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Protocol

Training Cognitive Functions Using DUAL-REHAB, a New Dual-Task Application in MCI and SMC: A Study Protocol of a Randomized Control Trial

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Abstract: Background: Current research on Alzheimer's Disease has progressively focused on Mild Cognitive Impairment (MCI) as a pre-dementia state, as well as on Subjective Memory Complaint (SMC), as a potential early indicator of cognitive change. Consequently, timely interventions to prevent cognitive decline are essential and are most effective when combined with motor training. Nevertheless, motor-cognitive dual-task training often employs non-ecological tasks and is confined to clinical contexts lacking generalizability to daily life. The integration of 360° media could overcome these limitations. Therefore, the aim of the current work is twofold: (a) to present a dual-task training using 360° technology for its interactivity, versatility, and ecological validity, and (b) to propose a protocol to test its efficacy through a randomized clinical trial. Methods: This study will recruit 90 older adults (MCI and SMC). Participants will follow two phases of training: in-hospital rehabilitation and at-home rehabilitation. The experimental design will follow a 2 × 3 × 2 structure with 3 factors: type of treatment (360° training vs. traditional rehabilitation), time (baseline, post in-hospital training, and post at-home training), and group (SMC vs. MCI). Results: The expected outcome is an improvement in cognitive and motor functioning after the experimental training. Conclusion: This study will advance the literature on non-pharmacological interventions and innovative technological tools for cognitive trainings in the early stages of cognitive decline.

Keywords: dual-task; rehabilitation; 360-degree video; aging; cognitive impairment

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1. Introduction

According to the World Alzheimer Report (2022) [1], the projected number of individuals affected by dementia in 2050 is approximately 139 million. Within this population, it is estimated that Alzheimer's disease (AD) accounts for approximately 70–80% of diagnosed cases [2]. The aforementioned statistics are experiencing a significant surge due to the continuous rise in life expectancy [3,4]. The underlying pathophysiological mechanisms in AD manifest over an extended period, ranging from several years to several decades, preceding the onset of the clinical syndrome characterized by dementia [5]. The pre-dementia phase presents an opportunity to mitigate deterioration, underscoring the importance of promptly

addressing subtle cognitive changes during this interval [6,7]. Therefore, current research on AD has increasingly focused on comprehending and addressing pre-dementia clinical states, including Mild Cognitive Impairment (MCI). MCI is conceptualized as a transitional phase that occurs between normal and pathological cognitive aging. It is characterized by a gradual decline in cognitive functions, with a particular emphasis on memory, although other cognitive domains may also be affected. Individuals with MCI typically exhibit the ability to maintain a majority of their functional and daily activities, despite the presence of cognitive decline. However, they do not fulfill the specific criteria necessary for a definitive diagnosis of dementia. The etiology, type of cognitive domain impaired, and extent of functional impairment in this condition exhibit significant heterogeneity [8–10].

Recent studies have significantly broadened the scope of research on the early stages of cognitive decline, particularly focusing on Subjective Memory Complaint (SMC). Although SMC is not included as a generally accepted nosological entity, for the pre-dementia stages, it is often considered a stage antedating objective impairment and an at-risk condition for subsequent dementia [11]. SMC refers to individuals' self-reported perception of memory decline relative to their previous cognitive abilities, without any identifiable organic or major psychiatric causes [12]. Although the potential implications of SMC are noteworthy, there is a notable lack of assessment with neuropsychological and cognitive measures for this condition. Furthermore, research on SMC is even more scarce than MCI [12]. Furthermore, this terminology may lead to ambiguity, as it has been employed in certain instances to refer to individuals exhibiting verifiable impairments in memory function [13]. At the same time, in other cases, it has been associated with elevated levels of anxiety and depression [14,15]. While a segment of the literature is dedicated to enhancing the diagnostic criteria for pre-dementia stages, another segment focuses on developing specific therapeutic interventions. Considerable efforts have been dedicated to advancing pharmacological and non-pharmacological interventions in various studies [16–18]. Particularly, recent literature highlights a growing focus on dual-task (DT) [7,19–21]. Exercise-based interventions incorporating DT training have gained considerable attention in recent years as a promising approach in the field [19,22,23]. DT training includes either two motor tasks (motor–motor DT) or one motor task and one cognitive task (motor–cognitive DT). Regardless of the types of tasks involved, DT is defined as the simultaneous execution of two tasks that can be completed independently, be measured independently, and have different objectives [24]. These interventions have shown great potential and are becoming increasingly recognized as a viable option. Numerous researchers have observed the positive impacts of DT training on various aspects such as balance, mobility, overall functional status, as well as general cognition, memory, and attention [10,19,23].

The DT training appears to facilitate the activation of the supplementary motor area and premotor cortex, enhance neural efficiency, increase the utilization of neural resources, upregulate neurotrophic factor levels, and subsequently promote neuroplasticity [7,25,26]. According to a recent review, individuals with MCI who engage in DT training exhibit varied outcomes in terms of their motor and cognitive functions; specifically, when compared to active control groups, MCI patients showed greater improvements in executive functions, memory, and global cognition. Additionally, they also exhibited improvements in gait, strength, mobility, balance, cardiorespiratory fitness, and physical activity levels [25]. Nevertheless, the impact of DT training on mitigating falls has not been definitively established, and it remains uncertain whether the motor and cognitive tasks should be executed consecutively or concurrently [25]. The aforementioned finding deviates from a prior study, which demonstrated that engaging in concurrent cognitive and motor tasks yields more substantial enhancements in cognitive function [26,27].

