HHS Public Access

Author manuscript

Lancet Neurol. Author manuscript; available in PMC 2016 November 14.

Published in final edited form as:

Lancet Neurol. 2016 September ; 15(10): 1019–1027. doi:10.1016/S1474-4422(16)30121-1.

Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial

Gustavo Saposnik, **Leonardo G Cohen**, **Muhammad Mamdani**, **Sepideth Pooyania**, **Michelle Ploughman**, **Donna Cheung**, **Jennifer Shaw**, **Judith Hall**, **Peter Nord**, **Sean Dukelow**, **Yongchai Nilanont**, **Felipe De los Rios**, **Lisandro Olmos**, **Mindy Levin**, **Robert Teasell**, **Ashley Cohen**, **Kevin Thorpe**, **Andreas Laupacis**, **Mark Bayley**, and **for Stroke Outcomes Research Canada**

Division of Neurology (G Saposnik MD) and Stroke Program (G Saposnik, D Cheung OT), St Michael's Hospital, University of Toronto, Canada; Human Cortical Physiology and Stroke Neurorehabilitation Section, NINDS, NIH, Bethesda, USA (L G Cohen MD); Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Canada (G Saposnik, M Mamdani PharmD, J Hall MSc, A Cohen MSc, Prof K Thorpe MMath, Prof A Laupacis MD); Riverview Health Centre, Winnipeg, Manitoba, Canada (S Pooyania MD); Miller Centre at Memorial University, St John's, Newfoundland, Canada (M Ploughman PhD); UHN-Toronto Rehabilitation Institute, University of Toronto, Canada (J Shaw RhT, M Bayley MD); Providence Healthcare, Toronto, Ontario, Canada (P Nord MD); Foothills Medical Centre, Calgary, Alberta, Canada (S Dukelow MD); Mahidol University, Siriraj Hospital, Bangkok, Thailand (Y Nilanont MD); Hospital Nacional Cayetano Heredia, Lima, Peru (F De los Rios MD); FLENI Rehabilitation Institute, Escobar, Buenos Aires, Argentina (L Olmos MD); Jewish Rehabilitation Hospital, CRIR Research Centre, McGill University, Montreal, Canada (M Levin PhD); and Parkwood Institute, University of Western Ontario, London, Ontario, Canada (R Teasell MD)

Summary

Background—Non-immersive virtual reality is an emerging strategy to enhance motor performance for stroke rehabilitation. There has been rapid adoption of non-immersive virtual reality as a rehabilitation strategy despite the limited evidence about its safety and effectiveness.

Correspondence to: Dr Gustavo Saposnik, Stroke Outcomes Research & Virtual Reality Center, Stroke Outcome Research Canada Working Group, Department of Medicine, St Michael's Hospital, University of Toronto, 55 Queen St E, Toronto, Ontario, M5C 1R6, Canada, saposnikg@smh.ca.

See Online for appendix

For more information on **Stroke Outcomes Research Canada** see http://www.sorcan.ca

Contributors

GS, MM, RT, ML, LGC, AL, MB, and KT participated in the conception, study design, interpretation of the results, drafting of the manuscript, and made a critical revision of the manuscript. AC and JH contributed to the data analysis, interpretation of results, and drafting the manuscript. SP, MP, DC, JS, PN, SD, YN, FdlR, and LO contributed to the interpretation of results and drafting of the manuscript. GS was responsible for obtaining funds.

Steering committee

Gustavo Saposnik, Mark Bayley, Judith Hall, and Muhammad Mamdani.

Declaration of interests

GS is supported by a Clinician-Scientist Award from Heart and Stroke Foundation Canada. All other authors declare no competing interests.

Our aim was to compare the safety and efficacy of virtual reality with recreational therapy on motor recovery in patients after an acute ischaemic stroke.

Methods—In this randomised, controlled, single-blind, parallel-group trial we enrolled adults (aged 18–85 years) who had a first-ever ischaemic stroke and a motor deficit of the upper extremity score of 3 or more (measured with the Chedoke-McMaster scale) within 3 months of randomisation from 14 in-patient stroke rehabilitation units from four countries (Canada [11], Argentina [1], Peru [1], and Thailand [1]). Participants were randomly allocated (1:1) by a computer-generated assignment at enrolment to receive a programme of structured, task-oriented, upper extremity sessions (ten sessions, 60 min each) of either non-immersive virtual reality using the Nintendo Wii gaming system (VRWii) or simple recreational activities (playing cards, bingo, Jenga, or ball game) as add-on therapies to conventional rehabilitation over a 2 week period. All investigators assessing outcomes were masked to treatment assignment. The primary outcome was upper extremity motor performance measured by total time to complete the Wolf Motor Function Test (WMFT) at the end of the 2 week intervention period, analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NTC01406912.

Findings—The study was done between May 12, 2012, and Oct 1, 2015. We randomly assigned 141 patients: 71 received VRWii therapy and 70 received recreational activity. 121 (86%) patients (59 in the VRWii group and 62 in the recreational activity group) completed the final assessment and were included in the primary analysis. Each group improved WMFT performance time relative to baseline (decrease in median time from 43·7 s [IQR 26·1–68·0] to 29·7 s [21·4–45·2], 32·0% reduction for VRWii *vs* 38·0 s [IQR 28·0–64·1] to 27·1 s [21·2–45·5], 28·7% reduction for recreational activity). Mean time of conventional rehabilitation during the trial was similar between groups (VRWii, 373 min [SD 322] *vs* recreational activity, 397 min [345] ; p=0·70) as was the total duration of study intervention (VRWii, 528 min [SD 155] *vs* recreational activity, 541 min [142]; p=0·60). Multivariable analysis adjusted for baseline WMFT score, age, sex, baseline Chedoke-McMaster, and stroke severity revealed no significant difference between groups in the primary outcome (adjusted mean estimate of difference in WMFT: 4·1 s, 95% CI −14·4 to 22·6). There were three serious adverse events during the trial, all deemed to be unrelated to the interventions (seizure after discharge and intracerebral haemorrhage in the recreational activity group and heart attack in the VRWii group). Overall incidences of adverse events and serious adverse events were similar between treatment groups.

