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Immersive virtual reality cognitive training in older adults with mild cognitive impairment: Feasibility results from a randomized controlled trial

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ABSTRACT

Background: Immersive virtual reality (VR)–based cognitive training has shown potential benefits in neuropsychiatric populations, but evidence in older adults with mild cognitive impairment (MCI) remains limited, particularly regarding feasibility and short-term effects on vulnerability factors.
Objective: To evaluate the feasibility of a 6-week immersive VR cognitive training program in older adults with MCI and to explore preliminary effects on cognitive performance, depressive symptoms, and social and behavioral rhythms.
Methods: This single center randomized controlled feasibility trial allocated participants aged ≥65 years with MCI to either an immersive VR cognitive training program (Virtual Sail 3D) or an active control intervention based on healthy lifestyle education. Feasibility outcomes included dropout rates and VR-related adverse effects. Secondary outcomes assessed changes in cognitive performance (MMSE, ACE-R), depressive symptoms (PHQ-9), and social and behavioral rhythms (Brief Social Rhythms Scale) from baseline (T0) to 6 weeks (T1).
Results: Forty participants were randomized. No dropouts occurred in the VR group, whereas a 30% dropout rate was observed in the control group. VR-related side effects were mild and transient. No significant between-group differences emerged in cognitive or depressive outcomes. However, social and behavioral rhythms remained stable in the VR group and worsened in the control group, with a borderline between-group difference. A significantly higher proportion of VR participants showed clinically meaningful improvement in rhythm regulation.
Conclusions: Immersive VR cognitive training is feasible and well-tolerated in older adults with MCI. While short-term cognitive benefits were not observed, preservation of social and behavioral rhythms suggests a potential protective effect, supporting larger and longer phase III trials.

1. Introduction

The steady rise in life expectancy and the progressive aging of the global population have been accompanied by a corresponding growth in the prevalence of mild cognitive impairment (MCI) and dementia within the community [1,2]. This trend has resulted in a substantial escalation of healthcare and social expenditures [3,4] and, in many countries, a concerning reduction in the proportion of individuals of working age

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[4].

MCI is often considered an intermediate condition that confers a heightened risk of progression to the early stages of dementia [5,6]. Cognitive deterioration is frequently associated with disruptions in social rhythms, as well as symptoms of depression and anxiety, and a decline in overall quality of life [7,8]. These factors may further exacerbate vulnerability and accelerate the transition to overt dementia [9,10]. In response, public health strategies have increasingly emphasized the promotion of active aging [11,12], while research efforts have focused on assessing the efficacy of interventions, particularly non-pharmacological approaches considering that this fraction of the population on average takes many drugs [13], aimed at preventing or delaying cognitive decline and mitigating associated affective symptoms [14–17]. Recent literature supports even the beneficial effects of cognitive training and cognitive rehabilitation interventions on cognitive performance in older adults [18–20]. In recent years, there has also been an increase in the experimental use of immersive virtual reality (VR) software in clinical and rehabilitation settings as a tool for rehabilitation and for the enhancement of various skills [21,22]. Indeed, VR, by providing highly realistic and immersive learning environments, can simultaneously offer elements of cognitive rehabilitation and physical stimulation (albeit indirect) [22]. These stimuli may be even more intense and impactful than those experienced in natural conditions due to the "bombardment" effect on the mirror neuron system [23]. Hypothetically, this could support the improvement and/or maintenance of cognitive and functional skills while offering easy accessibility [24]. Preliminary evidence from studies conducted in heterogeneous populations, including individuals with neuropsychiatric disorders and older adults, suggests improvements in cognitive performance and overall functioning [25,26]. More specifically, studies focusing on patients with MCI and dementia have reported improvements in cognitive function, emotional state, and daily functioning following VR-based interventions [27–30]. However, to date, despite these encouraging findings, studies conducted on older adults remain limited in value due to poor methodological rigor and limited replicability of the protocols. This is largely attributable to the lack of detailed and structured descriptions of the interventions, which hinders the definition of a standardized operating procedure [31,32].

A recent line of research conducted by our group using immersive cognitive training in virtual reality on people with bipolar disorder has demonstrated, using randomized controlled models, significant improvements in cognitive performance [33], social and personal rhythm regulation [34], and anxiety and depressive symptoms [35]. Although bipolar disorder and mild cognitive impairment (MCI) differ substantially in terms of etiology, clinical course, and underlying neuropathology, they share several relevant features, including impairments in cognitive domains (e.g., attention, executive function, and memory), as well as alterations in circadian and social rhythms and a high prevalence of affective symptoms [36,37]. These factors are increasingly recognized as transdiagnostic mechanisms contributing to functional impairment and cognitive decline across different clinical populations [5,38–41]. These results have led to the hypothesis that a similar intervention could also be useful for counteracting cognitive decline in older adults, even those without mood disorders. Indeed, the intervention not only appeared to have a direct effect on cognitive decline but also impacted risk factors such as rhythm dysregulation and anxiety and depressive symptoms.

The aim of this study is to assess the feasibility of a 6-week intervention (primary outcome) to improve cognitive function using immersive virtual reality software. The intervention is based on a previously developed platform tested in individuals with bipolar disorder, with scenarios specifically developed to also meet the needs of older adults with MCI. In particular, the virtual environment was redesigned to include naturalistic and ecologically valid contexts (e.g., sailing scenarios in open sea and harbor settings), consistent with emerging evidence suggesting that immersive and naturalistic VR environments can enhance engagement, motivation, and acceptability in older adults and clinical populations [42,43].

Consistent with the second stage of intervention development, focused on feasibility and preliminary clinical effectiveness in clinical populations, this single center randomized controlled trial (RCT) also aims to inform the design of future confirmatory studies evaluating efficacy (secondary outcome). In addition, the study explores vulnerability factors associated with cognitive decline, such as depressive symptoms, and considers the potential applicability of similar interventions in older adults with traits of hyperactivity and novelty-seeking behavior [44–46].

The study addresses the following research questions: (i) Is the adapted VR intervention feasible and acceptable in older adults with MCI? (ii) Does the intervention provide preliminary evidence of benefit on cognitive performance and on modifiable vulnerability factors? It is hypothesized that the intervention will be feasible and associated with improvements in cognitive functioning, as well as in risk factors such as depressive symptoms and rhythm dysregulation. A robust body of evidence indicates that dysregulation of social and circadian rhythms represents a key predictor of cognitive impairment [47–49], depressive symptoms [50–53] or both [54], while rhythm regularity may act as a protective factor in older adults [55]. On this basis, it is further hypothesized that even short-term modifications in these factors induced by the VR intervention may serve as early indicators of the potential effectiveness of longer and larger-scale interventions.

2. Methods

2.1. Design

The methodology of this feasibility RCT, has been already deposited (ClinicalTrial.gov NCT06579378; https://clinicaltrials.gov/search?term=NCT06579378) and published [56]. The cited publication followed the 2010 CONSORT (Consolidated Standards of Reporting Trials) guidelines, specifically the extension for randomized pilot and feasibility studies [57]. The study used a two-arm, parallel design, independently randomized in a 1:1 ratio. Participants were assigned to an experimental intervention based on the Virtual Sail 3D (VSail) protocol or, in the control arm, to a healthy lifestyle education and active aging promotion online intervention ("WEB-Health"). This article presents the assessments at T0 (0 weeks - baseline) and T1 (6 weeks) related to the primary outcome and the most relevant secondary outcomes.

2.2. Participants and setting

Participants were eligible if they were aged 65 years or older, irrespective of sex, had no medical or functional conditions preventing participation in the "VR-Sail" intervention, retained adequate independent mobility, met criteria for mild cognitive impairment (MCI) based on the Addenbrooke's Cognitive Examination–Revised (ACE-R) and/or the Mini-Mental State Examination (MMSE) scores within the predefined ranges for MCI (ACE-R: 66.93–84.93; MMSE: 26.02–27.11) [58,59,64,65], and provided written informed consent prior to enrollment.

Exclusion criteria included severe medical conditions (cardiovascular, respiratory, renal, oncological), severe metabolic diseases not compensated for by medication, severe mobility impairment and/or severe neurological conditions (such as stroke in the last 2 years, Parkinson's disease, epilepsy) that could prevent participation in the experimental protocol and/or severe visual impairment that would prevent the safe use of VR technology, and active malignancies. Recruitment activities were conducted at the project partner units at the Cagliari University Hospital (AOU Cagliari), Italy. Informational brochures about the project were available in the participating units' outpatient clinics so that participants could freely express their interest in participating. Participants who screened positive for MCI were

enrolled and subsequently randomized to the two study arms. Recruitment continued until the predetermined sample size was reached, allowing for randomization and implementation of the interventions. All randomization and evaluation activities using the protocol-defined tools, as well as the implementation of the experimental and control group interventions, took place at the Liaison Psychiatry and Psychosomatics Center of the AOU Cagliari. The study was coordinated by the unit's researchers, while the evaluation and interventions were conducted by professionals trained in the use of assessment tools (Clinical Psychologists and Engineers) and in the delivery of the virtual reality-based cognitive rehabilitation protocol (Psychiatric Rehabilitation Technicians / Occupational Therapists / Speech and Language Therapists / Physiotherapists) and webinars on healthy lifestyle (Health Psychologists). Given the complexity of the intervention and the fact that virtual reality is well known, it was not impossible to blind both the participants and the professionals involved in the study to the intervention being delivered.