Given that this field of study is relatively new, several unresolved practical considerations exist regarding treatments. Specifically, the most effective dosage, encompassing the frequency, duration, and length of the sessions, has yet to be clearly defined. Furthermore, it has been observed that while group interventions have a positive impact on cognitive and physical functions, individualized rehabilitation may be more effective in enhancing specific motor aspects, such as reducing fall rates [25]. Although the effectiveness of DT training remains consistent regardless of treatment dose and modalities, it is imperative for future research to address this issue considering patients' attributes.

Furthermore, most of these training sessions have been conducted within controlled laboratory settings or in commercially available gaming environments, thereby constraining the generalizability of acquired skills to real-world contexts [28–30]. One potential solution to this problem is using 360° technology, which allows the curation of ecological, evidence-based, and cost-effective solutions [31–33]. With these instruments, patients are immersed in 360° real-life situations and can be actively involved in engaging in cognitive and physical exercises, thus offering greater chances for transferring abilities to real life [34]. Furthermore, these environments also facilitate the integration of multiple sensory modalities, such as visual, auditory, and motor stimuli, which, in turn, have a positive impact on the brain's ability to adapt and change (i.e., brain plasticity) [35].

Despite the broad panorama of interventions described in the literature, research has predominantly focused on addressing cognitive [36–38], as well as motor [39], impairments in patients with MCI and dementia [18]. However, there remains a paucity of research investigating the efficacy of cognitive stimulation interventions specifically in patients with SMC.

On these bases, we explored using 360° media to create a DT training program for improving cognitive and motor abilities in individuals with SMC and MCI. The adaptable nature of 360° technology enables the integration of DT exercises into realistic, yet controlled, safe environments.

2. Materials and Methods

2.1. Description of the Protocol: DUAL-REHAB Training

Based on protocol objectives, we propose DUAL-REHAB: a dual-task training application that requires the simultaneous performance of cognitive and motor tasks, utilizing 360° media technology. This intervention will be designed to be implemented in two distinct phases, each with specific delivery modalities: an immersive hospital-based phase and a non-immersive home-based one. This dual-modality approach was selected to maximize the discussed benefits of immersive virtual reality in clinical settings while addressing potential safety concerns during unsupervised home-based training. Additionally, this design enables training opportunities beyond the clinical environment, allowing participants to maintain consistent practice in their home settings.

DUAL-REHAB requires participants to perform cognitive and motor tasks simultaneously. While continuously maintaining a cycling or stepping rhythm synchronized with a metronome, participants must concurrently perform cognitive tasks targeting attention, memory, and executive function (e.g., responding to auditory cues by reversing pedaling direction while maintaining a specific cycling rhythm). The intervention will be structured into 10 sessions for each modality, with progressive difficulty levels to ensure appropriate challenge and engagement. Each session will comprise approximately 10 interconnected exercises embedded within scenarios, such as simulated workday activities and mountain excursions. These contextual scenarios serve as cohesive frameworks within which participants complete specific rehabilitation exercises. The exercises will be performed

through either a head-mounted display (HMD) for immersive sessions or a tablet device for non-immersive sessions, in conjunction with gym equipment (i.e., a cycle ergometer).

The training program will be structured into two sequential phases, each comprising 10 biweekly sessions of about 45 min duration: (i) in-hospital rehabilitation, where older adults will receive 10 sessions of the 360° DT training under professional supervision from psychologists and physiotherapists, and (ii) at-home rehabilitation, where older adults will engage with the non-immersive version after a teaching session to become familiar with the technology.

2.2. Study Design

This study will aim to examine the efficacy of a novel 360° DT training for improving cognitive and motor functioning in two different populations: older individuals reporting SMC and older adults with MCI. To achieve this objective, a randomized clinical trial will be conducted. Within each group (SMC vs. MCI), individuals will be randomly assigned to the experimental training group (i.e., DUAL-REHAB application training) or the control group (a traditional rehabilitation program of the same duration).

The experimental group will complete the DUAL-REHAB program, which includes both the hospital-based immersive phase and the home-based non-immersive phase. Participants assigned to the control group will follow a similar training period in a DT traditional rehabilitation program. This intervention comprises in-hospital conventional cognitive exercises (delivered via paper and pencil and computer), as well as physical practice using gym equipment with supervision from specialized clinicians. In contrast to tablet-based exercises performed at home, participants will receive cognitive and motor exercises through a paper and pencil protocol with gym equipment (e.g., a portable cycle ergometer) for their rehabilitation treatment at home. Both interventions consist of 10 biweekly sections. Specifically, the proposed experimental design will be $2 \times 3 \times 2$ with these 3 main factors: (i) type of treatment (360° DT training vs. traditional rehabilitation program), (ii) time (baseline, after in-hospital training, and after at-home training), and (iii) group (SMC vs. MCI), as shown in Figure 1.

