

The Growing Use of Virtual Reality in Cognitive Rehabilitation: Fact, Fake or Vision? A Scoping Review

Maria Grazia Maggio, Psy.D., Giuseppa Maresca, Psy.D., Rosaria De Luca, M.Sc.,
 Maria Chiara Stagnitti, Psy.D., Bruno Porcari, P.T., Maria Cristina Ferrera, M.Sc., Franco Galletti, M.D.,
 Carmela Casella, M.D., Alfredo Manuli, M.Sc., Rocco Salvatore Calabrò, M.D., Ph.D.

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Abstract: Objective: This review aims to evaluate the role of Virtual Reality (VR) in cognitive rehabilitation of different neurological diseases, and the accessibility to healthcare systems providing this type of treatment.

Method of Research: Studies performed between 2003 and 2017 and fulfilling the selected criteria were found on PubMed, Scopus, Cochrane and Web of Sciences databases. The search combined the terms VR rehabilitation with different neurological disease.

Results: Our findings showed that neurological patients performed significant improvement in many cognitive domains (executive and visual-spatial abilities; speech, attention and memory skills) following the use of VR training.

Conclusions: This review supports the idea that rehabilitation through new VR tools could positively affect neurological patients' outcomes, by boosting motivation and participation so to get a better response to treatment. In particular, VR can be used to enhance the effects of conventional therapies, promoting longer training sessions and a reduction in overall hospitalization time.

Keywords: Neurological diseases ■ Cognition ■ Neurorehabilitation ■ Virtual reality training ■ Healthcare allocation

Author affiliations: Maria Grazia Maggio, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Giuseppa Maresca, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Rosaria De Luca, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Maria Chiara Stagnitti, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Bruno Porcari, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Maria Cristina Ferrera, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Franco Galletti, AOU Policlinico G Martino, Messina, Italy; Carmela Casella, AOU Policlinico G Martino, Messina, Italy; Alfredo Manuli, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; Rocco Salvatore Calabrò, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Correspondence: Rocco Salvatore Calabrò, M.D., Ph.D., IRCCS Centro Neurolesi "Bonino-Pulejo", S.S. 113, Contrada Casazza, 98124, Messina, Italy., email: salbro77@iscali.it

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INTRODUCTION

Cognitive Rehabilitation (CR) is a method that allows rehabilitation of people with brain injuries or cognitive difficulties to compensate for the impairment or recover normal functioning. In clinical practice, it is possible to perform two types of CR: i) the restorative one that allows the patient to develop the lost cognitive domain through specific cognitive exercises, and ii) the compensatory one, which promote the use of aids and tools useful to go beyond the deficits. Moreover, it is possible to classify CR techniques in conventional (paper/pencil exercises) and computer-assisted neurorehabilitation, both using cognitive strategies to overcome the deficit in executive functions,

reasoning and problem solving, visual processing, language, memory, attention, and concentration. The brain's ability to transform its neural organization through interactions with the external environment,¹ called neuroplasticity, is the foundation of CR. Thus, all patients showing disorders in behaviour and cognitive function, because of neurological damage, should perform a CR. Among the novel techniques for motor, cognitive, and sensory rehabilitation, Virtual Reality (VR) is demonstrating promising results, so to be considered the new frontier of CR.²⁻⁴ Weiss et al. defined VR as the "use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real world objects and events".⁵ VR system, based on the characteristics of immersion, interaction and imagination, could be used to monitor, manipulate and increase the patients' interaction with their environment, promoting functional recovery.^{6,7} In particular, VR offers the possibility to modulate the exercises on the patient's capabilities and monitor the performance through visual and auditory feedback. Furthermore, VR allows increasing patients' motivation and active participation and intensifying the quality of interventions thanks to the several likable activities. Some studies have confirmed that VR systems can be effective in the rehabilitation of different neurological diseases and can be useful for both children and adults,²⁻⁴ allowing the improvement of damaged functions, the stimulation of residual abilities and the promotion of global well-being. Thus, VR is a rehabilitative method that, thanks to the total involvement of the senses (and thus sensorimotor cortex), implements specific cognitive and behavioural functions, such as executive functions, attention, spatial cognition, perceptive abilities, memory, language and psychosomatic anxiety.⁸⁻¹¹

This review aims to evaluate the role of VR tools in CR of different neurological diseases and the accessibility to healthcare systems providing this type of treatment.