Interpretation—In patients who had a stroke within the 3 months before enrolment and had mild-to-moderate upper extremity motor impairment, non-immersive virtual reality as an add-on therapy to conventional rehabilitation was not superior to a recreational activity intervention in improving motor function, as measured by WMFT. Our study suggests that the type of task used in motor rehabilitation post-stroke might be less relevant, as long as it is intensive enough and task-specific. Simple, low-cost, and widely available recreational activities might be as effective as innovative non-immersive virtual reality technologies.

Funding—Heart and Stroke Foundation of Canada and Ontario Ministry of Health.

Introduction

Every year about 15 million people have a new or recurrent stroke worldwide,[1,2] and about two thirds of stroke survivors have motor deficits associated with diminished quality of life.[3]

The greatest burden occurs in low-income and middle-income countries lacking the basic infrastructure facilities to support resource-intensive interventions in stroke rehabilitation.[4,5]

Conventional rehabilitation techniques, including motor relearning, neurodevelopmental therapy, or proprioceptive neuromuscular facilitation, are similarly effective in improving motor function.[6–10] However, conventional rehabilitation can be resource-intensive and costly, often requiring specialised facilities not always widely available.[11,12] Virtual reality is a novel rehabilitation strategy regarded as an enjoyable alternative to enhance motor recovery after stroke where specialised facilities are scarce. Virtual reality ranges from non-immersive to fully immersive, depending on the degree to which the user is isolated from the physical surroundings when interacting with the virtual environment.[13] A variety of non-immersive video-game systems developed by the entertainment industry for home use have made this technology less costly and more accessible for potential rehabilitation interventions.

Research in context

Evidence before this study

We searched PubMed and the Cochrane Database for relevant articles published from Jan 1, 1980, to Dec 18, 2015. We used the keywords “virtual reality” combined with “stroke” and “stroke rehabilitation”. We restricted the search to articles published in English. We identified 12 small, single-centre studies (including our EVREST pilot study); when the results from these studies were combined in a meta-analysis published in a Cochrane review published in 2015, virtual reality-assisted rehabilitation appeared to confer modest improvement in motor function of the upper extremity after stroke. Considerable heterogeneity was observed, as each study included five to 40 participants (less than 200 participants in total). Most of the studies compared non-immersive virtual reality added to conventional rehabilitation versus conventional rehabilitation alone, with no active control.

Added value of this study

To our knowledge, this multicentre study is the first randomised trial to compare the effect of non-immersive virtual reality and recreational activity (active control) as add-on therapies to conventional rehabilitation after an acute stroke. Outcomes were assessed at the end of the 2 week intervention and again 4 weeks post-intervention. We found no significant difference in motor recovery after stroke between non-immersive virtual reality and simple recreational activities, although each group showed a significant improvement relative to baseline.

Implications of all the available evidence

Our findings suggest that added intensity of training, whether with virtual reality or other simple and inexpensive arm activities (eg, playing cards or dominoes), improves early motor recovery of the upper limb after stroke. Considering that the greatest burden of stroke occurs in low-income and middle-income countries with constrained resources and limited access to technologies and rehabilitation therapists, simple, low-cost, high-

intensity, and task-specific home-based therapies appear comparable with virtual reality to optimise motor recovery post-stroke.

Despite promising results from initial studies,[14] meta-analyses have suggested marginal benefits of virtual reality systems in improving motor function of the upper extremity after stroke.[15] Benefits were typically observed when the intervention was done in the first 6 months after stroke.[15] However, some of the studies included[16–18] in one meta-analysis[19] compared virtual reality added to conventional rehabilitation with conventional rehabilitation alone with no active control. Such a design might allow more treatment time among patients receiving virtual reality interventions, creating an imbalance in the total rehabilitation time between groups that might explain the observed benefits, although total intervention time was not reported.[14,15,19] Despite this limited evidence, virtual reality is commonly used in clinical practice and recommended in stroke guidelines.[20–22]

To address confounding factors in previous studies, we did a multicentre, single-blind, parallel-group, randomised trial to compare the effect of non-immersive virtual reality with recreational therapy (active control), with both added to customary conventional rehabilitation, on motor recovery in patients after acute stroke. We hypothesised that using non-immersive virtual reality after an ischaemic stroke would result in better motor recovery of the upper extremity required for activities of daily living than with recreational therapy.

Methods

Study design and participants

This controlled, single-blind, parallel-group, randomised trial was done at 14 participating rehabilitation centres from four countries (Canada [11]: Toronto, Calgary, London, Mississauga, North York, St Johns, Hamilton, Montreal; Argentina [1]: Buenos Aires; Peru [1]: Lima; Thailand [1]: Bangkok). We included patients aged 18–85 years who had a first-time ischaemic stroke within 3 months of enrolment and had a mild-to-moderate motor disability (defined as Chedoke-McMaster Stroke Assessment stage >3).[23,24] Diagnosis of acute stroke was confirmed by neuroimaging (CT or MRI), neurological assessment, and Chedoke-McMaster inclusion criteria.

Potential participants were excluded if they had no disability in the upper extremity (arm components of the Chedoke-McMaster scale=7); were unable to follow instructions; had a pre-stroke modified Rankin score of 2 or higher; were medically unstable or had uncontrolled hypertension; had a severe illness with a life expectancy of less than 3 months; experienced unstable angina or had a myocardial infarction within 3 months; had a history of seizures or epilepsy (except for febrile seizures of childhood); were participating in another clinical trial involving an investigational drug or physical therapy; or had any condition that might put the patient at risk (ie, known shoulder subluxation or fracture) at study entry.

Data management, research coordination, and statistical analyses were done at the Applied Health Research Centre of the Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Canada. Operational procedures, guidelines for the implementation of both arms of the study, and the consent form were approved by the ethics review boards at St Michael's

Hospital and at each participating institution. Written informed consent was obtained from all patients at each participating institution.

