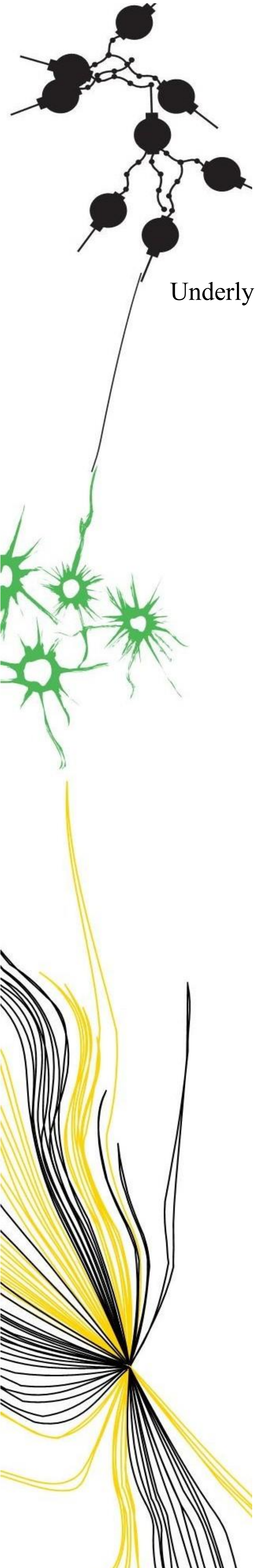

Underlying Mechanisms of Virtual Reality Therapies in Acute and Chronic Pain Management:

A Systematic Review

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17th of July 2020

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Abstract

Pain is a major healthcare problem globally. Despite the enormous individual and societal burdens of pain, evidence shows that acute and chronic pain remains inadequately treated, which highlights the need for alternative treatment methods. Virtual reality (VR) has presented itself as a promising alternative strategy for the treatment of pain. The aim of this review was to describe the underlying mechanisms of VR therapies in acute and chronic pain management, and to examine to what extent these mechanisms differ in acute versus chronic pain. Three databases were searched using the search term ("virtual reality") AND pain AND (treatment OR intervention OR therapy): Scopus, PubMed and PsychINFO. Of the 560 identified studies, 21 studies were included published between January 2015 and April 2020, of which 11 acute pain studies and 10 chronic pain studies. Both adult and paediatric populations were included in this review. It was found that all acute pain studies used the mechanism of distraction in their VR therapies and two studies also used relaxation. In contrast, most chronic pain studies aimed to reverse cortical misrepresentations through neuromodulatory mechanisms, however, chronic pain studies also employed distraction, relaxation, graded exposure, and biofeedback mechanisms. The findings are discussed using the gate control theory of pain and the neuromatrix theory of pain. These findings are in line with the nature of acute versus chronic pain, as acute pain is accompanied by nociceptive stimuli, whereas chronic pain can occur in the absence of actual tissue damage but is produced by neural networks in the brain and is accompanied with maladaptive but reversible changes in the brain.

Keywords: virtual reality, pain, analgesia, acute, chronic, distraction, neuromodulation

Mechanisms of Virtual Reality Therapies in Acute and Chronic Pain Management: A Systematic Review

Pain is a major healthcare problem globally. In 2016, according to The Global Burden of Diseases study, low back pain and migraine were the two leading causes of disability worldwide. Neck pain and other musculoskeletal disorders, characterised by persistent pain, were also listed in the top ten causes of years lived with disability globally (Vos et al., 2017). Studies have shown that acute pain remains treated inadequately (Lynch et al., 2008; Sinatra, 2010; U.S. Department of Health and Human Services, 2019). Consequently, this may lead to a reduced quality of life, impaired sleep, and impaired physical functioning. Moreover, untreated acute pain is a serious risk factor for developing chronic pain (Sinatra, 2010). Chronic pain is associated with significant distress, it impairs daily functioning, and it can be a major source of suffering for affected individuals (Treede et al., 2019). In the United States (US), it is approximated that chronic pain affects 100 million adults, and the economic costs of pain are estimated at between $560 and $635 billion annually by the costs of lost productivity (Gaskin & Richard, 2012). Moreover, 22% of primary care appointments in the US are due to pain-related reasons (Rasu et al., 2014). Additionally, the US is facing an opioid crisis, which has resulted in many deaths due to opioid overdose in the last 20 years (U.S. Department of Health and Human Services, 2019). However, not only in the US but also in the Netherlands, pain is an important healthcare issue. In the Netherlands, 18% of the adults reported to suffer from moderate to severe chronic pain (Breivik et al., 2013), which accounts to roughly three million Dutch adults. Nevertheless, a large proportion of Dutch chronic pain patients report that their pain is insufficiently treated (Bekkering et al., 2011). Despite the known prevalence and the enormous individual and societal burdens of pain, evidence shows that pain remains inadequately treated (Bekkering et al., 2011;

Lynch et al., 2008; U.S. Department of Health and Human Services, 2019), which stresses the need for alternative non-opioid pain management strategies. In the last two decades, virtual reality (VR) has presented itself as an alternative strategy for the treatment of pain. This systematic review focuses on the underlying mechanisms of virtual reality therapies in acute and chronic pain management.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage” (Merskey & Bogduk, 1994). Pain can be categorised in different ways. One distinction that is generally made is between acute pain and chronic pain. Acute pain is pain that persists for less than three months (Johnson, 2019), and commonly occurs during medical procedures (e.g., post-operatively, wound care), after trauma and acute illness (i.e., as symptom; Carr & Goudas, 1999). Acute pain is generally considered to be an adaptive, protective reflex. However, when pain persists for a longer period of time it is no longer considered protective or adaptive, and it can become debilitating and a source of suffering (Niv & Devor, 2004; Raffaeli & Arnaudo, 2017). Chronic pain refers to pain that is persistent or recurrent for longer than three months (Treede et al., 2019). Although chronic pain is at times considered mainly as a symptom of other diseases (e.g., cancer, rheumatoid arthritis), it is presently acknowledged as a disease in its own rights (e.g., fibromyalgia, complex regional pain syndrome; Treede et al., 2019). In 2019, the IASP Task Force for the classification of chronic pain presented the first systematic classification of chronic pain (Treede et al., 2019). It is hoped that this step will advance the recognition of chronic pain, facilitate research in a systematic manner toward the discovery of novel treatments, and eventually reduce the major suffering that chronic pain patients are experiencing (Treede et al., 2019). To better understand how pain works, it is important to

examine two influential theoretical models that have been put forth by Melzack and colleagues (Melzack, 2001; Melzack & Wall, 1965)

The gate control theory by Melzack and Wall (1965) can help to explain which factors contribute to the perception of pain. According to this theory, nociceptive (i.e., damaging, or potentially damaging) stimuli have to pass through a gate control mechanism located in the spinal cord, before they can reach the brain (Triberti et al., 2014). Depending on whether the gate is open or closed, the pain signals can either reach the brain or are inhibited in doing so. The gate control theory holds that not only sensory factors but also many other factors can open or close the gate, such as behavioural and psychological factors (e.g., attention, emotion). Hence, the gate control theory shows that psychological factors can have a significant impact on the perception of pain (Indovina et al., 2018; Triberti et al., 2014). Although currently scholars believe that the gate control theory, as suggested by Melzack and Wall (1965), is oversimplified, its main idea of a gate mechanism is still supported (Braz et al., 2014; Indovina et al., 2018).

A more recent theory that explains how psychological factors influence pain is the neuromatrix theory of pain (Melzack, 2001, 2005), which posits that pain is a multidimensional experience generated by an extensive neural network of different areas in the brain. This neural network produces characteristic “neurosignature” patterns which may be triggered by sensory (e.g., skin injury), affective (e.g., emotion, motivation), and cognitive (e.g., attention, anxiety) inputs, and additionally by genetic influences, to contribute to the outputs. The outputs are not only in the form of pain perception but they are also aimed at restoring homeostasis to the human body (i.e., self-regulation of the body; Melzack, 2001, 2005). Chronic pain states can also be explained through the neuromatrix theory of pain, as Melzack (2005) postulates that these states are not caused by tissue damage, rather they are produced within the brain as a result of a

prolonged state of alertness to threat (i.e., stress). When stress is chronic, it may trigger a neuromatrix program which continuously anticipates danger, and fails to turn “off”, which may result in pain that is not produced by actual tissue damage, instead it is the result of outputs of the neural network in the brain (i.e., neuromatrix; Melzack, 2005).

The consequences that chronic pain has on patients are immense. Chronic pain profoundly impacts nearly all aspects of life of affected individuals, as it impairs patients’ daily functioning (e.g., family and home responsibilities), physical functioning (e.g., recreational activities, exercise), emotional functioning (e.g., depression, anxiety, irritable), occupational functioning (e.g., losing employment, lost productivity), and social functioning (e.g., social isolation, family relations). By doing so, it severely impacts individuals’ quality of life (Bekkering et al., 2011; Breivik et al., 2013; Turk et al., 2011), underscoring the need for adequate treatment for patients with chronic pain.

Despite these serious consequences, 24.8 to 43% of Dutch patients report not receiving treatment for their chronic pain, according to a systematic, best-evidence epidemiological review by Bekkering et al. (2011). For those that do receive treatment, a substantial proportion of Dutch patients, between 22% and 58% receive pharmacological treatment in an attempt to alleviate the pain (Bekkering et al., 2011). The most prescribed pain medication for chronic pain are non-steroid anti-inflammatory drugs (NSAIDs), paracetamol, and opioids (Bekkering et al., 2011; Nalamachu, 2013). However, these pain medications can have serious side effects. NSAIDS are associated with gastrointestinal, cardiovascular, and renal systems complications, paracetamol can cause serious liver damage, and opioids can cause dependence and addiction in addition to other adverse complications (Nalamachu, 2013).

Given the disadvantages of pharmacological treatments, alternative pain management

strategies are warranted to support pain medication. Indeed, Dutch national and international guidelines on chronic pain are increasingly recognising the importance of biopsychosocial interventions (British Pain Society, 2013; Vereniging Samenwerkingsverband Pijnpatiënten naar één stem [VSP], 2017), complementary to pharmacological treatments. Here, pharmacological treatments are considered merely as supplementary to the biopsychosocial treatment. In fact, these guidelines emphasise the relevance of pain management programmes, which consist of a range of methods such as cognitive behavioural therapy (CBT), psychoeducation (i.e., pain education), skills training, and physical exercise (British Pain Society, 2013; VSP, 2017). Currently, however, only a small proportion (<10%) of chronic pain treatments in the Netherlands focus on psychosocial factors (Bekkering et al., 2011). Examples of other treatments that are currently provided to chronic pain patients in the Netherlands are physiotherapy, acupuncture, exercise, relaxation, and surgical procedures. In spite of these treatment options, 34% to 76% of Dutch chronic pain patients indicate that their pain is inadequately treated (Bekkering et al., 2011). Despite the known prevalence and the enormous individual and societal burdens of pain, evidence shows that pain remains inadequately treated (Bekkering et al., 2011; Lynch et al., 2008; U.S. Department of Health and Human Services, 2019), which emphasises the need for alternative non-opioid pain management strategies.

Virtual reality (VR) is such an alternative strategy that has made its way into pain management. Virtual reality can be defined as a computed-generated simulation of an artificial three-dimensional (3D) environment, which allows users to interact in real-time with 3D objects that are present in the simulated virtual environment (VE; Dionisio et al., 2013). Users can immerse themselves in the VE by wearing a head-mounted display (HMD), which is typically connected to a computer or mobile phone (Arane et al., 2017). Other VR equipment that are

often used in combination with an HMD are headphones, motion sensors, and devices such as a computer mouse or a keyboard to be able to interact with the VE. Through these devices, users can receive feedback through multiple modalities, by means of visual, auditory, tactile, and sometimes also kinaesthetic stimuli (Indovina et al., 2018). This can lead to a sense of “presence” in the VE, which is the psychological feeling of being and acting in the VE (Cummings & Bailenson, 2015). Another term that is often used when referring to VR is “immersion”. Where presence is a subjective experience of an individual, immersion is defined as an objective technological feature of VR such as the field of view or image quality (Cummings & Bailenson, 2015). These definitions also help to clarify the relationship between these two seemingly related concepts. That is, the more immersive a VR technology is, the more presence one feels in the VE (Cummings & Bailenson, 2015). As VR technologies are increasingly becoming more advanced and immersive, this also increase the sense of presence, and in turn, demand more attentional resources from users (Hoffman et al., 2006). The ability of immersive VR to be able to draw attentional resources away from the real world, and into the VE is one of the reasons why VR is particularly suitable for the treatment of pain (Ahmadpour et al., 2019; Gold & Mahrer, 2018).

