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Virtual Reality-Based Cognitive Stimulation on People with Mild to Moderate Dementia due to Alzheimer's Disease: A Randomized Controlled Trial

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Abstract: The use of ecologically oriented approaches with virtual reality (VR) depicting instrumental activities of daily living (IADL) is a promising approach for intervention on acquired brain injuries. However, results of such an approach on dementia caused by Alzheimer's disease (AD) are still lacking. This research reports on a pilot randomized controlled trial that aims to explore the effect of cognitive stimulation reproducing several IADL in VR on people with mild to moderate dementia caused by AD. Patients are being recruited from residential care homes of Santa Casa da Misericórdia da Amadora (SCMA) which is a relevant non-profit social and healthcare provider in Portugal. This intervention lasts 2 months with a total of 10 sessions (2 sessions/week). Neuropsychological assessment is carried out at baseline and follow-up using established neuropsychological instruments for assessing memory, attention and executive functions. The sample consisted of 17 patients of both genders randomly assigned to the experimental and control groups. The preliminary results show an improvement in the overall cognitive function in the experimental group, which suggest this approach to be effective for neurocognitive stimulation for older adults with dementia, contributing to maintain cognitive function in AD.

Keywords: Alzheimer's disease; ageing; computerized cognitive stimulation; dementia; ecological validity; virtual reality

1. Introduction

As the global population ages, the incidence of major neurocognitive disorders (NCDs), such as Alzheimer's disease (AD), is expected to rise in the following years [1].

According to the World Health Organization [2], AD is the most common form of dementia and may contribute to 60–70% of cases. In 2015, dementia affected 47 million people worldwide (accounting approximately for 5% of the older adult population); however, recent reviews estimate that, globally, nearly 9.9 million people develop dementia each year - this figure translates into one new case every three seconds.

Dementia has a physical, psychological, social, and economic impact, not only on people with dementia, but also on their caregivers, families, and society at large. Furthermore, it is one of the major causes of disability and dependency among older people worldwide [3]. Individuals with a diagnosis of dementia will require a diversity of

services that include case-finding, diagnosis, treatment (including pharmacological and psychosocial), rehabilitation, palliative/end-of-life care, and other support (e.g., home help, transport, food, and the provision of a structured day with meaningful activities [2].

In Portugal, for every 100 young citizens, there were 129.6 citizens over 65 years old in 2011, but this number increased dramatically in the last ten years to 157 in 2020 [4]. By 2050 in Portugal, as well as Japan, Italy, and Spain, dementia´s prevalence will be of more than one in 25 people, with an estimated prevalence of dementia between 2019 and 2050, of 40.5 per 1.000 population [5].

1.1. Alzheimer's Disease

Dementia is an umbrella term for several diseases (including AD), usually characterized by a significant decline in one or more cognitive domains (e.g., language, memory, executive functioning) considering the individual's age and education. Dementia due to AD is generally characterized by an insidious onset, with a progressive course leading to a deterioration of functional abilities that eventually culminates in global cognitive impairment and compromised functional independence, baring a huge personal and societal impact [6].

Cognitive symptoms of AD most commonly include deficits in complex attention, executive functions, perceptual-motor function, language abilities (i.e., aphasia) and semantic knowledge, in learning, and social cognition. However, episodic memory impairment (i.e., amnesia) is usually the earliest and the most pervasive feature of AD [7-9]. In the early stages of the disease process, recent episodic memories are most affected, while memories of the distant past are usually spared. As the disease progresses, all aspects of episodic memory become affected. In contrast, working memory and semantic memory are retained until the later stages of the disease process [7].

Between healthy aging and pathological dementia aging, a pre-dementia territory characterized by Ron Petersen, Glenn Smith, and colleagues from the Mayo Clinic as "mild cognitive impairment" (MCI) [10] may be considered. MCI was defined as a condition in which individuals experience memory loss to a greater extent than one would expect for age, yet do not meet the criteria for dementia [10]. This is less severe degree of cognitive impairment when compared to dementia and categorized in DSM-5 as Mild Neurocognitive Disorder characterized by a great heterogeneity of deficit profiles. However, the capacity for independence in Activities of Daily Living and Instrumental Activities of Daily Living is preserved, unlike major NCDs [11].

