20 Basis and Clinical Evidence of Virtual Reality-Based Rehabilitation of Sensorimotor Impairments After Stroke

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Abstract

In the recent years, the use of virtual reality (VR) to enhance motor skills of persons with activity and participation restriction due to disease or injury has become an important area of research and translation to practice. In this chapter, we describe the design of such VR systems and their underlying principles, such as experience-dependent neuroplasticity and motor learning. Further, psychological constructs related to motivation, including salience, goal setting, and rewards are commonly utilized in VR to optimize motivation during rehabilitation activities. Hence, virtually simulated activities are considered to be ideal for [1] the delivery of specific feedback, [2] the ability to perform large volumes of training, and [3] the presentation of precisely calibrated difficulty levels, which maintain a high level of challenge throughout long training sessions. These underlying principles are contrasted with a growing body of research comparing the efficacy of VR with traditionally presented rehabilitation activities in persons with stroke that demonstrate comparable or better outcomes for VR. In addition, a small body of literature has utilized direct assays of neuroplasticity to evaluate the effects of virtual rehabilitation interventions in persons with stroke. Promising developments and findings also arise from the use of off-the-shelf video game systems for virtual rehabilitation purposes and the integration of VR with robots and brain-computer interfaces. Several challenges limiting the translation of virtual rehabilitation into routine rehabilitation practice need to be addressed but the field continues to hold promise to answer key issues faced by modern healthcare.

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20.1 Principles of Virtual Reality in Stroke Sensorimotor Neurorehabilitation

Virtual reality (VR) is an approach to user-computer interface that involves real-time simulation of an environment, scenario, or activity that allows for user interaction via multiple sensory channels [1]. VR is created by using hardware and software (virtual environments- VEs) that allow users to interact with objects and events that appear and sound, and in some cases feel, like those in the real world [2]. VR is used in a rehabilitation context as an approach to improve the sensorimotor and cognitive ability of persons with body function structure, activity, and participation limitations through the use of interactions with VEs [3].

VR aims to substitute the real-world sensations with computer-generated sensory information and to facilitate natural interaction with the virtual world. These characteristics modulate immersion, which is related to the multimodal nature of the perceptual senses. In this chapter, we address how VEs leverage aspects such as immersion and presence to describe the quality of the VE and the user's experience. Further, experience-dependent neuroplasticity and motor learning serve as the basis for modern approaches to the rehabilitation of persons with neurologic dysfunction and inform the design of many virtual rehabilitation systems. Brief orientations to these concepts and examples of virtual rehabilitation applications incorporating them will begin this chapter (Sects. 20.1.1 and 20.1.2). Motivation drives several key attributes of behavior consistent with motor learning, including salience, attention, and repetition. The psychology of motivation as it relates to participation in simulated activities will follow in Sect. 20.1.3, and its importance related to the future of virtual rehabilitation will be underscored in the conclusion section. Sect. 20.2 reviews the literature describing the role of interfaces and sensory presentations in virtual rehabilitation and their impact on the user experience. Sects. 20.1 and 20.2 can be used by the reader to inform the design or refinement of newer technology-based rehabilitation systems, virtually simulated or otherwise. A review of studies examining the efficacy of a wide variety of virtual rehabilitation systems applied to sensorimotor rehabilitation of persons with stroke will complete the chapter. A majority of these studies compare the relative efficacy of virtual rehabilitation to traditional rehabilitation. This type of evidence can be used to evaluate current approaches to virtual rehabilitation and justify further study. The conclusion section that follows will identify several possible next steps for the efficacy literature, proposing a shift in its focus as well as a discussion of the impact of new technologies.

20.1.1 Immersion, Presence, and Embodiment in Virtual Reality

Immersion, presence, and embodiment are different constructs that are, however, interrelated. The fidelity of the delivered sensory information by VR systems and the extent to which their interaction can support users' sensorimotor contingencies (SCs) modulates immersion [4]. The higher the accuracy of the presentation of sensory stimuli (such as display resolution and field of view, sound, and haptic information) and the more SCs supported (such as head, hand, arm, or full-body tracking), the higher the immersion of a system. Immersion, in turn, affects the sense of presence. Even though there is no standardized definition for presence, it can be understood as the psychological state in which an individual responds to a VE like in the real world [5]. However, there is not a linear relationship between immersion and sense of presence. There is a consensus to characterize presence as a multicomponent construct [6]. According to Slater, the sense of presence relies on the place illusion—the illusion of being there—and the plausibility illusion—the credibility of what is happening [4]. Whereas place illusion is more directly liked to the immersive characteristics of a VR system, plausibility illusion is highly dependent on the implemented VEs. It has been commonly thought that presence is the key mechanism that makes VR work. Presence may be especially relevant in a neurologic population, since the subjective perception when interacting with VEs elicited in persons with CNS dysfunction has been shown to be different to that of healthy subjects [7]. Characteristics of both the user and what and how sensory information are presented by the VE determine the level of presence in VR. With regard to the user, the demographic (age, sex, educational level, etc.), psycho-cultural (social habits, interaction, etc.), and also clinical characteristics (sensorimotor, cognitive, and psychological condition) modulate the perception of the virtual world and the interaction with it [8]. Likewise, a previous experience with VR systems may influence presence [8].

Like presence, embodiment is a multicomponent psychological construct. It has been defined as the sense of one's own body [9], as the bodily self-consciousness [10], or as corporeal awareness [11]. All the existing evidence seems to indicate that presence and embodiment are innately linked since both place illusion and plausibility illusion can support the ownership of a virtual body [4]. This relationship is evidenced by studies showing that the sense of presence can be modulated with avatars that accurately represent the users' actual selves (rather than avatars representing their ideal selves), which can facilitate their embodiment [12]. Although an increasing number of studies investigate the plausibility of physiological indices and behavioral data to evaluate both the subjective sense of presence [13] and embodiment [14], the use of dedicated questionnaires, administered either in the physical or in the virtual world [15], is most frequent in the literature.

Recent research has focused on unifying aspects of the embodied cognition theories and identifying its subcomponents, such as body ownership and agency [16]. Agency refers to the sense that one can move and control one's body [17]. Body ownership can be defined as the sense that the body that one inhabits is one's own [17]. Consequently, body ownership is continuous and omnipresent and is not only elicited during the movement but also during passive mobilization and at rest. Body ownership and agency are key mechanisms to facilitate embodiment in VR, which has traditionally been mediated by avatars representing the user's actions.

Research has shown that specific multisensory stimulation can promote not only illusory ownership of parts of the body, such as rubber hands [18], but of the whole body. Multiple studies report that it is possible to perceive another person's body as one's own [19], but also to induce full-body ownership of a mannequin [20] or a complete virtual body [21]. Embodiment in avatars determines the body ownership and agency of the virtual representation and the user's perception of the world and their behavior. For instance, the illusory ownership of a smaller virtual body (a virtual child) has been shown to cause overestimation of object sizes [22], while the ownership of taller avatars has been shown to promote confidence [23]. In contrast, presence can be elicited by adding emotional valence to the media content, regardless of the media form [6]. In healthy adults the salience of the VE, the hardware used to deliver the VE, and the personal qualities of the participants have been shown to interact in creating a sense of presence and immersion [24]. Complete immersion, however, is not a requirement for presence, as participants post-stroke were shown to be present even in semi-immersive environments [25]. Thus, some characteristics of VR systems such as synchronism of stimuli [21], alignment and continuity of the real and virtual bodies [26], and perspective [20], are determinants for inducing a sense of presence and embodiment and consequently are contributing factors in the effectiveness of VR-mediated therapies. Importantly, these findings have been shown to transfer to individuals with stroke. Borrego and colleagues compared both the sense of embodiment and presence in VR of both healthy subjects and individuals with stroke under different perspectives and levels of immersion [14]. The results of their study showed that, although less intensively, embodiment and presence were similarly experienced by individuals with stroke and by healthy individuals, which could support the vividness of their experience and, consequently, the effectiveness of the VR-based interventions.

20.1.2 Immersion and Cybersickness

Potential users of VR, and practitioners have concerns regarding the use of more immersive VR modalities (head-mounted displays and wide field of view projection screens) and the possibility of developing cyber-sickness, a term used to describe a wide variety of uncomfortable symptoms that include but are not limited to nausea and dizziness, caused by interacting with a VE. Sensory conflict is frequently cited as an important contributor to cyber-sickness. Temporal mismatches between virtual presentations of visual movement and vestibular signals caused by actual patient head movement are the most frequently cited causes of symptoms [27, 28]. Logically, non-immersive displays, typically presented on a television or computer monitor do not eliminate the peripheral visual cues that the brain uses to monitor head movement in space should lead to a lower incidence of symptoms. This said changes in visual information that are temporally matched to head movements would decrease this effect in immersive systems. Improvements in the intuitiveness of virtual world movement and higher levels of user control of navigation within the virtual world have been linked to lower levels of cyber-sickness as well [27].

The literature regarding the impact of immersive VR presentations on virtual rehabilitation interventions is often conflicting. A review by Specht et al. focusing specifically on HMD describes this approach to immersive VR as well tolerated by older adults as well as those with stroke and that treatment with HMD are not hindered by cyber-sickness [29]. Another review by Hoeg et al. describes a slightly higher incidence of reports of cyber-sickness and a higher rate of subject dropouts associated with more immersive equipment. These authors also pose that slight symptoms of cyber-sickness might be under-reported and could contribute to poor compliance and sub-optimal outcomes [30]. Multiple authors call for better controlled studies of the impact of cyber-sickness on virtual rehabilitation as a priority for future research [27, 29, 30].

20.1.3 Motor Learning Principles

Motor learning principles are defined as the set of processes associated with practice or experience that lead to relatively permanent changes in the ability to perform actions [31]. Different principles have been postulated to modulate motor learning after stroke. Salient, goal-directed, task-specific movement and practice of sufficient intensity are important determinants in motor learning in human skill motor learning [32]. Even though these principles have rarely been analyzed in isolation after VR interventions, the role of motor learning principles has been discussed by authors who described their systems [33], in review papers [3, 34–38], as well as book chapters [39]. One can find motor learning principles embedded in VEs for motor rehabilitation [34, 39]. In the following section, we will discuss a number of principles that have become integral to VEs for promoting skill acquisition in the real world such as enriched environments, augmented feedback, practice dosing, adaptation, motivation, and task-oriented experiences.