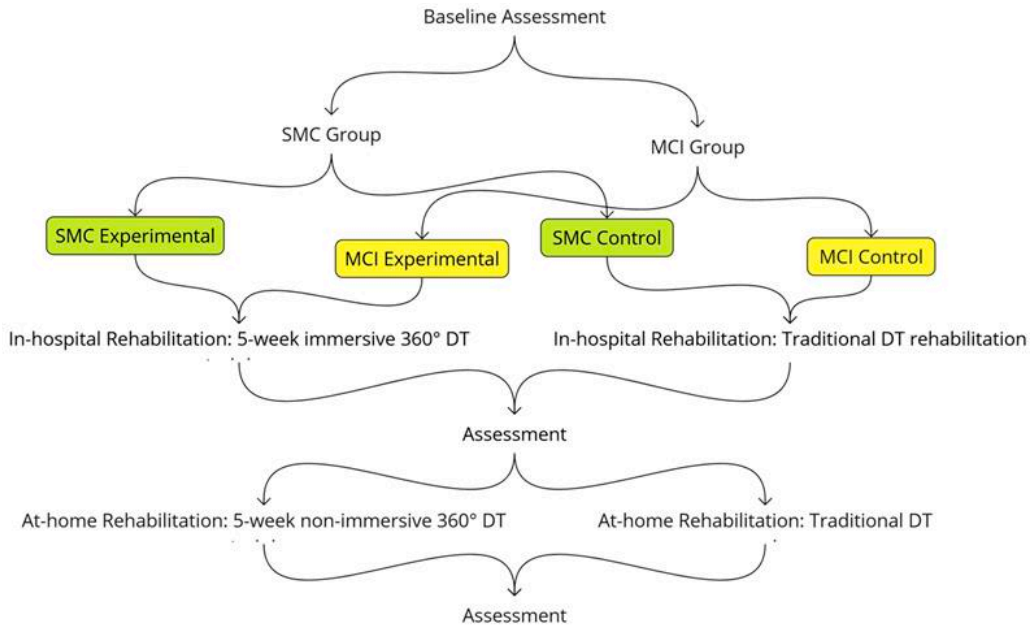

Figure 1. Schematic representation of the randomized clinical trial design. Yellow indicates participants with Mild Cognitive Impairment, while green represents those with Subjective Memory Complaints.

The participants will be assigned to either the experimental group or the control group in a 1:1 ratio using simple randomization procedures, specifically, computerized random numbers. Due to the nature of the intervention, we will follow a single-blinded methodology where the researchers responsible for conducting the assessments will be blinded about the allocation of participants into different groups to mitigate the potential influence of ascertainment bias. All individuals engaged in the facilitation of the training, including researchers and clinicians, will receive comprehensive training to ensure adherence to standardized research protocols during the implementation of the 360°-based intervention. The management of potential data losses during the at-home rehabilitation and follow-up assessment will involve the implementation of specific statistical techniques to address missing data.

This trial was registered on the ClinicalTrials.gov (https://clinicaltrials.gov/) database (NCT06290167) on 4 March 2024.

2.3. Sample and Recruitment

Based on the sample size described below, this study will recruit 90 older adults divided into two groups (45 SMC and 45 MCI). The participants will be recruited through a mixed strategy incorporating consecutive sampling within the IRCCS Istituto Auxologico Italiano as a primary source and snowball sampling (participants help to provide others) to reach even cases that do not access hospital services, improving the representativeness of our sample. In particular, we will screen patients who have access to the Department of Medicine, Neurology and Rehabilitation at the hospital. Eligible SMC participants will be older individuals ($\geq$65 years old) with self-reported memory complaints [40]. To evaluate this aspect, we will design a brief semi-structured interview developed based on key features commonly reported in the literature, including the frequency of memory difficulties, temporal onset of reported impairments, and impact in everyday life [40]. Additional inclusion criteria will be a score on the Mini-Mental State Examination within the normal range, as suggested by [41], no evidence of objective impairments identified in neuropsychological testing (see Section 2.4.1 below), and scores on the Clinical Dementia Rating (CDR) < 0.5 (where a higher CDR score reflects possible dementia, as assessed with the CDR interview [42]). Eligible MCI participants will be older individuals ($\geq$65 years old) with a self-reported cognitive decline at the previous interview, with an objective impairment identified in neuropsychological testing (see assessment instruments below), with preservation in functional abilities, and without evidence of significant impairment in social or occupational functioning (i.e., not demented), as reported in literature recommendations [43].

Informed consent will be obtained from all participants in accordance with the ethical approval granted by the IRCCS Istituto Auxologico Italiano, and the study will comply with the ethical principles established in the Helsinki Declaration. No financial compensation will be provided to the participants.

2.4. Assessment Instruments

All participants will undergo a comprehensive baseline paper and pencil assessments upon enrollment. The same assessment protocol will be administered at three time points: baseline (T0), after 5 weeks of hospital treatment (T1), and following the completion of the home-based intervention (T2). This assessment schedule will be identical for both the experimental and control groups and will last approximately one hour.

2.4.1. Measure of Cognitive Functions

A comprehensive neuropsychological battery will be used, as previously described. All evaluations will be administered by a certified psychologist blinded to group allocation. The battery comprises the following standardized tests.

