Chapter 14
Virtual Reality Environments in Pain Management

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ABSTRACT

Pain is a distressing and subjective feeling that occurs in different intensities and may result from the stimulation of a nerve due to injury, illness, or emotional disturbance. This chapter aims to understand how VR can contribute to pain management. To this end, the authors will address topics such as: pain – types of pain and its consequences in everyday life, as well as ways to relieve it; virtual reality – what it consists of, its functionalities and components, as well as its application to health and well-being, its advantages and limitations; and virtual reality in pain management. It is intended to emphasize the importance of pain management for the daily lives of individuals and the consequent improvement in the quality of life of those who benefit from this type of intervention.

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INTRODUCTION

It is undeniable that, throughout life, we all experience some pain. Characterized as a sensory or emotional experience, pain is a distressing and subjective feeling that occurs in different intensities and may result from the stimulation of a nerve due to injury, illness, or emotional disturbance (Riva et al., 2011; Tait et al., 2009). More specifically, the International Association for the Study of Pain determines that this unpleasant experience is "associated with, or resembling that associated with, actual or potential tissue damage". It is a personal experience influenced by several unique and individual factors, which can translate into negative consequences, not only at the physical level, compromising the individual's functionality, but also the social and mental well-being (Merskey, 1994).

This reaction to harmful stimuli is regulated by non-nociceptive blocked mechanisms located in the spinal cord, as explained by the "gate control theory", allowing the increase or attenuation of perceived pain. It may also be due to distracting stimuli, which helps a harmful reduction of nociceptive neuronal signaling, attenuating perceived pain (Melzack & Wall, 1965; Triberti et al., 2014). In 2006, Luna considered that, as well as cardiorespiratory and thermal functions, pain should be considered a fifth vital sign, which informs the person about the danger to their physical integrity. That is why it is so important to know how to distinguish physiological from pathological pain. While the first assumes protective and adaptive functions, namely inflammatory and nociceptive pain, the second does not (Luna, 2006; Sneddon, 2017).

Nociception is the process that describes pain processing and responses that pose a threat to the normal state of nervous tissue. In general, pain is classified in two different kinds: acute pain, being transitive, manifests itself in a short period, usually resulting from easily identifiable causes; and chronic pain, a constant or intermittent painful feeling, that extends over time (Riva et al., 2011; Tait et al., 2009).

Even so, pain may differ according to its pathophysiology: nociceptive pain - caused by damage to the body, serving a purpose (protection, for example); neuropathic pain - presupposes a direct consequence of an injury or disease of the somatosensory system but which can be felt in areas far from the injured one; and nociplastic pain - emerges from a nociceptive change, even if there is no evidence or threat of tissue or somatosensory system damage (Jensen et al., 2011; Jensen & Gebhart, 2008; Kosek et al., 2016).

As a typical sign of acute pain, physiological pain responds to stop exposure to the harmful stimulus to preserve tissue homeostasis. For this to happen, it is necessary to intervene with the free nerve endings of first-order neurons, called nociceptors. The harmful external stimulus is transmitted to the Central Nervous System through processes of transduction, transmission, modulation, and perception of the neural signals generated as a response (Pace et al., 2018; Sneddon, 2017).

In a simplified way, this process consists of a chain where the first-order neuron originates from the periphery and protrudes into the spinal cord; the second-order neuron ascends through it, and the third-order neuron protrudes into the cerebral cortex. Projection neurons carry nociceptive information through five main ascending pathways that innervate the thalamus, midbrain, limbic system, and reticular formation, which in turn are responsible for the location of pain, its intensity, and its effective and cognitive aspects (Klaumann et al., 2008; Lamont et al., 2000). The periaqueductal gray of the midbrain is considered the most crucial anatomical region to the endogenous analgesia system, comprising the pathways that originate in the brain stem and spinal cord that end. The inhibition of the nociceptive neurons presents here is made by excitatory connections with serotonergic and noradrenergic neurons which lead to the dorsal horn of the spinal cord which results from the inhibitory neurons of the blades connections I, II, and V (Klaumann et al., 2008; Lamont et al., 2000).

As for nociceptive pain, the potential damage of the tissue is recognized by the sensory endings of the nerves mentioned above – nociceptors. It is called “potential damage” since damage to the nervous tissue may not occur if the exposure time to the harmful stimulus is short, resulting in temporary pain and indicative of danger, as an alert system – acute pain. When there is nociceptive signaling/excitation, the event is experienced as painful, depending on factors such as the context and the priority that the brain gives to the stimulus. Examples of this kind of pain are episodes when we place our hand on a hot surface or sprain an ankle (Moseley & Flor, 2012).

On the other hand, when nervous tissue damage occurs, the body triggers an inflammatory response – (nociceptive) inflammatory pain. This response, which involves chemicals from the blood, the immune system and released by specialized nerve fibers, will allow tissue regeneration. It is possible to verify that tissue healing occurs when edema, redness, and hypersensitivity to touch and movement appear. In these situations, acetaminophen or anti-inflammatory non-steroidal recurs to control the pain and thus allow the person to remain active, returning more quickly to their daily tasks.(Moseley & Flor, 2012; Schug & Goddard, 2014). This kind of pain is characteristic of the neck or nonspecific lower back injuries, bone fractures, or pulled muscles.

Concerning inflammatory pain, cases of hypersensitivity are recurring, resulting from severe changes in the function of the nervous system. In these cases, it is important to understand the adaptive mechanisms of the neuroplasticity nervous system, responsible for adaptations and neurochemicals in cells. These neuroplastic processes occur both in the nociceptive pathways, as in the spinal cord and the brain, and are related to memory storage and consolidation, resulting in cortical remapping (Pace et al., 2018).

When damage to the somatosensory nervous system occurs, we are faced with neuropathic pain, where can ocuur hyperalgesia - overreaction to painful stimuli; paraesthesia - pins and needles, tingling, pricking or a feeling as if ants are crawling over/under the skin; mechanical allodynia - extremely sensitive to touch; and spontaneous pain. The neurobiology of pain is extremely complex and the etiology and pathogenesis of this type of damage are very different, with several patterns of sensory symptomatology being verified (Baron et al., 2017; Finnerup et al., 2016; Maier et al., 2010).

Numerous parallel and interdependent pathophysiological processes in the periphery, spinal cord, and higher centers contribute to neuropathic pain. This is distinguished from chronic pain by pathophysiological changes, as it is marked by changes in normal sensory signaling, triggered over weeks or months, at the level of the periphery, spinal cord, as well as the thalamus and cortex. When inflammatory mediators are released, primary afferent neurons increase their excitability, which leads to the appearance of stimulus-independent ectopic activity (Alvarado et al., 2013; Costigan et al., 2009; Luo et al., 2014; Tajerian et al., 2013). It is also relevant to mention that an axonal injury of this nature can cause changes in the sensory mapping of the spinal cord, and these neuropathic pain disorders can be related to changes in the excitability of the injured neuron (Devor & Wall, 1978).

With these changes in synaptic transmission, excitatory processes are intensified, and, in contrast, inhibitory ones are attenuated. Even so, the intrinsic properties of dorsal horn neurons are little altered, which corroborates the hypothesis that central sensitization is conducted and maintained by continuous ectopic activity in peripheral nerves (Balasubramanyan et al., 2006; Daou et al., 2016; Sexton et al., 2018; West et al., 2015).

In this sense, the complexity of the physiological basis of neuropathic pain greatly complicates the search for effective therapeutic targets due to the various consequences of the use of gabapentinoids - drug class derived from inhibitory neurotransmitters - for synaptic transmission, the selective actions of neurons, and the excitability of the network, both at the spinal level and from the higher brain centers (Bannister et al., 2017; Biggs et al., 2014; Offord & Isom, 2016).

Beyond these, there are other ways to classify pain, knowing that uncontrolled pain can be translated into severe physical, mental, and social complications depending on the intensity, duration, and location. In addition to impairing functional capacity, studies have shown that pain can decrease satisfaction with basic needs, affect mood and promote aggressivity (Z. Chen et al., 2008; Riva et al., 2011; Tait et al., 2009). Believing that pain can totally change the way someone performs daily tasks and, in extreme cases, can even challenge the will to live, Cicely Saunders developed the concept of "Total Pain", which states that pain cannot be separated from personality or environment (Samoilova et al., 2010).

