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Exergaming improves functional fitness in MCI patients. Does the APOE genotype moderate the outcome?

Anthoula C. Tsolaki[1,2*], Magda Tsolaki[2], Niki Pandria[1], Eftychia Lazarou[2], Olympia Gkatzima[3], Vasiliki Zilidou[1], Maria Karagianni[1], Zafiroura Iakovidou- Kritsi[4], Vasilios K. Kimiskidis[2], Panagiotis D. Bamidis[1]

[1]Medical Physics Laboratory, School of Medicine, Aristotle University of Thessaloniki, Greece., orcid: 0000-0002-5563-7776, orcid: 0000-0002-4859-6996, orcid: 0000-0002-4492-4382, orcid: 0000-0002-7130-5739, orcid: 0000-0002-9936-5805. [2]1st Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki.Greece, orcid: 0000-0003-1272-9782, orcid:0000-0002-2072-8010, orcid: 0000-0002-3335-3019. [3]Panhellenic Institute of Neurodegenerative Diseases, Thessaloniki, Greece, orcid: 0000-0002-2415-0498. [4]Laboratory of Medical Biology-Genetics Department, School of Medicine, Aristotle University of Thessaloniki, Greece, orcid: 0000-0001-6800-2369.

ABSTRACT

Objectives: Mild cognitive impairment could be defined as the condition between healthy aging and dementia. MCI patients seem to retain the neuroplasticity to benefit from Physical Exercise (PE) interventions delaying the progression to dementia.

The present study investigates the impact of PE via “Exergaming” on the functional fitness of MCI adults, depending on the presence of the APOEε4 allele.

Methods: 159 MCI participants were recruited. They were separated to two groups (performing PE or not). The Fullerton Functional Test was used as a primary outcome measure in two-time points (prior to and after PE).

Results: The Active group showed more considerable improvement compared to the Passive group in all Fullerton components despite the presence of APOEε4.

Discussion: PE via exergaming has a beneficial functional effect in MCI patients, whether carrying the APOEε4 allele or not.

Keywords: Mild Cognitive Impairment; APOEε4; Exergaming; Functional fitness; Physical Exercise; Fullerton

***Correspondence to Author:**
Anthoula C. Tsolaki, MD, Ph.D
1st Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki. Medical Physics Laboratory, School of Medicine, Aristotle University of Thessaloniki. PO Box 376, 54124, Thessaloniki, Greece.
Tel. 0030 6947568776

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1. Introduction

The motto "Exercise is medicine" was started by the American College of Sports Medicine [1]. This notion is based on the fact that lifelong physical exercise (PE) is related to a longer lifespan and delays the onset of more than forty (40) chronic conditions/diseases [2].

Mild cognitive impairment (MCI) could be defined as the condition between normal aging and dementia [3]. MCI patients present a neuronal loss of about 36.5% at that stage, along with a synaptic dysfunction [4]. However, they seem to retain sufficient neuroplasticity to benefit from PE interventions, delaying the progression to dementia [5]

APOEε4 presence was found to have a considerable impact on brain metabolism and structure [6]. It is also related to the progression of healthy elderly to MCI and AD [6]. However, all APOE ε4 carriers will not develop AD suggesting the interactive effects of APOE genotype with other genetic or environmental factors [7].

PE could improve cognitive function and play a protective role against neurodegeneration, the underlying mechanisms, though, for these protective effects, have not yet been fully elucidated [8]. There is evidence indicating that PE activates the release of neurotrophic factors [9] and promotes angiogenesis [10], facilitates neurogenesis and synaptogenesis, which in turn improve memory and cognitive functions [11]. Research has also shown that PE has a neuroprotective role [12].

Recent research though suggests that prolonged exercise habits are required for cognitive enhancement, while benefits on functioning can be observed when individuals take up an exercise routine later in life or even after the cognitive impairment onset [13].

Exergaming is an effective training or rehabilitation tool for elderly [14], comparable to conventional forms of PE, with a personalized approach adapting the level of challenge according to the subject's performance. Hence, it provides a safe and effective solution with constant monitoring in older adults living in institutions or rural areas away from organized Day care centers.

This study is part of a more extensive study, the Long Lasting Memories (LLM) Project [15] originally funded by the ICT-CIP-PSP Program of the European Commission, assessing both cognitive and somatometric/ physical effects of non-pharmacological computer- based interventions in MCI patients based on the presence of APOEε4. Because of the amount of the factors under investigation, the results have been split in different manuscripts, the first already published [16].

The aim of this study is to investigate the impact of the computerized PE via "Exergaming" on the functional fitness of older adults with MCI in general and its likely dependence in the presence of APOEε4.

2. Materials and methods

A Quasi-Experimental Study Design took place in Thessaloniki from 2009 to 2017, in order to explore the efficacy of different computer-based interventions in elderly.