In the last two decades, VR has been extensively studied for the management of pain (Indovina et al., 2018; Mallari et al., 2019; Malloy & Milling, 2010). Most of the earlier VR studies focused on the management of acute pain through the underlying mechanism of distraction (Hoffman et al., 2000). Distraction is based on the notion that the processing of pain requires attention (Eccleston & Crombez, 1999). Moreover, it has been shown that human beings have limited attentional resources. Therefore, if a distractor demands much attentional resources, this leaves fewer cognitive resources for the processing of painful stimuli (Ahmadpour et al., 2019; Eccleston & Crombez, 1999). Malloy and Milling (2010) conducted a systematic review on the effectiveness of VR distraction for pain reduction. VR was found to be effective in reducing experimental pain, as well as in studies examining burn injuries. Moreover, they highlighted that immersive VR was more effective than non-immersive VR. That is, studies that used HMDs reported greater benefits in relieving pain compared with studies that did not fully immerse the participants in VR (Malloy & Milling, 2010). More recently, Mallari et al. (2019) performed a systematic review and meta-analysis where they compared the effectiveness of VR in acute and chronic pain in adults. They reviewed 10 acute pain and 10 chronic pain studies which were published between 2007 and 2018. Their results showed that for acute pain there exists solid evidence regarding its effectiveness, and the acute pain studies were rated of high methodological quality. However, concerning chronic pain, the authors reported mixed findings. Although they found some evidence for pain relief during and directly after the VR therapies, the chronic pain studies did not show long-lasting analgesic (i.e., pain relieving) effects (Mallari et al., 2019).

Besides reviews on the effectiveness of VR in pain management, some reviews also examined the psychological factors and the underlying mechanisms of VR therapies. Triberti and colleagues (2014) performed a systematic review to examine the psychological factors that impact VR as a distraction technology (Triberti et al., 2014). These authors found that presence was one of the most important psychological factors linked to the experience of VR. They argue that a sense of presence is strongly linked to attention, and that a higher sense of presence is associated with greater analgesic effects through attentional mechanisms (i.e., distraction). Moreover, Triberti et al. (2014) assert that where presence indirectly affects pain through attention, affective (i.e., fun) and anxiolytic factors (i.e., reducing anxiety) are directly related to

the experience of pain. Additionally, Indovina et al. (2018) performed a comprehensive literature review on VR as a distraction intervention for paediatric patients during medical procedures. In accordance with Triberti et al. (2014), they suggest that the analgesic mechanism of VR distraction is mediated by attentional (i.e., through multisensory stimulation and sense of presence), anxiolytic (i.e., through reducing stress and anxiety), and/or affective factors (i.e., by increasing fun and positive affect). Conversely, another review examined the underlying mechanisms of VR therapies in pain management beyond merely distraction-based mechanisms. Gupta et al. (2018) conducted a selective review in which they included six studies of which two used distraction and four studies used non-distraction mechanisms. Their review included three chronic pain studies, two cold pressor (i.e., experimentally induced pain) studies, one acute pain study, and included both adult and paediatric studies. One of the chronic pain studies combined VR and biofeedback to treat paediatric chronic headaches, and was aimed to accomplish relaxation (Gupta et al., 2018). The two other chronic pain studies both focused on treating fibromyalgia. One of these studies used imaginary exposure therapy in VR to reduce pain catastrophisation by showing images of active (i.e., healthy exercise) and passive activities to patients while using functional magnetic resonance imaging. The other study used a cognitive behavioural therapy assisted by VR to promote activity management, aimed at inducing positive affect and motivation. Finally, one cold pressor study used a technique designed to enhance pain control, as participants were presented with unpleasant shapes and sounds (representing pain), which they had manipulate to pleasant shapes and sounds (representing calmness or no pain). Notably, in the review by Gupta et al. (2018), the studies that examined non-distraction mechanisms mostly targeted chronic pain rather than acute pain. Considering the major burden of chronic pain, the authors acknowledge the importance of investigating mechanisms other than distraction, as particularly for chronic pain states other mechanisms are likely needed to extend the effectiveness of VR beyond acute pain (Gupta et al., 2018).

Altogether, these reviews suggest that the analgesic mechanism of VR distraction is mediated by attentional, anxiolytic, and/or affective factors (Indovina et al., 2018; Triberti et al., 2014). Moreover, particularly, for chronic pain several non-distraction mechanisms have been explored such as biofeedback, relaxation, imaginary exposure, positive affect, motivation and pain control. Additionally, the significance of investigating non-distraction mechanism is highlighted given the enormous burden of chronic pain (Gupta et al., 2018).

In recent years, research on VR has developed quite rapidly as technology has become more advanced and the VR delivery systems have become more affordable (Senkowski & Heinz, 2016). Fully immersive VR, using head-mounted displays, have become more common and are the topic of much research on the management of pain (Indovina et al., 2018; Mallari et al., 2019). These technological advancements also bring new possibilities for the treatment of chronic pain, that is, to investigate non-distraction mechanisms, as well as to provide VR therapy in the home setting. As the field of VR in pain management is growing exponentially, and methods are improving rapidly, particularly for the treatment of chronic pain, the present systematic review focuses on the underlying mechanisms of VR therapies in both acute and chronic pain management for articles published between 2015 and 2020.

Additionally, this review will include both adult and paediatric populations to examine to what extent the underlying mechanisms of VR therapies differ between these age groups. This systematic review by no means aims to provide a comprehensive review of all studies conducted on VR pain management, or its effectiveness for that matter, rather the specific focus of this review lies on the mechanisms underlying VR therapies in acute and chronic pain management.

Therefore, the general aim of this systematic review is to describe the underlying mechanisms of VR therapies in acute and chronic pain management, and moreover, to examine to what extent these mechanisms differ in acute versus chronic pain management. Furthermore, a second aim is to compare the underlying mechanisms of VR therapies in adult versus paediatric populations.

Method

Search Strategy

After preliminary searches, the final search was performed on 14 April 2020 using the following search string: ("virtual reality") AND pain AND (treatment OR intervention OR therapy). The search was carried out in three databases: Scopus, PubMed and PsychINFO (see Appendix A for logbook).

Deduplication

To optimise the detection of duplicates, the process was conducted using two different methods. First, identified records were imported in the citation manager Mendeley, which automatically detects duplicates among imported citations. Second, the Systematic Review Assistant-Deduplication Module (SRA-DM) by Rathbone et al. (2015) was used. It was chosen to use two methods to minimise the number of false positives (i.e., records that were falsely deleted) and false negatives (i.e., records that were falsely kept; Kwon et al., 2015; Rathbone et al., 2015). Subsequently, the results of the two methods were manually compared. The manual comparison revealed that the SRA-DM had removed two records which Mendeley had not deleted. Further, it highlighted one duplicate which both methods had not detected which was removed manually.

Screening

To aid the screening process, Rayyan was used, a web and mobile app for systematic reviews (Ouzzani et al., 2016). The studies were screened in two steps: (1) screening of titles and abstracts; (2) full-text analysis to assess eligibility.

Eligibility Criteria

Studies were included on the basis of the following criteria: (1) journal article; (2) written in English; (3) published between January 2015 and April 2020; (4) describing use of VR in acute or chronic pain; (5) describing the underlying mechanisms of the VR therapy; (6) all research designs; (7) immersive VR. Acute pain was defined as pain that persists for less than three months. Chronic was defined as pain that persists or recurs for longer than three months. Due to the specific focus of the systematic review on the underlying mechanisms of VR therapies in acute and chronic pain management, it was chosen to include all research designs. That is, not only quantitative (e.g., experimental) designs but also qualitative designs are included, as these type of designs in particular may examine the underlying mechanisms of VR therapies in more depth. Immersive VR was defined as VR that uses an head-mounted display to fully immerse the user inside the computer-generated simulation (Furht, 2008).

The exclusion criteria were the following: (1) reviews; (2) not sufficiently describing the underlying mechanisms of VR therapies; (3) experimental pain; (4) not incorporating VR as an intervention, therapy, or treatment; (5) the use of VR for other purposes than pain management; (5) non-immersive VR. Non-immersive VR was defined as VR where users are in a computer-generated environment without being fully immersed, an example is this study by Garcia-Palacios et al. (2015).

Data Extraction

The following data were extracted from included studies: (1) study characteristics: first author name, year of publication, location, study design; (2) sample characteristics: sample size, age, gender, type of pain; pain condition; (3) VR characteristics: VR intervention, virtual environment, VR equipment; (4) underlying mechanisms of VR therapy; (5) main outcomes.

Results

Search Results

The literature review identified a total of 560 articles through database searches. After duplicate removal, 378 studies were screened on titles and abstracts (see Figure 1). This resulted in 78 articles eligible for full-text review, which were reviewed for the inclusion and exclusion criteria. Of these, a total of 21 articles were included in this systematic review. Of the full-text articles assessed for eligibility, 40 articles were excluded because the underlying mechanism of the VR therapy was not described sufficiently; six articles because they used non-immersive VR; four articles because the full-text was not accessible; four articles because the VR was used for other purposes than pain management (e.g., functional magnetic resonance imaging task); two articles because of wrong publication type (i.e., conference paper, review); and one article because it targeted experimental pain.

Characteristics of Included Studies

The characteristics of the 21 included articles are presented in Table 1. All studies were published between 2015 and 2020. Of the included studies, 11 examined the use of VR for acute pain conditions and 10 studies examined VR for chronic pain conditions. Of the acute pain studies, eight studies focused on paediatric populations and three focused on adult populations. Of the chronic pain studies, nine examined adult populations, and one study focused on a

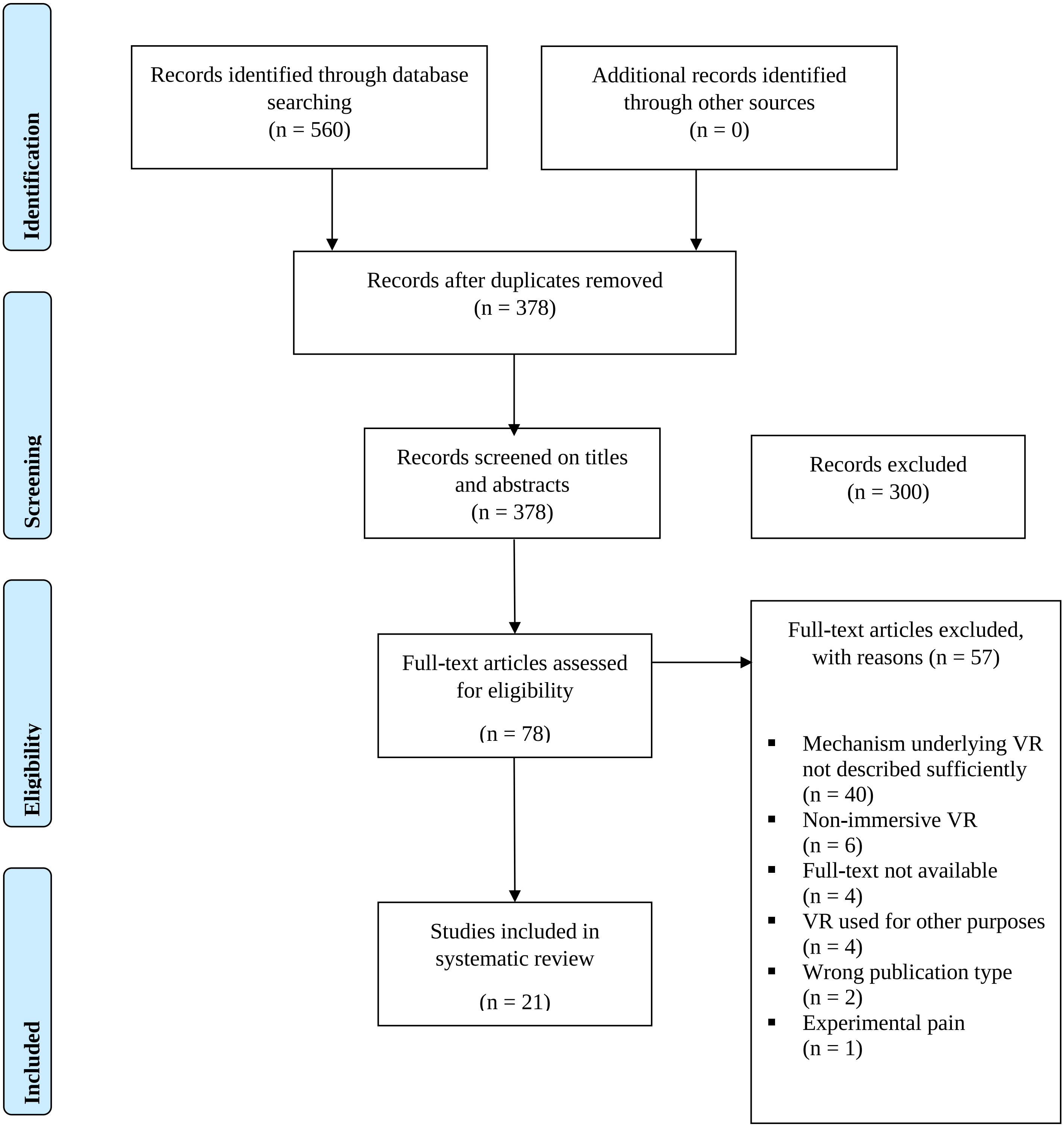

Figure 1. PRISMA flow-diagram depicting the study selection process in this systematic review. VR, virtual reality

