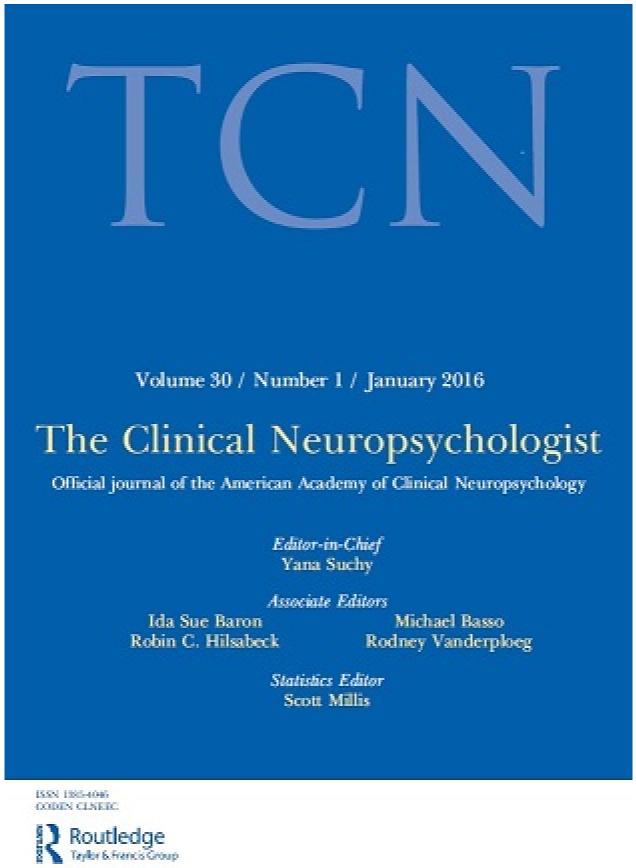

Effectiveness of virtual reality-based neuropsychological interventions in improving cognitive functioning in patients with mild cognitive impairment: a systematic review and meta-analysis

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Effectiveness of virtual reality-based neuropsychological interventions in improving cognitive functioning in patients with mild cognitive impairment: a systematic review and meta-analysis

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Abstract

Objective: Increased prevalence of mild cognitive impairment (MCI) has led to a need for new neuropsychological intervention tools in this population. This meta-analysis aimed to learn about the efficacy of virtual reality (VR)-based neuropsychological interventions in improving cognitive functioning in patients with MCI.

Method: This review followed the recommendations of the PRISMA statement, and it was registered in PROSPERO. The studies examined were collected from the PsycINFO, Web of Science, Pubmed/MEDLINE, Embase, Scopus, and Cochrane Library databases.

Results: The systematic search yielded 258 articles, of which 13 randomized controlled trials were selected. VR-based neuropsychological interventions had moderate effects on global cognition (g = 0.30; 95% CI = 0.05, 0.56; p = 0.02), small effects on attention (g = 0.27; 95% CI = 0.04, 0.49; p = 0.02), and large effects on executive function (g = 0.60; 95% CI = 0.38, 0.81; p < 0.0001), but non-significant effects on working memory, episodic memory, language, or visuoconstruction. When the length of the intervention was considered, VR-based interventions of 15 or more hours had moderate effects on working memory (g = 0.55; 95% CI = 0.11, 0.99; p = 0.01), and large effects on language (g = 0.60; 95% CI = 0.01, 1.20; p = 0.05) and visuoconstruction (g = 1.13; 95% CI = 0.58, 1.67; p < 0.0001).

Conclusions: Results suggest that VR-based interventions are beneficial for improving cognitive functioning in patients with MCI, and allow us to make recommendations that could have implications for clinical decision-making in this population.

Keywords: mild cognitive impairment; neuropsychological intervention; virtual reality; cognition.

1. Introduction

The increase in life expectancy has resulted in the progressive aging of the population, with the global population over 60 years of age expected to reach 2.1 billion in 2050 (World Health Organization, 2021). During the normal aging process, it is common to experience a cognitive decline (Josefsson et al., 2012) that depends on factors such as age and sex (Cano-López et al., 2021; Fonseca et al., 2015; Levine et al., 2021; Lipnicki et al., 2017). In some cases, these cognitive changes exceed what would be expected due to age and progress to mild cognitive impairment (MCI) (American Psychiatric Association, 2013), with a prevalence ranging from 6.7% to 25.2% in older adults, depending on the age range (Petersen et al., 2018). Cognitive deficits in patients with MCI may limit their quality of life and functionality (Giebel et al., 2014), which justifies the implementation of neuropsychological intervention programs aimed at this population. Clinical practice guidelines suggest that neuropsychological interventions could help to improve specific cognitive domains in patients with MCI, although there is insufficient evidence to recommend specific cognitive strategies (Petersen et al., 2018). In this context, virtual reality (VR) emerges as a new tool for implementing neuropsychological interventions in this population (Słyk et al., 2019).

VR is generated by a computer and an interactive device that produce images and sounds that allow the representation of different scenarios, so that the individual perceives that he/she is in this artificial reality (Słyk et al., 2019). Depending on the degree to which the simulation seems real, there are three levels of VR immersion: (a) non-immersive: it has a low cost and a low sense of immersion, and it uses simple display media (e.g., TV, computer monitor, and screen); (b) semi-immersive: it has a medium cost and sense of immersion and uses more complex tools (e.g., panoramic TV); and (c) fully immersive: it has a variable cost and a medium-high sense of immersion and uses more elaborate display media (e.g., head-mounted display and CAVE Automatic Virtual Environment) (Liu et al., 2019a; Rose et al., 2018). Immersion has been proposed as the mechanism of action of VR-based interventions for improving cognitive function, favoring a sense of embodiment that results in a realistic experience (Strong, 2020; Tieri et al., 2018) and eliciting associated psychological and physiological responses (Meehan et al., 2005; Slater et al., 2008). It has been suggested that VR is a promising tool for intervention, since it provides immediate performance feedback, allows the scenario to be customized to make it more appealing to the patient, and may favor the implementation of tasks with high ecological validity (Ferreira-Brito et al., 2020; Manera et al., 2016).

In patients with MCI, VR is primarily known as a tool that allows clinicians and other professionals to present a first-person experience of how individuals with this diagnosis seem to live (D'Cunha et al., 2019). However, recently this device has been under investigation to evaluate its effectiveness in the intervention of this population (D'Cunha et al., 2019). The intervention format may vary from playing serious games or video games to the guided practice of a set of standardized tasks to exercise various cognitive domains (e.g., attention and memory) (Bahar-Fuchs et al., 2019). Most of these tasks are focused on activities of daily living (ADLs) such as using familiar image-based virtual environments to improve episodic autobiographical memory (Benoit et al., 2015). In a recent systematic review, D'Cunha et al. (2019) showed that VR interventions are adequately tolerated by patients with MCI and have positive effects on their mood. Patients prefer VR over non-VR interventions. In fact, greater treatment adherence has been found when implementing a VR intervention compared to a non-VR-based intervention (Manera et al., 2016).

It is worth noting that most of the studies based on this technology have focused on the feasibility of carrying out intervention programs with VR, but very few have analyzed its effectiveness for cognitive functioning, despite its cognitive benefits in other populations with a history of brain injury (Aminov et al., 2018; Santos et al., 2019). To our knowledge, only one meta-analysis has focused on the effects of VR-based interventions on specific cognitive functions in patients with MCI, including randomized controlled trials (RCTs) published from inception to April 2020 (Zhu et al., 2021). It should be noted that the meta-analysis by Zhu et al. (2021) included studies of both patients with MCI and dementia, but it has been suggested that the effect of neuropsychological interventions in improving cognitive function may be different among these populations (Clare and Woods, 2014; D'Cunha et al., 2019), probably due to the less severity of MCI compared to dementia and the benefits of the intervention in the early stage of cognitive impairment (Langa and Levine, 2014). Additionally, the meta-analysis by Zhu et al. (2021) included VR-based interventions consisting specifically of physical stimulation (i.e., without specific cognitive training) and others that focused directly on the improvement of cognitive functions (i.e., including or not physical stimulation). Consequently, it remains difficult to identify the influence of tasks directly focused on cognitive functions on the cognitive improvement of patients with MCI. Furthermore, despite the efforts made in the review by Zhu et al. (2021) to analyze the effects of these interventions on specific cognitive functions, their search strategy used terms referring to cognitive function or motor function in a general way, which might have reduced the likelihood of finding certain studies focused on specific cognitive functions such as language. Considering that this is a new field in continuous evolution, the present study aims to know the effectiveness of neuropsychological interventions that included tasks directly focused on cognitive function with VR in improving the cognitive functioning of patients with MCI by carrying out a systematic review and meta-analysis of the updated literature (from inception to August 2022), and analyzing the possible effect modulating factors of this effectiveness (i.e., the intervention type, the inclusion of aspects related to ADLs, the length of the intervention). To this end, the search strategy will include specific terms referring to the different cognitive functions (i.e., attention, executive function, memory, language), in addition to referring to cognition globally, and RCTs will be selected.

2. Materials and methods

2.1. Search strategy and information sources

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Page et al., 2021), and it was registered in PROSPERO (CRD42021290589).

The search was conducted in the following databases: PsycINFO, Web of Science, Pubmed/MEDLINE, Embase, Scopus, and Cochrane Library, from inception to August 31, 2022. The terms used were formulated as follows: (dementia OR mild cognitive impairment) AND (neuropsychological intervention OR neuropsychological stimulation OR neuropsychological rehabilitation OR cognitive stimulation OR cognitive rehabilitation) AND (virtual reality OR virtual environment) AND (cognition OR memory OR attention OR executive function* OR language). These keywords were examined in the title section, keywords, and abstract. In addition, a reverse search was performed by reviewing the reference lists of systematic reviews and empirical studies to identify records not indexed in these databases.

2.2. Eligibility criteria

Eligibility criteria were formulated following the PICOS method (Page et al., 2021). According to this method, the search strategy was based on population (P), intervention (I), group (C), outcomes (O), and study design (S). Specifically, the inclusion criteria were as follows: (P): adult participants with a diagnosis of MCI; (I): articles that included a VR-based neuropsychological intervention consisting of tasks focused directly on the improvement of cognitive functions, regardless of the immersion level; (C): studies with a control group that received a non-VR-based intervention or no intervention; (O): articles that assessed change in cognitive functioning (e.g., attention, executive functions, memory, language, and visuoconstruction) after the intervention with respect to baseline; and (S): empirical studies (RCTs) published in peer-reviewed scientific journals in English or Spanish.

