# Immersive Virtual Reality for the Cognitive Rehabilitation of Stroke Survivors

Kausik Chatterjee, Alastair Buchanan, Katy Cottrell, Sara Hughes, Thomas W. Day, and Nigel W. John

***Abstract*— We present the results of a double-blind phase 2b randomized control trial that used a custom built virtual reality environment for the cognitive rehabilitation of stroke survivors. A stroke causes damage to the brain and problem solving, memory and task sequencing are commonly affected. The brain can recover to some extent, however, and stroke patients have to relearn how to carry out activities of daily living. We have created an application called VIRTUE to enable such activities to be practiced using immersive virtual reality. Gamification techniques enhance the motivation of patients such as by making the level of difficulty of a task increase over time. The design and implementation of VIRTUE is described together with the results of the trial conducted within the Stroke Unit of a large hospital. We report on the safety and acceptability of VIRTUE. We have also observed particular benefits of VR treatment for stroke survivors that experienced more severe cognitive impairment, and an encouraging reduction in time spent in the hospital for all patients that received the VR treatment.**

***Index Terms*— Virtual reality, cognitive rehabilitation, stroke recovery.**

## I. Introduction

VIRTUAL Reality (VR) has become far more accessible to the general public in recent years. Affordable Head Mounted Displays (HMDs) offer high resolution display technology and accurate tracking of the headset and handheld controllers. The entertainment market dominates their use but more and more application areas are leveraging this technology to produce serious games. One possible use is for the rehabilitation of patients following a trauma that has effected their mobility and/or mental state. This includes patients who have suffered a stroke, when the blood supply to a part of the brain has been cut off or a bleeding in or around the brain has resulted in damage to brain cells. The resulting damage from a stroke can have different effects, depending on which part of the brain is affected. Common presentation include hemiparesis which is weakness of one entire side of the body, visual impairment, an inability to speak, read or write (aphasia), and post-stroke cognitive impairment (PSCI) that involves issues with problem solving, memory and task sequencing. Cognitive dysfunction following stroke has been identified as an important, but relatively neglected area [1] and we investigate whether VR can have a role to play in the rehabilitation process.

The brain does have the ability to form and reorganize synaptic connections, called neuroplasticity, and this helps the patient's long term recovery from the above conditions. The typical rehabilitation routine of a stroke patient consists of them being taken to a therapy room where they would practice different tasks based on Activities of Daily Living (ADL). These tasks are designed to help them to recover their physical and cognitive abilities through repetitive actions. The therapy requires the assistance of specially trained staff, including occupational therapists, physiotherapists and communication training with a speech therapist. Typically patients should receive at least 45 minutes of therapy a day, five days a week, with the amount being tailored at later stages depending on the patient's requirements [2]. It is often a challenge to provide this amount of therapy and in between times the patient has little or no opportunity to continue to practice.

In this paper we describe the development and evaluation of an application called VIRTUE (VIRTUal reality for strokE), a serious game with an explicit and carefully thought-out programme for cognitive rehabilitation. A review of the state of the art has shown that several VR systems already exist for physical rehabilitation of patients but few have addressed cognitive rehabilitation. Figure 1 shows one example of VIRTUE in use. The patient wears a HMD and is immersed in a 3D environment such as a kitchen - they feel present in the virtual world. They can interact with objects such as a loaf of bread as if they were real physical objects. In this scenario the ADL is making toast, and they have to complete all of the steps involved in the correct sequence. The goal is to improve the recovery and reduce the time that a patient spends in the hospital. In the next section we review related work that has applied VR to rehabilitation problems. We then describe the VIRTUE system. A double-blind phase 2b randomized control trial has been completed with 40 patients at the collaborating hospital and the results are presented. The trial was designed to develop and test VR-based serious games for practicing day-to-day tasks for patients with PSCI with the objectives to: determine the feasibility and acceptability of the VR based cognitive rehabilitation treatment among the patients and staff;

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Fig. 1. An example task from VIRTUE allows the patient to practice making toast. The HMD Touch Controller allows objects such as a knife to be manipulated. Audio and text instructions are given to the patient and they receive feedback as they progress.

to assess the safety of the treatment, and; identify any trend in improvement of cognitive function and functional outcome at post-treatment and at three months in the VR group, which can be adapted for power calculations in a future Phase III randomized-controlled-trial.

## II. Background

Currently, rehabilitation for cognitive impairments following a stroke follows a varying combination of remedial therapy and compensation for underlying impairments utilizing practice and repetition of tasks or actions guided by therapists [3]. Reviews of outcomes for this approach for cognitive impairments following a stroke are mixed, suggesting a need for further research and improved interventions [4]. Despite the intervention method, the dose of intervention plays a vital role in improving physical and cognitive function in these patients [5], [6]. VR certainly has the potential to add value to this process by providing scenarios and challenges that would be difficult to recreate safely in a real-world situation. It also facilitates a task being repeated multiple times using the same conditions and can track progress using different metrics within the environment providing immediate visual feedback. However, the available technology has proven to be a hindrance and a decade ago systems could only demonstrate proof of concept [7]. In subsequent years many systems have appeared and they continue to improve. Laver et al have performed a systematic review on using VR for stroke rehabilitation that looked at data from 72 trials involving 2470 participants [8]. They concluded VR may be beneficial in improving activities of daily living function when used as an adjunct to usual care (to increase overall therapy time) but there was insufficient evidence to reach conclusions about the effect of VR and interactive video gaming on gait speed, balance, participation, quality of life, or cognitive function. Only a few studies have reported improved outcomes for cognitive impairments in the subacute [9] and the chronic phase [10] after a stroke. Although these preliminary findings were encouraging, more research is needed to understand the recruitment rate, participants' acceptability, adherence to the treatment, as well as the efficacy of the VR based cognitive rehabilitation in the most crucial first few weeks of recovery following a stroke [11] before conducting a multi-center phase III trial for this treatment.

