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Assessment of virtual teacher feedback for the recovery of the upper limb after a stroke. Study protocol for a randomized controlled trial.

Ocena wpływu wzrokowej informacji zwrotnej na poprawę funkcji kończyny górnej po udarze mózgu. Protokół badania randomizowanego

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Key words
Virtual reality, stroke, rehabilitation, visual feedback

Abstract
Introduction: Enhanced feedback provided by virtual reality has been shown to promote motor learning both in healthy subjects and patients with motor impairments following lesions of the central nervous system. The aim of this study is to evaluate the effect of displaying a virtual teacher as visual feedback to promote the recovery of upper limb motor function after a stroke.
Methods: The protocol reports the design of a single blind randomized controlled trial (RCT), blinded to outcome assessment. Two different treatments based on virtual reality will be compared: in the "Teacher" group, the patients receive treatment with continuous displaying of a virtual teacher, while in the "No-Teacher" group, the same exercises will be proposed without visualisation of a virtual teacher.
The Fugl-Meyer upper extremity scale will be considered as the primary outcome, while the Functional Independence Measure scale, Reaching Performance Scale and Modified Ashworth Scale will be considered as secondary outcomes. Moreover, kinematic parameters such as mean duration (seconds), mean linear velocity (cm/s) and smoothness (i.e. number of sub-movements) will be registered when performing standardised tasks. All tests will be performed before and after treatments. Both treatments will last four weeks with a daily session lasting one hour, five days a week (20 overall sessions).
Discussion: This study is designed to systematically assess the influence of using enhanced visual feedback for the recovery of upper limb motor function after a stroke. These findings will help to determine whether the use of a virtual teacher as enhanced visual feedback is effective for promoting better recovery of upper limb motor function over four weeks of post-stroke treatment.
Trial registration: Current Controlled Trials registration number: NCT02234531 (registered on 29 August 2014, ClinicalTrials.gov)

The individual division on this paper was as follows: a – research work project; B – data collection; C – statistical analysis; D – data interpretation; E – manuscript compilation; F – publication search

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Słowa kluczowe
rzeczywistość wirtualna, udar mózgu, rehabilitacja, wizualna informacja zwrotna

Streszczenie
Wprowadzenie: Badania wykazały, że generowana w rzeczywistości wirtualnej wzmocniona informacja zwrotna pozwala na zwiększenie możliwości ponownego uczenia się ruchu zarówno u osób zdrowych jak i pacjentów po uszkodzeniu ośrodkowego układu nerwowego. Celem obecnego badania jest ocena wpływu wirtualnego nauczyciela prezentowanego, jako wzrokowa informacja zwrotna na poprawę motoryki kończyny górnej u pacjentów po udarze mózgu.
Metody: Protokół przedstawia badanie randomizowane z pojedynczą ślepa próbą dla oceny początkowej i końcowej. W badaniu zostaną porównane dwa zabiegi oparte na rzeczywistości wirtualnej. Pacjenci będą podzieleni na dwie grupy, tj.; grupa „Teacher", w której pacjenci będą otrzymywać wzmocnioną informację zwrotną poprzez wizualizację wirtualnego nauczyciela, natomiast w grupie „No-Teacher" pacjenci będą wykonywać te same ćwiczenia bez wizualizacji wirtualnego nauczyciela. Zostaną zastosowane następujące testy kliniczne: Fugl-Meyer dla kończyny górnej, Functional Independence Measure – FIM, Reaching Performance Scale i zmodyfikowana skala Ashworth. Ponadto badane będą parametry kinematyczne jak: średni czas wykonanego ruchu (sekundy), średnia liniowa szybkość wykonanego ruchu (cm/s) i odchylenia od prawidłowej trajektorii ruchu (nr). Wszystkie testy zostaną przeprowadzone przed i po zakończeniu badania. Oba zabiegi będą trwały 4 tygodnie z jedno godzinnymi sesjami terapeutycznymi (20 sesji ogółem).
Dyskusja: Badanie zostało zaprojektowane, aby ocenić wpływ wizualnej informacji zwrotnej w formie wzmocnionej na poprawę funkcji kończyny górnej u osób po udarze mózgu. Badanie to pozwoli ustalić czy zastosowanie wirtualnego nauczyciela w formie wzmocnionego sprzężenia zwrotnego jest skuteczne w rehabilitacji funkcji kończyny górnej w ciągu 4-tygodniowych sesji terapeutycznych.
Badanie rejestrowane: Aktualny numer rejestracji badania to NCT02234531 (zarejestrowany w dniu 29 sierpnia 2014 roku na ClinicalTrials.gov)