Randomisation and masking

Patients were randomly assigned (1:1) within 2 months of stroke onset to non-immersive virtual reality using the Nintendo Wii (Nintendo Co., Ltd, Kyoto, Japan) gaming system (VRWii) or recreational activities by computer-generated assignment at enrolment (stratified by site), employing random permuted blocks of sizes 2 and 4, which were assigned remotely via the internet. The study coordinator (JH) and patients participating in this study were not masked to the intervention group. To limit the participants from knowing how to use the games beforehand, and to ensure that other caregivers and support staff were not aware of patient allocation, all study interventions were done by dedicated trial staff out of sight of ward staff. Trial staff and patients were instructed not to divulge the intervention allocation to caregivers or other ward staff. Interventions were not recorded in the medical record. All baseline, post-intervention, and 4 week follow-up assessments were done by trained outcome assessors (DC and others) who were masked to the patient's treatment allocation.

Procedures

Within their in-patient stroke rehabilitation centres, patients were assessed at baseline (randomisation), at 2 weeks (post-intervention), and at 4 weeks (follow-up) by the trained outcome assessors. The intensity and duration of the interventions was the same in the VRWii and recreational activity groups, consisting of an intensive programme of ten sessions, 60 min each, over a 2 week period. A rehabilitation therapist administered the interventions (either VRWii or recreational activity) at each participating facility, in a one-to-one session providing feedback to avoid inappropriate compensatory movements. Patients were not allowed to play against each other. Further details are described in the protocol (appendix).

We used the Wii Nintendo gaming system as a paradigm of non-immersive virtual reality devices that are inexpensive, easy to use, comprising simple graphics, and with readily available commercial games. We used commercially available software, including Wii Sports and Game Party 3. Progression through the intervention allowed participants to choose some specific activities within those games (last 30 min of the intervention) based on their capabilities and interest, with the goals of enhancing flexibility, range of motion, strength, and coordination of the affected arm. The recreational activity was designed as a customary active control with similar intensity and complexity to simulate the skills required in the VRWii group and favouring motivation. As in the VRWii group, progression through the intervention allowed patients to choose specific activities (playing cards, bingo, Jenga, or ball game; appendix).

Outcomes

The primary endpoint was motor function at the end of the 2 week interventions as measured by the time in doing a number of tasks on the Wolf Motor Function Test (WMFT). We used an abbreviated version of WMFT that included six tasks (hand to table, hand to box, reach and retrieve, lift can, lift pencil, and fold towel),[25] and added grip strength and flip a card

tasks. Secondary endpoints at the end of the 2 week interventions were: gross manual dexterity assessed using the Box and Block Test (BBT); quality of life after stroke and hand function, both measured by the Stroke Impact Scale (SIS); score on the functional independence measure (FIM); independence for activities of daily living as measured by the Barthel Index; score on the Modified Rankin Scale; and grip strength measured using a dynamometer. All outcome measures were also assessed 4 weeks post-intervention, which was about 3 months after stroke onset. Additionally, at the Toronto Rehabilitation Institute, kinematics of limb movement were measured using the Reaching Performance Scale (RPS; appendix) at the beginning and end of the intervention to determine the characteristics of motor learning in both groups. The RPS was also used to assess compensatory movements.

Death, life-threatening events (stroke, myocardial infarction, and fracture), hospital readmissions, or new disability leading to prolongation of existing hospitalisation were considered serious adverse events. Minor adverse events included the proportion of patients experiencing intervention-related pain, dizziness, light-headedness, back or shoulder pain, or muscle aches during the study period. We also measured patients' perceived exertion and fatigue after each treatment session by using the Borg Perceived Level of Exertion scale (excessive fatigue defined as any score >13 points).

Statistical analysis

The study sample size of 140 was calculated according to the results of the EVREST pilot study.[26] This sample size would allow detection of change at the patient level of 5 s using the WMFT[27] and the SD was estimated to be 9 s. If only 70% of patients completed the intervention (leaving 52 in each group), there would still be 80% power to detect the 5 s difference.

The primary outcome analysis was done in the intention-to-treat population and examined the total WMFT score tasks. Adverse events are reported descriptively. A two-sided p value of less than 0·05 was considered statistically significant. Despite the one-sided nature of the clinical hypothesis, the primary outcome was tested with a two-sided alternative to be statistically conservative. Statistical analysis was done in the R language for statistical computing (version 3.3.23; R Foundation for Statistical Computing, Vienna, Austria). A linear regression model was constructed for the primary outcome, controlling for baseline WMFT score, treatment group, age, sex, baseline Chedoke-McMaster score, and stroke severity. A sensitivity analysis was done to determine whether patients who were not able to complete the test and were given a score of 120 significantly affected the outcome. An examination of the residual plots did not suggest concerns regarding model assumptions (eg, normality of errors) and no transformations of the outcome were needed. A planned subgroup analysis included age, sex, handedness, stroke severity, Chedoke-McMaster score, time from stroke onset to randomisation, and FIM.

The average total therapy time, the average therapy time per session, and differences 4 weeks post-intervention from baseline in primary and secondary outcomes were computed for each group, along with 95% CIs. For relevant clinical outcomes, descriptive statistics (mean and SD or median and IQR) were computed for each assessment. Inferential analyses comparing treatment groups for the secondary outcomes also employed a linear model in

which the baseline value was adjusted for in addition to age, sex, baseline Chedoke-McMaster score, and stroke severity. Additionally, the effectiveness of masking of the outcome assessors was examined by asking them to guess which treatment group the patient was in. The proportion correctly guessed was compared with a χ^2 test. The trial is registered with ClinicalTrials.gov, number NTC01406912.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

Results

We screened 893 individuals between May 12, 2012, and Oct 1, 2015. The most common reason for exclusion was motor deficits that were too mild (282 [32%] of 893 patients). Of the screened individuals, 141 eligible patients were randomly assigned: 71 patients were assigned to VRWii and 70 patients were assigned to the recreational activity (active control) group. 59 (83%) of 71 patients in the VRWii group and 62 (89%) of 70 patients in the recreational activity group completed the 2 week intervention and were included in the primary outcome analysis; 47 (66%) of 71 patients in the VRWii group and 54 (77%) of 70 patients in the recreational activity group completed the 4 week post-intervention assessment and were included in secondary analyses.