Many of the VR studies that have been conducted in both physical and cognitive rehabilitation typically did not use immersive HMDs to experience the virtual content. They used a standard PC monitor or a television to view a virtual environment, and the participants interaction was with a joystick, controller, or other body tracking technology, providing a non-immersive experience. However, immersive VR has been proven to enhance attention and reduce distraction [12] and this suggests that it will be a good medium to deliver cognitive rehabilitation therapies. Huygelier et al [13] have also reported on the use of immersive head mounted VR with older adults and found that the contribution of VR applications to health is not hindered by negative attitudes nor by cybersickness. In addition, immersing the patient in a more stimulating and familiar environment provides the ability to engage them in a unique way [7].

A recent survey of the use of immersive VR to improve cognitive function in dementia and mild cognitive impairment [14] was unable to reach definitive conclusions over the use, acceptability, and effectiveness of this approach. They recommended that future studies focus on ensuring their interventions are truly immersive and developing more robust controls. We address this in the context of stroke survivors.

## III. The VIRTUE System

VIRTUE has been developed collaboratively between a medical devices company, a University research group and the Stroke Unit at a major hospital [15]. It has focused on using cost effective and readily available equipment for immersive VR. The functionality and scenarios created in VIRTUE have been driven by the clinicians and patient representatives from conception. An Occupational Therapist (OT) ensured that each scenario followed real life therapy treatment situations in stroke rehabilitation and provided an opportunity to practice functional tasks virtually thus challenging cognitive processes such as attention, planning, sequencing, problem solving and memory. Feedback was also provided by the Therapy Assistant and OT throughout the trial for future development of each of the scenarios. A stroke Patient Public Involvement (PPI) group including stroke survivors with cognitive dysfunction, was involved from the development stage and provided feedback on using the system, with two members of the PPI group regularly meeting the developers. (The results were fed back to the PPI group at the end of the trial.) VIRTUE was developed using Agile software development methods [16], particularly the Scrum framework. A series of 2-weekly sprints built up the application in an iterative manner, using the feedback from the clinical team and PPI group to refine the content.

VIRTUE uses a modular architecture partitioned across the PC and VR headset. The therapy assistant was able to select the scenario to use and configure it to suit each patient from a control panel interface (Fig. 2), adjusting difficulty by changing the number of steps in each task sequence. Tasks were grouped by location (e.g., kitchen, restaurant) with each containing several smaller modules (e.g., make toast, pay for a meal.) The goal of each task was for it to be completed in the correct order, with metrics collected to help the clinician

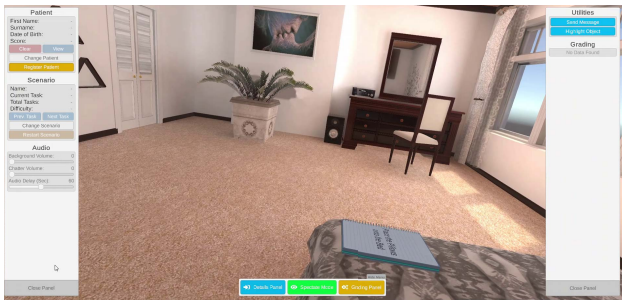

Fig. 2. A control panel interface for use by the therapist is displayed on the PC together with a view of what the patient is seeing. The therapist can load data for a particular patient, select a scanario, change the level of difficulty, or communicate with the patient whilst they are immersed in the scene.


Fig. 3. Counting out coins to pay for a meal at the cafe.

assess performance. As appropriate the patients will practice an ADL activity repeatedly, based on their clinical need and therapy requirement before moving on to the next level. This built-in flexibility facilitates personalised medicine without any limitation and this unique feature of VIRTUE makes it different from other existing solutions in this area.

### A. VIRTUE Hardware

The latest generation of affordable HMDs provides the necessary interface for an immersive VR experience. We can support models from different manufacturers and are currently using the Oculus Rift S. This HMD cost £300 and provides a resolution of 2560 by 1440 pixels and a refresh rate of 80 Hz. Some studies have used disposable masks made from medical non-woven fabrics that act as an interface between the patients face and the HMD (e.g. [17]). These do reduce risk of spreading infection between patients who are sharing the device but the accumulation of skin cells and hairs on the HMD is difficult to avoid. The head straps that are used to hold the HMD in place are also a concern as a source of infection. An advantage of the Rift S is that it has a replaceable headband and facial interface so that the parts of the headset that are in contact with the patient can be used just with that particular patient. This adds an additional cost of £90 per patient.

The Rift S has integrated audio and is also equipped with two 6 Degree-of-Freedom Touch Controllers that support both orientation and positional tracking, allowing the integration of virtual hands to interact with VR environments. The controller has proven to be simple to use for the level of patient interaction required, and depending on the patient's disability this may be one or two handed. The Touch Controllers are cleaned between use with alcoholic wipes.

The HMD is connected to a PC with an appropriate hardware configuration for supporting VR.

### B. VIRTUE Scenarios

The scenarios implemented were designed in close consultation with clinical experts and patient representatives. They were: a bedroom scene (make bed, select clothes); a bathroom scene (brush teeth, run bath); a kitchen scene (make toast; prepare a cup of tea, washing up, cook pasta meal, use coffee machine); a cafe scene (choose meal deal, pay for meal - Fig. 3); a restaurant scene (interact with waiter, order meal, pay); and a garden scene (water plants). The main requirement was to allow the patients to practice ADLs in full or in part when placed within a suitable environment. The materials needed such as food items, kitchen gadgets and coins are within reach of the patient when they are immersed in the environment. All the tasks were designed to be completed from a sitting position using a single hand held controller so that a patient would be able to use their strongest arm. The patient used VIRTUE with the help of a therapy assistant.