INTRODUCTION

Impairments induced by a stroke usually affect the ability of the upper limbs, interfering with most activities of daily living (ADL). One aim of upper limb rehabilitation after a stroke is to restore the best possible level of autonomy. Recent findings suggest that therapeutic modalities should be deployed on the basis of motor learning principles[1] to reshape disrupted neural mechanisms and allow voluntary motor activation, the tuning of which depends on feedback augmentation and specificity[2]. This means that the recovery process underpinned by rehabilitation modalities could be intended as a learning process exploited by the central nervous system (CNS). This augmented feedback can be provided to patients as standardized scores (e.g. knowledge of results, KR) as well as information on their arm movements during the execution of motor tasks (e.g. knowledge of performance, KP). One of the motor learning–based rehabilitation modalities currently emerging as effective for the recovery of the upper limb after a stroke is based on Virtual Reality (VR) technologies, allowing for the substitution of sensory feedback coming from the environment with feedback that is artificial[3]. Among all the VR approaches available, the Reinforced Feedback in Virtual Environment (RFVE)[4-6] has been demonstrated as an effective modality for the treatment of the upper limb after a stroke[7,8]. With this approach, it is possible to provide patients with several augmented feedbacks on the performed motor task, thus optimizing both the sense of presence and environmental control in clinical settings.

Innovative technologies have provided the opportunity to enrich the environments in which motor rehabilitation programs are carried out. This enrichment could potentially facilitate the physiological activation of the brain areas devoted to motor learning. Following these principles, exercises should involve multiple sensory modalities exploiting the adaptive nature of the nervous system, in order to promote active patient participation[9]. Previous evidence has demonstrated that training in a virtual environment promotes learning in normal subjects, as well as in post-stroke patients, which is underpinned by providing augmented feedback related to motor performance and results[10-14]. Moreover, other effects dependent on the interaction with virtual environments have been measured at the cortical activation level using functional magnetic resonance imaging (fMRI). To date, neuroimaging evidence has shown that reorganization of the motor cortex and related motor recovery change significantly after VR based treatments[15-17]. Based on this data, it has been argued that RFVE can promote the recovery of motor function in post-stroke patients by means of regular, intensive and supervised training[18-20]. Doya[21] suggests that different brain areas (i.e. the cerebellum, basal ganglia, cortex) are involved in the process of learning new motor tasks; each one encoding for different learning paradigms (i.e. supervised, reinforced, unsupervised). Training with the opportunity to emulate a teacher doing the correct kinematics has been proposed as the most useful feedback for promoting the supervised learning paradigm. This paradigm argues for the involvement of cerebellum in the real-time fine-tuning of movements by means of its feed-forward structure based on massive synaptic convergence of granule cell axons (parallel fibers) onto Purkinje cells, which send inhibitory connections to the deep cerebellar nuclei and the inferior olive. The circuit of the cerebellum may be capable of implementing the supervised learning paradigm, which consists of error driven learning behaviors[21]. Based on this rationale, we argue that motor learning could be improved by an enriched environment in which affordances are focused on optimizing the interaction between the motor system and the physical environment. VR is a feasible technological framework that allows the creation of specific settings where those affordances are optimized.

AIM

In this protocol, we designed a randomised clinical trial (RCT) aimed at studying the effect of using the continuous visualisation of an on-line virtual teacher while doing upper limb motor exercises in a VR environment for the recovery of upper limb motor function after a stroke.

METHODS AND DESIGN

A single-blind RCT was designed to compare the effects of treatment provided in a virtual environment based on continuous displaying of a virtual teacher (TEACHER group) with the same treatment but without displaying the virtual teacher (NO-TEACHER group).

