Annals of Physical and Rehabilitation Medicine 62 (2019) 49–57

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Annals of Physical & Rehabilitation Medicine
SOFMER

Review

Virtual reality for spinal cord injury-associated neuropathic pain: Systematic review

B. Chi [a,b,*], B. Chau [a,c], E. Yeo [d], P. Ta [a]

[a] Department of Physical Medicine and Rehabilitation, Loma Linda University Health, 11406 Loma Linda Drive, Suite 516, 92354 Loma Linda, CA, USA
[b] Zucker School of Medicine at Hofstra/Northwell, 500 Hofstra Boulevard, 11549 Hempstead, NY, USA
[c] VA Loma Linda Healthcare System, 11201 Benton Street, 92357 Loma Linda, CA, USA
[d] Loma Linda University School of Medicine, 11175 Campus Street, 92350 Loma Linda, CA, USA

ARTICLE INFO

Article history:
Received 7 June 2018
Accepted 15 September 2018

Keywords:
Virtual reality
Spinal cord injury
Neuropathic pain

ABSTRACT

Background: Treatment of spinal cord injury (SCI)-associated neuropathic pain is challenging, with limited efficacy and no definitive options, and SCI patients often show resistance to pharmacologic treatment. Virtual reality (VR) therapy is a non-invasive, non-pharmacologic alternative with minimal adverse effects.
Objective: To investigate the effect of VR therapy on SCI-associated neuropathic pain in a systematic review.
Methods: Articles needed to 1) be written in English; 2) include adult subjects, with at least half the study population with a SCI diagnosis; 3) involve any form of VR therapy; and 4) assess neuropathic pain by quantitative outcome measures. Articles were searched in MEDLINE/PubMed, CINAHL®, EMBASE, and PsycINFO up to April 2018. Reference lists of retrieved articles were hand-searched. Methodologic quality was assessed by the Physiotherapy Evidence Database Score (PEDro) for randomized controlled trials and Modified Downs and Black Tool (D&B) for all other studies. Level of evidence was determined by using a modified Sackett scale.
Results: Among 333 studies identified, 9 included in this review ($n = 150$ participants) evaluated 4 methods of VR therapy (virtual walking, VR-augmented training, virtual illusion, and VR hypnosis) for treating neuropathic pain in SCI patients. Each VR method reduced neuropathic pain: 4 studies supported virtual walking, and the other 3 VR methods were each supported by a different study. Combined treatment with virtual walking and transcranial direct current stimulation was the most effective. The quality of studies was a major limitation.
Conclusion: VR therapy could reduce SCI-associated neuropathic pain, although the clinical significance of this analgesic effect is unclear. Clinical trials evaluating VR therapy as standalone and/or adjunct therapy for neuropathic pain in SCI patients are warranted.

1. Introduction

Patients with spinal cord injury (SCI) frequently experience pain, with rates reported between 26% and 96% [1], over one-third with severe pain [2–4]. This pain has impacts on function, quality of life, and mood that can exceed the other consequences of SCI such as physical impairment or psychologic distress [1,5,6]. Because of the impact, combined with overall prevalence, SCI-associated pain is an important topic to address [1].

Multiple types of pain occur with SCI. To classify pain in SCI patients, the International Spinal Cord Injury Pain Classification (ISCIP) was developed and validated [7,8] to provide a standard approach to SCI pain for clinicians and researchers, potentially facilitating assessment and treatment [7]. In addition, the International Spinal Cord Injury (ISCI) Data Sets provide a standardized, validated approach for clinicians and researchers to collect information on pain related to SCI [9–12].

This systematic review focused on neuropathic pain, defined as “pain caused by a lesion or disease of the somatosensory nervous system” [13]. This type of pain is reported in 40% to 50% of SCI

* Corresponding author. Department of PM&R, LLUH, 11406 Loma Linda Drive, Suite 516, 92354 Loma Linda, CA, USA.
E-mail address: bchi1@pride.hofstra.edu (B. Chi).

https://doi.org/10.1016/j.rehab.2018.09.006
1877-0657/

patients and typically develops within the first year following injury, often becoming chronic [2,14,15]. SCI-related neuropathic pain can be subtyped as "at level", referring to pain experienced at or within 3 dermatomes of the neurologic level of injury, or "below level", referring to pain experienced more than 3 dermatomes below the neurologic level of injury [7]. Currently, multiple mechanisms are believed to play a role in neuropathic pain of SCI patients, although the process is not completely understood [16]. Despite this understanding, treatment options for neuropathic pain are limited because in most cases of neuropathic pain, an underlying cause is not found [17]. Importantly, treatment of neuropathic pain is difficult and the efficacy of the current recommended treatment options are modest [18].

Virtual reality (VR) is a computer-based technology that allows users to gain immersion and presence within a virtual environment. Two general categories of VR exist: immersive and non-immersive. In immersive VR, users' sensations are completely encompassed by the virtual environment. This VR typically involves a head-mounted display that blocks the users' vision of the real world. Conversely, non-immersive VR allows users to retain some sensory connection with the real-world environment. Virtual illusion was first used successfully in 1992 by Ramachandran for neuropathic pain in patients with phantom limb pain (PLP) [19]. Pain reduction seen with Mirror Visual Feedback (MVF) is believed to be due a various mechanisms including reversal of maladaptive neuroplastic changes and effects on central regulation [19].

Since the development of MVF, the use of VR to treat chronic pain has increased because of its similarity to MVF. Additionally, some advantages of VR over traditional MVF include improved interaction, compatibility for bilaterally affected patients, and potential for customization [19]. VR treatment has been successful for chronic neuropathic pain, including musculoskeletal pain [20–22], PLP [23], complex regional pain syndrome [24], and fibromyalgia [25].

As previously discussed, treatment of SCI-associated neuropathic pain is challenging, with limited efficacy and no definitive options [18]. Furthermore, SCI patients often show resistance to pharmacologic treatment and request alternative treatment [26]. VR is a non-invasive, non-pharmacologic therapeutic alternative with minimal adverse effects. This review aimed to examine the role of VR therapy for treating SCI-associated neuropathic pain in patients with SCI.

2. Methods

2.1. Search strategy

In April 2018, multiple databases (Medline/Pubmed, CINAHL®, EMBASE, PsycINFO) were searched for articles published up to April 2018 by using the keywords "spinal cord injury", "tetraplegia", "quadriplegia", or "paraplegia" with "virtual reality". Each pairing was then searched with and without "pain". Therefore, 8 searches per database were performed, for a total of 32 searches. Abstracts of all articles were read, and those indicating use of VR with SCI patients were read in full. Articles that met inclusion criteria were selected for the review. References and bibliographies of all selected articles were also examined. We included articles of studies that 1) were written in English, (2) included adults with at least half the study population with a SCI diagnosis, (3) used any form of VR therapy, and (4) assessed neuropathic pain by quantitative outcome measures. The exclusion criterion was publication in non-peer-reviewed journals.

2.2. Data extraction

Data were extracted separately by 2 authors (BC, EY) who used a table specifically designed for this review. The extracted data included 1) study author name and publication date, 2) study design, 3) sample size, 4) methodologic quality, 5) study population demographics, 6) VR system, 7) pain outcomes, and 8) major results and 9) adverse events. Discrepancies were resolved by discussion by all authors for consensus.