We excluded: (1) studies with patients with dementia; (2) animal studies; (3) books and book chapters, single-case studies, reviews, meta-analyses, study protocols, editorials, or conference abstracts; (4) studies focused on transcranial magnetic stimulation; and (5) studies with fewer than 10 participants.

2.3. Selection process

Two authors (BGC and ICL) independently assessed titles and abstracts for possible agreement with the inclusion criteria. Discrepancies were resolved through critical discussion with other reviewers (MA and SPP) until 100% agreement was reached. Next, each researcher individually assessed the full text of the articles selected to determine whether they met the inclusion criteria. Studies that failed to meet the inclusion criteria were excluded.

2.4. Data extraction

Two authors (BGC and ICL) independently extracted data from all the included studies following the Template for Intervention Description and Replication (TIDIeR; Hoffmann et al., 2014). If data were missing from the selected studies, their authors were contacted for additional details. Data from the selected studies were displayed in customized tables. The data extracted from each article were as follows: (1) authors; (2) sample size; (3) mean age; (4) sex of the sample; (5) characteristics of the VR-based neuropsychological intervention (including cognitive domains targeted) and the control intervention; (6) number of sessions in the VR-based neuropsychological intervention and the control intervention; (7) time of evaluation and statistics used for the analyses of cognitive change; (8) neuropsychological assessment instruments; and

(9) results of the intervention in terms of cognitive functioning. These data were verified by two reviewers (MA and SPP), and differences were resolved through discussion.

2.5. Methodological quality assessment

The methodological quality of the studies was assessed by two independent reviewers (BGC and ICL). Discrepancies were resolved through discussion and consensus. Two additional reviewers (MA and SPP) were consulted when necessary.

The Critical Appraisal Checklist for Randomized Controlled Trials (Moola et al., 2020) was used to assess the risk of bias in all studies included in the systematic review. It consists of 13 questions and includes aspects such as: (a) the validity of the randomization; (b) the way the allocation was carried out; (c) groups' similarity at baseline; (d) participants' knowledge about the treatment; (e) evaluators' knowledge about the treatment; (f) equal treatment of participants; (g) compliance with follow-up; (h) homogeneity of assessments across groups; (i) appropriate use of statistical analyses; and (j) use of an appropriate design for the subject matter (Moola et al., 2020).

2.6. Meta-analyses

Meta-analyses were conducted using the Review Manager computer program (RevMan 5.4.1) (The Cochrane Collaboration, 2020). The main outcomes analyzed were global cognitive functioning, attention, executive function, working memory, immediate episodic memory, delayed episodic memory, language, and visuoconstruction. For each cognitive domain, a hierarchy of instruments was established based on their frequency of use in the RCTs included in the meta-analysis, and data were entered based on the instrument highest on that list for each study. Data were entered as the mean difference from baseline and the SD of this mean difference for VR-based intervention and non-

VR-based intervention groups. When data from more than one follow-up period were reported, data from the immediate post-intervention period were included in the meta-analysis. The SD of the mean changes from baseline is a frequent missing outcome data (Higgins et al., 2021), so we followed the following process for obtaining the missing outcome data. First, missing SD changes from baseline were estimated using RevMan for studies in which additional data were available (e.g., *p*-values, t-vales, confidence intervals, standard errors). Second, when these data were not available, the corresponding authors of the included studies were contacted to request their database or the mean and *SD* changes from baseline values, as recommended (Higgins et al., 2021; Viana et al., 2021). Third, if the corresponding authors did not share their data, and the pre-intervention and post-intervention SD values were known, the SD change value was computed using the formula proposed by Borenstein et al. (2009) and Higgins and Green (2011), by assigning a value of 0.7 to the *r* (Borenstein et al., 2009; Higgins and Green, 2011) to provide a conservative estimate (Rosenthal, 1993), as in previous meta-analyses (Berlim et al., 2017; Kallapiran et al., 2015; Yagiz et al., 2022). It is worth noting that Manenti et al. (2020) included two VR-based intervention groups and a non-VR-based intervention group, so the two VR-based intervention groups were combined in a single group, and the weighted mean and SD were obtained.

We employed a random-effects model for continuous data, inverse variance, and a 95% CI, which assumes that the observed estimates of intervention effect can vary across studies because of real differences in the treatment effect in each study (e.g., intervention type, duration, outcome measures) as well as sampling variability (Borenstein et al., 2010). The Hedges' (adjusted) *g* effects size (standardized mean difference [*SMD*]) was computed to estimate the intervention effect. Hedge's g estimates of less than 0.3 were considered as small, between 0.3 and less than 0.6 as moderate, and equal to or greater than 0.6 as large (Hill et al., 2017; Zhu et al., 2021). The degree of heterogeneity (I^2) was computed to determine whether the studies included in the meta-analysis were consistent. I^2 results were interpreted as low (25%), moderate (50%), and high (75%) (Higgins et al., 2003). The Galbraith plot method was utilized to identify potential outliers (Galbraith, 1988). Subgroup analyses were also carried out based on the type of intervention (only cognitive training or cognitive training interspersed with physical exercise), the inclusion or not of aspects related to ADLs in the intervention, and the length of the intervention (less than 15 hours of intervention versus 15 or more hours).

3. Results

3.1. Study selection

The initial search yielded a total of 258 articles. After eliminating duplicates, 172 articles were obtained. The titles and abstracts of these 172 articles were reviewed, and 136 studies were excluded because they did not meet the inclusion criteria. Consequently, the full text of 36 articles was reviewed. Of them, 27 were excluded because they: did not assess the change in cognitive functioning after the intervention from baseline (n= 6); they were not empirical studies (n= 6); they did not include a VR-based neuropsychological intervention (n= 4); they did not include an intervention focused directly on the improvement of cognitive functions (n = 1); they were not RCTs (n= 7); or they included patients with dementia, but not patients with MCI (n = 3). These last three studies were carried out by Man et al. (2012) - who included patients with questionable dementia as determined by the CDR scale-, Oliveira et al. (2021) - that included patients with questionable, mild, or moderate dementia as established by the Clinical Dementia Rating (CDR) scale-, and Serino et al. (2017) – who included patients with probable dementia as determined by the Milan Overall Dementia Scale. On the other hand, four studies identified by reverse search were included. Thus, 13 studies were included in the systematic review and marked with the symbol (*) in the reference section. Figure 1 shows the flow diagram of the study selection process, and Table 1 includes a summary of the selected studies.

3.2. Evaluation of the quality of the studies

Regarding the evaluation of the quality of the RCTs included in the systematic review (Table 2), the percentage of compliance with the JBI criteria ranged from 46% to 92%, depending on the study.

All of the RCTs examined met the following criteria: (1) They carried out a randomization method to assign participants to each group; (2) They treated the treatment groups equally, with the exception of the different types of intervention; (3) Full follow-up was provided, and, if not, possible differences between groups in terms of their follow-up were adequately described and analyzed; (4) Participants were analyzed within the groups to which they were assigned; (5) Outcomes were measured in the same way in the treatment groups; and (6) The trial design was appropriate, and possible deviations from the standard design were taken into account when carrying out and analyzing the trials (Delbroek et al., 2017; Hughes et al., 2014; Hwang & Lee, 2017; Kang et al., 2021; Liao et al., 2019, 2020; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020; Torpil et al., 2021).

Five of the 13 RCTs analyzed used hidden treatment assignments (Liao et al., 2019, 2020; Manenti et al., 2020; Park et al., 2020b; Torpil et al., 2021), with seven of them established as unclear in this category (Delbroek et al., 2017; Hughes et al., 2014; Hwang & Lee, 2017; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a; Thapa et al., 2020), whereas the remaining one did not meet this criterion (Kang et al., 2021).

Regarding between-group similarity at baseline, 12 of the 13 RCTs met this criterion (Delbroek et al., 2017; Hughes et al., 2014; Kang et al., 2021; Liao et al., 2019, 2020; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020; Torpil et al., 2021), with only one study in the unclear category (Hwang and Lee, 2017).

Regarding the criterion of keeping group participants blinded to the tasks delivered during treatment, in 10 of the 13 RCTs, this criterion was assessed as unclear (Delbroek et al., 2017; Hughes et al., 2014; Hwang and Lee, 2017; Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020b; Thapa et al., 2020; Torpil et al., 2021), whereas three of the RCTs did not meet this criterion (Kang et al., 2021; Manenti et al., 2020; Park et al., 2020a).

Two of the 13 RCTs reviewed indicated that the specialists who performed the treatment were unaware of the treatment assignments (Delbroek et al., 2017; Manenti et al., 2020), 10 RCTs were considered unclear in this domain (Hughes et al., 2014; Hwang and Lee, 2017; Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020; Torpil et al., 2021), and the remaining one did not meet this criterion (Kang et al., 2021).

With regard to keeping the evaluators blind to the treatment, five of the 13 RCTs met this criterion (Liao et al., 2019, 2020; Manenti et al., 2020; Park et al., 2019; Torpil et al., 2021), seven studies fell into the unclear category (Delbroek et al., 2017; Hughes et al., 2014; Hwang and Lee, 2017; Mrakic-Sposta et al., 2018; Park et al., 2020a, 2020b; Thapa et al., 2020), and one study did not meet the criterion (Kang et al., 2021).

Six of the 13 RCTs evaluated met the criterion for the use of appropriate statistical analyses (Hughes et al., 2014; Kang et al., 2021; Liao et al., 2020; Park et al., 2020b; Thapa et al., 2020; Torpil et al, 2021), three studies fell into the unclear category (Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a), and the remaining four studies did not qualify (Delbroek et al., 2017; Hwang and Lee, 2017; Liao et al., 2019; Manenti et al., 2020).

Four of the 13 RCTs examined used reliable outcome measures (Kang et al., 2021; Mrakic-Sposta et al., 2018; Park et al., 2019; Thapa et al., 2020), whereas the remaining nine studies fell into the unclear category on this criterion (Delbroek et al., 2017; Hughes et al., 2014; Hwang and Lee, 2017; Liao et al., 2019, 2020; Manenti et al., 2020; Park et al., 2020a, 2020b; Torpil et al., 2021).