paediatric population. In total, 1039 participants were included in the studies. Participants ranged from five to 80 years. The mean gender composition was 38% female across studies. The sample sizes of the acute pain studies ranged from 1 to 182 participants. For chronic pain studies, the sample size ranged from 1 to 48 participants. The mean sample size for acute pain studies was 76 and for chronic pain studies 20. Study locations were United States of America (n=7), Canada (n=2), Japan (n=2), Poland (n=2), Switzerland (n=2), China (n=1), Denmark (n=1), Iran (n=1), Italy (n=1), Spain (n=1), and Turkey (n=1). With regard to the study design, six studies were randomised controlled trials, four studies used non-experimental within-subjects designs, three studies used quasi-experimental designs, two studies used experimental designs, two studies were case reports (i.e., one mixed-methods and one quantitative design), one study was a comparative cohort study, one study used a crossover design, one study used a mixed-methods design, and one study used a mixed-methods case series design. For acute pain studies, seven out of 11 used experimental designs, of which six were RCTs. Of the studies examining VR in chronic pain, one study used an experimental design. Seven acute pain studies focused on needle-related pain (i.e., venipuncture, intravenous placement), two focused on wound-related pain (i.e., wound dressing change, wound infection), and one article examined a wide range of somatic and visceral pain conditions. Six chronic pain studies examined chronic neuropathic pain (e.g., phantom limb pain, complex regional pain syndrome), three studies focused on diverse pain conditions (e.g., lower back pain, rheumatoid arthritis), and one study focused on cancer-related pain. Concerning the VR equipment, all but one of the studies used HMDs (n=20). One study used VR goggles mounted on a robot-like articulated arm. Two studies used two different HMDs during the same study. The two most frequently used HMDs were Samsung Gear (n=9) and Oculus (n=7). Of the studies on acute pain, six studies used only HMDs, four studies used

Table 1

Characteristics of Included Studies in Alphabetic Order on First Author, Divided by Type of Pain (Acute or Chronic)

Study (first author)	Year	Country	Sample			Study design	Type of pain	Type of pain condition	VR equipment
			n	Age range (years) or M ± SD	Gender % ♀				
Atzori	2018	Italy	15	7–17	33	RCT, within-subject post-test only design	Acute	Needle-related pain (venipuncture)	HMD (Personal 3D Viewer Sony HMZ-T2 with 45° FOV), earphones, supported by a laptop to interact with VR software.
Ding	2019	China	182	18–65	60	RCT	Acute	Wound-related pain (following haemorrhoid surgery)	HMD (eMagin Z800 3DVISOR with 40° FOV), and a FasTrak VR control box. Supported by a computer for VR software.
Dumoulin	2019	Canada	59	8–17	35	RCT	Acute	Needle-related pain (venipuncture, IV placement)	HMD (eMagin Z800), supported by a computer for VR software, and a wireless computer mouse.
Esumi	2020	Japan	1	40	♂	Quantitative case report	Acute	Wound-related pain (fasciotomy wound infection)	HMD (Samsung Gear Oculus) fitted with a Samsung Galaxy S7 phone loaded with appliedVR^{TM}
Gold	2018	USA	143	10–21	50	RCT, parallel design	Acute	Needle-related pain (venipuncture)	HMD (Samsung Gear) fitted with a Samsung Galaxy S6 phone (ages 13-21 years); HMD (Google Pixel mobile-based Merge VR) (ages 10-12 years).

(continued)

Table 1 (continued)

Study (first author)	Year	Country	Sample			Study design	Type of pain	Type of pain condition	VR equipment
			n	Age range (years) or M ± SD	Gender % ♀				
Hoffman	2019	USA	48	6–17	29	Within-subjects, within-wound care design; pilot study	Acute	Burn pain	Portable water-friendly VR (MX90 VR goggles with 90° FOV) held by a robot-like articulated arm goggle holder (Magula arm), supported by a laptop, an audio-visual unit, stereo speakers, and a wireless computer mouse.
Özalp Gerçeker	2020	Turkey	136	5–12	46	RCT	Acute	Needle-related pain (venipuncture)	HMD (Samsung Gear Oculus) fitted with a Samsung Galaxy S5 Note phone
Piskorz	2018	Poland	38	7–17	47	Post-test only between-subjects quasi-experimental design	Acute	Needle-related pain (venipuncture)	HMD (Oculus Rift DK2 with 100° FOV)
Piskorz	2020	Poland	57	7–17	53	Between-subjects experimental design	Acute	Needle-related pain (venipuncture)	HMD (Samsung Gear) (not further specified)
Tashjian	2017	USA	100	51 ± 17	53	Nonrandomised comparative cohort study	Acute	Wide range of somatic and visceral pain conditions	HMD (Samsung Gear Oculus) fitted with a Samsung Galaxy S7 phone

(continued)

Table 1 (continued)

Study (first author)	Year	Country	Sample			Study design	Type of pain	Type of pain condition	VR equipment
			n	Age range (years) or M ± SD	Gender % ♀				
Walther-Larsen	2019	Denmark	59	7–16	12	RCT, observer-blinded design	Acute	Needle-related pain (IV placement)	HMD (Samsung Gear) fitted with a Samsung Galaxy S6 phone, and a controller
Chau	2017	USA	1	49	♂	Mixed-methods case report	Chronic	Neuropathic pain (PLP)	HMD (HTC Vive VR), 2 handheld controllers, 2 positional tracking sensors, an armband myoelectric controller (MyoBand). Supported by a computer for VR software.
Fowler	2019	USA	16	28–63	19	Within-subjects pretest-posttest design; feasibility study	Chronic	Diverse pain locations: low back (n=11); head (n=2); other (n=3)	HMD (Oculus Rift VR) with a hand-tracking controller; HMD (Samsung Oculus Gear VR) fitted with Samsung Galaxy phone, with a hand controller.
Garrett	2017	Canada	8	31–71	75	Mixed-methods pilot case series	Chronic	Diverse chronic pain conditions (e.g., lower back pain, knee pain, CRPS)	HMD (Oculus Rift DK2 with a 110° FOV), a game controller, supported by a computer.
Ichinose	2017	Japan	9	43–75	11	Quasi-experimental design	Chronic	Neuropathic pain (PLP)	HMD (Oculus Rift DK2), a Microsoft Kinect sensor, vibration motors, and earphones.

(continued)

Table 1 (continued)

Study (first author)	Year	Country	Sample			Study design	Type of pain	Type of pain condition	VR equipment
			n	Age range (years) or M ± SD	Gender % ♀				
Matamala-Gomez	2019	Spain	19	40–55	74	Within-subjects experimental design	Chronic	Neuropathic pain (CRPS, PNI)	HMD (Oculus Rift DK2 with 100° FOV), headphones for task instructions, and vibrators for visuo-tactile stimulations.
Pozeg	2017	Switzerland	40	23–71	10	Factorial, randomised, within-subjects design	Chronic	Neuropathic pain (SCI)	HMD (not specified), headphones, a camera, and a wheelchair.
Rutledge	2019	USA	14	37–76	7	Within-subjects design	Chronic	Neuropathic pain (PLP)	HMD (Oculus Rift VR), wireless motion sensor, bicycle peddler, prosthetic pedal, supported by a computer.
Sharifpour	2020	Iran	30	14–18	Not stated	Quasi-experimental pretest-posttest design with follow-up	Chronic	Cancer-related pain	HMD (Samsung Gear VR) fitted with Samsung Galaxy Note8 phone, and a VR video player application (AAA VR Cinema, InstaVR).
Solca	2017	Switzerland	48	23–80	58	Crossover double-blind study	Chronic	Neuropathic pain (CRPS)	HMD (Oculus DK1 with 90° FOV), headphones, supported by a computer, VR stimulus presentation software (ExpyVR), and a microcontroller for ECG signals.

(continued)

Table 1 (continued)

Study (first author)	Year	Country	Sample			Study design	Type of pain	Type of pain condition	VR equipment
			n	Age range (years) or M ± SD	Gender % ♀				
Venuturupalli	2019	USA	17	53 ± 16	88	Mixed-methods design, pilot study	Chronic	Chronic autoimmune disorders: rheumatoid arthritis (n=11); lupus (n=4); fibromyalgia (n=3).	HMD (Samsung Gear VR) fitted with a Samsung Galaxy S7 phone, and headphones (Nubwo N2) equipped with a microphone for breath tracking.

Note. 3D, three-dimensional; CRPS, complex regional pain syndrome; FOV, field of view; HMD, head-mounted display; M, mean; n, number of participants; PLP, phantom limb pain; PNI, peripheral nerve injury; RCT, randomised clinical trial; SCI, spinal cord injury; SD, standard deviation; USA, United States of America; VR, virtual reality; ♂, only male

HMDs which were supported by a laptop/computer for VR software, and three studies used a computer mouse or controller to interact with the VE. Chronic pain studies used a variety of VR equipment (e.g., motion sensors, myoelectric armband controller, hand-tracking controllers) to be able to create more advanced VR setups.

Virtual Reality in Acute Pain Management

All studies in this review which examined VR in acute pain management used *distraction* as an underlying mechanism of the VR therapy (see Table 2). However, two studies used not only *distraction* but also *relaxation* in addition to *distraction* to treat pain. The following section is divided according to these underlying mechanisms: (1) *distraction*; (2) *distraction and relaxation*.

Distraction

The analgesic effect of VR has most frequently been attributed to *distraction.* The mechanism of *distraction* is based on the notion that the processing of pain requires attention. However, human beings have limited attentional resources (Eccleston & Crombez, 1999). When users are immersed in multisensory (e.g., visual, auditory, proprioception) VR, their attention is diverted away from the painful stimuli into the VE, which creates the illusion of presence (i.e., the sense of being there). Consequently, this places high demands on the limited attentional resources, and fewer attentional resources are available to process incoming painful stimuli. In summary, pain is reduced by an increase in cognitive load through multisensory VR, which hinders the processing of nociceptive stimuli as these have to compete for available attentional resources (Atzori et al., 2018; Ding et al., 2019; Dumoulin et al., 2019; Gold & Mahrer, 2018; Hoffman et al., 2019; Piskorz et al., 2020; Piskorz & Czub, 2018; Tashjian et al., 2017; Walther-Larsen et al., 2019). In the next section, first, the adult studies that employed *distraction* as an underlying mechanism of the VR therapy will be described, followed by the paediatric studies thereafter.

Two studies in this review used *distraction* as the underlying mechanism of the VR therapy to reduce acute pain in adult populations. Ding et al. (2019) performed a relatively large-scale randomised control trial (RCT), using VR during the first wound dressing change following haemorrhoid surgery. Notably, this study had the highest number of participants of all included studies in this review, with 182 adults. After surgery, both groups had received pain medication, hence, VR was used adjunctively (i.e., complementary) in this study. Patients in the VR group interacted with SnowWorld, an immersive VR software specifically created to *distract* patients during medical procedures. In SnowWorld (Hoffman et al., 2011), patients were immersed in an interactive 3D icy canyon in VR where they interacted with snowmen, penguins, and mammoths by throwing snowballs in the virtual environment (VE), while hearing music and 3D sound effects. The authors found that VR reduced pain significantly throughout the wound dressing change, compared with the control group. However, the control group in this study received routine dressing change, which did not entail any distraction techniques (Ding et al., 2019). Hence, it is unclear whether the effect can be attributed to merely the use of a distraction technique, rather than the specific use of VR *distraction*.

In a similar vein, Tashjian et al. (2017) conducted a comparative cohort study where patients in the VR cohort interacted with Pain RelieVR, an immersive 360° game where patients shot balls at moving objects in the fantasy world by the movement of their head, while listening to motivational music and positively reinforcing sounds. In this study, VR was not used during a specific painful procedure, rather the study consisted of hospitalised patients with a diverse range of somatic and visceral pain conditions (Tashjian et al., 2017). In contrast to the study by

Table 2

Description of VR Therapies and its Main Results, Ordered by Underlying Mechanisms of VR Therapies in Acute Pain Management:

(1) Distraction; (2) Distraction and Relaxation

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
1. *Distraction* mechanism (*n* = 9)							
Ding	2019	182 adult patients who had undergone haemorrhoid surgery	Acute	SnowWorld: 3D interactive snowy canyon in VR where patients could shoot snowballs at objects in the VE, while hearing music and 3D sound effects. The VG interacted with SnowWorld for ~21 min.	Distraction	During the wound dressing change, patients in the VG reported significantly lower pain scores compared with the CG, at the 5-, 10-, 15-, and 20-minute time-points. No significant differences were found between groups 5 min after dressing change.	Use of VR during the first dressing change after surgery. Both groups had received pain medication. CG received routine dressing change (no distraction techniques). Limitations include the use of a relatively old HMD with limited FOV.
Tashjian	2017	100 adult medical acute care inpatients, with wide range of somatic and visceral pain conditions	Acute	Pain RelieVR: Immersive 360° game, fantasy world, head-tracking, with motivational music and positively reinforcing sounds. Patients in the VR cohort played the Pain RelieVR game for 15 min.	Distraction	Both cohorts reported significant reductions in pain scores. The mean pain reduction was significantly larger in the VR cohort compared with the control cohort. No adverse outcomes (i.e., blood pressure, heart rate) were reported in the VR cohort.	Control cohort watched a 15-min 2D HD video displaying relaxing nature scenes (music included) on a 14-inch screen. Limitations include lack of randomisation, and lack of information on reasons of patients refusing to use VR.

