Cognitive interventions through virtual reality in people with Mild Cognitive Impairment: A Systematic Review

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ABSTRACT

Introduction: *The possibility of Mild Cognitive Impairment (MCI) reversal has generated numerous studies in search of treatment, including cognitive stimulation through virtual reality (VR). Despite its use, there is still no evidence about the modalities and effects in people with MCI. Aim: To systematize the characteristics of the studies that have used cognitive interventions with VR cognitive in people with MCI, describe their effects and to establish recommendations for future research based on the limitations reported.* ***Methods:*** *systematic review of studies published between 2010 and 2020, in the Web of Science, Scopus and Pubmed databases.* ***Results:*** *14 studies were identified with programs that mostly used immersive VR, with the "supermarket" as the most frequent virtual scenario. In seven studies only one cognitive function was involved, with memory and executive functions being the most intervened. The assessment instruments focused on cognitive measures, with little assessment of neuropsychiatric and quality of life variables. Thirteen studies reported improvements on the general cognitive level or by specific domain.* ***Conclusions:*** *The use of immersive and non-immersive VR has had positive results in the general or domain-specific cognitive performance of people with MCI, however, due to the incipient and limited evidence of its use in people with this pathology, it is not possible to determine the sustainability of these results and the generalization of these interventions regarding daily living activities. Interventions with real environments and post-intervention follow-up are recommended.*

Key words: *Mild Cognitive Impairment, Cognitive Stimulation, Cognitive Training, Virtual Reality, Systematic Review.*

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INTRODUCTION

People with a Mild Cognitive Impairment (MCI) diagnosis present a greater risk of progressing to a diagnosis of dementia than people of the same age range, who present cognitive aging according to their stage[1-5].

MCI is defined as a condition in which individuals show deterioration, in any cognitive function, a minimal impairment of instrumental activities of daily living (AVDI) and without meeting the diagnostic criteria for dementia[6].

A critical aspect in the study of MCI is its progression. A prospective study conducted at the Mayo Clinic in 2014, aimed at estimating the rates of progression from MCI to dementia, and indicated that, with a median of 5.1 years of follow-up, 153 (28.7%) of 534 participants progressed to dementia. In addition, it was shown that the cumulative incidence for dementia was 5.4% at 1 year, 16.1% at 2 years, 23.4% at 3 years, 31.1% at 4 years and 42.5% at 5 years. It was concluded that there was an increased risk of dementia in people with MCI compared to people whose cognition was according to their chronological age[7].

However, there are various investigations that have shown that MCI could evolve towards dementia, but it could also remain stable, or people could return to a cognitive state according to their chronological age, managing to reverse this condition[1,2,7,8].

In view of the possibility of reversion of this pathology, there are several proposals for pharmacological and non-pharmacological treatments for MCI. The most commonly studied are physical exercise and cognitive stimulation[9].

Regarding the efficacy of cognitive stimulation (CS) in people diagnosed with MCI, there is evidence of its positive effects, demonstrated both objectively and subjectively, and duration would range between 1 month and 5 years and would generate activation of left hippocampal neurons[10-13].

One of the suggestions made to CS programs is to promote the transfer or generalization of training to ADLs, in order to improve cognitive functioning in real life and not only in experimental contexts[11,14-17]. Thus, recent findings have shown the ability of the nervous system to rebuild neuronal synapses as a result of interaction with enriched environments, promoting new ways of performing cognitive stimulation, including the use of virtual reality (VR)[18-22].

VR is defined as a real or imagined three-dimensional environment, simulated by a computer, that allows users to experience the sensation of being present in a different physical place[19]. It has two modalities, the Head mounted device that consists of a helmet or glasses connected to a computer that presents the information for each visual field, which is known as immersive VR; and the Cave automatic virtual environment, in which virtual environments are projected in a cubic room onto the different walls, floor and ceiling, generating a 3D sensation, without the use of a helmet or virtual glasses, which is known as non-immersive VR[23].

There are systematic reviews regarding cognitive stimulation performed through VR[24-28]. However, these are not exclusive to people diagnosed with MCI[25,27,28]. A review of ten studies, aimed to know the effects of the programs on the participant´s perception of well-being, quality of life and safety[29].

Thus, this study´s objective is to systematize the characteristics of the studies that have used cognitive interventions through VR in with MCI described in the recent scientific literature. It is expected to have a description of the interventions and their effects, in addition to establishing recommendations for future research based on the limitations and orientations declared by the studies.

