Immersive Virtual Reality Enhanced Reinforcement Induced Physical Therapy (EVEREST)

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Abstract

Background

Motor impairment of the upper limb (UL) after a stroke is common, which negatively impacts patients’ quality of life. Stroke survivors may develop a condition known as learned non-use, resulting in a tendency to avoid using the affected hand due to failure. Previous research has shown that constraint-induced movement therapy (CIMT), where the healthy arm is physically constrained to encourage the use of the stroke-affected arm, is effective in UL rehabilitation. However, some patients find it exhausting and tiring. New technologies have been applied to stroke rehabilitation alongside conventional techniques in recent years. For example, immersive virtual reality (IVR) has emerged as a new treatment approach for stroke rehabilitation, simulating real-life activities to work on self-care skills. Method: In this pilot study, we evaluated the efficacy of the IVR, which incorporates positive reinforcement components in motor coordination as opposed to CIMT using IVR technology. Eighteen participants were randomized to an IVR group to receive VR intervention plus physical therapy (PT) sessions or a control group to receive PT sessions alone. Participants were instructed to reach with either their affected or unaffected hand to a randomly assigned target in the VR. The movement of the virtual image of the UL was reinforced by visual feedback to the participants. Treatment effects on motor recovery were investigated using the Fugl-Meyer (FM) scale for the UL, kinematic dataset, and a questionnaire.

Results

The IVR group exhibited significant improvements in FM scores (p < 0.05) between the first and fifth session, signifying a substantial recovery of UL motor function, with the fifth session showing higher scores. The time to target in the last session reduced compared with that in the first session, suggesting motor learning and recovery (p < 0.05). The patients were highly engaged and motivated during the sessions because they felt like they were in charge of the virtual image of their upper body.

Conclusions

The results suggest that positive reinforcement within the IVR could encourage motor recovery of the affected hand and may facilitate the application of motor learning and neuroplasticity principles during neurological rehabilitation.

Introduction

A stroke occurs when blood flow to the brain is interrupted or is insufficient, leading to brain injury or cell death and subsequent impairment of physical and mental functions [1–3]. This may cause sensory, motor, and cognitive impairments as well as impaired self-care ability and participation in social and communal activities [4, 5]. The number of stroke deaths in England decreased by half during the first
decade of the 21st century [6], and in 2018 it ranked as the fourth leading cause of mortality [7]. Nonetheless, a significant proportion of stroke survivors continue to live with disabilities. Motor impairment is the most common complication after a stroke, and it can negatively affect health and motor skills, particularly when it affects the upper limbs [8, 9].

According to Adamovich et al. [10], stroke patients undergoing treatment for upper limb impairment encounter various challenges. The functional outcome is highly variable; some patients are unable to fully recover functionality and are forced to live with varying degrees of upper limb paresis for the rest of their lives. It has also been reported that the treatment of upper limb hemiparesis is time-sensitive and involves various therapeutic modalities [11, 12]. Thus, these scientific studies emphasize the need for appropriate rehabilitation procedures that can provide highly effective therapy and a greater possibility of a higher-level functional recovery. Successful rehabilitation depends on the stroke's characteristics (such as severity, nature, and location) as well as the patient's age, general health, and pre-stroke function [13].

Otherwise, the stroke patient whose impaired hand is rendered inactive for an extended period may acquire learned non-use. Learned non-use is the outcome of repeated unsuccessful attempts to use the affected upper limb coupled with the reinforcement of compensatory methods (such as the use of the unaffected upper limb), which leads to deterrence in using the affected arm [14–17]. Therefore, it is necessary to consider the optimal rehabilitation therapy for stroke patients with upper limb disability and limitations.

According to the International Classification of Functioning, Disability, and Health, physiotherapists are an essential component of multidisciplinary stroke rehabilitation teams [18, 19], as they assist patients in regaining mobility and independence by addressing impairments in bodily functions, activity limitations, and participation restrictions [20]. To recover movement, coordination, and balance, a physiotherapist provides conventional physical therapy (PT) for upper limb rehabilitation through exercises, training, and physical movement of the limbs [21].

It has been established that repetitive task training is beneficial in certain aspects of rehabilitation, such as improving upper limb function [22, 23]. Hence, the term “sensory motor training” was established to represent various physical activities designed to improve motor performance, strength, power, endurance, and sensory integrity, such as proprioception. Moreover, the neuroscience and rehabilitation literature are supporting the idea that task-specific or task-oriented practice is essential for restoring functionality in stroke-impaired limbs. This implies that repeatedly practicing a difficult activity can alter brain networks responsible for motor control, leading to long-term improvements in motor learning and performance [24].

Motor coordination can only be regained through a neuroplasticity process [25], which is described as the rewiring of the brain's synaptic connections to develop appropriate communication with the body's muscles [26].

The most crucial component is performing repeated movements, which provides patients with the ability to perform an activity normally [27]. Constraint-induced movement therapy (CIMT) has been reported to
be effective in treating severe paralysis in the body by training the nerve impulses of damaged muscles through constant repetition of movement on the affected side [23, 28, 29]. However, CIMT has major disadvantages, such as exhausting the patient owing to its intensity [30, 31]. Consequently, recent technological solutions have shown promise in terms of improving the function of impaired limbs without exhausting patients.

Virtual reality (VR) has emerged as a new treatment approach for stroke rehabilitation, simulating real-life activities to improve self-care skills [32, 33]. In virtual rehabilitation, patients receive visual feedback from simulated environments and objects through a head-mounted device, projection system, or flat screen, while all body senses offer feedback [34]. Virtual tasks and environments affect the users’ senses, and they perceive their presence in the virtual world [35, 36]. By adjusting stimuli to movements in real time and incorporating and modifying feedback, VR may enhance the application of motor learning and neuroplasticity principles during rehabilitation [35] as it provides components (such as goal-oriented tasks and repetition) demonstrated to be vital in rehabilitation [10].