2.3. Methodological quality

The methodological quality of studies was assessed by the previously established Spinal Cord Injury Research Evidence (SCIRE) methodology [27]. Quality was assessed by 2 reviewers (BC, EY) who used the Physiotherapy Evidence Database Score (PEDro) [28] for randomized controlled trials (RCTs) or the modified Downs and Black Tool (D&B) [27,29] for all other study types. Both tools are validated and have been used in reviews of SCI rehabilitation [27]. The strength of evidence for each study was determined by using a modified Sackett scale with 5 levels of evidence as described by the SCIRE (Table 1) [27]. The protocol of this review was not registered.

This review is reported according to PRISMA guidelines [30].

3. Results

The flow of studies in the review is in Fig. 1. After an initial screening, 35 of 104 studies were selected for full review; the most common reason for exclusion was lack of quantitative pain outcome measure. Ultimately, 9 articles met inclusion criteria for this review.

The study quality and level of evidence across studies varied. Two of the 9 studies were RCTs, with PEDro scores of 8 (level 1) [31] and 5 (level 2) [32]; 6 were pre-post studies, with D&B scores ranging from 18–21 (level 4) [33–38]; and 1 was a case report (D&B = 15, level 5) [39] (Table 2).

Various pain-assessment tools were used. The most common measures of pain intensity were the numerical rating scale (NRS, $n = 6$) [40] and visual analog scale (VAS, $n = 3$) [41] (Table 2). Other outcome measures included the McGill pain questionnaire (MPQ) [42], neuropathic pain symptom inventory (NPSI) [43], brief pain inventory (BPI) [44,45], and patient global impression of change (PGIC) [40] (Table 2).

Studies varied in protocol, ranging from a single 10-min session to 33 sessions of 90 min each over a 6-month period. Outcomes were also measured at various times including before the study (baseline), immediately before and after individual sessions (pre-post session), after completion of all study sessions (post-treatment), or an extended period of time after study completion (follow-up) (Table 2).

3.1. Methods of VR therapy

3.1.1. Virtual walking

The most frequent method of VR was virtual walking, which involves a VR environment that enhances the subjects' ability to imagine themselves walking. Moseley [33] first described virtual walking by using a setup in which subjects viewed a large screen

Table 1
Modified Sackett's Levels of Evidence.

Levels	Evidence
1	RCTs with PEDro score ≥ 6
2	RCTs with PEDro score < 6, cohort and non-RCTs
3	Case control studies
4	Pre-post studies, post-test studies or case series
5	Observational studies, clinical consensus, or case reports

RCT: Randomized controlled trial; PEDro: Physiotherapy Evidence Database. Adapted from Eng et al. [27].

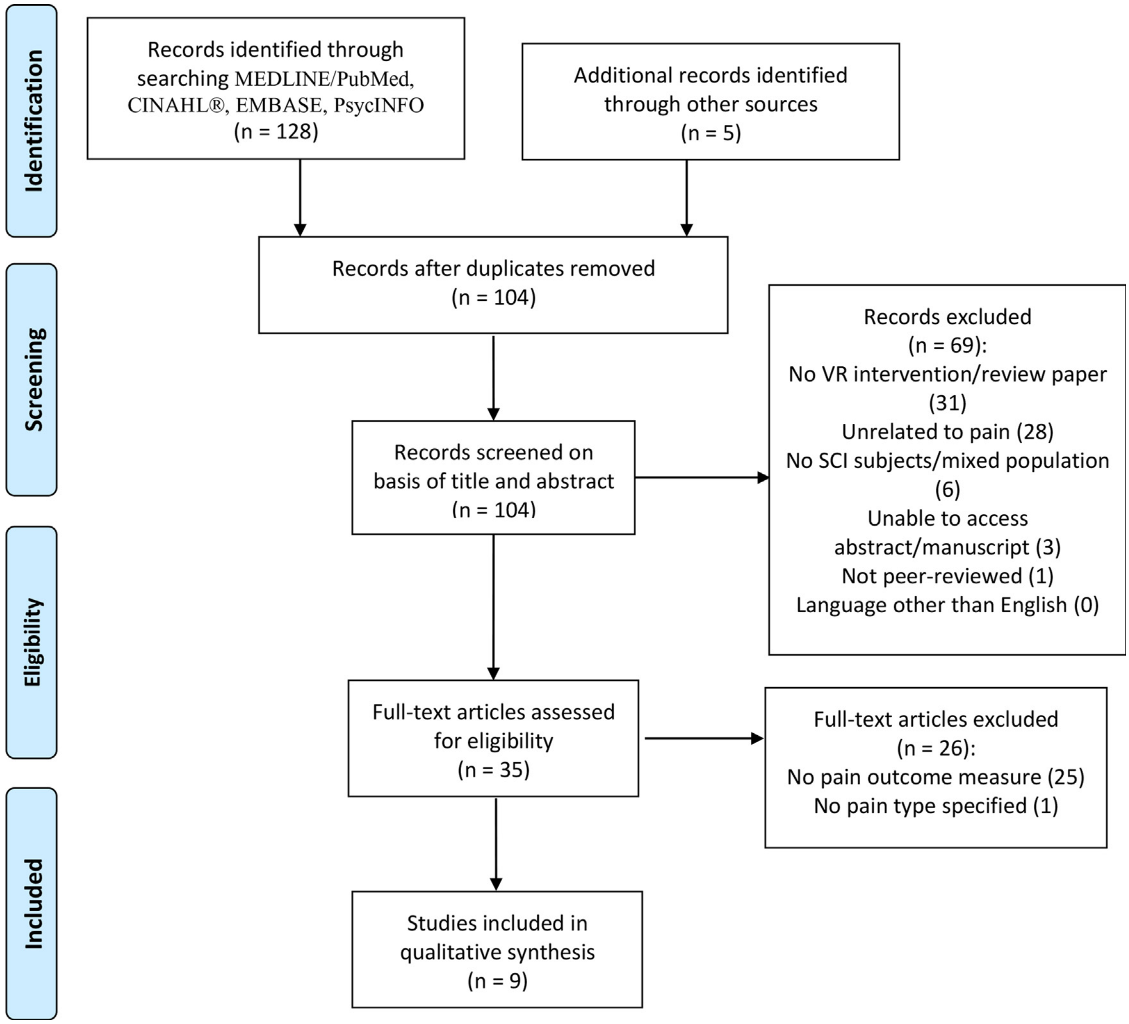

Fig. 1. PRISMA flow diagram describing screening and review process [30]. SCI, spinal cord injury.

with a life-size projection of an actor walking. The top half of the screen could be covered with a mirror so that subjects saw a reflection of their own upper body aligned with the actor's lower body. Subject were asked to move their upper body in time with the projected lower body, creating the illusion that the subject was walking. Soler et al. [31], Kumru et al. [37] and Ozkul et al. [32] adopted the same methodology. In Jordan and Richardson [35], participants viewed a video presented on a 3-D monitor of an actor in first-person view walking along a path. The control group viewed a video of the same actor pushing a wheelchair. Roosink et al. [38] created an interactive virtual walking system in which a 3-D virtual avatar in third-person view walking forward or backward along a path was displayed on a large screen in front of the subject. The subject controlled the movement and speed of the avatar by using an inertial movement sensor attached to the subject's arm.

