Chapter 17

Reality, from virtual to augmented

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17.1 Introduction

Virtual reality (VR) and augmented reality (AR) are human-computer interface technologies that allow users to interact with computers in novel ways. These technologies have a long and rich history, but with recent advancements in computer technology and decreasing costs of AR/VR hardware, application of these technologies to the medical and healthcare industries has been rapidly evolving. These advancements have allowed AR/VR hardware-components of which may be worn on the head and covering the eyes to become smaller, lighter, and more portable "wearable technology." This chapter will explore three broad categories in which AR and VR are being utilized as medical applications: (1) as a medical education tool for clinicians and patients, (2) as a visualization tool for presurgical planning and intraoperative guidance, and (3) as a therapeutic tool to treat health disorders.

17.2 Terminology

The term *virtual reality* was first coined in 1978 by Jaron Lanier, an early innovator of VR technology. VR describes a fully enclosed, computer-generated environment that is separate from the real world and allows for realistic sensory interaction. For example, VR allows users to be immersed in, navigate through, and interact with a virtual environment [1]. An immersive VR experience creates *presence*, the feeling that the virtual world is real [2]. *Augmented reality*, or AR, is defined as a real world composited with virtual objects [3]. By donning transparent AR headsets, users see the real physical world augmented with digital content, which can range from two-dimensional (2D) static images to three-dimensional (3D) interactive models, and anything in between. Mixed reality, or MR, is often confused with AR but is a distinct technology. MR systems are aware of the real world, thereby enabling digital components to react realistically to real-world objects. For example, a digital avatar in an MR system would be able to recognize and interact with a real-world physical chair, and be able to do things like walk around, jump over, or take a seat on this chair.

As the AR/VR/MR technology continues to progress, the terminology that describes it continues to evolve as well. Increasingly, the term XR, or *extended reality*, is being employed as an umbrella term to describe all AR/VR/MR technology. It is possible we will continue to see increased use of the term XR in the future, but it is important to keep in mind the distinct aspects of AR, VR, and MR systems.

17.3 Virtual reality and augmented reality systems

There are many forms of VR and AR technology that exist and are used for medical application today. VR systems can be sorted into fully-immersive and semi-immersive categories. Perhaps the most well-known fully-immersive VR hardware is the head mounted display (HMD). HMDs such as Oculus Rift and HTC Vive are worn on the head and present visuals directly to both eyes while blocking out the real world, thereby fully immersing the user in the virtual world. These HMDs can be "tethered" to an external computer via cables, such as Oculus Rift S (Fig. 17.1) and HTC Vive (Fig. 17.2), wirelessly synced to an external computer, such as the HTC Vive with the Vive Wireless Adapter, contain the computer inside the headset itself, such as the stand-alone Vive Focus or Oculus Quest (Fig. 17.3), or run from a mobile phone, like the Samsung Gear or Oculus Go (Fig. 17.4). In all cases, the computing device, whether an external computer, internal computer, or mobile phone calculates and renders the virtual scene, while the HMD displays the scene to the user.

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FIGURE 17.1 Oculus Rift.

FIGURE 17.2 HTC Vive.

Because the HMD fully blocks out the outside world, this kind of VR is known as *fully immersive* VR. Later in this chapter we will see how enhancing presence through fully immersive VR experiences can improve the therapeutic effect of VR.

As previously mentioned, VR hardware has recently become more portable and less expensive. In 2014 researchers at the Stanford's Virtual Human Interaction Lab were using expensive and bulky HMDs such as the NVIS SX111 that weighed almost 3 lbs. and was tethered to a powerful computer with heavy cables (Fig. 17.5). The HMD and its tracking system cost upwards of $100,000. In comparison, today's Oculus Quest weighs a little over 1 lb., does not need to be plugged into an external computer, and costs about $400.

Although the HMD is probably the most recognizable form of VR hardware to the general audience, other forms of VR systems have been used frequently in the academic world. An example of a semi-immersive VR system is the CAVE (Cave Automatic Virtual Environment). The original CAVE was designed, implemented, and described by Cruz-Neira and colleagues at the University of Illinois at Chicago in 1993 [4]. The CAVE VR system

FIGURE 17.3 Oculus Quest.

FIGURE 17.4 Oculus Go.

FIGURE 17.5 NVIS SX111.

is comprised of one large room that is lined with stereoscopic display-screen faces. The user views the environment through 3D eyewear and can use hand controllers to interact with 3D content (Fig. 17.6). Though the original CAVE was developed at the University of Illinois, similar systems are now employed at universities and research centers around the world. Although the exact hardware specifications differ between these systems, the overarching visualization mediums are similar. As the viewer moves through the CAVE, the digitally-displayed environment is updated to reflect the correct perspective in relation to the user's position in space. This kind of VR is known as *semi-immersive* VR.

A VR system frequently utilized and discussed in the medical literature is the stereoscopic monitor. Users don specialized eyewear to examine 3D content displayed on the monitor (Fig. 17.7). Some systems include haptic devices that are able to interact with the 3D content. These kinds of systems have often been used to create surgical simulators. While viewing 3D anatomy onscreen, users can simulate surgical procedures by manipulating haptic devices which are

FIGURE 17.6 CAVE.

FIGURE 17.7 Dextroscope Semi Immersive.

linked to the system. Like the CAVE, these systems are also considered *semi-immersive*. These kinds of systems have been shown to be very beneficial in simulating surgical procedures.

The term “virtual reality” appears frequently in the medical literature and may refer to any one of the previously described systems, or even a system that has not been outlined here. Hopefully, as the technology continues to progress and VR and AR technologies become more accessible and conventional, we will see a convergence of the terminology used to define and describe the various VR systems. For now, we must understand the differences between the various VR medical systems that have been described to date.

Compared to VR, AR is a more recent technology. Because of this, there is a smaller body of research investigating medical AR applications today. However, there is much excitement surrounding AR’s potential in fields such as medical education and surgical guidance. Today’s medical AR technologies can be grouped into two broad categories: mobile AR and headset-based AR. Mobile AR utilizes a smartphone or tablet and is therefore fairly accessible to the average consumer (Fig. 17.8). Headset-based AR is available on HMDs such as the Magic Leap and HoloLens (Fig. 17.9). These headsets boast increased computing power but carry an increased cost compared to mobile AR. We will discuss examples of how both kinds of AR technology are being used in the medical field.

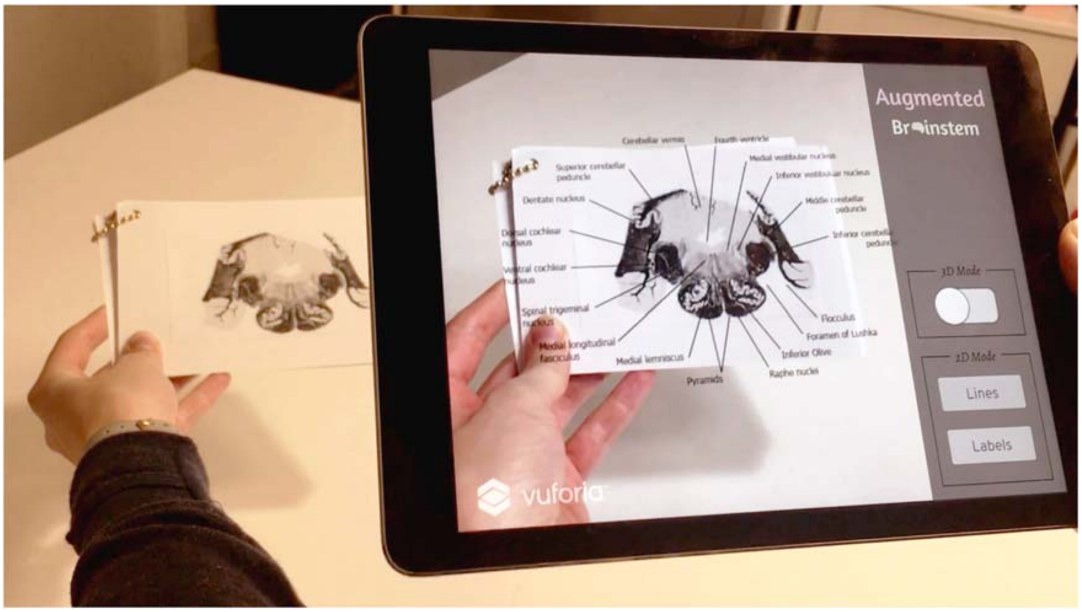

FIGURE 17.8 Augmented Brainstem.

FIGURE 17.9 Hololens.

17.4 Building virtual and augmented reality environments

These previously mentioned hardware systems are not sufficient to allow one to interact with a virtual or AR environment. Although the hardware is, of course, necessary for the experience, one must also create or acquire VR/AR software programs. Today, many of these software programs can be purchased from online digital distribution services such as Steam, the Oculus Store, or Viveport, among others. However, it can actually be quite simple to create your own virtual or AR environment.

A designer should first determine their target audience and learning objectives. With these in mind, the designer will need to determine what form of VR or AR environment will best suit their needs. For example, if it's important for the user to be fully immersed and experience a high degree of presence in the situation (e.g., perhaps training on how to triage a mass casualty case), VR may be the better choice over AR. If it's important for the user to physically move through the environment (e.g., perhaps a physical therapy trainer), then a six degrees-of-freedom system may be superior to 3 degrees-of-freedom. The answers to these questions will guide the design of the VR or AR experience.

Typically, a team of designers, artists, and programmers will work together to create a VR or AR environment. The environment will usually require 3D assets, which may be created in 3D modeling programs such as Blender, Pixologic Zbrush, Autodesk 3Ds Max or Maya, among others. These assets are then brought into a VR/AR-supported game development platform. Two of the most common VR/AR creation tools today are the game development platforms Unity and Unreal Engine. Developers will then program a variety of scripts to allow users to interact with the scene. When completed, users may don the headset and step into the world they've previously only seen on the screen—such as a virtual operating room (Fig. 17.10).

Above represents the briefest overview of the AR/VR environment creation process. In reality, there are many different approaches to designing AR/VR experiences, and many different tools that can be used to create them.

17.5 Augmented reality/virtual reality as a medical education tool

In today's world of smartphones, tablets, wearables, and other interconnected digital devices, technology is rapidly shaping the way we approach education. AR and VR technologies are naturally suited to be learning and training tools due to their immersive nature, intuitive interface, and realistic simulated environments. The medical world in particular is ripe with opportunity for AR/VR educational application. AR/VR technology can be used to allow patients to travel inside their own bodies in order to better understand their medical conditions, view results from imaging tests, and learn how a procedure will be performed or how a specific medication will work. AR/VR technology can also be used to

FIGURE 17.10 Osso.

efficiently educate clinicians by disseminating knowledge or by developing technical skills based on evidenced-based practices and procedures. For example, personalized and precise learning for gross and fine motor skills is highly useful in surgical subspecialties to ensure high standards of care. Facilitating the cognitive skills necessary for medical decision-making and effective communication is another use. AR/VR can be used as a medium to help clinicians understand and empathize with their patients, enhancing the therapeutic alliance which is correlated with patient outcomes. These examples will be fully explored in the following sections.

17.6 Embodied cognition: learning by doing

One of the reasons AR/VR technology may be so well suited for learning and education is its ability to encourage physical movement. When you enter a VR environment or participate in a VR simulation, you move your body as if you're experiencing an event in the physical world. The theory of embodied cognition stipulates that these movements of the physical body can actually influence cognition. According to this framework, our cognitive activity is caused by the bodily states, actions, and mental simulations that we generate [5]. For example, research has shown that people who nod their head while listening to spoken statements are more likely to agree with these statements [6] and that sitting upright as opposed to slumping causes more pride in achievement when people receive performance feedback [7]. Importantly, this influence of the body on cognition has been shown to predict learning. A study by Thomas and Lleras [8] demonstrated that participants who actively swung their arms in a manner that resembled the solution to a physics problem were more likely to find the correct answer as compared to those who stretched their arms randomly. A 2015 study found that in college, physics students who learned torque and angular momentum concepts by spinning bicycle wheels did better on a subsequent quiz as compared to those who only watched the bicycle wheel spin, demonstrating that people may learn better by doing than by watching [9].

Physical movement is inherent to VR and AR experiences. VR applications generally encourage users to explore virtual scenes and interact with virtual objects through movement. AR applications prompt users to view augmented media from different angles and perspectives and, in the case of the HoloLens or Magic Leap, interact with the media using hand gestures. Educators can explicitly use physical movement inherent in AR/VR systems to leverage this theory of embodied cognition to enhance medical learning goals.

17.7 Patient education

Patient education plays an important role in a patient's experience interacting with the healthcare system. Increased patient education regarding medical procedures and diagnoses lowers anxiety [10] and improves coping with and managing disease and treatments [11]. Additionally, patient education has been shown to reduce readmission rates [12] and length of hospital stay [13], which may both benefit patients and reduce societal costs of illness. Modern patient education typically consists of verbal and written material such as pamphlets, written documents, and clinician advice. However, there is increasing interest in augmenting or replacing these conventional forms of teaching aides with innovative, interactive applications such as videos, apps, and AR and VR systems that are more engaging, personalized, and standardized for best practices.

Young patients in particular may greatly benefit from visual teaching tools rather than written materials and verbal explanations from physicians. For example, a young child diagnosed with ulcerative colitis may have difficulty understanding what this diagnosis actually means and its complex terminology. Using VR, a patient can travel inside his own gastrointestinal tract to actually see how ulcerative colitis affects his body. HealthVoyager is an example of a tool that leverages VR to educate young patients [14]. Developed by Boston Children's Hospital and Klick Health, HealthVoyager aims to make complex medical test results more accessible to pediatric patients. By flying through a 3D reconstruction of their own gastrointestinal tract, pediatric patients and their caregivers are given a personalized, visual representation of their endoscopic test results. Patients are given access to these personalized 3D test results on their own smartphones and can be viewed with simple VR headsets such as Google Cardboard. Currently, the HealthVoyager platform is being piloted at Boston Children's Hospital to investigate its impact on patient understanding, satisfaction, and treatment adherence.