The randomization of the participants was not feasible mainly for practical issues, time and financial limitation of the study. Allocation to groups was driven by non- systematic practical and logistic reasons (National holiday time, number of successfully screened participants at a given time point etc.). Moreover, the allocation was not influenced by the participant's choice, motivation or compliance. The type of the intervention applied each time in each place (Spiritual center, Open Care Centers) was determined before the initiation of the screening procedure and it was an open call to the elderly whether were cognitively intact or not. Thus, interventions took place both in the East and West area of Thessaloniki, minimizing the geographical socioeconomic differences of the participants. From all the participants who enrolled in the LLM project, we retrospectively collected and analyzed all of those who had an initial diagnosis of MCI, fulfilling the inclusion-exclusion criteria, to explore the impact of the computerized PE on the functional fitness of

older adults with MCI in general, and its likely dependence on the presence of APOEε4 allele.
One hundred fifty-nine (159) MCI participants were recruited during a thorough screening procedure (see Figure 1). Males and females, aged ≥60 years old, fluent in Greek, were invited to participate. The call was made in Church Spiritual Centers, in Open Care Centers for the elderly in East and West area of Thessaloniki, and the Day Care centers of Greek Alzheimer Association. Participants provided written informed consent and were compensated for their participation in the study. The study protocol was approved by the Ethics Committee of Aristotle University of Thessaloniki and Greek Alzheimer Association (Protocol No **38/5.6.2013** and **221/14-09-2013**). (see Table 1A)

Table 1:. A Demographic characteristic of the study groups. Total sample and B. Neuropsychological assessment of the Total sample

A.

Groups	*Gender Male/Female*	*Age Median, IQR*	*Education years Median, IQR*	*CIRS Median, IQR*	*BMI cm/Kg Mean (SD)*
Active N=82	12/70	68.75, [65.00,73.00]	6.0, [6.00, 9.25]	1.67, [1.44,2.00]	28.73 (3.57)
Passive N=77	17/60	68.00, [63.00,72.50]	6.0, [6.00,11.00]	1.50, [1.33,1.83]	29.77 (4.40)
Total	29/130	68.5, [64.00, 73.00]	6.0, [6.00, 10.00]	1.57, [1.40, 2.00]	29.29 (4.06)

B.

Groups	*MMSE Median, IQR*	*MoCA Median, IQR*	*Trail B Median, IQR*	*IADL Mean rank*	*GDS Median, IQR*
Active	27.00, [26.00, 28.00]	23.00, [21.00, 25.00]	202.00, [145.00, 256.00	81.86	2.00, [1.00, 4.00]
Passive	26.00, [24.00, 28.00]	23.00, [19.75, 25.00]	152.00, [115.00, 216.00]	68.79	1.00, [0.00, 4.00]
test statistic p-value	U=2345.50; ***p=0.046***	U=2464.50; p=0.858	U=1496.50; ***p=0.012***	U=2321.00; ***p=0.002***	U=2509.50; p=0.165

MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; IADL: Instrumental Activities of Daily Living; GDS: Geriatric Depression Scale

Exclusion criteria included any severe physical illness, current psychiatric or other neurological disorder, history of drug or alcohol abuse and use of neuro-modifying drugs (other than cholinesterase inhibitors). All participants reported normal or corrected-to-normal vision and hearing. Prior to the PE intervention, all the participants underwent a neuropsychological evaluation (see Table 1B). The Senior Fitness Fullerton Test was used to assess the functional fitness of older adults. It consists of six tests and evaluates the flexibility of low back and hamstrings, the functional capacity of individuals through the strength of the lower limbs and the dynamic balance, the speed, agility and balance during movement [17,18]. Specifically, the tests used are Chair Stand Test (CST), Arm Curl Test (ACT), 2- Minute Step Test (2-MST), Chair Sit-and-Reach Test (CSaRT), Back Scratch Test (BST) and Foot Up-and-Go Test (FUaG).
They were also subjected to blood tests and neuroimaging via CT/MRI. The neuropsychological, medical and laboratory results were evaluated by a cognitive neurologist (MT). The diagnosis and categorization were based on clinical criteria [3,19] and supported by neuroimaging evidence of media-temporal atrophy. The diagnosis was performed by a dementia expert neurologist (MT).
At first, during the LLM project, the participants were assigned to four different interventional groups and one passive group. The first group attended a combined cognitive and PE implemented in the framework of the LLM project

[20]. All the PE programs were implemented via the exergaming platform Fit For All (FFA) [21]. The second group was the Cognitive training control (CTC) group which performed only cognitive sessions using the Brain HQ software, the third group was the Physical Training Control (PTC) group which was exposed to PE by using the Fit For All platform, and the fourth group was the Active control (AC) group which was exposed to a computerized cognitive training via a short documentary video about nature, art, history, and culture. All the interventional groups had an identical number of sessions. The fifth group was the Passive control group, which did not receive any training and it was on the waiting list (see Figure 1).

The program lasted 8-12 weeks and participants completed at least 24 sessions of cognitive training and/or 16 sessions of PE. The screening neuropsychological evaluation was conducted 1-2 weeks prior to the intervention, the post-test evaluation 1-2 weeks after the end of the training, and the follow-up was six months later. Neuropsychologists and physical trainers who performed the neuropsychological and somatometric assessment both before and after the training were different from those who administered the program.

For the purposes of the present study, all the above participants were divided into two larger groups depending on whether they did PE or not, namely, Active (LLM and PTC participants) and Passive physical training group (AC, CTC and Passive participants) (see Figure 1), to investigate the impact of the computerized PE via "Exergaming" on the functional fitness of older adults with MCI in general and its likely dependence on the presence of APOEε4 allele.

A sample of some 159 participants, males and females (29/130), with a median age of 68.5 years, with a median education level of 6 years and a median Cumulative Illness Rating Scale (CIRS) of 1.57 has been included in this study. Eighty-two (82) of these were included in the Active group, while seventy-seven (77) in the Passive group (see Table 1A).