All consecutive inpatients admitted to the Unit of Cerebrovascular Diseases at the IRCCS San Camillo Hospital Foundation (Venice, Italy) will be eligible for the study (Figure 1). Only patients fulfilling the inclusion/exclusion criteria reported in the following paragraphs, will be enrolled in the study. Ethical approval was obtained from the internal review

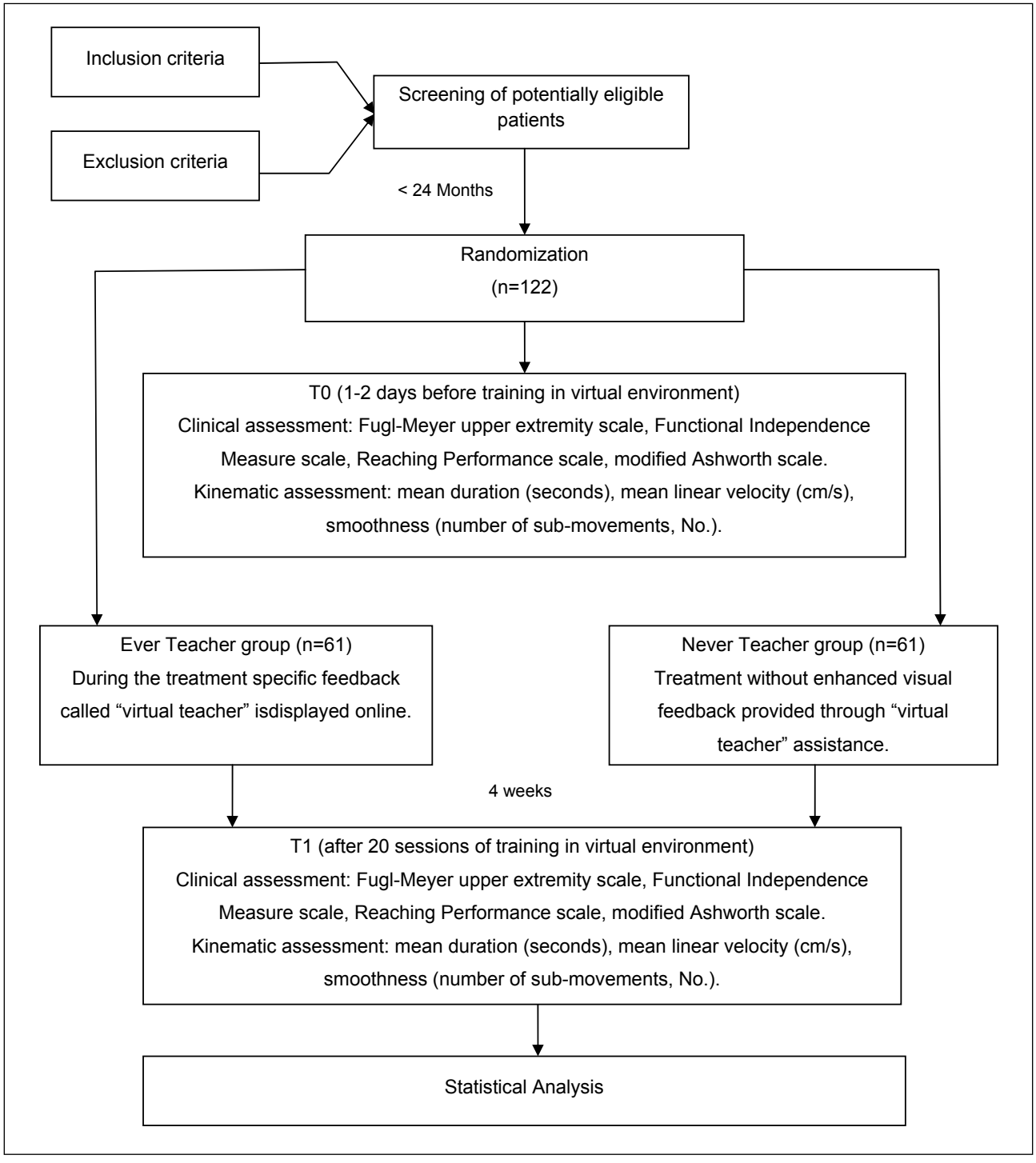

Figure 1

Participant flowchart throughout the study

board of IRCCS San Camillo Hospital Foundation (Prot. 2013.11) and the study will be conducted in accordance with the Declaration of Helsinki. The trial was registered in the ClinicalTrials.gov public repository and a unique identifier code was given (NCT02234531). All the patients will be informed about the study aim and the experimental procedures. In accordance with fulfilling the inclusion criteria for the study, written informed consent will be asked to all the participants.

