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Review

Virtual Reality in the Rehabilitation of Cognitive Impairment after Stroke

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Abstract: Virtual reality (VR) is seen by some as a tool that may greatly improve, or even revolutionize cognitive rehabilitation. VR offers distinct advantages compared to classic rehabilitation using paper-and-pencil or computer-based training, such as immersion, the feeling of presence, embodiment of virtual players, ecological and multisensory stimulation. We here review recent clinical studies examining the effects of VR training in patients with stroke-induced cognitive deficits. Several trials reported evidence that VR training improves general cognition compared to standard cognitive training. However, the evidence remains controversial, as some of these studies had a high risk of bias. Regarding mood, there is some indication that immersive training improves depression scores in stroke patients, but the number of studies examining mood changes is very low. Finally, in the domain of spatial cognition the development of specific intervention techniques such as virtual prism adaptation provide avenues for clinical interventions, though well-controlled clinical trials are lacking. Together, the available evidence suggests that VR has the potential to improve rehabilitation particularly in domains requiring repetitive training in an immersed, ecological setting, or when a mismatch between body frames and the environment is created. Controlled clinical studies are required to examine the specific advantages of VR compared to classic interventions.

Keywords: virtual reality; stroke; neurorehabilitation; prism adaptation; spatial neglect

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1. Introduction

Physical rehabilitation after stroke uses virtual reality (VR) as an add-on to maintain motivation and adherence, and add a playful component to repeated exercises, though newer studies indicate that VR also may have direct beneficial effects on walking speed, balance, and gait [1–5]. At face value, VR has several features that show distinct advantages for rehabilitation: it brings some of the complexity of the physical world into the laboratory or clinic; it often has greater ecological validity than paper-and-pencil exercises; it is a safe way to expose patients to situations that are potentially dangerous (such as street crossing) or may trigger anxiety; it can be used in small spaces yet provides access to a wide range of activities and virtual spaces; stimulation in VR is multisensory, and it allows repetition of exercises while varying the visual scene [6–9]. Additional advantages for rehabilitation are the online presentation of helpful cues and the support of errorless learning, together with the provision of rapid, real-time feedback about performance [10]. On the other hand, VR technology may be expensive, difficult to adapt, not well accepted, and lead to motion sickness [11].

Cognitive impairments may benefit from additional aspects of VR, such as the increased field of view for neglect rehabilitation, or ecological environments for rehabilitation of memory or executive function [9,12]. Here, we review and discuss studies using VR to improve cognitive function after stroke. The number of studies mentioning the terms 'virtual reality' and 'rehabilitation' is currently growing exponentially (Figure 1), as is the number of reviews and meta-analyses. However, many studies focus on physical rehabilitation, use

VR as an addition to standard therapy, or are small pilot studies or non-randomized trials. In addition, in the cognitive domain most clinical studies focus on patients with dementia or mild cognitive impairment (MCI). The results of these studies have been addressed in several reviews and meta-analyses [13–18]. We here discuss immersive VR applications for the rehabilitation of cognitive functions by discussing randomized-controlled trials (RCTs) of patients with acquired brain injury. Since most studies used cognitive screening tests or examined visual-spatial skills, we focus our review on the effects of VR training on these two aspects of cognition.

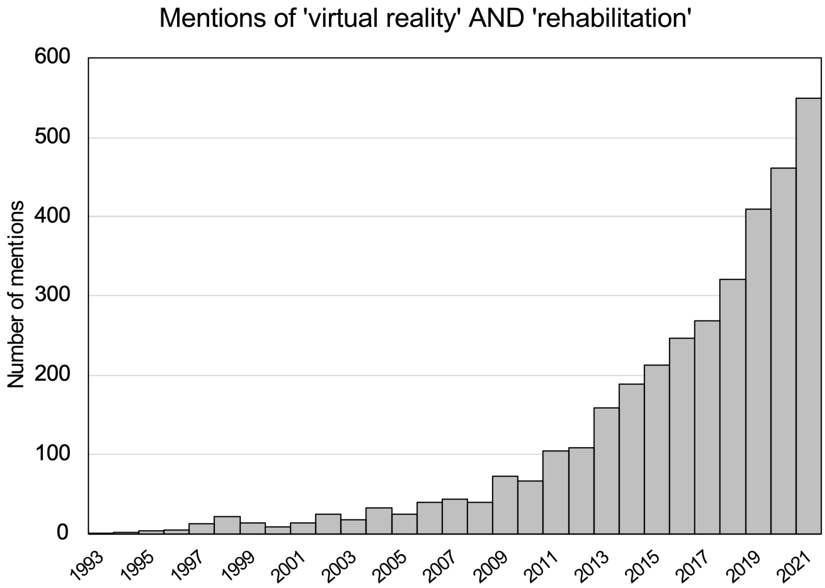

Figure 1. Number of mentions of 'virtual reality' and 'rehabilitation' in Medline (by 15 October 2022).