In the VRWii group, four patients discontinued after the training session, whereas none discontinued in the recreational activity group. 13 (18%) of 71 patients in the VRWii group and 13 (19%) of 70 patients in the recreational activity group did not complete the ten scheduled sessions (figure 1). Mean age of all patients was 62 years (SD 12). Demographic and baseline clinical characteristics, including time from stroke onset, were similar between groups (table 1). Mean time of conventional rehabilitation during the trial was similar between groups (VRWii 373 min [SD 322] ***vs*** recreational activity 397 min [345]; p=0·70). There was no difference in the total duration of each study intervention (VRWii 528 min [SD 155] ***vs*** recreational activity, 541 min [142]; p=0·60). We found no evidence of failure of concealment at the end of the study; the masked assessors correctly identified recreational activity patients on 55% (95% CI 43–67) of occasions versus 67% (55–77) for VRWii patients (p=0·24 for a difference between groups).

Analysis of the primary outcome showed improvements in the median WMFT performance time from baseline to the end of intervention in both groups (decrease in median time from 43·7 s [IQR 26·1–68·0] to 29·7 s [21·4–45·2], a 32·0% reduction for VRWii ***vs*** decrease from 38·0 s [IQR 28·0–64·1] to 27·1 s [21·2–45·5], a 28·7% reduction for recreational activity). Multivariable analysis revealed no significant difference between groups at the end of the intervention with respect to WMFT performance (adjusted between-group mean difference estimate: 4·1 s [95% CI −14·4 to 22·6], p=0·469) or 4-weeks post-intervention (−14·2 s [−52·0 to 23·7, p=0·346; table 2, figure 2A, B).

There were no differences in the secondary outcome measures between groups (table 2, appendix) with the exception of better performance in the BBT for the recreational activity group at the end of the intervention (30·9 [SD 13·2] ***vs*** 27·2 [15·5] blocks moved; adjusted p value 0·018). Patients in both groups had similar scores with respect to grip strength, recovery in activities for daily living measured by the Barthel Index, hand function, and quality of life at the end of the 2 week intervention. Similar results were observed 4 weeks post-intervention. Both groups showed a non-significant increase in the quality of movement of the affected arm as measured by the RPS compared with baseline (for the close target: mean RPS for recreational activity 1·66 [SD 0·53], 11% improvement ***vs*** VRWii 1·47 [0·60], 11% improvement [adjusted p value 0·81]; for the far target: recreational activity 1·22 [1·10], 9% improvement ***vs*** VRWii 1·52 [0·28], 12% improvement [adjusted p value 0·83]). The multivariable analysis revealed no difference in the quality of movements between groups (table 2).

There was no evidence of heterogeneity of effect across any of the prespecified subgroups (age, sex, handedness, stroke severity, functional arm assessment [Chedoke-McMaster score], time from stroke onset to randomisation, and functional assessment scale [FIM]; figure 3). A sensitivity analysis excluding patients who were not able to complete the WMFT at baseline (54 in the VRWii group and 61 in the recreational activity group) revealed no difference between groups (p=0·93; data not shown).

There were three serious adverse events during the trial, all deemed to be unrelated to the interventions. Two serious adverse events occurred in the recreational activity group (seizure after discharge and intracerebral haemorrhage) and one in the VRWii group (heart attack). Overall incidences of adverse events and serious adverse events were similar between treatment groups (table 3).

Discussion

The EVREST study is the first randomised trial designed and powered to evaluate the effectiveness of video-game-based, non-immersive virtual reality (VRWii) compared with recreational activity (active control) as add-on therapies to conventional rehabilitation early after an acute stroke. In this trial, patients randomly assigned to both groups had an average of 30% and 40% improvement in motor performance at the end of the 2 week intervention and 4 weeks post-intervention, respectively. Contrary to our hypothesis, there was no significant difference in hand function, grip strength, motor performance, activities of daily living, quality of movement, or quality of life between groups either at the end of the intervention or 4 weeks post-intervention. Of note, there were no differences in the duration of the assigned interventions or total time of conventional rehabilitation between groups, allowing a fair comparison between groups. The results remained unaltered after adjusting for potential confounders (age, sex, baseline performance measures, and stroke severity). No prespecified subgroups appeared to benefit from the VRWii intervention.

Some limitations of the study deserve mention. The intervention group received non-immersive virtual reality technology because it is low cost, less complex, and easier to deliver than immersive virtual reality systems. It is possible that immersive hospital-based

systems could provide more beneficial results. However, we would argue that our neutral results are compelling because they are based on patients who fully complied with the interventions; the non-completion rate was similar between groups and there was no obvious difference in baseline characteristics of those who did not complete the interventions. The duration of our intervention can be considered short. Nevertheless, it is similar to other virtual reality interventions used in meta-analysis of previous positive studies.[15,19] Another potential limitation is the lack of an additional study group receiving conventional therapy alone. However, this approach has been criticised by artificially creating potential benefits to the virtual reality technology group as these patients actually receive longer therapy than those receiving conventional therapy alone.

It is possible that a combination of different factors explain our neutral results compared with previous, more promising findings of virtual reality. For example, the use of an active control group and the greater variability of the intervention across centres in a multicentre design might have attenuated the mild effects of virtual reality previously observed in small, single-centre studies.[28,29] Indeed, the residual estimate of SD for the WMFT after the intervention was considerably larger than assumed in planning this study. However, there was no evidence of treatment effect in any of the outcomes.

Questions remain about the ideal intensity of physiotherapy in conventional rehabilitation to improve motor function.[30] There is a trade-off between the technological appeal associated with video gaming and the simplicity and lower costs of using recreational therapy. Future studies should help identify the best strategy to optimise motor recovery based on patients' preferences and availability of these interventions in a particular clinical setting. Future work could also study if virtual reality affects more subtle tasks than those reflected by the WMFT. However, taken together, the consistency of the results and the diverse domains evaluated by the different outcome measures presented here suggest we were unlikely to have missed a clinically important treatment effect. Virtual reality requires higher cognitive demands by extra spatial transformation of uncoupled eye–hand movements while looking at the television screen than the direct visual and proprioceptive feedback of a recreational activity.[31] It is possible that these differences play a part in explaining our results.

