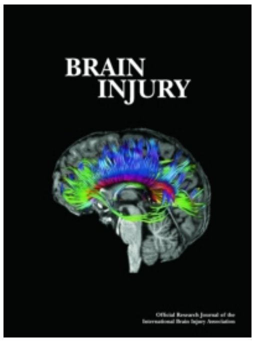

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Virtual reality therapy for upper limb rehabilitation in patients with stroke: a meta-analysis of randomized clinical trials

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ABSTRACT

Background: Stroke is a major cause of life-long disability in adults, associated with poor quality of life. Virtual reality (VR)-based therapy systems are known to be helpful in improving motor functions following stroke, but recent clinical findings have not been included in the previous publications of meta-analysis studies.
Aims: This meta-analysis was based on the available literature to evaluate the therapeutic potential of VR as compared to dose-matched conventional therapies (CT) in patients with stroke.
Methods: We retrieved relevant articles in EMBASE, MEDLINE, PubMed, and Web of Science published between 2010 and February 2019. Peer-reviewed randomized controlled trials that compared VR with CT were included.
Results: A total of 27 studies met the inclusion criteria. The analysis indicated that the VR group showed statistically significant improvement in the recovery of UL function (Fugl-Meyer Upper Extremity [FM-UE]: n = 20 studies, Mean Difference [MD] = 3.84, *P* = .01), activity (Box and Block Test [BBT]: n = 13, MD = 3.82, *P* = .04), and participation (Motor Activity Log [MAL]: n = 6, MD = 0.8, *P* = .0001) versus the control group.
Conclusion: VR appears to be a promising therapeutic technology for UL motor rehabilitation in patients with stroke.

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Stroke; stroke rehabilitation; virtual reality therapy; upper limb

Introduction

Stroke

Stroke is one of the leading causes of mortality and the most prominent cause of life-long adult disability (1). In recent years, there is a remarkable decline in stroke-related mortality because of accessibility to various options of acute stroke treatment, for example, recanalization therapy (2), decompressive therapies (3), and stroke unit management (4). However, neurologically impaired individuals living with considerable disabilities have dramatically increased (5). Of those, few may regain some functional use of the upper limbs (ULs) (6), which seriously affects self-care and societal participation. As most activities of daily living involve the ULs, it is crucial to improve UL functional use post-stroke.

Current clinical practice for UL rehabilitation relies on promoting neuroplasticity following brain injury (7,8). Neuroplasticity, after a brain injury, can be defined as the ability of the brain reorganizing itself by forming new neural connections in the adjacent normal tissue of the lesioned hemisphere or in the non-lesioned hemisphere to take over the lost function (9). To maximize the effect of brain plasticity, training should be learning-based, repetitive, challenging, motivating, and intensive (9,10). Conventional therapies including occupational and physical treatment help patients to improve the UL motor deficits following brain injury (11–13). However, these approaches are time consuming, tedious and outcomes often depend on the ability of medical staff. Also, repetition, intensity, and dose in conventional rehabilitation settings are reported to be insufficient to achieve plasticity-based optimal motor recovery (14). The limitation of conventional rehabilitation settings motivated the introduction of new types of efficient therapeutic approaches. Virtual reality therapy is deemed as one such therapy (7,15,16).

Virtual reality

Virtual reality (VR) is an advanced form of computer-simulated environment that allows a user to "interact" with objects and environments within the rendered virtual scenario (14), which now becomes an emerging treatment option for motor function rehabilitation post-stroke (16). In this computer-generated world, the user may receive visual feedback (virtual environments and objects) via a head-mounted device, flat screen, or projection system. In addition, the

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Supplemental data for this article can be accessed here

user may also receive other types of auditory and haptic feedback through hearing and touching, respectively. Conventional input devices such as a keyboard, mouse, trackball, and joystick or more complex systems such as cameras and sensors allow users to interact with the virtual environments.

VR therapy systems

VR-based rehabilitation therapy systems may be classified as (1) "off-the-shelf" commercial video gaming console (CVGC) and (2) custom-built virtual environment (CBVE). The CVGC systems such as Nintendo Wii or Xbox Kinect are motion-controlled VR gaming consoles and were originally designed for recreation (14). Because the CVGC systems are easy to use, enjoyable, inexpensive, and readily available, many clinicians and researchers have turned to use them as an adjunct to standard rehabilitation for UL training (8,17,18). Studies have confirmed that CVGC therapy systems encourage high intensity and repetitions, which are a key factor in neuroplasticity, and patients may thereby improve their UL functional use (19). Despite the potential utility of CVGC systems as a therapeutic tool for patients with stroke, a number of drawbacks have been identified (20) such as: they are typically designed for healthy persons, which is, in turn, excessively challenging for patients with stroke; the levels of task difficulty are not readily adjustable to the needs and capabilities of patients; and it does not integrate multiple environmental factors that may have positive impacts on UL functional recovery. CBVE systems, on the other hand, are usually designed in close collaboration with clinicians and other researchers to enhance the patient's sense of presence, to provide patient-centered training, to provide an automatic data recording system of patient movements, and to reduce excessive use of unwanted compensatory movements (21–23). In general, CBVE therapy systems provide several features such as repetition, intensity, increasing difficulty, motivation, and multiple exercise options that are helpful to speed up the recovery of UL motor deficits following stroke (7,24).

