Manuscript title: Computerized cognitive training using virtual reality on everyday life activities for patients recovering from stroke

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Jorge Oliveira^{1,2} Pedro Gamito^{1,2} Beatriz Lopes¹ Ana Rute Silva¹ João Galhordas³
Eduarda Pereira³ Elisabete Ramos³ Ana Paula Silva³ Áurea Jorge³ António Fantasia³

1) EPCV, Universidade Lusófona de Humanidades e Tecnologias (ULHT), Lisbon, Portugal.

2) HEI-Lab, Universidade Lusófona de Humanidades e Tecnologias (ULHT), Lisbon, Portugal.

3) Serviço de Psicologia, Centro de Medicina de Reabilitação de Alcoitão (CMRA), Alcabideche, Portugal.

Corresponding author: Jorge Oliveira; Address: Universidade Lusófona de Humanidades e Tecnologias, EPCV. Campo Grande, 376. 1749-024 Lisbon, Portugal; Tel: 00351 217 515 500; Fax: 00351 217 577 006; Email: jorge.oliveira@ulusofona.pt

ORCID ID:

Jorge Oliveira: 0000-0002-3467-4981

Pedro Gamito: 0000-0003-0585-8447

Abstract

Recent studies argue that the use of virtual reality tasks depicting activities daily living may be an effective means for cognitive rehabilitation. The aim of this study was to test an ecologically oriented approach in virtual reality resembling the demands of everyday life activities for cognitive rehabilitation following stroke. The sample comprised 30 sub-acute stroke patients recovering from stroke in a rehabilitation hospital. They were assessed in a single-arm pre-post intervention study on global cognition, executive functions, memory and attention abilities. The intervention consisted of virtual reality in a multidomain cognitive training approach depicting everyday life tasks (preparing food, choosing clothes, shopping, etc.). Improvements were found in the assessed cognitive domains at 6 to 10 post-treatment sessions. In-depth analysis through reliable change scores has suggested larger treatment effects on global cognition. Overall results suggest that the use of virtual reality-based exercises on everyday life activities may be a useful cognitive rehabilitation approach to provide short-term gains in cognition following stroke.

Keywords: Cognitive rehabilitation; Computerized Cognitive Training; Virtual reality; Stroke.

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Introduction

Worldwide data from the World Health Organization in 2016 estimate that about 6 million deaths related to stroke occur every year [1]. Stroke is a leading cause of long-term acquired disability among the adult population [2], comprising high social and economic burden due to hospitalization and outpatient treatment [3].

Stroke is responsible for cognitive deficits in most cases [4] with a high prevalence of executive dysfunction [5], which contribute to poorer treatment outcomes [6] and increase disability [7,8].

Stroke patients with cognitive impairments are referred to cognitive rehabilitation that may be conducted according to different methods. A recent meta-analysis on cognitive rehabilitation following stroke showed that most selected studies consisted of computerized cognitive training (CCT), while other methods consisted of therapist-led interventions along with paper-and-pencil activities or workbook materials targeting specific cognitive impairments [9].

Classical cognitive training is typically conducted under a cognitive-behavioural approach using paper-and-pencil exercises directed at specific cognitive functions. These approaches are supported in neuroplasticity by involving task-specific learning and repeated practice in paper-and-pencil exercises that aim neural reorganization and functional recovery [10]. Approaches consisting in CCT replace the paper-and-pencil materials with computerized exercises, but the use virtual reality is expanding this approach by offering the opportunity to create enriched and more realistic environments that resemble tasks based on instrumental activities of daily living [11]. Within virtual

reality environments, visual and auditory feedback may be also naturally delivered promoting task-specific learning [12]. Involving meaningful and interactive practice in CCT may increase treatment compliance [13] and contributes to improve patient's awareness about disability [14]. CCT is also well accepted by both patients and clinicians [15].

There are diverse virtual reality environments targeting body function and motor activity, but few have been used as multidomain CCT following stroke. Some examples are the Reh@City [16]; and the Systemic Lisbon Battery [17], which provided superior effects in cognition compared to treatment-as-usual controls.

A meta-analysis reveals small to moderate effect sizes of CCT using virtual reality on cognition of stroke patients [18]. Another meta-analysis [9] on CCT and classical interventions suggested a small overall effect on cognition but did not reveal specific effects related to cognitive rehabilitation approach (i.e. CCT did not produce higher effects than classical interventions).

