VR for Pain Relief

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Contents

Abstract The present chapter explores how immersive virtual reality (VR) systems can be used for pain research and treatment. Pain is a universal, yet entirely subjective and multifaceted unpleasant experience. One of the earliest VR studies

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on pain highlighted the role of attention in pain modulation. However, the role of body representation in pain modulation has also been described as a crucial factor. Through virtual reality systems, it is possible to modulate both attention to pain and body representation. In this chapter, first we define how immersive VR can be used to create the illusion of being present in immersive VR environments and argue why VR can be an effective tool for distracting patients from acute pain. However, distraction seems to be less useful in chronic pain treatment. Chronic pain can be highly disabling and can significantly impact not only the sufferer's quality of life, but also their perceptions of the bodily self. Close neural connections between the body matrix and pain open a chance for influencing pain through bodily illusions. This chapter explores approaches to inducing body ownership illusions in VR and discusses how they have been applied in pain research. The present chapter also covers a set of practical indications and methodological caveats of immersive VR and solutions for overcoming them. Finally, we outline several promising future research directions and highlight several yet unexplored areas.

Keywords Body representation · Embodiment · Pain relief · Virtual reality

1 Introduction

In 1965, Ronald Melzack and Pat Wall transformed the current views on pain with the introduction of gate control theory (Melzack and Wall 1965), which argued that the brain plays a crucial role in pain perception, as it filters, selects, and modulates the inputs arriving at or produced by the body (Melzack 1999a, b). The theory postulated that pain perception is not a simple sensory stimulus-response model, as our previous Cartesian understanding suggested, but a complex process in which the brain contributes not only to the ultimate perception of pain, but also to the nature of pain itself.

The primary purpose of pain is protection. It motivates the organism to stop what it is doing and seek help. From an experiential point of view then, pain is necessarily unpleasant (Merskey 2002) and demands attention (Eccleston and Crombez 1999). Further, pain reduces cortical processing capacity (Derbyshire et al. 1998), induces slowed decision-making (Crombez et al. 1996), and increases cognitive error rates (Buckelew et al. 1986). In addition, it modifies immune activity (Watkins and Maier 2000), the activity of the hypothalamus–pituitary–adrenal axes, and alters the sympathetic nervous system (Melzack 1999a, b), as well as reducing reproductive system function (Rivier 1995), and activating visuo-motor systems (Price 1999). From a neurobiological point of view, the following brain areas were previously thought to be pain specific: the primary (S1) and secondary (S2) somatosensory cortices, the insula, and the anterior cingulate cortex (ACC) (Iannetti and Mouraux 2010). This extensive network is known as the "pain matrix" for mediating pain experience itself (Ploghaus et al. 1999), although activation of these areas has subsequently been shown in other non-painful but strong sensory stimuli (Salomons et al. 2016).

In this regard, the concept of a pain matrix is often used to understand the neural mechanisms of pain in health and disease. For instance, it is known that chronic pain conditions, where pain persists for longer than 3 months, are associated with changes in the structure of the brain as a result of central plasticity (May 2008). Indeed, there is evidence demonstrating an altered localized brain chemistry and functional reorganization of cortical networks in patients suffering from chronic back pain (Flor 2003). Neuroplastic changes related to function, chemical profile, or structure during chronic pain conditions have been described for both the peripheral and central nervous systems in terms of reorganization of receptors and ion channels, changes in neurotransmitters at the peripheral level, and functional changes in cortical representational fields at the central level (May 2008; Yang and Chang 2019) Other examples of neuroplastic change due to chronic pain include spinal cord sensitization or disinhibition and the interaction of the nervous system with the immune system and higher cognitive functions (May 2008).

Accordingly, a large number of studies suggest that cortical reorganization takes place at a functional level in patients suffering from chronic pain conditions, such as in amputee patients with phantom limb pain (Flor et al. 1995), and in patients with chronic back pain (Flor et al. 1997). Moreover, such functional cortical reorganization has also been shown in patients with complex regional pain syndrome, in which a shrinkage of the representational field in the brain of the affected arm was found and was highly correlated with pain intensity (Maihöfner et al. 2003; Pleger et al. 2004) although this finding is controversial, with later studies showing enlarged representation of the healthy hand on the contralateral hemisphere (Di Pietro et al. 2015) and no interhemispheric differences (Mancini et al. 2019). In this regard, the neuromatrix pain theory, which was introduced by Melzack (1996), recognizes the influence of both ascending and descending inputs to the conscious experience of pain, as well as the important contributions of memory and past experiences to pain perception (Melzack 2001).

The neuromatrix pain theory has paved the way for the introduction of new nonpharmacologic methods for pain relief based on behavioral interventions. A crucial concept of this approach is that pain relies on a body image that is held by the brain like a "virtual body" (Moseley 2003). Pain perception may therefore induce some changes in the "virtual body." In patients suffering from phantom limb pain, for example, they may perceive a telescoped effect, which is the feeling that the proximal portion of the amputated limb is missing or has shrunk with the more distal portion floating near, attached to, or "within" the stump (Flor et al. 2006; Giummarra et al. 2007). Indeed, we know that in the case of chronic pain conditions, both the nociceptive system and the "virtual body" may experience profound changes that increase the sensitivity to noxious or non-noxious stimuli, and as a consequence of this may disrupt the integrity of motor output (Moseley 2003). In this case, the "virtual body" in the brain is continuously updated by the inputs from the sensory system.