Evidence of VR therapy in stroke rehabilitation

Many clinical trials have investigated the efficacy and mechanisms of VR therapy over Conventional therapy (CT) and reported that the recovery of the ULs proceeded in parallel with brain plasticity and functional reorganization (25,26). An experimenter-blinded trial conducted by Jang and colleagues (25) revealed that after 4 weeks of VR intervention, patients got significant benefit in the recovery of UL motor deficits as assessed by FM-UE and BBT. This study, for the first time, explored the neural mechanisms of UL motor recovery following VR intervention using functional MRI (fMRI). They noticed that before the VR therapy, broader bilateral motor networks were activated; however, following the VR therapy, only the ipsilesional primary sensorimotor cortex was activated. Wang and colleagues (26) conducted a randomized controlled trial (RCT) to explore the effect of VR-based UL training as compared with dose-matched CT. They reported that the VR group showed statistically more significant improvement in UL activity performance than the control group as assessed by the Wolf Motor Function (WMF) (27). This study also reported a novel demonstration of training-induced cortical plasticity changes related to motor recovery using fMRI. The findings revealed that the VR group showed broader brain activation changes in the contralesional motor network than did the control group after 4 weeks of interventions.

Previous meta-analysis comparing VR and CT

Over the past few years, a considerable number of meta-analyses have been conducted to provide evidence for VR therapy as an adjunct to CT in the recovery of UL motor deficits post-stroke. In 2011, Saposnik and colleagues (14) conducted a meta-analysis of 5 randomized control trials (RCTs) and 7 observational studies from 1966 to July 2011. Meta-analyses of the 5 RCTs indicated that the VR group improved UL motor impairments better than did the control group as assessed by FM-UE. They did not find statistically superior results in the VR group to the control group in the recovery of UL activity limitation as measured by BBT. A meta-analysis of VR therapy following stroke by Lohse and colleagues (15) in 2014 on 26 RCTs aimed to conduct separated analyses of the three domains of the International Classifications of Functioning, Disability, and Health (ICF) (28): (1) Body function and structure, (2) Activity, (3) Participation. They reported that patients treated by VR showed significant improvements across the three levels of ICF domains compared with the control group. They also conducted subgroup analyses to address the different effectiveness of CBVE- and CVGC-based therapy systems for UL motor recovery, although no statistically significant difference between CBVE and CVGC therapies was observed across the three levels of ICF domains. However, this study did not examine the impact of the potential factors that may affect the effectiveness of VR therapies over the control treatments such as initial severity of the UL, training dose, and length of therapy sessions. In 2017, Laver KE and colleagues (16) presented an updated Cochrane review of 72 RCTs published in 2011 and 2015. They concluded that the use of CBVE and CVGC had no superior impact on the use of CT in the recovery of upper limb function. Maier and colleagues (29) conducted a systematic meta-analysis that investigated the efficacy of CBVE and CVGC therapy systems versus CT in the recovery of UL function and activity post-stroke. They reported that the CBVE therapy systems had statistically superior impacts on body function and activity than did the CT, whereas the CVGC therapy systems did not.

Overall results in the recent meta-analysis were considerably variable. The major source of variability may be due to the inconsistency of therapy protocols: frequency, intensity, and dose; VR therapy systems: CBVE or CVGC; characteristics of study participants: stage of stroke recovery and initial severities. Furthermore, the results were mostly reported in composite measure. For instance, while the study originally reported two activity outcomes using two different evaluation scales, a review of the work may have averaged the two activity outcomes to provide a single outcome point (15,16). Hence, many researchers and healthcare professionals may be confused about which clinical scale to use for assessing UL motor recovery following VR therapy in stroke survivors.

There are only a few large RCTs on VR. New evidence in support of either VR therapies are or are not superior need to be collected and studied, perhaps by looking at various subgrouping strategies according to chronicity, total amount of intervention, and ICF levels (body structure/function level, activity level, and participation level). Therefore, the objectives of this meta-analysis are to: (1) evaluate the overall effectiveness of VR therapies compared to conventional therapies in the recovery of UL functions across the three ICF domains; (2) explore the impact of total amount of intervention and stage of stroke recovery that might be related to the effectiveness of VR therapies over conventional therapies across the three ICF domains; and (3) identify the frequently used outcome measures for each of the three ICF domains.

Methods

This study was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). It is to be noted that the study protocol was not registered.

