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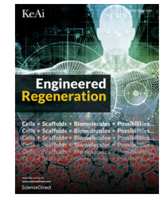

X-reality for phantom limb management for amputees: A systematic review and meta-analysis

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A R T I C L E I N F O

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Extended reality
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A B S T R A C T

Phantom limb is a disabling neuropsychiatric condition among amputees resulting in pain and disturbance that impact their functions, quality of life, and autonomy. While pharmacological approaches appeared to be ineffective, the emergence and integration of X-reality, including virtual reality, augmented reality, and mixed reality, might elevate the effectiveness of mirror therapy in managing phantom limb. The objective of this study is to review X-reality for managing phantom pain. A systematic search was conducted on PubMed, Scopus, Web of Science, PsycINFO, Embase, and CINAHL. Sixteen (n = 16) studies containing 66 lower-limb and 53 upper-limb amputees were included for the review over the thematic framework of amputee characteristics and intervention designs, while thirteen (n = 13) studies were further proceeded for the meta-analysis. We found eleven studies on virtual reality (n = 11), four studies on marker-based augmented reality (n = 4) and one study on mixed reality (n = 1) with a total of 40 game/task themes involving, motor skills, motor control, and stimulus-sensing. Regardless, all these interventions adopted the movement representation strategies with different techniques. Overall, the X-reality interventions reduced the pain level of the amputees (mean difference: -2.30, 95% CI, -3.38 to -1.22), especially the virtual reality subgroup (mean difference: -2.83, 95% CI, -4.43 to -1.22). However, there were substantial heterogeneity and partially explained by the subgroup analysis on publication year. The strength of evidence was limited by case reports and case series in this review.

1. Introduction

Amputation refers to the surgical removal of a body part (predominantly a limb or extremity) for survival because of significant trauma or prevention of disease progression. Lower limb amputees contribute the major proportion of the amputee population and dominated by non-traumatic cases of diabetes mellites or peripheral artery disease. It was reported that 115,000 people underwent lower limb amputation in the United States annually, in which 65% of them were underlined with diabetes and 85% with peripheral artery disease [1]. About 60,000 lower limb amputation procedures were carried out per five years in Japan [2]. Diabetic patients had 15 times higher incidence on major lower limb amputations than non-diabetic patients [2], while another study reported that the lifetime risk of amputation for diabetic patients was eight-fold [3]. In Germany, More than third-quarters of amputees suffered from diabetes mellites and peripheral artery disease [4]. Even though amputation was an agonizing decision to save life, unfortunately, re-amputation was arranged for 10% of amputated feet, and 17% of patients died in hospital after lower limb amputation [4].

Limb loss has a tremendous detrimental impact in every aspect of life, from appearance, sensation, to function, living, and autonomy [5,6]. Lower-limb amputees on prosthesis might ambulate with poor muscle and kinematic coordination, lower stability and endurance, higher level of fear and risks of falls [7–10]. Compensatory gait adjustment could induce muscle atrophy, back pain, and osteoarthritis [11–13]. On the other hand, more than a quarter of amputees developed depressive symptoms with perceived social stigma and poor self-efficacy on body image [14]. Especially, body image was associated with

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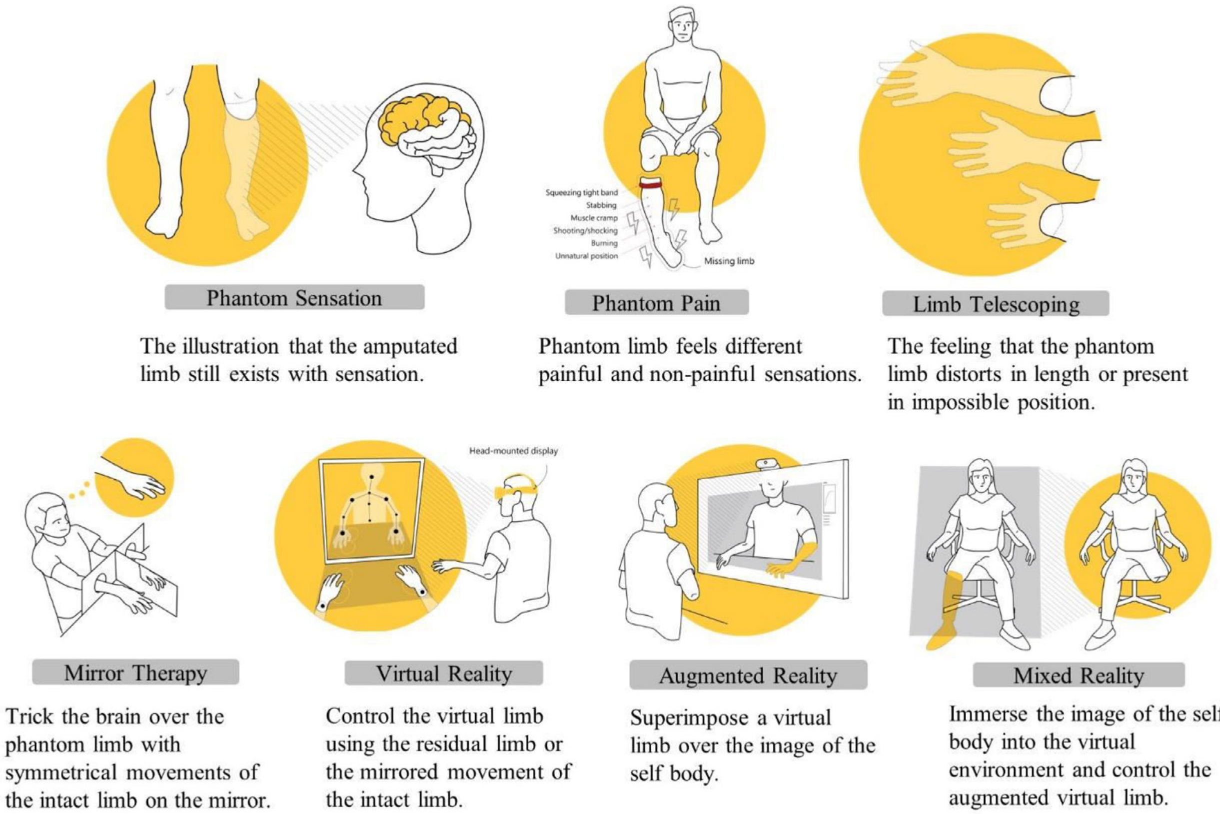

Fig. 1. Concepts of phantom sensation, phantom pain, and limb telescoping and the X-reality-based interventions.

their intention to physical activities, and thus their general health [15]. Amputees might also have a higher risk to develop atherosclerosis because of the change in spatial vasculature of the residuum [16]. Besides, it was reported that 78% of amputees quitted their jobs because of their amputation, in which unemployment triggered worse health experience [17].

Phantom limb is a prevalent and disabling neuropsychiatric entity to amputees [18,19]. The term, “phantom limb”, was first described by Mitchell [20], as the continued feeling of the presence of the amputated (or absent) limb. Phantom pain (in the phantom limb) could be painful sensations, such as burning, sharp, cramping, electric shooting, stabbing, and throbbing, or non-painful sensations, such as tingling, touch, numb, temperature, itching, and pressure [18,21]. Limb telescoping is a special kind of phantom limb sensation. Amputees may feel that the phantom limb distorts in length, retracts into the residual limb, or present in anatomically impossible positions [22]. Fig. 1 illustrates the concepts of phantom sensation, phantom pain, and limb telescoping. The estimated life time prevalence of phantom pain and sensation ranged from 76% to 87%, especially those with traumatic etiology [23], Besides, lower-limb amputees appeared to be more vulnerable to phantom sensation but not phantom pain [23,24]. The mechanism of phantom limb is not well-understood, while recent studies proposed the potential relationship with the maladaptive plasticity of the central nervous system [25]. Regardless, the pain and feeling of phantom limb could induce psychological distress, anxiety, and depression to amputees and interfere with their adaptation to life after amputation [26].

Pain management for phantom limb is one of the critical elements of amputee care [27], despite that there was no consensus and no effective first-line treatment [18,28]. Nevertheless, there were common medications prescribed for them, including pre-emptive analgesia and anesthesia, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAISs), Opioids, antidepressants, anticonvulsants, calcitonin, etc. [29]. Surgical interventions, such as lesioning of the dorsal root entry zone, stimulation on the spinal cord or motor cortex could be the last resort when other treatments failed [29].

Mirror therapy, the most common conservative treatment, aimed to reconnect the visual-proprioceptive entity of the brain [29], in response to the proposed underlying regarding the neuroplastic change of the somatosensory cortex and the reorganization of the cortical body map [25,30,31], The mirror therapy was actually an resemblance of the famous “Rubber Hand Illusion” [32], in which participants “felt” the sensation of the rubber arm by synchronously stroking the rubber hand and the actual hand [33]. In real practice, a mirror was placed mid-sagittal to show the reflection of the intact limb. The amputees observed the mirror and were asked to move the intact limb and the “amputated” limb simultaneously and symmetrically [29]. Tactile sensation could also be elicited by touching the intact limb and the virtual limb in the mirror simultaneously [29]. The somatosensory inputs of the task might be able to relieve the protopathic pain of the phantom limb [34]. Representational restitution in the brain could be the possible mechanism evidenced by fMRI (functional magnetic resonance imaging)-detected cortical reorganization [35]. While randomized-controlled trials advocated mirror therapy interventions [36–40], the sample size was small and there were high heterogeneity and mixed results regarding the effectiveness of mirror therapy [41,42]. Weeks, et al. [43] suggested that 40% of the amputees were not responsive to mirror therapy. Brodie, et al. [37] believed that mirror therapy could raise the awareness and “control” of phantom limb among amputees but failed to relieve the phantom pain and sensation.

In any case, through the plasticity-based approach, mirror therapy demonstrated some clinical evidence on pain relief with proposed plausibility towards the maladaptive brain state [44]. In contrast, the effects of pharmacological interventions were controversial and at risk of side effects [45]. Ortiz-Catalan, et al. [44] suggested that overcoming the technical constraints of mirror therapy might boost its effectiveness.

