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Longitudinal Cognitive and Physical Training Effectiveness in MCI, Based on the Experience of the Alzheimer's Hellas Day Care Centre

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Abstract

This study assesses the effectiveness of a multicomponent Longitudinal Cognitive Training (CT) program plus physical exercise (PE) for people with Mild Cognitive Impairment (MCI). 155 people with MCI, completed a 3 years (3Y) CT+PE, whilst 133 were control. Neuropsychological assessment was performed at baseline and 3 years later, whilst CT+PE had additional annual assessments. According to the results, the 3Y CT+PE outperformed control in cognitive abilities ($p < 0.002$), and Activities of Daily Living (ADL) ($p < 0.001$), stabilized their functional performances between 1st and 2nd year, but worsened in working and verbal memory between 2nd and 3 rd year ($p < 0.002$). Control deteriorated in cognitive functions ($p < 0.001$) and ADL ($p < 0.001$) after 3 years, whilst 1.33% of the experimental and 13.53% of the control group progressed to dementia ($p < 0.001$). Longitudinal CT+PE improves cognitive performance and ADL in MCI and delay the progression to dementia.

Keywords

cognitive training, longitudinal training, mild cognitive impairment, physical exercise, 3 years follow-up

Introduction

Mild Cognitive Impairment (MCI) is considered to be the intermediate diagnostic entity between normal ageing and dementia, as well as a risk factor for progression to dementia.[1] Taking into account its crucial role as an in-between stage for normal and abnormal functionality,[2] it is quite significant to boost our efforts towards implementing well-structured cognitive training programs, so as to delay dementia onset. Additionally, the amnestic and multiple domain MCI (aMCImd) subtype is the most frequent type of MCI in the general population,[3] mainly leading to AD, meaning that older adults with this subtype are at greater risk to develop dementia in the future.[4,5] According to several works,[6,7] cognitive training has been found to have a protective role in older adults and mainly those who are at risk of developing dementia. Moreover, Chertkow et al., (2006)[8] supported that structured intervention in MCI can reverse and prevent dementia onset through improvement of daily functionality.

Interventions designed to ameliorate cognitive deficits in MCI populations, involve cognitive stimulation (CS) and cognitive training (CT) implemented in group sessions, cognitive rehabilitation (CR) delivered individually and physical training (PT). Specifically, CS includes various activities aiming at improving social life and general cognitive ability, which understandably are not personalized to the attendants' needs. On the contrary, CT is designed to improve specific cognitive functions through guided practice and specialized techniques,[9,10] fact that constitutes it preferable. A typical example

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of CT effectiveness is that relatively recent data showed that cognitive training promotes neuroplasticity in hippocampus in MCI older adults,[11] and as such it is considered the cornerstone of early intervention.

As far as exercise is concerned, it has been found to improve cognitive functionality both in MCI as well as those at risk of developing dementia, both by several studies in literature,[12-14] as well as by neuroimaging studies,[15] which show that exercise increases prefrontal cortex[16] and anterior hippocampus.[17] Additionally, apart from the fact that exercise activates neurogenesis,[18] it also contributes to lower probability of cardiovascular risk.[19] Finally, it is worth mentioning that the combination of cognitive and physical intervention in MCI population has already be found to increase cognitive functionality as well as decrease the progression to dementia.[20]

To sum up, given that the combination of cognitive and physical activities in older adults (especially in those with MCI)[21] is highly recommended, it is of utmost importance to identify their longitudinal effect. Nevertheless, nearly none of the conducted studies has validated the long-term effects thus far, making this is a big gap the current study will try to fill. Additionally, given the fact that no consensus about available pharmacological treatment for MCI population exists, non-pharmacological interventions are the only eligible option for dementia protection. Moreover, another major task is to calculate conversion rates to dementia among people with MCI who have attended a longitudinal CT intervention. In case CT has positive effect on the neuropsychological performance of participants with MCI, it can be assumed that progression rates will be lower compared to the control group.[22] Conclusively, it is similarly important to determine the longitudinal benefits of cognitive training in MCI population, as well as whether CT could lead to slowing progression to dementia in older adults with MCI.

Day Care Center of the Greek Association of Alzheimer's Disease and Related Disorders "Saint Helen": Structure and Operation

The Day Care Centre of the Greek Association of Alzheimer's Disease and Related Disorders "Saint Helen", (DCCSH), started its operation in 2007 and provides early diagnosis via neuropsychological assessment and neurological examination for people with minor or major neurodegenerative disorders. In specific, DCCSH is a prototype and well-organized center with several facilities for the beneficiaries, this being the main reason for the low percentage of their dropouts. The psychologists of the DCCSH design specific prevention interventions for minimizing the progression to dementia in MCI population, as well as in cognitively intact older adults who are at risk of developing dementia due to family history or other relevant health problems. Therefore, any person who attends therapeutic programs is free to participate for several years if his/her cognitive deficits are maintained. Furthermore, the DCCSH also operates as a clinical center by designing and applying randomized control trials for research purposes.

In more detail, several non-pharmacological interventions for people with MCI are implemented in a daily basis, such as cognitive training, aiming at improving, maintaining or restoring cognitive function through structured tasks.[23] The main focus of cognitive training is the enhancement of specific cognitive functions such as attention, executive function, language and memory, with the purpose to activate brain plasticity.[24] Typical examples of tasks included in cognitive training are, apart from cognitive exercises, learning new technologies and foreign languages, as well as performing physical exercises and other leisure activities such as dance, choir, drama and painting. Based on the aforementioned programs' implementation, the therapeutic target of the DCCSH towards MCI population is the delay of cognitive decline. Most of the elders with MCI decide to participate in the cognitive training programs for diminishing the progression rates to dementia and therefore, have a great compliance to the programs' attendance. In specific, people with late MCI, who according to Alzheimer's Disease Neuroimaging Initiative (ADNI) observational study,[25] have multiple neuropsychological deficits, participate in many cognitive training programs for several days per week, as well as in several leisure activities. Finally, people with early MCI, i.e. those who belong to earlier stages of the MCI clinical spectrum,[26] also participate in a well-structured intervention program consisting of 3 therapeutic cognitive training programs plus physical intervention.

Conceptual Framework

The theoretical background behind the current study is that continuous and systematic training offers more benefits than short time interventions.[27,28] Continuous training can possibly help people with MCI to maintain or even improve their cognitive performance for several years, leading to reduced progression rates to dementia and better daily functionality, which is the ultimate goal of cognitive training. Therefore, it would be of significant importance to identify a) whether this kind of training could have longitudinal efficacy in MCI population, b) if the 3 years of training are better than one and c) if more training can actually stabilize the cognitive performance or increase it. Additionally, Wang et al. (2014)[29] highlighted the gap in the literature concerning the long-term benefits of cognitive training in MCI population. Hence, it is of clinical value to identify the protective role of cognitive training programs against progression to dementia. Finally, MCI is a quite heterogeneous group, and therefore it is really important to figure out whether cognitive training shows similar effects across different MCI subtypes.

