Article:
Wittkopf, PG, Lloyd, DM orcid.org/0000-0003-3589-7383 and Johnson, MI (2019) Managing limb pain using virtual reality: a systematic review of clinical and experimental studies. Disability and Rehabilitation, 41 (26). pp. 3103-3117. ISSN 0963-8288

https://doi.org/10.1080/09638288.2018.1485183

Managing limb pain using virtual reality: a systematic review of clinical and experimental studies.

Running head: Virtual reality for pain management

Article category: Review

Authors

Priscilla G. Wittkopf[1], Donna M. Lloyd[2], Mark I. Johnson[1]

[1] Centre for Pain Research, Leeds Beckett University, Leeds – UK.

[2]School of Psychology, University of Leeds, Leeds – UK.

Address for correspondence

Priscilla Wittkopf

Centre for Pain Research, School of Clinical and Applied Sciences, Leeds Beckett University

City Campus, Leeds LS1 3HE, United Kingdom

Telephone: +44 113 2025114

e-mail: p.wittkopf@leedsbeckett.ac.uk

Declaration of interest: The authors report no declaration of interest. Priscilla Wittkopf is funded by the Science without Borders program from CNpq Brazilian government.

Word count: 4002, Tables: 5, Figures: 1

ORCID Mark I. Johnson http://orcid.org/0000-0002-9421-9622

ORCID Priscilla G. Wittkopf http:// orcid.org/0000-0002-2957-6156

ORCID Donna M. Lloyd http://orcid.org/0000-0003-3589-7383

ETHICAL APPROVAL: N/A

ACKNOWLEDGEMENTS: None

Managing limb pain using virtual reality: a systematic review of clinical and experimental studies.

The aim of this systematic review was to assess the effect of virtual representation of body parts on pain perception in patients with pain and in pain-free participants exposed to experimentally-induced pain. **Methods:** Databases searched: Medline, PsychInfo, CINAHL, and Web of Science. Studies investigating participants with clinical pain or those who were pain free and exposed to experimentally-induced pain were analyzed separately. **Results:** 18 clinical studies and 7 experimental studies were included. Randomized controlled clinical trials showed no significant difference between intervention and control groups for pain intensity. Clinical studies with a single group pre-test post-test design showed a reduction in pain after intervention. In the studies including a sample of pain free participants exposed to experimentally-induced pain there was an increase in pain threshold when the virtual arm was collocated with the real arm, when it moved in synchrony with the real arm, and when the color of the stimulated part of the virtual arm became blue. Observing a virtual arm covered with iron armor reduced pain. **Conclusions:** The use of virtual representations of body parts to reduce pain is promising. However, due to the poor methodological quality and limitations of primary studies, we could not find conclusive evidence.

Key-words: pain; virtual reality; rehabilitation; experimental pain, embodiment

INTRODUCTION

Virtual reality enables individuals to be immersed in a multisensory 3-dimensional environment where users can interact with virtual objects. The virtual environment is generated by computerized software and delivered to the individual via a head-mounted head-set to generate a 3-dimensional visual experience. The head-set includes a motion-tracking device such that movements of the head in the virtual reality environment are congruent with movements of the head in the real world, facilitating an experience of bodily-self immersion.[1] A motion tracking system can also be used to track movements of the user's real limb in order to control movements of a virtual limb. There is increasing use of virtual reality technology in pain management, and studies have found that response to clinical pain and experimentally-induced pain varies when individuals are immersed in different virtual reality environments.[2]

Clinically, virtual reality can be used to distract attention away from acute pain and/or painful procedures, such as wound dressing changes. Recently, Kenney and Milling [3] meta-analyzed data from 14 studies and concluded that distraction using virtual reality alleviated pain and was more effective for adults compared with children. Virtual reality can also be used to provide contexts that reduce perceived threat. Immersion in a pleasant virtual environment has been shown to reduce pain, anxiety, and depression, and improve relaxation and mindfulness skills in patients with fibromyalgia.[4] Virtual reality may also provide corrective psychological and physiological environments.[5] For example, virtual reality can be used to generate augmented motion environments such that a small motion of the real body produces an amplified motion of a virtual body.[5] Harvie et al. [6] used virtual reality to amplify or reduce the visual appearance of neck rotation of participants with neck pain and found pain occurred with less rotation of the neck when visual feedback overstated the magnitude of real neck rotation. Participants were able to rotate the neck further before experiencing pain if visual feedback understated the real neck rotation. Virtual representation of body parts has also been used to provide a corrective re-embodiment of painful dysmorphic body parts. For example, Osumi et al. [7] used motion-tracking technology with individuals with phantom limb pain so that movements of their intact arm generated movements of a contralateral virtual arm that appeared over their phantom limb. Participants were instructed to touch virtual objects with the virtual representation of their limb and this was found to reduce pain and improve feelings of agency.

Recently, Dunn et al. [8] have reviewed the use of virtual representation of body parts in the treatment of phantom limb pain and concluded that there is only limited evidence to show that the technique may offer some immediate relief of pain, and insufficient data to establish a clear protocol for these interventions. Dunn et al. [8] did not evaluate the effect of virtual representation of body parts in other painful conditions known to produce disrupted perceptions, such as complex regional pain syndrome, or the outcome of studies that induced experimental pain in healthy pain-free participants. The findings of experimental studies are valuable because they enable investigators to control many of the confounding variables that influence pain experience in the clinical setting, and are often used as a precursor to clinical trials and to investigate the factors that influence treatment response.[9] For example, Nierula et al. [10] found that healthy pain-free participants reported higher pain thresholds and a stronger sense of embodiment towards a virtual arm collocated with their real arm compared with displacing the virtual arm 30 cm away from the body midline.

Virtual representation of body parts is a new approach to pain management. Findings from clinical studies using various types of patients and studies investigating pain-free participants exposed to experimentally-induced pain may offer insights into factors influencing response including optimal treatment protocols. A systematic review that evaluates the efficacy of virtual representation of body parts and treatment protocols would be valuable to inform the design of future studies. Thus, the aim of this systematic review was to assess the effect of virtual representations of body parts on pain perception in patients with pain and in pain-free participants exposed to experimentally-induced pain. The effects of virtual representation of body parts were compared against control conditions. A pre-post intervention comparison was conducted for studies with a no control condition.

METHODS

Data source and search methods

Guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement were used to develop the protocol of this systematic review.[11] The computerized databases Medline, PsychInfo, CINAHL, and Web of Science were used to search for relevant studies. Searches were performed between 1 and 13 August 2017 (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 supplementary material). Hand search of reference lists of included studies and previously published systematic reviews were also conducted.

Criteria for considering studies and study selection

Studies investigating participants with clinical pain, or those who were healthy and exposed to experimentally-induced pain were included. Studies using a virtual representation of any body part in a first person perspective were included. There were no restrictions regarding type of painful condition or participant's age. Studies that investigated virtual reality as a distraction, relaxation, gaming or hypnosis were excluded. A published full text of the study was required. Reviews, thesis, and abstracts were excluded. All types of study designs were included. Two reviewers (PGW and MIJ) screened titles and abstracts obtained from the searches 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 studies investigating participants with a clinical pain condition and the studies investigating pain-free participants exposed to experimentally-induced pain were analyzed separately. Information extracted from included studies was: study design, sample size, treatment characteristics, experimental conditions, type of experimental pain, pain outcome measures, embodiment measures and results.