Although the pain has a protective function and promotes healing, causing sensitivity to movement or any stimulus that has the potential to delay recovery, it is not always linked to tissue damage or fulfills this protective function (Auret & Schug, 2005; Finnerup, 2019). Nowadays, there are some interventions to alleviate and/or manage pain, depending on its nature. Pharmacological options, as long as they are well managed, can be an effective and safe response, being generally economical and, in some cases, accessible without a prescription. These opioids interrupt the C-fiber pathway, which transmits nociceptive signals to the Central Nervous System (Auret & Schug, 2005; Finnerup, 2019).

However, drug treatment of pain has some limitations due to adverse effects and a high probability of toxicity and because it represents an increased risk to cases that present comorbidities, such as deficits in balance or cognitive function. It is also essential to consider additive effects, with half of the overdose numbers resulting from prescribed narcotics and the abuse of these substances already exceeds traffic-related injuries as a cause of death in the USA (Auret & Schug, 2005; McLean & Le Couteur, 2004).

Thus, to minimize the side effects caused by prescribed narcotics, the development of non-pharmacological interventions has been a target of significant investment (Chiamulera, 2019; Riva et al., 2011). There is cognitive-behavioral therapy, hypnosis, and Virtual Reality (VR), affecting pain perception via attention, concentration, and emotional alteration (Chiamulera, 2019).

Although there is no evidence to support these complementary therapies, meditation, yoga, acupuncture, music therapy, chiropractic, guided imagination, and biofeedback are also recommended (L. Chen & Michalsen, 2017; Taylor et al., 2019). Furthermore, Transcutaneous Electrical Nerve Stimulation (TENS) is recommended due to the involvement of endogenous systems for controlling pain and brain plasticity and cognitive-behavioral therapies, relaxation, and psychotherapy, commonly called mind-body techniques (Coutaux, 2017). When pain represents an obstacle to functionality and where the underlying cause can be treated safely, and with clinical benefit, surgical intervention is also indicated (Cruccu et al., 2016).

Knowing that, in addition to medical treatments, psychotherapy is an essential aspect in pain control, about the understanding and management of thoughts and emotions, five theory-based functionalities were outlined: pain-related education, self-monitoring, goal setting, peer-based social support, and pain coping skills training and rehearsal (Alexander & Joshi, 2016; J. Stinson et al., 2013; J. N. Stinson et al., 2014). Even so, the integration of multimodal approaches has had some barriers, such as poor accessibility for geographic reasons, high costs, and, mainly, lack of availability of qualified professionals, not allowing an adequate acquisition of knowledge and training of skills to deal with and, consequently, promote self-care (J. N. Stinson et al., 2013).

Studies and research on experiences in virtual environments begin to open unimaginable ways to understand brain processes, human behavior, the mind-body relationship, and how human beings interact in the environment surrounding them in a bidirectional relationship (Chiamulera, 2019).

BACKGROUND

1. Gamification

Star rating systems to classify products and progress bars to motivate users to complete profiles or actions are examples of motivation strategies using game features in non-game contexts. These strategies are called gamification, which has proven to be quite useful in repetitive and monotonous tasks, through playful and interactive experiences to promote motivation and involvement (Deterding et al., 2011).

In general, it is possible to transform any system, service, or activity in light of gamification, having already been widely used in the areas of fitness, education and learning, commerce, information retrieval, organizational involvement and health, and well-being, with evidence of that this game mechanics has a significant impact on the behavioral results of individuals when compared to the performance in mechanisms (Rapp et al., 2019).

Despite being a promising concept, few studies determine the effects of gamification on individuals, what their true scale is, and how they unfold. There is already a great effort to establish accurate, efficient, and based research questions based on current theorizing, namely regarding the psychological processes underlying the interaction with gamified systems and the impact of specific elements (Landers et al., 2019; van Roy & Zaman, 2019).

Depending on the authors, it is based on theories such as Social Interdependence Theory (Johnson, 2003), Goal-Setting Theory (Locke & Latham, 1990), and Systematic Multiple Level Observation of Groups (SYMLOG) (Berdun et al., 2019) that the use of gamification for different purposes has been studied. Some authors also suggest studies based on Determination Theory (Deci & Ryan, 1985) to deepen the theoretical and empirical explanation of the psychological processes that explain the results observed to date, as well as the effects of gamification and how it works at the level psychological and functional (van Roy et al., 2019).

The findings in the studies of gamification and, consequently, the improvement of techniques and methods that allow its use will enabling the development of applications that make use of this technique and that allow integrating more elements of the game besides points, emblems, and tables of classification (Rapp et al., 2019).

2. Virtual Reality

VR consists of a virtual and technological environment that promotes the interaction between people and the virtual environment, enabling the user to (re)live pleasant experiences, allowing it to be completely abstracted from the reality in which it finds itself (Freitas & Spadoni, 2019). Using advanced technological instruments, the person receives various sensory stimuli, which provoke the sensation of interaction with the virtual environment (Gonçalves et al., 2019). It is important to note that, while VR provides a virtual environment that is totally independent of the real one, Augmented Reality uses digital content to enrich the real world (Zhan et al., 2020).

To put it in context, in the early 1930s, Edward Link invented the *Link Trainer*, which consisted of a commercial flight simulator. It was a device that was controlled by engines and used a rudder to simulate turbulence. Later, in the 1960s, appeared the first multisensory machine, named Sensorama, with stereoscopic color display, odor emitters, stereo sound system, and a motional chair, and also the Telesphere Mask, the first monitor mounted on the head (Hoffman et al., 2004; Kohut & Kreminskiy, 2018).

In the 80's, VR became a popular term with the development of Data Glove - an interactive device that facilitates tactile sensing and finemotion control; the Eye Phone, and the Audio Sphere. It was also in this decade that NASA promised the development of remotely controlled space hardware by introducing two small LCD screens and a helmet-mounted sensor. In 1995, Nintendo released the first console capable of displaying stereoscopic 3D graphics, "Virtual Boy" (Kohut & Kreminskiy, 2018).

Nowadays, we have access to panoramic views of roads, interior buildings and rural areas, thanks to Google, which in 2007 came up with Street View. Only later, in 2011, appeared the iPhone VRViewer, which consists of a device that is incorporated into the iPhone to provide a three-dimensional and immersive experience for the user. A year later, were launched the VR glasses, which are currently known and used (Kohut & Kreminskiy, 2018).

Sinse "The Oculus Rift", a headset device that allows a 90 degree field of vision, companies such as Microsoft, Samsung, Sony, HTC, and Valve have invested in the development of this technology in different areas, such as entertainment, medicine, telepresence and telerobotic systems, education and digital marketing (Kohut & Kreminskiy, 2018).

Nowadays, VR has great applicability in human beings' daily lives and can have a significant impact on health. In these experiences, the individual visualizes a scenario created on the computer and feels totally immersed in that virtual environment. Depending on the type of VR, some materials are required, such as a computer, a projector, a screen, joysticks, consoles (PlayStation, Xbox, Nintendo), smartphone, and a screen used on the head at eye level – Head-Mounted Display (HMD), covering the whole field of view. The HMD completely covers the vision in order to enhance the feeling of immersion (Kohut & Kreminskiy, 2018). In VR, it is important to know how to distinguish three main features: immersion, interaction, and engagement. While immersion is the feeling of being involved in an environment (which can be subdivided into different types), interaction is what characterizes the individual's response to the stimulus exposed by VR and, finally, engagement is the degree of involvement of the stimulus (Pourmand et al., 2018; Silva et al., 2020).

On the other hand, in Augmented Reality (AR), something is added to the real scenario where the person is. Using a marker, a webcam or a smartphone (IOS or Android), it is possible to add and interact with characters and/or objects in an initially empty scenario. With a focus on the real world, it's easy to distinguish the real from the virtual. The goal is not to provide an immersive experience, but rather to enhance interaction with the real world. Some examples may be the world-famous game "Pokemon Go" and the "Beat Saber", the most played game in 2019, according to Steam's bestseller list (Stamm et al., 2020; van Roy et al., 2019).