Often patients with PSCI struggle to complete the full task uninterrupted, however, when we break it down to small bite sizes, the task become easier for them to complete. For example, the task in Fig. 1 is to make toast in the correct sequence (get loaf; slice bread; insert into toaster; put onto a plate; etc.). Such a task is something that a healthy person takes for granted. However, for a person who has had a stroke, they often need to relearn how to do it (and for neuroplasticity to occur). The sequencing of the task and remembering the correct order to achieve the final goal is crucial. It is also important to implement the task so that it can be completed with either the left or right hand, or both. Many stroke patients will be unable to use one side of their body effectively. Implementing these tasks within a serious game also allows appropriate feedback to be given to the patient (e.g. time taken) and the difficulty changed such as the number of ingredients in a recipe. Only after completing the simpler tasks will the patient be exposed to a more difficult challenge.

Some stroke patients suffer from hemispatial neglect in which a deficit in attention to and awareness of one side of the field of vision is observed. In such cases the tasks can be set up so that the objects that must be selected are deliberately placed to force the patient to scan for them in the neglect area. The appearance of the environment is also made as realistic as possible. Use of audio is important for giving instructions and incorporating appropriate sound effects.

The Unity (Unity Technologies, San Francisco, CA) 3D game development platform in combination with the Virtual Reality Toolkit (VRTK) has been used to develop VIRTUE. It supports commercial off-the-shelf HMDs and can be used to create realistic 3D environments. Assets used can be built to minimise the number of polygons required, and to achieve lighting effects through the use of texture maps. This ensures a real time response can be achieved. Unity's in-built physics

engine and event driven mechanism support the interactions required within the virtual environment. Ideally the patient should interact with their own hands and some headsets do support direct hand tracking. However, we would have no way of providing a tangible haptics response when the patient grasps a virtual object. Given the goal of VIRTUE this was felt by the clinical experts to be too unrealistic. Continually holding a Touch Controller was considered an acceptable compromise particularly after trying out the controllers for picking up objects in initial testing. After a few minutes of use, most people attune to the virtual hands rendered in the scene and feel that they are their own. Many stroke survivors are not regular gamers and will be unfamiliar with the technology that we expect them to use. A final design principle of VIRTUE has therefore been to make it as simple to use as possible. For example, the multiple buttons on the hand controller are all programmed to do the same thing and so it does not matter if the patient presses a wrong button by mistake. Initial tests with stroke survivors also confirmed that VIRTUE does not result in any feeling of nausea (or other cybersickness effect) [15] as the patient is not required to navigate around a scenario.

## IV. Clinical Trial

A double-blind phase 2b randomized control trial was conducted to explore the feasibility, acceptability and any trend towards efficacy in improving the cognitive function of this system of VR-based cognitive rehabilitation amongst patients and staff in the subacute phase after a stroke. Ethical approval for this trial was obtained from the North West-Liverpool Central Research Ethics Committee (ref no: 19/NW/0419).

### A. Experimental Design

The trial was designed, and funded to recruit and follow-up 40 patients within one year from October 2019 to September 2020. However, because of the COVID-19 pandemic, the trial was paused between March 2020 and August 2020, and the trial funder and sponsor agreed to extend the trial until February 2021. Patients were recruited from the stroke unit at the Countess of Chester Hospital NHS Foundation Trust. The consort diagram in Fig. 4 summarises the flow of participants through each stage of the trial.

The trial made use of both the Montreal Cognitive Assessment (MoCA) test [18] and the Cognitive Assessment of Minnesota (CAM) [19] as a primary outcome measure to assess the trend for the efficacy, measured at the end of the treatment and at three months from randomisation (Fig. 4). MoCA is a fast to deliver screening tool commonly used in a hospital to assess several cognitive domains. It consists of pen and paper exercises that provide information on short term memory, visuospatial abilities, executive functions, attention, language skills, and orientation to time and place. It is routinely administered to patients who are admitted to a hospital following a stroke. The maximum score that can be obtained is 30, and anyone with a score below 25 are considered to be suffering from cognitive impairment. Similarly, CAM has 29 items and usually takes longer (35-45 minutes) to administer.

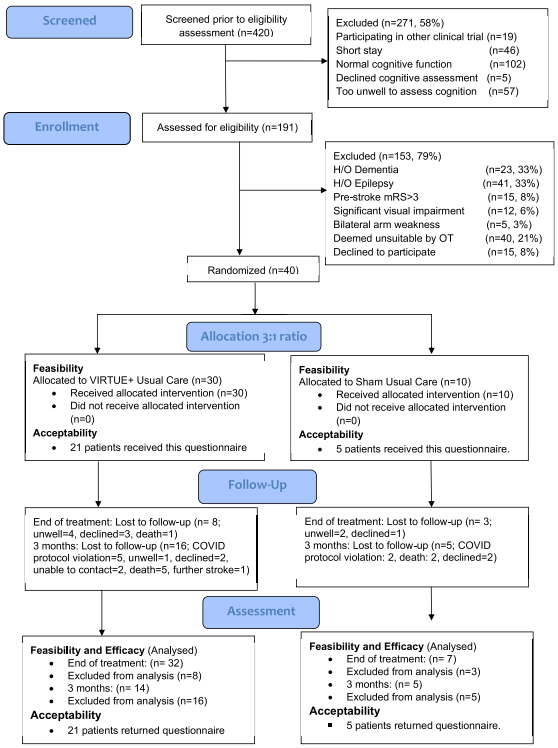


Fig. 4. Consort diagram showing the flow of participants through each stage of the trial.