Outcome measures

The clinical effect of different intervention modalities will be assessed with the following scales both before and after treatment: Fugl-Meyer Upper Extremity (F-M UE) scale (primary outcome), Functional Independence Measure (FIM) scale, Reaching Performance scale and the modified Ashworth scale. Moreover, the effect on changes in kinematic performance of voluntary movements will be assessed by: mean duration (seconds), mean linear velocity (cm/s), smoothness (number of sub-movements) extracted from a sequence of standard motor tasks repeated before and after treatment in both groups. Therefore, the standard movements for kinematic assessment will be as follow: forearm pronation and supination, elbow flexion and extension, shoulder abduction and adduction, shoulder internal and external rotation, shoulder flexion and extension and reaching movements. The VR assessment script is composed of eight standardized motor tasks covering the main axes of motion of the upper limb (e.g. flexion, abduction, adduction, rotations, pronation, supination), and in multiple joints (e.g. shoulder, elbow), each to be performed for ten consecutive trials. Thus, 80 overall trials will be recorded for every patient, which will provide the kinematic assessment. The aim of the instrumental assessment is to detect changes occurring in kinematic performance of the upper limb in standardized movements. The movement kinematics i.e. mean duration, mean linear velocity and smoothness, from each executed trial, will be recorded via the Virtual Reality Rehabilitation System (VRRS, Khymeia Group, Ltd. Noventa Padovana, Italy), and data from all 80 trials will be used to calculate kinematics of the upper extremity.

In order to run an intention to treat analysis, the outcomes will be assessed for all the enrolled patients independently from the time of their compliance with the treatment. The baseline value of patients who drop out will also be considered as their treatment result. Due to the treatment modality it will not be possible to blind patients. However, assessor blindness will be maintained.

Interventions

The RFVE treatment will be applied using the system described by Piron et al.[22]. The RFVE treatment is currently provided for stroke patients at the IRCCS San Camillo Hospital Foundation (Venice, Italy) within their rehabilitation program. The treatment will be performed in a darkened room to avoid distraction from other environmental stimuli. The patients will be seated on a standard chair in front of a wall screen handling the real sensorized object with the paretic hand. In the case of grasping impairments the hand's surface will be used as an end-effector, by means of a sensorized glove worn by the patient. The physiotherapist will be present during the rehabilitation session to adapt the VR tasks to patient's performance. The main role of the physiotherapist during the therapeutic session will be to focus on the quality of movement execution (i.e. motor behaviour of predicted trajectory and smoothness of movement) and correction of motor compensation behaviours (i.e. assisted exercises to abolish maladaptive compensation and to favour functional movement). The RFVE approach consists of performing different kinds of motor tasks by moving a sensorized object (end-effector) simultaneously displayed in a virtual scenario on a large wall-screen. The VRRS will be used to provide the artificial environment. The VRRS is composed of a desktop computer (Intel Core 3.2 GHz processor, RAM 2 GB with a dedicated video card, NVIDIA GeForce 8400 GS with 3D graphic accelerator driver), a high definition LCD projector, a wall-screen, an electromagnetic 3D motion tracking device (Polhemus