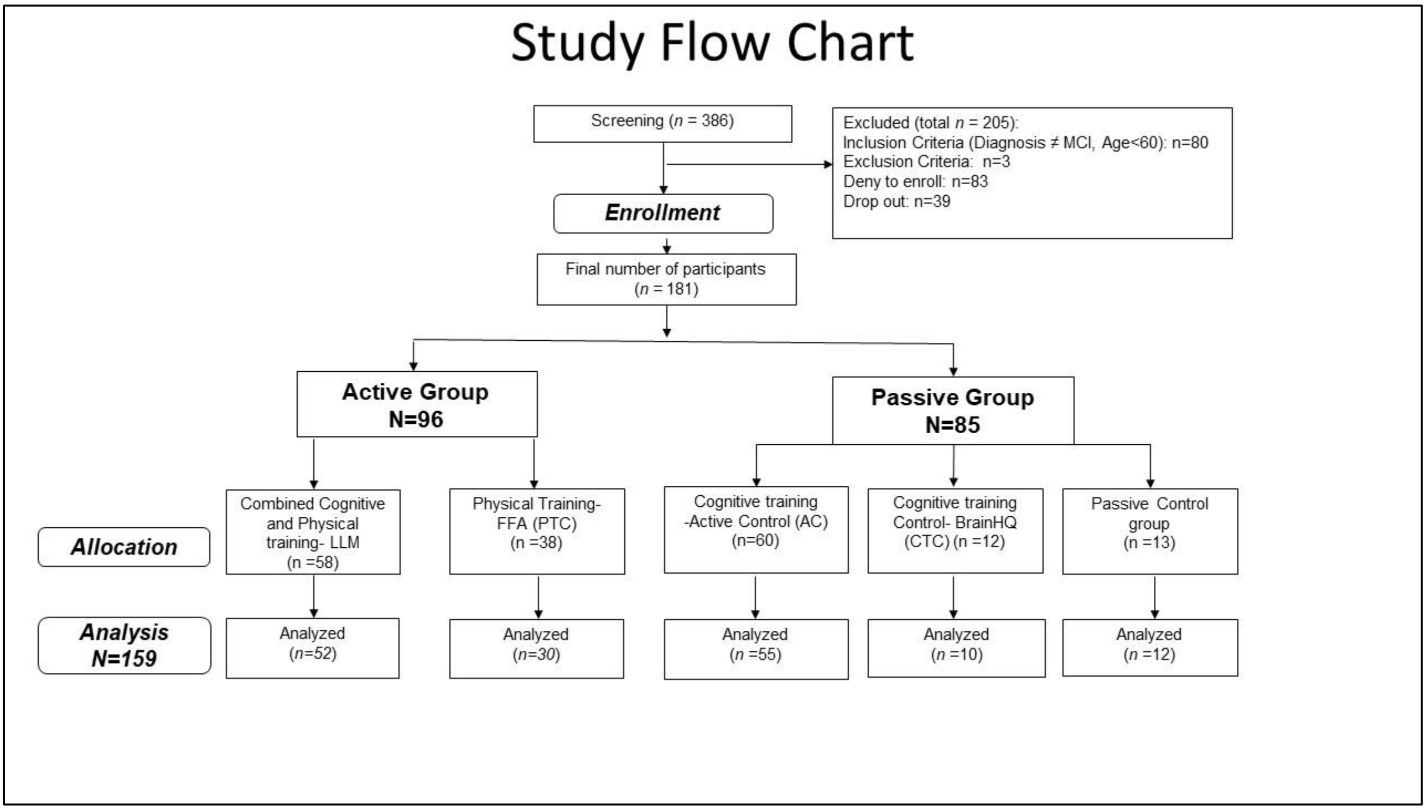

Figure 1: Study Flowchart.

Blood samples used for genotyping were collected in ethylenediaminetetraacetic acid (EDTA)-containing receptacles. DNA was extracted from peripheral blood using the

QIAamp Blood DNA purification kit (Qiagen Inc, USA). To determine the APOE genotype, part of the APOE gene (228 bp) containing both polymorphic sites (amino acid positions 112 and 158) was amplified by PCR analysis, using the following primers: forward:
5''-GGCACGGCTGTCCAAGGAGCTGCA-3''
and reverse:
5''-GCCCCGGCCTGGTACACTGCCAG-3'',
according to the method described in [22].

Statistical analysis was performed by means of IBM SPSS (version 23) and the significance level was set at 5%. The alpha inflation problem due to multiple comparisons was counteracted by applying Bonferroni correction.

Demographics characteristics were explored for normality assumption in the pool of participants as well as in both groups (Active, Passive). Depending on the normality assumption, appropriate descriptive statistics were calculated, and between-groups comparisons were performed. Comparisons of demographic data between groups were run using either Mann-Whitney U test or independent samples t-test.

Fullerton data

Fullerton components were measured both before and after the PE. Initially, the baseline performance in Fullerton test was compared between groups by means of Mann-Whitney U test. Subsequently, data collected were analyzed having as within-factor the time (before and after PE) and as between-factor the group (Active, Passive). Although Mixed Model Analysis of Variance should be the analysis of choice for the data collected, the assumptions of the corresponding test were not satisfied in each cell of the design. Thus, score differences (post-pre) were calculated and then tested for normality assumption. Within-group changes were investigated using Wilcoxon Signed Ranks test after grouping data by group (Active, Passive). Score change was compared between groups performing Mann-Whitney U test.

