

Health & Research Journal

Vol 8, No 3 (2022)

Volume 8 Issue 3 July - September 2022



Volume 8 Issue 3 July - September 2022

EDITORIAL

DIGITAL HEALTH: IS IT THE FUTURE FOR OUR LIVES?

RESEARCH ARTICLES

RENAL BIOMARKER COMBINATIONS PREDICT EARLY CRRT NEED IN A MIXED ICU POPULATION

TRANSLATION AND PRELIMINARY VALIDATION OF THE MODIFIED MINI MENTAL STATE (3MS) IN A GREEK SAMPLE

CLINICAL OUTCOMES OF ENHANCED RECOVERY AFTER SURGERY PROTOCOL FOR HEPATO-PANCREATO-BILIARY SURGERY; A FIVE-YEAR EXPERIENCE FROM A HELLENIC ONCOLOGICAL HOSPITAL

USE OF HERBAL PRODUCTS AND FOOD SUPPLEMENTS OF TYPE 2 DIABETES PATIENTS

SUBJECTIVE SLEEP QUALITY AND DAYTIME SLEEPINESS AMONG GREEK NURSING STAFF: A MULTICENTER CROSS-SECTIONAL STUDY

SYSTEMIC REVIEW

IMMERSIVE VIRTUAL REALITY IN COGNITIVE REHABILITATION: A SYSTEMATIC REVIEW

THE BENEFITS OF INSPIRATORY MUSCLE TRAINING IN HEART FAILURE PATIENTS - A SYSTEMATIC REVIEW

Published in cooperation with the Postgraduate Program "Intensive Care Units", the Hellenic Society of Nursing Research and Education and the Helerga

Immersive Virtual Reality in Cognitive Rehabilitation: A systematic Review

Akyllina Despoti, Eleftherios Karatzanos, Irimi Patsaki, Dimitra Tzoumi, Georgia Roussou, Nikolaos Leventakis, Argyro Papatthanasiou, Serafim Nanas, Nefeli Dimitriadi

doi: [10.12681/healthresj.28872](https://doi.org/10.12681/healthresj.28872)

To cite this article:

Despoti, A., Karatzanos, E., Patsaki, I., Tzoumi, D., Roussou, G., Leventakis, N., Papatthanasiou, A., Nanas, S., & Dimitriadi, N. (2022). Immersive Virtual Reality in Cognitive Rehabilitation: A systematic Review. *Health & Research Journal*, 8(3), 225-241. <https://doi.org/10.12681/healthresj.28872>

SYSTEMATIC REVIEW

IMMERSIVE VIRTUAL REALITY IN COGNITIVE REHABILITATION: A SYSTEMATIC REVIEW

Akyllina Despoti¹, Eleftherios Karatzanos¹, Irini Patsaki¹, Dimitra Tzoumi¹, Georgia Roussou¹, Nikolaos Leventakis¹, Argyro Papatathanasiou¹, Serafim Nanas¹, Nefeli Dimitriadi²

1. Clinical Ergospirometry, Exercise and Rehabilitation Laboratory, 1st Critical Care Department, Evangelismos Hospital, School of Medicine, National & Kapodistrian University of Athens, Greece

2. Higher School of Fine Arts, Faculty of Film, Aristotle University of Thessaloniki, Greece

Abstract

Background: Virtual Reality (VR) is a new technology used more and more in clinical trial.

Aim: The aim of this study is to investigate the effects of immersive VR as a rehabilitation approach of cognitive functions.

Method and Material: A systematic literature review was conducted in the electronic databases of PubMed, Cochrane, OTseeker and PsycINFO for articles published until August 2021. The main search terms were "immersive virtual reality," and "cognitive rehabilitation". The research was strictly limited in immersive technologies and adult patients suffering from neurological disorder or a traumatic injury or elderly with cognitive decline, and no reviews are included. Totally, 16 citations reviewed.

Results: All intervention studies reported improvements either in cognitive functions or in stress management and relaxation. In particular, most of the studies demonstrated improvement in attention (N=6) but also in executive functions (N=3), in memory (N=5) and in navigation skills (N=1). Regarding safety and feasibility, most of the participants in the studies completed successfully the tasks and did not report stimulation sickness.

Conclusions: The available limited data indicate that immersive VR environments can a) be feasible and safe and b) have a positive impact in cognitive functions in the dynamic process of rehabilitation. Further research is warranted in large-scale longitudinal clinical trials in various patients' groups in order to compare the effects of immersive and non-immersive VR interventions. Future studies should further investigate the long-term impact on cognitive functions in interventions using immersive VR.

Keywords: Immersive, virtual reality, rehabilitation, cognitive functions.

Corresponding Author: Eleftherios Karatzanos PhD, Clinical Ergospirometry, Exercise and Rehabilitation Laboratory, 1st Critical Care Department, School of Medicine, National and Kapodistrian University of Athens, Evangelismos Hospital, 45-47 Ypsilantou Str., 106 75, Athens, Greece, e-mail: lkaratzanos@gmail.com, a.icusn@gmail.com

Cite as: Despoti, A., Karatzanos, E., Patsaki, I., Tzoumi, D., Roussou, G., Leventakis, N., Papatathanasiou, A., Nanas, S., Dimitriadi, N. (2022). Immersive virtual reality in cognitive rehabilitation: a systematic review. *Health and Research Journal*, 8(3), 225-241. <https://ejournals.epublishing.ekt.gr/index.php/HealthRes/>