It is unanimous that VR has numerous advantages for educational, therapeutic, social, and entertainment purposes. The fact that it is incredibly stimulating and insulating from the real world allows promoting motor, cognitive and social skills, which may be less developed in the user. The interaction of a game with a joystick can promote improvements in users with difficulties in the entire upper limb. At the cognitive level, we can talk about games in which it is possible to place the user in a painful reality and work to become something comfortable to overcome specific phobias or fears. As for the social level, video games are clear examples of promoting socialization among colleagues, and it is on these same platforms that new friendships are created. The fact that there is not always face-to-face contact in this type of technology, using other strategies such as video calls, makes the interaction between people more accessible (Kohut & Kreminskiy, 2018).

This is a technology that also has some less favorable aspects, highlighting that it is still expensive and the software is complex. The hardware and all the materials necessary for its correct use still have a high price, making it challenging to use on larger scales (Kohut & Kreminskiy, 2018).

3. Virtual Reality in Health and Well-Being

Virtual Reality, as an immersive environment, has offered new opportunities for serious games in therapeutic exercises, already having a great impact on the training of activities and/or tasks that require the development of specialized technical skills, being considered as a teaching resource, especially for the health field (Barilli et al., 2011).

The existing literature describes some limitations to the use of Virtual Reality in healthcare, including secondary effects (such as nausea, disorientation and balance disorders), as well as the person's own limitations and/or cognitive deficits, which can be an obstacle to the intervention . In addition, usability issues, the high cost and time for preparation and/or resolution of possible problems are also mentioned (Dores et al., 2013; Kiryu & So, 2007; Lewis & Griffin, 1997; Park et al., 2019).

Even so, the advantages of this technology are highlighted, since it can be used in several domains (cognitive functions, neurological diseases, physical disabilities and behavioral disorders). Its immersive, interactive and realistic features allow you to work in any context, with total control of the environment and minimal supervision, constituting a safe therapeutic environment. This way, the rehabilitation can be more personalized, resorting to goal-oriented tasks, adjusting the repetitions and intensities of the exercises as necessary (Dores et al., 2013; Lewis & Griffin, 1997).

a) VR Applied to Medicine and Education

The quick results in the biomedical field and the constant evolution of technologies associated with the clinical procedures have facilitated the continuous updating on health professionals, aggravating the need for investment in virtual forms of training to facilitate access. Nowadays, VR programs can simulate clinical cases in different specialties, reducing the need for real contacts between the doctor and patients in the early stages of medical learning (Tang et al., 2020). The study of anatomy in virtual modules makes it possible to provide color images and more realistic behaviors than the atlas in paper format and reduces the adverse psychological effects generated by contact with real cadavers, further reducing the need for their use. However, the risk of medical errors involved in this practice is quite significant, leading to health problems for patients, ethical and legal issues for health professionals (Tang et al., 2020).

VR applied to surgery has also been developed, covering various situations that range from planning, procedure, and training of techniques to perform these. These programs result from virtual simulations of specific operations so that surgeons can train specific techniques and enhance total success in future surgeries. The first surgical simulator was developed in Brazil to collect bone marrow. In the simulation area, prostate cancer diagnosis and post-cancer breast reconstruction were among the first programs to be developed (Tang et al., 2020; Vaughan et al., 2016).

b) VR Applied to Neurology

In brain disorders or damage, strategies have been explored to support the treatment of different motor and cognitive sequelae using this technology. In general, virtual environments enable various associations not possible with other human-machine interfaces due to the multisensory and spatial qualities of these environments, contributing to the enrichment of applications in the rehabilitation area (Mrakic-Sposta et al., 2018; Serino et al., 2017).

To recover the affected skills or optimize possible effects, it is necessary to create specific therapeutic strategies for each type of deficiency or pathology detected. An example of this is the case of individuals who suffered a stroke, who usually have motor complications that are easily visible and often accompanied by pain but can also impair cognitive functions (Mrakic-Sposta et al., 2018; Serino et al., 2017). To this end, telerehabilitation has been well developed, allowing the therapist to conduct interactive sessions for the treatment of people with motor sequels and attention and perception deficits, developing exercises in a 3D virtual environment to stimulate and enhance the performance of activities of daily living, without having to leave home. These patients have collaborated with enthusiasm in the intervention, ending up significantly optimizing the results and, consequently, promoting their rehabilitation (Goo et al., 2020; Nunes et al., 2007).

Also, it was revealed that VR is a method to follow in monitoring spinal cord injury. Studies report improvements at the physical level mobility (movement of the upper and lower limbs), balance, endurance, and development of muscle strength. However, once again, the most significant difference between the use of traditional therapies and virtual reality therapies is the motivation felt by the patients, which allows the therapy session to be accepted in a more positive way, which consequently affects the results favorably (Abou et al., 2020; Correia et al., 2018).

In the matter of Multiple Sclerosis (MS), numerous studies prove that this can be a form of therapy complementary to physical therapy. This is a chronic disease of the central nervous system of an inflammatory and demyelinating nature. Consequently, it is possible to observe multiple symptoms, including visual disturbances, emotional instability, balance deficits, moderate/severe fatigue, weakness, and, in advanced stages, all these symptoms accompanied by pain. Through games that approach the real world, VR provides these patients with proprioceptive stimuli and external visual feedbacks, which will simplify the relearning of motor strategies and guidance for low, medium, and high-intensity tasks. This contributes to increasing patients' motivation through experiencing different stimuli, increasing the likelihood that they will achieve improvements, essentially in terms of attention. Thus, a better ability to concentrate on the activity leads to the evolution of performance in the remaining motor and cognitive parameters due to the possible excitation of cerebral neurotransmission. Currently, three VR devices (PlayStation Move, Xbox 360 Kinect, and Nintendo Wii) allow adapting challenges to rehabilitation, although they were not developed for this purpose (Abou et al., 2020; Durão, 2019).

Studies in neurological pathologies, such as Parkinson's disease, attest, in the overwhelming majority, to the remarkable effectiveness of this approach in the face of deficits in balance and fatigue. Usually, these individuals stroll with small, dragged steps, with reduced arm balance and flexed posture. These behaviors and characteristics can cause a reduction in gait speed, a decrease in stride length, and an increase in cadence. In more advanced cases, they have a frozen gait, in which, despite the patient's attempt to walk, the progression of the feet forward is significantly reduced, increasing the risk of falls, which consequently leads to pain (da Cruz Souza et al., 2020; Gandolfi et al., 2017).

As previously mentioned, the Nintendo Wii and Playstation have been widely used to treat these pathologies. In addition to having a relatively low cost, technologies and rehabilitation programs through Virtual Reality are capable of facilitating the performance of high-volume exercises and improving postural control, mobility, gait performance, and balance in people with Parkinson's Disease. Commercial video games, although not explicitly developed for individuals with neurological disorders, are capable of stimulating multidirectional displacements, weight transfers, a high number of repetitions, planning, and decision making, in addition to the sustained concentration that is necessary, promoting motivation and commitment to the tasks performed. VR in these video games also has a very positive role in terms of motivation and adherence of the participants since many games replicate real-life scenarios and are appealing. It becomes a personalized and motivating way that brings fun and pleasure to the recovery process (da Cruz Souza et al., 2020; Gandolfi et al., 2017).

It is also possible to apply this technology in intervention with people with dementia, namely in reminiscence therapy, cognitive stimulation activities, ADL training and relaxation. It is also possible to apply this technology in intervention with people with dementia, namely in reminiscence therapy, cognitive stimulation activities, ADL training and relaxation. Although it was not possible to find evidence to support the use of VR in reminiscence therapy, non-pharmacological interventions represent a decrease in disorientation and depressive symptoms, an increase in the sense of well-being and improvements in executive functions (Caiana et al., 2016; O'Philbin et al., 2018).

c) VR Applied to Mental Health

This technology has also been widely used in the treatment of phobias, exposing the individual to stimuli related to the phobic object. This exhibition is characterized as an intermediate procedure between exposure by imagination and exposure *in vivo*, and must be graduated (Cunha & Leitão, 2003; Haydu et al., 2016). This approach has been well received as it is a safe environment where existing trigger stimuli are easier to control than in the real world. The therapist can regulate the intensity and frequency of the stimulus presented and also present it in different contexts (Netto, 2006). The individual interacts with the virtual environment through an interface that best suits their needs: glasses or helmet with visors; joypads, mouse or real control simulators. In this approach, without ever losing contact with the therapist, it is very important that the person feels immersed and involved in the created environment, so that they experience emotional responses as close as possible to in vivo exposure (Haydu et al., 2016; Netto, 2006).