2. Effects of VR on General Cognition

In recent years several clinical trials targeted cognition in stroke patients with specific VR-based interventions. Some of these trials combined classic therapy with VR as an addition. For example, Shin et al. [19] reported that VR, added to occupational therapy had stronger effects on quality of life and depression in chronic stroke patients than occupational therapy alone. Patients either participated to one hour per day of occupational therapy targeting activities of daily living (ADL) and upper limb use, or 30 min of occupational therapy and 30 min of VR games that required active arm and trunk movements. The program was selected individually for each patient to address specific deficits of upper limb function. Both groups received five weekly sessions for four weeks. Results showed a significant decrease of depression symptoms in both groups, without a significant difference between them. In addition, there was an improvement of self-reported quality of life, which tended to be greater in the VR group. The authors interpreted the positive effects of VR on mood as resulting from the experience of flow, interest, and positive feelings during the playful, immersive therapy. Faria et al. [20] used a more general VR program that focused on use of memory, attention, visuo-spatial and executive functions in daily routine. The study involved 18 stroke patients without aphasia or neglect, who were randomly attributed to a VR group or a cognitive training group (puzzle and problem solving, mathematics or memory training). Patients in the VR group were required to accomplish everyday tasks at locations in a virtual city (such as a bank or a post-office). After training for 12 sessions the VR group significantly outperformed the control group on measures of general cognitive function, attention, and verbal fluency. In addition, within-group comparisons indicated improved visuo-spatial and executive functions only in the VR group. This small trial thus indicated greater impact of a VR-based intervention on cognitive functions than simple cognitive training. In a follow-up study the same authors [21] compared the VR program with paper-and-pencil exercises and found greater improvement of general cognitive functioning (assessed with the Montreal Cognitive Assessment, MoCA; [22]) in the VR group. Similar results were reported by De Luca et al. [23] in a small study with 12 stroke patients who were randomly assigned to a VR group or a group that trained diverse cognitive tasks. VR consisted of several tasks probing memory, attention or visual-spatial skills that were adapted for each patient. The authors observed a significant improvement of a general cognitive measure (MoCA) and visual attention in the VR group only, which was partly maintained at follow-up.

In a study by Maier et al. [24], an adaptive training using VR led to significantly lower levels of post-stroke depression compared to a control group who solved cognitive tasks at home. In addition, only the VR group showed improved performance in attention, spatial awareness, and general cognitive function after the training. Finally, the trial with the highest number of participants published so far included 90 stroke patients, who were randomly assigned to a robotic rehabilitation group with VR, robotic rehabilitation without VR and a control group with conventional cognitive rehabilitation [25]. The VR component required patients to collect diverse objects and to avoid obstacles while walking on a treadmill. After 40 therapy sessions, all three groups showed improvements in global cognitive functioning, mood, executive functions such as perseveration, and activities of daily living. A specific advantage of VR was observed in additional improvements of cognitive flexibility, selective attention, and self-perceived quality of life. In addition, a direct comparison between groups revealed that VR improved general cognition (MoCA) and mood more than robotic rehabilitation without VR. It also resulted in faster visual processing and visual search.

The two factors that appear to explain differences between studies are the number of therapy sessions and immersion. While the former can easily be adapted, the latter strongly depends on the available technology, with more modern systems being better suited to generate stereoscopic vision and fluid displays. Immersion may be the only factor that differentiates computer training from training in VR, and differences regarding immersion may explain why some reviews and meta-analyses disagree regarding the recommendations to be made for the addition of VR in rehabilitation settings. For example, Maggio et al. [26] make a positive recommendation that is based on several pilot studies, exploratory trials, or observational studies. In contrast, a systematic meta-analysis performed in 2017 noted no specific advantages of training with VR (as compared to conventional therapy) on measures of quality of life and independence in ADLs [27]. This is consistent with disappointing findings from a meta-analysis that examined VR effects on motor control, balance, gait and strength [28]. In addition to these studies we identified one report that specifically focused on training of prospective memory through exercises with increasing difficulty performed in a virtual environment [29]. The program required fifteen patients with mixed cognitive problems to solve different prospective tasks that were cued by external events (such as picking up a parcel), within a specific time interval. Ten hours of training resulted in significant gains on a prospective memory test, supporting transfer of training effects. However, the study did not involve a control group, which makes the extent of improvement difficult to evaluate.