Criteria for considering studies for this meta-analysis

Randomized control trials

The main inclusion criteria were RCTs (published in the English language) that assigned patients to a VR group to receive VR therapy or to a control group to receive a dose-matched CT. We excluded trials that compared two VR groups without a control condition. We did not include trials that primarily measured lower limbs. In addition, review articles, letters, editorials, and case reports were excluded from this meta-analysis.

Eligible participants

Eligible study participants were adults (older than 18 years) with a clinical diagnosis of stroke confirmed by computed tomography or MRI. Study participants were not filtered in terms of time post-stroke (acute/subacute or chronic), types of stroke (ischemic or hemorrhages), lesion locality (cortical or subcortical), or levels of initial UL severity (mild, moderate, or severe). Study participants were excluded if they had a previous stroke or comorbidities, or if they were children.

Types of UL therapies

We included studies that used CBVE and CVGC (8,18,30). We excluded studies that used a “hybrid” approach such as combining VR with robotics or approaches involving electrical augmentation (such as functional electrical stimulation, transcranial magnetic stimulation). The control group may receive conventional therapy (CT, physical and/or occupational therapy).

Outcome measures

We aimed to include studies based on the three ICF domains (Body Structure and Function, Activity, Participation). Multiple outcome measures from each comparable study were extracted and organized according to the three ICF domains (supplementary information, Table S2). Hence, we selected one outcome measure that was the most frequently occurring across the studies in each ICF domain, which turned out to be the FM-UE (31), BBT (32), and MAL (33). Therefore, we excluded a study if none of the three scales was employed in it.

The FM-UE measure was proposed to evaluate impairments in UL motor function (31). It comprises 33 items with a total score of 66 points (range: 0–66), such that the lower the score, the more severe of motor dysfunction. The BBT measure (32) was developed to assess the UL activity limitation of neurologically impaired populations such as patients with stroke. During the assessment, a patient is instructed to pick up and put small blocks from one portion to the other portion of a box using the UL that is relatively more severely affected. MAL is a structural interview used to evaluate the UL participation restriction. A patient is instructed to evaluate how much and how well the affected UL is used during a variety of daily activities (33). It rates on a 6 point scale ranging from 0 to 5. The lower the score, the weaker of the UL; and the higher the score indicates the better recovery of the UL.

Many differences exist across studies regarding classification of the BBT and MAL outcome measures. For instance, Laver et al (2015) classified BBT as body function outcome measure and MAL as participation (34). In their updated Cochrane review (2017) (16), they have classified BBT and MAL as body function. Meta-analysis conducted by Anna et al (2018) and Lohse et al (2014) classified BBT as activity outcome measurement and MAL as participation outcome measurement (15,35). A recent meta-analysis conducted by Maier et al (2019) classified BBT as activity outcome measurement (29). Based on these growing evidence, we classified BBT and MAL as a gold standard outcome measure for assessing the effect of VR therapy on activity and participation outcome measure, respectively.

Electronic databases and search strategy

Studies exploring the effects of VR therapies versus conventional therapies in UL motor recovery following stroke were searched in EMBASE, MEDLINE, PubMed, and Web of Science, which are the scientific literature databases that are most popularly used in the research community. Included trials were full-text articles in English published between 2010 and March 2019. Keywords used to identify potentially relevant articles were: stroke, after stroke, post-stroke, stroke rehabilitation, hand, arm, upper limb, upper extremity, virtual reality, virtual, augmented reality, and video game.

Study identification and data extraction

We searched published articles from each computerized database (EMBASE, MEDLINE, PubMed, and Web of Science) and identified the relevant articles by titles and abstracts. After removing duplicate articles, the remaining articles underwent full-text screening and were ranked as relevant or irrelevant according to the inclusion criteria. Then, we excluded all trials ranked as irrelevant. Finally, the remaining relevant articles underwent data extraction. Two reviewers (D.B.M and J.H.) extracted the following information: contents of therapies

(Table S1); characteristics of study participants, therapy schedule, and outcome measures (Table S2).

Data analysis

Quality assessments

The individual study quality was evaluated using the Physiotherapy Evidence Database (PEDro) scale (36). This scale comprises the following publication bias-reducing items: method of randomization, adequacy of allocation concealment, baseline group comparability, blindness of outcome assessor, blindness of patients and caregivers, incomplete outcome reporting rate, intention to treat analysis, availability of group comparison key outcome report, and availability of both mean scores and standard deviations. Hence, the authors scored the quality of trials using the individual PEDro bias-reduction items as "1" when a trial met the criteria and "0" when a trial did not meet the criteria.

Dealing with missing data

All articles were analyzed on a per-protocol basis. We did not contact the authors to retrieve their unpublished findings.