Since the 1990s, new behavioral therapies for pain relief have attempted to modulate such a distorted or corrupted internal "virtual body" by inducing body ownership illusions through mirrors (Ramachandran and Altschuler 2009), fake bodies (Hegedüs et al. 2014), and virtual bodies (Matamala-Gomez et al. 2019b, 2021b). Growing interest in new technologies such as VR systems is paving the way for the development of new clinical interventions to manage pain via non-pharmacological means (Carter et al. 2014). This chapter aims to show how VR and specifically virtual body ownership illusions can be applied for pain relief interventions. It also reviews the most recent literature and outlines several promising research lines which have become possible with current and future technological advancements.

2 VR and Pain

VR was introduced to the field of pain at the beginning of the twenty-first century. One of the first applications for pain relief in a clinical context was proposed by Hoffman and colleagues (Hoffman et al. 2000a, b, c), who found that adolescent and adult burns patients perceived less pain when playing a video game whilst having their dressings changed – a notoriously painful procedure. Later, an fMRI (functional-magnetic resonance imaging) study conducted by the same group found that VR exposure while experiencing a painful heat stimulus significantly reduced pain in five brain regions of interest related to pain: the anterior cingulate cortex, primary and secondary somatosensory cortex, insula, and thalamus (Hoffman et al. 2004a, b). Further, some years later, another fMRI study showed that when using VR systems for pain relief, the reduction of pain was comparable to the analgesic effect of a moderate dose of hydromorphone pain medication (Hoffman et al. 2007). Moreover, the effectiveness of VR systems for pain relief has been demonstrated in patients with mild and severe pain states (Hoffman et al. 2000a, b, c, 2011, 2014).

Whereas the first VR applications were non-immersive (i.e., they were presented on a computer screen), new VR applications are continuing to be developed for immersive VR systems. Immersive VR is a computer-generated 360°, 3D environment that is rendered through a head-tracked, head-mounted display (HMD) or in a cave automatic virtual environment (CAVE) (Slater 2018). Immersive VR systems allow users to be transported to an artificial world and even give them a full virtual body with which to explore it. Further, both the virtual world and body can be fully controlled and modified by the experimenter or clinician with the intention of achieving specific clinical outcomes, making VR systems an optimal tool for modulating the internal "virtual body," the sensory system, as well as the cognitive functions of patients suffering from pain conditions.

Nowadays, the dramatically lower costs for buying a VR system, with standalone headset systems available for less than €300, opens up the possibility for using VR for assessment and treatment of different pain conditions in hospital environments or even in patients' homes (Matamala-Gomez et al. 2021a; Scuteri et al. 2020; Slater 2014; Stasolla et al. 2021). It has been demonstrated that VR systems can effectively reduce pain perception in both (1) healthy subjects experiencing painful stimuli and (2) in patients with clinical pain, via two main mechanisms: (1) the distractive potential of VR and (2) the capability of modulating internal body representation (Donegan et al. 2020; Matamala-Gomez et al. 2019b). In addition, some evidence demonstrates that the positive pain-relieving effects of VR may also be mediated through a reduction in anxiety and through the user experiencing positive emotions such as a sense of fun when experiencing it (Triberti et al. 2014).

2.1 Evidence for Using Immersive VR for Pain Distraction

Distraction has been considered an effective cognitive behavioral procedure for pain relief, as a time-honored psychological pain intervention (Blount et al. 2003; Dahlquist 1999a, b). Some distractive strategies for pain relief are deep breathing, listening to soothing music, watching a video, or playing a video game (Austin and Siddall 2021; Bondin and Dingli 2021; Krupić et al. 2021). It is argued that distractive strategies consume some of our attentional resources leaving less cognitive capacity available for processing pain (McCaul and Malott 1984). The success of these techniques for pain relief has led to the use of VR systems to maximize distraction (Wiederhold et al. 2014a, b).

Today, there is a growing interest in using VR systems as a distractive intervention for pain reduction (Botella et al. 2008; Gorman 2006; Hoffman et al. 2007, 2011; Donegan et al. 2020; Matamala-Gomez et al. 2019a). Through VR, it is possible to draw attention away from the patients' mental processing, decreasing their pain perception (Wiederhold et al. 2014a, b). It is generally thought that the amount of attention directed to the VR intervention is inversely proportional to the available remaining attentional resources that can process incoming nociceptive signals. VR interventions for pain relief have been found to be effective in reducing reported pain in patients undergoing burn wound care, chemotherapy, or dental procedures (Bani Mohammad and Ahmad 2019; Hoffman et al. 2001, 2000a, b, c; Schneider et al. 2003; Schneider and Workman 1999; Tanja-Dijkstra et al. 2014; Wiederhold and Wiederhold 2012; Wiederhold et al. 2014a, b). Hence, distraction strategies using VR are considered a cognitive target with specific therapeutic utility in acute and procedural pain contexts (Trost et al. 2021).

Importantly, we know that the distracting effects of VR interventions are able to change how the brain integrates pain, not just the perception of painful stimuli (Birckhead et al. 2021). To verify this, Birckhead and colleagues have proposed to evaluate the effectiveness of three forms of VR for patients with chronic lower back pain in a forthcoming three-arm clinical trial. In detail, the authors aim to compare the effects of (1) a skills-based VR, a program incorporating principles of cognitive behavioral therapy, mindful meditation, and physiological biofeedback therapy using embedded biometric sensors; (2) a distraction-based VR program using 360°

immersive videos designed to distract users from pain; and (3) a sham VR program in which the patients were allocated to a non-immersive program using two-dimensional videos within a VR headset on pain perception.

It has also been shown that VR interventions facilitate positive affective states, which also contribute to the reduction of pain perception and bolster the diversionary power of the intervention (Sharar et al. 2016). To date, results from experimental research support VR as a tool for distraction and affecting modulation (Indovina et al. 2018; Malloy and Milling 2010 for reviews). These studies provide evidence that VR distraction is an effective intervention for reducing experimental pain in healthy subjects, as well as the pain associated with burn injury care, and other medical procedures such as wound care, and physical therapy. Moreover, VR seemed to decrease cancer-related symptoms in different settings, including during chemotherapy (Chirico et al. 2016). The studies from these reviews showed a clear pattern that immersive VR technology is more likely than non-immersive VR technology to generate relief from pain.