Our study suggests that the type of task used in motor rehabilitation post-stroke might be less relevant, as long as it is intensive enough and task-specific. This notion is supported by findings in previous studies applying innovative technologies (eg, arm robotics) with active control groups showing the interventions were beneficial compared with no active treatment, but not better than active controls.[32–34] Given the rapid adoption of virtual reality in stroke rehabilitation, our results reinforce the importance of testing interventions using randomised, multicentre trials that are powered to examine clinically important differences between groups. Moreover, although we expect that technology might enhance relearning of motor pathways by intensifying neuro-rehabilitation, simple motor tasks (that could be implemented worldwide) appear at least as safe and efficacious.

Our results have practical implications for stroke rehabilitation worldwide. Considering that the greatest burden of stroke occurs in low-income and middle-income countries with constrained resources and limited access to technologies and rehabilitation therapists,[1,4]

simple, low-cost, high-intensity, task-specific, home-based therapies might be considered to be comparable with virtual reality in optimising motor recovery.[28] Additional investments in virtual reality might not need to be made in resource-limited environments. People with stroke should be made aware of these activities (eg, playing cards or bingo) in addition to conventional therapy.

In summary, EVREST used a wireless, non-immersive virtual reality technology intervention in stroke rehabilitation to improve motor function. Virtual reality is safe, but showed no significant benefits as an add-on therapy to conventional rehabilitation when compared with recreational activity (active control). Our study suggests that the type of task used in motor rehabilitation post-stroke might not be so relevant, as long as it is intensive enough and task-specific. Simple, widely available, and inexpensive recreational activities might be as effective as innovative non-immersive virtual reality technologies.

Acknowledgments

The authors are indebted to all participants of the EVREST trial. We are very grateful to allied health members at each site who were instrumental for the successful implementation of EVREST. The authors would like to thank co-operative students at Li Ka Shing Knowledge Institute for their assistance with database development and data entry. The authors thank Sarah Blanton and Steven Wolf for the facilitation of the training video and suggestions regarding the analysis of the WMFT. The authors are most grateful for the initial funding provided by South East Toronto Stroke Network and to Jacqueline Willems for the unconditional support with the early organisation of the study design and coordination.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014; 383:245–54. [PubMed: 24449944]
2. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013; 1:e259–81. [PubMed: 25104492]
3. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors influencing stroke survivors' quality of life during subacute recovery. Stroke. 2005; 36:1480–04. [PubMed: 15947263]
4. Feigin VL, Mensah GA, Norrving B, Murray CJ, Roth GA. GBD 2013 Stroke Panel Experts Group. Atlas of the global burden of stroke (1990–2013): The GBD 2013 Study. Neuroepidemiology. 2015; 45:230–06. [PubMed: 26505985]
5. Anjos SM, Cohen LG, Sterr A, de Andrade KN, Conforto AB. Translational neurorehabilitation research in the third world: what barriers to trial participation can teach us. Stroke. 2014; 45:1495–97. [PubMed: 24643406]
6. Langhammer B, Stanghelle JK. Bobath or motor relearning programme? A comparison of two different approaches of physiotherapy in stroke rehabilitation: a randomized controlled study. Clin Rehabil. 2000; 14:361–69. [PubMed: 10945420]
7. Logigian MK, Samuels MA, Falconer J, Zagar R. Clinical exercise trial for stroke patients. Arch Phys Med Rehabil. 1983; 64:364–67. [PubMed: 6882175]
8. Lord JP, Hall K. Neuromuscular reeducation versus traditional programs for stroke rehabilitation. Arch Phys Med Rehabil. 1986; 67:88–91. [PubMed: 3954571]
9. van Vliet PM, Lincoln NB, Foxall A. Comparison of Bobath based and movement science based treatment for stroke: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2005; 76:503–08. [PubMed: 15774435]
10. Dimyan MA, Cohen LG. Neuroplasticity in the context of motor rehabilitation after stroke. Nat Rev Neurol. 2011; 7:76–85. [PubMed: 21243015]

