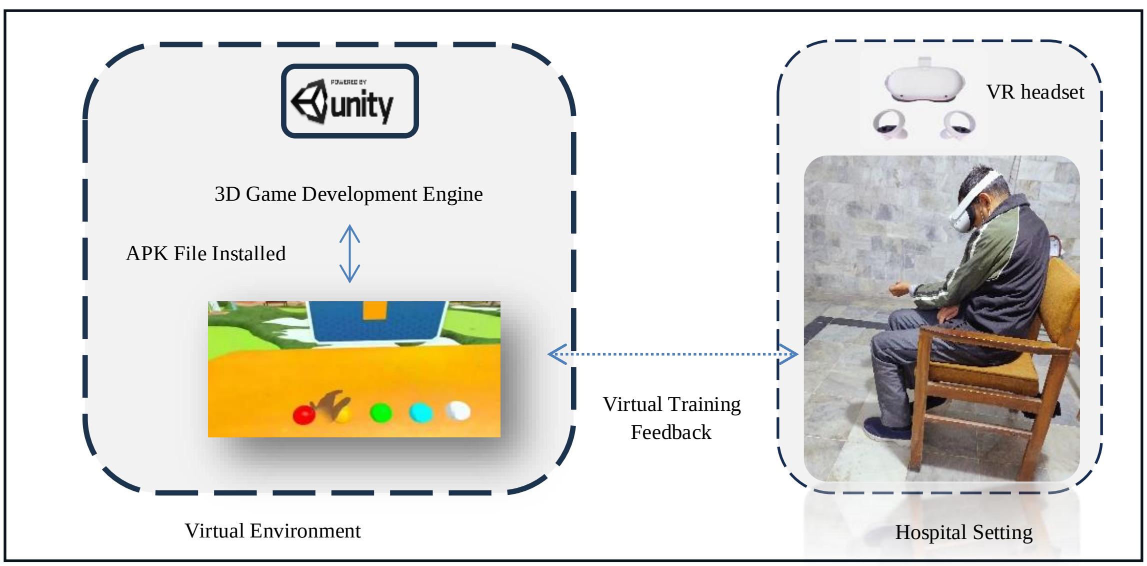

Figure 3.1: Virtual Reality Setting as a Game-Based Intervention for Stroke Patients Delivered in a Hospital Setting

01 **Hit the Rolling Ball**

Targeted Movement: Flexion and Extension
Objective: To enhance flexion and extension of wrist and motor coordination

Game Mechanics: Colored balls appear on the virtual table. By following the command from the command box, patient drags the ball towards them by flexing the wrist of the affected hand so that the palm touches the ball in the first half of the game time. Whereas, in the second half, the patient moves the wrist in extension to push the colored ball away from them by touching the dorsum of the hand

02 **Grab the Balloon**

Targeted Movement: Open and Close (Grasping)
Objective: To enhance gripping strength and fine motor skills

Game Mechanics: Colored balloons appear on the virtual table. Following the command from the command box, the patient opens the affected hand and grabs the balloon thread by tightly closing the hand by making a fist until the ballon disappears i-e after 5 seconds and the next set of ballons reappears and the patient follows the repetition.

03 **Pick the Pen**

Targeted Movement: Pinching
Objective: To enhance pinching strength and fine motor skills

Game Mechanics: Colored pens appear on the virtual table. By following the command from the command box, the patient reaches to pick and squeeze the instructed colored pen by using the two fingers and the thumb until the pen disappears i-e after 5 secs, and the next set of pens reappears and the patient follows the same instructions.

Figure 3.2: VR Games design mechanics incorporating (01) Hit a Rolling Ball (Flexion and Extension), (02) Grab the Balloon (Grasping) and (03) Pick the Pen (Pinch)

3.1.2 Virtual Reality Game Design

Interventional VR games were targeted and task-based activities for patients in the subacute stage with stroke. Games providing patients with rehabilitation through primary hand movement were developed and illustrated in Figure 3.2. Interaction with these three VR games includes flexion and extension, open and close, and pinch. The scenario in the VR games consists of an easy level i-e three-minute and an advanced level i-e five-minute. These games were played twice for one session to provide optimal time for intervention. The following details demonstrate the kind of game design used to be played by the affected hand to target depict hand movements.

3.2 Visual Training Feedback

The games were built with visually appealing and immersive VR settings containing virtual tables, balls, balloons, and pins. The environment also had a virtual component with an open sky and a vivid green view showing birds and trees in Figure 3.2. Visual training was a standard procedure for stroke patients where the gameplay screen was used to visualize the instructions, the square shape that could be hit, and the color as a color cue of the target items that needed to be captured, touched, and grabbed. The addition of visual training to VR games provides various exercises that can raise the level of spatial perception. By engaging in such activities, patients get to control virtual objects in a three-dimensional space and hence their spatial perception is sharpened, thus aiding in their recovery process. This is spatial awareness and means to understand the direction and location of objects around us and concerning ourselves. The situation is critical as many people take this skill for granted which may be especially important for those with a hand injury. In addition, the color cue that was played with the game was the one to be taken as the gameplay demonstrated correctly or not. In addition to that, the computer scoreboard showed the time and total, success, and failure in assisting the patient and observing the development process. For patients, there is an immediate visual feedback input from hand tracking showing them the hand movements they are making, and their interaction with virtual objects in space. The hand-tracking navigation enables VR games to have an ultra-realistic environment. This level of involvement reduces boredom and increases motivation hence VR therapy is more beneficial.

3.3 Study Design

This study was carried out in the physiotherapy department of Holy Family Hospital in Rawalpindi. The Research Ethical Committee (Reference Number: BMES/REC/22/027) approved this study, which was carried out under institutional guidelines and the Declaration of Helsinki's tenets. To participate in the trial, each patient had to complete a written informed permission form. The experiment study design flowchart for the Consolidated Standards of Reporting Trials (CONSORT) is shown in Fig. 3.3.

3.3.1 Inclusion and Exclusion Criteria

According to the study's inclusion and exclusion criteria, the patients were enrolled. Patients were deemed eligible for this study based on a set of inclusion criteria, which included (a) a Montreal Cognitive Assessment score of ≥ 21, which guarantees cognitive functioning for patients to effectively interact with virtual reality devices for task execution. The MoCA evaluates cognitive function with scores on a scale of 0-30, depicting the higher figures reflecting better cognition. Scores are within a normal range (24-30), 18-23 show mild to moderate impairs, while 18 and lower suggest a severe impairment. (b) The Modified Ashworth Scale (MAS) score of < 4 rates muscle spasticity from 0 to 4: 0 for no increase, 1 for slight resistance, 2 for more resistance, 3 for considerable resistance, and 4 for rigidity. Severe spasticity limits movement patterns in patients less spasticity guarantees that patients can participate in VR games successfully. (c) Fugl-Meyer Assessment for Upper Limb scored between 25 and 55. it is a comprehensive tool used to assess motor impairment following a stroke, with scores ranging from 0 to a maximum of 66. which verified that patients have the necessary motor abilities for efficient VR-based gaming interaction between the ages of (d) Age more than eighteen, this is favored since it indicates maturity and the ability to follow study guidelines and interaction directions and (e) Subacute stroke patients i-e 2 to 11 weeks post-stroke as this period has more potential for adaptability and neuroplasticity.