We planned to conduct a meta-analysis on studies investigating participants with a clinical pain condition and the studies investigating pain-free participants exposed to experimentally-induced pain. Data would be pooled for analysis if there were more than

two studies using similar outcome measures and the data were available. The mean difference and 95% confidence intervals would be calculated using a random effects model in studies with parallel groups. Studies with multiple comparison groups would be included combining the control groups creating a single pairwise comparison.[12] Data from cross-over trials and pre-test post-test designs 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 and to allow comparisons between parallel groups and cross-over studies a correlation coefficient would be imputed for both. Correlation coefficients would be 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 planed when imputing a correlation coefficient, as instructed in the Cochrane Handbook for Systematic Reviews of Interventions. [12] 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.[13] We planned to assess heterogeneity between comparable trials using a standard Chi^2 test and I^2 statistics.

For randomized controlled trials risk of bias was assessed using The Cochrane Collaboration's assessment tool.[12] It consisted of assessment of selection bias, attrition bias, blinding, and sample size. For clinical 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.[14] For experimental studies the Cochrane Collaboration's assessment tool was used but adapted to account for differences in the design (i.e., for studies with a repeated measures design the random sequence generation was analyzed for the order of presentation of conditions and control for crossover effects).

RESULTS

The search found 1,061 records, of which 702 were duplicates and 359 were screened by title and abstract. Thirty-seven studies were potentially relevant and full reports obtained and screened. Twelve studies were excluded with reasons. Twenty-five studies met the eligibility criteria and were included for review (Figure 1). Eighteen studies were categorized as including a sample of participants with clinical pain (168 participants) and seven studies were categorized as including a sample of pain-free participants exposed to experimentally-induced pain (186 participants).

[Insert figure 1 here]

Clinical Pain

Characteristics of included studies

Eighteen clinical studies (168 participants) were included for review (Tables 1 and 2). Two were randomized controlled trials, eight were single group pre-test post-test without a control group comparison, seven were case series, and one was a case study. Eleven studies evaluated participants with upper phantom limb pain,[7, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24] one study evaluated participants with upper and lower phantom limb pain.[25] One study evaluated upper limb complex regional pain syndrome,[26] one study evaluated lower limb complex regional pain syndrome,[27] and two studies evaluated upper and lower limb complex regional pain syndrome.[28, 29] One study evaluated patients with upper limb neuropathic pain,[30] and one evaluated patients with lower limbs neuropathic pain.[31] Mean age of participants ranged from 36.31 to 55 years. Only one case series report included teenagers .[27] Pain duration ranged from 2.75 to 26.86 years in the randomized controlled trials and pre-test post-test studies. In the case series and case studies pain duration ranged from 1 to 39 years.

Treatment Characteristics

Virtual limbs were presented on a computer screen in eight studies and on a virtual reality head-mounted display in 10 studies. Movement of virtual limbs was controlled by movements of the affected (painful) limb in five studies [15, 19, 25, 27, 31] or movements of the non-affected (non-painful) limb in nine studies.[7, 16, 17, 18, 21, 22, 23, 24, 30] In one study a virtual arm was controlled by movement of the participant's affected (painful) arm but the virtual hand and fingers were controlled by the participant's non-affected (non-

painful) hand and fingers.[26] In three studies participants did not control movement of virtual limbs but instead were required to imitate movements of a virtual limb,[20] and mentally imitate the movements of a virtual body.[28, 29]

Treatment frequency and duration of interventions varied between studies from one 10-minute session for phantom limb pain and complex regional pain syndrome [7, 28, 29], to two one-hour sessions per week for eight weeks for phantom limb pain. [16]

[Insert table 1 here]

[Insert table 2 here]

Quality assessment

The two randomized controlled trials had low risk of bias associated with random sequence generation and incomplete outcome data; unclear risk of bias associated with allocation concealment and blinding of participants or outcome assessor; and high risk of bias associated with an absence of sample size calculation (Table 3). Quality assessment of pre-test post-test studies indicated bias associated with specification and description of inclusion criteria, blinding of participants and outcome assessor, and an absence of sample size calculations (Table 4). Sample sizes were small and between 6 and 22 participants. Outcome measures of interest were taken multiple times before the intervention and multiple times after the intervention in only three studies.

[Insert table 3 here]

[Insert table 4 here]

Effects of interventions

Data could not be pooled due lack of available data and differences in study designs and types of controls prevented a meta-analysis. Therefore, a descriptive synthesis was performed.

The two randomized controlled trials found no significant difference pre-post intervention nor between intervention and control groups for pain intensity (Table 1). All eight pre-test post-test studies without a control found that the intervention alleviated pain

with the mean decrease in pain intensity post intervention relative to baseline between 64%[25] and 32%[15] (Table 2). In the case series, responses to the interventions were varied and included complete resolution of pain to worsening pain. There were seven reports of case series with 28 patients and one report of a single case (i.e., a total of 29 patients). Of these 29 patients, nine experienced more pain during the intervention or within a few hours after intervention, although in several of these cases pain was gradually reduced with the repetition of sessions. It was stated that patients did not experience adverse reactions from the intervention in one study report.[26] In one case series it was reported that one patient experienced motion sickness (i.e., dizziness, nausea).[21] There was no mention of adverse reactions in any of the other reports.

Three clinical studies evaluated a sense of embodiment of the virtual limb (i.e., ownership and agency of the virtual limb) and/or 'presence' in the virtual environment (i.e., the sense that the user is experiencing and interacting with the virtual environment).[32] Osumi et al. [7] found that ratings of the intensity of a sense of embodiment of the virtual limb (e.g., 'I felt as if I could control the movements of the virtual hand', and 'The virtual arm was obeying my will and I could make it move as I wanted to') were higher post-intervention. Cole et al. [25] found that a sense of agency toward the virtual limb was a pre-requisite for pain reduction. Jeon et al. [29] found higher ratings of embodiment when participants observed the virtual body moving whilst imaging the movement (i.e., with mental imagery) compared with not performing mental imagery.

Experimentally-induced pain

Characteristics of included studies

Seven studies (186 participants) were included for review and all used a within-subject repeated measures design (Table 5). Mean age of participants ranged from 21.1 to 24.9 years. Head-mounted displays were used to deliver virtual reality tasks in all studies. Experimental pain was induced using a variety of noxious stimuli including contact thermal heat,[10, 33, 34, 35, 36] non-invasive blunt needle,[37] and electrical stimulation.[38] Participants observed a virtual object touching the virtual body and received tactile stimulation on the real body;[10, 39] observed the virtual limb moving in synchrony or asynchronously with their real limb being passively moved by the experimenter;[33, 40] observed movements of the virtual hand whilst controlling its movements by moving their real hand;[38] or observed the virtual body part.[35, 36]

[Insert table 5 here]

Quality assessment

All studies using experimentally-induced pain were rated as having a high risk of bias due to an absence of sample size calculation and small sample sizes. Absence of information upon which a judgment could be made resulted in unclear risk of bias related to blinding of participants and outcome assessor in the majority of studies (Table 3). There was a low risk of bias due to adequate reporting of random sequence generation of conditions in five studies, and low risk of bias for reporting adequate control of crossover effects in four studies.

Effects of interventions

Data could not be pooled due lack of available data and differences in study designs and types of controls prevented a meta-analysis. Therefore, a descriptive synthesis was performed.