20.1.3.1 Enriched Environments

Preclinical research on enriched environments serves as the basis for hypothesizing that enriched VR experiences could serve as rehabilitation tools to promote motor learning [40]. Initial findings with animal models have shown that enriched environments promote sensorimotor functions and learning after stroke [41]. The benefits of enriched environments have also been postulated for human subjects. When persons post-stroke were exposed to enriched environments that motivated exploration, physical training, and social interaction, they increased activity and decreased their alone time [42]. In this context, VR is a promising tool to create synthetic computer-generated environments (VEs) that provide augmented stimulation to stroke survivors.

20.1.3.2 Intrinsic and Extrinsic Feedback

Movement performance is informed by both intrinsic and extrinsic feedback. Intrinsic feedback relates to the sensory-perceptual information that is naturally generated during or after a movement.

Augmented feedback—also known as extrinsic feedback—is an add-on to the intrinsic feedback with the goal of providing further information, in the form of knowledge of performance (KP) and/or knowledge of results (KR), that can facilitate skill learning [42]. Augmented feedback is provided by an external source and not by the movement itself [43]. VEs can provide augmented feedback through different sensory modalities such as visual and auditory information with audiovisual devices and proprioceptive information through specific interfaces such as a haptic apparatus, further described in Sect. 20.2. Consequently, VR systems capitalize on both intrinsic feedback and augmented feedback [42].

There is preliminary evidence supporting that augmented auditory feedback improves the speed and accuracy of virtually simulated activity performance in healthy participants as well as participants with brain injury [44]. Further, because VEs can track the motion of body targets or segments, movement monitoring allows the feedback about movement performance and outcome to be very specific. This fact could be key in the beneficial effect in the recovery of motor function after stroke present in VR approaches [see [45] for review]. In studies comparing real-world performance with comparable VE training, several authors have speculated that the cognitive processing required to process the KP in the VR enhances transfer of training to the real world [46, 47]. It is important to note that feedback from VEs, and in particular from games, can be nonspecific and focus on providing positive feedback to encourage participation. This is especially true with non-custom commercial video games that have been applied to rehabilitation [35]. To date, little is known about the impact of augmented feedback on the transfer of motor ability improvements from virtual activity to real-world activity [48].

20.1.3.3 Task Specificity

Task specificity has long been a fundamental requirement for designing recovery of function programs. The principle of specificity suggests that motor learning is more effective when practice includes environmental and movement conditions similar to those required for the execution of the movement [49]. This suggests that the benefit of the practice specificity occurs because motor learning is specific to the information available during the learning process. Therefore, removing a source of information that was present during practice (or adding another that was not present) impacts task performance. The specificity of practice hypothesis posits that motor skill learning can be enhanced by practice conditions, especially sensorimotor and perceptual information available, performance context characteristics, and cognitive processes involved [50]. Consistent with this hypothesis, VEs can build on the most appropriate available interfaces and feedback modalities to reproduce the relevant context of tasks, such as haptic feedback to recreate the physics of object manipulation [51], video projections to augment tasks with contextual visual information [52, 53], or combining walking on a treadmill while performing a shopping task [54].

VEs have also been used to recreate meaningful tasks to be performed with the upper limbs. Virtual tasks emulating tasks for independent living have been used for assessing the upper limb motor function after stroke [55], showing correlations with clinical scales. Many different VEs have been successfully used for upper limb rehabilitation with levels of ecological validity that varied widely [56, 57]. Given the multisensory training in VE, there may be essential task requirements, but perfect congruence with the real-world task may not be required [58].

Training walking is characteristically done using simulations in which participants walk on a treadmill as they navigate in parks, cityscapes, or corridors [59–61] (Fig. 20.1) or walk over obstacles [62]. However, several investigators have used pre-gait, balance, and other gait-related activities to train walking [46, 63]. The extent that which the task practiced sensorimotor and perceptual feedback is congruent between the VE and the real-world situation varies greatly based on the VR system. While both Fung and You [60, 63] sought to improve walking post-stroke, each approached it with a different degree of task specificity. For example, in a proof of concept study, Fung had participants post-stroke walking in a virtual scene on an actuated treadmill, which allowed changes in path speed as well as orientation, producing a high degree of vestibular and proprioceptive fidelity with the VE. In contrast, You had participants performing stepping and pre-gait activities on the ground with a level surface, in which a TheraBand™ was placed on the participants' limbs to augment the proprioceptive input. Fung measured and demonstrated participants' ability to adapt their walking based on the environmental demands, while You measured walking performance and demonstrated improvements after training. Their findings suggest that task specificity may be beneficial but not essential in VE constructions in order to demonstrate the transfer of training.

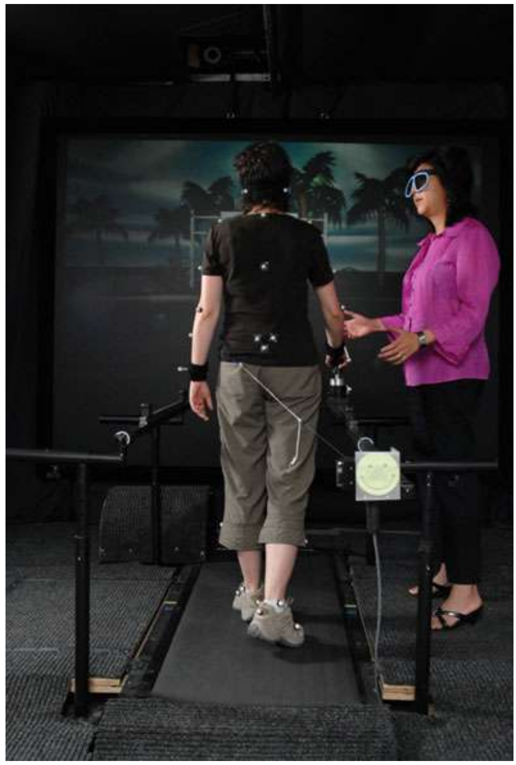

Fig. 20.1 An interactive VR-coupled locomotor system [55] incorporating a self-paced treadmill and dynamic haptics [58] mounted on a six-degree-of-freedom motion platform. Computer-controlled, synchronized animations are rear-projected onto a large screen that can be viewed in 3D with polarized glasses. Such a system can be used to train locomotor adaptation needed to meet demands related to the changing environment (obstruction and surface angle, etc.), tasks (speed requirements, avoiding moving obstacles, dual-tasking, etc.), and cognitive requirements (attention, planning, etc.). Reproduce with permission of Joyce Fung

20.1.3.4 Dosing

The dose of the training has been reported as a central factor in motor learning [64]. Dosing depends on three key parameters: training duration and frequency with which the individual performs training and the number of repetitions performed during training. It is known that a sufficient dose of practice needs to be performed in order to produce skilled behavior [65] and neuroplastic changes [66]. VEs are designed to promote repetitive task practice that can be tracked and progressed. The number of lower extremity repetitions in VE training has been reported to be comparable to repetitions in animal studies that successfully induced plasticity [33]. Further, work comparing the number of purposeful movements executed with the upper limb of persons post-stroke during standard of care was five times lower and slower than when playing Kinect™ [67]. Dose alone, however, is not sufficient for motor learning and neural plasticity (see Sect. 20.3).

20.1.3.5 Adaptability

The repetition of a task is critical for its learning and its refinement. However, the mere repetition of a task has not been shown to induce plastic changes in motor maps. Studies in animals have shown that exposure to a task that requires little or no learning does not produce changes in motor maps or neural morphology [68]. Based on this principle, rehabilitation interventions should involve motor skills with growing difficulty to always pose a motor challenge for post-stroke subjects [69]. The benefits of VEs are, on the one hand, that they can accurately assess the patients' motor condition and, on the other hand, that they can adapt the motor tasks to match this changing condition. Adaptability of the motor tasks has been integrated into several VEs, from the upper limb [56] to balance [70]. VR systems with built-in calibration capabilities or personalization algorithms to autonomously adjust the intensity of training sessions to each patient have been shown to be more effective as compared to conventional therapy [71–73].

20.1.3.6 Motivation

Motivation can be defined as the set of forces that move an individual to act, which may be extrinsic (prompted by an external reward) or intrinsic (propitiated because the task is inherently pleasurable: curiosity, play, etc.). Research has shown that motivation promotes learning [74]. As shown in the following section, motivation plays a major role in VE because it persuades patients to accomplish a task and facilitates presence in the virtual world.

20.1.4 Motivating Through Gaming Elements in Virtual Environments

There are multiple models of motivation, some of which explore intrinsic motivational factors in which the motivation is derived from the act of participation itself or extrinsic factors in which the person is motivated by the purpose of the activity [75]. In the context of sensorimotor rehabilitation, the goal is to facilitate clients to be self-directed and motivated, both because the activity is interesting in itself and because achieving the outcome is important [76]. There is agreement that gaming elements can improve motivation and that, if paired with other activities, they can be harnessed to engage users and achieve desired outcomes. However, there is no consensus regarding the required essential characteristics of these gaming elements [77], and less than 30% of the studies explicitly reference one or more motivational frameworks or principles [76]. Many elements have been suggested to be important for designing a successful game, such as fun, flow, goals, feedback, game balance, pacing, interesting choices, and narrative structure, among others [78]. In the following sections, we will discuss some of the intrinsic characteristics of games that can affect motivation and learning, and how those are used in the context of motor rehabilitation [79]. While these intrinsic characteristics are discussed as gaming elements in VE, it is important to note that many of them, for example, goal setting, balancing challenge, and reward, overlap with principles of motor learning.

20.1.4.1 Goal Setting

Games generally set multiple goals at different time scales. An appropriate balance of short, medium, and long-term goals has been shown to have a motivating effect in extending gameplay [80]. Further, goals should be achievable, but they should also be attained through a chain of interesting decisions. That is, when players are presented with choices, no one decision should be obviously correct. Most VEs exclusively designed for motor rehabilitation only consider immediate goals (to perform a specific motor task such as reaching or walking) and long-term goals (to collect a sufficiently high amount of rewards). Instead, VEs integrating both cognitive and motor domains seem to be better suited to pose goals at multiple time scales through nontrivial decisions [81–83].