Another very promising area is virtual exposure therapies for post traumatic stress disorders. Similar to the others already mentioned, using VR it is possible to verify that the person is more motivated to actively participate in the rehabilitation process. Furthermore, with this resource it is no longer necessary to use imagination to provoke emotional responses related to trauma, being in a safe environment (Rigoli & Kristensen, 2014).

d) VR Applied to Developmental Disorders

On the subject of Down Syndrome, these individuals have several perceptual-motor and sensory integration dysfunctions that are reflected in an atypical development in psychomotor and learning aspects. These neurological characteristics of the syndrome make it necessary for health professionals to work in ways that promote psychomotor skills since they are a prerequisite for developing higher cognitive skills. For this reason, many therapists turn to Virtual Reality (VR) to carry out activities aimed at the motor and cognitive skills, with possibilities for adjustments in the distribution of the steps of the actions relevant to the required performance times and functional capacities, constituting itself as an activity means and end of the intervention.

Sedentary behavior and low levels of physical activity are indicated as risk factors for health in the population with Down Syndrome. Researches also report that the sedentary lifestyle presented by most people with DS results from the motor limitations presented by many of them to perform numerous activities, especially when it comes to children. Therefore, VR enters this pathology as a motivating and playful intervention program, turning out to be attractive and promoting new active behavioral patterns.

MAIN FOCUS OF THE CHAPTER

Within the scope of health care, it is often necessary to resort to painful procedures, either for prevention, diagnosis, or treatment purposes. This threatening physical and psychological well-being situation affects all age groups, with a particular focus on children and adolescents (Wiederhold, 2006). With the growth of immersive and complex technologies, the aim is to obtain sensations or inhibit feelings through the modulation of afferent and efferent pathways to the human brain. In this sense, VR has been used as a mechanism capable of providing different sensations in adverse situations (Fernandes, 2019).

Similar to the rehabilitation of people with anxiety, psychosis, Parkinson's Disease, neurological syndromes, phobia, among others, VR has also been used to reduce pain in various age groups and different types of individualized pain, such as in burn and post-surgical patients (Pourmand et al., 2018; Silva et al., 2020). In the most recent years, the use of VR as a non-pharmacological therapy for pain management has been progressively gaining more adherence due to the decrease in analgesics and the possibility of being used at home with relatively reduced costs. There are several theories about the effects that VR has on pain relief. Some of them claim that this promotes distraction from the painful experience. Others suggest that VR affects how pain is processed in the Central Nervous System (Ahmadpour et al., 2019; Chiamulera, 2019).

The VR offers multisensory experiences in a virtual environment that can influence emotional processing in the brain and, consequently, pain. When presenting emotional stimuli, for example, through video images that transmit positive emotions to the patient, this approach can influence the perception of pain, involving downward modulating pathways, reducing it. Contrary to what was expected, the medical community has pleasantly accepted the use of VR as a therapeutic technology. Although there is still no consensus on the mechanisms through which VR has an impact on pain, it is known that, effectively, this new resource can alleviate different types of pain (Ahmadpour et al., 2019; Silva et al., 2020).

According to Hunter Hoffman, "using VR, we can teach chronic pain coping skills, techniques that patients can use on their own that will help decrease it. Learning changes the brain and gives patients something that keeps working when they take the device off. When they realize that their pain is not inevitable, they become more receptive to physical therapy exercises and more likely to move on their own" (Brody, 2019).

There are several theories about the action that VR has on pain relief; some claim that this feature promotes distraction from the painful experience. Others suggest that virtual reality affects the way pain is processed in the central nervous system. The literature argues that the method of distraction from the painful situation can alleviate the perception of pain. The device used allows the user to be immersed in a different environment, capable of distracting and stimulating them differently and filters out external information associated with pain or its source. In this way, its use allows inducing an analgesic sensation much superior to that felt during other types of distraction, such as games, films, or videos. Even so, it should be noted that the use of this technology does not annul or replace the analgesic treatment but serves as an adjunct to existing treatments (Chiamulera, 2019).

In recent years, several researchers have created techniques to control pain through technologies, such as VR. One of the pioneering projects with a VR approach to relieve the pain of burn patients is SnowWorld VR, developed at the University of Washington HITLab and Harborview Burn Center, Seattle, Washington. This system consists of an HMD through which patients visualize and interact with snow-themed characters and shoot virtual snowballs when approaching snowmen using a mouse or computer keyboard (Dascal, et al., 2017).

According to Scapin et al (2017), in the pediatric population, the use of VR allows shifting the focus of attention on pain during treatment, reducing the need to increase pharmacological analgesic doses. More importantly, it induces a significant drop in pain scores, where perceived pain decreased from 4 to 0 on the Visual Analog Scale (Scapin et al., 2017). Thus, the RV is known to be a high success rate technology for managing pain in burned patients, especially while performing the treatment, since it facilitates the abstraction of reality by allowing a total immersion in a virtual environment. Furthermore, it is a safe and fun technique, which can be adapted to people of different age groups, with no side effects or loss of effect from continuous use (Gonçalves et al., 2019).

VR benefits are also evident in the control of phantom pain, which is characterized as a problem that causes discomfort in amputee patients, who claim to feel pain in limbs they no longer have. In these cases, through digital applications, virtual reality helps the brain reconnect the stimulus areas, causing the patient a feeling of relaxation, making the pain lessened and even extinguished (Gromala et al., 2015).

As previously mentioned, chronic pain is considered an incurable disease due to its complexity. Perhaps, for this reason, the attentional distraction strategy allows for a decrease in pain. Still, there are no reports that it has successfully induced the hypoalgesic effect in patients with chronic pain. The lower effectiveness of this strategy is due to the selective attention to information related to the painful factor, especially when feelings of fear and pain catastrophization are (Indovina et al., 2018; Todd et al., 2018; Vlaeyen et al., 2016).

In any case, the evidence points to motivational factors as the focal point for the proper functioning of these strategies. In other words, to divert attention from pain, the distracting stimulus must be so motivating for the person that it is competitive with the painful stimulus and allows for almost complete involvement. It is in this sense that VR is promising, taking into account that, by itself, it is typically considered motivating due to its interactive characteristics (Indovina et al., 2018; Todd et al., 2018; Vlaeyen et al., 2016).

However, techniques, such as the *Virtual Meditative Walk*, are developed to help patients with this type of pain. This is an example of a VR system that incorporates biofeedback, virtual environment, and stereoscopic sound, addressing patients' specific conditions with chronic pain and low body awareness. Through stress reduction practice based on mindfulness (which has appeared as a primary approach to pain control), providing changes in the environment in real-time, patients have a mirrored view of themselves and learn to control their internal emotional states (Gromala et al., 2015).

To cope with pain, these researchers also invented *Mobius Floe*, which is characterized by being an immersed VR game developed for patients with chronic and/or acute pain, reducing their pain and anxiety. During the game, patients are immersed in a virtual winter setting and experience several moments of action. This game proves to be quite stimulating and captivating, making patients stay focused, inhibiting the focus on their physical pain (Gromala et al., 2015).

EaseVRx is a skills-based VR program that combines psychoeducation, pain education, breathing training, relaxation exercises, and executive functioning games. This is an evidence-based approach of Cognitive Behavior Therapy, mindfulness, and physiologic biofeedback therapy. It consists of a 56-

day standardized, prescriptive, and reproducible program, where each experience can last from 2 to 16 minutes. EaseVRx-Distraction is an identical program, with an identical user interface, and the same number of experiences, with the same approximate duration, but only including 360-degree videos. Both protocols were designed to be a safe, home-based, non-pharmacological intervention for chronic pain. (Birckhead et al., 2021).

Based on the assumption that pain is a subjective feeling and that it differs from individual to individual, the use of VR in medical procedures must be personalized. Anxieties, fears, thoughts, feelings, and other personal characteristics of the individual must be taken into account to select the most appropriate virtual experience to help reduce the processed and perceived pain (Ahmadpour et al., 2019; Freitas & Spadoni, 2019).