Participants were included in the trial if they were aged over 18 years and had suffered a unilateral, confirmed stroke in the past one day to three weeks, which had left them with cognitive impairment. Those with a bilateral weakness, or a history of dementia, epilepsy, visual acuity less than 6/60, or were judged by senior therapists to be too ill to take part in rehabilitation were excluded. Patients with a Modified Rankin Score (mRS) [20] (a 6 point disability scale with possible scores ranging from 0 to 5) greater than three (the patient has moderately severe or severe disability) were excluded in the initial protocol. However, following the suggestion from the senior occupational therapists and the patients' group, the protocol was amended and it was taken out from the list of exclusion criteria. After going through the inclusion and exclusion criteria, a trained healthcare professional (certified for good clinical practice) invited all eligible patients to take part in this trial. A proxy consent was sought from the next-of-kin if the participant lacked capacity.

As the trial's primary focus was on safety and acceptability, we did not perform a formal sample size calculation without fully knowing expected changes in PSCI recovery in the VRT group. In principle, this study was designed to allow us to detect a moderate effect size of mean 12 (+7) points improvements in total CAM score in the group receiving VR therapy as opposed to 7 points improvements in the Sham VRT group with 80% power and 5% significance with an attrition rate of up to 20%.

After obtaining informed consent and the baseline assessment, participants were randomized on a 3:1 allocation basis to receive in addition to their usual care: either VR-based cognitive treatment (VRT) using VIRTUE stratified by the patient's MoCA score (severe cognitive impairment: 0-14;

mild to moderate cognitive impairment: 15-24) [21]; or experience a sham VR treatment (the control group). Usual care comprises a range of individually tailored interventions delivered by physiotherapists, occupational therapists and speech and language therapists specializing in neurological rehabilitation. Patients allocated to the control group received the first session of VR similar to VRT group, whereby they had to complete a simple task to pick up an object using a hand-held controller and move it to a new location. Subsequently, they were offered this same VR initiation program repeatedly. The immersive VR treatment using VIRTUE was delivered five-days a week for up to 2 weeks before their hospital discharge. Block randomization with block sizes of 4 and 8 were used to generate the randomization lists. Researchers undertaking recruitment and randomization had no prior knowledge or involvement in the generation of randomization lists. The dose of the VIRTUE treatment varied depending on the benefit and tolerability based on a 3 + 3 model devised by Colucci *et al* [22].

Participants were supervised by a Therapy Assistant whilst taking part in the VR session. They were assisted to put on the headset and ensure comfort and correct seated positioning. The VIRTUE program was started by the Therapy Assistant and the difficulty of each scenario was graded depending on their needs. The VR session was monitored throughout on the console interface (Figure 2). Reducing Therapy Assistant input and facilitating families and patients to independently use VR is worthy of future study.

The patient outcome was assessed at the end of the treatment and at three months using MoCA by a blinded assessor. The original intention was to also use CAM but as the majority of the participants were either getting tired or refusing to complete the CAM examination, after recommendation from the independent data monitoring committee, it was taken out as a primary outcome measure. Secondary outcomes were also examined using the Nottingham Extended ADL (NEADL) [23], the Hospital Anxiety and Depression Scale (HADS) [24], and Quality of Life (EuroQoL [25]). The length of stay in the hospital for each patient was also recorded. Participants were interviewed at the end of their treatment for acceptability using a structured questionnaire. VR treatment ceased once a patient had been discharged from the hospital.

### B. Results

From October 2019 to March 2020 and from August 2020 to February 2021 (over a 12-month period) 420 patients were admitted in the stroke unit; and 191 of them were assessed for eligibility. Out of 55 patients who were eligible to participate, 40 of them were recruited, suggesting around one quarter of hospitalised patients would be eligible to participate in this treatment. Baseline characteristics of the groups are shown in Table I. The patients in the sham VRT group were significantly younger, and they had a more severe stroke with a mean National Institute of Health Stroke Scale (NIHSS) score of 2 points higher than those in the VRT group, however this difference was not statistically significant. The other baseline characteristics were similar between the groups. Eleven of the patients who started the trial were not able to complete it due to illness and in a few cases death (8 in the VRT group and 3 in the Sham VR group, Fig. 4). This is only to be expected given the sample population but has impacted the sample size used in the statistical analysis, particularly the size of the sham group. The jamovi statistical spreadsheet [26] was used to analyse the data, which is built using the R software environment for statistical computing [27].

TABLE I
BASELINE CHARACTERISTICS OF ALL PARTICIPANTS

| | VRT + usual care (n=30) | Sham VRT + usual care (n=10) |
|---|---|---|
| Time from stroke (days) | | |
| Median (IQR) | 9·5 (4·75) | 9 (8·25) |
| Range | [1,21] | [3,21] |
| Age | | |
| Median (IQR) | 77·5 (13·5) | 63 (26·5) |
| Range | [43,89] | [29,86]* |
| Gender (n, %) | | |
| Female | 13 (43%) | 6 (60%) |
| Male | 17 (57%) | 4 (40%)! |
| Former occupation (n, %) | | |
| Professional/White Collar | 15 (50%) | 6 (60%) |
| Skilled/ Semi-skilled | 10 (33%) | 2 (20%) |
| Unskilled | 5 (17%) | 2 (20%)! |
| Level of Education (n, %) | | |
| Postgraduate/Graduate | 9 (30%) | 4 (40%) |
| A Levels/GCSEs | 21 (70%) | 6 (60%)! |
| Smoking (n, %) | | |
| Never | 21 (70%) | 6 (60%) |
| Ex/current smoker | 9 (30%) | 4 (40%)! |
| Type of Stroke (n, %) | | |
| Ischaemic | 27 (90%) | 7 (70%) |
| Haemorrhagic | 3 (10%) | 3 (30%)! |
| Comorbitities (n, %) | | |
| H/O Diabetes | 4 (23%) | 3 (30%)! |
| H/O Hypertension | 18 (60%) | 4 (40%)! |
| H/O Atrial Fibrillation | 2 (7%) | 1 (10%)! |
| H/O Previous Stroke or TIA | 6 (20%) | 3 (30%)! |
| H/O Ischaemic Heart Disease | 6 (20%) | 0 |
| Admission NIHSS score | | |
| Median (IQR) | 8 (9) | 12.5 (15.3)! |
| Range | [2,28] | [1,22] |
| Pre-stroke mRS | | |
| Median (IQR) | 0 (1) | 1 (1)! |
| Range | [0,2] | [0,2] |

!p: not significant; *p<0·05.