A recent randomized controlled trial (RCT) comparing virtual reality immersive training with CCT in acute stroke patients suggested similar effects both at the level of attention and memory, but superior effects of CCT using virtual reality for improving daily living performance were found, supporting far transfer effects of this kind of training to overall functionality [19]. These findings suggest that CCT using virtual reality may be more effective at producing global improvements in cognition, which is aligned with a separate literature regarding the effects of CCT in old aged individuals [20]. Such results may be explained by the ecological validity of the cognitive exercises that are contextualized in the IADL's domains, such as shopping, choosing clothes, meal preparation, etc. It is possible that such exercises involve a more generalized training on cognition rather than being focused in isolated cognitive functions.

Therefore, this study aimed at contributing to this topic by providing the data on the effectiveness of an multidomain CCT in improving cognition following stroke. The virtual reality exercises used in the cognitive training program depicted everyday life activities involving diverse cognitive functions, which are expected to provide generalized effects in cognition and executive functions.

Method

Study Design

The study design consisted of a single-arm pre-post design involving stroke patients recovering from stroke in a rehabilitation hospital.

Sample size calculation

Sample size calculation in *a priori* power analysis was carried out with G*power software. To detect a medium effect size d (.50) [21] for the mean difference in matched pairs, given a significance level of .05 and statistical power of .80, the minimum required sample was 27 participants.

Sample

The patients were recruited at the *Centro de Medicina de Reabilitação de Alcoitão* which consists of a larger rehabilitation center in Lisbon region of Portugal assisting people with motor/cognitive impairments due to different clinical conditions. The inclusion criteria were: 1) time since stroke between 1 to 6 months; 2) aged over 18 years-old; 3) no visual/auditory deficits that would affect the administration of the neuropsychological tests; 4) no history of psychiatric or neurological disorder other than stroke; 5) no history of alcohol or drug abuse; 6) adequate cognitive and language abilities to provide informed consent to the study; 7) agreed to participate in the study after its objectives have been explained both orally and through the written informed consent. Patients were excluded if they do not complete at least 6 sessions of training

(i.e. at least 180 minutes of intervention), being this threshold dependent on the duration of medical treatment at the hospital. Nine patients were excluded due to this criterion that completed 4/5 sessions of training.

The final sample consisted of 30 sub-acute stroke patients (18 male) within the critical period of six months of stroke recovery [22]. They had an average age of 60 years ($SD = 10$), mostly with primary schooling ($n = 9$). All patients were right-handed. Regarding the clinical characteristics of stroke episode, the proportion of lesions in the left hemisphere was higher (40%) in comparison to the right hemisphere (35%) and those involving both hemispheres (25%), whereas the most common type of stroke was ischemic stroke (45%), in comparison to haemorrhagic stroke (15%) and non-determined stroke (40%).

Measures

The neuropsychological evaluation was based on established neuropsychological tests for global cognitive functioning, executive functions, memory and attention abilities.

The Montreal Cognitive Assessment (MoCA) (Portuguese version) [23], is a brief screening tool for mild cognitive deficits. The MoCA evaluates different cognitive domains: executive functioning, visual-spatial ability, memory, attention, concentration and working memory, language, temporal and spatial orientation. The test is scored between 0 to 30 points, where the higher scores reflect better the cognitive performance. The test-retest reliability for the Portuguese version was $\alpha = .90$ [23].

The Frontal Assessment Battery (FAB) (Portuguese version) [24] is a battery consisting of six subtests that evaluate frontal brain processes of executive functions: Similarities (conceptualization), Lexical fluency (mental flexibility), Motor series “Luria” test (programming), conflicting instructions (sensitivity to interference), Go-No-Go (inhibitory control) and prehension behaviour (environmental autonomy). Each

subtest is scored between 0-3, with total scores ranging 0-18, in which the higher the score the higher cognitive ability. The FAB test-retest reliability was retrieved from a prior Portuguese study with old-aged participants ($\alpha = .74$) [25].

The Wechsler Memory Scale - WMS-I [26] allows a brief assessment memory ability, which comprises tests for visual and verbal memory, mental control, logical memory and digit span. This test is scored in several subtests that are summed into a composite score, and a score correction based on age - Memory Quotient, in which higher scores reflect better memory skills. Test-retest reliability was not possible to ascertain for the Portuguese population; therefore, the alpha was retrieved from a study using a clinical sample of psychiatric and neurologic patients revealing an $\alpha = .89$ [27].