Quantitative analysis

Post-therapy mean scores, their precision (standard deviations), and group size for each comparable trial were entered into RevMan software version 5.3.5. Pooled results were estimated by calculating the mean difference (MD) with 95% confidence intervals (CI). In the data collection, some studies (21,22,37–39) reported findings in terms of median, minimum, maximum, and/or interquartile range (IQR), and we estimated the mean values and standard deviations following the method proposed by (40). Heterogeneity between trials was assessed using the I^2 statistic. When significant heterogeneity between trials existed (I^2>50%), the random-effect model was applied to pool trial results for outcomes FM-UE, BBT, and MAL; and when low heterogeneity was observed between trials (I^2 <50%), the fixed effect model was applied. Forest plot graphics were generated to present the pooled effect. All tests are two sided, and *P*-value <0.05 was considered to be statistically significant.

Subgroup analysis

We also performed subgroup meta-analyses by subdividing the studies according to time post-stroke (41)**:** subacute stage (within 6 months) versus chronic stage (more than 6 months); and total amount of intervention (16)**:** less than 15 h of intervention versus more than 15 h of intervention. While Bernhardt and colleagues' work (41) classified the time frame of stroke recovery as acute (within 7 days of onset of stroke), subacute (from 1 week of stroke onset to 6 months) and chronic phase (more than 6 months of stroke onset), our strategy merged acute into subacute to take all the work in our collection into consideration consistently.

Results

Flow of studies through review

As described in the method section, four computerized databases were used for searching potentially relevant published articles (Figure 1). The search strategy provided a total of 3,784 records. After removal of duplication, 2,405 studies were further screened based on their titles and contents in the abstracts. After the full-text screening, 27 randomized control trials met the inclusion criteria. All these studies targeted UL motor recovery, comparing VR versus dose-matched CT.

Characteristics of study participants

The included studies contained 1,094 participants; 555 of them were randomized to the experimental group to receive VR therapy plus CT if applicable and the remaining 539 participants were randomized to the control group to receive CT. The mean age of participants was 63.48 (SD = 12.47) years. Twelve studies (7,8,17,18,21,23,24,30,42–45) recruited patients in the subacute phase of stroke (range: 0.43–5.7 month); fourteen studies (22,37,38,46–56) recruited patients in the chronic phase of stroke (range: 6.11–51 months; Table S1). One study did not report the patients' recovery stage (39).

Quality assessment and publication bias

The quality of the individual trials judged by the review authors using the PEDro bias-reduction items is presented in supplementary Table S3. The overall quality of the included studies was high (average total PEDro score of 6.29). All trials properly reported eligibility criteria, method of randomization, outcome analysis between groups, and mean scores and standard deviations. Most studies reported outcome assessor blindness (23 studies, 85.18%), group comparability at baseline (22 studies, 81.48%), drop-out rate less than 15% participants (20 studies, 74.07%), adequacy of allocation concealment (13 studies, 48.14%), and intent-to-treat analysis (11 studies, 40.74%). Given the nature of the trials being studied, both participants and caregivers were not naive to the experimental or control therapy.

The content of VR and CT therapies

Of the 27 included studies, 21 used CBVE therapies and the remaining six studies used CVGC therapies. Most of the CBVE therapies involved a video capturing system, which required the patients to be seated facing a video camera while performing the task, which was typically reach-to-grasp exercises such as one that used the rehabilitation gaming system (7), YouGrabber (24), or RehabMaster (22,23). The CVGC therapy systems included Nintendo Wii and Xbox Kinect, which required patients to hold an interface device (8) or not hold any interface device but use an infrared camera to track the UL movements (30). Most of the included studies provided "conventional therapy" for both groups (VR and control). In some studies, the conventional therapy was mentioned as usual care (39), standard rehabilitation (7,52), or conventional rehabilitation program (18,30), which basically emphasized their nature of physical or occupational therapy.