A growing body of research has examined how VR systems can be used to increase patient knowledge of medical procedures and diagnoses [10,11,15,16]. The Virtual Environment for Radiotherapy Training (VERT) is one such VR system that has been studied in the patient education setting. VERT is a semi-immersive HIVE-based VR system that simulates radiation therapy (RT) equipment and displays internal patient anatomy (Fig. 17.11). A number of studies validated the utility of VERT as an educational tool, concluding that VERT provides images

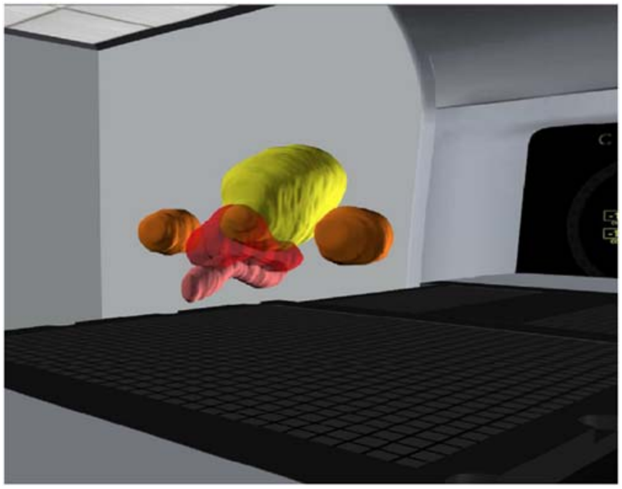

FIGURE 17.11 VERT.

that are valuable in understanding RT and that patients perceive VERT's visual features in a positive way [15−17]. Importantly, VERT has been shown to increase RT knowledge for breast, prostate, rectum, lung, and thymus cancer patients [15]. The results from a study by Jimenez et al. [10] suggest a high value of using VERT to improve RT knowledge and decrease patient anxiety. This type of VR case use has implications for improving preparation and preoperative care as well as improving informed consent and understanding the risks of procedure and treatment.

AR/VR technology can also easily allow for the delivery of individualized patient education. For example, VERT has been used to display patient-specific computed tomography (CT) data for cancer patients and treatment plans to deliver personalized education for patients [15]. VR is optimal for enabling patients to view inside their own bodies to enhance understanding of disease processes. A qualitative case series from Thompson-Butel et al. [11] investigated the role of personalized VR in education for patients post stroke. These patients were first given a structured interview to assess their level of brain anatomy knowledge, stroke knowledge, stroke risk, and motivation to manage their condition. Thompson-Butel and colleagues then constructed personalized anatomical visualizations from patients' individual magnetic resonance imaging (MRI)/CT DICOM datasets using 3D visualization software including Osirix, Maya, and Unity. These patient-specific 3D anatomical visualizations were loaded into the Oculus Rift HMD, and patients were guided through a VR environment constructed from their own stroke-affected vasculature. Following the intervention, the interview was repeated. Preliminary findings from the study suggest that patients had a greater understanding of personal stroke risk and an increased motivation to manage their condition following the personalized VR stroke education experience compared to preintervention.

17.8 Clinician education: from student to provider

Becoming a healthcare provider (HCP) requires making a lifelong commitment to learning. Years of extensive training are required, beginning with undergraduate studies focusing on premedical sciences, medical school, internships, residencies, subspecialty fellowships, and continuing education. Educators are looking for more effective and efficient ways to train current and future HCPs along the full educational continuum. VR and AR technologies provide novel ways to educate HCPs through all the stages of learning. Already VR and AR tools are being developed to address challenges faced by students, schools, and hospitals.

17.8.1 Anatomy education

Anatomy has always been an important staple of medical training. Cadavers have been used to teach anatomy and surgical skill training for hundreds of years. However, limitations exist for the use of clinical cadavers in medical education. The majority of clinical cadavers are elderly and therefore do not fully represent the clinical population that clinicians will encounter [18]. Additionally, cadavers lack dynamic blood circulation, limiting the fidelity of many biophysical responses to surgical procedures. It is also difficult to demonstrate the full range of anatomical and pathological variability in the human body when restricted to a limited number of cadavers in the classroom. The most commonly reported limitations to using clinical cadavers for medical education, however, are access and cost, which can range from $200 to $5000 per cadaver [18]. Because of these reasons, a growing number of medical schools and institutions are beginning to consider how technology can be used to lower costs and increase accessibility for anatomical learning. AR/VR technology has the opportunity to provide a realistic, comprehensive, and reusable approach to anatomical learning.

Although few studies have directly compared AR/VR educational tools to traditional cadaver dissection, AR/VR has been compared to other learning tools such as notes, images, and videos [19−27]. In these studies, half of the participants were given an AR or VR system to supplement their anatomy education, while the remaining participants were given notes, images, and videos. All participants were given an exam to assess their anatomical learning. Overall, results indicated that the AR/VR tools were significantly better at increasing motivation and spatial understanding of anatomical structures [28].

The few studies directly comparing AR/VR tools with traditional cadaver dissection are less clear. Kugelmann et al. [29] showed that the use of AR technology for anatomical and medical education increased motivation of students to learn anatomy as well as promoted active learning and transfer of knowledge to clinically relevant subjects. Codd and Choudhury [30] found no statistical significance when comparing VR models to traditional dissections and concluded that a VR model cannot replace traditional cadaver dissection. However, as technology continues to progress and simulation fidelity increases, it can be hypothesized that AR/VR technology may soon be able to fully simulate human cadaver dissection. Many AR/VR anatomical learning tools are already commercially available.

Visible Body and 3D4Medical are two of today's most successful digital human anatomy atlas applications. Visible Body is the creator of *Human Anatomy Atlas*, a human anatomy atlas app. *Human Anatomy Atlas* consistently ranks as one of the top paid apps across all categories in the United States, China, Japan, Germany, France, and other countries [31] and was selected as one of Apple's "Best of 2017." 3D4Medical is a similar cloud-based educational platform, and was acquired by Elsevier in 2019. Their product, *Complete Anatomy*, is used in over 250 universities as an educational tool. Additionally, the Complete Anatomy app was selected as one of Apples "Best of 2015" and won the Apple Design and Innovation Award of 2016 at Apple's Worldwide Developer's Conference [32,33]. Visible Body's *Human Anatomy Atlas*, and 3D4Medical's *Complete Anatomy* are web-based human anatomy learning platforms used by HCPs, students, and instructors to study and virtually dissect thousands of 3D anatomical models such as complete male and female gross anatomy, select microanatomy, and different pathologies. Both platforms also allow instructors to create custom anatomical lectures for students.

In 2017 Visible Body and 3D4Medical both announced the release of AR functionality that allows users to visualize anatomy from a 360-degree perspective. Both products allow users to turn any space into an anatomy lab by placing virtual cadavers or organs onto flat surfaces in a physical room. Students use their smartphones or tablets to view, identify, manipulate, and dissect the anatomy from different angles. The AR functionality also allows for a real-time multiuser experience, in which a group of students can follow along and view the same virtual dissection. This encourages greater interaction, conversation, and collaboration between students, which has been shown to benefit learning [34]. Additionally, the AR functionality encourages physical movement, as students are encouraged to view the anatomy from different angles. The theory of embodied cognition supports the idea that physical movement can help bridge the gap between the conceptual study of anatomy with the physical reality of our living bodies.

Augmented Brainstem is an educational neuroanatomy AR application developed by Talia Weiss at the University of Illinois at Chicago. Two vitally important aspects of neuroanatomy education include the ability to identify neuroanatomical structures from 2D scans (such as CT, MRI, or angiogram) and the ability to identify these same structures in real, 3D anatomy (the brain). Typically, students learn the former by studying 2D radiology slides provided by a university or hospital, and the latter from spending periods of time in the dissection lab examining a physical human brain. However, Weiss observed how it remains difficult for students to spatially relate the 2D structures seen in scans with their 3D counterpart in the physical brain. Weiss created Augmented Brainstem to help students learn to identify neuroanatomical landmarks from 2D scans, and to bridge the gap between radiology imaging and 3D brain structure. To address the first educational objective, Augmented Brainstem offers a flashcard functionality in which students can turn on and off AR labels to identify structures on physical MRI flashcards. To address the second educational objective, the app offers a "3D" mode in which students can view an AR brain superimposed on the MRI flashcard (Fig. 17.12). The AR brain contains a slice plane that demonstrates the exact position and orientation within the brain that the specific MRI slice was taken. Using this tool, students are able to gain a more complete understanding of the relationship between 2D radiology imaging and the more authentic 3D neuroanatomy.

FIGURE 17.12 Augmented Brainstem.

17.8.2 Surgical training and simulation

The concept of training by simulators is not a new one. Computer-generated simulations have been used for decades to train users in complex and dangerous tasks, beginning with Edward Link's flight simulator of 1929. The appeal of the VR simulator is obvious: create a safe space for users to practice and fail without the consequences risked in the real world. For airline pilots, this means flying virtual airplanes before being in charge of a real plane with real passengers. When it comes to medicine, VR simulators currently allow surgeons to practice and perfect surgical techniques in safe virtual spaces before performing these procedures with real patients.

There is a wealth of evidence showing simulation training can produce educational benefits that yield both immediate and long-term results [35]. Simulation is effective in training undergraduate students [36] and faculty [37], has positive impact on patients [38], reduces patient harm [39], and improves quality of care [40,41].

Surgical simulator technologies run the gamut from nonimmersive to fully-immersive systems. The minimally-invasive surgery trainer—VR (MIST-VR) is an example a nonimmersive, nonhaptic surgical simulator. The system contains two laparoscopic instruments with the ability to move with six degrees-of-freedom. The movement of the instruments translates as a real-time graphical display on a linked computer system. And though the system contains neither immersive nor haptic qualities, it is one of the most validated surgical simulators and has been shown to successfully measure laparoscopic surgery skills [42], train laparoscopic psychomotor skills to improve performance in the operating room [43], and add value to laparoscopic training curriculums [44].

In conventional surgical procedures, the combined effect of tactile and visual feedback enables optimal surgical performance. Of these two senses, however, tactile (or haptic) feedback is suggested to be the primary sense that guides surgeons during procedures [45]. Several studies have investigated the role of haptic feedback in surgical training. One study showed that early exposure to haptic feedback improved performance on a specific surgical task and suggested a role for haptics in the early training phase of skill acquisition [46]. A separate study by Panait et al. [47] demonstrated that haptic feedback allowed for increased precision in advanced tasks but not basic tasks. A study by Zhou et al. [48] compared the nonhaptic MIST-VR laparoscopic simulator with the haptic ProMIS laparoscopic simulator and concluded that learning with haptic feedback (via the ProMIS system) was significantly better than without haptic feedback (MIST-VR), but only in the first 5 hours of training. Many of today's surgical simulators support some form of haptic feedback.

Although haptic feedback may play an important role in surgical simulator fidelity, there is still a strong argument for the inclusion of immersive, 3D visual feedback that transforms a surgical simulator into a true VR environment in addition to haptic simulation. VR allows for greater immersion which can significantly enhance learning [49,50]. Semi-immersive and fully-immersive VR simulators have been constructed for surgery [51], neurosurgery [52,53], and more. Alaraj et al. [52] developed a semi-immersive VR aneurysm clipping simulation with haptic feedback using the ImmersiveTouch platform and investigated its impact on resident training. The team concluded that the

FIGURE 17.13 Osso.

semi-immersive, haptic simulator was helpful in training neurosurgical residents to perform aneurysm clipping, especially given that residents do not have hands-on training in this type of procedure until the end of residency.

Surgical simulators are now being developed for HMDs in fully-immersive and interactive VR environments. One company that is focused on delivering a scalable solution for orthopedic training is Osso VR. The company was founded in 2016 and its platform provides realistic, haptic-enhanced interactions in an immersive VR training environment. Users don an HMD such as Oculus Rift or HTC Vive and are able to physically learn, practice, and master the steps of specific orthopedic procedures (Fig. 17.13). Importantly, the Osso platform was validated in a pilot study that demonstrated that Osso-trained surgeons performed surgery nearly twice as well as surgeons trained through traditional means. The company is currently partnered with several of the leading medical device companies and orthopedic residency programs in the world and continues to expand. Today, Osso is working on utilizing machine learning and artificial intelligence to create robust assessment tools and analytics to evaluate surgeon technical skill with the ultimate goal of improving patient outcomes [54].

As demonstrated, the term “surgical simulator” defines a wide range of technologies, including nonimmersive, nonhaptic simulators like the MIST-VR system, nonimmersive, haptic simulators like the laparoscopic ProMIS platform, semi-immersive haptic-enabled training experiences such as the ImmersiveTouch aneurysm clipping simulation, and fully-immersive commercial products like Osso VR. All of these simulators have been classified as “virtual reality” technologies at some point in time, and all of these simulators have been shown to deliver some degree of benefit to surgeons or patients. The question is not which kind of simulator trumps all others, but which technological components are most appropriate for each clinical use-case and audience.

17.8.3 Clinical decision-making

VR’s capacity for providing a fail-safe training environment is not only useful for technical skill training (such as surgical simulation), but for high-stakes soft skill training as well. Indeed, medical VR simulators have been shown to improve communication skills [55], enhance critical thinking [56], and improve clinical decision-making [57], especially under high-pressure scenarios. VR not only recreates highly-realistic visual environments but elicits very real feelings of anxiety and stress. Mass casualty triage is a prime example of a high-stakes situation that requires clinicians to make quick and accurate clinical decisions under pressure. Multiple groups have demonstrated that VR is a valuable tool for simulating mass casualty triage situations [58–61].

Oxford Medical Simulation is a company that builds fully-immersive VR scenarios to deliver clinical training to physicians and nurses, with a focus on clinical decision-making under pressure, crisis resource management, team interaction, and patient engagement. HCPs use Oculus Rift HMDs to immerse themselves in virtual scenarios in which they manage unwell patients, perform investigations, offer treatment options, and interact with a multidisciplinary team. The focus of these simulations is not necessarily to train HCPs on specific procedures like surgical simulations might, but to train important communication and patient management skills [62].

These clinical decision-making simulations tend to be designed as fully-immersive VR experiences for the Oculus Rift, HTC Vive, or similar HMD. This is likely because fully-immersive VR is able to elicit feelings of presence, and therefore evoke emotional responses such as stress and anxiety to a much greater extent than nonimmersive or semi-immersive VR. Whereas the primary goal of a surgical simulator is to accurately train technical skills through repetition of physical movement, the objective of a clinical decision-making simulation is to recreate a high-pressure environment. Therefore where input device and hand tracking may be more important than presence for surgical simulators, the ability of a fully-immersive VR experience to elicit presence and emotional arousal is the most important factor for clinical decision-making simulations.

17.8.4 Empathy

VR has the unparalleled ability to allow a user to experience a perspective or point-of-view completely different from her own. There has been increasing interest within the medical community to utilize VR's empathy-eliciting ability to allow doctors to experience their patient's perspective to improve patient care.

There is empirical evidence supporting the claim that VR can be an effective method of eliciting empathy [63]. A growing body of literature has established the importance of empathy in all aspects of patient care including improved clinical competence [64], increased patient satisfaction [65,66], greater therapy adherence [66,67], and better clinical outcomes [68−71].

