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Virtual Reality Combined With Psychoeducation to Improve Emotional Well-Being in Informal Caregivers of Alzheimer's Disease Patients: Rationale and Study Design of a Randomized Controlled Trial

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ABSTRACT

Objectives: Care for community-dwelling people with dementia is frequently delegated to relatives, who find themselves in the role of informal caregivers with no practical management knowledge. This situation exposes caregivers to increased risk for emotional wellbeing. The current study aims to test whether the integration of the efficacy of an immersive virtual reality (VR) experience into an online psychoeducational program impacts caregiver empathy and therefore emotional wellbeing.

Methods: One-hundred informal caregivers of mild-to-moderate Alzheimer's disease (AD) patients will be enrolled and randomly assigned to (i) an online psychoeducational program (control arm); or (ii) an online psychoeducational program integrated with VR (experimental arm). VR will consist of 360-degree videos involving the caregivers to an immersive experience of dementia symptoms from the patient's perspective. Before, after the intervention and after 2 months, all participants will complete validated clinical scales for caregiver burden and anxiety (primary outcomes) and sense of competence and dispositional empathy (secondary outcomes). A subsample of 50 participants will also undergo MRI exam, including structural and functional (resting-state and task-functional MRI [fMRI]) sequences. The fMRI task paradigm will use emotional stimuli to evaluate the neural correlate of empathy, by stressing its cognitive and affective components. The main outcome will be the change in the clinical assessment; the secondary outcome will be the change in brain connectivity of networks subserving the empathic and emotional functioning.

Results: We expect that the psychoeducational program will decrease anxiety and stress, enabling caregivers to perceive themselves capable of managing AD patients at home, educating them on symptom handling and boosting their cognitive empathy. In the experimental intervention, the VR-based experience will act as an add-on to psychoeducation, leading to greater

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improvement in the assessed clinical dimensions. VR should, in fact, enable a deeper understanding of disease symptoms and improve caregivers' cognitive empathy. We expect that the experimental intervention will result in deeper comprehension of disease symptoms and further strengthen caregivers' cognitive empathy. At the neural level, we expect to observe increased activation in circuits subserving cognitive empathy and decreased activation in circuits underlying affective empathy.

Conclusions: To the best of our knowledge, this will be the first randomized controlled trial assessing the effect of combining psychoeducational interventions with VR-based experience in caregivers, and assessing both clinical and imaging outcomes.

Trial Registration: Registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05780476)

1 | Introduction

Alzheimer's disease (AD) is a neurocognitive disorder that leads to a progressive impairment of cognitive, emotional, and social functioning efficiency [1, 2]. Its progressively disabling nature makes AD a burdensome disease both to the person with dementia (PwD) and to their informal caregivers, that is, familiar untrained and unpaid persons who provide care to home-dwelling PwD [3]. The emotional and physical burden of caregiving is widely known. As the PwD's symptoms worsen, caregivers may encounter greater emotional stress and depression, new or worsening health difficulties, and decreased income and resources [4–6]. International policies and researches have so far emphasized the caregiver's need to be equipped with skills, knowledge, and empathetic understanding of the PwD condition [7, 8]. Several education interventions have been developed over the past decades [9, 10]; among them, psychoeducational interventions revealed the greatest effectiveness in improving caregivers' psychological health and quality of life [9–11]. Psychoeducation is a structured program that provides information about disease symptoms, potential management strategies, available resources and services. Discussions with experts and group support are also important components of psychoeducation. These features have been proven to enhance caregiving competency, mastery in PwD management and communication, and provide emotional support [12].

In the last years, and especially during the Covid-19 pandemic, the need to switch from in-person to remote assistance resulted in the fast development of technologies to improve dementia care services. Some protocols of technology-enabled dementia education have been developed and validated [13–16]. Among these the Tele-Savvy Caregiver programme (TSC), a technology-enabled dementia psychoeducation program, has been proven effective in reducing depression, perceived stress, insomnia symptoms, and enhancing caregiver master [15, 17].