Given the impact of major NCDs, it is crucial to develop effective, targeted treatments to delay the cognitive and functional decline associated with these diseases and to mitigate their devastating personal, family, and social consequences.

Pharmacological interventions, unfortunately, have not shown much efficacy in changing the course of AD dementia [12]. To ensure that people with dementia can maintain a level of functional ability, the need for more definitive cognitive assessment and effective non-pharmacological intervention for age-related NCDs, including AD, becomes of the utmost relevance given that no definitive diagnostics or efficacious therapeutics are currently available for these conditions [5].

1.2. Cognitive Stimulation and the Use of Virtual Reality

Cognitive stimulation (CS) depends on the regeneration potential of the adult brain and focuses on the overall improvement of the individual´s cognitive and social functioning [13], as he/she is involved in a set of specific and selected activities. Research suggests that CS leads to consistent gain in global cognition, especially, in individuals with the diagnosis of mild to moderate dementia [14,15]. Systematic reviews on this subject [15,16], suggest that CS´ benefits are comparatively greater than those from pharmacological intervention with additional and significant improvements of: quality of life and well-being, communication and social interaction.

Regarding CS, in recent years, virtual reality (VR) is seen as an important resource that can enhance therapeutic gains, namely, in patients with major NCDs as AD [17-19]. Studies indicate that VR has been effective with subjects with cognitive decline, specifically, by increasing their ability to perform IADL [20,21].

VR is defined as a technology that digitally provides a three-dimensional environment, allowing people to interact, to have different sensory inputs and to change the environment [19]. VR can be immersive or non-immersive, with immersion allowing a sense of presence in the environment [19].

Systematic reviews [19,22] on the effectiveness of interventions using VR resources in major NCDs, mainly with patients with AD, suggest significant improvements in cognition, as well as in well-being, being encouraging for improvements in executive functioning [22].

Despite the diversity of virtual environments that aim to achieve cognitive gains, most of them do not consider multidomain functioning [23,24]. The Systemic Lisbon Battery (SLB) stands out in this approach, having been used with different groups of participants (substance use disorders, aging, traumatic brain injury and stroke) to promote cognitive functioning with cognitive exercises depicting diverse instrumental activities of daily living [24-26]. The results of studies carried out with the SLB support the idea that this is an effective tool for functional cognitive improvement [24], mainly at the level of executive functions. Given the lack of consistent data on VR-based CS in dementia, this study aims to report the impact of CS using the SLB in a group of older adults with mild to moderate dementia due to AD.

2. Materials and Methods

2.1. Trial Design

The design of this study was based on an open label pilot randomized controlled trial (RCT), as it was not be possible to blind intervention to patients, therapists and assessors. This pilot trial aimed to provide the preliminary evidence for the feasibility of this intervention to inform subsequent validation trials regarding effectiveness of this intervention on major NCDs. The trial design consisted of a two-arm parallel design with A-B point assessments. The patients were randomly distributed by the experimental and control groups. The experimental group consisted of VR cognitive stimulation at the residential care homes for older adults, whereas the control group of treatment-as-usual at these care units for older adults.

2.2. Recruitment

Recruitment was conducted at the residential care homes from Santa Casa da Misericórdia da Amadora (SCMA), which is a large non-profit health and social care provider in the municipality of Amadora in Lisbon Metropolitan Area of Portugal. The users from these facilities have different comorbidities, but usually comprise older adults with ages above 65 years old with different physical and cognitive morbidities. The population selected for this study comprised older adults with major NCD due to AD, identified by a psychologist working at SCMA's premises. The potential participants received written and verbal information about the study for informed consent. The same information was provided to therapists and families of these patients. After agreeing to participate, the patients were included in a pool of participants for group allocation.

2.3. Eligibility Criteria

Eligibility criteria were assessed by the psychologists in the partner institution of this project. The inclusion criteria were the following: being older adults with AD, fluent in Portuguese language, above 65 years old keen to participate in the study.