Further, the sense of presence induced during a VR experience and the possibility to interact with the virtual environment correlate inversely with the perception of external pain induced during the experimental session (Gutierrez-Maldonado et al. 2011; Gutiérrez-Martínez et al. 2011; Hoffman et al. 2004b; Riva et al. 2007; Wender et al. 2009). Interestingly, a recent study conducted by Hoffman reported that interacting with virtual objects through embodied virtual hands increased the sense of presence within the virtual environment – an effect that was accompanied by diminished attentional resources available to perform an attention-demanding task in healthy subjects, as well as a decrease in perceived pain induced by brief thermal stimuli during the experimental session (Hoffman 2021). The results from this study implicate an attentional mechanism for how VR reduces pain and help us to understand how VR influences pain perception. Further, the results from this study indicate that the immersiveness of a VR system can be increased substantially (e.g., through avatars) with little or no increase in VR side effects – unlike opioids, which show a dose–response increase in side effects (e.g., increased nausea and constipation) with higher doses. Further, opioid side effects linger for hours after a medical procedure has been completed. Such results pave the way to include immersive VR as a behavioral non-pharmacological intervention for treating pain conditions.

In relation to the above-mentioned study by Hoffman and colleagues, the effects of virtual embodiment on pain relief are more related to brain plasticity changes to the internal body representation than on distractive mechanisms (Matamala-Gomez et al. 2021b). Specifically, these changes rely on the predictive coding hypothesis, which argues that the brain maintains an internal model of the body and the space around it (i.e., the body matrix) which allows the brain to create predictions about the upcoming sensory stimuli arriving at the body and to optimally interact with the dynamic environment around the body (Barrett 2017; Riva et al. 2019). Then, top-down and bottom-up multisensory processes converge into the body matrix and redefine the place of the self, inside the body, consequently modulating the internal body representation as we interact with the surrounding environment (Apps and Tsakiris 2014; Holmes and Spence 2004; Serino et al. 2018). More specifically, some authors argue that the brain creates an embodied simulation of the body to effectively control and regulate the body in the world, which includes predicting people's actions, concepts, and emotions (Riva et al. 2019). Along these lines, VR experiences attempt to replicate the sensory consequences of the individual's actions, providing them with the same scene or body representation that they can see in the real world. To achieve this, the VR system, like the brain, maintains a model (simulation) of the body and the space around it (Riva et al. 2019). Hence, the effectiveness of virtual body ownership illusions relies on its capability of simulating a body representation within a virtual environment while allowing the possibility to modulate the bodily experience by designing targeted virtual bodies and environments (De Oliveira et al. 2016).

2.2 Evidence for Using Virtual Embodiment for Pain Relief

Embodiment is a concept that has been defined in various ways. From the philosophical perspective it is a part of the general discussion on how one defines and experiences oneself (Blanke and Metzinger 2009), which means how the cognitive system utilizes the environment and the body as external informational structures that complement internal representations (Barsalou 2010). For cognitive neuroscience and psychology, it is concerned with the question of how the brain represents the body (Berlucchi and Aglioti 1997; Graziano and Botvinick 2002). It denotes the sense of having a body, and the body can be considered to be both the subject and object of medical science and practice (Gallagher 2001). Moreover, it can be also defined as the sense of being inside, having, and controlling a body, especially when referring to the sense of embodiment toward a virtual avatar (Kilteni et al. 2012). Indeed, in VR, embodiment is frequently associated with a sense of body ownership (Lopez et al. 2008), the concept of self-location (Arzy et al. 2006a, b), and a sense of agency (Newport et al. 2010). Hence, having a sense of embodiment toward a virtual body refers to the feeling of our self as being inside a body, a body that moves according to our intentions, and that interacts with the surrounding virtual environment.

A sense of self-location is described as one of the key components of inducing a sense of embodiment toward a fake body (Arzy et al. 2006a, b; Blanke and Metzinger 2009; Lenggenhager et al. 2007). However, some studies suggest that feeling embodied within a fake body does not require a sense of body ownership. In fact, it appears that these two phenomena can be dissociated, as shown in the study conducted by de Preester and Tsakiris, in which participants could feel a sense of embodiment toward a tool, that is the feeling that the tool is part of one's own body (de Preester and Tsakiris 2009) without reporting feelings of ownership (De Vignemont 2011). These studies support the idea of a pre-existing body-model (representation) that allows for the incorporation of objects into the current body representation model. This body-model is also a basis for the distinction between body extensions (e.g., in the case of tool-use) and incorporation (e.g., in

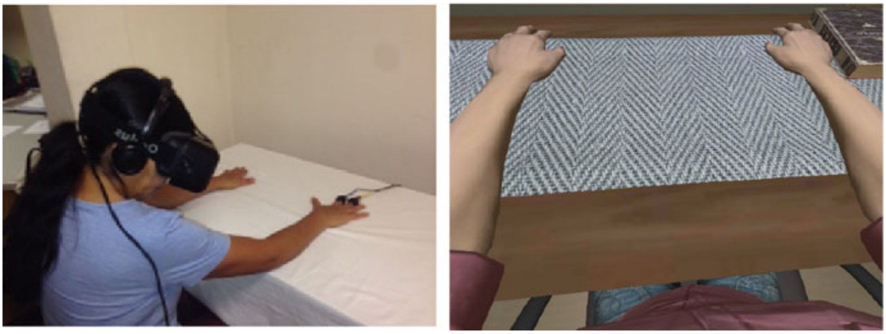

Fig. 1 Sense of embodiment in virtual reality

the case of successful prosthesis use). More specifically, it was demonstrated that in the case of incorporation, changes in the sense of body ownership involve a reorganization of the body-model, whereas extension of the body with tools does not involve changes in the sense of body ownership.

