Attention and Motor skill improvements in Mild Cognitive Impairment patients using COSMA Application

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Abstract

Serious games have grown rapidly to provide cognitive stimulation for people with cognitive impairment. In this endeavour, we have created the COSMA games. In this two-arm study with patients with mild cognitive impairment (MCI), we investigated information processing speed and cognitive skills with 28 days of use of COSMA games, a brain stimulation gaming platform. We measured reaction times during neuropsychological assessment with the Cambridge Neuropsychological Test Automated Battery and the COSMA games. Results showed that people with MCI who played COSMA for 28 days at home were faster in 48% of the COSMA games and the Control group which played only during the laboratory visits was faster in 20% of the COSMA games at the end of the study. Overall, these outcomes showed evidence that motor skill practice and learning retention are possible in people with MCI and that these skills are still able to improve with the regular practice of the COSMA games.

Keywords: *Serious Games, Mild Cognitive Impairment, COSMA;*

1 Introduction

Serious games in dementia are enjoyable non-pharmacological interventions that aim to slow down cognitive deterioration [1]–[4]. The demand for such treatments is growing, with 3-8% of the world's population now being diagnosed with dementia and these numbers will increase in the next few years [5]–[7]. Following the recommendations made by the National Institute for Health and Care Excellence (NICE) the suggested interventions may focus on cognitive stimulation, as this may be beneficial to cognition, independence and well-being of dementia patients [8].

In people with mild cognitive impairment (MCI), learning and motor skills are often impaired [9], [10]. While these skills are necessary for occupational and leisure purposes, not maintaining these skills for a long time might adversely affect people's health and quality of life. Reaction time measurements in neuropsychological testing are strongly associated with cognitive skills [11]. It is suggested that a positive correlation between reaction times during task performance and motor skill development exists during these kinds of assessments [12]. Also, there is a positive relationship between reaction time measurements and the brain's processing speed [13]. Reaction time, which is the minimal time needed to respond to a stimulus, is a basic measure of processing speed and is assumed to reflect the underlying cognitive processes such as decision making and action preparation [14].

Previous studies showed that reaction times are valid non-invasive measurements of cognitive function in people with dementia; therefore, some researchers documented the duration performance in these groups of patients while playing serious games and completed neuropsychological test assessments [11], [15]. There already are serious games used as screening and cognitive improvement tools in the elderly and people with dementia, for example, the Augmented Reality serious game Smartkuber and the TrainBrain [15]. These applications have been mainly designed to assess cognitive functions and minimize the effects of cognitive decline [11], [15]. Research evaluations of such software serious games developments, for example, the whack-a-mole without distractors and hit-the-ball with one distractor game, were used to analyze and explain the response times in people with MCI, dementia and healthy individuals [15]. Results showed that the time to complete tasks was longer for people with MCI and dementia and that the serious games created were valid methods to assess cognitive dysfunction in these groups of patients [15]. Also, the time measurements in whack-a-mole and hit-the-ball games correlated with the neuropsychological assessment Mini Mental State Examination and showed screening reliability for MCI and dementia.

Furthermore, the reaction time measurement is considered a valid method to differentiate between moderate or severe dementia, MCI and a healthy brain. A previous study investigated whether the game Continuous Visual Attention Performance Test, a Go/No-Go task with visual target stimulations, has clinical utility in elderly with low education [16]. Results indicated significant discrimination performance for people with MCI and moderate or severe dementia, independent of educational level, with psychometric properties, providing the clinicians with useful information about cognitive functions [16].

The above studies are inspiring and show the effectiveness of novel serious game interventions, which are reliable, non-invasive and non-pharmacological screening and cognitive stimulation instruments [11], [16]. In addition, they show that measuring reaction time via serious games might be clinically useful [16].

Cognitive stimulation, training and rehabilitation programs have often been implemented in people with MCI and dementia for the reason that pharmacological interventions do not seem to be effective in cognitive decline in dementia [17], [18]. They refer to various tasks focused on cognitive and social functioning, such as reminiscence and reality orientation therapy, and they aim to stimulate the brain through structured and guided practice [17]. These are usually computerised cognitive interventions and serious games for dementia and can be accessed through digital devices [17], [18]. For example, the Big Brain Academy video game, Complete Brain Workout, Lumosity, MasterQuiz I, Min Wii and Smart brain Games, puzzle and quiz games and easy physical exercises have been designed to stimulate processing speed and mental flexibility [19]. However, most of the serious game platforms have not been validated as reliable cognitive stimulation tools, and most of them are commercial [20]. They are used for the purpose of cognitive improvement with little evidence that they are successful in their goal. For this reason most of the nursing homes, psychogeriatric centers, hospitals, residential homes and rehabilitation centers implement physical games and discussions to motivate dementia patients in remaining cognitively and socially active [21]. Nonetheless, such serious games have inspired the creation of similar application platforms for MCI and dementia, and they have assisted patients with cognitive decline to remain cognitively alert [19].

Considering the huge impact on caregivers, patients [7], [22], [23] and healthcare systems [7], [24] we have developed a framework of serious games for people with cognitive impairments called ‘Cognitive Operational System for Mental Health Advancement’ (COSMA) [25] that measures reaction time for each game as shown in Table 1. Clinical neuropsychologists and clinicians with experience in dementia were constantly consulted during system development to ensure that the COSMA games would be easy and comfortable to play; and they would be created according to the NICE recommendations for people with cognitive decline and dementia [8], [15], [25]. The COSMA games were designed to offer a sense of positivity, motivation and engagement with activities, expecting cognitive, physical and psychosocial health outcomes, according to previous researchers

who created serious games for people with dementia [20], [25]–[27]. In addition, the COSMA games aim to promote engagement according to research that discussed the serious games creation and design on a health related topics and during game based learning activities [28]–[34].

The COSMA application is a brain stimulation gaming platform for people living with MCI and early dementia (Alzheimer's disease (AD) and/or vascular dementia) [25]. The gaming application aims to deliver cognitive rehabilitation and psychological well-being in the patients along with entertainment benefits [25].

COSMA contains 8 game-modules (36-games) which include reminiscence, visual, daily tasks, language, time-spatial, decision making, meditation, and biofeedback modules, each focusing on key symptoms of early dementia [25] (Table 1). There are 36 activities in total, and each one of them focuses on the symptoms mentioned above. All these activities are designed for therapeutic purposes, thereby allowing the user/player to have n number of attempts within timeframes to complete each game and calculate scores based on the reaction time and the number of attempts that took to finish each game. The dynamics of the game design is to assist users in repeating tasks (e.g., repeating making a cup of tea in the Daily tasks Module). The goal of the repetition is to create a memory on the particular task attempting to improve cognitive functions, which are of practical use for MCI. The overall dynamics of the games are to practise, learn and improve.

COSMA platform is also carefully designed to be an individualized therapy tool entwined with an application and an online portal (website-based). The online portal is a platform where the carers select and upload patient specific personal pictures such as life events at regular intervals which is accessible via the COSMA Application. The above aimed to provide comfort while playing the games, as the users get familiar and psychologically happy to reminiscence on the pictures of friends and family, and, of both past and present events. This was indeed a recommendation based on our research observations as the clinical researchers had witnessed emotional reactions during the clinical trials of people with dementia playing the COSMA games. In particular, it was observed by our research team that people with dementia occasionally started talking about the events viewed in the pictures in detail, and that inspired the collection and upload of personal pictures in the COSMA application and online portal.