The exclusion criteria were as follows: history of psychiatric (depression, anxiety, psychosis) diagnosed disorders, and severe language or sensory-motor impairments that prevent participation in these exercises.

2.4. Intervention

This program comprised twelve-session cognitive stimulation sessions delivered by clinical neuropsychologists for 45 minutes sessions, distributed in 2 days a week, with a dosage of approximately 9 hours, being considered an average dose length from the data of a recent meta-analysis [27]. The intervention was done using computerized cognitive stimulation program with non-immersive VR, with exercises depicting IADL for higher ecological validity. The sessions were structured aiming different proposed cognitive domains according to Supplementary Table S1. These sessions are presented with different difficulty levels for progression throughout intervention. This program was already studied in other populations for cognitive rehabilitation [28] or cognitive stimulation in healthy aging [24]. The SLB was used in this intervention, which is a computerized version of neuropsychological IADL to assess or promote neuropsychological functioning. The SLB has been in use for over 10 years in reference institutions in Portugal. Overall results suggest the SLB as a feasible approach for cognitive intervention, producing higher impacts in general cognitive functions related to and supporting everyday life activities. This study is the first attempt to study this intervention in patients with major NCDs due to AD. In this study, the SLB was used in a computer with non-immersive VR exposure in a laptop screen of 17 inches.

The SLB comprised nine different tasks, distributed in twelve sessions with different difficulty levels. The tasks used for this study were the following: T1 Morning hygiene, T2 Shoe closet test, T3 Wardrobe test, T4 Memory test, T5 Virtual kitchen, T6 TV news, T7 Grocery store, T8 Pharmacy, and T9 Art gallery test. Tasks T1-T6 are conducted inside a virtual apartment, whereas T7-T9 are outdoor tasks were participants needed to navigate to each of these locations in the virtual city (Figure 1).

2.5. Outcomes

The outcomes were assessed with established neuropsychological measures. The sociodemographic data was retrieved from the clinical files of each patient at these institutions. These data were related to gender, age, formal education, civil status and social support.

2.5.1. Primary Outcomes

Primary outcome was executive functioning, as this intervention focuses on ecological validity by using IADL in VR for promoting executive functions. Executive functions were assessed with the Frontal Assessment Battery and the Trail Making Test.

The Frontal Assessment Battery – FAB [29], the Portuguese version [30], is a brief instrument for assessment of abstraction, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy, which comprise different domains of executive functioning. Each dimension is scored from 0 to 3, in a maximum score of 18 points.

The Trail Making Test - TMT [31] is a performance test divided into two parts: part A that assesses attention, motor coordination and information processing speed, and part B that assesses working memory, executive functions and the mental flexibility [32]. For part A, the participants are asked to link numbers in ascending order, with a line drawing in a A4 sheet. For part B, the participants are asked to link numbers and letters alternately, in ascending order for numbers and alphabetical order for letters. In this study we assessed performance using a dichotomized score according to task accomplishment.

Table 1. Structure of the intervention protocol.

Session #	Structure	Proposed Cognitive Domains
Session 1	Training	N/A
Session 2	T1 and T2	Prospective memory (T1), planning and attention (T2)
Session 3	T3 and T4 (L1)	Planning (T3), visual memory (T4)
Session 4	T4 (L2) T5 (L1)	Visual memory (T4), executive functions, memory/attention (T5)
Session 5	T5 (L2)	Executive functions, memory and attention
Session 6	T6	Declarative memory
Session 7	T7 (L1)	Executive functions, working memory
Session 8	T7 (L2)	Executive functions, working memory
Session 9	T8 (L1)	Executive functions, working memory
Session 10	T9 (L1)	Attention, working memory
Session 11	T9 (L2)	Attention, working memory
Session 12	T9 (L3)	Attention, working memory

Note: T1 Morning hygiene, T2 Shoe closet test, T3 Wardrobe test, T4 Memory test, T5 Virtual kitchen, T6 TV news, T7 Grocery store, T8 Pharmacy, and T9 Art gallery test.