*1) Safety:* Only two distinct adverse events were reported as a result of using VR. Four patients in the VRT group complained that their nose was uncomfortable due to the additional 3D printed attachment for the headset initially produced to prevent the headset from coming in direct contact with the skin. This was solved by using the replaceable headband and facial interface available for the Rift S so that these parts were not shared between patients. Transient dizziness and fatigue were reported by one patient in each group.

*2) Acceptability:* Compared to the sham group, the acceptability of the treatment was significantly higher in the patient allocated to the VR treatment. When a patient was discharged they were asked to complete a likert-scale questionnaire related to their experience of participating in the trial. The results are summarised in Table II. There was also a free text space to include any other comments and all comments received have been included in the appendix. As previously mentioned, the sham group were given a VR experience which consisted of an introduction to the VIRTUE house environment but they did not get the opportunity to practice ADLs. It is not surprising,

TABLE II
ACCEPTABILITY QUESTIONNAIRE AND TREATMENT IDENTIFICATION RESULTS

| | VRT + usual care (n,%) | Sham VRT + usual care (n, %) |
|---|---|---|
| **"I enjoyed using the VIRTUE application"** | | |
| Strongly agree/Agree/Neither | 16 (76%) | 1 (20%) |
| Disagree/Strongly disagree | 5 (24%) | 4 (80%) |
| **"I thought the VIRTUE training was helpful"** | | |
| Strongly agree/Agree/Neither | 16 (76%) | 1 (20%) |
| Disagree/Strongly disagree | 5 (24%) | 4 (80%) |
| **"If opportunity arises, I would continue to use the VIRTUE application"** | | |
| Strongly agree/Agree/Neither | 15 (72%) | 2 (40%) |
| Disagree/Strongly disagree | 6 (28%) | 3 (60%) |
| **"I think I would benefit from using this over a long period"** | | |
| Strongly agree/Agree/Neither | 16 (76%) | 1 (20%) |
| Disagree/Strongly disagree | 5 (24%) | 4 (80%) |
| **Patient correctly identified their treatment allocation** | (n=24) 23 | (n=7) 5 |

TABLE III
PRIMARY OUTCOME MEASURES

| | VRT + usual care (Baseline MoCA<15) | VRT + usual care (Baseline MoCA 15 to 24) | Sham VRT + usual care |
|---|---|---|---|
| **Baseline MoCA** | (n=19) | (n=11) | (n=10) |
| Median (IQR) | 17 (9) | 22 (5) | 12.5 (19) |
| Range | [0,14] | [15,24] | [0,24] |
| **End MoCA** | (n=11) | (n=11) | (n=7) |
| Median (IQR) | 17 (12) | 22 (5) | 10 (24) |
| Range | [6,25] | [19,27] | [0,26] |
| **3 month MoCA** | (n=7) | (n=7) | (n=5) |
| Median (IQR) | 20 (6) | 24 (7) | 24 (19) |
| Range | [14,24] | [20,29] | [5,29] |

therefore, that they disagreed with the most of the statements on the questionnaire, although 50% of them did enjoy the VR experience. Both of the VR-based treatment groups gave positive responses with the mild to moderately impaired group rating VIRTUE the highest. The free text comments indicated that use of the VIRTUE was acceptable to many of the participants, with only a few adverse reactions reported. All but three patients correctly identified whether or not they were receiving VR Treatment. Despite having cognitive impairment, most patients participating in the trial managed to identify the treatment allocation correctly at the end of their treatment sessions. (Quadratic Kappa of 0.71 (95% CI: 0.4-1) between treatment opinion and actual treatment)

*3) Efficacy:* The primary outcome from the treatment was assessed at the end of the treatment sessions and again after three months. Table III presents the results from the three groups according to the stratification used at the time of randomization.

A Shapiro-Wilk test confirmed that this data is not normally distributed in all three groups and so a non parametric one-way ANOVA (the Kruskal-Wallis test) was applied and gave a p-value of 0.06, very close to being significant. A pairwise comparison (the Dwass-Steel-Critchlow-Fligner test procedure) between the three groups subsequently showed that the significant difference is between the sham group and the severely cognitively impaired (MoCA score $<$ 15) group. The latter have demonstrated a significant improvement of the MoCA score at the end of treatment assessment. Fig. 5 illustrates these results.

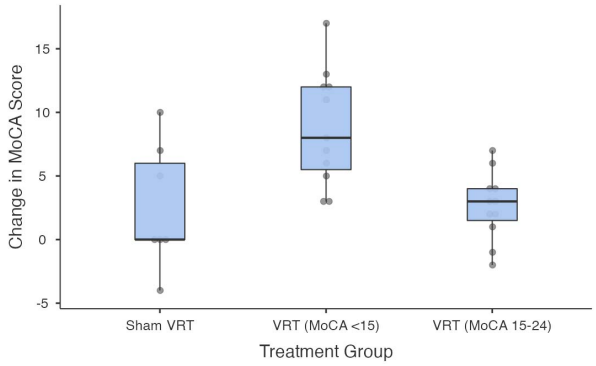


Fig. 5. Box plot of the change in MoCA scores between the baseline and end of treatment sessions. The median [range] change in MoCA score were 8 [3-17] in the severe group (MoCA<15), 3 [-2-7] in the moderate (MoCA 15-24) group and 0 [-4-10] in the Sham VR group.