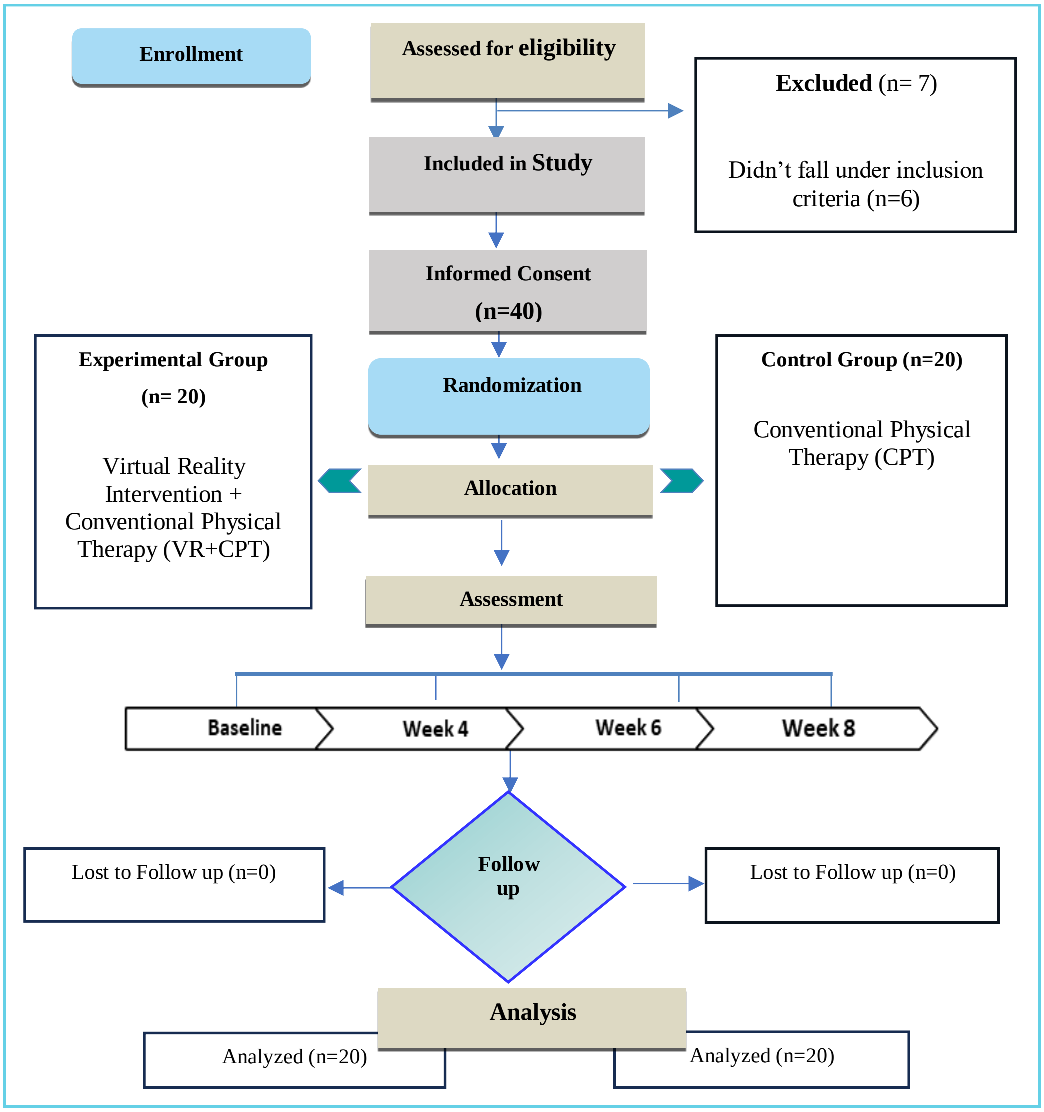

Figure 3.3 CONSORT Flowchart of Experimental Study Design

Patients with the following conditions are not eligible to participate in the study: (a) wrist impairments from a skeletal condition; these patients' reduced range of motion prevents them from correctly executing VR-based games; (b) burn contractures; stroke patients with these conditions have limited joint ranges of motion due to muscle loss, which makes it challenging for them to actively play VR games; (c) Patients with vestibular problems, like dizziness and vertigo which made it challenging to uphold commitment to the intervention and guarantee patient safety during the VR intervention, (d) Permanent External Fixation: By limiting stroke patients' ability to interact with VR devices, these devices reduced the effectiveness of the intervention.

3.3.2 Participants

For this study, a total of 47 people who had suffered a subacute stroke were recruited. Only 40 patients fulfilled the trial's eligibility criteria and were enrolled. Seven patients withdrew because they could not meet the criterion for eligibility. For the remaining 40 patients, a third party who was not involved in any portion of the trial completed the sealed envelope randomization process. A unique serial number was assigned to each enrolled patient

3.3.3 Intervention

Participants were equally divided into two groups (Figure 3.4); the Experimental group that received VR-based game intervention and Conventional Physical Therapy (VR+CPT) and the Control group that was only provided with Conventional Physical Therapy (CPT). The subjects of both groups were observed for 8 weeks i.e. they were taken through a six-week intervention program followed by a two-week follow-up. In each of the game levels, the patient repeated every game two times. In each VR game, there are two modes, easy and difficult, to choose from, and the time durations provided are respectively 3 min and 5 min.

3.3.3.1 Experimental Group

During the first and second weeks of intervention, the VR+CPT group received VR intervention for 18 minutes per day i-e 6 minutes of gameplay by playing each of the three games of easy level twice (i.e., three minutes + three minutes). During the third, fourth, fifth, and sixth weeks, the VR+CPT group experienced a VR intervention once again. They played all three of the same games, but this time for 10 minutes each i-e five minutes games two times (5 minutes + 5 minutes). This collectively makes up to 30 minutes per session per day from the third to sixth week. The seventh and eighth weeks are retention periods and patients did not receive any intervention during this period.

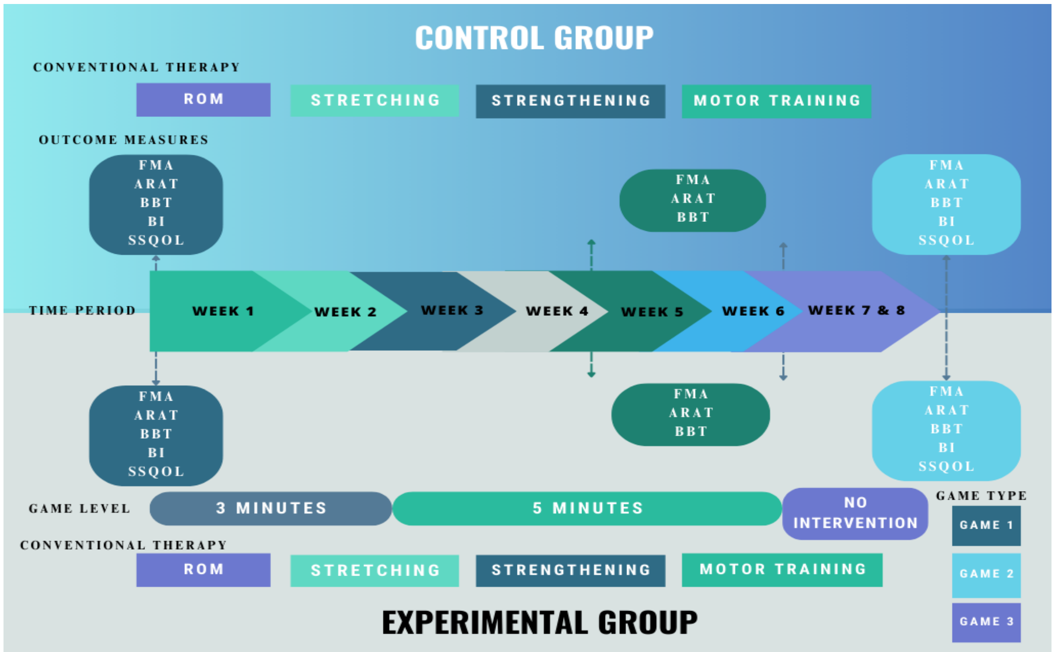

Figure 3.4: Experimental Model Employed for the Intervention of Stroke Patients

The VR+CPT group had 24 sessions overall—four days a week for a total of six weeks—of intervention. Additionally, the control group and the experimental group both got the same type of conventional therapy. The VR+CPT received 18 minutes of physical therapy sessions per day for the first 2 weeks and 30 minutes per day for the next 4 weeks (i.e. from week 3 to week 6). The details about conventional therapy and VR interventional games are further explained in Figure 1.4. Blinding was not possible for virtual reality intervention since the therapist oversaw the patients getting virtual reality-based therapy and the patients themselves.

3.3.3.2 Control Group

Similarly, the conventional intervention was given to the CPT group for 4 times a week for 6 weeks i.e., a total of 24 sessions. The CPT group was given 36 minutes of physical therapy sessions per day for weeks 1 and 2 followed by 60 minutes of comprehensive sessions per day for the next 4 weeks (i-e. 3rd to 6th week).

Experimental Group (VR+CPT)		Control Group (CPT)
Week 1 to 2 (36 minutes per session)		Week 1 to 2 (36 Minutes)
VR (18 min)	**CPT (18 min)**	**CPT**
Flexion/Extension Grasping Pinching	ROM Muscle Stretching Muscle Strengthening Motor Training	ROM Muscle Stretching Muscle Strengthening Motor Training
Week 3 to 6 (60 minutes)		Week 3 to 6 (60 minutes)
VR (30 min)	**CPT (30 min)**	**CPT**
Flexion/Extension Grasping Pinching	ROM Muscle Stretching Muscle Strengthening Motor Training	ROM Muscle Stretching Muscle Strengthening Motor Training

Table 3.1: Treatment Protocol for Stroke Patients

The duration of the intervention was increased to incorporate more repetitions and progression in the type of treatment.

To further elaborate on the physical therapy treatment protocol; (Table 3.1) these therapy sessions consisted of ROM exercises for joints (such as shoulder, elbow, and wrist), muscle stretching (shoulder flexors; abductors; external rotators, elbow and wrist extensors, hand musculature), strengthening exercises and resistive exercises for weak muscles (using power web and gym equipment) and motor skills training for the upper limb (Thera putty and occupational therapy equipment). This therapy promotes flexibility, hand dexterity, and retaining joint mobility.

3.3.4 Outcome Measures

This study aimed to determine whether the VR game intervention improved the motor function of stroke patients' hands. The experimental (VR+CPT) group and the control (CPT) group used the following outcome measures: the Fugl-Meyer Assessment's Upper Extremity (FMA-UE), the Action Research Arm Test (ARAT), the Box and Block Test (BBT), and the Modified Barthel Index (MBI). FMA-UE, ARAT, and BBT were the primary outcome measures; MBI was considered secondary. In clinical and scientific contexts, these sets of outcome measures are frequently employed [27]. Physiotherapists recorded these outcome indicators to assess individuals who had suffered a subacute stroke properly.

These outcome measures FMA, ARAT, BBT, and MBI were taken at baseline i-e before week 1 of the intervention. The next assessment is done after giving intervention for 4 weeks, then after 6 weeks, and lastly after 8 weeks, which is a retention period. Patients were assessed on follow-up to determine whether they still received benefits they encountered during the prior treatment process and if this intervention improved the outcome measures. The use of these outcome measures is explained below.