There was an increase in contact-heat pain threshold when the virtual arm was collocated with the real arm,[10] when it moved in synchrony with the real arm,[33] and when the color of the stimulated part of the virtual arm became blue[34] (Table 4). There was an increase in contact-heat pain threshold when participants observed a virtual arm compared with observing a virtual object.[33, 36] There was a reduction in pain intensity after electrical stimulation when a virtual arm appeared to be covered with iron armor plating compared with a naked arm or an arm covered with a t-shirt sleeve.[38] There were no changes in outcome measures when participants observed virtual legs presented in a variety of sizes or viewpoints.[37] There were no changes in pain threshold when the transparency of a virtual arm was manipulated.[35]

All experimentally-induced pain studies evaluated embodiment of the virtual limb and 'presence' in the virtual environment. Nierula et al. [10] found that higher ratings of a sense of ownership of a virtual hand was associated with higher heat pain threshold and that this was independent of whether the virtual hand was collocated or displaced 30 cm away from the body midline. Martini et al. [33] found that ratings of a sense of ownership of a virtual hand were higher when observing a virtual hand that moved in synchrony with the real hand compared with a virtual hand moving asynchronously with the real hand. Zanini et al. [36] found higher ratings of embodiment of a virtual arm compared with a virtual object and higher ratings of embodiment when the virtual arm was resting

compared with moving. Romano et al. [37] found higher ratings of ownership of a virtual leg when the virtual leg was collocated with the real leg compared with a virtual leg rotated by 90^{o}. Manipulations of the length of the virtual legs did not change the magnitude of ownership. Martini et al. [34] found that changing the color of the area of a virtual arm that received the noxious stimulus did not affect ratings of ownership of the virtual arm. Weeth et al. [38] found higher ratings of ownership of a virtual arm when it appeared naked compared with being covered with iron armor plating, although there were no differences in ratings of agency. Martini et al. [35] found that ratings of ownership of a virtual arm declined as the virtual arm appeared to be more transparent (Table S1 supplementary material).

DISCUSSION

There was a paucity of randomized controlled clinical trials of adequate methodological quality to judge the clinical efficacy of virtual representation of body parts on pain. There were only two randomized controlled clinical trials and neither had long-term follow-up. Both randomized controlled clinical trials found no statistically significant difference in pain intensity between virtual reality and control interventions. However, case series and clinical studies without controls found that virtual representation of virtual limbs reduced the intensity of phantom limb pain, complex regional pain, and neuropathic pain, with only a minority of individuals reporting no effect or worsening of pain. The two randomized controlled trials found a reduction in perceptual disturbances in the group watching a virtual body performing movements and mentally imitating these movements compared with controls. This is an important finding because patients with complex regional pain syndrome often present with perceptual disturbances, such as a sense that the affected limb is larger than reality or that the affected arm is no longer part of one's body (i.e., disownership).[41] In extreme cases patients are motivated to amputate the affected body part.[42]

Limitations of the evidence

The clinical studies were preliminary with small sample sizes and often without suitable controls. None of the included studies provided a sample size calculation (i.e. clinical and experimental), which is critical to determine the number of participants necessary to provide sufficiently high power to detect clinically meaningful treatment effects.[43] Control interventions enable the measurement of effect size[44, 45] and the Cochrane collaboration recommends that interventions be compared with either inactive controls (e.g., placebo, no treatment, standard care), or with active controls (e.g., a different variant of the same intervention, or a different kind of therapy).[12] There was not enough information in studies upon which to make a judgment related to blinding of participants and outcome assessor. Blinding of participants and outcome assessors is difficult, but extremely important, as it is known that lack of blinding is associated with a risk of biasing outcome in favor of the treatment intervention, especially in studies with subjective outcomes.[12, 46, 47]

Future challenges of clinical study designs

Authentic Controls

The randomized clinical trials tested the combination of virtual representation of a body and mental imagery, with control groups isolating each of these interventions. Mirror visual feedback was used as a control condition in case studies and single group clinical studies. Experimental studies used a variety of control conditions to isolate effects related to physiological mechanisms rather than clinically relevant outcomes. Nevertheless, control conditions that operate 'out' of the virtual environment, or that are not based on representation of body parts could also be relevant in future clinical studies. Future studies evaluating the clinical efficacy of virtual reality interventions should use standard care as a control group or a less costly intervention such as mirror visual feedback. A cost effectiveness analysis should be performed in comparisons with active interventions to guide practitioners' choice of treatment in clinical practice.

Controlling Sources of Bias

Blinding participants and outcome assessor may not be enough to reduce performance and ascertain bias in clinical studies investigating the effectiveness of virtual reality interventions. Strict protocols should include standardized instructions for the delivery of the therapy.[48]

Issues such as dose intensity and duration, use of single applications of interventions in chronic pain, and the lack of standardization regarding outcome measures and their timing are known sources of bias when measuring effectiveness of non-pharmacological interventions,[49, 50] and can be identified in the reviewed studies. Bennett et al. [48] demonstrated that potential sources of bias occur both in favor and against intervention, especially for treatments where the optimal technique and dosage are not known, as is the case with virtual reality studies. Evidence from number and duration of sessions and follow-up measures are required to include virtual reality in treatment protocols.

The mechanisms of action contributing to reports of pain reduction when using virtual representation of body parts are yet to be fully elucidated. It has been speculated that mechanisms may be similar to those observed for other visual feedback techniques such as mirror visual feedback and real-time video.[51] Mechanisms may include correction of a disrupted mental representation of body parts, promotion of sensorimotor congruence and reduction of fear and anxiety of moving a painful body part.[52, 53, 54] Virtual representation of body parts may elicit different mechanisms of action depending on pathology. Further research is needed.

Secondary Outcomes and Adverse Reactions

Secondary outcomes such as perceptual disturbances and embodiment should be assessed and clearly reported in future studies. All experimental studies included in our systematic review measured embodiment of the virtual body part and showed associations between embodiment and pain. Thus, the embodiment of the viewed body part seems to be an important factor contributing to pain reduction, but clinical studies have given little consideration to it.

Motion sickness, disorientation, and loss of balance are commonly reported as reactions to the use of virtual reality, especially when delivered using a head-mounted display. Adverse reactions of virtual reality therapy were given little consideration in the studies investigating the effect of virtual representation of body parts on pain perception. There are specially designed questionnaires to measure motion sickness and these aspects should be carefully addressed in future studies.[55, 56] Good-quality experimental studies are necessary in order to inform the design of randomized controlled trials. Especially when using virtual reality, testing healthy participants' reactions in a virtual environment will help to build a more controlled intervention for patients with clinical pain.

Optimal treatment characteristics

Our descriptive synthesis of clinical studies revealed inconsistencies in the type, frequency, and duration of virtual reality treatment and this suggests that optimal technical characteristics and treatment regimen for clinical practice are not known. The frequency and duration of interventions used in clinical studies was between one 10-minute session for phantom limb pain and complex regional pain syndrome,[7, 28, 29] to two one-hour sessions per week for eight weeks for phantom limb pain.[16] Frequency and time of exposure seem to be an important aspect of interventions using virtual representations of body parts especially when used to manage chronic pain. For instance, mirror visual feedback is recommended to be used little and often, and recent systematic reviews with meta-analysis indicate that a course of four to six weeks of treatment with mirror visual feedback significantly reduces pain, whereas a single session does not[51, 57].

Factors influencing the response to VR that could inform optimal treatment characteristics

Evidence from studies of participants exposed to experimentally-induced pain provides insights into the factors that influence response to virtual representation of body parts. Pain

threshold was increased when a virtual arm was collocated with the real arm, moved in synchrony with the real arm, and colored blue at the site of application of the noxious stimulus. Also covering the virtual arm with iron armor may reduce intensity ratings of electrically-induced pain. However, observing virtual limbs of difference sizes, viewpoints, or transparencies did not affect experimentally-induced pain.

A variety of protocols were used and may inform clinical practice. For example, Cole et al. [25] used movements of the stump to control the virtual arm, and found that the use of the virtual reality system without a feeling of agency did not reduce phantom limb pain. Villiger et al. [31] used movements of the affected lower limbs to control the virtual limbs and identified pain reduction in patients with neuropathic pain. Other studies with patients with phantom limb pain showed that visual feedback of movements of the healthy limb converted symmetrically so that the virtual limb of the affected side would move normally were also effective in reducing pain. Hwang et al. [28] and Jeon et al. [29] did not find any pain reduction when participants with complex regional pain syndrome watched a virtual body moving and mentally imitated it while sitting still. These findings suggest that movement may be necessary for pain reduction.