To test our hypothesis, we used the great amount of data existing to the DCCSH's electronic database. The DCCSH applies several combinations of different cognitive training programs to the participants for a long time, and therefore has a large database, which give us the capacity to evaluate the effectiveness of a continuous and systematic multicomponent

3-years intervention. Moreover, a second goal of the current study is to provide more data regarding the progression rates from MCI to dementia, in those who attended cognitive training programs and those who didn't over a 3 years' period.

The present study is a database one. The primary aim was to evaluate the impact of a combination of 6 different cognitive training programs and a physical exercise program, in Greek-speaking people, aged from 60 to 80 years with MCI, over a 3 years period and also to investigate if the 3 years of training offers more effectiveness in comparison to no training, to 1 and 2 years of training. The secondary aim was to determine the progression rates from MCI to dementia during this period. In more detail, our main hypotheses were the following: a) the experimental group after 3 years of continuous and systematic cognitive training would present a better cognitive (measured by neuropsychological tests which assess verbal & visual memory, attention and executive function) and functional performance (measured either by neuropsychological tests or rating scales of daily function) compared to the control group (between-group analysis), b) the experimental group after 3 years of training would improve their cognitive and functional performance, whereas the control group would present deterioration in the above abilities (within-group analyses), c) the experimental group would show stability of performance compared to the performance after 1 and 2 years of training (in contrast to b, where the comparison was performed between 1 and 3 years), and d) the experimental group would present lower progression rates after 3 years compared to the control group which would show higher progression rates.

Materials and Methods

Design

The current study has retrieved its sample from the electronic database of the DCCSH, during the period from 2008 to 2019. All participants registered to the electronic database gave written informed consent at the time of their initial clinical visit and in every follow-up assessment, agreeing that the DCCSH staff could use their basic demographic information such as age, gender, and education, as well as their total scores of neuropsychological tests for research reasons. Therefore, all necessary data were exported from the aforementioned database towards the conduction of the study. Finally, this study was approved by the Scientific and Ethics Committee of Alzheimer Hellas (Scientific Committee Approved Meeting Number: 6/28-3-2008) and the principles outlined in the Helsinki Declaration.

Participants

The participants exported from the electronic database were visitors of the DCCSH diagnosed with aMCImd according to Winblad criteria[30] by specialized health professionals. The diagnosis was supported by neurological examination, neuropsychological and neuropsychiatric assessment, medical/social history, neuroimaging, and blood tests, all of which were stored in the electronic database. Additionally, it is worthwhile mentioning that participant selection, group creation, and data analysis, were conducted by the researchers in a blind way, since the database was exported without any personalized information.

In this specific study 2 levels of user filtering (inclusion-exclusion criteria) were utilized: The first level included the baseline inclusion and exclusion criteria based on which each participant was selected from the aforementioned database. The inclusion criteria were the diagnosis of MCI based on Winblad criteria, the neuropsychological assessment and the neurological examination. The exclusion criteria were: (a) existence of severe behavioral or neuropsychiatric symptoms, such as aggressiveness, irritability, or apathy as that could affect the validity of the diagnosis, (b) other neurological disorders such as epilepsy, stroke, or hydrocephalus, (c) existence of any terminal illness, (d) mental illness, (e) pharmacological treatment with cholinesterase inhibitors, antipsychotic, and anticholinergic drugs, and (f) sensory deficits. The reason behind the exclusion of mental illnesses such as anxiety and depression is that the existence of such emotional diseases lower the effectiveness of cognitive training.

The second level of filtering consisted of specific research-oriented criteria which are described next. Out of the 5.299 people registered to the database, 730 had 3 follow-up neuropsychological assessments during the 3 years, and were therefore included in the study. According to the database, 227 people didn't take part in any kind of non-pharmacological interventions (even though they wanted to participate to interventions, they did not, due to family obligations, large distance to DCC, mobility problems etc.), whereas 503 participated in a combination of cognitive interventions and physical exercise. From the total sample of the control group, 94 people were excluded from the study for specific reasons that are presented in detail in Figure 1. The final total sample of the control group was 133 older adults with aMCImd. Concerning the experimental group, out of the 503 people who were exported from the database, 348 people were excluded. The reasons of exclusion are also presented at Figure 1. Therefore, the total number of participants of the experimental group was 155 people (Figure 1). Participants did not significantly differ in age ($p = 0.276$), gender ($p = 0.369$), education ($p = 0.246$) and severity of cognitive abilities ($p \geq 0.050$). Demographics characteristics of the participants are presented at Table 1.

The Interventions

During the 12 years of study, different cognitive training programs were administered to the DCCSH, towards avoiding the participants' drop out by giving them motivation to continue participating in the training groups. The theory behind the current study is that, by adding different stimuli and tasks to CT programs, new experiences and stimuli are offered to patients, that could be effective for the brain's function. All the CT programs were administered in groups of 8 people, who completed tasks with internal and external levels of difficulty. Every CT program approximately lasted 1 hour. The