Another crucial factor for inducing embodiment within a fake body is experiencing a sense of agency, which has been demonstrated to give coherence to the internal body representation (Tsakiris et al. 2006). Further, it is shown that a lack of agency can inhibit the sense of embodiment, as in the case, for example, of inducing the illusion that the participant's finger was being stretched to twice its normal length until it snapped and the tip came off, and moving it independently without participant's control (Newport and Preston 2010).

In summary, through VR it is possible to induce the three subcomponents of embodiment – body ownership, a sense of self-location, and a sense of agency – so that VR can be used to modulate a user's internal body representation. In turn, a users' changed body representation can influence his or her behavioral, cognitive, and physiological responses as the person engages with virtual surroundings (Moseley et al. 2012). In this way, VR can be an effective tool for inducing virtual body ownership illusions through which participants can feel fully embodied in the virtual body, the appearance of which can be determined by the experimenter (Kilteni et al. 2012) (Fig. 1). For instance, some studies suggest, that assuming the role in VR of a person of a different race can impact empathy and perspective taking (Thériault et al. 2021; Banakou et al. 2020). Given these studies, it may prove fruitful to explore the impact of empathy through the use of virtual embodiment on pain modulation.

Body Perception and Pain

In recent years, interest has grown in investigating how observing the body while being in pain may impact pain perception (Martini 2016). Cross-modal interactions between the vision of the body and somatosensory responses have been widely investigated (Macaluso and Maravita 2010; Medina and Coslett 2010; Serino and Haggard 2010; Wesslein et al. 2014). It was reported that in healthy subjects observing video clips of other hands receiving painful stimulation, while receiving a painful laser stimulation on their real hands, the neural processing of the early nociceptive-related responses was modulated by decreasing neural activity in the pain matrix sensory node, compared to the observation of a non-human control condition (Valeriani et al. 2008). Later, another study conducted by Longo and colleagues reported that seeing one's own painful body part can itself exert an analgesic effect (Longo et al. 2009). In three separate experiments with healthy subjects, the authors showed that while subjects were looking at their own painfully stimulated hand, they felt less pain compared to when they were looking at a box or even at somebody else's hand. Further, they observed a reduction of the late N2/P2 components of the laser-evoked potentials, which showed an analgesic effect related to the vision of the painful body part. The authors argued that this effect was driven by the visually induced activation of the inhibitory GABAergic interneurons in the brain somatosensory areas (SI, SII). Moreover, a different electroencephalogram (EEG) study with healthy subjects showed that seeing the body, compared to seeing a neutral object, increased beta oscillatory activity bilaterally in sensorimotor brain areas, indicating cortical inhibitory activity toward nociceptive stimuli processing (Mancini et al. 2013). Another neuroimaging study found that images of a body part subjected to painful stimulation increased the functional coupling between brain areas of the "pain matrix" and body representation brain areas within the posterior parietal cortex and the occipito-temporal areas (Longo et al. 2012). Interestingly, it has been shown that the analgesic effect while observing a body under painful conditions is site-specific, meaning that there is only pain relief to the site of the body that is homologous to the one being subjected to pain while the participant watches (Diers et al. 2013).

Intriguingly, visual modification of a body part has been found to shape pain perception. For instance, it has been shown in both healthy subjects (Mancini et al. 2011; Romano and Maravita 2014) and clinical populations (Diers et al. 2013; Moseley et al. 2008; Preston and Newport 2011; Ramachandran et al. 2009; Stanton et al. 2018) that by changing the size of the observed painful limb there is a modulation of pain perception in the viewer proportional to the enlargement or reduction of the size of the seen body part. Interestingly, resizing illusions has led to contrasting results in clinical populations with chronic pain, as well as healthy individuals in some cases (for a review, see Martini 2016).

A possible explanation for these contradictory results could reside in the altered neural representation of the body in chronic pain patients (Tsay et al. 2015). It is known that consequences of experiencing body representation alterations include changes in the perception of the size of the painful limb, as has been shown in patients with complex regional pain syndrome (Lewis et al. 2007), hand osteoarthritis (Themelis and Newport 2018), and painful phantom limb (Ramachandran and Hirstein 1998). Interestingly, altered body perceptions analogous to those reported in pathological conditions can be induced in healthy individuals using controlled experimental paradigms (Matamala-Gomez et al. 2020a; Moseley et al. 2012). All experimental manipulations that induce body illusions toward a fake body rely on exposing participants to altered multisensory stimulation through synchronous visuo-tactile or visuo-motor congruent stimulation. For instance, in the study conducted by Petkova and Ehrsson (2008), the authors applied synchronous visuo-tactile stimulation over a mannequin fake body and to the participants real body to induce the sense of ownership over the fake mannequin body. In the same way, Slater et al. (2008) induced a sense of ownership toward a virtual body using synchronous visuo-tactile stimulation. Further, others induced a sense of ownership toward fake virtual bodies using synchronous visuo-motor correlations (Kokkinara et al. 2015). This research supports the overall view that self-body representations in the brain are built dynamically through multisensory integration processes and through our existing knowledge about the human body (Maselli and Slater 2013; Tajadura-Jiménez et al. 2012).