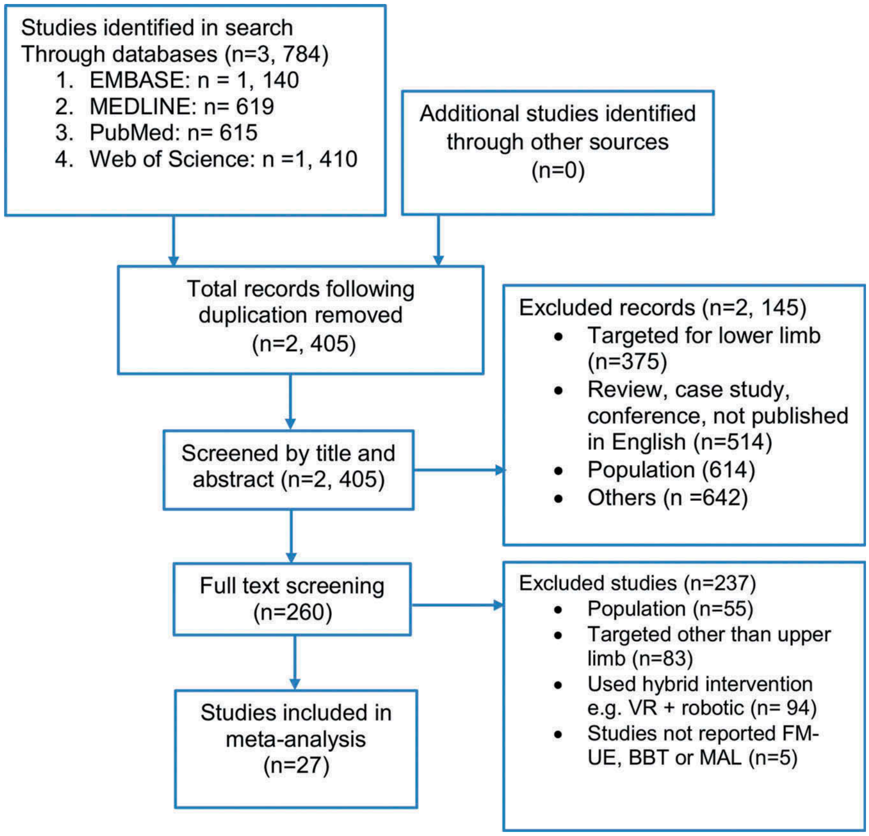

Figure 1. Flowchart of our study screening procedure.

Total amount of intervention

Nineteen studies (7,8,17,18,21–24,37,44,46,48–53,55,56) providing less than 15 h of VR therapy (mean [SD] = 9 [2.8] hours) and the remaining 8 studies (30,38,39,42,43,45,47,54) providing more than 15 h of VR therapy (mean [SD] = 24.25 [12.85] hours).

Meta-analysis at post-therapy

FM-UE meta-analysis

When analyzing the overall FM-UE outcomes, the VR group showed significantly more improvement in the recovery of UL functionality than did the control group (20 studies, MD = 3.84,

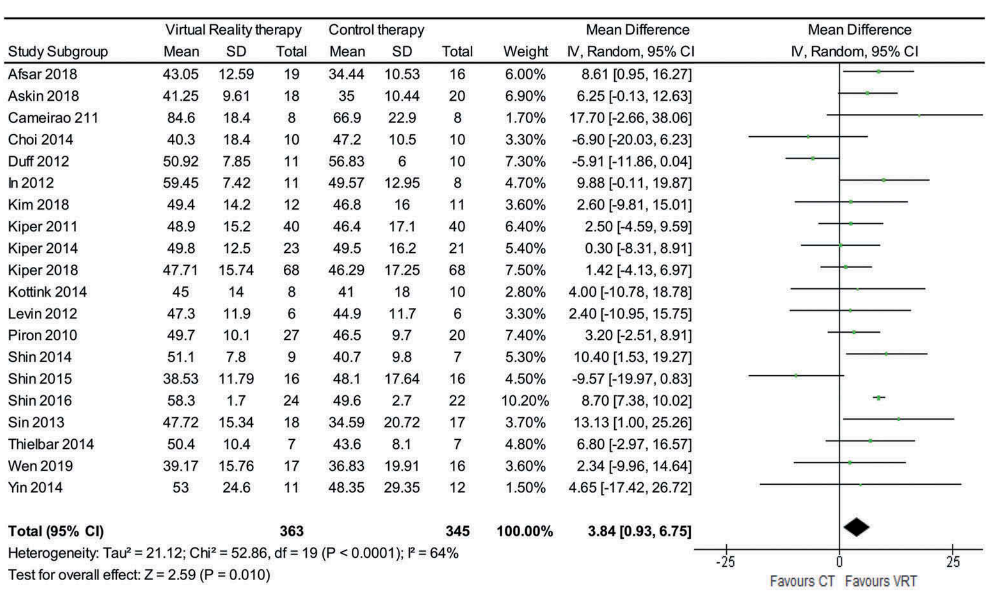

Figure 2. Forest plot of FM-UE outcome. A pooled result favoring VRT indicates positive values, and favoring CT indicates negative differences between VRT and CT. Note: VRT = Virtual reality therapy, CT = Conventional therapy.

VRT = Virtual reality therapy, CT = Conventional therapy

95% CI = 0.93 to 6.75, P = .01, Figure 2). Heterogeneity was considerably high (I^2 = 64%).

BBT meta-analysis

When analyzing the overall BBT outcomes, the VR group showed significantly more improvement in the recovery of UL activity limitation than did the control group (13 studies, MD = 3.82, 95% CI = [0.26 to 7.38], P = .04, Figure 3). Heterogeneity was considerably high (I^2 = 53%).

MAL meta-analyses

Only six trials with 124 participants examined the participation restriction outcome. When analyzing the MAL amount of use outcomes, VR-based treated patients showed significantly more improvement on the MAL scale than did the CT group (MD = 0.8, 95% CI = [0.44 to 1.15], P = .0001, I^2 = 0%, Figure 4). Because of inadequate statistical power in this group of samples, we were unable to pool subgroup analysis.