Moreover, the genotype of participants was also available. Therefore, we planned comparisons taking into account the presence or the absence of APOEe4 allele. We determined as within-factor the time (before and after PE) and as between-factors the group (Active, Passive) and the genotype (non-ε4-carriers, ε4-carriers). Even though, we investigated the assumptions of the Mixed Model Analysis of Variance, they were not fulfilled. Therefore, score changes within each group, Active/Passive or Carriers/Non-Carriers respectively, were investigated using Wilcoxon Signed Ranks test after grouping data by group and genotype. Additionally, score changes between groups were explored using Mann-Whitney U test grouping data by group type (Active, Passive) and genotype (Carrier, Non-carrier).

3. Results

Active and Passive participants were not significantly different in their demographic data such as age, education years, CIRS and BMI *(Age: U=2891.50; p=0.359; Education: U=3082.50; p=0.782; CIRS: U=2607.50; p=0.056; BMI: t (141) =-1.543; p=0.125) (see Table 1A).*

Table 1 about here

The baseline performance between the two groups revealed a statistically significant better performance of the passive group in two tasks ACT *(U=1816.50;* ***p<0.001****) and Foot-up-and-go (U=1655.00;* ***p<0.001****).*

Participants recruited in the Active group significantly improved their performance in all Fullerton components when comparing their scores at the two time points *(All p values <0.001).* On the other hand, Passive participants significantly improved their performance only in CST task *(W=-2.265;* ***p=0.023****) (See Table 2A and Figure 2)*.

Planned comparisons in score changes between groups (Active, Passive) revealed group-differences in all Fullerton components. More precisely, the Active group showed greater improvement compared to the Passive group in all Fullerton components *(All p values ≤0.005).* (See Table 2B).

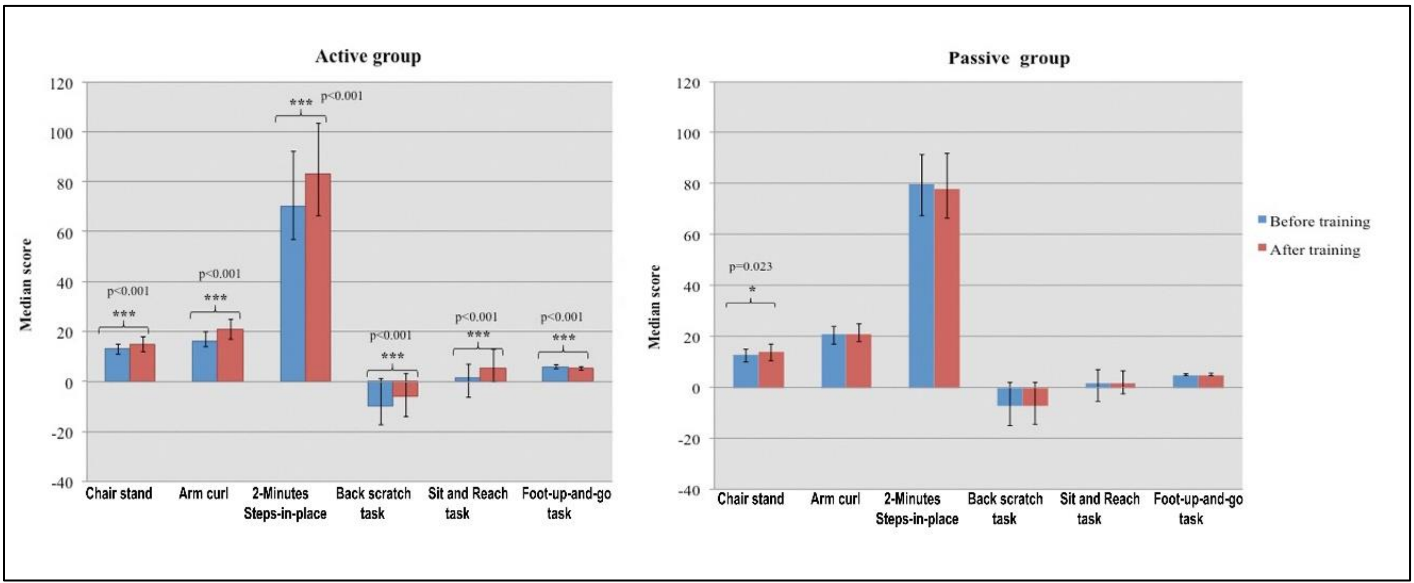

Figure 2: Within-Group Comparisons at different Fullerton tasks before and after the training period. * p<0.05, ** p<0.01 &*** p<0.001.

Table 2: Fullerton Assessment before and after training period. Within group (A) and between groups (B) comparisons.

