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The effect of interactive virtual reality on pain perception: a systematic review of clinical studies

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Purpose: The aim of this systematic review was to evaluate the effect of immersive and non-immersive interactive virtual reality on pain perception in patients with a clinical pain condition. **Methods:** The following databases were searched from inception: Medline (Ovid), PsychInfo, CINAHL, Cochrane library and Web of Science. Two reviewers screened reports and extracted the data. A third reviewer acted as an arbiter. Studies were eligible if they were randomized controlled trials, quasi-randomized trials, and uncontrolled trials. Crossover and parallel-group designs were included. Risk of bias was assessed for all included studies. **Results:** Thirteen clinical studies were included. The majority of studies investigated a sample of participants with chronic pain. Six were controlled trials and seven uncontrolled studies. Controlled research showed that interactive virtual reality reduces pain associated with ankylosing spondylitis and post-mastectomy, but results are inconsistent for patients with neck pain. Findings from uncontrolled studies showed that interactive virtual reality reduced neuropathic limb pain, and phantom limb pain, but had no effect on non-specific chronic back pain. **Conclusions:** There is not enough evidence upon which to judge the effectiveness of the use of virtual reality for the management of pain.

Keywords: Virtual reality, chronic pain, rehabilitation, interactive

INTRODUCTION

Chronic pain is a global healthcare problem and a financial burden to patients and healthcare services.[1] Although pharmacological interventions are still frequently the first line of treatment for chronic pain, the side effects and high costs are barriers for long-term use. Pain is a multimodal perceptual experience mediated by attention, cognition, emotion, expectation, motivation and memory.[2] The multimodal nature of pain has allowed clinicians to employ techniques, such as virtual reality (VR), to alter components of the painful experience in order to modulate the subjective experience of pain. For example, VR has been used to distract patients from painful procedures [3] and gradually expose patients to painful exercises.[4] VR can also be used to reduce the threat associated with moving a body part by augmenting the visual feedback of movement, such that a small motion of the real body part produces an amplified or reduced motion of a virtual body.[5] Most recently, virtual representation of body parts has been used to create the illusion of a healthy, functional limb and reduce pain and perceptual disturbances in painful and dysmorphic limbs.[6]

VR involves the generation of a virtual environment by computerized software, which can be delivered to the individual via a head-mounted display or computer screen.[7] When using a head-mounted display, the experience is considered immersive and when the virtual environment is presented on a flat screen (e.g., computer screen) the experience is considered non-immersive.[8] Immersive and non-immersive VR has been used to distract patients from acute pain. Chan et al. [3] meta-analyzed data from 16 clinical trials and found that VR as a distraction is effective in reducing pain during medical procedures such as burn wound care and intravenous cannulation.

Recently, the development of portable and affordable motion tracking systems have broadened the use of VR in the rehabilitation of patients with pain. Motion tracking systems allow for movements of a virtual body (i.e., avatar) to be controlled by movements of the user's real body, resulting in an interactive experience. For example, Karahan et al. [9] found that a course of eight weeks of VR treatment using the Xbox 360 Kinect, a motion-tracking technology primarily developed for games and entertainment, was effective in the rehabilitation of patients with ankylosing spondylitis (an inflammatory condition that predominantly affects the spine causing pain and disability). More complex technologies involve the use of infrared cameras and sensors attached to participants' bodies.[10] Recently, Ortiz-Catalan et al. [11] used surface electrodes to record muscle

activation over the stump whilst the amputee attempted to drive a virtual car using muscles of the stump. The authors reported phantom limb pain reduction after 12 treatment sessions.[11] These isolated cases suggest that interactive VR may be effective for reducing clinical pain but that this may be dependent on the clinical condition and type of VR intervention used. A systematic review of the literature to evaluate the efficacy of interactive VR interventions and treatment protocols would be valuable to inform clinical practice and the design of future studies. Thus, the aim of this systematic review was to evaluate the effect of immersive and non-immersive interactive VR on pain perception in patients with a clinical pain condition.

METHODS

Data source and search methods

Guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement were used.[12] The computerized databases Medline (Ovid), PsychInfo, CINAHL, Cochrane library and Web of Science were used to search for relevant studies. Searches were performed between 9th and 16th of July 2018 (from the date of inception of each database) using a combination of controlled vocabulary (i.e., medical subject headings) and free-text terms. Search strategies were modified to meet the specific requirements of each database (Medline search strategy can be found in supplementary material). A hand search of reference lists of included studies and previously published systematic reviews was also conducted.