(continued)

Table 2 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Atzori	2018	15 children and adolescents with cancer (n=11) and blood diseases (n=4) undergoing venipuncture	Acute	SnowWorld: 3D interactive snowy canyon in VR where patients could shoot snowballs at objects (e.g., snowmen, penguins, mammoths) in the VE, while hearing music and 3D sound effects. Patients used VR for 3 min during the venipuncture.	Distraction	During VR, patients reported significant reductions in “time spent thinking about pain”, “pain unpleasantness” and “worst pain”, compared with during “No VR”. Patients reported significantly more fun with VR, experienced a strong illusion of presence, and rated the VR objects as “moderately real”.	Patients underwent one venipuncture with VR, and one with SOC (order randomised). Pain was only measured after the procedure. ”No VR” condition consisted of SOC: non-medical conversation by nurse. Limitations include the small sample, and the SOC as control condition instead of other distraction techniques.
Gold	2018	143 children and adolescents undergoing venipuncture	Acute	Bear Blast: Multisensory game where patients travel through an energetic, highly interactive cartoon world, while soothing music plays in the background. Using head-tracking, patients can shoot balls at targets in the VE. VR condition received SOC plus VR during blood draw (~5min total).	Distraction	VR significantly reduced pain and anxiety during venipuncture compared with SOC. Patients with higher anxiety sensitivity experienced significantly less anxiety than patients with lower anxiety sensitivity when using VR.	SOC consisted of a brief interaction with the phlebotomist before the venipuncture, and a cartoon playing on a TV. Limitations include a high proportion (36%) of patients who declined to participate during screening (most common reason: time constraints).

(continued)

Table 2 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Dumoulin	2019	59 children and adolescents at the ED undergoing needle-related procedures (IV placement, venipuncture, or both)	Acute	Shoot the Flies: VG was immersed in VR in a virtual apartment. The aim was to distract from painful stimuli by looking at the flies, and to shoot as many flies as possible by clicking a button on the wireless mouse (~10 min VR time)	Distraction	Patients reported significant reductions in pain intensity and fear of pain in all three conditions, compared with baseline. Patients in the VR condition reported significantly less fear of pain, compared with both control conditions, but no significant difference was found for pain intensity.	Control conditions: watching TV (minimal control condition), and distraction by Child Life (gold standard control condition). Majority of patients used a topical anaesthetic. Study was conducted in a natural uncontrolled environment of the ED, with its restrictions.
Walther-Larsen	2019	59 children and adolescents undergoing IV placement before anaesthesia	Acute	Seagull Splash: Interactive 3D game where a boat with a bucket of fish was approached by seagulls aiming to eat the fish. The aim was to prevent this by shooting water balloons with a slingshot at the seagulls. Patients played the VR game for ~10-15 min VG received SOC+ Seagull Splash.	Distraction	No significant difference in pain scores was found between the VG and the CG. Patients in the VG reported high satisfaction levels. All patients in the VG indicated their preference to use the same distraction technique again, a borderline significant result compared with controls.	CG received SOC: topical numbing cream, positioning, and distraction by a specialised pain nurse. Three patients (10%) did not want to use the VR equipment, because they disliked the VR game/setup. These were excluded from the analysis. The study consisted largely of boys. Pain was only measured after the procedure.

(continued)

Table 2 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Piskorz	2018	38 children and adolescents with kidney diseases undergoing venipuncture	Acute	MOT VR Game: Patients had to memorise and simultaneously track several moving objects. The game was controlled by head movements only. The difficulty level of the game could be adjusted by the researchers.	Distraction	VG reported significantly lower levels of pain intensity and stress, compared with the CG.	During screening, 6 patients (24%) were not willing to participate (most reported to not experience pain/stress during blood draw). CG underwent standard procedure (no other distraction). Patients in VG could test the VR for 10-15 min before deciding to participate.
Piskorz	2020	57 children and adolescents with kidney diseases undergoing venipuncture	Acute	Active VR: MOT game, patients had to memorise and simultaneously track several moving objects. Passive VR: patients watched a video, resembling the MOT game. The video displayed flying objects that were moving.	Distraction	Both VGs experienced significantly less pain and stress compared with the CG. No significant differences were found between the active VG and the passive VG. A significant difference was found for stress scores, in favour of the active VR.	It was not stated how many patients declined to participate, and for what reason. Patients were not randomly assigned in treatment groups, instead in the VGs they were allowed to first test the VR before deciding to participate. CG received no additional procedures.

(continued)

Table 2 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Hoffman	2019	48 children and adolescents with large severe burn injuries (44 of 48 from developing Latin countries)	Acute	SnowWorld: 3D interactive snowy canyon in VR where patients could shoot snowballs at objects in the VE, while hearing music and 3D sound effects. During wound care, every 5 min patients alternated between Yes VR or No VR.	Distraction	On Day 1, VR significantly reduced worst pain, time spent thinking about pain, pain unpleasantness, and patients reported higher satisfaction during VR. Patients reported 27% more fun with VR (non-significant). During multiple sessions, VR persisted to significantly reduce worst pain ratings.	During wound care, patients received alternately Yes VR or No VR, for approximately equal portions of the same wound care session. Yes VR: VR in addition to pain medications, No VR: SOC pain medications. Treatment order was randomised.
2. *Distraction* and *relaxation* mechanisms (*n* = 2)							
Esumi	2020	Adult male suffering from acute compartment syndrome	Acute	Dream Beach: The VE stimulates the experience of relaxing at the beach, with a 360° view, and with calming nature sounds. Over 2 days, the patient received 3 sessions of VR analgesic therapy for 30 min per session.	Distraction Relaxation	VR effectively relieved the pain, and resulted in a 25-75% dose reduction in opioid administration, which alleviated the opioid-induced respiratory depression.	Case report of patient with ACS, complicated with fasciotomy wound infection. Patient was treated with a high-dose opioid which became unbearable due to opioid-induced nausea, hyperalgesia, and respiratory depression.

(continued)

Table 2 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Özalp Gerçeker	2020	136 children undergoing venipuncture	Acute	VR-Rollercoaster: The VE simulates the experience of riding a rollercoaster. VR-Ocean Rift: Relaxing underwater tour in VR animates the experience of swimming with marine animals, while listening to soothing music. During venipuncture, the children watched the VR video they were assigned to.	Distraction Relaxation	Both VGs reported significant reductions in pain scores, compared with the CG. The two VR conditions did not differ significantly from each other in pain scores.	Pain scores were self-, parent-, nurse- and researcher-reported. During screening 18 children (10%) refused to participate (reason not stated). Five children (5%) dropped out in the VR conditions because they wanted to remove the headset. Both VR conditions were videos (no interaction with VE). CG received no distraction techniques.

Note. 2D, two-dimensional; 3D, three-dimensional; ACS, acute compartment syndrome; CG, control group; ED, emergency department; FOV, field of view; HD, high definition; HMD, head-mounted display; IV, intravenous; min, minutes; MOT, multiple object tracking; s, seconds; SOC, standard of care; TV, television; VE, virtual environment; VG, virtual reality group; VR, virtual reality

Ding et al. (2019), the control cohort in this study watched a 2D HD distraction video displaying relaxing nature scenes. Tashjian et al. (2017) found that both cohorts reported significantly reduced pain scores compared with baseline scores. However, the difference between the two cohorts was significant, in favour of the VR cohort. That is, the pain reduction was significantly higher in the VR cohort, in comparison with the control cohort. In this study, the control cohort was intended to watch a 2D distraction video (Tashjian et al., 2017), however, it can be argued whether the 2D relaxing nature video only accomplishes distraction, or also relaxation, which can also have analgesic effects as is shown in other studies (Ahmadpour et al., 2019).

Besides these two adult studies, seven paediatric studies used VR *distraction* to manage acute pain. Atzori and colleagues (2018) performed a RCT to evaluate the effect of an immersive VR intervention during venipuncture (i.e., blood draw) in a paediatric population suffering from oncological or hematological diseases (Atzori et al., 2018). Using a within-subjects design, 15 children and adolescent patients underwent one blood draw with VR, and one with standard of care (SOC). The SOC consisted of a non-medical conversation by a nurse. In accordance with the previous study by Ding et al. (2019), this study used the same VR software (i.e., SnowWorld). The result showed that during VR, patients reported significant reductions in worst pain (sensory component of pain), time spent thinking about pain (cognitive component of pain), and pain unpleasantness (affective component of pain), compared with SOC. Furthermore, patients reported significantly more fun with VR, experienced a strong illusion of presence, and rated the VR objects as “moderately real”. Limitations of this study include the small sample and the use of SOC as the control condition instead of other distraction techniques (Atzori et al., 2018).

Likewise, Gold and Mahrer (2018) conducted a RCT where they examined the effect of immersive VR compared with SOC on pain and anxiety during venipuncture in a paediatric hospital population. The SOC consisted of a brief interaction with the phlebotomist before the blood draw, and a cartoon playing on a television. Patients in the VR condition received SOC and interacted with the VR game Bear Blast during the venipuncture. Bear Blast is a multisensory (i.e., visual, auditory) game where patients travel through an energetic, highly interactive cartoon world, while soothing music plays in the background. By the movement of their head, patients could shoot balls at targets in the VE which positively reinforced experimentation and activity (Gold & Mahrer, 2018). The results showed that VR significantly reduced pain and anxiety during venipuncture, compared with SOC. Moreover, when using VR patients with a higher anxiety sensitivity at baseline experienced significantly less anxiety than patients with a lower anxiety sensitivity. A limitation of this study was the high proportion (36%) of patients who declined to participate during screening (mostly due to time constraints), which may limit the generalisability of the findings due to selection bias (Gold & Mahrer, 2018).

In a similar fashion, Dumoulin and colleagues (2019) performed a RCT to investigate the effectiveness of VR to reduce pain during needle-related procedures (i.e., venipuncture, intravenous placement) in paediatric patients at the emergency department (Dumoulin et al., 2019). Patients in the VR group were immersed in the VR game Shoot the Flies, which consisted of a virtual apartment where the aim was to distract from painful stimuli by looking at the flies, and shooting as many flies as possible using a wireless mouse. In this study, VR was compared with two control conditions: watching television (minimal control condition) and distraction by Child Life (gold standard control condition). A majority of the 59 children and adolescent patients (75%-87%) used a topical anaesthetic before the procedure, hence VR was used

adjunctively (i.e., in addition to traditional pain medications). Dumoulin et al. (2019) found that patients reported significant reductions in pain intensity and fear of pain in all three conditions, compared with baseline. Patients in the VR condition experienced significantly less fear of pain compared with the control conditions. However, no significant differences between the conditions were found for pain intensity (Dumoulin et al., 2019).

Additionally, Walther-Larsen et al. (2019) examined the effect of an interactive 3D VR game on pain levels and patient satisfaction using a RCT design among 59 children and adolescents undergoing intravenous placement before anaesthesia. The control group in this study received SOC: topical numbing cream, positioning, and distraction by a specialised pain nurse (i.e., child playing 2D game on a smartphone). The patients in the VR group received SOC, and in addition, they played the VR game Seagull Splash. In this interactive 3D game, a boat with a bucket of fish is approached by seagulls aiming to eat the fish. The patient's objective was to prevent this from happening by shooting water balloons with a slingshot at the seagulls. As the patient obtained a higher score, the game became increasingly difficult (Walther-Larsen et al., 2019). The results showed no significant difference in pain scores between the VR group and the control group. However, the children and adolescent patients in the VR group reported high satisfaction levels using the novel VR game. All patients in the VR group indicated their preference to use the same distraction technique again, a borderline significant result compared with controls. Of note, Walther-Larsen et al. (2019) used evidence-based SOC, which was more elaborate than the SOC used in other studies reviewed here.