Subgroup analyses

Stage of stroke recovery. We subdivided studies based on whether their participants recruited within 6 months (subacute) or more than 6 months (chronic) post-stroke. Patients with subacute stroke demonstrated significant improvements in the recovery of UL functional impairment (FM-UE: 9 studies; MD 3.72; P = .03; Supplementary Figure S3 upper panel), but chronic patients had non-significant improvements (FM-UE: 11 studies; MD 3.76; P = .08; Supplementary Figure S3 lower panel). The BBT subgroup meta-analysis showed no significant effects neither studies recruited patients with subacute stroke (6 studies; MD 3; P = .26; Supplementary Figure S4 upper panel) nor patients with chronic stroke (7 studies; P = .07; Supplementary Figure S4 lower panel).

Total amount of intervention. We compared studies delivering less than or equal to 15 h of VR intervention versus those more than 15 h of VR intervention. In the studies delivering less 15 h of intervention, the VR group did not show significant improvements in the recovery of UL functional impairment (FM-UE: 14 studies; MD 4.11; P = .06; Supplementary Figure S1 upper panel) and activity limitation (BBT: 11 studies; MD 2.98; P = .13; Supplementary Figure S2 upper panel) when compared with the control group. Whereas in the studies delivering more than 15 h of VR intervention, the VR group showed statistically significant improvements in the recovery of UL functional impairments (FM-UE: 6 studies; MD 3.21; P = .02, Supplementary Figure S1 lower panel)

	Virtual Reality therapy			Control therapy				Mean Difference
Study Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Afsar 2018	28.53	11.15	19	20.81	10.03	16	9.90%	7.72 [0.70, 14.74]
Askin 2018	19.75	18.94	18	10	10.17	20	7.20%	9.75 [-0.07, 19.57]
Brunner 2017	26	18.7	62	25	19.1	58	10.20%	1.00 [-5.77, 7.77]
Choi 2014	26.6	17.5	10	14.3	8.8	10	5.60%	12.30 [0.16, 24.44]
In 2012	16.91	9.76	11	16.29	10.55	8	7.70%	0.62 [-8.69, 9.93]
Kim 2018	13.2	12.5	12	15.6	15.1	11	6.10%	-2.40 [-13.79, 8.99]
Lee 2014	35.79	14.51	10	15.63	13.19	8	5.20%	20.16 [7.34, 32.98]
Levin 2012	30.3	27.7	6	23.9	21.2	6	1.50%	6.40 [-21.51, 34.31]
Saposnik 2016	27.2	15.5	71	30.9	13.2	70	12.50%	-3.70 [-8.45, 1.05]
Schuster 2018	24.43	16.09	22	20.17	22.25	32	6.90%	4.26 [-5.97, 14.49]
Sin 2013	20.67	14.38	18	16.29	11.7	17	8.20%	4.38 [-4.28, 13.04]
Türkbey 2017	32.5	11.53	10	24.78	10.31	9	7.20%	7.72 [-2.10, 17.54]
Zondervan 2016	2.3	6.2	9	4.3	5	8	11.80%	-2.00 [-7.33, 3.33]
Total (95% CI)			**278**			**273**	**100.00%**	**3.82 [0.26, 7.38]**

Heterogeneity: Tau² = 20.48; Chi² = 25.71, df = 12 (P = 0.01); I² = 53%
Test for overall effect: Z = 2.10 (P = 0.04)

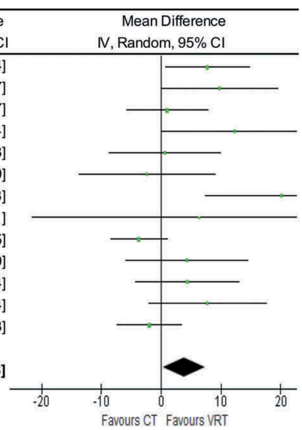

Figure 3. Forest plot of BBT outcome. A pooled result favoring VRT indicates positive values, and favoring CT indicates negative differences between VRT and CT. Note: VRT = Virtual reality therapy, CT = Conventional therapy.

VRT = Virtual reality therapy, CT = Conventional therapy

	Virtual Reality therapy			Control therapy				Mean Difference
Study Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Duff 2012	2.81	1.66	11	2.95	7.93	10	0.50%	-0.14 [-5.15, 4.87]
Levin 2012	1.08	1.12	6	1.65	1.87	6	4.20%	-0.57 [-2.31, 1.17]
Standen 2017	77.25	37.81	9	63.75	35.81	9	0.00%	13.5 [-20.52, 47.52]
Wen 2019	2.13	0.92	17	1.11	0.25	16	61.80%	1.02 [0.57, 1.47]
Yin 2014	2.23	3.22	11	2.29	3.09	12	1.90%	-0.06 [-2.64, 2.52]
Zondervan 2016	0.86	0.64	9	0.26	0.69	8	31.60%	0.60 [-0.04, 1.24]
Total (95% CI)			**63**			**61**	**100.00%**	**0.80 [0.44, 1.15]**

Heterogeneity: Chi² = 4.75, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.37 (P < 0.0001)

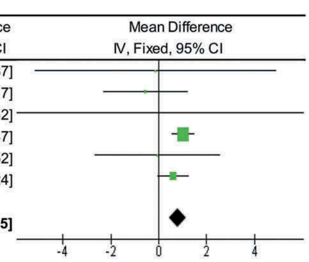

Figure 4. Forest plot of MAL outcome. A pooled result favoring VRT indicates positive values, and favoring CT indicates negative differences between VRT and CT. Note: VRT = Virtual reality therapy, CT = Conventional therapy.