A.					
Fullerton components	Group	N	Descriptive statistics		Test results
			Before training	After training	
Within-group comparison					
Chair stand	Active	82	13.00, [11.00, 15.00]	15.00, [12.00, 18.00]	W=-5.693; **p<0.001**
	Passive	77	13.00, [10.00, 15.00]	14.00, [10.50, 17.00]	W=-2.265; **p=0.023**
Arm curl	Active	82	16.00, [14.00, 20.00]	21.00, [17.00, 25.00]	W=-6.015; **p<0.001**
	Passive	77	21.00, [17.00, 24.00]	21.00, [18.00, 25.00]	W=-1.583; p=0.114
2- Minutes Step in Place	Active	82	70.00, [57.00, 92.25]	83.00, [66.50, 103.50]	W=-4.524; **p<0.001**
	Passive	77	80.00, [67.50, 91.50]	78.00, [66.50, 92.00]	W=-0.531; p=0.595
Back scratch	Active	82	-10.00, [-17.25, 1.25]	-6.00, [-14.00, 3.25]	W=-5.839; **p<0.001**
	Passive	77	-7.00, [-15.00, 2.00]	-7.00, [-14.50, 2.00]	W=-1.451; p=0.147
Sit and Reach	Active	82	1.50, [-6.25, 7.00]	5.50, [0.00, 13.00]	W=-6.173; **p<0.001**
	Passive	77	2.00, [-5.00, 7.00]	2.00, [-2.50, 6.50]	W=-0.028; p=0.978
Foot-up-and-go	Active	82	5.82, [5.20, 6.82]	5.26, [4.60, 6.00]	W=-5.636; **p<0.001**
	Passive	77	5.00, [4.68, 5.41]	5.03, [4.61, 5.60]	W=-0.401; p=0.688
B.					
Between-group comparison					
Chair stand	Active	82	2.00, [0.00, 4.00]		
	Passive	77	0.00, [-1.00, 3.00]		U=2341.00; **p=0.005**
Arm curl	Active	82	3.00, [0.00, 8.00]		
	Passive	77	0.00, [-2.00, 2.00]		U=1813.00; **p<0.001**
2- Minutes Step in Place	Active	82	10.00, [0.00, 21.00]		
	Passive	77	1.00, [-7.50, 5.50]		U=1926.50; **p<0.001**
Back scratch	Active	82	2.50, [0.00, 5.00]		
	Passive	77	0.00, [-1.00, 2.00]		U=1880.00; **p<0.001**
Sit and Reach	Active	82	4.00, [1.00, 8.00]		
	Passive	77	0.50, [-2.00, 2.00]		U=1585.00; **p<0.001**
Foot-up-and-go	Active	82	-0.60, [-1.16, -0.03]		
	Passive	77	0.02, [-0.26, 0.34]		U=1624.50; **p<0.001**

Non-ε4-carriers of the Active group showed significant changes in all Fullerton components *(All p values <0.001).* Active ε4-carriers significantly improved their performance at all Fullerton tasks apart from 2-Minutes Steps in Place test *(CST: W=-3.224; **p=0.001**; ACT: W=-3.063; **p=0.002**; CSaRT: W=-3.055; **p=0.002**; BST: W=-2.568; **p=0.010**; FUaG: W=-2.273; **p=0.023**).*

Non-ε4-carriers of the Passive group increased their scores only at CST *(W=-2.165; **p=0.030**).* On the other hand, Passive ε4-carriers did not change their performance at any test *(see Table 3A and Figure 3).*