INTRODUCTION

Even though virtual reality (VR) is a technology applied since 1980 in space and military (NASA- Virtual Interface Environment Workstation, 1980; Thomas A. Furness- Visually Coupled Airborne Systems Simulator, 1982), their use in medical rehabilitation is emerging the last decade.¹ Regarding, the field of clinical neuropsychology, VR has been used as a tool for the assessment (and rehabilitation of various cognitive functions, such as executive functions, memory, attention and visuospatial abilities, that have been degraded due to various neurological conditions and brain damage.²⁻⁵

Researchers claim that VR intervention methods have several advantages compared to traditional, face to face and paper-and-pencil methods.⁶ More specifically, VR provides safe and engaging environment simulating the real world, and therefore high ecological validity. Their performance tracking is accurate, detailed and automated, and can record data which a human eye would not report eliminating the loss of important data due to the limitations of subjective observation. Furthermore, health care professionals thanks to VR systems own a great level flexibility and control over the tasks and they can offer personalization on the therapeutic protocols.

The VR technology can be presented in fully immersive, semi-immersive and non-immersive environments. High levels of immersion may provide a high sense of presence in the virtual world affecting both the physical and emotional reaction to the input from the VR system.⁷ The impact of immersion in rehabilitation using VR technologies needs to be assessed.

Immersive VR constitutes of a real-time three-dimensional virtual world where the user maintains a first-person view of the VR environment with which they interact, in a embodied experience, whilst in non-immersive or semi-immersive VR the "mirror" view can be used in a non-embodied experience with "mirror" view of the user, or with the use of two-dimensional (2D) graphics. The VR rehabilitation scenarios have been performed to either 2D or 3D graphics.⁸ A 3D environment is perceived to be more realistic and with higher sense of presence than a 2D environment.⁹

Spatial presence refers to "the sense of being in an environment".¹⁰ Higher levels of immersion have been linked to side

effects as dizziness, nausea, discomfort, eye fatigue, disorientation or motion-sickness which is referred as VR sickness.¹¹ However, these symptoms have been reported to only 5% of the participants in a VR environment.¹²

The type of graphics can affect the participants' perception of the task and intentions.¹³ 2D and 3DVR-systems lead to different presence experiences and to different cortical activation patterns. In particular, presence experiences associated with activity of a fronto-parietal network, which is modulated by the Dorsolateral Prefrontal Cortex (DLPFC).¹⁰ Fully immersive 3D enriched-environment requires allocation of more brain and sensory resources for cognitive/motor tasks than 2D.¹⁴ However, the study of Lledó et al.,¹⁵ suggest that 2D VR environments may be a more efficient for post-stroke patients in rehabilitation of upper limb, mainly because of the accuracy in order to effectuate optimal kinematic trajectories.

There are more and more clinical trials that include VR. Most of the studies in cognitive rehabilitation, use semi or non-immersive environments, mostly due to high economic software and hardware requirements or other development complications and issue related to the technologies interfacing and the three-dimensional graphics representation of the user in virtual space. The aim of this study is to review and investigate the effects of immersive VR as a rehabilitation approach of cognitive functions. Furthermore, safety and reliability will be also examined.

METHODOLOGY

The current review was conducted and reported with guidance of with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Data sources and search strategy

The electronic data bases of PubMed, Scopus, Cochrane, OTseeker and PsycINFO were systematically searched from inception until August of 2021. Keywords for strategy searching were: immersive virtual reality, cognitive rehabilitation and neuropsychological rehabilitation.

For example, a sample search strategy for the PubMed database was: (((immersive virtual real*)) OR (immersive virtual-real*)) OR (immersive VR)) AND (((neuropsychological) OR (neuro rehab*)) OR ((cogn*) OR (CR))).

<https://ejournals.epublishing.ekt.gr/index.php/HealthResJ>

Eligibility criteria and study selection

The inclusion criteria were the following: a) studies with immersive VR technologies published in English in peer-reviewed journals, b) studies with VR technologies that measure rehabilitation in cognitive functions (memory, attention and concentration, language, executive and visuospatial function, navigation), c) adult patients with diagnosis of neurological disorder or traumatic brain injury) (d) elderly with cognitive decline. The studies with psychiatric disorders were excluded. First, all articles were evaluated by two authors according to the title, abstract, and text. Then, all those who considered potentially eligible were fully read and initially analyzed. The last machine engine research was on 30 August 2021.

Data extraction

Extracted data of the studies were organized according to PICO process: (1) author and date of publication, (2) neurological disorder (3) sample size (4) experimental intervention, (5) control interventions (7) sessions details (number, duration and frequency), (8) outcomes, (9) type of study (Table 1). Furthermore, the neuropsychological outcome measures were arranged by cognitive functions: (1) attention/ concentration, (2) executive function, (3) memory, (4) visuospatial/orientation/navigation, (5) language and also stress (Table 2). Also, follow up sessions and ecological validity was also taken into account.

Quality assessment

Two authors (AD, EK) assessed the quality of the research of each RCT articles using the Physiotherapy Evidence Database (PEDro) Scale (Table 3). Total scores from 6 to 10 considered high quality, from 4-5 considered fair quality and ≤ 3 considered poor quality. Two authors conducted a blinded rating of the methodological quality of the studies. Different rates and unclear issues were discussed.