The World Alzheimer Report 2022 urged for innovative dementia education programmes that increase empathy and enable caregivers to gain a real-life perspective on the disease [18], leading to an expansion of technology-based simulations, including experiential learning using virtual reality (VR), in dementia care protocols [19–21]. The first results of their application are currently appearing. For instance, the Through the D'mentia Lens (TDL) intervention, a virtual reality simulation movie and e-course of three 20-min lessons, has shown significant improvements in caregiver's empathy, confidence in caring for the person with dementia, and positive interactions

with the person with dementia [21]. Tsai, Hsu, and Hsieh [22], found that caregivers who participated in a VR-based experiential training course on personalized care for behavioral and psychological symptoms improved their understanding of dementia patients, providing better care services. All these approaches, which leverage empathic processes, offer caregivers a realistic and memorable learning experience in safely and cost-effectively practicing care procedures [23].

Empathy is the ability to understand and respond appropriately to others's feelings [24]. Recent evidence has suggested that empathy is a multidimensional construct, consisting of cognitive and affective components. Cognitive empathy involves advanced cognitive perspective-taking system connected to empathic care and compassion, and associated to positive emotions; affective empathy involves a basic emotional contagion system strongly related to empathic distress, and associated to negative emotions [25, 26]. The components are supported by distinct neural systems, with cognitive empathy involving ventromedial prefrontal-striatal systems [27–29], and affective empathy involving anterior cingulate cortex, anterior insula, and mirror neuron areas (i.e., somatosensory and premotor cortex) [27, 30, 31]. Modulating these components can provide an effective approach to reduce distress and enhance positive emotions in caregivers. However, properly controlled randomized clinical trials (RCTs) are lacking [19].

This trial aims to test a novel e-health intervention that combines an online psychoeducational program with a VR experience to reduce caregivers' anxiety and burden, by fostering empathetic behaviors, and enabling a deeper knowledge of the dementia needs. We will evaluate the short- and medium-term clinical and neural effects of the intervention using a RCT methodology. The objective is to assess the impact to the experimental intervention on anxiety and burden (primary outcomes), empathy, attitude, and perceived competence (secondary outcomes). The intervention aims to enhance patient management and reduce caregiver distress by enhancing empathy. Since empathy arises when we experience it and cannot be taught or forced [24] and used to be evaluated as a psychological trait [32], we will use functional Magnetic Resonance Imaging (fMRI) to assess changes in neural circuits underlying both cognitive and affective empathic processes (surrogate outcome).

To the best of our knowledge, this will be the first randomized controlled trials, that integrates a VR-experience in a psychoeducation program and test its efficacy using both clinical and imaging outcomes.

Summary

- To the best of our knowledge, this will be the first randomized controlled trial evaluating the effect of an e-health intervention integrating VR technologies, using clinical and imaging outcomes.
- The integration of a VR-based experience should enhance the effects of the online psychoeducational program (e.g., reduction of caregiver burden and improvement of self-efficacy in managing persons with AD) leveraging on the experiential learning.
- The intervention might have a recruitment bias because it is fully online and incorporates use of virtual reality technology (e.g., greater engagement of informal secondary caregivers).

2 | Materials and Methods

2.1 | Study Design

The study is a monocentric RCT with two intervention arms: (i) an online psychoeducational program (control arm), and (ii) a VR experience combined with the online psychoeducational program (experimental arm).

Participants are assigned to the arms using an adaptive randomization, having sex and baseline level of perceived stress as covariates. Given the nature of the intervention, participants are not blind to the condition they will receive, nor the team members conducting the intervention.

The protocol is developed and guided by the SPIRIT checklist (Table 1) [33]. Participants were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

2.2 | Participants

One hundred unpaid informal caregivers ((i) i.e., family members or friends, regardless of gender, education level or employment status) of persons diagnosed with AD will be recruited from relatives of outpatients at the IRCCS Fatebenefratelli memory clinic, in Brescia (Italy), and from the community via public dissemination of the study (e.g., websites; information brochure, newsletters). The inclusion criteria for informal caregivers are: (i) age greater than 18 years old; (ii) fluent Italian speaker; (iii) living with or caring for a person with AD for at least 4 h per day and for at least 6 months prior to enrollment. The patient must still be living at home and have a clinical diagnosis of AD with a Mini-Mental State Examination (MMSE) score range of 18–24) [34].