METHODOLOGY

This study corresponds to a systematic review that

followed the preparation and writing guidelines suggested by the specialized literature[30]. The process took place in two stages: 1. search and selection of sources to analyze, and 2. extraction and systematization of information from the selected studies.

The search and selection of sources was carried out through a 4-phase protocol: (see **figure 1**).

First phase of identification: corresponds to the search results in the electronic databases Web of Science, Scopus and Pubmed. The search algorithm included the terms: "cognitive training", "cognitive stimulation", "cognitive rehabilitation", "cognitive interventions", "cognitive therapy", "cognitive programs", "virtual reality", "immersive reality", "increased reality", "virtual environment", "gamification", "mild cognitive impairment", "MCI", "mild neurocognitive disorder", "memory", "attention", "executive function", "perception", "learning", " problem solving", "decision making", "spatial awareness", "language", which were related to the "AND" "OR" connector in English, Spanish and Portuguese, between 2009 and May 23, 2020 (see syntax in supplementary material).

Second phase of duplicates: those articles that were in more than one database were included only once.

Third phase of eligibility or screening: articles were eliminated according to title and abstract review, which should contain the terms "mild

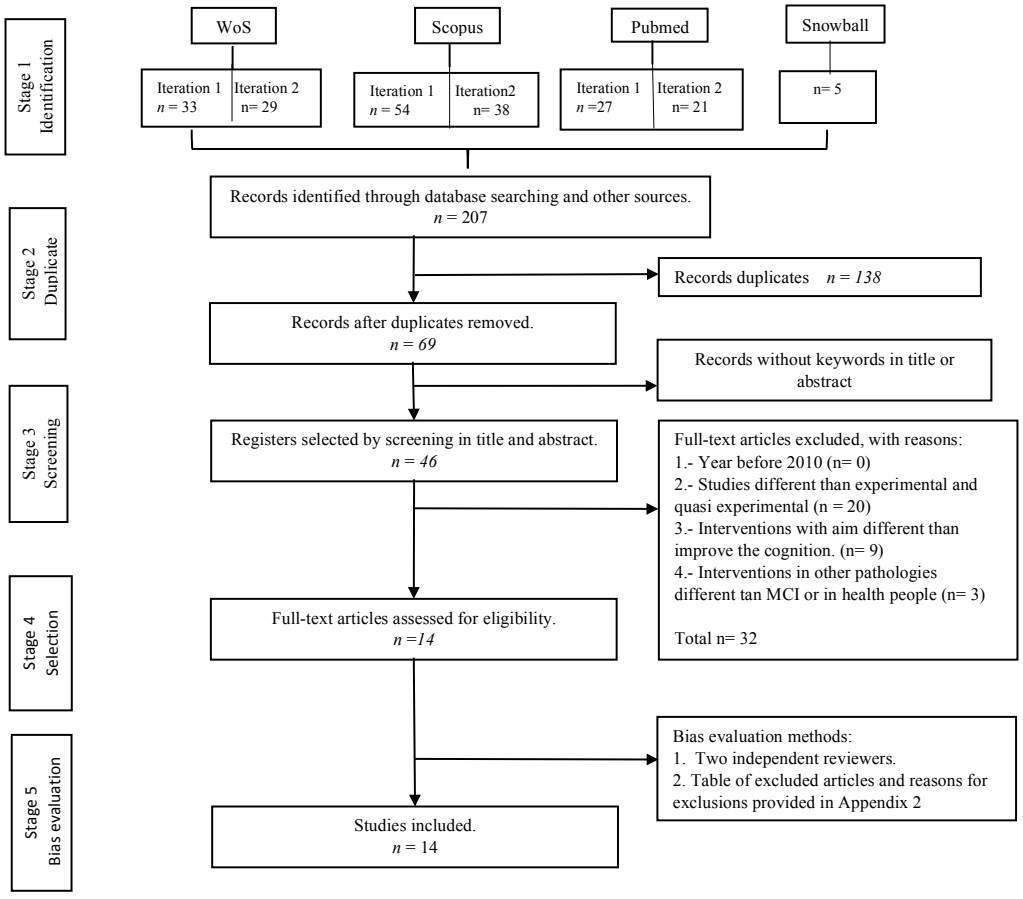

Figure 1: Article sample selection process flowchart.

cognitive impairment", and "intervention", or "program", or "training", or "rehabilitation", or "stimulation", or "therapy", and "virtual reality" in title and/or summary.