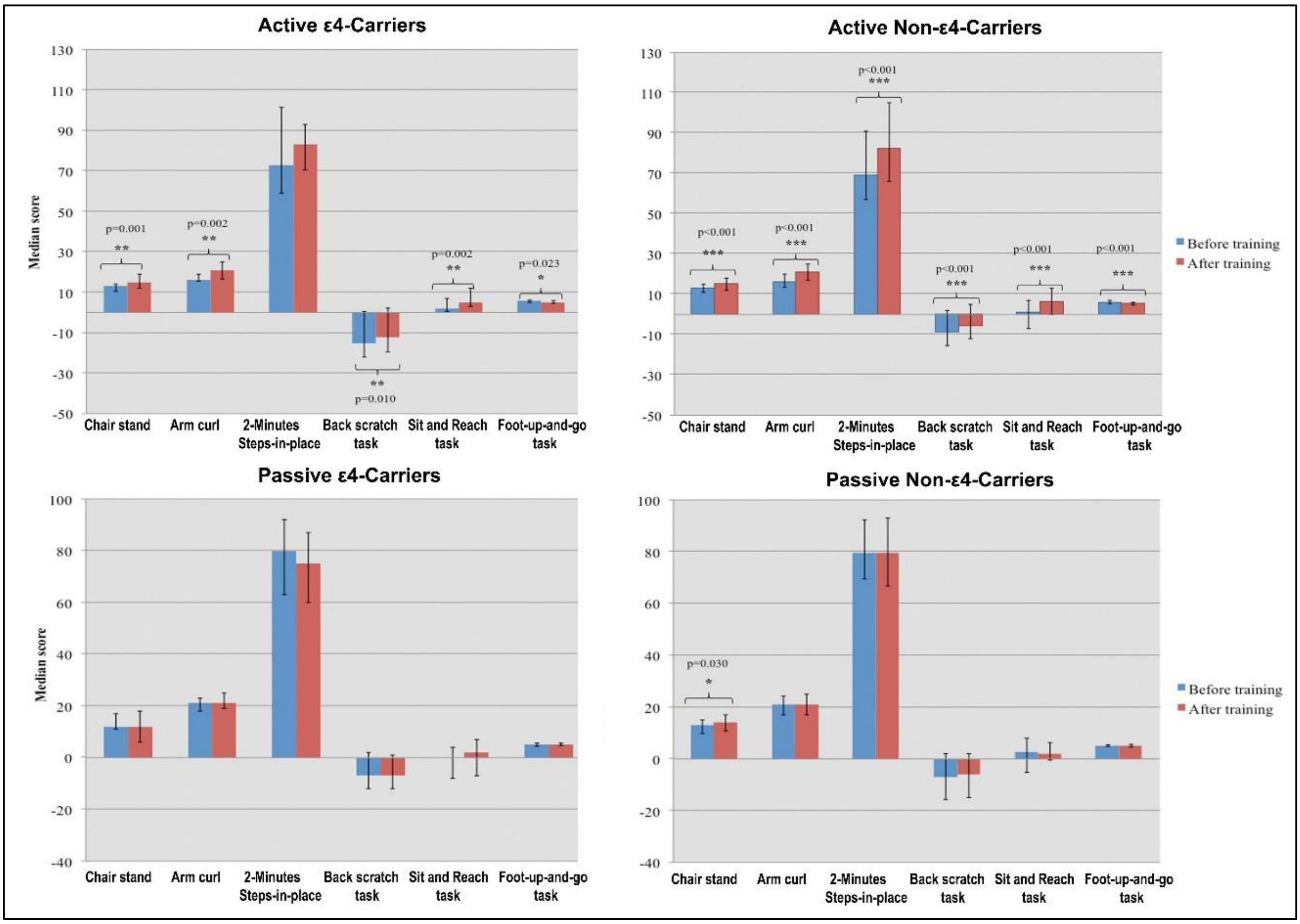

Figure 3*:* Within-Group Comparisons at different Fullerton tasks, based on genotype, before and after the training period. * p<0.05, ** p<0.01 &*** p<0.001

The comparison of performance change between the APOEε4-carriers and non-ε4-carriers within each group (Active, Passive) did not show significant differences in their performance change at the Fullerton tasks in the two-time points either in Active or in the Passive group (see Table 4).

Additionally, Active non-ε4-carriers were found to show superior performance compared to the Passive non-ε4-carriers in all Fullerton tasks *(CST: U=1542.50; **p=0.021**; ACT: U=1194.00; **p<0.001**; CSaRT: U=904.50; **p<0.001**; BST: U=1311.50; **p=0.001**; FUaG: U=1009.50; **p<0.001**; 2-MST: U=1210.00; **p<0.001**)*. On the other hand, Active ε4-carriers showed greater performance at the ACT *(U=68.00; **p=0.024**)*, the BST *(U=48.50; **p=0.003**)* and the FUaG *(U=72.50; **p=0.038**)* compared to the Passive ε4-carriers (see Table 3B).

Table 3: Fullerton Assessment before and after training period. Within group based on APOEε4 (A) and between groups based on APOEε4(B) comparisons.

A.					
Fullerton components	Group	N	Descriptive statistics		Test results
			Before training	After training	
Within-group comparison in ε4-Carriers					
Chair stand	Active	17	13.00, [10.50, 14.00]	15.00, [12.00, 19.00]	W=-3.224; **p=0.001**
	Passive	15	12.00, [11.00, 17.00]	12.00, [6.00, 18.00]	W=-0.669; p=0.504
Arm curl	Active	17	16.00, [15.50, 19.00]	21.00, [16.50, 25.00]	W=-3.063; **p=0.002**
	Passive	15	21.00, [18.00, 23.00]	21.00, [19.00, 25.00]	W=-1.303; p=0.192
2- Minutes Step in Place	Active	17	73.00, [59.00, 101.50]	83.00, [70.50, 93.00]	W=-1.553; p=0.120
	Passive	15	80.00, [63.00, 92.00]	75.0, [60.00, 87.00]	W=-0.881; p=0.378
Back scratch	Active	17	-15.00, [-22.00, 0.50]	-12.00, [-19.50, 2.25]	W=-2.568; **p=0.010**
	Passive	15	-7.00, [-12.00, 2.00]	-7.00, [-12.00, 1.00]	W=-0.931; p=0.352
Sit and Reach	Active	17	2.00, [0.50, 7.00]	5.00, [3.00, 12.00]	W=-3.055; **p=0.002**
	Passive	15	0.00, [-8.00, 4.00]	2.00, [-7.00, 7.00]	W=-1.282; p=0.200
Foot-up-and-go	Active	17	5.72, [4.99, 6.21]	5.02, [4.50, 5.83]	W=-2.273; **p=0.023**
	Passive	15	4.99, [4.40, 5.63]	5.15, [4.69, 5.67]	W=-0.227; p=0.820
Within-group comparison in Non-ε4-carriers					
Chair stand	Active	65	13.00, [11.00, 15.50]	15.00, [12.00, 18.00]	W=-5.693; **p<0.001**
	Passive	62	13.00, [9.75, 15.00]	14.00, [10.75, 17.00]	W=-2.165; **p=0.030**
Arm curl	Active	65	16.00, [13.50, 20.00]	21.00, [17.00, 25.00]	W=-6.015; **p<0.001**
	Passive	62	21.00, [17.00, 24.25]	21.00, [17.00, 25.00]	W=-1.097; p=0.272
2- Minutes Step in Place	Active	65	69.00, [57.00, 91.00]	82.00, [66.00, 105.00]	W=-4.524; **p<0.001**
	Passive	62	79.50, [69.50, 92.25]	79.50, [66.75, 93.00]	W=-0.083; p=0.934
Back scratch	Active	65	-9.00, [-15.50, 2.00]	-6.00, [-12.00, 5.00]	W=-5.839; **p<0.001**
	Passive	62	-7.00, [-15.75, 2.00]	6.00, [-15.00, 2.00]	W=-1.827; p=0.068
Sit and Reach	Active	65	1.00, [-7.00, 7.00]	6.00, [0.00, 13.00]	W=-6.173; **p<0.001**
	Passive	62	2.75, [-5.25, 8.00]	2.00, [-0.50, 6.25]	W=-0.806; p=0.420
Foot-up-and-go	Active	65	5.90, [5.30, 7.04]	5.30, [4.65, 6.00]	W=-5.636; **p<0.001**
	Passive	62	5.00, [4.78, 5.41]	5.03, [4.60, 5.60]	W=-0.276; p=0.782
B.					
Between-group comparison in ε4-Carriers					
Chair stand	Active	17	2.00, [1.50, 4.00]		U=90.00; p=0.154
	Passive	15	0.00, [1.00, 4.00]		
Arm curl	Active	17	5.00, [1.50, 8.00]		U=68.00; **p=0.024**
	Passive	15	1.00, [-1.00, 3.00]		
2- Minutes Step in Place	Active	17	5.00, [-3.50, 16.50]		U=81.00; p=0.079
	Passive	15	-4.00, [-7.00, 4.00]		
Back scratch	Active	17	3.00, [0.75, 5.00]		U=48.50; **p=0.003**
	Passive	15	-1.00, [-1.00, 0.00]		
Sit and Reach	Active	17	4.00, [1.00, 7.00]		U=95.00; p=0.218