11. Jutai JW, Teasell RW. The necessity and limitations of evidence-based practice in stroke rehabilitation. Top Stroke Rehabil. 2003; 10:71–78. [PubMed: 12970832]
12. Teasell R, Meyer MJ, McClure A, et al. Stroke rehabilitation: an international perspective. Top Stroke Rehabil. 2009; 16:44–56. [PubMed: 19443347]
13. Henderson A, Korner-Bitensky N, Levin M. Virtual reality in stroke rehabilitation: a systematic review of its effectiveness for upper limb motor recovery. Top Stroke Rehabil. 2007; 14:52–61.
14. Saposnik G, Levin M. Outcome Research Canada Working Group. Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. Stroke. 2011; 42:1380–86. [PubMed: 21474804]
15. Laver KE, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev. 2015; 2:CD008349.
16. Broeren J, Claesson L, Goude D, Rydmark M, Sunnerhagen KS. Virtual rehabilitation in an activity centre for community-dwelling persons with stroke. The possibilities of 3-dimensional computer games. Cerebrovasc Dis. 2008; 26:289–96. [PubMed: 18667809]
17. Kwon JS, Park MJ, Yoon IJ, Park SH. Effects of virtual reality on upper extremity function and activities of daily living performance in acute stroke: a double-blind randomized clinical trial. NeuroRehabilitation. 2012; 31:379–85. [PubMed: 23232161]
18. Cho K, Yu J, Jung J. Effects of virtual reality-based rehabilitation on upper extremity function and visual perception in stroke patients: a randomized control trial. J Phys Ther Sci. 2012; 24:1205–08.
19. Lohse KR, Hilderman CG, Cheung KL, Tatla S, Van der Loos HF. Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. PloS ONE. 2014; 9:e93318. [PubMed: 24681826]
20. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2014; 45:2532–53. [PubMed: 24846875]
21. Management of Stroke Rehabilitation Working Group. VA/DoD clinical practice guideline for the management of stroke rehabilitation. J Rehab Res Devel. 2010; 47:1–43.
22. Dawson, AS., Knox, J., McClure, JA., Foley, N., Teasell, R. Stroke Best Practice Working Group. [accessed Nov 28, 2015] Stroke rehabilitation. 2013. http://strokebestpractices.ca/wp-content/uploads/2013/07/SBP2013_Stroke-Rehabilitation-Update_July-10_FINAL.pdf
23. Barreca S, Wolf SL, Fasoli S, Bohannon R. Treatment interventions for the paretic upper limb of stroke survivors: a critical review. Neurorehabil Neural Repair. 2003; 17:220–06. [PubMed: 14677218]
24. Gowland C, Stratford P, Ward M, et al. Measuring physical impairment and disability with the Chedoke-McMaster Stroke Assessment. Stroke. 1993; 24:58–63. [PubMed: 8418551]
25. Bogard K, Wolf S, Zhang Q, Thompson P, Morris D, Nichols-Larsen D. Can the Wolf Motor Function Test be streamlined? Neurorehabil Neural Repair. 2009; 23:422–28. [PubMed: 19276293]
26. Saposnik G, Teasell R, Mamdani M, et al. Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation: a pilot randomized clinical trial and proof of principle. Stroke. 2010; 41:1477–84. [PubMed: 20508185]
27. Lin KC, Hsieh YW, Wu CY, Chen CL, Jang Y, Liu JS. Minimal detectable change and clinically important difference of the Wolf Motor Function Test in stroke patients. Neurorehabil Neural Repair. 2009; 23:429–34. [PubMed: 19289487]
28. Teasell R, Rice D, Richardson M, et al. The next revolution in stroke care. Expert Rev Neurother. 2014; 14:1307–14. [PubMed: 25331417]
29. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009; 8:741–54. [PubMed: 19608100]
30. Han CE, Arbib MA, Schweighofer N. Stroke rehabilitation reaches a threshold. PLoS Comput Biol. 2008; 4:e1000133. [PubMed: 18769588]
31. Mousavi Hondori H, Khademi M, Dodakian L, McKenzie A, Lopes CV, Cramer SC. Choice of human–computer interaction mode in stroke rehabilitation. Neurorehabil Neural Repair. 2016; 30:258–65. [PubMed: 26138411]

32. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010; 362:1772–83. [PubMed: 20400552]

33. Duncan PW, Sullivan KJ, Behrman AL, et al. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011; 364:2026–36. [PubMed: 21612471]

34. Dromerick AW, Lang CE, Birkenmeier RL, et al. Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-center RCT. Neurology. 2009; 73:195–201. [PubMed: 19458319]