These findings are particularly exciting for VR researchers in that they suggest the possibility of inducing full body ownership illusions through VR by applying synchronous visuo-tactile or visuo-motor congruent stimulations. Moreover, through VR, it is possible to observe the virtual body from a first-person perspective – which could represent a crucial factor to feeling fully embodied in a virtual avatar (Maselli and Slater 2013). Hence, immersive VR systems are a promising tool for both representing the possible body distortions due to the chronic pain condition and for normalizing the altered representation of the painful part of the body reducing pain perception. Then, one may postulate that virtual body ownership illusions can be used for both the assessment and treatment of chronic pain conditions.

Virtual Embodiment for Pain Relief

In line with the ideas outlined above, a large number of studies have attempted over the past decade to leverage the power of virtual embodiment by inducing virtual body ownership illusions in healthy and clinical populations (see Matamala-Gomez et al. 2019b, 2021b; Donegan et al. 2020; Martini 2016). The benefits of virtual body ownership illusions in clinical populations can be explained by recourse to the predictive coding hypothesis, which argues that the brain maintains an internal representation of the body and the space around it. These representations allow the brain to predict upcoming sensory stimuli arriving at the body and to optimally interact with the dynamic environment around the body (Barrett 2017; Riva et al. 2019). Then, top-down and bottom-up multisensory signals arriving to the body redefine the place of the self, inside the body, consequently modulating internal body representation as we interact with the surrounding environment, whether real or virtual (Holmes and Spence 2004; Ribu et al. 2013).

The effectiveness of virtual embodiment stems from its capacity to simulate a virtual body representation that is experienced as genuinely present in the virtual environment, while also allowing this virtual body to be felt as one's own even if its appearance differs from the real body (De Oliveira et al. 2016; Slater and Sanchez-Vives 2016). VR offers the possibility of inducing a sense of body ownership toward fake virtual bodies that are present in the virtual environment through the use of multisensory stimulation (e.g., visuo-tactile or visuo-motor), such that the researcher can modify the morphological characteristics of the virtual body, designing targeted virtual bodies depending on the aim of the intervention. Some evidence

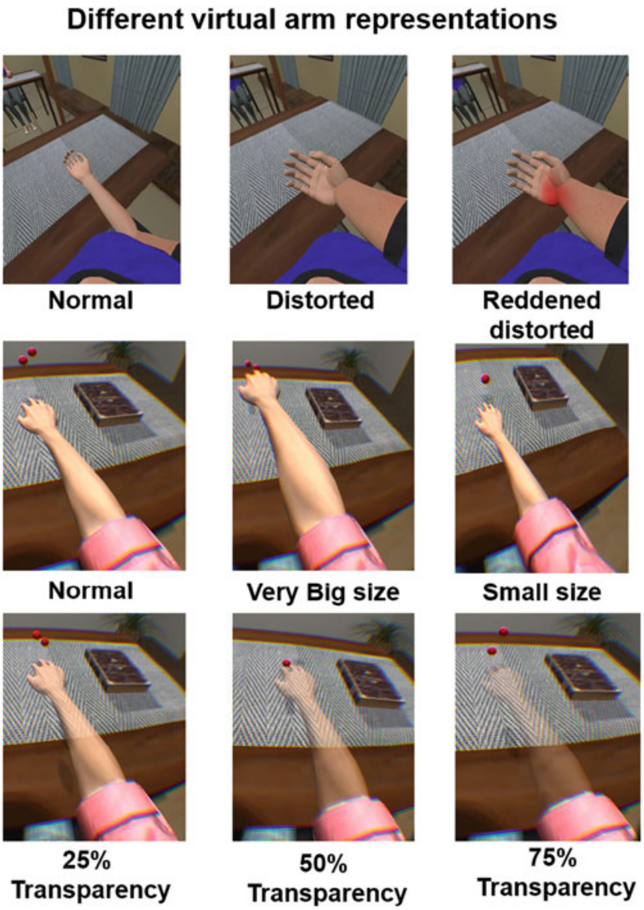

Fig. 2 Virtual body distortions used for upper limb pain relief. Pictures were retrieved from Matamala-Gomez et al. (2019b, 2020a, b)

demonstrates that by changing the morphological characteristics of the virtual body, it is possible to modulate aspects of participants' behavior (Slater and Sanchez-Vives 2016). For instance, it has been shown that a sense of ownership over virtual bodies with different skin colors can be instilled in VR users, decreasing implicit racial bias (Banakou et al. 2016). Similarly, inducing ownership over a child's virtual body has allowed researchers to assess changes in object size estimation and behavioral attitudes (Banakou et al. 2013). Likewise, it has been shown that virtual body ownership illusions can be used in order to prompt functional brain alterations in patients with chronic pain and to decrease pain perception by changing the morphological characteristics of the virtual body (Matamala-Gomez et al. 2019b, 2021b) (Fig. 2).

These studies suggest a bidirectional link between pain and body perception (Matamala-Gomez et al. 2019b, 2020a, b, 2021a, b). However, work from the authors' own group has shown that the best strategy needs to be tuned to the etiology of a source of pain (Matamala-Gomez et al. 2019b). In detail, it was demonstrated that by increasing the level of transparency of the virtual homolog of a painful part of the body, it was possible to decrease pain perception in patients suffering from complex regional pain syndrome – but the opposite effect was found in patients suffering from peripheral nerve injury (Matamala-Gomez et al. 2019b). Further, in this study, an increase in pain ratings was found to correspond with an increase in the size of the virtual painful limb in patients with complex regional pain syndrome – and again, this pattern did not occur in patients with peripheral nerve injury (Matamala-Gomez et al. 2019b).