Evidence suggests that VR is not only effective in treating acute pain, but also has great potential in distraction therapy, allowing effective analgesia (Chan et al., 2018; Pourmand et al., 2018). Even thoug, the quality of the remaining studies is limited and statistically heterogeneous. There are numerous areas in which this innovative tool operates, and we will undoubtedly evolve further in this area. However, although the benefits of using VR as a therapeutic technique are notorious, it is necessary to continue to study this variable so that its results are more consistent and its benefits more concrete (Chan et al., 2018).

Some studies reveal a positive impact on the use of games, of downward movement, in immersive environments to treat chronic pain. In these studies, there is a 33% decrease in pain and a substantial difference between the use of 3D VR and 2D videos, demonstrating the patients' receptivity and the effectiveness and safety of using VR for pain control (Jones et al., 2016). However, although there are already applications designed to distract pain, specific applications for VR active exercise therapy and psychotherapeutic pain therapy cannot be found on the market, revealing a significant lack of studies in this area (Stamm et al., 2020). Existing applications have gaps in quality and quantity of content, being imperative the involvement of qualified health professionals in developing prototypes and a faithful following of the evidence (Hoffmann et al., 2020).

Another study, using functional magnetic resonance imaging, compared the use of opioids with the results obtained by using Virtual Reality, when exposed to a painful stimulus. There was a reduction of more than 50% in the activity of 5 brain areas, when the person exposed to a painful stimulus made use of Virtual Reality (Hoffman et al., 2004). Other studies carried out investigated the results of using Virtual Reality to control pain during other procedures, such as vaccination of children, physiotherapy sessions and dressings for burns. Although perceived pain was subjectively assessed through self-report questionnaires, the results of these studies were equally positive (Schmitt et al., 2011; Silverberg et al., 2017; van Twillert et al., 2007).

In 2020 a qualitative study was carried out on RV in pain therapy, and four dimensions were found to be essential to consider: the overall system, hardware, software, and gamification elements. The results of this study revealed that, with the overall system, the interviewed physiotherapists felt that it should contain an individual briefing, carried out by personal assistance, and a tutorial for correct operation. The system must also be easy to handle and incorporate exercises with a maximum duration of 30 minutes, with a break between them and 15 min of relaxation at the end, allowing the user to sit down (Stamm et al., 2020).

As for the software, it was defined that the system must perform an individual calibration to detect movement limitations and allow the therapist to intervene in patients, mainly when pain, anxiety, or incorrect execution of movements occurs. On the other hand, when it comes to hardware, it was defined that users should be able to put on the googles by themselves, and these should be easy to put on and take off (Stamm et al., 2020). Finally, regarding the gamification dimension, it was considered that the system should always give positive feedback, and never negative feedback, displaying verbal and/or visual praise and rewards, while also providing the user with behavioral recommendations, such as advice on how to relax (Stamm et al., 2020).

CONCLUSION

As already mentioned, these and other studies are insufficient. They often lack a quality theoretical basis, although it is increasingly evident that it is promising to invest in VR in pain management, as in other health-related issues. For this reason, it is urgent to invest in research and qualified health professionals to carry it out, to evolve in the area of pain therapies, and improve the quality of life of people who experience any pain (Chuan et al., 2020).

Also, it should be noted that the use of this technology does not annul the analgesic treatment but serves as an adjunct to the existing therapies. However, VR is beneficial when associated with traditional therapies, as it allows for significant reductions in pain perception, cognitive pain (time spent thinking about pain), affective pain (emotional discomfort), and sensory pain (Dascal, et al., 2017). To this end, the attentional distraction strategy is used, which, as the name implies, consists of diverting attention from the pain felt, hoping that it will lead to an effect of hypoalgesia - decreased sensitivity to painful stimuli (Van Ryckeghem et al., 2018).

REFERENCES

Abou, L., Malala, V. D., Yarnot, R., Alluri, A., & Rice, L. A. (2020). Effects of Virtual Reality Therapy on Gait and Balance Among Individuals With Spinal Cord Injury: A Systematic Review and Meta-analysis. *Neurorehabilitation and Neural Repair*, *34*(5), 375–388. doi:10.1177/1545968320913515 PMID:32270736

Ahmadpour, N., Randall, H., Choksi, H., Gao, A., Vaughan, C., & Poronnik, P. (2019). Virtual Reality interventions for acute and chronic pain management. *The International Journal of Biochemistry & Cell Biology*, *114*, 105568. doi:10.1016/j.biocel.2019.105568 PMID:31306747

Alexander, J. C., & Joshi, G. P. (2016). Smartphone applications for chronic pain management: A critical appraisal. *Journal of Pain Research*, *9*, 731–734. doi:10.2147/JPR.S119966 PMID:27713649

Alvarado, S., Tajerian, M., Millecamps, M., Suderman, M., Stone, L. S., & Szyf, M. (2013). Peripheral nerve injury is accompanied by chronic transcriptome-wide changes in the mouse prefrontal cortex. *Molecular Pain*, *9*, 1744–8069. doi:10.1186/1744-8069-9-21 PMID:23597049

Auret, K., & Schug, S. A. (2005). Underutilisation of opioids in elderly patients with chronic pain. *Drugs & Aging*, *22*(8), 641–654. doi:10.2165/00002512-200522080-00002 PMID:16060715

Balasubramanyan, S., Stemkowski, P. L., Stebbing, M. J., & Smith, P. A. (2006). Sciatic chronic constriction injury produces cell-type-specific changes in the electrophysiological properties of rat substantia gelatinosa neurons. *Journal of Neurophysiology*, *96*(2), 579–590. doi:10.1152/jn.00087.2006 PMID:16611846

Bannister, K., Qu, C., Navratilova, E., Oyarzo, J., Xie, J. Y., King, T., Dickenson, A. H., & Porreca, F. (2017). Multiple sites and actions of gabapentin-induced relief of ongoing experimental neuropathic pain. *Pain*, *158*(12), 2386–2395. doi:10.1097/j.pain.0000000000001040 PMID:28832395

Barilli, E. C. V. C., Ebecken, N. F. F., & Cunha, G. G. (2011). The technology of virtual reality resource for formation in public health in the distance: An application for the learning of anthropometric procedures. *Ciencia & Saude Coletiva*, *16*, 1247–1256. doi:10.1590/S1413-81232011000700057 PMID:21503473

Baron, R., Maier, C., Attal, N., Binder, A., Bouhassira, D., Cruccu, G., Finnerup, N. B., Haanpää, M., Hansson, P., Hüllemann, P., Jensen, T. S., Freynhagen, R., Kennedy, J. D., Magerl, W., Mainka, T., Reimer, M., Rice, A. S. C., Segerdahl, M., Serra, J., ... Treede, R.-D. (2017). Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. *Pain*, *158*(2), 261–272. doi:10.1097/j.pain.0000000000000753 PMID:27893485

Berdun, F. D., Armentano, M. G., Berdun, L. S., & Cincunegui, M. (2019). Building SYMLOG profiles with an online collaborative game. *International Journal of Human-Computer Studies*, *127*, 25–37. doi:10.1016/j.ijhcs.2018.07.002

Biggs, J. E., Boakye, P. A., Ganesan, N., Stemkowski, P. L., Lantero, A., Ballanyi, K., & Smith, P. A. (2014). Analysis of the long-term actions of gabapentin and pregabalin in dorsal root ganglia and substantia gelatinosa. *Journal of Neurophysiology*, *112*(10), 2398–2412. doi:10.1152/jn.00168.2014 PMID:25122705

Birckhead, B., Eberlein, S., Alvarez, G., Gale, R., Dupuy, T., Makaroff, K., Fuller, G., Liu, X., Yu, K.-S., Black, J. T., Ishimori, M., Venuturupalli, S., Tu, J., Norris, T., Tighiouart, M., Ross, L., McKelvey, K., Vrahas, M., Danovitch, I., & Spiegel, B. (2021). Home-based virtual reality for chronic pain: Protocol for an NIH-supported randomised-controlled trial. *BMJ Open*, *11*(6), e050545. doi:10.1136/bmjopen-2021-050545 PMID:34130965

Caiana, T. L., Nogueira, D. de L., & Dantas de Lima, A. C. (2016). Virtual reality and its use as occupational therapeutic resource: An integrative review. *Cadernos Brasileiros De Terapia Ocupacional-Brazilian Journal Of Occupational Therapy*, *24*(3), 575–589.