The Color Trails Test – CTT [28] is a neuropsychological measure for focused and divided attention that also assesses sequencing ability and mental flexibility, visual search, and motor functions. In the CTT participants are asked to link the numbered circles in the right order in an A4 sheet. The CTT has two different forms (CTT1 and CTT2) in CTT2 with more distractors. In this study we focused only in execution times for the outcomes of this test. In addition, the interference index was also calculated from execution times, according to the following expression: $(CTT2-CTT1)/CTT2$. A score of 1.0 in this measure indicates that participants need twice the time to complete CTT2 than time spent to complete CTT1 [29]. Test-retest in this study was $\alpha = .76$ and $\alpha = .82$ for execution times in CTT1 and CTT2, respectively.

Instruments

The Systemic Lisbon Battery is a virtual reality program consisting of a virtual city in which the activities/exercises mirror cognitive activities of daily living. The Systemic Lisbon Battery depicts a city where the patients have to perform different activities that include tasks as using a toothbrush and a shower, choosing the right clothes to wear in

the wardrobe, pack up a shoe closet, following the steps of a recipe to bake a cake, or by watching news on a television and recollect pieces of this information on latter tasks. Outside the virtual apartment, the tasks consist of buying products in the grocery store/pharmacy or to perform visual search tasks in a virtual art gallery. During each session, spatial orientation and memory are involved by recalling the door numbers as well as specific details on each street of the virtual city. The intervention plan was structured according to the degree of difficulty and the proposed cognitive domains being trained.

The interaction with the software was done with the computer mouse. The level of difficulty of the patient in interacting with the virtual reality environment was rated by the clinician in a Likert scale (0 – independent, 1 – partially dependent to 2 – completely dependent). A frequency analysis was conducted to this data revealing that in most cases (73%) the patient used the mouse in a partially dependent way by asking help in some tasks, and that 10% interacted with the software in a totally independent way, whereas 17% of the users were totally dependent on the help of the psychologist. In such patients, it was the psychologist who used the computer mouse following the indications of the patient. The actions that were available were head movement in the X and Y axis along with the left mouse button to move and the right mouse button to interact with the objects. Figure 1 depicts some of the tasks used in these sessions, where the upper row depicts some of the tasks in the virtual apartment (from left to right – wardrobe, shoe closet, television and kitchen), whereas in the bottom row (from left to right – city, grocery store experimenter menu, grocery store products, and the pharmacy).

Procedure

This research was carried out in *Centro de Medicina de Reabilitação de Alcoitão* in Portugal, where patients were included in an integrative rehabilitation program. This study is in compliance with ethical standards on human research and follows the principles of the Declaration of Helsinki, having been approved by the ethics committee of the host institution of this study.

Patients recruited for this study were patients undergoing rehabilitation of stroke sequelae. Conventional treatment involves a multidisciplinary team that provides rehabilitation in an organized, goal-oriented and user-centred approach. After an initial medical evaluation, the patients were included in the study if they have met the above inclusion criteria. The patients included in the study were not deprived from treatment-as-usual that involved physiotherapy, occupational therapy, speech therapy and psychology counselling. Physiotherapy sessions aimed at recovering motor and sensory functions through training on balance, gait and mobility; whereas occupational therapy was directed at improving functionality and autonomy in the basic and instrumental activities of daily living. The patients had daily sessions of physiotherapy and occupational therapy. Psychology sessions were also included in a weekly basis mainly to help promoting better psychological adjustment.

The cognitive intervention with virtual reality exercises occurred twice a week. The sessions and the data collection took place inside the hospital facilities, in the Psychology department. The participants underwent a neuropsychological evaluation through the MoCA, FAB, WMS, and CTT in two different assessment moments (i.e. one week before and one week after the rehabilitation program).

Each patient performed on average 7 sessions (*Min.* 6 and *Max.* 10), with an average duration of 30 minutes. No significant associations were found between the number of sessions with the main neuropsychological outcomes at post-treatment

assessment ($p > .05$). The sessions were scheduled in days without other rehabilitation activities such as physiotherapy or occupation therapy.

Statistical analysis

Before conducting the inferential statistics, the main outcomes were tested for normality using the Shapiro-Wilk test along with the analysis of skewness and kurtosis of each distribution. None of the distributions from the neuropsychological outcomes violated the normality assumptions. Inferential statistics were calculated using paired-samples t student tests for differences between pre- and post-treatment assessments for each of the neuropsychological outcomes (i.e. total scores from the MoCA, FAB, WMS and the execution times and interference index of the CTT). Degrees of freedom for t tests are shown in brackets. Effect sizes for the expected change were calculated according to Cohen's d as a basis for the design of future RCT studies. According to Cohen [21] a small effect size corresponds to .20, medium to .50 and large to .80.