Although there is limited evidence of neuroplasticity during VR training, neuroimaging discoveries are guiding the development of VR to meet the highest treatment standards [37]. As technology becomes a broader component of daily life, it is anticipated that the use of VR in rehabilitation settings will increase [38, 39]. Thus, it is essential to evaluate the effectiveness of VR in order to define its future designs and implementations. The VR environment motivates patients to perform repetitive, motor-intensive tasks that are crucial for rehabilitation [40–44]. Compared with conventional rehabilitation techniques, a concise adaptive game can improve mobility, motor function, and mental wellbeing.

Neurological patients generally lack therapy motivation [44]. Possible explanations for this lack of motivation include patients’ belief that therapy only intends to enable adaptation to the disease rather than providing complete healing, or a lack of motivating input from a therapist [44, 45]. Other logistic, financial, environmental, and human obstacles may restrict the efficacy and commitment to long-term rehabilitation regimens [42] found that combining VR with modified CIMT encouraged stroke patients to use the affected hand without constraining the unaffected side (both hands were free to move). Another study investigated the safety and effectiveness of VR and modified CIMT [46].

Relevant to our investigation, [47] proposed a new treatment that combines CIMT and reinforcement-induced movement therapy (RIMT). They demonstrated the efficacy of RIMT by speeding up the hindered hand in VR using the goal-oriented reaching task. After the RIMT intervention, the Fugl-Meyer (FM) scores of stroke patients improved; however, their study did not report the subjective feeling of being completely engaged in VR. Although they pioneered positive reinforcement utilizing computer-simulated limbs in the display, the RIMT concept should be developed to use immersive VR (IVR).

Visual feedback in IVR simply displays the simulated upper limb. Only the simulated hand should be seen during the task. If people watch their real hand move in front of them while viewing the simulated hand on the display, the discrepancy in visual feedback of motor coordination will induce a sense of loss of
ownership of the simulated upper limb or, in certain situations, the subjective awareness of the loss of bodily control.

Our study by [48] that used IVR on healthy subjects with a weight attached to their dominant hand to simulate the impairment of a stroke patient is also relevant to our investigation. Their system was portable (head-mounted VR), and the objective was to reach a target in VR without forcing the subjects to use their dominant hand, with an option to use either hand. The movement of the virtual image of the upper limb was reinforced by visual feedback to the participants, such that they perceived their motor coordination as if their upper limb was moving to a greater extent than normal. These findings suggest that positive reinforcement within IVR can influence hand usage decision-making.

Thus, herein, we modified the protocol developed by [48] for stroke survivors to accommodate the specific requirements of the patients, including extended task completion time and breaks to prevent fatigue, as detailed in the method section. Our study aimed to evaluate a new therapeutic approach for the rehabilitation of the upper limbs of stroke patients to demonstrate the effectiveness of IVR-enhanced PT by measuring the improvement in upper limb motion using the FM score. Additionally, to conduct a larger study in the future, a participant experience questionnaire was administered to evaluate the acceptability of the therapy.

**Methods**

**Participants**

Eighteen subjects (69.4 ± 13.5 years, eight women) with acute post-stroke hemiparesis (16 ischemic strokes) were recruited in the study at the stroke unit of the Royal Berkshire Hospital in Reading, United Kingdom. The sample size was limited by the number of patients that could be enrolled over the project’s duration. The experiment was approved by the ethics committee Health Research Authority and Health and Care Research Wales (IRAS project ID: 264096) and performed according to relevant guidelines and regulations.

The participants were screened for study eligibility by the clinical team according to the inclusion and exclusion criteria. The inclusion criteria were (i) age ≥ 18 years; (ii) recent stroke (ischemic/hemorrhagic) within the last 4 weeks; (iii) Montreal Cognitive Assessment score > 18; (iv) ability to sit independently in a chair; (v) upper limb weakness; and (vi) ability to speak and read English. The exclusion criteria were (i) visual field defect; (ii) visual or sensory neglect; (iii) strokes affecting both upper limbs; (iv) poor static and dynamic balance in sitting; (v) shoulder subluxation or dislocation; (vi) upper limb weakness due to conditions other than stroke; (vii) presence of emotional and/or cognitive deficits (such as global aphasia, apraxia, dementia, and depression) that could interfere with the understanding and execution of the task; and (viii) history of photosensitive epilepsy.

Participants provided written informed consent after being informed about the aims and procedure of the experiment. They were allocated to either receive IVR and conventional PT (intervention group, 10
patients) or receive conventional PT alone (control group, 8 patients) (Tables 1 and 2). Both groups received conventional PT on the ward, administered in accordance with national guidelines. The patient allocation, conducted through a randomization process, occurred at a 1:1 ratio using pre-prepared sealed opaque envelopes. These envelopes, numbered by the Trust the Research & Development department before recruitment began, contained information identifying the assigned group for each patient. To ensure equitable and unbiased distribution, an online random number generator utilizing atmospheric noise assigned numbers to each envelope [49]. The research team sequentially opened the sealed envelopes (numbered 1–30) to determine group allocation for each participant. Additionally, the assigned number served as the participant identification number throughout the study. This rigorous randomization process aimed to enhance the validity and reliability of the research findings.

Participants could withdraw consent at any time during the study, yet the collected data were retained and used without additional procedures on or in relation to the participant. Two patients in the intervention group withdrew from the trial owing to difficulty to complete the task, a perception of therapy being ineffective, or a desire to concentrate more on the lower limb.

### Table 1

Table 1: Demographic characteristic and stroke subtypes (N = 10) of the intervention group.