SEARCH STRATEGY

The studies were identified by searching on Scopus, PubMed, Web of Science, and Cochrane database. All the

studies fulfilling our selected criteria and published between 2010 and 2017 were evaluated for possible inclusion. The search combined the following terms: “virtual reality” AND/OR “cognitive rehabilitation”; “virtual reality” AND/OR neurological patients”; “virtual reality” AND/OR “dementia”; “virtual reality” AND/OR “brain injuries, traumatic” AND/OR “stroke”; “virtual reality” AND/OR “multiple sclerosis”; “virtual reality” AND/OR “Parkinson”. We have only selected texts in English and removed duplicates. All articles have been evaluated according to title, abstracts and text. We included studies that examined VR in several neurological patients, excluding studies with patients who had a psychiatric history.

DEMENTIA AND VR

Dementia consists of cognitive impairment causing a deterioration in social functioning and/or work ability, besides normal activities of daily living. Alzheimer’s disease is diagnosed when the impairment affects at least two cognitive domains, one of which must be memory. On the contrary, to diagnose Mild Cognitive Impairment (MCI), a modest damage must be present in at least one cognitive domain, including memory, without abnormal functioning. Worldwide, it is estimated that 35.6 million people live with dementia, a number that should reach 115.4 million people by 2050.¹² Cognitive decline presents itself insidiously and with a gradual and constant progression. In general, executive and memory processes are among the first to be compromised, while the visuo-constructive/perceptive-motor, linguistic and social cognition functions are subsequently altered.^{10,11} The application of VR in different stages of cognitive impairment, including subjective cognitive decline,¹³ MCI,¹⁴ and Alzheimer Disease,^{10,11} turns up as a promising method of rehabilitation. In fact, VR has been demonstrated to be effective to promote the reactivation of some cortex areas by boosting the neuroplasticity processes.^{8–11,15} Growing evidence is demonstrating that VR may be useful in different cognitive domains,¹⁵ including spatial memory, episodic memory, everyday autonomies, language, executive function, short-term and working memory, attention, movement and equilibrium.^{10–18} In patients with dementia, it was shown that the application of VR was more effective than conventional approaches, achieving efficacy in patient recovery in a shorter time than conventional treatments, as confirmed by neuropsychological and neuroimaging tools.¹⁹

STROKE AND VR

Stroke is the third cause of death and the main cause of adults’ disability.²⁰ The clinical examination presents a

sudden onset of signs and symptoms indicative of a focal damage resulting from an alteration of the cerebral circulation (either “ischemic”, 80%, or “haemorrhagic”, 20%). Based on the specific area involved, stroke can cause sensory, motor and cognitive deficits as well as a further dependence on the activities of daily living and a decreased interaction in social and community events. The post-stroke cognitive impairment can appear in 23–55% within three months of the injury onset, and can decrease between 11 and 31% after one year.^{20–25} The major cognitive deficits observed in stroke patients can concern several functions, such as spatial awareness, praxis, perception, attention and concentration, memory, and executive functions. As demonstrated by some research, thanks to the use of goal-oriented tasks and repetitions, VR in stroke patients can be a promising and effective tool in the recovery of neurological symptoms, including cognitive ones.^{21–25} VR can provide a motivating and stimulating environment that allows patients with stroke to reduce their deficits and learn new skills.²¹ The functional improvements of post-stroke patients achieved thanks to the use of VR, have been confirmed by instrumental examinations that show the change in sensorimotor activation of the neural representation from contralesional to ipsilesional site.^{22–25} Tunik and colleagues have shown that in post-stroke patients the activation of a primary motor region (M1) is recorded only in situations where discordant feedback was presented.²² Specifically, the contralateral M1 region was activated when the discordant feedback corresponded to the moving of the affected hand.²¹ Quite the opposite, there was an activation of the ipsilateral M1 region affected by the ischemic event only in case the patients moved the unaffected hand through the virtual mirror feedback (even if the affected hand did not move).²⁴ Therefore, we can understand how visual feedback provided by VR can be used as a rehabilitative tool. For this reason, various programs have been created to customize the exercises on patients’ difficulties and needs.²⁵ Although Laver et al. have observed that there isn’t high-quality evidence that guarantees the effectiveness of VR training without the simultaneous recourse to other therapeutic interventions, it emerged that VR could allow the improvement of arm function and activities of daily life (ADL) becoming one of the most specified rehabilitation methods for stroke patients.²⁵