3.3.4.1 Fugl-Meyer Assessment-Upper Extremity (FMA -UE)

This test evaluated the sensorimotor function recovery of stroke patients in the upper extremities after therapies using the Fugl-Meyer Assessment's-Upper Extremity (FMA-UE) subscale. The upper extremity motor function deficit is measured by the 33 items that include scores for volitional movements, reflex activity, wrist function, hand function, speed, and coordination. Every movement was assessed and graded on a 3-point scale. The sensory portion included the assessment of pain, sensation, and joint motions. It has a total score ranging from 0-66. [30]

3.3.4.2 Action Research Arm Test (ARAT)

The Action Research Arm Test (ARAT) was used to score the capacity to do functional tasks, a measure of upper limb function. A four-point ordinal scale, ranging from zero (cannot complete any part of the activity) to three (performs task normally), is used to rate the 19 elements on the scale. The items can be reported as four subscales (grasp, grip, pinch, and general movement), although the overall total has a range of 0–57.[31]

3.3.4.3 Box and Block Test (BBT)

This assessed and gauged dexterity in addition to grabbing, holding, and throwing abilities. The person undergoing the evaluation is sitting in front of a box that has a huge divider dividing it into two equal squares. The patient's task is to move the little wooden blocks back and forth between the two for one minute. The number of blocks is recorded for the right and left hands independently after three trials are completed with each hand. The BBT is regarded as a quick, easy, and trustworthy test that is frequently administered to stroke survivors and older persons.[32]

Figure 3.5 Patient performing BBT with affected hand

3.3.4.4 Modified Barthel Index (MBI)

The individual's ability to perform instrumental and daily tasks was assessed by the MBI. Ten elements make up the MBI, with a five-step scoring system and each one is rated either on the patient's level of independence or the quantity of assistance they require. [33, 34]

3.3.4.5 Stroke Specific Quality of Life Scale (SSQoL)

The SS-QOL is a disease-specific QOL measure that consists of 49 items and covers 12 domains such as the social role (five questions), mobility (six questions), energy (three questions), language (five questions), self-care (five questions), mood (five questions), personality (three questions), thinking (three questions), upper extremity function (five questions), family role (three questions), vision (three questions), and work/productivity Every single item is rated on a five-point Likert scale through which a one implies completely agree and five shows disagree. The domain score from this scale is a simple (unweighted) average of the 12 domains. The final score is between 49 and 245, with higher scores meaning a better QOL. [46]

3.3.5 Data Analysis

To analyze the data acquired from the experimental and control groups, IBM SPSS statistical software was used. The statistical significance criteria were set at a p-value < 0.05. Firstly, Levene's test was performed to analyze the homogeneity of variances for patient demographic and clinical data. Secondly, the Shapiro-Wilk test was used to assess the normality of the data distribution of variables. Then, the Mann-Whitney U Test was performed to evaluate the difference comparison between the experimental group (VR) and control group (CPT) for FMA-UE, ARAT, and BBT because data was not normally distributed for these outcomes measures whereas for MBI and SSQoL, ANOVA Test was performed to assess the comparison difference between two independent groups i-e experimental group (VR) and control group (CPT) as data was normally distributed. Lastly, the Wilcoxon Signed Ranks test was conducted to evaluate the difference comparison within the experimental group (VR) and control group (CPT) for outcome measures FMA-UE, ARAT, and BBT. However, due to the normality of data acquired through MBI and SSQOL assessments, a paired t-test was performed to assess the within-group difference comparison.

CHAPTER 4: RESULTS

This study was comprised of n=40 stroke patients who were at the subacute stage of their disease. These patients met the trial's eligibility requirements. A randomized controlled trial was carried out to evaluate the effect of VR-based rehabilitation on hand motor function, activities of daily living (ADL), and quality of life (QoL) compared to conventional therapeutic procedures. The VR and CPT groups were equally randomized to get these patients. There were 20 patients assigned to each group through non-probability convenience sampling (sealed envelope). The experimental model used in this study for hand rehabilitation games has been already presented in Figure 3.4.

4.1 Sample Demographic and Clinical Data

The patient’s clinical and demographic information is presented in Table 4.1. It includes Age, Montreal Cognitive Assessment (MoCA), and FMA-UE (Fugl Meyer Assessment Scale for Upper Extremity) are reported with Mean scores and Standard Deviation separately for both groups. In contrast, the Gender, Involved Hand, and Modified Ashworth Scale (MAS) data are presented in frequency and as percentages (n%) for both groups. The graphical representation is in Fig 4.1 The significance level was set at $p < 0.05$. To perform the inclusion criteria analysis and check the association between the two groups Mann- Whitney U test was performed for the variables i-e. Gender, Involved Hand, Age, MoCA, FMA-UE, and MAS. The values for all baseline data of demographic and clinical features of both the groups were $p > 0.05$ which depicts that the data did not significantly vary from each other. Furthermore, Levene’s test was performed to determine the homogeneity of variances between both groups. The results showed that all p-values for clinical and demographic data are greater in this test which depicts that both experimental and control groups have no significant difference in their variances.

4.2 Data Distribution Analysis

Shapiro Wilk Test was performed to analyze the data for normality i-e if the data collected from the stroke patients in both experimental (VR) and control groups (CPT) are normally distributed. Mean and Standard deviation were measured for the baseline data of all outcome measures. After that, inter-quantile values were calculated for each outcome measure along with the percentile and z-score of each data sample to determine if the samples were normally distributed. The level of significance was p<0.05. As Table 4.2 demonstrates, the p-values of FMA-UE, ARAT, and BBT were lower than 0.05 which indicated that data in these measures were not normally distributed whereas the data obtained for MBI and SSQoL were normally distributed because the p-values were higher than the set significance level of 0.05. The distribution for data samples in both groups is represented through scatter plots in Fig 4.2 and Fig 4.3

Table 4.1 Demographic and Clinical Data for Stroke Patients

Data		VR	CPT	*p*-value[1]	*p*-value[2]
Age in years (Mean±SD)		51.55±13.7	48.95±10.8	0.766	0.236
Gender	**Male (n%)**	11(27.5)	12(30)		
	Female (n%)	9(22.5)	8(20)	0.343	0.555
Involved Hand	**Left (n%)**	9(22.5)	7(17.5)		
	Right (n%)	11(27.5)	13(32.5)	0.206	0.257
MoCA (Mean±SD)		22.60±1.5	22.45±1.8	0.528	0.589
FMA – UE (Mean±SD)		35.30±9.1	36.35±7.7	0.364	0.137
MAS (n%)	**Grade 0**	7(35)	6(30)		
	Grade 1	5(25)	6(30)		
	Grade 1+	4(20)	4(20)	0.566	0.516
	Grade 2	4(20)	4(20)		

VR: Virtual Reality, CPT: Conventional Physical Therapy, Mean±SD: Mean±Stanadard Deviation, n%: Percentage

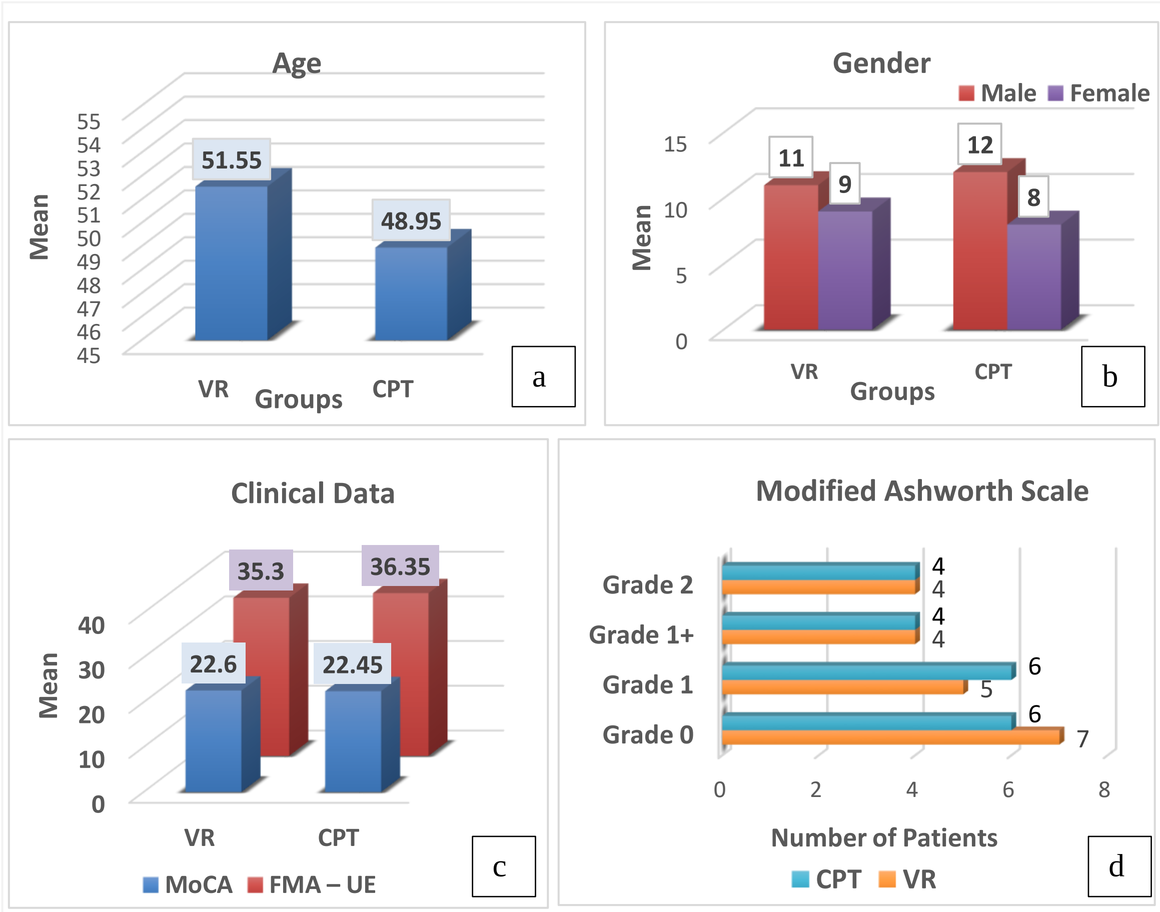

Figure 4.1 a. Mean Age in both groups, b. Gender distribution in both groups, c. Baseline scores of MoCA and FMA-UE, d. Baseline Modified Ashworth Score

4.3 Effect of Virtual Reality Intervention on Hand Motor Function

To assess the recovery of Upper Extremity Motor function of subacute stroke patients, the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) scale was used to measure the outcomes before and after the intervention at 4 different assessment time points i-e at baseline, then at week 4, week 6, and the end of week 8. Since FMA-UE data was not normally distributed, non-parametric tests were applied to assess the difference between group and within-group analysis. Table 4.3 shows the Mean and Standard Deviation of the baseline assessment, Week 4, Week 6, and Week 8. For between-group analysis, Mann-Whitney U tests were employed. At the baseline, it was observed that there appeared to be no

Table 4.2 Normality Test Results

Outcome Measures	Group	Baseline (Mean±SD)	IQR	*p-value*	*Normally Distributed*
FMA-UE	VR	35.30±9.1	18	0.006	No
	CPT	36.35±7.7	13	0.035	No
ARAT	VR	20.95±8.7	14	0.025	No
	CPT	20.25±8.3	12	0.046	No
BBT	VR	13.20±9.6	16	0.003	No
	CPT	11.65± 8.7	12	0.001	No
MBI	VR	9.40±4.5	6	0.247	Yes
	CPT	9.20±3.4	4	0.174	Yes
SSQoL	VR	130.95±25.4	36	0.890	Yes
	CPT	125.5±23.1	29	0.297	Yes