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>Sex</th>
<th>Age</th>
<th>Stroke type</th>
<th>Lesion site</th>
<th>Affected side</th>
<th>Dominant hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET001</td>
<td>F</td>
<td>38</td>
<td>Ischemic</td>
<td>Right LACI</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET004</td>
<td>F</td>
<td>73</td>
<td>Ischemic</td>
<td>Right LACI</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET007</td>
<td>M</td>
<td>62</td>
<td>Ischemic</td>
<td>Right posterior cerebral circulation</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET008</td>
<td>M</td>
<td>88</td>
<td>Ischemic</td>
<td>Right total anterior cerebral circulation</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET009</td>
<td>F</td>
<td>82</td>
<td>Ischemic</td>
<td>Right partial anterior cerebral circulation</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET013</td>
<td>M</td>
<td>76</td>
<td>Ischemic</td>
<td>Left partial anterior cerebral circulation</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>ET014</td>
<td>F</td>
<td>65</td>
<td>Ischemic</td>
<td>Right posterior circulation stroke</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET017</td>
<td>F</td>
<td>59</td>
<td>Haemorrhage</td>
<td>Left LACI</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>ET018</td>
<td>M</td>
<td>67</td>
<td>Ischemic with haemorrhagic transformation</td>
<td>Right MCA infarct</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET019</td>
<td>F</td>
<td>67</td>
<td>Ischemic</td>
<td>Right LACI</td>
<td>Left</td>
<td>Right</td>
</tr>
</tbody>
</table>

F = Female, M = Male, LACI = Lacunar Cerebral Infarction, and MCA = Middle Cerebral Artery
Table 2
Demographic characteristics and stroke subtypes (N = 8) of the control group.

<table>
<thead>
<tr>
<th>Control group</th>
<th>Sex</th>
<th>Age</th>
<th>Stroke type</th>
<th>Lesion site</th>
<th>Affected side</th>
<th>Dominant hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET002</td>
<td>M</td>
<td>76</td>
<td>Ischemic</td>
<td>Right posterior cerebral circulation</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET005</td>
<td>M</td>
<td>42</td>
<td>Ischemic</td>
<td>Right total anterior cerebral circulation</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>ET006</td>
<td>M</td>
<td>81</td>
<td>Ischemic</td>
<td>Right partial anterior cerebral circulation</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET010</td>
<td>M</td>
<td>66</td>
<td>Ischemic</td>
<td>Left posterior cerebral circulation infarction</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>ET011</td>
<td>F</td>
<td>88</td>
<td>Ischemic</td>
<td>Right total anterior cerebral circulation s</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET012</td>
<td>M</td>
<td>77</td>
<td>Ischemic</td>
<td>Right pontine infarct</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET015</td>
<td>F</td>
<td>70</td>
<td>Ischemic</td>
<td>Right partial anterior cerebral circulation infarct</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>ET016</td>
<td>F</td>
<td>72</td>
<td>Ischemic</td>
<td>Right lacunar infarct</td>
<td>Left</td>
<td>Left</td>
</tr>
</tbody>
</table>

F = Female and M = Male

**Experimental Setup**

We utilized the same method as used for healthy subjects; for more information, please refer to the paper by [48]. An integrated IVR system consists of a VR headset (Oculus Rift) and a small motion capture sensor (Leap Motion) attached to the headset (Fig. 1) Both products are CE marked. This system can monitor the actual upper limb movements of the participants and create a virtual image of the corresponding upper limb in the IVR environment. It also provides a real time motion of the corresponding virtual upper limb. The person using IVR equipment can “look around” the artificial world and interact with virtual features or objects. Through iterative visual-motor loops in the brain, the person experiences a feeling of controlling the virtual image of their body in such a way that the virtual world can be perceived as a real one. Stroke survivors go through task-oriented training of the upper limb in the IVR environment. As they experience the ideal motor coordination of their upper limb’s avatar, successful matching of motor intention and resultant motor coordination in the IVR allows brain networks to form new neuronal pathways for spontaneous motion in their daily life. Therefore, IVR-enhanced therapy may offer a
powerful rehabilitation approach, allowing PT to be tailored to the specific needs of survivors with chronic stroke.

**Task**

Participants were asked to sit comfortably on a chair and place their upper extremities on a table in front of them (Fig. 1A). Seven targets were arranged in a semi-circular orientation within the IVR environment (Fig. 2A). As a goal-oriented task, participants were asked to reach for the target immediately by choosing their healthy or impaired upper limb hand (Fig. 2B). To implement reinforcement-induced PT, the velocity of the hand of the impaired upper limb was amplified in the virtual environment in the direction of the target. The target turned blue when reached by the virtual hand and immediately disappeared. Unlike for healthy individuals, we increased the time to 4 seconds after the ball appeared to prevent in-depth consideration regarding choosing, as stroke patients require more time. If this condition was not fulfilled, the target disappeared, and the trial was invalidated.

**Procedure**

The experiment included three stages: familiarization, intervention, and washout (Fig. 3). At each stage, visual amplification is consistently applied to the affected side (right or left), in contrast to the healthy experiment where the visual amplification depended on the experimental phase, specifically for the right side. The visual amplification, defined as increasing the velocity of the virtual hand corresponding to the impaired upper limb by 1.4 times compared to the actual hand motion, will be described. It was hypothesized that the participants would start to use the affected hand more often as the velocity was amplified in the IVR environment.

The aim of the familiarization stage was to acquaint the participants with the task. In this stage, five targets (excluding the far right and far left targets) appeared randomly in a semi-circular array in the virtual environment (see Fig. 2A), each target appeared four times. For example, participants completed 20 reaching trials, equally divided between using the right hand (the five targets appearing twice) and the left hand in 10 trials each (the five targets appearing twice). This stage was applied only once at the beginning of each session.

Subsequently, the primary stage in this experiment was the intervention stage/free choice stage, wherein the participants were free to choose the right or left hand (unaffected or affected limb) to reach the target that randomly appeared in seven different positions. To accommodate the patients in the study, we reduced the number of times they reached for the ball from 70 to 35 (5 times per target). This adjustment was implemented due to our concern about potential participant fatigue. Post-stroke fatigue, which is prevalent throughout the acute and chronic phases following a stroke and can substantially impact rehabilitation outcomes, should also be considered when designing a treatment plan [50]. Due to brain
damage and limb weakening, stroke survivors are more likely to experience fatigue than healthy individuals. In this stage, the participants repeated the reaching task at their own pace, with varying repetitions per person in each session. Each task comprised 35 balls and lasted for 3–5 minutes. To avoid fatigue, participants were given 2-minute rest periods between each task. The term "session" refers to the time when patients receive IVR training, occurring once per day. The number of sessions is determined by the duration of the patient's hospital stay until discharge or completion of 15 sessions— whichever comes sooner.