TRAUMATIC BRAIN INJURY AND VR

Traumatic brain injury (TBI) is any damage to the skull and/or the brain and its frameworks due to an external force, i.e. when an object strikes the head or the brain

undergoes an acceleration/deceleration movement without direct external trauma to the head.

Recent studies suggest that, in the general population, the prevalence of TBI of 12–16.7% in males and 8.5% in females.^{26,27} Focal syndromes (such as aphasia observed in 7–10% of cases, and unilateral spatial neglect in 0.5–1% of cases) are rare following TBI, whereas diffuse syndromes are more common as multiple brain areas are usually involved. Thus, specific clinical and neuropsychological assessments are needed. Epidemiologically, severe brain injury (serious global dysfunctioning) occurs in 8–10% with GCS score of 8 to 3.^{26,27} Following TBI, patients may report cognitive, physiological and psycho-social changes with a devastating impact on important aspects of the patient's life. A recent systematic review has demonstrated that new cognitive interventions, including computer-based cognitive retraining and VR training may be useful in patients with TBI.²⁸ VR has been shown to enhance TBI patients' motivation and enjoyment,²⁹ which are important factors in successful rehabilitation training. Virtual environments represent many real-life situations and are programmed either to record accurate measurement of the individual's performance or to train memory functions and other cognitive abilities.^{30,31} French et al. has found that in TBI patients, during rehabilitation in a virtual environment, the central nervous system receives increased feedback signals (augmented feedback), inducing profound changes in neural plasticity that are responsible for the reinstatement of motor activity and/or cognitive function.³¹ In fact, Imam et al. has shown that the repetitive virtual task was effective in different aspects of rehabilitation, such as improving walking distance and speed, gait and balance, and upper limb function as well as cognition, perception and functional tasks (i.e. crossing a street, driving, preparing food and shopping).³⁰ The evidence that the use of VR in rehabilitation of TBI improves motor and cognitive functionality is currently very limited. However, this approach (by means of telerehabilitation) has the potential to provide alternative and more available rehabilitation, where access to therapy is limited by geographical or financial constraints.³² Nonetheless, Kim, et al. have suggested that VR combined with CR may be of additional benefit for treating cognitive impairment (with regard to visual attention and short-term visuospatial memory) in TBI patients.³³

MULTIPLE SCLEROSIS AND VR

Multiple sclerosis (MS) is a neurodegenerative demyelinating disease, implicating injuries to the central nervous system, and can evolve from a beginning inflammatory stage to a chronic phase. MS can begin at any age of life, causing deficits to various cognitive domain, besides motor

and sensory abnormalities. Cognitive deficits carry weight on the 70% of the patients with MS, and 10% of them shows serious symptoms, while 50–60% of the patients have mild or moderate symptoms.³⁴ The most affected areas concern attention, short and long-term memory, information processing speed and planning, reasoning and abstraction processes, concurrently with language difficulties. If cognitive deficits are not properly identified, these one can become stressful for both patients and healthcare professionals, and, when combined to anxiety and depression, may compromise considerably the quality of life of the patients and their families.³⁵ Indeed, the therapy provides a strengthening of residual abilities and learning of new strategies in a multidisciplinary viewpoint. Recently, in the field of MS rehabilitation, a promising instrument that has been employed is VR, considering also that the studies concerning the use of serious videogaming is a growing field of rehabilitation.^{36–41} However, the application of VR in MS has mainly focused on motor outcomes. Leocani et al. have carried out a rehabilitation training of the short-term motor learning on twelve patients by using VR, with promising results.⁴⁰ Other studies have confirmed the important role of VR in both motor and cognitive rehabilitation in patients affected by MS.^{36,39,41} Indeed, it has been shown that VR is feasible and safe in patients with moderate disabilities, and can influence positively their walk in complex conditions (as the double tasking and the negotiation of obstacles), beyond the cognitive skills. Consequently, VR turns out to be a useful instrument for the assessment and rehabilitation in patients affected by MS. These promising results should be confirmed in larger sample studies and carrying out longer-lasting follow-up.