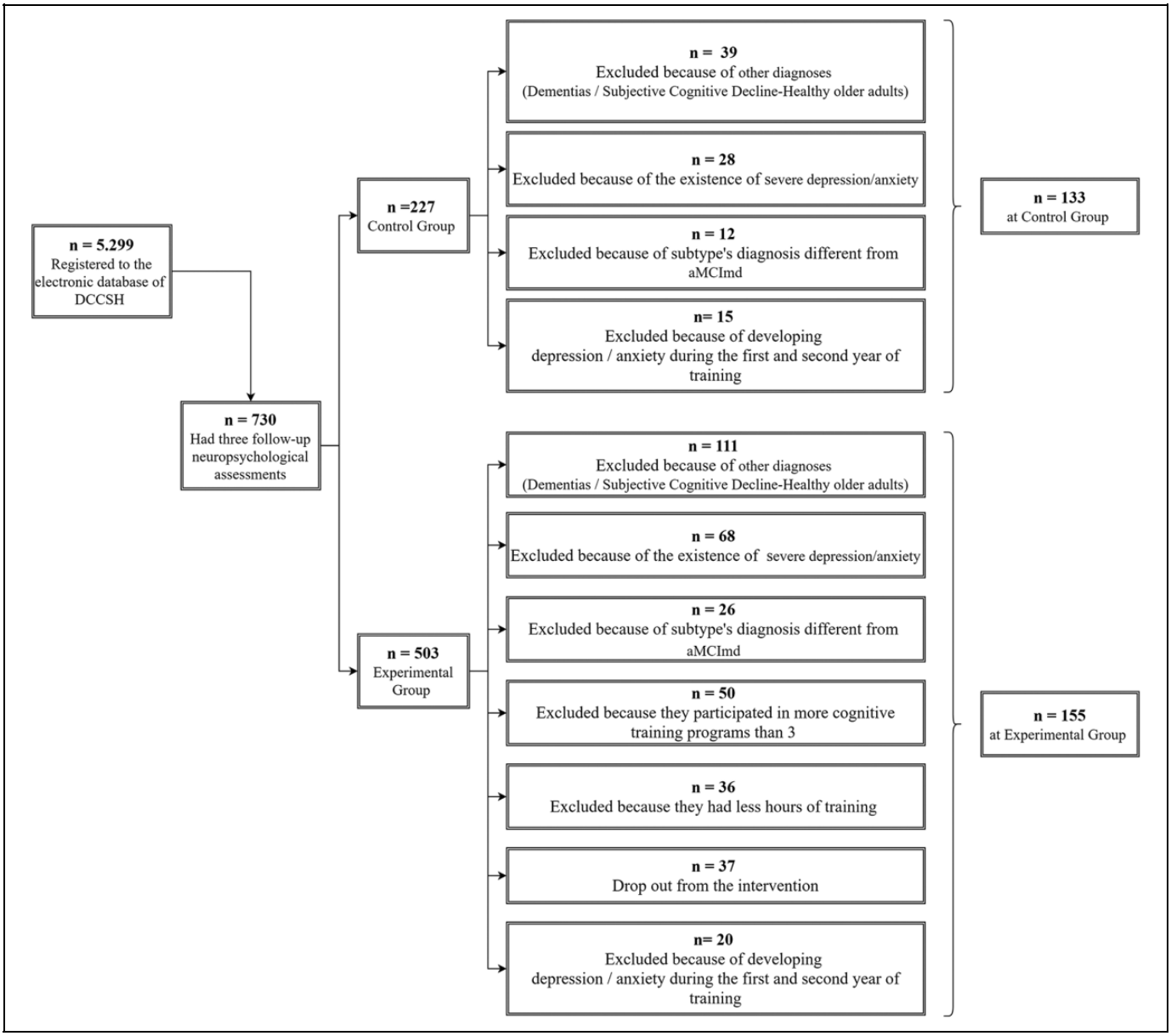

Figure 1. Chart flow of the study.

participants were visiting the DCCSH once a week and they completed a combination of 3 different CT programs (for 3 hours with an intermediate break) and 1 hour of physical activity. Overall, they had to complete 36 sessions per year, including an intermediate break for 3 months, during the summer. Each program was practicing a broad area of cognitive functions such as attention (visual-auditory, sustained-divided), language (naming) and aspects of executive function (working memory, inhibition, shifting, cognitive flexibility). As regards the training programs, Table 2 presents a summary of the selected programs, the cognitive abilities each program practices, as well as the means each cognitive training program utilizes. Afterwards, an extended description of the cognitive training programs is also presented.

Ist Year of Training

During the first year of training, people with MCI participated in a specific combination of programs. The cognitive training programs, as well as the specific abilities they were practicing are the following:

1. **Training by using discussion and commentary on a documentary video**

In this program, different videos with social, scientific, and religious content, are used as sources of visual and auditory stimulation. The training includes 4 tasks. Initially, participants are asked to watch part of a video and afterwards they are encouraged to recall parts of its content, and

answer related questions by using paper and pencil. Selective auditory attention and working memory are triggered in each session.

Table 1. Demographic Characteristics, M (SD) of Group's Participants.

Characteristics / cognitive - functional performance M (SD)	C/G (n = 133)	CT+PE/G (n = 150)	P
Age	67.11 (9.10)	68.12 (6.31)	0.276
Gender M/F (χ^2)	22/111	31/118	0.369
Education	10.69 (4.68)	11.31 (4.19)	0.246
MMSE[a]	27.28 (2.24)	27.70 (1.82)	0.088
FUCAS[b]	43.93 (2.36)	43.87 (2.36)	0.813
FRSSD[b]	3.54 (2.17)	3.61 (2.22)	0.788
RAVLT2[a]	10.73 (4.15)	10.55 (2.59)	0.578
RAVLT3[a]	7.90 (3.25)	7.68 (3.23)	0.570
RBMT2[a]	11.06 (3.67)	11.42 (3.90)	0.516
ROCFT[a]	11.71 (6.42)	12.94 (6.34)	0.116
RAVLT[a]	4.87 (2.01)	4.90 (1.98)	0.892
RBMT1[a]	12.11 (3.39)	12.39 (3.53)	0.434
FAS[a]	10.26 (4.15)	9.77 (3.47)	0.327
TEA[a]	47.82 (12.63)	47.00 (11.72)	0.246

Abbreviations: C/G, control group; CT+PE/G cognitive training plus physical exercises group; MMSE, Mini Mental State Examination; FUCAS, Functional Cognitive Assessment; FRSSD, Functional Rating Scale for Symptoms of Dementia; RAVLT2, Rey Auditory Verbal Learning Test-Learning Ability; RAVLT2, Rey Auditory Verbal Learning Test-Delayed words recall; RBMT2, Rivermead Behavioral Memory Test-Delayed History Recall; ROCFT, Rey Osterrieth Complex Figure Test-Figure recall; RAVLT1, Rey Auditory Verbal Learning-Working memory; RBMT1, Rivermead Behavioral Memory Test-Working Memory; FAS, Verbal Fluency Test; TEA, Visual selective attention; M (SD), mean (standard deviation); χ^2, Pearson chi square.
a More points/better performance.
b Less Points/better performance.

Example

At this point, you will hear some information regarding obesity. It is important to carefully listen and try to answer the following questions, once the audio passage is completed.

1. What is obesity?
2. What type of obesity is more frequent in men?
3. How many surgical methods exist?

Subsequently, a dual-task (divided attention) is given where participants are encouraged to perform 2 tasks at the same time; an auditory one, which is to count the number of a specific word being heard while watching the video, and a motor one, that is to open and close their hands in an alternative way. During the next task, a distinct frame on the video is being freezed and participants are asked to pay attention to the specific image. Afterwards, they try to answer questions in order to train the selective visual attention, visuospatial attention, updating of visual working memory and finally shifting of visual attention. At the end of the training, a task of abstract thinking is also included. Participants are given a few minutes to complete their view towards the pros and cons of the particular subject that is presented through the initial video they watched earlier. Enrichment of verbal fluency is also expected to occur, among other cognitive benefits.

2. Attention and executive function tasks applied by paper and pencil

The primary aim of this program was to enhance the various subtypes of attention and aspects of executive function, while the secondary one was the enhancement of visual-verbal

Table 2. Summary of Programs, Cognitive Abilities and Means of Cognitive Training.