3.3. Qualitative analysis of reviewed studies

3.3.1. Intervention characteristics

According to the type of intervention, the interventions carried out in each of the experimental groups can be divided into two sections: (1) those that only included cognitive training (n= 7) (Kang et al., 2021; Manenti et al., 2020; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020; Torpil et al., 2021); and (2) those in which cognitive training was interspersed with physical exercise (n= 6) (Delbroek et al., 2017; Hughes et al., 2014; Hwang and Lee, 2017; Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018). According to the main format of the intervention, the interventions were classified into three different categories: (1) those that applied ADL-based tasks (n = 6) (Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b), (2) those that used video games (n = 2) (Hughes et al., 2014; Torpil et al., 2021) and (3) those that included serious games (n = 4) (Delbroek et al., 2017; Kang et al., 2021; Manenti et al., 2020; Thapa et al., 2020). The study carried out by Hwang and Lee (2017) did not specify the format of the intervention. Studies that applied ADL-based tasks in their VR-based intervention program (n = 6) were focused on basic (Park et al., 2020b) and instrumental ADLs (Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b). It should be noted that, despite Thapa et al. (2020) used mainly serious games, one of the games was focused on an instrumental ADL (i.e., juice making). Therefore, seven of the 13 studies included aspects related to ADLs in their VR-based intervention programs (Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020), whereas six studies did not include these ADL-related aspects (Delbroek et al., 2017; Hughes et al., 2014; Hwang and Lee, 2017; Kang et al., 2021; Manenti et al., 2020; Torpil et al., 2021).

Regarding the type of intervention carried out in the control group, different programs were used: (1) non-VR-based cognitive rehabilitation using pencil-and-paper or computer-assisted tasks (n= 4) (Manenti et al., 2020; Park et al., 2019, 2020b; Torpil et al., 2021); (2) usual treatment conducted at the center (n= 2) (Delbroek et al., 2017; Kang et al., 2021); (3) general health education program (n= 2) (Hughes et al., 2014; Thapa et al., 2020); (4) simultaneous non-VR-based physical and cognitive training (n= 2) (Liao et al., 2019, 2020); (5) occupational therapy (n= 1) (Hwang and Lee, 2017); and (6) no treatment (n= 2) (Mrakic-Sposta et al., 2018; Park et al., 2020a).

The length of the intervention was 15 hours or more in eight studies (Hughes et al., 2014; Hwang and Lee, 2017; Liao et al., 2019, 2020; Manenti et al., 2020; Park et al., 2020b, Thapa et al., 2020, Torpil et al., 2021), whereas it was less than 15 hours in five studies (Delbroek et al., 2017; Kang et al., 2021; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a).

3.3.2. Neuropsychological assessment

Eleven of the 13 studies analyzed performed a neuropsychological assessment before the intervention and another one after the intervention (Delbroek et al., 2017; Hwang and Lee, 2017; Kang et al., 2021; Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020; Torpil et al., 2021). In contrast, only one study conducted an assessment before, after, and one year after starting the intervention (Hughes et al., 2014). Additionally, only one article included four assessments: (1) before the intervention; (2) at the end of the intervention; (3) four months after starting the intervention; and (4) seven months after starting the intervention (Manenti et al., 2020). Improvement was defined in all RCTs as significant differences between the pre- and post-intervention neuropsychological assessments, using statistical tests. Clinically significant change indices (e.g., reliable change index) were not computed in any of the RCTs.

Regarding neuropsychological assessment tests, eight studies used screening tests to assess the evolution of global cognitive functioning after the intervention (Delbroek et al., 2017; Hughes et al., 2014; Kang et al., 2021; Liao et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2020a, 2020b; Thapa et al., 2020). The tests used were: (1) the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) (Delbroek et al., 2017; Liao et al., 2020; Park et al., 2020b); (2) the Mini-mental State Examination (MMSE; Folstein et al., 1975) (Mrakic-Sposta et al., 2018); (3) the Korean version-Mini-mental State Examination (K-MMSE; Kang et al., 1997) (Kang et al., 2021; Park et al., 2020a); (4) the Korean version-Mini-mental State Examination-Screening Dementia (K-MMSE-DS; Kim et al., 2010) (Thapa et al., 2020); and (5) the Computerized Assessment of Mild Cognitive Impairment (CAMCI; Saxton et al., 2009) (Hughes et al., 2014).

Ten studies assessed intervention effects on attention (Hwang and Lee, 2017; Kang et al., 2021; Liao et al., 2019; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020; Torpil et al., 2021). Of these 10 studies, seven used the Trail Making Test A (TMT A; Reitan and Wolfson, 1985) (Kang et al., 2021; Mrakic-Sposta et al., 2018; Liao et al., 2019; Manenti et al., 2020; Park et al., 2019, 2020b; Thapa et al., 2020). Four studies employed both letter and color sections of the Stroop test (Golden, 1978) (Kang et al., 2021; Liao et al., 2019; Park et al., 2020a) or the Word Color Test (WCT; Hwang and Lee, 2017) as an indicator of attention. Other tests used to assess attention were Attentional Matrices (AM; Spinnler and Tognoni, 1987) (Mrakic-Sposta et al., 2018), Symbol Digit Substitute Test (SDST; Weschler, 2008) (Thapa et al., 2020), and attention/concentration from the Loewenstein Occupational Therapy Cognitive Assessment-Geriatric Version (LOTCA-G; Katz et al., 1995) (Torpil et al., 2021).

Nine studies assessed intervention effects on executive functions (Kang et al., 2021; Liao et al., 2019, 2020; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020b; Thapa et al., 2020; Torpil et al., 2021). Of these nine studies, six used the Trail Making Test B (TMT B; Reitan and Wolfson, 1985) (Kang et al., 2021; Liao et al., 2019; Manenti et al., 2020; Park et al., 2019, 2020b; Thapa et al., 2020). Other tests used to assess executive functions were the Frontal Lobe Assessment Battery (FAB; Dubois et al., 2000) (Mrakic-Sposta et al., 2018), the Executive Interview 25 (EXIT-25; Royall et al., 1992) (Liao et al., 2020), and thinking operation from the LOTCA-G (Katz et al., 1995) (Torpil et al., 2021).

Four studies assessed working memory. Three of them employed the Digit Span Test (Weschler, 2008) (Kang et al., 2021; Park et al., 2020a, 2020b), whereas the remaining one employed the Visual Span Test (VST; Gualtieri and Johnson, 2006) (Hwang and Lee et al., 2017).

Five of the 13 studies reviewed assessed immediate memory (Kang et al., 2021; Liao et al., 2020; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019). These five studies, together with the study by Torpil et al. (2021), assessed delayed memory. Two of these studies used the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) (Manenti et al., 2020; Mrakic-Sposta et al., 2018). Additionally, Manenti et al. (2020) used the Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984) and the Rey-Osterrieth Complex Figure Test (ROCFT; Caffarra et al., 2002). The other studies administered the following tests: Chinese version of the Verbal Learning Test (CVVLT; Chang et al., 2010; Delis et al., 1987) (Liao et al., 2020), CERAD-K (Morris et al., 1989) (Park et al., 2019), Seoul Verbal Learning Test (SVLT; Kang et al., 2012) (Kang et al., 2021), and LOTCA-G (Katz et al., 1995) (Torpil et al., 2021).

Regarding language, five of the 13 studies evaluated this domain (Kang et al., 2021; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a). All these five studies assessed semantic verbal fluency, so this was the variable considered in the meta-analysis. The employed tests were the following: Verbal Fluency Test (semantic) (VF; Novelli et al., 1986) (Kang et al., 2021; Manenti et al., 2020; Mrakic-Sposta et al., 2018), CERAD-K (Morris et al., 1989) (Park et al., 2019), and Word Fluency Test (Choi et al., 2011) (Park et al., 2020a).

Five of the 13 studies reviewed assessed visuoconstruction (Kang et al., 2021; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2019; Torpil et al., 2021). The following tests were used: the ROCFT (Caffarra et al., 2002) (Mrakic-Sposta et al., 2018), the ROCFT from the Seoul Neuropsychological Screening Battery (Kang et al., 2012) (Kang et al., 2021), Clock Drawing Test (CDT; Tuokko et al., 1995) (Manenti et al., 2020), CERAD-K (Morris et al., 1989) (Park et al., 2019), and LOTCA-G (Katz et al., 1995) (Torpil et al., 2021).

3.4. Meta-analyses

Global cognitive functioning. We included eight studies (245 participants) in the meta-analysis for global cognitive functioning. A significant positive effect of VR-based intervention on global cognitive functioning was found (g = 0.30; 95% CI = 0.05, 0.56; p = 0.02), and heterogeneity was low (I^2 = 0%) (Figure 2). VR-based interventions of 15 or more hours resulted in significantly greater efficacy on global cognitive functioning (g = 0.52; 95% CI = 0.20, 0.84; p = 0.002) than those of less than 15 hours (g = -0.07; 95% CI = -0.49, 0.35; p = 0.75). No significant differences were found depending on the type of intervention (p = 0.39) or the inclusion of aspects related to ADLs in the intervention (p = 0.50).

Attention. We included ten studies (388 participants) in the meta-analysis for attention. Considering that Hwang and Lee (2017) used scores of both letter and color sections of the Word Color Test jointly as an indicator of attentional functioning and that Park et al. (2020a) provided the scores of the color and word sections of the Stroop test separately, a global score was calculated based on both sections for this last study. We found a positive effect of VR-based intervention on attention that did not reach statistical significance (g = 0.47; 95% CI = -0.03, 0.96; p = 0.06), and a high heterogeneity (I^2 = 81%). Sources of this heterogeneity were analyzed using the Galbraith plot, which identified one outlier study (Torpil et al., 2021). After the outlier's exclusion, nine studies were examined (327 participants). Heterogeneity was low (0%), and participants allocated in the VR-based intervention showed a significant improvement on attention (g = 0.27; 95% CI = 0.04, 0.49; p = 0.02) (Figure 3). VR-based interventions of 15 or more hours resulted in significantly greater effectiveness on attention (g = 0.42; 95% CI = 0.16, 0.68; p = 0.002) than those of less than 15 hours (g = -0.11; 95% CI = -0.52, 0.30; p = 0.60). No significant differences were found depending on the type of intervention (p = 0.61) or the inclusion of aspects related to ADLs in the intervention (p = 1.00).