Fourth phase of inclusion: the following inclusion criteria were applied: (1) studies published between 2010 and 2020, (2) experimental and quasi-experimental designs, (3) cognitive interventions, (4) in people diagnosed with MCI; and exclusion: (1) healthy subjects and/or with traumatic and/or vascular alterations and (2) qualitative studies, editorials, systematic reviews, book chapters.

Fifth phase of bias evaluation: to ensure the quality of the sample selection, two methods were used: (1) evaluation by a third independent reviewer, (2) presentation of the excluded articles and their justification.

Information Systematization for data extraction

For data extraction, a matrix was prepared. Its operationalization is presented in **Table 1**.

Table 1. Description of the operationalization of the extraction of information from the studies.

Objective:	#	Column name	Description
	1	ID	Identifier of the studies included in this research
	2	Reference	Citation of the studies included in this research
	3	Participants N	N: corresponds to the total number of participants in each intervention group (GC= control group; GE= experimental group).
Characteristics interventions and effectiveness	4	Frequency sessions	Periodicity with which the intervention sessions are carried out.
	5	Intervention actions.	Intervention duration
	6	Number of sessions	Total number of sessions that took place during the intervention program.
	7	Cognitive function	Cognitive domain(s) intervened during the intervention program.
	8	Virtual reality type	Corresponds to the form of VR presentation: immersive (RVI) or non-immersive (RVNI).
	9	Physical activity.	Corresponds to the description of the physical activity included in the study. In case of not presenting, it is reported as not performed.
	10	Virtual stage	It corresponds to the scenario designed to be used in the intervention through VR.
	11	Therapist	Professional who performs the intervention sessions.
	12	Instruments	They correspond to the measurement instruments used before and after the intervention.
	13	Effectiveness	Corresponds to the effect obtained in the EG after the intervention performed.
Future research recommendations	14	Limitations.	They correspond to the limitations stated in the studies explicitly by the authors. In the event that they are not described, "Does not report" will be indicated.
	15	Orientations	They correspond to the orientations for future research described in the studies. In the event that they are not described, "Does not report" will be indicated.

RESULTS

Characteristics of the interventions

The characterization of the interventions is presented in **Table 2**.

The mean number of participants per study was 46.7 people, and between 46 and 6 people for the experimental group (GE) and 45 and 5 people for the control group (GC). The sessions frequency was three times per week (n=7), while less than two sessions and more than four sessions per week were the least conducted. The duration of each session ranged between 20 to 100 minutes, but more commonly averaged to 60 minutes. In relation to the number of sessions, they ranged between 8 to 72 sessions, with a median of 19 sessions. Only two studies report a number of sessions greater than or equal to 60 (ID 1 and 12) **(Table 2)**.

Eight studies used immersive VR and 6, non-immersive VR. Regarding the virtual scenarios used, three used only one virtual scenario: cycling (ID: 1 and 12) and rowing (ID: 13). Eleven studies used more than one virtual scenario, with an observed maximum of five scenarios for only one intervention program (ID: 2 y 3). One of the most frequent scenarios corresponded to the supermarket/minimarket, followed by rooms in a house and cycling **(Table 2)**. Memory was the most intervened cognitive function (n=11) followed by executive functions (n=8), attention (n=4), language and calculation (n=2) and finally, accordingly). In seven studies, only one cognitive function was intervened (ID: 1, 2, 7, 9, 11, 12 and 14), while in the other studies, three or more were intervened (ID: 3, 4, 5, 6, 8, 10 y 13). Nine studies intervened with a combination of cognitive functions and physical activity (ID: 1, 2, 3, 5, 6, 7, 8, 12, and 13), the remaining five focused only on cognitive tasks. Of those studies that included physical activity tasks, aerobic exercise (n=8), resistance (n= 2) and balance (n= 4) were included. Physical activities were performed during the same session.

Table 2. Characteristics of the cognitive interventions included in the review.