Benjamin Lok and his colleagues from the University of Florida were one of the first research groups to recognize that while empathy has been shown to improve interpersonal communication, correlate with patient and provide satisfaction, and improve clinical outcomes, there were few tools available for the deliberate practice of empathy. Lok's group designed a virtual patient tool to teach empathy to medical students and found that interacting with the virtual patient while receiving immediate feedback on empathy was able to increase students' empathy with real patients [72]. And while a virtual patient may be perceived as artificial, there is educational benefit to employing a virtual patient to train empathetic communication skills due to the low-pressure environment that the virtual patient offers [73].

In addition to providing simulated environments to practice empathetic communication, VR may improve empathy by allowing the user to see the world through a patient's eyes. Embodied Labs is a company that has created immersive embodied patient experiences for HCPs, medical students, and caregivers with the goal of increasing patient satisfaction and clinical outcomes. The platform offers different modules that explore various health conditions. One module brings users into the body and life of an elderly man named Alfred, who is suffering from advanced macular degeneration, high-frequency hearing loss, and cognitive impairment. Other modules allow users to embody a woman suffering from progressive Alzheimer's disease, or experience the life as a veteran with stage 4 lung cancer who must navigate the difficult task of having an end of life conversation with his physician and family [74]. In 2016 Embodied Labs ran a pilot study to investigate how embodying Alfred affects user empathy and knowledge. Their results suggest that the embodied learning experience has a significant effect on the ability for users to empathize with older patients, increased understanding of common pathologies seen in older adults, and increased interest in the geriatrics specialty [75].

17.9 Augmented reality/virtual reality as a visualization tool for surgical planning and intraoperative guidance

We have previously seen how AR/VR technology is being used to enrich HCP medical education in areas such as anatomy knowledge, surgical simulation, clinical decision-making, and empathy. However, these technologies are now moving beyond the classroom and into the operating room in order to facilitate surgical planning and guide physicians in real-time during surgery. While many educational VR surgical simulators can double as surgical planning tools when patient-specific data is loaded, AR appears to be the medium of choice for intraoperative guidance systems due to its ability to overlay digital markers onto patients in real-time.

17.10 Surgical planning

Surgery requires a precise understanding of the body's complex anatomical relationships. Not only is the human body complex, but standard anatomical variance is such that the anatomy of no two patients is ever the same. Because of the complicated and varied nature of human anatomy, physicians must gain an in-depth understanding of the patient-specific anatomy prior to performing surgery. Traditionally, this has been done through 2D imaging modalities such as X-rays, CT scans, MRIs, and/or angiograms, among others. However, because of the 2D nature of the images, these scans rarely tell the whole story. Surgeons must extrapolate from these 2D images in order to understand the body's 3D form. VR visualizations provide an innovative and enhanced way to assess anatomical spatial architecture and relationships by reintroducing stereoscopic depth cues and total 3D immersion [76] (Fig. 17.14). Surgeons are using VR to plan for many kinds of procedures, including but not limited to aneurysm surgery [52,77], twin-to-twin transfusion syndrome surgery [78], conjoined twin separation [79], and plastic surgery [80].

Cerebral aneurysm surgery is one such procedure that requires a spatial understanding of neurovascular and neuroanatomical structures. During the preoperative planning process, neurosurgeons study the aneurysm neck and its 3D relationships to surrounding vasculature to identify the optimal surgical strategy [77]. 3D digital subtraction angiography (3D DSA), 3D CT angiography (3D-CTA), and 3D magnetic resonance angiography (3D-MRA), which reconstruct a series of 2D images into a 3D image viewed on the computer screen, are currently used to supplement traditional 2D scans during the preoperative planning process [81]. However, the 2D screen on which these 3D reconstructions are displayed may limit a neurosurgeon's 3D spatial understanding of the aneurysm anatomy. Because VR imaging reintroduces stereoscopic depth cues and total 3D immersion, it has been suggested that VR may increase neurosurgeons' 3D anatomical understanding.

A 2016 study by Kockro et al. [77] assessed the role of VR in surgical planning for aneurysm repair using Dextroscope, a stereoscopic, patient-specific semi-immersive VR environment. Dextroscope integrated CT and MRI images to create 3D renderings projected onto a mirror and viewed stereoscopically. The resulting 3D rendering could be manipulated by the surgeon and used to evaluate different surgical approaches [82]. In Kockro's study, neurosurgeons used Dextroscope to plan the clipping of 115 aneurysms. Researchers found that planning the surgery in a 3D, VR environment enhanced the surgeons' spatial understanding of the vasculature and was correlated with positive clinical outcomes. In a similar study by Wong, Zhu, Ahuja, and Poon, [83] researchers utilized Dextroscope to simulate craniotomy and microsurgical clipping procedures. Neurosurgeons reported this application helpful for operative planning purposes and for educational training for craniotomy and microsurgical aneurysm clippings.

Alaraj et al. [52] examined the benefits of using a real-time haptic feedback VR system to simulate aneurysm clipping using the ImmersiveTouch platform. A visual representation of a middle cerebral artery aneurysm was created from CTA data and combined with volume deformation and haptic feedback to simulate clipping surgery. Two thirds of the neurosurgical residents agreed that the simulator was helpful in preparing for aneurysm clipping surgery.

Surgical Theater and Novarad are two companies with Food and Drug Administration -cleared products that use VR and AR to facilitate surgical planning. Surgical Theater creates fully-immersive VR medical visualization platforms for neurosurgeons at medical centers and academic institutions. Surgical Theater's visualization platform reconstructs 3D anatomical models from conventional CT and MRI scans. Physicians are then able to view exact 3D anatomy and vasculature in VR on HMDs such as the Oculus Rift or HTC Vive [84]. Universities such as Stanford are utilizing Surgical Theater's product to educate students, plan for surgeries, and guide physicians during surgery [85].

Novarad is a healthcare Information Technology company that provides imaging solutions to healthcare professionals. Their suite of products includes an AR system that utilizes the HoloLens to overlay medical images such as computed radiography (CR), CT, and MRI directly onto the patient's body to enable accurate registration for surgical planning and guidance [86]. Because the images are colocated to the patient, this system allows for good understanding of anatomical relationships. This AR system is the first AR medical solution for the HoloLens to be cleared by the FDA for use in preoperative surgical planning.

FIGURE 17.14 VR vasculature.

17.11 Intraoperative guidance

AR/VR is not only being used as a training and planning tool prior to surgery, but as a guidance tool during live procedures. AR systems enable a hands-free, convenient method for surgeons to access important patient information onscreen during surgery or can accurately overlay patient-specific imaging directly onto the patient's body to guide surgical procedures. For technology-delivered intraoperative guidance, surgeons are looking to AR HMDs such as the HoloLens and Magic Leap. These headsets are hands-free and transparent, allowing surgeons the full use of their hands during surgery, and an unobstructed field-of-view of the real world. An additional advantage of these wearable systems is that they do not compromise the sterility of the operating environment because they are controlled with voice commands and hand gestures rather than touch.

UK Children's Hospital is deploying the HoloLens for use by surgical teams to display relevant patient information during surgery. The application will display ultrasounds, CT scans, angiograms, and other important patient information and records in the surgeon's field-of-view [87]. This allows for a hands-free way for surgeons to quickly access information they need while conducting the surgical procedure.

Enabling surgeons to quickly and unobtrusively access patient history, anatomical scans, and other relevant information during surgery is one benefit of intraoperative AR HMD use. However, one can argue that the real value is the ability for these AR systems to colocate images directly onto the environment, and in the case of surgery, the patient. By using position-tracked markers, these AR HMDs can allow patients to see the position and orientation of previously-hidden patient-specific structures. In short, a surgeon sees her patient, viewed through the transparent lenses, overlaid with digital internal anatomical structures which have been projected onto the patient by the AR system. These digital structures are mapped and anchored to their accurate anatomical position and orientation, such that surgeons can walk around the patient and the digital structure remains fixed in its correct location. These AR systems not only help physicians develop more accurate surgical plans but help guide surgeons during surgery.

A team from the Brain Tool Laboratory at Duke led by neurosurgery residents Cutler and Rahimpour [88] prototyped an AR tool for the HoloLens to guide surgeons during external ventricular drain (EVD) placement procedures. EVD placement is an example of a blind surgery in which surgeons rely on bony landmarks of the skull to guide insertion of a drain into the brain to relieve excess fluid and pressure. Cutler and Rahimpour's AR application overlays patient-specific CT data on the patient's skull to enable a novel visualization method for EVD target location. Li and colleagues [89] went on to assess the feasibility and accuracy of using the HoloLens to guide EVD placement compared to the existing freehand technique. Patients requiring EVD insertion were either operated on using the traditional freehand technique, or with the AR-guided technique. For those in the AR condition, physicians constructed 3D CT models and calculated surgical trajectory. During surgery, the surgeon used the HoloLens to overlay the CT-generated holograms of the surgical plan directly onto patient, in registration with the patient's skull. This allowed the surgeon to perform EVD placement by keeping the catheter aligned with the holographic trajectory. No adverse events related to the AR-guided technique were reported, and the study demonstrated successful use of an AR-guided EVD procedure.

Pratt et al. [90] similarly examined the use of a HoloLens-based AR system to aid the identification of surgical landmarks when performing vascular pedunculated flaps of the lower extremities for reconstructive surgery (Fig. 17.15). This procedure involves attaching a piece of skin, taken from elsewhere on the body, to the wounded area. Then, surgeons connect the newly grafted skin to the surrounding blood vessels so that it is properly oxygenated. During surgery,

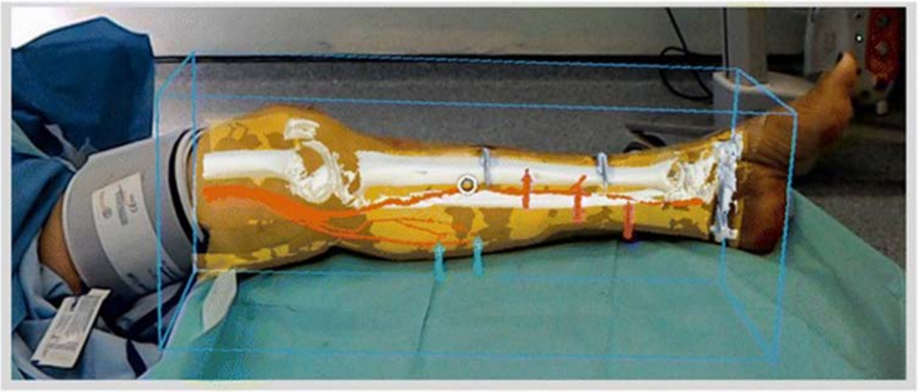

FIGURE 17.15 AR Guided Surgery.

surgeons must quickly and accurately locate these blood vessels. Typically, this is done by using ultrasound to identify blood vessels beneath the skin. However, AR offers a novel solution by overlaying patient scans on the patient's body and viewing these digital models in registration with the patient's physical anatomy to locate these important vessels. The surgical team performed AR-guided vascular pedunculated flap procedure on six patients and qualitatively reported that the HoloLens demonstrated potential to reduce anesthetic time and morbidity and was more reliable and less time-consuming than the prevailing standard ultrasound approach.

Many companies are seeing the potential for AR technology in the medical industry and developing AR tools for the surgical guidance space. One such company, Stryker, specializes in orthopedics and neurotechnology products. Stryker's services include products specialized for surgical navigation, including their Target Guided Surgery (TGS) navigation platform with AR technology [91]. TGS provides surgeons with AR-based image guidance for Functional Endoscopic Sinus Surgery (FESS). FESS is a minimally-invasive procedure to treat sinusitis by surgically enlarging the sinus drainage pathways [92]. Patients' unique anatomy and pathology require surgeons to plan distinct surgical pathways for each patient case. TGS allows surgeons to overlay the digitally planned, patient-specific surgical pathways onto the endoscopic image in real-time and leads the surgeon's endoscopic instrument along the surgical pathway to the target anatomy using the guidance and alarm system [91]. Ultimately, this AR-guided system is designed and implemented to help surgeons perform more accurate minimally-invasive surgeries.

As AR technology evolves, we will continue to see innovation and progress in the intraoperative guidance space. Already, AR's application to this field offers exciting possibilities, such as the simplification or increased accuracy of procedures that could result in improved clinical outcomes. It may not be implausible that in the future, AR-guided surgical systems will become commonplace in operating rooms across the world.

17.12 Augmented reality/virtual reality as a therapeutic intervention

As seen in the previous two sections, AR and VR can be advantageous educational tools for students and valuable surgical supplementation tools for physicians. However, the role in which AR/VR may become a significant game-changer may lie in its ability to directly cause therapeutic change in patients. There is a rapidly growing body of research supporting the use of AR/VR technology as a therapeutic intervention across a host of health-related problems. Whereas physicians may traditionally reach for pharmacological or psychotherapy interventions to address conditions such as pain, ADHD, or anxiety, there is increasing interest in the role that digital therapeutics such as AR and VR can play in patient health, recovery, and management. Although the precise underlying mechanisms and uses are still being investigated, it is believed that immersive technology's unparalleled ability to engender feelings of presence largely enables its capacity to address mental health issues, treat acute and chronic pain, and assist in motor and sensory rehabilitation. AR/VR technology is being studied as a therapeutic tool for a range of developmental conditions including neurodevelopment disorders like autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) as well as visual system development disorders like amblyopia (lazy-eye). Digital therapeutics for ASD and ADHD address behavioral and cognitive aspects of the disorder, while amblyopia VR therapy works to address and correct underlying motor and sensory pathology.

17.13 Mental health

VR therapy has been used in many ways to address a series of mental and behavioral health problems including anxiety, mood, psychotic, trauma related, substance use, eating, and body image disorders [93]. Most mental health illnesses are multifactorial in nature and influenced by behavioral principals and environment forces. AR/VR is well suited to simulate and control these factors systematically, most often through classical and operant conditioning.

17.13.1 Exposure

Anxiety disorders including simple phobias, social phobia, generalized anxiety and posttraumatic stress are the most frequent mental health problems in the world today with a lifetime prevalence of 20% and a very high economic burden on society [94]. One of the most effective treatments to date for anxiety is exposure therapy [95]. The American Psychological Association (APA) defines exposure therapy as a scientifically proven psychological treatment developed to help patients confront their fears decreasing avoidance to feared objects, situations or activities through desensitization [96]. There are many forms of exposure therapy. *In vivo exposure* refers to the direct interaction with fears in the real world. *Imaginal exposure* refers to the vivid imagining of feared objects or situations. *Interoceptive exposure* refers to provoking physical sensations that are feared, to help patients understand they are harmless sensations. This is often used in panic disorder by using intentional hyperventilation. Today, the APA explicitly lists *virtual reality exposure therapy* (VRET) or *in virtuo exposure* as an evidenced-based form of this therapy for anxiety disorders.