PARKINSON DISEASE AND VR

Parkinson's disease (PD) is a progressive neurodegenerative condition, caused by the depletion of the neurons that contain dopamine in specific brain areas and involving different motor (motion control and balance), vegetative, behavioural and cognitive functions, with consequences on quality of life. The prevalence of PD in Western countries is 0.3% in the general population (1–3% in people aged over 65) with incidence rates of 8–18 per 100,000 person-years.⁴² The main motor symptoms of PD are shaking, rigidity, bradykinesia and loss of balance, which occur asymmetrically. Among the non-motor symptoms, vegetative disorders, smell, sleep, mood, cognitive, behavioural and social disabilities can be found.⁴² The cognitive functions most involved in the neurodegenerative process are executive functions, working memory, visual-spatial abilities and verbal fluency, often in co-morbidity with depression and anxiety, which have a negative impact on

the quality of life of patients and their caregivers.⁴³ It seems that PD is best management with the combination of dopaminergic drugs, physiotherapy and CR.⁴³ Many studies show that CR is important to improve cognitive skills, both by using traditional and/or innovative tools with advanced techniques. In fact, there is growing evidence that the use of pc-based and VR tools can be useful to improve the performance of PD patients and therefore their quality of life.^{44–46} In fact, it has been demonstrated that both commercial (Nintendo Wii or Xbox Kinect) and customized VR tools (designed specifically to face PD's symptoms) have been used with positive results especially on balance and gait. In PD, cognitive symptoms mainly involve the frontal lobe, and therefore cause impairment of executive and visuo-spatial abilities (planning skills, spatial management, organization, problem solving, evaluation and abstract thinking) that are important to manage everyday life and take care of ourselves (i.e. shopping, cooking, taking drugs ...). In this regard, the existing research considers VR as a promising rehabilitation tool for impaired functions and suggests that the cognitive and behavioural characteristics of this disease may be better managed by using innovative tools than with traditional therapy.^{42–46} Unfortunately, although previous research has shown how important it is to implement CR in individuals with PD, only a few surveys compared VR with traditional CR, showing that VR has a better effect on patients' quality of life.⁴⁷ The benefit of VR on cognitive functions in PD's patients is due to the fact that the cognitive training in a virtual environment may activate specific neurological mechanisms, including the strengthening of cholinergic and dopaminergic pathways.³³ Thus, the use of VR influences the processes of brain reorganization and encourages neuroplasticity processes.

DISCUSSION

This review highlighted that VR represents a promising methodological approach to neurorehabilitation, with regard to CR. In fact, the multisensory stimulation of augmented reality training promotes the recovery of mnemonic-attentive functions, visuo-spatial cognition, executive processes and behavioural abilities in patients with neurological disorders. VR can be used to enhance the effects of conventional therapies, promoting longer training sessions and a reduction in overall hospitalization time.^{2–4} The advantage of using VR in the rehabilitation program is to create a positive, funny and motivating learning experience for the patients,^{2–4} allowing a better compliance.^{36,47} This review demonstrates that VR training can facilitate the rehabilitation of attention processes in neurological patients, enhancing other cognitive domains with a significant improvement in global cognitive

functioning, promoting brain plasticity processes through complex mechanisms.^{5,48} These effects may be related to the reactivation of brain neurotransmitter capacities, such as cholinergic and dopamine systems, through the cognitive treatment performed by VR, which is maximized compared to the results obtained by conventional treatment.^{2,36} Although a relationship between motor and cognitive outcomes has been postulated, the effects of VR training in same neurological diseases are still poorly studied.^{48–50}