20.1.4.2 Feedback and Rewards

Recent findings suggest that providing appropriate feedback to exercises can stimulate the learning process in rehabilitation therapy [45]. VEs are exceptionally well suited to provide immediate and specific feedback to users, this feature being essential for sustained attention, learning, motivation, and fun [79, 84]. Actions can be rewarded with positive visual and auditory feedback, scores, and specific KP and KR [85, 86]. The simplest way to incorporate KR feedback in VR-based rehabilitation activities is to reinforce successful task completion via general "celebratory" sounds or appropriate sounds when acquiring a target (i.e., explosions during a shooting task). Comparable negative feedback can be provided for unsuccessful performance (collision with an obstacle) [87]. This approach to feedback provides the participant KR, a modality of feedback associated with rapid, effective motor learning [88]. However, rewards can also negatively affect high-interest tasks when rewards are predictable and not associated with performance [89]. More advanced reward systems consider point systems [90, 91], medals [92], bonuses [93], new challenges and tools [94]. Hence, in the ideal scenario, multiple rewards systems need to be selected and manipulated in their number, timing, and quality in order to achieve sustained attention over extended periods. In the case of KP, it does not necessarily require rewards as it can be implemented by providing cues that enable the patient to assess performance, such as the representation of virtual limbs [56, 95], haptic feedback [95], or auditory cues [96].

20.1.4.3 Challenge

VEs for motor rehabilitation should be adjusted in terms of movement demands and dynamics, avoiding situations in which patients lose the ability to control the task directly. It has been suggested that players desire a level of challenge that is neither too easy nor too difficult to perform [97], which is consistent with the early findings of Yerkes and Dodson, when the relation between induced stress and task-learning performance was studied in mice [98] and later replicated in humans in multiple domains [99, 100]. In his flow theory, Csikszentmihalyi describes that user experience during play (anxiety, boredom, and flow) is modulated through the challenge posed and the level of skills required [101]. Flow, defined as the moment of maximum player engagement, is placed at the right balance between user skills and level of challenge. For this reason, the tasks are given as well as the time available to complete them must be calibrated to introduce a controlled challenge [102]. Therefore, recent developments in VEs for motor training already incorporate transparent and automated modules for the personalization of training by adjusting task difficulty depending on the patient's success rate or by modifying the time available to accomplish a goal [103]. In the cases when VEs are designed to teach complex skills, it is suggested that complex and demanding tasks should be broken down into simpler and more achievable tasks to enhance learning [80]. While simple tasks can be trained by increasing their difficulty in more demanding task settings, complex tasks need to be trained by bringing together previously learned simpler ones, providing a balance of challenge and engagement [104].

20.1.4.4 Sense of Progress

Playing a game entails making decisions and doing actions, with each action influencing the game as a whole. The player must be able to comprehend the immediate effect of their action and how that result was incorporated into the greater context of the game to maintain the motivation to keep playing [105]. Flat and static training tasks can be monotonous and eventually limit the patient's engagement. Malone and Lepper [97] identified curiosity as one of the principal drivers of user engagement in serious games, being it either interest evoked by novel sensations or the desire for knowledge. Narrative elements can be exploited to build an interesting dramatic arc around the training task to increase patients' engagement, facilitate the comprehension of the training objectives, and, most importantly, deliver a clear sense of progress. Multiple elements can be used to shape a narrative curve, such as story events, task difficulty, novel environments, new challenges, or skills. VEs designed to realistically simulate activities, such as navigating a virtual city or shopping in a virtual supermarket, generally provide richer narratives than tasks with simpler cognitive demands [106–109].

20.1.4.5 Socialization

There are multiple ways VEs and games can be used to promote socialization among users.

Thielbar compared a VE for home-based rehabilitation used in multiuser or single-user mode [110]. The multiuser configuration showed a higher compliance rate (10% more), and participants spent more time training when compared to the single-mode version of the system. However, engagement and social involvement do not depend exclusively on VEs being single or multiuser, but also on how user interaction is mediated through the VEs. This can be implemented as a competitive, cooperative, or collaborative interaction [111]. Competitive games have been demonstrated to increase enjoyment [111, 112] and intensity [113]. Collaboration (working together) and cooperation (operating together) have been less studied, with data suggesting that collaboration promotes more behavioral involvement at the expense of having a higher cognitive load [111].

20.1.5 Summary

Motor learning and motivation theories have informed the development of virtual environments and serious games (Table 20.1). Recommendations for the use of augmented feedback or rewards, specifically knowledge of results, are

Table 20.1 Table summarizing some of the key features and their evidence for the design of effective VR systems for motor rehabilitation

		Evidence	References
Motor Learning	Enriched Environments	• Promote activity levels	[41]
	Intrinsic and Extrinsic Feedback	• Knowledge of performance and knowledge of results facilitate skill learning	[42, 45]
		• Knowledge of results has been associated with rapid, effective motor learning	[88]
	Task Specificity	• Virtual tasks emulating ADLs can be used to assess upper limb motor function	[55–57]
		• May be beneficial but not necessary in VR	[144]
	Dosing	• The number of repetitions in VR is comparable to animal studies that induced plasticity	[33]
		• Purposeful movements in VR are performed faster and with higher frequency	[33]
	Adaptability	• VR systems with calibration and/or personalization capabilities are more effective than to conventional therapy	[71, 73, 141]
Motivation	Goal Setting	• An appropriate balance of short, medium and long-term goals has a motivating effect	[80]
		• VEs integrating cognitive and motor domains are better suited to pose goals at multiple time scales	[82, 83, 300]
	Rewards	• Actions should be rewarded with positive visual and auditory feedback, scores and specific knowledge of performance and knowledge of results	[85, 86]
	Challenge	• Task difficulty and time available to complete them should calibrated to control challenge	[102]
		• Complex and demanding tasks should be broken down into simpler and more achievable tasks	[104]
	Sense of progress	• Players must understand the impact of their actions on gameplay	[105]
	Socialization	• Competition increases enjoyment and intensity	[111, 113]
		• Collaboration enhances engagement at the expense of having a higher cognitive load	[111]

consistently found in the VR literature; yet there are few studies to support its use empirically. Instead, the assumption has been made that augmented feedback principles apply in real-world practice and should therefore inform VR design. In contrast, there is modest evidence that VEs promote a high degree of repetition and intensity, and video games deliver higher doses than standard exercises. Until recently, motor learning principles dominated the VR landscape; it is only in more recently that the motivation and game design literature has contributed design principles to guide the appropriate challenge, sense of progress and game modality [79, 114]. Nonetheless, the assumption that motor learning and motivation are essential for the efficacy of virtual rehabilitation is still an open question.

20.1.6 Visual Presentation

VR systems are frequently classified by the visual presentations they provide to a user and the presence or absence of somatosensory feedback. Visual stimuli are generally grouped by their degree of immersion. Two-dimensional presentations delivered on flat screens are generally considered non-immersive. Three-dimensional presentations utilizing stereoscopic projections or flicker glasses with fixed visual perspectives are considered semi-immersive. Fully immersive systems provide three-dimensional visual information, and perspective is updated with head movements. Full immersion is provided via head-mounted devices or within cave-type environments. Higher levels of immersion are associated with higher levels of agency, presence, and immersion [115–118]

A steadily growing literature has examined the impact of visual presentation on movement kinematics of persons performing reaching movements. Measurable differences in end point and angular measures of upper extremity movement have been noted when comparing two-dimensional simulated movements and comparable real-world activities [119, 120]. Similar differences have been identified in the upper limb when comparing three-dimensional simulated and real-world activities [121–123] as well as differences between two-dimensional and three-dimensional simulated reaching activities [124], and narrow field of view presentations to wide field of view presentations [125]. While there are measurable differences in the movements elicited by comparable activities presented in virtual and veridical worlds, multiple authors describing the training of upper extremity reaching and functional activities by persons with stroke in VEs have shown that comparable real-world improvements in motor abilities can be elicited through repetitive practice in a variety of VEs. Most importantly, upper limb studies show that these improvements are comparable to or better than those elicited by real-world training [36, 126–128].

20.1.7 Point of View

Most immersive and semi-immersive systems, and even some non-immersive systems, present first-person points of view of the workspace during virtual rehabilitation activities. These presentations typically include virtual representations of the participant's limbs or a landscape in which the person might be navigating or acting. However, VR also offers the opportunity to provide users a perspective on movement they may not ordinarily have. For example, video capture-type VR systems present mirror images of the patient as they interact with a VE. These types of augmented reality systems designed for rehabilitation frequently incorporate the ability for the subject to view an image of their own limbs interacting with a VE. One of the reported strengths of this point of view is the high-fidelity feedback regarding patient's posture [129]. This approach presents higher quality information related to limb movement and reduces the need for the brain to rectify differences in somatosensory and visual information associated with the other approaches to VR. One study describes a superior motor performance on a task using an augmented reality system providing a first-person view of the task with the participants' own arms interacting with the VE when compared to a two-dimensional system requiring incongruent motor actions—horizontal forward reaching to elicit vertical movement—in the VE [130]. Two studies suggest that this effect may be enhanced by attaching cameras to a head-mounted device, which improves the fidelity of changes in first-person views of the hands as subtle changes in head position occur [131, 132]. Walking simulations have used both the first- [59] and third-person perspectives [46, 62]. A recent study demonstrated that a first-person point of view enhanced a sense of embodiment in healthy persons and persons with stroke as compared to a third-person view [14]. There are no studies suggesting that an enhanced sense of embodiment might enhance rehabilitation outcomes, but a recent study suggests that an enhanced sense of embodiment might positively affect implicit learning [133].

20.1.8 Auditory Stimuli

Auditory information is a key sensory component of most VEs and has a broad impact on the participant's experience. It is used to enhance immersion in the VE by providing sounds consistent with an activity (i.e., automobile-related sounds for a driving game or the sound of liquid hitting a surface during a pouring activity) [87]. The combination of auditory feedback has also been combined with vibrotactile feedback to enhance collision perception during gait [134], balance [135], and upper extremity training [136]. Spatial sound rendering can also be used to increase the realism of a VE and aid user navigation within a VE (i.e., volume increasing as the virtual representation of the participant approaches the source of a sound in the VE) [87]. The addition of music and specific attributes such as rhythm and cadence has been shown to have a direct impact on the motor performance of healthy and disabled participants [137], particularly when continuous tasks such as gait are simulated [138]. Friedman et al. also found that the addition of music enhanced hand motor performance as well as motivation in the training of functional hand movements [139].