2.3. Intervention

The experimental intervention (VSail) consisted of 50–60-min virtual reality (VR) sessions delivered twice a week for six consecutive weeks. The sessions were conducted within immersive sailing-based virtual environments simulating a real-life sailing maneuvers (see Figs. 1, 2, 3, 4, 5 for an illustration of the VR environment). The intervention was implemented using the VR software "CEREBRUM" developed by the Cerebrum VR Society, compatible with the Oculus Quest headset and compliant with European safety, health, and environmental protection standards [60]. Compared to earlier applications used in bipolar disorder, the software was further expanded with dedicated sailing scenarios and tasks (for more detailed description see [56]). The VR training provided structured and progressively complex cognitive-motor stimulation through modules organized into increasing levels of difficulty (easy, intermediate, and advanced). Participants actively moved within the virtual environment and interacted with it to accomplish task goals, using handheld controllers to point, select, and manipulate objects and to perform actions such as steering, pulling ropes, or operating sailing equipment. The main training components included: (i) familiarization and free exploration of the virtual boat; (ii) identification of boat components through visual search tasks; (iii) execution of ordered sequences; (iv) coordinated sailing maneuvers performed while the boat was moored in the harbor; and (v) Coordinated sailing maneuvers performed while the boat was navigating in open waters, with tasks requiring goal-directed interaction with dynamic environmental stimuli. Across all sessions, attentional, mnemonic, and executive strategies were systematically trained with progressively increasing complexity as task difficulty increased. Attention was engaged through continuous monitoring and selection of relevant stimuli in a 360° environment; memory (particularly working and sequential memory) was trained through the retention and execution of ordered actions; and executive functions were involved in planning, sequencing, inhibition, and problem-solving during multi-step tasks. Motor coordination and visuomotor integration were also stimulated through interaction with virtual sailing elements, while verbal abilities were engaged through comprehension of verbal instructions delivered within the VR scenario. Each session followed a structured protocol including initial welcome, psychoeducation, and introduction to both the VR tool and the cognitive function targeted by the exercise. Participants then performed one or more VR exercises lasting approximately 15–20 min. During task execution, participants received immediate, performance-contingent audiovisual feedback directly from the software, reinforcing correct responses and supporting learning processes. In addition, the therapist provided real-time guidance when necessary. After VR exposure, the clinician conducted a structured debriefing phase including positive and corrective feedback, metacognitive reflection, and discussion of task strategies. Importantly, the psychoeducational components and the generalization of the trained cognitive strategies to real-life contexts were explicitly mediated by the operator, who provided practical

Fig. 1. Virtual Sailing Scenario

Fig. 2. Virtual Sailing Scenario

Fig. 3. Virtual Sailing Scenario

Fig. 4. Virtual Sailing Scenario

Fig. 5. Virtual Sailing Scenario

suggestions and homework exercises to promote transfer to daily functioning.

The control intervention focused on education about healthy lifestyle habits to promote active aging. It consisted of a cycle of three seminars delivered as webinars via online platforms (e.g., Skype, Zoom) over a period of six consecutive weeks. Sessions were held on a biweekly schedule (i.e., once every two weeks), with each webinar lasting approximately 50–60 min. The content covered topics such as active aging, physical activity in older adulthood, effective communication, stress management, and the use of technology in health.

2.4. Outcomes, timeline, and evaluation tools

As specified in the published study protocol [56], the primary outcomes were related to feasibility and included participant retention (dropout rates between T0 and T1), recruitment rate, occurrence of adverse events associated with immersive virtual reality exposure, and participants' satisfaction with the intervention. Secondary outcomes concerned cognitive functioning and encompassed executive functions, memory, visuospatial abilities, selective attention, and global cognitive performance. Tertiary outcomes addressed psychosocial and physical functioning, including quality of life, depressive and anxiety symptoms, regulation of social and biological rhythms, body awareness, physical activity levels, and mobility. In addition, sociodemographic and clinical variables were collected for all participants.

Regarding the maintenance of treatment effects, the study protocol included follow-up assessments at T2 (12 weeks from T1), T3 (24 weeks from T1), T4 (36 weeks from T1), and T5 (48 weeks from T1), in addition to baseline (T0) and post-intervention (T1) evaluations. Therefore, the persistence of intervention-related effects over time is being investigated; however, the present article reports only baseline and post-intervention outcomes, focusing on feasibility and short-term effects on secondary and tertiary outcomes.

Given the scope of the current report, we focused on a subset of the prespecified outcomes. Feasibility was assessed through tolerability, operationalized as dropout rates between T0 and T1, and through side effects measured using the Simulator Sickness Questionnaire (SSQ) [61], a 16-item self-administered instrument evaluating VR-related adverse effects such as nausea, dizziness, headache, and eye strain.

Specifically, cognitive functioning was evaluated as the main efficacy-related (secondary) domain using the ACE-R [59,62], which assesses five cognitive domains (attention, memory, verbal fluency, language, and visuospatial skills) and incorporates the MMSE [63]. Cut-off scores indicative of mild cognitive impairment have been previously reported as ranging from 66.93 to 84.93 for the ACE-R [59,64] and 26.02 to 27.11 for the MMSE [65].

Among the tertiary outcomes specified in the protocol, we report findings on depressive symptoms and regulation of social and biological rhythms. Depressive symptom severity was assessed using the Italian version [66,67] of the Patient Health Questionnaire-9 (PHQ-9) [68], useful for the diagnosis of a Major Depressive Episode according to the DSM system [69]. It measures the frequency of nine depressive symptoms over the previous two weeks, with total scores ranging from 0 to 27, higher scores indicating greater severity [70]. Social and biological rhythm functioning was evaluated using the Italian version of the Brief Social Rhythms Scale (BSRS) [71], where higher scores reflect poorer rhythmic regularity. In addition to mean score changes, we also examined the proportion of participants exceeding a previously established clinical cut-off defined as scores higher than one standard deviation above the mean of a community sample, consistent with prior literature [55].

The remaining protocol-defined outcomes are not reported in the present article and will be addressed in future analyses.

2.5. Sample size, randomization and blinding

Given the absence of previous randomized controlled trials investigating immersive VR interventions based on virtual sailing scenarios in this target population, the present study was conceived as a feasibility and exploratory trial. Since the study was designed as a feasibility trial, no formal power calculations for efficacy outcomes were undertaken. The sample size was determined to assess the feasibility of study procedures and to provide preliminary estimates of outcome variability and effect sizes for future confirmatory trials, rather than to support hypothesis testing. The proposed sample size was determined with reference to prior VR-based feasibility studies, which generally involved relatively small cohorts [27,72]. Accordingly, the enrollment of 40 participants (20 per group) was considered sufficient to evaluate the feasibility of study procedures, generate preliminary estimates of variability, and provide initial indications of potential intervention effects to support the planning of a future adequately powered RCT.

Participants were randomly allocated to the experimental and control groups with a 1:1 allocation ratio using computer-generated randomization software. The randomization sequence was generated by an independent researcher who was not involved in participant recruitment, assessment, or intervention delivery.

Allocation concealment was ensured by having the sequence generated and managed independently, preventing those involved in enrollment and assessment from foreseeing group assignments.

Outcome assessors were blinded to group allocation to minimize assessment bias. Due to the nature of the intervention, participants and intervention providers could not be blinded.

2.6. Statistical analysis

Between-group characteristics measured on numerical scales were compared using one-way ANOVA or the Mann-Whitney test when the conditions for applying a parametric test were not met. Numerical data were compared using the Chi-square test with Yates' correction, if necessary. The difference in dropouts between group was calculated by means of Fisher Exact Test. To evaluate intervention effects, differences between T1 and T0 were calculated for each outcome measure and compared between groups (Control vs. Experimental) using one-way ANOVA with Bonferroni correction. This approach allowed for direct assessment of between-group differences in change over time. Within-group changes between T1 and T0 were also examined descriptively. Given that all dropouts occurred in the control group, a secondary analysis was conducted to account for potential group imbalance. Specifically, five participants from the experimental group were selected to match dropouts by age (±5 years) and sex, and analyses were repeated in this subsample.