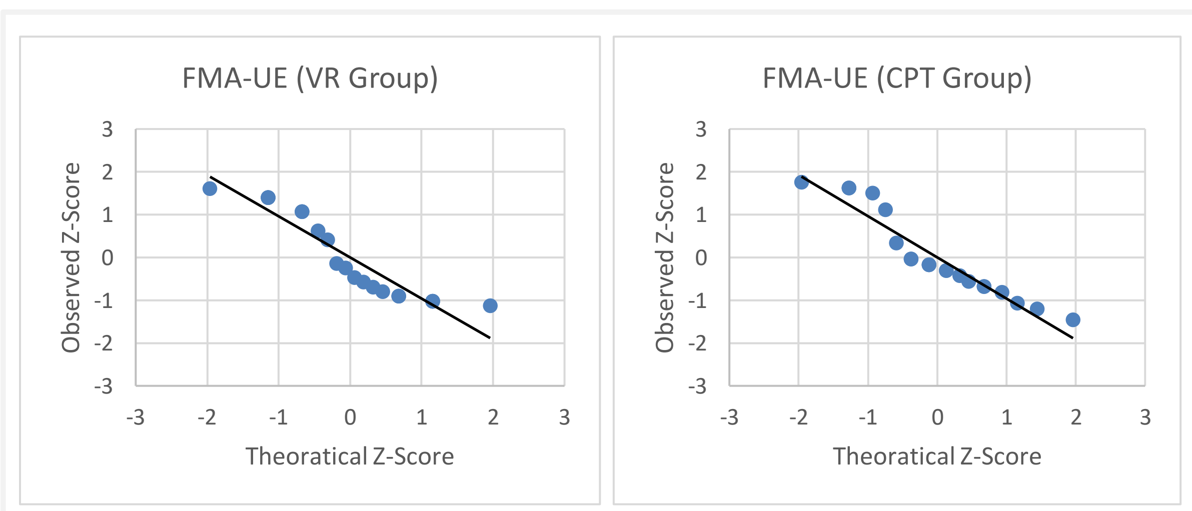

Figure 4.3 Q-Q plots for data samples of FMA-UE for both groups showing data is not normally distributed.

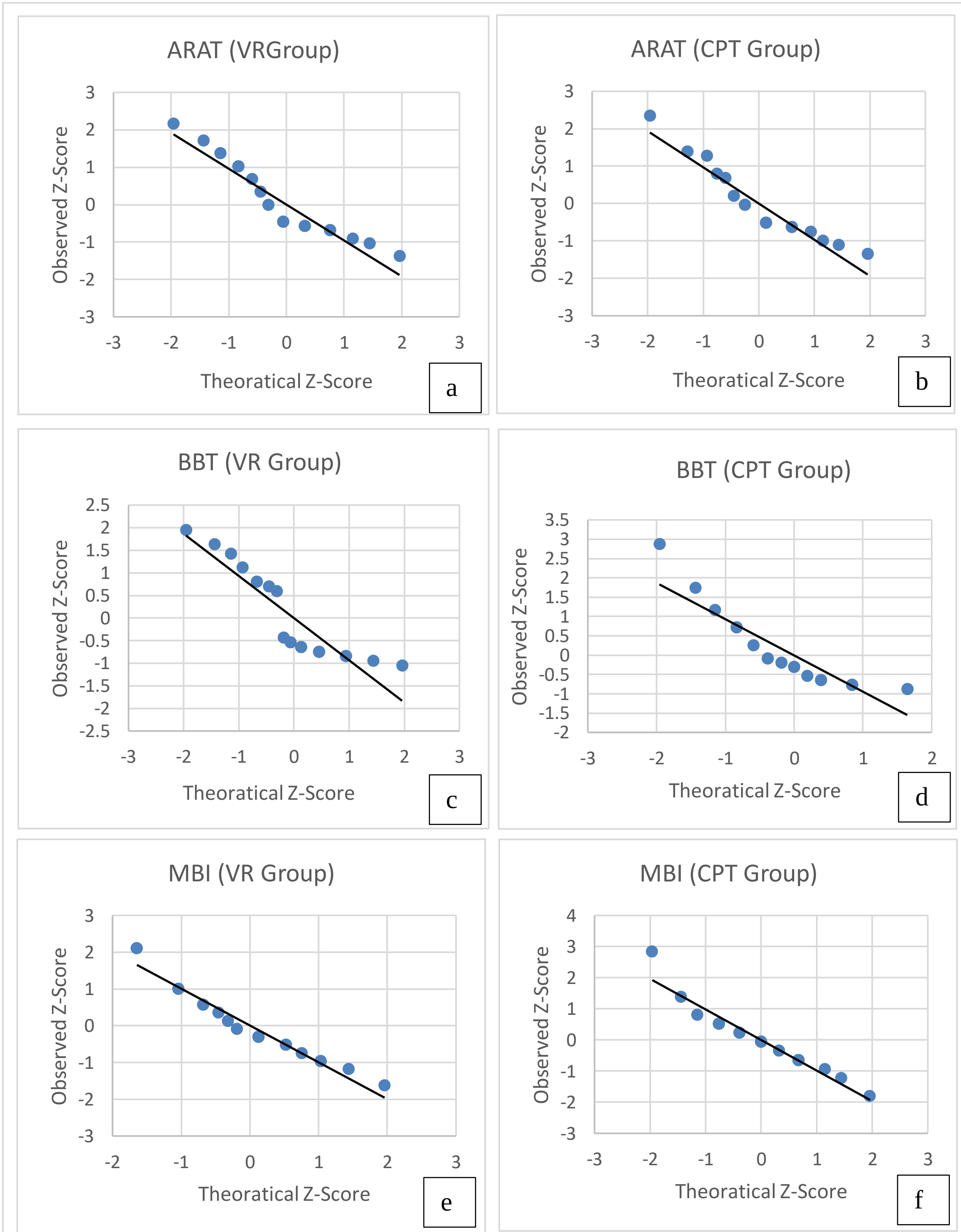

Figure 4.3 a, b Q-Q plots for data samples of ARAT for both groups. c, d Q-Q plots for data samples of BBT for both groups. All 4 plots depict not normally distributed data. e, f Q-Q plots for data samples of MBI for both groups show normally distributed data.

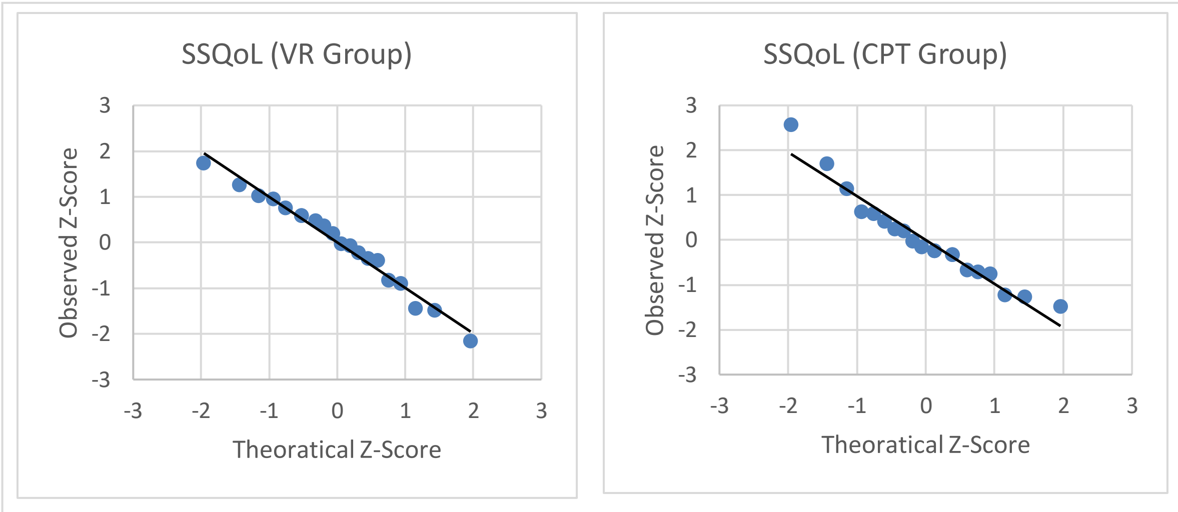

Figure 4.3 Q-Q plots for data samples of SSQoL for both groups showing data is normally distributed.

significant difference between the Experimental (VR) and Control groups (CPT) with p= 0.364 which is higher than the significance level of p=0.05. After week 4, week 6, and Week 8 assessments, the analysis revealed that p values were 0.042, 0.002, and 0.000 respectively, suggesting significant differences (all, $p<0.05$) between the two groups at these assessment points. These differences signify that patients in the Experimental group gain more motor benefits than patients in the Control group due to the virtual reality intervention.

For within-group analysis, the Wilcoxon Signed Rank test is used for all assessment points for both groups. Starting from the experimental group, a significant difference is observed (z = -3.930, p= 0.000) between baseline and week 4, with an improvement of 7.6 +2.6. Similarly, the improvement between Week 4 and Week 6 is also significant (z= 3.940, p= 0.000) with a measure of 6.4+2.3. Lastly, there is also a substantial difference (z= -3.647, p= 0.000) between week 6 and week 8 with an improvement of 6.45+2.0. In the Control group, an improvement of 2.35+2.4 is observed between baseline and week 4 readings with a difference of (z= -3.959, p = 0.000). Moreover, the difference of (z= -3.967, p= 0.000) is observed with an improvement of 2.8+2. from week 4 to week 6 and a difference of (z= -3.488, p= 0.000) from week 6 to week 8 with a mean improvement of

1.95+2.6. these higher mean values for improvement in the experimental group indicate a more positive effect of VR on the motor function of the upper extremities of stroke patients as compared to the control group.