	Passive	15	2.00, [-2.00, 5.00]	
Foot-up-and-go	Active	17	-0.41, [-1.10, 0.13]	U=72.50; **p=0.038**
	Passive	15	-0.06, [-0.2, 0.4]	
Between-group comparison in Non-ε4-carriers				
Chair stand	Active	65	1.00, [0.00, 3.50]	U=1542.50; **p=0.021**
	Passive	62	0.50, [-1.00, 2.25]	
Arm curl	Active	65	2.00, [0.00, 9.00]	U=1194.00; **p<0.001**
	Passive	62	0.00, [-2.00, 2.00]	
2- Minutes Step in Place	Active	65	0.00, [-2.25, 2.00]	U=1210.00; **p<0.001**
	Passive	62	1.50, [-8.00, 6.00]	
Back scratch	Active	65	2.00, [0.00, 5.50]	U=1311.50; **p=0.001**
	Passive	62	0.00, [-1.00, 2.25]	
Sit and Reach	Active	65	4.00, [0.50, 8.50]	U=904.50; **p<0.001**
	Passive	62	0.00, [-2.25, 2.00]	
Foot-up-and-go	Active	65	-0.60, [-1.25, -0.03]	U=1009.50; **p<0.001**
	Passive	62	0.04, [-0.29, 0.31]	

Table 4: Fullerton Assessment comparison between ε4-carriers and nonε4-carriers within Active and Passive group respectively, before and after training.

Fullerton components Change in time (post-pre)	Group	N	Descriptive statistics	Test results
Between-group comparison in the Active group				
Chair stand	Carriers	17	2.00, [1.50, 4.00]	U=461.50; p=0.294
	Non-carriers	65	1.00, [0.00, 3.50]	
Arm curl	Carriers	17	5.00, [1.50, 8.00]	U=486.50; p=0.448
	Non-carriers	65	2.00, [0.00, 9.00]	
2- Minutes Step in Place	Carriers	17	5.00, [-3.50, 16.50]	U=467.00; p=0.328
	Non-carriers	65	14.00, [0.00, 21.00]	
Back scratch	Carriers	17	3.00, [0.75, 5.00]	U=549.00; p=0.968
	Non-carriers	65	2.00, [0.00, 5.50]	
Sit and Reach	Carriers	17	4.00, [1.00, 7.00]	U=531.50; p=0.809
	Non-carriers	65	4.00, [0.50, 8.50]	
Foot-up-and-go	Carriers	17	-0.41, [-1.10, 0.13]	U=513.00; p=0.651
	Non-carriers	65	-0.60, [-1.25, -0.03]	
Between-group comparison in the Passive group				
Chair stand	Carriers	15	0.00, [-1.00, 4.00]	U=451.50; p=0.861
	Non-carriers	62	0.50, [-1.00, 2.25]	
Arm curl	Carriers	15	1.00, [-1.00, 3.00]	U=404.50; p=0.433
	Non-carriers	62	0.00, [-2.00, 2.00]	
2- Minutes Step in Place	Carriers	15	-4.00, [-7.00, 4.00]	U=404.00; p=0.432
	Non-carriers	62	1.50, [-8.00, 6.00]	
Back scratch	Carriers	15	-1.00, [-1.00, 0.00]	U=329.50; p=0.076
	Non-carriers	62	0.00, [-1.00, 2.25]	
Sit and Reach	Carriers	15	2.00, [-2.00, 5.00]	U=324.50; p=0.070
	Non-carriers	62	0.00, [-2.25, 2.00]	
Foot-up-and-go	Carriers	15	-0.06, [-0.20, 0.40]	U=460.00; p=0.949
	Non-carriers	62	0.04, [-0.29, 0.31]	

Discussion

To our knowledge, there is no similar study in MCI seniors to investigate the impact of the computerized PE on functional fitness test depending on the APOEε4 allele presence.