Several recent reviews and meta-analyses also examined the effects of VR interventions on general cognition in patients with stroke. Unfortunately, there is no consensus among these reports. For example, Wiley et al. [30] found standardized mean differences between VR and control groups ranging between 0 and 0.56 for general cognition, memory and language, none of these being significant. This confirms the conclusions from an earlier Cochrane review [27] that VR does not add significant benefits to standard cognitive rehabilitation. The latter review also observed a high risk of bias in many published studies, due to underreporting of critical information. In contrast Chen et al. [31] observed significant mean differences between VR and control groups for general cognition (MMSE: 2.84; MoCA: 2.51), the Trail Making Test (A: −20.6; B: −64.4, indicating much faster performance in the VR group) and even latency of the P300 EEG potential (mean difference:

−35.3, indicating shorter latency in the VR group). We found these findings difficult to verify since many studies cited in the latter review were not accessible at the time of writing. However, when considering the more recent clinical trials we find the conclusion justified that VR interventions have slightly superior effects on general cognition than conventional therapy. This is particularly the case when immersive systems are used, as such systems generally have increased ecological validity of the task [4,32]. Such systems are highly engaging and produce a sense of presence in the observer that may concurrently stimulate attention, working memory and the awareness of space, which is one of the main advantages of VR [33]. Whether these, or simply higher motivation are the drivers of improvement in cognitive domains remains to be elucidated. In contrast, a later study [34] did not find an advantage of dual-task training in VR compared to visual scanning training. By 2017 the evidence for a specific advantage of immersive VR training over traditional (paper-and-pencil, or computer-based) training was judged as inconclusive [35,36]. However, it should be noted that the development of VR technology is very dynamic, and systems that were used in studies published five years ago are barely comparable to up-to-date technology. This is particularly the case of immersive systems, which seem to have the greatest effects on measures of general cognition, mood, or attention. These effects may strongly rely on motivational factors, engagement and effort, compliance with the intervention, and increased alertness, which all may affect outcomes of the intervention. Unfortunately, such factors are difficult to capture and are not routinely examined in clinical trials. Future studies need to address these issues to identify the working ingredients of VR interventions.

3. Effects of Training in Virtual Reality on Spatial Cognition

The three-dimensional, ecologically valid representation of space offered by immersive VR presents a particular advantage for the assessment and rehabilitation of spatial cognition and spatial memory [9]. For example, an early study by Kim et al. [37] showed that interactive training in VR (such as catching virtual objects) resulted in better visual search and lower values on a behavioral scale measuring spatial neglect than visual scanning training. This study also demonstrated one of the major advantages of VR, namely immersion into a virtual world where patients may interact with objects and directly experience feedback about their actions. Other studies revealed positive effects of visual scanning training or search in VR on neglect measured with specific neglect tests and observation in everyday life [38,39]. However, the domain in which VR has shown the most elegant applications is prismatic adaptation (PA). PA with wedge prisms is a non-invasive technique widely used to study visuo-motor plasticity in healthy individuals, that is claimed to decrease the right attentional bias observed in brain-damaged patients with neglect. Left optical prisms displace the entire visual field and induce a rightward bias in manual reaching or pointing to visual targets, which appears already after a few pointing movements [40]. After removal of the prisms, reaching initially deviates in the direction opposite to the optical shift (here, towards the left side), a phenomenon called visuomotor after-effect. In a classic PA paradigm, three phases can be distinguished: a phase composed of different pre-tests, followed by a period of prism exposure (closed-loop pointing, i.e., pointing while the arm and target are visible) and finally specific post-tests designed to reveal PA after-effects and eventual transfer to visuo-spatial tasks. The primary measure of PA after-effects is open-loop pointing (OLP), during which participants lack visual feedback about arm position, i.e., they see the target but not their arm. In addition, various tests such as bisection judgments can be performed at pre- and post-tests to study generalization of adaptation effects in tasks different from the exposure context. The comparison of OLP bias between pre- and post-tests is used to compute the amount of adaptation. The exposure is a crucial period of a PA experiment during which participants wear the prisms and perform pointing or reaching movements that provide error signals about their performance. We will next discuss some results found with classic (wedge prism) PA, before presenting principles and findings of PA in VR.

