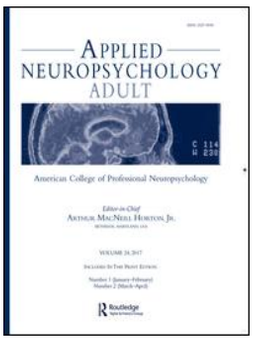

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Beneficial effect of computer-based multidomain cognitive training in patients with mild cognitive impairment

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ABSTRACT

The purpose of the present study was to explore the effects of computer-based multidomain cognitive training program on Greek patients with Mild Cognitive Impairment (MCI). Forty-six patients with MCI were randomly divided into two groups; (a) the training group, which received a computer-based multidomain cognitive training program with the use of the RehaCom software and (b) the control group, which underwent standard-clinical care. The duration of the computer-based training program was 15 weeks, administered twice a week for approximately one hour per session. Analysis of the baseline versus endpoint performance of each group demonstrated that in the control group delayed memory and executive function had deteriorated over the observation period of 15 weeks, while improvement was observed in the training group's performance on delayed memory, word recognition, Boston Naming Test (BNT), Clock Drawing Test (CDT), Semantic Fluency (SF), Trail Making Test-A (TMT-A) and Trail Making Test-B (TMT-B). Comparison between the two groups presented asignificant effect of the intervention for most cognitive domains. These findings are promising for the development of training methods designed to delay cognitive decline in patients with MCI, which is considered to be the prodromal stage of Alzheimer's Disease (AD).

KEYWORDS

Computer-based cognitive training; mild cognitive impairment; multidomain; RehaCom software; neuropsychological performance

Introduction

Mild Cognitive Impairment (MCI) often appears in the precursor period between normal ageing and dementia and is thus considered as the first step towards dementia (Dardiotis et al., 2019; Greenaway, Duncan, & Smith, 2013; Jelcic et al., 2012; Manouilidou, Dolenc, Marvin, & Pirtosek, 2016; Stamati et al., 2019). Epidemiological studies have shown that 8–15% of individuals with MCI will progress to dementia every year, and up to 80% will progress to dementia within six years. A group of MCI patients with memory impairment is the typical prodromal stage of dementia and carries a high conversion risk to Alzheimer's disease (AD) (Petersen et al., 2013). Indeed, the majority of patients with MCI develop AD, although some do stay stable and a few of them even get better (Schaefer, Dibble, & Duff, 2015).

Prior research has revealed that patients with MCI face problems with memory (Ganguli, Dodge, Shen, & DeKosky, 2004; Olchik, Farina, Steibel, Teixeira, & Yassuda, 2013; Savulich et al., 2017; Tsapanou et al., 2017), attention (Herrera, Chambon, Michel, Paban, & Alescio-Lautier, 2012) executive function (Barekatain, Alavirad, Tavakoli, Emsaki, & Maracy, 2016; Huckans et al., 2013), verbal fluency (Taler, Klepousniotou, & Phillips, 2009) and lexical decision tasks (Taler & Jarema, 2004). Moreover, they have been found to present less sensitivity to semantic violations when compared to healthy controls (semantic priming) (Davie et al., 2004) and to face difficulties categorizing the words based on their meaning (Olchik et al., 2013) or rhyme (Dwolatzky et al., 2003).

To date, no approved pharmacological treatment for cognitive decline in MCI has been made available (Vlachos et al., 2019). Consequently, research has focused on finding effective, non-pharmacological interventions (Cooper, Li, Lyketsos, & Livingston, 2013). Computer-based cognitive training seems to be beneficial for individuals with MCI since it can slow down their cognitive decline, or even, in some cases, optimize their cognitive functioning (Mueller, 2016; Tsolaki et al., 2017). Several studies using computer-based cognitive training interventions have reported that, at the end of the intervention, the training group performed better on working memory (Oskoei, Nejati, & Fathabadi, 2013), delayed memory (Herrera et al., 2012; Olchik et al., 2013), executive function (Greenaway et al., 2013; Herrera et al., 2012), episodic recall and recognition (Herrera et al.,

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2012), semantic fluency (Olchik et al., 2013; Rojas et al., 2013; Rozzini et al., 2007; Talassi et al., 2007) and naming (Rojas et al., 2013) when compared to passive or control groups with MCI.