The final stage was the washout, similar to the intervention stage (35 target per task) but gradual reduction in the velocity of amplification in the IVR environment to 1.2 times the actual hand motion. We hypothesized that even when the amplification is reduced in the IVR environment, the participants would continue to utilize the affected upper limb, resulting in increased use of the affected upper limb in daily life. This stage was intended to commence from the 10th session and extend until the 15th session. However, because of early discharge of patients, we could complete this stage with only two patients. The entire session lasted for 20–40 minutes, depending on the patient's condition.

**Primary Outcome Measure (Clinical Outcome)**

The Fugl Meyer for upper limb (FM) assessment was used to evaluate the functional motor condition as the primary outcome in this study. FM score was selected as the primary outcome measure because FM assessment is a well-designed, feasible, and effective clinical examination technique that has been extensively used in the stroke population [51–54]. This scale is highly recommended as a clinical and research instrument for assessing changes in motor impairment after stroke [55]. The evaluation was conducted by a physiotherapist who participated in the program. The FM assessment is crucial for determining motor recovery and disease severity [56]. It has five domains: motor function, sensory function, balance, joint range of motion, and joint pain [57, 58]. The motor function domain is the most widely used and plays a primary role in monitoring motor recovery after stroke. The items in the FM motor function domain are based on patient motion, coordination, and reflex action in the shoulder, elbow, forearm, wrist, and hand. Each domain contains multiple items, each scored on a 3-point ordinal scale (0 = cannot perform, 1 = performs partially, 2 = performs fully). The total score varies from 0 to 66. The measurements were utilized to assess the efficacy of IVR feedback in restoring motor coordination affecting the patient’s QoL. Our initial plan was to collect FM scores from participants at the beginning, middle, and end of their participation in the study. However, because of the COVID-19 pandemic, the length of hospitalization varied, and patients could be discharged without notice. Hence, depending on the length of stay, we evaluated the patients in the first, fifth, and tenth sessions. The control group underwent evaluations during corresponding sessions, ensuring consistent assessment across both groups with the same timescales as the intervention group. Note that the ethical approval allowed a certain period for our clinical study, not allowing us to extend our study to recruit more patients.
Secondary Outcome Measures

A. Questionnaire

We used a questionnaire administered at the end of the last session to evaluate patient experience, provide information regarding the sense of agency (subjective awareness of initiating and controlling one's own activities) [59], and obtain comments about the training sessions in the IVR environment. The questionnaire contained four short items that required participants to respond with a simple “yes,” “no,” or “somewhat.”

The following questions were asked:

• Did you feel that you were controlling the virtual hand?

• Did you feel a sense of achievement during the virtual reality therapy?

• Did you feel dizzy when looking around in the virtual reality?

• Did you feel any fatigue in any of your muscles during the therapy?

• If you have any comments or feedback on your experience, please include them below.

B. Barthel Index (Clinical Outcome)

The Barthel index (BI; modified 10-item version) is used to measure the amount of independence and mobility of patients in their activities of daily living (ADL), such as feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing [60]. The evaluation was conducted by a physiotherapist who was not involved in the training. This tool indicates the need for assistance in care and is widely used as a measure of functional disability [61]. Depending on the item, functional categories may be rated 0–1, 0–2, or 0–3 points. The range of possible total scores is 0–20. Two measurements were taken at both the baseline and discharge stages.

C. Virtual Reality Kinematic Dataset Outcome

I. Border Angle (BA)

To evaluate the use of unaffected and affected hands in the VR environment during the training sessions based on enhanced visual feedback, we calculated the border angle (BA) of the first two repetitions of the task (total of 70 times) in each patient across the sessions. A psychometric function was fitted to the plots of the probability of affected hand usage as a function of the target angles; (see Fig. 2B in [48]). The angle at which the psychometric function corresponds to a 50% probability was defined as the BA.

II. Time to Target

To determine the time to target for each subject, the reaction time of the affected hand for each target was recorded, encompassing the duration from the ball's onset to the participant reaching it. Each trial
commenced with participants placing their hands at the starting point (home position), triggering the appearance of the ball upon accurate hand placement. Following this, participants reached the target, returned their hands to the starting position, and repeated the process for successive targets in different locations (35 balls). We considered it important to compare subjects’ reaction times during the therapy across the sessions to evaluate the improvements; we hypothesized that faster reaction times indicated effective motor learning resulting in motor recovery.

D. Observation of Patient’s Strategy

The physiotherapist who participated in the training sessions reported all vital observations, which were necessary to comprehend the patient’s treatment strategies.

Analysis and Statistics

To establish the efficacy of IVR feedback in the recovery of motor coordination, the statistical difference in FM scores between the first and fifth sessions for each patient in both groups was analyzed. For further analysis, we conducted paired compression test for BI, BA and time to target. The Shapiro-Wilk test was used to check the normality of the distribution, and the Wilcoxon signed-rank test or the paired Student’s t-test was applied to evaluate. The level of significance was set at p < 0.05. In addition, repeated measures analysis of variance (ANOVA) mixed model was employed to determine the influence of two factors, namely the target locations and the sessions, on the reaction time.

The answers derived from the questionnaire were not compared statistically between the groups. However, subjective experience is crucial for determining whether a larger community would be interested in IVR physical treatment.

In this study with stroke patients, we noted that they adopted certain intriguing methods while undergoing therapy. The observations were made from the perspective of a physiotherapist. These findings were considered important in the study because they revealed how the patients coped or utilized other motor movements to complete the task. Hence, the patients were separated into distinct groups based on the similarity of their strategies.