4. Effects of Prism Adaptation on Spatial Neglect

Spatial neglect is a neurological syndrome affecting a large proportion of patients with right-hemisphere stroke. Neglect is characterized by severe unawareness of visual, auditory, or tactile stimuli in left space, together with a severe spatial bias to the right [41–43]. It has highly negative impact on the independence in ADLs, the quality of life, and motor recovery [44,45]. This syndrome is notorious for being difficult to treat, as the spatial bias underlying neglect is not accessible to conscious awareness [46]. Therefore, cognitive strategies (such as to direct attention 'consciously' towards the neglected side) may only improve performance in the presence of external prompting. For example, when moving on the ward with their wheelchair patients must often be reminded of impending obstacles.

The first report suggesting that adaptation to rightward-deviating optical prisms can reduce left spatial bias in neglect on measures of cancellation, line bisection or drawing was published in 1998 [47]. Since then, several clinical reports and randomized-controlled trials (RCTs) have demonstrated beneficial effects of rightward PA measured in classical neglect tests and in ADLs [47–49]. Significant improvement of neglect signs has been observed after a single application of PA for a few minutes (3–5 min), while PA repeated for two weeks led to long-term effects lasting up to 6 months [48–51]. However, neglect does not improve in all treated patients, and clinical studies including several RCTs failed to provide evidence for lasting effects of PA on its clinical manifestations [48,52–56]. In a meta-analysis of eight RCTs [52–54,57–59], Li et al. [60] found five reports showing that patients treated with PA showed significantly better scores in a neglect battery [61] than the control group [49,53,58,59,62]. However, there were no significant differences between groups in the three studies [52,54,58] that adopted the Catherine Bergego scale (CBS, [63]), a clinical scale assessing neglect in daily life. Furthermore, Li et al. [60] found no significant long-term (more than 1 month post-intervention) therapeutic effects of PA, based on the results of three studies for which follow-up data were available [53,58,59]. More recently, Mizuno et al. [64] performed a secondary analysis on ADLs examined in their own RCT dating from 2011 [58]. They found that only two of 10 items of the CBS (gaze orientation and exploration of personal belongings) were significantly improved in the prism group compared with the control group. Finally, a more recent meta-analysis on 430 patients found no evidence for a beneficial effect of PA on paper-and-pencil tests such as cancellation, or ADLs measured with the CBS [65].

These inconsistencies may reflect different factors, such as differences in PA procedures [66,67], treatment intensity or prism strength [68], patient selection or variability of lesions [69,70]. Moreover, the sample size of individual studies was generally small (from 13 to 20 patients in the treatment group). An additional problem—shared with most studies evaluating behavioral interventions—is absence of adequate blinding. Indeed, it is notoriously difficult—if not impossible—to conduct a completely blinded behavioral intervention study, and PA does not make an exception. Since the compensation of the PA-induced bias relies on conscious perception of the mismatch between target and hand position, complete blinding with classic wedge prisms is virtually impossible. Though several studies have tested control patients with sham prisms, the shape and weight of wedge prisms (particularly those with high diopters) makes them easily identifiable for the experimenter. Biases, such as experimenter expectations or placebo effects are therefore difficult to exclude.

5. Mimicking Prism Adaptation with Virtual Reality

Our research group has recently developed a prismatic adaptation protocol using virtual reality [71] that is based on the idea of applying a shift between true hand position and the position of a hand-held controller whose image is perceived in the VR environment [72]. Similar applications have been proposed by other authors [73,74]. Modern VR systems allow interactions with the virtual world through controllers that are held by the observer and provide an image within VR that moves in coherence with the hand/arm movement. The spatial coordinates of the controller can not only be accessed through the software (for example, when reading the ending position of a pointing movement) but may also be modified in every direction and by any desired amount (see Figure 2A and related videos at https://www.frontiersin.org/articles/10.3389/fnins.2021.658353/full#supplementary-material; URL accessed on 25 October 2021). The resulting image is shifted, but still moves in an entirely consistent way as the arm of the observer moves. We hypothesized that by inducing a rightward shift we may mimic the effects of wedge prisms and thus induce a compensatory adaptation of reaching or pointing movements towards the left.