Chan, E., Foster, S., Sambell, R., & Leong, P. (2018). Clinical efficacy of virtual reality for acute procedural pain management: A systematic review and meta-analysis. *PLoS One*, *13*(7), e0200987. doi:10.1371/journal.pone.0200987 PMID:30052655

Chen, L., & Michalsen, A. (2017). Management of chronic pain using complementary and integrative medicine. *BMJ (Clinical Research Ed.)*, 357. doi:10.1136/bmj.j1284 PMID:28438745

Chen, Z., Williams, K. D., Fitness, J., & Newton, N. C. (2008). When hurt will not heal: Exploring the capacity to relive social and physical pain. *Psychological Science*, *19*(8), 789–795. doi:10.1111/j.1467-9280.2008.02158.x PMID:18816286

Chiamulera, C. (2019). *Réalité Virtuelle. Le esperienze virtuali tra technologie e cervello*. Atlântico Press.

Chuan, A., Zhou, J. J., Hou, R. M., Stevens, C. J., & Bogdanovych, A. (2020). Virtual reality for acute and chronic pain management in adult patients: A narrative review. *Anaesthesia*. Advance online publication. doi:10.1111/anae.15202 PMID:32720308

Correia, F., Santos, C., Quaresma, C., & Fonseca, M. (2018). *Utilização da realidade virtual na reabilitação de indivíduos com lesão da espinal medula: revisão sistemática*. Academic Press.

Costigan, M., Scholz, J., & Woolf, C. J. (2009). Neuropathic pain: A maladaptive response of the nervous system to damage. *Annual Review of Neuroscience*, *32*(1), 1–32. doi:10.1146/annurev.neuro.051508.135531 PMID:19400724

Coutaux, A. (2017). Non-pharmacological treatments for pain relief: TENS and acupuncture. *Joint, Bone, Spine*, *84*(6), 657–661. doi:10.1016/j.jbspin.2017.02.005 PMID:28219657

Cruccu, G., Garcia-Larrea, L., Hansson, P., Keindl, M., Lefaucheur, J., Paulus, W., Taylor, R., Tronnier, V., Truini, A., & Attal, N. (2016). EAN guidelines on central neurostimulation therapy in chronic pain conditions. *European Journal of Neurology*, *23*(10), 1489–1499. doi:10.1111/ene.13103 PMID:27511815

Cunha, V., & Leitão, M. (2003). *Sistema de Realidade Virtual para tratamento de Fobias. 12th Encontro Português de Computação Gráfica*. Instituto Superior de Engenharia.

da Cruz Souza, M., de Araujo Biazini, P. L., Toshimi Furuta, D., Haniuda Moliterno, A., Ribeiro Uliam, N., Fernandes de Oliveira, D., Cristina Leoci, I., Bortolim Frasson, I., de Oliveira Damasceno, S., & Nunes Gonzaga, C. (2020). A influência da realidade virtual sobre a velocidade da marcha e avaliação da satisfação de indivíduos com doença de parkinson. *Colloquium Vitae*, *12*(3), 01–09. doi:10.5747/cv.2020.v12.n3.v304

Daou, I., Beaudry, H., Ase, A. R., Wieskopf, J. S., Ribeiro-da-Silva, A., Mogil, J. S., & Séguéla, P. (2016). Optogenetic silencing of Nav1. 8-positive afferents alleviates inflammatory and neuropathic pain. *eNeuro*, *3*(1). doi:10.1523/ENEURO.0140-15.2016 PMID:27022626

Deci, E. L., & Ryan, R. M. (1985). Cognitive evaluation theory. In *Intrinsic motivation and self-determination in human behavior* (pp. 43–85). Springer. doi:10.1007/978-1-4899-2271-7_3

Deterding, S., Dixon, D., Khaled, R., & Nacke, L. (2011). From game design elements to gamefulness: defining "gamification". *Proceedings of the 15th International Academic MindTrek Conference: Envisioning Future Media Environments*, 9–15. 10.1145/2181037.2181040

Devor, M., & Wall, P. D. (1978). Reorganisation of spinal cord sensory map after peripheral nerve injury. *Nature*, *276*(5683), 75–76. doi:10.1038/276075a0 PMID:570248

Dores, A. R., Barbosa, F., Marques, A., Carvalho, I. P., De Sousa, L., & Castro-Caldas, A. (2013). Virtual reality and rehabilitation: Why or why not? A systematic literature review. *Acta Medica Portuguesa*, *25*(6), 414–421. PMID:23534593

Durão, E. A. C. (2019). *Os efeitos da realidade virtual no equilíbrio e no impacto na qualidade de vida de pacientes com esclerose múltipla: revisão bibliográfica*. Academic Press.

Finnerup, N. B. (2019). Nonnarcotic methods of pain management. *The New England Journal of Medicine*, *380*(25), 2440–2448. doi:10.1056/NEJMra1807061 PMID:31216399

Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L. H., Bouhassira, D., Cruccu, G., Freeman, R., Hansson, P., Nurmikko, T., Raja, S. N., Rice, A. S. C., Serra, J., Smith, B. H., Treede, R.-D., & Jensen, T. S. (2016). Neuropathic pain: An updated grading system for research and clinical practice. *Pain*, *157*(8), 1599–1606. doi:10.1097/j.pain.0000000000000492 PMID:27115670

Freitas, D. M. de O., & Spadoni, V. S. (2019). Is virtual reality useful for pain management in patients who undergo medical procedures? *Einstein (Sao Paulo, Brazil)*, *17*(2), eMD4837. doi:10.31744/einstein_journal/2019MD4837 PMID:31116237

Gandolfi, M., Geroin, C., Dimitrova, E., Boldrini, P., Waldner, A., Bonadiman, S., Picelli, A., Regazzo, S., Stirbu, E., Primon, D., Bosello, C., Gravina, A. R., Peron, L., Trevisan, M., Garcia, A. C., Menel, A., Bloccari, L., Valè, N., Saltuari, L., ... Smania, N. (2017). Virtual reality telerehabilitation for postural instability in Parkinson's disease: A multicenter, single-blind, randomized, controlled trial. *BioMed Research International*, *2017*, 2017. doi:10.1155/2017/7962826 PMID:29333454

Gonçalves, S., Tenente, C., Ralha, S., & Encarnação, P. (2019). *Realidade Virtual, uma opção para o controlo da dor no tratamento de queimaduras*. Academic Press.

Goo, H. W., Park, S. J., & Yoo, S.-J. (2020). Advanced medical use of three-dimensional imaging in congenital heart disease: Augmented reality, mixed reality, virtual reality, and three-dimensional printing. *Korean Journal of Radiology*, *21*(2), 133. doi:10.3348/kjr.2019.0625 PMID:31997589

Gromala, D., Tong, X., Choo, A., Karamnejad, M., & Shaw, C. (2015). *The Virtual Meditative Walk: Virtual Reality Therapy for Chronic Pain Management*. doi:10.1145/2702123.2702344

Haydu, V. B., de Paula, M. B., Zacarin, M. R. J., dos Santos, A., Borloti, E., & Fornazari, S. A. (2016). Virtual reality exposure therapy for fear and driving phobia: A literature review. *Avances en Psicología Latinoamericana*, *34*(1), 67–81.