Name of program	Cognitive trained abilities	Mean of training
Training by using discussion and commentary on a documentary video	Selective auditory and visual attention, working memory, updating of working memory, divided attention, shifting of visual attention, abstract thinking, semantic vocabulary	Video, oral discussion, paper and pencil
Attention and executive function tasks applied by paper and pencil	Visual selective attention, updating of working memory, switching of attention, shifting of visuospatial attention, divided attention, visual-verbal memory	Paper and pencil
Computer-based training of attention and executive function	Visual/verbal memory, visual-spatial abilities, visual selective attention, working memory, abstract thinking, language, updating of working memory, processing speed	Complete brain workout software, tasks of Pyramids, Color ties, Linker, Matching pairs, Symbol block, Box Pacer, Color matching, Shape Match, Correct change, Number balance
RHEA: Cognitive training by using kinetic instructions	Visuospatial abilities, attentional abilities, executive function, and language skills	Motion, wreaths, boards with letters, cards with colors, shapes, and numbers, corridors with numbers, balls, wands, rings, and cones.
Language Intervention	Semantic expression, semantic comprehension and phonemic expression of language, selective attention and shift of attention, working memory, inhibition control, executive function	Paper and pencil
Cognitive training through musical stimuli	Selective attention, divided attention, working memory, short-term and long-term memory, language	Greek familiar songs, lyrics of music
Physical Intervention	Visual perception, attention, memory, abstract thinking, and language	Physical exercises

memory, including the teaching of memory strategies and comprised levels of difficulty. The program is presented in detail by Kosta-Tsolaki et al., 2017.[31]

3. Computer-based training of attention and executive function

The primary aim of the computer-based (C-BCT) program was the enhancement of attention and executive function, while the secondary one was the enhancement of visual /verbal memory and visual-spatial abilities. The C-BCT used the 10 different tasks (Pyramids, Color tiles, Linker, Matching pairs, Symbol block, Box Pacer, Color matching, Shape Match, Correct change, Number balance) chosen from the "Complete brain workout" software (Oak Systems). For more information regarding the program's implementation and its effectiveness see Kosta-Tsolaki et al., 2017.[31]

2nd Year of Training

The CT programs of the second year of intervention and the specific abilities they were practicing were:

1. **RHEA: Cognitive training by using kinetic instructions**

This program was designed in order to enhance visuospatial abilities, attentional abilities, executive function, and language skills via the execution of motion instructions. Each session includes 5 visuomotor and verbal-kinetic tasks, including visual and verbal kinetic stimuli, respectively. The program comprised 2 increasing levels of difficulty. During the tasks, participants are encouraged to use personal strategies towards executing and completing the tasks. The program's implementation and its effectiveness are presented in Kounti et al., in 2011.[32]

2. Language Intervention

Language training included tasks, focused on the training and enhancement of semantic expression, semantic comprehension and phonemic expression of language. The tasks were ecologically valid, as they were derived from activities of daily living (ADL). Each set of cognitive tasks had 3 levels of difficulty. For more information see Poptsi et al, 2019.[33]

3. Cognitive Training Through Musical Stimuli

Cognitive training through musical stimuli includes directed music application for achieving specific therapeutic aims, such as the improvement of cognitive and functional performance. Training sessions include 5 cognitive tasks and each of them activates specific cognitive abilities. The trained cognitive abilities are selective attention, divided attention, working memory, short-term and long-term memory, as well as language. The program utilizes a great variety of cognitive tasks in order to keep participants' interest vivid. Music stimuli, which are famous Greek songs, play a major role in cognitive training, accompanying the cognitive tasks. The meaning, the number and the category of the provided cues (lyrics of music), are utilized as stimuli in order to activate cognitive abilities. Patients are asked to fill gaps, match sounds with images, and also name and mark images which they hear in the songs, etc.

Example of the music stimuli session

Task 1: At this task, the participants are given a paper with the lyrics of a song in the wrong order. Simultaneously, the aforementioned song is heard and the participants are asked to change the order of the lyrics by placing the correct number in front of each verse.

Physical Intervention

The physical intervention took part during all 3 years of intervention. The program was a multicomponent one (combination of aerobic, strength, flexibility and balance exercises) designed to address the physical, functional and cognitive impairments of people with MCI. The aims of the exercises were a) to maintain muscle strength and joint flexibility, b) to provide a gentle cardiopulmonary workout, c) to help the participants maintain body awareness through the sensation of movement, d) to provide a pleasurable experience and a sense of competence in being able to participate along with the other members of the group and move freely, and e) to enhance their cognitive functions such as visual perception, attention, memory, abstract thinking, and language. Each PE group was exercised for 2-3 times/week for 60 min. each time. The intensity was between 45% to 75% of HR (heart rate).

The program consists of simple and complex exercise routines, where the exercise leader provides simple, rhythmic instructions with simple verbal, visual and manual cues, since their combination makes them more effective. The same words are used each time, and the exercise routine is presented in the same way each time, using a calm, rhythmic intonation, which helps towards reinforcing learning and establishment of patterns. Instructions are faded out as soon as it is obvious that the participant knows what is doing. The participants should execute the exercise routines by counting loud each repetition either using digits or the alphabet letters in ascending or descending way.

Example of an exercise session at a seated position

Exercise 1. Simple exercise routine: Shoulders: Shrug both shoulders x 10 (counting each repetition using digits from 1 to 10 slowly – keeping the same rhythm).

Exercise 2. Complex exercise routine – dual task: Shrug both shoulders while performing knee extensions with both legs X 10 (counting each repetition using digits from 10 to 1 slowly – keeping the same rhythm).

3 rd Year of Training

The CT programs of the first year, as well as the program of the physical exercise, were repeated in the third year of intervention by using a different version of tasks.

Instruments of Neuropsychological Assessment

The assessment used in order to support the diagnosis included psychometric tests and specifically the MMSE[34,35] which assesses general cognitive function and the Functional Cognitive Assessment Scale,[36] which assesses directly from the examinee the ability to execute 6 different activities of daily life. The Functional Rating Scale for Symptoms of Dementia[37] was used for evaluating ADL (evaluates caregiver's opinion about daily function of people with cognitive disorders), while the Geriatric Depression Scale[38,39] and the Short Anxiety Screening Test[40,41] were used in order to exclude people with affective disorders. Finally, the Neuropsychiatric Inventory[42,43] was employed for the evaluation of neuropsychiatric symptoms and the Global Deterioration Scale,[44] to set the stage of the diagnosis.

The program's effectiveness was examined by neuropsychological assessment performed at baseline, and at the end of each year for 3 consecutive years. Therefore, the 2 groups had 3 hours neuropsychological assessments at baseline, at the first, the second and the third year. Each group was examined and followed up at the same time and place from the same neuropsychologist. Neuropsychological assessment included also a comprehensive battery of psychometric tests (1) Rey Auditory Verbal Learning test (RAVLT)[45,46] for verbal memory; (2) Rey Osterrieth Complex Figure test for visual memory and visual constructive abilities;[47,48] (3) Rivermead Behavioral test (RBMT; history subtest),[49,50] for verbal episodic memory; (4) the total score of Verbal Fluency test (FAS),[51,52] for executive function, and (5) the Test of Everyday Attention (subtask map searching),[53] for the assessment of visual selective attention. In order to avoid practice effects different test versions were utilized wherever necessary, namely, the Taylor's Complex Figure Test[54] for visual memory and visual constructive abilities and California Auditory Verbal Learning[55] for verbal memory.

Data Statistical Analysis

The statistical analysis was performed with the IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp[1] 23.0. Age, gender and education were analyzed at baseline using a Univariate analysis (ANOVA) and Fisher's exact test, when necessary. In order to determine whether there was any significant difference among the groups and times of assessment, a mixed measures ANOVA with a 2 (group: experimental-control) x 2 (time of assessment: pretest, posttest) was used. Multivariate analysis of variance (MANOVA) was also used. The within group effect of training for both groups among the baseline and the 3 rd follow-up assessment was analyzed with repeated measures analysis of variance (rANOVAS). Moreover, extra within group comparisons among the 1st and 3 rd year and the 2nd and 3 rd year for the CT+PE/G, were also conducted. The rANOVAS were also used for the evaluation of the effect of time of assessment for the control group between the baseline and 3rd year. Because of the expanded assessment battery, the Bonferroni correction was utilized. Therefore, the level of statistical significance was set at $\alpha = 0.003$. Finally, Pearson's chi square was used for calculating whether or not the difference between the 2 groups progression rates to dementia were statistically significant.