20.1.9 Haptic, Tactile Stimuli and Their Interfaces

Simple or robotic haptic interfaces have allowed for the addition of tactile information and interaction forces into what was previously an essentially visual and auditory experience. Devices of varying complexity are interfaced with more traditional VE presentations to provide haptic feedback that enriches the sensory experience, add physical task parameters, and provide forces that produce biomechanical and neuromuscular interactions with the VE that approximate real-world movement more accurately than visual-only VEs. Simple haptic feedback has been utilized to add the perception of contact to skills like kicking a soccer ball or striking a piano key [140, 141] (Fig. 20.2). Collisions with virtual world obstacles can be used to teach normal movement trajectories such as to place an object on a shelf or the action required to step over a

Fig. 20.2 The NJIT-TrackGlove system utilizes a six-degree-of-freedom magnetic tracker, the TrakStar (Ascension Technology Corporation, USA) and a 22-DOF CyberGlove (CyberGlove Systems USA). The simulation pictured also utilizes the CyberGrasp, a cable-actuated robotic exoskeleton. In the pictured simulation, the Virtual Piano Trainer, the magnetic tracker allows the participant to position their hand over the virtual keyboard and the CyberGlove allows them to strike keys with a specific finger. The CyberGrasp can be programmed to provide haptically rendered collisions when keys are pressed or assistance in maintaining extension of non-cued fingers for more impaired subjects [105]

Fig. 20.3 The NJIT-RAVR system utilizes a three-degree-of-freedom robotic (DOF) interface, the Haptic Master (Moog, The Netherlands), three additional passive DOF via a ring-gimbal, and a 22-DOF CyberGlove (CyberGlove Systems USA). The Haptic Master is used to provide haptic rendering of virtual workspaces and add global forces such as gravity to the virtual environments. The ring-gimbal allows for normal positioning of the hand during simulated tasks and the CyberGlove collects data related to finger position. These interfaces are integrated with a suite of complex, virtually simulated tasks to allow for task-based sensorimotor training for persons with upper extremity hemiparesis [67]

curb [62, 72], (Fig. 20.3). Haptic forces can also be synchronized with visual feedback to improve a users' sense of agency in the virtual world. In two small studies involving healthy subjects, this feedback combination was found to be more effective for skill learning than visual-only feedback in healthy subjects [142, 143]. Simulations that aim to shape the behavior of the upper limb have successfully combined haptic feedback with KP to improve upper limb trajectories as post-stroke individuals placed virtual cups on a cupboard [144]. Participants placed their limbs in the haptic master, which augmented the intrinsic feedback with proprioceptive cues, and the simulation provided information on the trajectory. The coupling of the feedback smoothed out the movement trajectories. Further, haptics has also been used to simulate the interaction forces produced by tools in VEs [117], which increase the sense of immersion and activate neural networks involved with tool manipulation [145]. In a lower extremity application, the addition of haptics improved the accuracy of the limb movement in the VE [33].

20.1.10 Brain-Computer Interfaces

The combination of brain-computer interfaces (BCIs) and VR for stroke rehabilitation has increased in popularity and acceptance during the last decade [146] (Fig. 20.4). BCIs are systems that detect changes in brain signals and translate them into control commands [147]. Such systems exploit the relationships between users' mental states and corresponding electrophysiological signals. In noninvasive BCIs, electroencephalography is commonly used for measuring brain activity. BCIs have gained popularity because evidence relates the mental practice of motor actions with actual movement performance [148]. Motor imagery (MI), the mental practice of motor actions, has been the basis of most BCI approaches to stroke rehabilitation, with a focus on hand and arm training and relying on visual feedback and sometimes combined with Functional Electric Stimulation (FES) or robotic assistance [see [146] for review]. Evidence indicates that the presence of neurofeedback improves MI practice [149]. However, feedback is not the only factor that plays a role. For instance, evidence suggests that motor priming prior to BCI MI can enhance neural activity and improve BCI performance [150]. Avatars in VR and visuo-proprioceptive information can also affect body ownership illusions and modulate the sensorimotor rhythms associated with MI [151, 152]. Also, there are differences between relying on a motor attempt or MI in the underlying neural signals, with evidence suggesting that motor attempt renders

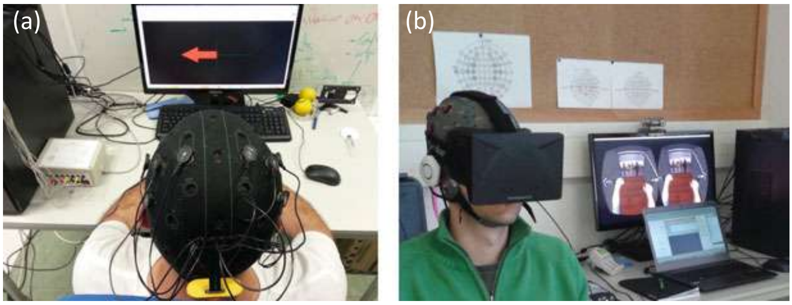

Fig. 20.4 The RehabNet system interfaces a large number of BCI technologies (g.mobiLab, Enobio, OpenBCI, EPOC, Neurosky) and tracking devices (Kinect v1 & v2, Leap Motion, Wii controllers, android phones) with VEs to deliver immersive VR experiences. The RehabNet system is flexible and can work in multiple configurations: **a** MI-BCI neurofeedback training using standard Graz visualization feedback with an 8-channel Enobio acquisition system (Neuroelectrics, Spain); **b** MI-BCI VR training with the virtual representation of upper limbs in a goal-oriented task presented through a head-mounted display and an 8-channel g.mobiLab acquisition system (g.tec, Austria) [114]

better BCI performance [153]. Hence, the lack of standardization on BCI MI methodologies renders BCI studies discrepant and very difficult to compare [154], and consequently, requires significant efforts for the optimization of the settings [155] until standardized protocols are defined [156]. Regardless of the existing difficulties, case studies [157] and RCT findings corroborate that the benefits of MI-based post-stroke rehabilitation are boosted when trained in the context of a BCI paradigm that provides online visual feedback through a VR presentation of the patient's hands [53]. In addition, BCI paradigms allow studying the underlying mechanisms and plastic changes [155, 157], making them a very interesting approach.

20.1.11 Summary

Research into the impact of visual, auditory, and tactile information on virtual rehabilitation activity has started to establish a tentative set of best practices for virtual rehabilitation in terms of the user experience to varying degrees (Table 20.2). The impact of auditory feedback on virtual rehabilitation is at an early stage of development but preliminary work supports the additive effects of rhythm and auditory rendering on the overall effectiveness of the virtual activity. There is a larger body of evidence supporting that the visual stimulus has a direct, predictable impact on the motor output elicited during simulated activities. However, there is no evidence supporting the notion that higher fidelity visual presentations during virtual rehabilitation translate into larger improvements in the ability of persons with disability to function in the real world. This mismatch between user experience and effectiveness needs to be considered because higher fidelity, fully immersive visual presentations currently require more expensive equipment and more challenging programming to produce. A similar dichotomy exists between VR simulations interfaced with robots to provide tactile feedback and add global forces or with BCIs. Research supports that motor skill learning within the VE is more efficient with these additions. However, this benefit comes at the cost of greater complexity and expense for these integrated systems. These two factors are frequently cited as reasons for the slow adoption of integrated VR-robotic systems into routine clinical practice.

20.2 Neuroscience of Virtual Reality

Knowledge of the neural processes occurring after the central nervous system damage as well as the nervous system's response to activity is necessary to understand the impact of virtual

Table 20.2 Table summarizing key evidence on the role of multisensory information for post-stroke rehabilitation

		Evidence	References
Visual information	2D and 3D simulations	• Exist differences in end point and angular measures with real-world activities	2D: [119, 120] 3D: [121, 122]
		• Improvements are comparable to real-world training	[128, 301]
	Video capture	• Provides high-fidelity feedback on patient's posture	[129]
	1st person view	• Superior task performance	[130]
		• Boosts the effects of motor imagery training supported with online BCI feedback	[53]
Auditory information	Spatial sound	• Increases realism and aids navigation	[87]
	Music	• Rhythm has a direct impact in performance of motor tasks	[137–139]
Haptics and tactile information	Collisions	• Can be used to teach normal movement trajectories	[62, 72, 302]
	Haptic guidance	• Is more effective for skill learning than visual information only	[142, 143]
		• Augments intrinsic feedback with knowledge of performance	[144]
		• Improves accuracy of movements	[144]
	Interaction forces with tools	• Increase immersion and brain activation	[145]

rehabilitation on neural recovery. True recovery is based on behavioral change associated with brain plasticity or neuroplastic changes. After stroke, it is known that perilesional and contralesional brain networks become more excitable, facilitating their reorganization [69, 158]. Research has shown that the recruitment of contralateral or ipsilateral networks largely depends on the integrity of the remaining cortical, subcortical, and corticospinal tracts [159]. As recovery progresses, brain activation patterns of stroke patients become more similar to those of healthy individuals [160, 161], showing that restoration to normal activity patterns correlates with the restoration of motor function.

20.2.1 Brain Plasticity

VR is a particularly interesting research field as it allows creating computer-generated environments that provide customized experiences involving different sensory channels. The motivation of using VR in sensorimotor rehabilitation after a brain lesion is the administration of specific experiences that drive cortical reorganization to support the reacquisition of motor skills. Consequently, neural plasticity is commonly used as an efficacy measure of VR training. Neurophysiological adaptations to training in virtual and real-world environments by people with stroke have been shown to rely on similar neural reorganization processes [117].

An increasing number of studies with many different designs and methodologies have investigated the neural correlates of VR-based interventions focused on sensorimotor rehabilitation (see a recent paper by Hao and colleagues for a review [162]. Interventions included custom and off-the-shelf systems that mostly targeted the upper limb function, followed by lower limb function and balance. Evidences of neural plasticity were explored using functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and transcranial magnetic stimulation. Despite some inconsistent results among studies, fMRI findings support that participation in VR-based sensorimotor interventions increased brain functional connectivity [163–167] and addressed interhemispheric imbalance by increasing cortical activity in the ipsilesional hemisphere [163–165, 168–175]. Interestingly, the increase of the ipsilesional activity ties in with an increase of the cortical representation of the body parts targeted by the VR-based intervention, as derived from the studies that used transcranial magnetic stimulation to explore the plasticity of brain mappings [176–178]. The concomitant manifestation of plastic changes in the brain and improvements in the sensorimotor function after VR-based interventions, as reported by several studies [165, 167, 174, 178–181], could provide evidence of a positive association, although not necessarily causal, between both phenomena.