ID	Sources	Participants (N)	Frequency session*	Duration session**	Number of sessions	VR type	Cognitive function	Physical Activity (PA)	Virtual stage	Therapist
1	Anderson-Hanley C, et al. 2012	GE= 38, GC= 41	5	45	60	Immersive.	Executive functions.	Aerobic exercise (cycling).	Cycling	Does not report
2	Liao Y Y, et al. 2019	GE= 21, GC=21	3	60	36	Immersive.	Executive functions.	Resistance, aerobic and balance exercises.	Subway station, kitchen, minimarket, tai-chi, soccer.	Kinesiologist.
3	Liao Y Y, et al. 2020	GE= 17, GC=21	3	60	36	Immersive.	Executive functions, , verbal memory.	Resistance, aerobic and balance exercises.	Subway station, kitchen, minimarket, tai-chi, soccer.	Kinesiologist.
4	Ngeemasara T, et al. 2020	GE= 34, GC= 34	3	100	24	Immersive.	Attention, memory and processing speed.	Not performed.	Preparing juices, "crow shooting", counting fireworks, remembering objects in the house.	Kinesiologist or other health professional.
5	Marzorati M, et al. 2017	GE= 5, GC= 5	3	40 – 45	18	Immersive.	Memory, attention.	Aerobic exercise (cycling).	Cycling in park and city, shopping in market.	Does not report
6	Mirza R A, et al. 2018	GE= 1 (control case).	3	60 (30 EC+ 30 AF).	36	Not immersive	Logical reasoning, calculation, memory.	Aerobic exercise (cycling).	Dr. Kawashima's body and brain exercises.	Does not report
7	Hwang J, et al. 2017	GE= 12, GC= 12	5	30	20	Immersive.	Memory.	Balance	Does not report	Occupational therapist.
8	Mrakic-Sposta S, et al.2018	GE= 5, GC=5	3	40 – 45 (15-20 AF+ 20 EC).	18	Immersive.	Episodic memory, visuospatial abilities, executive functions, language.	Aerobic exercise (cycling).	Cycling in park, crossing streets avoiding cars, shopping in supermarket.	Does not report
9	Nakamura, K, et al. 2016	GE= 39, GC1= 23, GC2= 32	1	60 on site and 60 off site.	12	Not immersive	Memory.	Not performed.	Does not report	Occupational therapist and assistant.
10	Park E, et al. 2019	GE= 10, GC=21	3	30	18	Immersive.	Attention, visual and verbal working memory, executive functions, calculation.	Not performed.	House: children's room, living room, kitchen and bathroom.	Does not report
11	Savulich G, et al. 2017	GE= 21, GC=21	1	60	8	Not immersive	Memory.	Not performed.	Memory game "game show" for IPad.	Does not report
12	Anderson-Hanley C, et al. 2018	GE= 46, GC= 45, GC= 20	2 a 5	20 a 45	68-72	Not immersive	Executive functions.	Aerobic exercise (cycling).	Cycling	Does not report
13	Choi W, et al. 2019	GE= 30, GC= 30	2	60	12	Not immersive	Attention, memory, language, executive functions.	Aerobic exercise and balance (rowing).	Rowing on lake in South Korea.	Kinesiologist plus two assistants.
14	Man K W D, et al. 2011	GE= 20, GC= 24	2 a 3	30	10	Not immersive	Memory	Not performed.	Home: 2 bedrooms, living room, dining room, kitchen, and bathroom. Minimarket: 6 product trays, 1 fruit tray, 6 freezers and 1 ATM.	Two occupational therapists.

*Number of sessions held per week. ** Duration of sessions expressed in minutes.

The instruments used in the pre- and post-intervention measurement were classified into evaluation instruments of: a) cognitive functions, b) physical activity, c) quality of life and functionality, d) neuropsychiatric variables, and e) physiological variables. Cognitive assessment instruments were used in all studies, identifying 25 different instruments of which three corresponded to cognitive screening (MMSE, MoCA, GPAoC), two to neuropsychological batteries (CERAD-K and CANTAB), one to a deterioration scale (GDS). Regarding the cognitive screening tests, the most used corresponded to the MMSE (n= 6), followed by the MoCA test (n= 4). In addition, 17 instruments were reported for the evaluation of specific cognitive domains (executive functions, language, visuospatial skills, memory and attention), among the most used were: TMT A-B (attention and executive functions) (n=5), followed by the Stroop Test (attention and executive functions) (n= 4) and RAVLT (auditory-verbal memory) (n=3). Physical activity was evaluated in four studies, identifying a total of five instruments **(Table 3)**. The quality of life (QOL) and functionality instruments were used in four studies with a total of four instruments, three to measure functionality and one to assess quality of life. The neuropsychiatric instruments used were three, two of them for depression and one for apathy. Finally, the physiological measurements included measures such as: blood pressure, oxygen saturation, heart rate, insulinemia, glycemia, among others **(Table 3)**.