Table 3. Differences in Performance at the 3rd Follow-Up (After 3 Years) Between the Groups.

Cognitive / functional performance MO (SD)	C/G (n = 133)	CT+PE/G (n = 150)	p
MMSE[a]	26.79 (3.47)	27.90 (2.65)	0.024
FUCAS[b]	45.66 (5.72)	43.64 (2.00)	**0.000**
FRSSD[b]	4.34 (3.29)	3.22 (2.01)	**0.003**
RAVLT2[a]	10.75 (3.97)	11.78 (2.47)	**0.002**
RAVLT3[a]	7.80 (3.77)	9.65 (3.29)	**0.002**
RBMT2[a]	9.82 (4.33)	11.13 (3.62)	0.016
ROCFT[a]	12.98 (6.25)	15.60 (7.06)	0.042
RAVLT1[a]	5.22 (2.15)	6.28 (2.46)	0.026
RBMT1[a]	10.72 (3.90)	11.85 (3.49)	0.021
FAS[a]	10.05 (3.69)	12.00 (3.34)	**0.000**
TEA[a]	47.82 (12.68)	47.00 (11.72)	0.246

Abbreviations: C/G, control group; CT+PE/G cognitive training plus physical exercises group; MMSE, Mini Mental State Examination; FUCAS, Functional Cognitive Assessment; FRSSD, Functional Rating Scale for Symptoms of Dementia; RAVLT2, Rey Auditory Verbal Learning Test-Learning Ability; RAVLT2, Rey Auditory Verbal Learning Test-Delayed words recall; RBMT2, Rivermead Behavioral Memory Test-Delayed History Recall; ROCFT, Rey Osterrieth Complex Figure Test-Figure recall; RAVLT1, Rey Auditory Verbal Learning-Working memory; RBMT1, Rivermead Behavioral Memory Test-Working Memory; FAS, Verbal Fluency Test; TEA, Visual selective attention; M (SD), mean (standard deviation);
a More points/better performance.
b Less Points/better performance.

Results

The Effect of Group and Assessment Time among the Baseline Assessment and the 3 Years Follow-up

Baseline measurements showed that there were no statistically significant differences between the 2 groups in demographic characteristics such as age ($p = 0.276$), gender ($p = 0.369$) or education ($p = 0.246$), and also in all measures of cognitive and functional tests that were used (Table 1). The effects of groups and assessment time among the experimental and control groups among the pre-test (baseline assessment) and the post-test assessment (3 years later) are presented below.

The Effects of Groups and Assessment Time in ADL

Mixed measures analysis of variance showed that there was not a main effect of time of assessment, but a significant interaction effect, $F(1, 283) = 14.5\ p < 0.001$, $\eta^2 = .05$ was noticed in the Functional Rating Scale for Dementia - ADL (FRSSD). The subsequent MANOVA, with group as the independent variable and performance in 2 times of assessment as the dependent ones, $F(1, 283) = 2.59\ p < 0.001$, $\eta^2 = .16$, showed that at the post test the experimental group was better than the control group ($p < 0.003$) (Table 3).

Table 4. Difference in Groups' Performance Between Baseline and 3 Years Follow-Up.

Cognitive /functional performance	Groups	At baseline M (SD)	3 years follow-up M (SD)	p
MMSE[a]	**CT+PE/G**	27.70 (1.82)	27.90 (2.65)	0.385
	C/G	27.28 (2.24)	26.79 (3.47)	0.031
FUCAS[b]	**CT+PE/G**	43.87 (2.36)	43.64 (2.00)	0.342
	C/G	43.93 (2.36)	45.66 (5.72)	**0.000**
FRSSD[b]	**CT+PE/G**	3.61 (2.22)	3.22 (2.01)	0.090
	C/G	3.54 (2.17)	4.34 (3.29)	**0.001**
RAVLT2[a]	**CT+PE/G**	10.55 (2.59)	11.78 (2.47)	**0.000**
	C/G	10.73 (4.15)	10.75 (3.97)	0.644
RAVLT3[a]	**CT+PE/G**	7.68 (3.23)	9.65 (3.29)	**0.000**
	C/G	7.90 (3.25)	7.80 (3.77)	0.653
RBMT2[a]	**CT+PE/G**	11.42 (3.90)	11.13 (3.62)	0.355
	C/G	11.06 (3.67)	9.82 (4.33)	**0.000**
ROCFT[a]	**CT+PE/G**	12.94 (6.34)	15.60 (7.06)	**0.000**
	C/G	11.71 (6.42)	12.98 (6.25)	0.040
RAVLT1[a]	**CT+PE/G**	4.90 (1.98)	6.28 (2.46)	0.009
	C/G	4.87 (2.01)	5.22 (2.15)	0.040
RBMT1[a]	**CT+PE/G**	12.39 (3.53)	11.85 (3.49)	0.068
	C/G	12.11 (3.39)	10.72 (3.90)	**0.000**
FAS[a]	**CT+PE/G**	9.77 (3.47)	12.00 (3.34)	**0.000**
	C/G	10.26 (4.15)	10.05 (3.69)	0.117
TEA[a]	**CT+PE/G**	47.00 (11.72)	47.29 (11.72)	0.068
	C/G	47.82 (12.63)	43.83 (14.82)	**0.000**

Abbreviations: C/G, control group; CT+PE/G cognitive training plus physical exercises group; MMSE, Mini Mental State Examination; FUCAS, Functional Cognitive Assessment; FRSSD, Functional Rating Scale for Symptoms of Dementia; RAVLT2, Rey Auditory Verbal Learning Test-Learning Ability; RAVLT2, Rey Auditory Verbal Learning Test-Delayed words recall; RBMT2, Rivermead Behavioral Memory Test-Delayed History Recall; ROCFT, Rey Osterrieth Complex Figure Test-Figure recall; RAVLT1, Rey Auditory Verbal Learning-Working memory; RBMT1, Rivermead Behavioral Memory Test-Working Memory; FAS, Verbal Fluency Test; TEA, Visual selective attention; M (SD), mean (standard deviation);
[a]More points/better performance.
[b]Less Points/better performance.

As far as the second test of ADL is concerned (FUCAS), there was a main effect of time of assessment, $F(1, 283) = 10.8$, $p < 0.001$, $\eta^2 = .03$, and a significant interaction effect, $F(1, 283) = 17.3$, $p < 0.001$, $\eta^2 = .05$. The subsequent MANOVA with group as the independent variable and performance in 2 times of assessment as the dependent ones, $F(1, 283) = 2.59$ $p < 0.001$, $\eta^2 = 16$, showed that at the follow-up of 3 years there was a significant effect of group in general functional assessment $F(1, 283) = 12.95$, $p < 0.001$, $\eta^2 = .06$. The CT+PE/G was found to have better performance than C/G ($p < 0.001$) (Table 3). Within group analysis of variance (repeated measures) between pre-test and post-test in each group separately, showed that C/G deteriorated ($p < 0.001$), while non-significant differences were noticed regarding the CT+PE/G performance in the above ability (Table 4).