Criteria for considering studies and study selection

Studies investigating participants with clinical pain and using interactive VR were included. Virtual reality intervention was considered interactive when a motion tracking system was used in order to allow the participant to use their own body movements to control those of a virtual object or avatar in real time. Studies were eligible if they were randomized controlled trials, quasi-randomized trials, and uncontrolled trials. Crossover (within-subject) and parallel-group (between-subject) designs were included. Studies that utilized VR as a non-interactive distraction, to induce relaxation, or hypnosis, were excluded. A published full text of the study was required. Case studies, reviews, theses, and abstracts were excluded. Studies were excluded when measures of effect of intervention were not statistically analyzed or data were not available. Two reviewers (PGW and JB) screened titles and abstracts obtained from the searches (carried out by JB, OC and SY) to identify potentially relevant studies, and then screened full reports of studies against the eligibility criteria. A third reviewer (DML) acted as arbiter.

Data synthesis and quality assessment for primary studies

The information extracted from studies included: study design, sample size, treatment characteristics, control group characteristics, pain outcome measures, and results.

We planned to conduct a meta-analysis if there were more than two studies using similar outcome measures and the data were available. For the meta-analysis, the mean difference and 95% confidence intervals would be calculated using a random effects

model in studies with parallel groups and for studies with multiple comparison groups, where control groups would be combined creating a single pairwise comparison.[13] Furthermore, data from cross-over trials would be analyzed as standardized mean difference using the generic inverse-variance random effects model. The standard error of the standard mean difference would be calculated imputing a correlation coefficient calculated from raw data when available, and when not available the correlation coefficient from a study with similar design and comparisons would be used. A sensitivity analysis was planned when imputing a correlation coefficient, as instructed in the Cochrane Handbook for Systematic Reviews of Interventions.[13] If analyses resulted in a significant effect ($p \leq 0.05$) the standard mean difference would be interpreted according to Cohen's d effect size, in which less than 0.2 is considered small, between 0.3 and 0.5 small to medium, between 0.6 and 0.8 moderate to large, and more than 0.8 large.[14] If a meta-analysis was conducted we planned to assess heterogeneity between comparable trials using a standard Chi^2 test and I^2 statistics. When data were not available or more details about studies were needed, the corresponding author of each study was contacted.

For randomized controlled trials risk of bias was assessed using The Cochrane Collaboration's assessment tool.[13] This consisted of assessment of selection bias, attrition bias, blinding, and sample size. For studies with a within-subject repeated measures design the Cochrane Collaboration's assessment tool was used but adapted to account for differences in the design (i.e., the random sequence generation was analyzed for the order of presentation of conditions and control for crossover effects). For studies with a single group pre-test post-test design the tool used was the Quality Assessment of Before-After (Pre-Post) Studies developed by the National Heart, Lung, and Blood Institute.[15]

RESULTS

The search found 2,071 records, of which 587 were duplicates and 1,484 were screened by title and abstract. Ninety-nine studies were potentially relevant and full reports obtained and screened. Eighty-six studies were excluded with reasons. Thirteen studies met the eligibility criteria and were included for review (figure 1).

[Insert figure 1 here]

Characteristics of included studies

Thirteen studies (469 participants) were included for review (table 1 and 2). Five were randomized controlled trials, one was a non-randomized controlled trial, six were single group pre-test post-test without a control group comparison and one was a within-subject repeated measures design study. The randomized controlled trial conducted by Sarig Bahat et al. [16] was divided into two phases and the two phases are reported separately. Three studies evaluated participants with neck pain [5, 16, 17], three studies evaluated participants with phantom limb pain [18, 19, 20], and two studies evaluated participants with chronic back pain.[10, 21] Two studies evaluated participants with neuropathic pain [22, 23], one study evaluated participants with ankylosing spondylitis [9], one study evaluated participants post-mastectomy and one study evaluated participants with subacromial impingement syndrome and scapular dyskinesis.[4] Mean age of participants ranged from 23.9 ± 6.8 years to 54.9 ± 11.8 years. Majority of studies included participants with pain duration of more than 3 months with mean pain duration ranging from 5.5 ± 4.92 years to 26.86 ± 35.92 years. Only one study included a sample of participants with acute pain (i.e., post-mastectomy).[24] Four studies did not report pain duration.

[Insert table 1 here]

[Insert table 2 here]

Treatment Characteristics

The VR intervention was delivered using head-mounted displays in five studies (immersive) and a flat screen in eight studies (non-immersive). One study used the Xbox

360 Kinect to track movements of participants' bodies.[9] Two studies used the Wii controller to track movements of participants' upper limbs.[4, 24] Participants controlled movements of an avatar via motion tracking devices attached to participants' bodies in three studies.[10, 21, 23] In the three studies investigating participants with neck pain, movements of the head were tracked by accelerometers attached to the head-mounted display.[16, 17] Movements of virtual limbs were controlled by movements of the non-affected limb in three studies investigating phantom limb pain [19, 20, 22] and by the affected limb in one study.[18] Treatment frequency and duration of interventions varied between studies from one 10-minute session for phantom limb pain [19], to five 30-minute sessions per week for eight weeks for ankylosing spondylitis.[9]