Of the seven key components assessed by MoCA, not all improved uniformly at the end of the treatment in the intervention group with severe cognitive impairment. Compared to the Sham VRT group, the 'Attention' and the 'Orientation' were the two main components that showed significant improvement in this group (median [range] change in 'Attention' score of 3 [-1, 5] vs 0 [-2, 1] and 'Orientation' score of 2 [-1, 4] vs 0 [-1, 4] in the severely cognitively impaired and Sham group, respectively). We did not observe any significant differences in the primary outcome measures at three months; however, the improvement in the MoCA score continued in all three groups.

The amount of time that each patient spent in a VR session was very specific to the individual. It would depend on their level of wellness on the day and how tired they were feeling. The Sham VRT Group did spend significantly less time in VR (Table V) than the treatment group, but they were less engaged as they were only offered the same VR experience repeatedly. There was no significant difference in the times spent in VR by the stratified treatment groups. The patient was allowed to stop a session whenever they wanted. The hospital length of stay and both in-patient physio and occupational therapy (OT) time were significantly lower in the treatment group (Table IV and Table V). When plotted against the improvement in the MoCA score at the end of the treatment with total inpatient occupational therapy and VR time, a positive linear correlation was observed in the severe cognitive impairment with the VRT group and the Sham VRT group. However, the slope of the relationship was steep in the severe cognitive impaired group, suggesting a possible synergistic effect of VR treatment with conventional therapy (Fig. 6).

TABLE IV
LENGTH OF HOSPITAL STAY (DAYS)

| | VRT + usual care (Baseline MoCA<15) | VRT + usual care (Baseline MoCA 15 to 24) | Sham VRT + usual care |
|---|---|---|---|
| **To Home** Median Range | (n=12) 22.5 [10,92] | (n=10) 22 [3,44] | (n=9) 48* [8,87] |
| **To Nursing Home** Median Range | (n=5) 85 [59,123] | (n=1) 62 | (n=1) 57 |
| **Died in hospital** Median Range | (n=2) 57 [37,77] | | |

*p<0·05

TABLE V
TREATMENT TIMES (MINUTES)

| | VRT + usual care (Baseline MoCA<15) | VRT + usual care (Baseline MoCA 15 to 24) | Sham VRT + usual care |
|---|---|---|---|
| **Inpatient Physio** Median (IQR) Range | (n=19) 355 (645) [30,1325]* | (n=11) 395 (515) [60,2115]* | (n=10) 1053 (1618)* [130,2930] |
| **Inpatient OT** Median (IQR) Range | (n=19) 605 (730) [180,1690] | (n=11) 700 (605) [185,2285] | (n=10) 1298 (1294)* [345,2905] |
| **VR Time** Median (IQR) Range | (n=19) 40 (100) [10,211] | (n=11) 83 (146) [18,352] | (n=10) 10 (16)* [0,20] |

*p<0·05

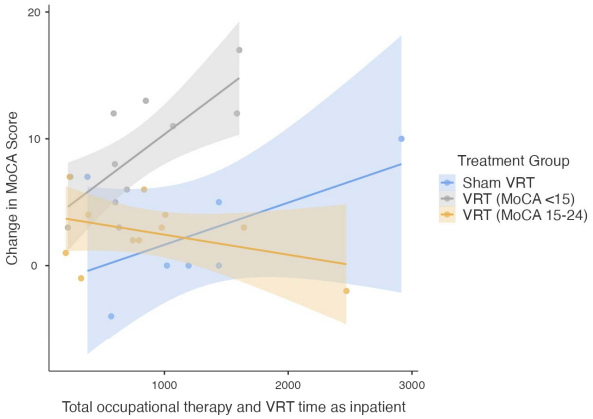


Fig. 6. Scatterplot with a linear regression line showing the relationship between the End of Treatment change in MoCA scores and the total amount of Occupational Therapy and VR time received.

Table IV summarises the length of stay in the hospital. Some patients from the trial were not well enough to return to their own homes and had a much longer period in hospital whilst a place was found for them in a nursing home. We examined the length of stay for those patients that did leave the hospital to return to their own home, see Fig. 7. The data is normally distributed (according to a Kruskal-Wallis test) and

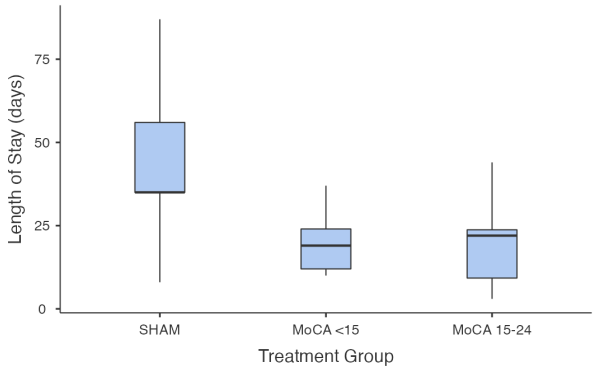


Fig. 7. Box plot of the length of stay in the hospital before returning to their own homes.