Some computer-based cognitive training programs have mainly focused on specific areas, such as memory and attention (Han et al., 2014; Herrera et al., 2012; Hyer et al., 2016; Man, Chung, & Lee, 2012; Mansbach, Mace, & Clark, 2017; Savulich et al., 2017; Styliadis, Kartsidis, Paraskevopoulos, Ioannides, & Bamidis, 2015), since these domains are considered to be the first to be affected in the progression of the impairment. On the other hand, other studies have pointed out the advantages of a multidomain computer-based cognitive training, instead of a domain-focused approach (Bahar-Fuchs et al., 2017; Barban et al., 2016; Delbroek, Vermeylen, & Spildooren, 2017; Fiatarone Singh et al., 2014; Gooding et al., 2016). Ge, Zhu, Wu, and McConnell (2018), in their recent review, observed that in studies in which interventions were focused on a specific cognitive domain, patients' performance improved in this specific domain (e.g., memory or attention) only, whereas in studies where multiple cognitive domain intervention programs were used, participants' performance improved in most of the cognitive domains (Bahar-Fuchs et al., 2017; Delbroek et al., 2017; Ge et al., 2018; Gooding et al., 2016). This general improvement of their cognitive ability is reported to have positively affected their daily life as well and mood (Bahar-Fuchs, Clare, & Woods, 2013; Gooding et al., 2016; Savulich et al., 2017).

In the present study, forty-six Greek patients with MCI were carefully chosen based on the criteria proposed by Petersen et al. (2013). Almost half of them (25 patients) received a 15-week, computer-based multidomain cognitive training with the use of the RehaCom software. RehaCom trains several cognitive domains, such as memory, attention, logical thinking, visuo-motor disturbances, executive function and processing speed.

Although many studies have reported the benefits of RehaCom in Parkinson's disease (Diez-Cirarda et al., 2017; Pena et al., 2014), mild AD (Nousia et al., 2018), multiple sclerosis (Dardiotis et al., 2017; Nasios, Messinis, Kosmidis, & Papathanasopoulos, 2018; Rilo et al., 2018), brain injuries (Fernandez et al., 2012; Pantzartzidou et al., 2017) and schizophrenia (d'Amato et al., 2011; Guerrero Pertinez & Garcia Linares, 2015; Mak et al., 2013), its effect on MCI has not been explored before. Moreover, RehaCom is a relatively new intervention program for Greek researchers and clinicians (Dardiotis et al., 2017; Messinis, Papathanasopoulos, Kosmidis, Nasios, & Kambanaros, 2018; Nasios et al., 2018; Nousia et al., 2018; Pantzartzidou et al., 2017; Yoo, Yong, Chung, & Yang, 2015). In particular, Nousia et al. (2018), who explored the effect of RehaCom in mild AD, a disease more closely related to MCI compared to the other studies, reported its significantly beneficial effect on attention, processing speed, naming, semantic fluency, delayed memory, visuospatial ability and executive function. As expected, the general cognitive improvement was connected to patients' higher quality of life.

Therefore, based on the outcomes of the aforementioned studies, in which RehaCom was used, the training group of the present study is predicted to demonstrate: (a) an improvement on its performance in several cognitive domains, compared to its performance before the intervention and (b) better performance in most of the trained domains compared to the controls.

Method

Participants

In the time period from January to June 2018, a total of 87 patients with MCI, native speakers of the Greek language, attending the Clinical Laboratory of Speech and Language Therapy of the University of Ioannina, were screened for suitability of participation in the study. Forty-one patients, however, were excluded for specific reasons (Figure 1) and consequently, 46 MCI patients were enrolled in the study, none of whom dropped out during the training period. These patients were randomly divided into two groups; (a) the training group which underwent multidomain cognitive training intervention with the RehaCom software (Training Group, TG; 6 males, 19 females), and (b) the control group (CG; 5 males, 16 females), whose members received the standard clinical care, namely they continued taking their prescribed medication and receiving the needed treatment (e.g., physiotherapy, psychotherapy etc). This group of patients, for ethical reasons, was offered the opportunity to undertake cognitive training after completion of the study period.

The diagnosis of MCI was made in accordance with Petersen's criteria (Petersen et al., 2013). According to Petersen et al. (2013), the diagnostic criteria of MCI are: (1) memory complaints, (2) intact activities of daily living (using Instrumental Activities of Daily Living; IADL; Lawton, Moss, Fulcomer, & Kleban, 2003; for Greek Theotoka, et al., 2007), (3) a score of 1.5 SD below the mean on neuropsychological measures (which is considered to be the standard cutoff point between healthy subjects and subjects with cognitive deficits), (4) no dementia, (5) impairment in at least one cognitive domain (e.g., complex attention, executive function, learning, memory). All patients fulfilled all five criteria. Other patients' inclusion criteria were: (1) general cognitive function (MoCa score from 20 to 25) (Jak et al., 2016; Konstantopoulos, Vogazianos, & Doskas, 2016), (2) age between 60–80 years and (3) at least 6 years of education, (4) the severity of functional impairment with Clinical Dementia Rating Scale (CDR; Golomb, Kluger, & Ferris, 2004) to be 0.5 = mild cognitive impairment. The researcher submits the scores to a computer program which presents each participant's dementia rating.