Finally, changes in the frequency of dysfunctional rhythms (defined as SBSR >1 standard deviation of a previous community sample) across time (T1 vs. T0) were analyzed using the McNemar test for paired nominal data.

3. Results

Based on the study eligibility criteria, 153 individuals were identified by the partner units as potentially eligible. Fourteen individuals could not be contacted and were therefore excluded before eligibility assessment. Consequently, 139 individuals were assessed for eligibility. Among those assessed, 99 individuals were excluded. 72 declined to participate, specifically, 41 (29.5%) declared they were not interested, 14 (10.1%) declared they were interested but not available to take part in the study, 17 (29.8%) refused to participate in the intervention for health reasons, family organizational impediments, or reconsideration of participating. 27 did not meet the inclusion criteria. The reasons for ineligibility were macular degeneration 5 (18.5%), inability to walk independently 2 (7.4%), and 20 (74.1%) tested negative for MCI. A total

of 40 participants met all eligibility criteria, agreed to participate, and were randomized. Twenty participants were allocated to the intervention group and 20 to the control group (see Fig. 6).

All participants in the experimental group completed the 6-week trial and were reassessed at T1, while 6 participants in the control group dropped out at the beginning of the control intervention the trial (drop out 30% in controls vs 0% in experimental group). The difference in dropouts between group does not reach statistical significance but is close (Fisher Exact tailed for OR > 1 [OR = inf CI95% Not calculable] $p = 0.053$). As reported in Table 1, participants who completed the trial reported few symptoms potentially attributable to the adverse effects of immersive virtual reality technology, particularly difficulty concentrating. However, none of these symptoms required discontinuation. Out of the 12 planned sessions, the 20 participants in the experimental group completed a mean ± sd of 9.95 ± 2.7) sessions.

All dropouts in the control group were explained by unforeseen commitments and, in two cases, by health problems unrelated to the trial. Table 2 illustrates the characteristics of the dropouts compared to the total sample that completed the trial. The dropouts (all in the control group) were found to be older (mean age 82.66 ± 6.47 vs 74.64 ± 6.17; $p = 0.021$) and tended to be more frequently male (66.6% vs 35%), but the difference by sex was not statistically significant.

Table 3 shows the characteristics by sex and age in the two groups being compared. Probably due to the dropout of older participants, the control sample tends to be older. This difference is attenuated in the standardized sample (in which six participants matched by sex and age to the dropouts were selected). However, in the "standardized" sample, the composition by sex is slightly unbalanced, again without statistically significant differences.

Table 4 presents a comparison at T0 and T1 of the three secondary outcome measures: MMSE score, ACE-R score, and PHQ-9 score, in the control sample compared to the experimental sample and the standardized experimental sample. At T0, it is noted that the ACE-R and MMSE scores tend to be higher in the control sample than in the experimental sample, although the difference does not reach statistical significance. The difference is only partially evened out in the standardized experimental sample. Another very important element is the high average PHQ-9 score across all samples (remembering that a score of 4 to 9 indicates possible mild depression). The comparison over time

Table 1
Potential adverse events due to the use of immersive virtual reality technology.

SSQ item	N (%) after the first session	N (%) after the last session
Nausea	3 (15%)	1 (5%)
General discomfort	0 (0%)	1 (5%)
Stomach discomfort	1 (5%)	2 (10%)
Sweating	3 (15%)	3 (15%)
Increased salivation	1 (5%)	2 (10%)
Vertigo	1 (5%)	1 (5%)
Burping	3 (15%)	1 (5%)
Difficulty concentrating	5 (25%)	7 (35%)
Attention difficulties	4 (20%)	4 (20%)
Eyes strain	3 (15%)	4 (20%)
General fatigue	2 (10%)	2 (10%)
Headache	4 (20%)	3 (15%)
Blurred vision	2 (10%)	1 (5%)
Ightheadedness with eyes open)	1 (5%)	1 (5%)
Ightheadedness with eyes closed	1 (5%)	1 (5%)
Head pressure	2 (10%)	4 (20%)

Legend: SSQ (Sickness Simulator Questionnaire); N (number of subjects); % (percentage).

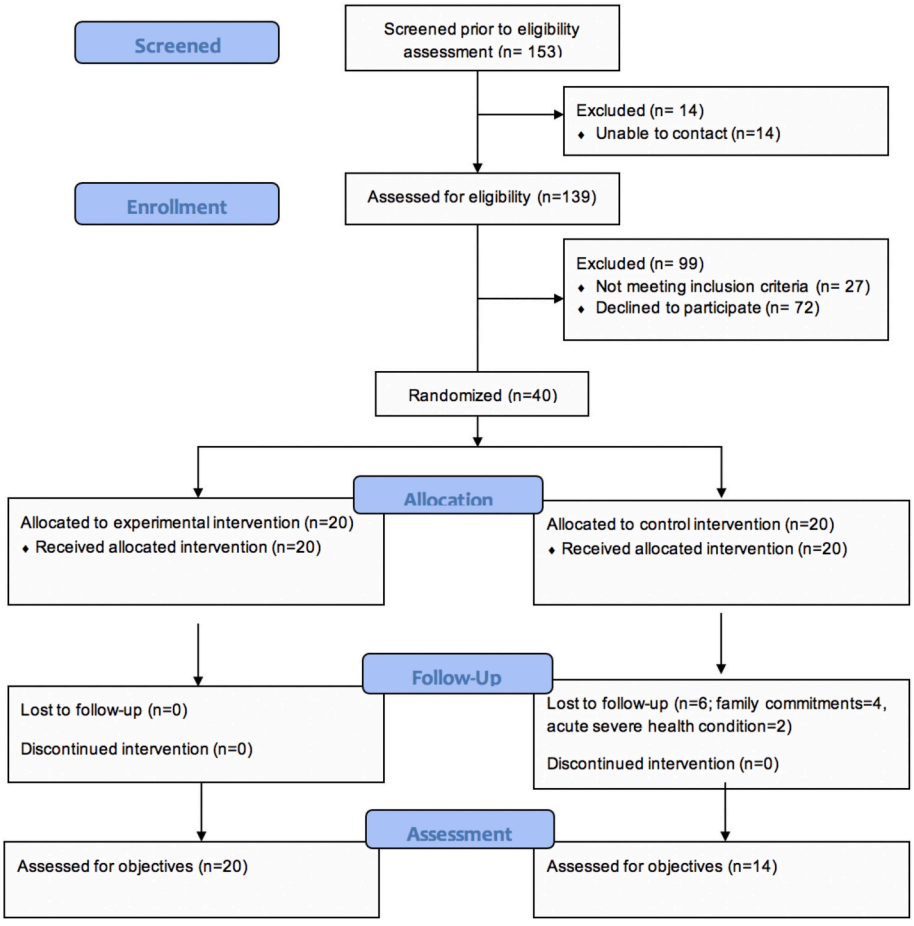

Fig. 6. Flow Diagram CONSORT 2010 statement: extension to randomized pilot and feasibility trials.

Table 2
Characteristics of participants comparing who dropped out with those who completed the study.

	Male N (%)	Age mean ± sd	MMSE T0 mean ± sd
Drop Out $N = 6$	4 (66.6%)	82.66 ± 6.47	25.33 ± 2.49
Not Drop Out $N = 34$	12 (35.3%)	74.64 ± 6.17	26.54 ± 2.75
Statistics	Chi square with Yate's correction =1.216	Mann Withney $z = -2.31054$	Mann Withney $z = 0.5871$
p	0.270	0.021	0.5552

Legend: MMSE (Mini Mental State Examination); N (number of subjects); % (percentage); sd (standard deviation).

Table 3
Comparison of characteristics at T0 of the participants concluding the trial in the two study samples.

	Male N (%)	Age mean ± sd
Control Sample ($N = 14$)	6 (35.3%)	74.00 ± 4.95
Control Sample including drop-out ($n = 20$)	10 (50%)	76.60 ± 6.748
Experimental Sample (N = 20)	6 (30%)	75.10 ± 6.86
Experimental Standardized ($N = 17$)	3 (17.6%)	73.14 ± 6.18
Statistics Experimental vs Control	Chi square = 0.118; $p = 0.732$	ANOVA 1 way $F(1,32) = 0.303$ $p = 0.586$
Statistics Standardized Experimental vs Control	Chi square correction =0.360 $p = 0.244$	ANOVA 1 way $F(1,32) = 0.201$ $p = 0.657$

Legend: N (number of subjects); % (percentage); sd (standard deviation).

indicates a slight increase in the differences in the scores of the two measures of general cognitive functioning (MMSE and ACE-R), with differences in improvement always, paradoxically, in favor of the control group in all comparisons with the experimental sample and the standardized experimental sample. This difference reaches the limits of statistical significance with regard to the change in the MMSE score compared to the experimental group (1-way ANOVA 1,32 df, $F = 4.015$, $p = 0.054$). The change in the PHQ-9 score also shows a slightly greater improvement in the control group, but without statistically significant differences, and without the comparison of the change over time between the groups showing significant differences.