4.4 Effect of Virtual Reality Intervention on Functional Performance

To assess the functional performance of the upper extremities among the subacute stroke patients, the Action Research Arm Test (ARAT) was used to measure the outcomes before and after the intervention at 4 different assessment time points i-e at baseline, then at week 4, week 6, and the end of week 8. Since ARAT data was not normally distributed, non-parametric tests are applied to assess the difference between group and within-group analysis. Table 4.3 shows the Mean and Standard Deviation of the baseline assessment, Week 4, Week 6, and Week 8. For between-group analysis, Mann-Whitney U tests is employed. At the baseline, it is observed that there appeared to be no significant difference between the Experimental (VR) and Control groups (CPT) with p= 0.693 which is higher than the significance level of p=0.05. After week 4, week 6, and Week 8 assessments, the analysis revealed that p values are 0.025, 0.001, and 0.000 respectively, suggesting significant differences (all, p<0.05) between the two groups at these assessment points. These differences signify those patients in the experimental group improved their functional performance more pointedly than patients in the Control group due to the virtual reality intervention. For within-group analysis, the Wilcoxon Signed Rank test is used for all assessment points for both groups starting from the experimental group (VR). A significant difference is observed (z = -3.946, p= 0.000) between baseline and week 4, with an improvement of 8+2.7. Similarly, the improvement between Week 4 and Week 6 is also significant (z= -3.947, p= 0.000) with a measure of 6.4+2.7. Lastly, there is also a significant difference (z= -3.983, p= 0.000) between week 6 and week 8 with an improvement of 5.75+2.6. Moving forward, in the control group (CPT), an improvement of 3.2+2.6 is observed between baseline and week 4 readings with a difference of (z= -3.957, p = 0.000). Moreover, the difference of (z= -3.852, p= 0.000) is observed with an improvement of 3.05+2.6 from week 4 to week 6, and lastly, a difference of (z= -3.485, p= 0.000) from week 6 to week 8 with a mean improvement of 1.75+26. These higher mean values for improvement in the experimental group indicate a significant effect of VR on the improvement of functional performance of the upper extremities of stroke patients as compared to the control group.

Table 4.3 Effect of Virtual Reality Training on the Clinical Outcome Measures

	Group	*Assessments (Mean ± SD)*				*Baseline & Week 4*	*Week 4 & Week 6*	*Week 6 & Week 8*	*Baseline & Week 8*
		Baseline	*Week 4*	*Week 6*	*Week 8*	*p-value²*	*p-value²*	*p-value²*	*p-value²*
FMA-UE	**VR**	35.3±9.1	42.9±7.7	49.3±7.4	54.7±5.6	0.000	0.000	0.000	0.000
	CPT	36.3±7.7	38.7±8.1	41.5±8.1	43.4±8.4	0.000	0.000	0.000	0.000
	p-value¹	0.364	0.042	0.002	0.000	-	-		
ARAT	**VR**	20.9±8.7	28.9±8.7	35.3±8.5	41.1±8.1	0.000	0.000	0.000	0.000
	CPT	20.2±8.3	23.4±8.4	26.5±8.5	28.2±8.5	0.000	0.000	0.000	0.000
	p-value¹	0.693	0.025	0.001	0.000	-	-		
BBT	**VR**	13.2±9.6	19.8±10.9	27.9±13.2	35.9±13.4	0.000	0.000	0.000	0.000
	CPT	11.6± 8.7	13.6±9.3	14.8±8.8	16.0±8.8	0.000	0.004	0.010	0.000
	p-value¹	0.734	0.024	0.000	0.000	-	-		

[1]Mann Whitney U test for difference in comparison between Experimental and Control Groups
[2]Wilcoxon Signed Rank test for difference in comparison between Baseline to Week 4, Week 4 to Week 6, Week 6 to Week 8, and Baseline to Week 8 for both groups

4.5 Effect of Virtual Reality Intervention on Hand Dexterity

To assess the hand dexterity (fine motor skills) of the hand among the subacute stroke patients, the Box and Block Test (BBT) was used to measure the outcomes at 4 different assessment time points i-e. at baseline, at week 4, week 6, and the end of week 8.

As already mentioned, BBT data was not normally distributed, and non-parametric tests were applied to assess the difference between group and within-group analysis. Table 4.3 shows the Mean and Standard Deviation of the baseline assessment, Week 4, Week 6, and Week 8. For between-group analysis, Mann-Whitney U tests are employed. At the baseline, there was no significant difference between the Experimental (VR) and Control groups (CPT) with p= 0.743 which is higher than the set significance level of p=0.05. After week 4, week 6, and week 8 assessments, the non-parametric tests revealed p values to be 0.024, 0.000, and 0.000 respectively, suggesting significant differences (all, $p<0.05$) between the two groups at these assessment points. These differences signify that the fine motor skills of patients in the experimental group have more implicitly improved than patients in the control group due to the virtual reality intervention. For within-group analysis, the application of the Wilcoxon Signed Rank test on the experimental group (VR) revealed a significant difference (z = -3.931, p= 0.000) between baseline and week 4, with an improvement of 6.6+3.2. Similarly, the improvement between Week 4 and Week 6 is also substantial (z= -3.927, p= 0.000) with a measure of 8.15+3.8. Lastly, there is also a significant difference (z= -3.934, p= 0.000) between week 6 and week 8 with an improvement of 7.95+4.2. In the control group (CPT), a difference of (z= -3.545, p = 0.000) is observed between baseline and week 4 with an improvement of 2+2.8. Moreover, the difference of (z= -2.857, p= 0.004) is observed with an improvement of 1.2+2.8 from week 4 to week 6, and lastly, a difference of (z= -2.582, p= 0.010) from week 6 to week 8 with a mean improvement of 1.2+2.7. These higher mean values of improvement in the experimental group indicate a significant effect of VR on the improvement of hand dexterity of the hands of stroke patients as compared to the control group.

4.6 Effect of Virtual Reality Intervention on Activities of Daily Living

For assessing the performance of activities of daily living (ADL) of subacute stroke patients, the Modified Barthel Index (MBI) was used to measure the results at two different assessment time points i-e at baseline and the end of week 8. As data obtained from MBI was normally distributed, parametric tests were applied to assess the difference between group and within-group analysis. Table 4.4 shows the Mean and Standard Deviation of the baseline assessment and Week 8 assessments. For between-group analysis, ANOVA tests are employed. At the baseline, no significant difference between the Experimental (VR) and Control groups (CPT) was observed with p= 0.873 which is p> 0.05. At the week 8 assessment, the tests revealed the p-value to be 0.000, suggesting significant differences between the two groups at the follow-up. This difference signifies that the ADLs of patients in the experimental group have more improvement than patients in the control group due to the virtual reality intervention. For within-group analysis, the application of the Paired t-test on the experimental group (VR) revealed a substantial (p= 0.000) improvement of 6+1.3 from baseline to week 8. Whereas in the control group, an improvement of 1.55+1.0 is observed when p<0.05. These advanced improvements in mean values in the experimental group indicate a significant effect of VR on performing the activities of daily living in stroke patients as compared to the control group.

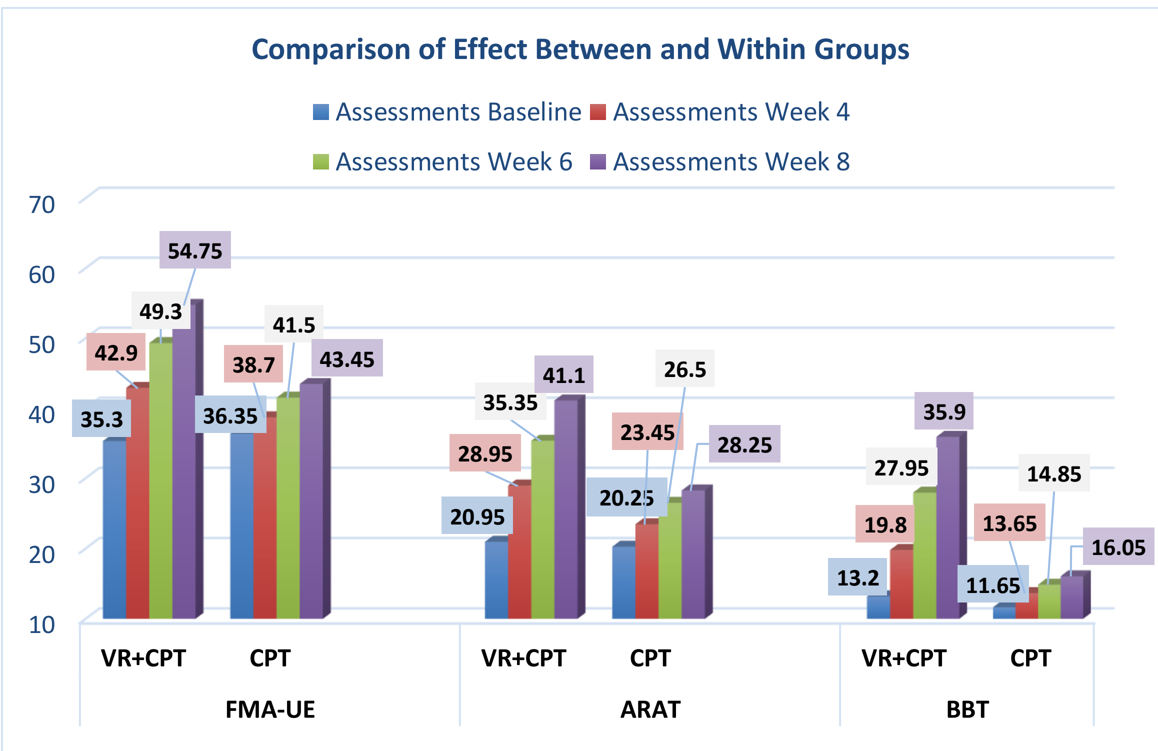

Figure 4.4 Mean values of clinical outcome measures (FMA-UE, ARAT, BBT) taken at Baseline, Week 4, Week 6 and Week 8 for both Groups

Table 4.4 Effect of Virtual Reality Training on the Clinical Outcome Measures (MBI, SSQoL)