- The Mini-Mental State Examination [41], a screening battery used to obtain information about general cognitive performance;
- The Digit Span [44], where participants listen to a series of digits read aloud and must repeat them in the same order;
- The Digit Span Backward [44], where the researcher reads a series of digits aloud to the participants, who are requested to repeat the same series of digits in the opposite sequence;
- The Corsi Span Test [44], measuring short-term spatial memory, where the researcher taps a sequence of blocks that the patient needs to reproduce afterwards, in the same order;
- Rey-Osterrieth complex figure [45], where the researcher asks the patient to copy a complex figure, then the patient has to recall the same one after 20 min;
- The Trail Making Test [46], which measures attention and ability of set-shifting and is composed of two parts: the first part (A) is a searching task, and the second part (B) requires shifting in alternatively searching numbers and letters;
- The Clock Drawing Test [47], a valid screening tool for evaluating cognitive decline including visuospatial abilities, executive function, and conceptual understanding, wherein, in this version of the test, participants are presented with a pre-drawn clock face and instructed to insert the numbers and draw the clock hands to indicate a specified time;
- The oral naming of nouns and verbs of E.N.P.A [48], where participants have to name the drawn element or action in tasks that each consist of 10 pictures;
- The Phonological, Semantic verbal fluency [49], a measure of language production;
- The Attentional Matrices Test [50], which is used for measuring selective attention, that is, the patient's ability to detect visual targets among distractors;
- The Frontal Assessment Battery [51], a short cognitive and behavioral six-subtest battery for the screening of global executive dysfunction;
- Short-Story recall [45], which requires participants to memorize and recall a short story after a period of 20 min;
- The Stroop Colour Word Test [52], which is used in clinical practice to assess several abilities linked to the frontal lobe, such as selective attention, cognitive flexibility, and sensitivity to interference. It consists of three different parts: (i) Participants read color-word names printed in black ink, (ii) they name the color of neutral stimuli, and (iii) they must name the ink color of incongruent color words. This last condition generates the "Stroop effect," a slowing in response times and increased errors due to interference between automatic reading and the required color-naming task;
- Dual-task performance [53], a test consisting of performing digit recall and tracking tasks separately and then simultaneously.

2.4.2. Measure of Motor Functioning

The motor measures will be defined with the collaboration with a group of physiotherapists and include the following tests.

- The cognitive Timed Up & Go Test [54]: This is a test of balance traditionally used to evaluate functional mobility in frail older adults. The cognitive part requires participants to complete the test while counting backward by threes; in the motor part,

patients have to stand up from a chair, walk for 3 m quickly, turn around, walk back, and sit down.

- The Timed 10-Meter Walk [55]: This is used for evaluating gait speed and functional mobility. The test measures the time required for participants to walk 10 m at their preferred walking speed along a straight path.

Moreover, we will assess the quality of life using the World Health Organization Quality of Life Scale (WHOQol-brief) [56]. It is a widely used questionnaire designed to assess the individual's quality of life through four domains: physical health, psychological health, social relationships, and environment.

All the used tests will be corrected properly using the Italian normative data, if available.

2.5. Statistical Analysis

The randomized trial assessing memory improvements using virtual reality by Optale and colleagues [57] found medium/high effect sizes. Using their data, it is possible to estimate a minimum of 45 individuals for each group to be included in the experiment, in order to achieve a minimum power of 95%, considering a medium effect size of 0.7 and a significance level of 0.05. The sample size analysis has been computed with the software GPower*3.1.

All collected data will be organized and preprocessed using Microsoft Excel. A comprehensive data cleaning will be implemented, including checks for data entry errors and missing values. If necessary, appropriate imputation techniques will be applied. Statistical analysis will be performed using appropriate software, like SPSS 28.0, JASP 0.17, and JAMOVI 2.3. Demographic characteristics and outcome measures will be summarized using descriptive statistics, including means, standard error, and percentages. The primary analysis will employ a mixed ANOVA to assess training effectiveness. Following the verification of statistical assumptions (including sphericity), we will examine between-subjects (experimental vs. control group) and within-subjects (baseline, T1, and T2) factors. Greenhouse-Geisser and Huynh-Feldt corrections will be applied when sphericity assumptions are violated. The ANOVA will encompass all outcome measures. Moreover, the effect size will be calculated using Cohen's d. To account for multiple comparisons, a post-hoc analysis will be conducted using Tukey's HSD and Bonferroni correction to control this aspect.

Secondly, relationships between cognitive and motor indices will be examined using Pearson's correlation coefficients (r), after verifying the necessary statistical assumptions. The significance level will be set at $\alpha = 0.05$. A dropout rate of up 15% will be considered acceptable for the study's validity.

3. Expected Results

The primary outcome of this study will be the evaluation of cognitive performance improvements, as measured by the assessment battery for cognitive functions. We hypothesize that participants in the experimental group will demonstrate significantly greater improvements compared to the control group regardless of their baseline cognitive status (MCI or SMC). Our expectations include enhanced performance across many outcomes cognitive measures previously described. Specifically, we expect to observe a significant improvement in the experimental group compared to controls and consistent treatment effects across both MCI and SMC subgroups.

As secondary outcomes, we anticipate similar patterns of improvement in physical performance measures. We hypothesize that the experimental group will show greater enhancements in motor functions compared to the control group, with comparable treatment effects expected across both MCI and SMC subgroups. These physical improvements will

be assessed through the previously described motor assessment battery. Additionally, we focus on quality-of-life improvements. We hypothesize that WHOQol-brief questionnaire scores will show significant increases from baseline to post-intervention in both groups, with the experimental group demonstrating more substantial improvements. This pattern is expected to be consistent across both the MCI and SMC conditions, with the realistic training environment facilitating better transfer of learned skills to daily life situations.

The results of this study may have important implications for the development and implementation of non-pharmacological interventions, providing compelling evidence for the effectiveness of technology-based DT intervention. The use of 360° media represents a significant advancement over traditional approaches, providing scalable and cost-effective solutions to early intervention, potentially delaying or preventing further decline. If proven effective, this methodology could establish a new standard particularly valuable for health care systems seeking sustainable solutions for an aging population.