The significant tests were explored further using the modified reliable change index (RCIm), which allows analysing the individual changes between pre- and post-treatment [30]. The RCI approach standardizes individual changes according to the standard error of difference, which accounts also for test-retest stability in the calculation of a standardized difference between test scores [31]. Test-retest stability for each main neuropsychological outcome were retrieved from the Portuguese population when available. This was the case for the MoCA and FAB, but not for the WMS and CTT in which test-retest scores were not available for the Portuguese population. As for the WMS, test-retest scores were retrieved from a seminal study of Ryan et al. [27], whereas for the CTT a Brazilian study [29]. The resulting Z-score from RCIm analysis describes the performance of the participant at post-treatment relative to their baseline.

Accordingly, a change exceeding $Z = 1.96$ reflects a reliable change between pre- and post-test scores for a 95% confidence interval.

Results

Comparisons between pre- vs. post-treatment assessments for neuropsychological outcomes

The neuropsychological data from the measures used in the study are provided in Table 1 with the scores from the main neuropsychological outcomes along with the scores for each of the subtests. These differences were tested for the main outcomes of each neuropsychological measure. The t student tests showed statistically significant differences in the total scores of each of the neuropsychological measures and in execution time in CTT2, suggesting improvements in these scores at post-treatment assessment in global cognitive function [MoCA total score: $t(29) = -4.746$; $d = .54$; $p < .001$], executive functions [FAB total score: $t(28) = -2.801$; $d = .40$; $p < .01$], memory [WMS Memory Quotient: $t(25) = -3.297$; $d = .39$; $p < .01$], and attention [CCT2 Execution Time: $t(12) = -6.199$; $d = .70$; $p < .001$], as shown in Table 2.

Modified Reliable Change Index in neuropsychological data

The RCIm was computed for the significant paired-samples t student tests. The resulting variables related to RCIm are given in a standardized scale, in which positive scores describe improvements while negative scores describe a decrease in cognitive performance. The distribution of these scores are shown in Figure 2 and Figure 3 which reveal a positive change in the distributions of the RCIm scores. The proportion of positive and negative changes that are unlikely to occur by chance (95% CI) is shown in Table 3. Therefore, a positive change exceeding ($Z > 1.96$) threshold in more than 5% for one-tailed hypothesis would probably have been due to a treatment effect. This analysis showed that 38% of the sample improved global cognitive function, 15%

improved memory and attention abilities and 8% improved executive functions above $Z > 1.96$.

Discussion

The aim of this study was to explore the effectiveness of a multidomain CCT approach using virtual reality exercises for cognitive rehabilitation following stroke. One important aspect in virtual reality for rehabilitation is that it allows to train patients in exercises that mimic the demands of activities of daily living requiring the use of cognitive processes in a similar way as they operate in real life contexts [32]. This is a crucial aspect that may help promoting the transfer of gains to everyday life activities [19]. It is also possible ecological validity of such approaches foster global improvements in cognition and executive functions that result from training cognition in an integrated manner rather than being focused in isolated cognitive functions. In fact, most of the tasks used in this study involve executive functions as planning and working memory or selective and sustained attention/concentration, or other cognitive abilities as visual and declarative memory.

The results revealed better performance in tests measuring global cognition, executive functions, attention and memory. However, given the lack of a control group, it is difficult to dissociate the effects of spontaneous recovery from treatment-related factors. In-depth analysis was then performed using RCI_m to help determining whether these improvements are larger than those expected by chance in a 95% confidence interval. We have calculated the RCI_m for each significant outcome, which provided an individual analysis on the change between pre- and post-assessments while accounting for temporal stability of each measure [31]. These results have suggested larger improvements in global cognition than in the other outcomes, revealing that 38% of the sample improved global cognition beyond the 95% confidence interval. Such

improvements contrast this approach with other more focused interventions as provided in computer-based cognitive training showing specific effects on verbal memory and visual attention [33].