The study aims to prove the efficacy of the COSMA application in improving cognitive functions in people with MCI. We also aim to investigate the mechanism of calculating cognitive functions in COSMA software concerning reaction time calculations. Thereby, in this study the cognitive functions to be investigated are measured using the reaction/duration time calculations from the neuropsychological test battery Cambridge Neuropsychological Test Automated Battery (CANTAB) and the reaction time calculation from COSMA. We hypothesize that the MCI treatment group would exhibit lesser reaction times in comparison to the MCI control group indicating cognitive function improvements.

Table 1. *The COSMA modules and games*

COSMA Modules	Games	Description
Reminiscence	Family tree	Recognise family members
	Identify the person	Recall family members
	Jigsaw puzzle	Reconstruct picture
	Match the events	Match pictures that are the same
	Presence of time	Identify people who are present in one's life
Visual tools	Identify item colour	Identify the colour of a shape
	Identify shapes	Remember shapes
	Identify colours	Remember colours
	Flicker colours	Find the colour that flashed on the screen
	Flicker patterns	Find pattern that flashed on the screen
Spatial time	Spot the area	Recall important locations
	Construct time	Set the clock to the correct time
Daily tasks	Daily schedule	Remember daily habits
	Grocery shopping	Engage in grocery shopping
	Make a recipe	Engage in meal and drink preparation
	Calendar	Recall dates, years, and days
Decision making	Highlight the order	Present order of shapes
	Sudoku	Fill in the empty boxes with appropriate numbers
	Match pictures	Match pictures that are the same
	Math	Make calculations
Language	Identify object 1	Find picture that is described with a word
	Identify object 2	Find word that describes the picture
	Identify object 3	Write the name of the picture
	Recall	Recall the word that flashed on the screen
	Word search	Spell the word

2 Materials and Methods

2.1 Selection and description of participants

The clinical study was designed to evaluate the effectiveness of gaming platform COSMA conceptualized and designed by Brainberry Ltd [25] and Auroville Health Care Research (CRO); and conducted by Bangalore Neuro Centre, India on adults with MCI. The study followed the ethical principles of the 2013 declaration of Helsinki involving human subjects; and it was approved by the CDSCO & USFDA OHRP Registered Independent Ethics Committee, in Bangalore, India.

Edinburgh handedness questionnaire [35] was used to select right handed subjects. The reason behind this choice was that each hand use activates specific cortical motor areas in the brain [36]. Also, people tend to be faster when they use a tablet with their right hand [37], and thus, it would be logical to control for any biases and confounding variables when we considered the reaction times in the MCI groups. The questionnaire was administered during the screening visit.

All participants were recruited from the Bangalore Neuro Centre, India, via their MCI patient database. All participants were diagnosed with MCI by neurologists and neuropsychologists according to their medical history, the Petersen et al. [38] criteria, neurological assessment, and the inclusion/exclusion criteria that are listed in Table 2.

A total number of 31 participants with a clinical diagnosis of MCI took part in the study: 21 people (16 males and 5 females, mean age ±SD, 46.47±1.77 years) participated in the Treatment group, whereas 10 participants (5 males and 5 females, 51.30±7.29 years), comprised the Control group. The study design included participants with young-onset cognitive decline, considering previous research that showed this decline in adults 40 to 65 years of age [39]–[42]. Also, the decision to recruit MCI subjects younger than 65 years was to avoid participant withdrawal. Therefore, there were no dropouts in the study.

Table 2. *Inclusion and exclusion criteria for the MCI subjects*

Inclusion criteria	Exclusion criteria
Males and females	Subjects with mental illness and/or neuropsychiatric disorders
Verified neurological evaluation from a neurologist	Subjects who are on anti-depressants
Brain MRI examination performed that verify the presence and severity of indication and diagnosis of mild neurocognitive impairment fulfilling the MCI criteria[38]	Subjects with significant primary visual impairments
Younger than 65 years of age	Subjects with any significant medical condition (e.g., significant psychiatric or neurological disorders, active alcohol/drug abuse, etc.)

Classified as right-handed	Any medical condition that is unstable/poorly controlled or other factor (e.g., planned relocation) that the Investigator felt would interfere with study evaluations and study participation
Read and write in English language	Subjects who have participated in any clinical study within 3 months from the date of enrolment
Use Android Tablet	Subjects who mentally unable to comprehend the responsibilities and adhere to the stipulations of the protocol
Willing to give informed consent for participation	
Able to comprehend and understand the responsibilities during the testing period	

2.2 Cognitive tests

In COSMA games, the reaction time to complete each test referred to the processing speed that was taken to make decisions in the tasks and act upon them during testing [43]. All subjects played the COSMA games during the visit arrangements; and the Treatment group only played at home for 28 days.

The CANTAB tests were conducted to assess cognitive impairment in the subjects. The CANTAB tests are able to show cognitive changes in people with dementia related diseases, in pre-post treatment protocols [44], [45] (see Table 3).

Table 3. *Screening and repeated metrics in the study*

Screening			
Visit 0		Magnetic Resonance Imaging (MRI) brain scan	MRI methodologies are essential to diagnose MCI in patients [46], [47].
Assessment			
Visit 1 -2 -3	CANTAB Battery Tests	Motor Screening Task Mean Latency (MOTML)	The Motor screening task assessed the mean response latency (MOTML) based on the selection of stimuli presented in different locations on the screen, one at a time [44].
		One Touch Stockings Mean Latency to Correct (OTSMLC)	The One touch stockings of Cambridge task assessed the mean latency for correctly choosing stocking balls (OTSMLC) [44] .

		One Touch Stockings Median Latency to First Choice (OTSMLFC)	Also, the One touch stockings of Cambridge task assessed the mean latency of the first correct choice (OTSMLFC) [44].
		Pattern Recognition Memory Mean Correct Latency Immediate (PRMMCLI)	The Pattern Recognition Memory test assessed the mean latency to correctly select an appropriate pattern (PRMMCLI) [44].
		Reaction Time Task Simple Mean Movement Time (RTISMMT)	The Reaction Time Task assessed the mean time taken for a subject to release the response button and select the target stimulus after it flashed with a colour on screen (RTISMMT) [44].
		Reaction Time Task Simple Mean Reaction Time (RTISMRT)	Also, the Reaction Time Task assessed the mean duration it took for a subject to release the response after the presentation of a target stimulus (RTISMRT) [44]
		Rapid Visual Information Processing Mean Response Latency (RVPML)	The Rapid Visual Information Processing task assessed mean response latency on trials where the subject responded correctly (RVPML) [44].
Visit 1-2-3	COSMA games	Reaction times	All COSMA games measured the reaction times, duration in seconds. The reaction times were calculated for each question in a game and then averaged for each game in each visit.

2.3 Study Protocol

The subjects enrolled in this study were divided into Treatment group who played COSMA every day for 28 days for 60 - 90 min with breaks and Control group played COSMA only on the measurement days (Day 1, Day14 and Day 28). The study was designed as an open label, prospective, randomized, comparative, two arm study, and followed the enclosed protocol:

Visit 0 - Screening Visit: The screening procedure was commenced only upon informed consent from the subject. All participants were selected from the MCI patient database in Bangalore Neuro Centre and included vigorous MRI brain scans.

Visit 1 (Day 1): Baseline evaluation: Eligible patients were enrolled and randomized. All subjects were trained to upload their family pictures into the software with the help of a clinician/technician/carer.

All participants including Control group commenced to play all the COSMA games. They had a neuropsychological assessment of the following scales and questionnaires: CANTAB [44] tests: 1. Motor screening task, 2. One touch stockings of Cambridge task, 3. Pattern recognition memory task, 4. Reaction time task, and, 5. Rapid visual information processing task.

The Treatment group players were given tablets with COSMA to take home and play every day, with instructions to both the participant and the carer. Control group players were not given a tablet with COSMA but asked to continue with regular life and return after 14 and 28 days.