Executive function. Nine studies (353 participants) were included in the meta-analysis for executive function. A significant positive effect of VR-based intervention on executive function was found (g = 0.60; 95% CI = 0.38, 0.81; p < 0.0001), and heterogeneity was low (I^2 = 0%) (Figure 4). For the length of the intervention, 15 or more hours of VR-based intervention showed large effect size (g = 0.61; 95% CI = 0.37, 0.86; p < 0.0001), whereas less than 15 hours showed moderate effect size (g = 0.54; 95% CI = 0.06, 1.01; p = 0.03), but differences were not significant. No significant differences were found depending on the type of intervention (p = 0.25) or the inclusion of aspects related to ADLs in the intervention (p = 0.28).

Working memory. Four studies (144 participants) were included in the meta-analysis for working memory. It is worth noting that Kang et al. (2021) and Park et al. (2020a, 2020b) provided both forward and backward digit span scores separately, so an overall score was calculated for both tasks as an indicator of working memory. Primary analyses showed a non-significant effect of VR-based intervention on this outcome (g = 0.25; 95% CI = -0.15, 0.66; p = 0.22), and heterogeneity was low (I^2 = 32%) (Figure 5). Subgroup analyses showed significant differences in the effect of VR-based intervention depending on the length of the intervention, 15 or more hours of VR-based intervention having a significant moderate effect size (*g* = 0.55; 95% CI = 0.11, 0.99; *p* = 0.01), and less than 15 hours of intervention having a no significant effect (*g* = -0.13; 95% CI = -0.63, 0.38; *p* = 0.62). No significant differences were found depending on the type of intervention (*p* = 0.45) or the inclusion of aspects related to ADLs in the intervention (*p* = 0.48).

Immediate memory. Five studies (155 participants) were included in the meta-analysis for immediate memory. The effect of VR-based intervention on immediate memory was not significant (*g* = 0.17; 95% CI = -0.15, 0.50; *p* = 0.29), and heterogeneity was low (I^2 = 0%) (Figure 6). Subgroup analyses showed no significant differences in the effect of VR-based intervention depending on the length of the intervention (*p* = 0.51), the type of intervention (*p* = 0.20), or the inclusion of aspects related to ADLs in the intervention (*p* = 0.99).

Delayed memory. Six studies (216 participants) were included in the meta-analysis for delayed memory. We found a no significant positive effect of VR-based intervention on delayed memory (*g* = 0.19; 95% CI = -0.08, 0.47; *p* = 0.16), and a low heterogeneity (I^2 = 0%) (Figure 7). Subgroup analyses showed no significant differences in the effect of VR-based intervention depending on the length of the intervention (*p* = 0.48), the type of intervention (*p* = 0.16), or the inclusion of aspects related to ADLs in the intervention (*p* = 0.28).

Language. Five studies (141 participants) were included in the meta-analysis for language. Primary analyses showed no significant effects of VR-based intervention on language (*g* = -0.08; 95% CI = -0.66, 0.50; *p* = 0.78), with moderate heterogeneity (I^2 = 61%) (Figure 8). Subgroup analyses showed significant differences in the effect of VR-based intervention depending on the length of the intervention, 15 or more hours of VR-based intervention having a significant large effect size (*g* = 0.60; 95% CI = 0.01, 1.20; *p* = 0.05), whereas less than 15 hours of intervention had no significant effects (*g* = -0.30; 95% CI = -0.86, 0.26; *p* = 0.29). No significant differences were found depending on the type of intervention (*p* = 0.64) or the inclusion of aspects related to ADLs in the intervention (*p* = 0.15).

Visuoconstruction. We included five studies (182 participants) in the meta-analysis for visuoconstruction. Primary analyses showed no significant effects of VR-based intervention on language (g = 0.29; 95% CI = -0.52, 1.10; p = 0.48), with high heterogeneity (I^2 = 84%). Sources of this heterogeneity were analyzed using the Galbraith plot, which identified one outlier study (Manenti et al., 2020). After the outlier's exclusion, four studies were examined (133 participants). Heterogeneity was moderate (73%), and participants allocated in the VR-based intervention showed a no significant improvement on visuoconstruction (g = 0.55; 95% CI = -0.20, 1.31; p = 0.15) (Figure 9). Subgroup analyses showed that 15 or more hours of VR-based intervention had a significant large effect on visuoconstruction (g = 1.13; 95% CI = 0.58, 1.67; p < 0.0001), whereas less than 15 hours of intervention had no significant effects (g = 0.29; 95% CI = -0.75, 1.34; p = 0.58), although test for subgroup differences did not reach statistical significance (p = 0.17). No significant differences were found depending on the type of intervention (p = 0.56) or the inclusion of aspects related to ADLs in the intervention (p = 0.17).

4. Discussion

This meta-analysis evaluated the effectiveness of VR-based neuropsychological interventions that included tasks directly focused on cognitive function in improving cognitive processes in patients with MCI. Thirteen studies that met the inclusion criteria were selected. The results show that VR-based interventions significantly improved global cognitive function, attention, and executive function, with no significant effects on episodic memory. The effects of VR-based interventions on language and visuoconstruction were only significant for interventions of 15 or more hours. These findings are discussed below.

All studies included in this meta-analysis were RCTs, which are the gold standard for assessing treatment effectiveness (Miller et al., 2014). The mean age of the participants in the RCTs included in the review was 74 years, and 66% of the participants were women. Both age and sex are relevant variables when generalizing the results obtained, given that previous studies have shown that the decline in processing speed and executive functions increases with age (Cano-López et al., 2021; Fonseca et al., 2015; Lipnicki et al., 2017), and that there is a greater cognitive decline in women than in men (Cano-López et al., 2021; Levine et al., 2021). It should be noted that cognitive improvement was defined in all RCTs included in the review as significant differences between the pre- and post-intervention neuropsychological assessment, without exploring clinically significant changes. Although significant changes are important from a research perspective, clinically significant changes are considered more meaningful in the assessment of neuropsychological functions (Duff, 2012), so future studies should include reliable change indices (RCIs) (Chelune et al., 1993).

Regarding global cognitive function, a moderate positive effect of VR-based intervention was found, as well as significant differences depending on the length of the intervention, so interventions of 15 or more hours resulted in greater efficacy than those of less than 15 hours. Our results are comparable with those of Zhu et al. (2021), who also found a moderate effect of VR-based interventions on global cognition, but this effect did not significantly differ depending on whether the intervention was longer or shorter than 20 hours (considering all cognitive domains jointly). However, there are relevant differences between the inclusion criteria of our meta-analysis and that of Zhu et al. (2021). First, our meta-analysis examined VR-based neuropsychological interventions directly focused on cognitive function, whereas the meta-analysis by Zhu et al. (2021) also included VR-based interventions consisting specifically of physical stimulation (i.e., without specific cognitive training), and did not analyze separately the influence of tasks directly focused on cognitive functions on cognitive improvement. Second, our meta-analysis only included studies with patients with MCI, whereas the meta-analysis by Zhu et al. (2021) was focused on patients with MCI and dementia.

These differences justify discrepancies between the studies selected in our review and those selected by Zhu et al. (2021). Thus, six of the studies included in the meta-analysis by Zhu et al. (2021) were also included in our meta-analysis, as they were studies focused on interventions specifically targeting cognitive functioning in patients with MCI (Delbroek et al., 2017; Hughes et al., 2014; Hwang and Lee, 2017; Liao et al., 2019; Park et al., 2019; Thapa et al., 2020). We additionally included seven studies not reviewed by Zhu et al. (2021) (Kang et al., 2021; Liao et al., 2020; Manenti et al., 2020; Mrakic-Sposta et al., 2018; Park et al., 2020a, 2020b; Torpil et al., 2021). Furthermore, five studies reviewed by Zhu et al. (2021) were not included in our meta-analysis since their VR-based intervention consisted exclusively of physical stimulation (Padala et al., 2012; Schwenk et al., 2016), were book chapters (Tarnanas et al., 2014) or were focused on patients with dementia (Man et al., 2012; Serino et al., 2017). Despite these discrepancies, the fact that we found an effect size similar to that found by Zhu et al (2021) on global cognitive functioning allows us to corroborate the positive effects of VR-based intervention using a more homogeneous sample and type of intervention, evidencing the effectiveness of VR-based intervention directly targeting cognitive functions. Moreover, the fact that we found that the length of the intervention had a significant effect, contrary to Zhu et al. (2021), suggests that intervention effects are found from 15 hours of training onwards. Thus, our study provides an update of the systematic search using more restrictive inclusion criteria, favoring the generalization of results in patients with MCI.

Our meta-analysis showed a small positive effect of VR-based intervention on attention. It should be noted that the length of the intervention ranged from four hours (Kang et al., 2021) to 50 hours (Hwang and Lee, 2017), depending on the study. The length of the intervention was a significant modulator of the effectiveness of the VR-based intervention on attention, so VR-based interventions of 15 or more hours had a moderate positive effect on attention, whereas those of less than 15 hours had a non-significant effect. Thus, all the RCTs that found beneficial results of the VR-based intervention on attention compared to the control intervention included more than 15 hours of intervention (Hwang and Lee, 2017; Liao et al., 2019; Manenti et al. 2020; Park et al., 2020b; Thapa et al., 2020). However, all the studies that failed to find significant differences between groups employed interventions lasting less than 15 hours (Kang et al., 2021; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a). This suggests that the duration of the VR-based intervention could be a key factor in finding benefits for attention. It should be noted that the VR-based intervention used by Hwang and Lee (2017) did not specifically focus on improving attention, but rather on memory and balance. However, this study employs a longer intervention than the other studies (50 hours), so memory training could have favored attention, with attention being a prerequisite for good memory functioning (Posner and Peterson, 1990).

We also found a large positive effect of VR-based interventions on executive function, without significant differences depending on the length of the intervention. The fact that an important proportion of the RCTs reviewed included goal-oriented tasks directly focused on basic or instrumental ADLs in their VR-based interventions may explain these results since executive functions play an important role in the maintenance of autonomy in day-to-day activities (Corbo and Casagrande, 2022). Other relevant factors that could explain the beneficial effects of the VR-based intervention on both attention and executive functions are the use of real-time feedback, which allows participants to remediate their errors and increases motivation to improve their abilities (Liao et al., 2019; Park et al., 2020b), and the therapist-patient interaction (Manenti et al., 2020).