4. Discussion

The current study will be one of the first to analyze and investigate the effectiveness of ecological DT training for older adults with MCI and SMC. The work aims to clarify the numerous benefits provided by the integration of cognitive and motor tasks, as well as advanced technology with rehabilitation paradigms. Using innovative technological advancements and DT provides a rich multisensory experience, transcending traditional therapeutic limitations. The multisensory nature of DT 360-degree media training promotes coordinated activation of diverse functions. The simultaneous integration of visual, auditory, and motor stimuli provides comprehensive engagement, potentially enhancing neuroplasticity through complex activation patterns. This multimodal approach offers a more complete and effective rehabilitation experience than traditional single-modality interventions [58,59]. Another key advantage lies in its capacity to create highly realistic scenarios, particularly crucial for neurorehabilitation settings where real-world complexity needs to be replicated. The enhanced ecological validity not only develops task-specific abilities, but also facilitates skill transfer from clinical to daily life activities [25]. Indeed, the lack of an appropriate reflection of the needs of real abilities in neuropsychological instruments is cited as the cause of issues in predicting everyday cognitive functioning [60].

Therefore, we would like to offer the possibility of an innovative intervention for improving patients' care that does not stop in the clinical context, but rather, continues at home, with the required adjustments. Our protocol could lighten the load on hospital services and allow us to continue with the guided rehabilitation at home. Bringing rehabilitation into the patient's home has several significant benefits [61]. Firstly, it promotes greater continuity of care, allowing patients to maintain progress achieved in clinical settings, leading to better long-term outcomes. Consequently, it reduces the need for frequent hospital visits, thereby minimizing the associated costs and logistical challenges for patients and health care systems. Home-based rehabilitation may also increase patient comfort and convenience, as individuals can engage in therapeutic activities within their familiar environments. This might result in higher adherence to the prescribed regimen.

By leveraging innovative methodologies, we aim to deliver a holistic rehabilitation experience that seamlessly integrates into patients' daily lives, achieving important goals in the pre-clinical phase regarding research and clinical practice.

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Informed Consent Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano (protocol code 2023_01_31_10, date of approval 31 January 2023). All methods were conducted in accordance with relevant institutional guidelines and regulations. Informed consent was obtained from all subjects.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript.

MCI	Mild cognitive impairment
SMC	Subjective memory complaint
AD	Alzheimer's Disease
DT	Dual-task
HMD	Head-mounted display
CDR	Clinical dementia rating

References

1. Aguzzoli, C.S.; Anstey, K.J.; Atri, A.; Barbarino, P.; Benoist, C.; Brijnath, B.; Bruno, M.A.; Cose, L.; Darge, D.; Dean, W.; et al. *World Alzheimer Report 2024 Global Changes in Attitudes to Dementia Contributors: Survey Translators*; Alzheimer's Disease International: London, UK, 2024.
2. Moustafa, A.A.; Tindle, R.; Alashwal, H.; Diallo, T.M.O. A Longitudinal Study Using Latent Curve Models of Groups with Mild Cognitive Impairment and Alzheimer's Disease. *J. Neurosci. Methods* **2021**, *350*, 109040. [CrossRef] [PubMed]
3. Moustafar, A. *Alzheimer's Disease Understanding Biomarkers, Big Data, and Therapy*, 1st ed.; Academic Press: Cambridge, MA, USA, 2021.
4. Aisen, P.S.; Cummings, J.; Jack, C.R.J.; Morris, J.C.; Sperling, R.; Frölich, L.; Jones, R.W.; Dowsett, S.A.; Matthews, B.R.; Raskin, J.; et al. On the Path to 2025: Understanding the Alzheimer's Disease Continuum. *Alzheimers Res Ther* **2017**, *9*, 60. [CrossRef] [PubMed]
5. Jack, C.R.J.; Holtzman, D.M. Biomarker Modeling of Alzheimer's Disease. *Neuron* **2013**, *80*, 1347–1358. [CrossRef]
6. Weintraub, S.; Carrillo, M.C.; Farias, S.T.; Goldberg, T.E.; Hendrix, J.A.; Jaeger, J.; Knopman, D.S.; Langbaum, J.B.; Park, D.C.; Ropacki, M.T.; et al. Measuring Cognition and Function in the Preclinical Stage of Alzheimer's Disease. *Alzheimers Dement.* **2018**, *4*, 64–75. [CrossRef]
7. Park, J.-H. Effects of Cognitive-Physical Dual-Task Training on Executive Function and Activity in the Prefrontal Cortex of Older Adults with Mild Cognitive Impairment. *Brain NeuroRehabil.* **2021**, *14*, e23. [CrossRef]
8. Cheng, Y.-W.; Chen, T.-F.; Chiu, M.-J. From Mild Cognitive Impairment to Subjective Cognitive Decline: Conceptual and Methodological Evolution. *Neuropsychiatr. Dis. Treat.* **2017**, *13*, 491–498. [CrossRef]
9. Tuena, C.; Mancuso, V.; Stramba-Badiale, C.; Pedroli, E.; Stramba-Badiale, M.; Riva, G.; Repetto, C. Egocentric and Allocentric Spatial Memory in Mild Cognitive Impairment with Real-World and Virtual Navigation Tasks: A Systematic Review. *J. Alzheimers Dis.* **2021**, *79*, 95–116. [CrossRef]
10. Gallou-Guyot, M.; Mandigout, S.; Combourieu-Donnezan, L.; Bherer, L.; Perrochon, A. Cognitive and Physical Impact of Cognitive-Motor Dual-Task Training in Cognitively Impaired Older Adults: An Overview. *Neurophysiol. Clin.* **2020**, *50*, 441–453. [CrossRef]