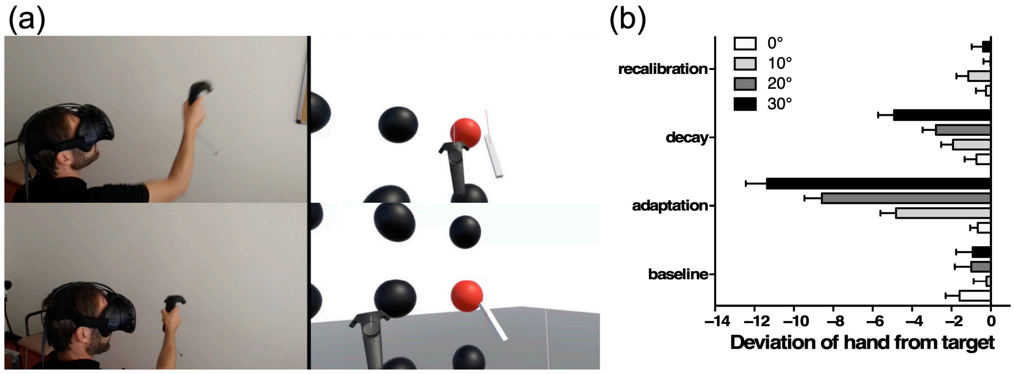

Figure 2. (**a**) Principles of virtual prismatic adaptation. Participants are required to point to the red sphere. Only the white rod is visible for the participant, the image of the controller is only shown here for illustration. Note the increasing mismatch between the controller and the white rod (upper image: 10th trial; lower image: 50th trial), requiring the participant to point further to the left. (**b**) Results of open-loop pointing before (baseline) and after (adaptation) virtual prism adaptation. Note the increasing pointing error with increasing mismatch. Decay was measured after a period of rest, and recalibration indicates performance after pointing without a mismatch [adapted with permission from Ref. [71], 2020, Taylor & Francis].

The advantages of VR for inducing adaptation effects are multiple. First, they allow different degrees of deviation to be used within the same experimental design. Second, VR makes it possible to apply much greater degrees of deviation than when prismatic glasses are used, without inducing visual distortions. In addition, the deviation can be induced gradually, making it difficult to be noticed by participants, which enables the planning of single-blind or even double-blind studies, thus limiting certain confounding factors such as placebo effects. This point is particularly crucial when studying the effectiveness of PA in the rehabilitation of neglect and is difficult if not impossible to achieve with prismatic glasses.

In a proof-of-concept study [71] we examined the performance of four groups of healthy subjects that were either not adapted (no shift), or adapted to a 10-, 20- or 30-degree shift. Adaptation was induced progressively, by fractions of a degree in every additional pointing movement, eventually reaching the desired shift after approximately 50 movements. As expected, adaptation effects (measured as OLP performance) increased with increasing shift (Figure 2B). Surprisingly, there was also a significant transfer to a line bisection task in the 30-degree group, who tended to bisect lines further to the left after adaptation. In addition, we found that the adaptation effects were very short-lived and disappeared almost immediately after a brief period of recalibration (consisting of several pointing movements without a lateral shift). Finally, participants were entirely unaware of the shift and the gradual compensation of pointing movements. Our study thus suggests that it is possible to reproduce adaptation effects observed when using prismatic glasses in VR.

One question arising from these results is whether PA in VR induces similar adaptation effects (measured as errors in OLP) as standard PA. Adaptation effects in our study were approximately 40–50% of the induced bias (i.e., ∼5 degrees with a 10-degree deviation, ∼9 degrees with 20-degree deviation and ∼12 degrees with a 30-degree deviation). Ramos and colleagues [75] compared the performance of healthy subjects following exposure with conventional prismatic glasses or by simulating a 10-degree deviation in virtual reality.

They found that the after-effects were greater after simulating the deviation in virtual reality, indicating that virtual PA may produce similar, if not better results than classic PA. A recent study using virtual PA confirmed our finding of greater deviations in the 20-degree compared to a 10-degree condition, and reported that the post-PA adaptation effect was related to right-hemispheric frontoparietal activation as measured with functional near-infrared spectroscopy [76]. Another study also measured quick adaptation to a shift 25 degrees and additionally observed a transfer of adaptation effects from near to far space and far to near space [74]. However, both studies induced a sudden shift and therefore participants may have been aware of the adaptation.