It should be noted that Zhu et al. (2021) assessed attention and executive functions jointly, showing a moderate effect of VR-based intervention. Nevertheless, the analysis of the effects of VR-based neuropsychological intervention on these domains separately could contribute to providing a framework for clinical decision-making. As detailed above, we found a moderated effect of VR-based interventions of 15 or more hours on attention, and a large effect of VR-based interventions on executive function, regardless of the length of the intervention. Possibly we found a slightly larger effect size than Zhu et al. (2021) in executive function due to the exclusion of studies with patients with dementia. Given that MCI has been defined as a pre-dementia stage (American Psychiatric Association, 2013), applying a neuropsychological intervention program to patients who are in a more advanced stage of cognitive impairment may imply difficulties, especially when several intervention groups are established. Thus, it may be difficult for patients with severe cognitive impairment to finish the goal-oriented tasks included in the VR-based interventions (Zhu et al., 2021).

Regarding working memory, primary analyses showed a non-significant effect of VR-based intervention. Nevertheless, when the length of the intervention was considered, VR-based interventions of 15 or more hours had a significant moderate effect, whereas less than 15 hours of intervention had a non-significant effect, suggesting that the length of the intervention is also a key factor for effectiveness in this domain. It should be noted that only four studies analyzed this domain, so results should be interpreted with caution. Zhu et al. (2021) did not analyze this domain specifically. However, working memory acts as active short-term maintenance of information that allows more complex tasks such as planning, problem-solving, or language comprehension (Shah and Miyake, 1999). Thus, it may operate as a domain-general cognitive resource that regulates ability in various seemingly disparate cognitive processes (Hyer et al., 2016), and consequently, it may be relevant to explore this domain separately.

Our meta-analysis showed no significant effects of VR-based intervention on episodic memory, as well as no significant differences depending on the length of the intervention. Although VR may create an enriched environment with visual stimuli and allows real-time interaction and feedback elicitation, facilitating the encoding of information (Man et al., 2012), the six RCTs that evaluated memory were multidomain interventions, being focused on various cognitive domains at the same time, and this may explain the results found. From this multidomain approach, three of the six RCTs included tasks focused on episodic memory in their VR-based intervention (Kang et al., 2021; Liao et al., 2020; Manenti et al., 2020), whereas the remaining three did not include these tasks (Mrakic-Sposta et al., 2018; Park et al., 2019; Torpil et al., 2021). Regardless of the inclusion of memory tasks, any of the RCTs included the teaching of mnemonic strategies, except for those by Manenti et al. (2020), which specified that, in certain cases, therapists suggested strategies to participants to improve their performance, so one of the reasons the VR-based intervention might have improved objective memory functioning could be the synchronous and asynchronous support received from the therapist. In a recent meta-analysis focused on neuropsychological intervention without VR in patients with MCI, Sherman et al. (2017) suggest that memory-based approaches are more effective than multidomain methods for memory improvement, and teaching of mnemonic strategies may facilitate partial activation of neuroplastic reorganization and compensatory processes in several areas. In fact, using successful memory techniques (e.g., spaced retrieval, encoding support, and retrieval strategies) is a key component in maintaining good memory performance in patients with dementia (Man et al., 2012). Therefore, future studies should evaluate the effectiveness of VR-based neuropsychological interventions with memory-based approaches that include the teaching of mnemonic strategies. Zhu et al. (2021) found a moderate effect of VR-based intervention on memory, despite two of the five studies reviewed included patients with dementia. However, the meta-analysis by Zhu et al. (2021) for memory outcome included tasks focused on episodic memory and other cognitive processes (working memory and naming), and this may explain the discrepancies between our results and those of Zhu et al. (2021).

Regarding language, primary analyses showed a non-significant effect of VR-based intervention. Nevertheless, when the length of the intervention was considered, VR-based interventions of 15 or more hours had a significant large effect, whereas less than 15 hours of intervention had a non-significant effect. It should be underlined that, of the five studies that evaluated this domain, only one includes an intervention of more than 15 hours, showing a significant improvement in the experimental group compared to the control group (Manenti et al., 2020), and suggesting that the exchange between the therapist and the participant may have influenced this result. It should be noted that none of the reviewed studies, except for Mrakic-Sposta et al. (2018), focused specifically on language improvement, which could explain why most studies do not find benefits of VR-based interventions in this domain. As far as we know, no previous meta-analyses have analyzed the effectiveness of VR-based interventions on language improvement in patients with MCI, so this study represents an advance for research in this field.

Regarding visuoconstruction, no significant effects of VR-based intervention were found, in line with the results found by Zhu et al. (2021), who reviewed only two studies that evaluated this domain. Notably, in our meta-analysis, the studies that found more beneficial effects of the VR-based intervention compared to the control intervention were those that specifically focused on improving visuoconstruction (Kang et al., 2021; Manenti et al., 2020; Torpil et al., 2021). Despite subgroups differences depending on the length of the intervention did not reach statistical significance, 15 or more hours of VR-based intervention had a large effect on visuoconstruction, whereas interventions of less than 15 hours had no significant effects. The VR system may favor interaction with intense visual stimuli (Torpil et al., 2021), which could facilitate the effectiveness of the intervention when working with this cognitive domain, and results from our meta-analysis suggest that the length of the intervention could be a relevant factor for this facilitation. It should be noted that the effect of the length of the intervention had not been specifically assessed for this domain in the meta-analysis by Zhu et al. (2021), so, as far as we know, our study represents the first meta-analysis evaluating the relevance of this modulating factor for the effectiveness of VR-based interventions on visuoconstruction in patients with MCI.

An important issue to consider is the combination of physical exercise and cognitive training in VR-based intervention programs, which was used in six out of the 13 reviewed studies (Delbroek et al., 2017; Hughes et al., 2014; Hwan and Lee, 2017; Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018). Although it would be logical that studies that focused exclusively on cognitive training would show better effects on cognitive functioning than those in which cognitive training was interspersed with physical exercise, no significant differences were found in any cognitive domain depending on the type of intervention. This suggests that the combination of cognitive training and physical exercise can be as effective as placing greater emphasis on cognitive training, especially when they are conducted simultaneously rather than sequentially (McEwen et al., 2018; Liao et al., 2020). The benefits of this combination could be due to the fact that high-intensity exercise increases the release of brain-derived neurotrophic factor (BDNF), a protein responsible for regulating certain processes of neurogenesis, such as differentiation and survival (Liu and Nusslock, 2018). Increasing BDNF in specific brain areas such as the hippocampus or dentate gyrus could promote better memory functioning and prevent cognitive decline (Liu et al., 2019b).

It is noteworthy that seven out of the 13 studies included aspects related to ADLs in their VR-based intervention programs (Liao et al., 2019, 2020; Mrakic-Sposta et al., 2018; Park et al., 2019, 2020a, 2020b; Thapa et al., 2020). Although our meta-analysis showed a non-significant effect of the inclusion of these aspects on objective cognitive change, it has been suggested that an ADL-based perspective could increase patients' motivation and reduce their effort in understanding the process of performing the cognitive task, which would allow them to direct their attention to another task and improve the results of the intervention (Liao et al., 2019). The variability in the length of the intervention between studies that included aspects related to ADLs could have influenced the results obtained. Future studies should address this issue by employing interventions with a homogeneous length.

Therapist accompaniment and support throughout the intervention is a factor that was considered a key in explaining the benefits of the VR-based intervention. Manenti et al. (2020) suggest that the benefits of the VR-based intervention could be due to the adherence to the intervention program generated by asynchronous interactions. Thus, the importance of having the support of a therapist throughout the treatment, but not necessarily in real-time, is emphasized (Manenti et al., 2020). These findings suggest that the accompaniment of a professional is an essential element in the effectiveness of VR-based neuropsychological interventions in patients with MCI or dementia.

One of the strengths of this meta-analysis is that it allows us to update the available scientific evidence about the effects of VR-based neuropsychological interventions on specific cognitive functions in patients with MCI, using specific terms for these functions (i.e., attention, executive function, memory, language) in the search strategy. In doing so, we aim to expand and update the only meta-analysis, to our knowledge, that focused on the effects of VR interventions on the evolution of specific cognitive functions in patients with MCI and dementia (Zhu et al., 2021), by including cognitive domains that have not previously been analyzed (i.e., working memory and language) in addition to attention, executive functions, memory, and visuoconstruction. Another strength is that this review includes only RCTs, allowing enhanced control over causes of spurious intervention effectiveness. In turn, this review analyzes the main factors that could modulate the efficacy of VR-based interventions in improving cognitive functioning in patients with MCI, allowing us to make recommendations that may be useful in the Clinical Neuropsychology area. Despite these strengths, this meta-analysis has several limitations. First, the sample size in most of the studies reviewed was small, limiting the statistical power and generalization of the results. Second, the characteristics of the VR environment varied depending on the study, limiting the generalizability of the conclusions. Future studies should adapt the VR software to specifically target individuals with MCI, so that the virtual environment is tailored to the needs of each participant (e.g., establishing cues and aids, level of difficulty, and an environment closer to the individual's reality). Third, there was no follow-up after the end of the intervention in most of the studies, so it is not possible to draw conclusions about the long-term efficacy of VR-based interventions in this population. Fourth, most of the studies did not take into account factors that could modulate participants' cognitive functioning (e.g., cognitive reserve, diet, sleep, physical and cognitive activity outside the intervention). Future studies should analyze the modulatory role of these factors. Finally, only three studies evaluated the effects of a neuropsychological intervention on brain functioning, in addition to assessing the cognitive evolution of the participants (Kang et al., 2021; Liao et al., 2020; Thapa et al., 2020), and so further studies are needed in this regard.

Despite these limitations, this meta-analysis shows that VR-based neuropsychological interventions are effective in improving cognitive functioning in patients with MCI, with attention and executive functions being the functions that benefitted the most, and the length of the intervention being a key factor for their effectiveness on language and visuoconstruction. Considering the findings of the reviewed studies, it is possible to make certain recommendations for future studies. First, VR-based interventions should have a duration of at least 15 hours. Second, future studies should evaluate the generalization of the results of interventions focused on basic and instrumental ADLs by employing interventions with a homogeneous length. Third, the virtual environment should be as close as possible to the patient's reality to ensure the transfer of cognitive improvements to ADLs. Fourth, the effectiveness of VR-based neuropsychological interventions that include the teaching of mnemonic strategies should be assessed in future studies. Fifth, follow-ups should be established after the intervention to find out whether the benefits of the VR-based intervention are maintained over time. Sixth, reliable change indices should be considered in future RCTs. Finally, it should be noted that the results of this meta-analysis could have relevant implications for clinical decision-making about patients with MCI, especially because the pandemic caused by COVID-19 has forced different professionals to use virtual tools in interventions. This situation prompts the field of Neuropsychology to expand its research on these tools.