In another study conducted by Matamala-Gomez et al. (2020a, b), the authors aimed to investigate whether distorting an embodied virtual arm in virtual reality (simulating the telescoping effect in amputees) modulated pain perception and anticipatory responses to pain in healthy participants. The authors evaluated pain/discomfort ratings, levels of ownership, and skin conductance response (SCR) after the observation of each virtual arm condition (normal, distorted, reddened-distorted). It was found that viewing a distorted virtual arm enhanced the SCR to a threatening event with respect to viewing a normal control arm, but when viewing a reddened-distorted virtual arm, SCR was comparatively reduced in response to the threat. There was a positive relationship between the reported level of ownership over the distorted and reddened-distorted virtual arms and the level of reported pain/discomfort, but not in the normal control arm. Based on these outcomes, one may postulate that even though observing changes in the morphological characteristics of the virtual body may have an impact on pain perception, these changes are most likely to exert an effect when they are tailored to the specific characteristics of patients with chronic pain and their pain etiology. This idea can be in terms of interactions between body image and pain perception (Matamala-Gomez et al. 2019b, 2021a, b) such that patients with different chronic pain conditions can present different distortions, in terms of body representation, of the painful limb of the body. According to this hypothesis, an intervention using virtual embodiment to modulate such distortions should thus be tailored to each specific group of patients.

A recent study demonstrated that increasing immersiveness by inducing virtual body ownership illusions of virtual avatars may increase the analgesic effect of VR, compared to a VR exposure without using virtual avatars (Hoffman 2021). In this study, the author showed that inducing a sense of embodiment toward an interactive virtual hand substantially augments the analgesic effect of the intervention over a non-embodied condition with minimal environmental interaction. Similarly, a number of studies have shown that increasing the immersiveness of a VR experience through interactive or realistic scenarios that evoke a sense of presence amplifies the analgesic impact of that VR experience in cases of acute pain perception (Al-Ghamdi et al. 2020; Donegan et al. 2020; Hoffman et al. 2004b; Wender et al. 2009). Moreover, since having a virtual body in virtual reality has also been shown to increase the sense of presence in VR (Slater et al. 2010; Slater and Usoh 1993), adding virtual embodiment to the VR experience is likely to have additional analgesic effects. Another crucial component when using virtual body ownership illusions for pain relief is the co-location of the virtual body with the real one (Nierula et al. 2017). In this study, the authors found that to increase pain threshold while applying external heat stimulation with a thermode to the real body, the virtual and real body should be co-located. Further, the authors observed that for the arm, this analgesic effect diminishes when there are more than 30 cm difference between the virtual and real arm (Nierula et al. 2017).

3 Creating Effective Analgesic VR Illusions

As discussed, one of the key elements of the analgesic effect of VR is thought to operate via distraction or divided attention. In theory, the more engaged the subject is in the virtual task, the less "neural bandwidth" is available for processing of nociception and production of pain (Hoffman 2021). So how can we more fully engage our subjects, and immerse them more completely in the virtual scenario? Mel Slater (Slater 2009) describes two constituent parts of an effective "sense of presence" VR illusion that can induce real-life responses as the place illusion (the participant's sense that they are in a real place) and plausibility illusion (the participant's sense that the events taking place in the virtual scenario are actually happening). Of course, the participant *knows* that they are only experiencing an illusion, but *responds* as if the situation and events are real.

To ensure a more effective presence illusion, the sensorimotor contingencies that occur in VR should, as closely as possible, mimic those of reality. In addition, real-world distractions such as external light sources and sounds should be minimized, as well as any communication with the experimenter if present. Creating effective plausibility illusions also requires that the interactions that occur in VR between the subject and the environment have realistic consequences. For example, touching a moving object in VR may cause it to stop or change direction; or perhaps at a more social level, waving hello at someone in VR should cause a response (e.g., they smile or wave back) (Slater 2009).

There is a balance to be struck between making virtual scenarios engaging enough to provide significant distraction, yet realistic enough to be salient and relevant to the patient. Blasting lasers at space monsters on an alien planet might well be hugely entertaining and provide a significant distraction, and therefore analgesia, *at the time*, but once the patient removes the headset and returns to the real world, how much carryover is there from the session? How relevant is such a scenario to normal activities of daily living for the patient? Perhaps one needs to focus on the reasons for trying to induce VR analgesia. For acute pain or for painful procedures, virtual scenarios with highly distractive fantastical elements may indeed be useful (see Hoffman et al. 2000a, b, c; Hoffman et al. 2011; Hoffman et al. 2014). For chronic pain, however, VR interventions that focus on real-world challenges, or those that are particularly relevant for the individual patient, and combined with elements of graded exposure, may be a better option.

For VR interventions that utilize embodiment of a virtual body seen from a first-person perspective, there are a number of factors that make for a stronger illusion. First and foremost, the multisensory stimulation used to induce the illusion must be spatiotemporally congruent or the illusion is easily broken. Visuo-motor congruent stimulation has the additional advantage of producing a sense of agency over the virtual body's movements, which is an important component of embodiment. Finally, whereas spatiotemporal congruency is crucial, avatars do not need to closely match the subject's real body. A "lookalike" avatar may be more easily embodied, and, thanks to customizable photorealistic facial mapping, "lookalike" avatars are easily and readily available; however, it is not essential for embodiment. Indeed, Lugrin and colleagues showed that in fact cartoon-like and machine-like avatars were more readily embodied than more realistic human avatars, perhaps a demonstration of an uncanny valley effect (Lugrin et al. 2015). As discussed previously, embodying non-realistic or fantastic avatars may confer therapeutic benefit (Lugrin et al. 2015; Hoffman et al. 2014, 2011).