Results

Two significant observations were made in this study. Firstly, each patient underwent a varying number of sessions, as outlined in Table 3. This number was correlated with the duration of hospitalization, with some patients receiving five sessions and others having more or fewer; there was no standard quantity for sessions. Secondly, each patient was able to repeat the number of tasks per session according to their condition and endurance level. Some patients repeated the task twice, while others repeated it more times per session. Consequently, patients were categorized into three main groups (Table 4).
Table 3  
Number of sessions for each patient. DC = discharge

<table>
<thead>
<tr>
<th>Two sessions</th>
<th>Four sessions</th>
<th>Five sessions</th>
<th>Seven sessions</th>
<th>10–14 sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET009 (withdraw)</td>
<td>ET017 (DC)</td>
<td>1. ET001</td>
<td>ET018</td>
<td>1. ET013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. ET004</td>
<td></td>
<td>2. ET019</td>
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<td></td>
<td>3. ET007</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>4. ET008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4  The number of task repetition per session. The first row under each patient's ID indicates the number of sessions, whereas the second row indicates the number of times they could repeat the task in each session.
For the Primary Outcome (FM Assessment)

The FM score measured predominantly in the first and fifth sessions (seven and eight patients in the intervention and control groups, respectively) as shown in Table 5A and B. One patient's (ET017) data was eliminated from the intervention group because he underwent only four sessions, and we could not repeat the evaluation due to his discharge from the stroke unit. Additionally, two patients (ET013 and
ET019) who stayed longer in the hospital were evaluated three times. Nevertheless, data from only the first and fifth sessions were analyzed (Table 5A).

Conversely, two patients in the control group (ET010 and ET015) had a full score at the beginning of the study. However, we repeated the assessment in the fifth session to ensure that there was no deterioration in their motor function, as neurological deterioration is common in some stroke patients [62] and we observed that their scores remained unchanged (Table 5B).

As shown in (Fig. 4A and B), all seven patients in the intervention group showed improvement in the FM score following IVR-enhanced visual feedback, while only two of eight patients in the control group showed improvement in the FM score. Moreover, there was no change in the FM score between the first and fifth sessions for six patients.

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>FM_1st_session</th>
<th>FM_5th_session</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET001</td>
<td>62</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>ET004</td>
<td>59</td>
<td>63</td>
<td>4</td>
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<td>ET007</td>
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<td>ET008</td>
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<td>46</td>
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</tr>
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<td>ET018</td>
<td>9</td>
<td>10</td>
<td>1</td>
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<tr>
<td>ET013</td>
<td>47</td>
<td>53</td>
<td>6</td>
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<tr>
<td>ET019</td>
<td>55</td>
<td>63</td>
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</table>
Before conducting paired comparison analysis, we used the Shapiro–Wilk test to ensure that the data met normal distribution requirements. For the intervention group, the p-values obtained from the normality test were 0.23 and 0.02 for FM assessments in the first and fifth sessions, respectively, whereas for the control group, they were 0.03 and 0.01, respectively. Because the data obtained from FM assessments in both groups were not normally distributed, we used the Wilcoxon signed-rank test for the paired sample comparison of the data. As shown in the box plot in Fig. 5, the FM scores differed significantly between the first and fifth sessions for the intervention group (P = 0.08) but not for the control group (P = 0.16), indicating that IVR enhanced the motor function of the affected upper extremity.

### Secondary Outcome

**A. Questionnaire**

Only seven patients responded to the questionnaire. Their responses indicate that they were engaged in the therapy, motivated, and felt a sense of achievement. The crucial part was that this therapy induced a sense of agency over the virtual hand because they felt as if they were controlling the avatar. Their answers were “somewhat” and “no” when they were asked if they felt dizzy during the therapy. They all reported that they experienced no muscle fatigue during the task. Finally, they provided comments regarding the therapy, such as “Enjoyed the therapy,” “Therapy was fun,” and “It improved my hand coordination and control.” However, one of them stated that the “headset was quite heavy.”

**B. Barthel Index (BI)**

In terms of BI, not all individuals were evaluated twice; only nine participants (four in the intervention group and five in control group) had their data recorded twice (see the supplementary files A1 and A2).
We used the Shapiro–Wilk test to compare the normality of the distributions of the two groups’ data. For the intervention group, the p-values obtained from the normality test were 0.07 and 0.02 for the first and last sessions, respectively, whereas p-values in the control group were 0.19 and 0.80, respectively. As we had a small data size and some of them were not normally distributed, we considered that our data were not normally distributed.

Therefore, the Wilcoxon signed-rank test was used. We found that BI scores did not differ significantly between the first and last sessions in the intervention group (p = 0.07), whereas they differed significantly in the control group (p = 0.04).

C. Virtual Reality Kinematic Dataset Outcome

I. Border Angle (BA)

Three of nine patients were excluded from further analysis as the BA could not be calculated because they chose a biased strategy, such as using their affected hand for all the targets (ET001, ET009, and ET017). We only calculated the BA for each session’s two task repetitions (total of 70 balls). Additionally, we only analyzed the data of patients who underwent five sessions and calculated their BA. Patients who underwent less than five sessions were therefore excluded from the analysis. Nevertheless, the data from only the first five sessions were analyzed for individuals who underwent more than five sessions (ET013, ET018, and ET019).

We excluded the patient whose right side was affected (ET017) from the analysis because the data of the patient could not be combined with that of the group with the left side affected as each group had a different strategy for achieving targets. Before performing the paired comparison analysis, we used the Shapiro–Wilk test to ensure that the data met normal distribution requirements. The p-values obtained from the test for normality were 0.20, 0.15, 0.83, 0.52, and 0.59 for sessions 1, 2, 3, 4, and 5, respectively. Owing to the normal distribution of the BA data across all sessions, we used the paired Student’s t-test to assess the differences in BA between sessions and the results indicated that there was no statistically significant difference across the session, as indicated by a p-value greater than 0.05. Unlike the healthy participants in Sakabe et al. study [48] the stroke patients used a different strategy to reach the target. For example, they developed their own exercise plan, i.e., they used the affected hand only in reaching most of the targets, and other time they train the non-affected side.