Level of immersion

The level of immersiveness of VR technologies that were included on the studies was assessed using the criteria of Michael Heim (1998) by the 3Is: Immersion, Interaction and Information intensity, and the classification of sense of presence (SoP) in VR can be assessed by examination both of the interfaces and technologies used (360 stereoscopic view, interaction

interfaces, embodiment of the user in virtual space) and the multimedia content (real-time three-dimensional graphics, interaction mechanisms, gamification techniques and real-world physics and properties simulation).

RESULTS

The selection process is summarized according to PRISMA guidelines as a flow chart (Fig. 1). Firstly, 468 records identified through databases searching. After deleting duplicate papers, 466 were screened by the authors to assess the inclusion criteria. A total number of 223 articles assessed full-text for eligibility. Consequently, 16 studies included in qualitative synthesis. For articles meeting inclusion criteria, data on study design, participant characteristics, and intervention outcomes were extracted by two of the authors (AD and EK). Disagreements between reviewers were resolved by consensus.

There were 16 studies selected that were relevant to the aim of this review (Table 1). Most of the studies were RCTs (N=6) and five feasibility and one reliability study. There were some low-level evidences including two case studies and two non-randomized controlled trials. All studies investigated immersive VR as rehabilitation tool in persons with neurological disorders (as stroke, Traumatic Brain Injury (TBI), Alzheimer Disease (AD)) MCI and elderly.

Participants

The number of participants ranged from 66 to 1 (mean= 26 persons). The total number of participants was 404 (Table 1). The majority of the studies¹⁶⁻²⁰ developed VR systems to train patients with traumatic brain injury (TBI). There were four VR rehabilitation systems²¹⁻²⁴ practiced form elderly participants with cognitive decline. In addition, there are systems created aimed to train various cognitive functions for patients suffering from stroke,²⁵⁻²⁷ Alzheimer's disease²⁸ and mild cognitive impairment.²⁹⁻³¹

Aim of studies

The aim of the studies (Table 2) was either to test the feasibility of the VR systems,^{20,21,24,27,31} and the reliability¹⁶ or to train specific cognitive functions such as attention,^{18,19,20,29} executive functions,^{17,22} memory,²³ navigation,²⁸ general cognitive abilities and daily living,^{25,30} as well as stress relief and relaxation.²¹

One study compared screen displays as an alternative to HMD within virtual reality (VR)-based applications to train memory and attention functions.²⁶

Interventions

Some types of interventions concerned activities of the everyday life^{16,19,26,29,30} such as preparation of meal, interacting in a virtual store and accomplishing morning hygiene etc. Further, other scenarios included path finding and navigation^{19,23,24,26,28} and various kind of exercises such as card play and fishing,²⁵ fruit ninja,²² target detection in outdoor space such as garden²⁷ or Stroop tasks in VR Apartment and Classroom.¹⁷ One study uses scenes from nature for relaxation.²¹ Two studies^{18,20} designed simple interventions with minimal graphics such as just a black board with target and cursor or cancellation tasks, for patients with severe brain injuries on the early stages of recovery.

Comparison

Six out of the 15 studies^{22,25,26,29,30,23} included comparison group. In two studies^{23,29} the comparison group performed traditional, face to face training such as physical and cognitive rehabilitation or music therapy. Furthermore, in two study the experimental group was compared to non-immersive VR training,^{22,26} In two studies^{25,30} the comparison group submitted to computerized cognitive training.

Duration of interventions

Even though time of sessions was not included in every study, sessions lasted from two to 60 min (mean time = 30 min ca.), ranging from one to 60 sessions spread over the course of 1 single day to 6 months. Feasibility studies consist the shorter trials, ranging from one to 8 sessions.

Measures

The intervention studies (Table 2) included pre and post measures of functions by using neuropsychological assessment tools such as Mini Mental State Examination (MMSE), Digit Span, Phonemic Verbal Fluency, Dual Task, Clock, Instrumental Activity of Daily Living (IADL), Stroop Color Test, Word Test, Montreal Cognitive Assessment (MOCA), Paced Auditory Serial Addition Task (PASAT), Delis-Kaplan Executive Function System (D-KEFS), Wechsler Memory Scale, Toulouse-Piéron Trail Making or behavioral scales such as Geriatric Depression Scale

(GDS), Music in Dementia Assessment Scales, State-Trait Anxiety Inventory (STAI) questionnaire. Four studies contained computerized neurocognitive function test (CNFT)²⁵ and automated neuropsychological assessment metrics (ANAM),¹⁷ Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K)³⁰ and the Dutch version of the Oxford Cognitive Screen (OCS-NL).²⁷ Additionally, two studies^{18,20} measured attention with kinematic analysis of movements, the performance data and observations of behavior. One study³¹ used custom-made hand motion tracking module and 3-dimensional positions of the hands for assessing the finger tapping as an indication for attention and response time.

The feasibility of the VR systems was measured by observations, custom-developed Likert-scale questionnaire consisting of several open-ended questions regarding the VR experience and self-reported scales such as stress arousal checklist (SAC), simulator sickness questionnaire (SSQ), ITC sense of presence inventory (ITC-SOPI) and Borg rate of perceived exertion (RPE) scale.

Outcomes Feasibility

Regarding safety and feasibility^{20,21,24,27,31} most participants (N=134 out of 142 in total) completed successfully the tasks although the cognitive abilities varied from normal to severe. All the four studies conclude that VR is a safe, feasible, usable and engaging system for cognitive rehabilitation. Most of the participants did not face stimulation sickness from the immersive environment and had no negative side-effects such as dizziness, headache, disorientation. In addition, most participants experienced positive the iVR with low stress, enjoyment and high levels of engagement and tolerated well with the technology and the equipment of HMD.