TABLE VI
SECONDARY OUTCOME MEASURES

| | VRT + usual care (Baseline MoCA<15) | VRT + usual care (Baseline MoCA 15 to 24) | Sham VRT + usual care |
|---|---|---|---|
| **Diff in NEADL (3 mths-baseline)** Median (IQR) Range | (n=7) -6 (-44) [-59,53] | (n=10) 13 (32) [-71,54] | (n=5) 0 (22) [-13,47]! |
| **Diff in Depression (3 mths-baseline)** Median (IQR) Range | (n=8) -2.5 (7.5) [-8,18] | (n=9) 0 (-4.5) [-7,3] | (n=5) 1 (3) [-6,6]! |
| **Diff in Anxiety (3 mths-baseline)** Median (IQR) Range | (n=8) -1 (3) [-4.5,7.5] | (n=9) -4 (-8.5) [-11,2] | (n=5) 1 (4.5) [-2,7] |
| **Diff in EuroQol (3 mths-baseline)** Median (IQR) Range | (n=7) 0 (4) [-12,4] | (n=9) 0 (-7.5) [-12,4] | (n=5) 0 (-2) [-4,2]! |

! p: not significant

an ANOVA test produced a p-value of 0.022. Post Hoc tests produced a significant difference between both the sham group and the severe cognitive impairment group (p-value=0.034), and the sham group and the group with moderate cognitive impairment (p-value=0.028).

Secondary outcomes were also examined both at the baseline and at the end of three months, summarized in Table VI. The only difference observed was a reduction in the anxiety score in the mild to moderate cognitive impairment (MoCA 15-24) treatment group.

## V. DISCUSSION

As far as we are aware, this was the first trial of VR treatment in the late-acute phase of stroke and was designed to include patients with severe cognitive impairment, who were commonly excluded from most of the clinical trials in this area. We have integrated cognitive evaluation and outcome into our design and are compatible with the criteria recommended by the Stroke Recovery and Rehabilitation Roundtable (SRRR) [1]. Despite our initial concern of trialing a new

technology in a group with severe cognitive impairment, there were no safety issues identified as a result of using VR Treatment. A custom experience has been successfully developed that provides functionality for patients to practice ADLs at differing levels of difficulty, with treatment tailored by an occupational therapist. No serious adverse events were reported by the patients. There were some initial hurdles that had to be overcome in setting up hardware so that it passed infection control procedures whilst remaining acceptable for the patients to use. The dose (amount of VR time applied) was restricted as a part of the trial protocol for a safety-first approach and was guided by the tolerability of each individual patient.

The demographics between the VR Treatment group and sham group are similar, with no significant differences in gender, occupation, education, smoking habits and comorbidities. The average age of the sham group is younger, but this is down to a single individual who suffered a stroke at age 29. The type of stroke, time from stroke to randomization, and pre-stroke modified Rankin Scale (mRS) for both groups are also aligned. The sample size is relatively small, and the final assessment at three months was hampered by the temporary postponement of the trial by the ongoing pandemic. Therefore, a larger multicentric trial is needed to reinforce the results. Nevertheless, there are some interesting trends observed by providing VR Treatment in the first three weeks of recovery following a stroke. Stratifying the treatment group into those with a severe or moderate cognitive impairment revealed the most significant trend. Those who had more severe cognitive impairment following stroke (baseline MoCA less than 15) had a far greater improvement at the end of the treatment. Our results are consistent with the sparse data available in this area [10], [28]. This difference was statistically significant compared with the sham VR group and the higher baseline MoCA score group - within the restrictions of the sample size. VR treatment stopped once a patient was discharged from the hospital and the MoCA scores obtained three months after the trial showed no further differences. The linear relationship between the dose of rehabilitation and improvement in the motor function at the chronic phase is well established in literature [29]. We observed a similar effect with cognitive improvement in the MoCA less than 15 with VR treatment and the sham VR group, except the slope of this relationship was steeper in the MoCA less than 15 group. As the VR dose was restricted, the improvement observed at the end of the treatment is not due to VR treatment alone, as the total amount of occupational therapy and VR treatment time received shows a possible synergistic effect with the improvement in MoCA scores. However, we did not observe a similar effect of treatment time on improvement in cognitive score in patients with mild to moderate cognitive impairment (MoCA score 15-24, Fig. 6). This is an interesting observation, suggesting that the cut off of MoCA score in the inclusion criteria for the Phase III trial could be lowered to less than 19 when identifying those who might have a maximum benefit from receiving VRT. Due to the small number of patients in the Sham VRT group, it was not stratified and it is difficult to extrapolate whether the trajectory of recovery would be different for those in this group with severe, or mild to moderate cognitive defects. Continued improvements in the more severely cognitively impaired group could be due to natural recovery rather than any interaction of the VR and therapy. This will be investigated further in the Phase III trial.

Not all participants were fortunate enough to return home, which was not unexpected in this cohort [30], and some had extended hospital stays before being discharged to a nursing home. However, for those patients who were able to return to their own homes, we observe that the VR Treatment group spent a significantly shorter period in the hospital. The higher NIHSS score of the sham group could be a contributing factor, and due to the small sample size, we could not statistically assess this effect, but the amount of the reduction in the length of stay of the treatment group suggest that the possible synergy of VR treatment with the conventional rehabilitation process is the major factor behind this finding. The observed reduction in anxiety may be related to the findings of other studies that have demonstrated that VR can help people overcome anxiety problems, e.g., phobia sufferers [31]. Note, however, that secondary outcomes must be interpreted with care due to the smaller number of participants available after three months due to the covid pandemic.

This study was not effective to implement as a double-blind trial as most patients were able to deduce whether they were a part of the treatment group. A different VR experience providing no cognitive therapy would be needed for the sham group, perhaps just using an off-the-shelf game designed for VR along with a no VR group. In this way, we could compare the efficacy of the custom-made VIRTUE software as opposed to the general VR treatment itself. Patients were, however, receptive to receiving VR treatment with largely positive comments from the post-treatment questionnaire.