Considerations when Using Immersive VR in Patients with Pain

While VR is considered to be low risk (see (Corbetta et al. 2015) for a review on safety), patients in pain often have decreased mobility, tire easily, and have poor concentration spans and therefore need careful consideration when designing, testing, and implementing therapeutic VR treatment. Patients should be positioned comfortably before starting, usually seated with neck or back support, if necessary, but encouraged to move and change position should they feel the need to. For scenarios involving movement, the available range of movement should be considered and either kept within a comfortable range, or patients can be challenged to move beyond a comfortable range, depending on the goals of therapy.

As a general rule of thumb, VR exposure time should be kept to 10–15 min initially, and not extend beyond 20 min with repeated sessions once patients become accustomed to VR (Donegan et al. 2020). They should be encouraged beforehand to immediately discontinue if any symptoms of nausea or dizziness are experienced, since once these symptoms are felt, it is very difficult to get them to settle whilst still in VR. Such symptoms are more likely to occur if there are mismatches between observed visual movement in VR and real-life movement (LaViola 2000). Other ways to reduce nausea include the use of airflow (e.g., with a fan) (D'Amour et al. 2017); slower movements (Kemeny et al. 2017); temporarily narrowing the field of view during head movement (Fernandes and Feiner 2016); and ensuring the interpupillary distance (IPD) is matched to that of the patient (Fulvio et al. 2019).

The virtual task should be set at an appropriate level for the patient. More elderly patients are less likely to be familiar with VR and may be unsure what is required of them. A comprehensive discussion beforehand may be helpful, in which any doubts and questions can be answered. Often, interaction with a virtual therapist in VR, who responds in a realistic way, can be reassuring and can provide motivation for the patient (Matamala-Gomez et al. 2021a; Rehm et al. 2016).

4 Current Trends and Future Directions of IVR in the Field of Pain

Even in its early stages of development, the promise of immersive VR as a tool for mitigating pain through distraction has been clear. Since then, IVR has also become an important tool for understanding and treating pain. What are current trends and potential future developments of the discipline? Which topics are still underexplored and what may become possible only with further technological advancements?

4.1 Recent Developments in IVR and Biosignal Research

Combining biosignal recording, such as electroencephalography or near-infrared spectroscopy, and immersive VR has been successfully implemented in many research areas, including chronic pain research (e.g., Gentile et al. 2020). A novel approach, not fully explored in rehabilitation, is combining an immersive VR experience and non-invasive brain stimulation (NIBS). The two most common NIBS techniques are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). Cassani et al. (2020) have recently reviewed the literature in which NIBS and immersive VR are used for rehabilitation and found two (out of sixteen) studies where NIBS-immersive VR was used for the treatment of neuropathic pain as a result of spinal cord injury, which remains poorly understood and very difficult to treat. It is important to note that both cited studies used an early, non-immersive VR system following the one described by Moseley (2007) and not what we would call immersive VR today. The illusion was based on a video which showed the legs of a gender-matched person walking on a treadmill. To induce the experience of realistic gait perception, a vertical mirror was placed on top of the projected video, so that the own patient's upper part of the body and the walking legs displayed on the screen were aligned in the most realistic position possible, and a synchronized sound of walking shoes was played to increase the realism of the experience. The first study included a 12-week-long intervention and had a 2 (real stimulation/sham stimulation) × 2 (visual illusion/control illusion) design (Soler et al. 2010). The real tDCS with visual illusion condition yielded the largest reduction of all pain subtypes. Results suggest that virtual walking may be a viable treatment for pain after spinal cord injury.

The second study also used a visual illusion of walking to improve neuropathic pain in severe spinal cord injury (Kumru et al. 2013). The study included 5 min of tDCS alone and another 15 min where the stimulation was accompanied by the visual illusion. A 2-week intervention of daily tDCS and visual illusion resulted in an average of 50% pain reduction, which was significantly higher than in the two control conditions.

Despite these promising results, this line of research had received little attention until recent years, which have witnessed the return of NIBS+immersive VR in a new, more advanced form. One example is a study protocol, for two randomized, controlled trials for treating pain in Parkinson's disease patients (González-Zamorano et al. 2021). The studies include a combination of tDCS over the primary motor cortex, action observation, and motor imagery training based on a brain–computer interface using immersive VR. Although the results are not yet known, we may see that the conceptual and technological jump of the last decade opens completely new possibilities for pain research.

Another, almost non-existent approach in this field is a combination of immersive VR and eye tracking (ET), widely used in non-clinical research, such as marketing (Meißner et al. 2019). Although the role of ET in pain modulation has been explored in prior studies (for a review, see Chan et al. 2020), surprisingly only now are we starting to see published research that includes immersive VR + ET paradigms. There are numerous applications of immersive VR + ET. For instance, in chronic pain, it can be used as a measure of attention paid to a specific body part or events in the virtual environment. Moreover, in acute pain, it can be a tool for actively drawing attention to the virtual world to maximize the distraction from a painful procedure. For instance, Al-Ghamdi et al. (2020) used it to test the analgesic effect of interactive vs. non-interactive VR after receiving a thermal pain stimulus. The active condition included a "hands-free" ET-based manipulation of the virtual objects. In the control condition, patients could only passively watch the virtual objects. The study yielded a clear advantage of using the immersive VR + ET technology, as patients reported more fun, stronger presence, and reduced worst pain in this condition, compared to the passive one. As the HMDs with built-in ET become more accessible, we would expect to see a growing number of studies taking advantage of this technology.