An important aspect of virtual reality interventions is the mode of delivery of the virtual task, i.e., head-mounted display (immersive) or computer screen (non-immersive).[32, 58] Based on the studies included in our review there does not seem to have been a difference whether the virtual representation of the body part was presented on a computer screen or on a head-mounted display. Nevertheless, in a systematic review on the effectiveness of virtual reality distraction for pain reduction, Malloy and Milling [59] reported that immersive virtual reality is more effective in reducing pain compared with non-immersive virtual reality. In addition, Hoffman et al. [60] found that a 60-degree field-of-view head-mounted display reduces pain more effectively than a 35-degree field-of-view head-mounted display.

CONCLUSIONS

The use of virtual reality in rehabilitation settings has become more popular and affordable with lowering of prices and development of new software. Based on primary studies, the use of virtual representation of body parts to reduce pain is promising. However, due to the poor methodological quality and limitations of primary studies, we could not find conclusive evidence. The embodiment of the virtual representation of the body part seems to be important when using the technique. However, adverse reactions were not

investigated in any great depth in the studies and caution is recommended when using the technique.

REFERENCES

1. Sharar SR, Miller W, Teeley A, et al. Applications of virtual reality for pain management in burn-injured patients. Expert Rev Neurother. 2008 November;8(11):1667-1674. PubMed PMID: 2008532568.
2. Shahrbanian S, Simmonds MJ. Effects of different virtual reality environments on experimental pain rating in post-stroke individuals with and without pain in comparison to pain free healthy individuals. Annual Review of CyberTherapy and Telemedicine. 2008;6:53-59. PubMed PMID: 2009-07493-011.
3. Kenney MP, Milling LS. The Effectiveness of Virtual Reality Distraction for Reducing Pain. Psychology of Consciousness: Theory, Research, and Practice. 2016;3(3):199-210.
4. Garcia-Palacios A, Herrero R, Vizcaino Y, et al. Integrating virtual reality with activity management for the treatment of fibromyalgia: Acceptability and preliminary efficacy [Journal: Article]. Clin J Pain. 2015;31(6):564-72. doi: 10.1097/AJP.0000000000000196. PubMed PMID: CN-01074903.
5. Won AS, Bailey J, Bailenson J, et al. Immersive Virtual Reality for Pediatric Pain. Children (Basel, Switzerland). 2017 Jun 23;4(7). doi: 10.3390/children4070052. PubMed PMID: 28644422; PubMed Central PMCID: PMCPMC5532544. eng.
6. Harvie DS, Broecker M, Smith RT, et al. Bogus visual feedback alters onset of movement-evoked pain in people with neck pain. Psychol Sci. 2015 Apr;26(4):385-92. doi: 10.1177/0956797614563339. PubMed PMID: 25691362; eng.
7. Osumi M, Ichinose A, Sumitani M, et al. Restoring movement representation and alleviating phantom limb pain through short-term neurorehabilitation with a virtual reality system. Eur J Pain. 2017;21(1):140-147. doi: 10.1002/ejp.910. PubMed PMID: 2016-33328-001.
8. Dunn J, Yeo E, Moghaddampour P, et al. Virtual and augmented reality in the treatment of phantom limb pain: a literature review. NeuroRehabilitation. 2017;40(4):595-601.
9. Handwerker H, Kobal G. Psychophysiology of experimentally induced pain. Physiol Rev. 1993;73(3):639-671.
10. Nierula B, Martini M, Matamala-Gomez M, et al. Seeing an Embodied Virtual Hand is Analgesic Contingent on Colocation. J Pain. 2017 Jun;18(6):645-655. doi: 10.1016/j.jpain.2017.01.003. PubMed PMID: 28108385; eng.
11. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4(1):1.
12. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 [Updated March 2011] 2011.
13. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Second Edition ed.: Lawrence Erlbaum Associates; 1998.
14. U.S. Department of Health and Human Services. National Heart, Lung, and Blood Institute. Study quality assessment tools 2014 [cited 2018 6 Jully]. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools.
15. Ortiz-Catalan M, Guethmundsdottir RA, Kristoffersen MB, et al. Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain. Lancet. 2016 Dec 10;388(10062):2885-2894. doi: 10.1016/s0140-6736(16)31598-7. PubMed PMID: 27916234; eng.
16. Mercier C, Sirigu A. Training with virtual visual feedback to alleviate phantom limb pain. Neurorehabil Neural Repair. 2009;23(6):587-594. doi: 10.1177/1545968308328717. PubMed PMID: 105365479. Language: English. Entry Date: 20090814. Revision Date: 20150711. Publication Type: Journal Article.

17. Sano Y, Ichinose A, Wake N, et al. Reliability of phantom pain relief in neurorehabilitation using a multimodal virtual reality system. Conf Proc IEEE Eng Med Biol Soc. 2015 Aug;2015:2482-5. doi: 10.1109/embc.2015.7318897. PubMed PMID: 26736797; eng.
18. Desmond DM, O'Neill K, De Paor A, et al. Augmenting the reality of phantom limbs: three case studies using an augmented mirror box procedure. Journal of Prosthetics & Orthotics (JPO). 2006;18(3):74-79. PubMed PMID: 106302115. Language: English. Entry Date: 20070615. Revision Date: 20150820. Publication Type: Journal Article.
19. Ortiz-Catalan M, Sander N, Kristoffersen MB, et al. Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: a case study of a chronic PLP patient. Front Neurosci. 2014;8:24. doi: 10.3389/fnins.2014.00024. PubMed PMID: 24616655; PubMed Central PMCID: PMCPmc3935120. eng.
20. Alphonso AL, Monson BT, Zeher MJ, et al. Use of a virtual integrated environment in prosthetic limb development and phantom limb pain. Annual Review of CyberTherapy and Telemedicine. 2012;10:305-309. PubMed PMID: 2014-01026-057.
21. Murray CD, Patchick E, Pettifer S, et al. Investigating the efficacy of a virtual mirror box in treating phantom limb pain in a sample of chronic sufferers. International Journal on Disability and Human Development. 2006;5(3):227-234. doi: 10.1515/IJDHD.2006.5.3.227. PubMed PMID: 2008-18788-006.
22. Murray CD, Pettifer S, Howard T, et al. The treatment of phantom limb pain using immersive virtual reality: three case studies. Disabil Rehabil. 2007 Sep 30;29(18):1465-9. doi: 10.1080/09638280601107385. PubMed PMID: 17729094; eng.
23. Wake N, Sano Y, Oya R, et al. Multimodal Virtual Reality Platform for the Rehabilitation of Phantom Limb Pain. 2015 7th International Ieee/Embs Conference on Neural Engineering. International IEEE EMBS Conference on Neural Engineering2015. p. 787-790.
24. Ichinose A, Sano Y, Osumi M, et al. Somatosensory Feedback to the Cheek During Virtual Visual Feedback Therapy Enhances Pain Alleviation for Phantom Arms. Neurorehabil Neural Repair. 2017 Aug;31(8):717-725. doi: 10.1177/1545968317718268. PubMed PMID: 28691602; eng.
25. Cole J, Crowle S, Austwick G, et al. Exploratory findings with virtual reality for phantom limb pain; from stump motion to agency and analgesia. Disabil Rehabil. 2009;31(10):846-54. doi: 10.1080/09638280802355197. PubMed PMID: 19191061; eng.
26. Sato K, Fukumori S, Matsusaki T, et al. Nonimmersive virtual reality mirror visual feedback therapy and its application for the treatment of complex regional pain syndrome: an open-label pilot study. Pain Med. 2010;11(4):622-629. doi: 10.1111/j.1526-4637.2010.00819.x. PubMed PMID: 105169695. Language: English. Entry Date: 20100604. Revision Date: 20150711. Publication Type: Journal Article.
27. Won AS, Tataru CA, Cojocaru CM, et al. Two Virtual Reality Pilot Studies for the Treatment of Pediatric CRPS. Pain Med. 2015;16(8):1644-1647. doi: 10.1111/pme.12755. PubMed PMID: 109834653. Language: English. Entry Date: 20150821. Revision Date: 20160801. Publication Type: Journal Article.
28. Hwang H, Cho S, Lee JH. The effect of virtual body swapping with mental rehearsal on pain intensity and body perception disturbance in complex regional pain syndrome. Int J Rehabil Res. 2014 Jun;37(2):167-172. doi: 10.1097/mrr.0000000000000053. PubMed PMID: WOS:000336215800011.
29. Jeon B, Cho S, Lee J-H. Application of virtual body swapping to patients with complex regional pain syndrome: A pilot study. Cyberpsychology, Behavior, and Social Networking. 2014;17(6):366-370. doi: 10.1089/cyber.2014.0046. PubMed PMID: 2014-24219-008.
30. Mouraux D, Brassinne E, Sobczak S, et al. 3D augmented reality mirror visual feedback therapy applied to the treatment of persistent, unilateral upper extremity neuropathic pain: a preliminary study. J Man Manip Ther. 2017 Jul;25(3):137-143. doi:

10.1080/10669817.2016.1176726. PubMed PMID: 28694676; PubMed Central PMCID: PMCPMC5498794. eng.
31. Villiger M, Bohli D, Kiper D, et al. Virtual reality–augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. Neurorehabil Neural Repair. 2013;27(8):675-683. doi: 10.1177/1545968313490999. PubMed PMID: 2013-33809-001.
32. Sanchez-Vives MV, Slater M. From presence to consciousness through virtual reality. Nature Reviews Neuroscience. 2005 April;6(4):332-339. PubMed PMID: 2005157666.
33. Martini M, Perez-Marcos D, Sanchez-Vives MV. Modulation of pain threshold by virtual body ownership. Eur J Pain. 2014;18(7):1040-1048.
34. Martini M, Perez-Marcos D, Sanchez-Vives MV. What color is my arm? Changes in skin color of an embodied virtual arm modulates pain threshold. Front Hum Neurosci. 2013;7. PubMed PMID: 2013-31129-001.
35. Martini M, Kilteni K, Maselli A, et al. The body fades away: investigating the effects of transparency of an embodied virtual body on pain threshold and body ownership. Sci Rep. 2015 Sep;5. doi: 10.1038/srep13948. PubMed PMID: WOS:000361877100001.
36. Zanini A, Montalti M, Caola B, et al. PAIN DURING ILLUSORY OWN ARM MOVEMENT: A STUDY IN IMMERSIVE VIRTUAL REALITY. EMJ. 2017;2(2):90-97.
37. Romano D, Llobera J, Blanke O. Size and Viewpoint of an Embodied Virtual Body Affect the Processing of Painful Stimuli. J Pain. 2016 Mar;17(3):350-8. doi: 10.1016/j.jpain.2015.11.005. PubMed PMID: 26656236; eng.
38. Weeth A, Mühlberger A, Shiban Y. Was it less painful for knights? Influence of appearance on pain perception. Eur J Pain. 2017.
39. Romano D, Llobera J, Blanke O. Size and viewpoint of an embodied virtual body affect the processing of painful stimuli. J Pain. 2016;17(3):350-358. doi: 10.1016/j.jpain.2015.11.005. PubMed PMID: 2016-05016-001.
40. Martini M, Perez-Marcos D, Sanchez-Vives MV. What Color is My Arm? Changes in Skin Color of an Embodied Virtual Arm Modulates Pain Threshold. Front Hum Neurosci. 2013;7:438. doi: 10.3389/fnhum.2013.00438. PubMed PMID: 23914172; PubMed Central PMCID: PMCPMC3728482. eng.
41. Moseley GL. Distorted body image in complex regional pain syndrome. Neurology. 2005 Sep;65(5):773. doi: 10.1212/01.wnl.0000174515.07205.11. PubMed PMID: 16157921; eng.
42. Lewis J, McCabe C. Body perception disturbance (BPD) in CRPS. Practical Pain Management. 2010:60-66.
43. McKeown A, Gewandter JS, McDermott MP, et al. Reporting of sample size calculations in analgesic clinical trials: ACTTION systematic review. J Pain. 2015;16(3):199-206. e7.
44. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55. doi: 10.1016/j.ijsu.2011.10.001. PubMed PMID: 22036893; Eng.
45. Magill M, Longabaugh R. Efficacy combined with specified ingredients: A new direction for empirically-supported addiction treatment. Addiction. 2013 May;108(5):874-81. doi: 10.1111/add.12013. PubMed PMID: 23072622; PubMed Central PMCID: PMCPMC3566277. eng.
46. Djavadkhani Y, Marshall NS, D'Rozario AL, et al. Ethics, consent and blinding: lessons from a placebo/sham controlled CPAP crossover trial. Thorax. 2015 Mar;70(3):265-9. doi: 10.1136/thoraxjnl-2014-206354. PubMed PMID: 25595508; Eng.
47. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008;336(7644):601-605.
48. Bennett MI, Hughes N, Johnson MI. Methodological quality in randomised controlled trials of transcutaneous electric nerve stimulation for pain: low fidelity may explain negative findings.

Pain. 2011 Jun;152(6):1226-32. doi: 10.1016/j.pain.2010.12.009. PubMed PMID: 21435786; eng.
49. Robb KA, Bennett MI, Johnson MI, et al. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. The Cochrane Library. 2008.
50. Walsh DM, Howe TE, Johnson MI, et al. Transcutaneous electrical nerve stimulation for acute pain. Cochrane Database Syst Rev. 2009;2(2).
51. Wittkopf PG, Lloyd DM, Johnson MI. The effect of visual feedback of body parts on pain perception: A systematic review of clinical and experimental studies. Eur J Pain. 2018;22(4):647-662. doi: doi:10.1002/ejp.1162.
52. Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: Physiological and clinical perspectives and the concept of a cortical 'body matrix'. Neurosci Biobehav Rev. 2012 January;36(1):34-46. PubMed PMID: 2011668871.
53. McCabe C. Mirror visual feedback therapy. A practical approach. J Hand Ther. 2011 Apr-Jun;24(2):170-8; quiz 179. doi: 10.1016/j.jht.2010.08.003. PubMed PMID: 21106347; eng.
54. McCabe CS. When illusion becomes reality. Rheumatology. 2011;50(12):2151-2152.
55. Brunnström K, Wang K, Tavakoli S, et al. Symptoms analysis of 3D TV viewing based on Simulator Sickness Questionnaires. Quality and User Experience. 2017;2(1):1.
56. Kennedy RS, Lane NE, Berbaum KS, et al. Simulator sickness questionnaire: An enhanced method for quantifying simulator sickness. The international journal of aviation psychology. 1993;3(3):203-220.
57. Boesch E, Bellan V, Moseley GL, et al. The effect of bodily illusions on clinical pain: a systematic review and meta-analysis. Pain. 2016 Mar;157(3):516-29. doi: 10.1097/j.pain.0000000000000423. PubMed PMID: 26588692; eng.
58. Chirico A, Lucidi F, De Laurentiis M, et al. Virtual Reality in Health System: Beyond Entertainment. A Mini-Review on the Efficacy of VR During Cancer Treatment. J Cell Physiol. 2016 Februaryy;231(2):275-287. PubMed PMID: 2015470617.
59. Malloy KM, Milling LS. The effectiveness of virtual reality distraction for pain reduction: a systematic review. Clin Psychol Rev. 2010;30(8):1011-1018.
60. Hoffman HG, Seibel EJ, Richards TL, et al. Virtual Reality Helmet Display Quality Influences the Magnitude of Virtual Reality Analgesia. J Pain. 2006 2006/11/01/;7(11):843-850. doi: https://doi.org/10.1016/j.jpain.2006.04.006.