Table 5 presents the changes in SBRS scores over time by group, as well as the proportion of participants who achieved an improvement greater than one quarter of a standard deviation in each group at the end of the trial. In the experimental group, the end-of-trial SBRS score improved by 0.25 ± 9.77 points (0.8%), whereas in the control group, the SBRS score worsened by 5.65 ± 7.12 points (20.2%). The between-group difference was of borderline statistical significance ($p = 0.056$), with an overall gain attributable to the intervention of 21%. On this basis, a hypothetical phase III study with a dichotomous endpoint and a two–independent-sample design, assuming an alpha level of 0.05, a beta of 0.20, and a statistical power of 0.80, would require a total sample size of at least 64 participants, equally divided into two groups of 32. The proportion of participants showing an improvement greater than one quarter of a standard deviation was 20% in the experimental group and 0% in the control group ($p = 0.029$).

4. Discussion

The primary aim of this study was to evaluate the feasibility of a VR–based protocol specifically designed to stimulate cognitive functioning in older adults. From this perspective, the protocol demonstrated

Table 5
Dysregulation of social and behavioral rhythms by Time and Group.

	Score SBSR T0 mean ± sd	Score SBSR T1 mean ± sd	Difference T1-T0 ± sd
Experimental	30.40 ± 13.50	30.15 ± 13.33	0.25 ± 9.77
Control	27.92 ± 10.43	33.57 ± 14.10	−5.65 ± 7.12
Statistics (ANOVA 1 way)	$F(1,32) = 0.332$	$F(1,32) = 0.517$	$F(1,32) = 3.912$
p	0.568	0.477	0.056
N (%) with improving rhythms of at least ¼ of sd (experimental)			5/20 (25%)
N (%) with improving rhythms of at least ¼ of sd (control)			0/17 (0%)
Chi square			4.919 $p = 0.029$

Legend: SBRS (Social and behavioral Rhythms); N (number of subjects); % (percentage); sd (standard deviation).

Table 4
Comparison at T0 and T1 of general cognitive functioning and depressive symptoms.

	MMSE T0 mean ± sd	MMSE T1 mean ± sd	MMSE difference T1-T0 ±sd	ACE-R T0 mean ± sd	ACE-R T1 mean ± sd	ACE-R difference T1-T0 ± sd	PHQ-9 T0 mean ± sd	PHQ-9 T1 mean ± sd	PHQ-9 difference T1-T0 ± sd
Control Sample (N = 14)	26.35 ± 2.04	28.78 ± 0.86	2.43 ± 1.61	77.86 ± 5.19	83.43 ± 6.97	5.57 ± 4.91	5.28 ± 2.76	4.5 ± 1.72	−0.78 ± 2.31-
Experimental Sample (N = 20)	25.85 ± 1.87	26.85 ± 3.61	1.00 ± 2.30	74.66 ± 7.80	77.62 ± 11.08	2.96 ± 5.88	5.79 ± 4.32	5.3 ± 3.88	−0.49 ± 2.04
Experimental Standardized (N = 14)	26.00 ± 1.73	27.35 ± 2.63	1.35 ± 2.85	75.77 ± 8.45	79.96 ± 10.33	4.19 ± 5.12	6.35 ± 4.93	5.78 ± 4.45	−0.57 ± 3.93
Statistics Experimental vs Control (ANOVA 1 way)	$F(1,32) = 0.547$ $p = 0.465$	$F(1,32) = 3.816$; $p = 0.060$	$F(1,32) = 4.015$; $p = 0.054$	$F(1,32) = 1.798$ $p = 0.189$	$F(1,32) = 3.01$ $p = 0.093$	$F(1,32) = 1.850$, $p = 0.183$	$F(1,32) = 0.151$ $p = 0.700$	$F(1,32) = 0.520$ $p = 0.476$	$F(1,32) = 0.149$ $p = 0.702$
Statistics Standardized Experimental vs Control (ANOVA 1 way)	$F(1,25) = 0.291$ $p = 0.593$	$F(1,26) = 3.739$ $p = 0.064$	$F(1,32) = 1.524$ $p = 0.228$	$F(1,26) = 0.624$ $p = 0.437$	$F(1,26) = 1.083$ $p = 0.308$	$F(1,26) = 0.643$ $p = 0.428$	$F(1,26) = 0.501$ $p = 0.485$	$F(1,26) = 1.000$ $p = 0.327$	$F(1,26) = 0.050$ $p = 0.825$

Legend: MMSE (Mini Mental State Examination); PHQ-9 (Patient Health Questionnaire 9 items); ACE-R (Adensbruck cognitive Esamination-Revised); N (number of subjects); % (percentage); sd (standard deviation).

good applicability, as reflected by a lower dropout rate in the experimental group compared to the control group. Although this difference did not reach statistical significance, it approached significance and may suggest a trend toward greater acceptability of the VR-based intervention. One aspect that may have contributed to this result is the adoption of a naturalistic and ecologically valid virtual environment. As highlighted in the background, the scenarios (such as sailing in open sea and harbor settings) were specifically designed to enhance immersion and realism. This VR scenarios design choice is consistent with emerging evidence indicating that naturalistic VR environments can increase engagement, motivation, and overall acceptability, particularly in older adults and clinical populations [42]. In this context, greater engagement may play a key role in supporting adherence to the intervention, which represents a well-known challenge in traditional cognitive training programs often perceived as repetitive or insufficiently stimulating, particularly by older adults. At the same time, an important methodological aspect should be considered when interpreting the present findings. Although both groups participated in digitally delivered interventions over the same study period (6 weeks), the frequency and total amount of intervention exposure differed between conditions. Specifically, participants in the experimental group received two VR sessions per week for a total of 12 sessions, whereas participants in the control group attended one digital webinar every two weeks for a total of 3 sessions. Therefore, while both interventions maintained a digital format and were comparable in terms of overall duration, the unequal treatment dose represents a potential confounding factor, as differences in outcomes may partly reflect the greater frequency of contact and exposure in the experimental group rather than the specific effects of the VR-based intervention alone. This aspect should be considered when interpreting the results and should be addressed in future randomized controlled trials by matching intervention dose and contact frequency across study arms.

Beyond this consideration, other limitations of the present study should also be acknowledged. The sample size was small, and the duration of the intervention was shorter than that of previous studies that reported significant effects on cognitive decline [33]. These factors may have limited the ability to detect between-group differences. Interestingly, not only did the experimental group fail to show clear improvements, but a trend toward improvement was observed in the control group. This unexpected finding may offer useful insights for future research, suggesting the need for larger samples, longer intervention periods, and potentially a more intensive or tailored use of VR-based cognitive training protocols.

Two baseline characteristics of the sample warrant consideration. First, an imbalance in general cognitive performance was observed between groups, with higher baseline scores in the control group, even the MCI screening was in line with the eligible criteria for both groups. Thus, it reflects a pre-intervention group difference rather than a study result. Future studies should consider incorporating baseline cognitive performance into the randomization procedure (e.g., block randomization) in addition to sex and age, in order to reduce the risk of baseline imbalance.

Second, a relatively high proportion of participants across the sample showed relatively high depressive symptoms scores. In older adults, the co-occurrence of MCI and depressive symptomatology has been associated with conditions such as vascular depression [73,74], which has been hypothesized to be less responsive to cognitive rehabilitation approaches, including VR-based interventions [75,76]. This interpretation should be considered cautiously and requires confirmation in larger, well-characterized samples.

Within the tertiary outcomes, social and biological rhythm regulation showed a differential pattern between groups. Although between-group differences in mean SBRS change scores (T1-T0) did not reach statistical significance, a trend toward greater stability in the experimental group was observed. However, interpretation of this finding requires caution, as social and biological rhythm measures are sensitive not only to clinical status but also to contextual, environmental, and study-related factors. In particular, variability in daily routines and rhythm stability in older adults may be influenced by seasonal and temporal fluctuations [77–79], and the tendency toward worsening social rhythms observed in the control group may therefore be consistent with naturally occurring variability. Beyond these natural influences, rhythm regularity may also be affected by the external structuring imposed by study participation itself, including the frequency and scheduling of participant contacts. In the present trial, both the experimental and control groups followed comparable assessment schedules and participated in structured activities, namely immersive VR sessions and online webinars, respectively. Consequently, participation in either study condition may have provided a more regular temporal framework and increased behavioral structuring, potentially contributing to rhythm stabilization irrespective of the specific intervention content. Therefore, the observed differences in SBRS should be interpreted as reflecting a combination of intervention-specific effects and non-specific effects related to contact frequency and routine regularization.