Improvements of cognitive functions

All intervention studies reported improvements either in cognitive functions or in stress management and relaxation (Table 2). In particular, most of the studies (N=6) demonstrated improvement in attention.^{18,19,20,25,26,27} Better performance was also found in executive functions (N=3),^{17,22,29} in memory (N=5)^{19,23,25,26,30} and in navigation skills (N=1).²⁸ One study referred to stress relief in older adults with various kind of cognitive abilities.²¹ As far as the studies with comparison groups^{22,23,25,29,30}

when the control group performed traditional face to face cognitive training, in the one case²³ there was no improvements but progressive decline of cognitive functions of participants although iVR group had improvements in memory tests, especially in long-term recall. Furthermore, in the other case²⁹ even though both groups had significant improvements in Stroop test, only iVR group showed improvements in cognitive dual-task gait and more improvements in the TMT-B.

Immersive vs Non-immersive

In a study comparing iVR with computerized cognitive training²⁵ both groups demonstrated similar improvement. In the study of Park et al.,³⁰ in which they compared Mixed Reality with conventional computer-assisted cognitive training, even though experimental group showed significant more improvements than control group in visuospatial working memory and recall in visuospatial tasks, both groups did not improve significantly in the other cognitive domains.

Two studies^{22,26} compared immersive with non-immersive rehabilitation training, with mixed results. The study of Gamito et al.,³⁰ found improvements in working memory and sustained attention for both groups, regardless of the level of immersion. The study of Huang²² the experimental group improved significantly in executive functions (Stroop Test and Trail Making Test). In advance, Huang²² supports that engaging in a more immersive environment may lead to a greater improvement of inhibitory control and task switching in older adults. Furthermore, when the participants felt located within an iVR and perceived the possibility of moving within the environment, they were more likely to improve their inhibitory control and tasks switching after experiencing presence.

Quality of RCT's

Six studies of the study were RCT's.^{22,23,25,26,29,30} The PEDro score for each study is reported in Table 3. The mean PEDro score of the studies included in the review was 7.2 with scores ranging from 6 to 8. In total, all included studied had high quality. The most common methodological weaknesses referred to the blinding of patients, therapists, and assessors. Furthermore, in most of the studies^{23,25,26,30} all patients received treatments as allocated, while two^{22,29} did not meet the criteria of "intention to treat".

DISCUSSION

The purpose of the present study was to systematically review and investigate the effects of immersive VR as a rehabilitation approach of cognitive functions in patients suffering from neurological disorder or a traumatic injury or elderly with cognitive decline. Furthermore, we also examined safety and feasibility. Of the 16 studies included, all intervention studies reported improvements in cognitive functions and in particular, in attention, executive functions, memory and in navigation skills. Furthermore, all conclude that immersive VR is feasible, safe and usable for neurorehabilitation of patients with cognitive impairments.

More specifically, in patients with stroke it was noted significant improvement in Computerized neurological test that examined visual and auditory attention along with verbal and visual memory in comparison when cognitive training was performed in a fully immersive environment,²⁵ in working memory and attention²⁶ and in neglect.²⁷ Most of the studies demonstrated improvement in attention.^{18,19,20,25,26} More RCTs have examined the beneficial effects of VR in elderly facing with cognitive challenges regarding executive functioning.^{22,29,30} Additionally, benefits were demonstrated even in navigational tasks,²⁸ and in memory.^{19,23,25,26} One study referred to stress relief in older adults with various kind of cognitive abilities.²¹

Regarding safety and feasibility, most of the participants completed successfully the tasks and did not report any stimulation sickness, dizziness or disorientation.^{20,21,24,27,31} Sakhare et al.,²⁴ having examined the feasibility of VR training in elderly noted high levels of arousal and low stress levels indicating a level of excitement and enjoyment. And even in patients with Traumatic Brain Injury the immersion was well tolerated.¹⁶⁻²⁰

Even though the available data is still limited, VR could promote neurorehabilitation in different pathologies, such as stroke, MCI, dementia and TBI. In recent years, more and more studies, support that VR interventions provoke neuroplasticity, by promoting the activation of different neuronal connections, such as the fronto-parietal network¹⁰ and by activating cortical reorganization.³²⁻³⁴ Hence, VR technology is leading to improvements in motor, cognitive and psychological functions. Immer-

sive VR seems to be a promising tool in cognitive rehabilitation both for patients and for therapist as it can provide a feasible, safe, accurate, flexible and enjoyable training environment. Further research is warranted in large-scale longitudinal clinical trials in various patients' groups in order to investigate the long-term impact on cognitive functions in interventions using immersive VR. Longitudinal studies on cognitive VR interventions would provide better evidence of the VR efficacy on rehabilitation. Studies should also include follow-up to report the maintenance of cognitive improvements. Furthermore, immersive VR intervention could be combined with quantitative techniques such as EEG, eye-tracking, heart-rate etc. to provide useful tracks about psychophysiological responses. Additionally, we suggest more studies comparing different levels of immersion as the results are still mixed. Lastly, VR rehabilitation applications could be examined as telerehabilitation systems, to ensure accessibility and long-term improvements in the everyday life of the patients.