On the other hand, exclusion criteria were: (1) presence of an additional neurological (e.g., stroke, epilepsy, and traumatic brain injury) or psychiatric disorder (e.g., psychotic symptoms or disorders, alcohol or illegal drug abuse), (2) presence of depression, which was evaluated with Geriatric Depression Scale-15 (GDS-15; Yesavage & Sheikh, 1986; for Greek Foutoulakis et al., 1999); a score below 5 points on the GDS-15 is suggestive of depression, (3) visual/hearing impairment or writing/reading disability sufficient to impair

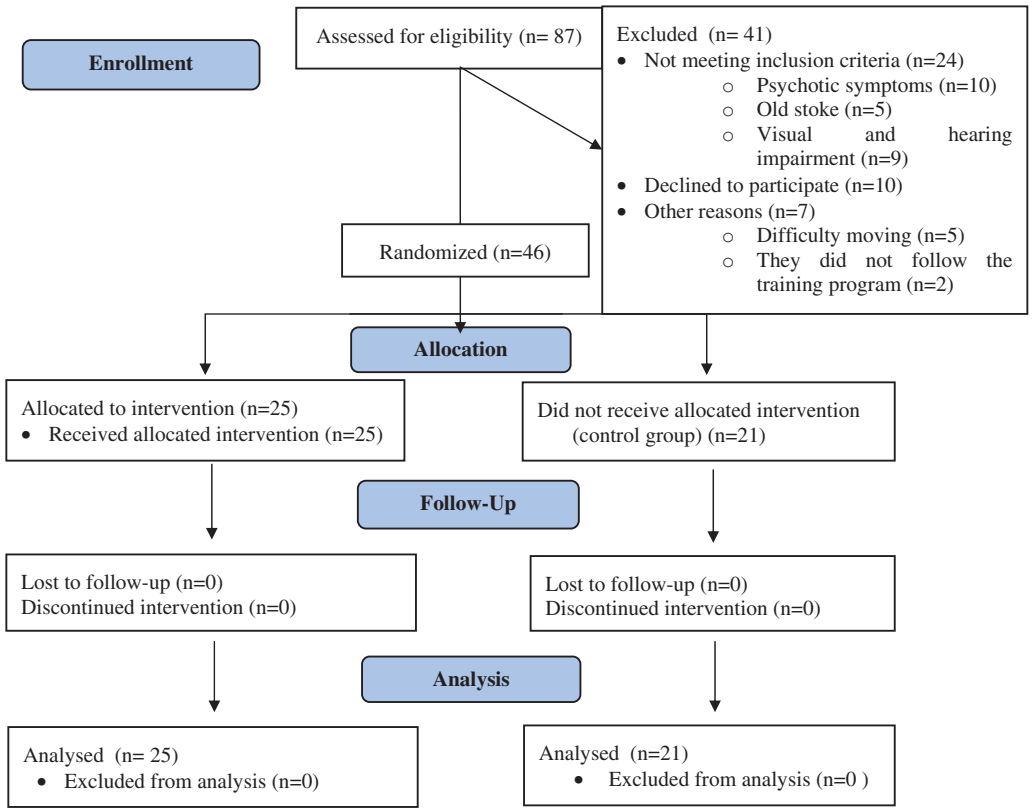

Figure 1. Participants flow diagram.

the performance in the assessment and the training. All participants had undergone a clinical neurological assessment with neurological examination, laboratory tests and brain magnetic resonance imaging scans, which presented no evidence of other neurological or psychiatric diseases.

The evaluation of the participants was performed separately by both a neurologist and an experienced neuropsychologist pre and post the intervention program. Both the neurologist and the neuropsychologist were blind to the allocation of participants to groups (training and control). All the collected data was reviewed, and diagnoses were assigned using published criteria, after expert consensus meetings, including the neurologists (who examined the participants) and the neuropsychologists (who performed the neuropsychological batteries). To sum up, the diagnosis of MCI was based on Petersen criteria, additional inclusion criteria and neurological and neuropsychological assessment. All subtypes of MCI patients were included in the study, namely with deficits in a single or multiple domains with and without memory problems. Due to the relatively small sample size, however, it was not able to assess the effects of the intervention on the subgroups separately.

Participants' neuropsychological assessment was performed via the use of the following measures:

1. Montreal Cognitive Assessment (MoCA; Smith, Gildeh, & Jolmes, 2007; for Greek Konstantopoulos et al., 2016): A brief 30-question test. Scores range from 0 to 30, with a score of 26 and higher generally considered normal. The cognitive areas and scoring breakdown is as follows: visuospatial and executive functioning: 5 points, animal naming: 3 points, attention: 6 points, language: 3 points, abstraction: 2 points, delayed recall (Short-term Memory): 5 points, orientation: 6 points. One point is added to participants' score if (s)he has 12 years or less of formal education.
2. Clock Drawing Test (CDT; (Nair et al., 2010): The clinician gives the person being tested a piece of paper with a pre-drawn circle on it and asks him/her to draw the numbers on the clock. Then the patients have to draw the clock hands indicating 10 min past 11. The 15-point range was divided into four subgroups: clock outline (2 points), numerals (6 points), time setting (6 points), and center (1 point).
3. Recall, recognition and delay memory were evaluated with the use of immediate word recall, word recognition and delayed word memory test (Kokkinins, 2019; Kosmidou, Bozikas, & Vlaxou, 2012): A list of 10 words is given to the patients and they have to repeat as many as they can in every try (4 tries). Then, a new list with twenty words is given verbally (10 words from the previous list and 10 new words). This time patients have to recognize which word is new and which is not. In the last task (delay memory), after 30 min, patients have to recall as many words as they can from the first list (10 words)
4. Boston Naming Test (BNT; Kaplan, Goodglass, & Weitraub, 2001; for Greek Messinis, Panagea, Kastelakis, & Papathanasopoulos, 2013): The participants are instructed to name 15 line drawings of both common