Exclusion criteria are: (i) daily assistance from a formal and paid caregiver >10 h per week; (ii) previous participation in other psychoeducational programs, or current psychotherapy, or psychological support for caregiver concerns; (iii) unavailability or inability to use an Internet-connected device (e.g.,

smartphone or PC); (iv) contraindications for VR and MRI (when applicable). Table S1 listed the inclusion and exclusion criteria.

This study is conducted according to the principles of the Declaration of Helsinki and all participants will give informed consent. The ethics Committee of the IRCCS Centro San Giovanni di Dio – Fatebenefratelli in Brescia (Italy) approved the study (approval date April 8, 2022; Number 19/2022).

2.3 | Visits and Assessments

During the screening visit, participants discuss the protocol procedures, provide informed consent and eligibility criteria are verified. Sociodemographic information (i.e., age, gender, educational level, patient–caregiver kinship, time devoted to care, duration of the caregiving role in months) are collected, including a screening of perceived stress assessed with the 4-item version of the Perceived Stress Scale (PSS) [35].

Clinical and medical assessments are conducted before initiation (T0, week 1), at the end of the intervention (T1, week 8), and after 2 months (T2, week 18). The assessments include standardized clinical scales either self-administered or administered by a psychologist. Two psychologists (C.F., C.S. S.) will be authorized to administer the clinical scales. However, participants will be followed-up with the same psychologist at each timepoint. Multi-morbidity is measured using the Cumulative Illness Rating Scale (CIRS) [36], a standardized index for chronic medical illness burden that take into consideration the severity of chronic diseases. Resource use of caregivers is assessed using the Resource Utilization in Dementia (RUD) [37]. Standardized self-administered clinical scales are used to measure different aspects of the emotional impact of care, such as (i) the Italian version of Zarit Burden Interview (ZBI) [38], a 22-items scale assessing caregivers perceived strain associated to the provision of care using a five level Likert scale); (ii) the State Trait Anxiety Inventory (STAI-Y, 1 & 2) [39], a self-report questionnaire consisting of two 20-item scales providing separate measures of state and trait anxiety; (iii) the Short Sense of Competence Questionnaire (SSCQ) [40], a brief scale evaluating caregivers' feelings of being capable of caring for a demented person and the Revised Scale for Caregiving Self-Efficacy (RSCE), a 15-item scale exploring the self-efficacy in obtaining respite, responding to patients' disruptive behaviors, and controlling upsetting thoughts [41, 42]. Changes in empathy are quantified using Interpersonal Reactivity Index (IRI) [32], a 28-items self-report instrument assessing empathic tendencies in four domains: empathic concern, perspective-taking, personal distress, and fantasy. Lastly, emotion regulation strategies are measured with the Emotion Regulation Questionnaire (ERQ) [43], a 10-item questionnaire assessing two emotion regulation strategies: cognitive reappraisal and expressive suppression. Sociodemographic and clinical features of person with AD (age, education, MMSE score; illness duration) are also collected. A psychologist assesses frequency and severity psychic and behavioral symptoms, using the Neuropsychiatric Inventory (NPI) [44].

TABLE 1 | Timeline of enrollment, interventions and assessments (adapted from SPIRIT checklist).

Time point	Study period				
	Screening & allocation	Baseline T0 (W1)	Intervention W2–W8	Post-intervention T1 (W9)	Follow-up T2 (W18)
Enrollment					
Eligibility screening	X				
Invitation to participate	X				
Informed consent	X				
Allocation	X				
Training to technologies		X			
Interventions					
Online psychoeducation + imagery session			◆◆◆◆◆◆◆◆		
Online psychoeducation + virtual reality session			◆◆◆◆◆◆◆◆		
Assessment					
Participant demographics	X				
4-item perceived stress scale ^a	X				
Perceived stress scale ^a		X		X	X
Cumulative illness rating scale ^b		X		X	X
Resource utilization in dementia ^b		X		X	X
Neuropsychiatric inventory ^b		X		X	X
Zarit burden interview ^a		X		X	X
State trait anxiety inventory ^a		X		X	X
Interpersonal reactivity index ^a		X		X	X
Short sense of competence questionnaire ^a		X		X	X
Revised scale for caregiving Self-efficacy ^a		X		X	X
Beck's depression inventory ^a		X		X	X
Impact of event scale ^a		X		X	X
Short-form 12 items health survey ^a		X		X	X
Positive aspects of caregiving ^a		X		X	X
CareQOI-7D ^a		X		X	X
Emotional regulational questionnaire ^a		X		X	X
Extended reality presence scale ^a			X		
MRI scan (on a voluntary basis)		X		X	