The Effects of Groups and Assessment Time in Episodic Verbal and Visual Memory

As far as the total learning ability (RAVLT) is concerned, there were also a main effect of time of assessment, $F(1, 283) = 16.9$, $p < 0.001$, $\eta^2 = .12$, and a significant interaction effect, $F(1, 283) = 11.6$, $p < 0.001$, $\eta^2 = .09$. The subsequent MANOVA with group as the independent variable and performance in 2 times of assessment as the dependent ones, $F(1, 283) = 2.59$ $p < 0.001$, $\eta^2 = .16$, showed that at the follow-up there was a significant effect of group on total learning ability (RAVLT), $F(1, 283) = 9.95$ $p < 0.001$, $\eta^2 = .02$. The CT+PE/G scored higher than the control group ($p < 0.003$) (Table 3). Within group analysis between baseline and follow-up, showed that the CT+PE/G improved in learning ability ($p < 0.002$), while the C/G showed no change at the above ability ($p > 0.05$) (Table 4).

Regarding the delayed recall (RAVLT), a main effect of time of assessment, $F(1, 283) = 32.5$ $p < 0.001$, $\eta^2 = .10$, and a significant interaction effect, $F(1, 283) = 40.7$ $p < 0.001$, $\eta^2 = 13$, were also noticed. The subsequent MANOVA, $F(1, 283) = 2.59$ $p < 0.001$, $\eta^2 = .16$, showed that at the post-test there was a significant effect of group on delayed recall (RAVLT), $F(1, 283) = 9.44$, $p < 0.001$, $\eta^2 = .04$. The CT+PE/G was better than the C/G ($p < 0.002$) (Table 3). Repeated measures between baseline and follow-up assessment showed that after the training, the CT+PE/G showed improvement in delayed recall (RAVLT) ($p < 0.001$), while the C/G stabilized its performance and showed neither improvement nor deterioration regarding delayed recall ($p > 0.05$) (Table 4).

The delayed recall of a history assessed by RBMT, showed that there was a significant main effect of time of assessment, $F(1, 283) = 12.6$ $p < 0.001$, $\eta^2 = .04$, and no interaction effect. Within group analysis showed that C/G was improved in

Table 5. Difference in Experimental's Group Performance Among the 1st and the 3rd Year and Among the 2nd and the 3rd Year's Follow-Up.

Cognitive / functional performance	1 year follow-up M (SD)	2 years follow-up M (SD)	3 years follow-up M (SD)	p*	p**
MMSE[a]	28.18 (1.80)	28.22 (1.62)	27.90 (2.65)	0.259	0.138
FUCAS[b]	43.70 (2.39)	43.47 (1.82)	43.64 (2.00)	0.791	0.354
FRSSD[b]	3.44 (2.16)	3.26 (1.73)	3.22 (2.01)	0.385	0.781
RAVLT2[a]	11.40 (2.70)	11.71 (2.51)	11.78 (2.47)	0.071	0.761
RAVLT3[a]	9.04 (3.54)	9.51 (3.19)	9.65 (3.29)	0.036	0.492
RBMT2[a]	11.76 (3.90)	12.38 (4.97)	11.13 (3.62)	0.026	**0.002**
ROCFT[a]	15.54 (9.42)	15.62 (6.94)	15.60 (7.06)	0.964	0.773
RAVLT1[a]	5.76 (2.07)	6.20 (2.21)	6.28 (2.46)	**0.011**	0.722
RBMT1[a]	12.52 (3.40)	12.83 (3.27)	11.85 (3.49)	0.026	**0.001**
FAS[a]	11.30 (3.13)	11.85 (3.36)	12.00 (3.34)	0.032	0.652
TEA[a]	49.15 (10.85)	49.13 (11.75)	47.00 (11.72)	0.675	0.371

Abbreviations: C/G, control group; CT+PE/G cognitive training plus physical exercises group; MMSE, Mini Mental State Examination; FUCAS, Functional Cognitive Assessment; FRSSD, Functional Rating Scale for Symptoms of Dementia; RAVLT2, Rey Auditory Verbal Learning Test-Learning Ability; RAVLT3, Rey Auditory Verbal Learning Test-Delayed words recall; RBMT2, Rivermead Behavioral Memory Test-Delayed History Recall; ROCFT, Rey Osterrieth Complex Figure Test-Figure recall; RAVLT1, Rey Auditory Verbal Learning-Working memory; RBMT1, Rivermead Behavioral Memory Test-Working Memory; FAS, Verbal Fluency Test; TEA, Visual selective attention; M (SD), mean (standard deviation); p* = significant difference among 1st and 3rd follow-up; p** = significant difference among 2nd and 3rd follow-up.
a More points/better performance.
b Less Points/better performance.

delayed recall of a history ($p < 0.001$), whereas CT+PE/G didn't show any improvement or deterioration ($p > 0.05$) (Table 4).

Regarding the visual memory (ROCFT) the analysis showed that there was a main effect of time of assessment $F(1, 283) = 26.5$ $p < 0.001$, $\eta^2 = .09$, and no interaction effect. Within group analysis showed that the CT+PE/G group at follow-up improved the ability of visual memory ($p < 0.001$). The C/G showed no improvement or deterioration in this ability ($p > 0.05$) (Table 4).

The Effects of Groups and Assessment Time in Executive Function and Attention

As far as the working memory of RBMT is concerned the analysis showed that there was a main effect of time of assessment, $F(1, 283) = 21.6$ $p < 0.001$, $\eta^2 = .07$, but not an interaction effect. Repeated measures between pre-test and post-test values showed that at the post-test the C/G showed deterioration ($p < 0.001$). The CT+PE/G showed neither deterioration nor improvement in this test ($p > 0.05$) (Table 4).

According to the results in the total verbal fluency assessed by FAS test, a main effect of time of assessment, $F(1, 283) = 24.2$ $p < 0.001$, $\eta^2 = .10$, and a significant interaction effect $F(1, 283) = 46.0$ $p < 0.001$, η^2 .17, were noticed. MANOVA test, $F(1, 283) = 2.59$ $p < 0.001$, $\eta^2 = .16$, showed that at the post-test there was a significant effect of group in total verbal fluency (FAS) $F(1, 283) = 23.8$ $p < 0.001$, $\eta^2 = .11$. The CT+PE/G showed better performance than the C/G ($p < 0.001$). Within group analysis showed that the CT+PE/G was improved in total verbal fluency (FAS) 3 years after the baseline assessment ($p < 0.001$). Control group didn't show any improvement or deterioration to the relative ability ($p > 0.05$) (Table 4).