A second question relating to virtual PA is whether adaptation effects are linked to the visual modality or might have a supramodal component. The reason behind this question is that neglect generally affects multimodal representations of space [77,78], and some studies with neglect patients reported positive effects of PA on auditory neglect signs, such as auditory extinction [79,80]. We therefore tested virtual adaptation effects of healthy participants by varying modality (visual or auditory) and degree of shift (0-degree or 30-degree) [81]. The visual condition was performed as shown in Figure 2A. In the auditory condition participants did neither see the visual target, nor the position of the controller (and consequently their hand). They were thus performing pointing movements in a blank space, entirely lacking visual information. The shift was induced by giving false feedback about the quality of pointing: subjects heard a voice through headphones commenting on their performance. If they hit the target the voice said 'Correct', while when they deviated the voice said, 'More to the right' or 'More to the left'. The position of the (invisible) controller in the 30-degree condition shifted gradually to the right, so that a consequential leftward correction was required. Participants in the visual and auditory 30-degree group exhibited a gradual leftward shift during the adaptation procedure, of which they were entirely unaware (Figure 3A). However, while this shift was very similar in both conditions OLP testing revealed a significant adaptation effect only in the visual group (Figure 3B). This finding indicates that the shift of PA affects visuo-motor, but not auditory-motor integration. Since OLP testing was performed with a visual target this absence of adaptation effects with auditory feedback may be due to a lack of transfer between modalities. Alternatively, auditory adaptation may be fundamentally different than visual adaptation, for example it may rely entirely on highly strategic processes.

On the basis of these results, we performed a study that tested the effects of virtual PA in patients with spatial neglect [82]. Fifteen patients with left spatial neglect after a right hemispheric stroke were tested in three adaptation sessions: no deviation, 15-degree deviation or 30-degree deviation. The degree of deviation was chosen randomly and was not known to the patient and the experimenter. The experiment was thus a double-blind design, which was achieved by letting the software choose among the three adaptation conditions. As expected, there were significant adaptation effects in the 15-degree and 30-degree condition, but no changes of OLP after the 0-degree condition (Figure 4). However, there were no transfer effects in line bisection or cancellation tasks performed in virtual reality. Thus, while this study demonstrated the feasibility of virtual PA with neglect patients, it also showed that a single session of PA is not sufficient to achieve transfer of adaptation effects to visuo-spatial tasks. A recent computational model of PA effects suggests the interplay between fast (strategic) adaptation and slower, more gradual effects [83]. These different processes reflect the implementation of inverse models [84,85] at different hierarchical levels relevant for motor control (e.g., frontoparietal networks, basal ganglia, cortico-cerebellar interactions). In this framework the gradual induction of adaptation effects in our paradigm may reflect involvement of slow cerebellar effects, rather than fast, strategic processes that are believed to be under cortical control. Since none of the previous studies of PA in neglect applied gradual adaptation, it remains to be determined whether different effects might be achieved when comparing sudden and gradual adaptation directly.