^aSelf-report scales.^bScale administrated by a psychologist.

A subsample ($N = 25$ subjects per group) will undergo, on a voluntary basis, 3T MRI scan before and after the treatment.

Figure 1 and Table 1 show the study design, the timeline of enrollment, interventions and assessments for this study. Data collection started in October 2022.

2.4 | Interventions

For both arms (experimental/control), the intervention will be administered in groups of 10 participants.

2.4.1 | Online Psychoeducational Program (Control Arm)

Caregivers assigned to this group will take part to a 12-h online psychoeducation course with the aims of being introduced to the caregiving role, providing them with the knowledge, skills, and attitudes needed to carry out that role, and alerting them to self-care issues. The program is an adaptation of the “Tele-savvy caregiver program” [45], whose main aim is to instruct caregivers about dementia and strategies they may implement to create an optimal environment and provide optimal quality of life of caregivers and PwD, despite the progressive

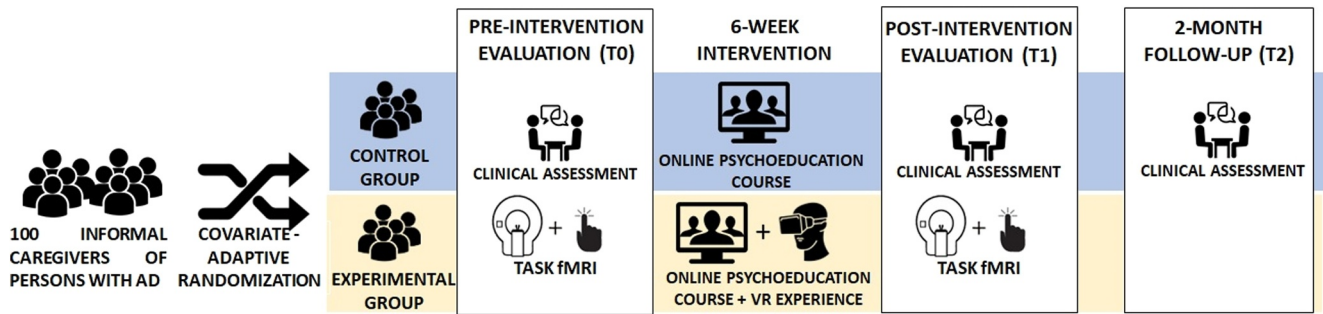


FIGURE 1 | Study design. One hundred caregivers of person with Alzheimer's disease (AD) will be randomly assigned to one of two arms of the intervention: Online psychoeducation for 6 weeks in the control arm; online psychoeducation combined with virtual reality (VR) for 6 weeks in the experimental arm. The enrolled participants will undergo a clinical examination before the intervention (T0), at the conclusion of the intervention (T1), and after 2 months (T2). A subsample of 25 subjects per arm will voluntarily undergo multimodal MRI scan at T0 and T1.