To compare the efficacy of a standalone virtual walking intervention with virtual walking as an adjunct to other interventions, study results were summarized by type of intervention. Four studies reported on a virtual walking-only intervention. Moseley [33], Soler et al. [31], and Jordan and Richardson [35] found reduced pain intensity after treatment (84%, 11%, and 15% to 25%, respectively). Conversely, Ozkul et al. [32] demonstrated pain reduction for only pre-post sessions (range: 19.8–26.8%). For the 2 studies that assessed pain at follow-up, Moseley [33] found sustained pain reduction (67%) at 3 months and Soler et al. [31] did not show a significant pain reduction during follow-up, However, Soler et al. [31] found significant decreases in neuropathic pain subtypes by using the NPSI; most notably, dysesthesia was decreased post-treatment (41%) and at 24-day follow-up (27%). Ozkul et al. [32] found decreased pain sharpness, hotness, unpleasantness, and depth parameters post-treatment. Of the 2 studies that measured BPI, Soler et al. [31] reported significantly reduced pain interference in mood, whereas Ozkul et al. [32] reported improved "ability to get around" post-treatment. The study measuring PGIC found that 10% of patients reported "markedly" improved pain [31]. Jordan and Richardson [35] found an inverse association between at-level hypersensitivity and below-level pain reduction. Soler et al. [31] found no correlation between general pain change and confounding factors such as age, sex, SCI etiology, time since SCI, level of injury, and SCI severity.

Two studies compared virtual walking to a control treatment [33,35]. Moseley [33] found that virtual walking resulted in greater amelioration of pain intensity and time to return to pre-intervention pain than guided imagery and film watching controls. Jordan and Richardson [35] found that virtual walking significantly reduced pain relative to the virtual wheeling control.

3.1.2. Virtual walking and transcranial direct current stimulation (tDCS)

Three studies examined the combined effects of virtual walking with tDCS [31,37,38]. tDCS involves non-invasive cortical brain

Table 2
Study characteristics.

Author/Reference Study design Score (PEDro/D&B) Level of evidence Type of VR	Population: n = persons with neuropathic pain Age in years (mean [SD]), Years since injury (mean [SD]), AIS classification (n of persons)	VR modality Session: number/duration, Treatment period duration Follow-up	Pain outcome indicators	Primary findings
[33] Moseley 2007 Pre-post D&B = 18 Level = 4 Non-immersive	(1) n = 5, (2) n = 4 32.3 (8.3), 11.2 (6.1) AIS B = 5	VW (1) Session: 1/10 min Treatment: 1 day (2) Session: 15/10 min Treatment: 3 wk Follow-up: 3 mo	MPQ, VAS	(1a) Decrease in pain VAS for VW* (42 mm [11–73 mm]) greater than GI* (18 mm [4–31 mm]) and film (4 mm [−3–11 mm]); (1b) Time to return to pre-task pain VAS longer for VW* (34.9 min [20.1–49.8 min]) than GI* (13.9 min [−0.9–28.8 min]) and film* (16.3 min [1.5–31.2 min]) (2) Decrease in pain VAS post-treatment* was 53 mm [45–61 mm] and at 3-month follow-up* was 43 mm [27–53 mm]
[32] Ozkul et al., 2015 RCT PEDr = 5 Level = 2 Non-immersive	n = 24 32.3 (13.0), 1.6 (2.2) AIS A = 17, B = 4, C = 3	VW Session: 10/15 min Treatment: 2 wk	MPQ, VAS, NPS, BPI	(1) Decreased pre-post session pain VAS*: range from 19.8–26.8% decrease (2) No significant post-treatment changes in VAS pain intensity; decrease in average pain: .42 [−0.03–0.86]; decrease in maximal pain: .09 [−0.31–0.48]; decrease in minimal pain: −0.04 [−0.62–0.54] (3) Improvement of sharpness*, hotness*, unpleasantness*, and depth* parameters of NPS post-treatment (4) Improved "ability to get around"* on BPI post-treatment
[35] Jordan and Richardson 2016 Pre-post D&B = 21 Level = 4 Immersive	(1) n = 35, (2) n = 15 47.5 (9.4), 16.1 (10.4) AIS A = 17, B/C/D = 18[a]	VW (1st person view) Session: 1/20 min Treatment: 1 day	NRS	(1a) Larger decrease in pain NRS in VW compared to wheeling group*: VW change in NRS pain A/L −1.58 (1.62) and B/L −0.78 (1.51); Wheeling change in NRS pain A/L −0.63 (1.49) and B/L 0.78 (1.51) (1b) No significant interaction between treatment condition and location of pain but relationship between higher A/L sensitivity and less favorable B/L pain outcome
[31] Soler et al., 2010 RCT PEDro = 8 Level = 1 Non-immersive	n = 40 45 (15.5), 8.4 (7.9) AIS A = 31, B = 8	VW, tDSC + VW Session: 10/20 min Treatment: 2 wk Follow-up: 10 days, 24 days, 12 wk	NRS, NPSI, BPI, PGIC	(1) Decreased overall pain NRS for VW group post-treatment* but not follow-up: baseline pain: 7.2 (1.6); post-treatment pain*: 6.4 (1.6); follow-up pain: 10-day 7.2 (1.5), 24-day 7.1 (1.4) (2) Decreased pain NRS for tDCS+VW group post-treatment* and follow-up*: baseline pain: 7.5 (1.2); post-treatment pain*: 5.2 (1.5); follow-up pain: 10-day* 5.3 (1.4), 24-day* 5.5 (1.8) (3) Greater pain reduction from tDCS+VW than other interventions: post-treatment: VW* and placebo*; 10-day follow-up: tDCS*, VW*, and placebo*; 24-day follow-up: no difference between groups; 12-week follow-up: tDCS* and VW* (4) Pain subtypes post-treatment: VW – decrease in continuous pain* and dysesthesia*; Continuous: baseline 8.4 (1.5), post-treatment 4.9 (1.9); Dysesthesia: baseline 7.4 (1.8), post-treatment* 4.4 (2.7), 24-day follow-up* 5.4 (1.8); tDCS+VW – decrease in all pain subtypes*; Paroxysmal: baseline 8.5 (2.3), 24-day follow-up* 5.5 (3.2); Dysesthesia: baseline 6.8 (1.7), 24-day follow-up* 5.1 (1.8) (5) Self-reported markedly improved pain-relieving effect (PGIC) post-treatment: a. tDCS + VW – 50%; b. tDCS – 30%; c. VW – 11% (6) No significant changes in overall pain NRS for tDCS and placebo:
[37] Kumru et al., 2013 Pre-post D&B = 20 Leve = 4 Non-immersive	n = 18 49.4 (12.4), 8.3 (10.0) AIS A = 3, B = 3, C = 1, D = 11	tDSC + VW Session: 10/20 min Treatment: 2 wk	NRS	(1) Average decrease in pain NRS post-treatment of 37.4% (24.8%); (2) Evoked heat pain perception decreased post-treatment* (2.8 [1.8]) and was no different from SCI without NP patients (2.7 [1.2])

Table 2 (*Continued*)