Table 1 Characteristics of studies investigating participants with clinical pain

Study and design	Clinical condition	Treatment characteristics	Pain outcome measures	Pain Results
Hwang et al. [28] Randomized controlled trial	Complex regional pain syndrome (n = 39; M28)	VR task Observe a whole virtual body in a first-person perspective moving: making fists and opening up the fingers, bending and unbending the elbows, bending the ankles forward and backward, bending and unbending the legs. Three groups: (1) participants watched the video clip and practiced mental movement rehearsal (n=13; 36.31 ± 1.9 years; pain duration median, range = 5.5, 2-10 years). (2) participants watched the video clip (without mental movement rehearsal) (n = 13; 43.00 ± 2.79 years; pain duration median, range 3.25, 1-13.16 years). (3) a voice recording guided mental rehearsal (no video) (n = 13; 43.08 ± 2.38 years; pain duration median, range 5.33, 1-15 years). Nº. VR sessions = 1 Duration each VR session = 10 min Body part = whole body Display = head-mounted (field-of-view = not reported)	Pain • Intensity – NRS Measurement Timing • Before and immediately after intervention	No significant difference in pain comparing measures pre-treatment and post-treatment. No significant difference in pain comparing the three groups
Jeon et al. [29] Randomised controlled trial	Complex regional pain syndrome (n = 10; 39.30 ± 10.99 years; M/F not reported; pain duration median, range = 2.75, 2.75-10 years)	VR task Observe a video clip of a whole virtual body in a first-person perspective moving: making fists and opening up the fingers, bending and unbending the elbows, bending the ankles forward and backward, bending and unbending the legs. Two groups: (1) participants watched the video clip and practiced mental movement rehearsal (n=5). (2)	Pain • Intensity – NRS Measurement Timing • Before and immediately after intervention	No significant difference in pain comparing measures pre-treatment and post-treatment. No significant difference in pain comparing the two groups.

		participants watched the video clip (without mental movement rehearsal) (n=5). Nº. VR sessions = 1 Duration each VR session = 10min Body part = whole body Display = head-mounted (field-of-view = not reported)		
Cole et al. [25] Single group pre-test post-test	Phantom limb pain (n = 14; 53 ± 17.4 years; M10; pain duration = 6.35 ± 4.94 years)	VR tasks (1) for arm amputees: actions to reach, grasp, retrieve and replace a virtual object. (2) for leg amputees: actions to raise the leg forward, press a virtual pedal, release the pedal, and return to a resting position. Movements of the stump controlled the ipsilateral virtual limb. Nº. VR sessions = 1 Duration each VR session = 60 to 90 min Body part = upper and lower limbs Display = computer screen	Pain • Intensity – VAS Measurement Timing • Before and immediately after intervention	Mean pain reduction of 64%.
Mercier and Sirigu [16] Single group pre-test post-test	Phantom limb pain (n = 8; 37.12 ± 11.34 years; M8; pain duration = 6.75 ± 5.77 years)	VR tasks (1) flexion/extension of the elbow. (2) pronosupination of the forearm. (3) flexion/extension of the wrist. (4) opening/closing the hand. (5) abduction/adduction of the fingers. (6) thumb-to-fingers opposition. (7) flexion/extension of the thumb. (8) grasping an object. (9) precision grip with small objects. (10) dialling a phone number The virtual images of the missing limb moving were obtained by filming the intact limb performing	Pain • Intensity – VAS Measurement Timing • Baseline (1 to 5 weeks prior to the intervention) • During the 8 weeks of intervention • At follow-up 4 weeks after last session	After 8 weeks, patients reported an average 38% decrease in pain. Pain decrease was maintained at 4 weeks post-intervention in 4 out of 5 participants.

		different actions. These video images were then digitally inverted. Feedback presented on a computer screen and using a mirror to reflect the image so that appeared in the place of the missing limb. Duration of course of VR = 8 weeks Nº. VR sessions = 16 (2 per week) Duration each VR session =30 to 60 min. Body part = upper limb Display = computer screen		
Villiger et al. [31] Single group pre-test post-test	Neuropathic pain (n = 9; 52.71 ± 14.85 years; M9; pain duration = 5.5 ± 4.92 years)	VR task 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. Patients used a virtual reality system with a first-person view of virtual lower limbs controlled via movement sensors fitted to the patients' shoes. Duration of course of VR = 3 to 5 weeks Nº. VR sessions = 6 to 20 Duration each VR session = 45 min Body part = Lower limbs Display = computer 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)	Percentage changes after treatment compared to baseline for pain intensity were 38.9% at post-intervention and 36.3% at follow-up.
Sano et al. [17] Single group pre-test post-test	Phantom limb pain (n = 6; 55.16 ± 10.49 years; M6; pain durations = 17.66 ± 10.74 years)	VR task Reach and touch virtual target objects with the virtual phantom limb. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Duration of course of VR = more than 4 weeks Nº. VR sessions = 2	Pain • Quality = Short-form McGill pain questionnaire Measurement Timing • Before and after the task	The average reduction rates of Short-form McGill pain questionnaire was 50.2% on the fist session. The average of the reduction rates in the second session was 44.6%.

		Duration each VR session = 5 min Body part = upper limb Display = head-mounted (field-of-view = not reported)		
Ortiz-Catalan et al. [15] 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)	VR tasks (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. Movement of the stump controlled the ipsilateral virtual limb. Duration of course of VR = 6 weeks Nº. VR sessions = 12 (2 per week) Duration each VR session = 2 h Note: 1 participant received VR daily Body part = upper limb Display = computer screen	Pain • Intensity - NRS • Frequency - pain rating index • Duration - weighted pain distribution Measurement Timing • Before each session • At 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 the NRS, and 51% for the pain rating index.
Ichinose et al. [24] Single group pre-test post-test	Phantom limb pain (n = 9; 53.89 ± 10.17 years; M8; pain duration 17 ± 9.73 years)	VR task Reach and touch virtual target objects with the virtual phantom limb. The 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. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Duration of course of VR = 2 to 4 days Nº. VR sessions = 2 to 3 per day Duration each VR session = 5 min	Pain • Intensity – NRS • Quality = short-form McGill pain questionnaire Measurement Timing • Before and immediately 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%).

		Body part = upper limb Display = head-mounted (field-of-view = not reported)		
Mouraux et al. [30] Single group pre-test post-test	Neuropathic pain (n = 22; 49.31 ± 12.2 years; M10; pain duration = 26.86 ± 35.92 years)	VR task (1) reach and touch virtual target objects with the virtual affected limb. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Duration of course of VR = 1 week Nº. VR sessions = 5 Duration each VR session = 20 min Body part = upper limb Display = 3D display and participants used 3D glasses.	Pain • Intensity – VAS • Quality - McGill Pain Questionnaire • Neuropathic pain diagnostic questionnaire (DN4) Measurement Timing • Pain intensity measured before and after each session. • The McGill Pain Questionnaire and the DN4 were completed before the first session and 24 h after the last session.	The mean improvement of pain intensity per session was 29%. 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. 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 and DN4.
Osumi et al. [7] Single group pre-test post-test	Phantom limb pain (n = 8; 52.12 ± 6.66 years; M7; pain duration = 20.12 ± 10.48 years)	VR task Reach and touch virtual target objects with the virtual phantom limb. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Nº. VR sessions = 1 Duration each VR session = 10 min Body part = upper limb Display = head-mounted (field-of-view = not reported)	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.