Effects of the interventions

Regarding the effects reported in the EE after the intervention, of the 14 studies, two reported improvements in general cognition (ID: 3 and 13), and 11 in specific cognitive domains (ID: 1, 2, 4, 6, 7, 8, 9, 10, 11, 12 and 14), such as executive functions (n=6), memory (n=6), attention (n=1), verbal fluency (n=1) and visuospatial skills (n=1). One study reported no post-intervention improvements (ID: 5). Of the studies that reported improvements in specific cognitive aspects, one of them reported a decrease in AVDI performance, despite the fact that participants reported subjective improvements (ID: 8).

Four studies stand out that reported an increase in the quality of life of people and/or improvements at the ADL level (ID:3, 8, 9, 12) achieving the transfer of the exercises into daily life . Those studies that combined EC and physical activity reported better results compared to their respective GC.

Limitations and Orientations of the reviewed studies

Limitations are concentrated in the small sample size and methodological design of the reviewed studies. The most frequent one was related to the sample size (n=7) and inequitable samples in gender and/or age (n=2), as well as the lack of follow-up (n=5 studies), and the limited number of program sessions (n=3).

Of the studies reviewed, nine refer to orientations, and focus on the need for follow-up of the participants once the intervention is finished (n=4), having a greater number of participants (n= 3) (ID: 5, 9 and 10) and adding measurement of additional variables such as: gait variability, comorbidities and depression (n=2).

DISCUSSION

One of the objectives of this review was to systematize the characteristics of the studies that have used cognitive interventions through VR in with MCI. The results indicated that immersive VR is used more than non-immersive, and that among the most frequent virtual settings were the supermarket and the rooms of a home. This follows the recommendations to out cognitive stimulation in everyday contexts, through tasks of lesser to greater complexity, in order to favor the transfer of training activities into daily life[23,31].

The most intervened cognitive functions were memory and executive functions, however, memory subtype or executive type of functions are not detailed. The MCI subtype of the participants were not stated, so the programs carried out are non-specific for the cognitive domains affected in each participant. Literature identifies four MCI subtypes: 1. Single domain amnestic

Table 3. Instruments.

Instruments	ID	n
a.- Cognitive		
Fuld Object Memory Evaluation (FOME)	14	1
Multifactorial Memory Questionnaire (MMQ)	14	1
Color Trails (CT)	1, 12	2
Korean Version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K).	10	1
Digits Span (DS)	12	1
Cambridge Neuropsychological Test Automated Battery (CANTAB)	11	1
Brief Visuoespatial Memory (BVM)	11	1
Visual Span Test (VST)	7	1
Verbal Fluency (VF)	5, 6	2
Global Deterioration Scale de Reisberg (GDS)	9	1
Attentive Matrices Test (AMT)	5,8	2
Test Stroop	1, 2, 7, 12	4
Digits Backward (DB)	1	1
Trail Making Test A-B (TMT A-B)	2, 4, 5, 6, 8, 11	5
Montreal Cognitive Assessment (MoCA)	3, 6, 12, 13	4
Excutive Interview 25	3	1
General Practitioner Assessment of Cognition.	13	1
Mini Mental de Folstein (MMSE)	4, 5, 6, 8, 9, 11	6
Chinese version of the Verbal Learning Test (CVVLT)	3	1
Rey Auditory Verbal Learning Test (RAVLT)	5; (8) 12:	3
Frontal Battery Assessment (FAB)	5, 8	2
Rey-Osterrieth Complex Figure (ROCF)	5	1
Symbol Digit Substitution Test	4	1
b.- Physical Activity		
Aerobics Center Longitudinal Study Physical Activity Questionnaire	1	1
Gait performance	2	1
Limit of Stability	7	1
One-Leg Stance Test	13	1
Good Balance System	13	1
c.- Quality of life and functionality		
Lawton and Brody scale	3	1
Functional Activities Questionnaire (FAQ)	5	1
Quality of Life Scale	9	1
Hong Kong Chinese version of Lawton y Brody Scale	14	1
d.- Neuropsychiatric		
Geriatric Depression Scale	11	1
Apathy Evaluation Scale	9, 11	1
Hospital Anxiety and Depression Scale	11	1
e.- Fisiológicas		
Anthropometric measurement and glycemia/insulin test	1	1
Neuroimaging and saliva.	12	1
Electroencephalogram	4	1
Electronic paramagnetic resonance	5, 8	1
Oxygen saturation, blood pressure, pulse	6	1
Blood and urine test	8	1

MCI is characterized by memory involvement, exclusively; especially episodic type memory. 2. In amnesic MCI involving multiple cognitive domains, other cognitive domains are affected in addition to memory. 3. In single domain non-amnestic MCI, there is an alteration of the cognitive domain without memory impairment. 4. Non-amnestic MCI with involvement of multiple cognitive domains, corresponds to the involvement of 2 or more cognitive domains other than memory[32-34]. This information is essential when designing a cognitive stimulation program, in order to be relevant to the functions that are deteriorated and preserved[31].