AUTHORS' PROSPECTIVE AND CONCLUSIONS

In recent decades, innovation in the health service has contributed to substantial improvements in the treatment of diseases with positive repercussions in terms of quality of life. However, the spread of new technologies, such as VR, has caused worries about the cost and convenience of these tools in health care, especially in terms of equity and accessibility of care, as well as in terms of health care costs.^{51,52} Decisions on the allocation and use of resources for the population should aim at maximizing health and well-being through the provision of what is needed, desired, clinically effective, addressable, equitable and responsible in the use of resources.^{53–56} However, the literature shows that for low and middle income countries, there are large inequalities in health service access and poorest resources, which should be mitigated by the Health System.⁵⁶ Therefore, every Health System should implement actions that might guarantee the correct and equitable use of medical devices, including new technologies, such as VR, which appear to be effective and efficient tools, as by literature and clinical data.⁵⁷ This aspect is central to social and political decisions, especially to ensure adequate access to the best care for all the people, including those living in poor countries. In conclusion, this review supports the idea that VR can be a feasible and effective tool to improve cognitive function in patients with neurological disorders. However, additional randomized clinical trials are needed to confirm these promising results. In particular, it is necessary to evaluate the effectiveness of these tools both in terms of cognitive and motor recovery compared to conventional rehabilitation, also evaluating healthcare costs/benefits and accessibility to resources and services.

REFERENCES

1. De Luca, R., Calabrò, R. S., & Bramanti, P. (2016). Cognitive rehabilitation after severe acquired brain injury: current evidence and future directions. *Neuropsychol Rehabil*, 25, 1–20. <https://doi.org/10.1080/09602011.2016.1211937>.