VR was originally applied and found to be efficacious as a treatment in 1995 when Rothbaum and colleagues demonstrated that VR-based exposure therapy could help patients overcome their fear of heights [97]. VRET works like traditional in vivo exposure therapy for a few key reasons. First, VRET has the ability to elicit presence and usually provokes the same psychological and physiological responses as real world stimuli. If a patient is afraid of heights, the same increased heart rate and galvanic skin response is experienced standing on the edge of a virtual building as would be felt on a real building. In short, the brain and body treat the virtual experience (the virtual feared stimuli) as if it is real. VR can be quite useful when in vivo exposure is not practical. For example, it is much more convenient and much less expensive to put patients in a virtual airplane to address a fear of flying than to ask them to make multiple flights. The inconvenience and risk of embarrassment and privacy breaches in doing in vivo experiments can be high. VR also allows a clinician personalized and precise levels of control over feared stimuli, which is not possible in the real world. For example, if a patient fears driving across bridges, then the clinician can alter the height of the bridge, speed of the car, or outside weather in a graded fashion based on level of fear or distress (i.e., a beautiful, clear day with great visibility, or a rainy, windy day with lots of fog). A clinician can help patients develop customized coping skills within a session during the exposure, so the patient does not have to face fears alone. This helps better prepare patients for when they do eventually face their real-life triggers. In addition to adjusting the intensity of the exposure, the frequency can also be modulated. One of the most useful aspects of in virtuo exposure is the ability to replay and practice the exact exposures over and over until habituation or desensitization occurs. Scenarios can be created in the clinicians' offices and practiced in therapy sessions or at home repeatedly as homework. VR devices also have ways of monitoring homework compliance that in vivo exposure lacks.

In the years since Rothbaum's first study, a number of reviews showed that VRET could be a successful form of exposure therapy for several types of phobias, as well as social anxiety disorder [98−103]. The first meta-analysis conducted by Parsons and Rizzo [104] suggested that VRET could reduce anxiety and phobia symptoms and possibly was superior to in vivo therapies. However, a larger follow-up meta-analysis by Carl et al. [105] indicates that VRET is most likely not superior but equal to in vivo exposure therapies across a variety of anxiety disorders with medium and large effect sizes for phobias, social anxiety disorder, Post Traumatic Stress Disorder and panic disorder. Given VRET is efficacious and not inferior to in vivo therapy, it is easier to disseminate, and studies report most patients prefer it over traditional in vivo exposure [106,107] and may experience less drop out [108], VRET may be a more acceptable and palatable therapy than traditional in vivo therapy making it a useful and promising treatment approach.

Among the many methods that have been used to treat PTSD, imaginal exposure therapy is one of the most important and has become the current standard of care for this disorder [109]. Imaginal exposure is part of a protocol called prolonged exposure (PE) developed for PTSD and used by the United States Veterans Administration to treat military veterans with PTSD [110,111]. PE consists of breathing retraining, imaginal exposure, processing of the traumatic material, and in vivo exposure to trauma reminders. The imaginal exposure component involves the repeated imagining and reliving of traumatic events within a therapeutic setting [112]. In 2002, Difede and Hoffman used VRET to treat a survivor of the 9/11 World Trade Center Attack who had developed PTSD and failed to respond to an imaginal-based exposure therapy [113]. Over the course of six sessions, the patient was gradually exposed to a virtual environment in which planes flew overhead, crashed into the World Trade Center, causing explosions and the ultimate collapse of the towers. Upon completion of VRET, this patient reported a reduction in acute PTSD symptoms. This case study was one of the first to report on the use of VRET as a medium for treating PSTD by augmenting imaginal exposure. This case illustrated how VR safely immersed a user in simulations of traumatic environments. The emotional intensity of these virtual events can be carefully controlled by the clinician, allowing for customization of pace and relevance. Additionally, VRET for PTSD allows clinicians to circumvent a common problem in imaginal exposure therapy which occurs when patients become overwhelmed and lose their ability to imagine or remember events due to becoming either over-aroused or sometimes under-engaged due to avoidance. VR thus becomes a prosthetic to the imagination and aids recollection process when needed. The first meta-analysis to examine the efficacy of VRET for PTSD included 13 controlled trials and concluded that it is not inferior to in vivo therapy with sustainable effects even after treatment end [114].

In 2007 Rizzo et al. [112] developed a VR exposure therapy application for combat-related PTSD. The application, called Virtual Iraq/Afghanistan, was designed using feedback from returning Iraq War veterans. Clinical tests of the Virtual Iraq/Afghanistan system demonstrated promising results. Initially, three published case studies reported positive results using this application [115,116], and positive clinical outcomes were observed in the first open clinical trial of

20 active duty patients [117]. Based on these encouraging clinical outcomes using VRET to treat combat-related PTSD, an expanded version of the Virtual Iraq/Afghanistan system was created, called BRAVEMIND. BRAVEMIND was built using the Unity game engine and included the original four environments from Virtual Iraq/Afghanistan, plus 10 additional scenarios including Iraq and Afghanistan cities, a rural Afghan village, a roadway checkpoint, and more. Additional features included weather and time of day controls, different sound options, and a clinical interface. Today, BRAVEMIND is in use in over 100 clinics, veterans' hospitals, and universities [118].

17.13.2 Mindfulness/meditation/relaxation

Exposure therapies are not the only evidenced-based form of mental health treatment for anxiety disorders. Mindfulness-based interventions (MBIs) are also efficacious in numerous studies of anxiety and mood disorders [119]. Mindfulness has its origins in Eastern Buddhism and can be defined as a specific form of attention that focuses on: (1) present moment awareness, (2) a nonjudgmental attitude, and (3) intention [120]. MBIs contain several components including group activities, psychoeducation, reflection, philosophical shifts, and daily practice exercises. Recent meta-analyses indicate that stand-alone daily practice using mindfulness meditation exercises may have similar effects to MBIs without the larger therapeutic framework and have few risks [121]. The daily practice of mindfulness meditation has been associated with improvements in emotional regulation, attention, self-awareness as shown on functional and structural brain imaging [122]. These findings open up the possibility of training and delivering mindfulness daily practices through VR/AR mediums without clinicians' involvement in stand-alone treatments.

Often mindfulness skills are delivered through forms of meditation. Various meta-analyses have also demonstrated the benefits of meditation on mental wellness such as stress and anxiety reduction [123–126]. VR has been suggested as a tool to facilitate meditation and reduction of stress and anxiety by removing outside stimuli and distractions and enabling dynamic environments that can use biofeedback to encourage and reward calm mental and physiological states [127–129]. Although clinicians, psychologists, social workers, and other mainstream health professionals use biofeedback, no systematic reviews have supported its use as an evidenced-based intervention in mental health disorders, leaving the field of biofeedback ripe for innovation and improvement. Multiple groups have examined how VR may be used alongside biofeedback systems to create adaptive meditative experiences that facilitate relaxation. Biofeedback sensors can easily track physiological markers like heart rate, respiration rate, galvanic skin response, and even brain activity in real-time. This information can be fed directly into the VR system and used to alter the virtual environment. In doing so, researchers build feedback loops that may be able to train users to relax more effectively (i.e., reduce heart and respiration rates). The Meditation Chamber [127], the Virtual Meditative Walk [128] and RelaWorld [129] are all examples of technology-guided meditative practices that leverage biometric feedback to create adaptive experiences. The Virtual Meditative Walk uses patient skin conductance to modify the weather in the virtual world. Increased anxiety (measured by increased skin conductance) results in increased virtual fog, while decreased anxiety (measured by decreased skin conductance) causes the fog to clear. In RelaWorld, patients don an HMD and enter a meditative environment that changes based on patients' brainwaves, measured by electroencephalogram (EEG). Increases in concentration, measured by theta-band power, enable virtual levitation, while increases in relaxation measured by alpha-band power increase opacity of the virtual bubble surrounding the user. RelaWorld has been shown to induce deeper levels of relaxation and meditation as compared to a nonVR meditation system, suggesting a role for VR in guided meditation experiences [129].

There are now quite a few healthcare and technology startups that are leveraging this body of research to create VR products targeting the mental health space. Limbix is one example of a company focused on the intersection of healthcare and VR. Limbix's medical-grade VR kit is intended for use in mental health clinics and hospitals and allows clinicians to guide patients through a library of therapeutic VR modules [130]. This library includes programs developed for exposure therapy and mindfulness, among other mental health applications. The exposure therapy modules target common phobias such as driving a car, public speaking, and claustrophobia. Several mindfulness modules encourage patients to concentrate, focus, and relax. Limbix plans to expand their library to include therapeutic content for depression and other mental health disorders.

17.13.3 Social skills training

People with severe mental illnesses (SMI) are notoriously underemployed with only 10%–15% working. However, employment rates can rise to 60% with individualized support leading to decreased distress and increased economic wellbeing. A recent series of RCTs funded by the National Institute of Mental Health demonstrated that VR Job

Interview Training (VR-JIT) in individuals with SMI was efficacious in improving interviewing skills and chances of receiving a job offer within 6 months of training. Patients with autism spectrum, substance abuse, mood disorders as well as schizophrenia and PTSD were included and now the intervention is being studied as an enhancement to a large community-based mental health service provider [131,132]. Mediation analysis suggests VR-JIT as the mechanism of action across various psychiatric diagnoses to help trainees obtain jobs in the community. VR-JIT was developed using recommendations from vocational rehabilitation experts involving role play training, integrating learning principles including repetition, graded degrees of difficulty, and an operant conditioning using reinforcers to create behavior changes.

The DSM defines ASD as "persistent deficits in social communication and social interaction across multiple contexts." These contexts can include social-emotional reciprocity, nonverbal communicative behaviors used for social interaction, or the development and maintenance of relationships. These social impairments can interfere with an individual's ability to build relationships, succeed in a job, and participate in the community [133]. There are several evidence-based interventions for adults with high functioning autism (HFA) that aim to increase functioning by focusing on social skills such as social cognition and social functioning [134]. Overall, previous literature has demonstrated that these interventions can improve social skills and social cognition. However, limitations of these interventions include restricted amount of time available to practice and interact with others and each individual's unique capacity for imagination [135,136]. VR may provide a novel way to provide social skill-targeted interventions, which allow for increased practice time and real-life social interaction. Previous studies have shown that VR can be used by children with ASD as a learning tool [137], to maintain interest [138,139], and monitor eye gaze [140], facilitate learning of pretend play [135], and help correct interpret emotions using avatars [141,142]. Floreo is a digital therapeutics startup that is leveraging VR to teach social and communication skills to individuals with ASD. The Floreo platform includes a library of games and activities that work to address some of the social difficulties experienced by individuals with autism. These games help individuals practice calming techniques, attention, social connection, and skills such as imitating actions, nonverbal communication, and shifting eye gaze during social interactions. Users can also immerse themselves in real-world scenarios to practice specific tasks they may face in everyday life, like crossing a street, navigating the lobby of a movie theater, or going through a TSA checkpoint at the airport. The HMD is powered by a mobile phone, making Floreo accessible and easy-to-use. Additionally, the experience displayed to the child is also mirrored on an external tablet, which allows the supervising adult to watch the child's progress and even guide specific tasks and interactions. In addition to currently being used in schools and therapy practices, the Floreo system is being studied in multiple research studies to examine its efficacy [143].

17.13.4 Cognitive/executive functioning

ADHD is the most common neurodevelopmental disorder [144]. Its hallmark is difficulties with sustained attention, distractibility, impulse control, and hyperactivity [145] and can significantly affect a child's social development and cause difficulties with school performance and employment [146]. The most common treatment for ADHD is medication such as Ritalin and Adderall that decreases impulsivity and increases attention and concentration. Randomized trials of neurofeedback in children with ADHD have had inconsistent results and multiple methodologic limitations [147]. VR behavioral management interventions are now being developed to address some of the difficulties experienced by children with ADHD. For example, VR environments can be designed to help promote focus in children who struggle with sustaining attention and provide children with a space for repeated practice of these skills. These VR environments have been shown to be successful in enhancing attention in children with ADHD [148]. VR has been shown to provide a host of other benefits for children with ADHD as well, including improving time-management skills [149], increasing flexibility, removing distractions, and improving executive function [150]. Overall, VR has been shown to be an effective form of therapy for children with ADHD [150] and could potentially provide a therapeutic alternative to Ritalin and Adderall.

Treatment for neurodegenerative disorders such as Alzheimer's and mild cognitive impairment can be maximized with early detection of navigational impairments. Detecting or quantifying these impairments in the real world is difficult and time-consuming. Virtual environment testing has been shown to be a valid and effective way of assessing navigational performance [151]. To date, no cognitive training within or outside of VR has been documented as efficacious for neurodegenerative disorders, but often these patients are living in sensory deprived environments that lead to worsening cognitive functioning into what is termed "pseudodementia." This type of cognitive impairment can be reversed through treatment of depression using behavioral activation in the form of sensory stimulation. VR has a potential to be applied to pseudodementias and mood disorders that can lead to improvements in executive functioning [152].

17.13.5 Body image/lifestyle behaviors

Paradoxically, VR may help patients better accept and accurately perceive their own bodies in reality. Evidence is mounting that VR helps treat body dissatisfaction and body image inaccuracies and distortions. Exploratory studies have shown that VR may change internal beliefs and cognitions to improve body satisfaction in healthy patients [153,154], patients with eating disorders [155,156], and patients with obesity [103,156,157]. VR helps patients to be aware of distortion in their body image, and to confront and correct these size distortions.

Not only can VR change the way we think about our bodies, but VR has been shown to alter and encourage healthy eating and exercise behaviors. A study by Fox and Bailenson [158] reported the use of VR encouraged exercise in participants. In this study, Fox and Bailenson used photographs to reconstruct 3D virtual representations of participants. Participants watched their virtual selves performing health-related behaviors from a third person point-of-view. For example, participants watched their virtual self gain or lose weight in accordance with physical exercise behaviors. The study not only examined immediate effects of these VR experiences on health, but considered whether effects would persist over time. The study determined observing the virtual self gaining or losing weight in accordance with exercise encourages exercise, and these results persisted for at least 24 hours after leaving the VR experience. Seeing one's virtual self exercise stimulated the individual to engage in exercise behavior. These studies indicate that virtual self-models may be helpful instigators of health behavior change. A large clinical trial with follow-up in patients with bulimia and binge eating disorder showed eating-related cue exposure therapy using VR (VR-CET) reduced desires, anxiety, and maladaptive urges around food and normalized eating patterns. Additionally, abstinence from binge episodes were higher than a traditional CBT approach. These gains and the superiority of the VR-CET over a traditional CBT approach was maintained after 6 months [159,160].