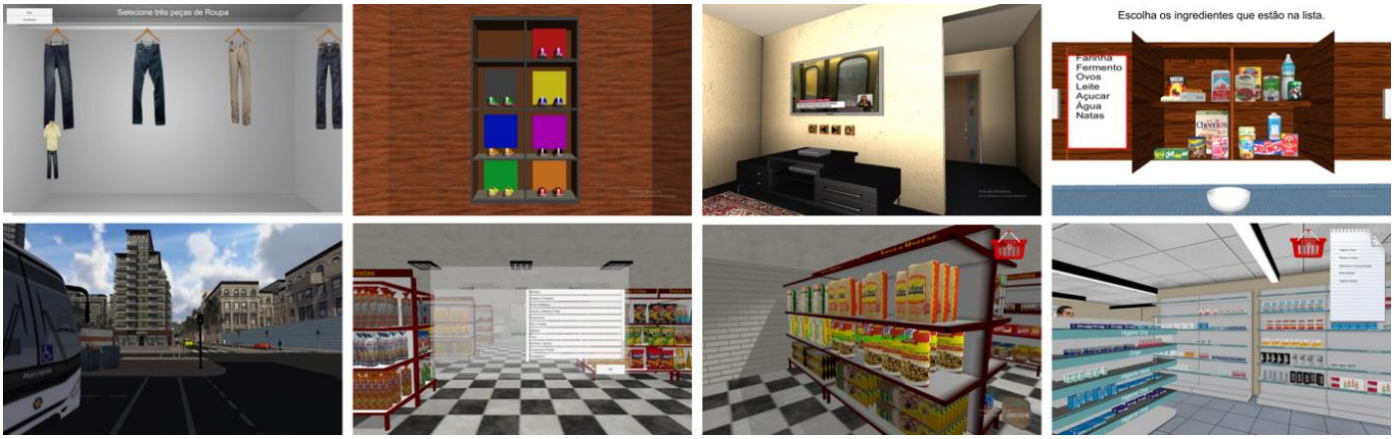

Figure 1. Examples of the tasks used in the Systemic Lisbon Battery

2.5.2. Secondary Outcomes

Secondary outcomes were global cognition, functionality, depression and dementia rating.

Global cognition was assessed with the Mini-Mental State Examination – MMSE [33], which is a brief cognitive screening test used to assess cognitive decline in different populations [34]. The total score is 30 points, where an higher score depicts better cognitive function. The validation for Portugal was conducted by Guerreiro and colleagues [35], whereas Santana and colleagues [34], provide cutoffs of 15 points for illiterate individuals; 22 points for 1-11 years of schooling; and 27 points for 11 years of schooling or above.

The Clock Drawing Test – CDT [36], Portuguese version [37] is a paper and pencil instrument for cognitive screening in dementia. The CDT assesses visuospatial, constructive and executive functions. The classification is based in the rating system that assesses the quality of the clock circumference and clock hands.

The Lawton –Brody Instrumental Activities of Daily Living Scale – IADL [38], aims to measure disability in instrumental everyday activities through the caregivers' reports. The instrument allows assessing the level of independence in eight functional domains, such as using the telephone, using transport, shopping, preparing food, housekeeping, laundry, medication and manage finances [39].

The Geriatric Depression Scale-15 - GDS-15 [40] was used as self-report instrument for depression. The translation and adaptation to the Portuguese population was prepared by

the Group of Studies on Brain Aging and Dementias in Portugal. The maximum is 15 points that suggests higher depression levels. The cutoffs are: 0-5 absence of depressive symptoms; 6-10 mild depressive symptoms; and 11-15 severe depressive symptoms.

The Clinical Dementia Scale - CDR [41], is aimed at evaluating cognition and behavior as well as the ability to perform activities of daily living. This scale is divided into six cognitive-behavioral categories: memory, orientation, judgment and problem solving, community activities, home activities, and personal care. Each of the categories are classified from 0 (absence); 0.5 (questionable); 1 (mild dementia); 2 (moderate dementia); to 3 (severe dementia), except for the personal care category that does not have 0.5 level. The memory category has greater relevance in this test as this comprise the main symptoms of major NCDs. The final classification of the CDR is obtained from classification in each individual category [42].