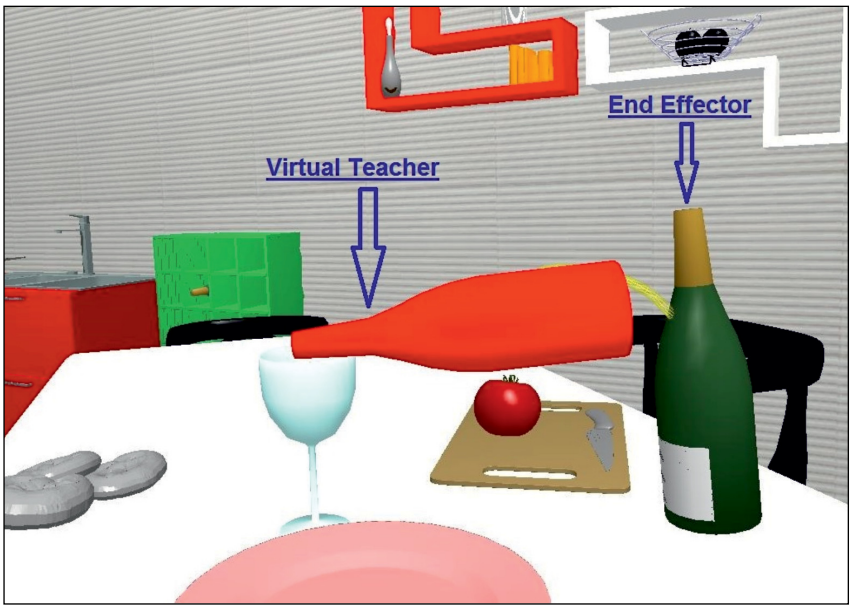

Figure 2

Visual feedback in the "Teacher" group

The reinforced feedback (i.e. virtual teacher) provided during the execution of a training task. "Virtual teacher" moves following the trajectory, showing the correct movement execution in real-time.

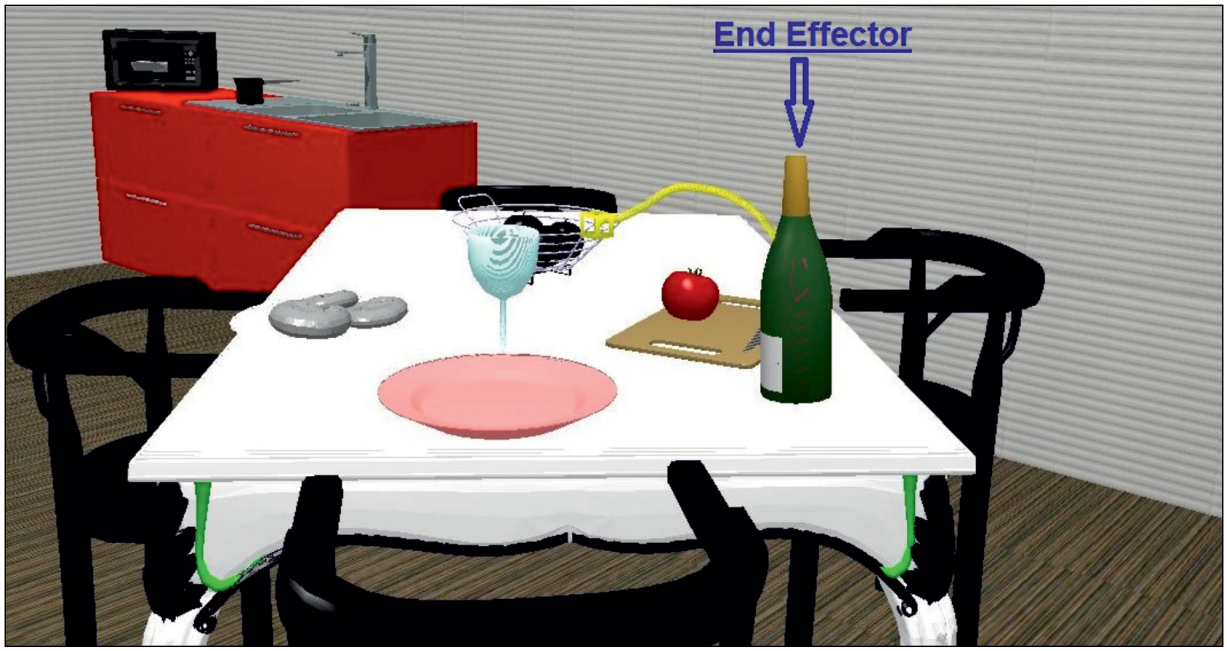

Figure 3

Visual feedback in the "No-Teacher" group

Execution of a motor task (without "virtual teacher") by moving a sensorized object (i.e. end-effector) that is simultaneously displayed in the virtual scenario.

LIBERTY, Colchester, VT, USA) and dedicated software.

In the TEACHER group, specific feedback called "virtual teacher" will be displayed (Figure 2) online during every task repetition. The virtual teacher will automatically executes the correct movement which the patient must emulate. This type of feedback is supposed to promote motor adaptation via a supervised learning mechanism. The visual feedback will provide online information on motor performance quality, allowing real time visual comparison between a patient's own execution and the virtual teacher's one. In the NO-TEACHER group, the patients will be asked to perform the same motor exercises using the upper limb without the enhanced visual feedback provided via the virtual teacher assistance (Figure 3), which will never be displayed during the therapy sessions. Both treatments will last four weeks with daily 60-minute sessions, five times per week (20 overall sessions).