and rarely seen objects, each one in around 20 s. Every correct answer is awarded with one point, thus the maximum score is 15.

5. Semantic Fluency measure (SF; Tombaugh, Kozak, & Rees, 1999; for Greek Kosmidou, Vlahou, Panagiotaki, & Kiosseoglou, 2004): The participants are given 30 s to generate as many distinct words as possible for each of three categories: fruit, vegetables and objects. The scores for all the categories are summed.
6. Attention and working memory were explored with the use of the digit span forward (DSF) and digit span backward (DSB) test (Richardson, 2007): It involves the oral presentation of spans of digits. The measure has both a 7-item digits forward task and a 7-item digits backward task, each one with its own individual score. As the two paradigms measure distinct function, the disparate scores allow for richer interpretation than that provided by similar assessment instruments on the market.
7. Visual attention, executive function and processing speed were evaluated with the use of the Trail-making Test, part A, part B (TMT-A & TMT-B; Tombaugh, Rees, & McIntyre, 1998; for Greek Vlachou & Kosmidou, 2012): Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered from 1 to 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1–13) and letters (A–L) and the patient has not only to draw lines to connect the circles in an ascending pattern, but also conduct the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient, in both tasks, is instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. It is unnecessary to continue the test if the patient has not completed both parts after 5 min have elapse.

The cognitive status of the participants (attention-processing speed, executive function, immediate and delayed word, recall and recognition, naming, semantic fluency) was measured before (at baseline) and one week after the completion of the computer- based multidomain cognitive training (endpoint).

Procedure

RehaCom

The TG received in total 30 60-min individual sessions over a period of 15 weeks (i.e., two sessions per week). The multi-domain cognitive training intervention program was based on the use of the elderly-friendly software package named RehaCom Cognitive Therapy Software which has been utilized extensively in Europe over the last couple of years for the purpose of providing computer-assisted cognitive rehabilitation. Moreover, the software which has over 20 modules is available in many languages, including Greek. The RehaCom consists of a specially-designed input panel and a large screen that helps patients be trained in several cognitive domains, such as episodic and delayed memory, verbal memory, attention, processing speed and executive function. All participants began training at the beginner's level of the RehaCom software. The training modules automatically adapted the training tasks to the user's level of performance, providing the opportunity to train patients on several levels of difficulty and length of sessions and, according to whether the patient succeeded or failed the task, the difficulty levels were automatically adjusted to meet the patient's ability. All patients were trained on the same tasks for equal duration (min/task) in every session. Neuropsychological assessment included tests of attention, processing speed, verbal fluency, working, delay and visuo-spatial memory, recall, recognition, naming and executive function. The cognitive training with the use of RehaCom software was also based on those evaluated sectors.

The research protocol was approved by the Ethics Committee of the Medical School of Larissa, University of Thessaly, and it was conducted in accordance with the principles of the Declaration of Helsinki. Written consent was obtained from all the participants after having been informed of the nature of the study they would take part in. Moreover, the participants were informed of the option of terminating the experiment at any time they wished without there being a requirement to provide any justification for their decision.

Statistical analysis

In order for the differences in baseline characteristics between the two groups to be examined, Independent Sample *T*-tests were performed. A series of 2×2 mixed ANOVAs, with Group as the between-subjects independent variable and Time as the within-subjects independent variable, was conducted to explore their interaction effects on the dependent variables (Recall, Delayed memory, Word recognition, BNT, SF, CDT, DSF, DSB, TMT-A, TMT-B). Further within group comparisons, using Paired Samples *T*-tests, were obtained, in order for the performance of each group before and after the intervention to be explored.

The effect of the intervention was estimated by comparing the mean difference of the two assessments (baseline minus endpoint in each group) between the groups (training group vs. controls), with the use of Independent-Samples *T*-test. Cohen's *d* and the effect size of the intervention were calculated according to the site https://www.uccs.edu/lbecker/. Correction for multiple testing comparison was assessed we used the false discovery rate (FDR) (Benjamini & Hochberg, 1995). The level of significance was set at 0.05 for all the analyses. All statistical analyses were performed using the SPSS (version 21) statistical software (SPSS Inc., Chicago, IL).