2.6. Procedure

This project started with the submission of ethical clearance to the ethics committee of Ethical and Deontological Committee for Scientific Research of the School of Psychology and Life Sciences (CEDIC) of Lusófona University in Lisbon. The project was approved from this ethics committee in October 2018.

The informed consent form was provided to patients, therapists and families in a simple and clear language, with information on objectives of the project, confidentiality and pseudonymisation of the data because of the repeated assessment. After agreeing (patients, family and professionals) with the informed consent, the patients were screened for eligibility according to the inclusion criteria for participating in this study. The eligibility criteria were screened by a psychologist from SCMA, that also created a schedule for each week of intervention with the days of the week for intervention for each patient recruited for the study. The baseline assessment session was done with a psychologist of the institution where patients receive regular follow-up. The baseline assessment was divided in two one-hour sessions. Another technician was responsible for conducting intervention with the computer for cognitive stimulation in the following 4–6-week period as stated above under intervention. After intervention has been completed, the same evaluator conducted the endpoint assessment in two different one-hour sessions. The matching between each user was done by a numeric keycode that linked the data with each user. No personal information was recorded. This file was available during the intervention for the clinical staff involved in this study at SCMA.

2.7. Statistical Analysis

The statistical procedures were conducted in SPSS v.25. The data was retrieved from each individual file and imported to SPSS for statistical analysis. As this study involved a mixed design (within and between group comparisons), these analyses were conducted for repeated measures. Before each analysis, the distribution of the dependent variable was assessed for normality with Kolmogorov-Smirnov (KS) test. The statistical analyses started with descriptive statistics for sample characterization. The neuropsychological outcomes were assessed with repeated measures ANOVA for 2X2 comparisons with normal distribution, whereas the Wilcoxon test for A-B comparisons was done for non-parametric distributions. The significant ANOVAs were further explored with simple effects with Bonferroni correction. The alpha level was set at .05 for all inference analyses.

3. Results

3.1. Sample Description

The first analysis aimed at describing the sample regarding the sociodemographic data. The initial sample comprised 18 patients, but one patient of the experimental group dropout from the study. The final sample comprised 17 older adults (12 women) with a mean age of 83 years (M = 83.24: SD = 5.66). Regarding the level of education, most participants (n = 11,

64.7%) had primary education, 2 (11.8%) had education below primary level but were literate, and 4 (23.5%) had education higher than primary schooling. As for civil status, most participants (n = 11, 64.7%) were widowed, 4 (23.5%) were divorced, and 2 (11.8%) were married, while most of them (n = 16; 94.1%) had descendants. The sample was randomly divided by the experimental group (n = 10) and the control group (n = 7). These groups were compared with Mann-Whitney for age and the Chi-square for testing independence between variables for the remaining sociodemographic variables. No statistically significant differences between groups were found for age (experimental group: M = 82.60 yrs, SD = 5.42; control group: M = 84.14 yrs, SD = 6.30), nor significant associations were found with the remaining sociodemographic variables ($p > 0.05$).

The dementia stage was assessed at baseline using the CDR classification, indicating that most participants were classified as moderate dementia (n = 8, 47.1%), followed by mild dementia (n = 7, 41.2%), and questionable dementia (n = 2, 11.8%). The same scoring is used for individual categories, ranging from at 0-3 (severe). Regarding the individual categories of CDR, most patients scored 1 point (n = 9; 52.9%) in memory, 2 points (n = 7; 41.2%) in orientation, 2 points (n = 6; 35.3%) in judgment and problem solving, 2 points (n = 10; 58.8%) in community activities, 1 point (n = 8; 47.1%) in home activities, and most scored 1-2 points (each n = 6; 35.3%) in personal care. The associations between group with the individual categories and total score of CDR were tested with Chi-square that did not reveal statistically significant associations, suggesting that frequency distributions of patients among these CDR categories are not different between experimental vs. control groups. These data are described in Table 1.

Table 1. Clinical Dementia Ratings at baseline assessment.