Finally, there was a main effect of time of assessment $F(1, 283) = 7.06$ $p < 0.001$, $\eta^2 = .01$, but not a significant effect on selective visual attention of the Test of Everyday Attention (TEA). The rANOVAS showed that at the post-test the C/G deteriorated in visual selective attention ($p < 0.001$), whereas CT+PE/G showed neither improvement nor deterioration to this test ($p > 0.05$) (Table 4).

The Effect of Time of Assessment Regarding the Experimental Group among the 1st and the 3 rd Year

As far as the comparison between the 1st and the 3 rd year is concerned, the within group comparison showed that there was no statistically significant difference between these assessments (Table 5).

The Effect of Time of Assessment Regarding the Experimental Group Between the 2nd and the 3 rd Year

Regarding the comparison between the 2nd and the 3 rd assessment, rANOVAS were used. According to the results, the within group analysis showed that there was a statistically significant difference between the 2nd and the 3 rd year. The CT+PE/G at the third follow-up (3 years later) deteriorated in working memory (RBMT) ($p < 0.001$) and in verbal memory (RBMT) ($p < 0.002$) (Table 5).

The Rate of Progression to Dementia, 3 Years After the Baseline Diagnosis

The rate of progression to dementia appeared to be significantly different among the groups, chi-square (2) = 17.54, $p < 0.001$. Two people (n = 2) out of the 155 participants of the CT+PE/G progressed to dementia (1.33%) in the third year while 18 out of 133 participants of the control group were

Table 6. Progression Rates Between the 2 Groups.

	Progressed	Percent %	No progressed	Total number
C/G	18	13.53%	115	133
CT+PE/G	2	1.33%	148	155

Abbreviations: C/G, control group; CT+PE/G cognitive training plus physical exercises group

diagnosed with dementia, 3 years after the baseline assessment (13.53%) (Table 6).

Post-Hoc Power Analysis

Finally, in order to assess whether our results had a strong statistical power, a post hoc power analysis was conducted using the software package, GPower 3.1.9.4.[56] The sample size of 283 was used for the statistical power analysis and the number of 11 measurements was used as a baseline. The effect size used for this assessment was the large one ($f\,2 = .35$) and the alpha level was $p < .05$. The post hoc analysis revealed that the statistical power for this study is .82. Thus, there was more than adequate power at the large effect size level.

Discussion

The current study aimed at identifying the longitudinal effect of CT, including cognitive tasks as well as physical exercise. Given that MCI population maintains a satisfactory level of cognitive functions, they are regarded as an ideal population for cognitive training deployment, as well as for measuring its efficacy.

The first assumption of our study was that after 3 years of continuous and systematic cognitive training, the experimental group would present a better cognitive and functional performance compared to the control group. As Table 3 indicates, the experimental group scored higher in almost all cognitive and functional tests in comparison to the control group. It is worth mentioning that at this study we utilized a quite strict level of statistical significance ($\alpha = 0.003$) according to Bonferroni correction, therefore we kept as significant different only the values which were lower or equal with 0.003.

In more detail, if we process the results, we can observe that the experimental group showed improvement to the overwhelming majority of cognitive tests used in this study. The most prominent differences were found in the total learning ability and delayed recall, as measured by RAVLT, and also in the phonemic fluency measured by FAS. Regarding ADL, measured by FRSSD, the experimental group outperformed the control group, constituting a quite important result, since it provides evidence that cognitive training can transfer the primary cognitive effect to daily life, being the ultimate goal of every similar program. Therefore, our study provides data that the combination of cognitive and physical training in a weekly basis over a 3 years period enhances cognition as well as ADL in people with aMCImd. This fact is quite important given that this diagnostic category is related to great risk of developing dementia.[4] Moreover, it is of foremost significance to highlight that due to the non-pharmacological programs' implementation, the progression to dementia was diminished in this population in comparison to the control group. Our results are in agreement with these of previous research.[57-59] However, the clinical significance of our results derives from the fact that in our study we recruited a large number of participants, which the aforementioned studies lacked. Additionally, despite that the previous studies suggested that the cognitive training approach is efficient in MCI population, to our knowledge, there are almost no previous studies measuring the longitudinal effect of a continuous cognitive training program along with physical exercise in such a long period of time.

Similar studies showed that RBMT and RAVLT immediate and delayed recall were found to be improved in MCI population after an 8-sessions training program compared to the control group, according to the study by Olchik, Farina, Steibel, Teixeira, & Yassuda (2013),[60] which is in agreement to our study, mainly for the RAVLT test. Therefore, authors suggest that MCI participants had similar scores to these of cognitively intact elders, providing strong support of the neuroplasticity theory. Perhaps if we had assessments after shorter periods, as in the aforementioned study,[60] we could also have better results in RBMT. However, in our study, attention abilities and also aspects of executive function were practiced. Therefore, we didn't expect great differences in all utilized tests that measure other cognitive functions (e.g., episodic memory), even though we expected some change/ improvement through the mechanism of generalization. Additionally, a relatively recent review by Jean, Bergeron, Thivierge, and Simard (2010)[61] showed significant improvement in the 44% of the objective psychometric tools which measure memory in comparison to the 12% of those that measure cognitive functions other than memory in amnestic MCI population. This evidence highlights the significant effect of cognitive training in memory which is concordant with our study. Furthermore, there is also evidence that visuo-spatial as well as attentional abilities were gradually impaired in individuals with MCI over a 12 months period, although the sequence of their development was heterogeneous.[62] These findings are also in accordance with ours, given that the participants with aMCImd who constituted our control group, had lower scores in almost the majority of cognitive as well as functional tests after the 3 rd year of assessment. Moreover, positive effects of cognitive and physical training on general cognitive ability, as measured by the ADAS-cog, were also observed in the study by Maffei et al. (2017).[57] It is worth mentioning that in their study they found increased cerebral blood flow in individuals with MCI who took part in the aforementioned non-pharmacological interventions. Specifically, they found that cerebral blood flow was increased in Medial Temporal Lobe, and mainly in para-hippocampal regions, in individuals with MCI who participated in cognitive as well as in physical training. Additionally, Zlokovic (2011)[63] suggests that the reduced cerebral blood flow contributes to increased beta-amyloidosis. However, no significant effects were found

between MCI and control group in the grey matter volume, which according to authors, can be attributed to the small number of participants.