Visit 2 (Day 14): Repeated metrics: Repeated metrics were measured. Subjects (including Control) played COSMA, and their neuropsychological assessment (mentioned above) was evaluated. The same procedures done on Visit 1 were repeated.

Visit 3: Day 28: Second repeated metrics: The same procedures as done on Visit 2 were repeated. This marked the end of the study for each enrolled subject.

The Treatment group participants were contacted by the principal investigator every day to ensure that they played the COSMA games, which were 36. In addition, a researcher would inspect their online COSMA activity and would inform them of the games they missed playing during the day in order to complete the study requirements. As a result, participants played most of the games every day, and it was ensured that they played more than 25 games per day.

2.4 Sample Size

The sample size for the study was calculated using a G*Power [48] statistical analysis based on the effect size of two studies. The effect size has clinical significance in studies assessing clinical populations and indicates whether a treatment/manipulation/clinical condition is essential for the patients' health, and it requires to be noticed by expert clinicians [49]. The effect size and the Power are critical points in sample size calculation because they determine how many participants are required in a study to reach statistical significance and they are derived from previous studies' statistical significant outcomes [49]. Cognitive training in older population [50] showed improvement with effect size 0.17; and cognitive training in people with MCI showed improvement with effect size 0.33 [51]. Taking into account a power of 0.80 and α level 0.05 we conducted two G*Power [48] analyses, using each effect size separately. The program was set to the F family of tests to Repeated measures ANOVA, within factors, and a 'A priori' power analysis to determine the required sample size. The measurements assigned for the study were the 25 COSMA games participants played in a visit, and 2 groups. Results showed that 6 to18 subjects, in each group are requested to participate to have significance in our study. Based on the above, a randomised design allocated the Treatment and Control group in a 2: 1 ratio. The unequal allocation scheme was implemented because a high drop-out-rate was expected in the Treatment group [52], [53]. Due to interindividual variability in the cognitive decline in people with dementia we suggested at least 20 subjects in the Treatment group and 10 subjects in the Control group.

2.5 Data Analysis

All statistical analysis was conducted with SPSS Inc. v.24 [54]. The CANTAB tests and the overall COSMA reaction times were presented in means and standard deviations. Repeated Measures (RM) ANOVA, with within subject factor Time (Day 1, Day 14 and Day 28) were conducted for the CANTAB tests and each one of the COSMA games. Pairwise comparisons were calculated with Bonferroni tests to identify which means were different between baseline Day 1 to Day 14 (V1-V2) and Day 28 (V1-V3). The Bonferroni

t tests were chosen in the pairwise comparison analysis as a simple and safe procedure due to small sample sizes that would violate the sphericity assumption [55], [56]. Data were presented in p-values with α=0.05. The RM ANOVA statistical design was chosen to inspect our research questions based on previous cognitive training studies which investigated the effects of an intervention/game in older adults and MCI patients, with the same statistical analyses [57]–[59]. In addition, the use of RM ANOVA is essential to implement in our study because of our methodological procedures. We measured the same variables repeatedly at different time points according to statistical knowledge about how to use RM ANOVA correctly in research when methodological procedures include repeated testing assessments [56]. In each game analysis the sample sizes were adjusted to be equal based on subjects who played each game in all visits because RM ANOVA excludes data points from the analysis entirely when participants have missing values [56]. Overall, subjects played 25 out of 36 games and those were accounted for in the statistical analyses. Two statistical analyses were of interest: the RM ANOVA and the pairwise comparisons.

3 Results

The cognitive improvement in both groups was assessed from the reaction times calculated after playing the COSMA games during the visits. The reaction time calculations were indicative of cognitive improvement when they were cross-validated with the CANTAB tests. The CANTAB duration measurements showed that the Treatment group improved in the Motor screening task and the Rapid visual information processing task from Visit 1 to Visit 2; while the Control group did not show any improvement in those tests (see Table 4).

The COSMA game statistical analyses showed improvement in 48% of the games, in the Treatment group, in Reminiscence, Spatial times, Daily tasks, Decision making and Language modules (see Table 5). The Control showed some improvement in 20% of the COSMA games, in the Decision making and Language module (See Table 6). In Tables 5 and 6 the grey lines show the COSMA games, which were significant in both RM ANOVA and pairwise comparisons.

The sections in COSMA games that showed significance in both Treatment and Control groups were the modules ‘Decision Making’ and ‘Language’. After a thorough inspection of the data that showed significance, we noticed that the reaction time calculations were reduced by 13.6 seconds in the Treatment group and 13.1 seconds in the Control group in ‘Decision Making’ module and decreased 5.8 seconds in Treatment and 6.7 seconds in Control in ‘Language’ module. Though, there is no remarkable difference in reaction time comparing the Treatment and Control group, the Treatment group has shown significance also in ‘Reminiscence’, ‘Spatial Time’ and ‘Daily Tasks’ modules which the Control did not show. The Treatment group reduced the time of playing the ‘Reminiscence’ games by 9.5 seconds, in ‘Spatial Time’ by 1.3 seconds, and in ‘Daily Tasks’ by 0.9 seconds.

Table 4: *The reaction time in CANTAB tests.*

		Treatment group						
		V1	V2	V3	F statistic	RM ANOVA p-values	V1-V2 p-values	V1-V3 p-values
CANTAB tests (milliseconds)	MOTML	1114.86 (±466)	778.19 (±276)	861.59 (±400)	$F_{(2,40)}$=4.942	**0.012**	**0.018**	0.196
	OTSMLC	10887.58 (±10277)	10560.01 (±7776.49)	8565.03 (±3761)	$F_{(1.50,30.03)}$=0.770	0.47	1	1
	OTSMLFC	8915.50 (±7456)	9238.48 (±6291)	7912.68 (±3783)	$F_{(2,40)}$=0.334	0.718	1	1
	PRMMCLI	1833.37 (±1663)	1483.89 (±486)	1566.18 (±1003)	$F_{(1.19,23.84)}$=0.542	0.499	1	1
	RTISMMT	259.06 (±81)	290.41 (±75)	302.48 (±60.47)	$F_{(2,38)}$=2.436	0.101	0.655	0.81

	RTISMRT	483.07 (±107)	503.79 (±124)	502.37 (±101)	$F_{(2,38)}$=0.199	0.821	1	1
	RVPML	581.74 (±212)	412.39 (±109)	414 (±211)	$F_{(1.50,28.5)}$=5.091	**0.02**	**0.027**	0.116

		Control group						
		V1	V2	V3	F statistic	RM ANOVA p-values	V1-V2 p-values	V1-V3 p-values
CANTAB tests (milliseconds)	MOTML	1167.19 (±420)	1135.85 (±645)	809.22 (±253)	$F_{(2,18)}$=1.868	0.183	1	0.069
	OTSMLC	7177.58 (±5130)	12247.91 (±12528)	8177.98 (±2155)	$F_{(1.29,11.62)}$=1.194	0.313	0.828	1
	OTSMLFC	6146.57 (±4871)	10410.76 (±9605)	7429.96 (±2255)	$F_{(2,18)}$=1.322	0.291	0.677	1
	PRMMCLI	1791.84 (±823)	1579.68 (±653)	1860.83 (±877)	$F_{(2,18)}$=0.604	0.557	1	1
	RTISMMT	267.31 (±97)	246.63 (±83)	281.65 (±127)	$F_{(2,16)}$=0.271	0.766	1	1
	RTISMRT	550.53 (±233)	429.11 (±54)	518.06 (±86)	$F_{(2,16)}$=1.704	0.213	0.568	1
	RVPML	504.03 (±119)	452.89 (±84)	419.88 (±134)	$F_{(2,18)}$=1.359	0.282	0.925	0.695