## VI. Conclusion and Future Work

We have developed a novel immersive VR system aimed at the cognitive rehabilitation of stroke survivors. The system has been deployed in a hospital setting and used to enhance the therapy of 40 patients recovering from a stroke. Although patient supervision was required for this trial, it was undertaken by a Therapy Assistant, freeing up time for the OT. Data was collected from a 12 month trial conducted over an 18 month time period (which included a six month suspension during 2020 due to the constraints of the covid-19 pandemic). Most stroke patients encountered had not previously been exposed to VR but this did not deter their enthusiasm to embrace the latest VR technology and to begin to use it to their advantage. VIRTUE is intended to benefit the health service and results from the trial indicate that it has accelerated patient recovery through intensive delivery of therapy with minimal supervision, shortened hospital stays and hence lowered healthcare costs. For clinicians, it is expected to free up time for patients with more complex needs. For patients, recovery will be more effective because the therapy is more engaging, delivered more often and could potentially continue at home. Our approach has started to transform the delivery of cognitive stroke rehabilitation through a new digital VR service.


Fig. 8. Post-it notes can be arranged on the fridge door to allow a patient to customise their therapy sessions.

We intend to expand the number of ADL scenarios available, e.g., one suggestion from patients was to have an activity that would be more fun than a typical ADL. We will support patients to have more control over what tasks they will do in their therapy sessions by allowing them to use virtual post-it notes in the kitchen environment to plan their day - see Fig. 8. We will also develop a version of VIRTUE for a standalone HMD that does not require a separate PC (e.g. the Oculus Quest 2) and can be used by the patient unsupervised. We already have a prototype that works on such devices but there is a trade-off required between the amount of realism possible whilst keeping the software interactive, as the graphics hardware specification is more limited. This will, however, enable patients to continue to receive VR treatment once they leave the hospital. Artificial intelligence techniques will be employed to deliver the right activity at the right level in a personalized fashion, and operate without direct intervention from the OT.

Our trial established that VR-based cognitive rehabilitation is a safe and acceptable form of treatment in hospitals for patients with cognitive impairment following an acute stroke. This form of treatment has the potential to complement the conventional rehabilitation therapy provided by the trained neurotherapy staff, help those with severe cognitive impairment and reduce the duration of hospital stay. The intention is to run a multicentric Phase III trial with a far larger number of stroke survivors participating.

## APPENDIX
## FREE TEXT RESPONSES

### A. What Was Good About the VIRTUE Trial?

#### 1) VRT + UC:

- It was something new. It was enjoyable.
- Didn't get a chance to try it for long. Wasn't highlighting or gripping objects.
- Found it good - it was also good to hear her [computer voice] prompting me.
- Found it interesting, but not for me.
- Fun.
- Fun activity. Provides a few laughs - especially with Stef [waitor] in the cafe.
- Fun and a laugh.
- Gives chance to analyse instructions. Made you think outside the box. Enjoyed doing the virtual reality.
- I hated it.
- It helped to make me remember how to do simple tasks and to re-train my thoughts so I could do it again.
- It was something new and different.
- Just working things out. Having things explained to me.
- Made me focus on using right hand.
- Making one think outside the box. Looking at the overall picture. Listening and following precise instructions.
- Nothing (x2)
- That it got me having to use my brain and we laughed all the way through.

#### 2) Sham VR + UC:

- Didn't have the best response. Good opportunity to improve.
- Just in one place.
- Not much
- Nothing.

### B. What Did You Dislike About the VIRTUE Trial?

#### 1) VRT + UC:

- Cooker - hard to turn.
- Couldn't make up my mind about what to do.
- Enjoyed virtual experience.
- Everything.
- Found it hard to achieve certain parts of the programme because it would skip to the next task
- Headset very uncomfortable. 45 mins is too long. Very heavy. Felt the whole set up was at the wrong height for me. Everything was too low. Definitely not the trial for me.
- I didn't dislike anything.
- It would sometimes be interrupted.
- Not quick acting enough.
- Not working consistently. There were problems with highlighting objects and gripping some of the objects which was frustrating.
- Nothing (x2).
- Some glitches in software.
- Technical glitches sometimes frustrating. The bathroom toothbrush difficult to manage. Also opening fridge door.

#### 2) Sham VR + UC:

- Everything.
- It didn't work properly.
- Kept freezing.
- Made my feel giddy - like being on a fairground ride.
- Repetitive.

### C. What Could be Improved in the Future Clinical Trial Similar to VIRTUE?

#### 1) VRT + UC:

- It would have to be adapted several times.
- Can see the benefits when working consistently.
- Ensure less technical problems.
- Feedback from trials to be fed in.
- Hard to recognise items in VR at times e.g. tray.
- I don't think there is anything.

- Length of trial too long.
- Making objects more accessible - kill off Stephanie.
- More choice.
- Needs upgrading to make it more realistic.
- Not a lot apart from the programme skipping.
- Would be better in a quieter room.

#### 2) Sham VR + UC:

- Get the programme working properly. (x2)
- It wasn't suitable.
- Not a clue.
- Nothing.

### D. Do You Want to Make Any Comment/s on the VIRTUE Trial?"

#### 1) VRT + UC:

- Excellent.
- I enjoyed using the VR. It was very helpful and the therapist was very helpful.
- It was just right (x3).
- More involved.
- It was all fine for me.
- I can see how it would benefit those more cognitively impaired.
- Timed to suit individuals.
- Too long (x2).
- VR gave me something to do to occupy my brain.

#### 2) Sham VR + UC:

- Didn't like it.
- Too long.
- Too short.

## ACKNOWLEDGMENT

The funder monitored the project independently. The trial was also monitored by an independent data monitoring committee, who reported back to the trial sponsor. The trial sponsor is responsible for archiving the trial material. The trial was registered at the ISRCTN registry (Registration number: ISRCTN16608742).

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