Conversely, Piskorz and Czub (2018) used a different form of *distraction* compared with previously described studies. Using a quasi-experimental design, they examined the effect of a novel VR game, based on a Multiple Object Tracking (MOT) paradigm, on pain and stress during venipuncture in 38 patients with kidney diseases. The control group in this study underwent standard procedure without any distraction technique being administered. The children and adolescent patients in the VR group were immersed in the MOT game, where they had to memorise and simultaneously track several moving objects (e.g., planes, birds). Furthermore, the game was controlled by head movements only (i.e., hands-free), and the difficulty level of the game could be adjusted by the researchers to the skill levels of the participants. The authors found that patients in the VR group reported significantly lower levels of pain intensity and stress, in comparison with the control group. Piskorz and Czub (2018) argue that MOT differs from most traditional *distraction* methods in a number of ways. MOT requires attention continuously instead of brief attentional shifts, as it requires users to pay attention to multiple objects at once. Further, the authors posit that the MOT is an “inherently active attentional task”, instead of passive distraction (Piskorz & Czub, 2018, p. 3). Finally, by adjusting the difficulty level, the attentional demands can be manipulated by the researchers to match the skill levels of participants. Altogether, the authors designed the MOT game to be highly engaging, therefore, demanding much of the available attentional resources, arguably leading to a greater pain reduction than regular VR *distraction*. An important limitation of this study was that patients in the VR group received the opportunity to interact for 10 to 15 minutes with the VR game before deciding whether they wanted to participate in the study (Piskorz & Czub, 2018). Furthermore, in this study, Piskorz and Czub (2018) did not compare the effects of the MOT game to a regular VR *distraction* condition.

However, in a follow-up experimental study, the same authors investigated whether the type of VR *distraction* (active VR vs passive VR) had an effect on pain and stress during venipuncture in 38 paediatric patients with kidney diseases (Piskorz et al., 2020). The active VR

group received a similar MOT game as in their previous study (Piskorz & Czub, 2018), which consisted of a Multiple Object Tracking game, controlled by head movements only, where they had to memorise and simultaneously track several moving objects. The experimenter adjusted the degree of difficulty of the game according to the skill level of participants. The passive VR consisted of a video in which flying objects were moving, and was supposed to maximally resemble the active VR, except for the MOT component. The control group received no additional procedures during venipuncture. The results showed that both VR groups experienced significantly less pain and stress compared with the control group. However, no significant difference was found for pain scores between the active VR group and the passive VR group. Nevertheless, a significant difference was found for stress scores in favour of the active VR. This study has the same limitation as their previous study, that is, before deciding to participate in both the active VR as well as the passive VR condition, patients were allowed to try out the VR for 10 to 15 minutes. This may lead to selection bias as it might be that those patients that decide to participate have a more favourable attitude towards VR than those who decline. In this study, it was not stated how many patients declined to participate, and for what reason (Piskorz et al., 2020).

In contrast to most previous studies which focused on needle-related procedures, Hoffman et al. (2019) conducted a pilot study to evaluate whether immersive VR can be used adjunctively in a paediatric population with large severe burn wounds in the intensive care unit (ICU). Using a within-subjects, within-wound care design, patients received alternately VR during some portions of the wound care session, and no VR during other portions of the same wound care session (initial treatment order randomised). In this preliminary study, every five minutes, patients alternated between Yes VR and No VR to establish approximately equal

portions. On average, patients spent 16 minutes of wound care during No VR versus 13 minutes during Yes VR. In both conditions, VR was used adjunctively to pain medications. Because most of the patients in this study had severe head and face burns, it was not possible for them to wear a standard HMD on their head. To address this issue, Hoffman et al. (2019) used a so-called Magula arm, a robot-like articulated arm goggle holder, which could hold the water-friendly VR goggles near the patient’s eyes. The VR software used was SnowWorld, which was also used by two other studies in this review (Atzori et al., 2018; Ding et al., 2019). Using a wireless mouse, the patients were able to interact with SnowWorld during wound care. The results showed that on day 1, VR significantly reduced worst pain, time spent thinking about pain, and pain unpleasantness. Moreover, patients reported significantly higher satisfaction using VR. Further, patients reported 27% more fun with VR (non-significant). VR continued to significantly reduce worst pain ratings during multiple sessions (Hoffman et al., 2019).

Distraction and Relaxation

Besides *distraction*, another mechanism underlying the VR therapy used in acute pain management was *relaxation*. *Relaxation* can be defined as a calming state that counters the stress response by reducing physical tension and/or anxiety (Olpin & Hesson, 2015). Since pain is commonly accompanied by anxiety and physical tension, *relaxation* may be helpful in alleviating pain (Özalp Gerçeker et al., 2020). The following two studies used the mechanism of *distraction* in combination with *relaxation* in their VR therapies to manage acute pain.

Indeed, Esumi et al. (2020) used an immersive VR therapy that aimed not only at *distraction* but also at *relaxation*. In their case report, they describe the case of an adult man with acute compartment syndrome, who was treated with VR, after his fasciotomy wound got infected. The patient was initially treated with a high-dose opioid which became unbearable due to opioid-induced nausea, hyperalgesia (i.e., increased pain sensitivity), and respiratory depression. Therefore, Esumi et al. (2020) started an immersive VR therapy during which the patient was immersed in Dream Beach, a VE which stimulates the experience of relaxing at the beach on a sunny day, with a 360° view, while listening to calming nature sounds. The VR therapy effectively relieved the pain, and resulted in a 25-75% dose reduction in opioid administration, which, in turn, alleviated the accompanying opioid-induced respiratory depression (Esumi et al., 2020). In this study, the authors ascribed the mechanism of *relaxation* to the increase of positive affect. That is, they argue that the VR created a shift in the patient's experience from feeling distressed lying in a hospital bed, to feeling more positive emotions by being immersed in a relaxing and more pleasant VE (Esumi et al., 2020).

Moreover, Özalp Gerçeker et al. (2020) conducted a RCT to evaluate the effectiveness of two different VR methods on pain, fear, and anxiety in 136 children undergoing venipuncture. The children were randomised in three conditions: VR-Rollercoaster, VR-Ocean Rift, or the control group. VR-Rollercoaster simulates the exciting experience of riding a rollercoaster, which speeds up and slows down. VR-Ocean Rift, a relaxing underwater tour in VR, animates the experience of swimming with marine animals, while listening to soothing music. Both VR conditions were videos, hence no interaction with the VE was possible. The control group received no distraction techniques. The results showed that both VR groups reported significant reductions in pain scores, compared with the control group. The two VR conditions did not differ significantly from one another in pain scores. Here, it should be noted that Özalp Gerçeker et al. (2020) lacked to sufficiently explain the underlying mechanisms of their VR therapy.

Virtual Reality in Chronic Pain Management

The studies that examined VR in chronic pain management used several distinct mechanisms. Studies that used similar mechanisms are discussed together (see Table 3). The following section is divided according to these underlying mechanisms: (1) *neuromodulation*; (2) *distraction* and *relaxation*; (3) *distraction* and *graded exposure*; (4) *biofeedback* and *relaxation*.

Neuromodulation

Under certain conditions, the human brain is capable of long-lasting changes in neural pathways (i.e., brain plasticity). Neuromodulation is based on this premise of brain plasticity, and consists of methods which aim to reverse maladaptive changes, or to promote adaptive changes in the brain (Knotkova & Rasche, 2015). In the brain, a somatotopic organisation exists within the somatosensory and motor cortices, which contains somatosensory and motor maps where each body part corresponds to a certain area of the brain. Research has shown that certain types of chronic pain are associated with changes in these functional maps in the brain, a phenomenon called *cortical reorganisation* (Knotkova & Rasche, 2015). Cortical reorganisation occurs most commonly following a change in sensory input, such as for example in the case of phantom limb pain (PLP), where a decrease in sensory input of the amputated limb may lead to maladaptive cortical reorganisation (i.e., cortical representation of affected limb shrinks, and the representation of the adjacent area expands) of the amputated limb representation in the functional maps of the brain. Notably, these changes in the brain may be reversible through neuromodulatory treatments, which in turn may lead to a reduction in pain (Knotkova & Rasche, 2015).

Therefore, neuromodulatory treatments for chronic pain have aimed to *induce adaptive cortical reorganisation*. In this review, six articles aimed at *neuromodulation* in one form or another to manage chronic pain. The next section is divided according to the underlying mechanisms used in the VR therapies: (1) *cortical reorganisation* through *virtual embodiment* by *the vision of the body*; (2) *cortical reorganisation* through *virtual embodiment* by *the vision of the body and manipulating body representations*; (3) *cortical reorganisation* through *virtual embodiment* by *multisensory congruence*.

Cortical Reorganisation through Virtual Embodiment by the Vision of the Body.

Virtual embodiment refers to the illusion of ownership of a virtual body (i.e., experiencing the virtual body as one's own body; Matamala-Gomez et al., 2019). Research has shown that *the vision of the own body in pain*, or painful parts of the body, can have an analgesic effect. This phenomenon has also been termed visually induced analgesia (Longo et al., 2009). This finding has been confirmed for a virtual body, provided that one feels a sense of ownership over the virtual body (Martini, 2016). It has been suggested that the vision of one's intact phantom limb in motion can activate mirror neurons in the brain (Diers et al., 2010), which in turn, can *induce cortical reorganisation* (Chau et al., 2017; Rutledge et al., 2019). Two studies in this review, both of which the VR therapy was based on principles of traditional mirror therapy, used this mechanism of *visually induced analgesia* to treat chronic pain (Chau et al., 2017; Rutledge et al., 2019).

Chau et al. (2017) conducted a mixed-methods case report where they treated an adult patient with severe PLP following an upper limb amputation with immersive VR with myoelectric control (i.e., controlled by electrical signals generated by own muscles). Through myoelectric control and real-time motion-tracking, the patient could interact with objects in the 3D kitchen environment using virtual hands, while wearing an HMD. Additionally, the patient played 2 VR games (Audioshield and Eleven) which required simulated hand motions using a motion controller tracking. The results showed that during each VR session, the patient reported significant pain reductions on all pain scales. Likewise, qualitatively, the patient reported subjective pain relief, a high degree of presence and immersion, as well as positive impressions of the VR sessions in general. Hence, immersive VR therapy with myoelectric control was effective in reducing pain for a patient with severe PLP for whom traditional treatments had yielded little pain relief (Chau et al., 2017).

Likewise, Rutledge et al. (2019) developed a customised VR treatment modelled after mirror therapy for adult veterans with PLP. During the VR treatment, patients wore an HMD and cycled through one of the three VEs (i.e., Royal Garden, Grand Canyon, Jurassic Park) using a bicycle peddler. The patient’s prosthesis was attached to the pedal, and the motion sensor precisely calibrated the patient’s cadence to that of the VR avatar. After the VR treatment, the 14 adult veterans reported significant reductions in PLP intensity and phantom sensations. Four users completed a total of 57 VR sessions and reported similar benefits as initial users. Both initial and repeat users reported high satisfaction, immersion, realism, and helpfulness with the VR treatment (Rutledge et al., 2019).

Cortical Reorganisation through Virtual Embodiment by the Vision of the Body and by Manipulating Body Representations. Matamala-Gomez et al. (2019) induced *virtual embodiment* in participants *by the vision of a virtual arm*, which was co-located with their real body. In patients with complex regional pain syndrome (CRPS), the representation of the painful limb in the brain is similarly arranged to that of patients with PLP. This distorted body representation in the brain (i.e., cortical reorganisation) may influence how CRPS patients perceive pain. Therefore, Matamala-Gomez et al. (2019) examined the analgesic effect of *manipulating body representations* by modifying the properties (transparency, size) of a virtual arm in adult patients with CRPS and peripheral nerve injury (PNI). Wearing an HMD, patients were immersed in a VE where they saw a virtual arm that was co-located with their body from a first-person perspective. The VE was the same in both the transparency and the size test. In each condition, the virtual arm was distorted by varying its transparency levels (0, 25, 50, 75%) or its size (small, normal, big). Using a within-subjects design, Matamala-Gomez et al. (2019) found that pain ratings were reduced in all seven VR conditions. Additionally, during the transparency test increasing transparency levels of the virtual arm reduced pain in CRPS patients but not in PNI patients. Modifying the size of the virtual arm slightly increased pain only in CRPS patients. Moreover, it was found that both the CRPS and the PNI groups were able to reach levels of ownership and agency (i.e., the notion that one can control their own actions at will) over a virtual arm comparable to healthy participants. Hence, *manipulating body representations* by modifying the properties of a virtual arm showed to have differential effects in different types of chronic pain (i.e., CRPS, PNI; Matamala-Gomez et al., 2019).

Cortical Reorganisation through Virtual Embodiment by Multisensory Congruence. The following three studies suggest that when chronic pain patients are presented with *congruent multisensory information*, this induces the sense of body ownership over the virtual body (i.e., *virtual embodiment*), which activates the denervated brain region (i.e., *promotes adaptive cortical reorganisation*), which consequently may reduce pain (Ichinose et al., 2017; Pozeg et al., 2017; Solca et al., 2018). Indeed, Ichinose et al. (2017) assert that in PLP patients a perceived *match across multiple sensory modalities* (i.e., tactile, auditory, visual) increases *virtual embodiment* which facilitates the acquisition of voluntary motor imagery of the phantom limb. Likewise, Solca et al. (2018) postulate that the *synchrony of multisensory* (i.e., cardiovisual) *information* contributed to the analgesic effect in CRPS patients. Additionally, Pozeg et al. (2017) posit that in spinal cord injury (SCI) patients the *congruent multisensory* (i.e., visual, tactile, proprioceptive) *stimulation* induced the sense of *embodiment*, and may *promote cortical reorganisation*. These three studies will be described in more detail next.