Results

No statistically significant differences were found in baseline characteristics between the two groups, apart from their performance in the Semantic Fluency task, in which the CG achieved higher scores compared to the TG [$t_{(44)} = 3.363$, $p = 0.002$]. Table 1 presents the demographic and clinical

Table 1. Demographic and clinical characteristics of the sample at baseline.

	MCI-training group ($N = 25$)	MCI-control group ($N = 21$)	p-Value[a]
Gender, *N* (%)			0.631
Males	6 (24%)	5 (23.81%)	
Females	19 (76%)	16 (76.19%)	
Educational level	8.92 (±3.37)	8.43 (±3.06)	0.666
Age	71.20 (±5.07)	71.90 (±6.24)	0.748
CDR	0.50 (±0.00)	0.50 (±0.00)	1.00
IADL	8.20 (±0.50)	8.29 (±0.46)	0.356
GDS	2.64 (±1.60)	2.48 (±1.47)	0.718
MOCA	21.80 (±1.38)	21.86 (±1.85)	0.928

CDR: clinical dementia rating; IADL: instrumental activities of daily living; GDS: geriatric depression scale; MOCA: Montreal cognitive assessment.
[a]Independent *T* tests.

Table 2. Neuropsychological test scores of the training and control group at baseline.

	MCI-training group ($N = 25$)	MCI-control group ($N = 21$)	p-Value[a]
Recall, mean (SD)	19.36 (3.38)	19.90 (3.78)	0.608
Delayed memory, mean (SD)	1.80 (0.76)	1.43 (1.29)	0.232
Word recognition, mean (SD)	18.96 (1.43)	19.24 (1.09)	0.469[b]
BNT, mean (SD)	13.56 (1.45)	13.10 (1.64)	0.313
SF, mean (SD)	30.44 (7.76)	38.05 (7.49)	**0.002**
CDT, mean (SD)	13.68 (1.25)	14.00 (1.34)	0.407
DSF, mean (SD)	6.60 (1.32)	6.33 (1.59)	0.538
DSB, mean (SD)	4.48 (1.23)	4.52 (1.29)	0.907
TMT A, mean (SD)	98.44 (27.31)	110.14 (37.02)	0.224
TMT B, mean (SD)	222.48 (53.79)	238.38 (52.25)	0.317

Abbreviations: BNT: Boston Naming Test; SF: semantic fluency; CDT: clock drawing test; DSF: digit span forward; DSB: digit span backward; TMT A: trail making test A; TMT B: trail making test B.
[a]Independent *T* tests.
$p < 0.05$; statistically significant value is highlighted in bold.

characteristics of both groups, whereas the baseline scores in neuropsychological measures of the training and the control group are shown in Table 2.