deteriorating nature of dementia. Although sharing the same theoretical framework, our programme differs from the TSC programme in that the caregivers participating in each group (10 people instead of 8) are not involved in any asynchronous activities. The caregivers take part in a weekly 2-h synchronous teleconference (instead of the 75 min suggested by the TSC) for 6 weeks, held by a psychotherapist expert in neuropsychology (C.B., S.R.). Each meeting is structured in a lecture- and discussion-like style: following introductions (20 min), the psychologist presents the theoretical material with a power point presentation (40 min), and then opens the discussion (30 min): each participant is free to ask open and direct questions about the issue or recount a comparable experience. The psychotherapist answers technical questions, directs and moderates the talk, and keeps emotions in check. During the last 30 min of the teleconference, participants are guided in a training of empathy, through activities requiring them to put themselves in the shoes of the patient: while the experimental group will experience VR (details in the next paragraph), the control group will be engaged in mental imagery exercises (detailed content and aims of psychoeducation and of trainings of empathy are provided in Table 2). Caregivers are then invited to contribute their personal insights in a final discussion. At the end of the teleconference, the psychologist summarizes the topic discussed by reviewing it in light of what emerged, integrating the pedagogical part with the content shared by the participants. This report, as well as the coaching component, are critical for the development and reinforcement of caregiver mastery.

2.4.2 | Virtual Reality Experience (Experimental Arm)

The VR experience is done with the ViveDe program, an audio-visual dementia simulator developed to foster a Dementia-friendly culture (www.vivede.it) [46]. The ViveDe program consists of six 360° videos, fully explorable on the x/y axis, describing everyday indoor and outdoor situations (e.g., living alone, preparing meals, shopping, and having a walk). It is designed to help participants experience specific dementia symptoms, such as disorientation, agnosia, apraxia, and memory loss, from the perspective of a PwD.

ViveDe is developed with the use of the VR headset v2 (a commercial device for smartphones with 100° FOV lenses, farsightedness and near-sightedness settings, IPD and immersion adjustment) and a set of headphones.

Participants in the experimental arm are equipped with VR headset v2 (cardboard version) and trained in their use prior to the start of the psychoeducation. Under the guidance of psychologists, participants in each teleconference experience a ViveDe video, then compare their emotional reactions, and try to propose patient management options that take into account the new perspective.

Measures of the experience of presence in immersive environments is evaluated using Extended Reality Presence Scale (XRPS) [43].

2.5 | MRI Protocol

Before and after the intervention, a subsample of participants ($N = 25$, for each arm) will undergo a multimodal MRI exam on a 3T scanner (Siemens Skyra), equipped with a 64-channels coil, at the Neuroradiology Unit of the Spedali Civili Hospital in Brescia, Italy. The acquisition protocol will include the following sequences: (i) resting-state fMRI (rs-fMRI; TR = 1000 ms, TE = 27 ms, flip angle = 60°, voxel = 2.1 mm isotropic, 70 slices, 600 volumes); (ii) fMRI during the administration of an emotion eliciting task (TR = 1000 ms, TE = 27 ms, flip angle = 60°, voxel = 2.1 mm isotropic, 70 slices, 1128 volumes); (iii) 3D T1-weighted MPRAGE (TR = 2300 ms, TE = 2 ms, flip angle = 9°, voxel = 1 mm isotropic, 176 slices); (iv) 3D T2 FLAIR (TR = 5000 ms, TE = 393 ms, voxel = 1 mm isotropic, 192 slices). MRI acquisition will last 38 min.

2.5.1 | fMRI Task With Emotional Stimuli

Neural activity in brain systems regulating components of empathy will be assessed on MRI using emotional stimuli. The task is adapted from Ashar et al. [27]. Specifically, participants will read 24 biographies describing human suffering of different forms of disease (i.e., neurodevelopmental disorders,

TABLE 2 | Summary of psychoeducation themes and training empathic strategies. Psychoeducation focuses on the development of caring knowledge, skills, and mastery. During trainings on empathy, psychotherapists guide caregivers to assume the patient's perspective in every-day activities. Under the guidance of a psychotherapist, the experimental group will test the 10-min VR experience. The control group will be led through the identical VR situation utilizing mental imagery exercises. Caregivers would be able to use the facts taught and experienced via empathy training on cognitive, emotional, and behavioral impairment caused by AD to plan and use caring ways to lead their loved one's daily life at the end of the psychoeducation.