Memory domain-specific interventions and cognitive multi-domain interventions, which include aspects of daily life, can facilitate compensatory activation and neuronal reorganization[35]. Eleven of the reviewed studies included specific memory intervention, or jointly, two or more cognitive functions. For future research, it is recommended to create CE programs that specifically include memory function or cognitive multidomain, and involve aspects of daily life.

There is evidence that six months long physical activity programs improve the cognitive performance of people with MCI[36]. Most of the reviewed studies did not consider the exclusive use of CE, but they did include a combination with PA, so it is difficult to establish the differential post-intervention effects. Future research should include a design that allows establishing the effects of each one, for example, CE with and without physical activity, thus determining the effect of CE in the absence of other types of interventions.

The measurement instruments used corresponded to cognitive screening instruments, instruments to measure specific cognitive domains, and quality of life scales and AVDI, which together, allow a better differentiation between MCI and dementia[36]. In addition, measures of neuropsychiatric and physiological aspects were included, however, none of the reviewed studies held the complete evaluation suggested by the literature[36],focusing on cognitive measuring. The measures of QoL and AVDI were the least considered despite the fact that their evaluation is recommended given that people with MCI have greater limitations in both aspects, compared to non impaired older people[43,44].

Only two studies reported using measurement of neuropsychiatric variables, however, it has been shown that people with MCI not only present cognitive impairment, but are also impacted in there QoL[38]. In this regard, a cohort study of 465 people with MCI presented neuropsychiatric symptoms such as nocturnal behavior (20.8%), depression (17.3%), anxiety (13.2%) and apathy (12.7%).), and in the three-year follow-up, 26.9% of those who presented depression developed Alzheimer's disease (AD)[39]. Although the specialized literature does not include a neuropsychiatric evaluation in patients with MCI[6,34,36,40], it seems to be important, at least, to evaluate the presence of depression, as it is considered a risk factor for progression to AD. In future research, it is suggested to include in the evaluation of the participants and instruments related to: general cognition, specific cognitive domains, quality of life, functionality at the AVDI level and psychiatric symptoms.

Of all the studies reviewed, 13 reported improvements in specific cognitive aspects or at a general cognition level, however, no study presented post-intervention follow-up, so it is not possible to establish whether these effects were supported in the long term. Since MCI has a progressive nature, and a 5.4% cumulative incidence for dementia during year 1 to 42.5% in year 5[7], annual follow-ups should be carried out once each intervention is finished. This is also one of the points to consider in all randomized clinical trials according to the CONSORT 2010 criteria[41].

Although the use of CE with VR helps the transfer of CE to daily life activities[11,14-17], only four studies reported that the training carried out could be generalized to everyday situations. This could be related to the low evaluation of variables

associated with AVDI and QOL, as well as the lack of follow-up reported in the studies.

In methodological terms, limitations that may affect the validity of the reported results are noted, Among them is the small sample sizes and lack of randomization. The scarce number of intervention sessions was considered one of the most frequent limitations, therefore, a minimum duration of 12 months should be considered; and 48 months being optimal[40,42,43].

This review made it possible to organize and systematize recent research on cognitive interventions using VR in people with MCI, however, it is not free of limitations. Focusing on three databases may result in restricted access to literature in other languages or cultural contexts. On the other hand, the search was not limited to studies that exclusively included cognitive intervention, which could make it difficult to isolate the effects of this type of intervention.

CONCLUSION

The possibility of reversing MCI to reach cognition according to chronological age has generated several actions in search of treatment, one of which is CD through VR. The ability to recreate real virtual environments through immersive and non-immersive VR, and incorporate them into EC, has shown an increase in cognitive performance in specific domains and, to a lesser extent, on a general cognition level, achieving in some cases, the transfer of these results to daily routine activities.

According to the reviewed studies, it is recommended to carry out interventions with real and everyday virtual environments, that stimulate memory or diminished cognitive functions and that use evaluation instruments that include all the variables recommended for MCI. The sustainability and generalization of the effects requires, in turn, longer follow-up periods.

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