20.2.2 Visuomotor Representations

It is known that cortical areas involved in the preparation and execution of motor actions undergo plastic changes [182] either due to repeated sessions of proprioceptive stimulation through passive physical training [183] or as a result of task-oriented physical training [184]. Motor deficits do not only arise from the directly damaged tracts by stroke but the networks they disrupt. Hence, its recovery also depends on the intra- and interhemispheric interactions among motor regions [185]. For instance, bilateral recruitment of motor networks can result from unilateral motor movements in hemiparetic stroke patients [185, 186]. Motor training through VE interaction may involve different elements such as object-oriented action planning, action observation, and feedback of the performed action. Unfortunately, there are no standardized protocols for VR motor rehabilitation after stroke, and different interventions have produced distinct effects in both neural reorganization and motor recovery [see [187] for review]. To deliver an optimal rehabilitation process, it becomes essential to identify and understand the neural systems and cerebral processes engaged during motor training mediated by VR.

One of these candidate systems is the human mirror-neuron system (MNS), which is primarily composed of neurons located in the inferior parietal lobe, the ventral premotor cortex, and the caudal part of the inferior frontal gyrus [188]. These are candidate areas for sensory control of action, movement imagery, and imitation [188, 189]. The MNS is of great relevance because it has been shown to be active during the performance of goal-directed actions, their passive observation, and their mental simulation [190]. The MNS has been hypothesized to be involved in action understanding and imitation [191], and, as such, it may represent an important neurophysiological substrate for regaining impaired motor function after stroke [192, 193]. It was suggested that the mere observation of goal-oriented motor actions can be used as a driver [194], and findings corroborate that the use of passive observation of goal-oriented actions can have a positive effect on motor recovery after stroke [195, 196].

From these findings, it is clear that manipulating visual feedback for motor rehabilitation purposes can be an effective ingredient of VR systems. Maeda et al. [197] showed that movement observation can directly enhance and facilitate the motor outcome of the muscles involved in the observed action. In addition, the MNS has been shown to respond to biological as well as robotic effectors [198] and to the manipulation of tools in the real world [199] and VR [200]. Consequently, there is strong evidence supporting that VE interaction can be effective in engaging primary and secondary motor areas for upper extremities [201], locomotion [168], as well as the mirror mechanisms [200, 202]. Consistent with the above findings, the activation of the human MNS has also been documented during the imagination of motor actions [193, 202]. As discussed in Sect. 20.1.10, MI-based BCIs rely on the detection of sensorimotor rhythms, an oscillatory rhythm of synchronized neural brain activity in the alpha and lower beta frequency bands that is measured in sensorimotor brain areas. It has been shown that sensorimotor rhythms can be enhanced utilizing BCI training and that they correlate with motor recovery [53]. Restorative BCIs relying on MI aim at mobilizing neuroplastic changes of the brain in order to achieve reorganization of motor networks and enhance motor recovery [203, 204]. In addition, imaging studies have shown that the combination of first-person observation VR and motor imagery is more effective at recruiting more task-related networks than other conditions for both lower limb [205] and upper limb [206] movements.

The ability to distort visual feedback is an area of inquiry that has been investigated as a possible method to optimize motor adaptations to VR-based rehabilitation activities as well. Preliminary investigations into the visual "augmentation" of small errors during virtual rehabilitation activities performed by persons with stroke have suggested that this approach might enhance motor training outcomes in this population [207]. One possible mechanism for this effect might be an increased level of cortical activity necessary for the brain to rectify virtual movement amplitude that is not scaled to participant movement [208]. One distortion of visual feedback that has been associated with poor responses has been temporal lags between participant movement and corresponding movement within the VE. This may interfere with feed-forward/feedback control of movement, making delayed visual feedback confusing [209]. Recent findings of an RCT also suggest that the visual amplification of upper limb movements can be used to counteract the acquired nonuse of the hemiparetic limb in stroke patients [210].

20.2.3 Summary

After stroke, relearning of motor function is mediated by neuroplasticity. Evidence shows that VR can be a valid tool to drive motor networks, brain plasticity, and functional recovery

Table 20.3 Table summarizing evidence supporting the use of VR to drive neural processes involved in motor recovery

	Evidence	References
Brain plasticity	• Participation in VR-based sensorimotor interventions may increase brain functional connectivity	[164–167]
	• Participation in VR-based sensorimotor interventions may increase cortical activity in the lesioned hemisphere	[165, 173–175]
	• VR-based interventions are associated with increased cortical representation of the body parts targeted by training	[177, 178]
	• Improvements in the sensorimotor function subsequent to VR-based interventions are associated with plastic changes in the brain	[167, 174, 178, 180, 181]
Visuomotor representations	• Bilateral recruitment of motor networks can result from unimanual motor actions	[185, 186]
	• MNS is active during motor action execution, motor observation and mental simulation of motor actions	[190, 193, 202]
	• MNS could be involved in action understanding and imitation	[191]
	• MNS responds to biological, VR, tools and robotic effectors	[198–200]
	• Movement observation facilitates movement of muscles involved in the observed action	[197]
	• Passive observation of motor actions has a positive effect in motor recovery after stroke	[195, 196]
	• Motor imagery BCI training enhances motor recovery	[53, 203, 303]
	• First person VR combined with motor imagery is more effective at recruiting task-related networks	[205, 206]
	• Visual amplification of movements and/or errors in VR might enhance motor training outcomes	[207, 208]

(Table 20.3). Research has shown that after stroke, a window opens when networks become more excitable, and VR has been revealed as an effective tool to engage visuomotor processes such as the ones related to action execution, observation, understanding, and mental simulation. In fact, the manipulation of visual representations has been shown to engage motor networks during passive observation and mental simulation and facilitate the movement of muscles. Thus, the manipulation of these processes through VR cannot only enhance neural activation but also improve motor outcomes.

20.3 Evidence Base: Impact of VR

Virtual reality systems or applications may be divided into custom, those specifically developed for science or rehabilitation and non-custom those that were developed for other purposes (e.g., recreation) but are being adapted for science or recreation. These non-custom systems are often called serious games as they are being applied for science or rehabilitation. We propose that serious games can be further distinguished into rehabilitation or active video games: used to rehabilitate upper limb use, gait and balance, and exergames: used to promote physical activity or exercise. Custom VR systems may include gamification but under these definitions would not be considered a serious game. Defining these terms is an area of ongoing discussion.

Non-custom systems for VR or serious games have included game consoles from Sony, Nintendo, and Microsoft, which were coupled with vision or sensor interfaces. The earliest was the Sony® Eye-Toy®, a camera-based motion capture system designed to be compatible with the PlayStation™ two-entertainment system, which was initially released in 2003. A majority of the initial studies examining rehabilitation applications of this system involved balance activities or gross reaching movements [211]. There were also some upper limb studies that showed evidence of efficacy [212]. Two subsequent systems were released more broadly and have had more substantial impact on the field of rehabilitation, the Wii™ manufactured by Nintendo® and the Kinect™ manufactured by Microsoft®.

The Nintendo® Wii™, which features two accelerometer-based controllers in addition to infrared motion capture capabilities, initially became available in 2006. It was bundled with the Wii-Sports Games and later updated with a more precise controller released with the Wii™ Resort Games. In 2012, the Wii™ Fit game became available. This game was bundled with the Wii™ Balance Board, a force sensor that interfaces with the Wii™ console. These systems have been widely adopted in rehabilitation facilities and nursing homes without modification as a recreation and rehabilitation modality [213]. Surveys of clinicians in Canada and the United States indicate that this system, while discontinued, continues to have the greatest use [214, 215].

The Microsoft® Kinect™, a peripheral for the Xbox series that detects user's movements through a depth-sensing camera, was released to interface with the Xbox 360 in 2010. A substantial body of research related to the validity of measurements of human movement with the Kinect™ has been developed [see [216] for a detailed review]. Analyses of these non-custom games to allow the application to rehabilitation have been conducted for the Wii [35] and the Kinect [217]. These analyses have interpreted the content of the non-custom system's games to include elements of feedback, in particular greater amounts of knowledge of results which may promote game play and engagement, but less knowledge of performance which may lead to poor movement patterns. Therefore, clinicians choosing to incorporate these games into rehabilitation need to carefully observe their clients' movement performance.

The sections on evidence of the impact of VR will be divided by motor control (e.g., upper limb, balance, and gait) and VR system (e.g., custom and non-custom).

20.3.1 Upper Extremities

20.3.1.1 Custom Systems

In 2017, an update was performed on a Cochrane review by Laver et al., which considered the effect of Virtual Reality on upper limb function along with secondary outcomes such as gait, balance, cognitive function, and various QOL measures [128]. This review drew from 72 randomized and quasi-randomized trials and included a sample size of 2470 participants who had experienced a stroke. The results of this review can be broken into two primary categories regarding upper limb function, trials that used VR as the sole treatment strategy for experimental groups, and trials that used VR as a supplementary intervention for experimental subjects. When Virtual Reality was the only intervention, it was found that there was no significant difference in outcomes for intervention versus control groups. However, when Virtual Reality was supplemented to standard therapy it was found that intervention groups had significantly better outcomes when compared to control groups.

It could be argued that the addition of VR as a supplemental form of therapy resulted in more total time spent performing therapeutic interventions, thereby producing significantly better outcomes. Following a stroke, patients are assigned a home exercise program as an adjunct to their regular therapeutic interventions. Normally adherence for such HEPs is low; however, due to VR's effectiveness as a supplemental intervention, it is plausible that the addition of VR interventions could improve adherence, and thereby significantly improve patient outcomes. Studies focused on the relative effects of VR as an adjunct to in-clinic therapy versus traditionally presented exercise as an adjunct are indicated to validate this hypothesis. The balance of this discussion will focus on evidence examining the impact of the effectors trained, interfaces utilized and the severity of the impairment of participants. In addition, some key studies that were not included in these meta-analyses for methodological reasons and papers published following the Cochrane review by Laver [128] will be discussed.