The emerging technology, "eXtended" reality (X-reality) that includes virtual, augmented, and mixed reality, provides a toolbox to supplement and amplify the effects of mirror therapy. The first report of virtual reality started with a set of goggles and gloves on the mid-1980s by Jaron Lanier, the founder of VPL Research Company. Nonetheless, the first head-mounted display patent, "Telesphere Mask", was issued in 1960 by Morton Heilig. He introduced the concept of immersion in simulated environments "Sensorama" for a Hollywood movie with multisensory stimulation. The augmented reality blends the digital objects into the real world, first introduced by the United States Air Force Armstrong Laboratory, named "Virtual Flexture System", in 1992 [46] and was later disseminate to education, entertainment, and other applications. Mixed reality arrived at the debate on the definition of augmented reality and the transpiring concept of "Reality-Virtuality Continuum" [47]. The definition planted augmented reality in a subset of mixed reality but not virtual reality, in which the continuum shall not embed the case of virtual reality at the extrema [48]. In practice, mixed reality accents by integrating real-world and virtual-world objects with real-time interactions, which could ameliorate the immersive level of the virtuality [49]

Virtual rehabilitation or training with X-reality-based interventions were readily used and demonstrated promising results in different areas, including motor [50], cognitive [51], behavioural [52], emotional [53,54], in addition to physiotherapy [55], physical training [56], promotion of physical fitness [57]. They were also applied in scenarios, such as life skills training [58], and career training [59]. Meanwhile, it was also applied in treating phantom limb. As shown in Fig. 1, X-reality interventions imitated the principle of mirror therapy to treat phantom limb by observing and/or the virtual limb. A literature review has been done in 2017 that identified eight articles using the keywords, "virtual reality, "augmented reality", and "phantom limb" [60]. The review found that virtual and augmented reality-based treatments could relieve phantom limb pain, but the strength of evidence was limited [60]. To this end, we endeavoured to conduct a more comprehensive and contemporary review framework that targeted on phantom pain reduction with a more generic scope over X-reality.

The objective of this review was to produce a systematic map on the amputee characteristics and X-reality intervention designs for phantom limb management, in addition to an estimate on the overall effects in pain reduction. The review questions of this paper are as follows:

- What are the current state-of-the-arts X-reality-based modalities, intervention designs and protocols to manage phantom limb ?
- What are the characteristics of amputees that had been tested on the interventions ?
- Were X-reality-based interventions effective in reducing phantom limb pain?

2. Methods

2.1. Search strategy

Literature search was performed on electronic database, including PubMed, Scopus, Web of Science, PsycINFO (via ProQuest), Embase (via OVID), and CINAHL (via EBSCOHost) from the oldest available date. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist was used to guide the reporting items in this review [61]. The literature search was conducted on the 7th of Dec 2022 by two independent authors (J.C.-W.C. and M.N.) and subsequently screened. Any disagreements would be resolved by consensus with the corresponding author.

The search was conducted using a combination of keywords on the population and concept domains. We did not impose boundaries at the context level (such as country or experimental setting). Keywords related to the features of the population domains included "phantom limb*", "phantom sensation*", "phantom limb pain*", "phantom pain", "pseudomelia*", "limb telescop*", "telescoping sensation*", ("phantom" AND "telescoping"). Keywords related to the concepts of X-reality included "x-reality", "virtual reality", "virtual healthcare", "virtual rehabilitation", "virtual visit*", "virtual world", "augmented reality", "metaverse", "mixed reality", "immersion", "immersive reality", "haptic*", "stereoscop*", "head mounted display*", "hypermedia". The keywords were joined using the Boolean logic "OR" within the domains and "AND" between the domains. Besides, we implemented a "NOT" search on the keywords, "stroke", "cerebrovascular accident", "phantom premium", and "phantom haptic" to exclude a volume of irrelevant references that we discovered in our pilot search.

2.2. Screen strategy

The search was limited to English original research journal articles or referred conference full papers, excluding books, webpages, review, perspective, commentary, protocol, letter articles and conference abstracts, presentations, and symposium synopsis. The inclusion criteria included studies with patients of upper (including forequarter) or lower limb amputation. The articles shall apply X-reality-based interventions (including virtual reality, augmented reality, and mixed reality) with an objective to treat or manage phantom limb issues. Exclusion criteria included similar but indeed non-X-reality interventions (e.g., simple visual feedback and a controller). Studies were excluded if their experiment mixed with patients of non-amputation pathologies (such as brachial plexus injury and stroke). They were also excluded if they did not implement a formal evaluation process (e.g., just one or two sentences mentioned that the patients felt satisfactory) or they did not include any outcome measures (either qualitative or quantitative) related to phantom pain and sensation.

2.3. Data extraction

Firstly, basic information of the eligible articles was extracted, including the publication information (surname of the first author, year of publication), study design and characteristics, and patient demographic information. Secondly, a thematic framework would be created with the core content, including the technology (systems and modalities of X-reality, controller, and feedback), and the training theme (game design, gameplay task, and training protocol). A mapping analysis would be carried out to portray the proportion of different classes of amputees and training themes. Sankey diagrams were drawn by RAWGraphs (https://app.rawgraphs.io/).

2.4. Meta-analysis

We conducted a meta-analysis to estimate the overall effectiveness of phantom pain reduction by the X-reality interventions. Pain levels at 10-point scale before and after the intervention were extracted from eligible articles, including case report, case series, before-after arm of randomized or nonrandomized controlled trial. If there were multiple measurement timepoints, such as those within the session course or follow-ups, we only selected timepoints that were immediate before and after the training sessions. If they were drop-offs or missing data in the study, we analysed the data using the last measurement of the participant.

The analysis was performed through a random-effects model and illustrated using a forest plot. The overall effect was estimated by pooling the mean difference of the before and after assessments. If the before-after mean difference (MD) and the standard error of mean difference (σ_ε) were not available, the mean difference would be imputed by the difference in mean and the standard error of MD would be estimated using Eq. (1), according to the Cochrane guidelines [62]. Standard error of case reports was imputed by that of the other studies [62]. A preplanned subgroup analysis on the modality (i.e., virtual, augmented or mixed reality) and publication year was proceeded. A sensitivity test was conducted by removing studies with imputation. We did not conduct the

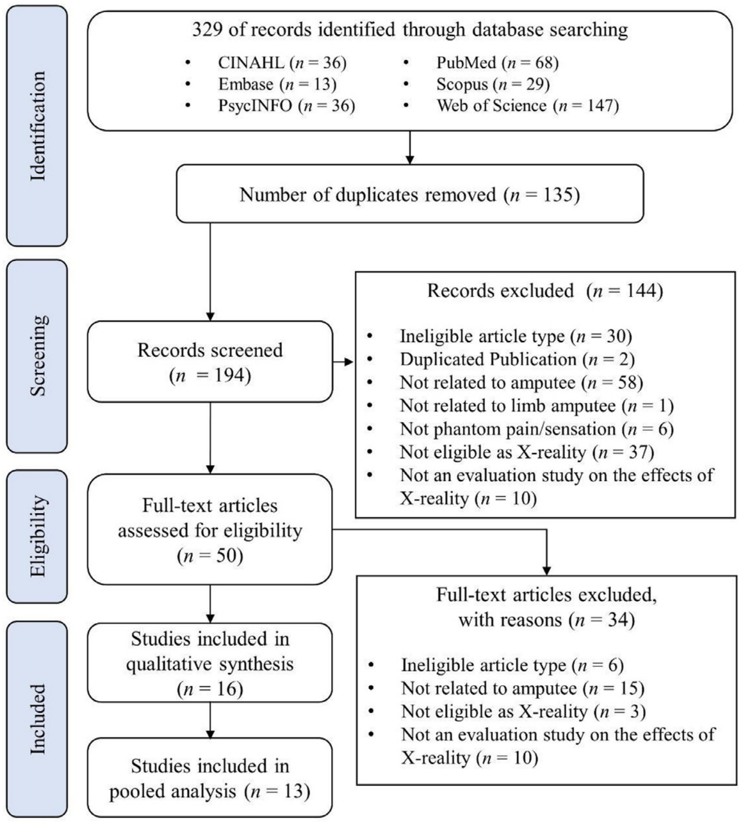

Fig. 2. Flowchart of the systematic search and screening process.

funnel plot or Egger's test to evaluate publication bias that might deem inappropriate in case of substantial heterogeneity [62].

$$\sigma_{\bar{\varepsilon}} = \sqrt{\sigma_{t1}^2 + \sigma_{t2}^2 - (2R\sigma_{t1}\sigma_{t2})} \quad (1)$$

where σ_{t1}, and σ_{t2} represent the standard deviation of pain level before and after the intervention, while R represents the correlation coefficient, assumed to be 0.5.

3. Results

3.1. Search results

- The search and screen process are illustrated in Fig. 2. The initial search has identified 329 records from the database. The search records were pooled, and duplicates (n = 135) were removed. Next, we screened 194 records by the article title, abstract, and keywords. There were 144 articles excluded at this stage. Thirty (n = 30) studies were removed because they did not fulfill the article type requirements (e.g., review article, commentary article, etc.). Two (n = 2) studies were excluded because they were duplicated publication (conference papers published again in journals). We retained the one with more comprehensive content. There were 58 papers excluded because they were not relevant to amputees, in particular majority were brachial plexus injury, supernumerary phantom limbs, and psychiatric problems. Other reasons were those not related to phantom pain or sensation (n = 6), not recognized as X-reality interventions, e.g., simple visual feedback (n = 37), not an evaluation on the effects of managing or treating phantom pain/sensation (n = 10).

Full-text assessment were performed on 50 articles after the first screening. Thirty-four (n = 34) articles were further excluded, with reasons: ineligible article type (n = 6), not related to amputee (n = 15), not recognized as X-reality (n = 3), and not an evaluation on the effects of X-reality on phantom pain/sensation (n = 10). Finally, there were 16 studies eligible for the qualitative synthesis in this review [44,63–77], and 13 of them further proceed to the pooled analysis. Table 1 shows the basic information of the review articles.