Table 5: *The reaction times in the COSMA games showed that there were significant differences between the visits in the Treatment group.*

Treatment group								
Modules	**COSMA games**					**RM-ANOVA**	**Pairwise comparisons**	
		V1	**V2**	**V3**	**F statistic**	**p-values**	**V1-2 p-values**	**V1-3 p-values**
Reminiscence	**Family tree**	**1.86 (±0.60)**	**2.04 (±3.22)**	**1.29 (±0.44)**	**$F_{(1.05, 20.08)}$=0.92**	**0.353**	**1**	**0.003**
	Identify the person	**16.18 (±12.85)**	**8.02 (±4.19)**	**6.61 (±2.46)**	**$F_{(1.11,21.9)}$=10.77**	**0.003**	**0.025**	**0.004**
	Jigsaw puzzle	**51.10 (±22.80)**	**39.85 (±20.74)**	**27.88 (±12.78)**	**$F_{(2,18)}$=3.84**	**0.041**	**0.818**	**0.088**
	Match the events	**1.92 (±0.94)**	**1.37 (±0.50)**	**1.37 (±0.59)**	**$F_{(1.21,20.67)}$=3.57**	**0.066**	**0.17**	**0.23**
	Presence of time	**1.34 (±1.14)**	**1.04 (±0.10)**	**1.02 (±0.07)**	**$F_{(1.01, 20.35)}$=1.50**	**0.235**	**0.749**	**0.251**
Visual tools	**Identify item colour**	**1.37 (±0.65)**	**1.29 (±0.42)**	**1.14 (±0.34)**	**$F_{(1.32, 26.44)}$=1.57**	**0.226**	**1**	**0.338**
	Identify shapes	**1.20 (±0.37)**	**1.12 (±0.24)**	**1.03 (±0.07)**	**$F_{(1.39,23.77)}$=1.98**	**0.169**	**1**	**0.179**
	Identify colours	**1.61 (±1.20)**	**1.12 (±0.22)**	**1.07 (±0.12)**	**$F_{(1.05,17.89)}$=2.98**	**0.1**	**0.364**	**0.247**
	Flicker colours	**1.56 (±0.86)**	**1.13 (±0.27)**	**1.03 (±0.07)**	**$F_{(1.12, 18.4)}$=4.57**	**0.042**	**0.251**	**0.072**
	Flicker patterns	**1.36 (±0.75)**	**1.21(±0.47)**	**1.11 (±0.27)**	**$F_{(2,36)}$=0.98**	**0.382**	**1**	**0.61**
Spatial time	**Spot the area**	**1.57 (±0.77)**	**1.18 (±0.31)**	**1.08 (±0.16)**	**$F_{(1.26,21.50)}$=5.33**	**0.024**	**0.184**	**0.042**
	Construct time	**8.91 (±2.26)**	**6.34 (±3.33)**	**5.02 (±1.17)**	**$F_{(2,34)}$=13.06**	**<0.001**	**0.047**	**<0.001**
Daily tasks	**Daily schedule**	**1.43 (±0.81)**	**1.84 (±1.54)**	**1.62 (±0.96)**	**$F_{(1.31,24.97)}$=0.99**	**0.353**	**0.874**	**1**
	Grocery shopping	**1.77 (±1.13)**	**1.14 (±0.27)**	**1.05 (±0.11)**	**$F_{(1.08,20.57)}$=6.51**	**0.017**	**0.091**	**0.034**
	Make a recipe	**2.15 (±1.00)**	**1.22 (±0.29)**	**1.13 (±0.25)**	**$F_{(1.13,21.63)}$=21.55**	**<0.001**	**<0.001**	**<0.001**

	Calendar	1.38 (±0.37)	1.19 (±0.24)	1.19 (±0.53)	$F_{(2,34)}=1.71$	0.196	0.22	0.36
Decision making	Highlight the order	28.94 (±11.39)	12.54 (±5.97)	10.67 (±7.48)	$F_{(1.32,23.83)}=35.08$	<0.001	<0.001	<0.001
	Sudoku	41.28 (±14.73)	27.22 (±8.89)	22.67 (±5.92)	$F_{(1.49,25.30)}=23.03$	<0.001	0.002	<0.001
	Match pictures	39.29 (±10.36)	27.70 (±5.39)	24.35 (±3.80)	$F_{(1.34,21.48)}=22.95$	<0.001	<0.001	<0.001
	Math	6.18 (±2.90)	3.46 (±1.06)	2.93 (±0.89)	$F_{(1.29,23.25)}=19.48$	<0.001	0.001	<0.001
Language	Identify object 1	1.25 (±0.50)	1.01 (±0.02)	1.05 (±0.15)	$F_{(1.07,16.03)}=3.05$	0.098	0.217	0.424
	Identify object 2	1.47 (±0.96)	1.01 (±0.05)	1.05 (±0.15)	$F_{(1.03,16.58)}=3.5$	0.078	0.211	0.265
	Identify object 3	6.91 (±2.63)	4.43 (±0.82)	3.48 (±0.90)	$F_{(1.29,19.39)}=23.72$	<0.001	0.004	<0.001
	Recall	7.01 (±2.79)	4.72 (±1.85)	3.78 (±0.74)	$F_{(1.37,17.70)}=10.07$	0.003	0.093	0.001
	Word search	21.44 (±11.15)	14.16 (±8.46)	10.73 (±5.33)	$F_{(1.34,16.12)}=23.84$	<0.001	0.001	0.001

Table 6: The reaction times in the COSMA games showed that there were fewer significant differences between the visits in the Control group.

Control group								
Modules	COSMA games					RM-ANOVA	Pairwise comparisons	
		V1	V2	V3	F statistic	p-values	V1-2 p-values	V1-3 p-values
Reminiscence	Family tree	2.06 (±3.20)	1.14 (±0.23)	1.10 (±0.44)	F(1.00, 9.06)=2.31	0.16	0.5	0.468
	Identify the person	11.30 (±06.99)	10.8 (±05.60)	6.60 (±02.17)	F(2,18)=3.94	0.038	1	0.155
	Jigsaw puzzle	50.20 (±23.91)	26.28 (±7.05)	18.80 (±4.02)	F(2,8)=7.00	0.017	0.228	0.133
	Match the events	2.50 (±2.07)	2.30 (±1.06)	1.00 (±0.00)	F(2,18)=4.70	0.023	1	0.143
	Presence of time	1.27 (±0.44)	1.00 (±0.00)	1.00 (±0.00)	F(1.00, 8.00)=3.57	0.09	0.286	0.286
Visual tools	Identify item colour	1.33 (±0.70)	1.25 (±0.44)	1.44 (±1.33)	F(2,16)=0.09	0.915	1	1
	Identify shapes	1.37 (±0.74)	2.00 (±0.00)	1.25 (±0.70)	F(2,14)=4.42	0.032	0.148	1
	Identify colours	2.60 (±1.64)	1.26 (±0.49)	1.40 (±1.26)	F(2,18)=2.958	0.077	0.123	0.442
	Flicker colours	2.3 (±1.94)	1.56 (±0.83)	1.40 (±1.26)	F(2,18)=1.45	0.26	0.595	0.547
	Flicker patterns	2.0 (±1.19)	1.88 (±1.9)	1.37 (±1.06)	F(2,14)=0.58	0.573	1	1
Spatial time	Spot the area	2.30 (±1.70)	1.05 (±0.10)	1.30 (±0.94)	F(2,18)=3.30	0.06	0.145	0.445
	Construct time	11.75 (±7.16)	9.65 (±3.48)	5.25 (±1.03)	F(2,14)=6.25	0.011	0.847	0.089
Daily tasks	Daily schedule	2.33 (±1.87)	2.07 (±0.89)	1.44 (±1.33)	F(2,16)=0.808	0.463	1	0.99
	Grocery shopping	2.90 (±2.23)	1.42 (±0.83)	1.30 (±0.94)	$F_{(2,18)}=4.039$	0.036	0.097	0.235
	Make a recipe	3.89 (±2.84)	1.25 (±0.66)	1.11 (±0.33)	$F_{(1.09,8.75)}=7.59$	0.021	0.074	0.067
	Calendar	2.66 (±2.44)	1.44 (±0.77)	1.00 (±0.00)	F(1.15,9.25)=3.28	0.099	0.483	0.227