Acknowledgments

This review has been conducted in the framework of "REACT – Virtual Reality applications in medical rehabilitation" project, led by National and Kapodistrian University of Athens and co-funded by "RESEARCH - CREATE - INNOVATE« program, ESPA 2014-2020, and the European Union

REFERENCES

1. Keshner EA, Weiss PT, Geifman D, Raban D. Tracking the evolution of virtual reality applications to rehabilitation as a field of study. *Journal of NeuroEngineering and Rehabilitation*. 2019;16(1).
2. Aida J, Chau B, Dunn J. Immersive virtual reality in Traumatic Brain Injury Rehabilitation: A literature review. *NeuroRehabilitation*. 2018;42(4):441–8.
3. Clay F, Howett D, FitzGerald J, Fletcher P, Chan D, Price A. Use of immersive virtual reality in the assessment and treatment of Alzheimer's disease: A systematic review. *Journal of Alzheimer's Disease*. 2020;75(1):23–43.
4. Maggio MG, Latella D, Maresca G, Sciarrone F, Manuli A, Naro A, et al. Virtual reality and cognitive rehabilitation in people with stroke: An overview. *Journal of Neuroscience Nursing*. 2019;51(2):101–5.
5. Moreno A, Wall KJ, Thangavelu K, Craven L, Ward E, Disanayaka NN. A systematic review of the use of virtual reality and its effects on cognition in individuals with neurocognitive disorders. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2019;5(1):834–50.
6. Ventura S, Brivio E, Riva G, Baños RM. Immersive versus non-immersive experience: Exploring the feasibility of memory assessment through 360° technology. *Frontiers in Psychology*. 2019;10.
7. Kim SJ, Laine TH, Suk HJ. Presence effects in virtual reality based on user characteristics: Attention, enjoyment, and memory. *Electronics*. 2021;10(9):1051.
8. García-Betances RI, Arredondo Waldmeyer MT, Fico G, Cabrera-Umpiérrez MF. A succinct overview of virtual reality technology use in alzheimer's disease. *Frontiers in Aging Neuroscience*. 2015;7.
9. Roettl J, Terlutter R. The same video game in 2D, 3D or virtual reality – how does technology impact game evaluation and brand placements? *PLOS ONE*. 2018;13(7).
10. Kober SE, Kurzmann J, Neuper C. Cortical correlate of spatial presence in 2D and 3D Interactive Virtual Reality: An EEG study. *International Journal of Psychophysiology*. 2012;83(3):365–74.
11. Chang E, Kim HT, Yoo B. Virtual reality sickness: A review of causes and Measurements. *International Journal of Human–Computer Interaction*. 2020;36(17):1658–82.
12. Regan C. An investigation into nausea and other side-effects of head-coupled immersive virtual reality. *Virtual Reality*. 1995;1(1):17–31.
13. Riva G, Waterworth JA, Waterworth EL, Mantovani F. From intention to action: The role of presence. *New Ideas in Psychology*. 2011;29(1):24–37.
14. Slobounov SM, Ray W, Johnson B, Slobounov E, Newell KM. Modulation of cortical activity in 2D versus 3D virtual reality environments: An EEG study. *International Journal of Psychophysiology*. 2015;95(3):254–60.
15. Lledó LD, Díez JA, Bertomeu-Motos A, Ezquerro S, Badesa

- FJ, Sabater-Navarro JM, et al. A comparative analysis of 2D and 3D tasks for virtual reality therapies based on robotic-assisted neurorehabilitation for post-stroke patients. *Frontiers in Aging Neuroscience*. 2016;8.
16. Christiansen C, Abreu B, Ottenbacher K, Huffman K, Masel B, Culpepper R. Task performance in virtual environments used for cognitive rehabilitation after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*. 1998;79(8):888–92.
17. Dahdah MN, Bennett M, Prajapati P, Parsons TD, Sullivan E, Driver S. Application of virtual environments in a multi-disciplinary day neurorehabilitation program to improve executive functioning using the Stroop task. *NeuroRehabilitation*. 2017;41(4):721–34.
18. Dvorkin AY, Ramaiya M, Larson EB, Zollman FS, Hsu N, Pacini S, et al. A “virtually minimal” visuo-haptic training of attention in severe traumatic brain injury. *Journal of NeuroEngineering and Rehabilitation*. 2013;10(1):92.
19. Gamito P, Oliveira J, Pacheco J, Morais D, Saraiva T, Lacerda R, et al. Traumatic brain injury memory training: A virtual reality online solution. *International Journal on Disability and Human Development*. 2011;10(4).
20. Larson EB, Ramaiya M, Zollman FS, Pacini S, Hsu N, Patton JL, et al. Tolerance of a virtual reality intervention for attention remediation in persons with severe TBI. *Brain Injury*. 2011;25(3):274–81.
21. Appel L, Appel E, Bogler O, Wiseman M, Cohen L, Ein N, et al. Older adults with cognitive and/or physical impairments can benefit from immersive virtual reality experiences: A feasibility study. *Frontiers in Medicine*. 2020;6.
22. Huang K-T. Exergaming executive functions: An immersive virtual reality-based cognitive training for adults aged 50 and older. *Cyberpsychology, Behavior, and Social Networking*. 2020;23(3):143–9.
23. Optale G, Urgesi C, Busato V, Marin S, Piron L, Priftis K, et al. Controlling memory impairment in elderly adults using virtual reality memory training: A randomized controlled pilot study. *Neurorehabilitation and Neural Repair*. 2009;24(4):348–57.
24. Sakhare AR, Yang V, Stradford J, Tsang I, Ravichandran R, Pa J. Cycling and spatial navigation in an enriched, immersive 3D virtual park environment: A feasibility study in younger and older adults. *Frontiers in Aging Neuroscience*. 2019;11.
25. Cho D, Lee SH. Effects of virtual reality immersive training with computerized cognitive training on cognitive function and activities of daily living performance in patients with acute stage stroke. *Medicine*. 2019;98(11).
26. Gamito P, Oliveira J, Santos N, Pacheco J, Morais D, Saraiva T, et al. Virtual exercises to promote cognitive recovery in stroke patients: The comparison between head mounted displays versus screen exposure methods. *International Journal on Disability and Human Development*. 2014;13(3).
27. Huygelier H, Schraepen B, Lafosse C, Vaes N, Schillebeeckx F, Michiels K et al. An immersive virtual reality game to train spatial attention orientation after stroke: A feasibility study. *Applied Neuropsychology: Adult*. 2020;1-21.
28. White P, Moussavi Z. Neurocognitive Treatment for a Patient with Alzheimer's Disease Using a Virtual Reality Navigational Environment. *Journal of Experimental Neuroscience*. 2016;10:JEN.S40827.
29. Liao Y, Chen I, Lin Y, Chen Y, Hsu W. Effects of Virtual Reality-Based Physical and Cognitive Training on Executive Function and Dual-Task Gait Performance in Older Adults With Mild Cognitive Impairment: A Randomized Control Trial. *Frontiers in Aging Neuroscience*. 2019;11.
30. Park E, Yun B, Min Y, Lee Y, Moon S, Huh J et al. Effects of a Mixed Reality- based Cognitive Training System Compared to a Conventional Computer-assisted Cognitive Training System on Mild Cognitive Impairment: A Pilot Study. *Cognitive and Behavioral Neurology*. 2019;32(3):172-178.
31. Yun S, Kang M, Yang D, Choi Y, Kim H, Oh B et al. Cognitive Training Using Fully Immersive, Enriched Environment Virtual Reality for Patients With Mild Cognitive Impairment and Mild Dementia: Feasibility and Usability Study. *JMIR Serious Games*. 2020;8(4):e18127.
32. Coco-Martin M, Piñero D, Leal-Vega L, Hernández-Rodríguez C, Adiego J, Molina-Martín A et al. The Potential of Virtual Reality for Inducing Neuroplasticity in Children with Amblyopia. *Journal of Ophthalmology*. 2020;2020:1-9.