Author/Reference Study design Score (PEDro/D&B) Level of evidence Type of VR	Population: *n* = persons with neuropathic pain Age in years (mean [SD]), Years since injury (mean [SD]), AIS classification (*n* of persons)	VR modality Session: number/duration, Treatment period duration Follow-up	Pain outcome indicators	Primary findings
[38] Roosink et al., 2016 Pre-post D&B = 19 Level = 4 Non-immersive	*n* = 7 56.7 (9.5), 6.5 (3.9) AIS A = 4, C = 1, D = 2	tDCS + VW Session: 2/90 min Treatment: 2 wk	NRS	(1) No significant effect of tDCS + VW on pain intensity (2) Average change in pain NRS[c] post-treatment was −2 [−6–2]
[36] Villiger et al., 2013 Pre-post D&B = 20 Level = 4 Non-immersive	*n* = 9 50.8 (14.3), 6.8 (5.7) AIS C = 2, D = 7	VR-augmented training Session: 16–20/45 min Treatment: 4 wk Follow-up: 12–16 wk	NRS, PGIC	(1) Decreased pain NRS: a. intensity – post-treatment* (38.9%) and follow-up* (36.3%); b. unpleasantness – post-treatment* (37.9%) and follow-up* (29.6%) (2) Clinical improvement in pain: a. post-treatment – 6/9 met MDC and 5/9 met MCID; b. follow-up – 5/9 met MDC and MCID (3) Self-reported improved pain-relieving effect (PGIC) post-treatment: a. markedly reduced – 4/9; b. minimally reduced – 4/9; c. no change – 1/9
[34] Pozeg et al., 2017 Pre-post D&B = 20 Level = 4 Immersive	*n* = 11 47.3 (12.0), 17.1 (18.1)[b] AIS A = 15, B = 3, C = 2[b]	Virtual illusion Session: 1/not specified Treatment: 1 day	VAS	(1) No significant decrease in pain VAS with VLI group (2) Decrease in pain VAS for FBI group*: Synchronous*: 0.43 [0.03–0.84]; Asynchronous*: .46 [0.03–0.88] (3) Synchronous visuotactile stimulation induced greater ownership in VLI* and FBI* groups
[39] Oneal et al., 2008 Case report D&B = 15 Level = 5 Immersive	*n* = 1 36, 5 AIS Not specified	VR hypnosis Session: 33/40 min Treatment: 6 mo	NRS	(1) No significant decrease in post-treatment pain intensity and unpleasantness VAS (2) Pre-post session reduction in pain VAS: a. 36% reduction in average intensity; b. 33% reduction in average unpleasantness (3) Average duration of post-session pain reduction: No pain for 3.86 hrs (8.90 hrs); Reduced pain for 12.21 hrs (27.06 hrs)

wk: week; mo: month; RCT: randomized controlled trial; PEDro: Physiotherapy Evidence Database Score; D&B: Modified Downs and Black Tool; AIS: American Spinal Injury Association Impairment Scale; VAS: visual analogue scale; VW: Virtual walking; GI: Guided imagery; tDCS: Transcranial direct current stimulation; PGIC: Patient global impression of change; MDC: Minimal Detectable Change; MCID: Minimal Clinically Important Difference; NP: Neuropathic pain; NRS: numeric rating scale; NPS: Neuropathy Pain Scale; NPSI: Neuropathic Pain Symptom Inventory; BPI: brief pain inventory; VLI: virtual leg illusion; FBI: full-body illusion; A/L: at-level; B/L: below-level. Mean [95% confidence interval]. Mean (standard deviation).

* $P < 0.05$.

[a] Eighteen individuals with incomplete SCI but unknown AIS classification.

[b] Includes individuals without neuropathic pain.

[c] Scale 0–100.

stimulation delivered by electrodes [31]. Kumru et al. [37] and Soler et al. [31] found a significant reduction in neuropathic pain intensity after treatment (37% and 31%, respectively). Conversely, Roosink et al. [38] found that combined treatment had no effect on neuropathic pain. In the sole study following patients after treatment, Soler et al. [31] reported decreased pain (18%) up to 12 weeks' follow-up. The authors also found a reduction in all pain subtypes post-treatment, with reduced paroxysmal (61%) and dysesthesia pain (26%) persisting for more than 24 days' follow-up (35% and 25%, respectively). The same study reported a significant improvement in 5 of 7 BPI variables post-treatment, including the "ability to get around" and mood. Also, 50% of participants in the combined group reported "markedly" improved pain-relieving effect by the PGIC.

The Soler et al. [31] study was the only one to compare combined treatment to other treatment conditions and found that the combined intervention performed better than all other interventions in reducing pain intensity: tDCS only, virtual walking only, and placebo. Also, PGIC improvement was better than with all other treatments. Kumru et al. [37] found decreased heat pain perception after treatment, with post-treatment mean values (2.8 ± 1.8) not significantly different from those for SCI patients without neuropathic pain (2.7 ± 1.2). A significant positive correlation was found between amelioration of neuropathic pain and reduced evoked heat pain perception.

3.1.3. *VR augmented training*

Villiger et al. [36] developed a VR augmented therapy system for lower-limb training. The system differs from augmented reality, which involves using virtual objects to supplement the real world [46]. Subjects participated in four virtual training environments involving interactive use of virtual lower-limb avatars that they controlled by using motion sensors attached to the leg. The study found significant decreases in pain intensity and unpleasantness post-treatment (38.9% and 37.9%, respectively) and at 12- to 16-week follow-up (36.3% and 29.6%, respectively). Post-treatment change in NRS pain for 6 of 9 participants reached the minimal detectable change (MDC, NRS = 2 points), and 5 of 9 reached the minimal clinically important difference (MCID, NRS = 1.71 points or 27.9% reduction). At follow-up, 5 of 9 participants continued to meet the MDC and MCID; 4 of 9 reported "markedly" reduced PGIC pain.

3.1.4. Virtual illusion

Pozeg et al. [34] used VR to induce virtual leg illusions (VLI) and full-body illusions (FBI). Participants were shown a real-time video of realistic legs in the first-person view (VLI) or their back (FBI) via a head-mounted display. Tactile stimuli were delivered to the participant and the object in the video in a synchronized or asynchronized manner. The FBI group showed significant post-treatment reduction in mean VAS pain (sync = 0.43 [95% confidence interval 0.03–0.84], async = 0.46 [0.03–0.88]), regardless of the synchronicity of tactile stimulus. The VLI group did not show significantly reduced pain.

3.1.5. Virtual reality hypnosis (VRH)

The VRH developed by Oneal et al. [39] consisted of the participant "travelling" through a snowy mountain virtual environment accompanied by hypnotic audio recordings. Pain relief was reported after each session, with mean reduction in NRS pain intensity of 36% and unpleasantness of 33%. The mean duration of analgesia after sessions was 3.9 hr pain-free and 12.2 hr with reduced pain. VRH outperformed a prior non-VR hypnosis treatment for pain reduction.

3.1.6. Adverse effects

Seven of the studies reported on adverse events [31–33,36–39]. Four reported adverse effects [31,33,36,38]. One patient withdrew 45 sec into the virtual walking treatment because of distress [33]. Reported adverse effects were all mild and transient, including musculoskeletal pain and physical fatigue attributed to increased activity during the interventions.