Topic	Content description	Training of empathy	
		Experimental arm: VR experience	Control arm: Mental imagery exercise
Session 1 Disclosure of Alzheimer disease diagnosis: Meaning and emotional impact	The emotional impact of the diagnosis disclosure. Description and evolution of clinical AD. Understand and come to grips with the disease that is affecting the person	The VR video describes the emotive impact of diagnosis disclosure	Participant attempts to imagine being diagnosed with AD
Session 2 Cognitive symptoms: What are they and what can I do?	Description, evolution, and management of most frequent cognitive deficits in AD (i.e., memory lost, attention impairment, language disorders). Develop a strategic sense of what cognitive losses are occurring and how caregiver behavior has to adapt to these as they take place and progress. Be able to communicate effectively with the person to promote and maintain involvement. Design opportunities for satisfying occupation	The VR video shows difficulties a patient may face when cooking	Participant tries to imagine the difficulties they may face when cooking in a kitchen not their own
Session 3 Behavioral symptoms: What are they and what can I do?	Description, evolution, and management of most frequent behavioral deficits in AD. Develop emotional tolerance recognize the central role of confusion in dementia and how it contributes to troubling behaviors	VR video gives participant the experience of losing his/her way home and hallucinating	The participant imagines being lost in a foreign country
Session 4 Functional impairment and residual resources	Understand that dementia gradually erodes autonomy. Recognize the need to take control and be willing and able to do so. Gauge the care recipient's capabilities. Small adjustments to the house to make it a prosthetic environment	The VR video shows difficulties a patient may face when shopping	The participant imagines shopping in a foreign country with foreign money
Session 5 Social support	Provide knowledge about the importance of social support. Teach family caregiver to access community resources and refer to resource guide. Appreciate the social and emotional difficulties involved in taking control of another	Through the VR video, the participant experiences unfamiliarity with his/her home	The participant imagines the emotional impact of being unfamiliar with a rental house

(Continues)

TABLE 2 | (Continued)

Topic	Content description	Training of empathy	
		Experimental arm: VR experience	Control arm: Mental imagery exercise
Session 6 Caregiver self-care and healthy behaviors	adult (thinking of the other as somehow not equal) Enhance family caregiver's physical well-being and teach self-care behaviors. Establish a realistic care goal	The VR video shows difficulties a patient may face during a social lunch	The participant imagines the emotional impact of a chaotic social lunch

Abbreviations: AD, Alzheimer's disease; VR, virtual reality.

neurocognitive disorders, cancers, substance abuse, gambling, and physical or emotional maltreatment) and then score their degree of emotional activation on a five Likert scale. The fictional biographies are adapted from Ashar et al. [27] and paired with fictional photos of individuals unfamiliar to the subject. Photos are taken from a public dataset [47] or internet repositories and paired with the biographies based on age (e.g., children for neurodevelopmental disorders, older subjects for neurocognitive disorders) and relevance to the biographies. The individuals described in the biographies are balanced for gender and age (childhood, adulthood, and seniority). Two separate sets of stimuli are created, one for baseline (T0) and one for follow-up (T1). Biographies and faces are uniquely assigned either to the baseline or follow-up experiment to avoid practice effects. fMRI stimuli are presented for 30 s in 24 blocks and followed by the cultural adaptation of the question proposed by Ashar et al. [27] ("How tender/distressed do you feel right now?"). Participants rate their level of empathic care or distress by pressing one of five buttons corresponding to a Likert 5-point scale (ranging from "not at all" to "extremely"; 5 s). The rating is followed by a 6-s baseline task in which participants are presented with arrows and asked to detect the direction of the arrow (up or down) via button press. This task is designed as a non-affective condition to interfere with any continuing thinking on the biographies between blocks.

2.6 | Retention and Adherence Strategies

To ensure high adherence and retention, we will adopt the following strategies. Recruiters will maintain regular communications with emails and phone calls with participants to identify and monitor red flags of attrition (e.g., missed appointments or virtual meetings, major personal or family events, deteriorating health, or loss of support). Contacts will be weekly during intervention periods and monthly during follow-up periods. Moreover, caregivers will be trained in the use of the technologies (the online platform and the VR devices) before the intervention. Finally, participants will receive the slide-kit presented during each meeting. In a preliminary study [16], the slides were highly appreciated and allowed participants to formulate questions that were discussed at the follow-up meeting or privately with the referring psychologist. In our preliminary study, these strategies resulted in a very low attrition rate (2.4%).