17.14 Pain

There is now a rather substantial body of literature supporting the use of VR to treat both acute and chronic pain. VR has been studied and proven to be a useful distraction therapy for the management of acute pain and distressing medical procedures [161]. Current research on the use of VR for chronic pain relief suggests it may also be efficacious but may only last for minimal lengths of time following VR exposure. Ways to harness the brain's natural neuroplasticity using perceptual illusions for chronic pain is currently being explored and developed. As these technologies continue to permeate the clinical world, we should expect to see a variety of VR applications for pain management and therapy used in hospitals, clinics, and at home for both chronic and acute pain.

17.14.1 Distraction therapy for acute pain

To address excessive pain during medical procedures, clinicians typically turn to pharmacological analgesics. However, novel research by Hoffman and colleagues reported on how VR can be used to reduce pain in a series of now well-cited studies. Hoffman measured the subjective pain ratings of burn victims undergoing wound dressing changes while either using VR or not using VR [162–164]. Patients using VR were placed in SnowWorld, a cool, snowy, virtual environment in which they could throw snowballs at penguins, igloos, and snowmen. Patients in the VR condition reported up to 50% less pain while immersed in SnowWorld during the dressing change procedure as compared to typical treatment without VR in a crossover design [164]. Though these subjective measures alone are compelling, Hoffman and colleagues also conducted functional imaging studies to assess pain-related brain activity in these patients. Using fMRI, Hoffman demonstrated that pain-related brain activity was significantly reduced for patients using VR [165]. These results strongly suggested a role for VR in pain management.

By putting on an HMD and entering a virtual world, patients are effectively removed from their physical bodies and therefore their bodily pain. But what exactly are the mechanisms underlying this distraction effect? Hoffman suggests VR distraction therapy works on the brain's attention system. Perceiving pain requires one to direct attention towards the pain. When placed in an immersive and interactive VR world, attention is refocused away from the pain and towards the VR experience. Therefore a patient in a VR environment has less attention available to process incoming pain signals, resulting in decreased reports of pain [166].

Since Hoffman's pioneering studies, VR has been investigated for its role in pain management of other diseases, disorders, and procedures. VR distraction therapy has been shown to be efficacious for reducing acute pain during various medical procedures in randomized controlled trials including labor contractions, episiotomy repair, dental procedures and burn-related wound debridement and mobilization of joints [161]. A review by Garrett et al. [167] examined 17 research studies for evidence of VR therapy in short- and long-term benefit of pain management. The review found strong evidence for the short-term effects of VR therapy on physical function but found little evidence for long-term benefits. Importantly, the study found no significant adverse effects or safety issues pertaining to VR therapy apart from slight nausea in a small number of patients. Garrett and colleagues suggest that as the cost of newer VR technologies decreases and accessibility increases, there is a great potential from more widespread public use of VR pain therapies, which should support clinicians to further investigate, validate, and implement VR for pain management.

Firsthand Technology is the company that helped create SnowWorld, the virtual environment used by Hoffman and colleagues in the early VR pain management studies. Firsthand Technology has continued to harness the extensive VR pain research to create tools for clinical institutions. Their product, Cool! can be described as the next-generation SnowWorld and is targeted at patients undergoing painful and anxiety-inducing medical procedures. Using a VR headset, patients shift their focus toward the virtual environment in which they can play paintball with otters and explore vivid environments like caves and streams. In a clinical study of 30 participants, Cool! was found to reduce pain from presession to postsession by 33% in patients with chronic pain [168].

17.14.2 Chronic pain

Although initial VR pain research focused on acute and procedural pain, there is increasing interest in using VR to target chronic pain as well, especially given the current overuse of opiates and its consequences. Because of the nature of some chronic pain conditions, VR treatment may not only work as a distraction therapy, but as a method of inducing permanent neuroplastic changes in the brain. Phantom limb pain (PLP) is an example and is thought to be the result of sensorimotor changes in the brain [169]. PLP is the sensation of pain in a limb that is commonly experienced after limb amputation. Standard treatments to reduce PLP include both pharmacological and nonpharmacological therapies. One nonpharmacological treatment option is mirror visual feedback (MVF) or mirror box therapy, which was first outlined by Ramachandran and Rogers-Ramachandran in 1996 [170]. In traditional MVF, patients view their own nonamputated limb in a mirror, reflecting in such a way to cause the illusion that their amputated limb is restored and moving. As patients move and see movement in their amputated limb, they receive visual feedback contrary to the lack of sensory feedback in response to movement. Neuroimaging studies support the hypothesis that this incongruence in visual feedback promotes neuroplasticity and a reorganization of the circuitry within the somatosensory cortex, resulting in a reduction of the sense of pain [171].

MVF is an illusion delivered with mirrors and a box that uses visual input to trick the brain into believing that the affected limb is once again present and can therefore be manipulated. VR is arguably a more immersive and convincing way to deliver the same illusion. In a virtual world, the user can be placed into and embody an entire virtual avatar rather than just a limb. This avatar can be fully functional, regardless of the user's physical functionality. In short, a patient with a missing arm can enter a virtual world in a virtual body, look down, and see himself in a body with two fully functional arms. This form of virtual MVF is beneficial for several reasons. First, because of what is known regarding VR's ability to induce presence, VR can create a truly convincing illusion of the amputated limb, perhaps more convincing than a traditional mirror box can. Additionally, VR allows patients to perform tasks that are impossible with a mirror box, such as playing a game of catch. Because of these benefits, several groups have worked to translate MVF into VR for several types of pain that involve maladaptive disuse syndromes.

Research groups are striving to recreate MVF in VR using several different techniques. Murray and colleagues [172] built a virtual environment most similar to traditional MVF, in which movements from the patient's healthy limb were transposed onto the phantom limb in the virtual world. Therefore when the patient moved their healthy limb, they saw a virtual representation of their amputated limb move in the virtual world. Murray conducted a study with five amputees and found some reduction of pain over a 2.5-month period. In 2009 Cole and colleagues [173] developed a VR application that, rather than transposing motion data from the healthy limb to the phantom limb, used motion data captured directly from a patient's stump to create movement of the virtual phantom limb. Cole argued that the use of the motion-controlled avatar returned a sense of agency to the patient, and that this agency led to pain reduction. Patients reported reductions in PLP that were greater than expected for distraction alone. A case study by Chau et al. [174] investigated the use of VR therapy for the treatment of PLP in a patient who had unsuccessfully tried traditional MVF and pharmacological treatment. Chau and colleagues designed a VR kitchen with interactive elements such as pots and pans that the patient would interact with. By holding one controller with his nonamputated hand and strapping the second controller to his stump, the patient was able to see two hands appear in the virtual world. Using his virtual hands, the patient was able to interact with the virtual kitchen. After five VR sessions, the patient noted a significant decrease in pain that lasted several days. Chau and colleagues concluded that while marked improvement was seen in this case study, additional research must be done to validate these findings and establish a protocol for a wider range of patients. Of the various hypotheses regarding how VR contributes to pain management of PLP, beneficial neuroplasticity remains one of high interest.

Similar concepts have been applied to chronic pain conditions outside of PLP, including complex regional pain syndrome (CRPS). In 2015, Won et al. [175] described two pilot studies testing the use of VR therapy for pediatric patients with CRPS. Won and colleagues leveraged the capability of VR technology to change the relationship between the participant's actions in the physical world and the corresponding perceived actions in the virtual world. This concept stems from Lanier's concept of homuncular flexibility: that people can quickly learn to inhabit virtual bodies very different from their own [176]. Won proposed building on these ideas to develop a VR therapeutic experience for patients with CRPS. In the study, Won manipulated the relationship between the physical body and the virtual body in two separate ways. First, gain and dampening factors were applied to participant's virtual movements so that a small movement of the physical legs resulted in a large movement of the virtual legs, and a large movement of the physical arms resulted in a small movement of the virtual arms. Second, control over virtual arms and legs were swapped, so that movement of the physical arms resulted in movement of the virtual legs, and vice versa. Participants were asked to complete a balloon popping task, in which they used their virtual arms and legs to pop virtual balloons that appeared randomly in front of them. The results of the pilot study showed that participants complained of pain less and moved their affected limb more during the VR condition as compared to standard physical therapy sessions [175]. Won goes on to suggest that the flexibility of VR may suggest a new path forward for treating chronic pain.

Although there currently seems to be a greater number of VR companies focused on managing acute pain, a handful of startups are leveraging the research behind VR MVF and homuncular flexibility to deliver treatment for chronic and neuropathic pain. Karuna is an example of a therapeutic VR startup focused on this space. Karuna develops immersive environments and exercises to deliver chronic pain treatment due to CRPS, PLP, stroke-related pain and fibromyalgia, among others [177]. Similar to the examples described above, patients don VR headsets and interact with a series of environments designed to create an illusion of pain-free or reduced-pain movements. One such example is the "bubble-touch" game, in which patients reach out to touch and grab bubbles floating in front of them (Fig. 17.16). Research into the effects of VR MVF therapy is still ongoing, but if shown to be effective may have significant implications for the treatment of chronic pain.

17.15 Rehabilitation

Medical rehabilitation is another therapeutic field that is poised to benefit from VR technology. Therapeutic VR applications have already been developed to rehabilitate patients suffering from stroke, traumatic brain injury, cerebral palsy, and more. The scientific rationale supporting the use of VR in rehabilitation includes concepts of repetition, feedback, and motivation. Holden [178] describes how repetition and practice are important for the motor learning component of rehabilitation. Additionally, patients must receive some form of feedback about the success of these repetitions, typically in the form of visual or proprioceptive cues. And finally, participants must be motivated to practice movements again and again. VR is a powerful medium which easily provides participants with the elements of repetitive practice, performance feedback, and motivation necessary to support rehabilitation.

Many groups are investigating the impact of VR therapies on stroke rehabilitation. Holden and colleagues [179] were the first group to report on the use of VR to rehabilitate motor performance in stroke patients. Their rehabilitative

FIGURE 17.16 Chronic Pain.

training system trained the patient in a wide variety of arm movements to overcome stroke-induce deficits. The patient practiced specific activities within the context of a VR scene, such as placing a letter in a mailbox. Motion trackers captured the accuracy of the patient's movements, and provided feedback based on an ideal trajectory. Results from the initial study indicated that participants could transfer what they learned in VR to the real world as well as generalize their motor learning to other tasks [178]. A second series of studies provided further evidence that patients with stroke can generalize movements trained in VR to similar, yet untrained tasks in the real world [180,181]. These findings are important because they suggest that any rehabilitative benefit gained in the virtual world may result in rehabilitative benefit in the real world. These findings also demonstrate potential efficiencies in the delivery of physical and occupational therapies. Although VR and interactive video gaming have started to emerge as prevalent stroke rehabilitation approaches, a meta-analysis by Laver et al. [182] which included 72 trials and 2470 participants concluded that the use of VR and video games was not more beneficial than conventional therapy in improving upper limb function. However, VR may be beneficial in improving upper limb function when used in addition to conventional therapy, as this increases overall therapy time. A recent meta-analysis appears to support similar findings in lower limb function as well [183].

Similarly, Merians et al. [184] reported on three case studies examining the effects of VR therapy on patients with stroke. Their VR system was constructed of two hand input devices, including a CyberGlove and the Rutgers Master II-ND force feedback glove prototype, integrated with a computer that displayed 3D graphics. Patients performed four hand exercises within the context of a computer game designed to target aspects of hand movement including range of motion, speed of motion, individual finger motion, and strengthening of the fingers. Merians and colleagues found that each of three patients showed improvement following VR-based training and suggest that this success is due to VR's ability to create interactive, motivating environments that allow for practice and feedback. Merians suggests that the full potential of rehabilitative VR therapy will be achieved when it is used by patients in the home or tele-rehabilitation setting in addition to the clinical setting.

VR rehabilitation has been examined as a therapeutic in a variety of other disorders. Early studies examining the use of VR as a rehabilitative tool for cerebral palsy in children have produced mixed results [185,186], although there is some evidence in support of VR rehabilitation intervention for improving balance and motor skills. Rose et al. [187] describe the role of VR as a rehabilitation took for specific impairments resulting from brain injury. Specifically, Rose suggests how VR can be used to test for and treat executive dysfunction, memory impairments, attention deficits, and spatial ability impairments. Lange et al. [188] argue that VR rehabilitation tools have the potential to deliver groundbreaking therapies, but low-cost methods for tracking movement are needed. To promote accessibility and increase use, more affordable home-based systems are needed. Newer VR technologies such as the stand-alone Oculus Quest are bringing us closer to this goal.

Neuro Rehab VR is an example of a company that designs and creates VR exercises targeted for patients with traumatic brain injuries, spinal cord injuries, stroke, and more. Their VR exercises are designed alongside doctors and physical therapists and are customized for each patient's specific needs. By measuring and tracking movement, the Neuro Rehab VR platform is capable of quantifying progress. The Neuro Rehab VR system is used in hospitals, physical therapy centers, neurological rehabilitation facilities, and senior care living centers. The team is also currently working on developing an at-home solution to allow patients to continue their VR therapy remotely [189].

17.15.1 Amblyopia (Lazy-eye)

Amblyopia is a developmental disorder characterized by a decrease in one eye's visual acuity that leads to a mismatch between the images perceived with eye [190]. Today's gold standard in amblyopia treatment is penalizing therapy: patching or blurring vision of the good eye to bring the visual acuity of each eye to similar levels. However, newer therapies being developed, such as dichoptic visual training, don't require eye patching. Dichoptic visual training works by delivering simultaneous and separate stimuli to both eyes to bring the good eye into balance with the amblyopic eye [191]. VR is one tool being investigated for this purpose.

Vivid Vision and Luminopia are two companies using VR to treat amblyopia. Because VR technology features binocular visual input, or the delivery of two separate images to each eye to create depth perception, this technology is primed to administer dichoptic visual training. By placing patients in a virtual world inside an HMD, clinicians can decrease the signal strength of the image in the strong eye and increase the signal strength of the image in the weak eye, making it easier for the two eyes to work together. Currently, the Vivid Vision team is validating their VR product as an amblyopia intervention. Preliminary evidence shows that dichoptic training using Vivid Vision's VR product is an effective treatment option for adults with amblyopia [192]. Vivid Vision plans to build on this research to continue developing their product, which they are positioning as an adjunct treatment for amblyopia, strabismus, and vergence disorders.