11. Cappa, S.F.; Ribaldi, F.; Chicherio, C.; Frisoni, G.B. Subjective Cognitive Decline: Memory Complaints, Cognitive Awareness, and Metacognition. *Alzheimer's Dement.* **2024**, *20*, 6622–6631. [CrossRef]
12. Warren, S.L.; Reid, E.; Whitfield, P.; Moustafa, A.A. Subjective Memory Complaints as a Predictor of Mild Cognitive Impairment and Alzheimer's Disease. *Discov. Psychol.* **2022**, *2*, 13. [CrossRef]
13. Metternich, B.; Kosch, D.; Kriston, L.; Härter, M.; Hüll, M. The Effects of Nonpharmacological Interventions on Subjective Memory Complaints: A Systematic Review and Meta-Analysis. *Psychother. Psychosom.* **2010**, *79*, 6–19. [CrossRef] [PubMed]
14. Zapater-Fajarí, M.; Crespo-Sanmiguel, I.; Pérez, V.; Hidalgo, V.; Salvador, A. Subjective Memory Complaints in Young and Older Healthy People: Importance of Anxiety, Positivity, and Cortisol Indexes. *Pers. Individ. Dif.* **2022**, *197*, 111768. [CrossRef]
15. Smith, L.; Shin, J.I.; Song, T.-J.; Underwood, B.R.; Jacob, L.; López Sánchez, G.F.; Schuch, F.; Oh, H.; Veronese, N.; Soysal, P.; et al. Association between Depression and Subjective Cognitive Complaints in 47 Low- and Middle-Income Countries. *J. Psychiatr. Res.* **2022**, *154*, 28–34. [CrossRef] [PubMed]
16. Pérez Palmer, N.; Trejo Ortega, B.; Joshi, P. Cognitive Impairment in Older Adults: Epidemiology, Diagnosis, and Treatment. *Psychiatr. Clin. N. Am.* **2022**, *45*, 639–661. [CrossRef]
17. Sukontapol, C.; Kemsen, S.; Chansirikarn, S.; Nakawiro, D.; Kuha, O.; Taemeeyapradit, U. The Effectiveness of a Cognitive Training Program in People with Mild Cognitive Impairment: A Study in Urban Community. *Asian J. Psychiatr.* **2018**, *35*, 18–23. [CrossRef]
18. Wang, Y.-Y.; Wang, X.-X.; Chen, L.; Liu, Y.; Li, Y.-R. A Systematic Review and Network Meta-Analysis Comparing Various Non-Pharmacological Treatments for Older People with Mild Cognitive Impairment. *Asian J. Psychiatr.* **2023**, *86*, 103635. [CrossRef]
19. Pereira Oliva, H.N.; Mansur Machado, F.S.; Rodrigues, V.D.; Leão, L.L.; Monteiro-Júnior, R.S. The Effect of Dual-Task Training on Cognition of People with Different Clinical Conditions: An Overview of Systematic Reviews. *IBRO Rep.* **2020**, *9*, 24–31. [CrossRef]
20. Ali, N.; Tian, H.; Thabane, L.; Ma, J.; Wu, H.; Zhong, Q.; Gao, Y.; Sun, C.; Zhu, Y.; Wang, T. The Effects of Dual-Task Training on Cognitive and Physical Functions in Older Adults with Cognitive Impairment; A Systematic Review and Meta-Analysis. *J. Prev. Alzheimers Dis.* **2022**, *9*, 359–370. [CrossRef]
21. Kim, J.-H.; Park, J.-H. Does Cognitive-Physical Dual-Task Training Have Better Clinical Outcomes than Cognitive Single-Task Training Does? A Single-Blind, Randomized Controlled Trial. *Healthcare* **2023**, *11*, 1544. [CrossRef]
22. Fritz, N.E.; Cheek, F.M.; Nichols-Larsen, D.S. Motor-Cognitive Dual-Task Training in Persons With Neurologic Disorders: A Systematic Review. *J. Neurol. Phys. Ther.* **2015**, *39*, 142–153. [CrossRef]
23. Norouzi, E.; Vaezmosavi, M.; Gerber, M.; Pühse, U.; Brand, S. Dual-Task Training on Cognition and Resistance Training Improved Both Balance and Working Memory in Older People. *Phys. Sportsmed.* **2019**, *47*, 471–478. [CrossRef] [PubMed]
24. McIsaac, T.L.; Lamberg, E.M.; Muratori, L.M. Building a Framework for a Dual Task Taxonomy. *Biomed. Res. Int.* **2015**, *2015*, 591475. [CrossRef] [PubMed]
25. Gallou-Guyot, M.; Mandigout, S.; Bherer, L.; Perrochon, A. Effects of Exergames and Cognitive-Motor Dual-Task Training on Cognitive, Physical and Dual-Task Functions in Cognitively Healthy Older Adults: An Overview. *Ageing Res. Rev.* **2020**, *63*, 101135. [CrossRef]
26. Gheysen, F.; Poppe, L.; DeSmet, A.; Swinnen, S.; Cardon, G.; De Bourdeaudhuij, I.; Chastin, S.; Fias, W. Physical Activity to Improve Cognition in Older Adults: Can Physical Activity Programs Enriched with Cognitive Challenges Enhance the Effects? A Systematic Review and Meta-Analysis. *Int. J. Behav. Nutr. Phys. Act.* **2018**, *15*, 63. [CrossRef]
27. Versi, N.; Murphy, K.; Robinson, C.; Franklin, M. Simultaneous Dual-Task Interventions That Improve Cognition in Older Adults: A Scoping Review of Implementation-Relevant Details. *J. Aging Res.* **2022**, *2022*, 6686910. [CrossRef]
28. Franzen, M.D.; Wilhelm, K.L. Conceptual Foundations of Ecological Validity in Neuropsychological Assessment. In *Ecological Validity of Neuropsychological Testing*; Sbordone, R.J., Long, C.J., Eds.; Gr Press/St Lucie Press, Inc.: Delray Beach, FL, USA, 1996; pp. 91–112.
29. Mellinger, C.D.; Hanson, T.A. Considerations of Ecological Validity in Cognitive Translation and Interpreting Studies. *Transl. Cogn. Behav.* **2022**, *5*, 1–26. [CrossRef]
30. Burgess, P.W.; Alderman, N.; Forbes, C.; Costello, A.; Coates, L.M.-A.; Dawson, D.R.; Anderson, N.D.; Gilbert, S.J.; Dumontheil, I.; Channon, S. The Case for the Development and Use of "Ecologically Valid" Measures of Executive Function in Experimental and Clinical Neuropsychology. *J. Int. Neuropsychol. Soc.* **2006**, *12*, 194–209. [CrossRef]
31. Borghesi, F.; Mancuso, V.; Pedroli, E.; Cipresso, P. From virtual reality to 360 videos: Upgrade or downgrade? The multidimensional healthcare VR technology. In *Handbook of Research on Implementing Digital Reality and Interactive Technologies to Achieve Society 5.0*; Cipresso, P., Ed.; IGI Global: Hershey, PA, USA, 2022; pp. 549–572. [CrossRef]
32. Riva, G.; Mancuso, V.; Cavedoni, S.; Stramba-Badiale, C. Virtual Reality in Neurorehabilitation: A Review of Its Effects on Multiple Cognitive Domains. *Expert Rev. Med. Devices* **2020**, *17*, 1035–1061. [CrossRef]
33. Mancuso, V.; Bruni, F.; Stramba-Badiale, C.; Riva, G.; Cipresso, P.; Pedroli, E. How Do Emotions Elicited in Virtual Reality Affect Our Memory? A Systematic Review. *Comput. Hum. Behav.* **2023**, *146*, 107812. [CrossRef]