VRT = Virtual reality therapy, CT = Conventional therapy and activity limitation (BBT: 2 studies; MD 8.74; P = .01; Supplementary Figure S2 lower panel) when compared with the control group.

Discussion

Summary

Rehabilitation following stroke is a fundamental component in any program that aims to restore an individual's ability to participate in normal life roles. Novel therapeutic approaches such as VR have been introduced to overcome the "modest" benefits of conventional therapies. A meta-analysis conducted in 2011 by Saposnik and colleagues (14) suggested that future practice for assessing the therapeutic potential of VR should include an evaluation of the three ICF domains. With this in mind, we screened 2,402 trials and identified 27 RCTs with good quality that involved 1,094 participants who met the inclusion criteria.

This study confirmed that VR-based therapy systems may have significant impacts on the recovery of UL functional impairment when the study participants were in the subacute phase of stroke or when the studies provided more than 15 h of therapy dose. In addition, patients may also benefit from VR in improving their UL activity limitation when they received a therapy dose of more than 15 h. VR also had a significant impact on improving participation restriction as assessed by the MAL outcome. Furthermore, this study also identified FM-UE, BBT, and MAL as the most frequently used gold standard outcome measures to evaluate the effect of VR therapies.

The overall FM-UE pooled effects revealed that recovery of the UL functional impairments in the VR group was superior to that in the control group with statistical significance. Our results are in accordance with the findings of two recent meta-analyses (14,16) which reported that the VR groups showed more improvements in FM-UE score compared with their respective control group.

The Meta-analysis of BBT revealed that patients treated by VR-based therapies achieved more UL activity performance improvement than patients treated by CT-based therapies. Our results differ from the earlier meta-analysis reported (14), in which Saposnik and colleagues did not find superior effects in the VR group compared to the CT group concerning the recovery of activity limitation. Because of the rapid advancements in VR technology, which can provide patient-centered, repetitive training, this meta-analysis has included a relatively larger number of studies than in the meta-analysis reported by Saposnik and colleagues (only three RCTs were pooled). Our results agree with the results reported in the recent meta-analyses (15,35), in which Lohse and colleagues (15) reported that regardless of the type of VR interventions (CBVE or CVGC), the VR group got significantly better improvement in recovery of the UL activity limitations than the control group.

The VR group showed statistically significant improvement in participation outcome compared with the control group. This finding differed from the earlier meta-analysis (15,35), in which the authors did not find a statistically superior impact of VR on participation outcome versus CT. This discrepancy may be due to the availability of one study, which is included in our meta-analysis (55). Due to the lack of adequate number of samples, we were unable to conduct subgroup meta-analysis of MAL with respect to total amount of intervention and stage of stroke recovery. Future studies are encouraged to administer the participation assessment as part of the standard outcome measure.

Subacute versus chronic stage

As to the FM-UE subgroup meta-analysis with regard to time post-stroke, our findings, based on nine comparable trials that initiated therapies in the subacute phase of stroke, confirmed that the VR group received statistically more improvement in UL functional impairments than did the control group. Although in 11 studies that initiated therapies in the chronic phase of stroke showed positive effects favoring the VR group, the observed effect was not statistically significant between the VR and control groups. Our findings support the recent knowledge in neuroplasticity-induced motor recovery (7). The fact that VR therapies are more effective in the recovery of UL function in subacute phases of stroke has been attributed to the fact that brain plasticity and cortical reorganization should typically be high within a few days or weeks after stroke onset (57) and reports have indicated that the recovery of the ULs proceeds in parallel with brain plasticity and functional reorganization (58). For the BBT subgroup meta-analysis, we did not find statistically significant differences between the VR and control groups, when VR therapy was administered in the subacute or in the chronic phase of stroke.

Total amount of intervention: higher versus lower VR therapy dose

The impact of using a higher dose of VR therapy (more than 15-h intervention) in the recovery of UL functional impairments and activity limitation had more positive effects than did the lower dose of VR therapy (less than 15-h intervention). These findings differed from the recent meta-analysis of VR studies (16,35). Laver and colleagues (16) reported that the impact of lower (less than 15 h) and higher (more than 15 h) dose of VR therapy has similar effect in the recovery of UL functional impairment with statistically significant than did the control group. Anna and colleagues (35) did not find a clear benefit of VR therapy dose in the recovery of UL functionality. This meta-analysis included relatively new articles (17,30,38,43,44,48,49,55,56), which have not been included in the previous studies. Overall, our results indicated that VR therapies may have a significant impact on the recovery of UL functional impairments and activity limitation better than did CT while studies providing more than 15 h of VR intervention. However, only 6 studies (6 versus 14 studies) providing more than 15 h of intervention while pooling the FM-UE outcomes and 2 studies (2 versus 11 studies) in pooling BBT results.