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Declaration of interest statement

The authors report there are no competing interests to declare.

Data availability

Data sharing is not applicable to this article as no new data were created in this study. The authors confirm that the data supporting the findings of this study are available within the article.

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Table 1

Summary of studies

Author Sample Age (SD) (% of women)	VR-based intervention		Non VR-based intervention		Assessment	Assessment instruments	Results
	Characteristics of intervention in EG	Number of sessions	Characteristics of intervention in CG	Number of sessions			
Delbroek et al. (2017) *N*= 20 participants with MCI EG: n= 10; age: 86.9 (5.6) (80%) CG: n= 10; age: 87.5 (6.6) (50%)	*Serious games* BioRescue training program containing 9 exercises focused on improving balance, weight bearing, memory, attention, and dual tasks. Combined with regular treatment. *Multidomain*: attention and memory.	12 sessions, twice a week with a duration that gradually increased from 18 minutes in the first week to 30 minutes in the fifth week.	Usual treatment carried out in the residential care center.	n.s.	Pre- and post-intervention evaluation. Mann-Whitney U test, and Wilcoxon signed-rank test.	Tinetti-POMA scale, iTUG, D-MoCA, D-IMI, and OERS.	EG vs CG: N.s.d. in no domain. EG: ↑ in the total time of the gait balance and gait performance test (iTUG).
Hughes et al. (2014) *N*= 20 participants with MCI EG: n= 10; age: 78.5 (7.1) (80%) CG: n= 10; age: 76.2 (4.3) (60%)	*Video games* Cognitive training through Nintendo Wii (e.g., bowling, golf, tennis, and baseball) focused on improving global cognitive functioning. *Multidomain*: specific functions n.s.	24 sessions, 90 minutes once a week for 24 weeks.	A passive cognitive stimulation program called Healthy Aging Education Program (includes 10 keys to healthy aging).	24 sessions, 90 minutes each, once a week for 24 weeks.	Evaluation pre-, post, and one year after the intervention. Wilcoxon signed-rank test, and Wilcoxon rank sum.	CAMCI, CSRQ-25, and TIADL.	EG vs. CG: N.s.d. in global cognitive functioning.
Hwang and Lee (2017) *N*= 24 participants with MCI EG: n= 12; age: 74.1 (6.0) (66.67%) CG: n= 12; age: 70.01 (5.3) (75%)	*Format of the intervention: n.s.* Cognitive training focused on memory and balance capacity. *Specific cognitive domain*: memory.	100 sessions, 30 minutes each, 5 days a week for 20 weeks.	Traditional occupational therapy.	n.s.	Pre- and post-intervention evaluation. Paired-samples t-test, and independent two-samples t-test.	VST, WCT, and LOS.	EG vs CG: > working memory (VST), concentration (WCT), and balance ability (LOS) at the end of the intervention. EG: ↑ working memory (VST), concentration (WCT), and balance ability (LOS).

Author Sample Age (SD) (% of women)	VR-based intervention		Non VR-based intervention		Assessment	Assessment instruments	Results
	Characteristics of intervention in EG	Number of sessions	Characteristics of intervention in CG	Number of sessions			
Kang et al. (2021) *N*= 41 participants with MCI EG: n = 23; age: 75.48 (4.67) (73.9%) CG: n= 18; age: 73.28 (6.96) (66.7%)	*Serious games* Cognitive training aimed at attention, executive function, memory, visuospatial orientation, and processing speed. *Multidomain:* attention, executive function, memory and visuoconstruction.	8 sessions lasting 20-30 min each, twice a week for a month.	Usual therapy as pharmacotherapy	n.s.	Pre- and post-intervention evaluation (at the end of 8 weeks). Paired t-test and repeated measures ANOVA.	K-MMSE, CDR, CDR-SOB, Global impairment scale, IADL Scale, ROCFT, Phonemic Word Fluency Test, QOL-AD, TMT-A, TMT-B, K-BNT, SVLT, Stroop, GDS, AES, PANAS, SSQ, and rsfMRI.	EG vs CG: ↑ visuoconstruction (ROCFT) and regional functional connectivity in cerebral cortexes and white matter (ROCFT-related areas).
Liao et al. (2019) *N*= 34 participants with MCI EG: n = 18; age= 75.5 (5.2) (61.1%) CG: n = 16; age= 73.1 (6.8) (75%)	*ADL-based tasks* Physical training: VR-based exercises of 24-form Yang-style Tai chi, resistance, aerobic and functional. Cognitive training: VR-based games from IADL (i.e., mass rapid transit, store finder, kitchen chef, and store clerk). *Multidomain*: attention, executive function, memory, and visuoconstruction.	36 sessions. 60 min per session, 3 times a week for 12 weeks.	Physical training: endurance, aerobic, and balance exercises to reach 50-75% of maximum heart rate. Cognitive training: simultaneous with physical training (e.g., walking and turning around while reciting poems).	36 sessions. 60 minutes per session, 3 times a week for 12 weeks.	Pre- and post-intervention evaluation (at the end of 36 sessions). Repeated measures ANOVAs.	TMT A and B, Stroop and gait performance.	EG vs CG: ↑ alternating attention (TMT-B) and ↓ interference in gait performance during dual task after intervention. N.s.d. on other variables. EG: ↑ Stroop test performance (numbers and time), delta TMT performance (TMT-B-TMT-A). CG: ↑ Stroop test performance (numbers and time).

Author Sample Age (SD) (% of women)	VR-based intervention		Non VR-based intervention		Assessment	Assessment instruments	Results
	Characteristics of intervention in EG	Number of sessions	Characteristics of intervention in CG	Number of sessions			
Liao et al. (2020) *N*= 34 participants with MCI EG: n = 18; age= 75.5 (5.2) (61.1%) CG: n = 16; age= 73.1 (6.8) (75%)	*ADL-based tasks* Physical training: VR-based exercises of 24-form Yang-style Tai chi, endurance, aerobic and functional. Cognitive training: IADL VR-based games (i.e., shopping, preparing food, managing finances, and using transportation). *Multidomain:* attention, executive function, memory, and visuocontruction.	36 sessions. 60 min per session (40 min of physical exercise and 20 min of cognitive training), 3 times a week for 12 weeks.	Physical training: endurance, aerobic, and balance exercises, with gradually increasing difficulty. Cognitive training: simultaneous to physical training (e.g., walking and turning while reciting poems).	36 sessions. 60 minutes per session, 3 times a week for 12 weeks.	Pre- and post-intervention evaluation (at the end of 36 sessions). Repeated measures ANOVAs.	MoCA, EXIT-25, CVVLT, IADL Scale and NIRS.	EG vs CG: ↑ in IADL after intervention. N.s.d. in other variables. CG: ↑ in executive function and immediate verbal memory and ↓ in right prefrontal activation after intervention. EG: ↑ executive function, global cognitive functioning, and immediate and long-term verbal memory, IADL and ↓ in left, right and bilateral prefrontal activation after intervention.
Manenti et al. (2020) *N*= 49 participants with amnesic and non-amnesic MCI EG1: n = 18; age: 75.3 (3.3) (27.8%) EG2: n = 14; age: 76.3 (4.9) (71.4%) CG: n = 17; age: 78.1 (4.1) (58.82%)	*Serious games* EG 1: VRRS (12 exercises for memory, visuospatial skills, attention, and executive functions) + Tele@H-VRRS (cognitive stimulation at home with VR). EG 2: VRRS + Tele@H-UCS (unstructured cognitive stimulation at home: diary, reading the newspaper…) *Multidomain:* attention, executive functions, memory, and visuoconstruction.	EG 1: VRRS: 12 sessions lasting 60 min each for 4 weeks. Tele@H-VRRS: 36 sessions lasting 60 min each at home (3 sessions per week) for 3 months. EG 2: VRRS: 12 sessions lasting 60 min each for 4 weeks. Tele@H-UCS: 36 sessions lasting 60 min each at home (3 sessions per week) for 3 months.	Conventional face-to-face cognitive rehabilitation (clinic-TAU).	12 sessions lasting 60 min each. At the end of these sessions, participants were asked not to perform cognitive activities until the end of the intervention.	4 evaluations: before starting the intervention (T0), at the end of the intervention (T1), 4 months after starting the intervention (T2), and 7 months after starting the intervention (T3). Generalized linear mixed models.	EMQ, BADL, IADL Scale, GDS, NPI, QOL-AD, Raven's Colored Progressive Matrices, BADA, ROCFT, CDT, TMT, RAVLT, FCSRT.	EG1 vs CG (T1): ↑ in memory, language, attention, and visuoconstruction. EG2: ↓ memory at T2-T3 with respect to T1. EG1 and CG: no significant changes at T2-T3 with respect to T1. EG1 vs EG2: better performance on executive functions at T2 and T3.

Author Sample Age (SD) (% of women)	VR-based intervention		Non VR-based intervention		Assessment	Assessment instruments	Results
	Characteristics of intervention in EG	Number of sessions	Characteristics of intervention in CG	Number of sessions			
Mrakic-Sposta et al. (2018) *N*= 10 participants with MCI EG: n = 5; age: 72.00 (5.15) (60%) CG: n = 5; age: 74.60 (6.43) (60%)	*ADL-based tasks* Physical and cognitive training through 3 virtual environments: cycling in a park (physical), crossing streets avoiding cars (cognitive), and shopping in a supermarket (cognitive). *Multidomain:* attention, executive function, language and visuoconstruction.	3 times a week for 6 weeks (18 sessions in total). Each session lasted 40-45 minutes.	They did not receive treatment.	-	Pre- and post-intervention evaluation (at the end of the 6 weeks). Mann Whitney U-test, and Wilcoxon matched pair signed rank test.	MMSE, RAVLT, ROCFT, AM, TMT, FAB, VF and FAQ.	EG vs CG: N.s.d. EG: mild ↑ in MMSE, ROCF, FAB, AM, and ADL (after removal of an outlier) after the intervention. CG: ↓ in MMSE, ROCFT, FAB, AM, and ADL after the intervention.
Park et al. (2019) N= 21 participants with MCI EG: n =10; age: 70.60 (4.29) (80%) CG: n =11; age: 73.36 (5.50) (81.8%)	*ADL-based tasks* Cognitive training system based on mixed reality. 15 ADL-related tasks focused on: selective attention, visual and verbal working memory, executive functions (sequencing, planning and problem solving), and computation. *Multidomain*: attention, executive function, and working memory.	Three 30-minute sessions per week for 6 weeks (total of 540 minutes)	Conventional computer-assisted cognitive training system	Three 30-minute sessions per week for 6 weeks (total of 540 minutes)	Pre- and post-intervention evaluation (at the end of the 6 weeks). Repeated measures ANOVAs.	CERAD-K, CDR, BDI, Modified Barthel Index.	EG vs CG: ↑ in visuospatial working memory after the intervention. N.s.d. in other domains.