34. Parsons, C.E.; Crane, C.; Parsons, L.J.; Fjorback, L.O.; Kuyken, W. Home Practice in Mindfulness-Based Cognitive Therapy and Mindfulness-Based Stress Reduction: A Systematic Review and Meta-Analysis of Participants' Mindfulness Practice and Its Association with Outcomes. *Behav. Res. Ther.* **2017**, *95*, 29–41. [CrossRef]
35. Serino, S.; Repetto, C. New Trends in Episodic Memory Assessment: Immersive 360° Ecological Videos. *Front. Psychol.* **2018**, *9*, 1878. [CrossRef] [PubMed]
36. Horr, T.; Messinger-Rapport, B.; Pillai, J.A. Systematic Review of Strengths and Limitations of Randomized Controlled Trials for Non-Pharmacological Interventions in Mild Cognitive Impairment: Focus on Alzheimer's Disease. *J. Nutr. Health Aging* **2015**, *19*, 141–153. [CrossRef] [PubMed]
37. Ribarič, S. Physical Exercise, a Potential Non-Pharmacological Intervention for Attenuating Neuroinflammation and Cognitive Decline in Alzheimer's Disease Patients. *Int. J. Mol. Sci.* **2022**, *23*, 3245. [CrossRef] [PubMed]
38. Sherman, D.S.; Mauser, J.; Nuno, M.; Sherzai, D. The Efficacy of Cognitive Intervention in Mild Cognitive Impairment (MCI): A Meta-Analysis of Outcomes on Neuropsychological Measures. *Neuropsychol. Rev.* **2017**, *27*, 440–484. [CrossRef]
39. Chan, W.C.; Yeung, J.W.F.; Wong, C.S.M.; Lam, L.C.W.; Chung, K.F.; Luk, J.K.H.; Lee, J.S.W.; Law, A.C.K. Efficacy of Physical Exercise in Preventing Falls in Older Adults with Cognitive Impairment: A Systematic Review and Meta-Analysis. *J. Am. Med. Dir. Assoc.* **2015**, *16*, 149–154. [CrossRef]
40. Abdulrab, K.; Heun, R. Subjective Memory Impairment. A Review of Its Definitions Indicates the Need for a Comprehensive Set of Standardised and Validated Criteria. *Eur. Psychiatry* **2008**, *23*, 321–330. [CrossRef]
41. Magni, E.; Binetti, G.; Bianchetti, A.; Rozzini, R.; Trabucchi, M. Study in Italian Elderly Population. *Eur. J. Neurol.* **1996**, *3*, 198–202. [CrossRef]
42. Morris, J.C. Clinical Dementia Rating: A Reliable and Valid Diagnostic and Staging Measure for Dementia of the Alzheimer Type. *Int. Psychogeriatr.* **1997**, *9* (Suppl. S1), 173–178. [CrossRef]
43. Albert, M.S.; DeKosky, S.T.; Dickson, D.; Dubois, B.; Feldman, H.H.; Fox, N.C.; Gamst, A.; Holtzman, D.M.; Jagust, W.J.; Petersen, R.C.; et al. The Diagnosis of Mild Cognitive Impairment Due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease. *Alzheimer's Dement.* **2011**, *7*, 270–279. [CrossRef]
44. Monaco, M.; Costa, A.; Caltagirone, C.; Carlesimo, G.A. Forward and Backward Span for Verbal and Visuo-Spatial Data: Standardization and Normative Data from an Italian Adult Population. *Neurol. Sci.* **2013**, *34*, 749–754. [CrossRef]
45. Carlesimo, G.; Buccione, I.; Fadda, L.; Graceffa, A.; Mauri, M.; Lorusso, S.; Bevilacqua, G.; Caltagirone, C. Normative Data of Two Memory Tasks: Short-Story Recall and Rey's Figure. *Nuova Riv. Neurol.* **2002**, *12*, 1–13.
46. Siciliano, M.; Chiorri, C.; Battini, V.; Sant'Elia, V.; Altieri, M.; Trojano, L.; Santangelo, G. Regression-Based Normative Data and Equivalent Scores for Trail Making Test (TMT): An Updated Italian Normative Study. *Neurol. Sci.* **2019**, *40*, 469–477. [CrossRef] [PubMed]
47. Caffarra, P.; Gardini, S.; Zonato, F.; Concari, L.; Dieci, F.; Copelli, S.; Freedman, M.; Stracciari, A.; Venneri, A. Italian Norms for the Freedman Version of the Clock Drawing Test. *J. Clin. Exp. Neuropsychol.* **2011**, *33*, 982–988. [CrossRef]
48. Capasso, R.; Miceli, G. *Esame Neuropsicologico per l'Afasia: ENPA*; Springer Science & Business Media: Berlin/Heidelberg, Germany, 2001; Volume 4.
49. Costa, A.; Bagoj, E.; Monaco, M.; Zabberoni, S.; De Rosa, S.; Papantonio, A.M.; Mundi, C.; Caltagirone, C.; Carlesimo, G.A. Standardization and Normative Data Obtained in the Italian Population for a New Verbal Fluency Instrument, the Phonemic/Semantic Alternate Fluency Test. *Neurol. Sci.* **2014**, *35*, 365–372. [CrossRef]
50. Sala, S.D.; Laiacona, M.; Spinnler, H.; Ubezio, C. A Cancellation Test: Its Reliability in Assessing Attentional Deficits in Alzheimer's Disease. *Psychol. Med.* **1992**, *22*, 885–901. [CrossRef]
51. Appollonio, I.; Piamarta, M.L.; Isella, V.; Villa, F.; Consoli, T.; Nichelli, M.L.; Russo, A. The Frontal Assessment Battery (FAB): Normative Values in an Italian Population Sample. *Neurol. Sci.* **2005**, *26*, 108–116. [CrossRef]
52. Caffarra, P.; Vezzadini, G.; Francesca, D.; Zonato, F.; Venneri, A. A Short Version of the Stroop Test: Normative Data in an Italian Population Sample. *Nuova Riv. Neurol.* **2002**, *12*, 111–115.
53. Della Sala, S.; Foley, J.A.; Beschin, N.; Allerhand, M.; Logie, R.H. Assessing Dual-Task Performance Using a Paper-and-Pencil Test: Normative Data. *Arch. Clin. Neuropsychol.* **2010**, *25*, 410–419. [CrossRef]
54. Podsiadlo, D.; Richardson, S. The Timed "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons. *J. Am. Geriatr. Soc.* **1991**, *39*, 142–148. [CrossRef]
55. Bohannon, R.W. Comfortable and Maximum Walking Speed of Adults Aged 20-79 Years: Reference Values and Determinants. *Age Ageing* **1997**, *26*, 15–19. [CrossRef]
56. De Girolamo, G.; Rucci, P.; Scocco, P.; Becchi, A.; Coppa, F.; D'Addario, A.; Daru, E.; De Leo, D.; Galassi, L.; Mangelli, L. Quality of Life Assessment: Validation of the Italian Version of the WHOQOL-Brief. *Epidemiol. Psychiatr. Sci.* **2000**, *9*, 45–55. [CrossRef] [PubMed]