Quality assessment

The randomized controlled trials had low risk of bias associated with random sequence generation.[4, 9, 16, 17, 21] Five randomized controlled trials and the non-randomized controlled trial had high or unclear risk of bias associated with blinding the participants [4, 9, 16, 21, 24] and four had high or unclear risk of bias associated with blinding the assessor.[4, 9, 24] Sample size calculation was reported in only one randomized controlled trial (table 3).[21] There was not enough information upon which a risk of bias judgment could be made regarding allocation concealment for the study with a within-subject repeated measures design; the study presented low risk of bias in all other criteria (table 3).[5]

Quality assessment of pre-test post-test studies indicated flaws associated with specification and description of inclusion criteria,[10, 18, 19, 20, 22] blinding of participants and outcome assessor,[10, 18, 19, 20, 22, 23] and an absence of sample size calculations (table 4).[10, 18, 19, 20, 22, 23] Sample sizes were small and between 8 [19] and 24 participants.[5] Outcome measures of interest were taken multiple times before the intervention and multiple times after the intervention in only two studies.[18, 23]

[Insert table 3 here]

[Insert table 4 here]

Effects of interventions

A meta-analysis could not be conducted due to differences in study designs and types of controls. When data could be pooled, effect sizes of comparisons within studies are reported. When data could not be pooled a descriptive synthesis is presented.

Pain was reduced post-VR intervention in 13 out of 14 comparisons. There were four active control comparisons and pain was reduced post-intervention in all four instances. There were four no-intervention control comparisons and pain was reduced in the post-intervention measurements in one instance.

Two randomized controlled trials [16, 25] investigated the use of a VR intervention to treat neck pain. There was a significant small to moderate effect in favor of VR post-intervention and at 3-month follow-up on the second phase of the randomized controlled trial conducted by Sarig Bahat et al. [16] (SMD: -0.47; 95%CI: -0.69, -0.25 and SMD: -0.26; 95%CI: -0.50, -0.02). There were no differences in pain intensity between the VR group and the no-intervention control group or the active control group in phase one of the study conducted by Sarig Bahat et al. [16] and the randomized control trial conducted by Sarig Bahat et al. [25]. The randomized controlled trial investigating 60 participants with ankylosing spondylitis showed that exergames, such as table tennis and bowling, delivered as VR interventions using full body movements tracked by Xbox 360 Kinect significantly reduced pain with a moderate to large effect size compared with a no-intervention control (SMD: -0.67; 95%CI: -1.02, -0.32) [9]. Pekyavas and Ergun [4] conducted a randomized controlled trial investigating 30 participants with subacromial impingement syndrome and scapular dyskinesis and found no differences between the virtual intervention using Wii exergames and kinematic exercises for pain intensity at rest, during movement, and at night.[4] The randomized controlled trial investigating 52 chronic low back pain participants found no differences in pain scores between a VR intervention involving a game of dodgeball, and the no-intervention control.[21] The non-randomized controlled trial investigating 77 breast cancer survivors post-mastectomy showed that an intervention using Wii exergames significantly reduced pain with a moderate to large effect size compared with a no-intervention control (SMD: -0.75; 95%CI: -1.16, -0.34).[24]

Harvie et al. [5] used a within-subject repeated measures design to investigate 24 participants with neck pain and found that overstating and understating visual-proprioceptive feedback of neck rotation had no effect on pain intensity. The authors found that pain-free range of motion was increased by 6% when the visual feedback of rotation was understated. A pre-test post-test study without a control investigating 10 participants with low back pain found no pain reduction post-virtual exergame

intervention using a whole-body motion tracking device.[10] Five pre-test post-test studies without a control investigated limb pain (e.g., neuropathic pain, phantom limb pain and complex regional pain syndrome) and the intervention involved the use of virtual representation of body parts, in which the affected (2 studies) or unaffected (3 studies) limb controlled movements of the virtual limb. In all five studies the intervention alleviated pain with the mean decrease in pain intensity post-intervention relative to baseline ranging from 32% [18] to 39.1%.[19]

Side effects of intervention

Four participants experienced motion sickness with the use of the head-mounted display and were excluded or withdrew from the randomized controlled trial conducted by Sarig Bahat et al. [25]. In the follow-up randomized controlled trial conducted by Sarig Bahat et al. [16] there were five drop-outs due to VR associated motion sickness and headache. In the pre-test post-test study without a control conducted by Villiger et al. [23] there was one report of transient musculoskeletal pain in the participant's leg due to increased use during the VR intervention sessions. It was stated that patients did not experience adverse reactions from the intervention in two studies.[9, 21] There was no mention of adverse reactions in any of the other reports.