Recruitment and randomisation

The eligible population will be screened according to the inclusion criteria described in the following paragraph. The enrolled patients (122 overall) will be randomly allocated to one of the two groups using sequentially numbered, opaque sealed envelopes (TEACHER group, N=61; NO-TEACHER group, N=61).

Inclusion criteria

Patients affected by their first, single stroke at least 24 months before enrolment will be included. Inclusion criteria include absence of ideomotor apraxia, neglect and aphasia interfering with verbal comprehension, FIM score[23] less than 100 points out of 126, and F-M UE scale[24] score between 10 and 55. The FIM scale is a reference standard to measure independence in activities of daily living, while the F-M UE scale is considered as the reference assessment scale used to measure residual motor function after a stroke. These criteria will assure the enrolment of a representative population of stroke patients who can still benefit from intensive rehabilitation care aimed at stimulating the highest possible level of independence.

Exclusion criteria

Fracture, major depressive disorders, other acquired brain injuries and drug-resistant seizures will be considered as exclusion criteria.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS

Laver et al.[13] estimated the efficacy of VR compared to standard physiotherapy for post-stroke upper limb rehabilitation. The F-M UE scale was the main outcome for motor function, and meta-analysis demonstrated that the score on this scale was significantly higher (4.43 points, CI = 1.98-6.88) in patients allocated to the experimental group. The experimental treatment proposed in this RCT is based on the same principles and technologies as those that were confirmed to be effective in previous studies. Based on available evidence, the F-M UE scale can be considered as a primary outcome, and an effect size of d=0.54 is adequately large to detect a clinically and statistically significant difference between the experimental and control groups. Power calculation indicates

that the sample size of 55 patients per group (TEACHER and NO-TEACHER), for $\alpha=0.05$ and $1-\beta=0.8$, would be sufficient to observe a significant difference in treatment effects. Nonetheless, considering a potential dropout rate of 10% (i.e. 6 patients), the final sample size will be 61 per group (i.e. 122 patients overall). Parametric and non parametric statistics will be used to compare differences within and between the two groups, depending on the skewness of the distribution.

EQUIPMENT CHECK

The VRRS equipment will be cleaned with antiseptic liquid and visually inspected before every use on all participants.

ADVERSE EVENT RECORDING

Any adverse event observed by clinicians, or self-reported by patients, will be registered and referred to the physician and trial steering committee.

DATA COLLECTION

Data will be recorded on study-specific data collection forms (case report forms – CRF). Researchers authorized to collect and record trial data will be listed on the study site delegation log and authorized by the Principal Investigator. All study data will be recorded on a CRF. The CRF will contain the patient's ID, date of enrollment, results of assessments collected before and after treatment, adverse events and clinical data. Completed CRFs will be registered, and forms will be tracked through a trial management system. Discrepant data will be verified using the original paper data sheets.

PATIENT COMPLETION AND WITHDRAWAL

Participants will be considered to have finished the study upon completion of four weeks of the VRRS treatment. Completing less than four weeks of treatment will be treated as a premature termination of the study for the patient. Even in case of premature termination of the treatment, data will be maintained on the CRF until study completion. A patient may withdraw from treatment prematurely because of deciding to interrupt the treatment, or due to significant adverse events.

ETHICAL ISSUES

The informed consent form will explicitly report the following:

a) All the procedures to voluntarily withdraw from the study. The same procedures will also be communicated to the referring neurologist and general practitioner.
b) The assurance that all therapists will be trained before their enrolment in the research team on the benefits and limitations of using technologies to provide VR-based therapies.

METHODS OF DISSEMINATION

Dissemination of the findings to scientific and social communities will be guaranteed by publication of abstracts and full paper reports in peer-reviewed scientific journals, as well as in newspapers with a general circulation. Moreover, to promote the knowledge of the findings, abstracts will be submitted for presentation to national and international conferences and dissemination via other media will be actively encouraged to reach a wide general audience.