17.16 Future directions

This chapter has explored some of the many uses of VR and AR technologies in medicine. As technology continues to progress and cost continues to decrease, we expect to see AR/VR technologies become more accessible to healthcare providers and patients. These technologies will continue to be studied in the academic world, but we will increasingly see their adoption in hospitals, clinics, schools, and even at home. This adoption will be enabled by the release of newer, more portable stand-alone HMDs such as the Oculus Quest and Vive Focus. As these consumer products become more accessible, we will likely see increased interest in VR development from students and other individuals who had no previous way to access the technology. And, as an increasing number of digital therapeutics look for FDA approval and additional real-world data is collected, it will become more likely that AR/VR therapies will be reimbursed by insurance companies or become part of standard workflows to further increase access. VR and AR are poised to make a lasting impact on the medical world.

References

[1] W.J. Greenleaf, Medical applications of virtual reality [white paper], February 2004, (cited 30.04.2019). Available from: <http://bme2.aut.ac.ir/~towhidkhah/MI/Discussion86-1/VR%2520Med%2520overview.pdf>.

[2] J.M. Loomis, Distal attribution and presence, Presence: Teleoper Virtual Environ. 1 (1) (1992) 113−119.

[3] R.T. Azuma, A survey of augmented reality, Presence: Teleoper Virtual Environ. 6 (4) (1997) 355−385.

[4] C. Cruz-Neira, D.J. Sandin, T.A. DeFanti, Surround-screen projection-based virtual reality: the design and implementation of the CAVE, in: Proceedings of the 20th Annual Conference On Computer Graphics and Interactive Techniques 1993, pp. 135−142.

[5] L.W. Barsalou, Grounded cognition, Annu. Rev. Psychol. 59 (2008) 617−645.

[6] G.L. Wells, R.E. Petty, The effects of over head movements on persuasion: compatibility and incompatibility of responses, Basic. Appl. Soc. Psychol. 1 (3) (1980) 219−230.

[7] S. Stepper, F. Strack, Proprioceptive determinants of emotional and nonemotional feelings, J. Personality Soc. Psychol. 64 (2) (1993) 211.

[8] L.E. Thomas, A. Lleras, Swinging into thought: directed movement guides insight in problem solving, Psychonomic Bull. Rev. 16 (4) (2009) 719−723.

[9] C. Kontra, D.J. Lyons, S.M. Fischer, S.L. Beilock, Physical experience enhances science learning, Psychol Sci. 26 (6) (2015) 737−749.

[10] Y.A. Jimenez, S. Cumming, W. Wang, K. Stuart, D.I. Thwaites, S.J. Lewis, Patient education using virtual reality increases knowledge and positive experience for breast cancer patients undergoing radiation therapy, Supportive Care Cancer 26 (8) (2018) 2879−2888.

[11] A.G. Thompson-Butel, C.T. Shiner, J. McGhee, B.J. Bailey, P. Bou-Haidar, M. McCorriston, et al., The role of personalized virtual reality in education for patients post stroke—a qualitative case series, J. Stroke Cerebrovasc. Dis. 28 (2) (2019) 450−457.

[12] D. Peter, P. Robinson, M. Jordan, S. Lawrence, K. Casey, D. Salas-Lopez, Reducing readmissions using teach-back: enhancing patient and family education, JONA: J. Nurs. Adm. 45 (1) (2015) 35−42.

[13] R.S. Yoon, K.W. Nellans, J.A. Geller, A.D. Kim, M.R. Jacobs, W. Macaulay, Patient education before hip or knee arthroplasty lowers length of stay, J. Arthroplasty 25 (4) (2010) 547−551.

[14] The new standard in patient engagement, in: HealthVoyager. Available from: <https://www.healthvoyager.com/>, (accessed 28.06.2019).

[15] J. Sulé-Suso, S. Finney, J. Bisson, S. Hammersley, S. Jassel, R. Knight, et al., Pilot study on virtual imaging for patient information on radiotherapy planning and delivery, Radiography 21 (3) (2015) 273−277.

[16] Y.A. Jimenez, W. Wang, K. Stuart, S. Cumming, D. Thwaites, S. Lewis, Breast cancer patients' perceptions of a virtual learning environment for pretreatment education, J. Cancer Educ. 33 (5) (2018) 983−990.

[17] A. Stewart-Lord, M. Brown, S. Noor, J. Cook, O. Jallow, The utilisation of virtual images in patient information giving sessions for prostate cancer patients prior to radiotherapy, Radiography 22 (4) (2016) 269−273.

[18] G. Kovacs, R. Levitan, R. Sandeski, Clinical cadavers as a simulation resource for procedural learning, AEM Educ. Train. 2 (3) (2018) 239−247.

[19] F. Curnier, Teaching dentistry by means of virtual reality-the Geneva project, Int. J. Comput Dent. 13 (3) (2010) 251−263.

[20] S.A. Seixas-Mikelus, A. Adal, T. Kesavadas, A. Baheti, G. Srimathveeravalli, A. Hussain, et al., Can image-based virtual reality help teach anatomy? J. Endourol 24 (4) (2010) 629−634.

[21] R.G. Thomas, N. William John, J.M. Delieu, Augmented reality for anatomical education, J. Vis. Commun. Med. 33 (1) (2010) 6−15.

[22] Z. Khot, K. Quinlan, G.R. Norman, B. Wainman, The relative effectiveness of computer-based and traditional resources for education in anatomy, Anat. Sci. Educ. 6 (4) (2013) 211−215.

[23] J.W. de Faria, M.J. Teixeira, L.D. Júnior, J.P. Otoch, E.G. Figueiredo, Virtual and stereoscopic anatomy: when virtual reality meets medical education, J. Neurosurg. 125 (5) (2016) 1105−1111.

[24] J. Ferrer-Torregrosa, M.Á. Jiménez-Rodríguez, J. Torralba-Estelles, F. Garzón-Farinós, M. Pérez-Bermejo, N. Fernández-Ehrling, Distance learning ects and flipped classroom in the anatomy learning: comparative study of the use of augmented reality, video and notes, BMC Med. Educ. 16 (1) (2016) 230.

[25] D.C. Peterson, G.S. Mlynarczyk, Analysis of traditional versus three-dimensional augmented curriculum on anatomical learning outcome measures, Anat. Sci. Educ. 9 (6) (2016) 529−536.

[26] C. Moro, Z. Štromberga, A. Raikos, A. Stirling, The effectiveness of virtual and augmented reality in health sciences and medical anatomy, Anat. Sci. Educ. 10 (6) (2017) 549−559.

[27] R. Ramlogan, A.U. Niazi, R. Jin, J. Johnson, V.W. Chan, A. Perlas, A virtual reality simulation model of spinal ultrasound: role in teaching spinal sonoanatomy, Regional Anesthesia Pain Med. 42 (2) (2017) 217−222.

[28] P. Fallavollita, N. Navab, Augmented reality in aging and medical education, Mixed and Augmented Reality in Medicine, CRC Press, 2018, pp. 127−134.

[29] D. Kugelmann, L. Stratmann, N. Nühlen, F. Bork, S. Hoffmann, G. Samarbarksh, et al., An augmented reality magic mirror as additive teaching device for gross anatomy, Ann. Anat.-Anatomischer Anz. 215 (2018) 71−77.

[30] A.M. Codd, B. Choudhury, Virtual reality anatomy: Is it comparable with traditional methods in the teaching of human forearm musculoskeletal anatomy? Anat. Sci. Educ. 4 (3) (2011) 119−125.

[31] Business Wire, Human anatomy atlas app now features augmented reality for AR-ready iPhones and iPads [press release], 12 September 2017 (cited 30.07.2019). Available from: <https://www.businesswire.com/news/home/20170912006745/en/Human-Anatomy-Atlas-App-Features-Augmented-Reality>.

[32] C. O'Brien, 3D4Medical's software being used by 'top US medical schools'. The Irish Times [newspaper on the Internet], 15 September 2016 (cited 30.07.2019); Business:[about 1 p.]. Available from: <https://www.irishtimes.com/business/technology/3d4medical-s-software-being-used-by-top-us-medical-schools-1.2789879>.

[33] Complete Anatomy, Advanced 3D anatomy platform, in: 3d4medical. Available from: <https://3d4medical.com/>, (accessed 28.06.2019).

[34] M. Laal, M. Laal, Z.K. Kermanshahi, 21st century learning; learning in collaboration, Proc-Social Behav. Sci. 47 (2012) 1696−1701.

[35] W.C. McGaghie, S.B. Issenberg, E.R. Petrusa, R.J. Scalese, A critical review of simulation-based medical education research: 2003−2009, Med. Educ. 44 (1) (2010) 50−63.

[36] J.M. Weller, Simulation in undergraduate medical education: bridging the gap between theory and practice, Med. Educ. 38 (1) (2004) 32−38.

[37] P.J. Morgan, D. Cleave-Hogg, Simulation technology in training students, residents and faculty, Curr Opin Anesthesiol. 18 (2) (2005) 199−203.

[38] B. Zendejas, R. Brydges, A.T. Wang, D.A. Cook, Patient outcomes in simulation-based medical education: a systematic review, J. Gen. Intern. Med. 28 (8) (2013) 1078−1089.

[39] M.C. Pian-Smith, R. Simon, R.D. Minehart, M. Podraza, J. Rudolph, T. Walzer, et al., Teaching residents the two-challenge rule: a simulation-based approach to improve education and patient safety, Simul. Healthcare 4 (2) (2009) 84−91.

[40] P.J. O'Connor, J.M. Sperl-Hillen, P.E. Johnson, W.A. Rush, S.E. Asche, P. Dutta, et al., Simulated physician learning intervention to improve safety and quality of diabetes care: a randomized trial, Diabetes Care 32 (4) (2009) 585−590.

[41] R. Morrow, J. Fletcher, M. Mulvihill, H. Park, The asthma dialogues: a model of interactive education for skills, J. Continuing Educ. Health Prof. 27 (1) (2007) 49−58.

[42] T.P. Grantcharov, L. Bardram, P. Funch-Jensen, J. Rosenberg, Learning curves and impact of previous operative experience on performance on a virtual reality simulator to test laparoscopic surgical skills, Am. J. Surg. 185 (2) (2003) 146−149.

[43] T.P. Grantcharov, V.B. Kristiansen, J. Bendix, L. Bardram, J. Rosenberg, P. Funch-Jensen, Randomized clinical trial of virtual reality simulation for laparoscopic skills training, Br. J. Surg. 91 (2) (2004) 146−150.

[44] R. Aggarwal, T. Grantcharov, K. Moorthy, J. Hance, A. Darzi, A competency-based virtual reality training curriculum for the acquisition of laparoscopic psychomotor skill, Am. J. Surg. 191 (1) (2006) 128−133.

[45] P.K. Plinkert, I. Baumann, E. Flemming, H. Loewenheim, G.F. Buess, The use of a vibrotactile sensor as an artificial sense of touch for tissues of the head and neck, Minim. Invasive Ther. Allied Technol. 7 (2) (1998) 111−115.

[46] P. Ström, L. Hedman, L. Särnå, A. Kjellin, T. Wredmark, L. Felländer-Tsai, Early exposure to haptic feedback enhances performance in surgical simulator training: a prospective randomized crossover study in surgical residents, Surg Endosc Other Interventional Tech. 20 (9) (2006) 1383−1388.

[47] L. Panait, E. Akkary, R.L. Bell, K.E. Roberts, S.J. Dudrick, A.J. Duffy, The role of haptic feedback in laparoscopic simulation training, J. Surg Res. 156 (2) (2009) 312−316.

[48] M. Zhou, S. Tse, A. Derevianko, D.B. Jones, S.D. Schwaitzberg, C.G. Cao, Effect of haptic feedback in laparoscopic surgery skill acquisition, Surg Endosc 26 (4) (2012) 1128−1134.

[49] M. Hirose, D. Schmalstieg, C.A. Wingrave, K. Nishimura, Higher levels of immersion improve procedure memorization performance, in: Proceedings of the 15th Joint Virtual Reality Eurographics Conference on Virtual Environments 2009, pp. 121−128.

[50] R. Coulter, L. Saland, T. Caudell, T.E. Goldsmith, D. Alverson, The effect of degree of immersion upon learning performance in virtual reality simulations for medical education, InMedicine Meets Virtual Real. 15 (2007) 155.

[51] J. Forsslund, E.L. Sallnas, K.J. Palmerius, A user-centered designed FOSS implementation of bone surgery simulations, in: World Haptics 2009-Third Joint EuroHaptics Conference and Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, IEEE, 18 March 2009, pp. 391−392.

[52] A. Alaraj, C.J. Luciano, D.P. Bailey, A. Elsenousi, B.Z. Roitberg, A. Bernardo, et al., Virtual reality cerebral aneurysm clipping simulation with real-time haptic feedback, Operative Neurosurg. 11 (1) (2015) 52−58.

[53] A.E. Mostafa, W.H. Ryu, S. Chan, K. Takashima, G. Kopp, M. Costa Sousa, et al., Designing NeuroSimVR: a stereoscopic virtual reality spine surgery simulator, Science (2017).

[54] The Osso Story—Osso VR, in: Osso VR. Available from: <https://ossovr.com/the-osso-story/>, (accessed 28.06.2019).

[55] F.J. Real, D. DeBlasio, A.F. Beck, N.J. Ollberding, D. Davis, B. Cruse, et al., A virtual reality curriculum for pediatric residents decreases rates of influenza vaccine refusal, Acad Pediatr 17 (4) (2017) 431−435.

[56] S.M. Burke, Cultivating critical thinking using virtual interactive case studies, J. Pediatr Nurs. 33 (2017) 94−96.

[57] C.M. Harrington, D.O. Kavanagh, J.F. Quinlan, D. Ryan, P. Dicker, D. O'Keeffe, et al., Development and evaluation of a trauma decision-making simulator in Oculus virtual reality, Am. J. Surg. 215 (1) (2018) 42−47.

[58] P.L. Ingrassia, L. Ragazzoni, L. Carenzo, D. Colombo, A.R. Gallardo, F.D. Corte, et al., Virtual reality and live simulation: a comparison between two simulation tools for assessing mass casualty triage skills, Eur. J. Emerg. Med. 22 (2) (2015) 121−127.

[59] C.L. Foronda, K. Shubeck, S.M. Swoboda, K.W. Hudson, C. Budhathoki, N. Sullivan, et al., Impact of virtual simulation to teach concepts of disaster triage, Clin. Simul. Nurs. 12 (4) (2016) 137−144.

[60] M.F. Price, D.E. Tortosa, A.N. Fernandez-Pacheco, N.P. Alonso, J.J. Madrigal, R. Melendreras-Ruiz, et al., Comparative study of a simulated incident with multiple victims and immersive virtual reality, Nurse Educ. Today 71 (2018) 48−53.