DISCUSSION

This systematic review included 13 clinical studies of which five were randomized controlled trials. However, a meta-analysis could not be conducted due to differences in intervention, sample characteristics and controls. Findings from controlled research suggest that interactive virtual reality (VR) may reduce pain associated with ankylosing spondylitis and post-mastectomy, but results from studies including participants with neck pain are inconsistent. Findings from uncontrolled studies suggest that interactive VR may reduce neuropathic limb pain, and phantom limb pain, but has no effect on non-specific chronic back pain. These findings should be interpreted carefully due to high risk of bias and small sample sizes.

From seven studies with a control group or condition, only two successfully blinded the participants [5, 17] and three successfully blinded the outcome assessor.[5, 16, 17] None of the six studies with a single group pre-post-test design blinded the outcome assessor. The difficulties of blinding participants and outcome assessors when using VR interventions have been discussed previously.[26] Blinding of participants and outcome assessor is extremely important, as it is known that lack of blinding is associated with a risk of biasing outcomes especially in studies with more subjective outcomes, such as pain perception.[13, 27, 28] From the 13 included studies, only two presented sample size calculations, which is critical in determining the number of participants necessary to provide sufficiently high power to detect clinically meaningful treatment effects.[29] Control interventions enable the measurement of effect size [30, 31], and from thirteen included studies, six were without controls.

The Cochrane collaboration recommends that interventions be compared with either inactive controls (e.g., placebo or no treatment), or with active controls (e.g., a different variant of the same intervention, or a different kind of therapy).[13] The six controlled trials included in our review presented a variety of controls: four active and four inactive controls. There was a reduction in pain intensity following all virtual reality interventions; and also following three out of four active control interventions, and in one no-intervention control. However, VR was superior to active controls in only one instance and to inactive controls (no-intervention) in two instances. It is possible that VR is not better than active control interventions for reducing pain intensity but it may be for other measures, such as reducing fear avoidance, improving adherence to treatments and enjoyment during therapy sessions (although there were no differences between groups

related to adherence to treatment between VR intervention and controls in included studies).[32] VR interventions may be more effective in treating other aspects of musculoskeletal conditions such as functionality and range of motion as they have an enhanced ecological validity by simulating realistic environments, in which performance can be tested and trained in a systematic fashion.[32] Future reviews of the literature should investigate the effect of interactive VR intervention on functional aspects of musculoskeletal painful conditions.

Although controls were missing in all five studies investigating the effect of virtual representation of body parts on neuropathic and phantom limb pain, pain was reduced in all five studies after VR intervention. It is suggested that the analgesic effect of virtual representation of body parts is similar to that of mirror visual feedback. During mirror visual feedback, the painful limb is hidden behind the mirror (out of view) whilst the non-painful limb is placed in front of the mirror so that the patient can observe a reflection of the non-painful limb such that it appears to be in the same position as the painful limb (which is out of view).[33, 34] Mirror visual feedback has been used to create the illusion of having a “healthy-looking” limb in individuals with phantom limb pain, complex regional pain syndrome and neuropathic pain. The mechanisms of action of mirror visual feedback are not fully elucidated but it is hypothesized that the view of a healthy-functional limb will promote sensory-motor congruence and correct disrupted mental representations of body parts by reducing dysfunctional cortical reorganization.[35, 36, 37, 38] Recent systematic reviews with meta-analyses indicate that mirror visual feedback is effective to reduce pain.[26, 39] Our findings indicate that virtual representation of body parts may be effective in the treatment of neuropathic and phantom limb pain; however, conclusive evidence can only be achieved by conducting randomized controlled trials where the effect of virtual representation of body parts can be compared with a suitable control intervention.

Frequency and time of exposure seem to be an important aspect of VR interventions especially when used to manage chronic pain. The included studies presented inconsistencies in the type, frequency, and duration of VR treatment with frequency and duration ranging from one 10-minute session for phantom limb pain [19], to five 30-minute sessions per week for eight weeks for ankylosing spondylitis.[9] It is possible that different types of techniques and conditions require a tailored protocol regarding frequency and duration of intervention. For example, Woods and Asmundson [40] found that graded exposure therapy during 8 sessions of 45 minutes reduces fear of movement in

patients with low back pain; but only 3 sessions of 15 minutes each were used in the study investigating the use of graded exposure via interactive VR to reduce fear of movement in patients with low back pain in the study conducted by Thomas et al. [21]. Further investigations into number and duration of sessions are required to include interactive VR in treatment and trial protocols.

An important aspect of interactive VR interventions is the use of immersive (i.e., virtual environment delivered via head-mounted display) and non-immersive (i.e., virtual environment delivered via computer screen) environments. Findings from studies included in this review indicate that there is no difference in efficacy whether it is delivered as an immersive or non-immersive VR intervention. However, side effects associated with the use of head-mounted displays, such as motion sickness, caused drop-outs and participants to be excluded from the trials conducted by Sarig Bahat et al. [16], [17]. Motion sickness and disorientation are reactions commonly associated with the use of head-mounted displays. There are specially designed questionnaires to measure motion sickness and these aspects should be carefully addressed during clinical practice and in future studies [41, 42].