Author Sample Age (SD) (% of women)	VR-based intervention		Non VR-based intervention		Assessment	Assessment instruments	Results
	Characteristics of intervention in EG	Number of sessions	Characteristics of intervention in CG	Number of sessions			
Park et al. (2020a) N= 21 participants with amnestic MCI EG: n=10; age: 71.80 (6.61) (72.7%) CG: n=11; age: 69.45 (7.45) (66.6%)	*ADL-based tasks* VR-based cognitive training focused on attention, processing speed, executive function, and memory. *Multidomain*: attention, executive function, and memory.	30 min, 2 days a week for 3 months (24 sessions in total).	They did not receive treatment.	-	Pre- and post-intervention evaluation (at the end of 24 sessions). Repeated measures ANOVAs.	K-MMSE, SGDS-K, SNSB-D, DST, Stroop, and word fluency test.	EG vs. CG: N.s.d. on any test.
Park et al. (2020b) N= 35 participants with MCI EG: n=18; age: 75.8 (8.5) (44.4%) CG: n= 17; age: 77.2 (7.2) (58.8%)	*ADL-based tasks* VR-based software to perform activities such as driving, bathing, cooking, shopping. *Multidomain*: attention, executive function, and memory.	30 min per day, 5 times a week for 6 weeks.	Pencil and paper activities (puzzles, mazes, wooden blocks, card games, and stick building activities).	30 min per day, 5 times a week for 6 weeks.	Pre- and post-intervention evaluation (at the end of the 6 weeks). Independent t-tests.	MoCA, TMT (A and B) and DST (direct and inverse) and self-report to measure motivation towards the intervention.	EG vs CG: ↑ general cognition (MoCA), attention (TMT-A and TMT-B), and working memory (direct digits) after intervention, and > motivation toward intervention. N.s.d. in reverse digits. EG: ↑ performance on all tests after the intervention. CG: ↑ general cognition (MoCA), working memory (digits) after the intervention. No change in attention (TMT).
Thapa et al. (2020) N= 68 participants with MCI EG: n= 34; age: 72.6 (5.4) (82.35%) CG: n= 34; age: 72.27 (5.6) (70.59%)	*Serious games* Cognitive training program: 4 games (i.e. juice making, crow shooting, fireworks and house of love). *Multidomain*: attention and memory.	24 sessions of 100 minutes, 3 times a week for 8 weeks.	General health care education program.	8 sessions of 30-50 min, once a week.	Pre- and post-intervention evaluation. Repeated measures ANOVAs.	K-MMSE, NCGG-FAT (TMT-A, TMT-B y SDST) and EGG.	EG vs CG: ↓ TMT-B time N.s.d in any other domain. EG: ↓ theta waves in parietal and temporal lobe after intervention.

Author Sample Age (SD) (% of women)	VR-based intervention		Non VR-based intervention		Assessment	Assessment instruments	Results
	Characteristics of intervention in EG	Number of sessions	Characteristics of intervention in CG	Number of sessions			
Torpil et al. (2021) N= 61 participants with MCI EG: n=30; age: 70.30 (2.73) (54.8%) CG: n= 31; age: 70.12 (2.57) (63.3%)	*Video games* VR + conventional cognitive rehabilitation. - VR: 4 games (BoxingTrainer, Jet Run, Superkick and Air Challenge) aimed at attention, visuospatial perception, visuomotor organization, reaction time, and orientation. - Conventional cognitive rehabilitation: designed based on the LOTCA-G subtests. *Multidomain*: attention and visuoconstruction.	VR: 45 min sessions, 2 times a week for 12 weeks. Conventional cognitive rehabilitation: 45 min sessions, 2 times a week for 12 weeks.	Conventional cognitive rehabilitation designed based on the LOTCA-G subtests. Week 1-8: attention, memory, orientation, visuospatial perception, visuomotor organization, praxias, and operative thinking. Week 9-12: all cognitive functions.	Sessions lasting 45 minutes each, twice a week for 12 weeks.	Pre- and post-intervention evaluation (at the end of the 12 weeks). Mann–Whitney U-test andWilcoxon matched pair signed rank test.	LOTCA-G.	EG vs CG: ↑ orientation, visuospatial perception, visuomotor organization, operant thinking, and attention-concentration.

Note. ADL= activities of daily living; AES= Apathy Evaluation Scale; BADA= Battery for the Assessment of Aphasic Disorders; BADL= basic activities of daily living; BDI= Beck Depression Inventory; CAMCI= Computerized Assessment of Mild Cognitive Impairment; CDR= Clinical Dementia Rating Scale; CDR-SOB= Clinical Dementia Rating Scale Sum of Boxes; CDT= Clock Drawing Test; CERAD-K= Consortium to Establish a Registry for Alzheimer's Disease-Korean Version; CG= control group; CSRQ-25= Cognitive Self-Report Questionnaire-25; clinic-TAU= conventional cognitive rehabilitation; CVVLT= Chinese version of the Verbal Learning Test; D-IMI= Dutch Version- Intrinsic Motivation Inventory; DST= Digit Span Test; D-MoCA= Dutch Version-Montreal Cognitive Assessment; EG= experimental group; EGG= Electroencephalogram; EMQ= Everyday Memory Questionnaire; EXIT-25= Executive Interview 25; FAB= Frontal Lobe Assessment Battery; FAQ= Functional Activity Questionnaire; FCSRT= Free and Cued Selective Reminding Test; GDS= Geriatric Depression Scale; IADL = instrumental activities of daily living; iTUG= Timed Up and Go Test; K-BNT= Korean Version of the Boston Naming Test; K-MMSE= Mini Mental State Examination-Korean Version; LOTCA-G= Loewenstein Occupational Therapy Cognitive Assessment Geriatric version; LOS= Limit of Stability; MCI= mild cognitive impairment; MMSE= Mini Mental State Examination; MoCA= Montreal Cognitive Assessment; NCGG-FAT= National Center for Geriatrics and Gerontology Functional Assessment Tool; NIRS= near-infrared spectroscopy; NPI= Neuropsychiatric Inventory; N.s.d.: no significant differences; n.s.= not specified; OERS= Observed Emotion Rating Scale; PANAS= Positive and Negative Affect Schedule; QOL-AD= Quality of Life in Alzheimer's Disease; RAVLT= Rey Auditory Verbal Learning Test; ROCFT= Rey-Osterrieth Complex Figure Test; rsfMRI= Functional Magnetic Resonance Imaging in the Resting State; SDST= Symbol Digit Substitution Test; SGDS-K= Korean version of the Geriatric Depression Scale; SNSB-D= Seoul Neuropsychological Screening Battery-Dementia Version; SSQ= Simulator Sickness Questionnaire; SVLT= Seoul Verbal Learning Test; TIADL= Timed Instrumental Activities of Daily Living; Tinetti-POMA Scale= Tinetti-Performance-Oriented Mobility Assessment; TMT = Trail Making Test; Tele@H-VRRS= VR Cognitive Telerehabilitation at Home; Tele@H-UCS= Unstructured Cognitive Stimulation at Home; VF= Verbal Fluency Test; VR: virtual reality; VRRS= Face-to-Face Virtual Rehab System with Virtual Reality; VST= Visual Span Test; WCT= Word Color Test; WCST= Wisconsin Card Sorting Test.

Table 2

Risk of bias of RCTs

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of compliance
Delbroek et al. (2017)	Y	U	Y	U	Y	U	Y	Y	Y	Y	U	N	Y	62%
Hughes et al. (2014)	Y	U	Y	U	U	U	Y	Y	Y	Y	U	Y	Y	62%
Hwang and Lee (2017)	Y	U	U	U	U	U	Y	Y	Y	Y	U	N	Y	46%
Kang et al. (2021)	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	69%
Liao et al. (2019)	Y	Y	Y	U	U	Y	Y	Y	Y	Y	U	N	Y	69%
Liao et al. (2020)	Y	Y	Y	U	U	Y	Y	Y	Y	Y	U	Y	Y	77%
Manenti et al. (2020)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	U	N	Y	77%
Mrakic-Sposta et al. (2018)	Y	U	Y	U	U	U	Y	Y	Y	Y	Y	U	Y	62%
Park et al. (2019)	Y	U	Y	U	U	Y	Y	Y	Y	Y	Y	U	Y	69%
Park et al. (2020a)	Y	U	Y	N	U	U	Y	Y	Y	Y	U	U	Y	54%
Park et al. (2020b)	Y	Y	Y	U	U	U	Y	Y	Y	Y	U	Y	Y	69%
Thapa et al. (2020)	Y	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	69%
Torpil et al. (2021)	Y	Y	Y	U	U	Y	Y	Y	Y	Y	U	Y	Y	92%

Note. N: no; U: unclear; Y: yes; Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatment groups treated identically other than the intervention of interest?; Q8: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Figure 1. Flow diagram.

Figure 2. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving global cognitive functioning.

Figure 3. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving attention.

Figure 4. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving executive function.

Figure 5. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving working memory.

Figure 6. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving immediate memory.

Figure 7. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving delayed memory.

Figure 8. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving language.

Figure 9. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving visuoconstruction.