2.7 | Sample Size

Sample size for the clinical outcomes is computed based on our own previous single-arm pilot study [16]. Briefly, in 2020 we conducted a web-based psychoeducational program for caregivers of patients with mild to moderate dementia. Results showed that the 72% of caregivers reported a subjective mental benefit. The benefit was confirmed by a statistically significant decrease between pre-test and post-test scores in STAI-Y ($p < 0.003$) and ZBI ($p = 0.027$).

In particular, in our pilot study, we observed, for the STAI-Y variable, a mean change (pre-post) of 5 points and a standard deviation at baseline equal to 8 and a correlation of 0.8. For the current study, we hypothesized a mean change pre-post for STAI-Y in the control group equal to the pilot study, while we hypothesized for the experimental group an augmented effect of about 50% with respect control group, that is, we expected a change pre-post in STAI-Y of about 8 points.

By using the formula in Rosner B, 7th edition (chapter 8) for the difference in longitudinal changes between two groups (i.e., $[n = (2 \times \text{Sigma2difference} \times (1.96 + 0.84)^2) / \text{delta}^2]$), where delta is the difference of the change between the two groups and Sigma2difference is the standard deviation pre-post obtained considering $\text{sigmapre} = \text{sigmapost} = 8$ and a correlation of 0.8), the computed sample size is equal to 90 (45 per groups), obtained considering an alpha = 0.05 and a power of 0.8. The final sample size will be increased up to $N = 100$ (50 per group) in order to consider a dropout rate of 10%.

Sample size estimates for the imaging outcomes are based on previous recommendations for fMRI studies and previous studies with a similar design. According to the seminal article by Desmond and Glover [48], a sample size of 24 participants is recommended as the minimum to achieve a 80% power at $\alpha = 0.05$ at the single voxel level for fMRI studies. Furthermore, a recent study reported an increase in brain activity, as measured by Statistical Parametric Mapping, after an empathy education training in a sample of 17 young subjects, of whom $n = 13$ underwent fMRI before and after the intervention [49]. In our case, the sample size is larger ($n = 25$ subjects per experimental group), so we expect to detect at least similar or larger effects using a paired test.

2.8 | Statistical Analysis

We will compare clinical outcomes before and after interventions within and across groups, to identify the effects of each intervention on psychological well-being. We will describe sociodemographic, clinical, basic and advanced brain imaging markers in the two groups by using mean and standard deviation, or median and quantiles. Longitudinal evaluation of the clinical and imaging outcomes across the two groups will be evaluated by generalized linear mixed models for repeated measures, including arm (experimental vs. control) and time (pre vs. post) as factors. For all outcomes, we will test for interactions between arm and time. The per-protocol analysis will be carried out on the individuals that will complete at least 80% of sessions (i.e., participating at least in five meetings).

2.9 | Analysis of MRI Data

Imaging data will be processed using standard procedures and softwares, including the Statistical Parametric Mapping (SPM), FMRIB Software Library (FSL) and Advanced Normalization Tools (ANTs).

Task fMRI data will be analyzed to evaluate the variation of the blood-oxygen level dependent (BOLD) signal and the relative brain activation in relation to the emotional stimuli. The condition of interest will be the fictional biographies and our control condition will be the arrow task.

Resting-state fMRI will be used to assess differences between groups in functional connectivity of brain networks involved in emotion and cognition, such as the salience network and the default mode network. Data will be pre-processed according to standard procedures (i.e., denoising, motion and distortions corrections, registration to standard space, bandpass filtering, nuisance regression, smoothing) and brain networks extracted with independent component analysis (ICA).

3 | Conclusions

Informal caregivers play a crucial role in providing personal care and medication monitoring for PwD. However, they often lack adequate preparation for this role. Supporting caregivers involves providing theoretical and practical knowledge, increasing awareness of their own emotional needs, and preventing effects of chronic stress on mental and physical health.