[61] D.S. Vincent, A. Sherstyuk, L. Burgess, K.K. Connolly, Teaching mass casualty triage skills using immersive three-dimensional virtual reality, Acad Emerg. Med. 15 (11) (2008) 1160−1165.

[62] Oxford Medical Simulation-Virtual Reality Healthcare Training, in: Oxford Medical simulation. Available from: <https://oxfordmedicalsimulation.com/>, (accessed 28.06.2019).

[63] F. Herrera, J. Bailenson, E. Weisz, E. Ogle, J. Zaki, Building long-term empathy: a large-scale comparison of traditional and virtual reality perspective-taking, PLoS One 13 (10) (2018) e0204494.

[64] J. Ogle, J.A. Bushnell, P. Caputi, Empathy is related to clinical competence in medical care, Med. Educ. 47 (8) (2013) 824−831.

[65] R. Zachariae, C.G. Pedersen, A.B. Jensen, E. Ehrnrooth, P.B. Rossen, H. von der Maase, Association of perceived physician communication style with patient satisfaction, distress, cancer-related self-efficacy, and perceived control over the disease, Br. J. Cancer 88 (5) (2003) 658−665.

[66] S.S. Kim, S. Kaplowitz, M.V. Johnston, The effects of physician empathy on patient satisfaction and compliance, Eval Health Prof. 27 (3) (2004) 237−251.

[67] E. Vermeire, H. Hearnshaw, P. Van Royen, J. Denekens, Patient adherence to treatment: three decades of research. A comprehensive review, J. Clin. Pharm. Therapeutics 26 (5) (2001) 331−342.

[68] M. Hojat, D.Z. Louis, F.W. Markham, R. Wender, C. Rabinowitz, J.S. Gonnella, Physicians' empathy and clinical outcomes for diabetic patients, Acad Med. 86 (3) (2011) 359−364.

[69] Z. Di Blasi, E. Harkness, E. Ernst, A. Georgiou, J. Kleijnen, Influence of context effects on health outcomes: a systematic review, Lancet 357 (9258) (2001) 757−762.

[70] D.P. Rakel, T.J. Hoeft, B.P. Barrett, B.A. Chewning, B.M. Craig, M. Niu, Practitioner empathy and the duration of the common cold, Family Med. 41 (7) (2009) 494.

[71] D. Rakel, B. Barrett, Z. Zhang, T. Hoeft, B. Chewning, L. Marchand, et al., Perception of empathy in the therapeutic encounter: effects on the common cold, Patient Educ. Counseling 85 (3) (2011) 390−397.

[72] A. Foster, N. Chaudhary, T. Kim, J.L. Waller, J. Wong, M. Borish, et al., Using virtual patients to teach empathy: a randomized controlled study to enhance medical students' empathic communication, Simul. Healthcare 11 (3) (2016) 181−189.

[73] A. Kleinsmith, D. Rivera-Gutierrez, G. Finney, J. Cendan, B. Lok, Understanding empathy training with virtual patients, Comput Hum. Behav. 52 (2015) 151−158.

[74] Embodied, Labs—Immersive training platform, in: Embodied Labs. Available from: <https://embodiedlabs.com/>, (accessed 28.06.2019).

[75] E. Washington, C. Shaw, The effects of a VR intervention on career interest, empathy, communication skills and learning with 2nd year medical students [white paper]. (cited 15.04.2019). Available from: <https://embodiedlabs.com/how-it-works>.

[76] M. Ros, J.V. Trives, N. Lonjon, From stereoscopic recording to virtual reality headsets: Designing a new way to learn surgery, Neurochirurgie 63 (1) (2017) 1−5.

[77] R.A. Kockro, T. Killeen, A. Ayyad, M. Glaser, A. Stadie, R. Reisch, et al., Aneurysm surgery with preoperative three-dimensional planning in a virtual reality environment: technique and outcome analysis, World Neurosurg. 96 (2016) 489−499.

[78] R. Miller, J. Novotny, H. Laidlaw, F. Luks, D. Merck, S. Collins, Virtually visualizing vessels: a study of the annotation of placental vasculature from mri in large-scale virtual reality for surgical planning. Brown University, Providence, 2016.

[79] B. Juhnke, A. Mattson, D. Saltzman, A. Azakie, E. Hoggard, M. Ambrose, et al., Preparing for conjoined twins separation through virtual reality, in: 2018 Design of Medical Devices Conference, 9 April 2018. American Society of Mechanical Engineers Digital Collection.

[80] Y. Kim, H. Kim, Y.O. Kim, Virtual reality and augmented reality in plastic surgery: a review, Arch. Plastic Surg. 44 (3) (2017) 179.

[81] N.K. Yoon, S. McNally, P. Taussky, M.S. Park, Imaging of cerebral aneurysms: a clinical perspective, Neurovasc Imaging 2 (1) (2016) 1−7.

[82] Bracco Diagnostic Inc, Dextroscope changes the neurosurgical planning paradigm 3D virtual reality system [press release], August 16 2006, (cited 28.06.2019). Available from: <http://www.braccoimaging.com/us-en/dextroscope-changes-neurosurgical-planning-paradigm-3d-virtual-reality-system>.

[83] G.K. Wong, C.X. Zhu, A.T. Ahuja, W.S. Poon, Craniotomy and clipping of intracranial aneurysm in a stereoscopic virtual reality environment, Neurosurgery 61 (3) (2007) 564−569.

[84] Precision VR, VR medical visualization platform, in: <Surgicaltheater.net>. Available from: <http://www.surgicaltheater.net/services/>, (accessed 28.06.2019)

[85] M. Erickson Virtual reality system helps surgeons, reassures patients. Stanford Medicine News Center. [online]. 11 July 2017 (cited 05.05.2019). Available from: <https://med.stanford.edu/news/all-news/2017/07/virtual-reality-system-helps-surgeons-reassures-patients.html>.

[86] Opensight, Augmented reality for surgical applications, in: <Novarad.net>. Available from: <https://www.novarad.net/products/opensight/>, (accessed 28.06.2019).

[87] D. Muoio, UK children's hospital deploying HoloLens, Surface Hubs for surgical teams. MobiHealthNews [online]. 2018 Aug 13 (cited 05.05.2019). Available from: <https://www.mobihealthnews.com/content/uk-childrens-hospital-deploying-hololens-surface-hubs-surgical-teams>.

[88] K. Manke, Brain surgery may get a bit easier, with augmented reality, in: Duke Today [online], October 5 2018, (cited 28.06.2019) Available from: <https://www.today.duke.edu/2016/10/brain-surgery-may-get-bit-easier-augmented-reality>.

[89] Y. Li, X. Chen, N. Wang, W. Zhang, D. Li, L. Zhang, et al., A wearable mixed-reality holographic computer for guiding external ventricular drain insertion at the bedside, J. Neurosurg. 131 (5) (2018) 1599−1606.

[90] P. Pratt, M. Ives, G. Lawton, J. Simmons, N. Radev, L. Spyropoulou, et al., Through the HoloLens™ looking glass: augmented reality for extremity reconstruction surgery using 3D vascular models with perforating vessels, Eur. Radiol. Exp. 2 (1) (2018) 2.

[91] Target guided surgery, in: Stryker. Available from: <https://www.stryker.com/us/en/navigation/products/target-guided-surgery.html/>, (accessed 28.06.2019).

[92] H. Stammberger, W. Posawetz, Functional endoscopic sinus surgery: concepts, indications and results of the Messerklinger technique, Eur. Arch. Otorhinolaryngol. 247 (2) (1990) 63−76.

[93] M.J. Park, D.J. Kim, U. Lee, E.J. Na, H.J. Jeon, A literature overview of virtual reality (VR) in treatment of psychiatric disorders: recent advances and limitations, Front. Psychiatry (2019) 10.

[94] J.M. Somers, E.M. Goldner, P. Waraich, L. Hsu, Prevalence and incidence studies of anxiety disorders: a systematic review of the literature, Can. J. Psychiatry 51 (2) (2006) 100−113.

[95] D.A. Moscovitch, M.M. Antony, R.P. Swinson, Exposure-based treatments for anxiety disorders: theory and process. Oxford handbook of anxiety and related disorders. 2009, pp. 461-475.

[96] PTSD Clinical Practice Guideline: What is exposure therapy?, in: American Psychological Association, 2017. Available from: <https://www-apa-org.stanford.idm.oclc.org/ptsd-guideline/patients-and-families/exposure-therapy.pdf>.

[97] D. Opdyke, J.S. Williford, M. North, Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia, Am. J. Psychiatry 1 (152) (1995) 626−628.

[98] C. Botella, S. Quero, R.M. Baños, C. Perpiñá, A. García-Palacios, G. Riva, Virtual reality and psychotherapy, Cybertherapy 99 (2004) 37−52.

[99] K. Glanz, A.S. Rizzo, K. Graap, Virtual reality for psychotherapy: current reality and future possibilities, Psychother: Theory, Res, Pract Training. 40 (1−2) (2003) 55.

[100] L.F. Hodges, P. Anderson, G.C. Burdea, H.G. Hoffmann, B.O. Rothbaum, Treating psychological and physical disorders with VR, IEEE Comput Graph. Appl. 21 (6) (2001) 25−33.

[101] M. Krijn, P.M. Emmelkamp, R.P. Olafsson, R. Biemond, Virtual reality exposure therapy of anxiety disorders: a review, Clin. Psychol. Rev. 24 (3) (2004) 259−281.

[102] C.B. Pull, Current status of virtual reality exposure therapy in anxiety disorders: editorial review, Curr. Opin. Psychiatry 18 (1) (2005) 7−14.

[103] G. Riva, Virtual reality in psychotherapy, Cyberpsychol Behav. 8 (3) (2005) 220−230.

[104] T.D. Parsons, A.A. Rizzo, Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: a meta-analysis, J. Behav. Ther. Exp. Psychiatry 39 (3) (2008) 250−261.

[105] E. Carl, A.T. Stein, A. Levihn-Coon, J.R. Pogue, B. Rothbaum, P. Emmelkamp, et al., Virtual reality exposure therapy for anxiety and related disorders: a meta-analysis of randomized controlled trials, J. Anxiety Disord. 61 (2019) 27−36.

[106] A. Garcia-Palacios, H.G. Hoffman, S. Kwong See, A.M. Tsai, C. Botella, Redefining therapeutic success with virtual reality exposure therapy, CyberPsychol Behav. 4 (3) (2001) 341−348.

[107] A. Garcia-Palacios, C. Botella, H. Hoffman, S. Fabregat, Comparing acceptance and refusal rates of virtual reality exposure vs. in vivo exposure by patients with specific phobias, Cyberpsychol Behav. 10 (5) (2007) 722−724.

[108] A.A. Benbow, P.L. Anderson, A meta-analytic examination of attrition in virtual reality exposure therapy for anxiety disorders, J. Anxiety Disord. 61 (2019) 18−26.

[109] B.O. Rothbaum, A.C. Schwartz, Exposure therapy for posttraumatic stress disorder, Am. J. Psychother 56 (1) (2002) 59−75.

[110] E. Foa, E. Hembree, B.O. Rothbaum, Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences Therapist Guide, Oxford University Press, 2007.

[111] M.B. Stein, Psychotherapy for posttraumatic stress disorder in adult, in: J.A. Melin (Ed.), UpToDate, 2019. Retrieved August 17, 2019, from <https://www.uptodate.com/contents/psychotherapy-for-posttraumatic-stress-disorder-in-adults>.

[112] A.A. Rizzo, K. Graap, R.N. Mclay, K. Perlman, B.O. Rothbaum, G. Reger, et al., Virtual Iraq: initial case reports from a VR exposure therapy application for combat-related post traumatic stress disorder, 2007 Virtual Rehabilitation, IEEE, 2007, pp. 124−130.

[113] J. Difede, H.G. Hoffman, Virtual reality exposure therapy for World Trade Center post-traumatic stress disorder: a case report, Cyberpsychol Behav. 5 (6) (2002) 529−535.

[114] W. Deng, D. Hu, S. Xu, X. Liu, J. Zhao, Q. Chen, et al., The efficacy of virtual reality exposure therapy for PTSD symptoms: a systematic review and meta-analysis, J. Affect. Disord. 257 (2019) 698−709.

[115] M. Gerardi, B.O. Rothbaum, K. Ressler, M. Heekin, A. Rizzo, Virtual reality exposure therapy using a virtual Iraq: case report, J. Trauma. Stress.: Off. Publ. Int. Soc. Trauma. Stress Stud. 21 (2) (2008) 209−213.

[116] G.M. Reger, G.A. Gahm, Virtual reality exposure therapy for active duty soldiers, J. Clin. Psychol. 64 (8) (2008) 940−946.

[117] A.S. Rizzo, J. Difede, B.O. Rothbaum, G. Reger, J. Spitalnick, J. Cukor, et al., Development and early evaluation of the virtual Iraq/Afghanistan exposure therapy system for combat-related PTSD, Ann. N. Y. Acad. Sci. 1208 (1) (2010) 114−125.

[118] E. Craig, M. Georgieva, VR and AR: Driving a Revolution in Medical Education & Patient Care, EDUCAUSE, Louisville, 2017.

[119] B. Khoury, T. Lecomte, G. Fortin, M. Masse, P. Therien, V. Bouchard, et al., Mindfulness-based therapy: a comprehensive meta-analysis, Clin. Psychol. Rev. 33 (6) (2013) 763−771.

[120] J. Kabat-Zinn, T.N. Hanh, Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness. Delta, July 22 2009.

[121] P. Blanck, S. Perleth, T. Heidenreich, P. Kröger, B. Ditzen, H. Bents, et al., Effects of mindfulness exercises as stand-alone intervention on symptoms of anxiety and depression: systematic review and meta-analysis, Behav. Res. Ther. 102 (2018) 25−35.

[122] K.C. Fox, S. Nijeboer, M.L. Dixon, J.L. Floman, M. Ellamil, S.P. Rumak, et al., Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners, Neurosci. Biobehav. Rev. 43 (2014) 48−73.

[123] M. Goyal, S. Singh, E.M. Sibinga, N.F. Gould, A. Rowland-Seymour, R. Sharma, et al., Meditation programs for psychological stress and well-being: a systematic review and meta-analysis, JAMA Intern. Med. 174 (3) (2014) 357−368.

[124] P. Grossman, L. Niemann, S. Schmidt, H. Walach, Mindfulness-based stress reduction and health benefits: a meta-analysis, J. Psychosom. Res. 57 (1) (2004) 35−43.

[125] A. Chiesa, A. Serretti, Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis, J. Altern Complement Med. 15 (5) (2009) 593−600.