Decision making	Highlight the order	19.68 (±12.16)	25.04 (±13.94)	9.55 (±8.80)	F(1.82,14.60)=4.50	0.028	0.796	0.268
	Sudoku	46.33 (±12.52)	33.33 (±12.08)	23.44 (±6.89)	$F_{(2,16)}$=13.40	<0.001	0.103	<0.001
	Match pictures	40.78 (±16.38)	9.44 (±2.60)	24.55 (±6.82)	$F_{(1.24,9.91)}$=22.63	0.001	0.002	0.033
	Math	5.55 (±2.96)	2.21 (±0.83)	2.33 (±0.70)	$F_{(2,16)}$=9.69	0.002	0.036	0.034
Language	Identify object 1	1.00 (±0.00)	1.00 (±0.00)	1.25 (±0.50)	$F_{(1.00,3.00)}$=1.00	0.391	1	1
	Identify object 2	1.00 (±0.00)	1.00 (±0.00)	1.20 (±0.44)	$F_{(1.00,4.00)}$=1.00	0.374	1	1
	Identify object 3	7.44 (±2.52)	6.40 (±2.39)	3.87 (±2.03)	$F_{(2,14)}$=7.51	0.006	0.669	0.016
	Recall	12.87 (±19.53)	8.00 (±3.98)	3.62 (±1.06)	F(1.07,7.51)=1.25	0.303	1	0.683
	Word search	21.37 (±7.48)	16.50 (±6.56)	11.38 (±5.15)	$F_{(2,14)}$=10.04	0.002	0.019	0.017

4 Discussion

The present study investigated the impact of the serious games COSMA application in MCI subjects over a 28-day testing period. The study results have shown an improvement in reaction times in 48% of the COSMA games in Treatment and 20% in the Control group taking into account the baseline measurement. The results presented in this study mainly focused on the processing speed through reaction time calculations. The observed reduction in processing speed in the Treatment group over the 28 days of playing COSMA scheme showed that people with MCI still acquire the mental ability to improve certain cognitive skills. This is in line with previous research that demonstrated that it is possible to enhance the ability to hold new information and the brain activity in people with MCI, [60]–[62].

The Treatment group showed improvement in 48% of games while the Control showed 20%. This indicated that the Control group, who played the games only 3 times during the clinical visits, showed improvement in 20% of games. The reaction time improvement in the games seen was only in decision-making and language modules and it emphasised that the MCI participants have skills to retain cognitive functions related to language and simple decision-making functions.

Something important to note here is that the COSMA language games refer only to picture naming and do not test or measure verbal, speaking and communication abilities. This is in alignment with literature showing that language impairment in individuals with MCI is primarily present at the semantic level of processing, which is the meaning of words, and at the syntactic processing, which is the structure of phrases and the association of words to each other within phrases and remains partially unaffected [63].

The Treatment group played the games for 28 days showing improvements in areas like reminiscence, spatial times, daily tasks, decision making and language, which might indicate improvement in episodic memory, spatial and daily-task based attention. The results demonstrated that practising the COSMA games may assist MCI patients in retaining their mental/cognitive capability in various executive functions. The study outcomes may also show that COSMA can significantly impact cognitive improvement in people with MCI and assist them daily, thereby improving their quality of life.

Specifically, similar research which investigated the effects of computerised cognitive training in people with MCI showed that the serious game Complete Brain Workout consisting of verbal, arithmetic, logic, spatial and memory tasks, provided cognitive improvement in attention, verbal fluency, visual and verbal memory and learning through feedback in MCI patients in 6 months of training [19], [64]. Another study, which investigated the effects of computerised games which focused on attention, processing speed, visual memory and cognitive control, showed that cognitive performance was

overall improved with 12 weeks of training in people with MCI [59]. Furthermore, cognitive improvement was evident in an intervention MCI group whose participants played digital (on screen) and traditional (in groups) games, such as memory games e.g., remembering the sequence and colour of balls presented on the screen, coordination and emotional games, solitaire, puzzles, and board games in 8 weeks [65]. Also, people with MCI were able to improve their cognitive processes with the video game 'Body and Brain Exercises' which focused on brain training of logic and reasoning, physical skills, memory, body reflexes and math calculations [66]. Therefore, the previous studies may support the cognitive improvements in our study and show evidence that the use of the COSMA games may positively affect cognitive skills when these are being played regularly in MCI. There is evidence in the cognitive literature that shows the direct propagation of reaction time and cognitive decline. For example, in MCI and AD there is a gradual declining in reaction time performance during tasks, which was validated with the Cognitive Abilities Screening Instrument, a computer administered simple reaction time task and a flanker reaction time [11]. In addition, the cognitive decline is strongly associated with decline in motor skills in both MCI and AD which might affect attention and information processing skills in these groups of patients [67]. In comparison to old and elder populations for which the cognitive and motor decline are deteriorating slowly because of ageing processes, the MCI showed overall 11% slower reaction times during tasks that involved the use of perceptual process, such as signal stimuli relevance, the use of decision making in triggering motor responses and the use of attentional processes, such as the sustained alertness [68].

The calculation of reaction times with respect to the COSMA games were cross validated and directly related with the CANTAB tests. Out of the 7 CANTAB tests executed, the Control group showed no significance to any of them, while the Treatment group showed significance in the motor skills (MOT) and sustained attention (RVP).

The results from this study showed improvement of motor and visual processing skills in MCI patients with 4 weeks regular use of COSMA platform. These gained skills can assist and promote the independence in people with dementia. Also, when comparing our results to those of older studies, it must be pointed out that there is indeed previous research that showed that cognitive stimulation and learning might improve motor speed in MCI; especially for those patients who have motor deficits [69]. Therefore, people with MCI who exhibit motor and cognitive deterioration such as upper limb bradykinesia [61], or having motor neurological disorders (i.e., Parkinson's disease or similar) may benefit from the COSMA application.

Even though MCI patients can function independently, the cognitive decline may affect their daily life, especially their relationships with family members and impact their daily mood [65]. It seems that the cognitive decline in MCI might affect mood and be responsible for severe psychological states such as depression [65]. Therefore, serious games created to enhance cognitive functions and stimulate the brain might be ideal in MCI [70]. Serious games for people with cognitive decline might be beneficial in increasing positive feelings, which could be one of the reasons why MCI should engage in playing them. A good example is the 'Kitchen and cooking' serious game. When people with MCI and AD played the 'Kitchen and cooking' for four weeks, they felt satisfied, motivated and experienced positive emotions at the end of the study [70]. Even more, when people with MCI and early dementia (mild AD and vascular dementia) played the COSMA games in one session, they reported that they felt more interested, inspired, alerted and excited, and that their negative feelings, for example, distress, fear, irritability and guilt decreased [25].

The results presented in this study focused on improving cognitive functions through reaction time calculations. It is important to note that the Control group shows some reaction time reductions in COSMA calculations; however, the cognitive functional improvement cannot be seen in the Control based on the CANTAB neuropsychological test battery.