4.2 VR for Pain Psychotherapy

Social immersive VR, where users can interact with each other in real time through avatars, is a big part of the VR industry. It is highly attractive because of the full anonymity offered by avatars, combined with an embodied, first-person perspective. It is also important that one can participate in such an experience without leaving home, but still feel "present" with others in cyberspace. This feature is particularly valuable for people with limited mobility or who are isolated, as has been the case in the COVID-19 pandemic. An intriguing study has recently demonstrated the usefulness of social immersive VR for acute pain. Won et al. (2020) showed that interacting in real time in immersive VR with another person can be successfully used for pain distraction, as it boosted thermal pain thresholds in participants. It corroborates the results from the above-mentioned ET study, suggesting that the immersive VR, where patients can interact with objects or others, may be more efficient than passive immersive VR, where patients are alone and not interacting actively.

In sum, immersive VR brings new opportunities for many kinds of group therapy (Cîmpean 2019), and therapy for chronic pain patients is not an exception. So far, to the best knowledge of the authors, no studies have tested such group therapy for pain. Nonetheless, one may predict that such studies will emerge, since various therapeutic groups already exist and are accessible freely through various social VR applications (for a review, see Best et al. 2022). The comparison between an in-person and teletherapy for chronic pain patients based on video-calls suggests a similarly positive effect in both groups (Mariano et al. 2021). It is too early to predict the future popularity and efficiency of an individual or group therapy for pain patients; nonetheless, it seems likely that this line of research will be developed, following spontaneous activity of immersive VR users and an overall growing acceptability among the stakeholders (Dilgul et al. 2021).

4.3 Immersive VR for Cancer Pain, Palliative, and Intensive Care

Immersive VR has also attracted the interest of researchers and practitioners seeking alternatives to opiates and other types of harsh or addictive medications for alleviating cancer-related pain or pain encountered in palliative and intensive care. Some of the first attempts did not yield entirely optimistic results: Laghlam et al. (2021) tested the efficiency of immersive VR for pain reduction during and after drain removal in patients in the intensive care unit. Compared to an inhaled equimolar mixture of N_2O and O_2 (Kalinox®), the immersive VR group was in significantly higher pain immediately after the procedure and equal pain 10 min later, suggesting that the distraction was not effective. However, the virtual experience consisted of a 360° video – thus, it was not interactive and not exactly immersive VR.

Another study investigated 360° videos of nature scenes for cancer patients during their intravenous (IV)/port access. Compared to the first visit, which served as a control, patients reported increased relaxation, feelings of peace, and positive distractions, although no change in pain or stress during the second visit (Scates et al. 2020). Based on these outcomes, it appears that to observe a significant analgesic effect, a more engaging experience may be necessary, especially for more invasive medical procedures. Hurd (2021) analyzed archival data to determine whether using audio-visual immersive VR and morphine is more efficient in inducing analgesia than morphine alone in hospice patients experiencing chronic cancer pain. The author did not find any analgesic effect of the immersive VR experience; however, due to the study limitations (no detailed information on the technical aspects of the immersive VR exactly, potential diversity of experiences, no information of the duration and frequency of the experience, etc.), it is hard to judge what was the reason for this lack of effect. Therefore, further, well-controlled experimental studies are necessary to understand whether and perhaps, how, immersive VR can be implemented in hospice care for palliative patients.

4.4 VR for Pain Diagnosis and Simulation

Among paths still to be explored thoroughly are pain diagnosis in immersive VR. Examples from other disciplines, such as neurology and cognitive psychology, suggest that immersive VR can be a useful tool for diagnosis of a range of medical conditions, including pain diagnosis (Llobera et al. 2012). In a study from Llobera et al. (2013), the authors presented a method that exploits virtual body ownership in combination with a simple brain–computer interface (BCI) based on EEG, while observing virtual movements of the painful limb in a virtual mirror and recording muscle activity (electromyography, EMG) in the corresponding real limb to complement a neurological assessment. The authors found that body ownership induced changes in both the recorded physiological measures and BCI task performance in one case study patient compared to five healthy controls – which suggests that induction of virtual body ownership combined with simple electrophysiological measures could be useful for the diagnosis of patients with neurological conditions.

Another unique possibility offered by immersive VR is a simulation of painful conditions in healthy participants, such as inducing phantom limb pain through avatars with body parts. This line of research may have several applications, such as a better understanding of the underlying mechanisms of pain disorders (Kocur et al. 2020) or an increase in empathy in healthcare employees working with pain patients (Brydon et al. 2021).

5 Conclusions

The present chapter examines the use of VR and more specifically the use of virtual embodiment for pain relief. The current literature in the field highlights the importance of immersiveness and evoking a sense of presence in order to create an effective virtual environment for pain relief. One way of increasing such aspects is by inducing a sense of embodiment within the virtual world via an avatar. Moreover, current studies in the field demonstrate that there is a link between body perception and clinical disorders such as pain, creating a viable therapeutic avenue for virtual embodiment using immersive VR systems. Nevertheless, there is a gap in the scientific literature on the use of immersive VR avatars to treat acute pain (Trost et al. 2021). Hence, robust and suitably powered randomized control trials are needed to further explore the full potential of embodiment technologies such as VR to modulate pain perception. Further investigations aimed at modulating pain perception through an embodied virtual body with larger sample sizes will allow a better understanding of the link between body representation and pain perception. Along these lines, future studies on this topic may make use of brain imaging techniques, which will allow better identification of the neural structures underlying the complex link between modification of body perception and pain.

To date, nearly all studies involving virtual embodiment have targeted treatments designed for patients with chronic pain (Llobera et al. 2013; Matamala-Gomez et al. 2020b, 2018; Pozeg et al. 2017; Solcà et al. 2018). However, while the use of VR generally for acute pain relief is well established, chronic pain management using embodiment in immersive VR in clinical populations requires further study. Rapid development of the VR hardware and software offers continuously new technological solutions which open novel research and treatment methods. This includes between others, combining NIBS and VR for pain mechanisms analysis and diagnosis, group teletherapy for chronic pain, and pain simulation in healthy participants.

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