Multiple authors have identified a critical period in which persons in the early subacute period after stroke (less than three months post-stroke) are more able to benefit from motor retraining interventions than persons in the chronic stage of recovery (greater than 6 months) [186, 218]. In order to assess this idea, six studies that evaluated VR's effectiveness in improving upper limb function post-stroke were grouped into two categories. The first category being studies that had sample populations less than 3 months post-stroke, and the second category being studies with sample populations over 6 months post-stroke. In the category of patients less than 3 months post-stroke, two studies were placed; the first study being from Gueye et al. 2020, found a significant difference from the implementation of VR, while the second study from Brunner et al. 2017 found no significant difference [219, 220]. Four different studies examined similar interventions in persons 6 months post-stroke. Two of these studies found a significant difference in upper limb function when VR was implemented [221, 222], but two other studies found no significant difference between control and experimental groups [223, 224]. Taken together, these studies suggest that virtually simulated interventions are not more effective for the delivery of upper extremity therapy during the initial recovery period after stroke. Further studies during the initial recovery period might benefit from refocusing, either on subjects who are too impaired to participate in traditionally presented therapy, or mildly impaired persons with stroke, who are discharged directly to home, without intensive rehabilitation.

Many studies have been written examining the impact of timing and total training volume on the outcomes of relatively short-term interventions utilizing VR (less than 4 weeks). This said, the motivational advantages associated with VR-based interventions and the efficiencies afforded by home-based VR training make the examination of longer intervention periods worthy of attention. To address this question, 12 recent RCT that studied the effectiveness of VR as a treatment for upper limb function post-stroke were examined. Of these 12 articles, 10 fit into the category of being 4 weeks of treatment or less. Of these 10 articles, only 4 showed clearly significant differences between experimental and control group results [219, 221, 225, 226]. Five articles showed no significant difference between VR and control conditions [220, 223, 227–229] and a sixth showed results that differed across outcome measures [230]. In contrast, two studies with treatment lengths of 4 weeks both showed significant differences between experimental and control group outcomes [222, 231]. The mixed results reported by shorter interventions and the consistent group time interactions demonstrated in these two longer studies might imply that treatment length might have some role to play in the effectiveness of VR as an intervention when compared to traditionally presented therapy. Furthermore, an uncontrolled pilot of a twelve-week, home-based intervention in persons with stroke demonstrated excellent adherence and clinically significant improvements in Upper Extremity Fugl Meyer Assessment (UEFMA) score suggests that longer treatment programs are feasible [232]. Clearly, more study of longer interventions is needed.

An important variable of consideration for clinicians designing interventions for patients post-stroke would be frequency. The term “frequency” in this case referring to times per week in which a virtual reality session would take place for a given patient. In order to understand the role of treatment frequency 13 Randomized Control Trials that studied upper limb functional improvement post-stroke when VR was implemented were considered. Nine of these studies utilized treatment protocols with 4 or more treatment sessions per week, and 4 examined protocols with three or less sessions per week. Three of the nine articles with four sessions per week protocols demonstrated statistically significant results [219, 221, 226]. The remaining 5 articles did not demonstrate any significant results [220, 223, 224, 227, 229] and a sixth demonstrated mixed results [230]. Three of the four studies with lower frequencies demonstrated statistically significant differences between VR and control groups [222, 225, 231] and a fourth demonstrated non-significant results [228]. These results suggest that more than two or three VR-based treatment sessions per week might not confer any additional benefits when compared to control therapies. This notion, that Virtual Reality treatment might elicit significant motor function improvements with a lower treatment frequency is potentially important and warrants further research.

For clinicians who wish to use VR post-stroke it is useful to consider if there are age groups that utilize this family of technology more successfully than others. In order to understand the effects age may have on the effectiveness VR interventions, 13 articles were collected and separated into 2 distinct categories. Ten of these articles examined study populations under the age of sixty. The first category contained all articles with sample populations above the age of 60. Six of these articles reported significant differences between experimental and control groups [221, 222, 225, 227, 231]. One article was found to have mixed results wherein the primary outcome measure, being the UEFMA, was found not to have significant differences between experimental and control trials. However, the secondary outcome measure, the Box and Block Test, did have significant differences. Three of these articles did not demonstrate a difference between VR and controls [220, 224, 227] and a fifth demonstrated mixed results [230]. Interestingly, none of the studies with mean ages above sixty demonstrated better outcomes for VR subjects when compared to controls [223, 228, 229]. This body of evidence suggests that age might play a role in VR therapy effectiveness and that it is plausible that individuals above 60 years of may not benefit from VR-based interventions more than those younger than 60. Alternatively, the differences in effectiveness identified across these studies may be an effect produced by differences in the lived experiences of older subjects, who had less exposure to computer gaming and virtual reality than younger subjects. Large trials with age-stratified samples or smaller studies specifically designed to answer this question are indicated. In addition, previous exposure to technology is a factor that needs to be considered when interpreting the results of technology supported rehabilitation studies. Clinicians should also include an assessment of patient’s technology literacy when proposing technology supported interventions.

20.3.1.2 Non-Custom Systems

Several studies of upper extremity rehabilitation have utilized the Wii™ system in patients with stroke. Subjects in several pilot studies of persons with stroke using the Wii™ have demonstrated statistically significant improvements in motor function and activity level clinical tests [233–235]. Even though the Wii™ interface does not collect individual finger movement or grip force data, subjects in another pilot study demonstrated fine motor improvements in persons with stroke following a Wii™-based intervention [236]. Two controlled studies comparing Wii™-based upper extremity interventions and a dose matched traditionally presented upper extremity intervention demonstrated statistically significant improvements at the function and activity levels. Improvements demonstrated by the two groups in both studies did not differ [213, 237]. The Wii™ training group in a third controlled trial made larger improvements on the UEFMA and Box and Blocks test than a dose-matched traditional training group [238]. The Cochrane review by Laver et al. in 2017 identified 7 RCT utilizing an off-the-shelf gaming system compared to 15 RCTs with upper extremity simulated interventions using custom VR systems in persons post-stroke that were methodologically suitable for comparison [128]. Both groups of studies demonstrated significant effects but were not more effective than conventional therapy approaches. A recent systematic review considering 30 studies identified significant benefits for body function and activity measures only for custom VR systems when compared to off-the-shelf VR [239].

A substantial body of research related to the validity of measurements of human movement with the Kinect™ has been developed see [216] for a detailed review as well as a review about translation into practice [240]. However, few studies of the clinical effectiveness of Kinect™-based rehabilitation programs for persons with upper extremity impairments have been published to date. A case/feasibility study with a severely impaired subject demonstrated increased upper extremity active range of motion but no improvements in UEFMA score after a 10-session training program [241]. This subject was severely impaired, which may underestimate the potential of this intervention for less impaired subjects. A case series of five subjects with moderate impairments demonstrated improvements in UEFMA and Wolf Motor Function Test (WMFT) scores that corresponded to increases in cortical activation of the lesioned hemisphere [172]. The changes in clinical test scores and cortical activation demonstrated by subjects in this case series were comparable to those demonstrated by subjects in studies of custom VR systems [164]. Two studies have examined the addition of Kinect™-based upper extremity rehabilitation activities to a program of traditionally presented therapy [57, 242]. Control groups for both of these studies performed the same volume of traditionally presented therapy as the experimental group. As would be expected, the subjects performing the additional Kinect™-based therapy demonstrated larger changes in active range of motion, ADL ability, and larger improvements in UEFMA, WMFT, and Motor Activity Log (MAL) tests. More rigorous testing of Kinect™-based rehabilitation activities will be necessary to evaluate their value relative to custom VR or traditionally presented therapy.

20.3.2 Balance and Gait

20.3.2.1 Custom Systems

Historically, the development and application of VR systems for neurorehabilitation focused on the upper limbs. This may have been motivated by two main factors. First, relative to upper limb use, balance and walking skills are more commonly and extensively recovered after a stroke. Second, building balance and walking VR-based systems require greater technical and space requirements to meet the special physical and safety challenges. In contrast to most upper limb systems, which allow patients to be seated while performing movements with the upper extremities, balance and walking skills, for the most part, require patients to be upright or to walk. There exists a modest yet increasing body of work on the development and use of customized VEs for walking recovery and balance, which is reported in several topic-specific reviews [243–249] as well as in overview reviews [250–252]. In contrast to the 1038 participants who participated in the upper extremity studies included in Laver's Cochrane Review of Stroke Rehabilitation, there were only 139 persons involved in balance and mobility training, with only seven studies where gait speed was measured.

Visual feedback is a common element in evidence-based interventions for balance training post-stroke [253]. It is used to provide participants information about the verticality of their posture, which may be impaired due to sensory and perceptual deficits, as well as their weight distribution. Both of these attributes are incorporated into VEs for balance rehabilitation. The GestureTek® IREX® video capture system based on chroma key technology was first used in studies involving individuals who had sustained a TBI, where slight improvements were detected in balance [254, 255], confidence [256], and reaction time [256], compared to conventional training protocols. The system has also been used with persons post-stroke, providing benefits to the sensory organization, motor function, and balance. In general, training with the system provided benefits that were detected in scales related to balance but not to gait. A randomized controlled trial involving higher functioning persons post-stroke who were inpatients examined the effects of using the system in addition to a conventional rehabilitation program. There was, however, no significant improvement in walking ability and gait speed derived from the use of the system [257].

Force platforms have been used to estimate and visualize participants' center of pressure providing visual feedback during displacements toward the target [253]. The use of force platforms in combination with customized virtual exercises has also been explored. The training of the ankle and hip strategies during weight-shifting exercises adapted to the particular limits of stability of each subject provided benefits to conventional physical therapy interventions in the general balance condition and in the maximum reachable distance [258] (Fig. 20.5). Interestingly, these effects were retained at follow-up after the intervention [259]. A recent analysis of aggregated data from different studies and unpublished data from Llorens corroborated these results and showed consistent improvements in the Berg Balance Scale and the Functional Reaches Test after an intervention using weight-shifting exercises. The gains were maintained, and even enhanced, one month after the intervention [260]. However, it is important to highlight that the improvement facilitated by these exercises, and more importantly, the maintenance of gains, are severely influenced by time since injury [261]. According to this, fewer gains and more difficulties in maintaining them should be expected with greater chronicity.