3.2. Basic information

3.2.1. Study characteristics and design

Case reports (n = 1) or case series (n = 11) contributed to majority of the eligible studies in our synthesis, which described the findings for each participant in details. Quasi-experimental studies were very similar to case series but often presented the data in statistics (i.e., no individual details), regardless of the sample size. There was only one study on randomized controlled trial [74] and one that considered a nonrandomized controlled trial in part of their work [73]. All articles involved a quantitative evaluation on the pain relief after the interventions, while seven studies integrated with formal qualitative analyses simultaneously (i.e., mixed approach). Six papers assessed the effects based on a pretest-posttest design, while ten longitudinal studies involved more than two assessment timepoints. For examples, follow-ups after the training, or assessments after a particular training session. Besides, three studies considered a pragmatic approach [65,70,74], in which the participants brought the system home and played the interventions themselves without controlled sessions. Rutledge, et al. [75] allowed the participants to choose whether the training shall be conducted at home or at the lab.

3.2.2. Patient demographics

Excluding control groups, the 16 articles involved a total of 118 patients (79 males, 23 females, and 16 gender unspecified). Only one study recruited more females than males and two studies did not specify the gender. The mean age of the participants was 57.6, (based on 13 articles with available information), ranging from 26 to 83. Out of the 16 papers, 43.8% (n = 7) and 31.3% (n = 5) considered only upper limb and lower limb amputees, respectively, while four studies recruited a

Table 1
Basic information, study design, and research approach.

Article	Publication	Study Design	Research Approach	Upper/Lower Limb Amputation
Ambron, et al. [63]	Frontiers in Neurology	Case series	Mixed	Lower limb:2
Ambron, et al. [64]	Neurorehabilitation & Neural Repair	Case series	Quantitative	Lower limb: 7
Annaswamy, et al. [65]	Pilot & Feasibility Studies	Case series	Mixed	Lower limb: 4
Chau, et al. [66]	Innovations in Clinical Neuroscience	Case report	Mixed	Upper limb: 1
Cole, et al. [67]	Disability & Rehabilitation	Case series	Quantitative	Lower limb:7 Upper limb: 7
Henriksen, et al. [68]	Virtual Reality International Conference	Case series	Quantitative	Upper limb: 3
Kulkarni, et al. [69]	British Journal of Pain	Case series	Mixed	Upper limb: 11
Lendaro, et al. [70]	Journal of Pain Research	Case series	Mixed	Lower limb: 2 Upper limb: 2
Murray, et al. [71]	International Journal on Disability and Human Development	Case series	Mixed	Lower limb: 2 Upper limb: 3
Ortiz-Catalan, et al. [72]	Frontiers in Neuroscience	Case series	Mixed	Upper limb: 1
Ortiz-Catalan, et al. [44]	Lancet	Quasi-experiment	Quantitative	Upper limb: 14 (2 bilateral cases)
Risso, et al. [73]	iScience	Case series & non-randomized controlled trial	Quantitative	Lower limb: 3
Rothgangel, et al. [74]	Clinical Rehabilitation	Randomized controlled trial	Quantitative	Lower limb: 26 (targeted group) Lower limb: 75 (all participants)
Rutledge, et al. [75]	Pain Medicine	Quasi-experiment	Quantitative	Lower limb: 13 Upper limb: 1
Snow, et al. [76]	International Conference on Rehabilitation Robotics	Case series	Quantitative	Upper limb: 3
Thøgersen, et al. [77]	Journal of Pain	Quasi-experiment	Quantitative	Upper limb: 7

mixture of patients with upper and lower limb amputation (Tables 1 and 2).

For the levels of amputation, they were classified as: forequarter (n = 5, 4.2%), shoulder disarticulation (n = 1, 0.8%), transhumeral (n = 21, 17.6%), transradial (n = 18, 15.1%), wrist disarticulation (n = 2, 1.7%), transmetacarpal (n = 2, 1.7%), hip disarticulation (n = 1, 0.8%), transfemoral (n = 22, 18.5%), knee disarticulation (n = 3, 2.5%), transtibial (n = 21, 17.6%), transmetatarsal amputation (n = 2, 1.7%). Twenty-one patients (n = 21, 17.6%) did not specify the level of amputation. Besides, only one study recruited bilateral amputees. The amputation causes were reported in 71 patients (60%), including those with diabetes, arterial or vascular problems (n = 16, 13.4%), trauma (n = 45, 37.8%), infection (n = 3, 2.5%), and tumor (n = 7, 5.9%). In other words, the ratio of traumatic to non-traumatic cases was 45:26. Fig. 3 shows a Sankey Diagram to illustrate the demographic proportion of patients in different classes.

There was a high variation on the time post-amputation until the experiment was taken place, ranging from 5 months to more than 50 years, which demonstrated that the problem of phantom pain or sensation could last for decades. Seven studies reported the occurrence time of phantom limb after amputation. Information from 23 patients showed that nearly half of them experience phantom limb immediate or shortly immediate post-amputation. Notably, there was one case that phantom pain appeared 19 years after amputation [70].

3.3. Thematic analysis

3.3.1. System and technology

Among the 16 articles, 68.8% (n = 11) of them used the virtual reality technology and only one study (n = 1) adopted the mixed reality, while the rest (n = 4) considered augmented reality (Table 3). For virtual reality and mixed reality, a gear with head-mounted display was necessary to facilitate the immersive experience. Fig. 4 illustrates common commercially available gears for X-reality. Only two brands appeared in our review: HTC Vive (HTC Corporation, Taiwan), and Oculus Rift (Oculus VR Company, Irvine, United States), which were famous gear manufacturers. HTC Vive had a resolution of 1080 × 1200 pixels per eye, a field of view of 110° and a refresh rate of 90 Hz, and was same as Oculus Rift.

Nowadays, there were more options on the gears with better specifications, such as Meta Quest Pro (Meta Technology Company, Menlo Park, United States), PlayStation VR (Sony Corporation, Minato City, Japan), HTC XR Elite (HTC Corporation, Taiwan), Valve Index (Valve Corporation, Bellevue, United States), Primax 5 K Super (Pimax Innovation Incorporation, Shanghai, China), HP Reverb G2 (Hewlett-Packard (HP) Company, Palo Alto, United States), etc. The Meta Quest Pro-improved the resolution to 1800 × 1920, while that of HTC XR Elite was 1920 × 1920 pixels per eye. Although there were gears commercially available for augmented reality, such as the HoloLens (Microsoft Corporation, Redmond, United States), Google Glass (Google LLC, Mountain View, United States), and Magic Leap (Magic Leap Incorporation, Plantation, United States), none of the studies used the gear-glasses and all of them adopted the marker-based approach. Specially, a fiducial marker was placed on the residual limb, which was then captured and recognized by a conventional web camera. Fig. 1 illustrates the concept of different X-reality interventions for phantom limb management.

Unlike those for entertainment, the interface between the amputees and the virtual limb is an important design factor for amputee-oriented virtual experience. For augmented reality, the amputees could drive the game using their residual limbs through the attached fiducial marker. A virtual limb model could be superimposed on the amputated site, in which the amputees could visualize themselves with the controlled virtual limb through the webcam captured screen [70,72,79]. Studies using the virtual reality system drove the three-dimensional model of the virtual limb by the residual limb or the intact limb of the patients. Kulkarni, et al. [69] and Murray, et al. [71] transposed and mirrored the movements of the intact limb to the phantom limb in the virtual environment. Besides, motion tracking could be facilitated by the bundled motion trackers of the gear [75,77], inertia measurement units (IMU) [63], electromagnetic sensors [64,67], haptic gloves with motion tracking functions [68,71,76], electromyography (EMG) sensors [66,70,72,76,77],

Table 2
Demographic information.

Article	Sample size (M/F/U)	Mean age (range)	Amputation cause	Average time after amputation	Phantom limb occurred postoperatively
Ambron, et al. [63]	2U	–	DAV: 2	7 months: 1	Immediate: 2
Ambron, et al. [64]	7 (4M3F)	51.4 (46 – 57)	DAV: 3 Trauma: 3 Infection: 1	4.38 years	Immediate: 1 < 1 month: 3 > 1 month: 3
Annaswamy, et al. [65]	4M	- (50 – 65)	–	5.27 years	–
Chau, et al. [66]	1M	49	Trauma: 1	–	5 months
Cole, et al. [67]	14(10M4F)	53 (27 – 83)	DAV: 3 Trauma: 3 Infection: 1	5 months - 10 years	–
Henriksen, et al. [68]	3(1M2F)	54 (45 – 60)	–	9 months	–
Kulkarni, et al. [69]	11(7M4F)	- (46 – 80)	–	>3 years: 9 <2 years: 1	–
Lendaro, et al. [70]	4 (3M1F)	58.3 (28 – 77)	Trauma: 4	50+ years	Immediate: 3 < 19 years: 1
Murray, et al. [71]	5 (3M2F)	61 (56 – 65)	–	17.5 years	Immediate: 3 3 months: 2
Ortiz-Catalan, et al. [72]	1M	72	Trauma: 1	49 years	Immediate: 1
Ortiz-Catalan, et al. [44]	14U	50.3 (26 – 74)	Trauma: 12 Infection: 1 tumor: 1	10.4 years	–
Risso, et al. [73]	3M	40 (31 – 54)	Trauma: 3	9.3 years	–
Rothgangel, et al. [74]	Traditional Therapy plus AR: 26 (21M5F)	59.7 (SD: 16.1)	DAV: 8 Trauma: 10 tumor: 4 Others: 4	Median: 56.5 months (IQR: 24.5 – 226.3)	–
	Traditional Therapy: 25 (14M11F)	62.5 (SD: 11.4)	DAV: 9 Trauma: 8 tumor: 5 Others: 3	Median: 38.0 months (IQR: 26 – 185.5)	–
	Controlled Exercises: 24 (17M7F)	61.0 (SD: 15.2)	DAV: 13 Trauma: 7 tumor: 1 Others: 3	Median: 31.0 months (IQR: 18.3 – 73.3)	–
Rutledge, et al. [75]	14 (13M1F)	63 (37 – 76)	–	<5 years: 5 6 – 10 years: 2 >10 years: 7	–
Snow, et al. [76]	3M	50.3 (26 – 67)	Trauma: 3	14 years	Immediate: 2 >6 months: 1
Thøgersen, et al. [77]	7(5M2F)	48 (33 – 75)	Trauma: 5 tumor: 2	21.3 years	–

AR: augmented reality; DAV: diabetes, arterial or vascular dysfunction; F: female; IQR: interquartile range; M: male; SD: standard deviation; U: unspecified.

and camera-based approaches (e.g., Kinect camera) [65,76]. It shall be noted that some studies implemented multiple controlling modalities.