	Experimental group			**Control group**		
	Mode	**Min.**	**Max.**	**Mode**	**Min.**	**Max.**
Memory	1	.5	2	1	1	2
Orientation	.5	.5	3	2	.5	2
Judgment and problem solving	2	.5	3	1	1	3
Community activities	2	.5	2	2	1	2
Home activities	1	.5	2	1	1	2
Personal care	1	0	2	2	0	2

3.2. Primary Outcomes of Intervention

The primary outcomes were executive functions that were assessed with the FAB and the TMT. The distribution of the total score from the FAB at the baseline and post-treatment assessment followed a normal distribution according to the KS test. Therefore, these differences were tested with a repeated measures ANOVA, with one within-subjects factor (baseline vs. post-treatment) and one between-subjects' factor (group: experimental vs. control). The results showed no statistically significant main or interaction effects ($p > .05$). Table 3 shows an increase in the mean score of the FAB to the post-treatment assessment for the experimental group, but without statistical significance, as well as the decrease found in mean score of the FAB in the control group.

The TMT scores were dichotomized in 0 and 1 for classifying performance in the test according to not accomplished and accomplished tasks, respectively. Therefore, the comparisons between baseline and post-treatment assessment were done with the Sign test to identify positive (change), negative (change) and ties (i.e., no change) between these assessment points. This analysis was done separately for the experimental and control groups. The results did not reveal a significant difference in either group ($p > .05$), but four comparisons showed positive changes (i.e., improvement from baseline to post-treatment assessment) and six described ties (i.e., no difference between baseline and post-treatment) in TMT part A. None of the comparisons revealed negative change in the experimental group (i.e., decrease from baseline to post-treatment assessment). For TMT part B,

two positive changes were found, but the number of ties was 10 in these comparisons. None of the comparisons described negative change. For the control group, no positive/negative changes were found. All comparisons in the control group were ties revealing no variation in the TMT part B score in controls (Table 4).

3.3. Secondary Outcomes of Intervention

The secondary outcomes were based on global cognition, functionality, depression and dementia rating score. Global cognition was assessed using an established cognitive screening test – MMSE along with the CDT. The distribution of total score for the MMSE was tested using the KS, which revealed adjustment to the normal distribution ($p > 0.05$). The repeated measures ANOVA was conducted under the same condition as for the FAB scores. These results revealed a statistically significant interaction between factors (F(1, 15) = 4.930; Eta^2 = 0.247; $p = 0.042$), as depicted in Table 2. The partial omega squared effect was calculated as this is considered to be less biased for comparison across studies than the partial eta squared [43]. The effect size Omega^2p = 0.187 is considered a large effect size given the benchmark provided by Cohen [44] for equivalent eta squared with the following cutoffs for small (Eta^2 = 0.01); medium (Eta^2 = 0.06) and large (Eta^2 = 0.14) effects.

This effect was decomposed using simple effects' analysis that indicated a significant improvement from baseline to post-treatment assessment only in the experimental group (MMSE Δmean = -1.20; SE = 0.51; p = 0.033). Regarding group comparisons, no differences were found between groups at the baseline assessment point. A marginally significant trend was found at post-treatment assessment for the difference between experimental vs. controls (MMSE Δmean = 5.60; SE = 3.41; $p = 0.056$).

The CDT was scored in an ordinal scale (0-10). Therefore, these comparisons were done separately for experimental vs. control groups with the Wilcoxon Signed Rank test for two related samples. These results did not reveal statistically significant comparisons in the experimental or the control groups ($p > 0.05$). In the experimental group there was one comparison with positive ranks (i.e., higher score at post-treatment assessment) and one comparison with negative ranks (i.e., higher score at baseline assessment), whereas the remaining comparisons were ties (i.e., no rank differences between assessment points). In the control group, all comparisons were ties, suggesting no variation in the CDT score from baseline to post-treatment assessment (Table 3).

Regarding the IADL assessment, the KS revealed adjustment to the normal distribution ($p > 0.05$). The ANOVA did not reveal statistically significant differences ($p > 0.05$) between baseline to post-treatment assessment (Table 2).