Similar to balance platforms, standing frames equipped with gyroscopes can detect postural tilts, enabling interaction with the VE through weight transferences. These systems have been used in home-based interventions with individuals post-stroke, reporting improvements in balance and gait [262, 263]. However, the use of VR did not provide significant benefits to the training with the standing frame alone. Research on the effectiveness of weight-shifting exercises in sitting is very limited. The scant literature about it has focused on training trunk movements through VR-based tasks that required trunk lean and reaching beyond arms' length using Jintronix software (Jintronix, Montreal, Quebec, Canada) interfaced with a pressure mat, showing comparable benefits to conventional physical therapy interventions and variable requirements of trunk stability [264, 265].

Walking on a treadmill interfaced with VE has been used to promote recovery of walking for persons post-stroke. The inclusion of visual and vibrotactile augmentation while stepping over virtual objects during walking on a treadmill improved walking better than stepping over real-world objects. Several studies have reported the combined use of treadmills and VR and its effects on the gait and, to a lesser extent, static balance of stroke survivors. Users commonly walk on a treadmill while the VE is displayed by projectors [59, 266] or TV screens [267–269],

Fig. 20.5 In the system by Llorens et al., after registering their maximum excursion in the medial–lateral and anterior–posterior plane, exercises are adapted to each client's particular motor limitations [186]. Exercises require participants to perform postural adjustments involving the ankle and hip strategies to displace their center of pressure toward different targets

showing real-world video recording [266, 269, 270] or virtual scenarios [267, 268]. Interventions involved tasks of variable difficulty, from walking, dual-task performance, such as remembering and identifying groceries while navigating through a pre-recorded walking scene in a real supermarket [269] or reaching objects with the upper limbs on the SeeMe system (Brontes Processing: Gliwice, Poland) [271], or stepping with either the paretic or nonparetic limb [59]. The use of feedback provided by VR favored not only gait [59, 266, 270–272], but also static balance, sway, sit-to-stand movements, and the use of the paretic limb [266, 267, 269, 271]. The enhanced motor performance after adding VEs to treadmill training could have been promoted by an increased entrainment of brain activity involved in motor planning and learning (maybe through the mirror-neuron system), as suggested by EEG findings on addition of VR to robot-assisted gait training [272].

In addition to treadmill walking simulations, several investigators have used stepping, pre-gait activities, and even training of the lower extremity in sitting to improve walking for persons in the chronic phase post-stroke [46, 70, 168]. Llorens et al. reported that the training through virtual stepping exercises improved balance compared to conventional interventions [273] (Fig. 20.6). Individuals were required to step on items that appeared around a circle with the closest foot while maintaining the other foot inside a circle. This intervention also promoted improvements in gait speed, which could be derived from the training of movements similar to those used in the stance phase of the gait cycle. The system was also used in a home-based intervention with similar results to those obtained in in-clinic interventions. The analysis of aggregated data from 131 individuals with stroke from different studies and unpublished data showed consistent improvements in the Berg Balance

Scale and the 10-m Walk Test after the intervention, which were improved and maintained, respectively, one month after the intervention [260]. Mirelman et al. coupled VR with a robot-based training of the lower extremity, where participants were required to perform movements with the ankle while sitting to navigate a plane or a boat through a VE. When compared to the robot alone, the VR-robot combination was superior in improving walking velocity and distance in laboratory, clinical, and community-based tests [46]. You and colleagues used the IREX® system to promote functional ambulation and waking through the training of stepping movements, side-to-side weight shifting, and sideways navigation. Interestingly, the locomotor recovery was associated with cortical reorganization from aberrant ipsilateral to more normal contralateral activation of the sensorimotor cortex [63]. Recent interventions involving VEs that required similar interaction, and also upper limb movements, provided consistent results with that seminal study, showing improvements in balance that were comparable and almost significantly greater than those provided by conventional physical therapy exercises [274–276].

20.3.2.2 Non-Custom Systems

Studies have reported on outcomes of non-custom systems (e.g., Wii and Kinect) for balance and mobility training of people post-stroke. Early on there were several case reports of people in the chronic phase post-stroke, which reported positive outcomes for balance and mobility interventions [277, 278]. More recently, eight pilot clinical trials using video games to improve balance and mobility have been reported. They have predominantly been conducted with subjects in the chronic phase post-stroke [35, 279–282], but there is now some support for application to persons in the subacute [283] and acute phases of recovery [284, 285].

The quality of the research is improving as more of the trials have active control groups and follow-up measurements [282–286]. However, comparing among studies is complicated based on substantial differences in dose and acuity. Several studies had unequal doses and did not use active controls [280, 281]. Studies conducted in the acute and subacute care setting using active controls showed a positive effect for balance and functional ambulation tests favoring the games [283, 285]. In contrast, studies with active controls and balanced doses of persons with chronic strokes favored standard of care [35] or showed no difference for balance and mobility measures, but favored the VR group for enjoyment measures [200, 282]. As with the upper limb studies, a better understanding of how acuity modifies the benefits of VE training will guide the future clinical application.

Non-custom systems have used similar technologies as the customized VR systems. PlayStation® two EyeToy: Play™ is similar to the IREX® system [205] and was tested at home in a case study with an individual 2 years post-stroke [277]. The training of postural adaptations during bilateral stance in subjects post-stroke has been mainly facilitated by the Nintendo® Wii™ Balance Board, a force platform peripheral device for the Nintendo® Wii™, which allows interaction through displacements of the center of pressure, it is, through weight shifting [280–283, 285]. Interestingly, some studies have analyzed the combination of static exercises using the Wii™ Balance Board with more dynamic exercises. Deutsch et al. compared standard of care with the Nintendo® Wii™ games and reported no between-group differences, but a greater number of within-group improvements for balance and mobility measures for the standard of care group [35]. Fritz et al. added EyeToy: Play™ games reporting small positive effects of this training compared to traditional therapy [279]. The combined training of weight transferences using the Wii™ Balance Board with dynamic balance exercises with the Microsoft® Kinect™ promoted improvement in the maximum reachable distance in acute subjects post-stroke [284], but were equally effective as conventional physical therapy in maintaining physical function outcomes and ADLs in the chronic population [287].

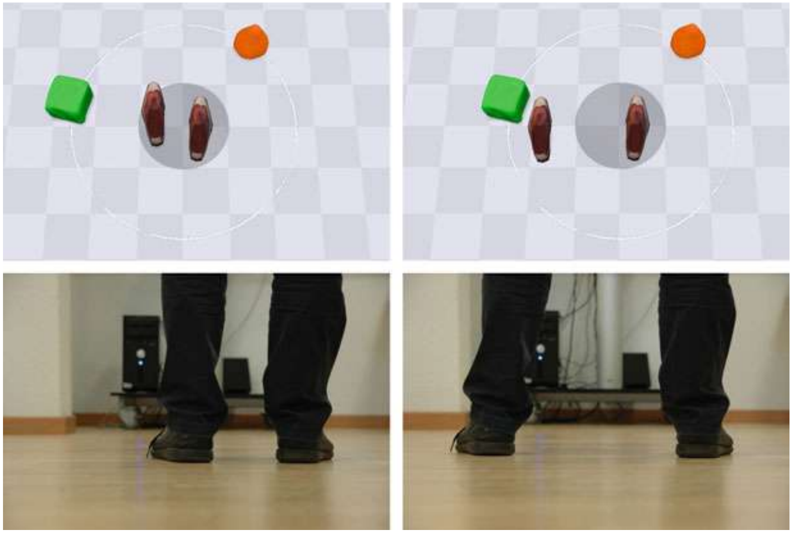

Fig. 20.6 In the system by Llorens et al., the virtual environment consisted of a checkered floor, whose center was indicated by a darkened circle, and jelly items that rose from the ground around the circle [194]. The goal of the exercise was to reach the items with the nearest feet while maintaining the supporting foot within the circle. After reaching the item, the extended extremity had to be recruited to the body within the boundaries of the circle. Otherwise the exercise did not allow new items to be reached

20.3.3 Activity Promotion

Movement-based VR systems have focused on sensorimotor rehabilitation, but there is an emerging application to fitness promotion in persons post-stroke. Given the importance of physical activity [288] and the barriers to exercise encountered by people post-stroke [289], VR is proposed as a facilitator of activity. The VR may be delivered using a custom system coupled with exercise equipment such as a bicycle or a treadmill, or a non-custom system played as an exergame. Custom systems allow the harnessing of heart rate to drive the exercise intensity. A group has developed a VR-augmented cycling system that uses heart rate as an input to the VE [290] (Fig. 20.7). In a pilot study, participants post-stroke who trained on the system had significant improvements in VO2 sub-max bicycle test and mobility outcomes as well as changes in force kinetics during cycling [291].