Recently, VR has attracted increasing interest as a potential intervention to train caregivers. Experiential learning through fully explorable 360° immersive videos can be an effective strategy for improving a caregiver's understanding of dementia symptoms. In such context, the ViveDe program showed promise tool in creating a dementia-friendly culture and, improving people's perspectives on dementia management [46]. As shown in a previous study conducted with a general population, that is, not involved in dementia care as relatives nor as health professional, ViveDe provides a personal perspective on dementia, shifting attitudes toward the degree of care required

by a PwD, and their options for independent life versus institutionalization. The immersive nature of the movies also helped persons comprehend the difficulties PwDs encounter on a regular basis, the significance of helping people with disabilities with both fundamental needs (such food and safety) and higher-level needs (like social belonging, esteem, and self-fulfillment).

We have hypothesized that the ViveDe program is suitable for our purposes. In fact, our intervention aims to enhance psychoeducation benefits by using empathic cognitive strategy training based on experiential learning. The combined program may promote skills, such as understanding dementia symptoms, effective communication, and empathy. It enables caregivers to deepen their understand of dementia, allowing them to better meet the patient's health care needs and reduce their own distress, overall resulting in better patient management. To date, only few studies have explored VR use and preliminary results support an improvement of caregiver's empathy and competences.

This e-health program, which utilizes virtual reality tools and is fully online, is ideal for the target population as it provides expert assistance to caregivers without the need to plan activities from distant locations or their homes, making it a suitable solution. However, technology can cause concerns and issues for elderly individuals. Potentially leading to recruitment bias, with secondary informal carers (such the patient's children) being more represented than primary informal caregivers (like spouses). Consistent with statistics from the literature, gender may be another source of bias, as women (wives, daughters, daughters-in-law, or sisters) represent 70% of informal caregivers [3]. Several sociological variables, personality traits, different experiences of the caregiver and type of pre-morbid relationship between caregiver and care recipient may influence baseline caregiver's distress and intervention impact. However, these measures will not be collected in our study, thus we will not be able to control for their potential confounding effect. The study lacks a non-caregiver group to compare baseline levels of stress (as assessed with clinical and neuronal measures) with a non-caregiver population. In addition, due to financial constraints, a voluntary subsample of participants will undergo MRI potentially causing sampling bias. Specific analyses will be conducted to assess differences between the whole sample and the MRI sub-group, and eventually control for these factors in the analysis.

The study is a RCT, a study design not frequent in caregiving field [50]. It allow to provide methodologically grounded and robust conclusions about the intervention's effectiveness. Another strength of the study is the assessment of the intervention impact using neuroimaging outcomes. To the best of our knowledge, very few research have examined the structural or connectivity changes in the brain following interventions on caregiver population [51–56]. Among them, three paper from the same research group used imaging as surrogate outcome of intervention efficacy [51, 52] Moreover, neural biomarkers will be used in future caregiver-oriented studies to identify predictors of response to the intervention.

In conclusion, this study will be the first RCT to the best of our knowledge to focus on informal caregivers, evaluate the synergistic effect of integrating a VR experience with a online

psychoeducational intervention, and analyze clinical and imaging indicators.

Author Contributions

All co-author were involved in the design of this study and made contributions to the conception of the project. C.F. is the Principal Investigator and the coordinating researcher of this project. F.M. is the co-Principal Investigator and M.P. the supervisor. C.F. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript, and approved the final version.

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Ethics Statement

This study is performed in accordance with the Declaration of Helsinki. Ethics approval for this study was obtained by the Ethics Committee of the IRCCS Centro San Giovanni di Dio – Fatebenefratelli in Brescia (Italy) approved the study (approval date April 8, 2022; Number 19/2022). All subjects in this study will provide written informed consent. The trial is registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (Identifier: NCT05780476).

Consent

All of the people who feature in ViveDe films have given their permission for publishing. The signed consent forms are kept at the University of Bergamo, under the responsibility of F.M.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. All research data will be archived and securely stored after the end point of the study. The datasets generated and/or analyzed during the current study will be available from the corresponding author on reasonable request.

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Supporting Information

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