The GDS-15 was tested form normality using the KS. The KS was only significant for the GDS-15 post-assessment ($p < 0.05$). These comparisons were then conducted using the Wilcoxon Signed Rank test given that one of these variables were not normally distributed. No significant differences were found between the baseline and post assessment in either the experimental or control groups ($p > .05$). In the experimental group five comparisons were positive (i.e., higher score at post-treatment assessment – in GDS-15, a higher score is indicative of higher depression), one was negative (i.e., higher score at baseline assessment), and four were ties (i.e., no variation from baseline to post-assessment). As for the control group, two comparisons were positive, one was negative and four were ties (Table 3).

The CDR is scored in an ordinal scale (0-3), being therefore assessed using the Wilcoxon Signed Rank test. These results did not reveal significant differences in either group ($p > .05$). No variation was found in CDR score as all the comparisons were given as ties in the Wilcoxon test (Table 3).

Table 2. Pre-post comparisons for parametric tests.

	Experimental group		**Control group**	
	Baseline	**Post-test**	**Baseline**	**Post-test**

	M	SD	M	SD	M	SD	M	SD	F
FAB	9.30	4.64	10.00	4.989	8.00	5.292	7.71	4.821	2.032
MMSE	18.60	6.484	19.80	7.269	13.00	7.528	12.43	7.185	4.930*
IADL	17.20	4.050	16.60	5.190	10.71	3.861	10.29	2.984	.015

Note: FAB – Frontal Assessment Battery; MMSE – Mini-Mental State Examination; IADL – Instrumental Activities of Daily Living. * $p < .05$.

Table 3. Pre-post comparisons for non-parametric tests.

	Experimental group$_1$			**Control group$_2$**			**Z_1**	**Z_2**
	(+) change	**(-) change**	**(0) change**	**(+) change**	**(-) change**	**(0) change**		
TMT-A	4	0	6	0	0	7	.125	1.000
TMT-B	2	0	8	0	0	7	.500	1.000
CDT	1	1	8	0	0	7	.000	.000
GDS-15	1	5	4	2	1	4	-1.897	-.272
CDR	0	0	10	0	0	7	.000	.000

Note: TMT-A/B – Trail Making Test part A/B; CDT – Clock Drawing Test; GDS15 – Geriatric Depression Scale; CDR – Clinical Dementia Rating. (+) change – *n* increase at post-test; (-) change – *n* decrease at post-test. In the Sign Test for the TMT the values are P (probability) as this test computes the p-value directly based on observed test statistic.

4. Discussion

This investigation aimed to explore the effects of computerized cognitive stimulation in patients with major NCDs due to AD. This study is framed in a project with SCMA that provides care to the population of a large city in the Metropolitan Area of Lisbon. The population ageing is reflected in increases of age-related diseases, where major NCDs are being considered as important challenges of developed countries for the next years. Portugal is no exception, where there is a urgent need for the development of non-pharmacological approaches for improving quality of life and promoting functionality of these patients. Therefore, we developed an intervention for patients with AD built on prior work at the level of cognitive stimulation of healthy older adults. The previous studies have been showing generalized effects in cognition and executive functions [e.g., 19,22,27]. Therefore, our aim was to explore the effects of this intervention in these patients to understand whether it is possible to improve cognition in AD using an ecologically-oriented approach with activities of daily living in virtual reality.

The results did not show improvements in executive functions, but a significant effect was found in global cognition from pre- and post -treatment assessment. This effect considering the benchmark of Cohen [44] is considered to be large. However, the differences between groups were marginally significant at the endpoint assessment, which highlight the need for further studies in this field.

Nevertheless, the improvement in the experiment group in global cognitive functioning is aligned with literature on cognitive stimulation in dementia that, in the absence of gains in specific cognitive dimensions, it suggests improvements at the global level [15]. On the other hand, it also supports the results of studies on rehabilitation and cognitive stimulation using VR [19,22].