CONCLUSIONS

There are many applications for the use of interactive VR for the rehabilitation of painful conditions. There is not enough evidence upon which to judge the effectiveness of the use of virtual reality for the management of pain. Results from controlled studies suggest that interactive VR may reduce pain associated with ankylosing spondylitis and pain post-mastectomy; but findings from studies including participant's with neck pain are inconsistent. Results from uncontrolled studies suggest that interactive VR interventions reduce neuropathic and phantom limb pain. However, more randomized controlled trials are needed before conclusive evidence can be achieved. In addition, more fundemental research is needed to understand mechanisms of action of the technique in attempt to optimize treatment protocols.

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Figure 1 Preferred reporting items for systematic review and meta-analysis flow diagram.

Table 1 Characteristics of the randomized and non-randomized controlled trials included in the review

Study and design	Clinical condition (total n)	Treatment characteristics	Control Group	Pain outcome measures	Pain Results
Sarig-Bahat et al. [25] RCT	Chronic neck pain (n = 32)	Movements of a virtual airplane was controlled by movements of participants' head. Participants moved their head to align the airplain with targets. Three modes of play: (1) Range of motion; (2) Velocity; (3) Accuracy. Nº sessions = 4-6 sessions (5 weeks) Duration each session = 15-20 min (plus 10-15 minutes of kinematic training without VR) Display = head-mounted n = 16, 40.63 ± 14.18 years, 11F, pain duration: 8.17 ± 8.07 years.	Active control: A laser pointer was mounted on the participant's head and projected onto a poster for feedback. Kinematic training involved active neck movements, quick head movement in-between targets, static head positioning while moving the body, and smooth head movement following a target. Nº sessions = 4-6 sessions (5 weeks) Duration each session = 30 min n = 16, 41.13 ± 12.59 years, 11F, pain duration: 7.27 ± 9.33 years.	Pain • Intensity VAS 100mm Measurement Timing • Pre-intervention • Post-intervention • Follow-up (3 months)	Pain intensity significantly reduced post-intervention in the VR group (mean change: 13.62 ± 17.23mm), but the effect was not maintained after 3 months. There were no significant differences in pain intensity at any time-point in the control group. There were no significant differences between groups.
Thomas et al. [21] RCT	Chronic low back pain (n = 52)	Participants controlled movements of an avatar. Movements of participants' whole body were tracked by infrared cameras and sensors attached to participants bodies. VR task: Play dodgeball against four avatars. Game involved blocking or avoiding the virtual ball thrown by the avatars. Nº sessions = 3 Duration each session = 15 min Display = 3D television (participants wore 3D glasses) n = 26, 23.9 ± 6.8 years, 12F, pain duration: NR.	No- intervention control n = 26; 26.7 ± 8.5 years; 13F, pain duration: NR.	Pain • McGill Pain Questionnaire (VAS 100mm, present pain index and pain rating index) Measurement Timing • Pre – one day prior to first intervention • Post – one day after last intervention	Significant reduction of pain intensity and present pain intensity post-intervention in both groups. No differences between groups.
Karahan et al. [9]	Ankylosing	Exergames delivered using Xbox 360 Kinect – games: (1) soccer, (2) table	No-intervention control n = 29, 36.6 ± 11.3 years, 23M,	Pain • Intensity VAS 10cm	Pain significantly reduced in the intervention group (mean

RCT	Spondylitis (n = 60)	tennis, (3) skiing, (4) tennis, (5) golfing, (6) volleyball, (7) bowling Nº sessions = 40 (5 days a week for 8 weeks) Duration each session = 30 min Display = Flat screen. n = 28, 36.1 ± 12.4 years, 24M, pain duration: 7.36 ± 4.51 years.	pain duration: 7.6 ± 3.95 years.	Measurement Timing • Pre intervention • Post-intervention	change 1.3 ± 1.4cm). No changes in pain intensity for control group. Pain was significantly reduced in the intervention group compared with the control group (SMD: -0.67; 95% CI: -1.02, -0.32; p = 0.0002).
Pekyavas and Ergun [4] RCT	Subacromial impingement syndrome and scapular dyskinesis (n = 30)	Exergames delivered using Wii. Games: (1) boxing, (2) bowling, (3) tennis. Resistance with Theraband was introduced from 2nd week. Nº sessions = 12 (6 weeks) Duration each session = 45 min Display = flat screen n = 15, 40.33 ± 13.20 years, 14F, pain duration: NR.	Active control Home exercise programme including posterior, anterior and inferior capsule stretching, pectoral muscle stretching, serratus anterior muscle strengthening, bilateral shoulder elevation, and scapular mobility exercises. Resistance with Theraband was introduced from 2nd week. Nº sessions = 12 (6 weeks) Duration each session = 45 min n = 15; 40.60 ± 11.77 years; 13F, pain duration: NR.	Pain • Intensity VAS 100mm (at rest, at night and during movement) Measurement Timing • Baseline • Post-intervention (6 weeks) • Follow-up (1 month)	Pain intensity at rest decreased at follow-up compared with baseline for the control group (mean change: 2.41 ± 0.83*mm). No statistical differences between groups. Pain intensity on movement decreased post-intervention (mean change: 3 ± 1.03*mm) and at follow-up (mean change: 4.16 ± 1.01*mm) compared with baseline for the control group. Pain intensity on movement decreased post-intervention (mean change: 5.85 ± 1.35*mm) and at follow-up (mean change: 5.85 ± 1.33*mm) compared with baseline for the VR group. No statistical differences between groups. Pain intensity at night decreased at follow-up (mean change: 2.58 ± 0.97*mm) compared with baseline for the control group. Pain intensity at night decreased post-intervention (mean