At the same time, these findings remain clinically meaningful, as regularity of social and biological rhythms has consistently been associated with mental health and cognitive functioning. Dysregulation of social and biological rhythms has been widely identified as a risk factor for mood disorders, including major depressive disorder (MDD) [80], and bipolar disorder [81], as well as for cognitive impairment [47–49]. Moreover, previous evidence suggests that maintaining regular rhythms may promote resilience to stress and contribute to psychological well-being [55].

Accordingly, to further explore the potential clinical relevance of our findings, we conducted an ad hoc exploratory analysis applying a clinically oriented threshold, defining improvement as a change of at least one-quarter of a standard deviation from the normative sample. Participants were subsequently classified as improved or not improved according to this criterion. Using this exploratory categorization, 5 out of 20 participants in the experimental group met the improvement threshold, compared with 0 out of 17 participants in the control group. Although this analysis was not pre-specified and should therefore be interpreted with caution, it provides preliminary information regarding the potential clinical relevance and magnitude of the observed changes, which may help inform the design and sample size estimation of future trials.

As is typical for Phase II exploratory studies, these results may inform the design and sample size estimation of a subsequent Phase III trial. In particular, future studies should ensure equivalence between study arms in terms of contact frequency and temporal structure in order to disentangle specific intervention effects from non-specific scheduling effects. Longer follow-up periods will also be necessary to determine whether short-term stabilization of rhythms translates into downstream effects on mood and cognitive outcomes.

In conclusion, this study confirms the feasibility and safety of the immersive virtual reality intervention, with a low incidence of adverse effects, in line with its primary objective. Efficacy-related findings should be interpreted as preliminary and with caution, given the limited sample size, short intervention duration, and baseline imbalances between groups. Nonetheless, these results support further investigation of this approach, with methodological refinements, including improved balance of baseline cognitive performance across study arms.

4.1. Limitations

Several limitations of the present study should be acknowledged. First, the small sample size and the short duration of the intervention substantially limit the statistical power and the ability to detect meaningful between-group differences in cognitive and affective outcomes. As expected in a feasibility trial, the study was not designed to demonstrate efficacy; however, these factors likely contributed to the absence of observable advantages of the experimental intervention over the

control condition. Second, the baseline differences in cognitive performance between groups, with higher scores in the control group, may have generated a ceiling effect, reducing the sensitivity of the cognitive measures to change. This suggests that future trials should consider stratified or block randomization based on baseline cognitive levels. Third, the experimental and control groups received substantially different amounts of intervention. Consequently, any between-group differences may have been influenced not only by the intervention content but also by the greater treatment exposure received by the experimental group. Future randomized controlled trials should match intervention dose across study arms to better isolate the specific effects of immersive virtual reality.

Fourth, depressive symptoms were highly prevalent across the sample, raising the possibility that underlying conditions such as vascular depression may have influenced responsiveness to cognitive rehabilitation, particularly in immersive virtual reality settings. Finally, the lack of blinding of participants and professionals, inherent to the nature of the intervention, may have introduced expectancy or performance biases. Taken together, these limitations highlight the need for larger, adequately powered phase III trials with longer follow-up periods, more refined participant stratification, and careful consideration of control conditions to better evaluate the potential efficacy of immersive virtual reality-based cognitive interventions in older adults with MCI.

CRediT authorship contribution statement

Federica Sancassiani: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization. **Alessandra Perra:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Veronica Vacca:** Writing – review & editing, Investigation. **Mariarita Monni:** Writing – review & editing, Investigation. **Andrea Corrias:** Writing – review & editing, Investigation. **Stefano Lorrai:** Writing – review & editing, Investigation. **Federico Arippa:** Writing – review & editing, Investigation. **Giulia Lorrai:** Writing – review & editing, Investigation. **Daniele Carta:** Writing – review & editing, Investigation. **Mariella Ardu:** Writing – review & editing, Investigation. **Francesco Muscas:** Writing – review & editing, Investigation. **Francesca Muggianu:** Writing – review & editing, Investigation. **Massimiliano Pau:** Writing – review & editing, Methodology, Formal analysis. **Roberta Montisci:** Writing – review & editing, Supervision, Methodology. **Stefania Redolfi:** Writing – review & editing, Supervision, Methodology. **Donatella Petretto:** Writing – review & editing, Supervision, Methodology. **Angelo Scuteri:** Writing – review & editing, Supervision, Methodology. **Sergio Machado:** Writing – review & editing, Supervision, Methodology. **Antonio E. Nardi:** Writing – review & editing, Supervision, Methodology. **Mauro G. Carta:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Ethical considerations

Ethical approval was obtained from the Institutional Ethics Committee of the Region of Sardinia on September 18, 2025, under protocol number 25569. This approval should be regarded as a continuation of Protocol No. PG/2018/8822, as well as of the subsequent amendment dated May 28, 2023. All study procedures adhered to the principles of the Declaration of Helsinki (World Medical Association, 2009). Data collection was anonymous, and participation was voluntary, with the option to withdraw at any time without consequence. Contact information, including a phone number and email address, was provided to participants seeking further information or clarification.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data supporting the findings of this study are not publicly available.

References

[1] Organisation for Economic Co-operation and Development, Dementia: Health at a Glance 2025, OECD, 2025. https://www.oecd.org/en/publications/health-at-a-glance-2025_8f9e3f98-en/full-report/dementia_8b14a2ea.html (accessed February 27, 2026).
[2] World Health Organization, Ageing and health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health, 2025 (accessed February 27, 2026).
[3] C. de Meijer, O. O'Donnell, M. Koopmanschap, E. van Doorslaer, Health expenditure growth: looking beyond the average through decomposition of the full distribution, J. Health Econ. 32 (2013) 88–105, https://doi.org/10.1016/j.jhealeco.2012.10.009.
[4] G.A. Williams, J. Cylus, T. Roubal, P. Ong, S. Barber, Sustainable Health Financing with an Ageing Population: Will Population Ageing Lead to Uncontrolled Health Expenditure Growth? European Observatory on Health Systems and Policies, Copenhagen (Denmark), 2019. http://www.ncbi.nlm.nih.gov/books/NBK550604/ (accessed February 27, 2026).
[5] G. Livingston, J. Huntley, A. Sommerlad, D. Ames, C. Ballard, S. Banerjee, C. Brayne, A. Burns, J. Cohen-Mansfield, C. Cooper, S.G. Costafreda, A. Dias, N. Fox, L.N. Gitlin, R. Howard, H.C. Kales, M. Kivimäki, E.B. Larson, A. Ogunniyi, V. Orgeta, K. Ritchie, K. Rockwood, E.L. Sampson, Q. Samus, L.S. Schneider, G. Selbæk, L. Teri, N. Mukadam, Dementia prevention, intervention, and care: 2020 report of the *Lancet* commission, Lancet 396 (2020) 413–446, https://doi.org/10.1016/S0140-6736(20)30367-6.
[6] J.A. Valdevila Figueira, R. Valdevila Santiesteban, I.D. Carvajal Parra, L. P. Benenaula Vargas, A. Ramírez, J.E. Leon-Rojas, J.A. Rodas, Multimorbidity patterns in dementia and mild cognitive impairment, Front. Psychiatry 15 (2024) 1432848, https://doi.org/10.3389/fpsyt.2024.1432848.
[7] P.C. Zee, H. Attarian, A. Videnovic, Circadian rhythm abnormalities, Continuum (Minneap Minn) 19 (2013) 132–147, https://doi.org/10.1212/01.CON.0000427209.21177.aa.
[8] P. Li, L. Gao, A. Gaba, L. Yu, L. Cui, W. Fan, A.S.P. Lim, D.A. Bennett, A. S. Buchman, K. Hu, Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults, Lancet Healthy Longev. 1 (2020) e96–e105, https://doi.org/10.1016/S2666-7568(20)30015-5.
[9] P. Gopalakrishnan, S. Tiwari, R. Nagaraja, G. Krishnan, Quality of life in persons with mild cognitive impairment: a systematic review and meta-analysis, Dement. Neuropsychol. 18 (2024) e20230093, https://doi.org/10.1590/1980-5764-DN-2023-0093.
[10] Z. Pu, H. Huang, M. Li, H. Li, X. Shen, L. Du, Q. Wu, X. Fang, X. Meng, Q. Ni, G. Li, D. Cui, Screening tools for subjective cognitive decline and mild cognitive impairment based on task-state prefrontal functional connectivity: a functional near-infrared spectroscopy study, Neuroimage 310 (2025) 121130, https://doi.org/10.1016/j.neuroimage.2025.121130.
[11] European Commission, Health, Demographic Change and Wellbeing. Horizon 2020. https://www.h2020.md/en/content/health-demographic-change-and-wellbeing, 2020 (accessed February 27, 2026).
[12] World Health Organization, in: World Health Organization, Geneva (Ed.), Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines, 2019.
[13] V.L. Forman-Hoffman, M. Flom, A. Williams, T. Mariano, Prevalence of mild to moderate mental illness, correlates of treatment patterns, and perceived unmet need among U.S. adults: results from the National Survey on Drug Use and Health, 2021, Clin. Pract. Epidemiol. Ment. Health 21 (2025) e17450179394114, https://doi.org/10.2174/0117450179394114251013063017.
[14] M.G. Carta, G. Cossu, E. Pintus, R. Zoccheddu, O. Callia, G. Conti, M. Pintus, C.I. A. Gonzalez, M.V. Massidda, G. Mura, C. Sardu, P. Contu, L. Minerba, R. Demontis, M. Pau, G. Finco, E. Cocco, M.P. Penna, G. Orrù, G. Kalcev, F. Cabras, S. Lorrai, A. Loviselli, F. Velluzzi, M. Monticone, E. Cacace, M. Musu, F. Rongioletti, A. Cauli,