As far as the third aim of this study is concerned, it was hypothesized that the experimental group would show stability of performance compared to the performance after 1 and 2 years of training. The further within analysis of the experimental group showed that there were no alterations among the first and the second year, whilst a significant deterioration was noticed among the second and the third year for working as well as for verbal memory. However, the CT+PE/G managed to maintain stable performance in the rest of the cognitive and functional tests. What is of foremost importance is the fact that the majority of cognitive domains were not found to differ between the first, second and third follow-up assessments. By comparing the performances between the 3 years, we assume that the experimental group managed to maintain the benefit yielded from the first year of training to the second and the third year, stabilizing the cognitive performance. However, the extra 2 years of training didn't manage to further improve the cognitive abilities. On the contrary there was a deterioration especially in working and verbal memory, which are abilities sensitive to deterioration during the years and early markers of further cognitive decline.[64,65] It is worth mentioning that in our study, even though the experimental group showed either stability or deterioration among the second and the third year, it didn't show deterioration between the baseline and the third year. This possibly reflects that the greater positive change in cognitive functions occurs at the first year of training, while more years of training can possibly help people with aMCImd to maintain stable the cognitive effect yielded from the first year. A previous study of our research group tried to investigate the effectiveness of cognitive training during 1 and 2 years.[27] Our previous results were similar as far as the first year of training was concerned, however they were a bit different regarding the second-year results. The aforementioned study provides evidence that 2 years of cognitive training in people with aMCImd is better than 1 year of training. Specifically, in our older study 74 people attended a systematic 1-year cognitive training program, while 41 of them attended the same cognitive training program for 1 more year. The results showed that compared to the group with 1 year of training, the 2 years training group managed to show further improvement at the second year of training in domains of episodic memory, executive function, and ADL, indicating that more training provides more cognitive effects, in contrast to the current study which presents stabilization and a slight deterioration in 2 tests. A possible reason for this difference might be that at the previous 2 year's study the sample was divided into 3 groups. Therefore, the participants who continued the second year of training were people with more powerful motivation than the 1-year experimental group, a reason that possibly led to further improvement. Also, in contrast to the present study the aforementioned one lasted 2 years and not 3.

Despite that similar studies should shed light to the current findings, in order to identify the real benefit of CT programs in this population, it is equally important for participants with aMCImd should have access to this kind of services, which seem to be maintained during their participation in them. Therefore, it is quite important to highlight the beneficial role of CT program in this population because it is an inhibitor for progressing to dementia.

As regards the last goal of our study, it was found that cognitive and physical training can be effective at diminishing the progression rates from MCI to dementia, which is in line with a majority of studies[27,28,29] highlighting the effective role of this combination on participants with MCI.[35] A complex multimodal activity intervention to reduce the risk of dementia in mild cognitive impairment, named ThinkingFit, has been found to significantly reduce the rates of conversion to dementia from MCI. Furthermore, according to the results of Finger study,[66] multidomain intervention including cognitive training combined with physical exercise components, showed positive effect in general cognitive function, as well as in secondary outcomes (e.g., executive functioning and processing speed), and also secondary benefits of health indexes (e.g., BMI, dietary habits, and physical activity). Finally, combining physical activity, which promotes neuronal activity and neurogenesis, with cognitive interventions, which empower brain activity, is a stepping stone for strengthening cognitive function, as well as dementia prevention in MCI.[67] To sum up, due to the fact that a large majority of studies include the combination of physical exercise and cognitive stimulation, the current research provided new knowledge about the combination of physical exercise along with cognitive training which is also very effective at reducing the risk of dementia.

Concerning the second goal related to dementia progression in MCI who attended longitudinal non-pharmacological interventions, evidence by Fischer et al. (2007)[68] showed that there are increased progression rates from MCI (amnestic and non-amnestic) to dementia after a 30 months period. Our results are of a great clinical value because the number of individuals with MCI who developed dementia after 36 months was smaller for those who attended the above non pharmacological intervention in comparison to the control group. Despite our findings that the control group was at higher risk of developing dementia, we didn't analyze which is the most predictive test of developing dementia, both in experimental, as well as in the control group. According to Tabert et al. (2006),[69] impairment in verbal memory as well as psychomotor speed / executive function can significantly predict progression to Alzheimer's disease. Moreover, according to a large study by Silva et al, in 2013,[70] conducted in non-demented patients with subjective complaints, Logical memory test significantly predicted the progression to dementia after a 5 years period. A previous study by Silva et al., (2012)[71] also stated that verbal memory tests, such as CVLT, are the most accurate predictors for dementia in individuals with subjective cognitive complaints. The aforementioned results can be indirectly verified by the current study, since the experimental group had significantly higher scores in episodic memory as well as in verbal memory tasks across the different time spans. To conclude, older adults with

aMCImd are in higher risk of progressing to dementia[5] and therefore they should be regarded as a population with high priority in the implementation of cognitive combined to physical training programs.

To the best of our knowledge, there are very few studies delineating the importance of cognitive training in reducing the progression to dementia in MCI population. In more detail, O'Caoimh, et al., in 2015,[72] supported that cognitive training can be regarded as a therapeutic approach in this population. Additionally, the review by Mowszowski, Batchelor, & Naismith (2010)[73] suggests that cognitive training can be beneficial in cognitively intact older adults and protective in MCI population with increased risk of dementia, however its efficacy in people living with mild dementia is still uncertain. Taking into account the limited studies existing in this scientific area, the added value of our study is the longitudinal effectiveness of cognitive training after a 3 years period. Given that we did not find previous studies including longitudinal interventions, it is infeasible to compare our results.

Moreover, another significant contribution of the current study is that via applying a well-structured cognitive training program along with physical exercise tailored to the participants needs, we provide a practical solution to health professionals who implement this kind of training. In specific, according to the review by Belleville (2008),[74] positive effects of cognitive training must be seen under the light of whether we can generalize them in MCI population. Hence, by recruiting a large number of participants, implementing 36 consecutive sessions, and analyzing our programs' structure, we aim at overcoming the aforementioned barriers as provided by Belleville's review.

Strengths and Limitations of the Study

The most important contribution of this study is that it comprises a large sample of people with MCI. There are many studies that evaluate the effectiveness of one or more cognitive training programs with or without programs of physical exercises, randomized or not.[57,75-77] However, the most non-pharmacological studies comprise small sample sizes, typically having fewer than 50 individuals.[78,79] Therefore, we consider that the main strength of this study is the large number of participants. The second advantage is that it concerns 3 years of continuous cognitive training, which is a very long time since most cognitive training studies last only for a few weeks.[62,80,81] Even though there are studies that last 2 years[27] according to our knowledge the current study is the first one which refers to 3 years of unceasing training (except for the summer months for which the participants were on vacation).

The main limitation of the present study is that it is a database study. There are many disadvantages of using databases for outcome of conclusions. Selection bias, recall bias, and of course many different healthcare professionals are involved in patient care. These are unavoidable limitations in retrospective studies.[82] Furthermore, our study lacks an active controls' group. The existence of an active control group would be helpful to rule out the possibility that our results concerning the improvement of the experimental group originated from a placebo effect, even though it is not always accepted that studies which include active control are better than the studies that don't comprise control groups.[83] Furthermore, one limitation that is common to longitudinal researches is the high dropout rates, which appeared in the current study as well. The last limitation is that our study is not a randomized one, which makes sense since it is a retrospective one. As a future work, the next challenge to our research is to choose from the Alzheimer Hellas electronic database all the cases who present raised rates of risk factors of progression from MCI to dementia and to control for biomarkers for determining the effectiveness of the same intervention in a specific high-risk group. Therefore, our next goal is to increase the homogeneity of the under-research groups and to further expand the research to more than 3 years.

In conclusion, the current study is the first which attempts to evaluate the effectiveness of a continuous and systematic multicomponent intervention comprising different programs of cognitive training plus physical exercises for 3 years. Our results showed that the present longitudinal intervention improved cognitive and functional status in people with MCI and can diminish the progression of MCI to dementia for at least 3 years' time period.

Declaration of Conflicting Interests

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Notes

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