4. Discussion

VR therapy is a promising non-pharmacologic, non-invasive alternative treatment for chronic neuropathic pain in SCI patients that can be used individually or to augment other therapies. Evidence supporting its efficacy is limited but suggests it can provide an immediate analgesic effect with questionable long-term benefit.

4.1. Virtual walking

All 4 studies investigating virtual walking for treating neuropathic pain in SCI patients found that it reduced pain intensity, which suggests that virtual walking has an analgesic effect. Still, some of the conflicting results from these studies raise multiple questions. First, the length of time that virtual walking reduces pain intensity is unclear because the studies reported pain reduction ranging from pre-post sessions to 3 months post-treatment.

Many reasons could explain these differences. First, the studies had no uniform protocol. Three studies used the same virtual walking set-up, but the number of treatment sessions ranged from 10 to 15 [31–33]. Jordan and Richardson [35] used a unique first-person view, immersive virtual walking set-up with only 1 treatment session. Moseley [33] demonstrated the greatest reduction in neuropathic pain but also used the most sessions, potentially indicating that session number is directly associated with analgesic impact. Furthermore, the number of sessions in other virtual-illusion studies has been higher, which suggests an added benefit [47,48]. Another notable difference in VR protocols was the first-person view and immersive VR used by Jordan and Richardson [35]. Considering that only a single session was completed, pain reduction was similar to studies using the other third-person–view virtual walking protocols.

Important demographic information varied between studies. The studies showing post-treatment and long-term effects studied individuals with significantly longer time since their injury than the study reporting only post-session effects (Table 2). This observation is interesting because the most significant recovery is achieved within the first year following SCI with a plateau in improvement thereafter [49,50], which suggests that the mechanism for SCI-related pain may evolve over time. Also, the degree and classification of injury differed among studies. All participants in Moseley [33] had incomplete SCI, classified as American Spinal Injury Association Impairment Scale (AIS) B. Conversely, the other studies enrolled people with complete and incomplete SCI, with close to half or more of patients having complete SCI (AIS A). The greater pain reduction seen in Moseley [33] may be consistent with the recovery being in general less with complete than incomplete SCI [50,51]. Additionally, the level of injury may impact the effect of virtual walking. The study population in Moseley [33] predominantly had lumbar-level lesions, and the other studies had a heterogeneous mix of cervical, thoracic, and lumbar level injuries. People with lumbar injuries report the highest prevalence of pain and pain intensity, primarily in the lower limbs [52]. Therefore, virtual walking may provide more benefit for these patients given the illusion of lower-limb movement.

Other relevant questions include the effect of virtual walking on the location and quality of neuropathic pain. The location of neuropathic pain is classified as at-level and below-level, which represent different pathophysiologic mechanisms. Only one study attempted to address this question, predicting that virtual walking therapy would have greater impact on below-level pain in patients with greater at-level hypersensitivity, because of the central pain mechanism [35,53,54]. The results suggested the opposite, showing an inverse association between at-level hypersensitivity and below-level pain. Further research is needed to investigate this association.

In addition to pain intensity, various treatment options can affect the quality of neuropathic pain and make the pain more tolerable to patients [32]. These findings suggest that virtual walking can have differing effects on specific types of pain, but the lack of overall evidence disallows drawing premature conclusions.

The findings suggest an association of increased number of treatment sessions with greater pain reduction. Other differences in protocol such as point-of-view may influence effects, but more evidence is needed. Among the patient characteristics, classification of SCI seems the most important and reliable predictor of success with virtual walking because pain reduction was greater with incomplete than complete SCI. Findings also suggest that length of time since SCI may influence the effects of VR therapy, with greater impact the further time away from injury. Finally, virtual walking may have greater benefit for lumbosacral SCI than higher-level injuries.

4.2. Virtual walking with tDCS

Evidence supporting combined virtual walking and tDCS in reducing neuropathic pain is relatively strong and suggests a synergistic effect between the 2 interventions. The effect size was larger in Kumru et al. [37] than Soler et al. [31] despite identical protocols. This finding may be explained by a greater proportion of incomplete SCI patients in Kumru et al. [37], which is consistent with the findings from virtual walking-only studies suggesting greater benefit with incomplete SCI (Table 2). The mechanism explaining the effects are not fully understood. Virtual walking combines imagery with visual observation, which has been shown to enhance corticospinal excitability and decrease intracortical inhibition [55,56]. Enhanced cortical excitability has also been found with tDCS, potentially explaining a mechanism for synergism [57,58]. The sole study that did not find a significant reduction in pain used a unique immersive VR protocol with a patient-controlled avatar motion. Immersive VR has been found to outperform non-immersive VR in reducing acute pain [59], with promising results for chronic pain, and was used successfully for virtual walking by Jordan and Richardson [35]. Furthermore, increased interaction in VR, as seen with subject-controlled motions, has been associated with greater pain reduction likely because of a distraction effect [60]. Therefore, the Roosink et al. [38] VR protocol should be more effective than non-immersive VR protocols, which contradicts their findings. However, the study also had a small sample size and older population, and participants completed significantly few sessions, which may better explain the lack of analgesic effect.

In summary, the findings suggest that virtual walking and tDCS combined can significantly reduce pain intensity, with potential for sustained benefit. Additionally, combined treatment reduced pain to a greater extent than with virtual walking alone. Studies comparing VR methods are needed to investigate the effects of different types of VR on SCI pain.

4.3. Other options

Alternative strategies for using VR showed potential to decrease neuropathic pain. Treatment with the VR-augmented lower-limb training system demonstrated sustained pain relief [36]. Importantly, this system differs from virtual walking in that subjects must retain adequate lower-extremity motor function. All study participants had incomplete motor SCI (AIS C or D). This type of system is particularly promising because similar set-ups have been shown to reduce neuropathic pain in other conditions such as PLP and complex regional pain syndrome [23]. The mechanism of these chronic pain conditions differs, but certain similarities such as maladaptive neuroplastic changes may underlie the analgesic effects of VR-augmented training.

The findings of Pozeg et al. [34] are consistent with prior work suggesting that VR can be used to modify body ownership and perception of pain [61–63]. An important consideration is that most of studies in this review used motor illusion. This study shows the potential for VR-based visuotactile illusion in reducing pain for SCI individuals. These findings could be considered when developing therapeutic systems.

Hypnotic therapy has been used widely for many types of acute and chronic pain [64]. Our findings suggest that although use of VRH is limited to short-term analgesia, it can provide hours of post-session pain reduction, which is considerably longer than that seen with hypnotic therapy alone. A potential advantage of VRH over traditional hypnosis is lowering the effort needed to induce hypnosis, thereby improving pain reduction [65]. Findings of greater pain reduction with VRH than traditional hypnosis despite a low hypnotizable score in the individual support this theory. Although limited by quality of evidence, VR shows promise in augmenting hypnosis therapy for pain.

4.4. Mechanism

An overall understanding of the mechanisms underlying the analgesic effects of VR is incomplete. Additionally, SCI-associated neuropathic pain is known to be multi-faceted and heterogenous, so isolating specific mechanisms is challenging [16]. Recently, functional cortical reorganization has been found associated with SCI and other chronic pain conditions, although whether this finding is causal or reactionary to chronic pain is unclear [66,67].