33. You S, Jang S, Kim Y, Kwon Y, Barrow I, Hallett M. Cortical reorganization induced by virtual reality therapy in a child with hemiparetic cerebral palsy. *Developmental Medicine & Child Neurology*. 2005;47(9):628-635.
34. Gatica-Rojas V, Méndez-Rebolledo G. Virtual reality interface devices in the reorganization of neural networks in the brain of patients with neurological diseases. *Neural Regeneration Research*. 2014;9(8):888.

ANNEX

Figure 1. PRISMA flow chart

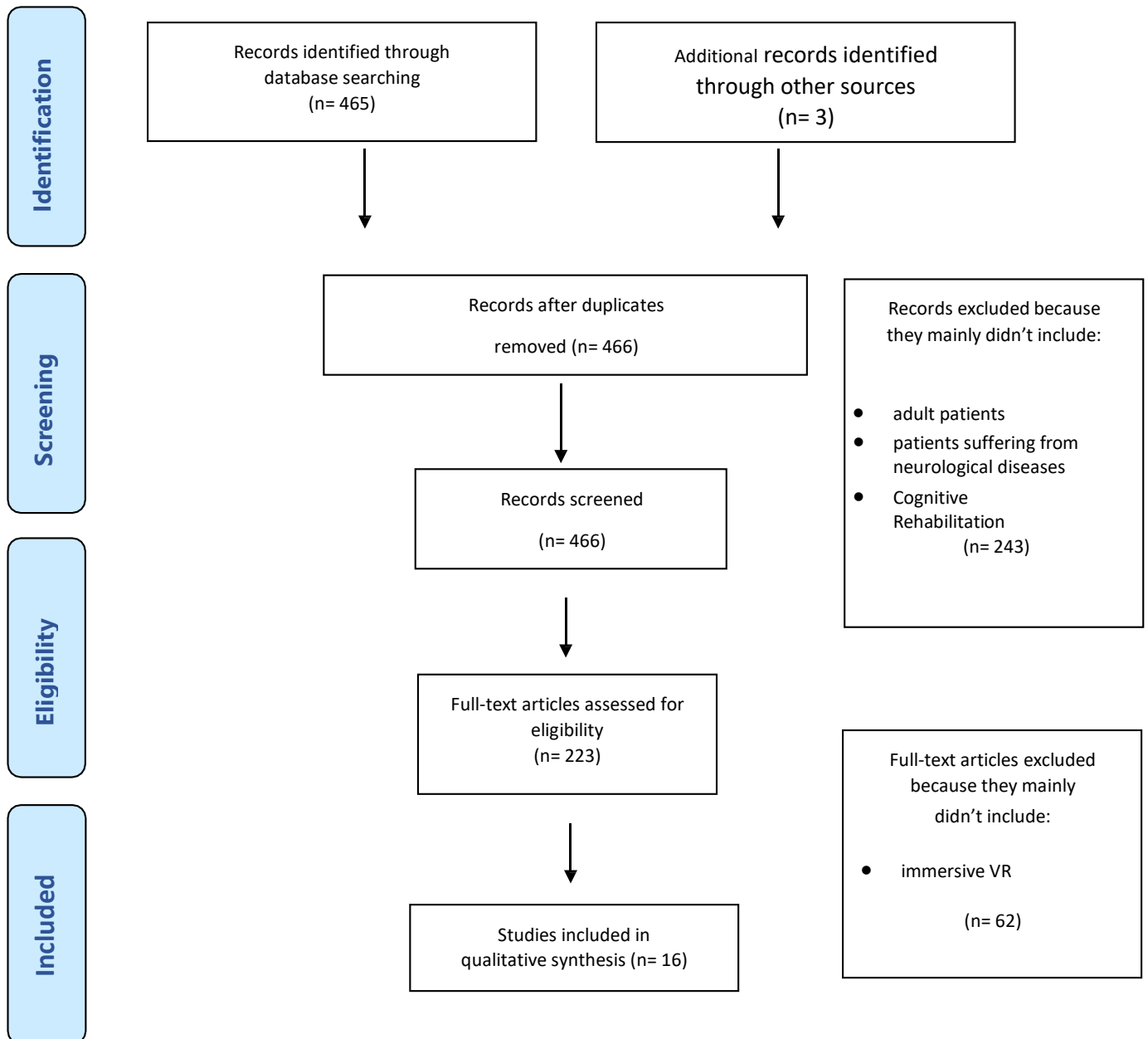


TABLE 1. Summary of the studies included.

Study	Participants	Population	Intervention	Comparison	Duration	Outcomes	Study Type
Cho & Lee, 2019	N=42 (EG=21, CG=21)	Stroke	VR (fishing, cards) + Computerized cognitive exercise (REHACOM)	Computerized cognitive exercise	4 weeks (5/week, for 30')	Attention, memory, per- formance of daily living improved in both groups	RCT
Gamito et al., 2014	N= 17 (EG=8, CG=9)	Stroke	HMD VR with 9 tasks of everyday life (such as morning hygiene and breakfast, find the way to minimarket, find a virtual character, a door number etc)	Desktop screen- based VR	12 sessions (1/week)	Improved working memory and sustained attention regardless of the VR device	RCT
Huang, 2019	N=32 (EG=16, CG=17)	Elderly	Immersive Fruit Ninja VR	Non immersive Fruit Ninja (Ki- nect)	8 sessions (within 4 weeks)	EG= significant effect on the Stroop Test and Trail Making Test. The feeling of presence could con- tribute to older adults' cognitive im- provement, and (b) the impacts of immersive exergame training on executive functions vary across individual do- mains	RCT
Optale et al., 2010	N=36 (EG=18, CG=18)	Elderly	VR training in path finding and in focused attention	Face to-face training ses- sions using mu- sic therapy	6 months (3 months (3 auditory and 3 VR sessions every 2 weeks) + 3 months (1 auditory and 1 VR session per week)	EG=improvements in memory tests, especially in long- term recall. CG=no improvements but progressive decline	RCT