Ichinose et al. (2017) investigated the analgesic effect of providing tactile feedback to the cheek during VR mirror visual feedback (VR-MVF) therapy in nine adult PLP patients. In PLP patients, research has shown that the representation of the amputated upper limb in the somatosensory cortex shrinks, and that the representation of the neighbouring brain area (e.g., face, shoulder) enlarges (Ichinose et al., 2017). Consequently, this adjacent brain area takes over cortical space that was originally allocated to the amputated upper limb. Therefore, when PLP patients are touched on the cheek of their affected side, they may perceive the illusory sensation that their phantom limb has been touched, a phenomenon called ‘referred sensation’ (Ichinose et al., 2017). In this study, PLP patients wore an HMD where they saw the virtual intact limb, the virtual phantom limb, and a target object in the VE. Patients were asked to touch the virtual target object with their virtual phantom limb, by moving their intact upper limb. When they touched the target object, synchronously, auditory (collision sound) and tactile (vibration) feedback was provided. Tactile feedback was applied to either the cheek (Cheek Condition), the intact hand (Intact Hand Condition), or not applied at all (No Stimulus Condition). Patients reported significant reductions in pain in the Cheek and Intact Hand Conditions. However, the pain reduction rate in the Cheek Condition (i.e., *multisensory congruence*) was significantly higher, compared with the Intact Hand and No Stimulus Conditions (Ichinose et al., 2017).

Similarly, Solca and colleagues (2018) developed and tested an immersive VR therapy that combined elements from mirror therapy and multisensory body processing (i.e., cardiovisual

stimulation; Solca et al., 2018). During heartbeat-enhanced VR (HEVR), 24 adult CRPS patients and 24 healthy controls viewed a 3D virtual depiction of their affected hand placed on a table in the VE, through an HMD. The hand flashed either synchronously or asynchronously (control condition) with their own online detected heartbeat. The results of this crossover study showed that CRPS patients reported significant pain reductions, improved grip strength, and modulation of a physiologic pain marker (heart rate variability) in the synchronous condition, compared with the asynchronous condition. These effects were reliable across sessions, and highly selective. That is, the effects only showed in the synchronous condition, and were not observed in healthy controls. Hence, the analgesic effects were attributed to the *synchrony of the multisensory information* (Solca et al., 2018).

Additionally, Pozeg and colleagues (2017) used multisensory own body illusions in VR to investigate changes in body ownership and neuropathic pain in SCI patients (Pozeg et al., 2017). The intervention consisted of two VR multisensory body illusion paradigms, and included 20 SCI patients and 20 healthy controls. Illusory leg and global body ownership were induced using a virtual leg illusion (VLI) and full body illusion (FBI) respectively. Throughout both illusions, participants sat in a wheelchair and wore an HMD and headphones. During the VLI, participants received asynchronous or synchronous tactile stimulation on their lower or upper back, while viewing a real-time video recording of the virtual legs being touched on the corresponding part through the HMD. In the FBI paradigm, participants received asynchronous or synchronous tactile stimulation on their back, while viewing a real-time video recording of their own virtual body being touched on the back through the HMD (Pozeg et al., 2017). The results showed that the VLI reduced pain significantly only when the lower back was stimulated synchronously (i.e., *multisensory congruence*), compared with baseline measurements. In the

FBI paradigm, both in the synchronous and asynchronous visuotactile stimulation conditions pain was significantly reduced. *Distraction* and *the vision of the body* were briefly mentioned as potential explanations of this unexpected finding in the FBI paradigm. Moreover, in the VLI paradigm SCI patients experienced significantly weaker illusory leg ownership compared with healthy controls. In contrast, during the FBI no differences were found between groups in illusory global body ownership. (Pozeg et al., 2017).

Distraction and Relaxation

Distraction and *relaxation* are mechanisms underlying the VR therapy that were also used in studies on acute pain in this review. Likewise, two studies that examined chronic pain also employed these mechanisms. Garrett et al. (2017) conducted a mixed-methods pilot case series where they investigated the effect of VR as a complementary home therapy for chronic pain patients. In this exploratory study, eight adult patients with chronic pain received VR therapy in their own homes for one month, for a total of 12 sessions of 30 minutes per session. To explore the patients' preferences for different VEs, and to compare the effects of these different VEs, every week of the study different categories of VR experiences were used. The first and second week used both *relaxation* and *distraction* mechanisms: week 1 used passive VR experiences (e.g., virtual Iceland, boat ride); week 2 focused on introversion/mindfulness-based VR (e.g., VR guided meditation). The third and fourth week used only a *distraction* mechanism: week 3 consisted of active exploratory VR experiences (e.g., underwater environment, solar system); week 4 employed active cognitive VR experiences (e.g., 3D puzzles). Quantitatively, Garrett et al. (2017) found no significant reductions in pre- and post-exposure pain scores, nor in weekly pain scores. Conversely, qualitatively, during the terminal interviews patients reported benefits using VR: five out of eight reported pain reductions only when using VR but responses

Table 3

Description of the VR Therapies and its Main Results, Ordered by the Underlying Mechanisms of VR in Chronic Pain Management: (1) Neuromodulation; (2) Distraction and Relaxation; (3) Distraction and Graded Exposure; (4) Biofeedback and Relaxation

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
1. *Neuromodulatory* mechanisms (*n* = 6)							
Chau	2017	Adult male patient with PLP following an upper limb amputation	Chronic	The VE consisted of an interactive 3D virtual kitchen. Besides the virtual kitchen, 2 VR games (Audioshield and Eleven) were used. The patient experienced 5 VR sessions of ~45 min, during which he used myoelectric control of the virtual hands as well as motion-tracking control.	Cortical reorganisation through virtual embodiment by the vision of the body	During each VR session, the patient reported significant reductions on all pain scales. Subjective pain relief was also reported, as well as positive impressions of the VR sessions, interest in more VR therapy, and a high degree of presence and immersion.	Single PLP patient received immersive VR therapy with myoelectric control with real-time motion tracking. Due to the experienced pain alleviation of the VR sessions, the patient unexpectedly stopped taking his pain medication resulting in worsened PLP.

(continued)

Table 3 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Rutledge	2019	14 adult veterans with PLP. Type of amputation: right leg (n=3); left leg (n=10); right arm (n=1)	Chronic	Wearing an HMD, patients bicycle through a VE with a bicycle peddler. A motion sensor calibrates the cadence of patient to that of the VR avatar. On average, the VR sessions lasted 13 min during initial trials and 25 min for repeat users.	Cortical reorganisation through virtual embodiment by the vision of the body	After the VR treatment, 14 patients reported significant reductions in PLP intensity and phantom sensations. Repeat users (n=4; 57 total VR sessions) reported similar benefits as initial users. Both initial and repeat users reported high satisfaction, immersion, realism, and helpfulness.	Feasibility study testing use of customised VR treatment in veterans with PLP. Factors contributing to lack of quality VR for PLP research are discussed: technical challenges, characteristics of PLP. Limitations included small sample and predominantly male population.
Matamala-Gomez	2019	19 adult patients with neuropathic pain in the upper limb: CRPS type I (n=9); PNI (n=10)	Chronic	Wearing an HMD, patients would see a virtual arm that was co-located with their real body. In each condition, the virtual arm was distorted by varying transparency levels (0, 25, 50, 75%) or size (small, normal, big). Each stimulus lasted 45 s, and the experimental session lasted ~55 min.	Cortical reorganisation through virtual embodiment by the vision of the body and manipulating body representations	Patients reported reduced pain ratings in all seven VR conditions. During the transparency test, increasing transparency levels of the virtual arm reduced pain in CRPS patients but not in PNI patients. During the size test, pain slightly increased only in CRPS patients.	Use of VR for embodiment of chronic arm pain patients. The transparency and the size test were presented in a counterbalanced order. Distraction is shortly mentioned as an alternative explanation for the finding that pain reduced in all seven VR conditions.

(continued)

Table 3 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Ichinose	2017	9 adult patients with PLP, following braxial plexus avulsion injury (n=8), or arm amputation (n=1).	Chronic	Wearing an HMD, patients were asked to touch a virtual target with their virtual phantom limb by moving their intact upper limb. When they touched the target, synchronously auditory and tactile feedback was provided. Patients performed this task under 3 conditions in VR, for 5 min per task.	Cortical reorganization through virtual embodiment by multisensory congruence	Patients reported significant reductions in pain in the Cheek and Intact Hand Conditions. The pain reduction rate was significantly higher in the Cheek Condition, compared with the Intact Hand and No Stimulus Conditions.	Multimodal VR-MVF therapy: VR exercises with tactile feedback condition, and 2 control conditions. Cheek Condition: tactile feedback applied to the cheek; Intact Hand Condition: tactile feedback applied to intact hand; No Stimulus Condition: no tactile feedback. Distraction is shortly mentioned as an alternative explanation for findings.
Solca	2017	48 adults: patients with upper limb CRPS (n=24); healthy controls (n=24)	Chronic	During HEVR, patients viewed a 3D virtual depiction of their affected hand placed on a table in the VE. The hand flashed in synchrony or asynchronously (control condition) with their own online detected heartbeat. The experiment lasted ~1,5 hours.	Cortical reorganization through virtual embodiment by multisensory congruence	CRPS patients reported significant pain reductions, improved grip strength, and modulation of a physiologic pain marker (HRV) in the synchronous condition, compared with the asynchronous condition. These effects were reliable across sessions, and highly selective.	Novel fully automatised VR for treatment of chronic pain on the basis of cardiovisual stimulations. Carefully designed control condition. Treatment order counterbalanced. Strength of the HEVR procedure include the analgesic effect without requiring tactile stimulation.

(continued)

Table 3 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
Pozeg	2017	40 adults: patients with SCI, with paraplegia (n=20); healthy controls (n=20)	Chronic	Participants sat in a wheelchair, while wearing an HMD and headphones. VLI: Asynchronous or synchronous visuotactile stimulation is applied to the participant's back and to the virtual legs as seen on the HMD. FBI: Asynchronous or synchronous visuotactile stimulation is applied to the participant's back and to the back of a virtual body, as seen on the HMD.	Cortical reorganization through virtual embodiment by multisensory congruence	VLI reduced pain significantly only when the lower back was stimulated in synchrony, compared with baseline. FBI reduced pain both in the synchronous and asynchronous conditions. During VLI, SCI patients experienced significantly weaker illusory leg ownership compared with healthy controls. During FBI, no differences were found between groups in illusory global body ownership.	Use of multisensory own body illusions in VR in neuropathic pain patients with SCI. Leg and global body ownership were induced using a VLI and FBI respectively.

(continued)

Table 3 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
2. *Distraction* and *relaxation* mechanisms (*n* = 2)							
Garrett	2017	8 adult patients with diverse chronic pain conditions (e.g., lower back pain, knee pain, shoulder pain, CRPS)	Chronic	Home-based VR: Week 1 Passive VR; Week 2 Introversion/ mindfulness-based VR; Week 3 Active exploratory VR; Week 4 Active cognitive VR. Patients used VR for 3 sessions a week for 4 weeks, for a total of 12 sessions of 30 min each.	Distraction Relaxation	Quantitatively, no significant reductions in pain scores were found. Qualitatively, patients reported benefits using VR: 5 out of 8 reported pain reductions when using VR but responses were highly individualised.	Home-based self-administered VR therapy for chronic pain. Limitations include the exploratory nature of the study: vulnerable to selection bias, small sample, and technological immaturity of the VR experimental setting.
Sharifpour	2020	30 adolescents with cancer during chemotherapy	Chronic	Ocean Journey: Multisensory VR therapy film, where patients experience a sunset at the beach, followed by an ocean journey, while listening to ocean sounds. The VG watched this therapy video for 8 sessions of 30 min each, once a week for 2 months.	Distraction Relaxation	VR therapy significantly reduced pain intensity, pain anxiety, pain catastrophising, and significantly improved pain self-efficacy, compared with the CG. These findings persisted during the first and second follow-up periods (at 7 days, and at 1 month).	The use of VR for the treatment of cancer-related chronic pain, during chemotherapy. The content of the VR therapy video was selected by experts. The CG received no intervention. A convenience sample was used.