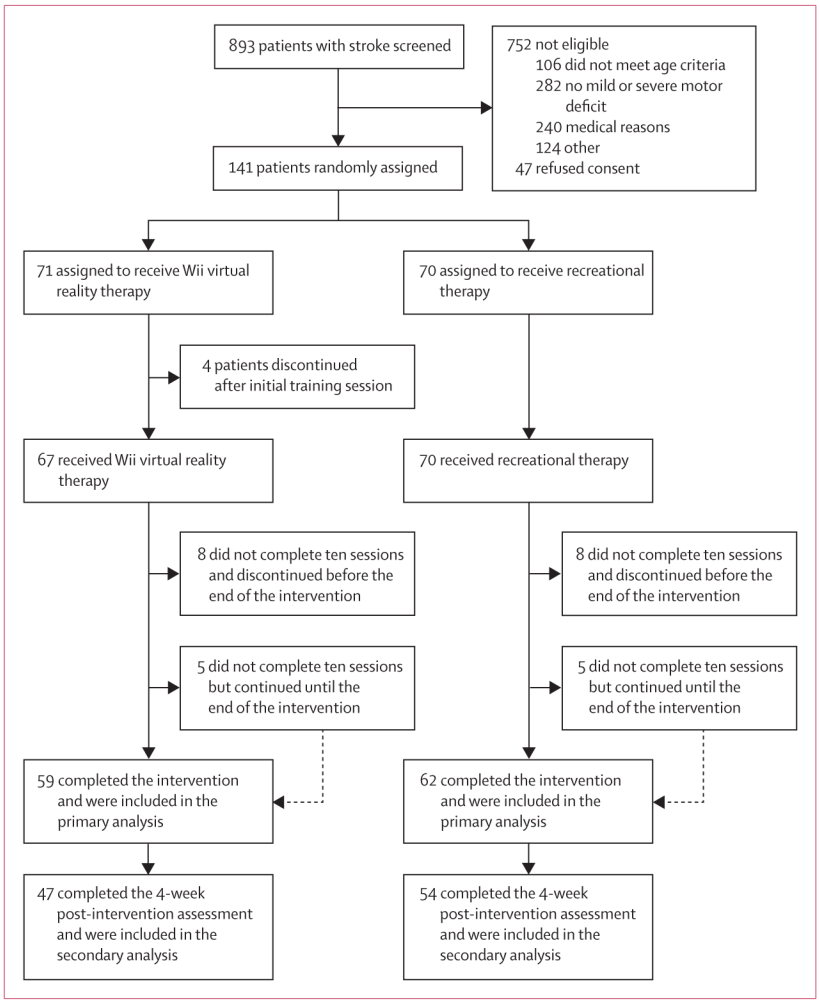

Figure 1.
Trial profile

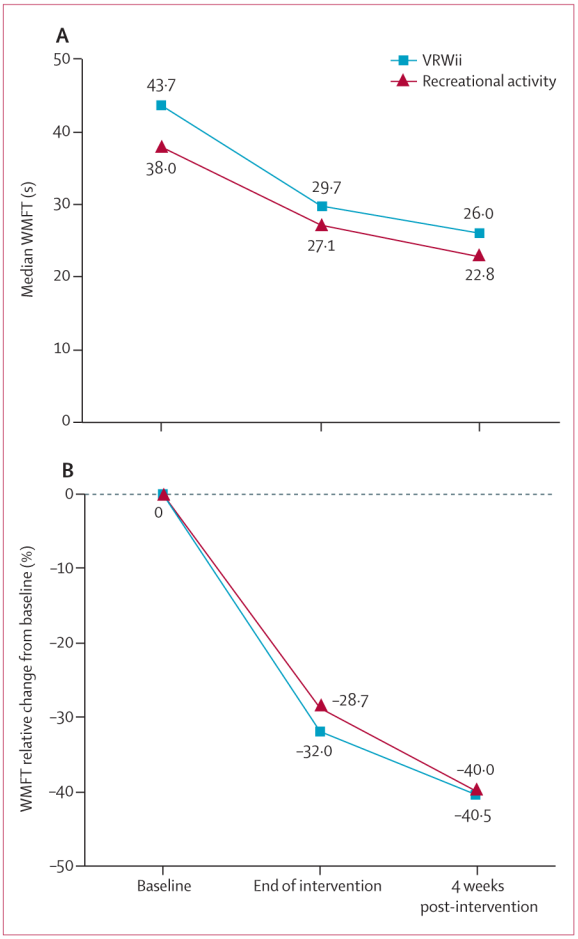

Figure 2. Median motor performance time (A) and change in motor performance (B) from baseline to the end of the intervention and 4 weeks post-intervention as measured by the Wolf Motor Function Test (WMFT)

WMFT is expressed as unadjusted median time (s) (A) and as change (%) relative to baseline (B), with a decrease indicating improvement. There was no significant difference between groups at the end of the intervention (p=0·469) or 4 weeks post-intervention (p=0·346) after adjustment for age, sex, baseline WMFT, stroke severity, and Chedoke-McMaster scores. VRWii=non-immersive virtual reality Wii group.

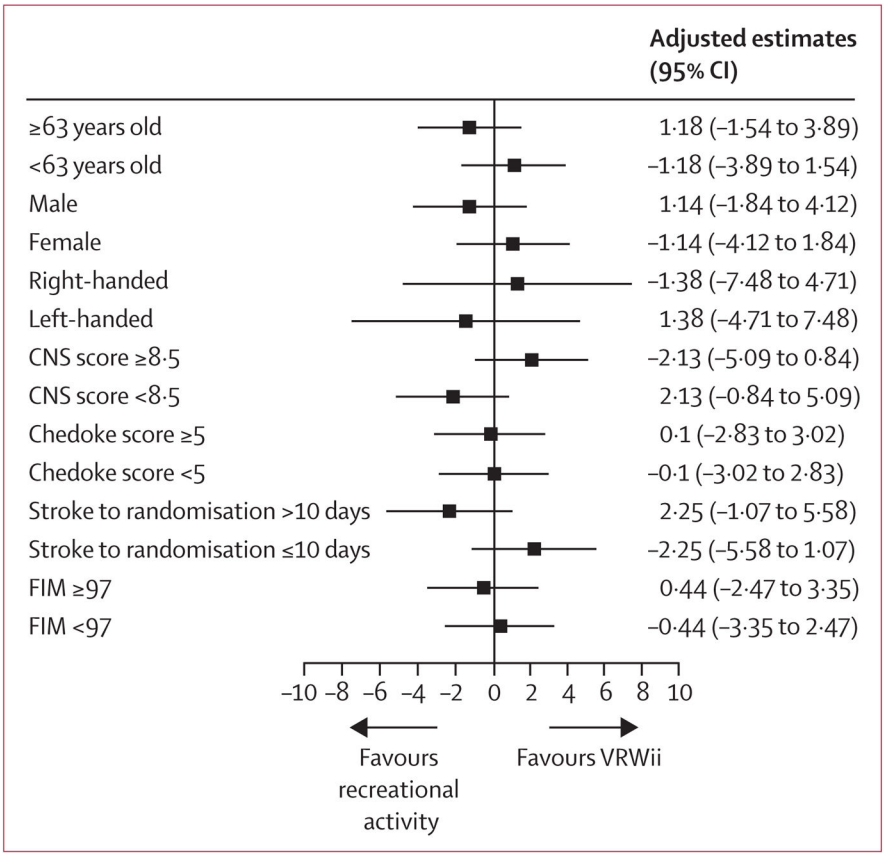

Figure 3. Subgroup analyses for Wolf Motor Function Test at the end of the intervention

None of the individual subgroup analyses had significant treatment-by-subgroup interactions (all p>0·05) after adjusting for age, sex, stroke severity, and Chedoke-McMaster scores (where relevant). CNS=Canadian Neurological Scale. fiM=Functional Independence Measure. VRWii=non-immersive virtual reality.

Table 1

Baseline demographic and clinical characteristics

	VRWii (n=71)	Recreational activity (n=70)
Age (years)	62 (13)	62 (12)
<55	19 (27%)	16 (23%)
56–69	34 (48%)	34 (49%)
≥70	18 (25%)	20 (29%)
Sex		
Male	46 (65%)	48 (69%)
Female	25 (35%)	22 (31%)
Handedness		
Ambidextrous	1 (1%)	0
Left	6 (8%)	9 (13%)
Right	64 (90%)	61 (87%)
Stroke severity (Canadian Neurological Scale)	8·5 (1·4)	8·5 (1·6)
Co-morbidities		
Hypertension	58 (82%)	48 (69%)
Diabetes	33 (46%)	27 (39%)
Coronary artery disease	15 (21%)	8 (11%)
Dyslipidaemia	42 (59%)	42 (60%)
Atrial fibrillation	11 (15%)	14 (20%)
Current smoker	12 (17%)	16 (23%)
Stroke subtype		
Lacunar	31 (48%)	31 (46%)
Non-lacunar	33 (52%)	36 (54%)
Affected side		
Left	36 (51%)	39 (56%)
Right	35 (49%)	31 (44%)
Chedoke-McMaster score	4 (3–5)	5 (4–5)
Modified Rankin Scale		
0–2	33 (46%)	27 (39%)
3–5	38 (54%)	43 (61%)
Hospital Anxiety and Depression Scale		
Anxiety score	5 (1–7)	5 (2–9)
Depression score	3 (1–7)	4 (2–8)
Days from onset to randomisation	27·0 (9·0–52·5)	24·5 (10·0–41·0)
Median duration of conventional rehabilitation during the study (min)	330 (95–543)	358 (120–555)

	VRWii (n=71)	Recreational activity (n=70)
Mean duration of conventional rehabilitation during the study (min)	373 (322)	397 (345)
Median duration of intervention (min)	595 (550–600)	600 (573–600)
Mean duration of intervention (min)	528 (155)	541 (142)

Data are n (%), mean (SD), or median (IQR) unless otherwise stated. VRWii=non-immersive virtual reality Wii group.