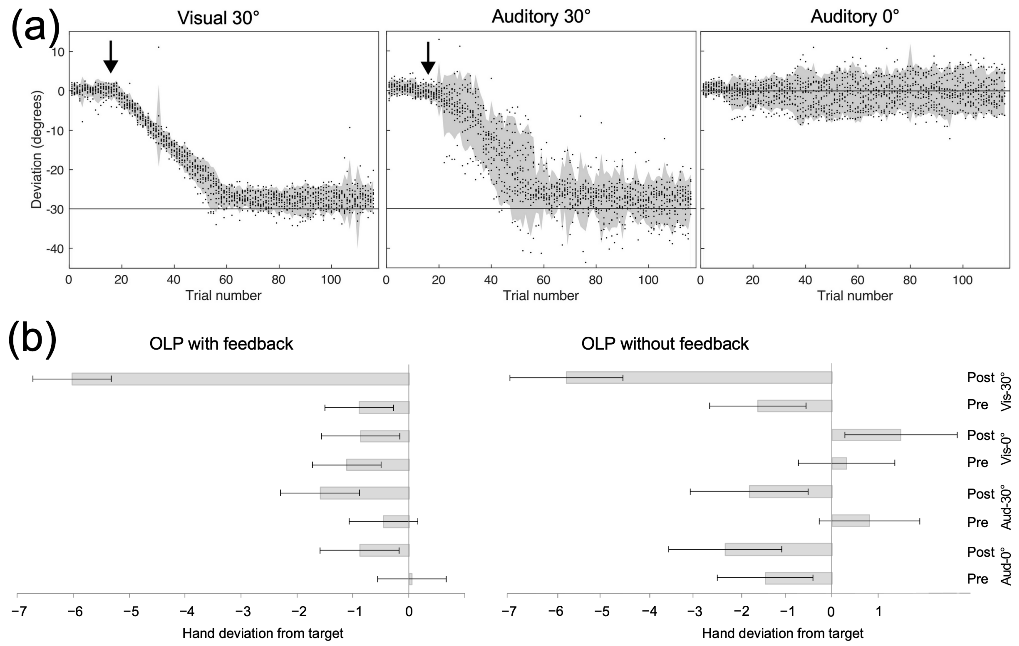

Figure 3. (**a**) Adaptation effects with visual and auditory feedback. The vertical arrow indicates the time-point when a mismatch was gradually induced. Dots indicate pointing performance of individual participants at each trial [adapted from [81]]. (**b**) Results of open-loop pointing (OLP) with (**left**) or without (**right**) vision of the target revealed only significant adaptation effects after visual adaptation with a shift of 30 degrees.

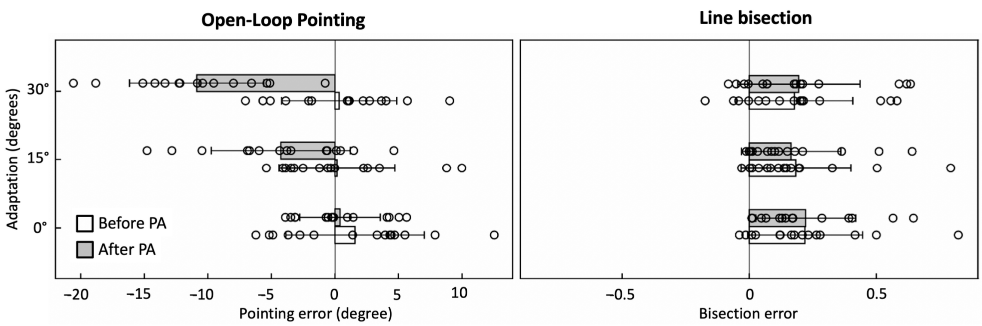

Figure 4. Adaptation effects of 15 patients with left spatial neglect (**left**), and absence of transfer to line bisection (**right**) [adapted from Ref. [82], 2022, Taylor & Francis].

6. Conclusions

Although VR technology becomes increasingly accessible, it is more expensive and requires greater technical skills than computer-based training (e.g., programming skills necessary to elaborate adaptive training). Such an investment would be justified if VR training showed far larger effect sizes than approaches that are easier to implement. However, the results of clinical studies published so far do not support strong superiority compared to classic rehabilitation techniques. In addition, immersive VR technologies currently do not benefit from advantages such as simple setup, reduced therapist support, or the possibility to be used in telerehabilitation.

Nevertheless, some recent clinical trials discussed in this article suggest that VR training may affect general cognition, alertness, and spatial cognition in stroke patients. Characteristics of VR that may drive such effects are repeated stimulation, high involvement in an immersive environment, and the playful aspect [32]. All these factors may increase attention, effort, motivation, and adherence to therapy, which may explain the positive effects of VR on general cognition (even if the latter is measured with simple screening tests, such as the MoCA).

The sense of presence in an immersive stimulation is particularly relevant for the therapy of impairments in which embodied representations contribute to recovery, such as upper limb deficits, phantom pain or spatial neglect [33]. The development of specific intervention techniques such as virtual PA may provide new avenues for the use of VR as a rehabilitation method. One example of a future application is that the optical shift inducing adaptation effects in virtual PA may differ among patients, thus providing the possibility of individualized interventions. Current state of research focuses on the question whether interventions using VR are beneficial, rather than whether different types of training that rely on specific advantages of the VR medium are beneficial. Future studies should also evaluate the specific factors that may lead to preference of VR over simple computer training.

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