Non-custom VR systems or exergames have been explored to promote activity and fitness for persons post-stroke. Studies have been either cross-sectional characterizing energy expenditure or clinical trials assessing the cardiovascular benefits of exergames. The ability of persons in the chronic phase post-stroke to increase their exercise intensity using exergames has been reported by three groups [292–294]. Hurkmans et al. characterized two predominantly upper limb Nintendo® Wii™ games (tennis and boxing) and reported that they produced moderate (three to five metabolic equivalents) exercise intensity [293]. Kafri and colleagues in a case-control series compared the energy expenditure and exercise intensity between individuals post-stroke with moderate mobility limitations to semi-active healthy matched controls while playing both Kinect™ and Wii™ games in sitting and standing [292]. The games were categorized as a standing balance task to upper limb predominant (boxing) and lower limb predominant (running). Generally, post-stroke individuals had lower energy expenditure (at the low end of moderate) than the healthy controls (moderate to low end of vigorous), during similar activities. They did, however, exercise in the heart rate intensity recommended for fitness. Silva de Sousa reported similar findings that playing

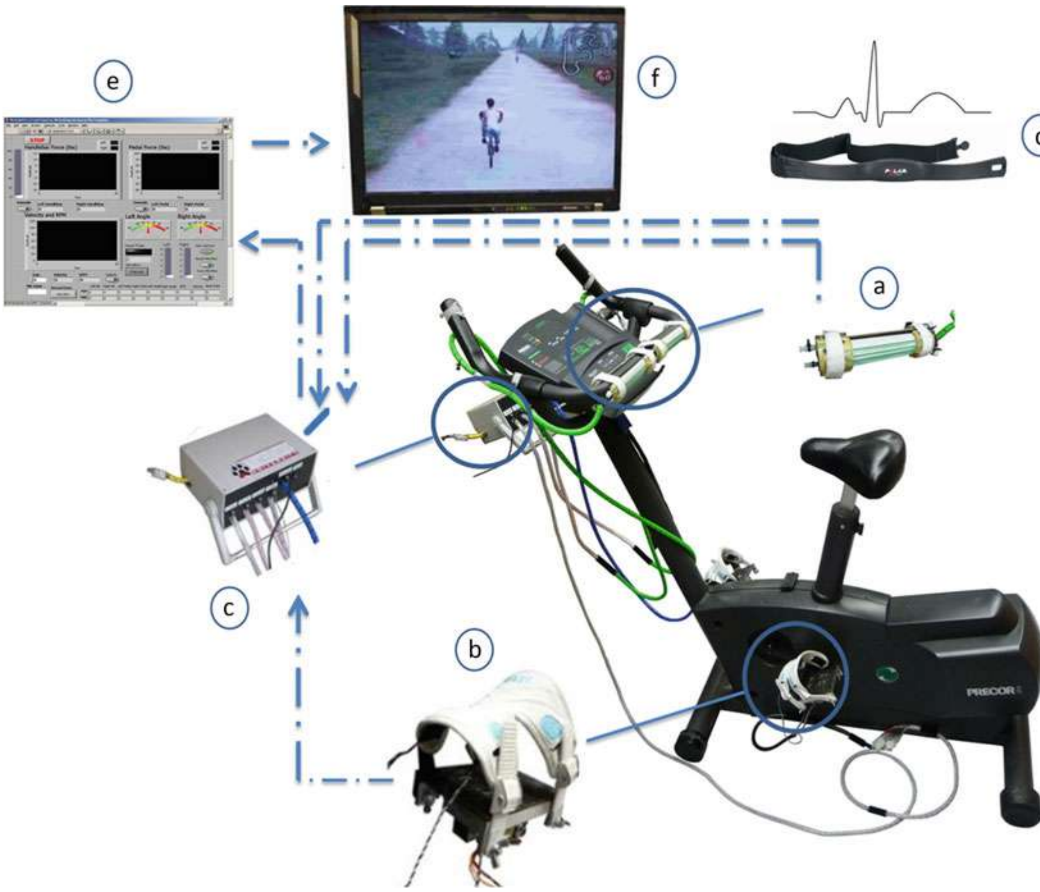

Fig. 20.7 VRACK system complete overview; **a** Handlebar module; **b** Smart pedal; **c** Power supply, preamplifier, and the data acquisition board; **d** Heart rate monitor, **e** Practitioner interface; **f** Virtual reality environment [209]. Reproduced with permission of the Rivers Lab

Kinect™ games of tennis and boxing produced reliable changes in VO_2 which were at a lower aerobic intensity and heart rate responses that were at a higher aerobic intensity [294].

Clinical trials that tested the efficacy of non-custom exergames to improve fitness have been conducted for persons in the chronic as well as subacute phase post-stroke. Game consoles have included the Microsoft with the Kinect™- with dance and Adventure games [295, 296], the Nintendo Wii™ with Sports games [297]. VO_2 and activity improvements were reported for persons in the chronic phase post-stroke who played the Kinect™ Just Dance 3 games [295]. In a large trial (n = 640), Tollar and colleagues reported positive outcomes for persons in the subacute phase (2–4 weeks) post-stroke who played Kinect™ Adventure exergames of Reflex Ridge and Space Pop plus Just Dance 3 \in addition to agility training. They specifically compared a dose of one time a day for five consecutive days over five weeks (25 sessions) to twice a day (for a total of 50 sessions). The higher dose produced significant and clinically meaningful gains both in the six-meter walk test and reductions in systolic blood pressure (interpreted by the authors as anti-hypertensive). These findings are important as they protect against a recurrent stroke. Interestingly in a study that focused on upper limb use comparing Wii-Sports games to modified constraint-induced movement therapy, the Wii™ movement therapy group demonstrated aerobic gains suggesting that upper limb therapy could be combined with aerobic activity [297].

Non-custom gains have been critiqued because they cannot be adjusted for persons post-stroke. A careful comparison between custom and non-custom Kinect™ exergames played in a single session by persons in the chronic phase post-stroke showed that the exercise intensity was statistically greater for the custom game but played in the same intensity bands for METs (moderate) and [298] Heart rate results were similar. Importantly, the participants reported less perceived effort and greater enjoyment with the custom games, and greater symmetry of lower extremity kinematics [299]. It appears the VR in the form of either non-custom or custom exergames may be a valid tool for activity promotion, given their potential to increase motivation for exercise and to promote adherence. Whether custom games are superior to non-custom games remains to be further tested.

20.3.4 Summary

A steady proliferation of studies comparing virtual rehabilitation interventions to traditionally presented rehabilitation in persons with stroke has developed over the past 15–20 years. Comparable outcomes have been reported when comparing virtual and real-world upper extremity training in subjects with more acute strokes. The best-developed area of this literature examines upper extremity interventions in subjects with chronic strokes using customized lab-based systems. These comparisons describe slightly better outcomes for virtual rehabilitation interventions. This advantage is more pronounced in mildly impaired subjects. More, larger, and better controlled studies are required to draw definitive conclusions along these two lines of inquiry.

A smaller literature has examined the relative efficacy of a VR-based rehabilitation on walking ability (as measured by gait speed and distance) in persons with stroke. A non-significant trend toward better outcomes for virtual reality-based training as compared to real-world gait training has been identified. The balance of studies comparing the impact of these two training approaches considers the kinetics and kinematics of gait. Neither approach to training has been associated with significant advantages across multiple studies. In contrast, balance interventions presented in virtual environments have been associated with significantly better outcomes than traditionally presented balance training across a wide range of balance measures. An expansion of the size and number of studies and a focus on a smaller set of outcome measures will be necessary to identify an additive effect for virtual environments on gait training. Further, VR primarily with non-custom games has some preliminary support as a tool for promoting physical activity.

20.4 Considerations for Future Research

While there is consensus that neuroplasticity is central to the motor recovery process, there is a relatively small literature examining the impact of VR interventions on positive, neuroplastic adaptations in persons with neurologic injuries. Some pioneering investigations utilizing neuroimaging have been conducted. An expansion of this area of inquiry could optimize and accelerate both the design and implementation of VR-based rehabilitation interventions. However, the cost and need for large transdisciplinary teams to perform studies of this type have kept progress in this area slow.

There is also consensus that motor learning is central to the process of neuroplasticity, and VR-based rehabilitation interventions are typically constructed with attention paid to accepted principles of motor learning. Examinations of the motor learning accomplished by virtual interventions have predominantly focused on the transfer of motor skills learned in VEs to veridical world motor skills and performance improvements achieved during virtual interventions to a lesser extent, both with favorable results. A broader implementation of formal motor learning paradigms to the study of virtual rehabilitation might offer a more efficient and cost-effective approach to optimizing virtual rehabilitation. By their nature, interfaces designed for VE-based activities are well suited to collect the necessary data. In addition, simulated activities are easily presented in the systematic, reproducible fashion necessary for studying within and between session learning.

Science related to motivation may, first, enhance the volume of motor practice performed independently by patients in their homes. Home practice is critical in areas with limited access to a therapist due to availability or reimbursement issues, and compliance with home practice schedules is typically poor. Second, motivation science may enhance the frequency and duration of the performance of fitness-oriented activities in persons with disabilities. Motivation and access are primary obstacles to the regular performance of fitness activities with a wide variety of disabilities, both of which can be overcome with well-designed, simulated exercise programs.

20.5 Conclusions

A review of this chapter should leave the reader with the impression that (1) there is a science underpinning virtual rehabilitation, (2) individuals with neurological impairments can effectively use VE, as they feel being as present and bodily represented in them as healthy subjects, and (3) the evidence base related to the efficacy of virtual rehabilitation has confirmed that it can be a viable and, for the upper limb, a superior alternative to traditionally presented activities. While these impressions are validating on the one hand, they also identify a need for continued improvement. This said, trends also emerge, indicating opportunities for optimizing virtual rehabilitation and expanding the populations and areas in which it is practiced.

Early work in virtual reality-based rehabilitation for persons with stroke was informed by concepts of neuroplasticity and motor learning. Simulations incorporated augmented feedback, knowledge of performance, and knowledge of results. An ideal combination of these principles has not been elucidated. Massed practice was promoted as tool to overcome lack of motivation for repetitive task practice required for behavioral outcomes and neural plasticity. The high number of repetitions per unit time has been robustly supported for both custom and non-custom virtual reality applications.

The user's experience as it is affected by the presentation of information via the user's visual, auditory, kinesthetic, and tactile senses has been another area of study. A small body of literature supports that the presentation approach and quality of sensory information provided to participants with strokes affects the way they move during virtual interventions. A parallel literature describes differences in brain activity during virtual interactions elicited by differing presentations of virtually simulated motor activity. This brain activity has been linked to processes related to the execution, observation, understanding, and mental simulation of real-world movement.

The literature comparing virtual rehabilitation interventions to traditionally presented rehabilitation in persons with stroke has grown slowly but steadily over the past 15–20 years. This literature cites that VR-based interventions produce comparable improvements in upper extremity function and balance when compared to traditionally presented rehabilitation interventions. To date the literature on virtual interventions to improve gait is not developed sufficiently to evaluate its efficacy compared to traditionally presented interventions.

Two important trends will be critical for shaping the future development of virtual reality. One key to the transition of virtual rehabilitation to the home environment has been the development of lower cost, but effective interfaces. The ability to customize the application of Kinect™ like sensors should prove to accelerate this transition, allowing for the use of off-the-shelf equipment to access simulations explicitly designed (custom) for rehabilitation. Clearly, virtual rehabilitation is an expanding area in the field of technology-based rehabilitation and has an evidence base that is growing in terms of size and quality. Several challenges described above need to be addressed but the field continues to hold promise to answer key issues faced by modern healthcare.

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