					change 4.65 ± 1.24*mm) and at follow-up (mean change: 4.65 ± 1.27*mm) compared with baseline for VR group. No statistical differences between groups.
Sarig Bahat et al. [16] RCT Phase 1	Chronic neck pain (n = 90)	Movements of a virtual airplane was controlled by movements of participants' head. Participants moved their head to align the airplane with targets. Three modules of play: (1) Range of motion; (2) Velocity; (3) Accuracy. N° sessions = 1st session 20 minutes in the clinic. 16 home sessions Duration each session = 5 minutes 4 times a day Display = head-mounted n = 30, median 48, Q1-Q3 38.5-857.5 years, 19F, pain duration: NR.	Active control: A laser pointer was mounted on the participant's head and projected onto a poster for feedback. Kinematic training involved active neck movements, quick head movement in-between targets, static head positioning while moving the body, and smooth head movement following a target. N° sessions = 1st session 20 minutes in the clinic. 16 home sessions Duration each session = 5 minutes 4 times a day n = 30, median 48, Q1-Q3 35.5-59 years, 21F No-intervention control: n = 30, median 48, Q1-Q3 35-59 years, 23F, pain duration: NR	Pain • Intensity during the past week VAS 100mm. Measurement Timing • Baseline • Post-intervention (4 weeks) • Follow-up (3 months) Measurement Timing No-intervention control group • Baseline • Post-intervention (4 weeks)	Pain intensity decreased post-intervention compared with baseline for VR group (mean change: 16.69 ± 17.41mm) and Laser group (mean change: 16.5 ± 16.71mm). No pain reduction on control gourp. No statistical differences between groups.
Sarig Bahat et al. [16] RCT Phase 2	Chronic neck pain (n = 32) 25 participants from phase 1 control group and 7 new participants randomised and allocated into VR or Laser group.	Same as phase 1 (n = 18)	Same as phase 1 (n = 14)	Pain • Intensity during the past week VAS 100mm. Measurement Timing • Baseline • Post-intervention (4 weeks) • Follow-up (3 months)	Pain intensity decreased at follow-up (mean change: 21.68 ± 17.21mm) and post-intervention (mean change: 21.28 ± 16.34mm) compared with baseline for VR group. Pain intensity decreased at follow-up (mean change:10.09 ± 18.06mm) compared with baseline for

					laser group. Pain intensity was lower in the VR group compared with the Laser group post-intervention (SMD: -0.47; 95%CI: -0.69, -0.25) and at follow-up (SMD: -0.26; 95%CI: -0.50, -0.02)
Aguirre-Carvajal and Marchant-Perez [24] Non-randomized controlled trial	Brest cancer patients after mastectomy (n = 77)	Sessions 1 and 2: Wii plane game – sitting with remote in ipsilateral hand, shoulder flexed at 90◦, elbow extended. Sessions 3 and 4: Wii wakeboard game – sitting with remote on both hands, sholders flexed and elbows extended. Session 5 and 6: Wii swords game – standing with Wii remote in ipsilateral hand, sholders and elbows flexed. Session 7 and 8: Wii Frisbee® game – standing, remote in ipsilateral hand, aduction and abduction of sholders with elbows flexed. Session 9 and 10: Wii Archery – standing with remote in ipsilateral hand, shoulder flexed at 90◦ and elbow extended. Nº sessions = 10 (3 times a week) Duration each session = 32 min Display = Flat screen n = 41, 57.66 ± 1.65 years, 41F	No-intervention control n = 36, 60.33 ± 2.51 years, 36F	Pain intensity • NRS (0-10) Measurement Timing • Pre (pre-operatory) • Baseline (day 7 post-surgery) • Post (30 days post-surgery)	Pain intensity significantly reduced post-intervention (day 30) compared with baseline (day 7) in the VR group (mean change: 1.99 ± 1.68). No significant difference on pain intensity for the control group. Pain was significantly reduced in the intervention group compared with the control group (SMD: -0.75; 95% CI: -1.16, -0.34).