POTENTIAL DIFFICULTIES/ RISKS OF CARRYING OUT THE RESEARCH

Possible critical aspects might include the time required to enrol suitable patients fulfilling adequate inclusion criteria. In the case that an adequate recruitment rate cannot be sustained, the involvement of a second unit might be considered to follow the planned timetable.

Possible patient dropout related to the proposed technological approach might also be an issue. To address this possible risk, sample size calculation has been increased accordingly to a predicted dropout rate of 10%, as observed in other similar studies and treatments. Moreover, the larger sample will allow an explorative estimation of treatment safety.

DISCUSSION

In the last decade, therapeutic modalities based on VR technologies for rehabilitation have received large attention from different scientific groups worldwide. Nowadays, many studies are performed confirming the usefulness and safe application of VR in a wide field of therapeutic applications[6,13,25,26]. The need to develop efficacious treatments for relieving symptoms in stroke-survivors is an important research topic and clinical purpose. Our study is designed considering the state-of-the-art technology in this field, which suggests that VR based treatments can be successfully integrated in individual rehabilitation programmes. Nevertheless, it is still unclear whether specific single feedback is useful for speeding up the motor learning process or whether it might present post-stroke patients with cognitive overload. In the study by Todorov et al.[14], the motor learning curve was assessed in a group of 42 healthy subjects. Participants were trained provided with enhanced feedback through a virtual teacher to emulate an augmented environment and were compared with 21 participants trained by a real teacher. The authors reported that "subjects who received the virtual environment training performed significantly better than subjects who received a comparable amount of real-tasks"[14].

Rehabilitation modalities can be enriched by many different sensorimotor strategies, most of which show that some forms of feedback improve the efficiency of learning simple movements. Winstein et al. observed this when testing the learning process phases (i.e. acquisition, maintenance and re-acquisition of motor tasks) by

performing simple movements with enhanced feedback. The comparison between a group of stroke patients with a control group of healthy subjects did not show any difference in the acquisition of motor functions related to the learning process. However, post-stroke patients (regardless of feedback delivery) committed more errors in each phase than those in the control group[27]. The authors concluded that a stroke in the sensorimotor area alters the ability to control and correct movement execution, but not the ability to re-learn motor tasks. Conversely, continuous interaction with the external environment unconsciously determines our behaviors. Motor memory mostly relies on the integrity of procedural memory, the capability to approximate likely responses to specific stimuli. Procedural memory is located in the structures associated with the motor system, especially in the cerebellum and basal ganglia (caudate nucleus), which is one of the main brain structures for cognitive and perceptual learning and motor efficiency[25]. Thus, motor learning can be defined as the ability to improve individual movements or sequences of movements through repetition and interaction with the environment. On the other hand, reinforced feedback provided by virtual reality can promote motor learning, which has been shown to be effective both in healthy subjects and stroke patients with motor impairments[6].

This protocol represents the first RCT study of virtual training for upper limb motor function in stroke patients where the effect of using the same environment with different types of feedback is assessed. The findings from this study will be relevant to researchers, clinicians and service users in decision making to provide appropriate effective therapy. Moreover, the results will improve the understanding of patients' needs when providing rehabilitation therapy after a stroke.

Trial status

The study is currently recruiting patients, and 57 participants have already been assessed.

Authors' contribution

CZ, AT, MA conceived the project, PK leading the coordination of the trial. PK, AT, CZ wrote the protocol manual, whereas MA, PT, AB, FD assisted with the study design and protocol preparation. PK, CZ, AT, MA have been entitled for project funding. AT performed the simple-size calculations and designed the statistical analysis. CZ, MA are the blind assessors for the project. PK, AB, FD, CB, CL provide enrolled participants with the virtual training. PK recruits and screens the patients. AT, MA, PT manage the project. All authors have read and approved the final manuscript.

Abbreviations

RCT – Randomized Controlled Trial
ADL – Activities of Daily Living
CNS – Central Nervous System
KR – Knowledge of Results
KP – Knowledge of Performance
VR – Virtual Reality
RFVE – Reinforced Feedback in Virtual Environment
F-M UE – Fugl-Meyer Upper Extremity
FIM – Functional Independence Measure
VRRS – Virtual Reality Rehabilitation System
CRF – Case Report Form

Source of support

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Conflict of interests

The authors declare that they have no conflict of interests.

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