2. De Luca, R., Russo, M., Naro, A., et al. (2017). Effects of virtual reality-based training with BTs-nirvana on functional recovery in stroke patients: preliminary considerations. *Int J Neurosci*, *17*, 0–7. <https://doi.org/10.1080/00207454.2017.1403915>.
3. De Luca, R., Torrisi, M., Piccolo, A., et al. (2017). Improving post-stroke cognitive and behavioral abnormalities by using virtual reality: a case report on a novel use of nirvana. *Appl Neuropsychol Adult*, *11*, 1–5. <https://doi.org/10.1080/23279095.2017.1338571>.
4. De Luca, R., Lo Buono, V., Leo, A., et al. (2017). Use of virtual reality in improving poststroke neglect: promising neuropsychological and neurophysiological findings from a case study. *Appl Neuropsychol Adult*, *22*, 1–5. <https://doi.org/10.1080/23279095.2017.1363040>.
5. Weiss, P. L., Kizony, R., Feintuch, U., & Katz, N. (2006). Virtual reality in neurorehabilitation. *Neurorehabilitation Neural Repair*, *51*, 182–197. <https://doi.org/10.1080/09638280500076079>.
6. Burdea, G. C., & Coiffet, P. (2003). *Virtual Reality Technology* (2nd ed.). Hoboken, NJ: John Wiley & Sons.
7. Wade, E., & Winstein, C. J. (2011). Virtual reality and robotics for stroke rehabilitation: where do we go from here? *Topics Stroke Rehabil*, *18*, 685–700. <https://doi.org/10.1310/tsr1806-685>.
8. Schedlbauer, A. M., Copara, M. S., Watrous, A. J., & Ekstrom, A. D. (2014). Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. *Sci Rep*, *4*, 6431. <https://doi.org/10.1038/srep06431>.
9. Carrieri, M., Petracca, A., Lancia, S., et al. (2016). Prefrontal cortex activation upon a demanding virtual hand controlled task: a new frontier for neuroergonomics. *Front Hum Neurosci*, *10*, 53. <https://doi.org/10.3389/fnhum.2016.00053>.
10. Allison, S. L., Fagan, A. M., Morris, J. C., & Head, D. (2016). Spatial navigation in preclinical Alzheimer's disease. *J Alzheimer Dis*, *52*, 77–90. <https://doi.org/10.3233/JAD-150855>.
11. Valladares-Rodriguez, S., Perez-Rodriguez, R., Facal, D., et al. (2017). Design process and preliminary psychometric study of a video game to detect cognitive impairment in senior adults. *Peer J*, *5*, e3508. <https://doi.org/10.7717/peerj.3508>.
12. Prince, M., Bryce, R., Albanese, E., et al. (2013). The global prevalence of dementia: a systematic review and meta-analysis. *Alzheim Dement*, *9*, 63–75. <https://doi.org/10.1016/j.jalz.2012.11.007>.
13. Innes, K. E., Selfe, T. K., Khalsa, D. S., & Kandati, S. (2016b). A randomized controlled trial of two simple mind-body programs, Kirtan Kriya meditation and music listening, for adults with subjective cognitive decline: feasibility and acceptability. *Complement Ther Med*, *26*, 98–107. <https://doi.org/10.1016/j.ctim.2016.03.002>.
14. Weniger, G., Ruhleder, M., Lange, C., et al. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnesic mild cognitive impairment. *Neuropsychology*, *49*, 518–527. <https://doi.org/10.1016/j.neuropsychologia.2010.12.031>.
15. Bus, B. (2009). *Virtual reality training system for patients with dementia*. Zürich: ETH: Institute of Neuroinformatics, Swiss Federal Institute of Technology.
16. Seo, K., Kim, J. K., Oh, D., et al. (2017). Virtual daily living test to screen for mild cognitive impairment using kinematic movement analysis. *PLoS One*, *12*, e0181883. <https://doi.org/10.1371/journal.pone.0181883>.
17. Montenegro, J. M. F., & Argyriou, V. (2017). Cognitive evaluation for the diagnosis of Alzheimer's disease based on turing test and virtual environments. *Physiol Behav*, *173*, 42–51. <https://doi.org/10.1016/j.physbeh.2017.01.034>.
18. Tost, D., Von Barnekow, A., Felix, E., et al. (2014). Early detection of cognitive impairments with the smart ageing serious game. In *International Workshop on ICTs for Improving Patients Rehabilitation Research Techniques* (183–195). Berlin, Heidelberg: Springer.
19. Wen, D., Lan, X., Zhou, Y., et al. (2018). The study of evaluation and rehabilitation of patients with different cognitive impairment phases based on virtual reality and EEG. *Front Aging Neurosci*, *10*, 88. <https://doi.org/10.3389/fnagi.2018.00088>.
20. Jones, K. M., Bhattacharjee, R., Krishnamurthi, R., et al. (2015). Methodology of the stroke self-management rehabilitation trial: an international, multisite pilot trial. *J Stroke Cerebrovasc Dis*, *24*, 297–303. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.08.029>.
21. Jang, S. H., You, S. H., Hallett, M., et al. (2005). Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. *Arch Phys Med Rehabil*, *86*, 2218–2223. [https://www.archives-pmr.org/article/S0003-9993\(05\)00411-9](https://www.archives-pmr.org/article/S0003-9993(05)00411-9).
22. Tunik, E., Saleh, S., & Adamovich, S. V. (2013). Visuomotor discordance during visually guided hand movement in virtual reality modulates sensorimotor cortical activity in healthy and hemiparetic subjects. *Neural Syst Rehab Engin*, *21*(2), 198–207. <https://doi.org/10.1109/TNSRE.2013.2238250>.
23. Saleh, S., Adamovich, S. V., & Tunik, E. (2014). Mirrored feedback in chronic stroke: recruitment and effective connectivity of ipsilesional sensorimotor networks. *Neurorehabilitation Neural Repair*, *28*(4), 344–354. <https://doi.org/10.1177/1545968313513074>.
24. Pedreira da Fonseca, E., Ribeiro da Silva, N. M., & Pinto, E. B. (2017). Therapeutic effect of virtual reality on post-stroke patients: randomized clinical trial. *J Stroke Cerebrovasc Dis*, *26*(1), 94–100. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.035>.
25. Laver, K. E., Lange, B., George, S., et al. (2017). Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev*, *11*. CD008349 <https://doi.org/10.1002/14651858.CD008349.pub4>.