V. Ruggiero, A. Scano, A. Crisafulli, S. Cosentino, L. Atzori, E. Massa, Q. Mela, D. Fortin, G. Migliaccio, A.E. Nardi, M. Angermeyer, A. Preti, Active elderly and health-can moderate exercise improve health and wellbeing in older adults? Protocol for a randomized controlled trial, Trials 22 (2021) 331, https://doi.org/10.1186/s13063-021-05278-6.

[15] L.F. de Souza, A.S.S. Filho, F. Paes, V. Aprigliano, P.A. Inacio, S. Machado, Acute effects of multicomponent training, resistance training and walking on affect and enjoyment of healthy elderly individuals: a randomized cross-sectional study, Clin. Pract. Epidemiol. Ment. Health 21 (2025) e17450179371185, https://doi.org/10.2174/0117450179371185250521110952.

[16] M.C. Hardoy, M.L. Seruis, F. Floris, F. Sancassiani, M.F. Moro, G. Mellino, M. E. Lecca, S. Adamo, M.G. Carta, Benefits of exercise with mini tennis in intellectual disabilities: effects on body image and psychopathology, Clin. Pract. Epidemiol. Ment. Health 7 (2011) 157–160, https://doi.org/10.2174/1745017901107010157.

[17] G. Mura, F. Sancassiani, G.M. Migliaccio, G. Collu, M.G. Carta, The association between different kinds of exercise and quality of life in the long term. Results of a randomized controlled trial on the elderly, Clin. Pract. Epidemiol. Ment. Health 10 (2014) 36–41, https://doi.org/10.2174/1745017901410010036.

[18] S.R. McGurk, K.T. Mueser, Introduction to special issue on cognitive remediation, Psychiatr. Rehabil. J. 40 (2017) 1–3, https://doi.org/10.1037/prj0000263.

[19] L. Mendes, J. Oliveira, F. Barbosa, M. Castelo-Branco, A conceptual view of cognitive intervention in older adults with and without cognitive decline-a systemic review, Front Aging 3 (2022) 844725, https://doi.org/10.3389/fragi.2022.844725.

[20] S. Yun, S. Ryu, The effects of cognitive-based interventions in older adults: a systematic review and Meta-analysis, Iran. J. Public Health 51 (2022) 1–11, https://doi.org/10.18502/ijph.v51i1.8286.

[21] J.L. Lima, P.A. Inacio, A. Sá Filho, F. Paes, R. Ferreira-Garcia, L. Lage, V. Aprigliano, M.G. Carta, H. Budde, A.E. Nardi, S. Machado, Effectiveness of virtual reality rehabilitation with exergames on functional rehabilitation in Parkinson's disease: a systematic review of chronic randomized controlled trials, Expert. Rev. Neurother. 25 (2025) 1357–1370, https://doi.org/10.1080/14737175.2025.2559180.

[22] S. Machado, F. Paes, R. Ferreira-Garcia, L.L. Gonçalves, M.G. Carta, J. C. Appolinario, A.E. Nardi, Virtual reality: challenges and perspectives in mental Health, Alpha Psychiat. 26 (2025) 47536, https://doi.org/10.31083/AP47536.

[23] M.G. Carta, A.E. Nardi, Virtual reality, social intelligence, mirror neurons, and bipolar spectrum: a new perspective, Braz. J. Psychiatry. 47 (2025) e20243901, https://doi.org/10.47626/1516-4446-2024-3901.

[24] G. Riva, S. Serino, Virtual reality in the assessment, understanding and treatment of mental health disorders, J. Clin. Med. 9 (2020) 3434, https://doi.org/10.3390/jcm9113434.

[25] Q. Du, Y. Wei, Y. Ma, C. Liu, S. Du, Q. Zhang, X. Gong, J. Yang, Q. Li, K. Li, Efficacy of virtual reality-based interventions on cognitive function in patients with neuropsychiatric disorders: systematic review and Meta-analysis of randomized controlled trials, JMIR Serious Games 13 (2025) e67501, https://doi.org/10.2196/67501.

[26] A. Ramalho, P. Duarte-Mendes, R. Paulo, J. Serrano, J. Petrica, Crossing the digital frontier: are older adults ready for virtual reality workouts? Front. Public Health 12 (2024) 1324004 https://doi.org/10.3389/fpubh.2024.1324004.

[27] C. Tortora, A. Di Crosta, P. La Malva, G. Prete, I. Ceccato, N. Mammarella, A. Di Domenico, R. Palumbo, Virtual reality and cognitive rehabilitation for older adults with mild cognitive impairment: a systematic review, Ageing Res. Rev. 93 (2024) 102146, https://doi.org/10.1016/j.arr.2023.102146.

[28] Y. Ren, Q. Wang, H. Liu, G. Wang, A. Lu, Effects of immersive and non-immersive virtual reality-based rehabilitation training on cognition, motor function, and daily functioning in patients with mild cognitive impairment or dementia: a systematic review and meta-analysis, Clin. Rehabil. 38 (2024) 305–321, https://doi.org/10.1177/02692155231213476.

[29] X. Li, Y. Zhang, L. Tang, L. Ye, M. Tang, Effects of virtual reality-based interventions on cognitive function, emotional state, and quality of life in patients with mild cognitive impairment: a meta-analysis, Front. Neurol. 16 (2025) 1496382, https://doi.org/10.3389/fneur.2025.1496382.

[30] Q. Yang, L. Zhang, F. Chang, H. Yang, B. Chen, Z. Liu, Virtual reality interventions for older adults with mild cognitive impairment: systematic review and Meta-analysis of randomized controlled trials, J. Med. Internet Res. 27 (2025) e59195, https://doi.org/10.2196/59195.

[31] K. Skivington, L. Matthews, S.A. Simpson, P. Craig, J. Baird, J.M. Blazeby, K. A. Boyd, N. Craig, D.P. French, E. McIntosh, M. Petticrew, J. Rycroft-Malone, M. White, L. Moore, A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance, BMJ 374 (2021) n2061, https://doi.org/10.1136/bmj.n2061.

[32] A. Perra, C.L. Riccardo, V. De Lorenzo, E. De Marco, L. Di Natale, P.K. Kurotschka, A. Preti, M.G. Carta, Fully immersive virtual reality-based cognitive remediation for adults with psychosocial disabilities: a systematic scoping review of methods intervention gaps and Meta-analysis of published effectiveness studies, Int. J. Environ. Res. Public Health 20 (2023) 1527, https://doi.org/10.3390/ijerph20021527.

[33] A. Perra, A. Galetti, R. Zaccheddu, A. Locci, F. Piludu, A. Preti, D. Primavera, L. Di Natale, A.E. Nardi, P.K. Kurotshka, G. Cossu, F. Sancassiani, G. Stella, V. De Lorenzo, T. Zreik, M.G. Carta, A recovery-oriented program for people with bipolar disorder through virtual reality-based cognitive remediation: results of a feasibility randomized clinical trial, J. Clin. Med. 12 (2023) 2142, https://doi.org/10.3390/jcm12062142.

[34] F. Sancassiani, A. Perra, P.K. Kurotschka, G. Kalcev, A. Galetti, R. Zaccheddu, A. Locci, F. Piludu, L. Di Natale, V. De Lorenzo, M. Fornaro, A.E. Nardi, D. Primavera, Improving social and personal rhythm dysregulation in Young and old adults with bipolar disorder: post-hoc analysis of a feasibility randomized controlled trial using virtual reality-based intervention, J. Clin. Med. 13 (2024) 3786, https://doi.org/10.3390/jcm13133786.