Park et al., 2019	N=21 (EG=11, CG=10)	MCI	MR-based cognitive training based on eve- ryday tasks such as home setting, caring for a grandchild	Same activities conventional computer- as- sisted cognitive training, using Comcog	18 sessions (3/week for 30')	EG= significant more improvements visuospa- tial working memory but no to other cognitive domain either for EG or CG	RCT

Liao et al., 2019	N=34 (EG=18, CG=18)	MCI	VR-based cognitive training (VR) like metro, kitchen chef, store clerk, football, tai chi	Traditional cognitive training (CPC)	12 weeks (3/week, 60', 36 sessions)	Both groups= significant improvements in the SCWT and single-task and motor dual-task gait performance measures. VR group= showed improvements in cognitive dual- task gait, more improvements in the TMT-B and DTC of cadence with borderline significances.	RCT
Appel et al., 2020	EG=66	Elderly	VR nature scenes for relaxation and stress relief	-	1 session (3-20')	Feasible and safe to expose older adults with various levels of cognitive decline in VR	Feasibility, non-randomized
Huygelier et al., 2020	EG=7	Stroke	VR outdoor space: vegetable garden, lake and forest	-	6 sessions (30-45')	It is promising to us immersive VR for neglect rehabilitation.	Feasibility, non-randomized
Larson et al., 2011	EG=18	TBI	3D cancellation exercises in both visual and haptic (tactile) stimuli	-	12 block protocol over 2 days	Within-subjects' comparisons of target acquisition time during treatment showed that a treatment condition that included haptic cues produced improved performance compared to a condition in which such cues were not provided.	Feasibility, Non-randomized
Sakhare et al., 2019	EG= 40 (older=20, younger=20)	Elderly	Navigating in aVR park while cycling stationary bike	--	1 session (4 trials)	Feasible and enjoyable in both younger and older adults	Feasibility, non-randomized
Yun et al., 2020	EG=11	MCI	Virtual harvest and cook games to improve various cognitive domains	--	1 session (30')	VR cognitive training system is feasible and usable in patients with MCI	Feasibility, Non-randomized