Abbreviation: VR: virtual reality, VAS, visual analogue scale; NRS, numerical rating scale; M, male; F, female.

Table 2 Characteristics of studies investigating participants with clinical pain - case studies and reports

Study	Clinical condition (n)	Treatment characteristics	Pain outcome measures	Results
Desmond et al [18]	Phantom limb pain (n = 3; Case 1 = 40 years, pain duration 3 years; case 2 = 25 years, pain duration 6 years; case 3 = 49 years, pain duration = 12 years)	VR tasks (1) holding one's hands (phantom and intact); (2) pronate and tapping one's index fingers simultaneously; (3) attempting to move all fingers simultaneously. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Duration of course of VR = not reported Nº. VR sessions = not reported Duration each VR session = not reported Body part = upper limb Display = head-mounted (field-of-view = not reported) Note: control condition was a standard mirror therapy	Pain • Quality - short-form McGill pain questionnaire	**Case 1:** Participant reported more pain with both techniques. Pain was reduced in the virtual reality condition when the image of the phantom was stationary and participant tried to move his phantom fingers. **Case 2:** No effect. **Case 3:** Participant reported more pain with both techniques.
Murray et al. [21]	Pantom limb pain (n = 5; case 1 = 63 years, pain duration = 12 years; case 2 = 60 years, pain duration 12 years; case 3 = 56 years, pain duration 39 years; case 4 = 61 years, pain duration 11 years; case 5 = 65 years, pain duration 1 year)	VR tasks (1) placing the virtual limb onto coloured tiles; (2) batting or kicking a virtual ball; (3) tracking the motion of a moving virtual stimulus; (4) directing a virtual stimulus towards a target. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Duration of course of VR = 7 to 10 weeks Nº. VR sessions = 7 to 10 (1 per week) Duration each VR session = 30 min	Pain • Quality = McGill Pain Questionnaire, and Short-Form McGill Pain Questionnaire • Pain diaries Measurement timing • McGill Pain Questionnaire completed on the first visit and 2 weeks after the last visit.	**Case 1:** After the fourth session phantom pain was reported to have eased overall. Slight increase in pain for a period immediately after sessions. There was an overall evaluative decrease in phantom pain following the first and last sessions from 'Discomforting' to 'Mild'. **Case 2:** There was an overall evaluative decrease in phantom pain following the

		Body part = upper limb Display = head-mounted (field-of-view = not reported)	• Short-Form McGill Pain Questionnaire administered following each session • Pain diaries completed daily.	first and last sessions from 'Distressing' to 'Discomforting'. **Case 3:** Initial score on the McGill Pain Questionnaire was 46.41 and decreased to 32.76 at follow-up. **Case 4:** Initial McGill Pain Questionnaire score was 44.54 and increased to 61.79. **Case 5:** Initial McGill Pain Questionnaire score was 21.72 and decreased to 11.89.
Murray et al. [22]	Phantom limb pain (n = 3; case 1 = 63 years, pain duration = 12 years; case 2 = 60 years, pain duration 12 years; case 3 = 65 years, pain duration 1 year)	VR tasks (1) placing the virtual limb onto coloured tiles; (2) batting or kicking a virtual ball; (3) tracking the motion of a moving virtual stimulus; (4) directing a virtual stimulus towards a target. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Duration of course of VR = 7 to 10 weeks Nº. VR sessions = 7 to 10 (1 per week) Duration each VR session = 30 min Body part = upper limb Display = head-mounted (field-of-view = not reported)	Pain • Quality = McGill Pain Questionnaire, and Short-Form McGill Pain Questionnaire • Pain diaries Measurement timing • McGill Pain Questionnaire completed on the first visit and 2 weeks after the last visit. • Short-Form McGill Pain Questionnaire administered following each session Pain diaries completed daily.	**Case 1:** Decreased pain during session but increased pain within a few hours after completion of each testing session. **Case 2:** No consistent alterations in pain ratings during use of the VR system for the first two sessions. Participant suffered with motion sickness in the first two sessions. In the third session participant did not report feelings of nausea and pain rating at the end of the session compared to the beginning showed a decrease of 4 points. **Case 3:** Reported a drastic decrease in pain after just one session.
Sato et al. [26]	Complex regional pain syndrome (n = 5; case 1 = 46 years, pain duration = 2	VR task Movements of reaching out, grasping, transferring, and placing three objects of different sizes and shapes.	Pain • Intensity – VAS Measurement Timing	All patients reported spontaneous pain in the affected limb that increased with movement. Pain

	years; case 2 = 65 years, pain duration = 2 years; case 3 = 46 years, pain duration = 3 years; case 4 = 48 years, pain duration = 3 years; case 5 = 74 years, pain duration = 1 year)	Movements of the affected arm controlled the virtual affected arm. Movements of the non-affected hand and fingers controlled the virtual hand and fingers of the affected side. Duration of course of VR = 5 to 8 weeks Nº. VR sessions = 5 to 8 (1 per week) Duration each VR session = no time limits. Body part = upper limb Display = computer screen	• Before and after each session.	decreased from 64 ± 14 to 31 ± 26 after consecutive treatment sessions. Four of the five participants (80%) showed 50% pain reduction. Case 4 discontinued therapy because no pain reduction was provided by the therapy.
Alphonso et al. [20]	Phantom limb pain (n = 3, age and pain duration not reported)	VR tasks (1) wrist flexion and extension; (2) wrist pronation and supination; (3) opening and closing of the hand to form a fist. Participants observed the virtual arm perform a series of movements while simultaneously attempting to imitate the same movements with their phantom limb. Duration of course of VR = 20 days Nº. VR sessions = not reported Duration each VR session = 25 min Body part = upper limb Display = computer screen	Pain • Intensity – VAS Measurement timing • After each session	Pain intensity decreased over time.
Ortiz-Catalan et al. [19]	Phantom limb pain (n = 1; 72 years; pain duration = 39 years)	VR tasks (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. Movement of the stump controlled the ipsilateral virtual limb.	Pain • Intensity – NRS • Quality - short-form McGill pain questionnaire. Measurement Timing • After each session	Pain was gradually reduced to complete pain-free periods. The phantom posture initially reported as a strongly closed fist was gradually relaxed. The patient acquired the ability to freely move his phantom limb,

		Duration of course of VR = 13 weeks Nº. VR sessions = 13 (1 per week) Duration each VR session = not reported Followed by: Duration of course of VR = 5 weeks Nº. VR sessions = 10 (2 per week) Duration each VR session = not reported Body part = upper limb Display = computer screen		and a telescopic effect was restored.
Wake et al. [23]	Phantom limb pain (n = 5; case 1 = 75 years, pain duration = 9 years; case 2 = 57 years, pain duration 10 years; case 3 = 64 years; pain duration = 8 years; case 4 = 46 years, pain duration = 21 years; case 5 = 47 years, pain duration = 14 years)	VR task Reaching and touching virtual targets. Three conditions: (1) no tactile feedback condition: patients received no tactile feedback on the intact limb; (2) tactile feedback on the intact limb condition: patients received tactile feedback on the back of the hand of the intact limb when touching the object with the virtual hand; (3) tactile feedback on the affected side condition: patients received tactile feedback on the base of the neck of the affected side when touching the object with the virtual hand. Movements from the contralateral hand converted symmetrically so that the virtual limb of the affected side would move normally. Nº. VR sessions =1 Duration each VR session = 5 min Body part = upper limb Display = head-mounted (field-of-view = not reported)	Pain • 15 item questionnaire with a 4-point NRS. Note: The questions were based on the short-form McGill Pain Questionnaire and McGill Pain Questionnaire.	Pain score decreased after training in 4 of the 5 patients with the maximum pain reduction rate in the tactile conditions.