The study's primary aim of showing cognitive improvements in MCI patients as be established with the improvement in sensorimotor skills and attention along with a decrease in reaction time after using COSMA application. These gained skills can assist and promote

independence in people with dementia or cognitive decline. Also, when comparing our results to those of research studies, it must be pointed out that there is indeed previous research that shows cognitive stimulation and learning might improve motor speed in MCI; especially for those patients with motor deficits [69]. Therefore, people with MCI who exhibit motor and cognitive deterioration such as upper limb bradykinesia[61], or having motor neurological disorders (i.e., Parkinson's disease or similar) may benefit from the COSMA application.

Consequently, our research team demonstrated that the COSMA games are effective during cognitive training and stimulation, and that they could benefit cognitive and motor skills in people with MCI. The study may inspire serious games designers to create serious games for people with cognitive decline, especially MCI; and other research teams to investigate the relationship between cognitive and motor skills decline and retention in people with MCI who regularly play serious games. We consider that COSMA was created for people with cognitive decline, especially MCI and early AD and that the gaming platform offers a variety of games and modules to engage the users and keep them motivated [25]. However, considering that there are not many serious games for people with MCI which are validated in literature, the COSMA application achieved the advancement of showing proof that people with MCI can use it and benefit from it. In addition, the intervention in this study was established in 4 weeks' time and this may highlight the efficiency of COSMA with respect to other serious games and digital interventions which showed cognitive improvement in MCI from 8 weeks to 6 months of use [19], [59], [64]–[66].

5 Limitations

One important limitation in the study was that we did not control for any confounding variable(s) that might have affected the results of the study, such as comorbidities, medication impact, education, previous familiarity with computer games, positive and negative emotions such as enthusiasm, stress, and anxiety during the visit sessions. Similarly, we did not record if participants in both groups engaged in brain stimulating activities besides the COSMA gaming application that might have affected the Control's performance. The other limitation of this study was the limited duration of the study (28 days) that is not sufficient to address the long-lasting impact of the COSMA app and to the see the other possible cognitive functions that can improve over time. For this longer treatment duration studies are required to explore the full capability of COSMA with respect to cognitive functions and longer follow-up to see the lasting effect of the COSMA serious games.

6 Conclusion

Considering the high demand for non-pharmacological interventions in people with MCI, COSMA is one of the few applications that aim to address the cognitive changes using serious games with research. The study has established the efficacy of COSMA in MCI patients by showing improvement in motor skills and sustained attention within 4 weeks' time of using the application. There are numerous applications in the market focusing on general cognition claiming cognitive improvements, which have no evidence of practical and social benefits to the patients [63]. This is how COSMA differs from the crowded market of cognitive applications, because it has been designed both practically and scientifically for people with cognitive impairments addressing their symptoms and trying to achieve the practical benefits of cognitive improvements in daily life. For example, improved motor skills promote physical activities, encourage being more active and increase attention can assist patients with cognitive deficits to retain their capability and do

their simple daily tasks. COSMA, therefore, is one among the few serious games that have taken a serious outlook on improving patient's cognition with practical benefits.

Our next steps are to repeat the same study for a longer intervention duration of 6 months with a 3-month follow-up to determine the possible cognitive functional improvement in MCI patients using COSMA, in other words determining the full capacity of the COSMA application, its long-lasting impact and their practical benefits including behavioural changes.

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References

[1] M. Cotelli, R. Manenti, and O. Zanetti, "Reminiscence therapy in dementia: A review," *Maturitas*. 2012, doi: 10.1016/j.maturitas.2012.04.008.

[2] R. Jin, A. Pilozzi, and X. Huang, "Current Cognition Tests, Potential Virtual Reality Applications, and Serious Games in Cognitive Assessment and Non-Pharmacological Therapy for Neurocognitive Disorders," *J. Clin. Med.*, vol. 9, no. 10, p. 3287, 2020, doi: 10.3390/jcm9103287.

[3] Y. Zhao *et al.*, "Effectiveness of exergaming in improving cognitive and physical function in people with mild cognitive impairment or dementia: systematic review," *JMIR serious games*, vol. 8, no. 2, p. e16841, 2020, doi: 10.2196/16841.

[4] W.H.O., "Dementia," *World Health Organization*, 2020. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/dementia#:~:text=Worldwide%2C around 50 million people have dementia%2C with nearly 60,is between 5-8%25.

[5] S. Alladi and V. Hachinski, "World dementia: One approach does not fit all.," *Neurology*, 2018, doi: 10.1212/WNL.0000000000005941.

[6] P. van den Dungen *et al.*, "The accuracy of family physicians' dementia diagnoses at different stages of dementia: a systematic review," *Int. J. Geriatr. Psychiatry*, vol. 27, no. 4, pp. 342–354, 2012, doi: 10.1002/gps.2726.

[7] D. B. Kaplan and B. Berkman, "Dementia care: A global concern and social work challenge," *Int. Soc. Work*, vol. 54, no. 3, pp. 361–373, 2011, doi: 10.1177/0020872810396255.

[8] National Institute for Health an Care Excellence, "Dementia: assessment, management and support for people living with dementia and their carers," *NICE guideline [NG97]*, 2018. [Online]. Available: https://www.nice.org.uk/.

[9] S. Rajan, J. Brettschneider, J. F. Collingwood, and A. D. N. Initiative, "Regional segmentation strategy for DTI analysis of human corpus callosum indicates motor function deficit in mild cognitive impairment," *J. Neurosci. Methods*, vol. 345, p. 108870, 2020, doi: 10.1016/j.jneumeth.2020.108870.

[10] S. Z. Klekociuk and M. J. Summers, "The learning profile of persistent mild cognitive impairment (MCI): a potential diagnostic marker of persistent amnestic MCI," *Eur. J. Neurol.*, vol. 21, no. 3, pp. 470-e24, 2014, doi: 10.1111/ene.12333.

[11] K. Chen, C. Weng, S. Hsiao, W. Tsao, and M. Koo, "Cognitive decline and slower reaction time in elderly individuals with mild cognitive impairment," *Psychogeriatrics*, vol. 17, no. 6, pp. 364–370, 2017, doi: 10.1111/psyg.12247.

[12] F. M. Henry, "Reaction time—movement time correlations," *Percept. Mot. Skills*, vol. 12, no. 1, pp. 63–66, 1961, doi: 10.2466/pms.1961.12.1.63.

[13] G. A. Kerchner *et al.*, "Cognitive processing speed in older adults: relationship with white matter integrity," *PLoS One*, vol. 7, no. 11, p. e50425, 2012, doi: 10.1371/journal.pone.0050425.

[14] F. Klapproth, "Time and decision making in humans," *Cogn. Affect. Behav. Neurosci.*, vol. 8, no. 4, pp. 509–524, 2008, doi: 10.3758/CABN.8.4.509.

[15] Y.-T. Chen, C.-J. Hou, N. Derek, S.-B. Huang, M.-W. Huang, and Y.-Y. Wang, "Evaluation of the reaction time and accuracy rate in normal subjects, MCI, and dementia using serious games," *Appl. Sci.*, vol. 11, no. 2, p. 628, 2021, doi: 10.3390/app11020628.

[16] S. L. Schmidt, Y. E. M. Boechat, G. J. Schmidt, D. Nicaretta, E. van Duinkerken, and J. J. Schmidt, "Clinical utility of a Reaction-Time Attention task in the evaluation of cognitive impairment in elderly with high educational disparity," *J. Alzheimer's Dis.*, vol. 81, no. 2, pp. 691–697, 2021, doi: 10.3233/jad-210151.