[35] D. Primavera, A. Urban, E. Cantone, M. Nonnis, C.I. Aviles Gonzalez, A. Perra, M. Tusconi, F. Sancassiani, The impact on anxiety symptoms of an immersive virtual reality remediation program in bipolar disorders: a randomized clinical trial, J. Clin. Med. 13 (2024) 4203, https://doi.org/10.3390/jcm13144203.

[36] C.A. Depp, B.T. Mausbach, A.L. Harmell, G.N. Savla, C.R. Bowie, P.D. Harvey, T. L. Patterson, Meta-Analysis of the Association Between Cognitive Abilities and Everyday Functioning in Bipolar Disorder, 2024.

[37] M. Simjanoski, A. McIntyre, F. Kapczinski, T. de Azevedo Cardoso, Cognitive impairment in bipolar disorder in comparison to mild cognitive impairment and dementia: a systematic review, Trends Psychiatry Psychother. 44 (2022) e20210300, https://doi.org/10.47626/2237-6089-2021-0300.

[38] L.D. Grandin, L.B. Alloy, L.Y. Abramson, The social zeitgeber theory, circadian rhythms, and mood disorders: review and evaluation, Clin. Psychol. Rev. 26 (2006) 679–694, https://doi.org/10.1016/j.cpr.2006.07.001.

[39] R.W. Logan, C.A. McClung, Rhythms of life: circadian disruption and brain disorders across the lifespan, Nat. Rev. Neurosci. 20 (2019) 49–65, https://doi.org/10.1038/s41583-018-0088-y.

[40] A.G. Harvey, G. Murray, R.A. Chandler, A. Soehner, Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms, Clin. Psychol. Rev. 31 (2011) 225–235, https://doi.org/10.1016/j.cpr.2010.04.003.

[41] Research Domain Criteria (RDoC), Toward a new classification framework for research on mental disorders, Am. J. Psychiatry 167 (7) (2026) 748–751. https://psychiatryonline.org/doi/10.1176/appi.ajp.2010.09091379 (accessed June 17, 2026).

[42] S. Pardini, S. Gabrielli, L. Gios, M. Dianti, O. Mayora-Ibarra, L. Appel, S. Olivetto, A. Torres, P. Rigatti, E. Trentini, L. Leonardelli, M. Bernardi, M. Lucianer, S. Forti, C. Novara, Customized virtual reality naturalistic scenarios promoting engagement and relaxation in patients with cognitive impairment: a proof-of-concept mixed-methods study, Sci. Rep. 13 (2023) 20516, https://doi.org/10.1038/s41598-023-47876-1.

[43] R. Menhas, H.M. Alghzawi, M.M. Saeed, H. Ali, Effectiveness of virtual reality-based nature interventions in promoting mental health outcomes among older adults with cognitive impairment: a systematic review and meta-regression analysis, Aust. J. Psychol. 78 (2026) 2679707, https://doi.org/10.1080/00049530.2026.2679707.

[44] M.G. Carta, G. Kalcev, A. Scano, D. Primavera, G. Orrù, O. Gureye, G. Cossu, A. E. Nardi, Is bipolar disorder the consequence of a genetic weakness or not having correctly used a potential adaptive condition? Brain Sci. 13 (2022) 16, https://doi.org/10.3390/brainsci13010016.

[45] G. Kalcev, G. Cossu, A. Preti, M.T. Littera, S. Frau, D. Primavera, R. Zaccheddu, V. Matza, M. Ermellino, E. Pintus, M.G. Carta, Development and validation of the questionnaire for adaptive hyperactivity and goal achievement (AHGA), Clin. Pract. Epidemiol. Ment. Health 19 (2023) e174501792303281, https://doi.org/10.2174/17450179-v19-e230419-2022-50.

[46] G. Kalcev, A. Scano, G. Orrù, D. Primavera, G. Cossu, A.E. Nardi, M.G. Carta, Is a genetic variant associated with bipolar disorder frequent in people without bipolar disorder but with characteristics of hyperactivity and novelty seeking? Clin. Pract. Epidemiol. Ment. Health 19 (2023) e174501792303280 https://doi.org/10.2174/17450179-v19-e230419-2022-53.

[47] S. Haghayegh, C. Gao, E. Sugg, X. Zheng, H.-W. Yang, R. Saxena, M.K. Rutter, M. Weedon, A. Ibanez, D.A. Bennett, P. Li, L. Gao, K. Hu, Association of Rest-Activity Rhythm and Risk of developing dementia or mild cognitive impairment in the middle-aged and older population: prospective cohort study, JMIR Public Health Surveill. 10 (2024) e55211, https://doi.org/10.2196/55211.

[48] T.S. Rogers-Soeder, T. Blackwell, K. Yaffe, S. Ancoli-Israel, S. Redline, J.A. Cauley, K.E. Ensrud, M. Paudel, E. Barrett-Connor, E. LeBlanc, K. Stone, N.E. Lane, G. Tranah, Osteoporotic fractures in men study research group, Rest-activity rhythms and cognitive decline in older men: the osteoporotic fractures in men sleep study, J. Am. Geriatr. Soc. 66 (2018) 2136–2143, https://doi.org/10.1111/jgs.15555.

[49] Q. Xiao, J.N. Sampson, A.Z. LaCroix, A.H. Shadyab, J.M. Zeitzer, S. Ancoli-Israel, K. Yaffe, K. Stone, Osteoporotic fractures in men (MrOS) study group, nonparametric parameters of 24-hour rest-activity rhythms and long-term cognitive decline and incident cognitive impairment in older men, J. Gerontol. A Biol. Sci. Med. Sci. 77 (2022) 250–258, https://doi.org/10.1093/gerona/glab275.

[50] M.G. Carta, U. Ouali, A. Perra, A. Ben Cheikh Ahmed, L. Boe, A. Aissa, S. Lorrai, G. Cossu, A. Aresti, A. Preti, F. Nacef, Living with bipolar disorder in the time of Covid-19: biorhythms during the severe lockdown in Cagliari, Italy, and the moderate lockdown in Tunis, Tunisia, Front. Psychiatry 12 (2021) 634765, https://doi.org/10.3389/fpsyt.2021.634765.

[51] U. Ouali, A. Aissa, S. Rejaibi, N. Zoghlami, A. Larnaout, Y. Zgueb, M. Zid, H. A. Skhiri, G. Kalcev, M. Tusconi, C.I. Aviles Gonzales, A. Preti, D. Primavera, Hyperactivity and risk for dysregulation of mood, energy, and social rhythms syndrome (DYMERS): standardization of a simple one-item screener versus the mood disorder questionnaire (MDQ), J. Clin. Med. 13 (2024) 4433, https://doi.org/10.3390/jcm13154433.

[52] S.M. Sabet, N.D. Dautovich, J.M. Dzierzewski, The rhythm is Gonna get you: social rhythms, sleep, depressive, and anxiety symptoms, J. Affect. Disord. 286 (2021) 197–203, https://doi.org/10.1016/j.jad.2021.02.061.