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26. Adams, H., Donnelly, J., Czosnyka, M., et al. (2017). Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: an observational study. *PLoS Med*, *14*(7), e1002353. <https://doi.org/10.1371/journal.pmed.1002353>.
27. Saatian, M., Ahmadpoor, J., Mohammadi, Y., & Mazloumi, E. (2018). Epidemiology and pattern of traumatic brain injury in a developing country regional trauma center. *Bull Emerg Trauma*, *6*(1), 45–53. <https://doi.org/10.29252/beat-060107>.
28. Rizzo, A., & Kim, G. J. (2005). A SWOT analysis of the field of VR rehabilitation and therapy. *Presence Teleoperators Virtual Environ*, *14*, 119–146.
29. Gamito, P., Oliveira, J., Coelho, C., et al. (2015). Cognitive training on stroke patients via virtual reality-based serious games. *Disabil Rehabil*, *5*, 1–4. <https://doi.org/10.3109/09638288.2014.934925>.
30. Imam, B., & Jarus, T. (2014). Virtual reality rehabilitation from social cognitive and motor learning theoretical perspectives in stroke population. *Rehabil Res Pract*, 594540. <https://doi.org/10.1155/2014/594540>.
31. French, B., Thomas, L. H., Leathley, M. J., et al. (2007). Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev*, *17*, 4 –00 <https://doi.org/10.1002/14651858.CD006073.pub2>.
32. Fasczewski, K. S., & Gill, D. L. (2018). A model of motivation for physical activity in individuals diagnosed with multiple sclerosis. *Disabil Rehabil*, *10*, 1–8. <https://doi.org/10.1080/09638288.2018.1459883>.
33. Kim, B. R., Chun, M. H., Kim, L. S., & Park, J. Y. (2011). Effect of virtual reality on cognition in stroke patients. *Arch Ann Rehab Med*, *35*, 450–459. <https://doi.org/10.5535/arm.2011.35.4.450>.
34. Sumowski, J. F., Benedict, R., Enzinger, C., et al. (2018). Cognition in multiple sclerosis: state of the field and priorities for the future. *Neurology*, *90*(6), 278–288. <https://doi.org/10.1212/WNL.0000000000004977>.
35. Al-Sharman, A., Khalil, H., Nazzal, M., et al. (2018). Living with multiple sclerosis: a Jordanian perspective. *Physiother Res Int*, *23*(2), e1709. <https://doi.org/10.1002/pri.1709>.
36. Calabrò, R. S., Russo, M., Naro, A., et al. (2017). Robotic gait training in multiple sclerosis rehabilitation: can virtual reality make the difference? Findings from a randomized controlled trial. *J Neurol Sci*, *377*, 25–30. <https://doi.org/10.1016/j.jns.2017.03.047>.
37. Lozano-Quilis, J. A., Gil-Gómez, H., Gil-Gómez, J. A., et al. (2014). Virtual rehabilitation for multiple sclerosis using a Kinect-based system: randomized controlled trial. *JMIR Serious Games*, *2*(2), e12. <https://doi.org/10.2196/games.2933>.
38. Jonsdottir, J., Bertoni, R., Lawo, M., et al. (2017). Serious games for arm rehabilitation of persons with multiple sclerosis. A randomized controlled pilot study. *Mult Scler Relat Disord*, *19*, 25–29. <https://doi.org/10.1016/j.msard.2017.10.010>.
39. Lamargue-Hamel, D., Deloire, M., Saubusse, A., et al. (2015). Cognitive evaluation by tasks in a virtual reality environment in multiple sclerosis. *J Neurol Sci*, *359*(1-2), 94–99. <https://doi.org/10.1016/j.jns.2015.10.039>.
40. Leocani, L., Comi, E., Annovazzi, P., et al. (2007). Impaired short-term motor learning in multiple sclerosis: evidence from virtual reality. *Neurorehabilitation Neural Repair*, *21*(3), 273–278. <https://doi.org/10.1177/1545968306294913>.
41. Peruzzi, A., Cereatti, A., Della Croce, U., & Mirelman, A. (2016). Effects of a virtual reality and treadmill training on gait of subjects with multiple sclerosis: a pilot study. *Mult Scler Relat Disord*, *5*, 91–96. <https://doi.org/10.1016/j.msard.2015.11.002>.
42. Lee, A., & Gilbert, R. M. (2016). Epidemiology of Parkinson disease. *Neurol Clin*, *34*(4), 955–965. <https://doi.org/10.1016/j.ncl.2016.06.012>.
43. Maggio, M. G., De Luca, R., Maresca, G., et al. (2018). Personal computer-based cognitive training in Parkinson's disease: a case study. *Psychoger*, *18*(5), 427–429. <https://doi.org/10.1111/psyg.12333>.
44. Ibiol-Pérez, S., Gil-Gómez, J. A., Muñoz-Tomás, M. T., et al. (2017). The effect of balance training on postural control in patients with Parkinson's disease using a virtual rehabilitation system. *Method Inf Med*, *56*(2), 138–144. <https://doi.org/10.3414/ME16-02-0004>.
45. Dockx, K., Bekkers, E. M., Van den Bergh, V., et al. (2016). Virtual reality for rehabilitation in Parkinson's disease. *Cochrane Database Syst Rev*, *12*, CD010760. <https://doi.org/10.1002/14651858.CD010760.pub2>.
46. Morales-Gomez, S., Elizagaray-Garcia, I., Yepes-Rojas, O., et al. (2018). Effectiveness of virtual immersion programmes in patients with Parkinson's disease. A systematic rev. *Rev Neurol*, *66*(3), 69–80.
47. Maidan, I., Rosenberg-Katz, K., Jacob, Y., et al. (2017). Disparate effects of training on brain activation in Parkinson disease. *Neurol*, *89*(17), 1804–1810. <https://doi.org/10.1212/WNL.0000000000004576>.
48. Calabrò, R. S., Naro, A., Russo, M., et al. (2017). The role of virtual reality in improving motor performance as revealed by EEG: a randomized clinical trial. *J NeuroEng Rehabil*, *14*, 53. <https://doi.org/10.1186/s12984-017-0268-4>.
49. Kizony, R., & Katz, N. (2003). Adapting an immersive virtual reality system for rehabilitation. *Comput Animat Virtual Worlds*, *14*, 261–268. <https://doi.org/10.1080/09638280500076079>.
50. Subramanian, S. K., Chilingaryan, G., Levin, M. F., & Sveistrup, H. (2015). Influence of training environment and cognitive deficits on use of feedback for motor learning in chronic stroke. In *Virtual Rehabilitation Proceedings (ICVR)* (38–43). New York: International Conference on IEEE.
51. Varabyova, Y., Blankart, C. R., Greer, A. L., & Schreyögg, J. (2017). The determinant of medical technology in different decisional systems: a systematic literature review. *Health Policy*, *121*, 230–242. <https://doi.org/10.1016/j.healthpol.2017.01.005>.