The improvements found in the other outcomes were less pronounced, possibly because these exercises did not train isolated cognitive abilities as memory or attention. On the other hand, it is also possible that improvements in executive functions require a higher treatment dosage than the maximum dose of 300 minutes used in this study. Although recent systematic reviews suggest no clear advantages for higher intensity or treatment dosage of CCT using virtual reality, our mean overall dose (i.e. ~240 minutes divided in 2 days/week in 30-minute sessions) is quite lower than other similar studies (i.e. ~685 minutes, ranging between 200–1440 minutes), as depicted in Aminov and colleagues' review [18]. In fact, Rogers and colleagues [9] states that dose effects describe a logarithmic function, in which higher doses are associated with larger effect sizes but reaching the plateau around 20h of treatment. In our study, the number of sessions was limited to the time of medical treatment for stroke at the hospital, which did not allow to conduct longer interventions. Moreover, given the visual demands of the virtual reality tasks, the duration of the individual sessions was restricted to 30-minute sessions. In a previous study using the Systemic Lisbon Battery using a higher treatment dose, it was found that the main improvements were observed at the level of attention and memory, but unfortunately, this study did not assess executive functions.

Another limitation was that patients recruited for our study were included in a integrative rehabilitation plan comprising physiotherapy, occupational therapy and psychology sessions. The inclusion of an active control group without virtual reality rehabilitation would have been important to distinguish the effects related to treatment

modality. Finally, a follow-up assessment would have been key to assess the long-term stability of such improvements.

Overall, the effect found in the current study may be important and suggests that CCT using virtual reality may be a useful approach to provide short-term gains in cognition following stroke. Further studies are required to provide more consistent evidence on the effects of CCT with virtual reality. It remains to be studied whether these effects are reflected by changes in everyday function or whether they remain stable during time at longer follow-ups.

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Declaration of Interest:

The authors report no conflicts of interest.

Table 1. Descriptive data of each subtest of the neuropsychological tests at pre- and post-treatment assessments

	M_1	SD_1	M_2	SD_2
MoCA				
Visuospatial/Executive	2.90	1.57	3.45	1.41
Naming	2.76	.50	2.90	0.30
Attention	4.20	1.62	4.90	1.56
Language	1.55	.94	2.18	.85
Abstraction	1.26	.74	1.73	.45
Delayed Recall	1.93	1.59	2.86	1.84
Orientation	5.70	.46	5.50	.68
Total Score	19.90	5.33	22.86	5.12
FAB				
Similarities	2.59	.68	2.90	.31
Lexical Fluency	1.67	1.04	1.86	1.08
Motor Series	2.21	.96	2.43	.87
Conflicting Instructions	2.10	1.05	2.28	.92
Go-No Go	2.07	.99	2.34	.86
Prehension Behavior	2.93	.26	2.93	.37
Total Score	13.37	3.14	14.58	2.91
WMS				
Current Information	5.15	.88	5.50	.58
Orientation	4.88	.43	4.92	.27
Mental Control	5.27	2.21	6.60	2.06
Logical Memory	14.24	7.07	10.36	5.48
Memory Span	8.88	3.54	8.64	3.71
Visual Reproduction	10.16	7.51	9.68	3.45
Associative Learning	16.92	8.40	21.65	6.61
Memory Quotient	48.92	18.48	57.19	23.53
CTT				
CTT1 Execution Time (s)	119.14	47.90	108.57	55.01
CTT2 Execution Time (s)	218.93	68.07	171.46	58.92
Interference Index	.96	.54	.71	.63

Note: MoCA – Montreal Cognitive Assessment; FAB – Frontal Assessment Battery; WMS – Wechsler Memory Scale-I; CTT – Colour Trails Test

Table 2. Neuropsychological data from paired t-tests between pre- vs. post-treatment assessments

	M_Z	SD_Z	t	d
MoCA Total Score	-2.87	3.30	-4.746***	.54
FAB Total Score	-1.21	2.32	-2.801**	.40
WMS Memory Quotient	-8.27	10.73	-3.927**	.39
CTT1 Execution Time	10.57	32.03	1.235	.20
CTT2 Execution Time	45.85	26.67	6.199***	.70
CTT Interference Index	.25	.53	1.798	.43

Note: * $p < .05$; ** $p < .001$

M_Z – Mean difference between post- vs. pre-assessment; SD_Z – Standard deviation of the mean difference; t – paired t -Student statistic; d – Cohen's d

Table 3. Reliable change proportions for the main neuropsychological outcomes

	Negative change	Positive change	$Z > 1.96$
MoCA Total Score	15%	85%	38%
FAB Total Score	35%	65%	8%
WMS Memory Quotient	20%	80%	15%
CTT2 Execution Time	0%	100%	15%

Note: RCI_m equal to 0 are not included.

Figure 1. Examples of the tasks used in virtual reality rehabilitation.

Figure 2. RCIIm scores for each outcome.

Figure 3. RCIIm distributions for each outcome.