The statistics revealed statistical significant main effect of Time [$F_{(1,44)} = 4.212$, $p = 0.046$], for the measure Recall, but no significant interaction of Group and Time [$F_{(1,44)} = 0.750$, $p_{corrected} = 0.488$]. Although, both groups' endpoint performance was improved compared to their baseline performance, this improvement was not statistically significant [TG: $t_{(24)} = 2.078$, $p_{corrected} = 0.081$; CG: $t_{(20)} = 0.846$, $p_{corrected} = 0.488$]. As for the Delayed memory, no main effect of Time was found [$F_{(1,44)} = 1.394$, $p = 0.244$], but an interaction of Group and Time [$F_{(1,44)} = 24.433$, $p_{corrected} \leq 0.001$] appeared. Further analysis, using Paired Samples *T*-tests, revealed that TG's performance was statistical significantly improved [$t_{(24)} = 4.272$, $p_{correcte} = 0.005$], whereas CG's performance was statistical significantly decreased between the two assessment times [$t_{(20)} = 2.769$, $p_{corrected} = 0.024$]. On the Word recognition measure, the ANOVA demonstrated a statistical significant main effect of Time [$F_{(1,44)} = 9.065$, $p = 0.004$], but no significant interaction of Group and Time [$F_{(1,44)} = 2.293$, $p_{corrected} = 0.216$]. The TG' performance was statistical significantly improved after the intervention, while CG' performance remained almost the same between the two assessment times [TG: $t_{(24)} = 2.823$, $p_{corrected} = 0.019$; CG: $t_{(20)} = 1.420$, $p_{corrected} = 0.244$]. As for BNT, there was no main effect of Time [$F_{(1,44)} = 3.015$, $p = 0.089$], but an interaction between Group and Time was found [$F_{(1,44)} = 6.326$, $p_{corrected} = 0.030$]. TG's performance was statistical significantly improved [$t_{(24)} = 5.316$, $p_{corrected} \leq 0.001$] after the intervention whereas CG's performance was only slightly *decreased* [$t_{(20)} = .396$, $p_{corrected} = 0.720$]. For the measure of SF, the statistics revealed a statistical significant main effect of Time [$F_{(1,44)} = 22.855$, $p \leq 0.001$] and significant interaction of Group and Time [$F_{(1,44)} = 82.138$, $p_{corrected} \leq 0.001$]. TG's performance was statistical significantly improved [$t_{(24)} = 9.424$, $p_{corrected} \leq 0.001$], whereas CG's performance was statistical significantly decreased between the two assessment times [$t_{(20)} = 3.284$, $p_{corrected} = 0.010$]. The 2×2 ANOVA showed a statistical significant main effect of Time [$F_{(1,44)} = 4.406$, $p = 0.042$] and significant interaction of Group and Time [$F_{(1,44)} = 7.292$, $p_{corrected} = 0.017$] for the CDT measure. Further analyses revealed statistical significant improvement only for the TG, whereas CG' performance remained stable [TG: $t_{(24)} = 2.854$, $p_{corrected} = 0.019$; CG: $t_{(20)} = .698$, $p_{corrected} = 0.560$]. For the DSF measure, no main effect of Time [$F_{(1,44)} = 0.151$, $p = 0.700$] and no interaction of Group and Time [$F_{(1,44)} = 1.386$, $p_{corrected} = 0.319$] was found. Although no further analysis was needed, Paired Samples *T*-tests were conducted for reasons of analogy [TG: $t_{(24)} = 0.499$, $p_{corrected} = 0.666$; CG: $t_{(20)} = 1.420$, $p_{corrected} = 0.244$]. As for DSB, no main effect of Time [$F_{(1,44)} = 1.490$, $p = 0.229$], but an interaction of Group and Time [$F_{(1,44)} = 5.265$, $p_{corrected} = 0.045$] was found. In the TG, participants' improvement did not reach significance [$t_{(24)} = 0.679$, $p_{corrected} = 0.560$], whereas CG's performance during the second assessment was significantly decreased compared to its performance during the first assessment [$t_{(20)} = 3.202$, $p_{corrected} = 0.010$]. In the last two measures (TMT-A and TMT-B) the fastest performance is also the best one. The 2×2 ANOVAs showed a statistical significant main effect of Time for both measures [TMT-A: $F_{(1,44)} = 10.919$, $p = 0.002$; TMT-B: $F_{(1,44)} = 10.073$, $p = 0.003$] and

Table 3. Mean score, standard deviation, *p* value pre and post assessment in control and training group.

	MCI-training group				MCI-control group			
	Pre assesment Mean (SD)	Post assesment Mean (SD)	*p*-Value[a]	*p*-Value$_{corrected}$*	Pre assesment Mean (SD)	Post assesment Mean (SD)	*p*-Value[a]	*p*-Value$_{corrected}$*
Recall	19.36 (3.38)	21.00 (2.72)	**0.049**	0.081	19.90 (3.78)	20.57 (2.93)	0.407	0.488
Delayed memory	1.80 (0.76)	3.04 (1.21)	**<0.001**	**0.005**	1.43 (1.29)	0.67 (0.58)	**0.012**	**0.024**
Word recognition	18.96 (1.43)	19.68 (0.48)	**0.009**	**0.019**	19.24 (1.09)	19.48 (0.81)	0.171	0.244
BNT	13.56 (1.45)	14.60 (0.65)	**<0.001**	**<0.001**	13.10 (1.64)	12.90 (2.63)	0.696	0.720
SF	30.44 (7.76)	40.60 (7.17)	**<0.001**	**<0.001**	38.05 (7.49)	34.90 (5.54)	**0.004**	**0.010**
CDT	13.68 (1.25)	14.44 (0.82)	**0.009**	**0.019**	14.00 (1.34)	13.90 (1.18)	0.493	0.560
DSF	6.60 (1.32)	6.72 (1.34)	0.622	0.666	6.33 (1.59)	6.10 (1.58)	0.171	0.244
DSB	4.48 (1.23)	4.64 (1.08)	0.504	0.560	4.52 (1.29)	4.00 (1.30)	**0.004**	**0.010**
TMT-A	98.44 (27.31)	80.72 (23.45)	**<0.001**	**<0.001**	110.14 (37.02)	113.67 (37.36)	0.203	0.276
TMT-B	222.48 (53.79)	174.16 (37.11)	**<0.001**	**<0.001**	238.38 (52.25)	237.86 (43.73)	0.959	0.959

Abbreviations: BNT: Boston naming test; SF: semantic fluency; CDT: clock drawing test; DSF: digit span forward; DSB: digit span backward; TMT-A: trail making test A; TMT-B: trail making test B.
[a]Paired samples *T*-tests.
*Corrected for multiple comparison testing *p*-values with false discovery rate (FDR).
$p < 0.05$; statistically significant values are highlighted in bold.

Table 4. The effect size correlation of the intervention* in the training group compared to the control group.