Multiple theories attempt to explain the effects of VR on pain, many based on virtual illusion (VI). VI was first used successfully for neuropathic pain in patients with PLP by using MVF. One theory suggests that VI corrects the disconnect between stimulus and response, experienced by many patients with chronic neuropathic pain [19]. A later study found a significant reversal of cortical dysfunction in the primary somatosensory cortex of PLP individuals after MVF [68]. Additionally, VI was found to activate sensorimotor areas known to have cortical reorganization in SCI patients with neuropathic pain [69]. These findings support the theory of reversal of maladaptive cortical reorganization. Another theory suggests that visualization in VI could train mirror neurons for rehabilitation and pain relief [19,70].

Other theories involve distraction and effects on emotion. VR can have a powerful effect on capturing a users' attention and influencing emotions. Studies of brain activity show a correlation between regions of the brain associated with distraction and pain perception [71–73]. Emotions can also significantly modulate the perception of pain [74].

4.5. Immersive vs non-immersive VR

Prior studies have found that immersive VR outperforms non-immersive VR in decreasing pain [75]. Three studies included in this review used immersive VR [34,35,39] but did not compare VR directly to non-immersive VR (Table 2). Because of the heterogeneity in study protocols, concluding on the effects of immersive versus non-immersive VR for SCI pain is difficult. Future studies may look to explore the differences.

4.6. Treatment implications

Treating SCI-associated neuropathic pain is challenging, with no gold standard treatment option. VR offers multiple advantages as a non-pharmacologic and non-invasive alternative treatment with minimal adverse effects. Other advantages include portability, ease of use, and potential for personal customization.

VR therapy likely has some analgesic effect, but the clinical importance of this effect is uncertain. The estimated decrease in MCID in chronic pain intensity measures is approximately 33% with both NRS and VAS scales [76,77]. Overall, the findings are mixed. For virtual walking, only 1 of 4 studies demonstrated an MCID [33]. For combined virtual walking and tDCS treatment, results were more favorable. Between one and two thirds of patients reported pain reduction consistent with an MCID and an average reduction across all patients also met criteria. Overall, conclusions are limited by the quality of evidence. The findings suggest that virtual walking does not consistently result in a clinically meaningfully reduction in pain although it could on an individual basis. The combined treatment likely results in clinically meaningfully pain reduction in a substantial proportion of patients.

In the other applications of VR, the Villiger et al. [36] findings were strongest, with more than half of patients achieving an MCID. VRH resulted in a clinically meaningful reduction in mean pre-post session pain intensity and unpleasantness [39]. Pain reduction in the visual illusion study did not meet this threshold [34]. Because of the limited number and quality of these studies, no strong conclusions can be made.

Chronic pain has wide-ranging impacts on patients; therefore, assessment of treatments should consider measures beyond just pain. The IMMPACT recommendations for outcome measures include physical functioning, emotional functioning, and patient ratings of global improvement and satisfaction [78]. These outcomes were inconsistently reported in the studies we examined, which limits the ability for conclusions. Overall, findings are generally associated with changes in neuropathic pain. Improvement in functioning and patient impression, measured by the BPI and PGIC, respectively, were consistent with pain intensity findings in that the combined treatment significantly outperformed virtual walking alone. Thus, VR therapies may have holistic benefits for patients.

4.7. Research implications

VR therapy for SCI warrants additional research, but inherent challenges in studying SCI and VR exist. For example, neuropathic pain associated with SCI is heterogeneous in nature and the mechanisms are not fully understood [17,79]. VR protocols vary significantly, which limits inter-study or multi-facility comparisons. Furthermore, the full mechanism of VR therapy is still incompletely understood. This review identified deficits in the current literature. Overall, the quality of studies was a major weakness. Quality could be improved by stronger study designs, homogenized population selection, and multivariate analysis for confounding factors. Future studies may aim to compare VR therapy against other treatment alternatives for SCI-associated neuropathic pain. Also, the impact of clinical factors such as SCI severity, time since injury, and level of injury on the effects of VR therapy should be further investigated. The review also highlights the importance of standardized data collection and its utility in research applications. In addition to the ISCI Data Sets, outcome measures of pain quality and patient impact associated with pain, as recommended by IMMPACT, should also be considered for study outcomes. Implementing these measures in future studies will help improve understanding and maximize research efforts.

5. Limitations

This review was limited by the included studies. Conclusions were significantly limited by the quality of studies and inherent biases. Pre-post studies were typically not blinded and so were at risk of detection bias. Furthermore, the limited number of studies published addressing the topic is concerning for reporting bias. All studies measured pain intensity, but other important outcomes including pain quality, functioning, and psychosocial response were inconsistently reported. Sample populations between studies were typically heterogeneous in age, time since injury, SCI etiology, level of injury, and AIS classification, which may limit the genealizability of findings. Alternatively, these factors could be considered in a multivariate analysis.

6. Conclusions

VR therapies are an attractive alternative for treating SCI-associated neuropathic pain, with potential for clinically significant analgesic effects. Further research is warranted to verify these benefits and the need to combine VR with other therapies such as tDCS.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

We thank the Loma Linda University Health Department of Physical Medicine and Rehabilitation.