Outcome Measure	***Groups***	***Assessments***		***Baseline and Week 8***
		Baseline	***Week 8***	***p-value²***
MBI	**VR**	9.40±4.5	15.40±3.7	0.000
	CPT	9.20±3.4	10.75±3.4	0.000
	***p*-value¹**	0.873	0.000	
SSQoL	**VR**	130.95±25.4	168.30±19.4	0.000
	CPT	125.5±23.1	139.20±21.7	0.000
	***p*-value¹**	0.487	0.000	

[1]ANOVA test for difference in comparison between Experimental and Control Groups
[2]Paired t-test for difference in comparison between Baseline to Week 8 for both groups

4.7 Effect of Virtual Reality Intervention on Quality of Life

For assessing the impact of VR on the Quality of life of subacute stroke patients, the Stroke Specific Quality of Life Scale (SS-QoL) was used to measure the results at two different assessment time points i-e at baseline and the end of week 8. As data obtained from SSQoL was normally distributed, parametric tests were applied to assess the difference between group and within-group analysis. Table 4.4 shows the Mean and Standard Deviation of the baseline assessment and Week 8 assessments. For between-group analysis, ANOVA tests are employed. At the baseline, no significant difference between the Experimental (VR) and Control groups (CPT) was observed with p= 0. 0.487 which is p> 0.05. At the week 8 assessment, the tests revealed the p-value to be p<0.05, suggesting significant differences between the two groups at the follow-up. This difference signifies that the quality of life of patients in the experimental group has more improvement than patients in the control group due to the virtual reality intervention. For within-group analysis, the application of the Paired t-test on the experimental group (VR) revealed a substantial (p= 0.000) improvement of 37.35+7.1 from baseline to week 8. Whereas in the control group, an improvement of 13.7+7.0 is observed where $p<0.05$. These notable improvements in mean values in the experimental group indicate a significant effect of VR on the overall quality of life of stroke patients as compared to the control group.

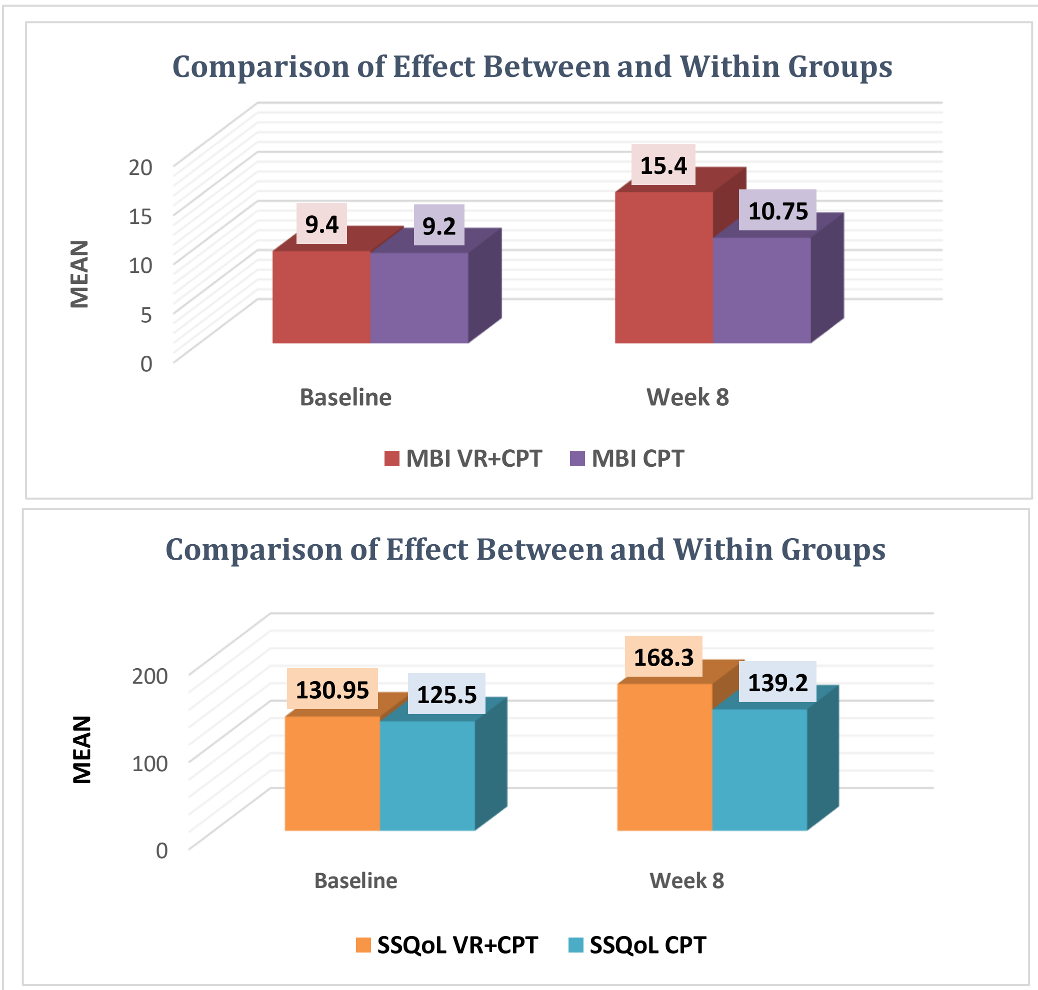

Figure 4.5 Mean values of clinical outcome measures (a. MBI, b. SSQoL) taken at Baseline and at Week 8 for both Groups

CHAPTER 05: DISCUSSION

In this randomized control study, the aim was to investigate the effects of VR-based game intervention combined with conventional therapy on the upper extremity motor function and activities of daily living performance in patients with subacute stroke. The games were designed to target the hand movements and mimic the hand motion exercises which were flexion and extension, grasping (open and close movements), and pinching. The exercises based on gamification that are done using VR technology help patients in motor recovery and improvement in coordination as well as in their daily living activities. VR can thus be used to improve people's lives significantly. These VR applications are not accessible on the market yet.

The clinical outcomes of VR games added to CPT significantly enhanced the hand motor function as compared to the results of CPT alone. The upper limb extremity function in the VRGI+CPT group improved after intervention which is in line with the conclusions of previous studies done in the same domain that highlighted those repetitive, intensive, and engaging tasks resulted in specific improvements in arm function and not just in the hand. [6, 14, 35]

Furthermore, cortical reconfiguration and mirror neuron firing rates—two neurological alterations that aid in motor recovery—may have been made easier by visual feedback. Jang and colleagues examined how VR therapy affected the cortical reorganization and motor recovery of five chronic stroke patients by using fMRI to show VR-induced neuroplastic changes [2]. To improve upper extremity functions, therefore, the use of intense and repetitive VR in addition to CT may be thought to be more helpful than CT alone, especially in the early stages of stroke.

In these virtual reality games, stroke patients used their affected hands to carry out purposeful task-based movements. VR-based games yield higher results for hand functioning than traditional therapeutic exercises. VR-based hand rehabilitation games proved to be a successful intervention for stroke patients during their recuperation. The efficiency of these games was confirmed by obtaining periodic assessments at the baseline i-e before any intervention for administered, at week 4, then at week 6, and finally after 8 weeks i-e follow-up assessment outcomes. There were four outcome measures used including ARAT, BBT, MBI, and FMA-UE to evaluate the performance of the stroke patients in both groups. The statistical significance (p-value) and the mean and standard deviation of each measurement, given as mean SD, are displayed.

The FMA (UE) data from Table 4.3 demonstrate that there is no significant difference between the two groups i-e Experimental and Control at the baseline, demonstrating the effectiveness of randomization. Nevertheless, following the VR-based game intervention, both groups' scores at the final three evaluation points showed significant differences (all, $p<0.05$). The table suggests that there were notable variations between the two groups as well. In the experimental group, the FMA-UE score rises with mean values of 7.6 $\pm$2.6 from baseline to week 4 and 6.4+2.3 from week 4 to week 6. During the assessment weeks, the FMA-UE in the control group similarly increased, with a mean value of and a mean value of 2.35$\pm$2.4 baseline to week 4 and a mean value of 2.8$\pm$2.5 from week 4 to week 6 respectively. However, it was noted that the VR-based group intervention of three games significantly improved the FMA-UE within the experimental group compared to the control group in overall assessment weeks. This demonstrated how a completely immersive virtual reality game intervention has been implemented successfully and led to a significant increase in motor recovery.

Similarly, results from the follow-up week showed that there was an increase in mean values of 6.45$\pm$2.0 between weeks six and nine. However, when the control group was assessed at week nine, which had a mean value of 1.95$\pm$2.6, the experimental group showed prospective improvement compared to the control group. This demonstrates how a VR-based intervention was able to significantly maintain subacute patients' motor improvement. The baseline to follow-up results showed that the experimental group had significantly improved than the control group. The three games that make up the VR gaming intervention shown in these results are beneficial for improving motor function.

In ARAT results demonstrated in Table 4.3, the randomization proved to be effective, which reveals no discernible difference between the two groups at the baseline. Nonetheless, in the final three assessment intervals, there were noteworthy distinctions in ARAT between the two cohorts, with (all, $p<0.05$) following VR game intervention. Analysis of the evaluation within the groups revealed that there was a notable improvement within the VRGI+CPT group, with the mean score of ARAT in the VR+CPT group from baseline to week 4 being 8 ± 2.7, and from week 4 to week 6 being 6.4 ± 2.7. Upon investigating the CPT group, the ARAT mean score increases from baseline to week 4 and week 4 to week 6 with mean values of 3.2 ± 2.6 and 3.05 ± 2.6, respectively.

When compared to the control group, the experimental group's ARAT improved significantly in each of the evaluation weeks, mostly as a result of the three VR-based games that were used as an intervention. When the assessment was compared between the baseline and follow-up, the experimental group showed a substantial improvement with 5.75 ± 2.6 compared to 1.75 ± 26 for the control group. This development suggested that the functional abilities had been effectively promoted using VR-based game intervention.