Christiansen et al., 1998	EG=30	TBI	VR Kitchen, meal preparation with multiple steps	-	2 times the task (30 steps) within 7-10 days	There is adequate initial reliability	Reliability, Non-randomized
Dahdah et al., 2017	EG=15	TBI	VR version of the Stroop in VR Apartment and Classroom	--	8 sessions(30-60')	Significantly reduced response time on the word-reading condition of VR Stroop and non-significantly reduced response time on the interference condition. Non-significant improvements in accuracy and inhibition were demonstrated on the color-naming condition of VR Stroop. Significantly improved accuracy under time pressure was found for the ANAM, after VR intervention	Non-randomized
Dvorkin et al., 2013	EG=21	TBI	Visuo-haptic VR, with one target and cursor	-	2 days (3 conditions -no haptic feedback, a break-through force, and haptic nudge- in 12, 4-minute blocks	Patients were attentive to the task, although had attention loss both before (prolonged initiation) and during (pauses during motion) a movement. Compared to no haptic feedback, patients benefited from haptic nudge cues but not break-through forces. Overall, patients improved and increased the number of targets acquired.	Non-randomized
Gamito et al., 2011	EG=1	TBI	9 tasks of everyday life (such as morning hygiene and breakfast, find the way to minimarket, find a virtual character, a door number etc)	-	10 online VR sessions	Improvement in working memory and attention	Case Study

White&M oussavi, 2016	EG=1	AD	Navigate to targets in a symmetric, landmark- less virtual building.	--	7 weeks	Learned to perfectly nav- igate, skill at navigating while driving improved noticeably and that he enjoyed cognitive im- provement in his daily life at home.	Case Study
-----------------------------	------	----	--	----	---------	---	------------

N= Number of Participants, EG= Experimental Group, CG= Control Group, MCI= Mild Cognitive Impairment, TBI=Traumatic Brain Injury,
AD=Alzheimer's Disease, VR=Virtual Reality, RCT=Randomized Control Trial

TABLE 2. Summary of the cognitive function improved in studies

Study	Participants	Population	Aim	Measures/ Assessment	Attention & Concentration	Executive functions	Memory	Visuospatial, Orientation, Navigation	Stress
Optale et al., 2010	36 (EG=18, CG=18)	Elderly	Lessen cognitive decline and improve memory functions	MMSE, Digit Span, Phonemic Verbal Fluency, Dual Task, Clock, IADL, GDS			✓		20
Cho & Lee, 2019	42 (EG=21, CG=21)	Stroke	Impact of cognitive function and activity of daily living	Computerized Neurocognitive Function Test (CNT)	✓		✓		
Gamito et al., 2014	17 (EG=8, CG=9)	Stroke	Compare HMD vs non-HMD VR in memory and attention rehabilitation	Wechsler Memory Scale, Toulouse- Piéron	✓		✓		
Huygelier et al., 2020	EG=7	Stroke	Feasibility of VR rehabilitation game for neglect	The Dutch version of the Oxford Cognitive Screen (OCS-NL), Behavioral Inattention Test (BIT) letter cancellation task and figure copy task	✓			✓	
Liao et al., 2019	34 (EG=18, CG=18)	MCI	Cognitive training on executive function and dual-task gait performance in older adults with MCI, as well as to compare VR-based cognitive training	Stroop Color and Word Test (SCWT)		✓			

			with traditional						
Park et al., 2019	21 (EG=11, CG=10)	MCI	Effectiveness in general cognition of an MR-based cognitive training	Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K)			✓		
Appel et al., 2020	EG=66	Elderly	Provide enjoyment/relaxation and reduce anxiety and depressive symptoms.	State-Trait Anxiety Inventory, Music in Dementia Assessment Scales, modified STAI questionnaire					✓
Dahdah et al., 2017	EG= 15	TBI	Whether immersive VR treatment interventions improve executive dysfunction in patients with brain injury and whether performance is stronger on a VR version of the Stroop than traditional Stroop	Woodcock-Johnson, 3rd Edition (WJ-III), Delis-Kaplan Executive Function System (D-KEFS), Automated Neuropsychological Assessment Metrics (ANAM), Simulator Sickness Questionnaire (SSQ)		✓			
White&Moussavi, 2016	EG= 1	AD	Learn to navigate in a simple VR navigation (VRN) environment and whether that training could also bring real-life cognitive benefits	MOCA				✓	
Gamito, et al., 2011	EG= 1	TBI	Train memory and attention	PASAT (Paced Audi-	✓		✓		

			outside clinic premises	tory Serial Addition Task)					
Dvorkin et al., 2013	EG=21	TBI	Attention training in early stages of recovery from severe TBI	Kinematic analysis of arm movements and analysis of the effect of force type on performance (i.e., the number of targets acquired in a block of trials)	✓				
Larson et al., 2011	EG= 18	TBI	Feasibility of VR and robotics technology to improve attention in patients with severe TBI in the early stages of recovery.	Performance data (i.e., time) and observations of behavior,	✓				
Huang, 2019	EG= 16, CG=17	Elderly	Exergaming and virtual reality (VR)-based training for executive functions in older adults	Stroop Test, Trail Making Test, Digit Span		✓			

EG= Experimental Group, CG= Control Group, MCI= Mild Cognitive Impairment, TBI=Traumatic Brain Injury, AD=Alzheimer's Disease, VR=Virtual Reality, MMSE= Mini Mental State Examination, MOCA= Montreal Cognitive Assessment, IADL= Instrumental Activities of Daily Living Scale, GDS= The Geriatric Depression Scale

TABLE 3. PEDro score for RCT's included in the systematic review

Study	Random allocation	Concealed allocation	Baseline comparability	Blinded subjects	Blinded therapists	Blinded assessors	Follow-up	"Intention to treat"	Between-group analysis	Point estimates and variability	Total Score PEDro Scale
Cho & Lee, 2019	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Gamito et al., 2014	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Huang, 2019	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7/10
Optalet et al., 2010	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Park et al., 2019	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
Liao et al., 2019	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7/10