References

[1] Dijkers M, Bryce T, Zanca J. Prevalence of chronic pain after traumatic spinal cord injury: a systematic review. J Rehabil Res Dev 2009;46:13–29.
[2] Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 2003;103:249–57.
[3] Siddall PJ, Taylor DA, McClelland JM, Rutkowski SB, Cousins MJ. Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. Pain 1999;81:187–97.
[4] Siddall P, Loeser J. Pain following spinal cord injury. Spinal Cord 2001;39:63–73. http://dx.doi.org/10.1038/sj.sc.3101116.
[5] van Leeuwen CMC, Post MWM, van Asbeck FWA, Bongers-Janssen HMH, van der Woude LHV, de Groot S, et al. Life satisfaction in people with spinal cord injury during the first five years after discharge from inpatient rehabilitation. Disabil Rehabil 2012;34:76–83. http://dx.doi.org/10.3109/09638288.2011.587089.
[6] Hoffman JM, Bombardier CH, Graves DE, Kalpakjian CZ, Krause JS. A Longitudinal Study of Depression From 1 to 5 Years After Spinal Cord Injury. Arch Phys Med Rehabil 2011;92:411–8. http://dx.doi.org/10.1016/j.apmr.2010.10.036.
[7] Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeberg T, et al. International Spinal Cord Injury Pain Classification: part I. Background and description. Spinal Cord 2012;50:413–7. http://dx.doi.org/10.1038/sc.2011.156.
[8] Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Ivan E, et al. International Spinal Cord Injury Pain (ISCIP) Classification: Part 2 Initial validation using vignettes. Spinal Cord 2012;50:404–12. http://dx.doi.org/10.1038/sc.2012.2.
[9] Biering-Sørensen F, Charlifue S, DeVivo MJ, Grinnon ST, Kleitman N, Lu Y, et al. Incorporation of the International Spinal Cord Injury Data Set elements into the National Institute of Neurological Disorders and Stroke Common Data Elements. Spinal Cord 2011;49:60–4. http://dx.doi.org/10.1038/sc.2010.90.
[10] Jensen MP, Widerström-Noga E, Richards JS, Finnerup NB, Biering-Sørensen F, Cardenas DD. Reliability and validity of the International Spinal Cord Injury Basic Pain Data Set items as self-report measures. Spinal Cord 2010;48:230–8. http://dx.doi.org/10.1038/sc.2009.112.
[11] Widerström-Noga E, Biering-Sørensen F, Bryce TN, Cardenas DD, Finnerup NB, Jensen MP, et al. The International Spinal Cord Injury Pain Basic Data Set (version 2.0). Spinal Cord 2014;52:282–6. http://dx.doi.org/10.1038/sc.2014.4.
[12] Widerström-Noga E, Biering-Sørensen F, Bryce TN, Cardenas DD, Finnerup NB, Jensen MP, et al. The International Spinal Cord Injury Pain Extended Data Set (Version 1.0). Spinal Cord 2016;54:1036–46. http://dx.doi.org/10.1038/sc.2016.51.
[13] Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain 2011;152:2204–5. http://dx.doi.org/10.1016/j.pain.2011.06.017.
[14] Budh CN, Lund I, Ertzgaard P, Holtz A, Hultling C, Levi R, et al. Pain in a Swedish spinal cord injury population. Clin Rehabil 2003;17:685–90. http://dx.doi.org/10.1191/0269215503cr664oa.
[15] Werhagen L, Budh CN, Hultling C, Molander C. Neuropathic pain after traumatic spinal cord injury – relations to gender, spinal level, completeness and age at the time of injury. Spinal Cord 2004;42:665–73. http://dx.doi.org/10.1038/sj.sc.3101641.
[16] Finnerup NB, Baastrup C. Spinal Cord Injury Pain: Mechanisms and Management. Curr Pain Headache Rep 2012;16:207–16. http://dx.doi.org/10.1007/s11916-012-0259-x.
[17] Finnerup NB. Pain in patients with spinal cord injury. Pain 2013;154:S71–6. http://dx.doi.org/10.1016/j.pain.2012.12.007.
[18] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73. http://dx.doi.org/10.1016/S1474-4422(14)70251-0.
[19] Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain 2009;132:1693–710. http://dx.doi.org/10.1093/brain/awp135.
[20] Wiederhold BK, Gao K, Sulea C, Wiederhold MD. Virtual Reality as a Distraction Technique in Chronic Pain Patients. Cyberpsychology. Behav Soc Netw 2014;17:346–52. http://dx.doi.org/10.1089/cyber.2014.0207.
[21] Jones T, Moore T, Choo J. The impact of virtual reality on chronic pain. PLoS One 2016;11:1–10. http://dx.doi.org/10.1371/journal.pone.0167523.
[22] Garrett B, Taverner T, McDade P. Virtual Reality as an Adjunct Home Therapy in Chronic Pain Management: An Exploratory Study. JMIR Med Informatics 2017;5:1–12. http://dx.doi.org/10.2196/medinform.7271.
[23] Dunn J, Yeo E, Moghaddampour P, Chau B, Humbert S. Virtual and augmented reality in the treatment of phantom limb pain: A literature review. NeuroRehabilitation 2017;40:595–601. http://dx.doi.org/10.3233/NRE-171447.
[24] Chau B, Phelan I, Dunn J, Yeo E, Hata JHS. Immersive Virtual Reality Therapy for Complex Regional Pain Syndrome: A Case Report; 93. 2017;p. 56. http://dx.doi.org/10.1097/PHM.0000000000000704.
[25] Chirico A, Lucidi F, De Laurentiis M, Milanese C, Napoli A, Giordano A. Virtual Reality in Health System: Beyond Entertainment. A Mini-Review on the Efficacy of VR During Cancer Treatment. J Cell Physiol 2016;231:275–2871. http://dx.doi.org/10.1002/jcp.25117.
[26] Löfgren M, Norrbrink C. But I know what works" – patients' experience of spinal cord injury neuropathic pain management Disabil Rehabil 2012;34:2139–47. http://dx.doi.org/10.3109/09638288.2012. 46 6761.
[27] Eng J, Teasell R, Miller W, Wolfe D, Townson A, Aubut J-A, et al. Spinal Cord Injury Rehabilitation Evidence: Method of the SCIRE Systematic Review. Top Spinal Cord Inj Rehabil 2007;13:1–10. http://dx.doi.org/10.1310/sci-1 1301.