According to a study by [3] on 46 subacute stroke patients using HandTutoM gloves and other specialized virtual reality (SVR) systems, hand recovery function improved as a result of FMA-UE and ARAT outcomes. Nevertheless, the study system was only partially immersive and did not effectively engage the patient. In a separate intervention study,[49] examined the use of virtual reality in conjunction with transcranial direct current stimulation (c-tDCS) on forty stroke patients. The results showed that, when compared to VR alone, VR combined with c-tDCS significantly improved FMA-UE, ARAT, and BI, and was effective in reducing motor impairment and improving quality of life. In contrast to these therapies, our study only employed VR hand names-based immersive virtual reality. Comparing our study to that of M. Rodrigue et al. [29] and X. Yao et al. [30], clinical outcome measure results indicated a significant increase in hand motor function as well as an improvement in quality of life and functional independence.

According to Table 4.3 results, the BBT mean score for the experimental group was 6.6±3.2 from baseline assessment to week four and 8.15+3.8 from week four to week six. The increase in the BBT mean score suggested that the patients in the VR+CPT group had improved hand dexterity. Likewise, the BBT score increased in the control group comparison as well, with mean values of 2±2.8 and 1.2±2.8 from baseline to week 4 and week 4 to week 6 respectively. Overall assessment weeks, the experimental group's hand dexterity significantly outperformed the control groups because of the administration of three VR-based game interventions. Improvements in hand dexterity between the experimental and control groups were also observed between the baseline and follow-up week, with a significant difference ($p<0.05$). Because of the task-specific and repetitive VR-based pinch game intervention, the hand dexterity of the patients in the experimental group significantly improved i-e the mean was 7.95±4.2 whereas the control group had a mean score of 1.2±2.7.

Playing completely immersive virtual reality games can help stroke survivors improve their motor abilities. As a result, the scores observed by the Modified Barthel Index (MBI) assessment in the experimental group increased indicating that patients have become more proficient at doing ADLs on their own. Task-specific training combined with repetitive practice of activities of daily living (ADL) is useful in the recovery of the upper extremities, according to the worldwide clinical guidelines for stroke care [50] Moreover, the experimental group's higher Stroke-Specific Quality of Life (SSQOL) scores were attributable to the regular immersive VR-based therapy that promoted motor ability recovery and enhanced patient quality of life.

These virtual reality (VR) games have the potential to be more engaging and motivating than traditional therapy, which could inspire the patient to work harder. The ability to play virtual reality games in a three-dimensional virtual environment and get instantaneous visual feedback enhances stroke patients' performance and eventually aids in movement adaptation and improvement. With a virtual reality headset, patients used hand tracking to actively play the games while seeing the hand that was afflicted. This helps patients manipulate and move the hand that is affected by stroke. The patients received instantaneous feedback on their performance in these games using visual training feedback, whereby the patients were able to focus on the target and execute the key movements required for that particular game. Moreover, giving patients the ability to monitor their progress by using gamification techniques to visualize the percentage of the target that they have correctly reached in a certain amount of time was another feature of visual feedback.

The improvement in neuroplasticity brought about by the efficient application of visual training is crucial for adapting to motions. Strengthening of the Neural pathway resulting from visual training with task-specific and repetitive workouts based on virtual reality games was the primary factor in improving motor function. This improved the prognosis for patients with subacute stroke during their rehabilitation. Due to the visual training feedback that enhanced the motor task during rehabilitation, patients who played virtual reality games and monitored their motions while undergoing therapy showed encouraging outcomes. Scores were shown on the VR game's gameplay screen, which helped give visual training feedback.

Getting feedback on their success helped stroke patients improve their techniques and modify their movements during therapy. Stroke patients can complete VR game-based exercises frequently, stay task-oriented, and monitor their progress because of the interactive environment and visual feedback, which enables them to achieve functional goals.

The mechanics of the games involved in our study do not require the patient to stand alone or to move from their place without any assistance. Therefore, adherence towards the games and less aversion to follow the complete duration of the protocol was seen among the patients. This indicates the feasible nature of the gaming intervention that keeps the patient involved throughout. Iosa et al. [45] also focused on increased participation due to the feasible nature of the game by assessing four elderly stroke patients in three trials. These elderly patients were assigned to undergo six sessions of leap motion controller-based intervention (30 minutes each) in addition to CT in the crossover trial. Three patients had very good participation in these sessions, while the other patients had great participation. Because this intervention is simple to apply and does not require the patient to be standing alone, it is a viable option for neurorehabilitation in this particular patient population.

Similarly, Nine patients in the pilot randomized controlled study [49] were assigned to undergo Nintendo Wii gaming, while the remaining eight patients received recreational therapy in the form of Jenga, bingo, or playing cards. The entire amount of time that the intervention was received indicated feasibility. The average overall VR time (388 vs. 364min; P = 0.75) was equivalent to the average total time for recreational therapy. In the meanwhile, Brunner et al.[50] collected 50 videos of subacute stroke patients who were assigned to receive either CT or VR. The authors found that the VR group was more feasible, with a longer mean period of active practice (77.6 minutes) than the CT group (67.3 minutes). Notably, the validity and interpretation of this finding are impacted by the patients' knowledge that they were being recorded. Therefore, larger, better-conducted trials are still required to corroborate these conclusions due to the small number of subjects who were included.

Our study is one of the few studies conducted to investigate the effects of virtual reality gaming intervention in improving the motor abilities of patients in the subacute phase. Previous studies have reported bias in terms of more treatment time given in the experimental group where Virtual reality training and physical therapy are provided as adjuncts whereas only physical therapy is administered in the control group. We aimed to reduce this discrepancy and designed the interventional protocol where the treatment time is the same for both groups so that there remains no bias in the beneficial functional outcomes of the intervention. However, there are limitations to the need for further research to determine the optimal intervention protocol, frequency, and intensity of the treatment protocol.

Apart from the benefits, 4 patients complained about fatigue and soreness while playing these games and were given more frequent breaks in between. However, it did not affect the participation of the patients or lead them to drop out as these symptoms didn't last longer than a day or two days. Similar issues arose in previous studies [58] All of them had to do with minor upper limb soreness and pain that went away in less than a day and had no bearing on the individuals' ability to participate in therapy. The low VAS pain levels both before and after intervention suggest that pain was not a major issue in the research.

The possibility that more frequent and intense gaming sessions could raise the risk of musculoskeletal pain and issues like repetitive strain injuries is somewhat concerning. Regular computer use may raise the risk of lower back pain, neck, and shoulder pain in the young population, as well as the development of "Wii shoulder," "Wii elbow," and "Wii-initis" due to repetitive strain.[69] The hemiplegic upper limb is at risk for injury even in cases of minimal impairment due to the combination of the prior elements such as the presence of major muscle weakness, skin flaccidity, joint vulnerability, shoulder subluxation, aberrant joint biomechanics, and sensory impairment. The intervention should be short in length or incorporate more breaks, thus, sufficient monitoring and control are mandatory.

Patients with stroke have different upper limb movement kinematics in VR and real-world settings. According to Viau et al., hemiparetic patients utilized more elbow extension and less wrist extension towards the conclusion of the putting phase when reaching, grasping, and completing tasks in virtual reality as opposed to in a real-world setting. [70]Parallel to this, several research utilizing reaching tasks also showed that the motions in virtual reality (VR) with head-mounted displays (HMDs) were slower than in the real world and that the spatial and temporal kinematics of VR and the real world are different. According to Lott et al., there are differences in the range of the center of pressure between real settings, non-immersive VR with 2D flat-screen displays, and immersive VR with head-mounted displays (HMDs) while reaching in standing (which is typically employed for balance training). [71] Therefore, when creating a VR-based rehabilitation program, various movement kinematics must be taken into account because the goal of rehabilitation is to increase independence in real-world life. This can affect how learning is transferred from virtual reality to actual situations.

VR gaming seems like a workable supplemental tool to support traditional treatment for subacute stroke patients who have mild impairments in upper limb function and strength. There are still a lot of unanswered concerns regarding the use of games in rehabilitation. Firstly, more clinical outcomes may need to be evaluated to fully evaluate VR-based hand games. Second, the VR games in this study are restricted to a certain set of workouts; hence, stroke patients may need to engage in exercises tailored to their own needs. The limited sample size of the study i.e., 40 patients may have an impact on the generalizability of our findings. There were no measures for engagement and motivation, and usability and safety concerns for longer-term or at-home use, etc. were not actively addressed. As more facilities use computer gaming in their rehabilitation programs, more study is required to address these and other pertinent issues. Lastly, results were evaluated as soon as the VR interventions were implemented, with a brief follow-up phase that lasted for two weeks. As a result, we are unsure if the improvement in motor function that occurs when VR methods are implemented will remain for a longer period.

A few studies have examined how older people utilize virtual reality, but as far as we know, not many have compared younger and older participants. Applications for virtual reality (VR) include those that encourage exercise, play interactive video games, stabilize platforms, and/or help robots. According to Zeng et al.'s systematic study [72] playing active video games can improve elderly patients' rehabilitative outcomes in terms of balance, physical functioning, and motivation. Nevertheless, there isn't enough data now available to justify VR's benefits over conventional therapy. Furthermore, it's not obvious if VR apps can be used as an effective rehabilitation technique to enhance cognitive results.

SUMMARY OF RESEARCH WORK

This randomized controlled trial investigated the efficacy of Virtual Reality (VR) gaming compared to Conventional Physical Therapy (CT) in subacute stroke patients, focusing on hand motor function, activities of daily living (ADLs), and quality of life. Forty stroke patients were randomly assigned to either the experimental group receiving VR games or the control group undergoing traditional physical therapy interventions through the sealed envelopes method. Outcome measures included the Fugl-Meyer Assessment for Upper Extremity (FMA-UE), Action Research Arm Test (ARAT), Box and Block Test (BBT), Modified Barthel Index (MBI), and Stroke-Specific Quality of Life (SSQOL). These Outcome measures were used at different assessment times for 8 weeks. FMA-UE, BBT, and ARAT were assessed at Baseline, 4 weeks, 6 weeks, and 8 weeks respectively. Whereas, the MBI and SS-QoL were assessed at Baseline and Week 8.