[53] S.F. Smagula, R.M. Boudreau, K. Stone, C.F. Reynolds, J.T. Bromberger, S. Ancoli-Israel, T.-T. Dam, E. Barrett-Connor, J.A. Cauley, Osteoporotic fractures in men (MrOS) research group, latent activity rhythm disturbance sub-groups and longitudinal change in depression symptoms among older men, Chronobiol. Int. 32 (2015) 1427–1437, https://doi.org/10.3109/07420528.2015.1102925.
[54] Y. Leng, T. Blackwell, P.M. Cawthon, S. Ancoli-Israel, K.L. Stone, K. Yaffe, Association of Circadian Abnormalities in older adults with an increased risk of developing Parkinson disease, JAMA Neurol. 77 (2020) 1270–1278, https://doi.org/10.1001/jamaneurol.2020.1623.
[55] M.G. Carta, M. Fornaro, L. Minerba, M. Pau, F. Velluzzi, L. Atzori, C.I. Aviles Gonzalez, F. Romano, R. Littera, L. Chessa, D. Firinu, S. Del Giacco, A. Restivo, S. Deidda, G. Orrù, A. Scano, S. Onali, F. Coghe, G. Kalcev, G. Cossu, Previous functional social and behavioral rhythms affect resilience to Covid-19-related stress among old adults, J. Public Health Res. 11 (2022) jphr.2022.2768, https://doi.org/10.4081/jphr.2022.2768.
[56] F. Sancassiani, A. Perra, V. Vacca, R. Montisci, M. Monni, S. Lorrai, G. Cossu, D. R. Petretto, L. di Natale, D. Primavera, S. Redolfi, A. Scuteri, A.E. Nardi, G. Kalcev, M. Pau, M.G. Carta, Enhancing cognitive functions in older adults with mild cognitive impairment via virtual sail 3D: protocol for a feasibility randomized controlled trial, JMIR Res Protoc 15 (2026) e85089, https://doi.org/10.2196/85089.
[57] S.M. Eldridge, C.L. Chan, M.J. Campbell, C.M. Bond, S. Hopewell, L. Thabane, G. A. Lancaster, PAFS consensus group, CONSORT 2010 statement: extension to randomised pilot and feasibility trials, BMJ 355 (2016) i5239, https://doi.org/10.1136/bmj.i5239.
[58] M. Siciliano, S. Raimo, D. Tufano, G. Basile, D. Grossi, F. Santangelo, L. Trojano, G. Santangelo, The Addenbrooke's cognitive examination revised (ACE-R) and its sub-scores: normative values in an Italian population sample, Neurol. Sci. 37 (2016) 385–392, https://doi.org/10.1007/s10072-015-2410-z.
[59] M. Pigliautile, M. Ricci, E. Mioshi, S. Ercolani, F. Mangialasche, R. Monastero, M. F. Croce, S. Federici, P. Mecocci, Validation study of the Italian Addenbrooke's cognitive examination revised in a young-old and old-old population, Dement. Geriatr. Cogn. Disord. 32 (2011) 301–307, https://doi.org/10.1159/000334657.
[60] European Parliament and of the Council, Regulation (EU) 2017/745. http://data.europa.eu/eli/reg/2017/745/oj, 2017 (accessed February 27, 2026).
[61] P. Brown, P. Spronck, W. Powell, The simulator sickness questionnaire, and the erroneous zero baseline assumption, Front. Virtual Real. 3 (2022), https://doi.org/10.3389/frvir.2022.945800.
[62] N. Habib, J. Stott, Systematic review of the diagnostic accuracy of the non-English versions of Addenbrooke's cognitive examination - revised and III, Aging Ment. Health 23 (2019) 297–304, https://doi.org/10.1080/13607863.2017.1411882.
[63] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198, https://doi.org/10.1016/0022-3956(75)90026-6.
[64] M. Pigliautile, F. Chiesi, S. Rossetti, M. Conestabile Della Staffa, M. Ricci, S. Federici, D. Chiloiro, C. Primi, P. Mecocci, Normative data for the ACE-R in an Italian population sample, Neurol. Sci. 36 (2015) 2185–2190, https://doi.org/10.1007/s10072-015-2330-y.
[65] G. Foderaro, V. Isella, A. Mazzone, E. Biglia, M. Di Gangi, F. Pasotti, F. Sansotera, M. Grobberio, V. Raimondi, C. Mapelli, F. Ferri, V. Impagnatiello, C. Ferrarese, I. M. Appollonio, Brand new norms for a good old test: northern Italy normative study of MiniMental state examination, Neurol. Sci. 43 (2022) 3053–3063, https://doi.org/10.1007/s10072-021-05845-4.
[66] E. Mazzotti, G. Fassone, A. Picardi, E. Sagoni, L. Ramieri, I. Lega, D. Camaioni, D. Abeni, P. Pasquini, Il Patient Health Questionnaire (PHQ) per lo screening dei disturbi psichiatrici: uno studio di validazione nei confronti della Intervista Clinica Strutturata per il DSM-IV asse I (SCID-I), Ital. J. Psychopathol. 9 (3) (2003) 235–242. https://old.jpsychopathol.it/article/il-patient-health-questionnaire-phq-per-lo-screening-dei-disturbi-psichiatrici-uno-studio-di-validazione-nei-confronti-della-intervista-clinica-strutturata-per-il-dsm-iv-asse-i-scid-i/ (accessed February 27, 2026).
[67] R. Rizzo, M. Piccinelli, M.A. Mazzi, C. Bellantuono, M. Tansella, The personal Health questionnaire: a new screening instrument for detection of ICD-10 depressive disorders in primary care, Psychol. Med. 30 (2000) 831–840, https://doi.org/10.1017/s0033291799002512.
[68] R.L. Spitzer, K. Kroenke, J.B. Williams, Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient Health questionnaire, JAMA 282 (1999) 1737–1744, https://doi.org/10.1001/jama.282.18.1737.
[69] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, American Psychiatric Association, 2013, https://doi.org/10.1176/appi.books.9780890425596.
[70] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (2001) 606–613, https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
[71] G. Cossu, M. Agus, L. Atzori, C.I. Aviles Gonzales, L. Minerba, C. Ferreli, R. Puxeddu, G. Orrù, A. Scano, F. Romano, E. Pintus, M.P. Penna, M.G. Carta, Principal component analysis of the social and Behavioral rhythms scale in elderly, J. Public Health Res. 11 (2021) 2546, https://doi.org/10.4081/jphr.2021.2546.
[72] C. Goumopoulos, G. Skikos, M. Frounta, Feasibility and effects of cognitive training with the COGNIPLAT game platform in elderly with mild cognitive impairment: pilot randomized controlled trial, Games. Health. J. 12 (2023) 414–425, https://doi.org/10.1089/g4h.2023.0029.
[73] G.S. Alexopoulos, B.S. Meyers, R.C. Young, S. Campbell, D. Silbersweig, M. Charlson, "Vascular depression" hypothesis, Arch. Gen. Psychiatry 54 (1997) 915–922, https://doi.org/10.1001/archpsyc.1997.01830220033006.
[74] K.A. Jellinger, Pathomechanisms of vascular depression in older adults, Int. J. Mol. Sci. 23 (2021) 308, https://doi.org/10.3390/ijms23010308.
[75] M.G. Carta, C.I. Aviles Gonzalez, L. Minerba, M. Pau, M. Musu, F. Velluzzi, C. Ferreli, E. Pintus, S. Machado, F. Romano, V. Vacca, A. Preti, G. Cossu, L. Atzori, Exercise in older adults to prevent depressive symptoms at the time of Covid-19: results of a randomized controlled trial with follow-up, Clin. Pract. Epidemiol. Ment. Health 18 (2022) e174501792112231, https://doi.org/10.2174/17450179-v18-e2112231.
[76] D. Primavera, C. Aviles Gonzalez, A. Perra, G. Kalcev, E. Cantone, G. Cossu, A. Holzinger, M.G. Carta, F. Sancassiani, Virtual reality cognitive remediation in older adults with bipolar disorder: the effects on cognitive performance and depression in a feasibility randomized controlled trial, Healthcare (Basel) 12 (2024) 1753, https://doi.org/10.3390/healthcare12171753.
[77] M.G. Carta, G. Cossu, E. Pintus, R. Zaccheddu, O. Callia, G. Conti, M. Pintus, C. I. Aviles Gonzalez, M.V. Massidda, G. Mura, C. Sardu, P. Contu, L. Minerba, R. Demontis, M. pau, G. Finco, E. Cocco, M.P. Penna, G. Orr, G. Kalcev, F. Cabras, S. Lorrai, A. Loviselli, F. Velluzzi, M. Monticone, E. Cacace, M. Musu, F. Rongioletti, A. Cauli, V. Ruggiero, A. Scano, A. Crisafulli, S. Cosentino, L. Atzori, E. Massa, Q. Mela, D. Fortin, G. Migliaccio, S. Machado, F. Romano, A. Preti, Moderate exercise improves cognitive function in healthy elderly people: results of a randomized controlled trial, Clin. Pract. Epidemiol. Ment. Health 17 (2021) 75–80, https://doi.org/10.2174/1745017902117010075.
[78] Y. Höller, B.E. Gudjónsdottir, S.K. Valgeirsdóttir, G.T. Heimisson, The effect of age and chronotype on seasonality, sleep problems, and mood, Psychiatry Res. 297 (2021) 113722, https://doi.org/10.1016/j.psychres.2021.113722.
[79] T.E. Perry, Seasonal variation and homes: understanding the social experiences of older adults, Care Manag. J. 15 (2014) 3–10, https://doi.org/10.1891/1521-0987.15.1.3.
[80] R. Lieverse, R. de Vries, A.W. Hoogendoorn, J.H. Smit, W.J.G. Hoogendijk, Social support and social rhythm regularity in elderly patients with major depressive disorder, Am. J. Geriatr. Psychiatry 21 (2013) 1144–1153, https://doi.org/10.1016/j.jagp.2013.01.052.
[81] E.C.-L. Lin, M.J. Weintraub, D.J. Miklowitz, P.-S. Chen, S.-K. Lee, H.-C. Chen, R.-B. Lu, The associations between illness perceptions and social rhythm stability on mood symptoms among patients with bipolar disorder, J. Affect. Disord. 273 (2020) 517–523, https://doi.org/10.1016/j.jad.2020.05.019.