[17] E. Irazoki, L. M. Contreras-Somoza, J. M. Toribio-Guzmán, C. Jenaro-Río, H. van der Roest, and M. A. Franco-Martín, “Technologies for Cognitive Training and Cognitive Rehabilitation for People With Mild Cognitive Impairment and Dementia. A Systematic Review,” *Front. Psychol.*, vol. 11, p. 648, 2020, doi: 10.3389/fpsyg.2020.00648.

[18] A. Abd-Alrazaq *et al.*, “The effectiveness and safety of serious games for improving cognitive abilities among elderly people with cognitive impairment: systematic review and meta-analysis,” *JMIR serious games*, vol. 10, no. 1, p. e34592, 2022, doi: 10.2196/34592.

[19] J. Asad, S. Kousar, and N. Q. Mehmood, “Dementia-Related Serious Games: A Comparative Study,” *Univ. Sindh J. Inf. Commun. Technol.*, vol. 3, no. 4, pp. 171–177, 2019, doi: 10.1016/j.entcom.2021.100458.

[20] S. McCallum and C. Boletsis, “Dementia Games: A Literature Review of Dementia-Related Serious Games,” in *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 2013, pp. 15–27, doi: 10.1007/978-3-642-40790-1_2.

[21] I. D. Saragih, S. I. Tonapa, I. S. Saragih, and B.-O. Lee, “Effects of Cognitive Stimulation Therapy for People with Dementia: A Systematic Review and Meta-Analysis of Randomized Controlled Studies: Cognitive stimulation therapy for dementia care,” *Int. J. Nurs. Stud.*, p. 104181, 2022, doi: 10.1016/j.ijnurstu.2022.104181.

[22] S. Teunisse, M. M. A. Derix, and H. van Crevel, “Assessing the Severity of Dementia: Patient and Caregiver,” *Arch. Neurol.*, vol. 48, no. 3, pp. 274–277, Mar. 1991, doi: 10.1001/archneur.1991.00530150042015.

[23] S. Mohamed, R. Rosenheck, C. G. Lyketsos, and L. S. Schneider, “Caregiver Burden in Alzheimer Disease: Cross-Sectional and Longitudinal Patient Correlates,” *Am. J. Geriatr. Psychiatry*, vol. 18, no. 10, pp. 917–927, 2010, doi: 10.1097/JGP.0b013e3181d5745d.

[24] M. Boustani, C. Schubert, and Y. Sennour, “The challenge of supporting care for dementia in primary care.,” *Clin. Interv. Aging*, vol. 2, no. 4, pp. 631–636, 2007, doi: 10.2147/CIA.S1802.

[25] K. Bojan *et al.*, “The effects of playing the COSMA cognitive games in dementia,” *Int. J. Serious Games*, vol. 8, no. 1, pp. 45–58, 2021, doi: 10.17083/ijsg.v8i1.412.

[26] B. Y. Zhang and M. Chignell, “A Person-Centered Design Framework for Serious Games for Dementia,” in *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 2020, vol. 64, no. 1, pp. 18–22, doi: 10.1177/1071181320641005.

[27] F. F. Imbeault, B. Bouchard, and A. Bouzouane, “Serious games in cognitive training for Alzheimer’s patients,” in *2011 IEEE 1st International Conference on Serious Games and Applications for Health (SeGAH)*, 2011, doi: 10.1109/SeGAH.2011.6165447.

[28] S. Matthews and R. Thomas, “Virtual Game Jam: Collaborative Pathway to Serious Games for Health,” *Int. J. Serious Games*, vol. 9, no. 1, pp. 35–42, 2022, doi: 10.17083/ijsg.v9i1.454.

[29] W.-H. Lee, H.-M. Shim, and H.-G. Kim, “Effect of Game-based Learning using Live Streaming on Learners’ Interest, Immersion, Satisfaction, and Instructors’ Perception,” *Int. J. Serious Games*, vol. 9, no. 2, pp. 3–26, 2022, doi: 10.17083/ijsg.v9i2.457.

[30] D. Gaurav, Y. Kaushik, S. Supraja, M. Yadav, M. P. Gupta, and M. Chaturvedi, “Empirical Study of Adaptive Serious Games in Enhancing Learning Outcome,” *Int. J. Serious Games*, vol. 9, no. 2, pp. 27–42, 2022, doi: 10.17083/ijsg.v9i2.486.

[31] M. Sousa, A. P. Antunes, N. Pinto, and N. Zagalo, “Serious Games in Spatial Planning: Strengths, Limitations and Support Frameworks,” *Int. J. Serious Games*, vol. 9, no. 2, pp. 115–133, 2022, doi: 10.17083/ijsg.v9i2.510.

[32] N. Zaric, R. Roepke, V. Lukarov, and U. Schroeder, “Gamified Learning Theory: The Moderating role of learners’ learning tendencies,” *Int. J. Serious Games*, vol. 8, no. 3, pp. 71–91, 2021, doi: 10.17083/ijsg.v8i3.438.

[33] J. Smith, M. D. Lee, L. A. Ellis, K. Ijaz, and K. Yin, “Developing a novel psychographic-behavioral qualitative mapping method for exergames,” *Int. J. Serious Games*, vol. 8, no. 2, pp. 87–107, 2021, doi: 10.17083/ijsg.v8i2.422.

[34] M. Sousa, “Serious board games: modding existing games for collaborative ideation processes,” *Int. J. Serious Games*, vol. 8, no. 2, pp. 129–146, 2021, doi: 10.17083/ijsg.v8i2.405.

[35] R. C. Oldfield, “The assessment and analysis of handedness: The Edinburgh inventory,” *Neuropsychologia*, 1971, doi: 10.1016/0028-3932(71)90067-4.

[36] K. Lutz, S. Koeneke, T. Wüstenberg, and L. Jäncke, “Asymmetry of cortical activation during maximum and convenient tapping speed,” *Neurosci. Lett.*, vol. 373, no. 1, pp. 61–66, 2004, doi: 10.1016/j.neulet.2004.09.058.

[37] C. Gutwin, A. Cockburn, J. Scarr, S. Malacria, and S. C. Olson, “Faster command selection on tablets with FastTap,” in *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems*, 2014, pp. 2617–2626, doi: 10.1145/2556288.2557136.

[38] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. Kokmen, and E. G. Tangelos, “Aging, Memory, and Mild Cognitive Impairment,” *Int. Psychogeriatrics*, vol. 9, no. 1, pp. 65–69, 1997, doi: 10.1017/s1041610297004717.