II. Time to Target

One participant was excluded from further analysis (ET008), for the reason that his reaction time was affected because of spatial neglect, for example, lack of attention towards the targets near the affected side and he needed to be reminded to refocus his attention. Furthermore, he employed a distinct approach when attempting to reach the target.

We found that the patients with left-side impairment were always able to reach the targets closest to the affected side (targets 7, 6, and 5) but occasionally reached the other targets, whereas patients with right-
side impairment were always able to reach targets 1, 2, and 3. Hence, a repeated measures analysis of variance (ANOVA) mixed model was employed to determine the influence of two factors, namely the target locations and the sessions, on the reaction time. The analysis revealed that there is no statistically significant difference in the Targets \( (p = 0.67) \). However, a significant difference was seen between sessions (first and last) \( (P < 0.01) \).

Therefore, we combined the average value of the reaction time of targets 5, 6, and 7 for the left sided patients and targets 1, 2 and 3 for the right sided patients. We then proceeded to compare the results obtained from the first and last sessions.

Before the paired sample comparison test, we used the Shapiro–Wilks test to determine whether the data met the normal distribution criteria. The resulting p-value was \( P < 0.05 \), indicating that the data were not normally distributed. We then performed the Wilcoxon signed rank test on eight patients in order to reveal the improvement of motor recovery between the first and last session in terms of the reaction time of the affected hand.

Based on the box plot depicted in (Fig. 6), there is a statistically significant difference found between the first session and the last session \( (P = 0.03) \), suggesting the motor recovery of the affected limb in terms of kinematics. In contrast, we found that there was no motor learning on the unaffected upper limb \( (P = 0.20) \).

D. Patients’ Strategies via the Therapist’s Observation

We subgrouped the patients based on the similarity of their strategies and highlighted the following three significant characteristics from the therapist’s observation:

I. Patients Categorized Based on the Frequency Hand Usage (Affected or Unaffected hand)

Based on the recorded data, we identified two categories of patients;

1. The Frequency of Using the Affected Side

This category comprised two types of patients who predominantly used their affected hand to reach the majority of targets, potentially indicating self-motivation and competitiveness. The first type achieving \( \geq 80\% \) of the affected hand usage (28 targets out of 35), The second type patients used 71–77\% (25 to 27 targets out of 35). Notably, this method was not used for every session; for example, patient ET001 used both methods.

2. The Frequency of Using the Unaffected Side
This category included patients who did not use the affected hand to reach targets because they wanted to train the opposite side; they used the affected 25% (0 to 8 times out of 35).

II. Patients Categorized Based on Strategy for Reaching Targets

Each patient employed a unique strategy for achieving the targets. For instance, some patients utilized trunk movement to assist in reaching the target, while others switched to their unaffected hand if they were unable to reach the target, returned to their starting position, and repeated the task. Additionally, certain patients exhibited circumduction movements rather than moving in a direct line. Moreover, some patients tapped the table upon successfully reaching the target.

III. Patient Categorised Based on Factors Affecting Performance

Some patients exhibited characteristics that could affect their performance. For instance, neglecting the affected side resulted in overlooking targets close to that side, while leaning towards the affected side led to neglecting targets on the opposite side. Others had hand deformities, although this did not impact the efficacy of the system. Additionally, negative mood and lack of sleep were observed to have detrimental effects on session performance.

Discussion

The primary goal of this pilot study was to investigate the feasibility of IVR technology in the upper limb rehabilitation of stroke patients, as opposed to traditional CIMT that combines positive reinforcement in PT. Our study by [48] confirmed that positive reinforcement in IVR influences hand usage decisions in healthy participants. In this study, we modified the IVR system in order to meet the specific requirements of the patients by reducing the target number and extending the time limit to reach the targets. The efficacy of the IVR-enhanced PT was validated using the Fugl-Meyer (FM) assessment to test the improvement of the upper limb motion with respect to the control group.

Based on our findings, it is evident that the intervention group, which received IVR combined with conventional physical therapy (PT), exhibited improvement in the FM score in all patients compared to the control group (Table 5 and Figs. 4 and 5) which received only PT. This observation is promising, indicating a positive trajectory that may offer insights into the efficacy of the IVR intervention. The positive outcomes observed in the intervention group suggest the effectiveness of IVR in enhancing motor function. However, the question persists: Can this improvement be attributed solely to the system, the physiotherapy sessions, or their combined synergistic impact, serving as compelling evidence of efficacy?

VR is frequently compared to conventional therapy (CT) administered by physio- and occupational therapists in studies on stroke rehabilitation. The updated Cochrane review by Laver et al. [8] concluded
that the efficacy of VR-based therapy was not superior to that of CT in enhancing upper limb function. Specifically, they reported that VR “may be beneficial in improving upper limb function and ADL function when used as an adjunct to conventional care (to increase overall therapy time)”. It is essential to note that their study primarily focused on commercial video gaming consoles, a prevalent choice in VR-based rehabilitation due to their ease of use, enjoyment, and cost-effectiveness [63, 64]. Nevertheless, present-day researchers are increasingly avoiding these approaches as these systems are primarily designed for healthy individuals, thereby presenting significant challenges for patients [63]. Consequently, our study implemented an IVR system that is tailored to the specific requirements, benefits, and conditions of the patients. The inherent simplicity of this approach may account for the observed improvement in their FM scores.

This simplicity aligns seamlessly with the overarching goals of stroke rehabilitation, particularly when considering early initiation to minimize the disease’s impact. Given that the participants in our study were acute cases, we promptly initiated IVR in combination with PT once they were medically stable. The combination of therapies in our study, emphasizing both task-oriented exercises and repetitive movements, holds the potential to facilitate patient recovery through intensive treatment.