Key: RCT, Randomised controlled trial; VR, virtual reality; VAS, visual analogue scale; NRS, numeric rating scale; NR, not reported; F, female; M, male; * standard error.

Table 2 Characteristics of studies with a within-subject repeated measures design and single group pre- post intervention studies included in the review

Study and design	Clinical condition (total n)	Treatment characteristics	Pain outcome measures	Pain Results
Jansen-Kosterink et al. [10] Single group pre-test post-test	Non-specific chronic back pain (n = 10; 54.9 ± 11.8 years; 8F, pain duration:NR)	Movements of participants' whole body were tracked by infrared cameras and sensors attached on a tight-fitting suit. Participant played PlayMancer exergame 3 minigames (1) walking on a treadmill to avoid virtual objects hitting the avatar; (2) climbing a rock face; (3) reproducing head movements shown by the avatar. Nº sessions = 4-8 sessions (4 weeks). Duration each session = 45-60 min. Display = Flat screen	Pain • Intensity VAS 100mm • Pain Disability Index (PDI) Measurement Timing • Pre-intervention • Post- intervention (4 weeks)	No statistical differences pre-post-intervention for pain intensity or PDI.
Villiger et al. [23] Single group pre-test post-test	Post-spinal cord injury neuropathic pain (n = 9; 52.71 ± 14.85 years; 9M; pain duration = 5.5 ± 4.92 years)	Participants used a virtual reality system with a first-person view of virtual lower limbs controlled via movement sensors fitted to the participants' shoes. Four tasks were used to deliver intensive training of individual muscles (tibialis anterior, quadriceps, leg ad-/abductors). The tasks engaged motivation through feedback of task success. Nº sessions = 6-20 (3-5 weeks) Duration each session = 45 min Display = flat screen.	Pain • Intensity – NRS • Unpleasantness – NRS Measurement Timing • Pre-baseline (4 to 6 weeks before intervention). • Baseline before intervention) • Post-intervention follow-up (12 to 16 weeks after last session).	Pain intensity significantly decreased. Percentage changes after treatment compared to baseline for pain intensity were 38.9% at post-intervention and 36.3% at follow-up. No significant differences on pain unpleasantness.
Harvie et al. [5] Within-subject repeated measures	Neck pain (n = 24; 45 ± 15 years; 18F; pain duration 11 ± 11 years; rage from 2 months to 45 years)	Visual-proprioceptive feedback of neck rotation modulated by tracking real-world movement and then feeding this back into the virtual environment in an understated or overstated form. Rotation gain (the factor by which real rotation is translated to virtual rotation) was manipulated such that virtual and physical rotation differ. Two conditions: (1) illusion of more movement (rotation) and (2) illusion of less (movement) rotation.	Pain • Intensity 11-point NRS • Pain-free range of motion (degrees) Measurement Timing • After each condition	No differences in pain intensity between conditions. During visual feedback that understated true rotation, pain-free range of motion was increased by 6% (95% CI = 2%, 11%); During visual feedback that overstated true rotation, pain-free range of

		Nº sessions = 1 Duration each session = N/R Display = head-mounted		motion decreased by 7% (95% CI = 3%, 11%).
Ortiz-Catalan et al. [18] Single group pre-test post-test	Phantom limb pain (n = 14; 50.3 ± 13.9 years; M/F not reported; pain duration = 10.3 ± 11.1 years)	Movement of the stump controlled the ipsilateral virtual limb. VR tasks involved: (1) practice motor execution in augmented reality; (2) gaming by racing car using phantom movements; (3) matching random target postures of a virtual arm in virtual reality. Nº sessions = 12 (2 per week for 6 weeks) Duration each session = 2 hrs Note: 1 participant received VR daily Display = computer screen	Pain • Intensity - NRS • Frequency - pain rating index • Duration - weigthed pain distribution. Measurement Timing • Before each session • Follow-up (1, 3, and 6 months after last session)	Significant improvements in all metrics of phantom limb pain. Phantom limb pain decreased from pre-treatment to the last treatment session by 47% for weighted pain distribution, 32% for intensity, and 51% for the pain rating index.
Osumi et al. [19] Single group pre-test post-test	Phantom limb pain (n = 8; 52.12 ± 6.66 years; 7M; pain duration = 20.12 ± 10.48 years)	Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. VR task involved reach and touch virtual target objects with the virtual phantom limb. Nº sessions = 1 Duration each session = 10 min Display = head-mounted	Pain • Intensity – NRS • Quality - short-form McGill pain questionnaire. Measurement Timing • Before and immediately after the intervention	Significant improvements in all metrics of phantom limb pain. 39.1% for NRS and 61.5% for short-form McGill pain questionnaire.
Ichinose et al. [20] Single group pre-test post-test	Phantom limb pain (n = 9; 53.89 ± 10.17 years; 8M; pain duration 17 ± 9.73 years)	Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. VR task involved reach and touch virtual target objects with the virtual phantom limb. Tasks were performed under 3 different conditions: (1) Cheek Condition - tactile feedback to the cheek when virtual limb touched a virtual object; (2) Intact Hand Condition – tactile feedback applied to the intact hand; (3) No Stimulus Condition - no tactile feedback. Nº sessions = 2-3 per day (2-4 days) Duration each session = 5 min	Pain • Intensity – NRS • Quality = short-form McGill pain questionnaire Measurement Timing • Before and immediatelly after each session	Significant pain reduction in the intact hand and the cheek condition. The median pain-reduction rate in the Cheek Condition (33.3 ± 24.4%) was significantly higher than in the Intact Hand Condition (16.7 ± 12.3%) and the No Stimulus Condition (12.5 ± 13.5%).