57. Optale, G.; Urgesi, C.; Busato, V.; Marin, S.; Piron, L.; Priftis, K.; Gamberini, L.; Capodieci, S.; Bordin, A. Controlling Memory Impairment in Elderly Adults Using Virtual Reality Memory Training: A Randomized Controlled Pilot Study. *Neurorehabil. Neural Repair.* **2010**, *24*, 348–357. [CrossRef] [PubMed]
58. Mancuso, V.; Borghesi, F.; Bruni, F.; Pedroli, E.; Cipresso, P. Mapping the Landscape of Research on 360-Degree Videos and Images: A Network and Cluster Analysis. *Virtual Real.* **2024**, *28*, 101. [CrossRef]
59. Pedroli, E.; Greci, L.; Colombo, D.; Serino, S.; Cipresso, P.; Arlati, S.; Mondellini, M.; Boilini, L.; Giussani, V.; Goulene, K.; et al. Characteristics, Usability, and Users Experience of a System Combining Cognitive and Physical Therapy in a Virtual Environment: Positive Bike. *Sensors* **2018**, *18*, 2343. [CrossRef]
60. Parsons, T.D. Virtual Reality for Enhanced Ecological Validity and Experimental Control in the Clinical, Affective and Social Neurosciences. *Front. Hum. Neurosci.* **2015**, *9*, 660. [CrossRef]
61. Bruni, F.; Mancuso, V.; Greci, L.; Arlati, S.; Cavallo, M.; Riva, G.; Goulene, K.; Stramba-Badiale, M.; Pedroli, E. A Cross-Platform Application for the Ecological and Remote Assessment of Memory Impairment in Aging: ECO-MEMORY. *Virtual Real.* **2023**, *27*, 2757–2767. [CrossRef]