[126] P. Sedlmeier, J. Eberth, M. Schwarz, D. Zimmermann, F. Haarig, S. Jaeger, et al., The psychological effects of meditation: a meta-analysis, Psychol Bull. 138 (6) (2012) 1139.

[127] C. Shaw, D. Gromala, M. Song, The meditation chamber: towards self-modulation, Metaplasticity in Virtual Worlds: Aesthetics and Semantic Concepts, IGI Global, 2011, pp. 121−133.

[128] D. Gromala, X. Tong, A. Choo, M. Karamnejad, C.D. Shaw, The virtual meditative walk: virtual reality therapy for chronic pain management, in: Proceedings of the 33rd Annual ACM Conference on Human Factors in Computing Systems, April 18 2015, pp. 521−524.

[129] I. Kosunen, M. Salminen, S. Järvelä, A. Ruonala, N. Ravaja, G. Jacucci, RelaWorld: neuroadaptive and immersive virtual reality meditation system, in: Proceedings of the 21st International Conference on Intelligent User Interfaces, March 7 2016, pp. 208−217.

[130] Virtual reality for mental health, in: Limbix. Available from: <https://www.limbix.com/>, (accessed 05.07.2019).

[131] M.J. Smith, M.F. Fleming, M.A. Wright, M. Losh, L.B. Humm, D. Olsen, et al., Brief report: vocational outcomes for young adults with autism spectrum disorders at six months after virtual reality job interview training, J. Autism Dev Disord. 45 (10) (2015) 3364−3369.

[132] M.J. Smith, J.D. Smith, M.F. Fleming, N. Jordan, E.A. Oulvey, M.D. Bell, et al., Enhancing individual placement and support (IPS)-supported employment: a Type 1 hybrid design randomized controlled trial to evaluate virtual reality job interview training among adults with severe mental illness, Contemporary Clin. Trials 77 (2019) 86−97.

[133] D.R. Hendricks, P. Wehman, Transition from school to adulthood for youth with autism spectrum disorders: review and recommendations, Focus. Autism Other Dev Disabilities 24 (2) (2009) 77−88.

[134] L. Moxon, D. Gates, Children with autism: supporting the transition to adulthood, Educ. Child. Psychol. 18 (2) (2001) 28−40.

[135] G. Herrera, F. Alcantud, R. Jordan, A. Blanquer, G. Labajo, C. De Pablo, et al., Development of symbolic play through the use of virtual reality tools in children with autistic spectrum disorders: two case studies, Autism 12 (2) (2008) 143−157.

[136] L. Wing, J. Gould, Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification, J. Autism Dev Disord. 9 (1) (1979) 11−29.

[137] D. Strickland, Virtual reality for the treatment of autism, Stud. Health Technol. Inform. (1997) 81−86.

[138] S. Cobb, L. Beardon, R. Eastgate, T. Glover, S. Kerr, H. Neale, et al., Applied virtual environments to support learning of social interaction skills in users with Asperger's syndrome, Digit Creativity 13 (1) (2002) 11−22.

[139] M.L. Max, J.C. Burke, Virtual reality for autism communication and education, with lessons for medical training simulators, Stud. Health Technol. Inform. 39 (1997) 46−53.

[140] U. Lahiri, Z. Warren, N. Sarkar, Design of a gaze-sensitive virtual social interactive system for children with autism, IEEE Trans. Neural Syst. Rehabil Eng. 19 (4) (2011) 443−452.

[141] D. Moore, Y. Cheng, P. McGrath, N.J. Powell, Collaborative virtual environment technology for people with autism, Focus. Autism Other Dev Disabil 20 (4) (2005) 231−243.

[142] Y. Cheng, J. Ye, Exploring the social competence of students with autism spectrum conditions in a collaborative virtual learning environment−the pilot study, Comput Educ. 54 (4) (2010) 1068−1077.

[143] A new world of learning, in: Floreo. Available from: <https://floreotech.com/>, (accessed 05.07.2019).

[144] A.S. Rowland, C.A. Lesesne, A.J. Abramowitz, The epidemiology of attention-deficit/hyperactivity disorder (ADHD): a public health view, Ment. Retardation Dev Disabil Res. Rev. 8 (3) (2002) 162−170.

[145] J. Biederman, Attention-deficit/hyperactivity disorder: a selective overview, Biol. Psychiatry 57 (11) (2005) 1215−1220.

[146] R.A. Barkley, Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder, J. Clin. Psychiatry (2002).

[147] T.S. Moriyama, G. Polanczyk, A. Caye, T. Banaschewski, D. Brandeis, L.A. Rohde, Evidence-based information on the clinical use of neurofeedback for ADHD, Neurotherapeutics. 9 (3) (2012) 588−598.

[148] B.H. Cho, J. Ku, D.P. Jang, S. Kim, Y.H. Lee, I.Y. Kim, et al., The effect of virtual reality cognitive training for attention enhancement, CyberPsychol Behav. 5 (2) (2002) 129−137.

[149] P. Gongsook, Time simulator in virtual reality for children with attention deficit hyperactivity disorder, in: International Conference on Entertainment Computing, September 26 2012, Springer, Berlin, Heidelberg, pp. 490−493.

[150] A. Bashiri, M. Ghazisaeedi, L. Shahmoradi, The opportunities of virtual reality in the rehabilitation of children with attention deficit hyperactivity disorder: a literature review, Korean J. Pediatr 60 (11) (2017) 337.

[151] L.A. Cushman, K. Stein, C.J. Duffy, Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality, Neurology 71 (12) (2008) 888−895.

[152] H. Kang, F. Zhao, L. You, C. Giorgetta, Pseudo-dementia: a neuropsychological review, Ann. Indian. Acad. Neurol. 17 (2) (2014) 147.

[153] G. Riva, L. Melis, Virtual reality for the treatment of body image disturbances, Stud. Health Technol. Inform. (1997) 95−112.

[154] G. Riva, Virtual environment for body image modification: virtual reality system for the treatment of body image disturbances, Comput Hum. Behav. 14 (3) (1998) 477−490.

[155] G. Riva, M. Bacchetta, M. Baruffi, E. Molinari, Virtual-reality-based multidimensional therapy for the treatment of body image disturbances in binge eating disorders: a preliminary controlled study, IEEE Trans. Inf. Technol. Biomed 6 (3) (2002) 224−234.

[156] C. Perpiñá, C. Botella, R. Baños, H. Marco, M. Alcañiz, S. Quero, Body image and virtual reality in eating disorders: is exposure to virtual reality more effective than the classical body image treatment? CyberPsychol Behav. 2 (2) (1999) 149−155.

[157] C.K. Purvis, M. Jones, J.O. Bailey, J. Bailenson, C.B. Taylor, Developing a novel measure of body satisfaction using virtual reality, PLoS One 10 (10) (2015) e0140158.

[158] J. Fox, J.N. Bailenson, Virtual self-modeling: the effects of vicarious reinforcement and identification on exercise behaviors, Media Psychol. 12 (1) (2009) 1−25.

[159] M. Ferrer-García, J. Gutiérrez-Maldonado, J. Pla-Sanjuanelo, F. Vilalta-Abella, G. Riva, M. Clerici, et al., A randomised controlled comparison of second-level treatment approaches for treatment-resistant adults with bulimia nervosa and binge eating disorder: assessing the benefits of virtual reality cue exposure therapy, Eur. Eat. Disord. Rev. 25 (6) (2017) 479−490.

[160] M. Ferrer-Garcia, J. Pla-Sanjuanelo, A. Dakanalis, F. Vilalta-Abella, G. Riva, F. Fernandez-Aranda, et al., A randomized trial of virtual reality-based cue exposure second-level therapy and cognitive behavior second-level therapy for bulimia nervosa and binge-eating disorder: Outcome at six-month followup, Cyberpsychol, Behav, Soc. Netw. 22 (1) (2019) 60−68.

[161] B. Mallari, E.K. Spaeth, H. Goh, B.S. Boyd, Virtual reality as an analgesic for acute and chronic pain in adults: a systematic review and meta-analysis, J. Pain Res. 12 (2019) 2053.

[162] H.G. Hoffman, J.N. Doctor, D.R. Patterson, G.J. Carrougher, T.A. Furness III, Virtual reality as an adjunctive pain control during burn wound care in adolescent patients, Pain 85 (1−2) (2000) 305−309.

[163] H.G. Hoffman, D.R. Patterson, G.J. Carrougher, S.R. Sharar, Effectiveness of virtual reality−based pain control with multiple treatments, Clin. J. Pain 17 (3) (2001) 229−235.

[164] H.G. Hoffman, D.R. Patterson, J. Magula, G.J. Carrougher, K. Zeltzer, S. Dagadakis, et al., Water-friendly virtual reality pain control during wound care, J. Clin. Psychol. 60 (2) (2004) 189−195.

[165] H.G. Hoffman, T.L. Richards, B. Coda, A.R. Bills, D. Blough, A.L. Richards, et al., Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI, Neuroreport 15 (8) (2004) 1245−1248.

[166] H.G. Hoffman, G.T. Chambers, W.J. Meyer III, L.L. Arceneaux, W.J. Russell, E.J. Seibel, et al., Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures, Ann. Behav. Med. 41 (2) (2011) 183−191.

[167] B. Garrett, T. Taverner, W. Masinde, D. Gromala, C. Shaw, M. Negraeff, A rapid evidence assessment of immersive virtual reality as an adjunct therapy in acute pain management in clinical practice, Clin. J. Pain 30 (12) (2014) 1089−1098.

[168] T. Jones, T. Moore, J. Choo, The impact of virtual reality on chronic pain, PLoS One 11 (12) (2016) e0167523.

[169] H. Flor, L. Nikolajsen, T.S. Jensen, Phantom limb pain: a case of maladaptive CNS plasticity? Nat. Rev. Neurosci. 7 (11) (2006) 873−881.

[170] V.S. Ramachandran, D. Rogers-Ramachandran, Synaesthesia in phantom limbs induced with mirrors, Proc. R. Soc. London. Ser. B: Biol. Sci. 263 (1369) (1996) 377−386.

[171] F.J. Deconinck, A.R. Smorenburg, A. Benham, A. Ledebt, M.G. Feltham, G.J. Savelsbergh, Reflections on mirror therapy: a systematic review of the effect of mirror visual feedback on the brain, Neurorehabil Neural Repair 29 (4) (2015) 349−361.

[172] C.D. Murray, S. Pettifer, T. Howard, E.L. Patchick, F. Caillette, J. Kulkarni, et al., The treatment of phantom limb pain using immersive virtual reality: three case studies, Disabil Rehabil 29 (18) (2007) 1465−1469.

[173] J. Cole, S. Crowle, G. Austwick, D. Henderson Slater, Exploratory findings with virtual reality for phantom limb pain; from stump motion to agency and analgesia, Disabil Rehabil 31 (10) (2009) 846−854.

[174] B. Chau, I. Phelan, P. Ta, S. Humbert, J. Hata, D. Tran, Immersive virtual reality therapy with myoelectric control for treatment-resistant phantom limb pain: case report, Innov. Clin. Neurosci. 14 (7−8) (2017) 3.

[175] A.S. Won, C.A. Tataru, C.M. Cojocaru, E.J. Krane, J.N. Bailenson, S. Niswonger, et al., Two virtual reality pilot studies for the treatment of pediatric CRPS, Pain Med. 16 (8) (2015) 1644−1647.

[176] J. Lanier, Homuncular Flexibility, Edge Foundation, Inc, 2006. Available from: < https://www.edge.org/response-detail/111822006 >.

[177] Karuna Labs Virtual Embodiment Training, in: Karunalabs. Available from: <http://karunavr.com/>, (accessed 05.07.2019).

[178] M.K. Holden, Virtual environments for motor rehabilitation, Cyberpsychol Behav. 8 (3) (2005) 187−211.

[179] M. Holden, E. Todorov, J. Callahan, E. Bizzi, Virtual environment training improves motor performance in two patients with stroke: case report, Pre 23 (2) (1999) 57−67.

[180] M.K. Holden, T. Dyar, J. Callahan, L. Schwamm, E. Bizzi, Quantitative assessment of motor generalization in the real world following training in a virtual environment in patients with stroke, Neurol. Rep. 25 (4) (2001) 129−130.

[181] M.K. Holden, T. Dyar, Virtual environment training-a new tool for neurorehabilitation? Neurol. Rep. 26 (2) (2002) 62−71.

[182] K.E. Laver, B. Lange, S. George, J.E. Deutsch, G. Saposnik, M. Crotty, Virtual reality for stroke rehabilitation, Stroke 49 (4) (2018) e160−e161.

[183] H.S. Lee, Y.J. Park, S.W. Park, The effects of virtual reality training on function in chronic stroke patients: a systematic review and meta-analysis, BioMed. Res. Int. 2019 (2019).

[184] A.S. Merians, D. Jack, R. Boian, M. Tremaine, G.C. Burdea, S.V. Adamovich, et al., Virtual reality−augmented rehabilitation for patients following stroke, Phys. Ther. 82 (9) (2002) 898−915.

[185] D. Levac, A. McCormick, M.F. Levin, M. Brien, R. Mills, E. Miller, et al., Active video gaming for children with cerebral palsy: does a clinic-based virtual reality component offer an additive benefit? A pilot study, Phys. Occup. Ther. Pediatr 38 (1) (2018) 74−87.

[186] D.K. Ravi, N. Kumar, P. Singhi, Effectiveness of virtual reality rehabilitation for children and adolescents with cerebral palsy: an updated evidence-based systematic review, Physiotherapy 103 (3) (2017) 245−258.

[187] F.D. Rose, B.M. Brooks, A.A. Rizzo, Virtual reality in brain damage rehabilitation, Cyberpsychol Behav. 8 (3) (2005) 241−262.

[188] B. Lange, S. Koenig, C.Y. Chang, E. McConnell, E. Suma, M. Bolas, et al., Designing informed game-based rehabilitation tasks leveraging advances in virtual reality, Disabil Rehabil 34 (22) (2012) 1863−1870.

[189] Neuro Rehab VR, in: Neuro Rehab VR. Available from: <https://www.neurorehabvr.com/>, (accessed 05.07.2019).

[190] J.M. Holmes, M.P. Clarke, Amblyopia, Lancet 367 (9519) (2006) 1343−1351.

[191] M. Bach, Dichoptic training for amblyopia, Der Ophthalmol 113 (4) (2016) 304−308.

[192] P. Žiak, A. Holm, J. Halička, P. Mojžiš, D.P. Piñero, Amblyopia treatment of adults with dichoptic training using the virtual reality oculus rift head mounted display: preliminary results, BMC Ophthalmol. 17 (1) (2017) 1−8.