		Display = head-mounted.		
Mouraux et al. [22] Single group pre-test post-test	Neuropathic pain (combination of: CRPS, myelopathy, phantom limb pain and plexopathy) (n = 22; 49.31 ± 12.2 years; 10M; pain duration = 2.23 ± 2.99 years)	Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. VR task involved (1) reach and touch virtual target objects with the virtual affected limb. Nº sessions = 5 (1 week) Duration each session = 20 min Display = 3D display and participants used 3D glasses.	Pain • Intensity – VAS • Quality - McGill Pain Questionnaire Measurement Timing • Pain intensity measured before and after each session. • The McGill Pain Questionnaire was completed before the first session and 24 h after the last session.	There was an improvement in pain between the beginning and the end of each session, and this pain reduction was partially preserved until the next session. The mean improvement of pain intensity per session was 29%. There was a significant decrease of pain of 37% between baseline and 24h after the last session. There was a significant decrease on ratings on the McGill Pain Questionnaire.

Key: VAS, visual analogue scale; VR, virtual reality; NRS, numeric rating scale; CRPS, complex regional pain syndrome; F, female; M, male.

Table 3 Risk of bias of controlled trials and within-subject repeated measures design studies assessed using The Cochrane Collaboration's assessment tool.[13]

Study	Random sequence generation	Allocation concealment	Incomplete outcome data	Blinding (Participant)	Blinding (Assessor)	Sample size calculation	Crossover effect
Controlled trials							
Sarig-Bahat et al. [25]	🟢	🟢	🟢	🟢	🟢	🔴	NA
Thomas et al. [21]	🟢	🟢	🟢	🔴	🔴	🟢	NA
Karahan et al. [9]	🟢	🟢	🟢	🟡	🟡	🔴	NA
Pekyavas and Ergun [4]	🟢	🟡	🟢	🟡	🟡	🟡	NA
Sarig Bahat et al. [16]	🟢	🟢	🟡	🟡	🟢	🔴	NA
Aguirre-Carvajal and Marchant-Perez [24]	🔴	🔴	🟢	🟡	🟡	🔴	NA
Within-subject repeated measures design study							
Harvie et al. [5]	🟢	🟡	🟢	🟢	🟢	🟢	🟢

Key: Green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias; N/A, not applicable

Table 4 Quality assessment of studies with a single group pre-post-test design using the Quality Assessment of Before-After (Pre-Post) Studies developed by the National Heart, Lung, and Blood Institute.[15]

Criteria	Jansen-Kosterink et al. [10]	Villiger et al. [23]	Ortiz-Catalan et al. [18]	Osumi et al. [19]	Ichinose et al. [20]	Mouraux et al. [22]
1. Was the study question or objective clearly stated?	Y	Y	Y	Y	Y	Y
2. Were eligibility/selection criteria for the study population pre-specified and clearly described?	Y	Y	Y	N	N	Y
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Y	Y	Y	Y	Y	Y
4. Were all eligible participants that met the pre-specified entry criteria enrolled?	CD	Y	CD	CD	CD	CD
5. Was the sample size sufficiently large to provide confidence in the findings?	CD	CD	CD	CD	CD	CD
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Y	Y	Y	Y	Y	Y
7. Were the outcome measures pre-specified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Y	Y	Y	Y	Y	Y
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	N	N	N	N	N	N
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	N	Y	Y	Y	Y	Y
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Y	Y	Y	Y	Y	Y
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e. did they use an interrupted time-series design)?	N	Y	Y	N	N	N
12. If the intervention was conducted at a group level (e.g. a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA	NA	NA	NA

Key: Y: yes; N: no; CD: cannot determine; NA: not applicable.