The generation and control of the virtual limb could be further optimized to enhance the realistic perception of the training. EMG electrodes measured myoelectric muscle activity of the residual limb to manifest a motor volition [44,72]. Ortiz-Catalan, et al. [80] developed a pattern recognition module, BioPatRec, to decode the volitional signal and improve the control of virtual limb. The module streamlined the signal processing, feature selection and extraction, pattern recognition through the Regulatory Feedback Networks, and real-time control [80]. Another work of the same team used different pattern recognition algorithms, including the linear discriminant analysis in a one-vs-one topology (LDA-OVO), and the multilayer perceptron in a dedicated topology per degree of degree (MLP-AAM) [79]. In the mixed reality study conducted by Annaswamy, et al. [65], the virtual limb was not pre-built by three-dimensional computer-aided design (CAD) models. Instead, the team developed the Mr. MAPP system [81] that captured and generated the photorealistic and natural limb of the amputee in the virtual environment by mirroring the intact limb images through the Red-Green-Blue-Depth (RGB-D) camera (Kinect). The system could further estimate the skeleton of the limb in real-time to enable realistic limb movement and interaction of object in the virtual environment.

3.3.2. *Game theme, gameplay and task design*

As shown in Table 4 and Fig. 5, we identified and sorted out 40 game or task themes from the 16 studies. More than half of them belonged to virtual reality ($n = 28$). The number of augmented reality and mixed reality themes was nine and three, respectively. Majority of them were developed in-house ($n = 26$), while 14 of them were commercially available. For those commercially available game themes, most of them are ordinary computer games (e.g., car-racing) but replaced the original controller (i.e., keyboard, joystick) with sensors on the amputated limb. Eight ($n = 8$) out of the 40 games were related to life skill training, in which the participants were immersed into a living environment to perform tasks, from grasping an apple to kitchen work. Music ($n = 3$) and sports game ($n = 4$) contributed about 18% of the themes. The former manifested a music-with-movement approach, while the sports game covered table tennis, biking, and ball games. Tasks on movements and control ($n = 13$) were the most common themes among the studies. Participants were asked to reproduce or imitate a certain posture, while some may assess the ability in precise control and positioning, which could also be used to quantitatively assess the motor capabilities in addition to managing phantom limb. In terms of the game type, of the 40 games, there were 19 training simulations, 12 action simulations, 6 action games, and 3 strategy game with simulation.

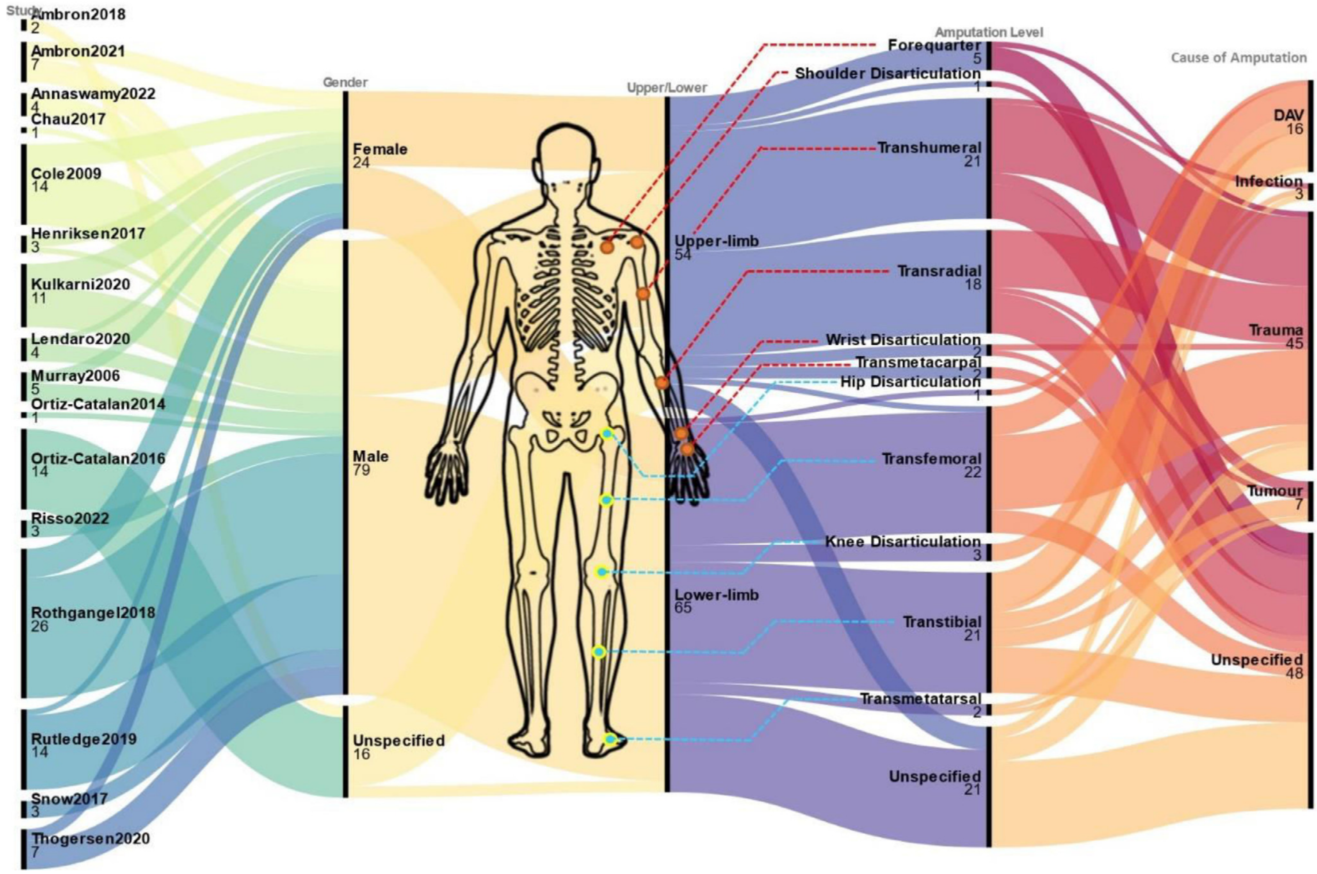

Fig. 3. Sankey diagram illustrating the proportion of participants on different demographic classes. (Note: Kulkarni, et al. [69], Rothgangel, et al. [78], Rutledge, et al. [75], and Thøgersen, et al. [77] did not detail the participant class-matching information. The alluvial in the diagram was simplified using alphabetical sequence in these articles). DAV: Diabetes, arterial and vascular dysfunction.

Fig. 4. Common virtual/augmented reality gears commercially available in the market: (a) HTC Vive COSMOS Elite (head-mounted display, joystick, tracker, base station); (b) Oculus Quest 2 head-mounted display; (c) HoloLens 2 head-mounted display.

Ambron, et al. [63] and Ambron, et al. [64] from the same team published two case series (one with two patients, another with seven patients) using very similar protocol and game, which were commercially available. The latter divided the course into two phases. The first phase was a distractor treatment using the game, "*Cool!*" (DeepStream VR Inc., 2014). The game provided relaxing music and users waved the virtual limbs to make bubbles or feed seals. This phase aimed to provide a general relief on chronic pain and provided no feedback function to limb movements. The second phase (lower-limb treatment) also appeared in the former study. An approximately one-hour session started with at least 20 to 30 min of a more physically demanding game, "*Quest of Fire*" (Thinking rabbit Inc.) or "*Doggie Feeder*" (game source unknown). "*Quest of Fire*" was a maze game with blockade. Users drove the avatar using the limb and push away any crates that impeded the path. For "*Doggie Feeder*", users "walked" towards the puppies and fed them with candies. Simultaneously, the users shall swing out any invading insects from the candies by their virtual limbs. The trainers could change the speed and number of invaders to adjust the difficulty of the game. Next, for the remaining session time, the authors allowed the patients to choose the game, including "*Web Browser*" (Thinking rabbit Inc.) and other board games [63,64]. The task trained the patients to use the limb to move the cursor, drag and press during gameplay in the virtual environment. Fig. 6 illustrates the gameplay of "*Quest of Fire*", "*Web Browser*" and chess.

Annaswamy, et al. [65] was the only study that utilized mixed reality. They developed three in-house games, including "*Bubble Burst*", "*Pedal*", and "*Piano*". In the first game, bubbles were generated from the floor in different locations and floated towards the ceiling. The goal

Table 3
X-reality systems and the course of the interventions.