In IVR training, it involved task-oriented exercises, particularly actions like reaching for ball—a movement integral to activities of daily living (ADL) that frequently necessitates the use of the arm [65, 66]. Additionally, the task contained repetitive movements [67]. This approach has the potential to enhance neuroplasticity [68, 69] by facilitating the restoration of movement on the impaired side through the activation of a new motor projection region and the resting of synapses [70, 71]. As mentioned in previous studies [8, 70, 72, 73], the current focus in clinical settings is on the combined use of VR and PT for rehabilitation. These associated technologies are becoming more accessible and prevalent [74].

Nevertheless, within the domain of VR, the direct effects of VR therapy on neuroplasticity are still under investigation, and current evidence is limited [8]. However, Wang et al. [70] employed functional magnetic resonance imaging to investigate neuronal remodelling in subacute stroke patients before and after training with a Leap Motion-based VR system. They compared it to CT alone. Patients were instructed to position their affected thumb on their palm. They found that sensorimotor cortex activation moved from the ipsilateral to the contralateral region and increased in the contralateral cortex in both groups. On the Wolf motor function test, which assesses upper limb motor function, the experimental VR group had a significantly greater improvement and better performance than the control group. These results demonstrate that repeated exercises with the affected arm combined with task-oriented practice in a virtual environment can enhance motor recovery of the upper limb more than CT alone. Neuroimaging research can help increase the training-dependent effects of VR and contribute to the development of VR therapies. These findings add to the current evidence that VR therapy should not be ignored in upper limb rehabilitation, as it may have apparent advantages for patients’ recovery. More conclusive findings to date suggest that VR can improve PT and increase the potential for rehabilitation [51, 52, 75, 76, 77]. Rather than relying solely on a single method, incorporating VR therapy into existing rehabilitation programs appears effective for enhancing stroke rehabilitation outcomes.
Furthermore, definitive conclusions regarding the effectiveness of IVR should be approached with caution, given the observed differences in FM scores between the groups. Especially in the control group, the presence of participants with both zero and maximum FM scores introduces variability that may impact the overall result. Moreover, it is essential to underscore that there was no deliberate control exerted in patient selection; the pivotal element lies in the random allocation of patients. This random assignment contributes robustness to the study design, serving as a mechanism to manage potential biases. It is recommended that future studies establish an initial standardised degree of motor function in order to facilitate a more equitable and precise comparison among groups.

As we shift our focus to the secondary outcome of patient independence in executing real-life tasks, the Barthel Index (BI) served as the instrumental metric for measuring their performance in crucial activities. However, the evaluation faced challenges, as not all BI data were consistently recorded, with some being only documented in the first or last session or not at all. This is because the length of hospitalization for stroke patients varied; some patients were discharged without notification, compromising the validity and reliability of the evaluation. As a result, the variation in the number of sessions is noteworthy; while some patients underwent five sessions, others underwent more or fewer. The accelerated discharge of patients due to the pandemic made it challenging to control this variation, which could potentially have influenced the study outcomes.

ADL that are essential to the patient can also increase treatment adherence and rehabilitation motivation [78]. Even though practicing ADL in a virtual environment is now feasible and has demonstrated significant gains, it remains unknown whether VR training improves actual performance [79]. The impact of VR-based therapy on ADL independence after discharge requires long-term investigation. The findings of trials that included a follow-up assessment [75, 80] suggest that the effect could be maintained if patients continued training for a longer period (i.e., longer than 4–8 weeks, which was the most common duration), considering adaptation to new interventions, technology acceptance, and motor learning. Therefore, if patients remained longer in the hospital or if there was a simple way to follow them up, the use of physiotherapy with our system could be beneficial to patients, thereby facilitating the execution of ADL.

Therefore, it is necessary to determine the duration of a patient’s hospitalization to develop an appropriate and beneficial plan, and several studies indicate that it takes time for stroke patients to demonstrate improvement in the independency level to perform ADL. For instance, a study conducted [64] reported a significant difference in FM scores (p = 0.007) but none in BI scores (p = 0.193). This indicates that the brief duration of rehabilitation could affect functional evaluation. Additionally, patients’ improvement depends on the location of the brain lesion [81]. The location of the brain injury, its extent, and the amount of recovery are key determinants of the stroke's final outcome [37]. Although we hypothesized that only patients in the intervention group would improve in BI due to the addition of VR to their therapy, both groups exhibited improvements on the BI compared with the first and last sessions (Table A1 and A2 in the supplementary files). However, owing to the small number of documented data, statistically significant results were found only in the control group.
Despite the challenges in conclusively asserting the efficacy of IVR in enhancing the motor function of the affected upper limb, our findings reveal several positive aspects.

Particularly notable is the fact that patients in the intervention group expressed enjoyment and engagement during the IVR sessions. Furthermore, the accuracy and smoothness of the visual avatar in the virtual environment played a crucial role in the positive experience. Patients felt a sense of control over the virtual hand ([82]) and this was validated by the questionnaire responses. The study's results align with previous research ([47, 48]) suggesting that the virtual therapy approach is effective in inducing a feeling of accomplishment ([83]) and control among patients.

These positive findings about the results can be categorized into four aspects. Firstly, the variability in the number of task repetitions within sessions should be considered. While there is indeed a range in the number of tasks performed from one session to another, it is noteworthy that some patients exhibited an increase in the repetition of tasks (Table 4). It suggests that IVR can enable patients to become more motivated, involved, and immersed in their rehabilitation, resulting in enhanced performance. However, other patients reported a gradual deterioration after a continual rise or fluctuation in session frequency. Potential explanations include insufficient sleep ([84]) and patient's mood ([85]) and endurance level ([86]), all of which could affect performance ([87]).

Secondly, it is essential to note that each patient employed a distinct strategy, particularly in evaluating which hand they utilized to reach the target. For example, several patients challenged themselves by using their impaired hand to reach at least 80% of the targets in the semi-circular array. Other patients adopted the reverse strategy, employing the affected hand to reach no more than 25% to reach the target. Considering that the task could be performed more than once per session, which depends on the patient's endurance level, the challenging technique was only used in some sessions. ET001, for example, was able to train the affected side intensively in session one by using 80% of the affected side in tasks 01, 04, and 05 to reach most of the targets. These particular motor performances may have been influenced by the patient's level of motivation throughout sessions ([87]). The use of multisensorial stimulation and challenging levels encourages patients, which is an essential factor for sustaining treatment and enhancing rehabilitation outcomes ([88]). Motor control training is hampered by low motivation and compliance, which can significantly impact its effectiveness.