In our study, the analysis within the groups before and after the training showed that the active group improved in all the physical parameters (flexibility of low back and hamstrings, the functional capacity of individuals through the strength of the lower limbs and the dynamic balance, the speed, agility and balance during movement) under investigation, which is in line with previous studies [23]. On the contrary, the Passive group showed minor or no improvement at all. The between groups analysis underlined, once again, the multiple training benefits on the Active group, even though, the baseline assessment was in favor of the passive group.

The analysis which was carried out based on the presence of the APOEε4 allele, a well-known risk factor for AD, showed similar improvement of the functional fitness variables in ε4-carriers and non- ε4-carriers of the Active group. These findings deviate from what is known so far regarding the questionable benefit of cognitive or combined exercise on the MCI APOEε4-carriers cognitive performance has been shown [24]. On the other hand, Passive non-ε4-carriers improved only in one task whereas Passive ε4-carriers did not improve at all.

Prevailing evidence suggests that differential effects of APOE isoforms on Aβ aggregation and clearance play a major role in neuro-degeneration[25]. Sedentary elderly APOEε4 individuals are at augmented risk for cerebral amyloid deposition, synaptic deterioration, hippocampal atrophy and decreased brain metabolism in distinct brain areas. Thus, APOEε4 has a direct pathological effect on the cerebrovascular system [26].

PE modifies the metabolic, structural, and functional brain state. The regular, moderate-intensity exercise may improve brain health by neuroprotective mechanisms. It also leads to cardiovascular disease risk reduction via numerous different mechanisms at a molecular and cellular level and via its sustainability, it enables gross anatomical remodeling [27].

Exergaming show comparable outcomes in physical [28] and cognitive functions [29] as well as in the psychosocial well-being of the elderly compared to the traditional physical exercise. It is also notable that exergames may reduce the incidence of falls [30], which is a leading cause for loss of independence among older adults.

MCI patients is a population at risk with preserved functionality through compensatory mechanisms, responding well in physical and cognitive intervention training [20]. Even though there is a growing interest in the PE cognition effect, existing knowledge is limited regarding how the functional fitness aspects, such as strength, endurance, balance, flexibility, of the MCI patients alter due to training and whether those changes, if any, are differentiated depending on the presence of APOEε4 allele.

Our results indicate that both MCI APOEε4 carriers and non-ε4-carriers experience beneficial effects induced by exergaming in multiple physical parameters. Even though APOEε4-carriers have been found to gain less cognitive benefits, we showed a prominent positive outcome on the physical fitness of MCI ε4-carriers seniors. Moreover, PE in this high-risk population may be crucial for the improvement of other important factors such as the cardiovascular disease load, the functional impairment, the social isolation, the falls, and the subsequent hospitalization, institutionalization and finally the mortality. Accordingly, PE may not improve directly cognition in MCI APOEε4-carriers [16], but it may eliminate the additional risk of all the aforementioned co-factors strengthening the notion that physical exercise may facilitate the benefits of any cognitive training, but also that “Exercise is medicine” [1].

5. Conclusion

PE via exergaming has a beneficial functional effect in MCI patients, whether carrying the APOEε4 allele or not. A continued and personalized, PE program is needed to maintain the physical status of the elderly, by improving the strength, the endurance and the balance of this high-risk elderly group. The "exergaming" may be one of the optimal choices for the elderly without access to organized social structures providing physical training.

Practical Implications

- PE via exergaming has a beneficial functional effect in MCI patients, whether carrying the APOEε4 allele or not
- Active group had a significant improvement at the post-training period compared to the baseline to all the physical parameters under in-
- vestigation.
- A continued and personalized, PE program, is necessary to maintain an elderly his/her physical status.
- The "exergaming" may be one of the optimal choices for the elderly without access to organized social structures providing physical training.

Disclosure

PDB discloses potential (non-financial and beyond the context of the submitted work) conflicts of interest with PositScience: there is a co-marketing agreement between the company and the Aristotle University of Thessaloniki (AUTH) to exploit Brain HQ within the LLM Care self-funded initiative that emerged as the non-for-profit business exploitation of the LLM Project originally funded by the ICT-CIP-PSP Program of the European Commission. FitForAll (FFA) has been developed in the AUTH during the LLM Project. It now forms part of LLM Care. The rest of the authors report no conflicts of interest in this work.

Lossary of Abbreviations

2-MST: 2- Minute Step Test
AC: Active Control
ACT: Arm Curl Test
AD: Alzheimer's disease
APOE: Apolipoprotein E
BDNF: Brain-derived neurotrophic factor
BMI: Body Mass Index
BST: Back Scratch Test
CIP: Competitiveness and Innovation framework Program
CIRS: Cumulative illness Rate Scale
CSaRT: Chair Sit-and-Reach Test
CST: Chair Stand Test
CT: Computed Tomography
CTC: Cognitive training Control
FFA: Fit For All
FRSSD: Functional Rating Scale of Symptoms of Dementia
FUaG: Foot Up-and-Go Test
FUCAS: Functional and Cognitive Assessment Test
GDS: Geriatric Depression Scale
IADL: Instrumental Activities of Daily Living scale
ICT: Information and Communication Technologies
LLM: Long Lasting Memories
MCI: Mild Cognitive Impairment
MMSE: Mini-Mental State Examination
MOCA: Montreal Cognitive Assessment
MRI: Magnetic Resonance Imaging
PSP: Policy Support Program
PTC: Physical training Control
TrailB: Trail Making Test part-B

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