Article	Mode	Main Gear	Controller or Feedback	Phase and Course
Ambron, et al. [63]	VR	Oculus Rift DK2	IMUs	Subject #1: 2 sessions Subject #2: 4 sessions over 6 weeks
Ambron, et al. [64]	VR	HTC Vive	Ascension trakSTAR electromagnetic motion-tracking	A total of 9 weeks Phase I (distractor treatment): 5 – 7 sessions Phase II (lower-limb treatment): 10 – 12 sessions
Annaswamy, et al. [65]	MR	Oculus Rift	Microsoft Kinect	Play each day for One month
Chau, et al. [66]	VR	HTC Vive	Thalmic Labs myoelectric armband	5 sessions over several weeks, no more than once a week
Cole, et al. [67]	VR	–	Nest of Birds electromagnetic sensors, Ascensions Technologies	2 sessions per several weeks for upper limb amputees. One session per several weeks for lower limb amputees
Henriksen, et al. [68]	VR	Oculus Rift DK2	Motion capture glove (Perception Neuron, Noitom) Tactile electrical stimulator (ISIS, Inomed)	15 sessions on a daily basis within 5 weeks
Kulkarni, et al. [69]	VR	Oculus Rift	-	One session per month for 3 months
Lendaro, et al. [70]	AR	Webcam and FM	Myoelectric sensors	12 months
Murray, et al. [71]	VR	V6, Virtual Research Systems	5DT-14 data glove Polhemus Fastrak	At least 7 times, maximum 10 sessions on a weekly basis
Ortiz-Catalan, et al. [72]	AR	Webcam and FM	Myoelectric sensors (MyoAmpF2F4VGI8)	18 weeks. 2 sessions per week.
Ortiz-Catalan, et al. [44]	AR	Webcam and FM	Myoelectric sensors	All patients received 2 sessions per week except one that conducted daily
Risso, et al. [73]	VR	HTC Vive	Electrocutaneous tactile stimulation (Tenscare) Functional electrical stimulation (Rehamove3)	No details
Rothgangel, et al. [74]	AR	Tablet-integrated camera	–	In the first 4 weeks, therapists delivered at least 10 sessions. The patients performed the treatment themselves for the next 6 weeks.
Rutledge, et al. [75]	VR	Oculus Rift	Bicycle pedal, Oculus motion sensor	All participants at least completed the baseline visit and a single treatment session. 4 participants further completed multiple sessions.
Snow, et al. [76]	VR	Oculus Rift	Nimble camera system (PrimeSense), Haptic device (HapticMaster), EMG sensors, respiration monitor, GSR	3 weeks involving 9 sessions
Thøgersen, et al. [77]	VR†	HTC Vive	HTC Vive motion tracker, Myo armband (Thalmic Lab)	Total 4 weeks, interventions performed in the 2nd and 3rd weeks

AR: augmented reality; b/n: between; EMG: electromyography; FM: fiducial marker; GSR: galvanic skin response; IMU: inertia measurement unit; MR: mixed reality; VR: virtual reality. †The article claimed their work as augmented reality intervention, but we viewed it as virtual reality.

of the players was to pop the bubbles before they reached the ceiling. During the game, bubbles were simultaneously generated on the left and right side of the players to train symmetric movement and synchronization of the intact and phantom limbs. Difficulty could be adjusted by changing the speed and the locations of the bubbles. For "*Pedal*", two pillars were placed virtually on the left and right side of the player. Each pillar hanged a ball that gradually fall along the pillar. With the participant sat on a chair, s/he need to continuously step and release the left and right colliders (pedals) that appear beneath the foot to keep the balls moving upwards [81]. Similarly, in the third game, the player sat on the chair during "*Piano*". S/he needed to stomp on the piano keys that randomly appeared on the floor. Music notes were played with successive hits [81].

Besides, Chau, et al. [66] implemented three virtual reality games in their studies. An interactive kitchen was facilitated in which participants could move freely in the virtual kitchen and manipulate the food and utensils. However, the study did not mention the specific tasks or goal of the game. Two commercially available virtual reality games, "*Audioshield*" (Dylan Fitterer Company) and "*Eleven: Table Tennis*" (Fun Labs Inc.) were also introduced (Fig. 7). The former was a rhythm game, in which music-synchronized halos would strike towards the players and they needed to block them with the left or right virtual hands correctly according to the color of the halos. On the other hand, there were several modes in the table tennis game, including ordinary game with an opponent, hitting the ball in cups on the table, and hit on a constant moving wooden block on the opposite side, etc. Nevertheless, the paper did not mention the game mode that the participant played. Besides, Lendaro, et al. [70] also implemented a commercially available racing game (Trackmania Nations Forever, Ubisoft) but did not provide specific information on the settings of the gameplay.

The work of Lendaro, et al. [70], Ortiz-Catalan, et al. [72], and Ortiz-Catalan, et al. [44] belonged to the same research team on augmented reality-based interventions (Fig. 8). There were two major themes in their studies. The first theme was a computer game to drive a F1 racing car (Trackmania Nations Forever), which was more inclined to a non-immersive virtual reality experience. Nevertheless, there was no information about the "car race", the number of rounds, or difficulty. The second theme was a modified target achievement control test through the augmented reality platform (Fig. 4). Originated by Simon, et al. [82], the amputees performed the test by positioning their virtual limbs to several targeted postures. In the modified version, the amputees were asked to return their virtual limbs to the neutral position before each attempt [79]. The performance was graded by completion time, dwelling time, accuracy (in distance) in reaching the postures, movement distance and

Table 4
Game, gameplay and protocol designs.

Article	Game	Type	Theme	Design	Task	Protocol
Ambron, et al. [63]	Quest for Fire	Action Simulation	Computer Games	Labyrinth with humanoid avatar	Push crates into pits that impeded the path	One hour (must start with < 20 min of Quest for Fire). Free to choose others in the remining time
	Web Browser	Training Simulation	Lifeskills	Virtual keyboard & screen showing internet	Move the cursor and type on the virtual keyboard by virtual limb	
	Chess	Strategy Game with Simulation	Lifeskills	Chessboard and chess	Play chess by virtual limb	
	Checkers	Strategy Game with Simulation	Lifeskills	Chessboard and chess	Play chess by virtual limb	
Ambron, et al. [64]	Phase I: Cool!	Action Game	Moves and Control	No environment and avatar but bubbles or feed seals	Use arms to make bubbles or feed seals	55 min
	Phase II: Quest for Fire	Action Simulation	Computer Games	Labyrinth with humanoid avatar	Push crates into pites that impeded the path	55 min session (must start with < 30 min of Quest for Fire or Dog Food) Free to choose others in the remaining time
	Phase II: Doggie Feeder	Action Simulation	Lifeskills	Puppy, candies, and insects	Approach the puppy with legs and push away insects from candies with virtual limb	
	Phase II: Web Browser	Training Simulation	Lifeskills	Virtual keyboard & screen showing internet	Move the cursor and type on the virtual keyboard by virtual limb	
	Phase II: Others boardgames	Strategy Game and Simulation	Lifeskills	Chess, Checkers, Solitaire, Spades, 2048, War Light	Play the game with virtual limb	
Annaswamy, et al. [65]	Bubble Burst	Action Game	Moves and Control	Bubbles generated from ground float towards ceiling	Pop the bubbles with knee flexion/extension to save the ceiling	Play 2 game sessions daily
	Pedal	Action Game	Moves and Control	Step and release on virtual collider to keep virtual balls moving up	Utilize ankle dorsiflexion and plantarflexion	
	Piano	Action Simulation	Music	Stomp correctly on the virtual keys randomly appeared on the ground for a correct music note	Utilize tandem bilateral lower extremity movements	
Chau, et al. [66]	Interactive kitchen	Training Simulation	Lifeskills	Kitchen with food and utensils	Freely moved in the kitchen and manipulate food and utensils	45 mins
	Audioshield	Action Game	Music	An abstract space with incoming halos	Use virtual hands to block incoming music-synchronised halo attack	
	Eleven: Table Tennis	Action Simulation	Sports	A playing field of table tennis with an opponent avatar	Table tennis game with a hand to throw the ball during the preparatory phase and the other hand hit the ball using a racket	
Cole, et al. [67]	Grasp an apple	Training Simulation	Lifeskills	A living room with table and chair	Reach, grasp, retrieve, and replace the apple on the surface of a table	60 – 90 mins
	Bass drum	Action Game	Music	A bass drum with pedal	Raising the leg, forward the leg, press the pedal, release the pedal, return to position	
Henriksen, et al. [68]	Bending nunchaku	Training Simulation	Moves and Control	Outdoor open field with a nunchaku	Grab the nunchaku, bend it and move it to a target position	60 – 90 mins
	Frequency discrimination	Training Simulation	Sensation	Outdoor open field with a dashboard showing frequency	Distinguish the frequency of the tactile feedback and press the correct answer on the dashboard	
	Local discrimination	Training Simulation	Sensation	Outdoor open field with a dashboard showing different hand regions	Distinguish the correct location of the tactile feedback and press the correct answer on the dashboard	
Kulkarni, et al. [69]	Ball game	Action Simulation	Sports	A ball inside a bedroom with bed	No details	Three blocks at 10 mins with inter-block rest of 10 mins and 15 mins reflection

(*continued on next page*)

Table 4 (*continued*)

Article	Game	Type	Theme	Design	Task	Protocol
Lendaro, et al. [70]	Car-racing game	Action Simulation	Computer Games	Formula-one cars and racing fields	No details	No details
	Target Achievement Control Test	Training Simulation	Moves and Control	A virtual limb with specific postures in randomized order	Match the targeted posture of the virtual limb with accuracy in virtual reality	
Murray, et al. [71]	Following lightened tiles	Action Games	Moves and Control	A room (no details for others)	Place the limb on coloured tiles that light up in sequence	30 mins
	Ball game	Action Simulation	Sports		batting or kicking a ball	
	Virtual control	Training Simulation	Moves and Control		tracking a moving stimulus, directing a virtual stimulus towards a target.	
Ortiz-Catalan, et al. [72]	Perform instructed movements	Action Game	Moves and Control	Web cam showing the room environment of the participants	Performed the instructed movement one-by-one in a random order	10 mins
	Car-racing game	Action Simulation	Computer Games	Formula-one cars and racing fields	No details	10 mins
	Modified Target Achievement Control test	Training Simulation	Moves and Control	A virtual limb with specific postures in randomized order	Match the targeted posture of the virtual limb with accuracy in virtual reality	Until test complete
	Motion test	Training Simulation	Moves and Control	Perform a series of joint movements	11 sets of elbow motions, three sets of wrist motions, and five sets of hand motions	Until test complete
Ortiz-Catalan, et al. [44]	Car-racing game	Action Simulation	Computer Games	No details	No details	Full session last for 2 h
	Target Achievement Control test	Training Simulation	Moves and Control	A virtual limb with specific postures in randomized order	Match the targeted posture of the virtual limb with accuracy in virtual reality	
Risso, et al. [73]	Sensory performance assessment	Training Simulation	Sensation	Rocks and trees environment. A virtual limb placed over a plank. Two bars put under the forefoot and rearfoot respectively	Judge which bar vibrated faster through visual and/or vibratory feedback	10 sets (bar couples) repeated 10 times
	Embodiment and phantom limb distortion	Training Simulation	Sensation	Beach with incoming water waves	Apply electrical stimulations that ere synchronous and asynchronous to the water waves	5 mins
Rothgangel, et al. [74]	Mirror therapy	Training Simulation	Moves an Control	A virtual limb mirrored by the intact limb	Limb movements (no details)	30 mins
Rutledge, et al. [75]	Ride a bicycle	Action Simulation	Sports	Bicycle and three environments (no details)	Ride a bicycle	60 – 120 mins in baseline visit. Time for further sessions was free.
Snow, et al. [76]	Activity of daily living tasks	Training Simulation	Lifeskills	4 environments: living room, grocery, restaurant, garden	No details	60 mins
Thøgersen, et al. [77]	Pick and Place	Training Simulation	Lifeskills	Living room with a table of objects	Use the virtual hand to grab an object and position and orient it precisely	5 mins for each task and repeated 3 times, with a total of 45 mins
	Imitation	Training Simulation	Moves and Control	Participants' virtual hand and the virtual hand to be imitated.	Follow a certain posture using the virtual hand	
	Sorting	Training Simulation	Lifeskills	A roller band, objects to-be sorted, bins	Sort items into the correct bins that approached from a roller band	