52. American Medical Association. (2011). *Medical Code of Ethics*. OMC.
53. Gray, J. (2013). The shift to personalised and population medicine. *Lancet*, 382(9888), 200–201.
54. Elshaug, A. G., Rosenthal, M. B., Lavis, J. N., et al. (2017). Right care 4. Levers for addressing medical underuse and overuse: achieving high-value health care. *Lancet*, 390(10090), 191–202. [https://doi.org/10.1016/S0140-6736\(16\)32586-7](https://doi.org/10.1016/S0140-6736(16)32586-7).
55. Gooch, R. A., & Kahn, J. M. (2014). ICU bed supply, utilization, and health care spending: an example of demand elasticity. *J Am Med Assoc*, 311(6), 567–568. <https://doi.org/10.1001/jama.2013.283800>.
56. Bhuiya, A., Hanifi, S., Urni, F., & Mahmood, S. S. (2009). Three methods to monitor utilization of healthcare services by the poor. *Int J Equity Health*, 8, 29. <https://doi.org/10.1186/1475-9276-8-29>.
57. Ciani, O., Wilcher, B., Blankart, C. R., et al. (2015). Health technology assessment of medical devices: a survey of non-European Union agencies. *Int J Technol Assess Health Care*, 31(3), 154–165. <https://doi.org/10.1017/S0266462315000185>.