Hoffman, H. G., Richards, T. L., Coda, B., Bills, A. R., Blough, D., Richards, A. L., & Sharar, S. R. (2004). Modulation of thermal pain-related brain activity with virtual reality: Evidence from fMRI. *Neuroreport*, *15*(8), 1245–1248. doi:10.1097/01.wnr.0000127826.73576.91 PMID:15167542

Hoffmann, A., Faust-Christmann, C. A., Zolynski, G., & Bleser, G. (2020). Toward Gamified Pain Management Apps: Mobile Application Rating Scale–Based Quality Assessment of Pain-Mentor's First Prototype Through an Expert Study. *JMIR Formative Research*, *4*(5), e13170. doi:10.2196/13170 PMID:32452803

Indovina, P., Barone, D., Gallo, L., Chirico, A., De Pietro, G., & Giordano, A. (2018). Virtual reality as a distraction intervention to relieve pain and distress during medical procedures. *The Clinical Journal of Pain*, *34*(9), 858–877. doi:10.1097/AJP.0000000000000599 PMID:29485536

Jensen, T. S., Baron, R., Haanpää, M., Kalso, E., Loeser, J. D., Rice, A. S. C., & Treede, R.-D. (2011). A new definition of neuropathic pain. *Pain*, *152*(10), 2204–2205. doi:10.1016/j.pain.2011.06.017 PMID:21764514

Jensen, T. S., & Gebhart, G. F. (2008). *New pain terminology: a work in progress*. LWW.

Johnson, D. W. (2003). Social interdependence: Interrelationships among theory, research, and practice. *The American Psychologist*, *58*(11), 934–945. doi:10.1037/0003-066X.58.11.934 PMID:14609388

Jones, T., Moore, T., & Choo, J. (2016). The impact of virtual reality on chronic pain. *PLoS One*, *11*(12), e0167523. doi:10.1371/journal.pone.0167523 PMID:27997539

Kiryu, T., & So, R. H. Y. (2007). Sensation of presence and cybersickness in applications of virtual reality for advanced rehabilitation. *Journal of Neuroengineering and Rehabilitation*, *4*(1), 1–5. doi:10.1186/1743-0003-4-34 PMID:17894857

Klaumann, P. R., Wouk, A., & Sillas, T. (2008). Pathophysiology of pain. *Archives of Veterinary Science*, *13*(1).

Kohut, I., & Kreminskiy, V. (2018). *History of virtual reality*. Тернопіль: ТНЕУ.

Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J.-A., Rice, A. S. C., Rief, W., & Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states? *Pain*, *157*(7), 1382–1386. doi:10.1097/j.pain.0000000000000507 PMID:26835783

Lamont, L. A., Tranquilli, W. J., & Grimm, K. A. (2000). Physiology of pain. *Veterinary Clinics: Small Animal Practice*, *30*(4), 703–728. PMID:10932821

Landers, R. N., Tondello, G. F., Kappen, D. L., Collmus, A. B., Mekler, E. D., & Nacke, L. E. (2019). Defining gameful experience as a psychological state caused by gameplay: Replacing the term 'Gamefulness' with three distinct constructs. *International Journal of Human-Computer Studies*, *127*, 81–94. doi:10.1016/j.ijhcs.2018.08.003

Lewis, C. H., & Griffin, M. J. (1997). Human factors consideration in clinical applications of virtual reality. *Studies in Health Technology and Informatics*, 35–58. PMID:10175342

Locke, E. A., & Latham, G. P. (1990). *A theory of goal setting & task performance*. Prentice-Hall, Inc.

Luna, S. P. L. (2006). Dor, analgesia e bem estar animal. *ANAIS-I Congresso Internacional de Conceitos Em Bem-Estar Animal*, 16–18.

Luo, C., Kuner, T., & Kuner, R. (2014). Synaptic plasticity in pathological pain. *Trends in Neurosciences*, *37*(6), 343–355. doi:10.1016/j.tins.2014.04.002 PMID:24833289

Maier, C., Baron, R., Tölle, T. R., Binder, A., Birbaumer, N., Birklein, F., Gierthmühlen, J., Flor, H., Geber, C., Huge, V., Krumova, E. K., Landwehrmeyer, G. B., Magerl, W., Maihöfner, C., Richter, H., Rolke, R., Scherens, A., Schwarz, A., Sommer, C., ... Treede, D.-R. (2010). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*, *150*(3), 439–450. doi:10.1016/j.pain.2010.05.002 PMID:20627413

McLean, A. J., & Le Couteur, D. G. (2004). Aging biology and geriatric clinical pharmacology. *Pharmacological Reviews*, *56*(2), 163–184. doi:10.1124/pr.56.2.4 PMID:15169926

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. *Science*, *150*(3699), 971–979. doi:10.1126cience.150.3699.971 PMID:5320816

Merskey, H. (1994). Part III pain terms, a current list with definitions and notes on usage. *Classification of Chronic Pain-Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*, 207–214.

Moseley, G. L., & Flor, H. (2012). Targeting cortical representations in the treatment of chronic pain: A review. *Neurorehabilitation and Neural Repair*, *26*(6), 646–652. doi:10.1177/1545968311433209 PMID:22331213

Mrakic-Sposta, S., Di Santo, S. G., Franchini, F., Arlati, S., Zangiacomi, A., Greci, L., Moretti, S., Jesuthasan, N., Marzorati, M., Rizzo, G., Sacco, M., & Vezzoli, A. (2018). Effects of combined physical and cognitive virtual reality-based training on cognitive impairment and oxidative stress in MCI patients: A pilot study. *Frontiers in Aging Neuroscience*, *10*, 282. doi:10.3389/fnagi.2018.00282 PMID:30327596

Netto, A. V. (2006). *Realidade Virtual aplicada ao tratamento de fobias. In Fundamentos e Tecnologia de Realidade Virtual e Aumentada*. SBC.

Nunes, F. L. S., Costa, R., Oliveira, A., Delfino, S. R., Pavarini, L., Rodello, I. A., Brega, J. R. F., & Sementille, A. C. (2007). Aplicações médicas usando realidade virtual e realidade aumentada. *Realidade Virtual: Conceito, Projeto e Aplicações. Cap*, *10*, 222–255.

O'Philbin, L., Woods, B., Farrell, E. M., Spector, A. E., & Orrell, M. (2018). Reminiscence therapy for dementia: An abridged Cochrane systematic review of the evidence from randomized controlled trials. *Expert Review of Neurotherapeutics*, *18*(9), 715–727. doi:10.1080/14737175.2018.1509709 PMID:30092689

Offord, J., & Isom, L. L. (2016). Drugging the undruggable: Gabapentin, pregabalin and the calcium channel α2δ subunit. *Critical Reviews in Biochemistry and Molecular Biology*, *51*(4), 246–256. doi:10.3109/10409238.2016.1173010 PMID:27112431

Pace, M. C., Passavanti, M. B., De Nardis, L., Bosco, F., Sansone, P., Pota, V., Barbarisi, M., Palagiano, A., Iannotti, F. A., Panza, E., & Aurilio, C. (2018). Nociceptor plasticity: A closer look. *Journal of Cellular Physiology*, *233*(4), 2824–2838. doi:10.1002/jcp.25993 PMID:28488779

Park, M. J., Kim, D. J., Lee, U., Na, E. J., & Jeon, H. J. (2019). A literature overview of virtual reality (VR) in treatment of psychiatric disorders: Recent advances and limitations. *Frontiers in Psychiatry*, *10*, 505. doi:10.3389/fpsyt.2019.00505 PMID:31379623

Pourmand, A., Davis, S., Marchak, A., Whiteside, T., & Sikka, N. (2018). Virtual reality as a clinical tool for pain management. *Current Pain and Headache Reports*, *22*(8), 1–6. doi:10.100711916-018-0708-2 PMID:29904806

Rapp, A., Hopfgartner, F., Hamari, J., Linehan, C., & Cena, F. (2019). *Strengthening gamification studies: Current trends and future opportunities of gamification research*. Elsevier.

Rigoli, M. M., & Kristensen, C. H. (2014). Virtual Reality Exposure for PTSD (Post-Traumatic Stress Disorder): A Systematic Review Virtual Reality PTSD Systematic Review. *Psychological Research*, *4*(1), 1.

Riva, P., Wirth, J. H., & Williams, K. D. (2011). The consequences of pain: The social and physical pain overlap on psychological responses. *European Journal of Social Psychology*, *41*(6), 681–687. doi:10.1002/ejsp.837

Samoilova, N., Ali, G., Amata, A. O., Avenant, C. C., Baker, J. N., Boni, F., Bruni, K., Cassileth, B., Davatchi, F., & Ddungu, H. (2010). *Guide to pain management in low-resource settings*. Academic Press.