number of redundant moves to reach the target [82]. Two more tasks were added in Ortiz-Catalan, et al. [72]. The first one was to start the session with a 10-minute mission that required the patients to perform isolated movements in a randomized order. Another one was to end the session with "*Motion test*", which involved eleven sets of pre-defined elbow motions, three sets of wrist motions, and five sets of hand motions [83].

There were similar tasks in other studies to train the participants to position their phantom limb or perform some manoeuvres precisely. Most of these "games" were developed in-house. One of the tasks from Thøgersen, et al. [77] asked participants to use their virtual hand to imitate the postures of a silhouette in the virtual environment. In addition, participants grabbed an object, then placed and oriented it according to instruction [77]. Similarly, another training design involved placing the virtual limb onto coloured tiles that would like up in sequence [71]. Henriksen, et al. [68] modelled a nunchaku and required the participants to bend in and placed it precisely in a dedicated zone. Rothgangel, et al. [74] resembled the task of traditional mirror therapy in performing different limb movements using augmented reality and optimized the design using an iterative user-centered approach [78]. On the other hand, activities of daily living that trained motor functions were incorporated in the virtual rehabilitation, including item-sorting [77], playing musical instrument [67], riding a bicycle [75], and kicking a ball [71]. Two studies did not include sufficient details on the tasks to be performed by the participants [69,76].

Training elements using haptics or tactile feedback were presented in the articles of Henriksen, et al. [68] and Risso, et al. [73]. On the one hand, the participants in Henriksen, et al. [68]'s study required par-

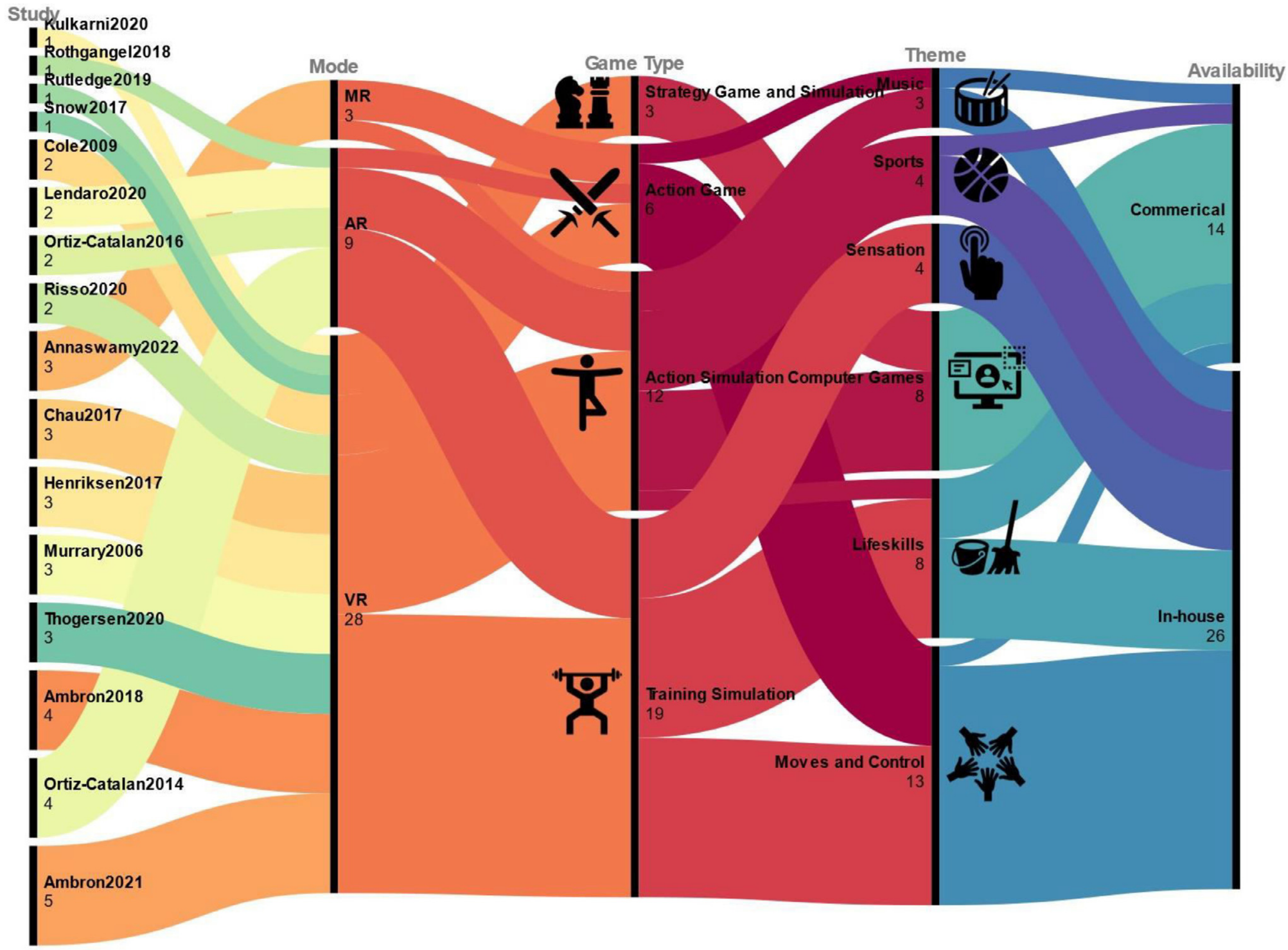

Fig. 5. Sankey Diagram illustrating type of X-reality, the theme availability (commercial versus and in-house) and the type of game or activity in the training session.

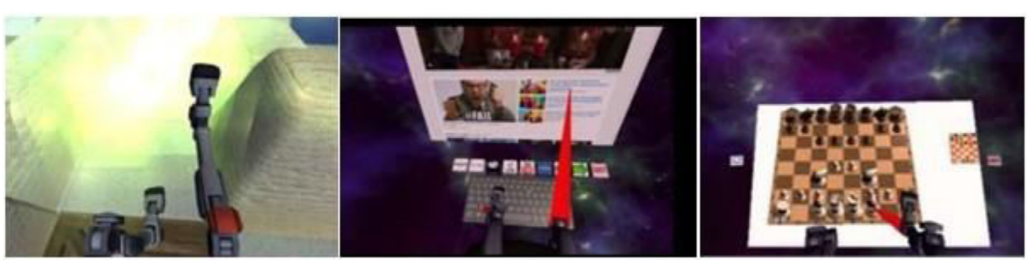

Fig. 6. Illustration of gameplay in "*Quest of Fire*" controlling an avatar in a labyrinth (left), "*Web Browser*" controlling the cursor and keyboard with the virtual limb (center), and playing chess (Figure Source: Ambron, et al. [63], under Creative Commons Attribution License).

ticipants to distinguish the intensity of the tactile feedback, as well as the positions of the six tactile electrodes on different locations of the hand. On the other hand, Risso, et al. [73] put two vibratory bars under the forefoot and rearfoot of the participants (Fig. 9). They needed to determine which bars vibrated faster through a visual and/or tactile feedback. Besides, they were immersed in a virtual environment on the breach with incoming water waves over their feet. Synchronous and asynchronous stimulations were applied to their plantar foot through the bars to enhance their perception of embodiment and phantom limb distortion [73].

3.3.3. Evaluation

All studies adopted pain level as the primary outcome and reported positive findings. Nearly all studies applied standardized instrument to quantify and evaluate the level of phantom pain before and after intervention. The visual analogue scale (VAS), numerical rating scale (NRS) and the short-form McGill Pain Questionnaire (also named as Pain Rating Index, PRI) [84] are the common instruments for evaluation. VAS and NRS are 10-point scales, while that of the PRI ranges from 0 to 75 points [84]. There are other less common instruments for pain evaluation, including the Brief Pain Inventory [85], the Wong-Baker FACE pain score [86], the Neuropathic Pain Symptom Inventory [87], the Pain Disability Index [88], and the Pain Catastrophizing Scales [89].