The results revealed significant improvements in all outcome measures for both groups post-intervention. However, the experimental group exhibited notably greater improvements in hand motor function, functional ability, hand dexterity, ADL performance, and quality of life compared to the control group ($p < 0.05$). This suggests that Virtual Reality (VR) gaming offers unique benefits beyond those provided by conventional physical therapy interventions. The immersive and interactive nature of VR experiences may facilitate more intensive and engaging practice sessions, leading to enhanced motor learning and functional recovery. Moreover, the gamified elements of VR interventions may stimulate cognitive processes such as attention, motivation, and executive function, which are crucial for motor skill acquisition and retention. Interestingly, in the follow-up week, the VR games group demonstrated sustained improvements, surpassing those observed in the physical therapy group. This finding suggests that VR-based interventions not only promote immediate gains in motor function but also contribute to longer-term retention of therapeutic effects. The enduring benefits observed in the VR group highlight the potential of VR technology to support

ongoing recovery and promote functional independence beyond the completion of formal rehabilitation programs.

This study addresses the practical issues associated with conventional therapies, such as their labor-intensive nature, difficulty in accessing specialized facilities, and insurance coverage requirements. By combining CT with intense and repetitive VR training, the study aimed to optimize neuroplasticity and improve upper extremity function and ADL performance in stroke patients. The findings support the hypothesis that game-based VR rehabilitation offers superior benefits over conventional therapy, highlighting the potential of VR-based interventions as a cost-effective adjunct to traditional therapy for upper limb rehabilitation.

The study also highlights the transformative potential of Virtual Reality (VR) technology in revolutionizing traditional rehabilitation paradigms. Unlike conventional therapies that often require specialized facilities and trained personnel, VR-based interventions offer a portable and scalable solution that can be easily integrated into existing care pathways. By leveraging immersive and interactive experiences, VR therapy not only facilitates motor learning but also taps into the brain's neuroplasticity to enhance recovery outcomes. The customizable nature of VR platforms allows therapists to tailor interventions to the unique needs and abilities of each patient, promoting individualized treatment plans that maximize efficacy and engagement. Moreover, the gamified nature of VR experiences introduces an element of enjoyment and challenge, motivating patients to actively participate in their rehabilitation journey. As such, VR-based rehabilitation holds promise not only as a complementary adjunct to conventional therapy but also as a catalyst for innovation in stroke rehabilitation, ushering in a new era of personalized and patient-centric care.

The study also identifies the research gap in the scarcity of published evidence for novel hand-tracking tools in upper limb rehabilitation. Current studies often rely on external input devices, posing technical challenges and hindering widespread clinical adoption. Furthermore, very limited studies are conducted in the subacute phase of stroke Thus, there is a pressing need to explore self-contained VR systems capable of catering to diverse groups undergoing occupational therapy for upper limb rehabilitation.

CHAPTER 6: CONCLUSIONS AND FUTURE RECOMMENDATION

The study's findings underscore the remarkable efficacy of virtual reality (VR) interventions in enhancing hand motor function and activities of daily living (ADL) performance among individuals recovering from stroke, particularly those with more severe initial impairments. Noteworthy improvements were observed in the VR group compared to the conventional rehabilitation (CR) group, encompassing significant enhancements in hand motor function, ADL performance, and quality of life (all, $p<0.05$). These results advocate for the integration of VR technology as a promising adjunct to conventional therapy in stroke rehabilitation frameworks. However, while VR demonstrates considerable potential in augmenting rehabilitation outcomes, further investigation is warranted to delineate its long-term effects, optimize implementation strategies, and explore its influence on cognitive function and broader physical performance measures in stroke survivors. Additionally, future research endeavors should encompass larger randomized clinical trials with extended follow-up periods to validate these preliminary findings and elucidate the comprehensive utility of VR in stroke rehabilitation contexts.

In the realm of stroke rehabilitation, several key areas require further exploration to enhance our understanding and improve patient outcomes. Firstly, identifying the most effective combinations of therapies and determining the optimal timing for intervention delivery is essential. Tailoring interventions to specific subgroups of stroke survivors could maximize their therapeutic benefits. Standardizing outcome measures and intervention strategies across different phases of stroke recovery would streamline research efforts and improve clinical practice. Moreover, conducting high-quality trials to evaluate the impact of interventions on functional activity and participation is crucial. Investigating the benefits of extended treatment durations and increased intervention dosage could optimize rehabilitation protocols. Additionally, integrating artificial intelligence into interventions and leveraging advancements in sensor technology offers promising avenues for enhancing therapy effectiveness and monitoring outcomes. By addressing these areas, future research in stroke rehabilitation can advance our understanding and improve care for stroke survivors.

The insights gleaned from the paragraphs highlighting the symbiotic relationship between neuroplasticity and recovery techniques in brain injury rehabilitation provide valuable guidance for future research and clinical practice. To build upon these insights and further advance the field of neurorehabilitation, several key recommendations emerge.

Moving forward, it is imperative to bridge the gap between theoretical knowledge of neuroplasticity and its practical application in medical practice. Clinicians should be equipped with a deeper understanding of cellular mechanics, synaptic plasticity, and neuroadaptation to tailor rehabilitation strategies that capitalize on the brain's inherent flexibility. Continuous education and training programs can facilitate the integration of neuroplasticity insights into clinical decision-making processes, thereby optimizing patient outcomes.

Given the complex nature of neuroplasticity and the multifactorial mechanisms underlying brain injury recovery, exploring the synergistic effects of combination therapies is warranted. Integrating various modalities such as cognitive rehabilitation, virtual reality (VR), brain-computer interfaces (BCIs), and constraint-induced movement therapy (CIMT) can potentially amplify neuroplastic effects and accelerate recovery trajectories. Future research endeavors should focus on identifying optimal combinations of therapies tailored to individual patient profiles and injury characteristics.

As the field of neurorehabilitation continues to evolve, ethical considerations must remain paramount to ensure patient welfare and safety. Innovations in rehabilitation technologies should adhere to rigorous ethical standards, balancing the pursuit of scientific advancement with patient-centered care. Ethical guidelines and regulatory frameworks should be established to govern the development and implementation of novel interventions, safeguarding against potential risks and ensuring equitable access to neurorehabilitation services.

Collaboration between researchers, clinicians, technology developers, and policymakers is essential to drive innovation and translate scientific discoveries into clinical practice effectively. Establishing multidisciplinary research consortia and fostering knowledge exchange platforms can facilitate the sharing of best practices, data, and resources, accelerating the pace of discovery and promoting evidence-based approaches to neurorehabilitation.

By embracing these recommendations and fostering a collaborative and ethically informed approach to neurorehabilitation, researchers and clinicians can unlock the full potential of neuroplasticity insights, ultimately improving outcomes and quality of life for individuals affected by brain damage.

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Effectiveness of Immersive Virtual Reality-Based Hand Rehabilitation Games for Improving Hand Motor Functions in Subacute Stroke Patients

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***Abstract*—Stroke rehabilitation faces challenges in attaining enduring improvements in hand motor function and is frequently constrained by interventional limitations. This research aims to present an innovative approach to the integration of cognitive engagement within visual feedback incorporated into fully immersive virtual reality (VR) based games to achieve enduring improvements. These innovative aspects of interaction provide more functional advantages beyond motivation to efficiently execute repeatedly hand motor tasks. The effectiveness of virtual reality games incorporated with innovative aspects has been investigated for improvements in hand motor functions. A randomized controlled trial was conducted, a total of (n=56) subacute stroke patients were assessed for eligibility and (n=52) patients fulfilled the inclusion criteria. (n=26) patients were assigned to the experimental group and (n=26) patients were assigned to the control group. VR intervention involves four VR based games, developed based on hand movements including flexion/extension, close/open, supination/pronation and pinch. All patients got therapy of 24 sessions, lasting 4 days/week for a total of 6 weeks. Five clinical outcome measures were Fugl- Meyer Assessment-Upper Extremity, Action Research Arm Test, Box and Block Test, Modified Barthel Index, and Stroke-Specific Quality of Life were assessed to evaluate patients' performance. Results revealed that after therapy there was significant improvement between the groups ($p<0.05$) and within groups ($p<0.05$) in all assessment weeks in all clinical outcome measures however, improvement was observed significantly greater in the experimental group due to fully immersive VR-based games. Results indicated that cognitive engagement within visual feedback incorporated in VR-based hand games effectively improved hand motor functions.**

***Index Terms*—Stroke rehabilitation, virtual reality, cognitive, visual feedback, clinical outcome measures.**

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This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Holy Family Hospital Rawalpindi in the Physiotherapy Department and the Research Ethical Committee under Application No. BMES/REC/22/027, and performed in line with the Declaration of Helsinki.

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I. Introduction

STROKE is a neurological disorder that mainly reduces the quality of life of patients which unable to perform their daily living activities. By 2030, it was anticipated that the prevalence of stroke would have increased to 21.9% globally [1], [2]. The most prevalent disability that makes it difficult for stroke survivors to conduct daily living activities is Upper Extremity (UE) [3], [4]. Many stroke patients are left with functional impairments and incapable of moving their hands due to inadequate rehabilitation. Therefore, patients struggle with functional tasks that reduce their everyday life and social interaction. Regaining the motor function of the hand impact greatly on daily living activities. Hand impairments induced by stroke are frequently associated with challenges in motor rehabilitation requiring creative therapy for effective recovery [5], [6].

Neuroplasticity studies [7], [8], [9], [10] revealed that the brain tends to reorganize when the activities are repetitious and subjected to task-oriented which improves the impaired motion abilities. The existing concepts used in neurorehabilitation after stroke to assist motor relearning and subsequently function enhancement are repetitive, intense, and task-specific functional training [8], [11]. Demotivation to therapy due to exercise repetitions is generally happens in conventional therapy due to which patients are less attentive to perform limited repetitions [12]. Additionally, conventional practices do not offer enough learning challenges to foster the plasticity necessary for motor rehabilitation [13].

Conventional exercises could not be sufficient to benefit stroke patients' concentration because of extended therapy sessions. The task-specific aspect that must be organized for relearning motions is highlighted in Carr and Shepherd's study