	MCI-training group ($N = 25$)	MCI-control group ($N = 21$)	*p*-Value	*p*-Value$_{corrected}$*	Cohen's *d*	Effect size
Recall (95% CI)	1.64 (0.1, 3.27)	0.67 (−0.98, 2.31)	0.391	0.488	0.26	0.13
Delay memory (95% CI)	1.24 (0.64, 1.84)	−0.76 (−1.34, −0.19)	**<0.001**	**<0.001**	1.47	0.59
Word Recognition (95% CI)	0.72 (0.19, 1.25)	0.24 (−0.11, 0.59)	0.137	0.216	0.46	0.22
BNT (95% CI)	1.04 (0.64, 1.44)	−0.19 (−1.19, 0.81)	**0.016**	**0.030**	0.72	0.34
SF (95% CI)	10.16 (7.93, 12.39)	−3.14 (−5.14, −1.15)	**<0.001**	**<0.001**	2.71	0.80
CDT (95% CI)	0.76 (0.21, 1.31)	−0.10 (−0.38, 0.19)	**0.007**	**0.017**	0.83	0.38
DSF (95% CI)	0.12 (−0.38, 0.62)	−0.24 (−0.59, 0.11)	0.245	0.319	0.36	0.18
DSB (95% CI)	0.16 (−0.33, 0.65)	−0.52 (−0.87, −0.18)	**0.027**	**0.045**	0.69	0.33
TMT-A (95% CI)	−17.72 (−24.38, −11.06)	3.52 (−2.06, 9.11)	**<0.001**	**<0.001**	−1.48	−0.60
TMT-B (95% CI)	−48.32 (−71.51, −25.13)	−0.52 (−21.68, 20.63)	**0.003**	**0.010**	−0.93	−0.42

Abbreviations: BNT: Boston naming test; SF: semantic fluency; CDT: clock drawing test; DSF: digit span forward; DSB: digit span backward; TMT-A: trail making test A; TMT-B: trail making test B.
*Estimated by comparing the mean difference of the two neuropsychological assessments (baseline minus endpoint in each group) between the two groups (training group vs controls) with the use of Independent-Samples *T*-tests.
*Corrected for multiple comparison testing *p*-values with false discovery rate (FDR).
$p < 0.05$; statistically significant values are highlighted in bold.

significant interaction of Group and Time [TMT-A: $F_{(1,44)} = 24.452$, $p_{corrected} < 0.001$; TMT-B: $F_{(1,44)} = 9.646$, $p_{corrected} = 0.010$]. Further analyses demonstrated that the TG performed significantly faster after the intervention in both TMT-A [$t_{(24)} = 5.487$, $p_{corrected} < 0.001$] and TMT-B [$t_{(24)} = 4.300$, $p_{corrected} < 0.001$], whereas no statistical difference was found between the two assessment times in the CG on either TMT-A [$t_{(20)} = 1.316$, $p_{corrected} = 0.276$] or TMT-B [$t_{(20)} = 0.052$, $p_{corrected} = 0.959$].

Table 3 presents the mean scores (and standard deviations) for each measure and each group in both assessment times, as well as the difference between the two assessments (*p*-values). As we can see, the TG improved its performance in all the tested cognitive domains. In particular, the TG patients' improvement, after the intervention, reached significance in, Delayed memory, Word recognition, BNT, SF, CDT, TMT-A and TMT-B. In DSF and DSB, however, TG patients' improvement did not manage to reach significance. On the contrary, the controls remained stable in most of the neuropsychological measures over the observation period of 15 weeks. In three cognitive measures, however, their endpoint performance was statistically significantly lower, compared to that of their initial performance (DSB, Delayed memory, SF).

Comparison between the two groups (TG vs. CG) in the mean difference of the two neuropsychological assessments (baseline minus endpoint in each group) presented a significant effect of the intervention; the TG's improved performance was statistically significantly better on Delayed memory [$t_{(44)} = 4.943$, $p_{corrected} < 0.001$], BNT [$t_{(44)} = 2.515$, $p_{corrected} = 0.030$], SF [$t_{(44)} = 9.063$, $p_{corrected} < 0.001$], CDT [$t_{(44)} = 2.700$, $p_{corrected} = 0.017$], DSB [$t_{(44)} = 2.295$, $p_{corrected} = 0.045$], TMT-A [$t_{(44)} = 4.945$, $p_{corrected} < 0.001$] and TMT-B [$t_{(44)} = 3.106$, $p_{corrected} = 0.010$] when compared to CG's performance. No significant difference, however, was noted between the two groups' mean difference of the two neuropsychological assessments on the Recall [$t_{(44)} = 0.866$, $p_{corrected} = 0.488$], the Word recognition [$t_{(44)} = 1.514$, $p_{corrected} = 0.216$] and the DSF [$t_{(44)} = 1.177$, $p_{corrected} = 0.319$] (see also Table 4). The absolute value of effect size correlation of the training ranged from −0.42 for TMT-B to 0.80 for SF.