Some instruments dedicate to the evaluation for specific experience for amputees and/or over phantom limb. The Trinity Amputation and Prosthetic Experience Scales aid physicians to understand how the amputee adapt to the artificial limb though different self-reported items [90], while the Amputee Body Image Scales evaluate the disturbance of body image upon amputation [91]. With regards to the phantom limb, the Phantom Limb Pain Questionnaire contains 25 items to be answered

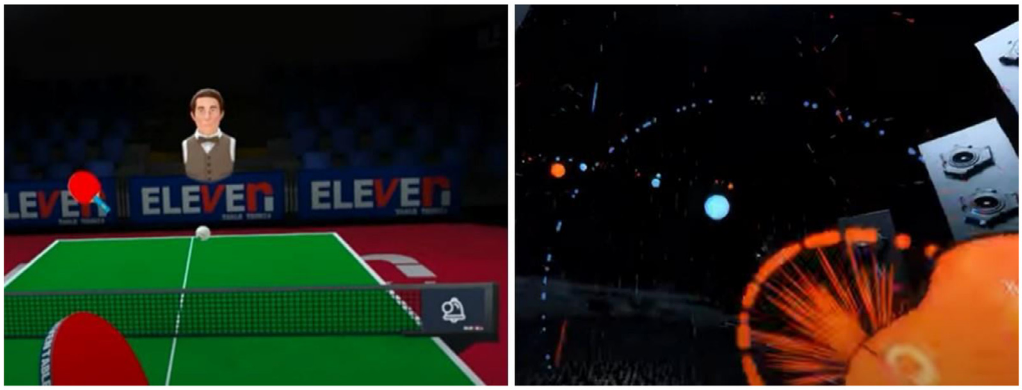

Fig. 7. Gameplay scene in "*Eleven: Table Tennis*" (Fun Labs Inc.) and "*Audioshield*" (Dylan Fitterer Comp.). The left figure illustrates a table tennis match versus computer-controlled avatar. The right figures illustrate incoming-coloured halos that shall be strike by the correct color of virtual fists.

Fig. 8. Augmented reality-based treatment for phantom limb: (A) Myoelectric sensors were mounted on the residual limb to control the virtual arm; (B) The users can watch himself controlling the virtual arm over a conventional webcam. (Figure Source: Ortiz-Catalan, et al. [72], under Creative Commons Attribution License).

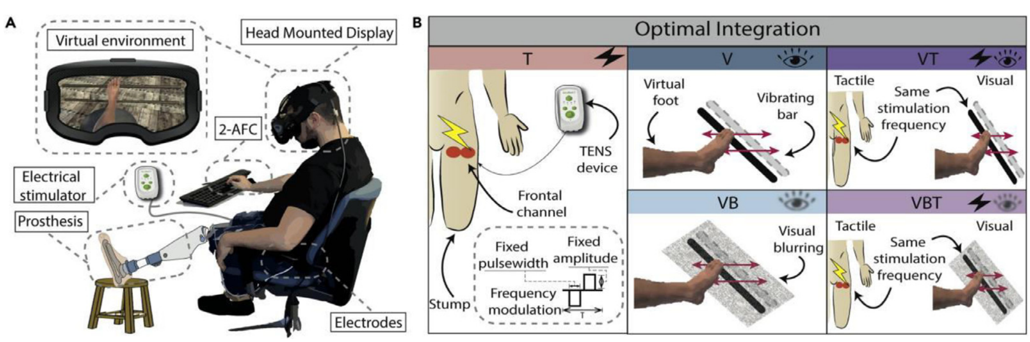

Fig. 9. The amputees watched their phantom limb in the virtual beach and sense the vibratory bar with and without tactile and visual clues (Figure Source: Risso, et al. [73] under Creative Commons Attribution License).

using a 10-point Likert scale [75]. Besides, Snow, et al. [76] applied the Botvinick's Embodiment Questionnaire [32] to quantify the sense of limb ownership of the amputees, while the Proprioceptive Drift Estimation aimed to measure the perceived minimum distance that the limbs are moved [76].

The assessments of health, well-being, and functions were often regarded as secondary measures, which encompass different areas. The general health and psychological well-being are evaluated using the Short-form Health Survey [92], Hospital Anxiety and Depression scale [93], while the quality of life is documented using the EuroQol Questionnaire [94]. The Patient-specific Functional Scale [95] measures the limitations of activities and functions of the amputees while the Frenchay Activities Index [96] estimates the frequency of daily activities.

Despite that some mixed designs studies employed qualitative approach, there were also instruments to assess the experience of the intervention. For pragmatic trials, the participants kept a diary to document their session time and duration, level of engagement and attendance patterns [65]. The System Usability Scale [97] and the Brief Slater-Usoh-Steed Presence Questionnaire [98] could check the perceived complexity and usability of the intervention, and the immersive feeling in the virtual environment, respectively. Besides, Henriksen, et al. [68] developed a set of questions to enquire the degree of illustration, hand-feeling of the game, controllability and realization, as well as the facilitator perceived symmetric motions of participants. Lastly, the Simulator Sickness Questionnaire quantifies the level of cybersickness [99].

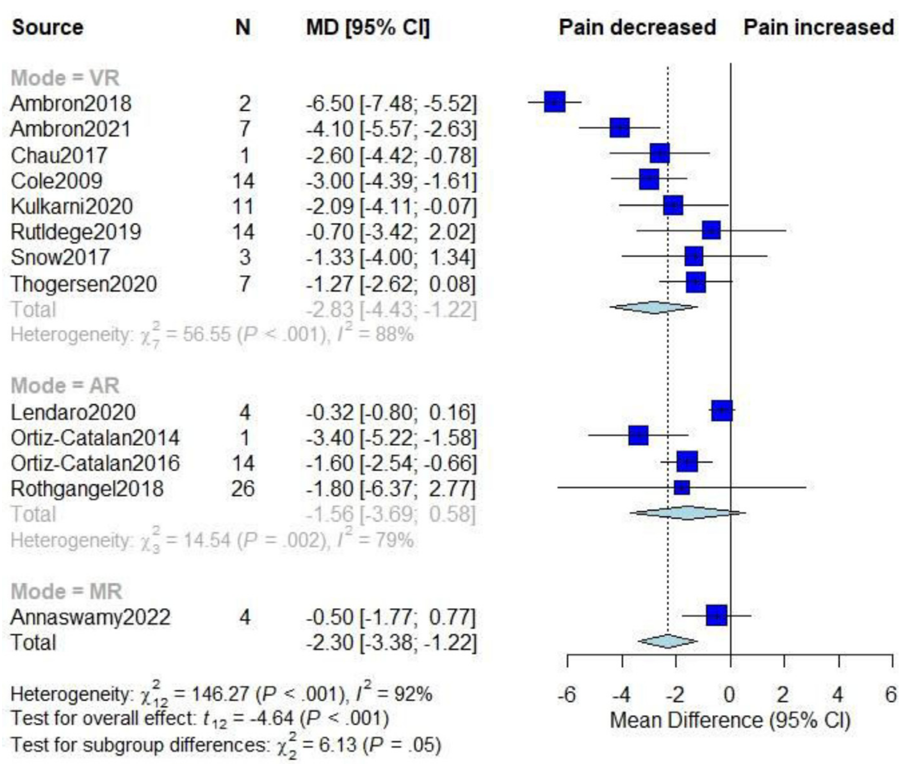

Fig. 10. Pooled analysis of the overall effects of X-reality-based interventions on phantom pain reduction for amputees with subgroup analysis on X-reality modalities. (N: sample size; MD: mean difference; CI: confidence interval; VR: virtual reality; AR: augmented reality; MR: mixed reality).

3.3.4. *Meta-analysis of phantom pain reduction*

Thirteen (n = 13) studies were further eligible to be included in the pooled analysis, as shown in Fig. 10. All studies reported a reduction of phantom pain level after the X-reality intervention. Ambron, et al. [63] accounted for the greatest level of reduction (MD −6.50, 95% CI, −7.48 to −5.52), while the smallest level of reduction was reported by Lendaro, et al. [70] (MD −0.32, 95% CI, −0.80 to 0.16). Overall, X-reality-interventions significantly reduced the level of phantom pain by about two points in a 10-point scale (MD −2.30, 95% CI, −3.38 to −1.22, $p < 0.001$). Nevertheless, substantial heterogeneity was observed (I^2 = 92%) in the overall estimate.

For the subgroup analysis of modality, the test for subgroup difference suggested that there was a statistically significant subgroup effect (p = 0.05) indicating that the choice of modality (i.e., virtual reality, augmented reality, and mixed reality) significantly modified the pain reduction effects. The overall estimate of pain reduction for the virtual reality subgroup (MD −2.83, 95% CI, −4.43 to −1.22) seemed to be larger than that of augmented reality (MD −1.56, 95% CI, −3.69 to 0.58). However, there was yet substantial unexplained heterogeneity between studies within each of the subgroups (virtual reality: I^2 = 88%; augmented reality: I^2 = 79%). Therefore, the validity of estimate for the subgroup could not be affirmed. Covariate distribution could also be a concern since there was only one mixed reality study.

As shown in Fig. 11, the subgroup analysis divided the studies based on the median of publication year (i.e., 2018). The pain reduction effect between studies published before/in 2018 (MD −2.24, 95% CI, −4.40 to −0.09) was similar to those published after 2018 (MD: −2.24, 95% CI, −3.10 to −1.39). Both subgroup effects were significant and there was no statistically significant subgroup effect (p > 0.99). Publication year seemed to partially resolve the heterogeneity. Findings of studies published before/in 2018 were more consistent (I^2 = 2%), while those published after 2018 could not render persistent results (I^2 = 96%).

For the sensitivity test, two case studies were removed from the meta-analysis. The overall pain reduction was yet significant (MD −2.17, 95% CI, −3.45 to −0.88) and consistent with the main analysis.

4. Discussion

Phantom limb is a complex neuropsychiatric condition that affected the functions, quality of life, and autonomy of amputees. Our reviewed articles reported that most of their participants suffered from “painful” phantom sensation, including electric shock, spasm, and burning pain [69,72], which were more severe and frequency among those with upper-limb amputation [67]. Phantom limb could not be effectively settled by oral analgesics, anticonvulsants, antidepressants, and local nerve blocker [66]. Supported by the time from post-amputation to the experiment in our review, the phantom limb problems persisted and bother the amputees for a long time (as long as 50 years). Other interventions failed to mitigate the problem, as described by a few articles in this review. Nevertheless, our pooled analysis indicated that X-reality-based interventions could relieve the phantom pain issue. Besides, patients reported reduction in their medications intakes [44] and they dramatically increased their overall level of activities [63]. The significance of this review lies in its potential to succinct evidence to support X-reality-based intervention in managing phantom limb problem and therefore, remedied their sufferings and improved their quality of life. The development of X-reality-based intervention relied on interdisciplinary work, including computer scientists, biomechatronist, neuroscientist and game designers, to facilitate engaging and patient-centered system and theme designs.