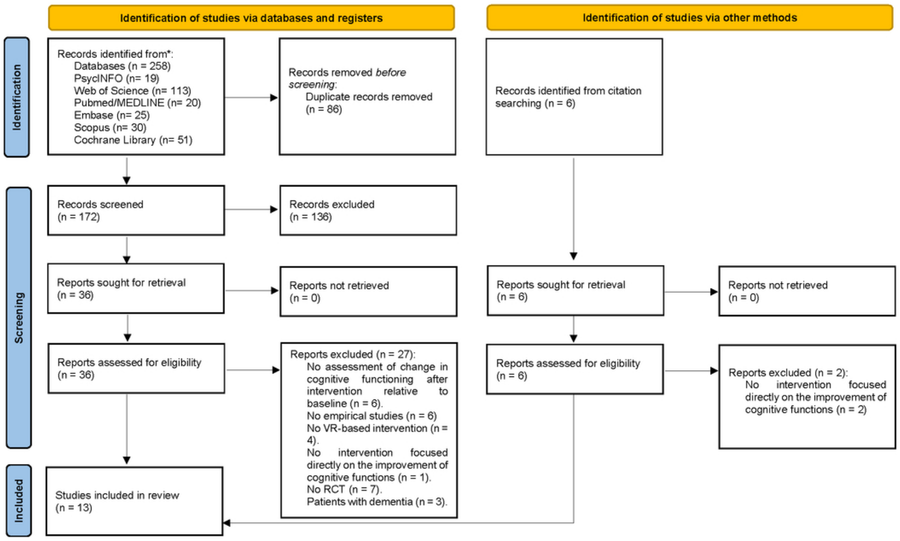

Figure 1. Flow diagram.

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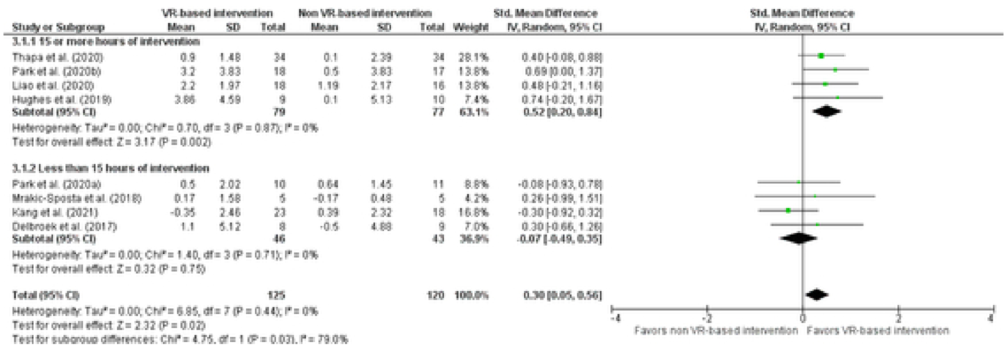

Figure 2. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving global cognitive functioning.

47x16mm (300 x 300 DPI)

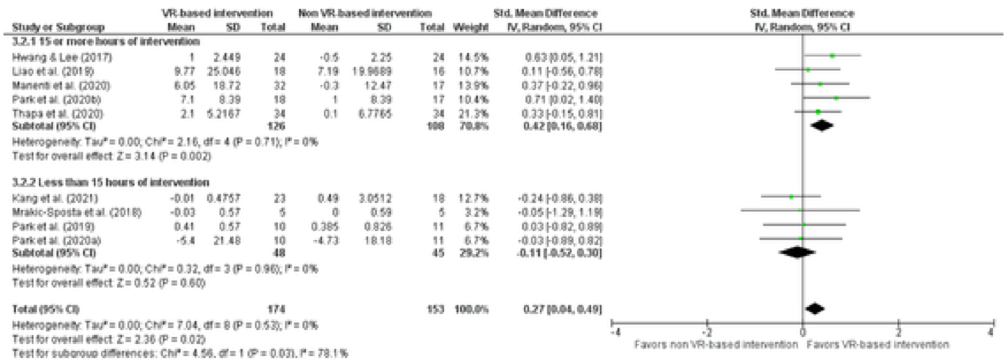

Figure 3. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving attention.

47x16mm (300 x 300 DPI)

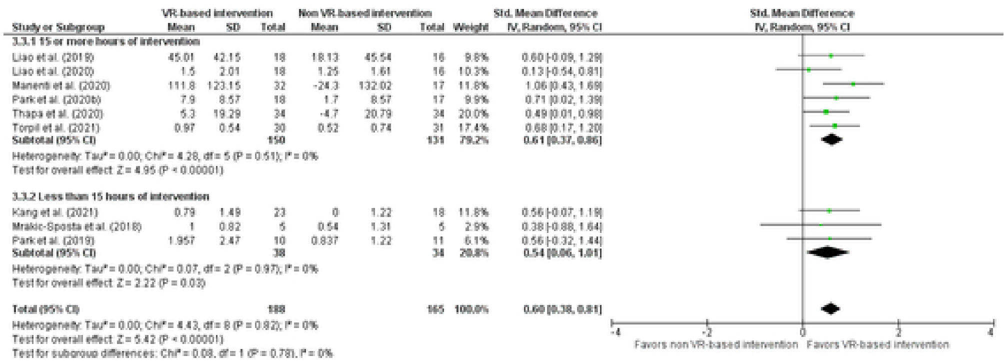

Figure 4. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving executive function.

47x16mm (300 x 300 DPI)

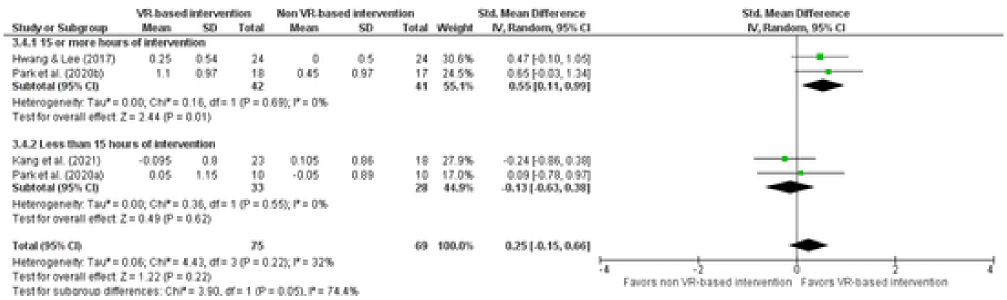

Figure 5. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving working memory.

46x13mm (300 x 300 DPI)

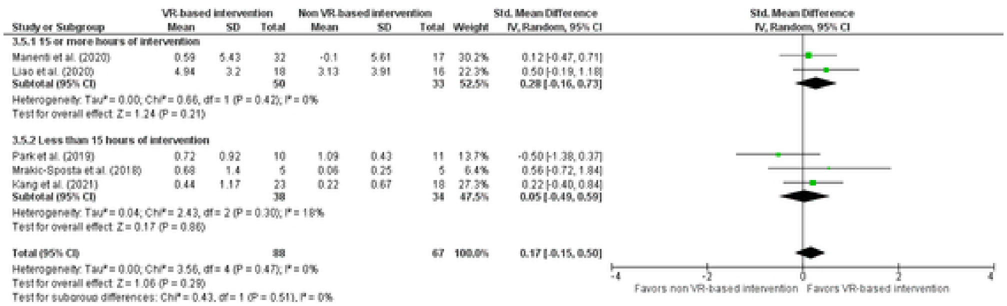

Figure 6. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving immediate memory.

47x14mm (300 x 300 DPI)

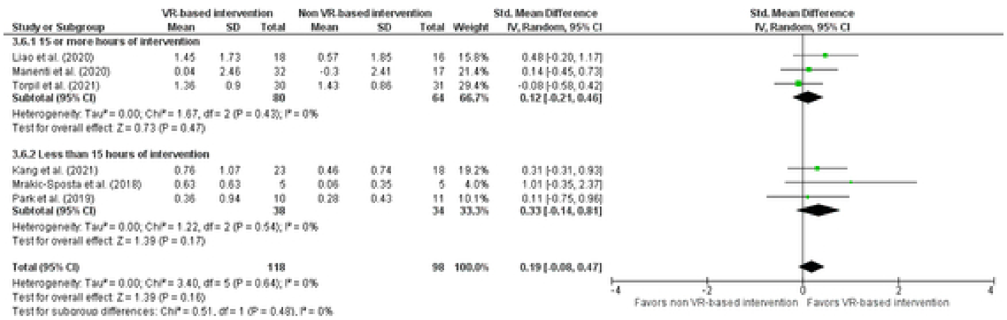

Figure 7. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving delayed memory.

47x14mm (300 x 300 DPI)

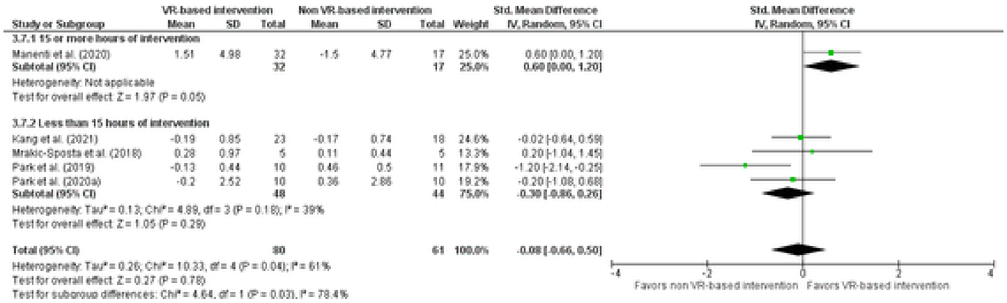

Figure 8. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving language.

47x14mm (300 x 300 DPI)

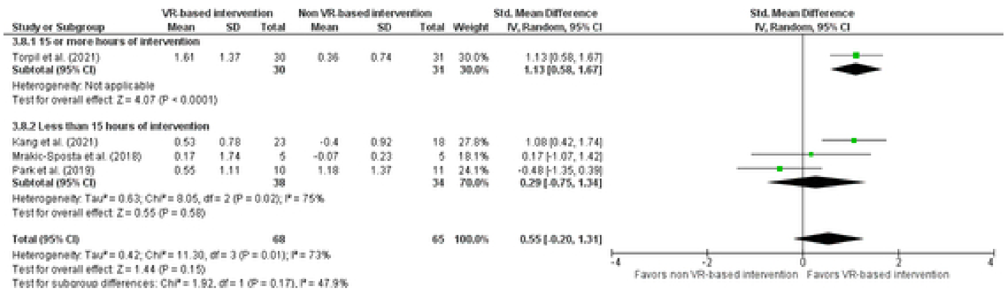

Figure 9. Forest plot for the effectiveness of VR-based neuropsychological interventions in improving visuoconstruction.

47x13mm (300 x 300 DPI)