[28] Moseley AM, Herbert RD, Sherrington C, Maher CG. Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). Aust J Physiother 2002;48:43–9.
[29] Downs S, Black N. The feasibility of creating a checklist for the assessment of the methodological quality of health care interventions. J Epidemiol Community Heal 1998;52:377–84.
[30] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:1–6. http://dx.doi.org/10.1371/journal.pmed.1000097.
[31] Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain 2010;133:2565–77. http://dx.doi.org/10./brain/awq184 1093.
[32] Özkul Ç, Kılınç M, Yıldırım SA, Topçuoğlu EY, Akyüz M. Effects of visual illusion and transcutaneous electrical nerve stimulation on neuropathic pain in patients with spinal cord injury: A randomised controlled cross-over trial. J Back Musculoskelet Rehabil 2015;28:709–19. http://dx.doi.org/10.3233/BMR-731405.
[33] Moseley GL. Using visual illusion to reduce at-level neuropathic pain in paraplegia. Pain 2007;130:294–8. http://dx.doi.org/10.1016/j.pain.01.007 2007.
[34] Pozeg P, Palluel E, Ronchi R, Solcà M, Al-Khodairy A-WW, Jordan X, et al. Virtual reality improves embodiment and neuropathic pain caused by spinal cord injury. Neurology 2017;89:1894–903. http://dx.doi.org/10.1212/WNL.0000000000004585.
[35] Jordan M, Richardson EJ. Effects of Virtual Walking Treatment on Spinal Cord Injury-Related Neuropathic Pain: Pilot Results and Trends Related to Location of Pain and at-level Neuronal Hypersensitivity. Am J Phys Med Rehabil 2016;95:390–6. http://dx.doi.org/10.1097/PHM.0000000000000417.
[36] Villiger M, Bohli D, Kiper D, Pyk P, Spillmann J, Meilick B, et al. Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. Neurorehabil Neural Repair 2013;27:675–83. http://dx.doi.org/10.1177/1545968313490999.
[37] Kumru H, Soler D, Vidal J, Navarro X, Tormos JM, Pascual-Leone A, et al. The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: An evoked potentials and quantitative thermal testing study. Eur J Pain (United Kingdom) 2013;17:55–66. http://dx.doi.org/10.1002/j.1532-2149.2012.7.x0016.
[38] Roosink M, Robitaille N, Jackson PL, Bouyer LJ, Mercier C. Interactive virtual feedback improves gait motor imagery after spinal cord injury: An exploratory study. Restor Neurol Neurosci 2016;34:227–35. http://dx.doi.org/10.3233/RNN-631505.
[39] Oneal BJ, Patterson DR, Soltani M, Teeley A, Jensen MP. Virtual reality hypnosis in the treatment of chronic neuropathic pain: a case report. Int J Clin Exp Hypn 2008;56:451–62. http://dx.doi.org/10.1080/00207140802255534.
[40] Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.
[41] Katz J, Melzack R. Measurement of pain. Surg Clin North Am 1999;79:231–52.
[42] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.
[43] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108:248–57. http://dx.doi.org/10.1016/j.pain.2003.12.024.
[44] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.
[45] Bryce TN, Budh CN, Cardenas DD, Dijkers M, Felix ER, Finnerup NB, et al. Pain After Spinal Cord Injury: An Evidence-based Review for Clinical Practice and Research. J Spinal Cord Med 2007;30:421–40. http://dx.doi.org/10.1080/10790268.2007.11753405.
[46] Krevelen DWF, van Poelman R. A Survey of Augmented Reality Technologies Applications and Limittions. Int J Virtual Real 2010;9:1–20. http://dx.doi.org/10.1155/2011/721827.
[47] Chan BL, Witt R, Charrow AP, Magee A, Howard R, Pasquina PF, et al. Mirror therapy for phantom limb pain. N Engl J Med 2007. http://dx.doi.org/10.1056/NEJMc071927.
[48] Darnall BD, Li H. Home-based self-delivered mirror therapy for phantom pain: a pilot study. J Rehabil Med 2012;44:254–60. http://dx.doi.org/10.2340/16501977-0933.
[49] Marino RJ, Burns S, Graves DE, Leiby BE, Kirshblum S, Lammertse DP. Upper- and lower-extremity motor recovery after traumatic cervical spinal cord injury: an update from the national spinal cord injury database. Arch Phys Med Rehabil 2011;92:369–75. http://dx.doi.org/10.1016/j.apmr.2010.09.027.
[50] Bryce TN. Spinal Cord Injury Braddom's Phys. Med. Rehabil, 5th ed., Philadelphia: Elsevier; 2016. p. 1095–136.
[51] Consortium for Spinal Cord Medicine. Outcomes following traumatic spinal cord injury: clinical practice guidelines for health-care professionals. J Spinal Cord Med 2000;23:289–316.
[52] Modirian E, Pirouzi P, Soroush M, Karbalaei-Esmaeili S, Shojaei H, Zamani H. Chronic Pain after Spinal Cord Injury: Results of a Long-Term Study. Pain Med 2010;11:1037–43. http://dx.doi.org/10.1111/j.1526-4637.2010.00865.x.
[53] Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. Brain 2003;126:57–70. http://dx.doi.org/10.1093/brain/awg007.
[54] Finnerup NB, Sorensen L, Bieringsorensen F, Johanesen I, Jensen T. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. Exp Neurol 2007;207:139–49. http://dx.doi.org/10.1016/j.expneurol.2007.06.001.
[55] Sakamoto M, Muraoka T, Mizuguchi N, Kanosue K. Combining observation and imagery of an action enhances human corticospinal excitability. Neurosci Res 2009;65:23–7. http://dx.doi.org/10.1016/j.neures.2009.05.003.
[56] Kumru H, Soto O, Casanova J, Valls-Sole J. Motor cortex excitability changes during imagery of simple reaction time. Exp Brain Res 2008;189:373–8. http://dx.doi.org/10.1007/s00221-008-1433-6.
[57] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57:1899–901.
[58] Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. Suppl Clin Neurophysiol 2003;56:255–76.
[59] Tashjian VC, Mosadeghi S, Howard AR, Lopez M, Dupuy T, Reid M, et al. Virtual Reality for Management of Pain in Hospitalized Patients: Results of a Controlled Trial. JMIR Ment Heal 2017;4:e9. http://dx.doi.org/10.2196/mental.7387.
[60] Gutierrez-Maldonado J, Gutierrez-Martinez O, Cabas-Hoyos K. Interactive and passive virtual reality distraction: effects on presence and pain intensity. Stud Health Technol Inform 2011;167:69–73.
[61] Lenggenhager B, Pazzaglia M, Scivoletto G, Molinari M, Aglioti SM. The Sense of the Body in Individuals with Spinal Cord Injury. PLoS One 2012;7:e50757. http://dx.doi.org/10.1371/journal.pone.0050757.
[62] Hänsel A, Lenggenhager B, von Känel R, Curatolo M, Blanke O. Seeing and identifying with a virtual body decreases pain perception. Eur J Pain 2011;15:874–9. http://dx.doi.org/10.1016/j.ejpain.2011.03.013.
[63] Lenggenhager B, Tadi T, Metzinger T, Blanke O. Video ergo sum: manipulating bodily self-consciousness. Science 2007;317:1096–9. http://dx.doi.org/10.1126/science.1143439.
[64] Patterson DR, Jensen MP. Hypnosis and clinical pain. Psychol Bull 2003;129:495–521.
[65] Patterson DR, Wiechman SA, Jensen M, Sharar SR. Hypnosis delivered through immersive virtual reality for burn pain: A clinical case series. Int J Clin Exp Hypn 2006;54:130–42. http://dx.doi.org/10.1080/00207140500528182.
[66] Flor H. Maladaptive plasticity, memory for pain and phantom limb pain: Review and suggestions for new therapies. Expert Rev Neurother 2008;8:809–18. http://dx.doi.org/10.1586/14737175.8.5.809.
[67] Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, et al. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain 2009;141:52–9. http://dx.doi.org/10.1016/j.pain.2008.10.007.
[68] Foell J, Bekrater-Bodmann R, Diers M, Flor H. Mirror therapy for phantom limb pain: Brain changes and the role of body representation. Eur J Pain (United Kingdom) 2014;18:729–39. http://dx.doi.org/10.1002/j.1532-2149.2013.00433.x.
[69] Eick J, Richardson EJ. Cortical activation during visual illusory walking in persons with spinal cord injury: a pilot study. Arch Phys Med Rehabil 2015;96:750–3. http://dx.doi.org/10.1016/j.apmr.2014.10.020.
[70] di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: a neurophysiological study. Exp Brain Res 1992;91:176–80. http://dx.doi.org/10.1007/BF00230027.
[71] Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125:310–9. http://dx.doi.org/10.1093/brain/awf022.
[72] Hoffman HG, Richards TL, Bills AR, Van Oostrom T, Magula J, Seibel EJ, et al. Using fMRI to study the neural correlates of virtual reality analgesia. CNS Spectr 2006;11:45–51. http://dx.doi.org/10.1017/S1092852900024202.
[73] Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, et al. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain - An fMRI analysis. Pain 2004;109:399–408. http://dx.doi.org/10.1016/j.pain.2004.02.033.
[74] Neugebauer V, Li W, Bird GC, Han JS. The amygdala and persistent pain. Neuroscientist 2004;10:221–34. http://dx.doi.org/10.1177/1073858403261077.
[75] Shahrbanian S, Ma X, Aghaei N, Korner-bitensky N, Simmonds MJ. Use of virtual reality (immersive vs. non immersive) for pain management in children and adults: A systematic review of evidence from randomized controlled trials. Eur J Exp Biol 2012;2:1408–22.
[76] Hanley MA, Jensen MP, Ehde DM, Robinson LR, Cardenas DD, Turner JA, et al. Clinically Significant Change in Pain Intensity Ratings in Persons With Spinal Cord Injury or Amputation. Clin J Pain 2006;22:25–31. http://dx.doi.org/10.1097/01.ajp.0000148628.69627.82.
[77] Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4:407–14. http://dx.doi.org/10.1016/S1526-5900(03)00716-8.
[78] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19. http://dx.doi.org/10.1016/j.pain.2004.09.012.
[79] Saulino M. Spinal Cord Injury Pain. Phys Med Rehabil Clin N Am 2014;25:397–410. http://dx.doi.org/10.1016/j.pmr.2014.01.002.