Table 2

Baseline, end of intervention, and 4 weeks post-intervention outcome measures, by treatment group

	VRWii (n=71)		Recreational activity (n=70)		Between group difference*	
	Baseline	Follow-up	Baseline	Follow-up	Adjusted coefficient estimate (95% CI)†	Adjusted p value†
Primary outcome						
WMFT total time (s)‡						
Mean (SD)	91·9 (122·3)	64·1 (104·0)	68·4 (101·2)	39·8 (35·5)	4·1 (−14·4 to 22·6)	0·469
Median (IQR)	43·7 (26·1–68·0)	29·7 (21·4–45·2)	38·0 (28·0–64·1)	27·1 (21·2–45·5)		
Secondary outcomes						
WMFT total time (s)§						
Mean (SD)	91·9 (122·3)	45·5 (51·3)	68·4 (101·2)	50·6 (120·7)	−14·2 (−52·0 to 23·7)	0·346
Median (IQR)	43·7 (26·1–68·0)	26·0 (18·0–40·5)	38·0 (28·0–64·1)	22·8 (17·4–36·6)		
BBT (mean number of blocks)						
End of the intervention	22·9 (14·4)	27·2 (15·5)	24·2 (14·2)	30·9 (13·2)	−3·4 (−6·1 to −0·7)	0·018
4 weeks post-intervention	22·9 (14·4)	30·5 (17·7)	24·2(14·2)	33·1 (15·3)	−2·7 (−7·3 to 1·8)	0·299
Barthel Index						
End of the intervention	64·7 (22·4)	83·4 (18·0)	64·2 (23·0)	80·3 (21·7)	3·5 (−2·3 to 9·3)	0·295
4 weeks post-intervention	64·7 (22·4)	90·2 (13·8)	64·2 (23·0)	89·3 (16·0)	0·8 (−4·3 to 6·0)	0·774
Functional independence measure						
End of the intervention	95·7(19·0)	108·8 (16·2)	92·6 (19·9)	106·1 (17·6)	0·9 (−3·4 to 5·2)	0·735
4 weeks post-intervention	95·7 (19·0)	113·6 (13·0)	92·6 (19·9)	111·7 (15·1)	0·8 (−3·9 to 5·5)	0·848
SIS hand function						
End of the intervention	13·0 (6·4)	17·0 (6·5)	13·2 (5·6)	18·0 (6·1)	−1·2 (−2·9 to 0·7)	0·314
4 weeks post-intervention	13·0 (6·4)	18·5(6·0)	13·2 (5·6)	20·4 (5·3)	−2·1 (−4·2 to −0·0)	0·074
SIS S16						
End of the intervention	88·7 (25·5)	104·0 (21·6)	83·1 (22·6)	101·6 (23·4)	−2·2 (−8·5 to 4·1)	0·494
4 weeks post-intervention	88·7 (25·5)	112·8 (20·0)	83·1 (22·6)	112·6 (21·3)	−2·8 (−10·2 to 4·5)	0·514
SIS perception of recovery						
End of the intervention	58·3 (22·8)	66·0 (21·3)	52·8 (18·6)	67·1 (16·5)	−4·4 (−10·9 to 2·2)	0·252
4 weeks post-intervention	58·3 (22·8)	70·5 (19·2)	52·8 (18·6)	71·6 (15·5)	−2·3 (−8·5 to 4·0)	0·352

	VRWii (n=71)		Recreational activity (n=70)		Between group difference*	
	Baseline	Follow-up	Baseline	Follow-up	Adjusted coefficient estimate (95% CI)†	Adjusted p value†
Grip strength (kg)						
End of the intervention	11·5(9·8)	14·8 (10·3)	15·4 (9·4)	17·9 (9·8)	0·2 (−1·8 to 2·3)	0·713
4 weeks post-intervention	11·5 (9·8)	15·9 (10·1)	15·4 (9·4)	17·8 (9·6)	1·2 (−1·4 to 3·7)	0·358

Data are mean (SD) or median (IQR) unless indicated otherwise. VRWii=non-immersive virtual reality Wii group. WMFT=Wolf Motor Function Test. BBT=Box and Block Test. SIS=Stroke Impact Scale (SIS hand function includes five items of the SIS 2.0; SIS perception of recovery represents the final question of the SIS 2.0 on how the patient feels recovered from stroke [scale 0–1]). SIS S16=outcome measure from the SIS based on factor analysis capturing strength, hand function, mobility, activities of daily living, and instrumental activities of daily living.

*Means unless otherwise specified; median values are also provided for the WMFT due to the skewed distribution of the data.

†Adjusted estimates after controlling for age, sex, treatment group, baseline Chedoke-McMaster score, stroke severity, and baseline measure (WMFT, SIS, BBT, Barthel Index) as appropriate.

‡End of intervention.

§4 weeks post-intervention.

Table 3

Safety outcomes

	VRWii (n=71)	Recreational activity (n=70)
Adverse events		
Dizziness	10 (15%)	12 (17%)
Light-headedness	6 (9%)	8 (11%)
Nausea	4 (6%)	4 (6%)
Pins and needless	10 (15%)	10 (14%)
Numbness	19 (28%)	33 (47%)
Muscle aches	18 (27%)	29 (41%)
Back pain	30 (45%)	33 (47%)
Fatigue (post-intervention)	38 (57%)	44 (63%)
Headache	9 (13%)	13 (19%)
Other	10 (15%)	10 (14%)
Serious adverse events		
Death	0	0
Stroke	0	1 (2%)
Heart attack	1 (2%)	0
Seizures	0	1 (2%)
All	1 (2%)	2 (3%)

Data are n (%). VRWii=non-immersive virtual reality Wii group.