Discussion

Since in the AD continuum, the prodromal state of MCI precedes AD (Dardiotis et al., 2019; Oltra-Cucarella et al., 2018; Slot et al., 2019; Varatharajah, Ramanan, Iyer, & Vemuri, 2019), being able to map and improve patients'

impairments in this early stage, is of significant importance, as it might lead to an effective way to dramatically delay or even prevent the appearance of AD.

Having this in mind, and based on systematic reviews on cognitive training, which have demonstrated promising effects on subjects with MCI (Belleville, 2008; Cooper et al., 2013; Gates, Sachdev, Fiatarone Singh, & Valenzuela, 2011; Ge et al., 2018; Jean, Bergeron, Thivierge, & Simard, 2010), especially when multidomain computer-based cognitive trainings were used (Ge et al., 2018), we wanted to examine the effects of the RehaCom software on Greek patients with MCI and add to the existing evidence.

The RehaCom software has already been used on Greek patients with mild AD (Nousia et al., 2018), multiple sclerosis (Dardiotis et al., 2017; Messinis et al., 2018; Nasios et al., 2018) and brain injuries (Pantzartzidou et al., 2017) with positive results, but never before has it been used in examining whether such an intervention can also positively affect people with mild cognitive problems.

The present study provides evidence that individualized, computer-based multidomain cognitive training in patients with MCI being applied twice a week, for 60 min per session improves all cognitive functions. In particular, our results demonstrated that the RehaCom software had a significant impact on delayed memory, word recognition, naming, semantic fluency, attention, processing speed and executive function. It is worth noting that, even though executive functions scores were slow before and after the training, the training group improved significantly compared to the control group. These low scores pre and post training are consistent with previous studies for TMT-A (Guo, Zhou, Zhao, Whang, & Hong, 2012; Wei et al., 2018; Zhao, Li, Lin, Wei, & Yang, 2018) and TMT-B (Guo et al., 2012; Terada et al., 2013; Wei et al., 2018; Zhao et al., 2018).

These findings confirm our hypothesis, according to which the training group's performance on standardized neuropsychological assessments was expected to be improved after the intervention, when compared to its baseline performance.

Moreover, these results are in agreement with previous research in MCI, according to which multidomain training programs had a significant impact in delayed memory (Hwang et al., 2012; Olchik et al., 2013; Savulich et al., 2017), executive function and processing speed (Greenaway et al., 2013), naming and semantic fluency (Gooding et al., 2016; Rojas et al., 2013). On the other hand, the study by Hwang et al. (2012) mentioned no statistical improvement in patients with MCI, as far as recognition and working memory is concerned (Hwang et al., 2012). Differences regarding the intervention program, as well as the frequency and the duration of the intervention sessions can possibly account for the different findings.

According to our second hypothesis, the training group was expected to demonstrate a better performance in most of the trained domains compared to the controls. This hypothesis was also supported, since the results revealed better performance of the TG in all cognitive domains compared to the controls, although in three out of the ten measures this performance did not reach the significance threshold. These results are in line with previous studies, where statistically significant differences between the two groups were found in some (Delbroek et al., 2017; Hwang et al., 2012) or even all (Bahar-Fuchs et al., 2013; Gooding et al., 2016; Mansbach et al., 2017) of the trained cognitive domains, with the trained group revealing a better performance when compared to the controls. Moreover, in order to evaluate the personal benefit to each patient gained from the intervention, we informally asked treated patients to provide feedback regarding the intervention on verbal questions at the post intervention assessment. Specifically, the TG mentioned positive feedback on daily activities and functional communication.

Certain limitations, however, need to be acknowledged. Firstly, the present study had a relatively short follow-up period. Thus, a longer follow-up period would have allowed for more robust and trustworthy results (Llewellyn-Bennett, Bowman, & Bulbulia, 2016). Furthermore, considering the relatively small sample size, our study might be underpowered to examine the complete and absolute effect of computer-based multidomain cognitive training on MCI. In addition, because of the relatively small sample size, it was not feasible to assess the effects of the intervention on MCI subtypes separately. Future studies should examine whether patients with a specific MCI subtype (i.e., amnestic MCI) may benefit more than other subtypes from a multidomain cognitive training program. Finally, a possible Hawthorne effect in the intervention cannot be completely excluded (Sedgwick & Greenwood, 2015). Thus, further studies applied to larger groups of patients are required in order for the effect of computer-based multidomain cognitive training and its clinical meaning on MCI patients to be properly illustrated.

Conclusions

The present study demonstrates the beneficial impact of computer-based multidomain cognitive training on the cognitive performance of patients with MCI. Considering the connection between MCI and AD, this data is promising for developing training methods in order to restrict cognitive decline or delay the progression of the disease to mild AD.

Disclosure statement

The authors declare that they have no conflicts of interest.

Data availability

All related data are included within the article or will be made available upon request.

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