[39] M. N. Rossor, N. C. Fox, C. J. Mummery, J. M. Schott, and J. D. Warren, “The diagnosis of young-onset dementia.,” *Lancet. Neurol.*, vol. 9, no. 8, pp. 793–806, Aug. 2010, doi: 10.1016/S1474-4422(10)70159-9.
[40] M. O’Malley, J. Carter, V. Stamou, J. LaFontaine, J. Oyebode, and J. Parkes, “Receiving a diagnosis of young onset dementia: a scoping review of lived experiences,” *Aging Ment. Health*, vol. 25, no. 1, pp. 1–12, 2021, doi: 10.1080/13607863.2019.1673699.
[41] Y. T. Quiroz *et al.*, “Association between amyloid and tau accumulation in young adults with autosomal dominant Alzheimer disease,” *JAMA Neurol.*, vol. 75, no. 5, pp. 548–556, 2018, doi: 10.1001/jamaneurol.2017.4907.
[42] M. W. Logue *et al.*, “Use of an Alzheimer’s disease polygenic risk score to identify mild cognitive impairment in adults in their 50s,” *Mol. Psychiatry*, vol. 24, no. 3, pp. 421–430, 2019, doi: 10.1038/s41380-018-0030-8.
[43] K. Wunderlich, A. Rangel, and J. P. O’Doherty, “Neural computations underlying action-based decision making in the human brain,” *Proc. Natl. Acad. Sci.*, vol. 106, no. 40, pp. 17199–17204, 2009, doi: 10.1073/pnas.0901077106.
[44] T. W. Robbins, M. James, A. M. Owen, B. J. Sahakian, L. McInnes, and P. Rabbitt, “Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers,” *Dement. Geriatr. Cogn. Disord.*, vol. 5, no. 5, pp. 266–281, 1994, doi: 10.1159/000106735.
[45] J. Kuzmickienė and G. Kaubrys, “Cognitive Results of CANTAB Tests and Their Change Due to the First Dose of Donepezil May Predict Treatment Efficacy in Alzheimer Disease,” *Med. Sci. Monit.*, vol. 21, pp. 3887–3899, Dec. 2015, doi: 10.12659/MSM.896327.
[46] S. Leandrou, S. Petroudi, P. A. Kyriacou, C. C. Reyes-Aldasoro, and C. S. Pattichis, “Quantitative MRI brain studies in mild cognitive impairment and Alzheimer’s disease: a methodological review,” *IEEE Rev. Biomed. Eng.*, vol. 11, pp. 97–111, 2018, doi: 10.1109/RBME.2018.2796598.
[47] S. Wang, Y. Shen, W. Chen, T. Xiao, and J. Hu, “Automatic recognition of mild cognitive impairment from mri images using expedited convolutional neural networks,” in *International Conference on Artificial Neural Networks*, 2017, pp. 373–380, doi: 10.1007/978-3-319-68600-4_43.
[48] S. Mayr, E. Erdfelder, A. Buchner, and F. Faul, “A short tutorial of GPower,” *Tutor. Quant. Methods Psychol.*, 2007, doi: 10.20982/TQMP.03.2.P051.
[49] C. C. Serdar, M. Cihan, D. Yücel, and M. A. Serdar, “Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies,” *Biochem. medica*, vol. 31, no. 1, pp. 27–53, 2021, doi: 10.11613/BM.2021.010502.
[50] T. Tong and M. Chignell, “Developing a serious game for cognitive assessment: choosing settings and measuring performance,” in *Proceedings of the second international symposium of Chinese CHI*, 2014, pp. 70–79, doi: 10.1145/2592235.2592246.
[51] D. E. Barnes *et al.*, “Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial,” *Alzheimer Dis. Assoc. Disord.*, vol. 23, no. 3, p. 205, 2009, doi: 10.1097/WAD.0b013e31819c6137
[52] S. P. Hey and J. Kimmelman, “The questionable use of unequal allocation in confirmatory trials,” *Neurology*, vol. 82, no. 1, pp. 77–79, 2014, doi: 10.1212/01.wnl.0000438226.10353.1c.
[53] R. Chin and B. Y. Lee, “Chapter 6 - Periods, Sequences, and Trial Design,” in *Principles and Practice of Clinical Trial Medicine*, R. Chin and B. Y. Lee, Eds. New York: Academic Press, 2008, pp. 95–117, ISBN: 9780123736956
[54] IBM Corp., “IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.” 2020.
[55] B. H. Cohen, *Explaining psychological statistics*. John Wiley & Sons, 2008.
[56] E. Park, M. Cho, and C.-S. Ki, “Correct use of repeated measures analysis of variance,” *Korean J. Lab. Med.*, vol. 29, no. 1, pp. 1–9, 2009, doi: 10.3343/kjlm.2009.29.1.1.
[57] K. Ball *et al.*, “Effects of cognitive training interventions with older adults: a randomized controlled trial,” *Jama*, vol. 288, no. 18, pp. 2271–2281, 2002, doi: 10.1001/jama.288.18.2271.
[58] P. Eggenberger, N. Theill, S. Holenstein, V. Schumacher, and E. D. de Bruin, “Multicomponent physical exercise with simultaneous cognitive training to enhance dual-task walking of older adults: a secondary analysis of a 6-month randomized controlled trial with 1-year follow-up,” *Clin. Interv. Aging*, vol. 10, p. 1711, 2015, doi: 10.2147/CIA.S91997.
[59] M. Finn and S. McDonald, “Computerised cognitive training for older persons with mild cognitive impairment: a pilot study using a randomised controlled trial design,” *Brain Impair.*, vol. 12, no. 3, pp. 187–199, 2011, doi: 10.1375/brim.12.3.187.
[60] F. Clément, S. Gauthier, and S. Belleville, “Executive functions in mild cognitive impairment: emergence and breakdown of neural plasticity,” *Cortex*, vol. 49, no. 5, pp. 1268–1279, 2013, doi: 10.1016/j.cortex.2012.06.004
[61] N. A. Kochan *et al.*, “Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge,” *Dement. Geriatr. Cogn. Disord.*, vol. 30, no. 6, pp. 553–568, 2010, doi: 10.1159/000322112.

[62] M. J. Summers and N. L. J. Saunders, “Neuropsychological measures predict decline to Alzheimer’s dementia from mild cognitive impairment.,” *Neuropsychology*, vol. 26, no. 4, p. 498, 2012, doi: 10.1037/a0028576.
[63] A. R. Khatoonabadi and J. Masumi, “Study protocol: Language profile in mild cognitive impairment: A prospective study,” *Med. J. Islam. Repub. Iran*, vol. 33, p. 53, 2019, doi: 10.3389/fnagi.2022.909582.
[64] S. Zafeiropoulos, F. Kounti, and M. Tsolaki, “Computer based cognitive training for patients with mild cognitive impairment (mci),” in *Proceedings of the 3rd international conference on pervasive technologies related to assistive environments*, 2010, pp. 1–3, doi: 10.1145/1839294.1839319.
[65] B. Xue, A. Xiao, X. Luo, and R. Li, “The effect of a game training intervention on cognitive functioning and depression symptoms in the elderly with mild cognitive impairment: A randomized controlled trial,” *Int. J. Methods Psychiatr. Res.*, vol. 30, no. 4, p. e1887, 2021, doi: 10.1002/mpr.1887.
[66] H. Arshad, K. Anwar, H. G. U. L. Khattak, I. Amjad, and Y. Majeed, “Effect of Brain Training Game on Mild Cognitive Impairment (MCI) in Older Adults,” PJMHS, vol. 15, no.9, 2021, 10.53350/pjmhs211592272
[67] E. Gorus, R. De Raedt, M. Lambert, J.-C. Lemper, and T. Mets, “Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer’s disease,” *J. Geriatr. Psychiatry Neurol.*, vol. 21, no. 3, pp. 204–218, 2008, doi: 10.1177/0891988708320973.
[68] D. Andriuta, M. Diouf, M. Roussel, and O. Godefroy, “Is reaction time slowing an early sign of Alzheimer’s disease? A meta-analysis,” *Dement. Geriatr. Cogn. Disord.*, vol. 47, no. 4–6, pp. 281–288, 2019, doi: 10.1159/000500348.
[69] J. H. Yan and C. L. Zhou, “Effects of motor practice on cognitive disorders in older adults,” *Eur. Rev. aging Phys. Act.*, vol. 6, no. 2, pp. 67–74, 2009, doi: 10.1007/s11556-009-0049-6.
[70] V. Manera *et al.*, “‘Kitchen and cooking,’a serious game for mild cognitive impairment and Alzheimer’s disease: a pilot study,” *Front. Aging Neurosci.*, vol. 7, p. 24, Mar. 2015, doi: 10.3389/fnagi.2015.00024.