Won et al. [27]	Complex regional pain syndrome (n = 4; case 1 = 17 years; case 2 = 13 years; case 3 = 14 years; case 4 = 16 years; pain duration = not reported)	VR task Reach virtual balloons. Audio and vibration feedback was provided. Movements of the real limb were tracked and reproduced by the avatar in the virtual environment. The flexibility of the relationship between tracked and rendered motion was manipulated in two ways: (1) altered how much effort must be exerted to take action in the virtual environment. (2) altered which patients' limbs controlled the limbs of the virtual body, switching arms with legs. Duration of course of VR = not reported Nº. VR sessions = 6 Duration each VR session = not reported Body part = whole body Display = head-mounted (field-of-view = not reported)	Not reported	During treatment, participants did not complain of pain, arrived eager to engage, and tolerated the therapy well, actively moving the affected extremity during sessions.

Abbreviation: VAS, visual analogue scale; NRS, numerical rating scale; VR, virtual reality

Table 3 Risk of bias of studies that included a control group, and studies investigating pain-free healthy participants exposed to experimentally-induced pain. Adapted from Risk of bias assessment of the Cochrane collaboration [12].

	Random sequence generation	Allocation concealment	Incomplete outcome data	Blinding (Participant)	Blinding (Assessor)	Sample size	Cross-over effect
Studies investigating participants with a clinical pain condition (Randomised Controlled Clinical Trials)							
Hwang et al. [28]	●	●	●	●	●	●	N/A
Jeon et al. [29]	●	●	●	●	●	●	N/A
Studies investigating pain free healthy participants exposed to experimentally-induced pain							
Martini et al. [34]	●	●	●	●	●	●	●
Martini et al. [33]	●	●	●	●	●	●	●
Martini et al. [35]	●	●	●	●	●	●	●
Romano et al. [37]	●	●	●	●	●	●	●
Nierula et al. [10]	●	●	●	●	●	●	●
Zanini et al. [36]	●	●	●	●	●	●	●
Weeth et al. [38]	●	●	●	●	●	●	●

Abbreviation: Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias; N/A: not applicable. In all experimental studies random sequence generation for order of presentation of conditions was analysed.

Table 4 Quality assessment of clinical studies with a single group pre-post-test design

Criteria	Cole et al. [25]	Mercier and Sirigu [16]	Villiger et al. [31]	Sano et al. [17]	Ortiz-Catalan et al. [15]	Ichinose et al. [24]	Mouraux et al. [30]	Osumi et al. [7]
1. Was the study question or objective clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y
2. Were eligibility/selection criteria for the study population pre-specified and clearly described?	N	N	Y	N	Y	N	Y	N
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	Y	Y
4. Were all eligible participants that met the pre-specified entry criteria enrolled?	CD	Y	Y	CD	CD	CD	CD	CD
5. Was the sample size sufficiently large to provide confidence in the findings?	CD	CD	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	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	Y	Y
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	N	N	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?	Y	Y	Y	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?	CD	Y	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	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	NA	NA

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

Table 5 Characteristics of studies investigating pain-free healthy participants exposed to experimentally-induced pain

Study & design	Participants (n)	Experimental procedure	Pain outcome measures	Pain Results
Martini et al. [34] Within subject repeated measures	Healthy volunteers (n = 30; 23.9 ± 5.7 years; F30)	Conditions (1) View virtual arm (a) virtual wrist became blue (b) virtual wrist became red (c) virtual wrist became green (2) View a grey spot placed on the virtual table, close to the participant's wrist, became red. In all conditions an experimenter constantly moved the participant's right index finger. Body part = upper limb Display = head-mounted (field-of-view =111° × 64°)	Stimuli • Contact heat Measure Heat pain threshold	Vision of the blue wrist led to a higher pain threshold compared with the red wrist condition. A significantly higher pain threshold was detected while participants viewed the red spot on the table compared with the red arm and the green arm.
Martini et al. [33] Within subject repeated measures	Healthy volunteers (n = 24; 23.9 ± 5.7 years; F19)	Conditions (1) View virtual index finger (a) moving in accordance with the real finger (synchronous) (b) moving independently from the real finger (asynchronous) (2) View non-corporeal virtual object (control) (3) View fixation mark outside virtual environment (control) In all conditions an experimenter constantly moved the participant's right index finger for 20 seconds. Body part = upper limb Display = head-mounted (field-of-view =111° × 64°)	Stimuli • Contact heat Measure Heat pain threshold	Contact heat pain threshold was higher in the synchronous condition compared with the two control conditions. There was no difference between synchronous and asynchronous conditions.
Martini et al. [35]	Healthy volunteers (n = 24; 21.1 ± 1.8 years; F24)	Conditions (1) View virtual body (a) 0% transparency (b) 25% transparency	Stimuli •Contact heat Measure	No differences on pain threshold among conditions.

Within subject repeated measures		(c) 50% transparency (d) 75% transparency Participants observed the virtual body in first person perspective. Body part = whole body Display = head-mounted (field-of-view =102° × 64°)	•Heat pain threshold	
Romano et al. [37] Within subject repeated measures	Healthy volunteers (n = 21; 23.0 ± 2.0 years; F9)	Conditions (1) View virtual legs from a first-person viewpoint (a) normal-sized (b) small (c) large (2) View virtual legs 90° rotated (a) normal-sized (b) small (c) large Participants observed a virtual object touching the virtual leg and received tactile feedback on their real leg. Body part = lower limbs Display = head-mounted (field-of-view = 60°)	Stimuli • Non-invasive needle with a blunt end. Measure • Intensity - VAS Unpleasantness - VAS	No differences in pain intensity or unpleasantness.
Nierula et al. [10] Within subject repeated measures	Healthy volunteers (n = 19; 24.1 ± 5.1 years; M19)	Conditions (1) View virtual arm in same place as real arm (i.e. virtual arm collocated) (a) synchronous tactile feedback (b) asynchronous tactile feedback (2) View virtual arm displaced 30cm from midline (a) synchronous tactile feedback (b) asynchronous tactile feedback Participants observed a virtual object touching the virtual hand and received tactile feedback on the real hand.	Stimuli • Contact heat Measure • Heat pain threshold	Heat pain threshold was higher when the virtual hand was collocated than when located at 30 cm from the real hand. There was no difference in heat pain threshold between synchronous and asynchronous conditions.

		Body part = upper limb Display = head-mounted (field-of-view = 100º)		
Zanini et al. [36] Within subject repeated measures	Healthy volunteers (n = 36; 24.9 ± 4.7 years; F20)	Conditions (1) View virtual arm in in first person perspective (a) virtual arm still (b) virtual arm moving sideways (2) View virtual object (a) virtual object still (b) virtual object moving sideways Participants observed the virtual arm and object while their real arm was still during all conditions. Body part = upper limb Display = head-mounted (field-of-view = 100º)	Stimuli •Contact heat Measure •Heat pain threshold	Higher pain threshold when observing the avatar's arm (still and on movement) compared with the object (still and on movement). No differences between arm still or on movement.
Weeth et al. [38] Within subject repeated measures	Healthy volunteers (n = 32; 24.60 ± 7.27; F27)	Conditions (1) View naked virtual arm (2) View virtual arm covered with a t-shirt sleeve (3) View virtual arm covered in iron armour. Participants controlled movements of the virtual hand with their real hand. Adaptive phase of 20 seconds. Body part = upper limb Display = head-mounted (field-of-view = not reported)	Stimuli •Electrical noxious stimuli Measure •Pain intensity - NRS	Participants reported less pain when observing the virtual arm covered with the armour compared with the other two conditions.

Abbreviation: VAS, visual analogue scale; NRS, numerical rating scale; M, male; F, female.