The added value of VR therapies on the recovery of UL functional impairments, activity limitations, and participation restrictions compared with CTs may be associated with multiple important factors. The first possible reason that may be attributed to the effectiveness of VR therapies may be related to providing multiple training options, in which the therapist can choose different types of UL therapy modes based on a patient's need and actual motor capabilities (8). VR systems may also allow creation of an individualized training program that could automatically adjust the training intensity and difficulty level to the patient's actual motor status (59). Most trials included in our meta-analysis incorporated graded training programs that aimed to induce optimal neural plasticity and continued active participation, which is necessary for achieving optimal motor recovery after brain injury (24). Therefore, flexibility in configuring a VR therapy system with multiple training options may be crucially important in the recovery of UL motor deficits after stroke.

The other possible reason that VR therapies may provide better effects may be associated with the multiple types of sensory feedback (e.g., visual, haptic, and auditory) that are concurrently available in VR therapy systems. Feedback can be classified as "intrinsic (inherent)" or "extrinsic (augmented)." Intrinsic feedback refers to an individual's inner representation of sensory information, including tactile, haptic, and proprioceptive information. This sensory representation may be impaired following a stroke (60). Patients with stroke are believed to benefit from practicing with augmented feedback (58). For instance, exercising based on slightly amplified movements may facilitate the learning rate of motor skills and recovery (59). All trials in this meta-analysis included visual feedback, which was not immersive in the sense of experiencing the reality of being in another world. Future studies encourage the use of head-mounted devices such as a VR goggle that may provide a strong sense of immersive presence and may increase the effect of motor training.

Limitation

This work has some limitations that should be taken into consideration when we interpret the effect of VR therapies in the recovery of UL functionality. One of the possible limitations would be the inclusion of a diverse stroke population with regard to stroke type (ischemic or hemorrhage), stroke locality (cortical or subcortical), level of initial UL severities (mild, moderate, or severe), and stage of recovery. Due to the small number of trials that were available, our analyses were unable to control for the impact of initial severity of stroke, stroke type, and locality on the effectiveness of VR therapy. The second limitation of this meta-analysis could be diverse therapies in the control group, which led to a variation in the comparison between the VR and control groups. Several of the included studies did not truly control the VR therapies by the CT in terms of frequency, intensity, level of task difficulty, motivation, and task specificity. For instance, in six studies (17,21,23,30,38,46), the VR group received a CBVE or CVGC therapy plus a CT, whereas the control group received a CT alone, without matching therapy frequency, intensity, and dose. In these studies, the VR group received significant benefits with respect to the ICF category; however, it remains unclear if the improvement was due to the additional time-training dose. The third potential limitation of this study is the diversity of VR therapy systems. We did not investigate the different effectiveness of CBVE- and CVGC-based therapy systems across the three ICF domains. A recent meta-analysis conducted by Martina et al 2019 (29) revealed that the use of CBVE-based therapy systems had more significant impacts on body functions and activities than did the CVGC. The fourth limitation of this meta-analysis was date of publication. Because of the rapid advancement in technology, a large number of older trials were excluded from this review, which might also lead to a selection bias.

Conclusion

Stroke rehabilitation is rapidly evolving. The use of VR therapies may help individuals improve UL functionality. Evidence from this meta-analysis suggests that VR has the potential to alleviate UL motor impairments and may encourage motor activities and societal participation. Subgroup analysis suggests that participating in VR training over an extended therapy time (more than 15 h of intervention) may be more advantageous compared to a shorter period of time for individuals with stroke to improve their UL motor impairments and activity limitation. Also, patients in the subacute phase of stroke may benefit from VR therapies more than patients in chronic phases of stroke. Finally, this meta-analysis suggests that the FM-UE, BBT, and MAL may be the gold standard clinical instruments for measuring the effect of VR therapy across the three ICF domains.

Author Contributions

Conceptualization: D.B.M., D.X., H.J. and A.W.R.; Methodology: D.B.M., A.W.R., D.X., H.J., J.H., L.Z., S.F. and J.Z.; Data extraction: D.B.M., L.Z., S.F. and J.H.; Formal analysis: D.B.M., D.X., J.H., H.J.; Writing—Original draft preparation: D.B.M., and D.X.; Writing—Review and editing: D.B.M., A.W.R., D.X., J.H., H.J., L.Z., S.F. and J.Z.; Supervision: D.X. and A.W.R., Fund acquisition: J.Z. and A.W.R.

Conflict of Interest

The authors declare no conflict of interest.

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