The outcomes on executive functioning from the TMT revealed that four patients that received intervention showed positive differences, improving from baseline to post-treatment assessment, and six showed no variation of results between baseline and post-treatment, in TMT part A. These results are different from those indicated by other studies (e.g., [22, 45]), which points to improvements at the level of TMT B and not at TMT A – i.e., gains in working memory [45], but not in attention [22], motor coordination and information processing speed [45]. However, it is not to be disregarded that, in the present study, two

subjects from the experimental group reveal positive changes also in TMT B, that is, in terms of working memory, executive functions and the ability to switch between stimuli.

Cognitive reserve (CR) theory has been used as an explanation for individual differences in one's capacity to maintain cognitive function, despite the emergence of brain pathology and individual differences in pathology [6]. For Mondini and colleagues [46], CR is a potential mechanism to cope with brain damage and thus facilitate cognitive performance in an impaired brain, promoting neuroplasticity mechanisms and brain reorganization following adverse events. Therefore, the CR hypothesis suggests that individuals differ in the ability to cope with AD and further predicts that people with a greater CR cope with advancing AD longer before the disease is observed clinically. CR is a complex construct that is viewed as an active mechanism in association with the brain´s potential to change enabled by neuroplasticity bare clear implications in the context of cognitive intervention [46-47].

As stated above, the CR hypothesis suggests that individuals differ in their ability to cope with the impact of AD at the level of executive and cognitive functioning. CR plays an active role in the brain´s potential to change and to respond positively to CS, therefore explaining the outcome of cognitive interventions. Despite the difficulties in measuring CR, this variable would be helpful to differentiate individuals´ performance and contribute with an explanation for intra and interindividual differences. It is important that future studies in this topic control for CR, to provide a more comprehensive understanding of the impact of CS in executive and cognitive outcomes. Hence, an effort has to be made in order to include the existing measures - Cognitive Reserve Scale (CRS), Cognitive Reserve Index Questionnaire (CRIq), Cognitive Reserve Questionnaire (CRQ) [48] - either in assessment protocols or in intervention plans.

Several studies also indicate that the use of VR may be beneficial for improving psychological functioning of individuals with cognitive impairment [19,22]. However, in our study, no positive effects were found at the level of self-reported depression, as measured with the GDS-15. It will be important also that further studies assess other domains of psychological functioning as quality of life and well-being, which may be important outcomes of cognitive interventions in AD.

In summary, the results indicate that VR-based cognitive stimulation has positive effects on global cognitive functioning in individuals with dementia due to AD, even though no significant changes were found in specific cognitive functions. It is worth mentioning the difficulty in making an adequate comparison with other studies, given the fact that very few focused exclusively on the use of VR-based cognitive intervention with people with AD (e.g., [27, 49]). Most of these studies integrate mild cognitive impairment (MCI) or dementia, without discriminating the results related to AD (e.g., [22]), which may justify some of the differences between the results of the present study and those found in other studies. It should also be noted that the reduced statistical significance of the results is most probably explained by the limited number of participants in this study. It is therefore important that further research addresses the limitations of this study, by controlling for potential confounders as CR, while assessing other domains of psychological functioning related to quality of life and well-being, in larger samples of older adults with major NCDs due to AD to understand whether it is possible to delay the progression of cognitive deficits of AD with ecologically-oriented VR cognitive interventions.

Finally, it should be noted that most studies use semi-immersive VR and, to a lesser extent, fully immersive VR [19], but a low proportion using non-immersive VR. In fact, researchers are currently debating whether fully immersive VR is better than moderate VR technology, stressing the relevance of immersion as it enhances participants' experience and promotes a greater sense of presence and involvement in the cognitive tasks. Thus, the fact that the SLB was used for the purpose of this study in a low immersion setup, according to the criteria of Miller and colleagues [50] on immersion levels, may also explain the lack of significant results at the level of the primary outcome, i.e., executive functioning. Nevertheless, the impact in global cognitive functioning is of interest and it is aligned with previous

research. Moreover, retention in this intervention program was considered high as only one dropout was observed throughout this intervention. It is possible that the use of serious-games elements (e.g., difficulty levels) contextualized in IADL have contributed to improve motivation and to retain patients in this intervention program.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Structure of the Intervention Protocol.

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