(continued)

Table 3 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
3. *Distraction* and *graded exposure* mechanisms (*n* = 1)							
Fowler	2019	16 adult veterans with diverse chronic pain locations: low back (n=11); head (n=2); other (n=3)	Chronic	Distraction-to-exposure hierarchy ranging from low stimulation intensity distraction apps to high movement intensity exposure. Veterans used VR for 20 min during daily therapy sessions over a 3-week period.	Distraction Graded exposure	Veterans classified all hierarchy levels as medium intensity. Self-selected activities were rated highest by veterans. Veterans experienced significant improvement in secondary outcomes: pain intensity, interference with mobility, and pain catastrophising	Measures were taken at intake and discharge (~3 weeks). Limitations include lack of CG, and the small sample size.

(continued)

Table 3 (continued)

Study	Year	Population	Type of pain	VR intervention/ environment	Mechanism(s)	Main results	Notes
4. *Biofeedback* and *relaxation* mechanisms (*n* = 1)							
Venuturupalli	2019	17 patients with autoimmune disorders: rheumatoid arthritis (n=11); lupus (n=4); fibromyalgia (n=3).	Chronic	2 similar immersive 3D VE with 360° nature views: respiratory BFD environment and GM environment. Patients received either first GM followed by BFD, or BFD followed by GM. Both modules were conducted back to back for a total of 30 min exposure.	Biofeedback Relaxation	Patients reported significant pain reductions after both the BFD and the GM condition. No significant differences were found between conditions. Anxiety was significantly reduced in the GM, but not in the BFD condition. The VR intervention was well tolerated and accepted.	Use of VR to examine feasibility of VR in rheumatology outpatient setting. Sample representative of real-life clinic setting (e.g., multiple diagnoses). Initial treatment order was randomised. Limitations include small sample size (pilot study).

Note. 3D, three-dimensional; BFD, biofeedback; CG, control group; CRPS: complex regional pain syndrome; FBI, full body illusion; GM, guided meditation; HEVR, heartbeat-enhanced virtual reality; HMD, head-mounted display; HRV, heart rate variability; min, minutes; MVF; mirror visual feedback; PLP, phantom limb pain; s, seconds; SCI, spinal cord injury; VE, virtual environment; VG, virtual reality group; VLI, virtual leg illusion; VR, virtual reality were highly individualised. During the interviews, patients particularly reported that the interactive *distraction* experiences were more beneficial, compared with the *relaxation-based* VR experiences. The authors argue that VR can mainly reduce pain through cognitive attentional and distractive mechanisms, by increasing the sense of presence in the VE (Garrett et al., 2017), however it should be noted that the authors in this study lacked to explain the underlying mechanisms of the VR therapy in more detail.

Additionally, Sharifpour et al. (2020) employed a quasi-experimental design to examine the effect of VR therapy on cancer-related chronic pain and other pain variables in 30 adolescents with cancer at the chemotherapy stage. Notably, this study is the only chronic pain study in this review which focused on a paediatric population. The VR group watched a multisensory (visual, auditory) VR therapy film called Ocean Journey, where patients experienced a sunset and a stroll on the beach, followed by a journey to the depths of the ocean, while listening to ocean sounds. Patients in the VR group used an HMD to watch this therapy video offline for eight sessions of 30 min each during chemotherapy, once a week for two months. The control group received no intervention. Sharifpour et al. (2020) found that VR therapy significantly reduced pain intensity, pain anxiety, pain catastrophising, and significantly improved pain self-efficacy, compared with the control group. These findings persisted during the first and second follow-up periods, which were at seven days and at one month. The authors attribute the analgesic effect of the VR therapy to a shift of the patients' attention away (i.e., *distraction*) from pain and pain-tracking behaviour, which reduces pain anxiety and increases pain tolerance, and to the use of calming nature-based scenes (i.e., *relaxation*) which may alter patients' perceptions of pain (Sharifpour et al., 2020)

Distraction and Graded Exposure

Besides *distraction*, *relaxation*, and *neuromodulation* mechanisms, another mechanism found in this review to manage chronic pain is *graded exposure*. One study in this review combined *distraction* in combination with *graded exposure* in their VR therapy to treat chronic pain (Fowler et al., 2019). *Gradual exposure* to feared movements may improve kinesiophobia (i.e., fear of movement), which can improve pain avoidance, and hence break the cycle as pain avoidance may lead to negative affect, disability, and more pain in the end (Fowler et al., 2019). However, considering that patients with chronic pain experience central sensitisation (i.e., increased responsiveness in the central nervous system), the study by Fowler et al. (2019) used a *gradual integration of VR exposure to movement* starting with *distraction* apps to treat veterans with chronic pain. Accordingly, the authors designed and examined the feasibility of a so-called *distraction*-to-*exposure*-hierarchy, which ranged from low stimulation intensity (i.e., pain *distraction*) to high movement intensity (i.e., *exposure*). In their feasibility study, Fowler et al. (2019) used a within-subjects design where veterans used the VR therapy for 20 minutes every day for 3 weeks. Veterans started with low intensity distraction apps (e.g., meditation, visual imagery) requiring minimal movement, followed by medium-intensity apps (e.g., virtual walking or swimming) requiring head and neck movement, and ending with high-intensity apps (e.g., 3D painting, rhythm-based) also requiring torso and upper body movement. Here, it should be noted that the low intensity distraction apps aimed not only at *distraction* but also at *relaxation*, however, it was not noted or explained as such by the authors. The results of the study showed that the veterans classified all designed hierarchy levels as medium intensity. Activities that were self-selected were rated with the highest intensity by veterans. Veterans experienced significant improvement in secondary outcomes, such as pain intensity, interference with mobility, and pain

catastrophising. However, no significant improvement was found for the primary outcome, fear of movement (Fowler et al., 2019).

Biofeedback and Relaxation

Additionally, one study in this review employed *biofeedback (BFD)* and *relaxation* as underlying mechanisms of the VR therapy to manage chronic pain (Venuturupalli et al., 2019). *BFD* is a technique which allows patients to control automatic physiological processes by providing them with meaningful auditory and/or visual feedback regarding these bodily processes. *Relaxation* occurred through the practice of meditation as this aims to create a calm and emotionally stable sense of being. Venuturupalli et al. (2019) conducted a mixed-methods design pilot study to investigate the feasibility of VR to administer BFD and guided meditation (GM) in the treatment of chronic pain among patients with rheumatoid arthritis, lupus, and fibromyalgia. Using a within-subjects design, patients were immersed in two similar 3D VEs with 360° nature environments, one consisted of a respiratory BFD environment and the second of a GM environment (Venuturupalli et al., 2019). In the BFD condition, patients were instructed to breathe at the same pace as an oscillating pacer. In the VE, they received BFD in the form of purple rings that moved inward and outward which reflected their respiratory rate (visual BFD), and additionally, they were guided by a virtual guide through audio prompts (auditory BFD). In the GM condition, patients received instructions during the meditation from a virtual guide, however, they received no auditory or visual feedback as the guided instructions were fixed. Venuturupalli et al. (2019) found that patients reported significant pain reductions after both the BFD and the GM condition. However, no significant differences were found between the two conditions. Moreover, anxiety was significantly reduced in the GM but not in the BFD condition. The qualitative analysis showed that a large proportion (71.4%) of patients reported increased *relaxation* during the GM. Notably, 60.0% of the patients reported *relaxation* for the *BFD* environment as well. Moreover, the VR intervention was well tolerated and accepted. Here, it must be noted that Venuturupalli et al. (2019) state that *BFD* has shown to reduce pain levels and stress-related symptoms, however, they do not explain how *BFD* theoretically can reduce pain. Similarly, the authors report that meditation can have a positive effect on the psychological aspects of chronic pain, but fail to explain how this analgesic effect might occur (Venuturupalli et al., 2019).

Discussion

A systematic review of the literature published between January 2015 and April 2020 on the underlying mechanisms of VR therapies in acute and chronic pain management was undertaken. Twente-one studies met the inclusion criteria for the review. The general aim of this review was to describe the underlying mechanisms of VR therapies in acute and chronic pain management, and moreover, to examine to what extent these mechanisms differ in acute versus chronic pain management. A second aim of this review was to compare the underlying mechanisms of VR therapies in adult versus paediatric populations. The results of this review showed that there is a large difference in the underlying mechanisms of VR therapies in acute versus chronic pain management. In acute pain management, the 11 reviewed studies mainly used *distraction* and additionally *relaxation* as underlying mechanisms of their VR therapies, whereas in chronic pain management the 10 reviewed studies used the mechanisms *neuromodulation*, *distraction*, *relaxation*, *biofeedback*, and *graded exposure*. These findings will be further explained in the following section.

The reviewed studies in acute pain management used the mechanisms *distraction* and *relaxation*, however, predominantly *distraction* was used. This attentional mechanism is the most

frequently studied mechanism of VR in pain management, and VR’s ability to reduce pain is often ascribed to this mechanism. *Distraction* is based on the idea that painful stimuli require attention to be processed. However, humans beings have limited attentional resources (Eccleston & Crombez, 1999). When users put on an HMD and are fully immersed in a VE, from which they can receive input on several modalities, this demands considerable amounts of attention. Consequently, there are fewer attentional resources left to process the painful stimuli (Gold & Mahrer, 2018; Hoffman et al., 2019). Additionally, *relaxation* was used in acute pain management. *Relaxation* is defined as a calming state that counteracts the stress response by reducing physical tension and/or anxiety (Olpin & Hesson, 2015). Since pain commonly occurs with anxiety and physical tension, *relaxation* may be helpful in relieving pain (Özalp Gerçeker et al., 2020). It is worth pointing out that the mechanism of *relaxation* was poorly explained in the two acute pain studies that employed this mechanism in this review (Esumi et al., 2020; Özalp Gerçeker et al., 2020). Esumi et al. (2020) attributed the mechanism of *relaxation* to the increase of *positive affect*. These authors argued that the VR creates a shift from feeling distressed in a hospital room, to feeling more positive emotions by being immersed in a relaxing VE. However, it seems that these authors are explaining the mechanism of *positive affect* and not *relaxation*. Additionally, Özalp Gerçeker et al. (2020) did not provide any theoretical explanation of how *relaxation* contributes to the reduction of acute pain. Nevertheless, *relaxation* may also be considered a form of *distraction*, as *distraction* can be seen as any cognitive or behavioural strategy that diverts one´s attention away from nociceptive stimuli towards other engaging or more attractive stimuli, and thereby reducing pain and anxiety (Dumoulin et al., 2019; Koller & Goldman, 2012; Triberti et al., 2014). In this sense, *relaxation* can be regarded as an active form of *distraction* (Koller & Goldman, 2012).

Conversely, the reviewed studies in chronic pain management employed several distinct mechanisms such as *neuromodulation*, *biofeedback*, and *graded exposure*, in addition to *distraction* and *relaxation*. *Neuromodulation* is based on the notion of brain plasticity, that is, the idea that the human brain is capable of enduring changes in neural pathways (Knotkova & Rasche, 2015). Research has shown that chronic pain states are associated with distorted body representations in the brain, a phenomenon termed *cortical reorganisation* (Knotkova & Rasche, 2015; Lotze & Moseley, 2007). *Cortical reorganisation* works following the “use it or lose it” principle: a decrease or loss in sensory input can shrink the cortical representation of a body part, whereas an increase in sensory input can expand the cortical representation in the functional maps of the brain (Lotze & Moseley, 2007, p. 489). From this principle follows that through neuromodulatory treatments, these cortical misrepresentations can be targeted and changes in the brain may be reversed, which consequently may lead to alleviation of pain (Knotkova & Rasche, 2015). In this review, six articles used a form of *neuromodulation* to *induce adaptive cortical reorganisation* through several related mechanisms, such as *virtual embodiment*, *the vision of the body*, *multisensory congruence*, and *manipulating body representations*. *Virtual embodiment* refers to the illusion of experiencing the virtual body as one’s own body (Matamala-Gomez et al., 2019). *The vision of the body* in pain, or parts of the body, has shown to be analgesic, as long as one feels a sense of ownership over the virtual body (Martini, 2016), as was also shown in two studies in this review (Chau et al., 2017; Rutledge et al., 2019). Three of the studies reviewed suggested that when chronic pain patients (i.e., PLP, CRPS, SCI patients) are presented with *multisensory congruent* information, this may increase the sense of *virtual embodiment*, which may activate the affected cortical misrepresentation and thereby reduce pain (Ichinose et al., 2017; Pozeg et al., 2017; Solca et al., 2018). Additionally, one study *manipulated body*

representations by altering the transparency and size of a virtual arm, and found differential effects for different types of chronic pain (i.e., CRPS, PNI), suggesting that different *virtual embodiment* treatments may be beneficial for different chronic pain states (Matamala-Gomez et al., 2019). Overall, these studies using *neuromodulatory* mechanisms provide a promising approach for the treatment of chronic pain, as they suggest that the immersive VR *embodiment* therapies were effective in reducing chronic neuropathic pain in the short term. Nonetheless, it must be noted that the effectiveness was not examined systematically in this review. It is also worth mentioning that most of these studies used small samples, non-experimental designs, and did not assess long-term changes in pain scores.