Thirdly, it is imperative to highlight that the reaction time to reach the target using the affected hand demonstrated a notable reduction for all patients in the intervention group when comparing the initial and final sessions (Fig. 6). This might demonstrate the treatment's efficacy by its potential to facilitate motor learning on the affected side. Additionally, no difference was found on the unaffected side, likely because it is not impaired. Promoting motor learning in upper limb rehabilitation may be possible by providing patients with more real time information about their results and performance during a single session. As feedback can be simultaneously provided when using VR, it may also encourage more active participation from patients, which is associated with increased motivation to succeed ([52, 73]). It has long been hypothesized that motor recovery after stroke is a form of relearning ([89, 90]). This is due to the
engaging and motivating nature of VR, which enables patients to improve their reaction time and complete tasks more efficiently through task-oriented and repetitive movement [91]. However, in patients aiming to improve the quality and precision of movement of the affected hand, focusing on a different aspect of performance may hinder their ability to reach the target quickly [92, 93], similar to the reaction time data of certain patients in our study. Lastly, the IVR system did not cause harm to the participants, and there were no adverse effects reported. This indicates that the IVR system is a safe and well-tolerated intervention for stroke rehabilitation.

Conclusion

In conclusion, our study suggests that the positive reinforcement component in IVR has the potential to enhance the motor function of stroke patients with upper limb impairment. This is indicated by the significant improvement in the Fugl Mayer score observed when comparing the first and fifth sessions in the intervention group. However, it is uncertain whether this improvement can be entirely attributable to the VR intervention or if it arises from a mix of both intervention approaches, namely PT and IVR. Notably, the lack of a direct comparison with a control group significantly hinders the interpretation of these data. The presence of significant score variations within the control group hampers our capacity to establish conclusive findings, and it is crucial to acknowledge this constraint in our work. Essentially, the intervention group benefited significantly from a task-oriented, intensive treatment incorporating both PT and VR. Participant engagement and motivation were evident, with no reported harm. Moreover, faster reaction times to reach the target, potentially indicating motor learning, were observed. Despite these positive findings, it is important to consider uncontrollable factors like limited sessions. Future studies should address session numbers and involve larger participant groups for a more comprehensive understanding of the intervention's effectiveness.

Limitations and Future Study

Like all other studies, this study had its limitations. Our greatest limitation seemed to be the intensity and frequency of the IVR therapy, which was beyond our control because it depended entirely on how long a patient required hospitalization. Our results may indicate a dose–effect relationship in VR therapy that requires additional research to precisely ascertain how many hours of VR intervention are required per week for VR-based therapy to be effective in upper limb rehabilitation and how dose influences outcomes and ability to perform ADL. Moreover, owing to the small sample size, the results must be considered preliminary, and the effects may be diminished. Future studies should investigate whether and how specific VR features, such as motion trajectories of the virtual avatar or the use of physical items that patients can grasp, enhance rehabilitation outcomes.

Abbreviations

ADL      Activities of daily living
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BA</td>
<td>Border angle</td>
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<tr>
<td>BI</td>
<td>Barthel index</td>
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<tr>
<td>CIMT</td>
<td>Constraint-induced movement therapy</td>
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<tr>
<td>CT</td>
<td>Conventional therapy</td>
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<td>FM</td>
<td>Fugl-Meyer</td>
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<td>IVR</td>
<td>Immersive virtual reality</td>
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<tr>
<td>PT</td>
<td>Physical therapy</td>
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<tr>
<td>RIMT</td>
<td>Reinforcement-induced movement therapy</td>
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<tr>
<td>UL</td>
<td>Upper limb</td>
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<tr>
<td>VR</td>
<td>Virtual reality</td>
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**Declarations**

**Ethics approval and consent to participate**

The experiment was approved by the ethics committee Health Research Authority and Health and Care Research Wales (IRAS project ID: 264096).

**Consent for publication**

All subjects consented to the publication of the results of this study.

**Availability of data and materials**

Datasets generated for this study are available upon request from the corresponding author.

**Competing interests**

The authors declare that they have no competing interests.

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Authors’ contributions

YH, TK, and KN conceived and supervised the study. NS developed the IVR. SA modified the system to optimize patients need. SA performed the experiments, write the manuscript and statistical analysis. All authors contributed to the discussion of the results and revised the final manuscript.

Acknowledgment

The authors would like to thank all individuals who participated in this study.

References


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Figures
Figure 1

Sample setup of the immersive virtual reality (IVR) system integrated with motion capture. (A) A person wearing an IVR headset and placing both hands on a table. (B) Sample setup at the Royal Berkshire Hospital.
Figure 2

(A) Virtual target locations that appeared randomly. (B) The participants placed their hands at the home positions, and the target appeared randomly along with the semicircle. The participants were asked to reach for the target immediately by choosing their virtual impaired or unaffected hands.
Figure 3

Flow of experiment. The experiment consisted of three experimental stages (Familiarisation, intervention, and washout). The visual amplification is always ON.

Figure 4
Line graphs comparing the first and fifth sessions of the Fugl-Meyer (FM) score for both groups, revealing who progressed and who did not. In graph (A), a comparison between the FM score of the first and fifth sessions revealed that all patients exhibited improvement, whereas in graph B, only two patients exhibited improvement and remaining patients maintained their scores.

Figure 5

Box plot of the Fugl-Meyer (FM) score for each group (n = 7 in the intervention group and n = 8 in the control group). For the intervention group, the differences in FM scores between first and fifth sessions were confirmed to be statistically significant (*p < 0.05).
Figure 6

Distribution of the reaction time of the affected side in first session and last session, $p < 0.05$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryfilesEVEREST.docx