Scapin, S. Q., Echevarría-Guanilo, M. E., Fuculo, P. R. B. Junior, Martins, J. C., & Barbosa, M. (2017). Use of virtual reality for treating burned children. *Revista Brasileira de Enfermagem*, *70*(6), 1291–1295. doi:10.1590/0034-7167-2016-0575 PMID:29160492

Schmitt, Y. S., Hoffman, H. G., Blough, D. K., Patterson, D. R., Jensen, M. P., Soltani, M., Carrougher, G. J., Nakamura, D., & Sharar, S. R. (2011). A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. *Burns*, *37*(1), 61–68. doi:10.1016/j.burns.2010.07.007 PMID:20692769

Schug, S. A., & Goddard, C. (2014). Recent advances in the pharmacological management of acute and chronic pain. *Annals of Palliative Medicine*, *3*(4), 263–275. PMID:25841906

Serino, S., Pedroli, E., Tuena, C., De Leo, G., Stramba-Badiale, M., Goulene, K., Mariotti, N. G., & Riva, G. (2017). A novel Virtual Reality-based training protocol for the enhancement of the "mental frame syncing" in individuals with Alzheimer's Disease: A development-of-concept trial. *Frontiers in Aging Neuroscience*, *9*, 240. doi:10.3389/fnagi.2017.00240 PMID:28798682

Sexton, J. E., Cox, J. J., Zhao, J., & Wood, J. N. (2018). The genetics of pain: Implications for therapeutics. *Annual Review of Pharmacology and Toxicology*, *58*(1), 123–142. doi:10.1146/annurev-pharmtox-010617-052554 PMID:28968191

Silva, T. C. A., Bandeira, P. M., Ranzatto, A. D. da S., Meziat-Filho, N. A., Nogueira, L. A. C., Fernandes Júnior, O., & Reis, F. J. J. dos. (2020). Comparison of the effect of two virtual reality stimuli on pressure pain sensitivity and autonomic response. *BrJP, 3*(4), 328–332.

Silverberg, Z., Silverberg, M., & La Puma, J. (2017). Virtual reality and vaccination: see the sea and be pain-free. *Travaux Présentés Au World Summit on Pediatrics, 24*.

Sneddon, L. U. (2017). Comparative physiology of nociception and pain. *Physiology (Bethesda, MD)*. PMID:29212893

Stamm, O., Dahms, R., & Müller-Werdan, U. (2020). Virtual reality in pain therapy: A requirements analysis for older adults with chronic back pain. *Journal of Neuroengineering and Rehabilitation*, *17*(1), 1–12. doi:10.118612984-020-00753-8 PMID:32993678

Stinson, J., White, M., Isaac, L., Campbell, F., Brown, S., Ruskin, D., Gordon, A., Galonski, M., Pink, L., Buckley, N., Henry, J. L., Lalloo, C., & Karim, A. (2013). Understanding the information and service needs of young adults with chronic pain: Perspectives of young adults and their providers. *The Clinical Journal of Pain*, *29*(7), 600–612. doi:10.1097/AJP.0b013e31826dce65 PMID:23328333

Stinson, J. N., Jibb, L. A., Nguyen, C., Nathan, P. C., Maloney, A. M., Dupuis, L. L., Gerstle, J. T., Alman, B., Hopyan, S., Strahlendorf, C., Portwine, C., Johnston, D. L., & Orr, M. (2013). Development and testing of a multidimensional iPhone pain assessment application for adolescents with cancer. *Journal of Medical Internet Research*, *15*(3), e51. doi:10.2196/jmir.2350 PMID:23475457

Stinson, J. N., Lalloo, C., Harris, L., Isaac, L., Campbell, F., Brown, S., Ruskin, D., Gordon, A., Galonski, M., Pink, L. R., Buckley, N., Henry, J. L., White, M., & Karim, A. (2014). iCanCope with Pain™: User-centred design of a web-and mobile-based self-management program for youth with chronic pain based on identified health care needs. *Pain Research & Management*, *19*(5), 257–265. doi:10.1155/2014/935278 PMID:25000507

Tait, R. C., Chibnall, J. T., & Kalauokalani, D. (2009). Provider judgments of patients in pain: Seeking symptom certainty. *Pain Medicine*, *10*(1), 11–34. doi:10.1111/j.1526-4637.2008.00527.x PMID:18992039

Tajerian, M., Alvarado, S., Millecamps, M., Vachon, P., Crosby, C., Bushnell, M. C., Szyf, M., & Stone, L. S. (2013). Peripheral nerve injury is associated with chronic, reversible changes in global DNA methylation in the mouse prefrontal cortex. *PLoS One*, *8*(1), e55259. doi:10.1371/journal.pone.0055259 PMID:23383129

Tang, K. S., Cheng, D. L., Mi, E., & Greenberg, P. B. (2020). Augmented reality in medical education: A systematic review. *Canadian Medical Education Journal*, *11*(1), e81. PMID:32215146

Taylor, S. L., Herman, P. M., Marshall, N. J., Zeng, Q., Yuan, A., Chu, K., Shao, Y., Morioka, C., & Lorenz, K. A. (2019). Use of complementary and integrated health: A retrospective analysis of US veterans with chronic musculoskeletal pain nationally. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *25*(1), 32–39. doi:10.1089/acm.2018.0276 PMID:30312109

Todd, J., van Ryckeghem, D. M. L., Sharpe, L., & Crombez, G. (2018). Attentional bias to pain-related information: A meta-analysis of dot-probe studies. *Health Psychology Review*, *12*(4), 419–436. doi:10.1080/17437199.2018.1521729 PMID:30205757

Triberti, S., Repetto, C., & Riva, G. (2014). Psychological factors influencing the effectiveness of virtual reality–based analgesia: A systematic review. *Cyberpsychology, Behavior, and Social Networking*, *17*(6), 335–345. doi:10.1089/cyber.2014.0054 PMID:24892195

van Roy, R., Deterding, S., & Zaman, B. (2019). Collecting Pokémon or receiving rewards? How people functionalise badges in gamified online learning environments in the wild. *International Journal of Human-Computer Studies*, *127*, 62–80. doi:10.1016/j.ijhcs.2018.09.003

van Roy, R., & Zaman, B. (2019). Unravelling the ambivalent motivational power of gamification: A basic psychological needs perspective. *International Journal of Human-Computer Studies*, *127*, 38–50. doi:10.1016/j.ijhcs.2018.04.009

Van Ryckeghem, D. M. L., Van Damme, S., Eccleston, C., & Crombez, G. (2018). The efficacy of attentional distraction and sensory monitoring in chronic pain patients: A meta-analysis. *Clinical Psychology Review*, *59*, 16–29. doi:10.1016/j.cpr.2017.10.008 PMID:29126746

van Twillert, B., Bremer, M., & Faber, A. W. (2007). Computer-generated virtual reality to control pain and anxiety in pediatric and adult burn patients during wound dressing changes. *Journal of Burn Care & Research; Official Publication of the American Burn Association*, *28*(5), 694–702. doi:10.1097/BCR.0B013E318148C96F PMID:17667488

Vaughan, N., Dubey, V. N., Wainwright, T. W., & Middleton, R. G. (2016). A review of virtual reality based training simulators for orthopaedic surgery. *Medical Engineering & Physics*, *38*(2), 59–71. doi:10.1016/j.medengphy.2015.11.021 PMID:26751581

Vlaeyen, J. W. S., Morley, S., & Crombez, G. (2016). The experimental analysis of the interruptive, interfering, and identity-distorting effects of chronic pain. *Behaviour Research and Therapy*, *86*, 23–34. doi:10.1016/j.brat.2016.08.016 PMID:27614948

West, S. J., Bannister, K., Dickenson, A. H., & Bennett, D. L. (2015). Circuitry and plasticity of the dorsal horn–toward a better understanding of neuropathic pain. *Neuroscience*, *300*, 254–275. doi:10.1016/j.neuroscience.2015.05.020 PMID:25987204

Wiederhold, B. K. (2006). *Cyber Therapy II, Virtual Healing, Designing Reality*. Interactive Media Inst.

Zhan, T., Yin, K., Xiong, J., He, Z., & Wu, S.-T. (2020). Augmented Reality and Virtual Reality Displays: Perspectives and Challenges. *iScience*, *23*(8), 101397. doi:10.1016/j.isci.2020.101397 PMID:32759057