Another mechanism employed in one of the chronic pain studies was *biofeedback*, a mechanism through which patients learn to control automatic physiological processes by receiving auditory and/or visual feedback regarding the bodily process (e.g., heart rate; Venuturupalli et al., 2019). However, in their study it was not clearly described how *biofeedback* reduces pain exactly, although one study suggests that *biofeedback* may also be considered a form of *distraction* (Dumoulin et al., 2019), which may suggest that *biofeedback* reduces pain through attentional mechanisms. Additionally, the study by Fowler et al. (2019) used the mechanism of *graded exposure*, which refers to the gradual increase in exposure to feared movements which can, in turn, improve the fear of movement in general in chronic pain patients. Consequently, this can improve pain avoidance, and therefore, break the cycle as pain avoidance may lead to negative affect, disability, and more pain (Fowler et al., 2019).

Previously conducted reviews in pain management suggest that the analgesic mechanism of VR *distraction* is mediated by attentional, anxiolytic, and/or affective factors (Indovina et al., 2018; Triberti et al., 2014). The findings in this systematic review are in accordance with these

reviews, as *distraction* was used in all acute pain studies included in this review, and was generally found to be effective in reducing pain. Moreover, the analgesic effect of the *distraction* mechanism was mostly attributed to the diversion of attention away from painful stimuli. Additionally, since all but one of the studies in this review used a HMD to fully immerse participants in the VE, and nearly all studies used multisensory stimulations, it may be tentatively stated that most VR therapies in this review demanded much attentional resources of participants, leaving less attentional resources to process nociceptive stimuli. Furthermore, several studies reported anxiolytic (i.e., reducing anxiety or stress) effects (Gold & Mahrer, 2018; Piskorz et al., 2020; Piskorz & Czub, 2018; Sharifpour et al., 2020), and affective (i.e., more fun with VR) effects (Atzori et al., 2018; Hoffman et al., 2019). Finally, several studies combined the use of a *distraction* mechanism with the mechanisms of *relaxation* (Esumi et al., 2020; Garrett et al., 2017; Özalp Gerçeker et al., 2020; Sharifpour et al., 2020), which can have anxiolytic and affective effects.

The previously conducted selective review by Gupta et al. (2018) highlighted several non-distraction mechanisms used mainly in chronic pain studies: biofeedback, relaxation, imaginary exposure, positive affect, motivation and pain control. The non-distraction mechanisms described in the current review are only partially in line with the mechanisms described by Gupta et al. (2018). That is, *biofeedback* (Venuturupalli et al., 2019) and *relaxation* (Esumi et al., 2020; Garrett et al., 2017; Özalp Gerçeker et al., 2020; Sharifpour et al., 2020) were also used in this review as underlying mechanisms of the VR therapies, however, the other four mechanisms were not employed in the studies reviewed here. Nevertheless, the current review makes a valuable contribution with, particularly, the description of *neuromodulatory* mechanisms (Chau et al., 2017; Ichinose et al., 2017; Matamala-Gomez et al., 2019; Pozeg et al., 2017; Rutledge et al., 2019; Solca et al., 2018), and to a lesser extent, the description of *graded exposure* (Fowler et al., 2019) in the treatment of chronic pain.

Comparing the underlying mechanisms of the VR therapies for acute and chronic pain management in this systematic review, two aspects can be noted. First, although some mechanisms are in agreement (i.e., *distraction*, *relaxation*), there is also a large divergence in the mechanisms used. Second, all acute pain studies used *distraction* mechanisms, and two of them used *relaxation* in addition to that, whereas chronic pain studies used a range of different mechanisms. *Neuromodulatory* mechanisms were used the most in chronic pain studies, moreover, other employed mechanisms were *distraction*, *relaxation*, *graded exposure*, and *biofeedback*.

The large divergence in the underlying mechanisms of the VR therapies found in this review in acute versus chronic pain studies can be explained in the light of the gate control theory of pain (Melzack & Wall, 1965) and the neuromatrix theory of pain (Melzack, 2001), particularly when considering the nature of both types of pain. Acute pain is pain that lasts for less than three months, and is always nociceptive of nature. Nociceptive stimuli refer to an actual damaging or potentially damaging stimuli (Carr & Goudas, 1999). According to the gate control theory of pain, nociceptive stimuli have to pass through a gate control mechanism in the dorsal horn of the spinal cord in order to reach the brain (Melzack & Wall, 1965). This theory holds that depending on how open or closed the gate is, it is determined how painful the stimuli is perceived. However, many factors can open or close the gate, for instance behavioural (e.g., skin injury) and psychological factors (e.g., attention, emotion; Melzack & Wall, 1965; Triberti et al., 2014). Hence, the gate control theory of pain can explain how *distraction* and *relaxation* can close the gate through attentional, anxiolytic, and affective mechanisms (Indovina et al., 2018;

Triberti et al., 2014). One can argue that being engaged in multisensory immersive VR demands much attentional resources, which can close the gate. Similarly, it can be argued that feeling calm and relaxed can reduce anxiety which can also close the gate, as well as by experiencing positive emotions (e.g., fun) when engaging in a VR distraction therapy. However, the gate control theory of pain is unable to explain chronic pain conditions. For this, one must turn to the neuromatrix theory of pain (Melzack, 2001).

In contrast to the gate control theory of pain, Melzack’s (2001) neuromatrix theory of pain is able to explain chronic pain states. The neuromatrix theory of pain holds that pain is a multidimensional experience generated by an extensive neural network in the brain, which can be triggered by sensory, affective, cognitive input as well as by genetic influences, to produce the output. However, the neuromatrix does not only produce outputs in the form of pain perception, but it also self-regulates the body to a state of homeostasis (Melzack, 2001, 2005). The neuromatrix theory posits that chronic pain is not caused by actual tissue damage, rather it is produced in the brain as a consequence of a prolonged stress state. Due to the prolonged stress, the brain constantly anticipates danger and consequently produces pain through the neuromatrix (Melzack, 2005). When the neuromatrix persists to produce pain for extended periods of time, this can trigger a number of changes (Moseley & Flor, 2012) in the brain: central sensitisation (i.e., increased responsiveness in the central nervous system); hyperalgesia (i.e., increased pain sensitivity); allodynia (i.e., normally non-painful stimuli cause pain). Eventually, this can lead to cortical reorganisation (i.e., the body representation shrinks in the functional map of the brain, and adjacent brain areas expand). However, most of these changes are reversible through treatments (Knotkova & Rasche, 2015), which explains why *neuromodulation* as a mechanism for VR therapies was most often use in chronic pain studies reviewed here.

When examining the effectiveness of VR interventions in acute versus chronic pain management, it shows that VR was quite effective in reducing pain in both conditions. However, it must be noted that the chronic pain studies mostly used small samples, and employed weaker research designs (only one experimental study). Acute pain studies, in contrast, had larger sample sizes and seven studies used experimental designs of which six were randomised controlled trials. Accordingly, the acute pain studies were of better methodological quality, although this was not examined systematically in this review.

The fact that VR therapies in acute pain management are currently of higher methodological quality can be explained through several factors. First, the study of VR in acute pain management has a longer research tradition, as a large body of research has accumulated over the last two decades (Gold et al., 2007; Mallari et al., 2019; Malloy & Milling, 2010). Secondly, the VR technology and software that has to be developed for chronic pain states presents technical challenges due to the more complex nature of chronic pain (Rutledge et al., 2019). Third, it may be argued that it is more challenging to obtain larger samples of chronic pain patients, and finally it may be argued that it is unethical to conduct experimental studies where one group of chronic pain patients receives no treatment.

A second aim of this review was to compare the underlying mechanisms of VR therapies in adult versus paediatric populations. When comparing the adult studies versus the paediatric studies, it should be first noted that all but one of the paediatric studies were acute pain studies. Due to the nature of acute pain, as explained in the previous section on the gate control theory of pain, it is logical that therefore nearly all paediatric studies employed *distraction* mechanisms, and two studies used *relaxation* mechanisms in addition to *distraction*. Perhaps more strikingly is the fact that only paediatric study was conducted on chronic pain conditions (i.e., cancer-related chronic pain; Sharifpour et al., 2020). Of the adult studies, three of them were conducted on acute pain, and the rest were chronic pain studies. Therefore, adult studies have used a mixture of mechanisms ranging from *distraction*, *relaxation*, *neuromodulation*, *graded exposure*, and *biofeedback*. In sum, this comparison seem to make not much sense in this review as it mainly compares acute versus chronic pain, however, what is important to point out is the lack of chronic pain studies in paediatric populations.

A limitation of the current review is the exclusion of experimentally induced pain. Experimental pain was excluded to gain more insight in the underlying mechanisms of VR therapies in acute and chronic pain management in daily clinical practice. However, experimental studies may be able to unravel valuable novel mechanisms as is shown in this study by Hughes et al. (2019). These authors demonstrated a reduction of an experimentally induced sensitised pain state through exposure to an immersive VR polar environment coupled with a conditioned pain modulation paradigm. These findings seem to be promising for chronic pain patients, although more research is needed here. Another limitation of this study was that the methodological quality of the studies included in this review were not systematically examined. Conversely, strengths of this review include the focus on both adult and paediatric populations, and the comparison of the underlying mechanisms of VR therapies in acute versus chronic pain management.

Although the reviewed studies on chronic pain provided a promising non-pharmacological treatment method for the management of chronic pain, more research is needed to unravel the complex interplay of neuromodulatory mechanisms, such as virtual embodiment, the vision of the body, and multisensory congruence. Moreover, future research is needed to extend these findings with higher quality designs, larger sample sizes, longitudinal, and

functional magnetic resonance imaging designs to investigate whether the reversible changes in the brain are sustainable in the long term, and to investigate the long-term analgesic effects of VR on chronic pain. Moreover, this review showed a gap in the literature, as in the published literature from 2015 to 2020, only one study was found which targeted chronic pain in a paediatric population using VR, thus more research is recommended here. Further, future research can benefit from implementing additional treatment modalities into VR, as VR provides a safe platform to remotely deliver traditional treatment methods such as cognitive behavioural therapy.

This systematic review described and compared the underlying mechanisms of VR therapies in acute versus chronic pain management. It was found that in acute pain management all studies used the attentional mechanism of distraction in their VR therapies, and in addition, relaxation was also used. In contrast, in chronic pain management, most studies aimed to reverse cortical misrepresentations through neuromodulatory mechanisms, however, chronic pain studies also employed distraction, relaxation, graded exposure, and biofeedback mechanisms. These findings are in line with the nature of acute versus chronic pain, as acute pain is accompanied by nociceptive stimuli whereas chronic pain can occur in the absence of actual tissue damage but is produced by neural networks in the brain, and is accompanied with maladaptive but reversible changes in the brain.

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Appendices

Appendix A – Search Strategies

Table 4

Search Strategies Used in the Systematic Review

Search	Date	Database	Terms	Filter1	Filter2	Filter3	Results
1	31-3-2020	Scopus	("virtual reality") AND pain	English	2015-2020	Articles	308
2	31-3-2020	PubMed	("virtual reality") AND pain	English	2015-2020	Journal Articles	328
3	31-3-2020	PsycINFO	("virtual reality") AND pain	English	2015-2020	Academic Journals	116
4	1-4-2020	Scopus	("virtual reality") AND (("acute pain" OR "chronic pain")	English			196
5	1-4-2020	Scopus	("virtual reality") AND (("acute pain" OR "chronic pain")	English	2015-2020		128
6	1-4-2020	Scopus	("virtual reality") AND (("acute pain" OR "chronic pain")	English	2015-2020	Articles	60
7	1-4-2020	PubMed	("virtual reality") AND (("acute pain" OR "chronic pain")	English			109
8	1-4-2020	PubMed	("virtual reality") AND (("acute pain" OR "chronic pain")	English	2015-2020		83
9	1-4-2020	PubMed	("virtual reality") AND (("acute pain" OR "chronic pain")	English	2015-2020	Journal Articles	82
10	1-4-2020	PsycINFO	("virtual reality") AND (("acute pain" OR "chronic pain")	English			62
11	1-4-2020	PsycINFO	("virtual reality") AND (("acute pain" OR "chronic pain")	English	2015-2020		27
12	1-4-2020	PsycINFO	("virtual reality") AND (("acute pain" OR "chronic pain")	English	2015-2020	Academic Journals	24
13	14-4-2020	Scopus	("virtual reality") AND pain AND (treatment OR intervention OR therapy)	English	2015-2020	Articles	202
14	14-4-2020	PubMed	("virtual reality") AND pain AND (treatment OR intervention OR therapy)	English	2015-2020	Journal Articles	282
15	14-4-2020	PsycINFO	("virtual reality") AND pain AND (treatment OR intervention OR therapy)	English	2015-2020	Academic Journals	76

Note. After preliminary searches, the final search was performed on 14 April 2020 using the following search string: ("virtual reality") AND pain AND (treatment OR intervention OR therapy), resulting in a total of 560 hits. The search was carried out in three databases: Scopus, PubMed and PsychINFO.