Regardless the modality and theme of the intervention, all studies could be covered in the umbrella of movement representation strategies with different techniques. Movement representation strategies are training methods that neurophysiologically triggers the perceptual-cognitive representation of movement through different techniques, such as observation of actions, actual execution of actions, or motor commands by stimulating afferent sensory pathway [100]. The underlying mechanism of therapy could be associated with the input from movement representation strategies that might reverse the maladaptive change and promote the cortical reorganization process in the primary somatosensory cortex [38,101]. In this review, the computerized mirror therapy by X-reality manifested the most common movement representation strategy.

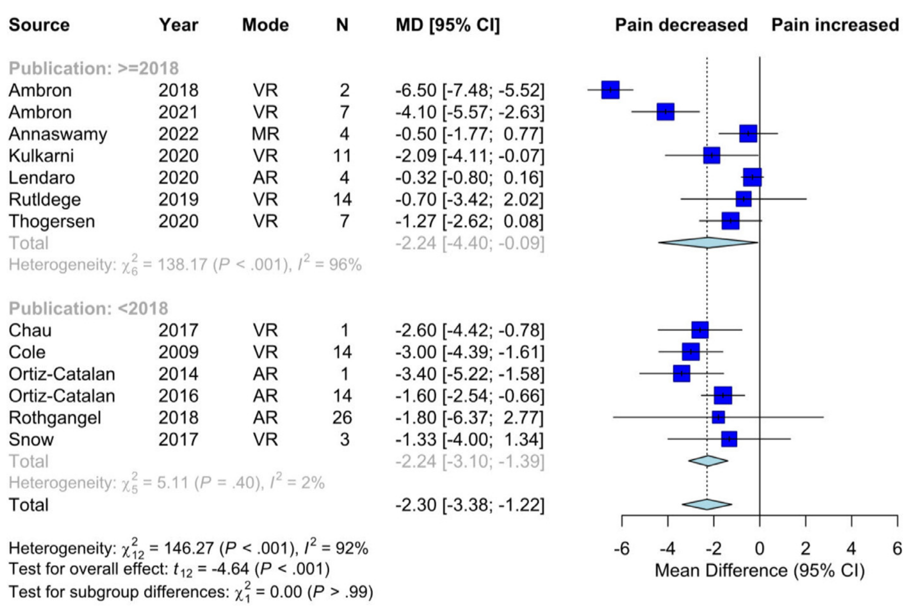

Fig. 11. Pooled analysis of the overall effects of X-reality-based interventions on phantom pain reduction for amputees with subgroup analysis on publication year. (N: sample size; MD: mean difference; CI: confidence interval; VR: virtual reality; AR: augmented reality; MR: mixed reality).

Other theme designs involved volition movement (i.e., motor imagery) to direct the virtual limb using electromyography or movement of the residual limb. In addition to biofeedback and observed touch, sensory stimulation using sensory discrimination and relaxation techniques was suggested to promote cortical reorganization [102] and has been considered in this review with the use of transcutaneous electrical nerve stimulation (TENS), functional electrical stimulus, and vibrotactile feedback [68,73].

Advancements of X-reality technology, including headsets, interfaces, controllers, embedded systems for accessories, and game designs, might produce better immersive effects on patients. Nowadays, headsets are lighter and with higher resolution. The better image quality could enable the rendering of more complex objects and environment space that manifests a better representation of the virtual world and thus immersive experience [103]. Gear weight and fitting affect user acceptance and treatment compliance, especially for long-term use [104–106]. Better computer processing power (from gigaflop to teraflop), sensitivity and sampling rate of controllers could enable a faster responding game with instantaneous simulation of the virtual limb, such as action game and sports game. In augmented reality systems, cameras were used for motion tracking, which could relieve distress in using hand-held devices or mounting wearable sensors on the body [104]. The advancement of computer technology gives rise to advanced computer vision techniques and artificial intelligence and enables mixed reality. Instead of observing the cartoonish virtual limb of the avatar, the users can view their photorealistic virtual limb with a better proprioception of virtual limb movement. In any case, our meta-analysis did not demonstrate apparent differences in pain reduction levels between older and newer systems (estimated by the year of publication). On the other hand, several game or task designs involved computerizing physiotherapy or occupational therapy to rehabilitate the motor functions or lifeskill capacity of amputees simultaneously. There could be a lack of fun and challenges in such cases, while other studies endeavored to encourage amputees to use their “phantom limbs” as controllers to play computer games. In both cases, the designs deviated from the original mechanism of mirror therapy. Notwithstanding falling under the motor imaginary principle of movement representation strategy, the exact mechanism for relieving phantom limb of these game designs warranted further investigation.

There were some limitations in this review. Firstly, there might be selection bias since we only confined the search to English-written journal articles and conference full papers. Moreover, we excluded studies that mixed amputees with patients of other pathologies (such as brachial plexus avulsion) [107,108] to reduce the heterogeneity. Secondly, we impute the standard error for single-subject case reports in the meta-analysis. Nevertheless, our sensitivity analysis demonstrated that the imputation did not substantially alert the findings. Besides, the substantial heterogeneity in our meta-analysis affected the strength of evidence of our overall estimate. We did not assess the publication bias because of the presence of substantial heterogeneity [62]. Heterogeneity could be contributed by the different intervention designs, instruments, and duration of training. Studies that published later (after 2018) seemed to be more inconsistent since they incorporated more different modalities, controller interfaces, and game themes. However, subgroup analysis on game themes was not conducted because some studies incorporated multiple game themes in the course of rehabilitation treatment.

The third limitation was about the mixed study design in our included articles. Further synthesis shall be made with a Mixed Method Systematic Review (MMSR) and/or a meta-ethnography of qualitative evidence. In fact, Stankevicius, et al. [23] suggested that amputees of different amputated level and aetiological cause could have different underlying mechanisms of phantom limb. Qualitative descriptions, such as the nature of the pain, the frequency, location, and occurrence of telescoping could facilitate better understanding and personalized game or treatment designs. Fourthly, there could be ambiguity and confusion to distinguish between virtual reality, augmented reality, and mixed reality. Existing study refereed a framework to describe the experience as a continuum that the modality could be in a dominant or a centered view [109]. Lastly, we only focused on the psychometric pain scale to evaluate the treatment effects on phantom pain. As discussed in Section 3.3.4, there were other evaluations on amputee-specific measures, general health, physical functions, and quality of life. Moreover, instrumented measurements, such as fMRI, were also implemented [73]. Brain activity assessment might help understand the cortical reorganization and uncover the mechanism of phantom limb and interventions [73,110]. Furthermore, similar to another review on traditional interventions for phantom limb, there was high heterogeneity in terms of the number of sessions, the duration the full course and single session, and the frequency of session that called for standardization or evidence-based protocol design [100]. Lastly, our review did not aim to explore the mechanisms of phantom limb and interventions, which could be found in another review [111].

Fig. 12. . A patient-centered graphic user interface to track the progress of phantom limb treatment (Figure source: Rothgangel, et al. [78], under Creative Commons Attribution License).

How the patients feel on the intervention was also evaluated qualitatively. Campelo, et al. [112] emphasized on the construct of engagement with components on accessibility, attitudes, cost, cultural sensitivity, and safety concern, while cybersickness and cyber-contraindication shall also be noted [99,113]. The Intrinsic Motivation Inventory (IMI) could also assess the subjective experience on virtual rehabilitation, including interest/enjoyment, perceived competence, effort/importance, pressure/tension, perceived choice, value/usefulness, and relatedness [114]. A patient-centered user interface could improve the compliance and facilitate better engagement in pragmatic trial, in addition to the continuous report of treatment progress and feedback to the physicians and designers (Fig. 12). The information could also be useful for policy makers for cost-effectiveness analyses [115]. Alternatively, patients may report their levels, positions, and nature of the pain inside the virtual environment, which could then be subsequently used to generate a map in the augmented reality [116] and to facilitate interactive game or treatment designs.

Apart from the above suggestions, we further recommended directions of future research on the improvement of study rigor and integration with other interventions. Meanwhile, the overall strength of evidence of the reviewed articles was hindered by the low sample size, non-vigorous study designs (e.g., case study and case series), and high drop-out rates because of the pre-existing health conditions (e.g., diabetes or tumor). Randomized controlled trials with sufficient sample size are necessary to demonstrate and substantiate the superiority of X-reality over other interventions in pain relief [44]. On the other hand, phantom limb interventions could be integrated with other rehabilitation paradigms for amputees. For example, gait retraining for lower-limb amputees not only help them regain ambulation capability but also improve gait symmetry and consequences of compensatory gait, which could be further facilitated by different modalities of biofeedback systems [117]. Compression garment not only manage edema in amputees but might also enhance proprioceptive information and thus movement coordination [118,119]. Wearable sensors can facilitate balance-training and improve proprioception with the use of lower-limb protheses [120,121]. For upper-limb amputees, the motor volition training could be integrated with that of EMG-driven upper-limb prothesis control [122]. In fact, there were already a couple of myoelectric game for the purpose [123,124], which was very similar to that for phantom limb management. Despite the lack of strong evidence, there were other nonpharmacological interventions that could be integrated and might complement the phantom limb management, such as TENS [125], electroconvulsive therapy [126], acupuncture [127], and psychologic management [128,129].

5. Conclusion

X-reality-based interventions, including virtual reality, augmented reality, and mixed reality have been implemented to manage phantom limb and demonstrated promising positive effects in pain reduction. Game themes targeted on action game, action simulation, and training simulation. Future work should consider randomized controlled trials to compare the effectiveness with other interventions and to develop patient-centered game themes or tasks that are engaging and could attenuate phantom pain and sensation.

Author statement

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Declaration of Competing Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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